ELEVENTH EDITION

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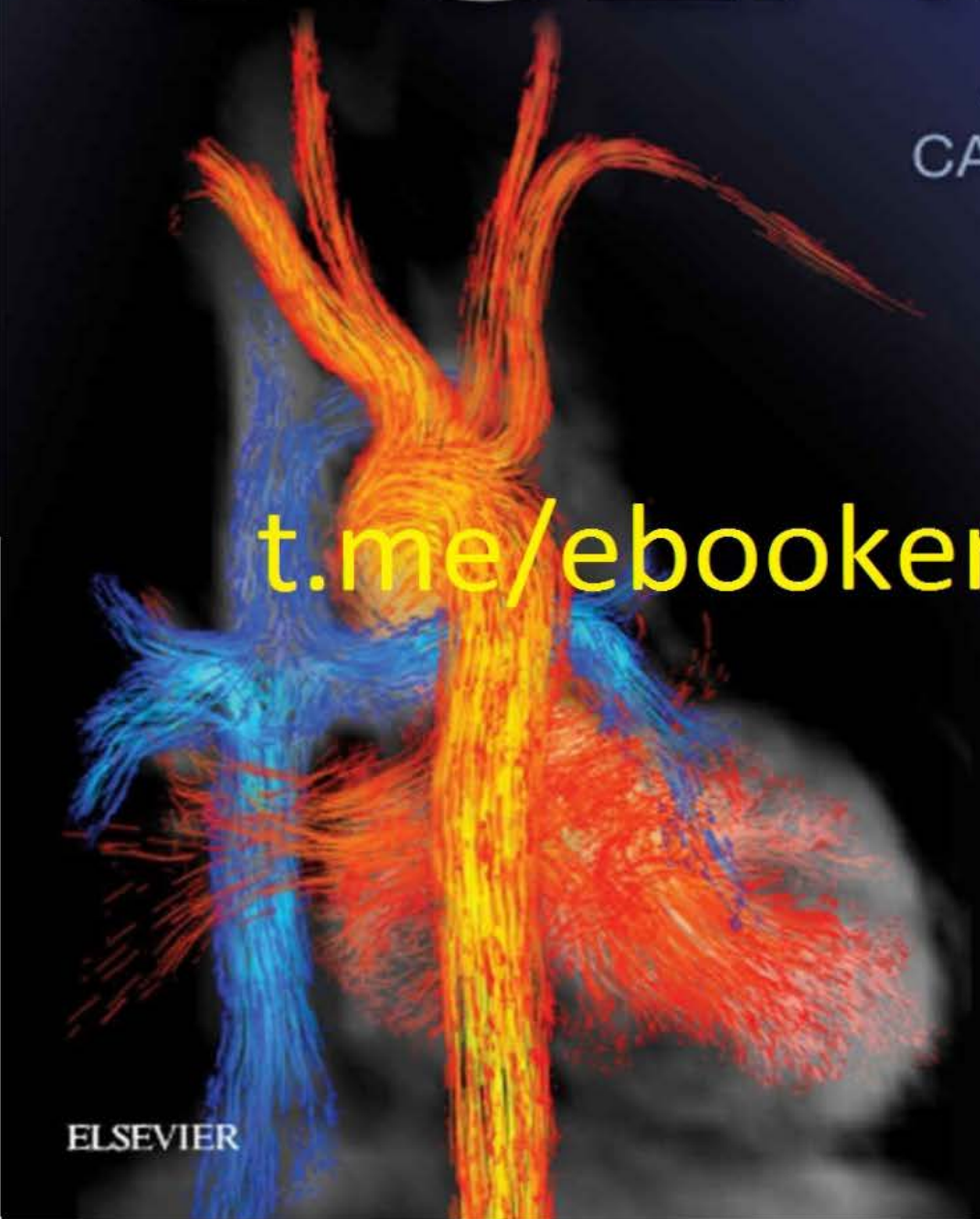
BRAUNWALD'S HEART DISEASE

A TEXTBOOK OF CARDIOVASCULAR MEDICINE



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Braunwald's Heart Disease

A TEXTBOOK OF CARDIOVASCULAR MEDICINE

ELEVENTH EDITION

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Dedication

To

Joan, Debra, Jeffrey, and David

Beryl, Oliver, and Brigitte

Pat, Rob, and Sam

Laura, Erica, Jonathan, and Stephanie

Charlene, Sarah, Emily, and Matthew

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Approach to the Patient with Cardiac Arrhythmias
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Pacemakers and Implantable Cardioverter-Defibrillators
Hypotension and Syncope
Neurologic Disorders and Cardiovascular Disease

Preface

This is the 11th edition of the classic textbook, *Heart Disease: A Textbook Of Cardiovascular Medicine*, that Dr. Eugene Braunwald began almost 40 years ago. The editors are pleased and honored to dedicate this edition to him for his extraordinary contributions to the discipline of cardiology, especially this textbook and its companions, and for his unique concept of creating a "living textbook."

In the past several decades, cardiology has advanced at a breakneck pace on many fronts. Knowledge of the diagnosis and management of patients with heart disease, as well as understanding of responsible mechanisms and preventive approaches, advance daily. Genetics, molecular biology and pharmacology, imaging, catheter-based therapy, and cardiac repair are only a sampling of what we encounter daily.

This constant flow of innovative research has generated a proliferation of new cardiovascular journals, cumulatively publishing an unprecedented amount of information. With the rapidly changing cardiovascular knowledge base, an authoritative textbook like *Heart Disease* to which readers can turn, confident that the statements are as accurate and up-to-date as possible, offers even greater value.

As with each edition of this reference work, international experts — household names to many readers — have totally revised *every* chapter. In addition, 14 new chapters have been added to recognize the ever-expanding role of cardiology into areas such as oncology, chronic lung disease, environmental toxins, catheter-based treatments of congenital heart disease, and other topics. Some sections have been revised for clarity, such as arrhythmias; some have been expanded, such as diseases of heart valves; others have had a shift of emphasis, such as congenital heart disease in the adult. Finally, to maintain vitality of standard topics, new authors have replaced more than a third of those who have tirelessly written for previous editions, in chapters on ethics, personalized and precision medicine, imaging, obesity, diabetes, sleep-disordered breathing, autonomic nervous system, and other areas.

In the preface for the 10th edition of *Heart Disease*, we emphasized that the online version contained audio, video, and written information not available in the print edition. We have continued and expanded this practice. To put this 11th edition in perspective, it contains more than 2700 illustrations and 565 tables, while maintaining the number of printed pages near 2000. The eBook includes an additional 400 illustrations, 60 tables, and 300 videos.

We have divided the book into 11 sections, including fundamentals of cardiovascular disease; genetics and personalized medicine; evaluation of the patient; heart failure; arrhythmias, sudden death, and syncope; preventive cardiology; atherosclerotic cardiovascular disease; diseases of heart valves; diseases of the myocardium, pericardium, and pulmonary vasculature bed; cardiovascular disease in special populations; and cardiovascular disease and disorders of other organs. We have continued the tradition of including practice guidelines, and have written the text for all levels of learners and for all specialties in cardiology. As before, information not directly relevant to practicing clinicians is presented in smaller font. More detailed information on many topics can be found in the companions to this book:

Cardiovascular Intervention by Deepak L. Bhatt
Cardiovascular Therapeutics by Elliott Antman and Marc Sabatine

Chronic Coronary Artery Disease by James DeLemos and Torbjorn Omland
Clinical Arrhythmology and Electrophysiology by Ziad Issa, John Miller, and Douglas Zipes
Clinical Lipidology by Christie Ballantyne
Diabetes in Cardiovascular Medicine by Darren McGuire and Nikolaus Marx
Heart Failure by Michael Felker and Douglas Mann
Hypertension by George Bakris and Matthew Sorrentino
Mechanical Circulatory Support by Robert Kormos and Leslie Miller
Myocardial Infarction by David Morrow
Preventive Cardiology by Roger Blumenthal, JoAnn Foody, and Nathan Wong
Valvular Heart Disease by Catherine Otto and Robert Bonow
Vascular Medicine by Marc Creager, Joshua Beckman, and Joseph Loscalzo
Braunwald's Heart Disease Review and Assessment by Leonard Lilly
Atlas of Cardiovascular CT by Allen Taylor
Atlas of Cardiovascular MR by Christopher Kramer and W Greg Hundley
Atlas of Nuclear Cardiology by Amil Iskandrian and Ernest Garcia

In keeping with the revitalization theme noted above, one of us (DPZ) will be leaving after this edition. Beginning with the 2nd edition of Heart Disease in 1984, Dr. Zipes has written the arrhythmia section and, in more recent editions, with co-authors, and has co-edited *Heart Disease* since the 6th edition. Gordon F. Tomaselli will be his very capable replacement.

The editors and authors, along with the Elsevier staff, have endeavored to make *Heart Disease* the go-to source for current cardiology knowledge, maintaining the high standards Dr. Braunwald set many years ago. We hope readers will enjoy reading this edition and learn from it, as we all strive to improve patient care, our ultimate goal.

Douglas P. Zipes

Peter Libby

Robert O. Bonow

Douglas L. Mann

Gordon F. Tomaselli

Preface to the First Edition

Cardiovascular disease is the greatest scourge affecting the industrialized nations. As with previous scourges — bubonic plague, yellow fever, and small pox — cardiovascular disease not only strikes down a significant fraction of the population without warning but also causes prolonged suffering and disability in an even larger number. In the United States alone, despite recent encouraging declines, cardiovascular disease is still responsible for almost 1 million fatalities each year and more than half of all deaths; almost 5 million persons afflicted with cardiovascular disease are hospitalized each year. The cost of these diseases in terms of human suffering and material resources is almost incalculable.

Fortunately, research focusing on the prevention, causes, diagnosis, and treatment of heart disease is moving ahead rapidly. Since the early part of the twentieth century, clinical cardiology has had a particularly strong foundation in the basic sciences of physiology and pharmacology. More recently, the disciplines of molecular biology, genetics, developmental biology, biophysics, biochemistry, experimental pathology and bioengineering have also begun to provide critically important information about cardiac function and malfunction.

In the past 25 years, in particular, we have witnessed an explosive expansion of our understanding of the structure and function of the cardiovascular system—both normal and abnormal—and of our ability to evaluate these parameters in the living patient, sometimes by means of techniques that require penetration of the skin but also with increasing accuracy, by noninvasive methods. Simultaneously, remarkable progress has been made in preventing and treating cardiovascular disease by medical and surgical means. Indeed, in the United States, a steady reduction in mortality from cardiovascular disease during the past decade suggests that the effective application of this increased knowledge is beginning to prolong human life span, the most valued resource on earth.

To provide a comprehensive, authoritative text in a field that has become as broad and deep as cardiovascular medicine, I enlisted the aid of a number of able colleagues. However, I hoped that my personal involvement in the writing of about half of the book would make it possible to minimize the fragmentation, gaps, inconsistencies, organizational difficulties, and impersonal tone that sometimes plague multiauthored texts. Although *Heart Disease: A Textbook of Cardiovascular Medicine* is primarily a clinical treatise and not a textbook of fundamental cardiovascular science, an effort has been made to explain, in some detail, the scientific bases of cardiovascular diseases.

To the extent that this book proves useful to those who wish to broaden their knowledge of cardiovascular medicine and thereby aids in the care of patients afflicted with heart disease, credit must be given to the many talented and dedicated persons involved in its preparation. I offer my deepest appreciation to my fellow contributors for their professional expertise, knowledge, and devoted scholarship, which has so enriched this book. I am deeply indebted to them for their cooperation and willingness to deal with a demanding editor.

Eugene Braunwald

1980

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Volume 1

OUTLINE

PART I
Fundamentals of Cardiovascular Disease

OUTLINE

1

Global Burden of Cardiovascular Disease

Thomas A. Gaziano, Dorairaj Prabhakaran, J. Michael Gaziano

Over the last decade, cardiovascular disease (CVD) has become the leading cause of death worldwide. In 2013, CVD caused an estimated 17.3 million deaths and led to 330 million disability-adjusted life-years (DALYs) lost[1]—about 32% of all deaths and 13% of all DALYs lost that year. Overall, these data represent increases in both absolute numbers and percentages of deaths and DALYs compared with 2010 estimates. As with many high-income countries during the last century, low- and middle-income countries are now experiencing an alarming and accelerating increase in CVD.

This chapter reviews the features of the epidemiologic transitions underlying this shift in CVD morbidity and mortality and evaluates the transition in different regions of the world. A survey of the current burden of risk factors and behaviors associated with CVD includes regional variations and trends. A review of the economic impact of CVD highlights the cost-effectiveness of various strategies to reduce it. The chapter ends with a discussion of the diverse challenges that the increasing burden of CVD poses for various regions of the world, along with potential solutions to this global problem.

Shifting Burden

Between 1990 and 2013, deaths from CVD increased from 26% to 32% of all deaths globally, a reflection of the rapid epidemiologic transition, particularly in low- and middle-income countries (LMICs). Although the net percentage of deaths caused by CVD overall has increased, this results from an increase in LMICs and a decline in high-income countries (HICs) (**Fig. 1.1**). CVD now causes the most deaths in all low- and middle-income regions, with the exception of sub-Saharan Africa, where it is the leading cause of death in those older than 45 years. In absolute numbers, CVD causes four to five times as many deaths in LMICs as in HICs. Within the six World Bank–defined low- and middle-income regions, the CVD burden differs vastly (**Fig. 1.2**), with CVD death rates as high as 59% in Eastern Europe and as low as 12% in sub-Saharan Africa. The CVD mortality rate is 38% in HICs.

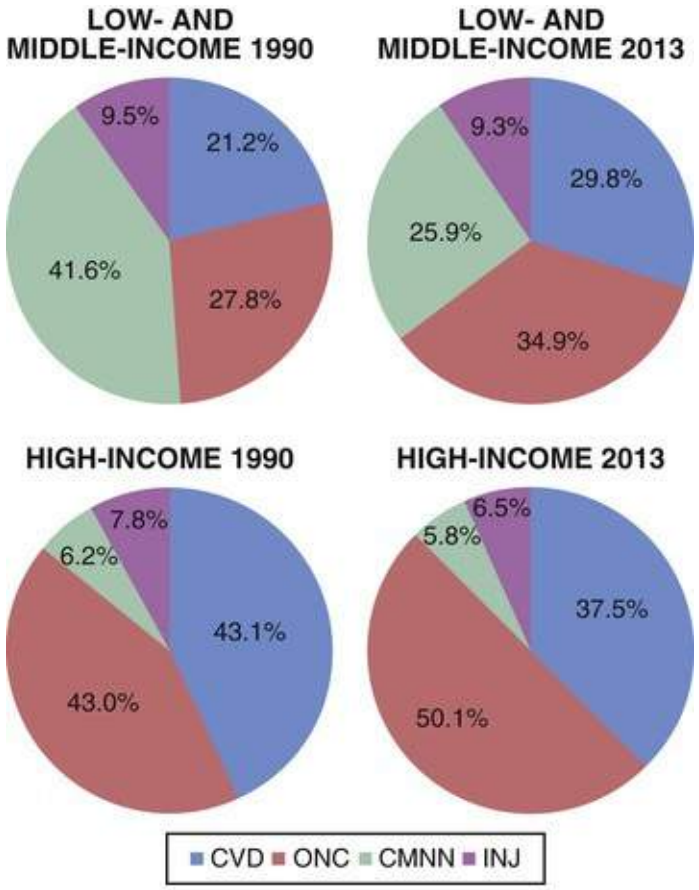

FIGURE 1.1 Changing pattern of mortality, 1990 to 2013. *CVD,* Cardiovascular disease; *ONC,* other noncommunicable diseases; *CMNN,* communicable, maternal, neonatal, and nutritional diseases; *INJ,* injury. (From Global Burden of Disease Study 2013. Age-sex specific all-cause and cause-specific mortality, 1990–2013, Seattle: Institute for Health Metrics and Evaluation; 2014.)

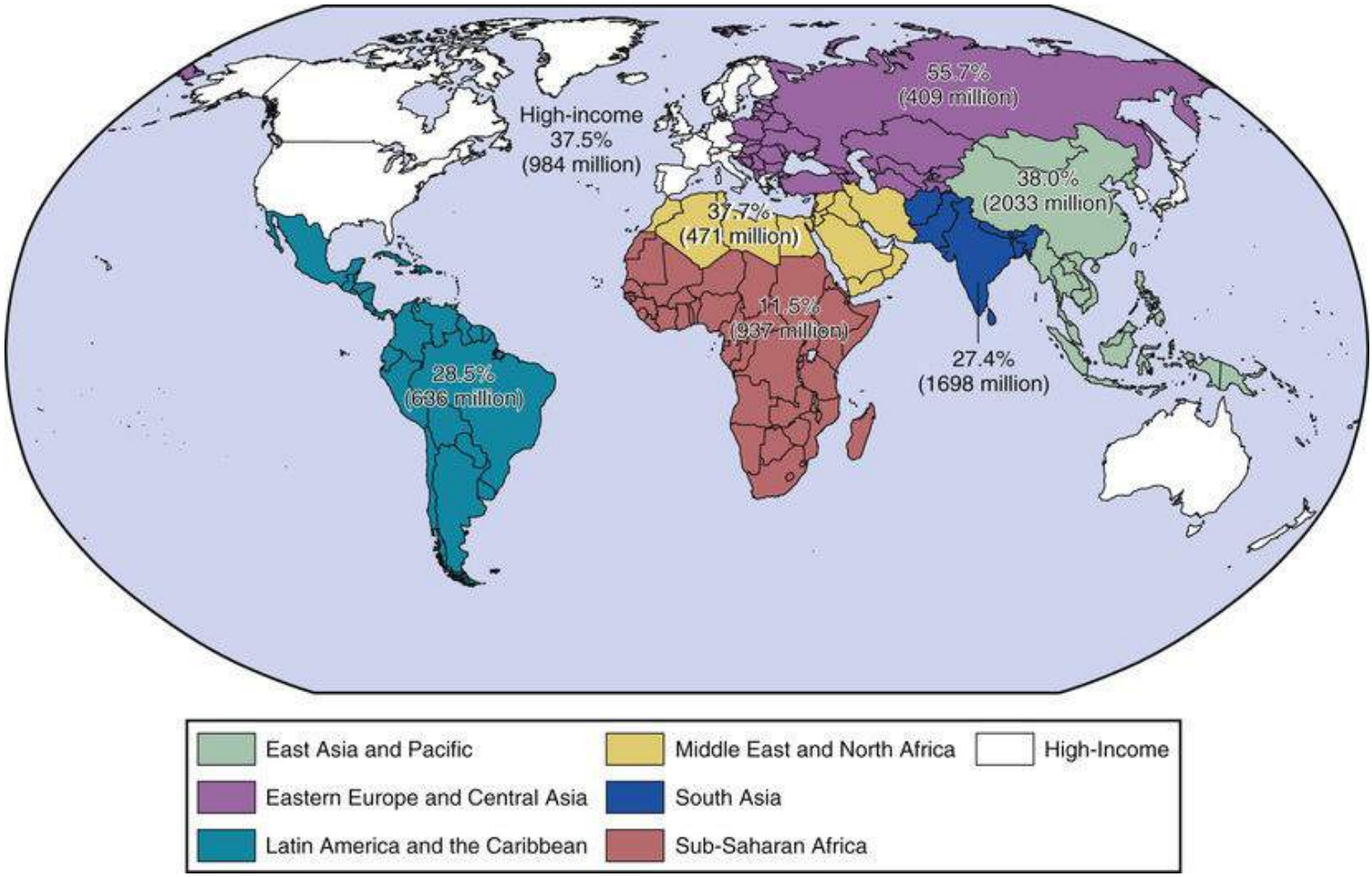

FIGURE 1.2 Cardiovascular disease deaths as a percentage of all deaths in each region and total regional population, 2013. (From Global Burden of Disease Study 2013: Age-sex specific all-cause and cause-specific mortality, 1990–2013. Seattle: Institute for Health Metrics and Evaluation; 2014; and World Health Organization. Global Health Observatory Data Repository. Demographic and socioeconomic statistics: population data by country. http://apps.who.int/gho/data/view.main.POP2040?lang=en.)

Epidemiologic Transitions

The overall increase in the global burden of CVD and the distinct regional patterns result in part from the "epidemiologic transition," which includes four basic stages (**Table 1.1**): Pestilence and Famine, Receding Pandemics, Degenerative and Man-Made Diseases, and Delayed Degenerative Diseases.[2,3] Movement through these stages has dramatically shifted the causes of death over the last two centuries, from infectious diseases and malnutrition in the first stage to CVD and cancer in the third and fourth stages. Although the transition through the age of Pestilence and Famine has occurred much later in LMICs, it has also occurred more rapidly, driven largely by the transfer of low-cost agricultural technologies, the overall globalization of world economies, and public health advances.

TABLE 1.1

Five Typical Stages of Epidemiologic Transition in CVD Mortality and Types

STAGE	DESCRIPTION	TYPICAL PROPORTION OF DEATHS CAUSED BY CVD (%)	PREDOMINANT TYPES OF CVD
Pestilence and Famine	Predominance of malnutrition and infectious diseases as causes of death; high rates of infant and child mortality; low mean life expectancy.	<10	Rheumatic heart disease, cardiomyopathies caused by infection and malnutrition
Receding Pandemics	Improvements in nutrition and public health lead to decrease in rates of deaths caused by malnutrition and infection; precipitous decline in infant and child mortality rates.	10-35	Rheumatic valvular disease, hypertension, CHD, stroke
Degenerative and Man-Made Diseases	Increased fat and caloric intake and decreased physical activity lead to emergency of hypertension and atherosclerosis; with increased life expectancy, mortality from chronic, noncommunicable diseases exceeds mortality from malnutrition and infectious diseases.	35-65	CHD, stroke
Delayed Degenerative Diseases	CVDs and cancer are the major causes of morbidity and mortality; better treatment and prevention efforts help avoid deaths among those with disease and delay primary events. Age-adjusted CVD mortality declines; CVD affects older and older individuals.	40-50	CHD, stroke, congestive heart failure
Inactivity and Obesity	Increasing prevalence of obesity and diabetes; some slowing of CVD mortality rates in women.	38	

CVD, Cardiovascular disease; *CHD,* coronary heart disease.

Modified from Omran AR. The epidemiologic transition: a theory of the epidemiology of population change. Milbank Mem Fund Q 1981;49:509; and Olshanksy SJ, Ault AB. The fourth stage of the epidemiologic transition: the age of delayed degenerative diseases. Milbank Q 1986;64:355.

Humans evolved during the age of **Pestilence and Famine** and have lived with epidemics and hunger for most of recorded history. Before 1900, infectious diseases and malnutrition constituted the most common causes of death in virtually every part of the world, with tuberculosis, pneumonia, and diarrheal diseases accounting for a majority of deaths. These conditions, along with high infant and child mortality rates, resulted in a mean life expectancy of approximately 30 years.

Per capita income and life expectancy increase during the age of **Receding Pandemics** as the emergence of public health systems, cleaner water supplies, and improved food production and distribution combine to reduce deaths from infectious disease and malnutrition. Improvements in medical education follow, and along with other public health changes, contribute to dramatic declines in infectious disease mortality rates. Rheumatic valvular disease, hypertension, and cerebrovascular accident (stroke) cause most CVD. Coronary heart disease (CHD) often occurs at a lower prevalence rate than stroke, and CVD accounts for 10% to 35% of deaths.

During the stage of **Degenerative and Man-Made Diseases,** continued improvements in economic circumstances, combined with urbanization and radical changes in the nature of work-related activities, led to dramatic changes in diet, activity levels, and behaviors such as smoking. For example, in the United States, deaths from infectious diseases decreased to fewer than 50 per 100,000 people per year, and life expectancy increased to almost 70 years. The increased availability of foods high in calories, coupled with decreased physical activity, contributes to an increase in atherosclerosis. In this stage, CHD and stroke predominate, and between 35% and 65% of all deaths are related to CVD. Typically, the ratio of CHD to stroke is 2 : 1 to 3 : 1.

In the age of **Delayed Degenerative Diseases**, CVD and cancer remain the major causes of morbidity and mortality, but CVD age-adjusted mortality rates decline by almost half, accounting for 25% to 40% of all deaths. Two significant advances have contributed to the decline in CVD mortality rates: new therapeutic approaches and prevention measures targeted at people with or at risk for CVD.[4]

Treatments once considered advanced—including the establishment of emergency medical systems, coronary care units, and the widespread use of new diagnostic and therapeutic technologies such as echocardiography, cardiac catheterization, percutaneous coronary intervention (PCI), bypass surgery, and

implantation of pacemakers and defibrillators—have now become the standard of care. Advances in drug development have also yielded major benefits on both acute and chronic outcomes. Efforts to improve the acute management of myocardial infarction (MI) led to the application of lifesaving interventions such as beta-adrenergic blocking agents (beta blockers), PCI, thrombolytics, statins, and angiotensin-converting enzyme (ACE) inhibitors (**see Chapters 58 and 59**). The widespread use of an "old" drug, aspirin, has also reduced the risk of dying of acute or secondary coronary events. Low-cost pharmacologic treatment for hypertension (**see Chapter 47**) and the development of highly effective cholesterol-lowering drugs such as statins have also made major contributions to both primary and secondary prevention by reducing CVD deaths (**see Chapter 48**).

In concert with these advances, public health campaigns have conveyed that certain behaviors increase the risk of CVD and that lifestyle modifications can reduce risk. In this regard, smoking cessation furnishes a model of success. In the United States, for example, 57% of men smoked cigarettes in 1955; in 2012, 20.5% of men smoked. The prevalence of smoking among U.S. women has fallen from 34% in 1965 to 15.8% in 2012.[5] Campaigns beginning in the 1970s dramatically improved the detection and treatment of hypertension in the United States. This intervention likely had an immediate and profound effect on stroke rates and a subtler effect on CHD rates. Public health messages concerning saturated fat and cholesterol had a similar impact on fat consumption and cholesterol levels. Population mean cholesterol levels also declined, from 220 mg/dL in the early 1960s to 192 mg/dL by 2014,[6] with a simultaneous decrease in the prevalence of elevated low-density lipoprotein (LDL) cholesterol.

Age of Inactivity and Obesity: a Fifth Phase?

Troubling trends in certain risk behaviors and risk factors may foreshadow a new phase of epidemiologic transition, the age of **Inactivity and Obesity**[7] (**see Chapters 49 and 50**). In many parts of the industrialized world, physical activity continues to decline while total caloric intake increases at alarming rates, resulting in an epidemic of overweight and obesity. Consequently, rates of type 2 diabetes, hypertension, and lipid abnormalities associated with obesity are rising—a particularly evident trend in children.[6] These changes are occurring while measurable improvements in other risk behaviors and risk factors, such as smoking, have slowed. If these trends continue, age-adjusted CVD mortality rates, which have declined over the past several decades in HICs, could plateau, as they have for young women in the United States, or even increase in the coming years. This trend pertains particularly to age-adjusted stroke death rates. This concerning increase in obesity also applies to LMICs.[8]

Fortunately, recent trends in the first decade of this century suggest a tapering in the increases in obesity among adults, although the rates remain alarmingly high at almost 34%.[9] Furthermore, continued progress in the development and application of therapeutic advances and other secular changes appear to have offset the effects from the changes in obesity and diabetes; cholesterol levels, for example, continue to decline. Overall, in this decade, age-adjusted mortality has continued to decline at about 3% per year, from a rate of 341 per 100,000 population in 2000 to 223 per 100,000 in 2013.[10]

Different Patterns of Epidemiologic Transition

The HICs have followed different patterns of the CVD transition, which differ in both peak death rate from CHD and time of transition. Three patterns emerge that rely on data from countries with an established death certification system[11] (**Fig. 1.3**). One pattern, followed by the United States and Canada, showed a rapid rise and peak in the 1960s and 1970s, followed by a relatively rapid decline through the

end of the 2000s. The peak was 300 to 700 CHD deaths per 100,000 population, with current rates between 100 and 200 per 100,000. This pattern also occurred in the Scandinavian countries, the United Kingdom, Ireland, Australia, and New Zealand. A second pattern showed a peak in the same period but a peak CHD death rate of only 100 to 300 per 100,000. Countries such as Portugal, Spain, Italy, France, Greece, and Japan followed this pattern. Some countries did not have the same rapid rate of decline, with slower rates in central European countries (Austria, Belgium, Germany) compared to northern European countries (Finland, Sweden, Denmark, Norway), but with lower peaks of 300 to 350 per 100,000 in the 1960s and 1970s. Some countries appear to display a third pattern of continued rise (particularly many components of the former Soviet Union), and others have yet to see any significant increase, such as many countries in sub-Saharan Africa (excluding South Africa). Latin America has less longitudinal data, but limited data suggest that many of the countries follow the pattern of either Mediterranean or Southern European countries, with peaks between 50 and 300 deaths per 100,000. Whether other LMICs will follow a “classic” pattern of significant increases then rapidly declining rates (as happened in North America, Australia, and northwestern European HICs), a more gradual rise and fall (as in the southern and central European countries), or some other pattern will depend in part on cultural differences, secular trends, and responses at the country level with regard to both public health and treatment infrastructures.

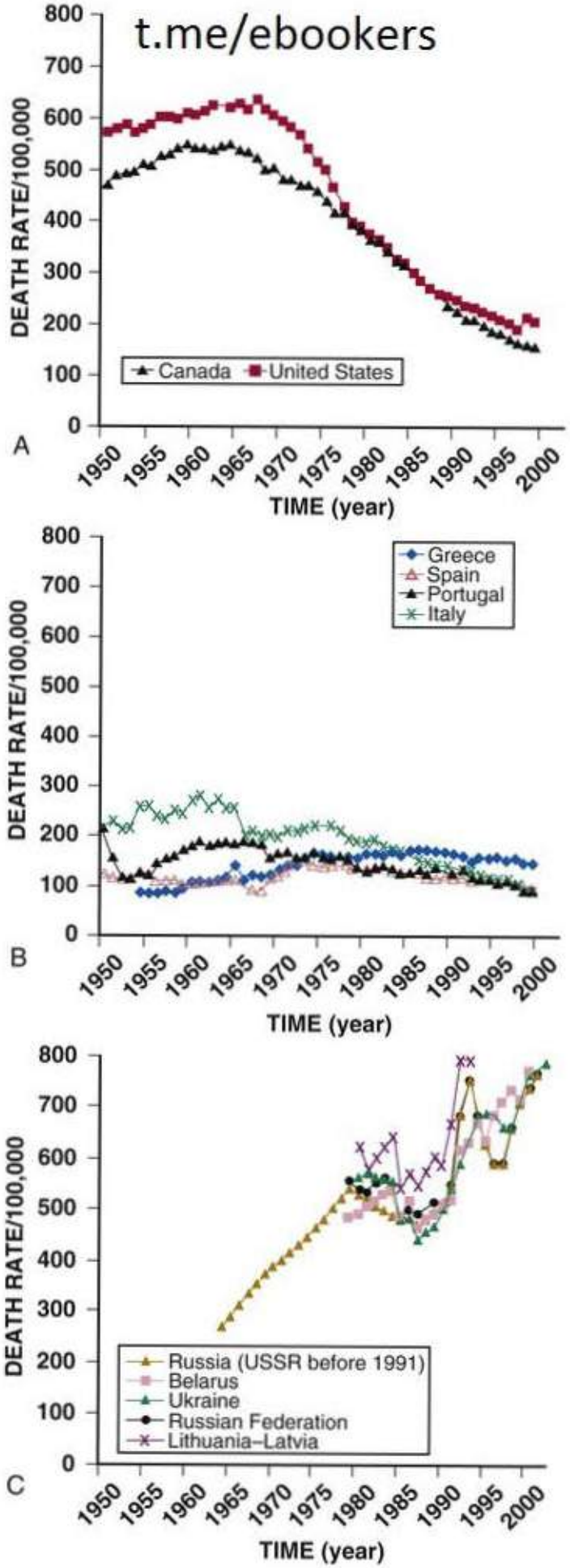

FIGURE 1.3 Differing coronary heart disease mortality patterns. **A,** Rapid rise and decline. **B,** Mild rise and decline. **C,** Continuing rapid rise. (From Mirzaei M, Truswell A, Taylor R, Leeder SR: Coronary heart disease epidemics: not all the same. Heart 2009;95(9):740-6.)

Current Variations in the Global Burden

Three phenomena impact the various metrics for disease burden. First, population growth increases the overall number of deaths caused by CVD globally. Second, a trend in general aging of the population has shifted the proportion of deaths caused by CVD in most regions as a result of better control of many communicable diseases that strike those at early ages. Third, prevention of CVD and treatment for those with CVD have both improved, which reduces age-adjusted mortality rates. We rely on data from the Global Burden of Disease (GBD) study data from 2013. Although extensive, data from GBD 2013 has limitations. The availability and reliability of data on cause of death, especially in LMICs without standardized protocols, are uncertain.

Globally, CVD deaths increased by 46% between 1990 and 2013. The increase in overall CVD deaths results from both increases in CHD and stroke-related deaths. In 2013, CHD accounted for 15% of all deaths worldwide. The second-ranking cause of death was stroke, at 12% (equally split between ischemic stroke and hemorrhagic stroke). An estimated 14.5 million people died from CHD and stroke, which together accounted for almost a quarter of all deaths worldwide in 2013.[1]

Although still substantial, deaths from communicable, neonatal, and maternal diseases are decreasing worldwide,[1,12] with a 27% decrease between 1990 and 2013. Deaths from noncommunicable diseases increased in the same period. In 2013, CHD accounted for the largest portion of global years of life lost (YLLs) and DALYs. Stroke was the third-ranking contributor to global YLLs and DALYs. On the other hand, in 1990, communicable diseases accounted for the largest portion of both YLLs and DALYs.

Despite the increase in overall CVD deaths, age-adjusted death rates decreased by 21.9% in the same period, from 374 to 292 per 100,000 population, suggesting significant delays in age of occurrence and/or improvements in case-fatality rates. Unfortunately, not all countries appear to share in the reductions. Examination of regional trends is helpful in estimating global trends in the burden of disease, particularly CVD. Because 85% of the world's population lives in LMICs, these countries largely drive global CVD rates. These estimates depend on modeling mortality rates in areas where established death certification–based vital registration systems do not cover an entire country. Even as age-adjusted rates have been falling globally, the pattern is different when assessed by income (**Fig. 1.4**) or by region (**Fig. 1.5**).

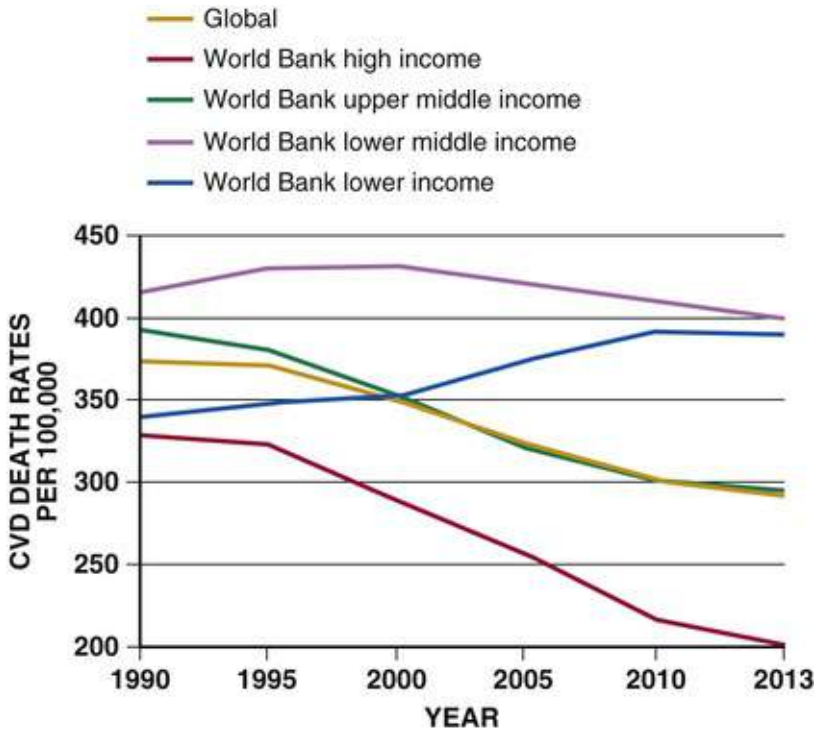

FIGURE 1.4 Cardiovascular disease death rates per 100,000 population from 1990 to 2013, by World Bank income categories. (From Global Burden of Disease Study 2013. Age-sex specific all-cause and cause-specific mortality, 1990–2013. Seattle: Institute for Health Metrics and Evaluation; 2014.)

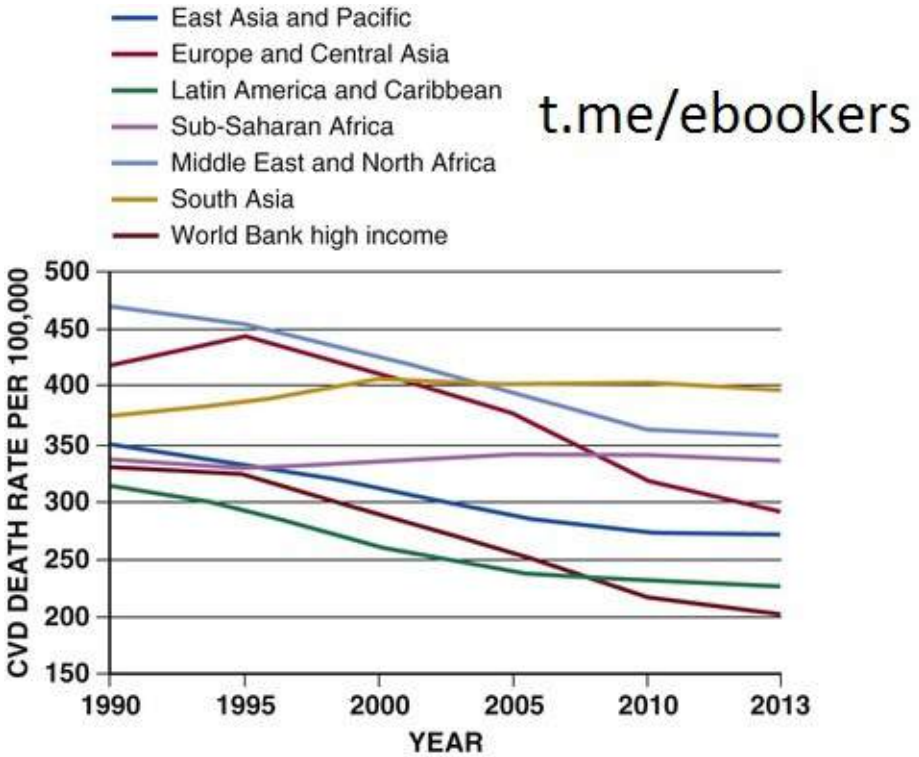

FIGURE 1.5 Cardiovascular disease death rates per 100,000 population from 1990 to 2013 in low- and middle-income countries by region, compared to World Bank high-income countries. (From Global Burden of Disease Study 2013. Age-sex specific all-cause and cause-specific mortality, 1990–2013. Seattle: Institute for Health Metrics and Evaluation; 2014.)

The magnitude of the peak of the CVD epidemic, and whether the peak has arrived at all, has a great range. Here we describe and highlight trends in the seven regions of the world as defined by the GBD project, which includes HICs as one grouping and divides the remaining LMICs into six geographic

regions with a variety of subregions. The East Asia and Pacific, Europe and Central Asia, Latin America and Caribbean, and Middle East and North Africa Regions all saw declines in age-adjusted CVD mortality from 1990 to 2013. Sub-Saharan Africa had little change in its age-adjusted CVD mortality rates. South Asia was the only region that experienced a significant increase in the age-adjusted mortality rates.

Much of the variation appears to relate to income, which is one proxy for the stages of the epidemiologic transition. Looking at age-adjusted CVD death rates by income reveals the different trends over the last two decades. In lower-income regions the death rates have increased from 340 per 100,000 in 1990 to 390 per 100,000 in 2013. Lower middle-income countries saw a small increase (416 to 432 per 100,000 deaths), followed by a decline to 400 per 100,000 population. Upper middle-income countries saw a 25% decline, from 392 per 100,000 in 1990 to 296 per 100,000. High-income countries had a nearly 37% decline, from 330 to 202 CVD deaths per 100,000.

The LMICs have a high degree of heterogeneity with respect to the phase of the epidemiologic transition. First, LMIC subregions differ by age-adjusted CVD death rates, as well as by trends over the last 20 years (**Fig. 1.6**). CVD mortality rates are increasing in most LMICs but are decreasing in HICs. Next, low- and middle-income subregions are unique, as illustrated by the different CVD disease rates by cause in each region (**Fig. 1.7**). Lastly, in the East Asia and Pacific and sub-Saharan Africa regions, stroke still exceeds CHD as a cause of CVD death. Hypertensive heart disease is the largest single contributor among remaining causes of CVD morbidity and mortality.

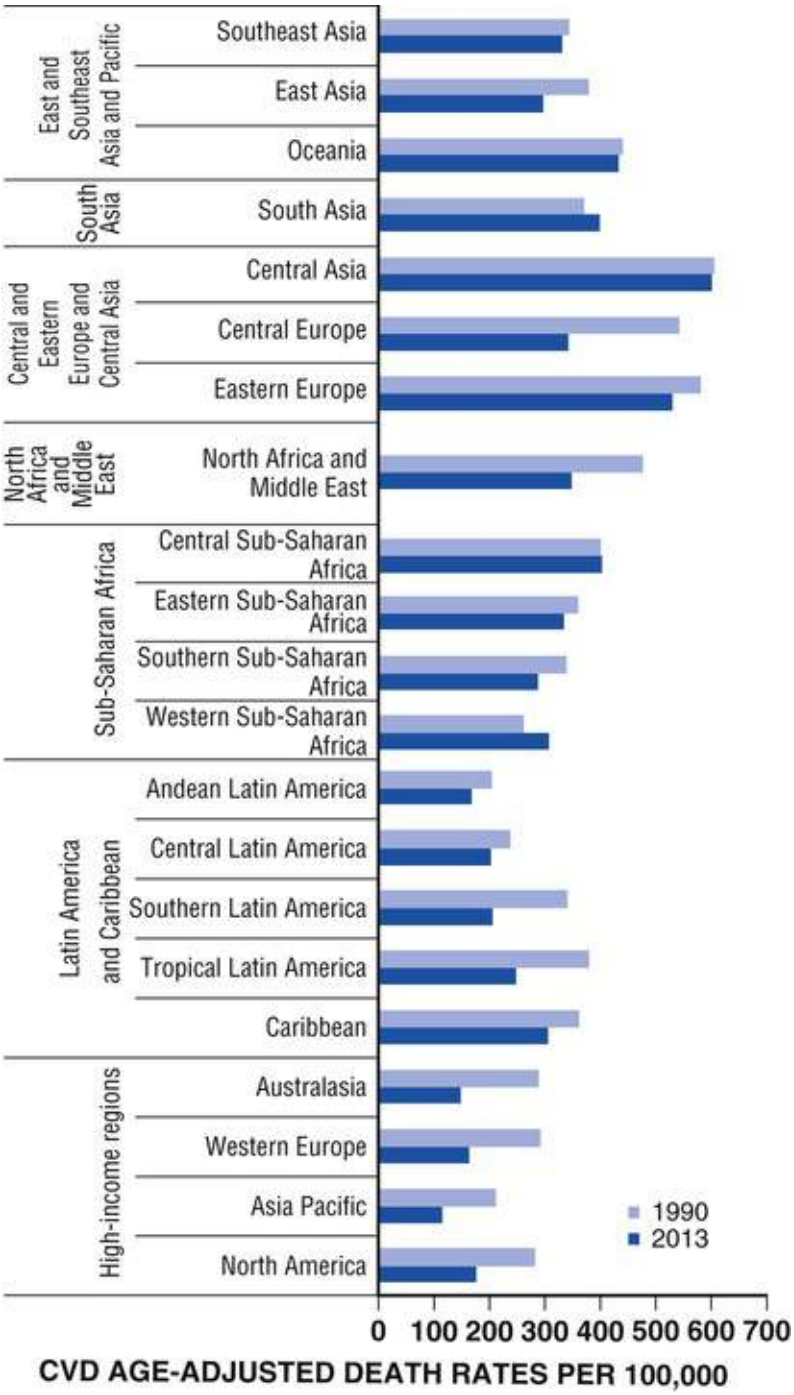

FIGURE 1.6 Age-adjusted death rates per 100,000 population for cardiovascular disease, 1990 and 2013. (From Global Burden of Disease Study 2013. Age-sex specific all-cause and cause-specific mortality, 1990–2013. Seattle: Institute for Health Metrics and Evaluation; 2014.)

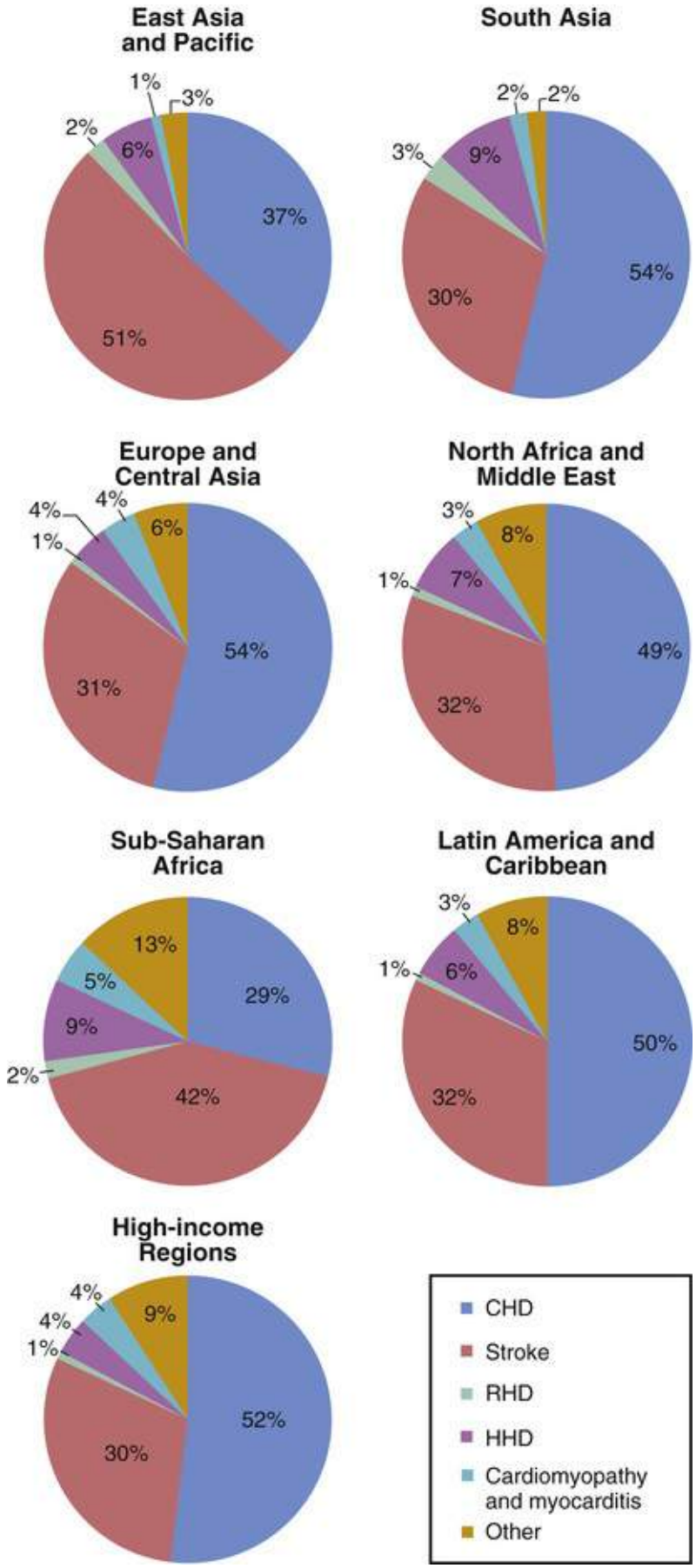

FIGURE 1.7 Cardiovascular disease death by specific cause and region. *CHD,* Coronary heart disease; *RHD,* rheumatic heart disease; *HHD,* hypertensive heart disease. (From Global Burden of Disease Study 2013. Age-sex specific all-cause and cause-specific mortality, 1990–2013. Seattle: Institute for Health Metrics and Evaluation; 2014.)

Variability in disease prevalence among various regions likely results from multiple factors. First, the countries are in various phases of the epidemiologic transition described earlier. Second, the regions may

have cultural and genetic differences that lead to varying levels of CVD risk. For example, per capita consumption of dairy products (and thus consumption of saturated fat) is much higher in India than in China, although it is rising in both countries. Third, certain additional competing pressures exist in some regions, such as war or infectious diseases (HIV/AIDS) in sub-Saharan Africa.

Because CHD affects a younger population in LMICs, the number of deaths is increased in the working population. For some LMICs, the severity of the epidemiologic transition has appeared to follow a reverse social gradient, with members of lower socioeconomic groups having the greatest rates of CHD and the highest levels of various risk factors. Unfortunately, reductions in risk factors do not follow the same trend. Compared with people in the upper and middle socioeconomic strata, those in the lowest stratum are less likely to acquire and apply information on risk factors and behavior modifications or to have access to advanced treatment. Consequently, CVD mortality rates decline later among those of lower socioeconomic status.

High-Income Countries

In 2013, CVD accounted for almost 38% of all deaths in high-income regions, and CHD caused more than half of these deaths (**see Fig. 1.7**). The movement of most HICs through the epidemiologic transition, with rising levels of risk factors and CVD death rates until the 1970s and then declines in both over the next 40 years, resembles what occurred in the United States. CHD is the dominant form, with rates that tend to be twofold to fivefold higher than stroke rates. Two notable exceptions are Portugal, where stroke rates for both men and women exceed CHD rates, and Japan, where stroke causes many more fatalities than CHD. In both these countries, however, the pattern seems to be moving toward that seen in other HICs, with more rapid declines in stroke rates than in CHD rates.

Age-adjusted mortality for CVD declined in all HICs. This age-adjusted decline results largely from preventive interventions that allow people to avert disease, treatments to prevent death during an acute manifestation of disease (particularly stroke or MI), and interventions that prolong survival once CVD is manifest. Thus the average age at death from CVD continues to climb, and as a result, CVD affects a larger retired population.

Western Europe, with an overall CVD mortality rate of 344 per 100,000 in 2013 and an age-standardized rate of 163 per 100,000, had the highest mortality rates, whereas Australasia had the lowest overall (234/100,000) rate, and Japan had the lowest age-adjusted rate (110/100,000). As mentioned, high-income regions have higher mortality rates for CHD than for stroke. The exception is the East Asia and Pacific region, where overall death rates for stroke and CHD are 132 per 100,000 and 88 per 100,000, respectively. Mortality rates and number of deaths attributable to stroke and CHD increased in this region between 1990 and 2010; stroke rates increased by approximately 18%, whereas CHD rates increased by almost 40%.[12] Japan is unique among HICs; as its communicable disease rates fell in the early 20th century, its stroke rates increased dramatically. CHD rates, however, did not rise as sharply in Japan as in other industrialized nations and have remained lower than in any other industrialized country. Overall, CVD rates have fallen 60% in Japan since the 1960s, largely because of a decrease in age-adjusted stroke rates. Japanese men and women currently have the highest life expectancy in the world: 86.4 years for women and 79.6 years for men. The difference between Japan and other industrialized countries may stem in part from genetic factors, although the traditional Japanese fish- and plant-based, low-fat diet and resultant low cholesterol levels may have also contributed. Nevertheless, as in many other countries, dietary habits in Japan are undergoing substantial changes. Since the late 1950s, cholesterol levels have progressively increased in both urban and rural populations. Although the

prevalence of CVD risk factors is increasing in the Japanese population, the incidence of coronary artery disease remains low and even declined.[13] This situation could change, however, because there seems to be a long lag phase before dietary changes manifest as CHD events.

East Asia and Pacific

Demographic and Social Indices

The East Asia and Pacific (EAP) region is the most populated low-income and middle-income region in the world, with almost 2 billion people; approximately 49% of the region is urban. The gross national income (GNI) per capita is $4243, ranging from $4420 in Thailand to $1130 in Laos. In 2004, total health expenditure was 4.8% of total gross domestic product (GDP), or $183 per capita.[14] The region is divided into three distinct subregions: Southeast Asia, East Asia, and Oceania. China is by far the most populated country, representing almost 70% of the region. Life expectancy has risen quickly across the EAP region in past decades, up to an average of 72 years. In China the increase has been dramatic: from 37 years in the mid-1950s to 73 years in 2010.[14] This increase associates with a large rural to urban migration pattern, rapid urban modernization, aging of the population, decreased birth rates, major dietary changes, increasing tobacco use, and a transition to work requiring low levels of physical activity.

Burden of Disease

CVD caused more than 5.2 million deaths in the EAP region in 2013, accounting for 38% of all deaths in the region. More than half of these deaths resulted from stroke, whereas only 31% were caused by CHD (**see Fig. 1.7**). CVD death rates differed significantly between subregions, most notably in Oceania. Age-adjusted mortality rates were highest in Oceania, at 439 per 100,000 in 2010, even though overall mortality for CVD was 205 per 100,000, suggesting that many premature deaths from CVD are occurring in Oceania.

Stroke and CHD lead as causes of death in the East Asia and Southeast Asia subregions. In Oceania, however, lower respiratory infections and diabetes account for the largest proportion of deaths. Whereas stroke and CHD rates increased in both East Asia and Southeast Asia, stroke rates decreased slightly in Oceania, from 40 to 36 per 100,000.[12] China appears to be straddling the second and third stages of a Japanese-like epidemiologic transition. Men in China age 50 to 69 have stroke death rates of 190 per 100,000, versus CHD death rates of 123 per 100,000.[1]

Central and Eastern Europe and Central Asia

Demographic and Social Indices

Of the three subregions that constitute this region—Central Asia, Central Europe, and Eastern Europe—Eastern Europe is the most populated. Russia alone accounts for more than 30% of the region's 404 million inhabitants. Sixty-five percent of the population in the region is urban, with an average life expectancy of 71 years. The average GNI per capita for the region ranges from $870 in Tajikistan to $23,610 in Slovenia. Russia has a GNI of $10,400. On average, the region spends more than 6% of total GDP on public and private health care. Health expenditure per capita ranges from $49 per capita in Tajikistan to $2154 in Hungary. Russia spends about $525 per capita, or 5.1% of its GDP.[14]

Burden of Disease

The highest rates of CVD mortality occur in this region. Overall CVD mortality rates are 793 per 100,000 in Eastern Europe and 547 per 100,000 in Central Europe. Overall rates resemble or exceed those seen in the United States in the 1960s, when CVD peaked. CHD is generally more common than stroke, which suggests that the countries that constitute Eastern Europe and Central Asia remain largely in the third phase of the epidemiologic transition. As expected in this phase, people who develop and die of CVD have a lower average age than that in HICs. In 2013, CVD accounted for almost 60% of all deaths in the region, 55% of which resulted from CHD and 33% from stroke.

A country-level analysis reveals important differences in CHD profiles within the Central and Eastern Europe and Central Asia region (**see Fig. 1.3**). Since the dissolution of the Soviet Union, CVD rates have increased surprisingly in some of these countries, with the highest rates (almost 800 per 100,000 for men) in Ukraine, Bulgaria, Belarus, and Russia.[11] By 2013, this region had the highest CVD mortality rates in the world. Of note, deaths resulting from CHD in these countries affect not only older adults; the GBD study estimates that working-age populations (15 to 69 years) have a significant CHD burden. Almost one third of all deaths in persons age 45 to 49, for example, result from CVD. For people age 60 to 64, CVD accounts for half of all deaths, 27% of which are caused by CHD.[12]

Latin America and the Caribbean

Demographic and Social Indices

The Latin America and Caribbean (LAM) region comprises Andean Latin America, Central Latin America, Southern Latin America, Tropical Latin America, and the Caribbean. The region has a total population of 589 million, 79% of which is urban.[14] Brazil, the region's most populous country, represents one third of the population, with Argentina, Colombia, Mexico, Peru, and Venezuela making up another third. The Caribbean nations, including the Dominican Republic, Jamaica, and Haiti, account for less than 10% of the population in the region. Life expectancy in the LAM region is approximately 74 years but varies greatly. In 2010, for example, Haiti and Cuba had life expectancies of 64 years and 79 years, respectively. Average GNI per capita in the region is about $8544 (purchasing power parity [PPP] of $11,587). The region spends an average of 7.7% of its GDP on health care. This level of spending translates into health care expenditures that range from $46 per capita in Haiti to $1003 per capita in Barbados.[14]

Burden of Disease

The LAM region bears a substantial CVD burden. In 2013, CVD caused 29% of all deaths in the region. As in HICs, CHD dominates among circulatory diseases (**see Fig. 1.7**). Mortality rates vary significantly by subregion. The Caribbean has the highest age-standardized mortality rates for CHD and stroke: 150 deaths per 100,000 and 110 per 100,000, respectively. As with other global trends, overall mortality increased between 1990 and 2013, but age-adjusted mortality declined for this region. Death rates also increased in Central Latin America and Andean Latin America; similar increases in mortality occurred in Tropical Latin America. Together, CHD (14%), stroke (6.9%), and hypertensive heart disease (2.1%) accounted for almost one quarter of all deaths in Central Latin America in 2010. Southern Latin America, which includes Argentina, Chile, and Uruguay, was the only subregion to have declines in both overall and age-adjusted CVD mortality rates. Overall CVD, CHD, and stroke mortality rates decreased in this subregion between 1990 and 2010, but to a lesser extent than for global changes.[12] The lower reductions in the LAM region may result from rapid lifestyle changes: unfavorable dietary changes, increased

smoking, increased obesity, and less exercise.

North Africa and the Middle East

Demographic and Social Indices

The 19 countries of the North Africa and Middle East region represent approximately 5% of the world's population (337 million people). Egypt and Iran are the two most populous countries in the region, with Egypt representing 24% of total inhabitants and Iran, 22%. Approximately 59% of the population is urban, with an average life expectancy of 72 years. The average GNI per capita for the region is $3869, ranging from $1070 in Yemen to $48,900 in Kuwait. Approximately 5.3% of the GDP, or approximately $203 per capita, is expended for health in the region. The per capita health expenditure ranges from $63 in Yemen to $1450 in the United Arab Emirates.[14]

Burden of Disease

Forty-two percent of all deaths in the North Africa and Middle East region result from CVD: 9% from CHD and 32% from stroke. The region has lower CVD mortality rates than global averages. In 2013 the overall death rate per 100,000 for CHD, stroke, and overall CVD were 89, 57, and 180, respectively. The mortality rate for CHD only declined marginally in the region since 1990, when the rates were 88, 62, and 192 deaths per 100,000 population, respectively. However, age-adjusted mortality rates for CVD declined by almost 25% across the region. In 2013, CVD accounted for 20 million DALYs lost, or 21% of all DALYs lost in the region. The DALYs lost were split differently between CHD and stroke, at 9.7 million and 5.7 million, respectively.[12]

South Asia

Demographic and Social Indices

The South Asia region (SAR), one of the world's most densely populated regions, accounts for about 24% of the world's population, with more than 1.6 billion residents. India, home to almost 75% of the region's inhabitants, is the largest country in the region. Only 31% of the region is urban, and life expectancy is approximately 65 years. Average GNI per capita for the region is $1299, ranging from $540 in Nepal to $6530 in Maldives. India's GNI per capita of $1410 sits near the regional average. Countries in the SAR spend an average of 3.9% of their total GDP, or $47 per capita, on health care. Maldives spends the most per capita at $208, and India spends $31, or 5% of its GDP. The lowest expenditures for health care are $22 per capita in Pakistan and $23 in Bangladesh.[14]

Burden of Disease

CVD accounts for 27% of all deaths in the SAR. CHD led causes of mortality in 2013—responsible for 15% of total reported fatalities, or 2 million deaths, and more than half of CVD mortality. Cerebrovascular disease accounted for 6.8% of all deaths and 30% of CVD deaths. The region loses almost 60.5 million DALYs from CVD, accounting for 10% of the total. CHD contributes 4.6% of the DALYs lost because of CVD, nearly twice as high as for stroke.[12] Mortality rates for CVD are increasing in the region.

CVD probably represents 31% of all deaths in India, the largest country in the SAR. Studies also show a higher CHD prevalence in men and in urban residents. The rise in CHD mortality contributes to the

economic burden in the Indian subcontinent. Data indicate that symptoms of CHD arise 5 to 10 years earlier in this region than in Western European and Latin American countries.[15]

Sub-Saharan Africa

Demographic and Social Indices

The GBD study divides sub-Saharan Africa into four subregions: Central Africa, East Africa, Southern Africa, and Western Africa. Approximately 875 million people live in these four regions, with Nigeria being the most populous (163 million) and Cape Verde being the least populous (500,600). Only 36% of the population in the region is urban. The average GNI per capita is $1255, ranging from $250 in Burundi to $7480 in Botswana. Overall, the region also has the lowest average life expectancy—54 years.[14] Average public and private health care expenditures for the region are 6.5% of the total GDP, or $84 per capita. The range of health care expenditures per capita for sub-Saharan Africa is similar to the GDP range for this region, from $3 in Burundi to $511 in Seychelles. Nigeria spends $23 per capita, or 4.6% of the total GDP.[14]

Burden of Disease

In Western Africa, CVD accounts for 7.5% of all deaths. The highest portion of CVD-caused deaths occurred in Southern Africa, where 13% of all deaths were caused by CVD. Mortality rates in the region are lower than global averages and are decreasing, in line with global trends. The exception is Southern Africa, where rates increased from 129 to 136 per 100,000. Communicable, neonatal, and maternal disorders still dominate causes of death in sub-Saharan Africa. Malaria and HIV/AIDS lead as causes of death, accounting for almost half of all deaths in the region.[12]

Risk Factors

Worldwide, CVD is largely driven by modifiable risk factors, such as smoking, lack of physical activity, and diets high in fat and salt (**see also Chapters 45 to 47 and 49 and 50**). Elevated levels of blood pressure (BP) and cholesterol remain the leading causes of CHD; tobacco, obesity, and physical inactivity remain important contributors as well. The GBD project estimated that the population-attributable fraction (PAF) for individual risk factors for CHD in LMICs in 2013 were as follows: high BP, 54%; high cholesterol, 32%; overweight and obesity, 18%; dietary intake, 67%; and smoking, 18%. Because factors may contribute to similar disease mechanisms, the sum exceeds 100%. Unique features regarding some CHD risk factors in LMICs are described next.

Tobacco

By many accounts, tobacco use is the most preventable cause of death in the world. More than 1.3 billion people use tobacco worldwide, with 5.8 trillion cigarettes smoked globally in 2014.[16] More than 80% of tobacco use occurs in LMICs, and if current trends continue unabated, tobacco will cause more than 1 billion deaths during the 21st century.

Tobacco use varies greatly across the world, as do deaths attributable to smoking in both sexes (**Fig. 1.8**). Although historically greatest in HICs, tobacco consumption has shifted dramatically to LMICs in recent decades; some of the highest tobacco use now occurs in the EAP region. Kiribati has the highest

prevalence of age-adjusted tobacco use in the world: 71.0% in men and 42.9% in women. Indonesia has similarly high rates (>60% prevalence in men). China is the largest consumer of tobacco in the world, with an estimated 301 million smokers in 2010 (>50% prevalence in men). Smoking rates have increased in China by 50% since 1980. Several countries in the Central and Eastern Europe regions also have alarmingly high prevalence rates, including Russia (approximately 60.0% in men and 24.3% in women), Ukraine (>50% prevalence in men), and Albania (60% prevalence in men). Latin America, the Middle East, and North Africa have high rates as well, although smoking is not as common among women in these regions as it is in the Pacific region. Countries in sub-Saharan Africa have some of the lowest prevalence rates; Niger and Ethiopia, for example, have less than 10% and 1% prevalence in men and women, respectively.

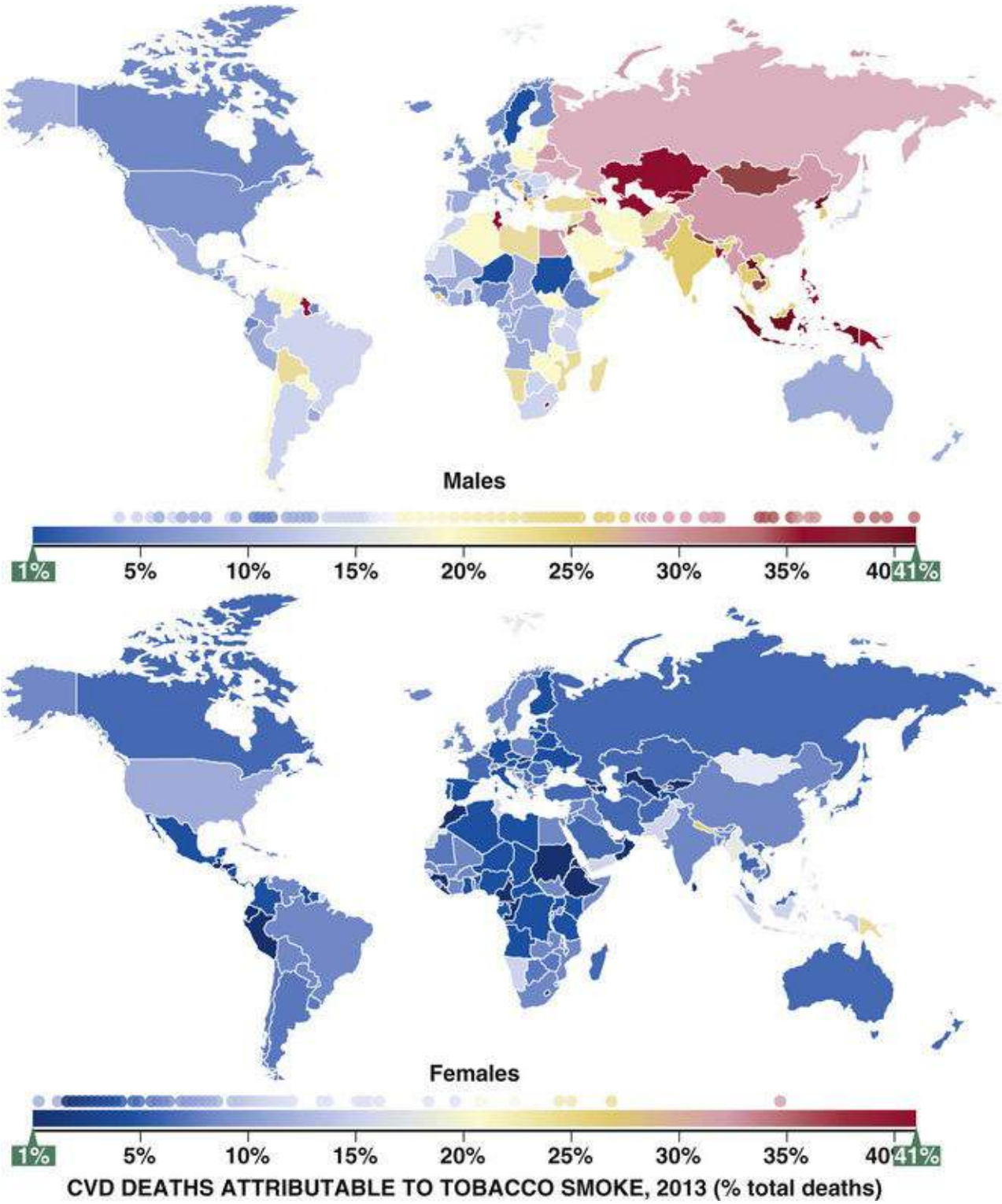

FIGURE 1.8 Cardiovascular disease mortality attributable to tobacco smoke in 2013, percentage of total deaths, males versus females. (From Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle: IHME, University of Washington; 2015. http://vizhub.healthdata.org/gbd-compare.)

Women also have a high—and increasing— smoking prevalence in several countries, including Kiribati (42.9%), Austria (45.1%), Nauru (50%), and Greece (41.4%). In general, however, considerably more men than women smoke. Exceptions to this pattern include Nauru and Greece, which have comparable tobacco use prevalence in men and in women. Where they do occur, variations by sex can be substantial. In China, for example, tobacco use prevalence is 50% in men but only 2.2% in women. Indonesia has similarly diverging trends: prevalence in men is 61.3% and only 5.1% in women. Significant variations also occur in North Africa, the Middle East, and some countries in sub-Saharan Africa. Tobacco use is generally less than 1% in women in these regions but is much higher in men.

Other forms of tobacco use increase risk for CHD. Bidis (hand-rolled cigarettes common in South Asia), kreteks (clove and tobacco cigarettes), hookah pipes (water pipes used for smoking flavored tobacco), and smokeless tobacco all link to increased CHD risk.[17] The combined use of different forms of tobacco associates with a higher risk of MI than using one type.

Secondhand smoke also contributes to CHD risk. In 2011, approximately 600,000 nonsmokers died as a consequence of exposure to secondhand smoke. A retrospective analysis of 192 countries found that the largest portion of secondhand smoke–related deaths in 2004 resulted from ischemic heart disease.[18] Smoking bans have both immediate and long-term effects in reducing admissions for acute coronary syndrome (ACS). In Ireland, implementation of a country-wide smoking ban in workplaces decreased ACS-related hospital admissions promptly by 12%, and after 2 years, such admissions decreased by an additional 13%.[19]

Hypertension

Elevated BP is an early indicator of epidemiologic transition. Rising mean population BP occurs as populations industrialize and move from rural to urban settings. Worldwide, approximately 62% of strokes and 49% of CHD cases are attributable to suboptimal (>115 mm Hg systolic) BP, a factor thought to account for more than 7 million deaths annually. The GBD project estimates that 19% of deaths and 9% of DALYs lost globally result from nonoptimal levels of BP.[20] The high rate of undetected, and therefore untreated, hypertension presents a major concern in LMICs. The high prevalence of undetected and untreated hypertension probably drives the elevated rates of hemorrhagic stroke throughout Asia.

The most recent update of the GBD study analyzed mean systolic BP between 1980 and 2008 using multiple published and unpublished health surveys and epidemiologic studies. The analysis, which applied a bayesian hierarchical model to each sex by age, country, and year, found a global decrease in mean systolic BP between 1980 and 2008 in both men and women.[21] Worldwide, the age-standardized prevalence of uncontrolled hypertension has decreased from 33% to 29% in men and from 29% to 25% in women. However, the number of people with uncontrolled hypertension (systolic BP ≥140 mm Hg) has increased; in 1980, 605 million had uncontrolled hypertension, and by 2008, the number increased to 978 million. The trend results largely from population growth and aging. Globally, mean systolic BP has decreased by 0.8 mm Hg per decade among men and by 1.0 mm Hg per decade among women. In 2008, age-standardized mean systolic BP values worldwide were 128.1 mm Hg in men and 124.4 mm Hg in women.

The proportion of CVD deaths attributable to BP by country in 2013 varied by gender (**Fig. 1.9**). The highest mean systolic BP in 2013 occurred in East and West African countries, where both men and women had systolic BP levels that were significantly higher than global averages. In Mozambique and in São Tomé and Príncipe, for example, mean systolic BP in women was 135.4 mm Hg and 136.3 mm Hg, respectively. In men, mean systolic BP was as high as 137.5 mm Hg in Mozambique and 139.4 mm Hg in Niger. Men in Eastern Europe had mean systolic BP levels comparable to those in East and West Africa. Mean systolic BP was lowest in high-income regions such as Australasia (117.4 mm Hg in Australian women) and North America (123.3 mm Hg in U.S. men).

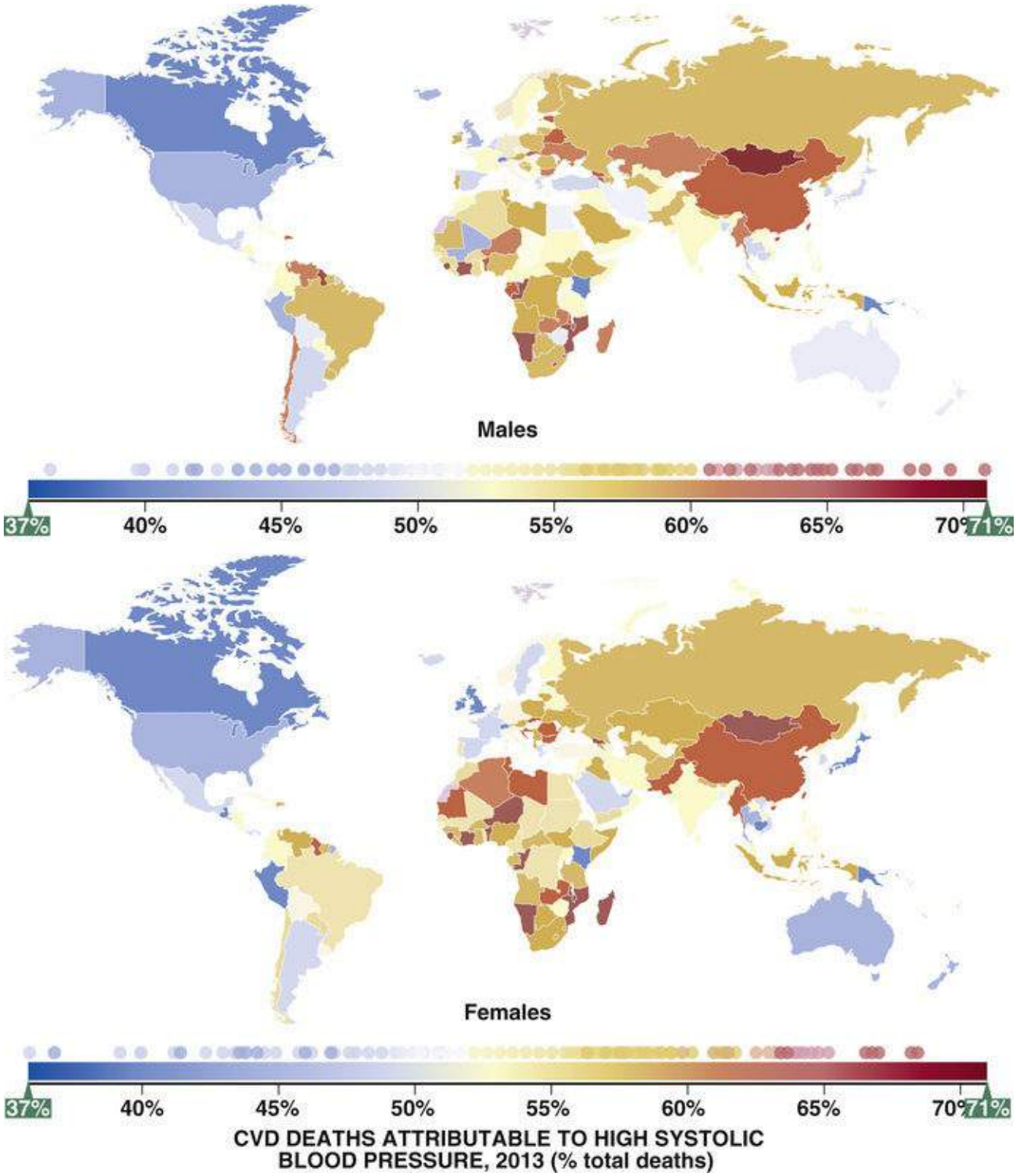

FIGURE 1.9 Cardiovascular disease mortality attributable to high systolic blood pressure in 2013, percentage of total deaths, males versus females. (From Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle: IHME, University of Washington; 2015. http://vizhub.healthdata.org/gbd-compare.)

The most significant decreases occurred in high-income regions, where mean systolic BP decreased by 2.4 mm Hg per decade in men and 3.1 mm Hg per decade in women. The decrease in men ranged from 1.7 to 2.8 mm Hg per decade, with the greatest decrease occurring in the North America subregion. The decrease in mean systolic BP in women ranged from 2.3 mm Hg per decade in North America to 3.9 mm Hg per decade in Australasia.

Mean systolic BP increased in several regions. In South Asia, systolic BP increased by 0.8 mm Hg per decade in men and 1.0 mm Hg per decade in women. Southeast Asia saw similar increases: 0.9 mm Hg per decade in men and 1.3 mm Hg per decade in women. In East Africa, mean systolic BP increased by

1.6 mm Hg per decade in men and 2.5 mm Hg per decade in women. The most significant increases in men occurred in East Africa (1.6 mm Hg per decade). In women, mean systolic BP increased the most in Oceania (2.7 mm Hg per decade).

Notable sex differences occurred in Oceania and West Africa. In Oceania, mean systolic BP in women increased by 2.7 mm Hg per decade, the largest increase in any female cohort in the world. In men in this region, however, mean systolic BP increased by only 1.2 mm Hg per decade. Data from West Africa show diverging trends in men and women: although mean systolic BP in men decreased by 0.4 mm Hg per decade, it decreased in women by 2.5 mm Hg.

Lipids

Worldwide, high cholesterol causes about 56% of ischemic heart disease and 18% of strokes, accounting for 4.4 million deaths annually. Unfortunately, most LMICs have limited data on cholesterol levels (often only total cholesterol). In HICs, mean population cholesterol levels are generally decreasing, but in LMICs, these levels vary widely. As countries move through epidemiologic transition, mean population plasma cholesterol levels typically rise. Changes accompanying urbanization clearly play a role, because urban residents tend to have higher plasma cholesterol levels than rural residents. This shift results largely from greater consumption of dietary fats, primarily from animal products and processed vegetable oils, and decreased physical activity.

Globally, mean serum total cholesterol levels have decreased.[22] The GBD study analyzed data between 1980 and 2008 using a bayesian model to estimate mean total cholesterol by age, country, and year. Age-standardized mean total cholesterol was 4.64 mmol/L (179.6 mg/dL) in men and 4.76 mmol/L in women in 2008 (184.2 mg/dL). CVD death rates attributable to cholesterol have changed between 1990 to 2013, with most of the larger LMICs (China, India, Brazil) worsening and most HICs improving (**Fig. 1.10**). In 2008 the combined regions of Australasia, North America, and Western Europe had a mean total cholesterol of 5.24 mmol/L in men and 5.23 mmol/L in women. In Greenland, mean total cholesterol was as high as 5.7 mmol/L for both sexes. Sub-Saharan Africa had the lowest levels for both sexes. Some cohorts, primarily men in Southern African countries such as Liberia, Nigeria, and Burkina Faso, had levels less than 4.0 mmol/L.

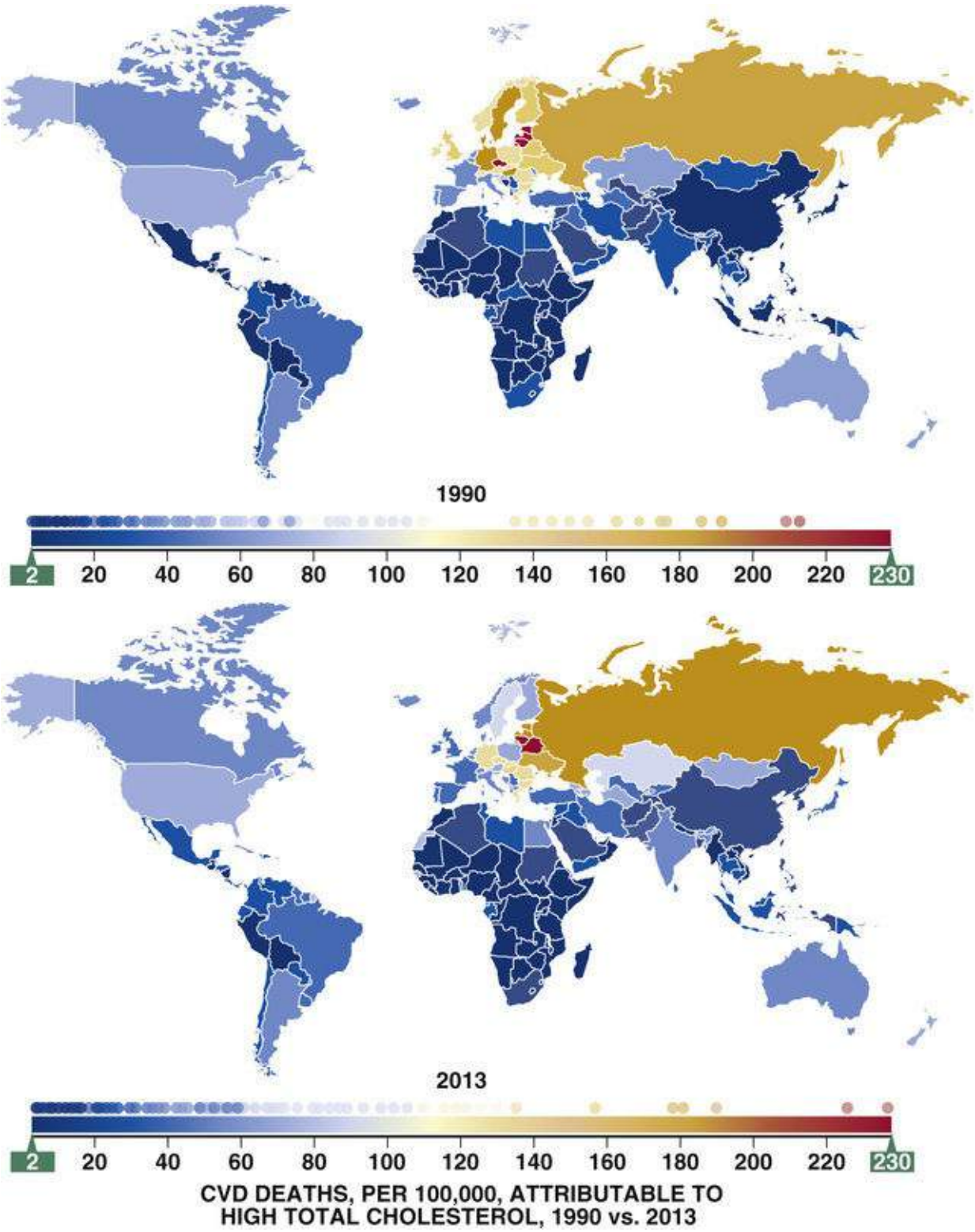

FIGURE 1.10 Cardiovascular disease mortality attributable to high total cholesterol, deaths per 100,000, 1990 versus 2013. (From Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle: IHME, University of Washington; 2015. http://vizhub.healthdata.org/gbd-compare.)

Between 1980 and 2008, mean total cholesterol levels decreased by 0.08 mmol/L per decade in men and by 0.07 mmol/L per decade in women. The most significant decreases in cholesterol levels occurred in the Central Europe, Eastern Europe, and Central Asia regions: 0.23 mmol/L per decade in men and 0.24 mmol/L per decade in women. The high-income regions of Australasia, North America, and Western Europe had similarly large decreases in cholesterol levels: 0.19 mmol/L per decade in men and 0.21 mmol/L per decade in women. Countries such as Finland and Sweden had notably faster decreases in cholesterol levels than other Western European countries.

Several exceptions to the worldwide downward trend in cholesterol levels occurred. In the EAP

region, levels increased by 0.08 mmol/L per decade in men and by 0.09 mmol/L per decade in women. The high-income Asia-Pacific subregion showed a similar trend, but the increase was more moderate (≤0.1 mmol/L per decade). South Korea demonstrated no change in cholesterol levels. Singapore data were also notable: In the 1980s, cholesterol levels decreased for both men and women, but beginning in 2000, the downward trend ended in men. In women the trend reversed, increasing from 4.7 mmol/L in 2000 to 5.3 mmol/L in 2008. Several regions, including North Africa and Middle East, sub-Saharan Africa, and South Asia, showed no notable change in cholesterol levels, in part because of a lack of available historical data. In general, women in LMIC subregions had higher total cholesterol than their counterparts in HICs.

Diabetes

Diabetes prevalence has grown rapidly worldwide in the past 30 years. As a result, death rates for CVD attributable to diabetes have increased for many LMICs, particularly in East Asia, South Asia, and Eastern Europe and Central Asia (**Fig. 1.11**). According to the GBD study, an estimated 346 million people worldwide have diabetes.[23] The more expansive International Diabetes Foundation (IDF) definition—which, in addition to fasting plasma glucose (FPG) as in the GBD study, includes oral glucose tolerance and hemoglobin A_{1c} tests—found that 366 million people had diabetes in 2011. Almost 50% of these cases were undiagnosed. By 2030 the number of people with diabetes is expected to increase to 522 million. This rise is estimated to occur at 2.7% annually, a higher growth rate than that of the total world adult population.

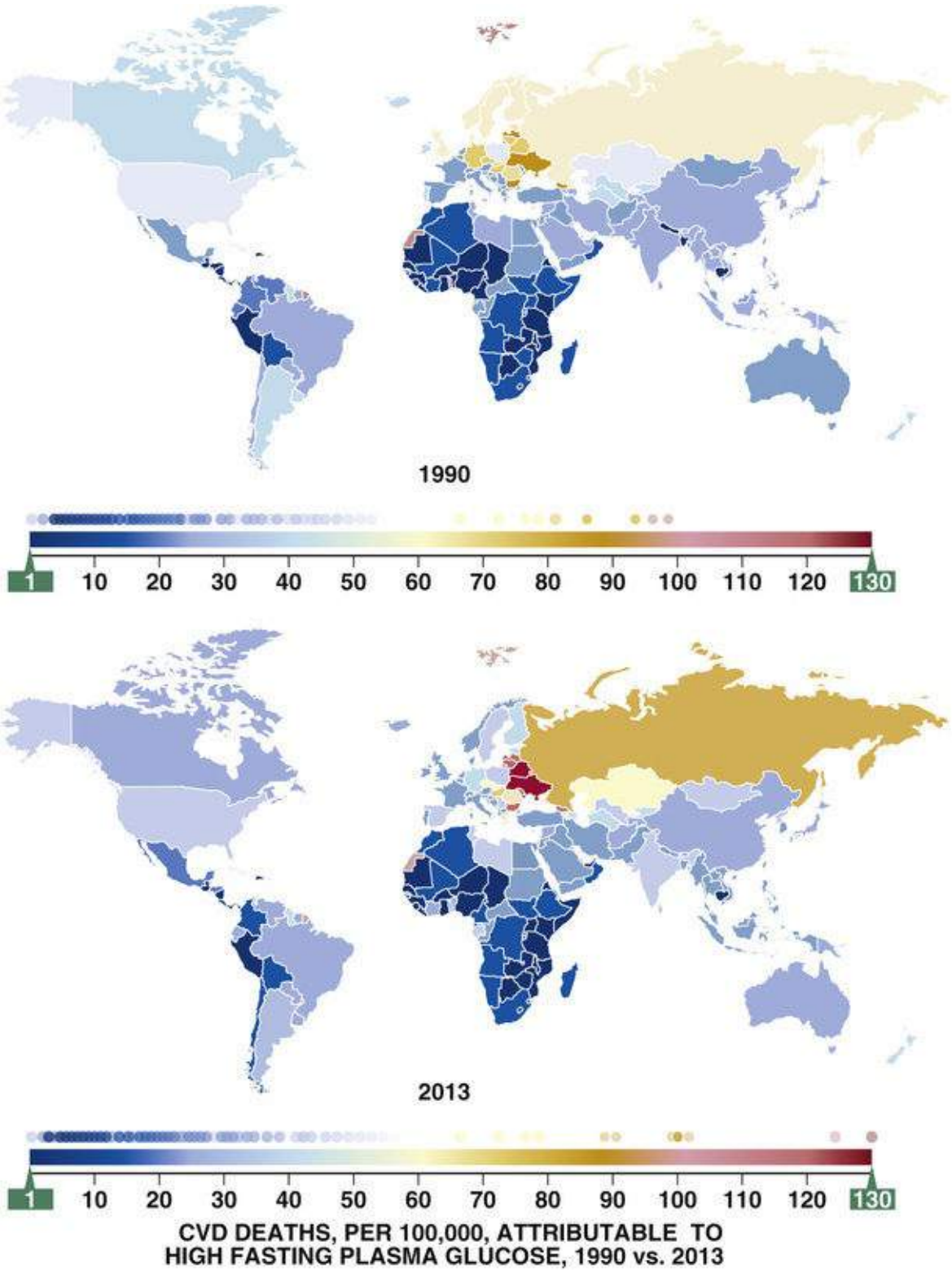

FIGURE 1.11 Cardiovascular disease mortality attributable to high fasting plasma glucose, deaths per 100,000, 1990 versus 2013. (From Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle: IHME, University of Washington; 2015. http://vizhub.healthdata.org/gbd-compare.)

Eighty percent of people with diabetes live in LMICs. The highest regional prevalence for diabetes occurs in the Middle East and North Africa, where an estimated 12.5% of the adult population (20 to 79 years of age) has diabetes. Pacific island and Middle Eastern countries have the highest prevalence, with age-adjusted prevalence ranging from 18.8% to 25.4%. Future growth will be concentrated in LMICs, especially in regions such as sub-Saharan Africa, Middle East and North Africa, and Southeast Asia.[24] In addition, a majority of cases will remain within those age 45 to 64 in LMICs, whereas those older than 65 are most affected in HICs. Rising rates of obesity, aging, and urbanization of the population are likely related to the diabetes epidemic. Almost 90% of type 2 diabetes cases are associated with obesity, and

diabetes and its related complications are the costliest consequence of obesity. Mortality from diabetes is also increasing, with approximately 4.6 million deaths in 2011.

Asian countries face a relatively larger burden of diabetes compared with the Europe and Central Asia or Latin America and Caribbean regions. India and China, for example, have the largest numbers of people with diabetes in the world: 61.3 million and 90 million, respectively. Asian populations may have a higher risk for developing diabetes even at a lower body mass index (BMI), because of a greater tendency toward visceral obesity. In addition, this population may experience both undernutrition (during the perinatal period) and rapid weight gain (during childhood), a combination that increases the risk for insulin resistance.[25]

The most recent GBD study found a global increase in mean FPG. The study analyzed multiple published and unpublished health surveys and epidemiologic studies by applying a bayesian hierarchical model for each sex by age, country, and year. Between 1980 and 2008, mean FPG increased by 0.07 mmol/L (1.26 mg/dL) per decade in men and 0.08 mmol/L (1.44 mg/dL) per decade in women. The upward trend in FPG was nearly universal.[23] In almost every region worldwide, mean FPG increased or remained unchanged; regions that displayed apparent decreases (e.g., men in the East Asia and Southeast Asia region) were not statistically different from flat trends (posterior probabilities ≤0.80).

Although some regions had unchanging mean FPG levels, other regions, including southern and tropical Latin America, Oceania, and high-income regions, experienced significant increases. The most notable region is Oceania; between 1980 and 2008, mean FPG increased by 0.22 mmol/L per decade in men and 0.32 mmol/L per decade in women. By 2008, Oceania had the highest mean FPG for both sexes (6.09 mmol/L for men, 6.09 mmol/L for women) and the highest prevalence of diabetes (15.5% in men, 15.9% in women) in the world.

In addition to Oceania, the Caribbean and North Africa and the Middle East have the highest mean FPG levels worldwide: 21% to 25% of men and 21% to 32% of women in these countries have diabetes. By contrast, men in sub-Saharan Africa and women in Asia-Pacific HICs had the lowest mean FPG in 2008: 5.27 mmol/L and 5.17 mmol/L, respectively. The only significant decrease in mean FPG occurred in women in Singapore, where levels fell by 0.21 mmol/L per decade.

Trends in mean FPG also varied by sex. In sub-Saharan Africa, for example, mean FPG increased by 0.05 mmol/L per decade in men, but by 0.13 mmol/L per decade in women. The Central Asia, North Africa, and Middle East region had similar differences in sex: mean FPG increased by 0.06 mmol/L per decade in men and by 0.16 mmol/L per decade in women.

Obesity

Obesity is increasing throughout the world and particularly in LMICs, which have steeper trajectories than in HICs. According to the latest GBD study, almost 1.46 billion adults were overweight (BMI ≥25 kg/m^2) in 2008; of these, approximately 502 million were obese (BMI ≥30 kg/m^2).[26] Explanations for this rapid rise include changes in dietary patterns, physical activity, and urbanization. Popkin and colleagues[27] report that the use of edible oils, caloric sweeteners, and animal-source foods is increasing. Annual animal food consumption tripled in China from the 1950s to 1990s. Physical activity declines as urbanization leads to increased use of motorized vehicles and a change to more sedentary occupations.

Unlike data from the 1980s, which showed that obesity affected predominantly the higher-income group in LMICs, a recent analysis shows a shift to the poor in the burden of overweight and obesity. Although higher-income groups still have the highest prevalence of overweight and obesity, rates are increasing faster in lower-income groups.[28] The poor are relatively more susceptible to obesity as a developing

country's GNP approaches the middle-income range.[28,29] Higher GDP is also associated with faster rates of increase in the prevalence of overweight and obesity in lower-income groups.[28]

Women are more affected than men, with overweight women generally outnumbering underweight women, as indicated by data from LMICs.[26] In the same survey, prevalence of overweight women exceeded 20% in more than 90% of surveyed countries. Even rural areas in half the countries surveyed exhibited such rates. Adolescents are at particular risk: 19% of U.S. adolescents are obese.[30] The number of overweight children is increasing in countries as diverse as China, Brazil, India, Mexico, and Nigeria. According to the most recent World Health Organization (WHO) estimates, 40 million children younger than 5 years are overweight. Brazil saw an alarming rise, from 4% to 14% over a two-decade period. In 1980 the worldwide obesity prevalence rate was 4.8% in men and 7.9% in women. By 2008, prevalence rates had almost doubled, to 9.8% in men and 13.8% in women.

Globally, BMI rose in both men and women. The GBD study analyzed published and unpublished health examination surveys and epidemiologic studies (linear regressions were developed to estimate mean BMI from overweight or obesity prevalence, when available) and found that between 1980 and 2008, global BMI rose by 0.4 kg/m^2 per decade in men and 0.5 kg/m^2 per decade in women.

BMI varied substantially between regions and by sex and over time. In more than two thirds of the countries, the contribution of obesity to attributable burden of CVD death rates worsened. The majority of countries that improved were from HICs, although some were from each of the LMICs that saw improvements except from South Asia (**Fig. 1.12**). In 2008 the age-standardized mean BMI in the United States was 28.5 kg/m^2 in men and 28.3 kg/m^2 in women. In contrast with the United States and other HICs with similarly high BMIs, the sub-Saharan Africa and Asia regions have some of the lowest mean BMIs. Men in Ethiopia, for example, have a mean BMI of 20.2 kg/m^2, and women in Bangladesh have a mean BMI of 20.5 kg/m^2.

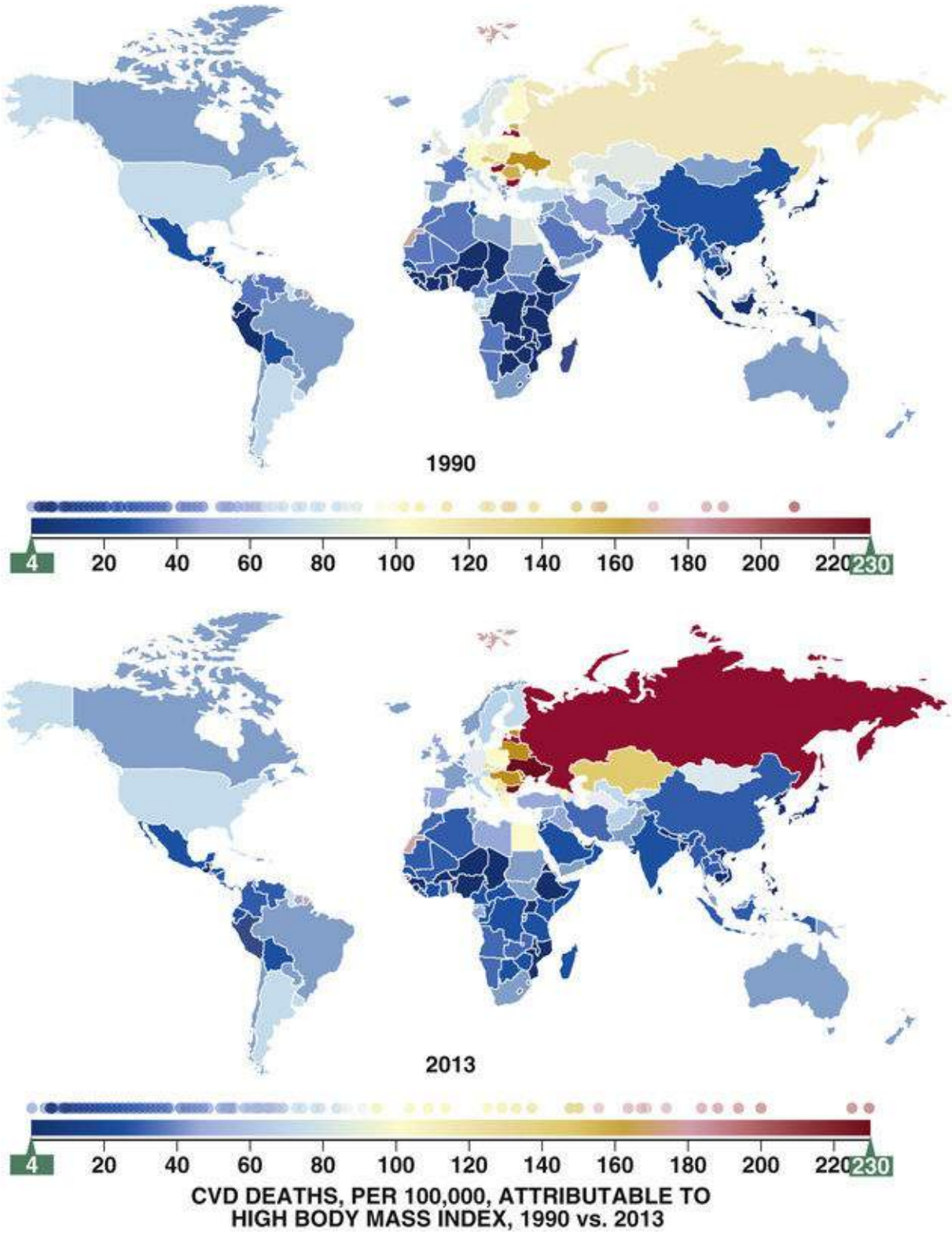

FIGURE 1.12 Cardiovascular disease mortality attributable to high body-mass index, deaths per 100,000, 1990 versus 2013. (From Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle: IHME, University of Washington; 2015. http://vizhub.healthdata.org/gbd-compare.)

The largest increase in BMI occurred in Oceania. Between 1980 and 2008, mean BMI rose by 1.3 kg/m^2 per decade in men and 1.8 kg/m^2 per decade in women. Of the islands in the Oceania region, Nauru had the largest BMI increase of more than 2 kg/m^2. BMI trends were similar in the North American high-income region (1.1 kg/m^2 per decade in men and 1.2 kg/m^2 per decade in women). In Latin America and the Caribbean, mean BMI for women increased 0.6 to 1.4 kg/m^2 per decade. By contrast, mean BMI decreased in Central African men by 0.2 kg/m^2 per decade and remained unchanged in South Asian men. In women, mean BMI remained static, with changes less than 0.2 kg/m^2 per decade in Central Asia, Central Europe, and Eastern Europe.

Although regional trends generally showed concordance between sexes, some exceptions occurred. There was no change in mean BMI in South Asian men, but mean BMI in women increased at a rate close to the global average, 0.4 kg/m^2 per decade. The most significant discrepancy in sex trends occurred in Central Africa. BMI in men in Central Africa decreased by 0.2 kg/m^2 per decade, the only significant decrease in any male population in the world. In women in Central Africa, however, mean BMI increased by 0.7 kg/m^2 per decade, a rate greater than the world average.

Diet

As humans have evolved, selective pressures have favored the ability to conserve and store fat as a defense against famine. This adaptive mechanism has become unfavorable in light of the larger portion sizes, processed foods, and sugary drinks that many people now regularly consume. Between 1970 and 2010, the average daily per capita caloric intake in the United States increased from 2076 to 2534 calories.[31] As per capita income increases, so does consumption of fats and simple carbohydrates, whereas intake of plant-based foods decreases. A key element of this dietary change is an increased intake of saturated animal fats and inexpensive hydrogenated vegetable fats, which contain atherogenic *trans* fatty acids. New evidence suggests that high intake of *trans* fats may also lead to abdominal obesity, another risk factor for CVD. (**See Chapters 49 and 50** for further discussion of diet, obesity, and CVD.)

China provides a good example of such a "nutritional transition"—rapid shifts in diet linked to socioeconomic changes. The China Nationwide Health Survey found that between 1982 and 2002, calories from fat increased from 25% to 35% in urban areas and from 14% to 28% in rural areas, as calories from carbohydrates fell from 70% to 47%. As recently as 1980, the average BMI for Chinese adults was about 20 kg/m^2, and less than 1% had a BMI of 30 kg/m^2 or greater. From 1992 to 2002, the number of overweight adults increased by 41%, and the number of obese adults increased by 97%.

China and other countries in transition have the opportunity to spare their populations from the high levels of *trans* fats that North Americans and Europeans have consumed over the past 50 years by avoiding government policies that can contribute to the CVD burden. An estimated 30,000 CVD deaths could be averted over 10 years in the United Kingdom with elimination of *trans* fats, reductions in saturated-fat consumption, reduced salt intake, and increased fruit and vegetable consumption.[32] Another facet of the nutritional transition for countries adopting a Western diet is the introduction of high-sugar beverages associated with weight gain and increased risk for type 2 diabetes. A meta-analysis suggests up to a 16% relative risk increase in CHD per unit of sugar-sweetened beverages consumed daily.[33]

Physical Inactivity

In HICs the widespread prevalence of physical inactivity produces a high population-attributable risk of cardiovascular consequences. Physical inactivity is also increasing in low- and middle-income regions of the world, witnessing a shift from physically demanding, agriculture-based work to largely sedentary, service industry–based and office-based work. A switch to mechanized transportation accompanies this work shift.

Current guidelines call for moderate exercise for at least 30 minutes 5 or more days a week, or vigorous exercise for 20 minutes 3 days a week. Gallup's November 2011 Health and Healthcare poll found that 51.6% of U.S. adults say they exercise three or more times a week. These numbers have remained essentially unchanged since 2008. Physical inactivity levels are similarly high in other regions of the world. In the Middle East and North Africa region, for example, physical inactivity is fairly

common, with a prevalence ranging from 32.9% in Syria to 56.7% in Iraq. In urban China the proportion of adults who participate in moderate- and high-level activity has decreased significantly, whereas participation in low-level activity has increased. The study of about 500,000 adults in China found that a lack of physical activity and an increase in sedentary leisure time were independently associated with greater adiposity.[34]

The Cuban economic crisis that began in 1989, when Cuba lost the Soviet Union as a trading partner, and the resultant hardship for its people improved their overall cardiovascular health. The crisis worsened for the next 5 years, and complete recovery did not take place until 2000. Sustained food rationing led to a reduction in per capita food intake, and the lack of public transportation resulting from fuel shortages meant that more people were walking and riding bikes. During the crisis period, the proportion of physically active adults increased from 30% to 67%, and a 1.5-unit shift in BMI distribution was observed; CHD declined up to 1995. However, a rebound in population weight mirrored a reduction in physical activity and resulted in the cessation of CHD mortality decline from 2000 to 2010.[35]

Aging Populations

Average life expectancy will reach 83 years in developed regions and 75 years in less developed regions by 2025, according to WHO.[36] This increase is associated with a decline in overall infant mortality and fertility rates. Although older adults will constitute a greater percentage of the population in HICs—more than 65 million Americans will be older than 65 by 2025—low- and middle-income regions will see the population over 60 more than double from 1995 to 2025.

The time of transition to an older population is sharply shorter in LMICs. For example, whereas it took the United States and Canada more than 65 years to double their over-65 population, LMICs will do so every 25 years for the next 50 years. Such acute changes in the population structure leave less time to expand an already overburdened health infrastructure to address the chronic diseases of older adults, which prominently include cardiovascular conditions (**see Chapter 88**).

Fetal Influences

Adverse influences such as undernutrition during fetal life (fetal “programming”) and early postnatal life appear to affect the prevalence of adult CVD and contribute to its risk factors. Barker,[37] in his “developmental origins of adult disease” hypothesis, suggested that adverse influences early in development, particularly during intrauterine life, could result in permanent changes in the physiology and metabolism of the pancreas, kidney, muscle, and vascular endothelium, resulting in adult insulin resistance, metabolic syndrome, hypertension, and CHD. Recent evidence indicates that the first 2 years of postnatal life are a sensitive or “critical” period of development, and any stimulus or insult during this period appears to have lasting or lifelong significance for adult-onset CVD.[38] Several epidemiologic studies have demonstrated these associations, and two randomized trials from Guatemala and India on nutritional supplementation for pregnant mothers demonstrated favorable cardiovascular risk profiles among the children of mothers who received such supplementation.[39,40]

The mechanisms of increased risk appear to be both biologic (alterations in fetal tissues and postnatal epigenetic modifications) and social (cognitive impairment, low productivity, and higher prevalence of cardiovascular risk factors among those with lower birth weight and early-life adverse influences), and childhood obesity and sedentary habits aggravate this risk. Thus the prevention of adverse fetal exposures

and subsequent long-term consequences require a holistic approach. An understanding of prenatal risk factors and their early childhood modifiers will provide an opportunity for interventions before the development of risk factors. Remedies include improved maternal nutrition during pregnancy and lactation, emphasis on breastfeeding through early infancy, and ensuring adequate balanced nutrition to infants. On the basis of current understanding, policymakers and health care professionals should design and develop preventive strategies that effectively influence these very early determinants of CVD development.[41]

Environmental Exposures

Environmental pollution, especially both indoor and outdoor air pollution, has emerged as a major cause of death and disease burden[42] (**see Chapter 52**). Exposure to particulate-matter (PM) air pollution,[43] heavy metals (e.g., cadmium, arsenic, lead, mercury),[44] and polyaromatic hydrocarbons[45] is associated with increased risk of mortality and morbidity from CVD. The GBD comparative risk assessments of 2010 and 2013 have shown that more than 30% of all DALYs from ischemic heart disease and about 40% of DALYs from strokes result from environmental risk factors,[46,47] approximately the same as those attributable to tobacco smoke. Of these exposures, air pollution (household and ambient) is the most prominent risk factor, contributing to approximately 7 million premature deaths annually, with a majority occurring in LMICs such as India and China.

In many developing countries, populations experience a continuum of exposure to ambient air pollution (from vehicles, industry, etc.) and household air pollution (from cooking, heating, and lighting), resulting in significant contributions to the health burden, as in India, where it is the second most important risk factor for poor health. More than half of all deaths associated with air pollution exposure are through cardiovascular and cerebrovascular pathways, involving ischemic heart disease,[48] heart failure,[49] stroke,[50] and hypertension.[51] Three pathways, listed below in order of the strength of the evidence base, may contribute to the mechanisms that link PM exposure to CVD and cerebrovascular disease:

1. Particle transport into the lungs provoking inflammatory responses and promoting systemic oxidative stress. This leads to increased risk of thrombosis, endothelial dysfunction, atherosclerosis progression, and dyslipidemia.
2. Particle transport into the lungs promoting autonomous nervous system imbalances. This leads to pathologic alterations in hypertension, endothelial dysfunction, vasoconstriction, and atherosclerosis.
3. Absorption of particles through the lungs into the bloodstream causing tissue-level interactions. This results in platelet aggregation, vasoconstriction, and endothelial dysfunction.

The epidemiologic evidence base suggests that exposure to arsenic,[52] cadmium,[53] and lead[54] follows the common physiologic pathways observed with air pollution. In addition, the mechanistic evidence from animal and human studies indicates that arsenic exposure is associated with carotid intima media thickness, a marker for atherosclerosis, with links to diabetes also observed.[55]

Regardless of the primary route and the pathophysiology involved, short- or long-term exposure to various environmental pollutants is associated with an increased risk of ischemic heart disease, stroke, heart failure, and preclinical conditions such as endothelial dysfunction, thrombosis, atherosclerosis, and hypertension. Although epidemiologic evidence has been well documented for single pollutants, the synergistic impacts are understudied. From a physician's perspective, informing patients on how to avoid

exposure and protect themselves should be part of primary prevention.

Economic Burden

Despite some overlap, at least three approaches can measure the economic burden associated with CHD. The first source of financial burden reflects the costs incurred in the health care system itself and reported in "cost-of-illness" studies. In these studies, the cost of CHD includes the costs of hospitalizations for angina and MI, as well as heart failure attributable to CHD. The cost of specific treatments or procedures related to CVD (e.g., thrombolytics, catheterization, PCI) and the cost associated with outpatient management and secondary prevention (e.g., office visits, pharmaceutical costs) are also included. In addition, nursing home, rehabilitation (inpatient and outpatient), and home nursing costs require consideration.

The second economic assessment is derived from microeconomic studies that assess the household impact of catastrophic health events such as MI. These studies look at out-of-pocket expenses incurred by the individual patient or family that might have other, downstream economic impacts, such as loss of savings or sale of property to cover medical costs. Many LMICs lack an extensive insurance scheme, and health care costs are almost entirely borne by individuals; 150 million people experience financial catastrophe each year because of medical expenditures.[56] Furthermore, the limited data do not confirm the causality between chronic disease and individual or household poverty. However, expenditures for CHD or its addictive risk factors (e.g., tobacco) could lead to substantial and even impoverishing costs.

The third method of determining financial burden from CHD is based on a macroeconomic analysis. These assessments examine lost worker productivity, or the economic growth lost as a result of adults with CHD or their caregivers being partially or completely out of the workforce because of illness. The data for the impact of chronic diseases on labor supply and productivity are more robust. An additional cost usually not accounted for is the intangible loss of welfare associated with pain, disability, or suffering by the affected person. These indirect costs are often addressed by "willingness-to-pay" analyses, asking generally how much would an individual pay to avert suffering or dying prematurely from CHD. The gains are not merely improved work performance, but also enjoying activities beyond productivity. U.S. studies suggest that as much as 1% to 3% of GDP is attributable to the cost of care for CVD, with almost half of that related to CHD.[57] In China, annual direct costs of CVD are estimated at more than $40 billion (U.S.), or about 4% of GNI. In South Africa, 2% to 3% of GNI is devoted to the direct treatment of CVD, which equates to about 25% of South African health care expenditures. The indirect costs are estimated at more than double that of the direct costs. Although few cost-of-illness studies for CHD have been performed in other regions, such studies have reported on the financial burdens attributed to risk factors for CHD. For example, the direct costs caused by diabetes in the Latin American and Caribbean countries were estimated at $10 billion (U.S.). Indirect costs were estimated at more than $50 billion in 2000. The limited studies available suggest that obesity-related diseases account for 2% to 8% of all health care expenditures in HICs. In India and China the costs for obesity are about 1.1% and 2.1% of GDP, respectively.

Recently, the costs attributable to nonoptimal BP levels as mediated through stroke and MI were evaluated for all regions of the world. Globally, the health care costs of elevated BP were estimated at $370 billion (U.S.) for 2001; this amount represented approximately 10% of all global health care expenditures for that year. Regional variations do exist, with hypertension being responsible for up to 25% of health care costs in the Eastern Europe region (**Fig. 1.13**). Over a 10-year period, BP-related

health care costs could equal $1 trillion (U.S.) globally, and indirect health care costs attributed to BP could be nearly four times as much.[58,59]

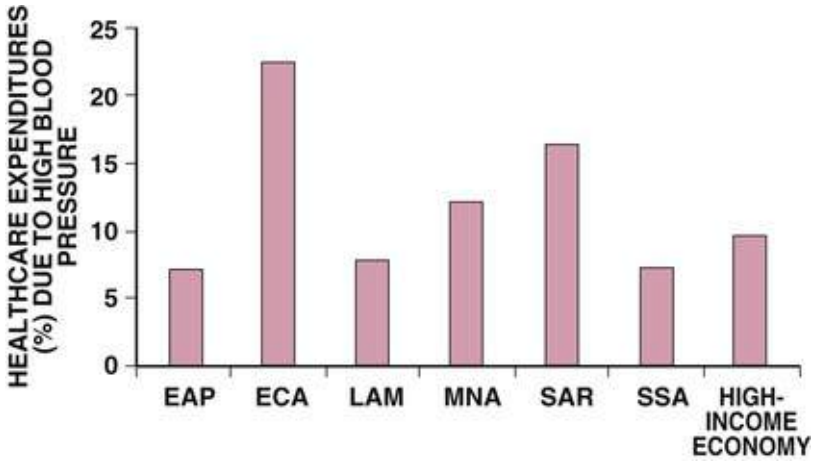

FIGURE 1.13 Percentage of health care expenditures attributed to high blood pressure. *EAP,* East Asia and Pacific; *ECA,* Europe and Central Asia; *LAM,* Latin America and the Caribbean; *MNA,* Middle East and North Africa; *SAR,* South Asia region; *SSA*, sub-Saharan Africa.

The high proportion of CVD burden that occurs earlier among adults of working age augments its macroeconomic impact in LMICs. Under current projections, in LMICs such as South Africa, CVD will strike 40% of adults between ages 35 and 64, compared with 10% in the United States. India and China will have death rates in the same age-group that are two and three times that for most HICs. In view of the large populations in these two rapidly growing economies, this trend could have profound economic effects over the next 25 years, as workers in their prime succumb to CVD.

Cost-Effective Solutions

The large reductions in age-adjusted CVD mortality rates that have occurred in HICs result from three complementary types of interventions. One strategy targets those with acute or established CVD. A second entails risk assessment and targeting persons at high risk because of multiple risk factors for intervention before their first CVD event. The third strategy uses mass education or policy interventions directed at the entire population to reduce the overall level of risk factors. This section reviews various cost-effective interventions (**see Chapter 45**). Much work remains undone in LMICs to determine the best strategies given limited resources, but if implemented, these interventions could help significantly in reducing the burden. **Table 1.2** lists the cost-effectiveness ratios for many high-yield interventions that could be or have been adopted in low- and middle-income regions.

TABLE 1.2

Cost-Effectiveness for a Selection of Coronary Heart Disease (CHD) Interventions in Developing Regions

INTERVENTION	COST-EFFECTIVENESS RATIO ($US/DALY)*
Drug Treatments	
Acute Myocardial Infarction	
ASA, BB (global)	11-22
ASA, BB, SK (global)	634-734
ASA, BB, t-PA (global)	15,860-18,893
Prehospital thrombolysis (Brazil)	457/LY
Secondary Treatment (CHD)	
Multidrug regimen (ASA, BB, ACEI, statin) (global)	1686-2026
Coronary artery bypass graft (global)	24,040-72,345
Primary Prevention	
Cholesterol lowering (Brazil)	441/LY
Multidrug regimen (AR > 20%-25%) (global)	771-1195
Policy Interventions	
Tobacco	
Price increase of 33%	2-85
Nonpolicy Interventions	33-1432
Salt Reduction‡	
2-8 mm Hg reduction	Cost-saving: 250
Fat-Related Interventions§	
Reduced saturated-fat intake	Cost-saving: 2900
Trans fat replacement: 7% reduction in CHD	50-1500
Devices	
Cardioverter-defibrillators: primary prevention (Brazil)	50,345 (US$PPP/QALY)

*Across six World Bank regions; *DALY,* disability-adjusted life-year; *PPP,* purchasing power parity; *QALY,* quality-adjusted life-year.

‡Range includes different estimates of cost of interventions, as well as blood pressure reduction (<$0.50-$1.00).

§Range includes estimates of cost of interventions (<$0.50-$6.00).

ASA, Acetylsalicylic acid (aspirin); *BB,* beta blocker; *SK,* streptokinase; *ACEI,* angiotensin-converting enzyme inhibitor; *t-PA,* tissue plasminogen activator; *AR,* absolute risk.

Data from Gaziano TA. Cardiovascular disease in the developing world and its cost-effective management. Circulation 2005;112:3547; and Gaziano TA, Galea G, Reddy KS. Chronic diseases 2—scaling up interventions for chronic disease prevention: the evidence. Lancet 2007;370:1939.

Established Cardiovascular Disease Management

People at highest risk are those having an MI or stroke; as many as half die before they ever receive medical attention. For those who do reach a hospital, many cost-effective strategies exist.[60] Four incremental strategies were evaluated for the treatment of MI and compared with a strategy of "no treatment" as a control for the six World Bank low- and middle-income regions. The four strategies compared were (1) aspirin; (2) aspirin and atenolol (beta blocker); (3) aspirin, atenolol, and streptokinase; and (4) aspirin, atenolol, and tissue plasminogen activator (t-PA). The incremental cost per quality-adjusted life-year (QALY) gained for the aspirin and beta-blocker interventions was less than $25 for all six regions. Costs per QALY gained for streptokinase were between $630 and $730 across the regions. Incremental cost-effectiveness ratios for t-PA were about $16,000/QALY gained, compared with streptokinase. Minor variations occurred between regions as a result of small differences in follow-up care based on regional costs.

Secondary prevention strategies have equal cost-effectiveness in LMICs. A combination of aspirin, an ACE inhibitor, a beta blocker, and a statin for secondary prevention can lead to acceptable cost-effectiveness ratios in all low- and middle-income regions. Use of currently available generic agents,

even in the absence of the "polypill," could be highly cost-effective, on the order of $300 to $400 per person per QALY gained.

Risk Assessment

Primary prevention is paramount for the large number of people who have high risk for acquiring CVD. In view of limited resources, finding low-cost prevention strategies is a top priority. Using prediction rules or risk scores to identify persons at higher risk to target specific behavioral or drug interventions is a well-established primary prevention strategy and has proved to be cost-effective.[61,62] Most such scoring systems include age, sex, hypertension, smoking status, diabetes mellitus, and lipid values; some also include family history.[63] Other markers of risk, such as C-reactive protein, have been used that improve reclassification and discrimination.[64] Coronary artery calcium scoring may add the most in terms of changes in C-statistic (discrimination) or the net reclassification improvement (NRI) in intermediate-risk populations, but it has limitations as a screening strategy[65] (**see Chapter 45**).

More attention is now focused on developing risk scores that would be easier to use in resource-poor countries, without loss of predictive discrimination. In LMICs with limited testing facilities, a prediction rule that requires a laboratory test may be too expensive for widespread screening, or the cost may preclude its use altogether. In response to this concern, WHO recently released risk-prediction charts for the different regions of the world, with and without cholesterol data. A study based on the U.S. National Health and Nutrition Examination Survey (NHANES) follow-up cohort demonstrated that a non–laboratory-based risk tool that uses information obtained in a single encounter (age, systolic BP, BMI, diabetes status, and smoking status) can predict CVD outcomes as effectively as one that requires laboratory testing, with C-statistics of 0.79 for men and 0.83 for women that were no different from those obtained using the Framingham-based risk tool, and has been shown to correlate with other scores in other countries.[66] Furthermore, the results of "goodness-of-fit" tests suggest that the non–laboratory-based model is well calibrated across a wide range of absolute risk levels and without changes in risk classification. The ankle-brachial index (ABI) also appears to add to risk discrimination and improve the NRI as an alternative noninvasive tool.[65] Furthermore, community health workers can use the simple risk score effectively, decreasing the cost of screening significantly.[67,68]

Policy and Community Interventions

Education and public policy interventions that have reduced smoking rates, lowered mean BP levels, and improved lipid profiles contribute to reduction in CHD rates.[4] Education and policy efforts directed at tobacco consumption have contributed substantially to the reductions in CVD. In addition, salt and cholesterol reduction has been evaluated as a cost-effective strategy to reduce stroke and MI in HICs.[69] Community interventions[70] have reduced levels of multiple risk factors and, in some cases, CHD mortality.

Tobacco Use

Tobacco control can be conceptualized in terms of strategies that reduce the supply of or the demand for tobacco. Most public health and clinical strategies to date focus on reducing demand through economic disincentives (taxes), health promotion (media and packaging efforts), restricted access (to advertising and tobacco), or clinical assistance for cessation. The WHO effort to catalyze the creation of a global treaty against tobacco use was a key milestone. In May 2003 the WHO World Health Assembly

unanimously adopted the WHO Framework Convention in Tobacco Control (FCTC), the first global tobacco treaty. The FCTC had been ratified by 168 countries as of 2016, making it one of the most widely embraced treaties in the United Nations. The FCTC has spurred efforts for tobacco control across the globe by providing both rich and poor nations with a common framework of evidence-based legislation and implementation strategies known to reduce tobacco use.

Jha and colleagues[71] presented a landmark analysis of the cost-effectiveness of tobacco control in 2006, and the findings have led it to be a major focus on noncommunicable diseases.[72] With tax, treatment, and nonprice interventions, a 33% price increase would result in a reduction of 19.7 to 56.8 million (5.4% to 15.9% of total) deaths in smokers in the developing world who were alive in 2000.[72] Calculations show that nicotine replacement therapy (NRT) could reduce the number of deaths by 2.9 to 14.3 million (0.8% to 4.0% of total) in the 2000 cohort. A range of nonprice interventions (e.g., advertising bans, health warnings, smoke-free laws) would reduce deaths by 5.7 to 28.6 million (1.6% to 7.9% of total) in that cohort. These reductions would translate into cost-effectiveness values in the developing world of $3 to $42/QALY saved for tax increases (not including tax revenue), $55 to $761/QALY for NRT, and $54 to $674/QALY for nonprice measures.[72]

Critically important for patients who have had a coronary event, smoking cessation saves lives at a greater rate than any individual medical treatment. Quitting smoking in the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS) 5 trial was associated with a 40% relative risk reduction for MI. Further studies suggest that varenicline leads to increased smoking cessation rates,[73] although it is unclear whether it is better than traditional NRTs.[74]

Salt and Lipid Reductions

The analyses on salt reduction achieved as a result of public education are quite favorable.[75] The intervention ranges from being cost-saving to $200/DALY averted. A campaign for reducing saturated fat and replacing it with polyunsaturated fat was also likely cost-effective. In the base case, a 3% decline in cholesterol and a $6 per capita education cost were assumed. Findings included a cost as low as $1800/DALY averted in the South Asia region and up to $4000/DALY averted in the Middle East and North Africa region. If the cost for the education plan were halved, however, the ratio would be approximately $900/DALY, which would be cost-saving if the reduction could be achieved for under $0.50 per capita—a possibility in areas with less expensive access to media. Simple measures such as changing prescription length for medications such as statins[76] or training community health workers to do screening for CVD can be cost-effective.[67,77]

Community Interventions

In the 1970s and 1980s, a series of population-based community intervention studies were conducted to reduce risk factors for chronic disease.[78] These studies focused on changes in health behaviors or risk factors such as tobacco use, body weight, cholesterol, and BP, as well as a reduction in CVD morbidity and mortality. In general, they included a combination of community-wide actions and those focused on persons identified as being at high risk for CVD-related health problems.

One of the earliest and most often-cited community interventions is the North Karelia project in Finland, begun in 1972. The community-based interventions included health education, screening, a hypertension control program, and treatment. Over the first 5 years of the study, reductions in risk factors occurred, along with a decline in CHD mortality by 2.9% per year, versus a 1% per year decline in the rest of Finland. During the next 10 years, declines were greater in the rest of Finland. Over a follow-up of

25 years, a large decline in CHD occurred in both the North Karelia region (73%) and the rest of Finland (63%). Although the overall difference in the decline in CHD deaths was not significantly greater in the study area of North Karelia, the reduction in tobacco-related cancers in men was significant. A similar study in the Palo Alto, California, area showed reductions in risk factors—cholesterol (2%), BP (4%), and smoking rates (13%)—compared with sites without the intervention, but no impact on disease endpoints.

Later, community interventions in HICs had mixed results, with some showing improvements in risk factors beyond the secular decline occurring throughout most HICs and others exhibiting no additional decline. A systematic review showed a net reduction in 10-year CVD risk of 0.65%.

Several community intervention studies have been conducted in LMICs, including China, Mauritius, and South Africa. The Tianjin project showed reductions in hypertension and obesity. The Mauritius project, among other interventions, resulted in a government-led program that changed the prime cooking oil from a predominantly saturated-fat palm oil to a soybean oil high in unsaturated fatty acids. Overall total cholesterol levels fell 14% during the 5-year study period (1987 to 1992). Changes in other risk factors were mixed, with declines in BP and smoking rates and increases in obesity and diabetes. The Coronary Risk Factor Study in South Africa compared a control community with two communities receiving interventions at two different levels of intensity. The interventions included mass-media messages, group-sponsored educational sessions, and BP screening and follow-up with the health sector when appropriate. Both high-intensity and low-intensity interventions resulted in improvements in BP, smoking rates, and high-density lipoprotein (HDL)–to–total cholesterol ratio over the control community, but with little difference between the two intervention communities.

Another significant reduction in CHD came not through a concerted community intervention but through changes in fiscal policy. In Poland, reductions in subsidies for animal products such as butter and lard led to a switch from saturated to polyunsaturated fats, mainly rapeseed-based and soybean-based oils. The decrease in CHD mortality by more than 25% between 1991 and 2002 could not be explained by increased fruit consumption or decline in smoking rates.

Success stories such as in Poland and Mauritius are rare, however, suggesting the challenges to achieving meaningful changes targeting single risk factors at a national level.

Summary and Conclusion

Cardiovascular disease remains a significant global problem. The swift pace of economic and social transformation in a postindustrial world with rapid globalization presents a greater challenge for low- and middle-income economies than for high-income economies. Although CVD age-adjusted rates have declined in HICs and some of the LMICs, the number of CVD survivors continues to increase because of aging populations and improvements in case-fatality rates for acute events. From a worldwide perspective, the rate of change in the global burden of CVD is accelerating, reflecting the changes in the low- and middle-income economies, which represent 85% of the world's population. This preventable epidemic will have substantial consequences on many levels: individual mortality and morbidity, family suffering, and staggering economic costs—both the direct costs of diagnosis and treatment and the indirect costs of lost productivity.

Different regions of the world face different stages of the epidemic. In HICs, managing an ever-older population with chronic manifestations of CVD such as heart failure will strain health care budgets. Currently, the Eastern European countries and members of the former Soviet Union face enormous

burdens, with more than half of all deaths attributed to CVD. Meanwhile, countries in sub-Saharan Africa are just beginning to see increases in these chronic illnesses while still grappling with HIV/AIDS. No single global solution to the rising burden of CVD exists, in view of the vast differences in social, cultural, and economic circumstances. HICs must minimize disparities, reverse unfavorable trends in CVD risk factors and behaviors, and deal with the increasing prevalence of CVD in an aging population. The most complex challenges face LMICs, with increasing access to low-cost tobacco products and ready access to less-than-favorable dietary options. Preventing the poverty-inducing effects of catastrophic CVD events will require efforts to improve access to low-cost prevention strategies at both the societal and the individual level and must include improved financing for at least catastrophic health coverage.

A reduction in the disease burden would similarly require both policy and personal changes. In the long term, allocation of resources to lower-cost strategies will likely prove more cost-effective than dedicating resources to high-cost management of CVD. From a societal perspective, efforts to strengthen tobacco-control strategies, improve dietary choices, and increase physical activity will be paramount. At the individual level, risk assessment strategies and treatment modalities require simplification. Furthermore, alternative deployments of allied health workers such as community health workers will need evaluation, in view of the limited human resources in most LMICs. HICs must share with leading and emerging middle-income countries the burden of research and development into every aspect of prevention and treatment. Through further expansion of the knowledge base, particularly regarding the economic consequences of various treatment and prevention strategies, the efficient transfer of low-cost preventive and therapeutic strategies may alter the natural course of epidemiologic transitions in every part of the world, thereby reducing the excess global burden of preventable CVD.

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2

Ethics in Cardiovascular Medicine

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Ethics continues to provide a bedrock for the practice of modern cardiovascular medicine. While often seen as addressing the distinction between what “can” and what “should” be done in clinical practice, the scope of ethics is much wider, encompassing such diverse topics as genetic testing, appropriateness-based reimbursement policies, and end-of-life decision making. No longer confined to American College of Cardiology (ACC) Bethesda Conferences or joint American Heart Association (AHA) and ACC conferences,[1-3] ethics is now prominently positioned in practice and publication guidelines. This attests to the awareness that, as technology and science have advanced cardiovascular medicine, so too has the need for ethical reasoning and clinically nuanced discussions of ethical challenges.

This chapter focuses on categories within cardiovascular medicine that highlight the need for ethical reasoning: informed consent and decision aids, clinical ethical judgments of futility, conflicts of interest and disclosure, public reporting, social media and mobile health, genetics, and transplantation.

Informed Consent and Decision Aids

One general approach to ethical reasoning is that of *principlism*, deploying the ethical principles, or

guides for clinical ethical judgment and action, of respect for autonomy, beneficence, nonmaleficence, and justice. Respect for autonomy, which has roots in 18th-century medical ethics, emphasizes the role of patient in self-determination, especially informed consent, shared decision making (SDM), and advance care planning. As a consequence, respect for autonomy is often regarded as the most important ethical principle.

Informed consent is often reduced to the verb, *to consent* (a patient consents). The nuances of the conversations that should take place with patients are difficult to master for clinicians and can become time-consuming when caring for patients with complex heart disease but are often relegated to junior staff or extenders. The goal of informed consent is to empower the patient with clinical information relevant to the decision at hand and to support the patient in making a voluntary decision, that is, a decision free of controlling internal influences (e.g., unreasoning fear) and external influences (e.g., well-meaning family members who attempt to usurp the patient's decision-making role). Informed consent has four requirements: (1) a patient with decision-making capacity (or their surrogate), (2) a discussion of relevant facts about the medically reasonable alternatives for managing the patient's condition (i.e., alternatives supported in evidence-based clinical judgment), (3) a determination of the patient's understanding, and (4) a voluntary decision. What constitutes “relevant facts” was established with the “reasonable patient standard” in the 1972 *Canterbury v. Spence* case. This standard requires the physician to provide information that any patient with a specific condition, such as stage C heart failure, needs to know. This is a patient-oriented standard and is the legal standard in the majority of the states in the United States. However, a *meaningful* informed consent additionally should include probable outcomes based on the main risks and benefits of the proposed intervention or procedure in that specific patient *and* a discussion about the patient's preferences. These would be relevant facts for the patient.

Although the accepted legal and ethical standard of practice, informed consent continues to be poorly done and is heavily biased by physician time and preference.[4] The common practice of “discussing” an angiographic finding while a patient is in the cardiac catheterization laboratory and making the decision to intervene is far from ideal; the practical constraints of time often interfere in many settings, as when it would otherwise be reasonable to perform a staged coronary intervention. In some settings, such as emergency care that often includes the presentation of an acute coronary syndrome or aborted sudden death, clinicians practice under the guise of “presumed consent,” and the best interest standard applies to medical care. This standard is based on the ethical principle of *beneficence,* which creates the ethical obligation to provide clinical management that is expected in evidence-based clinical judgment to result in net clinical benefit for the patient.

When patients lack decisional capacity or they are temporarily unable to make decisions, as when sedated, clinicians turn to legally designated surrogate decision makers. Surrogates should act with substituted judgment, making decisions the patient would have made, not necessarily what the surrogates themselves would want or think appropriate. In this situation the process of informed consent often becomes increasingly complicated and time sensitive. If, for example, a patient presents with an acute myocardial infarction and develops cardiogenic shock, the clinician might have to explain the procedure and potential benefit of percutaneous extracorporeal membrane oxygenation (ECMO) as a salvage therapy, while also making sure that the risks of bleeding, infection, and, importantly, lack of recovery are also heard by the surrogate decision maker. The impetus in clinical medicine is to rescue with all tools at hand, whereas the reality may be that rescuing someone from immediate death will only delay more difficult decisions about limiting life-sustaining treatment for only a few days or weeks. This does not mean that no emergency therapies should be performed because of the risk for misunderstanding, but rather that the process of informing patients and their families and updating them with current facts and

probable outcomes is iterative.

It is often in the setting of informed consent that tension between the principles of respect for patient autonomy and beneficence are most acutely experienced. Clinicians may believe that a particular intervention or medication is clearly superior to the alternative, but the patient may not agree. This tests not only respect for autonomy and beneficence, but also strains the fiduciary relationship of physicians and patients, in which the patient's interests (and preferences), as understood from an evidence-based clinical perspective, are given priority. Because of this tension, the use of decision-making aids has been increasingly adopted within cardiology. Meaningfully informed patients are less likely to undergo procedures that have limited benefit or benefits not consistent with their preferences. In addition, what physicians think patients need to know (e.g., clinical risks) and what patients want to know (e.g., costs, lifestyle changes) are often misaligned. Patients who have been meaningfully involved in decisions about their medications are more likely to be compliant with them. Indeed, complying with the 2013 ACC/AHA Guidelines on Cholesterol management will require discussion and shared decision making (SDM) between physician and patient.[5]

The domains of informed consent and end-of-life decision making also come together in the field of mechanical circulatory support (MCS) and ventricular assist device (VAD) technology. The “rise of the machines”[6] (LVADs) has brought the challenges of implantable devices that surpass those of implantable cardioverter-defibrillators (ICDs) and permanent pacemakers (PPMs). MCS, VADs, and to a lesser extent ICDs and PPMs are all forms of life-sustaining treatment undertaken to prevent imminent death and to secure an acceptable outcome: survival without significant morbidity. This especially refers to morbidity that significantly reduces or even eliminates the patient's capacity to engage in valued life tasks and derive satisfaction from them, the formal definition of an acceptable quality of life.

The American Heart Rhythm Society (AHRS) and European Heart Rhythm Association (ERHA) consensus statements in 2010 included a discussion on the deactivation of both ICDs and PPMs[7,8] (**see Chapters 27, 29, and 31**). Although it is well established ethically and legally that deactivation is no different than withdrawing any other life-sustaining therapies and allows a patient to die from underlying disease, there is still substantial physician discomfort in this practice, even with the relatively simple process of reprogramming an ICD/PPM.[9] Although often employed in these same patients, VAD technology is different and more complex. VADs can provide durable improvements in quality of life but can result in significant morbidity, with a predictable incidence of bleeding, cerebrovascular accidents (strokes), and drive-line infections. Unlike other implantable cardiac devices, VADs more completely replace cardiac function and thus are life sustaining. A PPM replaces or augments the conduction system but still requires that the native heart circulate the blood. An ICD is lifesaving for ventricular arrhythmias but is not in cases of progressive pump failure. A VAD requires neither native electrical conduction nor ventricular function to sustain life. In a simple model, a VAD is “cardiac replacement therapy” much as hemodialysis is renal replacement therapy.

Proper discussion about the implantation of a VAD should include patient options, goals of care, and patient preferences about deactivation should the outcome result in a quality of life not acceptable to the patient, a crucial autonomy-based consideration.[10,11] In this setting, use of a decision aid is valuable to allow for the time to discuss these issues. Decision aids or other tools are used to address the medical evidence, consider clinical judgment, and integrate patient preferences. As VAD technology and durability improve, it is increasingly apparent that primary consent is needed for durable VADs. Having a legally designated surrogate make the decision, in the absence of any prior discussion of the ramifications of this life-altering implantation, is not recommended, such as in cases of acute precipitous cardiogenic shock. In the situation of chronic systolic dysfunction where the patient may have had ongoing discussions with the

cardiologist, however, the surrogate might be equipped to make a decision that meets the standard of substituted judgment—a decision based reliably on the patient's values, beliefs, and preferences. The consequences of a durable VAD implant for a patient unaccustomed to chronic disease management or unprepared for the necessary changes in lifestyle can be overwhelming and has led to suicide. Turning off a VAD is also a more complex process than turning off ICD therapies or pacing with a PPM and should entail VAD-specific end-of-life discussions.

As patients survive their immediate cardiovascular disease with VAD implantation, they may develop catastrophic complications such as intracerebral hemorrhage, experience progressive device failure with aortic insufficiency and recurrent heart failure, or have recurrent gastrointestinal bleeding. Even in the setting of perfect VAD functioning, patients may develop dementia or terminal cancer. In a concise summary of patient-centered ethical issues in VAD support, Petrucci and colleagues[12] discuss the development of a withdrawal plan with patient and family. In the case of an ICD, discontinuing therapies will not lead to immediate or even imminent death. Turning off a device allows the patient to die from the underlying disease process, or malignant arrhythmia when and if it occurs (**see Chapter 41**). With a VAD, however, turning off a device can worsen remaining cardiac function (aortic or pump regurgitation) and in most cases will lead rapidly to circulatory death (**see Chapter 29**). The immediate consequences to the patient and surrogate as well as the clinician are inescapable. Although most similar to hemodialysis in replacement of an organ's function, a VAD's discontinuation is most similar to that of mechanical ventilation. A VAD is a *substitution* device rather than a replacement device; therefore discontinuation of an VAD in the patient with other lethal conditions is ethically acceptable, because the VAD support would be futile[13] (see next section). One important distinction is that although there are community-dwelling patients who are chronically supported by mechanical ventilation, their numbers are few and their medical condition usually obvious (e.g., tracheostomy, wheelchair bound). With VAD technology, it is possible to conceal one's dependence on the machine, so the mental and emotional effort to realize this dependency can make discontinuation discussions more difficult.

Clinical Ethical Judgments of Futility

In general, *futility* means that in evidence-based clinical judgment, there is no reasonable expectation that a clinical intervention will result in its usual outcome. When this is the case, the beneficence-based obligation to provide clinical management has reached its limits, and discontinuation should be offered. When continuation of futile treatment results in significant iatrogenic or disease-related burden, there is a beneficence-based obligation to recommend that the intervention be discontinued.[14]

For this general concept of futility to become clinically applicable, the concepts of “no reasonable expectation” and “outcome” must be specified.[15] Because the invocation of futility sets the clinician and patient on a path to limitation of life-sustaining treatment, the concept of “no reasonable expectation” should be specified conservatively. This concern was implicit in Blackhall's landmark article on limited cardiopulmonary resuscitation (CPR), when she set the expectation of failure at 97% to 100%, in the setting of a procedure that results in significant iatrogenic morbidity.[16,17]

There are three beneficence-based specifications of “outcome” and one autonomy-based specification that are clinically distinguishable and applicable. The first beneficence-based specification is physiologic outcome: a clinical intervention should be considered *physiologically futile* when there is no reasonable expectation that its physiologic outcome will occur. The outcome needs to be clearly stated; for example, restoration of spontaneous circulation is the outcome for which CPR is initiated. When CPR is

discontinued because there is no reasonable expectation that spontaneous circulation will be restored, physiologic futility is invoked. The addition of a fifth vasopressor in the setting of critical cardiogenic shock will not reasonably restore cardiac output and can be considered to be physiologically futile. The second beneficence-based specification is the outcome of death during the current admission and no recovery of interactive capacity before death occurs. This is known as *imminent-demise futility*. The third beneficence-based specification is the outcome of survival but with irreversible loss of interactive capacity, such as a permanent vegetative state as determined by American Academy of Neurology criteria.[18] This is known as *interactive capacity futility*. The one autonomy-based specification of the outcome is a functional status that the patient judges to be incompatible with engaging in valued life tasks and deriving satisfaction from doing so. This is known as *quality-of-life futility*.

Whenever one or more of these definitions of futility apply to a clinical intervention, the physician should offer discontinuation of that intervention, or importantly in cardiovascular medicine, the physicians *should not offer* an intervention. When continuation of such an intervention is resulting in significant iatrogenic or disease-related morbidity, the physician should recommend discontinuation of that intervention, such as limb ischemia in the setting of VA-ECMO, or ongoing high-level hemolysis with Impella support. The patient's legally designated surrogate and other involved family members should be provided sustained psychosocial and, for those who want it, spiritual support as they come to terms with the limits of life-sustaining treatment to alter life-taking diseases or injuries.

Conflicts of Interest and Disclosure

The profession of medicine is based on the *fiduciary* relationship, or “putting the patient first”; the maintenance of scientific competency; and being entrusted with the responsibility to improve the health of the public. This ethical concept of medicine as a profession was introduced into the history of medical ethics by two physician-ethicists in the 18th century, John Gregory (1724–1773) of Scotland and Thomas Percival (1740–1804) of England.[19]

The fiduciary relationship and the public trust it generates are part of what underpins the discussion of conflicts of interest. Conflicts of interest (COIs) are circumstances where there is a risk that the self-interest of an individual physician or health care organization will bias professional judgment and action, to the detriment of patient care or research. Not all forms of self-interest are illegal or even unethical. COIs cannot always be avoided, but specific influences can be eliminated, or mitigated and then disclosed. *Disclosure* is the primary method of managing COI in scientific publications, presentations, or committee works but is still limited primarily to financial conflicts, rather than positions on advisory or scientific boards. The Physician Financial Transparency Report, more commonly known as the Sunshine Act, was designed to improve the disclosure of potential financial conflicts, now requiring manufacturers to submit data, which are publically available after a period of review. Although its intent perhaps was to limit the blurring of obligations or undue influence, trainees are now subjected to stricter oversight, because textbooks and other educational material gifts are reported publicly.

The greatest concern with COI is that of undue industry influence on referral or prescription practices and on the use of devices. With the implementation of higher-cost technologies, such as transcatheter valve replacement, implantable hemodynamic monitors, and VADs, the presence or perceived presence of financial COI will become more prominent.[20]

Clinical research also is an increasing area of COI concern. An investigator may have possible financial and academic gains from greater patient enrollment, with authorship on multicenter publications.

The practice of some institutions is to have “neutral” study coordinators approach patients for study enrollment, but it is difficult if not impossible to separate patients from the recommendations of their physicians.

From the perspective of the fiduciary relationship in medical professionalism, the burden of proof is on the physician and the health care organization to permit a COI. Failure to identify a COI and failure to manage it in a professionally responsible way, by eliminating the COI or mitigating and disclosing it, are unacceptable threats to medical professionalism and have the potential to dissuade patient participation in clinical research and erode public trust.

Public Reporting

The development of appropriateness criteria for cardiovascular procedures and imaging is in part a consequence of a mismanaged public trust. Appropriateness of coronary interventions or imaging has been of interest to not only clinicians, but also policymakers and insurers, and has been the subject of quality improvement initiatives at the local and national level.

Cardiovascular medicine has been at the forefront in the movement to create evidence-based practice guidelines to improve patient quality while also reducing health care costs. However, public reporting is now commonplace in medical practice, having arisen from New York State's surgeon-specific reporting of coronary artery bypass grafting results in the late 1980s and 1990s.[21] The Centers for Medicare and Medicaid Services (CMS) publish hospital data for Medicare patients specifically for cardiovascular medicine, addressing acute myocardial infarction (AMI), heart failure hospitalization, stroke hospitalization, and the treatment and prevention of venous thromboembolic diseases. In addition, the CMS Hospital Web Compare site reports publically-accessible 30-day risk-adjusted admission and mortality rates for heart failure and AMI. Although welcomed by policymakers and payers, these data have only received lukewarm public reception and still are under criticism for their lack of uniform risk adjustment.[22] There are risks to this reporting as well, because hospitals may exaggerate their patients' risk or, alternatively, “cherry-pick” patients to improve their reporting statistics.

As part of the system-based measures to improve high value–based care, the efforts to decrease hospital readmission have met with unintended consequences that need to be addressed as the Medicare Access and CHIP (Children's Health Insurance Program) Reauthorization Act of 2015 (MACRA) continues to be implemented. The types of care for patients within the confines of a hospital are changing, challenging the resource and often scope of outpatient care.[23,24] Hospitals are facing what may constitute up to a 9% reduction in CMS reimbursement if they fail to meet quality measures, and those hospitals most affected are typically in underserved areas and are teaching hospitals. The downstream effects of this reduction in reimbursement may lead to worsening of the health care disparities seen among socioeconomic divisions.

This discussion occurs in the context of a larger, economic debate. Health care costs are rising at seemingly logarithmic if not exponential rates. The containment of resources in this way is seen as preferable to the overt concept of “rationing,” the forbidden “R” word in health care. Rationing is occurring without this label. Organ allocation and use of higher technologies for screening are a few examples. If there are a fixed number of slots to schedule patients for nuclear imaging, patients are prioritized, which is acceptable, necessary, and ethical. This can be justified on a beneficence-based approach for patient good, as long as the prioritization does not result in loss of access to clinical management supported by evidence-based clinical judgment. The pressure to discharge a patient earlier

from the hospital does not necessarily share this basis. As MACRA tightens and hospital and payment structure change, it will be the responsibility of the physicians to speak out for their patients for what is appropriate and acceptable care and to give a voice to those who are not empowered to do so.

Social Media and Mobile Health

The professionalism of medicine has also found new challenges with the rise of social media. Applications and programs such as LinkedIn, Twitter, and Facebook are embedded in social culture and are used by patients, providers, and health care systems alike. Patients use social media to participate in support groups and acquire more health information, but they also rely on social media for communication with their physicians. Social media have challenged conventional constructs of confidentiality, professionalism, and both professional and personal boundaries. Previously, episodes of poor judgment might have remained within an institution, but now, posting of comments or photographs about patients to these social media sites has resulted in lost employment, loss of patient trust, and potential harm. Clinicians may find themselves in the social media despite their preference to remain “off-line” and need to be aware of their ability to protect themselves with privacy managers. The American Medical Association (AMA) Council on Ethical and Judicial Affairs has published guidelines on Professionalism and Social Media, recognizing the role of social medial in everyday practice.[25] Similar guidelines have also been published by the British Medical Association.[26]

Image sharing on social media is now common. Pathology associations are using social media to share virtual histology images. Cardiovascular medicine is filled with studies that are as simple to export as image or movie files. Electrocardiograms (ECGs) or similar images are often posted on social media sites to show an interesting case or to ask for diagnostic help and interpretation. It is important to be mindful of the need to preserve patient confidentiality and to maintain professional considerations when engaging in these public conversations. Late-breaking news and trial results are posted on social media minutes after live presentation at conferences, so attention must be paid to conceal patient-specific information because images are disseminated worldwide.

There are also the potential benefits of social media, to help improve public health through information sharing. Hospitals and practices are increasingly using social media to increase their market presence and foothold. Clinical trials can increase recruitment through social media groups that are disease specific and, importantly, are consistent with institutional review board (IRB) guidelines if done correctly. Emerging technology is also improving public health through mobile health applications. Especially in the field of cardiovascular medicine, with devices to recognize common arrhythmias such as atrial fibrillation, patients now have some diagnostic tools available to them. This has potential for better health outcomes but also worse outcomes without the proper discussion and education by providers.

With the increase in a global presence that has accompanied social media, physicians and other providers may find themselves under increasing scrutiny or attack in a public forum. Although often hurtful and even potentially libelous or slanderous, responding to these attacks in the social media in clinical detail would violate the professional obligation of confidentiality. The risk management or legal representation on staff should be informed of these attacks in order to address them without violating patient confidentiality, allowing providers to continue to function in their professional capacity. Similarly, patients often try to connect with physicians through social media. If this link is accepted, the patient can then be “revealed” to all the other contacts, and his or her identity as a patient may no longer be private. Although the patient may have initiated this contact voluntarily, he or she may not be aware of its far-

reaching ramifications and is not “informed.” This highlights the difference between *privacy*, which the patient controls, and *confidentiality*, which is central to maintaining trust as a matter of professionalism. Physicians cannot be too careful in the era of social media in fulfilling this professional responsibility. One practical way to do so is to put a steep burden of proof on use of social media, to prevent breaches of the professional obligation of confidentiality.

Genetics

The role of genetic medicine is increasingly important in cardiovascular medicine. With the growth of personalized medicine and increased capability for both diagnosis and screening, genetic testing is now common. Many diseases have primary genetic origins that are increasingly recognized not only as causative, but as possible targets for therapies.

Personalized medicine, or precision medicine, refers to the practice of specifying as precisely as possible the patient's condition, by sorting patients with a shared diagnosis into clinically significant subgroups, such as based on genomic contributions to the patient's response to medication type or dose (**see Chapter 8**). As genomics moves from the laboratory into routine clinical practice, this increased precision holds the promise of improving the quality of care for patients with cardiovascular diseases.

The most common and traditional use of genetic testing involves the confirmation of a monogenic disease, as with the diagnosis of transthyretin amyloidosis (**Chapter 77**) or familial hypercholesterolemia (**Chapter 44**). This use of genetic testing for a specific diagnosis is well established and is less controversial, often because the phenotype of disease presentation is predictable. While this type of testing does have ramifications for families, because the phenotype is apparent, there is less controversy about discovery of disease.

Testing for genetic susceptibility, or trying to assess a risk profile based on genetic testing, is more challenging because these are *probabilistic* rather than confirmatory tests. The genetic variations associated with dilated cardiomyopathies (**Chapter 77**) or the long-QT syndrome (**Chapter 33**) may be single-gene disorders, occurring in less than 1 in 500 individuals. The presence of a single variation may lead to a diagnosis of risk leading to increased surveillance or even procedures, such as defibrillator placement or surgical intervention for aortic aneurysms. However, the obligations for reporting variations are still unclear and ethically challenging, especially since a “variant of uncertain significance” (VUS) may later prove to have pathologic potential. Because of this uncertainty, genetic testing should be directed toward a clinical phenotype rather than blind screening.[27]

The ethical principle of justice requires that like cases be treated alike, to prevent arbitrary treatment of individual patients. In the health care setting, patients are alike in their diagnoses. Health care justice therefore requires that every patient with a specific diagnosis be offered clinical management that is reliably expected to benefit the patient clinically, thus linking the principle of health care justice to the ethical principle of beneficence and to evidence-based reasoning. From a justice perspective, the accessibility to these tests and to the genetic counseling that should accompany them, as well as inclusion in databases and genetic registries, is limited to genetic evaluation that is reasonably expected to improve the processes of patient care. Insurance coverage may determine whether a patient can have genetic testing or potentially affected family members can be screened. Also, the testing may be feasible, but without the access to trained genetic counselors who can help ascertain the risk and benefits of a screening test. A further consideration is recognized as the “right not to know” (RNTK). Most frequently referenced in the setting of identical twins, genetic information can be a family condition rather than a

sporadic mutation. As such, the labeling of a disease in the proband can ripple through the family tree, with consequences related to family planning, career choices, and even hobbies (e.g., swimming).

In most of cardiovascular medicine, the proportion of attributable risk to monogenic disorders is low. Although genetics clearly influences cardiometabolic disease, environmental exposures have more impact and, importantly, are modifiable and can meaningfully influence health outcomes. As in other fields of medicine, genetic databases are still relatively homogeneous repositories within national and racial populations.[28] As the future of genetic testing evolves to the point of whole-exome and whole-genome sequencing, the responsibility for stewardship of this information and future ramifications is great.

The Genetic Information Nondiscrimination Act of 2008 (GINA) sought to address some of these issues. However, while providing some protection from employment and health insurance discrimination based on genetic information, it provides no assurances against genetic discrimination for either life or disability insurance. Importantly, GINA does not provide protection against phenotypically apparent genetic diseases, such as hypertrophic cardiomyopathy (**Chapter 78**) or against the use of information in a "family history."

Pharmacogenomics is an important component of precision cardiovascular medicine. Genotyping cytochrome P-450 (CYP) 2C9, or *VKORC1* variances to predict and therefore optimize response to warfarin therapy, did indeed have a modest success. Similarly, loss of function in CYP2C19 (*2) is associated with a poorer response to clopidogrel therapy, which has significant racial differences, but was not shown uniformly to affect clinical outcomes.[29] Beta-receptor and G-protein polymorphisms can predict response to therapy in heart failure and pulmonary hypertension and may help explain some of the survival benefits of African American or predominantly Caucasian populations. However, since widespread clinical use of such targeted therapy is still second to guideline-directed medical therapies, it must be recognized that exclusion of population subsets in trials that underpin the guideline-directed therapy, whether intentionally or not, does have social and medical implications. Also, beyond the poor enrollment of racial groups, patients with significant or end-stage renal disease are often excluded from device trials (ICD, PPM, VAD). Clearly, however, these technologies have slowly spread to these excluded populations.

"Big Data"

The near-universal acceptance of electronic health management systems is also changing the role of patients, putting stress on issues of patient confidentiality and autonomy. Patients will no longer be "patient," only subjects of medical care, but have the potential to become active by imputing data about side effects, response to interventions, and other patient-oriented data. The use of health applications in digital media also allows for data gathering on an unrivaled scale. Data regarding health and lifestyle practices are collected by these applications without significant oversight for their use, and fundamentally, with poor public understanding. Other "big data" now almost universally include the electronic health record (EHR), which is being used in "EHR-facilitated" clinical trials. Designed for clinical care and reimbursement, EHRs are heterogeneous and filled with incomplete or duplicated data. In addition to becoming agents in their care, patients may also unwittingly become subjects of research as EHR are mined for patient data to assist with disease modeling.

Machine-learning technology is using not only the databases from clinical trials, but also databases of imaging or laboratory information. These latter data are devoid of protected health information and identifiers; use of data in this way does constitute research, which is categorized as "non–human subjects research."

As more of these EHR-facilitated trials are undertaken, favored because of their ease of use and cost-savings, local IRBs will be responsible for assessing the appropriateness of their use to target potential trial participants.[30] Although it is common practice to use clinical information to screen potential trial participants without their consent, it is the vastness of scale and the potential ease of use that merit further consideration about how patients at institutions might be informed of the potential for being contacted for research purposes. Some institutions have addressed this potential in a transparent and upfront way, at least in spirit, by having a disclosure when one signs for the consent for treatment at a physician's office or hospital. This may meet some of the technical requirements for consent, but certainly fails to meet the requirements for informed consent.

Transplantation

Donation After Circulatory Death

Organ donation still faces the great challenge of supply/demand mismatch. As science and medicine improve the ability to survive illness and end-stage organ disease, the demand for organs has continued to outstrip efforts to increase supply or create alternative replacement strategies. Indeed, within cardiovascular medicine, with the technology of MCS, we are striving to create machines that achieve equipoise with transplantation.

To help meet the demand for organs, there has been increased focus on *controlled donation after circulatory determination of death* (cDCDD). Although death defined by lack of spontaneous circulation constitutes the vast majority of deaths, and before the Uniform Determination of Death Act was the only legally recognized death, organ donation after the common mode of death has its own unique ethical challenges. cDCDD is the process of procuring organs after a donor has been determined to be dead by cardiopulmonary criteria without reference to brain-function criteria, which is how cardiopulmonary criteria for death have always been applied. Circulatory death (i.e., irreversible cessation of circulation) occurs—often after withdrawal of life-sustaining therapies such as mechanical ventilation or ECMO and after a brief period (e.g., 2 to 5 minutes)—when there is no intervention, allowing procurement efforts to commence. An ethical concern arises from discussions about the meaning of “irreversible.” The concern is that if the cessation of cardiac function is truly irreversible, efforts to revive the person 5 minutes later should not succeed. If they do, should the person have been declared dead? The practice of cDCDD has the implicit understanding that if the patient or surrogate understands how death is determined, and the intent is to forgo attempts at resuscitation, after the legally mandated time of 2 minutes of no spontaneous circulation and breathing, a person is legally dead.

The concept of the irreversible is the basis for the ethical concern for the use of cDCDD hearts for transplantation. It should be mentioned that the first heart transplant was performed with what would now be considered a cDCDD heart. The abandonment of this practice coincided with the recognition that recipient outcomes were better with the establishment of *donation after brain death* (DBD). However, as the organ shortage continues and science matures, the outcomes of cDCDD may be viewed as preferable to the clinical alternatives, which may include a higher likelihood of death. For example, a negative cDCDD prospective-crossmatch local heart might be preferable to ongoing chemical desensitization while the patient depends on a left ventricular assist device (LVAD). It will be important to ensure that all parties involved in the process, from the medical and surgical team to especially the potential recipient, are aware of the risks that might accompany use of such organs.[31]

Another aspect of cDCDD distinct from DBD is that the testing to assess organs for donation and the

management to ensure organ viability are often performed on a “live” person rather than a brain-dead donor, simultaneously with end-of-life care. There is not only one patient, but rather a handful more whose interests are of concern. The suggested use of ECMO in the setting of cDCDD has potential conflicts.[32] The use of ECMO before death must be considered in a risk/benefit analysis; if the intention is solely to improve organ viability, then initiation would be inappropriate without clear discussions with the patient or surrogates. Maintaining ECMO or initiating interventions such as placing large-bore catheters or transferring the live patient to an operating room to allow for more controlled procurement is part of many hospital policies on cDCDD and is discussed in length with donor families.

Reinitiating or initiating ECMO after declaration of death might restore cerebral perfusion and stimulate or restore brain functioning. This would be ethically problematic, and the response to this concern has been to make efforts for aortic clamping to prevent cranial perfusion.

Stem Cells

Stem cells have as-yet poorly defined potential within medicine but have been the subject of ethical scrutiny. Leaving aside the challenges of embryonic stem cells, the use of induced pluripotent stem cells (iPSCs) does have ethical implications that will need to be considered as their use increases in research and therapies. As discussed earlier, the use of genetic testing for a discrete diagnosis has different implications from screening. Using iPSCs to redefine what currently may be a VUS through gene-editing techniques has the potential for scientific discovery.[33] However, it is important to remember the legacy of Henrietta Lacks and the HeLa cell controversy. The process of informed consent for research on biobanked specimens is varied.[34] If there is no interaction or intervention with the patient source of the material, this research is often not considered to be “human subjects research” and therefore does not require informed consent. However, if increasingly specific patient information is collected along with the biospecimen, different standards of informed consent, either general research consent or consent specific for a study, might be applicable per local IRB regulations. Clearly, the lesson to remember is to protect not only the individual patient, but also the family and descendants, because genetic information is shared and may have prognostic implications.

The iPSCs may be used to combine the predictive value of gene identification with the phenotypic presentation. They can be used ethically with sufficient forethought and planning of how to maintain public and patient trust while facilitating research.

Conclusion

As medicine and science evolve with emerging technologies and a better understanding of disease, the ethical challenges we face continue to change. At the core, we are still grounded by the fundamental principles of patient care and of professionalism set forth by Percival and Gregory. Research into incorporating mobile technology and its role in both clinical practice and clinical research will be important as the economics of health care delivery and drug development are increasingly stretched. We need to continue to be aware of the implications for progress and for potential harm or misuse as we embrace advancement.

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3

Clinical Decision Making in Cardiology

John E. Brush Jr, Harlan M. Krumholz

Medicine is an information science. Information is being produced at an unprecedented rate and is readily accessible using electronic searches and handheld devices, making skills to parse and use appropriate information ever more important. Memorization of medical facts is less a necessity, while processing knowledge and critical thinking are essential for high-value medical care. Clinical decisions and recommendations define medicine and, in the midst of a rapid expansion of medical knowledge, have never been more challenging. This chapter summarizes some of the core competencies for clinical reasoning that can be learned and should be expected of expert practicing cardiologists.

Clinical Reasoning

Clinical decisions are based on our understanding of medical facts and knowledge of our patients, including their preferences and goals. Good decisions take into account the limits of our information, uncertainty in our measurements, incompleteness of our understanding of human biology, and the play of chance.[1-3] Clinical reasoning is informed by experiential and formal knowledge learned through years of practice and study.[4-6] The translation of medical knowledge into good patient-centered decisions is a key goal of clinical reasoning and is the hallmark of an expert clinician.

Clinical reasoning is often guided by simplified rules. Early in training, physicians are taught how to recognize specific clusters of signs and symptoms, place patients in diagnostic categories, and follow the rules that apply to those categories.[7] For example, patients with particular findings might be labeled as having “acute myocardial infarction,” which would trigger treatment based on studies showing benefit from aspirin and beta-blocking agents. In this context, algorithmic tools are often used to direct actions. For example, guidelines recommend that a patient with a low ejection fraction should be considered for an automated implantable defibrillator, but only after considering the etiology of the systolic dysfunction and the time frame of the disorder. These algorithms are not intended to force actions, but to guide decisions. The best clinicians know when adherence to such algorithms is proper and when exceptions, based on the patient's situation or preferences, can lead to divergence from these algorithms. Divergence from guidelines may be appropriate but requires adequate justification, documentation, and transparency.

Most of medical decision making, however, lies outside of simple algorithms and requires judgment. There are two major settings, related to diagnosis and treatment, where clinical reasoning is critical.

First, there are decisions about classifying an individual who presents with symptoms or signs of disease into the proper diagnostic category. Book chapters and other reference materials are usually organized according to categories, such as a medical diagnosis. The chapter informs the reader about how a particular condition, such as aortic stenosis, might manifest. These labels are useful for understanding mechanism and predicting response to potential therapeutic strategies. However, patients often do not present according to assigned general diagnostic categories. They seek attention for symptoms, which requires the clinician to reverse the order of a typical textbook and to work inductively from a patient's signs and symptoms toward a diagnostic label before a therapeutic plan can be developed. For a patient with dyspnea on exertion and a systolic murmur, aortic stenosis is a possibility, but the diagnosis is not conclusive without further testing. In some cases, uncertainty persists. About one third of patients labeled with a principal discharge diagnosis of heart failure also receive treatments for other causes of dyspnea, such as pneumonia or chronic obstructive pulmonary disease.[8] This is the reality of current practice.

Second, there are decisions about treatments. These decisions are also challenging because they involve weighing risks and benefits, speculating about estimates for these parameters, and aligning choices with the preferences of those being treated. The likelihood of benefit is often probabilistic, because people are pursuing strategies to reduce risk without knowing whether they themselves will benefit. These decisions can occur in prevention, which addresses whether to intervene in the interest of preventing future health problems, based on an estimate of prognosis. In this setting the risks and costs occur immediately, while the benefit is anticipated to be in the future. These decisions can also involve treatments to address symptoms as well as reduce the immediate risk for someone with acute or chronic disease.

Risk stratification is an important application of probability and is often used to estimate patient risk and assist in decision making. This approach generally employs the results of statistical models that have identified prognostic factors and incorporated them into a tool that may assist clinicians. In recent years, many tools have been developed to assist in the rapid assessment of patients.

Recent decades have witnessed the emergence of *cognitive psychology*, a branch of psychology

focused on how people make decisions.[9] The field demonstrated that people frequently develop useful reasoning shortcuts to circumvent the need to explicitly calculate probabilities, but these shortcuts come with biases that can lead decision making to deviate from the rules of logic and probability in predictable ways. Thus a good understanding of clinical reasoning requires knowledge about logic and probability as well as cognitive psychology.

Diagnostic Decisions

Patients often present with descriptions of symptoms such as chest pain. Cues are scattered, like pieces of a jigsaw puzzle. Clinicians, as with all decision makers, often use mental shortcuts called *heuristics* to organize cues and to turn an unstructured problem into a set of structured decisions.[10,11] They are taught to collect the scattered cues of an unstructured clinical problem by using an organized history and physical examination.[12-14] Clinicians are able to reason by analogy by comparing a patient's narrative to prototypic descriptions of diseases. When experts take a history, they use a process known as “early hypothesis generation” to develop a list of three to five possible diagnoses very early in the process.[15] This enables the questioning to become more direct and the clinician to become more engaged in the fact-finding exercise.

After collecting, sorting, and organizing data, clinicians often use a problem list as a tool to list, group, and prioritize clinical findings. With additional information, a *problem statement* can be defined more specifically. For example, “shortness of breath” may be an initial problem statement that is replaced by “acute systolic heart failure,” as further clinical information leads to a more refined problem statement that moves from symptom to diagnosis. Clinicians then use a differential diagnosis to expand the list of possibilities to avoid premature closure of the search for the true diagnosis. This step-by-step process enables the clinician to formulate a set of hypothetical diagnostic possibilities, which can then be tested using iterative hypothesis testing. *Iterative hypothesis testing* allows the clinician to narrow the list of possible diagnoses and hone in on the most plausible hypothesis.[1-3]

Understanding *probability* is essential for clinical decision making.[1-3,16] Probability can be estimated for outcomes that are measured as continuous or categorical variables. **Fig. 3.1** shows how probability of an outcome or event is distributed across a range of possibilities. For example, a laboratory test might be measured in a population of patients resulting in a distribution where most patients are distributed to the middle of the range of possibilities and fewer scatter to the edges of the range, as shown in the probability density curve in the left panel of **Fig. 3.1**. The probability of categories or discrete variables can also be measured, as shown in the probability distribution graph in the right panel. If all the diagnostic possibilities are mutually exclusive and collectively exhaustive, the probability of all of the possibilities will add up to 1, as shown by the red cumulative probability curves in **Fig. 3.1**. Understanding cumulative probability is important for understanding sensitivity and specificity, as discussed later.

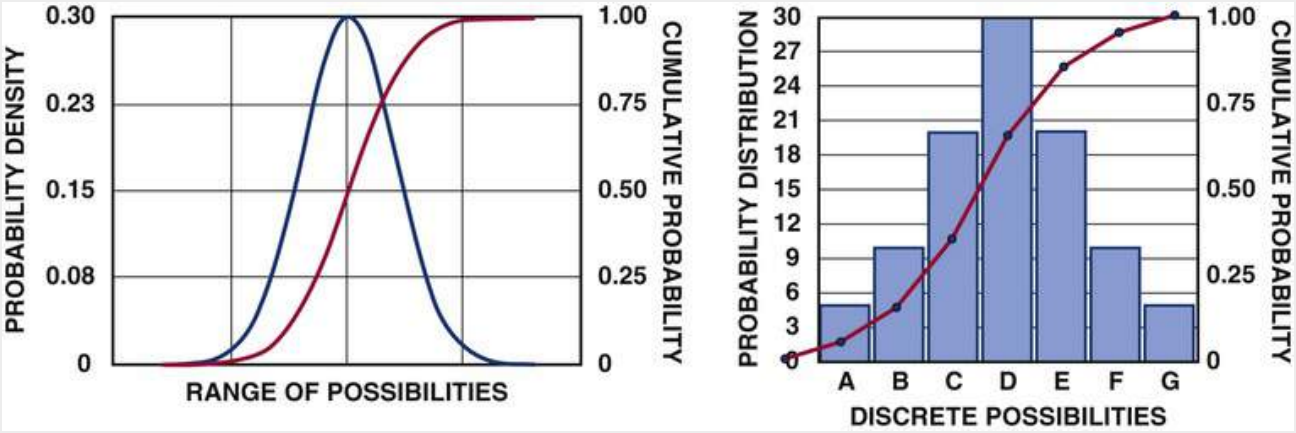

FIGURE 3.1 **Left panel** shows a probability density curve. The *blue curve* shows the probability of an event (left *y* axis), across a range of possibilities (*x* axis). **Right panel** shows a probability distribution. The *blue columns* show the probabilities (left *y* axis) of a variety of discrete possibilities (*x* axis). In both panels the cumulative probability across the range of possibilities (*x* axis) is shown by the *red curves* (right *y* axis).

To test a diagnostic hypothesis, we use *conditional probability*, which is the probability that something will happen, on the condition that something else happened. Conditional probability can tell us the probability of a diagnosis, on the condition of some new information, such as a positive test result. Bayesian reasoning enables us to form a probability estimate and revise that estimate based on new information using conditional probability. For example, a clinician might ask, What is the probability of coronary artery disease in my patient, given a positive stress echocardiogram? What is the probability of pulmonary embolus, given a negative D-dimer test? What is the probability of an acute coronary syndrome, given an abnormal troponin test? The post-test probability depends on a prior estimate of the probability for that particular patient, combined with the strength of the test result. Probability theory helps us understand the question and calculate the answer.

Bayesian reasoning requires both a prior estimate of probability and an estimate of the strength of a test result. Prior estimates can come from experience or published data on the prevalence of a disease. A classic paper by Diamond and Forrester,[17] for example, provides estimates of the prevalence of coronary artery disease in patients depending on age, gender, and symptom features. This type of observational research can be used to provide us with the prior probabilities needed for bayesian reasoning.

Understanding probability is essential to interpreting laboratory tests. A laboratory test might be measured in a population of presumably normal individuals to determine a distribution and to define a normal range, as shown in the probability density curve in the left panel of **Fig. 3.2**. A normal range is usually defined as the inner 95% cumulative probability, and the abnormal range is defined as values falling outside the normal range.

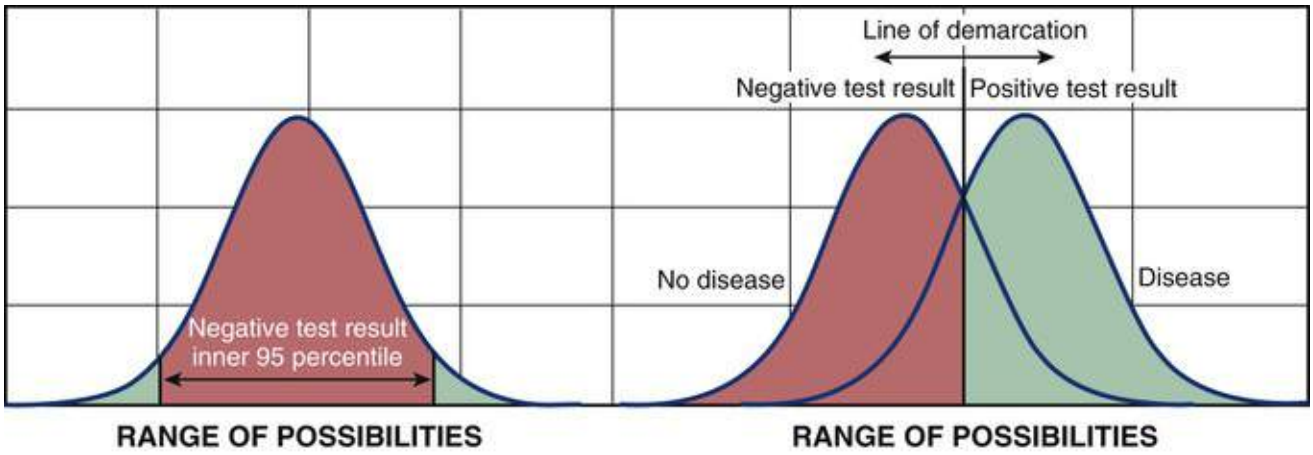

FIGURE 3.2 **Left panel** shows how the normal range of a test result is defined as the inner 95th percentile of a presumably normal population. **Right panel** shows how a normal and abnormal test result is defined by the line of demarcation between distributions of normal and abnormal test subjects, as defined by another, independent "gold standard" test.

Another way of defining a test result is by measuring the test result in a group of individuals who are defined as "normal" and "abnormal" by another, independent "gold standard" test, as shown in the right panel of **Fig. 3.2**. Typically, patients with and without disease will have test results that are distributed as bell-shaped curves. We can draw a line of demarcation to define how a new test would separate patients with positive and negative test results. Because there is overlap in individuals with and without disease, there will be false-positive and false-negative test results, as shown.

Understanding how to use clinical testing is essential to good decision making. The utility of a test result depends in part on the operating characteristics of a test: the *sensitivity* and *specificity*. These are *rates*, meaning the sensitivity and specificity are proportions with different units for the numerator and denominator. The terms *true positive rate* (TPR) for sensitivity and *true negative rate* (TNR) for specificity are alternative labels.

Patients with and without disease are shown separately in **Fig. 3.3** to show the cumulative probabilities of a truly positive result (sensitivity, or TPR) on the right and of a truly negative result (specificity, or TNR) on the left. Sensitivity and specificity are usually shown in a 2 × 2 table, but showing the TPR and TNR in **Fig. 3.3** demonstrates how these rates are variable, depending on the location of the line of demarcation between positive and negative test results.

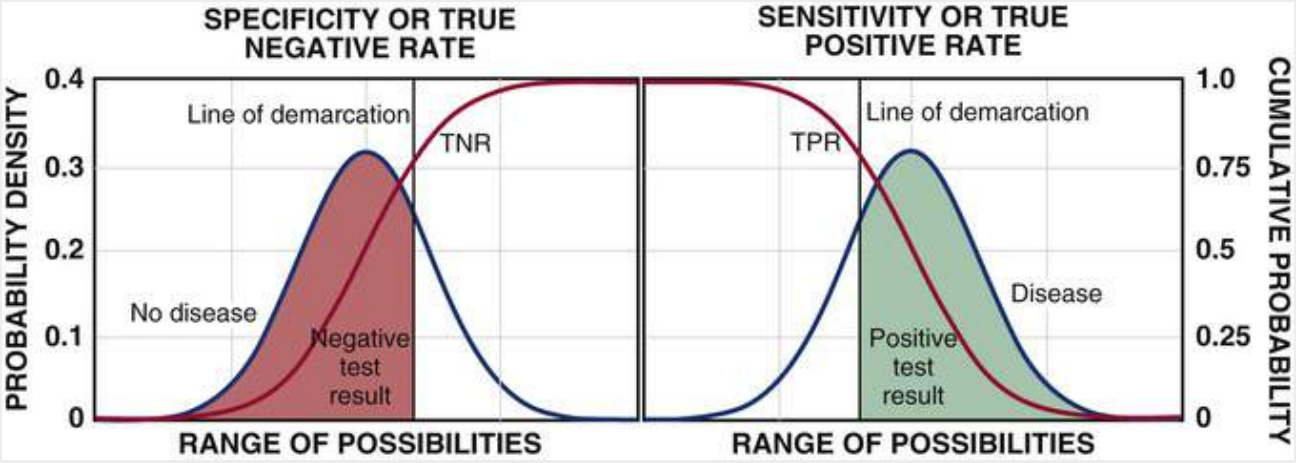

FIGURE 3.3 Distributions of normal and abnormal test subjects are shown separately to demonstrate that the true negative rate (*TNR*, or specificity) is the cumulative probability of a negative test result *(red curve)* in a distribution of subjects without disease *(blue curve,* **left panel***)*, and that the true positive rate (*TPR*, or sensitivity) is the cumulative probability of a positive test result *(red curve)* in a distribution of subjects with disease *(blue curve,* **right panel***)*, depending on the location of the line of demarcation.

The complementary probability of the TNR is the *false-positive rate* (FPR), as shown in the top panel of **Fig. 3.4**. If we create a new graph by plotting the TPR (sensitivity) of a test on the *y* axis and the FPR (1 − specificity) on the *x* axis, we can create a plot called a *receiver operating characteristic* (ROC) *curve*, as shown in the bottom panel of **Fig. 3.4**. ROC curves are useful for determining the optimal cutoff point for the line of demarcation of a test.

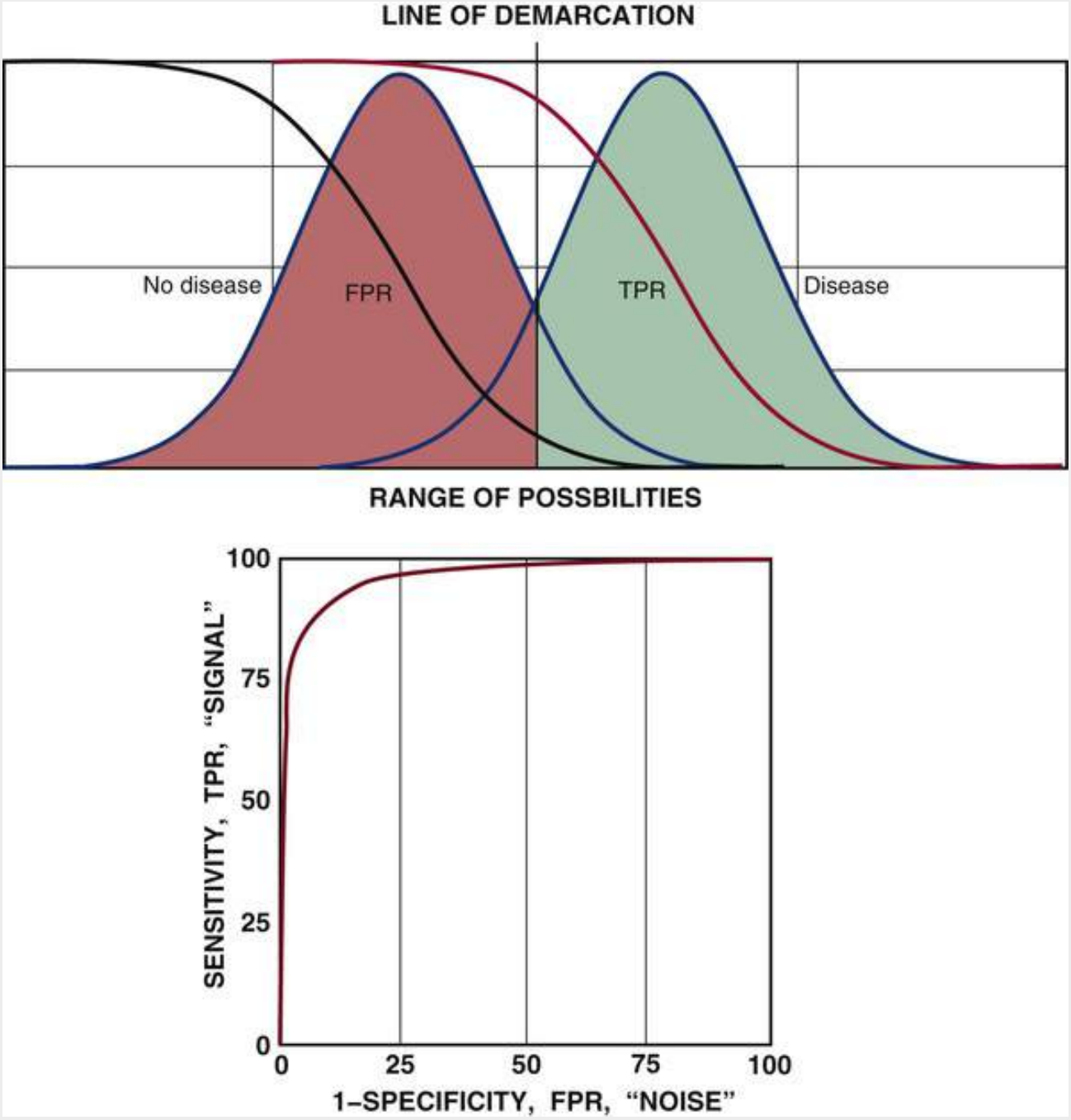

FIGURE 3.4 **Top panel** shows distributions of patients without and with disease *(blue curves)* along with the true positive rate (*TPR,* or sensitivity, *red curve*) and the false positive rate (*FPR,* or [1 − specificity], *black curve*). **Bottom panel** shows the TPR (sensitivity, or "the signal") on the *y* axis plotted against the FPR (1 − specificity, or "the noise") on the *x* axis, across the range of possibilities, depending on the location of the line of demarcation.

The denominators of sensitivity and specificity are patients with disease and patients with no disease, respectively. In clinical practice, when test results are reported as positive or negative, however, the results are reported using terms with different denominators. A clinician wants to know the probability that a positive test result is truly positive, or the *positive predictive value* (PPV), and also the probability of disease given a negative test result, which is 1 minus the *negative predictive value* (NPV). When changing from sensitivity and specificity to the PPV and NPV, the denominators of these rates change, making it difficult for a clinician to estimate these probabilities intuitively. In addition, the PPV and NPV depend not only on the sensitivity and specificity of the test, but also on the prevalence of the target condition in a population of test subjects. The difficulty of keeping track of denominators can be alleviated by using likelihood ratios rather than sensitivity and specificity.

*It should be noted that sensitivity and specificity can change if the spectrum of test subjects that defined them is different from the spectrum of patients for whom the test is used.[2] If the operating characteristics of the test are defined in a narrowly defined population (**Fig. 3.5, left panel**), but the test is used in a broadly defined population and the line of demarcation remains fixed (**Fig. 3.5, right panel**), the specificity, or TNR, will decrease. This frequently occurs with tests such as troponin testing, where the clinical sensitivity and specificity of the test are defined in a research setting, but the test is used indiscriminately in practice. When used as a general screening test in a broadly defined population, the width of the distribution of the individuals with no disease widens, yet the line of demarcation remains fixed, which decreases the TNR, as shown. This issue has also been shown in genetic testing.[18]*

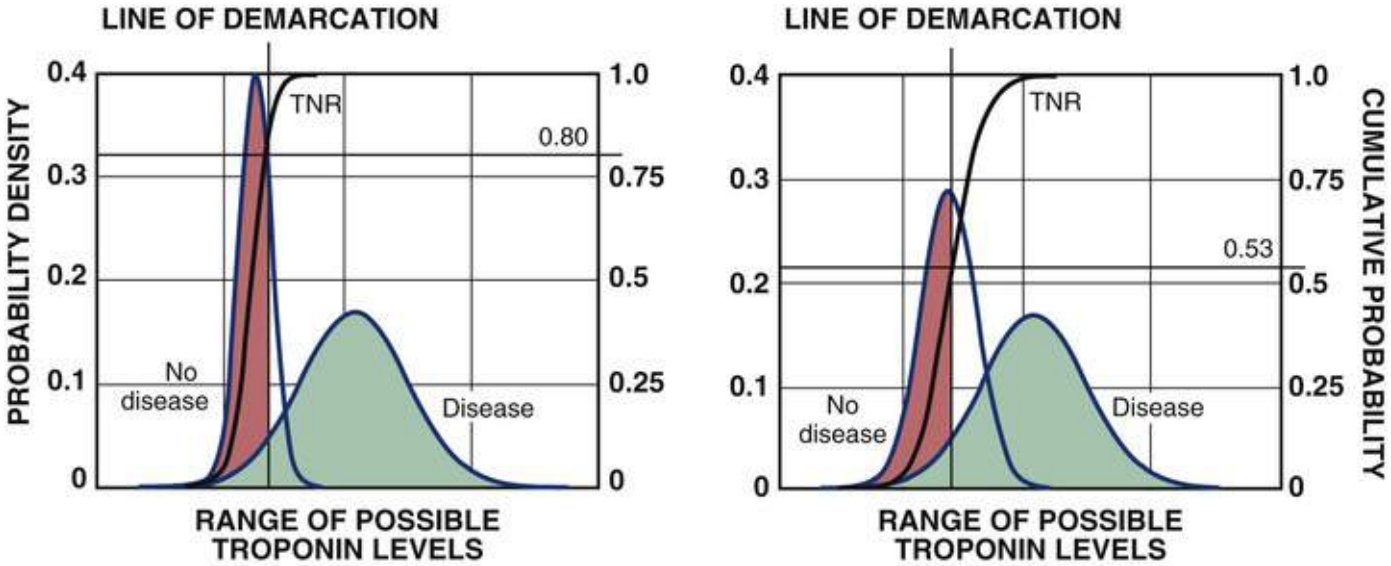

FIGURE 3.5 Distributions of patients without and with disease are shown by the *blue curves.* True negative test results for troponin levels are shown in *red,* and true positive results are shown in *green.* The true negative rates (*TNR,* or specificity) are shown by the *black* cumulative probability curves. **Left panel** shows the results when the test is ordered on a narrowly defined population of test subjects, and **right panel** shows the results when the test is ordered on a broadly defined population of test subjects, resulting in spectrum bias and a marked decrease in specificity of the test (80% to 53% in this example).

In practice, clinicians usually do not calculate bayesian probabilities. Clinicians, as with decision makers in general, use a heuristic that psychologists call "anchoring and adjusting."[3,9] Clinicians estimate a pretest probability (the anchor) and estimate the post-test probability by adjusting the anchor. For a patient with chest pain, for example, the anchor would be an estimate of the pretest probability of coronary artery disease, which would be intuitively adjusted on the basis of new information, such as a stress test result, to estimate a post-test probability. This is an expedient method for intuitively estimating conditional probability. There are two potential problems when using this heuristic. One fallacy, called "anchoring," is when the decision maker becomes too anchored on the pretest probability estimate and does not adequately adjust in estimating the post-test probability. The second fallacy is called "base-rate neglect," when the decision maker overly responds to the new information to estimate a post-test probability, without regard for the pretest probability. For example, troponin tests may be positive because of renal failure or sepsis in patients with a low pretest probability of acute thrombotic myocardial infarction. Taking the test result at face value and initiating therapy (e.g., antithrombotic drugs) in such a patient would be an example of base-rate neglect. Awareness of this heuristic and its

pitfalls can help clinicians avoid this common reasoning error.

Likelihood ratios are useful for bayesian reasoning.[19,20] Their advantage is that, unlike sensitivity and specificity, likelihood ratios are dimensionless numbers, so the need to keep track of the numerator and denominator is alleviated. Likelihood ratios give a measure of the persuasiveness of a positive and negative test result and can be used intuitively or used to calculate post-test odds.

A *likelihood ratio* is defined as the percentage of diseased patients with a given test result divided by the percentage of nondiseased patients with that same test result. Thus a *positive* likelihood ratio is the percentage of diseased patients with a positive test result divided by the percentage of nondiseased patients with a positive test result [TPR/FPR, or sensitivity/(1 − specificity)]. A *negative* likelihood ratio is the percentage of diseased patients with a negative test result divided by the percentage of nondiseased patients with a negative test result [FNR/TNR, or (1 − sensitivity)/specificity]. It is easy to calculate the positive and negative likelihood ratios from sensitivity and specificity. Once calculated, these numbers can be used to multiply the pretest odds to calculate the post-test odds of a diagnosis. They are multipliers, so a higher positive likelihood ratio and a lower negative likelihood ratio (which is a fraction) have stronger multiplying effects. A likelihood ratio that is close to 1 is weak because it would have very weak multiplying effect, meaning it has minimal effect on the pretest assessment.

Some tests are asymmetric, meaning that their positive or negative likelihood ratio is stronger. For example, congestion on a chest x-ray film has a very strong positive likelihood ratio of 13.5 and a relatively weak negative likelihood ratio of 0.48.[20] This reflects that the chest radiograph is highly specific but not very sensitive for heart failure. In other words, congestive findings on a chest radiograph are highly suggestive of heart failure, whereas their absence would not be reassuring about lack of heart failure. Tests that are highly specific are better for ruling in a diagnosis, and this can be remembered using the mnemonic “SpPin” (highly specific tests, if positive, are good for ruling in). On the other hand, a D-dimer for a pulmonary embolus has a very strong negative likelihood ratio of 0.09 and a modest positive likelihood ratio of 1.7.[20] This reflects that a D-dimer is highly sensitive but not very specific for pulmonary embolus. Tests that are highly sensitive are better for ruling out a diagnosis, and this can be remembered using the mnemonic “SnNout” (highly sensitive tests, if negative, are good for ruling out).[19]

The likelihood ratios, however, are only as useful and precise as the sensitivity and specificity that are used to calculate them. They give an approximate quantitative estimate of the strength of new information that provides a mechanism for calibrating intuitive probability estimates. When used with odds, likelihood ratios provide a way to calculate the conditional probabilities that are used for bayesian reasoning. Proceeding through this calculation demonstrates the conceptual framework for reasoning through iterative hypothesis testing.

Test-Ordering Strategies

Clinical reasoning should guide not only test interpretation, but also test ordering. Tests that are ordered for good reasons are more conclusive, and tests that are ordered indiscriminately can cause clinicians to arrive at the wrong conclusions. Ideally, a test should be used to validate or reject an *articulated hypothesis*—a plausible conjecture that is generated by a patient's condition.

To aid with test selection and avoid overtesting, the American College of Cardiology (ACC) and other

organizations have developed appropriate-use criteria to guide clinicians' decisions about ordering cardiac tests.[21] This effort is driven by both the need to avoid excessive false-positive test results and the need to contain the costs of medical care. The goal of appropriate-use guidelines is to reduce overuse errors and maximize the value of diagnostic testing and procedures. The general principle of any test-ordering strategy is that a plausible hypothesis (a provisional diagnosis) should be formulated first, followed by testing. The appropriate-use criteria are designed to avoid testing when the results are unlikely to improve patient care or outcomes.

Predicting Risk

Recent ACC/American Heart Association (AHA) guidelines have promoted the provision of preventive treatments according to an individual's risk of adverse outcomes.[22] These guideline recommendations emphasize the need to consider categories based on estimates of risk and prognosis, rather than diagnostic labels. *Risk* is another word for probability, and when used in this context, risk takes on a meaning of *propensity*, which is probability that has a modifiable tendency or disposition. It is important for clinicians to understand how risk is calculated from long-term observations from pooled cohorts of test subjects, in order to understand the strengths and limitations of these risk calculations. After calculating the risk, the challenge for clinicians is communicating risk to patients in an understandable way. Investigators have provided pictograms that can communicate risk and risk reduction to facilitate a discussion regarding long-term treatment options to diminish risk and to compare the degree of risk reduction with potential side effects and costs of treatment. Some new tools aim to put these risk models into use at the point of care. Since clinicians vary in their use of qualitative terms, such as “high risk,” there is a need to provide clear and understandable quantitative estimates.

Therapeutic Decisions

A preventive or therapeutic decision is a structured choice. For some situations, it is a simple and easy decision, such as deciding to give a diuretic to a patient with acute congestive heart failure. In this case the stakes are not high, the preference of the patient is clear, and the decision is straightforward. In other cases there is a difficult choice between therapeutic options. An elderly patient with moderate to severe mitral regurgitation and comorbid conditions presents a difficult choice based on estimated probabilities of the natural history of the disorder, versus the surgical risks and prospects for an improved outcome with a surgical intervention. These decisions require medical knowledge and a balanced sense of risks and benefits, as well as knowledge of the patient's preferences, to make optimal therapeutic decisions.

The therapeutic effect of a drug is ideally determined by a randomized controlled trial (RCT). Trial results are frequently reported as *relative risk reduction*. Of note, the relative benefit (or risk) of an intervention is often expressed as a relative risk or odds ratio. *Risk* is the probability of an event, and *odds* is the probability an event will occur against the probability that it will not occur. A probability of 25% (1 in 4) represents odds of 1 : 3 or 1/3. The *risk ratio* expresses the relative probability that an event will occur when two groups are compared. The *odds ratio* expresses the odds of the event in one group compared with another.

Despite its widespread use, the odds ratio is less helpful than relative risk in clinical decision making. The expressions are similar when baseline event rates are low (<5%), but deviate with higher risk and larger treatment effects. The odds ratio can express associations but, unlike the risk ratio, cannot express the relative size of the treatment effect; if clinicians assume odds to be equivalent to risk, it may lead to

overestimates of the treatment effect when the outcome is common. The odds ratio is often used in clinical research because of its mathematical properties and its utility for identifying associations in certain situations, but clinicians need to know its limitations for estimates of treatment effect.

Clinical trials report the average risk of an outcome for patients in a treatment group and in a comparison group. There may be heterogeneity of the treatment effect, in which some patients may receive a marked benefit and others receive no benefit at all. Subgroup analysis and tests for interaction can provide hints, but usually heterogeneity of treatment effect is not readily apparent, creating a challenge for clinicians trying to personalize treatment decisions. In a key example of heterogeneity, fibrinolytic therapy was effective in the treatment of suspected acute myocardial infarction (AMI) and subgroup analyses revealed the benefit to be substantial in patients with ST elevation but not in those without it.[23] The challenge is that subgroup analyses introduce the possibility that associations have occurred only by chance. In the Second International Study of Infarct Survival (ISIS-2), the authors provided perspective on subgroup analyses by demonstrating that patients born under the astrological signs of Gemini or Libra were significantly less likely to benefit from fibrinolytic therapy. Thus, subgroup analyses are capable of producing important insights, but must be interpreted with caution.[24]

Risk Stratification

A weakness of *relative benefit* estimates is that they do not convey information about what is achieved for patients at varying levels of risk. A small relative reduction in risk may be meaningful for a high-risk patient, whereas a large relative reduction may be inconsequential for a very-low-risk patient. *Absolute risk reduction,* the difference between two rates, varies with the risk of an individual patient. For example, a risk ratio of 2.0 does not distinguish between baseline risks of 80% and 40% and between 0.08%, and 0.04%. In one case, the absolute difference is 50% (5000 per 10,000), and in the other, 0.05% (5 per 10,000). In one case, 1 person out of 2 benefits, and in the other, 1 out of 2000 benefits. Unfortunately, *absolute benefit* is not emphasized adequately in many articles.[25]

Risk stratification is critically important for calculating the absolute risk reduction. In recent years, many tools have been developed to assist in the rapid assessment of patients, with variable uncertainty about their comparative effectiveness. For example, the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry–Get with the Guidelines (GWTG) model includes eight variables and can differentiate risk from 0.4% to 50%.[26]

In evaluating risk stratification studies, it is important to consider whether the score or approach has been validated in populations similar to the patients to whom it is applied in practice. The predictors should have been collected independently of knowledge of the outcome. The outcome and time frame should be appropriate for clinical decisions. The value of the stratification should also be clear. Improving precision in risk estimates without consequence is like ordering tests that have no implications for treatment. On the other hand, risk stratification can assist in calculation of absolute benefit and put the balance of risks and benefits of an intervention in proper perspective.

Several studies have shown a risk-treatment paradox in which the higher-risk patients are least likely to receive interventions that are expected to provide a benefit.[27,28] This pattern is paradoxical because the high-risk patients would be expected to have the most to gain from an intervention that reduces risk, assuming that the relative reduction in risk is constant across groups defined by their baseline risk. The source of the paradox is not known, although some have suggested that it is related to an aversion to the treatment of patients with a limited functional status, or a concern for greater degree of harm from the same therapy.[29] Another possibility is that concerns about the harm associated with an intervention are

increased in the highest-risk patients.

Cardiovascular drugs and procedures are often double-edged swords, having both benefit and harm. Also, patients may have strong preferences about potential benefit and harm. For example, a patient may have a strong fear of a side effect such as a cerebrovascular accident (stroke) that may overwhelm other considerations about a treatment decision. It is important to engage patients and families in a discussion to explain the considerations that go into therapeutic decisions, particularly for nuanced decisions about treatments that have substantial risks in addition to potential benefits.

Number Needed to Treat

Absolute risk reduction is better than relative risk reduction for estimating a treatment effect. The inverse of the absolute risk reduction, a term called *number needed to treat* (NNT), is even more intuitive.[19]

Consider a trial with a combined event rate of 10% in the treatment group and a 15% risk in the control group, giving an absolute risk reduction of 5%. This means that 5 events are avoided for every 100 patients in the treatment group. The reciprocal of this relationship indicates that there would be 100 patients treated for every 5 events avoided. By dividing 100 by 5, which reduces the denominator to 1, we can say that there would be 20 patients treated per 1 event avoided. Thus the NNT is 20. For NNT, the smaller the number is, the better the result.

NNT and absolute risk reduction depend on both the relative risk reduction and the baseline risk. For conditions with a high baseline risk, the NNT can become very small (desirable). As an extreme example, for a patient with ventricular fibrillation, the baseline risk of dying without defibrillation is 100%, making the NNT for defibrillation (if always effective) equal to 1.

Primary prevention with statin drugs has a relative risk reduction of about 20% over the several-year course of a typical prevention trial.[30] The absolute risk reduction and NNT depend on the baseline risk, which varies depending on a number of factors. At a baseline risk of 7.5%, the absolute risk reduction would be 1.5% and the NNT would be 67, a fairly high number, which suggests marginal benefit at this level of baseline risk.

NNT is a useful intuitive tool for comparing the efficacy of various treatment strategies. NNT is also a useful way to summarize the findings of a clinical trial in a single declarative sentence. For example, the Beta-Blocker Heart Attack Trial (BHAT) had an NNT of 34, meaning you would need to treat 34 patients with AMI with a beta-blocking agent for 25 months to prevent one death.[31] The Survival and Ventricular Enlargement (SAVE) trial had an NNT of 20, meaning you would need to treat 20 patients with heart failure and an ejection fraction of ≤40% with an angiotensin-converting enzyme (ACE) inhibitor for 42 months to prevent one death.[32] With NNT, a single sentence can provide the trial name, the magnitude of the treatment effect, the trial's entry criteria, the study drug, the duration of the trial, and the outcome measure. NNTs of 34 and 20 suggest that these treatments are strongly recommended, and that not treating patients with these drugs, without adequate justification, could be considered an error.

NNT is also a very personal notion of the probability of a treatment effect. Imagine bringing 20 untreated patients with congestive heart failure and an ejection fraction of ≤40% into a room and saying, “If I start all of you on an ACE inhibitor, over the next 42 months, I will save the life of one of you.” Capturing the essence of a treatment effect with NNT is a useful way to intuitively convey the impact of a treatment effect. This knowledge, packaged in a way that is more intuitive, can make it easier for us to combine this medical knowledge with the preferences and values of individual patients to make the best therapeutic decisions.

Nevertheless, there are limitations to NNT. NNT is an index of an average treatment effect over time

and does not provide information about whether the treatment effect is immediate, delayed, or highly variable. NNT does not provide information about whether there is meaningful heterogeneity in effect among different subgroups, because the NNT often is calculated based on an assumption of a uniform effect of the therapy, with the NNT just varying based on the baseline risk.

Changing Clinical Practice Based on New Findings

Science is a quantitative discipline that uses numbers to measure, analyze, and explain nature. *Evidence-based medicine* has been defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[33] To practice evidence-based medicine, clinicians must constantly monitor for new research findings; this vigilance must be accompanied by a basic knowledge of statistics to make proper inferences from clinical research.

When using statistics to compare two groups, the standard method is to assume that there is no difference between the two groups, the so-called null hypothesis. The trial results are reported, along with a *P* value, which is the probability of deriving the difference reported in the trial, or a more extreme difference, given the assumption that the null hypothesis is true (i.e., there is no real difference between the groups).[34] When a trial is designed, the investigators estimate the sample sizes that are required to avoid (1) claiming that there is a difference between treatment groups when there really is no difference (a Type I error, or alpha error) or (2) claiming that there is no difference between treatment groups when there really is a difference (a Type II error, or beta error). Similar to a clinical test (e.g., stress test) that can have false-positive and false-negative test results, clinical trials can have false-positive results (alpha errors) and false-negative results (beta errors). A trial with adequate sample size and rigorous statistical methods should allow investigators to avoid these errors.

When a trial is designed, the alpha level is usually set at 0.05. If the *P* value of the observed data is less than 0.05, one can conclude that a very improbable event occurred, a less than 1 in 20 event, assuming the null hypothesis is valid. According to the "frequentist" notion of statistics, one imagines that repeating a trial many times would create a distribution of possible trial results. The *P* value tells us where the observed results of a particular trial would lie in that imaginary distribution of trial results.

Since the *P* value is so commonly used in clinical research, clinicians need to be aware of several key issues. First, the threshold of 0.05 for statistical significance is arbitrary. A *P* value of 0.04 implies that the data could occur 4% of the time if the null hypothesis is true, and a *P* value of 0.06 would suggest the data would occur 6% of the time. Is the difference between 6% and 4% enough to reject the null hypothesis in one case and accept it in another? Clinicians should understand that *P* values are continuous values and are just one piece of information needed to assess a trial. Second, *P* values do not inform clinical importance. A large study sample can produce a small *P* value despite a clinically inconsequential difference between groups. Clinicians need to examine the size of the effects in addition to the statistical tests of whether the results could have occurred by chance.

Endpoints

In evaluating evidence, clinicians should be particularly attuned to the outcomes that are assessed. Ideally,

interventions are assessed for their effect on a patient's quality or quantity of life. Many studies employ *surrogate outcomes*, measures that are more distally related to the patient experience but might be related to the likelihood that a patient's quality or quantity of life will be affected. These surrogate outcomes often reflect information about a patient's biology, and in epidemiologic studies, these outcomes may have prognostic value. However, it is not possible to know that an intervention that modifies a surrogate outcome has the expected effect on patients. There are many examples in medicine of changes in surrogate measures that did not translate into benefits for patients.

Noninferiority Trials

Most RCTs are designed to show the superiority of a treatment over placebo. However, some conditions already have treatments with proven benefit, making it unethical to design a trial that compares a new treatment with placebo. For example, for chronic atrial fibrillation, it was not possible to test newer oral anticoagulant drugs against a placebo arm that would have withheld the proven benefit of warfarin. For these situations, investigators use a noninferiority trial. The premise is to show that a given treatment is at least no worse than the standard of care by more than a predefined investigator-selected margin (the treatment could be slightly worse, or even be superior for efficacy). However, because the new treatment has other ancillary advantages (e.g., less side effects, better costs or tolerability), it could become a reasonable alternative to the previous standard of care. This trial design requires making assumptions about the margin of decreased efficacy that would be considered acceptable before considering using a new treatment rather than an established treatment with known efficacy. Noninferiority trials are also subject to several other biases that are not seen with typical superiority trials.

Observational Research

There are other situations in which an RCT is impossible, and observational studies such as case-control studies or longitudinal cohort studies are required. RCTs have the advantage of a controlled experiment that eliminates potential biases but have the limitation of narrowly defining a study population, which may affect generalizability. Observational studies have the advantage of observing large groups of unselected individuals in the real-world setting, but have the disadvantage of potentially unrecognized and unmeasured sources of bias that could produce misleading study results. Expert opinion and clinical judgment often require evaluation of a variety of evidence from multiple types of clinical research studies to determine the best clinical practice.

Shared Decision Making

Clinical decisions are not the sole domain of physicians. The principle of autonomy maintains that patients retain control over their bodies and must consent to undergo interventions, except in rare circumstances. Informed consent is the cornerstone of this concept (**see Chapter 2**). Unfortunately, there is little consensus about how best to involve patients actively in decision making. Nevertheless, given the need to align goals of therapy with the patient's preferences and values, it is important to engage them as effectively as possible. This approach is most appropriate for major decisions, those with intermediate or low certainty, and those that are not emergent.

There are many aspects of communicating risks and benefits. First, this information takes many forms. The dimensions of risk and benefit include their identity, permanence, timing, probability, and value to an

individual patient.[35] All these should be considered in decision making. Unfortunately, there is relatively little evidence to guide physicians about how best to convey risks to patients.[36]

It is known that patients do not always understand benefit and risk well. For example, in a study of patients who gave consent for elective routine percutaneous coronary intervention, an intervention that does not improve survival or prevent AMI in this context, 75% thought it would prevent an AMI and 71% believed it would improve survival.[37] Moreover, only 46% could identify at least one possible complication. Among this group, 67% stated that they should be involved at least equally with the physician in making decisions. Other studies have also found that patients often have unrealistic expectations of benefit.[38] These deficiencies in patient understanding need to be addressed for shared decision making to occur.

The manner in which information is presented may influence patients. As with physicians, patients are also susceptible to framing effects.[39] Patients tend to be more likely to choose a therapy that is presented as having an advantage over an alternative in relative rather than absolute terms. The relative effect is almost always much greater than the absolute change. Patients may also be influenced by the order in which information is provided.

Some techniques have been proposed to help clinicians convey risk.[40] First, clinicians should avoid descriptive terms because these may not have a consistent meaning to patients. Terms such as “low risk” may be difficult for people to interpret. If clinicians express risk as ratios, they should use a consistent denominator (e.g., 40 out of 1000 and 5 out of 1000 instead of 1 in 25 and 1 in 200). Clinicians should offer multiple perspectives, revealing multiple ways of thinking about risk. They should use absolute numbers and natural frequencies (e.g., 1 out of 20), not relative risks or percentages. Visual aids are useful, if available, since poor numeracy or literacy skills may be a barrier for many patients. Many patients do not understand risk communication formats.[41] In addition, clinicians should recognize that information and data are not the same, and it is incumbent on the clinician to communicate health information that is meaningful to the patient.

Shared decision making can be understood as having five phases: assess, advise, agree, assist, and arrange, as follows:

1. The clinician must *assess* the patient.
2. The clinician should *advise* the patient of the options, with their benefits and risks.
3. The clinician and patient should *agree* on a plan that is aligned with the patient's preferences and values.
4. The clinician should then *assist* the patient in implementing the plan.
5. The patient and clinician *arrange* follow-up.

Monitoring the Quality of Clinical Decisions

Delivering the right care to the right patient at the right time every time requires good judgment. Learning the basic competencies of good judgment and step-by-step methods of clinical reasoning can help practitioners monitor the quality of their decisions. Knowledge about clinical reasoning is a structural attribute that can lead to more reliable processes and better clinical outcomes. Awareness of the logic, probability theory, and cognitive psychology of clinical reasoning can provide a theoretical foundation for better clinical practice.

Self-monitoring to self-diagnose errors and biases is important, but developing good habits that

systematically prevent cognitive errors may be a more effective strategy. Cognitive science provides justification for many of the good habits that are part of practice, such as consistently performing a standardized history and physical examination and a conscious habit of listing a differential diagnosis. Cognitive psychologists emphasize that measurement and feedback are a crucial process for the development of expert intuition, which is so often necessary for clinical decisions.

System 1 and System 2 Thinking

Cognitive psychologists describe two general thinking modes that people employ to make decisions.[9] *System 1 thinking* is highly intuitive and fast, but prone to jumping to conclusions. *System 2 thinking* is analytic and logical, but slow, effortful, and has difficulty with uncertainty. Used together, System 2 thinking provides a double-check for System 1 thinking, and System 1 thinking provides a work-around when System 2 thinking is constrained by uncertainty. Cardiology decisions require both thinking modes, and expert clinicians are able to use a balance of intuition and critical thinking to make optimal decisions. Calibrating intuitive thinking and organizing thinking by thoughtfully monitoring decisions ("meta-cognition") are key to good clinical practice.

Fallacies

Some psychologists describe three general types of fallacies: hasty judgments, biased judgments, and distorted probability estimates.[9] *Hasty judgments* occur when System 1 thinking is unmonitored. For example, premature closure of a diagnostic exercise, without the use of a differential diagnosis, or becoming anchored on a diagnosis can lead to a misdiagnosis. *Biased judgments* occur when unconscious thoughts influence clinicians' ideas, emotions, and actions. This can take the form of priming, stereotyping, overconfidence, risk aversion, or dread. Emotions can have a "halo effect," influencing clinicians' thinking in imperceptible ways. Exaggerated fear of malpractice, financial incentives, and conflict of interest can adversely affect their decisions. In *distorted probability estimates*, decision makers tend to overweight the probabilities of events or propositions at the extremes. At one end, they can develop an illusion of certainty, which creates certainty about something that, objectively, is not certain at all. At the other extreme is the "possibility effect," which causes them to think that highly improbable events or propositions are quite probable. Knowledge of these fallacies can help clinicians monitor the quality of their clinical reasoning.

Conclusion

Clinical reasoning can be learned and continuously improved through deliberate practice. Logic, probability theory, and cognitive science can provide a framework for good clinical reasoning. The ability to read, understand, and critique the literature is also essential. Knowledge of the components of clinical reasoning is crucial for clinical practice, for team-based care, and for shared decision making. The ability to reason and the ability to use reasoning to stay current and monitor one's performance are the essence of professionalism. Integrating scientific knowledge and calibrated intuition with a patient's personal preferences and values can provide the highest quality of care for our patients.

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4

Measuring and Improving Quality of Care

Relevance to Cardiovascular Clinical Practice

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The quality of health care is important for all stakeholders; the primary perspective of this chapter is that of cardiovascular clinicians. Our objectives are to provide cardiovascular clinicians with the definition of quality of care and the relevance of quality measurement and improvement in current cardiovascular practice. We focus on measures of health care quality, uses of these measures, and approaches to improving quality of care.

Defining Quality of Care

Quality of care is generally defined as the extent to which health care delivery optimizes the outcomes of care. The U.S. Institute of Medicine (IOM) has more specifically defined quality of care as “the degree to which health care systems, services, and supplies for individuals and populations increase the likelihood for desired health outcomes in a manner consistent with current professional knowledge” (see Classic

References, *Crossing the Quality Chasm*). Key outcomes of care include survival, patient health status (symptom burden, functional status, and health-related quality of life), morbidity (e.g., acute myocardial infarction [MI] or heart failure hospitalization), patient experience (e.g., satisfaction), and cost-effectiveness.

The IOM proposed six domains of quality: effectiveness, safety, equity, timeliness, efficiency, and patient-centeredness (**Table 4.1**). Quality of care can thus be conceptualized as the extent to which these domains are optimized. Accordingly, quality measures should focus on at least one of these six domains of quality or directly measure outcomes of care. *Quality improvement* (QI) is the action undertaken to improve one or more of these six domains to improve health outcomes.

TABLE 4.1

U.S. Institute of Medicine (IOM) Domains of Highest-Quality Health Care

QUALITY DOMAIN	BRIEF DEFINITION
Effective	Providing services based on scientific knowledge to all who could benefit and refraining from providing services to those not likely to benefit (avoiding underuse and misuse, respectively).
Safe	Avoiding harm to patients from the care that is intended to help them.
Equitable	Providing care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location, and socioeconomic status.
Timely	Reducing waits and sometimes harmful delays for both those who receive care and those who give care.
Efficient	Avoiding waste, including the waste of resources and patient time, as well as waste of ideas and energy.
Patient centered	Providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions. Patient-centered care attends to patients' physical and emotional needs, maintaining or improving their quality of life, and gives patients the opportunity to be the locus of control in decision making.

From IOM Committee on Quality Health Care in America. Crossing the Quality Chasm: a New Health System for the 21st Century. Washington, DC: National Academy Press; 2001.

Unfortunately, despite tremendous therapeutic advances in cardiovascular medicine over the last 50 years and the development of evidence-based guidelines that define optimal care, well-recognized deficiencies in health care delivery are manifest, and suboptimal quality and outcomes of care persist in practice. Despite spending more per capita on health care than any other country, the United States does not achieve commensurately high scores on most metrics of quality of care or health outcomes.[1] Further, marked geographic variation in health care spending within the United States does not correlate consistently with health outcomes. For example, significant variation in the use of cardiovascular tests and procedures that is not explained by case-mix does not clearly generate better patient outcomes.[2]

Numerous studies have documented unexplained variation in care delivery that reflect *underuse* of guideline-indicated care, *overuse* of therapies not likely to result in benefits, and *misuse*, including avoidable complications and medical errors, all of which contribute to suboptimal outcomes. Gaps in quality can result from deficiencies in any of the IOM domains of high-quality health care (**see Table 4.1**). For example, effective therapies may not be prescribed for eligible patients (e.g., statin therapy for patient with recent MI). Providers and health care systems may fail to minimize exposure of patients to unnecessary risk (e.g., prescribing drugs that create a high risk of adverse drug-drug interaction). Clinicians may employ ineffective therapies (e.g., primary prevention implantable cardioverter-defibrillator placement in patient with mild left ventricular systolic dysfunction) or may use resource-intensive care for marginal benefit (e.g., routine intra-aortic balloon pump use for high-risk percutaneous coronary intervention [PCI]). Care delivery may be delayed or may be delivered differentially based on patient age, sex, race/ethnicity, or insurance status without adequate clinical justification. Patients may not be optimally engaged in their care, manifested as lower adherence to recommended therapies and lifestyle behaviors.

Deficiencies in any of these areas contribute to observed variation in quality of care and patient

outcomes and generate unnecessary costs. According to the IOM, underuse, overuse, and misuse of medical therapies are estimated to result in excess annual U.S. health care costs of $55 billion, $210 billion, and $130 billion, respectively.[3] Rapidly rising health care costs and the knowledge that substantial proportions of these costs are unnecessary have propelled health care reform, in which measurement and reporting of quality of care are fundamental.

Relevance of Quality of Care in Cardiovascular Practice

Cardiovascular clinicians should play a central role in how quality is measured and how health systems are modified to optimize quality and patient outcomes. Too often, clinicians perceive quality of care as a problem of clinical documentation or "working to the test" of external mandates such as payer requirements. These views are often reinforced in the current health care environment, in which quality measurement and reporting are often placed in a "regulatory" context and are often executed separately from clinician-patient interactions and clinical decision-making. The interaction of patients and clinicians is central to high-quality care, given the impact of clinical decisions (e.g., therapeutics prescribed, procedures done) on patient outcomes.

Indeed, there are several reasons why cardiovascular providers should engage in quality-of-care measurement and improvement. First, quality of care reflects the degree to which clinicians practice *evidence-based medicine*. Inherent in evidence-based medicine is consideration of both the best available scientific evidence and individual patient factors and preferences. Optimally, informed patients, who understand the state of their health and the potential risks and benefits of health interventions ranging from prevention to acute and chronic disease management, interact with clinicians who observe the tenets of evidence-based medicine.

Second, quality of care lies at the center of *health care system improvement*. The outcomes of health decisions by patients and cardiovascular clinicians depend on the environment in which these decisions are made. From the perspective of cardiovascular clinicians, quality of care includes not only their actions, but also patient access, engagement, and behavior; the context and methods of health care delivery; and multiple aspects of the health care system, ranging from information technology and ancillary personnel support to health system policy and incentives. Ultimately, although essential, clinical knowledge and skill are not sufficient for ensuring high-quality health care; another primary driver is the health care delivery system.

Third, quality care provides a means for *professional accountability*. The concept of professionalism includes not only good clinical knowledge but also excellence in the delivery of health care and accountability for that care. Quality of care, through measurement and improvement of the IOM domains of quality and patient outcomes, directly addresses health care delivery and accountability. As such, quality of care is centric to cardiovascular professionalism.

Moreover, quality of care is increasingly tied to certification and licensure, particularly regarding involvement in practice improvement. Medical education is evolving to a model of lifelong learning, in which the principles of quality of care are integrated with clinical knowledge and decision making. Intrinsic to this new framework, cardiovascular clinicians will need to have the skills of quality-of-care measurement and improvement in addition to medical knowledge.

Lastly, major changes in the health care environment bring quality of care to the center of clinical practice. Performance-based reimbursement and public reporting of quality-of-care measures are increasingly prevalent, along with new health care delivery and reimbursement models, such as

accountable care organizations. These invariably emphasize performance on quality measures that reflect one or more of the IOM quality domains and the direct measurement of patient outcomes.

Importantly, reimbursement for medical care is transitioning from payment for quantity to payment for quality, also known as "value-based purchasing" of health services. The Medicare Access and CHIP [Children's Health Insurance Program] Reauthorization Act of 2015 (MACRA), which replaced the Sustainable Growth Rate, represents a dramatic change in the approach of the U.S. Centers for Medicare and Medicaid Services (CMS) to physician payment.[4] MACRA ties reimbursement to the delivery of high-quality care, implementation of electronic health resources, engagement in performance improvement activities, and participation in alternative payment models, which in turn are tied to providing high-quality care at lower cost.

Measuring Health Care Quality and Uses of Quality Measurements

This section describes types of quality measures, uses of measures, common data sources for quality measurement, and limitations of quality measures, including the potential for unintended consequences.

Types of Quality Measures

Fifty years ago, Avedis Donabedian articulated an enduring conceptual framework for measuring health care quality: characterizing quality according to structure, process, and outcome (see Classic References). While contemporary measurement extends beyond these domains, the Donabedian model remains central to understanding the quality of health care. The American College of Cardiology (ACC) and American Heart Association (AHA) have described in detail the methodologic principles of developing various types of measures.[5-8]

Structural measures are specific attributes of the health care delivery system that are considered surrogates for the care delivered; examples include procedural volume and accreditation status. In general, such measures are only weak surrogates and are frequently inadequate if more robust metrics of quality are available.[9,10]

Process measures reflect the actions of clinicians, such as prescribing medication, and are among the most commonly employed metrics of quality. For example, CMS has used processes of care for acute MI and heart failure as part of their Hospital Compare quality reporting system since 1995.[11] ACC/AHA have developed several sets of process measures for specific cardiovascular procedures and conditions (**Table 4.2**). Operationally, process measures are generally selected from among the care processes with strong support in practice guidelines (e.g., class I recommendations in the ACC/AHA guideline recommendation taxonomy). Not all strong guideline recommendations are appropriate for adoption as quality measures, but such measures should possess additional attributes that support their use for quality measurement (**Table 4.3**).

TABLE 4.2

Current ACC/AHA Performance Measure Sets

TOPIC AREA	YEAR OF PUBLICATION (UPDATE)*	SPONSORING ORGANIZATIONS
Heart failure	2005 (2011, *2017*)	2005: ACC/AHA (inpatient)
		2011: ACC/AHA/AMA-PCPI (outpatient and inpatient)
Chronic stable coronary artery disease	2005 (2011, *2018*)	AHA/ACC/AMA-PCPI
Hypertension	2005 (2011)	ACC/AHA/AMA-PCPI
Myocardial infarction	2006 (2008, *2017*)	ACC/AHA
Cardiac rehabilitation	2007 (2010, *2017*)	AACVPR/ACC/AHA
Atrial fibrillation	2008 (2016)	ACC/AHA/AMA-PCPI
Primary cardiovascular disease prevention	2009	ACC/AHA
Peripheral artery disease	2010	ACC/AHA/ACR/SCAI/SIR/SVM/ SVN/SVS
Percutaneous coronary intervention	2013	ACC/AHA/SCAI/AMA-PCPI/NCQA
Secondary prevention lipid therapy–focused update	2015	ACC/AHA
Sudden cardiac death prevention	2016 (est.)	ACC/AHA

*Estimated future update in italics.

ACC, American College of Cardiology; *AHA,* American Heart Association; *AMA-PCPI,* American Medical Association Physician Council on Performance Improvement; *AACVPR,* American Association of Cardiovascular and Pulmonary Rehabilitation; *SCAI,* Society of Cardiovascular Angiography and Interventions; *SIR,* Society of Interventional Radiology; *SVM,* Society of Vascular Medicine; *SVN,* Society of Vascular Nursing; *SVS,* Society of Vascular Surgeons; *ACR,* American College of Radiology; *NCQA,* National Committee for Quality Assurance.

TABLE 4.3

Attributes of Measures of Process, Outcome, and Value in Health Care

MEASURE TYPE	MEASURE ATTRIBUTES
Process[5]	Evidence based Interpretable Actionable Explicit numerator and denominator Valid Reliable Feasible
Outcomes[6]	Clear explicit definition of appropriate patient sample Clinically coherent variables for risk adjustment Sufficiently high-quality and timely data Designated time of covariate and outcome ascertainment Standardized period of outcome assessment Analysis accounting for multilevel organization of data Disclosure of methods employed
Value and efficiency[7]	Integration of both quality and cost Valid cost measurement and analysis No or minimal incentive to provide poor-quality care Proper attribution of the measure

Process measures have “face validity” because they focus on therapies and approaches that have been established in clinical studies and are readily interpretable. However, they generally typically require clinical data, thus requiring resources for data abstraction. The exclusion of individual patients from a process measure “denominator” because of contraindications to treatment is viewed favorably by clinicians but is controversial. Such exclusions further increase the burden of data collection but enhance the clinical validity of these measures. Moreover, there is not always a demonstrated association between higher performance on process measures and better patient outcomes.[12] Lastly, process measures may “top out,” where performance is consistently high and the measures lose the capacity to discriminate meaningfully among institutions. This has been the case with many of the process measures for cardiovascular conditions that have been reported to the public.[13]

Given the limitations of structural and process measures, a greater emphasis has been placed on *outcome measures.* Suitable outcome measures have several important attributes, the most important of

which may be risk adjustment[14] (**Table 4.3**). Risk, or "case-mix," adjustment can help address differences in patient populations receiving care. Robust risk adjustment requires advanced statistical methods and is generally limited by the availability of accurate data variables (e.g., patient characteristics) to include in risk models.

Outcome measures are appealing because they are patient centered, can be applied to all patients (unlike process measures, which apply to only a discrete "denominator" of patients), and reflect the actions of the health care system. However, risk adjustment methods must be valid, and some outcomes of great importance to patients (e.g., health status) are not currently measured systematically in large populations. Furthermore, unlike process measures, outcome measures do not explicitly inform the targets for QI.

Measures of *value*, broadly defined as quality delivered as a function of cost, have emerged as part of the quality measurement portfolio.[15] Importantly, cost alone is not synonymous with value; the easiest way to minimize cost is to withhold care, whereas value explicitly incorporates quality. Attributes of value measures have also been enumerated[14] (**see Table 4.3**). Developing robust measures of value involves the challenges attendant to measuring quality as well as those associated with measuring costs.

In response to evidence that escalating costs in part reflect overuse, the ACC, in conjunction with partner societies, has developed *appropriate use criteria* (AUC). These criteria provide ratings of the appropriateness of care for several cardiovascular diagnostic and therapeutic modalities for a range of commonly encountered clinical scenarios.[16] Because AUC are based on clinical scenarios that may not exactly reflect individual patient situations, and because the criteria are derived from expert consensus, their role in quality measurement and reporting is evolving.

Composite measures, which formally aggregate multiple aspects of quality, are appealing given the various structures, processes, and outcomes that can be measured for a particular condition or procedure.[17] Developing composite measures is complex and should be guided by an explicit methodology.[18] These measures have the advantage of combining various domains of quality but can obscure the impact of component measures and can decrease the understanding of where action for improvement is needed.

Data Sources

In general, quality measures are most useful when compared against an external standard, or "benchmark," of similar practice or national performance. Although single-center data can provide useful insights for local quality assessment and improvement, data used to characterize quality are most useful when compared across patients, providers, and settings. Sources meeting these criteria are often categorized as "claims data" (also known as "administrative data") or clinical data, each of which have distinct strengths and limitations. Ultimately, any measurement of quality will be no more robust than the quality of the data on which it is based.

Insurance payers maintain databases of claims for services as a means of identifying and paying for health services delivered to their members. Claims data have several strengths. First, they tend to include large numbers of patients, although this depends on the payer involved. Second, because these data are already collected for other purposes, there is lower incremental expense to employ claims data for this purpose. Finally, claims data employ a consistent standard (e.g., ICD-9 codes) for each claim.

However, several factors limit the value of claims data. Because their primary purpose is to facilitate billing, claims data are constrained in their capacity to inform clinical inferences. For instance, claims

data are limited with regard to measuring severity of disease, listing indications and results of procedures, and differentiating comorbidities from complications. Moreover, diagnostic codes may lack sensitivity and specificity, resulting in discordance with diagnoses established by clinicians. Claims data are also specific to the population receiving insurance from the entity that creates the database. Furthermore, claims data may require substantial time to elapse before they are adequately complete for use. Thus, measurements with these data will lag with respect to current practice.

The utility of claims data as a component of quality measurement largely depends on the specific use. In some cases, claims and clinical data perform similarly for case-mix adjustment at the institutional or hospital level for cardiovascular conditions. When used for risk adjustment at the patient level, however, clinical data generally provide better calibration and discrimination than claims data alone.[19]

Clinical data are appealing as the foundation of quality measurements for several reasons. The primary advantage of clinical data is their specificity regarding clinical details, such as severity of disease, coexisting conditions, and indications and results of procedures. For example, identifying contraindications to the use of a medication in a quality measure is likely to be incomplete using claims data, whereas clinical data are more likely to include the relevant information. There are also limitations to clinical data. Clinical data are generally more expensive and difficult to obtain on large populations than claims data. Aside from national clinical registry programs (discussed later), there are few sources of clinical data using consistent data standards and adequate in reach and scope to characterize quality on a large scale. Data in medical records, including electronic health records (EHRs), do not employ standardized definitions and may not include the specific elements necessary to compose a quality measure.

National clinical registry programs are currently the most widely used clinical data to measure quality.[20] In the United States the National Cardiovascular Data Registry (NCDR) program of the ACC and partner organizations (www.ncdr.com), the AHA Get With the Guidelines program (www.heart.org), and the Society of Thoracic Surgeons (STS) National Database (www.sts.org) are the most widely implemented cardiovascular registry programs. These programs provide quality measurements with national benchmarks, using detailed standardized clinical data, and can support QI initiatives.[21]

In some cases, clinical and claims data are used together for quality measurement purposes. This approach is often employed to take advantage of the detailed clinical data from a registry program for a specific episode of care (e.g., PCI, hospitalization for heart failure) and the assessment of events after that episode from claims data (e.g. death, rehospitalization). These hybrid data sources, while sharing the advantages and disadvantages of their component sources, allow assessment of longitudinal outcomes with a robust clinical foundation.

The increasing prevalence of EHRs in the U.S. health care system creates both opportunities and challenges for quality measurement. EHRs contain large amounts of clinical data but are currently not a panacea with respect to measuring quality. EHRs are not superior to paper records with respect to data structure and definitions or in ensuring that specific data elements are collected, unless the EHR platforms are specifically modified to do so. Moreover, EHR systems are not necessarily interoperable among institutions, limiting the extent to which they can be used for multi-institutional quality assessment without further efforts. Experience suggests that EHRs must evolve considerably to achieve their full potential as a source of robust, reliable data for quality measurement.[22]

Uses of Quality Measures

Quality measurements serve a range of purposes, but in broad terms they can be considered as supporting

QI or accountability (e.g., public reporting).[23] The distinction between these two uses is important: a broad range of measures may be suitable for the purposes of self-evaluation, benchmarking, and informing QI, but measures that will be used for accountability must withstand the scrutiny of those who are measured and the intended consumers of these measures.[24] The use of measures for accountability requires greater validity, reliability, and reproducibility of the measures, including the quality of the data that underlie the measures, as well as attribution of the measures.[25] The ACC/AHA and other measure developers apply specific standards and nomenclature to identify measures appropriate for accountability purposes (e.g., those designated as "performance measures") or those intended for QI purposes ("quality metrics" or "test metrics").[24] In the United States, most measures intended for the purposes of accountability are reviewed and endorsed by the National Quality Forum (www.nqf.org).

The past two decades have witnessed the evolution of programs that employ quality measures for the purposes of accountability. These include public reporting of quality measures (e.g., CMS Hospital Compare); "pay for reporting," in which participation in reporting efforts (but not specific results) leads to financial incentives; and expanding use of "pay for performance," in which reimbursement is tied to the specific results of outcomes (e.g., MACRA). Professional organizations are also taking leading roles in public reporting efforts based on clinical registry data, such as voluntary hospital programs sponsored by STS and NCDR to promote public reporting of cardiovascular quality.[26]

Ostensibly, accountability programs, including public reporting and pay-for-performance, are intended to incentivize quality improvement. Some evidence indicates that accountability may achieve this objective in some cases,[27-29] but there is no good evidence that it results in better quality of care or influences decisions by the consumers of health care services.[30] The heterogeneity of results likely reflects the variability in these programs in terms of what is measured, the context of implementation, and the incentive structure.

Concerns About Quality Measures: Unintended Consequences

Efforts to measure and improve quality of health care can potentially result in unintended consequences. For example, focusing on one process of care could detract from attention to other processes; incentives to increase rates of treatment could result in overtreatment in some cases; and threats of penalties for providers for adverse procedural outcomes or inadequate risk adjustment methods could result in biases against performing that procedure on high-risk patients.[31] These concerns support the importance of monitoring for potential unintended consequences as part of performance improvement efforts and programs. To date, however, QI and accountability efforts have generally not been evaluated with the rigor and to the extent of other medical interventions. Accountability may also incentivize "gaming" the measurement system, which undermines the credibility regarding meaningful QI and increases the importance of rigorous data quality and audit programs.

Improving Quality of Care

The principal reason to measure quality of care should be to inform meaningful improvement in health care delivery. QI, often also referred to as "performance improvement," is the set of actions undertaken to improve one or more of the six IOM domains of quality to improve health outcomes (**see Table 4.1**). Prior studies have helped identify key components of successful QI efforts, yet several activities familiar

to cardiovascular clinicians have been found to be largely ineffective.

Imploring clinicians to “do more” or “do better” in terms of following guidelines or documenting care is generally ineffective. Perhaps surprisingly, traditional continuing medical education (CME) and didactic lectures, utilization management, and availability of clinical practice guidelines are similarly ineffective.[32] On the other hand, the availability of quality measures with benchmarking (also called “audit and feedback”) can be successful, particularly when tied to health care delivery system improvement.

Successful QI involves identifying suboptimal performance in one or more aspects of care and then matching QI activities to improve performance. Data with benchmarking are central to choosing meaningful targets for improvement (**Fig. 4.1**). Once QI targets are chosen, a primary emphasis should be system changes to support higher-quality care delivery. Examples include using the EHR for computerized order entry to avoid prescription errors and provide automated drug-drug interaction alerts, standardized order sets and care pathways (e.g., for acute MI patients), use of multidisciplinary care teams, efforts to promote care coordination, and effective engagement of patients in decision making.

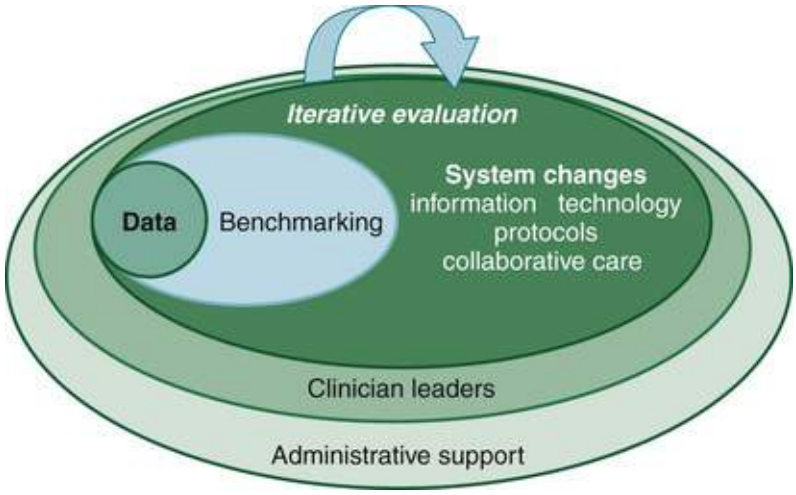

FIGURE 4.1 Key components of quality improvement. (From Rumsfeld JS, Dehmer GJ, Brindis RG. The National Cardiovascular Data Registry: its role in benchmarking and improving quality. US Cardiology 6:11, 2009.)

QI is only successful as a “team sport”; it should not focus on an individual clinician, but on a multidisciplinary team. Moreover, QI should be responsive to specific gaps in performance over time, striving continuously to improve the delivery system. Importantly, QI efforts should be evaluated in an iterative fashion, to assess progress in performance improvement and to monitor for unintended consequences. The measurement of the impact of QI, which can be considered part of “health care delivery research,” should be increasingly important in the future.[33]

Clinical leaders—those who are engaged and committed to quality measurement and improvement—are critical to successful QI efforts. Increasingly, training in quality measurement and QI is available to cardiovascular clinicians. Many hospitals and health systems are training clinical staff in quality. Organizations such as the ACC are embedding quality measurement and performance improvement into educational programs; these programs will increasingly support the performance improvement requirements of maintenance of certification and licensure.

Administrative support is also crucial. This includes not only financial support of quality measurement and improvement efforts, but also clear institutional leadership goals and commitment to achieving the highest quality of care. Indeed, among the most powerful drivers of QI is the *culture* of a practice or

institution. For example, in an evaluation of hospital characteristics associated with 30-day mortality rates after acute MI, hospitals that fostered “an organizational environment in which clinicians are encouraged to solve problems creatively,” in addition to having both physician and nurse “quality champions,” had significantly lower mortality rates.[34]

QI may be carried out at local levels (community, practice, hospital), or at regional, health system, national, or international levels. In other words, QI goals and strategies for performance improvement can be defined as part of local or broader-reaching quality initiatives, although the principles of QI are the same for each of these, and the QI activities ultimately must be executed at the local level following the key factors noted in Fig. 4.1. Several well-known approaches to QI are briefly described next.

Approaches to Quality Improvement

Fruitful QI requires the integration of the components previously described into a specific framework for action (**see Fig. 4.1**). Perhaps the most widely utilized framework in healthcare is Plan-Do-Study-Act (PDSA). This model, developed by Associates in Quality Improvement (www.apiweb.org), has been embraced by the Institute for Healthcare Improvement as the specific means for developing plans for health QI (www.ihi.org). PDSA comprises two interdependent steps: (1) formulating a plan by setting goals, establishing metrics of success, and identifying changes to implement, and (2) testing these changes in an iterative PDSA cycle (**Fig. 4.2**). The goals should be measurable, time delimited, and realistic. The measures should address at least one of the IOM domains of quality (**see Table 4.1**) but should also include measures to characterize possible adverse consequences of the improvement effort. Then, in evaluating changes, each step of the PDSA cycle contributes to the understanding of the impact of the change, both positive and negative, thus informing future cycles of improvement.

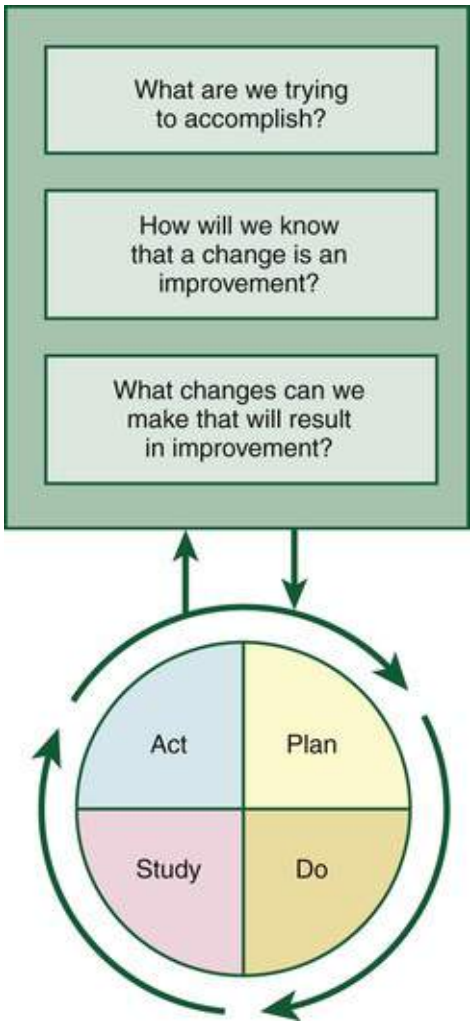

FIGURE 4.2 The PDSA (Plan-Do-Study-Act) cycle of quality improvement. (From Institute of Healthcare Improvement (www.ihi.org), attributed to Langley GL, Nolan KM, Nolan TW, et al. The Improvement Guide: a Practical Approach to Enhancing Organizational Performance. 2nd ed. San Francisco: Jossey-Bass Publishers; 2009).

The Lean approach builds on PDSA by specifically targeting wasteful health care processes. Lean was originally developed at Toyota to improve the efficiency of automobile production. Not surprisingly, with the rapid growth of medical expenditures and the understanding that more spending does not necessarily translate to better quality, the use of Lean in health care settings has expanded rapidly. In essence, the Lean QI approach includes a focus on patient needs, explicit evaluation of complex processes of care delivery in a given setting, and identification and improvement of those components of the process that do not promote one or more of the IOM domains of quality for improvement (**see Table 4.1**). Process-of-care mapping (e.g., the specific steps of how care is delivered in the emergency department, on a ward, or in the office), empowering all members of the health care team to help identify targets, and improving delivery in an iterative fashion are hallmarks of Lean.[35] Studies of the Lean approach suggest that it is an effective means of improving efficiency, both by reducing cost and improving quality.

Another well-known QI approach that builds on PDSA is Six Sigma, which focuses on reduction in unnecessary variation in care delivery. The term *Six Sigma* stems from "statistical process control," in which the goal is to have a care process executed with error rates that are six standard deviations below average. Unfortunately, medical errors generally occur at much higher rates (see Classic References, IOM: *To Err Is Human*). Therefore, Six Sigma emphasizes reducing errors in processes of care such as medication prescriptions or medical procedures (e.g., minimizing unnecessary procedural complications) through five steps (a modification of PDSA): Define, Measure, Analyze, Improve, and Control.[36] The last step emphasizes ongoing monitoring of care processes once error rates/variation has been reduced, such

that additional QI can be applied if variation/error rates increase. Lean and Six Sigma may be combined (Lean Six Sigma) for QI that leverages a PDSA approach to target reductions in wasteful processes of care and minimizes variation/error rates in care delivery.

Conclusion

Quality of care—the extent to which health care delivery optimizes patient outcomes—has become a clinical competency for cardiovascular clinicians. It is the practice of evidence-based medicine as well as accountability of care, both of which help define professionalism. Quality (or performance) improvement is increasingly central to clinical training, lifelong medical education, and reimbursement. Health care reimbursement in the future will reward quality over quantity.

Quality measurement and improvement are now an essential part of cardiovascular practice, as well as for the broader health care system. Quality measures, whether structural, process, outcome, value, or composite, depend on the extent of underlying scientific evidence, the validity of data sources, and clear specification. They can be used for QI as well as in accountability programs, such as public reporting and "pay for performance." Meaningful QI stems from having data with benchmarking to identify targets for improvement, making system changes to support high-quality care delivery, and having clinical leadership as well as administrative support. Robust, iterative evaluation of QI efforts is of critical importance, both to assess the impact of these efforts on intended quality measures and to monitor for unintended consequences.

Ultimately, cardiovascular clinicians should be fully engaged in quality of care, to help ensure that quality measurement, QI, and accountability programs are clinically meaningful, not just a regulatory burden. Only in this way will quality of care efforts truly promote health care that is more effective, safe, equitable, timely, efficient, and patient centered and that translates into improved patient outcomes.

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Critical Evaluation of Clinical Trials

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Despite many decades of advances in diagnosis and management, cardiovascular disease (CVD) remains the leading cause of death in the United States and other high-income countries, as well as many developing countries.[1] Managing the burden of CVD consumes substantial portions of health care expenditures globally; interventions to treat CVD are therefore a major focus of contemporary clinical research.[2] Therapeutic recommendations are no longer based on nonquantitative pathophysiologic reasoning but instead are evidence based. Rigorously performed trials are required before gaining regulatory approval and clinical acceptance of new treatments (drugs, devices, biologics) and biomarkers.[3] Thus the design, conduct, analysis, interpretation, and presentation of clinical trials constitute a central feature of the professional life of the contemporary cardiovascular specialist and will need to keep pace with the technology of the future.[3,4] Case-control studies and analyses from registries are integral to epidemiologic and outcomes research but are not strictly clinical trials and are not discussed in this chapter.[5,6]

Constructing the Research Question

Before embarking on a clinical trial, investigators should review the FINER criteria for a good research question (**Table 5.1**) and the phases of evaluation of new therapies (**Table 5.2**). They should also familiarize themselves with the processes of designing and implementing a research project, good clinical practice, and drawing conclusions from the findings[7-10] (**eFig. 5.1**). A clinical trial may be designed to test for superiority of the investigational treatment over the control therapy but also may be designed to show therapeutic similarity between the investigational and the control treatments (noninferiority design) (**Fig. 5.1 and Table 5.3**).[10]

TABLE 5.1

FINER Criteria for a Good Research Question

F	Feasible
I	Interesting
N	Novel
E	Ethical
R	Relevant

From Hulley SB, Cummings SF, Browner WS, et al. Designing Clinical Research. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2013.

TABLE 5.2

Phases of Evaluations of New Therapies

PHASE	FEATURES	PURPOSE
I	First administration of new treatment	Safety—is further investigation warranted?
II	Early trial in patients	Efficacy—dose ranging, adverse events, pathophysiologic insights
III	Large-scale comparison versus standard treatment	Registration pathway—definitive evaluation
IV	Monitoring in clinical practice	Postmarketing surveillance

Modified from Meinert C. Clinical Trials. Design, Conduct, and Analysis. New York: Oxford University Press; 1986; and Stanley K. Design of randomized controlled trials. Circulation 2007;115:1164.

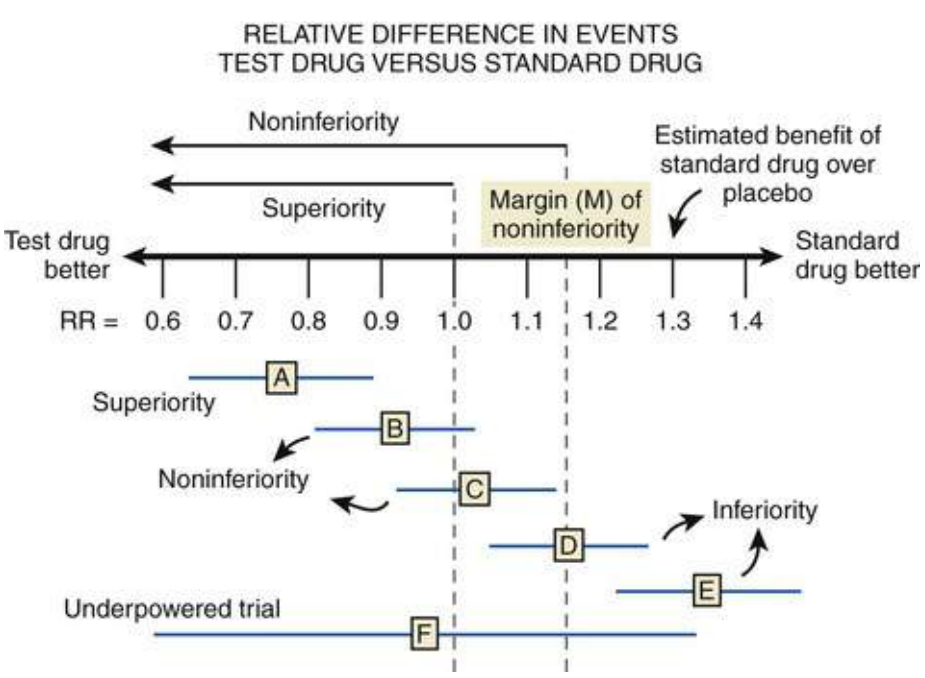


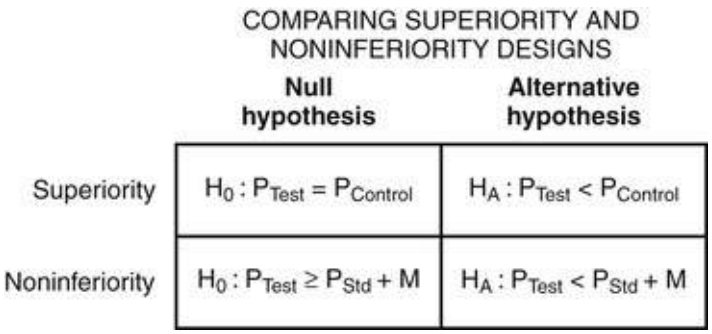
FIGURE 5.1 Example of design and interpretation of noninferiority trials. The margin (*M*) for noninferiority is prespecified based on previous trials comparing the standard drug with placebo. Examples of hypothetical trials A to F are shown, of which some (trials B and C) satisfy the definition of noninferiority. Trial A not only satisfies the criteria for noninferiority but, because the confidence interval is entirely to the left of a relative risk (*RR*) of 1.0, also shows superiority of the test drug over the standard drug.

TABLE 5.3

Trial Designs to Replace Standard of Care

PARAMETER	SUPERIORITY	NONINFERIORITY	
		Objective 1	Objective 2
Goal	Test beats control	Test beats placebo	Test as good as standard
H_0 H_A	$P_{test} = P_{control}$ $P_{test} < P_{control}$	Assessment of test made against putative placebo	$P_{test} \geq P_{standard} + M$ $P_{test} < P_{standard} + M$
Source of data	Trial	Historical data	Trial
Type I error	Set by regulatory authorities, typically 0.05	Set by regulatory authorities, typically 0.05	Set by regulatory authorities, typically 0.05
Type II error (power)	Set by investigator	N/A	Set by investigator
Major threats to validity	Assay sensitivity; bias	Assay constancy	Assay sensitivity; bias
Inferential reasoning from trial	Results in study cohort yield estimate of $P_{test} - P_{control}$ in population of patients with same clinical characteristics and disease state.	Combining results from the trial ($P_{test} - P_{standard}$) and historical data ($P_{standard} - P_{placebo}$) yields estimate of ($P_{test} - P_{placebo}$) in population of patients with same clinical characteristics and disease state.	Results in study cohort yield estimate of $P_{test} - P_{standard}$ in population of patients with same clinical characteristics and disease state.
Generalizability to universe of *all* patients with the disease state	Related to enrollment criteria; the more restrictive they are, the less generalizable are the results to the entire universe of patients with the disease state.	Enrollment criteria of prior trials and medical practice concurrent with those trials determine generalizability of estimate of $P_{standard} - P_{placebo}$ to contemporary practice.	Related to enrollment criteria; the more restrictive they are, the less generalizable are the results to the entire universe of patients with the disease state.

H_0, Null hypothesis; H_A, alternative hypothesis; *M*, noninferiority margin; *N/A*, not available.



EFIGURE 5.1 Statistical design of superiority and noninferiority trials. In both superiority and noninferiority trials, the investigators propose a null hypothesis (H_0) with the goal of the trial being to reject H_0 in favor of the alternative hypothesis (H_A). To determine whether the null hypothesis may be rejected, before initiation of the trial, the type I (α) and type II (β) errors are specified (not shown). In superiority trials, α is usually two-sided, whereas it is one-sided in noninferiority trials. The quantity (1 − β) is referred to as the "power" of the trial. *M,* Margin for noninferiority; P_{Std}, and P_{Test}, proportion of subjects experiencing the event of interest in the standard and test treatment groups.

In a noninferiority trial, investigators specify a noninferiority criterion (M) and consider the investigational treatment to be therapeutically similar to control (standard) therapy if, with a high degree of confidence, the true difference in treatment effects is less than M (**see Fig. 5.1**).[11,12] Specification of the noninferiority margin M involves considerable discussion between the investigators (advocating for clinical perception of minimally important difference) and regulatory authorities (advocating for assurance that the investigational treatment maintains a reasonable fraction of the efficacy of the standard treatment based on previous trials).[11-13] The investigational therapy may satisfy the definition of noninferiority and may or may not also show superiority over the control therapy.[14] Thus, superiority can be considered a special case of noninferiority in which the entire confidence interval for the difference in treatments falls in favor of the investigational treatment (**see Fig. 5.1**). Investigators can stipulate that a trial is being designed to test both noninferiority and superiority (**see Table 5.3**). For a trial that is configured as a noninferiority trial, it is acceptable to test for superiority conditional on having demonstrated noninferiority.[15] The reverse is not true—trials configured for superiority cannot later test for noninferiority unless the margin M was prespecified.

Regardless of the design of the trial, it is essential that investigators provide a statement of the hypothesis being examined, using a format that permits biostatistical assessment of the results (**see eFig. 5.1**). Typically, a null hypothesis (H_0) is specified (e.g., no difference exists between the treatments being studied), and the trial is designed to provide evidence leading to rejection of H_0 in favor of an alternative hypothesis (H_A) (a difference exists between treatments). To determine whether H_0 may be rejected, investigators specify Type I (alpha, α) and Type II (beta, β) errors, referred to as the false-positive rate and false-negative rate, respectively. By convention, α is set at 5%, indicating a willingness to accept a 5% probability that a significant difference will occur by chance when there is no true difference in efficacy. Regulatory authorities may on occasion demand a more stringent level of α—for example, when a single large trial is being proposed rather than two smaller trials—to gain approval of a new treatment. The value of β represents the probability that a specific difference in treatment efficacy might be missed, so that the investigators incorrectly fail to reject H_0 when there is a true difference in efficacy. The power of the trial is given by the quantity (1 − β) and is selected by the investigators, typically between 80% and

90%.[16] Using the quantities α, β, and the estimated event rates in the control group, the sample size of the trial can be calculated with formulas for comparison of dichotomous outcomes or for a comparison of the rate of development of events over a follow-up period (time to failure). **Table 5.3** summarizes the major features and concepts for superiority and noninferiority trials designed to change the standard of care for patients with a cardiovascular condition.

Clinical Trial Design

Controlled Trials

Randomized controlled trials (RCTs) are considered the "gold standard" for the evaluation of new treatments (**Fig. 5.2**), but because of their defined structure, RCTs have limitations when used to drive evidence-based practice recommendations.[9,17,18] The allocation of subjects to control and test treatments is not determined but is based on an impartial scheme (usually a computer algorithm). Randomization reduces the likelihood of patient selection bias in allocation of treatment, enhances the likelihood that any baseline differences between groups are random so that comparable groups of subjects can be compared, and validates the use of common statistical tests. Randomization may be fixed over the course of the trial or may be adaptive, based on the distribution of treatment assignments in the trial to a given point, baseline characteristics, or observed outcomes[15,19] (**Fig. 5.2A**). *Fixed* randomization schemes are more common and are specified further according to the allocation ratio (equal or unequal assignment to study groups), stratification levels, and block size (i.e., constraining the randomization of patients to ensure a balanced number of assignments to the study groups, especially if stratification [e.g., based on enrollment characteristics] is used in the trial). During the course of a trial, investigators may find it necessary to modify one or more treatments in response to evolving data (internal or external to the trial) or a recommendation from the trial's data safety monitoring board (DSMB)—that is, to implement an *adaptive* design[15,19] (**Fig. 5.2B**). Adaptive designs are most readily implemented during phase II of therapeutic development. Regulatory authorities are concerned about protection of the trial integrity and the studywise α level when adaptive designs are used in registration pathway trials.[19] The most desirable situation is for the control group to be studied concurrently and to comprise subjects distinct from those of the treatment group. Other trial formats that have been used in cardiovascular investigations include nonrandomized concurrent and historical controls (**Fig. 5.3A, B**), crossover designs (**Fig. 5.3C**), withdrawal trials (**Fig. 5.3D**), and group or cluster allocations (groups of subjects or investigative sites are assigned as a block to test or control). Depending on the clinical circumstances, the control agent may be a placebo or a drug or other intervention used in active treatment (standard of care).

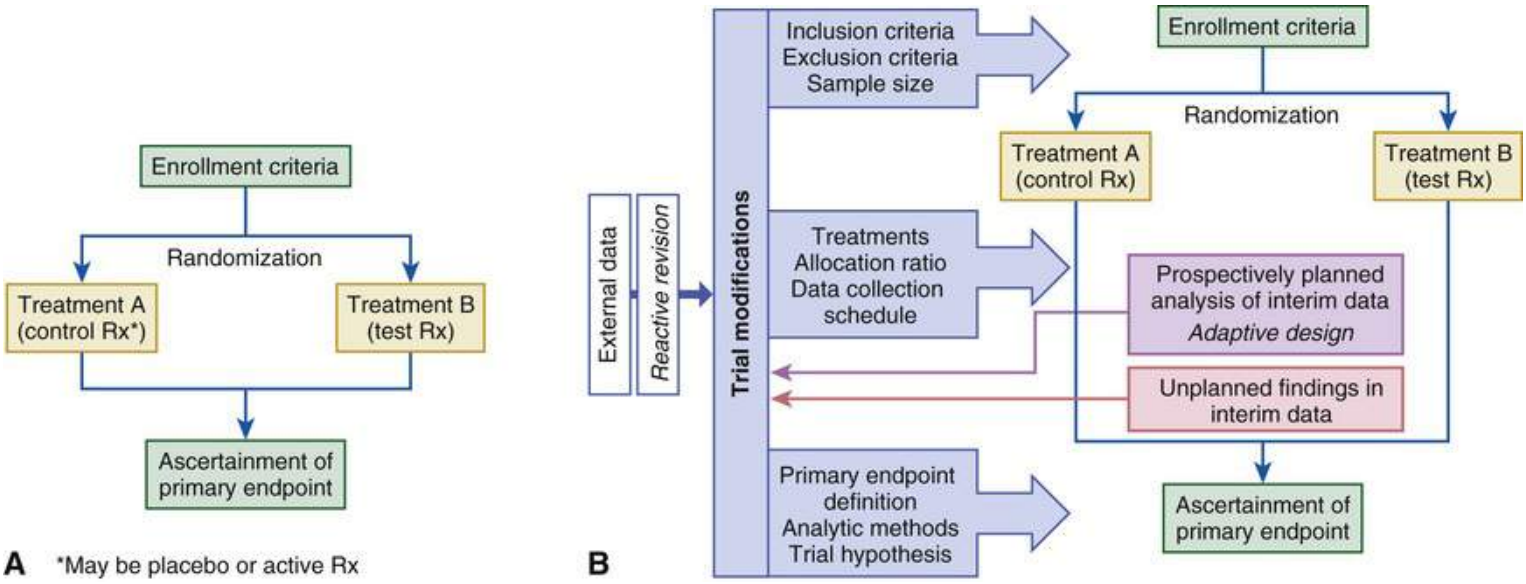


FIGURE 5.2 **A,** Basic structure of a randomized control trial (RCT). The investigators specify the enrollment criteria for the study population. Allocation to the treatment groups occurs through a randomization scheme, subjects are followed, and the primary endpoint is ascertained. **B,** Design of the RCT may be modified at the major levels shown. When the modification is in response to data external to the trial, it is referred to as a "reactive revision" (*left side*). When the investigators prospectively plan an analysis of interim data for the purposes of modifying the trial, it is referred to as an "adaptive design." Unplanned findings in interim data (e.g., data safety monitoring board recommendation) also may provoke a modification of the trial design. (Modified from Antman E, Weiss S, Loscalzo J. Systems pharmacology, pharmacogenetics, and clinical trial design in network medicine. Wiley Interdiscip Rev Syst Biol Med 2012;4:367.)

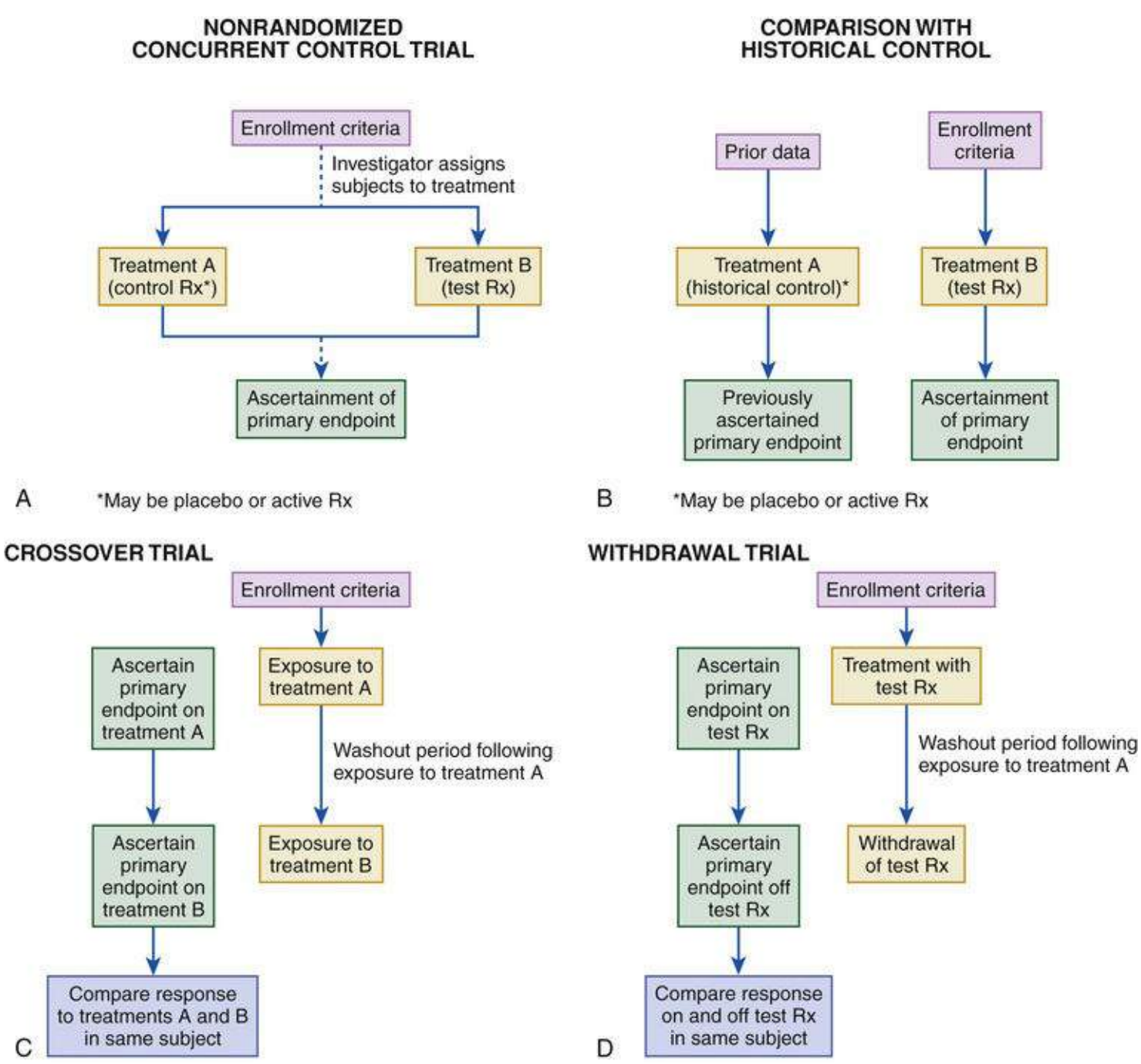


FIGURE 5.3 Other forms of controlled studies. **A,** Features of nonrandomized concurrent control trial. **B,** Design features of a trial using an historical control group. **C,** Design features of a crossover trial. (For an example of this type of trial to evaluate an intervention for angina pectoris, refer to Cole PL, Beamer AD, McGowan N, et al: Efficacy and safety of perhexiline maleate in refractory angina: a double-blind placebo-controlled clinical trial of a novel antianginal agent. Circulation 1990;81:1260.) **D,** Design features of a withdrawal trial. (For an example of the use of this type of trial to evaluate the use of digoxin in patients with chronic heart failure, refer to Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. N Engl J Med 1993;329:1.)

Other Forms of Controlled Studies

Trials in which the investigator selects the subjects to be allocated to the control and treatment groups are *nonrandomized, concurrent control studies* (**see Fig. 5.3A**).[18] In this type of trial design, clinicians do not leave the allocation of treatment in each patient to chance, and patients are not required to accept the concept of randomization. It is, however, difficult for investigators to match subjects in the test and

control groups for all relevant baseline characteristics, introducing the possibility of selection bias, which could influence the conclusions of the trial. Clinical trials that use *historical controls* compare a test intervention with data obtained earlier in a nonconcurrent, nonrandomized control group (**see Fig. 5.3B**). Potential sources for historical controls include previously published trials in cardiovascular medicine and electronic databases of clinic populations or registries. The use of historical controls allows investigators to offer the treatment(s) being investigated to all subjects enrolled in the trial. The major drawbacks are the potential for bias in the selection of the control population and failure of the historical controls to reflect accurately the contemporary picture of the disease under study.

The *crossover* design is a special case of the RCT in that each subject serves as his or her own control (**see Fig. 5.3C**). The appeal of this design is that the same subject is used for both test and control groups, thereby diminishing the influence of interindividual variability and allowing a smaller sample size. However, important limitations to a crossover design are the assumptions that the effects of the treatment assigned during the first period have no residual effect on the treatment assigned during the second period and that the patient's condition does not change during the periods being compared.

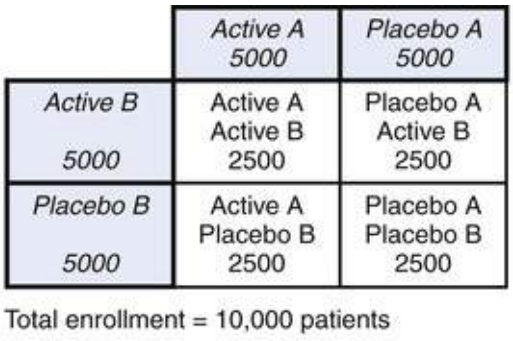
In a *fixed sample size* design, the trialists specify the necessary sample size before patient recruitment, whereas in an *open or closed sequential* design, subjects are enrolled only if the evolving test-control difference from previous subjects remains within prespecified boundaries.[15,19] Trials with a fixed design can be configured to continue until the requisite number of endpoints is reached (event driven), thus ensuring that enough endpoints will occur to provide intended power to evaluate the null (H_0) and alternative (H_A) hypotheses. When both the patient and the investigator are aware of the treatment assignment, the trial is said to be *unblinded*. *Single-blind* trials mask the treatment from the patient but permit it to be known by the investigator. *Double-blind* trials mask the treatment assignment from both the patient and the investigator, and *triple-blind* trials also mask the actual treatment assignment from the DSMB and provide data only in the form of group A and group B categories.

Withdrawal Studies

A withdrawal study evaluates the patient's response to discontinuation of treatment or reduction in the intensity of treatment for a cardiovascular condition (**see Fig. 5.3D**). Because patients previously experiencing incapacitating side effects would have been taken off the test intervention, they are not available for withdrawal. This bias toward selection of patients who tolerate a test intervention can overestimate benefit and underestimate toxicity associated with the treatment. In addition, changes in the natural history of the disease in a given patient may influence the response to withdrawal of therapy.

Factorial Design

In a factorial design, multiple treatments can be compared with control within a single trial through independent randomizations[10] (**eFig. 5.2**). Because patients with CVD typically receive multiple therapies, the factorial design is more reflective of actual clinical practice than trials in which only a single intervention is randomized. Multiple comparisons can be efficiently performed in a single large factorial design trial that is smaller than the sum of two independent clinical trials. Each intervention should be evaluated individually against control, and the possibility of interaction between the factors should be evaluated, because the validity of comparisons within each factor depends on the absence of interaction. Factorial designs may not be appropriate if there is an a priori reason to anticipate interactions (e.g., resulting from related mechanisms of action).



EFIGURE 5.2 Factorial design of clinical trial. In this example, 10,000 patients are randomized to receive or not to receive two interventions (drug A and drug B). Each patient will fall into one of the following four categories: Active A/Active B, Placebo A/Active B, Active A/Placebo B, or Placebo A/Placebo B. *Definitions/equations at bottom:* Differences in event rates for the comparisons permit an assessment of the treatment effect of drug A in the presence and absence of drug B. See text for further discussion. (From Antman E. Medical therapy for acute coronary syndromes: an overview. In Califf R, Braunwald E, editors. Acute Myocardial Infarction and Other Acute Ischemic Syndromes. Philadelphia: Current Medicine; 1996, pp 10.1-10.25.)

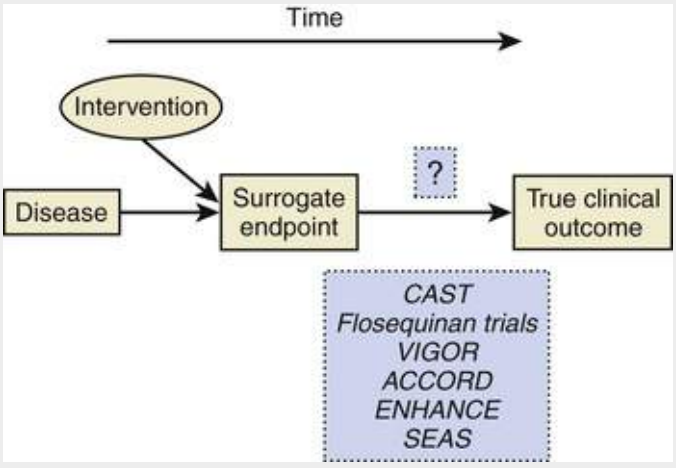
Selection of Endpoint of Clinical Trial

Evaluation of new treatments in the face of rising costs and reduced mortality rates for cardiovascular illnesses has resulted in two major approaches to the selection of endpoints. The first is to use a composite endpoint with a perceived logical grouping of events, whereby each of the elements of the endpoints is believed to be affected by the treatments being studied.[9] During the course of a trial but before unblinding, investigators may assess the aggregate (all treatment groups combined) event rate for the primary endpoint to ascertain whether the initial estimates of the event rate in the control arm and the anticipated treatment effect of the intervention were reasonable.[15] A low aggregate event rate may reflect inaccuracies in the estimated control rate or treatment effect; investigators may respond by modifying the sample size or expanding the definition of the primary endpoint (**see Fig. 5.2B**).

Some investigators use a term such as *MACE* (*m*ajor *a*dverse *c*ardiac *e*vents) to refer to the composite endpoint that they selected, but readers need to evaluate the methods section in clinical trial reports because such phrases may be used differently across trial groups. This situation may improve in the future as a result of a movement toward standardization of the definitions of endpoints in RCTs.[20] Interpretation of composite endpoints is challenging when the various component elements show different quantitative or qualitative responses to a new treatment. For example, the new treatment may reduce a nonfatal element such as hospitalization for heart failure but may increase total mortality. Efforts to address the complexities of composite endpoints include evaluating the total number of endpoints (first element as well as recurrent nonfatal components) as well as novel weighting schemes using matched pairs of patients in the treatment and control groups to calculate a "win ratio."[21,22]

The balance of benefit and risk associated with a new treatment may be described using terms such as *net clinical benefit*, *net clinical outcome*, or *NACE* (*n*et *a*dverse *c*ardiac *e*vents). Such terms typically combine elements of efficacy and safety (e.g., cardiovascular death, nonfatal myocardial infarction [MI], nonfatal stroke, nonfatal major bleed) and provide clinicians with a summary statement about what to expect from a new treatment. Although this is appealing, controversy remains because of a lack of agreement on weighting schemes to interpret composite endpoints, especially when nonfatal safety elements (e.g., bleeding) are combined with efficacy elements (e.g., prevention of MI).

Another approach is to use a surrogate endpoint as a substitute for measuring more traditional clinical outcomes.[23,24] Surrogate endpoints are attractive to investigators because they often are measured on an interval (continuous) scale and can lead to trials with a smaller sample size. However, the field of cardiology is replete with examples of trials configured around surrogate endpoints that not only failed to demonstrate benefit but actually uncovered harm (e.g., increased mortality) associated with a new treatment. Surrogate endpoints are useful if they lie in the causal pathway of a disease and if interventions that affect them are reliably associated with changes in clinical outcomes. **eFig. 5.3** illustrates a range of settings in which surrogate endpoints failed to serve as useful substitutes for measuring "hard" clinical events in cardiovascular trials.



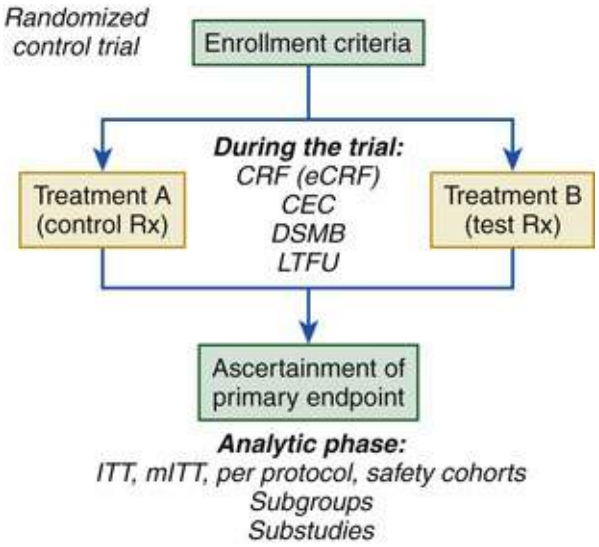
EFIGURE 5.3 Surrogate endpoints. Selection of a surrogate endpoint in a clinical trial provides reliable information for clinicians if the surrogate endpoint is in the causal pathway of the disease with respect to clinical outcomes, and if the intervention acts on the surrogate endpoint so as to truly affect clinical outcome. Some examples of trials in cardiovascular medicine for which this paradigm failed are CAST (Cardiac Arrhythmia Suppressor Trial); studies of flosequinan; VIGOR (Vioxx GI Outcomes Research); ACCORD (Action to Control Cardiovascular Risk in Diabetes); ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression); and SEAS (Simvastatin and Ezetimibe in Aortic Stenosis). (Modified from Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med 1996;125:605.)

Key Issues

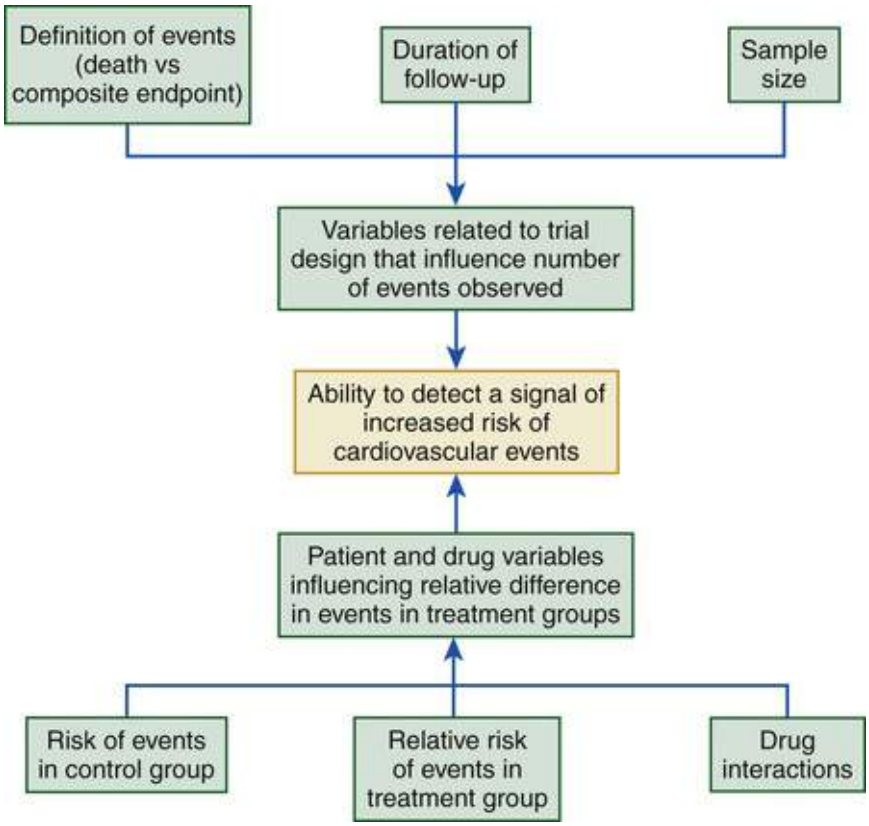
During Course of Trial

Contemporary trials require surveillance of multiple issues on a regular basis (**eFig. 5.4**). The determination as to whether an event (efficacy, safety) has occurred is the responsibility of a clinical events committee (CEC). Members of a CEC typically are experts in the field, remain blinded to the treatment assignment, and adjudicate events according to a charter established before initiation of

enrollment.[20] Because it would not be possible for investigators to maintain equipoise as the events in a trial begin to accumulate, the DSMB assesses the data at prespecified intervals to ascertain whether the accumulating evidence strongly suggests an advantage of one treatment[25] (**eFig. 5.5**).



EFIGURE 5.4 Conduct during recruitment and follow-up of subjects in the trial and during the analytic phase. The case report form (*CRF*) is an important barometer of the quality of the data being collected at investigative sites. Surveillance procedures need to be in place for central review of the data being submitted to trap for key items such as any violations of the enrollment criteria, range check errors (e.g., number of digits or units for age, weight, biomarkers), adequacy of the information being submitted for suspected endpoint events, and timely submission of adverse events (a regulatory reporting responsibility). Many of these tasks are facilitated by the use of an electronic case report form (*eCRF*) that can be completed using an Internet-based interface. The complexity of monitoring the tasks may be handled by a contract research organization (*CRO*) that has a large staff capable of visiting the enrolling sites. Additional quality checks that typically are conducted by a CRO include source document verification (inspection of primary medical record) for suspected endpoint events and random sampling of subjects who did not experience any events. Retention of subjects in the trial and minimizing loss to follow-up (*LTFU*) also are key quality measures. *CEC,* Clinical events committee; *DSMB,* data safety monitoring board; *ITT,* intention to treat; *mITT,* modified intention to treat.



EFIGURE 5.5 Detection of treatment effects in clinical trials. Factors related to trial design (*top*) and to the patient and drug being investigated (*bottom*) are shown. The interplay of these factors influences the ability to detect a treatment effect in a clinical trial. (Reproduced with permission from Antman EM, DeMets D, Loscalzo J. Cyclooxygenase inhibition and cardiovascular risk. Circulation 2005;112:759.)

A critical aspect of a trial that impacts the analysis and interpretation of the findings is *missing data* (see additional content online). Subjects who initially agree to participate in an RCT may decline to continue to take a blinded-study drug at some point during the course of the trial. Rather than ceasing follow-up in such subjects (i.e., censoring the data), trialists should strive to obtain follow-up data by asking subjects who stop taking a study drug to allow the investigators to obtain follow-up on them through office visits, telephone contact, or review of their medical records.[26,27] Every effort also should be made to track patients who move during the trial to avoid "loss to follow-up."[27]

Stopping boundaries to guide the DSMB are usually agreed on before the initiation of enrollment. Such stopping boundaries need to take into account the uncertainty of the evidence at iterative "interim looks" at the data and the play of chance, which may produce a situation in which one treatment appears to be favorable. During these interim looks at the data, DSMB members inspect the differences between treatment groups expressed as a standardized normal statistic (Z_i). Usually, Z_i plots depict evidence of superiority of the test treatment in the upward (positive) direction and inferiority of the test treatment in the downward direction.[25]

Stopping boundaries may be symmetric (**Fig. 5.4**) or asymmetric. Investigators and DSMB members may agree to use an asymmetric stopping-boundary scheme that requires less compelling evidence to cross a lower bound for inferiority of a new treatment when an acceptable standard treatment is clinically available and the new treatment is associated with safety concerns (e.g., intracranial hemorrhage during evaluation of a new fibrinolytic). The DSMB may also be called on to determine whether a particular dose group should be discontinued (adaptive design) (**see Fig. 5.2B**) and whether the trial is futile (e.g., that conditional on the data accumulated at the -*i*th look, there is only a 10% chance that H_0 would be rejected at the end of the trial).[10]

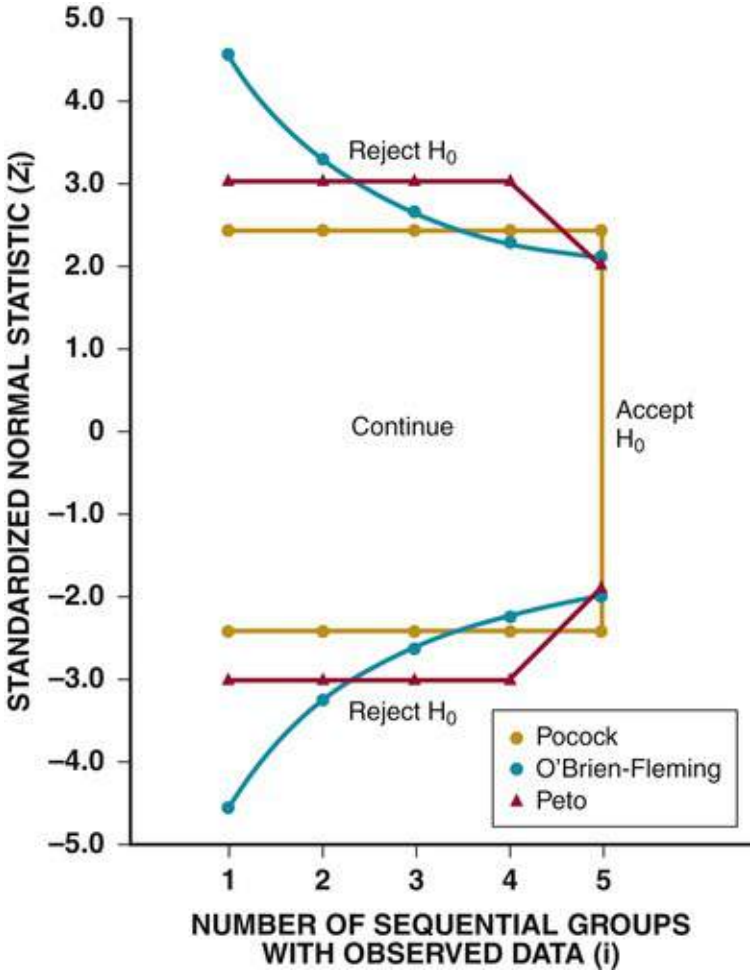


FIGURE 5.4 Sequential stopping boundaries used in monitoring a clinical trial. Shown are three sequential stopping boundaries for the standardized normal statistic (Z_i) for up to five sequential groups (of patients enrolled in the trial by the -*i*th analysis), with a final two-sided significance level of 0.05. (From Friedman LM, Furberg CD, DeMets DL. Fundamentals of Clinical Trials. 4th ed. New York: Springer Verlag; 1998.)

During Analytic Phase of Trial

Before unblinding the results of the trial (i.e., revealing patient outcomes by treatment group to investigators), the investigators should have finalized a statistical analysis plan (SAP). Key features of the SAP include a definition of the cohorts of trial subjects to be analyzed (**Table 5.4**), the statistical test(s) to be used to analyze the primary endpoint (e.g., for comparison of proportions or time to event), conventions for handling missing data,[26,28] time windows for analyzing data (e.g., randomization through common study end date), and subgroups of interest (**see eFig. 5.4**). Depending on the exact definitions used for the analytic cohorts, the denominators may vary; this may lead to slight variations in the estimates of event rates and treatment effects. Ideally, the main results of the trial will be similar in the intention to treatment and per protocol cohorts. If they are not, an explanation should be sought from additional analyses of the data.

TABLE 5.4

Examples of Definitions of Analytic Cohorts in a Clinical Trial

ANALYTIC COHORT	REFERENCE DATE	EXCLUDE IF PROTOCOL VIOLATIONS DISCOVERED	REQUIRE THAT SUBJECT RECEIVED AT LEAST ONE DOSE OF STUDY DRUG	TREATMENT ASSIGNMENT FOR ANALYTIC PURPOSES
Intention to treat	Randomization	No	No	As per randomization
Modified intention to treat	May start at initial dose of study drug	No (may vary)	May introduce this requirement	As per randomization
Per protocol	Initial dose of study drug	Yes	Yes	Usually as per randomization, but sensitivity analyses that account for actual treatment received may be performed
Safety	Usually at time of initial dose of study drug	No	Yes	Usually as per actual treatment received, but sensitivity analyses that use treatment assigned at randomization may be performed

Not all patients will respond to a given treatment in a clinical trial to the same extent. The role of pharmacogenomics in determining the response to therapeutic agents is discussed in **Chapter 8**. Because not all patients will respond to a given treatment, it is of clinical interest to inspect the data stratified by subgroups of interest. Although such an approach initially may seem appealing, a number of considerations limit the investigator's ability to draw conclusions from subgroup analyses. Typically, subgroups involve univariate analyses of the data (e.g., men versus women), but the clinical picture is more complex, such that an individual patient will belong to multiple subgroups. Responses in subgroups should be evaluated by an *interaction test*, which determines whether the relative efficacy of treatments differs among the subgroups being examined. A *quantitative* interaction is said to be present when the treatment effect varies in magnitude but not in direction across subgroups.[29] A *qualitative* interaction is said to be present when the direction of the treatment effect varies among the subgroups. Note that a qualitative interaction also must be a quantitative interaction. Of importance, the multiplicity of subgroup analyses inflates the false-positive rate (**Fig. 5.5**). Rather than relying on a *P* value for a subgroup response, investigators and readers should focus on a graphic display of subgroup data depicting the point estimates and confidence intervals for the treatment effect. Such an approach provides a summary of the range of plausible treatment effects observed in a trial. Ongoing improvements in genotyping and phenotyping subjects offers the potential for more precise definition of subgroups, but statistical complexity may increase as the number of subgroups grows.[3]

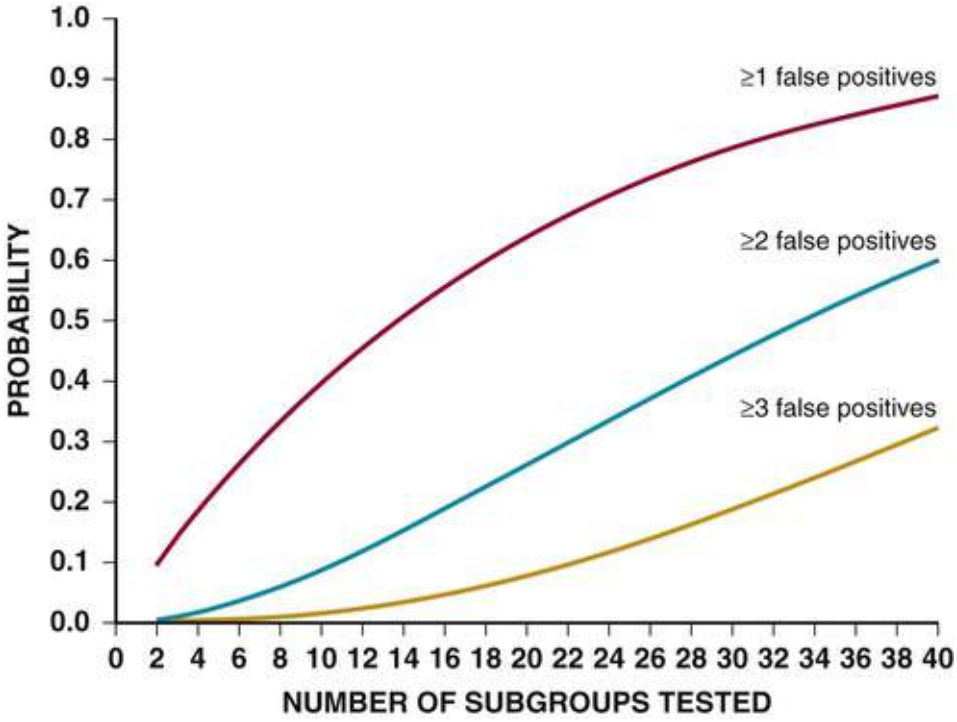


FIGURE 5.5 Probability that multiple subgroup analyses will yield at least one (*red line*), two (*blue line*), or three (*yellow line*) false-positive results. (From Lagakos SW: The challenge of subgroup analyses—reporting without distorting. N Engl J Med 2006;354:1667.)

Measures and Detection of Treatment Effect

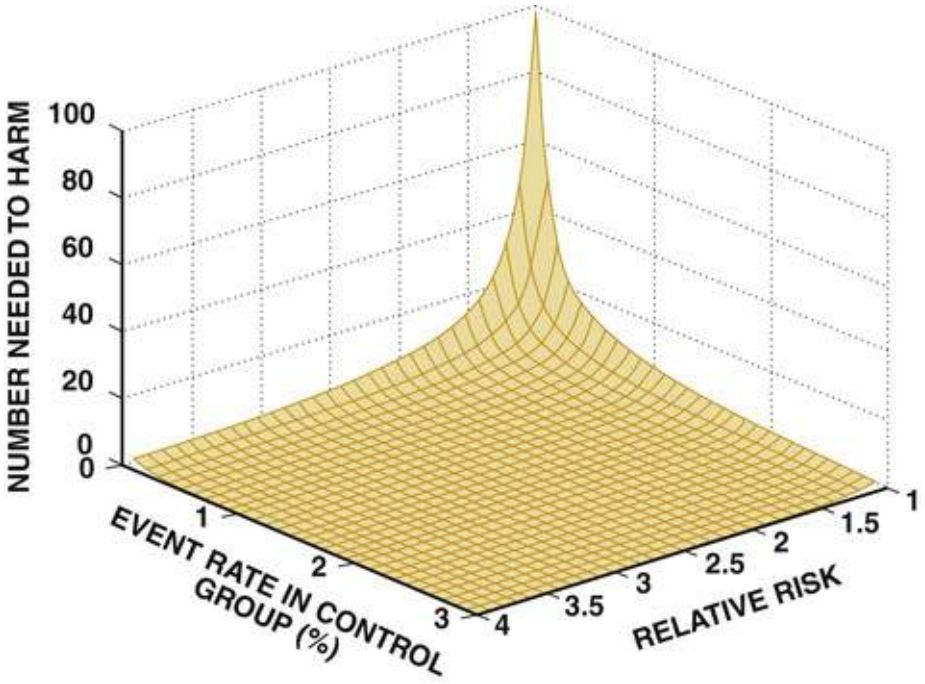
Events in a clinical trial may be measured on a nominal (dichotomous), categorical, or interval (continuous) scale.[30] Clinical trials reports should use descriptive statistics, graphic displays, and estimates of the precision of the observations appropriate for the scale of measurement being used in the trial.[30] A common assessment in a cardiovascular trial is comparison of the proportions of patients experiencing a dichotomous event (e.g., dead versus alive) during the follow-up period of the trial. When the outcome is an undesirable cardiovascular response and the data are arranged as investigational group compared with control group, a *relative risk* (RR) or *odds ratio* (OR) of less than 1 indicates benefit of the investigational treatment (**see Fig. 5.1**).

Interpretation of the treatment effect should take into account the absolute risk of the outcomes. The *absolute risk difference* (ARD) is the difference in events in the treatment group and the control group and is particularly useful when expressed as the number of patients that must be treated ($N = 1/\text{ARD}$), or *number needed to treat* (NNT), to observe the beneficial effect in one patient. Similarly, the *absolute risk increase* (ARI) in adverse events with the investigational treatment can be converted into the *number needed to harm* (NNH). By comparing the NNT and NNH for a given treatment, clinicians can assess the risk-benefit balance and also benchmark the treatment effects of the new therapy against other treatments used in contemporary cardiovascular practice. Another useful metric is to express the outcome for every 1000 patients treated.

The NNT (or NNH) should be interpreted in the context of the time frame of the trial. For example, in patients with an acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI), use of prasugrel instead of clopidogrel over 14.5 months is associated with an NNT of 46 (to prevent one

event of CV death, MI, or stroke) and NNH of 167 (to cause one excess major bleed)[31] (see **Chapter 62**). Use of rosuvastatin (versus placebo) in apparently healthy persons with a low-density lipoprotein cholesterol less than 130 mg/dL but elevated C-reactive protein level is associated with a 5-year NNT value of 20 (to prevent one event of MI, stroke, revascularization, or death)[32] (see **Chapter 45**). In some therapies, the balance of NNT and NNH is even more complex, because a treatment may have an early hazard (e.g., cardiac surgery versus PCI) but may be more effective over time[33]; the balance of NNT and NNH also may vary according to the baseline risk at the time of randomization.[34]

The interplay of variables set by investigators during the design of a clinical trial, the characteristics of the patients studied, and the features of the treatment being investigated influence the relative difference in events in the treatment groups (**see eFig. 5.5**). The interface of the patient and the treatment may change over the course of exposure to the treatment (e.g., lower risk of events over time as the patient moves from the acute to chronic phases of a disease), and background therapy also may change during the course of the trial (e.g., with treatments added or removed or doses modified). Although these considerations can influence the likelihood of a "positive" trial, they also have an impact on the ability to detect a signal of harm (**eFig. 5.6**).



EFIGURE 5.6 Number needed to harm. The relationship of the event rate in the control group and the relative risk of cardiovascular events with the treatment being investigated determines the number of patients who need to be treated with the drug to observe one cardiovascular event (number needed to harm). The surface generated can be used to understand the relative ease or difficulty of detecting a signal of harm with a particular treatment (e.g., cyclooxygenase inhibition). (Reproduced with permission from Antman EM, DeMets D, Loscalzo J. Cyclooxygenase inhibition and cardiovascular risk. Circulation 2005;112:759.)

Future Perspectives

Trialists, peer reviewers, and journal editors now have checklists and templates that codify the reporting of clinical trials (**eTable 5.1**). Clinicians can refer to guides for reading and interpreting clinical trials[35]

(**Table 5.5**). These advances, however, deal only with clinical trials that reach the point at which they are reported in a publicly available format. Considerable concern has been expressed in the past that some clinical trials, especially those with negative results, were never reported. The introduction of a requirement to register clinical trials in an online repository (e.g., Clinical Trials.gov) was an important step forward, but specific details typically are limited on such postings. Requirements that clinical trials post a final study report within a reasonable period after study completion (1 year) will assist investigators planning future trials, clinicians seeking the latest information about treatments, and writing committees charged with creating guidelines documents who need up-to-date and complete data to formulate recommendations.[36]

TABLE 5.5

Questions to Ask When Reading and Interpreting the Results of a Clinical Trial

Are the Results of the Study Valid?
Primary Guides
1. Was the assignment of patients to treatment randomized? 2. Were all patients who entered the trial properly accounted for and attributed at its conclusion? a. Was follow-up complete? b. Were patients analyzed in the groups to which they were randomized?
Secondary Guides
1. Were patients, their clinicians, and study personnel "blind" to treatment? a. Were the groups similar at the start of the trial? b. Aside from the experimental intervention, were the groups treated equally?
What Were the Results?
1. How large was the treatment effect? 2. How precise was the treatment effect?
Will the Results Help Me in Caring for My Patients?
1. Does my patient fulfill the enrollment criteria for the trial? If not, how close is my patient to the enrollment criteria? 2. Does my patient fit the features of a subgroup in the trial report? If so, are the results of the subgroup analysis in the trial valid? 3. Were all the clinically important outcomes considered? 4. Were important concomitant treatments described? 5. Are the likely treatment benefits worth the potential harm and costs?

Modified from material in Guyatt GH, Sackett DL, Cook DJ. The medical literature: users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? JAMA 1993;270:2598; Guyatt GH, Sackett DL, Cook DJ. The medical literature: users' guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? JAMA 1994;271:59; and Stanley K. Evaluation of randomized controlled trials. Circulation 2007;115:1819.

ETABLE 5.1

Checklist of Information for Inclusion in Reports of Clinical Trials

Introduction
Clear statement of a priori hypothesis and specific research objective(s)
Methods
Study as designed; include:
1. Planned study population, including controls
2. Inclusion and exclusion criteria
3. Planned subgroup analyses
4. Prognostic factors that may affect study results
5. Outcome measures and minimum difference(s) to be considered clinically important
6. Planned treatment interventions
7. Method of assignment of subjects to treatments (e.g., randomization method, stratification blinding or masking procedure, matching criteria)
8. Planned sample size, power calculations
9. Use of data safety and monitoring board and rules for stopping the study
10. Methods of statistical analysis in sufficient detail to permit replication
Results
Study as conducted; include:
1. Inclusive dates of accrual of study population
2. Sample size achieved
3. Report of extent of follow-up
4. How many subjects were excluded or withdrew and the reasons
5. Demographics and clinical characteristics of the study population, including controls
6. How the study as conducted deviated from the study as planned and the reasons (e.g., compliance)
Study findings; include:
1. Cohorts analyzed (e.g., intention to treat)
2. Estimates of treatment effects, stated as comparisons among treatment groups (e.g., differences in risks, rates, or means of outcome measures, as well as exact *P* values, not just $P < 0.05$)
3. Measures of precision for outcome measures and for estimates of treatment effects (e.g., confidence intervals)
4. Summary data and appropriate descriptive statistics
5. Complications of treatment
6. Repository where original data can be obtained
Discussion
Interpretation of study findings
Results considered in the context of results in other trials reported in the literature

Modified from Working Group on Recommendations for Reporting of Clinical Trials in Biomedical Literature. Call for comments on a proposal to improve reporting of clinical trials in the biomedical literature. Ann Intern Med 1994;121:894; and Stanley K: Evaluation of randomized controlled trials. Circulation 2007;115:1819.

Additional directions for RCTs in the future include (1) involving patients in structuring research questions assessing the value of health care options,[37] (2) engaging community representatives in the planning of trials (community-based participatory research),[38] (3) using a patient's electronic medical record and longitudinal registries to embed randomization between treatment options,[3,7,36] and (4) using biomarkers, enrichment strategies, and adaptive designs more frequently as precision medicine approaches to development of new therapies become more established[3,39] (**Fig. 5.6 and eFig. 5.7**).

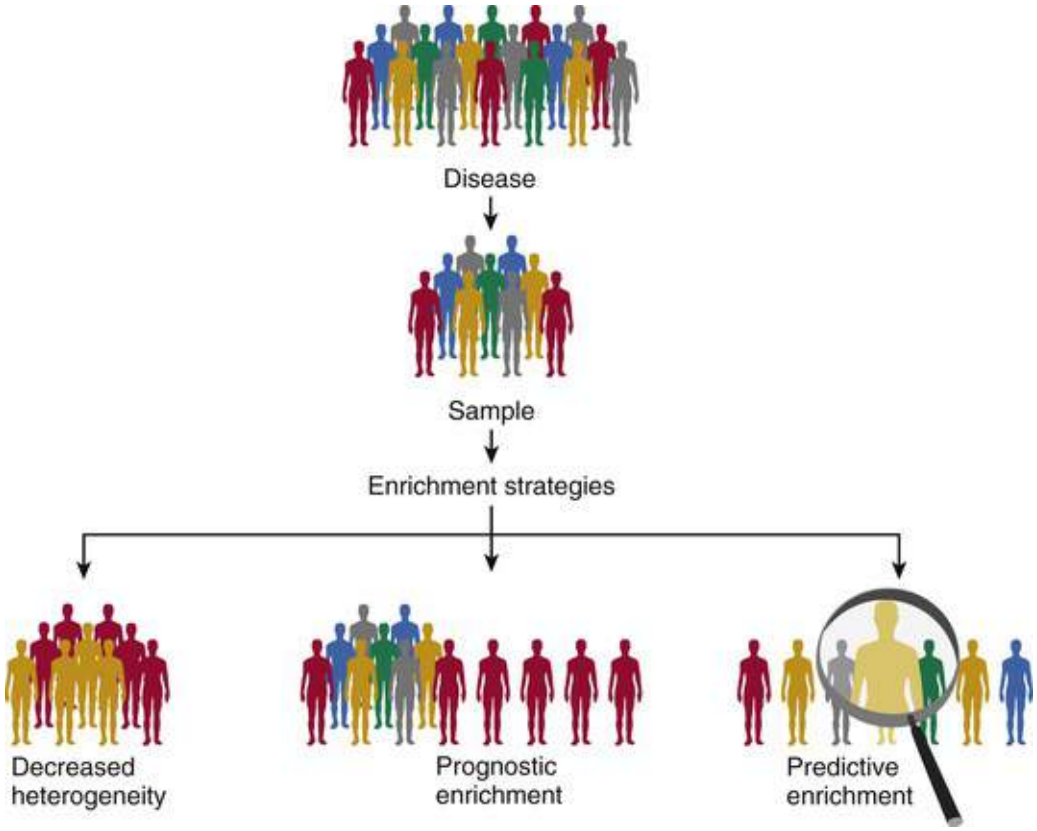
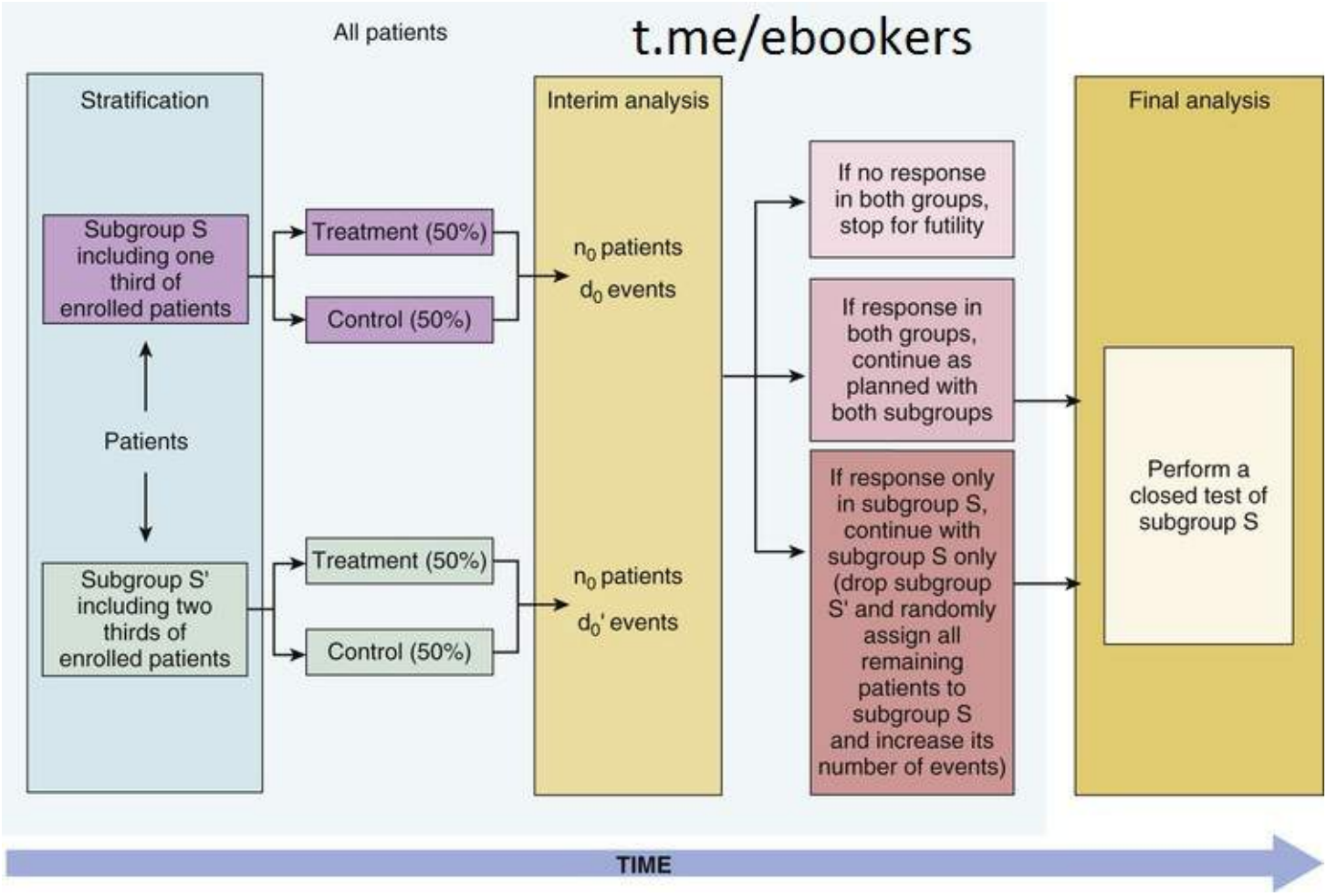


FIGURE 5.6 Enrichment strategies for clinical trials. From the whole population of patients with the disease of interest (e.g., hypertension), the investigators enroll a cohort of subjects (*sample*) that they hope are representative of the distribution of such patients in the broad population. Enrichment strategies to decrease the heterogeneity of the sample or to increase the representation of subjects with a high risk of events (*prognostic enrichment*), although facilitating the conduct of the trial, do not necessarily offer greater precision in matching a prospective treatment response to the clinical profile of the research subject. The predictive enrichment strategy utilizes both the characteristics of the trial subject and the data either from experiments before the trial or from during the trial (adaptive design) to "predict" who is likely to have a more robust response to the treatment(s) being tested. (From Antman EM, Loscalzo J. Precision medicine in cardiology. Nat Rev Cardiol 2016;13:591-602.)



EFIGURE 5.7 Schematic representation of an adaptive two-stage population-enrichment design. The population is stratified before randomization into two subgroups, S and S′, according to a binary biomarker. The interim analysis occurs when a specific number of patients (n_0) have been enrolled in each subgroup. At that time, there will be a specific number of events in each group: d_0 events in subgroup S and d_0' events in subgroup S′. The data are then examined, and the trial may be terminated for futility, continued as planned, or continued by enrolling patients only in subgroup S. In this design, there is a biologic basis for assuming that the biomarker may be predictive of response in subgroup S but not in subgroup S′. The purpose of the interim analysis is to verify whether this assumption is true and if so, to enrich the remainder of the trial with patients from subgroup S only. (From Bhatt DL, Mehta C. Adaptive designs for clinical trials. N Engl J Med 2016;375: 65.)

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Missing Data

Missing data present a serious challenge to analysis of trial results. Depending on the mechanism leading to the missing data, the information is considered in one of three categories: (1) missing completely at random, where “missingness” is unrelated to the study (e.g., flood destroys case report forms); (2) missing at random, where the characteristics of the subject can account for differences in the distribution of missing data (e.g., elderly subjects have more missing visits than younger subjects); and (3) missing not at random, where “missingness” depends on the value of the missing observation. The last category is especially problematic because it is likely to be informative and nonignorable—for example, subjects assigned to the test intervention are more likely to have side effects and to drop out of the study.[1] Biostatisticians advise against using simple adjustment methods for dealing with missing data (e.g., analyzing only subjects who complete the trial, or a single imputation such as carrying the last observation forward). They recommend instead using statistical models based on the data and performing sensitivity analyses to examine the robustness of the trial findings.[1]

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PART II
Genetics and Personalized Medicine

OUTLINE

6

Personalized and Precision Cardiovascular Medicine

Calum A. Macrae

The Core Concepts of Personalized and Precision Medicine

In many ways, medicine has always been personalized. Every therapeutic relationship has at its core the implicit trust that the outcome will be tailored to the patient's personal needs. At this level, *personalization* incorporates all the nuance and mystery of the patient-healer partnership and is unlikely ever to be replaced by a purely data-driven algorithm.

Over the last few decades, since the advent of molecular medicine, there have emerged several discrete terms for the prevailing vision of therapeutic intervention tailored to the biology of the individual patient. These terms have included *predictive*, *personalized*, *individualized*, and *stratified*, as well as several others.[1] A number of related concepts in which the analytic component is emphasized, such as *P4* (predictive, preventive, personalized, and participatory) *medicine*,[2] *systems medicine*, and *network medicine*, have also gained traction.[3] In essence, these terms all reflect the same fundamental set of goals: medicine that is informed by the biologic state of the individual patient rather than by aggregate or averaged information from a representative population or cohort. The central assumption is that the more

precisely defined the mechanism of any diagnosis or intervention, the more precisely the physician will be able to predict and modify the relevant outcomes. This tenet recently has been embodied in governmental programs, including the President's Precision Medicine Initiative in the United States and Personalized Medicine or Stratified Medicine consortia in other countries.[4,5] Increasingly, these initiatives all recognize that the rigor necessary for such individualized approaches demands active patient engagement at every stage, from data collection and discovery science through intervention and behavioral modification.

Ultimately, the specific terminology employed is less relevant than the goal of the approach: a probabilistic understanding of the fundamental mechanisms of health and disease, with a shared and evolving knowledge base around which patients and their health care teams can maintain wellness and heal disease.

Among the basic requirements for precision medicine are rigorous quantitative models of disease mechanisms, responses to therapy, and outcomes, all at multiple scales.[1,3,6] In current practice, predictive computational models are almost completely restricted to research venues, but as rigorous data accumulate in electronic medical records and other implementation systems, clinical medicine will adopt more of the principles of engineering and related applied sciences.

At present, remarkably few diseases permit generation of quantitative models that fully capture disease causation, diagnosis, and therapeutic outcome.[7] Numerous reasons contribute to this information deficit. In most instances, epidemiologic studies have had to focus on legacy data types defined decades earlier and to study disease entities already known to be aggregates across multiple discrete mechanisms, unified often only by the low biologic resolution of clinical imaging or biomarkers.[8] Although there are general population estimates of the relative contributions of genetic or environmental risk factors and stochastic factors in different disease syndromes, there are few situations where the predictive utility of such estimates is adequate to drive clinical decision making.

The lack of patient-level predictive utility for most modern diagnostic paradigms is a function of the broad range of pretest probabilities in which testing is deployed, the low specificity of most biomarkers outside very specific contexts, and underlying etiologic heterogeneity. Tests with excellent characteristics in one setting are often deployed erroneously in other settings. Genetic studies also support the presence of confounding factors in current diagnoses, with the majority of cardiovascular syndromes exhibiting remarkable *genetic* heterogeneity (multiple different causal genes) and *allelic* heterogeneity (high proportion of new variants in known disease genes).[9] Together, these findings suggest that our etiologic models for many major cardiovascular disorders fail to account for substantial genetic and environmental contributions.[10]

Clinical and translational science has necessarily emphasized later-stage phenotypes that are more readily correlated temporally with outcomes. Even in prevention, however, our ability to move to proximate causes has been limited. Traditional risk factors in many cases may simply reflect early disease manifestations or shared upstream mechanisms rather than true predictive antecedents. The magnitude of the biologic effect size of traditional or genetic biomarkers is probably the most important discriminant of clinical utility but is rarely measured across lifetimes in the general population.[11] Composite genetic risk scores for common disorders such as diabetes and atherosclerosis add only incremental information,[12] whereas even in single-gene disorders with uniform etiologic mechanisms, substantial effect sizes, and high penetrance, it can be difficult to predict discrete, clinically meaningful outcomes such as sudden death. The disconnect between population predictors and individual utility is another consequence of missing data and highlights a central inference of precision medicine: the need to collect biomedical data on a completely different scale. To realize fully the potential benefits of precision medicine, much more

comprehensive datasets must be collected in much larger cohorts and across lifetimes (**Fig. 6.1**).

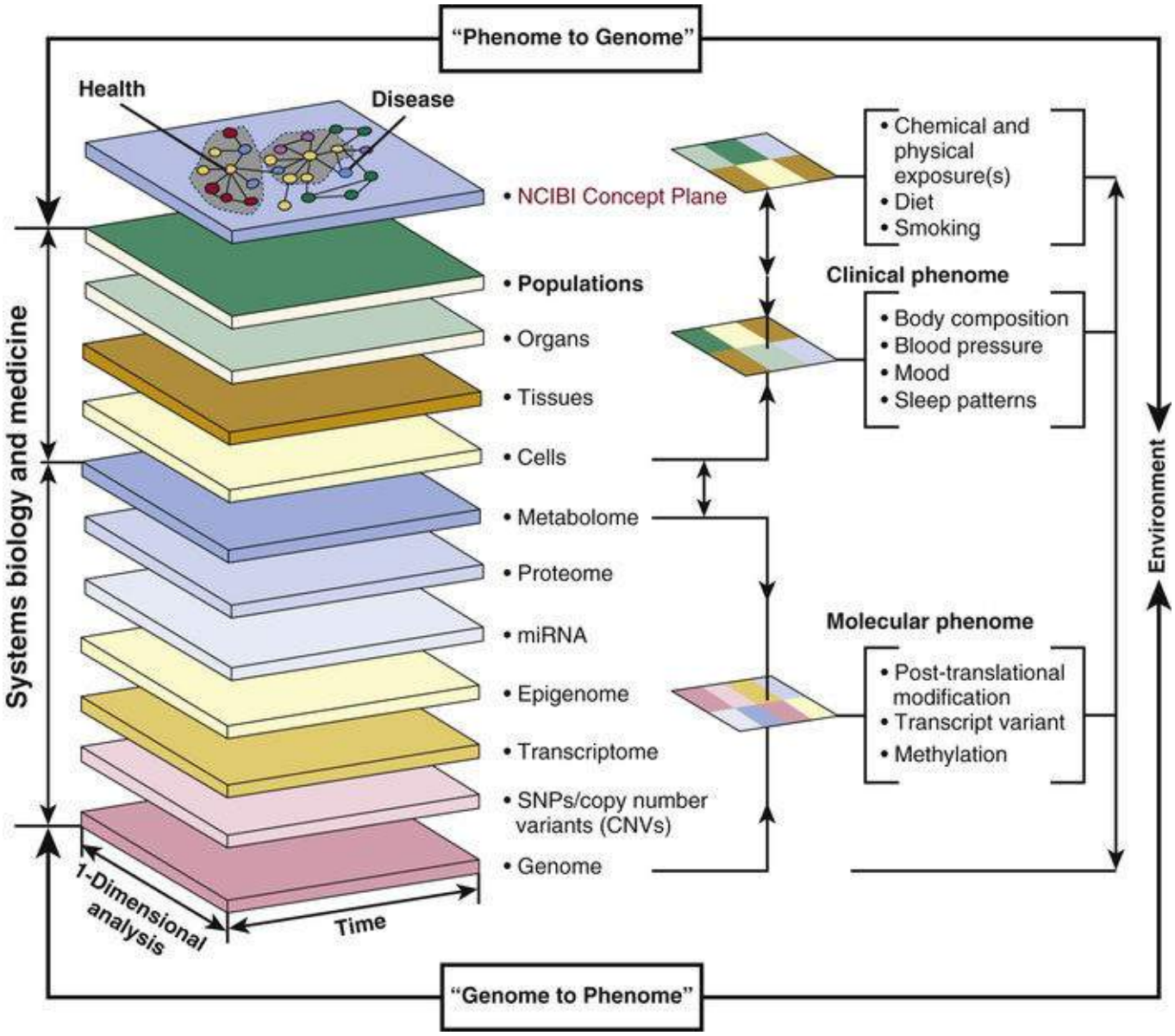

FIGURE 6.1 Systems medicine: layers of data. An infinite number of data layers can likely inform clinical medicine. Creating the informatic frameworks to understand how these datasets interact and how they can impact care, as well as defining those data necessary for decision making, will be a major undertaking that will determine the success of precision medicine. *NCIBI,* National Center for Integrative Biomedical Informatics; *SNPs,* single-nucleotide polymorphisms.

Genetics

The cardiovascular arena has seen much work on the practical application of genetics, including understanding complex paroxysmal phenotypes, such as arrhythmias and sudden death, which have challenged the ability to resolve traits into their constituent components.[13] The long tradition of physiologic measurements and classic risk factor epidemiology in cardiovascular research has also facilitated large genotype-phenotype correlation studies as genomic technologies have become available (**see Chapter 7**).

Large extended families, with what in retrospect seems to be relatively exceptional penetrance, have been the focus of pioneering work in the identification of causative genes and in ongoing efforts to define

disease mechanisms.[9] However, more typical families have inherited contributions to disease that are smaller and considerably less informative. Indeed, spurious "mutations" have proliferated, often in spurious disease genes, based on simple "guilt by association," without rigorous demonstration of mechanistic involvement.[14,15] Even mutations definitively characterized as "causal" in one family may have no discernible phenotype in another family or when seen in the general population, as recently demonstrated in population cohorts.[16,17] Differences in clinical manifestations may reflect differences in sensitizing genetic modifiers or in environmental exposures, but these mechanisms have proved difficult to establish in all but a few cases. Such observations emphasize the importance of developing approaches that allow clinicians to establish a mechanistic role for specific variants in individual patients if genetics is to influence clinical care in precision medicine. Although we have gleaned great etiologic insights from classic mendelian genetics, using simple genotypes to specify diagnoses or to drive therapies in individual patients is, at present, far from reality.

The limits of genotype-phenotype correlation are most obvious in disorders in which profound selection pressures drive elevated de novo mutation rates, often in multiple highly conserved genes, with consequent allelic and genetic heterogeneity. In some cases the imprecise relationship between genotype and phenotype may reflect real differences in the mechanism of action of different variants within the same gene. In severe congenital heart disease, where the survival of the organism during the neonatal period is at risk, despite familial recurrence rates consistent with single genes of large effect size,[18] few if any cases have a "sufficient and necessary" genetic explanation.[19] In this setting, gene-gene or gene-environment interactions are often cited as possible mechanisms for this discordance, but usually without empiric evidence.

Whole-genome or whole-exome approaches reveal the true scale of the genotype-phenotype conundrum, typically generating numerous potential causal variants in the absence of any systematic approaches to understanding which of the variants is causal.[20] Without probabilistic indices of causality, it will be difficult to define disease mechanism, identify novel drugs, and successfully render medicine precise.[6] Conditioning environmental stimuli (intra- and extra-uterine) are almost invariably unknown and unmeasured, which amplifies these limitations.[21] Where genetic selection pressures are less acute (e.g., coronary artery disease, hypertension), in addition to unmeasured environmental factors, the aggregation of different etiologies and the low specificity of negative diagnoses make clinical genetic interpretation challenging.

A rigorous bedside family history can identify potential disease risk and may allow the clinician to discriminate between environment and inheritance from the patterns of transmission. When undertaken systematically across patient cohorts, family history can also assist in the quantitative estimation of heritable and acquired contributions to disease architecture. The advent of the electronic health record (EHR) has diminished the quality of family and exposure data collection, although the success of precision medicine will depend on this information.[5,22] Eventually, relatedness will be estimated on measured genotypes, and heritability could be directly assessed from the EHR.

Similarly, exposures must be measured with quantitative rigor to define fully the role of *environment* in disease causation, prognosis, and therapy. Personal devices, detailed nutritional intake, and microbiota, among many other datasets, will eventually stream into medical records. The scale of investment necessary to capture and integrate this missing information is unlikely to be duplicated outside the EHR, supporting the eventual integration of care and discovery in a single system.

Genomics and Functional Genomics

The development of modern technologies for affordable and efficient genotyping of millions of variants in a single experiment led to the emergence of the *genome-wide association study* (GWAS)[23] (**see Chapters 7 and 45**). Large cardiovascular population studies and clinical trial datasets have been recast in terms of life-long exposure to particular genotypes. These techniques have identified hundreds of loci contributing to numerous continuous traits, from plasma lipids to electrocardiographic parameters. Binary phenotypes such as atrial fibrillation and myocardial infarction have also been successfully studied. Importantly, for the vast majority of identified GWAS loci to date, the underlying mechanism of their contribution to disease is unknown, at least partially reflecting that in most cases these alleles explain only a modest proportion of the observed heritable variance for the trait.[10] Exceptions to this rule typically reflect limited effects of the disease on reproductive efficiency.[11] Gene-gene or gene-environment interactions are rationally invoked as explanations for the "missing heritability," but few efforts have directly tested whether these mechanisms are important for most traits. Ever larger GWASs seem unlikely to address these concerns, not least as a result of the failure to resolve underlying heterogeneity, but also because the scale of study required to understand multiple interacting loci of small effect size is prohibitively expensive. In addition, a plausible alternative model for the source of missing heritability are alleles that are simply unmeasured because of limited phenotyping or a dependence on unknown conditioning variables. The adoption of more rigorous, proximate quantitative phenotypes and an approach to the objective measurement of environmental factors would leverage, through greater cohort homogeneity, much of the unrealized potential of modern genomics.[8]

Genomic measures of common variation have considerably greater predictive rigor than the highly pleiotropic mendelian variation. However, current limitations for this purpose are the lack of lifetime risk prediction models, the incremental nature of the genetic information over traditional risk factors, the very modest effect sizes, and the consequent absence of mechanistic discrimination. GWAS data may be useful for the evaluation of potential therapeutic targets identified by other means or for the assessment of potential pharmacologic safety concerns.[24]

One important attribute of a genome is its *completeness*. Indeed, at present, genomics represents one of the few accessible comprehensive datasets for an organism. As a result, genomics may well prove a useful organizing framework for much of biology and medicine, long before the data are reduced to practice. Genomic sequencing, if performed at birth or even earlier, not only could orchestrate the prioritization of collection for phenotypic data, but also would enable risk-driven preventive care in areas with no biomarkers, the efficient study of disease alleles in relevant model organisms, and the development of patient-specific narratives for lifetime disease.

Other "-Omic" Technologies

Genomic technologies have spawned parallel approaches to the collection of large and unbiased datasets in other areas of biology, including transcriptomics, metabolomics, proteomics, lipidomics, and metagenomics (**see Chapter 9**). Large-scale RNA sequencing has enabled the characterization of the true extent of transcription across the genome.[25] The massive complexity added to the output of each gene through differential splicing of different protein-coding exons or RNA regulatory exons and RNA editing adds new dimensions to the traditional exome.[26] However, the observation that much of the noncoding genome is also actively transcribed and has diverse functions through microRNAs, long intervening noncoding RNAs, and effects on access to DNA or RNA binding sites has changed the conceptual framework of how the genome functions.[25] Other regulatory RNAs, complex intermediates, and

exogenous sequences also exist, although their functions may be less obvious. Some of these represent the products of microbial commensals from skin, gut, or elsewhere, and DNA and RNA sequencing has begun to explore the complexities of the microbiome in health and disease.[27]

Improvements in quantitative mass spectrometry and new technologies such as aptamers (oligonucleotide-based reagents) are beginning to make rigorous proteomics a reality, but the vast differences in relative abundances of some proteins continue to hinder the field. Aptamer technologies may help overcome some of these limitations.[28] Mass spectrometry is also revolutionizing the ability to measure a wide range of physiologic small molecules, lipids, and metabolites.[29] Some of these molecules have been shown to mediate interactions between microbiome and host in the setting of chronic vascular disorders.[27] However, by their nature, each of these datasets remains less comprehensive than a genome.

Avenues already exist to move functional genomic technologies toward diagnostic and therapeutic use, but realizing their full utility requires much more rigorous understanding. As massively parallel datasets are collected and studied, it will also be vital to build dynamic time series in the context of structured perturbations. These perturbations might include standardized environmental, nutritional, or drug challenges. In addition, it will be necessary to understand fluxes between discrete tissue or cellular compartments. In most instances, there are very few data on interacting molecules, highlighting the need for much broader application of identified molecular components in individual classes and emphasizing the central role of systems or network biology in deciphering this new biology.[1,3] Despite some remarkable insights from functional genomics, the incorporation of new profiling technologies into the clinical arena has been slow, largely because of appropriate concerns regarding the need for robust validation through prospective approaches. It is difficult to see how traditional study designs can be appropriately scaled. Full exploitation of these approaches will require building investigative platforms that allow the study of integrative biology in large populations and in multiple different disease states.

Drug Responses and Pharmacogenetics

The effectiveness of a timed and structured challenge to assess the “state” of a complex system has been recognized in cardiology for decades (e.g., fluid challenges to assess hemodynamics). The dynamics of drug responses are among the most rigorously studied inherited traits, since the presence of a perturbation improves the power of most genetic analyses. Moreover, most drugs currently used have known major targets, so pharmacogenetic studies are often more efficiently validated. Despite these observations, the clinical collection of drug response data remains sparse, and the use of pharmacogenetics in clinical practice is rare outside of oncology (**see Chapter 8**).

Several factors have conspired to delay the routine implementation of pharmacogenetics. First, in most cases the drug responses themselves are reasonable surrogates for acute “on-target” efficacy or toxicity, and pharmacogenetic endpoints have not included mortality or morbidity.[30,31] Second, the turnaround time for genetic testing is usually discordant with clinical decision making, as in acute coronary syndromes where the use of higher doses or alternative agents to overcome potential hazards with clopidogrel in specific CYP2C19 genotypes precluded widespread use of genotyping.[32] Obviously, genome sequencing at birth and prospective lifetime analyses would resolve many of these concerns.

The real power of genetics is the unambiguous identification of causal mechanisms. An understanding of “mechanism” transforms the ability to discover and develop new drugs or therapies. Genetic-model organisms have had remarkable success in rare diseases but are not yet available for most common disorders that afflict humans. A major outcome of precision medicine might be the identification of novel

disease biology and thus new therapeutic targets.[8,33]

The identification of new targets through precision medicine would herald the need to transform the current approaches to drug discovery. When integrated with the evolving scientific fields of high-content, phenotype-driven screening and target identification, it will become increasingly feasible to use disease itself as the effective target in drug discovery, rather than one specific pathway downstream in the causal chain.[34,35] Innovation must change the scale and efficiency of drug discovery by almost an order of magnitude if society is to be able to afford precision medicine. Similarly, creative reappraisal of regulatory approaches in drug development would be necessary for the efficient introduction of novel precision therapies.[36] Without precision therapy, precision medicine will have limited effect.

Missing Data: What Is Needed for Precision

A refrain that emerges from precision medicine is the limited nature of data collected in the traditional clinical system. The massive complexity of genomic or functional genomic data contrasts with the modest scale even of the sum of all assays performed in clinical medicine. Deconvoluting the information content embedded in functional genomics requires a substantial change in the scale of modern clinical assessment. However, this shift must not jeopardize the patient-physician interaction (**Table 6.1**).

TABLE 6.1

Data Scales for Clinical Medicine and Genomics

DATA TYPES	DATA SCALE ESTIMATES	METADATA	RELEVANT DATA STANDARDS
History	10^3	No	Tradition but subjective
Physical examination	10^2	No	Largely subjective
Clinical testing	10^4	Few	Objective but few standards
Metabolomics	10^2	No	Emerging
Whole genome	3.0×10^9	N/A	Yes
RNA sequencing	$\approx 10^{18}$	Yes	Yes
Proteomics and post-translational modifications	$\approx 10^{20}$	Yes	Emerging
Cellular connectome	$>10^{69}$	Not yet	None

The clinical history must become more structured, focused on the individual, and rigorously documented. Simply digitizing the traditional cross-sectional retrospective history will not suffice. Ideally, personal histories would include long-term symptom trajectories, symptomatic correlates of objective responses to standardized dynamic challenges, quantitative data on prior exposures, and personal reference data on these same parameters.

In parallel, the core physical examination itself must be modernized. Defining a digital “physical exam” with sufficiently rigorous representation of the core systems and low enough cost for universal implementation is a priority for precision medicine, but has only begun to emerge as a focus through efforts in phenotype ontologies. Genome structure could act as a core comprehensive dataset, but others might include lifetime digital morphometry and wearable or portable technologies focused on quantitative cellular or molecular phenotypes. Ultimately, most data collection will be ambient, with parallel acquisition of metadata, including the administration of specific challenges (e.g., nutritional, pharmacologic). Short-term goals for modern medicine might include detailed lifetime trajectories for a shared set of representative orthogonal phenotypes—a computable physical examination in which deviations from normal would be readily detectable by existing technologies.

Expansion of the scope of phenotyping would extend the power of extant genotypic data and would allow stratification before the introduction of comprehensive functional genomics (**Table 6.2**). Another

rationale for these strategies is the assumption that, in conjunction with complete genomes, more rigorous phenotyping facilitates real-time modeling of disease, whether in silico or in animals. Disease modeling will be further refined by the incorporation of perturbations that can be uniformly applied to model systems and patients alike. A mechanism-centric conceptual framework could facilitate bringing the definition of causation, biomarker, or drug discovery and even drug development to the level of the individual patient or family.[37]

TABLE 6.2

Ideal Phenotype Characteristics

TRADITIONAL PHENOTYPES	PRECISION PHENOTYPES
Intuitive or serendipitous	Unbiased
Qualitative	Quantitative
Static	Dynamic
Few metadata	Dense metadata with translatable stimuli
Cross-sectional	Continuous
Final common pathway	Predisease
Limited translatability	Translatable by design

Integrating Discovery and Care

A major consequence of increasingly comprehensive strategies for the collection of genomic data, phenotypes, and environmental exposures across entire populations and over lifetimes will be the ability to approach gene-gene, gene-environment, and other complex interactions (e.g., host-commensal communication) in a rational manner. This scale of endeavor will require reimagining the clinical and the research enterprise. Indeed, the traditional division between these two spheres of activity will increasingly become blurred in what are currently imagined as “learning health systems.” The prevalent concept is that embedding data collection and data analytics in the EHR would enable real-world experimentation, even including randomization, to explore previously inaccessible questions.[38] Ultimately, the modular addition of new data acquisition tools and new implementation or care delivery platforms might evolve to the point where those elements of care amenable to algorithmic management extend beyond professional involvement, and professional activity would be fully integrated with discovery and translational science. Sharing quantitative genotypic, environmental (including pharmacologic), and phenotypic vocabularies will allow the various communities within biomedical science to work more cohesively.

Barriers to Precision Medicine

Several barriers currently impede the broad implementation of precision medicine, requiring substantive change to realize its full potential (**Table 6.3**). To resolve even one disease with all its complexities to the level of mechanism for a specific patient will require substantial societal changes in attitude toward the use of data in health care. Ultimately, personal control of information may be the most effective solution to many of the extant hurdles.

TABLE 6.3

Barriers to Precision Medicine

AREA OF ACTIVITY	BARRIERS	POTENTIAL OR EMERGING SOLUTIONS
Evidentiary framework	Cost of generating traditional evidence Lack of familiarity with technologies Few RCTs Wide range of risk and benefit	Cost reductions Education Real-world RCTs Alternative trial designs
Phenotypic data collection	Haphazard, serendipitous Legacy data types Few metadata Cross-sectional data collection	Fully embedded in clinical systems Phenomes by design Molecular interventions as metadata Ambient data collection/public engagement
Genomic data collection	Largely research-based reporting Cost Few metadata Limited evidence base	Development of rigorous reporting standards Cost reductions Parallel development of phenome science Development of rigorous evidence base
Data structure	Current EHRs limited in scope Legacy data architecture Data architecture institution-centric	Comprehensive personal records New data types Patient-centric architecture
Data sharing	Security risks Data provenance Privacy/HIPAA Lack of perceived value	Rigorous security and audit Data escrow Reevaluation of privacy trade-offs Objective evidence of value to individual
Analytics	Lack of availability in EHR Limited probabilistic models Lack of provider familiarity Lack of patient engagement	Creation of platforms on top of EHRs Development of probabilistic decision support Adaptive education for patient and provider
Data display	Massive growth in data density and data velocity Legacy data formats Mismatched provider training	Reimagining data display and workflow together across care redesign Investment in user interface development “On the fly” decision support
Clinical adoption and implementation	Legacy workflow Lack of evidence of clinical utility Limited perceived value Limited technical understanding Vested interests Perception of organizational intransigence	Comprehensive care redesign Test genomics in relevant clinical contexts Develop evidence of value Genome as part of the physical exam Care models outside traditional medicine Lay/patient engagement
Education	Rote learning overwhelmed Limited informatics training Decade-scale education cycles	Transition from rote learning to data science Rigorous informatics training Real-time adaptive learning
Regulation	Anchored in traditional evidence base Emphasis on population risk/benefit	Ongoing regulatory innovation Incorporation of individual risk/benefit
Reimbursement and funding	Cost of innovation and new technology Lack of perceived value No rigorous models for comprehensive testing with need for continuous reporting Limited revenue stream diversity	Reduction in cost Definition of added value Moving beyond transactional reimbursement Payment models outside traditional medicine Diversification of revenue streams
Ethics	Caution due to perceived determinism Professional practice restrictions; “turf wars” Archaic innovation cycle	Education for providers and patients Elimination of “genetic exceptionalism” Real-world implementation in clinical context

EHRs, Electronic health records; *HIPAA,* Health Insurance Portability and Accountability Act; *RCTs,* randomized controlled trials.

The goal of any precision medicine platform must be the development of biological frameworks for diagnosis and decision making, which cannot be achieved with the limited information content of the current EHR. Requirements for data collection, aggregation, management, and display will be incorporated in systems focused on the individual, with individual responsibilities, as with most activities outside health care. Data scientists predict that “learning health systems” will extract information from the perturbations of routine care. The deployment of such capabilities will require completely different information systems architecture than current platforms, which focus largely on provider transactions.

Compared with the enormous datasets in almost every other venue of daily life, the identification of environmental factors for understanding health and disease has progressed slowly. Exploiting data from numerous contexts in people's lives may seem like a forceful intrusion, but these approaches are commonplace in commerce or financial security and will be essential to dissect disease mechanisms.[39] Incorporating new data into the health care system will require investment in infrastructure, analytics, and security.

The exponential growth in knowledge implicit in precision medicine will also require new strategies for the management and display of information. One of the most important challenges in precision medicine is the balance between large-scale data collection across time, or across populations, and the highly specific data needed to define the current biological state in an individual. Navigating these distinctions will require a clinical workforce trained in information science.

As clinical care and discovery become more tightly integrated, so too professional and patient education must transform. The need for the collection and display of "just-in-time" information in every encounter will require adaptive learning platforms. Finding ways to incorporate rigorous data collection with high-impact education in the midst of routine care is a central design issue in precision medicine and will require leveraging the EHR for truly meaningful use.[40]

With these disruptive changes, it will be vital not to discard the "ground truth" in medicine painstakingly assembled over the years, while avoiding the urge to uphold the shibboleths of medicalization. Bringing scientific rigor to entire populations will require careful mapping of genomics and novel phenotypes onto existing frameworks. In the clinical arena, it will be important not to replace empathic physician-patient relationships with bland digital encounters. Rather, the seamless upload of objective information at scale will facilitate the elimination of the "provider as data-entry clerk" that has accompanied the implementation of EHRs, thereby promoting true professional-patient interactions.

Many of the hurdles to the implementation of precision medicine result at least in part from the intransigence of different constituencies within the current system. Numerous vested interests must adapt if precision medicine is to succeed, including the organization of the professional workforce. The interdependencies implicit in precision medicine will require the addition of new skills to medicine, new team structures, and new training paradigms.

Future Perspectives

Earlier diagnosis and therapy will lead health systems to reach back into ever-younger populations, with the latest sequencing technologies promising whole-genome coverage before birth. A convergence of technologies, new drugs, big data, and innovation from every other sphere of life together with societal pressures will push medicine to focus on *wellness*, with the goal of detecting and intervening at the first deviation from this state. The discrete steps to achieve broad implementation of precision medicine are not yet obvious. Cardiology, with a long history of successfully pivoting from late-stage disease toward progressively earlier intervention and prevention, is well positioned to lead precision medicine.

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7

Principles of Cardiovascular Genetics

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As physicians, we seek to understand the root cause of human disease. Human genetics provides a unique tool for generating new hypotheses about the root causes of disease based on genome-wide searches in the human population that avoid prior assumptions about the underlying pathophysiologic processes. Over the past several decades, application of the principles discussed here has successfully identified the

causative genes for a range of cardiovascular diseases. This information has provided explanations to our patients, improved the ability to predict risk for disease, and most importantly, enabled understanding of the pathophysiology as a foundation for designing rational approaches to improving prevention and therapy.[1] This chapter reviews the principles of human genetics used to make gene discoveries and to translate these findings to improve patient care. We highlight these principles in the context of a clinical case presentation.

Inherited Basis for the Variation in Risk for Cardiovascular Disease

Patient Case, Part I.

A 44-year-old man (JS) presents to a cardiologist's office for a follow-up visit after an ST-segment elevation myocardial infarction (STEMI) and treatment consisting of primary angioplasty and placement of a drug-eluting stent. His cardiovascular risk factors before STEMI included a fasting low-density lipoprotein cholesterol (LDL-C) level of 235 mg/dL and active cigarette smoking. His body mass index (BMI) is 25 kg/m^2, he does not have a history of type 2 diabetes, and he is normotensive. His father died at 45 years of age as a result of myocardial infarction (MI), and his paternal uncle had an MI at age 49. He has two brothers, 43 and 39 years old; both are free of clinical cardiovascular disease. The 43-year-old brother (KS) has an elevated LDL-C level (214 mg/dL). The 39-year-old brother (LS) has an LDL-C level of 130 mg/dL and a high-density lipoprotein cholesterol (HDL-C) level of 29 mg/dL. **Fig. 7.1** shows the family pedigree.

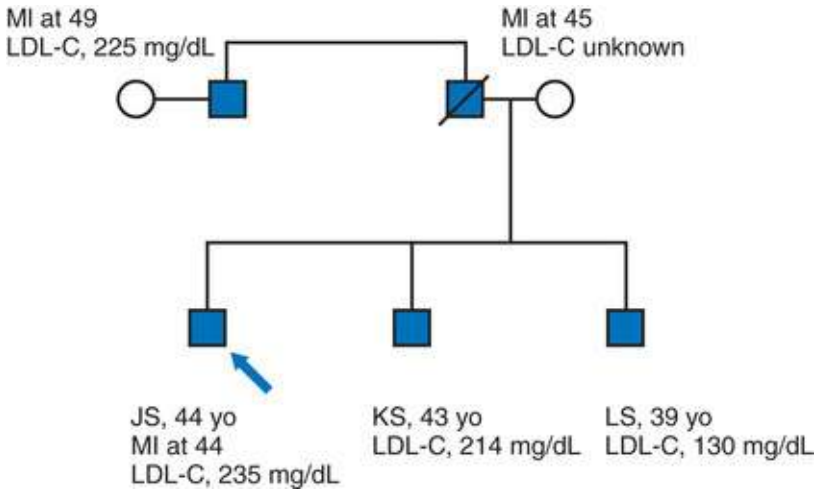

FIGURE 7.1 Pedigree of the case patient JS (indicated by the *arrow*), who had a STEMI when he was 44 years old (yo).

Many cardiovascular diseases cluster within families, and studies of familial aggregation can determine the extent to which inherited DNA sequence variants contribute to these patterns. A family history of premature coronary heart disease (CHD) elevates the risk for CHD in offspring approximately threefold.[2] Family history is an important risk factor for almost every cardiovascular disease, including atrial fibrillation, congenital heart disease, and hypertension, but familial clustering of disease can reflect shared environment in addition to shared genetic sequence.

Heritability—the fraction of interindividual variability in risk for disease attributable to additive

genetic influences—is a commonly used measure for isolating the role of shared genetic sequence. The remaining variability among individuals results from all other contributors: environmental influences on disease, nonadditive (*epistatic*) genetic effects (e.g., gene-gene interactions or gene-environment interactions), error in the measurement of relatedness or disease, and random chance. For most clinically important traits (diseases and risk factors), empiric estimates of heritability range from 20% to 80% (see Online Mendelian Inheritance in Man, available at www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?db=OMIM, for comprehensive information).

A Brief Primer on Molecular Biology

Genes are encoded in DNA, a polymeric molecule with two strands in a configuration known as a double helix. The "code" comprises four different DNA bases—adenine (A), cytosine (C), guanine (G), and thymine (T)—linked together in nonrandom order. The two strands contain redundant information by virtue of complementarity—an adenine on one strand is always paired with a thymine on the other strand, and a cytosine on one strand is always paired with a guanine on the other strand. Thus double-stranded DNA consists of a sequence of A-T, T-A, C-G, and G-C base pairs (**Fig. 7.2**).

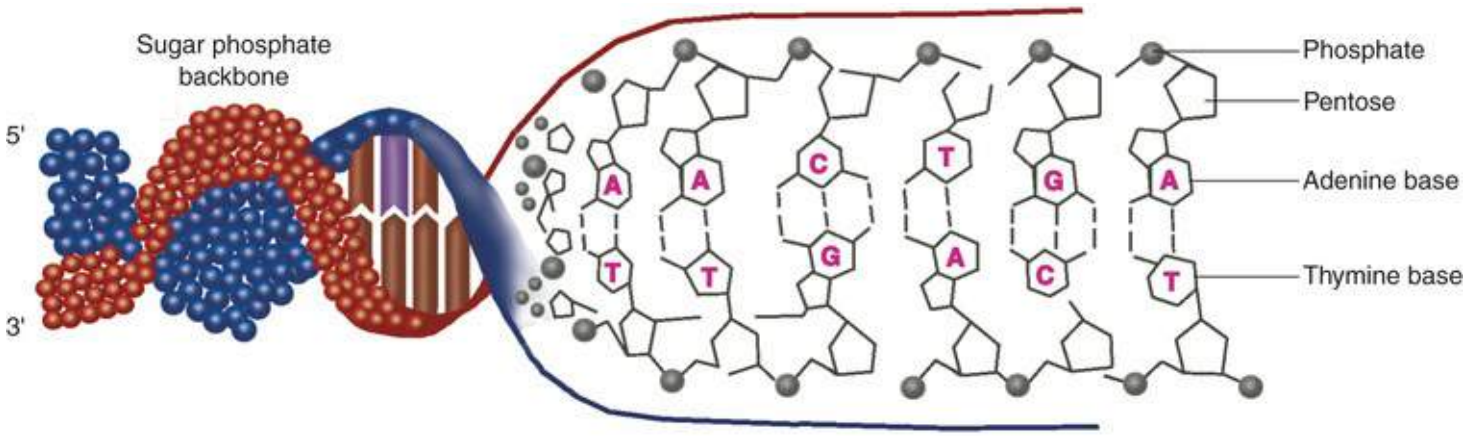

FIGURE 7.2 Schematic representation of the DNA double helix. The specificity of genetic information is carried in the four bases—guanine (G), adenine (A), thymine (T), and cytosine (C)—that extend inward from a sugar phosphate backbone and form pairs with complementary bases on the opposing strand.

Human DNA is organized into a total of 23 pairs of chromosomes, with each chromosome spanning millions of base pairs. The 46 chromosomes in total make up the genome. Each chromosome has numerous genes, which contain so-called coding DNA, separated by large stretches of noncoding DNA. A process called *transcription* copies the information in the DNA sequence into a single-strand coding RNA, also called a messenger RNA or mRNA, a polymer that is structurally similar to DNA but uses uracil (U) in place of thymine (T). Subsequently, the process of translation converts the mRNA sequence into an amino acid sequence that makes up a protein, which can serve in a variety of roles (e.g., structural elements, enzymes, hormones). Thus, genetic information flows from DNA to RNA to protein in what is classically known as the "central dogma" of molecular biology (**Fig. 7.3**).

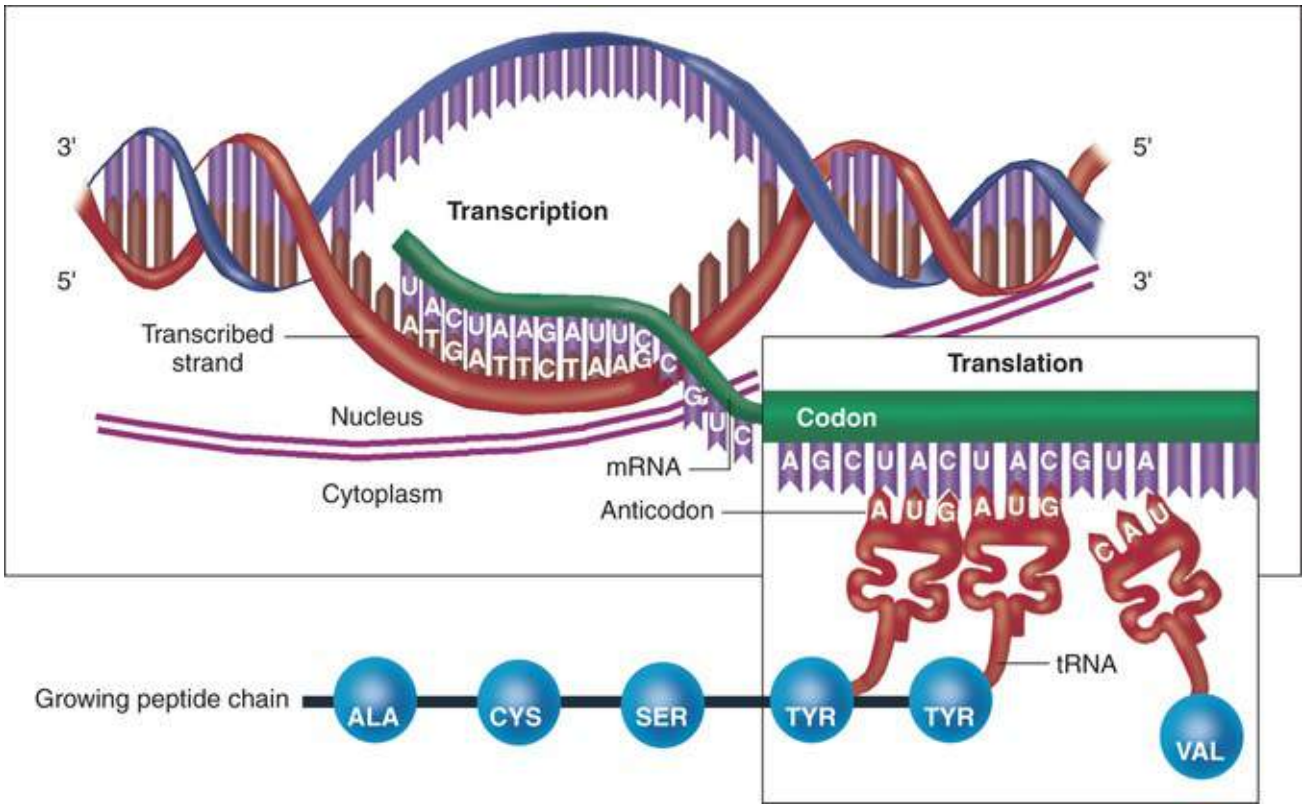

FIGURE 7.3 Flow of genetic information. Transcription in the nucleus creates a complementary RNA copy from one of the DNA strands in the double helix. mRNA is transported into the cytoplasm, where it is translated into protein.

According to the central dogma, a change in the DNA sequence in the genome, if it should occur in or near a gene, can result in a change in the protein encoded by the gene, which in turn can have important consequences on the phenotype of an organism. *Phenotype* refers to any observable characteristic in a human. Changes in DNA sequence leading to phenotypic changes underlie most of the heritability of diseases that have a genetic component.

Epigenetics pertains to phenotypic changes caused by external factors in addition to altered DNA sequence that influence the process of gene transcription. These factors can result in altered levels of RNA being transcribed from the DNA, which in turn result in altered levels of protein. In some cases, parents can transmit the epigenetic changes to offspring and thus represent an additional source of phenotypic heritability. Epigenetic changes include DNA-level modifications that do not involve the DNA sequence itself. The most common such modification is methylation of cytosine bases, which generally results in reduced transcription or “silencing” of a gene.

Within a chromosome, the DNA molecule coils in a complex known as *chromatin*, which includes a group of proteins called *histones*. The configuration of these histones around the DNA molecule can change through structural modifications (e.g., acetylation or deacetylation of certain amino acids), making an area of a chromosome more “open” or “closed” to transcription. Consequently, the genes within that area of the chromosome may undergo increased or decreased transcription.

Epigenetic mechanisms also include factors external to the DNA and chromatin that affect the transcription and translation of genes. In addition to genes, the genome harbors thousands of expressed RNA molecules that do not code for protein; such noncoding RNAs (ncRNAs) include microRNAs and long ncRNAs. The ncRNAs, particularly long ncRNAs, can regulate transcription through several mechanisms, including interactions with the cell's transcriptional machinery and with histone-modifying enzymes. ncRNAs also interact with and modulate the activity of mRNAs, thereby regulating protein amounts. For example, microRNAs physically bind to complementary sequences in mRNA molecules and

result in either suppression of RNA translation into proteins or degradation of the mRNAs.

Modes of Inheritance

The “genetic architecture” of a disease refers to the number and magnitude of genetic risk factors that exist in each patient and in the population, as well as their frequencies and interactions. Diseases can result from a single gene (*monogenic*) in each family or from multiple genes (*polygenic*). Identifying genetic risk factors is easiest when only a single gene is involved and this gene has a large impact on disease in that family. In cases in which a single gene is necessary and sufficient to cause disease, the condition is termed a *mendelian* disorder because the disease tracks perfectly with a mutation (in the family) that obeys Mendel's simple laws of inheritance.

For monogenic disorders, modes of inheritance include autosomal dominant, autosomal recessive, and X-linked. In autosomal dominant disorders, a single defective copy of a gene (either the maternal or paternal copy for every autosomal gene) suffices to cause the phenotype. In autosomal recessive disorders, both copies need to be defective to lead to the phenotype. In X-linked disorders, the defective gene resides on the X chromosome. Given that men have only one X chromosome and women have two X chromosomes, men who carry the defective copy are affected with the disorder, whereas women are unaffected carriers.

Most common cardiovascular diseases, however, do not obey Mendel's simple laws of inheritance but rather are complex—the result of an interplay between multiple genes and the environment. These polygenic disorders require variants in more than one gene to cause a disease. Accordingly, in these cases it becomes difficult to understand a disease by studying a single family. A corollary is that each contributing gene variant may have a small phenotypic effect that is not obvious by comparing a few people with and without that variant. For these reasons, elucidating the genetic architecture of a complex disorder is more feasible by studying a large population.

The patient case presented earlier describes both *discrete* cardiovascular phenotypes (i.e., traits defined by their presence or absence based on a set of criteria) and *quantitative* phenotypes. MI is a discrete (also called *dichotomous*) phenotype, whereas blood pressure, LDL-C, HDL-C, and BMI are continuous cardiovascular traits. In the general population, most of these traits display a complex pattern of inheritance.

For many complex traits, however, some subtypes of the disease are monogenic in inheritance. In our patient case, the co-occurrence of high LDL-C, early-onset MI, and a family history of premature MI suggests a specific mendelian disorder, namely, *familial hypercholesterolemia* (FH).[3] In FH the extremely high LDL-C level and MI result from defects in the LDL receptor gene. Severely high LDL-C and early MI can also be caused by defects in other genes, including proprotein convertase subtilisin/kexin type 9 (*PCSK9*) and apolipoprotein B (*APOB*). Other examples of monogenic subtypes of complex traits include extremely high or low blood pressure caused by rare mutations in genes involved in renal salt handling; extremely low LDL-C as a result of mutations in *APOB*, *PCSK9*, or *ANGPTL3*; and extreme obesity caused by mutations in *MC4R*.

Approaches to Discovering the Inherited Basis for Cardiovascular Disease

Human Genetic Variation

The human genome contains about 6 billion base pairs across the 46 chromosomes. Only about 1% of the genomic DNA actually encodes the estimated 20,000 genes in humans.[4] Although all humans share most of the DNA in the genome, variations in the DNA sequence—occurring in both coding DNA and noncoding DNA—distinguish individuals from one another. These DNA sequence variants partly account for why a disease is more or less likely to develop in some individuals or why some respond more favorably or more adversely to a medication (**see also Chapters 6 and 8**).

As alluded to earlier, some DNA sequence variants have large phenotypic effects, meaning that they can cause disease singlehandedly. These DNA sequence variants tend to be rare (and sometimes unique to a single person or family) because natural selection weeds them out of a population. Classically, they cause monogenic disorders. Other DNA sequence variants commonly occur in a population and tend to have smaller phenotypic effects. Typically, such variants, in combination, cause polygenic disorders. Because of natural selection, in general there is an inverse relationship between the frequency of a DNA sequence variant and the phenotypic effect conferred by that variant. For example, such a relationship applies to gene variants that affect LDL-C in the population[5-8] (**Fig. 7.4**).

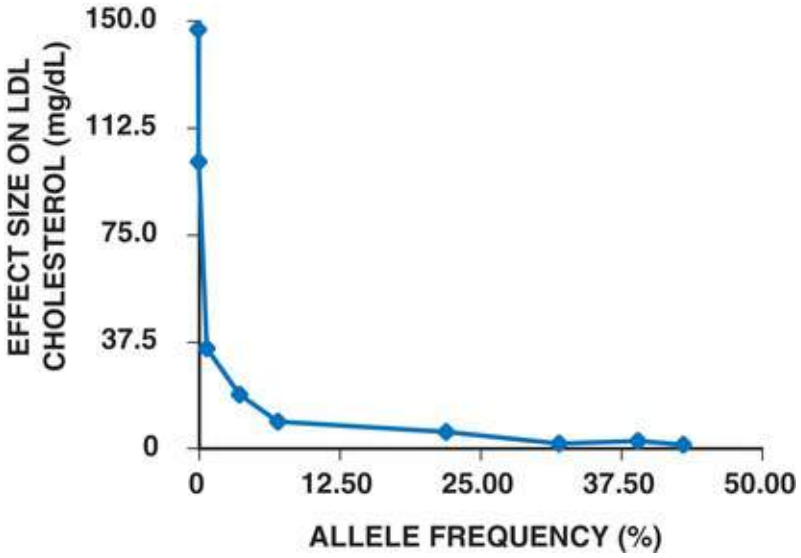

FIGURE 7.4 Effect sizes on LDL-C for DNA sequence variants at a range of allele frequencies. Gene, variant, frequency, and effect size on LDL-C are as follows: *NPC1L1*, rs217386,[5] 43%, 1.2 mg/dL; *HMGCR*, rs12916,[5] 39%, 2.5 mg/dL; *ANGPTL3*, rs2131925,[5] 32%, 1.6 mg/dL; *SORT1*, rs629301,[5] 22%, 5.7 mg/dL; *APOE*, rs429358/C130R,[6] 7.1%, 9.3 mg/dL; *APOE*, rs7412/R176C,[6] 3.7%, 18.8 mg/dL; *APOB*, R3500Q,[7] 0.08%, 100 mg/dL; *LDLR*, W23X or W66G or W556S,[8] 0.03%, 147 mg/dL.

Coding-sequence variants potentially disrupt the function of genes and their protein products[9] (**Fig. 7.5**). Some coding variants do not affect the amino acid sequence of a protein; such "synonymous" variants generally cause no phenotypic consequences. Other coding variants can cause a variety of alterations in a protein—substitution of a single amino acid in a protein with a different amino acid (*missense*), premature truncation of a protein (*nonsense*), scrambling of the amino acid sequence past the site of the variant (*frameshift*), or insertion or deletion of amino acids. Any of these so-called nonsynonymous variants can have phenotypic effects ranging from negligible to profound, although nonsense and frameshift variants tend to be more deleterious than missense variants to protein function. Also, sequence variants at splice sites (the first and second bases after the end of each exon and before the beginning of each exon) can lead to a severely disrupted protein product missing a domain encoded by

an entire exon.

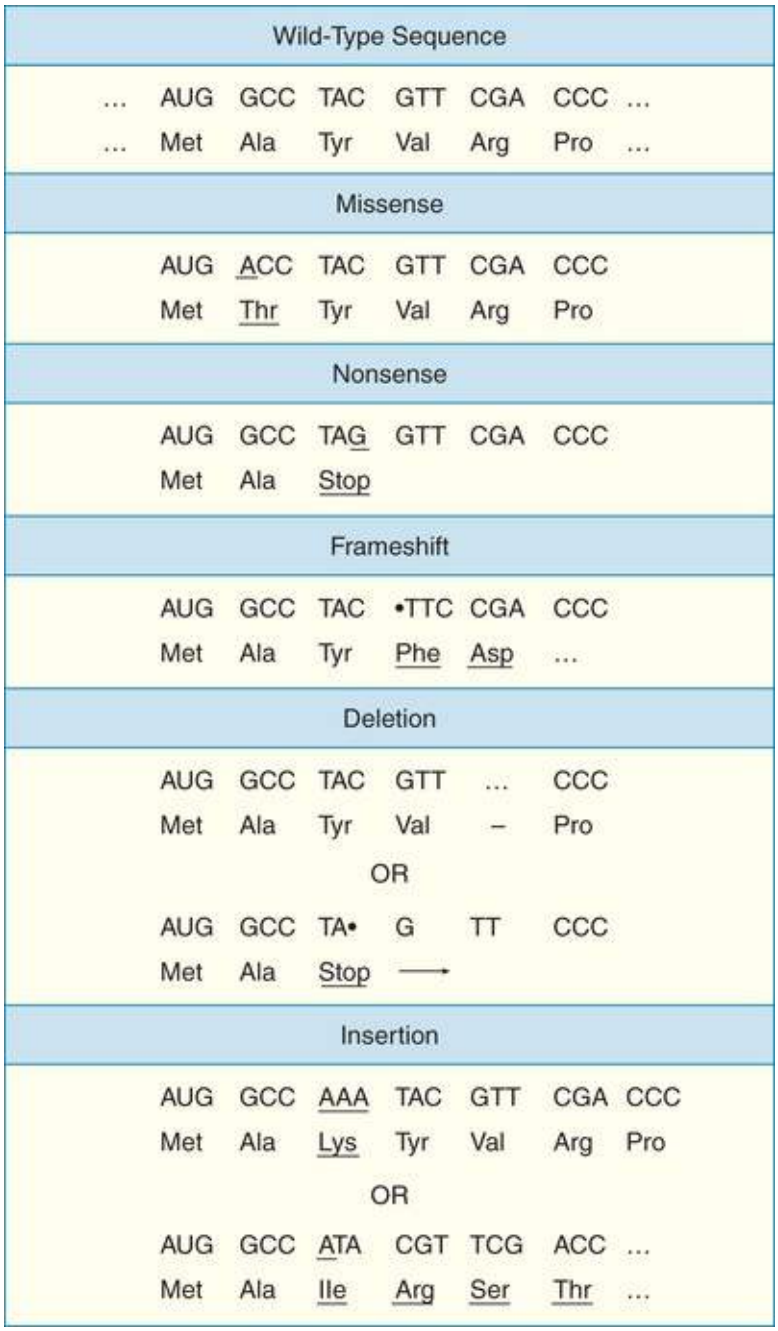

FIGURE 7.5 Different types of mutations that alter the structure and expression of human genes.

Noncoding variants, although they do not directly affect the amino acid sequences of proteins, can cause phenotypic changes in other ways. For example, a noncoding variant near a gene might affect transcription of the gene and result in an increased amount of RNA being produced from a gene, and consequently an increased amount of the protein product.[10] Noncoding variants can affect the processing of RNA in other ways; for example, a noncoding variant that falls in the midst of a microRNA sequence might impair or enhance the microRNA's ability to interact with specific mRNAs and thus result in phenotypic changes.

DNA sequence variants, also known as *polymorphisms* (from the Greek, “multiple forms”), consist of three major classes. *Single-nucleotide polymorphisms* (SNPs) involve the alteration of a single DNA base pair in the genome. SNPs are the most common and best cataloged of the DNA variants, with tens of millions having been identified to date across all human populations. *Variable number tandem repeats*

(VNTRs) involve a variable number of repeats of a short DNA sequence at a genomic location; the number of repeats ranges from very few to thousands. *Copy number variants* (CNVs) involve a variable number of repeats of a long DNA sequence (>1000 base pairs), typically ranging from zero to one or a few repeats. An *indel* (insertion/deletion) is a type of DNA variant in which a sequence is either present (insertion) or absent (deletion); it could be either a special type of a VNTR or a special type of a CNV, depending on the size of the involved sequence.

Characterizing Human Genetic Variation: Genotyping and Sequencing

In most cases a person has two copies of each DNA sequence because of the presence of paired chromosomes (the exceptions are DNA sequences on the X or Y chromosome in men, because these two chromosomes are entirely different). The two copies are known as *alleles*. For a DNA variant, the *genotype* is the identity of the two alleles at the site of the variant. The two alleles may be identical, in which case the person is said to be homozygous for the allele. If the two alleles are different, the person is heterozygous at the DNA variant. A *haplotype* is a series of genotypes at nearby sites of DNA variants. Because the haplotype is located on a single region of the chromosome, it tends to remain linked together as it passes from parents to offspring.

For polymorphisms that are primarily present in just two forms (typical of SNPs, i.e., one DNA base versus another DNA base, but not for VNTRs, which are usually found in at least a few forms, i.e., different numbers of repeats), the allele found more commonly in a given population is termed the *major* allele, with the less common allele being the *minor* allele. Common variants are so defined by virtue of the frequency of the minor allele being greater than 5% in the population. Low-frequency variants have a minor allele frequency of between 0.5% and 5%; rare variants have less than a 0.5% frequency. Rare variants are typically referred to as mutations. In some cases, mutations are so rare that they are found only in one individual or in one family.

Two types of methods can be used to determine genotypes at the sites of DNA variants. In the first type, a genotyping technology directly ascertains the genotype at a single location in the genome. In the second type, polymerase chain reaction (PCR) is used to amplify the region of DNA immediately surrounding the site of the DNA variant (**Fig. 7.6**). The PCR product undergoes DNA sequencing, which indirectly determines the genotype. The first type is generally cheaper—indeed, fabricated “chips” can directly genotype millions of DNA variants at a time—but requires optimization beforehand. Thus direct genotyping is most useful for common and low-frequency variants that have already been cataloged. The second type is more expensive and can be used only at one location at a time, but it can be flexibly adapted to any location in the genome. This approach can be used to discover previously uncataloged, rare DNA sequence variants.

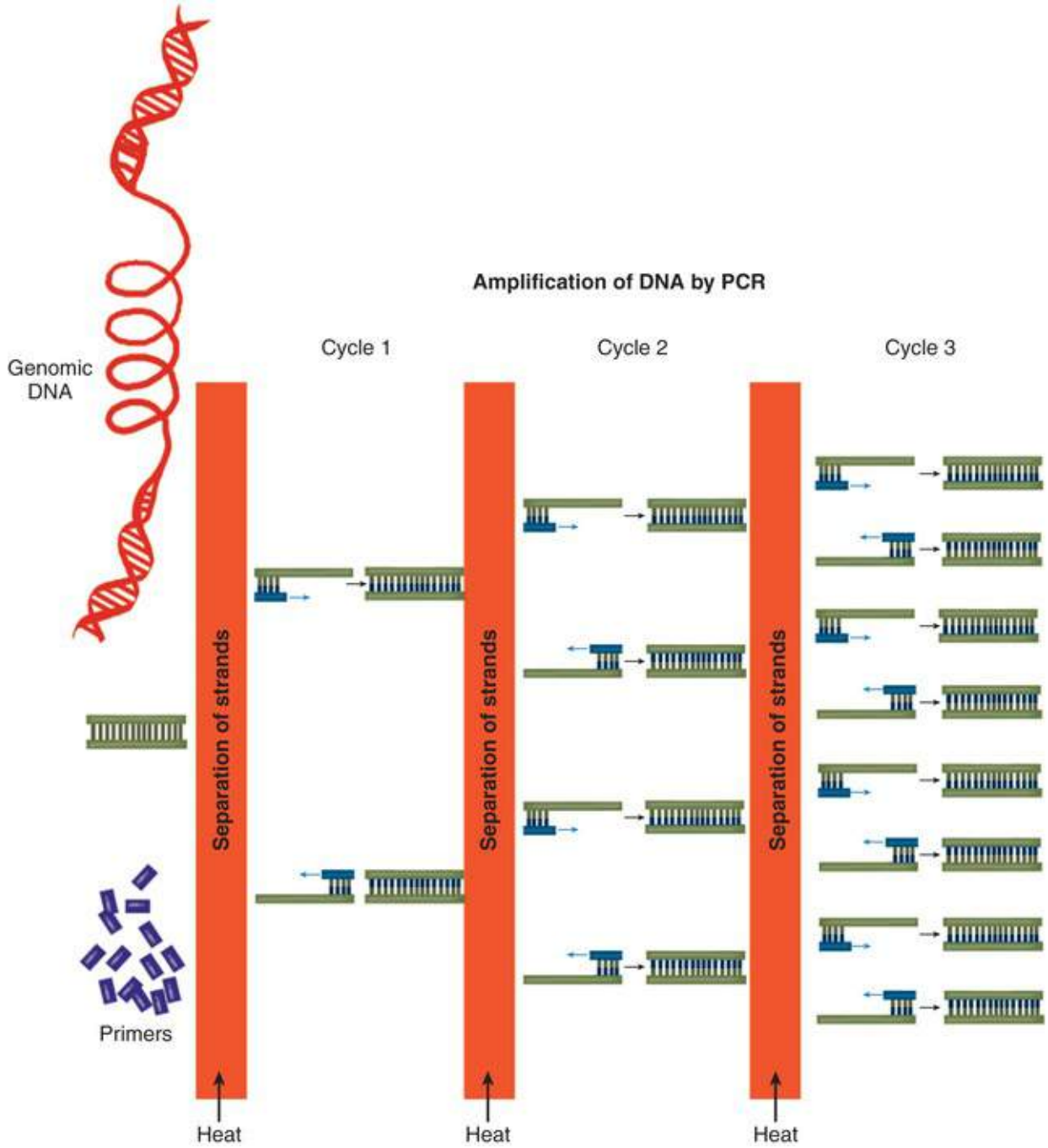

FIGURE 7.6 DNA amplification with PCR. Synthetic primers corresponding to the 5′ and 3′ ends of the DNA sequence are chemically synthesized. The double-stranded DNA is melted by heating to 95°C, followed by cooling to anneal the primers and then setting at 68°C to 72°C for optimal polymerase activity. A heat-stable DNA polymerase amplifies each strand of the target sequence, which produces two copies of the DNA sequence. The process is repeated multiple times to achieve amplification of the target sequence.

In recent years a third type of method has been devised to characterize a person's genetic variation. This method entails the use of any of a group of techniques known as “next-generation DNA sequencing.”[11] Although the operational details differ, these techniques share the ability to sequence billions of DNA base pairs at a time rapidly and at a reasonable cost. The techniques can sequence efficiently the entirety of a patient's coding DNA, known as the *exome*, which accounts for about 1% of the genome.[12,13] More recently, sequencing the entirety of a patient's genome for a few thousand U.S. dollars within 24 hours has become feasible, with the eagerly awaited “thousand-dollar genome” expected to emerge very soon.

Although performing DNA sequencing remains more expensive than direct genotyping, the decreasing cost of whole-genome sequencing will soon enable its application to large cohorts of people. Whole-

genome sequencing offers the advantage of determining genotypes at the locations of all known DNA sequence variants in a single experiment and simultaneously identifying the individual's possibly previously unknown DNA variants.

Study Designs to Correlate Genotype with Phenotype

Fig. 7.7 illustrates approaches to correlate genotype with phenotype. The *x* axis shows the frequency of the allele in the population, from rare to common; the *y* axis shows the size of the phenotypic effect conferred by the DNA sequence variant allele, from small to large. As described earlier, because of evolution and natural selection, an inverse relationship exists between allele frequency and effect size. Typically, to detect common DNA sequence variants of small to modest effect (e.g., increase in risk of 5% to 50%), genotyping characterizes the DNA sequence variation, and population-based association links genotype with phenotype. Rare variants with larger effect are discovered by sequencing to characterize their DNA sequence variation. One of two major approaches—family-based studies or extreme-phenotype studies—can be used to correlate rare variants with phenotype. Variants of low frequency (0.5% to 5%) can be approached by either genotyping or sequencing, and any of the three study designs may be useful in linking genotype with phenotype.

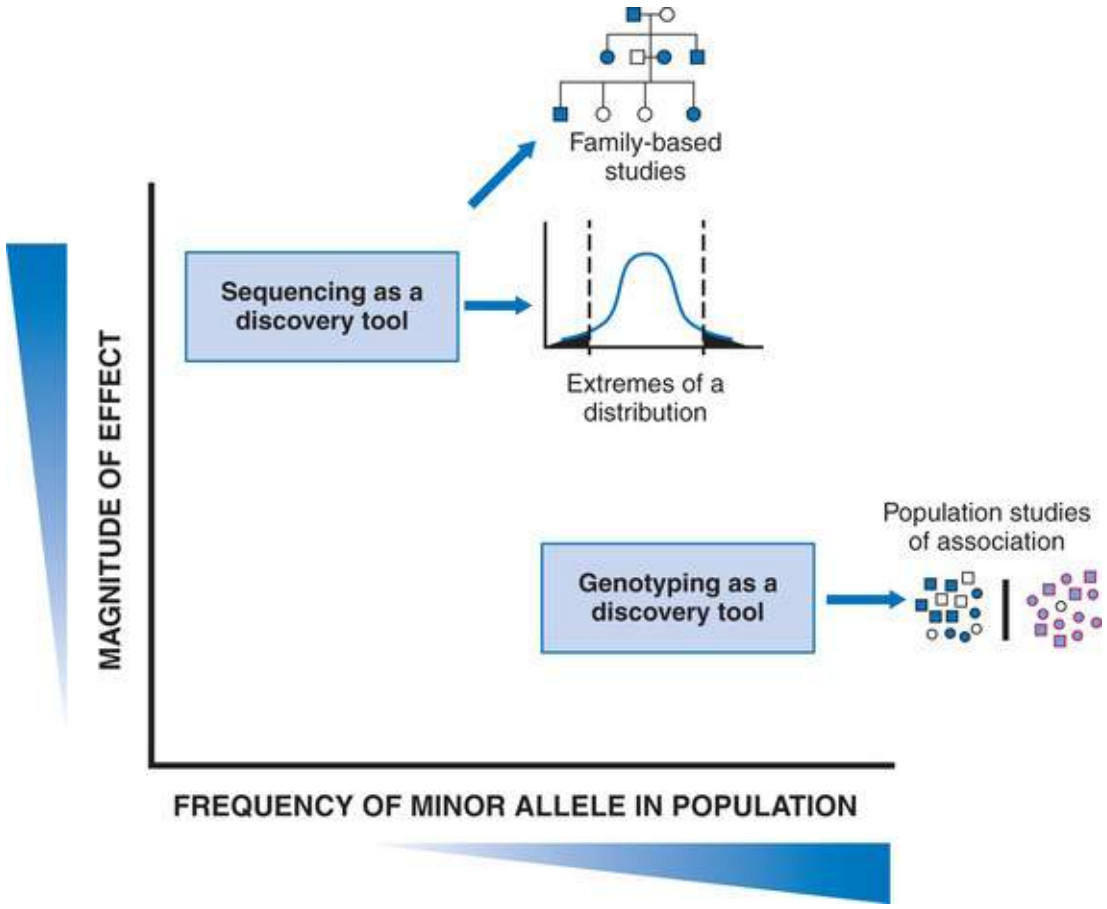

FIGURE 7.7 Approaches to correlate genotype with phenotype.

Family-Based Studies

Patient Case, Part II.

The cardiologist refers the 45-year-old patient (JS), who recently had an MI, to a geneticist for evaluation. The geneticist suspects that the patient has FH and arranges for clinical sequencing of the *LDLR*, *APOB*, and *PCSK9* genes. These tests identify a mutation in the *PCSK9* gene: a T → A substitution in exon 2 at nucleotide 625, which predicts a substitution of arginine at codon 127 for the conserved serine (Ser127Arg). This mutation causes gain of PCSK9 function and autosomal dominant hypercholesterolemia.[14]

Two major study designs serve to identify the gene mutations responsible for monogenic disorders. Both take advantage of family relationships. Classic *linkage* studies entail the genotyping of several hundred or thousand DNA variants (usually VNTRs with repeats that are two to six base pairs in length, also known as microsatellite markers) distributed across the genome. Linkage analysis identifies any markers that are strongly "linked" to the disease. For dominantly inherited disorders, linkage can be observed when one particular allele of the marker is found only in family members with the disease ("affecteds") and not in healthy family members ("unaffecteds"). For recessively inherited disorders, linkage is observed when two copies of a particular allele are found only in family members with the disease and not in healthy family members. The degree of linkage for each genomic marker with affected status is calculated to yield a metric known as the logarithm of odds (LOD) score. A LOD score higher than 3.0 is considered significant evidence of linkage.

As a practical matter, a high LOD score for a particular marker suggests that the causal disease mutation lies within several megabases (i.e., millions of base pairs) of the marker. This region of interest typically harbors dozens, if not hundreds, of candidate genes. The region can sometimes be narrowed further by genotyping a set of markers clustered around the original marker and assessing for linkage, a process called *positional cloning*. Identification of the disease mutation entails sequencing candidate genes in the hope of finding a rare coding variant. Traditionally, cost constraints prohibited sequencing of a large number of genes and forced judicious selection of a limited number of candidate genes thought most likely to have the causal mutation—an often fruitless approach.

Advances in next-generation DNA sequencing technologies have enabled a second study design. Rather than sequencing a few candidate genes, one can now perform *exome sequencing* and capture the coding DNA of all approximately 20,000 human genes in a single, relatively affordable experiment. In this study design, one chooses a few affected family members, performs exome sequencing on their DNA samples, and filters through the sequencing data to identify the handful of rare variants that all affected individuals share.[15] This list of variants can be narrowed down further in several ways, such as confirming that a variant is not present in unaffecteds or simultaneously performing a linkage study and filtering for variants that reside near a marker with a high LOD score.

Once the rare gene variant thought most likely to be the causal mutation is selected, it can be confirmed by sequencing the gene in unrelated individuals who have the same disorder. If some of these individuals have mutations in the same gene (either the same rare variant or, more likely, different variants), it strongly argues that the gene is responsible for the disease.

Extreme-Phenotype Studies

Study of individuals in a population who are at the extremes of a phenotype provides another approach to gene discovery.[16] For a quantitative phenotype such as blood cholesterol level, this undertaking might entail finding a sizable number of people with extremely high cholesterol and people with extremely low cholesterol. For a discrete phenotype such as MI, the desired individuals might be young people with premature disease versus elderly people with multiple risk factors but no evidence of coronary artery disease (CAD).

DNA samples from these extreme cohorts undergo either candidate gene sequencing, exome sequencing, or even whole-genome sequencing. The analysis entails identifying genes that have a preponderance of rare variants in one group versus the other group. For example, if a particular gene were to display a significantly higher frequency of rare variants in young people with MI than in elderly people without CAD, it would argue for that gene being causal for MI. Conversely, if the gene had a higher frequency of rare variants in elderly people without CAD than in young people with MI, the gene might protect against disease.

Population-Based Studies

Family-based studies lend themselves poorly to study polygenic disorders in which each contributing DNA variant has a small or moderate effect. Because these DNA variants tend to be common in a given population, population-based studies can more readily detect their small effects with statistical rigor.

The genome-wide association study (GWAS) is the primary population-based study design.[17,18] In a GWAS, DNA samples from many unrelated individuals in a population—as many as hundreds of thousands of people—undergo genotyping using chips of millions of SNP markers across the genome. The analysis entails a search for SNPs that have robust statistical associations with the phenotype of interest. For a GWAS on a quantitative phenotype such as blood cholesterol level, each SNP undergoes testing to determine whether individuals with one genotype at that SNP have on average a significant difference in cholesterol level from individuals with another genotype.

For a GWAS on a discrete phenotype such as MI, the study compares a group of individuals with the phenotype and a group of individuals without the phenotype (cases versus controls). Each individual SNP is evaluated to determine whether its minor allele frequency differs between the cases and controls (**Fig. 7.8**).

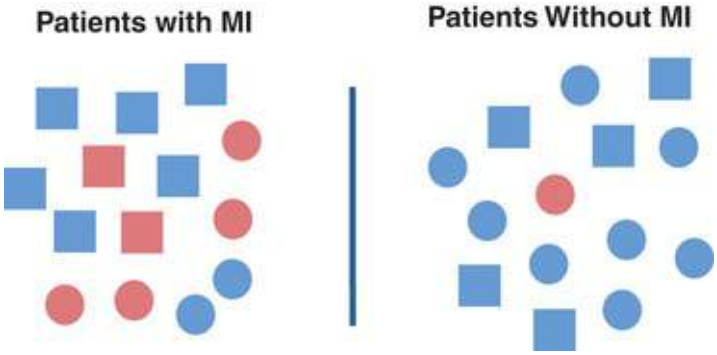

FIGURE 7.8 Analysis scheme for a GWAS involving a dichotomous phenotype. *Step 1:* Compare frequency of genetic variant in cases and controls. Carriers of a variant allele are shown in *pink* and noncarriers in *blue*. *Boxes* represent men and *circles,* women. Here the variant allele occurs more frequently in cases than controls. *Step 2:* For each genetic variant (typically 300,000 to 1 million in each experiment), generate *P* value for the difference in frequency being a chance observation.

Because GWASs evaluate many SNPs independently, the traditional statistical significance threshold of $P < 0.05$ requires adjustment for the number of SNPs tested. A GWAS typically tests about 1 million independent common SNPs. Accordingly, to minimize false-positive results, GWASs usually use a threshold for genome-wide statistical significance of $P < 5 \times 10^{-8}$ (i.e., Bonferroni correction of the traditional *P* value of 0.05 for 1 million independent tests). The need to meet a very rigorous significance threshold, as well as the small effects of most DNA variants that contribute to a polygenic trait, often dictates studying very large numbers of people to carry out a GWAS successfully.

GWASs typically display results in a “Manhattan plot,” with the *x* axis representing each variant in chromosomal order and the *y* axis plotting $-\log_{10}$ of the *P* value associating each variant with the trait of interest. **Fig. 7.9** displays the Manhattan plot from a large-scale GWAS for CAD that identified 25 chromosomal loci that achieved genome-wide significance.

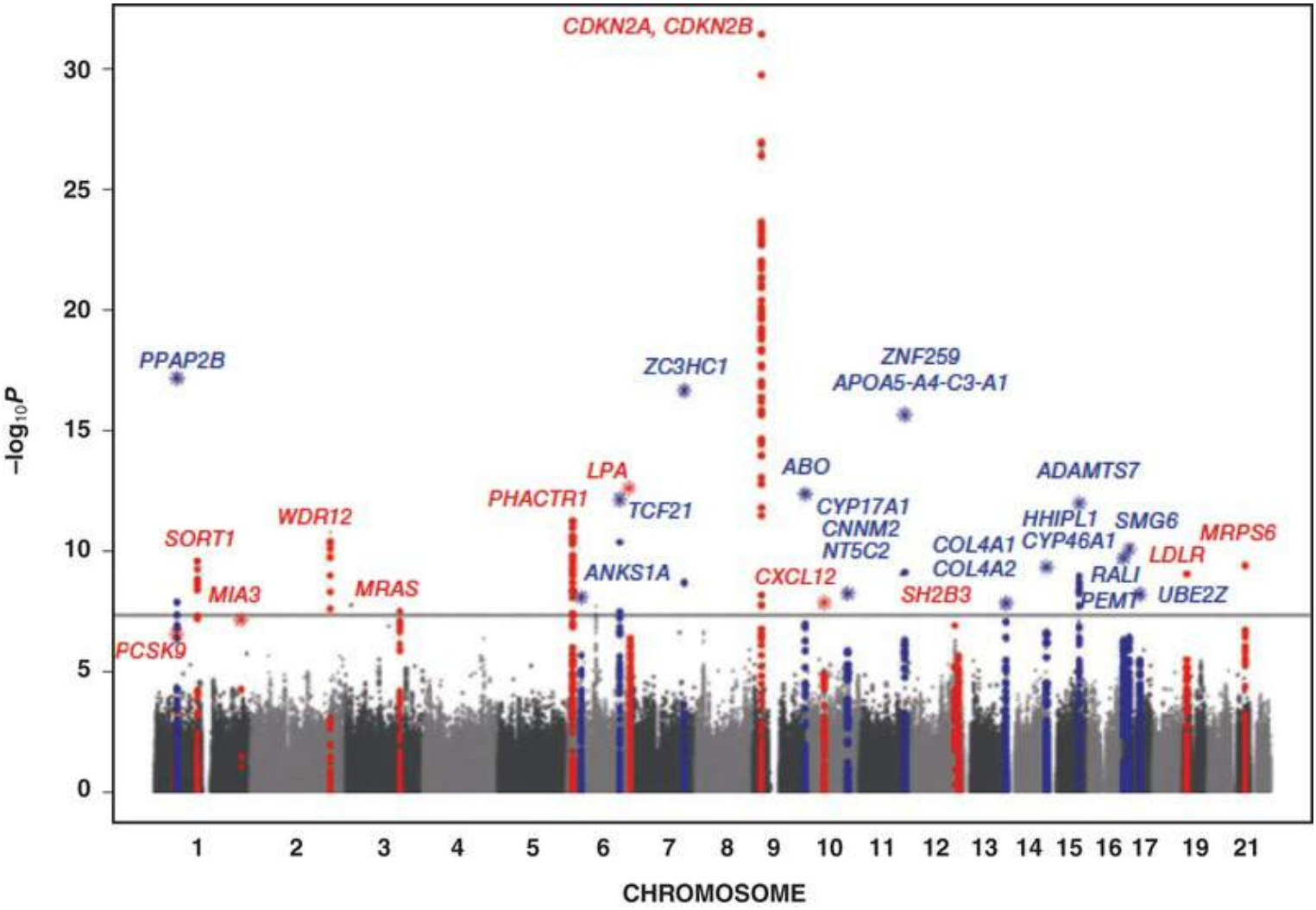

FIGURE 7.9 Graphic summary (Manhattan plot) of genome-wide association results. The *x* axis represents the genome in physical order; the *y* axis shows $-\log_{10}$ *P* for all SNPs. Data from the discovery phase are shown in *circles*, and data from the combined discovery and replication phases are shown in *stars*. Genes at the significant loci are listed above the signals. Known loci (before publication of this work) are shown in *red*, and newly discovered loci from this work are shown in *blue*. (From Schunkert H, Konig IR, Kathiresan S, et al. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. Nat Genet 2011;43:333.)

A GWAS uses a much denser distribution of markers across the genome and data from many more people than a linkage study does. Furthermore, a GWAS takes advantage of the genome's discrete recombination “hot spots,” between which regions of DNA remain relatively intact as they pass from parents to offspring. Consequently, a GWAS has much higher resolution than linkage studies; rather than megabases, the locus of interest is defined by flanking recombination hot spots, which on average occur just tens to hundreds of kilobases apart. For a given SNP with a positive association with a phenotype, this considerably narrows the number of candidate causal genes. Also in contrast to linkage studies, GWASs have successfully pinpointed noncoding causal DNA variants that affect gene expression.

Illustrative Examples

In presenting examples of the various approaches previously described, we focus on LDL-C—whether in the context of monogenic lipid disorders such as FH or in the context of the blood LDL-C level as a polygenic, quantitative trait.

Mendelian Disease Using Classic Linkage

Familial hypercholesterolemia is a monogenic disorder in which patients have extremely high blood LDL-C levels that result in abnormal deposition of cholesterol (xanthomas) and a severely increased risk for premature MI, as early as childhood. Initial studies in the 1970s and 1980s demonstrated that most cases of FH result from mutations in the LDL receptor gene (*LDLR*).[19] In 1989 a subset of cases were found to result from mutations in *APOB*.[20] Following these discoveries, other cases remained in which neither *LDLR* nor *APOB* mutations appeared to be responsible.

Abidfadel and coworkers[14] identified French families affected by FH without apparent *LDLR* or *APOB* mutations and, in performing a linkage study, identified a region on chromosome 1 where markers had strong linkage to the disease. Using positional cloning, they narrowed the region to an interval containing 41 genes. One gene, *PCSK9*, was a strong candidate because a similar gene had previously been reported to be involved in cholesterol metabolism. Sequencing *PCSK9* identified two different rare variants in different families. Subsequent studies in mice supported *PCSK9* as a regulator of blood cholesterol levels and indicated that the mutations discovered were likely to be gain-of-function rather than loss-of-function mutations.[21]

Mendelian Disease Using Direct DNA Sequencing

Musunuru and colleagues[22] identified a family in whom four siblings displayed extremely low blood LDL-C, HDL-C, and triglyceride levels—an apparently recessive disorder termed *familial combined hypolipidemia*. A linkage study could not identify the causal gene because of the prohibitively large number of genes in the linkage region. Years later, following the advent of exome sequencing, DNA samples from two of the siblings underwent such analysis. In a comparison of the siblings' exomes, only one gene harbored rare DNA variants in both alleles in both siblings—the angiopoietin-like 3 (*ANGPTL3*) gene, which had been implicated previously in the metabolism of triglycerides, but not LDL-C. Of note, the siblings had two different mutations, each of which was a nonsense mutation, consistent with total loss of *ANGPTL3* function. Subsequent studies confirmed the presence of various *ANGPTL3* mutations in unrelated individuals with familial combined hypolipidemia.

Complex Trait Using Extremes in a Population

Shortly after the discovery of *PCSK9* as a causal gene in FH, Cohen and colleagues[23,24] hypothesized that loss-of-function variants in *PCSK9* may contribute to differences in blood cholesterol levels in the general population. Reasoning that individuals with low LDL-C levels were more likely to have such loss-of-function variants (because gain-of-function mutations cause increased LDL-C levels in FH), they sequenced *PCSK9* in individuals at the phenotypic extreme in the multiethnic Dallas Heart Study—those with the lowest LDL-C levels. Several of these individuals had one copy of either of two different nonsense variants in the gene. The investigators then specifically genotyped at the sites of the two

nonsense variants in the entire Atherosclerosis Risk in Communities study and found that together, 2.6% of the black subjects in the study had either of the two variants. These individuals had on average a 28% reduction in LDL-C compared with those without *PCSK9* variants. Subsequent work demonstrated that individuals with *PCSK9* nonsense variants have significantly reduced risk for incident CHD (**Fig. 7.10**). Individuals with loss-of-function variants in *PCSK9* did not show adverse consequences, thus suggesting that therapies directed against *PCSK9* would offer beneficial cardiovascular effects without any accompanying undesirable effects.

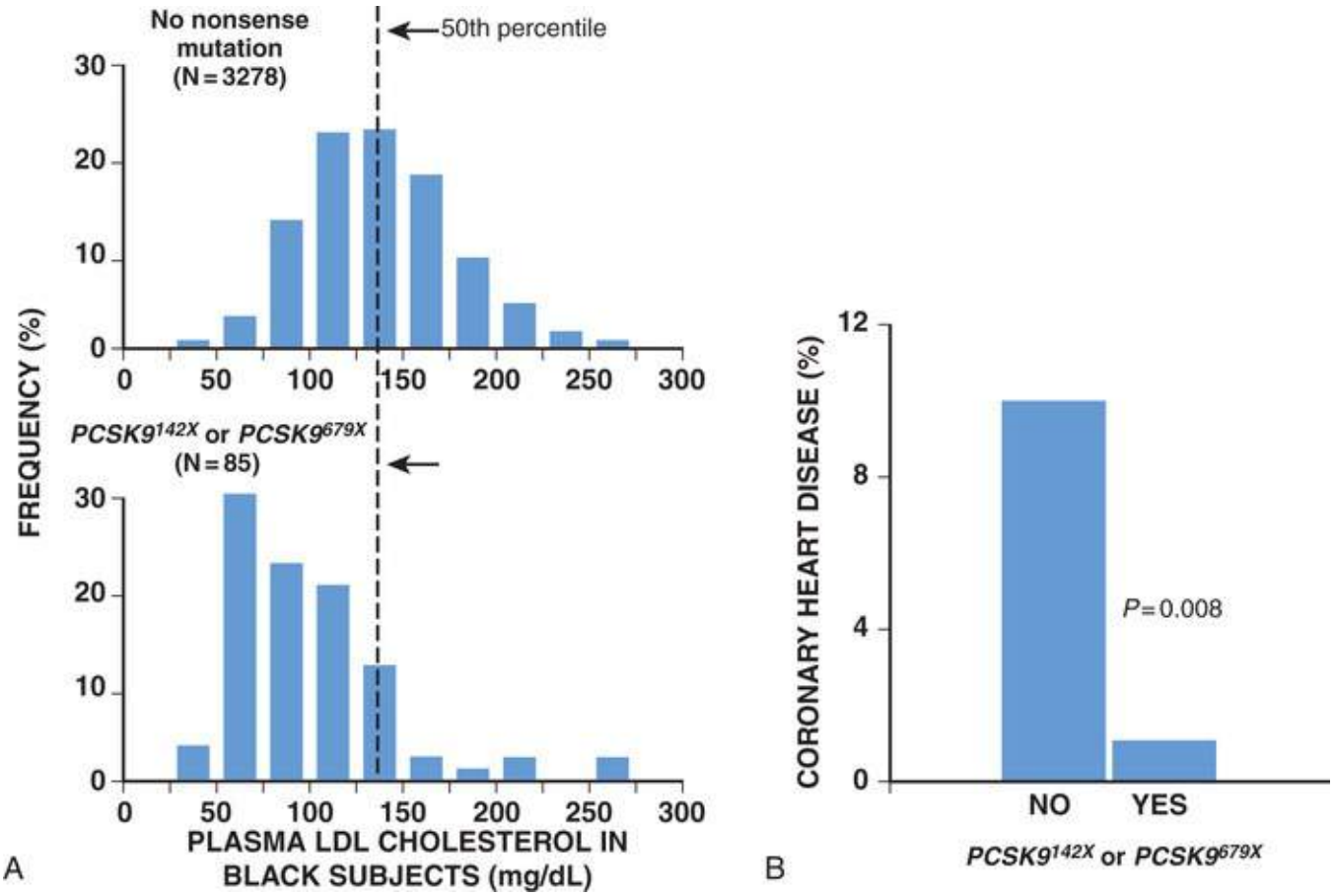

FIGURE 7.10 **A,** Distribution of LDL-C, and **B,** risk for CHD, in carriers versus noncarriers of nonsense mutations in the *PCSK9* gene. (From Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in *PCSK9,* low LDL, and protection against coronary heart disease. N Engl J Med 2006;354:1264.)

Complex Trait Using Genome-Wide Association

Starting in 2007, GWASs were performed on collections of individuals of European descent to identify SNPs associated with blood LDL-C, HDL-C, triglycerides, and/or total cholesterol levels. Each year brought a successively larger study and culminated in a collaborative study involving approximately 100,000 people in 2010.[5] This study identified a total of 95 loci associated with one or more of the lipid phenotypes. Remarkably, a third of the loci had genes previously known to be involved in lipid metabolism; indeed, more than a dozen genes had rare DNA variants previously deemed responsible for monogenic lipid disorders, including *LDLR*, *APOB*, *PCSK9*, and *ANGPTL3*. The other two thirds of the loci presumptively harbor novel lipid-regulating genes, inspiring considerable effort to characterize the functions of some of these genes (e.g., *GALNT2*, *SORT1*, and *TRIB1*.)

Clinical Application of Genetic Findings

Risk Prediction

Patient Case, Part III.

The two brothers of the patient JS are referred to a cardiologist for assessment of risk for MI. Both brothers are asymptomatic but are worried about their strong family history and that JS had a coronary event at a similarly young age. They inquire whether they have an increased risk for a coronary event, whether that risk can be quantified, and whether they should be changing their lifestyle or taking any medications. Both patients undergo DNA sequencing to determine whether they carry the *PCSK9* mutation responsible for disease in JS. The 43-year-old brother (KS) carries *PCSK9* Ser127Arg, but the 39-year-old brother (LS) does not.

Identifying individuals at increased risk for cardiovascular disease and implementing preventive interventions to reduce that risk are key goals of biomedicine (**see Chapters 6 and 45**). Genetic markers have long promised to discern patients at increased risk. The use of genetic markers to assess risk entails consideration of two scenarios.

The first is risk prediction in the context of a family with a mendelian disorder. Here, a single defective gene causes disease in the family. The central question is whether the asymptomatic family member carries the causal mutation (or two mutations for a recessive disease). Direct DNA sequencing can determine whether the mutation is present, which typically means a near-certain risk for disease. Yet, complexities may exist in even a single-gene disorder.[1] Among carriers of a mendelian mutation in a given family, some may exhibit the condition and others may not. *Penetrance* refers to the proportion of individuals with a given genotype who exhibit the phenotype associated with the genotype. In many mendelian cardiovascular conditions inherited in an autosomal dominant manner, evidence exists for incomplete penetrance. For example, Hobbs and colleagues[25] reported that in a pedigree with FH caused by a point mutation in *LDLR*, only 12 of 18 heterozygotes had high LDL-C (>95th percentile), whereas some of the remaining 6 heterozygotes had LDL-C as low as the 28th percentile for the population. The lack of a high-cholesterol phenotype given the same genotype may result from influences from modifier genes or from the environment.

The second scenario uses genetics to predict risk for a common, complex disease. Here, disease results from the interplay of multiple genetic and nongenetic factors. The central questions are whether genetic markers can identify a subset of the population at higher risk for disease and whether effective interventions can be allocated to this subset of individuals to reduce their risk. For example, we commonly use a nongenetic marker, the presence of type 2 diabetes mellitus, to identify a subset of the population at higher risk for CHD (those with type 2 diabetes have a twofold increase in CHD).[26] We target statin intervention to this group to reduce their absolute risk for CHD.

Use of the GWAS approach has recently identified 45 common variants for CAD or MI, thereby permitting construction of a genetic risk score using mapped variants.[27] The first 12 common variants mapped for CAD or MI using GWAS led to generation of a simple genetic risk score ranging from 0 to 24 alleles was generated (i.e., each individual can carry 0, 1, or 2 copies of the risk allele at each of these 12 sites), with 0 being ideal and 24 being the most unfavorable.[28] The distribution of this genetic risk score in the population approaches normal. Those in the top quintile of this distribution (the 20% of the population with the highest scores) had an approximately 1.7-fold increased risk for incident CHD, even after accounting for all other cardiovascular risk factors.

Will this information have clinical usefulness? Uncertainty prevails regarding whether young and middle-aged individuals (i.e., men age 30 to 50 and women age 40 to 60 years) should receive a statin to prevent a first MI. A genetic risk score might identify the subset of individuals at highest genetic risk and target statin treatment to these individuals. This hypothesis remains to be tested formally in randomized controlled trials (**see Chapter 45**)

Distinguishing Causal from Reactive Biomarkers

Patient Case, Part IV.

The 39-year-old brother of the patient JS has an HDL-C level of 29 mg/dL. Does his low HDL-C concentration causally contribute to risk for MI?

Hypotheses concerning causative agents for complex diseases have often initially come from observational epidemiology. In a 1961 paper titled "Factors of Risk in the Development of Coronary Heart Disease," Kannel and colleagues[29] in the Framingham Heart Study established an association of total plasma cholesterol with future risk for CHD. Since then, studies have linked hundreds of soluble biomarkers with risk for CAD (**see Chapters 9 and 45**). How many of these biomarkers directly cause CAD, how many simply reflect other causal processes, and why is this question important? Both causal and noncausal biomarkers may help to predict risk for future disease, but only a causal biomarker may be appropriate as a target of therapy. A randomized controlled trial (RCT) testing whether a treatment that alters the biomarker will affect risk for disease can support causality in humans. Because clinical trials are expensive and time-consuming, however, having evidence in humans before engaging in a clinical trial would be helpful.

A technique termed *mendelian randomization* uses DNA sequence variants to address the question of whether an epidemiologic association between a risk factor and disease reflects a causal influence of the former on the latter.[30-32] In principle, if a DNA sequence variant directly affects an intermediate phenotype (e.g., a variant in the promoter of a gene encoding a biomarker that alters its expression) and the intermediate phenotype truly contributes to the disease, the DNA variant should be associated with the disease to the extent predicted by (1) the size of the effect of the variant on the phenotype and (2) the size of the effect of the phenotype on the disease (**Fig. 7.11**). If the predicted association between the variant and disease does not emerge from study of an adequately powered sample, it would argue against a purely causal role for the intermediate phenotype in pathogenesis of the disease.

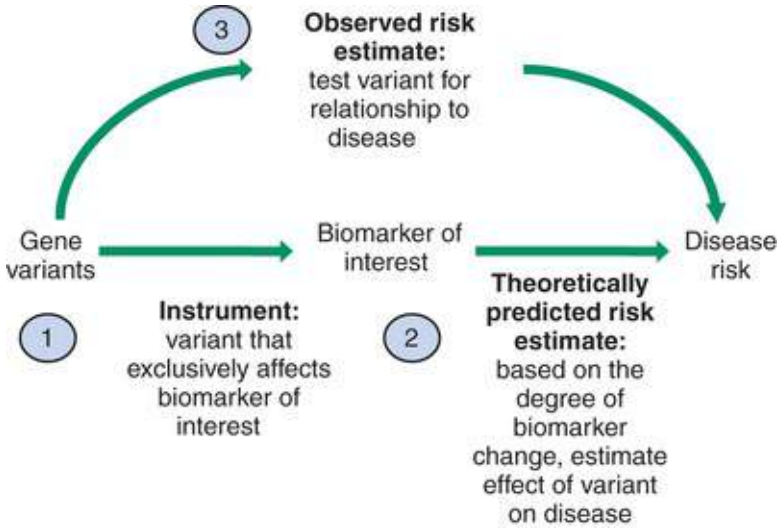

FIGURE 7.11 Design of a mendelian randomization study to test whether a biomarker causally influences risk for disease. The study design has three elements. First, one needs to identify a genetic variant, an instrument that exclusively alters the biomarker of interest. Second, one needs to derive a theoretically predicted estimate of disease risk for the instrument. This estimate is usually derived on the basis of (1) association of the gene variant to the biomarker (i.e., degree of change in biomarker conferred by variant) and (2) association of the biomarker to disease in the population (i.e., extent to which a given change in biomarker is expected to alter risk for disease in the population). Third, one derives an observed disease risk estimate for the instrument after testing the instrument for association with disease in the population. If the observed risk estimate for the instrument is consistent with that predicted theoretically, this supports the notion that the biomarker causally influences risk for disease.

The study design is akin to a prospective RCT in that randomization for each individual occurs at the moment of conception—genotypes of DNA variants are randomly "assigned" to gametes during meiosis, a process that avoids the typical confounders observed in observational epidemiologic studies. For example, a parent's disease status or socioeconomic status should not affect which of the parent's two alleles at a given SNP is passed to a child, with each allele having an equal (50%) chance of being transmitted by the gamete to the zygote. Thus, mendelian randomization should resist confounding or reverse causation. Mendelian randomization has potential shortcomings, however, including that (1) the technique is only as reliable as the robustness of the estimates of the effect sizes of the variant on the phenotype and of the phenotype on disease, and (2) it assumes that the DNA variant does not influence the disease by means other than the intermediate phenotype being studied (pleiotropy), which may not be true. In addition, a potential confounder of mendelian randomization is that, in certain situations, a disease might cause the allele of a DNA variant passed from a parent to an offspring to be expressed in a different way; for example, it could occur through inherited epigenetic effects. Nevertheless, mendelian randomization can prove as informative as a traditional RCT.

Several mendelian randomization studies have confirmed a causal relationship between LDL-C and CHD. Nonsense variants in the *PCSK9* gene that significantly reduce plasma LDL-C concentrations have been associated with a reduced incidence of CHD in a black cohort.[24] Similarly, in white patients, a low-frequency missense variant in *PCSK9* has been associated with lower LDL-C levels, as well as a lower risk for MI. Inactivating mutations in *NPC1L1*, the gene that encodes the drug target of ezetimibe, reduce both LDL-C levels and risk for CHD.[33] These observations suggest that lower LDL-C suffices to provide protection against CHD. Similar to LDL-C, several recent genetic studies have confirmed previous observations that plasma lipoprotein(a) (Lp[a]) relates causally to CHD.[34,35]

Unlike the results with plasma LDL-C and Lp(a) concentrations, a recent large mendelian randomization study of variants that affect plasma HDL-C, performed in more than 100,000 individuals, did not show an association between these variants and MI.[36] The investigators performed two mendelian

randomization analyses. First, an SNP in the endothelial lipase gene (*LIPG* Asn396Ser) served as an instrument, and this SNP was tested in 20 studies (20,913 MI cases, 95,407 controls). Second, a genetic score consisting of 14 common SNPs that associate exclusively with HDL-C provided an instrument, and this score was tested in up to 12,482 MI cases and 41,331 controls. As a positive control, the investigators tested a genetic score of 13 common SNPs exclusively associated with LDL-C. Carriers of the *LIPG* 396Ser allele (2.6% frequency) had higher HDL-C (5.5 mg/dL higher, $P = 8 \times 10^{-13}$) but similar levels of other lipid and nonlipid risk factors for MI compared with noncarriers. This difference in HDL-C was expected to decrease the risk for MI by 13% (odds ratio [OR], 0.87; 95% confidence interval [CI], 0.84 to 0.91), but the 396Ser allele was not associated with risk for MI (OR, 0.99; 95% CI, 0.88 to 1.11; $P = 0.85$) (**Fig. 7.12**). From observational epidemiology, an increase of 1 standard deviation (SD) in HDL-C is associated with a reduced risk for MI (OR, 0.62; 95% CI, 0.58 to 0.66). A 1-SD increase in HDL-C because of genetic score, however, was not associated with risk for MI (OR, 0.93; 95% CI, 0.68 to 1.26; $P = 0.63$). For LDL-C the estimate from observational epidemiology (a 1-SD increase in LDL-C was associated with risk for MI; OR, 1.54; 95% CI, 1.45 to 1.63) agreed with that from the genetic score (OR, 2.13; 95% CI, 1.69 to 2.69; $P = 2 \times 10^{-10}$). These findings indicate that some genetic mechanisms that raise plasma HDL-C do not lower the risk for MI. These data challenge the concept that raising plasma HDL-C therapeutically will uniformly translate into reductions in risk for MI.

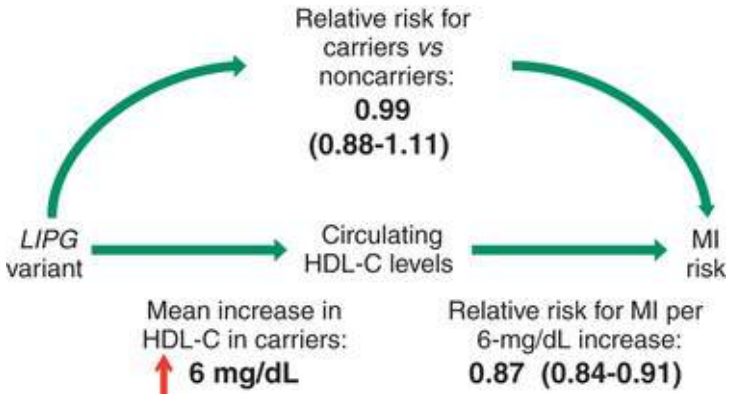

FIGURE 7.12 Mendelian randomization study for plasma HDL-C and risk for MI by using an instrument in the endothelial lipase (*LIPG*) gene. Individuals who carry the serine allele at amino acid 396 of the *LIPG* gene have about 6 mg/dL higher HDL-C. If HDL-C were a causal factor, carriers of the serine allele would be expected to be protected from risk for MI. After association testing in 116,320 individuals, the *LIPG* instrument was not associated with MI. Individuals who carried the HDL-boosting variants had the same risk for MI as did those who did not carry the variant.

A parallel line of clinical trial evidence also casts doubt on the notion that *any* intervention that raises HDL-C will reduce risk for MI. Three different inhibitors of cholesterol ester transfer protein (CETP) substantially raised HDL-C in comparison to placebo. Clinical trials with the three CETP inhibitors were all terminated prematurely because of lack of efficacy.[37-39] When combined, the clinical trial results and the human genetic findings summarized here cast doubt on the notion that raising HDL-C in isolation reduces CHD risk. For several decades the biomedical research community has assumed that if an intervention raises HDL-C, that intervention will reduce risk for CHD. It seems prudent now to rethink this assumption and reevaluate the use of HDL-C as a biomarker predictive of CHD in intervention studies.

In contrast to HDL-C, recent genetic evidence points to triglyceride-rich lipoproteins as a causal risk factor for CHD. Genetic studies have documented that inactivating mutations in the *APOA5*, *APOC3*, *ANPGTL4*, and *LPL* genes are associated with either decreased or increased risk for CHD.[40-44] These four

genes share the common property that each either encodes lipoprotein lipase or encodes a regulator of lipoprotein lipase, an enzyme that metabolizes the triglycerides contained in various lipoprotein particles. These findings suggest that novel therapeutic interventions targeting the lipoprotein lipase pathway will reduce risk for CHD.

Overall, with the recent explosion in our ability to measure soluble biomarkers (including metabolites and proteins; **see Chapter 9**) and genetic variation, mendelian randomization will aid increasingly to distinguish causal from noncausal biomarkers.

Personalized Medicine

Patient Case, Part V.

Shortly after his clinic visit, the 43-year-old brother (KS) goes to the emergency department (ED) because of severe chest pain. He is found to be in the throes of STEMI. He undergoes urgent percutaneous coronary intervention (PCI). The ED physician asks the cardiology consultant which antiplatelet agent in addition to aspirin the patient should receive at this time.

Just as genetic data can be used to predict a patient's risk for development of a disease, it can also be used to predict whether a patient will have a therapeutic response and/or an adverse response to a particular medication. Termed *pharmacogenetics* or, in broader terms, personalized medicine, its goal is to deliver safely the right therapy at the right dose to the right patient (**see also Chapters 6 and 8**).

One example of the emerging use of pharmacogenetics centers on use of the antiplatelet agent clopidogrel. Given routinely to patients after a coronary event, clopidogrel has reduced the risk for future coronary events and, in patients who have undergone coronary stent placement, has decreased the risk for in-stent thrombosis. Common loss-of-function variants in the *CYP2C19* gene, which encodes an enzyme that metabolizes clopidogrel into its active form, reduce the effectiveness of the medication, especially with respect to the prevention of in-stent thrombosis.[45,46] Accordingly, *CYP2C19* genotyping performed at the point of care could guide the choice of therapy. Alternatives for patients found to have loss-of-function *CYP2C19* variants could include an increased dose of clopidogrel or the use of an alternative medication of the same drug class not affected by *CYP2C19* function (**see Chapters 59 and 60**).

Therapeutic Targets: From Gene to Drug in a Decade

The example of *PCSK9* has emerged as a success story for the translation of cardiovascular genetics to the clinic in a relatively short time (**see Chapter 48**). The original report of the involvement of gain-of-function mutations in *PCSK9* in causing FH was published in 2003. Just 10 years later, several companies had developed antibody-based drugs targeting the PCSK9 protein that were being evaluated in clinical trials, with two such drugs, alirocumab and evolocumab, now approved for use in patients.[47,48] Development of these drugs followed directly from the finding that individuals with loss-of-function *PCSK9* mutations are genetically protected from CHD without suffering any known adverse effects. Clinical trials demonstrated a large reduction in blood LDL-C levels with these agents. Definitive outcomes trials remain to be completed.

Genome Editing

Recent advances in the set of technologies known as genome editing, most notably the adaptation of clustered, regularly interspaced, short palindromic repeats (CRISPR)–CRISPR-associated 9 (Cas9)

systems from bacterial species, enable the precise targeting of genes within human cells. Genome-editing tools such as CRISPR-Cas9 can introduce frameshift, nonsense, or missense mutations into a target gene, representing a novel therapeutic approach that is just beginning to be explored.

The recent discoveries that naturally occurring inactivating mutations in genes such as *PCSK9*, *APOC3*, and *ANGPTL4* are associated with decreased risk for CHD provide a rationale for using genome editing to introduce similar inactivating mutations into one or more of these genes in patients at high risk for CHD. In a proof-of-principle study, CRISPR-Cas9 was used to introduce frameshift mutations into the *PCSK9* gene in the liver cells of adult mice.[49] Within several days of administration of the CRISPR-Cas9 therapy, the plasma levels of PCSK9 protein had fallen by 90%, and the plasma cholesterol levels had fallen by 35% to 40%. In principle, one-time genome editing should result in permanent genetic alterations, and thus *PCSK9* targeting in a human should produce a beneficial effects far more enduring than existing medications such as statins and PCSK9 antibody–based drugs. Genome-editing approaches may ultimately prove useful for the prevention and treatment of a variety of cardiovascular disorders.

Future Perspectives

The last 15 years have witnessed remarkable advances in human genetics that promise to continue to transform our understanding of cardiovascular disease, as well as the approaches by which practitioners will prevent and treat disease. Although we remain largely in an information-gathering stage, the first practical applications of the information have begun to emerge, ranging from improvement in cardiovascular risk prediction, to the use of pharmacogenetics to tailor therapy for individual patients, to the development of novel therapies such as the PCSK9 antibody–based drugs. The decade to come should witness substantial progress in all these domains.

Indeed, not too far in the future, the standard of cardiovascular care may look quite different from current practices. Patients would undergo whole-genome sequencing at birth, thereby allowing so-called primordial prevention by assessing the genetic determinants of an individual's lifetime risk for cardiovascular disease and institution of appropriate counseling—starting with lifelong exercise and dietary habits and, as the patient advances in age, individually tailored preventive medications and therapies that address all the individual's various validated, causal genetic risk factors for disease. If cardiovascular disease should nevertheless emerge at some point in the patient's life, he or she would receive the specific therapies that have been demonstrated to be most efficacious and safest for individuals with that genetic profile, both in the acute setting and in the long term for secondary prevention. This standard of care would represent an important step toward ensuring that people everywhere enjoy longer lives free of cardiovascular disease.

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8

Drug Therapeutics and Personalized Medicine

Dan M. Roden

In 2014 the total cost of health care in the United States was approximately $3 trillion, and more than 10% was spent on prescription drugs.[1] Cardiovascular disease makes up the largest subcategory in this spending: In 2016 the American Heart Association estimated that the cost of care for cardiovascular disease was $317 billion/year, and total cost of prescription drugs for cardiovascular care was $33 billion.[2]

Not every patient responds to drug therapy in the same way; efficacy varies, and adverse effects range from minor to potentially fatal. Multiple mechanisms can result in this variability, such as poor

compliance, variable impact of diverse disease mechanisms on drug actions, drug interactions, and the increasingly well-recognized role of genomic variation. Indeed, adverse drug reactions across all therapeutic categories are estimated to be the fourth to sixth most common cause of death in the United States, costing $19 to $27 billion annually, and accounting directly for 3% to 6% of all hospital admissions.[3]

This chapter outlines principles of drug action, the major mechanisms underlying variability in drug effects, and current and future approaches to enable the safest and most effective therapy for an individual patient.

Risk Versus Benefit of Drug Therapy

The fundamental assumption underlying administration of any drug is that the real or expected benefit exceeds the anticipated risk. The benefits of drug therapy are initially defined in small clinical trials, perhaps involving several thousand patients, before a drug's marketing and approval. Ultimately, the efficacy and safety profiles of any drug are determined after the compound has been marketed and used widely in hundreds of thousands of patients.

When a drug is administered for the acute correction of a life-threatening condition, the benefits are often self-evident; insulin for diabetic ketoacidosis and nitroprusside for hypertensive encephalopathy are examples. However, extrapolation of such immediately obvious benefits to other clinical situations may not be warranted.

Clinical Trials Can Define Unexpected Adverse Drug Reactions

The outcome of the Cardiac Arrhythmia Suppression Trial (CAST) highlights the difficulties in extrapolating from an incomplete understanding of physiology to chronic drug therapy. CAST tested the hypothesis that suppression of ventricular ectopic activity, a recognized risk factor for sudden death after myocardial infarction (MI), would reduce mortality; this notion was highly ingrained in cardiovascular practice in the 1970s and 1980s. In CAST, sodium channel–blocking antiarrhythmic drugs did suppress ventricular ectopic beats but also unexpectedly increased mortality threefold. Similarly, with the development of a first-generation cholesterol ester transport protein (CETP) inhibitor, the goal of elevation of high-density lipoprotein (HDL) levels was achieved, but with an accompanying increase in mortality. Thus the use of arrhythmia suppression or HDL elevation as a surrogate marker did not produce the desired drug action—reduction in mortality—probably because the underlying pathophysiology or full range of drug actions were incompletely understood.

Similarly, drugs with positive inotropic activity augment cardiac output in patients with heart failure but also are associated with an increase in mortality, probably because of drug-induced arrhythmias. Nevertheless, clinical trials with these agents suggest symptom relief. Thus the prescriber and the patient may elect therapy with positive inotropic drugs to realize this benefit while recognizing the risk. This complex decision making is at the heart of the broad concept of personalized medicine, which incorporates into the care of an individual patient not only genomic (or other) markers of variable drug responses, but also factors such as patients' understanding of their disease and their willingness to tolerate minor or serious risks of treatment.

Classes of Adverse Drug Reactions

The risks of drug therapy may be a direct extension of the pharmacologic actions for which the drug is actually being prescribed. Hypoglycemia in a patient taking an antidiabetic agent and bleeding in a patient taking an anticoagulant are examples. In other cases, adverse effects develop as a consequence of pharmacologic actions that were not appreciated during a drug's initial development and use in patients. Examples include rhabdomyolysis occurring with HMG-CoA reductase inhibitors (statins), angioedema developing during ACE inhibitor therapy, and torsades de pointes during treatment with noncardiovascular drugs such as methadone. Of importance, these rarer but serious effects generally become evident only after a drug has been marketed and extensively used. Even rare adverse effects can alter the overall perception of risk versus benefit and can prompt removal of the drug from the market, particularly if alternate therapies thought to be safer are available. For example, withdrawal of the first insulin sensitizer, troglitazone, after recognition of hepatotoxicity was further spurred by the availability of other new drugs in this class.

The recognition of multiple cyclooxygenase (COX) isoforms led to the development of specific COX-2 inhibitors to retain aspirin's analgesic effects but reduce gastrointestinal side effects. However, one of these, rofecoxib, was withdrawn because of an apparent increase in cardiovascular mortality. The events surrounding the withdrawal of rofecoxib have important implications for drug development and utilization. First, specificity achieved by targeting a single molecular entity may not necessarily reduce adverse effects; one possibility is that by inhibiting COX-2, the drug removes a vascular protective effect of prostacyclin. Second, drug side effects may include not only readily identifiable events such as rhabdomyolysis or torsades de pointes but also an increase—that may be difficult to detect—in events such as MI that are common in the general population.

Pharmacokinetics and Pharmacodynamics

Two major processes determine how the interaction between a drug and its target molecule(s) can generate variable drug actions in a patient. The first, *pharmacokinetics*, describes drug delivery to and removal from the target molecule and includes the processes of absorption, distribution, metabolism, and excretion—collectively termed *drug disposition*. The second process, *pharmacodynamics*, describes how the interaction between a drug and its molecular target(s) generates downstream molecular, cellular, whole-organ, and whole-body effects.

Genes encoding drug-metabolizing enzymes and drug transport molecules determine pharmacokinetics. Genes encoding drug targets and the molecules modulating the biology in which the drug-target interaction occurs (including those causing the disease being treated) determine pharmacodynamics. *Pharmacogenetics* describes the concept that individual variants in the genes controlling these processes contribute to variable drug actions. *Pharmacogenomics* is often used to describe the way in which variability across multiple genes, up to whole genomes, explains differences in drug response among individuals and populations. The following overview of broad principles of pharmacokinetics, pharmacodynamics, and pharmacogenomics is followed by more detailed discussion of the specific genes, their function, and important variants influencing cardiovascular drug responses.

Pharmacokinetic Principles

Administration of an intravenous (IV) drug bolus results in maximal drug concentrations at the end of delivery of the bolus, followed by a decline in plasma drug concentrations over time (**Fig. 8.1A**),

generally because of drug elimination. In the simplest case this decline occurs monoexponentially over time. A useful parameter to describe this decline is the half-life ($t_{1/2}$), the time in which 50% of the drug is eliminated; for example, after two half-lives, 75% of the drug has been eliminated, and after three half-lives, 87.5%. A monoexponential process can be considered almost complete in four or five half-lives.

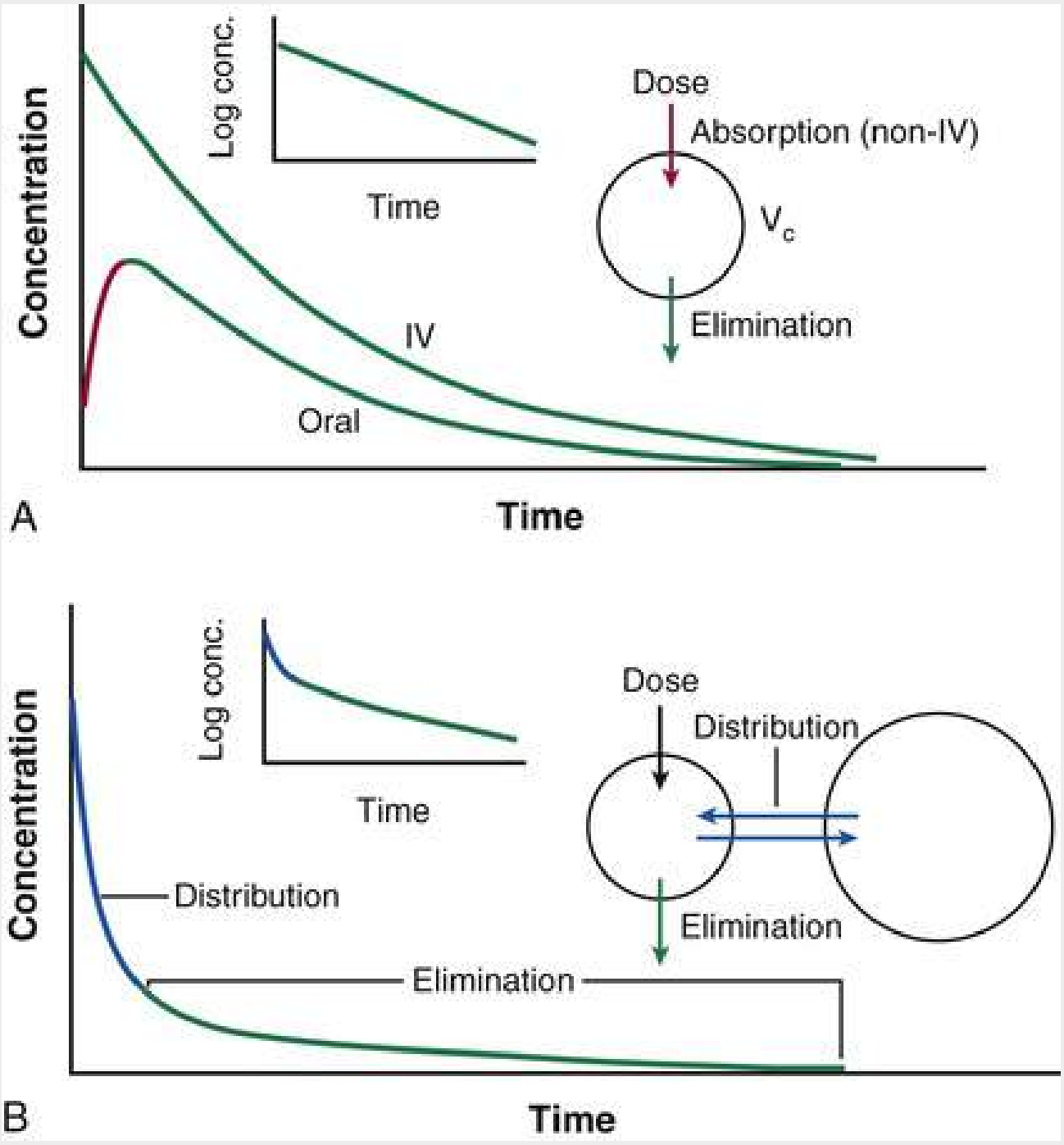

FIGURE 8.1 Models of plasma concentrations as a function of time after a single dose of a drug. **A,** The simplest situation is one in which a drug is administered as a rapid intravenous (IV) bolus into a volume (V_c), where it is instantaneously and uniformly distributed. Elimination then takes place from this volume. In this case, drug elimination is monoexponential; that is, a plot of the logarithm of concentration versus time is linear (*inset*). When the same dose of drug is administered orally, a distinct absorption phase is required before drug entry into V_c. Most absorption (shown here in *red*) is completed before elimination (shown in *green*), although the processes overlap. In this example, the amount of drug delivered by the oral route is less than that delivered by the intravenous route, assessed by the total areas under the two curves, indicating reduced bioavailability. **B,** In this example, drug is delivered to the central volume, from which it is not only eliminated but also undergoes distribution to the peripheral sites. This distribution process (*blue*) is more rapid than elimination, resulting in a distinct biexponential disappearance curve (*inset*).

In some cases the decline of drug concentrations after administration of an IV bolus dose is multiexponential. The most common explanation is that drug is not only eliminated (represented by terminal portion of time-concentration plot) but also undergoes more rapid distribution to peripheral tissues. Just as elimination may be usefully described by a half-life, distribution half-lives also can be derived from curves such as those shown in **Fig. 8.1B**.

The plasma concentration measured immediately after a bolus dose can be used to derive a volume into which the drug is distributed. When the decline of plasma concentrations is multiexponential, multiple distribution compartments can be defined; these volumes of distribution can be useful in considering dose adjustments in cases of disease but rarely correspond exactly to any physical volume, such as plasma or total body water. With drugs that are highly tissue-bound (e.g., some antidepressants), the volume of distribution can exceed total body volume by orders of magnitude.

Drugs are often administered by non-IV routes, such as oral, sublingual, transcutaneous, or intramuscular. Such routes of administration differ from the IV route in two ways (see **Fig. 8.1A**). First, concentrations in plasma demonstrate a distinct rising phase as the drug slowly enters plasma. Second, the total amount of drug that actually enters the systemic circulation may be less than that achieved by the IV route. The relative amount of drug entering by any route, compared with the same dose administered intravenously, is termed *bioavailability*, calculated as the ratio of the area under the time-concentration curves, as shown in **Fig. 8.1A**. Some drugs undergo extensive metabolism before entry into the systemic circulation, and as a result the amount of drug required to achieve a therapeutic effect is much greater (and often more variable) than that required for the same drug administered intravenously. Thus, small doses of IV propranolol (5 mg) may achieve heart rate slowing equivalent to that observed with much larger oral doses (80 to 120 mg). Propranolol is actually well absorbed but undergoes extensive metabolism in the intestine and liver before entering the systemic circulation. Another example is amiodarone; its physicochemical characteristics make it only 30% to 50% bioavailable when administered orally. Thus an IV infusion of 0.5 mg/min (720 mg/day) is equivalent to 1.5 to 2 g/day orally.

Drug elimination occurs by metabolism followed by the excretion of metabolites and unmetabolized parent drug, generally by the biliary tract or kidneys. This process can be quantified as *clearance*, the volume that is cleared of drug in any given period. Clearance may be organ specific (e.g., renal clearance, hepatic clearance) or whole-body clearance. Drug metabolism is conventionally divided into phase I oxidation and phase II conjugation, both of which enhance water solubility and, consequently, biliary or renal elimination.

The most common enzyme systems mediating phase I drug metabolism are those of the cytochrome P-450 superfamily, termed *CYPs*. Multiple CYPs are expressed in human liver and other tissues. A major source of variability in drug action is variability in CYP expression and/or genetic variants that alter CYP activity. **Table 8.1** lists CYPs and other drug-metabolizing enzymes important in cardiovascular therapy. Excretion of drugs or their metabolites into the urine or bile is accomplished by glomerular filtration or specific drug transport molecules, whose level of expression and genetic variation are only now being explored. One widely studied transporter is *P-glycoprotein*, the product of expression of the *MDR1* (or *ABCB1*) gene. Originally identified as a factor mediating multiple drug resistance in patients with cancer, P-glycoprotein expression is now well recognized in normal enterocytes, hepatocytes, renal tubular cells, the endothelium of the capillaries forming the blood-brain barrier, and the testes. In each of these sites, P-glycoprotein expression is restricted to the apical aspect of polarized cells, where it acts to enhance drug efflux. In the intestine, P-glycoprotein pumps substrates back into the lumen, thereby limiting bioavailability. In the liver and kidney, it promotes drug excretion into bile or urine. In central nervous system capillary endothelium, P-glycoprotein–mediated efflux is an important mechanism limiting drug access to the brain. Drug transporters play a role not only in drug elimination but also in drug uptake into many cells, including hepatocytes and enterocytes.

TABLE 8.1

Proteins Important in Drug Metabolism and Elimination

PROTEIN	SUBSTRATES
CYP3A4, CYP3A5*	Erythromycin, clarithromycin; quinidine, mexiletine; many benzodiazepines; cyclosporine, tacrolimus; many antiretrovirals HMG CoA reductase inhibitors: atorvastatin, simvastatin, lovastatin; not pravastatin Many calcium channel blockers; apixaban, rivaroxaban
CYP2D6*	Some beta blockers: propranolol, timolol, metoprolol, carvedilol Propafenone; desipramine and other tricyclics; codeine†; tamoxifen†; dextromethorphan
CYP2C9*	Warfarin, phenytoin, tolbutamide, losartan†, rosuvastatin
CYP2C19*	Omeprazole, clopidogrel†
P-glycoprotein	Digoxin, dabigatran
N-acetyltransferase*	Procainamide, hydralazine, isoniazid
Thiopurine methyltransferase*	6-Mercaptopurine, azathioprine
Pseudocholinesterase*	Succinylcholine
Serine esterase 1 (CES1)	Clopidogrel, dabigatran
Uridine diphosphate-glucuronosyltransferase*	Irinotecan†
SLCO1B1*	Simvastatin, atorvastatin; methotrexate; troglitazone; bosentan

*Clinically important genetic variants described.

†Prodrug bioactivated by drug metabolism.

Pharmacodynamic Principles

Drugs can exert variable effects, even in the absence of pharmacokinetic variability. This can arise as a function of variability in the molecular targets with which drugs interact to achieve their beneficial and adverse effects, as well as variability in the broader biologic context within which the drug-target interaction takes place. Variability in the number or function of a drug's target molecules can arise because of genetic factors (see later) or because disease alters the number of target molecules or their state (e.g., changes in extent of phosphorylation). Simple examples of variability in the biologic context are high dietary salt, which can inhibit the antihypertensive action of beta blockers, and hypokalemia, which increases the risk for drug-induced QT prolongation. In addition, disease itself can modulate drug response. For example, the effect of lytic therapy in a patient with no clot is manifestly different from that in a patient with an acute coronary syndrome, or the vasodilating effects of nitrates, beneficial in patients with coronary disease with angina, can be catastrophic in patients with aortic stenosis. These examples highlight the requirement for precision in diagnosis to avoid situations in which risk outweighs potential benefit. One hope is that emerging genomic or other molecular approaches can add to this precision.

Drug Targets

The targets with which drugs interact to produce beneficial effects may or may not be the same as those with which drugs interact to produce adverse effects. Drug targets may be in the circulation, at the cell surface, or within cells. Many drugs widely used in cardiovascular therapeutics (e.g., digoxin, amiodarone, aspirin) were developed when the technology to identify specific molecular targets was not available. Some drugs (e.g., amiodarone) have many drug targets. In other cases, however, even older drugs are found to have rather specific molecular targets. The actions of digitalis glycosides are mediated primarily by the inhibition of sodium/potassium–adenosine triphosphatase (Na^+,K^+-ATPase). Aspirin permanently acetylates a specific serine residue on the COX enzyme, an effect that is thought to mediate its analgesic effects and its gastrointestinal toxicity. Most newer drugs have been developed to interact with a specific drug target identified in the course of basic mechanistic studies; examples of such targets are 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase, angiotensin-converting enzyme (ACE), G protein–coupled receptors (GPCRs; e.g., alpha, beta, angiotensin II, histamine), and platelet IIb/IIIa receptors.

An emerging approach is to use modern genetic techniques to identify loss-of-function DNA variants

that are tolerated throughout life and associated with a desired phenotype, such as greatly reduced MI risk. Inhibitors of the corresponding gene products are thus predicted to exert a beneficial effect and lack serious on-target adverse effects. PCSK9 inhibitors are an excellent example[4] (**see Chapter 48**), and other potential drug targets are now being identified using this approach.[5-7]

Time Course of Drug Effects

With repeated doses, drug levels accumulate to a *steady state*, the condition under which the rate of drug administration is equal to the rate of drug elimination in any given period. Drug accumulation to steady state is near-complete in four to five elimination half-lives (**Fig. 8.2**). For many drugs, the target molecule is in plasma or readily accessible from plasma, so this time course also describes the development of pharmacologic effects. In other cases, however, although steady-state plasma concentrations are achieved in four to five elimination half-lives, steady-state drug effects take longer to achieve; there are several possible explanations for this. First, an active metabolite may need to be generated to achieve drug effects. Second, time may be required for translation of the drug effect at the molecular site to a physiologic endpoint. For example, inhibition of synthesis of vitamin K–dependent clotting factors by warfarin ultimately leads to a desired elevation of the international normalized ratio (INR), but the development of this desired effect occurs only as levels of clotting factors fall. Third, penetration of a drug into intracellular or other tissue sites of action may be required before development of a drug effect. One mechanism underlying such penetration is the variable function of specific drug uptake and efflux transport proteins that control intracellular drug concentrations.

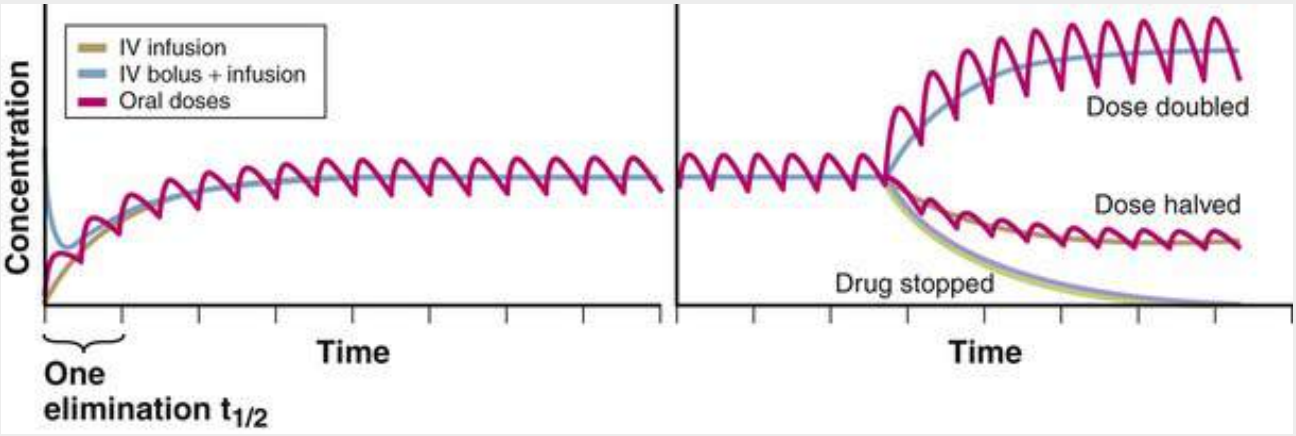

FIGURE 8.2 Time course of drug concentrations when treatment is started or dose changed. **Left,** The *hash lines* on the abscissa each indicate one elimination half-life ($t_{1/2}$). With a constant-rate intravenous (IV) infusion (*gold*), plasma concentrations accumulate to steady state in four or five elimination half-lives. When a loading bolus is administered with the maintenance infusion (*blue*), plasma concentrations are transiently higher but may dip, as shown here, before achieving the same steady state. When the same drug is administered by the oral route, the time course of drug accumulation is identical (*magenta*); in this case the drug was administered at intervals of 50% of a $t_{1/2}$. Steady-state plasma concentrations during oral therapy fluctuate around the mean determined by intravenous therapy. **Right,** This plot shows that when dosages are doubled, or halved, or the drug is stopped during steady-state administration, the time required to achieve the new steady state is four or five half-lives and is independent of the route of administration.

Pharmacogenomic Principles

A range of experimental techniques have been used to establish a role for both common and rare DNA polymorphisms in pharmacokinetic and pharmacodynamic pathways as mediators of variable drug actions. Rare variants associated with mendelian diseases such as familial hypercholesterolemia and

long-QT syndrome are traditionally termed *mutations*, whereas the term *polymorphism* is used more generically to describe variants that may or may not be associated with any human trait. Polymorphism frequency often varies strikingly by ancestry, and with the advent of inexpensive sequencing, it is apparent that the vast majority of DNA polymorphisms in any individual are actually rare (minor allele frequency [MAF] < 1%) across a large population of individuals of the same ancestry. The most common type is a single-nucleotide polymorphism (SNP); SNPs that change the encoded amino acid are termed *nonsynonymous*. Other types are short insertions or deletions (indels) or copy number variations (CNVs), in which large segments of DNA are deleted or duplicated (or more).

One of the great success stories of modern cardiovascular genetics has been the use of linkage analysis in large families to identify disease-causing rare variants (mutations) in familial syndromes with highly unusual clinical phenotypes, such as familial hypercholesterolemia (**see Chapter 48**), hypertrophic cardiomyopathy (**see Chapter 78**), and the ion channelopathies (**see Chapter 33**). Linkage analysis has not been widely applied to study pharmacogenomics because large kindreds with multiple individuals having clearly defined drug-response phenotypes generally are not available. In the syndrome of malignant hyperthermia occurring in response to general anesthetics, it was possible to assign phenotype using functional studies in muscle biopsies and thus identify a linkage signal at chromosomal region 19q, which includes the gene encoding RYR1, the skeletal muscle calcium-release channel in which mutations cause the disease.

DNA variation also contributes importantly to variability in common human traits, such as laboratory values or susceptibility to common disease. Methods are available to establish the extent to which that variability includes a heritable component, often by examining twins, large families, or groups of families; evidence for heritability provides strong justification for pursuing studies to identify contributing genetic variation. Indeed, this general approach has established that common phenotypes such as low-density lipoprotein (LDL) cholesterol, blood pressure, and susceptibility to atrial fibrillation are highly heritable. The extent that rare and common variants contribute to this variability is only now being addressed. Across populations, individual common (MAF > 5%) DNA polymorphisms rarely account for more than even 1% of variability in common traits. Variability in response to drug exposure presents a striking exception to this general rule, where even single common DNA polymorphisms may contribute substantially, 10% or more in many cases, to overall variability in drug response. It has been speculated that common variants with large effects on drug response can persist in a population because there is no evolutionary pressure against such variants since drug exposure is a recent event in human history.

One mechanism accounting for this large effect is that common SNPs in drug metabolism pathways can result in extremely large fluctuations in drug concentration and corresponding effects. Examples of specific cardiovascular phenotypes in which common SNPs have been associated with risk are presented in **Table 8.2** and discussed later. Of note, rarer variants in these (or other) genes are only now being described, so their role in mediating drug response is much less well understood. In addition, virtually all studies to date have focused primarily on populations of European ancestry, and data are only now being generated on specific polymorphisms mediating variable drug actions in other ancestries.

TABLE 8.2

Examples of Common Single-Nucleotide Polymorphisms (SNPs) Mediating Variable Drug Actions

DRUG EFFECT	PATHWAY	GENE	SNP*	dbSNP ID NUMBER	COMMENTS
Adverse outcomes during clopidogrel treatment for acute coronary syndrome	PK	*CYP2C19*	*CYP2C19*2*, *CYP2C19*3*: loss-of-function (LOF) variants *CYP2C19*17*	rs4244285	*2 and *3 result in defective clopidogrel bioactivation and decreased antiplatelet activity. About 3% of European- and 15% of Asian-ancestry individuals carry two LOF alleles. *17 increases *CYP2C19* activity and has been associated with increased bleeding during clopidogrel.
Excess beta-blocker effect: metoprolol, timolol	PK	*CYP2D6*	Many variants		
Warfarin steady-state dose	PK	*CYP2C9*	*CYP2C9*2:* R144C *CYP2C9*3:* I359L (decreased function)	rs1799853 rs1057910	*VKORC1* and *CYP2C9* variants account for ~50% of variability in warfarin steady-state dose. Bleeding risk has been associated with *CYP2C9*3* and variant *CYP4F2*.
	PD	*VKORC1*	Promoter variant: −1639G>A	rs9923231	
	PD	*CYP4F2*	V433M	rs2108622	
Statin myotoxicity	PK	*SLCO1B1*	*SLCO1B1*5:* V174A	rs4149056	Risk of simvastatin myotoxicity is increased 20-fold in homozygotes and 4-fold in heterozygotes.
Response to beta blockers for hypertension, heart failure	PD (target)	*ADRB1* *ADRB2*	S49G R389G	rs1801252 rs1801253	
Beta-blocker therapy in heart failure	PD (target)	*GRK5*	G41L	rs17098707	
Antihypertensive response during thiazide therapy	PD	*ADD1*	G460W	rs4961	
Torsades de pointes	PD	*KCNE1*	D85N	rs1805128	8% allele frequency in patients with torsades versus ~2% in control subjects (odds ratio ~10)

*Trivial name (e.g., *2, *3) and amino acid change provided.

dbSNP, National Center for Biotechnology Information's SNP database; *PD,* pharmacodynamic; *PK,* pharmacokinetic.

The Candidate Gene Approach.

One technique to identify associations between DNA polymorphisms and drug response (or other traits) uses an understanding of the physiology of the trait under question to identify candidate genes modulating the trait. Thus, for example, an investigator interested in variability in the PR interval might invoke polymorphisms in calcium channel genes, or an investigator interested in blood pressure might invoke variation in the ACE gene. The association between polymorphisms in these candidate genes and the phenotype under study is then examined in persons with well-characterized phenotypes. The candidate gene approach is intuitively appealing because it takes advantage of what is known about underlying physiology. Despite this appeal, however, the method is now recognized to carry with it the great potential for false-positive associations, especially when small numbers of participants are studied. An important exception has been in pharmacogenomics, where the candidate gene approach has yielded important and clinically reproducible associations between single common polymorphisms and drug response. This exception probably reflects the unusually high contribution of SNPs to overall variability in drug response previously mentioned.

Unbiased Approaches, Such as Genome-Wide Association.

Another approach to identifying polymorphisms contributing to variable human traits is the genome-wide association study (GWAS). Here, study participants are genotyped at hundreds of thousands or millions of sites known to harbor common SNPs across the genome. Because the GWAS platforms focus on common SNPs, effect sizes for individual SNPs are often small and difficult to identify and validate unless large numbers of participants, thousands or more, are studied. In addition, the SNPs associated

with the trait usually are not themselves functional but rather serve as markers for loci that harbor truly functional variants. The great advantage of the method is that it is unbiased, in that it makes no assumptions about underlying physiology, and one of its major accomplishments has been to identify entirely new pathways underlying variability in human traits.[8] The GWAS approach has been applied to study drug response phenotypes,[9] and even in relatively small sets, it has occasionally been successful in identifying associated common variants. Sometimes these are known from candidate gene studies. In other cases, notably drug hypersensitivity reactions,[10] GWASs in relatively small numbers (tens or hundreds of patients) have identified very strong signals that have then been replicated.

The GWAS paradigm is enabled by technology to generate the dense genotype datasets. New technologies being developed to generate other types of high-dimensional data similarly hold the promise of elucidating new biologic pathways in disease and drug response. Rapid, extremely high-throughput and increasingly inexpensive sequencing technologies are detecting rare DNA sequence variants whose contribution to disease is only now being appreciated.[11,12] RNA sequencing ("RNA-Seq") is replacing microarray analysis as the method of choice for cataloging RNA transcript profiles and abundance by specific cellular subtype and disease. Advances in mass spectrometry are similarly enabling development of catalogs (proteomic and metabolomic profiling) of all proteins or of small-molecule metabolites of cellular processes, including drug metabolites, by cell and disease. Other sources of high-dimensional data include electronic medical record (EMR) systems, as discussed later, and high-density digital images. Integrating these diverse data types into a comprehensive picture of the perturbations that result in disease or variable drug responses is the goal of the evolving discipline of *systems* biology and pharmacology. It has been proposed that future drug development would be better served by a focus on pathways identified by systems approaches rather than single targets.[13]

Molecular and Genetic Basis for Variable Drug Response

Many factors contribute to variable drug responses, including the patient's age, severity of the disease being treated, presence of disease of excretory organs, drug interactions, and poor compliance. This section describes major pathways leading to variable drug responses.

High-Risk Pharmacokinetics

When a drug is metabolized and excreted by multiple pathways, absence of one of these pathways, because of genetic variants, drug interactions, or dysfunction of excretory organs, generally does not affect drug concentrations or actions. By contrast, if a single pathway plays a critical role, the drug is more likely to exhibit marked variability in plasma concentration and associated effects, a situation that has been termed *high-risk pharmacokinetics* (**Fig. 8.3**).

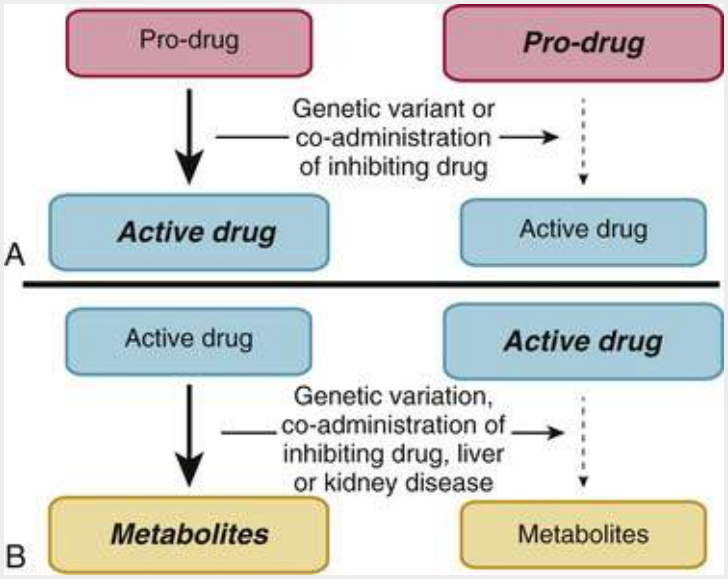

FIGURE 8.3 Two high-risk pharmacokinetic scenarios. **A,** Pro-drug activated by a single drug-metabolizing pathway. In this case, genetic variants or co-administration of a drug that inhibits the pathway will lead to failure of bioactivation and loss of drug effect. **B,** Active drug metabolized by a single pathway. In this case, genetic variants, co-administration of a drug that inhibits the pathway, or the presence of liver or kidney disease can inhibit drug elimination and thus lead to exaggerated drug action. This occurs because clinically important alternate pathways for drug elimination are absent, and increases in plasma parent drug concentrations can translate into serious drug toxicity. Note also that genetic variants or co-administered drugs that increase the rate of elimination will lead to decreased drug action. The overall effect is also modulated by the activity of the metabolites.

One high-risk scenario (**Fig. 8.3A**) involves bioactivation of a drug—that is, metabolism of the drug to active and potent metabolites that mediate pharmacologic action. Decreased function of such a pathway reduces or eliminates drug effect. Bioactivation of clopidogrel by CYP2C19 is an example; persons with reduced CYP2C19 activity (caused by genetic variants or possibly by interacting drugs; see **Tables 8.1** and **8.2**) have an increased incidence of cardiovascular events following coronary stent placement.[14] Similarly, the widely used analgesic codeine undergoes CYP2D6-mediated bioactivation to an active metabolite, morphine, and patients with reduced CYP2D6 activity ("poor metabolizers," PMs) display reduced analgesia. A small group of individuals with multiple functional copies of *CYP2D6*, and thus increased enzymatic activity ("ultrarapid metabolizers," UMs), has been identified; in this group, codeine may produce respiratory depression because of rapid morphine generation. In 2013 the U.S. Food and Drug Administration (FDA) label for codeine was revised to contraindicate its use in children after tonsillectomy, because deaths in UMs had been reported.[15] A third example is the angiotensin receptor blocker losartan, which is bioactivated by CYP2C9; reduced antihypertensive effect is a risk with common genetic variants that reduce CYP2C9 activity or with co-administration of CYP2C9 inhibitors such as phenytoin.

In a second high-risk pharmacokinetic scenario (**Fig. 8.3B**) a drug is eliminated by only a single pathway. In this case, absence of activity of that pathway will lead to marked accumulation of drug in plasma, and for many drugs, such accumulation results in a high risk of drug toxicity. A simple example is the dependence of sotalol or dofetilide elimination on renal function; failure to decrease the dosage in a patient with renal dysfunction leads to accumulation of these drugs in plasma and an increased risk for drug-induced QT prolongation and torsades de pointes. Similarly, administration of a wide range of P-glycoprotein inhibitors will predictably elevate plasma concentration of digoxin, which is eliminated primarily by P-glycoprotein–mediated efflux into bile and urine (see **Table 8.2**). Propafenone is metabolized by CYP2D6 to a metabolite that has some sodium channel–blocking actions but lacks the weak beta-blocking effect of the parent drug. Administration of propafenone to PMs, or co-administration

of CYP2D6 inhibitors (e.g., some SSRI antidepressants) to EMs, can lead to parent drug accumulation, bradycardia, and bronchospasm.

Other Important Pharmacogenetic Effects

Administration of CYP2D6-metabolized beta blockers, including metoprolol and carvedilol, to patients with defective enzyme activity may produce exaggerated heart rate slowing. Some antidepressants are CYP2D6 substrates; for these drugs, cardiovascular adverse effects are more common in CYP2D6 PMs, whereas therapeutic efficacy is more difficult to achieve in UMs.

The risk of aberrant drug responses caused by CYP variants is greatest in persons who are homozygous (i.e., PMs). However, for drugs with very narrow therapeutic margins (e.g., warfarin, clopidogrel), even heterozygotes may display unusual drug sensitivity. Although PMs make up a minority of persons in most populations, many drugs in common use can inhibit these enzymes and thereby "phenocopy" the PM trait. Omeprazole blocks CYP2C19 and in some studies has been associated with an increase in cardiovascular events during clopidogrel therapy; however, this effect is controversial and may not extend to other proton pump inhibitors.[16] Similarly, specific inhibitors of CYP2D6 and CYP2C9 can phenocopy the PM trait when co-administered with substrate drugs (**Table 8.3**).

TABLE 8.3

Drug Interactions: Mechanisms and Examples

MECHANISM	DRUG	INTERACTING DRUG	EFFECT
Decreased bioavailability	Digoxin	Antacids	Decreased digoxin effect secondary to decreased absorption
Increased bioavailability	Digoxin	Antibiotics	By eliminating gut flora that metabolize digoxin, some antibiotics may increase digoxin bioavailability. NOTE: Some antibiotics also interfere with P-glycoprotein (expressed in the intestine and elsewhere), another effect that can elevate digoxin concentration.
Induction of hepatic metabolism	*CYP3A/P-glycoprotein substrates:* Quinidine Mexiletine Verapamil Cyclosporine Apixaban Rivaroxaban	Phenytoin Rifampin Barbiturates St. John's wort	Loss of drug effect secondary to increased metabolism
Inhibition of hepatic metabolism	*CYP2C9:* Warfarin Losartan	Amiodarone Phenytoin	Decreased warfarin requirement Diminished conversion of losartan to its active metabolite, with decreased antihypertensive control
	CYP3A substrates: Quinidine Cyclosporine HMG-CoA reductase inhibitors: lovastatin, simvastatin, atorvastatin; not pravastatin Apixaban Rivaroxaban	Ketoconazole Itraconazole Erythromycin Clarithromycin Some calcium blockers Some HIV protease inhibitors (especially ritonavir)	Increased risk for drug toxicity
	CYP2D6 substrates: Beta blockers (Table 8.2) Propafenone Desipramine Codeine	Quinidine (even ultralow dose), fluoxetine, paroxetine	Increased beta blockade Increased adverse effects Decreased analgesia (due to failure of biotransformation to active metabolite morphine)
	CYP2C19: Clopidogrel	Omeprazole, possibly other proton pump inhibitors	Decreased clopidogrel efficacy
Inhibition of drug transport	*P-glycoprotein transport:* Digoxin, dabigatran	Amiodarone, quinidine, verapamil, cyclosporine, itraconazole, erythromycin, dronedarone	Increased digoxin or dabigatran plasma concentrations, with toxicity
	Renal tubular transport: Dofetilide	Verapamil	Slightly increased plasma concentration and QT effect
	Monoamine transport: Guanadrel	Tricyclic antidepressants	Blunted antihypertensive effects
Pharmacodynamic interactions	Aspirin + warfarin		Increased therapeutic antithrombotic effect; increased risk of bleeding
	Nonsteroidal anti-inflammatory drugs	Warfarin	Increased risk of gastrointestinal bleeding
	Antihypertensive drugs	Nonsteroidal anti-inflammatory drugs	Loss of blood pressure lowering
	QT-prolonging antiarrhythmics	Diuretics	Increased torsades de pointes risk secondary to diuretic-induced hypokalemia
	Supplemental potassium and/or spironolactone	ACE inhibitors	Hyperkalemia
	Sildenafil	Nitrates	Increased and persistent vasodilation; risk of myocardial ischemia

The widely used antirejection drug tacrolimus is bioinactivated by CYP3A5. A variant common in persons of European ancestry reduces enzyme activity. This variant is rare in patients of African ancestry, who therefore often require higher doses to avoid transplant rejection.[17]

An example of variant drug transporter function mediating variable drug actions is provided by *SLCO1B1*, encoding a drug uptake transporter in liver. A common nonsynonymous SNP in this gene has been associated with a greatly increased risk for simvastatin-induced myopathy by candidate studies with variability in simvastatin pharmacokinetics and by GWASs.[18]

The heart rate slowing and blood pressure effects of beta blockers and beta agonists have been associated with polymorphisms in the *drug targets*, the beta-1 and beta-2 receptors. A common variant in *ADRB1*, encoding the beta-1 receptor, has been implicated as a mediator of survival and prevention of atrial fibrillation[19] during therapy with the beta-blocker bucindolol in heart failure. Variability in warfarin dose requirements has been clearly associated with variants in both *CYP2C9*, which mediates

elimination of the active enantiomer of the drug, and *VKORC1*, part of the vitamin K complex that is the drug target. Indeed, these common variants account for up to half of the variability in warfarin dose requirement,[20] illustrating the large impact that common SNPs can exert on drug response phenotypes. Furthermore, allele frequencies vary strikingly by ancestry, probably accounting for warfarin dose requirements being low in Asian patients and high in African patients compared with white patients.[20] Lower rosuvastatin doses are also suggested in patients of Asian ancestry, and variants in multiple genes have been implicated.

Torsades de pointes during QT-prolonging drug therapy has been linked to polymorphisms not only in the ion channel that is the target for most QT-prolonging drugs (Kv11.1, encoded by *KCNH2*, also known as *HERG*) but also to other ion channel genes. A large candidate gene survey reported that a nonsynonymous SNP in *KCNE1*, a subunit for the slowly activating potassium current I_{Ks}, conferred an odds ratio of approximately 10 for torsades risk.[21] In addition, this adverse effect sometimes occurs in patients with clinically latent congenital long-QT syndrome, emphasizing the interrelationship among disease, genetic background, and drug therapy (**see Chapters 33 and 36**). Similarly, sodium channel–blocking drugs also can bring out latent Brugada syndrome. Patients with congenital long-QT syndrome or Brugada syndrome and their practitioners should be aware of websites that list potentially dangerous drugs (www.crediblemeds.org for long QT; www.brugadadrugs.org for Brugada syndrome).

The anticancer drug trastuzumab is effective only in patients with cancers that do not express the Her2/neu receptor. Because the drug also potentiates anthracycline-related cardiotoxicity, toxic therapy can be avoided in patients who are receptor negative (**see Chapter 95**). Indeed, the development of new "targeted" anticancer drugs has seen an increase in multiple types of cardiovascular adverse effects, including arterial and venous thrombosis, cardiomyopathy, myocarditis, and arrhythmias. Understanding the pathways leading to these effects could inform new approaches to prevent treat cardiovascular disease more broadly.[22]

Optimizing Drug Doses

The goals of drug therapy should be defined before the initiation of drug treatment. These may include acute correction of serious pathophysiology, acute or chronic symptom relief, or changes in surrogate endpoints (e.g., blood pressure, serum cholesterol, INR) that have been linked to beneficial outcomes in target patient populations. However, the lessons of CAST and of positive inotropic drugs should make prescribers skeptical about such surrogate-guided therapy in the absence of controlled clinical trials.

When the goal of drug therapy is to correct acutely a disturbance in physiology, the drug should be administered intravenously in doses designed to achieve a therapeutic effect rapidly. This approach is best justified when benefits clearly outweigh risks. Large boluses of IV drugs carry a risk of enhancing drug-related toxicity; therefore, even with the most urgent medical indication, this approach is rarely appropriate. An exception is adenosine, which must be administered as a rapidly delivered bolus because it undergoes extensive and rapid elimination from plasma by uptake into almost all cells. As a consequence, a slow bolus or infusion rarely achieves sufficiently high concentrations at the desired site of action (the coronary artery perfusing the atrioventricular node) to terminate arrhythmias. Similarly, the time course of anesthesia depends on anesthetic drug delivery to and removal from sites in the central nervous system.

The time required to achieve steady-state plasma concentrations is determined by the elimination half-life (see earlier). The administration of a loading dose may shorten this time, but only if the kinetics of

distribution and elimination are known beforehand in an individual patient and the correct loading regimen is chosen. Otherwise, overshoot or undershoot during the loading phase may occur (see **Fig. 8.2**). Thus the initiation of drug therapy by a loading strategy should be used only when the indication is acute.

Two dose-response curves describe the relationship between drug dose and the expected cumulative incidence of a beneficial effect or an adverse effect (**Fig. 8.4**). The distance along the *x* axis describing the difference between these curves, often termed the *therapeutic ratio* (or index, or window), provides an index of the likelihood that a chronic dosing regimen that provides benefits without adverse effects can be identified. Drugs with especially wide therapeutic indices often can be administered at infrequent intervals, even if they are rapidly eliminated (**Fig. 8.4A, C**).

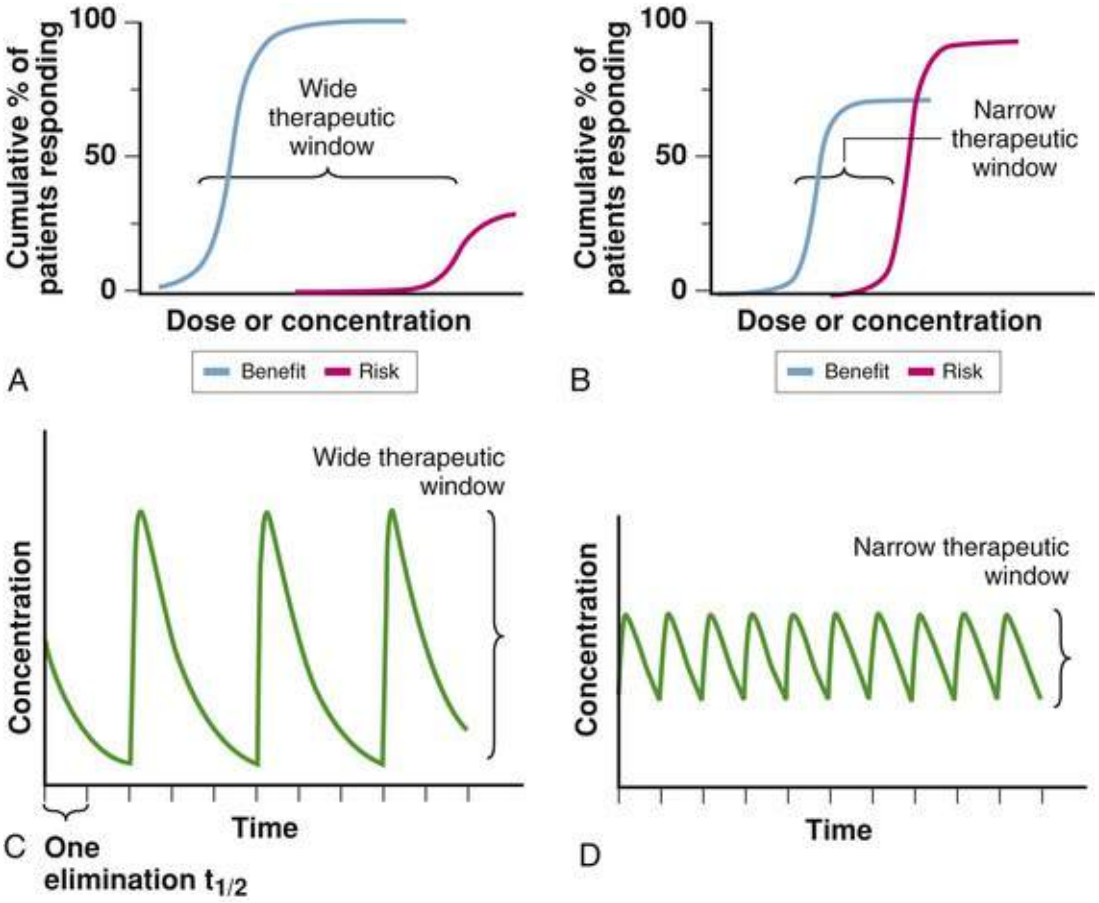

FIGURE 8.4 The concept of therapeutic ratio. **A** and **B,** Two dose-response (or concentration-response) curves. The *blue* lines describe the relationship between dose and cumulative incidence of beneficial effects, and the *magenta* line depicts the relationship between dose and dose-related adverse effects (risk). As depicted in **A,** a drug with a wide therapeutic ratio displays separation between the two curves, a high degree of efficacy, and low degree of dose-related toxicity. Under these conditions, a wide therapeutic ratio can be defined. In **B,** conversely, the curves describing cumulative efficacy and cumulative incidence of adverse effects are positioned near each other, the incidence of adverse effects is higher, and the expected beneficial response is lower. These characteristics define a narrow therapeutic ratio. **C** and **D,** Steady-state plasma concentrations with oral drug administration as a function of time with wide (*left*) and narrow (*right*) therapeutic ratios. The *hash marks* on the abscissae each indicate one elimination half-life ($t_{1/2}$). **C,** When the therapeutic window is wide, drug administration every three elimination half-lives can produce plasma concentrations that are maintained above the minimum for efficacy and below the maximum beyond which toxicity is anticipated. **D,** The opposite situation is illustrated. To maintain plasma concentrations within the narrow therapeutic range, the drug must be administered more frequently.

When anticipated adverse effects are serious, the most appropriate treatment strategy is to start at low doses and reevaluate the necessity for increasing drug dosages once steady-state drug effects have been achieved. This approach has the advantage of minimizing the risk of dose-related adverse effects but

carries with it a need to titrate doses to efficacy. Only when stable drug effects are achieved should increasing drug dosage to achieve the desired therapeutic effect be considered. An example is sotalol: because the risk of torsades de pointes increases with drug dosage, the starting dose should be low.

In other cases, anticipated toxicity is relatively mild and manageable. It may then be acceptable to start at dosages higher than the minimum required to achieve a therapeutic effect, accepting a greater-than-minimal risk of adverse effects; some antihypertensives can be administered in this way. However, the principle of using the lowest dose possible to minimize toxicity, particularly toxicity that is unpredictable and unrelated to recognized pharmacologic actions, should be the rule.

Occasionally, dose escalation into the high therapeutic range results in no beneficial drug effect and no side effects. In this circumstance the prescriber should be alert to the possibility of noncompliance or drug interactions at the pharmacokinetic or pharmacodynamic level. Depending on the nature of the anticipated toxicity, dose escalation beyond the usual therapeutic range may occasionally be acceptable, but only if anticipated toxicity is not serious and is readily manageable.

Plasma Concentration Monitoring

For some drugs, curves such as those shown in **Fig. 8.4A and B**, relating drug concentration to cumulative incidence of beneficial and adverse effects, can be generated. With such drugs, monitoring plasma drug concentrations to ensure that they remain within a desired therapeutic range (i.e., above a minimum required for efficacy and below a maximum likely to produce adverse effects) may be a useful adjunct to therapy. Monitoring drug concentrations also may be useful to ensure compliance and to detect pharmacokinetically based drug interactions that underlie unanticipated efficacy and/or toxicity at usual dosages. Samples for measurement of plasma concentrations generally should be obtained just before the next dose, at steady state. These trough concentrations provide an index of the minimum plasma concentration expected during a dosing interval.

On the other hand, patient monitoring, whether by plasma concentration or other physiologic indices, to detect incipient toxicity is best accomplished at the time of anticipated peak drug concentrations. Thus, patient surveillance for QT prolongation during therapy with sotalol or dofetilide is best timed for 1 to 2 hours after the administration of a dose of drug at a steady state.

A lag between the time courses of drug in plasma and drug effects may exist (see earlier). In addition, monitoring plasma drug concentrations relies on the assumption that the concentration measured is in equilibrium with that at the target molecular site. Of note, it is only the fraction of drug not bound to plasma proteins that is available to achieve such equilibration. Variability in the extent of protein binding can therefore affect the free fraction and anticipated drug effect, even in the presence of apparently therapeutic total plasma drug concentrations.

Dose Adjustments in Disease

Polypharmacy is common in patients with varying degrees of specific organ dysfunction. Although treatment with an individual agent may be justified, the practitioner should also recognize the risk of unanticipated drug effects, particularly drug toxicity, during therapy with multiple drugs.

The presence of renal disease mandates dose reductions (or choosing alternate therapies if renal dysfunction is severe) for drugs eliminated primarily by renal excretion. Examples include dabigatran, rivaroxaban, edoxaban, digoxin, dofetilide, and sotalol. Apixaban can be used even in patients undergoing dialysis, with reduced doses in certain subgroups (e.g., older patients, those weighing <60 kg). A

requirement for dose adjustment in cases of mild renal dysfunction is dictated by available clinical data and the likelihood of serious toxicity if drug accumulates in plasma because of impaired elimination. Renal failure reduces the protein binding of some drugs (e.g., phenytoin); in this case a total drug concentration value in the therapeutic range may actually represent a toxic value of unbound drug.

Advanced liver disease is characterized by decreased hepatic drug metabolism and portacaval shunts that decrease clearance, particularly first-pass clearance. Moreover, affected patients frequently have other profound disturbances of homeostasis, such as coagulopathy, severe ascites, and altered mental status. These pathophysiologic features of advanced liver disease can affect not only the dose of a drug required to achieve a potentially therapeutic effect, but also the perception of risks and benefits, thereby altering the prescriber's assessment of the actual need for therapy.

Heart disease is similarly associated with several disturbances of drug elimination and drug sensitivity that may alter the therapeutic doses or the practitioner's perception of the desirability of therapy based on evaluation of risks and benefits. Patients with left ventricular hypertrophy often have baseline QT prolongation, so risks associated with use of QT-prolonging antiarrhythmics may increase; most guidelines suggest avoiding QT-prolonging antiarrhythmics in such patients (**see Chapters 36, 96, and 98**).

In heart failure (**see Chapter 25**), hepatic congestion can lead to decreased clearance with a corresponding increased risk for toxicity with usual doses of certain drugs, including some sedatives, lidocaine, and beta blockers. On the other hand, gut congestion can lead to decreased absorption of oral drugs and decreased effects. In addition, patients with heart failure may demonstrate reduced renal perfusion and require dose adjustments on this basis. Heart failure also is characterized by a redistribution of regional blood flow, which can lead to reduced volume of distribution and enhanced risk for drug toxicity. Lidocaine probably is the best-studied example; loading doses of lidocaine should be reduced in patients with heart failure because of altered distribution, whereas maintenance doses should be reduced in both heart failure and liver disease because of altered clearance.

Age also is a major factor in determining drug doses, as well as sensitivity to drug effects. Doses in children generally are administered on an mg/kg body weight basis, although firm data to guide therapy are often not available. Variable postnatal maturation of drug disposition systems may present a special problem in the neonate. Older persons often have reduced creatinine clearance, even those with a normal serum creatinine level, and dosages of renally excreted drugs should be adjusted accordingly (**see Chapter 88**). Diastolic dysfunction with hepatic congestion is more common in older adults, and vascular disease and dementia often occur, which can lead to increased postural hypotension and risk of falling. Therapies such as sedatives, tricyclic antidepressants, or anticoagulants should be initiated only when the practitioner is convinced that the benefits of such therapies outweigh this increased risk.

Drug Interactions

As a result of therapeutic successes not only in heart disease but also in other disease areas, cardiovascular physicians are increasingly encountering patients receiving multiple medications for noncardiovascular indications. **Table 8.3** summarizes mechanisms that may underlie important drug interactions. Drug interactions may be based on altered absorption, distribution, metabolism, or excretion. In addition, drugs can interact at the pharmacodynamic level. A trivial example is the co-administration of two antihypertensive drugs, leading to excessive hypotension. Similarly, co-administration of aspirin and warfarin leads to an increased risk for bleeding, although benefits of the combination also can be demonstrated.

The most important principle in approaching a patient receiving polypharmacy is to recognize the high potential for drug interactions. A complete medication history should be obtained from each patient at regular intervals; patients will often omit topical medications such as eye drops, health food supplements, and medications prescribed by other practitioners unless specifically prompted. Each of these, however, carries a risk of important systemic drug actions and interactions. Even high dosages of grapefruit juice, which contains CYP3A and P-glycoprotein inhibitors, can affect drug responses. Beta-blocker eye drops can produce systemic beta blockade, particularly with CYP2D6 substrates (e.g., timolol) in patients with defective CYP2D6 activity. St. John's wort induces CYP3A and P-glycoprotein activity (similar to phenytoin and other drugs) and thus can greatly lower plasma concentrations of substrate drugs such as cyclosporine. As with many other interactions, this may not be a special problem provided both drugs are continued. However, if a patient stabilized on cyclosporine stops taking a concomitantly administered CYP3A inducer, plasma concentrations of the drug can rise dramatically, and toxicity can ensue. Similarly, initiation of an inducer may lead to greatly lowered cyclosporine concentrations and a risk of organ rejection. A number of natural supplements have been associated with serious drug toxicity (e.g., phenylpropanolamine-associated stroke) that has resulted in their withdrawal from the market.

Incorporating Pharmacogenetic Information Into Prescribing

The identification of polymorphisms associated with variable drug responses naturally raises the question of how these data could or should be used to optimize drug doses, avoid drugs likely to be ineffective, and avoid drugs likely to produce major toxicities. Indeed, in 2007 the FDA began systematically including pharmacogenetic information in drug labels.[23] Despite the intuitive appeal of a pharmacogenetically guided approach to drug therapy, however, practitioners wanting to adopt genetic testing to guide drug therapy encounter substantial practical barriers, including cost, varying levels of evidence supporting a role for genetics, and implementation issues such as how fast and accurately a genetic test result can be delivered. The nature of pharmacogenetic variation is that most patients will display average responses to most drugs, so systematically testing every patient in the hopes of finding the minority likely to display aberrant responses is cumbersome and seems inefficient in terms of time and cost unless the benefit for individual patients is large. An example of a large benefit is that routine genotyping of all patients receiving the antiretroviral agent abacavir is now the standard of care because it avoids a potentially life-threatening skin reaction in 3% of patients.[24] By contrast, randomized clinical trials[25-27] suggest either no effect or a modest effect on time within therapeutic range when genotype information is incorporated into warfarin dosing. These trials were underpowered to examine bleeding risk, which has been associated with variants in *CYP4F2*[28] or *CYP2C9*[29] in population- or EMR-based studies.

A difficulty with such drug-specific approaches is that the benefit of the genotype data must be large to justify the cumbersomeness and cost of testing all exposed individuals. Although the probability is small that genetic variation plays an important role in predicting the response of an individual patient to a specific drug, when many drugs are prescribed for a population of patients, each patient will display genetically determined aberrant responses to some drugs. This reasoning underlies the concept of *preemptive genotyping*, in which many genetic variants relevant to many variable drug responses are assayed in patients who have not yet been exposed to the drugs.[30,31] These data are then stored in EMR systems with advanced point-of-care decision support capabilities that deliver instantaneous advice when a drug is prescribed to a patient with known genomic variants.[32] Several technological developments enable this vision, including advanced EMRs and multiplexed inexpensive genotyping assays that

interrogate many polymorphisms for the same cost as a handful relevant to one drug. The concept is now being tested at a few medical centers, with the goals of establishing cost and benefit, understanding how health care providers react,[33] and optimizing decision support to integrate pharmacogenomic information seamlessly into health care.

Future Perspectives

The past 25 years have seen dramatic advances in the treatment of heart disease, in no small part because of the development of highly effective and well-tolerated drug therapies such as HMG-CoA reductase inhibitors, ACE inhibitors, and beta blockers. These developments, along with improved nonpharmacologic approaches, have led to dramatically enhanced survival of patients with advanced heart disease. Thus, polypharmacy in an aging and chronically ill population is becoming increasingly common. In this milieu, drug effects become increasingly variable, reflecting interactions among drugs, underlying disease and disease mechanisms, and genetic backgrounds. Furthermore, despite advances in the Western world, cardiovascular disease is emerging as an increasing problem worldwide as infectious diseases, formerly predominant contributors to morbidity and mortality, are coming under control and smoking and the metabolic syndrome are increasing. Understanding how genetic background plays into disease susceptibility and responses to drug therapy, concepts largely tested in only European-ancestry populations to date, represents a major challenge in cardiovascular medicine.

More generally, genomic medicine—the application of genetic variant information in health care—is still in its infancy, so reported associations require independent confirmation and assessment of clinical importance and cost-effectiveness before they can or should enter clinical practice. Importantly, most pharmacogenomic studies reported to date have focused on common variants, and we now recognize that the vast majority of polymorphisms in any gene, including CYPs and other “pharmacogenes,” are uncommon (MAF < 1%). Developing approaches to establish the clinical impact of such rare variants on drug responses is an emerging challenge.

This challenge is all the more acute because the cost of sequencing has fallen drastically since the completion of the first-draft human genome in 2000, and the under-$1000 whole-genome sequence is now a reality. This may be enabling for the preemptive pharmacogenomic strategy just outlined, as well as a broader vision of genome-guided health care, but presents major challenges in data storage and mining.

The relationship between the prescriber and the patient remains the centerpiece of modern therapeutics. An increasingly sophisticated molecular and genetic view of response to drug therapy should not change this view, but rather complement it. Each initiation of drug therapy represents a new clinical experiment. Prescribers must always be vigilant regarding the possibility of unusual drug effects, which could provide clues about unanticipated and important mechanisms of beneficial and adverse drug effects.

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9

Biomarkers and Use in Precision Medicine

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Clinicians use biomarkers daily in the practice of cardiovascular medicine. Moreover, the use of biomarkers can continue to improve physicians' ability to provide clinically effective and cost-effective cardiovascular medicine in the years ahead.[1] Appropriate risk stratification and targeting of therapies should not only help improve patient outcomes but also assist in responding to the urgent need to “bend the cost curve” of medical care. In particular, excessive use of imaging biomarkers increases the cost of medical care and can jeopardize patient outcomes (e.g., from radiation exposure or complications of administering contrast material or investigating incidental findings). Inappropriate use or interpretation of blood biomarkers (e.g., cardiac troponin levels) can lead to unnecessary hospitalization or procedures as

well.

Despite the current usefulness of biomarkers, their future promise, and the critical need to use them appropriately, much misunderstanding still surrounds their current clinical application.[1] In addition, contemporary technologies can greatly expand the gamut of biomarkers relevant to cardiovascular practice. Emerging genetic, proteomic, metabolomic, and molecular imaging strategies will surely transform the landscape of cardiovascular biomarkers (**see also Chapters 6 to 8 and 45**).

This chapter provides a primer on cardiovascular biomarkers by defining terms and discussing how the application of biomarkers can assist in clinical care, in addition to exploring some emerging technologies. We also discuss an approach to the rigorous evaluation of the clinical usefulness of biomarkers. Advances in cardiovascular biology and the application of novel technologies have identified a plethora of novel cardiovascular biomarkers of potential clinical usefulness—begging the question of whether a novel biomarker adds value to existing and often better-validated biomarkers. Thus, clinicians need tools to evaluate these emerging biomarkers, the adoption of which may elevate clinical practice and improve patient outcomes.

Overview of Biomarkers

For regulatory purposes, the U.S. Food and Drug Administration (FDA) first defined a *biomarker* in 1992 as "a laboratory measure or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful end point that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy." At that time the FDA considered a *surrogate endpoint* as "reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit." The National Institutes of Health (NIH) convened a working group in 1998 that offered some parallel operating definitions to guide the biomarker field (**Table 9.1**). NIH defined a *biologic marker,* or biomarker, as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." Thus the NIH definition includes not only soluble biomarkers in circulating blood but also "bedside biomarkers," such as anthropomorphic variables obtainable with a blood pressure cuff or a tape measure at the point of care. This broad definition encompasses measurements of biomarkers in blood (**Fig. 9.1A**) as well as measurements from imaging studies (**Fig. 9.1B**). Imaging biomarkers can include those derived from classic anatomic approaches. Imaging modalities now offer functional information, such as estimates of ventricular function and myocardial perfusion. Molecular imaging has the potential to target specific molecular processes. A functional classification of biomarkers helps sort through the plethora encountered by the clinician, in that biomarkers can reflect a variety of biologic processes or organs of origin. For example, as a first approximation, cardiac troponin reflects myocardial injury, brain natriuretic peptide reflects cardiac chamber stretch, C-reactive protein reflects inflammation, and the estimated glomerular filtration rate reflects kidney function.

TABLE 9.1
Biomarker Definitions

Biologic marker (biomarker) A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
Surrogate endpoint A biomarker intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm) or lack of benefit (or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.
Clinical endpoint A characteristic or variable that reflects how a patient feels, functions, or survives.

From National Institutes of Health (NIH) Biomarkers Definition Working Group, 1998.

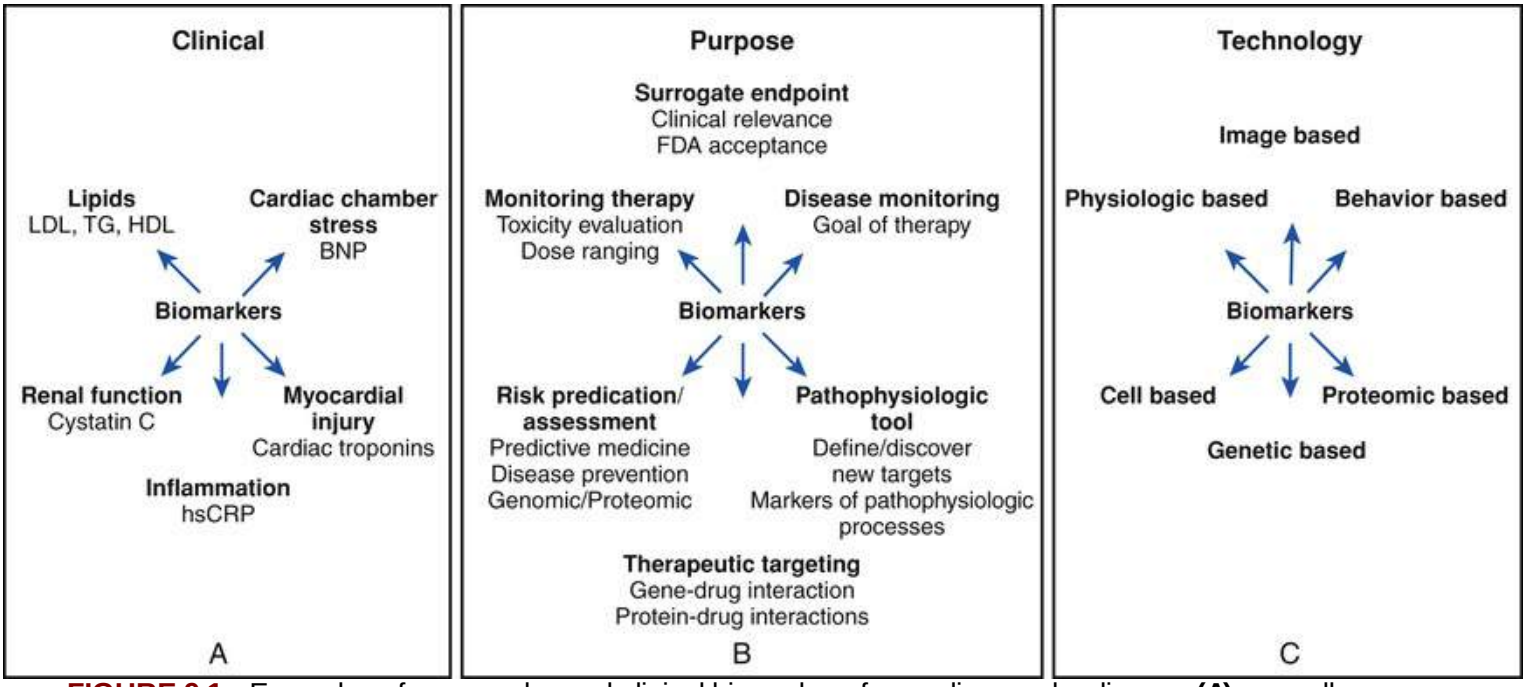

FIGURE 9.1 Examples of commonly used clinical biomarkers for cardiovascular disease **(A),** as well as research-oriented biomarkers categorized according to purpose **(B)** and technology **(C).** *BNP,* Brain natriuretic peptide; *hsCRP,* high-sensitivity C-reactive protein; *TG,* triglyceride.

The NIH working group defined a *surrogate endpoint* as "a biomarker intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm) or lack of benefit (or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence." (Note that the NIH definitions do not include the commonly used term *surrogate marker.*) Thus a surrogate endpoint is a biomarker that has been "elevated" to surrogate status. This distinction has particular importance in the regulatory aspects of cardiovascular medicine. For example, the FDA previously accepted a certain degree of reduction in hemoglobin A_{1c} (HbA_{1c}) as a criterion for registration of a novel oral hypoglycemic agent; thus HbA_{1c} was considered a biomarker accepted as a surrogate endpoint. Current FDA guidance now requires a cardiovascular safety study for the registration of new medications that target diabetes.[2] This policy indicates regulatory doubts about the fidelity of a decrease in HbA_{1c} as a surrogate endpoint for reduced cardiovascular risk, despite its value as a biomarker of glycemia.

The NIH working group defined a *clinical endpoint* as "a characteristic or variable that reflects how a patient feels, functions, or survives." Pivotal or phase III cardiovascular trials aspire to use clinical endpoints so defined. The distinction among biomarkers, surrogate endpoints, and clinical endpoints has crucial implications as practitioners, regulators, and payers increasingly demand evidence of improvements in actual clinical outcomes rather than mere manipulation of biomarkers as a criterion for

adoption of a treatment in clinical practice.

Clinical Applications of Cardiovascular Biomarkers

Much of the prevailing confusion regarding biomarkers involves framing the question that the clinician wants to answer with the use of a biomarker (**Fig. 9.1C**). We can classify the goals of application of cardiovascular biomarkers into the following rubrics:

1. *Diagnosis.* The use of biomarkers for cardiovascular diagnosis is part of daily medical practice. The current universal definition of myocardial infarction, for example, requires elevation of a biomarker of myocyte injury, such as cardiac-specific isoforms of troponin.
2. *Risk stratification.* Familiar examples of biomarkers used in risk stratification in cardiovascular medicine include systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDL-C). These biomarkers reliably predict future risk for cardiovascular events on a population basis.
3. *Goals for therapy.* Contemporary guidelines often specify cutoff points for targets of treatment, for example, a specific level of a biomarker (e.g., SBP, LDL-C) in a particular group of individuals. Practitioners of cardiovascular medicine typically use the biomarker international normalized ratio (INR) to titrate the dosage of warfarin administered to an individual patient. Abundant data support the clinical benefit of maintaining the INR within a certain range in various patient groups, an example of a widely used biomarker that has proven clinical usefulness as a goal for therapy.
4. *Targeting of therapy.* In clinical practice, using biomarkers to target therapy has great usefulness and promise as we move toward a more comprehensive "personalized medicine" approach to practice (**see Chapter 6**). Examples of biomarkers used to target therapy include troponin measurements to triage patients with acute coronary syndromes for early invasive management and measurement of high-sensitivity C-reactive protein (hsCRP) to allocate statin treatment to individuals with below-average LDL-C.
5. *Drug development, evaluation, and registration.* Biomarkers have critical importance in the development of new pharmacologic agents. Biomarkers can provide early signals of efficacy that will help prioritize agents more likely to provide benefit on clinical endpoints in large-scale trials. Clinical trials often fail because of inappropriate dose selection. Judicious use of biomarkers can help in selecting an appropriate dose of an agent to study in a large endpoint trial. Biomarkers accepted as surrogate endpoints also prove useful to regulatory agencies in granting approval for novel therapies.

Clinical use of cardiovascular biomarkers requires a clear understanding of *how* they should be used. Many biomarkers provide clinically useful information when measured once at "baseline." A baseline measurement of high-density lipoprotein cholesterol (HDL-C), for example, correlates inversely with future risk for cardiovascular events. However, serial measurement of biomarkers to document a change does not always guarantee a clinical benefit. In the case of HDL-C, recent large-scale trials that have measured clinical endpoints have cast doubt on the fidelity of a rise in HDL-C as a predictor of clinical benefit (**see Chapter 48**). Serial measurements of coronary calcium may prove misleading because statin therapy increases calcification but decreases coronary events.[3,4]

Biomarkers require rigorous validation before adoption into clinical practice. In cardiovascular medicine, LDL-C has high reliability as a biomarker; it satisfies the modified Koch postulates. LDL

levels prospectively predict cardiovascular risk, and decreases in LDL generally correlate with improved outcomes. Not all biomarkers, however, have proved as faithful in predicting clinical events. In the 1960s and 1970s, for example, most of the cardiovascular community considered ventricular premature depolarizations on the electrocardiogram (ECG) as important biomarkers for lethal arrhythmias. Numerous strategies have been aimed at suppressing ventricular ectopy. CAST (Cardiac Arrhythmia Suppression Trial), however, showed that drugs capable of suppressing ventricular premature depolarizations actually worsened clinical endpoints. The short-term improvements in indices of cardiac contractility produced by inotropic agents similarly led to worsened clinical outcomes, including increased mortality. These examples illustrate the necessity of rigorous validation of biomarkers before adoption into clinical practice.

Another important consideration in the use of cardiovascular biomarkers involves the question of *causality*. LDL-C exemplifies a *causal biomarker*, one that clearly participates in the pathogenesis of atherosclerosis. Its levels prospectively correlate with risk for cardiovascular events and the development of atherosclerotic lesions identified by a variety of imaging modalities. A variety of independent manipulations of LDL-C levels correlate with clinical outcomes. In addition, very strong genetic evidence based on mendelian disorders (e.g., familial hypercholesterolemia) and unbiased genome-wide association scans, as well as mendelian randomization analyses, have established LDL-C as a causal risk factor in atherosclerotic cardiovascular disease and as a generally valid surrogate endpoint offering great value in clinical practice[5,6] (**see Chapter 48**). Even a well-validated causal biomarker such as LDL-C, however, may mislead under some circumstances. For example, lowering of LDL-C with certain cholesteryl ester transfer protein inhibitors does not appear to lead to clinical benefit.

Other biomarkers, although clearly clinically useful, do not participate in the causal pathway for disease. For example, fever has served since antiquity as an important biomarker of infection. Resolution of fever correlates with successful resolution of infectious processes. However, fever does not participate causally in the pathogenesis of infection but merely serves as a biomarker of the host defenses against the infectious process. Similarly, the use of hsCRP measurements improves the prediction of cardiovascular risk, and reductions in CRP correlate with clinical benefit in many cases. Regardless, evidence supporting a causal role for CRP in the pathogenesis of cardiovascular disease lacks strength.[7]

These examples illustrate how a biomarker does not need to reside in the causal pathway of a disease to have clinical usefulness. A clear and early exposition of the uses and pitfalls in the application of biomarkers emerged from the landmark work of Fleming and DeMets (**Fig. 9.2**). Biomarkers have the greatest potential for validity when there is one causal pathway and when the effect of intervention on true clinical outcomes is mediated directly through the biomarker surrogate (**Fig. 9.2A**). However, biomarker development can fail when the biomarker is found not to be in the causal pathway, when the biomarker is insensitive to the specific intervention's effect, or when the intervention of interest has a mechanism of action (or a toxicity) that does not involve the pathway described by the biomarker (**Fig. 9.2B-E**). These examples do not mean that biomarkers lack value; few if any novel biologic fields could develop without biomarker discovery and validation. Still, surrogate endpoints probably will not replace large-scale randomized trials that address whether interventions reduce actual event rates.

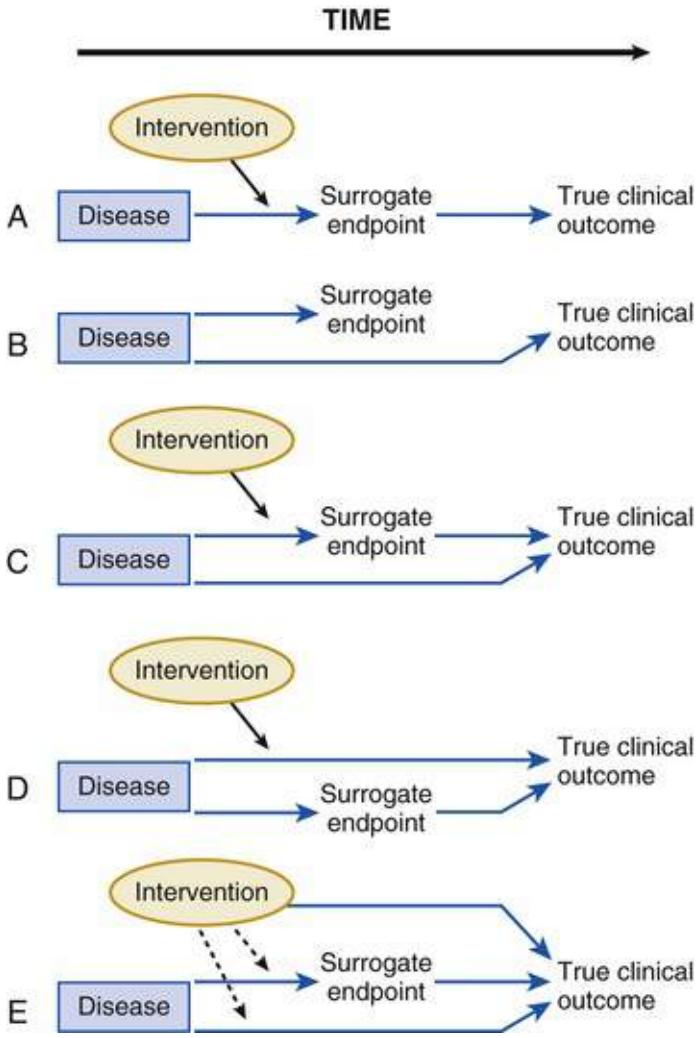

FIGURE 9.2 Biomarkers as surrogate endpoints in clinical research. **A,** The setting that provides the greatest potential for the surrogate endpoint to be valid. **B,** The surrogate is not in the causal pathway of the disease process. **C,** Of several causal pathways of disease, the intervention affects only the pathway mediated through the surrogate. **D,** The surrogate is not in the pathway of the intervention's effect or is insensitive to its effect. **E,** The intervention has mechanisms of action independent of the disease process. *Dotted lines* represent possible mechanisms of action. (Modified from Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med 1996;125:605.)

Novel Technologies in Biomarker Identification

The limitations of currently available biomarkers for screening or prognostic use underscore the importance of identifying “uncorrelated” or “orthogonal” biomarkers associated with novel disease pathways. Most current biomarkers have been developed as an extension of targeted physiologic studies investigating known pathways such as tissue injury, inflammation, or hemostasis. By contrast, emerging technologies now enable the systematic, unbiased characterization of variation in proteins and metabolites associated with disease conditions.

Proteomics and Metabolomics

Of the emerging platforms for biomarker discovery, perhaps none has garnered more recent attention than proteomics and metabolomics. *Proteomics* aims to catalog the entire protein products of the human genome. By contrast, *metabolomics* attempts systemically to capture smaller biochemical compounds, including simple amino acids and related amines, as well as lipids, sugars, nucleotides, and other

intermediary metabolites. Although still less mature than other approaches, proteomics and metabolomics offer insight into the full complexity of a given disease (**Fig. 9.3**). Because proteins and metabolites are downstream of genetic variation and transcriptional changes, they can provide instantaneous "snapshots" of the state of a cell or organism. They can rapidly change in response to environmental stressors such as exercise or directly by the ingestion of foods or other compounds. A growing body of literature suggests unanticipated roles of small proteins and metabolites in the control of biologic functions such as blood pressure and energy homeostasis.[8] Thus, metabolomics and proteomics may not only identify novel biomarkers but also provide information on biology and highlight potential therapeutic targets.

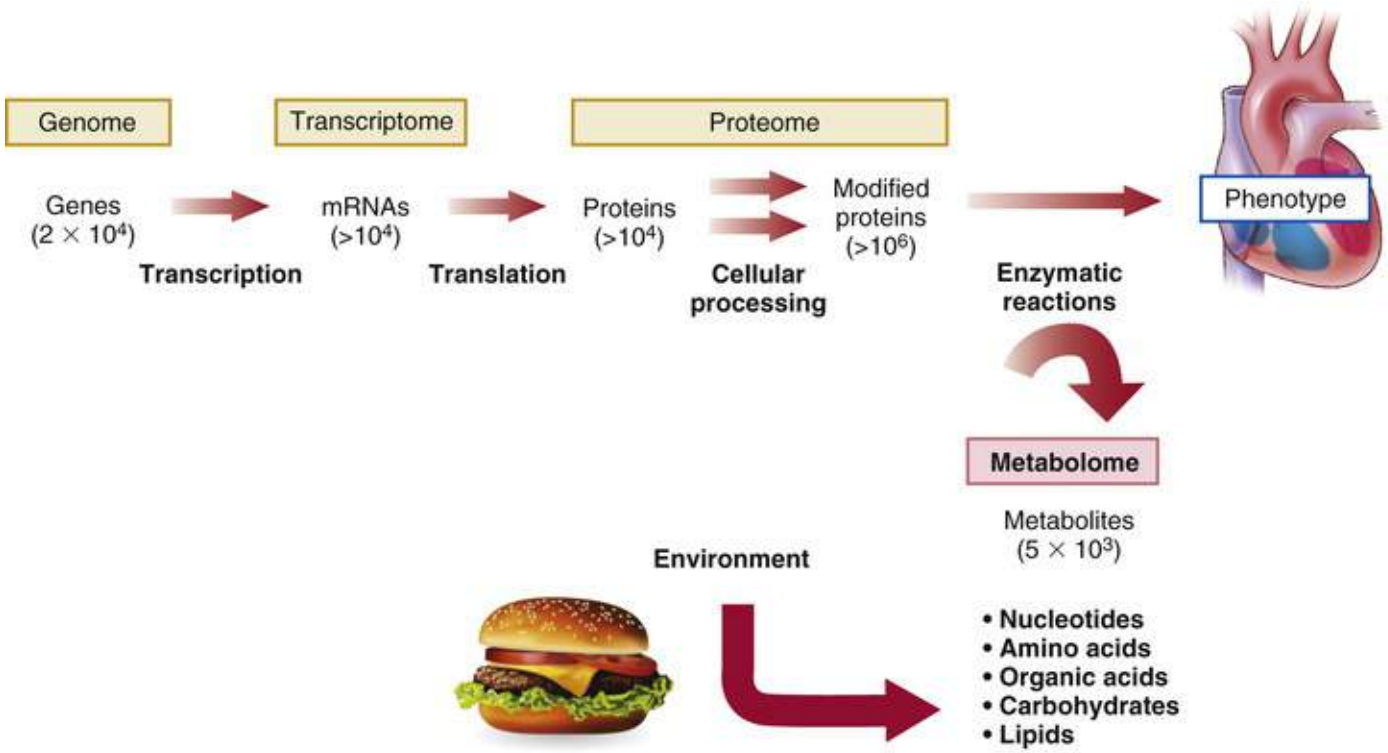

FIGURE 9.3 The conceptual relationship of the genome, transcriptome, proteome, and metabolome. Informational complexity increases from genome to transcriptome to proteome. The estimated number of entities of each type of molecule in humans is indicated in parentheses.

The term *proteome* was coined in the 1990s with the increasing realization that although all cells of a given organism contain an equivalent genomic content, their protein content does not represent all possible proteins that the genome can express. Selective gene expression during development and differentiation and in response to external stimuli results in each cell expressing only a subset of the encoded proteins at any given time. One can speak not only of the general human proteome but also more specifically about the proteome of tissues such as the heart, of specific cells such as cardiac myocytes, and even of subproteomes that correspond to particular organelles or biologic compartments, such as mitochondria.

The proteome provides information beyond the messenger RNA (mRNA) expression profile of a particular genome. Studies suggest that gene expression often correlates poorly with protein levels. Protein expression depends not only on transcription but also on mRNA stability and rates of protein synthesis and degradation, so the presence or absence of mRNA may not accurately reflect levels of the corresponding protein. Following transcription and translation, proteins may undergo one or more of dozens of potential post-translational modifications, which often modulate protein function (e.g., phosphorylation, glycosylation, acetylation, sulfation) at multiple sites. Subsequent enzymatic and

nonenzymatic alterations greatly expand the number of simultaneously existing protein species.

Compared with proteomic techniques, metabolomic technologies focus on smaller compounds, generally less than 2 kDa in size. Metabolites are usually easily separated from protein constituents by simple extraction techniques and precipitation and removal of the proteins. As early as the 1970s, Arthur Robinson and Linus Pauling postulated that the quantitative and qualitative pattern of metabolites in biologic fluids reflected the functional status of the complex biologic system from which they were derived. The term “metabolic profiling” was introduced to describe data obtained from gas chromatographic analysis of a patient sample. This emerging approach to quantitative metabolic profiling of large numbers of small molecules in biofluids was ultimately termed “metabonomics” or “metabolomics” by others.[9] Recently, more focused analyses of specific metabolite families or subsets have given rise to new terms such as “lipidomics.” In terms of applications to human diagnostics, seminal studies of inborn errors of metabolism in infants have served as a key springboard. Mass spectrometry (MS)–based methods permit monitoring of fatty acid oxidation, as well as organic and selected amino acids, enabling neonatal screening for metabolic disorders[9] and thus identification of infants with fatty acid oxidation disorders, organic acidemias, and aminoacidopathies. In certain situations, rapid identification of these disorders triggers intervention such as dietary modulation, with beneficial therapeutic effects. A global metabolomic or proteomic analysis of more common complex diseases might similarly spotlight pathways for dietary or drug modulation.

Analytic Challenges

The many classes of proteins and chemicals present analytic challenges, particularly as applied to searching for biomarkers in blood. Many different types of cells contribute to the plasma proteome and metabolome, thus increasing their complexities and presenting challenges to interpretation of the data that emerge. In the case of the proteome, the 22 most abundant proteins, including albumin and the immunoglobulins, account for 99% of the total proteome mass (**Fig. 9.4**). Many of the biologically interesting molecules relevant to human disease occur in low abundance. Cardiac markers such as troponin circulate in the nanomolar range, insulin in the picomolar range, and tumor necrosis factor in the femtomolar range. Plasma contains tens of thousands of unique protein species in concentrations spanning a range of more than 10 orders of magnitude. Indeed, some suggest that the plasma proteome might encompass the entire set of human polypeptide species resulting from splice variants and post-translational modifications, because the protein content of plasma unexpectedly includes proteins of all functional classes and from apparently all cellular localizations. Most low-abundance proteins in plasma are intracellular, or membrane proteins appear in plasma as a result of cellular turnover. Recent estimates suggest that the human metabolome consists of fewer molecular entities than the human proteome[10] and thus may be somewhat more tractable to analyze and systematize.

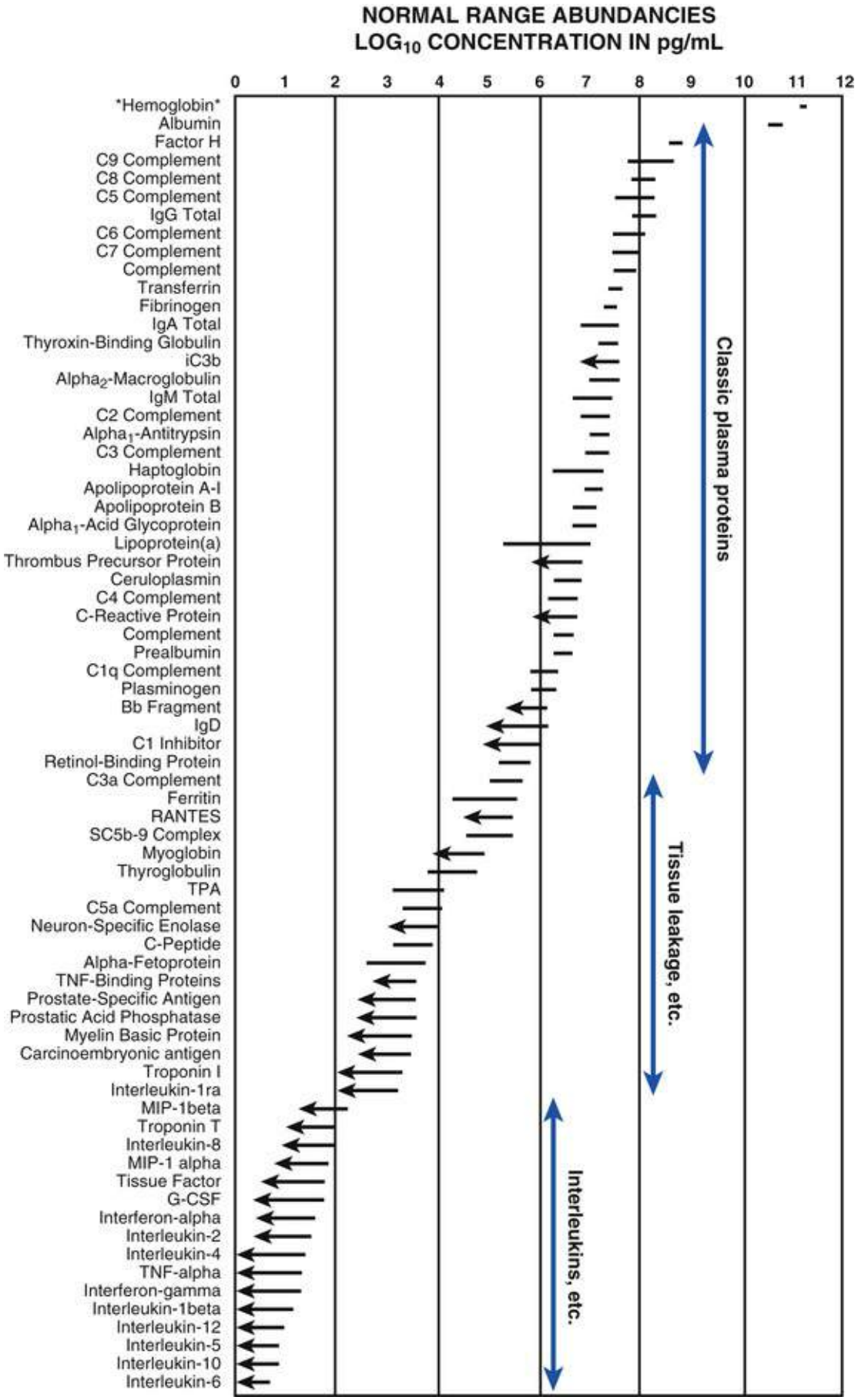

FIGURE 9.4 Reference concentration for representative protein analytes in plasma. Protein abundance is plotted on a log scale spanning 12 orders of magnitude. When only an upper limit is quoted, the lower end of the interval line shows an *arrowhead*. The classic plasma proteins are clustered to the left (high abundance), the tissue leakage markers (e.g., enzymes, troponins) are clustered in the center, and the cytokines are clustered to the right (low abundance). *G-CSF,* Granulocyte colony-stimulating factor; *MIP,* macrophage inflammatory protein; *RANTES,* regulated on activation, T cell expressed and secreted; *TNF,* tumor necrosis factor; *TPA,* tissue plasminogen activator. (From Anderson NL, Anderson NG. The human plasma proteome: history, character, and diagnostic prospects. Mol Cell Proteomics 2003;2:50.)

Several features contribute critically to the success of proteomic or metabolomic technologies. First, the technique must have the capability of identifying a wide breadth of proteins or metabolite analytes within complex biologic samples across a range of physical characteristics, including size and charge. Second, the technologies must be sensitive enough to probe the proteome or metabolome to adequate "depths"—that is, to provide resolution of biologically active compounds of the lowest abundance. Frequently, the least abundant entities play critical regulatory roles in the response to physiologic stressors. Third, tools must also work across a broad dynamic range, a notion underscored in Fig. 9.4—they must be able to simultaneously identify both more abundant and less abundant proteins in the same complex mixture. Unfortunately, most analytic techniques apply well only across concentrations of several orders of magnitude. Fourth, the ideal technology should be stable and reproducible, an attribute necessary for minimizing artifacts during initial discovery, validation, and testing for clinical applications.

Robust, searchable databases for validation of identified proteins or metabolites represent an increasingly crucial support for biomarker discovery. The scope of investigation addressable by these techniques has widened immeasurably since completion of the Human Genome Project. At present, the human databases are the largest and easiest to use, which will help accelerate translational investigation. Genomic databases collectively provide a catalog of all known or theoretical proteins expressed in organisms for which databases exist. Software that can search through databases for identification of candidates has proved essential to interpretation of the data; much of this software is available on the Internet. Collaborative efforts have recently begun to catalog both the human proteome and the plasma metabolome.

The Biomarker Discovery Process

Fig. 9.5 summarizes the essential elements of the discovery approach to biomarkers by using a proteomics experiment as an example. Biologic samples consist of a complex mixture containing intact and partially degraded proteins and metabolites of various molecular weights, modifications, and solubility. The chance of identifying proteins or metabolites in a mixture increases as the complexity of the mixture decreases. As suggested by Liebler,[11] the problem of complexity and how to deal with it resembles the process of printing a book. Printing all the words on a single page could be accomplished quickly, but the resulting page would be illegibly black with ink; dividing the text into multiple pages reduces the complexity to reveal organized text. Analogously, samples can be enriched for certain components through fractionation or affinity depletion columns, but all preparative procedures—including solubilization, denaturation, and reduction processes—should be compatible with the constraints of subsequent analysis steps. The quest to reduce complexity requires careful balance against the possibility that each additional step might also introduce undesired protein or metabolite modifications or loss.

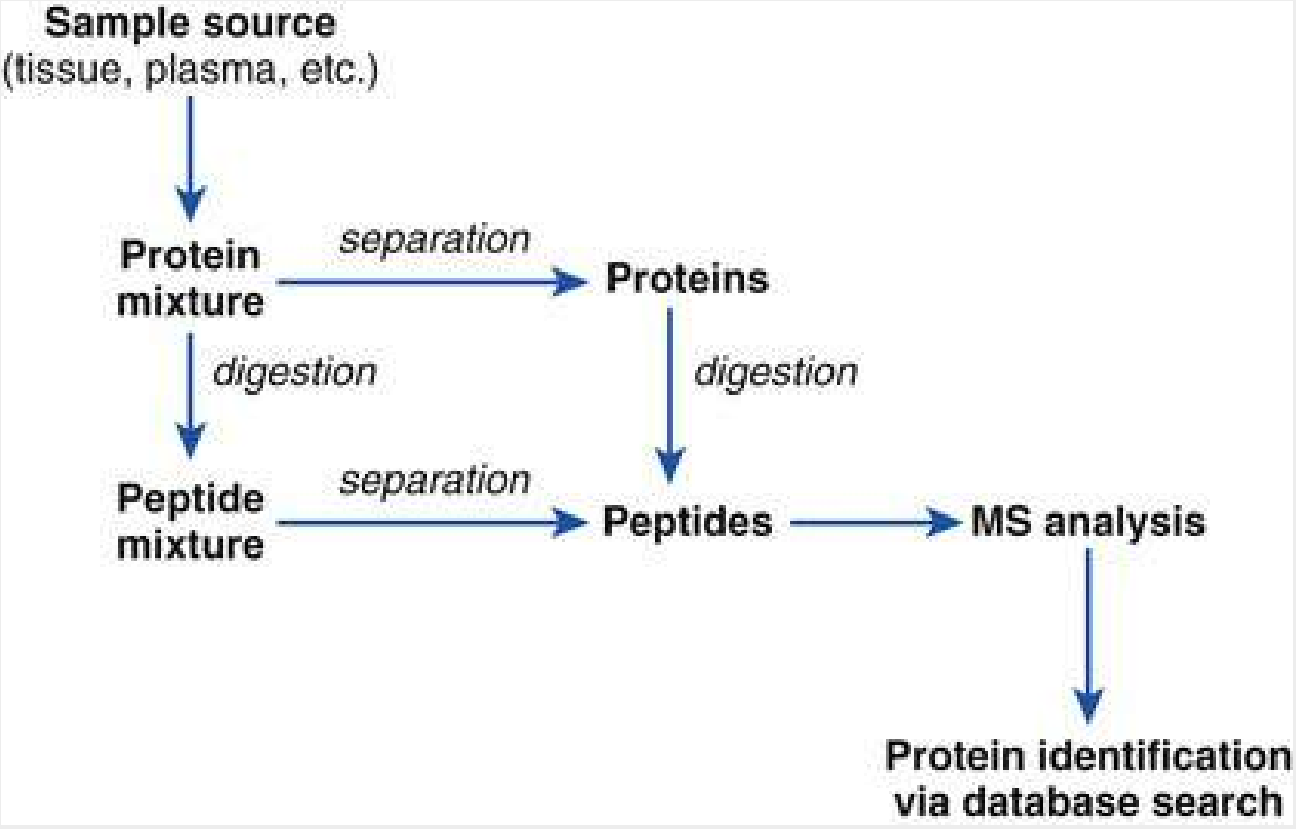

FIGURE 9.5 Overview of a proteomics experiment; *MS,* mass spectrometry.

Several analytic techniques can serve to identify metabolites or proteins, although MS instrumentation offers an unrivaled ability to provide several layers of complementary information, which has benefited tremendously from whole-genome analysis and the genomics revolution. MS provides accurate mass detection of peptides from proteolytic digests of complex protein mixtures or small metabolites derived from tissues or blood. The set of peptide or metabolite mass measurements can be searched in databases to obtain definitive identification of the parent proteins or metabolites of interest. Favorably compared against other proteomics and metabolomics technologies, MS offers high sensitivity and amenability to automation, thus promoting high-throughput processing. MS has a wide range of applicability and not only detects metabolites and proteins but also characterizes any post-translational modifications.

Mass spectrometers contain modular elements, including an ion source, mass analyzer, and a detector/recorder (**Fig. 9.6**). MS instruments differ by ionization source and mass analyzer used, but all process samples as gas-phase ions, the movements of which are measured precisely within an electromagnetic field. An ion source generates these gas-phase ions from the analyte through a variety of available techniques, from either the solid state by matrix-assisted laser desorption/ionization (MALDI) or directly from the liquid phase by electrospray ionization (ESI). A coupled chromatographic separation step fractionates complex sample mixtures before ESI spectroscopic analysis. The gas-phase ions then enter the mass analyzer, which resolves the peptides based on their mass-to-charge (m/z) ratio. Examples of commonly used mass analyzers include the quadrupole mass filter, ion trap mass analyzer, and time-of-flight mass analyzer. Lastly, the detector records the ions with an electronic multiplier and records ion intensity versus the m/z value to create the resulting MS spectra.

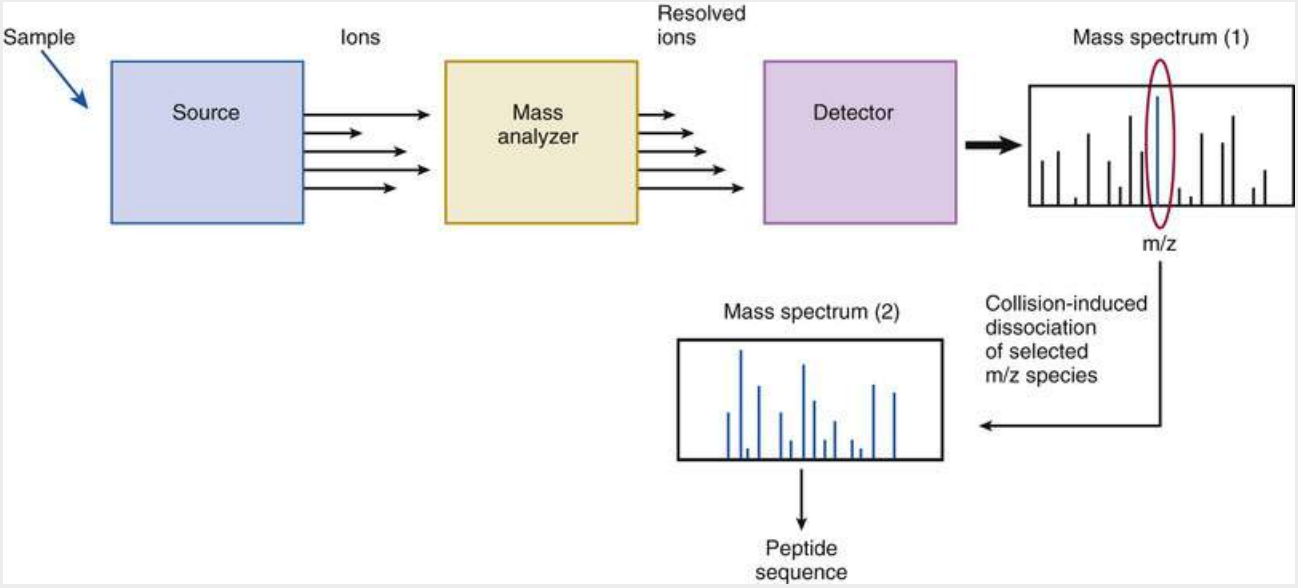

FIGURE 9.6 Schematic of tandem mass spectrometry; *m/z,* mass-to-charge ratio.

These technologies can characterize biologic fluids either in a targeted manner or in a pattern discovery manner. In the *targeted* approach, the investigator targets a predefined set of analytes to be quantitated. For example, libraries of metabolites can be purchased and their chromatographic and MS characteristics determined empirically by "spiking" reference standards into plasma. The information ascertained from the known standards then permits quantification of endogenous metabolites. The targeted approach now readily permits assay of several hundred metabolites in as little as tens of microliters of plasma. In the *pattern discovery* experiment, by contrast, the investigator confronts a complex pattern of peaks, many of which are anonymous—the molecular identities of the species that give rise to the peaks are not generally known. Although the targeted approach is more limiting, the analysis is more straightforward because the analytes yielding the signals are already known. The untargeted or "fingerprint" approach has less inherent bias, but unambiguous identification of the peaks can prove laborious and difficult. Analyses of clinical samples require considerable care to exclude spurious associations, such as confounding related to drug treatment.

Applications of Mass Spectrometry–Based Discovery to Cardiometabolic Disease

In an initial proof-of-principle study using a targeted metabolite profiling approach, Newgard and colleagues[12] profiled obese versus lean humans to gain a broad understanding of the metabolic and physiologic differences in these two disparate groups. Their studies identified a branched-chain amino acid signature that correlated highly with the metrics of insulin resistance. Complementary studies in two large population-based cohorts demonstrated that branched-chain and aromatic amino acid concentrations are significantly associated with incident type 2 diabetes up to 12 years before the onset of overt disease.[13] Adjustment for established clinical risk factors did not substantially attenuate the strength of these associations. Furthermore, the branched-chain amino acid signature also predicts atherosclerosis even after adjusting for the metrics of insulin resistance and diabetes.[14] For those in the top quartile of branched-chain amino acid levels, the odds for development of cardiometabolic disease exceeded any single-nucleotide polymorphism (SNP) identified to date. Taken together, these findings have disclosed dysregulation of amino acid metabolism very early in the development of cardiometabolic diseases. Ongoing studies are examining the relative genetic versus environmental contributions to these findings. A

recent report suggests that genetic variation in enzymes in branched-chain amino acid metabolism is associated with both circulating amino acid levels and diabetes in multiple large-scale human cohorts, suggesting that this class of compounds also contributes to disease pathogenesis.[15]

Using nontargeted liquid chromatography–MS–based metabolite profiling applied to cardiovascular disease, Wang and associates[13] first profiled the plasma of 75 individuals from a hospital-based cohort who experienced a myocardial infarction, stroke, or death in the ensuing 3 years and 75 age- and sex-matched controls who did not.[13] Of 18 analytes that differed significantly between cases and controls, three demonstrated significant correlations among one another, thus suggesting a potential common biochemical pathway. Using complementary analytic methods, these metabolites were identified as betaine, choline, and trimethylamine-*N*-oxide, all metabolites of dietary phosphatidylcholine. Dietary supplementation of choline was sufficient to promote atherosclerosis in mice, and suppression of the intestinal bacteria responsible for the conversion of phosphatidylcholine to choline inhibited this atherogenesis. In addition to reinforcing the interaction among diet, gut bacteria, and the metabolome, this study demonstrated how metabolomic biomarker discovery can elucidate novel pathways to disease.

The previous discussion describes methods of discovery for soluble biomarkers found in body fluids. Analysis of cells also provides another aspect of biomarker use. Fluorescent-activated cell sorting (FACS) has provided a robust method for classifying cells by their cell surface structures.[16] Modifications of this technique can quantify intracellular proteins such as cytokines as well. A recent advance in characterizing cells derived from cytometry and MS is cytometry by time-of-flight mass spectrometry (CyTOF).[17] This technology permits staining of complex cell mixtures with multiple antibodies. Site talk resembles flow cytometry but uses antibodies labeled with rare-earth metal isotopes to resolve as many as 50 cell markers simultaneously. The use of rare-earth tags yields a very low background and permits resolving multiple targets, because the masses of the marked antibodies have minimal overlap. The application of CyTOF promises to permit a deeper immunophenotyping of circulating cells than achievable with traditional fluorescent cell-sorting techniques.[17,18]

Future Directions

Identification of new biomarkers for cardiovascular disease depends on the complementary power of genetics, transcriptional profiling, proteomics, and metabolomics. As discussed in the next section, the clinical usefulness of new biomarkers will require rigorous evaluation of their ability to improve the prediction of risk or to direct and monitor management in an individual, the ultimate goal of personalized medicine. In addition to risk biomarkers, diagnostic biomarkers could help in making challenging acute diagnoses such as reversible myocardial ischemia, pulmonary embolism, and aortic dissection. The evolution of a clinical biomarker requires a long journey and an arduous transition from the research environment to clinical practice. Emerging technologies such as those previously described have the potential to permit systematic assessment of variation in genes, RNA, proteins, and metabolites for identification of “uncorrelated” or “orthogonal” biomarkers that probably would not emerge with a focus on candidates from well-studied pathways.

Aptamer-based technologies are one emerging approach to probe the plasma proteome selectively. *Aptamers*, often considered as “chemical antibodies,” are small RNA or single-stranded (ss) DNA nucleic acids that can bind with great specificity to targeted proteins and related cell targets.[19-22] When

modified with biotin and an activatable fluorophore, aptamers can be incubated with plasma and, using standard bead immobilization techniques, ultimately separated into bound and unbound fractions. Once eluted, these bound aptamers (reflecting their accompanying protein targets) are hybridized to microarrays with complementary ssDNA probes to quantify the specific fluorescent tags.[20] In a recent cardiovascular application of this technology, investigators in the Heart and Soul and HUNT-3 studies used an aptamer-based approach to evaluate 1130 proteins simultaneously. Of these, nine proteins were identified as being predictive of vascular risk, and a risk score derived from these nine proteins was able to separate high from low risk. A second study used a similar aptamer-based platform to identify dozens of novel markers of early myocardial injury. The generalizability of these findings requires much further work to validate clinical utility in terms or early diagnosis or reclassification, and perhaps most importantly, whether the aptamer approach can identify novel therapeutic targets.[21]

Clinical Measures of Biomarker Performance

When considering any biomarker in a clinical setting for risk prediction, physicians should ask two interrelated questions[23]:

- Is there clear evidence that the biomarker of interest predicts future cardiovascular events independent of other already measured biomarkers?
- Is there clear evidence that patients identified by the biomarker of interest will benefit from a therapy that they otherwise would not have received?

If the answer to both these questions is not a clear “yes,” it can be argued that measuring the biomarker will not probably have sufficient usefulness to justify its cost or unintended consequences. Such judgments require clinical expertise and will vary on a case-by-case basis.

Biomarker evaluation also typically involves repeated testing in multiple settings that include varied patient populations and that use different epidemiologic designs. *Prospective* cohort studies (in which the biomarker or exposure of interest is measured at baseline, when individuals are healthy, and then related to the future development of disease) provide a much stronger form of epidemiologic evidence than do data from *retrospective* case-control studies (in which the biomarker of interest is measured after the disease is present in the case participants).

After discovery by the technologies described earlier or identification by a candidate approach, a novel biomarker typically requires development in a translational laboratory for refinement of its assay to address issues of interassay and intra-assay variation before any clinical testing begins. Focused studies in specific patient populations typically follow and eventually broaden to encompass the population of greatest clinical interest. Beyond simple reproducibility, biomarkers under development for diagnostic, screening, or predictive purposes require further evaluation with a standard set of performance measures that include sensitivity, specificity, positive and negative predictive value, discrimination, calibration, reclassification, and tests for external validity.

Sensitivity, Specificity, and Positive and Negative Predictive Value

The validity of a screening or diagnostic test (or one used for prediction) is initially measured by its ability to categorize individuals who have preclinical disease correctly as “test positive” and those without preclinical disease as “test negative.” A simple two-by-two table is typically used to summarize the results of a screening test by dividing those screened into four distinct groups (**Table 9.2**). In this context, sensitivity and specificity provide fundamental measures of the test's clinical validity. *Sensitivity* is the probability of testing positive when the disease is truly present and is defined mathematically as a/(a + c). As sensitivity increases, the number of individuals with disease who are missed by the test decreases, so a test with perfect sensitivity will detect all individuals with disease correctly. In practice, tests with ever-higher sensitivity tend to also classify as “diseased” many individuals who are not actually affected (false positives). Thus the *specificity* of a test is the probability of screening negative if the disease is truly absent and is defined mathematically as d/(b + d). A test with high specificity will rarely be positive when disease is absent and will therefore lead to a lower proportion of individuals without disease being incorrectly classified as test positive (false positives). A simple way to remember these differences is that sensitivity is “positive in disease” whereas specificity is “negative in health.”

TABLE 9.2

Summarizing the Results of Screening, Diagnostic, or Predictive Tests

	DISEASE PRESENT	DISEASE ABSENT	
Test positive	a	b	a + b
Test negative	c	d	c + d
Total	a + c	b + d	
Sensitivity = a/(a + c) Specificity = d/(b + d) Positive predictive value = a (a + b) Negative predictive value = d/(c + d)			

a = Number of individuals for whom the screening test is positive and the individual actually has the disease (true positives).

b = Number of individuals for whom the test is positive but the individual does not have the disease (false positives).

c = Number of individuals for whom the test is negative but the individual actually has the disease (false negatives).

d = Number of individuals for whom the test is negative and the individual does not have the disease (true negatives).

Modified from Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69:89-95.

A perfect test has both very high sensitivity and specificity and thus low false-positive and false-negative classifications. Such test characteristics are rare, however, because there is a trade-off between sensitivity and specificity for almost every screening biomarker, diagnostic, or predictive test in common clinical use. For example, although high LDL-C levels usually serve as a biomarker for atherosclerotic risk, up to half of all incident cardiovascular events occur in those with LDL-C levels well within the normal range, and many events occur even when levels are low. If the diagnostic cutoff criterion for LDL-C is reduced so that more people who actually have high risk for disease will be test positive (i.e., increase sensitivity), an immediate consequence of this change will be an increase in the number of people without disease in whom the diagnosis is made incorrectly (i.e., reduced specificity). Conversely, if the criterion for diagnosis or prediction is made more stringent, a greater proportion of those who test negative will actually not have the disease (i.e., improved specificity), but a larger proportion of true cases will be missed (i.e., reduced sensitivity).

In addition to sensitivity and specificity, the performance or yield of a screening, diagnostic, or predictive test also varies depending on the characteristics of the population being evaluated. Positive and negative predictive values are terms used in epidemiology that refer to measurement of whether an individual actually has (or does not have) a disease, contingent on the result of the screening test itself.

The positive predictive value (PPV) is the probability that a person has the disease of interest, given that the individual tests positive, and is mathematically calculated as PPV = a/(a + b). High PPV can be anticipated when the disease is common in the population being tested. Conversely, the negative predictive value (NPV) is the probability that an individual is truly disease free, provided that the test has a negative result, and is mathematically calculated as NPV = d/(c + d). High NPV can be anticipated when the disease is rare in the population being tested. Although sensitivity and specificity are largely performance characteristics of the test itself (and thus tend to be fixed values), PPV and NPV depend in part on the population being tested (and thus tend to vary).

Discrimination, C-Statistics, and Receiver Operating Characteristic Curve

Discrimination is the ability of a test (or prognostic model) to separate those with disease or at high risk for disease (cases) from those without disease or at low risk for disease (controls). The most common method used to measure discrimination has been the *area under the receiver operating characteristic* (ROC) *curve* (AUC), which relates sensitivity (on the *y* axis) to (1 − specificity) (on the *x* axis) across a full range of cutoff values for the test or screening algorithm of interest (**Fig. 9.7**).

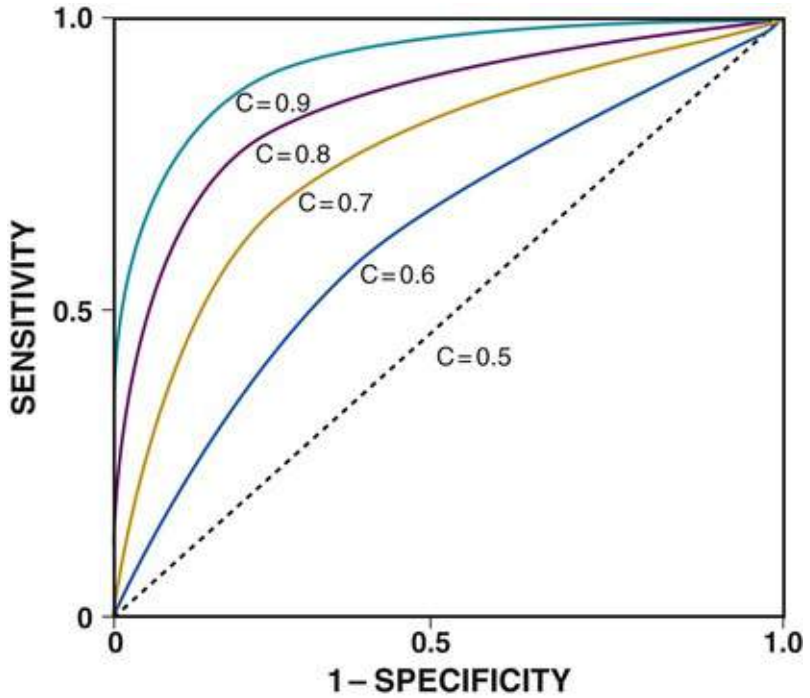

FIGURE 9.7 Receiver operating characteristic (ROC) curves for a series of biomarkers or risk prediction models with incremental improvement. The diagonal line corresponds to a random effect (C-statistic = 0.5), whereas the increasing C-statistic corresponds to improving model discrimination.

Given a population of individuals being evaluated, the area under the ROC curve, also called the *C-statistic*, equals the probability of correctly ranking risk for individuals by using the test or model under evaluation. A random test with no clinical usefulness would have a C-statistic (ROC AUC) of 0.5, which

corresponds to the diagonal line in Fig. 9.7. A perfect test that completely discriminates individuals with disease from those without disease would have a C-statistic that approaches 1.0. As the C-statistic increases from 0.5 to 1.0, model fit (or test accuracy) improves; thus the change in the C-statistic has been used historically to judge whether a new biomarker can "add" significantly to those already in use. This approach permits direct comparison of the relative efficiency of multimarker panels. For example, using comparative C-statistic analyses, investigators in the Emerging Risk Factors Collaboration recently found that the incremental clinical usefulness of CRP has similar magnitude as that of total and HDL-C.[24] Thus, when change in the C-statistic can be demonstrated and the overall power to do so is adequate, this test can assist in understanding the impact of novel pathways and novel risk biomarkers on prediction and prevention.

Unfortunately, as Cook[25,26] has shown in several settings, the traditional C-statistic approach is limited in that biomarkers with large associations may have minimal effect on ROC AUC. For example, a predictor (or set of predictors) would need an odds ratio (OR) as high as 16 (>2 standard deviations [SD]) to lead to a substantial increase in the C-statistic.[27] Almost no test in common use for risk prediction or prognostication in cardiovascular medicine has an OR in this range; high cholesterol, smoking, high blood pressure, and diabetes are all associated with OR of less than 2 and thus have little individual impact at all on ROC AUC. Consequently, sole reliance on the C-statistic as a method for developing and evaluating new biomarkers, at least in the setting of risk prediction, is insufficient.

Accuracy and Calibration

Discrimination is only one measure of model accuracy. The other important measure is *calibration*, or the ability of a predictive model to assign risk estimates accurately compared with the actual observed risk in the population being tested. Unlike discrimination, which is based solely on relative rankings of risk, calibration compares the risk predicted from a model or test with that actually observed.

For *binary* outcomes (e.g., disease or no disease), calibration is often evaluated with the Hosmer-Lemeshow test, which places individuals within categories of estimated risk by using the test biomarker or multivariable model and compares these estimates with the proportions actually observed. These "predicted" and "observed" probabilities can be compared with standard goodness-of-fit tests across categories of risk (e.g., across estimated quintiles or estimated deciles of risk). Calibration becomes particularly important when addressing a biomarker in different populations from the population in whom it was originally developed. A biomarker may calibrate well in men but not in women, or among whites but not among blacks. This consideration also applies to multimarker panels, such as the Framingham Risk Score, which calibrates well in whites but less well in other population groups. Newer risk models such as the Reynolds Risk Score show improved calibration, as well as discrimination, compared with the traditional Framingham model.[28]

Risk Reclassification

To address the shortcoming of biomarker validation via the C-statistic alone, contemporary biomarker development programs for risk prediction now use a series of "reclassification statistics," as initially developed by Cook and Ridker[29] and refined by Pencina[30] and Xanthakis[31] and associates. Rather than addressing whether a new biomarker of interest adds to ROC AUC, reclassification addresses whether the biomarker can shift overall risk estimates upward or downward in a clinically meaningful way. Specifically, reclassification methods compare risk strata formed from prediction models with and

without the new biomarker of interest and then determine which model leads to the most accurate classification of risk. Risk reclassification is particularly useful when actionable and clinically relevant risk categories already exist. For example, in primary cardiovascular prevention, 10-year estimated risk is often categorized as being less than 5%, 5% to 10%, 10% to 20%, or greater than 20%, and those above or below these cut points are frequently targeted for interventions such as aspirin and statin therapy. Thus a biomarker that reclassifies a proportion of individuals upward (or downward) might well be highly effective for targeting (or avoiding) drug therapy, even if the overall effect on discrimination is modest.

Mere reclassification of an individual by a given biomarker does not provide sufficient evidence to support clinical use. Rather, an effective biomarker should correctly reclassify risk higher or lower and thus lead to more accurate overall risk assessment. The *reclassification calibration* (RC) statistic is a tool that tests how well the average predicted risk within a given cell agrees with the observed risk of individuals who actually experience the event. Accordingly, the RC statistic addresses whether the predicted risk estimates after reclassification (using the new biomarker) are more accurate than before reclassification (without the new biomarker). Superior reclassification occurs when the new prediction model places case individuals into higher-risk categories and places control individuals into lower-risk categories, and when the net shift in these two effects is in the overall correct direction. This characteristic can be addressed by using the *net reclassification index* (NRI), analogous to a test of discrimination (the ability to separate cases from controls) in the context of a reclassification table. Broadly, the NRI does not depend as much on the actual predicted probabilities as on movement across a categorical risk border that is the result of the new probabilities predicted. When reclassification is not addressed across categories, an alternative measure is used, called the *integrated discrimination improvement* (IDI), based on the Yates slope, or the difference in predicted probabilities among case and control individuals.[32] Despite their relatively recent introduction, reclassification statistics have rapidly become the standard for clinical evaluation of emerging biomarkers and alternative multibiomarker prediction panels.

External Validation and Impact Studies

A final but important test for any biomarker or biomarker panel when used for prognostication, *external validation* refers to the ability of the panel to function with clinically acceptable levels of sensitivity, specificity, discrimination, and calibration in external populations, distinct from the population used for generation of the panel. As Moons and coworkers[33] note, prognosis research and prognostic biomarkers differ from those used in diagnosis and screening.[33]

Prognostic research involves three distinct phases in the development of multivariable prediction models. The first phase is identification of relevant predictors, assignment of weights to the model, estimation of predictive performance, and optimization of fit. The second phase involves validation or formal testing of calibration and discrimination in new patient groups, which can be similar to those used in the development stage or purposely different. The third phase involves impact studies to quantify directly whether use of a prognostic model in daily practice actually changes physician behavior and decision making, and whether this occurs in a net positive manner and is cost-effective. *Prognostic impact studies* also focus on the incremental usefulness of a given biomarker beyond simple clinical and nonclinical characteristics. Such studies tend to be less biologically driven than biomarker discovery work and recognize that prediction does not necessarily involve a causal pathway.

Practical Example: High-Sensitivity CRP, Lipids, and Reynolds Risk Score

The use of high-sensitivity C-reactive protein (hsCRP) in clinical practice is an example of how biomarker development programs can move from pathophysiologic principles to clinical use and onward to multinational trials evaluating novel targets for vascular risk reduction.[34,35] A prospective cohort of initially healthy individuals showed that hsCRP predicted future risk for a heart attack and stroke in men, an observation externally validated and quickly extended to women. Multiple commercial hsCRP assays —reproducible, internally calibrated, and externally validated to improve assay precision—then became clinically available. Multiple studies have shown that statins reduce hsCRP in a manner largely independent of reduction of LDL-C, thus suggesting that statins have both lipid-lowering and anti-inflammatory effects. The addition of hsCRP to the family history and HbA_{1c} was formally incorporated into the Reynolds Risk Score in 2008. This score was subsequently externally validated and shown to have superior calibration, discrimination, and reclassification over the more traditional Framingham Risk Score. Using hsCRP to define a high-risk population in need of treatment, JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) reported in 2008 that statin therapy (versus placebo) in those with elevated hsCRP but low levels of LDL-C resulted in a 50% reduction in myocardial infarction and stroke and a 20% reduction in all-cause mortality.[36] By 2010, more than 50 prospective cohort studies evaluating hsCRP were subjected to meta-analysis, which affirmed that the magnitude of vascular risk associated with a change of 1 SD in hsCRP was at least as large as that of a comparable change in cholesterol or blood pressure.[37] An updated 2012 meta-analysis of clinical usefulness and risk prediction found that the change in C-statistic associated with hsCRP was similar to that associated with the use of total and HDL cholesterol.[24] On this basis, several national guidelines incorporated hsCRP screening in primary and secondary prevention,[38] and the FDA approved a labeling claim for the use of statin therapy in those with elevated hsCRP levels.

CRP itself, however, probably does not cause atherothrombosis, but rather serves as a biomarker for the underlying inflammatory process.[39] Thus, as a direct outcome of the hsCRP development program, two randomized trials are now testing directly whether lowering inflammation per se can reduce vascular risk. These two trials—the NIH-funded CIRT (Cardiovascular Inflammation Reduction Trial), which evaluated low-dose methotrexate, and CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study), which evaluated interleukin-1beta inhibition—are ongoing and, when complete, will have involved more than 18,000 patients worldwide.[35]

Conclusion

We use biomarkers in our daily clinical practice, and cardiovascular journals contain numerous reports regarding biomarkers, new and old, that purport to show how they may aid clinical practice. Moreover, many cardiovascular trials use biomarkers—thus the current practice of cardiovascular medicine requires a firm foundation in understanding and evaluating biomarkers. The road map to the field of biomarkers provided in this chapter, including their use, development, and methods for evaluating their usefulness for various specific applications, should give practitioners tools to sort out the various uses of biomarkers encountered in practice and in the cardiovascular literature. Informed use of biomarkers can aid in decision making in daily patient care. Biomarkers should provide a key for personalized management by directing the right therapy to the right patient at the right time. They can also shed mechanistic insight on

human pathophysiology that is difficult to obtain in other ways. Rigorous and careful use of biomarkers can aid in the development of novel therapies to address the residual burden of cardiovascular risk.

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For citations to the older literature, see the additional reference list online for this chapter or the tenth edition of this textbook..

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PART III
Evaluation of The Patient

OUTLINE

10

History and Physical Examination

An Evidence-Based Approach

James C. Fang, Patrick T. O'Gara

Evaluation of the patient with known or suspected cardiovascular disease begins with a directed history

and targeted physical examination, the scope and duration of which depend on the clinical context of the patient encounter. Elective, ambulatory investigations allow comparatively more time for the development of a comprehensive assessment, whereas emergency department (ED) visits and urgent bedside consultations necessitate a more focused strategy. The elicitation of the history, with its emphasis on major cardiovascular symptoms and their change over time, demands a direct interaction between the clinician and patient; it should not be delegated to another or inferred from information gleaned from a cursory chart review. The history also affords a unique opportunity to assess the patient's personal attitudes, intelligence, comprehension, acceptance or denial, motivation, fear, and prejudices. Such insights allow a more informed understanding of the patient's preferences and values regarding shared decision-making. The interview also can reveal genetic or familial influences and the impact of other medical conditions on the manifesting illness. Although time constraints have limited the emphasis on careful history taking, the information gathered from the patient interview remains essential to inform the design of a resource-sensitive diagnostic and treatment plan.

Physical examination skills also have declined. Only a minority of internal medicine and family practice residents recognizes classic cardiac findings in relevant diseases. Performance does not predictably improve with experience.[1] Residency work hours and health care system efficiency standards have severely restricted the time and expertise devoted to the mentored cardiovascular examination. In turn, less attention to bedside skills has increased the use of noninvasive imaging, including the use of handheld ultrasound. Educational efforts, which utilize repetition, patient-centered teaching conferences, simulation, and visual display feedback of auscultatory and Doppler echocardiographic findings, can improve performance.[2-6]

The evidence base that justifies correlations between history and physical examination findings and cardiovascular disease severity and prognosis has been developed most rigorously for heart failure, valvular heart disease, and coronary artery disease (CAD). For example, vital signs and detection of pulmonary congestion and mitral regurgitation (MR) contribute importantly to bedside risk assessment in patients with acute coronary syndrome (ACS). The diagnosis of heart failure in ambulatory patients derives from attention to three basic elements of the history—dyspnea at one flight of stairs, orthopnea, and paroxysmal nocturnal dyspnea—and six validated elements of the physical examination—a displaced apex beat, rales, an irregularly irregular pulse, a heart murmur suggestive of MR, a heart rate greater than 60 beats/min, and an elevated jugular venous pressure.[7] Accurate auscultation provides important insight into many valvular and congenital heart lesions. This chapter reviews the fundamentals of the cardiovascular history and physical examination in light of evidence from correlative studies.

The History

The major signs and symptoms associated with cardiac disease include chest discomfort, dyspnea, fatigue, edema, palpitations, and syncope. In most cases, careful attention to the specific characteristics of chest discomfort—quality, location, radiation, triggers, mode of onset, and duration—along with alleviating factors and associated symptoms can narrow the differential diagnosis (**see Chapter 56**). Angina pectoris can usually be differentiated from the pain associated with pulmonary embolism, pericarditis, aortic dissection, esophageal reflux, or costochondritis. Cough, hemoptysis, and cyanosis may provide additional clues as to the cause of chest pain. Claudication, limb pain, edema, and skin discoloration usually indicate a vascular disorder. The cardiovascular clinician also should be familiar with common manifestations of acute cerebrovascular accident (stroke) and transient ischemic attack,

such as sudden weakness, sensory loss, incoordination, and visual disturbance.

Typical angina should satisfy three characteristics: (1) substernal discomfort, (2) initiated by exertion or stress, and (3) relieved with rest or sublingual nitroglycerin. Chest discomfort with two of these three criteria is considered atypical angina; pain with one or none of these features is considered nonanginal. When age and sex are considered, diagnostic accuracy for CAD is reasonable (receiver operating characteristic [ROC] area under the curve [AUC], 0.713). Incorporating a history of diabetes, hypertension, smoking, and dyslipidemia improves the diagnostic accuracy (ROC AUC, 0.791).[8] Several aspects of the presenting symptom of chest pain increase or decrease the likelihood of ACS. For example, pain that is sharp (likelihood ratio [LR], 0.3; 95% confidence interval [CI], 0.2 to 0.5), pleuritic (LR, 0.2; 95% CI, 0.1 to 0.3), positional (LR, 0.3; 95% CI, 0.2 to 0.5), or reproducible with palpation (LR, 0.3; 95% CI, 0.2 to 0.4) usually is noncardiac, whereas discomfort that radiates to both arms or shoulders (LR, 4.1; 95% CI, 2.5 to 6.5) or is precipitated by exertion (LR, 2.4; 95% CI, 1.5 to 3.8) has a higher likelihood of reflecting an ACS. Less classic symptoms (i.e., anginal equivalents), such as indigestion, belching, and dyspnea, also should command the clinician's attention when other features of the presentation suggest ACS, even in the absence of chest discomfort. Women, elderly persons, and patients with diabetes more often present with a less typical clinical picture. A history of a prior abnormal stress test (LR, 3.1; 95%CI, 2.0 to 4.7), known CAD (LR, 2.0; 95% CI, 1.4 to 2.6), or the presence of peripheral arterial disease (LR, 2.7; 95% CI, 1.5 to 4.8) increases the likelihood that the pain indicates an ACS.[9] In general, the accuracy of traditional risk factors and symptoms for the diagnosis of ACS is weak. Clinical prediction tools that incorporate aspects of the history and examination with serum biomarkers of cardiac injury (troponins) and electrocardiographic findings provide better diagnostic accuracy (**Tables 10.1 and 10.2**).

TABLE 10.1

Performance of Chest Pain Characteristics in Diagnosing Acute Coronary Syndrome

SYMPTOM	POSITIVE LR (95% CI)	NEGATIVE LR (95% CI)	PPV (%)	NPV (%)
Radiation to both arms	2.6 (1.8-3.7)	0.93 (0.89-0.96)	28	12
Pain similar to prior ischemia	2.2 (2.0-2.6)	0.67 (0.60-0.74)	25	9
Change in pattern over prior 24 hr	2.0 (1.6-2.5)	0.84 (0.79-0.90)	23	11
“Typical” chest pain	1.9 (0.94-2.9)	0.52 (0.35-0.69)	22	7
Worse with exertion	1.5-1.8	0.66-0.83	18-21	9-11
Radiation to neck or jaw	1.5 (1.3-1.8)	0.91 (0.87-0.95)	18	12
Recent episode of similar pain	1.3 (1.1-1.4)	0.80 (0.71-0.90)	16	11
Radiation to left arm	1.3 (1.2-1.4)	0.88 (0.81-0.96)	16	12
Radiation to right arm	1.3 (0.78-2.1)	0.99 (0.96-1.0)	16	13
Associated diaphoresis	1.3-1.4	0.91-0.93	16-17	12-12
Associated dyspnea	1.2 (1.1-1.3)	0.89 (0.82-0.96)	15	12
Abrupt onset	1.1 (1.0-1.2)	0.75 (0.61-0.91)	14	10
Any improvement with nitroglycerin	1.1 (0.93-1.3)	.90 (0.85-0.96)	14	12
“Typical” radiation	1.0-5.7	0.78-0.98	13-46	10.13
Burning pain	1.0-1.4	0.97-1.0	13-17	13-13
Associated nausea/vomiting	0.92-1.1	0.98-1.0	12-14	13-13
Associated palpitations	0.71 (0.37-1.3)	1.0 (0.98-1.1)	10	13
Associated syncope	0.55 (0.39-0.76)	1.1 (1.1-1.1)	8	14
Pleuritic pain	0.35-061	1.1-1.2	6.6-8.4	14-15

LR, Likelihood ratio; *PPV,* positive predictive value; *NPV,* negative predictive value.

From Fanaroff AC, Rymer JA, Goldstein SA, et al. Does this patient with chest pain have acute coronary syndrome? The rational clinical examination systematic review. JAMA 2015;314:1955-65.

TABLE 10.2

Performance of Physical Examination Findings in Diagnosing Acute Coronary Syndrome

SYMPTOM	POSITIVE LR (95% CI)	NEGATIVE LR (95% CI)	PPV (%)	NPV (%)
Hypotension (SBP <100 mm Hg)	3.9 (0.98-15)	0.98 (0.95-1.0)	37	13
Lung rales	2.0 (1.0-4.0)	0.95 (0.90-1.0)	23	12
Tachypnea	1.9 (0.99-3.5)	0.95 (0.89-1.0)	22	12
Tachycardia (heart rate >120 beats/min)	1.3 (0.42-3.94)	0.99 (0.96-1.0)	16	13
Pain reproduced on palpation	0.28 (0.14-0.54)	1.2 (1.0-1.2)	4.0	15

LR, Likelihood ratio; *PPV,* positive predictive value; *NPV,* negative predictive value; *SBP,* systolic blood pressure.

From Fanaroff AC, Rymer JA, Goldstein SA et al. Does this patient with chest pain have acute coronary syndrome? The rational clinical examination systematic review. JAMA 2015;314:1955-65.

Dyspnea may occur with exertion or in recumbency (orthopnea) or even on standing (platypnea). Paroxysmal nocturnal dyspnea of cardiac origin usually occurs 2 to 4 hours after onset of sleep; the dyspnea is sufficiently severe to compel the patient to sit upright or stand and then subsides gradually over several minutes. The patient's partner should be questioned about any signs of sleep-disordered breathing, such as loud snoring or periods of apnea. Pulmonary embolism often associates with dyspnea of sudden onset.

Patients may use a variety of terms to describe their awareness of the heartbeat (palpitations), such as “flutters,” “skips,” or “pounding.” The likelihood of a cardiac arrhythmia modestly increases with a known history of cardiac disease (LR, 2.03; 95% CI, 1.33 to 3.11) and decreases when symptoms resolve within 5 minutes (LR, 0.38; 95% CI, 0.22 to 0.63) or when associated with panic disorder (LR, 0.26; 95% CI, 0.07 to 1.01). A report of a regular, rapid-pounding sensation in the neck (LR, 177; 95% CI, 25 to 1251) or visible neck pulsations associated with palpitations (LR, 2.68; 95% CI, 1.25 to 5.78) increases the likelihood that atrioventricular nodal reentrant tachycardia (AVNRT) is the responsible arrhythmia. The absence of a regular, rapid-pounding sensation in the neck makes detecting AVNRT much less likely (LR, 0.07; 95% CI, 0.03 to 0.19). Cardiac syncope occurs suddenly, with rapid restoration of full consciousness thereafter. Patients with neurocardiogenic syncope may experience early warning signs (nausea, yawning), appear ashen and diaphoretic, and revive more slowly, although without signs of seizure or a prolonged postictal state. The complete history consists of information pertaining to traditional cardiovascular risk factors, a general medical history, occupation, social habits, activities, medications, drug allergies or intolerance, family history, and systems review.

It is important to obtain a semiquantitative assessment of symptom severity and to document any change over time. The New York Heart Association (NYHA) and the Canadian Cardiovascular Society (CCS) functional classification systems are useful for both patient care and clinical research, despite their inherent limitations.

The General Physical Examination

The physical examination can help determine the cause of a given symptom, assess disease severity and progression, and evaluate the impact of specific therapies. It also can identify the presence of early-stage disease in patients without signs or symptoms.

General Appearance

The examination begins with an appreciation of the general appearance of the patient, including age,

posture, demeanor, and general health status. Is the patient in pain, resting quietly, or visibly diaphoretic with a foreboding sense of doom? Does the patient choose to avoid certain positions to reduce or eliminate pain? The pain of acute pericarditis, for example, often diminishes with sitting up, leaning forward, or breathing shallowly. Pursing of the lips, a breathy quality to the voice, and an increased anteroposterior chest diameter would favor a pulmonary rather than a cardiovascular cause of dyspnea, although disorders in both etiologic categories may contribute in an individual patient. *Pallor* suggests anemia as a possible underlying disorder in patients with exercise intolerance or dyspnea, independent of cardiovascular disease. Cyanosis and jaundice also bear noting. Specific genetic cardiovascular disorders may be discernible from the patient's appearance. *Emaciation* suggests chronic heart failure or another systemic disorder (e.g., malignancy, infection).

The vital signs, including height, weight, temperature, pulse rate, blood pressure (in both arms), respiratory rate, and peripheral oxygen saturation, dictate the pace and scope of the evaluation and provide initial clues as to the presence of a cardiovascular disorder. The height and weight permit calculation of body mass index (BMI) and body surface area (BSA). Waist circumference (measured at the iliac crest) and waist-to-hip ratio (using the widest circumference around the buttocks) powerfully predict long-term cardiovascular risk. In patients with palpitations, a resting heart rate less than 60 beats/min may increase the likelihood of a clinically significant arrhythmia (LR, 3.00; 95% CI, 1.27 to 7.08). Observation of the respiratory pattern may reveal signs of disordered breathing (e.g., Cheyne-Stokes respirations, obstructive sleep apnea), a finding associated with reduced survival in patients with severe systolic heart failure.[10] Mental status should be assessed and is an important gauge of adequate cerebral and systemic perfusion. Finally, *frailty* should be specifically addressed and recognized. Several scales are available that incorporate quantifiable criteria such as unintentional weight loss, grip strength, and gait speed (**Table 10.3**). Frailty assessment, a common tool in the evaluation of patients with heart failure, has also entered into the preprocedural appraisal of patients referred for heart valve replacement or repair.

TABLE 10.3

The Fried Criteria for Frailty

CHARACTERISTIC	METRICS
Shrinking (Unintentional weight loss)	>10 pounds or >5% of total body weight in past year
Weakness (Reduced handgrip strength)	Maximum isometric contraction in dominant hand over 3 attempts using hand dynamometer
Exhaustion (Self-reported exhaustion)	Questions from the Center for Epidemiologic Studies—Depression Scale
Slowness (Slow gait speed)	Slowest quintile according to gender/height based on time to walk 15 feet
Inactivity (Low self-reported physical activity)	Lowest quintile of expended kcal/week using activity questionnaire

Frail: Three or more criteria present.

Intermediate/Prefrail: One or two criteria present.

From Joyce E. Frailty in advanced heart failure. Heart Fail Clin Adv Heart Fail 2016;12:363-74.

Skin

Central cyanosis is present with significant right-to-left shunting at the level of the heart or lungs. It also is a feature of hereditary methemoglobinemia. Peripheral cyanosis or acrocyanosis of the fingers, toes, nose, and ears is characteristic of the reduced blood flow that accompanies small-vessel constriction seen in

severe heart failure, shock, or peripheral vascular disease. Differential cyanosis affecting the lower but not the upper extremities occurs with a patent ductus arteriosus (PDA) and pulmonary artery (PA) hypertension with right-to-left shunting at the great vessel level.

Hereditary telangiectases on the lips, tongue, and mucous membranes (a finding in Osler-Weber-Rendu syndrome) resemble spider nevi; when present in the lungs, they can cause right-to-left shunting and central cyanosis. Telangiectasias also are seen in patients with scleroderma with or without pulmonary hypertension. Tanned or bronze discoloration of the skin in unexposed areas can suggest iron overload and hemochromatosis. With jaundice, often first appreciated in the sclerae, the differential diagnosis is broad in scope. *Ecchymoses* often occur with either anticoagulant and/or antiplatelet use, whereas *petechiae* characterize thrombocytopenia, and purpuric skin lesions can be seen with infective endocarditis and other causes of leukocytoclastic vasculitis. Various lipid disorders can manifest with *xanthomas*, located subcutaneously, along tendon sheaths, or over the extensor surfaces of the extremities. Xanthomas within the palmar creases are specific for type III hyperlipoproteinemia.

The leathery, cobblestone, "plucked chicken" appearance of the skin in the axillae and skinfolds of a young person is characteristic of pseudoxanthoma elasticum, a disease with multiple cardiovascular manifestations, including premature atherosclerosis. Extensive *lentiginoses* (freckle-like brown macules and café au lait spots over the trunk and neck) may be part of developmental delay–associated cardiovascular syndromes (LEOPARD, LAMB, and Carney) with multiple atrial myxomas, atrial septal defect (ASD), hypertrophic cardiomyopathy, and valvular stenoses. In a patient with heart failure or syncope, cardiovascular sarcoid should be suspected in the presence of lupus pernio, erythema nodosum, or granuloma annulare. Certain vascular disorders, such as erythromelalgia, chilblain, frostbite, and lymphangitis, also may be readily apparent from examination of the skin in the appropriate context.

Head and Neck

All patients should undergo assessment of the state of dentition, both as a source of infection and as an index of general health and hygiene. A high-arched palate is a feature of Marfan and other connective tissue disease syndromes. A large protruding tongue with parotid enlargement may suggest amyloidosis. Patients with Loeys-Dietz syndrome characteristically have a bifid uvula. Orange tonsils are typical of Tangier disease. Ptosis and ophthalmoplegia suggest muscular dystrophies, and congenital heart disease often is accompanied by hypertelorism, low-set ears, micrognathia, and a webbed neck, as with Noonan, Turner, and Down syndromes. Proptosis, lid lag, and stare point to Graves hyperthyroidism. Patients with osteogenesis imperfecta have blue sclerae, MR or aortic regurgitation (AR), and a history of recurrent nontraumatic skeletal fractures.

Attention to the extraocular movements and the size and symmetry of the pupils may reveal a neurologic disorder. The oft-omitted funduscopic (ophthalmoscopic) examination can aid in the evaluation of patients with hypertension, atherosclerosis, diabetes, endocarditis, neurologic signs or symptoms, or known carotid or aortic arch disease. Lacrimal gland hyperplasia is sometimes a feature of sarcoidosis. The "mitral facies" of rheumatic mitral stenosis (pink-purplish patches with telangiectasias over the malar eminences) also can accompany other disorders associated with pulmonary hypertension and reduced cardiac output. Relapsing polychondritis is suggested by inflammation of the pinnae and nasal cartilage in association with a saddle-nose deformity. Palpation of the thyroid gland assesses its size, symmetry, and consistency.

Extremities

Inspection can quickly ascertain the temperature of the extremities and the presence of clubbing, arachnodactyly, and nail changes . Clubbing implies the presence of central shunting (**Fig. 10.1**). An unopposable “fingerized” thumb occurs in Holt-Oram syndrome. Arachnodactyly characterizes Marfan syndrome. Janeway lesions (nontender, slightly raised areas of hemorrhage on the palms and soles), Osler nodes (tender, raised nodules on the pads of the fingers or toes), and splinter hemorrhages (linear petechiae in the mid-nailbed) may be signs of infective endocarditis. Ulcerations and tissue loss of the fingertips may suggest thromboangiitis obliterans in the appropriate context.

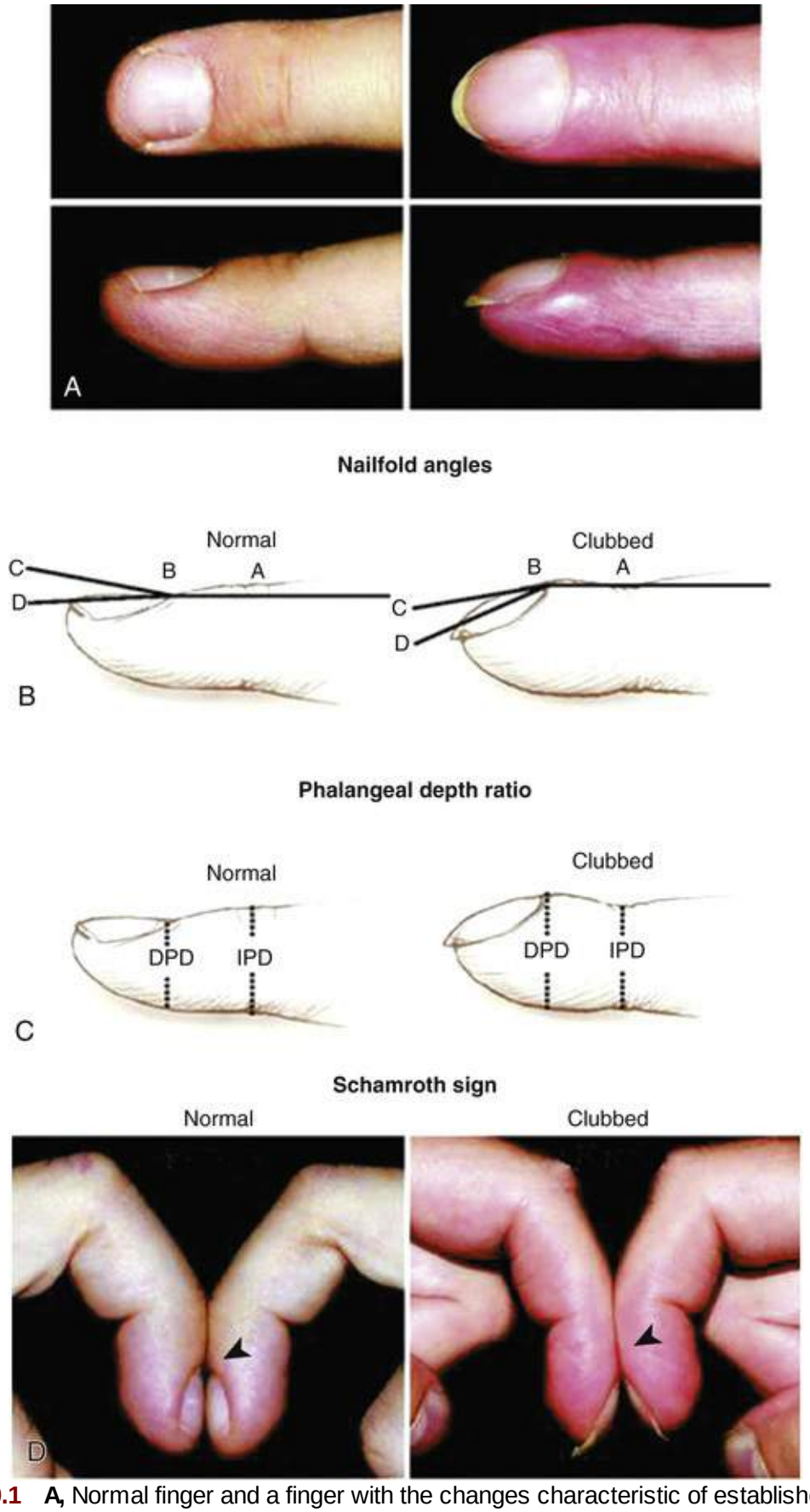


FIGURE 10.1 **A,** Normal finger and a finger with the changes characteristic of established clubbing, viewed from above and in profile. **B**, The finger on the *left* demonstrates normal profile (ABC) and normal hyponychial (ABD) nailfold angles of 169 degrees and 183 degrees, respectively. The clubbed finger on the *right* shows increased profile and hyponychial nailfold angles of 191 degrees and 203 degrees, respectively. **C**, Distal phalangeal finger depth (DPD)/interphalangeal finger depth (IPD) represents the phalangeal depth ratio. In normal fingers the IPD is greater than the DPD. In clubbing this relationship is reversed. **D**, Schamroth sign. In the absence of clubbing, nail-to-nail opposition creates a diamond-shaped window (*arrowhead*). In clubbed fingers, the loss of the profile angle with the increase in tissue at the nailbed causes obliteration of this space (*arrowhead*). (From Myers KA, Farquhar DR. Does this patient have clubbing? JAMA 2001;286:341.)

Lower extremity or presacral edema with elevated jugular venous pressure (JVP) occurs in many volume-overloaded states, including heart failure. With a normal JVP, additional signs of venous disease, such as extensive varicosities, medial ulcers, or brownish pigmentation from hemosiderin deposition, suggest chronic venous insufficiency. A history of lower extremity vein ligation and "stripping" should be recognized. Edema also can occur with dihydropyridine calcium channel blocker therapy. Anasarca seldom occurs in heart failure, unless the condition is longstanding, untreated, and accompanied by severe hypoalbuminemia. Asymmetric swelling can reflect local or unilateral venous thrombosis, the sequelae of previous vein graft harvesting, or lymphatic obstruction. Homans sign (calf pain elicited by forceful dorsiflexion of the foot) is neither specific nor sensitive for deep vein thrombosis. Muscular atrophy and the absence of hair in an extremity should suggest chronic arterial insufficiency or a neuromuscular disorder. Redistribution of fat from the extremities to central/abdominal stores (lipodystrophy) in some patients with HIV infection may relate to antiretroviral therapy and also is associated with insulin resistance and several features of the metabolic syndrome.

Chest and Abdomen

Cutaneous venous collaterals over the anterior chest suggest chronic obstruction of the superior vena cava (SVC) or subclavian vein, especially in the presence of indwelling catheters or leads from cardiac implantable electrical devices (CIEDs). Asymmetric breast enlargement or arm swelling ipsilateral to a CIED also may be present. Thoracic cage abnormalities, such as pectus carinatum (pigeon chest) or pectus excavatum (funnel chest), may accompany connective tissue disorders; the barrel chest of emphysema or advanced kyphoscoliosis may be associated with cor pulmonale. The severe kyphosis of ankylosing spondylitis should prompt careful auscultation for AR and scrutiny of the electrocardiogram (ECG) for first-degree atrioventricular block. The "straight back syndrome" (loss of normal kyphosis of the thoracic spine) can accompany mitral valve prolapse (MVP). A thrill may be present over well-developed intercostal artery collaterals in patients with aortic coarctation.

Patients with emphysema may exhibit prominence of the cardiac impulse in the epigastrium. The liver often is enlarged and tender in heart failure; systolic hepatic pulsations signify severe tricuspid regurgitation (TR). Patients with infective endocarditis of long duration may have splenomegaly. Ascites can develop with advanced and chronic right heart failure or constrictive pericarditis. The abdominal aorta normally may be palpated between the epigastrium and the umbilicus in thin patients and in children. The sensitivity of palpation for the detection of abdominal aortic aneurysm (AAA) disease increases as a function of aneurysm diameter and varies inversely with body size. Arterial bruits in the abdomen should be sought.

Careful chest auscultation is an essential component of the cardiovascular examination and is of prime importance when the presenting complaint is dyspnea. Technological advances have provided important insights into often-underappreciated pulmonary auscultatory phenomena that are frequently encountered in the evaluation of patients with cardiovascular disease[11] (**Fig. 10.2**).

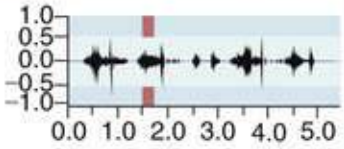
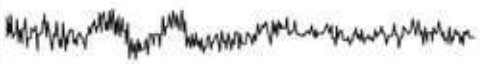
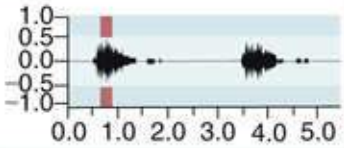
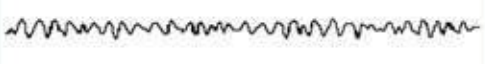
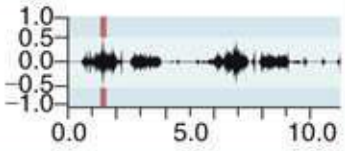
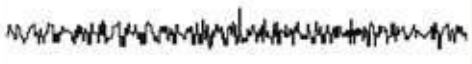
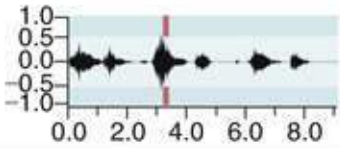
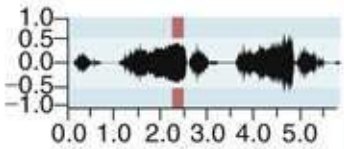
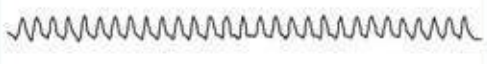
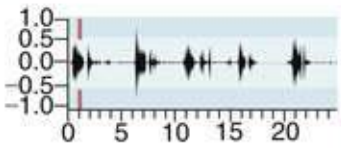
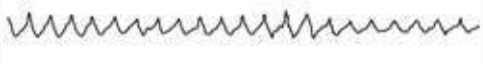
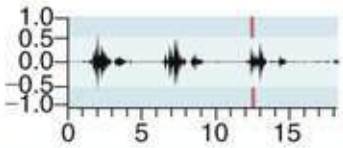
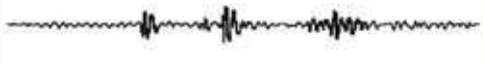
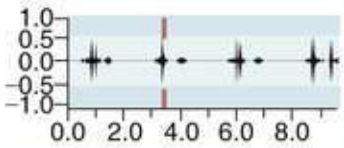
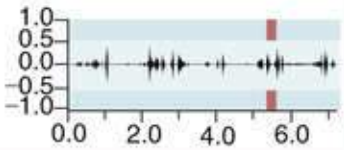
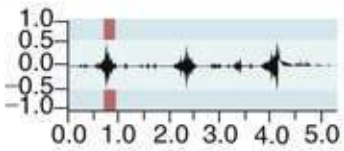
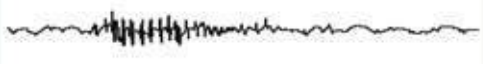
Respiratory sound	Amplitude–Time plot	
Acoustics	Unexpanded time	Expanded time
A Tracheal sound White noise Typical frequency, 100–5000 Hz Drop of energy at 800 Hz		
B Normal (vesicular) lung sound Low-pass-filtered noise Typical frequency, 100–1000 Hz Drop of energy at 200 Hz		
C Bronchial breathing Strong expiratory component An intermediate sound between tracheal and normal breathing		
D Stridor Sinusoid Fundamental frequency, >500 Hz		
E Wheeze Sinusoid Typical frequency, >100–5000 Hz Typical duration, >80 msec		
F Rhonchus Sinusoid Typical frequency, about 150 Hz Typical duration, >80 msec		
G Fine crackle Rapidly dampened wave deflection Typical frequency, about 650 Hz Typical duration, about 5 msec		
H Coarse crackles Rapidly dampened wave deflection Typical frequency, about 350 Hz Typical duration, about 15 msec		
I Pleural friction rub Rhythmic succession of short sounds Typical frequency, <350 Hz Typical duration, >15 msec		
J Squawk Sinusoid Typical frequency, 200–300 Hz Typical duration, about 200 msec Followed or preceded by crackles		

FIGURE 10.2 Respiratory sounds and the acoustic waveforms. (From Bohadana A, Izvicki G, Kraman SS. Fundamentals of lung auscultation. N Engl J Med 2014;370:2053.)

The Cardiovascular Examination

Jugular Venous Pressure and Waveform

The JVP aids in the estimation of volume status. The external (EJV) or internal (IJV) jugular vein may be used, although the IJV is preferred because the EJV is valved and not directly in line with the SVC and right atrium. The EJV is easier to visualize when distended, and its appearance can help to discriminate between low and high central venous pressure (CVP). An elevated left EJV pressure may also signify a persistent left-sided SVC or compression of the innominate vein from an intrathoracic structure. If an elevated CVP is suspected but venous pulsations cannot be appreciated, the patient should be asked to sit upright with the feet dangling. With subsequent pooling of blood in the lower extremities, venous pulsations may be evident. SVC syndrome should be suspected if the venous pressure is elevated, pulsations are still not discernible, and the skin of the head and neck appears dusky or cyanotic. When hypovolemia is suspected as a cause of hypotension, the patient may need to be lowered to a supine position to assess the waveform in the right supraclavicular fossa.

The venous waveform can sometimes be difficult to distinguish from the carotid artery pulse. The venous waveform has several characteristic features (**Fig. 10.3** and **Table 10.4**), and its individual components can usually be identified. The *a* and *v* waves, and *x* and *y* descents, are defined by their temporal relation to electrocardiographic events and heart sounds (S_1 and S_2, plus S_3 and S_4, as defined later). The estimated height of the venous pressure indicates the CVP or right atrial pressure. Although observers vary widely in their estimates of the CVP, knowledge that the pressure is elevated, and not its specific value, can inform diagnosis and management.

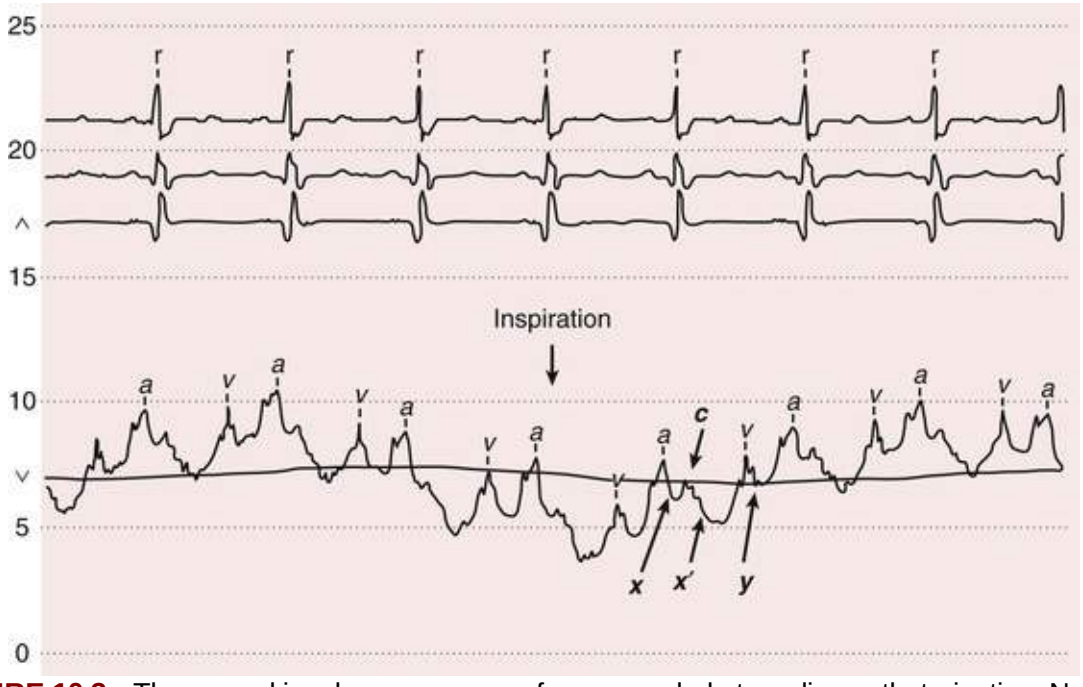


FIGURE 10.3 The normal jugular venous waveform recorded at cardiac catheterization. Note the inspiratory fall in pressure and the dominant *x*/*x*′ descent.

TABLE 10.4

Distinguishing Jugular Venous Pulse from Carotid Pulse

FEATURE	INTERNAL JUGULAR VEIN PULSE	CAROTID ARTERY PULSE
Appearance of pulse	Undulating two troughs and two peaks for every cardiac cycle (biphasic)	Single brisk upstroke (monophasic)
Response to inspiration	Height of column falls and troughs become more prominent	No respiratory change to contour
Palpability	Generally not palpable (except in severe TR)	Palpable
Effect of pressure	Can be obliterated with gentle pressure at base of vein/clavicle	Cannot be obliterated

TR, Tricuspid regurgitation.

The venous pressure is measured as the vertical distance between the top of the venous pulsation and the sternal inflection point, where the manubrium meets the sternum (angle of Louis). A distance of greater than 3 cm (1.2 inches) is considered abnormal, but the distance between the angle of Louis and the mid–right atrium varies considerably, especially in obese patients. On chest computed tomography (CT) scans in 160 consecutive patients, this distance varied considerably in accordance with body position. In general, use of the sternal angle as a reference leads to systematic underestimation of venous pressure. In practice, however, it is difficult to use even relatively simple landmarks, and on attempts to locate an external reference point to determine the CVP, measurements obtained by critical care nurses vary by several centimeters. Venous pulsations above the clavicle with the patient in the sitting position are clearly abnormal, because the distance from the right atrium is at least 10 cm (4 inches). Estimated CVP correlates only modestly with direct measurement. Measurements made at the bedside, in units of centimeters of blood or water, require conversion to millimeters of mercury (1.36 cm H_2O = 1.0 mm Hg), for comparison with values measured with catheterization.

The venous waveforms include several distinct peaks: *a*, *c*, and *v* (**see Fig. 10.3**). The *a* wave reflects right atrial presystolic contraction, occurs just after the electrocardiographic P wave, and precedes the first heart sound (S_1). Patients with reduced right ventricular (RV) compliance from any cause can have a prominent *a* wave. A cannon *a* wave occurs with atrioventricular dissociation and right atrial contraction against a closed tricuspid valve (**Fig. 10.4**). The presence of cannon *a* waves in a patient with wide-complex tachycardia identifies the rhythm as ventricular in origin. The *a* wave is absent with atrial fibrillation (AF). The *x* descent reflects the fall in right atrial pressure after the *a* wave peak. The *c* wave interrupts this descent as ventricular systole pushes the closed valve into the right atrium. In the neck the carotid pulse also may contribute to the *c* wave. As depicted in **Fig. 10.4**, the *x* descent follows because of atrial diastolic suction created by ventricular systole pulling the tricuspid valve downward. In normal persons the *x* descent is the predominant waveform in the jugular venous pulse. The *v* wave represents atrial filling, occurs at the end of ventricular systole, and follows just after S_2. Its height is determined by right atrial compliance and by the volume of blood returning to the right atrium from any source. The *v* wave is smaller than the *a* wave because of the normally compliant right atrium. In patients with ASD, the *a* and *v* waves may be of equal height; in TR, the *v* wave is accentuated (Video 10.1). With TR, the *v* wave will merge with the *c* wave because retrograde valve flow and antegrade right atrial filling occur simultaneously. The *y* descent follows the *v* wave peak and reflects the fall in right atrial pressure after tricuspid valve opening. Resistance to ventricular filling in early diastole blunts the *y* descent, as with pericardial tamponade or tricuspid stenosis. The *y* descent will be steep when ventricular diastolic filling occurs early and rapidly, as with pericardial constriction or isolated, severe TR.

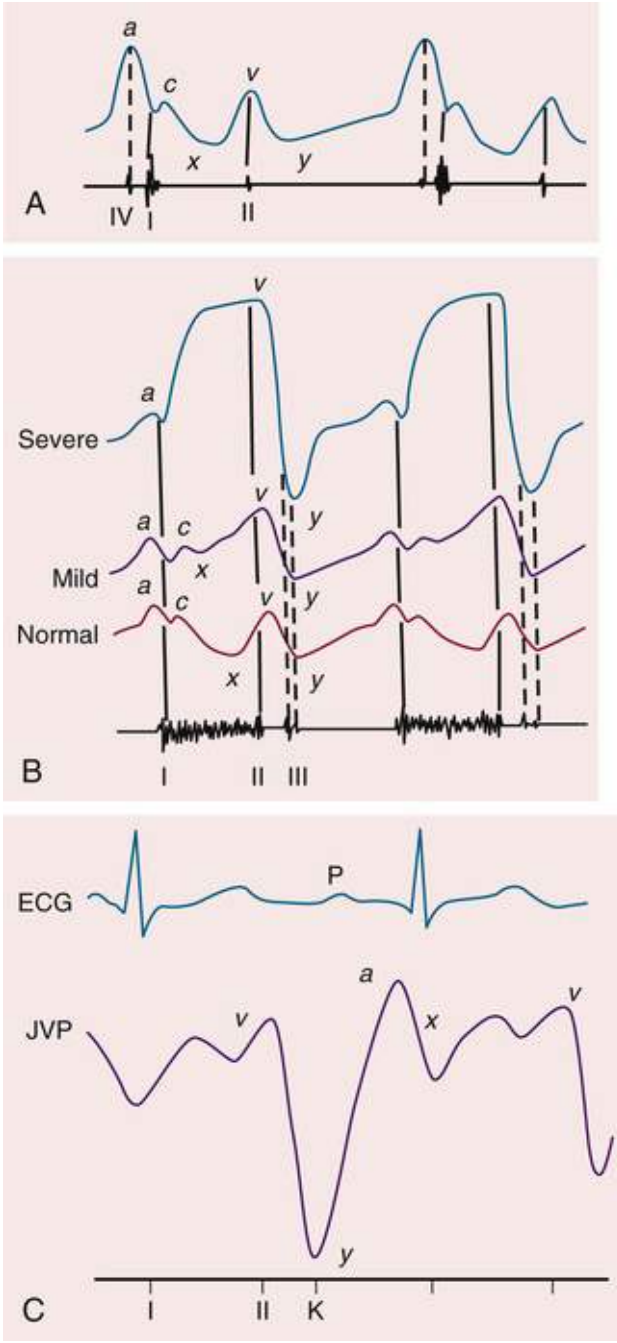


FIGURE 10.4 Abnormal jugular venous waveforms. **A,** Large *a* waves associated with reduced RV compliance or elevated RV end-diastolic pressure. Phonocardiographic tracing (*below*) shows timing of the corresponding right-sided S_4. **B,** Normal jugular venous waveform (*bottom*), mild tricuspid regurgitation (TR) (*middle*), and severe TR (*top*), with corresponding phonocardiogram. With severe TR, "ventricularization" of the jugular venous waveform is seen, with a prominent *v* wave and rapid *y* descent. The *x* descent is absent. **C,** Jugular venous waveform in constrictive pericarditis with a prominent *y* descent. Note the timing of the pericardial knock (*K*) relative to S_2. The abrupt rise in pressure after the nadir of the *y* descent is caused by the rapid rise in venous pressure with ventricular filling. *JVP,* Jugular venous pressure. (From Abrams J. Synopsis of Cardiac Physical Diagnosis. 2nd ed. Boston: Butterworth Heinemann; 2001, pp 25-35.)

The normal venous pressure should fall by at least 3 mm Hg with inspiration. A rise in venous pressure (or its failure to decrease) with inspiration (Kussmaul sign) is associated with constrictive pericarditis and also with restrictive cardiomyopathy, pulmonary embolism, RV infarction, and advanced systolic heart failure. A Kussmaul sign is seen with right-sided volume overload and reduced RV compliance (Video 10.2). Normally, the inspiratory increase in right-sided venous return is accommodated by increased RV ejection, facilitated by an increase in the capacitance of the pulmonary vascular bed. In states of RV diastolic dysfunction and volume overload, the right ventricle cannot accommodate the

enhanced volume, and the pressure rises.

The abdominojugular reflux maneuver or passive leg elevation can elicit venous hypertension. The abdominojugular reflux maneuver requires firm and consistent pressure over the upper abdomen, preferably the right upper quadrant, for at least 10 seconds. Classically, a positive abdominojugular reflux sign has been defined as a rise of more than 3 cm in the venous pressure sustained for at least 15 seconds, although in practice a shorter duration is usually accepted. The patient should be coached to refrain from holding the breath or performing a Valsalva-like maneuver, which can falsely elevate the venous pressure. A positive abdominojugular reflux sign can predict heart failure in patients with dyspnea as well as a PA wedge pressure higher than 15 mm Hg.

Measuring the Blood Pressure

Auscultatory measurement of blood pressure (BP) yields lower systolic and higher diastolic values than direct intra-arterial recording (**see Chapters 46 and 47**). Nurse-recorded BP usually is closer to the patient's average daytime BP than physician measured BP. BP should be measured with the patient in the seated position, with the arm at the level of the heart, using an appropriate-size cuff (**Table 10.5**). The use of an inappropriately small cuff can result in overestimation of the true BP, an issue of particular relevance in obese patients.

TABLE 10.5

Important Aspects of Blood Pressure Measurement

• Patient should be seated comfortably, with back supported and legs uncrossed, and the upper arm bared.
• Upper arm should be at heart level.
• Cuff length and width should be 80% and 40% of arm circumference, respectively.
• Cuff should be deflated at <3 mm Hg/sec.
• Column or dial should be read to nearest 2 mm Hg.
• First audible Korotkoff sound is systolic pressure; last sound, diastolic pressure.
• There should be no talking between subject and observer (or other person).

From Daskalopolou SS et al. The 2015 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol 2015;31:549-68; and Ringrose JS et al. Effect of cuff design on auscultatory and oscillometric blood pressure measurements. Am J Hypertens 2016;29:1063-9.

On occasion, the Korotkoff sounds may disappear soon after the first sound, only to recur later before finally disappearing at phase 5. This auscultatory gap is more likely to occur in older, hypertensive patients with target organ damage. The systolic BP should be recorded at the first Korotkoff sound and not when the sound reappears. This finding should be distinguished from pulsus paradoxus (see later). Korotkoff sounds may be heard all the way down to 0 mm Hg with the cuff completely deflated in children, in pregnant patients, in patients with chronic severe AR, or in the presence of a large arteriovenous fistula. In these cases, both the phase 4 and phase 5 pressures should be noted.

Blood pressure should be measured in both arms either in rapid succession or simultaneously; normally the measurements should differ by less than 10 mm Hg, independent of handedness. As many as 20% of normal individuals, however, exhibit a left-right arm BP differential of more than 10 mm Hg in the absence of symptoms or other examination findings. A BP differential of more than 10 mm Hg can be associated with subclavian artery disease, supravalvular aortic stenosis, aortic coarctation, or aortic dissection. Systolic leg pressures may exceed arm pressures by as much as 20 mm Hg; greater leg-arm systolic BP differences are seen in patients with severe AR (Hill sign) and patients with extensive and calcified (noncompressible) lower extremity peripheral arterial disease (PAD). Leg BP should be

measured using large thigh cuffs with auscultation at the popliteal artery or using a standard large arm cuff on the calf with simultaneous auscultation or palpation at the posterior tibial artery. Measurement of lower extremity BPs constitutes the basis of the ankle-brachial index (ABI) (**see Chapter 64**).

Consideration should be given to ambulatory BP monitoring when uncertainty exists about the significance of recordings obtained in the clinic. This approach is especially useful for the patient with suspected "white coat hypertension"[12] (**see Chapters 46 and 47**). Measurement of normal or even low BP with evidence of hypertensive end-organ damage should suggest masked hypertension caused by severe PAD. Masked hypertension occurs more often than clinicians appreciate and may present in the absence of severe PAD.[13]

Orthostatic hypotension (a fall in blood pressure of more than 20 mm Hg systolic and/or more than 10 mm Hg diastolic in response to moving from the supine to the standing position within 3 minutes) may be accompanied by a lack of compensatory tachycardia, a response suggestive of autonomic insufficiency, as can occur in patients with diabetes or Parkinson disease. The heart rate–blood pressure response to standing also depends on age, hydration, medications, food, conditioning, and ambient temperature and humidity.

An increase in pulse pressure can represent increased vascular stiffness, usually secondary to aging or atherosclerosis. Aortic stiffness is increased in patients with Marfan syndrome and other connective tissue disorders and may contribute to risk for dissection. Peripheral indices may not correlate well with central aortic stiffness, which is a primary determinant of ventricular-vascular coupling.

Assessing the Pulses

The carotid artery pulse wave occurs within 40 milliseconds of the ascending aortic pulse and reflects aortic valve and ascending aortic function. The temporal arteries can be easily palpated to aid in the diagnosis of temporal arteritis. One of the two pedal pulses may not be palpable in a normal person because of unusual anatomy (posterior tibial, <5%; dorsal pedis, <10%), but each pair should be symmetric. True congenital absence of a pulse is rare, and in most cases, pulses can be detected with a handheld Doppler device when not palpable. Simultaneous palpation of the brachial or radial pulse with the femoral pulse should be performed in patients with hypertension to screen for aortic coarctation.

The contour of the pulses depends on the stroke volume, ejection velocity, vascular capacity and compliance, and systemic resistance. The palpable pulse reflects the merging of the antegrade pulsatile flow of blood and the propagated pulse returning from the periphery. The amplitude of the arterial pulse increases with distance from the heart. Normally, the incident (percussion) wave begins with systolic ejection (just after S_1) and is the predominant monophasic pulse appreciated at the bedside (**Fig. 10.5**). The incisura or dicrotic notch identifies aortic valve closure. A *bounding* pulse may occur in hyperkinetic states, such as fever, anemia, and thyrotoxicosis, or in pathologic states such as severe bradycardia, AR, or arteriovenous fistula. A *bifid* pulse is created by two distinct pressure peaks. This phenomenon may occur with fever or after exercise in a normal person and is consistent with increased vascular compliance. With chronic severe AR, a large stroke volume ejected rapidly into a noncompliant arterial tree produces a reflected wave of sufficient amplitude to be palpated during systole, rendering the pulse bifid. Hypertrophic obstructive cardiomyopathy (HOCM) can rarely produce a bifid systolic pulse with percussion and tidal waves (**Fig. 10.5**). Diastolic augmentation of pressure with an intra-aortic balloon pump also results in a bifid pulse, although with the two components separated by aortic valve closure.

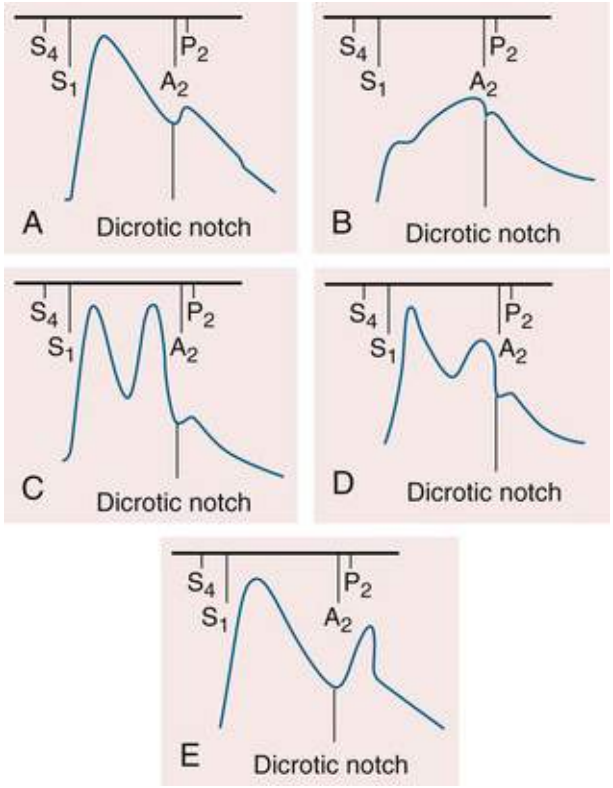


FIGURE 10.5 Carotid pulse waveforms and heart sounds. **A,** Normal. **B,** Aortic stenosis. Anacrotic pulse with slow upstroke and peak near S_2. **C,** Severe AR: bifid pulse with two systolic peaks. **D,** Hypertrophic obstructive cardiomyopathy (HOCM): bifid pulse with two systolic peaks. The second peak (tidal or reflected wave) is of lower amplitude than the initial percussion wave. **E,** Bifid pulse with systolic and diastolic peaks as may occur with sepsis or intra-aortic balloon counterpulsation. A_2, Aortic component of S_2; P_2, pulmonic component of S_2. (From Chatterjee K. Bedside evaluation of the heart: the physical examination. In Chatterjee K, Parmley W, editors. Cardiology: an Illustrated Text/Reference. Philadelphia: Lippincott; 1991, pp 3.11-3.51; and Braunwald E. The clinical examination. In Braunwald E, Goldman L, editors. Primary Cardiology. 2nd ed. Philadelphia: Saunders; 2003, p 36.)

Pulsus paradoxus, a fall in systolic pressure of more than 10 mm Hg with inspiration, is considered pathologic and a sign of pericardial tamponade or pulmonary disease. This phenomenon also can occur in obesity and pregnancy without clinical disease. Pulsus paradoxus is detected by noting the difference between the systolic BP at which the Korotkoff sounds are first heard (during expiration) and the systolic BP at which the Korotkoff sounds are heard with each beat, independent of respiratory phase. Between these two pressures, the sounds will be heard only intermittently (during expiration). Appreciation of this finding requires a slow decrease of the cuff pressure. Conditions such as tachycardia, AF, and tachypnea make its assessment difficult. Pulsus paradoxus may be palpable when the BP difference exceeds 15 to 20 mm Hg (**see Chapter 83**). Pulsus paradoxus is not specific for pericardial tamponade and can accompany massive pulmonary embolus, hemorrhagic shock, severe obstructive lung disease, or tension pneumothorax.

Pulsus alternans is defined by the beat-to-beat variability of the pulse amplitude (**Fig. 10.6**). It is present when only every other phase 1 Korotkoff sound is audible as the cuff pressure is slowly lowered, in a patient with a regular heart rhythm, independent of the respiratory cycle. Pulsus alternans generally occurs in severe heart failure, in severe AR, hypertension, and hypovolemic states. It is attributed to cyclic changes in intracellular calcium and action potential duration. Association with electrocardiographic T wave alternans appears to increase arrhythmic risk.

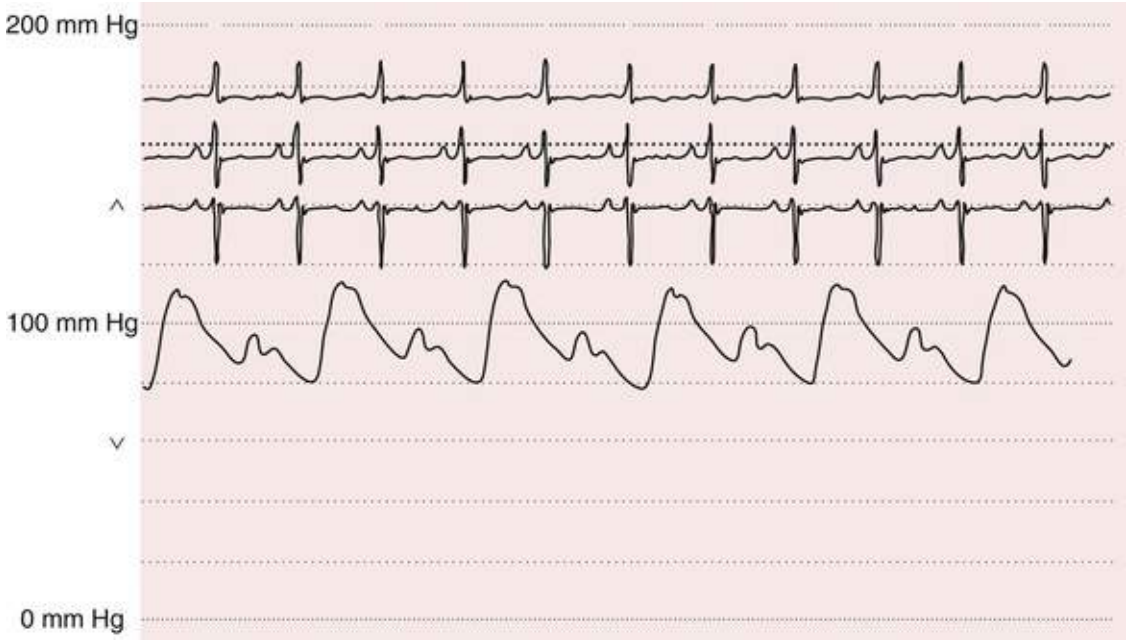


FIGURE 10.6 Pulsus alternans in a patient with severe left ventricular systolic dysfunction. The systolic pressure varies from beat to beat, independent of the respiratory cycle. The rhythm is sinus throughout.

Severe aortic stenosis may be suggested by a weak and delayed pulse *(pulsus parvus et tardus)*, and is best appreciated by careful palpation of the carotid arteries (**see Fig. 10.5** and **Chapter 68**). The delay is assessed during simultaneous auscultation of the heart sounds; the carotid upstroke should coincide with S_1. This finding is less specific in older, hypertensive patients with reduced vascular compliance and stiffer carotid arteries. An abrupt carotid upstroke with rapid falloff characterizes the pulse of chronic AR (Corrigan or water-hammer pulse). The carotid upstroke also is rapid in older patients with isolated systolic hypertension and wide pulse pressures.

Pulsation of the abdominal aorta can be appreciated in the epigastric area. Femoral and popliteal artery aneurysms should be sought in patients with AAA disease or underlying connective tissue disease.

The history and physical examination findings can help assess the level of arterial obstruction in patients with lower extremity claudication (**see Chapter 64**). Auscultation for aortic and femoral artery bruits should be routine. The correlation between the presence of a bruit and the degree of vascular obstruction is weak. Extension of a bruit into diastole or a thrill generally indicates severe obstruction. Other causes of a bruit include arteriovenous fistulas and enhanced flow through normal arteries, as in a young patient with fever.

Integrating the clinical history and presence of atherosclerotic risk factors improves the accuracy of the examination for the identification of lower extremity PAD. In an asymptomatic patient the presence of a femoral bruit (LR, 4.8; 95% CI, 2.4 to 9.5) or any abnormality of the pulse (LR, 3.1; 95% CI, 3.1 to 6.6) increases the likelihood of PAD. The likelihood of significant PAD increases when there are lower extremity symptoms and cool skin (LR, 5.9; 95% CI, 4.1 to 8.6), pulse abnormalities (LR, 4.7; 95% CI, 2.2 to 9.9), or any bruit (LR, 5.6; 95% CI, 4.7 to 6.7). Abnormal pulse oximetry, defined by a more than 2% difference between finger and toe oxygen saturation, can also indicate lower extremity PAD and is comparable to the ABI (LR, 30.0; 95% CI, 7.6 to 121 versus LR, 24.8; 95% CI, 6.2 to 99.8).

Inspection and Palpation of the Heart

The apical heartbeat may be visible in thin-chested adults. The left anterior chest wall may heave in patients with enlarged and hyperdynamic left ventricles. Right upper parasternal and sternoclavicular

pulsations suggest ascending AAA disease. A left parasternal lift indicates RV pressure or volume overload. A pulsation in the third intercostal space to the left of the sternum can indicate PA hypertension. In very thin, tall patients, or in patients with emphysema and flattened diaphragm, the RV impulse may be visible in the epigastrium and should be distinguished from a pulsatile liver edge.

Palpation of the heart should begin with the patient in the supine position inclined at 30 degrees. If the heart is not palpable in this position, the patient should be examined either in the left lateral decubitus position with the left arm above the head or in the seated position, leaning forward. The point of maximal impulse normally is over the left ventricular (LV) apex beat and should be located in the midclavicular line at the fifth intercostal space. It is smaller than 2 cm (0.8 inch) in diameter and moves quickly away from the fingers. It is best appreciated at end-expiration, when the heart is closest to the chest wall. The normal impulse may not be palpable in obese or muscular patients or in those with thoracic cage deformities. LV cavity enlargement displaces the apex beat leftward and downward. A sustained apex beat is a sign of LV pressure overload (as in aortic stenosis or hypertension). A palpable, presystolic impulse corresponds to a fourth heart sound (S_4) and reflects the atrial contribution to ventricular diastolic filling of a noncompliant left ventricle. A prominent, rapid early filling wave in patients with advanced systolic heart failure may result in a palpable third sound (S_3), which may be present when the gallop itself is not audible (Video 10.3). A large ventricular aneurysm may yield a palpable and visible ectopic impulse discrete from the apex beat. HOCM rarely may cause a triple-cadence apex beat, with contributions from a palpable S_4 and the two components of the systolic pulse.

A *parasternal lift* occurs with RV pressure or volume overload. Signs of TR (jugular venous *cv* waves) and PA hypertension (loud, single, or palpable P_2) should be sought. An enlarged right ventricle can give rise to a *precordial lift* that can extend across the precordium and obscure left-sided findings. Rarely, patients with severe MR will have a prominent left parasternal impulse because of systolic expansion of the left atrium and forward displacement of the heart. Lateral retraction of the chest wall may be present with isolated RV enlargement secondary to posterior displacement of the systolic LV impulse. Systolic and diastolic thrills signify turbulent, high-velocity blood flow. Their locations help to identify the origins of heart murmurs.

Auscultation of the Heart

Heart Sounds

First Heart Sound (S_1)

The normal S_1 comprises mitral (M_1) and tricuspid (T_1) valve closure. The two components usually are best heard at the lower left sternal border in younger individuals. Normal splitting of S_1 is accentuated with complete right bundle branch block (RBBB). S_1 intensity increases in the early stages of rheumatic mitral stenosis when the valve leaflets are still pliable, in hyperkinetic states, and with short P-R intervals (<160 msec). S_1 becomes softer in the late stages of stenosis, when the leaflets are rigid and calcified, with contractile dysfunction, beta-adrenergic receptor blockers, and long P-R intervals (>200 msec). Other factors that can decrease the intensity of the heart sounds and murmurs include mechanical ventilation, obstructive lung disease, obesity, pendulous breasts, pneumothorax, and pericardial effusion.

Second Heart Sound (S_2)

S_2 comprises aortic (A_2) and pulmonic (P_2) valve closure. With normal, or *physiologic*, splitting, the A_2-P_2 interval increases during inspiration and narrows with expiration. The individual components are best heard at the second left interspace with the patient in the supine position. The A_2-P_2 interval widens with complete RBBB because of delayed pulmonic valve closure, and with severe MR because of premature aortic valve closure. Unusually narrow but physiologic splitting of S_2, with an increase in the intensity of P_2 relative to A_2, indicates PA hypertension. With *fixed* splitting the A_2-P_2 interval is wide and remains unchanged during the respiratory cycle, indicating ostium secundum ASD. Reverse, or *paradoxical*, splitting occurs as a consequence of a pathologic delay in aortic valve closure, as may occur with complete left bundle branch block, RV apical pacing, severe aortic stenosis, HOCM, and myocardial ischemia. A_2 normally is louder than P_2 and can be heard at most sites across the precordium. When both components can be heard at the lower left sternal border or apex, or when P_2 can be palpated at the second left interspace, PA hypertension is present. The intensity of A_2 and P_2 decreases with aortic and pulmonic stenosis, respectively. A single S_2 may result.

Systolic Sounds

An *ejection sound* is a high-pitched, early systolic sound that coincides in timing with the upstroke of the carotid pulse and usually is associated with congenital bicuspid aortic or pulmonic valve disease, or sometimes with aortic or pulmonic root dilation and normal semilunar valves. The ejection sound accompanying pulmonic valve disease decreases in intensity with inspiration, the only right-sided cardiac event to behave in this manner. Ejection sounds disappear as the culprit valve loses its pliability over time. They often are better heard at the lower left sternal border than at the base of the heart. *Nonejection clicks*, which occur after the upstroke of the carotid pulse, are related to MVP. A systolic murmur may or may not follow. With standing, ventricular preload and afterload decrease, and the click (and murmur) move closer to S_1. With squatting, ventricular preload and afterload increase, the prolapsing mitral valve tenses later in systole, and the click (and murmur) move away from S_1 (**Fig. 10.7**).

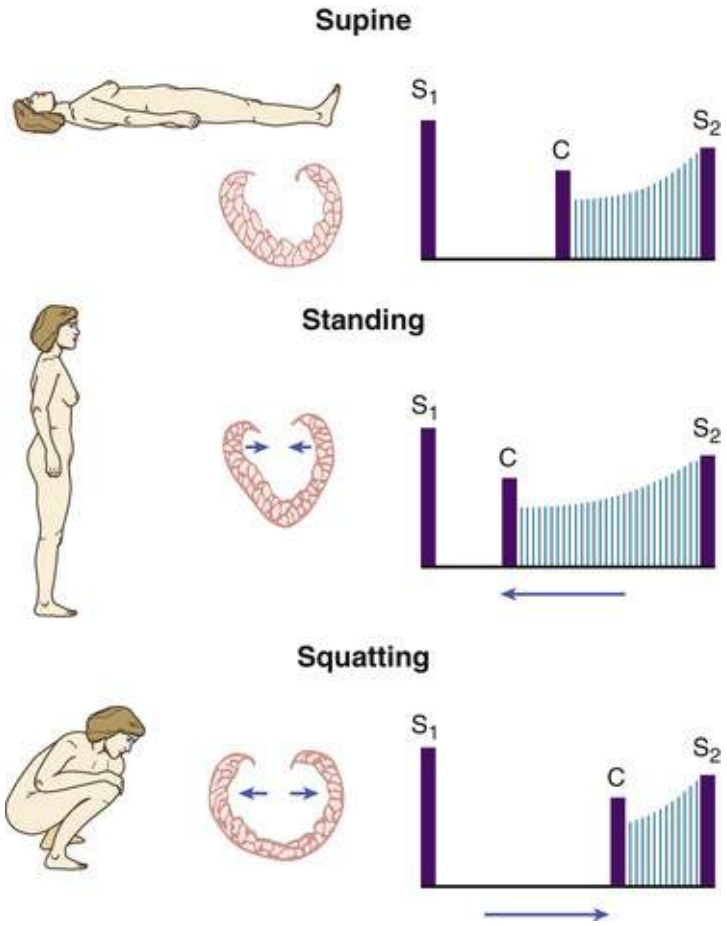


FIGURE 10.7 Behavior of the nonejection click (*C*) and systolic murmur of mitral valve prolapse. With standing, venous return decreases, the heart becomes smaller, and prolapse occurs earlier in systole. The click and murmur move closer to S_1. With squatting, venous return increases, causing an increase in left ventricular chamber size. The click and murmur occur later in systole and move away from S_1. (From Shaver JA, Leonard JJ, Leon DF. Examination of the Heart. Part IV. Auscultation of the heart. Dallas: American Heart Association; 1990, p 13. Copyright 1990, American Heart Association.)

Diastolic Sounds

The high-pitched *opening snap* (OS) of mitral stenosis occurs a short distance after S_2; the A_2-OS interval is inversely proportional to the height of the left atrial (LA)–LV diastolic pressure gradient. The intensity of both S_1 and OS decreases with progressive calcification and rigidity of the anterior mitral leaflet. A *pericardial knock* (PK) is a high-pitched early diastolic sound that corresponds in timing to the abrupt cessation of ventricular expansion after atrioventricular valve opening and to the prominent *y* descent seen in the jugular venous waveform in patients with constrictive pericarditis. A tumor "plop" rarely is heard with atrial myxoma; it is a low-pitched sound sometimes only heard in certain positions that arises from the diastolic prolapse of the tumor across the mitral valve. A diastolic murmur may be present, although most myxomas cause no sound.

A third heart sound (S_3) occurs during the rapid filling phase of ventricular diastole. An S_3 may be normally present in children, adolescents, and young adults but indicates systolic heart failure in older adults and carries important prognostic weight. A left-sided S_3 is a low-pitched sound best heard over the LV apex with the patient in the left lateral decubitus position, whereas a right-sided S_3 is usually heard at the lower left sternal border or in the subxiphoid position with the patient supine and may become louder with inspiration. A fourth heart sound (S_4) occurs during the atrial filling phase of ventricular diastole and is thought to indicate presystolic ventricular expansion. An S_4 is especially common in patients with

accentuated atrial contribution to ventricular filling (e.g., LV hypertrophy).

Cardiac Murmurs

Heart murmurs result from audible vibrations caused by increased turbulence and are defined by their timing within the cardiac cycle (**Table 10.6** and **Fig. 10.8**). Not all murmurs indicate valvular or structural heart disease. The accurate identification of a functional (benign) systolic murmur can obviate the need for echocardiography in many healthy individuals. The magnitude, dynamic change, and duration of the pressure difference between two cardiac chambers, or between the ventricles and their respective great arteries, dictate the duration, frequency, configuration, and intensity of murmurs. Intensity is graded on a scale of 1 to 6; a *palpable thrill* characterizes murmurs of grade 4 or higher intensity. Other important attributes that aid in identification include location, radiation, and response to bedside maneuvers, including quiet respiration.

TABLE 10.6

Principal Causes of Heart Murmurs

Systolic Murmurs
Early Systolic
Mitral—acute mitral regurgitation (MR)
Ventricular septal defect (VSD)
Muscular
Nonrestrictive with pulmonary hypertension
Tricuspid—tricuspid regurgitation (TR) with normal pulmonary artery pressure
Midsystolic
Aortic
Obstructive
Supravalvular—supravalvular aortic stenosis, coarctation of the aorta
Valvular—aortic stenosis and sclerosis
Subvalvular—discrete, tunnel, or HOCM
Increased flow, hyperkinetic states, aortic regurgitation (AR), complete heart block
Dilation of ascending aorta, atheroma, aortitis
Pulmonary
Obstructive
Supravalvular—pulmonary artery stenosis
Valvular—pulmonic valve stenosis
Subvalvular—infundibular stenosis (dynamic)
Increased flow, hyperkinetic states, left-to-right shunt (e.g., ASD)
Dilation of pulmonary artery
Late Systolic
Mitral—mitral valve prolapse (MVP), acute myocardial ischemia
Tricuspid—tricuspid valve prolapse
Holosystolic
Atrioventricular valve regurgitation (MR, TR)
Left-to-right shunt at ventricular level (VSD)
Diastolic Murmurs
Early Diastolic
Aortic regurgitation
Valvular—congenital (bicuspid valve), rheumatic deformity, endocarditis, prolapse, trauma, postvalvulotomy
Dilation of valve annulus—aortic dissection, annuloaortic ectasia, cystic medial degeneration, hypertension, ankylosing spondylitis
Widening of commissures—syphilis
Pulmonic regurgitation
Valvular—postvalvulotomy, endocarditis, rheumatic fever, carcinoid
Dilation of valve annulus—pulmonary hypertension; Marfan syndrome
Congenital—isolated or associated with tetralogy of Fallot, VSD, pulmonic stenosis
Mid-Diastolic
Mitral
Mitral stenosis
Carey Coombs murmur (mid-diastolic apical murmur in acute rheumatic fever)
Increased flow across nonstenotic mitral valve (e.g., MR, VSD, PDA, high-output states, complete heart block)
Tricuspid
Tricuspid stenosis
Increased flow across nonstenotic tricuspid valve (e.g., TR, ASD, anomalous pulmonary venous return)
Left and right atrial tumors (myxoma)
Severe or eccentric AR (Austin Flint murmur)
Late Diastolic
Presystolic accentuation of mitral stenosis murmur
Austin Flint murmur of severe or eccentric AR
Continuous Murmurs
Patent ductus arteriosus (PDA)
Coronary arteriovenous fistula
Ruptured sinus of Valsalva aneurysm
Atrial septal defect (ASD)
Cervical venous hum
Anomalous left coronary artery
Proximal coronary artery stenosis
Mammary souffle of pregnancy
Pulmonary artery branch stenosis
Bronchial collateral circulation
Small (restrictive) ASD with mitral stenosis
Intercostal arteriovenous fistula

From Braunwald E, Perloff JK. Physical examination of the heart and circulation. In Zipes DP, Libby P, Bonow RO, Braunwald E, editors. Braunwald's Heart Disease: a Textbook of Cardiovascular Medicine. 7th ed. Philadelphia: Saunders; 2005, pp 77-106; and Norton PJ, O'Rourke RA. Approach to the patient with a heart murmur. In Braunwald E, Goldman L, editors. Primary Cardiology. 2nd ed. Philadelphia: Elsevier; 2003, pp 151-68.

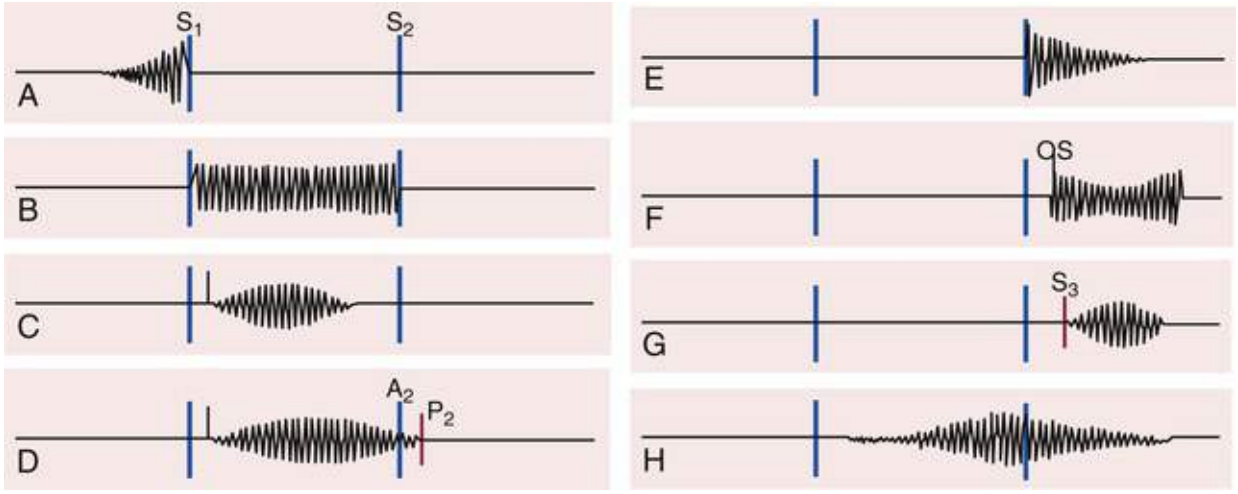


FIGURE 10.8 Diagram of principal heart murmurs. **A,** Presystolic accentuation of the murmur of mitral stenosis with sinus rhythm. **B,** Holosystolic murmur of chronic, severe mitral (MR) or tricuspid (TR) regurgitation, or ventricular septal defect without severe pulmonary hypertension. **C,** Ejection sound and crescendo-decrescendo murmur of bicuspid aortic stenosis. **D,** Ejection sound and crescendo-decrescendo murmur that extends to P_2 in bicuspid pulmonic stenosis; A_2, aortic component of S_2; P_2, pulmonic component of S_2. **E,** Early decrescendo diastolic murmur of aortic or pulmonic regurgitation. **F,** Opening snap (*OS*) and mid-diastolic rumble of mitral stenosis. **G,** Diastolic filling sound (S_3) and mid-diastolic murmur associated with severe MR, TR, or atrial septal defect with significant left-to-right shunt. **H,** Continuous murmur of patent ductus arteriosus that envelops S_2. (Modified from Wood P. Diseases of the Heart and Circulation. Philadelphia: Lippincott; 1968; and O'Rourke RA, Braunwald E. Physical examination of the cardiovascular system. In Kasper D, Braunwald E, Fauci A, et al, editors. Harrison's Principles of Internal Medicine. 16th ed. New York: McGraw-Hill; 2005, p 1309.)

Systolic Murmurs

Systolic murmurs are early, midsystolic, late, or holosystolic in timing. Acute severe MR results in a decrescendo, early systolic murmur because of the steep rise in pressure within the noncompliant left atrium (**Fig. 10.9**). Severe MR associated with posterior mitral leaflet prolapse or flail radiates anteriorly and to the base; MR caused by anterior leaflet involvement radiates posteriorly and to the axilla. With acute TR in patients with normal PA pressures, an *early* systolic murmur, which increases in intensity with inspiration, may be audible at the lower left sternal border, and regurgitant *cv* waves may be visible in the jugular venous pulse.

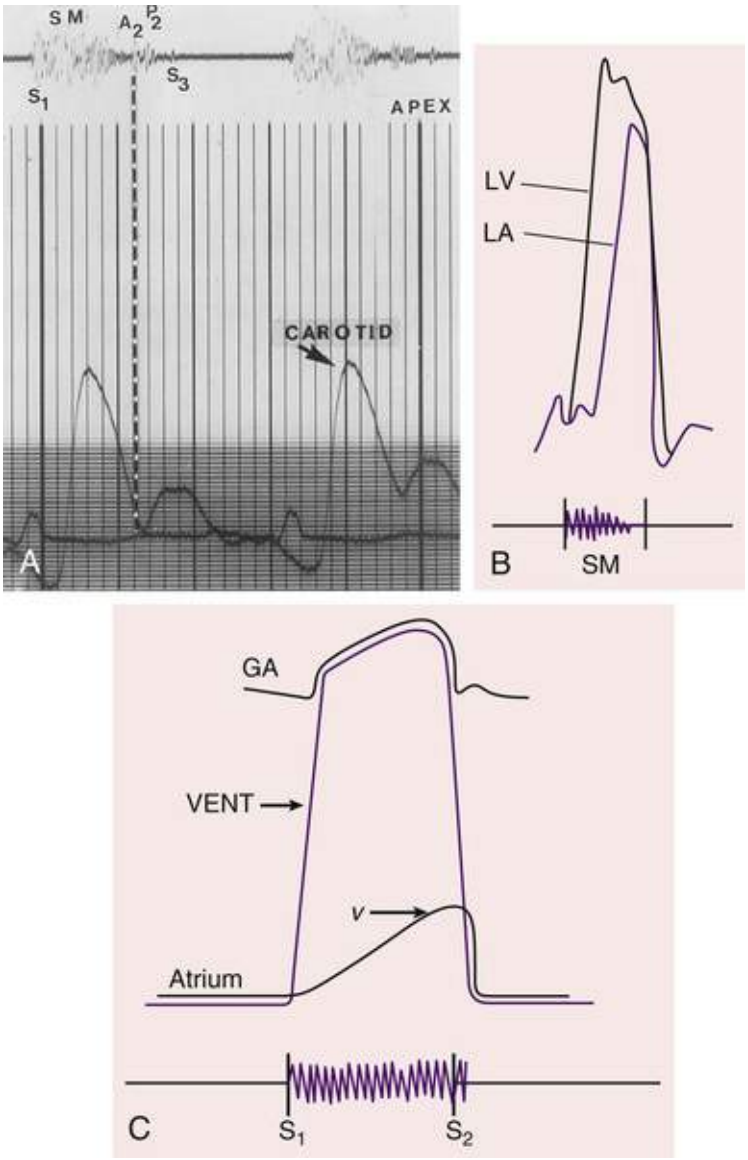


FIGURE 10.9 **A,** Phonocardiogram (*top*) obtained in a patient with acute severe mitral regurgitation (MR) showing a decrescendo early systolic murmur (*SM*) and diastolic filling sound (S_3). **B,** Left ventricular (LV) and left atrial (LA) pressure waveforms demonstrating the abrupt rise in LA pressure and attenuation of the LV-LA pressure gradient, resulting in the duration and configuration of the SM. **C,** Illustration of great artery (*GA*) and ventricular (*VENT*) and atrial pressures with corresponding phonocardiogram in chronic MR or TR. Note the holosystolic timing and plateau configuration of the murmur, both of which derive from the large ventricular-atrial pressure gradient throughout systole; *v, v* wave. (From Braunwald E, Perloff JK. Physical examination of the heart and circulation. In Zipes D, Libby P, Bonow RO, Braunwald E, editors. Braunwald's Heart Disease: a Textbook of Cardiovascular Medicine. 7th ed. Philadelphia: Saunders; 2005, p 97.)

Midsystolic murmurs begin after S_1 and end before S_2; they usually are crescendo-decrescendo in configuration. Aortic stenosis or sclerosis causes most midsystolic murmurs in adults. Accurate characterization of the severity of aortic stenosis at the bedside depends on cardiac output, stiffness of the carotid arteries, and associated findings. Other causes of a midsystolic heart murmur include HOCM, pulmonic stenosis, and increased pulmonary blood flow in patients with a large ASD and a left-to-right shunt. An isolated grade 1 or 2 midsystolic murmur in the absence of symptoms or other signs of heart disease is a benign finding that does not warrant further evaluation, including echocardiography.

A *late,* apical systolic murmur usually indicates MVP; one or more nonejection clicks may be present. A similar murmur may be heard transiently during an episode of acute myocardial ischemia. In this setting the MR is caused by apical tethering and mal-coaptation of the leaflets in response to structural and functional changes of the ventricle and mitral annulus. The intensity of the murmur will vary with LV afterload.

Holosystolic murmurs, which are plateau in configuration, derive from the continuous and wide pressure gradient between two cardiac chambers—the left ventricle and left atrium with chronic MR, the right ventricle and right atrium with chronic TR, and the left ventricle and right ventricle with membranous ventricular septal defect (VSD) without PA hypertension. MR is best heard over the cardiac apex, TR at the lower left sternal border, and a VSD murmur at the mid-left sternal border, where a thrill is palpable in most patients. TR most frequently is secondary to annular dilation from RV enlargement with papillary muscle displacement and failure of tricuspid leaflet coaptation. PA hypertension also may be present.

Diastolic Murmurs

Diastolic murmurs invariably signify cardiac disease. Chronic AR causes a high-pitched, decrescendo, early to mid-diastolic murmur. With primary aortic valve disease, the murmur is best heard along the left sternal border, whereas with root enlargement and secondary AR, the murmur may radiate along the right sternal border. A midsystolic murmur caused by augmented and accelerated blood flow is also present with moderate to severe AR and need not signify valve or outflow tract obstruction. The diastolic murmur is both softer and of shorter duration in acute AR, as a result of the rapid rise in LV diastolic pressure and the diminution of the aortic-LV diastolic pressure gradient. Additional features of acute AR include tachycardia, a soft S_1, and the absence of peripheral findings of significant diastolic runoff.

The murmur of pulmonic regurgitation (PR) is heard along the left sternal border and most often is caused by annular enlargement from chronic PA hypertension (*Graham Steell murmur*). Signs of RV pressure overload are present. PR also can occur with a congenitally deformed valve and is invariably present after repair of tetralogy of Fallot. In these settings the murmur is relatively softer and lower pitched. The severity of PR after surgical repair can be underappreciated.

Mitral stenosis is the classic cause of a mid- to late diastolic murmur (**see Fig. 10.8A, F**). The stenosis also may be "silent," as in patients with low cardiac output or large body habitus. The murmur is best heard over the apex with the patient in the left lateral decubitus position, is low pitched (rumbling), and is introduced by an OS in the early stages of the disease. Presystolic accentuation (an increase in the intensity of the murmur in late diastole following atrial contraction) occurs in patients in sinus rhythm. Left-sided events usually obscure findings in patients with rheumatic tricuspid stenosis. Functional mitral stenosis or tricuspid stenosis refers to mid-diastolic murmurs created by increased, accelerated transvalvular flow, without valvular obstruction, in the setting of severe MR or TR, respectively, or ASD with a large left-to-right shunt.

The low-pitched mid- to late apical diastolic murmur sometimes associated with AR (*Austin Flint murmur*) can be distinguished from mitral stenosis on the basis of its response to vasodilators and the presence of associated findings. Less common causes of a mid-diastolic murmur include atrial myxoma, complete heart block, and acute rheumatic mitral valvulitis (*Carey Coombs murmur*).

Continuous Murmurs

The presence of a continuous murmur implies a pressure gradient between two chambers or vessels during both systole and diastole. These murmurs begin in systole, peak near S_2, and continue into diastole. They can be difficult to distinguish from systolic and diastolic murmurs in patients with mixed aortic or pulmonic valve disease. Examples are the murmurs associated with PDA, ruptured sinus of Valsalva aneurysm, and coronary, great vessel, or hemodialysis-related arteriovenous fistulas. The cervical venous hum and mammary souffle of pregnancy are two benign variants.

Dynamic Auscultation

Simple bedside maneuvers can help identify heart murmurs and characterize their significance (**Table 10.7**). Right-sided events, except for the pulmonic ejection sound, increase with inspiration and decrease with expiration; left-sided events behave oppositely (100% sensitivity, 88% specificity). The intensity of the murmurs associated with MR, VSD, and AR will increase in response to maneuvers that increase LV afterload (e.g., handgrip, vasopressor administration) and decrease after exposure to vasodilating agents (e.g., amyl nitrite). The response of the murmur associated with MVP to standing and squatting has previously been described. The murmur of HOCM behaves in a directionally similar manner, becoming softer and shorter with squatting (95% sensitivity, 85% specificity) and longer and louder on rapid standing (95% sensitivity, 84% specificity). The intensity of the murmur of HOCM also increases with the Valsalva maneuver (65% sensitivity, 95% specificity). A change in the intensity of a systolic murmur in the first beat after a premature beat, or in the beat after a long cycle length in patients with AF, suggests aortic stenosis rather than MR, particularly in an older patient, in whom the murmur of aortic stenosis is well transmitted to the apex (*Gallavardin effect*). Systolic murmurs caused by LV outflow obstruction, including those caused by aortic stenosis, will increase in intensity in the beat following a premature beat because of the combined effects of enhanced LV filling and postextrasystolic potentiation of contractile function. Forward flow accelerates, causing an increase in the gradient and a louder murmur. The intensity of the murmur of MR does not change in the post–premature beat, because relatively minimal further increase occurs in mitral valve flow or change in the LV-LA gradient.

TABLE 10.7

Interventions for Altering Intensity of Cardiac Murmurs

Respiration: Right-sided murmurs generally increase with inspiration. Left-sided murmurs usually are louder during expiration.
Valsalva maneuver: Most murmurs decrease in length and intensity. Two exceptions are the systolic murmur of HOCM, which usually becomes much louder, and that of MVP, which becomes longer and often louder. After release of the Valsalva maneuver, right-sided murmurs tend to return to baseline intensity earlier than left-sided murmurs.
Exercise: Murmurs caused by blood flow across normal or obstructed valves (as in pulmonic and mitral stenosis) become louder with both isotonic and isometric (handgrip) exercise. Murmurs of MR, VSD, and AR also increase with handgrip exercise.
Positional changes: With standing, most murmurs diminish; two exceptions are the murmur of HOCM, which becomes louder, and that of MVP, which lengthens and often is intensified. With squatting, most murmurs become louder, but those of HOCM and MVP usually soften and may disappear. Passive leg raising usually produces the same results as squatting.
Post–ventricular premature beat or atrial fibrillation: Murmurs originating at normal or stenotic semilunar valves increase in intensity during the cardiac cycle after a ventricular premature beat or in the beat after a long cycle length in AF. By contrast, systolic murmurs caused by atrioventricular valve regurgitation do not change, diminish (papillary muscle dysfunction), or become shorter after a premature beat (MVP).
Pharmacologic interventions: During the initial relative hypotension after amyl nitrite inhalation, murmurs of MR, VSD, and AR decrease in intensity, whereas the murmur of AS increases in intensity because of increased stroke volume. During the later tachycardia phase, murmurs of mitral stenosis and right-sided lesions also become louder. This intervention may help distinguish the murmur of the Austin Flint phenomenon from that of mitral stenosis. The response in MVP often is biphasic (softer and then louder than control).
Transient arterial occlusion: Transient external compression of both brachial arteries by bilateral cuff inflation to 20 mm Hg greater than peak systolic pressure augments the murmurs of MR, VSD, and AR, but not murmurs from other causes.

From Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease). Developed in collaboration with the Society of Cardiovascular Anesthesiologists. Endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol 2006;48:e18.

Integrated, Evidence-Based Approach to Specific Cardiac Disorders

Heart Failure (see also Part IV)

History

Both exertional and resting symptoms should be investigated. Common signs and symptoms include dyspnea, fatigue, exercise limitation, orthopnea, and edema. In a review of 22 studies of adult patients presenting to an ED with dyspnea, the probability of heart failure (HF) was best predicted by a past history of HF (LR, 5.8; 95% CI, 4.1 to 8.0), paroxysmal nocturnal dyspnea (LR, 2.6; 95% CI, 1.5 to 4.5), a third heart sound (LR, 11; 95% CI, 4.9 to 25), or AF (LR, 3.8; 95% CI, 1.7 to 8.8).[14] An initial clinical impression of HF as noted by a physician was one of the stronger clinical predictors of this diagnosis (LR, 4.4; 95% CI, 1.8 to 10.0). With the exception of paroxysmal nocturnal dyspnea, these same features also predicted HF when there was concomitant pulmonary disease. The addition of testing for N-terminal pro–B-type natriuretic peptide (NT-proBNP) increases diagnostic accuracy only modestly (C-statistic, 0.83 versus 0.86).[7]

Severe and sudden-onset dyspnea indicates acute pulmonary edema, typically precipitated by ischemia, arrhythmia, sudden left-sided valvular regurgitation, and accelerated hypertension. It is important to exclude other causes, such as pulmonary embolism and pneumothorax. The extent of limitation also should be defined because functional capacity, as assessed by NYHA classification, strongly and independently predicts the risk of death for HF patients. Self-reported functional capacity and objectively measured cardiovascular performance can differ substantially. Symptoms that occur at rest may have greater predictive value for the diagnosis of HF than exertional symptoms. Orthopnea is not specific for HF and can occur in patients with asthma, ascites, or gastroesophageal reflux. *Trepopnea*, which is dyspnea or discomfort experienced in the lateral decubitus position, also may be present. Patients with HF prefer sleeping on their right side, and trepopnea probably accounts for the predominance of right-sided pleural effusions in this population. Shortness of breath may be particularly noticeable when bending forward, termed *bendopnea*. It is associated with higher supine right atrial and pulmonary capillary wedge pressures and is mediated by further elevations in these pressures with bending over. It is even more likely present when the resting cardiac index is low.[15] Paroxysmal nocturnal dyspnea also is common in HF patients. Cheyne-Stokes respirations may be apparent when the patient is awake.[16] The prevalence of central sleep apnea or Cheyne-Stokes respirations ranges from 20% to 62% in various HF studies,[10] and either of these disorders is associated with an increased mortality risk.

Clinically evident edema or weight gain over days indicates volume excess but lags behind the clinical redistribution of intravascular volume from the splanchnic beds to the central veins. In patients with advanced right-sided heart failure, uncomfortable hepatomegaly and ascites may predominate. Patients with chronic HF often lack pulmonary rales or lower extremity edema. Gastrointestinal symptoms such as early satiety, nausea, vomiting, and belching are also common and are related to decreases in GI blood flow and bowel edema, particularly in those with cardiac cachexia.[17]

Few studies have explored the predictive values of various signs and symptoms of HF. In a systematic review, orthopnea only modestly predicted increased filling pressures.[18] Dyspnea and edema were similarly useful but were most predictive when combined with physical examination findings (S_3, tachycardia, elevated JVP, low pulse pressure, rales, abdominojugular reflux sign). When combined with other findings, a total of three or more symptoms or signs predicted a greater than 90% likelihood of increased filling pressures if severe LV dysfunction was not known. By contrast, if one or no findings or symptoms were present, the likelihood of increased filling pressures was less than 10%. The commonly used Framingham criteria for HF diagnosis in patients with reduced ejection fraction (EF) have only modest specificity (63%) and sensitivity (63%). The distinction between HF with reduced EF and HF with preserved EF can be made at the bedside with modest accuracy. Systolic function is more likely to be preserved when patients are female or older and have an increased BMI, but such findings lack adequate specificity or sensitivity to guide therapy. Furthermore, diastolic dysfunction does not exclude

systolic dysfunction.

Physical Examination

In most patients with HF who require hospitalization, the reason for admission is volume overload; failure to relieve it has negative prognostic impact. Four signs are commonly used to predict elevated filling pressures: jugular venous distention/abdominojugular reflux sign, presence of an S_3 and/or S_4, rales, and pedal edema. In general, the use of a combination of findings, rather than reliance on isolated clinical findings, improves diagnostic accuracy. Some clinicians advocate assessment of the HF patient along two basic axes—volume status ("dry" or "wet") and perfusion status ("warm" or "cold")—as a useful guide to therapy (**see Fig. 21.3**). This approach has prognostic usefulness, particularly in assessing patients at discharge after admission for HF. For example, such patients discharged with a "wet" or "cold" profile experience worse outcomes (hazard ratio [HR], 1.5; 95% CI, 1.1 to 12.1; $P = 0.017$) compared with those discharged "warm and dry" (HR, 0.9; 95% CI, 0.7 to 2.1; $P = 0.5$).[18] Advanced training may be required to achieve this level of diagnostic precision with the physical examination.

Jugular Venous Pressure

The JVP provides the readiest bedside estimate of LV filling pressure. In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, 82% of patients whose estimated right atrial (RA) pressure was higher than 8 mm Hg (10.5 cm H_2O) had a measured RA pressure higher than 8 mm Hg. The same investigators also identified 9 of the 11 patients with RA pressures lower than 8 mm Hg.[18] Although the JVP estimates RV filling pressure, it has a predictable relationship with PA wedge pressure. Drazner and colleagues[18] found that the RA pressure reliably predicted the PA wedge pressure; the positive predictive value of RA pressure higher than 10 mm Hg for PA wedge pressure higher than 22 mm Hg was 88%. In addition, the PA systolic pressure could be estimated as twice the wedge pressure. In the ESCAPE trial, an estimated RA pressure higher than 12 mm Hg and two-pillow orthopnea were the only bedside parameters that provided incremental value to the prediction of a PA wedge pressure higher than 22 mm Hg, and compared favorably with BNP levels.[18] Echocardiography and BNP determinations may not always provide incremental value to the clinical assessment of HF by experienced observers.[19]

An elevated JVP has prognostic significance. Drazner and associates[18] demonstrated that the presence of jugular vein distention signifying elevated pressures at enrollment in a large clinical HF trial (11% of the Studies of Left Ventricular Dysfunction [SOLVD] treatment study participants), after adjustment for other markers of disease severity, predicted HF hospitalizations (relative risk [RR], 1.32; 95% CI, 1.08 to 1.62), death from pump failure (RR, 1.37; 95% CI, 1.07 to 1.75), and death plus HF hospitalization (RR, 1.30; 95% CI, 1.11 to 1.53) (**Fig. 10.10**). The investigators extended these observations to asymptomatic individuals enrolled in the SOLVD prevention study, among whom jugular vein distention was less common (1.7% of the study population).[18] In patients presenting with dyspnea, the abdominojugular reflux sign is useful in predicting HF (LR, 6.0; 95% CI, 0.8 to 51) and suggests a PA wedge pressure higher than 15 mm Hg (LR, 6.7; 95% CI, 3.3 to 13.4). The presence of jugular vein distention, either at rest or induced, had the best combination of sensitivity (81%), specificity (80%), and predictive accuracy (81%) for elevation of the PA wedge pressure. Ultrasound assessment of internal jugular vein dimension, both at rest and during the Valsalva maneuver, is independently associated with prognosis in ambulatory HF patients with reduced EF.[20]

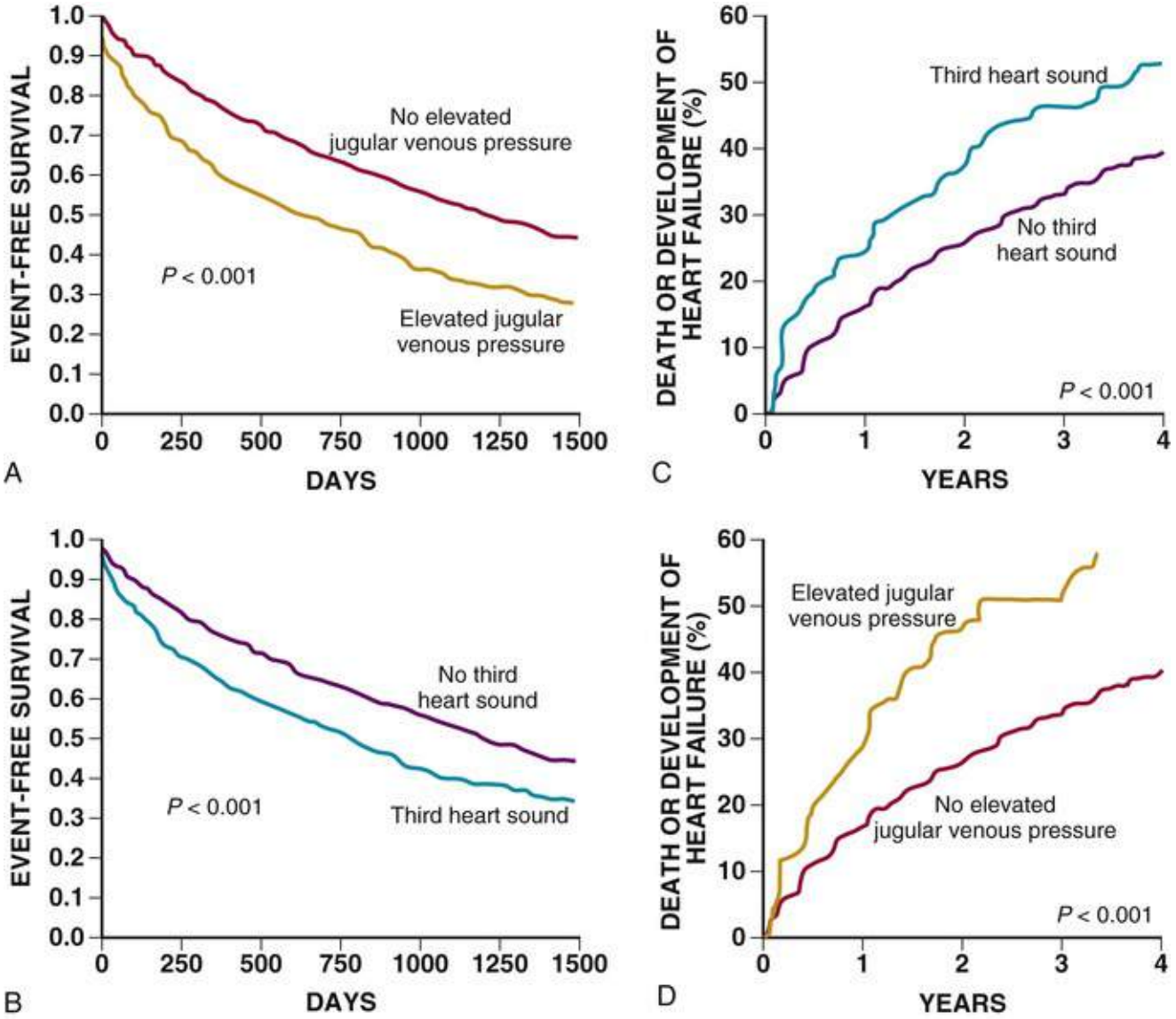


FIGURE 10.10 Kaplan-Meier plots demonstrating prognostic value of an elevated jugular venous pressure and third heart sound (S_3) in symptomatic (**A** and **B**) and asymptomatic (**C** and **D**) patients with heart failure who also had systolic dysfunction. (**A, B,** From Drazner MH, Rame JE, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. N Engl J Med 2001;345:574; **C, D,** from Drazner MH, Rame JE, Dries DL. Third heart sound and elevated jugular venous pressure as markers of the subsequent development of heart failure in patients with asymptomatic left ventricular dysfunction. Am J Med 2003;114:431.)

Third and Fourth Heart Sounds

The third heart sound (S_3) predicts EF poorly because it reflects primarily diastolic rather than systolic performance. In HF patients an S_3 is equally prevalent in those with and without LV systolic dysfunction. Marcus and colleagues conducted a rigorous assessment of S_3 in 100 patients with various cardiovascular conditions undergoing elective cardiac catheterization (see online References). Cardiology fellows (n = 18; K statistic, 0.37; $P < 0.001$) and faculty (n = 26; K statistic, 0.29; $P = 0.003$) performed better than residents (n = 102; no significant agreement) in the identification of a phonocardiographically confirmed S_3. Furthermore, an S_3 predicted an increase in both LV end-diastolic pressure (LVEDP) (>15 mm Hg) and BNP (>100 pg/mL) and depressed ventricular systolic function (EF <0.50), although sensitivities were low (32% to 52%) (**Fig. 10.11**). An S_4 had comparable sensitivity (40% to 46%) but inferior specificity (72% to 80% for S_4 versus 87% to 92% for S_3) (**Table 10.8**). S_3 frequently may be heard in patients referred for cardiac transplant evaluation but is a poor predictor of elevated filling pressures.

Alternatively, the lack of an S_3 cannot exclude a diagnosis of HF, but its presence reliably indicates ventricular dysfunction.

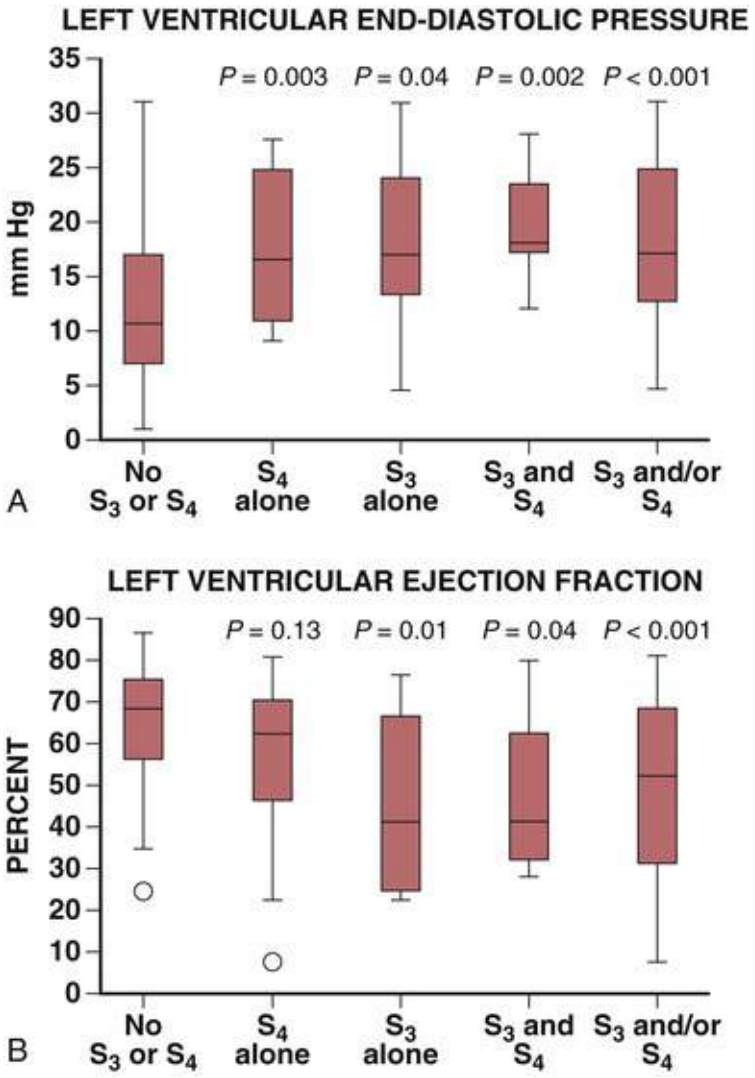


FIGURE 10.11 **A,** Median left ventricular end-diastolic pressure, and **B,** left ventricular ejection fraction, in patients in whom the phonocardiographic tracing demonstrated the presence of a third and/or fourth heart sound. Median and interquartile ranges, error bars, and outlier values (*circles*) are shown; *P* values are compared with data in the first column. (From Marcus GM, Gerber IL, McKeown BH, et al. Association between phonocardiographic third and fourth heart sounds and objective measures of left ventricular function. JAMA 2005;293:2238.)

TABLE 10.8

Test Characteristics in Computerized Detection of Heart Sounds*

CHARACTERISTIC	LVEDP > 15 mm Hg (%)	LVEF < 50% (%)	BNP > 100 pg/mL (%)
Third Heart Sound (S_3)			
Sensitivity	41 (26-58)	52 (31-73)	32 (20-46)
Specificity	92 (80-98)	87 (76-94)	92 (78-98)
PPV	81 (58-95)	57 (34-78)	85 (62-97)
NPV	65 (53-76)	84 (73-92)	48 (36-60)
Accuracy	69 (58-78)	78 (68-86)	56 (45-67)
Fourth Heart Sound (S_4)			
Sensitivity	46 (31-63)	43 (23-66)	40 (26-54)
Specificity	80 (66-90)	72 (59-82)	78 (61-90)
PPV	66 (46-82)	34 (18-54)	72 (52-87)
NPV	64 (51-76)	79 (66-88)	47 (34-60)
Accuracy	64 (54-74)	64 (54-74)	55 (44-66)
S_3 and/or S_4			
Sensitivity	68 (52-82)	74 (52-90)	57 (42-70)
Specificity	73 (59-85)	64 (52-76)	72 (55-86)
PPV	68 (52-82)	42 (26-58)	75 (59-87)
NPV	73 (59-85)	88 (75-95)	53 (38-67)
Accuracy	71 (61-80)	67 (56-76)	63 (52-73)

*Data are presented as percentages (with 95% confidence interval).

LVEDP, Left ventricular end-diastolic pressure; *LVEF,* left ventricular ejection fraction; *BNP,* brain (B-type) natriuretic peptide; *PPV,* positive predictive value; *NPV,* negative predictive value.

Modified from Marcus GM, Gerber IL, McKeown BH, et al. Association between phonocardiographic third and fourth heart sounds and objective measures of left ventricular function. JAMA 2005;293:2238.

The prognostic value of an S_3 in chronic HF was established in the SOLVD treatment and prevention studies.[18] The investigators found that an S_3 predicted cardiovascular morbidity and mortality (**see Fig. 10.10**). The relative risk for HF hospitalization and death in patients with an S_3 was of comparable magnitude in the prevention and treatment cohorts. These observations remained significant after adjustment for markers of disease severity and were even more powerful when combined with presence of elevated JVP. An S_3 also predicts a higher risk of adverse outcomes in other settings, such as myocardial infarction (MI) or noncardiac surgery.

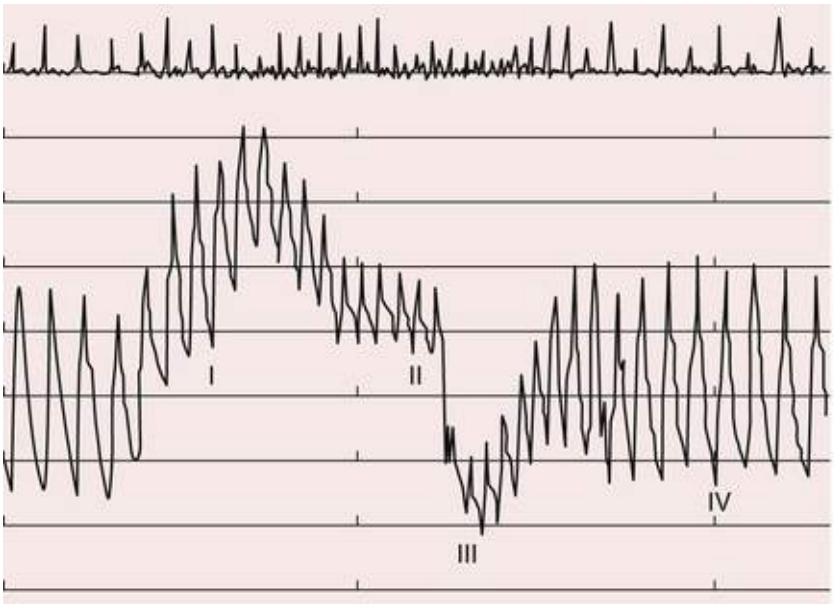
Rales and Edema

In patients with chronic HF, approximately 75% to 80% of participants lacked rales despite elevated PA wedge pressures, presumably because of enhanced lymphatic drainage. Recent studies have incorporated the findings from lung ultrasound (LR, 7.4; 95% CI, 4.2 to 12.8) in the assessment of ED patients with acute HF[21] and in ambulatory heart failure patients.[22] In the latter setting, lung ultrasound findings can identify patients with worse prognosis. When pulmonary adventitious sounds are present, specific characteristics may help elucidate a pulmonary rather than cardiac disorder (**see Fig. 10.2**). The chest radiograph similarly lacked sensitivity for increased filling pressures in these studies. Pedal edema is neither sensitive nor specific for the diagnosis of HF and has low predictive value as an isolated variable.

Valsalva Maneuver

The BP response to the Valsalva maneuver can be measured noninvasively using a BP cuff or commercially available devices. The Valsalva maneuver consists of four phases (**Fig. 10.12**). In a normal response, Korotkoff sounds are audible only during phases I and IV, because the systolic pressure

normally rises at the onset and release of the strain phase. Two abnormal responses to the Valsalva maneuver in HF are recognized: (1) absence of the phase IV overshoot and (2) the square-wave response (**Fig. 10.13**). The absent overshoot pattern indicates decreased systolic function; the square-wave response indicates elevated filling pressures and appears to be independent of EF. The responses can be quantified using the pulse amplitude ratio if the pulse pressure is measured during the maneuver. This ratio compares the minimum pulse pressure at the end of the strain phase against the maximum pulse pressure at the onset of the strain phase; a higher ratio is consistent with a square-wave response.



Phase I: Increase in systolic pressure with initial strain due to increase in intrathoracic pressure

Phase II: Decrease in stroke volume and pulse pressure and reflex tachycardia with continued strain due to decrease in venous return and increase in vascular resistance

Phase III: Brief, sudden decrease in systolic pressure due to sudden decrease in intrathoracic pressure

Phase IV: Overshoot of systolic pressure and reflex bradycardia due to increased venous return and decreased systemic vascular resistance

FIGURE 10.12 The normal Valsalva response. (From Nishimura RA, Tajik AJ. The Valsalva maneuver—3 centuries later. Mayo Clin Proc 2004;79:5774.)

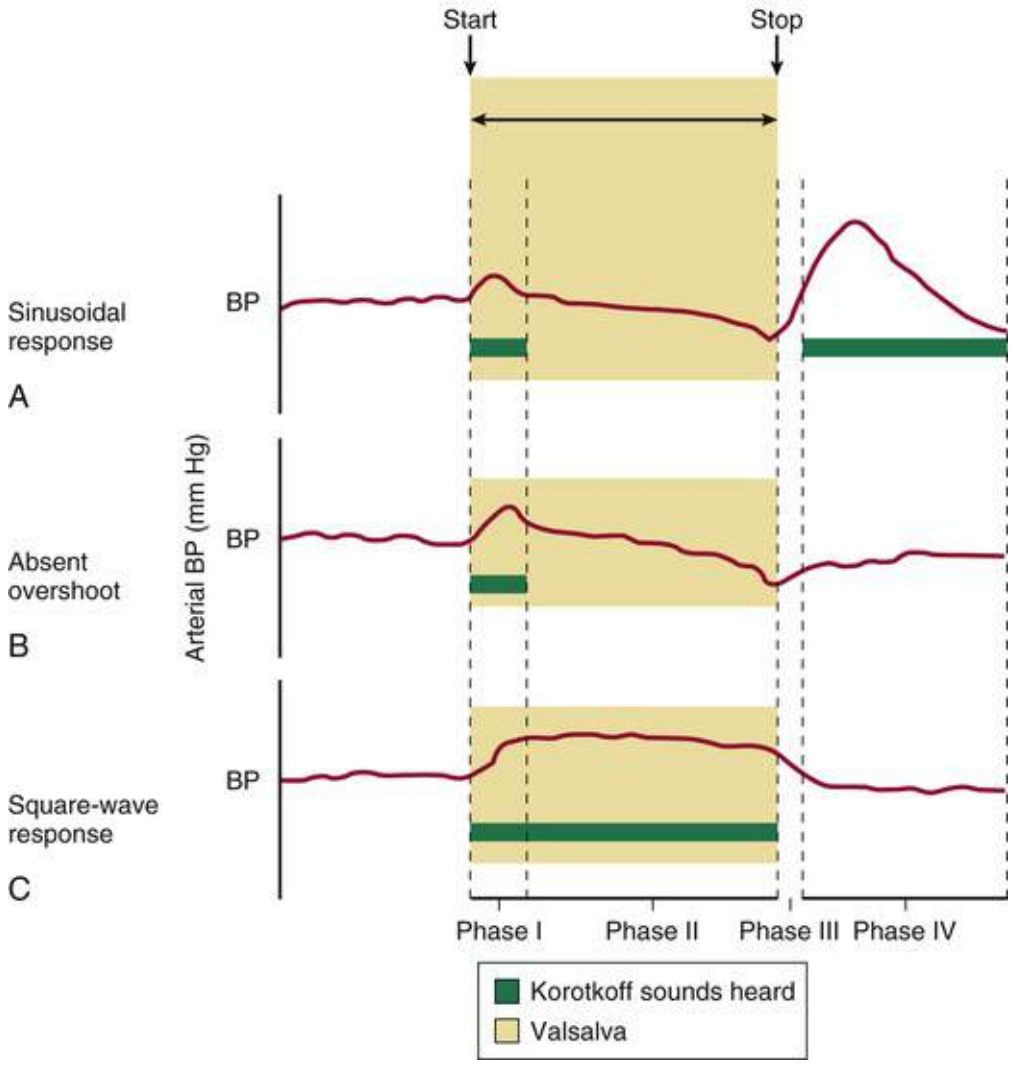


FIGURE 10.13 Abnormal Valsalva responses assessed using the pattern of Korotkoff sounds. **A,** Normal, sinusoidal response with sounds intermittent during strain and release. **B,** Briefly audible sounds during initial strain phase suggests only impaired systolic function in absence of fluid overload. **C,** Persistence of Korotkoff sounds throughout strain phase suggests elevated left ventricular filling pressures. *BP,* Blood pressure. (From Shamsham F, Mitchell J. Essentials of the diagnosis of heart failure. Am Fam Physician 2000;61:1319.)

Other Findings

In the absence of hypertension, the pulse pressure is determined by the stroke volume and vascular stiffness and can be used to assess cardiac output. In a cohort of patients with chronic systolic HF, the proportional pulse pressure ([systolic − diastolic]/systolic) correlated well with cardiac index (correlation coefficient [r] = 0.82; $P < 0.001$), stroke volume index ($r = 0.78$; $P < 0.001$), and the inverse of systemic vascular resistance ($r = 0.65$; $P < 0.001$). Using a proportional pulse pressure of 25%, the cardiac index could be predicted: if the value was lower than 25%, the cardiac index was less than 2.2 L/min/m^2 in 91% of patients; if the value was higher than 25%, the cardiac index was greater than 2.2 L/min/m^2 in 83% of patients.[23] Circulation time has also been used to assess the cardiac output. Using oxygen as the indicator, a time from a breath-hold to the nadir of finger oximetry of greater than 34 seconds has been associated with a cardiac output of less than 4 L/min.[24]

Heart rate is also a powerful indicator of prognosis in HF. A resting heart rate (in sinus rhythm) greater than 70 to 75 beats/min is an independent predictor of mortality. When the heart rate is decreased by ivabradine on a background of beta-blocker therapy, HF hospitalizations are decreased.[25] An attenuated heart rate increase with immediate standing (e.g., ≤3 beats/min) may also reflect the dysautonomia of HF

and has been associated with death or HF hospitalization. A greater increase of heart rate with standing over time is associated with longer HF hospitalization–free survival.[26]

Clinical experience may be the most helpful in assessing hemodynamic status. A good assessment for systemic perfusion and cardiac index appears to be overall clinical impression, the "cold" profile (**see Fig. 21.3**). The gestalt of specialized HF clinicians performed better than proportional pulse pressure, systolic blood pressure, cool extremities, or fatigue in predicting an invasively measured cardiac index lower than 2.3 L/min/m^2.[18] This prediction rule has not been reported in other patient groups, in larger cohorts, or in more contemporary studies. Pleural effusions also are common in patients with HF, in whom effusions typically are right sided, as noted previously. Dullness to percussion is the simplest finding to elicit in identifying a pleural effusion and is superior (LR, 8.7; 95% CI, 2.2 to 33.8) to auscultatory percussion, decreased breath sounds, asymmetric chest expansion, increased vocal resonance, crackles, or pleural friction rubs. By contrast, absence of reduced tactile vocal fremitus makes a pleural effusion less likely (negative LR, 0.21; 95% CI, 0.12 to 0.37).

Valvular Heart Disease (see also Part VIII)

A careful history and physical examination can reveal much regarding lesion severity, natural history, indications for intervention, and outcomes in patients with valvular heart disease. The history in patients with known or suspected valvular heart disease should rely on the use of a functional classification scheme and assessment of patient frailty when appropriate (**see Table 10.3**). Onset of even mild functional limitation is generally an indication for mechanical correction of the responsible valve lesion. Valvular heart disease most often is first suspected because of a heart murmur, but many patients go undetected until presentation with symptoms.[27,28] Cardiologists can detect systolic heart murmurs with fair reliability (interobserver kappa coefficient, 0.30 to 0.48) and usually can confirm or rule out aortic stenosis, HOCM, MR, MVP, TR, and functional murmurs. The use of handheld ultrasound devices may improve detection and accuracy rates.[29]

Mitral Stenosis

In patients with mitral stenosis, survival declines after symptom onset and worsens with increasing degrees of functional limitation (NYHA class) and as PA hypertension increases. Findings on physical examination vary with the chronicity of the disease, heart rate, rhythm, and cardiac output. It can be difficult to estimate the severity of the valve lesion in older patients with less pliable valves, rapid AF, or low cardiac output. Severe mitral stenosis is suggested by (1) a long or holodiastolic murmur, indicating a persistent LA-LV gradient; (2) a short A_2-OS interval, consistent with higher LA pressure; (3) a loud P_2 (or single S_2) and/or an RV lift, suggestive of pulmonary hypertension; and (4) elevated JVP with *cv* waves, hepatomegaly, and lower extremity edema—all signs of right heart failure. Neither the intensity of the diastolic murmur nor the presence of presystolic accentuation in patients with sinus rhythm accurately reflects lesion severity.

Mitral Regurgitation

The symptoms associated with MR depend on its severity and time course of development. Acute severe MR that occurs with papillary muscle rupture or infective endocarditis usually results in sudden and profound dyspnea from pulmonary edema. Examination findings may be misleading because the LV impulse usually is neither enlarged nor displaced, and the systolic murmur is early in timing and

decrescendo in configuration (**see Fig. 10.9**). The murmur also may be louder at the lower left sternal border or in the axilla than at the apex. A new systolic murmur developing early after an MI may not be audible in a ventilated or obese patient.

Several findings suggest chronic severe MR: (1) an enlarged, displaced, but dynamic LV apex beat; (2) an apical systolic thrill (murmur intensity of grade 4 or greater); (3) a mid-diastolic filling complex comprising an S_3 and a short, low-pitched murmur, indicative of accelerated and enhanced diastolic mitral inflow; (4) wide but physiologic splitting of S_2 caused by early aortic valve closure; and (5) a loud P_2 or RV lift. The findings in patients with MVP can vary, depending on LV loading conditions. The combination of a nonejection click and mid- to late systolic murmur predicts MVP best, as confirmed by transesophageal echocardiography (TTE) criteria (LR, 2.43). Dynamic auscultation should be performed.

Aortic Stenosis

A slowly rising carotid upstroke *(pulsus tardus),* reduced carotid pulse amplitude *(pulsus parvus),* reduced intensity of A_2, and mid- to late peaking of the systolic murmur help gauge the severity of aortic stenosis. The intensity of the murmur depends on cardiac output and body size (peak momentum transfer) and does not reliably reflect stenosis severity. In a 35-year follow-up study of 2014 apparently healthy middle-aged Norwegian men, the presence of even a low-grade systolic murmur was associated with an almost fivefold increased age-adjusted risk for aortic valve replacement.[30]

No single physical examination finding has both high sensitivity and high specificity for the diagnosis of severe aortic stenosis, and only a reduced carotid upstroke amplitude may independently predict outcome. Clinical experience has established the difficulty of assessing carotid upstroke characteristics in older patients, in patients with hypertension, and in low-output states. Distinguishing the murmur of hemodynamically significant aortic stenosis from that caused by lesser degrees of stenosis is also challenging. Even with aortic sclerosis, the murmur can be of grade 2 or 3 intensity, although it peaks in midsystole. The carotid upstroke should be normal, A_2 should be preserved, and the ECG should lack evidence of LV hypertrophy. Nevertheless, TTE often is necessary to clarify this distinction, especially in older patients with hypertension. Signal analysis of digitally captured cardiovascular sounds using spectral display can distinguish the murmur of aortic sclerosis from a murmur resulting from hemodynamically significant aortic stenosis.

The differential diagnosis of a systolic murmur related to LV outflow obstruction includes valvular aortic stenosis, HOCM, discrete membranous subaortic stenosis (DMSS), and supravalvular aortic stenosis (SVAS). The presence of an ejection sound indicates a valvular cause. HOCM can be distinguished on the basis of the response of the murmur to the Valsalva maneuver and standing or squatting. Patients with DMSS will usually have a diastolic murmur indicative of AR but not an ejection sound, whereas in patients with SVAS, the right arm BP is more than 10 mm Hg greater than the left arm BP. The increasing use of transcatheter aortic valve replacement (TAVR) for the treatment of prohibitive–, high–, or intermediate–surgical risk patients with symptomatic severe AS, many of whom are elderly, has obligated multidisciplinary heart teams to assess frailty status (**see Table 10.3**).

Aortic Regurgitation

Patients with acute severe AR present with pulmonary edema and symptoms and signs of low forward cardiac output. Tachycardia is invariably present, systolic BP is not elevated, and the pulse pressure is not significantly widened. S_1 is soft because of premature closure of the mitral valve. The intensity and

duration of the diastolic murmur are attenuated by the rapid rise in LV diastolic pressure and diminution of the aortic-LV diastolic pressure gradient. In patients with acute type A aortic dissection, the presence of a diastolic murmur (present in almost 30% of cases) does little to change the pretest probability of dissection. Acute severe AR is poorly tolerated and mandates emergency surgery. Typical symptoms associated with chronic, severe AR include dyspnea, fatigue, chest discomfort, and palpitations. A decrescendo diastolic blowing murmur suggests chronic AR. A midsystolic murmur indicative of augmented LV outflow is invariably heard at the base. Aortic stenosis may coexist. The absence of a diastolic murmur significantly reduces the likelihood of moderate or greater AR (LR, 0.1), whereas the presence of a typical diastolic murmur increases the likelihood of moderate or greater AR (LR, 4.0 to 8.3). In addition, in patients with chronic AR, the intensity of the murmur correlates with the severity of the lesion. A grade 3 diastolic murmur has an LR of 4.5 (95% CI, 1.6 to 14.0) for distinguishing severe AR from mild or moderate AR. Data conflict regarding the significance of an Austin Flint murmur. Little evidence supports the historical claims of the importance of almost all the eponymous peripheral signs of chronic AR, which number at least 12. The *Hill sign* (brachial-popliteal systolic BP gradient >20 mm Hg) may be the single exception (sensitivity of 89% for moderate to severe AR), although its supporting evidence base also is weak.

Tricuspid Valve Disease

Left-sided valve lesions often obscure the symptoms and signs of tricuspid stenosis. An elevated JVP together with a delayed *y* descent, abdominal ascites, and edema suggests severe tricuspid stenosis. Auscultatory findings are difficult to appreciate but mimic those in mitral stenosis and may worsen during inspiration. The symptoms of TR resemble those of tricuspid stenosis. Severe TR causes elevated JVP with prominent *cv* waves, a parasternal lift, pulsatile liver, ascites, and edema. The intensity of the holosystolic murmur of TR increases with inspiration (*Carvallo sign*). Murmur intensity does not accurately reflect the severity of the valve lesion. Primary and secondary causes of TR should be distinguished.

Pulmonic Valve Disease

Pulmonic stenosis may cause exertional fatigue, dyspnea, lightheadedness, and chest discomfort (“right ventricular angina”). Syncope denotes severe obstruction. The midsystolic murmur of pulmonic stenosis is best heard at the second left interspace. With severe pulmonic stenosis, the interval between S_1 and the pulmonic ejection sound narrows, and the murmur peaks in late systole and may extend beyond A_2. P_2 becomes inaudible. Signs of significant RV pressure overload include a prominent jugular venous *a* wave and a parasternal lift. Pulmonic regurgitation (PR) occurs most often as a secondary manifestation of significant PA hypertension and annular dilation, but it may also reflect a primary valve disorder (e.g., congenital bicuspid valve) or develop as a complication of RV outflow tract surgery, in which case characteristics of the murmur and Doppler echocardiographic signs differ. Symptoms vary as a function of the severity of PA hypertension and the level of RV compensation. The diastolic murmur of secondary PR (Graham Steell) can be distinguished from that caused by AR on the basis of its increase in intensity with inspiration, its later onset (after A_2 and with P_2), and its slightly lower pitch. When a typical murmur is audible, the likelihood of PR increases (LR, 17), but the absence of a murmur does not exclude PR (LR, 0.9). With severe PA hypertension and PR, P_2 is usually palpable and there are signs of RV pressure and volume overload on examination.

Prosthetic Heart Valves

The differential diagnosis of functional limitation after valve replacement surgery includes prosthetic valve dysfunction, arrhythmia, and impaired ventricular function. Prosthetic valve dysfunction can result from thrombosis, pannus ingrowth, infection, or structural deterioration. Symptoms and signs mimic those of native valve disease and may arise acutely or develop gradually. The first clue suggesting prosthetic valve dysfunction often is a *change* in the quality of the heart sounds or the appearance of a new murmur.

The heart sounds with a bioprosthetic valve resemble those generated by native valves. A bioprosthesis in the *mitral* position usually is associated with a midsystolic murmur (from turbulence created by systolic flow across valve struts that project into LV outflow tract) and a soft, mid-diastolic murmur that occurs with normal LV filling. The diastolic murmur usually is heard only in the left lateral decubitus position at the apex. A high-pitched or holosystolic apical murmur signifies para- or transvalvular regurgitation that requires echocardiographic verification and careful follow-up evaluation. Depending on the magnitude of the regurgitant volume, a diastolic murmur may be audible. Clinical deterioration can occur rapidly after initial manifestation of bioprosthetic failure.

A bioprosthesis in the *aortic* position is invariably associated with a midsystolic murmur at the base of grade 3 or less intensity. A diastolic murmur of AR is abnormal under any circumstance and merits additional investigation. A decrease in the intensity of either the opening or the closing sounds of a mechanical prosthesis, depending on its type, is a worrisome finding. A high-pitched apical systolic murmur in patients with a mechanical mitral prosthesis, or a decrescendo diastolic murmur in patients with a mechanical aortic prosthesis, indicates paravalvular regurgitation or prosthetic dysfunction. Signs of hemolysis should be sought. Patients with prosthetic valve thrombosis may present with signs of shock, muffled heart sounds, and soft murmurs. Pannus ingrowth is usually associated with an increase in the intensity of a systolic murmur and other signs indicative of prosthetic valve stenosis.

Acute Coronary Syndrome

Risk stratification of patients with ACS informs decision making regarding the intensity and pace of management and is recommended by international guidelines.[31-33] Clinical findings indicative of high risk of short-term death or MI in patients with non–ST-segment elevation ACS include older than age 75, tachycardia, hypotension, signs of pulmonary congestion, and a new or worsening murmur of MR (**see Chapters 56, 58, and 60**).

Pericardial Disease (see Chapter 83)

Pericarditis

The typical pain of acute pericarditis starts abruptly, is sharp, and varies with position. It can radiate to the trapezius ridge. Associated fever or history of a recent viral illness may provide additional clues. A pericardial friction rub is almost 100% specific for the diagnosis, although its sensitivity is not as high, because the rub may wax and wane over the course of an acute illness or may be difficult to elicit. This leathery or scratchy, typically two- or three-component sound also may be monophasic. It usually is necessary to auscultate the heart with the patient in several positions. The ECG may provide additional clues related to concave upward ST-segment elevation and P-R–segment deviation (elevation in lead aVR, depression in lead II). A transthoracic ECG is routinely obtained to assess the volume and appearance of any effusion and to look for early signs of hemodynamic compromise.

Pericardial Tamponade

Pericardial tamponade occurs when intrapericardial pressure equals or exceeds RA pressure. The time course of its development depends on the volume of the effusion, the rate at which it accumulates, and pericardial compliance. The most common associated symptom is dyspnea (sensitivity, 87% to 88%). Hypotension (sensitivity, 26%) and muffled heart sounds (sensitivity, 28%) are relatively insensitive indicators of tamponade. A pulsus paradoxus greater than 12 mm Hg in a patient with a large pericardial effusion predicts tamponade with sensitivity of 98%, specificity of 83%, and positive LR of 5.9 (95% CI, 2.4 to 14). Echocardiography is indicated in all patients with suspected pericardial tamponade.

Constrictive Pericarditis

Constrictive pericarditis is an uncommon clinical entity that occurs with previous chest irradiation, cardiac or mediastinal surgery, chronic tuberculosis, or malignancy. Dyspnea, fatigue, weight gain, abdominal bloating, and leg swelling dominate the clinical presentation. The diagnosis most often is first suspected after inspection of the JVP and waveforms, with elevation and inscription of the classic M or W contour caused by prominent *x* and *y* descents and a Kussmaul sign. Evidence of pleural effusions and ascites often can be found. On rare occasion, a PK is audible. Distinction from restrictive cardiomyopathy often is not possible on the basis of the history and physical examination alone.

Future Perspectives

The history and physical examination play an invaluable role in the initial assessment of the patient with known or suspected cardiovascular disease. Concerns regarding the escalating costs of medical care may reinforce the value of these time-honored traditions to guide appropriate use of imaging and invasive diagnostic modalities. Patients' perceptions of the quality of the care they receive may be influenced by the interactions associated with the performance of the history and examination. These considerations should spur additional efforts to establish the accuracy and predictive value of bedside findings across a spectrum of cardiovascular disorders. Recognition of the need to reestablish the mentored patient evaluation as a dedicated component of training programs, along with mechanisms to allow practice, repetition, and feedback, is essential. Improved teaching methods using simulation-based training aids are effective.[5] Electronic and digital stethoscopes may allow for computer automation and spectral display not only to enhance learning but also to improve the accuracy of diagnosis, while maintaining the physical link between the patient and provider.[6,34,35] The addition of handheld ultrasound may also improve learner performance, but whether it should replace the stethoscope controversial.[3,36-39] Continued improvements in the technical performance characteristics and declining costs of these devices are attractive features, as is the possibility of initiating treatment at the point of care without the need for additional testing in many patients.[39,40] Handheld ultrasound is a useful adjunct to screen for the presence of rheumatic heart disease in vulnerable populations and should be used routinely when available.[41]

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For citations to the older literature, see the additional reference list online for this chapter or the tenth edition of this textbook..

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11

Anesthesia and Noncardiac Surgery in Patients with Heart Disease

Lee A. Fleisher, Joshua A. Beckman

Cardiovascular morbidity and mortality represent a special concern in patients with known (or with risk factors for) cardiovascular disease who undergo noncardiac surgery. The cost of perioperative myocardial injury adds substantially to the total health care expenditure, with an average increased length of stay of 6.8 days for patients with perioperative myocardial ischemic injury. Perioperative cardiovascular complications not only affect the immediate period but may also the influence outcome over subsequent years. The evidence base for managing patients with cardiovascular disease in the context of noncardiac surgery has grown in recent decades, beginning with identification of those at greatest risk and progressing to randomized trials to identify strategies for reducing perioperative cardiovascular complications. Guidelines provide information for the management of high-risk patients and disseminate best practices. Indeed, over the last decade, mortality rates for all major surgeries have decreased in parallel with implementation of these practices. This chapter distills this information by incorporating guidelines available from the American College of Cardiology and American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC).[1,2] The ACCF/AHA guideline was updated in 2014, with a focused update on dual-antiplatelet therapy in 2016. (An update on this guideline is available online at ExpertConsult.)

Additionally, controversy surrounds research conducted at Erasmus University by Don Poldermans, the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography) studies, in which an investigative committee found serious shortcomings in the procedure used to record patient consent, submission of publications based on unreliable data, and scientifically inaccurate data collection. Since none of his perioperative papers was withdrawn, the committee chose to include the published papers in the discussion, but studies by Poldermans were not used to make formal recommendations.

Assessment of Risk

Numerous points of entry lead to evaluation of patients before they undergo noncardiac surgery. Primary physicians or cardiologists may examine such patients. History and physical examination represent the cornerstone of surgical risk evaluation, but risk assessment testing is rarely performed unless it changes management. Many patients undergo evaluation only immediately before surgery by the surgeon or anesthesiologist. Importantly, several cardiovascular conditions require assessment independent of the time before surgery.

Ischemic Heart Disease

The stress related to noncardiac surgery increases metabolic requirements and activates the sympathetic nervous system and may raise the heart rate preoperatively, which is associated with a high incidence of symptomatic and asymptomatic myocardial ischemia. Preoperative clinical evaluation of patients may

therefore identify stable or unstable coronary artery disease (CAD). Patients with acute manifestations of CAD such as unstable angina or decompensated heart failure have a high risk for the development of further decompensation or myocardial infarction (MI) and death during the perioperative period. Such patients clearly warrant further evaluation and medical stabilization. If the noncardiac surgery is truly an emergency, several older case series have shown that intra-aortic balloon pump counterpulsation can provide short-term myocardial protection beyond that afforded by maximal medical therapy, although this measure is seldom used today.

If the patient is not clinically unstable, identification of known or symptomatic stable CAD or risk factors for CAD can foster the implementation of guideline-based risk reduction therapies. In determining the extent of preoperative evaluation, it is important not to perform testing unless the results will affect perioperative management. In addition, the use of medications or interventions should mirror those that would be implemented in the absence of surgery. Infrequently, these changes in management may include cancellation of surgery (if the risk-benefit ratio is prohibitive) and consideration of palliative therapy, delay of surgery for further medical management, coronary interventions before surgery, use of an intensive care unit (ICU), and changes in monitoring. As discussed later, few evidence-based therapies are available independent of treating the underlying atherosclerotic risk, and except in the case of left main coronary artery stenosis, current data challenge the benefit of preoperative coronary revascularization. Thus, the primary reason to perform risk assessment is to determine clinical cardiovascular instability.

Over the last two decades, there has been a secular decrease in the rates of perioperative type 1 MI and mortality. Finks and colleagues[3] reported a 36% decrease in death after open abdominal aortic aneurysm repair from 2000 to 2008, to a risk-adjusted mortality of 2.8%. More recent data substantiate a decreasing frequency of type 1 and increasing rate of type 2 MI, indicating a predominance of subendocardial ischemic events resulting from hemodynamic challenge.[4] Although these events, characterized by increases in troponin, are strongly associated with death, the interval between troponin elevation and adverse events and the higher rate of nonvascular than cardiovascular mortality suggest that this is a marker of illness rather than a mechanism of mortality.

Traditionally, assessment of the coronary risk associated with noncardiac surgery in patients with previous MI was based on the time between the MI and surgery. Multiple studies have demonstrated an increased incidence of reinfarction after noncardiac surgery if the previous MI had occurred within 6 months of the operation. Improvements in MI management and perioperative care have shortened this interval. Although in some patients after a recent MI the myocardium may still be at risk for subsequent ischemia and infarction, most patients in the United States will have had critical coronary stenoses identified and revascularized when appropriate and should receive maximal medical therapy. The AHA/ACC Task Force on Perioperative Evaluation of the Cardiac Patient Undergoing Noncardiac Surgery has suggested that the highest-risk patients are those within 30 days of MI, during which time plaque and myocardial healing occur. After this period, risk stratification is based on the features of the disease (i.e., those with active ischemia are at highest risk). However, a study using administrative data from California demonstrated that the rate of perioperative cardiac morbidity and mortality remained elevated for at least 60 days after an MI, and the current iteration of the guidelines supports such a time frame.[5]

Hypertension

In the 1970s a series of case studies changed the prevailing thought that the use of antihypertensive agents

should be discontinued before surgery. The reports suggested that poorly controlled hypertension was associated with untoward hemodynamic responses and that antihypertensives should be continued perioperatively. However, several large prospective studies were unable to establish mild to moderate hypertension as an independent predictor of postoperative cardiac complications such as cardiac death, postoperative MI, heart failure, or arrhythmias. The approach to patients with hypertension therefore relies mostly on management strategies from the nonsurgical literature.

Blood pressure (BP) excursions in the operative and postoperative period portend worsening outcome. A hypertensive crisis in the postoperative period—defined as diastolic BP higher than 120 mm Hg and clinical evidence of impending or actual end-organ damage—poses a definite risk for MI and cerebrovascular accident (CVA, stroke). Iatrogenic precipitants of hypertensive crises include abrupt withdrawal of clonidine or beta-blocker therapy before surgery, chronic use of monoamine oxidase inhibitors with or without sympathomimetic drugs, and inadvertent discontinuation of antihypertensive therapy. Similarly, intraoperative hypotension is associated with both type 2 MI and increases in postoperative mortality.[6]

Although postulated to predict an increased rate of myocardial ischemia, none of the recent large clinical trials has shown that chronic hypertension predisposes patients to perioperative cardiovascular events.[4] This finding likely reflects the excellent perioperative management of hypertension in the current era. The pharmacologic management of patients with hypertension should be continued perioperatively, and BP should be maintained near preoperative levels to reduce the risk for myocardial ischemia. In patients with more severe hypertension, such as a diastolic BP higher than 110 mm Hg, little evidence suggests a benefit of delaying surgery to optimize antihypertensive medications in the absence of a hypertensive urgency or emergency. Currently, debate surrounds the optimal decision on withholding angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) on the day of surgery. Studies support both continuation and withholding, although continuation may require treatment with vasopressin for intractable hypotension. It is important to restart these agents as soon as possible postoperatively.

Heart Failure

Heart failure (HF) is associated with perioperative cardiac morbidity after noncardiac surgery in virtually all studies. Since the early work of Goldman and colleagues, who identified signs of HF as a significant risk of adverse events perioperatively, HF has become a more common problem with more varied presentations, including the presence or absence of ischemia and of reduced left ventricular ejection fraction. The underlying causes in patients with signs or symptoms of HF who are scheduled for noncardiac surgery require characterization. HF may eclipse CAD as a cause of postoperative adverse events. The 30-day postoperative mortality rate was significantly higher in patients with both nonischemic (9.3%) and ischemic (9.2%) HF compared to those with CAD (2.9%) in a population-based data analysis of 38,047 consecutive patients.[7]

The preoperative evaluation should aim to identify the underlying coronary, myocardial, and valvular heart disease and assess the severity of the systolic and diastolic dysfunction. Hammill and associates used Medicare claims data to evaluate short-term outcomes in patients with HF, CAD, or neither who underwent major noncardiac surgery. Elderly patients with HF who underwent major surgical procedures had substantially higher risk for operative mortality and hospital readmission than other patients, including those with CAD, admitted for the same procedures. In the absence of a surgical emergency, patients with decompensated HF should be treated to achieve a euvolemic, stable state before operation.

Ischemic cardiomyopathy is of greatest concern because the patient has substantial risk for the development of further ischemia, which can lead to myocardial necrosis and potentially a downward spiral.

Treatment of decompensated hypertrophic cardiomyopathy differs from that of dilated cardiomyopathy, and thus the preoperative evaluation can influence perioperative management. In particular, this assessment may influence perioperative fluid and vasopressor management. Obstructive hypertrophic cardiomyopathy was formerly regarded as a high-risk condition associated with high perioperative morbidity. A retrospective review of perioperative care in 35 patients, however, suggested low risk related to general anesthesia and major noncardiac surgery in such patients. This study also suggested that spinal anesthesia was a relative contraindication in view of the sensitivity of cardiac output to preload in this condition. Haering and colleagues studied 77 patients with asymmetric septal hypertrophy identified retrospectively from a large database; 40% had one or more adverse perioperative cardiac events, including one patient with MI and ventricular tachycardia who required emergency cardioversion. Most of the events consisted of perioperative congestive heart failure, and no perioperative deaths occurred. Unlike the finding in the original cohort of patients, the type of anesthesia was not an independent risk factor. Important independent risk factors for an adverse outcome (as seen generally) included major surgery and increasing duration of surgery.

Valvular Heart Disease (see also Part VIII)

Aortic stenosis places patients at increased risk. Critical stenosis is associated with the highest risk for cardiac decompensation in patients undergoing elective noncardiac surgery. Thus, the presence of any of the classic triad of angina, syncope, and HF in a patient with aortic stenosis should prompt further evaluation and potential interventions (usually valve replacement). Preoperative patients with aortic systolic murmurs warrant a careful history and physical examination—and often further evaluation. Several recent case series of patients with critical aortic stenosis have demonstrated that when necessary, noncardiac surgery can be performed with acceptable risk. In a matched-sample study using the Danish Health Care System, Andersson and colleagues demonstrated that patients with asymptomatic aortic stenosis did not experience a higher rate of major adverse cardiovascular events (MACE) or mortality in elective surgery. Emergency surgery type and symptomatic aortic stenosis increased both MACE and mortality. Aortic valvuloplasty is a bridging option for some patients who cannot undergo valve replacement or percutaneous intervention in the short term. The substantial risk for procedure-related morbidity and mortality and little evidence to demonstrate a perioperative risk reduction mandate careful consideration before recommending this strategy.

Mitral valve disease is associated with a lower risk for perioperative complications than aortic stenosis, although occult rheumatic mitral stenosis can sometimes lead to severe left-sided heart failure in patients with tachycardia (e.g., uncontrolled atrial fibrillation) and volume loading. In contrast to aortic valvuloplasty, mitral valve balloon valvuloplasty often yields both short- and long-term benefit, especially in younger patients with predominantly mitral stenosis but without severe mitral valve leaflet thickening or significant subvalvular fibrosis and calcification.

In perioperative patients with a functioning prosthetic heart valve, antibiotic prophylaxis and anticoagulation are major issues. All patients with prosthetic valves who undergo procedures that can cause transient bacteremia should receive prophylaxis. In patients with prosthetic valves, the risk for increased bleeding during a procedure while receiving antithrombotic therapy must be weighed against the increased risk for thromboembolism caused by stopping the therapy. Common practice in patients undergoing noncardiac surgery with a mechanical prosthetic valve in place is cessation of warfarin 3 days before surgery. This allows the international normalized ratio (INR) to fall to less than 1.5 times normal; oral anticoagulants can then be resumed on postoperative day 1. An alternative approach in patients at high risk for thromboembolism is conversion to heparin during the perioperative period, which can then be discontinued 4 to 6 hours before surgery and resumed shortly thereafter. A multicenter, single-arm cohort study of 224 high-risk patients (prosthetic valves, atrial fibrillation, and a major risk factor) investigated the use of low-molecular-weight heparin (LMWH) as a preoperative bridge to warfarin anticoagulation in which warfarin was withheld for 5 days and LMWH was given 3 days preoperatively and at least 4 days postoperatively. The overall rate of thromboembolism was 3.6% and of cardioembolism, 0.9%. Major bleeding was seen in 6.7% of patients, although only 8 of 15 episodes occurred during the administration of LMWH. LMWH is cost-effective because it helps reduce the duration of the hospital stay, but two studies have shown a residual anticoagulation effect in as many as two thirds of patients.

Many current prosthetic valves have a lower risk for valve thrombosis than the older designs, so the risk associated with heparin may outweigh its benefit in the perioperative setting. According to the AHA/ACC guidelines, heparin can usually be reserved for high-risk patients. *High risk* is defined by the presence of a mechanical mitral or tricuspid valve or a mechanical aortic valve and by certain risk factors, including atrial fibrillation, previous thromboembolism, hypercoagulable condition, older-

generation mechanical valves, an ejection fraction lower than 30%, or more than one mechanical valve. Subcutaneous LMWH or unfractionated heparin offers an alternative outpatient approach but has received only a tentative recommendation. Discussion between the surgeon and cardiologist regarding optimal perioperative management is critical. The ACC/AHA guidelines on valvular heart disease are being revised, and newer data questioning the value of bridge therapy in the atrial fibrillation setting are being incorporated into the recommendations.[8]

Congenital Heart Disease in Adults (see also Chapter 75)

Congenital heart disease afflicts 500,000 to 1 million adults in the United States. The nature of both the underlying anatomy and any anatomic correction affects the perioperative plan and incidence of complications, which include infection, bleeding, hypoxemia, hypotension, and paradoxical embolization. In a study using the National Surgical Quality Improvement Program (NSQIP) database, prior cardiac surgery in a population age 19 to 39 years significantly increased the risk of death, MI, stroke, reoperation, and length of stay.[9] Pulmonary hypertension and Eisenmenger syndrome present a major concern in patients with congenital heart disease. Regional anesthesia has traditionally been avoided in these patients because of the potential for sympathetic blockade and worsening of the right-to-left shunt. However, a review of 103 cases found that overall perioperative mortality was 14%; patients receiving regional anesthesia had a mortality of 5%, whereas those receiving general anesthesia had a mortality of 18%. The authors concluded that most deaths probably resulted from the surgical procedure and the disease rather than from anesthesia. Although perioperative and peripartum mortality was high, many anesthetic agents and techniques have been used with success. Patients with congenital heart disease are at risk for infective endocarditis and should receive antibiotic prophylaxis.

Arrhythmias (see Part V)

Cardiac arrhythmias frequently occur in the perioperative period, particularly in older adults or patients undergoing thoracic surgery. Predisposing factors include previous arrhythmias, underlying heart disease, hypertension, perioperative pain (e.g., hip fractures), severe anxiety, and other situations that heighten adrenergic tone. In a prospective study of 4181 patients 50 years or older, supraventricular arrhythmia occurred in 2% during surgery and in 6.1% after surgery. Perioperative atrial fibrillation (AF) raises several concerns, including the incidence of stroke (**see Chapters 38 and 65**). Winkel and colleagues evaluated 317 patients without AF who were undergoing major vascular surgery to determine the incidence of new-onset AF and its association with adverse cardiovascular outcomes. They reported an incidence of 4.7% and more than a sixfold increase in cardiovascular death, MI, unstable angina, and stroke in the first 30 days and a fourfold increase over the next 12 months. Early treatment to restore sinus rhythm or control the ventricular response and initiate anticoagulation is therefore indicated. Prophylactic use of intravenous (IV) diltiazem in randomized, placebo-controlled trials of patients undergoing high-risk thoracic surgery reduced the incidence of clinically significant atrial arrhythmias. Balser and colleagues studied 64 cases of postoperative supraventricular tachyarrhythmia. After the administration of adenosine, patients who remained in supraventricular tachyarrhythmia were prospectively randomly assigned to receive either IV diltiazem or IV esmolol for control of the ventricular rate; esmolol produced a more rapid (2-hour) conversion to sinus rhythm than diltiazem.

Although older studies identified ventricular arrhythmias as a risk factor for perioperative morbidity, recent studies have not confirmed this finding. O'Kelly, as cited in the guidelines, studied a consecutive sample of 230 male patients with known CAD or at high risk for CAD who underwent major noncardiac surgical procedures. Preoperative arrhythmias were associated with intraoperative and postoperative arrhythmias, but nonfatal MI and cardiac death were not substantially more common in those with previous perioperative arrhythmias. Recent data suggest otherwise. In a population-based study from Alberta, Canada, the risk of mortality at 30 days was 6.4% in patients with AF preoperatively compared with 2.9% for patients with CAD.[7] Despite this finding, a preoperative arrhythmia should provoke a search for underlying cardiopulmonary disease, ongoing myocardial ischemia or infarction, drug toxicity, or electrolyte or metabolic derangements.

Conduction abnormalities can increase perioperative risk and may require placement of a temporary or permanent pacemaker. On the other hand, patients with intraventricular conduction delays, even in the presence of a left or right bundle branch block but without a history of advanced heart block or symptoms, rarely progress to complete heart block perioperatively. The availability of transthoracic pacing units has decreased the need for temporary transvenous pacemakers.

The Decision to Undergo Diagnostic Testing

The ACC/AHA and ESC proposed algorithms for CAD evaluation based on the available evidence and incorporated the class of recommendations and level of evidence into each step (**Figs. 11.1 and 11.2**). Current algorithms use a stepwise bayesian strategy that relies on assessment of clinical markers, previous coronary evaluation and treatment, functional capacity, and surgery-specific risk, Successful use of the ACC/AHA algorithm requires an appreciation of the different levels of risk attributable to the combination of clinical circumstances and type of surgery, levels of functional capacity, and how the information from any diagnostic testing will influence perioperative management.

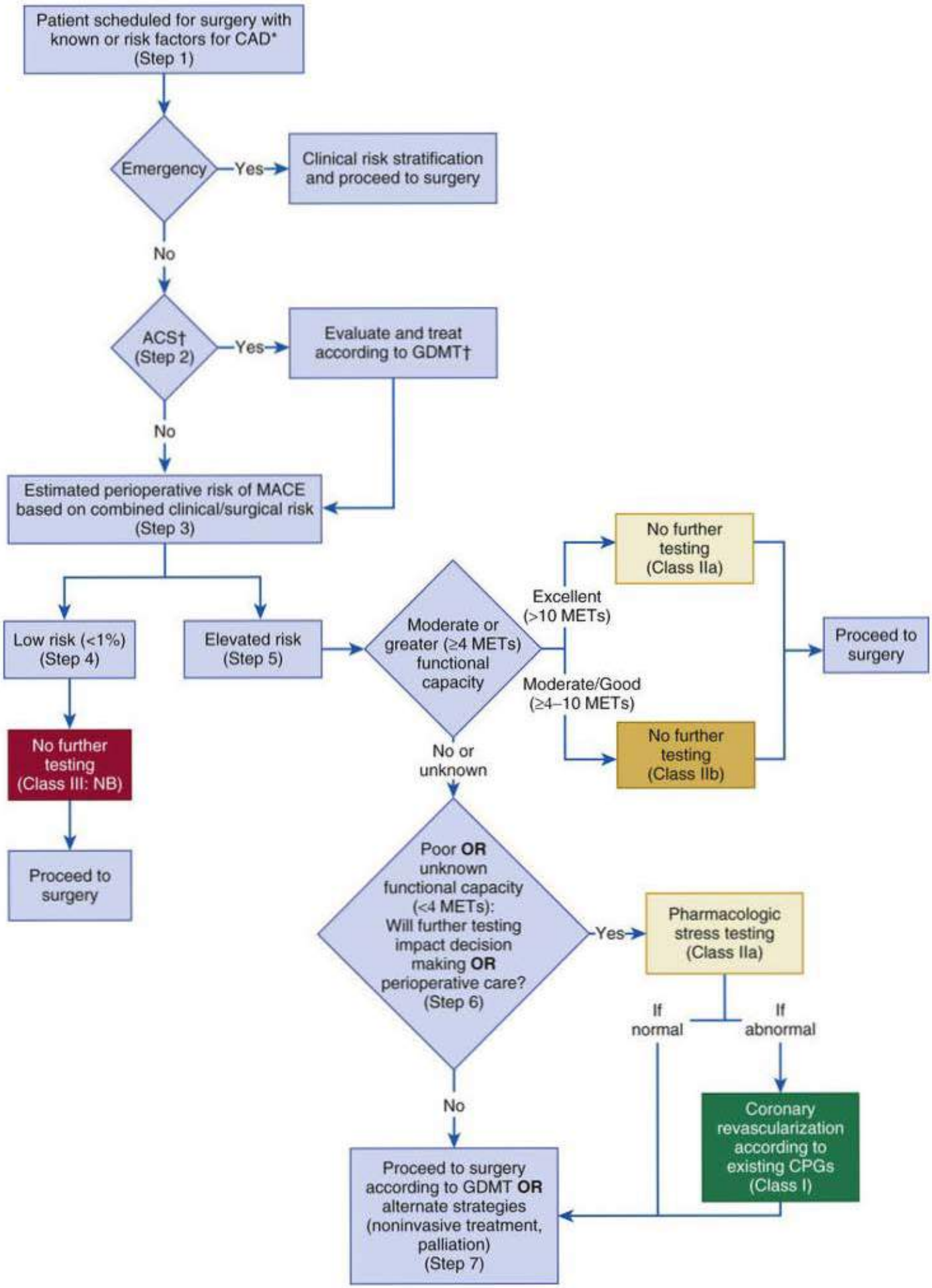

FIGURE 11.1 The 2014 ACC/AHA guideline algorithm depicting the stepwise approach to perioperative cardiac assessment for CAD. *ACS,* Acute coronary syndrome; *CAD,* coronary artery disease; *CPG,* clinical practice guideline; *GDMT,* guideline-directed medical therapy; *MACE,* major adverse cardiac event; *MET,* metabolic equivalent; *NB,* no benefit; *PCI,* percutaneous coronary intervention. (From Fleisher

LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e77-137.)

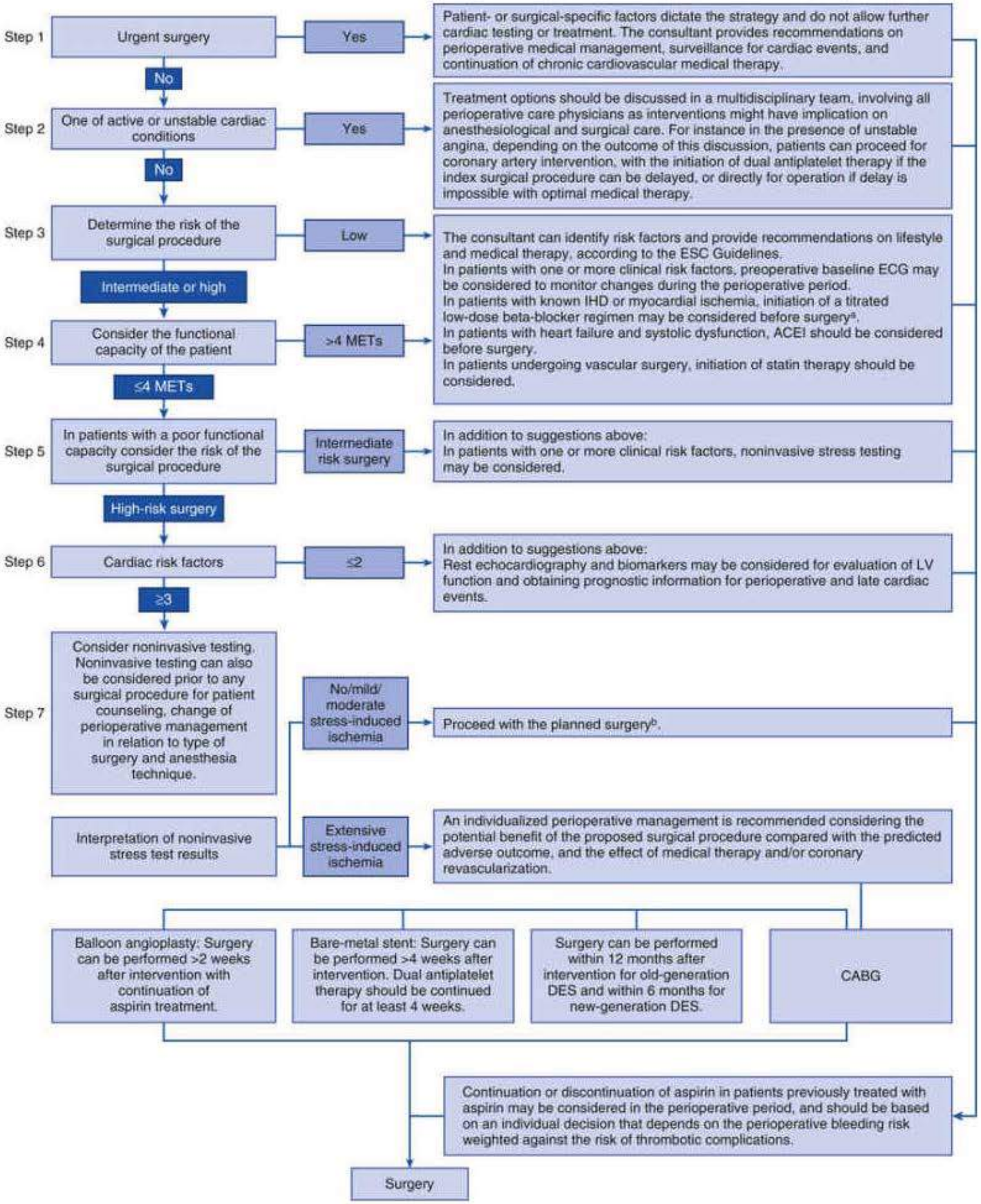

FIGURE 11.2 Summary of preoperative cardiac risk evaluation and perioperative management. *ACEI,* Angiotensin-converting enzyme inhibitors; *CABG,* coronary artery bypass graft; *DES,* drug-eluting stents; *IHD,* ischemic heart disease; LV, left ventricular; *METs,* metabolic equivalents. a b (From Kristensen SD,

Multiple studies have attempted to identify clinical risk markers for perioperative cardiovascular morbidity and mortality. As described earlier, patients with unstable coronary syndromes and severe valvular disease have active cardiac conditions. Risk can be divided into low (<1%) and elevated clinical risk. The 2014 ACC/AHA guidelines advocate using a risk index. This includes either the American College of Surgeons (ACS) NSQIP risk calculator or myocardial infarction and cardiac arrest (MICA) risk calculator, which incorporates both surgical and clinical risk. Alternatively, the clinician can incorporate the revised cardiac risk index with the estimated surgical risk to differentiate low from elevated risk (**Table 11.1**). Cardiovascular disease also has clinical risk markers classified as "low-risk factors," each of which is associated with variable levels of perioperative risk. The previous classification of perioperative, active clinical risk markers to assess the need for further testing includes issues beyond ischemic heart disease (**Table 11.2**).

TABLE 11.1

Cardiac Risk* Stratification for Noncardiac Surgical Procedures

RISK STRATIFICATION	EXAMPLES OF PROCEDURES
High (reported cardiac risk often >5%)	Aortic and other major vascular surgery Peripheral vascular surgery
Intermediate (reported cardiac risk generally 1%-5%)	Intraperitoneal and intrathoracic surgery Carotid endarterectomy Head and neck surgery Orthopedic surgery Prostate surgery
Low† (reported cardiac risk generally <1%)	Endoscopic procedures Superficial procedure Cataract surgery Breast surgery Ambulatory surgery

*Combined incidence of cardiac death and nonfatal myocardial infarction.

†These procedures do not generally require further preoperative cardiac testing.

From Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;54(22):e13.

TABLE 11.2

Active Cardiac Conditions for Which Patients Should Undergo Evaluation and Treatment Before Noncardiac Surgery (Class I; Level of Evidence: B)

CONDITION	EXAMPLES
Unstable coronary syndromes	Unstable or severe angina* (CCS class III or IV)† Recent myocardial infarction (MI)‡
Decompensated HF (NYHA functional class IV; worsening or new-onset HF)	
Significant arrhythmias	High-grade atrioventricular block Mobitz II atrioventricular block Third-degree atrioventricular heart block Symptomatic ventricular arrhythmias Supraventricular arrhythmias (including atrial fibrillation) with an uncontrolled ventricular rate (heart rate >100 beats/min at rest) Symptomatic bradycardia Newly recognized ventricular tachycardia
Severe valvular disease	Severe aortic stenosis (mean pressure gradient >40 mm Hg, aortic valve area <1.0 cm^2, or symptomatic) Symptomatic mitral stenosis (progressive dyspnea on exertion, exertional presyncope, or HF)

*According to Campeau L, Enjalbert M, Lesperance J, et al. Atherosclerosis and late closure of aortocoronary saphenous vein grafts: sequential angiographic studies at 2 weeks, 1 year, 5 to 7 years, and 10 to 12 years after surgery. Circulation 1983;68(Suppl II):1.

†May include “stable” angina in patients who are unusually sedentary.

‡The American College of Cardiology National Database Library defines “recent” MI as more than 7 days but 1 month or less (within 30 days) although the 2014 guidelines suggest 60 days.

CCS, Canadian Cardiovascular Society; *HF,* heart failure; *NYHA,* New York Heart Association.

From Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;54(22):e13.

As described for the anginal pattern, exercise tolerance is one of the strongest determinants of perioperative risk and the need for invasive monitoring. In one study of outpatients referred for evaluation before major noncardiac procedures, patients were asked to estimate the number of blocks that they could walk and flights of stairs that they could climb without experiencing cardiac symptoms. Patients who could not walk four blocks and could not climb two flights of stairs were considered to have poor exercise tolerance and had twice as many perioperative cardiovascular complications as those with better functional status. The likelihood of a serious complication is inversely related to the number of blocks that could be walked or flights of stairs climbed. Several scales based on activities of daily living have been proposed to assess exercise tolerance; current guidelines advocate the Duke Activity Scale Index (**Table 11.3**).

TABLE 11.3

Estimated Energy Requirements for Various Activities

	CAN YOU …
1 MET	Take care of yourself? Eat, dress, or use the toilet? Walk indoors around the house? Walk a block or two on level ground at 2-3 mph (3.2-4.8 kph)?
4 METs	Do light work around the house such as dusting or washing dishes? Climb a flight of stairs or walk up a hill? Walk on level ground at 4 mph (6.4 kph)? Run a short distance? Do heavy work around the house such as scrubbing floors or lifting or moving heavy furniture? Participate in moderate recreational activities such as golf, bowling, dancing, doubles tennis, or throwing a baseball or football?
>10 METs	Participate in strenuous sports such as swimming, singles tennis, football, basketball, or skiing?

MET, Metabolic equivalent; *mph,* miles per hour; *kph,* kilometers per hour.

Modified from Hlatky MA, Boineau RE, Higgenbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). Am J Cardiol 1989;64:65; and Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;54(22):e13.

The type of surgical procedure significantly impacts perioperative risk and the amount of preparation required to perform anesthesia safely. For surgical procedures not associated with significant stress or a high incidence of perioperative myocardial ischemia or morbidity, the cost of the evaluation often exceeds any benefit from the information gained by preoperative assessment. Outpatient procedures, for example, cause minimal morbidity and mortality; in such patients, cardiovascular status rarely changes perioperative management unless the patient has unstable angina or overt congestive heart failure. In fact, 30-day mortality after outpatient surgery may actually be lower than that expected if the patient did not undergo surgery. In contrast, open surgery for vascular disease entails a high risk for morbidity and the potential for ischemia. Intra-abdominal, thoracic, and orthopedic procedures are associated with elevated risk, which can then be combined with clinical risk factors to determine overall perioperative risk. Endovascular procedures fall into this intermediate-risk category because of their associated perioperative morbidity and mortality, although long-term survival appears to be similar to that in patients who undergo open procedures.

In addition to the risk related to the surgical procedure itself, risk is also correlated with the surgical volume in a given center. Several studies have demonstrated differential mortality rates in both cancer and vascular surgery, with higher mortality occurring in low-volume centers, although recent studies have demonstrated that low-volume centers may also have low mortality rates if proper care systems are in place. Surgical mortality rates may therefore be institution specific, which may influence the decision to perform further perioperative evaluations and interventions.

Risk Calculators

Much of the contemporary study of perioperative cardiac risk has focused on the development of clinical risk indices. The most widely used index was developed in a study of 4315 patients age 50 or older undergoing elective major noncardiac procedures in a tertiary care teaching hospital. The index includes six independent predictors of complications in a *revised cardiac risk index* (RCRI): high-risk type of surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative treatment with insulin, and preoperative serum creatinine concentration greater than 2.0 mg/dL. Cardiac complication rates rise with an increasing number of these risk factors. Patients are

stratified into low, intermediate, or high cardiovascular risk on the basis of having 0, 1 or 2, or 3 or more factors included in the RCRI, respectively. The RCRI has become the standard tool for assessing the probability of perioperative cardiac risk in a given individual and serves to direct the decision to perform cardiovascular testing and implement perioperative management protocols. The RCRI has undergone validation in vascular surgery populations and serves to predict long-term outcome and quality of life, although one group has advocated inclusion of age as a risk factor.

Additional risk indices were developed from the ACS-NSQIP database. Gupta and colleagues[10] developed a risk calculator for predicting perioperative *myocardial infarction and cardiac arrest* (MICA). In a study of 211,410 patients, perioperative MI or cardiac arrest developed in 1371 (0.65%). Multivariate logistic regression analysis identified five predictors of perioperative MI or cardiac arrest: type of surgery, dependent functional status, abnormal creatinine level, American Society of Anesthesiologists class, and increasing age.

A universal risk calculator recently developed to predict multiple outcomes was based on 1,414,006 patients encompassing 1557 unique surgical procedure codes, which had excellent performance for mortality (C-statistic = 0.944) and morbidity (C-statistic = 0.816) (any of the following intraoperative or postoperative events: surgical site infection [SSI], wound disruption, pneumonia, unplanned intubation, pulmonary embolism, on ventilator >48 hours, progressive renal insufficiency, acute renal failure, urinary tract infection [UTI], stroke/CVA, cardiac arrest, MI, deep venous thrombosis [venous thromboembolism, VTE], systemic sepsis), pneumonia, cardiac event (cardiac arrest or MI), SSI, UTI, VTE, and renal failure (progressive renal insufficiency or acute renal failure) (http://riskcalculator.facs.org). The risk calculator incorporates 21 preoperative risk factors and therefore has more discriminative ability than the MICA-specific risk calculator.

The Guidelines Approach

The ACC/AHA Task Force for Guidelines for Perioperative Cardiovascular Evaluation and Management for Noncardiac Surgery presented their recommendations in algorithmic form as a framework for determining which patients are candidates for cardiac testing (**see Fig. 11.1**). Given the availability of the evidence, the writing committee included the level of the recommendations and strength of evidence for each of the pathways. The current algorithm focuses exclusively on the evaluation for CAD. Valvular or other forms of heart disease are not included in the current algorithm.

Step 1: The consultant should determine the urgency of performing noncardiac surgery. In many cases, patient- or surgery-specific factors dictate an obvious strategy (e.g., emergency surgery) that may not allow further cardiac assessment or treatment.

Step 2: Does the patient have an acute coronary syndrome? Acute coronary syndromes include previous MI with evidence of substantial ischemic risk as determined by clinical symptoms or noninvasive study, unstable or severe angina, and new or poorly controlled ischemia-mediated HF. Depending on the results of tests or interventions and the risk inherent in delaying surgery, it may be appropriate to proceed to the planned surgery with maximal medical therapy.

Step 3: What is the estimated perioperative risk of a major adverse cardiac event (MACE) based on the combined clinical and surgical risk? The use of a validated risk index is advocated, either one of the ACS-NSQIP risk indices or combining the RCRI with the estimated surgical risk.

Step 4: Does the patient have low perioperative risk (<1%)? In such cases, no further testing is required.

Step 5: Does the patient have elevated risk? Such circumstances merit assessment of functional capacity. If the patient has at least moderate exercise capacity (≥4 metabolic equivalents [METs]), management rarely changes on the basis of the results of any further cardiovascular testing, and it is therefore appropriate to proceed with the planned surgery. The strength of the evidence and the recommendation depends on the degree of exercise capacity, with excellent capacity having stronger evidence and recommendation.

Step 6: In patients with poor (<4 METs) or unknown functional capacity, the physicians and patient should jointly determine if further testing will impact decision making or perioperative care. If not, proceeding to surgery with goal-directed medical therapy is appropriate. In the current guidelines, the identification of elevated risk with poor functional capacity may also lead to the decision to proceed with alternative strategies, such as noninvasive treatment or palliation.

Tests to Improve Identification and Definition of Cardiovascular Disease

Several noninvasive diagnostic methods can evaluate the extent of CAD before noncardiac surgery. The exercise electrocardiogram (ECG) has traditionally served to evaluate individuals for the presence of CAD, but as outlined earlier, patients with excellent exercise tolerance in daily life will rarely benefit from further testing. Patients with poor exercise capacity, in contrast, may not achieve an adequate heart rate and blood pressure for diagnostic purposes on electrocardiographic stress tests. Such patients often require concomitant imaging.

Many high-risk patients either cannot exercise or have limitations to exercise (e.g., patients with claudication or an abdominal aortic aneurysm who are undergoing vascular surgery, both of which have a high rate of perioperative cardiac morbidity). Pharmacologic stress testing has therefore become popular, particularly as a preoperative test in patients undergoing vascular surgery. Several studies have shown that the presence of a redistribution defect on dipyridamole or adenosine thallium or sestamibi imaging in patients undergoing peripheral vascular surgery predicts postoperative cardiac events. Pharmacologic stress imaging is best used in patients at moderate clinical risk. Several strategies may increase the predictive value of such tests. The redistribution defect can be quantitated, with larger areas of defect being associated with increased risk. Additionally, either increased lung uptake or dilation of the left ventricular cavity indicate ventricular dysfunction with ischemia. Several investigative groups have demonstrated that delineation of low-risk and high-risk myocardial perfusion scans (larger area of defect, increased lung uptake, and dilation of the left ventricular cavity) greatly improves the test's predictive value. Patients with high-risk scans have a particularly increased risk for perioperative morbidity and long-term mortality.

Stress echocardiography has also been used widely as a preoperative test. One advantage of this test is that it dynamically assesses myocardial ischemia in response to increased inotropy and heart rate, stimuli relevant to the perioperative period. The presence of new wall motion abnormalities occurring at a low heart rate is the best predictor of increased perioperative risk, with large areas of contractile dysfunction having secondary importance. As part of the DECREASE studies, Boersma and colleagues (as cited in the guidelines) assessed the value of dobutamine stress echocardiography with respect to the extent of wall motion abnormalities and the ability of preoperative treatment with beta blockers to attenuate risk in patients undergoing major aortic surgery. They assigned 1 point for each of the following characteristics: age older than 70 years, current angina, MI, congestive heart failure, previous cerebrovascular disease,

diabetes mellitus, and renal failure. As the total number of clinical risk factors increases, perioperative cardiac event rates also increase. Furthermore, with a high-risk score, abnormal findings on an echocardiogram predict higher risk.

Several groups have published meta-analyses examining various preoperative diagnostic tests. Such studies report good predictive values for ambulatory electrocardiographic monitoring, radionuclide angiography, dipyridamole-thallium imaging, and dobutamine stress echocardiography. Shaw and colleagues also demonstrated excellent predictive values for dipyridamole thallium imaging and dobutamine stress echocardiography.[2] Beattie and colleagues performed a meta-analysis of 25 stress echocardiography studies and 50 thallium imaging studies.[2] The likelihood ratio for stress echocardiography was more indicative of a postoperative cardiac event than that for thallium imaging (likelihood ratio [LR], 4.09; 95% confidence interval [CI], 3.21 to 6.56; versus LR, 1.83; 95% CI, 1.59 to 2.10; $P < 0.001$). The difference was attributable to fewer false-negative stress echocardiograms. A moderate to large abnormality found by either test predicted postoperative MI and death.

Institutional expertise should guide the choice of preoperative testing. The relevant clinical questions also influence the choice of test. For example, if valve function or myocardial thickness is of interest, echocardiography has advantages over perfusion imaging. Stress nuclear imaging may have slightly higher sensitivity, but stress echocardiography may have fewer false-positive results. The role of newer imaging modalities such as magnetic resonance imaging, multislice computed tomography, coronary calcium scores, and positron emission tomography in preoperative risk assessment is rapidly evolving.

Over the past decade, cardiopulmonary exercise testing (CPET) has been used as a preoperative test, particularly in Great Britain. A consistent finding of the studies was that a low anaerobic threshold was predictive of perioperative cardiovascular complications, postoperative death, or midterm and late death after surgery. An anaerobic threshold of approximately 10 mL O_2/kg/min was proposed as the optimal discrimination point, with a range in these studies of 9.9 to 11 mL O_2/kg/min. CPET is being evaluated as a means of determining the need for “prehabilitation,” in which a strategy of exercise is advocated to increase aerobic capacity before surgery.[12] Current research is determining if such strategies improve outcome. Additionally, several groups are studying the value of CPET in determining the appropriateness of surgery given the intermediate- and long-term outcome in high-risk patients and helping to inform shared decision making.

Overview of Anesthesia for Cardiac Patients Undergoing Noncardiac Surgery

Three classes of anesthetics exist: general, regional, and local/sedation or monitored anesthesia care (MAC). General anesthesia can be defined best as a state that includes unconsciousness, amnesia, analgesia, immobility, and attenuation of autonomic responses to noxious stimulation, and it can be achieved with inhalational agents, intravenous agents, or a combination of these (frequently called a “balanced technique”). Contemporary general anesthesia does not always require an endotracheal tube. Laryngoscopy and intubation were traditionally considered the time of greatest stress and risk for myocardial ischemia, but extubation may actually engender greater risk. Alternative methods for delivering general anesthesia use a mask or a laryngeal mask airway—a device that fits above the epiglottis and does not require laryngoscopy or intubation.

Five inhalational anesthetic agents (in addition to nitrous oxide) are currently approved in the United States, although enflurane and halothane are rarely used today. All inhalational agents have reversible myocardial depressant effects and lead to decreases in myocardial oxygen demand. The degree to which they depress cardiac output depends on their concentration, their effects on systemic vascular resistance, and their effects on baroreceptor responsiveness; agents therefore differ in their specific effects on heart rate and blood pressure. Isoflurane causes negative inotropic effects and potent vascular smooth muscle relaxation and has minimal effects on baroreceptor function. Desflurane has the fastest onset and is commonly used in the outpatient setting. The onset and offset of action of sevoflurane are intermediate to those of isoflurane and desflurane; the major advantage of sevoflurane is an extremely pleasant smell, which makes it the agent of choice in children.

Issues have arisen regarding the safety of inhalational agents in patients with CAD. Several large-scale, randomized and nonrandomized studies of patients undergoing coronary artery bypass grafting (CABG), however, demonstrated no increased incidence of myocardial ischemia or infarction in patients receiving inhalational agents versus narcotic-based techniques. The use of inhalational anesthetics in patients with CAD also has theoretical advantages. Several investigative groups demonstrated in vitro and in animals that inhalational agents have protective effects on myocardium similar to ischemic preconditioning, although the clinical relevance of this remains unclear.[13]

High-dose narcotic techniques offer the advantages of hemodynamic stability and lack of myocardial depression. Narcotic-based anesthetics were frequently considered the “cardiac anesthesia” and were advocated for use in all high-risk patients, including those undergoing noncardiac surgery. The disadvantage of these traditional high-dose narcotic techniques is the requirement for postoperative ventilation. The ultrashort-acting narcotic remifentanil obviates the need for prolonged ventilation but provides hemodynamic stability. This agent can assist in early extubation of patients undergoing cardiac surgery and may aid in managing short periods of intense intraoperative stress in high-risk patients.

Despite the theoretical advantages of a high-dose narcotic technique, large-scale trials in patients undergoing CABG showed no difference in survival or major morbidity compared to the inhalation-based technique. This observation has contributed to the abandonment of high-dose narcotics in much of cardiac surgery and to an emphasis on early extubation. Most anesthesiologists use a balanced technique involving the administration of lower doses of narcotics with an inhalational agent. This approach allows the anesthesiologist to derive the benefits of each of these agents while minimizing side effects.

The IV agent propofol is an alternative mode of delivering general anesthesia. An alkyl phenol that can be used for both induction and maintenance of general anesthesia, propofol can cause profound hypotension because of reduced arterial tone with no change in heart rate. Its major advantage is rapid clearance with few residual effects on awakening, but because it is expensive, its current use tends to be limited to operations of brief duration. Despite its hemodynamic effects, propofol has been used extensively to assist in early extubation after CABG.

Current evidence indicates that there is no single “best” general anesthetic technique for patients with CAD who are undergoing noncardiac surgery, which has led to abandonment of the concept of a cardiac anesthetic.

Regional Anesthesia

Regional anesthesia includes spinal, epidural, and peripheral nerve blocks, and each technique has advantages and risks. Peripheral techniques, such as brachial plexus or Bier blocks, offer the advantage

of causing minimal or no hemodynamic effects. In contrast, spinal or epidural techniques can produce sympathetic blockade, which can reduce blood pressure and slow the heart rate. Spinal anesthesia and lumbar or low thoracic epidural anesthesia can also evoke reflex sympathetic activation mediated above the level of blockade, which might lead to myocardial ischemia.

The primary clinical difference between epidural and spinal anesthesia is the ability to provide continuous anesthesia or analgesia with placement of an epidural catheter, as opposed to a single dose with spinal anesthesia, although some clinicians will place a catheter in the intrathecal space. Even though the speed of onset depends on the local anesthetic agent used, spinal anesthesia and its associated autonomic effects occur sooner than when the same agent is administered epidurally. A catheter, usually left in place for epidural anesthesia, permits titration of the agent. Epidural catheters can also be used postoperatively to provide analgesia.

Extensive research has compared regional with general anesthesia for patients with CAD, particularly in those undergoing infrainguinal bypass surgery. In one meta-analysis, overall mortality was reduced by approximately one third in patients allocated to neuraxial blockade, although the findings were controversial because most of the benefit was observed in older studies. Reductions in MI and renal failure also occurred. A large-scale study of regional versus general anesthesia in noncardiac surgery patients did not demonstrate a difference in outcome.

Regional anesthesia has become very common with recent advances in ultrasound-guided administration and development of *enhanced recovery after surgery* (ERAS) protocols. Regional anesthesia offers the opportunity to provide excellent pain relief after surgery, which has proved advantageous and reduces perioperative cardiac stress.[14]

Monitored Anesthesia Care

MAC encompasses local anesthesia administered by the surgeon, with or without sedation. In a large-scale cohort study, MAC was associated with increased 30-day mortality compared with general anesthesia in a univariate analysis, although it did not remain significant in multivariate analysis once patient comorbidity was taken into account. The major issue with MAC is the ability to block the stress response adequately, because the tachycardia associated with inadequate analgesia may be worse than the potential hemodynamic effects of general or regional anesthesia. Since the introduction of newer, short-acting IV agents, general anesthesia can now be administered essentially without an endotracheal tube. This approach allows the anesthesiologist to provide intense anesthesia for short or peripheral procedures without the potential effects of endotracheal intubation and extubation and therefore blurs the distinction between general anesthesia and MAC. An analysis of closed insurance claims demonstrated a high incidence of respiratory complications with MAC.

Intraoperative Hemodynamics and Myocardial Ischemia

Over the last two decades, numerous studies have explored the relationship between hemodynamics and perioperative ischemia and MI. Tachycardia is the strongest predictor of perioperative ischemia. Although traditionally a heart rate (HR) greater than 100 beats/min defines tachycardia, slower HRs may result in myocardial ischemia. As described later, control of HR with beta blockers decreases the incidence of myocardial ischemia and infarction. In the DECREASE studies, HR control reduced the incidence of perioperative MI, with the greatest benefit achieved if HR was controlled to less than 70 beats/min. Although some are concerned about beta blockers causing intraoperative hypotension in

patients with CAD, no evidence supports this contention. However, the Perioperative Ischemic Evaluation (POISE) trial demonstrated that an acute beta blockade protocol was associated with hypotension and a higher rate of stroke in the metoprolol arm. During CABG, the vast majority of episodes of intraoperative ischemia are not correlated with hemodynamic changes. In the absence of tachycardia, hypotension is not associated with myocardial ischemia.

Postoperative Management

Postoperative Response to Surgery

Understanding the pathophysiology of perioperative cardiac events helps in determining the best approach to preoperative testing. A full discussion of the pathophysiology of perioperative MI has been published.[15] All surgical procedures cause a stress response, although the extent of the response depends on the extent of the surgery and the use of anesthetics and analgesics to reduce the response. The stress response can increase heart rate and blood pressure, which can precipitate episodes of myocardial ischemia in areas distal to coronary artery stenoses. Prolonged myocardial ischemia (either prolonged individual episodes or prolonged cumulative duration of shorter episodes) can cause myocardial necrosis and perioperative MI and death. Identification of patients at high risk for coronary artery stenosis, through either the history or cardiovascular testing, can lead to the implementation of strategies to reduce morbidity as a result of supply-demand mismatches. Recent work with highly sensitive markers of myocardial damage has shown a high rate of cardiac injury even in the absence of frank infarction. In the POISE trial, 8.3% of the patients had an elevated cardiac biomarker without other evidence of infarction, whereas 5% also had a second confirmatory marker of MI.

A major mechanism of MI in the nonoperative setting is plaque rupture with subsequent coronary thrombosis (**see Chapters 44 and 58**). Inasmuch as the perioperative period is marked by tachycardia and a hypercoagulable state, plaque disruption and thrombosis may occur quite often. Because noncritical stenosis can furnish the nidus for coronary artery thrombosis, preoperative cardiac evaluation may fail to identify patients at risk before surgery. The areas distal to the noncritical stenosis might not have developed collateral coronary flow, and therefore any acute thrombosis may have a greater detrimental effect than it would in a previously severely narrowed vessel. If a prolonged increase in myocardial oxygen demand in a patient with one or more critical fixed stenoses provoked postoperative MI, preoperative testing would probably identify such a patient.

Evidence from several autopsy and postinfarction angiography studies after surgery supports both mechanisms. Ellis and colleagues demonstrated that one third of all patients sustained events in areas distal to noncritical stenoses. Dawood and associates, as cited in the guidelines, demonstrated that fatal perioperative MI occurs predominantly in patients with multivessel coronary disease, especially left main and three-vessel disease, but the severity of preexisting stenosis did not predict the infarct territory. This analysis suggested that fatal events occurred primarily in patients with advanced fixed stenoses, but that the infarct may result from plaque rupture in a mild or only moderately stenotic segment of the diseased vessel. Duvall and colleagues reviewed hospital records and coronary angiograms from patients who underwent noncardiac surgery complicated by perioperative MI from 1998 to 2006. The distribution of demand, thrombotic, and nonobstructive MI was 55%, 26%, and 19%, respectively. In contrast, Gualandro and colleagues found that almost 50% of patients with perioperative acute coronary syndromes have evidence of ruptured coronary plaque. The evidence therefore shows that several mechanisms may cause perioperative MI.

Postoperative Intensive Care

Provision of intensive care by intensivists has now become a patient safety goal. Pronovost and coworkers performed a systematic review of the literature on physician staffing patterns and clinical outcomes in critically ill patients. They grouped ICU physician staffing into low-intensity (no intensivist or elective intensivist consultation) and high-intensity (mandatory intensivist consultation or closed ICU [all care directed by an intensivist]) groups. High-intensity staffing was associated with lower hospital mortality in 16 of 17 studies (94%) and with a pooled estimate of the relative risk for hospital mortality of 0.71 (95% CI, 0.62 to 0.82). High-intensity staffing was associated with lower ICU mortality in 14 of 15 studies (93%) and with a pooled estimate of the relative risk for ICU mortality of 0.61 (95% CI, 0.50 to 0.75). High-intensity staffing reduced hospital length of stay (LOS) in 10 of 13 studies and reduced ICU LOS in 14 of 18 studies without case-mix adjustment. High-intensity staffing was associated with reduced hospital LOS in two of four studies and lowered ICU LOS in both studies that adjusted for case-mix. No study found increased LOS with high-intensity staffing after case-mix adjustment. High-intensity versus low-intensity ICU physician staffing was associated with reduced hospital and ICU mortality and LOS.

Postoperative Pain Management

Postoperative analgesia may reduce perioperative cardiac morbidity. Because postoperative tachycardia and catecholamine surges probably promote myocardial ischemia and/or rupture of coronary plaque, and because postoperative pain can produce tachycardia and increase catecholamines, effective postoperative analgesia may reduce cardiac complications. Postoperative analgesia may also reduce the hypercoagulable state. Epidural anesthesia may decrease platelet aggregability compared with general anesthesia. Whether this decrease relates to intraoperative or postoperative management is unclear. In an analysis of Medicare claims data, the use of epidural analgesia (as determined by billing codes for postoperative epidural pain management) was associated with decreased risk for death at 7 days. As previously noted, regional anesthesia may be advantageous for postoperative pain relief. Future research will focus on how best to deliver postoperative analgesia to maximize the potential benefits and reduce complications.[14]

Surveillance and Implications of Perioperative Cardiac Complications

The optimal and most cost-effective strategy for monitoring high-risk patients for major morbidity after noncardiac surgery is unknown. Myocardial ischemia and infarctions that occur postoperatively are usually silent, most likely because of the confounding effects of analgesics and postoperative surgical pain. Intraoperative hypotension confers a fourfold increase in the risk of troponin elevation.[6] Most perioperative MIs do not cause ST-segment elevation, and less specific ST-T wave changes are common after surgery with or without MI. These considerations therefore render the diagnosis of perioperative MI particularly difficult to make.

A marked elevation in mortality associated with postoperative MI provides continuing impetus for improved methods of detection. Biomarkers may help identify myocardial necrosis. Lee and colleagues found that troponin T had similar efficacy as creatine kinase (CK) MB in diagnosing perioperative MI but significantly better correlation with major cardiac complications developing after acute MI. Mohler and

colleagues evaluated troponin I (cTnI) and CK-MB in 784 high-risk vascular surgery patients on the day of surgery and at 24 hours, 72 hours, and 120 hours postoperatively. They reported a sensitivity of 51% and a specificity of 91% for the defined cardiovascular event by using a receiver operating characteristic (ROC)–defined cutoff point for CK-MB of 3.1 ng/mL.

In the VISION (Vascular Events in Noncardiac Surgery Cohort Evaluation) study, 15,133 participants undergoing noncardiac surgery had troponin T measurements performed between 6 and 12 hours postoperatively and on postoperative days 1, 2, and 3.[4] Troponin T levels above the baseline level of 0.01 ng/mL or lower were associated with increased rates of 30-day mortality. Indeed, a troponin T level of 0.02 ng/mL was associated with more than a twofold risk for death. With a troponin T level of 0.3 ng/mL or higher, the hazard ratio for death increased to more than 10-fold above that in patients without any elevation in troponin. Mortality was 16.9% with a troponin T level of 0.3 ng/mL or higher, versus 1% in the group without troponin elevation. Although troponin T levels stratified the rate of mortality across a low spectrum of positive levels, it could not predict the cause of death. Both vascular and nonvascular death increased similarly with increasing troponin T levels, and more than half of all deaths were from nonvascular causes. An elevated troponin T level thus provides adverse prognostication without direction for appropriate therapy.

Three important points can be made from these data: First, noncardiovascular causes of mortality outnumber cardiovascular causes, indicating important new areas for research. Second, even if there is evidence of troponin elevation, the death is remote from the event, suggesting it is not an immediate cause but a marker of illness. Third, true type 1 MI is rare. In the POISE trial, 7521 participants were screened to find 697 (9.2%) with troponin elevations, but only two individuals of the total cohort were referred for coronary revascularization.[16] In our opinion, troponin measurement should be avoided in the asymptomatic patient without hemodynamic embarrassment or ischemic ECG change. Troponin elevations in this setting provide neither diagnostic direction nor specific management to implement. Should future trials identify management strategies for troponin elevations, we would reconsider routine troponin measurement in high-risk patients.

Several studies have evaluated brain (B-type) natriuretic peptide (BNP) in the perioperative period. In a meta-analysis of seven prospective observational studies, BNP or N-terminal (NT)–pro-BNP above the ROC-determined optimal threshold was associated with marked increases in 30-day and intermediate-term cardiac death, nonfatal MI, and major adverse cardiac events. One meta-analysis demonstrated that preoperative BNP measurement independently predicted perioperative cardiovascular events in studies that considered only the outcomes of death, cardiovascular death, or MI (odds ratio [OR], 44.2; 95% CI, 7.6 to 257.0; I[2] = 51.6%), and in studies that included other outcomes, the OR was 14.7 (95% CI, 5.7 to 38.2; I[2] = 62.2%). A subsequent meta-analysis showed that the addition of postoperative BNP measurements to a risk prediction model of 30-day death and MI had a net reclassification index of 20%. Moreover, elevated postoperative BNP increased the rate of death and MI by 3.7-fold.[17]

Traditionally, perioperative MI has been associated with 30% to 50% short-term mortality, but recent series have reported a fatality rate of less than 20% for perioperative MI. Studies from the 1980s suggested a peak incidence on the second and third postoperative days. Badner and colleagues, using troponin I as a marker for MI, suggested that the highest incidence occurred during the immediate and first postoperative days, as confirmed in other studies. The finding that hypotension in the postanesthetic care unit best predicted release of troponin suggests a hemodynamic consequence rather than plaque rupture event (type 2 versus type 1 MI). Thus the change is probably related to more robust surveillance methods, not to a fundamental shift in how or when myocardial ischemia or infarction occurs.

Increasing evidence has associated perioperative MI or biomarker elevation with worse long-term

outcome. Oberweis and colleagues[18] studied 3050 patients who underwent orthopedic surgery. Of the 179 in whom myocardial necrosis occurred, mortality was 16.8% in patients with biomarker elevation at a mean follow-up of 3 years compared to 5.8% in patients without elevation.[18] Landesberg and coworkers, as cited in the guidelines, demonstrated that postoperative CK-MB and troponin, even at low cutoff levels, are independent and complementary predictors of long-term mortality after major vascular surgery. Mahla and colleagues have also shown that elevations in BNP are associated with a fivefold increased long-term risk for cardiac events. The appropriate use of screening biomarkers in current preoperative risk assessment algorithms remains unstudied because there is no evidence-based intervention to apply in response to a biomarker elevation.

Recent evidence has suggested that biomarker elevation before surgery identifies a population at particularly high risk. Maile and coworkers reviewed 6030 patients with troponin measured in the 30 days before nonemergent noncardiac surgery and found a 30-day mortality of 4.7% in the group without detectable troponin levels, but a 12.7% mortality in the group with the highest tercile of troponin elevation. The closer in time that an elevated troponin was drawn to the date of surgery, the higher the risk. Similar results are reported with BNP. A meta-analysis of 15 studies reported that preoperative BNP elevation was associated with approximately a 20-fold increase in major adverse cardiovascular events, ninefold increase in all-cause mortality, and 24-fold increase in cardiac death. These data suggest future avenues for identification of high-risk noncardiac surgical patients in the study of risk reduction therapies.

Strategies to Reduce the Cardiac Risk Associated With Noncardiac Surgery

Coronary Artery Revascularization

The treatment of patients before noncardiac surgery should follow the same trajectory in the absence of impending surgery. Over optimum medical treatment, coronary revascularization in stable patients has limited value.[19] Despite this evidence and recent data that the postoperative incidence of type 1 MI requiring revascularization is 0.3% to 0.5%,[15,16] some have suggested coronary revascularization as a means of reducing the perioperative risk related to noncardiac surgery. This view is derived from retrospective evidence such as the Coronary Artery Surgery Study (CASS) registry, which enrolled patients from 1978 to 1981, an era that antedates almost all the current therapies shown to be effective for reducing coronary events. This observational analysis did not randomly assign patients, however, and reflects a different era in preventive strategies and higher rates of adverse outcomes after noncardiac surgery.

Several cohort studies have examined the benefit of percutaneous coronary intervention (PCI) before noncardiac surgery. Posner and colleagues, as cited in the guidelines, used an administrative dataset of patients who underwent PCI and noncardiac surgery.[2] They matched patients with coronary disease undergoing noncardiac surgery with and without previous PCI and examined cardiac complications. In this nonrandomized analysis, they noted a significantly lower rate of 30-day cardiac complications in patients who underwent PCI at least 90 days before the noncardiac surgery. PCI within 90 days of noncardiac surgery did not improve outcomes. The advent of drug-eluting stents requiring prolonged antiplatelet therapy may promote operative bleeding complications or increase subacute stent thrombosis if antiplatelet treatment is stopped perioperatively.

Several randomized trials have now addressed the value of both CABG and PCI in a subset of patients.

McFalls and coauthors reported the results of a multicenter randomized trial in the Veterans Affairs Health System in which patients with documented CAD on coronary angiography, excluding those with left main coronary artery disease or a severely depressed ejection fraction (≤20%), were randomly assigned before elective major vascular surgery to CABG (59%) or PCI (41%) versus routine medical therapy. At 2.7 years after randomization, mortality in the revascularization group did not differ significantly (22%) from that in the no-revascularization group (23%). Within 30 days after the vascular operation, postoperative MI, defined as elevated troponin levels, occurred in 12% of the revascularization group and in 14% of the no-revascularization group ($P = 0.37$). The authors suggested that coronary revascularization is not indicated in patients with stable CAD and that PCI or CABG for one- or two-vessel disease before noncardiac surgery does not prevent perioperative MI. A reanalysis of the data found that the completeness of revascularization affects the rate of perioperative MI, with CABG being more effective than PCI. Most recently, Garcia and colleagues analyzed both randomly and nonrandomly assigned patients who underwent coronary angiography before vascular surgery in the CARP trial registry; 4.6% of these patients had unprotected left main CAD. Only this subset of patients showed a benefit of preoperative coronary artery revascularization.

Monaco and associates studied 208 patients at moderate clinical risk who underwent major vascular surgery and were randomly allocated to either a “selective strategy” group, in whom coronary angiography was performed on the basis of noninvasive test results, or to a “systematic strategy” group, in whom preoperative coronary angiography was systematically performed. The strategy of routine coronary angiography had no effect on the short-term outcome, but the long-term outcome was improved in surgical patients with peripheral arterial disease at medium to high risk.

One issue in interpreting the results is that the length of time between coronary revascularization and noncardiac surgery most likely affects its protective effect and potential risks. Back and colleagues studied 425 consecutive patients undergoing 481 elective major vascular operations at an academic Veterans Affairs Medical Center. Coronary revascularization was classified as “recent” (CABG, <1 year; percutaneous transluminal coronary angioplasty [PTCA], <6 months) in 35 cases, as “previous” (CABG, 1 to 5 years; PTCA, 6 months to 2 years) in 45 cases, and as “remote” (CABG, >5 years; PTCA, >2 years) in 48 cases. Patients with previous PTCA had similar outcomes as those after CABG. Significant differences in adverse cardiac events and mortality were found between patients with CABG performed within 5 years or PTCA within 2 years (6.3% and 1.3%, respectively), individuals with remote revascularization (10.4% and 6.3%, respectively), and nonrevascularized patients stratified at high risk (13.3% and 3.3%, respectively) or intermediate to low risk (2.8% and 0.9%, respectively). The authors concluded that previous coronary revascularization (CABG, <5 years; PTCA, <2 years) provides only modest protection against adverse cardiac events and mortality following major arterial reconstruction.

In our opinion, the randomized controlled trials provide strong evidence of the limited benefit in preoperative coronary artery revascularization to reduce cardiovascular risk. In the absence of unusual circumstances, percutaneous and surgical revascularization should not be pursued before noncardiac surgery.

Coronary Stenting and Noncardiac Surgery

PCI using coronary stenting poses several special issues.[20] Kaluza and colleagues reported the outcome of 40 patients who underwent prophylactic coronary stent placement less than 6 weeks before major noncardiac surgery requiring general anesthesia. They reported seven MIs, 11 major bleeding episodes, and eight deaths. All the deaths and MIs, as well as 8 of the 11 bleeding episodes, occurred in patients subjected to surgery less than 14 days after stenting. Four patients died after undergoing surgery 1 day

after stenting. Wilson and colleagues, as cited in the guidelines, reported on 207 patients in whom noncardiac surgery was performed within 2 months of stent placement. Eight patients died or had an MI, and all of them were among the 168 patients who underwent surgery 6 weeks after stent placement. Vincenzi and coworkers studied 103 patients and reported that the risk for a perioperative cardiac event was 2.11-fold greater in patients with recent stents (<35 days before surgery) than in those undergoing PCI more than 90 days before surgery. These data point to the importance of delaying surgery after stenting, even though the investigators either continued antiplatelet drug therapy or only briefly interrupted it, and all patients received heparin.

Drug-eluting stents may represent an even greater problem during the perioperative period. Emerging data from a series of recent analyses in the nonoperative setting and several perioperative case reports suggest that the risk for thrombosis continues for at least 1 year after insertion. Several reports suggest that drug-eluting stents may represent an additional risk over a prolonged period (up to 12 months), particularly if the use of antiplatelet agents is discontinued.

Schouten's group retrospectively evaluated 192 patients who underwent noncardiac surgery after successful PCI for unstable CAD within 2 years of the procedure. Drug-eluting stents accounted for 52% of the stents placed. Of the 192 patients, 30 underwent surgery before the recommended discontinuation of dual-antiplatelet therapy for the particular stent (30 days for bare-metal stents and up to 6 months for sirolimus-eluting stents). In patients in whom antiplatelet therapy was stopped before the required time for use of clopidogrel (early-surgery group), the incidence of death or nonfatal MI was 30.7% compared with 0% in patients who continued antiplatelet therapy. The elevated risk for stent thrombosis and cardiovascular events, however, seems to abate over time. In the EVENT (Evaluation of Drug-Eluting Stents and Ischemic Events) registry of 4637 consecutive patients, 4.4% underwent major noncardiac surgery in the ensuing year. A relative 27-fold increased rate of cardiovascular events occurred in the week after surgery versus any other week after stent implantation, but the absolute rate was only 1.9%.

Wijeysundera and colleagues[21] evaluated 8116 patients who underwent noncardiac surgery in Ontario, Canada, and found that 34% had a coronary stent implanted within the 2 years before surgery. Drug-eluting stents represented one third of the stents placed. Patients with bare-metal stents implanted less than 45 days before surgery had a 6.7% cardiovascular event rate, which dropped to 2.6% with a stent implanted 45 to 180 days before surgery. Patients with a drug-eluting stent had a 20.2% cardiovascular event rate in the first 45 days after stent implantation, and the rate became similar to that in patients without stenting when the stent was implanted more than 180 days before surgery. Bangalore and colleagues[22] studied the impact of drug-eluting stents compared with bare-metal stents placed preoperatively in 8415 patients in Massachusetts. In this cohort the death, MI, and bleeding event rate was 8.6% in the first 30 days after PCI, dropping to 5.2% when surgery was performed more than 90 days after coronary revascularization. Using propensity matching to compare the bare-metal stent and drug-eluting stent populations, the death and MI rate was higher in the bare-metal stent cohort.

In a Scotland-wide retrospective cohort analysis, perioperative death and ischemic cardiac events were much more common within the first 6 weeks after stent implantation than after 6 weeks, 42.4% versus 12.8%, respectively. Forty-five percent of the revascularizations in this cohort were performed for an acute coronary syndrome, increasing the baseline risk of the cohort. The event rate was higher in patients who underwent revascularization because of acute coronary syndromes within 6 weeks, in whom it reached 65%. In contrast to other reports, no temporal differences were noted between the bare-metal and drug-eluting stent groups.

Data from more recent large observational studies suggest that the time frame of increased risk of stent thrombosis is on the order of 6 months, regardless of stent type (bare metal or drug eluting). In a large

cohort of patients from the Veterans Health Administration hospitals, the increased risk of surgery for the 6 months after stent placement was most pronounced in patients in whom the indication for PCI was an MI.[23,24]

In 2016, ACC/AHA published a focused update on duration of dual-antiplatelet therapy in CAD patients, including revising the perioperative guidelines.[20] The current recommendations for delay after coronary stent placement include 30 days for bare-metal stent implantation and 6 months after drug-eluting stent placement (**Fig. 11.3**). The guidelines writing committee noted that elective noncardiac surgery may be considered more than 180 days after drug-eluting stent implantation if the risk of delay is thought to be greater than the risk of stent thrombosis. The guideline committee gave a class IIb recommendation that elective surgery may be considered after 3 months for patients in whom the P2Y12 inhibitor needs to be discontinued if further delay of surgery is greater than the risk of stent thrombosis. In patients with illness requiring more timely surgery, strategies for bridging the cessation of antiplatelet therapy until the procedure include the use of IV eptifibatide and tirofiban, but these strategies lack outcomes data.

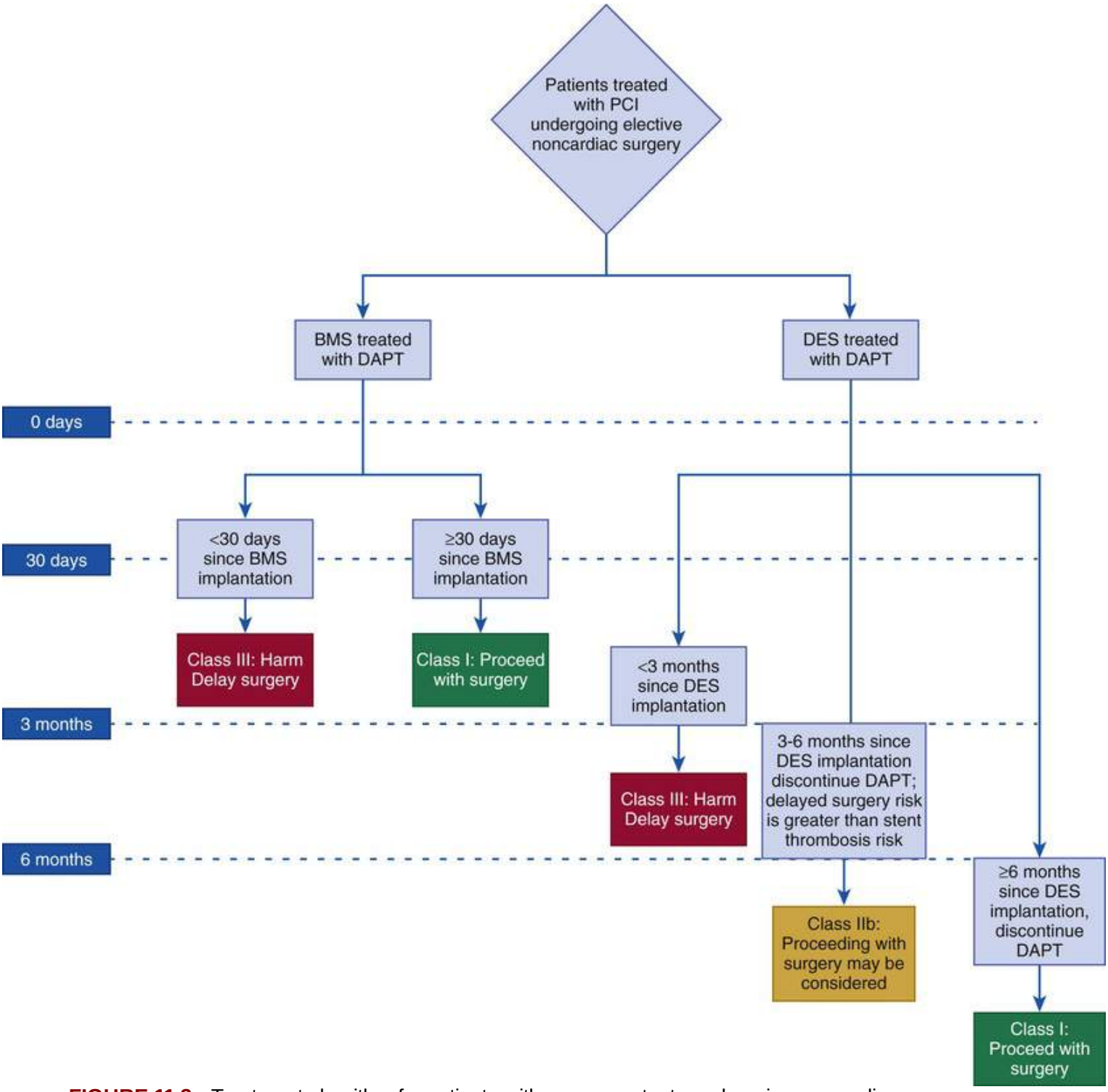

FIGURE 11.3 Treatment algorithm for patients with coronary stents undergoing noncardiac surgery. *BMS,* Bare metal stent; *DAPT,* dual-antiplatelet therapy; *DES,* drug-eluting stent; *PCI,* percutaneous coronary intervention. (From Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082-115.)

Pharmacologic Interventions

Beta-Adrenergic Blocking Agents

Beta-adrenergic blocking agents have undergone extensive study in perioperative risk management. As noted earlier, some of the trial data used to support recent recommendations on the titrated use of beta blockers from Poldermans and colleagues have become uncertain. A recent meta-analysis of all the beta-

blocker trials demonstrates that beta blockers decrease nonfatal MI but increase stroke and death.[25] As a result, ACC/AHA guidelines suggest that perioperative beta blockers can be considered on a case-by-case basis in patients with significant myocardial ischemia, three or more RCRI risk factors, or a compelling long-term indication for beta blockers. Aggregate impact of beta blockers seems to be low. Of the more than 10,000 participants in the trials, 75 nonfatal MIs were prevented and 19 strokes and 35 deaths instigated (**Table 11.4**).

TABLE 11.4

Recommendations for Perioperative Therapy with Beta Blockers

Class I
• Continue beta blockers in patients who are receiving beta blockers chronically.
Class IIa
• Guide management of beta blockers after surgery by clinical circumstances.
Class IIb
• In patients with intermediate- or high-risk preoperative tests, it may be reasonable to begin beta blockers. • In patients with ≥3 Revised Cardiac Risk Index (RCRI) factors, it may be reasonable to begin beta blockers before surgery. • Initiating beta blockers in the perioperative setting as an approach to reduce perioperative risk is of uncertain benefit in those with a long-term indication but no other RCRI risk factors.* • It may be reasonable to begin perioperative beta blockers long enough in advance to assess safety and tolerability, preferably >1 day before surgery.
Class III
• Beta-blocker therapy should not be started on the day of surgery

*Clinical risk factors include a history of ischemic heart disease, history of compensated or previous heart failure, history of cerebrovascular disease, diabetes mellitus, and renal insufficiency (defined in the RCRI as a preoperative serum creatinine level of 2 mg/dL).

From Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e77-137.

Most of these trials did not titrate beta blockers in the same manner as they are used in other conditions, such as heart failure or hypertension. For example, in the POISE trial, Devereaux and colleagues randomly assigned 8351 high-risk patients undergoing noncardiac surgery to metoprolol succinate, 200 mg daily, or matching placebo. The use of high-dose, long-acting medications may have worsened outcomes by limiting the physician's flexibility to modify treatment on the basis of the rapidly shifting perioperative environment. Other trials used lower doses without titration to hemodynamic parameters as well. Administration of beta blockers as performed in the clinical trials clearly does not provide a benefit sufficient for their routine use.

Current guidelines suggest that beta blockade may be reasonable in patients with intermediate- or high-risk myocardial ischemia reported in preoperative noninvasive testing or patients with three or more RCRI risk factors, although there is no direct evidence to support routine use even in this higher-risk population.[1] If beta blockers are to be used, it is recommended that initiation begin 1 day or more before surgery. Initiation on the day of surgery has been associated with an increase in stroke and mortality.[26] In hospital, short-acting oral or IV beta blockers should be used to permit titration to hemodynamics. No specific blood pressure or heart rate targets have been validated, although blood pressure control to less than 140/90 mm Hg and heart rates of 60 to 80 beats/min may be reasonable when beta blockers are used.

Statin Therapy

Statins are routinely recommended for patients with atherosclerosis and diabetes (**see Chapters 45 and 48**). Their role in surgery is less well defined. In a retrospective analysis of 750 patients, 10% of whom had the composite outcome (30-day death, MI, and AF), statin use was associated with a 45% reduction in adverse events, including a 5% absolute reduction in 30-day mortality. In addition to their cholesterol-

lowering properties, statins have anti-inflammatory actions that may provide benefit as well. In an NSQIP study of 7777 patients undergoing various surgeries, statin use was associated with reductions in noncardiac events, including a 47% reduction in respiratory complications, 59% reduction in VTE, and 35% reduction in infectious complications.[27] The evidence suggests that statin therapy should be continued during the perioperative period. Le Manach and associates evaluated the effect of statin discontinuation in a vascular surgery population. When compared with a control population, discontinuation of statins was associated with more than a twofold increase in troponin elevation, whereas continuation reduced the rate of troponin release by more than 40%. In patients already receiving statins, a prospective randomized trial of 500 patients with stable CAD about to undergo emergency surgery randomly received placebo or atorvastatin (80 mg) 2 hours before surgery. In the group who received the statin, cardiac death, MI, or unplanned revascularization occurred in 2.4% of patients compared with 8% in the placebo arm.[28] Indeed, starting statin therapy should be considered in patients who meet ACC/AHA lipid guideline recommendations and in high-risk patients, because they probably merit this treatment even without surgery.

Perioperative Ischemic Evaluation 2 (POISE 2), a blind randomized trial with a 2 × 2 factorial design, allowed separate evaluation of low-dose clonidine versus placebo and low-dose aspirin versus placebo in 10,010 patients with, or at risk for, atherosclerotic disease who were undergoing noncardiac surgery. Low-dose clonidine did not reduce the rate of death or nonfatal MI but was associated with an increased risk of clinically important hypotension and nonfatal cardiac arrest.[29] Administration of aspirin was not associated with any difference in the rate of death or nonfatal MI but increased the risk of major bleeding.[30]

Two small randomized trials have evaluated the potential protective effect of prophylactic nitroglycerin in reducing perioperative cardiac complications after noncardiac surgery. Neither established a benefit for the prophylactic use of nitroglycerin. Because prophylactic nitroglycerin has considerable hemodynamic effects and is not known to prevent MI or cardiac death, the data do not support its routine use.

One large trial currently in progress may affect the management of patients during noncardiac surgery in the near future. The Management of Myocardial Injury after Noncardiac Surgery Trial (MANAGE) has a 2 × 2 factorial design testing the efficacy of dabigatran and omeprazole in patients undergoing noncardiac surgery who develop an elevated troponin or CK-MB level with evidence of an ischemic event or no alternative explanation for biomarker elevation.

Nonpharmacologic Interventions

Temperature

Frank and colleagues, as cited in the guidelines, completed a randomized trial of regional versus general anesthesia for lower extremity vascular bypass procedures and noted an association between hypothermia (temperature <35°C) and myocardial ischemia. They subsequently performed a trial in 300 high-risk patients undergoing a diverse range of intermediate- and high-risk procedures and randomly assigned to maintenance of normothermia or routine care. They observed a significantly reduced incidence of perioperative cardiac morbidity and mortality within 24 hours of surgery in the normothermic group.

Electrocardiographic, Hemodynamic, and Echocardiographic Monitoring

Multiple studies have demonstrated the predictive value of correlating perioperative ST-segment changes

and major cardiac events, as described earlier. Furthermore, the duration (cumulative or continuous) of perioperative ST changes strongly predicts poor outcomes. ST-segment monitoring has therefore become standard during the intraoperative and ICU periods for high-risk patients. However, ST-segment changes may also develop in patients at low to moderate risk. These changes may not reflect true myocardial ischemia, as suggested in a recent series.

Postoperative patients may have the greatest risk for a cardiac event when on the ward and unmonitored. Few studies have tested the efficacy of ST-segment telemetric monitoring during the perioperative period. The issue of whether early treatment of prolonged ST-segment changes improves outcomes in this situation remains unresolved.

Much controversy surrounds the value of pulmonary artery (PA) catheterization for noncardiac surgery. Several small, randomized trials did not demonstrate a significant reduction in major cardiac morbidity and mortality in patients so monitored during aortic surgery. In a large-scale cohort study, Polanczyk and colleagues[31] found that patients with PA catheters who were matched to those without catheters by a propensity score also failed to demonstrate significant benefit. In fact, they observed an increased incidence of congestive heart failure and untoward noncardiac outcomes in the catheter group. A total of 1994 patients were randomly allocated to goal-directed therapy guided by a PA catheter or to standard care without the use of a PA catheter in patients undergoing urgent or elective major surgery. No difference in survival occurred, but pulmonary embolism developed at a higher rate in the catheter group than in the standard-care group. Current evidence therefore does not support the routine use of PA catheterization for high-risk patients undergoing major noncardiac surgery. Determining whether these results apply to the high-risk vascular surgical population and whether use of a PA catheter provides benefit in specific clinical situations will require further work.

Transesophageal echocardiography (TEE) represents another means of assessing intraoperative cardiac function. This tool sensitively monitors intraoperative wall motion abnormalities and fluid status. In patients undergoing aortic cross-clamping, TEE showed significantly better sensitivity in detecting intraoperative ischemia than electrocardiographic monitoring. For noncardiac surgery, a study of TEE, 2-lead electrocardiography, and 12-lead electrocardiography demonstrated minimal additive value of TEE over 2-lead electrocardiography. TEE monitoring may nonetheless prove valuable in guiding treatment in patients with unstable hemodynamics who have uncertain fluid status and myocardial function.

Transfusion Threshold

Much controversy surrounds the optimal hemoglobin level at which transfusion is indicated in high-risk noncardiac surgical patients. No randomized trials have evaluated the optimal transfusion threshold, although much anecdotal evidence exists. A large-scale trial of transfusion triggers in the ICU did not document increased morbidity or mortality when a hemoglobin concentration lower than 7 g/dL was used as a transfusion threshold, but trends toward increased morbidity emerged in the subset of patients with ischemic heart disease. In the FOCUS (Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair) trial, Carson and colleagues[32] randomly assigned hip fracture patients to a liberal transfusion strategy (hemoglobin threshold of 10 g/dL) or a restrictive transfusion strategy (symptoms of anemia or at physician's discretion for hemoglobin level <8 g/dL). A liberal transfusion strategy, compared with a restrictive strategy, did not reduce rates of death or inability to walk independently on 60-day follow-up and did not reduce in-hospital morbidity in elderly patients at high cardiovascular risk. The impact of transfusion may depend on the severity of the precipitating anemia. Smilowitz and coworkers[33] followed 3050 patients after orthopedic surgery. In this cohort the presence of anemia, hemorrhage, and transfusion were independently associated with long-term

mortality. Interestingly, the effect of transfusion was attenuated by the severity of anemia. For patients with no anemia, transfusion increased the hazard ratio (HR) 4.4-fold; for those with mild anemia, HR was only 2.3-fold; and for those with moderate/severe anemia (hemoglobin <11 g/dL), there was benefit, with HR of 0.81. These data suggest a restrictive policy of transfusion may be the most beneficial for patients undergoing noncardiac surgery.

Conclusion

Three trends are notable in the perioperative management of patients undergoing noncardiac surgery: (1) the rate of myocardial infarction and cardiovascular death are declining; (2) noncardiovascular death now accounts for the majority of perioperative mortality; and (3) the evidence base supporting current management practices continues to grow rapidly. As overall mortality risk declines over time, the future goal of preoperative assessment will be to identify patients at clinically inapparent increased risk and devise and test interventions to reduce this risk. Additionally, preoperative risk assessment will increasingly serve to determine if the long-term benefits of surgery outweigh the perioperative risks. The predictive value of biomarkers and treatment of biomarker elevations, novel medications, and presurgical rehabilitation (prehabilitation) are currently under investigation and may represent the next frontier in perioperative management.

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We refer the reader to older references mentioned in the text to the bibliography of the guideline cited in reference 1 below..

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12

Electrocardiography

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The technology and the clinical value of the electrocardiogram (ECG) have continuously evolved since the invention of the string galvanometer by Einthoven in 1901. By 1910, the ECG had emerged from the research laboratory into the clinic and soon became the most commonly used cardiac diagnostic test. Although other techniques have evolved to assess cardiac structure and mechanical function, the ECG remains the fundamental method to assess the heart's electrical activity. This chapter outlines the criteria for and the utility of the most common ECG diagnoses in adults.

Fundamental Principles

The ECG is the final outcome of a complex series of physiologic and technologic processes. First, transmembrane ionic currents are generated by ion fluxes across cell membranes and between adjacent cells (**see Chapter 34**). These currents are synchronized during cardiac activation and recovery sequences to generate a physiologically meaningful time-varying electrical field in and around the heart. This field is altered as it passes through numerous other structures, including the lungs, blood, and skeletal muscle.

Electrodes placed in specific locations on the extremities and torso detect the currents reaching the skin. These electrodes (sensors) are configured to produce leads (also called “derivations”). The outputs of these leads are then amplified, filtered, digitized, stored, and displayed to produce an electrocardiographic (ECG) recording. These signals are typically processed by pattern recognition software to provide a preliminary interpretation, subject to careful clinician review.

Genesis of Cardiac Electrical Fields

Ionic Currents and Cardiac Electrical Fields During Activation.

Transmembrane ionic currents (**see Chapter 34**) are ultimately responsible for the potentials recorded as an ECG. As sites along a cardiac fiber are activated, the polarity of the transmembrane potential converts from negative to positive, as represented in the typical cardiac action potential. Thus, sites on a cardiac fiber that have already undergone excitation have positive transmembrane potentials (i.e., the inside of the cell is positive relative to the outside of the cell), whereas more distal sites still in a resting state have negative transmembrane potentials (i.e., the inside of the cell is negative relative to the outside).

This reversal of polarity along a fiber creates a flow of positively charged current from the already activated to the more distal, inactivated portions of the fiber. As activation of multiple adjacent fibers proceeds, an activation *wavefront* is produced that moves in the direction of activation and that generates an electrical field characterized by positive potentials ahead of the front and negative potentials behind it.

An electrode senses positive potentials when an activation front is moving toward it and senses negative potentials when the activation front is moving away from it. The magnitude of the potential recorded by an electrode at any site is directly proportional to the average rate of change of intracellular potential, as determined by action potential shapes; directly proportional to the size of the wavefront; inversely proportional to the square of the distance from the activation front to the recording site; and

directly proportional to the cosine of the angle between the direction of activation spread and a line drawn from the site of activation to the recording site. Thus, if activation proceeds directly toward an electrode such that the angle between the direction of activation to the location of the electrode equals zero (and its cosine equals 1), the voltage sensed by the electrode will be maximal. In contrast, if activation proceeds in a direction perpendicular to that direction (cosine equals 0), the sensed potential will be zero.

Cardiac Electrical Field Generation During Recovery.

The cardiac electrical field during recovery phases differs in several important ways from that during activation. First, the gradient of intercellular potentials and thus the direction of current flow during recovery are the opposite of those described for activation. As a cell undergoes recovery, its intracellular potential becomes progressively more negative. For a cardiac fiber, the intracellular potential of the region whose recovery has progressed further is more negative than that of the adjacent, less recovered region. Intracellular currents then flow from the less recovered toward the more recovered portion of the fiber. That is, recovery wavefronts will have an orientation opposite that of activation wavefronts.

The strength of the recovery front also differs from that of the activation front. As noted, the strength of a wavefront is proportional to the rate of change in transmembrane potential. Rates of change in transmembrane potential during the recovery phases of the action potential are considerably slower than during activation, and thus the strength of the recovery wavefronts during recovery is less than during activation.

The rate of movement of the activation and recovery wavefronts is a third difference between activation and recovery. Activation is rapid (as short as 1 millisecond in duration) and occurs over only a small distance along the fiber. Recovery, by contrast, lasts 100 milliseconds or longer and occurs simultaneously over extensive portions of the heart.

These features result in ECG differences between activation and recovery patterns. All other factors being equal (an assumption that often is not true, as described later), ECG waveforms generated during recovery of a fiber with uniform recovery properties would be of opposite polarity, lower amplitude, and longer duration than those generated by activation.

Role of Transmission Factors.

The activation and recovery fields are perturbed by the complex three-dimensional physical environment in which they are generated. These transmission factors include the biophysical characteristics of the heart itself as well as those of the surrounding organs and tissues.

The most important *cardiac factor* is the presence of connective tissue between cardiac fibers that disrupts efficient electrical coupling of adjacent fibers. Waveforms recorded from fibers with little or no intervening connective tissue are narrow in width and smooth in contour, whereas those recorded from tissues with abnormal fibrosis are prolonged and sometimes exhibit prominent notching.

Extracardiac factors include the effects of all the tissues and structures that lie between the activation region and the body surface, including intracardiac blood, lungs, skeletal muscle, subcutaneous fat, and skin. These tissues alter the intensity and the orientation of the cardiac field because of differences in the electrical resistivity of adjacent tissues within the torso. For example, intracardiac blood has much lower resistivity (approximately 160 Ω cm) than the lungs (~2150 Ω cm).

Physical factors also reflect basic laws of physics. Potential magnitudes change in proportion to the square of the distance between the heart and recording electrode. One consequence of this principle is that eccentricity of the heart within the chest affects the surface waveforms. The right ventricle and

anteroseptal aspect of the left ventricle are closer to the anterior chest wall than are other parts of the left ventricle and atria. Therefore, ECG potentials will be higher on the anterior than on the posterior chest, and the amplitudes of waveforms projected from the anterior left ventricle to the chest wall will be greater than those generated by posterior regions.

An additional physical factor affecting the recording of cardiac signals is *cancellation*. When two or more wavefronts are simultaneously active during activation (or repolarization) and have different orientations, the vectorial components of the wavefronts may augment (if oriented in the same directions) or cancel (if oriented in opposite directions) each other when viewed from remote electrode positions. The magnitude of this effect is substantial. During the inscription of both the QRS and the ST-T waves, as much as 90% of cardiac activity is obscured by cancellation effects.

As a result of these transmission factors, body surface potentials (1) have an amplitude of only 1% of the amplitude of transmembrane potentials, (2) are smoothed in detail so that they have only a general spatial relationship to the underlying cardiac events, (3) preferentially reflect electrical activity in some cardiac regions over others, and (4) represent only limited amounts of total cardiac electrical activity.

Recording Electrodes and Leads Systems

Electrode Characteristics.

The standard clinical ECG is recorded from electrodes placed on each of the four extremities and six placed on the chest.[1] These electrodes are connected to form *leads* that record the potential difference between two electrodes. One electrode is designated as the positive input. The potential at the other (negative) electrode is subtracted from the potential at the positive electrode to yield the *bipolar potential*. The actual potential at either electrode is not known; only the difference between them is recorded.

In some cases, as described later, multiple electrodes are electrically connected together to form the negative member of the bipolar pair. This electrode network is commonly referred to as a *compound* or *reference electrode*. The lead then records the potential difference between a single electrode serving as the positive input (the *exploring electrode*) and the potential in the reference electrode.

The clinical ECG is performed using 12 leads: three standard *limb leads* (leads I, II, and III), six *precordial leads* (leads V_1 through V_6), and three *augmented limb leads* (leads aVR, aVL, and aVF). Specifics of electrode placement and definitions of the positive and negative inputs for each lead are presented in **Table 12.1**.

TABLE 12.1

Location of Electrodes and Lead Connections for the Standard 12-Lead ECG and Additional Leads

LEAD TYPE	POSITIVE INPUT	NEGATIVE INPUT
Standard Limb Leads*		
I	Left arm	Right arm
II	Left leg	Right arm
III	Left leg	Left arm
Augmented Limb Leads		
aVR	Right arm	Left arm plus left leg
aVL	Left arm	Right arm plus left leg
aVF	Left leg	Left arm plus right arm
Precordial Leads†		
V_1	Right sternal margin, fourth intercostal space	Wilson central terminal
V_2	Left sternal margin, fourth intercostal space	Wilson central terminal
V_3	Midway between V_2 and V_4	Wilson central terminal
V_4	Left midclavicular line, 5th intercostal space	Wilson central terminal
V_5	Left anterior axillary line at same horizontal plane as for V_4 electrode	Wilson central terminal
V_6	Left midaxillary line at same horizontal plane as for V_4 electrode	Wilson central terminal
V_7	Posterior axillary line at same horizontal plane as for V_4 electrode	Wilson central terminal
V_8	Posterior scapular line at same horizontal plane as for V_4 electrode	Wilson central terminal
V_9	Left border of spine at same horizontal plane as for V_4 electrode	Wilson central terminal

*Limb electrodes should be placed near the wrists and ankles or, at a minimum, distal to the shoulders and hips.

†The right-sided precordial leads V_3R to V_6R are placed in mirror-image positions on the right side of the chest.

Standard Limb Leads.

The standard limb leads record the potential differences between two limbs, as detailed in **Table 12.1** and illustrated in **Fig. 12.1 (top)**. Lead I registers the potential difference between the left arm (positive electrode) and right arm (negative electrode); lead II displays the potential difference between the left leg (positive electrode) and right arm (negative electrode); and lead III records the potential difference between the left leg (positive electrode) and left arm (negative electrode). The electrode on the right leg serves as an electronic reference that reduces noise and is not included in these lead configurations.

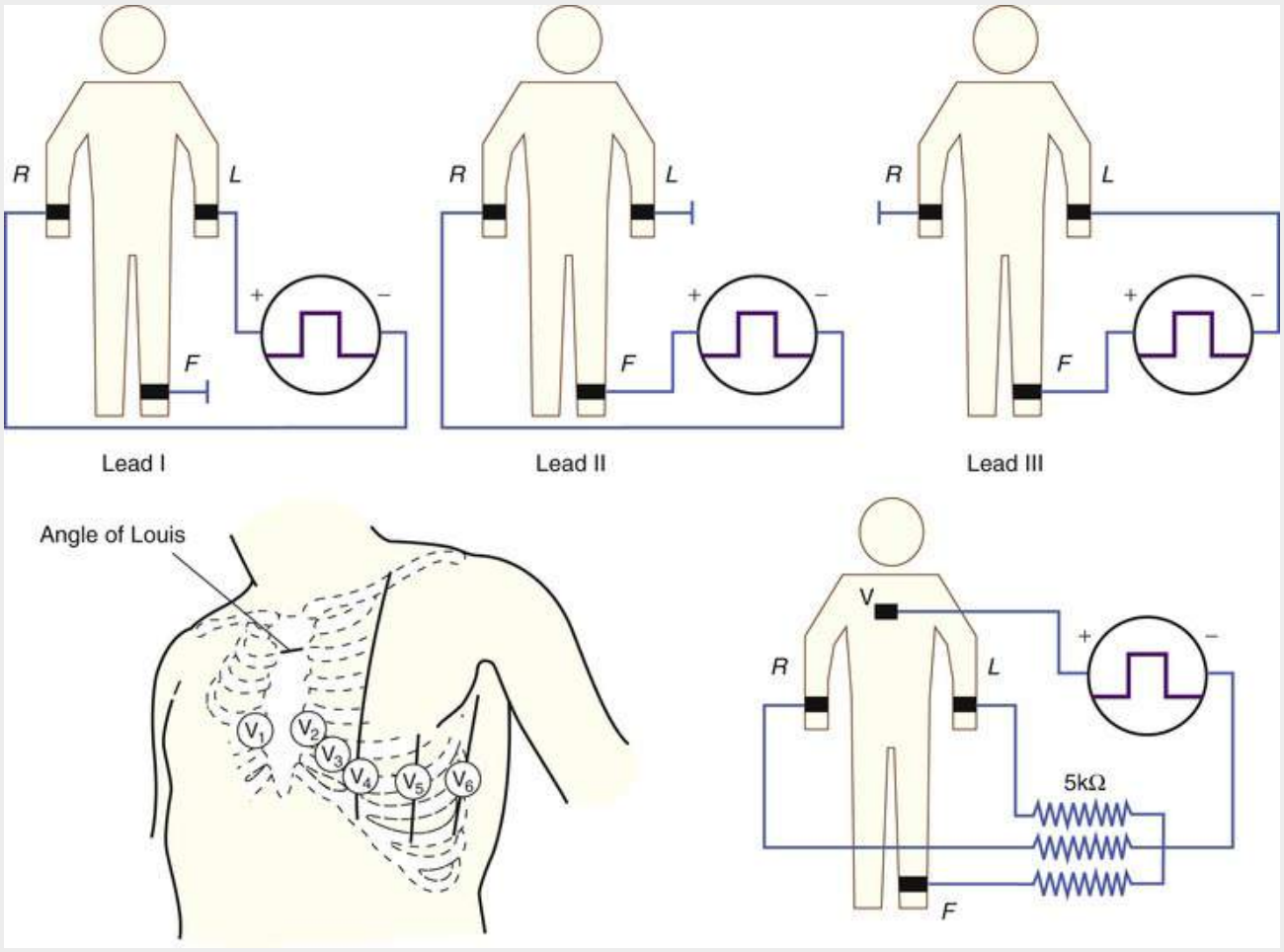

FIGURE 12.1 **Top,** Electrode connections for recording the standard limb leads I, II, and III and the augmented limb leads aVR, aVL, and aVF, with electrodes on the right arm, left arm, and left foot. **Bottom,** Electrode locations and electrical connections for recording a precordial lead. *Left,* The positions of the exploring electrode (V) for the six precordial leads. *Right,* Connections to form the Wilson central terminal for recording a precordial (V) lead. Five-thousand ohm resistors (5kΩ) are connected to each limb electrode when constructing the Wilson central terminal.

The electrical connections for each of these leads can be represented as a vector oriented from its negative toward the positive pole. These vectors form a triangle, known as the *Einthoven triangle,* in which the potential in lead II equals the vectorial sum of potentials sensed in leads I and III, that is:

$$I + III = II$$

Precordial Leads and the Wilson Central Terminal.

The precordial leads register the potential at each of the six specific torso sites (**see Fig. 12.1, bottom left panel**) in relation to a reference potential. For this purpose, an exploring electrode is placed at each of six specific precordial sites and connected to the positive input of the recording system (**see Fig. 12.1, bottom right**). The negative input is the mean value of the potentials recorded at each of the three limb electrodes, referred to as the *Wilson central terminal* (WCT).

The potential in each V lead can be expressed as:

$$V_i = E_i - WCT$$

where

$$WCT = (LA + LL + RA)/3$$

and V_i is the potential recorded in precordial lead i, E_i is the voltage sensed at the exploring electrode for lead V_i, and WCT is the potential in the composite Wilson central terminal.

The potential recorded by the Wilson central terminal remains relatively constant during the cardiac cycle, and the output of a precordial lead is determined predominantly by time-dependent changes in the potential recorded at that site.* Thus the potentials registered by these leads preferentially reflect activity in cardiac regions near the electrode, with lesser contributions by potential generated from more distant cardiac sources.

Augmented Limb Leads.

The three augmented limb leads are designated aVR, aVL, and aVF. For lead aVR, the exploring electrode (**Fig. 12.2**) that forms the positive input is the right arm electrode, for lead aVL it is the left arm electrode, and for aVF it is the left leg electrode. The reference potential for these leads is formed by connecting the two limb electrodes that are not used as the exploring electrode. For lead aVL, for example, the exploring electrode is on the left arm, and the reference electrode is the combined output of the electrodes on the right arm and the left foot.

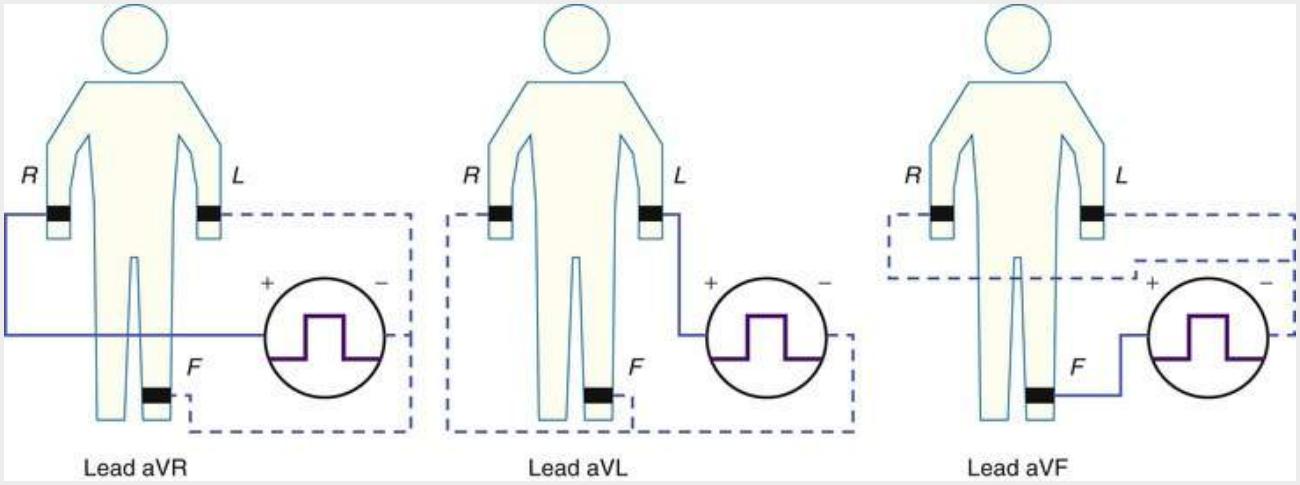

FIGURE 12.2 Electrode locations and electrical connections for recording the augmented limb leads aVR, aVL, and aVF. *Dotted lines* indicate connections to generate the reference electrode potential.

Thus,

$$aVR = RA - (LA + LL)/2$$

$$aVL = LA - (RA + LL)/2$$

and

$$aVF = LL - (RA + LA)/2$$

This modified reference system produces a larger-amplitude signal than if the full Wilson central terminal were used as the reference electrode. When the Wilson central terminal was used, the output was small, in part because the same electrode potential was included in both the exploring and the reference potential inputs. Eliminating this duplication results in a theoretical 50% increase in amplitude.

The three standard limb leads and the three augmented limb leads are aligned in the *frontal plane* of the torso. The six precordial leads are aligned in the *horizontal plane* of the chest.

The 12 leads are usually divided into subgroups corresponding to the cardiac regions to which they may be most sensitive. Various definitions of these groupings have been offered in the literature. For example, anterior lead groups have been defined as including V_1 through V_4 or only V_2 and V_3, and leads I and aVL have been described as being lateral or anterobasal. These designations are nonspecific, and the recommendation of expert committees has been not to use them in ECG interpretation, except in the case of estimating the location of certain types of myocardial infarction.[2]

Other Lead Systems.

Expanded lead systems that are frequently used include recordings from additional electrodes placed on the right precordium to assess right ventricular abnormalities such as right ventricular infarction,[2] and on the left posterior torso (**see Table 12.1**) to detect acute posterolateral infarctions. Electrodes placed higher on the anterior torso than normal may also help detect abnormalities such as the Brugada pattern and its variants (**see Chapters 33 and 37**).

Other lead sets have sought to minimize movement artifacts during exercise and long-term monitoring (**see Chapters 13 and 35**) by placing limb electrodes on the torso rather than near the ankles and wrists as recommended. The resulting waveforms may differ substantially from those recorded from the standard ECG sites with altered QRS and ST-T wave patterns in all 12 leads. These differences change the mean QRS axis and may impact the diagnostic accuracy of criteria of, for example, ventricular hypertrophy and myocardial infarction.[1] Thus these alternative lead sets should not be used to record a diagnostic ECG.

Less frequently used lead systems include those designed to record a *vectorcardiogram* (VCG), which depicts the orientation and strength of a single cardiac vector representing overall cardiac activity throughout the cardiac cycle. Electrode sets including 80 or more electrodes that sense cardiac potentials over large portions of the torso have been used to display the spatial distributions as well as the amplitudes of potentials throughout the cardiac cycle. Also, electrodes may be passed into the esophagus to enhance detection of atrial activity in, for example, the diagnosis of various arrhythmias (**see Chapter 35**).

Hexaxial Reference Frame and the Electrical Axis

Each ECG lead can be represented as a vector, which is referred to as the *lead vector*. As previously noted, for leads I, II, and III, the lead vectors are directed from the negative electrode toward the positive one, as from the right arm to the left arm for lead I (**Fig. 12.3, left**). For an augmented limb and for a precordial lead, the origin of the lead vector passes through the midpoint of the axis connecting the electrodes that comprise the reference electrode. That is, for lead aVL, the vector points from the midpoint of the axis connecting the right arm and left leg electrodes toward the left arm (**Fig. 12.3, left**). For each precordial lead, the lead vector points from the center of the triangle formed by the three standard limb leads to the precordial electrode site (**Fig. 12.3, right**).

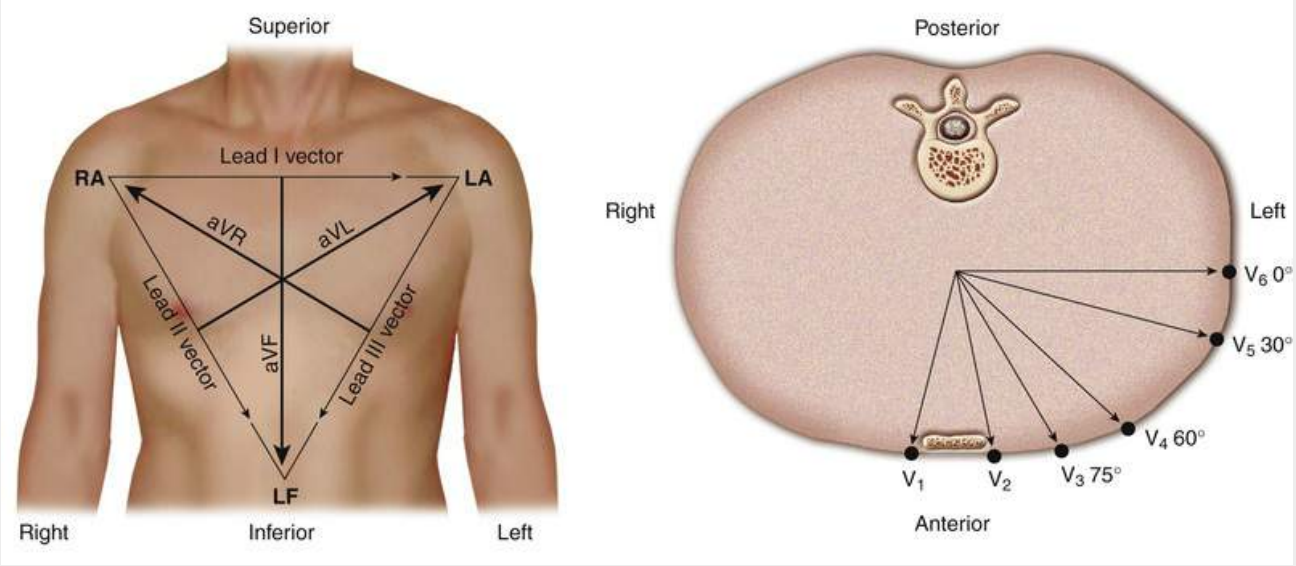

FIGURE 12.3 Lead vectors for the three standard limb leads, the three augmented limb leads (*left*), and the six unipolar precordial leads (*right*). *LA,* Left arm; *LF,* left foot; *RA,* right arm.

Instantaneous cardiac activity also can be approximated as a single vector, the *heart vector,* representing the vectoral sum of the activity of all active wavefronts. This vector's location, orientation, and intensity vary from instant to instant as cardiac activation proceeds. The amplitude of the recorded waveform in a lead then equals the length the projection of the heart vector onto the lead vector.

The lead axes of the six frontal plane leads can be superimposed to produce the *hexaxial reference system.* As depicted in **Fig. 12.4**, the six lead axes divide the frontal plane into 12 segments, each subtending 30 degrees.

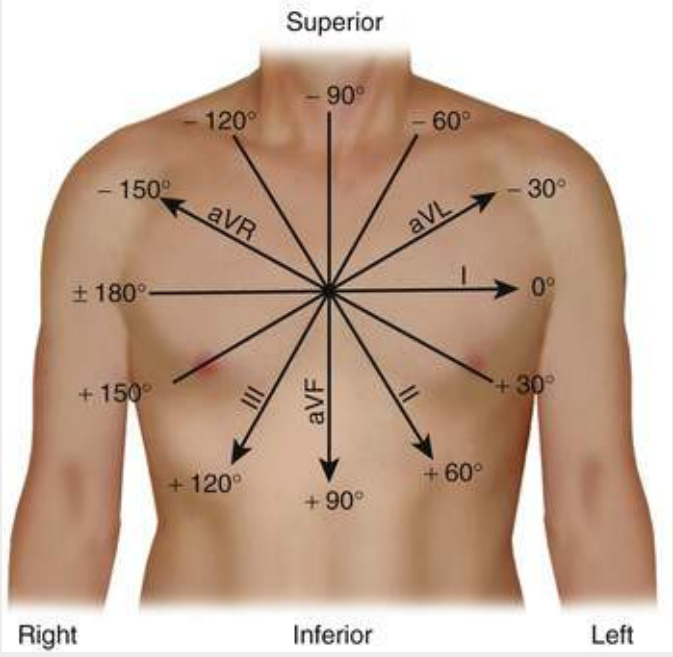

FIGURE 12.4 The hexaxial reference system constructed from the lead axes of the six frontal plane leads. The lead axes of the six frontal plane leads have been rearranged so that their centers overlie one another. Positive ends of each axis are labeled with the name of the lead.

This presentation allows calculation of the *mean electrical axis* of the heart. The orientation of the mean electrical axis represents the direction of activation in a theoretical “average” cardiac fiber. This direction is determined by the properties of the cardiac conduction system and properties of the

myocardium. Differences in the relation of cardiac to torso anatomy contribute relatively little to shifts in the axis.

The process for computing the mean electrical axis during ventricular activation in the frontal plane is illustrated in **Fig. 12.5**. First, the mean electrical force (i.e., the heart vector) as recorded in each lead is estimated by computing the area under the QRS waveform, measured as millivolt-milliseconds, in that lead. Areas above the baseline (the TP segment; see later) are assigned a positive polarity, and those below the baseline are assigned a negative polarity. The overall area equals the sum of the positive and the negative areas.

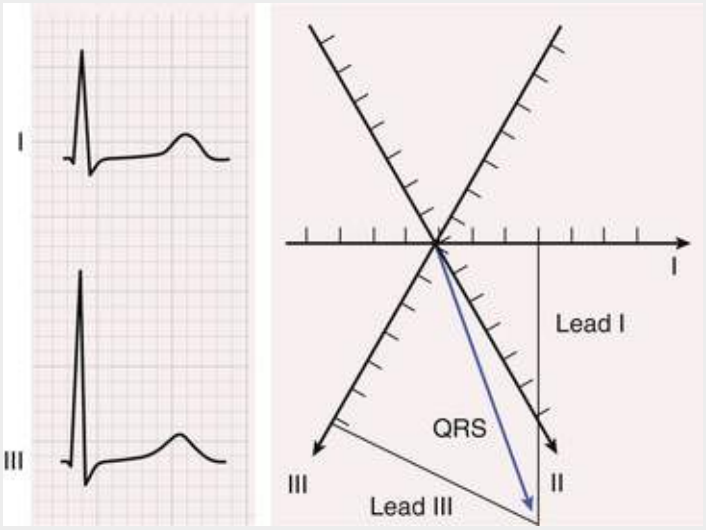

FIGURE 12.5 Calculation of the mean electrical axis during ventricular depolarization from the areas under the QRS complex in leads I and III. Magnitudes of the areas of the two leads are plotted as vectors on the appropriate lead axes, and the mean QRS axis is the sum of these two vectors. (From Mirvis DM. Electrocardiography: a Physiologic Approach. St Louis: Mosby–Year Book; 1993.)

Second, the area in each lead (typically, two are chosen) is represented as a vector oriented along the appropriate lead axis in the hexaxial reference system. The mean electrical axis equals the resultant sum of the (two) vectors.

An axis directed toward the positive end of the lead axis of lead I, that is, oriented directly away from the right arm and toward the left arm, is designated as being directed at 0 degrees. Axes oriented in a clockwise direction from this arbitrary zero level are assigned positive values, and those oriented in a counterclockwise direction are assigned negative values, as discussed further below.

The mean electrical axis during ventricular activation in the horizontal plane can be computed in an analogous manner by using the areas under and lead axes of the six precordial leads (**see Fig. 12.3, right**). A horizontal plane axis located along the lead axis of lead V_6 is assigned a value of 0 degrees; axes directed more anteriorly have positive values.

This approach can also be applied to compute the mean electrical axis for other phases of cardiac activity. Thus the mean force during atrial activation is represented by the areas under the P wave and the mean force during ventricular recovery by the areas under the ST-T wave.

Electrocardiographic Processing and Display Systems

ECG recording using computerized systems involves several steps: (1) signal acquisition, (2) data transformation, waveform recognition, and feature extraction, (3) diagnostic classification, and (4) display of the final ECG.

Signal Acquisition.

Signal acquisition includes amplifying the recorded signals, converting the analog signals into digital form, and filtering the signals to reduce noise. The standard amplifier gain for routine electrocardiography is 1000. Lower (e.g., 500, or *half-standard*) or higher (e.g., 2000, or *double-standard*) gains may be used to compensate for unusually large or small signals, respectively.

Analog signals are converted to a digital form at rates of 1000 samples per second (1000 hertz, Hz) to as high as 15,000 Hz. Too low a sampling rate may miss brief, high-frequency signals, such as notches in QRS complexes or pacemaker spikes, and may result in altered waveform morphologies. Too fast a sampling rate may introduce artifacts, including high-frequency noise, and will generate excessive amounts of data necessitating extensive digital storage capacity.

ECG potentials are filtered to reduce unwanted, distorting signals. Low-pass filters reduce the distortions caused by high-frequency interference from, for example, muscle tremor and nearby electrical devices; high-pass filters reduce the effects of body motion or respiration. For routine electrocardiography, the standards set by professional groups require an overall bandwidth of 0.05 to 150 Hz for adults.[1] Narrower filter settings, such as 1 to 30 Hz, as typically used in rhythm monitoring, will reduce baseline "wander" related to motion and respiration but may result in significant distortion of both the QRS complex (including width, amplitude, and Q wave patterns) and the ST-T wave.

ECG amplifiers include a capacitor stage between the input and output; they are *capacitor-coupled*. The ECG may be modeled as a time-varying or alternating current (AC) signal producing the waveforms superimposed on a fixed direct current (DC) baseline. Capacitor-coupling blocks unwanted DC potentials, such as those produced by the electrode interfaces, while permitting flow of AC signals, which account for the waveform shape. The elimination of the DC potential from the final product, however, means that ECG potentials will not be calibrated against an external reference level (e.g., a ground potential). Clinical ECG potentials are measured in relation to another portion of the waveform that serves as a baseline. The TP segment, which begins at the end of the T wave of one cardiac cycle and ends with the onset of the P wave of the next cycle (as detailed later), usually is the most appropriate internal ECG baseline (e.g., for measuring ST-segment deviation).

Data Transformation, Waveform Identification, and Feature Extraction.

The multiple cardiac cycles are recorded for each lead and are overlaid electronically to form a single representative beat for each lead. This reduces the effects of minor beat-to-beat variation in the waveforms and random noise. In addition, the averaged waveforms from each lead are overlaid on each other to measure intervals.[1]

Diagnostic Classification.

These measurements are then compared with specific diagnostic criteria to establish the interpretation of the ECG. A lexicon of preferred diagnostic statements has been proposed.[3] In some cases the criteria are derived from physiologic constructs and constitute the sole basis for a diagnosis, with no anatomic or functional correlation. For example, the criteria for intraventricular conduction defects are diagnostic without reference to an anatomic standard.

For other diagnoses, criteria are based on statistical correlations between anatomic or physiologic findings and ECG measurements in large populations (e.g., criteria for ECG diagnosis of ventricular hypertrophy). For such population-based criteria, the diagnosis is not absolute but represents a statistical probability that a structural abnormality exists based on the presence or absence of a specified set of ECG findings. Because different populations may be studied and different ECG and structural measurements may be included in the analyses, numerous criteria with highly varying accuracies have

been developed for common clinical conditions.

Display.

Cardiac potentials are most often displayed as the classic scalar ECG, which depicts the potentials recorded from each lead as a function of time. Amplitudes are displayed on a scale of 0.1 mV/mm on the vertical axis and time as 40 msec/mm on the horizontal scale. Leads generally are displayed in three groups—the three standard limb leads, followed by the three augmented limb leads, followed by the six precordial leads.

Alternative display formats have been proposed in which the six limb leads are displayed in the sequence of the frontal plane reference frame[4] (**see Fig. 12.4**). In addition, the polarity of lead aVR is reversed. Based on this scheme, waveforms are ordered as follows: lead aVL, lead I, negative lead aVR, lead II, lead aVF, and lead III. Advantages of this system may include facilitating estimation of the electrical axis by presenting the leads in the order in which they appear on the frontal plane reference frame and emphasizing the relevance of abnormalities in lead aVR by reversing its polarity.

*The precordial electrodes and the augmented limb leads have often been referred to as "unipolar" leads. However, true unipolar leads register the potential at one site in relation to an absolute zero potential. Referring to these leads as unipolar leads is based on the imprecise notion that the Wilson central terminal represents a true zero potential. Classifying these leads as "bipolar" more rigorously reflects the recognition that the reference electrode is not at exactly zero potential.

The Normal Electrocardiogram

The waveforms and intervals that make up the standard ECG are displayed in **Fig. 12.6**, and a normal 12-lead ECG is shown in **Fig. 12.7**. The *P wave* is generated by activation of the atria, the *PR interval* corresponds to the duration of atrioventricular conduction, the *QRS complex* is produced by the activation of the two ventricles, and the *ST-T wave* reflects ventricular recovery.

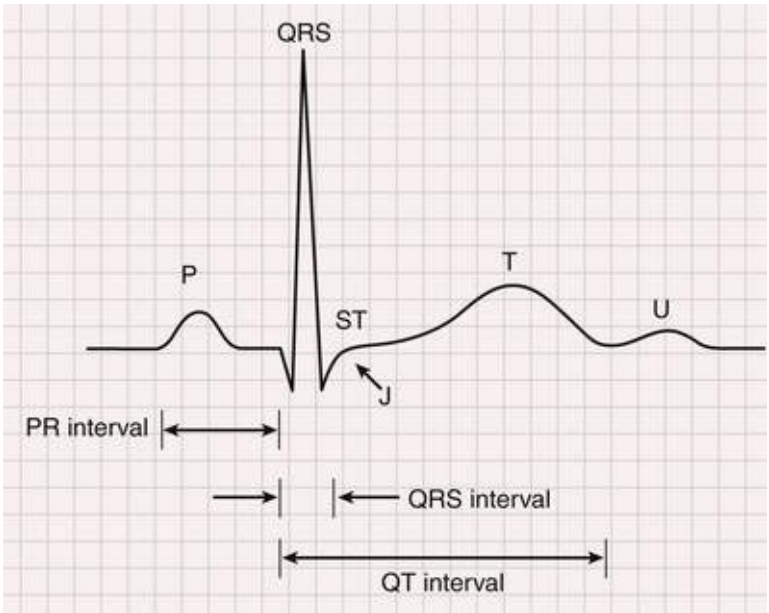

FIGURE 12.6 The waves and intervals of a normal electrocardiogram. (From Goldberger AL, Goldberger ZD, Shvilkin S. Goldberger's Clinical Electrocardiography: a Simplified Approach. 9th ed. Philadelphia: Saunders; 2017.)

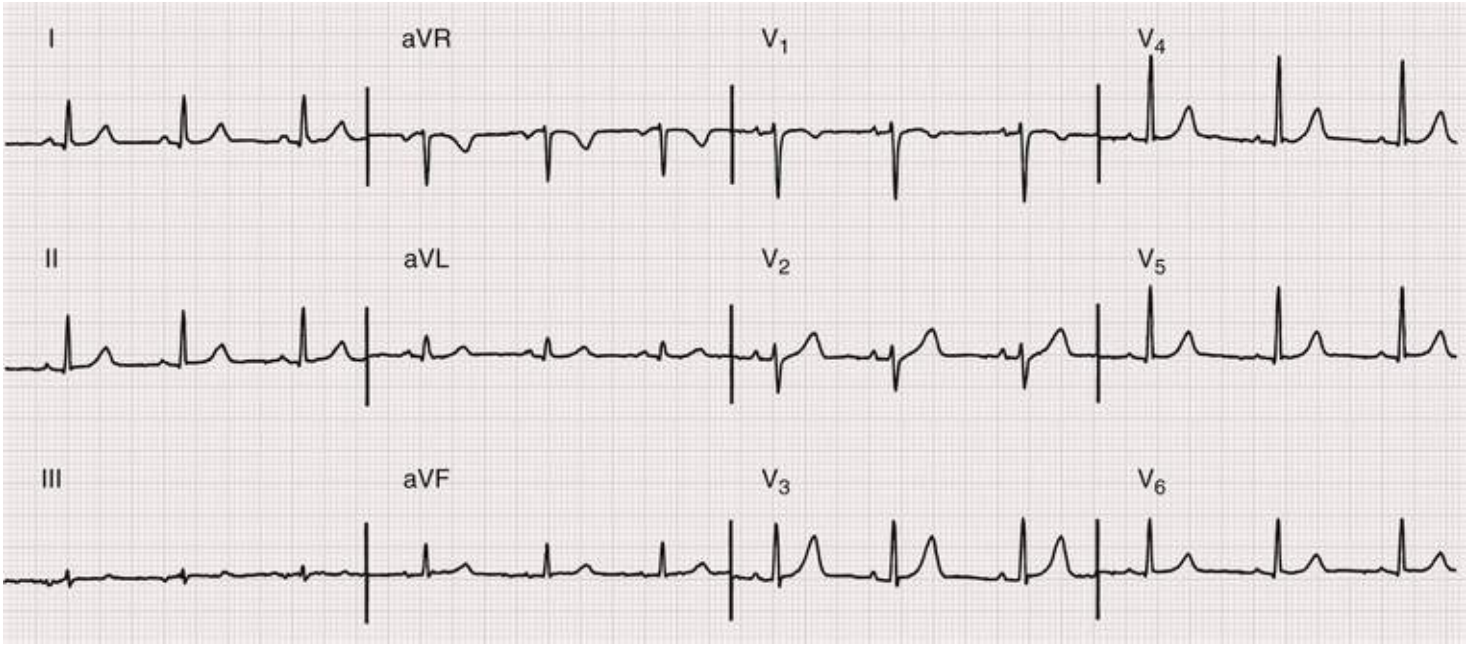

FIGURE 12.7 Normal ECG recorded from a 48-year-old woman. The *vertical lines* of the grid represent time intervals, with lines spaced at 40-millisecond intervals. *Horizontal lines* represent voltage amplitude, with lines spaced at 0.1 mV intervals. Every fifth line on each axis is darkened. The heart rate is approximately 76 beats/min (with physiologic variations due to respiratory sinus arrhythmia); the PR interval, QRS, and QTc durations measure approximately 140, 84, and 400 milliseconds, respectively; and the mean QRS axis is approximately +35 degrees.

Table 12.2 lists the classic normal values for the various intervals and waveforms of the ECG. The range of normal values of these measurements reflects the substantial intra- and interindividual variability in ECG patterns. Intraindividual differences in ECG patterns may even occur between ECGs recorded days, hours, or even minutes apart because of technical issues (e.g., changes in electrode position) or the biophysical effects of changes in, for example, posture, temperature, eating, or heart rate.

TABLE 12.2

Normal Values for Durations of ECG Waves and Intervals in Adults

WAVE OR INTERVAL	DURATION (msec)
P wave duration	<120
PR interval	<200
QRS duration	<110-120*
QT interval (corrected)	≤440-450*

*See text for further discussion.

Variability between individuals may reflect differences in age, sex, race, body habitus, heart orientation, and physiology. For example, in the Atherosclerosis Risk in Communities (ARIC) Study, the normal range for measures of ventricular repolarization, including both duration (QT interval) and magnitude (ST-segment amplitude) varied substantially between males and females and between white and African American cohorts.[5] The observed upper limits for ST-segment elevation (see later) in leads V_1 and V_2 were 50 microvolts (μV) higher in white men than in white women and almost 100 μV higher in African American men than in white men.

The observed differences among various subpopulations suggests that a single range of normal values for all individuals may be inappropriate and may lead to errors in diagnosis. Computerized ECG interpretation may facilitate the identification and use of different criteria for various population subgroups based on, for example, age, sex, and race.

Atrial Activation and the P Wave

Atrial Activation.
Atrial activation begins with impulse generation in the atrial pacemaker complex in or near the sinoatrial node (**see Chapter 34**). Once the impulse leaves this pacemaker site, atrial activation proceeds anteriorly toward the lower portion of the right atrium and inferiorly toward the atrioventricular (AV) node and the top of the interventricular septum.

The left atrium is most frequently activated after the onset of right atrial activation by propagation across Bachmann's bundle, which extends from the anterior right atrium to the left atrium near the right upper pulmonary vein. Activation continues in both atria during much of the middle of the overall atrial activation period, with left atrial activation continuing after the end of right atrial activation.

The Normal P Wave

The normal P wave reflects these activation patterns. Thus, P waves are positive in lead II and usually in leads I, aVL, and aVF, reflecting the leftward and inferior direction of activation during sinus rhythm. This corresponds to a mean frontal plane P wave axis of approximately 60 degrees. The pattern in leads aVL and III may be upright or downward, depending on the exact orientation of the mean P wave axis.

In the horizontal plane, atrial early activation of the right atrium generates a P wave that is oriented primarily anteriorly. Later, it shifts leftward and posteriorly as activation proceeds over the left atrium. Thus the P wave in the right precordial leads is typically upright. In lead V_1 and occasionally in lead V_2, the P wave may be biphasic with an initial positive deflection followed by a later negative wave. The P wave in the more lateral leads is upright and reflects continual right-to-left spread of the activation fronts. Variations in this pattern may reflect differences in pathways of interatrial conduction, described later.

The upper limit for a normal P wave duration is conventionally set at 120 milliseconds, as measured in the lead with the widest P wave. The amplitude in the limb leads normally is less than 0.25 mV, and the terminal negative deflection in the right precordial leads normally is less than 0.1 mV in depth.

Atrial Repolarization

The potentials generated by atrial repolarization are not usually seen on the surface ECG because of their low amplitude (usually <100 µV) and because they may be superimposed on the much higher-amplitude QRS complex. They may be observed as a low-amplitude wave with a polarity opposite that of the P wave (T_a *wave*) during AV block. Deviation of the PR segment has special significance in influencing ST-segment patterns during exercise testing and as an important marker of acute pericarditis (**see Chapter 83**) or atrial infarction (**see Chapters 58 and 59**).

Heart Rate Variability

Analysis of beat-to-beat changes in heart rate and related dynamics, termed *heart rate variability*, can provide insight into neuroautonomic control mechanisms and their perturbations with aging, disease, and drug effects (**see Chapters 35 and 36**). For example, relatively high-frequency (0.15 to 0.4 Hz) fluctuations are mediated primarily by vagus nerve traffic, such that heart rate increases during inspiration and decreases during expiration. Attenuation of this respiratory sinus arrhythmia at rest is a marker of physiologic aging and also occurs with diabetes mellitus, congestive heart failure, and a wide range of

other conditions that alter autonomic tone modulation. Relatively lower-frequency (0.05 to 0.15 Hz) physiologic oscillations in heart rate appear to be jointly regulated by sympathetic and parasympathetic interactions. A variety of complementary signal-processing techniques have been developed to analyze heart rate variability and its interactions with other physiologic signals, including time domain statistics, frequency domain techniques based on spectral methods, and newer computational tools derived from nonlinear dynamics and complex systems theory.[6] However, the relationship between specific autonomic effects (e.g., sympathovagal balance) cannot be reliably inferred from the ratio of relatively low- to higher-frequency components.

Atrioventricular Node Conduction and the PR Segment

The *PR segment* is the usually isoelectric region beginning with the end of the P wave and ending with the onset of the QRS complex. It forms part of the *PR interval* that extends from the onset of the P wave to the onset of the QRS complex. The normal PR interval measures 120 to 200 milliseconds in duration in adults and is best determined from the lead with the shortest PR intervals (to avoid missing various preexcitation syndromes) (**see Chapter 37**).

The PR segment serves as the temporal bridge between atrial activation and ventricular activation. This time period includes atrial repolarization and slow conduction within the AV node plus the more rapid conduction through the ventricular conduction system. The segment ends when enough ventricular myocardium has been activated to initiate the QRS complex.

The PR segment appears isoelectric because the potentials generated by atrial recovery and transmission through the conduction system structures are too small to be detected on the body surface at amplifier gains used in clinical electrocardiography. Signals from elements of the conduction system can be recorded from intracardiac recording electrodes placed against the base of the interventricular septum near the bundle of His (**see Chapter 35**).

Ventricular Activation and the QRS Complex

Normal ventricular activation is a complex process that depends on interactions between the physiology and anatomy of both the specialized ventricular conducting system and the ventricular myocardium.

Ventricular Activation.

Ventricular activation (and thus the QRS complex) is the net product of two events: endocardial activation and transmural activation of the two ventricles. *Endocardial* activation is guided by the anatomic distribution and physiology of the His-Purkinje system. The rapid conduction within the broadly dispersed ramifications of this treelike (*fractal*) system results in the rapid, synchronized activation of multiple endocardial sites and the depolarization of most of the endocardial surfaces of both ventricles within several milliseconds.

The sequence of left ventricular endocardial activation, depicted in **Fig. 12.8**, begins at three sites: (1) the anterior paraseptal wall of the left ventricle, (2) the posterior paraseptal wall of the left ventricle, and (3) the center of the left side of the septum. These loci generally correspond to the sites of insertion of the fascicles of the left bundle branch.

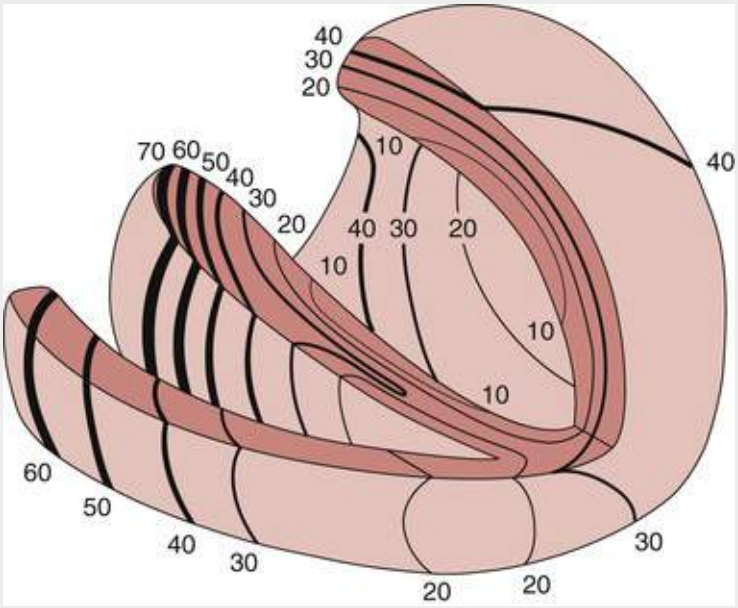

FIGURE 12.8 Activation sequence of the normal right and left ventricles. Portions of the left and right ventricles have been removed so that the endocardial surfaces of the ventricles and the interventricular septum can be seen. *Isochrone lines* connect sites that are activated at equal instants after the earliest evidence of ventricular activation. (From Durrer D. Electrical aspects of human cardiac activity: a clinical-physiological approach to excitation and stimulation. Cardiovasc Res 1968;2:1.)

Septal activation begins on the left side and spreads across the septum from left to right and from apex to base. Wavefronts sweep from these initial sites of activation in anterior and inferior and then superior directions to activate the anterior and lateral walls of the left ventricle. The posterobasal areas of the left ventricle are the last to be activated.

Excitation of the right ventricular endocardium begins near the insertion point of the right bundle branch near the base of the anterior papillary muscle and spreads to the free wall. The final areas to be activated are the pulmonary conus and the posterobasal right ventricular areas.

Thus, in both ventricles, the overall endocardial excitation pattern begins on septal surfaces and sweeps down toward the apex and then around the free walls to the basal regions, in an apex-to-base direction.

Activation then moves across the ventricular wall from endocardium to epicardium. Excitation of the endocardium begins at sites of Purkinje–ventricular muscle junctions and proceeds by muscle cell–to–muscle cell conduction in an oblique direction toward the epicardium. Multiple regions of both ventricles are usually activated simultaneously, resulting in substantial cancellation of the electrical forces that are generated, as previously described.

Normal QRS Complex

QRS patterns are described by the sequence of waves constituting the complex. An initial negative deflection is called the *Q wave*, the first positive wave is the *R wave*, and the first negative wave after a positive wave is the *S wave*. A second upright wave following an S wave, when present, is an *R′ wave*. Tall waves are denoted by uppercase letters and smaller ones by lowercase letters. A monophasic negative complex is referred to as a *QS complex*. Thus, for example, the overall QRS complex may be described as qRS if it consists of an initial small negative wave (q) followed by a tall upright one (R) and a deep negative one (S). In an RSr′ complex, initial tall R and S waves are followed by a small positive wave (*r′*). In each case, the deflection must cross the baseline to be designated a discrete wave.

Changes in waveform patterns that do not cross the baseline result in notches or slurs. A *notch* is an

abrupt change in waveform direction similar to the underlying wave but that does not cross the baseline. A *slur* is a more gradual change in the slope or rate of change in waveform amplitude. These patterns may reflect disruptions in the normally smooth patterns of activation by scarring, as with ventricular hypertrophy or infarction. Slurring of the initial QRS is caused by anomalous ventricular activation via a bypass tract with Wolff-Parkinson-White preexcitation (**see Chapter 37**).

Early QRS Patterns.

The complex pattern of activation described earlier may be simplified into two forces, the first representing septal activation and the second representing left ventricular free wall activation (**Fig. 12.9**). Initial activation of the interventricular septum is oriented from left to right in the frontal plane and anteriorly in the horizontal plane, corresponding to the anatomic position of the septum within the chest. This wavefront produces an initial positive wave in leads with axes directed to the right (lead aVR) or anteriorly (lead V_1). Leads with axes directed to the left (leads I, aVL, V_5, and V_6) will register initial negative waves known as *septal q waves*. These initial forces are normally of low amplitude and are brief (<30 msec in duration). The absence of these septal q waves, with QS complexes evident in the right precordial leads or with initial R waves in leads I, V_5, and V_6, is a common normal variant and not associated with any specific cardiac disease.

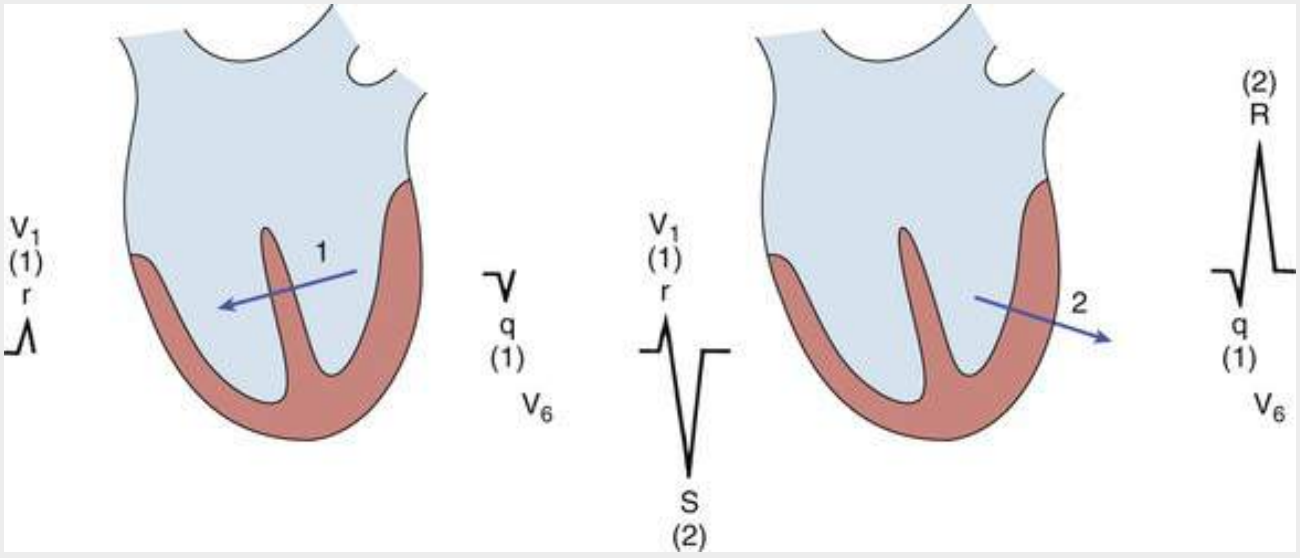

FIGURE 12.9 Schematic representation of ventricular depolarization as two sequential vectors representing septal (*left*) and left ventricular free wall (*right*) activation. QRS waveforms generated by each stage of activation in leads V_1 and V_6 are shown.

Mid- and Late QRS Patterns.

Subsequent parts of the QRS complex reflect activation of the free walls of the left and right ventricles. Because right ventricular muscle mass is considerably smaller than that of the left ventricle, most of the electrical activity it generates in canceled by the much greater forces from the left ventricle so that it contributes little to normal QRS complexes. Thus, the normal QRS can be considered to represent only septal and left ventricular activity with little meaningful oversimplification, as depicted in **Fig. 12.9**.

The complex interrelationships among cardiac position, conduction system function, and ventricular geometry result in a wide range of normal QRS patterns in the limb leads. The QRS pattern in leads II,

III, and aVF may be predominantly upright, with qR complexes, or these leads may show rS or RS patterns. Lead I may record a qR pattern or an isoelectric RS pattern.

Electrical Axis.

The wide range of QRS patterns can be interpreted by referring to the hexaxial reference system in **Fig. 12.4**. The normal mean QRS axis in adults lies between −30 degrees and +90 degrees. If the mean axis is near 90 degrees, the QRS complex in leads II, III, and aVF will be predominantly upright, with qR complexes; lead I will record an isoelectric RS pattern because the heart vector lies perpendicular to the lead axis. If the mean axis is nearer 0 degrees, the patterns will be reversed; leads I and aVL will register a predominantly upright qR pattern, and leads II, III, and aVF will show rS or RS patterns. This variation largely reflects physiologic differences in conduction system; the anatomic position of the heart within the torso has a minor role.

Mean QRS axes more positive than +90 degrees (usually with an rS pattern in lead I) represent *right axis deviation*. Axes between +90 and +120 degrees are referred to as *moderate right axis deviation*, and those between +120 and +180 degrees, *marked right axis deviation*. Axes more negative than −30 degrees (with an rS pattern in lead II) represent *left axis deviation*, with axes between −30 and −45 degrees called *moderate* and those between −45 and −90 degrees called *marked left axis deviation*.

Mean axes lying between −90 degrees and −180 degrees (or, equivalently, between +180 degrees and +270 degrees) are referred to as *extreme axis deviations* or, alternatively, as *right superior axis deviations*. The term *indeterminate axis* is applied when all six extremity leads show biphasic (QR or RS) patterns, indicating a mean axis that is perpendicular to the frontal plane. This finding may occur as a normal variant or may be seen in a variety of pathologic conditions discussed later.

Normal QRS patterns in the precordial leads follow an orderly progression from right (V_1) to left (V_6). In leads V_1 and V_2, initial r waves generated by septal activation are followed by S waves (an rS pattern) reflecting leftward and posterior activation of the left ventricular free wall (i.e., proceeding away from the precordial electrode).

Patterns in midprecordial leads V_3 and V_4 reflect the movement of the activation front in the ventricular free wall. It first approaches the exploring electrode and then moves leftward and posteriorly to more remote regions of the left ventricle and away from the exploring electrode. This sequence generates an R or r wave as it moves toward the electrode, followed by an S wave as it moves away from the electrode to produce rS or RS complexes.

As the exploring electrode moves further to the left, the R wave becomes more dominant and the S wave becomes smaller (or is totally lost) because of the longer time period during which the activation front moves toward the positive end of the electrode. In the leftmost leads (i.e., leads V_5 and V_6), the normal pattern also includes the septal q wave, to produce a qR (or qRs) pattern.

Thus, in the precordial leads, the QRS complex usually is characterized by a consistent progression from an rS complex in the right precordial leads, to an RS pattern in the midprecordial leads, and to a qR pattern in the left precordial leads. The site at which the pattern changes from a dominant S wave to a dominant R wave pattern is known as the *transition zone*. It normally occurs between lead V_3 and V_4. Transition zones that are shifted to the right (e.g., to lead V_2) are *early transitions*, and those shifted leftward (e.g., to V_5 or V_6) are *delayed transitions*.

Normal variability in QRS amplitudes, axes, and QRS duration are related to demographic and physiologic factors. QRS amplitudes are greater in men than in women and higher in African Americans than in those of other races. In addition, left ventricular mass (within the normal range) affects both QRS amplitude and duration. Higher-than-normal amplitudes are characteristic of chamber hypertrophy and

conduction defects. Low-amplitude QRS complexes, that is, complexes with overall amplitudes of less than 0.5 mV in all frontal plane leads and less than 1.0 mV in the precordial leads, may occur as a normal variant or as a result of cardiac (e.g., multiple infarctions, infiltrative cardiomyopathies, myocarditis) or extracardiac (e.g., pericardial effusion, anasarca, chronic obstructive pulmonary disease, pneumothorax) conditions.

QRS Duration

The upper normal value for QRS duration traditionally is set at less than 120 milliseconds, measured in the lead with the widest QRS complex. Recent epidemiologic studies have suggested that the median QRS duration may be shorter, as low as 100 milliseconds in men and 92 milliseconds in women.[7]

The Intrinsicoid Deflection.

As previously described, an electrode overlying the ventricular free wall will record a rising R wave as transmural activation proceeds toward it. Once the activation front reaches the epicardium, the full thickness of the wall under the electrode will be in an active state. After that moment, the electrode will register negative potentials as activation proceeds in remote cardiac areas. The sudden reversal of potential produces a sharp downslope, the *intrinsicoid deflection,* that approximates the timing of activation of the epicardium under the electrode. The term *R wave peak time* is sometimes used with reference to this subinterval on the surface ECG.

Ventricular Recovery and the ST-T Wave

Genesis of Ventricular Recovery Potentials.

The ST-T wave reflects activity during the plateau phase (the *ST segment)* and the later repolarization phases (the *T wave*) of the cardiac action potential.

ST-T wave patterns depend on the interaction of two factors: (1) the direction of intracellular current flow in cardiac fibers during repolarization and (2) the sequence of recovery within the ventricles. As described earlier, cellular current flow during recovery phases is directed away from less recovered to more recovered regions, that is, in a direction opposite to that during activation.

Ventricular repolarization, like activation, occurs in characteristic geometric patterns, with differences in recovery times between regions of the left ventricle and across the ventricular wall. In general, the repolarization sequence is the opposite of the activation sequence; that is, regions activated later have shorter action potentials and begin to repolarize before areas activated early. Thus, action potential durations are shorter in the anterobasal region than in the posteroapical region of the left ventricle. Similarly, action potential durations are shorter and repolarization begins earlier in the epicardium than in the endocardium.

In each case, the shortening of recovery time is greater than the delay in onset of activation so that the net resulting current flow will then be directed away from the basal left ventricle and the endocardium toward the apex and the epicardium. That is, repolarization current flow will be in the same direction as during activation.

The final result is that, in normal persons, QRS and ST-T wave patterns are relatively concordant. That is, the ST-T wave has approximately the same polarity as that of the QRS complex.

Evidence suggests that the regional differences in action potential duration are the major cause of ST-T wave,[8] with lesser contributions by transmural forces. Transmural differences may be augmented by the

presence of putative *midwall* or *M cells* that have action potentials longer than those of endocardial or epicardial cells.[9] In this model the ST-T wave begins when epicardial cells begin to recover ahead of both M cells and endocardial cells, with current flowing from midmyocardial and endocardial regions toward the epicardium. This initiates the rising portion of the ST-T wave, with the peak of the T wave corresponding to the end of epicardial repolarization.

The Normal ST-T Wave

The normal ST-T wave begins as a low-amplitude, slowly changing wave (the *ST segment*) that gradually evolves into a larger wave, the *T wave*. The onset of the ST-T wave is the *junction* or *J point*, and it is normally at or near the isoelectric baseline of the ECG (**see Fig. 12.7**). The level of the ST segment generally is measured at the J point or, in some applications such as exercise testing, 40 or 80 milliseconds after the J point.

The polarity of the ST-T wave generally is the same as the net polarity of the preceding QRS complex. Thus, T waves usually are upright in leads I, II, aVL, and aVF and the lateral precordial leads. T waves are normally negative in lead aVR and variable in leads III, V_1, and V_2.

The amplitude of the normal J point and ST segment varies with race, sex, and age.[5,10] It typically is greatest in lead V_2, and it is higher in young men than in young women and higher in African Americans than in whites. Recommendations[10] for the upper limits of normal J point elevation in leads V_2 and V_3 are 0.2 mV for men age 40 or older, 0.25 mV for men younger than 40, and 0.15 mV for women. In other leads the recommended upper limit is 0.1 mV for men and women. Higher levels, however, are common in normal persons, especially among athletes; in one report, 30% of athletes had ST elevation exceeding 0.2 mV in the anterior precordial leads.[11]

The J Wave

A *J wave* is a dome- or hump-shaped wave or notch that appears at the end of the QRS complex and that has the same polarity as the preceding QRS complex. It may be prominent as a normal variant (see later) and in certain pathologic conditions, such as systemic hypothermia (sometimes referred to as an *Osborn wave*) and in a set of conditions commonly referred to as the *J wave syndromes*. These syndromes include the *Brugada patterns* (**see Chapters 33 and 35**) and the *early repolarization pattern* (discussed later and in **Chapter 39**). Its origin has been postulated to be associated with a prominent notch in phase 1 of the action potentials on the epicardium (related to an augmented net outward current, I_{to}) but not on the endocardium, creating a transmural potential gradient leading to QRS notching and ST elevation.[12]

The U Wave

The T wave may be followed by an additional low-amplitude wave known as the *U wave*. This wave, usually less than 0.1 mV in amplitude, normally has the same polarity as the preceding T wave. The U wave is largest in the leads V_2 and V_3 and is most often seen at slow heart rates. Its electrophysiologic basis is uncertain. Suggestions include delayed repolarization in areas of the ventricle that undergo late mechanical relaxation, late repolarization of the Purkinje fibers, and long action potentials of (putative) midmyocardial M cells.

The QT Interval

The QT interval extends from the onset of the QRS complex to the end of the T wave. Thus, it includes the

total duration of ventricular activation and recovery and, in a general sense, reflects the duration of the ventricular action potential.

Accurately measuring the QT interval is challenging. Difficulties include identifying the beginning of the QRS complex and especially the end of the T wave, determining which lead(s) to use, and adjusting the measured interval for rate, QRS duration, and sex. Because the onset of the QRS and the end of the T wave do not occur simultaneously in every lead, the QT interval duration will vary from lead to lead by as much as 50 to 65 milliseconds (*QT dispersion*). In automated ECG systems, the QT interval typically is measured from a composite of all leads, with the interval beginning with the earliest onset of the QRS in any lead and terminating with the latest end of the T wave in any lead. When the interval is measured from a single lead, the lead in which the interval is the longest (most frequently lead V_2 or V_3) and in which a prominent U wave is absent (usually aVR or aVL) is preferred.

The normal QT interval is rate dependent, decreasing as heart rate increases. This corresponds to rate-related changes in the duration of the normal ventricular action potential. Numerous formulas have been proposed to correct the measured QT interval for this rate effect,[13] including one proposed by Bazett in 1920. The result is the *corrected QT interval*, or *QTc*, defined by the following equation:

$$QTc = QT/\sqrt{RR}$$

where the QT and RR intervals are measured in seconds. (The latter is considered as unitless for the calculation and the index is first calculated in seconds and often reported in milliseconds.) A joint report of the American Hospital Association (AHA), American College of Cardiology (ACC), and other professional organizations[10] suggested that the upper limit for QTc be set (in milliseconds) at 460 for women and 450 for men, and that the lower limit be set at 390 (although 360 for the latter has been suggested elsewhere).

The Bazett formula has limited accuracy in correcting for the effects of heart rate on the QT interval. Large database studies have shown that the QTc interval based on the Bazett formula remains significantly affected by heart rate, and that as many as 30% of normal ECGs may be diagnosed as having a prolonged QT interval when this formula is used.[14] The formula, in general, overcorrects the QT interval at high heart rates and undercorrects it at low rates.

Many other formulas and methods for correcting the QT interval for the effects of heart rate have been proposed, including linear, logarithmic, hyperbolic, and exponential functions. The AHA/ACC joint committee suggested using a linear regression function.[10] Several linear models have been proposed. One linear formula has been shown to be relatively insensitive to heart rate,[13] as follows:

$$QTc = QT + 1.75(HR - 60)$$

where HR is heart rate and the intervals are measured in milliseconds. Another commonly used correction is Fridericia's formula:

$$QT/(RR)^{0.33}$$

Other approaches include regression analyses based on the specific population being studied or computing individual-specific corrections to assess serial changes.

QT prolongation and shortening occur in numerous syndromes associated with tachyarrhythmias and sudden death (**see Chapters 37, 39 and 42**). A meta-analysis of 23 studies demonstrated that a 50-millisecond increase in the QT interval is associated with a relative risk (RR) of 1.20 for all-cause mortality and 1.29 for cardiovascular mortality.[14] Drug-induced prolongations and its relation to sudden death have made assessment of QT interval responses to new drugs an important topic for manufacturers and regulatory agencies.

Other Measures of Ventricular Recovery

The QRST Angle.

The concordance between the orientation of the normal QRS complex and the normal ST-T wave described earlier can be expressed vectorially. An angle can be visualized in three-dimensional space between the vector representing the mean QRS force and the vector representing the mean ST-T force. This angle is the *spatial QRST angle*. The angle between the two vectors in the frontal plane represents a reasonable simplification and normally is less than 90 degrees for women and 107 degrees for men.[15] Abnormalities of the QRST angle reflect abnormal relationships between the properties of activation and recovery. An analysis of the Third National Health and Nutrition Examination Survey (NHANES III) reported a significant increase in both all-cause and cardiovascular mortality over a 14-year period in persons with increased QRST angles.[15]

The Ventricular Gradient.

If the two vectors representing mean activation and mean recovery forces are added, a third vector known as the *ventricular gradient* is created. This vector represents the net area under the QRST complex. The ventricular gradient was originally conceptualized to assess the variability that exists in regional repolarization properties; the greater these differences, the larger will be the ventricular gradient. In addition, because changes in activation patterns produced by bundle branch block, for example, cause corresponding changes in recovery patterns (see later), no change in the ventricular gradient would be expected. The ventricular gradient should thus allow a measure of regional recovery properties that is independent of the activation pattern. This measurement has possible although unproven relevance to the genesis of reentrant arrhythmias that may be caused in part by abnormal regional variations in refractory periods.

Normal Variants

Numerous variations of these normal ECG patterns frequently occur in persons without heart disease. The presence of such findings without coexistent cardiac pathology is particularly common among athletes (**see Chapter 53**). These variations are important to recognize because they may be mistaken for significant abnormalities, leading to erroneous and potentially harmful diagnoses of heart disease.

T waves usually are inverted in all precordial leads at birth and become upright as time passes. However, T waves can remain inverted in the right precordial leads in normal adults (**Fig. 12.10**). This *persistent juvenile pattern*, with inverted T waves in leads to the left of V_1, occurs in 1% to 3% of adults and is more common in women than in men and more common in African Americans than in other racial or ethnic groups.

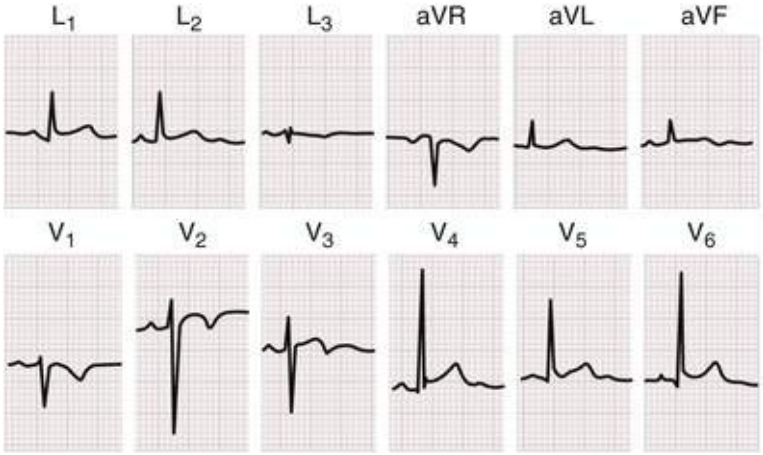

FIGURE 12.10 Normal tracing with a juvenile T wave inversion pattern in leads V_1, V_2, and V_3, as well as early repolarization pattern manifested by ST-segment elevation in leads I, II, aVF, V_4, V_5, and V_6. A J point notch is present in lead V_4. (Courtesy Dr. C. Fisch.)

Elevation of the J point and the following ST segment is common in normal persons. The pattern typically has a rapidly upsloping shape and is most prominent in the right and midprecordial leads (**Fig. 12.11**). This pattern occurs in as many as 30% of the general population[16] and is most prevalent in young adults, especially African American men and those who are athletically active. Its appearance is labile, being most prominent under conditions of increased vagal tone.

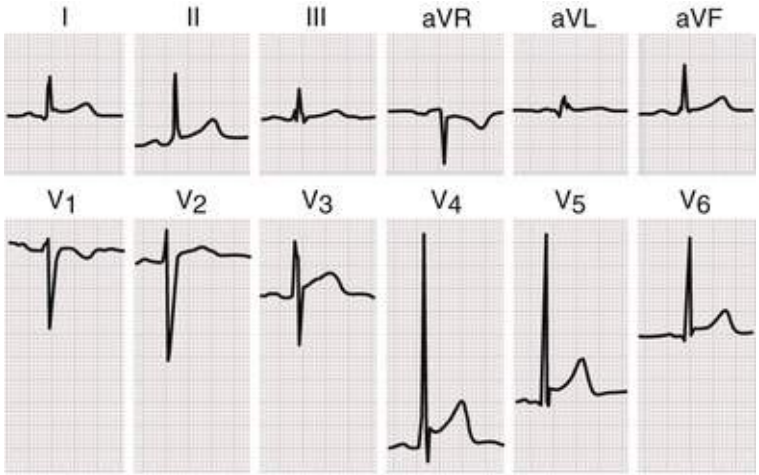

FIGURE 12.11 Normal variant pattern with the "early repolarization" pattern of a J point notch and ST-segment elevation. The ST-segment elevation and a J point notch are most marked in the midprecordial lead V_4. Reciprocal ST-segment depression and PR-segment depression are absent (except in lead aVR). (From Goldberger AL, Goldberger ZD, Shvilkin A. Goldberger's Clinical Electrocardiography: a Simplified Approach. 9th ed. Philadelphia: Elsevier; 2017.)

J point elevation is also often considered to represent the *early repolarization pattern* (**see Chapter 39**). Although diagnostic criteria for this pattern vary widely, recent recommendations by an expert panel[12] have suggested that this ECG diagnosis may be diagnosed if (1) there is a notch at the end of QRS complex or slur on the downstroke of the R wave, (2) the peak of the notch or J wave is 0.1 mV or greater in amplitude in two or more contiguous leads, excluding V_1 to V_3, and (3) the QRS duration is normal. Although commonly associated with these findings, ST-segment elevation is not required. The identification and the clinical significance of benign and potentially malignant variants of early repolarization patterns continue to be a subject of ongoing controversy and study (**see Chapters 33 and**

39).

The Abnormal Electrocardiogram

The prevalence of abnormal ECGs in the general population is substantial and increases progressively with age and in certain population groups. For example, screening ECGs revealed abnormalities requiring follow-up investigation in 2.5% of more than 32,000 high school students.[17] In contrast, abnormal ECGs were recorded in 36% of adults 70 to 79 years of age without overt cardiovascular disease.[18] Many of these abnormalities have prognostic as well as diagnostic import; a review of reports that included more than 173,000 persons demonstrated the prognostic value of six ECG abnormalities (ST-segment abnormalities, T wave abnormalities, combined ST-segment and T wave abnormalities, left ventricular hypertrophy, bundle branch block, and left axis deviation), with RR factors for subsequent cardiovascular events of 1.5 to 1.9.[19]

Atrial Abnormalities

Various pathophysiologic events can produce P wave abnormalities reflecting changes in (1) the origin of the initiating sinus node impulse that may affect atrial activation sequences, (2) conduction from the right to the left atrium that determines left atrial activation, or (3) the size and shape of the atria that determine the duration and path of atrial activation. These may result in abnormal patterns of activation and conduction, left atrial abnormalities, and right atrial abnormalities.

Abnormal Atrial Activation and Conduction.

Small shifts in the site of initial activation within or near the sinoatrial (SA) node or to ectopic sites within the atria can lead to major changes in the pattern of atrial activation and thus in the morphology of P waves. These shifts may occur as *escape rhythms* if the normal SA nodal pacemaker fails or as *accelerated atrial rhythms* if the automaticity of an ectopic site is enhanced (**see Chapter 37**).

P wave patterns may suggest the site of impulse formation and the path of subsequent activation. A negative P wave in lead I suggests activation beginning in the left atrium, and an inverted P wave in the inferior leads generally corresponds to a posterior atrial activation site. However, the correlations of P wave patterns with the location of origin are highly variable. Accordingly, these patterns, as a group, may be referred to as *atrial rhythms*, rather than assigned anatomic terms inferring a specific site of origin.

Interatrial block, with conduction delay between the atria, alters the duration and pattern of P waves.[20] When conduction from the right to the left atrium is delayed, the normal lag in left atrial activation relative to that of the right atrium increases. P wave duration is prolonged beyond 120 milliseconds, and P waves typically have two humps in lead II, with the first representing right atrial and the second reflecting left atrial activation.

With more advanced block, the sinus node impulses reach the left atrium only after passing inferiorly toward the atrioventricular junction and then superiorly through the left atrium. In such cases, P waves are wide and biphasic (an initial positive wave followed by a negative deflection) in the inferior leads.

Interatrial block is common, being found in approximately 10% of young adults and in as many as 60% of hospitalized adults. Although often associated with left atrial enlargement, it also is seen as an isolated conduction defect without concomitant structural abnormalities. It is an independent predictor of atrial fibrillation and other supraventricular tachyarrhythmias, and it has been associated with left atrial

thrombi and systemic embolization.

Left Atrial Abnormality

Anatomic abnormalities of the left atrium that alter the P waves include atrial dilation, atrial muscular hypertrophy, and elevated intra-atrial pressures. Because these pathophysiologic abnormalities often coexist and produce similar ECG effects, the resulting patterns are often referred to as *left atrial abnormality* (or *abnormalities*).[21]

Diagnostic Criteria.

Abnormalities in left atrial structure and function produce wide and notched P waves, with prominent terminal negative deflections in the right precordial leads. The most common criteria for diagnosing left atrial abnormality are listed in **Table 12.3** and illustrated in **Figs. 12.12 and 12.13**.

TABLE 12.3

Common Diagnostic Criteria for Left and Right Atrial Abnormalities

LEFT ATRIAL ABNORMALITY	RIGHT ATRIAL ABNORMALITY*
Prolonged P wave duration to >120 msec in lead II	Peaked P waves with amplitudes in lead II to >0.25 mV ("P pulmonale")
Prominent notching of P wave, usually most obvious in lead II, with interval between notches of >40 msec ("P mitrale")	Prominent initial positivity in lead V_1 or V_2 >0.15 mV
Ratio between duration of P wave in lead II and duration of PR segment >1.6	Increased area under initial positive portion of P wave in lead V_1 to >0.06 mm-sec
Increased duration and depth of terminal-negative portion of P wave in lead V_1 (P terminal force) so that area subtended by it >0.04 mm-sec	Rightward shift of mean P wave axis to >+75 degrees
Leftward shift of mean P wave axis to between −30 and −45 degrees	

*In addition to criteria based on P wave morphologies, right atrial abnormality is suggested by QRS changes as described in the text.

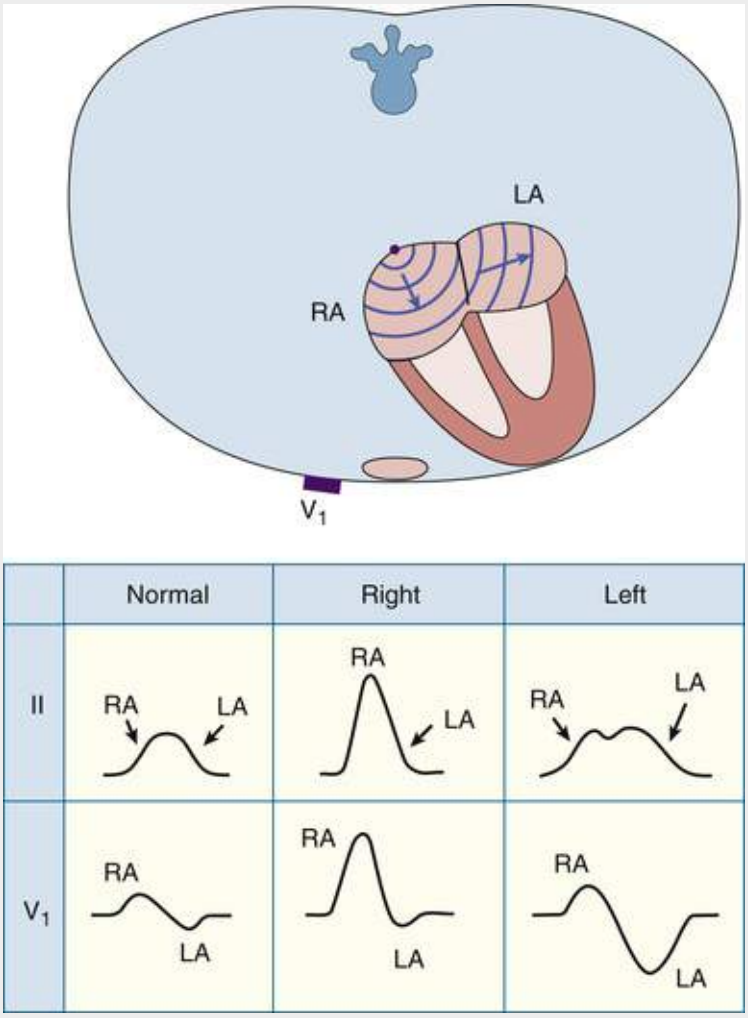

FIGURE 12.12 **Top,** Schematic representation of atrial depolarization. **Bottom,** P wave patterns associated with normal atrial activation (*left*) and with right atrial (*middle*) and left atrial (*right*) abnormalities. (Modified from Park MK, Guntheroth WG. How to Read Pediatric ECGs. 4th ed. St Louis: Mosby; 2006.)

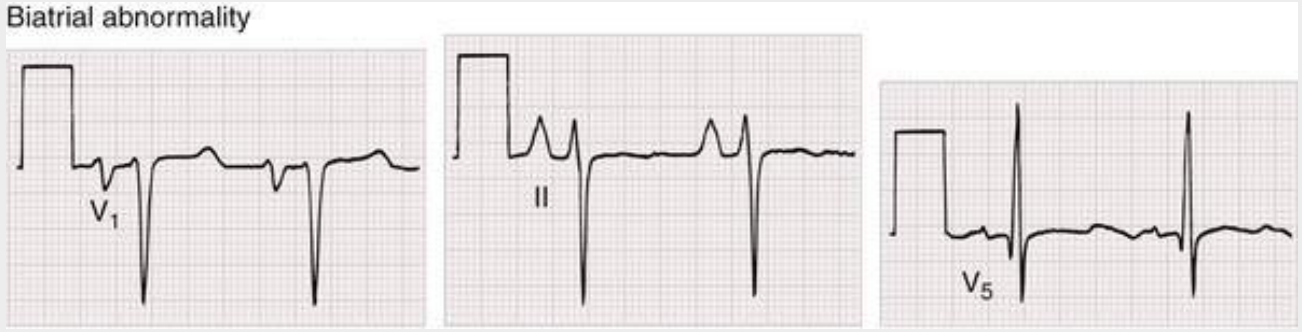

FIGURE 12.13 Biatrial abnormality, with tall P waves in lead II (right atrial abnormality) and an abnormally large terminal negative component of the P wave in lead V_1 (left atrial abnormality). The P wave also is notched in lead V_5.

Mechanisms for the ECG Abnormalities.

Enlargement and prolonged activation time of the left atrium that is located posteriorly in the chest produces prolonged P wave duration, notching of P waves that is most prominent in inferolateral leads, and increased amplitude of terminal negative P wave forces in the right precordial leads. Widening of the P wave has also been associated with abnormal levels of fibrosis and fatty infiltration of the major atrial conduction pathways.[22]

Diagnostic Accuracy.

Recent studies correlating these ECG criteria with left atrial volumes determined by magnetic resonance imaging (MRI)[23] have demonstrated the limited accuracy of the criteria. A prolonged P wave duration has a high sensitivity (84%) but low specificity (35%). By contrast, bifid P waves and increased negative terminal P wave amplitude in lead V_1 have low sensitivities (8% and 37%, respectively) and high specificities (90% and 88%, respectively).

Clinical Significance.

The ECG features of left atrial abnormality are associated with more severe left ventricular dysfunction in patients with ischemic heart disease (**see Chapter 61**) and with more severe valve damage in patients with mitral or aortic valve disease (**see Chapters 68 to 70**). Patients with left atrial abnormalities also have a higher-than-normal incidence of atrial tachyarrhythmias, including atrial fibrillation, cerebrovascular accident (stroke), and all-cause and cardiovascular mortality[24] (**see Chapter 38**).

Right Atrial Abnormality

The ECG features of right atrial abnormality are illustrated in **Figs. 12.12 and 12.13**. As in the case of left atrial abnormality, the term *right atrial abnormality* may be used rather than designations such as "right atrial enlargement" that suggest a particular underlying pathophysiology.[21]

Diagnostic Criteria.

P wave amplitudes in the limb and right precordial leads typically are abnormally high, with normal durations. Criteria commonly used to diagnose right atrial abnormality are listed in **Table 12.3**. In addition to criteria based on P wave morphology, right atrial abnormality is suggested by certain QRS changes, including a qR-type pattern in the right precordial leads without evidence of myocardial infarction or low-amplitude QRS complexes in lead V_1 together with a threefold or greater increase in lead V_2.

Mechanisms for the ECG Abnormalities.

Greater right atrial mass and size generate greater electrical force early during atrial activation, producing taller P waves in limb leads and increasing the initial P wave deflection in leads such as lead V_1 that face the right heart. Because right atrial activation occurs early during the P wave, P wave duration is not prolonged, in contrast to the pattern with left atrial changes. It has also been suggested that downward displacement of the heart may be responsible for the increase in P-terminal force and tall P waves in patients with emphysema.[25]

Diagnostic Accuracy.

Imaging studies have shown that the ECG features of right atrial abnormality have limited sensitivity (7% to 17%) but high specificity (96% to 100%) for detecting anatomic right atrial enlargement.[25]

Clinical Significance.

Patients with chronic obstructive pulmonary disease and this ECG pattern (often referred to as P pulmonale) have more severe pulmonary dysfunction, with significantly reduced survival, than in others (**see Chapters 85 and 86**). However, comparison of ECG and hemodynamic parameters has not demonstrated a close correlation between P wave patterns and right atrial hypertension.

Other Atrial Abnormalities.

Patients with biatrial abnormalities may have ECG patterns reflecting each defect. Findings suggestive of biatrial abnormalities include large, biphasic P waves in lead V_1 and tall, broad P waves in leads II, III, and aVF (**see Fig. 12.13**).

Ventricular Hypertrophy

Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) produces changes in the QRS complex, the ST segment, and the T wave. QRS changes include increased QRS amplitudes often with prolonged QRS durations, left axis deviation, notching or slurring of R waves, and patterns suggesting intraventricular conduction defects. The most characteristic finding is increased amplitude of the QRS complex. R waves in leads facing the left ventricle (i.e., leads I, aVL, V_5, and V_6) are taller than normal, and S waves in leads overlying the opposite side of the heart (i.e., V_1 and V_2) are deeper than normal. These changes are illustrated in **Fig. 12.14**.

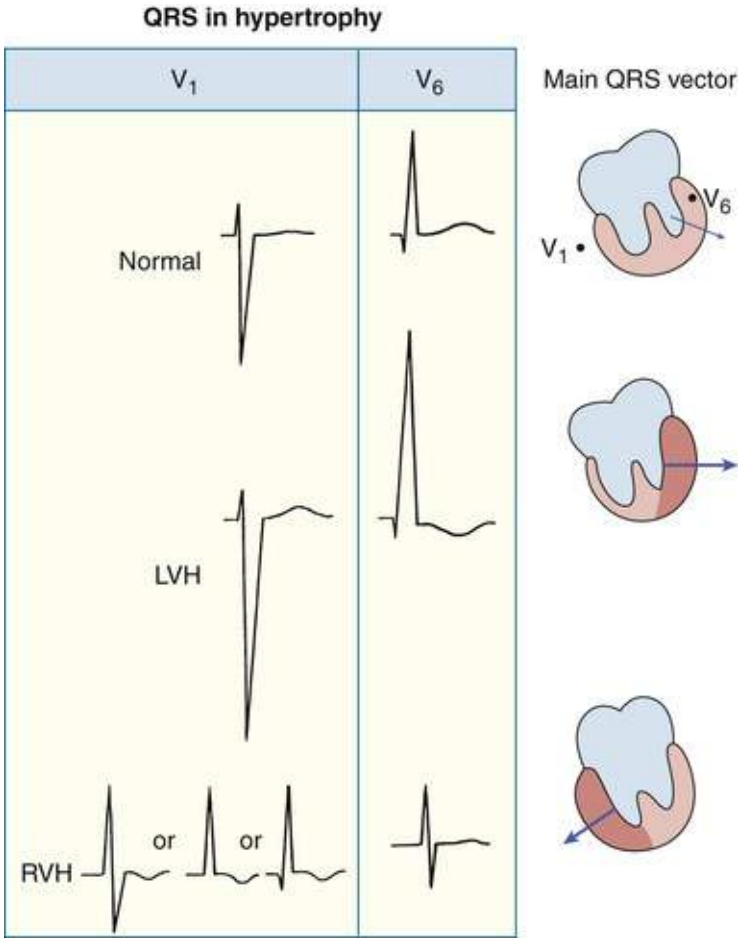

FIGURE 12.14 LVH increases the amplitude of electrical forces directed to the left and posteriorly. In addition, repolarization abnormalities can cause ST-segment depression and T wave inversion in leads with a prominent R wave. RVH can shift the QRS vector to the right, usually with an R, RS, or qR complex in lead V_1, especially when caused by severe pressure overload. T wave inversions may be present in the right-mid precordial leads. (From Goldberger AL, Goldberger ZD, Shvilkin A. Goldberger's Clinical Electrocardiography: a Simplified Approach. 9th ed. Philadelphia: Saunders; 2017.)

The ST segment may be normal or somewhat elevated in leads with tall R waves. In many patients, however, the ST segment is depressed and followed by an inverted T wave (**Fig. 12.15**) in leads I, II,

aVL, and V_5-V_6. In these cases the depressed ST segment is typically either flat or slopes downward from a depressed J point, and the T wave is asymmetrically inverted. These LVH-related repolarization changes usually occur in patients with QRS changes but may appear alone. Additional abnormalities may include prolongation of the QT interval and evidence of left atrial abnormality.

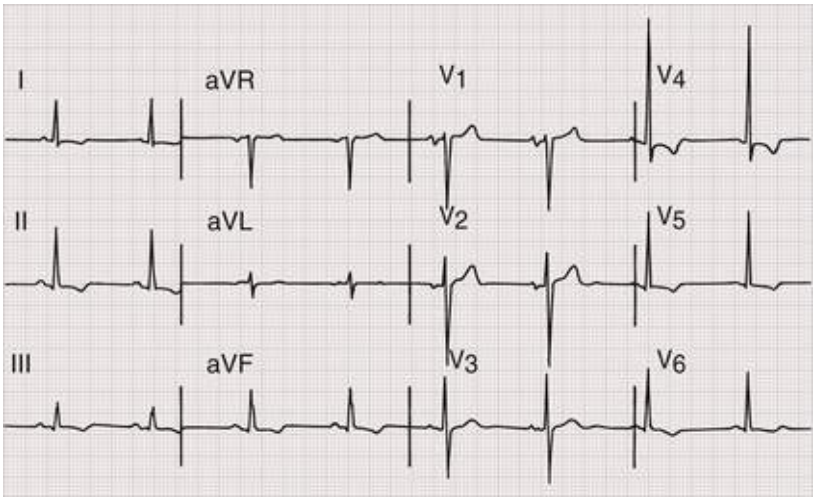

FIGURE 12.15 Marked LVH pattern with prominent precordial lead QRS voltages, ST-segment depression, and T wave inversion (compare with **Fig. 12.16**). Left atrial abnormality also is present.

These ECG features are most typical of LVH induced by pressure overload of the left ventricle, such as hypertension (**see Chapter 46**). Volume overload may produce a somewhat different pattern, including tall upright T waves, and sometimes narrow (<25 msec) but deep (≥0.2 mV) Q waves in leads I, aVL, and $V_{4\text{-}6}$ (**Fig. 12.16**) (**see Chapter 77**). These distinctions have limited value in identifying hemodynamic conditions, and their diagnostic use has been discouraged.[21]

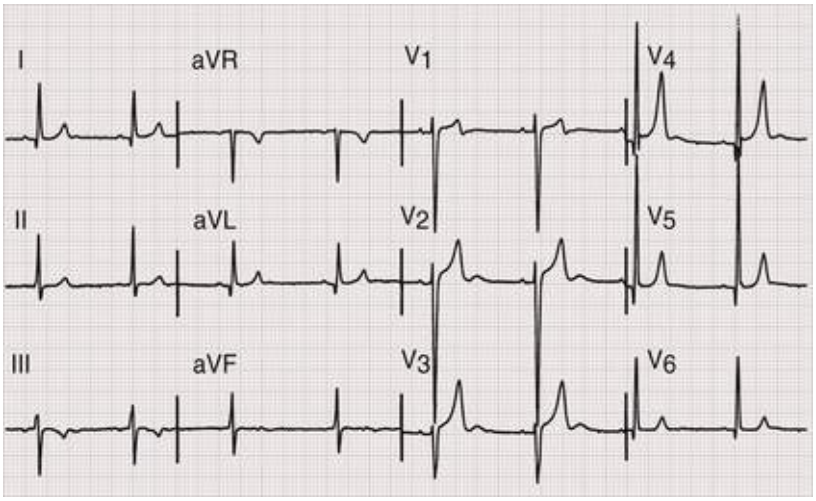

FIGURE 12.16 LVH pattern with prominent positive anterior T waves on an ECG from a patient with severe aortic regurgitation.

Mechanisms for the ECG Abnormalities.

ECG changes of LVH result from interrelated structural, biochemical, and bioelectric changes.[26,27]

Structural abnormalities include (1) an increase in the size of activation fronts moving across the thickened wall that generate higher body surface voltages, (2) thickened walls that require more time to fully activate, and (3) an increase in fibrosis resulting in fragmented and slower-than-normal conduction within the myocardium.

At the cellular level, hypertrophy is associated with a form of electrical remodeling.[27] This includes biochemical changes in gap junctions and ion channels that alter the intensity of current flow. Changes in fiber diameter and length and changes in myocyte branching patterns alter impulse propagation. The heterogeneous distribution of these abnormalities and intramural scarring associated with hypertrophy can disrupt smooth propagation of wavefronts to produce notching of the QRS complex.[28]

ST-T abnormalities may reflect any of several phenomena related to ventricular hypertrophy. These include primary disorders of repolarization that accompany the cellular processes of hypertrophy, and myocardial ischemia related to inadequate compensatory dilation of coronary arteries, inadequate growth of arterioles and capillaries in relation to the increased muscle mass, greater oxygen demand related to increased wall stress, and underlying coronary artery disease.

Diagnostic Criteria

Many sets of criteria to detect anatomic LVH have been developed based on these ECG abnormalities. Widely used criteria are listed in **Table 12.4**; Hancock and colleagues[21] have presented a comprehensive list.

TABLE 12.4

Common Diagnostic Criteria for Left Ventricular Hypertrophy (LVH)

MEASUREMENT	CRITERIA
Sokolow-Lyon voltages	$SV_1 + RV_5 > 3.5$ mV
	RaVL > 1.1 mV
Romhilt-Estes point score system*	Any limb lead R wave or S wave > 2.0 mV (3 points)
	or SV_1 or $SV_2 \geq 3.0$ mV (3 points)
	or RV_5 to $RV_6 \geq 3.0$ mV (3 points)
	ST-T wave abnormality, no digitalis therapy (3 points)
	ST-T wave abnormality, digitalis therapy (1 point)
	Left atrial abnormality (3 points)
	Left axis deviation ≥ −30 degrees (2 points)
	QRS duration ≥ 90 msec (1 point)
	Intrinsicoid deflection in V_5 or $V_6 \geq 50$ msec (1 point)
Cornell voltage criteria	SV_3 + RaVL > 2.8 mV (for men)
	SV_3 + RaVL > 2.0 mV (for women)
Cornell regression equation	Risk of LVH = $1/(1 + e^{-exp})$†
Cornell voltage duration measurement	QRS duration × Cornell voltage > 2436 mm-sec‡
	QRS duration × sum of voltages in all leads > 1742 mm-sec

*Probable LVH is diagnosed with totals of 4 points, and definite LVH is diagnosed with totals of 5 or more points.

†For persons in sinus rhythm, exp = 4.558 − 0.092 (SV_3 + RaVL) − 0.306 TV_1 − 0.212 QRS − 0.278 $PTFV_1$ − 0.559 (sex). Voltages are in mV, QRS is QRS duration in msec, $PTFV_1$ is the area under the P terminal force in lead V_1 (in mm-sec), and sex = 1 for men and 2 for women. LVH is diagnosed as present if exp < −1.55.

‡For women, add 8 mm.

PTF, P terminal force; *$PTFV_1$,* P terminal force in lead V_1.

Most methods assess the presence or absence of LVH as a binary function, indicating that structural LVH either does or does not exist, based on an empirically determined set of criteria. For example, the widely used Sokolow-Lyon and Cornell voltage criteria require that voltages in specific leads exceed certain values. The Romhilt-Estes point score system assigns point values to amplitude and other criteria,

including QRS axis and P wave patterns; definite LVH is diagnosed with a score of 5 points or more and probable LVH with a score of 4 points. The Cornell voltage duration method includes measurement of QRS duration as well as amplitudes. Other methods seek to quantify left ventricular mass as a continuum. Diagnosis of LVH can then be based on a computed mass that exceeds an independently determined threshold. One set of criteria applying this approach is used for the Cornell regression equation, shown in **Table 12.4**.

Diagnostic Accuracy.

The accuracy of these criteria depend on the ultimate outcome being predicted. This may be, as most frequently practiced, the presence or absence of structural left ventricular hypertrophy or enlargement. Alternatively, as recently emphasized,[27,28] the ECG criteria may be applied to predict clinical outcomes, as discussed later.

The reported diagnostic accuracies of these ECG criteria to detect structural LVH are highly variable, differing with the specific criteria tested, the imaging method used to determine anatomic measurements, and the population studied. Most studies have reported low sensitivity and high specificity. One review of 21 studies relying on echocardiographic measures reported a median sensitivity for six commonly used criteria ranging from 10.5% to 21% and a median specificity of 89% to 99%.[29]

More recent studies relying on cardiac MRI have similarly reported low sensitivities and high specificities of standard ECG criteria for detecting structural LVH. An analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) results demonstrated sensitivities of 5.7 to 26.0% and specificities of 88.7 to 99.2% for commonly applied ECG measures.[23] Because of the variability in the accuracy of the various criteria from one trial to another, no single criterion can be established as the preferred method.[21]

Accuracy also varies with sex (with women having lower QRS amplitudes than men), race (with African Americans having higher QRS amplitudes than whites), age (with lower voltages with increasing age), and body habitus (with obesity reducing QRS amplitudes).[21]

Clinical Significance

Although the low sensitivities of ECG measurements limit the value of these criteria as screening tools for structural LVH in both the general population and cohorts with a higher prevalence of LVH, the significance of an ECG diagnosis of LVH may also be measured by its ability to identify patients at high risk for future cardiac clinical events.[27,28] Thus, ECG findings may provide independent, clinically important information that reflect the underlying cellular abnormalities that may impact prognosis.[27]

The presence of ECG criteria for LVH identifies a subset of the general population and of those with hypertension, aortic stenosis, and other conditions with a significantly increased risk for cardiovascular morbidity, including new-onset heart failure, atrial and ventricular arrhythmias, and cardiovascular and all-cause mortality. For example, data from the ARIC study demonstrated that the incidence of all-cause mortality in the general population rose progressively with increasing scores using the Romhilt-Estes criteria; rates increased from 13.8 per 1000 person-years with a score of zero to 60.5 per 1000 person-years with a score of 5 or greater.[30] Findings that the ECG abnormalities are associated with increased risk whether they represent true or false-positive results in relation to MRI-determined left ventricular mass, and that the risks posed by ECG and imaging evidence of LVH are complementary,[27,28] suggest the structural and electrical changes of hypertrophy have additive value and reflect different although overlapping consequences of the hypertrophic process on outcomes.

The clinical significance of ST-T wave changes has been demonstrated in, for example, the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study.[31] The presence of ST-T changes by the Sokolow-Lyon or Cornell voltage criteria among hypertensive patients increased the 5-year risk of heart failure by more than threefold and the risk of heart failure–related mortality by more than fourfold. In addition, the onset of ST-T changes during the first year of follow-up was associated with a three- to fivefold increase in clinical events. Conversely, regression of ST-T changes during treatment was associated with reduced risk of cardiovascular death, nonfatal infarction, and other outcomes.

In addition to these clinical impacts, the ECG changes of LVH may confound or obscure ECG changes of other common conditions.[21] The widened, notched, and leftward QRS complex may mimic intraventricular conduction defects, and the ST-T wave changes may suggest myocardial ischemia or infarction (see later). Similarly, the ECG changes of other conditions may confound the value of ECG criteria for LVH. These include left anterior fascicular block, left bundle branch block, and right bundle branch block, as discussed later.

Right Ventricular Hypertrophy

Right ventricular hypertrophy (RVH), especially when resulting from pressure overload, changes fundamental aspects of the ECG, whereas an enlarged left ventricle produces predominantly quantitative changes in underlying normal waveforms. The ECG changes associated with moderate to severe concentric RVH most often include abnormally tall R waves in anteriorly and rightward-directed leads (leads aVR, V_1, and V_2) and deep S waves and abnormally small r waves in leftward-directed leads (I, aVL, and lateral precordial leads) (**Fig. 12.17**). These changes result in a reversal of normal R wave progression in the precordial leads, a shift in the frontal plane QRS axis to the right, and the presence of S waves in leads I, II, and III (the *$S_1S_2S_3$ pattern)* (**see Chapters 84 to 86**).

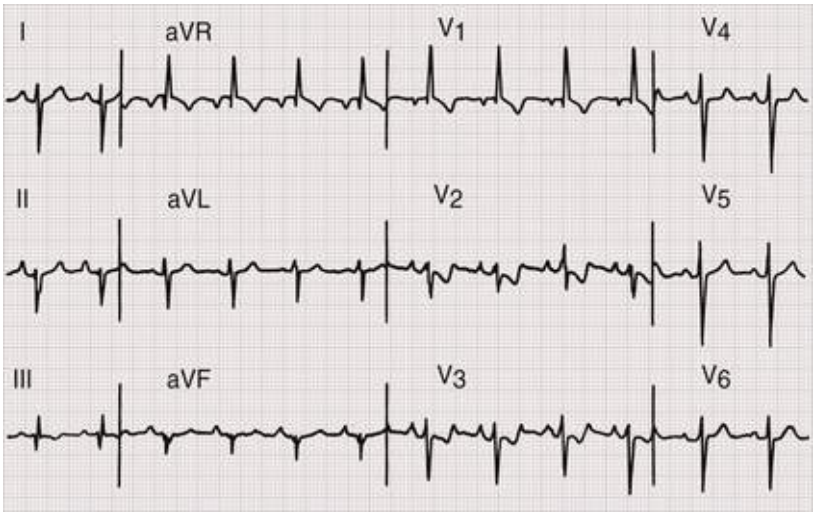

FIGURE 12.17 RVH pattern most consistent with severe pressure overload of the right ventricle. Findings include (1) a tall R wave in V_1 (as part of the qR complex), (2) right axis deviation, (3) ST-segment depression and T wave inversion in V_1 through V_3, (4) delayed precordial transition zone (rS in V_6), (5) right atrial abnormality, and (6) an $S_1Q_3T_3$ pattern.

Less severe hypertrophy, especially when limited to the outflow tract of the right ventricle that is activated late during the QRS complex, produces less marked changes. Abnormalities may be limited to an rSr′ pattern in V_1 and persistence of s (or S) waves in the left precordial leads. This pattern is typical

of right ventricular volume overload, such as that produced by an atrial septal defect and is also seen in persons without manifest cardiac abnormalities.

Diagnostic Criteria

Commonly relied-on criteria for the ECG diagnosis of RVH are listed in **Table 12.5**. Other criteria that have been used recently include the Butler-Leggett score (maximum R_{V1-2} + Max $S_{I,V6} - S_{V1} > 6$ mV) and the Lewis criterion ($R_I + S_{III} - [S_I + R_{III}] < 1.5$ mV). Although right axis deviation is not listed as a diagnostic criterion, it is present in most cases of significant structural RVH.[21]

TABLE 12.5

Common Diagnostic Criteria for Right Ventricular Hypertrophy (RVH)

Tall R in $V_1 > 0.6$ mV
Increased R/S in $V_1 > 1$
Deep S in $V_5 > 1.0$ mV
Deep S in $V_6 > 0.3$ mV
Tall R in aVR > 0.4 mV
Small S in $V_1 < 0.2$ mV
Small R in $V_{5-6} < 0.3$ mV
Reduced R/R ratio in $V_5 < 0.75$
Reduced R/S ratio in $V_6 < 0.4$
Reduced R/S ratio in $V_1 < 0.04$
$(R_I + S_{III}) - (S_I + R_{III}) < 1.5$ mV
Max R_{V1-2} + Max $S_{I, aVL} - S_{V1} > 0.6$ mV
$RV_1 + S_{V5-6} > 1.05$ mV
R peak $V_1 > 0.035$ msec
QR in V_1 present

Data from Hancock EW, Deal B, Mirvis DM, et al. Recommendations for the standardization and interpretation of the electrocardiogram. Part V. ECG changes associated with cardiac chamber hypertrophy. J Am Coll Cardiol 2009;53:982.

In addition, other ECG findings have been considered supportive of a diagnosis of RVH, although not by themselves diagnostic. These include an RSR′ pattern in V_1 with a QRS duration longer than 120 milliseconds, positive S/R ratio in I, II and III, an S_IQ_{III} pattern, R/R ratio in V_1 greater than in V_{3-4}, negative T waves in V_{1-3}, and evidence of left atrial abnormality.[21]

Diagnostic Accuracy.

The diagnostic accuracies of these criteria, as with those of LVH, typically show low sensitivities and high specificities. Recent studies using cardiac MRI to assess right ventricular structure have reported sensitivities of most criteria in populations without clinical heart disease to be less than 10%,[32] although higher sensitivities (as high as 74%) have been reported in patient cohorts with pulmonary hypertension.[33] Accuracies have been reported to be greatest in congenital heart disease, intermediate with acquired heart disease, and pulmonary hypertension, and lowest with chronic lung disease.[21]

The normal right ventricle is considerably smaller than the left ventricle and produces electrical forces largely canceled by those generated by the left ventricle. Thus, for RVH to be manifest on the ECG, it must be severe enough to overcome the masking effects of the larger left ventricular forces.

Mechanisms for the ECG Abnormalities.

As in LVH, RVH increases current fluxes between hypertrophied cells and the size of activation fronts moving through the enlarged and thickened right ventricle to produce higher-than-normal voltages on the

body surface. In addition, the activation time of the right ventricle is prolonged. Right ventricular activation now ends after activation of the left ventricle is completed. As a result, cancellation of forces generated by the right ventricle by the more powerful forces of the left ventricle is reduced, so that right ventricular forces become manifest late in the QRS complex (e.g., generation of S waves). Because the right ventricle is located anteriorly and to the right of the left ventricle, these changes are most prominent in leads directed anteriorly and to the right, that is, in the right precordial leads.

Clinical Significance

Chronic obstructive pulmonary disease (**see Chapter 86**) can induce ECG changes by producing RVH, by changing the position of the heart within the chest, and by hyperinflation of the lungs (**Fig. 12.18**). QRS changes caused by the insulating and positional changes produced by pulmonary hyperinflation include reduced amplitude of the QRS complex, right axis deviation in the frontal plane, and delayed transition in the precordial leads. Evidence of true RVH includes right axis deviation, deep S waves in the lateral precordial leads, and an $S_1Q_3T_3$ pattern, with an S wave in lead I (as an RS or rS complex), an abnormal Q wave in lead III, and an inverted T wave in the inferior leads.

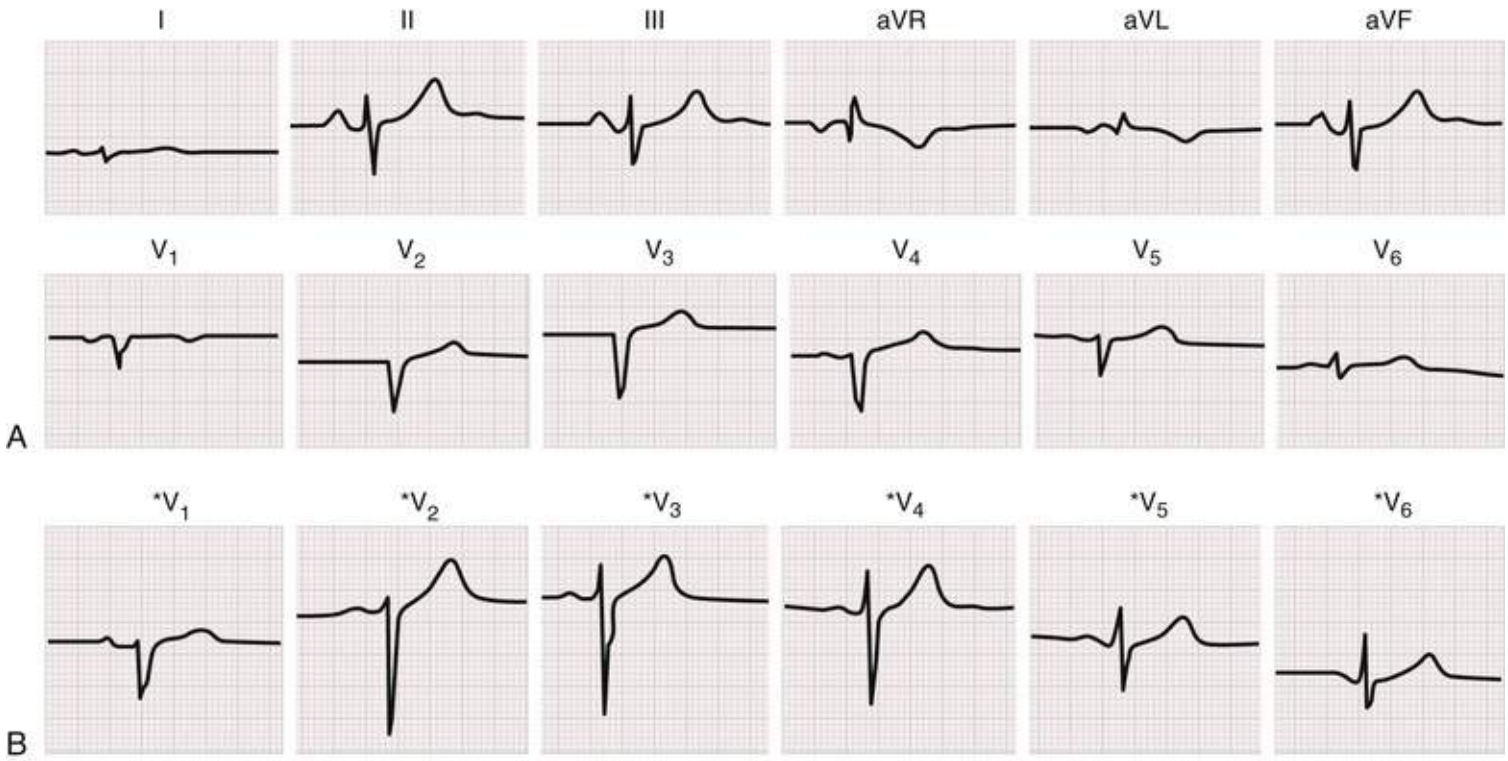

FIGURE 12.18 Pulmonary emphysema simulating anterior infarction in a 58-year-old man with no clinical evidence of coronary disease. In the tracing in **A,** note the loss of anterior R waves in the precordial leads. In **B**, the tracing shows relative normalization of R wave progression with placement of the chest leads an interspace below their usual position (e.g., $*V_1$, $*V_2$). (Modified from Chou TC. Pseudo-infarction (noninfarction Q waves). In Fisch C, editor. Complex Electrocardiography. Vol 1. Philadelphia: FA Davis; 1973.)

Conventional ECG evidence of RVH, however, has limited value in assessing the severity of pulmonary hypertension or lung disease. QRS changes generally do not appear until ventilatory function is significantly depressed, and the correlation with ventilatory function or hemodynamics is low.

Pulmonary embolism causing acute right ventricular pressure overload may generate characteristic ECG patterns (**Fig. 12.19**) (**see Chapter 84**). These include a QR or qR pattern in the right ventricular

leads, an $S_1Q_3T_3$ pattern, ST-segment deviation and T wave inversions in leads V_1 to V_3, and incomplete or complete right bundle branch block. Sinus tachycardia usually is present. Occasionally, with massive pulmonary arterial obstruction, ST-segment elevations may be seen in the right midprecordial leads. Even with major pulmonary artery obstruction, however, the ECG may show little more than minor or nonspecific waveform changes or may be normal in appearance. Thus the ECG changes are of limited clinical value.

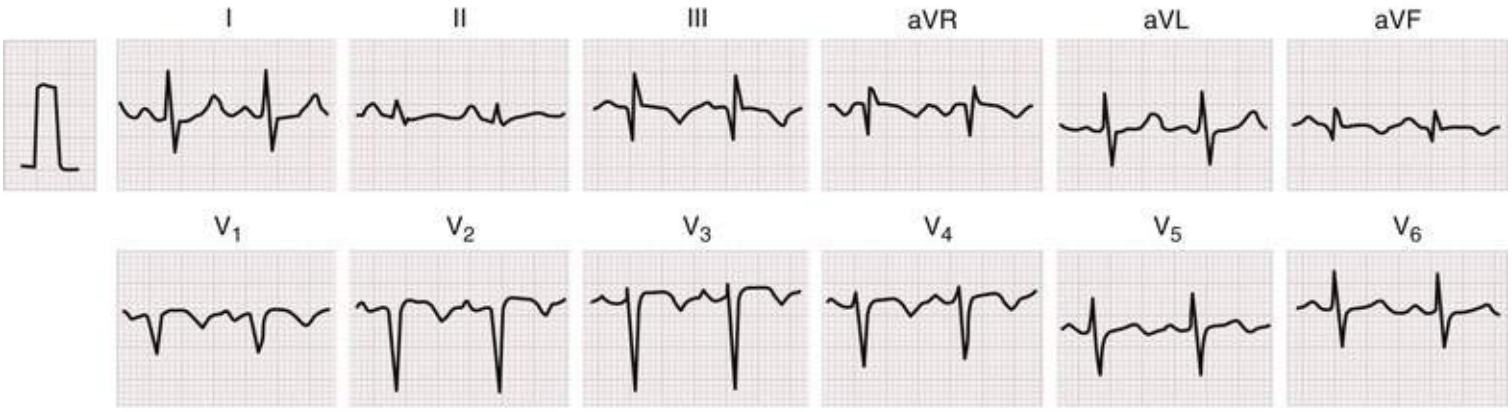

FIGURE 12.19 Acute cor pulmonale secondary to pulmonary embolism simulating inferior and anterior infarction. This tracing exemplifies the classic pseudoinfarction patterns sometimes seen with an $S_1Q_3T_3$ pattern, a QR in lead V_1 with poor R wave progression in the right precordial leads (clockwise rotation), and right precordial to midprecordial ST elevation and T wave inversion (V_1 to V_4). (From Goldberger AL, Goldberger ZD, Shvilkin A. Goldberger's Clinical Electrocardiography: a Simplified Approach. 9th ed. Philadelphia: Elsevier; 2017.)

Biventricular Hypertrophy

Hypertrophy of both ventricles produces complex ECG patterns. In contrast to biatrial enlargement, the result is not the simple sum of the two sets of abnormalities. The effects of enlargement of one chamber may cancel the effects of enlargement of the other. The greater left ventricular forces generated in LVH increase the degree of RVH needed to overcome the dominance of the left ventricle, and the anterior forces produced by RVH may cancel the enhanced posterior forces generated by LVH.

Because of these factors, specific ECG criteria for either RVH or LVH are seldom observed with biventricular enlargement. Rather, ECG patterns usually are a modification of the features of LVH, such as tall R waves in the right and left precordial leads, vertical heart position or right axis deviation, deep S waves in the left precordial leads, or a shift in the precordial transition zone to the left—all with evidence of LVH. The presence of prominent left atrial abnormality or of atrial fibrillation with evidence of right ventricular or biventricular enlargement (especially LVH with a vertical or rightward QRS axis) should suggest chronic rheumatic valvular disease (**Fig. 12.20**).

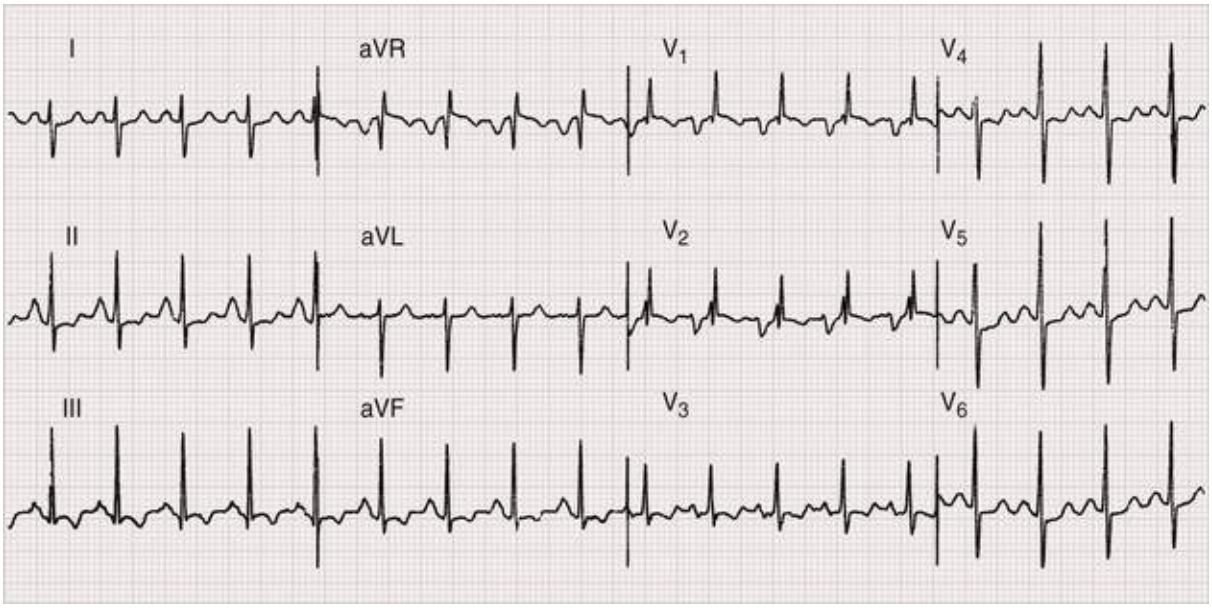

FIGURE 12.20 ECG from a 45-year-old woman with severe mitral stenosis showing multiple abnormalities. Right axis deviation and a tall R wave in lead V_1 are consistent with RVH. The very prominent biphasic P wave in lead V_1 indicates left atrial abnormality. The tall P waves in lead II suggest concomitant right atrial abnormality. Nonspecific ST-T changes and incomplete RBBB also are present. The combination of RVH and marked left or biatrial abnormality is highly suggestive of mitral stenosis. (From Goldberger AL, Goldberger ZD, Shvilkin A. Goldberger's Clinical Electrocardiography: a Simplified Approach. 9th ed. Philadelphia: Elsevier; 2017.)

Intraventricular Conduction Delays or Defects

Intraventricular conduction delays or defects (IVCDs) may result from permanent structural abnormalities in the specialized conducting tissues of the atria or ventricles or in cardiac muscle. IVCDs also may result from transient functional abnormalities in conduction in the major structures of the conduction system[34] (**see Chapters 37, 39, and 40**).

Fascicular Blocks

Absolute or relative delays in conduction in one fascicle of the left bundle system, *fascicular block*, result in an abnormal sequence of early left ventricular activation and lead to characteristic ECG patterns. Only modest delays in conduction are enough to alter ventricular activation patterns sufficiently to produce characteristic ECG patterns; a complete block of conduction is not required.

Left Anterior Fascicular Block (LAFB)

With LAFB, the regions of the left ventricular activated by the left anterior fascicle (i.e., uppermost portion of septum, anterosuperior portion of left ventricle, and left anterior papillary muscle) are activated later than normal. This results in unbalanced inferior and posterior forces early during ventricular activation (activated by the normal left posterior fascicle) followed by unopposed anterosuperior forces later during the QRS complex (the region activated late).

The resulting ECG features of LAFB are listed in **Table 12.6** and illustrated in **Fig. 12.21**. The most characteristic finding is marked left axis deviation, with a shift of the mean frontal plane QRS axis to

between −45 and −90 degrees. Lesser degrees of block may cause lesser shifts of the mean axis from previous values toward the left without exceeding the normal limits.

TABLE 12.6
Common Diagnostic Criteria for Fascicular Blocks

Left Anterior Fascicular Block
Frontal plane mean QRS axis between −45 and −90 degrees
qR pattern in lead aVL
QRS duration < 120 msec
Time to peak R wave in aVL ≥ 45 msec
Left Posterior Fascicular Block
Frontal plane mean QRS axis between +90 and +180 degrees
rS pattern in leads I and aVL with qR patterns in leads III and aVF
QRS duration < 120 msec
Exclusion of other factors causing right axis deviation (e.g., right ventricular overload patterns, lateral infarction)

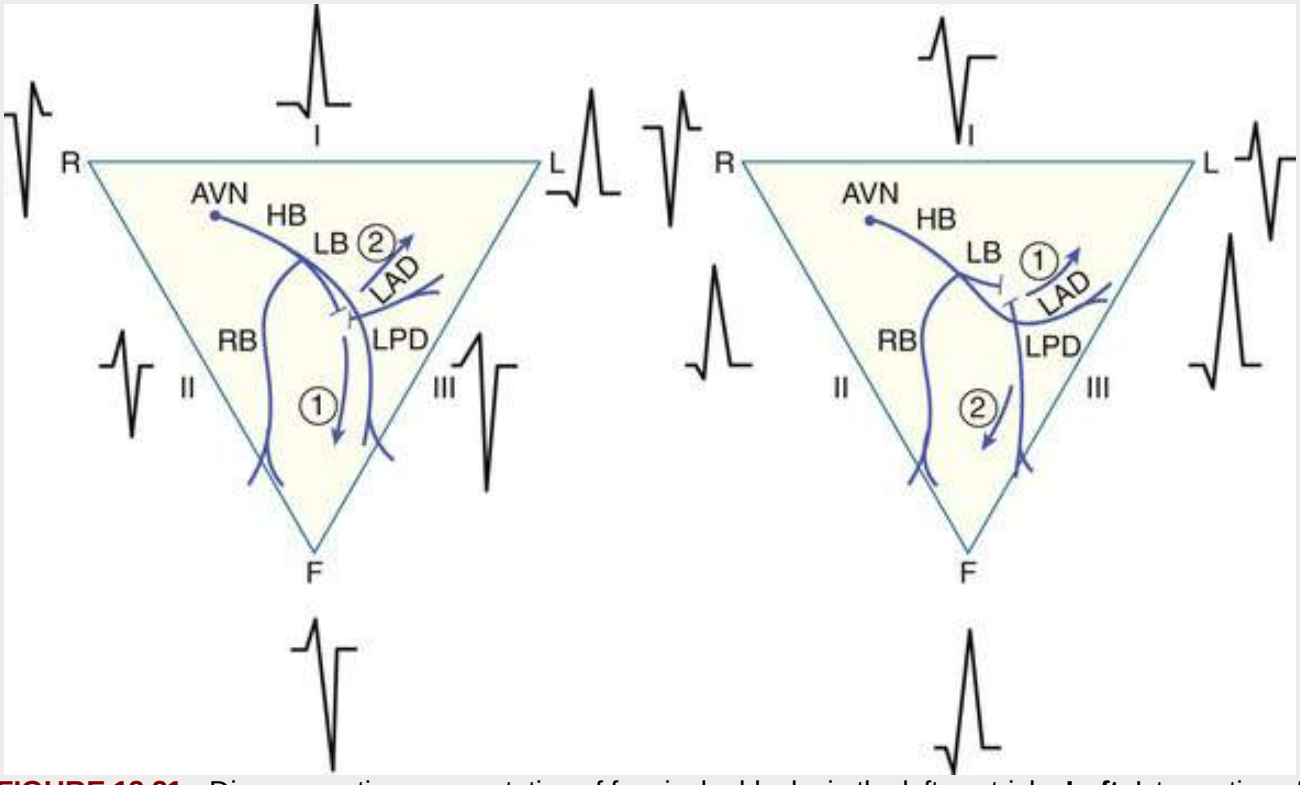

FIGURE 12.21 Diagrammatic representation of fascicular blocks in the left ventricle. **Left,** Interruption of the left anterior fascicle or division (here labeled *LAD*) results in an initial inferior (*1*) followed by a dominant superior (*2*) direction of activation. **Right,** Interruption of the left posterior fascicle or division (here labeled *LPD*) results in an initial superior (*1*) followed by a dominant inferior (*2*) direction of activation. *AVN,* Atrioventricular node; *HB,* His bundle; *LB,* left bundle; *RB,* right bundle. (Courtesy Dr. C. Fisch.)

The resulting QRS pattern in the inferior leads includes initial r waves (caused by early unopposed activation of the inferoposterior left ventricle) followed by deep S waves (caused by late unopposed activation of the anterosuperior left ventricle). Therefore, leads II, III, and aVF show rS patterns. Leads I, aVL, V_5, and V_6 show small q waves and qR patterns.

LAFB can also produce prominent changes in the precordial leads. Leads V_4 through V_6 typically show deep S waves (i.e., a delayed transition zone pattern), produced by the late activation of the anterosuperior left ventricle. The overall QRS duration is not prolonged; fascicular blocks alter the sequence but not the overall duration of left ventricular activation.

LAFB probably is the most common cause of marked left axis deviation, although it is not synonymous with it. Lesser axis shifts to between −30 and −45 degrees usually reflect other conditions, such as LVH.

LAFB is common in persons without overt cardiac disease and in a variety of cardiac conditions, reflecting the delicate nature of the structure. Some evidence indicates that this finding has a negative impact on prognosis or on progression of conduction system disease. A review in support of U.S. Preventive Services Task Force data reported a pooled adjusted hazard ratio for mortality of 1.5 based on three studies.[19]

LAFB can mask or mimic ECG changes from other conditions. The development of rS complexes in leads II, III, and aVF can mask the Q waves of an inferior myocardial infarction. Conversely, concomitant inferior infarction may cause a loss of inferior lead r waves that are expected with LAFB, instead producing QS patterns in II, III, and aVF. The larger R waves in leads I and aVL and smaller R waves but deeper S waves in leads V_5 and V_6 also make LVH criteria relying on R wave amplitude less accurate.

Left Posterior Fascicular Block (LPFB)

LPFB is caused by damage to the left posterior fascicle of the left bundle branch. It is less common than injury in the anterior fascicle because of its thicker structure and more protected location near the left ventricular inflow tract. Conduction delay results in early unopposed activation of the anterosuperior left ventricular free wall, followed by late activation of the inferoposterior aspect of the left ventricle—that is, the reverse of the pattern observed with LAFB.

The ECG features of LPFB (**see Table 12.6 and Fig. 12.21**) reflect this altered activation pattern. Right axis deviation, with rS patterns in leads I and aVL as well as qR complexes in the inferior leads, is the result of early unopposed activation forces from the anterosuperior aspect of the left ventricle (activated normally via the left anterior fascicle and producing the initial q and r waves) and late unopposed forces from the inferoposterior free wall (activated late via the left posterior fascicle and generating the late S and R waves). As in LAFB, the overall activation time of the ventricles is not prolonged, and the QRS duration remains normal.

LPFB can occur in patients with any cardiac disease but is unusual in otherwise healthy persons. The specific diagnosis of LPFB requires first excluding other causes of right axis deviation and including right ventricular overload syndromes and extensive high or anterolateral infarction.

Other Forms of Fascicular Block

An estimated one third of people have an anatomic third branch of the left bundle system: the *left median* or *septal fascicle*. ECG patterns that suggest left septal or median fascicular block include the absence of septal q waves. However, this term is not currently recommended for use in clinical diagnosis because clear diagnostic criteria have not been generally accepted.[34]

Left Bundle Branch Block (LBBB)

LBBB results from conduction delay or block in any of several sites in the intraventricular conduction system, including the main left bundle branch or in each of its two major fascicles; the distal conduction system of the left ventricle; the fibers of the bundle of His that become the main left bundle branch; or in the ventricular myocardium.

LBBB causes extensive reorganization of the activation and recovery patterns of the left ventricle to produce a widened QRS complex with characteristic changes in the shape of the QRS complex and ST-T wave (**Fig. 12.22**). Commonly relied-on diagnostic criteria for LBBB are listed in **Table 12.7**. Basic requirements include QRS duration of 120 milliseconds or more; broad and, typically, notched R waves in leads I and aVL and the left precordial leads; narrow r waves followed by broad and deep S waves in the right precordial leads; and, in most cases, absence of septal q waves. The mean QRS axis may be normal, deviated to the left, or rarely, deviated to the right.

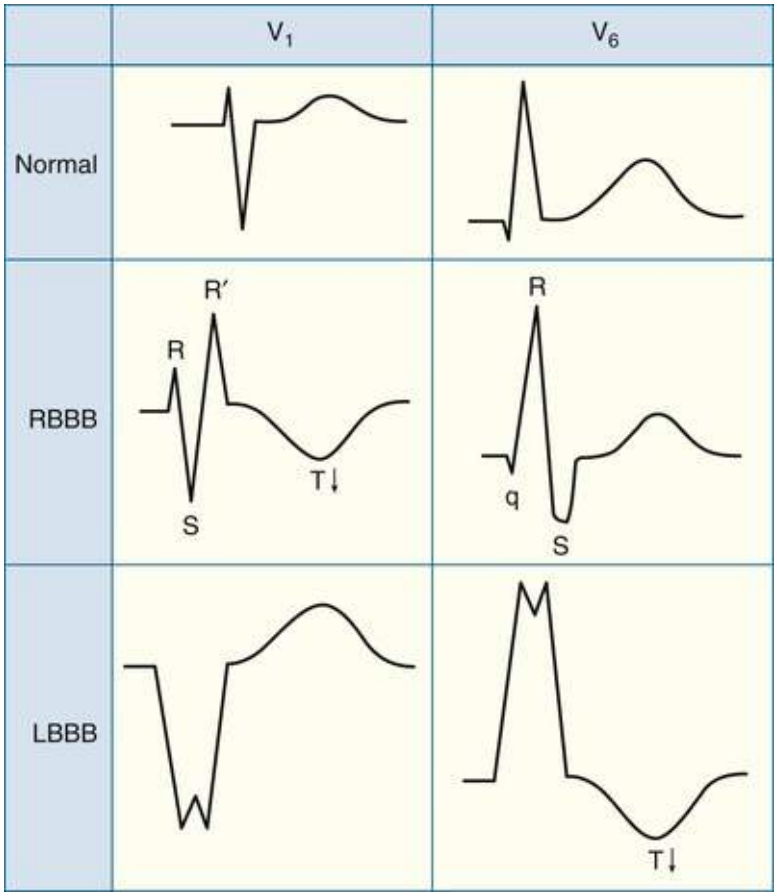

FIGURE 12.22 Comparison of typical QRS-T patterns in RBBB and LBBB with the normal pattern in leads V_1 and V_6. Note the secondary T wave inversions (*arrows*) in leads with an rSR′ complex with RBBB and in leads with a wide R wave with LBBB. (From Goldberger AL, Goldberger ZD, Shvilkin A. Goldberger's Clinical Electrocardiography: a Simplified Approach. 9th ed. Philadelphia: Elsevier; 2017.)

TABLE 12.7

Common Diagnostic Criteria for Bundle Branch Blocks

Complete Left Bundle Branch Block
QRS duration ≥ 120 msec
Broad, notched, or slurred R waves in leads I, aVL, V_5, and V_6
Small or absent initial r waves in leads V_1 and V_2 followed by deep S waves
Absent septal q waves in leads I, V_5, and V_6
Prolonged time to peak R wave (>60 msec) in V_5 and V_6
Complete Right Bundle Branch Block
QRS duration ≥ 120 msec
rsr′, rsR′, or rSR′, patterns in leads V_1 and V_2
S waves in leads I and V_6 ≥ 40 msec wide
Normal time to peak R wave in leads V_5 and V_6 but > 50 msec in V_1

Recently proposed, stricter criteria mandate a QRS duration of 140 milliseconds or more and mid-QRS notching in left-facing leads. These criteria may have better correlation with disordered endocardial activation patterns (see later) and higher predictive value of benefit from resynchronization pacemaker therapy[35] (**see Chapters 27 and 41**). Other criteria require a prolonged time to the peak of the R wave (≥60 msec) in the left precordial leads to diagnose LBBB.[34]

The ST segment and T wave are discordant with the QRS complex in most cases. The ST segments are depressed and T waves inverted in leads with positive QRS waves (e.g., leads I, aVL, V_5, and V_6). ST segments are elevated and T waves upright in leads with predominantly negative QRS complexes (e.g., leads V_1 and V_2).

Incomplete LBBB may result from lesser degrees of conduction delay in the left bundle branch system. Features include modest prolongation of the QRS complex (100 to 119 msec); loss of septal q waves; slurring and notching of the upstroke of tall R waves; and delay in time to peak of the R wave in left precordial leads.

Mechanisms for the ECG Abnormalities.

LBBB causes extensive reorganization of left ventricular activation. Initial septal activation with LBBB typically occurs on the right (rather than on the left as in normal conditions) septal surface, leading to right-to-left (rather than left-to-right) activation of the septum; as a result, normal septal q waves are absent. Left ventricular activation follows slow transseptal spread from the right ventricular side of the septum and is substantially delayed.

In as many as one third of cases, however, earliest septal activation occurs in the left midseptal region. This suggests activation by the left bundle system rather than by transseptal spread. In these cases the LBBB pattern may reflect damage to the distal left bundle system or primarily delays in intramuscular conduction within the ventricular myocardium.[36] In such cases, septal q waves may persist.

The subsequent activation of the ventricular free wall is highly variable, depending on the type, location, and extent of the underlying cardiac disease. Spread is disrupted by regions of block, forcing activation to maneuver around the block through slowly conducting, working myocardium to activate the more distal portions of the ventricle. This results in a prolonged QRS complex with prominent notching and slurring. Overall activation may require more than 180 milliseconds, depending on the functional status of the distal left bundle and Purkinje systems and on the speed of propagation through working cardiac muscle. Studies have suggested that LBBB patterns may develop solely from disordered conduction within ventricular walls even without disordered ventricular endocardial activation.[36]

The discordant ST-T wave pattern is a reflection of the altered pattern of ventricular activation. With LBBB, the right ventricle is activated and recovers earlier than the left so that recovery currents are directed toward the right and away from the left ventricle. Therefore, positive ST-T waves will be registered in leads over the right ventricle that show S waves and negative ones are detected over the left ventricular leads showing prominent R waves. These ST-T wave changes are referred to *secondary ST-T abnormalities* because they are generated predominantly by abnormalities in conduction. As discussed later, ST-T wave changes produced by direct abnormalities of the recovery process (e.g., ischemia, drug effects, electrolyte abnormalities) are referred to as *primary ST-T abnormalities*.

Clinical Significance.

LBBB occurs in fewer than 1% of the general population but in more than one third of patients with heart failure. As many as 70% of persons in whom LBBB develops have preceding ECG evidence of LVH. Fewer than 10% of patients with LBBB have no clinically demonstrable heart disease.

In persons with or without overt heart disease, LBBB is associated with a higher-than-normal risk of mortality and morbidity from infarction, heart failure, and arrhythmias, including high-grade atrioventricular block. In two recent population-based studies, LBBB was significantly related to an increase in new onset of heart failure (with a RR of 2.8 to 3.0) and in cardiovascular death (with a RR of 2.2).[37,38] Among patients with coronary artery disease, including acute myocardial infarction, the presence of LBBB is associated with more extensive disease, more severe left ventricular dysfunction, and reduced survival rates.

Patients with LBBB and either left or right axis deviation have more extensive cardiac disease and more severe clinical manifestations. Left axis deviation is associated with more severe conduction system disease that involves the fascicles and the main left bundle, whereas right axis deviation suggests dilated cardiomyopathy with biventricular enlargement.

The abnormal ventricular activation pattern of LBBB itself induces hemodynamic changes that are superimposed on the abnormalities caused by the underlying heart disease. Whereas normal left ventricular contraction is highly synchronized and begins in all sites within 40 milliseconds, the pattern with LBBB is less coordinated and requires much more time. The result is asynchronous and prolonged left ventricular contraction that causes regional differences in workload, regional changes in blood flow and metabolism, structural remodeling, and functional mitral valve regurgitation.[39] These perturbations may lead to or exacerbate clinical heart failure and serve as a basis for resynchronization cardiac therapy, especially with greatly prolonged QRS duration (**see Chapters 27 and 41**).

A major impact of LBBB lies in obscuring or simulating other ECG patterns. The diagnosis of LVH is complicated by the increased QRS amplitude intrinsic to LBBB, and the very high prevalence of anatomic LVH in patients with LBBB makes defining criteria with high specificity difficult. Patterns suggestive of coexistent LVH include left atrial P wave abnormalities, greatly prolonged QRS duration (>155 msec), and precordial voltage criteria.[34] The diagnosis of myocardial infarction may be obscured, as discussed in detail later.

The diffuse ST-T wave abnormalities associated with LBBB also render detection of ischemia at rest and on standard exercise testing unreliable. This clinical problem is compounded by the frequency of reversible myocardial perfusion defects in the septal and anteroseptal left ventricle during exercise stress testing in the absence of significant disease of the left coronary system, reflecting functional abnormalities in regional myocardial blood flow rather than ischemia related to fixed coronary artery lesions.

Right Bundle Branch Block (RBBB)

RBBB is a result of conduction delay in any portion of the right-sided intraventricular conduction system. The delay is most common in the main right bundle branch itself and may also occur in the bundle of His or in the distal right ventricular conduction system, such as after right ventriculotomy.

ECG Abnormalities.

Major features of RBBB are illustrated in **Fig. 12.22**, and common diagnostic criteria are listed in **Table 12.7**. As with LBBB, the QRS complex duration exceeds 120 milliseconds. The right precordial leads show prominent and notched R waves with rsr′, rsR′, or rSR′ patterns, whereas leads I and aVL and the left precordial leads demonstrate S waves that are wider than the preceding R wave. As in LBBB, the ST-T waves are discordant with the QRS complex; T waves are inverted in the right precordial leads and upright in the left precordial leads and in leads I and aVL.

The mean QRS axis is not altered by RBBB. Axis shifts can occur, however, as a result of the simultaneous occurrence of left fascicular block along with RBBB (see later).

Incomplete RBBB, produced by lesser delays in conduction in the right bundle branch system, is characterized by an rSr′ pattern in lead V_1 with a QRS duration between 100 and 120 milliseconds. These changes also may reflect underlying RVH (especially with a rightward QRS axis) without intrinsic dysfunction of the conduction system or as a manifestation of the Brugada pattern (**see Chapters 33 and 37**). An rSr′ morphology in lead V_1 (and sometimes V_2) with a normal QRS duration is also a common finding in patients without cardiovascular disease, especially in athletes or in association with pectus excavatum, and may normalize when the right precordial electrodes are placed one interspace lower than usual.[40]

Mechanisms for ECG Abnormalities.

With delay or block in the proximal right bundle branch system, activation of the right side of the septum is initiated only after slow transseptal spread of activation from the left septal surface. The right ventricular anterior free wall is then excited slowly, followed by activation of the remaining right ventricle.

The delayed and slowed activation of the right ventricle causes much or all of the right ventricle to activate after depolarization of the left ventricle has been completed. This reduces the cancellation of right ventricular activation forces by the more powerful left ventricular activation forces. The late unopposed emergence of right ventricular forces then produces increased anterior and rightward voltage observed in the latter half of the QRS, as well as a prolonged QRS duration.

Discordant ST-T wave patterns are generated by the same mechanisms as for LBBB. With RBBB, recovery forces are directed away from the right and toward the earlier activated left ventricle. The result is inverted T waves in the right precordial leads and positive ones in the left precordial leads.

Clinical Significance.

RBBB is a common finding in the general population, and many persons with RBBB have no clinical evidence of structural heart disease. The high prevalence of RBBB is attributable to the relative fragility of the right bundle branch, as suggested by the development of RBBB after the minor trauma produced by

right ventricular catheterization.

In patients without manifest cardiac disease, RBBB or incomplete RBBB patterns generally are not associated with increased risk of cardiac morbidity or mortality,[37,38,41] although right ventricular dilation and reduced function may be present. When cardiac disease is present, the coexistence of RBBB suggests advanced disease with more extensive multivessel disease and reduced long-term survival in patients with ischemic heart disease. An RBBB-like pattern with persistent ST-segment elevation in the right precordial leads may indicate the Brugada pattern, with susceptibility to ventricular tachyarrhythmias and sudden cardiac death (Brugada syndrome; **see Chapters 33 and 37**). Patterns of complete or incomplete RBBB are also common among trained athletes (**see Chapter 53**).

RBBB interferes with other ECG diagnoses, although to a lesser extent than for LBBB. The diagnosis of RVH is more difficult to make with RBBB because of the accentuated positive potentials in lead V_1. RVH is suggested, although with limited accuracy, by the presence of an R wave in lead V_1 that exceeds 1.5 mV and a rightward shift of the mean QRS axis.

The usual criteria for LVH can be applied but have lower sensitivities than with normal conduction. RBBB reduces the amplitude of (or eliminates) the S wave in the right precordial leads and that of the R waves in the left precordial leads, thus reducing the accuracy of ECG criteria for LVH. The combination of left atrial abnormality or left axis deviation with RBBB also suggests underlying LVH. Ventricular dyssynchrony also occurs with RBBB but to a lesser extent than with LBBB.

Multifascicular Blocks

The term *multifascicular block* refers to conduction delay or block in more than one of the structural components of the specialized conduction system, including the main left bundle and its major fascicles and the right bundle branch.

Bifascicular block involves delay or block in any two of these structures. It may have several forms depending on the sites of conduction delay. Delay in the RBBB and LAFB is characterized by RBBB plus left axis deviation beyond −45 degrees (**Fig. 12.23**). RBBB with LPFB produces a pattern of RBBB and a mean QRS axis deviation to the right of +120 degrees (**Fig. 12.24**). LBBB alone, which may be caused by delay in both the anterior and the posterior fascicle, is also usually considered a form of bifascicular block, even though the site or sites of delay are not known.

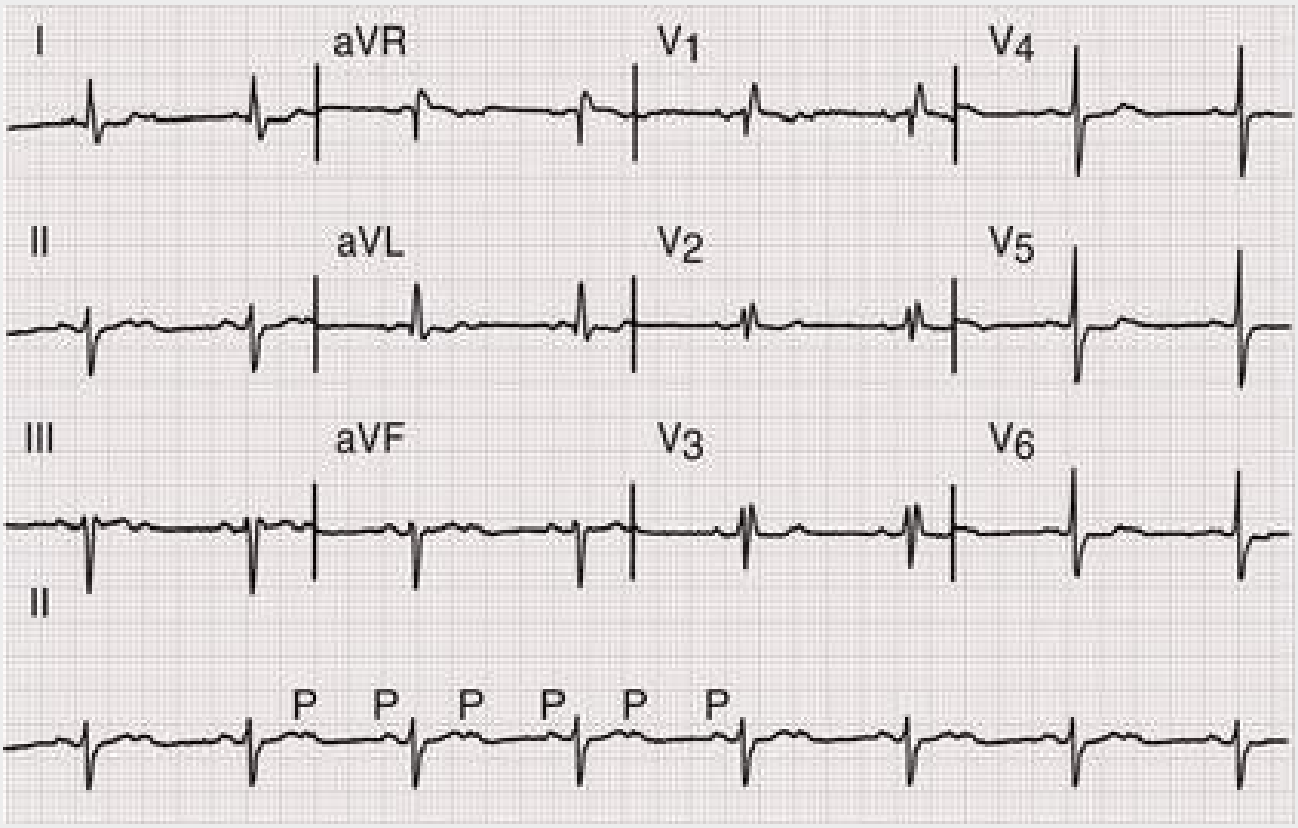

FIGURE 12.23 Sinus rhythm at 95 beats/minute with 2 : 1 atrioventricular block. Conducted ventricular beats show a pattern consistent with bifascicular block with delay or block in the right bundle and left anterior fascicle. The patient underwent pacemaker implantation for presumed infra-Hisian block, which was symptomatic.

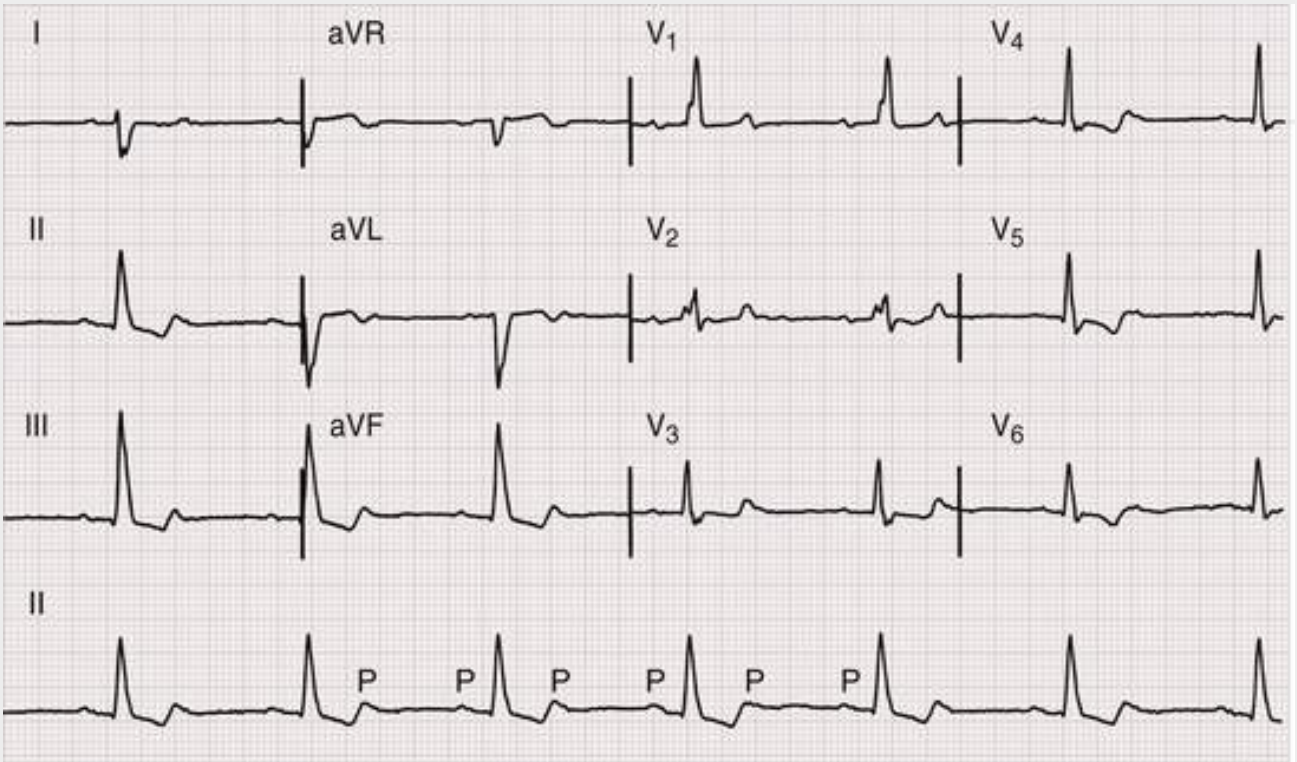

FIGURE 12.24 Sinus rhythm with 2 : 1 atrioventricular block. QRS morphology in the conducted beats is consistent with bifascicular block with delay or block in the right bundle and left posterior fascicle. Subsequently, complete heart block was noted. The patient underwent pacemaker implantation.

Trifascicular block involves conduction delay in the right bundle branch plus delay in either the main

left bundle branch or in both the left anterior and the left posterior fascicle. The resulting ECG pattern depends on the relative degree of delay in the affected structures. If conduction delay exists in both the right and the left bundle branch and the delay in the right bundle branch is less than the delay in the left bundle branch, activation will begin in the right ventricle, and the QRS pattern will resemble that of LBBB. If the delay is greater in the right bundle branch than in the left bundle branch, the ECG pattern will be that of RBBB.

A diagnosis of trifascicular block requires an ECG pattern of bifascicular block plus evidence of prolonged conduction below the atrioventricular (AV) node. In bifascicular block, conduction time through the unaffected fascicle (and thus minimum conduction time) is normal, and conduction time from the AV node to ventricular muscle is normal. Accordingly, the PR interval will be normal (in the absence of AV nodal conduction delay). In trifascicular block, however, the delay in conduction through even the least affected path is abnormally prolonged so that the minimal conduction time from the AV node to the ventricular myocardium also is prolonged. Only delay, not block, of conduction in at least one of the conduction pathways is required. If complete block were present in the right bundle branch and in the left bundle or in of its fascicles, conduction would fail and complete heart block would result.

In some cases the path with the longest delay can vary with the heart rate. In these cases, conduction patterns vary or alternate between two or more IVCD types to produce *alternating bundle branch block* (**Fig. 12.25**).

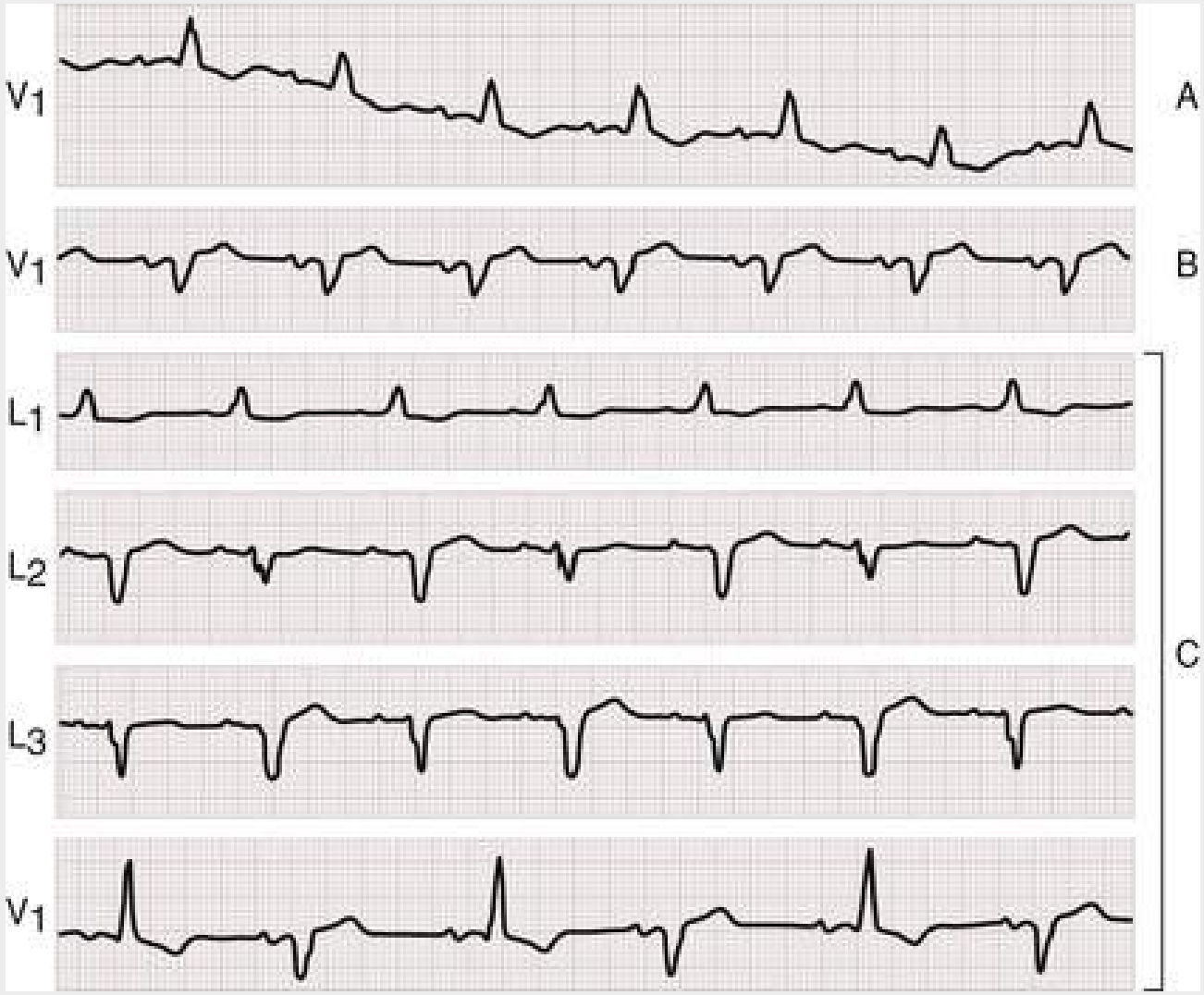

FIGURE 12.25 Multifascicular block manifested by alternating bundle branch blocks and PR intervals (sections *A-C*), recorded on separate days. *A,* Lead V_1 recording shows a RBBB with a prolonged PR interval of 280 milliseconds. *B,* Lead V_1 shows LBBB with a PR of 180 milliseconds. *C,* Leads I, II, III, and V_1 show alternating RBBB and LBBB patterns, along with PR alternation. The limb leads also show left anterior fascicular block (with subtle alternation of the QRS morphology). (From Fisch C. Electrocardiography of Arrhythmias. Philadelphia: Lea & Febiger; 1990.)

On the surface ECG, the delay in conduction may be manifested as a prolonged PR interval. However, the PR interval in mostly determined by the conduction time through the AV node with a lesser contribution by the conduction time in the infranodal conduction system. Prolonged intraventricular conduction may be insufficient to extend the PR interval beyond normal limits, whereas a greatly prolonged PR interval most often reflects delay in the AV node rather than in all three intraventricular fascicles. *Thus the finding of a prolonged PR interval in the presence of an ECG pattern consistent with bifascicular block is not diagnostic of trifascicular block, whereas the presence of a normal PR interval does not exclude it.* This delay in conduction is most specifically observed as a prolongation of the His-ventricular (HV) time in intracardiac recordings (**see Chapter 34**).

The major clinical implication of a multifascicular block is its relation to advanced conduction system disease. It may be a marker for severe myocardial disease and may identify patients at risk for heart block (**see Fig. 12.23**), as discussed in **Chapter 40**.

Other Forms of Conduction Abnormalities

Rate-Dependent Conduction Blocks

Rate-dependent block usually occurs as a transient IVCD pattern (**see Chapter 34**). In *acceleration (tachycardia)-dependent block*, conduction delay occurs when the heart rate exceeds a critical value. This form of rate-related block is relatively common and can have the ECG pattern of RBBB or LBBB (**Fig. 12.26**). In *deceleration (bradycardia)-dependent block*, conduction delay occurs when the heart rate falls below a critical level. Deceleration-dependent block is less common than acceleration-dependent block and usually is seen only in patients with advanced conduction system disease (**Fig. 12.27**). The electrophysiologic bases for these patterns are discussed in **Chapter 34**.

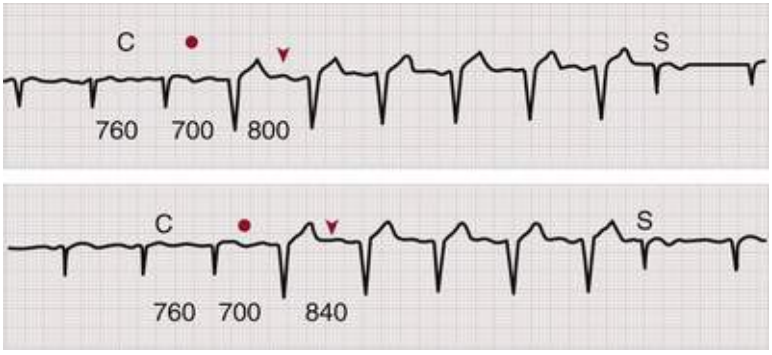

FIGURE 12.26 Acceleration-dependent QRS aberration with the persistence at a longer cycle and normalization at a shorter cycle than that initiating the aberration, indicating conduction hysteresis in the conduction system. The basic duration of the basic cycle (*C*) is 760 milliseconds. LBBB appears at a cycle length of 700 milliseconds (*dot*) and is perpetuated at cycle lengths (*arrowhead*) of 800 and 840 milliseconds; conduction normalizes after a cycle length of 600 milliseconds. Perpetuation of LBBB at cycle lengths of 800 and 840 milliseconds is probably caused by transseptal concealment. Unexpected normalization of the QRS (*S*) after the atrial premature contraction probably is caused by equalization of conduction in the two bundles. (From Fisch C, Zipes DP, McHenry PL. Rate dependent aberrancy. Circulation 1973;48:714.)

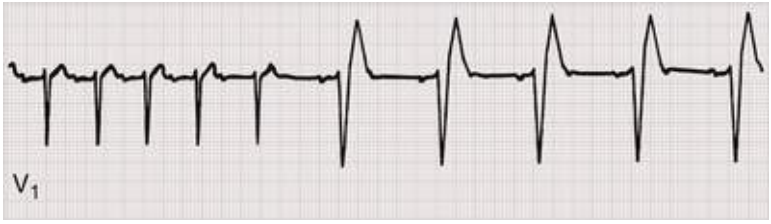

FIGURE 12.27 Deceleration-dependent aberration. The basic rhythm is sinus with a Wenckebach (type I) atrioventricular block. With 1 : 1 atrioventricular conduction, the QRS complexes are normal in duration; with a 2 : 1 atrioventricular block or after the longer pause of a Wenckebach sequence, LBBB appears. (Courtesy Dr. C. Fisch).

Other mechanisms of ventricular aberration include concealed conduction in the bundle branches, preexcitation syndromes, depressed myocardial conduction from drugs or hyperkalemia, and the effect on refractoriness of abrupt changes in cycle length (the basis of the *Ashman phenomenon*) and are discussed in **Chapters 34 and 37**. **Table 12.8** summarizes the major causes of a wide QRS occurring at physiologic heart rates. The more specific topic of wide complex tachycardias is discussed in **Chapters 35 and 37**.

TABLE 12.8

Major Causes of a Wide QRS (at Physiologic Rates)

Chronic (intrinsic) intraventricular conduction delays or defects (IVCDs)
Right bundle branch block (RBBB)
Left bundle branch block (LBBB)
"Nonspecific" IVCDs
Transient IVCDs
Rate related
Acceleration dependent
Deceleration dependent
Retrograde (transseptal) activation
Ashman type
"Toxic" (extrinsic) conduction delays
Hyperkalemia
Drugs (especially those with class I activity)
Ventricular-originating complexes
Premature ventricular complexes (PVCs)
Ventricular escape beats
Ventricular paced beats
Ventricular preexcitation (WPW and related patterns)

For causes of wide-complex tachycardias, see **Chapters 34 and 37**.

WPW, Wolff-Parkinson-White.

Peri-Infarction Block.

Peri-infarction block refers to conduction delay in the region of a myocardial infarction. It is manifested in ECG leads by pathologic Q waves when the terminal portion of the QRS complex is wide and directed opposite to the Q wave, such as a QR complex in leads III and aVF. A related abnormality is *peri-ischemic block,* with reversible widening of the QRS complex in leads with ST-segment elevation caused by acute injury.

Nonspecific Intraventricular Conduction Defect (Delay).

This term is often used to refer to patterns with a widened QRS complex (>120 msec) but without the specific patterns characteristic of RBBB or LBBB.

Myocardial Ischemia and Infarction

The ECG remains a key test for the diagnosis and management of acute and chronic coronary syndromes.[2,42-50] The waveform findings vary considerably depending on four major factors: (1) the duration of the ischemic process (acute versus evolving versus chronic), (2) its extent (size and degree of transmural involvement), (3) its topography (anterior versus inferior-posterior-lateral or right ventricular), and (4) the presence of other underlying abnormalities (e.g., prior infarction, LBBB, Wolff-Parkinson-White syndrome, or pacemaker patterns) because they can alter or mask the classic patterns. A critical clinical distinction is between *ST-segment elevation myocardial infarction* (or ischemia) (STEMI) and *non-STEMI infarction* (or ischemia) syndromes. With STEMI, an invasive approach aimed toward immediate reperfusion therapy with a percutaneous coronary intervention is the goal, unless contraindicated. With non-STEMI, urgent diagnostic angiography with revascularization, if feasible, is indicated by the presence of refractory angina, or hemodynamic or electrical instability (**see Chapters 59 and 60**).

Repolarization (ST-T Wave) Abnormalities

The earliest and most consistent ECG finding during acute severe ischemia is deviation of the ST segment occurring as a result of complicated current of injury mechanisms (**see Chapter 59**). Under normal

conditions, the ST segment usually is nearly isoelectric, because almost all healthy myocardial cells attain approximately the same potential during the plateau phase of the ventricular action potential.

Ischemia, however, produces complex time-dependent effects on the electrical properties of myocardial cells. Severe acute ischemia can reduce the resting membrane potential, shorten the duration of the action potential, and decrease the rate of rise and amplitude of phase 0 in the ischemic area (**Fig. 12.28**). The key concept is that these perturbations cause a *voltage gradient* between normal and ischemic zones that leads to current flow between these regions. The resulting *injury currents* are represented on the surface ECG as deviations of the ST segment.

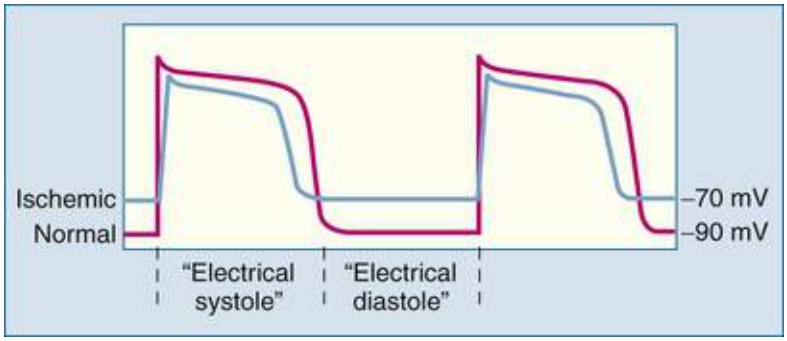

FIGURE 12.28 Acute ischemia may alter ventricular action potentials in a number of ways that result in lower resting membrane potential, decreased amplitude and velocity of phase 0, and an abbreviated action potential duration (a pathologic form of early repolarization). These electrophysiologic effects, singly or in combination, create a voltage gradient between ischemic and normal cells during different phases of the cardiac electrical cycle. The resulting currents of injury are reflected on the surface ECG by deviation of the ST segment (**see Fig. 12.29**).

The precise electrophysiologic mechanisms underlying injury currents and their directionality with ischemia and related conditions remains an area of active research and some controversy even after decades of study. Both "diastolic" and "systolic" injury currents have been proposed, based primarily on animal studies, to explain ischemic ST-segment elevations[2,46,48] (**Fig. 12.29**). According to the "diastolic current of injury" hypothesis, ischemic ST-segment elevation is attributable to negative (downward) displacement of the electrical diastolic baseline (the TQ segment of the ECG). Ischemic cells remain relatively depolarized, probably related importantly to potassium ion leakage, during phase 4 of the ventricular action potential (i.e., lower membrane resting potential; **see Fig. 12.28**) and depolarized muscle carries a negative extracellular charge relative to repolarized muscle. Therefore, during electrical diastole, current (the diastolic current of injury) will flow between the partly or completely depolarized ischemic myocardium and the neighboring, normally repolarized, uninjured myocardium. The injury current vector will be directed away from the more negative ischemic zone toward the more positive normal myocardium. As a result, leads overlying the ischemic zone will record a negative deflection during electrical diastole and produce depression of the TQ segment.

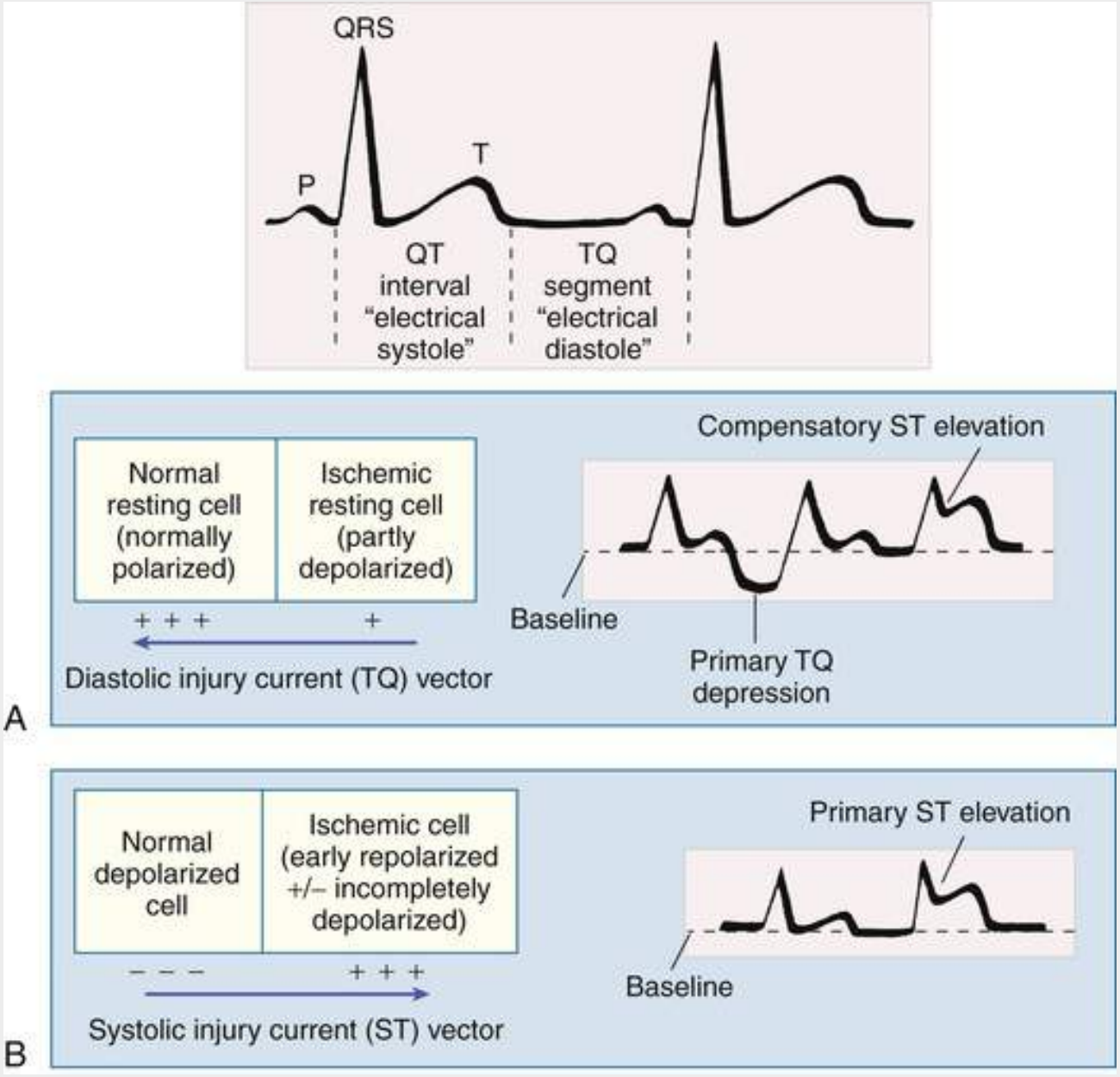

FIGURE 12.29 A simplified scheme of the pathophysiology of ischemic ST elevation. Two basic mechanisms have been advanced to explain the ST elevation seen with acute myocardial injury. **A,** Diastolic current of injury. In this case (first QRS-T complex), the ST vector will be directed away from the relatively negative, partly depolarized ischemic region during electrical diastole (TQ segment), and the result will be primary TQ depression. Conventional alternating current ECGs "compensate" for the baseline shift, and apparent ST-segment elevation (second QRS-T complex) results. **B,** Systolic current of injury. In this scenario, the ischemic zone will be relatively positive during electrical systole because the cells are repolarized early, and the amplitude and upstroke velocity of their action potentials may be decreased. This so-called systolic injury current vector will be oriented toward the electropositive zone, and the result will be primary ST-segment elevation. In clinical recordings, the contributions of diastolic and systolic injury currents to the observed ST-segment elevation cannot be determined (see text).

TQ-segment depression appears as ST-segment elevation, because the ECG recorders in clinical practice use AC-coupled amplifiers that automatically "compensate" or adjust for any negative shift in the TQ segment. As a result of this electronic effect, the ST segment will be proportionately elevated. Therefore, according to the diastolic current of injury theory, ST-segment elevation represents an apparent shift. The true shift, observable only with DC-coupled ECG amplifiers, is the negative displacement of the TQ baseline.

Evidence also suggests that ischemic ST-segment elevations (and hyperacute T waves) may also be related to systolic injury currents. Three pathologic factors may make acutely ischemic myocardial cells relatively positive compared with normal cells in regard to their extracellular charge during electrical

systole (QT interval): (1) abbreviation of action potential duration, (2) decreased action potential upstroke velocity, and (3) decreased action potential amplitude (**see Fig. 12.28**). The presence of one or more of these effects will establish a voltage gradient between normal and ischemic zones during the QT interval such that the current of injury vector will be directed toward the ischemic region. This systolic current of injury mechanism, also probably related in part to potassium leakage, will result in primary ST-segment elevation, sometimes with tall positive (*hyperacute*) T waves.

When acute ischemia is transmural (or nearly so), the overall ST vector (whether caused by diastolic or systolic injury currents, or both) usually is shifted in the direction of the outer (epicardial) layers, and ST-segment elevation and sometimes tall, positive (hyperacute) T waves are recorded over the ischemic zone (**Fig. 12.30**). Reciprocal ST-segment depression can appear in leads reflecting the contralateral surface of the heart. Occasionally, the reciprocal changes can be more apparent than the primary ST-segment elevations.

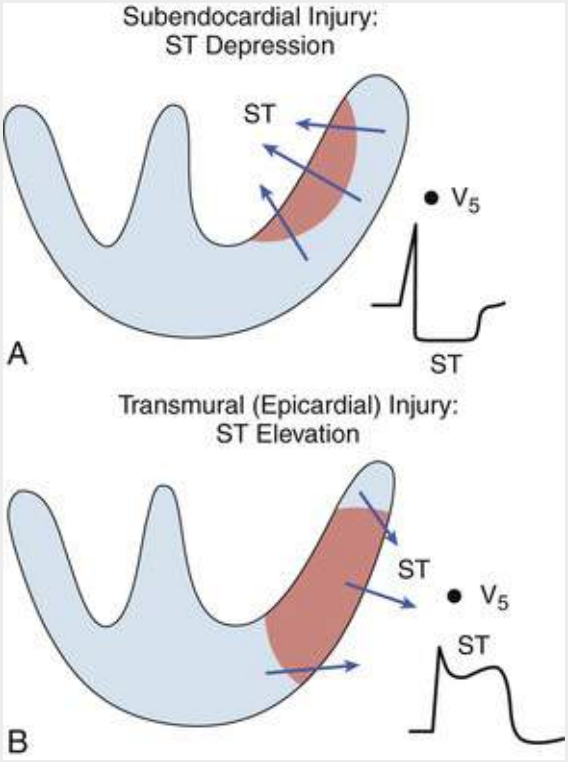

FIGURE 12.30 Directionality of current of injury patterns (ST vectors) with acute ischemia. **A,** With predominant subendocardial ischemia, the resultant ST vector is directed toward the inner layer of the affected ventricle and the ventricular cavity. Overlying leads therefore record ST depression, as may be seen during abnormal exercise stress tests or with spontaneous angina pectoris. **B,** With ischemia involving the outer ventricular layer (transmural or epicardial injury), the ST vector is directed outward. Overlying leads record ST-segment elevation. Reciprocal ST-segment depression can appear in contralateral leads.

When ischemia is confined primarily to the subendocardium (approximately the inner half of the ventricular wall), the overall ST vector typically shifts toward the inner ventricular layer and the ventricular cavity such that the overlying (e.g., anterior precordial) leads show ST-segment depression, with ST-segment elevation in lead aVR (**Fig. 12.30**). This subendocardial ischemia pattern is the typical finding during spontaneous episodes of angina pectoris or during symptomatic or asymptomatic (silent) ischemia induced by exercise or pharmacologic stress tests (**see Chapter 13**). However, inspection of the surface ECG, with either ST elevation or ST depression ischemia, cannot differentiate between the contributions of systolic and diastolic currents of injury. Furthermore, associated alterations in

myocardial conduction and action potential properties may contribute to the ST deviations observed on the ECG.[48]

Multiple factors can affect the amplitude of acute ischemic ST-segment deviations. Profound ST-segment elevation or depression in multiple leads usually indicates very severe or widespread ischemia. Conversely, prompt resolution of ST-segment elevation after reperfusion with percutaneous coronary interventions or thrombolytic therapy is a useful marker of successful reperfusion.[49] These relationships are not universal, however, because severe ischemia or even infarction can occur with slight or absent ST-T changes. Furthermore, a relative increase in T wave amplitude (hyperacute T waves) can accompany or precede the ST-segment elevations with ischemia with or without infarction (**Fig. 12.31**).

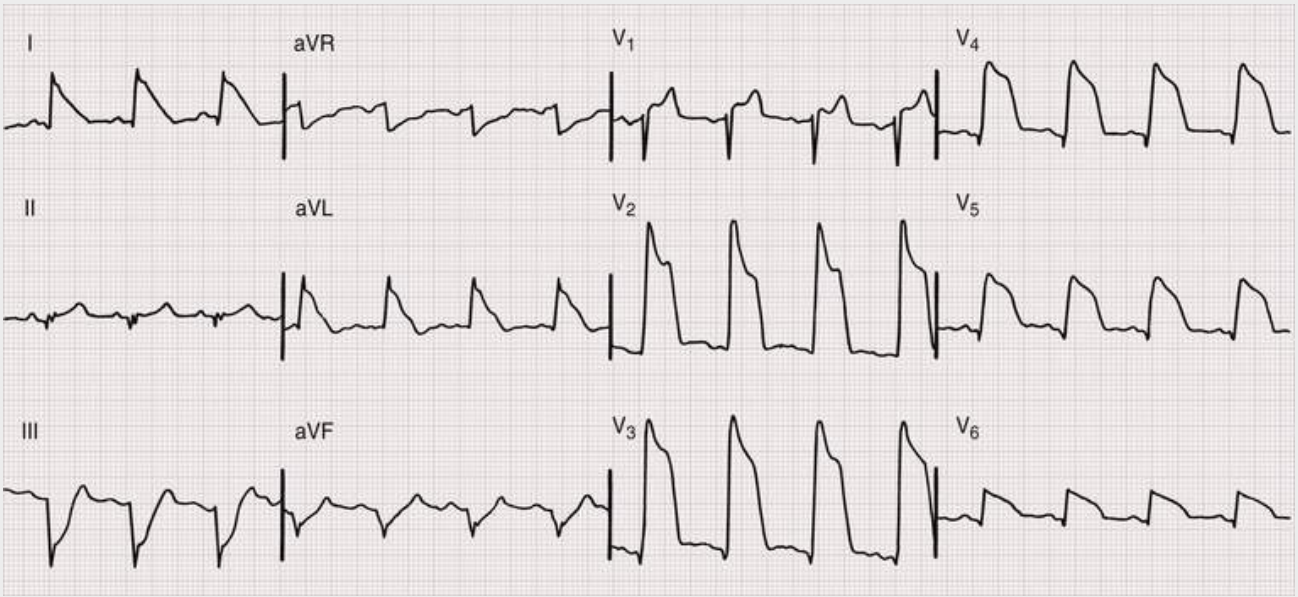

FIGURE 12.31 Hyperacute phase of extensive anterolateral myocardial infarction. Marked ST-segment elevation melding with prominent T waves is present across the precordium, as well as in leads I and aVL. ST-segment depression, consistent with a reciprocal change, is seen in leads III and aVF. Q waves are present in leads V_3 through V_6. Marked ST-segment elevations with tall T waves caused by severe ischemia are sometimes referred to as a "monophasic current of injury pattern." A paradoxical increase in R wave amplitude (V_2 and V_3) may accompany this pattern. This tracing also shows left axis deviation with small or absent inferior R waves, which raises the possibility of a previous inferior infarct.

QRS Changes

With actual infarction, depolarization (QRS) changes often accompany repolarization (ST-T) abnormalities (**Fig. 12.32**). Necrosis of sufficient myocardial tissue can lead to decreased R wave amplitude or Q waves in the anterior, lateral, or inferior leads as a result of loss of electromotive forces in the infarcted area. Local conduction delays caused by acute ischemia also can contribute to Q wave pathogenesis in selected cases.

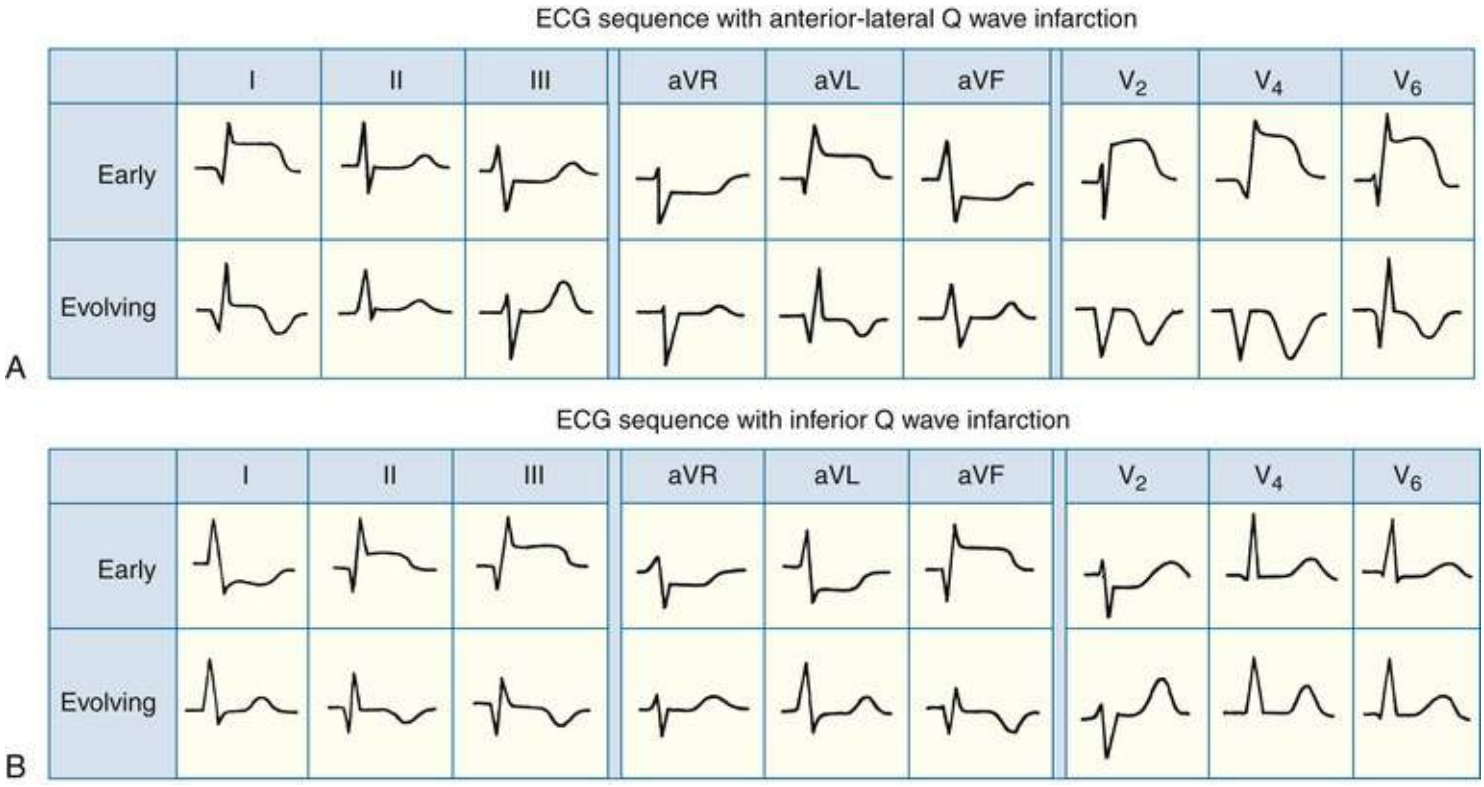

FIGURE 12.32 Sequence of depolarization and repolarization changes with acute anterior-lateral and inferior wall Q wave infarctions. **A,** With anterior-lateral infarcts, ST-segment elevation in leads I, aVL, and the precordial leads can be accompanied by reciprocal ST-segment depression in leads II, III, and aVF. **B,** Conversely, acute inferior (or posterior) infarcts can be associated with reciprocal ST-segment depression in leads V_1 to V_3. (From Goldberger AL, Goldberger ZD, Shvilkin A. Goldberger's Clinical Electrocardiography: a Simplified Approach. 9th ed. Philadelphia: Elsevier; 2017.)

Abnormal Q waves were once considered markers of transmural myocardial infarction, whereas subendocardial (*nontransmural*) infarcts were thought not to produce Q waves. However, careful experimental and correlative studies based on necropsy and imaging findings have convincingly indicated that transmural infarcts can occur without Q waves and that subendocardial or other nontransmural infarcts can be associated with Q waves.[2,42,46] Accordingly, evolving or chronic infarcts are more appropriately designated by ECG as "Q wave" or "non–Q wave," rather than as "transmural" or "nontransmural."

The QRS findings may also be somewhat different with posterior or lateral infarction (**Fig. 12.33**). Loss of depolarization forces in these regions can reciprocally increase R wave amplitude in lead V_1 and sometimes V_2, rarely without causing diagnostic Q waves in any of the conventional leads. The differential diagnosis for major causes of prominent right precordial R waves is presented in **Table 12.9**. In certain patients, fragmentation of the QRS complex, even without Q waves, may be a marker of myocardial scarring from ischemic or nonischemic causes.[51]

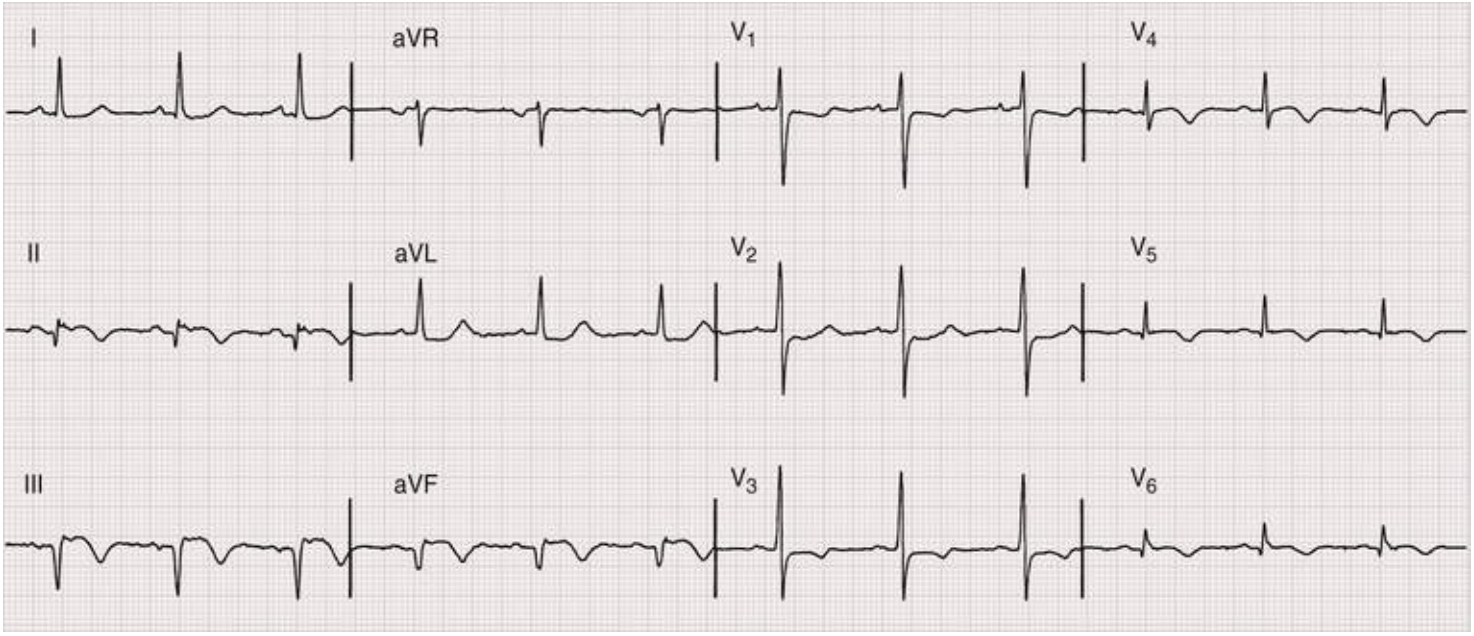

FIGURE 12.33 Evolving infero-posterolateral infarction. Note the prominent Q waves in II, III, and aVF, along with ST-segment elevation and T wave inversion in these leads, as well as V_3 through V_6. ST depression in I, aVL, V_1, and V_2 is consistent with a reciprocal change. Relatively tall R waves also are present in V_1 and V_2.

TABLE 12.9

Differential Diagnosis of Tall R Waves in Leads V_1 and V_2

Physiologic and Positional Factors
Misplacement of chest leads Normal variants Displacement of heart toward right side of chest (dextroversion), congenital or acquired
Myocardial Injury
Lateral or "true posterior" myocardial infarction Duchenne muscular dystrophy (**see Chapter 97**)
Ventricular Enlargement
RVH (usually with right axis deviation) Hypertrophic cardiomyopathy
Altered Ventricular Depolarization
Right ventricular conduction abnormalities WPW patterns (caused by posterior or lateral wall preexcitation)

Modified from Goldberger AL, Goldberger ZD, Shvilkin A. Goldberger's Clinical Electrocardiography: a Simplified Approach. 9th ed. Philadelphia: Elsevier; 2017.

Evolution of ECG Changes

Ischemic ST-segment elevation and hyperacute T wave changes may occur as the earliest ECG manifestations of STEMI. These are typically followed within hours to days by evolving T wave inversion and sometimes Q waves in the same lead distribution (**see Fig. 12.32 and Chapter 59**). T wave inversion from evolving or chronic ischemia correlates with increased ventricular action potential duration, and these ischemic changes are often associated with QT prolongation. The T wave inversions can resolve after days or weeks or may persist indefinitely.

The extent of the infarct may be an important determinant of T wave evolution. In one series, T waves that were persistently negative (inverted) for more than 1 year in leads with Q waves were associated with transmural infarction; by contrast, T waves that were positive in leads with Q waves correlated with nontransmural infarction, with viable myocardium within the wall.[52]

In the days to weeks or longer after infarction, the QRS changes can persist or begin to resolve.[46,53] Complete normalization of the ECG after Q wave infarction is uncommon but can occur, particularly with smaller infarcts, and with subsequent improvement of the left ventricular ejection fraction and regional wall motion. This development usually is associated with spontaneous recanalization or good collateral circulation and is a positive prognostic sign. By contrast, persistent Q waves and ST-segment elevation seen several weeks or more after infarction correlate strongly with severe underlying wall motion disorders (akinetic or dyskinetic zone), although not necessarily a frank ventricular aneurysm. The presence of an rSR′ or similar type of complex in the mid-left chest leads or lead I is another reported marker of a left ventricular aneurysm.

Other Ischemic ST-T Patterns

Reversible transmural ischemia, such as that caused by coronary vasospasm, may result in transient ST-segment elevation[42,44,46] (**Fig. 12.34**). This pattern is the classic ECG marker of *Prinzmetal variant angina* (**see Chapter 60**). Depending on the severity and duration of such noninfarction ischemia, the ST-segment elevation either can resolve within minutes or can be followed by T wave inversion that can persist for hours or even days.

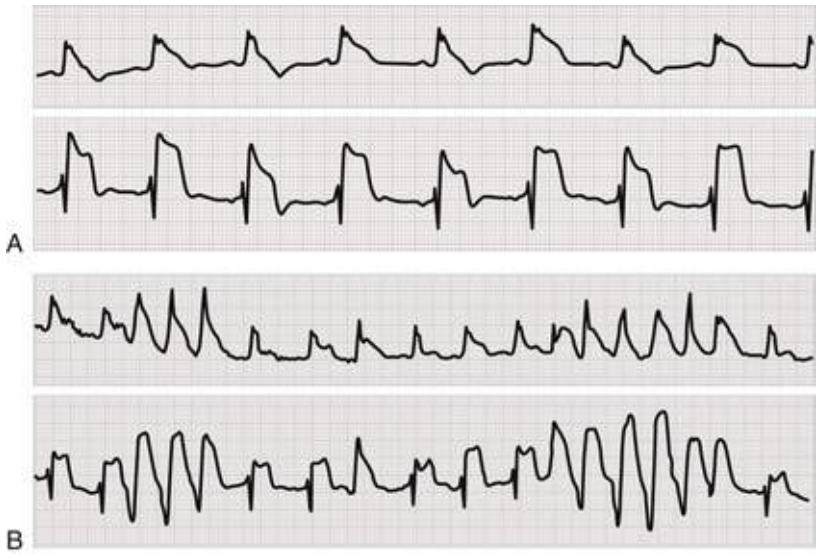

FIGURE 12.34 **A,** ECG tracing from a patient with Prinzmetal angina with ST-segment elevation and ST-T wave (repolarization) alternans. **B,** ECG shows ST segment elevation and T wave alternans associated with nonsustained ventricular tachycardia. (Courtesy Dr. C. Fisch.)

Some patients with ischemic chest pain exhibit deep coronary T wave inversion in multiple precordial leads (e.g., V_1 through V_4), with or without cardiac enzyme level elevations. This finding typically is the result of severe ischemia associated with a high-grade stenosis in the proximal left anterior descending (LAD) coronary artery system (referred to as the LAD–T wave or *Wellens' pattern*). These T wave inversions may be preceded by transient ST-segment elevations that resolve by the time the patient arrives at the hospital. Furthermore, T wave inversions of this type, especially in the setting of unstable angina, can correlate with segmental hypokinesis of the anterior wall and suggest a myocardial stunning syndrome. The natural history of this syndrome is unfavorable, with a high incidence of recurrent angina and myocardial infarction.[42-44]

On the other hand, patients whose baseline ECG shows abnormal T wave inversion can experience paradoxical T wave normalization (*pseudonormalization*) during episodes of acute transmural ischemia

(**Fig. 12.35**). In summary, there are four major classes of acute coronary artery syndrome in which myocardial ischemia is associated with distinct ECG findings (**Fig. 12.36**).

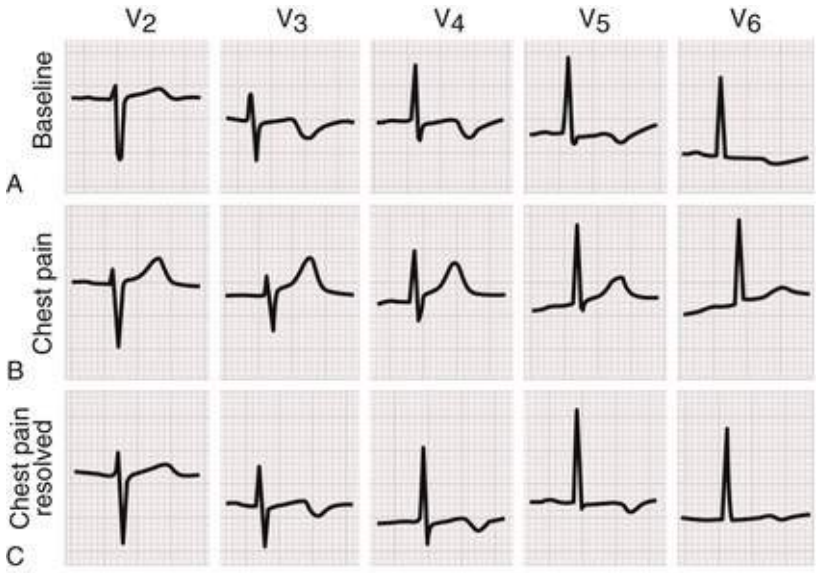

FIGURE 12.35 Pseudo– (paradoxical) T wave normalization. **A,** Baseline ECG of a patient with coronary artery disease shows ischemic T wave inversion. **B,** T wave "normalization" during an episode of ischemic chest pain. **C,** Following resolution of the chest pain, the T waves reverted to their baseline appearance. (**A, B,** From Goldberger AL, Goldberger ZD, Shvilkin A. Goldberger's Clinical Electrocardiography: a Simplified Approach. 9th ed. Philadelphia: Elsevier; 2017.)

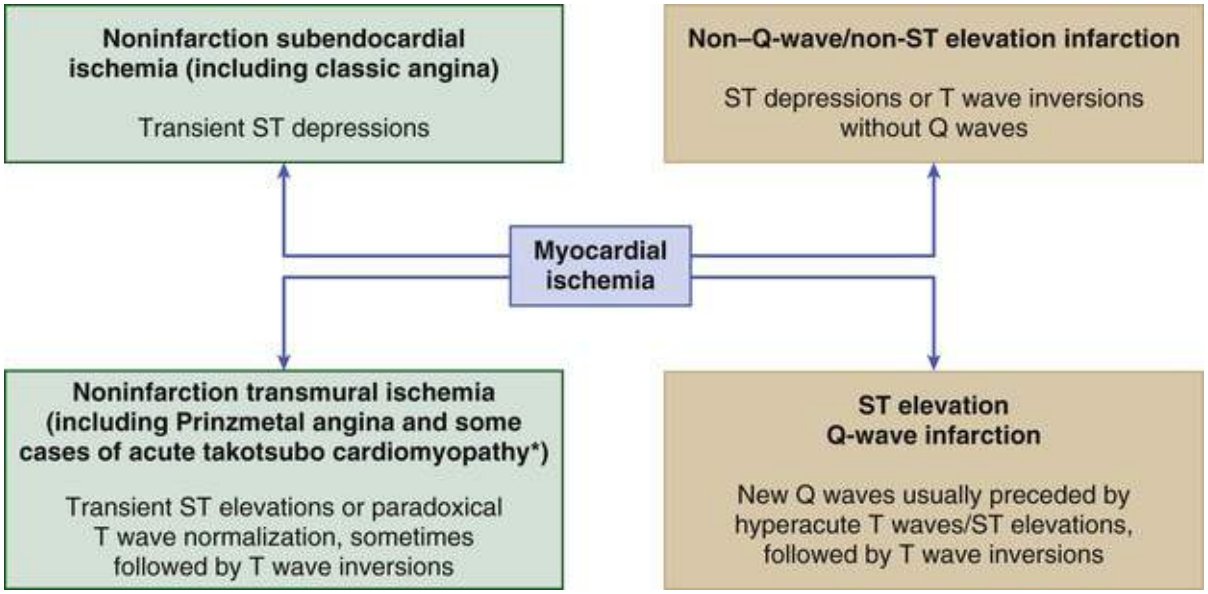

FIGURE 12.36 Variability of ECG patterns with acute myocardial ischemia. The ECG also may be normal or nonspecifically abnormal. Furthermore, these categorizations are not mutually exclusive. For example, a non–Q-wave infarct can evolve into a Q wave infarct, ST-segment elevation can be followed by a non–Q-wave infarct or ST-segment depression, and T wave inversion can be followed by a Q wave infarct. *May exactly mimic acute infarction. (From Goldberger AL, Goldberger ZD, Shvilkin A. Goldberger's Clinical Electrocardiography: a Simplified Approach. 9th ed. Philadelphia: Elsevier; 2017.)

Ischemic U Wave Changes

Alterations in U wave amplitude or polarity have been reported with acute ischemia or infarction.[54] For example, exercise-induced transient inversion of precordial U waves has been correlated with severe stenosis of the LAD coronary artery. Rarely, U wave inversion can be the earliest ECG sign of an acute coronary syndrome.

ECG Localization of Myocardial Ischemia and Infarction

The ECG leads are more helpful in localizing regions associated with ST-segment elevation than with ST-segment depression. ST-segment elevation and hyperacute T waves are seen in the following: (1) two or more contiguous precordial leads (V_1 through V_6) and/or in leads I and aVL with acute transmural anterior or anterolateral wall ischemia; (2) leads V_1 to V_3 with anteroseptal or apical ischemia; (3) leads V_4 to V_6 with apical or lateral ischemia; (4) leads II, III, and aVF with inferior wall ischemia; and (5) right-sided precordial leads with right ventricular ischemia.

In addition, posterior or posterolateral wall infarction induce ST-segment elevation in leads placed over the back of the heart, such as leads V_7 to V_9 (**see Table 12.1**), can be produced by lesions in the right coronary artery (RCA) or the left circumflex artery. Such blockages can produce both inferior and posterolateral injuries, which may be indirectly recognized by reciprocal ST-segment depression in leads V_1 to V_3. Similar ST changes also can be the primary ECG manifestation of anterior subendocardial ischemia. Posterolateral or inferolateral wall infarction with reciprocal changes can sometimes be differentiated from primary anterior wall ischemia by the presence of ST-segment elevations in posterior leads, although these are not routinely recorded.[55]

The ECG also can suggest specific information about the location of an acute occlusion within the coronary system (the “culprit lesion”).[2,42,47,50,56-59] With an inferior wall myocardial infarction, ST-segment elevation in lead III exceeding that in lead II, particularly combined with ST-elevation in lead V_1 (and other right-sided chest leads), is a reliable predictor of occlusion in the proximal to midportion of the RCA (**Fig. 12.37**). By contrast, the presence of ST-segment elevation in lead II equal to or exceeding that in lead III, especially in concert with ST-segment depression in leads V_1 to V_3 or ST-segment elevation in leads I and aVL, suggests occlusion of the left circumflex artery or a distal occlusion of a dominant RCA.

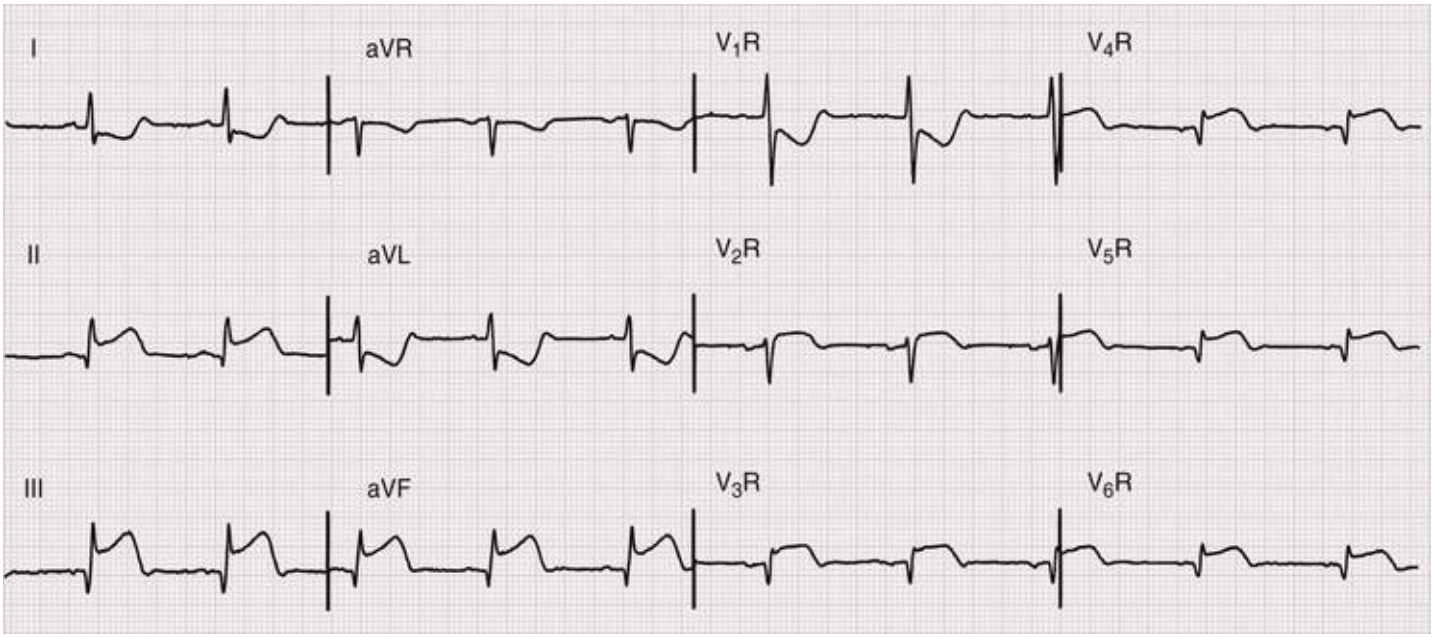

FIGURE 12.37 Acute right ventricular infarction in concert with an acute inferior wall ST-segment elevation infarction. Note the ST-segment elevation in the right precordial leads, as well as in leads II, III, and aVF, with reciprocal changes in leads I and aVL. ST-segment elevation in lead III greater than in lead II and right precordial ST-segment elevation are consistent with proximal to middle occlusion of the right coronary artery. The combination of ST-segment elevation in conventional lead V_1 (note: V_2R here) juxtaposed with ST-segment depression in lead V_2 (note: lead V_1R here) also has been reported with acute right ventricular ischemia or infarction.

Right-sided ST-segment elevation is indicative of acute right ventricular injury and usually indicates occlusion of the proximal RCA. Of note is the finding that acute right ventricular infarction can project an injury current pattern in leads V_1 through V_3 or even V_4, thus simulating anterior infarction. In other cases, simultaneous ST-segment elevation in V_1 (V_2R) and ST-segment depression in V_2 (V_1R) can occur (**Fig. 12.37**).

Lead aVR[56,57] may provide important clues to the location of artery occlusion in acute myocardial infarction. Left main (or severe multivessel) coronary artery disease should be considered when leads aVR and V_1 show ST-segment elevation, especially in concert with diffuse prominent ST-segment depression in other leads.

These and multiple other criteria proposed for localization of the site of acute coronary occlusion based on the initial ECG still require additional validation in larger populations. Current and future criteria will always be subject to limitations and exceptions based on interindividual variations in coronary anatomy, the dynamic nature of acute ECG changes, the presence of multivessel involvement, collateral flow, and the presence of ventricular conduction delays.

For example, in some cases, ischemia can affect more than one region of the myocardium (e.g., inferolateral; **see Fig. 12.32**). The ECG may show the characteristic features of involvement in each region. Sometimes, however, partial normalization can result from cancellation of opposing vectorial forces. Similarly, inferior lead ST-segment elevation accompanying acute anterior wall infarction suggests either occlusion of a left anterior descending artery that extends onto the inferior wall of the left ventricle (the wraparound vessel) or multivessel disease with jeopardized collaterals.

ECG Diagnosis of Myocardial Infarction with Bundle Branch Blocks

The diagnosis of myocardial infarction (MI) often is more difficult when the baseline ECG shows a bundle branch block pattern or when bundle branch block develops as a complication of the MI. The

diagnosis of Q wave infarction usually is not impeded by the presence of RBBB, which affects primarily the terminal phase of ventricular depolarization (see earlier). The net effect is that the criteria for the diagnosis of a Q wave infarct in a patient with RBBB are the same as in patients with normal conduction (**Fig. 12.38**).

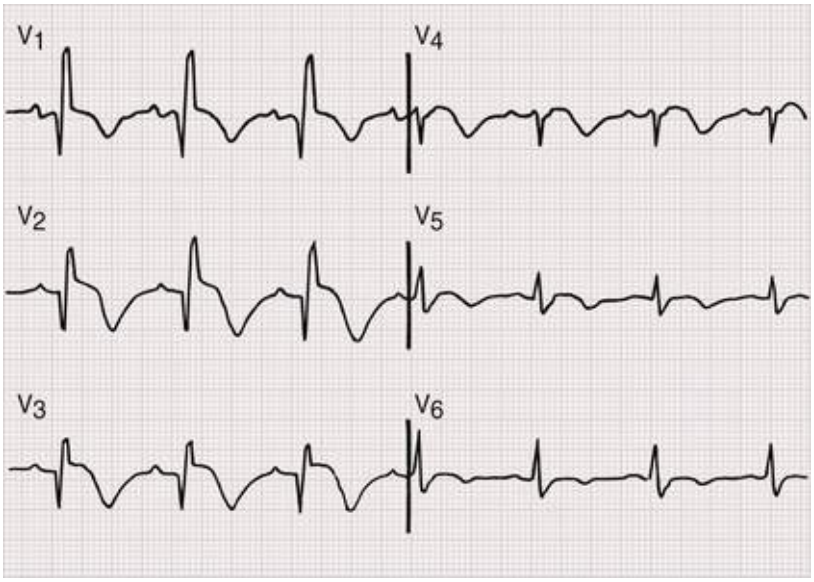

FIGURE 12.38 RBBB with acute anterior infarction. Loss of anterior depolarization forces results in QR-type complexes in the right precordial to midprecordial leads, with ST-segment elevations and evolving T wave inversions (V_1 through V_6).

The diagnosis of infarction in the presence of LBBB is considerably more complicated and confusing, because LBBB alters the early and the late phases of ventricular depolarization and produces secondary ST-T changes. These changes may mask and/or mimic MI findings. As a result, considerable attention has been directed to the problem of diagnosing acute and chronic MI in patients with LBBB[60] (**Fig. 12.39**).

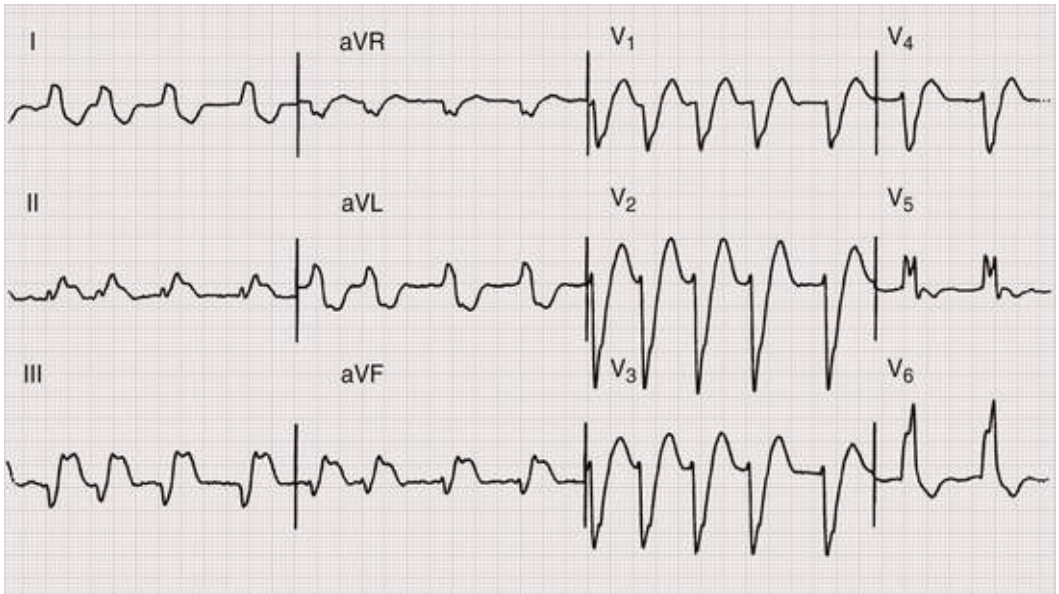

FIGURE 12.39 Complete LBBB with acute inferior myocardial infarction. Note the prominent ST-segment elevation in leads II, III, and aVF, with reciprocal ST-segment depression in leads I and aVL superimposed on secondary ST-T changes. The underlying rhythm is atrial fibrillation.

Infarction of the left ventricular free (or lateral) wall ordinarily results in abnormal Q waves in the midprecordial to lateral precordial leads and in selected limb leads. However, the initial septal depolarization forces with LBBB are directed from right to left. These leftward forces produce an initial R wave in the midprecordial to lateral precordial leads, usually masking the loss of electrical potential (Q waves) caused by the MI. Therefore, acute or chronic left ventricular free wall infarction by itself will not usually produce diagnostic Q waves in the presence of LBBB. Acute or chronic MI involving both the free wall and septum (or the septum itself) may produce abnormal Q waves (usually as part of QR-type complexes) in leads V_4 to V_6. These initial Q waves probably reflect posterior and superior forces from the spared basal portion of the septum (**Fig. 12.40**). Thus a wide Q wave (40 milliseconds) in one or more of these leads is a reliable sign of underlying MI. The sequence of repolarization also is altered in LBBB, as described earlier, and these changes can mask or simulate the ST-segment changes of actual ischemia.

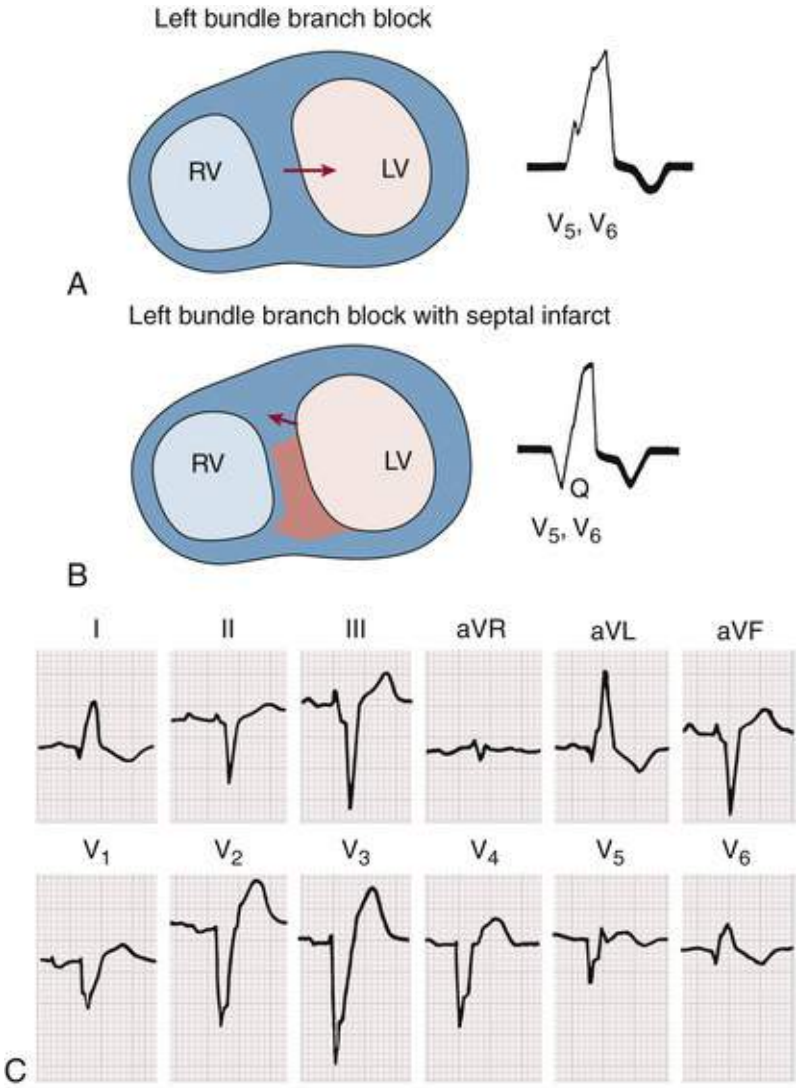

FIGURE 12.40 **A,** With uncomplicated LBBB, early septal forces are directed to the left (*arrow*). Therefore, no Q waves will be seen in V_5 and V_6 on the ECG tracing. **B,** With LBBB complicated by anteroseptal infarction, early septal forces can be directed posteriorly and rightward (*arrow*). Therefore, prominent Q waves may appear in leads V_5 and V_6 as a paradoxical marker of septal infarction. **C,** ECG from patient with anterior wall infarction (involving septum) with LBBB. Note the presence of QR complexes in leads I, aVL, V_5, and V_6. *LV,* Left ventricle; *RV,* right ventricle. (**A, B,** Modified from Dunn MI, Lipman BS. Lipman-Massie Clinical Electrocardiography. 8th ed. Chicago: Year Book; 1989.)

The following points summarize the ECG signs of MI in LBBB:

1. ST-segment elevation with tall, positive T waves frequently is seen in the right precordial leads with uncomplicated LBBB. Secondary T wave inversions are characteristically seen in the lateral precordial leads. However, the appearance of ST-segment elevations in the lateral leads or ST-segment depressions or deep T wave inversions in leads V_1 to V_3 strongly suggests underlying ischemia. More marked ST-segment elevations (>0.5 mV) in leads with QS or rS waves also may be caused by acute ischemia, but false-positive findings occur, especially with large-amplitude negative QRS complexes. Use of the ratio of the *absolute* amplitude of the ST-segment to S wave, determined in any relevant lead of greater than 0.25 has been proposed as having greater accuracy than that of the original criterion.[59] Further studies are needed to confirm this finding and test other proposed criteria.
2. The presence of QR complexes in leads I, V_5, or V_6 or in II, III, and aVF with LBBB strongly suggests underlying MI.
3. Chronic MI also is suggested by notching of the ascending part of a wide S wave in the midprecordial leads or the ascending limb of a wide R wave in lead I, aVL, V_5, or V_6.

Similar principles can apply to the diagnosis of acute and chronic MI in the presence of right ventricular pacing. Comparison between an ECG exhibiting the LBBB before the infarction and the present ECG often is helpful to show these changes.

The diagnosis of concomitant LAFB and inferior wall MI also can pose challenges. This combination can result in loss of the small r waves in the inferior leads, so leads II, III, and aVF show QS, not rS, complexes.

However, LAFB may also hide the diagnosis of inferior wall MI. The inferior orientation of the initial QRS forces caused by the fascicular block can mask inferior Q waves, with resultant rS complexes in leads II, III, and aVF. In other cases, the combination of LAFB and inferior wall MI will produce qrS complexes in the inferior limb leads, with the initial q wave the result of the infarct and the minuscule r wave the result of the fascicular block.

Atrial Infarction

A number of ECG clues to the diagnosis of atrial infarction have been suggested. These include localized deviations of the PR segment, such as PR elevation in lead V_5 or V_6 or the inferior leads,[60,61] changes in P wave morphology, and atrial arrhythmias. The sensitivity and specificity of these signs are limited, however.

ECG Differential Diagnosis of Ischemia and Infarction

The ECG has important limitations in sensitivity and specificity in the diagnosis of coronary syndromes.[42,43,46] A normal or nondiagnostic ECG does not exclude ischemia or even acute infarction.[62,63] If the initial ECG is not diagnostic, but the patient remains symptomatic, with a clinical picture strongly suggestive of acute ischemia, the ECG should be repeated at 15- to 30-minute intervals or shorter.[45] However, a normal ECG throughout the course of an acute infarction is distinctly uncommon. As a result, prolonged chest pain without suggestive or diagnostic ECG changes on repeat ECGs should always prompt a careful search for noncoronary causes of chest pain (**see Chapter 56**).

Noninfarction Q Waves and Related Depolarization Changes

Loss of electromotive force associated with myocardial necrosis contributes to R wave loss and Q wave formation in MI. This mechanism of Q wave pathogenesis, however, is not specific for coronary artery disease with infarction. Any process, acute or chronic, that causes sufficient loss of regional electromotive potential can result in Q waves. For example, replacement of myocardial tissue by electrically inert material such as amyloid or tumor can cause noninfarction Q waves (**see Chapters 77 and 95**). A variety of dilated cardiomyopathies associated with extensive myocardial fibrosis can cause pseudoinfarction patterns. Ventricular hypertrophy also can contribute to the appearance of Q waves.

Q waves simulating the ECG pattern of coronary artery disease can be related to one (or a combination) of the following four factors[46] (**Table 12.10**): (1) physiologic or positional variants, (2) altered ventricular conduction, (3) ventricular enlargement, and (4) myocardial damage or replacement.

TABLE 12.10

Differential Diagnosis of Noninfarction Q Waves (With Select Examples)

Physiologic or Positional Factors
Normal variant "septal" Q waves
Normal variant Q waves in V_1-V_2, III, and aVF
Left pneumothorax or dextrocardia—loss of lateral R wave progression
Myocardial Injury or Infiltration
Acute processes—myocardial ischemia without infarction, takotsubo cardiomyopathy myocarditis, hyperkalemia (rare cause of transient Q waves)
Chronic myocardial processes—idiopathic cardiomyopathies, myocarditis, amyloid, tumor, sarcoid
Ventricular Hypertrophy or Enlargement
Left ventricular (slow R wave progression)*
Right ventricular (reversed R wave progression† or slow R wave progression, particularly with chronic obstructive lung disease)
Hypertrophic cardiomyopathy (can simulate anterior, inferior, posterior, or lateral infarcts
Conduction Abnormalities
LBBB (slow R wave progression*)
WPW patterns

*Small or absent R waves in the right precordial to midprecordial leads.

†Progressive decrease in R wave amplitude from V_1 to the midlateral precordial leads.

Modified from Goldberger AL, Goldberger ZD, Shvilkin A. Goldberger's Clinical Electrocardiography: a Simplified Approach. 9th ed. Philadelphia: Elsevier; 2017.

Prominent Q waves can be associated with a variety of positional factors that alter the orientation of the heart vis-à-vis a specific lead axis. Depending on the electrical axis, prominent Q waves (as part of QS- or QR-type complexes) can appear in the limb leads (aVL with a vertical axis and III and aVF with a horizontal axis). A QS complex can appear in lead V_1 as a normal variant but rarely in leads V_1 and V_2. Slow R wave progression, sometimes with actual QS waves, can be caused solely by improper placement of chest electrodes above their usual position. With dextrocardia (**see Chapter 75**), in the absence of underlying structural abnormalities, normal R wave progression can be restored by recording leads V_2 to V_6 on the right side of the chest (with lead V_1 placed in the V_2 position). A rightward mediastinal shift with left pneumothorax can contribute to the apparent loss of left precordial R waves. Other positional factors associated with slow R wave progression include pectus excavatum and congenitally corrected transposition of the great vessels.

An intrinsic change in the sequence of ventricular depolarization can lead to pathologic, noninfarct Q waves. The two most important conduction disturbances associated with pseudoinfarction Q waves are LBBB and the Wolff-Parkinson-White (WPW) preexcitation patterns. With LBBB, QS complexes can appear in the right precordial to midprecordial leads and occasionally in leads II, III, and/or aVF. Depending on the location of the bypass tract, WPW preexcitation can mimic anteroseptal, lateral, or

inferior-posterior infarction.

LAFB is sometimes cited as a cause of anteroseptal infarct patterns; however, LAFB usually has only minor effects on the QRS complex in horizontal plane leads. Probably the most common findings are relatively prominent S waves in leads V_5 and V_6. Slow R wave progression is not a consistent feature of LAFB, although minuscule q waves in leads V_1 to V_3 have been reported in this setting. These small q waves can become more apparent if the leads are recorded one interspace above their usual position and disappear in leads that are one interspace below their usual position. As a general clinical rule, however, prominent Q waves (as part of QS or QR complexes) in the right precordial to midprecordial leads should *not* be attributed to LAFB alone.

Q waves caused by myocardial injury, whether ischemic or nonischemic in origin, can appear transiently and do not necessarily signify irreversible heart muscle damage. Severe ischemia can cause regional loss of electromotive potential without actual cell death (*electrical stunning* phenomenon). Transient conduction disturbances also can cause alterations in ventricular activation and result in noninfarctional Q waves. In some cases, transient Q waves may represent unmasking of a previous Q wave infarct. New but transient Q waves have been described in patients with severe hypotension from a variety of causes, as well as with tachyarrhythmias, myocarditis, Prinzmetal angina, protracted hypoglycemia, phosphorus poisoning, and hyperkalemia.

Slow ("poor") R wave progression is a nonspecific finding and is frequently observed with LVH and with acute or chronic right ventricular overload. Q waves in such settings can reflect a variety of mechanisms, including a change in the balance of early ventricular depolarization forces and altered cardiac geometry and position. A marked loss of R wave voltage, sometimes with frank Q waves from lead V_1 to the lateral chest leads, can be seen with chronic obstructive pulmonary disease (**see Fig. 12.18**). The presence of low limb voltage and signs of right atrial abnormality (P pulmonale) can serve as additional diagnostic clues. This loss of R wave progression in part may be related to right ventricular dilation and downward displacement of the heart in an emphysematous chest, as discussed earlier. Partial or complete normalization of R wave progression can be achieved in some of these cases by recording the chest leads an interspace lower than usual.

Other ventricular overload syndromes, acute or chronic, can also mimic ischemia and infarction. Acute cor pulmonale caused by pulmonary embolism (**see Chapter 84**) can cause a variety of pseudoinfarct patterns. Acute right ventricular overload in this setting can cause slow R wave progression and sometimes right precordial to midprecordial T wave inversion (sometimes still referred to as right ventricular "strain"), mimicking anterior ischemia or infarction. The classic $S_1Q_3T_3$ pattern can occur but, as noted, is neither sensitive nor specific. A prominent Q wave (usually as part of a QR complex) also can occur in lead aVF along with this pattern (**see Fig. 12.19**). However, acute right overload by itself does not cause a pathologic Q wave in lead II. Right-sided heart overload, acute or chronic, also may be associated with a QR complex in lead V_1, simulating anteroseptal infarction.

Pseudoinfarction patterns are important findings in patients with hypertrophic cardiomyopathy, and the ECG changes can simulate those in anterior, inferior, posterior, or lateral infarction. The pathogenesis of depolarization abnormalities in this cardiomyopathy is not certain. Prominent inferolateral Q waves (leads II, III, aVF, and V_4 to V_6) and tall, right precordial R waves probably are related to increased depolarization forces generated by the markedly hypertrophied septum (**Fig. 12.41**). Abnormal septal depolarization also can contribute to bizarre QRS complexes.

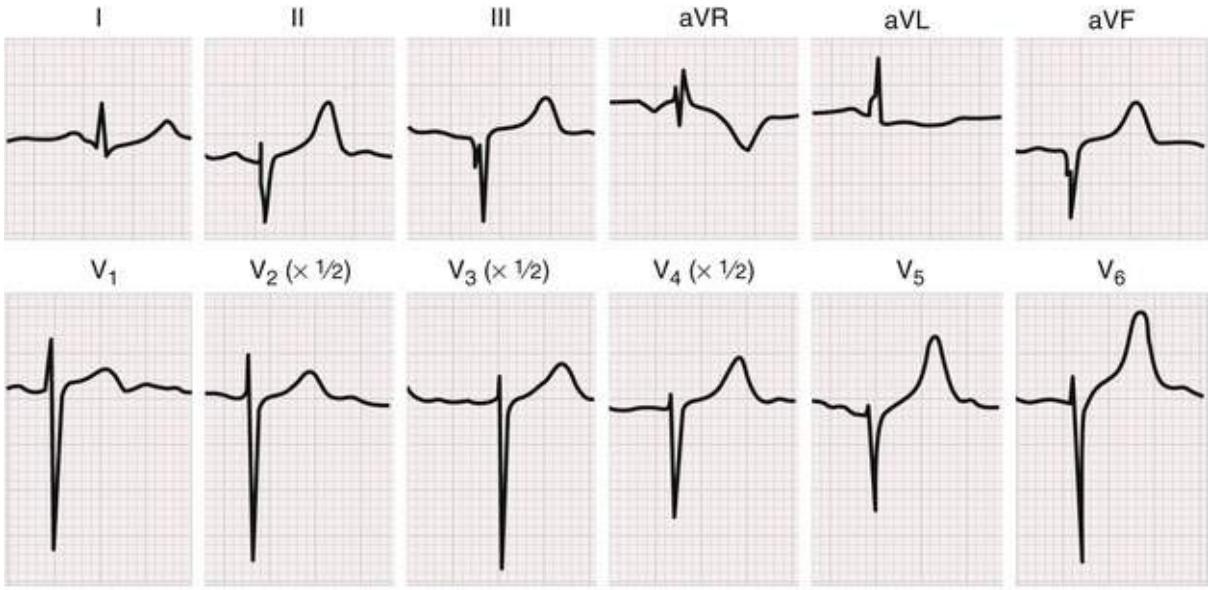

FIGURE 12.41 Hypertrophic cardiomyopathy simulating inferolateral infarction. This ECG was obtained in an 11-year-old girl who had a family history of hypertrophic cardiomyopathy. Note the W-shaped QS waves and the qrS complexes in the inferior and lateral precordial leads. (From Goldberger AL, Goldberger ZD, Shvilkin A. Goldberger's Clinical Electrocardiography: a Simplified Approach. 7th ed. Philadelphia: Elsevier; 2017.)

ST-T Changes Simulating Ischemia and Infarction

The differential diagnosis of STEMI (or ischemia)[44-50] caused by obstructive coronary disease encompasses a wide variety of clinical entities, including acute pericarditis (**Fig. 12.42**) (**see Chapter 83 and Fig. 83.2**), acute myocarditis (**Chapter 79**), normal variants, including classic "early repolarization" patterns (**see Fig. 12.11**), takotsubo (stress) cardiomyopathy,[64,65] Brugada patterns (**Chapters 33 and 39**), and other conditions (**Table 12.11**). Acute pericarditis, unlike MI, typically induces diffuse ST-segment elevation, usually in most of the chest leads and also in leads I, aVL, II, and aVF. Reciprocal ST-segment depression is seen in lead aVR. An important clue to acute pericarditis, in addition to the diffuse nature of the ST-segment elevation, is the frequent presence of PR-segment elevation in aVR, with reciprocal PR-segment depression in other leads, caused by a concomitant atrial current of injury (**see Fig. 12.42**). Abnormal Q waves do not occur with acute pericarditis, and the ST-segment elevation may be followed by T wave inversion after a variable period. Severe acute myocarditis can produce identical ECG patterns of acute myocardial infarction (AMI), including ST-segment elevations and Q waves. These findings can be associated with a rapidly progressive course and increased mortality.

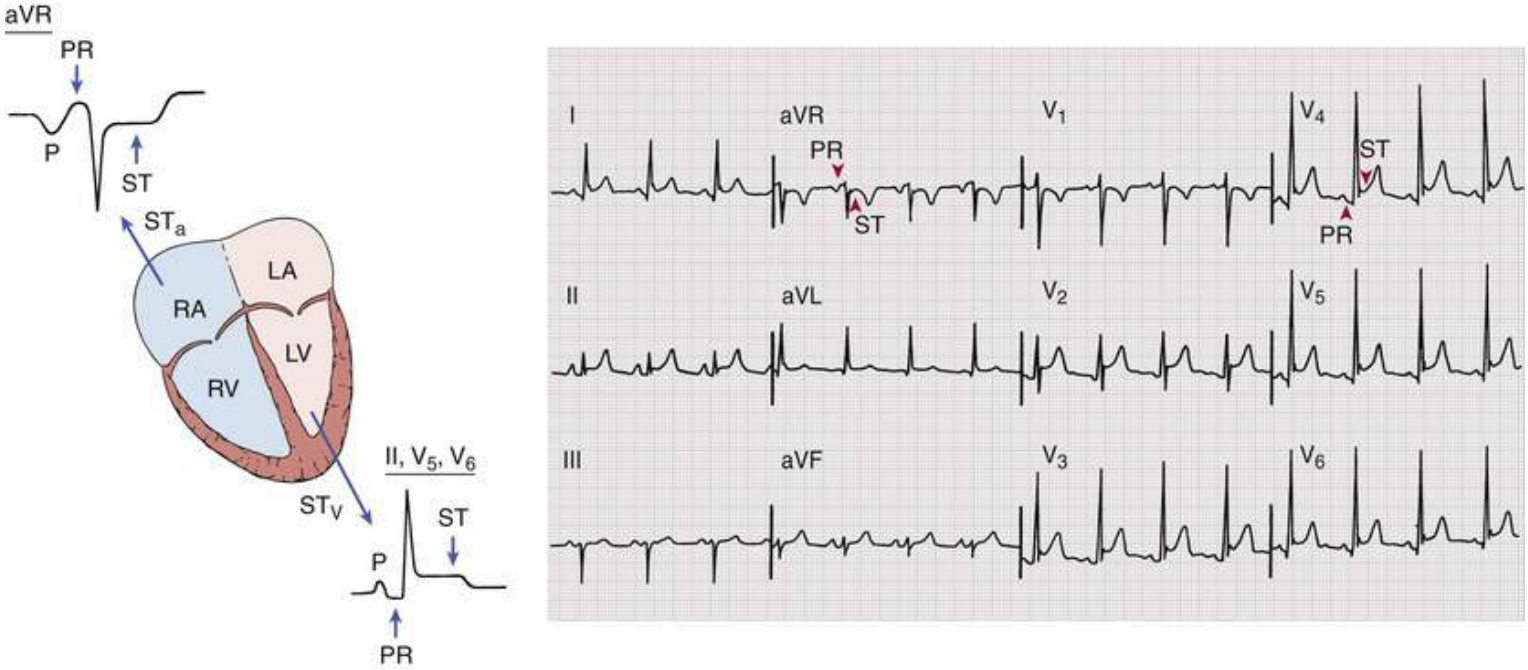

FIGURE 12.42 Acute pericarditis often is characterized by two apparent injury currents, one atrial and the other ventricular. The atrial injury current vector (ST_a) usually is directed upward and to the right (see diagram at *left*) and produces PR-segment elevation in aVR, with reciprocal PR depression in II, V_5, and V_6. The ventricular injury current (ST_V) is directed downward and to the left, associated with ST-segment elevation in leads II, V_5, and V_6. This characteristic PR-ST segment discordance is illustrated in the bottommost tracing. Note the diffuse distribution of ST-segment elevation in acute pericarditis (e.g., I, II, and V_2 through V_6, with reciprocal changes in aVR and perhaps minimally in V_1). *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (From Goldberger AL. Myocardial Infarction: Electrocardiographic Differential Diagnosis. 4th ed. St Louis: Mosby–Year Book; 1991.)

TABLE 12.11
Differential Diagnosis of ST-Segment Elevation

Myocardial ischemia or infarction
Noninfarction, transmural ischemia (e.g., Prinzmetal angina pattern, takotsubo syndrome)
Acute myocardial infarction (caused by obstructive coronary occlusion or other causes)
Post–myocardial infarction (ventricular aneurysm pattern)
Acute pericarditis
Normal variants (including the classic "early repolarization" pattern)
LVH, LBBB (V_1-V_2 or V_3 only)
Other (rarer) causes
Acute pulmonary embolism (right to mid-chest leads)
Brugada pattern (RBBB-like pattern and ST-segment elevations in right precordial leads)*
Class IC antiarrhythmic drugs*
Hypercalcemia*
DC cardioversion (immediately after procedure)
Hyperkalemia*
Hypothermia (J or Osborn wave)
Intracranial hemorrhage
Myocardial injury (e.g., caused by trauma)
Myocarditis (may resemble myocardial infarction or pericarditis)
Tumor invading the left ventricle

*Usually most apparent in leads V_1 to V_2.

Modified from Goldberger AL, Goldberger ZD, Shvilkin A. Goldberger's Clinical Electrocardiography: a Simplified Approach. 9th ed. Philadelphia: Saunders; 2017.

Takotsubo cardiomyopathy (**see Chapter 77**), also called *transient left ventricular apical ballooning syndrome* or *stress cardiomyopathy*, is characterized by reversible wall motion abnormalities of the left ventricular apex and midventricle.[65,66] Patients, usually postmenopausal women, may present with chest pain, ST-segment elevations, and elevated cardiac enzyme levels, mimicking AMI caused by obstructive

coronary disease. The syndrome typically is reported in the setting of emotional or physiologic stress.

Fixed epicardial coronary disease is absent. The exact pathophysiology is not known but may relate to coronary vasospasm or adrenergically mediated myocardial damage,[65] resulting in a variety of ST-T elevation (or depression) changes simulating coronary occlusion.

A number of factors, such as digitalis, ventricular hypertrophy, hypokalemia, secondary ST-T changes, and hyperventilation, can cause *ST-segment depression* mimicking that in non–ST-segment elevation ischemic syndromes. Similarly, *tall positive T waves* do not invariably represent hyperacute ischemic changes but can reflect normal variants, hyperkalemia, cerebrovascular injury, and left ventricular volume loads resulting from mitral or aortic regurgitation (**see Fig. 12.16**), among other causes. ST-segment elevation, J point elevations, and tall positive T waves also are common chronic findings in leads V_1 and V_2 with LBBB or LVH patterns, which may simulate acute ischemia.

As noted, a variety of other factors, pathologic and sometimes physiologic, can alter repolarization, causing prominent T wave inversion, sometimes simulating ischemia or evolving MI. For example, prominent primary T wave inversions also are a well-described feature of the ECG in cerebrovascular accidents (strokes), particularly with subarachnoid hemorrhage. The so-called *cerebrovascular accident (CVA) T wave pattern* characteristically is seen in multiple leads, with a widely splayed appearance usually associated with marked QT prolongation (**Fig. 12.43; see also Chapters 33 and 39**). Some studies have implicated structural damage (termed *myocytolysis*) in the hearts of patients with such T wave changes, probably induced by excessive sympathetic stimulation mediated through the hypothalamus. A role for concomitant vagal hyperactivation has also been postulated in the pathogenesis of such T wave changes, which usually are associated with bradycardia. Similar T wave changes have been reported after truncal vagotomy, radical neck dissection, and bilateral carotid endarterectomy. In addition, the massive diffuse T wave inversion seen in some patients after Stokes-Adams syncope may be related to a similar neurocardiogenic mechanism. Patients with subarachnoid hemorrhage also can show transient ST-segment elevation, as well as arrhythmias, including torsades de pointes. Ventricular dysfunction can even occur and may be related to takotsubo cardiomyopathy[64,65] or neurogenic stress–type syndromes (**see Chapters 65 and 99**).

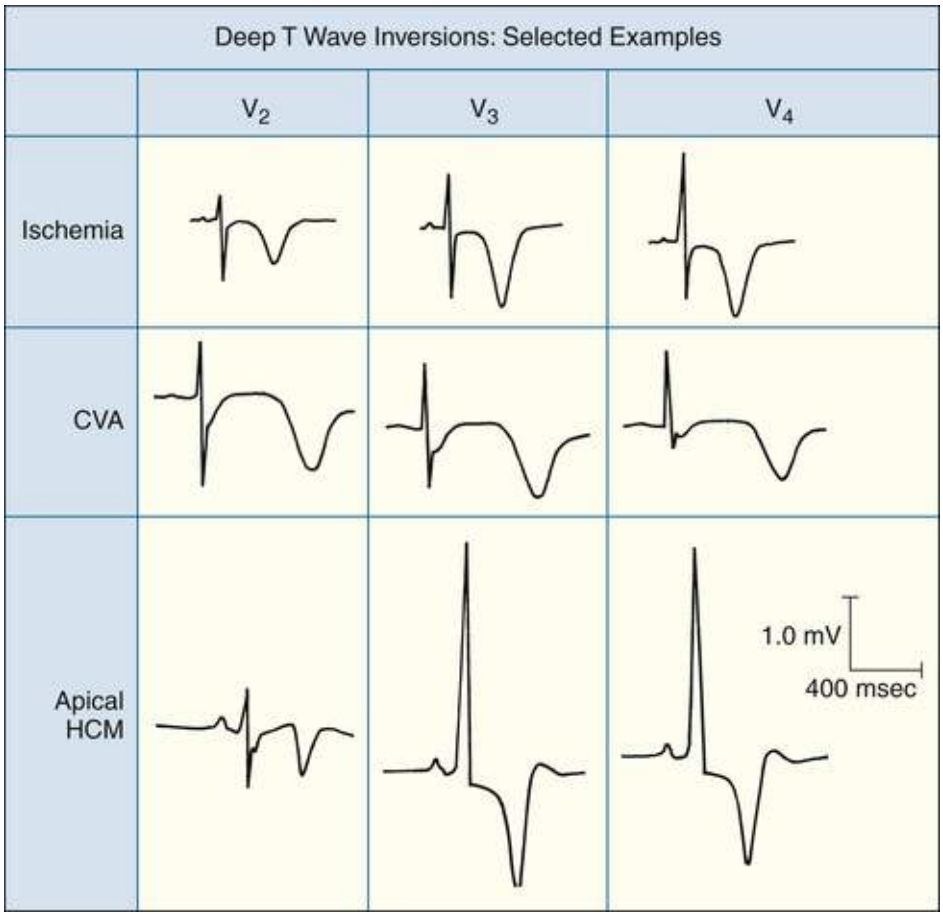

FIGURE 12.43 Deep T wave inversion can have various causes. In the *middle* tracing, note the marked QT prolongation in conjunction with the cerebrovascular accident (*CVA*) T wave pattern, caused here by subarachnoid hemorrhage. Apical hypertrophic cardiomyopathy (*HCM*), "memory T waves," and takotsubo syndrome are other causes of deep T wave inversion that can be mistaken for ischemia from acute/evolving or chronic obstructive coronary disease. (From Goldberger AL. Deep T wave inversions. ACC Curr J Rev 1996;5:28.)

In contrast to these primary ST-T wave abnormalities, secondary ST-T wave changes are caused by altered ventricular activation, without changes in action potential characteristics (discussed earlier). Examples include bundle branch block, WPW preexcitation, and ventricular ectopic or paced beats. In addition, transiently altered ventricular activation (associated with QRS interval prolongation) can induce T wave changes which can persist for hours to days after normal ventricular depolarization has resumed. The term *cardiac memory T wave changes* has been used in this context to describe repolarization changes after depolarization changes caused by ventricular pacing, intermittent LBBB, intermittent WPW preexcitation, and other alterations of ventricular activation[66] (**see Chapters 37 and 40**). T wave inversions also may occur. The term *idiopathic global T wave inversion* has been applied in cases in which no identifiable cause for prominent diffuse repolarization abnormalities can be found. Some of these cases may represent unrecognized takotsubo cardiomyopathy.

When caused by physiologic variants, T wave inversion is sometimes mistaken for ischemia. T waves in the right precordial leads can be slightly inverted, particularly in leads V_1 and V_2. Some adults show persistence of the juvenile T wave pattern (**see Fig. 12.10**), with more prominent T wave inversion in right precordial to midprecordial leads showing an rS or RS morphology. Such patterns, especially associated with LBBB-type premature ventricular beats or relevant family history, also raise strong consideration of *arrhythmogenic right ventricular cardiomyopathy* (formerly "dysplasia").[67] The other major normal variant that can be associated with notable T wave inversion is the so-called early repolarization pattern (**see Fig. 12.11**). As described earlier, some persons, especially athletes, with this

variant have prominent, biphasic T wave inversion in association with the ST-segment elevation. This pattern, which may simulate the initial stages of an evolving infarct, is most prevalent in young black men and endurance athletes. These functional ST-T changes probably are the result of regional disparities in repolarization and usually can be “normalized” by exercise. An important consideration in the differential diagnosis for such changes, especially in athletes, is apical hypertrophic cardiomyopathy.

Drug Effects

Numerous drugs can affect the ECG and often are associated with nonspecific ST-T alterations.[42,43] More marked changes, as well as atrioventricular and intraventricular conduction disturbances, can occur with select agents (**see Chapters 33 and 36**).

The term *digitalis effect*[68] refers to the relatively distinctive “scooped” appearance of the ST-T complex and shortening of the QT interval, which correlates with abbreviation of the ventricular action potential duration (**Fig. 12.44**). Digitalis-related ST-T changes can be accentuated by an increased heart rate during exercise, with consequent false-positive results on stress testing (**see Chapter 13**), and can occur with therapeutic or toxic doses of the drug. *Digitalis toxicity* refers specifically to systemic effects (e.g., nausea, anorexia) or conduction disturbances and arrhythmias caused by drug excess or increased sensitivity.

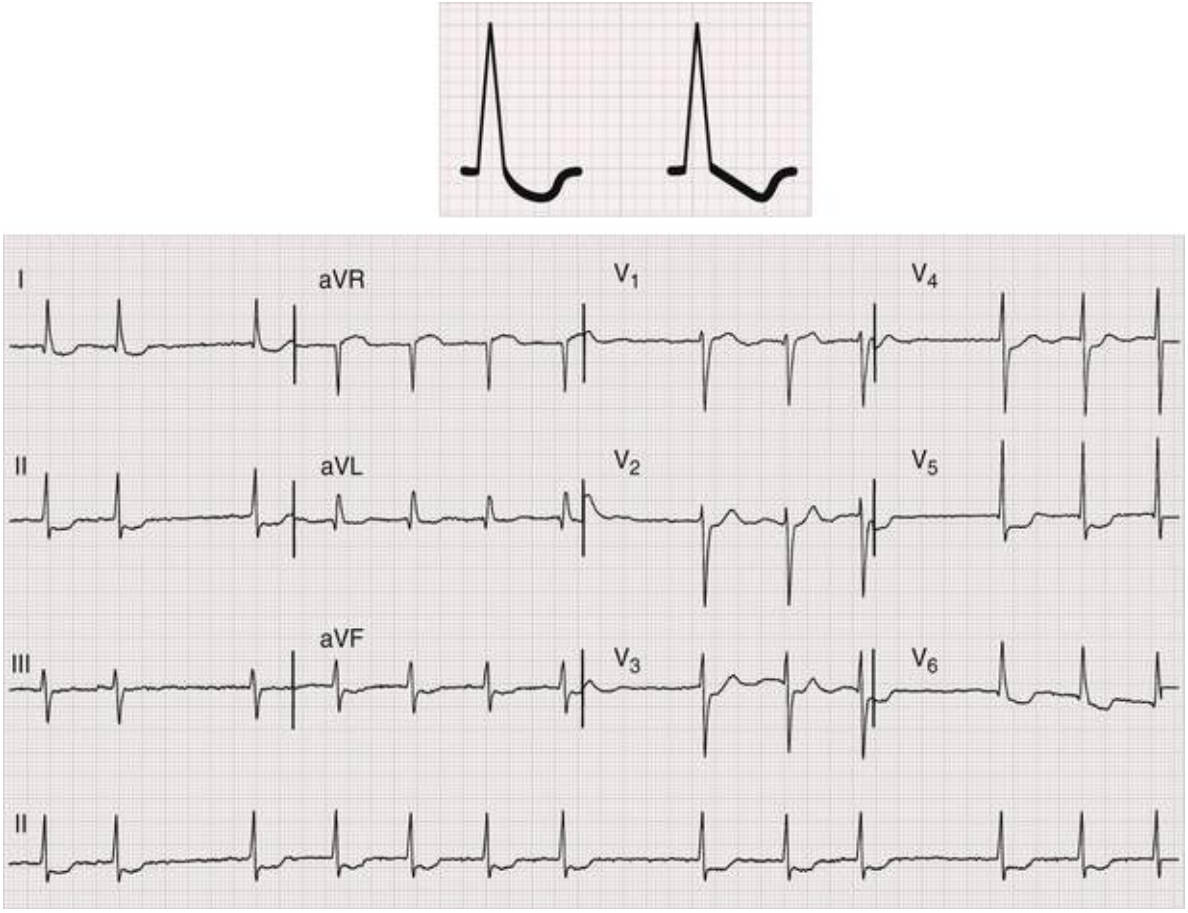

FIGURE 12.44 **Top,** Digitalis effect. Digitalis glycosides characteristically produce shortening of the QT interval with a scooped or downsloping ST-T complex. **Bottom,** Digitalis effect in combination with digitalis toxicity. The underlying rhythm is atrial fibrillation. A group beating pattern of QRS complexes with shortening of the R-R intervals is consistent with nonparoxysmal junctional tachycardia with probable exit (block atrioventricular Wenckebach) variant. ST-segment depression and scooping (lead V_6) are consistent with the digitalis effect, although ischemia or LVH cannot be excluded. These ECG findings are strongly suggestive of digitalis excess; the serum digoxin level was higher than 3 ng/mL. Note that digitalis effect (ST-T changes) does not necessarily imply digitalis toxicity. Most patients with digitalis toxicity, however, do show digitalis effect on the ECG. (**Top,** From Goldberger AL, Goldberger ZD, Shvilkin A. Goldberger's Clinical Electrocardiography: a Simplified Approach. 9th ed. Philadelphia: Elsevier; 2017.)

The ECG effects and toxicities of other cardioactive agents can be anticipated in part from ion channel effects (**see Chapter 33**). Inactivation of sodium channels by class I agents (e.g., quinidine, procainamide, disopyramide, flecainide) can cause QRS prolongation. Class IA (e.g., quinidine) and class III (e.g., amiodarone, dronedarone, dofetilide, ibutilide, sotalol) agents can induce an *acquired long QT(U) syndrome* (**see Chapters 34 and 36**). Psychotropic drugs (e.g., tricyclic antidepressants, phenothiazines), which have class IA–like properties, also can lead to QRS and QT(U) prolongation (**see Chapter 96**). Toxicity can produce asystole or torsades de pointes. Right axis shift of the terminal 40-millisecond frontal plane QRS axis may be a helpful additional marker of tricyclic antidepressant overdose. QT prolongation has been reported with methadone. Cocaine (**see Chapter 80**) can cause a variety of ECG changes, including those of STEMI, as well as life-threatening arrhythmias.

Electrolyte and Metabolic Abnormalities

In addition to the structural and functional cardiac conditions already discussed, numerous systemic metabolic aberrations may affect the ECG, including electrolyte abnormalities and acid-base disorders, as well as systemic hypothermia.[12,42,43]

Calcium

Hypercalcemia and hypocalcemia predominantly alter the action potential duration. An increased extracellular calcium concentration shortens the ventricular action potential duration by shortening phase 2. By contrast, hypocalcemia prolongs phase 2. These cellular changes are reflected in abbreviation or prolongation of the QT interval (ST-segment portion) with hypercalcemia or hypocalcemia, respectively (**Fig. 12.45**). Severe hypercalcemia (e.g., serum Ca^{2+} > 15 mg/dL) also can be associated with decreased T wave amplitude, sometimes with T wave notching or inversion. Hypercalcemia sometimes produces a high takeoff of the J point/ST segment in leads V_1 and V_2 and can thus simulate acute ischemia (**see Table 12.11**).

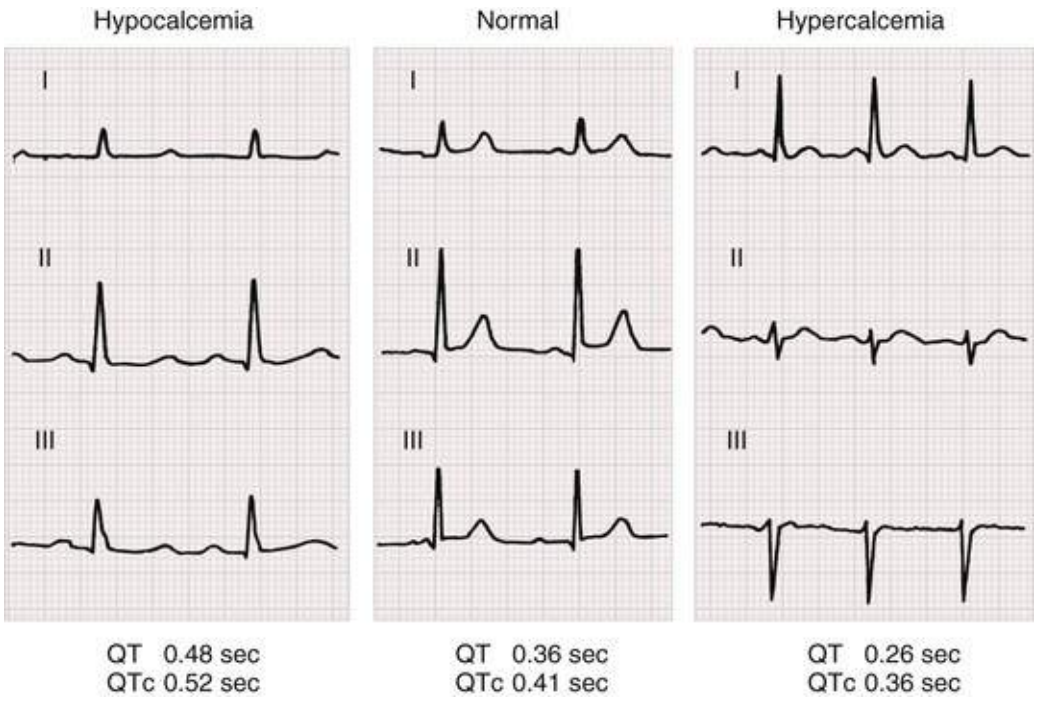

FIGURE 12.45 Prolongation of the QT interval (ST-segment portion) is typical of hypocalcemia. Hypercalcemia may cause abbreviation of the ST segment and shortening of the QT interval. (From Goldberger AL, Goldberger ZD, Shvilkin A. Goldberger's Clinical Electrocardiography: a Simplified Approach. 9th ed. Philadelphia: Elsevier; 2017.)

Potassium

Hyperkalemia is associated with a distinctive sequence of ECG changes (**Fig. 12.46A**). The earliest effect usually is narrowing and peaking (or *tenting*) of the T wave. The QT interval is shortened at this stage, reflecting a decreased action potential duration.

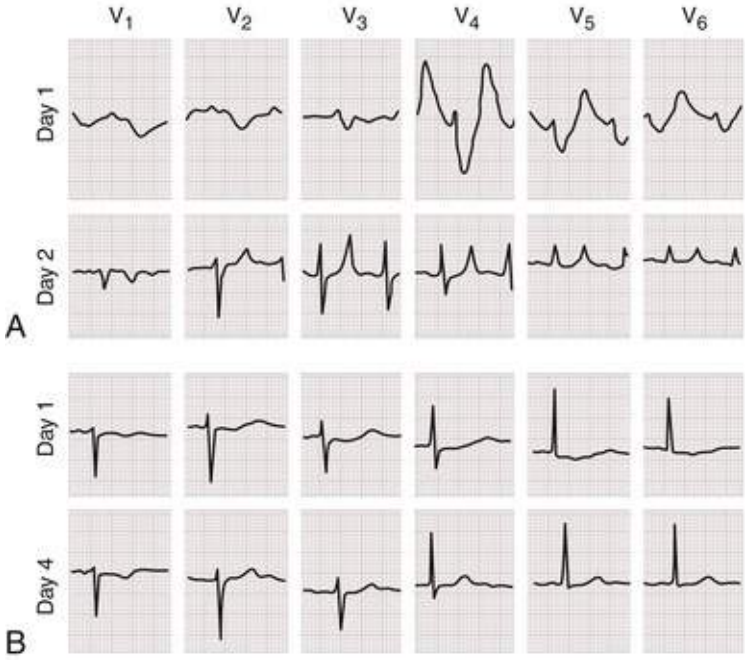

FIGURE 12.46 ECG changes in hyperkalemia **(A)** and hypokalemia **(B). A,** On day 1, at a K^+ level of 8.6 mEq/liter, the P wave is no longer recognizable and the QRS complex is diffusely prolonged. Initial and terminal QRS delays are characteristic of K^+-induced intraventricular conduction slowing and are best illustrated in leads V_2 and V_6. On day 2, at a K^+ level of 5.8 mEq/liter, the P wave is recognizable, with a PR interval of 0.24 second; the duration of the QRS complex is approximately 0.10 second, and the T waves are characteristically "tented." **B,** On day 1, at a K^+ level of 1.5 mEq/liter, the T and U waves are merged. The U wave is prominent and the QU interval is prolonged. On day 4, at a K^+ level of 3.7 mEq/liter, the tracing is normal. (**A, B,** Courtesy Dr. C. Fisch.)

Progressive extracellular hyperkalemia reduces atrial and ventricular resting membrane potentials, thereby inactivating sodium channels, which decreases Vmax and conduction velocity. The QRS begins to widen, and P wave amplitude decreases. PR interval prolongation can occur, followed sometimes by second- or third-degree atrioventricular block. Complete loss of P waves may be associated with a junctional escape rhythm or putative *sinoventricular rhythm*. In the latter, sinus rhythm persists with conduction (possibly over internodal tracts or muscle bundles) between the sinoatrial and atrioventricular nodes, but without producing an overt P wave.

Moderate to severe hyperkalemia occasionally induces ST elevations in the right precordial leads (V_1 and V_2), simulating an ischemic current of injury or Brugada-type patterns. Even severe hyperkalemia, however, can be associated with atypical or nondiagnostic ECG findings. Marked hyperkalemia leads to eventual asystole, sometimes preceded by a slow undulatory (or *sine wave*) ventricular flutter-like pattern. The ECG triad of peaked T waves (from hyperkalemia), QT (ST portion) prolongation (from hypocalcemia), and LVH (from hypertension) is strongly suggestive of chronic renal failure (**see Chapter 98**).

Electrophysiologic changes associated with hypokalemia, by contrast, include hyperpolarization of myocardial cell membranes and increased action potential duration. The major ECG manifestations are ST depression with flattened T waves and increased U wave prominence (**Fig. 12.46B**). U waves can exceed the amplitude of T waves, and distinguishing T waves from U waves can be difficult or impossible from the surface ECG. Indeed, apparent U waves in hypokalemia and other pathologic settings may actually be part of T waves whose morphology is altered by the effects of voltage gradients between M, or midmyocardial, cells and adjacent myocardial layers.[10,13] The prolongation of repolarization with hypokalemia, as part of an acquired long QT(U) syndrome, predisposes to the development of torsades de

pointes (**see Chapter 39**) and to tachyarrhythmias during digitalis therapy.

Magnesium.
Specific ECG effects of mild to moderate isolated abnormalities in magnesium ion concentration are not well characterized. Severe hypermagnesemia (serum Mg^{2+} > 15 mEq/L) can cause atrioventricular and intraventricular conduction disturbances that may culminate in complete heart block and cardiac arrest. Hypomagnesemia usually is associated with hypocalcemia or hypokalemia and can potentiate certain digitalis toxic arrhythmias The role of magnesium deficiency in the pathogenesis and treatment of the acquired long QT(U) syndrome with torsades de pointes is discussed in **Chapters 36 and 39**.

Other Factors.
Isolated hypernatremia or hyponatremia does not produce consistent effects on the ECG. Acidemia and alkalemia are often associated with hyperkalemia and hypokalemia, respectively. Systemic hypothermia may be associated with the appearance of a distinctive convex elevation at the junction (J point) of the ST segment and QRS complex (J wave or Osborn wave)[9,12] (**Fig. 12.47**). The cellular mechanism of this type of pathologic J wave appears to be related to an epicardial-endocardial voltage gradient associated with the localized appearance of a prominent epicardial action potential notch.

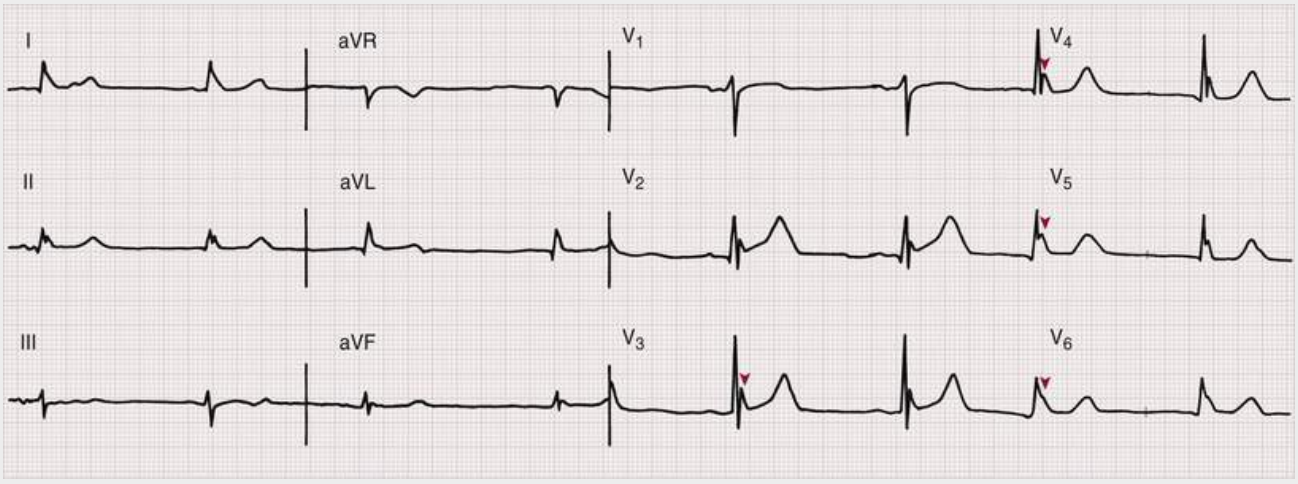

FIGURE 12.47 Systemic hypothermia. The *arrowheads* (leads V_3 through V_6) point to the characteristic convex J waves, termed *Osborn waves.* Prominent sinus bradycardia is also present, along with QT prolongation.

Nonspecific QRS and ST-T Changes

Low QRS voltage is considered to be present when the total (positive-to-negative peak) amplitude of the QRS complexes in each of the six extremity leads is 0.5 mV or less or 1.0 mV or less in leads V_1 through V_6. Low QRS voltage, as described earlier, can be caused by a variety of mechanisms, including increased insulation of the heart by air (chronic obstructive pulmonary disease) or adipose tissue (obesity); replacement of myocardium by fibrous tissue (ischemic or nonischemic cardiomyopathy), amyloid, or tumor; and possibly to short-circuiting (shunting) effects resulting from low resistance of fluids (especially with pericardial or pleural effusions, or anasarca). The combination of relatively low limb voltage (QRS voltage < 0.8 mV in each of the limb leads), relatively prominent QRS voltage in the chest leads (SV_1 or SV_2 + RV_5 or RV_6 > 3.5 mV), and slow R wave progression (R wave < S wave

amplitude in V_1 through V_4) has been reported as a relatively specific but not sensitive sign of dilated-type cardiomyopathies (sometimes referred to as the ECG "congestive heart failure triad").[42]

Ventricular repolarization is particularly sensitive to the effects of many factors in addition to ischemia (e.g., postural changes, meals, drugs, hypertrophy, electrolyte and metabolic disorders, central nervous system lesions, infections, pulmonary diseases) that can lead to a variety of *nonspecific ST-T changes*. The term usually is applied to slight ST-segment depression or T wave inversion or to T wave flattening without evident specific cause. Care must be taken not to overinterpret such changes, especially in persons with a low previous probability of heart disease. At the same time, subtle repolarization abnormalities can be markers of coronary or hypertensive heart disease or other types of structural heart disease; these probably account for the association of relatively minor but persistent nonspecific ST-T changes with increased cardiovascular mortality in middle-aged and older men and women.[69]

Alternans Patterns

The term *alternans* applies to conditions characterized by the sudden appearance of a periodic beat-to-beat change in some property of cardiac electrical or mechanical behavior. These abrupt changes (AAAA → ABAB pattern) are reminiscent of a generic class of patterns observed in perturbed nonlinear control systems. Many different forms of electrical alternans have been described clinically. Most familiar is total electrical alternans with sinus tachycardia, a specific but not highly sensitive marker of pericardial effusion with tamponade physiology (**Fig. 12.48**) (**see Chapter 34**). This finding is associated with an abrupt transition from a 1 : 1 to a 2 : 1 pattern in the "to-and-fro" swinging motion of the heart in the effusion.

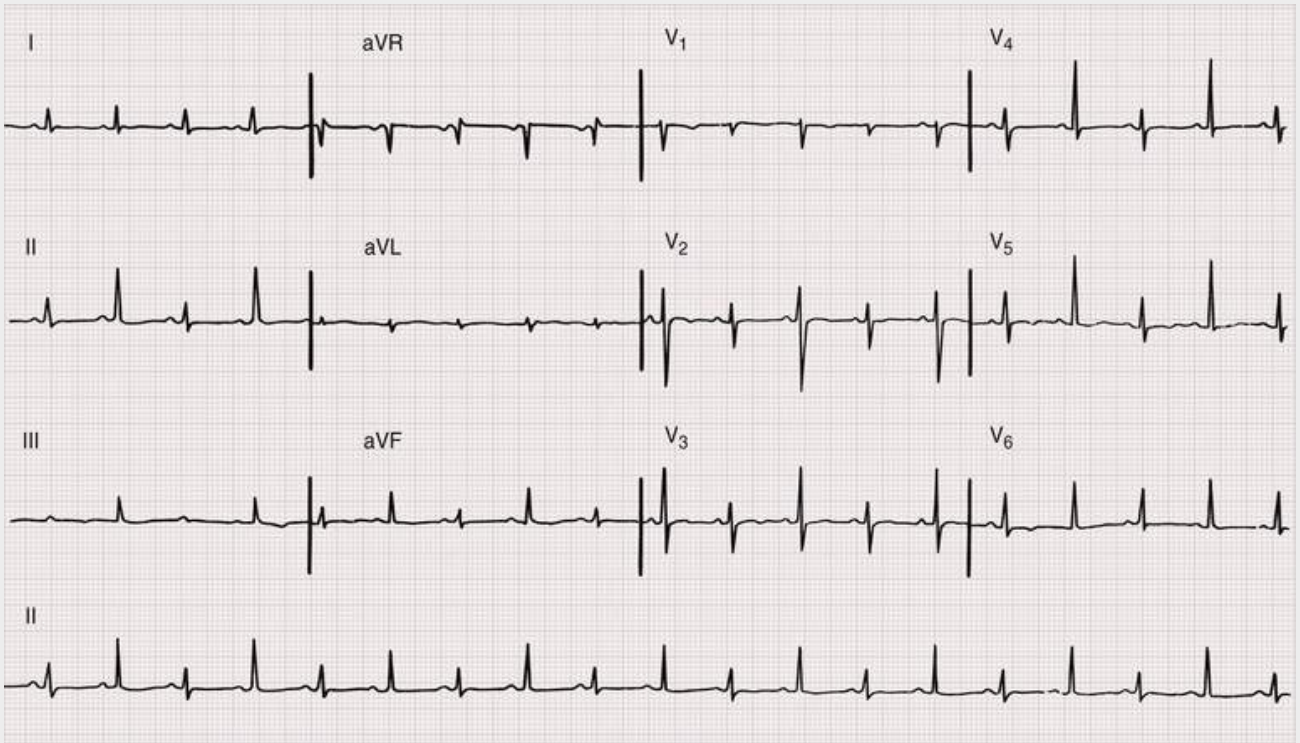

FIGURE 12.48 Total electrical alternans (P-QRS-T) caused by pericardial effusion with tamponade. This finding, particularly in concert with sinus tachycardia and relatively low voltage, is a highly specific, although not sensitive, marker of cardiac tamponade.

Other alternans patterns have primary electrical rather than mechanical causes. QRS (and sometimes R-R) alternans may occur with a number of different types of supraventricular tachycardias.[70] Alternans

has long been recognized as a marker of electrical instability of repolarization in cases of acute ischemia, in which it may precede ventricular tachyarrhythmia (**see Fig. 12.34**). Therefore, considerable interest continues to be directed at the detection of microvolt T wave (or ST-T) alternans as a noninvasive marker for increased risk of ventricular tachyarrhythmias in patients with chronic heart disease[71-73] (**see Chapter 39**). Similarly, T-U wave alternans (**Fig. 12.49**) may be a marker of imminent risk of torsades de pointes in hereditary or acquired long QT syndromes.

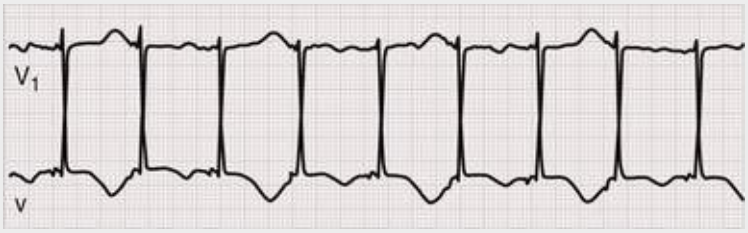

FIGURE 12.49 The QT(U) interval is prolonged (approximately 600 milliseconds) with T-U wave alternans. The tracing was recorded in a patient with chronic renal disease shortly after dialysis. This type of repolarization alternans may be a precursor to torsades de pointes. (Courtesy Dr. C. Fisch.)

Clinical Issues in Electrocardiographic Interpretation

The clinical effectiveness of the ECG as a diagnostic tool depends on numerous "real world" factors such as the appropriateness of the procedure, proper recording technique, and the skills of the interpreter.

Indications and Clinical Value

Relatively limited attention has been paid to the indications for an ECG, probably because of its seeming simplicity, safety, and low cost. However, direct out-of-pocket costs to patients and the potential risks and costs to the patient of both false-negative and false-positive diagnoses of cardiac disease can be substantial.[74] Recommendations for performing ECGs have been proposed by various organizations (see Guidelines supplement for chapter online).

Concerns appropriately include both overuse and underuse of the ECG. The American College of Physicians,[74] American Heart Association,[75] U.S. Preventive Services Task Force,[21] and other professional groups recommend that routine ECGs not be used as a screening approach in asymptomatic persons in an effort to reduce overuse. On the other hand, fewer than two-thirds of emergency medical services record and interpret on-site 12-lead ECGs in cases of suspected STEMI,[76] a procedure accepted to improve outcomes (**see Chapter 42**).

The clinical value of the ECG is optimized when a technically adequate recording is interpreted by a skilled professional who has knowledge of the accuracy of the various ECG diagnoses and who integrates findings from prior ECG recordings, clinical information, and the results of other cardiac and noncardiac tests. Key factors include reader competency and interobserver variability in ECG interpretation, technical issues in ECG recording that impact reliability and consistency, and the appropriate application of computer technology and interpretation.

Reading Competency

Developing and maintaining competency in interpretation of the ECG are critical to successful clinical practice. The American College of Cardiology (ACC) recommends supervised and documented interpretation of a minimum of 3500 ECGs, covering a broad spectrum of diagnoses and clinical settings, over the training period for cardiology fellows.[77] In addition, follow-up assessment of interpretation accuracy has been recommended to maintain skills and to assess updated knowledge of new criteria and applications. Both the ACC and the American College of Physicians[78] have provided lists of patterns to be recognized and recommend knowledge of basic electrophysiology and electrocardiology as well as in waveform analysis.

The actual adequacy of training and the level of competency of trainees remain limited. In one study, cardiology fellows at an academic institution correctly interpreted only 58% of a test set of ECGs and missed 36% of potentially life-threatening abnormalities.[79] The challenge of adequate training is compounded by the number of physician specialties as well as nonphysicians with various modes and intensity of training in interpretation of ECGs.

Various tools are available to assess and improve proficiency. Programs such as the ECG Self-Assessment Program of the ACC are useful for identifying knowledge levels of proficiency and areas of specific weakness. A number of websites feature ECGs for self-assessment and clinical instruction. For example, ECG Wave-Maven (http://ecg.bidmc.harvard.edu) provides free access to more than 490 case studies of ECGs, with answers and multimedia adjuncts.

A related issue is the common phenomenon of differing diagnoses even among expert readers, that is, inter-reader variability. One recent study reported that, based on a test set of 20 ECGs read by 21 experts, agreement occurred in 79% of tracings with evidence of STEMI and in only 37% of cases showing chamber hypertrophy.[80] These issues can lead to clinical mismanagement, including failure to identify and appropriately triage patients with AMI eligible for urgent revascularization.[81] A set of common pitfalls in the ECG diagnosis of MI has recently been published.[82]

Technical Errors

Technical errors can lead to clinically significant diagnostic mistakes. Artifacts that may interfere with interpretation can result from movement of the patient, misplacement of electrodes or poorly secured electrodes, electrical disturbances related to current leakage and grounding failure, and external interference from nearby electrical sources, such as stimulators or cauteries. Electrical or motion (e.g., parkinsonian tremor) artifacts can simulate life-threatening arrhythmias (**Fig. 12.50**). Body motion can cause excessive baseline wander that may simulate or obscure ST-segment shifts of myocardial ischemia or injury.

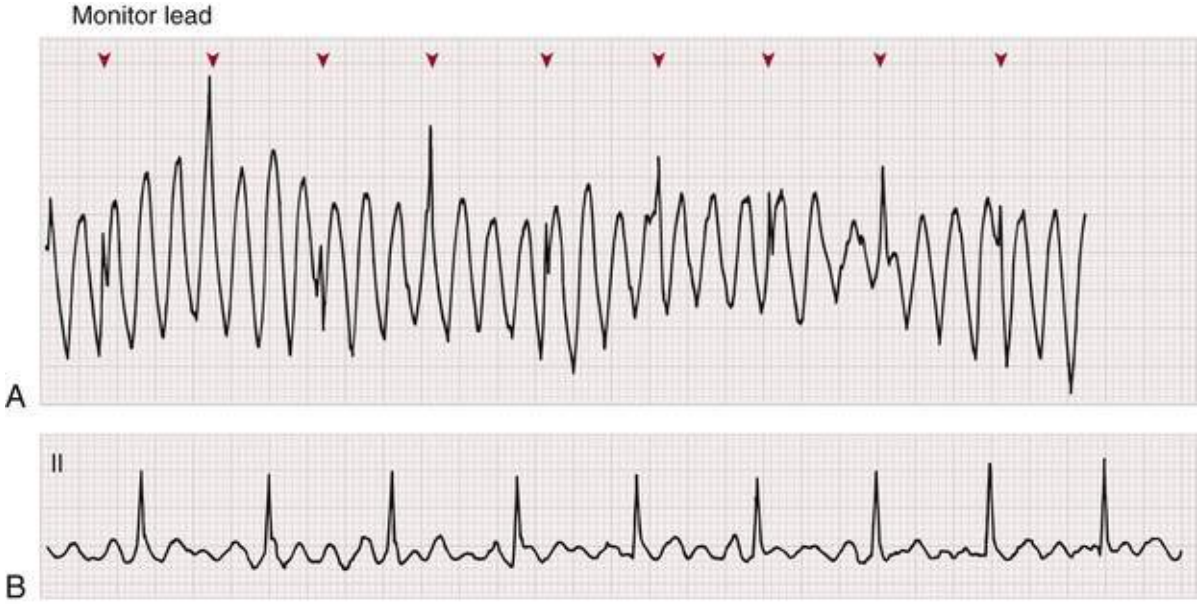

FIGURE 12.50 Artifacts simulating serious arrhythmias. **A,** Motion artifact mimicking ventricular tachyarrhythmia. Partly obscured normal QRS complexes (*arrowheads*) can be seen with a heart rate of approximately 100 beats/min. **B,** Parkinsonian tremor causing baseline oscillations mimicking atrial fibrillation. The regularity of QRS complexes may provide a clue to the source of this artifact.

Misplacement of one or more electrodes is a common cause for errors in interpretation of the ECG. Many limb lead switches produce ECG patterns that can aid in their identification. Reversal of the two arm electrodes, for example, results in an inverted P and QRS waveforms in lead I but not in lead V_6, two leads that would normally be expected to have similar polarities.

The most common precordial electrode misplacements are placement of V_1 and V_2 electrodes in the second or third rather than in the fourth intercostal place and placement of the V_5 and V_6 electrodes above or below the horizontal line of V_4. These misplacements may be more difficult to detect but may result in changes in R wave progression, accentuation of r' waves, and ST-segment elevation in the right precordial leads simulating IVCDs or MI. In addition, variation in placement of electrodes between recordings, even to a small extent, may cause diagnostically confusing changes in waveform patterns, especially when relying on serial changes to detect acute ischemia or infarction.

Similarly, ECGs recorded using nonstandard electrode locations or altered filter settings often lead to clinically important waveform changes. Recordings from electrode subsets, such as used for exercise testing or in intensive care settings, are significantly different from those recorded using standard electrode sets and should not be used for diagnostic purposes. Increasing the low-frequency cutoff to reduce baseline wander and respiratory effects can produce a range of artifactual ST-segment abnormalities. Lowering the high-frequency cutoff to reduce motion and tremor artifacts reduces R wave amplitudes and Q wave measurements and decreases the accuracy of diagnoses of hypertrophy and infarction.[1]

Computer Interpretation

Other technical issues reflect characteristics of computerized systems. Computerized recording and interpretation systems have become the norm and have many clinical and technical advantages. However, important distinctions and challenges remain. Whereas intervals and amplitudes measured in manual systems are typically based on features of individual leads, those reported by computerized systems are based on measurements from an overlay of averaged beats from all leads. As a result, computerized

measurements are usually longer than those from manual readings because they include portions of the ECG waveform that appear to be isoelectric in some leads but not in others. Differences in the duration of the Q wave, the QRS complex, or the QT interval may be sufficient to meet criteria for infarction, conduction defects, and repolarization abnormalities that were based on manual recordings.

An ongoing concern is overreliance on computerized interpretations. Although computerized diagnostic algorithms have become more accurate and serve as important adjuncts to the clinical interpretation of ECGs, such measurements and diagnoses are currently not sufficiently accurate to be relied on in critical clinical environments without expert review. Reports have described limited accuracies for computerized systems, with error rates as high as 30% for pattern-based diagnoses and as high as 40% for arrhythmias.[83] In addition, clinically relevant discrepancies in measurements and interpretation terminology may be reported by systems from different manufacturers and even by different software versions from the same manufacturer.[84]

Future Perspectives

Clinical electrocardiography represents a mature cardiovascular methodology based on extensive electrophysiologic and clinical correlates that have evolved over more than a century of study. Although recent and future advances in other imaging techniques provide a more direct assessment of cardiac structural abnormalities, the ECG uniquely provides essential information about the electrical properties of the heart with potentially life-threatening conditions such as brady- and tachyarrhythmia, ischemia, and hyperkalemia.

Several areas for expanded knowledge and clinical relevance may be suggested. Advances in computerized diagnostic criteria stratified for race, age, and sex as well as other demographic and clinical variables may improve the value of the standard ECG. Incorporating ECG findings into broader electronic medical record and database systems may facilitate automated interpretation of serial ECG recordings as well as linkage to other clinical information, leading to more relevant interpretations. Development of meticulously annotated, open-access databases of high-resolution digital ECGs with detailed clinical correlates will help refine current diagnostic criteria.

Other advances may represent major changes in approach. Examples are mathematical analysis of body surface potentials, such as those that estimate direct cardiac potentials from surface recordings,[85] and the assessment of genomic and biomarker patterns that permit more direct understanding of the abnormal physiology[86] underlying ECG patterns (**see Chapters 8 and 34**).

Guidelines

Electrocardiography

David M. Mirvis and Ary L. Goldberger

The clinical uses of the electrocardiogram (ECG) include both (1) the identification and characterization of existing or suspected cardiovascular disease and (2) the prediction of future clinical events related to cardiac function, that is, risk stratification. To meet these goals with maximal efficiency and efficacy, numerous professional organizations have proposed appropriateness guidelines for recording an ECG. These may be considered for several different populations—persons with known heart

disease, those with suspected heart disease or at high risk for heart disease, and those without evidence of heart disease. In addition, more specific recommendations have been proposed for the use of the ECG in special groups, including preoperative patients, persons with dangerous occupations, athletes, and patients taking medications with electrophysiologic effects.

Patients With Known Cardiovascular Disease

Guidelines published jointly by the American College of Cardiology (ACC) and the American Heart Association (AHA)[1-3] are summarized in **Tables 12G.1 to 12G.3**. **Table 12G.1** summarizes the ACC/AHA guidelines in patients with known cardiovascular disease. They support the use of ECGs as part of the baseline evaluation of all patients with known cardiovascular disease after initiating therapy known to produce ECG changes that correlate with therapeutic responses, progression of disease, or adverse effects; for intermittent follow-up evaluations for investigation of new or changes in signs or symptoms of cardiovascular disease or relevant laboratory findings; and after significant intervals (usually 1 year or longer) in the absence of clinical changes. Follow-up ECGs are not considered appropriate for patients with mild chronic cardiovascular conditions that are not deemed likely to progress (e.g., mild mitral valve prolapse) and are not considered to be appropriate at each visit for patients with stable heart disease who are seen frequently (e.g., within 4 months) without evidence of clinical change.

TABLE 12G.1

ACC/AHA Guidelines for Electrocardiography in Patients with Known Cardiovascular Disease or Dysfunction*

INDICATION	CLASS I† (INDICATED)	CLASS II (EQUIVOCAL)	CLASS III (NOT INDICATED)
Baseline or initial evaluation	All patients	None	None
Response to therapy	Patients in whom prescribed therapy is known to produce changes in the ECG that correlate with therapeutic responses or progression of disease or adverse effects	Patients prescribed drugs known to alter serum electrolyte concentrations	Patients receiving pharmacologic or nonpharmacologic therapy not known to produce changes in the ECG or to affect conditions that may be associated with such changes
Follow-up evaluation	Patients with a new or a change in symptoms, signs, or laboratory findings related to cardiovascular status Patients with an implanted pacemaker device Patients with cardiovascular disease in the absence of new symptoms or signs after an interval of time appropriate for the condition or disease	None	Adult patients whose cardiovascular condition is usually benign and unlikely to progress (e.g., patients with asymptomatic mild mitral valve prolapse or mild hypertension) Adult patients with chronic stable heart disease seen at frequent intervals (e.g., 4 months) without unexplained findings

*Based on published recommendations of the AHA/ACC.[1-3]

†Classifications are based on those used by Schlant and colleagues.[1]

TABLE 12G.2

ACC/AHA Guidelines for Electrocardiography in Patients Suspected of Having or at Increased Risk for Cardiovascular Disease or Dysfunction*

SETTING	CLASS I (APPROPRIATE)	CLASS II (EQUIVOCAL)	CLASS III (NOT INDICATED)
Baseline or initial evaluation	All patients suspected of having or being at increased risk for cardiovascular disease Patients who may have used cocaine, amphetamines, or other illicit drugs known to have cardiac effects	None	None
Response to therapy	Patients in whom prescribed therapy is known to produce changes in the ECG that correlate with therapeutic responses or progression of disease or adverse effects	Patients prescribed drugs known to alter serum electrolyte concentrations	Patients receiving pharmacologic or nonpharmacologic therapy not known to produce changes in the ECG or to affect conditions that may be associated with such changes
Follow-up examination, once	Presence of any change in clinical status or laboratory findings suggesting interval development of cardiac disease or dysfunction Periodic follow-up examination of patients (e.g., every 1 to 5 years) known to be at increased risk for cardiac disease	None	Follow-up ECGs more often than yearly for patients who remain clinically stable

*Based on published recommendations of the AHA/ACC.[1-3]

TABLE 12G.3

ACC/AHA Guidelines for Electrocardiography in Patients with No Apparent or Suspected Heart Disease or Dysfunction*

Setting	Class I (Appropriate)	Class II (Equivocal)	Class III (Not Indicated)
Baseline or initial evaluation	Before administration of pharmacologic agents known to be associated with a high incidence of cardiovascular effects (e.g., antineoplastic agents) People of any age in special occupations that require very high cardiovascular performance (e.g., firefighters, police officers) or whose cardiovascular performance is linked to public safety (e.g., pilots, air traffic controllers, critical process operators, bus or truck drivers, railroad engineers)	Initial evaluation of patients with risk factors such as diabetes and hypertension	Routine screening, risk assessment, or as a baseline in asymptomatic, low-risk persons
Response to therapy	To evaluate patients in whom prescribed therapy (e.g., doxorubicin) is known to produce cardiovascular effects	None	To assess treatment not known to produce any cardiovascular effects
Follow-up	To evaluate interval changes in symptoms or signs	None	To evaluate asymptomatic adults who have had no interval change in symptoms, signs, or risk factors
Before surgery	Patients being evaluated as donor for heart transplantation or as recipient of noncardiopulmonary transplant	Patients undergoing vascular or other high-risk procedures	Asymptomatic persons undergoing low-risk procedures

*Based on published recommendations of the AHA/ACC,[1-3] and other groups as described in the text.

Patients Suspected of Having Cardiovascular Disease

Table 12G.2 summarizes the AHA/ACC recommendation for patients suspected of having cardiac disease or those at high risk for cardiac disease. An ECG is appropriate as part of an initial evaluation in the presence of signs or symptoms suggesting cardiac disease; in patients with important risk factors such as cigarette smoking, diabetes mellitus, peripheral vascular disease, or a family history of cardiac disease; during therapy with cardioactive medications; and during follow-up if new clinical findings or events develop or at prolonged intervals if the patient is clinically stable. In follow-up evaluation of patients at increased risk for heart disease, ECGs every 1 to 5 years are considered appropriate, but routine ECGs more frequently than yearly are not supported for patients who remain clinically stable.

Patients Without Known or Suspected Cardiovascular Disease

The ECG in persons without known or suspected cardiovascular disease has been discouraged by major

professional groups. Although they recognize that certain ECG findings do have prognostic value, and that the impetus to identify these abnormalities in the general population to reduce the risk of cardiovascular morbidity and mortality is understandable, they conclude that there is inadequate evidence that the ECG has the practical ability to accurately identify persons at high risk within the general, seemingly healthy population; that adding an ECG to the standard risk assessment approach based on history and physical examination improves risk stratification, alters the risk management approach, or improves outcome; and that high rates of false-positive results in this population have significant consequences, including unnecessary, expensive and potentially hazardous noninvasive and invasive diagnostic testing, overtreatment, and labeling.

Based on these concepts, recommendations for routine clinical screening by numerous organizations, including the AHA/ACC[1-3] U.S. Preventive Services Task Force (USPSTF)[4] and the American College of Physicians discourage the use of the ECG as part of a routine health or risk factor assessment.

The 2010 ACC/AHA guidelines (**Table 12G.3**) do suggest that an ECG is reasonable for cardiovascular risk assessment in asymptomatic persons with diabetes or hypertension (a Class IIa recommendation, with benefits substantially exceeding risk). The AHA/ACC recommendations are based on information from limited population studies and relied on consensus opinions and existing standards of care (Level C). The USPSTF[4] similarly concluded that for persons with moderate to high risk of events (>10% likelihood within 10 years, based on other risk factor analyses) the existing data are insufficient to make a definitive recommendation about the relative benefits and risks of a routine ECG.

Special Populations

Persons with Dangerous Occupations

Recommendations for screening of persons with dangerous jobs or jobs that place other people at risk—for example, airline pilots and bus drivers—also are controversial. Although no specific data defining the value of routine screening are available, some groups, including USPSTF[4] and AHA,[1] recognize the potential for benefit in relation to the possible risk to others. The U.S. Federal Aviation Administration currently requires an ECG at age 35 and annually after age 40 (for first-class airline transport pilots) for commercial pilots.

Preoperative Evaluation

The common practice of routinely recording an ECG before noncardiac surgery in patients without other indications has been based on the putative value of the ECG in predicting intraoperative or postoperative events and as a baseline for comparison if a later event occurs. However, most (although not all) studies have documented the absence or limited value of the routine preoperative ECG in identifying patients with coronary artery disease and in predicting postoperative outcomes.[5-7]

Thus the ACC/AHA[5] concluded that a routine preoperative ECG is reasonable (Class IIa recommendation based on limited randomized or nonrandomized studies [Level B]) for patients with known coronary heart, peripheral vascular, or cerebrovascular disease; significant arrhythmias; or other structural heart disease, except for those undergoing low-risk procedures.

These groups also concluded that a preoperative ECG (within 1 to 3 months of the procedure) may be considered for other asymptomatic patients without coronary artery disease except those undergoing low-risk procedures (Class IIb recommendation, Level B evidence). However, routine ECGs for patients undergoing low-risk procedures are determined not to be beneficial and are deemed to be inappropriate

(Class III recommendation).

Likewise, the European Society of Cardiology[6] and the American Society of Anesthesiologists Task Force on Preanesthesia Evaluation[7] have concluded that a preoperative ECG is not indicated for patients undergoing low-risk procedures who do not have risk factors. They do suggest that preoperative testing may be performed on a selective basis based on the clinical features of individual patients. Important clinical characteristics may include cardiovascular or respiratory disease, known cardiovascular risk factors, or risk factors and the patient's age.

Screening of Athletes

The requirement for an ECG as part of the preparticipation clinical evaluation of competitive athletes remains very controversial[8] (**see Chapter 53**). Both the European Society of Cardiology[9] and the International Olympic Committee[10] recommend including the ECG as part of preparticipation medical assessment. These recommendations are based on some studies that have reported an added diagnostic value and high sensitivity of the ECG for detecting the most common underlying causes of athlete deaths, such as hypertrophic cardiomyopathy and the long-QT interval syndromes, and the experience of the 30-year national screening program in Italy to prospectively identify these abnormalities and greatly reduce the occurrence of sudden death by facilitating the disqualification of high-risk affected persons.[11]

The AHA, in contrast, does not recommend routine ECG screening.[8,12] Rather, they recommend a complete 14-point clinical evaluation based on history and physical examination. Reasons for this position include the limited and conflicting data on the benefits, the significant false-positive rate leading to the inappropriate disqualification of many athletes and the need for unnecessary secondary testing (and logistical) manpower, and financial and resource limitations within the U.S. health care system. Rather, the AHA recommends an ECG only if suggestive abnormalities are revealed in the personal and family history or found on physical examination.

Similarly, a multidisciplinary task force convened by the National Collegiate Athletic Association (NCAA)[13] did not recommend a mandatory preparticipation ECG based on their conclusion that the evidence that the has a substantially positive risk/benefit ratio was lacking. The NCAA as well as the AHA do support local, community, or institutional efforts to provide screening ECGs if (1) athletes are well informed about the potential benefits and limits of the test, (2) tests are performed by adequately trained staff and interpreted based on accepted criteria for abnormalities in athletic hearts, and (3) appropriate cardiologic oversight and backup provide secondary testing if ECG abnormalities are found. The NCAA also recommends that ECG testing be accompanied by establishment of registries to expand knowledge about the value of such testing.

Recommendations do support a standard 12-lead ECG as part of routine evaluation for all athletes older than 40 seeking to engage in competitive sports. No conclusive data exist on the value of ECG screening for recreational athletes of any age.

Cardioactive Drug Administration

Numerous drugs have potentially harmful electrophysiologic effects that may be associated with ECG changes, including antiarrhythmic agents, methadone, tricyclic antidepressants and other psychotropic agents, stimulants, and illicit drugs. The role of the ECG as a baseline examination and in follow-up evaluation of patients taking such drugs remains poorly defined and, in some cases, controversial.

Although definitive data are not yet available, the AHA[14] has recommended that it would be “prudent” to obtain a baseline ECG before beginning tricyclic antidepressant or phenothiazine treatment in children

and adolescents and another ECG once steady-state dosage has been reached. They likewise suggest that an ECG may be reasonable (Class IIA recommendation, Level C evidence) in children and adolescents before initial therapy for attention-deficit hyperactivity disorder (ADHD) as part of a complete clinical assessment.[15] The American Pain Society and the Heart Rhythm Society[16] have also published recommendations that patients receiving methadone who have risk factors for prolonged QTc intervals or a history of ventricular arrhythmias have a baseline ECG before beginning therapy and periodically during therapy based on the baseline ECG, dosage changes, and other risk factors.

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13

Exercise Electrocardiographic Testing

Gary J. Balady, Anthony P. Morise

Exercise electrocardiographic testing is among the most fundamental and widely used tests for the evaluation of patients with cardiovascular disease (CVD). It is easy to administer, perform, and interpret; it is flexible and adaptable; and it is reliable, inexpensive, and readily available in hospital or practice settings. The exercise test has been used by clinicians for more than half a century, and its durability can be attributed to its evolution over time. Initially developed to detect the presence of myocardial ischemia secondary to coronary artery disease (CAD), the exercise electrocardiogram (ECG) is now recognized for its power in predicting prognosis. Exercise test variables beyond the ST segment yield important information, particularly when used in combination with clinical information, to predict outcomes and guide therapy in a broad range of individuals, from the healthy to those crippled by heart disease. Emerging applications of exercise electrocardiography have demonstrated its usefulness in the evaluation and management of patients with a wide variety of cardiovascular conditions, including valvular heart disease, congenital heart disease, genetic cardiovascular conditions, arrhythmias, and peripheral artery disease. When used appropriately with adjunctive modalities to measure gas exchange and ventilation or with imaging techniques such as echocardiography or nuclear perfusion imaging (**see Chapters 14 and 16**), the power of the exercise ECG is greatly enhanced. The exercise ECG is the clinician's beacon that can guide optimal care for a great majority of patients with known or suspected CVD. This chapter provides a detailed foundation of information on the exercise ECG. Other chapters address adjunctive imaging techniques and further discuss the use of exercise testing in patients with specific cardiovascular conditions.

Exercise Physiology

Total-Body Oxygen Uptake

Exercising muscles require energy to contract and relax. Most of this energy is derived from oxidative metabolism to generate adenosine triphosphate; thus energy requirements at rest and for any given amount of physical activity (*work rate*) can be estimated from measurements of total-body oxygen uptake (V_{O_2}). The Fick equation (**Fig. 13.1**) demonstrates that V_{O_2} is equal to the product of cardiac output and oxygen extraction at the periphery (i.e., arteriovenous oxygen difference). V_{O_2} is easily expressed in multiples of resting oxygen requirements (metabolic equivalents [METs]), with 1 MET being resting energy

expenditure and defined as approximately 3.5 mL O_2/kg body weight/min. This convenient system indexes the amount of energy used during any given physical activity against that used at rest. Accordingly, 5-MET activity requires five times the energy expenditure at rest. VO_2max is the peak oxygen uptake achieved during performance of the highest level of dynamic exercise involving large muscle groups and by definition cannot be exceeded despite increases in work rate. It is related to age, sex, heredity, exercise habits, and cardiovascular status. Cardiac output can increase as much as four to six times resting levels in the upright position. Maximum cardiac output is the result of a twofold to threefold increase in heart rate from resting levels and an increase in stroke volume. Stroke volume in healthy persons generally plateaus at 50% to 60% of VO_2max. Oxygen extraction at the periphery can increase as much as threefold, and the maximum arteriovenous O_2 difference has a physiologic limit of 15 to 17 mL O_2/100 mL blood. During clinical exercise testing, patients are prompted to exercise not until they attain VO_2max but rather to the VO_2 that is attained during symptom-limited, maximum tolerated exercise; this level is termed the VO_2 peak.[1]

$$\text{Resting } VO_2 = \text{C.O.} \times \text{A-}VO_2 \text{ Difference}$$

$$\text{Maximal Exercise } VO_2 = \text{C.O.} \times \text{A-}VO_2 \text{ Difference}$$

$$= \text{HR (2-3x resting)} \times \text{SV (2x resting)} \times \text{A-}VO_2 \text{ Difference (3x resting)}$$

FIGURE 13.1 Fick equations at rest and during exercise; see text for details. *A-VO_2 Difference,* Arteriovenous oxygen difference; *C.O.,* cardiac output; *HR,* heart rate; *SV,* stroke volume; *VO_2,* total body oxygen uptake.

Myocardial Oxygen Demand and Supply Relationships During Exercise

Myocardial ischemia occurs when the supply of oxygenated blood to myocardial cells is inadequate to meet demands. Many factors affect the delicate balance of supply and demand (**Fig. 13.2**). Exercise testing is performed to stress these relationships and observe the physiologic responses that ensue. This enables the clinician not only to assess for the development of myocardial ischemia, but also to evaluate at what level of myocardial oxygen demand and physical activity (work rate) ischemia occurs.[1]

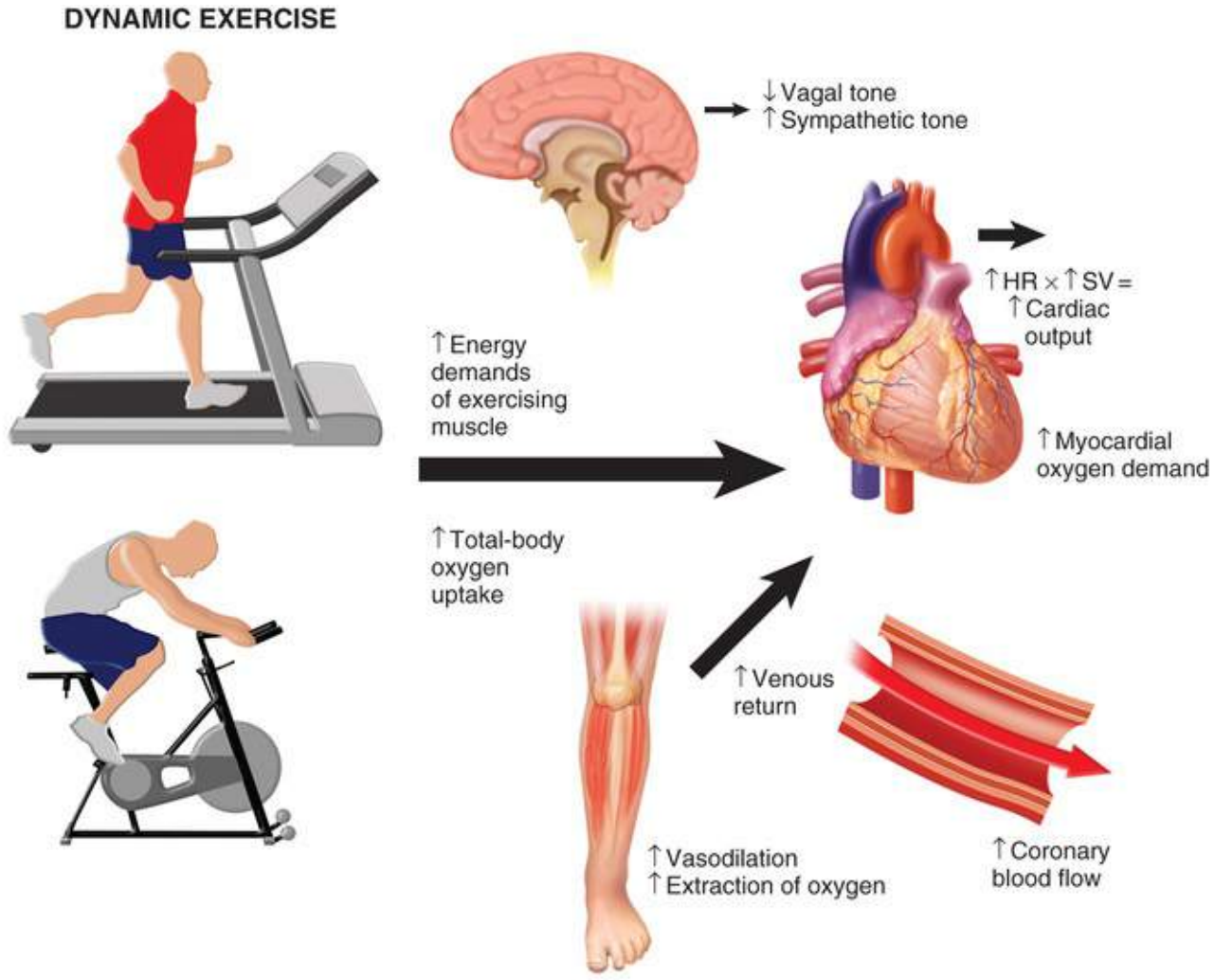

FIGURE 13.2 Physiologic responses to acute exercise. (See text for details.)

Myocardial Oxygen Demand.

Myocardial oxygen demand is related to heart rate (HR), blood pressure (BP), left ventricular (LV) contractility (myocardial shortening per beat), and LV wall stress. The latter is related to LV pressure, wall thickness, and cavity size. Changes in any of these interdependent factors can affect myocardial need for oxygenated blood. Of these parameters, HR and BP are the easiest to measure and monitor. The product of HR and systolic BP, termed the *rate-pressure product*, is a reliable index of myocardial oxygen demand and can be readily assessed clinically.

During acute endurance (high-repetition/low-resistance) exercise (e.g., walking or cycling), cardiac output rises in response to the metabolic needs of the exercising muscles (estimated by measured V_{O_2}). Diminution of vagal tone and a rise in sympathetic tone lead to an increase in HR and LV contractility. Stroke volume also rises because of increases in venous return of blood from exercising muscles, and blood flow is redistributed from the renal, splanchnic, and cutaneous circulation to the exercising muscles. Accumulation of metabolites in the actively contracting muscles causes vasodilation of muscle arterioles, which increases skeletal muscle blood flow up to four times that of resting levels and results in a reduction in aortic outflow impedance. This in turn allows more complete systolic ejection, thereby further increasing stroke volume. Systolic BP increases mostly because of the rise in cardiac output, whereas diastolic BP either remains constant or falls as a result of the reduction in vascular resistance. The size and location of the exercising muscle groups will have different effects on the hemodynamic

response to exercise. Dynamic arm exercise elicits higher HR and BP responses at any given work rate than does dynamic leg exercise. Arm work yields differences in sympathetic output, peripheral vasodilation, venous return, and metabolic requirements, which are influenced not only by the exercising muscle mass but also by the stabilizing muscles recruited during arm exercise.[1]

Resistance (low-repetition/high-load) exercise (e.g., weightlifting) is not generally used during graded exercise testing but may be used in work simulation testing or exercise training regimens. This type of exercise generates an increased sympathetic response, leading to an increase in HR; however, venous return, especially during straining, may decrease. Therefore the rise in cardiac output is relatively small in comparison to that achieved with endurance exercise and is primarily caused by increases in HR. Muscle contraction during resistance exercise generates compressive force on muscle capillaries that leads to elevated peripheral resistance. This rise in vascular resistance coupled with an increase in cardiac output yields an increase in both systolic and diastolic BP. Elevations in systolic BP from rest to exercise are proportionally greater than the elevations in HR during resistance exercise than during endurance exercise. Therefore, both endurance exercise and resistance exercise increase myocardial oxygen demand because of increases in HR, BP, LV contractility, and LV wall stress (the latter caused by increases in LV pressure and volume during exercise).[1]

Myocardial Oxygen Supply.

Coronary blood flow increases during exercise in response to neurohumoral stimulation (primarily sympathetic beta receptor stimulation) and as a result of the release of endothelial substances, including nitric oxide. In healthy persons during acute exercise, coronary arteries dilate and coronary blood flow rises in response to the increases in myocardial oxygen demand. Most often, coronary flow is compromised as a result of atherosclerotic plaque within the lumen of the coronary artery (**see Chapter 44**). Plaque may cause minimal stenosis or complete occlusion of the artery. Several factors influence the significance of a given luminal stenosis, including the degree of luminal obstruction, the length of the obstruction, the number and size of functioning collateral vessels, the magnitude of the muscle mass supplied, the shape and dynamic properties of the stenosis, and the autoregulatory capacity of the vascular bed. In general, a 50% to 70% reduction in luminal diameter will impair peak reactive hyperemia, whereas 90% or greater stenosis will reduce resting flow. However, exercise stimulates local changes in vasomotor tone as a result of neuromodulation, endothelial dysfunction, and local factors, and these changes can further influence the supply of oxygenated blood to the myocardium. Atherosclerotic arteries often fail to dilate and may actually constrict with exercise, thus further reducing the supply of blood in the setting of increased demand.[1]

Technical Components of Exercise Testing

Patient Preparation

Patient Assessment

It is important to assess the patient before performing the exercise test to evaluate the indications for the test, the appropriateness of the specific test that has been ordered to answer the question posed, the ability of the patient to perform exercise, and whether the patient has any contraindications to exercise testing (**Table 13.1**). Information from the medical history as provided by the patient, chart review, and the ordering provider and/or the patient's primary care physician or cardiologist can be most useful in this pretest evaluation. A brief physical examination that addresses the components outlined in **Table 13.2** can

also be helpful. A current standard resting 12-lead ECG is useful in assessing heart rate, rhythm, conduction abnormalities, and evidence of previous myocardial infarction (MI) and should be compared with the most recent previous ECG, if available.

TABLE 13.1
Contraindications to Exercise Testing

Absolute Contraindications
Acute myocardial infarction, within 2 days
High-risk unstable angina
Uncontrolled cardiac arrhythmia with hemodynamic compromise
Active endocarditis
Symptomatic severe aortic stenosis
Decompensated heart failure
Acute pulmonary embolism or pulmonary infarction
Acute myocarditis or pericarditis
Physical disability that precludes safe and adequate testing
Relative Contraindications
Known left main coronary artery stenosis
Moderate aortic stenosis with uncertain relation to symptoms
Tachyarrhythmias with uncontrolled ventricular rates
Acquired complete heart block
Hypertrophic cardiomyopathy with severe resting gradient
Mental impairment with limited ability to cooperate

From Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation 2013;128:873.

TABLE 13.2
Patient Assessment for Exercise Testing

History
1. **Medical diagnoses and past medical history:** A variety of diagnoses should be reviewed, including cardiovascular disease (known existing coronary artery disease [CAD], previous myocardial infarction, or coronary revascularization); arrhythmias, syncope or presyncope; pulmonary disease, including asthma, emphysema, and bronchitis or recent pulmonary embolism; cerebrovascular disease, including stroke; peripheral artery disease; current pregnancy; and musculoskeletal, neuromuscular, or joint disease.
2. **Symptoms:** Angina; chest, jaw, or arm discomfort; shortness of breath; and palpitations, especially if associated with physical activity, eating a large meal, emotional upset, or exposure to cold
3. **Risk factors for atherosclerotic disease:** Hypertension, diabetes, obesity, dyslipidemia, and smoking
4. If patient is without known CAD, determine the pretest probability of CAD (see Table 13.11).
5. Recent illness, hospitalization, or surgical procedure
6. Medication dose and schedule
7. Ability to perform physical activity
Physical Examination
1. Pulse rate and regularity
2. Resting blood pressure sitting and standing
3. Auscultation of the lungs, with specific attention to uniformity of breath sounds in all areas, particularly in patients with shortness of breath, a history of heart failure, or pulmonary disease
4. Auscultation of the heart, particularly in patients with heart failure or valvular disease
5. Examination related to orthopedic, neurologic, or other medical conditions that might limit exercise

Although diagnostic exercise tests in patients without known CAD are best performed by withholding cardioactive medications on the day of the test to better assess for an ischemic response, functional testing in patients with known CAD might best be performed with patients having taken their usual medications to evaluate the effects of the medications on HR, BP, symptoms, and ischemia during exercise (see later, Pharmacologic Influences on Interpretation).

In patients with permanent cardiac pacemakers, it is important to obtain information from the patient's cardiologist regarding the type of pacemaker (single or dual chamber), programmed mode, rate responsiveness, and pacing HR limits before the test. Similarly, in patients with implantable cardioverter-defibrillators (ICDs), information regarding ICD rhythm detection and treatment algorithms should be obtained so that the peak HR during the exercise test is maintained at least 10 beats/min below the programmed HR threshold for antitachycardia pacing and defibrillation.[2] Additional details of patient

assessment are provided elsewhere.[1]

Symptom Rating Scales

Before exercising, patients should be made familiar with the symptom rating scales that might be used during testing. These are described further elsewhere[2] and may include the Borg Scale of Perceived Exertion.[1]

Electrocardiographic Lead Systems

As the technology of exercise electrocardiographic testing has evolved, several different types of lead systems have been developed and used. Details regarding these lead systems, along with skin preparation techniques, are provided elsewhere.[1,3] The importance of adequate skin preparation cannot be overstated; this is essential to optimize the quality of the exercise ECG. To obtain a high-quality 12-lead ECG during testing, electrode placement on the torso is standard for routine testing. Torso electrodes are placed under the lateral aspect of the clavicles for the arm leads and on the lower end of the rib cage or high under the rib cage for the leg leads. A standard 12-lead ECG should be performed before placement of the torso limb leads because such lead placement may alter the inferior lead complexes and result in previous Q waves being either mimicked or hidden.

Exercise Test Modality and Protocols

The testing modality and protocol should be selected in accordance with the patient's estimated functional capacity based on age, estimated physical fitness from the patient's history, and underlying disease. Several exercise test protocols are available for both treadmill and stationary cycle ergometers. Patients who have low estimated fitness levels or are deemed to be at higher risk because of underlying disease (e.g., recent MI, heart failure) should be tested with a less aggressive exercise protocol. Treadmill and cycle ergometers may use stepped or continuous ramp protocols. Work rate increments (stages) during stepped protocols can vary from 1 to 2.5 METs. Ramp protocols are designed with stages that are no longer than 1 minute and for the patient to attain peak effort within 8 to 12 minutes. Accordingly, ramp protocols must be individualized and selected to accommodate the patient's estimated exercise capacity. Because there are no widely published or standard sets of ramp protocols, individual exercise testing laboratories usually develop their own customized protocols that accommodate a wide range of fitness levels. **Table 13.3** provides examples of such protocols.[4,5] The American College of Sports Medicine (ACSM)[2] details a variety of treadmill and cycle ergometer testing protocols.

TABLE 13.3

Boston Medical Center Treadmill Ramp Protocols

STAGE*	VERY LOW RAMP			LOW RAMP			MODERATE RAMP			HIGH RAMP			ATHLETE'S RAMP		
	mph	% Grade	METs	mph	% Grade	METs	mph	% Grade	METs	mph	% Grade	METs	mph	% Grade	METs
1	1.0	0.0	1.8	1.0	0.0	1.8	1.5	1.5	2.5	2.1	3.0	3.5	1.8	0.0	2.4
2	1.1	0.2	1.9	1.1	0.5	1.9	1.6	2.0	2.7	2.2	4.0	3.9	2.1	0.5	2.7
3	1.2	0.4	2.0	1.2	1.0	2.1	1.7	2.5	2.9	2.3	4.5	4.2	2.4	1.0	3.2
4	1.3	0.6	2.1	1.3	1.5	2.3	1.8	3.0	3.1	2.4	5.5	4.6	2.7	1.5	3.6
5	1.4	0.8	2.2	1.4	2.0	2.5	1.9	3.5	3.4	2.5	6.0	5.0	3.3	2.0	4.1
6	1.5	1.0	2.3	1.5	2.5	2.7	2.0	4.0	3.6	2.6	7.0	5.5	3.3	2.5	4.6
7	1.6	1.2	2.5	1.6	3.0	2.9	2.1	4.5	3.9	2.7	7.5	5.8	3.6	3.0	5.2
8	1.7	1.4	2.6	1.7	3.5	3.1	2.2	5.0	4.2	2.8	8.5	6.4	3.9	3.5	6.1
9	1.8	1.6	2.8	1.8	4.0	3.4	2.3	5.5	4.5	2.9	9.0	6.8	4.2	4.0	7.3
10	1.9	1.8	2.9	1.9	4.5	3.6	2.4	6.0	4.8	3.0	10.0	7.4	4.5	4.5	8.4
11	2.0	2.0	3.1	2.0	5.0	3.9	2.5	6.5	5.1	3.1	10.5	7.8	4.8	5.0	9.5
12	2.1	2.2	3.2	2.1	5.5	4.2	2.6	7.0	5.5	3.2	11.5	8.5	5.1	5.5	10.6
13	2.2	2.4	3.4	2.2	6.0	4.5	2.7	7.5	5.8	3.3	12.0	8.9	5.4	6.0	11.5
14	2.3	2.6	3.6	2.3	6.5	4.8	2.8	8.0	6.2	3.4	13.0	9.7	5.7	6.5	12.2
15	2.4	2.8	3.8	2.4	7.0	5.1	2.9	8.5	6.6	3.5	13.5	10.1	6.0	7.0	13.0
16	2.5	3.0	3.9	2.5	7.5	5.5	3.0	9.0	7.0	3.6	14.5	10.9	6.3	7.5	13.8
17	2.6	3.2	4.1	2.6	8.0	5.8	3.1	9.5	7.4	3.7	15.0	11.4	6.6	8.0	14.7
18	2.7	3.4	4.3	2.7	8.5	6.2	3.2	10.0	7.8	3.8	16.0	12.2	6.9	8.5	15.5
19	2.8	3.6	4.5	2.8	9.0	6.6	3.3	10.5	8.3	3.9	16.5	12.6	7.2	9.0	16.4
20	2.9	3.8	4.7	2.9	9.5	7.0	3.4	11.0	8.7	4.0	17.5	13.3	7.5	9.5	17.3

*Stages are each 30 seconds in duration.

Exercise tests may be submaximal or maximal relative to the patient's effort. In addition to common indications for stopping the exercise test (**Table 13.4**), submaximal exercise testing has a predetermined endpoint, often defined as a peak heart rate (e.g., 120 beats/min or 70% of predicted maximum HR) or an arbitrary MET level (e.g., 5 METs). Submaximal tests are used in patients early after MI before discharge from the hospital because they can provide prognostic information to guide management. They can also be useful in the evaluation of a patient's ability to engage in daily activities after discharge and can serve as a baseline for cardiac rehabilitative exercise therapy (see later, Physical Activity and Exercise Prescription). Symptom-limited tests are designed to continue until the patient demonstrates signs and/or symptoms necessitating termination of exercise (**Table 13.4**). Whatever modality or protocol is used, standard patient monitoring and measurements are made during and early after exercise (**Table 13.5**).

TABLE 13.4

Indications for Terminating the Exercise Test

Absolute Indications
ST-segment elevation (>1.0 mm) in leads without Q waves caused by prior myocardial infarction (other than aVR, aVL, or V_1)
Drop in systolic blood pressure of >10 mm Hg, despite an increase in workload, when accompanied by any other evidence of ischemia
Moderate to severe angina
Central nervous system symptoms (e.g., ataxia, dizziness, or near-syncope)
Signs of poor perfusion (cyanosis or pallor)
Sustained ventricular tachycardia or other arrhythmia that interferes with normal maintenance of cardiac output during exercise
Technical difficulties monitoring the ECG or systolic blood pressure
Patient's request to stop
Relative Indications
Marked ST-segment displacement (horizontal or downsloping of >2 mm) in a patient with suspected ischemia
Drop in systolic blood pressure of >10 mm Hg (persistently below baseline) despite an increase in workload, in the absence of other evidence of ischemia
Increasing chest pain
Fatigue, shortness of breath, wheezing, leg cramps, or claudication
Arrhythmias other than sustained ventricular tachycardia, including multifocal ectopy, ventricular triplets, supraventricular tachycardia, atrioventricular heart block, or bradyarrhythmias
Exaggerated hypertensive response (systolic blood pressure >250 mm Hg and/or diastolic blood pressure >115 mm Hg)
Development of bundle branch block that cannot be distinguished from ventricular tachycardia

From Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation 2013;128:873.

TABLE 13.5

Patient Monitoring During Exercise Testing

During the Exercise Period
12-lead ECG during last minute of each stage, or at least every 3 minutes
Blood pressure during last minute of each stage, or at least every 3 minutes
Symptom rating scales as appropriate for the test indication and laboratory protocol
During the Recovery Period
Monitoring for a minimum of 6 minutes after exercise in sitting or supine position, or until near baseline heart rate, blood pressure, ECG, and symptom measures are reached. A period of active cool-down may be included in the recovery period, particularly following high levels of exercise, to minimize the postexercise hypotensive effects of venous pooling in the lower extremities.
12-lead ECG every minute
Heart rate and blood pressure immediately after exercise, then every 1 or 2 minutes until near-baseline measures are reached
Symptomatic ratings every minute as long as they persist after exercise. Patients should be observed until all symptoms have resolved or returned to baseline levels.

Treadmill.

Treadmill testing provides a more common form of physiologic stress (i.e., walking) in which patients are more likely to attain a higher oxygen uptake and peak heart rate than during stationary cycling. Cycling may be preferable when orthopedic or other specific patient characteristics limit treadmill testing or during exercise echocardiographic testing to facilitate acquisition of images at peak exercise. The most frequently used stepped treadmill protocols are the Naughton, Bruce, and modified Bruce[2] (**Table 13.6**).

TABLE 13.6

Bruce Protocol for Treadmill Testing

STAGE	TIME	SPEED (mph)	GRADE (%)	METs
Rest	00.00	0.0	0.0	1.0
1	03.00	1.7	10.0	4.6
2	03.00	2.5	12.0	7.0
3	03.00	3.4	14.0	10.1
4	03.00	4.2	16.0	12.9
5	03.00	5.0	18.0	15.1
6	03.00	5.5	20.0	16.9
7	03.00	6.8	22.0	19.2

The modified Bruce protocol employs 2 initial low level 3-minutes stages at a speed of 1.7 mph and grades 0 % and 5%, respectively, and then continues into the full Bruce protocol. *METs,* Metabolic equivalents.

From American College of Sports Medicine Guidelines for Exercise Testing and Prescription. 9th ed. Philadelphia: Lippincott, Williams & Wilkins; 2013.

During treadmill exercise, patients should be encouraged to walk freely and use the handrails for balance only when necessary. Excessive handrail gripping and support alter the BP response and decrease the oxygen requirement (METs) per given workload, thereby resulting in an overestimation of exercise capacity and an inaccurate HR- and BP-to-workload relationship. Exercise capacity (peak METs) can be reasonably estimated for treadmill exercise by using common equations provided by ACSM,[2] as long as the equipment is calibrated regularly. When precise determination of oxygen uptake is necessary, such as assessment of patients for heart transplantation (**see Chapter 28**), evaluation by expired gas analysis is preferred over estimation (see Cardiopulmonary Exercise Testing). Normal values for exercise capacity in healthy adults at different ages are available and may serve as a useful reference in the evaluation of a patient's exercise capacity.[6]

Stationary Cycle.

A cycle ergometer is smaller, quieter, and less expensive than a treadmill. Because a cycle ergometer requires less movement of the arms and thorax, quality electrocardiographic recordings and BP measurements are easier to obtain. However, stationary cycling may be unfamiliar to many patients, and its success as a testing tool is highly dependent on patient skill and motivation. Thus the test may end before the patient reaches a true cardiopulmonary endpoint. Unlike treadmill testing, in which the work being performed involves movement of the patient's body weight at a given pace, stationary cycle work involves cycling at a given pace against an external force and is generally independent of the patient's body weight, which is supported by the seat. As shown in **Table 13.7**, the MET level attained at a given work rate varies with the patient's body weight. Accordingly, at the same given cycle ergometer work rate, a lighter person will attain higher METs than will a heavier person. Mechanically braked ergometers require that the patient's cycling speed be kept constant. Electronically braked cycle ergometers automatically adjust external resistance to the cycling speed to maintain a constant work rate at a given stage. Electronically braked cycle ergometers allow simple programming of ramp protocols. As with treadmill ramp protocols, customized cycle ergometer ramp protocols that accommodate a wide range of fitness levels need to be established by individual exercise testing laboratories.

TABLE 13.7

Approximate MET Levels During Cycle Ergometer Testing

BODY WEIGHT		EXERCISE RATE (kpm • min^{-1} and watts)						
kg	lb	kpm • min^{-1} 300 Watts 50	450 75	600 100	750 125	900 150	1050 175	1200 200
50	110	5.1	6.9	8.6	10.3	12.0	13.7	15.4
60	132	4.3	5.7	7.1	8.6	10.0	11.4	12.9
70	154	3.7	4.9	6.1	7.3	8.6	9.8	11.0
80	176	3.2	4.3	5.4	6.4	7.5	8.6	9.6
90	198	2.9	3.8	4.8	5.7	6.7	7.6	8.6
100	220	2.6	3.4	4.3	5.1	6.0	6.9	7.7

MET, Metabolic equivalent; *kpm,* kilopond-meter.

From American College of Sports Medicine Guidelines for Exercise Testing and Prescription. 9th ed. Philadelphia: Lippincott, Williams & Wilkins; 2013.

Arm Cycle Ergometry.

Arm ergometry is an alternative method of exercise testing for patients who cannot perform leg exercise. Although this test has diagnostic usefulness, it has been largely replaced by nonexercise pharmacologic stress techniques.

Six-Minute Walk Test.

The 6-minute walk test can be used as a surrogate measure of exercise capacity when standard treadmill or cycle testing is not available. Distance walked is the primary outcome of the test. It is not useful in the objective determination of myocardial ischemia and is best used in a serial manner to evaluate changes in exercise capacity and the response to interventions that may affect exercise capacity over time. The 6-minute walk test protocol is discussed in detail elsewhere[7] (**Table 13.8**).

TABLE 13.8
Six Minute Walk Test Protocol

Testing Site
• The Six Minute Walk Test Protocol should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course must be 30 m in length. • A 30-m (100-ft) hallway is required, and its length should be marked every 3 m. • The turnaround points should be marked with a cone (e.g., orange traffic cone). • A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.
Measurements
• Assemble all necessary equipment (lap counter, timer, clipboard, worksheet) and move to the starting point. • Set the lap counter to zero and the timer to 6 minutes. Position the patient at the starting line. • You should also stand near the starting line during the test. • Do not walk with the patient. • As soon as the patient starts to walk, start the timer. • Do not talk to anyone during the walk. • Use an even tone of voice when voicing the standard phrases of encouragement. • Each time the patient returns to the starting line, click the lap counter once (or mark the lap on the worksheet). • At the end of 6 minutes, tell the patient to stop walking, and measure the total distance traveled (meters).
Patient Instructions
Standardized scripted patient instructions should be used, and are provided elsewhere.

Data from American Thoracic Society. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111.

Cardiopulmonary Exercise Testing (Exercise Testing with Gas Exchange Analysis).

Because of the inaccuracies associated with estimating oxygen uptake (V_{O_2}) and METs from work rate with the treadmill or cycle ergometer, many laboratories perform cardiopulmonary exercise testing (CPX), which uses ventilatory gas exchange analysis during exercise to provide a more reliable and reproducible measure of V_{O_2}. Peak V_{O_2} is the most accurate measure of exercise capacity and is a useful reflection of overall cardiopulmonary health. Measurement of expired gases is not necessary for all clinical exercise testing, but the additional information can provide important physiologic data that can be useful in both clinical and research applications. Measures of gas exchange primarily include V_{O_2}, carbon dioxide output (V_{CO_2}), and minute ventilation. Use of these variables in graphic form provides further information on the ventilatory threshold and ventilatory efficiency.[6,8]

CPX is well established as useful in the following situations[6,8,9]:

- Evaluation of exercise capacity in selected patients with heart failure, to assist in estimation of prognosis, evaluate the response to medications and other interventions, and assess the need for cardiac transplantation.
- Evaluation of exertional dyspnea. Such testing can provide useful information for differentiating cardiac from pulmonary limitations as a cause of exercise-induced dyspnea or impaired exercise capacity when the cause is uncertain.
- Evaluation of the patient's response to specific therapeutic interventions in which improvement in exercise tolerance is an important goal or endpoint.

Emerging evidence demonstrates that CPX can provide valuable clinical information in patients with hypertrophic cardiomyopathy (HCM), suspected or confirmed pulmonary hypertension, suspected myocardial ischemia, suspected mitochondrial myopathy, and confirmed chronic obstructive pulmonary disease or interstitial lung disease. More recently, utility of CPX has been demonstrated in the assessment of perioperative risk and valvular heart disease.[9]

The technical aspects of CPX have become simplified with contemporary systems, but meticulous maintenance and calibration of these systems are required for optimal use. The personnel involved in

administering and interpreting the test must be trained and proficient in this technique. The test also requires additional time, as well as patient cooperation.[6,9] CPX used in combination with Doppler echocardiography can provide complementary information regarding cardiac output, myocardial contractile function, and valvular function.[9]

Exercise Test Supervision

Over the past 30 years since the American Heart Association (AHA) published its first set of *Standards for Adult Exercise Testing Laboratories*, the role of the physician in ensuring that the exercise laboratory is properly equipped and appropriately staffed with qualified personnel who adhere to a written set of policies and procedures specific to that laboratory has not changed. In subsequent iterations of their respective guidelines, the AHA, ACSM, American College of Cardiology (ACC), and American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) have consistently addressed this issue. In 2000 the ACC/AHA/American College of Physicians/American College of Sports Medicine Competency Task Force focused its efforts on outlining the specific cognitive and training requirements for personnel involved in supervising and interpreting exercise ECGs and was the first to look beyond the specific professional type (e.g., physician, nurse, exercise physiologist) and focus on specific competencies of the individual staff member.[10] In 2014 these recommendations were updated to define further the roles of each staff member involved with exercise testing.[11] This statement clearly defined different levels of supervision as follows: (1) “personal supervision” requires a physician's presence in the room; (2) “direct supervision” requires a physician to be in the immediate vicinity, on the premises or the floor, and available for emergencies; and (3) “general supervision” requires the physician to be available by phone or by page. Common to every guideline is the recommendation that patients be screened before exercise testing to assess their risk for an exercise-related adverse event so that the most appropriate personnel to supervise the test can be provided. Exercise testing may be supervised by nonphysician staff members who are deemed competent according to the criteria outlined in the ACC/AHA statement.[11] In all such cases the physician should be immediately available to assist as needed (i.e., provide direct supervision). In high-risk patients the physician should personally supervise the test (i.e., provide personal supervision).

Risks of Exercise Testing

Exercise is associated with increased risk for an adverse cardiovascular event, and details regarding the safety of exercise testing and emergency preparedness in exercise laboratories are addressed in depth in guidelines from the AHA[1,3] and the ACSM.[2] Nonetheless, the safety of exercise testing is well documented, and the overall risk for adverse events is quite low. In several large series of individuals with and without known CVD, the rate of major complications (including MI and other events requiring hospitalization) was less than 1 to as high as 5 per 10,000 tests, and the rate of death was less than 0.5 per 10,000 tests. The incidence of adverse events depends on the study population.[6] Patients with recent MI, reduced LV systolic function, exertion-induced myocardial ischemia, and serious ventricular arrhythmias are at highest risk.[1] In more than 2000 participants with New York Heart Association (NYHA) Functional Class II to IV systolic heart failure who completed exercise testing in the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) study, there were no deaths, and the rate of nonfatal major cardiovascular events was lower than 0.5 per 1000 tests.[12] A recent report of 5060 CPX studies performed in patients with severe functional impairment and a variety of high-risk cardiac

diseases, including heart failure, HCM, pulmonary hypertension, and aortic stenosis, further supports the safety of exercise testing. The adverse event rate was 0.16%, and the most common adverse event was sustained ventricular tachycardia. No fatal events were reported.[13]

Maintenance of appropriate emergency equipment, establishment of an emergency plan, and regular practice in carrying out the plan are fundamental to ensuring safety in an exercise testing laboratory.[3]

Exercise Testing in Coronary Artery Disease

Exercise-Induced Symptoms

Any chest pain produced during the exercise test needs to be factored into the exercise test conclusion and report.

First, are the symptoms reported during the test the same or similar to the reported historical symptoms that prompted the exercise test? If the answer is yes, the provider can assess the objective test responses and discern whether they support the presence of CAD. If the answer is no, differences between the produced and historical symptoms need to be clarified. In addition, the symptoms produced need to be categorized according to whether they are consistent with angina. Distinguishing anginal from nonanginal chest pain is important at the time of occurrence of the chest pain. Angina is not well localized, pleuritic, or associated with palpable tenderness (**see Chapters 56 and 61**), and the only opportunity to define these qualities may be after the exercise test.

Second, exercise-induced angina is an important clinical predictor of the presence and severity of CAD, equal to or greater than ST-segment depression. Consideration of limiting versus nonlimiting chest pain, in addition to any induced angina, has been incorporated into the Duke treadmill score, as well as into other treadmill scores (see later). These factors will have an impact on the prognostic and diagnostic assessment of the test results and ultimately the next step in the clinical evaluation.

Third, exercise-induced angina predicts an adverse prognosis and is worthy of further evaluation regardless of the ST-segment response or the exercise capacity. In a series of 3270 patients without known coronary disease referred for exercise testing, Christman and colleagues[14] found that typical angina defined by physicians and exercise physiologists at the exercise test was a predictor of adverse events, including death, nonfatal MI, and revascularization. This was found irrespective of the absence of a positive ST-segment response or good exercise capacity.[15]

Lastly, if the patient stops exercise earlier than anticipated because of dyspnea, careful consideration should be given as to whether an anginal equivalent is present. If the presenting symptom was dyspnea with exertion, this becomes even more relevant.

Functional Capacity

Functional capacity is a strong predictor of mortality and nonfatal cardiovascular outcomes in both men and women with and without CAD.[16] Even though exercise capacity is most accurately measured by CPX, a reasonable estimate can be obtained from treadmill testing alone. The best methods for estimating predicted METs are the following simple regression equations[1]:

$$\text{Men: Predicted METs} = 18 - (0.15 \times \text{Age})$$

$$\text{Women: Predicted METs} = 14.7 - (0.13 \times \text{Age})$$

The reported exercise time can be translated into metabolic equivalents or METs based on the exercise test protocol. The reported METs can then be expressed as a percentage of the predicted METs. **Table 13.9** provides an alternative qualitative classification of functional capacity[1] that adjusts for age and sex.

TABLE 13.9

Estimated Functional Capacity Relative to Age and Sex

AGE (yr)	ESTIMATED FUNCTIONAL CAPACITY (METs)				
	Poor	Fair	Average	Good	High
Women					
≤29	<7.5	8-10	10-13	13-16	>16
30-39	<7	7-9	9-11	11-15	>15
40-49	<6	6-8	8-10	10-14	>14
50-59	<5	5-7	7-9	9-13	>13
≥60	<4.5	4.5-6	6-8	8-11.5	>11.5
Men					
≤29	<8	8-11	11-14	14-17	>17
30-39	<7.5	7.5-10	10-12.5	12.5-16	>16
40-49	<7	7-8.5	8.5-11.5	11.5-15	>15
50-59	<6	6-8	8-11	11-14	>14
≥60	<5.5	5.5-7	7-9.5	9.5-13	>13

1 metabolic equivalent (MET) = 3.5 mL/kg/min of oxygen consumption.

From Snader CE, Marwick TH, Pashkow FJ, et al. Importance of estimated functional capacity as a predictor of all-cause mortality among patients referred for exercise thallium single-photon emission computed tomography: report of 3,400 patients from a single center. J Am Coll Cardiol 1997;30:641.

In addition to clinical factors, functional capacity can be related to familiarity with the exercise equipment, level of training, and environmental conditions in the exercise laboratory. Patients who cannot perform an exercise test or who undergo a pharmacologic stress test have a worse prognosis than do those who can perform an exercise test.

Functional capacity should always be incorporated into the results, conclusions, and/or recommendations of the exercise test report. Functional capacity can be incorporated into available multivariable scores such as the Duke treadmill score or the method of Lauer (see later) to classify the prognosis as low, intermediate, or high risk (**Fig. 13.3**).

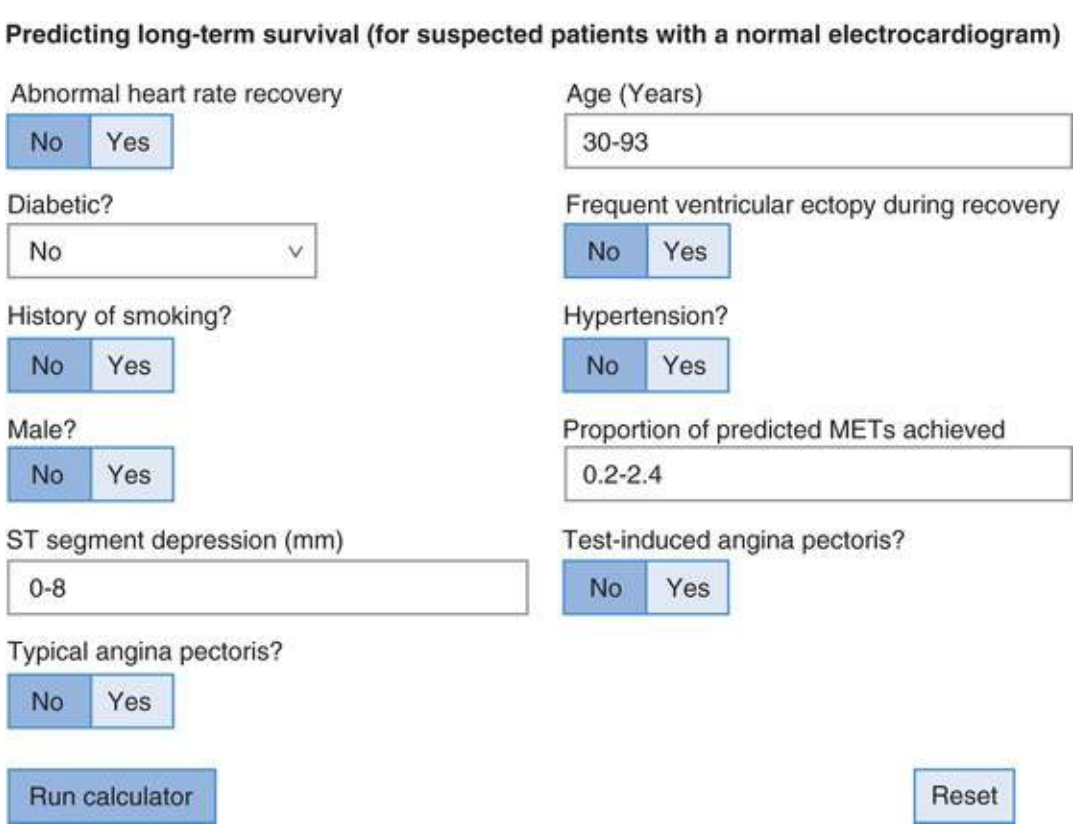

FIGURE 13.3 Cleveland Clinic Score. The Cleveland Clinic Score Calculator is available at https://apervita.com/community/clevelandclinic. Entering this URL will bring you to the site listing many scores developed at the Cleveland Clinic. Choose "Coronary Artery Disease." You will need to register one time at no cost. Once the score is open, you can create a shortcut to your desktop. The score will then always be open and ready for use. Definition of terms used in this calculator follow. *Typical angina*: chest discomfort that is substernal, is brought on by physical or mental exertion, and is relieved within minutes by rest or nitroglycerin. *Smoking*: regular smoking now or within the past year. *Hypertension:* resting systolic BP ≥140 mm Hg, resting diastolic BP ≥90 mm Hg, or use of medications for treatment of hypertension. *Proportion of predicted METs* (metabolic equivalents) *achieved*: in men, predicted METs = [14.7 − (0.11 × age)]; in women, [14.7 − (0.13 × age)]. *ST depression:* only count horizontal or downsloping ST depression that it at least 1 mm; otherwise record as 0. *Exercise-induced angina:* any angina is included, whether or not it is test terminating. *Abnormal heart rate recovery:* calculated as HR at the end of graded exercise minus HR 1 min later; for upright cool-down, consider abnormal if ≤12 beats/min; for supine cool-down, consider abnormal if ≤18 beats/min. *Frequent ventricular ectopy in recovery:* includes at least 7 premature ventricular beats/min, frequent ventricular couplets, any ventricular triplets, nonsustained or sustained ventricular tachycardia or torsade des pointes, or ventricular fibrillation occurring in the first 5 minutes of recovery.

Heart Rate Responses

Peak Heart Rate.

The maximum heart rate with exercise is a fundamental physiologic parameter that provides the provider relevant information concerning the intensity of exercise, the adequacy of the exercise test, the effect of medications that influence heart rate, the potential contribution to exercise intolerance, and the patient's prognosis.[17] The maximum achievable heart rate (HRmax) is unique for each patient but can be estimated by using regression equations that adjust for the patient's age. The most familiar equation, which was developed principally in middle-aged men, is:

$$\text{HRmax} = 220 - \text{Age}$$

Although easy to apply and calculate, there is considerable variability with this equation, especially in patients with CAD who are taking beta blockers. Newer equations[2,17] have been proposed to replace the "220 – age" rule to generate the maximum age-predicted heart rate (MPHR):

$$\text{Men: HRmax} = 208 - (0.7 \times \text{Age})$$

$$\text{Women: HRmax} = 206 - (0.88 \times \text{Age})$$

$$\text{CAD with beta blockers: HRmax} = 164 - (0.7 \times \text{Age})$$

Chronotropic Incompetence.

The inability of the heart to increase its rate to meet the demand placed on it is termed chronotropic incompetence. It is considered an independent predictor (including the well-established Duke treadmill score) of cardiac or all-cause mortality, as well as other adverse other adverse cardiovascular outcomes.[17]

A *submaximal* study is assigned when the peak HR achieved is below the MPHR. An *inadequate* study is defined by failure to achieve a predefined goal, such as 85% of MPHR. If a patient without known CAD has an inadequate study, the term *nondiagnostic* study is often applied. As usual, this "nondiagnostic" status is relative. In the presence of any other diagnostic endpoints, such as 2-mm or greater ST-segment depression, exercise-induced hypotension, or exercise-induced anginal chest pain, the heart rate adequacy question becomes irrelevant.

Chronotropic incompetence typically has been defined by the adjusted heart rate reserve, which incorporates both resting and peak HRs, as well as the age-adjusted HRmax. However, before "chronotropic incompetence" is applied, consideration should be given to the effort exerted in performing exercise, present medications, and the reason for termination of the exercise test. Effort applied to the exercise is often defined by the symptoms produced or by indices of perceived exertion (e.g., Borg scale).[1] These work well in most settings but can also be defined quantitatively by using CPX parameters such as the respiratory exchange ratio. For the usual non-CPX application, the following formula[17] defines the chronotropic index:

$$[(\text{HRmax} - \text{HRrest})/(220 - \text{Age} - \text{HRrest})] \times 100$$

Failure to achieve a chronotropic index higher than 80% defines the presence of chronotropic incompetence.[17] In patients taking nontrivial doses of beta blockers who are compliant with their medication, a value lower than 62% is considered chronotropic incompetence.[1] Criteria for assessing chronotropic incompetence in patients with atrial fibrillation (AF) have not been established.

Heart Rate Recovery.

The HR increases during exercise because of an increase in sympathetic tone and a decrease in

parasympathetic tone. At the cessation of exercise, under normal circumstances, the reverse process occurs. In athletes and normal persons, there is a biexponential response, with an initial steep 30-second fall in HR followed by a more shallow decline thereafter. This biexponential response disappears with the administration of atropine and becomes similar to the response in patients with heart failure. Abnormal *heart rate recovery* (HRR) has been defined by many methods, but the most commonly accepted include less than 12 beats/min after 1 minute with postexercise cool down, less than 18 beats/min after 1 minute with immediate cessation of movement into either the supine or sitting position, and less than 22 beats/min after 2 minutes. In healthy individuals, short-term reproducibility has been demonstrated.[17]

Abnormal HRR is associated with an increase in all-cause mortality in both asymptomatic individuals and patients with established heart disease. This association is independent of the chronotropic index, beta blockade, CAD severity, LV function, Duke treadmill score, and ST-segment depression. HRR adds to the prognostic ability of peak V_{O_2}. When considered in a multivariable format assessing prognosis, HRR has been found to be an independent predictor of adverse outcomes even when combined with nuclear variables.[18]

Most of the literature focuses on the early phase of HRR, but later HRR, expressed as a percentage of change in cycle length, may be independently predictive of adverse cardiovascular outcomes.[19] This aspect requires further investigation.

Blood Pressure Responses

Exercise BP responses, as with those for HR, reflect the balance between sympathetic and parasympathetic influences. Systolic blood pressure, pulse pressure (difference between systolic and diastolic BP), HR-BP product (also called the *double product*), and double-product reserve (change in double product from peak to rest) all increase steadily as workload increases. Diastolic BP increases only minimally or may fall. In most normal individuals, systolic BP will increase to higher than 140 mm Hg and the double product to higher than 20,000.

Hypertensive Systolic Pressure Response.

This response is usually defined as greater than 210 mm Hg in men and greater than 190 mm Hg in women. Even though these exercise responses are considered abnormal, they are not generally reasons to terminate exercise. Such responses may be indicative of the future development of hypertension or adverse cardiac events.[20]

Exercise-Induced Systolic Hypotension.

This has been variably defined but most frequently as systolic pressure during exercise falling below resting systolic pressure.[1] Another definition is a 20 mm Hg fall after an initial rise. Either of these definitions would be an absolute reason to terminate the exercise test. The former definition is more predictive of a poor prognosis and is usually related to severe multivessel CAD with LV dysfunction, especially when noted with other signs of ischemia, such as ST depression or angina at a low workload. Its positive predictive value is higher in men than in women. Its presence usually warrants consideration of prompt invasive evaluation. Exercise-associated hypotension may also be seen in patients with cardiomyopathy, LV outflow tract obstruction, enhanced vagal tone, hypovolemia, antihypertensive medications, and arrhythmias. In addition, one study of 57,442 patients suggests that exercise-induced hypotension may be a predictor of future AF.[21]

One systolic BP response that needs to be appreciated might be called “pseudo–exercise-induced hypotension.” This response occurs in patients who are anxious about the exercise study and begin exercise with a somewhat elevated systolic pressure. As exercise proceeds in the first stage, this

elevated BP usually settles down or “falls” toward its customary resting level. As exercise continues, continued observation reveals a gradual upward trend in BP. Considerable judgment needs to be used when interpreting this response.

Low Maximum Systolic Pressure Peak.
This is defined as a rise to less than 140 mm Hg or a lower than 10 mm Hg rise overall. After excluding poor exercise effort, this response is often associated with severe CAD and worse cardiovascular outcomes in persons with and without known CAD and warrants further evaluation.[2]

ST-Segment Changes

For decades, the change in ST segments was the principal factor considered in the analysis of exercise ECG results (**Fig. 13.4**). However, the diagnostic value of ST-segment depression has been recognized to be mediocre by current noninvasive test standards, with a sensitivity and specificity of 60% to 70% and 70% to 80%, respectively, based on coronary angiography. When adjusted for referral or workup bias, its sensitivity is lower (45% to 50%) and specificity higher (85% to 90%).[1] Accordingly, the prognostic value of ST-segment changes has been appropriately placed behind the prognostic value of non–ST-segment variables, such as functional capacity and heart rate responses. Despite these issues, it is still appropriate to consider ST-segment changes, but only in the context of other clinical and non–ST-segment data.

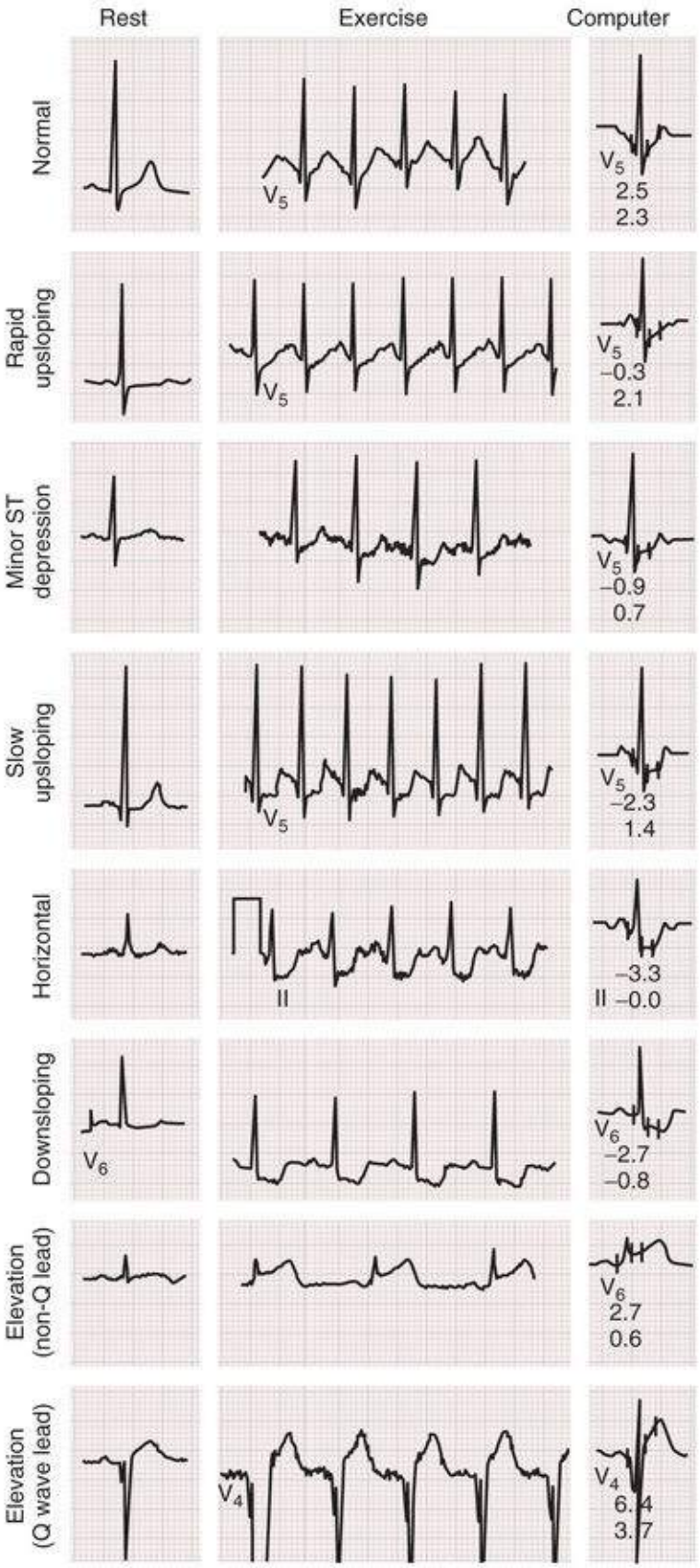

FIGURE 13.4 Eight typical exercise electrocardiographic patterns at rest and at peak exertion. The computer-processed incrementally averaged beat corresponds with the raw data taken at the same time point during exercise and is illustrated in the last column. The patterns represent worsening ECG responses during exercise. In the column of computer-averaged beats, ST80 displacement (*top* number) indicates the magnitude of ST-segment displacement 80 milliseconds after the J point relative to the PQ junction or E point. ST-segment slope measurement (*bottom* number) indicates the ST-segment slope at a fixed time point after the J point to the ST80 measurement. At least three non–computer-averaged complexes with a stable baseline should meet criteria for abnormality before the exercise ECG result can be considered abnormal. The *normal* and *rapid upsloping ST-segment* responses are normal responses to exercise. J point depression with rapid upsloping ST segments is a common response in an older, apparently healthy person. *Minor ST-segment depression* can occur occasionally at submaximal

workloads in patients with CAD; in this figure, the ST segment is depressed 0.09 mV (0.9 mm) 80 milliseconds after the J point. The *slow upsloping ST-segment pattern* may suggest an ischemic response in patients with known CAD or those with a high pretest clinical risk of CAD. Criteria for slow upsloping ST-segment depression include J point and ST80 depression of 0.15 mV or more and ST-segment slope of more than 1.0 mV/sec. This pattern may also precede horizontal or downsloping ST-segment depression that will occur in recovery. *Classic criteria for myocardial ischemia* include horizontal ST-segment depression observed when both the J point and ST80 depression are 0.1 mV or more and the ST-segment slope is within the range of 1.0 mV/sec. Downsloping ST-segment depression occurs when the J point and ST80 depression are 0.1 mV and the ST-segment slope is −1.0 mV/sec. *ST-segment elevation in a non–Q wave noninfarct lead* occurs when the J point and ST60 are 1.0 mV or higher and represents a severe ischemic response. *ST-segment elevation in an infarct territory (Q wave lead)* indicates a severe wall motion abnormality and, in most cases, is not considered an ischemic response. (From Chaitman BR. Exercise electrocardiographic stress testing. In Beller GA, editor. Chronic Ischemic Heart Disease. In Braunwald E, series editor. Atlas of Heart Diseases. Vol 5. Philadelphia: Current Medicine; 1995, pp 2.1-30.)

ST Depression

When considering ST-segment depression, it is important to use standards that allow application of uniform criteria. The usual criterion applied to raw data is 1 mm or greater or 0.1 mV or greater of horizontal or downsloping (i.e., <0.5 mV/sec) ST-segment depression in three consecutive beats. This assumes that the PQ point (not the TP segment) is used as the isoelectric reference and that the point of ST-segment measurement is 60 to 80 milliseconds after the J point. The 60-millisecond post–J point criterion is used at HR higher than 130 beats/min. This criterion should be added to and not included with existing resting ST-segment depression. ST-segment changes in the presence of early repolarization should be measured from the isoelectric line and not the baseline ST elevation. Unlike ST-segment elevation, exercise-induced ST-segment depression does not localize ischemia to a precise region or vascular bed. The lateral precordial leads are the best for defining positive responses. However, the inferior leads can be helpful in assessing the extent of ischemia when the lateral leads are abnormal as well. Isolated inferior ST depression is frequently falsely abnormal because of the influence of atrial repolarization in these leads.

Although raw data should always be examined, the use of signal-averaged data can be useful, especially when moderate baseline wandering or motion artifact is present. Particular care must be taken to avoid signal averaging that incorporates gross distortions as a result of motion and transient ventricular aberrations such as premature ventricular contractions and intraventricular conduction defects.

Postexercise recovery responses are also important to assess. First, positive responses are occasionally limited to the recovery period, and these have equal significance to changes that occur at peak exercise. Second, positive changes during exercise that resolve within 1 minute of recovery are associated with a favorable prognosis and low downstream diagnostic test yield.[14] In addition, compared to ST changes longer than 1 minute, early-recovery ST changes are associated with significantly smaller summed stress scores on myocardial perfusion imaging and a lower prevalence of CAD.[22]

Upsloping ST Depression

Rapidly upsloping ST depression that resolves quickly is rarely a true-positive response. However, ST-segment depression that is slowly upsloping (0.5 to 1.0 mV/sec) may be considered abnormal, especially if it occurs at low workloads. Its presence during exercise may presage horizontal or downsloping depression in recovery. HR adjustment can be applied to upsloping ST segments (see later).

Lead aVR ST Elevation

Emerging literature suggests that 1-mm or greater ST-segment elevation in lead aVR may be a significant predictor of left main coronary artery disease, proximal left anterior descending (LAD) artery disease, or at least multivessel CAD.[23] As an isolated marker, it appears to be sensitive and has moderate specificity and a high negative predictive value. What is yet unclear is where it fits into the multivariate approach for assessing prognosis.

ST Adjustments

Heart rate adjustments of ST segments have been proposed as an alternative way to analyze ST-segment depression.[1] However, comparative studies have not shown an increase in accuracy. Nevertheless, HR adjustments can be helpful for borderline cases in which ST depression is upsloping or barely abnormal, or traditional criteria and other clinical or exercise data suggest a false-positive result (e.g., low pretest probability or very high HR or workload achieved during exercise). HR adjustment can be accomplished by two methods (complicated and simple). The complicated method, known as *ST/heart rate slope*, is automated and available on most stress testing machines as an option to be toggled on or off. It plots ST depression as a function of HR at numerous points during exercise and generates the terminal ST/HR slope for each lead. The criterion for abnormality is 2.4 µV/beat/min. Depending on the protocol used and the duration of exercise, the ST/HR slope will not always be calculated because of insufficient data points. The developers of the method proposed a modification of the standard Bruce protocol to increase the points available for analysis. The slightly less intensive Cornell protocol uses 2-minute rather than 3-minute stages and is useful in patients who are not anticipated to exercise beyond stage 2 of the Bruce protocol. The simple method, known as *ST/heart rate index*, can easily be calculated by dividing the maximum ST-segment depression in microvolts by the difference in resting and peak HR. The criterion for abnormality is 1.6 µV/beat/min.

ST Elevation

The usual criterion applied to raw data is 1 mm or greater or 0.1 mV of ST-segment elevation above the PQ point at 60 milliseconds after the J point in three consecutive beats. The J point may or may not be elevated as well. Without pathologic Q waves, exercise-induced ST elevation usually indicates either significant proximal coronary stenosis or epicardial coronary spasm. In either case the ST-segment elevation precisely localizes the transmural ischemia to a particular vascular region (e.g., anterior = LAD, and thus coronary angiography is an appropriate next step). In contrast, when pathologic Q waves are present, ST-segment elevation is usually indicative of an LV aneurysm or significant wall motion change. Ischemia may be involved in this process, and myocardial perfusion imaging is generally required to determine this.

Quantitative QRS Changes

R Wave Amplitude.

Precordial R waves normally increase during exercise. They peak before achieving maximal exercise and decrease as maximal exercise is achieved. If exercise is limited to a submaximal level by any cause, the R waves will appear to increase in height at peak exercise. This increase in R wave height has not been found to have predictive power.[1]

QRS Duration.

During exercise there is a normal shortening of the QRS complex, as well as the PR and QT intervals. Exercise-induced bundle branch block (BBB) is rare and occurs at a frequency of 0.5% or less. Exercise-induced left BBB (EI-LBBB) has been reported.[1] When EI-LBBB occurs at HRs higher than 125 beats/min, significant CAD is unlikely. The incidence of CAD does increase when it occurs at progressively lower HRs. One study suggested an increased association of EI-LBBB with death and major cardiac events. The ST-segment changes before onset of the LBBB are still interpretable, but they become uninterpretable once the LBBB begins. Onset and offset of the LBBB usually occur at different heart rates.

In contrast, exercise-induced right BBB (EI-RBBB) from one recent large Veterans Affairs series correlated with age and was not associated with added incremental risk.[24] Limited data are available in women. EI-RBBB does not invalidate interpretation of the ST segment for the inferior (II, III, aVf) and lateral leads (V_5, V_6). However, ST-segment changes limited to V_1 to V_4 are nondiagnostic.

Exercise-Induced Rhythm Changes

Ventricular ectopic activity is noted in up to 20% of patients during exercise testing. It varies from isolated premature ventricular beats (PVBs) to nonsustained ventricular tachycardia. However, frequent ventricular ectopy occurs during exercise or recovery in only 2% to 3% of patients. Suppression of resting ventricular ectopic activity during exercise is a nonspecific finding that can occur with or without CAD.

In clinical populations referred for testing because of symptoms, ventricular ectopic activity during exercise was predictive of mortality in most studies. In addition, ventricular ectopic beats occurring during exercise or recovery increase the likelihood of future cardiac death.[1] For asymptomatic populations, one study of 2099 participants followed for 13 years found no correlation between nonsustained ventricular arrhythmias and mortality.[25]

Exercise-induced supraventricular arrhythmias are not predictive of ischemia or any cardiovascular endpoint. However, they may be a marker for the later occurrence of AF or supraventricular tachycardia.

Miscellaneous Electrocardiographic Changes

The following factors have been reported to improve the accuracy of the exercise ECG[1] but have not been studied in large, unselected populations.

Duration of the P Wave.

The duration of the P wave in lead V_5 has been reported to increase sensitivity. A duration of 20 milliseconds or less is considered normal, whereas 30 milliseconds or longer is considered abnormal. From a practical standpoint, it is more realistic to expect that these changes would be easier to appreciate with signal-averaged complexes.

ST Changes in Premature Ventricular Beats.

Comparing the ST segments of PVBs before and during exercise has been reported to increase sensitivity.

T Wave Amplitude Increase.

An increase in T wave height by more than 2.5 mV in leads V_2 to V_4 in patients with exercise-induced chest pain has been noted as a highly specific finding of ischemia.

Pharmacologic Influences on Interpretation

Digitalis Glycosides

That digitalis can have an adverse effect on ST-segment interpretation is generally common knowledge. The principal issue has been false-positive results and reduced specificity. The absence of ST-segment change at rest does not eliminate the effect occurring during exercise. Sensitivity is not affected by digitalis. Therefore a negative ST-segment response with digitalis is still reliable.

However, this issue arises much less frequently in the current era. Although still used, digitalis has become a secondary drug for both HR control for patients in AF and treatment of symptomatic heart failure. Its use for the treatment of other supraventricular arrhythmias is virtually nonexistent. For many if not most patients taking digitalis, stress imaging with or without pharmacologic stress is appropriate for reasons other than the presence of digitalis. For the relatively few patients who are taking digitalis and qualify for a simple exercise ECG, individualized decision-making can obviate the need for a general policy statement, beyond repeating the exercise ECG with imaging if the ST-segment response is abnormal while taking digitalis.

Beta Adrenoreceptor Blockers

Beta blockers clearly reduce the rate-pressure product in most patients receiving proper doses. Evidence indicates that the diagnostic sensitivity and negative predictive value of exercise testing are adversely affected.

For those without established CAD who are undergoing a diagnostic-level exercise ECG, beta blockers should ideally be withheld to allow an adequate HR response. For those undergoing supplemental stress imaging, the issue is less critical given the availability of conversion to pharmacologic stress if the patient fails to achieve the desired HR response.

For those with established CAD, the situation is less clear. For most patients with CAD, beta blockers are part of their standard medical therapy and have significant effects on both quality and quantity of life (i.e., their prognosis). Many laboratories routinely have patients discontinue beta blockers before stress testing of all sorts without apparent harm. The principal justification for this seems to be to enhance diagnostic sensitivity (e.g., with myocardial perfusion imaging, to allow a larger defect size). Conversely, many laboratories do not discontinue these medications. Discontinuing beta blockers in patients with CAD creates a clinical state that is unlike their usual day-to-day existence. We are unaware of any reported studies in patients with established CAD indicating that beta blockers adversely affected the ability of exercise testing (with or without imaging) to detect prognostically important myocardial ischemia such that it would have significantly altered their clinical management. Therefore, discontinuation of beta blockers before exercise testing may be left to the discretion of the referring provider.

Diagnostic Value

Sensitivity and Specificity

Table 13.10 outlines the diagnostic characteristics of stress testing. Sensitivity and specificity define how effectively a test discriminates individuals with disease from those without disease. *Sensitivity* is the percentage of individuals with a disease who have abnormal test results and, in the case of CAD, is influenced by disease severity, effort level, and the use of anti-ischemic drugs. *Specificity* is the percentage of those without disease who have normal test results, and it may be affected by resting ECG patterns (e.g., LV hypertrophy, ST-T abnormalities, interventricular conduction delay) and drugs such as digoxin. All tests have a range of inversely related sensitivities and specificities such that when

sensitivity is the highest, specificity is lowest, and vice versa. These can be selected by specifying a *discriminant* or diagnostic cut point.[26] The standard exercise test cut point of 0.1 mV (1 mm) of horizontal or downsloping ST-segment depression in three consecutive beats of at least a single lead has been selected as the discriminating cut point and has a sensitivity of 68% and specificity of 77%.[27]

TABLE 13.10

Diagnostic Characteristics of the Exercise ECG Test

TERM	DEFINITION
True positive (TP)	Abnormal test result in individual with disease
False positive (FP)	Abnormal test result in individual without disease
True negative (TN)	Normal test result in individual without disease
False negative (FN)	Normal test result in individual with disease
Sensitivity	Percentage of patients with CAD who have an abnormal result = TP/(TP + FN)
Specificity	Percentage of patients without CAD who have a normal result = TN/(TN + FP)
Predictive value of a positive test	Percentage of patients with an abnormal result who have CAD = TP/(TP + FP)
Predictive value of a negative test	Percentage of patients with a normal result who do not have CAD = TN/(TN + FN)
Test accuracy	Percentage of true test results = (TP + TN)/total number tests performed

CAD, Coronary artery disease; *ECG,* electrocardiogram.

Modified from Chaitman BR. Exercise stress testing. In Bonow RO, Mann DL, Zipes DP, Libby P, editors. Braunwald's Heart Disease. 9th ed. Saunders: Philadelphia; 2012.

Once a discriminant value that determines a test's specificity and sensitivity is chosen, the population tested must be considered. If the population is skewed toward individuals with a greater severity of disease, the test will have higher sensitivity. Thus the exercise test has higher sensitivity in individuals with triple-vessel disease than in those with single-vessel disease.[1] The sensitivity and specificity of stress testing are limited by the use of angiographic CAD as the diagnostic "gold standard," so most data are derived from studies in which patients underwent both exercise testing and cardiac catheterization. The data are therefore subject to workup bias, which inflates the estimated sensitivity and deflates the specificity, because patients selected for coronary arteriography are more likely to have obstructive CAD,[1] and in some studies, patients with a positive test result were more likely to be referred for angiography.

The *diagnostic accuracy* of a test is the percentage of true test results (total true positives plus total true negatives) among all tests performed. Diagnostic accuracy is additionally influenced by the criteria used to determine whether an adequate level of stress has been achieved. This is currently defined as having attained 85% of the maximum age-predicted heart rate, with HRmax estimated as "220 − age" (see earlier, Heart Rate Responses). Despite many limitations in using this equation for diagnostic purposes, it remains a standard criterion for test adequacy but should not be used as a reason to terminate the test.

Positive and Negative Predictive Values

Predictive values further define the diagnostic value of a test (**Table 13.10**). The predictive value of a test is heavily influenced by the prevalence of disease in the group being tested. Bayes' theorem states that the probability of a person having the disease after the test is performed is the product of the probability of the disease before testing and the probability that the test provided a true result. Thus a test has a higher positive predictive value (PPV) and lower negative predictive value (NPV) when used in a population with a high prevalence; conversely, a higher NPV and lower PPV occur in a population with a lower prevalence. For example, an exercise ECG that demonstrates ST depression in an elderly person with typical anginal symptoms is most likely a true-positive result, whereas that in a young asymptomatic person without cardiac risk factors is most likely a false-positive result.

Pretest and Post-Test Probability of Disease

Table 13.11 demonstrates the pretest probability of obstructive CAD based on age, sex, and symptoms. However, these can be refined further with knowledge of the presence and extent of traditional atherosclerotic risk factors (e.g., hypertension, hyperlipidemia, smoking, diabetes).[28,29] Using exercise ST-segment criteria, the post-test likelihood of obstructive CAD can be estimated for a given individual if an ischemic response was demonstrated at any HR or if the patient attained HR of 85% or greater of the predicted maximum without an ischemic response.

TABLE 13.11

ACC/AHA Practice Guidelines on Exercise Testing: Pretest Probability of Coronary Artery Disease by Age, Sex, and Symptoms

AGE (yr)	TYPICAL/DEFINITE ANGINA PECTORIS	ATYPICAL/PROBABLE ANGINA PECTORIS	NONANGINAL CHEST PAIN	ASYMPTOMATIC
30-39	Intermediate	Very low	Very low	Very low
40-49	Intermediate	Low	Very low	Very low
50-59	Intermediate	Intermediate	Low	Very low
60-69	High	Intermediate	Intermediate	Low
≥70	High	Intermediate	Intermediate	Low

Modified from Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation 2002;106:1883-92.

Assessment of Anatomic and Functional Extent of Disease

As discussed earlier, several factors influence the significance of a given coronary artery luminal stenosis, and these factors may affect the presence and extent of myocardial ischemia relative to exercise-induced increases in myocardial oxygen demand. Furthermore, exercise-induced ST-segment depression does not provide a reliable assessment of the extent of disease or the specific coronary vessel or vessels involved. ST-segment elevation in leads without Q waves, although an uncommon response, generally reflects transmural ischemia that can be localized by the leads involved: leads V_2 to V_4 reflect LAD disease; lateral leads reflect left circumflex and diagonal vessel disease; and leads II, III, and AVF reflect right coronary artery disease (in a right-dominant circulation).[27] Other factors related to the probability and severity of CAD include the degree, time of appearance, duration, and number of leads with ST-segment depression or elevation. It is important to realize, however, that prognostically important CAD may be present in the absence of obstructive lesions. Therefore the use of diagnostic ST-segment analysis alone during exercise testing is inadequate and should be done with consideration of several non–ST-segment variables, as discussed later (see Prognostic Value).

Testing in Women

Identification of ischemic heart disease in women can be a diagnostic challenge because of several factors, including the lower prevalence of obstructive CAD in women younger than 65, more atypical manifestations of ischemic symptoms, and more frequent resting ST changes. In women with a low pretest likelihood of CAD, exercise electrocardiographic testing results in a minimal change in assessment from pretest levels. Premenopausal women with one or fewer risk factors for CAD and with nonanginal or atypical symptoms will have a high rate of false-positive tests. Thus the exercise ECG in such women is

of little value, except perhaps in selected cases to reassure women with atypical symptoms regarding their low likelihood of obstructive CAD when they have no exercise-induced ischemic ST changes and a low-risk Duke treadmill score.

The reported sensitivity and specificity of exercise electrocardiographic testing in symptomatic women vary greatly depending on the study characteristics and range from 31% to 71% and 66% to 86%, respectively.[30] However, exercise testing has similar diagnostic characteristics in women with an intermediate probability of CAD as it does for men. Thus, exercise testing has the greatest incremental value in intermediate-risk women, particularly when coupled with the Duke treadmill score. In a series of 976 symptomatic women referred for exercise testing and coronary angiography, a low-, intermediate-, and high-risk score was associated with obstructive CAD (>75% luminal narrowing) in 19%, 35%, and 89% of women, respectively. Moreover, 2-year cardiac mortality rates in this same cohort of women with low-, moderate-, and high-risk Duke treadmill scores were 1%, 2%, and 4%, respectively. Non–ST-segment variables, including peak exercise capacity (METs), chronotropic response, HRR, and BP response, have prognostic value in women[30,31] (**Table 13.12**) and are most useful when incorporated into the prognostic scores discussed next. The usefulness of exercise stress testing in the assessment of ischemic heart disease in women has been reviewed and updated in detail by the AHA[31] (**Fig. 13.5**). The exercise ECG remains the recommended test of first choice for the assessment of symptomatic, intermediate-risk women who can exercise and have normal findings on a resting ECG. A negative and diagnostically adequate test, particularly when associated with low risk scores, makes the likelihood of obstructive CAD very low. A positive or inconclusive test generally requires further evaluation with either a stress imaging test or coronary angiography.

TABLE 13.12

ECG and Non-ECG Variables Associated with Elevated Ischemic Heart Disease Risk from Exercise Testing in Women

STRESS TESTING VARIABLES	METHOD OF ASSESSMENT	HIGH-RISK VALUE
Exercise capacity	Estimated by ETT protocol (speed and grade)	<5 METs <100% Age-predicted METs = 14.7 − (0.13 × age)
HR recovery	Difference between peak HR at 1 min of recovery	≤12 beats/min after 1 min of recovery (upright cool-down period)
ST-segment changes	Difference in ST-segment changes (at 60 msec after the J point) between peak exercise (or recovery) and rest ECG	ST-segment depression ≥2 mm ST-segment depression ≥1 mm at <5 METs or >5 min into recovery ST-segment elevation ≥2 mm (not in q wave lead or aVR)
Duke treadmill score (DTS)	DTS = Exercise time − (5 × ST change) − (4 × angina index)	High-risk DTS: −11 or less
BP response	Assessment of BP response to exercise, change in SBP from rest to peak exercise	Decrease in SBP >10 mm Hg from rest
Ventricular arrhythmias		Persistent ventricular tachycardia/fibrillation

BP, Blood pressure; *ETT,* exercise treadmill testing; *HR,* heart rate; *METs,* metabolic equivalents; *SPB,* systolic blood pressure.

From Mieres JH, Gulati M, Bairey Merz N, et. al. Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association. Circulation 2014;130:350-79.

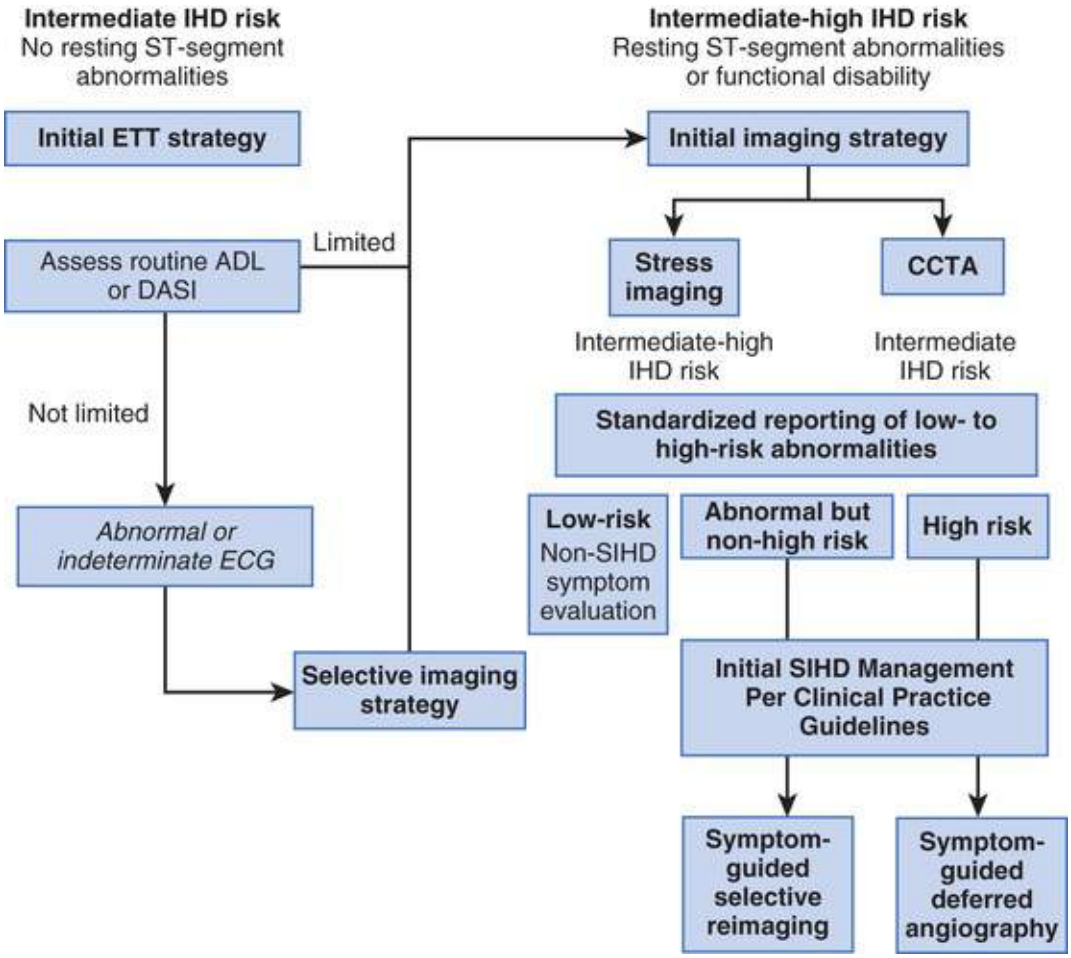

FIGURE 13.5 Index IHD risk estimate: diagnostic algorithm for women presenting with suspected ischemic heart disease (*IHD*). *ADL,* Activities of daily living; *CCTA,* coronary computed tomographic angiography; *DASI,* Duke Activity Status Index; *ETT,* exercise treadmill testing; *SIHD,* stable ischemic heart disease. (From Mieres JH, Gulati M, Bairey Merz N, et al. Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association. Circulation 2014;130:350-79.)

Prognostic Value

Predictive Variables

The strongest predictor of prognosis derived from the exercise test is functional capacity. The weakest predictor is ST-segment depression. All other variables, such as the heart rate achieved, HRR, BP response, ventricular arrhythmias, and exercise-induced angina, fall between these two extremes. This prognostic hierarchy is similar in both men and women.

Multivariable Scores

Multivariable scores are the best way to distill the relative prognostic values of many variables into a single indicator of risk that can be expressed as both continuous (e.g., 0 to 100) and ordinal variables (e.g., low, intermediate, and high). To date, three scores have been developed and validated and are worthy of consideration in analyzing exercise tests.[1]

Duke Treadmill Prognostic Score.

This score has been available since the early 1990s and is the most widely recognized, used, and

validated score. It was cited in the 1997 and subsequent updates of the ACC/AHA exercise test guidelines. It incorporates three treadmill variables: exercise time (Bruce protocol), millimeters of any ST-segment deviation (except aVR), and angina score index (1 = nonlimiting angina and 2 = exercise-limiting angina). It is simple enough to present as the following equation:

$$\text{Score} = \text{Exercise time} - (5 \times \text{ST deviation}) - (4 \times \text{Angina index})$$

ST deviation is the largest net ST-segment displacement in any lead. It is equally valid in men and women, and its prognostic value is independent of clinical, coronary anatomic, and LV function data. The principal criticism of the Duke score is the absence of consideration of clinical variables, especially age, or other exercise test variables such as HR.

Separate Scores for Men and Women.

These scores were developed and validated in the early 2000s. Separate scores for men and women incorporate three standard exercise test variables (ST-segment depression, peak HR, exercise angina score) and several other clinical variables (**Fig. 13.6**). These scores are not as simple as the Duke treadmill score but lend themselves to easy clinical application.

VARIABLE	CHOOSE RESPONSE	SUM	Exercise test score
Maximal heart rate	Less than 100 bpm = 30		MEN
	100 to 129 bpm = 24		Choose one per group
	130 to 159 bpm = 18		
	160 to 189 bpm = 12		
	190 to 220 bpm = 6		<40 = low probability
Exercise ST depression	1 to 2 mm = 15		
	Greater than 2 mm = 25		40-60 = intermediate probability
Age	Greater than 55 yr = 20		
	40 to 55 yr = 12		>60 = high probability
Angina history	Definite/typical = 5		
	Probable/atypical = 3		
	Noncardiac pain = 1		
Hypercholesterolemia?	Yes = 5		
Diabetes?	Yes = 5		
Exercise test: induced angina	Occurred = 3		
	Reason for stopping = 5		
	Total score:		

A

VARIABLE	CHOOSE RESPONSE	SUM	Exercise test score
Maximal heart rate	Less than 100 bpm = 20		WOMEN
	100 to 129 bpm = 16		Choose one per group
	130 to 159 bpm = 12		
	160 to 189 bpm = 8		
	190 to 220 bpm = 4		<40 = low probability
Exercise ST depression	1 to 2 mm = 6		
	Greater than 2 mm = 10		40-60 = intermediate probability
Age	Greater than 65 yr = 25		
	50 to 65 yr = 15		>60 = high probability
Angina history	Definite/typical = 10		
	Probable/atypical = 6		
	Noncardiac pain = 2		
Smoking?	Yes = 10		
Diabetes?	Yes = 10		
Exercise test: induced angina	Occurred = 9		
	Reason for stopping = 15		
Estrogen status	Positive = –5, Negative = 5		
	Total score:		

B

FIGURE 13.6 Exercise test scores for men **(A)** and women **(B)**; *bpm,* beats per minute. To determine risk group, total points for the appropriate choice for each clinical and exercise test variable. If there is no appropriate choice for a particular variable, score points as zero for that variable. *Exercise ST depression* is only horizontal or downsloping. *Diabetes* is insulin or noninsulin requiring. *Smoking* is any current or prior cigarette smoking. *Estrogen status* positive includes women who are premenopausal, receiving hormone replacement therapy, or with intact ovaries under age 50. Otherwise, women are estrogen status negative. (From Morise AP, Jalisi F. Evaluation of pretest and exercise test scores to assess all-cause mortality in unselected patients presenting for exercise testing with symptoms of suspected coronary artery disease. J Am Coll Cardiol 2003;42:842-50.)

Cleveland Clinic Prognostic Score.

This score was initially reported in 2007. It incorporates most of the important prognostic exercise test variables, as well as other important clinical variables. The originally published nomogram is more

difficult to apply in routine clinical settings, but it is available in a more user-friendly, free, online software application (**see Fig. 13.3**).

Newer Scores and Observations.

Several published scores and methods for patients with and without CAD emphasize non–ST-segment variables. None of these has been validated outside the derivation institution or compared to other scores (e.g., Duke treadmill) but nevertheless demonstrate the prognostic power of the non–ST-segment variables in a variety of populations.

The FIT treadmill score was derived using more than 58,000 adults without established heart disease (about half women) to assess for all-cause mortality.[16] Patients were followed 10 years on average. The maximum predicted HR and functional capacity were the best exercise predictors. The score equation is:

$$\text{Maximum heart rate (\%)} + 12\,(\text{METs}) - 4\,(\text{Age}) + 43\,(\text{if female})$$

Score ranges of greater than 100, 0 to 100, −1 to −100, and less than −100 yielded mean survival at 10 years of 98%, 97%, 89%, and 62%, respectively.

Investigators in Finland proposed the SCOREexe, which included functional capacity and HR responses to exercise and recovery.[32] In a population of 1531 patients with stable CAD taking beta blockers, these three variables had significant independent prognostic value over other clinical data on cardiovascular death and heart failure admissions. This score is not yet easily applied in the clinical setting.

Park and colleagues[33] followed 898 adults without cardiac disease prospectively for up to 27 years after undergoing treadmill exercise testing. Main outcome measures were silent and overt MI. They found that ST-segment change, inability to achieve target HR, abnormal HRR, and chronotropic incompetence were independent predictors of the outcomes. An integrated scoring model using these four parameters demonstrated a stepwise increase in risk as the number of abnormal parameters increased.

Arbit and associates[18] analyzed 11,218 patients with and without CAD not receiving beta blockers and demonstrated that reduced functional capacity (<7 METs), HRR less than 22 beats after 2 minutes, and chronotropic index less than 80 added significant incremental prognostic value to myocardial perfusion imaging for cardiac death and all-cause mortality. As the number of these three abnormal treadmill variables increased, the risk of mortality increased regardless of the scan interpretation. A patient with a normal scan but two or three variables that were abnormal had the same all-cause mortality risk as a patient with a severely abnormal scan but two or three variables that were normal. This study provides a simple method to incorporate non–ST-segment variables into the interpretation of both stand-alone exercise ECGs and myocardial perfusion studies.

Post–Myocardial Infarction Evaluation

Since 2002, when the last full set of exercise testing guidelines was updated, treatment of MI and evaluation of post-MI patients have evolved greatly. In the original guidelines, exercise testing carried class I indications before hospital discharge (submaximal, 4 to 7 days), 14 to 21 days after discharge (symptom limited if not performed before discharge), and 3 to 6 weeks after discharge (symptom limited if predischarge submaximal exercise performed). These recommendations were based largely on the existing ACC/AHA guidelines for the management of acute MI. In this setting the exercise test was found to be safe, with a reported mortality rate of 0.03% and a nonfatal event rate of 0.09%.

Since 1997, the use of coronary angiography as part of the diagnostic evaluation and treatment of MI has taken priority. This evolution has limited the role of exercise testing in the stratification of post-MI patients. The most recent guidelines for both ST-segment elevation MI (STEMI)[34] and non-STEMI[35] state that the role of the simple exercise ECG is limited to patients who did not undergo coronary angiography following thrombolytic therapy, or patients who did not receive reperfusion therapy. In addition, these patients should have LV ejection fractions greater than 40% and no other high-risk features, should be able to exercise, and should have interpretable ECGs. This subset of patients is likely to be a small percentage of the total postinfarction group. In addition, it is highly likely that many of these patients will undergo stress imaging rather than a simple exercise test. Nevertheless, when exercise testing is performed, the variables of prognostic importance are the same as in all other settings: functional capacity, HR, systolic BP, and ventricular arrhythmias.

In the present clinical environment, realistic goals of exercise testing in the post-MI setting, whenever it is performed, should be threefold: to provide (1) a functional evaluation to guide the exercise rehabilitation prescription, (2) a basis for advice concerning return to work and other physical activities, and (3) an evaluation of present therapy.

Preoperative Evaluation in Noncardiac Surgery

Published guidelines for the preoperative evaluation of patients undergoing noncardiac surgery indicate a limited role for simple exercise testing in this process[36] (**see Chapter 11**). For patients with low preoperative cardiac risk or who are undergoing low-risk surgery, no exercise testing is indicated (class III, level of evidence B). Likewise, for patients with increased risk and excellent functional capacity (i.e., >10 METs, defined primarily by history), no further exercise testing with imaging is required (class IIa, level of evidence B). For patients with increased risk and more moderate functional capacity (i.e., 4 to 10 METs), it may be reasonable to forego further exercise imaging (class IIb, level of evidence B). Finally, for those with increased risk and poor or unclear functional capacity, it may be reasonable to perform stress imaging, especially if it will alter management (class IIb, level of evidence C). In most if not all patients who are candidates for stress imaging, this will be done with (or with the potential to convert to) pharmacologic stress.

Assessment of Therapy

The exercise ECG can be applied to assess the efficacy of therapy, whether medication, revascularization, ablation, or other. Serial exercise testing can be performed to assess HR and double product at the onset of ischemia (i.e., angina or ST-segment depression). These parameters are generally chosen because of their reproducibility. Peak V_{O_2} is the most reproducible measure, but CPX is not performed routinely. Exercise time is not generally chosen because of the influence of exercise training on the peripheral musculature with serial testing.

Exercise Testing in Nonatherosclerotic Heart Disease

The latest iteration of ACSM guidelines on exercise testing is dominated by diagnostic and prognostic assessments of atherosclerotic CAD.[2] Less prominent are applications that pertain to certain nonatherosclerotic conditions. In each case, exercise imaging, especially with echocardiography, provides important information for evaluation of these conditions. This section emphasizes and expands

on the value of the simple exercise test.[37]

Valvular Heart Disease

The role of exercise ECG testing in patients with valvular heart disease is best exemplified in the current valvular heart disease guidelines from AHA/ACC,[38] which were updated in 2017 (**see Chapter 67**). Exercise testing also has a role in patients with valvular heart disease who want to participate in competitive athletic activity.[39] Frequently, exercise testing is combined with echocardiography to assess structural and physiologic responses. This is the preferred approach in evaluating patients with mitral stenosis and disparate clinical and resting echocardiographic data, such as severe stenosis without symptoms or symptoms with mild to moderate stenosis. In patients with chronic severe mitral or aortic regurgitation, the diagnostic role of exercise testing is limited to the evaluation of functional capacity in patients with equivocal symptoms. The only valve lesion in which the simple exercise ECG still has a significant role in management is aortic stenosis.

Aortic Stenosis

It is universally agreed that exercise testing is absolutely contraindicated in patients with symptomatic severe valvular aortic stenosis.[38,40] However, for asymptomatic patients, exercise testing has found a role in two specific scenarios (**see Chapter 68**).

Severe Acquired Aortic Valve Stenosis

The first scenario is asymptomatic patients with severe acquired valvular aortic stenosis, defined as a peak Doppler velocity of 4 m/sec or greater, valve area less than 1 cm^2, or a mean valve gradient greater than 40 mm Hg with associated normal LV systolic function.[37] Patients with more moderate stenosis but suspected symptoms might also be considered. When peak aortic velocity exceeds 5.5 m/sec, exercise testing should not be done even in the absence of symptoms.[40,41] In addition, patients with severe aortic stenosis and high-gradient and normal LV function are to be distinguished from those with low-gradient stenosis and either normal or reduced LV systolic function.

Customary practice is to defer aortic valve replacement until symptoms develop (**see Chapter 67**). However, some patients with asymptomatic severe aortic stenosis who do not undergo early aortic valve replacement are still at increased short- and longer-term risk. The purpose of exercise testing in this setting is to induce either symptoms or an abnormal BP response (class IIa, level of evidence B). The class IIa indication clearly places it in the “it is reasonable” category. The intent is to provide a basis for a recommendation for valve replacement in patients who do not report any of the expected symptoms of severe aortic stenosis. The safety of exercise testing in this setting is established within the guidelines provided later.

Exercise testing in this scenario should be performed only in those with no reported symptoms or with symptoms that are equivocal at worst, such that aortic valve surgery is not indicated on that basis. They should have no extracardiac factors that limit exercise and no contraindications to aortic valve replacement. Considering that replacement of the aortic valve can currently be performed surgically or percutaneously, absolute contraindications for replacement are evolving. Protocols less intense than the standard Bruce protocol should be used, especially in elderly or untrained individuals. A modified Bruce or other low-level protocol can be used for patients who might manifest an earlier-than-anticipated adverse response. Special emphasis should be placed on the minute-by-minute BP response, patient

symptoms, and heart rhythm. Exercise should be terminated for limiting dyspnea and fatigue at a low workload, any angina or dizziness, any decrease in systolic BP, and complex ventricular ectopy. All these should be considered abnormal responses, placing the patient in a higher-risk group. Limiting dyspnea and fatigue must be interpreted carefully according to what is appropriate for age- and sex-based expectations. Isolated ST-segment depression (i.e., >2 mm of horizontal or downsloping depression) is very prevalent but is rarely an indication to stop the exercise test. If possible, termination should include a 2-minute cool-down walk and avoidance of the supine position to obviate acute LV volume overload. The average follow-up in exercise studies was approximately 1 year, suggesting a potential warranty period for favorable exercise test results. Magne and colleagues[40] review further application of exercise echocardiography to this setting.

Moderate to Severe Congenital Valvular Aortic Stenosis

The second scenario consists of young or adolescent patients with congenital aortic valve stenosis that is moderate to severe, defined as a mean Doppler gradient greater than 30 mm Hg or a peak Doppler gradient greater than 50 mm Hg (class IIa, level of evidence B).[42] Exercise testing in this specific scenario is done to provide advice for patients wanting to participate in athletic activities, as well as to evaluate asymptomatic patients with severe stenosis to assess the BP response and exercise tolerance, as with acquired stenosis. The testing procedure is similar to that for acquired aortic stenosis.

Hypertrophic Cardiomyopathy

Exercise testing in HCM has been historically considered a relative contraindication (**see Chapter 78**). In the 2011 ACC/AHA guidelines on HCM,[43] the exercise test carries a class IIa indication for assessing response to therapy (level of evidence C), for risk stratification (i.e., rhythm and blood pressure; level of evidence B), and for the decision concerning placement of a defibrillator when other sudden cardiac death (SCD) risk factors are present (class IIb without other SCD risk factors). On the issue of safety, several reported series have indicated a low and acceptable incidence of fatal and nonfatal complications.

Exercise testing in patients with HCM appears to have clinical value in three clinical situations.[37] The first is defining the presence of exercise-induced outflow tract obstruction with Doppler echocardiography in patients with no gradient at rest. The second is identifying patients with coexistent CAD, and the third is detecting patients with the high-risk indicator of an abnormal BP response.

The first two questions require exercise testing with imaging. Exercise testing in symptomatic patients with no significant resting peak outflow tract gradient (<50 mm Hg) appears to be safe and useful for detecting an exercise-induced gradient (class IIa, level of evidence B). A positive gradient response indicates obstructive rather than nonobstructive HCM. When the presence of significant CAD is being considered, LV hypertrophy and associated ST-segment changes at rest contribute to the reduced specificity of the exercise ST-segment response in this setting. In actual practice, when upright treadmill exercise is performed to address this question, imaging will be used with careful assessment of the BP response.

An abnormal BP response during maximal upright treadmill exercise is a risk factor for SCD in patients with HCM (**see Chapter 78**). It is of greater predictive value in patients younger than 50 years. An abnormal BP response is defined as either an initial increase in systolic pressure with a subsequent fall of greater than 20 mm Hg or a continuous fall from the start of exercise of greater than 20 mm Hg. Patients with abnormal BP responses tend to have more frequent exercise-induced ST-segment depression. The

NPV for SCD is reported to be in the mid-90% range, whereas the PPV is low. According to the HCM guidelines,[43] patients are considered low risk if they demonstrate eight characteristics, including a normal exercise BP response. Therefore, although a normal BP response can be reassuring, an abnormal response only places the patient into a high-risk cohort. The implication is that further stratification is required beyond the abnormal BP response. It is considered reasonable to reassess the BP response after therapy to reduce the outflow tract obstruction, but no data exist on this issue.

Adult Congenital Heart Disease

The 2010 European Society of Cardiology (ESC) guidelines for the management of adult congenital heart disease outline the role of the simple exercise test for the evaluation of patients with selected congenital defects[42] (**see Chapter 75**). In each case a specific class recommendation was given. The following recommendations do not include assessment of exercise capacity with CPX or assessment of ischemia with stress imaging. A more recent review indicates no significant change to these recommendations.[44]

For patients with outflow tract obstruction, the exercise test has a role with or without consideration of athletic participation (class IIa, level of evidence C). For valvular aortic stenosis, see the previous section on valvular heart disease. Similar recommendations are found for discrete subaortic and supravalvular aortic stenosis.

In patients with coarctation of the aorta, exercise testing should be done to assess for exercise-induced hypertension (peak systolic pressure >230 mm Hg). All patients with a noninvasive pressure difference greater than 20 mm Hg between upper and lower limbs, regardless of symptoms but with upper limb hypertension (>140/90 mm Hg in adults), pathologic BP response during exercise, or significant LV hypertrophy, should have intervention (class Ic).

Exercise testing plays a critical role in patients with repaired coronary anomalies and residual coronary abnormalities associated with Kawasaki disease, but stress imaging is recommended concomitantly.

A 2015 scientific statement from ACC/AHA addressed the selective use of simple exercise testing in individuals with congenital heart disease who want to participate in athletics. This does not include the individualized exercise prescription that could be done on any patient in this scenario. The specific entities where the simple exercise test has a role include repaired and unrepaired aortic coarctation, repaired tetralogy of Fallot, surgically and congenitally corrected transposition of the great arteries, and coronary artery anomalies. Van Hare and colleagues[45] address sport-specific intensity levels and recommendations.

Cardiac Rhythm Disturbances

Exercise testing can be used in the evaluation of suspected cardiac arrhythmias, premature ventricular complexes (PVCs), or nonsustained ventricular tachycardia (VT).[1,46] **Table 13.13** summarizes indications for exercise testing in the evaluation of arrhythmias. In addition, concerning the eligibility recommendations for competitive athletes with cardiac arrhythmias, an ACC/AHA statement covers the role of exercise testing in the settings of sinus bradycardia, heart block, isolated ventricular ectopic beats, nonsustained VT, and sustained monomorphic VT.[47]

TABLE 13.13

Guideline Recommendations for Exercise-ECG Testing in Heart Rhythm Disorders

Class I
Exercise testing is recommended for adult patients with ventricular arrhythmias who have an intermediate or greater probability of having coronary heart disease by age, gender, and symptoms to provoke ischemic changes or ventricular arrhythmias. *(Level of evidence: B)*
Exercise testing, regardless of age, is useful for patients with known or suspected exercise-induced ventricular arrhythmias, including catecholaminergic ventricular tachycardia, to provoke the arrhythmia, achieve a diagnosis, and determine the patient's response to tachycardia. *(Level of evidence: B)*
In asymptomatic patients with preexcitation, the findings of abrupt loss of conduction over a manifest pathway during exercise testing in sinus rhythm. *(Level of evidence: B-NR)*
In symptomatic patients with preexcitation, the findings of abrupt loss of conduction over the pathway during exercise testing in sinus rhythm. *(Level of evidence: B-NR)*
Class IIa
Exercise testing can be useful for evaluating response to medical or ablation therapy in patients with known exercise-induced ventricular arrhythmias. *(Level of evidence: B)*
Class IIb
Exercise testing may be useful in patients with ventricular arrhythmias and a low probability of coronary heart disease by age, gender, and symptoms. *(Level of evidence: C)*
Exercise testing may be useful in the investigation of isolated premature ventricular complexes in middle-aged or older patients without other evidence of coronary heart disease. *(Level of evidence: C)*
Class III
Routine investigation of isolated ectopic beats in young patients.
Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise.
High-degree atrioventricular block.
Atrial Fibrillation
The following are included as indications for exercise testing in atrial fibrillation, but are not given a recommendation class or level of evidence:
• If adequacy of rate control is in question.
• To reproduce exercise-induced atrial fibrillation.
• To exclude ischemia before treatment of selected patients with a class IC antiarrhythmic drug.

From Zipes DP et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Circulation 2006;114:e385; January CT et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. Circulation 2014;130:e199-267; and Page RL et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia. Circulation 2016;133;e506-74.

Atrial Fibrillation.

The AF guidelines state that exercise testing should be performed for three specific scenarios[48] (**see Chapter 38**). The first indication is when myocardial ischemia is suspected and initiation of type IC antiarrhythmic drug therapy is being considered. The second indication involves assessing the adequacy of HR control across a full spectrum of activity in patients with persistent or permanent AF (class Ic). No standard method for assessment of HR control has been established to guide management in patients with AF. Criteria for HR control vary with patient age but usually involve achieving ventricular rates between 90 and 115 beats/min during moderate exercise. Lastly, exercise testing may be used to induce possible exercise-induced AF.

Ventricular Preexcitation.

Exercise testing carries a class Ib recommendation in either symptomatic or asymptomatic patients with preexcitation.[49] Identifying accessory pathways that are at risk of developing rapid conduction and life-threatening ventricular arrhythmias in response to AF is an important consideration. The abrupt loss of preexcitation during exercise testing identifies a low-risk patient in this respect. Care should be taken to ensure that the delta wave is truly absent.

Ventricular Arrhythmias.

The 2014 European Heart Rhythm Association, Heart Rhythm Society, and Asia Pacific Heart Rhythm Society (EHRA/HRS/APHRS) Expert Consensus on Ventricular Arrhythmias recommend that exercise testing be performed for known or suspected exercise-induced ventricular arrhythmias to provoke and diagnose the arrhythmia and determine response to the tachycardia.[46] Exercise-induced ventricular arrhythmias can be associated with CAD. Therefore, detection of ischemia with or without associated ventricular arrhythmias defines a role for the exercise test.

With respect to patients with known or suspected exercise-induced ventricular arrhythmias, it should be understood that exercise testing in this high-risk cohort is not a low-risk endeavor. However, an exercise test may assist in uncovering significant arrhythmias in a controlled clinical environment rather

than in the patient's everyday setting.

Catecholaminergic Polymorphic Ventricular Tachycardia.

This arrhythmia occurs in genetically predisposed individuals when they are subjected to intense emotional or physical stress.[37] Standard cardiac testing, including the ECG at rest, usually produces normal results. The arrhythmia is almost always inducible by a maximal exercise test and is frequently not inducible with programmed electrical stimulation. Catecholaminergic polymorphic VT generally appears in HRs above 120 to 130 beats/min and begins with polymorphic ventricular premature beats progressing to nonsustained VT and eventually to bidirectional or polymorphic VT. The purpose of the exercise test, therefore, is to achieve a diagnosis and determine the patient's response to treatment, namely, beta blockade.[46]

Long-QT Syndrome.

When LQTS is suspected and the rest QTc is borderline, exercise testing can be performed safely given that arrhythmias do not usually develop in patients with LQTS during exercise (**see Chapter 33**). In addition, changes in the QT interval with exercise can be useful in identifying and stratifying patients with LQTS.[46] Further prolongation of (or failure to shorten) an already prolonged QT interval with exercise is typical of LQT1. LQT2 has normal shortening, whereas LQT3 has supranormal shortening of the QT interval with exercise. Beta blockade normalizes these responses. These responses can be useful in predicting and directing genetic testing in patients with LQTS.

Arrhythmogenic Right Ventricular Cardiomyopathy.

Even though arrhythmias and SCD can occur during exercise in patients with arrhythmogenic right ventricular cardiomyopathy, exercise testing has no significant role in the management of these patients. Serious ventricular arrhythmias that do occur during exercise usually take the form of monomorphic VT with an LBBB pattern.[44]

Brugada Syndrome.

Exercise testing generally plays little role in the diagnosis of this condition but might have a role in risk-stratifying patients who are asymptomatic. A recent report suggested that augmentation of early precordial ST-segment elevation early in recovery from exercise is both specific to Brugada syndrome and a predictor of a poor prognosis.[50]

Assessment of Therapy.

Assessing the response to medical, ablative, or surgical therapy for exercise-induced ventricular arrhythmias is a class IIa, level of evidence B indication. Unlike anti-ischemic therapy, the endpoint is the presence or absence of significant ventricular arrhythmias with reasonable levels of exercise, depending on patient-specific factors.

Assessment of Pacemaker Function

Even though earlier guidelines endorse exercise testing with rate-adaptive pacemakers to fine-tune or maximize the physiologic response, the 2012 guidelines regarding device-based treatment of cardiac arrhythmias do not even mention the use of exercise testing with implanted pacemakers.[51] This discrepancy raises a practical question. Despite the original endorsement of exercise testing in patients with rate-adaptive pacemakers, do pacemaker physicians actually use exercise testing in clinical decision making for rate-adaptive pacemakers? Exercise testing could play a role with rate-adaptive pacemakers when exercise intolerance is not completely relieved by factory settings or empiric adjustments. This would be especially true in patients involved in significant physical activities or athletic participation.[37]

Additional Uses for Exercise Testing

Chest Pain Units

Chest pain units are designed to assist in the triage and management of low-risk patients among the more than 8 million patients evaluated in emergency departments annually. Low-risk patients have stable hemodynamic signs, no arrhythmias, normal or near-normal findings on the ECG, and negative cardiac injury biomarkers and are appropriate for admission and observation in a chest pain unit. Such units are designed to provide an integrated approach to further risk stratification by short-term observation, repeated ECGs, and serial cardiac injury biomarkers. In patients without further chest pain and no objective evidence of ischemia, an exercise test can be performed after 8 to 12 hours of observation. Such testing is often performed with a symptom-limited treadmill protocol. Several studies encompassing more than 3000 such patients have demonstrated that a negative test has a high NPV for subsequent cardiac events (**Table 13.14**). No adverse events during exercise testing have been reported. Those with a positive test are admitted for further evaluation, whereas those with a negative test can be discharged safely with outpatient follow-up. This strategy has been shown to be cost-effective compared with usual care in which such patients are admitted to the hospital.[52] Patients who are unable to exercise or who have baseline electrocardiographic abnormalities can undergo stress imaging tests or computed tomographic angiography. The usefulness of such tests is discussed in detail elsewhere[52] (**see Chapters 14, 16, and 18**).

TABLE 13.14

Chest Pain Unit: Patient Selection, Testing Procedure, and Endpoints

Patient Selection Criteria
Able to exercise ECG: Normal or minor ST-T changes Hemodynamically stable, no arrhythmia Negative cardiac injury markers
Procedure
Bruce or modified Bruce protocol
Endpoints
Symptom-limited Ischemia (≥0.10 mV of horizontal ST depression or elevation) Decreased blood pressure (≥10 mm Hg systolic) during exercise test
Result
Positive: ≥0.10 mV of horizontal ST-segment depression Negative: No exercise-induced abnormalities at 85% MPHR Nondiagnostic: <85% MPHR with no ECG evidence of ischemia

MPHR, Maximum age-predicted heart rate.

From Amsterdam EA, Kirk JD, Bluemke DA, et al. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. Circulation 2010;122:1756.

Physical Activity and Exercise Prescription

Data derived from the exercise test can yield valuable objective information to assist in providing physical activity recommendations for patients with CVD, specifically regarding domestic, occupational, recreational, and athletic activities. The 2011 Compendium of Physical Activities: a Second Update of Codes and MET Values[53] and its associated web link (http://links.lww.com/MSS/A82) provide 821 codes that reflect 21 major headings, numerous specific activities and their detailed descriptions, and associated MET values that can be used to identify the energy cost associated with a given activity. By

using the exercise test to measure peak exercise capacity in METs and evaluate the HR, BP, and symptomatic responses to peak and submaximal MET levels, the clinician can combine this information with that derived from the compendium to counsel patients on their ability to perform a broad spectrum of activities and tasks. It is important to realize, however, that the exercise test does not yield information regarding the patient's ability to perform sustained tasks for long periods or take into account the environmental conditions (e.g., temperature, humidity, altitude, wind) where the activity is performed. Therefore, data from the exercise test and the compendium can serve only as a guide to prudent activity counseling. Patients must be made aware of these other factors and instructed to use subjective symptoms scales (e.g., Borg Scale of Perceived Exertion)[1,2] to further tailor their activity performance.

Exercise training programs are designed to maintain or improve fitness and include the prescriptive components of intensity, duration, frequency, and modality. Details regarding the exercise prescription for patients with CVD are provided elsewhere.[1,2] For patients with CVD, the *intensity* of dynamic aerobic exercise is usually determined from the results of a pretraining exercise test by using either of two methods: 40% to 80% of peak exercise capacity using the *heart rate reserve* method ([peak HR− resting HR] × [percent intensity] + [resting HR]), and in patients who have performed a CPX, the heart rate at 40% to 80% of the measured peak V_{O_2}. Intensity may be modified further by using the subjective perceived exertion scale at a rating of 11 to 16 on a scale of 6 to 20.[1] In patients with an ischemic response during exercise, the intensity should be prescribed at a heart rate that is at least 10 beats below the ischemic threshold (i.e., the HR at which ischemic ST depressions and typical angina begin to occur). The goal *duration* of exercise at the prescribed intensity is generally 20 to 60 minutes per session at a *frequency* of 3 to 5 days per week. Training *modalities* should ideally incorporate exercises that include rhythmic, large muscle group activities of both the upper and the lower extremities with varying types of exercise equipment.

Emerging data on aerobic interval training (AIT) offer promise for patients with CVD. AIT involves alternating 3- to 4-minute periods of exercise at very high intensity (90% to 95% of peak HR) with exercise at moderate intensity (60% to 70% of peak HR). When such training is performed for approximately 40 minutes, three times per week, studies demonstrate greater improvements in peak V_{O_2}, endothelial function, and metabolic parameters than with standard continuous, moderate-intensity exercise.[54,55] A large cross-sectional study has found that the cardiovascular risks of AIT are low in a supervised cardiac rehabilitation setting. Although more such studies are needed, AIT should be considered in select patients as an alternative training modality for those with CVD enrolled in cardiac rehabilitation programs.[56]

Disability Assessment

The U.S. Social Security Administration defines disability as “the inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment(s) which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months.”[57] In several cardiovascular conditions, disability is not based solely on the diagnosis but also on the functional limitations imposed by the condition. Thus, exercise testing plays an integral role in the determination of disability for several cardiovascular conditions, including chronic heart failure, ischemic heart disease, congenital heart disease, peripheral artery disease (PAD), and valvular heart disease. The Institute of Medicine (IOM) convened a panel of experts to provide recommendations for updating the Social Security listings for cardiovascular conditions. Although each

of the previous conditions have specific criteria to define the condition, functional disability in almost all of them is defined by the inability to attain a peak VO_2 of 15 mL/kg/min (or 5 METs) on a symptom-limited treadmill or stationary cycle test. **Table 13.15** outlines details regarding exercise test criteria for specific cardiovascular conditions as recommended by IOM.

TABLE 13.15

Exercise Test Criteria for Disability Determination in Specific Cardiovascular Conditions

CARDIOVASCULAR CONDITION	SOCIAL SECURITY CRITERIA	IOM RECOMMENDATIONS
Chronic heart failure	Inability to attain 5 METs due to symptoms of dyspnea, fatigue, palpitations, or chest discomfort; frequent or complex ventricular ectopy >10 mm Hg decrease in SBP during graded exercise; signs due to inadequate cerebral perfusion	Exercise testing in chronic heart failure is safe. CPX testing requires less subjective endpoint interpretation, using criteria of peak VO_2 <15 mL/kg/min with RER >1.1, or <5 METs on standard treadmill test without gas exchange. Frequent exercise-induced ventricular ectopy alone should not be listed as a criteria.
Ischemic heart disease	Exercise tolerance testing that demonstrates ischemia, or ≥10 mm Hg fall in SBP at ≤5 METs	Additional specific criteria when stress imaging tests are used
Peripheral artery disease	≥50% decrease in SBP at the ankle from resting levels that requires ≥10 minutes to recover	
Congenital heart disease (adults)	Intermittent right-to-left shunting leading to cyanosis and arterial PO_2 of ≤60 mm Hg at ≤5 METs.	Intermittent right-to-left shunting with pulse oximetry ≤85% at ≤5 METs Exercise capacity with peak VO_2 <15 ml/kg/min or <5 METs
Pulmonary hypertension	No previous criteria	Exercise capacity <5 METs
Valvular heart disease	No previous criteria	Exercise capacity <5 METs

CPX, Cardiopulmonary exercise testing; *METs,* metabolic equivalents; *RER,* respiratory exchange ratio; *SBP,* systolic blood pressure; VO_2, oxygen uptake.

Data from the Institute of Medicine (IOM) of the National Academies. Cardiovascular Disability. Updating the Social Security Listings. Washington, DC: National Academies Press; 2010.

Evaluation of Peripheral Artery Disease

Exercise testing can be performed in patients with PAD to establish further the diagnosis by noninvasive techniques, particularly in patients with calf pain and borderline ankle-brachial indices (ABIs: 0.91 to 1.0), and objectively evaluate functional limitations imposed by PAD and the subsequent response to therapies (**see Chapter 64**). Assessment of the time to initial claudication symptoms (*claudication onset time*) and the *peak exercise time* to maximum tolerated calf pain should be done by using a gradual graded exercise treadmill, such as the Gardner protocol (**Table 13.16**). For functional assessment, the 6-minute walk test (**see Table 13.8**) can also be used; during this test, both time and distance are measured to onset and to peak calf pain.

Table 13.16

Gardner Testing Protocol for Patients with Peripheral Artery Disease

STAGE	SPEED/GRADE	METs
1	2 mph/0%	2.5
2	2 mph/2%	3.1
3	2 mph/4%	3.6
4	2 mph/6%	4.2
5	2 mph/8%	4.7
6	2 mph/10%	5.3
7	2 mph/12%	5.8
8	2 mph/14%	6.4
9	2 mph/16%	6.9
10	2 mph/18%	7.5

Each stage is 2 minutes in duration. *METs,* Metabolic equivalents.

From Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs single-stage treadmill tests for evaluation of claudication. Med Sci Sports Exerc 1991;23:402.

The postexercise ABI can provide additional diagnostic information and is done by measuring the ABI in both ankles at rest and again immediately after exercise (**see Chapters 10 and 64**). During leg exercise, systolic BP normally increases in the arms but decreases in the ankles because of the peripheral vasodilation that occurs in exercising leg muscles. This leads to a mild decrease in the ABI in healthy patients that returns to normal within 1 to 2 minutes of recovery. In patients with PAD, ankle pressure decreases even more, thereby leading to a further decrease in the ABI and also a prolonged recovery time. Several diagnostic criteria have been proposed and include greater than a 5% drop in postexercise ABI from resting levels, postexercise ABI lower than 0.9, greater than a 30 mm Hg drop in systolic BP at the ankle, and recovery time to baseline ABI longer than 3 minutes.[58] Details regarding the use of exercise testing are also discussed in the ACC/AHA guidelines for the management of patients with PAD[59] (**Table 13.17**).

TABLE 13.17

ACC/AHA Guidelines for Exercise Testing in Peripheral Artery Disease (PAD)

Class I
Exercise treadmill tests are recommended to provide the most objective evidence of the magnitude of the functional limitation of claudication and to measure the response to therapy. *(Level of evidence: B)*
A standardized exercise protocol (either fixed or graded) with a motorized treadmill should be used to ensure reproducibility of measurements of pain-free walking distance and maximal walking distance. *(Level of evidence: B)*
Exercise treadmill tests with measurement of preexercise and postexercise ankle-brachial index (ABI) values are recommended to provide diagnostic data useful in differentiating arterial claudication from nonarterial claudication ("pseudoclaudication"). *(Level of evidence: B)*
Exercise treadmill tests should be performed in individuals with claudication who are to undergo exercise training (lower extremity PAD rehabilitation) so as to determine functional capacity, assess nonvascular exercise limitations, and demonstrate the safety of exercise. *(Level of evidence: B)*
Class IIa
An exercise ABI measurement can be useful to diagnose lower extremity PAD in individuals who are at risk for lower extremity PAD and who have a normal ABI (0.91 to 1.30), are without classic claudication symptoms, and have no other clinical evidence of atherosclerosis. *(Level of evidence: C)*
Long-term patency of infrainguinal bypass grafts may be considered for evaluation in a surveillance program, which may include conducting exercise ABIs and other arterial imaging studies at regular intervals. *(Level of evidence: B)*
Long-term patency of endovascular sites may be evaluated in a surveillance program, which may include conducting exercise ABIs and other arterial imaging studies at regular intervals. *(Level of evidence: B)*
Class IIb
A 6-minute walk test may be reasonable to provide an objective assessment of the functional limitation of claudication and response to therapy in elderly individuals or others not amenable to treadmill testing. *(Level of evidence: B)*

From Anderson JL et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127:1425-43.

Patients with Diabetes

CAD remains the most common cause of morbidity and mortality in patients with diabetes mellitus (**see Chapter 51**). In recent years, strategies for the treatment of CAD in patients with diabetes have undergone much evolution such that regardless of symptoms or documented CAD, diabetic patients are treated with preventive therapies. In this context, the ability to specifically identify diabetic patients with disease who will benefit from more aggressive and, perhaps, invasive therapies remains a challenge. A comprehensive review of screening methods to detect CAD in patients with diabetes is found elsewhere.[60] Exercise electrocardiographic testing has similar diagnostic sensitivity (approximately 60%) and specificity (80%) for diabetic patients with angina as for nondiabetic patients. It can also identify a subgroup of asymptomatic diabetic patients who have significant CAD as defined by angiography and, more importantly, in lower-risk asymptomatic diabetic cohorts may offer short-term prognostic reassurance to those with negative test results. However, considerable prognostic power of the exercise ECG test lies beyond the ST-segment response. Poor exercise capacity and slow HRR in diabetic patients are markers of an adverse outcome. The value of the Duke prognostic score in patients with diabetes has not been well studied, and unlike the Morise score[28] and the Cleveland Clinic Foundation risk score,[29] it did not specifically address the presence of diabetes in the original cohort study. Therefore, at present, the Morise and Cleveland Clinic scores are more appropriate to apply in patients with diabetes who have normal resting ECG findings and undergo exercise electrocardiography.

At present, evidence is inadequate for recommending routine screening of asymptomatic diabetic patients with an exercise ECG. The American Diabetes Association standards of medical care conclude that in asymptomatic patients, routine screening for CAD is not recommended, even before initiation of an exercise training program, because it does not improve outcomes as long as risk factors for CVD are treated.[61] They recommend that diabetic persons who might be considered for advanced or invasive cardiac testing include those with (1) typical or atypical cardiac symptoms and (2) an abnormal resting ECG. Exercise ECG testing without or with echocardiography may be used initially. Pharmacologic stress echocardiography or nuclear imaging should be considered in diabetic persons in whom resting ECG abnormalities preclude exercise stress testing (e.g., LBBB or ST-T abnormalities) or in those who are not able to exercise.

These recommendations have arisen from the observation that intensive medical therapy, which would be indicated in any case for diabetic patients at high risk for CVD, appears to provide similar outcomes as invasive revascularization, raising the question of how the results of screening would change management. This position is supported by data from the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study, which evaluated 1123 patients with type 2 diabetes and no symptoms of CAD. They were randomly assigned to be screened with adenosine stress radionuclide myocardial perfusion imaging or not to be screened. Cardiac death and nonfatal MI event rates were low in both groups (2.7% versus 3%) over 4.8 years and not significantly reduced by myocardial perfusion imaging (MPI) screening for myocardial ischemia. Importantly, during the course of this study, there was a significant and similar increase in primary medical prevention in both groups.[62]

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Additional Uses for Exercise Testing

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14

Echocardiography

Scott D. Solomon, Justina C. Wu, Linda Gillam

Illustrated by, Bernard Bulwer

Echocardiography remains the most commonly used comprehensive cardiac imaging modality and is often the first test of choice for assessing cardiac structure and function. When compared with other imaging methods, echocardiography can be performed quickly, with minimal patient inconvenience or risk, and provides immediate clinically relevant information at relatively low cost. Echocardiography provides detailed data on cardiac structure, including the size and shape of cardiac chambers, as well as the morphology and function of cardiac valves. Furthermore, the real-time nature of echocardiography makes it uniquely suited to immediate noninvasive assessment of systolic and diastolic function and intracardiac hemodynamics. In most echocardiography laboratories, standard *transthoracic echocardiography* (TTE) is complemented by *transesophageal echocardiography* (TEE), which offers improved resolution, and by *stress echocardiography,* which is routinely used to assess myocardial ischemia and valvular function with exercise. Technical advancements in echocardiography over the past several decades have led to progressively improved diagnostic capabilities; these include advances in three-dimensional (3D) and tissue strain imaging, miniaturization of equipment, and contrast echocardiography for better cavity visualization and assessment of myocardial perfusion.

Because two-dimensional (2D) echocardiography is not a tomographic technique such as cardiac computed tomography (CT) or cardiac magnetic resonance (CMR) imaging (**see Chapters 17 and 18**), acquisition of ultrasound images is dependent on an operator—either a sonographer or a physician—applying an ultrasound transducer to a patient's chest. Both acquisition and interpretation of echocardiograms require substantial training and skill. Thus echocardiography is best described as an "examination" rather than a "test." Although cardiologists receive this training routinely, a growing number of noncardiologists, including emergency physicians, anesthesiologists, intensivists, and inpatient hospital staff, are increasingly using echocardiography in their practice, in some cases with small, handheld ultrasound devices. Knowledge of the basic principles, utility, and limitations of echocardiography is becoming essential for all physicians who care for patients with cardiovascular problems.

Principles of Ultrasound and Instrumentation

Principles of Image Generation

Echocardiography is based on the standard principles of ultrasound imaging in which high-frequency sound waves in the 1- to 10-MHz range are emitted from piezoelectric crystals housed in a transducer, traverse through internal body structures, interact with tissues, reflect back to the transducer, and are then processed by microcomputers to generate an image. An understanding of the physical principles that underlie echocardiography is essential to understanding its usefulness and limitations.[1]

Ultrasound machines calculate the time required for sound waves to reflect from structures and return to the transducer, thereby determining the depth of reflecting structures. This information is used to generate scan lines that comprise data on both *location* (depth of reflection) and *amplitude* (intensity of reflection). Early ultrasound equipment projected a single beam of ultrasound, which resulted in a single scan line that could be "painted" across a moving paper or screen, with depth being depicted on the vertical axis and time on the horizontal axis. This method, known as *M-mode* (for motion) echocardiography (**Fig. 14.1, lower right**), has largely been replaced by 2D imaging (**Fig. 14.1, lower left**). However, M-mode is still used routinely and is particularly useful for making linear measurements and assessments that require precise timing with respect to the cardiac cycle.

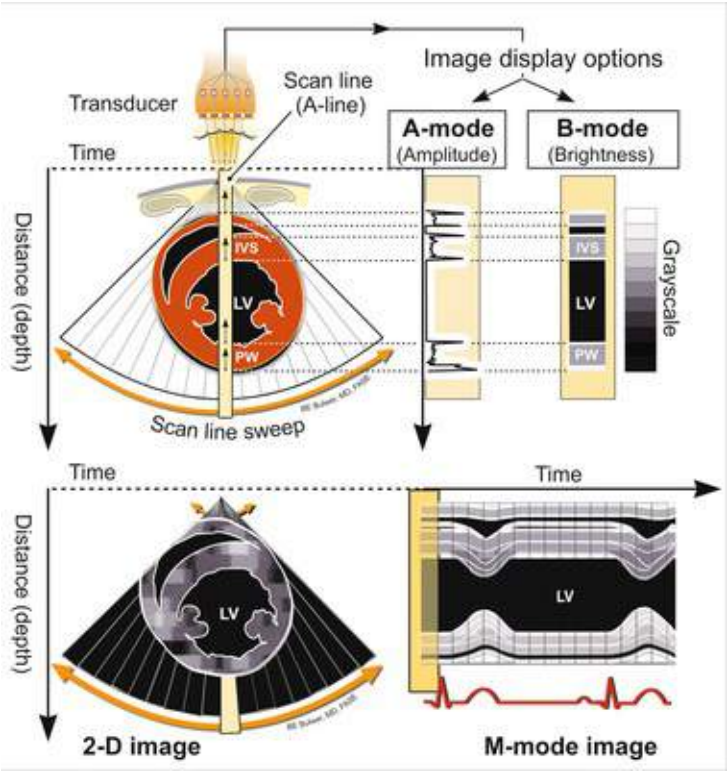


FIGURE 14.1 Generation of ultrasound images. An ultrasound pulse transmitted from piezoelectric elements housed in a transducer **(upper left)** reflects off structures and returns to the transducer. These signals are processed and displayed based on their amplitudes **(upper right)**. Echoes with the highest amplitudes emerge from tissue interfaces such as the pericardial-pleural and endocardial-blood borders. In original A-mode scans, such signals are visualized as amplitude spikes. On B-mode, the echo amplitudes are displayed via gray scale. B-mode images can then be displayed in one dimension over time, i.e., M (motion)–mode **(bottom right),** or as a two-dimensional cross-sectional image **(bottom left)**. *IVS,* Interventricular septum; *LV,* left ventricle; *PW,* posterior wall. (Modified from Bulwer BE, Rivero JM, editors. Echocardiography Pocket Guide: The Transthoracic Examination. Burlington, Mass: Jones & Bartlett Learning; 2011, 2013. Reprinted with permission.)

Current 2D imaging uses phased-array transducers, in which the piezoelectric crystal is precisely diced into multiple (currently up to 512) elements that emit and receive sonar pulses elements; the beam is electronically steered through an arc side-to-side to create a scan plane (**Fig. 14.2**). The transducer emits pulses of ultrasound in an ordered sequence and sequentially "listens" for returning echoes, referred to as the *pulse-echo principle*. Repetition of this sequence generates the moving images. The rate at which these pulses are emitted is termed the *pulse repetition frequency* (PRF). Proper interpretation of returning signals is physically limited by the speed of sound in tissues (approximately 1540 m/sec) and the depth of the tissues being interrogated, which dictates the time it takes for the ultrasound signal to return to the transducer. Nevertheless, improvements in processing speed have allowed "frame" rates, a major determinant of temporal resolution, to reach speeds higher than 100 image frames per second. In practice, the echo machine operator can increase frame rate by narrowing the scan sector, imaging at shallower depths, and reducing scan line density. 3D echocardiography extends the phased-array concept to make use of a planar waffle-like grid or matrix-array of elements (2500+), which allows both simultaneous multiplanar 2D imaging and true volumetric 3D imaging and rendering (see Three-Dimensional Echocardiography).

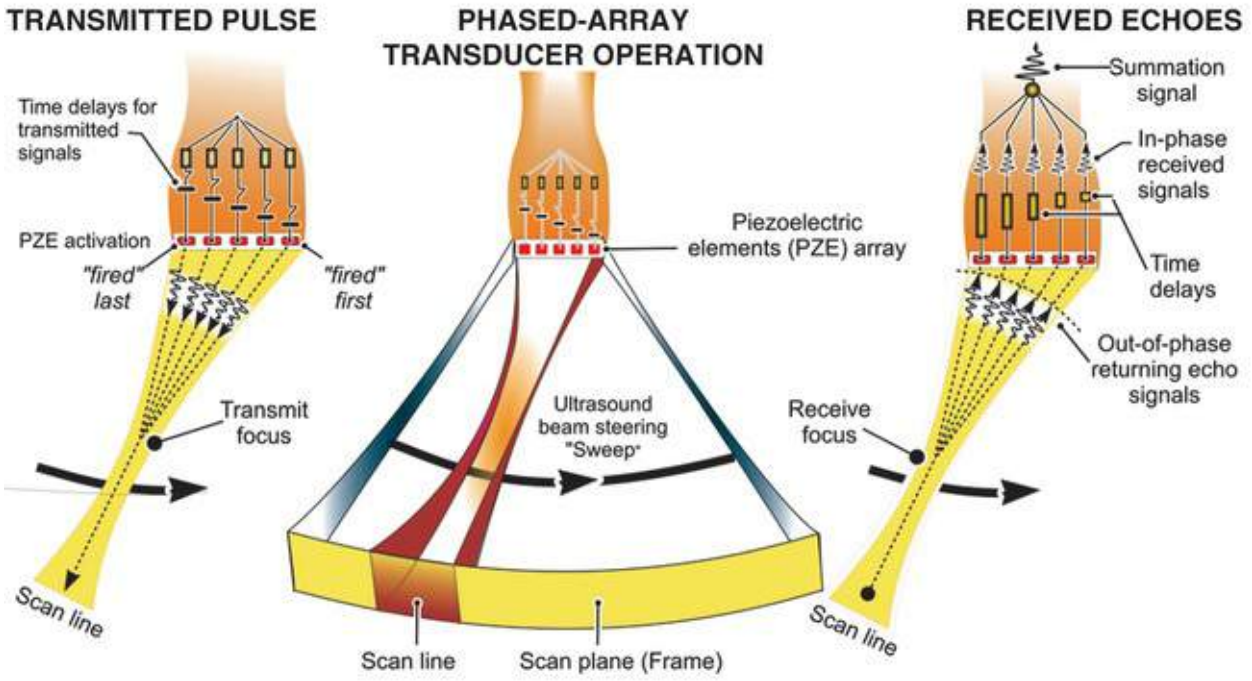


FIGURE 14.2 Phased-array transducer operation. Modern echocardiography transducers scan through a relatively wide scan sector by steering the electronic beam across the scan plane **(center)**. During transmission **(left)**, electronic time delays in firing the piezoelectric elements of the transducer cause the scan line to sweep in an arc. During reception **(right),** the returning echo signals received by each transducer element must be time-shifted or phased before being summated and processed. (Modified from Bulwer BE, Shernan SK, Thomas JD. Physics of echocardiography. In Savage RM, Aronson S, Shernan SK, editors. Comprehensive Textbook of Perioperative Transesophageal Echocardiography. Philadelphia: Wolters Kluwer: Lippincott, Williams & Wilkins; 2009, pp 1-41.)

Physical Principles of Ultrasound

The physical characteristics of ultrasound are exploited to generate images representative of the heart. The wavelength of the ultrasound used, which is inversely related to ultrasound frequency, is the principal determinant of axial imaging resolution, which equals approximately half the wavelength. The higher the ultrasound frequency (i.e., shorter the wavelength), the higher is the spatial resolution. Imaging resolution is also dependent on the depth of the structure being interrogated. Therefore, the choice of imaging frequency involves a trade-off between image resolution and target tissue depth: higher frequencies are capable of increased resolution, but at the expense of reduced tissue penetration. Most TTE machines operate across frequencies of 2.5 to 5 MHz. Higher frequencies up to 7 to 10 MHz can be used in pediatric imaging, in TEE where the transducer is closer to the heart, or when interrogating near-field structures, such as the apex of the heart from the apical window.

The speed of ultrasound through body tissues averages 1540 meters per second (m/sec), essentially the speed of sound through water, but varies minutely as ultrasound waves traverse various body constituents. These slight differences in ultrasound speed through different media (e.g., blood, muscle, fat, air) result in impedance mismatches at the tissue interfaces, which produces the *specular reflections* that mark the boundaries between different tissues. The most intense reflections occur when ultrasound strikes these interfaces perpendicularly and when the tissues differ greatly in density. When ultrasound encounters inhomogeneous tissue regions, such as myocardium, liver, or other tissues, multidirectional reflection, or *backscatter*, occurs and results in speckled-appearing images. The combination of specular reflections and backscatter, together with the unique interactions between ultrasound and tissue such as refraction, interference, and attenuation, contributes to the characteristic gray-scale appearance of ultrasound images.

Ultrasound penetrates poorly through air and bone, which is one of the greatest challenges to echocardiography because the heart is surrounded by the lungs and the rib cage. The ability to circumvent these limitations during image acquisition underscores the importance of the operator's skill and the advantages of a TEE approach in specific clinical situations.

Several advances in the past decade have improved the quality of ultrasonic imaging. The higher number of elements in phased-array transducers has increased the number of scan lines and thus lateral resolution. *Tissue harmonic imaging* is now the norm, in which the receiver "listens" for returning second-harmonic ultrasound signals that are twice the fundamental frequency of the emitted ultrasound. By doing so, it effectively filters out the weaker noisy signals from cardiac chambers and has substantially improved the definition of tissue interfaces, in particular that of the endocardial borders (**Fig. 14.3**), when compared to fundamental imaging.

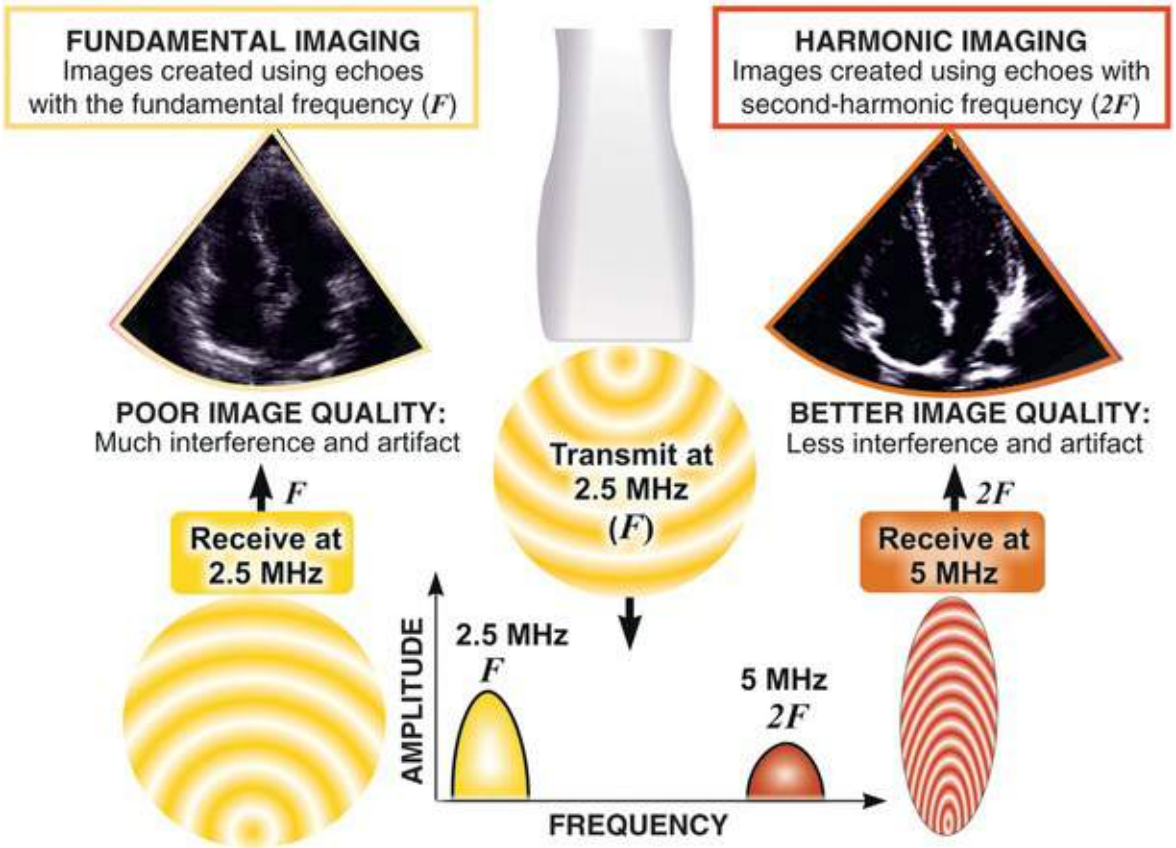


FIGURE 14.3 Tissue harmonic imaging. Tissue harmonic imaging improves image quality by using second-order harmonics. Ultrasound causes tissues to vibrate at a the fundamental frequency **(left)** but also multiples (harmonics) of that frequency. By listening for the higher (second-order) frequency returning echoes, signal-to-noise ratio and tissue definition are dramatically improved **(right)**. (Modified from Bulwer BE, Shernan SK, Thomas JD. Physics of echocardiography. In Savage RM, Aronson S, Shernan SK, editors. Comprehensive Textbook of Perioperative Transesophageal Echocardiography. Philadelphia: Wolters Kluwer: Lippincott, Williams & Wilkins; 2009, pp 1-41.)

Principles of Doppler Imaging

In addition to generating images of cardiac structures, ultrasound can be used to interrogate the velocity of blood flow through the heart and to quantify myocardial motion. These techniques are based on the Doppler principle, which states that the frequency of a waveform bounced back from a moving object

will be altered (shifted) from the emitting frequency, depending on whether the object is moving toward or away from the observer. Ultrasound that is reflected from red blood cells moving toward the emitter will return at higher frequency, whereas blood flow away from the transducer will cause a lower-frequency waveform to return (**Fig. 14.4**). This difference between the frequency emitted and that received is termed the *Doppler frequency shift* and is dependent on the speed of ultrasound through the medium and the velocity of blood flow. The basic equation for Doppler shift (f_d) is $f_d = f_t V/c$, where f_t is the transmitted ultrasound frequency, V is the velocity of blood flow, and c is the speed of ultrasound in the tissue. For cardiac ultrasound, multiplication by a factor of 2 occurs because the Doppler shift occurs twice (when the wave goes to and from the moving object). Notably, the velocity information obtained is most accurate when the ultrasound beam is aligned parallel to the direction of blood flow (i.e., an optimal angle of insonation is 0 degrees). When the angle of insonation (θ) cannot be physically corrected, the correction factor *cos*θ may be applied. Thus the refined formula for Doppler shift is:

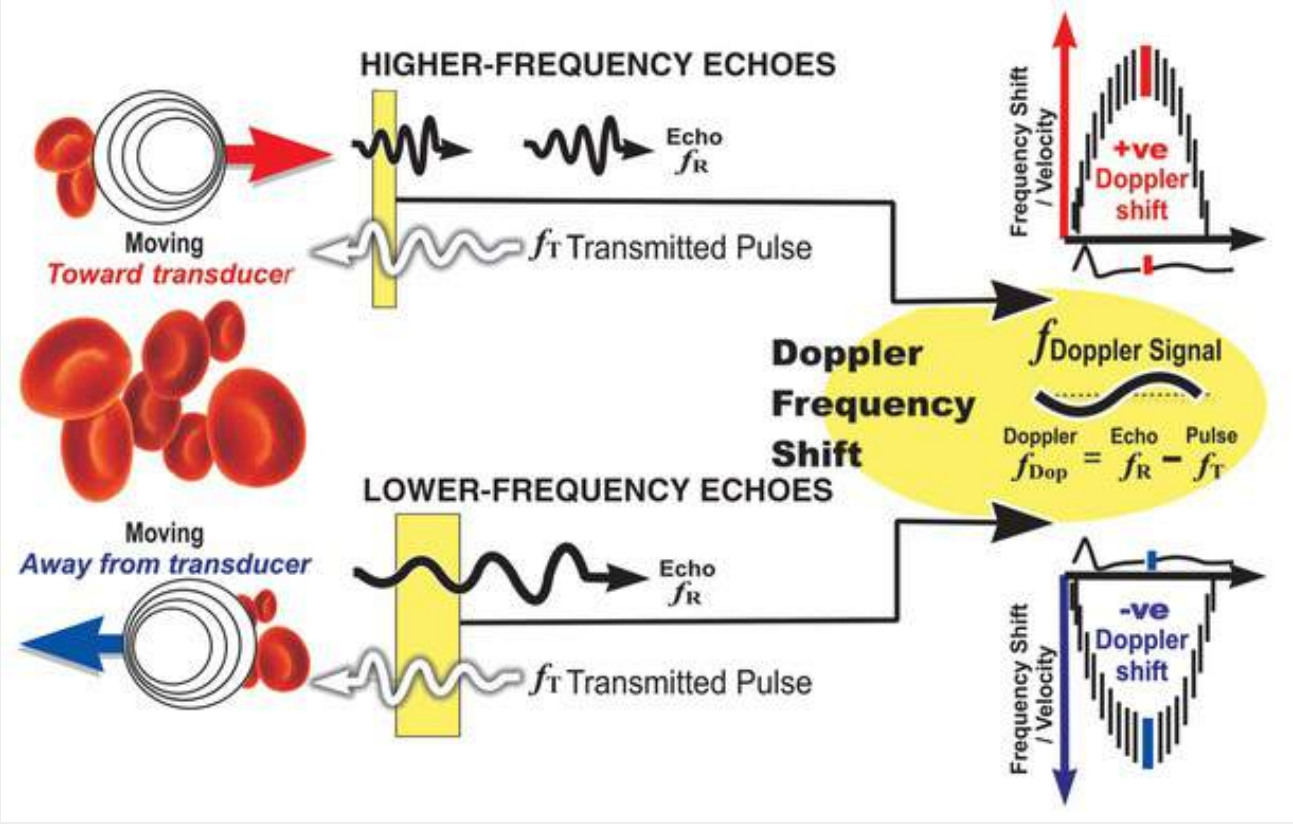


FIGURE 14.4 The Doppler frequency shift. Echoes reflected from blood cells moving toward the transducer will return at a higher frequency than the transmitted ultrasound pulse **(upper panels)**. The opposite is seen with blood moving away from the transducer **(lower panels)**. Doppler echocardiography instruments harness this shift in frequency to derive blood flow velocities. The direction of flow is displayed graphically as a time-velocity spectrum above or below the baseline (in spectral Doppler) or as color-coded velocities with color flow Doppler.

$$F_d = 2f_t V(\cos\theta)/c$$

Ultimately, the equation above is used to solve for velocity, V, of blood flow.

Pulsed-Wave and Continuous-Wave Doppler

The two principal types of Doppler imaging are pulsed-wave (PW) and continuous-wave (CW) Doppler. In PW Doppler (**Fig. 14.5, left panel**), discrete pulses of ultrasound reflect off moving structures (i.e., red blood cells moving through the heart) and return to the transducer. By *gating*, or defining a specific time window during which the machine "listens" for reflected signal, this technique can be used to ascertain the velocity of blood flow at a prespecified depth within the heart. Thus, when an operator places the cursor (sample volume) on the 2D ultrasound image at a particular location, the equipment will assess the velocity at that point. Because it takes time for the pulses to reflect and return to the transducer, they cannot be transmitted too frequently, or the equipment will fail to discern whether a given pulse has returned, and the velocity information obtained at that depth will be ambiguous. The PRF is essentially the sampling rate; the higher the blood flow velocity, the higher is the frequency of the Doppler shift and thus the higher the sampling rate needed to accurately sample that shift (**eFig. 14.1**). These physical principles limit the upper range of velocities that can be interrogated with PW Doppler. The *Nyquist limit* refers to the maximum velocity that can be accurately quantified within a given sample volume and is directly related to the PRF (the numeric value equals ½ the PRF). PRF in turn is inversely related to the distance from the sample volume to the transducer. The machine is unable to assess velocities that are higher than the Nyquist limit, because the values will go off-scale and appear to "alias" (wrap around) in the generated spectrogram; adjusting the Nyquist limit setting on the machine upward effectively adjusts the PRF upward until the physical limit is reached.

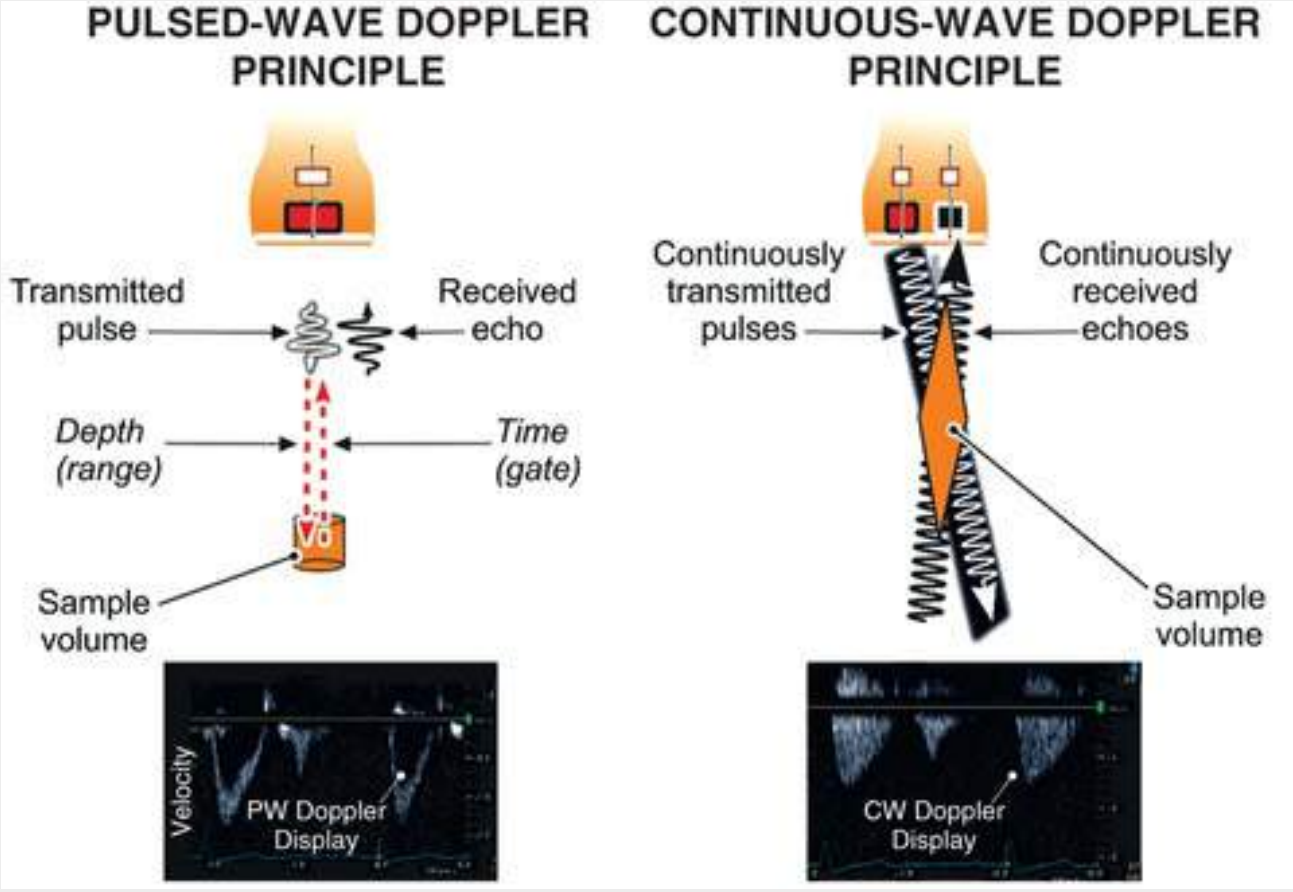
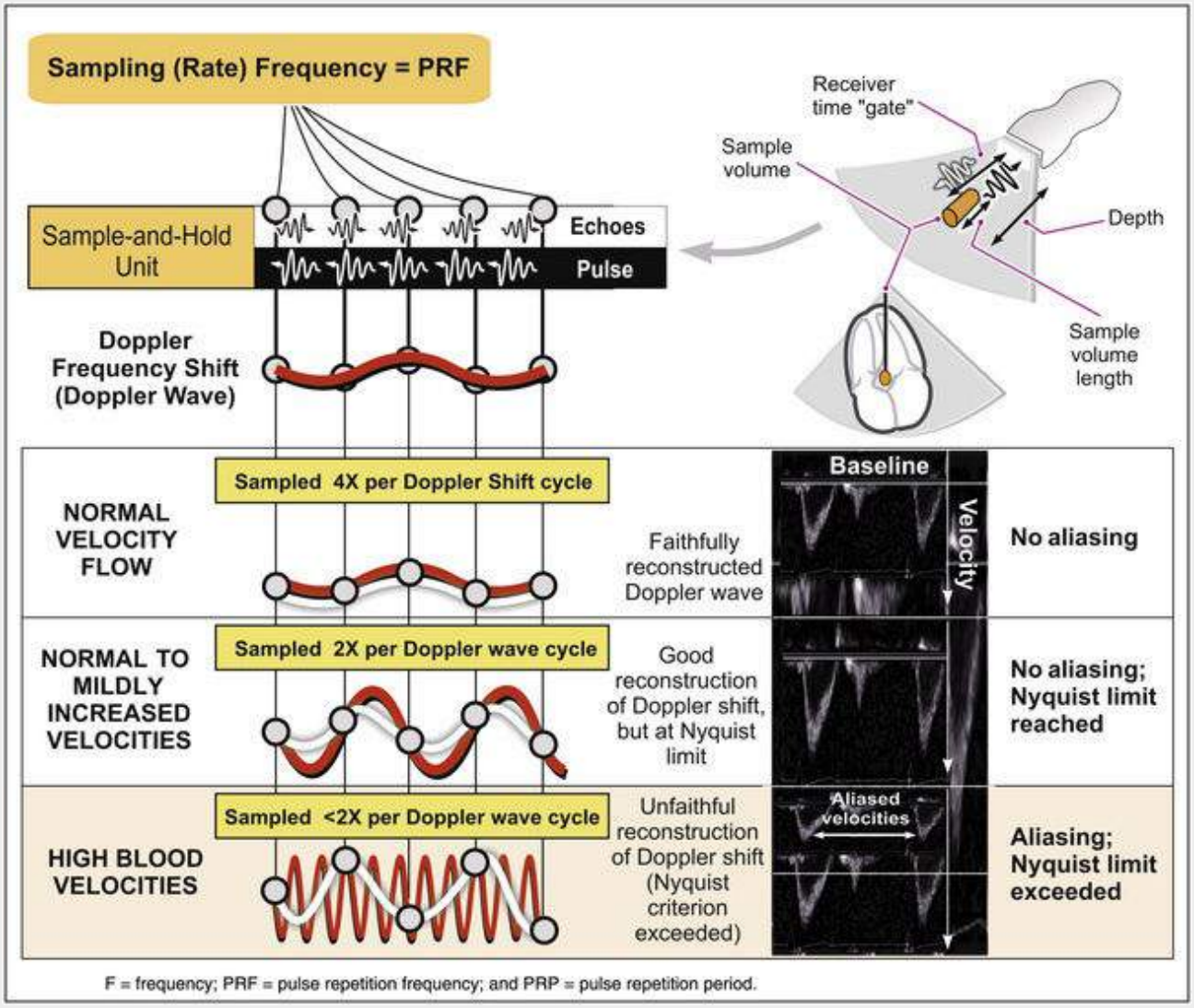


FIGURE 14.5 Pulsed-wave (PW) versus continuous-wave (CW) Doppler. **Left,** PW Doppler technique uses a single piezoelectric element that generates the pulse, interrogates a small sample volume at a specific depth, and receives the emerging echoes within the specified time window. **Right,** CW Doppler technique uses two separate transducer elements, one continuously transmitting pulses and the other receiving echoes across a large sample volume, and thus cannot localize the depth of the site with highest velocity.



EFIGURE 14.1 Velocities derived from Doppler frequency shifts are extracted through sampling and transformation (Fourier) before being graphically displayed. PW Doppler is subject to the limitation of aliasing when the Nyquist criterion or limit is exceeded, thus limiting the velocities that can be accurately depicted with this modality. The sampling frequency (pulse repetition frequency, PRF) must be at least twice the frequency of the sampled waveform. In Doppler ultrasound, the sampling rate must be high enough to sample the Doppler shift, which is the difference between the ultrasound frequency emitted by the transducer and the ultrasound frequency returning to the transducer. As shown by the Doppler equation, $f_d = \frac{2f_t V \cos\theta}{C}$, this difference, the Doppler frequency shift, is directly related to the velocity of the flow being assessed. PW Doppler can accurately sample and reconstruct lower blood velocities (from the Doppler shift) with no ambiguity (aliasing) **(upper panels)**. The frequency at which waveform sampling will become ambiguous is referred to as the Nyquist limit and is half the PRF. When velocities being assessed exceed the Nyquist limit, the system cannot accurately determine these velocities, and aliasing occurs **(lower panels)**. These higher aliased velocities will appear on the opposite side of the baseline on the spectral Doppler display or will result in mosaic patterns in color flow Doppler imaging. How can this problem be minimized? Simply increasing the PRF works only up to a certain point because the farther the ultrasound pulse has to travel, the greater the time delay must be between pulses to avoid ambiguity. Newer ultrasound machines can perform high-PRF Doppler imaging, in which pulses are emitted without waiting for the original pulses to return to the transducer. This allows an unaliased signal at the expense of some range ambiguity. The technique is meant to be used in conjunction with standard PW Doppler, with the operator determining the region of highest velocity along a scan line with color Doppler and then switching to the high-PRF mode to determine this velocity.

With CW Doppler (**Fig. 14.5, right panel**) a dedicated piezoelectric element continuously emits ultrasound, and a separate element simultaneously continuously receives the returning signals. Because the ultrasound tone is continuous rather than pulsed, depth of the target cannot be determined from the signal received. However, unlike the situation with PW Doppler, no limit is imposed on the velocities

discernible with this technique. *Thus PW Doppler is primarily used to assess flow with relatively low velocity (typically ≤1.5 m/sec) present at a specific location, whereas CW Doppler is used to assess higher velocities (typically ≥1.5 m/sec) along the transducer beam, but cannot specify at what location the highest velocity occurs.* Note that PW Doppler envelopes have a linear "hollowed-out" profile because the blood within the small sample volume tends to travel at similar velocities (laminar flow), whereas CW Doppler envelopes are "filled in" because all the varying velocities along the ultrasound beam are received and recorded.

Color Flow Doppler

Color flow Doppler is a PW Doppler–based technique in which the velocities in a region of interest are encoded with colors that represent both mean velocities and directionality of the flow, which are superimposed on a 2D image in the region of interest (**Fig. 14.6**). By convention, flow moving away from the transducer is encoded in blue, and flow toward the transducer is encoded in red. Because color flow Doppler is a form of PW Doppler, it is subject to aliasing, such that high velocities (greater than the Nyquist limit) demonstrate "wraparound" in the color coding to the color of the opposite direction. Turbulent flow, in which a wide range of velocities exist, appears as a multicolored mosaic pattern (usually green and yellow). In some systems the variance in the velocities relative to the mean is color-coded in superimposed shades of green. Color flow Doppler allows direct real-time visualization of the movement of blood in the heart and is particularly useful for identifying blood flow acceleration and turbulence. Therefore, this technology is useful for delineating both regurgitant lesions, in which blood moves rapidly and opposite to the expected direction of flow, and discrete stenoses in which there is flow acceleration.

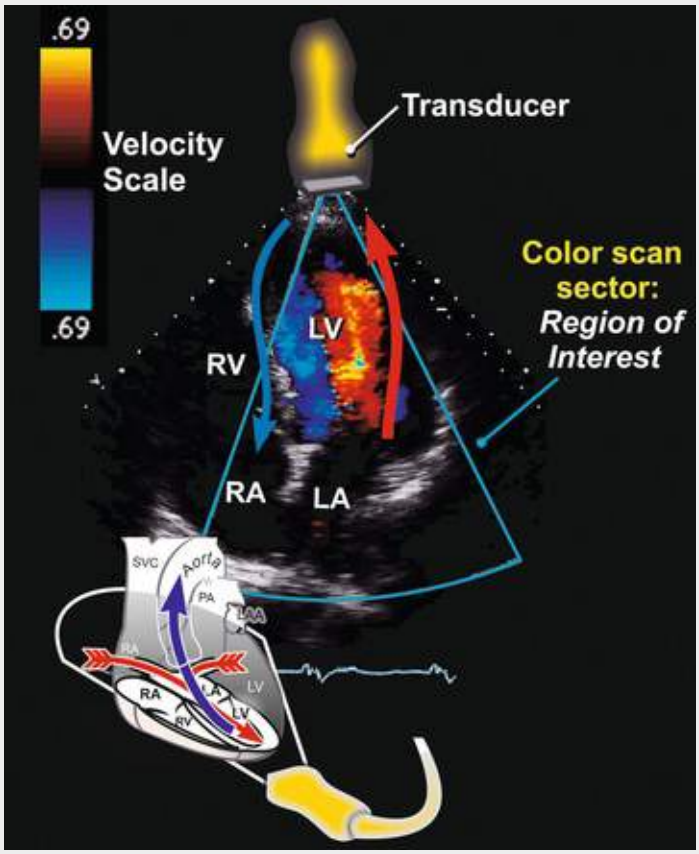


FIGURE 14.6 Color flow Doppler. By convention, blood flow moving toward the transducer is color-coded *red* and flow away from the transducer is shown in *blue*. The color velocity scale (*upper left vertical bar*) represents increasing velocities in either direction. with higher velocities depicted in progressively brighter hues. Note the Nyquist limit (69 cm/sec) displayed above and below the color scale bar. Velocities greater than the Nyquist limit cause aliasing, i.e., an apparent wraparound in the color-coding to that of the opposite direction. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (Modified from Bulwer BE, Rivero JM, editors. Echocardiography Pocket Guide: The Transthoracic Examination. Burlington, Mass: Jones & Bartlett Learning; 2011, 2013, p 156. Reprinted with permission.)

Blood Flow Profiles and Doppler Signals

Laminar Versus Turbulent Flow.

Blood flow through the normal heart and great vessels is predominantly *laminar,* meaning that the direction and velocity of flow are streamlined and uniform, even across valves. **Fig. 14.7** shows that the spectral Doppler flow signal observed when interrogating laminar flow is characterized by a hollowed-out waveform with a narrow outline, indicating that flow velocities throughout the sample are similar. In a Doppler assessment of the left ventricular outflow tract (LVOT), for example, the Doppler profile represents the velocity of blood flow throughout systole and is usually laminar. In contrast, valvular or vessel stenoses or obstructive lesions often cause turbulent flow, in which blood moves at different velocities and in multiple directions. In these cases the displayed spectrum of velocities will be wider on PW Doppler, a phenomenon termed *spectral broadening.* On color Doppler, turbulent flow appears brighter with mixture of colors.

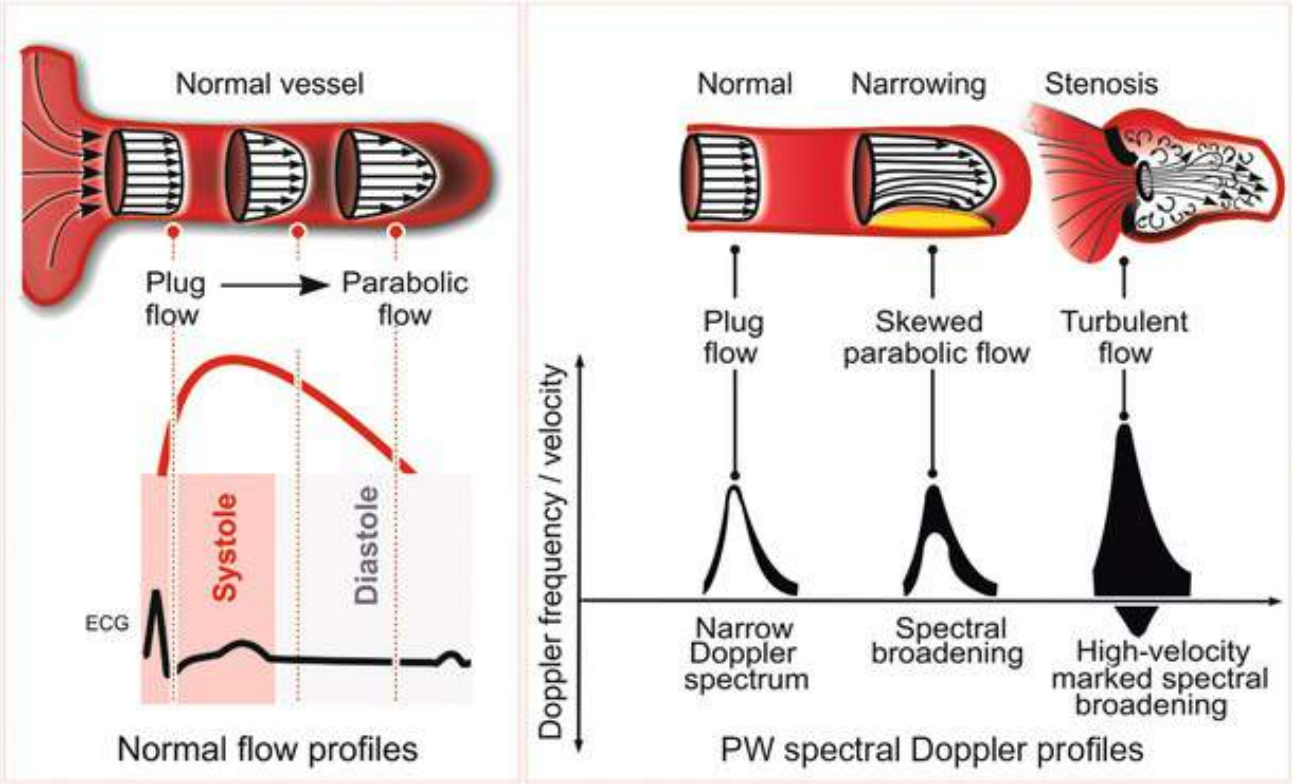


FIGURE 14.7 Flow velocity profiles on spectral Doppler. **Left,** During the cardiac cycle, most intracardiac and large arterial flows exhibit a laminar flow profile termed "plug flow" proximally that progresses distally to a more parabolic profile because of drag force and blood viscosity. **Right,** The narrowest range or spectrum of flow velocities is seen during the initial phases of systole or when valves open (plug flow). As the vessel becomes stenotic, the turbulence causes progressively wider variation in flow velocities and directions. On spectral Doppler this manifests as a splay in velocities both above and below the baseline. (Modified from Bulwer BE, Shernan SK, Thomas J. Physics of echocardiography. In Savage RM, Aronson S, Shernan SK, editors. Comprehensive Textbook of Perioperative Transesophageal Echocardiography. Philadelphia: Wolters Kluwer: Lippincott, Williams & Wilkins; 2009, p 23.)

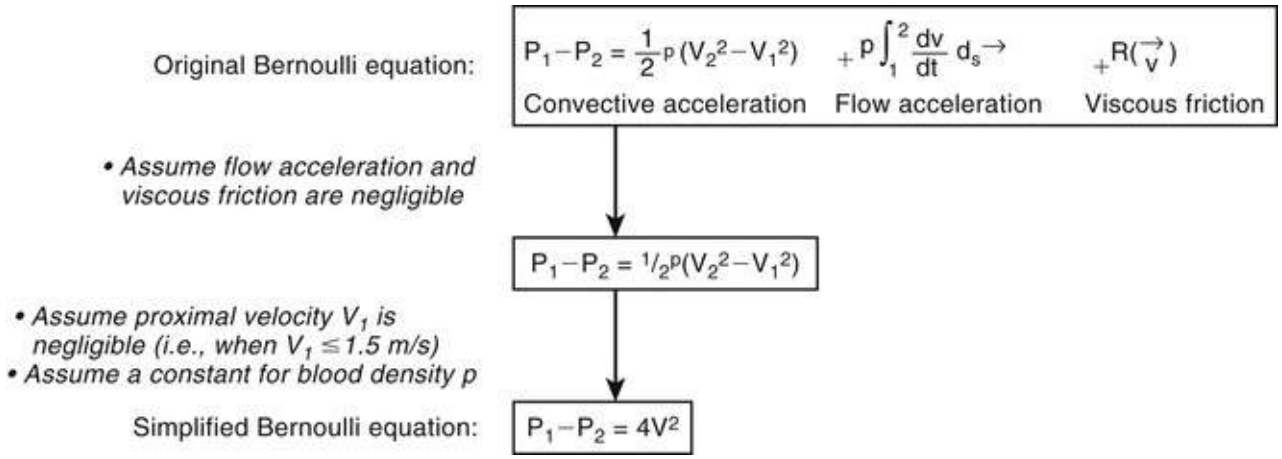
As illustrated by the Doppler equation and discussed earlier, the velocity of blood flow determined from the Doppler shift will change with the angle of insonation. If the vector of flow is not directly in line with the ultrasound beam, the velocities calculated by the Doppler shift will be underestimated. This problem can be corrected by applying an angle adjustment that is computed in at the machine level. However, the further the angle of flow deviates from the angle of the beam, the greater the likelihood for error in the calculation. In practice, for cardiac ultrasound it is recommended simply to minimize the angle of insonation as much as possible by probe and patient positioning and to avoid Doppler assessments that are substantially off-angle. It is for this reason that multiple windows are used in assessing peak flow velocities of aortic stenosis and tricuspid regurgitation, so that the lowest angle of insonation can be selected to avoid underestimation. In specific cases where flow is very laminar and insonation angles are unavoidable, such as in vascular ultrasound, the correction factor proves to be useful.

Doppler Echocardiography in Practice

Doppler echocardiography is used primarily to assess blood flow velocity in the heart and blood vessels. Within the heart the velocity of blood flow is itself dependent on the pressure gradient between cardiac chambers, with higher gradients resulting in higher velocities. This relationship can be described by the Bernoulli equation, which estimates the pressure gradient (ΔP) between two chambers separated by an orifice based on the velocity of flow through the orifice. The original Bernoulli equation (**eFig. 14.2**) is

complex and includes variables for flow acceleration and viscous friction and a constant for fluid density. The clinical equation used in echocardiography assumes that these two factors are negligible, and that the velocity (V_1) proximal to an orifice is relatively low in comparison to that distal velocity. This leaves the vastly simplified equation for use in clinical echocardiography for ΔP:

$$\mathbb{P}_1 - \mathbb{P}_2 = 4\mathbb{V}^2$$



EFIGURE 14.2 The Bernoulli equation. Derivations of the Bernoulli equation as applied to echocardiography. This equation is used to estimate the pressure difference $\Delta P = P_1 - P_2$ across orifices or stenoses in the heart. Simply put, the narrower the orifice, and the higher the change in velocity (and thus the higher the pressure gradient).

For example, the peak flow velocity of a tricuspid regurgitant jet can be used to calculate the pressure gradient ΔP between the right ventricle and the right atrium, which when added to an estimate of right atrial (RA) pressure, provides an estimate of right ventricular systolic pressure (and hence pulmonary artery systolic pressure in most cases). Similarly, the blood flow velocity difference between the LVOT and the aorta can be used to calculate the peak instantaneous pressure gradient across a stenotic aortic valve. It is important to appreciate that Doppler echocardiography measures *velocity* but neither pressure nor flow directly. Pressure gradients are inferred from velocities based on the Bernoulli equation, but the absolute pressure within chambers cannot be directly measured as in cardiac catheterization. Similarly, the amount of flow cannot be measured directly, although there are Doppler-based methods that permit fairly accurate estimation of flow volumes (see later).

Assessment of Flow and Continuity Equation

Doppler methods are used to assess blood flow velocities, but the magnitude of flow can also be inferred by multiplying the *velocity-time integral* (VTI; i.e., integrated velocity throughout the cardiac interval) by the cross-sectional area (CSA) of the region being interrogated (**Fig. 14.8**). For example, stroke volume (SV) can be estimated by interrogating the LVOT region with PW Doppler and multiplying the VTI by the CSA (calculated by measuring the diameter of the LVOT and assuming a circular area = πr^2):

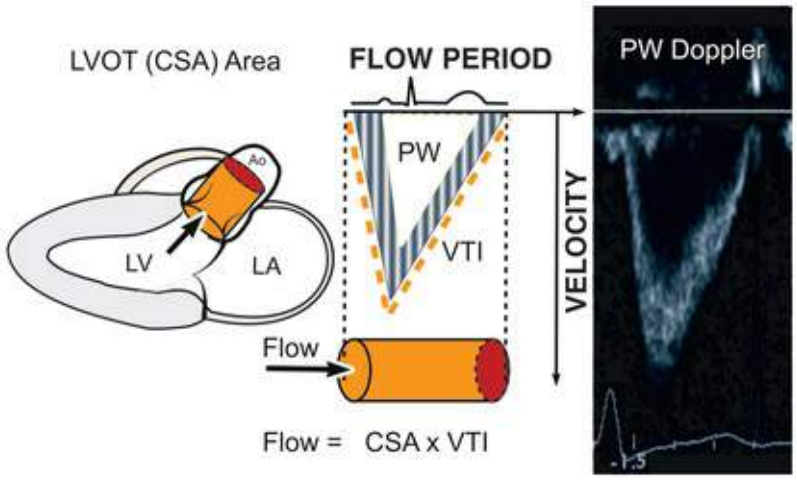


FIGURE 14.8 Volumetric flow assessments using spectral Doppler. The volume of a cylinder is cross-sectional area (CSA) multiplied by length. Using this geometric assumption and assuming constant flow during systole, stroke volume (SV) can then be derived from the CSA of the left ventricular outflow tract (LVOT) measured on the parasternal long-axis view. This is then multiplied by the Doppler velocity-time integral (VTI) measured on apical windows. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle.

$$SV = VTI_{LVOT} \times Area_{LVOT}$$

The continuity principle is based on conservation of mass and states that flow in one region of the heart should be equivalent to flow in another region (assuming no intervening shunt). It can be used together with Doppler analysis to determine an unknown area, such as that of a stenotic valve. The CSA of a stenotic valve can be difficult to measure directly (i.e., by planimetry) if image quality is suboptimal. By measuring the CSA and VTI proximal to the valve and the VTI at the valve itself with 2D and Doppler imaging, the area of stenosis can be calculated. Since velocities through stenotic valves are usually too high to assess with PW Doppler, CW Doppler is usually used, assuming that the highest attained velocities correspond to the narrowest region along the ultrasound beam. Because the continuity principle states that flow through the LVOT must equal flow through the aortic valve (AV),

$$VTI_{LVOT} \times Area_{LVOT} = VTI_{AV} \times Area_{AV}$$

rearranging the equation to solve for $Area_{AV}$ will give the desired valve CSA. The accuracy of this estimate depends on the accuracy of the LVOT CSA calculation (and thus LVOT diameter measurement) and optimal positioning of the PW and CW Doppler cursor.

The Standard Adult Transthoracic Echocardiographic Examination

The standard adult TTE examination consists of a combination of 2D, M-mode, and Doppler imaging. The recommended comprehensive examination protocol involves a series of views, each of which is described in terms of three principal components: (1) the standard transducer position or “window,” (2) the orthogonal imaging planes, and (3) the anatomic region of interest (**Figs. 14.9 and 14.10**). At each

transducer position the operator optimally acquires 2D images with M-mode images, spectral Doppler, and color flow Doppler as indicated.

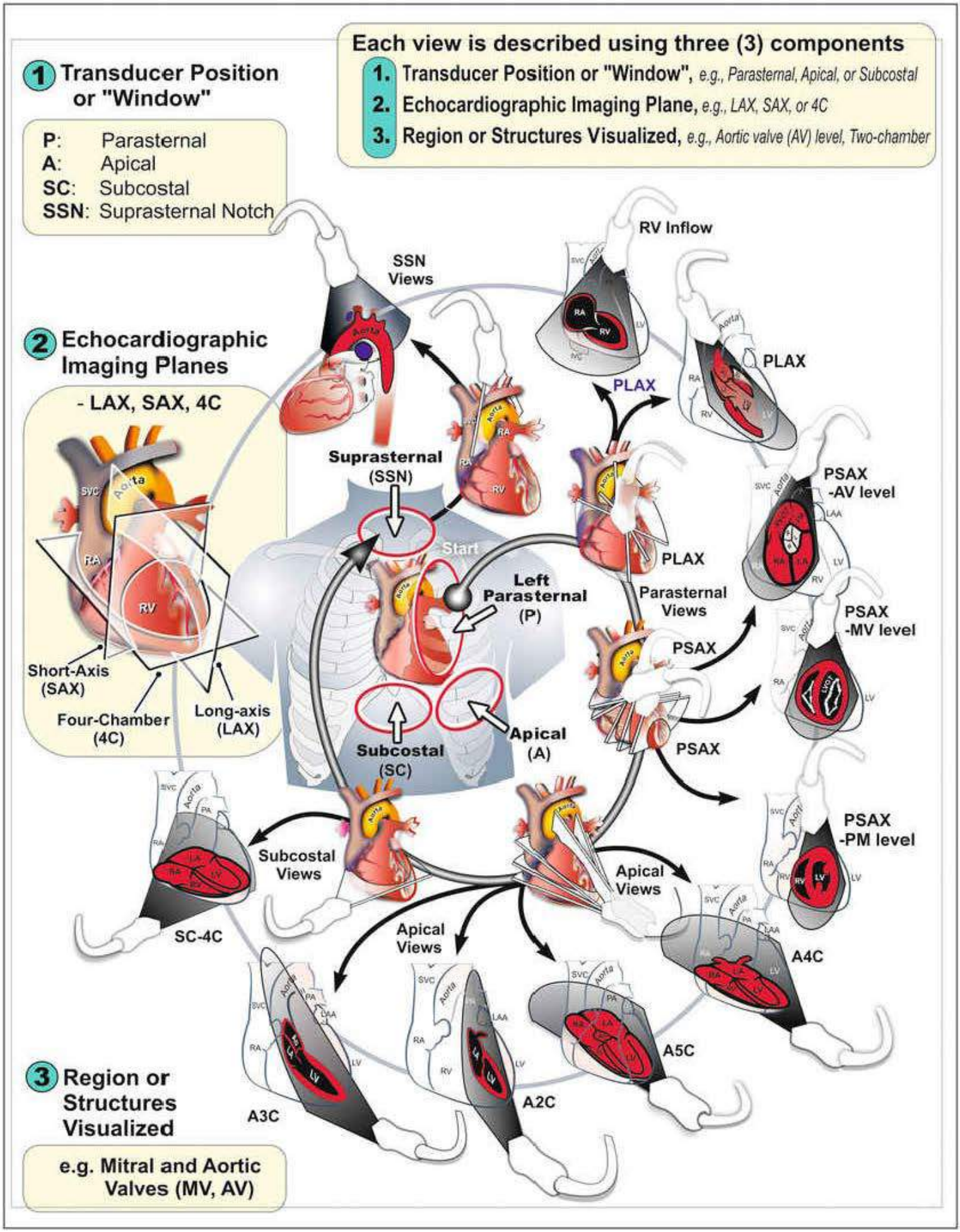


FIGURE 14.9 Standard adult transthoracic echocardiography imaging planes, protocol, and nomenclature recommended by the American Society of Echocardiography (ASE). Each echocardiographic view can be described by three parameters: window, plane, and structure visualized.

See Fig. 14.10 for abbreviations. (Modified from Bulwer BE, Shernan SK, Thomas JD. Physics of echocardiography. In Savage RM, Aronson S, Shernan SK, editors. Comprehensive Textbook of Perioperative Transesophageal Echocardiography. Philadelphia: Wolters Kluwer: Lippincott, Williams & Wilkins; 2009, pp 1-41.)

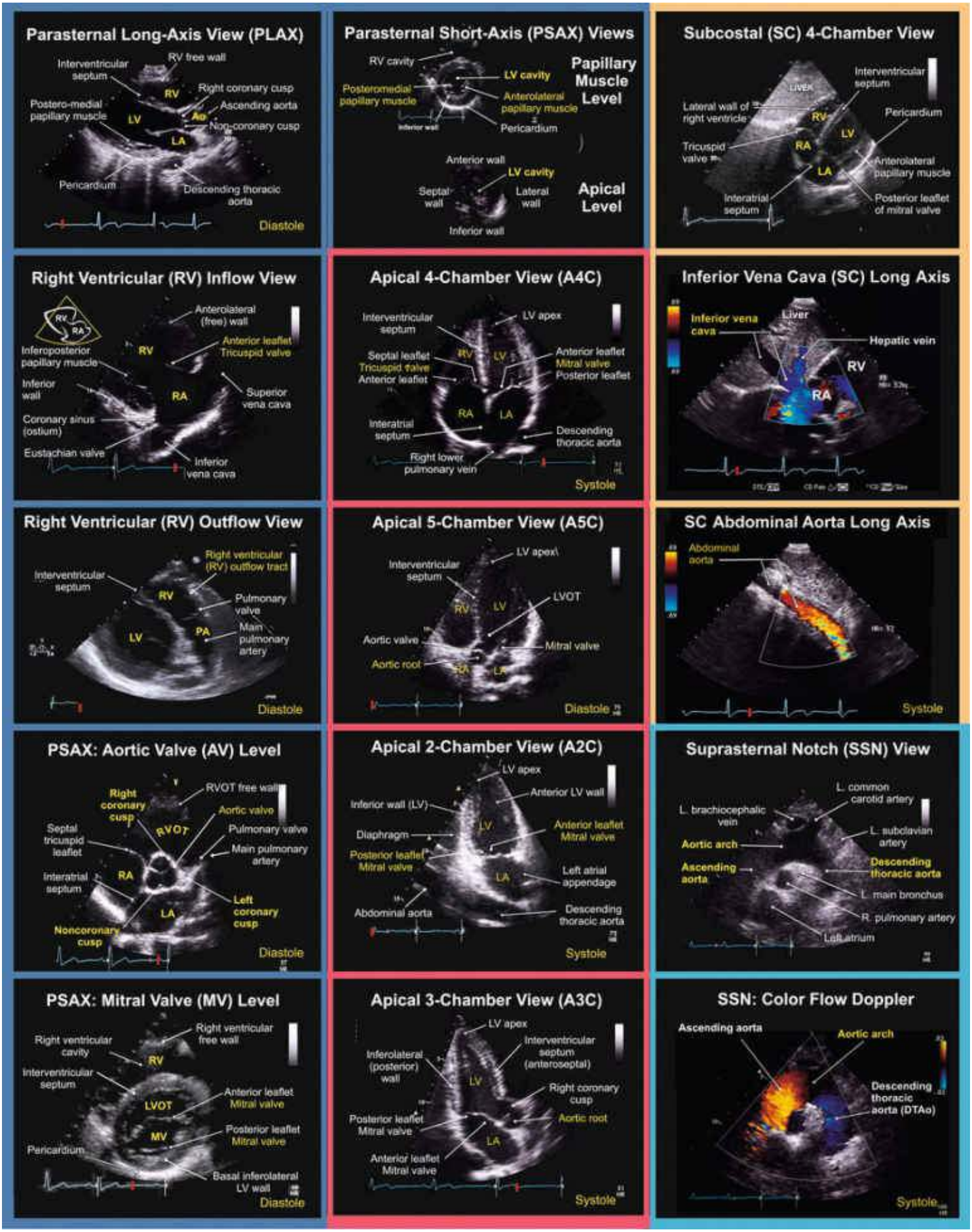


FIGURE 14.10 Labeled still frames of standard adult TTE views. Compare with **Fig. 14.9**. *Ao,* Aorta; *LA,* left atrium; *RA,* right atrium; *LV,* left ventricle; *RV,* right ventricle; *PA,* pulmonary artery; *LVOT,* left ventricular outflow tract.

M-Mode Echocardiography

M-mode echocardiography provides greater temporal resolution than does standard 2D imaging and remains the method of choice for certain linear measurements, particularly those that are collinear with the ultrasound beam. Standard reports will include measurements of septal and posterior wall thickness and left ventricular (LV) chamber dimensions on parasternal views by convention (**Fig. 14.11A** shows a normal M-mode at the basal left ventricle). Because M-mode echocardiography is essentially a one-dimensional imaging technique, it has several limitations that should be recognized. For accurate measurements the cursor scan line must be oriented perpendicular to the long axis of the left ventricle or left atrium, which may require operator or machine correction to achieve. M-mode–based estimates of LV volume, mass, and function can be inaccurate in patients with LV geometries that deviate substantially from normal, such as those with aneurysms or focal wall motion abnormalities. M-mode of valvular leaflets is of historical importance for diagnosis and still remains useful for demonstrating abnormalities in valvular motion, including rheumatic mitral stenosis, mitral valve prolapse, and systolic anterior motion of the mitral valve as occurs in obstructive hypertrophic cardiomyopathy (HCM) (**Fig. 14.11**). M-mode can also be combined with 2D imaging to reveal subtle changes in interventricular septal motion and chamber wall movement in pericardial disease. In combination with color flow Doppler (color M-mode), accurate information about the timing and direction of flow and assessment of diastolic function can also be augmented.

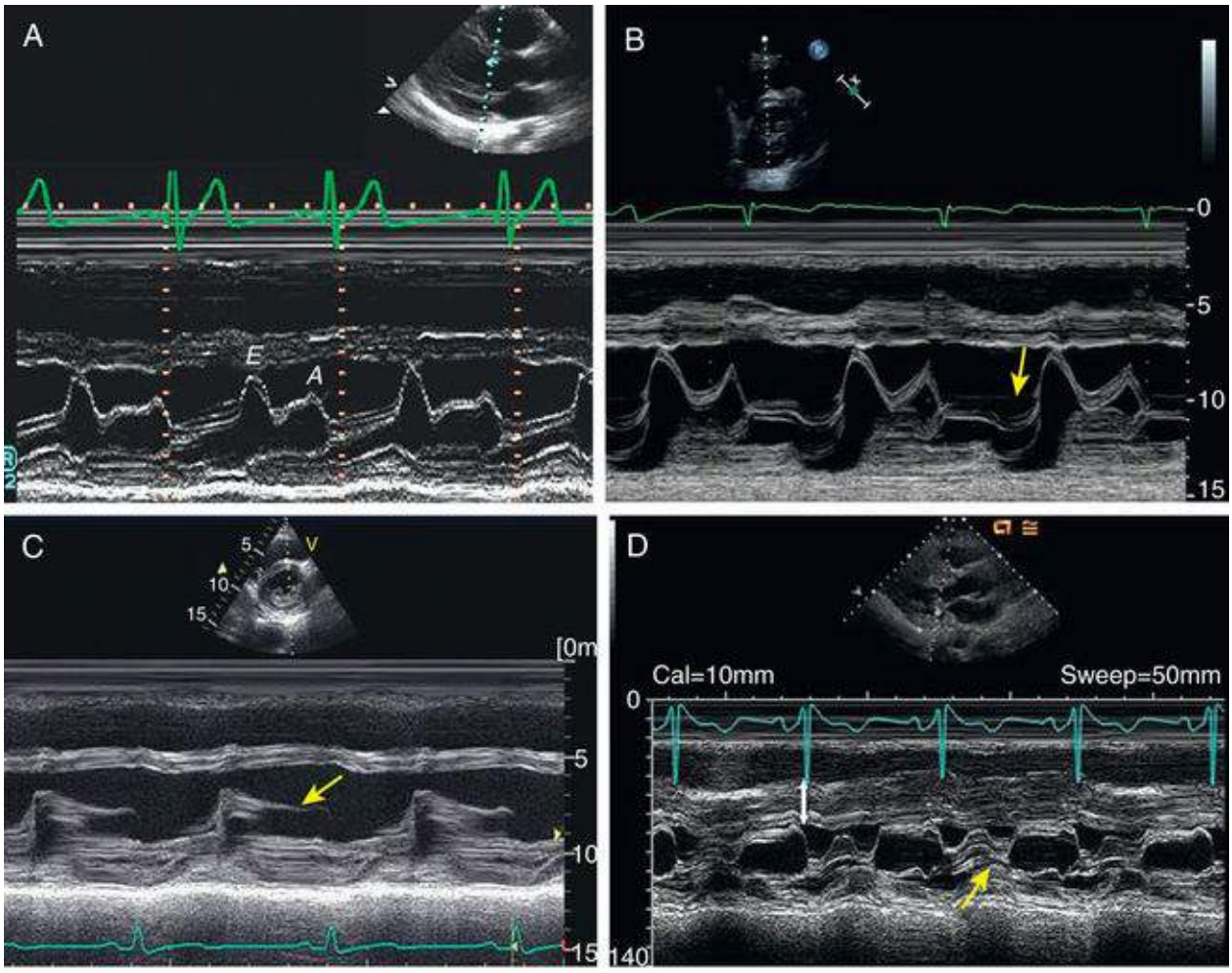


FIGURE 14.11 M-mode tracings. **A**, Normal M-mode across the base of the left ventricle at the level of the mitral leaflet tips. Note the E and A waves corresponding to the anterior mitral leaflet motion in early diastole (E) and with atrial contraction (A), respectively. Compare with **B,** which shows a patient with mitral valve prolapse, where there is late systolic posterior bowing (*arrow*) of the mitral leaflets on M-mode. **C,** Rheumatic mitral stenosis, with thickened mitral leaflets that move parallel to each other, straightening of the slope after the E wave (E-F slope), and reduced leaflet opening in diastole. **D,** Hypertrophic obstructive cardiomyopathy, displaying a very thickened interventricular septum (*white double-headed arrow*) and systolic anterior motion of the mitral valve leaflets (*yellow arrow*).

Imaging Artifacts

Ultrasound imaging artifacts are ubiquitous in echocardiography and are incurred by the physical principles of ultrasound. Artifacts can include the resemblance of structures that do not exist or that can be caused by real structures, such as the ribs obscuring visualization of the heart. Most artifacts are caused by physical interactions between ultrasound and tissue. Common artifacts include (1) *attenuation artifacts*, which result in "shadowing" typically caused by ribs or bony structures; (2) *side lobe artifacts*, which occur when lower-energy side beams (side lobes) aside from the main ultrasound beam reflect off of lateral structures and are mapped onto the central image; (3) *multiple reflection artifacts*, in which the sound waves bounce between a strong reflector, often the pericardium, pleura, or aortic wall, and the transducer more than once, giving rise to mirror images (Video 14.1) or near-field clutter; and (4) *reverberation artifacts*, which are caused by continuing repetition of internal reflections, often seen behind mechanical valve prostheses or left ventricular assist device (LVAD) cannulas (**Fig. 14.12**). One type of reverberation artifact, the *comet-tail artifact*, can be useful diagnostically to detect interstitial fluid in the lungs.

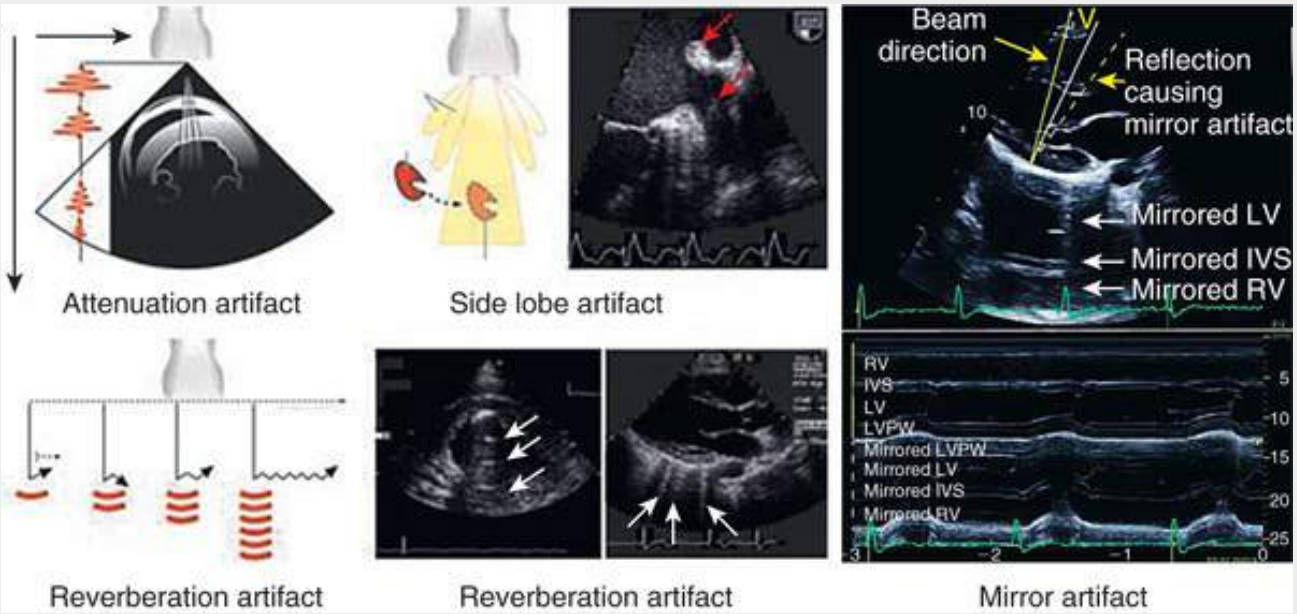


FIGURE 14.12 Common imaging artifacts seen in echocardiography. Attenuation artifacts, caused by diminution in ultrasound beam intensity with increasing depth, resulting in fading and dropout **(upper left)**. Side lobe artifacts occur when structures in the path of the side lobe beams are erroneously mapped into the image **(upper middle)**. Reverberation artifacts are common **(lower left and middle panels)**. They may be large, as in the case of reflections from the inflow tube of an LVAD (three parallel *arrows,* below center), or appear as fine comet-tail or "ring-down" artifacts because of multiple reverberations that invariably occur at the highly specular epicardial-pleural interface **(lower right)**. **Right panels,** Mirror artifact, caused by reflection between tissue interfaces and the transducer.

Assessment of Cardiac Structure and Function

The primary goal of the echocardiographic examination remains assessment of cardiac structure and function. Each chamber, valve, and great vessel can be assessed qualitatively and quantitatively to define any alterations in size, geometry, and patency. Measurements of cardiac structures are typically made in various locations throughout the heart, and linear, area, or volumetric measures can be obtained. These methods are often complementary to one another. For example, although volumetric measurements of the left ventricle (see later) are generally considered best suited to characterize LV size, many laboratories continue to record linear cavity measurements, because there is extensive literature correlating these measures with outcomes in numerous disease states. Moreover, linear measures may be subject to less variability than area- or volume-based measures and therefore may be more reliable for assessing changes over time.

Tables 14.1 to 14.3 show established normal values on echocardiography. For LV linear dimensions and volume, **Table 14.1** gives the normal ranges for the general population, but ideally one should take into account not only sex, but also body surface area (BSA) and age[2] (**eFigs. 14.3 and 14.4**). Current American Society of Echocardiography (ASE) consensus statements also provide partition values—that is, mild, moderate, and severely abnormal ranges—for LV size, mass, and ejection fraction and left atrial (LA) volume, but caution that the ranges were arrived at by experience-based consensus only, and that degree of abnormality does not necessarily connotate a direct correlation with outcomes or prognosis (**Table 14.2**). Normal values for LV parameters obtained with 3D echocardiography also exist and appear accurate and reproducible when image quality is good. In general, LV volumes calculated by 3D imaging are smaller than data generated from CMR data, but correlations with trends in sex and body surface area hold true.[2]

TABLE 14.1

Normal Values for Two-Dimensional Echocardiographic Parameters of Left Ventricular Size and Function According to Sex

Parameter	MALE		FEMALE	
	Mean ±SD	2-SD Range	Mean ±SD	2-SD Range
Left Ventricular (LV) Internal Dimension				
Diastolic dimension (mm)	50.2 ±4.1	42.0-58.4	45.0 ±3.6	37.8-52.2
Systolic dimension (mm)	32.4 ±3.7	25.0-39.8	28.2 ±3.3	21.6-34.8
LV Volumes (Biplane)				
LV EDV (mL)	106 ±22	62-150	76 ±15	46-106
LV ESV (mL)	41 ±10	21-61	28 ±7	14-42
LV Volumes Normalized by Body Surface Area				
LV EDV (mL/m^2)	54 ±10	34-74	45 ±8	29-61
LV ESV (mL/m^2)	21 ±5	11-31	16 ±4	8-24
LV EF (biplane)	62 ±5	52-72	64 ±5	54-74

EDV, End-diastolic volume; *EF,* ejection fraction; *ESV,* end-systolic volume; *SD,* standard deviation.

From Lang RM, Badano LP, Mor-Avi Victor, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1.

TABLE 14.2

Normal Ranges and Severity Partition Cutoff Values for Two-Dimensional Echocardiography–Derived Left Ventricular Ejection Fraction (LVEF) and Left Atrial (LA) Volume

	MALE				FEMALE			
	Normal Range	Mildly Abnormal	Moderately Abnormal	Severely Abnormal	Normal Range	Mildly Abnormal	Moderately Abnormal	Severely Abnormal
LVEF (%)	52-72	41-51	30-40	<30	54-74	41-53	30-40	<30
Max LA vol/BSA (mL/m^2)	16-34	35-41	42-48	>48	16-34	35-41	42-48	>48

BSA, Body surface area.

From Lang RM, Badano LP, Mor-Avi Victor, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1.

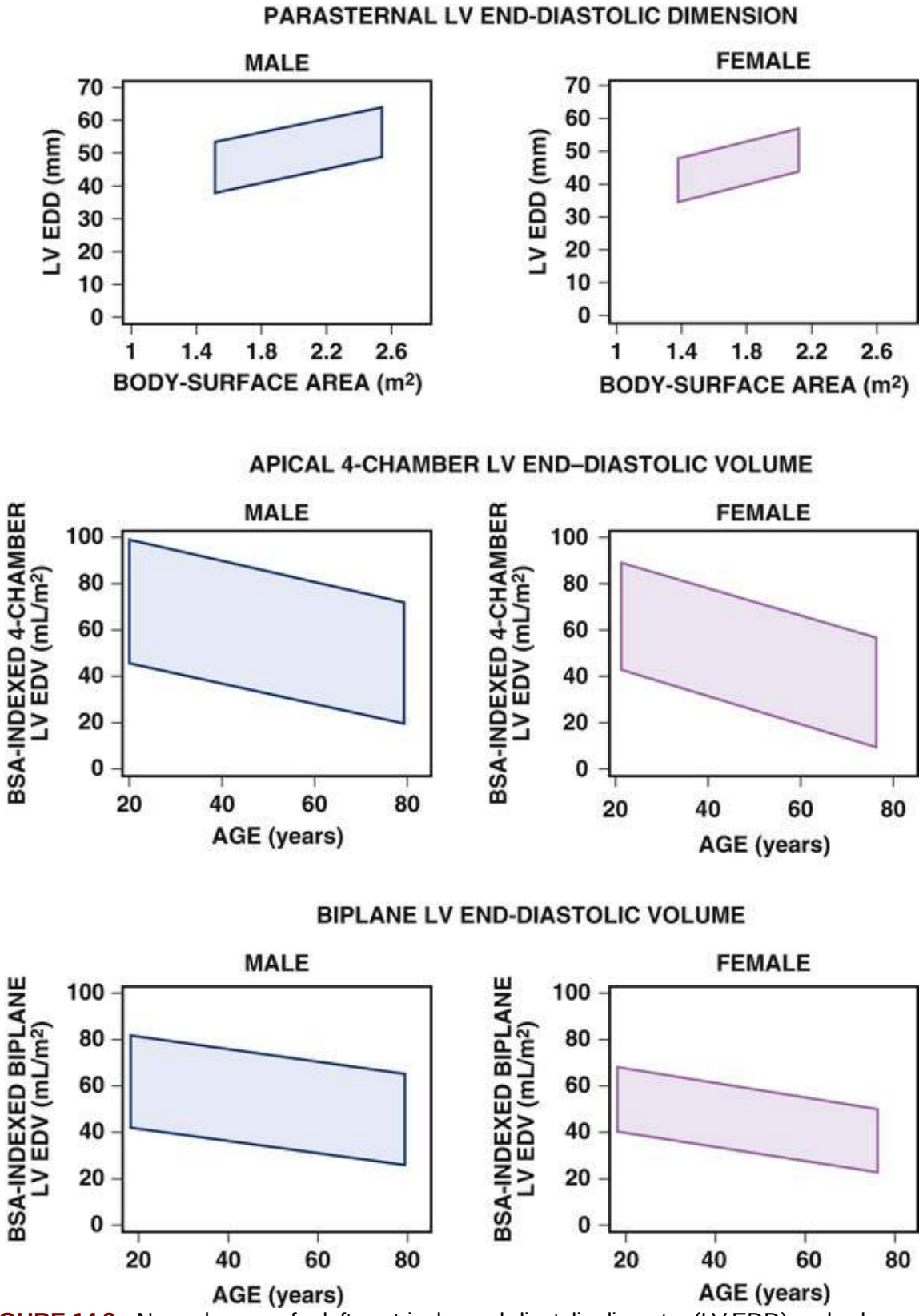
TABLE 14.3

Normal Ranges for Left Ventricular (LV) Mass Indices

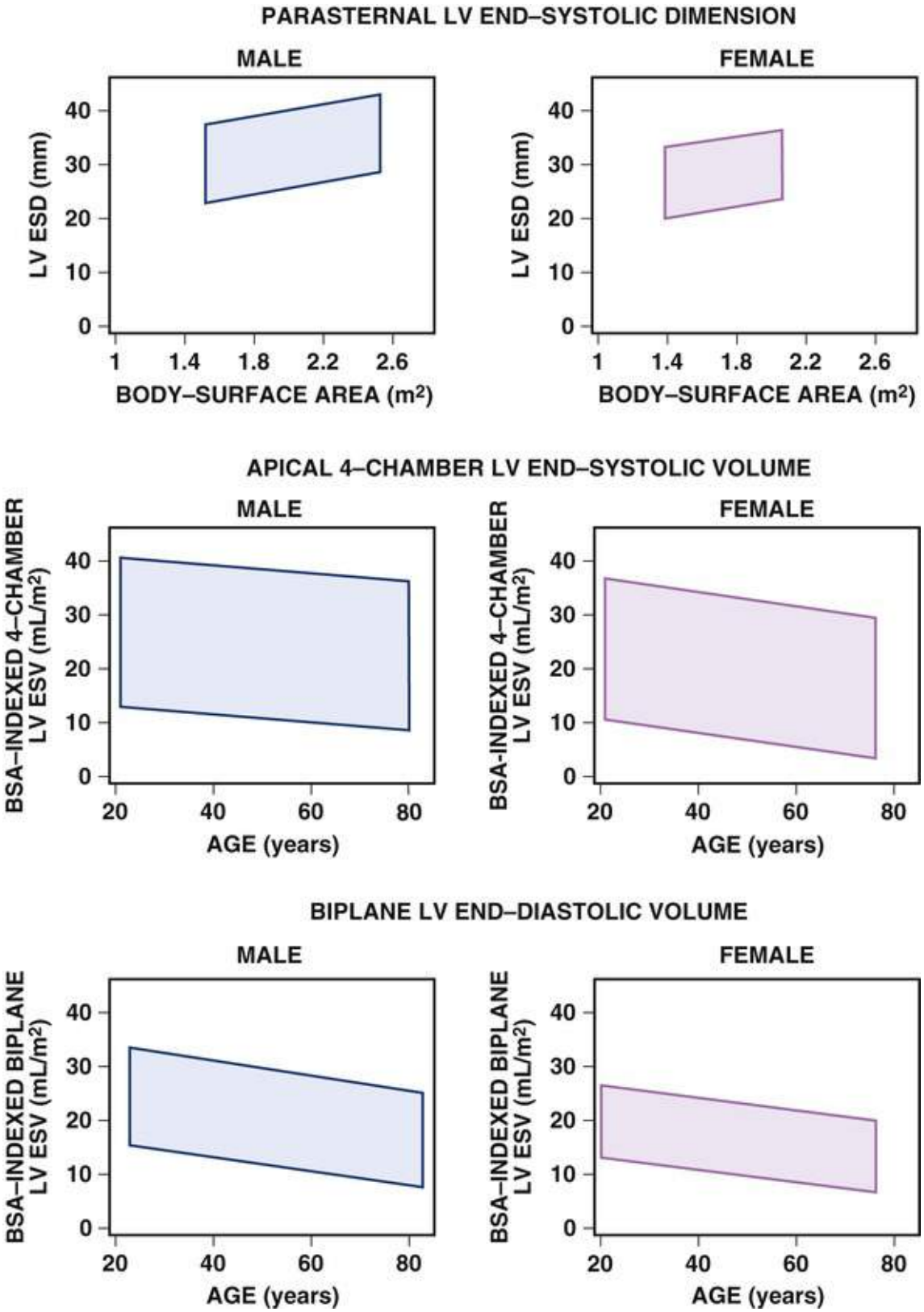
INDEX	WOMEN	MEN
Linear Method		
LV mass (g)	67-162	88-224
LV mass/BSA (g/m^2)	***43-95***	***49-115***
Relative wall thickness (cm)	0.22-0.42	0.24-0.42
Septal thickness (cm)	***0.6-0.9***	***0.6-1.0***
Posterior wall thickness (cm)	***0.6-0.9***	***0.6-1.0***
Two-Dimensional Method		
LV mass (g)	66-150	96-200
LV mass/BSA (g/m^2)	***44-88***	***50-102***

Bold/italic values: Recommended and best validated.

From Lang RM, Badano LP, Mor-Avi Victor, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1.



EFIGURE 14.3 Normal ranges for left ventricular end-diastolic diameter (LV EDD) and volumes (LV EDV). For men **(left)** and women **(right),** the 95% confidence intervals for the following measurements are presented: LV end-diastolic dimension measured from a parasternal long-axis window on the basis of body surface area (BSA) **(top),** BSA-indexed LV EDV measured from an apical four-chamber view on the basis of age **(middle),** and BSA-indexed biplane LV EDV on the basis of age **(bottom).** For example, a normal BSA-indexed LV EDV measured from the four-chamber view in a 40-year-old woman would fall between approximately 30 and 78 mL/m^2. Similar charts for absolute (non-BSA indexed) LVEDV versus age (including two-chamber measurements) can be found in the following credit reference (Lang RM et al.) and its Supplemental Fig. 1. Absolute LVEDV versus BSA (including two-chamber measurements, without breakdown for age) can also be found within the Lang RM et al. reference, in Supplemental Fig. 3. (From Lang RM, Badano LP, Mor-Avi Victor, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1.)



EFIGURE 14.4 Normal ranges for LV end-systolic diameter (LV ESD) and volumes (LV ESV). For men **(left)** and women **(right),** the 95% confidence intervals for the following measurements are presented: LV end-systolic dimensions measured from a parasternal long-axis window on the basis of BSA **(top),** BSA-indexed LV ESVs measured from an apical four-chamber view on the basis of age **(middle),** and BSA-indexed biplane LV ESVs based on age **(bottom).** Similar charts for absolute (non-BSA indexed) LVESV versus age (including two-chamber measurements) can be found within the credit reference (Lang RM et al.) and its Supplemental Fig. 2. Absolute LVESV versus BSA indexing (including two-chamber measurements, without breakdown for age) can also be found in the Lang reference and Supplemental Fig. 4. (From Lang RM, Badano LP, Mor-Avi Victor, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1.)

Left Ventricular Structure: Size and Mass

Historically, LV volumes can be estimated from one of several formulas that use either linear or 2D measurements to calculate a volume based on the assumption that the left ventricle approximates a prolate ellipsoid or cylinder hemiellipsoid shape (**Fig. 14.13**). These approaches had the advantages of being relatively reproducible and simple to calculate. Much published research relies on M-mode data, but the estimation of LV volume is less accurate when ventricular geometry deviates from normal because of wall motion abnormalities or remodeling. For all LV geometries, the modified biplane Simpson method of discs has been demonstrated to be the most accurate method and is recommended (**Fig. 14.14**). This method requires tracing the endocardial border in the apical four- and two-chamber views with computerized assistance to measure the diameter and height of equally distributed slices along the ventricle. With these measurements, the volume of each axial slice can be calculated, and the volume of all the slices summed to give the total chamber volume. The method is very accurate when image quality is good. However, in actual practice, suboptimal image quality can make definition of the endocardial border challenging. Moreover, foreshortening of the ventricle in one of the apical views, which can occur simply by minor changes in the transducer angle, can dramatically reduce the measured volume. The development and utilization of LV echocardiographic contrast, 3D echocardiography, and strain analysis can mitigate the impact of these limitations (see later) and appear to permit greater accuracy and reproducibility.

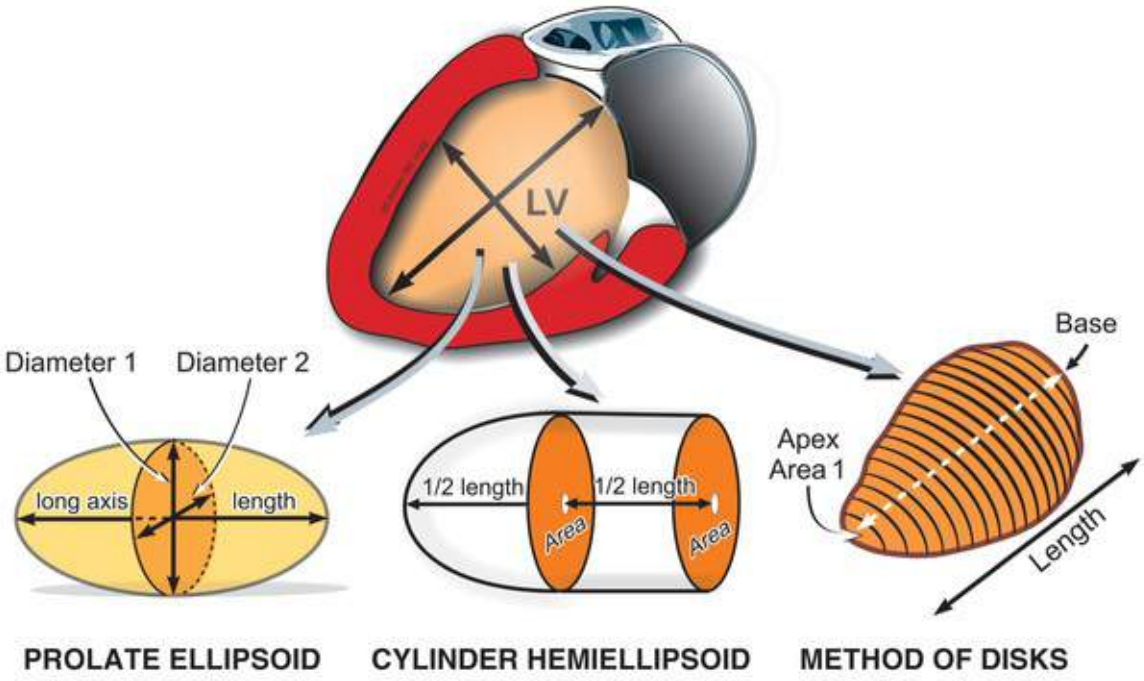


FIGURE 14.13 Geometric models and assumptions used in quantification of volumes of the left ventricle (*LV*) in two-dimensional echocardiography. (Modified from Bulwer BE, Rivero J, Solomon SD. Basic principles of echocardiography and tomographic anatomy. In Solomon SD, editor. Atlas of Echocardiography. 2nd ed. Philadelphia: Current Science/Springer Science; 2009, pp 1-24.)

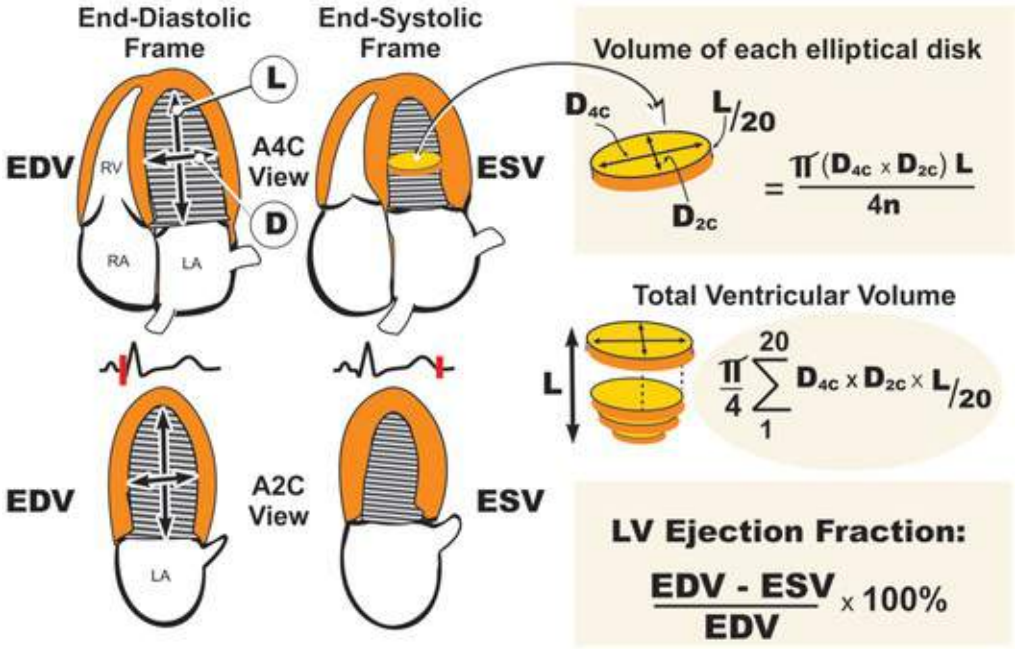
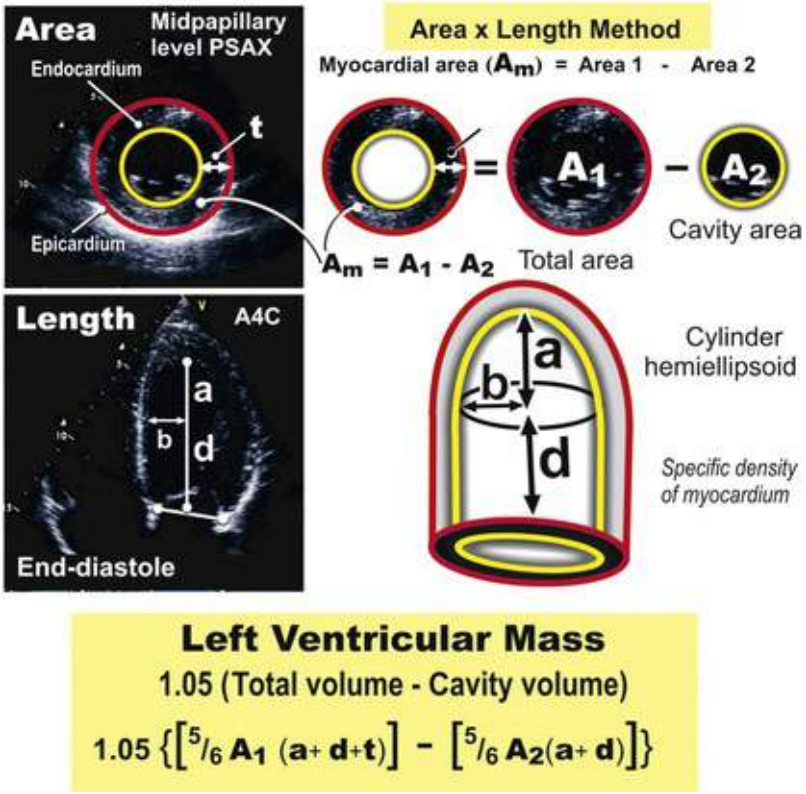


FIGURE 14.14 Simpson method of discs for quantification of left ventricular (LV) volumes and LV ejection fraction on two-dimensional (2D) echocardiography. *A2C,* Apical two-chamber view; *A4C,* apical four-chamber view; *D,* LV diameter; *EDV,* end-diastolic volume; *ESV,* end-systolic volume; *L,* LV length; *n,* number of discs. (Modified from Bulwer BE, Rivero J, Solomon SD. Basic principles of echocardiography and tomographic anatomy. In Solomon SD, editor. Atlas of Echocardiography. 2nd ed. Philadelphia: Current Science/Springer Science; 2009, pp 1-24.)

Left ventricular mass may be calculated by using one of several formulas that take into account both wall thickness and chamber size,[2] typically using either linear (M-mode) or 2D measurements together with geometric modeling of the shape of the LV myocardial "shell" (**eFig. 14.5**). These formulas have been validated in normal ventricles; however, as in volume calculations, accuracy suffers when applied to abnormally shaped ventricles. 3D datasets, in which wall thicknesses are measured at a multitude of points and mass is calculated without assumptions about cavity geometry, appear more accurate but again depend on image quality. Normal values are also less well established for 3D data.



EFIGURE 14.5 LV mass calculation in 2D echocardiography using an area-length method for a cylinder hemiellipsoid. Area 1 (A_1) is the total planimetered area at the mid-LV level on the parasternal short-axis (PSAX) view in diastole; area 2 (A_2) is the planimetered LV cavity area; A_m is the myocardial "shell" area; *b,* minor axis radius; *t,* wall thickness. (Modified from Bulwer BE, Rivero J, Solomon SD. Basic principles of echocardiography and tomographic anatomy. In Solomon SD, editor. Atlas of Echocardiography. 2nd ed. Philadelphia: Current Science/Springer Science; 2009, pp 1-24.)

With all methods, care must be taken to measure the walls at end-diastole, because small errors may be exponentially multiplied depending on the calculation used; **Table 14.3** shows currently accepted normal values. An LV mass index (derived from 2D measurements) of greater than 95 g/m^2 for women or more than 115 g/m^2 for men is considered abnormally high. Pathologically, LV *hypertrophy* is defined as increased overall LV mass and is distinct from wall thickness per se. However, in general, if LV diameter is not decreased, wall thicknesses of 12 mm or more correlates with LV hypertrophy. Alterations in LV size and mass can be categorized based on the ratio of relative wall thickness to the total LV mass index (**Fig. 14.15**). The specific pattern of ventricular remodeling has been related to prognosis in a variety of diseases, of both myocardial and valvular etiology.[3]

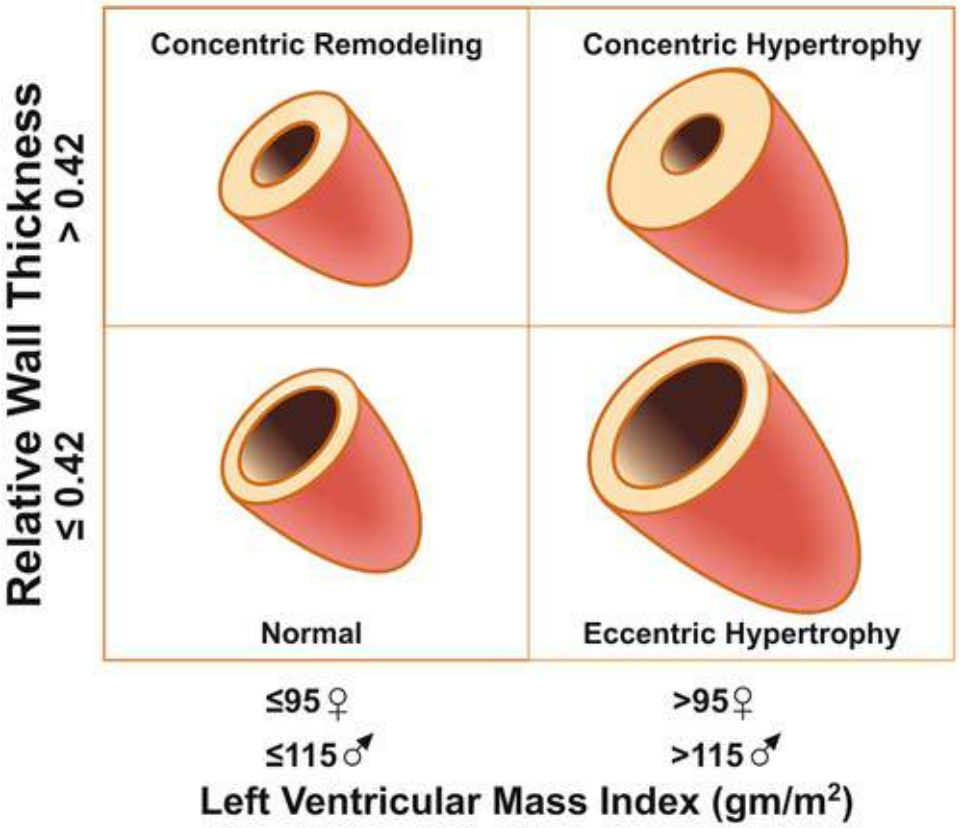


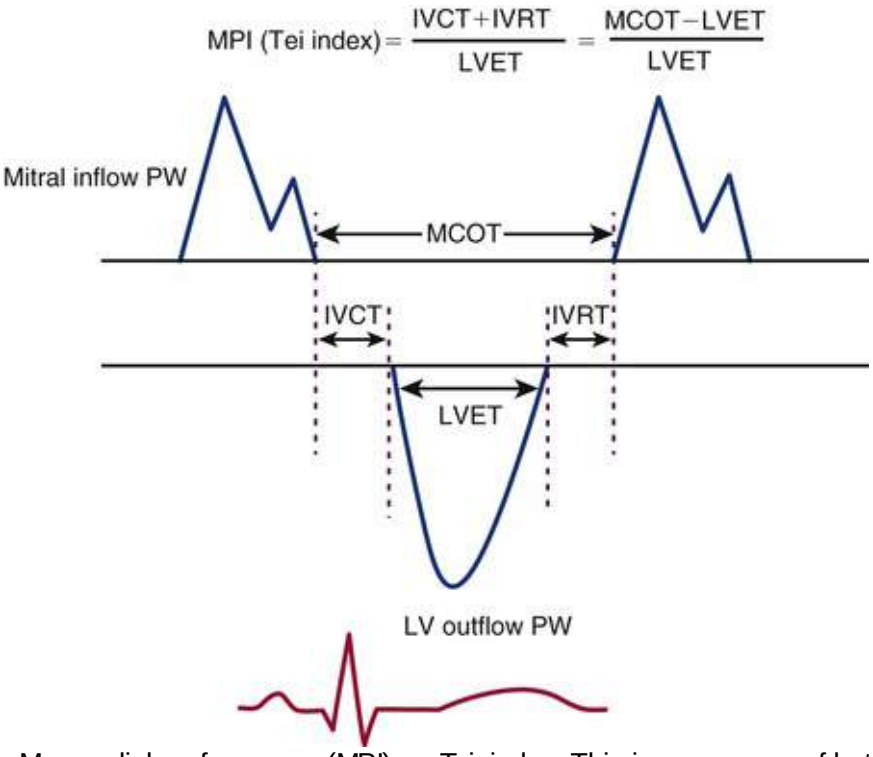
FIGURE 14.15 Patterns of left ventricular (LV) remodeling. Three patterns of LV remodeling can be defined based on measurement of left ventricular mass index (LVMI) and relative wall thickness (RWT): concentric remodeling (normal LVMI and increased RWT), eccentric hypertrophy (increased LVMI and normal RWT), and concentric hypertrophy (both LVMI and RWT are increased). (Modified from Konstam MA, Kramer DG, Patel AR, et al. Left ventricular remodeling in heart failure. current concepts in clinical significance and assessment. J Am Coll Cardiol Imaging 2011;4:98.)

Left Ventricular Systolic Function

Echocardiography offers several methods for assessment of systolic function. The most common remains left ventricular ejection fraction (LVEF), calculated as the difference between end-diastolic volume and end-systolic volume divided by end-diastolic volume (**see Fig. 14.14**). LVEF is one of the best-studied measures in cardiovascular medicine for diagnosis and risk stratification. In echocardiography the volumes are preferably calculated by the modified Simpson formula (see earlier), and normal values are greater than 50%. Most echocardiography machines have basic analysis packages for automatically estimating the LVEF based on linear measurements at the base of the heart (e.g., Teicholz and Quinones formulas), which are helpful for a quick approximation but are less accurate in remodeled ventricles. In reality, the accuracy of all methods is affected by image quality, endocardial border definition, ventricular geometry, and imaging plane. When one or more of these factors are suboptimal, a visual “eyeball” estimation by experienced echocardiographers can be reliable and sufficient for most clinical scenarios. Although this is common practice and can actually be more accurate than mathematical computation in many cases, the presence of intra- and interobserver variability needs to be acknowledged, and reproducibility should be monitored.[4]

Other approaches are commonly used in addition to LVEF to assess systolic function. Stroke volume can be determined from 2D images by subtracting end-systolic volume from end-diastolic volume. An alternative method is to use Doppler data (discussed earlier), in which the VTI within the LVOT is multiplied by the LVOT CSA to calculate SV (**see Fig. 14.8**). Multiplication of SV by the heart rate gives the cardiac output.

Several other methods have been proposed for assessment of both LV and right ventricular (RV) function. The *myocardial performance index* (MPI), also known as the Tei index, is defined as the sum of isovolumic relaxation time and isovolumic contraction time divided by ejection time, and this method takes into account both systolic and diastolic performance (**eFig. 14.6**). A higher index is associated with worse function.[2] In adults, values of LV MPI greater than 0.40 and RV MPI greater than 0.43 are considered abnormal. This measure has been related to outcomes in a variety of conditions, including heart failure and following myocardial infarction (MI). *Doppler tissue imaging* (DTI) can be used to assess myocardial contraction velocity, or S′, although this technique has proved to be more useful for assessment of diastolic function (see later).



EFIGURE 14.6 Myocardial performance (MPI), or Tei, index. This is a measure of both global systolic and diastolic ventricular function and can be calculated from spectral Doppler tracings of mitral valve inflow and left ventricular (LV) outflow. *IVCT,* Isovolumetric contraction time, *IVRT,* isovolumetric relaxation time, *LVET,* LV ejection time, *MCOT,* mitral closure time. See also **eFig. 14.11** to correlate hemodynamics over the cardiac cycle. Alternatively, it can be measured by tissue Doppler. For above spectral Doppler method: normal LV Tei index is ≤0.40. Similar calculations can be performed for the right heart, and normal RV Tei index is ≤0.43.

Myocardial Strain Imaging.

Myocardial deformation, or strain imaging, has evolved to become a sensitive method for assessment of cardiac function. *Strain* refers to the percent deformation between two regions, such as shortening of myocardial muscle in systole or lengthening in diastole.[2] Myocardial strain can be assessed by Doppler methods in which myocardial tissue velocities are integrated to obtain the change in distance between points, but these are relatively noisy, require dedicated acquisition, and are angle dependent. In contrast, strain imaging based on 2D speckle-tracking techniques has proved to be much more robust and reliable (but with poorer temporal resolution) and thus has virtually replaced Doppler-based strain assessments for most applications. The technique has been validated by sonomicrometry and takes advantage of the

coherent speckle within the myocardial tissue signature (**eFig. 14.7**) to determine regions that are contracting versus those that are moving passively. Strain can be estimated in the longitudinal, circumferential, and radial directions by using the appropriate imaging plane (**Fig. 14.16**).

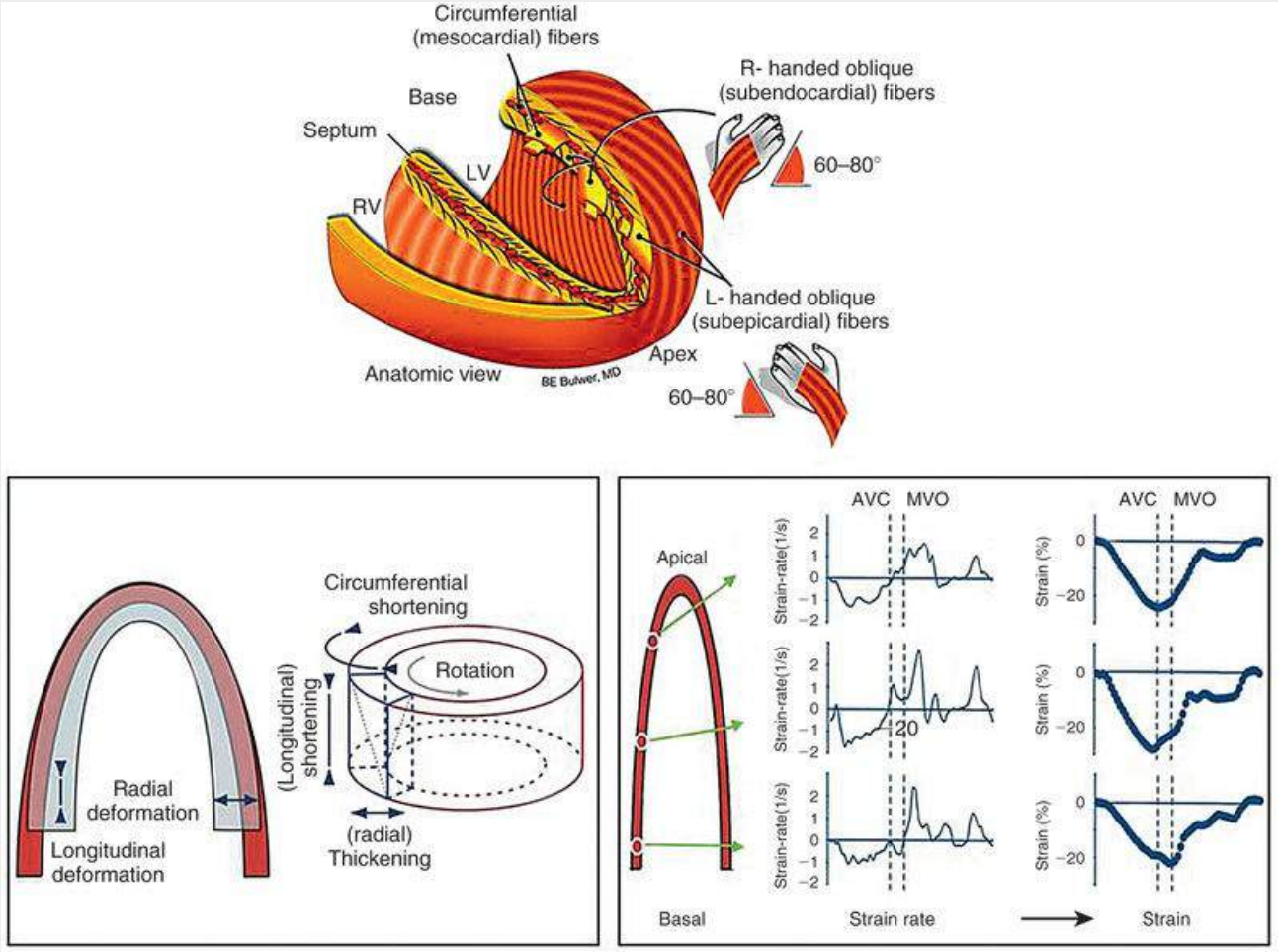
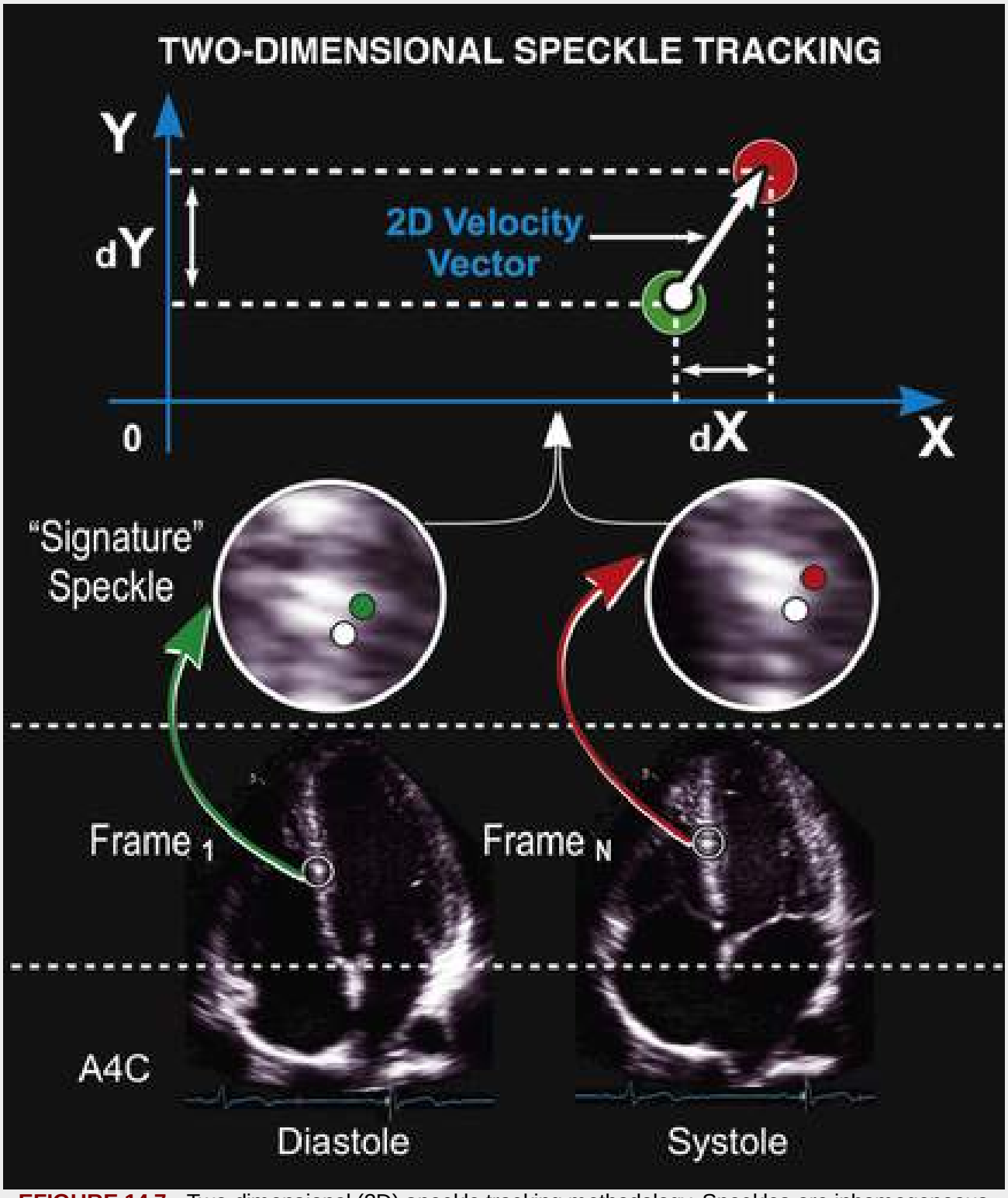


FIGURE 14.16 Normal myocardial fiber orientation, deformation planes, and typical longitudinal strain rate and strain traces. **Upper panel,** Left ventricular endo- and epicardial longitudinal fibers and their opposing oblique directions, midmyocardial circumferential fibers. **Lower panel: Left,** The three planes of myocardial motion and deformation at systole: longitudinal shortening, radial thickening, and circumferential shortening. **Right,** Typical traces of longitudinal strain rate and strain from a healthy adult. *AVC,* Aortic valve closure; *AVO,* aortic valve opening; *MVO,* mitral valve opening. (From Cikes M, Solomon SD. Beyond ejection fraction: an integrative approach for assessment of cardiac structure and function in heart failure. Eur Heart J 2016;37:1642.)



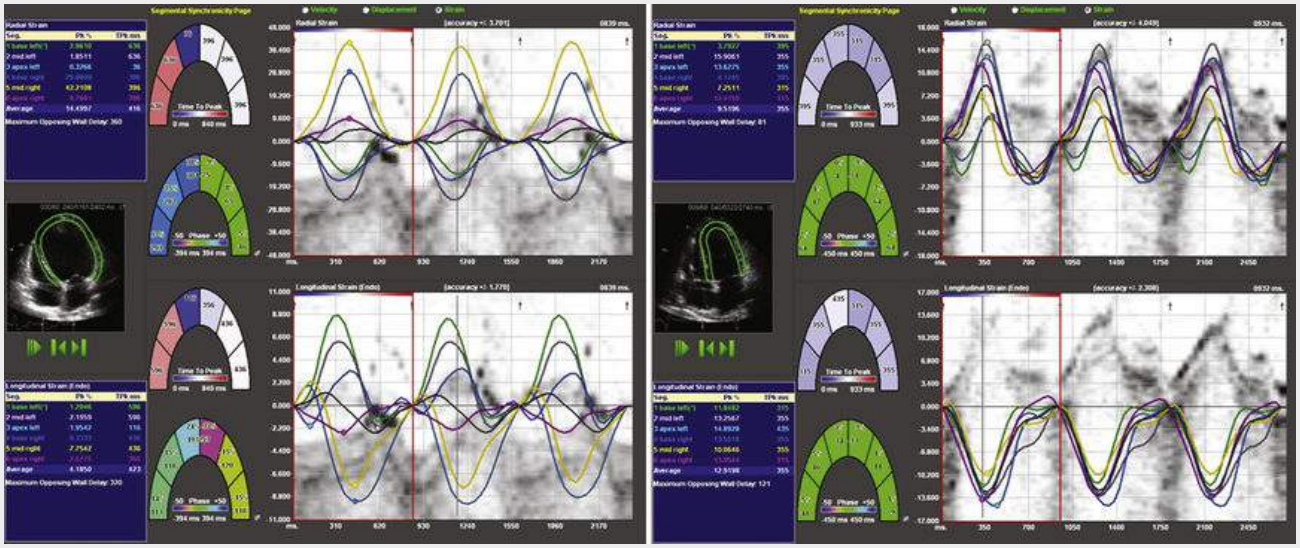
EFIGURE 14.7 Two-dimensional (2D) speckle tracking methodology. Speckles are inhomogeneous interference patterns that result from the interaction of ultrasound with the myocardium. Each area of myocardium, with its unique signature speckle, can be tracked during the myocardial deformation cycle. Unlike Doppler-based deformation imaging measures, speckle tracking–derived deformation measures are angle independent. *A4C,* Apical four-chamber view.

Current equipment can assess regional strain and then calculate global longitudinal strain either by averaging regional strain values or by determining the percent difference in the endocardial perimeter between systole and diastole. Longitudinal deformation reflects function of the subendocardial myocardial fiber bands primarily, whereas circumferential deformation, best assessed on short-axis views, may reflect the function of more epicardial layers.

Global strain, particularly *global longitudinal strain* (GLS, or the relative change in length of myocardium during systole), has emerged as an important measure of cardiac performance that has been

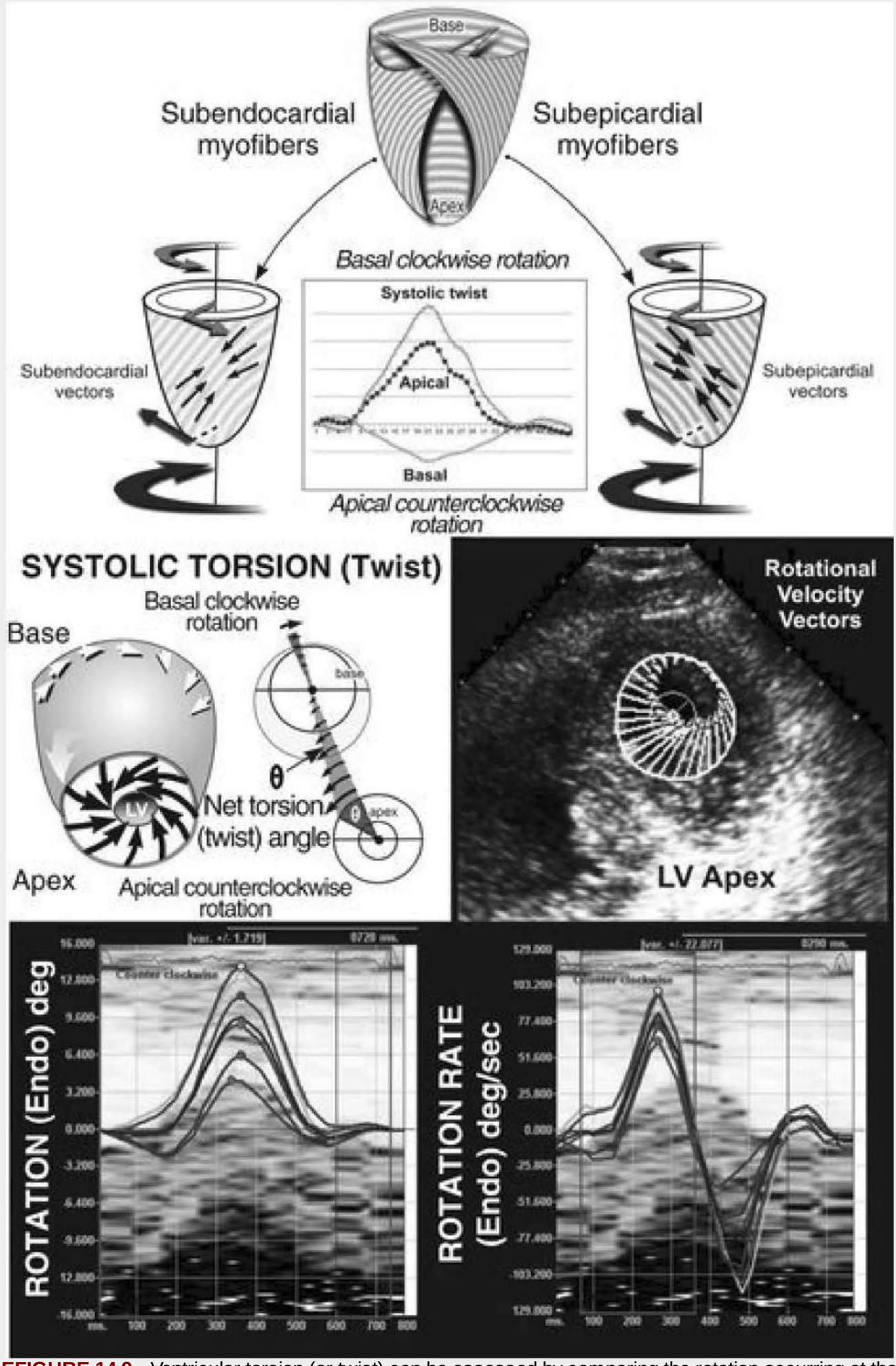
shown to add incremental predictive value to standard measures such as the LVEF.[5] Several diseases have been associated with a reduction in GLS, including hypertension, diabetes mellitus, renal insufficiency, infiltrative cardiomyopathies, HCM, and valvular heart disease. This measure also appears to predict survival or the development of heart failure in patients following MI. Global strain measurements are also useful in assessing the effect of cardiotoxic chemotherapies on individual patients over time.

Myocardial deformation imaging has been used for the evaluation of cardiac synchrony by assessing the time to peak strain (maximal contraction) across many cardiac regions (**eFig. 14.8**). Both regional timing, reflecting synchrony, and myocardial peak strain, reflecting contractile function, have prognostic significance in patients undergoing cardiac resynchronization therapy (CRT) (**see Chapters 25 and 41**) and may be used to stratify those who will benefit most from CRT.[6,7]



EFIGURE 14.8 Dyssynchrony versus synchrony, as assessed by myocardial strain before and after CRT. Average radial and longitudinal strain is calculated from six different regions in the ventricle on apical four-chamber views. The waveforms depicted demonstrate both timing and magnitude of peak strain in these regions. **Left panel** shows a patient with cardiomyopathy before therapy with a cardiac resynchronization device. **Right panel** shows same patient after 12 months of CRT with dramatic improvement in ventricular synchrony.

In addition to assessment of global function, strain imaging can be used to assess and quantify regional function. Regional strain correlates with the degree of myocardial scar in patients with ischemic heart disease (**see Chapter 17**) and in HCM[8,9] (**Chapter 78**). These measures can also be used to assess ischemia during stress echocardiography. An offshoot of myocardial strain imaging has been the quantitative assessment of ventricular twist and torsion, or the wringing motion of the heart during contraction and relaxation (**eFig. 14.9**).

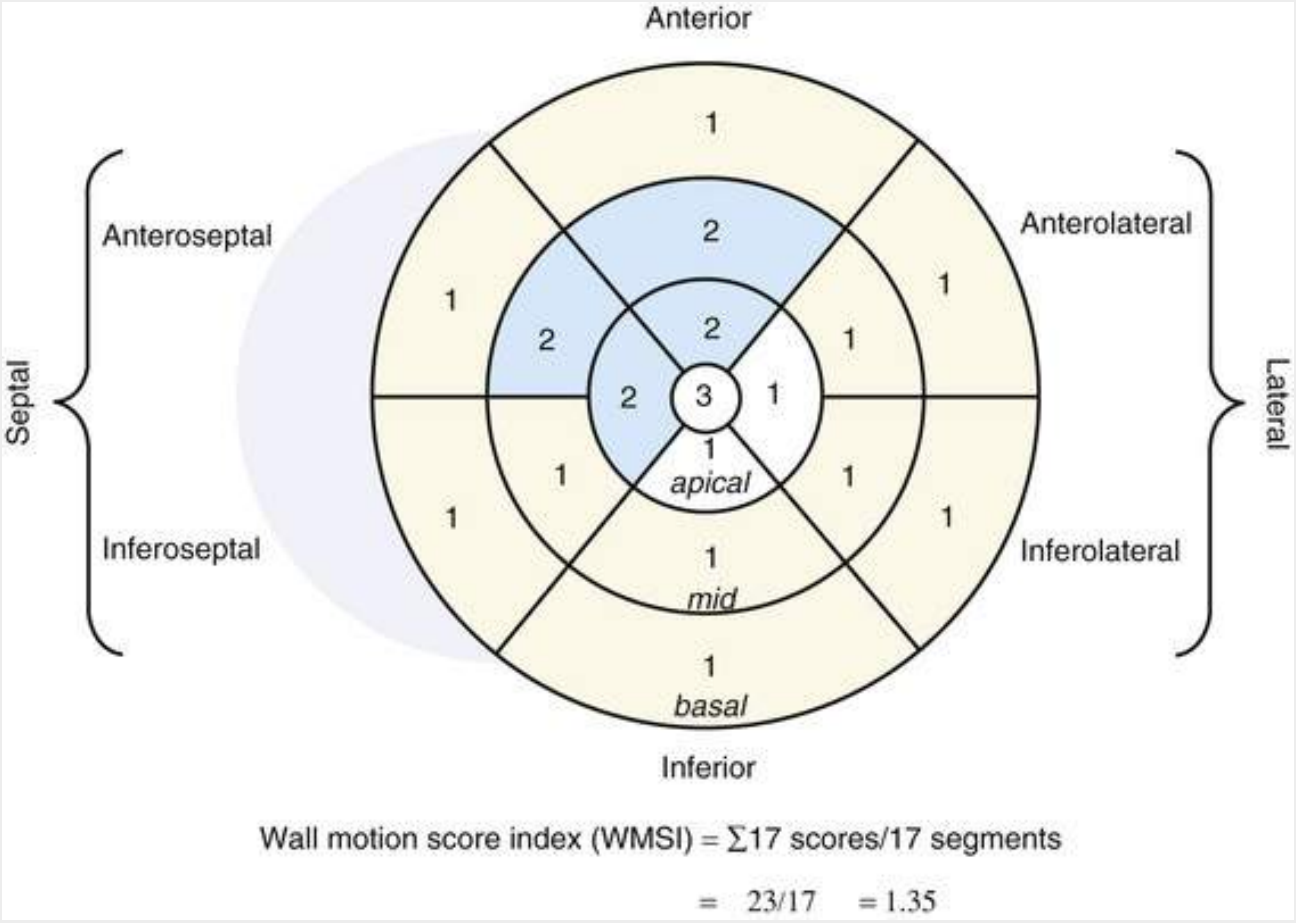


EFIGURE 14.9 Ventricular torsion (or twist) can be assessed by comparing the rotation occurring at the base of the heart with that occurring at the apex using speckle tracking. Rotation and the rate of rotation can be assessed and displayed. (Modified from Bulwer BE, Solomon SD. Assessment of systolic function. In Solomon

There are several limitations of strain imaging based on 2D echocardiography. First, myocardial deformation occurs in three dimensions, and out-of-imaging plane movement is lost. Second, these measures are subject to the same limitations as conventional ultrasound images, including frame rate and image quality, with limited time resolution at high heart rates. Third, the technique, data acquisition and calculations, and normal values still remain to be standardized among the many vendors. Until this is achieved, it is highly recommended that the same vendor equipment and software be used to follow strain in a given individual. As strain techniques become more standardized, refined, and automated, their usefulness and applicability will increase.

Left Ventricular Regional Function.

Even though measures of global LV function provide quantification of overall cardiac performance and have prognostic value, regional function can vary substantially, such as in ischemic heart disease or other focal processes. Acute MI can cause regional wall motion abnormalities: each specific myocardial region is supplied by a respective coronary artery (see later, Myocardial Infarction). Regional wall motion may be assessed qualitatively or semiqualitatively with a scoring system (**eFig. 14.10**). The most popular current scoring system is based on a 17-segment model advocated by the ASE in which each segment is scored as normal (1 point), hypokinetic (2 points), akinetic (3 points), or dyskinetic (4 points). The *wall motion score index* (WMSI) is equal to the sum of these grades divided by the number of segments visualized, so a normally contracting ventricle should have a score of 1.0. A WMSI of 1.7 or higher is usually associated with the physical examination findings of heart failure. A higher score is also an independent predictor of mortality and morbidity, including increased hospitalization for heart failure, following MI.



EFIGURE 14.10 Wall motion score index (WMSI). A polar map or "bulls-eye" view, one way to schematically depict the area of regional wall motion abnormalities (WMA) and calculation of the wall motion score index. Scores are 1 = normokinetic, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic. The example displayed here is of mid-to-distal anteroseptal and anterior hypokinesis with an akinetic apex, giving a WMSI of 1.35. See **Fig. 14.28** in text for coronary distributions.

The main goal of detecting regional myocardial dysfunction is to identify patients with coronary artery disease (CAD). Assessment of regional wall motion cannot easily distinguish between old and new wall motion abnormalities, although local myocardial thinning and increased brightness would be suggestive of chronic infarction and scar tissue. Typically, MI is associated with discrete regions of severe hypokinesis, akinesis, or even dyskinesis. Focal wall motion abnormality can be apparent even within the first few minutes of acute MI, thus making assessment of regional wall motion particularly suited for diagnosis in the acute setting, for example, in patients with acute chest pain and equivocal abnormalities on the electrocardiogram (ECG) in whom a new discrete wall motion abnormality might argue for early intervention (**see Chapters 58 and 59**). Although MI, either acute or old, is the most likely reason for regional wall motion abnormalities, other conditions such as myocarditis or sarcoidosis can affect the myocardium regionally, but generally not in a clear coronary distribution. The LV dysfunction that can accompany valvular or hypertensive heart disease may also have some minor regional variability.

Assessment of regional wall motion is particularly important in stress echocardiography, in which induced regional wall motion abnormalities in the setting of exercise-induced or pharmacologic stress indicate myocardial ischemia. For stress echocardiography, regions are compared before and after stress in a side-by-side fashion, and wall segments with unchanged or worsening systolic function are compared qualitatively and scored (see later).

Left Ventricular Diastolic Function

Diastolic dysfunction is extremely prevalent in patients with hypertension and in older adults (**see**

Chapter 26). It is described mechanistically as impaired LV relaxation and increased LV stiffness. The "gold standard" for assessment of diastolic function has been the invasively obtained pressure-volume loop, in which diastolic function is assessed as the instantaneous relationship between pressure and volume. Noninvasively, several echo-based methods can be used to assess cardiac diastolic performance and estimate LV end-diastolic pressure (LVEDP). The more commonly used variables are summarized in **Figs. 14.17 and 14.18**, with age-adjusted reference values in **eTable 14.1**.[10] Analysis of diastolic dysfunction must be carried out with acknowledgment that (1) there are overlapping spectra of both echo values and degrees of diastolic dysfunction at any LVEF; (2) a patient's age, hemodynamics, and presence of disease (particularly mitral disease) may affect many values; and (3) no single index is accurate in isolation.

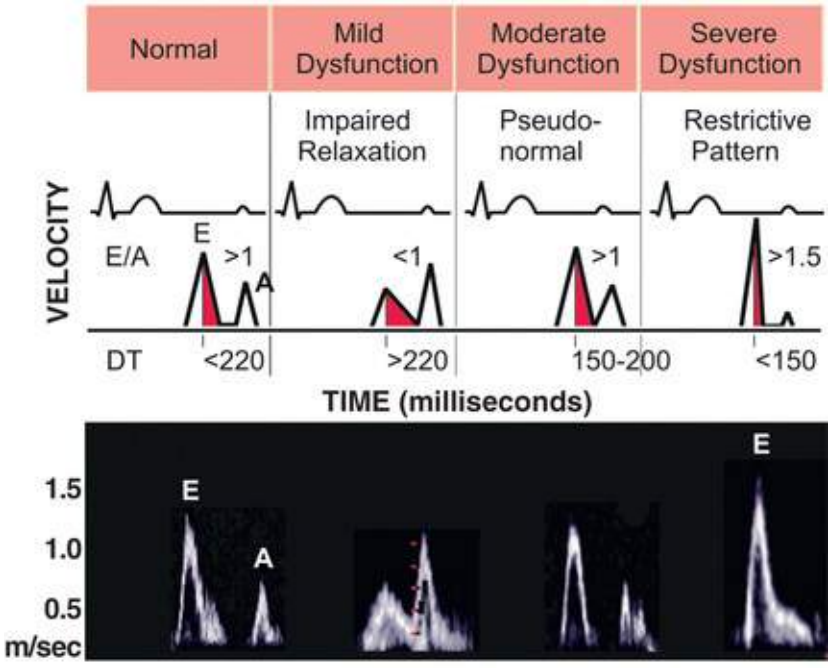


FIGURE 14.17 Mitral inflow Doppler waveforms in diastolic dysfunction. *DT,* Deceleration time. (Modified from Ho CY, Bulwer BE. Echocardiographic assessment of diastolic function. In Solomon SD, Bulwer BE, editors. Essential Echocardiography. A Practical Handbook with DVD. Totowa, NJ: Humana Press; 2007, p 124.)

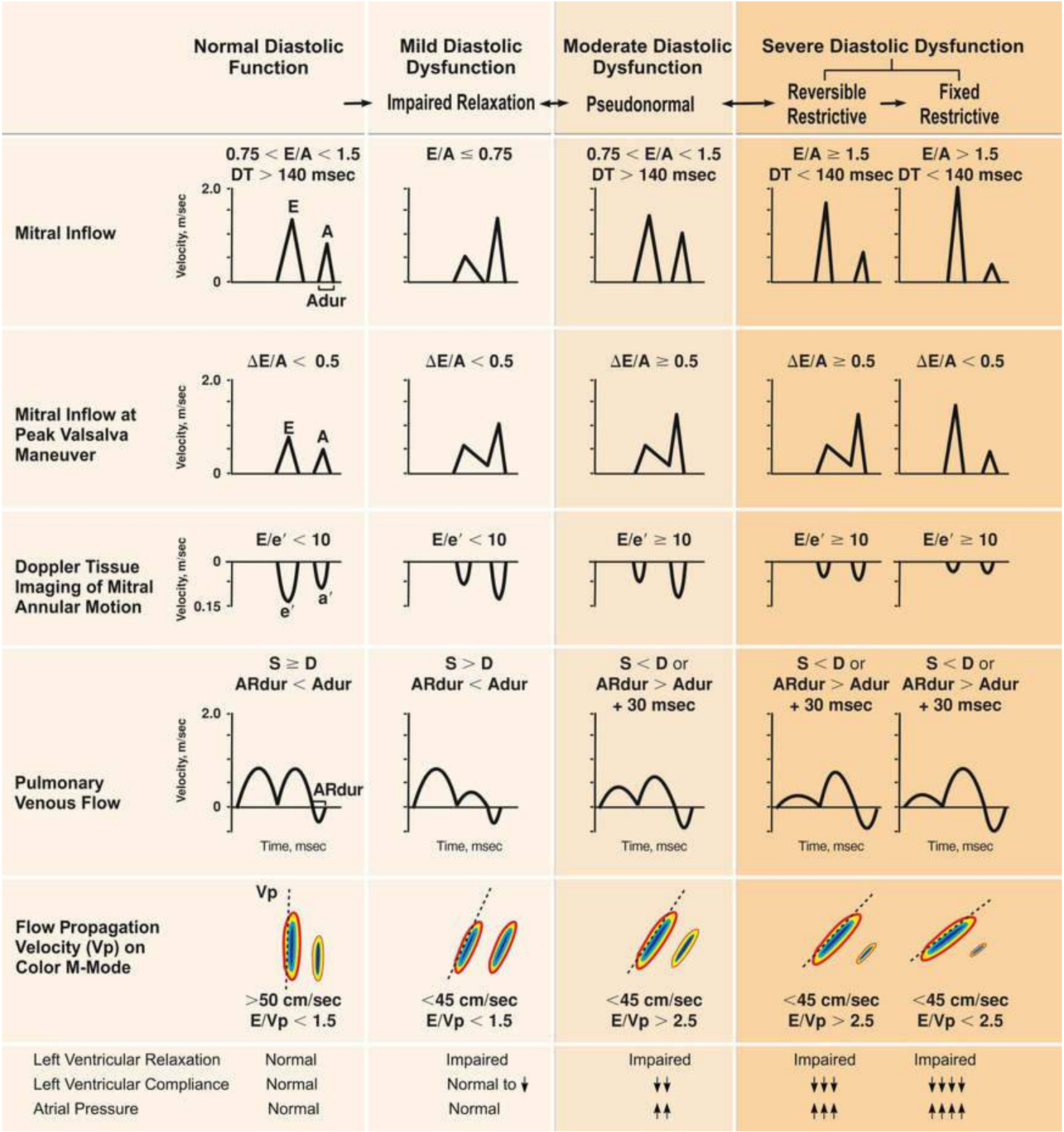


FIGURE 14.18 Diastolic function classification scheme. *A,* Transmitral flow velocity with atrial contraction; a′, velocity of mitral annular motion with atrial systole; *Adur,* duration of A; *AR,* flow from the left atrium to the pulmonary veins during atrial contraction; *ARdur,* duration of AR; *D,* diastolic; *E,* early diastolic flow velocity; e′, velocity of early diastolic mitral annular motion; *S,* systolic; *Vp,* transmitral flow propagation velocity. (Modified from Redfield MM, Jacobsen SJ, Burnett JC Jr, et al. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194.)

ETABLE 14.1

Age-Adjusted Reference Range for Diastolic Function Parameters

	AGE GROUPS (yr)					
	45-49	**50-54**	**55-59**	**60-64**	**65-69**	**≥70**
Mitral Inflow Parameters						
E (m/sec)	0.7 (0.5-0.9)	0.6 (0.5-0.9)	0.7 (0.5-0.9)	0.7 (0.5-0.9)	0.6 (0.4-0.8)	0.6 (0.4-1.0)
A (m/sec)	0.5 (0.3-0.7)	0.5 (0.4-0.8)	0.6 (0.4-0.9)	0.6 (0.4-0.9)	0.7 (0.4-1.0)	0.8 (0.5-1.1)
E/A	1.3 (1.0-2.0)	1.2 (0.8-2.0)	1.2 (0.7-1.8)	1.0 (0.7-1.6)	1.0 (0.6-1.5)	0.8 (0.6-1.3)
DT (msec)	208 (180-258)	217 (178-266)	210 (183-287)	222 (180-282)	227 (188-298)	242 (188-320)
TDI—Mitral Annulus						
Septal						
e'_S (m/sec)	0.10 (0.07-0.14)	0.09 (0.06-0.14)	0.09 (0.05-0.12)	0.09 (0.06-0.13)	0.08 (0.05-0.11)	0.07 (0.05-0.11)
E/e'_S	6.67 (4.62-11.25)	7.00 (4.55-11.67)	7.78 (4.62-13.33)	7.64 (5.00-12.00)	8.57 (5.45-13.33)	8.57 (4.55-16.67)
Lateral						
e'_L (m/sec)	0.13 (0.09-0.17)	0.12 (0.08-0.16)	0.11 (0.07-0.15)	0.10 (0.07-0.15)	0.09 (0.07-0.12)	0.08 (0.05-0.11)
E/e'_L	5.38 (3.75-7.78)	5.45 (3.75-8.89)	6.00 (3.85-10.00)	6.67 (4.62-8.89)	7.00 (4.17-11.25)	7.78 (5.00-14.00)
Pulmonary Vein Flow Parameters						
P_S/P_D	1.25 (0.86-2.00)	1.40 (1.00-2.00)	1.40 (1.00-2.00)	1.50 (1.00-2.25)	1.60 (1.00-2.50)	1.67 (1.00-2.50)
$PVAR_{dur}$ (msec)	118 (100-140)	122 (103-142)	123 (105-157)	123 (103-160)	127 (110-152)	130 (112-170)

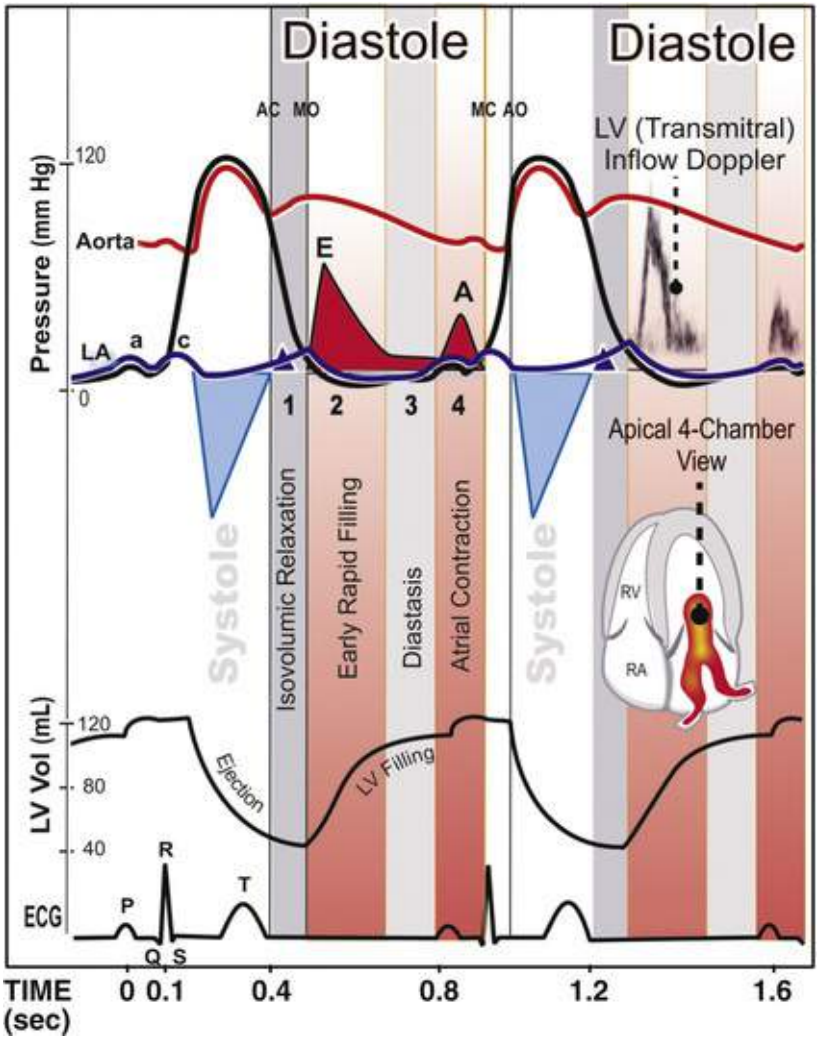
Data are median (5th and 95th percentile).

A, Late diastolic mitral flow velocity; *DT,* deceleration time of early diastolic mitral flow; *E,* early diastolic mitral flow velocity; e'_L, early diastolic lateral annular velocity; e'_S, early diastolic septal annular velocity; P_D, pulmonary vein diastolic flow velocity; P_S, pulmonary vein systolic flow velocity; $PVAR_{dur}$, duration of pulmonary vein atrial flow reversal; *TDI,* tissue Doppler imaging;

Modified from Munagala VK, Jacobsen SJ, Mahoney DW, et al. Association of newer diastolic function parameters with age in healthy subjects: a population-based study. J Am Soc Echocardiogr 2003;16:1049.

Mitral Inflow Patterns

Mitral inflow Doppler can be used to assess flow from the left atrium to the left ventricle during diastole (**eFig. 14.11**). The transmitral inflow velocity at a given point in time correlates with the pressure gradient between the chambers. The E wave occurs during early diastole when the ventricle is filling actively. The A wave represents the velocity of blood flow during late diastole during atrial contraction. Initial classification of diastolic function has been based on the pattern (i.e., relative heights) of the E and A waves (**Fig. 14.17**). E wave velocity is dependent on the transmitral pressure gradient and is thus directly related to LA pressure and inversely related to LV compliance. The height of the A wave is additionally dependent on the strength of atrial contraction. Normally in individuals younger than 65, E wave height is greater than A wave height, with ratios of 1.0 or higher. LV compliance declines with age, and so the E wave generally diminishes. Simultaneously, the A wave typically increases as atrial contraction augments to compensate for the reduced LV compliance. Moreover, the deceleration time of the E wave increases as compliance worsens initially. However, as diastolic function continues to worsen and LA pressures rises, the E wave will heighten again, and the size of the A wave declines as LV pressure rises and LA function begins to worsen, so the E/A ratio may revert to relatively normal (*pseudonormalization*). Because pseudonormal patterns can appear similar to normal patterns, E and A measures alone can be misleading. Further worsening of diastolic function leads to the so-called restrictive pattern, in which the descending slope of the E wave becomes very steep (rapid deceleration time) because of abrupt cessation of mitral inflow. Thus, both the pattern of the E and the A waves and the mitral deceleration time follow a biphasic course as diastolic function worsens, which limits the usefulness of these measures alone in assessment of diastolic function.



EFIGURE 14.11 The cardiac cycle and phases of diastole. *AC,* Aortic closure; *AO,* aortic opening; *MC,* mitral closure; *MO,* mitral opening; *RA,* right atrium; *RV,* right ventricle.

Doppler Tissue Imaging

DTI applies Doppler imaging principles to the assessment of myocardial contraction and relaxation. Rather than assessing signals from rapidly moving red blood cells, DTI uses filters to optimize reception of the higher-amplitude signals that arise from the much slower-moving myocardium. When applied to assess myocardial motion at the mitral annulus (typically at both medial and lateral sampling points), the Doppler velocities are recorded over the cardiac cycle. Three distinct waveforms are seen: systolic contraction (the S′ wave) toward the relatively fixed apex, followed by early (e′) and late relaxation (a′) signals in diastole. The timing of the e′ and a′ waves is coincident and analogous in many ways to standard Doppler of mitral inflow, but the movement is in the opposite direction to blood flow and of much lower velocity. The e′ peak value is inversely related to tau (τ), the time constant of ventricular relaxation. The e′ velocity ranges up to greater than 20 cm/sec in children and young adults but declines rapidly in early adulthood and beyond. Values less than 5 cm/sec are seen in patients with severe diastolic dysfunction (e.g., amyloidosis).

Because E velocity reflects the atrial-to-ventricular pressure gradient, it is dependent on both LV compliance and LA pressure (i.e., preload dependent). In contrast, DTI e′ in principle is a measure of LV compliance alone. Therefore, dividing E by e′ yields a measure that reflects LA pressure, which usually approximates LVEDP. An E/e′ ratio greater than 14 is considered abnormally high at any age and is usually indicative of elevated LVEDP. However, this ratio may be insensitive to acute changes and thus

may not be suitable for monitoring patients during therapy.[11]

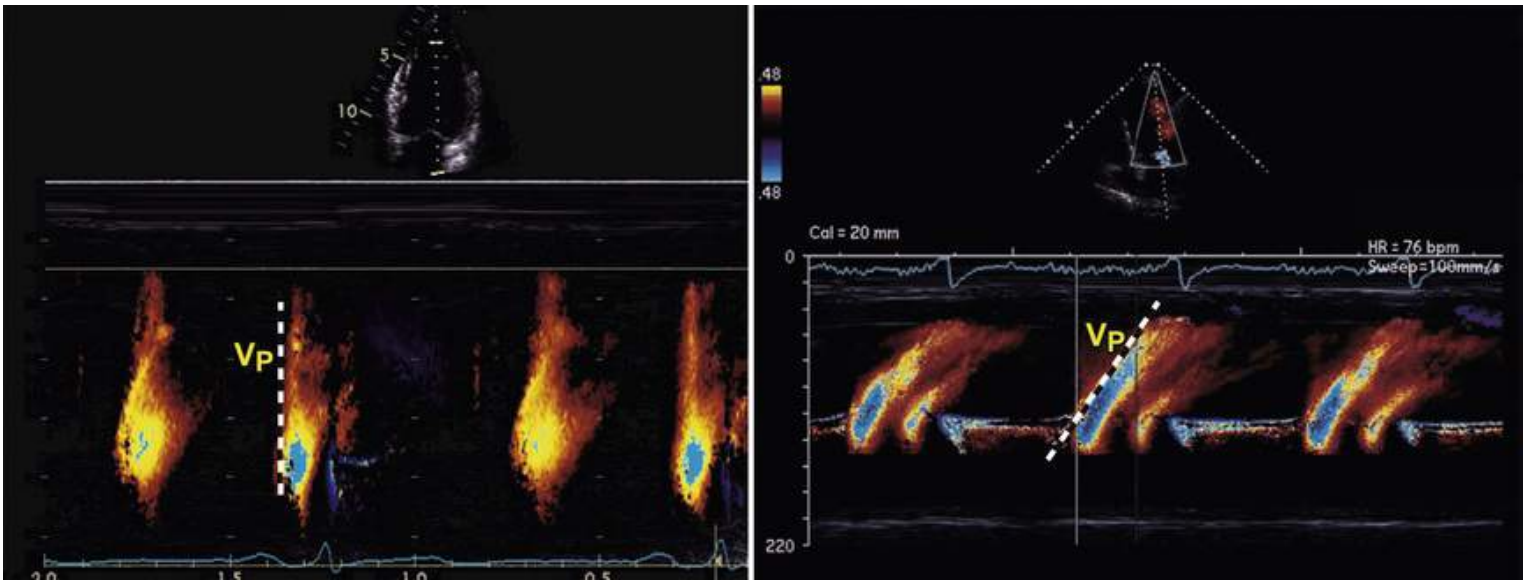
Pulmonary Venous Doppler Flow Patterns

Pulmonary flow patterns are complementary to mitral inflow Doppler patterns for assessment of diastolic function. Pulmonary vein flow has three components: (1) the S wave, which consists of forward flow from the pulmonary veins to the left atrium during ventricular systole; (2) the D wave, which consists of passive flow during ventricular diastole; and (3) the AR wave, which is the slight flow reversal into the pulmonary veins during atrial contraction (**see Fig. 14.18**). Patients with impaired LV relaxation will demonstrate blunting of the S wave relative to the D wave. Reduced LV compliance may also result in greater flow into the pulmonary veins during atrial contraction (broader A wave).

A number of other Doppler parameters change with declining diastolic function. The *isovolumic relaxation time* (IVRT) represents the period between closure of the aortic valve and the start of ventricular filling (i.e., end of LVOT flow and beginning of mitral inflow E wave; **see eFig. 14.6**). Prolongation of the IVRT is associated with abnormal relaxation, and shortening of the IVRT can occur in patients with restrictive LV filling. Mitral E wave deceleration time (DT; **see Fig. 14.17**) is the interval from peak to no mitral inflow in early diastole. In early diastolic dysfunction, deceleration time can actually increase. However, in patients with severe restrictive physiology where the stiff ventricle reaches its volume limit suddenly, the DT will be very rapid (<140 msec). This has been associated with an adverse prognosis in patients with heart failure and after MI (i.e., in patients with both systolic and advanced diastolic dysfunction).[12]

Color M-Mode and Flow Propagation

Color M-mode can be used to assess transmitral flow propagation velocity (Vp). While performing color flow Doppler through the mitral valve in apical windows, one can initiate the M-mode function to superimpose the color flow information onto the M-mode image (**eFig. 14.12**). The slope of the E wave flow (Vp) represents flow propagation, which correlates inversely with tau, the time constant of relaxation. Patients with impaired active relaxation will have a reduced “suction” action of the left ventricle, with abrupt slowing of blood once it enters the ventricle. On color M-mode, this manifests as a more shallow slope of Vp (abnormal is considered <0.45 in middle-aged adults, and <0.55 in younger adults). In practice, despite refinements in calculation of parameters based on flow propagation, Vp measures have lower reproducibility and appear reliable only in patients with depressed LVEF.[10]



EFIGURE 14.12 Transmitral flow propagation demonstrated by color M-mode. Flow propagation velocity is assessed as the linear slope of the isovelocity contour (the aliasing portion) of the mitral inflow pattern at 4 cm into the LV cavity. This slope will be more shallow when velocity is impaired (as in **right panel**). Vp is transmitral flow propagation velocity. Determination of Vp is often more difficult when the early diastolic flow velocities form a curved isovelocity inflow pattern, rather than a single straight slope.

Assessing Diastolic Function in Clinical Practice

In clinical practice, assessment of diastolic function requires an integrated approach. Main parameters and rough cutoffs for initial assessment include mitral inflow Doppler (particularly E/A ratio) and tissue Doppler (e′ and E/e′ ratio) criteria, but also estimation of pulmonary artery systolic pressure and LA volume (**Table 14.4**). A majority of evidence (initially at least two of four) of abnormal parameters is required to parse diastolic dysfunction, with use of additional parameters as needed for corroboration.[10] Several schemes have been developed to grade diastolic function based on these parameters (as in **Fig. 14.18 and Table 14.4**). Although these schemes allow for some standardization in description of diastolic dysfunction, data on the relationship between specific grades, resting hemodynamics, and clinical outcomes remain limited. Abnormalities in diastole are extremely prevalent in patients with hypertension and in elderly patients, but are not necessarily associated with clinical symptoms or overt heart failure.[10,13] Assessment of diastolic function during exercise, termed the “diastolic stress test,” may help unmask abnormalities that contribute to symptoms only during exertion.[14]

TABLE 14.4

Expected Findings for Left Ventricular (LV) Relaxation, Filling Pressures, and Two-Dimensional and Doppler Findings According to LV Diastolic Function

PARAMETER	NORMAL	GRADE I	GRADE II	GRADE III
LV relaxation	Normal	Impaired	Impaired	Impaired
LA pressure	Normal	Low or normal	Elevated	Elevated
Mitral E/A ratio	≥0.8	≤0.8	>0.8 to <2	>2
Average E/e′ ratio	<10	<10	10-14	>14
Peak TR velocity (m/sec)	<2.8	<2.8	>2.8	>2.8
LA volume index	Normal	Normal or increased (>34 ml/m^2)	Increased	Increased

LA, Left atrial; *TR,* tricuspid regurgitation.

From Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277.

Right Ventricular Structure and Function

Assessment of the right ventricle has proved especially challenging for 2D echocardiography. Even though the left ventricle is relatively easily characterized as a prolate ellipsoid, the odd crescentic shape of the right ventricle makes modeling of volumes considerably more complex. Moreover, because visualization of the entire right ventricle is not encompassed by any single 2D plane, multiple measurements from multiple views are necessary to fully assess this chamber (**eFig. 14.13**). Normal linear RV measurements are shown in **Table 14.5**. The normal right ventricle is accustomed to low pulmonary vascular resistance (PVR) and is thus extremely sensitive to changes in afterload. Conditions that increase PVR acutely, such as pulmonary embolism (**see Chapter 84**), will cause marked RV dilation and dysfunction. Conditions that cause a chronic increase in PVR will lead to RV hypertrophy and dilation, but RV function is usually maintained until the late stages of disease (**see Chapter 85**).

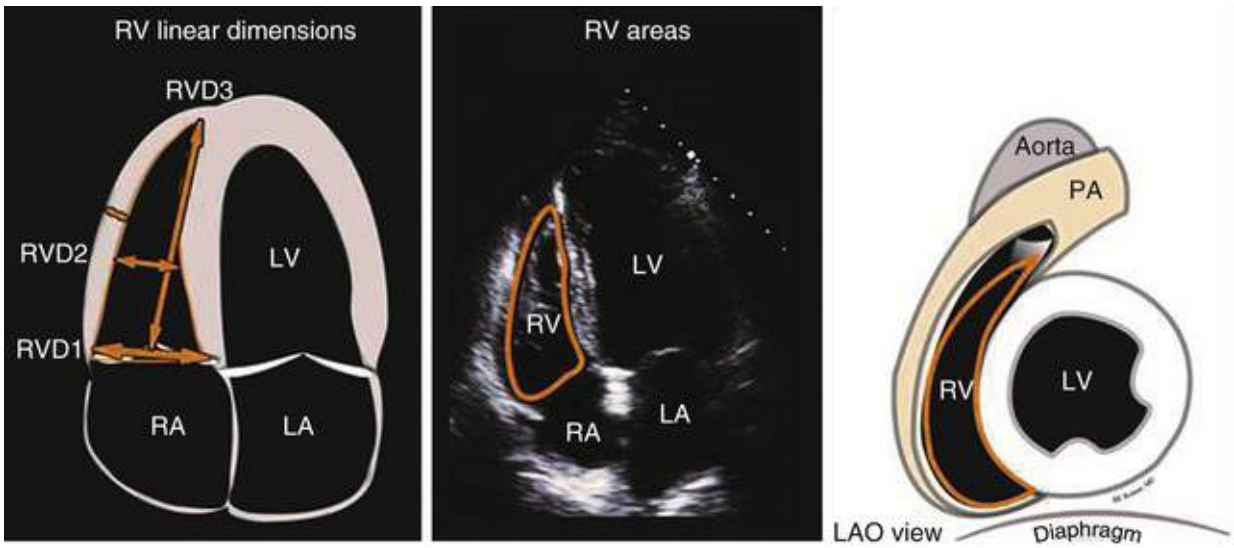
TABLE 14.5

Normal Values for Right Ventricular (RV) Chamber Size

PARAMETER	MEAN ±SD	NORMAL RANGE
RV basal diameter (mm)	33 ±4	25-41
RV mid diameter (mm)	27 ±4	19-35
RV longitudinal diameter (mm)	71 ±6	59-83
RVOT PLAX diameter (mm)	25 ±2.5	20-30
RVOT proximal diameter (mm)	28 ±3.5	21-35
RVOT distal diameter (mm)	22 ±2.5	17-27
RV wall thickness (mm)	3 ±1	1-5
RVOT EDA (cm^2)		
Men	17 ±3.5	10-24
Women	14 ±3	8-20
RV EDA indexed to BSA (cm^2/m^2)		
Men	8.8 ±1.9	5-12.6
Women	8.0 ±1.75	4.5-11.5
RV ESA (cm^2)		
Men	9 ±3	3-15
Women	7 ±2	3-11
RV ESA indexed to BSA (cm^2/m^2)		
Men	4.7 ±1.35	2.0-7.4
Women	4.0 ±1.2	1.6-6.4
RV EDV indexed to BSA (mL/m^2)		
Men	61 ±13	35-87
Women	53 ±10.5	32-74
RV ESV indexed to BSA (mL/m^2)		
Men	27 ±8.5	10-44
Women	22 ±7	8-36

BSA, Body surface area; *EDA*, end-diastolic area; *ESA*, end-systolic area; *PLAX*, parasternal long-axis view; *RVOT*, RV outflow tract.

From Lang RM, Badano LP, Mor-Avi Victor, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1.



EFIGURE 14.13 Right ventricular linear and area measurements on 2D echocardiography. The right ventricle is a tripartite shape, with a half-crescent shape in long-axis windows and a crescentic cross section in short-axis views. As a rough guide, from RV-focused apical views (which display the largest basal RV diameter but still center the LV apex at the top of the scanning sector) an RV basal diameter >41 mm and midlevel diameter >35 mm is indicative of RV enlargement (**see Table 14.5**). *LA,* Left atrium; *LV,* left ventricle; *PA,* pulmonary artery; *RA,* right atrium; *RV,* right ventricle. (Modified from Bulwer BE, Solomon SD. Assessment of systolic function. In Solomon SD, editor. Atlas of Echocardiography. 2nd ed. Philadelphia: Current Science/Springer Science; 2009, p 65.)

Several methods are commonly used to assess global RV function initially on conventional echocardiography (**Table 14. 6**).[2] RV fractional area change (FAC) (**Fig. 14.19**) is easily determined by calculating the RV area in diastole (RVAd) and systole (RVAs) on the apical four-chamber view:

TABLE 14.6

Normal Values for Parameters of Right Ventricular (RV) Function

PARAMETER	MEAN ±SD	ABNORMALITY THRESHOLD
TAPSE (mm)	24 ±3.5	<17
Pulsed Doppler S wave (cm/sec)	14.1 ±2.3	<9.5
Color Doppler S wave (cm/sec)	9.7 ±1.85	<6.0
RV fractional area change (%)	49 ±7	<35
RV free wall 2D strain* (%)	−29 ±4.5	>−20†
RV 3D EF (%)	58 ±6.5	<45
Pulsed Doppler MPI	0.26 ±0.085	>0.43
Tissue Doppler MPI	0.38 ±0.08	>0.54
E wave deceleration time (msec)	180 ±31	<119 or >242
E/A	1.4 ±0.3	<0.8 or >2.0
e′/a′	1.18 ±0.33	<0.52
e′	14.0 ±3.1	<7.8
E/e′	4.0 ±1.0	>6.0

*Limited data; values may vary depending on vendor and software version.

†<20 in magnitude with the negative sign.

MPI, Myocardial performance (Tei) index; *TAPSE,* tricuspid annular plane systolic excursion.

From Lang RM, Badano LP, Mor-Avi Victor, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1.

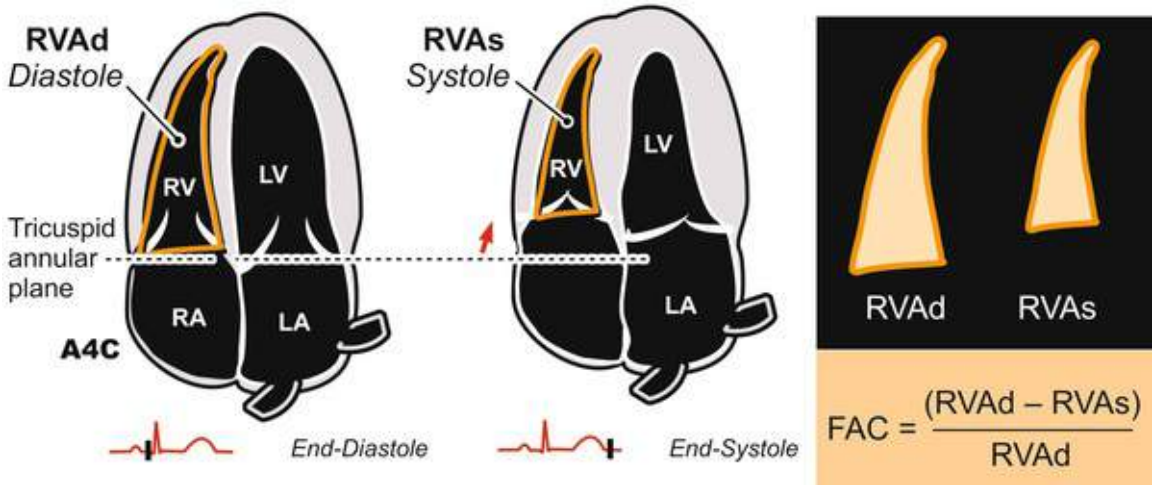


FIGURE 14.19 Right ventricular area (*RVA*) measurement and fractional area change (*FAC*) used to assess RV function with the apical four-chamber view (*A4C*). *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

$$FAC = (RVAd) - RVAs)/RVAd$$

Assessment of RV function by FAC has been shown to provide incremental prognostic value in patients with heart failure and following MI.[15] *Tricuspid annular plane systolic excursion* (TAPSE) is a measure of RV contractility that is usually measured with M-mode imaging (**Fig. 14.20**). This longitudinal motion

of the tricuspid annulus can similarly be assessed with pulsed or tissue Doppler as the peak velocity of the systolic wave, S′ (**Fig. 14.20, right**). Also exactly analogous to the left ventricle, an RV Tei index and RV GLS values can similarly be obtained. RV regional, as opposed to global, dysfunction has particular importance in conditions in which RV afterload increases abruptly, such as pulmonary embolism (see later), in which regional RV function is often preserved in the apical and basal free wall segments but dyskinetic or akinetic in the midregion. Both global and segmental RV wall motion abnormalities also notably occur in RCA infarcts.

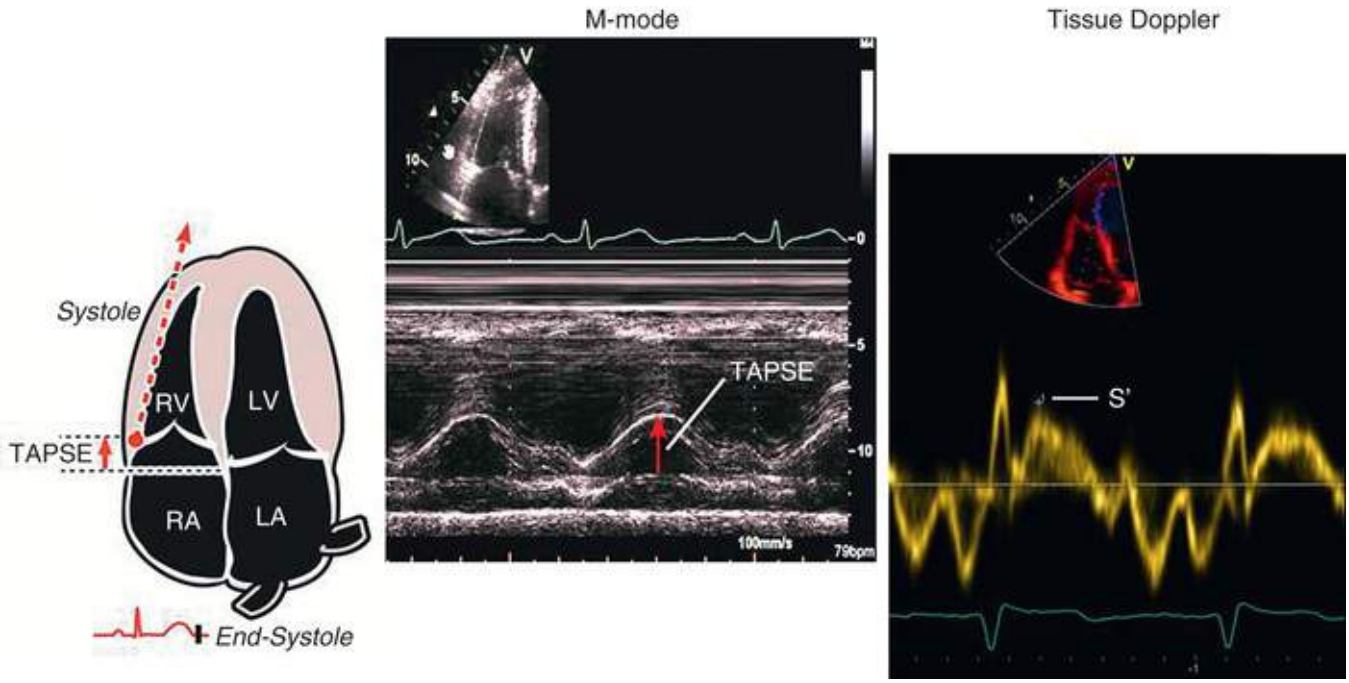


FIGURE 14.20 M-mode and Doppler tissue imaging (DTI) measurements of RV systolic function. **Left and middle panels,** On M-mode, the tissue annular plane systolic excursion (TAPSE) can be measured. **Right,** DTI is used to map tricuspid annular motion, where S′ is the analogous measurement to TAPSE.

Three-dimensional imaging of the right ventricle is now available, and reconstructed views beautifully illustrate its geometric complexity (**Fig. 14.21**). 3D imaging allows for calculation of volumes that are not as angle dependent as all the measures previously discussed. Image acquisition still relies on an experienced sonographer, and the volume measurements require additional training, are only semiautomatic, and must to be done off-line. However, normal reference values for RV volumes and RV ejection fractions now exist (**see Tables 14.5 and 14.6**).[2] Similar to LV volume data, the accuracy appears comparable with that of CMR imaging, although volumes tend to be lower on echocardiography.

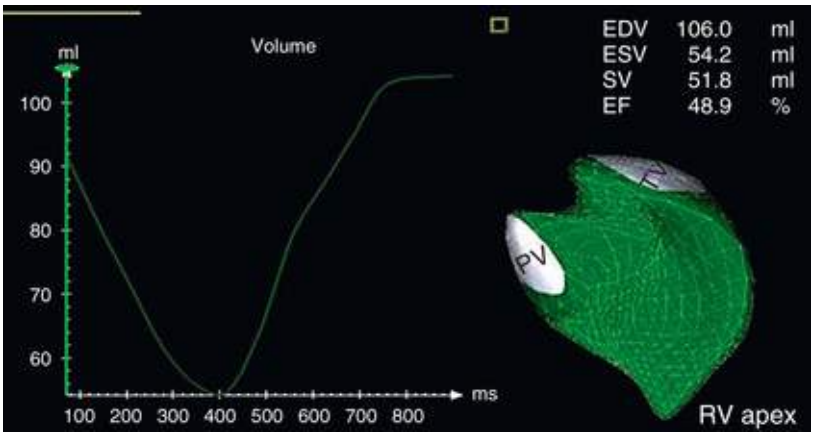


FIGURE 14.21 Three-dimensional measurements of right ventricular (RV) volume and function. A 3D echocardiographic reconstruction of the RV shape and volume, as viewed from the septal surface. The graph at *left* shows RV volumes plotted against time over the cardiac cycle, with data obtained from RV-focused apical four-chamber windows. RV stroke volume (SV) = EDV − ESV. RV ejection fraction (EF) =SV/EDV. *EDV,* end-diastolic volume; *ESV,* end-systolic volume; *PV,* pulmonic valve; *TV,* tricuspid valve.

Left and Right Atria

LA enlargement has been associated with adverse cardiovascular outcomes. The left atrium enlarges under several pathologic conditions, including LV systolic and diastolic dysfunction and atrial fibrillation (AF). Other frequent causes of LA enlargement include hypertension and mitral valve regurgitation or stenosis. LA size is thought to reflect LV filling pressure and thus has been considered a useful indicator of diastolic function over time. Several methods can be used to quantify LA size. A linear measurement of the left atrium is traditionally obtained on the parasternal and in the early days of echocardiography was the initial screen of LA size. A longstanding reference standard for parasternal long-axis LA dimension has been 3.8 cm as the upper limit of normal in women and 4.0 cm in men (or 2.3 cm/m^2 BSA for both). Other axes in the apical windows may also be measured. However, any single linear measurement is inadequate, and LA area is more fully assessed from orthogonal apical views, with volume subsequently calculated by applying the Simpson biplane method. Volumes are typically indexed to body surface area (BSA; **see Table 14.2**). LA function contributes to overall cardiac performance and is itself also affected by LV compliance.

Assessment of the right atrium is best performed from the apical and subcostal views. Right atrial (RA) size is a reflection of right-sided filling pressure and volume. The most frequent causes of RA enlargement are AF and tricuspid regurgitation. Isolated right heart enlargement should always raise the question of whether interatrial (left-to-right) shunting is occurring, and a search for an atrial septal defect should be undertaken with intravenous saline contrast if necessary. Biatrial enlargement can occur with AF or with restrictive cardiomyopathy.

Indexed RA volumes based on volumetric assessment are similar to LA volumes in healthy men and are slightly smaller in healthy women (**eTable 14.2**). Assessment of both the right atrium and the inferior vena cava (IVC) is important in the estimation of RA pressure, which is essential for calculating pulmonary artery systolic pressure from tricuspid regurgitant velocity. Qualitative evidence of elevated RA pressure includes a dilated right atrium, dilation of the IVC, or attenuation of IVC collapse during inspiration. Several methods have been used to estimate RA pressure by echocardiography, but most involve a combination of IVC size and the amount that the IVC collapses with inspiration. A rough scale of RA pressure has been developed that combines assessment of IVC size and respirophasic collapse (**Table 14.7**): complete (>50%) collapse, RA pressure of 0 to 5 mm Hg; partial collapse, 5 to 10 mm Hg; and no (<50%) collapse, 15 mm Hg.[16] Notably, the IVC is occasionally dilated in healthy young individuals and

in athletes, particularly when imaged completely supine.

TABLE 14.7

Estimation of Right Atrial Pressure Based on Inferior Vena Cava (IVC) Diameter and Collapse

VARIABLE	NORMAL (0-5 [3] mm Hg)	INTERMEDIATE (5-10 [8] mm Hg)		HIGH (15 mm Hg)
IVC diameter	≤2.1 cm	≤2.1 cm	>2.1 cm	>2.1 cm
Collapse with sniff	>50%	<50%	>50%	<50%
Secondary indices				Restrictive filling by tricuspid valve inflow Tricuspid E/e′ >6 Diastolic flow predominance in hepatic veins (systolic filling <55%)

Ranges are provided for low and intermediate categories, but for simplicity, midrange values of 3 mm Hg for normal and 8 mm Hg for intermediate are suggested. Intermediate (8 mm Hg) RA pressures may be downgraded to normal if no secondary indices of elevated RA pressure are present, upgraded to high if minimal collapse with nasal inhalation (<35%) and secondary indices of elevated RA pressure are present, or left at 8 mm Hg if uncertain.

ETABLE 14.2

Normal Right Atrial (RA) Size Obtained From Two-Dimensional (2D) Echocardiographic Studies

	WOMEN	MEN
RA minor axis dimension (cm/m^2)	1.9 ±0.3	1.9 ±0.3
RA major axis dimension (cm/m^2)	2.5 ±0.3	2.4 ±0.3
2D echocardiographic RA volume (mL/m^2)	21 ±6	25 ±7

Data are expressed as mean ±SD.

From Lang RM, Badano LP, Mor-Avi Victor, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1.

Transesophageal Echocardiography

TEE is an alternative method to obtain ultrasound images of the heart in which a smaller ultrasound transducer is introduced into the patient's esophagus through a manipulable flexible probe. Similar to transthoracic scanning, multiplane 2D and 3D, color flow, and spectral Doppler imaging can be performed at the bedside, but with a higher-frequency transducer and from a position that is posterior and closer to the heart than can be achieved with TTE. The result is superior image quality and spatial resolution with less artifact with TEE, particularly when assessing the left atrium and left-sided valves, which are directly adjacent to the esophagus. Because it is semi-invasive, TEE is generally used as an adjunctive or follow-up test to an initial TTE if additional information is sought or the TTE images are inconclusive. **Table 14.8** summarizes the advantages and disadvantages of TTE versus TEE.

TABLE 14.8

Advantages and Disadvantages of Transesophageal Echocardiography (TEE) Relative to Transthoracic Echocardiography (TTE)

ADVANTAGES	DISADVANTAGES
Useful in percutaneous and surgical procedures, as well as at the bedside	Semi-invasive—usually requires sedation, hence associated risks with probe intubation (gastrointestinal and pulmonary implications) and sedation effects (hypotension). Long procedures may necessitate general anesthesia. Generally a minimum of two staff members required: one operator and one person to monitor the sedation needed
Higher resolution: better to definitively detect vegetations, thrombi, masses, and intracardiac shunts. Superior imaging of valves, especially the mitral and aortic, left atrium and appendage, left ventricle, thoracic aorta and arch, and interatrial septum, as well as the pulmonary veins	May not view the LV apex or right-sided structures well (structures that are further from probe, particularly in large patients)
"Continuous" acoustic window when compared with TTE (no ribs to cause acoustic shadowing)	"Blind spot" of acoustic shadowing where the trachea is interposed between the esophagus and heart Much of the abdominal aorta is out of range
Superior imaging of the mitral valve and mitral prostheses in general, with the ability to precisely localize valvular and paravalvular defects	Mechanical aortic prostheses can cause excessive shadowing May be technically difficult to achieve the best angle of insonation (i.e., less reproducible and accurate) for assessing aortic stenosis gradients Maneuvers to increase or decrease preload may be more difficult (e.g., Valsalva maneuver), although most patients can cooperate Real-time 3D imaging and reconstruction dependent on a slow regular heart rate and "stable" window (i.e., still patient)

TEE is particularly useful in the evaluation of valve dysfunction, diagnosis or follow-up of endocarditis (**see Chapter 73**), searching for potential causes of stroke, and better characterization of cardiac masses and congenital heart disease. In some circumstances, TEE is appropriately the first test of choice, such as evaluation of aortic pathology and assessment for LA appendage thrombi[17] (see Diseases of the Aorta and Cardiac Masses). TEE can be used to determine the presence of thrombus in patients in whom rapid cardioversion of AF is necessary (**see Chapter 38**) or when elective atrial arrhythmia ablation/cardioversion is planned, particularly in the patient found to be underanticoagulated or at high risk for stroke[18] (**eTable 14.3**). In addition, TEE has a major role in optimizing and evaluating cardiac surgical and percutaneous procedures, particularly with respect to valvular procedures, closure of intracardiac shunts, and implantation of LVADs.[19-21]

ETABLE 14.3

Indications for Transesophageal Echocardiography–Guided Cardioversion

APPROPRIATE	INAPPROPRIATE
CHF exacerbation or hemodynamic compromise	Stable with therapeutic anticoagulation >3 weeks
Symptomatic from AF	AF <48 hours (insufficient time for thrombus to form)
Hospitalized and symptomatic	Permanent AF (sinus rhythm unable to be sustained after cardioversion)
New-onset AF (first-time diagnosis)	Hospitalized but asymptomatic
High stroke risk (including history of stroke or TIA, previous history of LA thrombus, rheumatic heart disease, HOCM)	
Subtherapeutic anticoagulation (INR <2) within preceding 3 weeks, or significant interruption in NOAC therapy	
Miscellaneous (including need for TEE unrelated to AF but otherwise appropriate, such as evaluation of valve function or endocarditis, with timing of TEE coincidentally helpful for expediting cardioversion)	

AF, Atrial fibrillation; *CHF,* congestive heart failure; *HOCM,* hypertrophic obstructive cardiomyopathy; *INR,* international normalized ratio; *TIA,* transient ischemic attack; *NOAC,* non–vitamin K antagonist oral anticoagulant.

TEE may be performed on an inpatient or outpatient basis, and most patients require topical anesthesia and/or intravenous (IV) conscious sedation for comfort. This is usually achieved with IV midazolam and fentanyl or alternatively with propofol if issues with respiratory or hemodynamic stability or patient comfort are anticipated. Risks are relatively low but include trauma to the oropharynx and esophagus, aspiration, bronchospasm or laryngospasm, accidental tracheal intubation, and arrhythmia, as well as risks associated with sedation (transient hypotension).[19,22] General anesthesia is used for patients in the

operating room and appears associated with higher complication rates (as high as 1.2% for major complications). The most serious complication is upper gastrointestinal perforation, which typically occurs in the esophagus or hypopharynx. Patients with esophageal diverticular strictures, significant thoracic radiation-induced fibrosis, distorted anatomy of the mediastinal organs, or difficult probe placement are at higher risk. TEE may also cause bleeding (0.02% to 1.0%) from direct abrasion of the mucosa, esophageal varices, or tumor. The overall risk for major adverse events with TEE is 0.2% to 0.5% in the nonsurgical setting, and the overall mortality rate is exceedingly low (0.0004%). These risks may be minimized by screening patients for potential contraindications (**eTable 14.4**); if one is found, TEE is best deferred until the situation can be better assessed or ameliorated. Alternatively, another imaging modality (e.g., intravascular ultrasound or epiaortic scanning, CT, CMR) or strategy could be considered if an underlying risk factor cannot be mitigated.

ETABLE 14.4

Relative Contraindications to Transesophageal Echocardiography and Potential Strategies

RELATIVE CONTRAINDICATION	POTENTIAL STRATEGIES
Esophageal strictures or diverticula	GI consultation to evaluate, consider use of a pediatric TEE probe or limited TEE only to a depth proximal to the lesion
Esophagitis, especially radiation induced	GI consultation to evaluate, consider alternative procedure
Esophageal varices or recent UGI bleeding	GI consultation to evaluate, correct any coagulopathy, limit TEE only to a depth proximal to the lesion, avoid unnecessary probe manipulation
Recent esophageal dilation or UGI surgery	GI/surgery consultation, consider delaying TEE to at least 4-6 weeks, consider limited TEE proximal to the intervention
Unstable airway and/or hemodynamically tenuous or unstable	Consider intubation and pressors
Unstable cervical spine (e.g., after trauma)	Stabilize with a cervical spine collar, consider paralysis, neurologic and/or orthopedic consultation to clear
Uncooperative patient, restricted cervical mobility	Anesthesia consultation for intravenous propofol, consider higher levels of sedation or general anesthesia
History of significant opioid use/abuse	Anesthesia consultation for intravenous propofol
Severe coagulopathy or thrombocytopenia	Consider correction with blood products and vitamin K

GI, Gastrointestinal; *UGI,* upper GI.

The Standard Transesophageal Echocardiographic Examination

Fig. 14.22 shows a standard TEE examination. It is usually prudent to address the main indication first in the event that the examination must be aborted because of clinical instability. If the patient remains stable, a comprehensive examination is performed, with the majority of the images at the midesophageal level (probe tip approximately 35 cm from the incisors). For a frame of reference with respect to the imaging planes, at midesophageal level when the transducer angle set at 0 to 30 degrees and flexed, the imaging plane cuts the heart in a short-axis (transverse) plane. A TEE transducer angle of 90 to 120 degrees corresponds to a long-axis (longitudinal, or sagittal) plane.

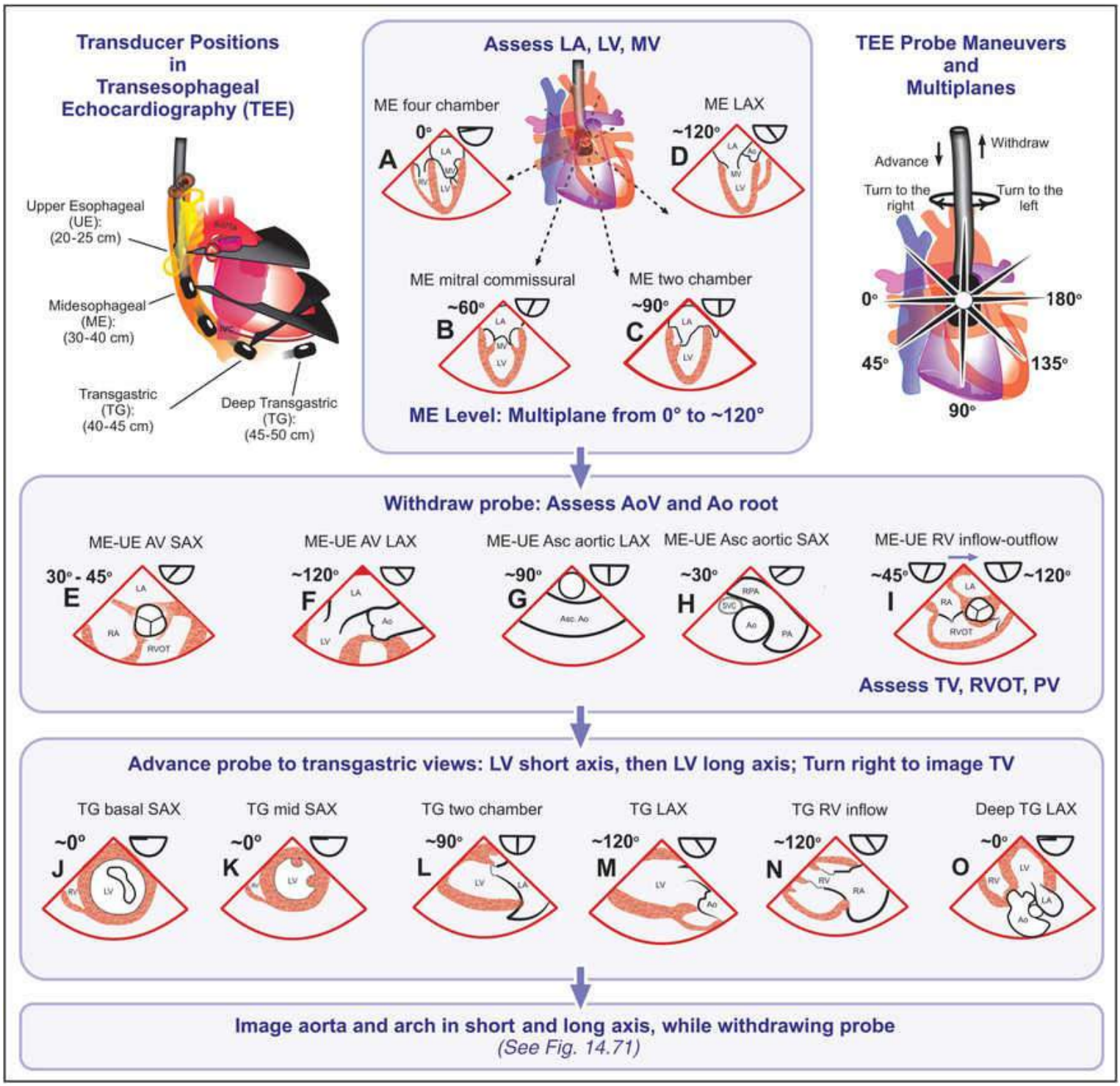


FIGURE 14.22 A suggested standard TEE examination, showing basic probe positioning, manipulations, and views. The sequence illustrated allows a basic survey of all the cardiac chambers and valves. Additional views are obtained as required for the specific indication. *Ao,* Aorta; *AoV,* aortic valve; *Asc,* ascending; *AV,* aortic valve; *Desc,* descending; *LAX,* long axis; *ME,* midesophageal; *PV,* pulmonic valve; *SAX,* short axis; *TG,* transgastric; *TV,* tricuspid valve; *UE,* upper esophageal.

Most transesophageal examinations start with the standard four-chamber view of the heart, similar to the transthoracic apical four-chamber view. At midesophageal level, 0 degrees, this is achieved by slight retroflexion of the probe to tilt the imaging plane in order to include the cardiac apex. At this level the multiplane "omni" controller is used to rotate the scanning plane counterclockwise to slice the left ventricle into two-chamber (approximately 90-degree) and then three-chamber (long-axis or 120-degree) views. These views are optimal for assessing the left ventricle, left atrium, and mitral valve structure and function. If desired, the LA appendage may be thoroughly examined by withdrawing the probe slightly cephalad, centering the image sector on the appendage, and scanning from 30 to 150 degrees. To examine

the aortic valve, the operator retracts the probe slightly, and the aortic valve should be imaged just superior to the mitral valve, at approximately 30 degrees for short-axis images and 120 degrees for long-axis views. The tricuspid valve may be examined at approximately 45 degrees, with subsequent views of the right ventricular outflow tract (RVOT), pulmonary artery and valve, and pulmonary bifurcation sought by gradually increasing the omni angle up toward 120 degrees again. Minor additional manipulations of the TEE probe and transducer angle will provide views of the pulmonary veins, right atrium, interatrial septum, superior vena cava (SVC), IVC, coronary sinus, and abdominal aorta. For transgastric windows, the TEE probe is advanced gently past the gastroesophageal sphincter with the transducer plane reset back to 0 degrees. One can view the left ventricle and mitral valve in the short axis and also obtain transaortic gradients from an apical five- or three-chamber view if needed. By increasing the omni angle up to 90 degrees and rotating the transducer plane to the right, more detailed views of the tricuspid valve and right side of the heart are attainable. Lastly, the thoracic aorta is usually examined in cross-sectional and longitudinal views as the probe is withdrawn, to document any significant atherosclerosis or other pathology.

Three-Dimensional Echocardiography

Acquisition and display of 3D images have been a long-term goal of echocardiography. Although 3D datasets can be obtained from transthoracic or transesophageal rotational acquisition, true 3D echocardiography is accomplished by using a matrix-array transducer that emits and receives beams of ultrasound in two dimensions (**Fig. 14.23**), which results in the acquisition of a pyramidal dataset in three dimensions. Matrix-array probes for both transthoracic and transesophageal use are available. The 3D datasets can be used to display simultaneous orthogonal 2D images (e.g., four- and two-chamber apical views) or a 3D-rendered image. 3D echocardiography offers the potential to better orient valvular structures (see Valvular Heart Disease) or congenital abnormalities and can be particularly useful in planning surgical and percutaneous interventions. As discussed earlier, 3D echocardiography can also improve the accuracy of quantification of LV and RV volume and function. Useful 3D imaging depends heavily on good 2D images, and in fact there is some loss of spatial and temporal resolution in comparison. However, 3D echocardiography has become extremely useful as a way to delineate complex structures that extend beyond one plane or to find and localize measurements and abnormalities that are difficult to encompass using 2D images. Examples include finding clefts and localizing prolapsed segments in the mitral valve, delineating paravalvular leaks, measuring the distance of the coronary artery origins from the aortic valve, and providing comprehensive quantitative analysis of the valve leaflets and annuli (**Fig. 14.24** and Video 14.2), as well as guiding percutaneous device implantation (see Cardiac Procedures). As technologic advances improve 3D image quality and the ability to interpret these images in real time, 3D acquisition is becoming standard in echocardiography and in the operating room.

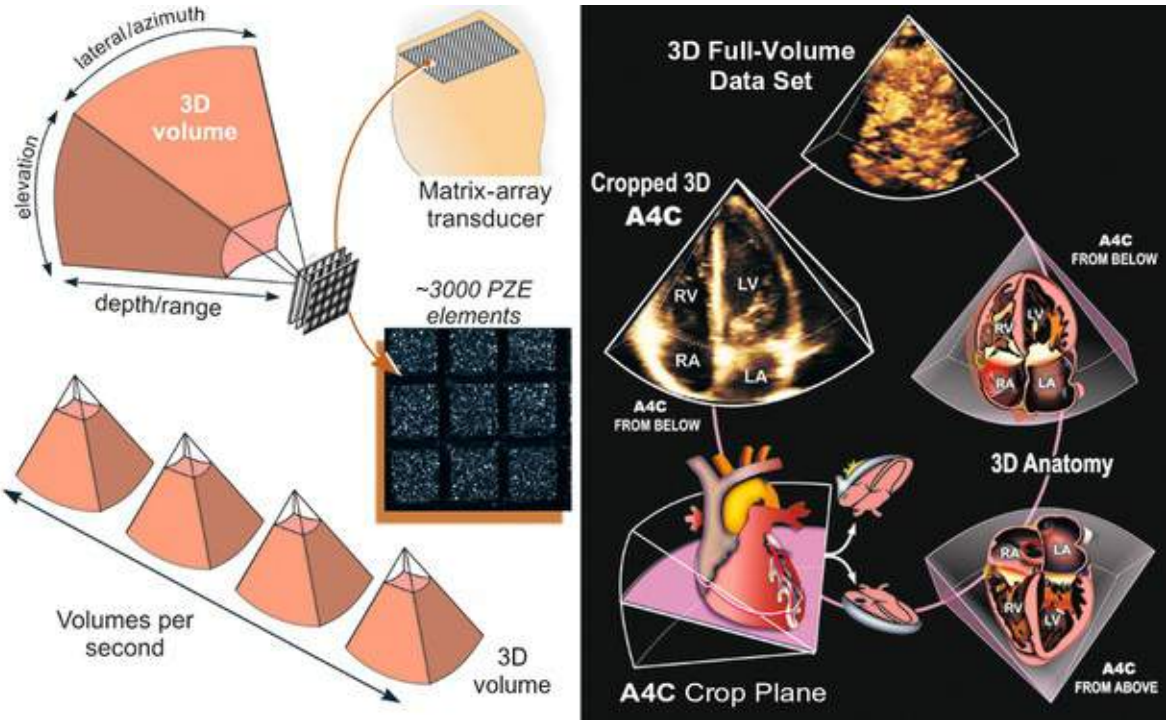


FIGURE 14.23 Three-dimensional echocardiography using a matrix-array transducer. A waffle-like matrix array **(left panel)** is used to obtain pyramidal "volumes" for real-time 3D data sets that can be cropped **(right panel)** and rendered in three dimensions. Alternatively, two-dimensional planes can be "cut" through any part of the 3D data set. *A4C,* Apical four-chamber view. (Modified from Bulwer BE, Rivero JM, editors. Echocardiography Pocket Guide: The Transthoracic Examination. Burlington, Mass: Jones & Bartlett Learning, 2011, 2013, p 208. Reprinted with permission.)

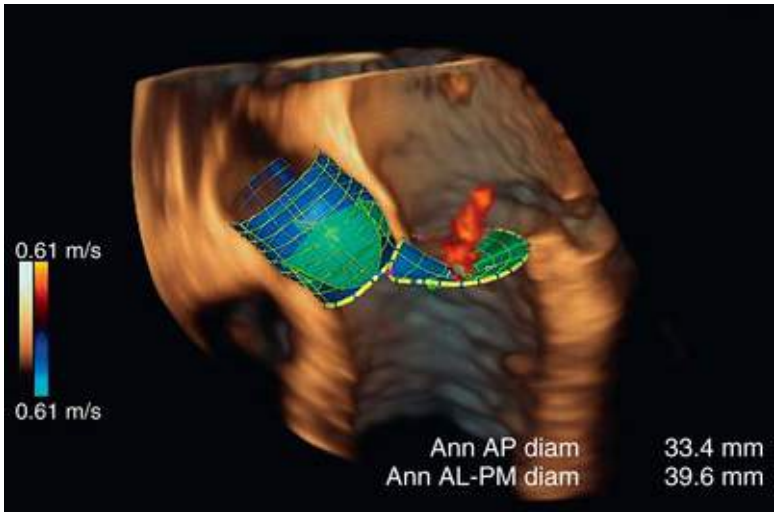
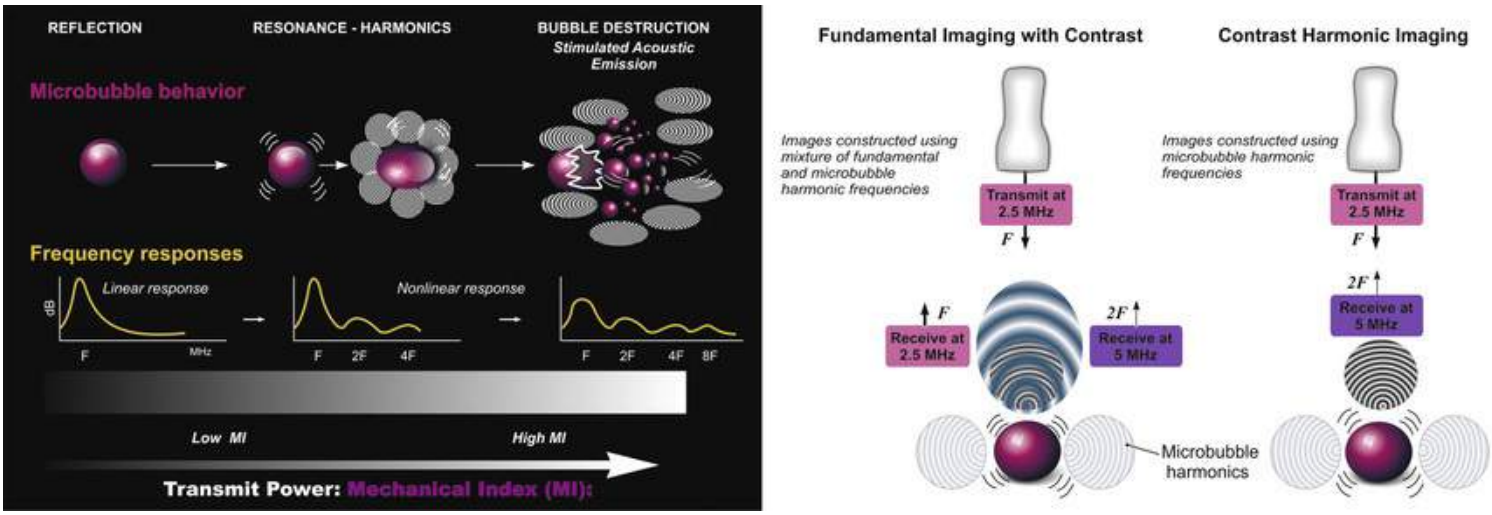


FIGURE 14.24 Three-dimensional TEE reconstructed view of the heart, showing the aortic and mitral valve geometry with mitral regurgitant jet (*red*) originating between the midscallops of the mitral valve. (See Video 14.2 for corresponding 4D images.)

Contrast Echocardiography

Contemporary echocardiographic contrast agents are stabilized gas microspheres of 2 to 8 µm, similar in size to red blood cells, and can move through the circulatory system accordingly after IV injection. Currently approved agents consist of perfluorocarbon gases, chosen because of their resistance to diffusion into the blood, which are enclosed within either albumin or phospholipid shells. Unlike the larger bubbles created by agitating saline, commercial contrast bubbles are small enough to transit the pulmonary vascular bed and are therefore capable of opacifying the left side of the heart.

Because their shells are not rigid, contrast bubbles will contract in response to the peak acoustic pressure of the sinusoidal ultrasound wave and expand when acoustic pressure is at its trough. Optimal imaging of contrast agents capitalizes on the way in which this oscillation in size varies with ultrasound system transmit powers (mechanical index). When exposed to sound waves at lower mechanical indices, the bubbles will undergo resonant oscillation in a linear fashion and reflect sound at the same fundamental frequency. With higher transmit frequencies, the bubbles will resonate in a nonlinear fashion and reflect sound at both fundamental frequency and harmonic frequencies, multiples of the fundamental frequency. At even higher transmit powers, the bubbles will be destroyed, thereby generating very strong nonlinear backscatter of extremely short duration (**eFig. 14.14**). Therefore, to distinguish bubbles from surrounding tissue, ultrasound systems are set at mechanical indices (0.15 to 0.3) that will generate nonlinear resonance without bubble destruction and then selectively "listen" only at harmonic frequencies, thereby improving the strength of the bubble signal relative to that of tissue.



EFIGURE 14.14 Principles of contrast-enhanced imaging.

By opacifying the blood pool, contrast agents improve detection of the endocardial–blood pool interface and thus facilitate assessment of ventricular volume, as well as global and regional ventricular function[23,24] (**Fig. 14.25**). It has been demonstrated that contrast agents can convert nondiagnostic (defined as inadequate visualization of two or more of six LV segments seen on apical views) to diagnostic studies in up to 90% of patients. This can be particularly helpful in the intensive care unit (ICU), as well as with stress echocardiography, in which obtaining adequate images in the immediate postexercise period may be challenging. By better delineating the cardiac anatomy, contrast agents facilitate the discovery of aneurysms and diverticula, mechanical complications of MI such as free wall rupture and

pseudoaneurysms (Video 14.3), apical hypertrophy, transient apical ballooning, endomyocardial fibrosis, and the spongelike trabeculations of noncompaction cardiomyopathy. Contrast is also helpful in detecting intracardiac masses such as thrombi and tumors and assessing their vascularity. In addition, contrast agents may help distinguish imaging artifact from pathology (**Fig. 14.26**). Despite being considered off-label use, contrast agents may be used to intensify spectral Doppler signals, which may be particularly helpful in delineating transvalvular gradients in aortic stenosis (**eFig. 14.15**), and can delineate extracardiac pathology such as vascular dissection. Finally, in patients undergoing alcohol septal ablation for obstructive HCM (**see Chapter 78**), contrast agents are used to delineate the perfusion bed of target septal perforators.

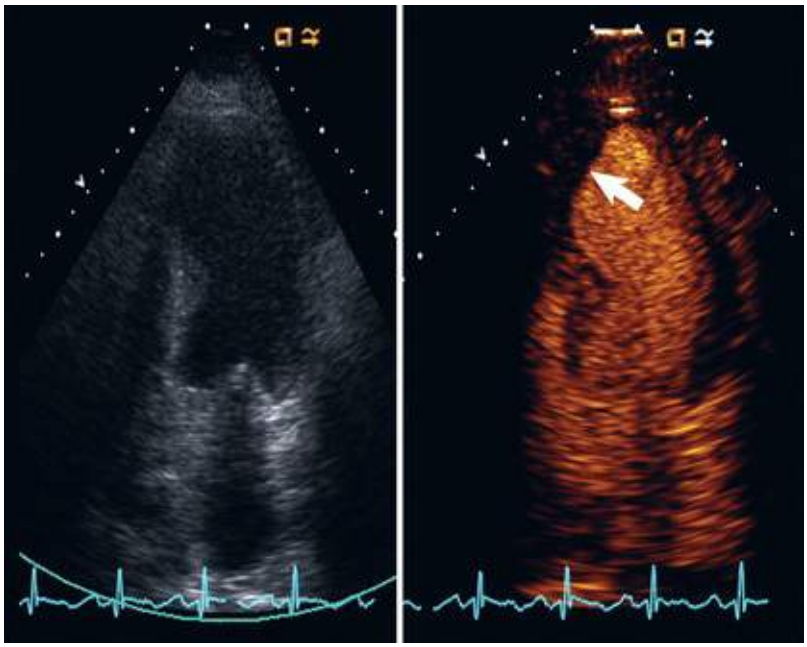


FIGURE 14.25 Unenhanced **(left)** and contrast-enhanced **(right)** apical four-chamber systolic images. In the unenhanced image it is impossible to define the endocardium, whereas with contrast enhancement the endocardium is clearly delineated and the straight margin characteristic of a sessile apical thrombus (*arrow*) is appreciated.

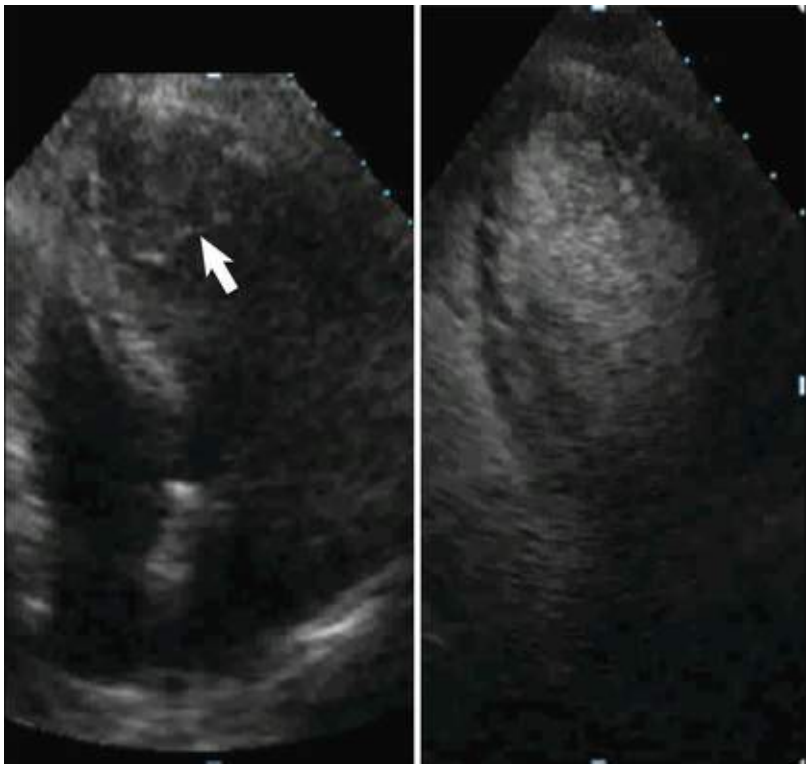
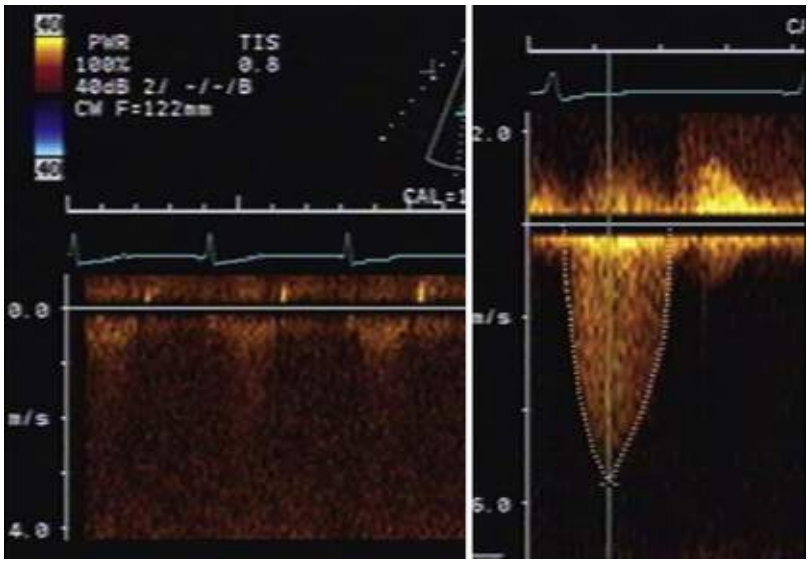


FIGURE 14.26 Apical four-chamber unenhanced **(left)** and contrast-enhanced **(right)** images. In the unenhanced image a thrombus-like structure is visualized in the apical region (*arrow*). The enhanced version shows that there is no filling defect, thus suggesting that this was an acoustic artifact and not a true thrombus.



EFIGURE 14.15 Use of echocardiographic contrast to enhance CW envelopes. Baseline unenhanced Doppler spectra **(left panel)** in this patient with valvular aortic stenosis are indistinct. Following administration of contrast material **(right panel)**, the CW spectra are clearly defined.

Myocardial perfusion contrast-enhanced echocardiography is another application that is based on the ability of ultrasound to detect contrast bubbles within the myocardial vasculature. Approaches depend on the fact that a burst of ultrasound with a high mechanical index “flash” will predictably destroy all microbubbles in the sector, and the rate at which myocardial contrast will subsequently be replenished depends on myocardial blood flow (**Fig. 14.27**). There are two options for imaging protocols following the high–mechanical index flash: continuous low–mechanical index real-time imaging, which preserves the ability simultaneously to see wall motion in the segment, versus a higher–mechanical index approach

with progressively longer intervals between ultrasound frames, which enhances the perfusion signal but at the expense of attaining wall motion information. Although myocardial perfusion imaging has been shown to be of value in both rest and stress imaging for detecting ischemia (**eFig. 14.16**) and identifying viable but stunned or hibernating myocardium,[24] contrast perfusion imaging requires expertise to optimize and is not yet in mainstream use.

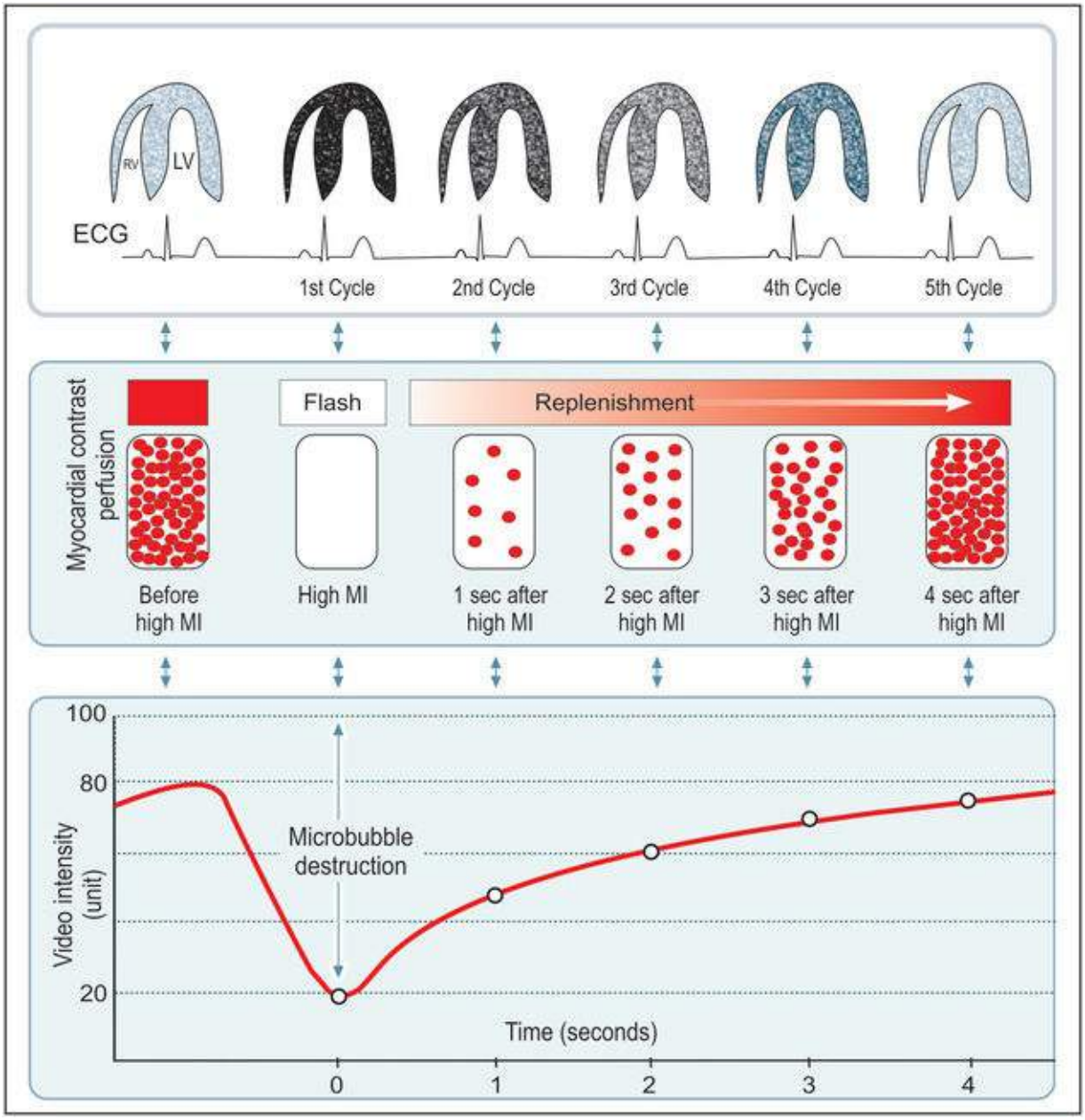
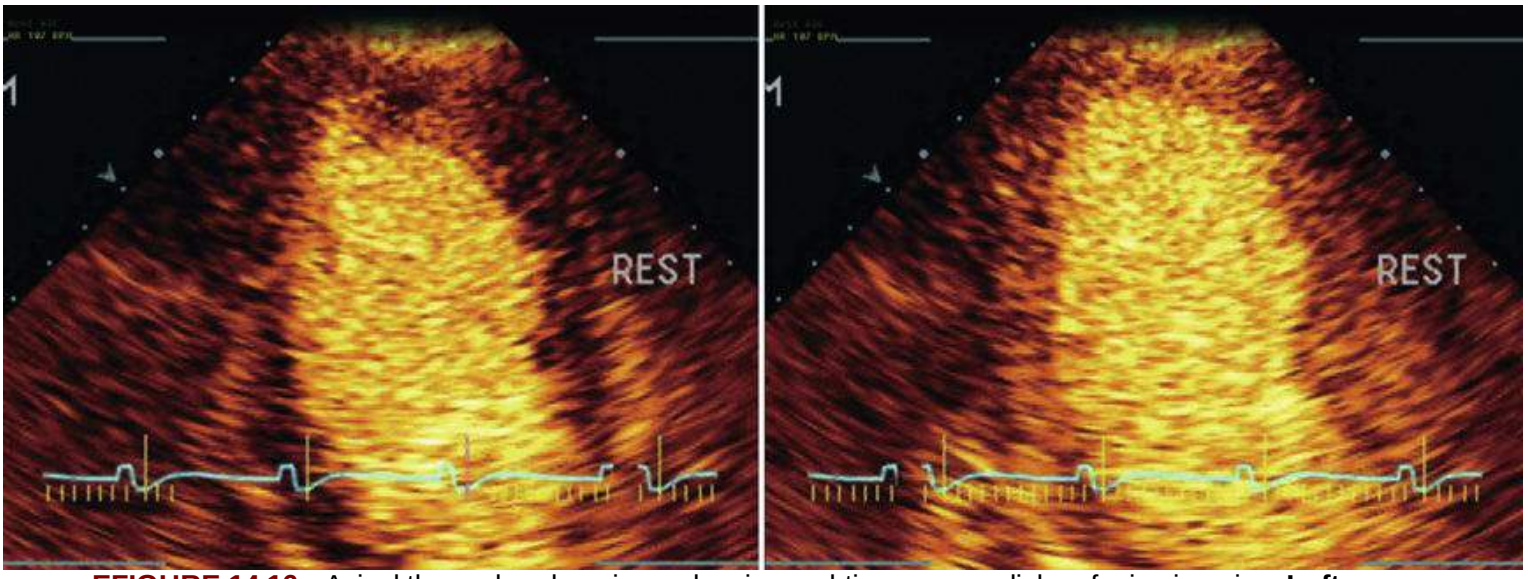


FIGURE 14.27 Myocardial contrast-enhanced echocardiography: schematic demonstrating the approach to myocardial perfusion imaging during steady-state infusion of a contrast agent. A high–mechanical index impulse (MI) destroys all the intramyocardial bubbles to yield an unenhanced image that will serve as the reference baseline. Subsequently, bubbles will return by coronary perfusion and progressively enhance the myocardium until a steady-state concentration is reached. This may be monitored by either a triggered approach in which imaging is performed on end-systolic images at increasing numbers of beats after the flash (1, 2, 3, 4, etc.) or by using low-MI continuous imaging. Enhancement will increase until a steady-state level is achieved (in this hypothetical example, at a five-beat pulsing interval or after 4 seconds of low-MI imaging). The rate at which replenishment occurs and the degree of enhancement under steady-state conditions, as quantitated by video intensity, reflect myocardial perfusion. (Modified from Wei K, Jayaweera AR, Firoozan S, et al. Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered as a constant venous infusion. Circulation 1998;97:473.)



EFIGURE 14.16 Apical three-chamber views showing real-time myocardial perfusion imaging. **Left,** Unenhanced baseline immediately after a high–mechanical index impulse flash. **Right,** Uniform enhancement consistent with normal perfusion. (Courtesy F. Xie and T. Porter, University of Nebraska Medical Center.)

Echocardiography in the Context of Cardiac Imaging

The arsenal of noninvasive cardiovascular imaging modalities includes nuclear imaging (single-photon emission computed tomography [SPECT] and positron emission tomography [PET]), cardiac CT, and CMR (**see Chapters 16, 17, and 18**) and will undoubtedly continue to expand. Of these choices, echocardiography continues to hold the major advantage of being the most rapid, portable, and real-time imaging modality available today. Therefore, TTE or TEE is often the first tool used in emergency situations such as cardiac tamponade, aortic dissection, peri-infarct or postoperative complication, and shock, in which rapid assessment of a very unstable patient may be carried out at the bedside. When a large number of patients need to be screened or patients need to be monitored long term with serial examinations, the fact that ultrasound imaging involves no ionizing radiation or nephrotoxic dye is a particularly important consideration. It is thus ideal for monitoring valvular dysfunction, cardiotoxic chemotherapy, and cardiomyopathies. Although the spatial resolution of other modalities such as CMR or CT may be greater than that of echocardiography, the superior temporal resolution of TTE and TEE render these techniques ideal for detection of small mobile vegetations, thrombi, and fibrinous strands in the heart, which move too rapidly to be easily visualized by techniques with slower frame rates. On the other hand, PET with ^{18}F-fluorodeoxyglucose (FDG) has emerged as a sensitive method for detecting inflammation and abscesses (**see Chapter 73**) when suspicion of endocarditis and intracardiac abscess is high but TEE is nondiagnostic.[25] Use of contrast-enhanced CT for diagnosis of aortic dissections has increased over the past two decades, largely because of the increasing accessibility of high-speed scanners and their ability to scan the entire aorta expeditiously.

Stress echocardiography using either treadmill, bicycle, or pharmacologic (dobutamine or vasodilator) stress has proved to be more accurate than the exercise ECG alone for diagnosing flow-limiting CAD, particularly in women and patients with LV hypertrophy.[26] When compared with nuclear imaging, stress echocardiography is equally sensitive and specific. It also has the advantage of allowing simultaneous assessment of hemodynamics, valvular disease (particularly aortic and mitral stenosis), and estimation of pulmonary artery systolic pressures in the same examination. However, the presence of previous

infarcted segments, known multivessel CAD, and a left bundle branch block may decrease the sensitivity and specificity of stress echocardiography because of difficulty interpreting wall thickening in the presence of resting regional dysfunction and translational motion.

In addition to diagnosing structural abnormalities of the myocardium, pericardium, valves, and vessels, echocardiography can directly demonstrate the consequent physiologic and hemodynamic derangements. This is particularly true for pericardial effusions (**see Chapter 83**), in which echocardiography can demonstrate impending or actual tamponade in real time within seconds. For more refined tissue characterization, CMR often offers higher resolution and specificity in defining tumor characteristics such as tissue density and vascularity, infiltrative/inflammatory processes, and nontransmural fibrosis. CT is particularly useful in defining calcified cardiac structures, and CT angiography is capable of imaging the coronary arteries along their full extent much more reliably than echocardiography (provided that the patient has a relatively slow and regular heart rate). Defining the thickness of the pericardium is also another "Achilles heel" of echocardiography. Cardiac ultrasound is poorly sensitive for pericardial thickening, and CT and CMR provide a more sensitive and comprehensive method of evaluation. However, echocardiography remains the first-line modality for detecting the characteristic respirophasic septal bounce and respiratory variations in cardiac output caused by constriction and continues to be the mainstay of follow-up regardless of treatment.[27]

Acoustic shadowing from prosthetic valves, ventricular assist devices (VADs), calcification, or air between the transducer and the far-field portions of the heart can preclude adequate visualization of portions of the heart by echocardiography. In these cases, fluoroscopy and CT are useful alternative or adjunctive modalities. A common example would be the dysfunctional mechanical aortic prosthesis, which can be difficult to visualize directly on TEE because of acoustic shadowing. However, the valve discs and disc excursion are easily visible on fluoroscopy or CT angiography. Similarly, because the sternum and ribs impede transthoracic ultrasound imaging and the air-filled trachea produces a "blind spot" on TEE, echocardiographic evaluation of the aorta is limited to the proximal root, arch, and segments of the thoracic and abdominal aorta. However, for unstable patients (e.g., after a motor vehicle accident or those in profound shock), TTE or TEE is often the only suitable bedside tool and is sufficient rapidly to diagnose or rule out most type A dissections (**see Chapter 63**). With TEE one can also expeditiously determine whether the proximal coronary arteries and arch vessels are patent without the use of nephrotoxic contrast material.

It should be emphasized that in many cases the use of two or more modalities is appropriate and complementary to diagnose more definitively the nature and extent of a pathology and plan appropriate treatment. This is particularly true in cases of ischemic and nonischemic cardiomyopathy,[28] for which CMR and SPECT/PET and FDG methods can more clearly define the locations of hypertrophy, fibrosis, or inflammation. Extensive aortic dissections in which one needs to define precisely the extent to which major coronary, head, and systemic arteries are involved also often calls for multimodality imaging. Nuclear molecular imaging is also useful for confirming or refuting suspected diagnoses of sarcoidosis and ATTR amyloidosis (**see Chapter 77**) made initially on clinical and echocardiographic grounds.

Echocardiography can unfortunately render a variety of artifacts that mimic masses, thrombi, tumors, or mobile tissue flaps. Although most can be discerned as false findings by experienced sonographers, a minority may require additional tailored echocardiographic views in varying tissue planes to put the question to rest. The adjunctive use of 3D echocardiography and echocardiographic contrast can reveal the true nature of these artifacts without the nephrotoxic effects of the iodinated and gadolinium agents used in radiologic imaging.

Currently, the newer techniques for assessing tissue strain, dyssynchrony, and diastolic function have

evolved in almost parallel fashion in echocardiography and CMR.[29] These techniques have been used extensively in research and are being validated in a clinical setting with larger populations. In summary, although ultrasound and radiology continue to advance, familiarity with the relative advantages and limitations of each imaging modality greatly assists in determining which tool is best suited to answer the clinical question at hand.

Myocardial Infarction

Echocardiography plays an essential diagnostic and prognostic role in assessing patients during and after acute MI. Normal wall contractility (normokinesis) is seen as wall thickening caused by the contraction of individual myocardial fibers during systole. On echocardiography the radial distance between the epicardial and endocardial borders normally increases by at least 20% during systole. Global LVEF, as calculated by 2D echocardiography and preferably by the 2D biplane method of discs, provides an indication of overall infarct size and location. It has remained the single measure with the greatest prognostic and clinical significance during and after MI.

Myocardial ischemia affects LV systolic function both focally and globally. Focal hypokinesis—decreased systolic thickening—occurs within seconds of the onset of myocardial ischemia, before chest pain and changes on the ECG. This pathognomonic finding will occur in the region of the left and/or right ventricle supplied by the compromised artery (at least 70% stenosis) and give the appearance of a hinge point compared with adjacent perfused segments (Video 14.4). Ischemia may also manifest as delayed contractility of a segment. Ischemia is a dynamic condition, and if sufficient blood flow is restored in time, either through a decrease in metabolic demand (as when a stress test ends) or through reperfusion, contractility of the affected segment can recover rapidly. However, after reperfusion, a marked reduction in LVEF during the initial few days after MI can be secondary to myocardial stunning rather than permanent myocardial dysfunction and can improve substantially over days to weeks[30,31] (**see Chapter 57**).

Persistence or increasing severity of the wall motion abnormality after the initial insult implies that the tissue is becoming nonfunctional (i.e., not metabolically active or hibernating) or nonviable (infarcted). Akinetic myocardial segments do not thicken at all, and dyskinetic segments bulge paradoxically outward in systole, thus implying that no functioning myocardium is present. Thinning of the walls to less than 6 mm, echo brightness, and dyskinesis usually indicate scar. Sudden dilation of the left ventricle and a decrease in the LVEF are predictive signs of larger areas of ischemia (more proximal and/or multivessel disease). More refined techniques, including IV echocardiographic contrast enhancement to examine myocardial perfusion, low-dose dobutamine echocardiography, or regional strain analysis, may be useful in demonstrating whether segments that are still akinetic after reperfusion remain viable but hibernating.[31]

Specific regions in the heart can be mapped to specific coronary artery territories (**Fig. 14.28**), thereby allowing determination of the infarct-related vessel in patients with MI or detection of ischemic territory during stress echocardiography (see later, Stress Echocardiography). Very proximal CAD can actually be detected by examining the ostia of the coronary arteries with TEE. A proximal coronary artery stenosis will cause wall motion abnormality in a large territory (i.e., an entire wall from base to apex), whereas more distal blockage will affect only more apical segments. An acute left main occlusion will result in such extensive dysfunction (anterior septum, anterior and lateral walls) that if untreated, is usually lethal. Proximal right coronary artery (RCA) lesions can additionally cause RV dysfunction and infarction (Video 14.5). The presence of previously existing CAD can modify the extent of new wall motion

abnormalities seen during acute MI. Small collateral vessels from other unobstructed coronary arteries can develop and perfuse the peripheral territory of affected vessels, thus diminishing the dysfunctional territory. Wall motion scoring can be used as a complementary tool to the ejection fraction for quantifying the extent and severity of LV systolic function (**see eFig. 14.10**).

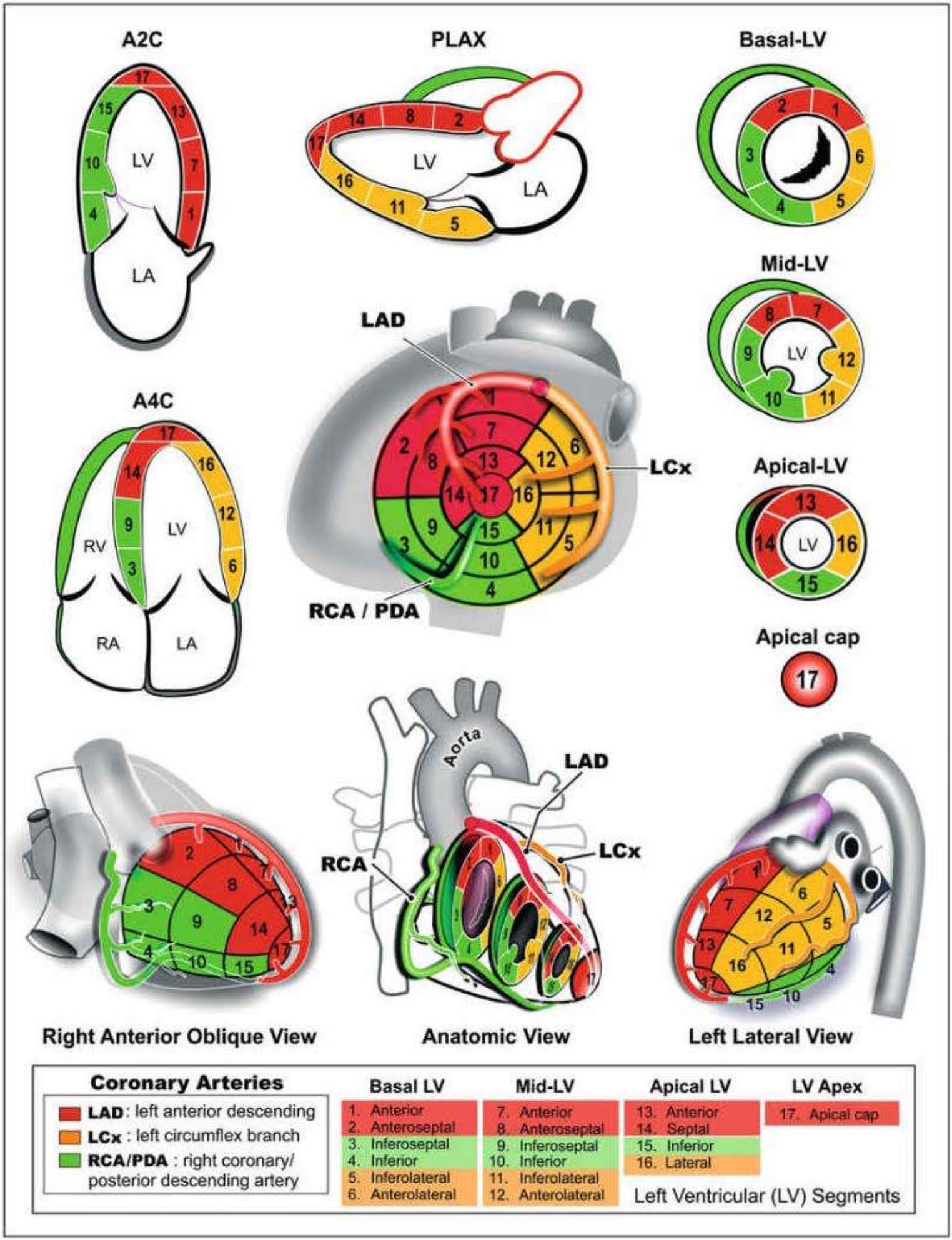


FIGURE 14.28 Coronary artery territories. The main epicardial coronary arteries each supply distinct myocardial territories, which may be mapped and evaluated during the ultrasound examination. For standardization, the left ventricle (LV) is divided along the long axis into anterior, inferior, septal, and lateral

quadrants. At the basal and midventricular levels, the septal and lateral walls are further subdivided into anterior and inferior segments. Each wall is further sectioned in short-axis planes into basal, middle, and apical thirds, with the distal apex beyond the LV cavity forming a cap segment, to yield a total of 17 wall segments. Most of the blood supply to the heart is from the left main coronary artery, which divides into the left anterior descending (LAD) and left circumflex (LCx) arteries. The LAD supplies most of the anterior ventricular wall, and its septal branches supply the anterior two thirds of the septum. In addition, diagonal branches of the LAD supply the anterolateral wall. Large LADs may wrap around the apex of the heart and supply the distal-most portion of the inferior wall. The LCx runs in the atrioventricular groove, and its obtuse marginal branches supply the inferolateral wall. The right coronary artery (RCA) supplies blood to the inferior third of the septum and the inferior wall. The RCA also supplies the right ventricle. *A2C,* apical two-chamber view; *A4C,* apical four-chamber view; *LA,* left atrium; *PDA,* posterior descending artery; *PLAX,* parasternal long axis; *RA,* right atrium; *RV,* right ventricle. (Modified from Bulwer BE, Rivero JM, editors. Echocardiography Pocket Guide: The Transthoracic Examination. Burlington, Mass: Jones & Bartlett Learning; 2011, 2013, p 131. Reprinted with permission.)

Practical Considerations in Assessment of Regional Wall Motion

It is important to distinguish carefully between wall thickening as opposed to just epicardial or endocardial border movement during systole. The many pitfalls in diagnosing wall motion abnormalities include false positives because of poor visualization of the endocardium, superior angulation of the probe such that the membranous nonmuscular portion of the upper interventricular septum is misinterpreted as a nonmoving myocardial segment, extracardiac compression of the inferior wall by ascites or abdominal contents (“pseudodyskinesis”), and paradoxical or dyssynchronous septal motion as a result of bundle branch block or the postsurgical state. False negatives, such as missing a wall motion abnormality that is present, can also occur because of poor image quality or off-axis imaging. Injection of an IV contrast agent can often help delineate the endocardial borders.

Notably, echocardiography in a patient who is free of chest pain at the time of imaging may not reveal a resting wall motion abnormality (because of decreased demand or reperfusion at that point in time). Furthermore, this technique is relatively insensitive for small areas of subendocardial or microvascular ischemia. Nevertheless, when a patient has ongoing acute chest pain but echocardiography does not reveal new wall motion abnormalities, a broader differential diagnosis than epicardial coronary artery occlusion must be entertained. Possible nonischemic cardiac causes of chest pain that can be also diagnosed by cardiac ultrasound include pericarditis, aortic or coronary aneurysm or dissection, myocarditis, cardiac contusion, and ruptured mitral chordae. Noncardiac causes include pulmonary emboli (which can cause acute right-sided heart dysfunction in a distinctive pattern), as well as gastroenterologic processes (e.g., reflux, peptic ulcer disease, esophageal spasm), pleuritis, and costochondritis.

Mechanical Complications After Myocardial Infarction

MI can cause serious collateral damage from tissue necrosis and bleeding, which is often heralded by cardiogenic shock (**see Chapter 59**). These events may appear within days of the initial infarct or may be delayed by years. All cardiologists should be familiar with causes of infarct-related shock and their appearance on echocardiography (**Fig. 14.29**). Indications for echocardiography after MI are detailed in the appropriate use criteria developed by the American College of Cardiology and other societies (**see Table 14G.1**).[17]

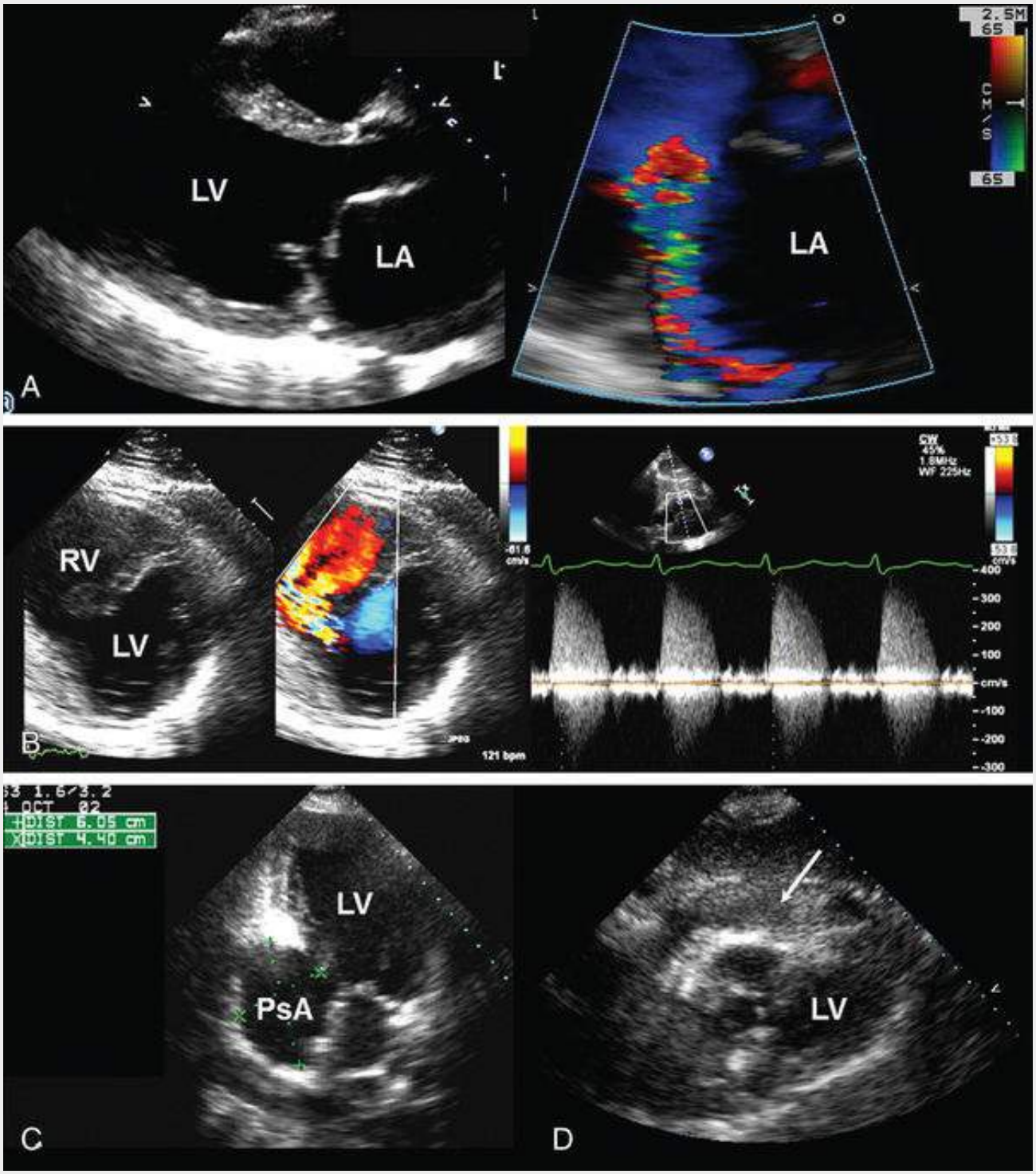


FIGURE 14.29 Acute complications of myocardial infarction. **A,** Flail mitral leaflet **(left panel)** with severe mitral regurgitation **(right panel). B,** Ventricular septal defect **(left panel)** in the basal inferoseptum with **(right panel)** an intraventricular pressure gradient of 58 mm Hg by spectral Doppler. **C,** Pseudoaneurysm (*PsA*) of the basal inferior wall. **D,** Hemopericardium (*arrow*) caused by free wall rupture. *LA,* Left atrium; *LV,* left ventricle; *RV,* right ventricle.

Mitral Regurgitation.

Acute severe mitral regurgitation (MR) is most often caused by infarction and consequent rupture of a papillary muscle. It results in "flail" of the associated mitral leaflet into the left atrium during systole with valve incompetence (**Fig. 14.29A** and Videos 14.6 and 14.7). The anterolateral papillary muscle receives dual blood supply from both the left anterior descending (LAD) coronary artery and its diagonals and the left circumflex artery (**see Chapter 20**); thus a very large infarct would be required to disrupt this papillary muscle, which supports more of the anterior mitral leaflet. In contrast, the posterior descending artery, which arises from the RCA in right-dominant individuals, supplies solely the

posteromedial papillary muscle. For this reason, papillary muscle rupture and flail posterior leaflet occur more frequently with inferior infarcts. There is, however, overlap between the papillary muscle support of the leaflets, and only one head or a tip of a papillary muscle may be disrupted rather than the entire trunk. Thus, in small infarcts there may be a focally flail segment or just the tip of an opposing mitral leaflet affected. The jet of MR is eccentric and directed *away* from the affected mitral leaflet; that is, posterior leaflet flail directs the MR jet anteroseptally, whereas anterior leaflet flail directs the regurgitant jet posterolaterally (**Fig. 14.30**). *If clinical suspicion for acute infarct-related MR is high and TTE is not definitive, proceeding expeditiously to surgical consultation and TEE is recommended.*

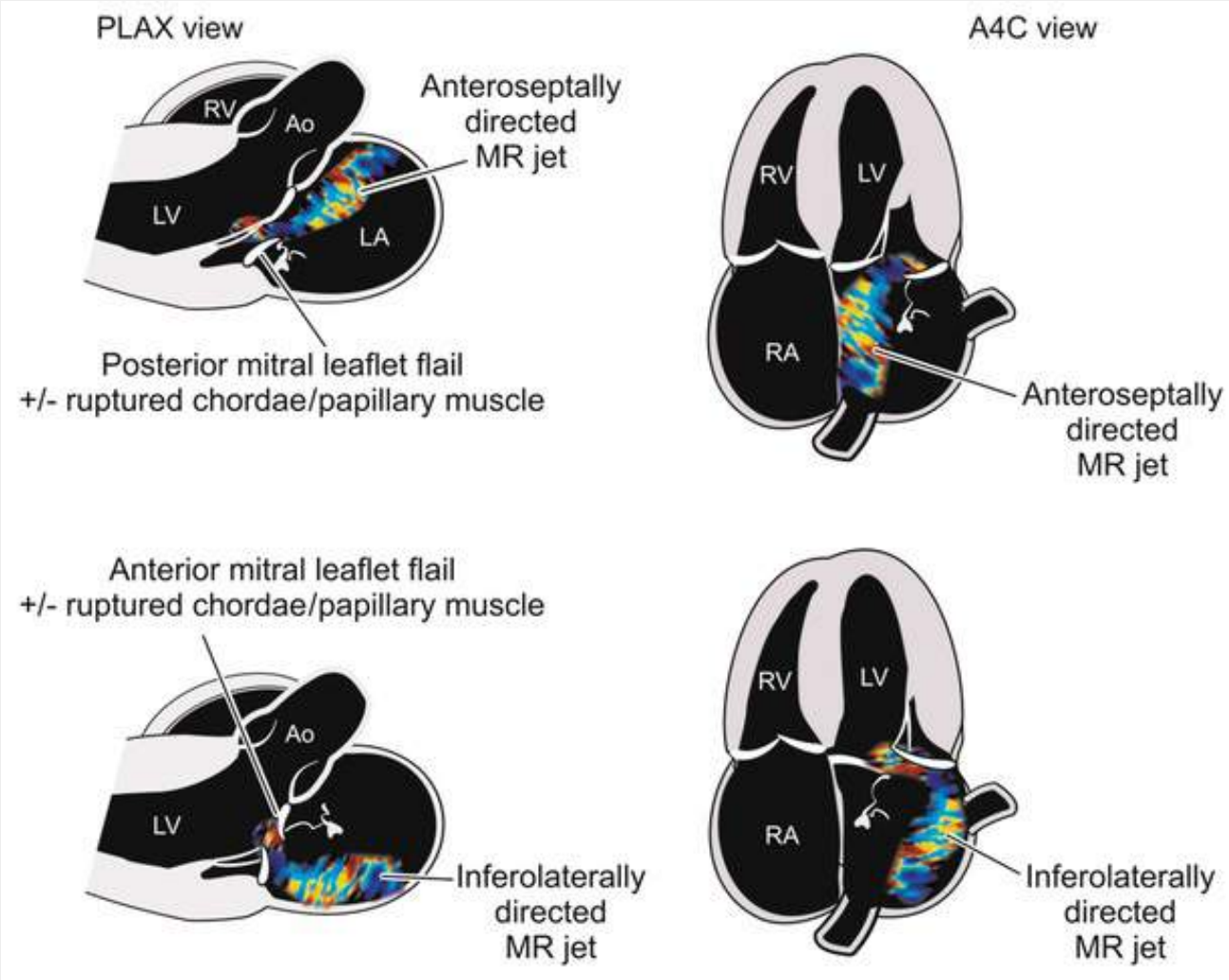


FIGURE 14.30 Acute structural mitral regurgitation (MR). The consequences of rupture of the posterior papillary muscle and chordae **(upper figure)** versus the anterior papillary muscle and chordae **(lower figure)** are shown with respect to the direction of the MR jet. Posterior mitral leaflet flail will cause a very eccentric jet to be directed anteroseptally, and this can occasionally cause clinicians to erroneously detect a "new aortic stenosis" murmur. Anterior mitral leaflet flail will cause the MR jet to be directed inferolaterally, and this murmur may be missed unless one auscultates the back. *A4C,* Apical four-chamber; *Ao,* aorta; *LA,* left atrium; *LV,* left ventricle; *PLAX,* parasternal long axis; *RA,* right atrium; *RV,* right ventricle.

Ventricular Septal Defect (VSD).

Defects in the ventricular septum may appear as discrete areas of echo dropout with interventricular flow coursing through, as demonstrated by color Doppler (**Fig. 14.29B** and Video 14.8). Echocardiography should define the location, type (simple or complex), and size of the defect. Anterior VSDs tend to be simple (i.e., direct slitlike perforations through both sides of the septum at the same level) and are

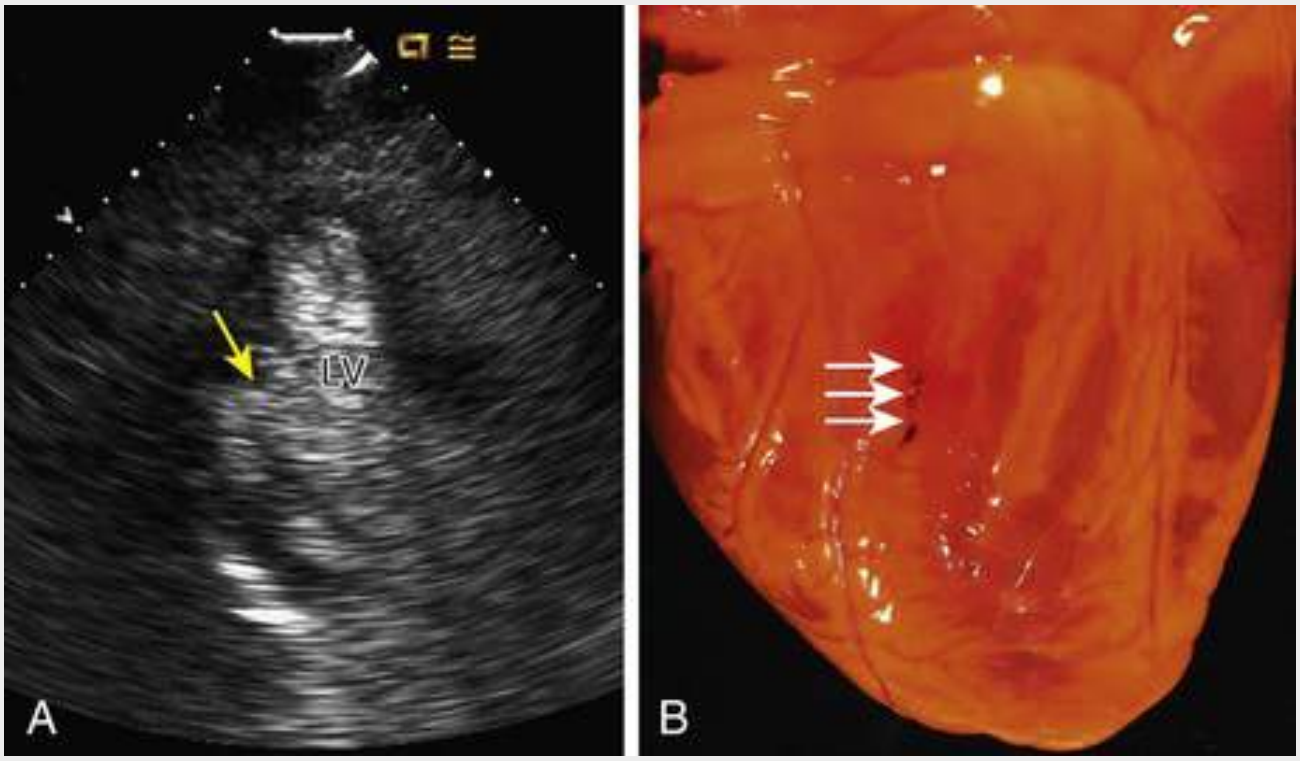
usually located more apically. In contrast, inferior infarctions often involve the adjacent basal inferior septum or even the right ventricle and can be complex (with serpiginous or multiple fissures). Unless the defect is very large, 2D echocardiographic images alone may only be suggestive of thinned or focally absent myocardium, but color flow Doppler can definitively demonstrate both location and extent of the shunt at the "break" area (Video 14.9). A small (restrictive) VSD will have a high interventricular pressure gradient, whereas a large (unrestrictive) VSD will have lower gradients and is more likely to be associated with further tissue damage, including even papillary muscle rupture or free wall rupture in catastrophic cases. By applying the Bernoulli equation, the pressure gradient across a restrictive VSD can be calculated. RV systolic pressure should be equal to systolic blood pressure minus the interventricular pressure gradient. Significant and prolonged shunting across the VSD can lead to biventricular failure and eventually cause right-sided pressures to increase and the amount of left-to-right shunting paradoxically to decrease over time.

Pseudoaneurysm.

A pseudoaneurysm is a ventricular free wall perforation that is locally contained by adjacent pericardium and adhesions. Pseudoaneurysms appear more often after inferior MI, although they may arise in the lateral and apical regions. On echocardiography, pseudoaneurysms appear as echo-free spaces or extra chambers adjacent to and continuous with the LV cavity (**Fig. 14.29C** and Video 14.10). The appearance can be similar to that of a true LV aneurysm or diverticulum, but unlike these two pathologies, the definitive feature of a pseudoaneurysm is disruption of all three layers: endocardium, myocardium, and epicardium. Thus a pseudoaneurysm is more likely to have distinguishing traits such as a narrower neck with more ragged edges and turbulent bidirectional flow (as opposed to the smoother margins and flow pattern typically seen with true aneurysms). However, no single echocardiographic criterion is specific enough to distinguish false from true LV aneurysms accurately. IV echocardiographic contrast agents can be very helpful in delineating the area of the perforation and extravasation into the pericardial space if the patient is sufficiently stable (see Video 14.3). Although pseudoaneurysms are typically subacute complications of MI and may hemorrhage suddenly, a fair percentage of pseudoaneurysms are surprisingly stable and go undetected for months and even years. In stable patients, CMR or even angiography is often useful in distinguishing pseudoaneurysm from aneurysm.

Free Wall Rupture.

Free wall rupture is usually so acutely lethal that it is rarely imaged, but findings consist of a sudden new pericardial effusion in a patient with marked thinning and akinesis at the terminal myocardial territory of the occluded artery. Echocardiographic features of tamponade are usually present. The pericardial effusion may contain spontaneous echocardiographic contrast or organized clot (*hemopericardium*) (Video 14.11). Demonstration of low-velocity color Doppler flow or extravasation of intravenous echocardiographic contrast from the LV cavity into the effusion (**eFig. 14.17**) would confirm wall rupture, but care must be taken not to confuse rupture with the low-velocity color signal generated within pericardial fluid by the adjacent moving heart.



EFIGURE 14.17 LV wall rupture, as demonstrated by **A,** extravasation of intravenous echo contrast from the LV cavity through a slitlike orifice (*yellow arrow*) into the pericardium inferolaterally, on this apical three-chamber view. **B,** Posterior view of the heart, with the site of rupture (*white arrows*) at the posterolateral left ventricle, causing this patient's demise 5 days after diagnosis of a large posterolateral myocardial infarction.

Tamponade.

Mechanical causes of tamponade related to infarcts include pseudoaneurysm and free wall rupture, as previously described, but also aortic dissection (in some cases caused iatrogenically by percutaneous intervention). All cause frank bleeding into the pericardial sac. Hemopericardium is associated with a distinctive gel-like appearance of pericardial fluid on echocardiography (**Fig. 14.29D** and Video14.11). Fully organized thrombus found in otherwise echolucent pericardial effusions may be indicative of past wall rupture that has been sealed off in the interim (i.e., intermittent bleeding).

Other Causes of Cardiogenic Shock in Myocardial Infarction.

In addition to the mechanical complications described earlier, there are other potential explanations for hypotension in the setting of acute MI. Simple loss of pump function in large infarcts is probably the most common reason. RV infarction can occur concomitantly with inferoposterior injury or as isolated RV injury in a patient with occlusion of a nondominant RCA (**see Chapter 59**). It may reveal itself when nitroglycerin is administered and decreases preload. The most reliable echocardiographic sign of RV infarction is new dilation and hypokinesis of the right ventricle. Typically, the lateral or posterior RV walls are most affected (the posterior wall represents the distalmost RCA territory), with sparing of the apex (which is also supplied by the distal LAD). Depressed RV function can often be illustrated by a low tissue Doppler peak velocity of the tricuspid annulus at systole or by a slow upstroke to the tricuspid regurgitant (TR) Doppler envelope (low dP/dT) and can be quantified by a low RV ejection fraction or FAC.[15] Annular dilation may cause associated TR and RA dilation with relatively low or normal peak TR flow velocity (because of low or normal RV systolic pressure). Because RV walls are thinner than those of the left ventricle, the right ventricle can recover relatively quickly from ischemic insults and return to normal function after revascularization. Other potential causes of hypotension and cardiogenic shock include reocclusion of coronary arteries with infarct expansion, related effusive pericarditis

(Dressler syndrome), and acute dynamic LVOT obstruction with mitral systolic anterior motion, when the basal portion of the heart becomes hypercontractile in response to more apical wall motion abnormalities in patients with upper septal hypertrophy.

Late Complications of Myocardial Infarction

Even after a MI is completed, ongoing changes in heart structure and function can cause negative sequelae that can be clinically silent. *Left ventricular aneurysms* are discrete dyskinetic outpouchings of the left ventricle with preservation of the integrity of the three heart layers (endocardium, myocardium, and epicardium). The most common locations of LV aneurysms are the basal inferior wall and the apex, where they may grow to a size that rivals the other cardiac chambers (Video 14.12). Spontaneous echocardiographic contrast within the aneurysms signifies local stasis of blood flow.

In the absence of anticoagulation, ongoing sluggish flow within an LV aneurysm may lead to the formation of *left ventricular thrombus* (**Fig. 14.31A**). Patients with large aneurysms, anterior MIs, or LVEF less than 40% are at particular risk for LV thrombus. Intracavitary thrombi may be detected within the first 1 to 2 weeks after MI and appear as discrete, homogeneously echogenic, deformable masses abutting the endocardial border of an akinetic or dyskinetic wall segment. Earlier studies indicated that the sensitivity and positive predictive value (PPV) of echocardiography for LV thrombus were 95% and 86%, respectively, compared with surgical/pathologic or radionuclide imaging. However, compared more recently with CMR, the sensitivity (60%) and PPV (75%) appear to be significantly less than originally assumed. Accuracy is undoubtedly affected by pretest probability, image quality, and the size and type of thrombus (the mural type being more difficult to detect).[32] The use of IV echocardiographic contrast material can double the detection rate of intracavitary thrombi and is highly recommended (**see Fig. 14.25**). Thrombi may appear mural (i.e., fixed, flattened, and adherent to the endocardial wall, as in **Fig. 14.31A**) or may have independently mobile and protuberant portions (Video 14.13). Larger and more mobile thrombi, as well as those residing adjacent to hyperkinetic myocardial segments, are more likely to embolize. As the thrombi age, they tend to become less mobile, more compact, and echobright in appearance. With anticoagulation, LV thrombi have been observed to resolve in almost 50% of patients by 1 year and in approximately 75% by 2 years of follow-up.

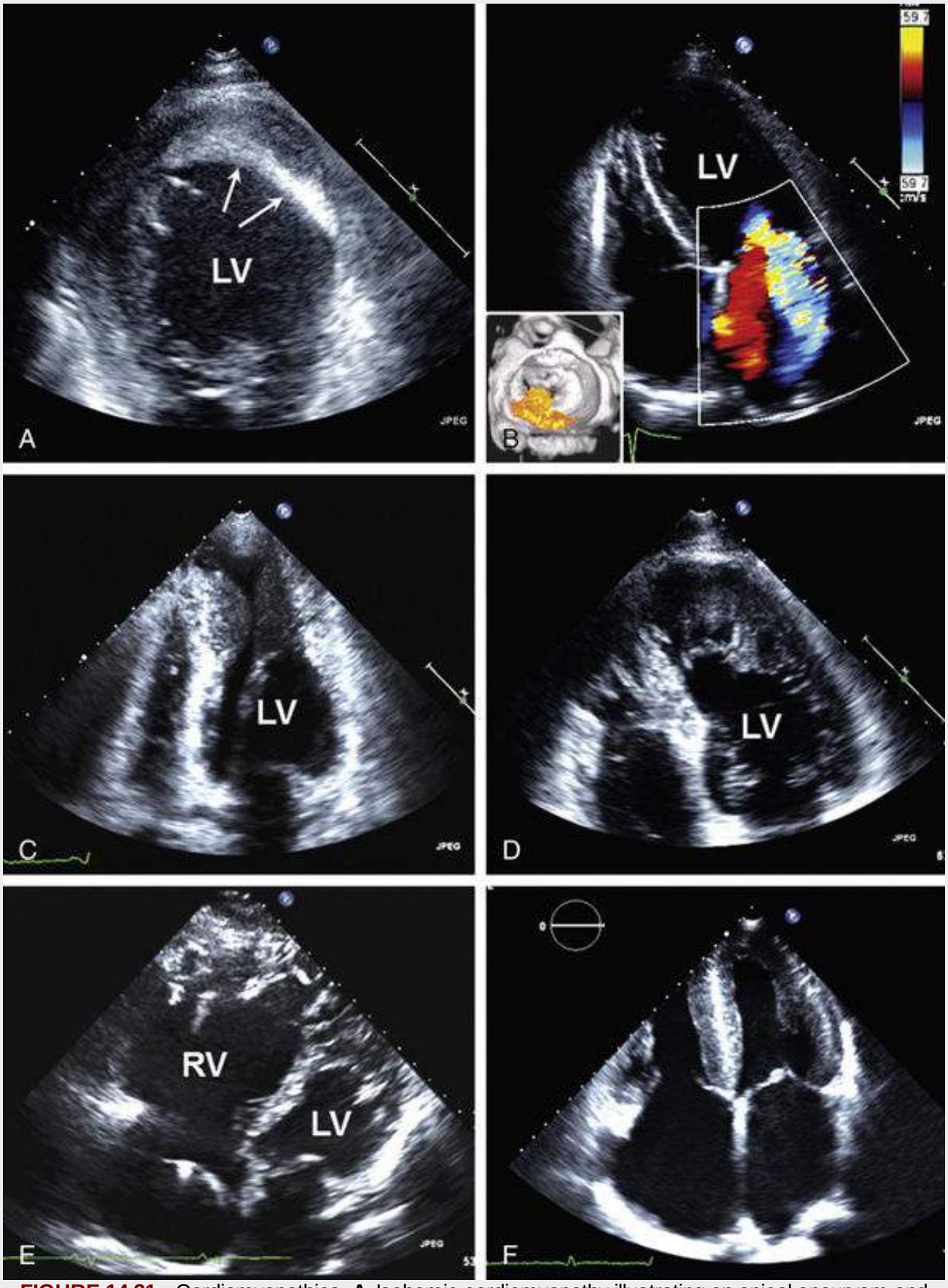


FIGURE 14.31 Cardiomyopathies. **A,** Ischemic cardiomyopathy illustrating an apical aneurysm and thrombus (*arrows*). **B,** Ischemic cardiomyopathy illustrating severe functional MR. **C,** Apical hypertrophic cardiomyopathy with midcavity systolic obliteration and an apical aneurysm. **D,** LV noncompaction. **E**, Arrhythmogenic RV dysplasia. **F,** Amyloid heart disease. *LV,* Left ventricle; *RV,* right ventricle. (See accompanying Videos 14.15 to 14.22.)

The left ventricle can continue to expand in size and mass and display hypokinesis in noninfarcted areas, even after the initial insult has ended, a process termed *left ventricular remodeling*. In the

broadest context, remodeling is defined as an increase in LV volume, but concomitant changes in the geometry of the ventricle are also frequently observed. An increase in the globular shape of the heart is quantified by the *sphericity index*. On 2D echocardiography, this is the ratio of the long-axis dimension to the short-axis dimension. Sphericity index is 1.5 or higher in normal hearts but approaches 1.0 in globular hearts (see later, Dilated Cardiomyopathy).

Ischemic MR refers to mitral incompetence in the setting of ischemic LV dysfunction and in the absence of structural abnormalities, such as prolapse, thickening, or calcification, that would otherwise cause regurgitation (**see Chapter 69**). This process has been intensively studied, and there appears to be interplay between the LV, mitral, and subvalvular components, as well as the left atrium, all of which contribute to the pathophysiology of MR. Displacement of the papillary muscle positions inferiorly and toward the apex contributes to tethering of the mitral leaflets at abnormal angles that restrict leaflet closure. Mitral annular and LA dilation, as well as insufficient mitral leaflet area to compensate for the enlarged orifice, appears to play a role in enhancing ischemic MR as well[33] (**Fig. 14.31B**). The *effective regurgitant orifice area* (EROA) is a simple measure of the degree of mitral insufficiency derived from color and spectral Doppler measurements and has a direct correlation with overall mortality (see later, Mitral Regurgitation).

Echocardiographic Prognostic Indicators After Myocardial Infarction

After acute MI, echocardiography can assist in assessing (1) the prognosis for patients at risk for recurrent ischemia and heart failure and (2) overall risk for morbidity and mortality. LVEF is one of the most important predictors of overall morbidity and mortality after acute MI and is used as a surrogate endpoint in most major clinical trials of medical and procedural interventions. As LVEF declines, the rate of sudden cardiac death (SCD) increases. Based on current evidence the incidence of SCD at an LVEF of 35% or less is high enough to consider implantation of an implantable cardioverter-defibrillator (ICD) for primary prevention in selected patients with intraventricular conduction delay and heart failure[34] (**see Chapters 25 and 27**). As mentioned previously, after reperfusion, stunned or hibernating myocardium may recover function days to weeks later, so it is generally recommended that one wait at least 40 days after acute MI, or as long as 3 months after coronary artery bypass graft (CABG) or percutaneous revascularization, to reevaluate LVEF before making a decision on ICD implantation for primary prevention. Reduced global longitudinal (GLS) and circumferential strain have emerged as important risk indicators for death or heart failure after MI. A high degree of dyssynchrony, quantitated by the same technique, is also a risk factor.[2,5,35] In addition to LVEF, overall LV size (as assessed by LV end-diastolic diameter and volume) and sphericity are important prognostic indicators. Other measures independently predictive of heart failure in patients with stable CAD include increasing LV mass index (LVMI >90 g/m^2), a pseudonormalized or restrictive pattern of diastolic dysfunction, an LVOT VTI less than 22 mm, and an LA volume index greater than 29 mL/m^2. The presence of even mild MR (especially if EROA ≥20 mm^2 or regurgitant volume ≥30 mL) is now well established as an independent predictor of cardiac mortality, as well as heart failure or recurrent MI.[36]

The WMSI may be a more discriminatory measure than LVEF (as measured by echocardiography or nuclear methods) in predicting cardiac events, in particular, rehospitalization for heart failure. On resting echocardiography, WMSI higher than 1.7 that persists after treatment of MI suggests a substantial (>20%) perfusion defect and increased risk for complications. In stress echocardiography, WMSI higher than 1.7 at peak stress and LVEF of 45% or less are independent markers of patients at high risk for recurrent MI

or cardiac death. When there is a question of whether revascularization will improve akinetic but viable areas, dobutamine or contrast-enhanced echocardiography may delineate the extent of myocardium that is hibernating (hypocontractile yet viable and still perfused)[37] (see later, Stress Echocardiography).

Finally, it should be noted that wall motion abnormalities are indicative of focal myocardial dysfunction but are not entirely specific for atherosclerosis-related MI. Vasospasm, inflammation, or fibrosis secondary to myocarditis; swelling from intramural hematoma or edema; takotsubo cardiomyopathy (**see Chapter 77**); and any focal myocardial insult are also causes of wall motion abnormality. A comprehensive synthesis of the history, clinical and physical examination findings, and ECG together with appropriate cardiac imaging will allow the clinician to narrow down the differential diagnoses and pursue appropriate therapy.

Cardiomyopathies

Dilated Cardiomyopathy

Dilated cardiomyopathies share the common characteristics of an enlarged LV and/or RV cavity with systolic dysfunction (**see Chapter 77**). Left ventricular end-diastolic (LVED) and end-systolic volumes, as well as LVED dimensions and overall LV mass, are increased (with normal or thinned walls), and the overall LVEF is subnormal. With persistence of the underlying condition, the left ventricle becomes less ellipsoid and more globular in shape, and the sphericity index decreases toward 1. The actual SV and cardiac output may remain preserved because of increased overall intraventricular volumes, as well as increased heart rate.

Dilated cardiomyopathies caused by processes such as viral, postpartum, genetic, chemotherapy, tachycardia, and toxic-metabolic causes typically display diffuse LV hypokinesis; those caused by more focal processes such as sarcoidosis are more likely to have discrete areas of hypokinesis or akinesis (Video 14.14). Ischemic heart disease is often accompanied by focal wall motion abnormalities in a coronary distribution, as well as visible atherosclerotic plaque in the aortic root and other portions of the aorta. One clue to the presence of focal inflammatory processes is wall motion abnormalities that do not follow a coronary distribution and associated thickening secondary to edema. Approximately half of symptomatic patients with Chagas disease classically have an apical or inferobasal aneurysm, but more advanced cases feature global hypokinesis.[38] *Takotsubo cardiomyopathy,* which appears to be a stress- or neuroendocrine-mediated process, is unique in displaying a distinctive pattern of apical ballooning and basal hyperkinesis in the majority (>80%) of patients[39] (see Video 14.13). Although the degree of dysfunction can be impressive in stress cardiomyopathy, remarkable and complete resolution can take place within days to weeks. Rarer “reverse” or alternate patterns of stress cardiomyopathy have also been encountered, in which basal or midventricular wall motion abnormalities occur with preservation of apical function. With sustained left-sided heart failure (and thus secondary pulmonary hypertension) or systemic causes of myocardial dysfunction, the right ventricle may also become dilated and hypokinetic, and enlargement of both atria—and thus four-chamber enlargement—is also common.

The degree of impairment in LV contractility is quantifiable by several means (see earlier, Assessment of Cardiac Structure and Function, and later, Echocardiography in Heart Failure). Historically, M-mode findings such as increased separation of the mitral E point from the interventricular septum, decreased mitral leaflet opening, and early closure of the aortic valve are known to correlate with poor cardiac output. A universally used measure of systolic function is LVEF, which is considered subnormal if less than 50%. The total SV of the ventricle (reflected by VTI_{LVOT}) may be diminished, and tissue Doppler S′

(systolic) excursion is diminished. RV size and contractility may be assessed by parallel means (**see Tables 14.5 and 14.6**), although it is more difficult to assess RV volume without the use of 3D echocardiography. One easily obtainable measure of RV function is TAPSE, which reflects shortening in the long-axis dimension of RV myocardial fibers; a TAPSE of less than 17 mm is considered abnormal, and 14 mm or less confers a worse prognosis in patients with dilated cardiomyopathy.

Functional (secondary) MR with incomplete leaflet coaptation, caused by multiple processes similar to that seen with ischemic cardiomyopathy, often accompanies and exacerbates dilated cardiomyopathy[33] (**see Fig. 14.31B** and Videos 14.15 and 14.16). If the patient begins to experience right-sided heart failure because of left-sided heart failure (i.e., elevated LVED pressure), the pulmonary venous inflow patterns will show diminution of systolic inflow (the S wave) in the pulmonary venous waveforms because of elevated atrial pressure, and this may precede a rise in estimated pulmonary artery systolic pressure (as reflected by TR velocity).

Regardless of cause, a worse prognosis is associated with declining LVEF and elevated end-diastolic and end-systolic volume, increasing LV mass, the development of restrictive physiology by Doppler indices, and the presence of right-sided heart failure, pulmonary hypertension, and severe TR.[10,40] If the LVEF is 35% or lower and the patient has an intraventricular conduction delay and clinical heart failure, CRT (**see Chapters 27 and 41**) may improve pump cardiac output, reverse the LV remodeling, and improve functional MR[41] (see later, Echocardiography in Heart Failure). Whereas chamber enlargement and systolic dysfunction are the prominent features in dilated cardiomyopathies, in *hypertrophic* and *restrictive cardiomyopathies* the ventricles are not dilated, but diastolic filling of the ventricle is impaired. Declining systolic function typically appears only very late in the process. Both cardiomyopathies typically have thickened LV walls, caused by infiltration, myocyte hypertrophy, or both. Biatrial enlargement is frequent because the atria become the low-compliance reservoirs for cardiac inflow, particularly if AF is present.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is a primary, genetic disease of the sarcomere in which the ventricular walls are inappropriately hypertrophied and frequently asymmetrically thickened (**see Chapter 78**). HCM should be distinguished from the more common *focal upper septal hypertrophy,* a discrete septal bulge frequently observed in older adults, not usually associated with significant LVOT obstruction, and with a benign prognosis. In contrast, the most common forms of HCM of the obstructive type show these echocardiographic features (**Fig. 14.32**): a small, hyperdynamic left ventricle with a thick sigmoid septum and/or banana-shaped cavity, asymmetric septal hypertrophy (septal thickness ≥1.6 times the thickness of the posterior wall), a relatively small LVOT, elevated flow velocity in the LVOT that peaks in late systole (when the LVOT is smallest), systolic anterior motion of the mitral valve, and often a significant amount of posteriorly directed MR (Videos 14.17 and 14.18). The LVOT gradient (ΔP) is calculated from PW Doppler LVOT peak velocity by the Bernoulli equation $\Delta P = 4(V_{LVOT})^2$. It reflects the degree of outflow obstruction caused by altered LV and mitral valve geometry. The combination of small LVOT area and motion of a relatively large, anteriorly positioned, slack mitral apparatus causes the mitral leaflets to be pushed into the LVOT in early systole by flow drag forces and, to a lesser extent, by suctioning via the LVOT gradient and Venturi effect. A maximum wall thickness greater than 30 mm or a resting LVOT gradient greater than 30 mm Hg is associated with increased risk for SCD and progression to New York Heart Association (NYHA) Functional Class III heart failure. The LVOT obstruction is highly dynamic, and in some individuals the LVOT obstruction and gradient can be significantly augmented by conditions

that decrease preload and consequently also diminish LVOT size. Such movements include the Valsalva maneuver, sudden standing, and exercise, all of which may be performed during echocardiographic evaluation of these patients.

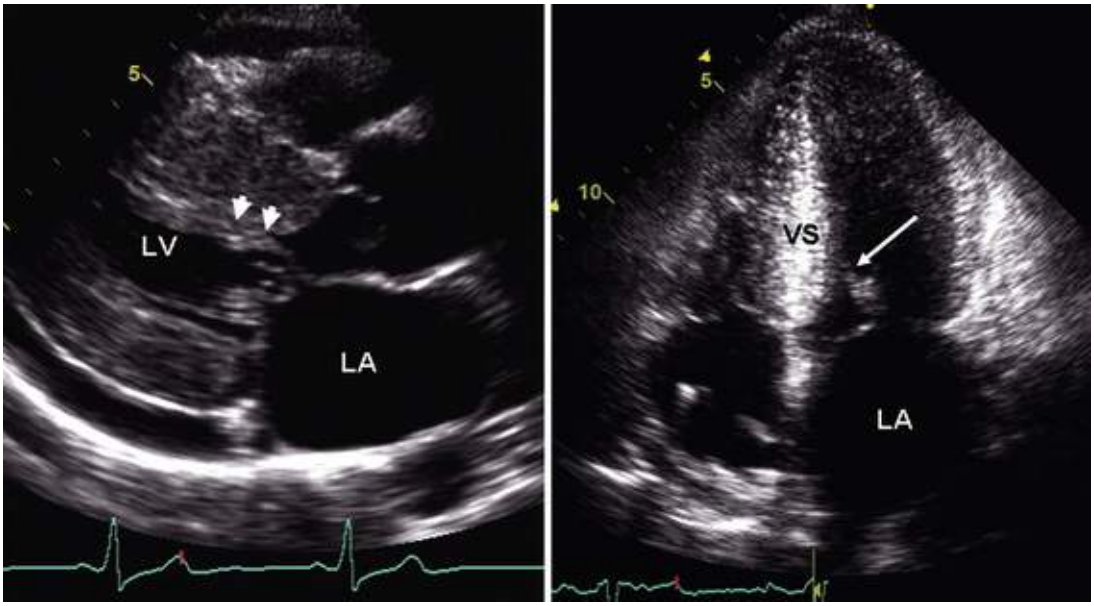


FIGURE 14.32 Hypertrophic cardiomyopathy. A parasternal long-axis view **(left)** shows markedly increased septal wall thickness and systolic anterior motion of the mitral valve (*arrows*), also visualized in the apical four-chamber view **(right)**. Note the sigmoid, banana-shaped septum. *LA,* Left atrium; *LV,* left ventricle; *VS,* interventricular septum. (See Videos 14.17 and 14.18.)

Other forms of HCM may easily be recognized by echocardiography. In *apical* HCM, basal wall thickness may be normal, but the midventricular and apical portions are unusually thickened, and a midcavity gradient may exist; in more advanced cases, a distal apical aneurysmal area may develop (**see Fig. 14.31C** and Video 14.19) and may be associated with a higher incidence of arrhythmias, stroke, and SCD.[42] In a minority (10% to 15%) of patients with HCM, systolic dysfunction ultimately develops, and the heart becomes progressively more dilated and globally hypokinetic. For screening purposes, it is important to keep in mind that some patients with HCM by genotype may have normal or only slightly increased wall thickness or may not manifest hypertrophy until late in adulthood.[43]

Other Cardiomyopathies With Regional or Global Variations in Myocardial Composition

Left Ventricular Noncompaction

LV noncompaction is also thought to be a genetic abnormality and is characterized by abundant trabeculations and deep endothelial-lined recesses extending into the myocardial layer that have failed to compact. On echocardiography this confers a “spongy” appearance to the inner layer of the myocardium, whereas the outer layer has the normal “compacted” morphology (**see Fig. 14.31D** and Video 14.20). Using color flow Doppler and/or echocardiographic contrast enhancement, blood perfusion between the intratrabecular recesses and the LV cavity can be demonstrated. With noncompaction there is a spectrum of expression: the condition may affect the entire mid- and apical ventricle or merely a portion of the apicolateral wall in less affected individuals, and the severity of trabeculation may vary. Because of this variable expression and rising awareness of this entity, definitive imaging and clinical criteria continue to

be refined. In general, a ratio of trabeculated/compacted layer thickness of greater than 2, as measured on short-axis views at the mid- and apical levels, is considered to be consistent with noncompaction.[44] A more specific echocardiographic criterion may be a maximal systolic compacta thickness of less than 8 mm (in the segment with the most prominent recesses), which appears to better discriminate noncompaction from normal patients and those with pressure overload hypertrophy.[45]

Arrhythmogenic Cardiomyopathy

Previously called "arrhythmogenic right ventricular dysplasia" (ARVD), arrhythmogenic cardiomyopathy is distinct from the other nonischemic cardiomyopathies in that often primarily the right ventricle is usually affected (**see Chapter 77**). However, as use of CMR and familial screening has increased, we now know that biventricular or even LV-predominant expressivity occurs. In the most classic form, RV dilation (RVOT long-axis dimension >30 mm) is the most commonly associated abnormality, and RV global hypokinesis (FAC <32%) is present in most (**see Fig. 14.31E** and Video 14.21). Segmental wall motion abnormalities, including thinning and aneurysms, may be present and are caused by fibrofatty infiltration. The inferoposterior wall of the RV inflow tract is the most frequent segment affected. RV trabecular derangement and subsequent tricuspid regurgitation (TR) secondary to annular dilation is common.[46] Echocardiography alone is insufficiently sensitive or specific for the diagnosis of arrhythmogenic cardiomyopathy, and other causes of right-sided heart dilation and arrhythmia need to be excluded.

Restrictive Cardiomyopathies

Systemic diseases that can infiltrate the heart may lead to restrictive cardiomyopathies (**see Chapter 77**); the most common is *amyloidosis*. Deposition of amyloid proteins in the heart causes a very distinct appearance on echocardiography, including increased LV and RV wall thickness in association with a very finely granular or "scintillating" echobright appearance of the myocardium and initially a preserved LVEF (**see Fig. 14.31F** and Video 14.22). Advanced diastolic dysfunction is manifested both by Doppler indices and by worsening longitudinal strain measured by speckle tracking. Features that distinguish infiltrative cardiomyopathy from true LV hypertrophy include the concomitant presence of diffusely thickened valves, biatrial enlargement ("owl eyes" pattern), RV hypertrophy, pericardial effusion, and low voltage on the ECG. Although LVEF can appear to be normal even in clinically affected individuals, there is often marked systolic dysfunction in the longitudinal axis, as detected by both tissue Doppler and strain imaging. Amyloidosis in particular has a characteristic regional pattern of severely reduced longitudinal strain at the base of the left ventricle, but relatively preserved apical strain.[47]

Apart from amyloid heart disease, echocardiography is frequently used to screen for cardiac involvement by other infiltrative diseases.[48] It may reveal abnormalities ranging from dilated to restrictive phenotypes, but no specific pattern is pathognomonic of any single cause. Heart failure develops in more than one third of patients with idiopathic or hereditary *hemochromatosis*, and their echocardiograms reveal LV and LA dilation and global hypokinesis with normal LV wall thickness. A restrictive filling pattern may occur earlier than the manifestations of systolic heart failure. All these parameters of function have been shown to improve with iron removal therapy. *Fabry disease* is associated with accumulation of glycosphingolipid in the heart and a high incidence of cardiovascular signs and symptoms in addition to renal, dermatologic, and neurologic abnormalities. More than 80% of individuals with Fabry disease will display concentric hypertrophy, although concentric remodeling and asymmetric hypertrophy occur in a smaller proportion. The presence of LV hypertrophy is associated with lower alpha-galactosidase activity

and more cardiovascular symptoms. Mitral leaflet thickening and significant MR are common, and focal or global LV systolic dysfunction occurs in a minority of patients.

Endomyocardial fibrosis, also termed Löffler endocarditis, is a rare restrictive cardiomyopathy frequently accompanied by peripheral eosinophilia, which may be idiopathic or associated with helminthic infection in the tropics. Eosinophilic endocarditis and infiltration of the myocardium lead to changes that can be striking on echocardiography. LV size and systolic function may be preserved, but a hallmark of this condition is the formation of prominent diffuse thrombi along the endocardium in one or both LV apices that may embolize and can grow large enough to actually obliterate the cavities (Video 14.23). The ventricular cavities themselves are small with restrictive physiology because of the fibrotic process. Patients may display retracted and incompetent atrioventricular valves and marked biatrial enlargement. Because most patients are identified relatively late in the disease, the time course of development of these changes is unclear.

Heart Failure

Echocardiography is key in the diagnosis and management of patients with heart failure (**see Chapters 25 and 26**). Determination of LVEF is the primary method to distinguish heart failure with reduced ejection fraction (HFrEF) from HFpEF, with the latter generally being considered when the LVEF is 45% or greater. Echocardiography can help distinguish among the different types and narrow down the potential causes of heart failure from the main categories discussed earlier. Abnormalities in diastolic function are common in patients with heart failure and either reduced or preserved LVEF and may have prognostic implications. MR can occur in heart failure patients secondary to apical displacement of the papillary muscles, annular dilation, or both, and progressive ventricular dilation can develop in patients with primary valvular MR (**see Chapter 69**). Increasing degrees of MR are associated with a poor outcome in patients with heart failure.

Assessment of Ventricular Synchrony

Cardiac resynchronization therapy has been associated with a reduction in heart failure and death in patients with reduced LV function and a wide QRS complex in several outcomes trials[49] (**see Chapters 27 and 41**). Use of CRT appears to reverse ventricular remodeling and improve pump performance; in numerous studies it has also been associated with marked improvement in LV end-diastolic and end-systolic volume, ejection fraction, RV function, and LA size.[50] While the benefit of CRT is seen most often in patients with LVEF less than 35%, wide QRS, and heart failure symptoms, it is estimated that 30% to 40% are nonresponders. The ability of echocardiography to predict which patients will or will not benefit remains to be proved. After numerous single-center studies reported a variety of M-mode, conventional Doppler, and DTI parameters that appeared to discriminate for dyssynchrony and CRT response, the PROSPECT multicenter prospective trial concluded that of the dozen echocardiographic measures implemented, none was able to reliably predict clinical or echocardiographic response to CRT in a generalized setting. Thus, at present, echocardiography is not recommended for assessing candidates for CRT.[51,52]

However, in this cautionary background, *speckle tracking* has emerged over the past decade as the most broadly used technique for measuring strain (tissue deformation) and dyssynchrony, in large part because it appears to be more angle- and operator-independent, robust, and reliable than prior techniques (**see eFig. 14.8**). Speckle tracking has been validated with sonomicrometry and tagged magnetic resonance angiography (MRA) data and can now be measured in three dimensions simultaneously within

one heartbeat.[2,5,6] Data using this technique are accumulating, but standardization is needed among vendors and researchers. In the meantime, echocardiographic dyssynchrony studies are useful on a case-by-case basis and for tailoring CRT, particularly regarding lead placement in the cardiac veins relative to scar to increase cardiac output, but should not be used at present to select which patients are candidates for CRT.[41]

Assessment After Orthotopic Heart Transplantation

Echocardiography is used both to certify that cardiac structure and function are normal in potential heart donors and to monitor for rejection in cardiac transplant recipients[53] (**see Chapter 28**). After uncomplicated orthotopic heart transplantation, the "normal" transplanted heart should display normal LV size, wall thickness, and systolic function, although RV size and function can be abnormal. In patients who have undergone the standard Shumway-Lower technique of transplantation, the resultant atria are very enlarged and deformed because of the retained upper portion of the dilated native heart. In these patients the anastomosis between the donor and recipient heart may be visible as a thickened ridge of plicated tissue that encircles the atria. The ridge may be mistaken for thrombus by inexperienced observers. There is a trend toward newer surgical methods that either retain no recipient myocardium (i.e., total atrioventricular transplantation) or retain only a limited cuff of LA wall with pulmonary vein ostia (in the bicaval technique) and thus preserve more normal atrial architecture with less obvious suture lines. A "normal" transplanted heart often has slight paradoxical septal motion—anterior motion of the septum in systole and a slight decrease in septal systolic thickening—that persists in the postoperative state. Over time, in part because of distortions in atrial geometry, supraventricular arrhythmias, and repeated endomyocardial biopsies causing incidental damage to the tricuspid valve, significant TR and MR, as well as atrial thrombi, may develop in the allograft heart.

Cardiac allograft dysfunction may result from acute rejection, coronary artery vasculopathy, myocardial fibrosis, acute myocarditis from opportunistic infections, or tachycardia-mediated cardiomyopathy. Cardiac ultrasound may detect the "downstream" effects of these pathologic mechanisms. Acute cellular rejection, which results in edema and interstitial infiltrates in the myocardium, has been shown to cause detectable increases in LV wall thickness and mass, systolic dysfunction, and Doppler indices of elevated LA pressure and restrictive physiology (increased E wave velocity, decreased IVRT and mitral deceleration time), but these changes are of insufficient sensitivity and specificity to rely on for routine clinical screening. Speckle tracking, used for global LV and RV strain and LV torsion measurements, may have a potential role in serial monitoring for rejection, but wider validation and outcome-based studies are required.[54] For now the gold standard for detecting acute rejection remains endomyocardial biopsy, although echocardiography has an appropriate supplementary role in monitoring for rejection and other complications after transplantation.

For detecting cardiac allograft vasculopathy, coronary intravascular ultrasound (IVUS) is the gold standard, although coronary angiography is used more routinely for practical reasons. Among noninvasive imaging techniques, echocardiography is the most widely investigated and used. The presence of depressed LVEF or focal wall motion abnormalities on a *resting* echocardiogram is relatively specific (>80% in multiple studies) for allograft vasculopathy but has poor (<50%) sensitivity. Some centers use dobutamine stress echocardiography (DSE), which is preferred over exercise stress echocardiography because denervation of the allografted heart blunts the heart rate response to exercise. Meta-analysis of the published data on the accuracy of DSE indicates a mean specificity of 88% and a sensitivity of 72%. The use of longitudinal strain rate imaging or myocardial echocardiographic contrast enhancement with DSE may increase the sensitivity, but again, more validation is needed. For prognostic purposes,

however, normal findings on DSE have been shown to have a high negative predictive value for adverse cardiac events (0.6% incidence) over short-term follow-up. Conversely, worsening findings on serial DSE confer increased risk in comparison to stable findings. Currently, therefore, DSE (as well as SPECT) is considered by the International Society of Heart and Lung Transplantation[55] as possibly being useful (class IIa, level of evidence B) in transplant recipients who are unable to undergo invasive evaluation. Some centers use DSE to minimize exposure of transplant patients to coronary angiography, although currently no noninvasive imaging modality is sufficiently accurate to supplant it.

Assessment of Left Ventricular Assist Devices.

The advent and increasing use of a variety of VADs for both bridge and destination therapy (**see Chapter 29**) have mandated that echocardiography play an integral role in assisting in the optimal selection of patients for left and right VADs, implantation, optimization, and troubleshooting. Here we address the principles for the more widely used HeartMate devices, which are now continuous-flow pumps.

All LV assist devices (LVADs) work by unloading the ventricle (i.e., removing some or all of the inflow and pumping it to the aorta). Echocardiography is useful for evaluation of the patient *preoperatively* for VAD implantation and for evaluating LV as well as RV function.[53] If RV failure is too severe, as may be indicated by a number of parameters such as RV FAC, TAPSE, and the RV Tei index (see earlier), there will be insufficient preload to fill the VAD and left ventricle. The incidence of right-sided heart failure is 20% to 30% in patients implanted with an isolated LVAD, and a preoperative RV FAC less than 20% is associated with RV failure on activation of the LVAD. In addition, echocardiography (TTE and/or TEE) can identify aortic insufficiency, intracardiac shunting, thrombi in the LV or LA appendage, or structural problems with inflow and outflow site cannulation such as excessive necrosis or atherosclerotic plaque, which are detrimental to proper LVAD function. *Intraoperatively*, TEE is used to ensure proper LV apical coring, de-airing, and cannula position and to reassess RV function on initial start-up of the LVAD. Extreme RV failure may mandate placement of an RV assist device (RVAD) as well.

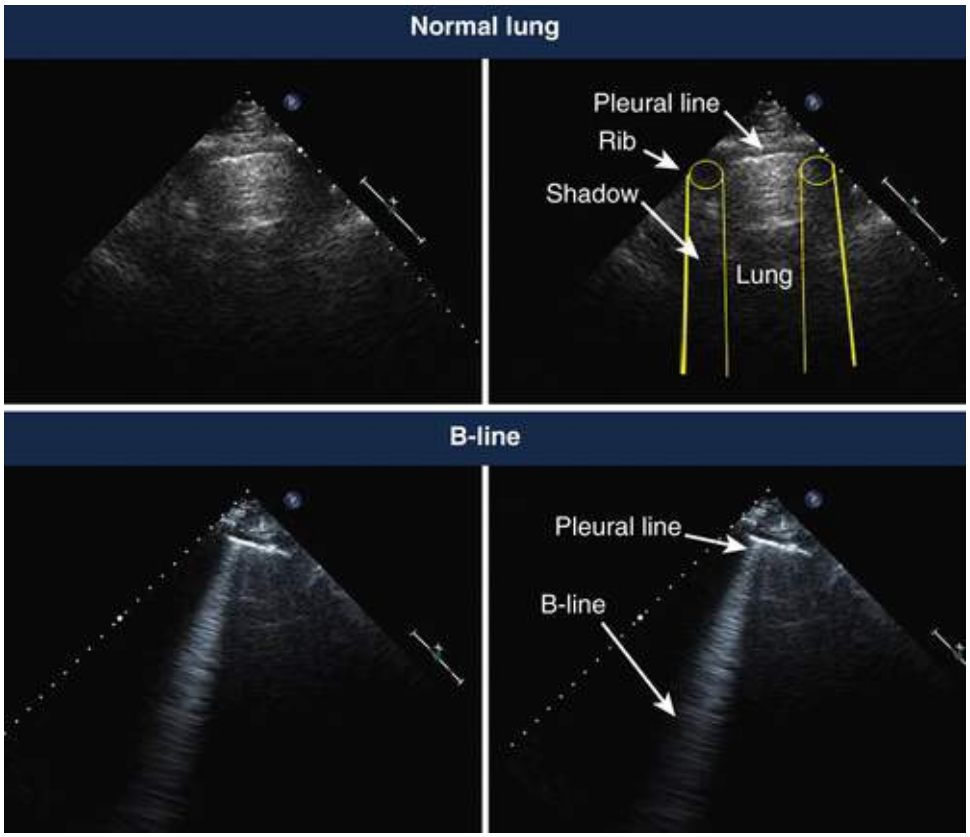
Postoperatively the echocardiogram may be used to identify causes of LVAD dysfunction and fine-tune its operation. When the LVAD is working properly, the ventricle should be “decompressed,” that is, smaller than its original dilated size with the interventricular septum in a neutral position. The aortic valve in a completely decompressed heart stays completely closed throughout the cardiac cycle. Thickening and fusion of the aortic valve may occur over time, particularly in nonpulsatile LVADs; growing experience with these continuous-flow devices supports a rationale for adjusting flow settings to permit at least occasional opening of the aortic valve (i.e., on a 1 : 3 or smaller cyclic ratio) to avoid this valvulopathy and associated aortic regurgitation (AR). This is ideally assessed with both M-mode and 2D imaging of the aortic valve over multiple beats. Enlargement of the left ventricle, distention of the interventricular septum rightward, and rising estimated pulmonary artery systolic pressure are signals of a relatively underfunctioning device that may be caused by an inadequate pump rate, worsening ventricular function, AR, volume overload, or systemic factors (e.g., sepsis). If the left ventricle appears small with a left-shifted interventricular septum, this indicates inadequate preload to the ventricle, and factors such as RV failure, pulmonary embolus, tamponade, hypovolemia (e.g., bleeding), or obstruction of the inflow cannula should be sought. Obstruction may be caused by LV thrombus, a papillary muscle or chorda, or bending or slippage of the cannula or outflow graft. Such abnormalities may be demonstrated by 2D echocardiography or by increased velocities and turbulence seen with Doppler evaluation at the

cannula/graft orifices. The LVAD inflow cannula should be visible at the apex, and the outflow graft/cannula can occasionally be detected by angling into the ascending aorta with a right parasternal view. Occasionally, positional kinks in the LVAD cannulas or the aortic outflow graft, which tend to occur in smaller patients, can be demonstrated by scanning the patient in the supine, sitting, and standing positions. Many centers now perform echocardiography "ramp" studies for continuous-flow LVADs, where many of the previous parameters (LV and RV dimensions, septal position, aortic valve opening, valvular insufficiency, and calculated pulmonary artery systolic pressure) are tracked at incrementally varying rpm settings, with the aim of optimizing LVAD function and diagnosing malfunction.[53]

Percutaneously implanted ventricular assist devices (PVADs) are often used to provide temporary or partial support for the left ventricle. Echocardiography is useful for confirming that the cannulas are positioned appropriately across the interatrial septum (in the case of the TandemHeart PVAD, CardiacAssist, Pittsburgh, Pa) or the aortic valve/LVOT (for the Impella).[53]

Lung Ultrasound in Heart Failure

Lung ultrasound is a technique that can provide semiquantitative assessment of lung fluid in patients with heart failure. *B-lines* are vertical echogenic reverberation artifacts that arise from the pleural line and extend raylike with respirophasic movement and are markers of increased extravascular lung water (**eFig. 14.18**). B-lines are most frequently seen in pulmonary edema but also in other processes such as acute respiratory distress syndrome and pulmonary fibrosis. In patients with heart failure, the number of B-lines within prespecified thoracic segments correlates with chest x-ray findings and N-terminal pro–brain natriuretic peptide (NT-proBNP) levels, clears contemporaneously with treatment, and is a prognostic marker for short-term (3 to 6 months) hospital readmission and death. B-lines are relatively sensitive and specific for cardiogenic dyspnea in the emergency department setting, and the simplicity and availability of the technique makes it attractive for early diagnosis and monitoring of therapy, particularly in limited-resource environments.[56]



EFIGURE 14.18 B-lines on lung ultrasound. For studies, typically the number of B-lines are summed from two to eight segments of the chest using a 1.5- to 7.5-mHz transducer. **Top panels,** Normal lung. **Bottom panels,** Example of B-line. Annotated images are on the right. (Courtesy Dr. Elke Platz, Brigham and Women's Hospital.)

The Athlete's Heart

Physiologic changes, including enlargement of the heart and bradycardia, can be induced in the heart through intensive athletic training. Echocardiography, along with ECG and ECG exercise testing, is often used to distinguish the athlete's beneficial cardiac adaptive changes from pathologic entities such as hypertrophic, arrhythmogenic, or other cardiomyopathies that are associated with SCD. Different forms of exercise are hypothesized to favor different remodeling patterns: endurance athletes have been well documented to develop LV (and RV) dilation and a proportionate increase in wall thickening (eccentric hypertrophy), whereas strength/isometric training has long been thought to predispose toward concentric hypertrophy (LV walls thickened relative to LV diameter, or RWT >0.42), although this latter trend is less well supported by data.[57] Although “cutoff” values for normal LVED diameter are less helpful for distinguishing physiologic from pathologic remodeling (a variable percentage of athletes have diameters >60 mm), absolute wall thicknesses greater than 15 mm are unusual even in elite athletes and should trigger further investigation for HCM, especially if the hypertrophy is asymmetric. Typically, the resting LVEF is in the low-normal (approximately 50%) range in trained athletes. The standard flow and tissue Doppler metrics of diastolic dysfunction are normal or even supranormal (higher E' velocities and transmitral E/A >2) in athletes compared with HCM patients, and speckle-based local and global longitudinal strain parameters are generally higher as well. Further CMR testing, exercise testing to confirm LV augmentation and document high exercise capacity and in “gray-zone” cases, and even a period of detraining to see if LV hypertrophy regresses may be necessary to distinguish the athlete's heart from a true cardiomyopathy.[58]

Stress Echocardiography

Stress echocardiography is a well-validated tool for the evaluation of ischemia. In particular, it is an appropriate first-line test in patients who have baseline abnormalities on the ECG that preclude interpretation of exercise ECGs, and it is both time- and cost-efficient. The accuracy of stress echocardiography is similar to that of stress radionuclide perfusion imaging (**see Chapter 16**). From meta-analyses, as well as from comparisons of the accuracy of stress echocardiography and nuclear imaging in the same patient population, the sensitivity of stress echocardiography for significant CAD (generally defined as >50% coronary artery stenosis by angiography) averages approximately 88% (range, 76% to 94%), and its specificity is 83%.[59] The specificity of stress echocardiography appears to be higher than that of nuclear imaging for left main and triple-vessel CAD. As with other tests, stress echocardiography is best used for diagnosis or to identify the extent, severity, and location of ischemia in patients with an intermediate pretest probability of disease.

The Stress Echocardiographic Protocol.

In the standard stress protocol, baseline images are obtained at rest, before the patient exercises on either a treadmill or stationary bicycle. The same Bruce protocol used for routine (ECG only) exercise stress tests is standard (**see Chapter 13**), with echocardiographic imaging performed at rest and during immediate recovery as close to the peak exercise time as possible. If a stationary (upright or supine) bicycle is used, the workload is increased by 25 W every 2 or 3 minutes, and echocardiographic images can be obtained on the cycle precisely at the time of peak stress. Patients who cannot exercise can undergo pharmacologic stress with a graded dobutamine infusion of up to 40 µg/kg/min (and added atropine, if necessary, to achieve the target heart rate), which increases the heart rate and myocardial contractility. This method, although less physiologic than exercise, produces a smaller rise in blood pressure and also allows imaging exactly at time of peak stress. Vasodilator stress with dipyridamole and pacing stress—via a preexisting permanent pacemaker or a transesophageal pacing catheter—are also possible but less widely used. The test endpoint is completed by exercise-limiting symptoms or completion of the protocol (reaching at least 85% of the age-predicted maximal heart rate).

Absolute indications to terminate the test early include moderate to severe angina, ST-segment elevation, sustained ventricular tachycardia, near-syncope or signs of poor perfusion, a drop in systolic blood pressure of more than 10 mm Hg from baseline when accompanied by any other evidence of ischemia, and patient request to stop (intolerable symptoms). Relative indications to stop early include a hypertensive response (systolic blood pressure >250 mm Hg and/or diastolic blood pressure >115 mm Hg).[59] The risks associated with exercise echocardiography or DSE are very low. In the largest survey to date, the overall rate of life-threatening events was 1 per 1000 examinations (0.015% for exercise and 0.18% for dobutamine).[60] The most frequent complications were acute MI or ventricular tachycardia or fibrillation.

If a previous echocardiogram has not been performed, a brief survey of the ventricular chambers, valves, and aortic root should be performed to screen for significant pathology or contraindications to stress and to ensure adequate image quality (usually obtainable in at least 90% of patients with harmonic imaging). If endocardial resolution is poor in two or more segments, IV echocardiographic contrast enhancement should be used to improve accuracy.[31] Images of the left ventricle are then obtained in the parasternal long, parasternal short, and apical windows at rest and then with stress. Side-by-side

comparison of the baseline versus stress digitized images, which are gated by the ECG and synchronized in systole, allows quantification of overall LV size and systolic function, as well as identification of regional wall motion abnormalities. The standard 17-segment ASE model is used as the guide for grading function in each segment as normal, hyperkinetic, hypokinetic, akinetic, or dyskinetic at rest and with stress or increasing doses of dobutamine. A normal ventricle has normal size and wall thickness and an ejection fraction of 50% or higher with no focal wall motion abnormalities (WMSI = 1.0); with stress the ventricle should become hypercontractile and the cavity size should shrink. The presence of baseline wall motion abnormalities that remain "fixed" (unchanged) with stress is indicative of a previous infarct. The development of a new or worsening wall motion abnormality indicates a flow-limiting stenosis in the coronary artery supplying the abnormal segment or segments (**Fig. 14.33** and Video 14.24). A large ischemic territory (i.e., left main or multivessel disease) will be manifested as diminished global LVEF and chamber dilation with stress.

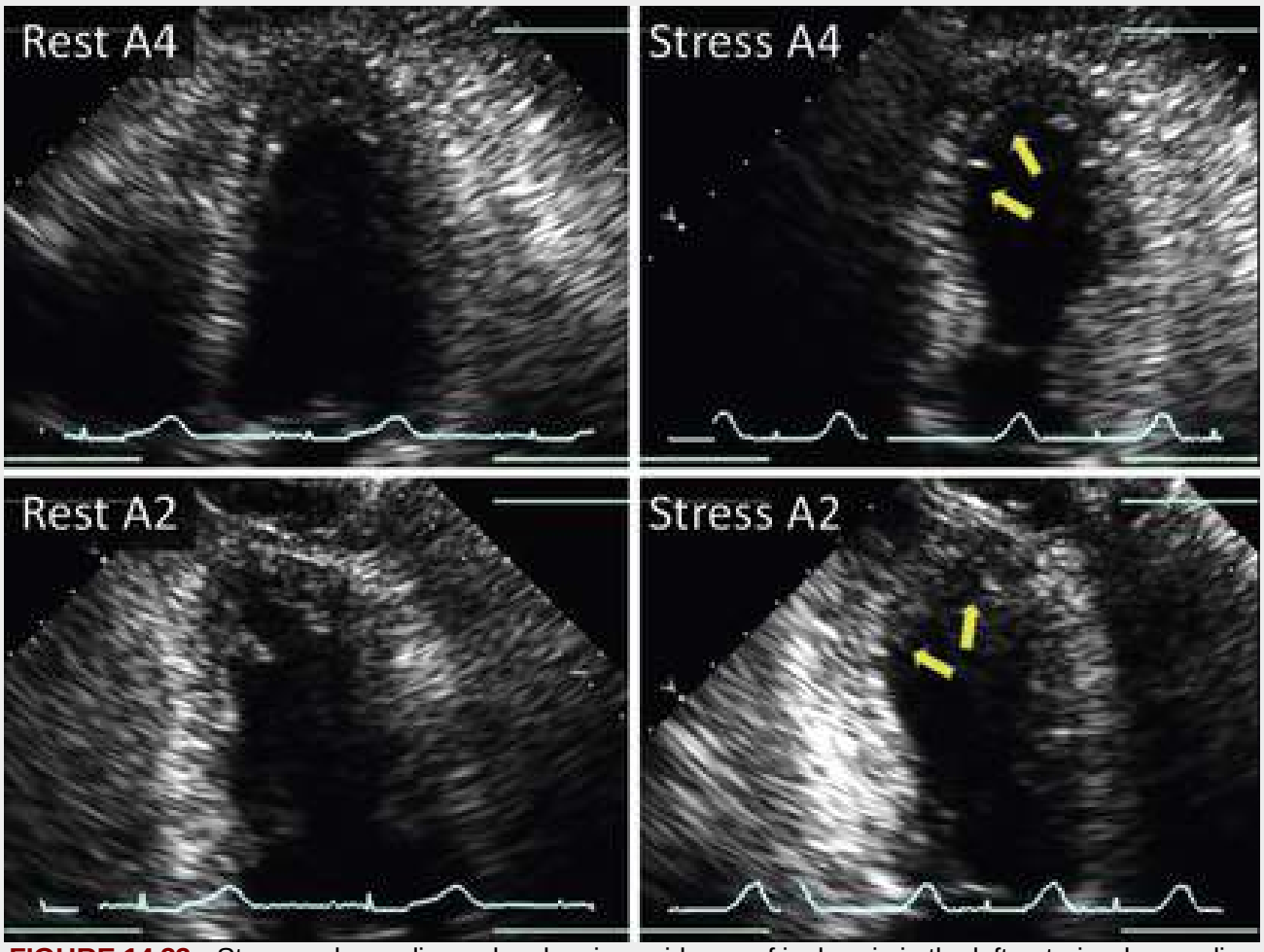


FIGURE 14.33 Stress echocardiography showing evidence of ischemia in the left anterior descending (LAD) distribution. Resting and stress echocardiograms in the apical four-chamber (*A4*) and apical two-chamber (*A2*) views reveal new severe middle to distal septal, apical, and distal inferior LV hypokinesis (*arrows*). This patient was found to have greater than 90% mid-LAD stenosis on cardiac catheterization. (See Video 14.24.)

Limitations of Stress Echocardiography

When compared with the gold standard of coronary angiography, the results of stress echocardiography can be discrepant.[61] When false-negative results occur, primary causes include a suboptimal level of

stress (from inadequate exercise capacity or beta-blocker use), limited image quality, a small area of ischemia (particularly for single-vessel or left circumflex disease), or preexisting conditions such as marked LV hypertrophy or a hyperdynamic state. False-positive results may also occur, particularly when the pretest probability is low. Diagnosis of wall motion abnormalities is particularly challenging in patients with left bundle branch block or septal dyssynchrony (e.g., as a result of pacing or the postoperative state). In these patients, because exercise can exaggerate the abnormal septal motion and thereby obfuscate interpretation, DSE is recommended. A focus on wall thickening rather than on endocardial excursion may also be helpful in such situations. Other conditions that can cause nonspecific or nondiagnostic findings include the presence of preexisting wall motion abnormalities that tether adjacent segments, severe hypertension, HCM, and other cardiomyopathies in which myocardial perfusion reserve is diminished as a result of microvascular disease.[31]

Risk Stratification with Stress Echocardiography

Numerous studies have demonstrated that in patients who complete normal exercise or pharmacologic stress echocardiograms (reaching good exercise capacity and the target heart rate), the risk for cardiac events is very low and at or close to that of a "normal" population (<1% per year for exercise and <2% per year for pharmacologic tests). In patients with suspected or known CAD, both the extent of resting wall motion abnormalities and the extent of ischemia—specifically quantified by the change in WMSI, four or more LV wall segments affected, and/or no change or decrease in exercise LVEF—correlate with a fourfold or greater increased risk for cardiac death or MI.[31]

Assessment of Myocardial Viability

DSE can also be used to quantify viability (contractile reserve) and thus functional recovery after reperfusion,[61] although its overall sensitivity appears to be lower than that of nuclear and CMR studies. A biphasic response, in which improvement in wall thickening occurs at low-dose dobutamine but then deteriorates with high-dose dobutamine, is the most specific sign. However, any improvement in wall motion abnormality by at least one grade in two or more segments during stress is likely to signify viability (either stunned or hibernating myocardium).

Coronary Flow Reserve and Perfusion

It is feasible to assess coronary flow and flow reserve (**see Chapter 57**), most reliably in the LAD territory, by using Doppler TTE and vasodilators (adenosine or dipyridamole) to provide additional prognostic information. Coronary flow reserve reduced to less than 1.9 to 2.0 in the LAD territory correlates with greater than 70% angiographic stenosis and is a predictor of future adverse cardiac events. Microperfusion to the myocardium at rest and with stress echocardiography may also be demonstrated with the use of IV echocardiographic contrast enhancement on 2D and 3D images (see Contrast Echocardiography and **Fig. 14.27**). In laboratories with expertise, both techniques of assessing myocardial perfusion appear to have acceptable agreement compared with angiography and nuclear stress tests. However, technical challenges and a learning curve presently exist, which has currently limited widespread adoption of these methods.[61]

Stress echocardiography is also used to assess factors beyond LV systolic function, particularly in patients who are dyspneic for unclear reasons. Valvular disease, diastolic function, pulmonary hypertension, and hemodynamics may all be assessed under stress conditions.[62]

Stress Echocardiography in Valvular Heart Disease

Resting echocardiography may lead to conflicting interpretations of the degree of aortic stenosis (AS) in patients with very calcified valves and low LVEF, because leaflet excursion and both the LVOT and the aortic gradients are diminished simply by low forward flow (**see Chapter 68**). In patients with "low-gradient, low-output aortic stenosis" and LV dysfunction (defined classically as a calculated aortic valve area by Doppler <1.0 cm^2 [0.6 cm^2/m^2], mean transaortic gradient <30-40 mm Hg, and LVEF ≤40%), DSE can be used to assess both the true severity of AS and the amount of LV contractile reserve (see later, Valvular Aortic Stenosis). In this test, dobutamine is infused in graded doses from 5 to 20 µg/kg/min, typically for longer stages than used for ischemia testing, to allow for steady-state measurements of spectral Doppler of the LVOT and CW Doppler across the aortic valve. SV is calculated from VTI_{LVOT}. An increase of 20% or higher in SV is indicative of significant contractile reserve. The test is indeterminate if little or no augmentation of LV function takes place (no contractile reserve, or SV <20%). Aortic valve area is calculated at both baseline and with dobutamine; in true AS, the ratio of aortic/LVOT velocity will increase, whereas in "pseudosevere" or "functional" AS, the LVOT and aortic gradients change relatively little, and the calculated valve area remains the same or increases as the leaflets open more. Patients with true severe AS generally benefit from aortic valve replacement, but if contractile reserve is absent or concomitant CAD is present, surgical mortality is high.[62,63]

A subset of patients, often women with small ventricles and hypertension, with advanced AS have been described who have low-gradient/low-flow states despite preserved LVEF[63] (**see Chapter 68**). On DSE these "paradoxical low-flow low-gradient AS" patients usually appear to have low aortic valve areas consistent with true severe AS even with stress, but only modest gradients despite preserved LVEF. These patients have a poor prognosis, which is improved by aortic valve replacement. The explanation appears to be pronounced LV concentric remodeling and myocardial fibrosis that results in severe restrictive physiology and low SV (not reflected by the LVEF because of small total chamber size and reduced LV systolic longitudinal contractility). If this state is suspected, it may be useful to further elucidate the degree of AS and restrictive pathophysiology by indexing measurements to body size (SV ≤35 mL/m^2 is considered low) and measuring GLS. Optimizing antihypertensive therapy may be useful, and the aortic valve may also be evaluated directly with CT for aortic valve calcium scores.

Patients with rheumatic or calcific mitral stenosis (MS) may have severe exertional symptoms despite relatively modest gradients on the resting echocardiogram. Conversely, sedentary patients with severe MS may be relatively asymptomatic because they are inactive. Valve gradients are notoriously dependent on the flow rate and heart rate. Stress echocardiography can define the true exercise capacity and quantitate the degree of valvular stenosis and regurgitation. A rise in the mean transmitral pressure gradient greater than 15 mm Hg or an increase in calculated pulmonary artery systolic pressure greater than 60 mm Hg is correlated with significant MS, and such patients should be considered for valvotomy (if the cause is rheumatic and there is no more than mild MR) or mitral valve replacement[31,62] (**see Chapter 69**). Mitral valve surgery should also be considered if severe MR occurs with stress. If symptoms and pulmonary artery systolic pressure increase markedly while transmitral gradients remain low, however, a pulmonary cause should be sought.

In patients with MR, stress echocardiography may be instrumental in revealing acute reversible ischemic MR caused by inferior wall ischemia (**Fig. 14.34** and Video 14.25). This would characteristically be associated with stress-induced inferior wall motion abnormalities and improvement in both abnormalities during recovery. In chronic severe MR, even if the LVEF is preserved, demonstration of a rise in pulmonary artery systolic pressure to greater than 60 mm Hg with exercise and

reduced LV contractile reserve are reasonable indications for mitral valve surgery.[31,62]

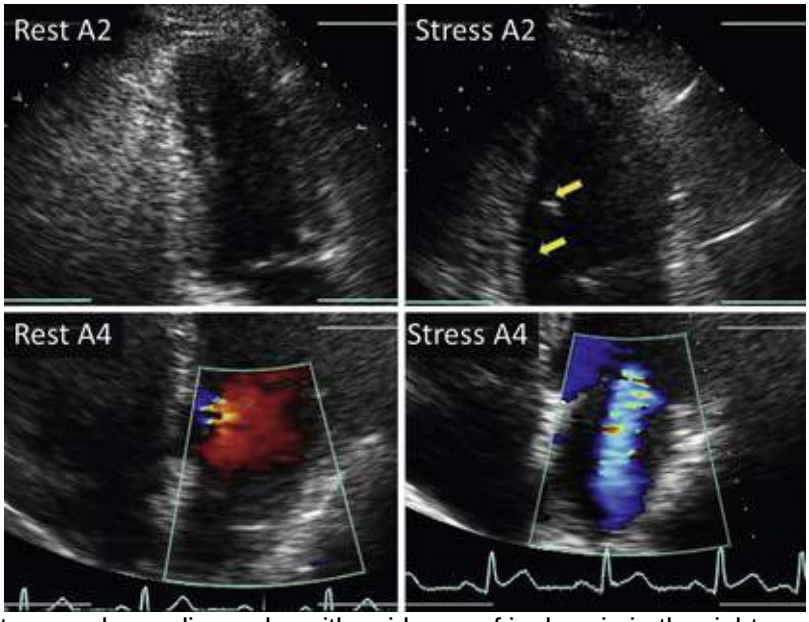


FIGURE 14.34 Stress echocardiography with evidence of ischemia in the right coronary artery (RCA) territory and acute ischemic MR. Resting and stress echocardiograms in the apical two-chamber (*A2*) and apical four-chamber (*A4*) views with color Doppler reveal new stress-induced inferior hypokinesis (*arrows*) in the area containing the posteromedial papillary muscle and increased MR. This patient was found to have 90% stenoses of the RCA and left circumflex artery on cardiac catheterization. (See Video 14.25.)

Stress echocardiography may be refined or tailored in other conditions. In patients with HCM, exercise can bring out latent gradients and is also used to monitor response to therapy and assess symptoms such as syncope (**see Chapter 78**). In conjunction with cardiopulmonary testing, stress echocardiography may aid in identifying other causes of dyspnea and fatigue, such as diastolic dysfunction. Delayed diastolic relaxation, as measured by strain and strain rate imaging, may also be a more sensitive and persistent indicator of exercise-induced ischemia than wall thickening. With the advent of real-time 3D and four-dimensional (4D) imaging, automatic endocardial border tracking, and volumetric imaging, there is now the capability to capture images of LV systolic and diastolic function simultaneously at peak exercise, thereby potentially improving the sensitivity, accuracy, and reproducibility of this test for ischemia.

Valvular Heart Disease (See Chapters 67 Through 72)

Mitral Valve

Mitral Valve Anatomy.
The mitral valve apparatus is a complex structure consisting of two leaflets attached to the left atrium by the mitral annulus and to the left ventricle through the mitral chordae and papillary muscles. The posterior leaflet is divided naturally into three scallops termed P1, P2, and P3 (using the Carpentier nomenclature), with P1 being lateral and P3 being medial. Opposing scallops of the anterior leaflet are termed A1, A2, and A3. Localization of pathology to specific scallops is important, particularly in surgical decision making for degenerative MR. The annulus is a nonplanar saddle-shaped structure, with

its highest points seen on the parasternal long-axis view and its nadir seen in the apical four-chamber view (**see Fig. 14.24**). The chordae consist of a complex arcade of primary (first-order) and secondary (second-order) chordae radiating from both papillary muscles, with the former being inserted along free margin of both leaflets and the latter serving as strut supports to the leaflet undersurfaces. Tertiary (third-order) chordae arise from the ventricular wall and insert into the base of the posterior leaflet only (**Fig. 14.35 and eFig. 14.19**).

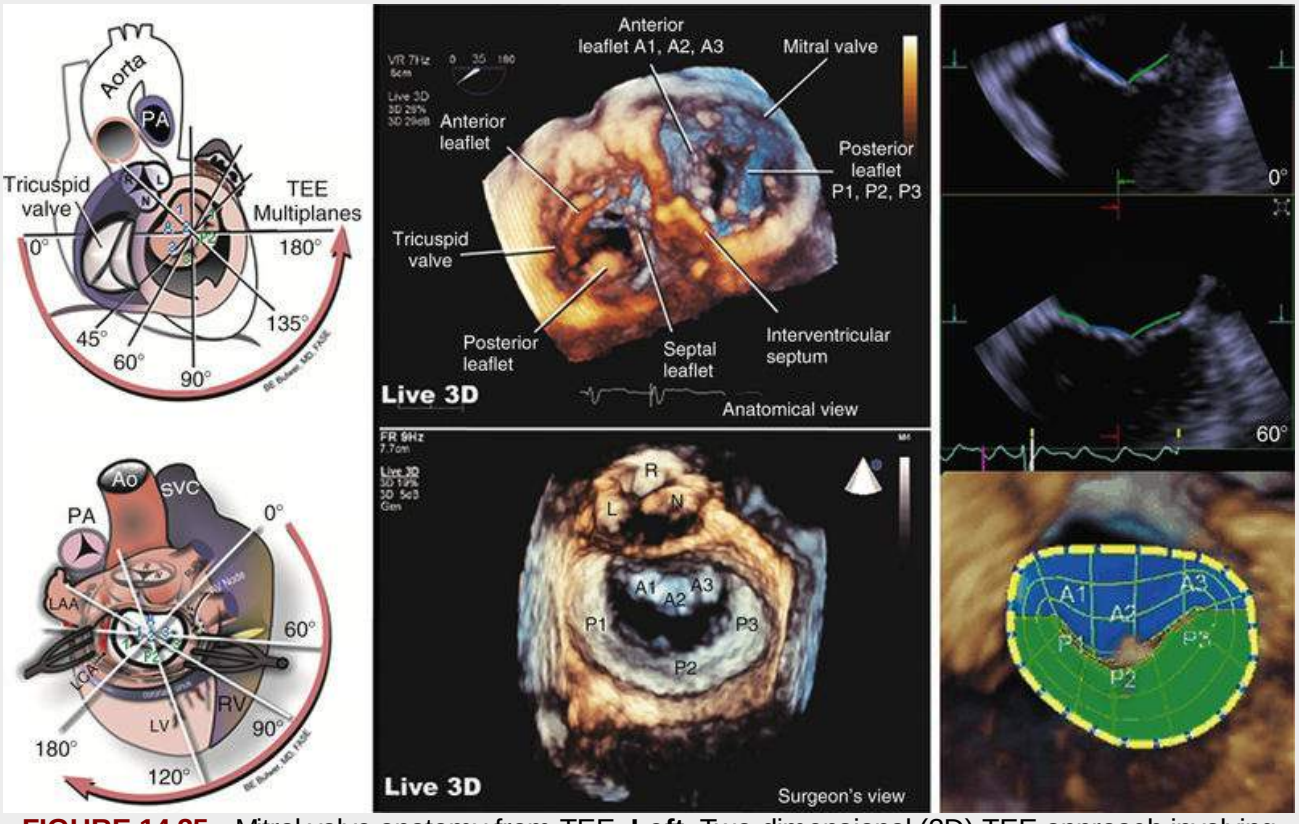
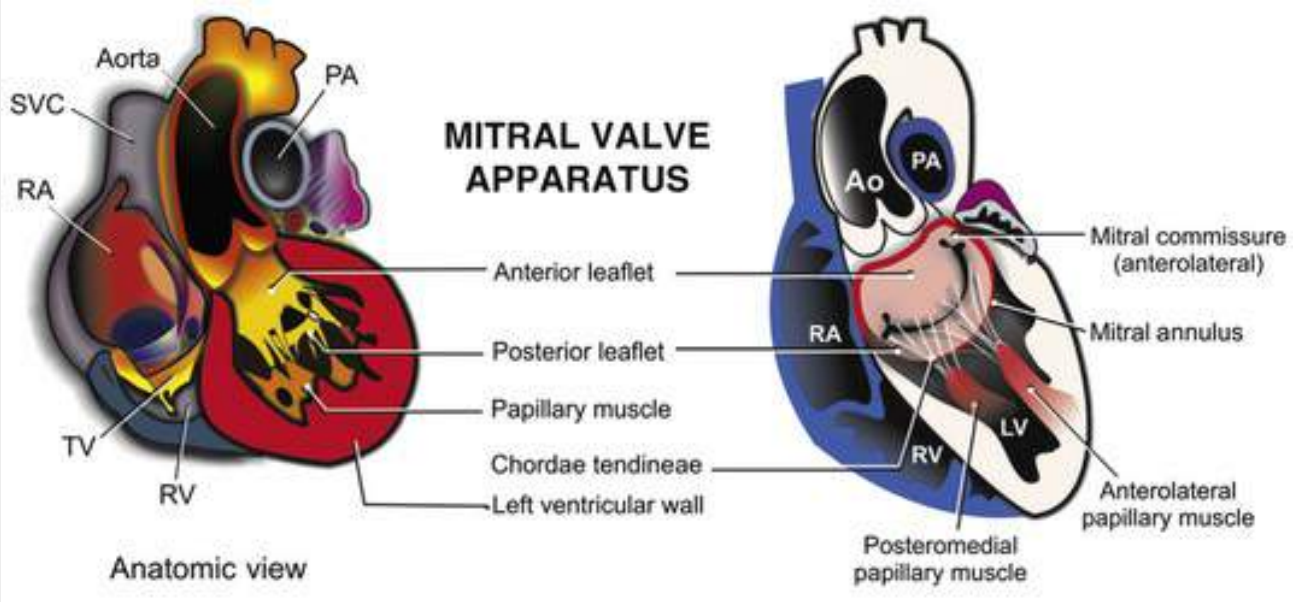


FIGURE 14.35 Mitral valve anatomy from TEE. **Left,** Two-dimensional (2D) TEE approach involving adjustment of probe position and omni orientation (degrees), sweeping to image all scallops. **Middle,** Three-dimensional (3D) appearance of the valve from the TEE view **(upper)** and surgeon's view **(lower)** with the mitral leaflet scallops labeled. **Right,** 3D TEE images delineating the mitral valve scallops at 0 degrees (four-chamber) and 60 degrees (two-chamber) planes, and below superimposed 3D analysis of leaflet areas from the left atrial aspect. *Ao,* Aorta; *PA,* pulmonary artery, *LAA,* left atrial appendage. The aortic valve right (*R*), left (*L*), and non- (*N*) coronary cusps are also shown. (See Video14.26.)



EFIGURE 14.19 Normal mitral valve anatomy. *Ao,* aorta; *LV,* left ventricle; *PA,* pulmonary artery; *RA,* right atrium; *RV,* right ventricle; *TV,* tricuspid valve. (Modified from Bulwer BE, Rivero JM, editors. Echocardiography Pocket Guide: The Transthoracic Examination. Burlington, Mass: Jones & Bartlett Learning; 2011, 2013, p 132. Reprinted with permission.)

Although it is possible to identify each of the scallops with 2D TTE on the parasternal short-axis view at the level of the mitral valve, it may be challenging to identify the scallops in the other views. Consequently, TEE plays a particularly important role in assessment of the mitral valve. 3D TEE has rapidly become an essential tool because of its ability to provide images that replicate the surgeon's view of the valve (**Fig. 14.35**), as well as improved methods for assessing mitral pathophysiology in a variety of disease states. Leaflet morphology, focal disruptions, and detailed measurements can now be made virtually real-time (Video 14.26). Congenital anomalies of the mitral valve are unusual, but those that might be newly diagnosed in adulthood include double-orifice and parachute mitral valve.

Mitral Stenosis

Echocardiographic Features

The commissural fusion, chordal thickening and fusion, and leaflet thickening and calcification that develop in patients with rheumatic MS result in narrowing of the mitral orifice, classically with a fish-mouth configuration (**Fig. 14.36**). Other pathognomonic echocardiographic features of rheumatic mitral disease are best appreciated on the parasternal long- and short-axis views and apical views. Commissural fusion results in restricted diastolic excursion of the tips of the leaflets, with relatively preserved mobility of the belly of the leaflet, particularly in early or milder forms of the disease. The result is a pattern of opening in which excursion of the midsection of the leaflet exceeds that of the leaflet tips. This pattern, also encountered in rheumatic tricuspid stenosis and congenital anomalies of the aortic valve (discussed later), is termed *doming*. In rheumatic mitral disease, anterior leaflet doming is more readily appreciated because the posterior leaflet is shorter and tends to become immobilized early in the rheumatic process (Videos 14.27 and 14.28). Leaflet and chordal thickening with or without calcification is also seen. Despite the fact that degenerative mitral annular calcification is a common anomaly that occurs with aging and renal disease, it infrequently causes MS unless very severe.

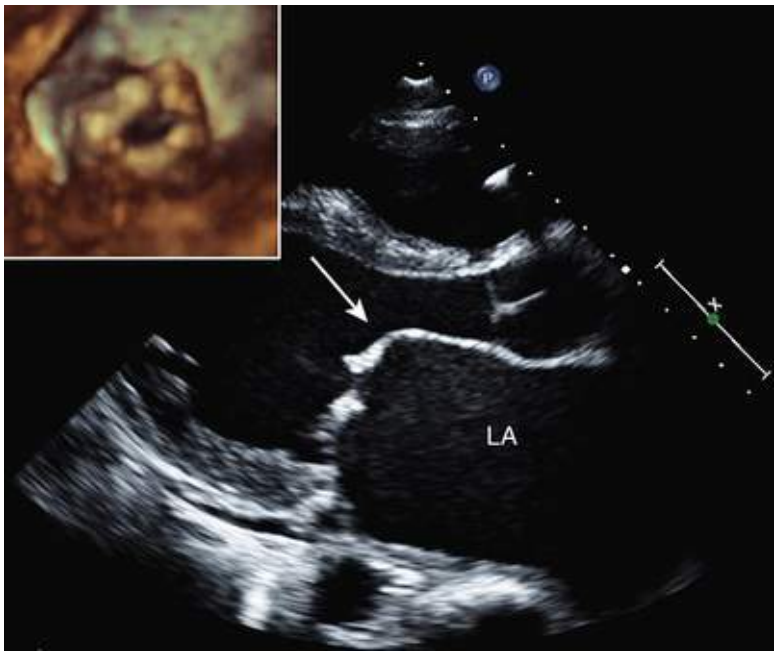


FIGURE 14.36 Rheumatic mitral stenosis. Parasternal long-axis view (diastolic frame) of a rheumatic mitral valve. Diastolic doming of the anterior mitral leaflet (*arrow*) is present, as well as a fixed posterior leaflet. *Inset,* Doming and fish-mouth appearance of the valve, as seen by 3D TTE from the LV aspect. *LA,* Left atrium. (See Videos 14.27 and 14.28.)

Quantification of Severity

The normal mitral valve area (MVA) is 4 to 5 cm^2. Direct planimetry of the orifice area from a parasternal short-axis view was first validated in the pre-Doppler era. It relies on meticulous positioning of the imaging plane at the level of the flow-limiting orifice; misleadingly larger-appearing "orifices" will be captured if the plane used is at the level of more mobile leaflet segments. It is equally important for the gain to be set at the lowest possible setting that will provide a complete orifice. Overgained images will also underestimate the true MVA. 3D echocardiography has proved to be a valuable tool because it provides a robust means of precisely identifying the valve orifice (**Fig. 14.37**).

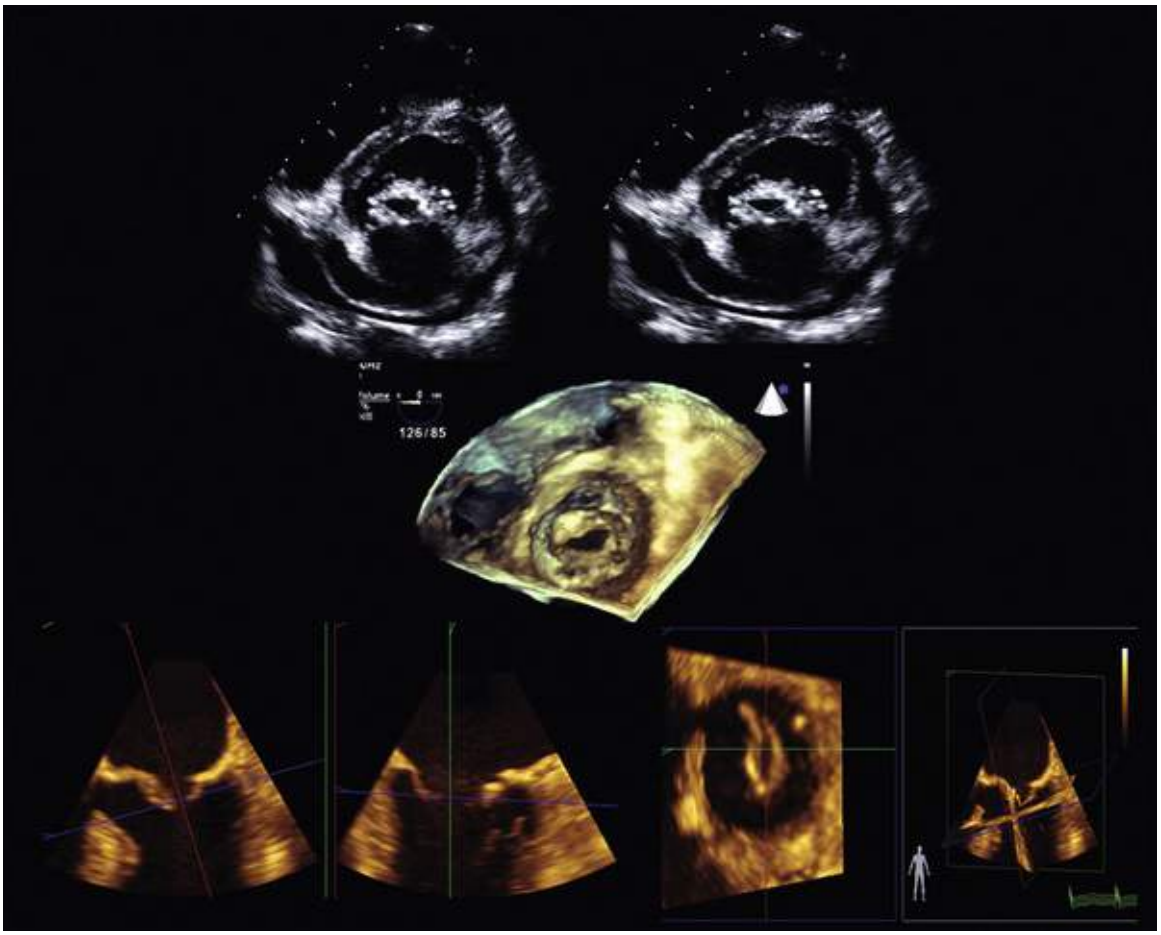


FIGURE 14.37 Approaches to planimetry of the mitral valve area (MVA) in rheumatic mitral stenosis. **Top panel,** Planimetry of 2D parasternal short-axis images. **Middle panel,** 3D TEE view of the stenotic orifice from the perspective of the left ventricle, which can be directly planimetered. **Lower panel,** Multiplanar reconstruction of 3D TEE volumes can ensure that a short-axis view precisely at the level of the limiting orifice is selected for planimetry.

Determination of the mean gradient is the simplest Doppler method for assessing the severity of MS. Given the degree to which gradients are influenced by flow rate, it is important to report the heart rate at which the gradient was determined and to know the impact of concomitant MR, which can increase transmitral flow. Abnormalities that increase LVED pressure independent of transmitral flow, such as reduced LV compliance and AR, can attenuate the transmitral gradient and result in underestimation of the severity of MS.

Doppler echocardiography also provides alternative methods to planimetry for determining MVA. The most widely used approach is the pressure half-time method, which relies on the rate at which LA and LV pressures equalize. Using a simplified derivation of a catheterization laboratory–validated method, MVA is calculated as 220 divided by pressure half-time, with 220 being an empirically derived constant. Pressure half-time is the time that it takes the initial transvalvular gradient to fall to half its initial value. This calculation can rapidly be done online with the basic analysis packages available on echocardiographic machines (**Fig. 14.38**). The pressure half-time method should not be used in the immediate postvalvuloplasty setting because acute changes in the LA-LV compliance relationship and in the initial transmitral gradient may have occurred. As discussed, it may also be invalid in the setting of significant AR and reduced LV compliance, each of which will result in overestimation of MVA. Additionally, the pressure half-time may be indeterminate when the mitral inflow Doppler spectrum has a biphasic contour. Finally, this method has not been validated for other causes of MS, such as mitral annular calcification, or for prosthetic valves.

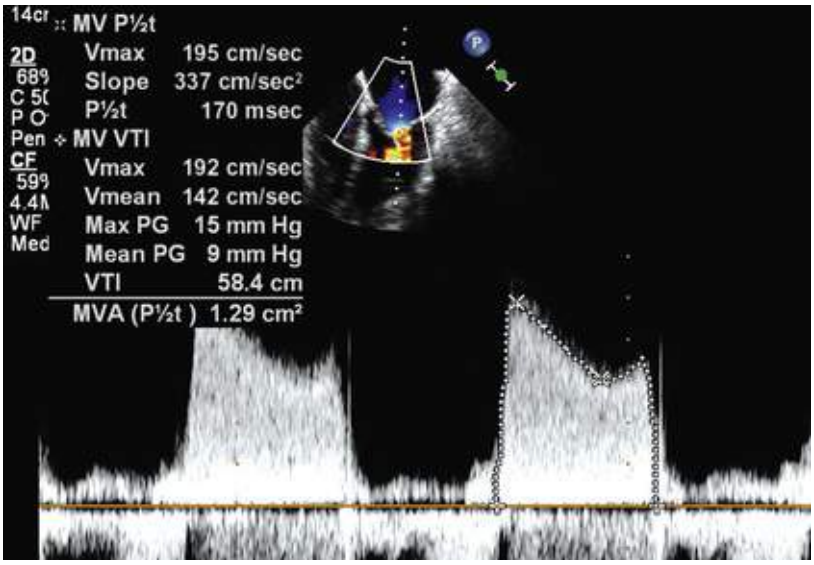


FIGURE 14.38 Tracing the CW mitral stenotic spectrum (*dotted line*) for VTI provides the mean transvalvular gradient, whereas assessment of the rate at which the gradient between the left atrium and left ventricle falls (marked by the two Xs) can be used to calculate valve area from the pressure half-time method ($P_{½t}$). *MV,* Mitral valve; *MVA,* MV area; *PG,* pressure gradient.

An alternative method is the *proximal isovelocity surface area* (PISA) approach (**Fig. 14.39**), in which $MVA = 2(\pi r^2)(V_{aliasing})/(\text{Peak } V_{mitral}) \times \alpha/180$, where α is the angle formed by the doming cusps, or a simplification of this equation in which α is assumed to be 100 degrees. A continuity-based method has also been proposed whereby $MVA = \pi(D_{LVOT}/2)^2(VTI_{LVOT}/VTI_{MV})$, where D is the diameter of the LVOT measured on the parasternal long-axis view. As with other forms of valvular heart disease, an approach that integrates imaging and Doppler findings will optimize assessment of mitral stenotic severity.[64]

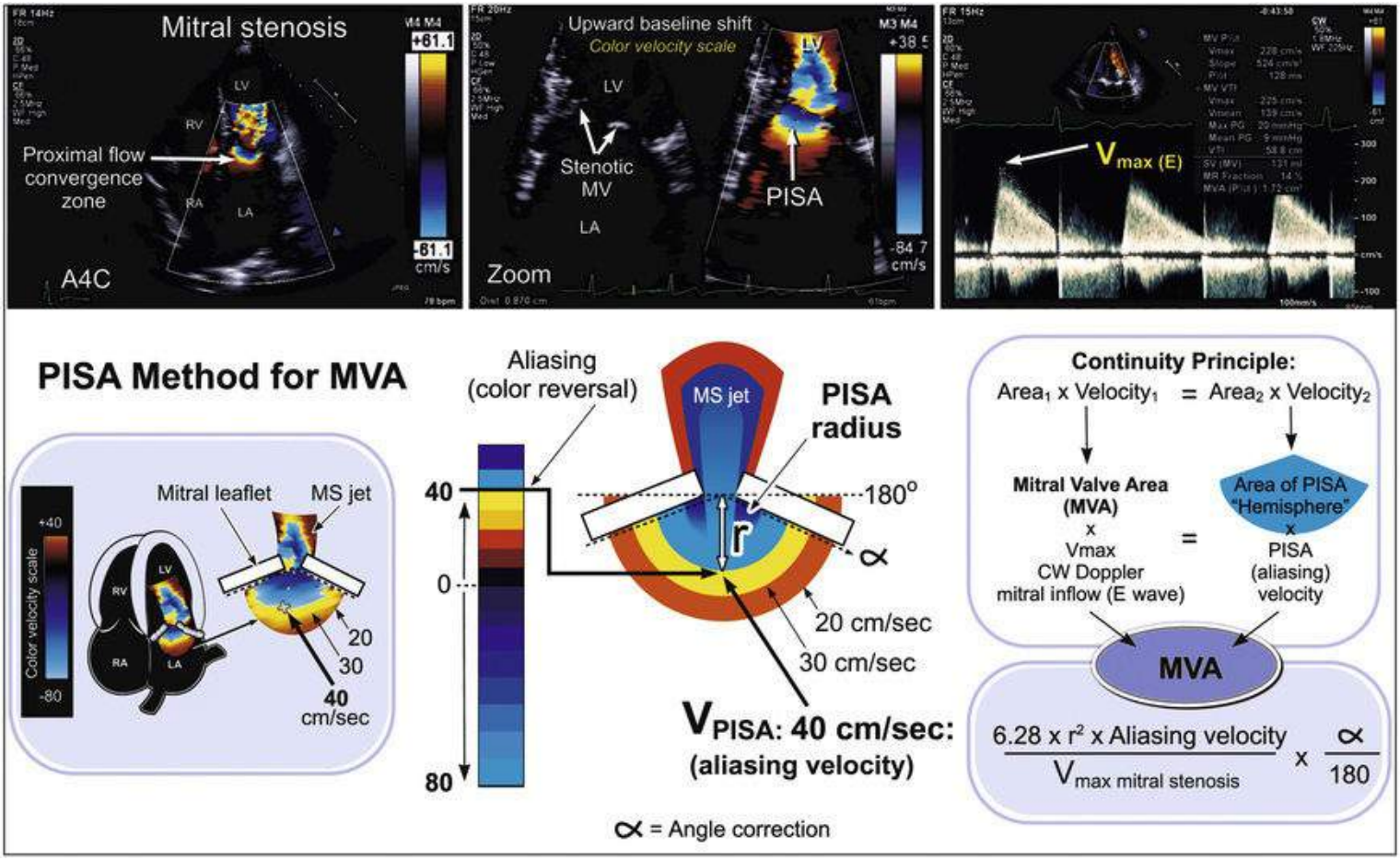


FIGURE 14.39 Proximal isovelocity surface area (PISA) method for calculation of MVA. In patients with mitral stenosis (MS), flow acceleration proximal to the stenotic orifice will result in a flow convergence zone that is characterized by color aliasing and a PISA shell **(upper left)**. The definition of the PISA shell and thus accuracy of the PISA radius measurement can be improved by shifting the baseline Nyquist limit in the direction of flow **(upper middle)**. In the **lower left** and **middle panels,** the aliasing velocity is 40 cm/sec. Application of the continuity equation allows MVA to be calculated as MVA = $[2(\pi r^2)(V_{aliasing})/(\text{Peak } V_{mitral})] \times \alpha/180$. The angle correction is used to correct for deviation of the shell from hemisphericity. *A4C,* Apical four-chamber view.

Patient Selection for Balloon Valvuloplasty

In patients with severe MS in whom transcatheter intervention is planned, the Wilkins echocardiographic scoring system is useful in determining the likelihood of overall procedural success (**Table 14.9**); the less widely used Padial scoring system is useful in predicting freedom from severe MR. A Wilkins score greater than 8 or Padial score of 10 or more are predictors of poorer outcomes. It is also important to determine the amount of associated MR on echocardiography, because percutaneous balloon mitral valvotomy will increase the severity of regurgitation by at least one grade; thus the presence of moderate or greater MR should deter one from pursuing a percutaneous approach. The presence of LA appendage thrombus, which must be ruled out by TEE, is also a contraindication to percutaneous intervention because of the risk of embolization from guidewires and catheters.

TABLE 14.9

Wilkins Scoring System for Mitral Valvuloplasty

GRADE	LEAFLET MOBILITY	VALVE THICKENING	CALCIFICATION	SUBVALVULAR THICKENING
1	Highly mobile	Minimal thickening	Single area of brightness	Minimal chordal thickening
2	Reduced mobility	Thickened tips	Scattered areas at leaflet margins	Chordal thickening up to one-third
3	Basal leaflet motion only	Entire leaflet thickened	Brightness extends to mid leaflets	Distal third of chordae thickened
4	Minimal motion	Marked leaflet thickening	Extensive leaflet brightness	Extensive thickening to papillary muscles

A desirable score is 8 or lower.

Mitral Regurgitation

Causes of Mitral Regurgitation.
Minor leakage of the mitral valve is a common physiologic finding. There are many causes of pathologic regurgitation, and echocardiography should be used not only to diagnose and quantify MR, but also to determine the underlying functional disturbance and, when possible, to identify the disease causing the disturbance (**see Chapter 69**). Carpentier proposed a useful classification system based on the pathophysiology of MR that lends itself to an echocardiographic approach. In type I, leaflet motion is normal, and the most common abnormalities are leaflet perforation, alteration in coaptation because of bulky vegetation, or annular dilation secondary to chronic atrial fibrillation. In type II, at least one leaflet overrides the most superior plane of the annulus, that is, mitral prolapse or flail on the basis of either intrinsic valvular abnormality or rupture of either the chordae or papillary muscles. In type IIIA, leaflet motion is restricted during both systole and diastole, usually because of rheumatic disease, whereas in type IIIB, motion is limited in systole because of pathologic tethering on the basis of LV systolic dysfunction and remodeling, so-called functional MR.

Primary (Degenerative) Mitral Regurgitation

Mitral prolapse or flail that is attributable to primary leaflet and/or chordal pathology is termed *degenerative* MR. Echocardiography is the gold standard for the diagnosis of mitral prolapse or flail, distinguished as follows: in mitral flail, the unsupported free edge of the mitral leaflet extends into the left atrium because of loss of chordal support, whereas in mitral prolapse, the free edge remains tethered by chordae, and the leaflet billows pathologically into the left atrium. The diagnosis of prolapse is made from the parasternal long-axis view when any part of the leaflet extends 2 mm above a line drawn from the insertion of the anterior and posterior leaflets (**Fig. 14.40** and Video 14.29). This line represents the most superior aspect of the saddle-shaped annulus (**see Fig. 14.24** for 3D mitral valve shape). In the apical four- and two-chamber views, some extension of leaflet tissue above the annular boundaries is a normal variant and in most cases is not diagnostic of prolapse, although these views may demonstrate the classic billowing motion of a truly prolapsing mitral valve. It may be difficult to differentiate between mitral prolapse and flail with TTE alone, but TEE can assist in making the correct diagnosis.

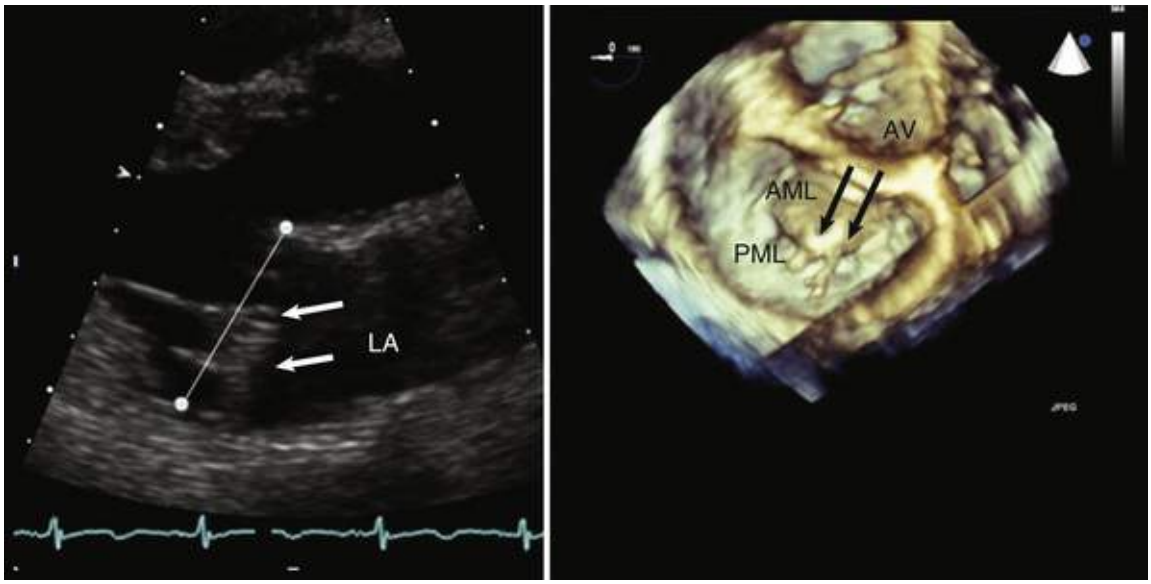


FIGURE 14.40 Degenerative MR. **Left,** Parasternal long-axis view showing bileaflet prolapse, as evidenced by billowing of both leaflets (*arrows*) above the annular plane, defined by the insertion of the anterior and posterior leaflets (*line*). **Right,** 3D TEE image of the mitral valve from the left atrial perspective. There is a large flail segment of the anterior mitral leaflet (*AML*). *Arrows* point to ruptured chordae. *AV,* Aortic valve; *LA,* left atrium; *PML,* posterior mitral leaflet.

The anatomic substrate for degenerative MR spans the spectrum from diffuse myxomatous change (Barlow) to localized abnormalities characterized as fibroelastic deficiency. Mitral valve prolapse is more prevalent in patients with Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, and other connective tissue disorders. 3D echocardiographic assessment of the extent of billowing has been reported to be useful in characterizing the nature of the pathology but, more importantly, has assumed a key role in determining precisely which scallop or scallops are prolapsing or flail. This information is essential in predicting the likelihood of successful repair. There is a high probability of successful repair for isolated P2 pathology, which is fortunately the most common pattern. Next in frequency and ease of repair is A2 disease, followed by abnormalities in the medial and lateral scallops. 3D TEE (see Video 14.26) is also helpful in identifying involvement of multiple scallops or unexpected associated anomalies such as localized mitral valve clefts. In the absence of 3D capability, a systematic approach to assessment of all three scallops via 2D TEE can be used (**see Fig. 14.35**). Complete assessment of the mitral scallops is difficult with TTE, although when achievable, high-quality 3D TTE images may be used for this purpose.

Secondary (Functional) Mitral Regurgitation

The term *functional MR* refers to MR that has as its root cause LV systolic dysfunction and remodeling. When the dysfunction is on the basis of CAD, the term *ischemic MR* is used. 3D echocardiography has shown that functional/ischemic MR reflects an imbalance between the forces that close versus those that tether the mitral leaflets (**Fig. 14.41**). The end result is pathologic tethering seen as apical displacement of leaflet coaptation. This pattern, which is appreciable on parasternal long-axis or apical views, is the echocardiographic hallmark of functional/ischemic MR (see Video 14.15). Reduced closing forces are attributable to impaired LV systolic function, whereas pathologic tethering forces can occur because of traction on the mitral leaflets from either their annular insertion (as a result of annular dilation and/or reduced annular contraction) or from their chordal connection to the papillary muscles. The latter has been shown to result from geometric displacement of the papillary muscles because of global or regional remodeling. It has been shown convincingly that papillary muscle contractile dysfunction per se does not

cause functional/ischemic MR.

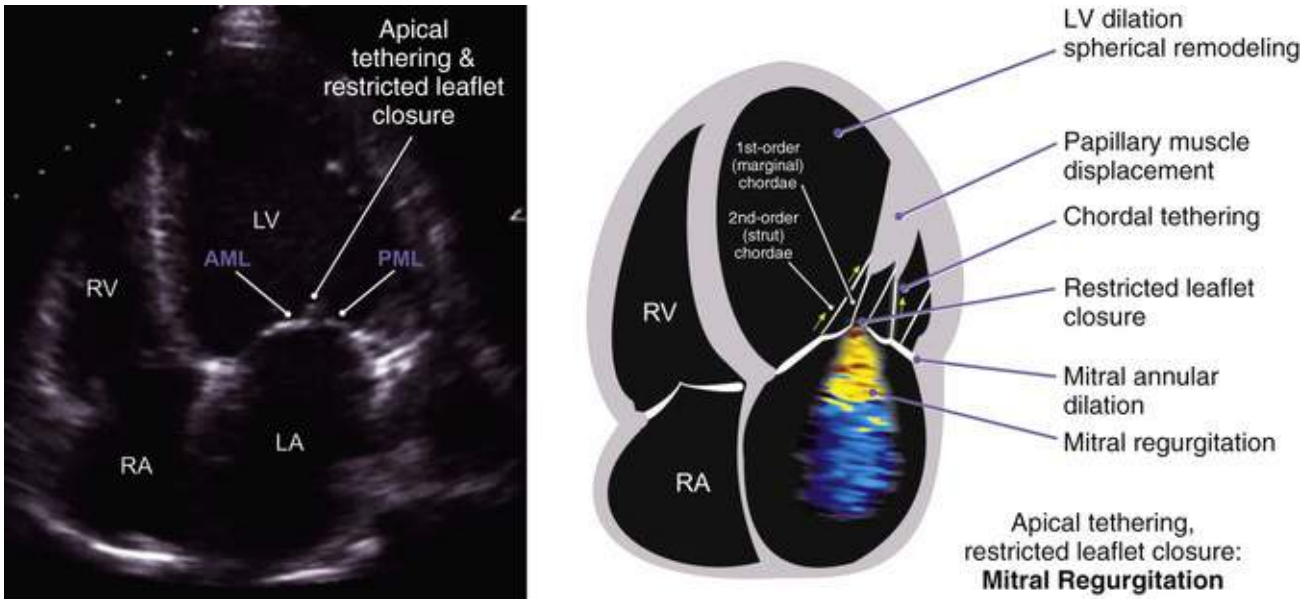


FIGURE 14.41 Functional/ischemic MR. Mitral tethering forces are increased because of both annular dilation and papillary muscle traction, which occur as a result of LV remodeling. Closing forces are reduced because of impaired LV systolic function. The end result is apical displacement of leaflet coaptation, as shown in the apical four-chamber view on the **left.** *AML,* Anterior mitral leaflet; *LA,* left atrium; *LV,* left ventricle; *PML,* posterior mitral leaflet; *RA,* right atrium; *RV,* right ventricle.

Quantitation of Mitral Regurgitation

The ASE recommends an integrated approach to the quantitation of MR[65] that incorporates semiquantitative measures such as assessment of jet area (ratio of jet area to LA area), the size of the peak mitral E wave, vena contracta diameter, and pulmonary venous flow patterns (**eFig. 14.20**). The peak E velocity reflects the initial diastolic gradient between the left atrium and left ventricle and will be elevated when MR has resulted in elevation of LA pressure. The vena contracta is the narrowest region of a jet and is best assessed in zoom mode on the parasternal long-axis view. Pulmonary venous flow patterns reflect the impact of the MR jet on flow into the left atrium with, in some cases, severe regurgitant systolic flow reversal. Quantitation of regurgitant volume and the EROA is possible with the PISA approach, which is based on the concept of acceleration of flow proximal to the regurgitant orifice (**Fig. 14.42**). The quantitative Doppler approach that uses the continuity equation provides a means of calculating regurgitant volume and fraction by comparing the total antegrade flow across the mitral valve with that across a nonstenotic nonregurgitant reference valve, typically the aortic valve (**Fig. 14.43**). In general, an EROA of 0.4 cm^2 or greater and RV volume of 60 mL is indicative of severe primary MR.

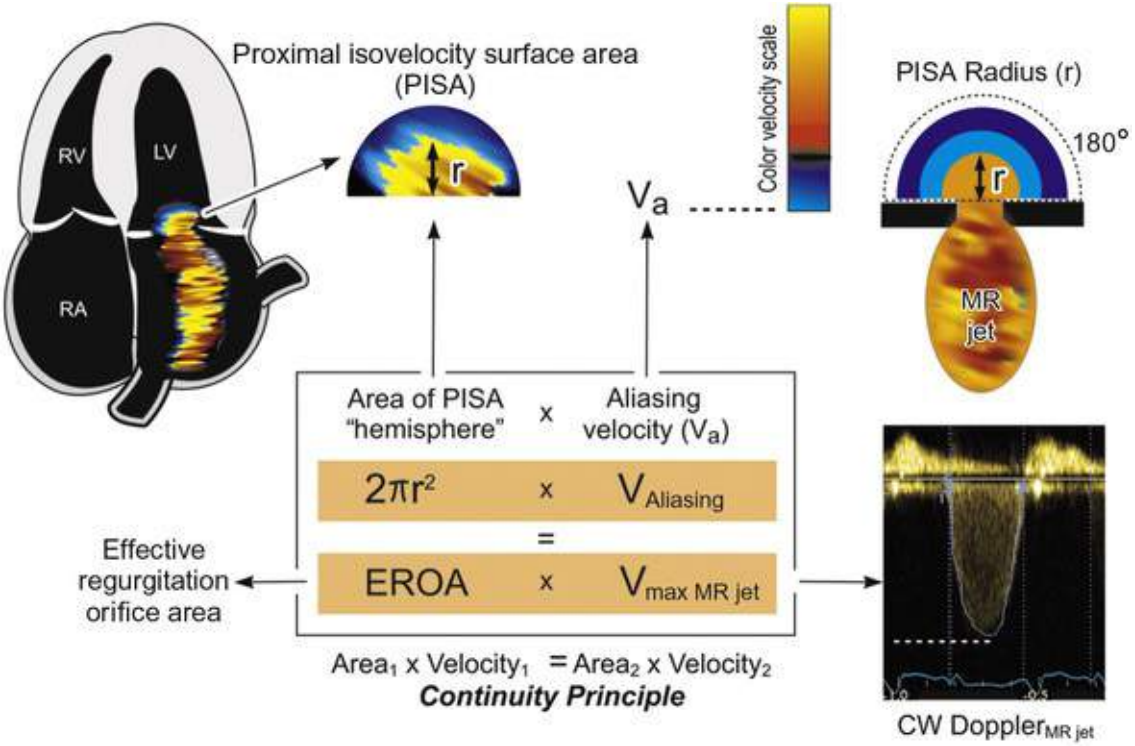


FIGURE 14.42 PISA approach to quantitating the aortic regurgitant orifice area (EROA) for MR. To optimize the PISA shell, the baseline is shifted in the direction of the jet. EROA is computed as EROA = $2(\pi r^2)(V_{aliasing})/(V_{MaxMR})$. Regurgitant volume can be calculated as EROA × VTI_{MR}, where VTI_{MR} is the velocity-time integral of the MR spectrum.

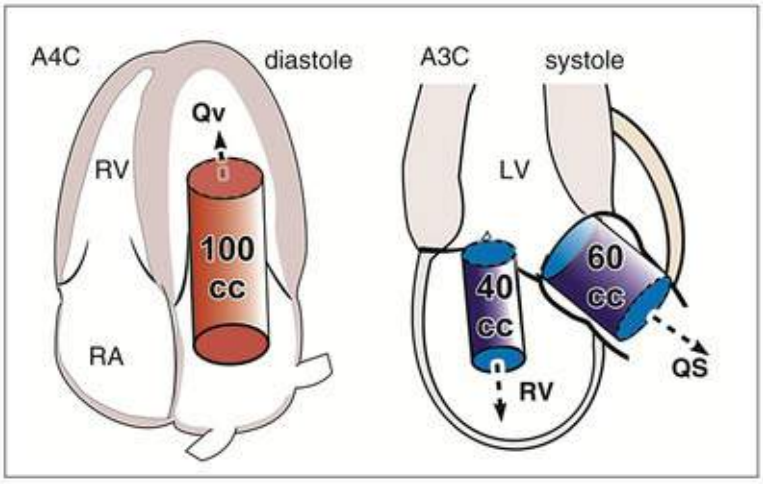
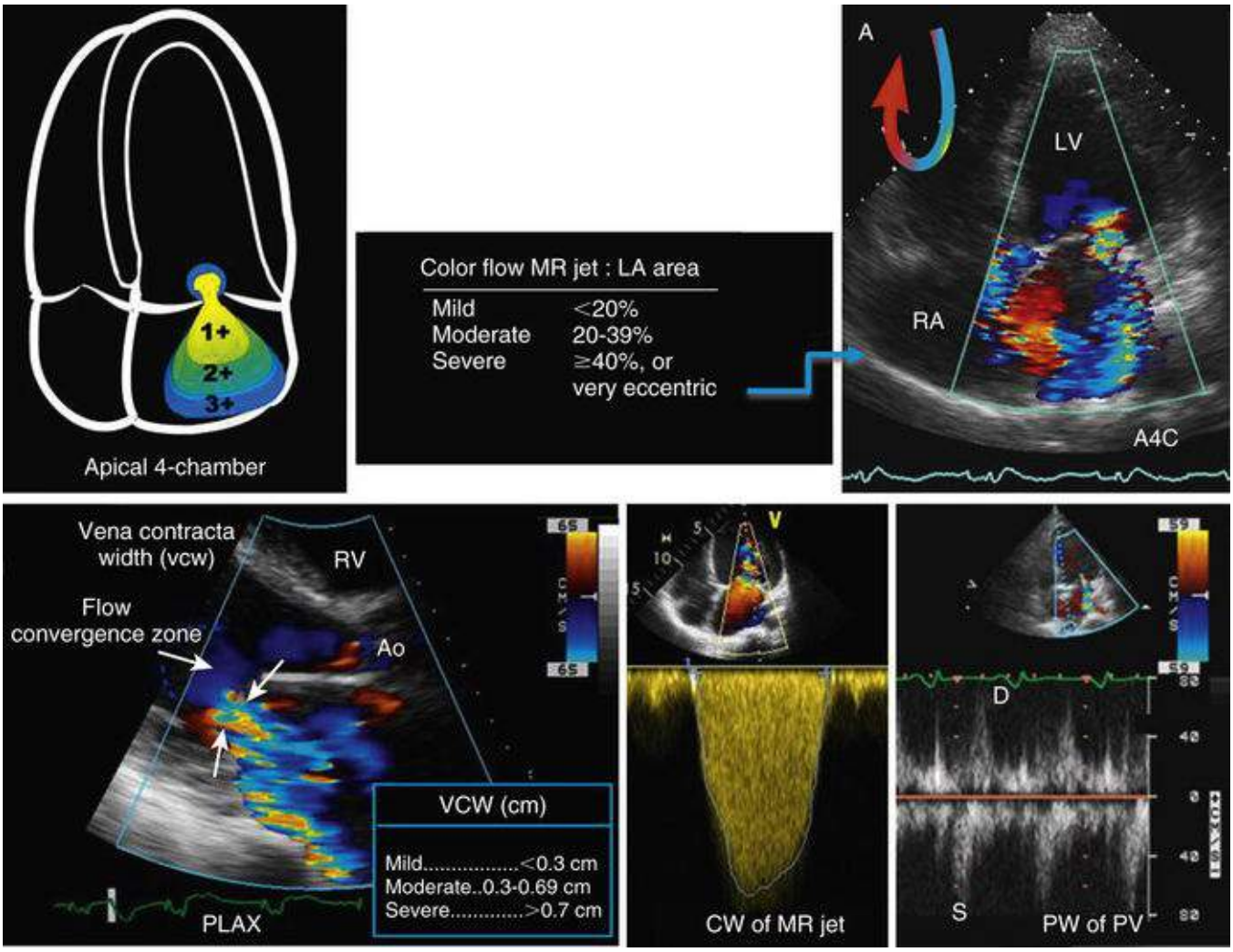


FIGURE 14.43 Quantitative Doppler approach to assessing the severity of MR. Regurgitant volume (RV) is calculated as the difference between total transmitral flow (Qv) and antegrade flow across the LVOT (Qs). Qv and Qs are calculated via the continuity method approach (CSA × VTI). Alternatively, Qv, which is identical to LV SV in the absence of a ventricular shunt or aortic regurgitation, may be calculated as LVEDV − LVESV, where LVEDV and LVESV are the LV end-diastolic and end-systolic volumes, respectively. *A4C,* Apical four-chamber view; *ALAX,* apical long axis; *RA,* right atrium.



EFIGURE 14.20 Mitral regurgitation (MR) grading by semiquantitative parameters. **Top panels,** A time-honored technique of grading simple central mitral regurgitant jets by freezing the apical window when the color flow jet is greatest (at usual Nyquist limits of 50 to 70 cm/sec), then tracing the area of the jet and expressing it as a ratio to the area of the left atrium. Ideally this is done in two orthogonal planes and the results averaged. If the jet is very eccentric (i.e., "hugs a wall"), the grade is generally increased by one grade in this scale. **Bottom panels: Left**, Vena contracta, or "neck," of color flow Doppler is measured ideally in the parasternal long-axis window (or alternatively, apical three-chamber window), and is a linear estimate that correlates with the actual orifice size of the mitral valve during systole. **Middle,** MR CW Doppler jet is very dense, consistent with more severe mitral regurgitation. **Right,** There is systolic flow reversal (the S wave is negative, or below the baseline) in the right upper pulmonary vein on PW Doppler.

Even though the color jet size approach is easy and widely utilized, it is influenced by machine settings and many other factors.[66] It underestimates MR severity with eccentric jets and overestimates severity with nonholosystolic MR. The PISA method is limited in situations where the assumption of a hemispheric PISA shell and circular regurgitant orifice is invalid; this is often true for eccentric jets caused by degenerative MR, as well as for functional MR cases where the PISA shell is flatter and hemi-elliptical. In fact, for functional ischemic MR, the values that suggest severe regurgitation and that correlate with poor clinical outcome are lower than the same cutoffs used for organic MR, possibly because the PISA method underestimates the true EROA; in this population, a calculated EROA of 0.2 cm^2 or greater and RV volume of 30 mL or more is considered severe.[66] Conversely, in nonholosystolic MR (e.g., late systolic MR that frequently occurs in MV prolapse), the EROA calculated with the PISA approach will overestimate severity because it reflects the maximum rather than the EROA averaged over all of systole. The major limitation of the quantitative Doppler technique lies in the assumption of circular or oval mitral orifice geometry in calculating transmitral flow. The use of LV SV calculated from echocardiographically measured LV volume versus aortic outflow has been suggested as an alternative

approach. The advent of 3D echocardiography has provided methods for direct planimetry of regurgitant orifices and has optimized assessment of nonhemispheric PISA shells, but these methods are not yet widely used clinically.

It is important to recognize that functional MR, and to a lesser degree MR of other causes, is afterload dependent, and thus determination of severity must take into account LV systolic pressure. Clinical decision making based on echo parameters made under general anesthesia is to be avoided, because anesthesia is associated with a predictable fall in systemic vascular resistance, which may dramatically reduce the degree of regurgitation.

Aortic Valve

Aortic Valve Anatomy.
The normal aortic valve consists of three symmetric cusps that are supported by the aortic annulus and extend into the aortic root. The right and left coronary cusps lie within the sinuses of Valsalva that give rise to the corresponding coronary arteries, and the remaining cusp is termed the *noncoronary* cusp. The ideal views for assessing aortic valvular anatomy are the parasternal short- and long-axis views (**see Fig. 14.10**) and their comparable views on TEE (**see Fig. 14.22E, F**). The short-axis view shows all three cusps, which when open create a triangular-shaped orifice and when closed have a Y-shaped appearance. The long axis typically displays the right and noncoronary cusps, which when normally open will flatten against the walls of the aortic root and with normal closure will meet centrally without prolapse below the plane of the aortic annulus.

The most common congenital abnormalities of the aortic valve result from failure of cusp development and include, in order of decreasing frequency, bicuspid, unicuspid, and quadricuspid valves (**Fig. 14.44**). Bicuspid valves can be distinguished on the basis of the position of the coronary arteries relative to the line of closure. When both arteries arise on the same side, the commissure is termed *horizontal*, whereas with a *vertical* commissure the arteries arise on opposite sides. Because of the inability of bicuspid valves to open fully, the systolic orifice of a bicuspid aortic valve is oval when seen in short axis, whereas the long-axis view demonstrates convex bulging of the leaflet midportions into the aortic lumen (doming) (Videos 14.30 and 14.31). Although bicuspid aortic valves classically have a single line of closure, many such valves additionally have an echogenic ridge or raphe that represents a vestigial commissure. The closed appearance of such valves may be echocardiographically indistinguishable from a tricuspid valve. Thus, bicuspid aortic valve is a systolic diagnosis. Unicuspid valves (Video 14.32) typically have circular openings that may be central or asymmetrically positioned, and quadricuspid valves (Video 14.33) have a square appearance in systole and a crosslike appearance in diastole.

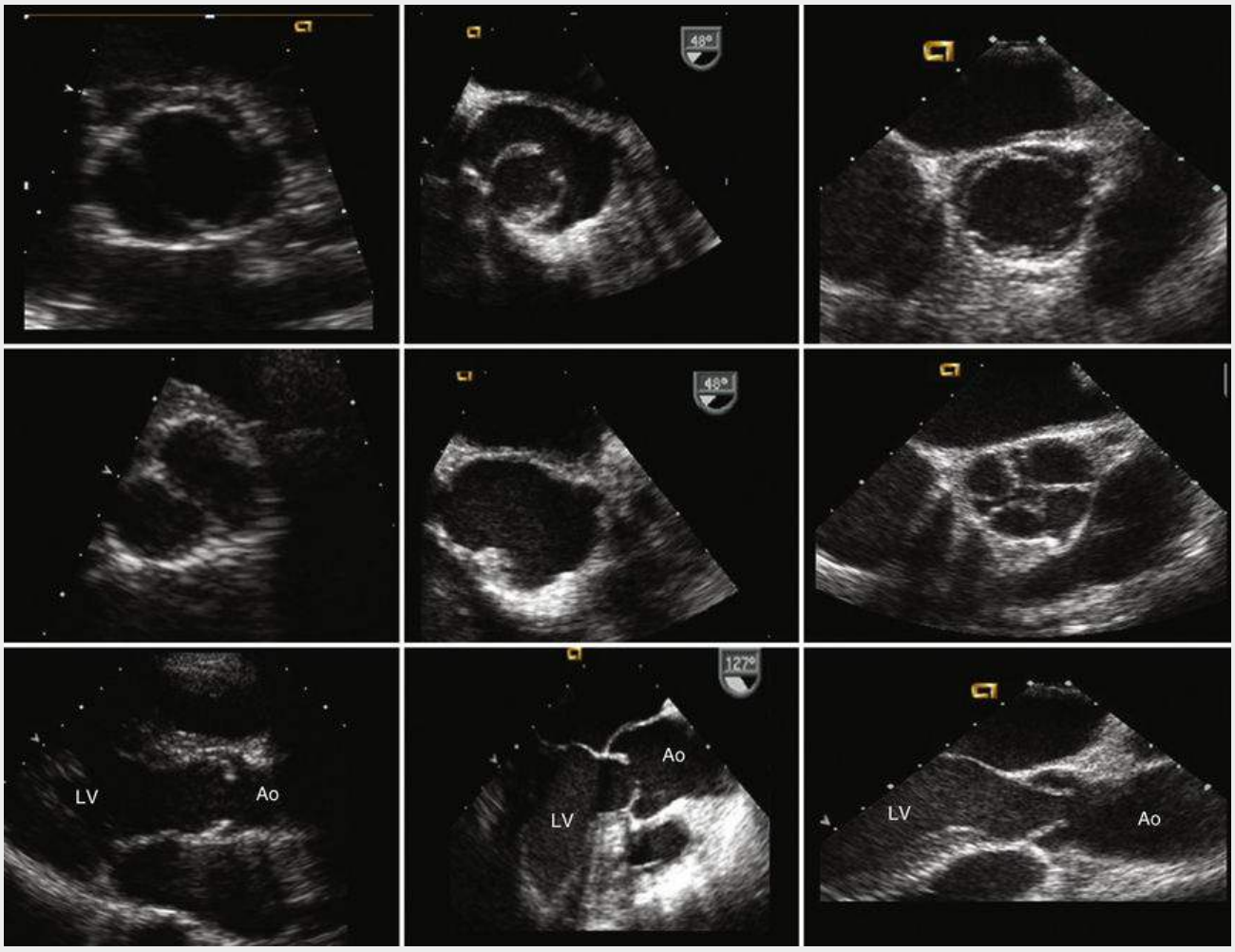


FIGURE 14.44 Congenital abnormalities of the aortic valve with (*top to bottom*) systolic short-axis, diastolic short-axis, and systolic long-axis views. **Left panels,** Bicuspid aortic valve. **Middle panels,** Unicuspid unicommissural aortic valve. **Right panels,** Quadricuspid aortic valve. *Ao,* Aorta; *LV,* left ventricle.

Congenital abnormalities of the LVOT include subaortic membranes, characterized by linear echoes extending from the anterior mitral leaflet to the septum or fibromuscular tunnels in which there is an echogenic ridge extending into the LVOT (**Fig. 14.45**). The presence of subaortic systolic turbulence on color Doppler should prompt close inspection of the LVOT for evidence of obstruction. Associated valvular AR is seen frequently and results from valve trauma caused by the subaortic stenotic jet. Supravalvular AS is a rare phenomenon that consists of localized or diffuse narrowing of the ascending aorta distal to the sinuses of Valsalva.

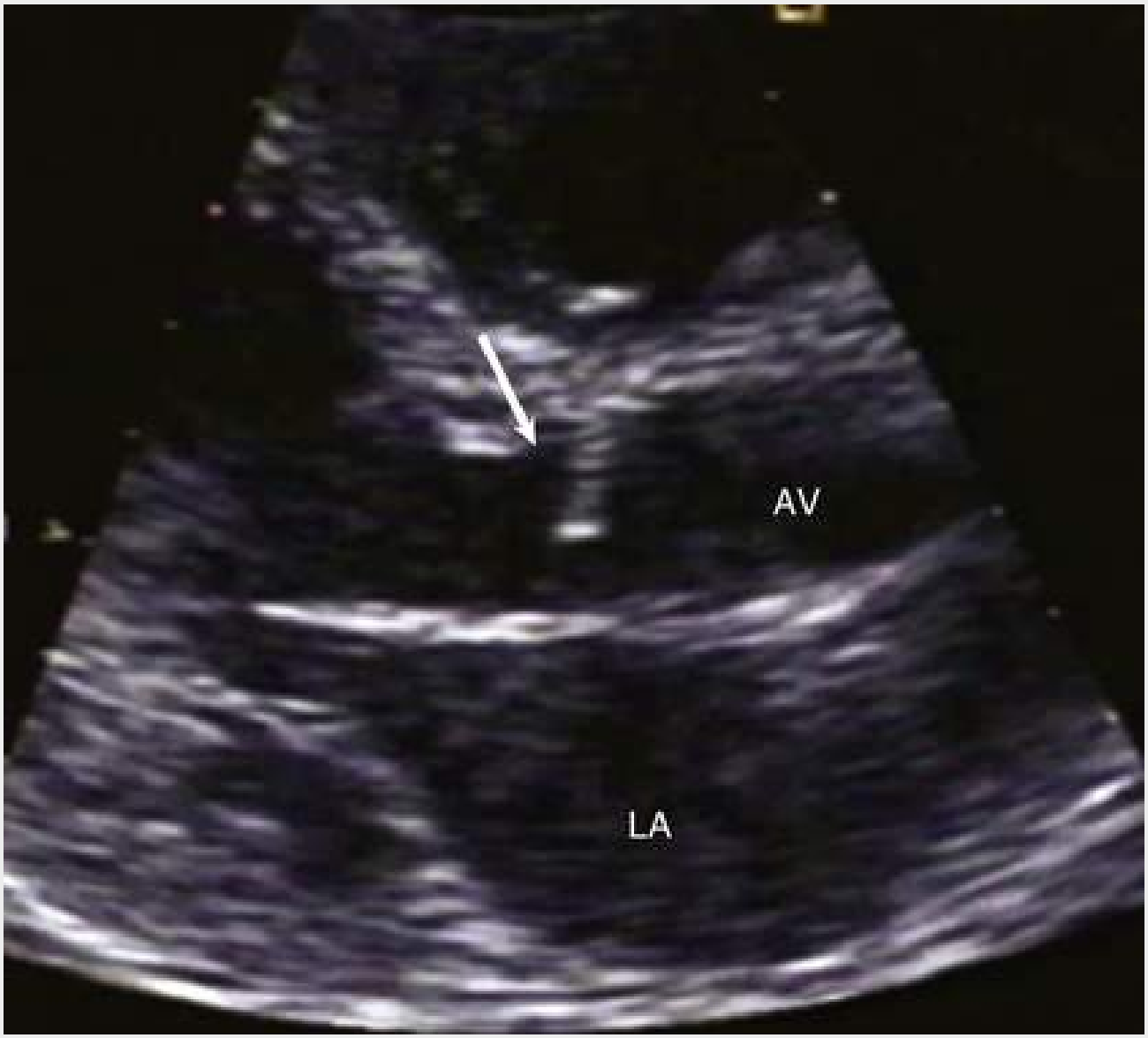


FIGURE 14.45 Nonstandard parasternal long-axis view demonstrating a subaortic membrane (*arrow*). The image is angled to show the membrane well with the result that the aortic valve (*AV*) is not well seen. *LA,* Left atrium.

Valvular Aortic Stenosis

Although the impeded cusp excursion of a bicuspid or unicuspid aortic valve may alone result in AS, calcium deposition on a congenitally normal tricuspid aortic valve is a common cause of AS in adults. The echocardiographic appearance is restricted cusp excursion with irregular nodular cusp thickening (**Fig. 14.46**).

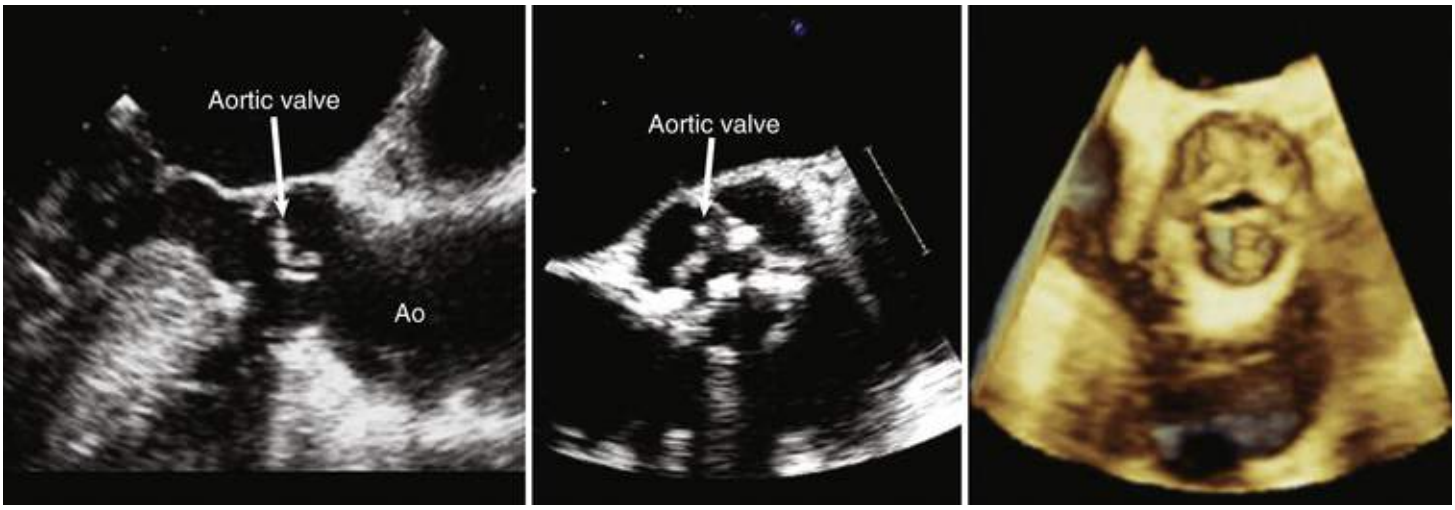


FIGURE 14.46 Systolic TEE images of calcific aortic stenosis in a patient with a tricuspid valve. **Left,** Two-dimensional long axis. There is minimal opening of the valve. *Ao,* Aorta. **Middle,** Short axis. **Right,** Three-dimensional image. The latter two views better demonstrate the distribution of calcium.

Quantitation of Severity

The normal aortic valve area (AVA) is 3 to 4 cm^2. Application of the Bernoulli equation to CW Doppler interrogation of transvalvular flow provides accurate measures of the mean and peak instantaneous gradients in aortic stenosis. Typically, the simplified form of the equation ($\Delta P = 4\ V^2$) may be used, but when LVOT velocity significantly exceeds 1 m/sec, the expanded version, $\Delta P = 4\ (V_2^2 - V_1^2)$, where V_2 is transaortic velocity and V_1 is LVOT velocity, should be used.

In recognition of the importance of recording Doppler signals parallel to flow, aortic gradients are best recorded from the apical five- or three-chamber, suprasternal notch, and right parasternal windows; typically, the highest velocities are found on the right parasternal view. The nonimaging Pedoff probe has a smaller footprint, making it essential for optimal assessment of patients with AS. When TEE is used, velocities are recorded from the deep transgastric views (**see Fig. 14.22, position O**). It should be noted that although echocardiographically derived mean gradients are generally identical to those obtained invasively, the echocardiographically derived peak *instantaneous* gradient is typically higher than the *peak-to-peak* gradient calculated in the catheterization laboratory (**see Chapter 19**). The latter is the arithmetic difference between peak LV and aortic pressure (**Fig. 14.47**), which may not be coincident in time.

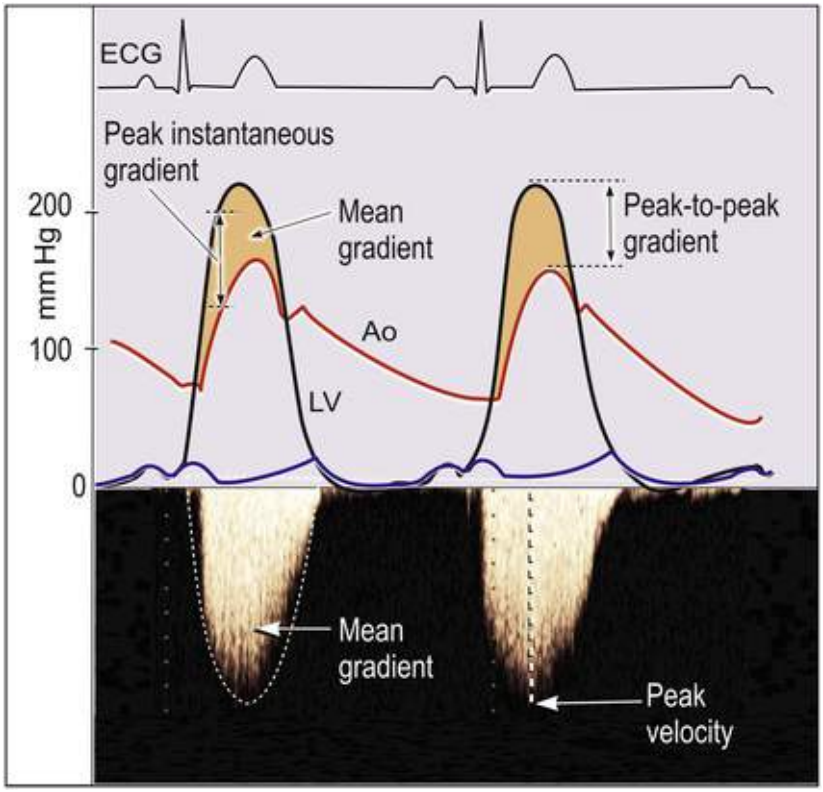


FIGURE 14.47 Doppler methods provide peak instantaneous and mean gradients. The peak instantaneous gradient is typically higher than the peak-to-peak gradient calculated from invasively measured peak left ventricular (*LV*) and aortic (*Ao*) pressure, which is not instantaneous, although mean gradients measured with both techniques are identical.

Although gradients alone provide a reasonable assessment of the severity of AS when transaortic flow is normal, they may underestimate severity in the setting of low-flow states and overestimate severity when flow is elevated (e.g., high-output states such as those caused by sepsis and anemia). For this reason it is important to determine AVA. Direct planimetry of TEE images may be used for this purpose, but TTE planimetry is not sufficiently accurate. The most common approach is therefore by application of the continuity equation (**Fig. 14.48**). AVA is calculated as follows:

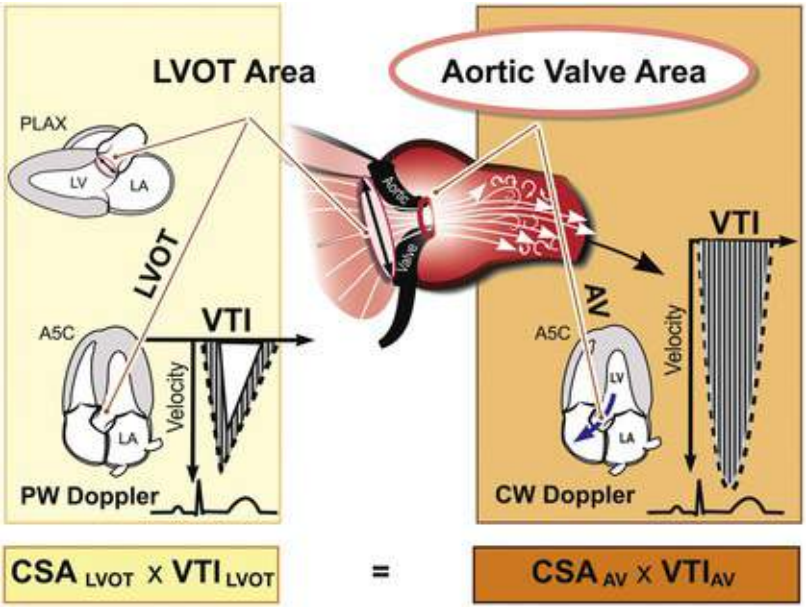


FIGURE 14.48 Continuity equation approach to calculating aortic valve area. The cross-sectional area (CSA) of the aortic valve (CSA_{AV}) is calculated as ($CSA_{LVOT} \times VTI_{LVOT}$)/$VTI_{AV}$). LVOT CSA is calculated as $\pi(D/2)^2$, where *D* is LVOT diameter. LVOT VTI should be measured from the modal rather than the maximal velocity (**see Fig. 14.49**).

$$AVA = (CSA_{LVOT} \times VTI_{LVOT})/VTI_{AV}$$

Less desirable is the simplified version:

$$AVA = (CSA_{LVOT} \times V_{LVOT})/V_{AV}$$

where V represents peak velocity. The CSA of the LVOT is typically calculated by assuming circular geometry with the formula $CSA = \pi(D/2)^2$, where D is the systolic LVOT diameter measured on the parasternal or TEE-equivalent long-axis view. According to the ASE convention, the diameter is measured just proximal to the aortic annulus. It is cautioned that because the LVOT velocity incorporated into the calculation is the *modal* velocity, displayed as the densest part of the pulsed Doppler envelope, the VTI should not be traced by using the outer edge of the spectrum, which represents the maximal (not modal) velocity at each time point (**Fig. 14.49**). Optimal sample volume placement is in the LVOT immediately proximal to the site of subvalvular flow acceleration, typically 1 to 2 mm proximal to the valve on the apical five- or three-chamber (TTE) or deep transgastric (TEE) views.

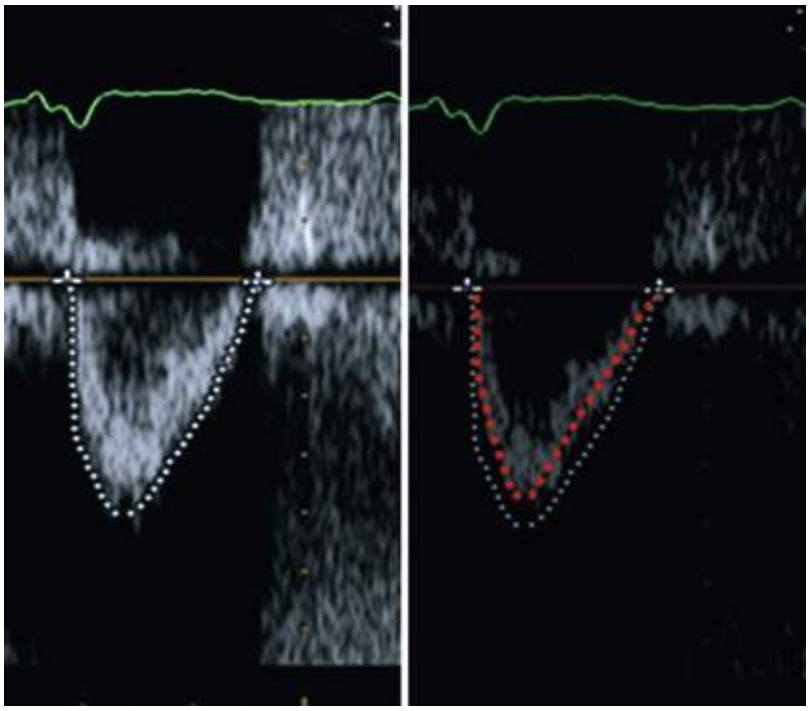


FIGURE 14.49 Doppler spectra demonstrating the error that may be introduced if the maximal (*white dotted line*) rather than the modal (*red dotted line*) velocity is measured. The modal velocity (the most commonly occurring velocity) corresponds to the brightest portion of the Doppler spectrum.

Low-Gradient Severe Aortic Stenosis

In the setting of reduced SV because of LV systolic dysfunction, leaflet excursion may appear reduced and calculated effective orifice area may be small despite low gradients, and it becomes important to determine whether the valve obstruction is fixed (true severe AS) or the valve is intrinsically capable of opening more fully at higher flow rates (pseudosevere aortic stenosis). As noted previously, DSE is routinely used in this setting, typically with close physician supervision to evaluate the true AVA, as well as LV contractile reserve. The effective orifice area may also be severely reduced despite low gradients when the LVEF is within the normal range but SV is impaired, so-called paradoxical low-gradient, preserved–ejection fraction, severe AS (discussed earlier).

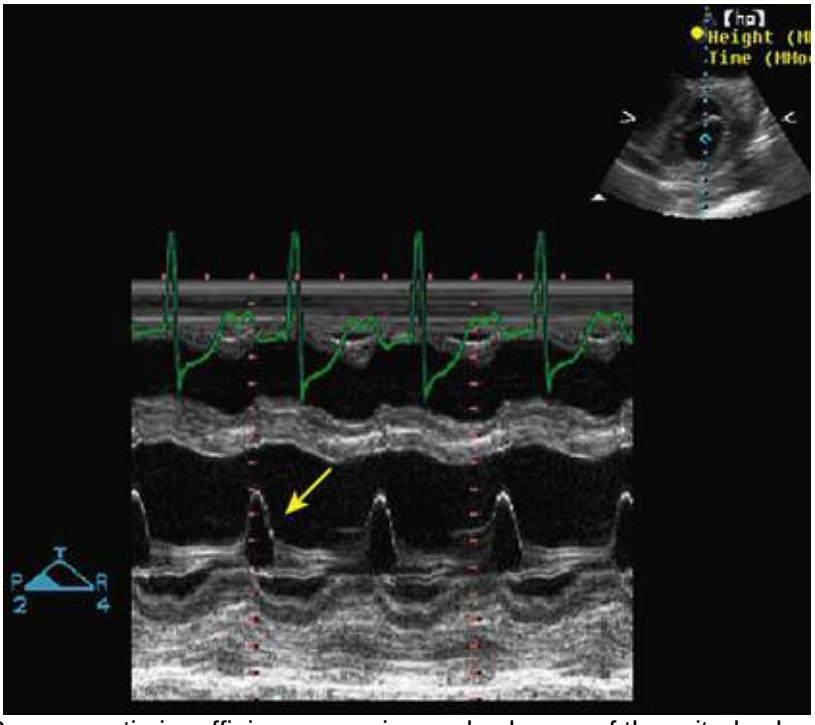
Subvalvular or Supravalvular Aortic Stenosis.

CW Doppler echocardiographic assessment of peak and mean gradients is the cornerstone in evaluating patients with LVOT obstruction below or above the valve. However, by demonstrating the site of flow acceleration relative to the 2D images, color Doppler may provide a clue that the obstruction is not at the level of the valve and prompt the more detailed imaging investigation of the pathophysiology. In some patients, evaluation is complicated by the presence of obstruction at multiple levels, such as the presence of both subaortic and valvular AS. In such cases, because of the trade-off between range resolution and the inability to measure accurately the high velocities inherent in the PW Nyquist limit, it may be impossible to discern accurately the gradients created at each level of obstruction.

Aortic Regurgitation

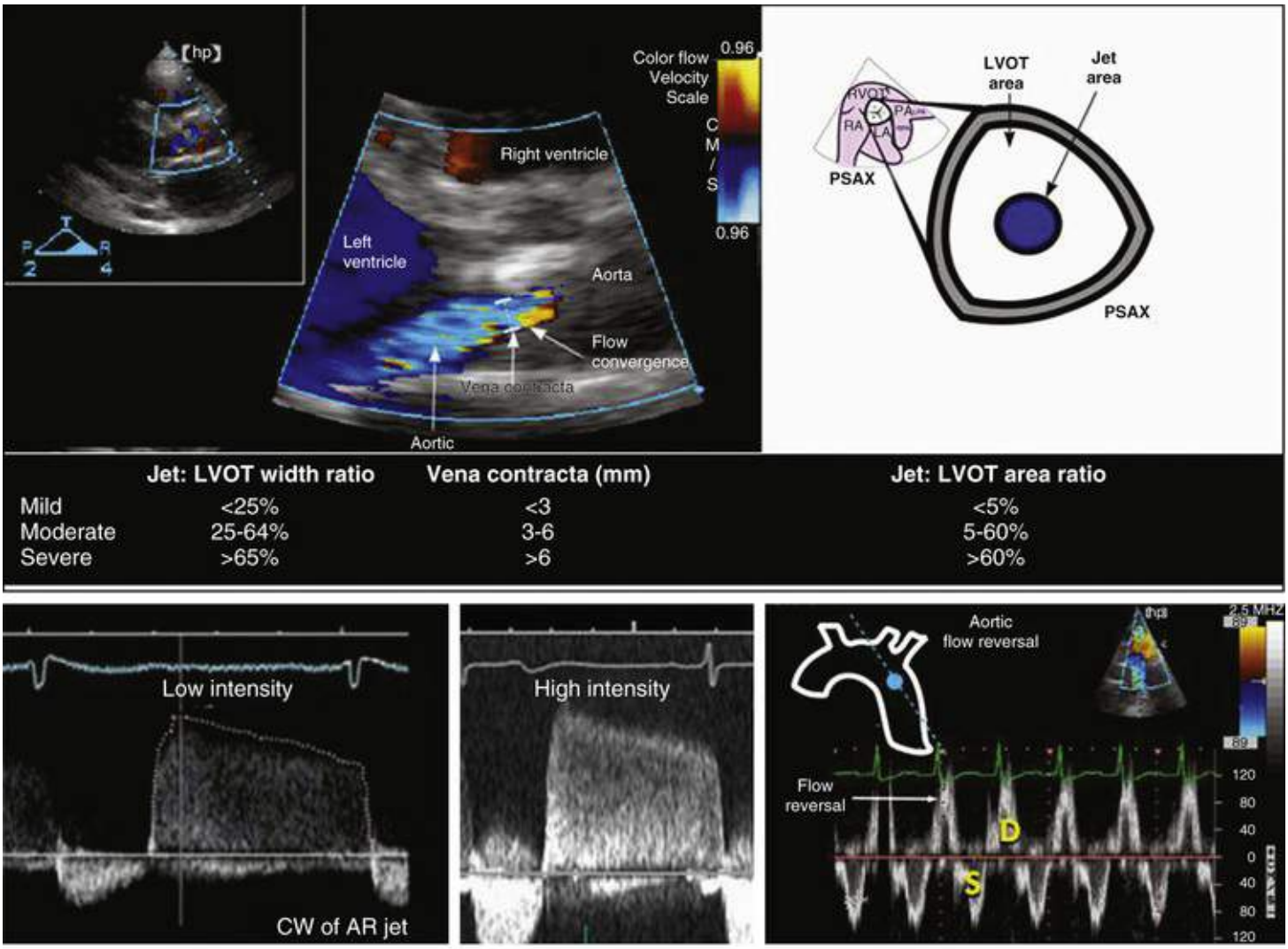
Aortic regurgitation (AR) may result from abnormalities in the valve cusps, normal cusps whose coaptation is altered by enlargement of the annulus and/or sinuses, or rarely, prolapse of an aortic

dissection flap through the valve (see Diseases of the Aorta). Echocardiographic imaging (TTE and TEE) will establish a causative diagnosis and typically demonstrates LVED enlargement if the regurgitation is hemodynamically significant. High-frequency fluttering of the anterior mitral leaflet caused by the impact of the regurgitant jet may be evident on M-mode, and in cases of acute severe regurgitation, the mitral valve may close prematurely before ventricular systole because of a rise in LV pressure exceeding the LA pressure before ventricular contraction (**eFig. 14.21**).



EFIGURE 14.21 Severe aortic insufficiency causing early closure of the mitral valve (*arrow*) on M-mode.

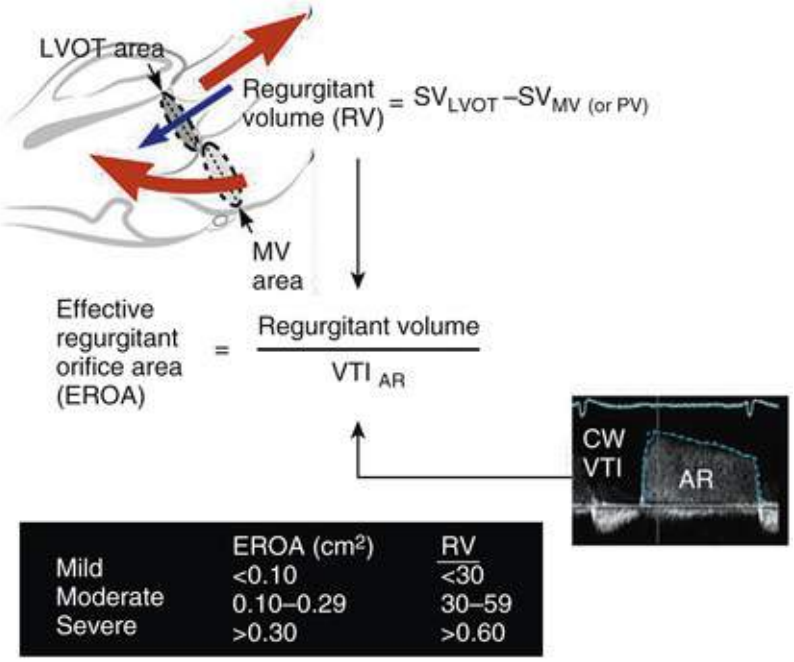
The diagnosis of AR is most easily made when a diastolic color Doppler jet is seen in the LVOT. Small transient jets can be normal variants. Again, an integrated approach is best for determining the severity of AR, with elements including evidence of LV enlargement, color jet dimensions, spectral Doppler signal intensity, pressure half-time, vena contracta, and diastolic flow reversal in the descending thoracic or abdominal aorta (**eFig. 14.22**). Regurgitant volume and fraction can be calculated using a continuity-based approach (**eFig. 14.23**), or alternatively, both measures and EROA may be calculated with the PISA approach. A regurgitant volume of 60 mL or more and EROA of 0.30 cm^2 or greater are consistent with severe AR.[65,66]



	Jet: LVOT width ratio	Vena contracta (mm)	Jet: LVOT area ratio
Mild	<25%	<3	<5%
Moderate	25-64%	3-6	5-60%
Severe	>65%	>6	>60%

Mild | Moderate to severe | Moderate to severe AR

EFIGURE 14.22 Aortic regurgitation (AR) grading by semiquantitative parameters. **Top panel,** Color Doppler zoomed in on the parasternal long axis (*left*) view of the aortic valve showing the AR jet. Parameters that correlate roughly with grades of AR are shown chart below each measurement. The jet height and left ventricular outflow tract (LVOT) height are measured directly on the images. The jet area can be traced by planimetry. LVOT area is calculated as 0.785 × (LVOT diameter/2)^2. **Bottom: Left panels,** CW Doppler of the jet in apical five-chamber view, showing that the density of the CW jet in diastole, relative to the forward-flow envelope, correlates roughly with the severity of AR. **Right panel,** PW Doppler with the pulse sample volume placed in the descending thoracic aorta near the origin of the left subclavian artery, showing that there is diastolic flow reversal suggestive of at least moderate AR. If diastolic flow reversal is seen even more distally, in the abdominal aorta, the AR is likely severe.



EFIGURE 14.23 Calculation of the aortic effective regurgitant orifice area (EROA), using quantitative Doppler methods based on the continuity equation. The EROA represents the average size of the defect in the aortic valve during diastole and is proportional to regurgitant severity. The regurgitant volume (RV) across the aortic valve may be calculated as the difference between the LVOT volume (SV_{LVOT}) and the transmitral volume (SV_{MV}) or transpulmonic volume (SV_{PV}), assuming there is no significant mitral (or pulmonic) regurgitation. Alternatively SV_{LVOT} may be calculated as LVEDV − LVESV, where LVEDV and LVESV are the LV end-diastolic and endsystolic volumes traced from endocardial borders and calculated by modified Simpson's equation, respectively.

Color jet dimensions should be assessed with Nyquist settings of 50 to 60 cm/sec. The best dimensional predictors of angiographic severity are the jet area/LV short-axis area ratio (parasternal short-axis view) and jet diameter indexed to LVOT diameter immediately proximal to the valve (parasternal long-axis view). Jet length is not a reliable index of severity. The pressure half-time reflects the rate at which aortic and LV pressures equalize and is most reliable in the setting of acute AR, as long as care is taken to ensure that the early diastolic velocity is captured accurately (**Fig. 14.50**). The vena contracta is the waist (smallest diameter) of the regurgitant flow jet at the level of the valve measured in zoom mode on a parasternal long-axis or TEE-equivalent view. A measurement greater than 6 mm generally correlates with severe AR. Holodiastolic flow reversal in the descending thoracic aorta as detected with the pulsed Doppler is a marker of at least moderate AR (**see Fig. 14.50 and eFig. 14.22**). Reversal of comparable duration as measured in the abdominal aorta generally reflects severe AR. Although the PISA approach that is widely used to assess the severity of MR has similarly been used to calculate EROA and regurgitant volume for AR, it may be challenging to measure accurately the PISA radius when only mild regurgitation is present (particularly with TTE). The quantitative Doppler approach (**eFig. 14.23**) that calculates regurgitant volume by comparing flow through the LVOT with that across a competent nonstenotic valve is most robust when the pulmonic valve is used as the reference for normal flow (image quality permitting). The mitral valve can theoretically be used as the reference but is more geometrically complex and thus more prone to error.

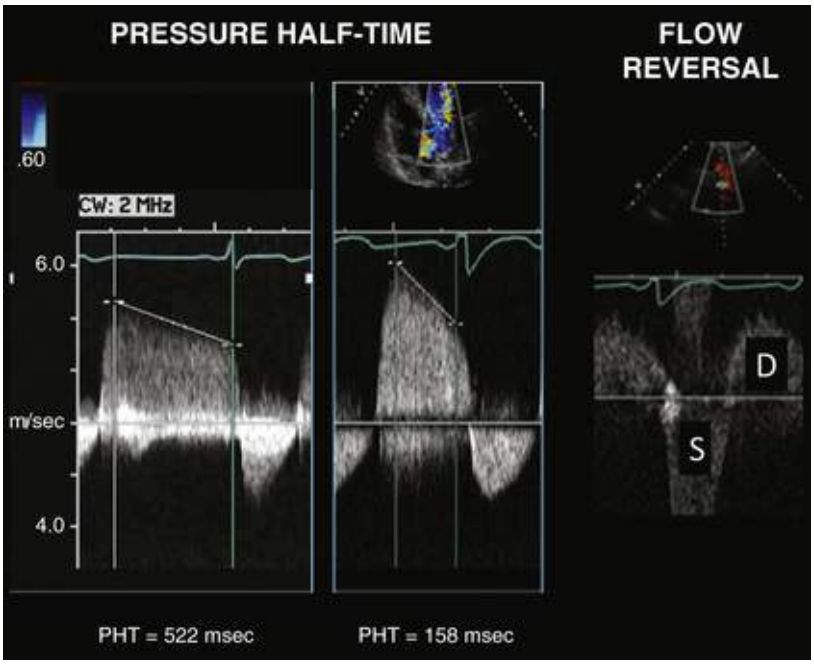


FIGURE 14.50 Doppler methods of quantitating aortic regurgitation (AR). A pressure half-time (PHT) greater than 500 milliseconds suggests mild AR, 200 to 500 milliseconds suggests moderate AR, and less than 200 milliseconds suggests severe AR. Holodiastolic flow reversal in the descending thoracic aorta, as shown here, is consistent with at least moderate AR. *S,* Systole; *D,* diastole.

Tricuspid Valve

Tricuspid Valve Anatomy.
The tricuspid valve is anatomically complex, with anterior, posterior, and septal leaflets extending from the tricuspid annulus to chordae and variable papillary muscle/trabecular attachments. Even though the anterior and septal leaflets are well seen on multiple echocardiographic views, the posterior leaflet is visualized only on the RV inflow tract view and on short-axis views of the right ventricle (which can display all three leaflets). Because of its importance in imaging the tricuspid valve, the RV inflow tract view must be acquired in a manner that displays the inferior (diaphragmatic) wall but avoids the interventricular septum and septal leaflet of the tricuspid valve (**see Fig. 14.10**).

Acquired Disorders of the Tricuspid Valve

Tricuspid stenosis occurs in approximately 11% of patients with rheumatic mitral disease and is characterized by diastolic leaflet doming, as well as by leaflet and chordal thickening (**Fig. 14.51** and Video 14.34). Severity is best assessed by Doppler-derived mean gradients. Methods for calculating valve area, including the pressure half-time approach, have not been validated for tricuspid stenosis (**see Chapter 70**).

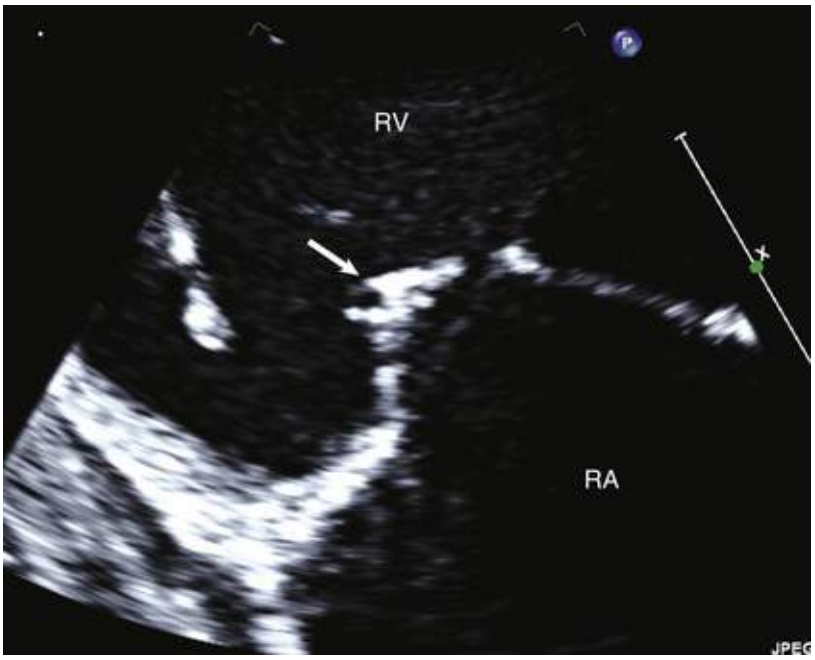


FIGURE 14.51 Right ventricular inflow tract view demonstrating diastolic doming of the posterior leaflet (*arrow*) characteristic of rheumatic tricuspid valve disease. *RA,* Right atrium; *RV,* right ventricle.

Pathologic tricuspid regurgitation (TR) most frequently occurs on a functional basis, that is, attributable to RV enlargement or dysfunction. RV abnormalities may be primary or secondary to pulmonary hypertension and left-sided cardiac abnormalities. The echocardiographic hallmark of functional TR is apical tethering, which when severe may result in a visible regurgitant orifice (noncoaptation of the leaflets) (**Fig. 14.52**). Under these conditions the regurgitant jet could be laminar and relatively low velocity because of the almost complete equalization of pressures between the right ventricle and the right atrium and could lead to underestimation of the severity of the TR. Similarly, estimation of pulmonary artery systolic pressure from TR jet velocity will be inaccurate in this situation.

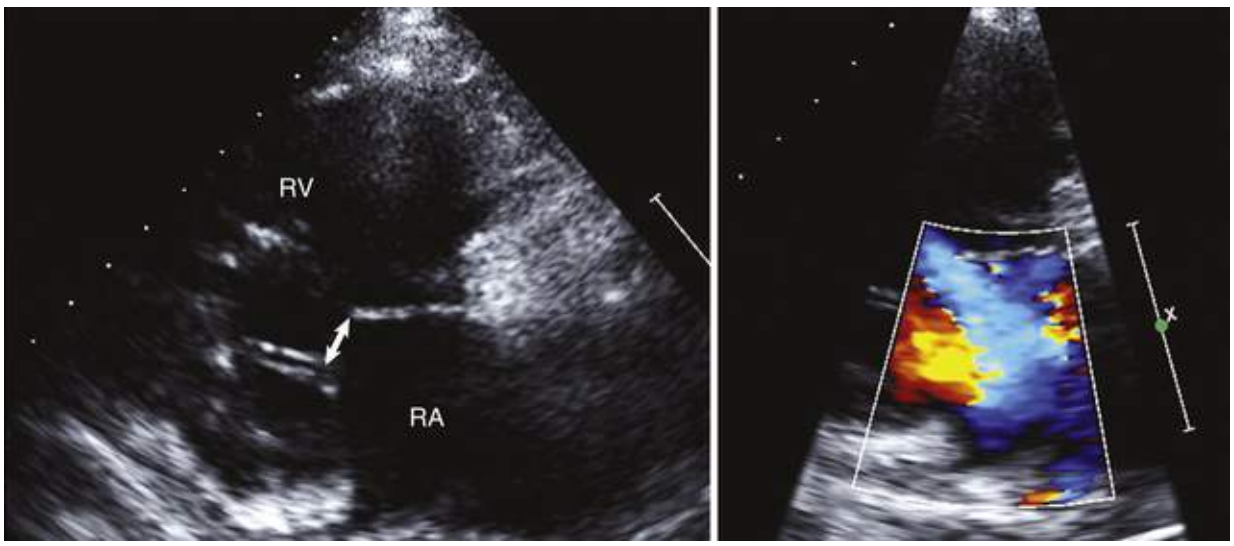


FIGURE 14.52 **Left,** Right ventricular inflow tract view showing failure of coaptation of the anterior and posterior leaflets (*arrow*) in a patient with severe functional tricuspid regurgitation. *RA,* Right atrium; *RV,* right ventricle. **Right,** Severity may be underestimated because of its low velocity and monochromatic appearance.

Less common acquired causes of TR include carcinoid, rheumatic disease, endocarditis, trauma (including iatrogenic injury to the valve during RV biopsy), pacemaker and defibrillator wires, and

myxomatous disease with prolapse. The characteristic echocardiographic appearance of carcinoid heart disease is drumstick-like, rigid, and shortened leaflets with at times a visible regurgitant orifice (**Fig. 14.53** and Video 14.35). Spontaneous flail of the tricuspid valve virtually never occurs but is precipitated by the previous causes. Myxomatous tricuspid valve disease has been less well studied than mitral disease, with less clear-cut criteria for the diagnosis of prolapse. It frequently accompanies myxomatous mitral disease.

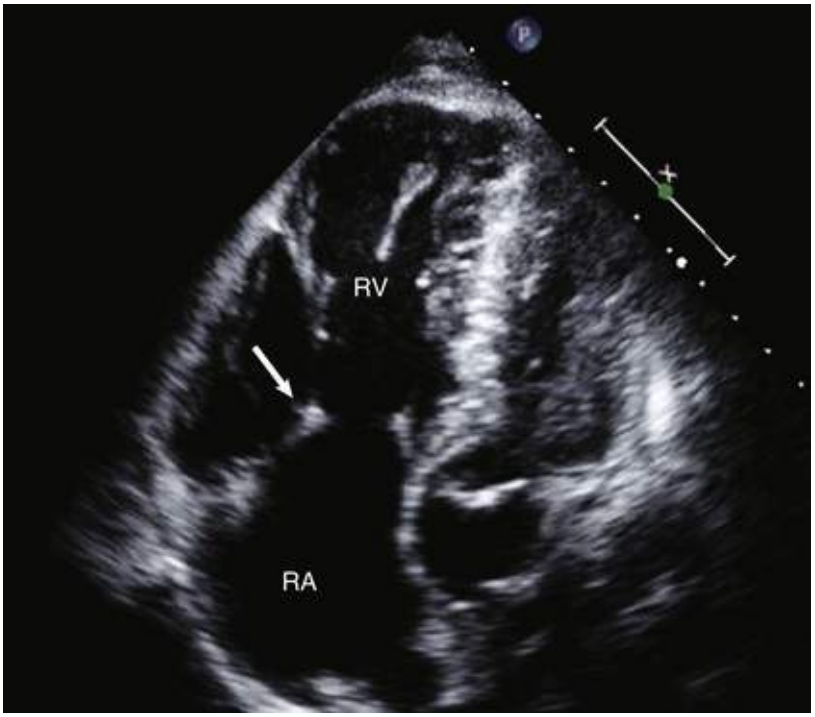


FIGURE 14.53 Apical four-chamber view showing the drumstick appearance of the tricuspid valve (*arrow*), which is characteristic of carcinoid valvopathy. *RA,* Right atrium; *RV,* right ventricle.

Quantitation of Tricuspid Regurgitation

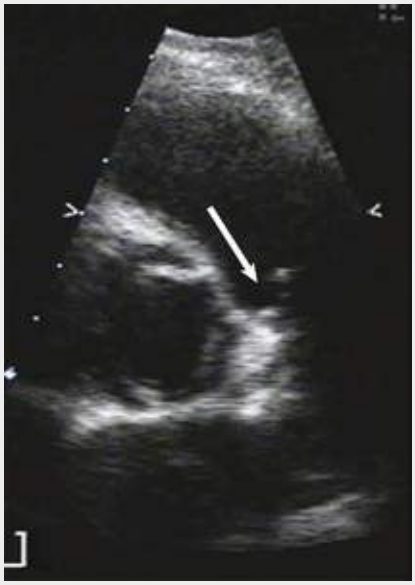
Quantitation of TR is similar to that for MR and consists of an integrated approach,[65,66] including measures of jet size, vena contracta, and PISA-derived regurgitant volume and EROA. Systolic flow reversal into the hepatic veins is specific for severe TR.

Pulmonic Valve

Pulmonic Valve Anatomy.

The normal pulmonic valve is tricuspid with a structure that is similar to that of the aortic valve. The cusps are named right, left, and anterior, although it is unusual to be able to see all three cusps simultaneously with 2D imaging. The pulmonic valve can be seen on parasternal and subcostal views, as well as on anteriorly oriented apical views. TEE windows include the midesophageal, deep transgastric, and high esophageal (at the level of the aortic arch). The most common congenital anomaly is valvular stenosis, based on developmental abnormalities that mimic those of a bicuspid aortic valve (**eFig. 14.24**). It is characterized by systolic doming and a jump rope–like appearance of the valve (Video 14.36

). Congenital pulmonic stenosis may be isolated or may occur as a feature of more complex congenital anomalies. Acquired pulmonic disease is rare and includes carcinoid and endocarditis, as well as iatrogenic disruption of the valve because of balloon or surgical valvuloplasty for congenital stenosis.



EFIGURE 14.24 Systolic parasternal short-axis view demonstrating systolic doming of this congenitally stenotic pulmonic valve (*arrow*). In real time the valve has a jump rope appearance.

Quantitation of Valve Dysfunction

Pulmonic stenosis is most reliably quantitated with mean and peak gradients, although the continuity equation provides a means of calculating valve area. Pulmonic regurgitation is usually graded on the basis of jet dimensions, with the caveat that there may be little turbulence in the setting of severe regurgitation with normal pulmonary pressure, which can lead to inadvertent underestimation of the true severity. Laminar regurgitant flow is a clue to severe regurgitation (**Fig. 14.54**).

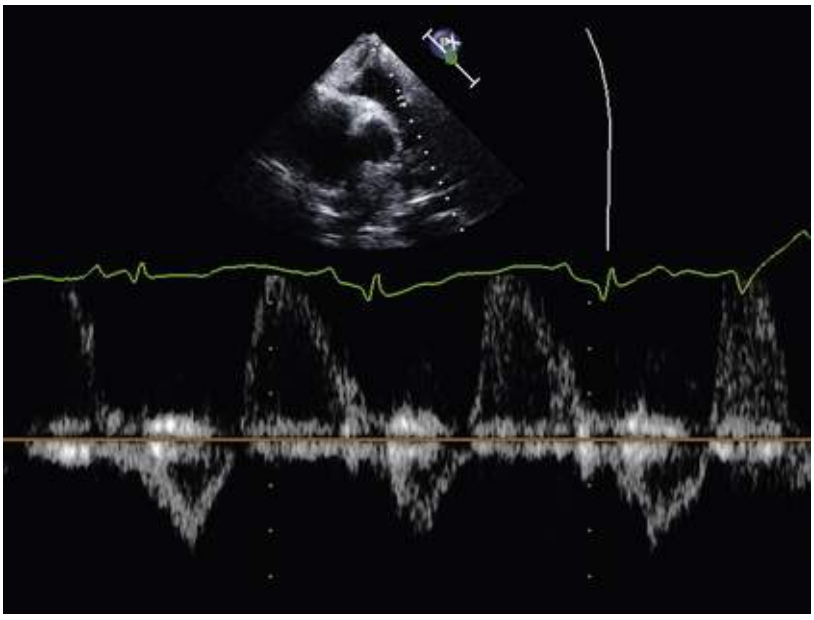


FIGURE 14.54 PW Doppler interrogation of the RVOT in a patient who has undergone pulmonary valvotomy. There is severe pulmonic regurgitation resulting in a laminar regurgitant signal.

Prosthetic Valves

Echocardiographic assessment of prosthetic valves requires an understanding of valve design, normal functional characteristics, and the imaging artifacts introduced by valve elements (**see Chapter 71**).

The most commonly encountered mechanical valves are bileaflet or single, tilting disc valves. Ball-and-cage valves, which are no longer implanted, are becoming increasingly rare. Most bioprosthetic valves are stented porcine or bovine pericardial valves, although freestyle (stentless) xenograft, cadaveric homograft, autograft (Ross procedure), and transcatheter and sutureless surgical valves are also available. Prosthetic annular rings are also often used for mitral and tricuspid repair. The sewing rings of all valves, as well as the occluders of mechanical valves, may cause acoustic shadowing that limits imaging and Doppler assessment; the exceptions to this are the stentless, homograft, and autograft valves, which may be indistinguishable from that of native valves. Additionally, the material of the ball in ball-and-cage valves transmits sound more slowly than human tissue does, with the result that the ball appears much larger than its actual size when imaged echocardiographically.

Even normally functioning prostheses tend to be intrinsically stenotic, with the degree of stenosis inversely related to valve size. Additionally, trivial degrees of valvular regurgitation are normal findings, and although not normal, trivial paravalvular regurgitation is not uncommon. Intraventricular microcavitations (apparent “microbubbles”) are often seen in the left heart in the presence of mechanical valves and are not considered abnormal. **Figs. 14.55 to 14.57** and Video 14.37 demonstrate the normal echocardiographic appearance of the most common prostheses. **eTable 14.5** provides normal echocardiographic values for the most common implanted valves.[67] More current data, including recently introduced prostheses, are collated from the literature and valve manufacturers at www.valveguide.ch.[68] A helpful rule of thumb when valve size is unknown is that for common-size prostheses in patients with physiologic heart rates and SV, the peak transaortic velocity should be less than 3 m/sec and the mean transmitral gradient 5 mm Hg or lower. Stentless bioprosthetic valves, which have little or no acoustic shadowing due to lack of a rigid annulus, are designed to have lower hemodynamic profiles (i.e., lower gradients) than their equivalently sized first-generation predecessors and appear useful for implantation in patients with a small annulus or severely reduced LV function.

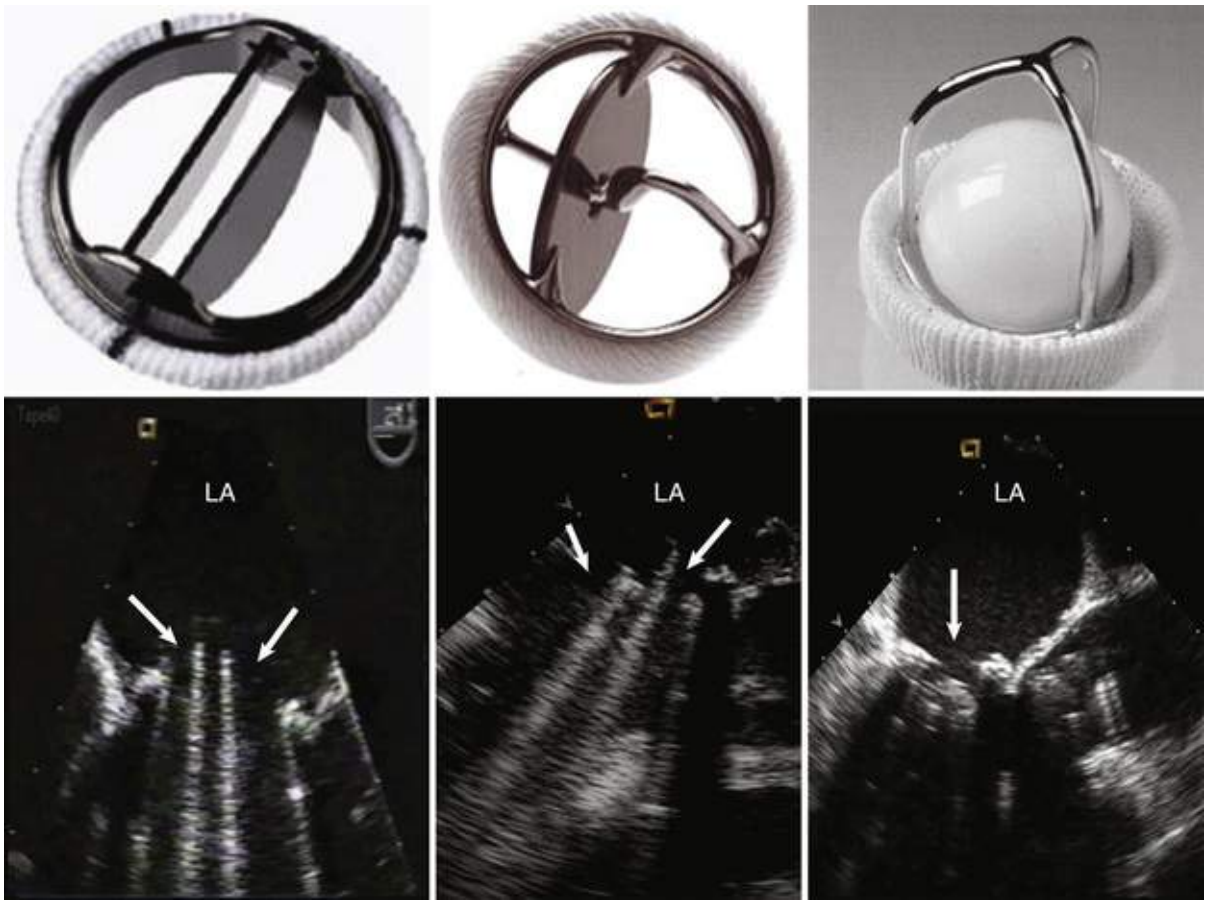


FIGURE 14.55 Mechanical prostheses and their transesophageal echocardiographic (TEE) appearance when implanted in the mitral position. **Left panels**, St. Jude bileaflet valve. *Arrows* indicate discs in the open position. **Middle panels,** Medtronic-Hall tilting single disc valve. The *right arrow* indicates the disc in the open position, and the *left arrow* indicates reverberation from the central pivot. **Right panels,** Starr Edwards ball-and-cage valve. The *arrow* points to the valve in the open position. *LA,* Left atrium.

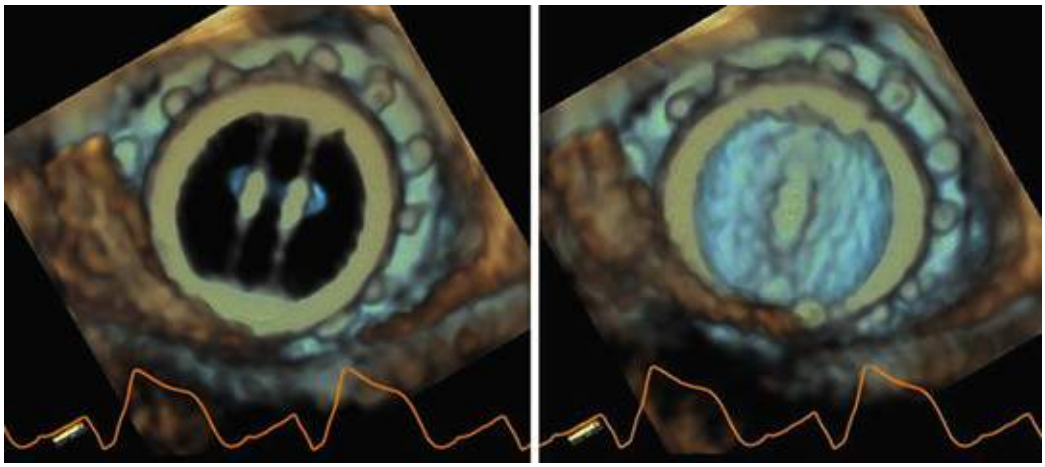


FIGURE 14.56 Three-dimensional TEE views of a bileaflet mechanical prosthesis as viewed from the left atrial aspect in diastole (**left**, with discs open) and systole (**right**, with discs closed). (See corresponding Video 14.37.)

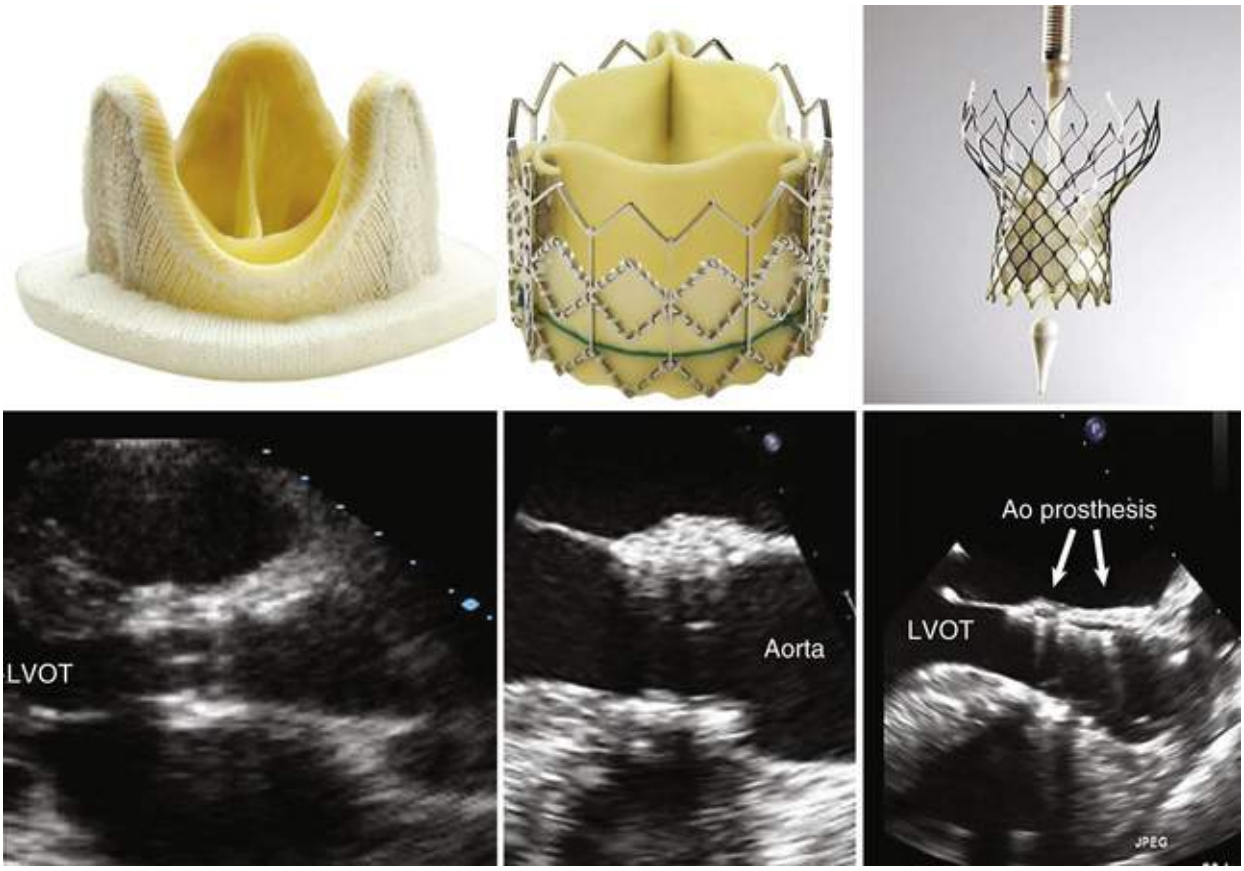


FIGURE 14.57 Bioprostheses and their echocardiographic long-axis appearance when implanted in the aortic (*Ao*) position. **Left panels,** Heterograft stented bioprosthesis. **Middle panels,** Sapien balloon expandable transcatheter aortic valve. **Right panels,** CoreValve self-expanding transcatheter aortic valve. *LVOT,* Left ventricular outflow tract.

ETABLE 14.5

Normal Values for Implanted Valves

AORTIC VALVES	SIZE (mm)	PEAK GRADIENT (mm Hg)	MEAN GRADIENT (mm Hg)	EFFECTIVE ORIFICE AREA (cm^2)
Carpentier-Edwards Pericardial Stented bovine pericardial	19	32.1 ±3.4	24.2 ±8.6	1.2 ±0.3
	21	25.7 ±9.9	20.3 ±9.1	1.5 ±0.4
	23	21.7 ±8.6	13.0 ±5.3	1.8 ±0.3
	25	16.5 ±5.4	9.0 ±2.3	
Carpentier-Edwards Standard Stented porcine	19	43.5 ±12.7	25.6 ±8.0	0.9 ±0.2
	21	27.7 ±7.6	17.3 ±6.2	1.5 ±0.3
	23	28.9 ±7.5	16.1 ±6.2	1.7 ±0.5
	25	24.0 ±7.1	12.9 ±4.6	1.9 ±0.5
	27	22.1 ±8.2	12.1 ±5.5	2.3 ±0.6
	29		9.9 ±2.9	2.8 ±0.5
Hancock Stented porcine	21	18.0 ±6.0	12.0 ±2.0	
	23	16.0 ±2.0	11.0 ±2.0	
	25	15.0 ±3.0	10.0 ±3.0	
Hancock II Stented porcine	21		14.8 ±4.1	1.3 ±0.4
	23	34.0 ±13.0	16.6 ±8.5	1.3 ±0.4
	25	22.0 ±5.3	10.8 ±2.8	1.6 ±0.4
	29	16.2 ±1.5	8.2 ±1.7	1.6 ±0.2
Medtronic Mosaic Stented porcine	21		14.2 ±5.0	1.4 ±0.4
	23	23.8 ±11.0	13.7 ±4.8	1.5 ±0.4
	25	22.5 ±10.0	11.7 ±5.1	1.8 ±0.5
	27		10.4 ±4.3	1.9 ±0.1
	29		11.1 ±4.3	2.1 ±0.2
Medtronic-Hall Single tilting disc	20	34.4 ±13.1	17.1 ±5.3	1.2 ±0.5
	21	26.9 ±10.5	14.1 ±5.9	1.1 ±0.2
	23	26.9 ±8.9	13.5 ±4.8	1.4 ±0.4
	25	17.1 ±7.0	9.5 ±4.3	1.5 ±0.5
	27	18.9 ±9.7	8.7 ±5.6	1.9 ±0.2
St. Jude Medical Standard Bileaflet	19	42.0 ±10.0	24.5 ±5.8	1.5 ±0.1
	21	25.7 ±9.5	15.2 ±5.0	1.4 ±0.4
	23	21.8 ±7.5	13.4 ±5.6	1.6 ±0.4
	25	18.9 ±7.3	11.0 ±5.3	1.9 ±0.5
	27	13.7 ±4.2	8.4 ±3.4	2.5 ±0.4
	29	13.5 ±5.8	7.0 ±1.7	2.8 ±0.5

MITRAL VALVES	SIZE (mm)	PEAK GRADIENT (mm Hg)	MEAN GRADIENT (mm Hg)	PEAK VELOCITY (m/sec)	PRESSURE HALF-TIME (msec)	EFFECTIVE ORIFICE AREA (cm^2)
Carpentier-Edwards Stented bioprosthesis	27		6 ±2	1.7 ±0.3	98 ±28	
	29		4.7 ±2	1.76 ±0.27	92 ±14	
	31		4.4 ±2	1.54 ±0.15	92 ±19	
	33		6 ±3		93 ±12	
Carpentier-Edwards Pericardial Stented bioprosthesis	27		3.6	1.6	100	
	29		5.25 ±2.36	1.67 ±0.3	110 ±15	
	31		4.05 ±0.83	1.53 ±0.1	90 ±11	
	33		1	0.8	80	
Hancock I or not specified Stented bioprosthesis	27	10 ±4	5 ±2		115 ±20	1.3 ±0.8
	29	7 ±3	2.46 ±0.79		95 ±17	1.5 ±0.2
	31	4 ±0.86	4.86 ±1.69		90 ±12	1.6 ±0.2
	33	3 ±2	3.87 ±2			1.9 ±0.2
Hancock II Stented bioprosthesis	27					2.21 ±0.14
	29					2.77 ±0.11
	31					2.84 ±0.1
	33					3.15 ±0.22
Medtronic-Hall Tilting disc	27			1.4	78	
	29			1.57 ±0.1	69 ±15	
	31			1.45 ±0.12	77 ±17	
St. Jude Medical Bileaflet	23		4	1.5	160	1
	25		2.5 ±1	1.34 ±1.13	75 ±4	1.35 ±0.17
	27	11 ±4	5 ±1.82	1.61 ±0.29	75 ±10	1.67 ±0.17
	29	10 ±3	4.15 ±1.8	1.57 ±0.29	85 ±10	1.75 ±0.24
	31	12 ±6	4.46 ±2.22	1.59 ±0.33	74 ±13	2.03 ±0.32

See also www.valveguide.ch for more recent data and models.

From Zoghbi WA et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound. A report from the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves. J Am Soc Echocardiogr 2009;22:975.

The echocardiographic approach to prosthetic valves is similar to but often more challenging than that

of native valves. Peak and mean gradients are calculated by using the conventional application of the Bernoulli equation, and effective orifice area may be calculated with the continuity equation. Additionally, the Doppler velocity or "dimensionless" index, defined as the ratio of the VTI (or peak velocity) proximal to the valve to that distal to the valve, provides an alternative metric of aortic prosthetic function that is useful when LVOT diameter cannot be measured. As for native valves, it is critical that LVOT sampling be proximal to the site of flow acceleration; in the case of transcatheter or sutureless valves, the sampling volume should be proximal to the inlet of the metal frame because in these valves there is acceleration of flow at the inlet, as well as at the level of the cusps. For mitral prostheses, the comparable measure is the ratio of mitral to aortic VTI. In the patient with AF, matching of cycle lengths for beats used for LVOT and valvular VTIs is preferred to averaging over multiple beats. Beats corresponding to physiologic heart rates should be used if available. Although the pressure half-time may be useful in a relative sense in patients with mitral prostheses, it does not provide a valid measure of effective orifice area.

In many centers, intraoperative TEE is performed routinely during valve procedures, and these studies can both alert the surgeon to remediable complications before chest closure and serve as reference studies for follow-up evaluation. It is also recommended that TTE be performed soon after implantation to define the baseline appearance and structure with this modality and under more physiologic conditions than those present in the immediate postpump period (**see Chapter 67**). For all studies, chamber dimensions and function and estimated pulmonary artery systolic pressure, as well as heart rate, blood pressure, and BSA, should be included in the report. Before postoperative echocardiographic evaluation, it is important to obtain information on valve type and size and details of the valve implantation when possible.

Abnormalities in Valve Appearance.

Abnormalities in valve appearance include evidence of an unusual implantation position or valvular dehiscence, which when extensive is characterized by pathologic valve rocking (Video 14.38). Although extensive bioprosthetic cusp thickening is typically associated with functional disturbance (see later), mild abnormalities may not affect valve function. Similarly, valve vegetation and thrombus may be functionally silent. Therefore, echocardiographic evaluation must focus on structure even when function is normal, with ensuing TEE planned if TTE images are nondiagnostic.

Approach to Assessing Elevated Prosthetic Gradients.

The diagnosis of prosthetic stenosis is suggested when gradients are elevated and the effective orifice area is reduced relative to published norms. For aortic prostheses, a Doppler velocity index less than 0.25 or a ratio of acceleration to ejection times greater than 0.4 supports the diagnosis. For mitral prostheses, a pressure half-time longer than 200 milliseconds, peak E wave greater than 1.9 m/sec, or VTI_{MV}/VTI_{LVOT} of 2.2 or greater is considered abnormally high. As with native valves, gradients must be interpreted in the context of heart rate. Causes of prosthetic stenosis include restricted leaflet/disc motion because of thrombus (**Fig. 14.58** and Video 14.39), pannus ingrowth (**Fig. 14.59**), vegetation, or in the case of bioprostheses, cusp degeneration often with calcification (**Fig. 14.60**). Differentiation between pannus and thrombus may be challenging, although thrombi tend to have a softer echotexture than pannus and may be larger with extension beyond the sewing ring. Clinical factors suggesting thrombus include the acuity of symptom onset and a history of inadequate anticoagulation. Because the restricted motion may be intermittent, it is important to capture multiple beats if prosthetic dysfunction is clinically

suspected. TEE is frequently required to image valves optimally, and fluoroscopy may be helpful when abnormal occluder motion is suspected in mechanical valves.

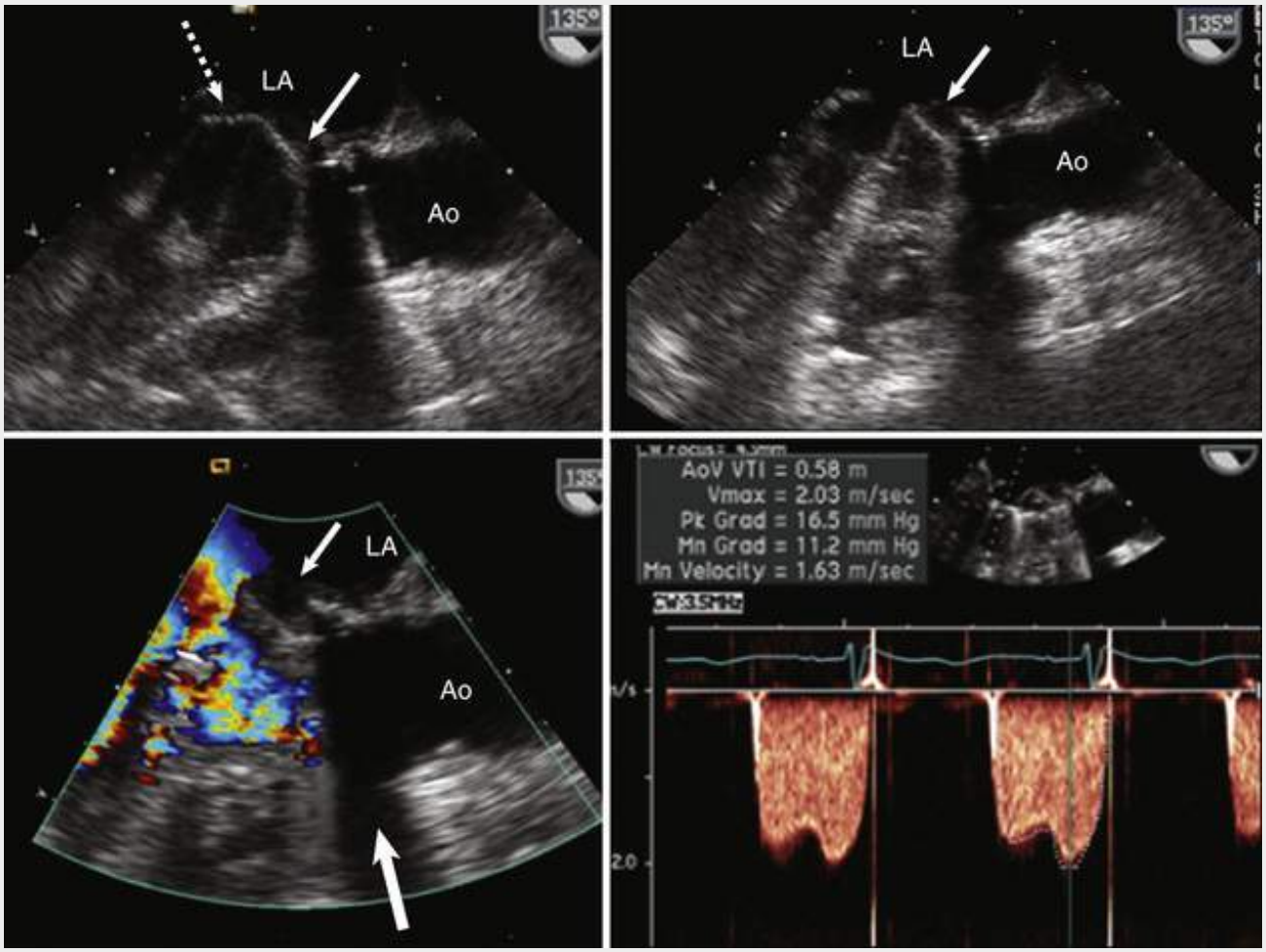


FIGURE 14.58 TEE showing a bileaflet mechanical mitral prosthesis in which one disc is immobilized because of thrombus. **Upper left,** Systolic frame showing that neither disc (*arrows*) closes completely. **Upper right,** While the left disc opens fully, the right disc is immobile. **Lower left,** Color flow Doppler demonstrating high-velocity flow through a single orifice. The *large arrow* indicates acoustic shadowing because of the mitral sewing ring. **Lower right,** Doppler demonstrating an elevated transmitral gradient (11 mm Hg at a heart rate of 65 beats/min). *Ao,* Aorta; *LA,* left atrium.

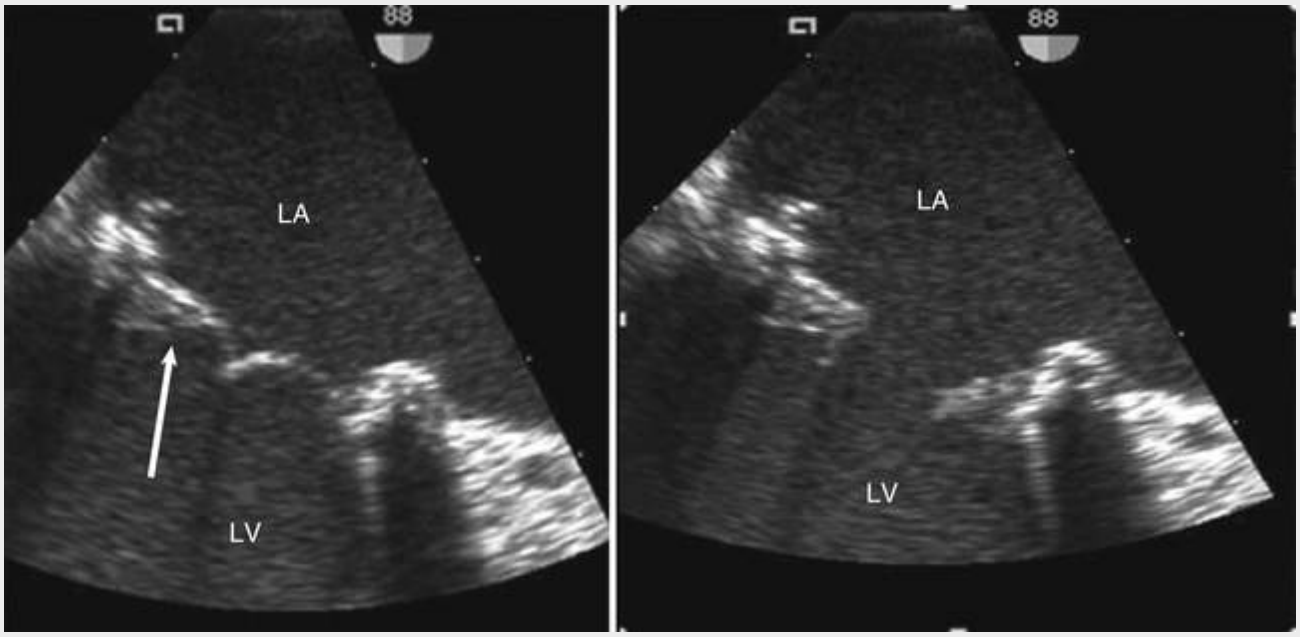


FIGURE 14.59 TEE appearance of pannus ingrowth (*arrow*) in a mitral bioprosthesis. **Left,** Systole. **Right,** Diastole. The pannus has immobilized the base of the left-sided cusp and created a hinge point midway along the cusp and an narrow orifice. *LA,* Left atrium; *LV,* left ventricle.

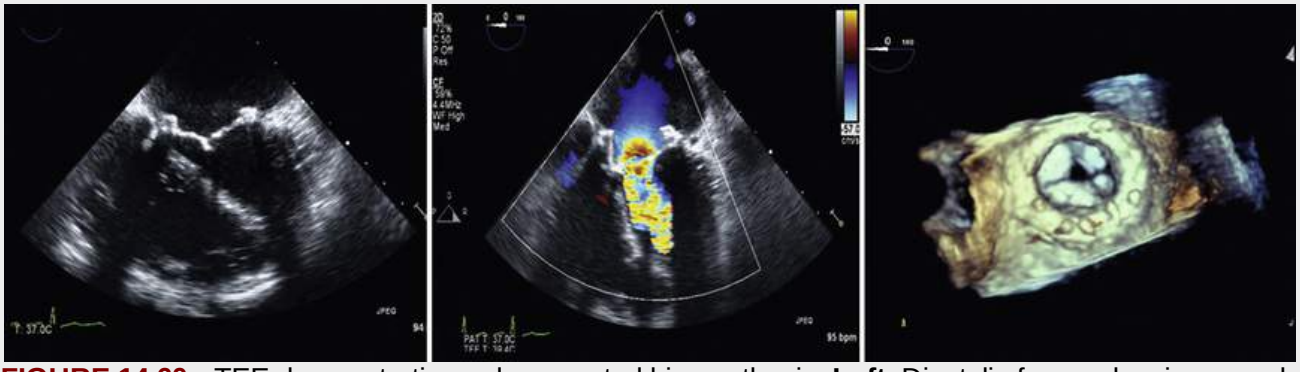
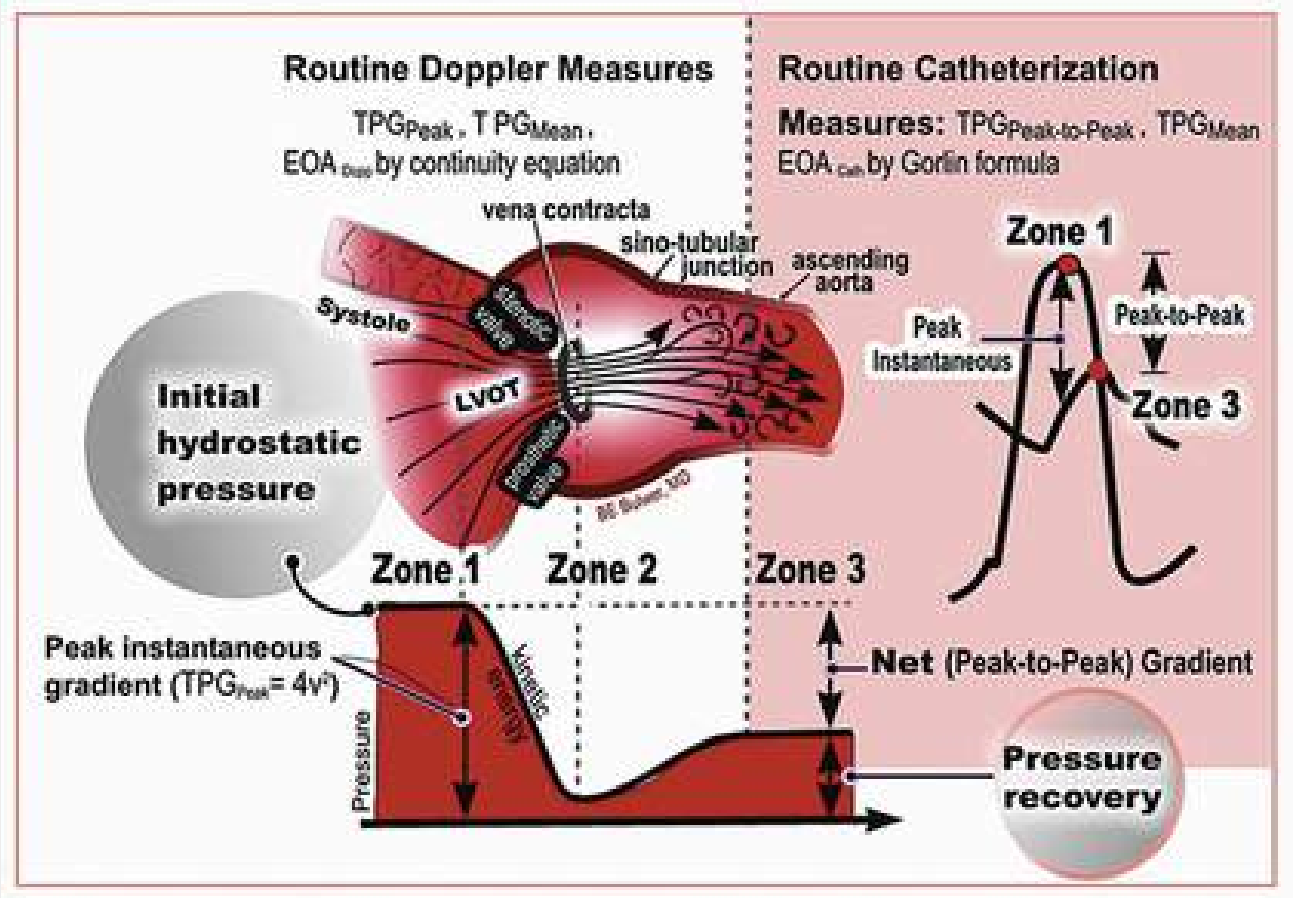


FIGURE 14.60 TEE demonstrating a degenerated bioprosthesis. **Left,** Diastolic frame showing grossly restricted cusp motion. **Middle,** Color Doppler demonstrating turbulent transmitral flow and an easily identifiable proximal isovelocity hemispheric surface area shell. **Right,** 3D TEE view of the prosthesis from the left atrial perspective. The mitral orifice is greatly restricted.

Notably, elevated gradients do not always reflect prosthetic stenosis. *Patient-prosthesis mismatch* (PPM) refers to the situation in which the implanted valve, although functioning normally, has elevated gradients (**see Chapter 71**). This occurs when patient anatomy results in the implantation of a smaller-than-ideal valve. The diagnosis is made by confirming that the calculated effective orifice area is consistent with normal function, but the indexed orifice area is 0.85 cm^2/m^2 or less for aortic prostheses and less than 1.2 cm^2/m^2 for mitral prostheses. For aortic prostheses an indexed effective orifice area less than 0.65 cm^2/m^2 is considered severe PPM, a phenomenon encountered in 2% to 11% of patients. PPM is best studied for the aortic valve and is reportedly associated with poorer outcomes,[69] although in obese patients it is unclear whether the indexed effective orifice area should be calculated on the basis of lean rather than actual body mass.

Elevated gradients may also be a consequence of significant regurgitation, which when paravalvular may be underappreciated on initial evaluation. A final important cause of elevated gradients in aortic prostheses, *pressure recovery*, refers to the tendency for Doppler-derived gradients to overestimate those registered invasively. This occurs because Doppler measures the largest gradient, typically encountered

at the vena contracta, whereas invasive measurements reflect pressure distal to the valve where there has been recovery either because blood has moved from the narrow valve orifice into the wider aorta (i.e., a flask-shaped aortic root, which is a significant factor only in the setting of aortas measuring <3 cm) or, in the case of bileaflet mechanical valves, because the lower pressure encountered in the central orifice is augmented by higher pressure caused by eddies at the lateral orifices (**eFig. 14.25**). Pressure recovery is most important clinically in the setting of small (≤19 mm) bileaflet valves in the aortic position. As demonstrated, the measurements most representative of invasive gradients is obtained by carefully interrogating the lateral orifices, but this generally requires TEE. Alternatively, it has been suggested that gradients recorded through the central orifice may be corrected by applying the pressure loss coefficient of 0.64. (Of note, the reported normal values in **eTable 14.5** are uncorrected.)



EFIGURE 14.25 The pressure recovery phenomenon.

Prosthetic Regurgitation.

Trivial degrees of valvular regurgitation are normal findings, although the location of normal jets varies depending on the valve type. Pathologic regurgitation may be valvular and may arise within the sewing ring or may be paravalvular, exterior to the sewing ring. *Valvular* regurgitation in mechanical valves typically reflects occluder malfunction as a result of pannus, thrombus, vegetation, or rarely, retained mitral valve apparatus, whereas in bioprostheses, this is typically a result of cusp degeneration or disruption from endocarditis. *Paravalvular* regurgitation may be a residual finding resulting from suboptimal implantation or may develop de novo from endocarditis or spontaneous valve dehiscence. Some degree of paravalvular regurgitation is a common finding after transcatheter aortic valve implantation (**see Chapter 72**), but moderate or greater degrees appear to be associated with a worse prognosis (**Fig. 14.61**).

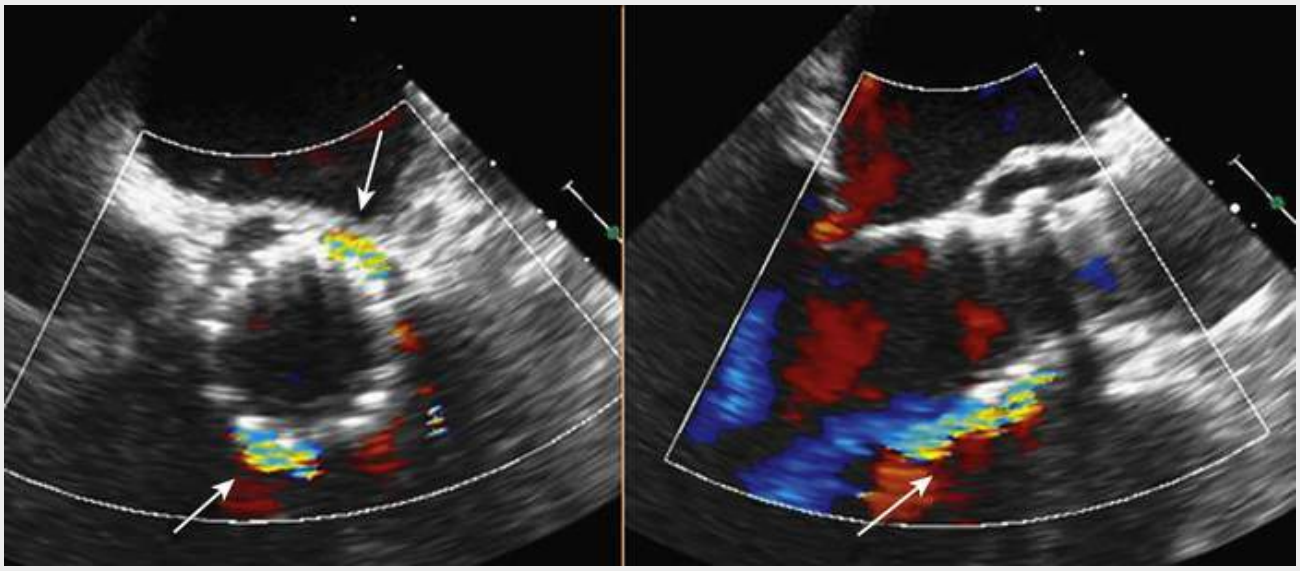


FIGURE 14.61 Orthogonal TEE views of a balloon-expandable aortic prosthesis (TAVI, CoreValve) with at least two sites of significant paravalvular regurgitation (*arrows*), seen as turbulent diastolic flow on **left panel** (45 degrees) and **right panel** (120 degrees).

Detection of prosthetic regurgitation may require nonstandard views. Quantitation of prosthetic regurgitation may be challenging because jets frequently are highly eccentric and may be multiple, thus limiting the value of approaches based on jet dimensions. For mechanical valves the acoustic shadowing cast by mitral prostheses can greatly limit detection of MR, because the shadowing predictably falls directly over the left atrium in TTE views. The use of TEE is extremely advantageous in this respect since it insonifies the valve from an aspect posterior and directly adjacent to the left atrium. Assessment of paravalvular regurgitation in transcatheter or sutureless valves is particularly difficult because multiple pinhole jets may be present.[70] As in native AR, the presence of a shortened pressure half-time (<200 msec) and holodiastolic flow reversal in the descending thoracic or abdominal aorta are clues to significant regurgitation. For mitral prostheses, VTI_{MV}/VTI_{LVOT} of 2.2 or greater (as seen in stenotic valves as well), but in particular an elevated E wave (i.e., peak gradient elevated out of proportion to the mean gradient) and pulmonary venous flow reversal in systole, should raise suspicion for significant regurgitation. The quantitative Doppler approach using the pulmonic valve as the reference may also be helpful for aortic prostheses. As in native valvular regurgitation, regurgitant volume values less than 30 mL, 30 to 59 mL, and 60 mL or more and regurgitant fraction values less than 30%, 30% to 50%, and more than 50% are consistent with mild, moderate, and severe prosthetic AR, respectively. For mitral valves the presence of well-defined flow convergence suggests significant regurgitation, and the PISA approach may be used to quantitate central valvular or well-defined single paravalvular jets. 3D TEE approaches that allow direct planimetry of regurgitant orifices and better localization of paravalvular leaks facilitate these tasks and may be more accurate.

Prosthetic tricuspid and pulmonic valves are much less common than their left-sided counterparts. In general, methods developed for assessment of the mitral and aortic valves are extrapolated to the tricuspid and pulmonic valves, although the evidence base for their use is less robust.

Pericardial Disease

Echocardiography is the imaging modality of choice for the identification of pericardial effusion and is an important tool in the diagnosis of tamponade and pericardial constriction (**see Chapter 83**).

Pericardial Effusion

Identification of pericardial effusion was one of the earliest applications of echocardiography. The diagnosis is made when an echo-free space separates the visceral and parietal pericardial echoes throughout the cardiac cycle, including diastole (**Fig. 14.62**). Systolic separation alone may be a normal finding. In most cases the diagnosis of pericardial effusion is straightforward because the parietal pericardium is a strong echo reflector and the visceral pericardium is adherent to the epicardial surface of the heart. “Echo free” is defined as having an echotexture that is equivalent to that of the intracardiac blood pool. Although it is typically black, in some cases suboptimal image quality results in both blood pool and pericardial effusion with a grayish or intermediate echotexture. In such cases it may be difficult to differentiate a small pericardial effusion from epicardial fat, although the latter typically has a more reticulated inhomogeneous appearance than a fluid effusion.

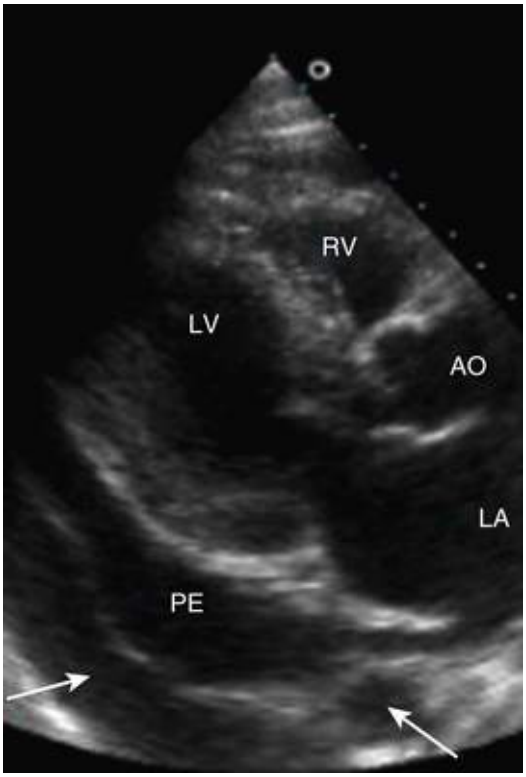


FIGURE 14.62 Pericardial effusion. A parasternal long-axis view shows both pericardial effusion (*PE*) and pleural effusion (*short arrow*). Note that the descending thoracic aorta (*long arrow*) is displaced from the heart by the pericardial effusion. With isolated pleural effusion, the descending aorta (*Ao*) remains immediately posterior to the heart. In this case the pericardial effusion extends posterior to the left atrium (*LA*), although this is not always the case. *LV,* Left ventricle; *RV,* right ventricle.

Another source of confusion may be left pleural effusion. Differentiating features include displacement of the aorta from the heart by pericardial (but not pleural) fluid and extension of pleural (but not pericardial) fluid behind the left atrium (**Fig. 14.62**). Of the two features, the relative position of the aorta

is the most definitive because the position of the pericardial reflection is somewhat variable. Pericardial effusions may extend cephalad beyond the atrioventricular groove. It is therefore essential that sonographers routinely provide views that demonstrate the descending thoracic aorta and its position relative to the heart. Multiple windows—particularly the subcostal view, because fluid is gravity dependent and thus tends to collect inferiorly—are essential to rule out localized effusions.

Sizing of pericardial effusions is typically somewhat subjective, with the terms *trace*, *small*, *medium*, and *large* being used. For reporting the size of effusions when longitudinal comparison will be important, it is helpful to report the maximal diameter of the effusion while noting the view(s) and time of the cardiac cycle (systole versus diastole) when the measurement is taken. Earlier estimates of the volume of the effusion, calculated using linear measures of pericardial and epicardial diameter, relied on a symmetric distribution of fluid and assumptions on the shape of the pericardial sac and heart. In a small case series, tracing pericardial and epicardial borders at end-diastole, and using the biplane Simpson method of discs instead to calculate the difference between the two volumes, has been shown to correlate much better with volumes drained by pericardiocentesis, underestimating the pericardial effusion by a mean of 9%.[71]

Pericardial Hematoma

Pericardial hematoma results from bleeding into the pericardial space and may be caused by bleeding along suture lines after open heart surgery, trauma, myocardial rupture, or aortic dissection or may occur as a complication of catheter-based or surgical intervention. Hematomas typically have an echotexture that is more coalescent and echodense than that of free fluid. They may be unevenly distributed and localized to the bleeding site, such as the anterior mediastinum post-CABG. When images are obtained in the acute setting, there may be evidence of both clot and free fluid (**Fig. 14.63**).

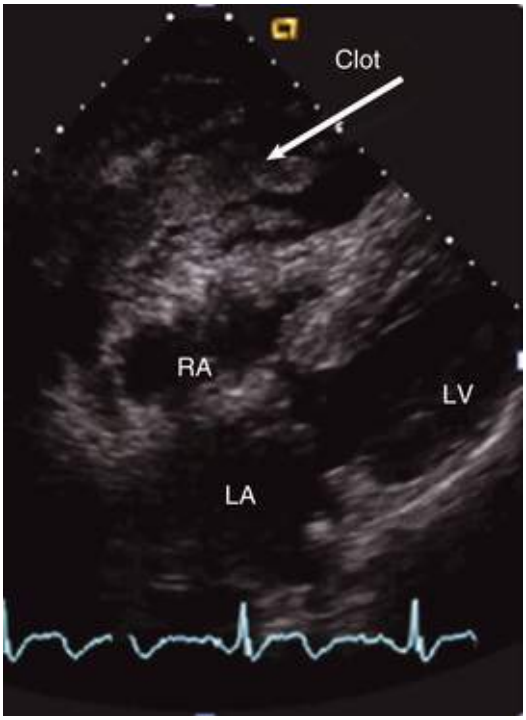


FIGURE 14.63 Pericardial hematoma. A subcostal view shows clotted (*arrow*) and free blood (black echotexture) within the pericardial space. In this patient the cause was acute aortic dissection. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium.

Echocardiographic Markers of Tamponade.

Echocardiographic markers of cardiac tamponade fall into two categories: (1) cardiac chamber invagination reflecting *elevated intrapericardial pressure* and the resultant pressure gradients across the chamber walls and (2) echocardiographic markers of pulsus paradoxus, which reflect exaggerated respiratory variation in left-sided heart filling and ejection relative to that of the right side of the heart (*ventricular interdependence*).

Right atrial inversion is a dynamic phenomenon with onset when RA volume and pressure are lowest: in late ventricular diastole immediately after atrial contraction (**Fig. 14.64, left panel**, and Video 14.40). Inversion continues through a variable portion of ventricular systole and resolves as the right atrium fills and RA pressure rises. This sign can be detected in any view where the RA wall and adjacent effusion are well seen, typically the parasternal short-axis view at the level of the great vessels and the apical four-chamber and subcostal four-chamber views. This sign is highly sensitive (100%) but may be present when hemodynamic disturbances are invasively detectable but fall below the threshold for the clinical diagnosis of tamponade, resulting in a specificity for clinical tamponade of 82%. Empirically, an RA inversion time index (readily calculated as number of frames during which the right atrium is inverted divided by number of frames per cardiac cycle) of at least 0.33 is associated with clinically evident tamponade (100% specificity, 95% sensitivity). *Left atrial inversion* as a marker of tamponade is rare and typically occurs in the setting of loculated effusions or those in which the pericardial reflection is relatively high and the left atrium is exposed to the effects of intrapericardial pressure.

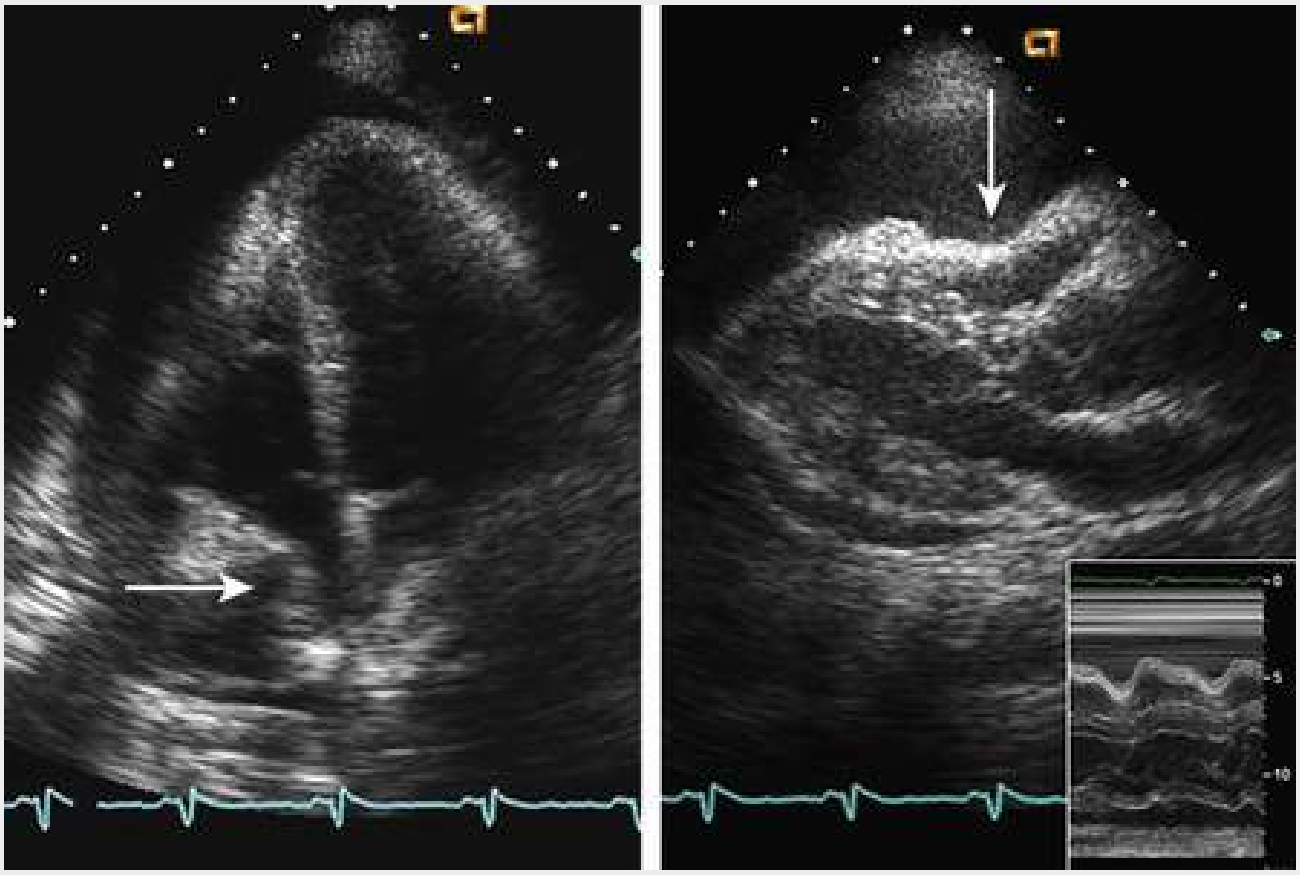


FIGURE 14.64 Signs of cardiac tamponade. **Left,** Apical four-chamber view showing RA inversion (*arrow*), a marker of tamponade. In this case, inversion, which is initiated in late ventricular diastole, has persisted well into ventricular systole. **Right**, Parasternal long-axis view showing RV collapse in diastole (*arrow*). *Inset,* An M-mode cursor placed down the RVOT shows diastolic inversion of the RV wall (note timing with respect to the ECG, closed aortic valve, and open mitral valve). (See Videos 14.40 and 14.41 .)

Right ventricular inversion has its onset when RV volume and pressure are lowest: during isovolumic relaxation (**Fig. 14.64, right panel**). It continues through a variable portion of ventricular diastole, with the RV contour normalizing as the ventricle fills and RV pressure rises. This sign is most easily detected on the parasternal long-axis view, which displays the RVOT (Video 14.41). Its reported sensitivity is 82% to 94%, with a specificity of 88% to 100%.

It is important to note that RA inversion and RV inversion are defined by actual wall invagination rather than by the normal flattening that may occur with respective chamber systole. RA or RV inversion may also be absent (i.e., false negative) in the setting of underlying right-sided heart dysfunction associated with elevated intracavitary pressure. With pericardial hematoma in which no free blood is present, dynamic inversion of the chambers will not be observed, but the presence of fixed compression and underfilling of the cardiac chambers may be clues to the presence of tamponade physiology.

There is an echocardiographic correlate to the clinical phenomenon of pulsus paradoxus. In the normal state, a slight increase (up to 17%) in flow velocities through the right heart occurs on inspiration, and a reciprocal but smaller decrease (up to 10%) in flow velocities through the left heart occurs during expiration. These tendencies are exaggerated when a tense, fluid-filled pericardium constrains the overall heart size and increases interdependence between the right and left ventricles. The most widely used signs are an exaggerated (>25%, and often >60% in frank tamponade) increase in the tricuspid inflow Doppler E wave peak velocities with a reciprocal decrease (of >30%) in the mitral E wave velocities (**Fig. 14.65**), as well as corresponding changes in the pulmonic and aortic (or LVOT) systolic Doppler spectra. Additional signs of tamponade include the characteristic appearance of the heart oscillating or “swimming” in the pericardial fluid (see Video 14.41), which has its counterpart in

electrical alternans on ECG, and a dilated IVC consistent with elevated RA pressures.

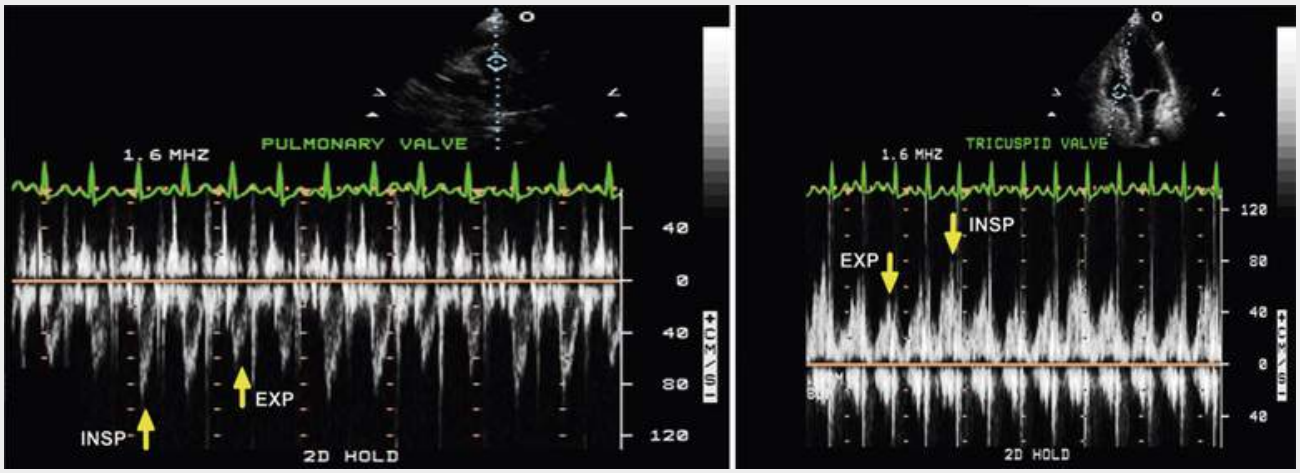


FIGURE 14.65 Doppler spectra showing the characteristic exaggerated respiratory variation in right-sided pulmonary valve outflow **(left panel)** and tricuspid valve inflow **(right panel)** peak flow velocities. On inspiration, right-sided flow increases. In the left heart, PW tracings of LVOT outflow and mitral valve inflow (not shown) would demonstrate reciprocal reductions in left-sided flow on inspiration. *EXP,* Expiration; *INSP,* inspiration.

Pericardiocentesis.

Echocardiography may also be useful in guiding needle pericardiocentesis, particularly in the setting of loculated effusions. Imaging may help identify the best puncture site and angle of needle introduction, then confirm that the needle has entered the pericardial space. The latter is accomplished by the injection of a small amount of agitated saline, which will opacify the pericardial effusion with proper needle placement, but this will result in intracardiac contrast bubbles if the needle inadvertently penetrates the heart. Echocardiography is used to document the reduction in effusion size that should occur with successful drainage.

Constrictive Pericarditis

Pericardial constriction occurs when there is thickening, with or without calcification, of the pericardium that results in impaired cardiac diastolic filling, particularly during inspiration (**Fig. 14.66**). The clinical features mimic those of biventricular heart failure, although the presence of a pericardial knock and Kussmaul sign (inspiratory increase in jugular venous pressure) should raise suspicion for constriction. Frequently, when the patient is referred for echocardiographic evaluation, the clinical differential diagnosis is “restrictive cardiomyopathy” versus pericardial constriction, since ejection fraction (EF) is generally preserved in both. Pericardial thickening is a hallmark of constriction but is a relatively insensitive finding; furthermore, echocardiography can be relatively insensitive for detecting pericardial thickening compared with CT and CMR. When the pericardial space is expanded because of adhesions and fibrous tissue, the visceral and parietal pericardia are separated by tissue of variable echogenicity, unlike the echolucent appearance of pericardial effusion. Also, with effusion the parietal pericardial echo will be relatively stationary, whereas with pericardial thickening, visceral and parietal pericardial echoes will move in tandem. Calcification will result in acoustic shadowing.

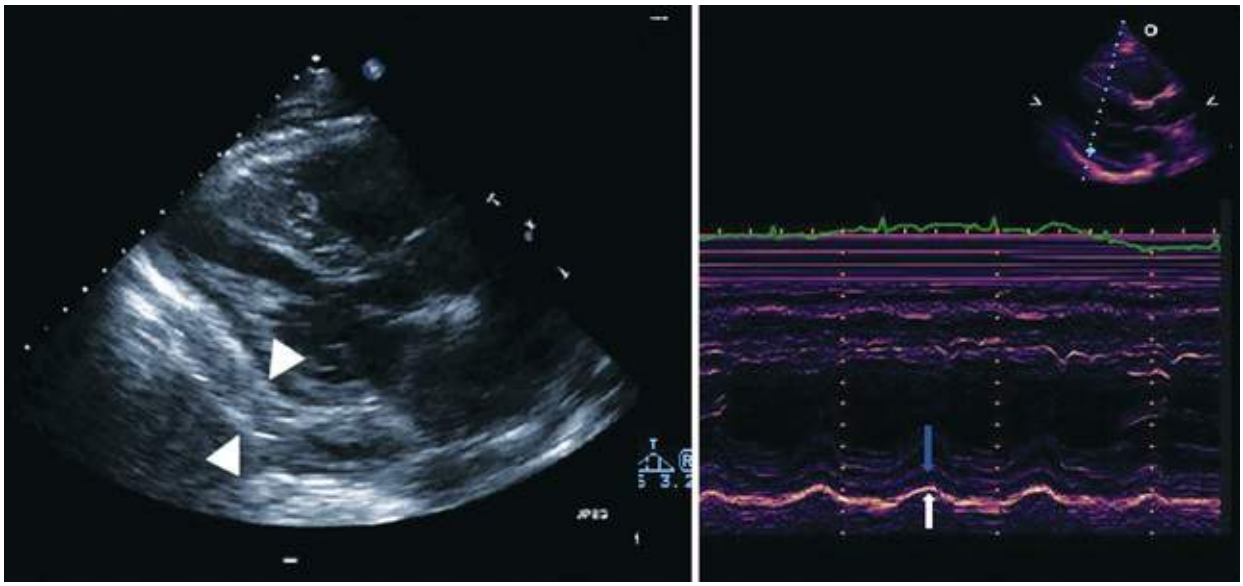


FIGURE 14.66 **Left,** Parasternal long-axis view demonstrating thickened pericardium (between the *arrowheads*). **Right,** M-mode echocardiogram. The bright posterior echo (*white arrow*) representing the parietal pericardium moves in parallel with the visceral pericardial/epicardial echoes (*blue arrow*), a finding indicative of adhesion between the two layers. If the pericardial space were expanded by free fluid (pericardial effusion), the parietal pericardial echo would be relatively stationary (compare with the M-mode *inset* of **Fig. 14.64**).

Restrictive and constrictive physiology share a mitral diastolic filling pattern characterized by a prominent E wave (E/A ratio >2) and shortened deceleration time caused by rapid early filling, biatrial enlargement, and a fixed dilated IVC that does not change size with a sniff. However, the two may be distinguished by tissue and color Doppler diastolic indices, as well as respirophasic effects on septal motion (interventricular interdependence and septal bounce) that are specific to constriction. Mitral annular DTI waves generally have normal or increased amplitude in constriction (peak e′ of ≥8 cm/sec is reported to be 89% sensitive and 100% specific for constriction), reflecting compensatory exaggerated longitudinal motion of the heart, in contrast to the reduced e′ seen with restriction. Notably, the peak e′ of the lateral site may be smaller than that of the medial annulus, which is the opposite of the normal pattern; this phenomenon is termed *annulus reversus* and is believed to result from calcification and tethering effects of the pericardium on the lateral heart wall. Color M-mode propagation velocity is typically normal or even increased in constriction, but reduced in restriction. In addition, pulmonary artery systolic pressure rarely exceeds 50 mm Hg in constriction.

In constriction the rigid pericardium abruptly limits filling to a fixed volume. When inspiration causes increased venous return to the right side of the heart, there is a sudden leftward septal shift and thus obligatory reduction in the amount of blood that the left ventricle can accommodate. The leftward septal shift may be seen on echocardiography during inspiration (**Fig. 14.67** and Video 14.42), and often a transient left-right septal “bounce” occurs in early and late diastole. There are also exaggerated respirophasic changes in the magnitude of the mitral and tricuspid E waves (in opposing directions, similar to the patterns in tamponade). Additional markers of constriction include premature opening of the pulmonic valve, which is most pronounced with inspiration (reflecting a rapid rise in end-diastolic RV pressure that exceeds pulmonary artery pressure), diastolic MR, and expiratory diastolic hepatic vein flow reversal (**Fig. 14.68**).

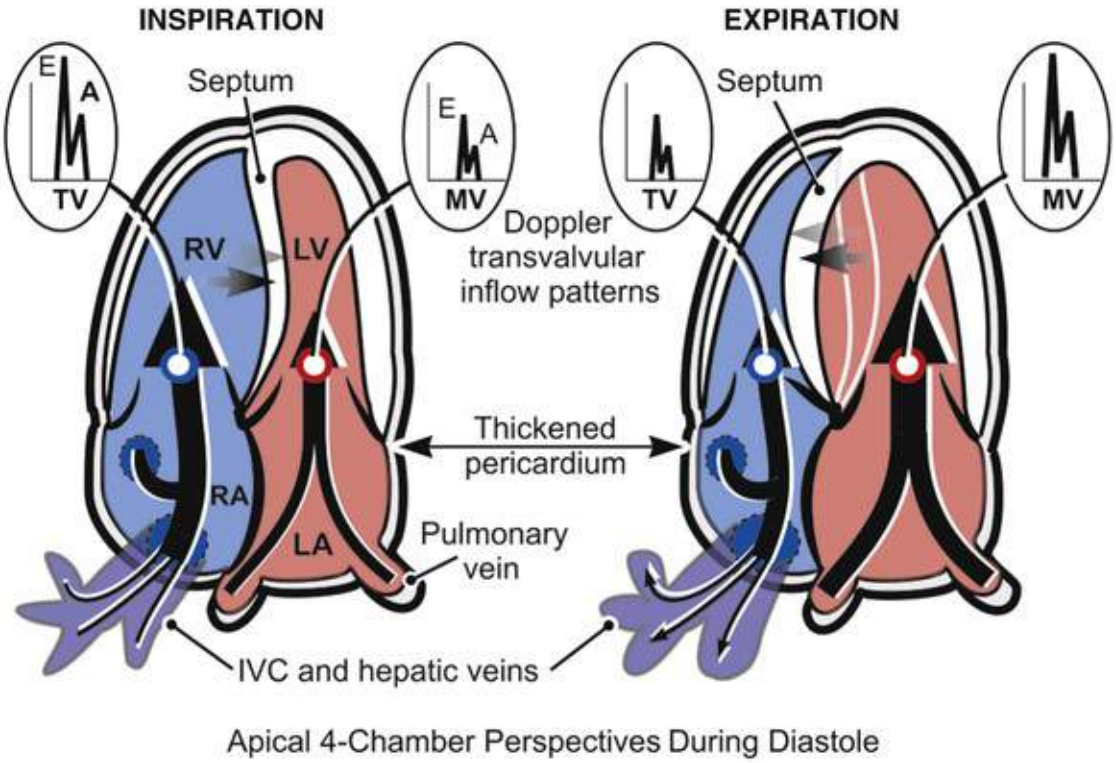


FIGURE 14.67 Schematic representing the echocardiographic manifestations of constriction that may be appreciated on the apical four-chamber view and PW Dopper. Mitral (*MV*) and tricuspid (*TV*) valve Doppler spectra are characterized by an increased E/A ratio and shortened deceleration time. With inspiration there is increased venous return to the right side of the heart, which can be accommodated within the rigid pericardium only by displacement of the interventricular septum to the left and reduced left-sided filling. On expiration, left-sided filling increases, the septum moves to the right, and there is flow reversal in the hepatic veins (**see Fig. 14.68**). *IVC,* Inferior vena cava; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (Modified from Bulwer BE, Rivero JM, editors. Echocardiography Pocket Guide: The Transthoracic Examination. Burlington, Mass: Jones & Bartlett Learning; 2011, 2013, p 141. Reprinted with permission.)

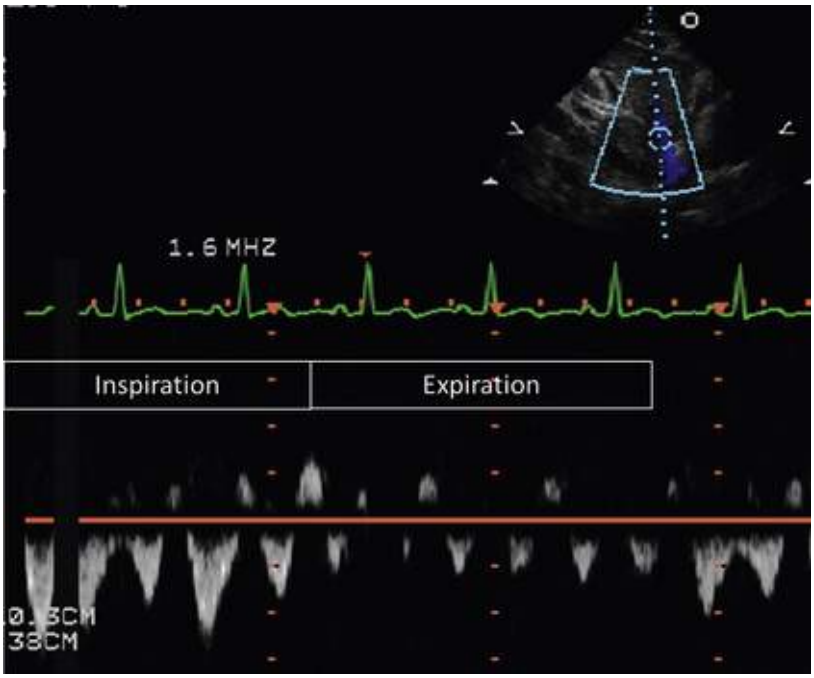


FIGURE 14.68 Hepatic venous flow recordings demonstrate expiratory diastolic flow reversal, seen in constriction.

In digital echocardiography laboratories where acquisitions are frequently limited to one to three beat

clips, it is essential that longer captures with respiratory gating be obtained to assess the impact of respiration. M-mode echocardiography in the parasternal window over multiple cycles is particularly useful for detection of leftward (posterior) motion of the septum on inspiration, the diastolic septal bounce, and pericardial thickening, as well as the flattened diastolic motion of the posterior wall.

Differentiation between conditions can be further complicated by coexisting pathologies in the patient. Fibrotic involvement extending from the pericardium into the myocardium may result in mixed constrictive-restrictive physiology. Echocardiographic reassessment after removal of the pericardial fluid causing tamponade may unmask underlying constriction (i.e., effusive-constrictive physiology while the effusion was present).

Malignant Involvement of the Pericardium

Malignant pericardial disease typically occurs on the basis of local spread or distal metastases, with lung and breast cancer being the most common primaries. Primary pericardial tumors are uncommon. The echocardiographic appearance may be that of pericardial effusion and/or solid tumor, which frequently invades locally into the myocardium (**Fig. 14.69**).

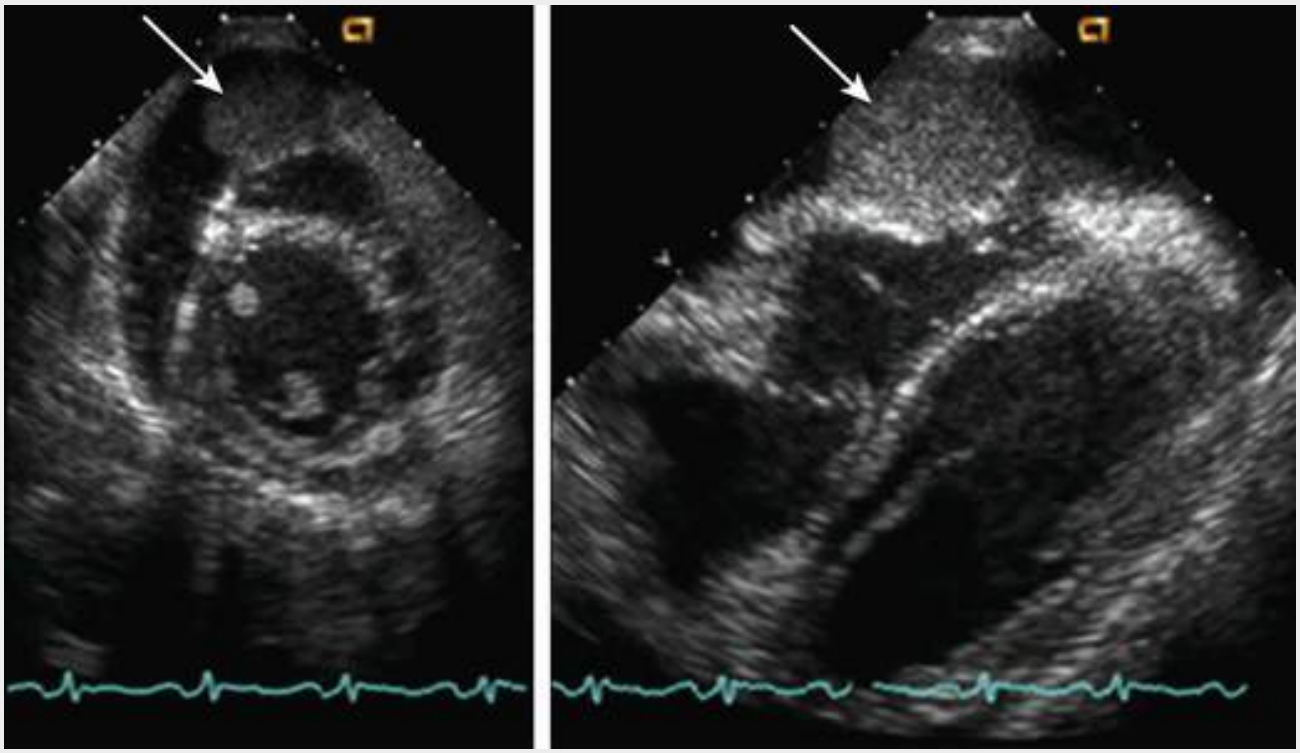


FIGURE 14.69 Subcostal echocardiograms showing a tumor metastasis *(arrows)* within the pericardial space and invading the right ventricular myocardium. The tumor is surrounded by pericardial effusion.

Other Pericardial Pathology

Congenital absence of the pericardium is a rare abnormality that usually involves the left pericardium and is associated with a leftward shift in the position of the heart, as well as exaggerated translation. The net result is an echocardiographic pattern that mimics RV volume overload. A *pericardial cyst* is a benign abnormality that is typically detected as an incidental finding of an echo-free accumulation adjacent to the heart.

Diseases of the Aorta

Transthoracic echocardiography is a first-line tool to assess the thoracic aorta for pathologic processes[17,72] (**see Chapter 63**). TTE can visualize the proximal aortic root and ascending aorta, aortic arch up to the isthmus (takeoff of the left subclavian artery), and limited portions of the descending thoracic and proximal abdominal aorta (**Fig. 14.70**). TEE can be used to more comprehensively examine the entire thoracic aorta (**Fig. 14.71**), with the exception of a small area of distal ascending aorta (because of shadowing from the air-filled trachea interposed between the esophagus and the heart). Therefore, for screening purposes or for serially monitoring a known aortic abnormality for stability, TTE may be sufficient. Higher degrees of suspicion for an acute aortic process or disease extending beyond the TTE windows require TEE evaluation (or alternatively, CT or magnetic resonance angiography [MRA]).

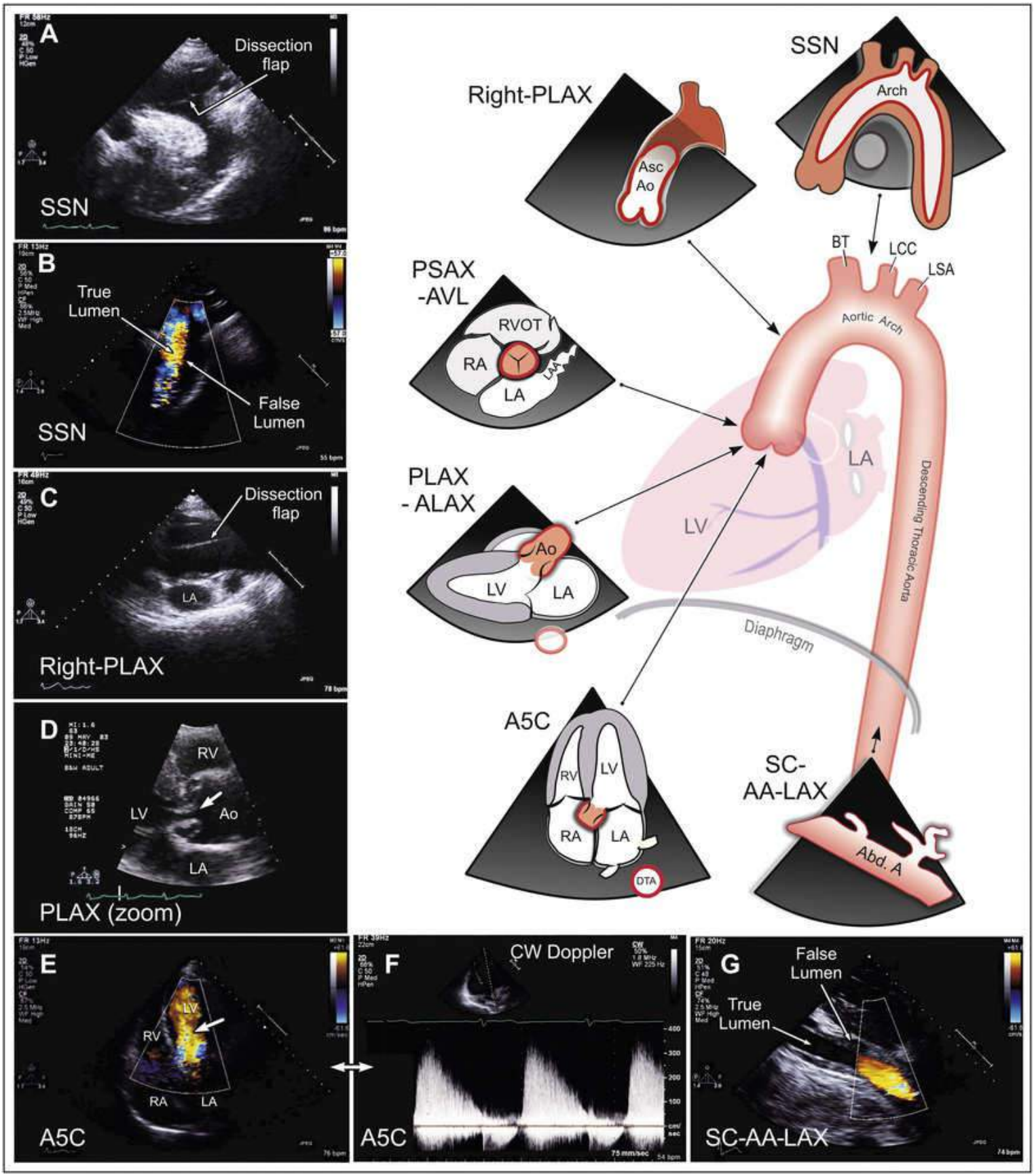


FIGURE 14.70 Transthoracic views of the aorta and examples of acute aortic pathologies from each window. The composite illustrates **(A, B)** suprasternal notch 2D and color Doppler views of a type A dissection flap that is seen extending into the brachiocephalic artery; **(C, D)** a type A dissection flap that originates at the level of the aortic sinuses, prolapses through the aortic valve, and also extends into the ascending aorta in the parasternal long-axis view (see Video 14.43); **(E, F)** color and spectral Doppler apical five-chamber views illustrating the resultant severe aortic insufficiency (see Video 14.44); and **(G)** an abdominal aortic type B dissection with a small central true lumen and chronic thrombus in the circumferential false lumen in the subcostal long-axis view. *ALAX,* Apical long axis; *PLAX,* parasternal long axis; *PSAX,* parasternal short axis; *SSN,* suprasternal notch; *SC,* subcostal; *Ao,* aorta; *AVL,* aortic valve level; *BT,* brachiocephalic trunk; *DTA,* descending thoracic aorta; *LCC,* left common carotid artery;

LSA, left subclavian artery; *TL,* true lumen; *FL,* false lumen.

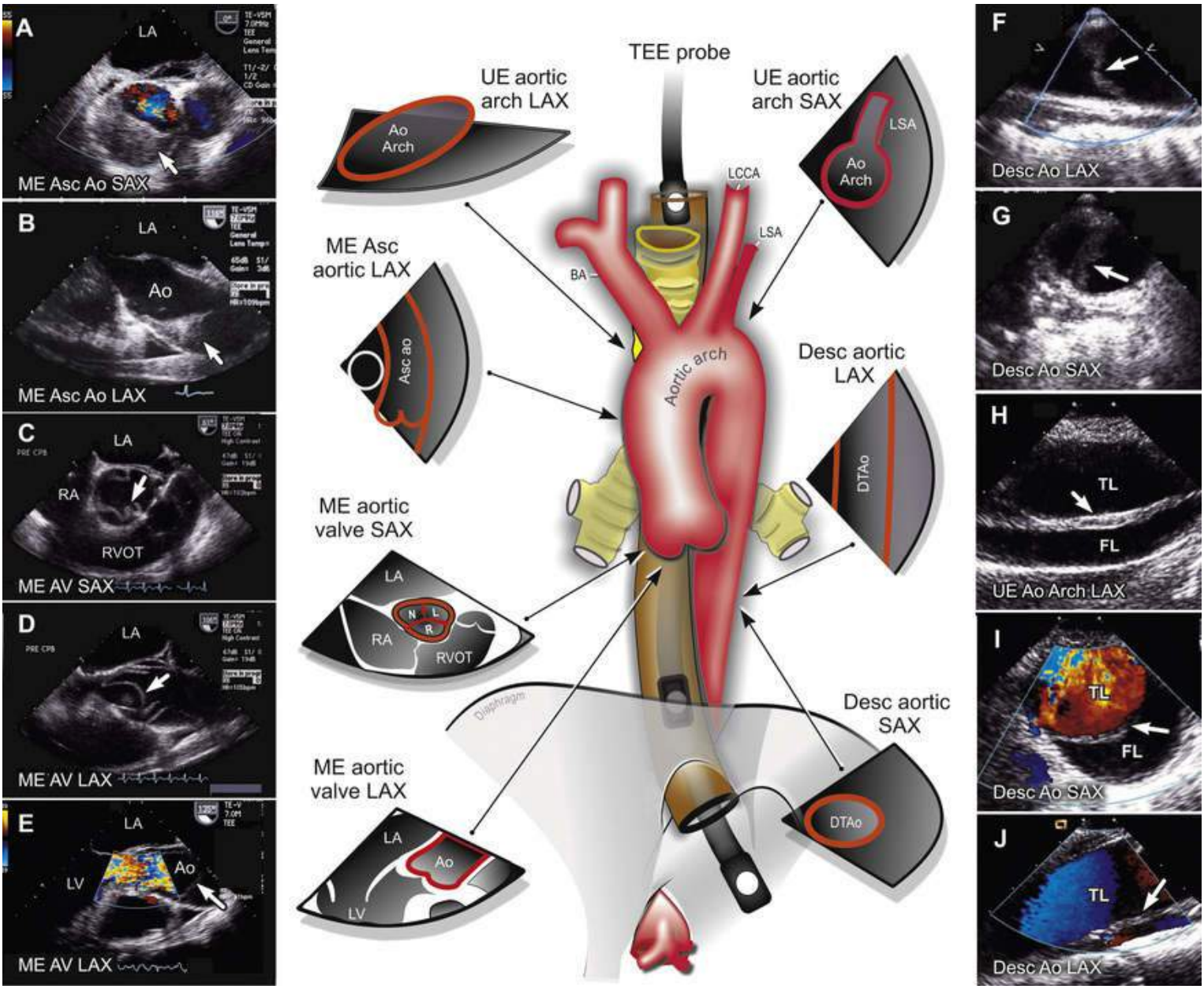


FIGURE 14.71 This TEE composite illustrates **(A, B)** short- and long-axis views of an intramural hematoma in the ascending aorta (*arrow*); **(C, D)** a type A dissection flap that originates at the level of the aortic sinuses, prolapses through the aortic valve, and also extends into the ascending aorta (see Video 14.45); **(E)** severe aortic insufficiency resulting from dissection in the same patient; **(F, G)** long- and short-axis views of partial aortic transection occurring in the descending thoracic aorta just distal to the origin of the left subclavian artery as a result of sudden deceleration during a motor vehicle accident; and **(H-J)** long- and short-axis views of a type B aortic dissection flap A (*arrow*) visualized in the distal descending thoracic aorta (see Video 14.46). *FL,* False lumen; *TL,* true lumen; *ME,* midesophageal; *ME,* midesophageal; *UE,* upper esophageal.

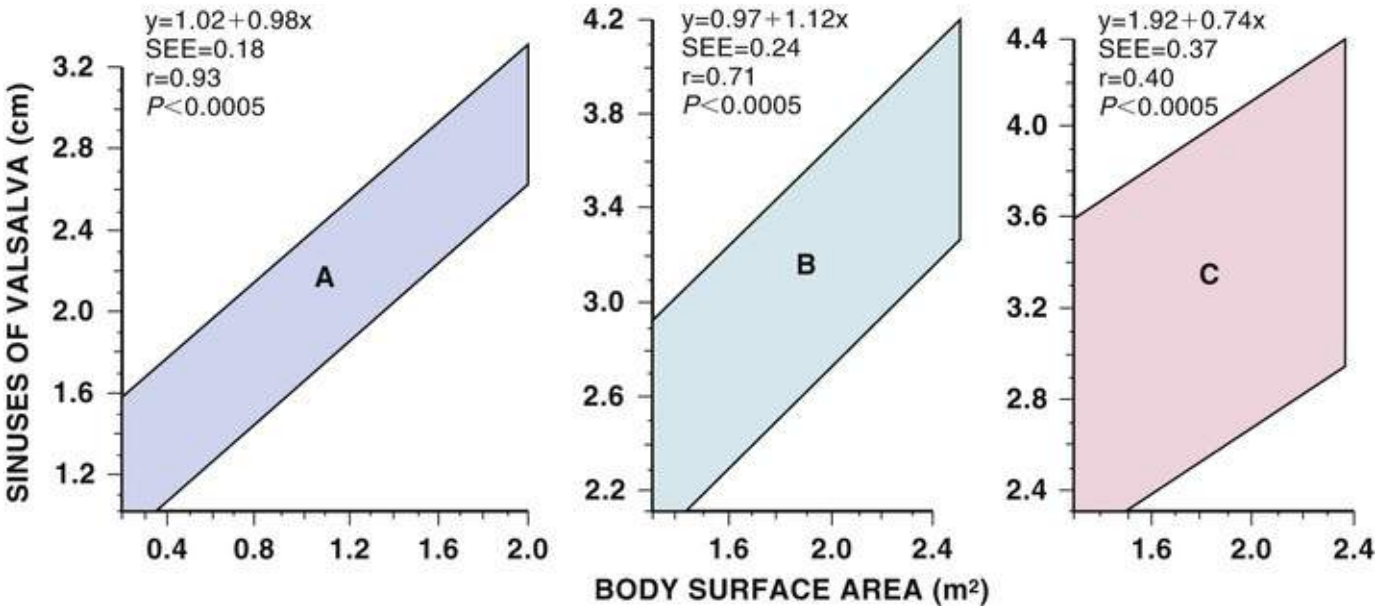
During the standard echocardiographic examination, the normal diameter of the aorta should be assessed at the aortic annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta. The upper limit of normal varies with age, sex, and BSA (**Table 14.10 and eFig. 14.26**). More of the ascending aorta can be viewed by moving the transthoracic probe up one interspace, angling the probe more cephalad, or utilizing right parasternal windows.

TABLE 14.10

Normal Values for Aortic Size in Adults

Aortic Root	ABSOLUTE VALUES (cm)		INDEXED VALUES (cm/m^2)	
	Men	Women	Men	Women
Annulus	2.6 ±0.3	2.3 ±0.2	1.3 ±0.1	1.3 ±0.1
Sinuses of Valsalva	3.4 ±0.3	3.0 ±0.3	1.7 ±0.2	1.8 ±0.2
Sinotubular junction	2.9 ±0.3	2.6 ±0.3	1.5 ±0.2	1.5 ±0.2
Proximal ascending aorta	3.0 ±0.4	2.7 ±0.4	1.5 ±0.2	1.6 ±0.3

From Lang RM, Badano LP, Mor-Avi Victor, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1.



EFIGURE 14.26 Normal aortic root sizes. The 95% confidence intervals for aortic root diameter at sinuses of Valsalva on the basis of body surface area (BSA) in **A,** children and adolescents; **B,** adults age 20 to 39; and **C,** adults age 40 or older.

Focal Aortic Pathology

Atherosclerotic plaque can be visualized as irregular, heterogeneous, or echobright calcified foci adherent to the endothelial side of the lumen. These plaques often accumulate at the sinotubular junction and aortic arch. Plaque that is thicker than 5 mm or that has mobile or protruding elements appears to be at higher risk of being associated with stroke (**Fig. 14.72A**). *Ulcerated aortic plaque* is thought to be a potential precursor to intramural hematomas (see later). In patients with bicuspid valves, the descending aorta should always be evaluated carefully for signs of narrowing and blood flow acceleration at the isthmus to rule out *aortic coarctation*.

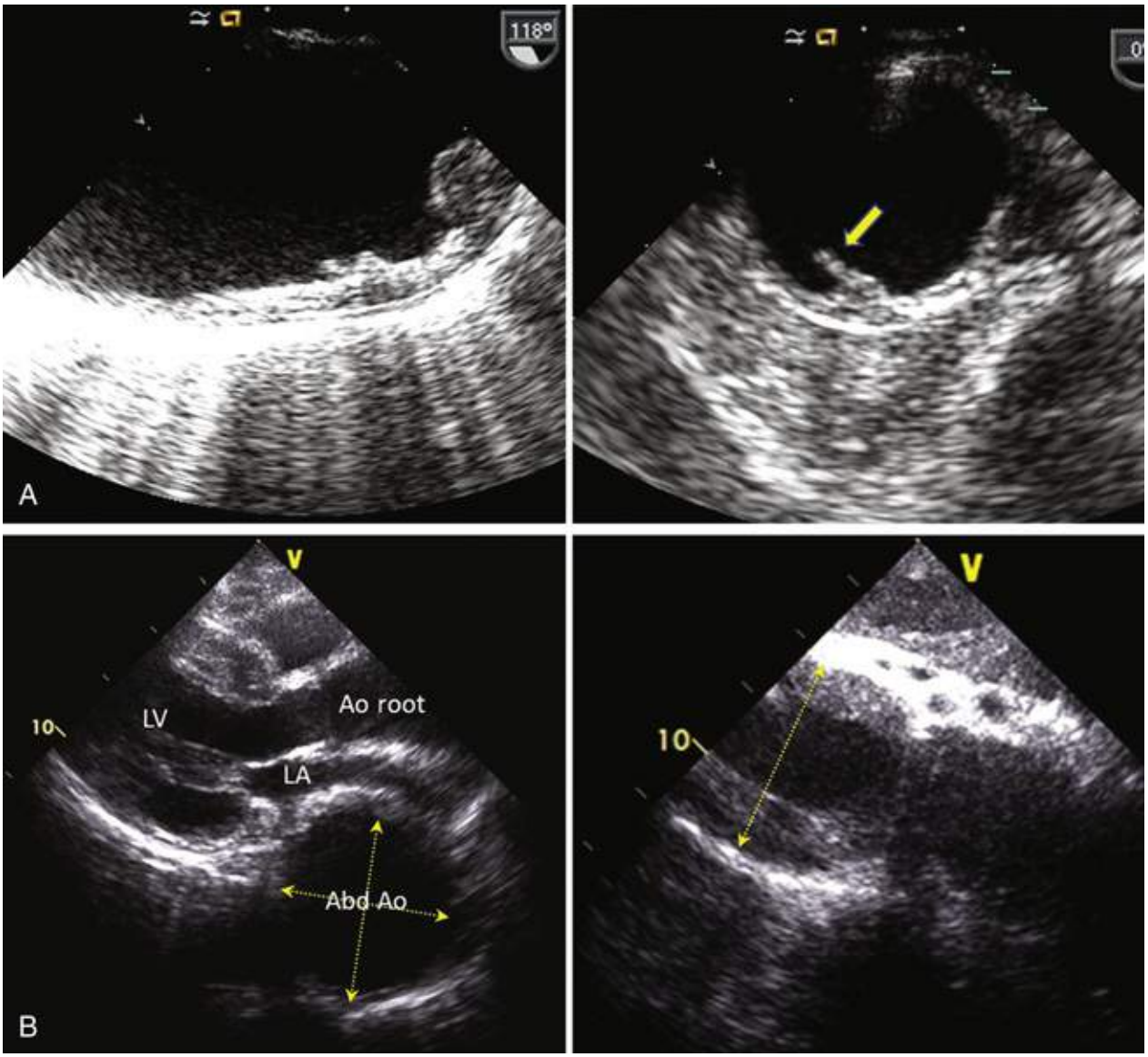


FIGURE 14.72 Aortic atheroma and aneurysm. **A,** TEE views of complex aortic atheroma in the ascending aorta. In the long-axis view **(left),** the atheroma is seen to be irregular and measures up to 1.0 cm in thickness. In the short-axis view **(right),** a protuberant finger-like atheroma is seen and is independently mobile. **B,** Transthoracic parasternal long-axis (**left**) and subcostal (**right**) views of a large 7-cm-diameter descending thoracoabdominal aortic aneurysm (*dotted arrows* spanning the diameter) compressing the posterior aspect of the left atrium (*LA*), within which diffuse circumferential thick mural thrombus is layered. *Ao,* Aortic; *LV,* left ventricle.

Aortic Emergencies

Aortic aneurysms, technically defined as vessel dilation greater than 50% above the normal diameter of the aorta, may occur anywhere along the course of the aorta (**Fig. 14.72B**), although they are more common in the abdominal location. Patients with connective tissue syndromes (e.g., Marfan, Loeys-Dietz, Ehlers-Danlos type IV) and patients with bicuspid aortic valves are thought to have defects in the elastic and smooth muscle composition of the aorta and thus appear to be prone to the development of ascending aneurysms (generally defined as ascending aortic diameter >3.6 cm). Marfan syndrome in particular often affects only the sinuses of Valsalva symmetrically, whereas diameters at the sinotubular junction and ascending aorta are relatively preserved. If the aneurysm involves the ascending aorta, sinuses, and the proximal root all the way to the annulus (termed *aortoannular ectasia*), the resulting incomplete cusp coaptation may cause aortic insufficiency and necessitate valve repair as well. Isolated *sinus of Valsalva aneurysms* are focal dilations that asymmetrically affect only one sinus (most often the right, as shown in

Fig. 14.73). They are usually discovered incidentally, and their cause is uncertain. Although not considered an acute aortic emergency, there have been case reports of rupture of these aneurysms into the right ventricle, right atrium, and other locations. In contrast to *ascending* aneurysms, most *descending* aortic aneurysms are associated with atherosclerosis. Whereas ascending aneurysms are typically fusiform, abdominal aneurysms may be more irregular, focal, and saccular in shape.

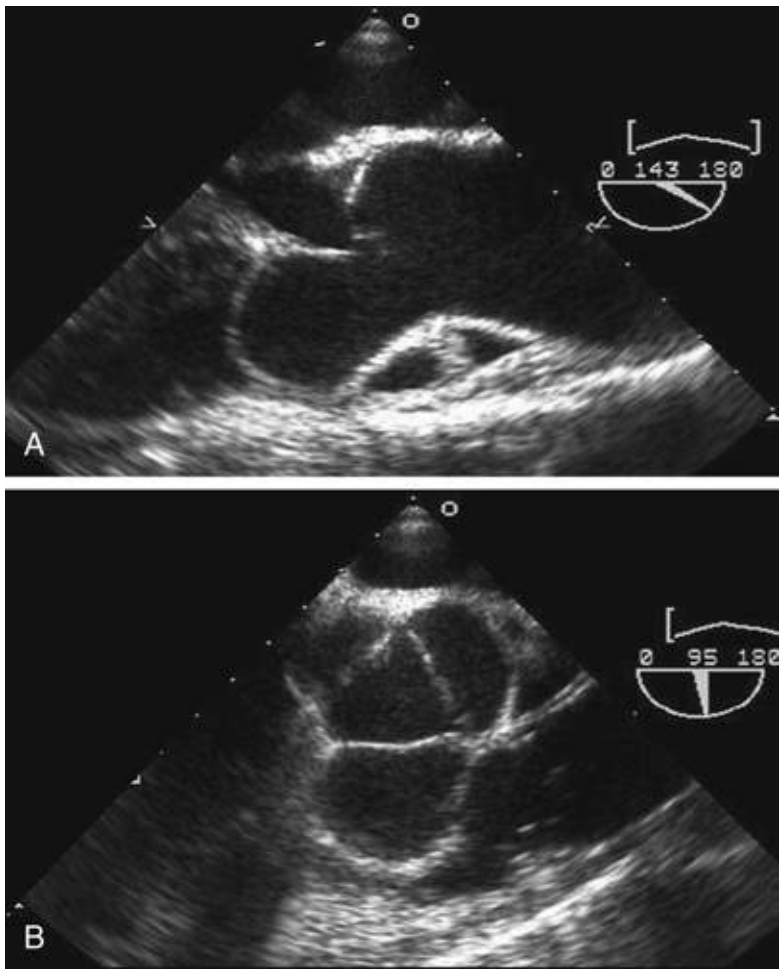


FIGURE 14.73 Sinus of Valsalva aneurysm. **A,** TEE long-axis view of a right sinus of Valsalva aneurysm (measuring 2.5 × 2.8 cm). **B,** TEE short-axis view of the trileaflet aortic valve in the open position showing the right sinus aneurysm in cross section. The patient had mild aortic insufficiency.

The most common emergency indication for echocardiography in patients with aortic diseases is to detect *aortic dissection*, a tear in the aortic intima that enables blood to force its way between the other layers of the vessel wall. Although it can arise de novo, aortic dissection and rupture are the most feared sequelae of aortic aneurysms and thus share the same causative associations and risk factors, including connective tissue disorders, aortic valve disease (personal or family history), hypertension, smoking, and atherosclerosis. **Figs. 14.70 and 14.71** show examples of aortic dissection and their location and appearance (Videos 14.43 and 14.44). Recent aortic manipulation, such as cardiac catheterization, cardiac surgical bypass, placement of intra-aortic balloon pumps, and intravascular stenting, is also considered a high-risk condition.[72] Serious morbidity from compromised blood flow to the coronary arteries, central nervous system, renal arteries, and other organs may occur, and if the dissection ruptures through all three layers, massive bleeding and death can rapidly ensue. Dissection tends to propagate in antegrade fashion (i.e., from the proximal toward the distal aorta), although retrograde extension may also occur all the way back to the sinuses, causing aortic insufficiency or occluding coronary artery ostia

(Video 14.45). The mortality rate is high, and surgical treatment has been shown to be the most effective therapy for patients with ascending (DeBakey types I and II or Stanford type A) dissections. *Blunt chest trauma,* in particular rapid-deceleration injuries such as in motor vehicle accidents, may cause tears at the ligamentum arteriosum (near the aortic isthmus, just distal to the left subclavian artery), which demarcates a hinge point between the relatively tethered descending thoracic aorta and the more mobile arch and ascending aorta. Tertiary syphilis, now a rare disease in the developed world, can cause *aortitis,* that is, inflammation of the aortic adventitia, weakening of the walls, and subsequent development of descending aortic aneurysms and dissections. Rarely, other systemic arteritides, such as giant cell arteritis, can also cause aneurysm formation in the ascending aorta.

TTE has somewhat limited sensitivity (70% to 80% for all locations with higher sensitivity in type A dissections) and specificity (63% to 93%) for aortic dissection because of limited views of the abdominal aorta. TEE has been shown to have a sensitivity reaching 99% and specificity of 89%, particularly with ascending dissections.[72] An aortic dissection flap on echocardiography appears as a linear or thin serpiginous tissue plane extending parallel (in the long-axis plane) (**Fig. 14.74A; see also Fig. 14.70A, C**) or semicircumferentially (in the short-axis plane) (**see Fig. 14.71I**) to the aortic walls. It represents the intima that has split from the other layers of the aorta. An acute, unthrombosed flap will undulate independently and usually bulge outward from the true lumen in pulsatile fashion during systole. These characteristics can be demonstrated by M-mode and can be used to distinguish true disease from reverberation artifact. If color Doppler is used to sweep along the flap, one may occasionally be able to identify the site of the primary tear as a communication between the false and true lumen (Video 14.46). The false lumen may be seen to contain more spontaneous echocardiographic contrast or even formed thrombus. By color and spectral Doppler, forward flow in systole can also help identify the true lumen (**Fig. 14.74B, E**). Complications arising from aortic dissection that may be directly imaged by ultrasound include (1) extension of the flap into the coronary arteries with loss of the diastolic-dominant coronary flow by spectral and color Doppler and wall motion abnormality signaling MI; (2) AR (**see Fig. 14.70E, F**); (3) extension of the flap into the carotid arteries (causing stroke) or the innominate or subclavian arteries (**see Fig. 14.70A**); (4) pericardial effusion, which is frequently frank hemopericardium; (5) pleural effusion, which is more common on the left than on the right side; and (6) periaortic hematoma, signifying a leak in the adventitia and impending complete rupture.

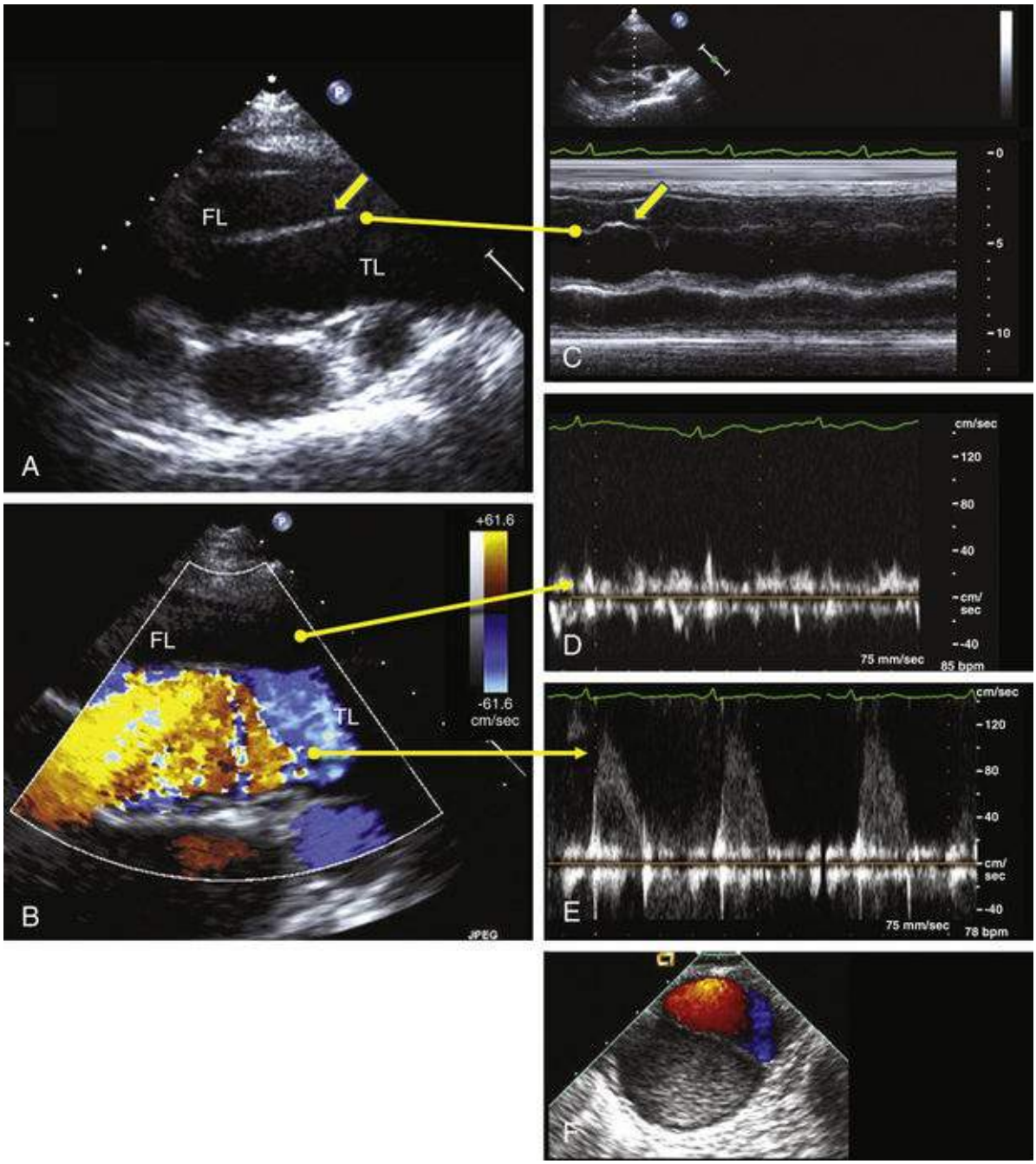


FIGURE 14.74 Aortic dissection demonstrating true and false lumens. **A,** TTE high parasternal long-axis view of a type A aortic dissection. The linear dissection flap is indicated by the *arrow. FL,* False lumen; *TL*, true lumen. **B,** TTE view at the same level with color flow Doppler illustrating brisk and turbulent color flow within the true lumen. **C,** M-mode illustrating systolic pulsation of the dissection flap *(arrow)* outward from the true aortic lumen. **D,** Low-velocity spectral Doppler flow without clear cyclic variation in the false lumen. **E,** Systolic forward high-velocity spectral Doppler flow in the true lumen. **F,** TEE short-axis view of the ascending aorta in a different type A dissection case demonstrating spontaneous echocardiographic contrast in the false (larger) lumen and brisk systolic flow in the true (smaller) lumen by color Doppler.

Other aortic emergencies are less common but equally life threatening. *Aortic transection* occurs as a result of severe deceleration injury and consists of complete shearing of the aorta at the isthmus, with the severed ends of the aorta floating freely within hematoma. This is so lethal that examples are rarely captured on TEE during emergency surgery or endovascular repair, although local containment of blood within the mediastinum can permit a very brief window of survival. A partial transection is shown in **Fig. 14.71F, G**. *Aortic intramural hematoma* is an accumulation of blood that remains contained within the aortic media; it accounts for approximately 5% to 20% of acute aortic syndromes (**see Fig. 14.71A, B**). On echocardiography, intramural hematoma appears as a smooth, homogeneously echogenic bulge within the medial layer of aortic wall. It is hypothesized to arise from rupture of a penetrating atherosclerotic

ulcer, spontaneous rupture of the vasa vasorum, or more frequently, blunt trauma. Intramural hematomas are distinguished from the typically focal, echobright, and irregular plaque in that they lie within the aortic wall and extend smoothly and longitudinally along the aorta. On cross-sectional views the hematoma appears as a crescentic or circular area of homogeneous thickening around the central aortic lumen. Unlike dissection, the intimal layer is still intact and is not mobilized, so there is no detectable intimal tear and no blood flow communication with the aortic lumen. If the intramural hematoma is relatively small, additional imaging with CT or MRA may be required to identify the hematoma definitively and distinguish it from the differential diagnoses of plaque or periaortic fat. Intramural hematomas can arise in either ascending or descending locations and may enlarge or progress to frank aortic dissection and may have similar mortality rates. Thus the principles of medical and surgical management are essentially the same as for typical aortic dissections.[72]

Pulmonary Embolism

Echocardiography can be extremely useful in the diagnosis and management of acute pulmonary embolism (**see Chapter 84**). Although not generally used as the primary diagnostic method for assessing pulmonary embolism, echocardiography provides information complementary to other diagnostic tests, has prognostic value, and may inform or monitor therapy (particularly if CT angiography is not feasible).[73] Echocardiography performed for other indications, including dyspnea, chest pain, and hypotension, also occasionally leads to the incidental discovery of pulmonary embolus. Thrombi that result in pulmonary embolism generally arise from the deep venous system in the legs; echocardiography can be used to directly visualize thrombus anywhere from the vena cava to the pulmonary arteries (**Fig. 14.75** and Video 14.47). Thrombi in the pulmonary arteries can generally be visualized to approximately just past the bifurcation with TTE; when found, they are associated with RV dysfunction and high early mortality. Although TEE can image slightly farther into the main pulmonary artery branches, it is rarely used as a primary diagnostic modality for pulmonary embolism. The pulmonary artery bifurcation should be carefully assessed from the short-axis views in patients with suspected pulmonary embolism, and it is not uncommon for so-called saddle emboli to become lodged at the bifurcation (**Fig. 14.75, right**). Putative thrombi need to be distinguished from other cardiac masses, including myxomas, fibroelastomas, and vegetations (see later, Cardiac Masses).

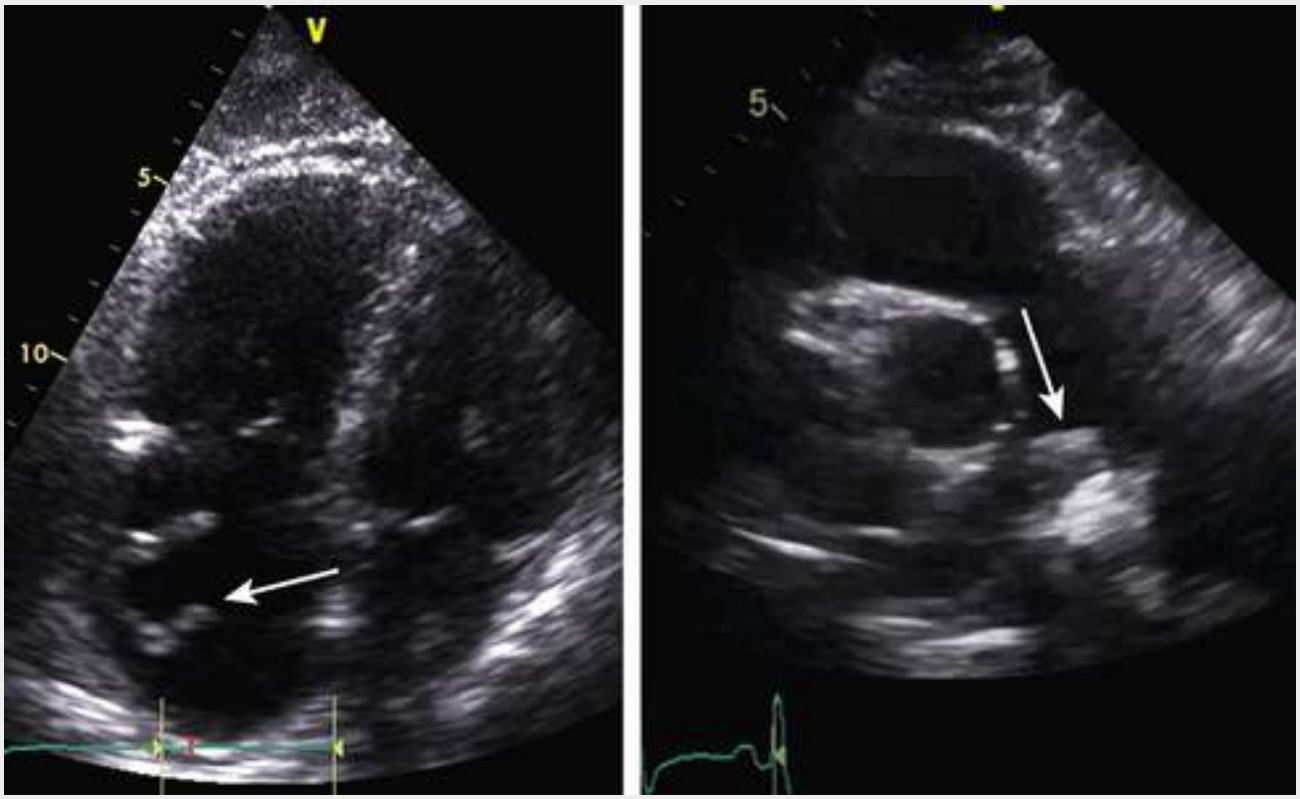


FIGURE 14.75 **Left,** Thromboembolus in the right atrium (*RA*). The *arrow* indicates a serpentine mass that is a thrombotic "cast" of a deep vein of the lower extremities that has embolized to the RA. *RV,* Right ventricle. (See Video 14.47.) Note the right-sided heart dilation and hypokinesis, clues indicating that a significant acute pulmonary embolus has also occurred. **Right**, Saddle embolus at the bifurcation of the pulmonary artery (*arrow*). (See Video 14.48.)

The characteristic echocardiographic findings in pulmonary embolism result in part from the unique physiology of the right ventricle. The normal right ventricle is generally accustomed to low pulmonary vascular resistance (PVR) and thus extremely low afterload, and RV systolic pressure normally is low. In acute pulmonary embolism, PVR rises substantially and abruptly, which results in RV dilation and, in severe cases, failure. Thus, RV dilation is the echocardiographic hallmark of pulmonary embolism. It is best visualized on the apical four-chamber view, where classic findings include RV diameter greater than LV diameter (ratio >1.0) and a small, underfilled, but normally functioning left ventricle. A distinctive regional wall motion abnormality has been recognized in acute pulmonary embolism in which the free RV midwall becomes dyskinetic, with relative sparing of the apex and base. This pattern, known as the *McConnell sign*, is highly specific for conditions in which PVR increases abruptly[74] (**Fig. 14.76** and Video 14.48). RV TAPSE may also be decreased in patients with acute pulmonary embolus. Both RV dilation and RV regional dysfunction will be less apparent in patients in whom PVR has been elevated for a longer period, resulting in RV hypertrophy. In these patients, pulmonary pressure will ultimately rise, and the right ventricle may not show evidence of dilation or dysfunction in acute pulmonary embolism. Thus the classic echocardiographic RV patterns are of lower sensitivity and have low negative predictive value in patients with longstanding pulmonary hypertension, such as those with chronic obstructive pulmonary disease (COPD) or chronic thromboembolic disease.

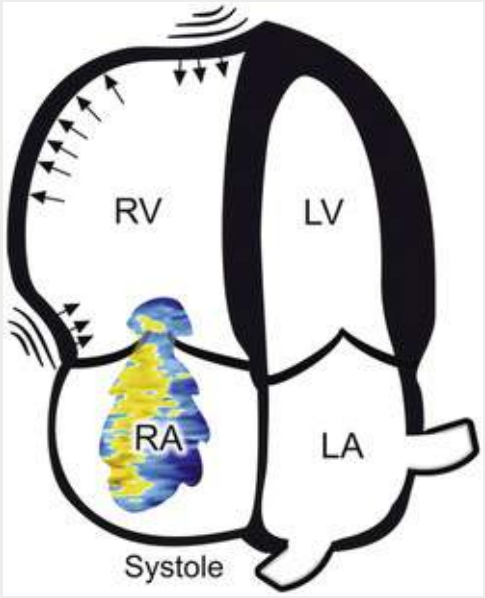


FIGURE 14.76 Regional right ventricular dysfunction (McConnell sign) in acute pulmonary embolism. The right ventricle (RV) is enlarged and right ventricular regional function is abnormal, with dyskinesis of the midwall region and relative sparing of the apex and base. Tricuspid regurgitation is usually present. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium.

In patients without a previous history of pulmonary hypertension, even in the setting of acute pulmonary embolus, the tricuspid regurgitant (TR) velocity will remain relatively normal, rarely exceeding 3 m/sec. Patients with preexisting pulmonary vascular disease, however, may have increased TR velocity consistent with elevated pulmonary systolic pressure. Assessment of RV dilation and dysfunction has now been incorporated into treatment algorithms and are useful particularly in intermediate-risk patients.[73] The presence of RV dilation or dysfunction in acute pulmonary embolism is an independent predictor of adverse outcomes and short-term mortality, even in hemodynamically stable patients. In terms of response to therapy for acute pulmonary embolism, improvement in RV function can be seen on echocardiography within several days of successful treatment (reperfusion by either embolectomy or thrombolysis) of pulmonary embolism.

Infective Endocarditis

Echocardiography is the first-line modality for the detection, evaluation, and management of endocarditis (**see Chapter 73**). American College of Cardiology/American Heart Association Class I indications for echocardiography apply to the following settings: (1) in patients with suspected endocarditis (with or without positive blood cultures) to detect valvular vegetations; (2) in patients with known infective endocarditis to evaluate for valve lesions such as regurgitation and to assess for complications such as abscess and intracardiac shunts; (3) to reevaluate patients with known endocarditis who have high-risk features such as a virulent organism, clinical deterioration, persistent or recurrent fever or bacteremia, and a new murmur; and (4) in symptomatic patients with nondiagnostic TTE or prosthetic valves, for which TEE is likely to have higher sensitivity for both vegetations and complications.[75]

Infective endocarditis is definitively diagnosed by culture or pathologic examination of a vegetation (in situ or embolized) or intracardiac abscess. However, many cases are diagnosed on clinical grounds by using the modified Duke criteria as a guideline. The first criterion is positive blood cultures consistent with infective endocarditis. The second major criterion is an echocardiogram demonstrating (1) a vegetation (**Fig. 14.77A, B**, and Video 14.49) (i.e., an oscillating intracardiac mass on a valve, in the path of a regurgitant jet, or on implanted material) in the absence of an alternative anatomic explanation,

(2) an abscess (**Fig. 14.77C** and Video 14.50), or (3) new partial dehiscence of a prosthetic valve[75] (**Fig. 14.77D**; see Video 14.38). The sensitivity of TTE ranges up to 63%, with a specificity close to 100%. The suboptimal sensitivity often results from physical imaging factors causing poor image quality and acoustic shadowing and also depends on the size of the vegetation. Because of its higher 2D resolution and different windows, TEE has much higher sensitivity (94% to 100%) and is especially advantageous in assessing prosthetic valves and diagnosing abscesses. Thus a reasonable diagnostic approach is to use TTE as the first-line screening tool; if this is nondiagnostic, one may turn to TEE if clinical suspicion for endocarditis is high, as in the patient with a prosthetic valve or predisposing condition, clinical features suspicious for a complicated endocarditis, or a potential indication for cardiac surgery.[76]

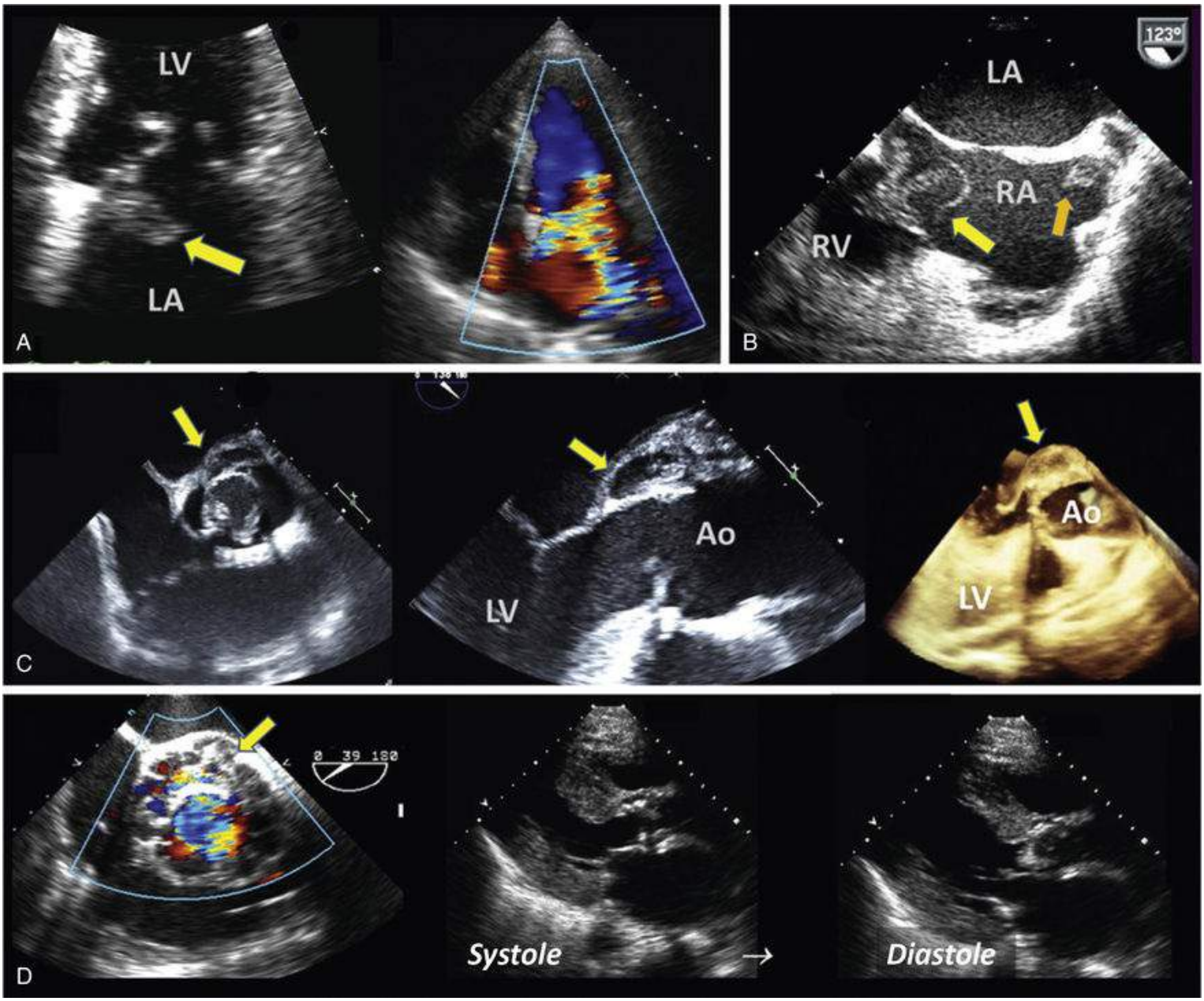


FIGURE 14.77 Echocardiography in endocarditis. **A,** Vegetation (*arrow*) on the left atrial aspect of a rheumatic mitral valve **(left panel)** with color Doppler demonstration of a second noncentral jet of MR at the base of the leaflet and vegetation indicative of leaflet perforation **(right panel).** (See corresponding Video 14.49.) **B,** Vegetation (*yellow arrow*) on the right atrial aspect of the tricuspid valve on a TEE long-axis view. An additional vegetation (*orange arrow*) in the superior vena cava associated with a previous indwelling catheter is noted, and the eustachian valve was also infected in this patient with a history of intravenous drug abuse. **C,** Paravalvular abscess (*arrow*) as indicated by the crescentic echolucent area with thickening from the 11- 1 o'clock position on short-axis **(left panel)** and long-axis **(middle panel)** TEE views anterior to the annulus of a bicuspid aortic valve (open in systole), also visualized on the 3D TEE view **(right panel).** (See Video 14.50.) **D,** Ringlike abscess around the annulus of a bioprosthetic aortic valve as seen on a short-axis TEE view **(left panel).** This causes dehiscence of the valve, as seen on long-axis TEE views **(middle and right panels),** in which it rocks forward in systole and prolapses into the LVOT in diastole. (See Video 14.38.) *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

Vegetations appear as discrete echogenic masses that are adherent to but distinct from the leaflet itself. A typical mitral vegetation is shown in **Fig. 14.77A**; see Video 14.49. Characteristics of vegetations that aid in distinguishing them from other masses include localization, texture, motion, shape, and associated abnormalities. Vegetations are typically located on the upstream, or low-pressure, side of the valve, in the path of any regurgitant bloodstream (i.e., the atrial aspect of atrioventricular valves and the ventricular aspect of semilunar valves); less often, they are attached to the periphery of septal defects, to chordae, or

to the mural endocardium. The *echodensity* of a vegetation is usually similar to that of myocardium, although advanced vegetations can be inhomogeneous, with findings indicative of liquefaction (which is echolucent) or calcification (which is echodense or bright). Independent *motion* of vegetations is frequently oscillating or erratic. Large vegetations can prolapse into the upstream chamber and create a "ball-and-chain" effect that causes leaflet flail and regurgitation. Vegetations vary tremendously in *shape* but often appear as compact multilobulated or pedunculated, amorphous, and friable agglomerations compared with tumor tissue or thrombus. The vegetation can extend some distance from the valve to which it is tethered and may occur in multiples on the same or different valves. *Associated abnormalities* such as regurgitation, abscesses, and intracardiac channels can accompany advanced endocarditis. There are no distinguishing characteristics that are organism specific, although staphylococcal infections (particularly methicillin-resistant *Staphylococcus aureus* and *S. lugdunensis*) tend to be more destructive and form abscesses, and fungal infections are often impressively large and dendritic in appearance.[77]

Vegetations devoid of microorganisms are the hallmark of *noninfectious endocarditis*, also called "nonbacterial thrombotic" or "nonbacterial marantic" endocarditis (**see Chapter 73**). The typical lesions are small (1 to 5 mm), verrucous, nondestructive nodules that adhere to the upstream side of the valve (typically mitral or aortic) along the line of closure and contain only cellular and fibrin elements. These aseptic lesions are seen in up to 43% of patients with systemic lupus erythematosus (SLE) and 29% of those with antiphospholipid syndrome (APS), in whom they can cause cerebral embolization. These also occur in patients with advanced neoplasms, sepsis, and prothrombotic tendencies in association with clinical features indistinguishable from those of typical infective endocarditis[78] (see later, Systemic Diseases and Echocardiography).

Of note, the presence of preexisting thickening and degenerative changes in leaflets can render the diagnosis challenging. On occasion, myxomatous leaflets, ruptured chordae, calcified structures, and fibrin strands can either mask or mimic a vegetation. Papillary fibroelastomas and thrombi can resemble valvular vegetations. In these circumstances, clinical correlation with other Duke diagnostic criteria is important. Comparison with previous echocardiograms should also be undertaken; a stable finding over years is unlikely to represent a vegetation. Use of TEE for higher-resolution images is often indicated, particularly if a cardiac device is involved[79] or a complication (e.g., embolization, valve destruction, abscess) is suspected.

Among patients with endocarditis, 66% to 75% have risk factors for infection, and echocardiography should be used to scrutinize the relevant structures at risk especially carefully. Patients with prosthetic valves, complex cyanotic congenital heart disease, surgical systemic-pulmonary shunts, bicuspid aortic valves, rheumatic heart disease, or mitral valve prolapse are at higher risk. Previous endocarditis and IV drug abuse are strong predisposing factors for tricuspid and pulmonic valve endocarditis. Other intracardiac structures that are prone to infection, usually at the time of placement or access, include defibrillator/pacemaker wires and chronic indwelling IV catheters, particularly when used for total parenteral nutrition or hemodialysis in immunocompromised patients. Echocardiographic characteristics associated with a poorer prognosis and embolization include vegetation size greater than 1.0 cm (which confers a 2.5-fold higher risk for embolization, especially if on the mitral valve), increasing size of the vegetation over time despite therapy, very mobile vegetation, and paravalvular abscess (more common with prosthetic valves and increasing mortality twofold).[79,80]

The natural history of vegetations after medical therapy is of interest because most will still be apparent on follow-up echocardiography in 1 to 2 months, even after successful medical treatment. Approximately half will become more echodense over time. These observations probably reflect the varied components of the vegetation, which include not only bacteria but also inflammatory cells,

fibroblasts, and extracellular matrix. Growth of a vegetation over time and increasing valvular regurgitation are poor prognostic signs. However, the mere persistence of vegetations in the absence of symptoms or positive blood cultures is not associated with increased clinical complications. Thus, treatment of endocarditis should not be guided by the echocardiographic morphology of the vegetation over time but by clinical response to therapy.

Role of Echocardiography in Surgery for Endocarditis

If left untreated, infective vegetations are destructive via pathways that are apparent on echocardiograms and ECGs and by clinical sequelae. If present, these vegetations are indications for surgery, particularly if recalcitrant to medical therapy. Indications include (1) embolism to the coronary arteries, brain, lungs, spleen, kidney, or extremities; (2) severe valvular regurgitation and heart failure secondary to leaflet malcoaptation, perforations, or flail; (3) abscess, which may invade the cardiac conduction system; (4) mycotic aneurysms of vessels and valves; (5) pseudoaneurysms or fistulas of the heart; and (6) suppurative or hemorrhagic pericarditis.

Typical paravalvular extension patterns can be detected on echocardiograms (and ECGs). On the *aortic valve*, involvement of the right cusp can lead to necrosis of the membranous interventricular septum, aneurysm of the right sinus of Valsalva, and valve dehiscence. Embolization into the RCA can also occur and cause MI. Involvement of the left cusp can affect the intervalvular fibrosa and extend to infect the base of the anterior mitral valve leaflet. There is also the potential to form an aortic-to-LVOT fistula, or paravalvular leak. Involvement of the noncoronary cusp can extend to the posterior interventricular septum, where the His conduction fibers are located, which can lead to the development of an intra- or infrahisian block (third-degree atrioventricular block) or bundle branch block.

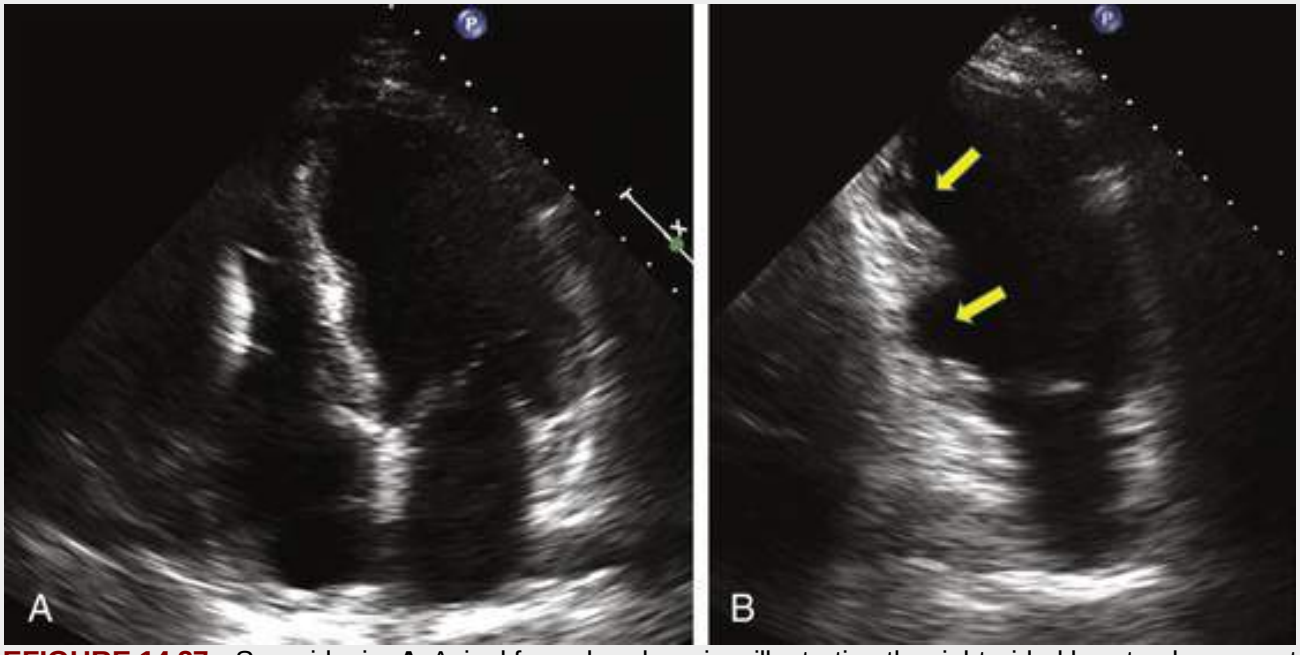
Severe infection of the *mitral valve* less frequently leads to conduction disturbances. Although first- or second-degree atrioventricular block can occur, supraventricular tachycardias are more common. *Tricuspid valve* infection can extend to involve the tricuspid annulus and eustachian valves (**Fig. 14.77B**), seed the pulmonic valve, and cause septic pulmonary emboli in 25% to 80% of cases.[79]

Systemic Diseases and Echocardiography

Aside from conditions that directly affect the heart itself, many systemic diseases with cardiac manifestations are detectable on echocardiography. Uncontrolled hypertension causes symmetrically increased wall thickness and LV hypertrophy in association with LA enlargement and diastolic dysfunction. Renal disease causes early calcification of the valves and potentially uremic pericardial effusions. Hypothyroidism can be associated with a myxedematous pericardial effusion. COPD can cause conspicuous right-sided heart enlargement, RV hypertrophy, elevated TR velocity, and a prominent pericardial fat pad secondary to corticosteroid treatment.

There are diseases that affect all tissue layers of the heart. Amyloidosis is notorious for causing restrictive cardiomyopathy (see earlier and **Fig. 14.31F**), but also frequently causes valvular thickening and pericardial effusions. Infiltration of amyloid into the atrial walls leads to poor atrial contractility and a high prevalence of atrial thrombi, even when sinus rhythm is still present.[47] Granulomatous diseases such as sarcoidosis can cause a focal myocarditis with granulomas (**eFig. 14.27**), which results in very localized areas of akinesis in a noncoronary distribution (see Video 14.14). Pericarditis, valvulitis, and coronary and aortic arteritis have also been reported with Wegener granulomatosis. Although

scleroderma is known to cause direct myocardial fibrosis histologically, on echocardiography this becomes apparent in only a minority of patients, usually late in the course of disease. Instead, the most common echocardiographic abnormalities in scleroderma are elevated RV systolic pressure, RV dilation, and pericardial effusion, as well as LA enlargement and diastolic dysfunction.



EFIGURE 14.27 Sarcoidosis. **A,** Apical four-chamber view illustrating the right-sided heart enlargement (containing a pacemaker wire) and the septal focal wall motion abnormalities in the left ventricle ("scalloping") typically seen in sarcoid heart disease. RV dilation is often secondary to pulmonary hypertension from sarcoid lung involvement. **B,** Apical two-chamber view illustrating very focal areas of thinning and akinesis (*arrows*) in the inferior LV wall because of sarcoid granulomas and/or myocardial scarring. (See corresponding Video 14.14.)

Other diseases that have echocardiographic manifestations include human immunodeficiency virus (HIV) infection (**see Chapter 82**), in which the most common abnormalities are dilated cardiomyopathy, pericardial effusion (seen in 12% to 25% of cases), but also HIV-related pulmonary hypertension and cardiac lymphomas. The prolonged duration of HIV infection and highly active antiretroviral therapy (HAART) regimens may contribute directly and indirectly (via lipodystrophic effects and chronic inflammation) to both cardiomyopathy and the excess risk of CAD in this population.[81]

Similarly, even when cancers spare the heart, the radiation and chemotherapy regimens used to attack the neoplasms can have cardiac effects (**see Chapter 81**). Ideally, the early detection of cardiomyopathy in patients who receive chemotherapy, particularly with anthracyclines (as well as tyrosine kinase inhibitors and immunomodulators), allows modification of the protocol before irreversible damage occurs. Screening for LVEF is the most widely used strategy, but a growing body of evidence indicates that a decrease in peak systolic GLS (>15% change from baseline) is a more sensitive and earlier predictor of cardiotoxicity. Currently, however, GLS is still greatly in need of standardization among vendors and researchers, and insufficient data exist to indicate if decrements in GLS during chemotherapy will predict chronic irreversible heart failure.[82] Aside from chemotherapy damage, survivors of Hodgkin disease also frequently have early thickening and stenosis of the aortic valves, as well as accelerated CAD from radiotherapy.

Several other conditions predispose to valvular abnormalities (see earlier, Valvular Heart Disease). Rheumatic carditis and its sequelae are well-known historical examples and are still a significant cause

of heart disease in developing nations (**see Chapter 74**). More than 50% of patients with carcinoid tumors have cardiac involvement in which plaquelike deposits build up on the right-sided heart valves (typically the ventricular aspect of the tricuspid valve and the arterial aspect of the pulmonic valve). This causes a characteristic retracted and fixed appearance of the tricuspid and pulmonary leaflets and a combination of valvular stenosis and regurgitation (**see Fig. 14.53**; see Video 14.35). Cardiac involvement confers a worse median survival time for carcinoid. The hematologic malignancies and any thrombophilic state (e.g., sepsis, disseminated intravascular coagulation, SLE, APS) can cause nonbacterial marantic endocarditis in which the sterile vegetations and fibrin strands undergo frequent cycles of growth and subsequent fragmentation and embolization, with associated valvulitis and leaflet destruction. The systemic vasculitides such as Takayasu arteritis and Behçet disease are notable causes of AR, particularly in younger patients.[83]

Pulmonary Hypertension

Echocardiography can assess for pulmonary hypertension and causative conditions. In the absence of known pulmonary disease, the presence of an enlarged right side of the heart with a normal-appearing left ventricle prompt a search for secondary causes of pulmonary hypertension (**Fig. 14.78**) (**see Chapter 85**). Causes that are detectable by echocardiography include intracardiac shunts with atrial septal defects (ASDs) (and most shunts above the tricuspid valve), MS, and occasionally pulmonary thromboembolism. Noncardiac causes include mixed connective tissue disease, systemic sclerosis, SLE, and sickle cell disease, in which pulmonary hypertension is an important cause of morbidity and mortality. In general, most of the indices of pulmonary artery systolic pressure and right-sided heart failure (e.g., interventricular septal flattening, TAPSE, FAC) have been shown to be predictors of mortality in patients with diverse causes of both primary and secondary pulmonary hypertension.[84]

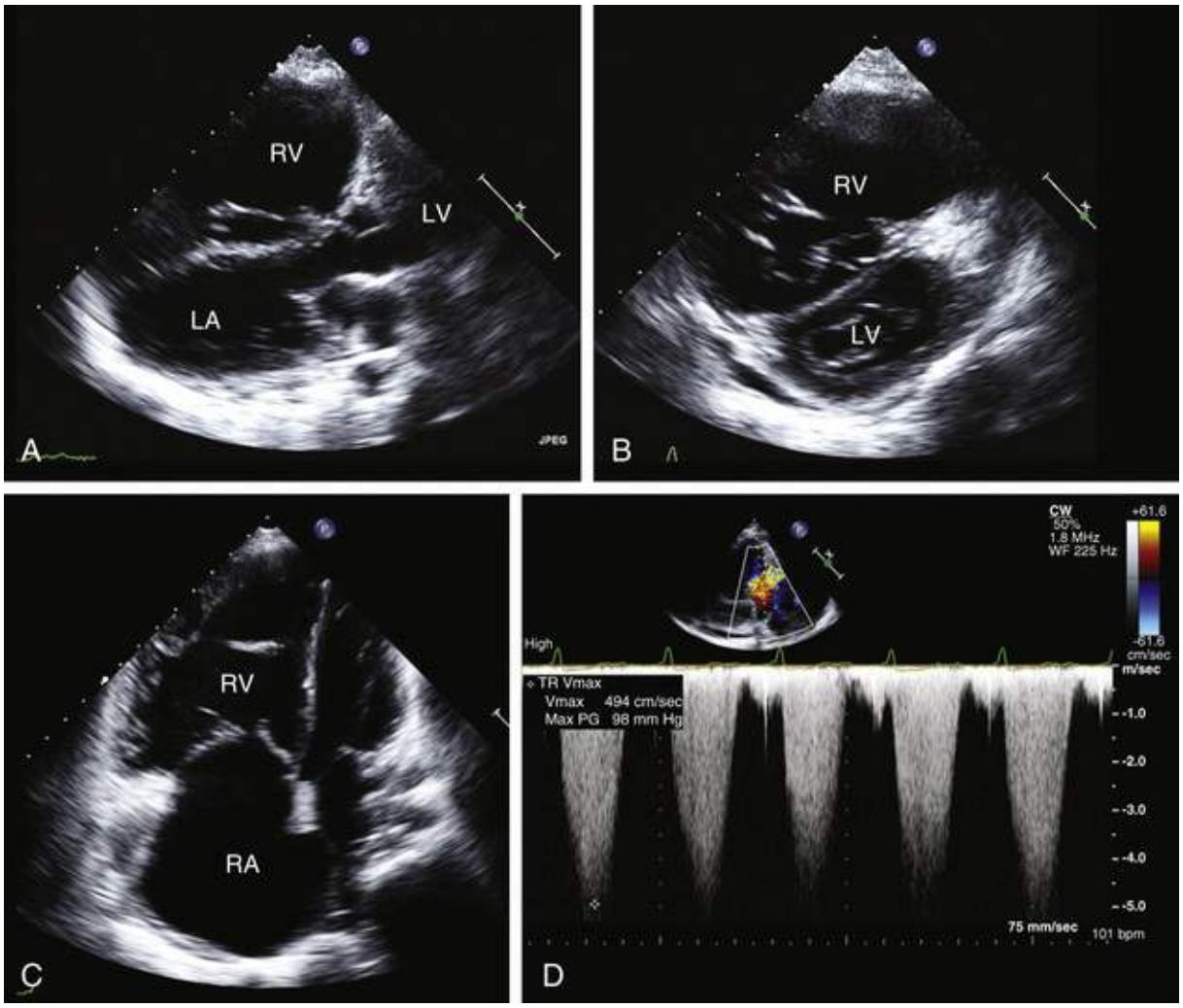


FIGURE 14.78 Pulmonary hypertension secondary to chronic thromboembolic disease. **A,** Parasternal long-axis view illustrating a small left ventricular cavity and enlarged right ventricular outflow tract. **B,** Parasternal short-axis view demonstrating the D-shaped left ventricular cavity caused by systolic and diastolic septal flattening, i.e., pancyclic elevated right ventricular pressure. **C,** Apical four-chamber view. Note the dilated right atrium and tricuspid annulus with incomplete closure of the tricuspid valve, as well as leftward distention of the interatrial septum. **D,** Severe tricuspid regurgitation (TR) with an elevated TR velocity corresponding to a calculated right ventricular systolic pressure of 98 mm Hg plus right atrial pressure. The upslope of the tricuspid regurgitant jet is slow, indicative of poor right ventricular contractility. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

Two-dimensional echocardiographic findings in patients with pulmonary hypertension include flattening of the interventricular septum (first in diastole and subsequently, as pressure rises further, in systole), dilation of the pulmonary artery, RV hypertrophy, RV dilation, and ultimately RV dysfunction. Typical Doppler findings include elevated TR velocity, enlargement of the right atrium, dilation of the IVC and hepatic veins, and loss of respirophasic size variation in the IVC.

Pulmonary artery pressure (PAP) can be assessed relatively accurately by using the Bernoulli equation to estimate the pressure gradient between the right ventricle and the right atrium. If TR is not present or the TR jet is acquired off-axis, this measurement will be impossible to make or will underestimate the severity of pulmonary hypertension. In addition to PAP assessment, PVR (in Woods units) can be measured noninvasively by using the validated formula:

$$\text{PVR} = 10(\text{TR peak velocity}/\text{VTI}_{\text{RVOT}}) + 0.16$$

where TR peak velocity is measured in m/sec and VTI_{RVOT} in cm. This approach may have utility in

distinguishing high PAP caused by increased pulmonary blood flow (as occurs in high-output states such as hyperthyroidism, anemia, and obesity) from that caused by elevated PVR.

Assessment of RV size and function is essential in pulmonary hypertension. RV FAC, TAPSE, RV Tei index, and tricuspid annular systolic velocity (S′) are typically used to assess RV function in patients with pulmonary hypertension (**see Table 14.6**). Myocardial strain imaging of the right ventricle may prove to be useful in patients with pulmonary hypertension, but the wide range in normative data limits its clinical application at present.[85]

There are several distinguishing features between the echocardiographic findings of pulmonary hypertension and acute pulmonary embolism. Acute pulmonary embolism is not usually associated with RV hypertrophy, elevation in PAP, or flattening of the interventricular septum in systole, unless the pulmonary embolism is chronic or longstanding thromboembolic disease has resulted in pulmonary hypertension. In addition, the regional RV dysfunction in acute pulmonary embolism usually spares the apex, whereas there is global RV hypokinesis in pulmonary hypertension.

Cardiac Masses

Cardiac tumors are relatively rare, ranging from an incidence of 1% to 2% in general autopsy series but up to 4% to 8% in cancer patient autopsies, so routine screening is not recommended. Among primary tumors of the heart, up to 90% or more are detected incidentally and three quarters are benign. It is the location of an intracardiac or extracardiac mass—in the context of the patient's age, clinical findings, and comorbidities—that is often the best indicator of the type of tumor; morphologic features of the mass play a secondary role in identification[86] (**Table 14.11**).

TABLE 14.11

Site-Specific Differential Diagnosis of Cardiac Tumors

SITE	ONCOLOGIC	ALSO CONSIDER NON-NEOPLASTIC MASSES	NORMAL OR VARIANT STRUCTURES
Left atrium	Myxoma Lipoma Bronchogenic carcinoma Sarcoma (involving the wall/pericardium) Hemangioma Paraganglioma	Thrombus Endocardial blood cyst	Lipomatous hypertrophy of interatrial septum External compression (by hernia, thoracic aorta, bezoar) Echocardiographic artifact: left upper pulmonary vein limbus (“Coumadin ridge”) Appendage pectinate muscles Atrial suture anastomosis after heart transplantation Inverted LA appendage (postoperative) Aberrant LA chorda
Right atrium	Myxoma Nephroblastoma, renal cell cancer Hepatocellular carcinoma Sarcoma (angiosarcoma) Paraganglioma Adrenal tumors	Thrombus (deep venous or in situ) or fibrin casts (of previous indwelling catheter/wire) Vegetation (on pacer/ICD wires) Lipomatous hypertrophy of interatrial septum	Eustachian valve Chiari network Crista terminalis Interatrial septal aneurysm Pectus excavatum
Left ventricle	Rhabdomyoma (often multiple) Fibroma Hamartomas Purkinje cell tumors (usually infants)	Thrombus Apical hypertrophic cardiomyopathy Subaortic membrane	Calcified or multilobed papillary muscles Redundant or severed mitral chordae Trabeculations, false tendons Focal upper septal hypertrophy Swirling from inhomogeneous intravenous echocardiographic contrast distribution
Right ventricle	Rhabdomyoma Fibroma	Thrombus	Redundant tricuspid chordae Tricuspid papillary muscle Moderator band
Valves/annuli	Papillary fibroelastoma Myxoma Hamartoma Lipomas	Lambl excrescences Focal or caseous mitral annular calcification Vegetation Marantic endocarditis Thrombus (especially on prosthetics) Pannus (especially on prosthetics) Abscess Blood cyst Rheumatoid nodule	Nodules of Arantius Myxomatous/degenerative changes Pannus; loose suture; bioglue or pledgets around prosthetic valves
Pericardium	Malignant involvement from lung, breast, lymphoma/leukemia, or gastrointestinal tract melanoma Mesothelioma Primary: spindle cell tumor, fibrous tumors, lipoma, liposarcoma, teratoma Paraganglioma	Pericardial or bronchogenic cyst Rheumatoid nodule Thrombus Hydatid cyst (*Echinococcus*)	Epicardial or mediastinal fat Pectus excavatum Atelectatic lung or fibrin in pleural/peritoneal spaces Vascular pseudoaneurysm Thymus (in infants)

ICD, Implantable cardioverter-defibrillator; *LA,* left atrial.

Modified from Wu J. Cardiac tumors and masses. In Stergiopoulos K, Brown DL, editors. Evidence-Based Cardiology Consult. New York: Springer Science + Business Media; 2014.

Nonetheless, the overall appearance of the mass (with respect to size, solid versus cystic, shape, degree of independent mobility, and fragility), its attachments, and the extent of myocardial, endocardial, or pericardial invasion can offer clues to its nature. Calcified or fibrotic areas appear echobright, whereas cystic degeneration causes echolucent foci on echocardiography. Obstruction to caval or valvular inflow will cause increases in peak spectral Doppler velocities, often with a mosaic color Doppler pattern signifying turbulent flow. Mitral stenosis and MR caused by an LA myxoma prolapsing across the mitral valve is a classic example (**Fig. 14.79** and Video 14.51). The echocardiographic appearance of this entity is so pathognomonic that usually no further workup is required before surgical resection. Similarly, papillary fibroelastomas occur so characteristically on the aortic and mitral valves and are so commonly seen as filamentous or amorphous growths that shimmer, undulate, and prolapse, that further assessment may not be required before surgery. However, the smaller lesions may be difficult to differentiate from highly mobile Lambl's excrescences (**Fig. 14.80** and Video 14.52).

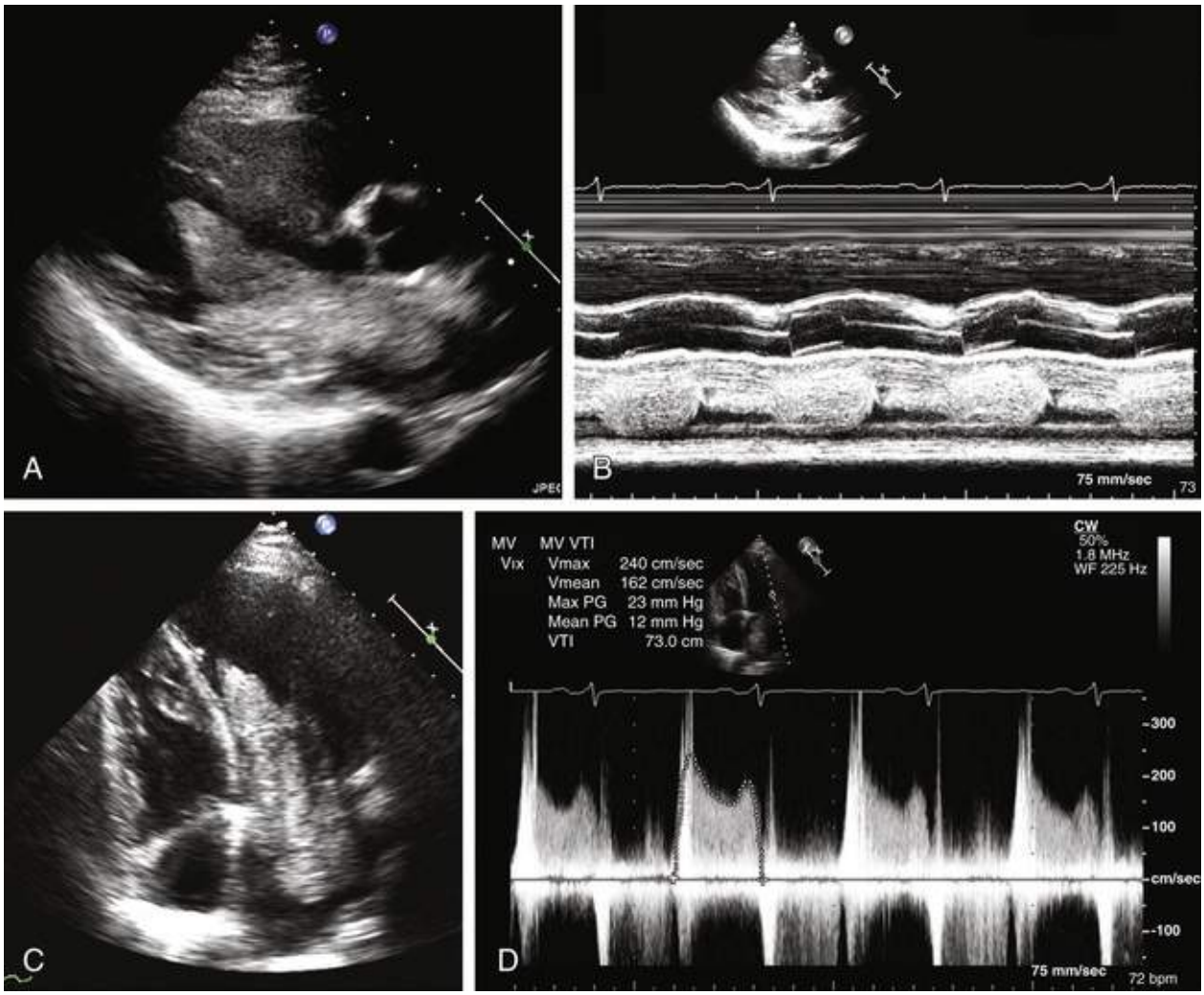


FIGURE 14.79 Left atrial myxoma. **A,** Parasternal long-axis view. **B,** M-mode view showing the mass prolapsing through the mitral valve into the left ventricle in diastole. **C,** Apical 4-chamber view. **D,** Transmitral gradients (mitral stenosis) as shown by CW Doppler, with peak and mean gradients of 23 and 12 mm Hg. (Modified from Wu J. Cardiac tumors and masses. In Stergiopoulos K, Brown DL, editors. Evidence-Based Cardiology Consult. New York: Springer Science + Business Media; 2014.)

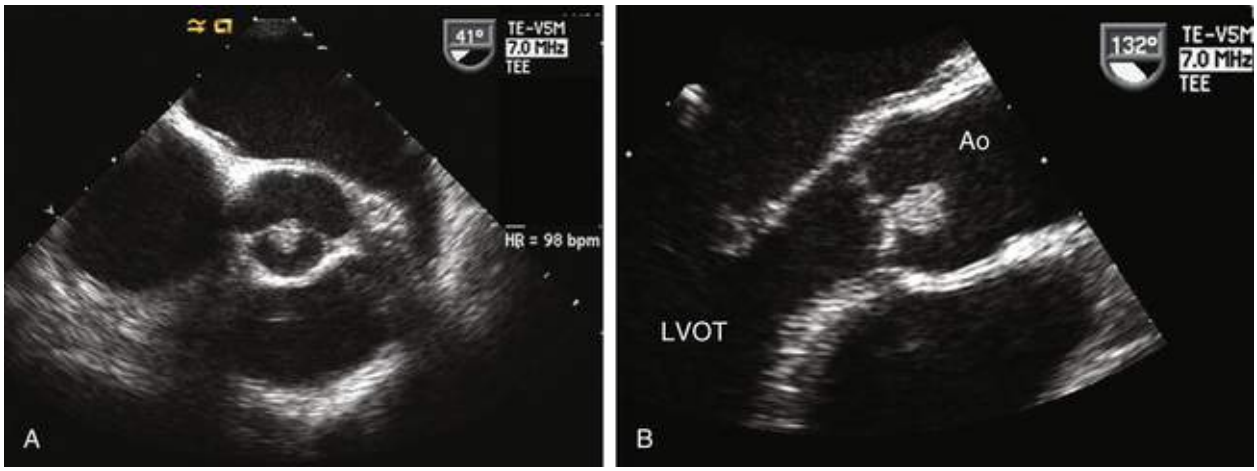


FIGURE 14.80 Papillary fibroelastoma on the aortic valve. **A,** TEE short-axis view showing the mass on the aortic aspect of the noncoronary cusp. **B,** TEE long-axis view. *Ao,* Aorta; *LVOT,* left ventricular outflow tact. (See Video 14.53.) (Modified from Wu J: Cardiac tumors and masses. *In* Stergiopoulos K, Brown DL [eds]: Evidence-Based Cardiology Consult. Springer Science + Business Media, Inc., 2014.)

In select patients, to refine the diagnostic possibilities, IV echocardiographic contrast material may be

used to determine whether a tumor hyperenhances. Hyperenhancement indicates that the mass is neovascularized and thus more likely to be malignant than a benign stromal tumor or thrombus.[23,24] One can also use 3D echocardiography to better illustrate the overall size, location, and attachments of intracavitary masses. Following diagnosis, echocardiography is a convenient way to monitor for recurrence, growth, or adverse sequelae after excision or treatment.

Common Primary Tumors

Myxoma accounts for more than 50% of primary cardiac tumors in adults, followed by papillary fibroelastomas and lipomas. Myxoma is a primary benign tumor believed to arise from mesenchymal (endocardial) cells. It typically arises in the left atrium (75% of cases, with the other 20% occurring in the right atrium and 5% in the ventricles) and is attached to the interatrial septum near the fossa ovalis by a stalklike pedicle. Attachments to the mitral valve have been described in a small percentage of cases. Grossly and on echocardiography, myxomas frequently appear as a gelatinous, compact mass, but there is a spectrum of morphologies. Smaller tumors tend to be more papillary or villous and are friable and thus prone to embolize. Larger myxomas have a smoother, globular, or grape cluster–like appearance and can grow large enough to fill the left atrium and cause both MS and a renowned tumor "plop" on auscultation as the mass prolapses into the left ventricle in diastole (**see Fig. 14.79** and Video 14.51). Approximately 7% of cases result from an autosomal dominant mutation and are part of the "Carney complex" syndrome, associated with skin lentiginosis and endocrine disorders.[87]

In adults, *papillary fibroelastomas* are the next most common cardiac benign tumors and the most common valvular tumor. Most (>80%) are found on left-sided (aortic or mitral) valves, although any valve may be affected, and 9% occur as multiple lesions. Pathologists usually classify fibroelastomas as an advanced or more florid form of *Lambl excrescences*, which are degenerative changes in the valves. Fibroelastomas tend to appear on either side of the aortic valve or on the atrial side of the mitral valve. Less frequently, they have also been known to arise on mitral chordae or papillary muscles. On echocardiography, papillary fibroelastomas appear round, oval, or irregular in shape and homogeneous in texture (**see Fig. 14.80** and Video 14.52). Almost half have a short stalk, which confers more mobility. Fibroelastomas are found most frequently in older adults as solitary lesions (<10% occur as multiple lesions), and shedding of the threadlike elements and associated clot accounts for their frequent manifestation as embolization (transient ischemic attack or stroke, angina, or sudden death).[86,87]

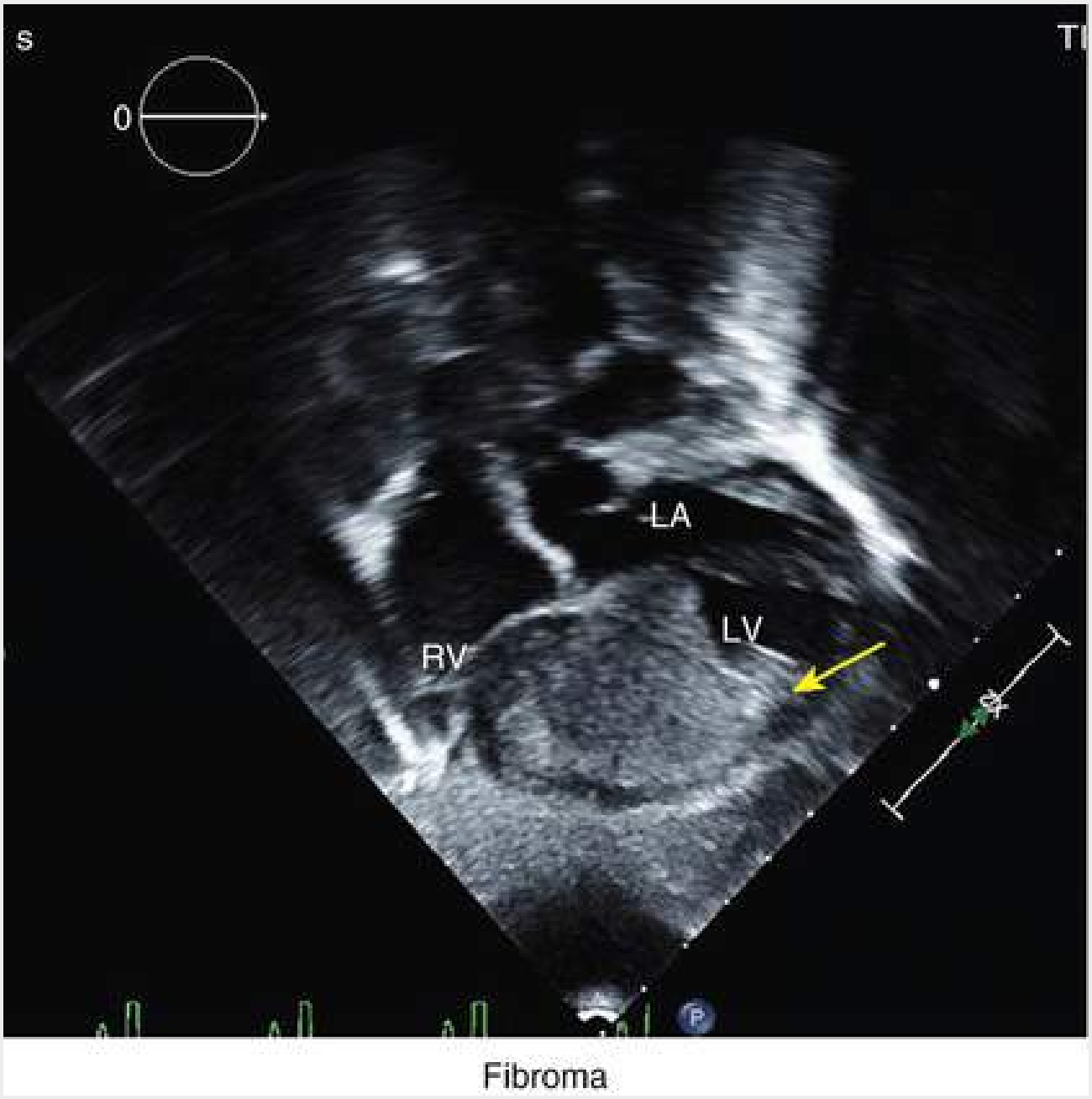
Lipomas are encapsulated collections of benign fat cells that tend to occur in subepicardial or subendocardial locations and may grow into the pericardial space. Although benign, usually discovered incidentally, and easily distinguished by CMR characteristics (**see Chapter 17**), these tumors tend to increase progressively and can cause mass effect, heart block, or tachyarrhythmias. On imaging, lipomas can be difficult to distinguish from *lipomatous hypertrophy of the interatrial septum*, which is a normal finding, particularly in elderly or obese patients (see later, Pseudoneoplasms). However, lipomatous hypertrophy is technically hyperplasia of epicardial adipocytes within the groove between the LA and RA walls and inferior pyramidal space, which spares the fossa ovalis and produces a characteristic dumbbell-shaped mass. Although lipomatous hypertrophy is unencapsulated and may reach an impressive thickness (1 to 2 cm or more), if the location is typical and no associated atrial arrhythmias or caval obstruction are present, no treatment is indicated.[88]

Pericardial cysts are benign fluid-filled tumors of the parietal pericardium and are thought to be a congenital abnormality.[89] They may be solitary or multilocular, and some have been documented to grow

to massive (>20 cm) size. They account for approximately 20% of benign primary cardiac masses (overall incidence of 1 in 10,000) and usually occur near the cardiophrenic borders (right more often than the left). This gives the appearance of cardiomegaly on chest radiographs and forms an encapsulated echolucent area on echocardiography. Of known cases, 75% are asymptomatic. If large, however, pericardial cysts may cause atypical chest pain, breathlessness, AF, persistent cough, or compressive problems such as RVOT obstruction. Rare cases of cardiac tamponade secondary to intrapericardial rupture and hemorrhage have been reported.

Rhabdomyomas are the most common primary cardiac neoplasm in children and are usually found during the first year of life. They tend to be solid intramyocardial lesions containing striated myocyte fibers, and 90% occur as multiple tumors. Although most patients are asymptomatic, larger tumors have been known to cause arrhythmias, LVOT obstruction, and heart failure. Half the cases are associated with tuberous sclerosis. Most regress spontaneously, and overall these tumors are rare in young adults.[86,87]

Fibromas are the second most common pediatric cardiac neoplasm. They arise in the ventricular myocardial layer, are five times more common in the left ventricle, and consist of solid tumors containing fibroblasts. These tumors often occur in the LV septum or free wall, where they can become quite large and develop calcific foci (**eFig. 14.28**). Unlike rhabdomyomas, fibromas do not spontaneously regress and may grow to a size that obliterates the heart chamber, interferes with valvular function, or causes arrhythmia and necessitates surgical resection.[88]



EFIGURE 14.28 Fibroma. Transthoracic pediatric echocardiogram five-chamber view showing a large (5-cm) fibroma (*arrow*) arising in the distal left ventricle and exerting mass effect on the right ventricle.

Secondary Tumors

Secondary cardiac tumors outnumber primary ones by 20 to 40 to 1. In principle, any malignant tumor may metastasize to the heart. The most common site of involvement is the pericardium, with invasion of the myocardium seen next in frequency.[86]

Pericardial involvement in cancers may arise from direct invasion of tumor from adjacent lung or mediastinum (e.g., mesothelioma, lymphoma), or there may be more diffuse involvement and effusive/constrictive changes. The most frequent sources of malignant pericardial disease are lung cancer, lymphoma/leukemia, and breast cancer because of their relatively high prevalence,[86] with some worldwide variability. Of all malignancies, *melanoma* has the highest predilection to metastasize to the heart and pericardium. Cardiac metastases from any source typically are small and multiple or cause effusion or diffuse thickening of the pericardium. However, bulky large solitary tumor lesions may also occur (**see Fig. 14.69**).

Secondary tumors may also invade the heart by direct extension[86]: renal cell carcinoma, Wilms tumor, uterine leiomyosarcoma, hepatomas, and adrenal tumors can be detected extending into the right atrium via the IVC on echocardiography. Bronchogenic carcinomas can invade the left atrium through the pulmonary veins. Lymphatic and hematogenous routes are also pathways to the heart. The location and mass effect of the metastases, rather than type of primary, tend to determine the patient's symptomatology.

Alternative Diagnoses

Pseudoneoplasms

With the abundance of cardiac imaging being performed by various modalities, it is inevitable that normal or slight variants of normal structures, degenerative or acquired lesions, and noncancerous masses may be detected. The onus is on the cardiologist or radiologist to distinguish between the following entities (listed in Table 14.11) and a true neoplasm.

Intracardiac Thrombus

Masses such as thrombi and vegetations have obvious clinical implications. On echocardiography, formed thrombi appear relatively homogeneous in echodensity and have a gel-like or deformable appearance (**Fig. 14.81B**). Old thrombi may have more echobright regions and a compact immobile or laminated appearance (**see Fig. 14.31A**). Clues that a mass is actually a thrombus include residence in areas of stasis (e.g., tip of LA appendage or within LV aneurysm), “wisps” of spontaneous echocardiographic contrast associated with the surface (**Fig. 14.81A** and Video 14.53), and associated predisposing cardiac conditions, including mitral stenosis, prosthetic valves, cardiomyopathy, aneurysms of any chamber, or AF (Video 14.54). Ropelike vacillating masses in the right side of the heart often represent thromboemboli from the deep venous system (**see Fig. 14.75, left**, and Video 14.47), in which case the IVC, as well as the pulmonary arteries, should be inspected for portions of the same clot. With anticoagulation, intracardiac thrombi frequently regress or remain stable.

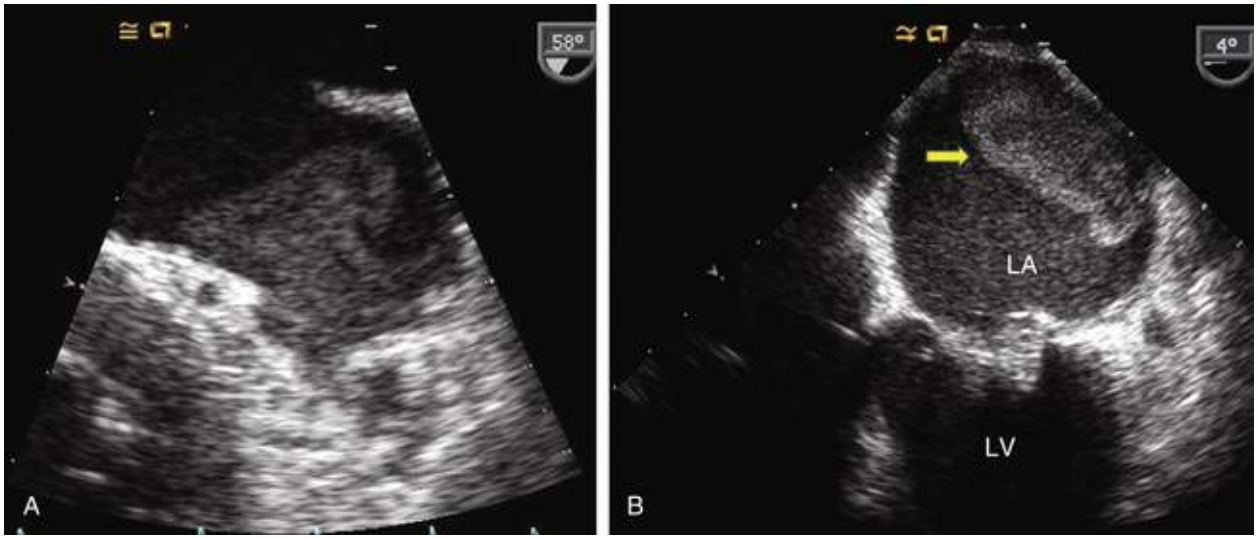


FIGURE 14.81 Spontaneous echocardiographic contrast and left atrial appendage thrombus. **A**, Zoomed TEE view of spontaneous echocardiographic contrast in the left atrial appendage in a patient with a bileaflet mechanical mitral prosthesis who was subtherapeutic with warfarin treatment. **B,** TEE view of organized thrombus (*arrow*) in the left atrial appendage in a patient following mitral annuloplasty. *LA,* Left atrium; *LV,* left ventricle. (See Videos 14.53 and 14.54.)

The presence of LV aneurysms or severe dilated cardiomyopathy should always prompt vigilance for thrombi. Conversely, it would be highly unusual for a thrombus to form in an area with normal wall motion. Use of a high-frequency (7 to 8 MHz) probe to focus on the cardiac apex, angling it at unconventional views and sweeping across the field as needed, can better define thrombus versus myocardium and trabeculations and will also decrease noise and reverberation artifact. Ultrasound contrast enhancement is often the key when endocardial border definition is poor.

With its higher resolution and proximity to the base of the heart, TEE plays a major role in ruling out intracardiac thrombi (or other sources of emboli, such as atheroma or vegetation) when no identifiable source is found after imaging the head and neck arteries and the heart by TTE. An embolic stroke or unusually high transvalvular gradients in a patient with a mechanical (or even bioprosthetic) valve should prompt referral for TEE, contingent on the assumption that the findings on TTE were nondiagnostic and that they would alter management. TEE is also frequently used to facilitate the decision to anticoagulate, cardiovert, or perform radiofrequency ablation of a tachyarrhythmia, particularly in high-risk patients (i.e., those with the predisposing cardiac conditions mentioned earlier or those found to be underanticoagulated before a planned procedure). TEE should be performed before percutaneous mitral valvuloplasty for rheumatic mitral stenosis to rule out LA thrombus (as well as to better define the mitral anatomy and degree of regurgitation) and thus avert potentially catastrophic embolic complications.[17-19,76]

Vegetations and Pannus.

Vegetations tend to arise on the upstream side of valves or at areas of flow turbulence. Valves with degenerative changes, prosthetic valves, and indwelling catheters or pacemaker/defibrillator wires are well-recognized nidi for infection. Thick, immobile, heaped-up irregular masses affixed to the annuli of older prosthetic valves may represent pannus (fibrovascular granulation tissue) (**see Fig. 14.59**). For both thrombi and vegetations, the larger and/or highly mobile masses that threaten the pulmonary, systemic, or cerebral circulation with embolization or cause severe valvular dysfunction may compel emergency surgical resection (see earlier, Infective Endocarditis).

Normal Variants and Artifacts.

Normal or mild variants of normal structures have also been mistaken for neoplasms on echocardiography. The most common errors are mistaking lipomatous hypertrophy, upper septal hypertrophy, a redundant mitral chorda or prominent/multilobed papillary muscle, interatrial septal aneurysm, or pericardial fat for a mass. Degenerative changes such as valvular calcification or external compression of chambers of the heart by adjacent structures (e.g., from esophageal hernia indenting posterior wall of left atrium) can give the appearance of a large mass when viewed in only one plane. Knowledge of the typical appearance of these abnormalities, use of echocardiographic contrast, and either careful tilting and sweeping of the transducer plane or use of 3D echocardiography to track the boundaries and attachments of these entities can reveal their true nature.

Adult Congenital Heart Disease

Echocardiography plays a critical role in the evaluation and management of both children and adults with congenital heart disease (**see Chapter 75**). Consequently, this section focuses on the role of echocardiography in diagnosing common shunts (ASDs and VSDs), as well as transposition of the great arteries and tetralogy of Fallot, complex lesions that may be seen by cardiologists caring for adults. The

use of echocardiography for the selection and implantation of ASD closure devices is also covered.

Atrial Septal Defect

ASDs account for approximately 10% of all congenital heart disease and 20% to 40% of congenital heart disease occurring in adulthood. The initial diagnosis of ASD is often made at echocardiography for nonspecific symptoms or for a heart murmur in an asymptomatic individual.

General Imaging Principles.

Fig. 14.82 provides the anatomic classification of ASDs. Although secundum defects are often isolated anomalies, ASDs of other types are frequently associated with other structural anomalies. Multiple ASDs may be encountered in the same patient. Secundum and primum ASDs can generally be diagnosed with 2D TTE, but TEE is typically required to detect sinus venosus and coronary sinus defects. On TTE, although parasternal and apical views are useful, the subcostal view is particularly important because it optimizes the Doppler detection of shunts and minimizes the chance that normal thinning of the fossa will be mistaken for a secundum defect. In the absence of significant pulmonary hypertension, ASD flow is typically left to right, reflecting normal intracardiac pressures. However, agitated saline injections may demonstrate the transient right-to-left shunts that can occur in patients with ASDs or show negative contrast enhancement ("ghosting") when the shunt flow from the left atrium meets the contrast-enhanced RA blood pool.

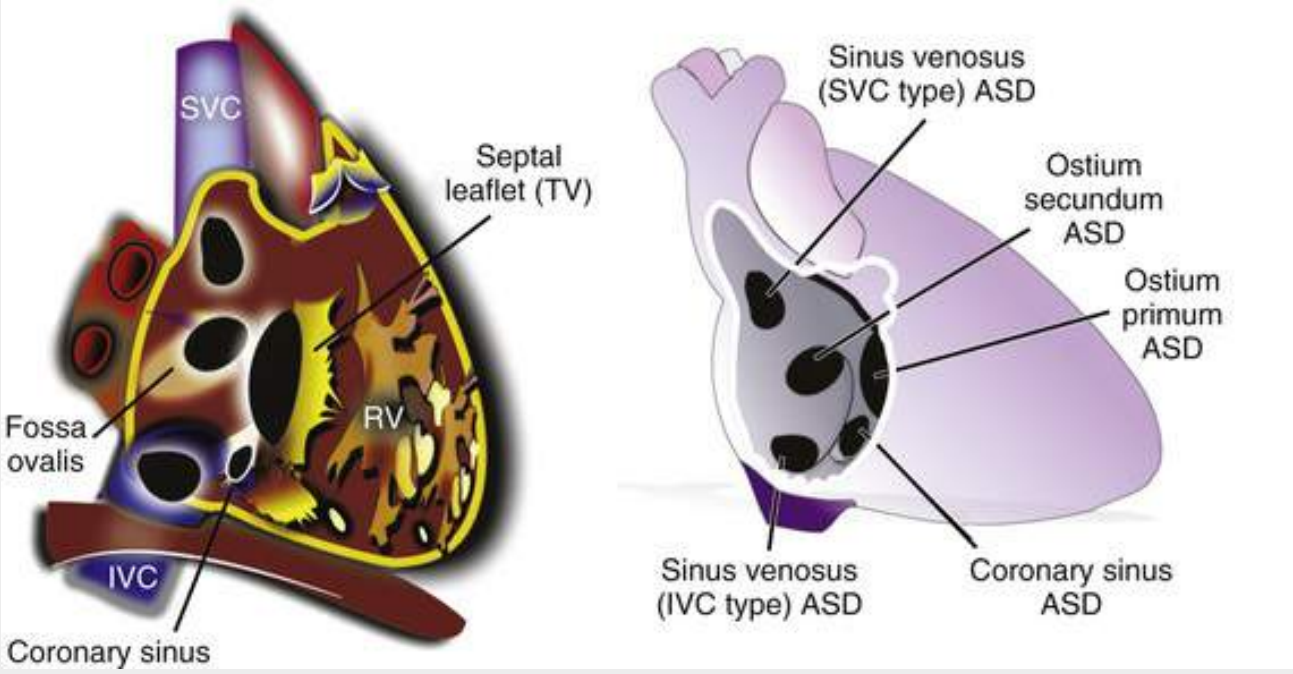


FIGURE 14.82 Classification of atrial septal defects (ASDs). *IVC, SVC,* Inferior, superior vena cava; *RV,* right ventricle; *TV,* tricuspid valve.

Regardless of location, hemodynamically significant ASDs will be associated with evidence of RV volume overload, characterized by RV enlargement and diastolic flattening of the interventricular septum. Pulmonary hypertension, which may complicate large defects, will result in flattening that persists through systole. This 2D appearance of RV volume overload and right-sided heart enlargement is

considered evidence of a hemodynamically significant shunt ($Q_p/Q_s \geq 1.5 : 1$). Q_p/Q_s, or the ratio of RV output (RV SV) to LV output (LV SV), may be calculated directly by applying the principles of the continuity equation:

$$Q_p/Q_s = (\pi[D_{RVOT}/2]^2 \times VTI_{RVOT})/[\pi(D_{LVOT}/2]^2 \times VTI_{LVOT})$$

where D indicates the diameter of the RVOT and LVOT, respectively (**Fig. 14.83**). Additionally, PVR can be calculated in Wood units (see earlier, Pulmonary Hypertension); normal PVR is 0.5 to 1.5 Wood units.[84]

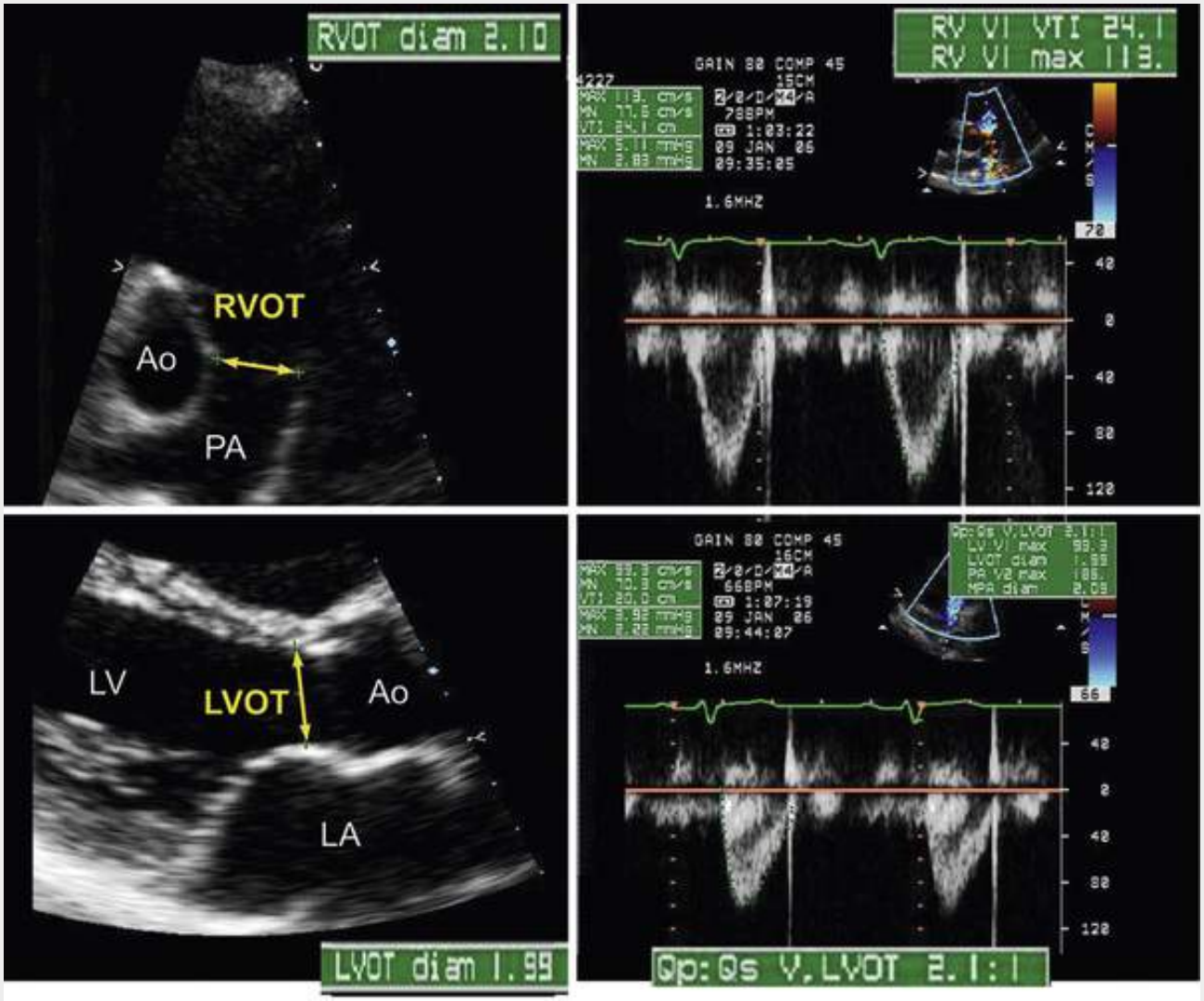


FIGURE 14.83 Q_p/Q_s calculation. For ASDs, Q_p is equivalent to RV stroke volume (SV), which equals $CSA_{RVOT} \times VTI_{RVOT}$, in which $CSA_{RVOT} = \pi(D/2)^2$. Q_s is equivalent to LV SV calculated as $CSA_{LVOT} \times VTI_{LVOT}$, where $CSA_{LVOT} = \pi(D/2)^2$. The **upper and lower panels** illustrate the derivation of RV and LV SV, respectively, from echo data. *Ao,* Aorta; *LA,* left atrium; *PA,* pulmonary artery.

If clinically appropriate, secundum ASDs may be potentially closed by transcatheter techniques. The other types of ASD require surgical closure.

Secundum Atrial Septal Defect

Secundum ASDs account for 75% of all ASDs and 30% to 40% of congenital disease seen in patients older than 40 (**see Chapter 75**). **Figs. 14.84 and 14.85** show the 2D TTE and TEE echocardiographic appearance of these defects. They are the only ASDs that are eligible for catheter-based closure. In planning transcatheter closure, TEE is used to (1) ensure that only one (or more) secundum ASD is present, and not other interatrial shunts that cannot be closed percutaneously, (2) precisely size the defect, and (3) ensure that there is enough adjacent tissue rim to anchor the device. 3D TEE is especially advantageous for displaying en face displays of the septum before and during implantation[90,91] (**eFig. 14.29**). Of the two devices currently approved by the U.S. Food and Drug Administration, the Amplatzer may be used for defects up to 35 mm, whereas the Helex device may be used only for defects up to 17 to 18 mm, although it may be placed successfully in patients with deficient anterior rims.

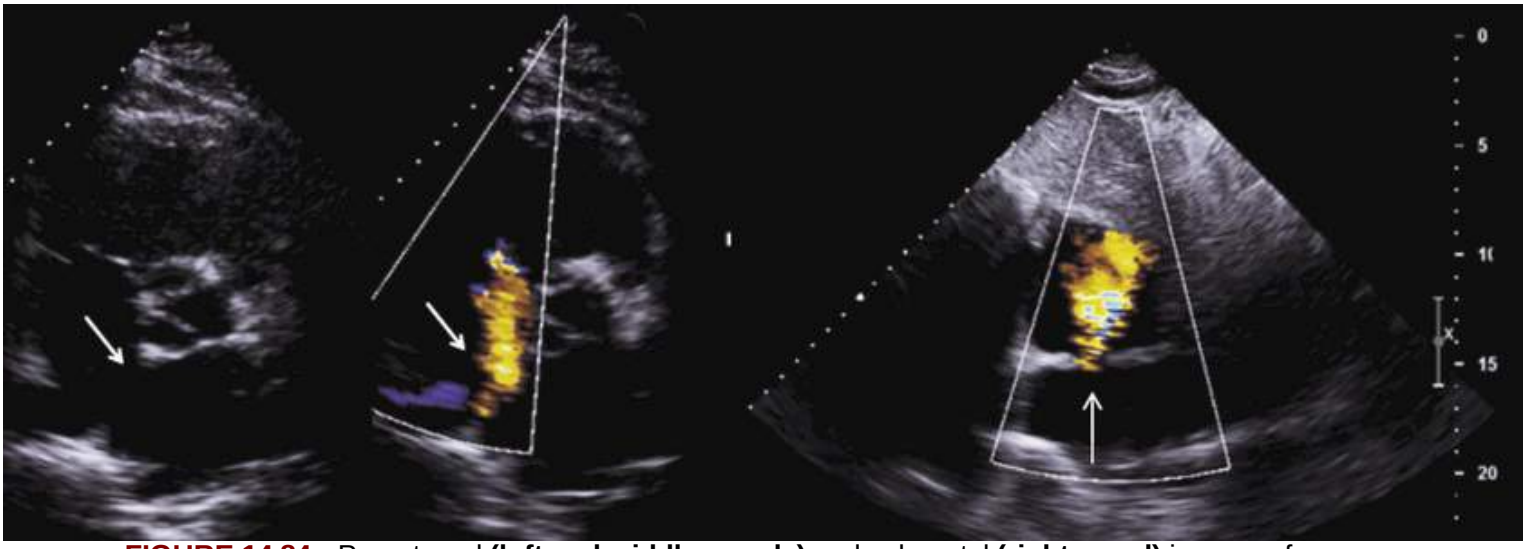


FIGURE 14.84 Parasternal **(left and middle panels)** and subcostal **(right panel)** images of a secundum ASD and its associated left-to-right shunt (*arrows*).

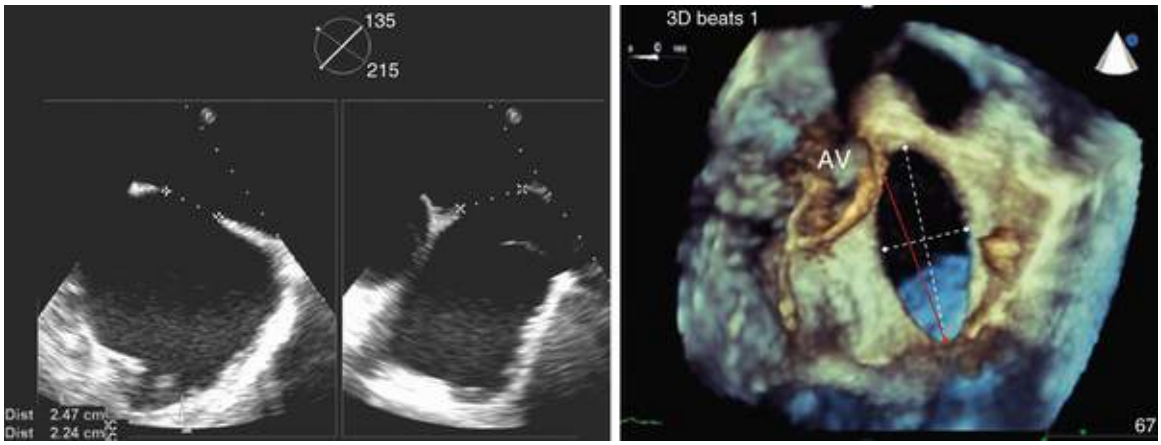
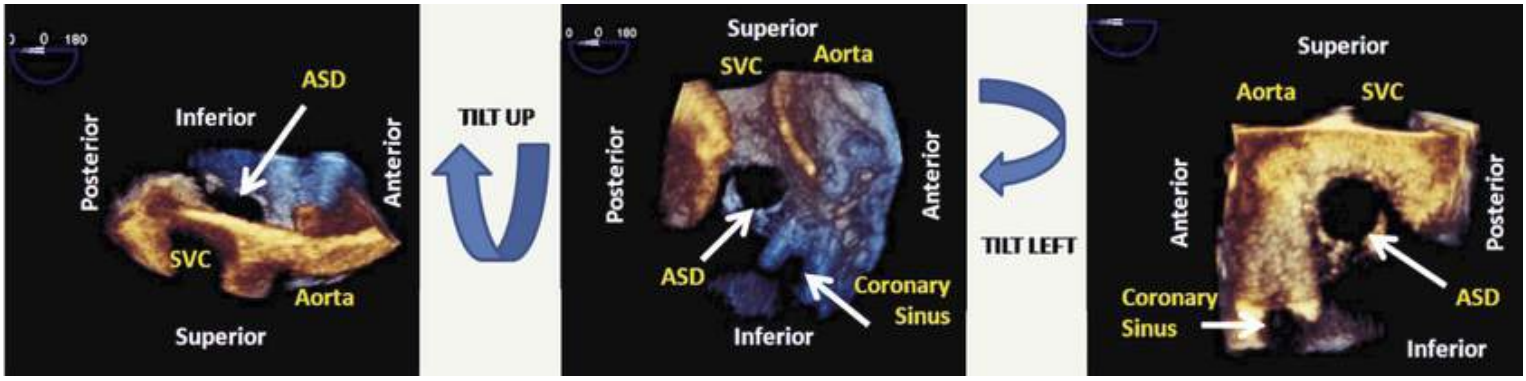


FIGURE 14.85 Biplane two- and three-dimensional TEE measurement of ASD dimensions. **Left**, Biplane 2D TEE measurement of ASD dimensions. The 0 to 45-degree midesophageal view can be used to measure the anterior (toward aorta) and posterior (toward pulmonary veins) rims, whereas the 90- to 120-degree view images the superior (toward SVC) and inferior (toward IVC) rims. **Right**, Large secundum ASD viewed by 3D TEE from the left atrial perspective. Note that the 2D TEE–measured diameter (*red line*) is typically smaller than that measured by 3D TEE (*white dotted lines*). Also note that there is a deficient anterior rim, i.e., no separation between the defect and the aortic valve (*AV*).



EFIGURE 14.29 Three-dimensional TEE imaging of atrial septal defects (ASDs). The TUPLE maneuver provides an easy method to image the right and left sides of the interatrial septum. The initial image is a zoomed 3D volume set acquired from a midesophageal zero-degree window. (From Saric M, Perk G, Purgess JR, Kronzon I. Imaging atrial septal defects by real-time three-dimensional transesophageal echocardiography: step-by-step approach. J. Am Soc Echocardiogr 2010;23:1128.)

With 2D TEE, orthogonal diameters are recorded during ventricular systole, and a screen for presence of fenestrations is performed. 3D echocardiography allows en face displays of the entire defect in relation to the surrounding landmarks; measurements can be performed online with less risk of undersizing the defect compared to standard 2D imaging (**Fig. 14.85**). Acceptable rim margins are at least 3 mm for the anterior rim and 5 mm for all other rims. Deficiency of the anterior rim is the most common[92,93] (**Fig. 14.85, right, and Fig. 14.86**).

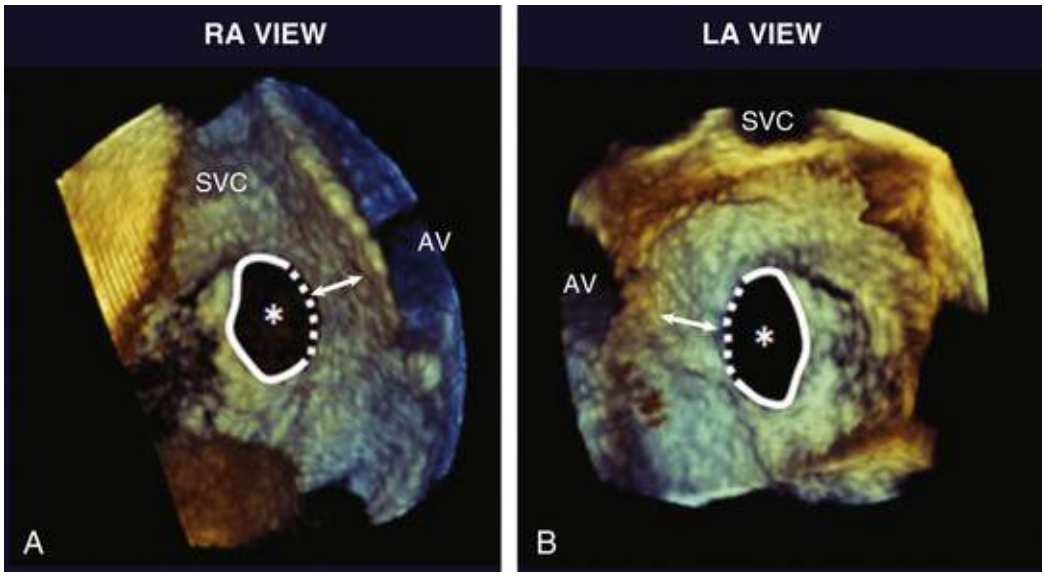


FIGURE 14.86 Assessment of ASD rims with 3D TEE in the **A,** right atrial (RA), and **B,** left atrial (LA), views. The anterior rim is represented as the distance between the *dotted line* and the aorta (*arrow*). *AV,* Aortic valve. (From Saric M et al. Imaging atrial septal defects by real-time three-dimensional transesophageal echocardiography: step-by-step approach. J Am Soc Echocardiogr 2010;23:1128.)

Device closure is guided by either TEE or intracardiac echocardiography (ICE). In sequential order, the key steps are placement of the guidewire across the defect (avoiding any smaller secondary fenestrations), balloon sizing of the defect, occluder placement followed by a tug to ensure optimal seating, assessment for residual shunt by color Doppler, and a survey for any complications such as pericardial effusion. Small residual shunts may be present immediately following deployment but often resolve after endothelialization of the device. **Fig. 14.87** illustrates the 2D and 3D TEE appearance of a successfully deployed Amplatzer device.

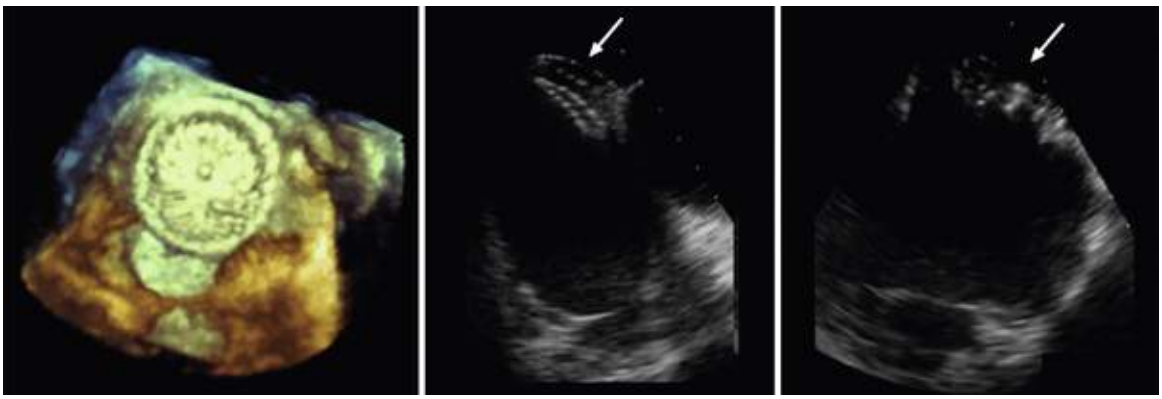


FIGURE 14.87 Postimplantation appearance of an Amplatzer ASD closure device. **Left panel,** 3D left atrial perspective. **Middle** and **right panels,** Orthogonal 2D TEE views. The *arrow* points to the left atrial disc.

A *patent foramen ovale* (PFO) is a related condition characterized by incomplete fusion of the septum primum and septum secundum following birth. It may be detected by saline contrast demonstration of a right-to-left interatrial shunt, typically with maneuvers that raise RA pressure (cough, Valsalva or Müller maneuver). PFO is a common condition that occurs in 20% to 35% of the normal population. It is also frequently associated with aneurysm of the interatrial septum. Echocardiography with saline contrast injection is often used to elucidate whether a PFO is present and could allow a paradoxical embolism to occur in patients without a clear source of left-sided embolic events. Video 14.55 shows both a PFO

and an interatrial septal aneurysm. Evaluation for a PFO is one reason for performing TTE and TEE in patients with transient ischemic attacks, embolic stroke, or other embolic events.[80]

Primum Atrial Septal Defect

Primum ASDs account for 15% to 20% of ASDs and occur as part of the spectrum of atrioventricular (AV) canal defects. They may occur as isolated defects (partial AV canal defect) or may be accompanied by inlet VSDs (complete AV canal defect). Partial AV canal defects typically have an associated cleft mitral valve. In complete AV canal defects there is a common single AV valve. AV canal defects are the most common congenital heart abnormality in Down syndrome. Primum defects can be seen on apical or subcostal views if posterior angulation is ensured to demonstrate the inlet portion of the ventricular septum (**Fig. 14.88**). These defects must be closed surgically.

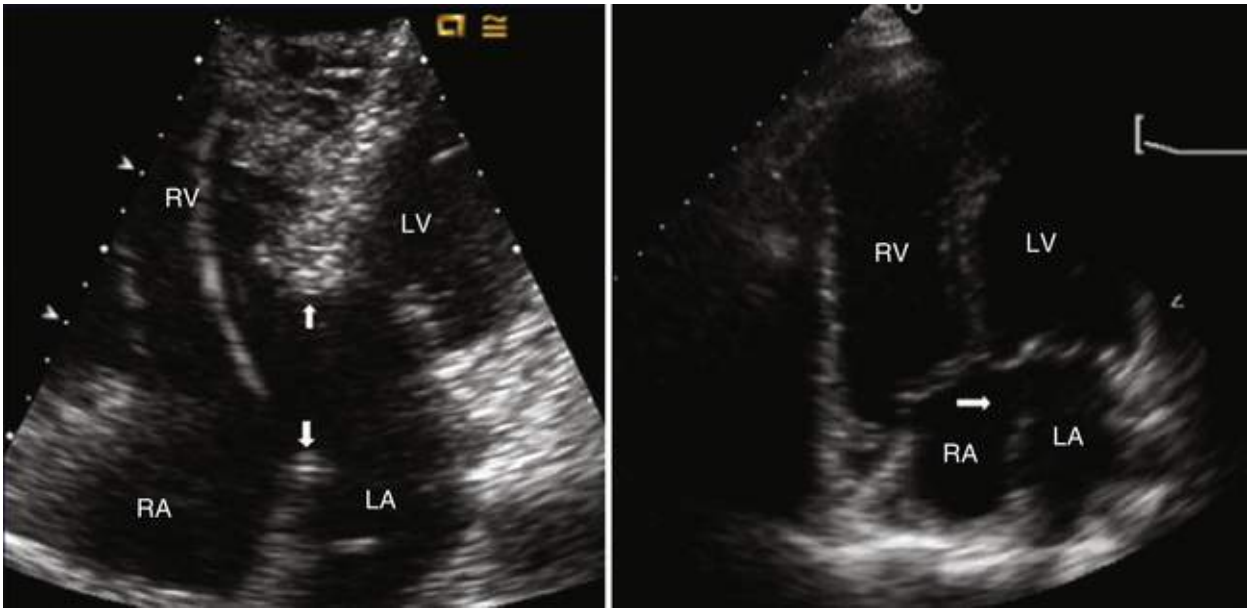


FIGURE 14.88 Apical four-chamber views showing complete **(left)** and partial **(right)** atrioventricular canal defects. In the **left panel,** *arrows* outline a large defect with atrial and ventricular components. In the **right panel** there is a primum ASD (*arrow*) with an intact ventricular septum. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

Sinus Venosus Atrial Septal Defect

Sinus venosus ASDs account for 2% to 10% of ASDs and occur in two locations. The SVC type creates a confluence among the left atrium, right atrium, and SVC as it enters the right atrium. It is frequently accompanied by partial anomalous drainage of the right upper pulmonary vein, which is created when this vein enters the confluence. Partial anomalous drainage contributes to the left-to-right shunt. IVC-type defects are less common and create a confluence among the left atrium, right atrium, and IVC as it enters the right atrium. They may be accompanied by partial anomalous drainage of the right lower pulmonary vein. These defects should be suspected in patients with markers of RV volume overload without apparent cause. Typically, TEE is required to make the diagnosis, although SVC-type defects may be demonstrated with subcostal TTE. **Fig. 14.89** shows the TEE appearance of a sinus venosus ASD with partial anomalous pulmonary venous drainage. Sinus venosus ASDs must be closed surgically.

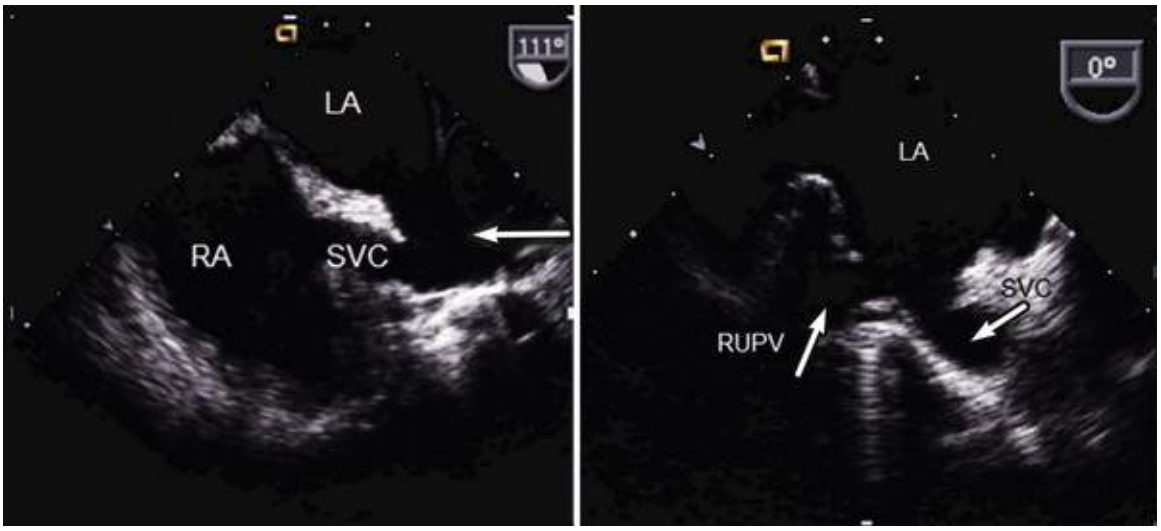


FIGURE 14.89 TEE images of a sinus venosus ASD (SVC type) with anomalous drainage of the right upper pulmonary vein (*RUPV*). A confluence is created between the superior vena cava (*SVC*), RUPV, and adjoining atria. *LA,* Left atrium; *RA,* right atrium.

Coronary Sinus Atrial Septal Defect

Coronary sinus ASDs are rare and may be associated with fenestrations or complete unroofing of the coronary sinus into the left atrium. They are frequently associated with a persistent left SVC, a more frequent finding (0.3% of the general population) and the most common cause of a dilated coronary sinus in general. The diagnosis is facilitated with TEE.

Ventricular Septal Defect

There are a number of classifications for VSDs. **Fig. 14.90** shows one anatomic classification, and **Fig. 14.91** outlines the division of the interventricular septum into its membranous, inlet, outlet, and trabecular portions along with the echocardiographic views that may be used to identify defects in each of these locations. VSDs vary in size and are considered to be small (restrictive) when less than half the size of the aortic root and when the LV-RV pressure gradient is greater than 64 mm Hg. Moderately restrictive VSDs are approximately half the size of the root, with gradients of approximately 36 mm Hg. With larger nonrestrictive defects, LV and RV systolic pressures are equalized. These latter defects are those that most often result in irreversible pulmonary vascular changes (Eisenmenger syndrome). Echocardiography may be used to size defects and LV-RV gradients. Shunting may be assessed by both color flow mapping and Q_p/Q_s calculated with the continuity equation. Although chamber size may be normal in the setting of small defects, LV and LA enlargement is expected in those that are hemodynamically significant.

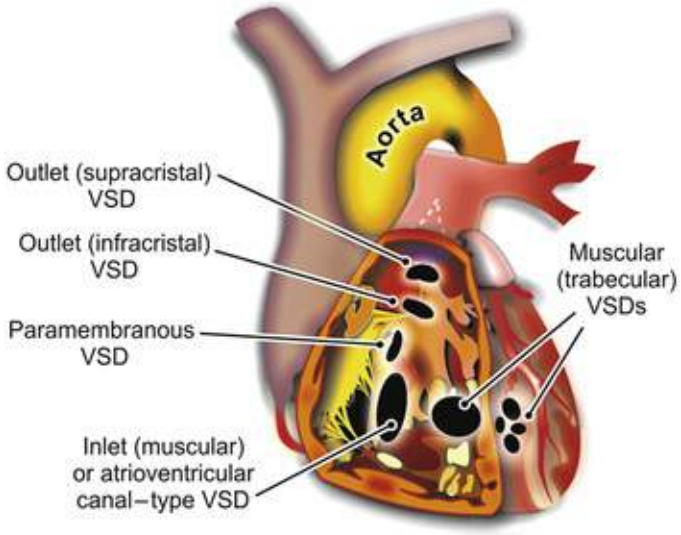


FIGURE 14.90 Anatomic classification system for ventricular septal defects (VSDs).

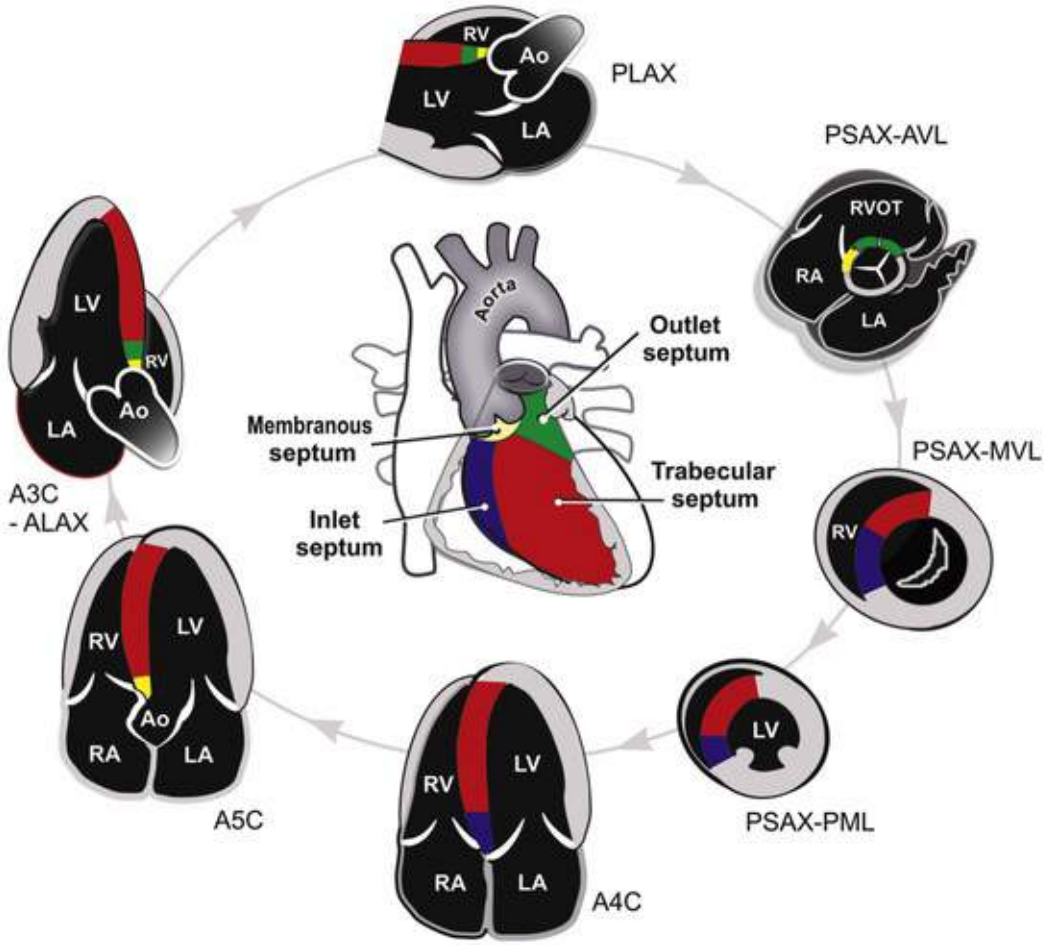


FIGURE 14.91 Echocardiographic views used in imaging the interventricular septum. *A3C,* Apical three-chamber view; *Ao,* aorta; *AVL,* aortic valve level; *LA,* left atrium; *LV,* left ventricle; *MVL,* mitral valve leaflet; *PLAX,* parasternal long-axis view; *PML,* papillary muscle level; *RA,* right atrium; *RV,* right ventricle.
(Modified from Bulwer BE, Rivero JM, editors. Echocardiography Pocket Guide: The Transthoracic Examination. Burlington, Mass: Jones & Bartlett Learning; 2011, 2013, p 142. Reprinted with permission.)

Membranous (Paramembranous) and Outlet Ventricular Septal Defects

Eighty percent of VSDs involve the membranous septum. They vary in size, but even small defects can

generally be detected on the parasternal long-axis view, as revealed by a high-velocity color Doppler jet. Membranous defects may be associated with wind-sock aneurysms that reflect varying degrees of spontaneous closure (**Fig. 14.92**). Even though the jets of membranous and outlet defects appear similar on the parasternal long-axis view, these defects may be distinguished from one another on short-axis views at the level of the great vessels. Membranous defects will be directed toward the septal leaflet of the tricuspid valve (10 to 11 o'clock position on the short-axis clock face), whereas outlet defects will be associated with jets that are directed toward the pulmonic valve (**Fig. 14.93**). Either defect may be accompanied by aortic cusp prolapse and consequent AR.

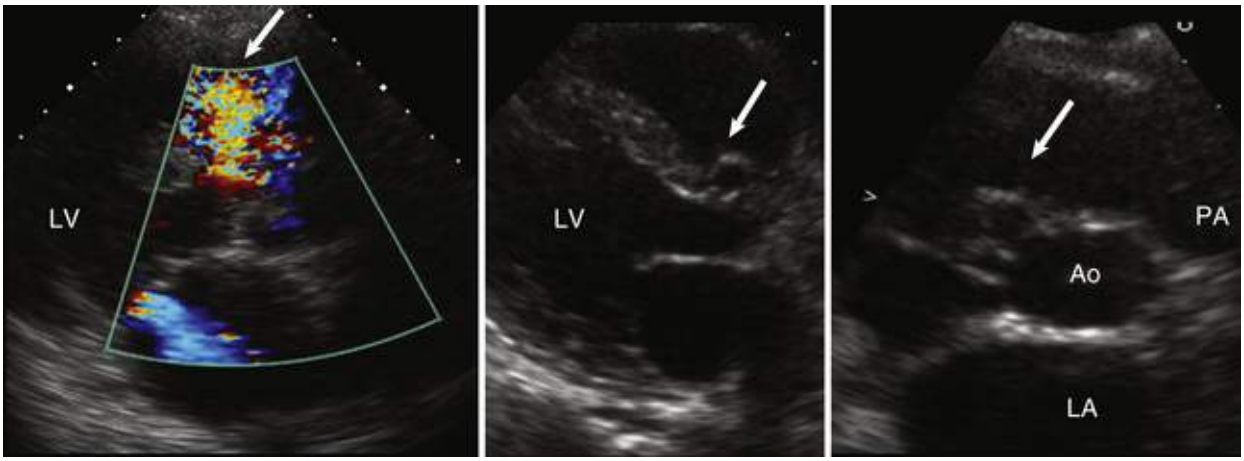


FIGURE 14.92 Parasternal views of a membranous VSD partially closed with a wind-sock aneurysm. **Left,** A systolic left-to-right jet is identified. **Middle,** With slight angulation, a wind-sock aneurysm representing partial spontaneous closure of the defect is identified. *LV,* Left ventricle. **Right,** In the short-axis view, the wind sock helps localize the VSD to the 11 o'clock position, as opposed to outlet defects, which are seen in the 12 to 2 o'clock position (compare with **Fig. 14.93**). *Ao,* Aorta; *LA,* left atrium; *PA,* pulmonary artery.

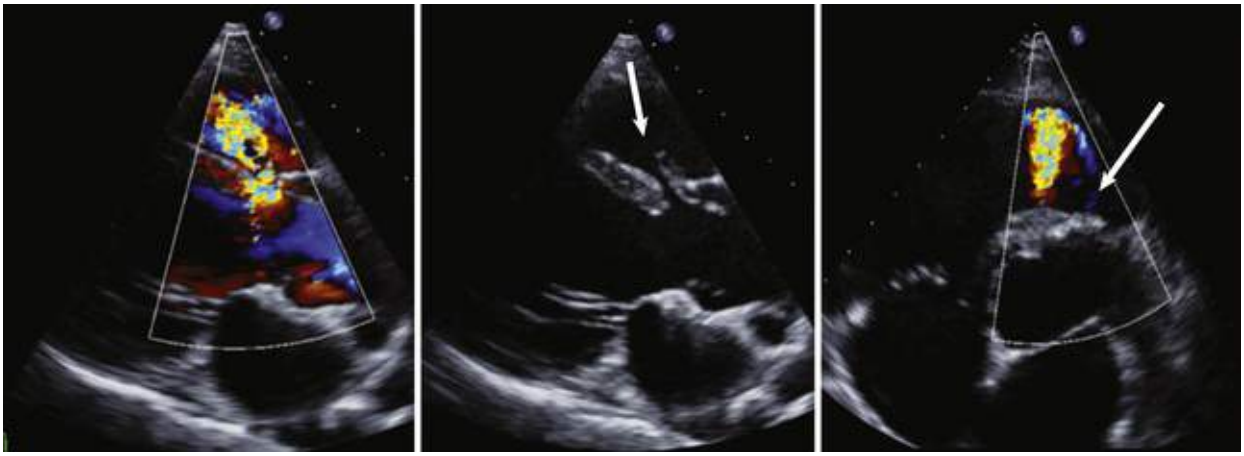


FIGURE 14.93 Parasternal images illustrating an outlet VSD. In the parasternal long-axis view **(left** and **middle panels)**, the VSD jet and the defect (*arrow*) may be indistinguishable from those of a membranous defect. However, in the short axis **(right panel)**, the jet is seen at the 12 o'clock position immediately next to the pulmonic valve (*arrow*). (Compare with **Fig. 14.92**.)

Inlet Ventricular Septal Defects

Inlet defects have been addressed in the preceding discussion of complete AV canal defects. Although

often easily detected (**see Fig. 14.88**, left panel), inlet VSDs may be partially closed by adjacent AV valve tissue. In such situations, nonstandard views and TEE may be required to detect the ventricular component of the AV canal defect.

Muscular Ventricular Septal Defects

Muscular defects vary considerably in size and location and may be multiple. When small and serpiginous, they may easily be missed with conventional echocardiographic views. Because these small defects are associated with loud murmurs with or without a thrill, a detailed evaluation using nonstandard views, such as sliding/tilting the transducer systematically down the barrel of the left ventricle with color Doppler sweeps, is warranted in any patient with these clinical manifestations (**Fig. 14.94**).

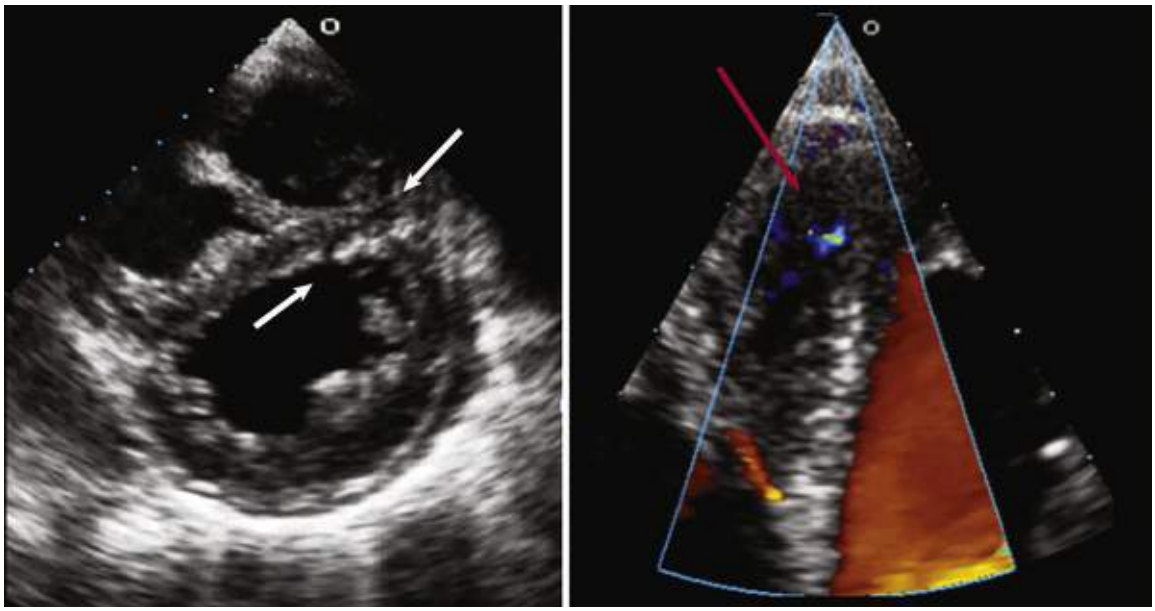
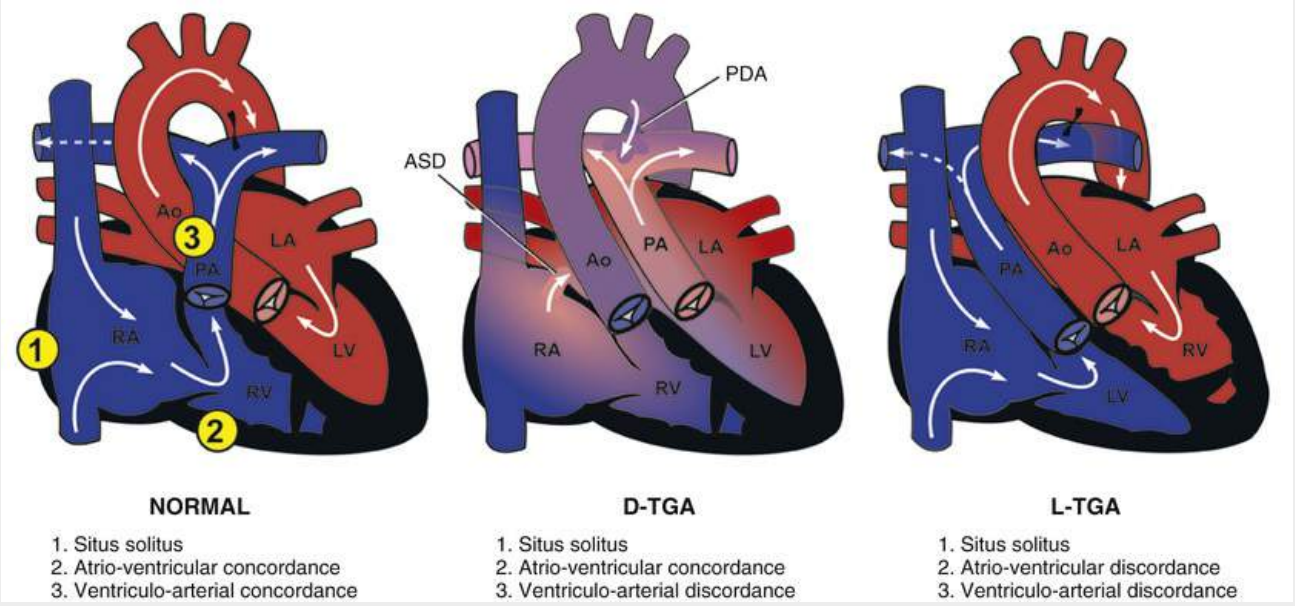


FIGURE 14.94 Parasternal short-axis **(left)** and off-axis apical **(right)** views demonstrating a serpiginous muscular VSD. The *white arrows* point to LV and RV entry points. The *red arrow* identifies a small left-to-right shunt.

Transposition of the Great Arteries

Transposition of the great arteries (TGA) arises from failure of the aorticopulmonary septum to take its normal spiraling course (**see Chapter 75**). In dextro (D)–TGA the aorta lies anterior and to the right of the pulmonary artery and arises from the right ventricle, with the pulmonary artery arising from the left ventricle (**eFig. 14.30, middle panel**). D-TGA accounts for 5% to 7% of all congenital heart disease and, in the absence of shunting (VSD, ASD, patent ductus arteriosus) or surgery, D-TGA would be fatal. The most common associated anomalies are VSD (30% to 45%), pulmonary outflow tract obstruction (25%), and coarctation. Patients seen by cardiologists treating adults with congenital heart disease will have undergone corrective surgery consisting of either an atrial baffle/switch (Mustard or Senning) procedure in the past, or more recently an arterial switch procedure.[92]



EFIGURE 14.30 Schematic representation of blood flow through hearts with D-transposition of the great arteries (TGA) and L-TGA.

With baffle procedures the systemic venous baffle directs deoxygenated blood across the mitral valve into the left ventricle, from which it is ejected into the pulmonary artery. The pulmonary venous baffle directs oxygenated blood returning from the lungs to the tricuspid valve and into the right ventricle, from which it is pumped into the aorta. The end result is a "physiologic" circulation. Although short- and mid-term results are good, the right ventricle ultimately fails because of its inability to sustain its role as the systemic ventricle. Other complications detectable by echocardiography include baffle obstruction, baffle leaks, and pulmonary hypertension (the cause of which is incompletely understood).

The echocardiographic hallmark of transposition is parallel orientation of the great vessels, best appreciated on parasternal long-axis or apical views (**Fig. 14.95**). The diagnosis can be confirmed by demonstrating that the posterior great vessel (the pulmonary artery) bifurcates and the anterior aorta gives off arch vessels. In patients with D-TGA who have undergone atrial switch surgery, the baffles can be traced as they crisscross the atrium, with color flow mapping and spectral Doppler identifying areas of obstruction and baffle leak. The hypertrophied right ventricle has the rounded contour typically associated with the left ventricle, whereas the left ventricle is crescentic, a result of reversal of the normal septal curvature because of systemic RV pressures. RV systolic function may be reduced with accompanying functional TR.

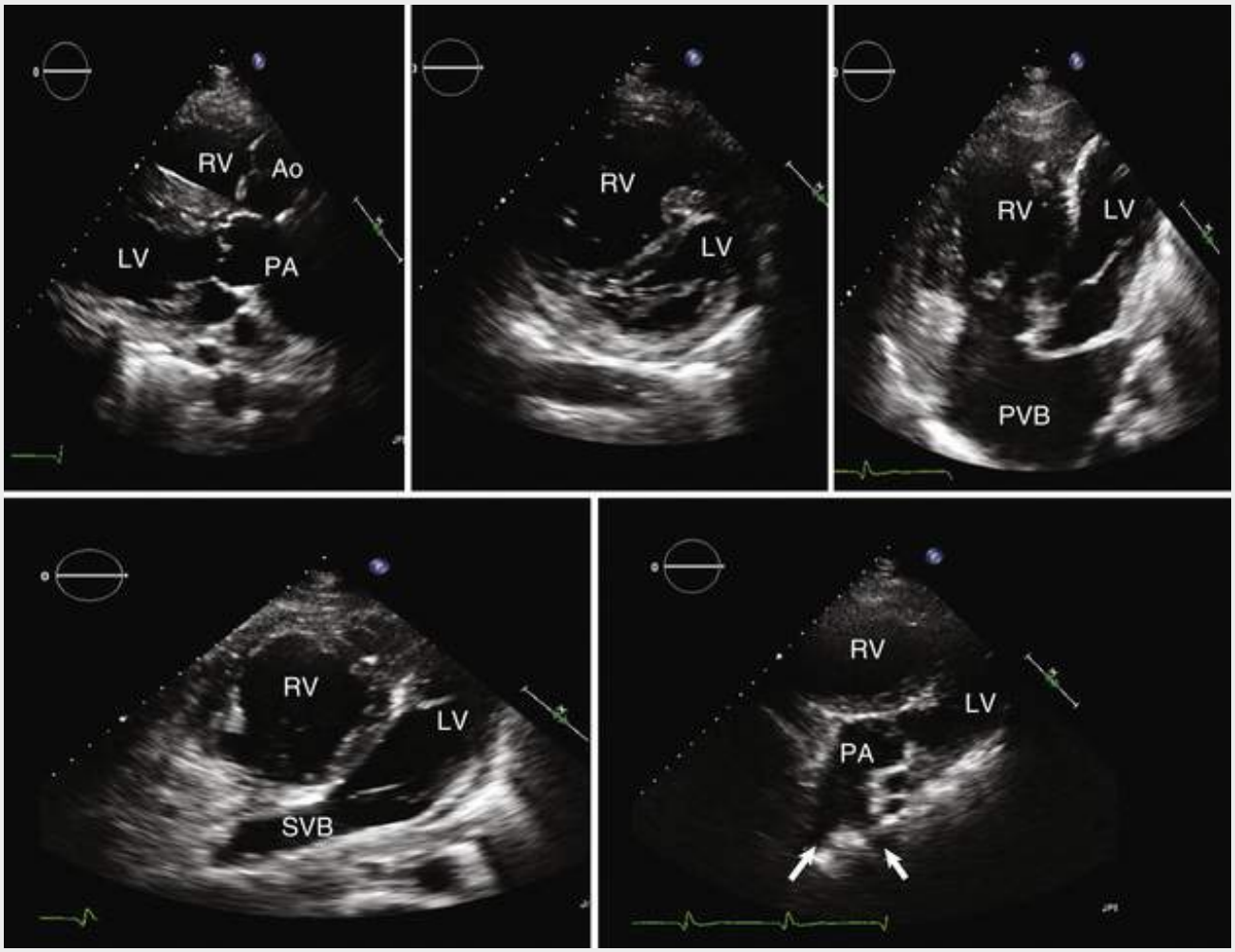


FIGURE 14.95 D-Transposition of the great arteries after Mustard baffle surgery. **Top left,** Parasternal long-axis view showing parallel orientation of the aorta (*Ao*) and pulmonary artery (*PA*). The aorta is anterior. **Top middle,** Parasternal short-axis view showing septal inversion reflecting the fact that the right ventricle (*RV*) is the systemic ventricle. **Top right,** Apical four-chamber view showing the pulmonary venous baffle (*PVB*), which directs pulmonary venous flow across the tricuspid valve into the RV. **Bottom left,** The four-chamber view has been angulated to demonstrate the systemic venous baffle (*SVB*), which directs systemic venous return across the mitral valve into the left ventricle (*LV*). Note the right ventricular hypertrophy and enlargement. **Bottom right,** The four-chamber view is angulated anteriorly to demonstrate the connection between the LV and PA. *Arrows* point to the PA bifurcation.

Levo (L)–TGA, also termed *congenitally corrected transposition*, is rare and accounts for less than 1% of all congenital heart disease. In L-TGA, transposition, with the aorta anterior and typically to the left of the pulmonary artery, is also accompanied by ventricular inversion. Thus, systemic venous blood returning to the right atrium drains into the morphologic left ventricle and is pumped into the pulmonary artery. Pulmonary venous blood returning to the left atrium crosses the tricuspid valve into the morphologic right ventricle, from which it is ejected into the aorta. Therefore the circulation is "normalized" (**eFig. 14.30, right panel**). Associated abnormalities are common and include VSD (70% of patients), pulmonary outflow tract obstruction that is typically subvalvular (40%), and abnormalities of the tricuspid (systemic AV) valve (90%). Patients, particularly those without associated anomalies, may remain undiagnosed until adulthood, but eventually the morphologic right ventricle will fail because it cannot meet the pressure demands of the systemic circulation.

Echocardiographic features of L-TGA again include parallel orientation of the great vessels as with all cases of transposition, but on apical views, ventricular inversion becomes apparent. Ventricular morphology may be determined by the structure of its AV valve and the pattern of trabeculation. The morphologic right ventricle is associated with a tricuspid AV valve, which is identified by the presence of three leaflets and leaflet insertion that is apical to that of the mitral valve. The morphologic right

ventricle is coarsely trabeculated with a moderator band, whereas the morphologic left ventricle is smooth walled and has two discrete papillary muscles. In assessing ventricular morphology by the four-chamber view, it is essential to maintain standard transducer orientation and avoid rotating the transducer so that an image is created in which the right and left ventricles occupy their expected positions. **Fig. 14.96** illustrates ventricular inversion in a patient with L-TGA. As with D-TGA, the morphologic right ventricle is hypertrophied with a round contour, and the morphologic left ventricle is crescentic. The septal curvature is reversed, consistent with the systemic pressure in the morphologic right ventricle.[92]

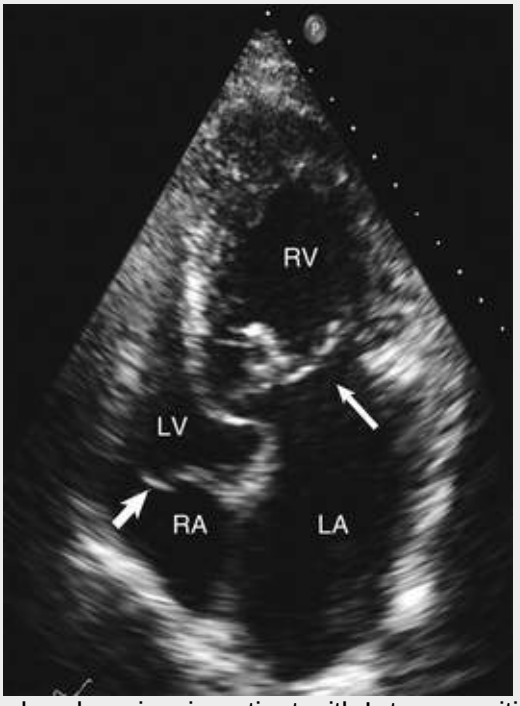


FIGURE 14.96 Apical four-chamber view in patient with L-transposition of the great arteries. The ventricles are inverted with the right ventricle (*RV*) to the right, identified on the basis of its heavy trabeculation and tricuspid atrioventricular valve (*thin arrow*). Although the insertion of the tricuspid valve is always apical to that of the mitral valve, in this case the offset is accentuated, consistent with the Ebstein anomaly. Unlike isolated Ebstein anomaly, that seen with L-TGA does not have a sail-like leaflet or adherence of the septal leaflet to the septum. The *thick arrow* points to the mitral valve. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium.

Tetralogy of Fallot

Tetralogy of Fallot is the most common form of cyanotic congenital heart disease and accounts for 10% of all congenital heart cases. The tetralogy of abnormalities consists of an overriding aorta, nonrestrictive subaortic VSD, RVOT obstruction (typically infundibular with variable valvular abnormalities), and secondary RV hypertrophy. Each of these features is readily identifiable with echocardiography (**Fig. 14.97**). *Pentalogy of Fallot* refers to the condition in which an ASD is also present.

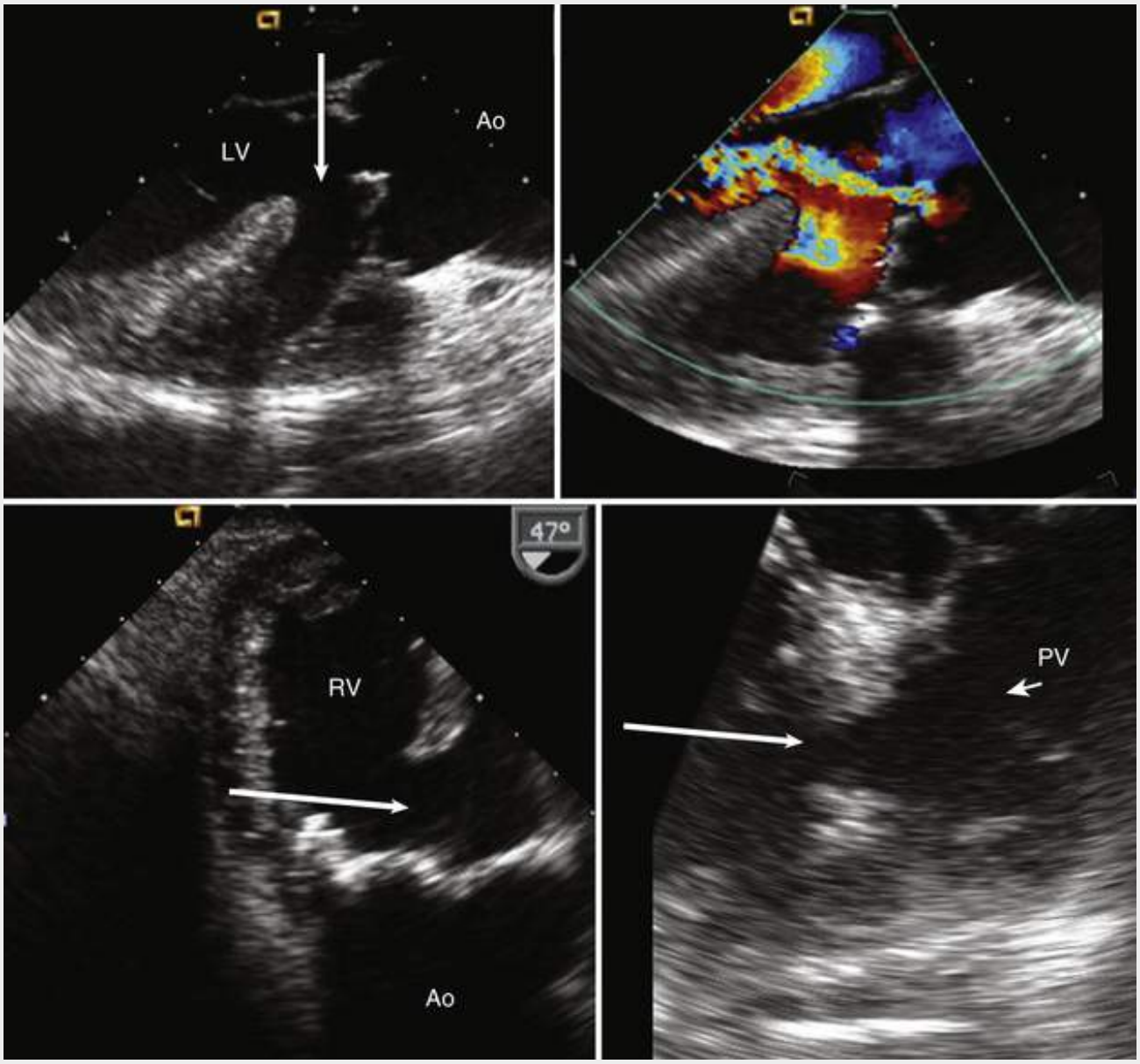


FIGURE 14.97 TEE images of a patient with tetralogy of Fallot. **Upper left,** Midesophageal image showing the aorta (*Ao*) overriding a large (nonrestrictive) VSD (*arrow*). **Upper right,** There is mild aortic regurgitation. **Lower left,** From a deep transgastric view, severe right ventricular hypertrophy is seen. The *arrow* points to the VSD. **Lower right,** In this midesophageal view, focal infundibular narrowing is seen (*arrow*). The pulmonic valve (*PV*) is not well seen but, in other views, was shown to be normal. *LV,* Left ventricle; *RV,* right ventricle.

Surgery for the tetralogy consists of patching the VSD and a tailored approach to relieving the RVOT obstruction. Pulmonic regurgitation, sometimes severe, is a frequent finding after surgery for tetralogy of Fallot and may drive the need for repeated surgery. Other problems to remain vigilant for in the years after surgery include residual infundibular (subvalvular) and supravalvular pulmonic stenosis, as well as aneurysmal degeneration of the patch used to open up the infundibulum and/or pulmonary artery.[93]

Cardiac Procedures and Future Directions

The role of TTE and TEE has been discussed in conventional surgical procedures, particularly in the setting of evaluation and treatment of CAD, cardiomyopathies, valvular disease, LVADs, and intracardiac shunts and congenital heart disease. The past decade has seen swift and remarkable advances in percutaneous interventions, which often require accurate preprocedural assessment and skilled intraprocedural echocardiography to guide effective deployment of devices. Knowledge of how these

newer and developing devices work and their potential failings is essential for complete follow-up echocardiographic evaluation. Transcatheter treatment of AS and MR is currently an attractive alternative for patients at high surgical risk (**see Chapter 72**). *Transcatheter pulmonary valve implantation* is now routine in pediatric centers experienced in congenital heart disease. In general, echocardiographic guidance is required for patient screening for appropriate anatomy, followed by proper device selection (type and size), placement, and deployment of most of the available percutaneous devices.

Transcatheter aortic valve implantation (TAVI) can be performed through transfemoral, LV apical, or transaortic approaches, using only TTE guidance and fluoroscopy/angiography. A preprocedural CT angiogram or TEE may be used to assess the aortic annular and root size. The coronary ostia need to be high enough—ideally 1.0 cm or more from the annulus—to avoid being occluded by the stented valve or displaced native leaflets. This latter measurement, as well as precise annular measurements, was inaccurate or virtually impossible without 3D TEE, and some platforms now allow precise detailed online measurements throughout the cardiac cycle (4D TEE) and volume reconstruction at bedside (**Fig. 14.98**). Intraprocedural TEE is used to ensure that the stented valve is properly seated across the aortic annulus and to assess for paravalvular leakage. Paravalvular aortic insufficiency is not uncommon (**see Fig. 14.61**); if the degree is significant, further reexpansion of the stented valve or even implantation of a second valve may be undertaken. Surveillance for wall motion abnormalities caused by coronary ostial inclusion and pericardial effusion should continue during and after balloon inflations.[94]

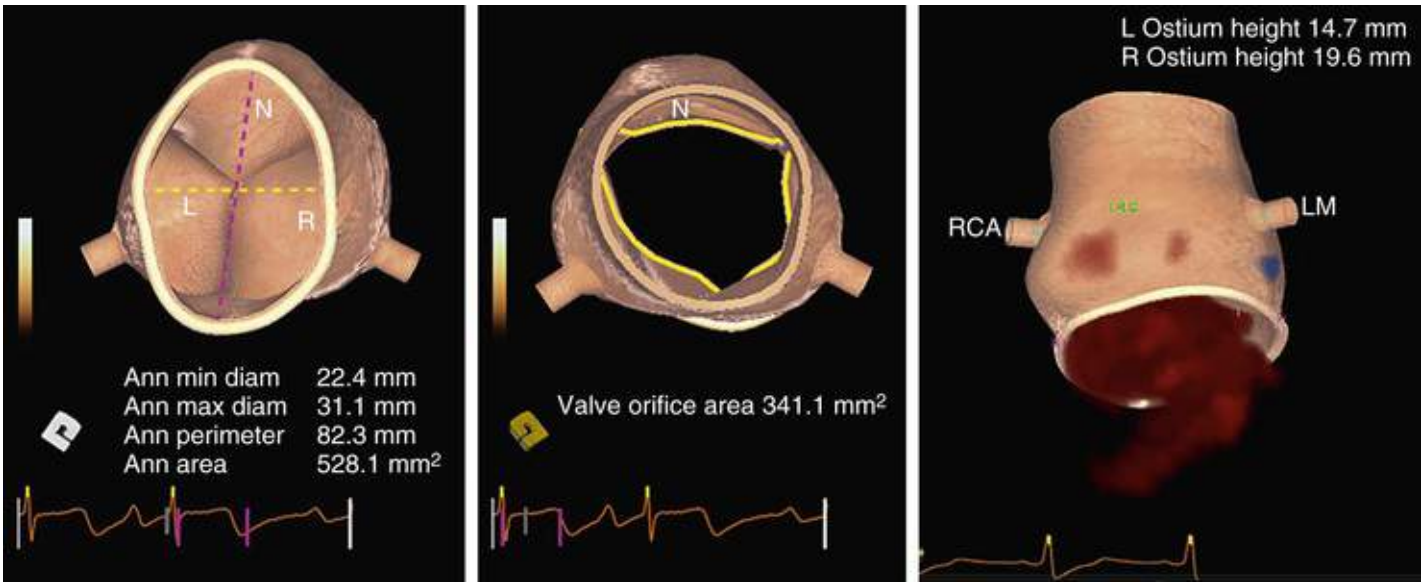


FIGURE 14.98 Three-dimensional TEE volume-rendered still frames of a normal aortic root. **Left,** The true orthogonal long and short axes of the annulus may be determined, as well as annular area. **Middle,** Valve orifice area and leaflet lengths. **Right,** Heights of the coronary ostia from the annulus (which is of particular importance in planning for TAVI).

Transcatheter mitral valvuloplasty devices for MR are now commercially available for degenerative MR and are undergoing clinical trials for functional MR. They are ideally implanted under TEE guidance, although use of TTE alone is feasible. Echo imaging is essential to select appropriate candidates for treatment, properly deliver the devices, and assess for the degree of reduction in MR. The MitraClip in particular requires both echocardiographer and interventionalist expertise to approach the mitral valve via transseptal puncture, then ensure that the device arms are being placed on the midscallops of the mitral valve perpendicular to the coaptation line, which ultimately creates the percutaneous equivalent of the Alfieri stitch (i.e., edge-to-edge repair). Previously, clip deployment was not feasible without good

transgastric views, but 3D technology has made the procedure easier and more accurate[94] (**Fig. 14.99** and Video 14.56).

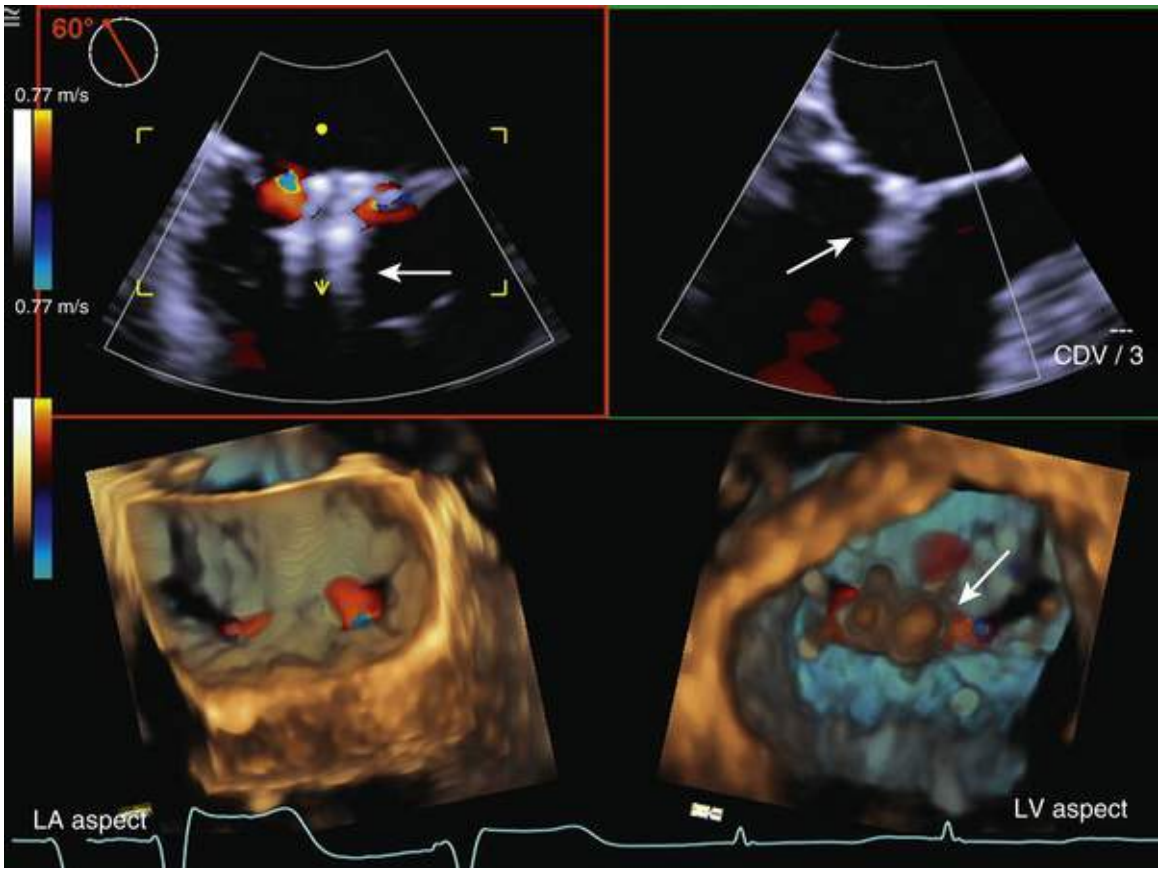
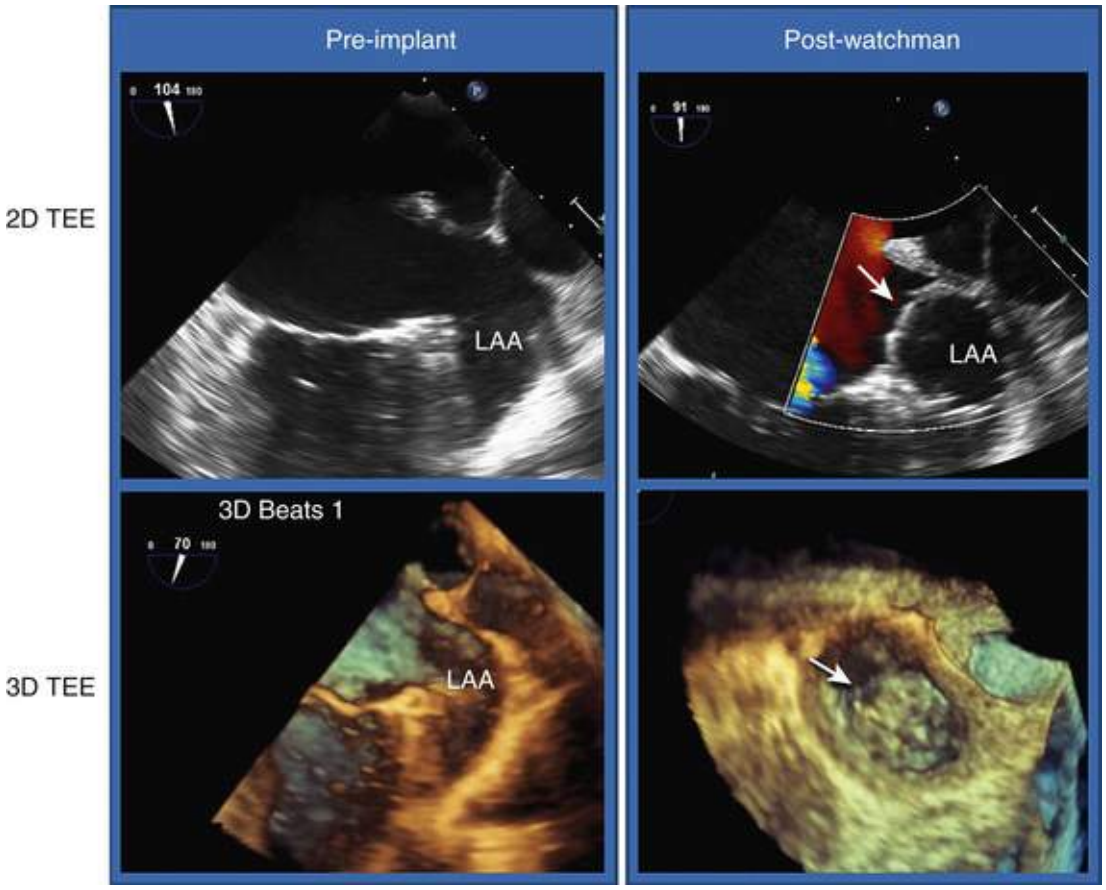


FIGURE 14.99 Three-dimensional TEE images in a patient following MitraClip placement, with trace residual mitral regurgitation (MR) seen in the now double-orifice valve. **Upper panels,** Apical 60-degree and 120-degree views of the device in early systole. **Lower panels,** The valve as viewed from the left atrial and left ventricular aspects. *White arrow,* MitraClip device. (See corresponding Video 14.56.)

In the subspecialty of electrophysiology, occlusion of the LA appendage is possible with a variety of devices and is targeted toward patients at high risk for recurrent strokes (despite anticoagulation or unable to take anticoagulants) (**eFig. 14.31**). TEE is performed before the procedure primarily to size the LA appendage and ensure that it can receive an appropriately sized device, as well as to exclude appendage thrombus. For the Watchman device, the ostia of the appendage diameters are measured at several angles, and the appendage must be longer than its width.



EFIGURE 14.31 The Watchman device to occlude the left atrial appendage (LAA) for stroke prevention. **Left panels,** 2D and 3D TEE views of the LAA before implantation. Measurements of the LAA ostia taken at multiple angles for selection of the appropriate Watchman device. The appendage length must be longer than its width to accommodate device implantation. **Right panels,** Appendage occluder device (*arrow*) well seated at the neck of the appendage, with no residual flow around the device by color Doppler; **top panel,** 2D view; **bottom panel,** 3D en face view).

The increasing population of patients with structural and adult congenital heart disease has led to demand for continued innovation in structural interventions. Current interventions include stenting of the pulmonary arteries or veins, percutaneous treatment of complex lesions (coronary fistulas, other vascular malformations, and collaterals), angioplasty and stenting of surgical conduits and aortic coarctation, and a growing list of other minimally invasive interventions for conditions that were previously remediable only by open surgery. Occluder devices are now used also to treat paravalvular leaks in high-risk patients. TAVI is now being performed for failed bioprostheses (“valve-in-valve” procedures), severe AR, bicuspid or unicuspid valves, and other situations in which surgery is too risky or undesirable. It will be imperative to have continued follow-up within registries and intermediate- and long-term echocardiographic data analyzed, because these and other interventions move through experimental trials and ultimately filter into the clinical arena.

Handheld Echocardiography

The era of miniaturization has ushered in increasingly smaller and capable portable ultrasound machines, which were introduced commercially in 2004. Current laptop-size devices are a lightweight alternative to the traditional 400-lb full-size machines and have increased the availability and usefulness of cardiac ultrasound at the point of care. Laptop ultrasound has virtually all the capabilities of full-size machines, including the capability for tissue Doppler and strain imaging, stress and TEE studies, automatic quantification of LVEF, and more recently, 4D imaging. They can operate wirelessly. Many systems offer

the capability to perform vascular, abdominal, and obstetric ultrasound on the same machine and can accommodate a wide range of transducers, including pediatric.

Handheld ultrasound devices introduced this decade are small enough to fit in the physician's coat pocket. They may serve as an extension to the physical examination and are more likely to be readily available in an acute emergency for a focused examination. In the hands of experienced sonographers, the current devices offer harmonic 2D and color Doppler imaging with good image quality and accuracy compared with conventional machines.[95] None of the current handheld devices supports spectral Doppler and thus are limited in the quantification of valve stenosis. Recent developments include miniaturized disposable TEE probes, intended for continuous monitoring of cardiac preload in ICUs and during surgeries, as well as smartphone-based ultrasound systems in which a stand-alone transducer (3.5 to 5 mHz and higher) can be plugged into a smartphone or tablet that processes the data into images and can transfer the data wirelessly.

The lower cost and portability also render the technology more accessible for health care in underdeveloped regions. Along with these innovations, however, education and training are required for optimal use by noncardiologists.[95,96] With sufficient user experience and continual improvements in design and function, these instruments likely will become as familiar in clinical settings as the stethoscope. At present, although handheld devices can complement the physical examination, they do not supplant a complete formal echocardiographic study with a high-end machine and experienced sonographer.

Appropriate Use Criteria

Echocardiography

Scott D. Solomon and Robert O. Bonow

During the past three decades, there has been explosive growth in the use of cardiac imaging, particularly in the applications of echocardiography, Doppler echocardiography, and stress echocardiography. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the use of echocardiography were last updated in 2003. Whether cardiac imaging and in particular echocardiography leads to enhanced quality of care and improved patient outcomes is unclear. It is difficult to tie an imaging test to patient outcomes because any impact of diagnostic testing on patient-related outcomes is ultimately tied to downstream management strategies that the diagnostic tests may or may not set in motion. In addition, no prospective randomized trials have been designed to demonstrate the efficacy of imaging in achieving optimal patient outcomes. Thus, no firm foundation on which to develop evidence-based guidelines is available.

Against this background, the ACC has moved from the development of practice guidelines in cardiovascular imaging to the development of appropriate use criteria (AUC). Partnering with a number of subspecialty societies, the ACC has spearheaded the delivery of AUC for imaging, which are designed to define the appropriate test for the appropriate indication in the appropriate patient. The process used for development of appropriateness criteria is only partially evidence based and is heavily weighted by expert consensus.

The AUC for echocardiography are based on a number of common clinical scenarios in which imaging is often used. These scenarios are then rated by a panel with a broad array of expertise (i.e., not just imaging experts) to evaluate the “appropriateness” of echocardiography in each situation in terms of the following definition: “An appropriate imaging study is one in which the expected incremental

information, combined with clinical judgment, exceeds the expected negative consequences by a sufficiently wide margin for a specific indication that the procedure is generally considered acceptable care and a reasonable approach for the indication." Rating scores are made on a scale of 1 to 9, in which a score of 9 indicates highly appropriate use of testing. Using an iterative modified Delphi exercise process with predefined rules, a final rating score is established for each indication and grouped as A, score of 7 to 9, indicating an *appropriate* test for the specific indication (the test *is* generally acceptable and *is* a reasonable approach for the indication); M, score of 4 to 6, indicating that the test *may* be generally appropriate for the indication); and R, score of 1 to 3, indicating that the test would *rarely* be appropriate for that indication.[1]

The AUC for echocardiography were first published in 2007, followed by AUC for stress echocardiography in 2008. The echocardiography AUC were updated in 2011.[2] These criteria are summarized in **Table 14G.1**. These AUC criteria were published before the updated terminology noted above[1] and use the previous methodology in which the term "inappropriate" (I) is used for ratings of 1 to 3 and ratings of 4 to 6 are termed "uncertain" (U) appropriateness. Ratings of 7 to 9 remain "appropriate" (A). The more recent AUC documents for multimodality imaging in patients with stable ischemic heart disease, heart failure, and chest pain[3-5] do conform to the updated terminology and provide criteria for the use of echocardiography in these conditions relative to the applications of the other imaging modalities (**see Chapter 18** Appropriate Use Criteria).

TABLE 14G.1

Echocardiography Appropriate Use: Transthoracic, Transesophageal, and Stress

TRANSESOPHAGEAL ECHOCARDIOGRAPHY FOR GENERAL EVALUATION OF CARDIAC STRUCTURE AND FUNCTION		
	Indication	Appropriateness Score* (1-9)
Suspected Cardiac Cause—General		
1.	Symptoms or conditions potentially related to a suspected cardiac cause, including but not limited to chest pain, shortness of breath, TIA, stroke, or peripheral embolic event	A (9)
2.	Previous testing that is concerning for heart disease or structural abnormality, including but not limited to chest radiography, baseline scout images for stress echocardiography, electrocardiography, or cardiac biomarkers	A (9)
Arrhythmias		
3.	Infrequent APCs or VPCs or palpitations without other evidence of heart disease	I (2)
4.	Frequent VPCs or exercise-induced VPCs	A (8)
5.	Sustained or nonsustained atrial fibrillation, SVT, or VT	A (9)
6.	Asymptomatic isolated sinus bradycardia	I (2)
Lightheadedness/Presyncope/Syncope		
7.	Clinical symptoms or signs consistent with a cardiac diagnosis known to cause lightheadedness/presyncope/syncope (including but not limited to aortic stenosis, hypertrophic cardiomyopathy, or heart failure)	A (9)
8.	Lightheadedness/presyncope/syncope when there is very low clinical suspicion for cardiovascular disease	I (3)
9.	Syncope when no other symptoms or signs of cardiovascular disease are present	A (7)
Evaluation of Ventricular Function		
10.	Initial evaluation of ventricular function (e.g., screening) with no symptoms or signs of cardiovascular disease	I (2)
11.	Routine reevaluation of ventricular function with known CAD and no change in clinical status or findings on cardiac examination	I (3)
12.	Evaluation of left ventricular function with previous ventricular function evaluation showing normal function (e.g., previous echocardiography, left ventriculography, CT, SPECT, CMR) in patients in whom there has been no change in clinical status or findings on cardiac examination	I (1)
Perioperative Evaluation		
13.	Routine perioperative evaluation of ventricular function with no symptoms or signs of cardiovascular disease	I (2)
14.	Routine perioperative evaluation of cardiac structure and function before noncardiac solid-organ transplantation	U (6)
Pulmonary Hypertension		
15.	Evaluation of suspected pulmonary hypertension, including evaluation of right ventricular function and estimated pulmonary artery pressure	A (9)
16.	Routine (<1 year) reevaluation of known pulmonary hypertension without change in clinical status or findings on cardiac examination	I (3)
17.	Routine (≥1 year) reevaluation of known pulmonary hypertension without change in clinical status or findings on cardiac examination	A (7)
18.	Reevaluation of known pulmonary hypertension if change in clinical status or findings on cardiac examination occurs or to guide therapy	A (9)
TRANSTHORACIC ECHOCARDIOGRAPHY FOR CARDIOVASCULAR EVALUATION IN AN ACUTE SETTING		
Hypotension or Hemodynamic Instability		
19.	Hypotension or hemodynamic instability of uncertain or suspected cardiac cause	A (9)
20.	Assessment/monitoring of volume status in a critically ill patient	U (5)
Myocardial Ischemia/Infarction		
21.	Acute chest pain with suspected myocardial infarction and nondiagnostic ECG when a resting echocardiogram can be performed during pain	A (9)
22.	Evaluation of a patient without chest pain but with other features of an ischemic equivalent or laboratory markers indicative of ongoing myocardial infarction	A (8)

23.	Suspected complication of myocardial ischemia/infarction, including but not limited to acute mitral regurgitation, ventricular septal defect, free wall rupture/tamponade, shock, right ventricular involvement, heart failure, or thrombus	A (9)
Evaluation of Ventricular Function After Acute Coronary Syndrome		
24.	Initial evaluation of ventricular function following ACS	A (9)
25.	Reevaluation of ventricular function following ACS during recovery phase when results will guide therapy	A (9)
Respiratory Failure		
26.	Respiratory failure or hypoxemia of uncertain cause	A (8)
27.	Respiratory failure or hypoxemia when a noncardiac cause of respiratory failure has been established	U (5)
Pulmonary Embolism		
28.	Suspected pulmonary embolism to establish the diagnosis	I (2)
29.	Known acute pulmonary embolism to guide therapy (e.g., thrombectomy and thrombolytics)	A (8)
30.	Routine reevaluation of previous pulmonary embolism with normal right ventricular function and pulmonary artery systolic pressure	I (1)
31.	Reevaluation of known pulmonary embolism after thrombolysis or thrombectomy for assessment of change in right ventricular function and/or pulmonary artery pressure	A (7)
Cardiac Trauma		
32.	Severe deceleration injury or chest trauma when valve injury, pericardial effusion, or cardiac injury is possible or suspected	A (9)
33.	Routine evaluation in the setting of mild chest trauma with no changes on the ECG or biomarker elevation	I (2)
TRANSTHORACIC ECHOCARDIOGRAPHY FOR EVALUATION OF VALVULAR FUNCTION		
Murmur or Click		
34.	Initial evaluation when there is a reasonable suspicion of valvular or structural heart disease	A (9)
35.	Initial evaluation when there is very low suspicion of valvular or structural heart disease	I (2)
36.	Reevaluation in a patient without valvular disease on a previous echocardiogram and no change in clinical status or findings on cardiac examination	I (1)
37.	Reevaluation of known valvular heart disease with a change in clinical status or findings on cardiac examination or to guide therapy	A (9)
Native Valvular Stenosis		
38.	Routine (<3 years) reevaluation of mild valvular stenosis without change in clinical status or findings on cardiac examination	I (3)
39.	Routine (≥3 years) reevaluation of mild valvular stenosis without change in clinical status or findings on cardiac examination	A (7)
40.	Routine (<1 year) reevaluation of moderate or severe valvular stenosis without change in clinical status or findings on cardiac examination	I (3)
41.	Routine (≥1 year) reevaluation of moderate or severe valvular stenosis without change in clinical status or findings on cardiac examination	A (8)
Native Valvular Regurgitation		
42.	Routine reevaluation of trace valvular regurgitation	I (1)
43.	Routine (<3 years) reevaluation of mild valvular regurgitation without change in clinical status or findings on cardiac examination	I (1)
44.	Routine (≥3 years) reevaluation of mild valvular regurgitation without change in clinical status or findings on cardiac examination	U (4)
45.	Routine (<1 year) reevaluation of moderate or severe valvular regurgitation without change in clinical status or findings on cardiac examination	U (6)
46.	Routine (≥1 year) reevaluation of moderate or severe valvular regurgitation without change in clinical status or findings on cardiac examination	A (8)
Prosthetic Valve		
47.	Initial postoperative evaluation of prosthetic valve for establishment of baseline	A (9)
48.	Routine (<3 years) reevaluation of prosthetic valve if no known or suspected valve dysfunction	I (3)
49.	Routine (≥3 years) reevaluation of prosthetic valve if no known or suspected valve dysfunction	A (7)
50.	Evaluation of prosthetic valve with suspected dysfunction or change in clinical status or findings on cardiac examination	A (9)
51.	Reevaluation of known prosthetic valve dysfunction when it would change management or guide therapy	A (9)
Infective Endocarditis (Native or Prosthetic Valves)		
52.	Initial evaluation of suspected infective endocarditis with positive blood cultures or a new murmur	A (9)
53.	Transient fever without evidence of bacteremia or a new murmur	I (2)
54.	Transient bacteremia with a pathogen not typically associated with infective endocarditis and/or documented nonendovascular source of infection	I (3)
55.	Reevaluation of infective endocarditis at high risk for progression or complication or with a change in clinical status or findings on cardiac examination	A (9)
56.	Routine reevaluation of uncomplicated infective endocarditis when no change in management is contemplated	I (2)
TRANSTHORACIC ECHOCARDIOGRAPHY FOR EVALUATION OF INTRACARDIAC AND EXTRACARDIAC STRUCTURES AND CHAMBERS		
57.	Suspected cardiac mass	A (9)
58.	Suspected cardiovascular source of embolus	A (9)
59.	Suspected pericardial conditions	A (9)
60.	Routine reevaluation of known small pericardial effusion with no change in clinical status	I (2)
61.	Reevaluation of known pericardial effusion to guide management or therapy	A (8)
62.	Guidance of percutaneous noncoronary cardiac procedures, including but not limited to pericardiocentesis, septal ablation, or right ventricular biopsy	A (9)
TRANSTHORACIC ECHOCARDIOGRAPHY FOR EVALUATION OF AORTIC DISEASE		
63.	Evaluation of the ascending aorta in the setting of a known or suspected connective tissue disease or genetic condition that predisposes to aortic aneurysm or dissection (e.g., Marfan syndrome)	A (9)
64.	Reevaluation of known ascending aortic dilation or history of aortic dissection to establish a baseline rate of expansion or when the rate of expansion is excessive	A (9)
65.	Reevaluation of known ascending aortic dilation or history of aortic dissection with a change in clinical status or findings on cardiac examination or when findings may alter management or therapy	A (9)
66.	Reevaluation of known ascending aortic dilation or history of aortic dissection without a change in clinical status or findings on cardiac examination when findings would not change management or therapy	I (3)
TRANSTHORACIC ECHOCARDIOGRAPHY FOR EVALUATION OF HYPERTENSION, HEART FAILURE, OR CARDIOMYOPATHY		
Hypertension		
67.	Initial evaluation of suspected hypertensive heart disease	A (8)
68.	Routine evaluation of systemic hypertension without suspected hypertensive heart disease	I (3)
69.	Reevaluation of known hypertensive heart disease without change in clinical status or findings on cardiac examination	U (4)
Heart Failure		
70.	Initial evaluation of known or suspected heart failure (systolic or diastolic) based on symptoms, signs, or abnormal test results	A (9)
71.	Reevaluation of known heart failure (systolic or diastolic) with change in clinical status or findings on cardiac examination and no clear precipitating change in medication or diet	A (8)
72.	Reevaluation of known heart failure (systolic or diastolic) with change in clinical status or findings on cardiac examination and a clear precipitating change in medication or diet	U (4)
73.	Reevaluation of known heart failure (systolic or diastolic) to guide therapy	A (9)
74.	Routine (<1 year) reevaluation of heart failure (systolic or diastolic) when there is no change in clinical status or findings on cardiac examination	I (2)
75.	Routine (≥1 year) reevaluation of heart failure (systolic or diastolic) when there is no change in clinical status or findings on cardiac examination	U (6)
Device Evaluation (Including Pacemaker, Implantable Cardioverter-Defibrillator, or Cardiac Resynchronization Therapy)		
76.	Initial evaluation or reevaluation after revascularization and/or optimal medical therapy to determine candidacy for device therapy and/or to determine	A (9)

	optimal choice of device	
77.	Initial evaluation for optimization of device for cardiac resynchronization therapy after implantation	U (6)
78.	Known implanted pacing device with symptoms possibly caused by device complication or suboptimal pacing device settings	A (8)
79.	Routine (<1 year) reevaluation of implanted device without change in clinical status or findings on cardiac examination	I (1)
80.	Routine (≥1 year) reevaluation of implanted device without change in clinical status or findings on cardiac examination	I (3)
Ventricular Assist Devices and Cardiac Transplantation		
81.	To determine candidacy for ventricular assist device	A (9)
82.	Optimization of ventricular assist device settings	A (7)
83.	Reevaluation of signs/symptoms suggestive of ventricular assist device–related complications	A (9)
84.	Monitoring for rejection in a cardiac transplant recipient	A (7)
85.	Cardiac structure and function evaluation in a potential heart donor	A (9)
Cardiomyopathies		
86.	Initial evaluation of known or suspected cardiomyopathy (e.g., restrictive, infiltrative, dilated, hypertrophic, or genetic cardiomyopathy)	A (9)
87.	Reevaluation of known cardiomyopathy with change in clinical status or findings on cardiac examination or to guide therapy	A (9)
88.	Routine (<1 year) reevaluation of known cardiomyopathy without change in clinical status or findings on cardiac examination	I (2)
89.	Routine (≥1 year) reevaluation of known cardiomyopathy without change in clinical status or findings on cardiac examination	U (5)
90.	Screening evaluation for structure and function in first-degree relatives of a patient with inherited cardiomyopathy	A (9)
91.	Baseline and serial reevaluations in patients undergoing therapy with cardiotoxic agents	A (9)
TRANSTHORACIC ECHOCARDIOGRAPHY FOR ADULT CONGENITAL HEART DISEASE		
92.	Initial evaluation of known or suspected adult congenital heart disease	A (9)
93.	Known adult congenital heart disease with change in clinical status or findings on cardiac examination	A (9)
94.	Reevaluation to guide therapy for known adult congenital heart disease	A (9)
95.	Routine (<2 years) reevaluation of adult congenital heart disease following complete repair: Without residual structural or hemodynamic abnormality Without change in clinical status or findings on cardiac examination	I (3)
96.	Routine (≥2 years) reevaluation of adult congenital heart disease following complete repair: Without residual structural or hemodynamic abnormality Without change in clinical status or findings on cardiac examination	U (6)
97.	Routine (<1 year) reevaluation of congenital heart disease following incomplete or palliative repair: With residual structural or hemodynamic abnormality Without change in clinical status or findings on cardiac examination	U (5)
98.	Routine (≥1 year) reevaluation of congenital heart disease following incomplete or palliative repair: With residual structural or hemodynamic abnormality Without change in clinical status findings on cardiac examination	A (8)
TRANSESOPHAGEAL ECHOCARDIOGRAPHY		
TEE as Initial or Supplemental Test—General Uses		
99.	Use of TEE when there is a high likelihood of a nondiagnostic TTE because of patient characteristics or inadequate visualization of relevant structures	A (8)
100.	Routine use of TEE when a diagnostic TTE is reasonably anticipated to resolve all diagnostic and management concerns	I (1)
101.	Reevaluation of previous TEE findings for interval change (e.g., resolution of thrombus after anticoagulation, resolution of vegetation after antibiotic therapy) when a change in therapy is anticipated	A (8)
102.	Reevaluation of previous TEE findings for interval change (e.g., resolution of thrombus after anticoagulation, resolution of vegetation after antibiotic therapy) when no change in therapy is anticipated	I (2)
103.	Guidance during percutaneous noncoronary cardiac interventions, including but not limited to closure device placement, radiofrequency ablation, and percutaneous valve procedures	A (9)
104.	Suspected acute aortic pathology, including but not limited to dissection/transection	A (9)
105.	Routine assessment of pulmonary veins in asymptomatic patient after pulmonary vein isolation	I (3)
TEE as Initial or Supplemental Test—Valvular Disease		
106.	Evaluation of valvular structure and function to assess suitability for and assist in planning of an intervention	A (9)
107.	To diagnose/manage infective endocarditis with a low pretest probability (e.g., transient fever, known alternative source of infection, or negative blood cultures/atypical pathogen for endocarditis)	I (3)
108.	To diagnose/manage infective endocarditis with a moderate or high pretest probability (e.g., staphylococcal bacteremia, fungemia, prosthetic heart valve, or intracardiac device)	A (9)
TEE as Initial or Supplemental Test—Embolic Event		
109.	Evaluation for cardiovascular source of embolus with no identified noncardiac source	A (7)
110.	Evaluation for cardiovascular source of embolus with a previously identified noncardiac source	U (5)
111.	Evaluation for cardiovascular source of embolus with a known cardiac source in which TEE would not change management	I (1)
TEE as Initial Test—Atrial Fibrillation/Flutter		
112.	Evaluation to facilitate clinical decision making with regard to anticoagulation, cardioversion, and/or radiofrequency ablation	A (9)
113.	Evaluation when a decision has been made to anticoagulate and not to perform cardioversion	I (2)
STRESS ECHOCARDIOGRAPHY FOR DETECTION OF CORONARY ARTERY/RISK ASSESSMENT: SYMPTOMATIC OR ISCHEMIC EQUIVALENT		
Evaluation of Ischemic Equivalent (Nonacute)		
114.	Low pretest probability of CAD ECG interpretable *and* able to exercise	I (3)
115.	Low pretest probability of CAD ECG uninterpretable *or* unable to exercise	A (7)
116.	Intermediate pretest probability of CAD ECG interpretable *and* able to exercise	A (7)
117.	Intermediate pretest probability of CAD ECG uninterpretable *or* unable to exercise	A (9)
118.	High pretest probability of CAD Regardless of ECG interpretability and ability to exercise	A (7)
Acute Chest Pain		
119.	Possible ACS ECG: no ischemic changes or uninterpretable ECG Low-risk TIMI score Negative troponin levels	A (7)
120.	Possible ACS ECG: no ischemic changes or uninterpretable ECG Low-risk TIMI score	A (7)

	Peak troponin: borderline, equivocal, minimally elevated	
121.	Possible ACS ECG: no ischemic changes or uninterpretable ECG High-risk TIMI score Negative troponin levels	A (7)
122.	Possible ACS ECG: no ischemic changes or uninterpretable ECG High-risk TIMI score Peak troponin: borderline, equivocal, minimally elevated	A (7)
123.	Definite ACS	I (1)
STRESS ECHOCARDIOGRAPHY FOR DETECTION OF CORONARY ARTERY DISEASE/RISK ASSESSMENT: ASYMPTOMATIC (WITHOUT ISCHEMIC EQUIVALENT)		
General Patient Populations		
124.	Low global CHD risk	U (1)
125.	Intermediate global CHD risk ECG interpretable	I (2)
126.	Intermediate global CHD risk ECG uninterpretable	U (5)
127.	High global CHD risk	U (5)
STRESS ECHOCARDIOGRAPHY FOR DETECTION OF CORONARY ARTERY DISEASE/RISK ASSESSMENT: ASYMPTOMATIC (WITHOUT ISCHEMIC EQUIVALENT) IN PATIENT POPULATIONS WITH DEFINED COMORBID CONDITIONS		
New-Onset or Newly Diagnosed Heart Failure or Left Ventricular Systolic Dysfunction		
128.	No previous CAD evaluation *and* no planned coronary angiography	A (7)
Arrhythmias		
129.	Sustained VT	A (7)
130.	Frequent PVCs, exercise-induced VT, or nonsustained VT	A (7)
131.	Infrequent PVCs	I (3)
132.	Atrial fibrillation or other SVT	U (6)
Syncope		
133.	Low global CHD risk	I (3)
134.	Intermediate or high global CHD risk	A (7)
Elevated Troponin		
135.	Troponin elevation without symptoms or additional evidence of ACS	A (7)
STRESS ECHOCARDIOGRAPHY FOLLOWING PREVIOUS TEST RESULTS		
Asymptomatic: Previous Evidence of Subclinical Disease		
136.	Coronary calcium Agatston score <100	I (2)
137.	Low to intermediate global CHD risk Coronary calcium Agatston score between 100 and 400	U (5)
138.	High global CHD risk Coronary calcium Agatston score between 100 and 400	U (6)
139.	Coronary calcium Agatston score >400	A (7)
140.	Abnormal carotid intimal medial thickness (≥0.9 mm and/or the presence of plaque encroaching into the arterial lumen)	U (5)
Coronary Angiography (Invasive or Noninvasive)		
141.	Coronary artery stenosis of unclear significance	A (8)
Asymptomatic *or* Stable Symptoms, Normal Findings on Previous Stress Imaging Study		
142.	Low global CHD risk Last stress imaging study <2 years ago	I (1)
143.	Low global CHD risk Last stress imaging study ≥2 years ago	I (2)
144.	Intermediate to high global CHD risk Last stress imaging study <2 years ago	I (2)
145.	Intermediate to high global CHD risk Last stress imaging study ≥2 years ago	U (4)
Asymptomatic *or* Stable Symptoms With Abnormal Findings on Coronary Angiography *or* Previous Stress Study, No Previous Revascularization		
146.	Known CAD on coronary angiography *or* previous abnormal findings on stress imaging study Last stress imaging study <2 years ago	I (3)
147.	Known CAD on coronary angiography *or* previous abnormal findings on stress imaging study Last stress imaging study ≥2 years ago	U (5)
Treadmill Electrocardiographic Stress Test		
148.	Low-risk treadmill score (e.g., Duke)	I (1)
149.	Intermediate-risk treadmill score (e.g., Duke)	A (7)
150.	High-risk treadmill score (e.g., Duke)	A (7)
New, Worsening, or Unresolved Symptoms		
151.	Abnormal findings on coronary angiography *or* abnormal findings on previous stress imaging study	A (7)
152.	Normal findings on coronary angiography *or* normal finding on previous stress imaging study	U (6)
Previous Noninvasive Evaluation		
153.	Equivocal, borderline, or discordant stress testing when obstructive CAD remains a concern	A (8)
STRESS ECHOCARDIOGRAPHY FOR RISK ASSESSMENT: PERIOPERATIVE EVALUATION FOR NONCARDIAC SURGERY WITHOUT ACTIVE CARDIAC CONDITIONS		
Low-Risk Surgery		
154.	Perioperative evaluation for risk assessment	I (1)
Intermediate-Risk Surgery		
155.	Moderate to good functional capacity (≥4 METs)	I (3)
156.	No clinical risk factors	I (2)
157.	≥1 clinical risk factor Poor or unknown functional capacity (<4 METs)	U (6)
158.	Asymptomatic <1 year after normal findings on catheterization, noninvasive test, or previous revascularization	I (1)
Vascular Surgery		
159.	Moderate to good functional capacity (≥4 METs)	I (3)

160.	No clinical risk factors	I (2)
161.	≥1 clinical risk factor Poor or unknown functional capacity (<4 METs)	A (7)
162.	Asymptomatic <1 year after normal findings on catheterization, noninvasive test, or previous revascularization	I (2)
STRESS ECHOCARDIOGRAPHY FOR RISK ASSESSMENT: WITHIN THREE MONTHS OF AN ACUTE CORONARY SYNDROME		
ST-Segment Elevation Myocardial Infarction		
163.	Primary PCI with complete revascularization No recurrent symptoms	I (2)
164.	Hemodynamically stable, no recurrent chest pain symptoms or signs of heart failure To evaluate for inducible ischemia No previous coronary angiography since the index event	A (7)
165.	Hemodynamically unstable, signs of cardiogenic shock, or mechanical complications	I (1)
Unstable Angina/Non–ST-Segment Elevation Myocardial Infarction		
166.	Hemodynamically stable, no recurrent chest pain symptoms or signs of heart failure To evaluate for inducible ischemia No previous coronary angiography since the index event	A (8)
ACS—Asymptomatic after Revascularization (PCI or CABG)		
167.	Before hospital discharge	I (1)
Cardiac Rehabilitation		
168.	Before initiation of cardiac rehabilitation (as a stand-alone indication)	I (3)
STRESS ECHOCARDIOGRAPHY FOR RISK ASSESSMENT: AFTER REVASCULARIZATION (PCI OR CABG)		
Symptomatic		
169.	Ischemic equivalent	A (8)
Asymptomatic		
170.	Incomplete revascularization Additional revascularization feasible	A (7)
171.	<5 years after CABG	I (2)
172.	≥5 years after CABG	U (6)
173.	<2 years after PCI	I (2)
174.	≥2 years after PCI	U (5)
Cardiac Rehabilitation		
175.	Before initiation of cardiac rehabilitation (as a stand-alone indication)	I (3)
STRESS ECHOCARDIOGRAPHY FOR ASSESSMENT OF VIABILITY/ISCHEMIA		
Ischemic Cardiomyopathy/Assessment of Viability		
176.	Known moderate or severe left ventricular dysfunction Patient eligible for revascularization Use of dobutamine only	A (8)
STRESS ECHOCARDIOGRAPHY FOR HEMODYNAMICS (INCLUDES DOPPLER DURING STRESS)		
Chronic Valvular Disease—Asymptomatic		
177.	Mild mitral stenosis	I (2)
178.	Moderate mitral stenosis	U (5)
179.	Severe mitral stenosis	A (7)
180.	Mild aortic stenosis	I (3)
181.	Moderate aortic stenosis	U (6)
182.	Severe aortic stenosis	U (5)
183.	Mild mitral regurgitation	I (2)
184.	Moderate mitral regurgitation	U (5)
185.	Severe mitral regurgitation Left ventricular size and function not meeting surgical criteria	A (7)
186.	Mild aortic regurgitation	I (2)
187.	Moderate aortic regurgitation	U (5)
188.	Severe aortic regurgitation Left ventricular size and function not meeting surgical criteria	A (7)
Chronic Valvular Disease—Symptomatic		
189.	Mild mitral stenosis	U (5)
190.	Moderate mitral stenosis	A (7)
191.	Severe mitral stenosis	I (3)
192.	Severe aortic stenosis	I (1)
193.	Evaluation of equivocal aortic stenosis Evidence of low cardiac output or left ventricular systolic dysfunction (“low-gradient aortic stenosis”) Use of dobutamine only	A (8)
194.	Mild mitral regurgitation	U (4)
195.	Moderate mitral regurgitation	A (7)
196.	Severe mitral regurgitation Severe left ventricular enlargement or systolic dysfunction	I (3)
Acute Valvular Disease		
197.	Acute moderate or severe mitral or aortic regurgitation	I (3)
Pulmonary Hypertension		
198.	Suspected pulmonary hypertension Normal or indeterminate findings on resting echocardiographic study	U (5)
199.	Routine evaluation of patients with known resting pulmonary hypertension	I (3)
200.	Reevaluation of patient with exercise-induced pulmonary hypertension to evaluate response to therapy	U (5)
CONTRAST USE IN TRANSTHORACIC/TRANSESOPHAGEAL ECHOCARDIOGRAPHY OR STRESS ECHOCARDIOGRAPHY		
201.	Routine use of contrast All left ventricular segments visualized on non–contrast-enhanced images	I (1)
202.	Selective use of contrast ≥2 contiguous left ventricular segments are *not* seen on non–contrast-enhanced images	A (8)

[*] *A,* Appropriate; *I,* inappropriate; *U,* uncertain.

ACS, Acute coronary syndrome; *APC,* atrial premature contraction; *CABG,* coronary artery bypass grafting; *CAD,* coronary artery disease; *CHD,* coronary heart disease; *ECG,* electrocardiogram; *METs,* metabolic equivalents; *MRI,* magnetic resonance imaging; *PCI,* percutaneous coronary intervention; *SVT,* supraventricular tachycardia; *TEE,* transesophageal echocardiography; *TTE,* transthoracic echocardiography; *TIA,* transient ischemic attack; *TIMI,* Thrombolysis in Myocardial Infarction; *UA,* unstable angina; *VPC,* ventricular premature contraction; *VT,* ventricular tachycardia.

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15

The Chest Radiograph in Cardiovascular Disease

Cylen Javidan-Nejad, Sanjeev Bhalla

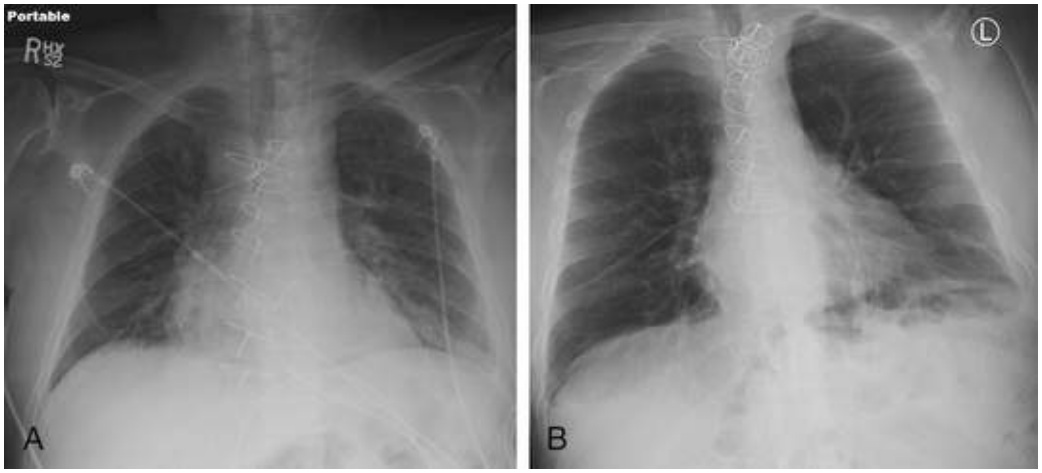
The chest radiograph, or chest x-ray film (CXR), is the most common imaging study. It is relatively inexpensive, readily available, and low in radiation dose, exposing the patient to less ionizing radiation than computed tomography (CT), conventional angiography, or cardiac scintigraphy (**see Chapters 16, 18, and 20**). The CXR is often first-line imaging for most medical conditions, including suspected cardiovascular disease.[1]

Overview

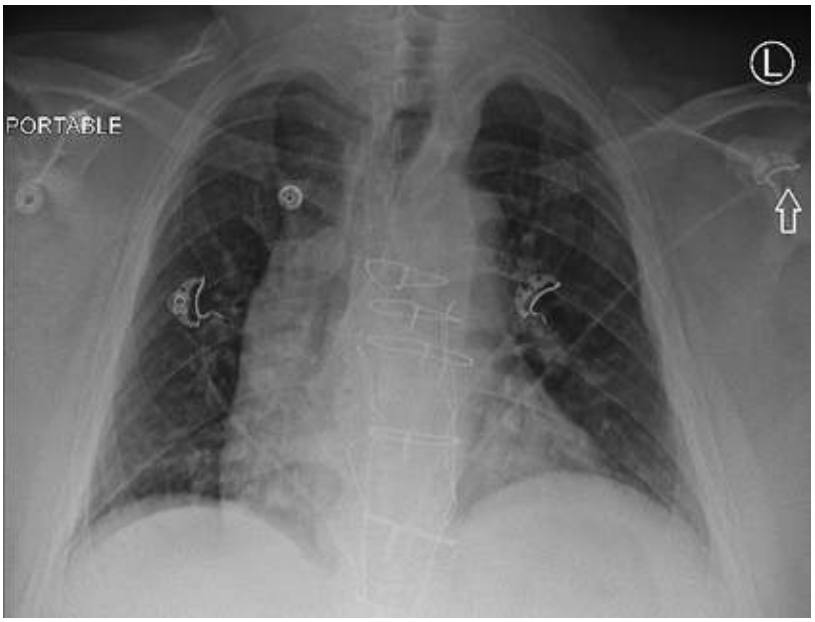
A standard CXR is acquired with the patient upright in deep inspiration and consists of posteroanterior (PA) and lateral views. The PA view is a frontal view acquired with the patient facing the image detector, with the x-ray tube directed to the center of the patient's upper back. The lateral view is acquired with the left side of the patient against the detector and the x-ray tube directed to the patient's right side. For both views, the x-ray tube is placed 6 feet (1.8 m) from the recording surface, which is the optimal distance to minimize image distortion and maximize spatial resolution, while exposing the patient to the least possible radiation dose. An anteroposterior (AP) view is also a frontal radiograph performed for patients who are unable to stand. It is typically used for portable bedside radiography. The AP view is obtained

with the patient facing the tube and lying on the detector plate.[2]

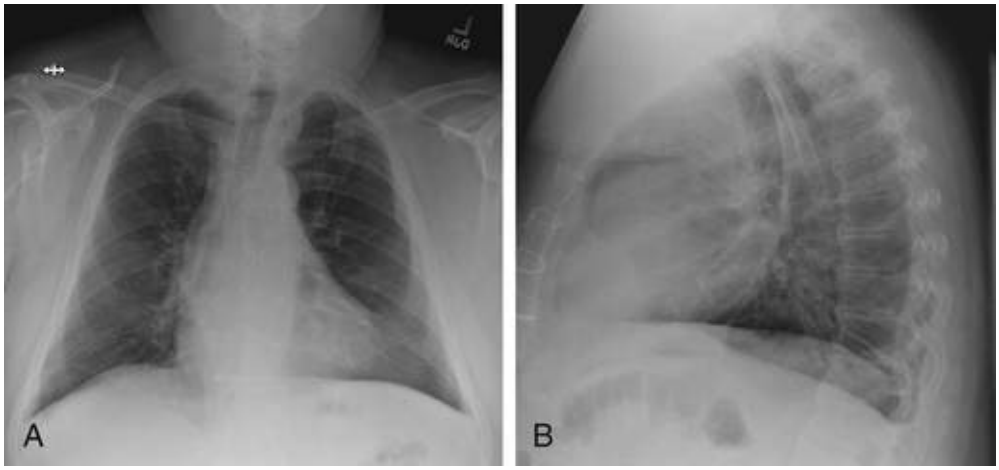
The positioning of the PA and lateral CXR is performed to minimize magnification of the heart and mediastinum by placing these structures as close as possible to the image recording surface. On a PA view the heart size and mediastinal vessels are smaller and more sharply defined than on an AP view (**eFig. 15.1**). This difference is caused by the divergence of the x-ray beam from the source, which magnifies structures located farther from the image detector. A useful analogy is to contrast the size of the shadow of your hand when you lift your hand away from the sidewalk. In this example the sun is the x-ray point source, and the sidewalk is the detector (**eFig. 15.2**). On a lateral view the right hemithorax is magnified relative to the left hemithorax. This feature may be helpful in determining if a small pleural effusion is right or left sided when visible only on the lateral view[3] (**eFig. 15.3**).



EFIGURE 15.1 Comparison of anteroposterior (AP) and posteroanterior (PA) views. **A,** Portable AP view shows an enlarged cardiac silhouette, indistinct hilar vasculature, and a widened mediastinum. **B,** PA view of the same patient obtained 5 hours later after removal of the central venous catheter shows the true normal size of the heart with no mediastinal widening.

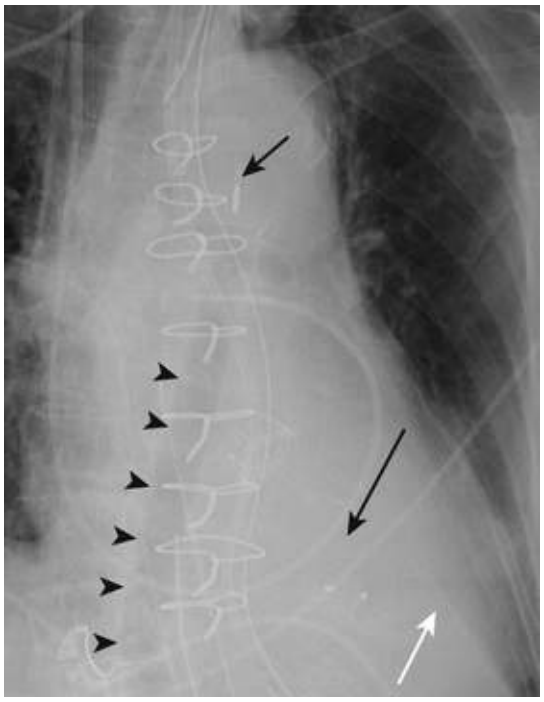


EFIGURE 15.2 Limitations of portable technique. Portable radiograph shows an apparent large right atrial contour and a mediastinal widening to the right of the spine. Comparison with a standard PA chest radiograph obtained the previous day (**see eFig. 15.3A**) would reveal that these apparent abnormalities were caused by the portable technique and patient rotation.



EFIGURE 15.3 Costophrenic angles (CPAs) on the lateral view. Standard PA **(A)** and lateral **(B)** radiographs of the same patient shown in **eFig. 15.2** were obtained the previous day and show no blunting of the right lateral CPA on the PA view, with blunting of the right posterior CPA on the lateral view. The posterior right CPA is located farther behind the spine than the posterior left CPA due to magnification of the right-sided structures, which are located farther from the image recording surface.

On a portable AP CXR, the heart appears relatively larger and the hilar vasculature crowded, a result of the study's recumbent nature and the inability to achieve full inspiration. Portable x-ray machines have lower tube output power, with resultant longer exposure times and increased cardiac and respiratory motion artifacts, as well as decreased resolution.[4] The most common application of portable radiographs is in evaluating the proper course and positioning of mechanical devices placed in a patient, such as endotracheal tubes, central venous catheters, gastric and feeding tubes, and cardiac devices such as pacemakers and implantable cardioverter-defibrillators (ICDs)[5] (**eFig. 15.4**).



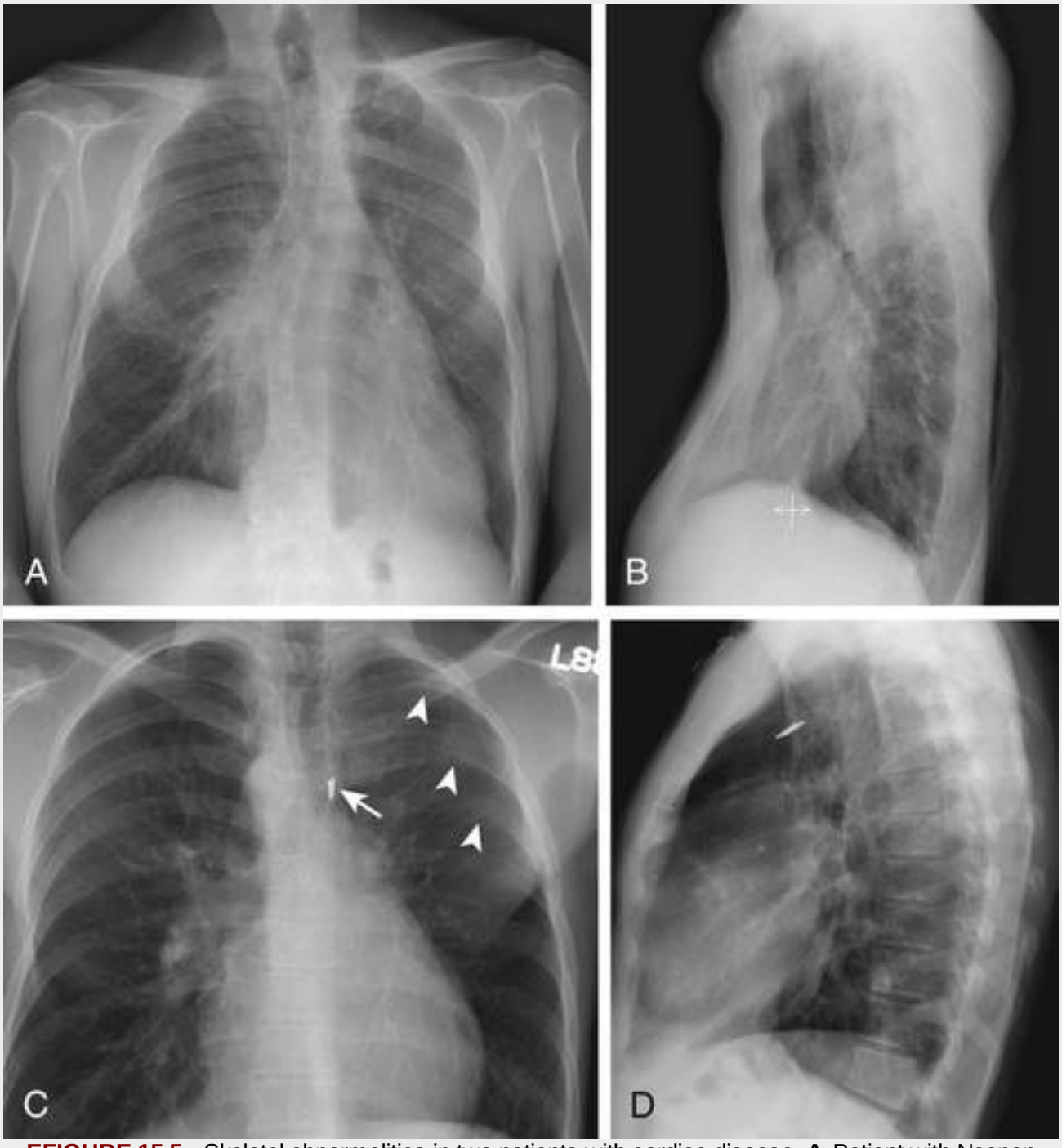
EFIGURE 15.4 Assessment of cardiac and intravascular devices. Coned-down view of portable chest radiograph of patient in intensive care unit shows an intra-aortic balloon device (IABP), with its metallic marker (*short black arrow*) projecting a few centimeters below the aortic arch, indicating that it is well positioned. The inflated balloon of the IABP creates a radiolucent column (*arrowheads*) over the descending aorta. A ventricular septal occluder device (*long arrow*) projects over the heart. The positions of other tubes and catheters are also depicted, such as the pulmonary arterial catheter with its tip in the right pulmonary artery. The left ventricle apex is obscured by a small, left pleural effusion (*white arrow*).

The Normal Chest Radiograph

A CXR can reveal abnormalities of anatomy and physiology by demonstrating an abnormal size or shape of the heart or of specific cardiac chambers; enlarged or diminished size of a normal mediastinal structure; unusual calcifications; and extracardiac findings in the lungs, chest wall, or abdominal organs. The first (and arguably the most difficult) step in the evaluation of a CXR is to distinguish normal findings and normal variants from pathology.

A systematic approach to evaluation of the CXR can begin by assessing the heart size. On a PA radiograph the cardiac/thoracic ratio is approximately 0.5 to 0.6. To calculate this ratio, the horizontal thoracic diameter is measured along the inner margins of the ribs at the level of the dome of the right hemidiaphragm, and the cardiac diameter is calculated as the sum of the most rightward and the most leftward diameters of the heart from the midline. In practice this is done qualitatively. Normally the heart projects over the spine, with about one quarter of its diameter projecting to the right of the midline and three quarters to the left of the midline. The cardiac apex is normally directed to the left, located adjacent to the diaphragm[6] (**see eFig. 15.4**).

Because the cardiac silhouette represents a summation of the heart and surrounding structures, the heart size can erroneously appear enlarged when abundant mediastinal fat and prominent pericardial fat pad or a large pericardial effusion are present.[7] When the lungs are hyperinflated (e.g., emphysema), the cardiac/thoracic ratio decreases, and the heart can seem abnormally small. A truly decreased heart size occurs when the patient is hypovolemic, as in Addison disease or chronic malnourishment (**eFig. 15.5**). Skeletal abnormalities such as pectus excavatum and scoliosis of the thoracic spine can alter the rotation of the heart and make it appear enlarged on a frontal radiograph.



EFIGURE 15.5 Skeletal abnormalities in two patients with cardiac disease. **A,** Patient with Noonan syndrome and spontaneously healed ventriculoseptal defect presents with scoliosis and severe pectus excavatum deformity. The very short distance between the sternum and the spine causes a leftward rotation and displacement of the heart into the left hemithorax defect **(A, B). C,** Patient with tetralogy of Fallot who had a Blalock-Taussig shunt in childhood presents with unilateral inferior rib notching (*arrowheads*). The left fourth and fifth ribs are fused due to lateral thoracotomy in early childhood. Surgical clips above the expected location of the main pulmonary artery (*white arrow*) is related to previous Blalock-Taussig shunt, which before definitive repair provided blood flow from the left subclavian artery to the left pulmonary artery **(C, D).** Note the right-sided aortic arch and the small, pediatric sternotomy wires.

The right heart border is created by the right atrium. The left heart border is formed by the left ventricle inferiorly and the left atrial (LA) appendage superiorly. The outline of the normal right ventricle is not visible on the frontal CXR because of its position anteriorly behind the sternum, with its outer edge located medial to the left ventricle (**Fig. 15.1A**).

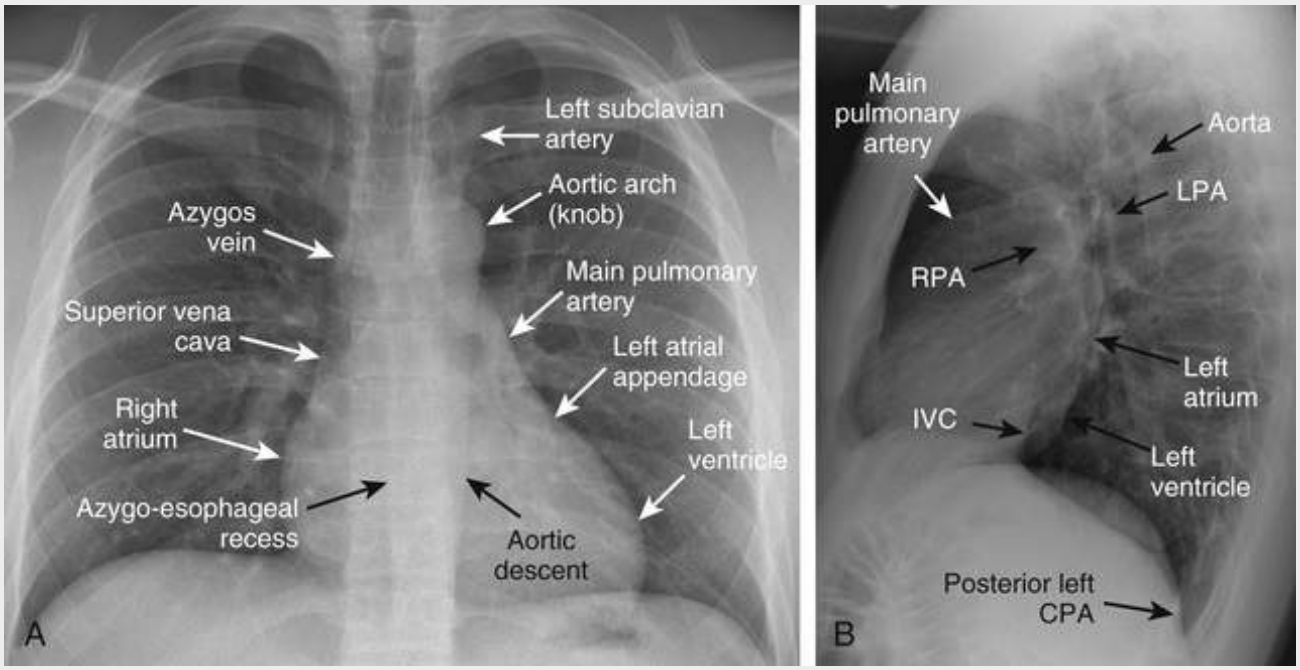


FIGURE 15.1 Normal standard two-view chest radiograph. PA **(A)** and lateral **(B)** views of the chest depict various normal cardiovascular structures. *CPA,* Costophrenic angle; *IVC,* inferior vena cava; *LPA,* left pulmonary artery; *RPA,* right pulmonary artery.

The right border of the mediastinum is created by the superior vena cava (SVC) at this level. The elliptical density projecting on the SVC, just above the right main bronchus, is the arch of the azygos vein as it travels anteroposteriorly from the spine to drain into the SVC. The normal azygos arch contour measures 1.0 cm in diameter and when enlarged can indicate increased systemic venous pressure from systemic fluid overload, right heart failure, or collateral flow through the azygos vein, as in congenital absence of the inferior vena cava (IVC).

The left border of the mediastinum above the heart is composed of two outward bulges, formed by the aortic arch (or aortic knob) superiorly and the main pulmonary artery (MPA) inferiorly. As a general guideline, the MPA and the aorta can be seen above the left main bronchus, whereas the LA appendage is seen just below. The left lateral wall of the descending aorta creates a vertical line projecting lateral to the spine superiorly and over the spine inferiorly as the aorta descends to the diaphragm. The right wall of the aorta is not visible because there is no interface between it and the right lung. Care should be taken not to confuse the azygoesophageal recess for the right aortic border (**Fig. 15.1A**).

On the lateral view the normal right ventricle should be flush with about one third of the lower sternum. Above that, the retrosternal space should be clear in a nonobese patient. The upper cardiac border mostly consists of the right ventricular outflow tract (RVOT), which normally has a relatively flat contour and is angled posteriorly. The posterior cardiac border consists of the left atrium superiorly and the left ventricle inferiorly. A linear vertical line extending from the right hemidiaphragm to project over the heart represents the posterior wall of the IVC.[8]

On the lateral view the vessels of the hila can be assessed. In the center of the hilum is an oval-shaped density composed of the right pulmonary artery (RPA) and right pulmonary veins, known as the “right hilar vascular confluence.” The left pulmonary artery (LPA) is located posterior to RPA and has an archlike configuration, parallel and inferior to the aortic arch. The right and left inferior pulmonary veins appear as branching, elongated densities posterior to the heart and inferior to the hila[9] (**Fig. 15.1B**).

On both PA and lateral views the ascending aorta is normally obscured by the MPA and both atria. The aorta normally increases in size with age, and the great arterial branches off the aortic arch become more tortuous, creating a widened superior mediastinum. Normally on an upright PA chest radiograph, the

vessels should not be visible in the outer third of the lungs, and the lower lung zone vessels should be larger in caliber than the upper vessels because of gravity. The right and left lungs should be symmetric in size and pulmonary vascular markings.[10]

Approach to Evaluation of a Chest Radiograph

A well-developed approach to the chest radiograph takes years to develop and is beyond the scope of this chapter. Each interpreter must develop a consistent approach that carefully looks at the bones, lungs (with attention for pleural abnormalities), vasculature, and heart.[11] Knowledge of the type of study (PA versus AP) will allow for a more accurate assessment of heart size and mediastinal contour.

Prior radiographs should be reviewed routinely because many abnormalities are put into appropriate perspective by determining whether they are new or old and the rate of change. For example, new enlargement of the aortic arch may be seen in the setting of aortic dissection, whereas chronic mediastinal widening is more likely to be related to a congenital variant such as a double aortic arch. The final step in image interpretation relies on the generation of a differential diagnosis based on the constellation of findings and an appropriate clinical history.[12]

Specific Cardiovascular Diseases

The specific cardiovascular diseases discussed next are grouped into four main categories to highlight the variety of cardiovascular conditions that may be seen on a CXR: diseases affecting (1) the heart size and morphology, (2) the coronary arteries, (3) the pericardium, and (4) the aorta.

Diseases Affecting Heart Size and Morphology

When the cardiac silhouette is enlarged, it is most often related to biventricular failure, with no definable individual chamber enlargement. In valvular disease and many types of congenital heart disease, however, individual chamber enlargement develops, identification of which is central to diagnosis. Acquired left heart disease can cause left ventricular (LV) or global cardiac enlargement when more than one cardiac chamber is enlarged. LV enlargement manifests as downward and leftward displacement of the LV apex on the frontal view and posterior displacement of the lower cardiac border on the lateral view (**Fig. 15.2**) (see Classic References, Higgins). Diseases that lead to LV enlargement are those associated with a volume-overload status, such as congestive heart failure, ischemic and nonischemic cardiomyopathies, and valvular regurgitation. True and false cardiac aneurysms and pericardial masses cause a focal convexity or masslike density along a cardiac border. Acquired heart diseases associated with normal LV size tend to be those diseases associated with a pressure-overload status, such as aortic stenosis or systemic arterial hypertension, or those associated with decreased myocardial compliance, such as hypertrophic or restrictive cardiomyopathies.

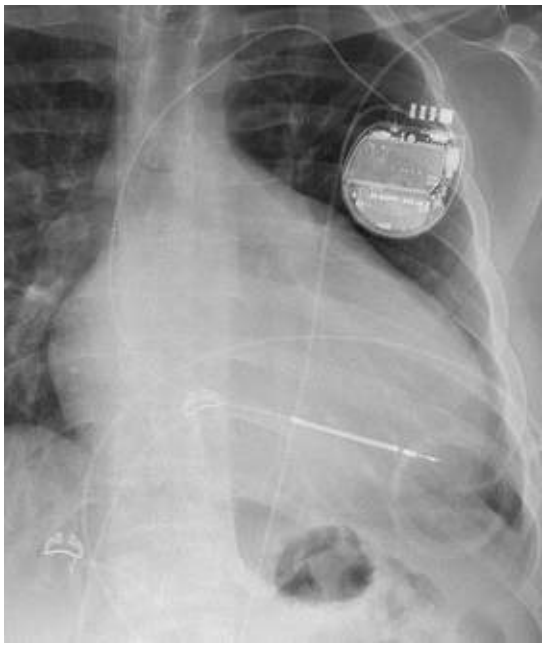


FIGURE 15.2 Left ventricle enlargement. Coned-down PA chest radiograph of 20-year-old man with severe nonischemic cardiomyopathy shows an extremely large left ventricle with the cardiac apex displaced toward the left. The patient also had pulmonary hypertension with an enlarged contour of the main pulmonary artery.

Left atrial enlargement (LAE) can be identified by a convex (versus normal concave) LA appendage contour. When LAE is present, the right border of the left atrium (seen as a retrocardiac curvilinear density) becomes laterally displaced and more convex, creating the *double density sign*. In LAE the distance from the midportion of this double density line to the middle of the left main bronchus exceeds 7 cm. Another finding of LAE is widening of the angle of the carina and upward deviation of the left main bronchus, caused by the mass effect of the left atrium on this bronchus. On the lateral view the upper aspect of the posterior cardiac contour becomes more convex when there is LAE (**Fig. 15.3**).

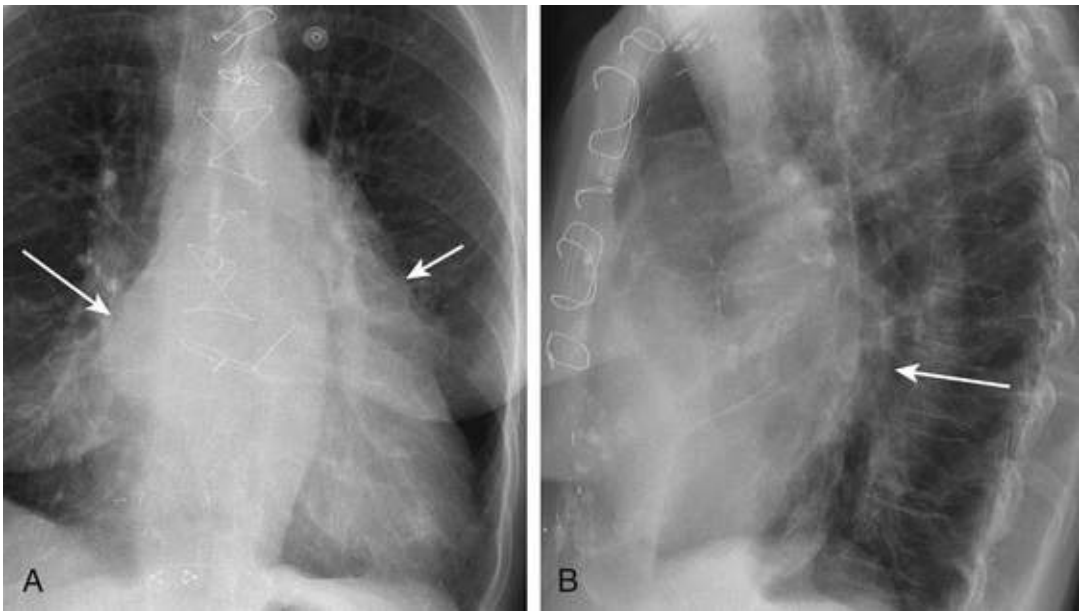


FIGURE 15.3 Left atrial enlargement (LAE). Coned-down PA **(A)** and lateral **(B)** chest radiographs in patient with mitral stenosis show findings of severe left atrial dilation. **A,** On the frontal view, a double density sign (*long arrow*) along the right cardiac border and a convexity along the upper left cardiac border (*short arrow*) reveal the LAE. **B,** Lateral view shows the posterior bulge of the left atrium (*arrow*).

When the right ventricle becomes enlarged, it pushes the left ventricle laterally, resulting in an enlarged appearance of the left heart. In certain situations, right ventricular (RV) enlargement will result in upturning of the cardiac apex. An enlarged RV outflow tract (RVOT) rarely results in a prominent upper cardiac border in the expected location of the LA appendage. The lateral chest radiograph is helpful in confirming RV enlargement by filling in of the lower aspect of the retrosternal space. RV hypertrophy can cause displacement of the entire posterior cardiac border toward the spine, simulating LV enlargement. The key to understanding this variant is to realize that, unlike in LV enlargement, the extension of the cardiac border posterior to the IVC is not increased (**Fig. 15.4**).

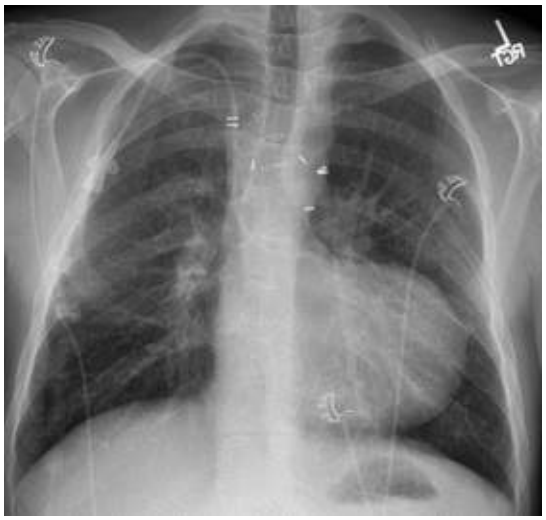


FIGURE 15.4 Boot-shaped heart in 30-year-old man with history of dextro-transposition of the great arteries (D-TGA) and hypoplastic left ventricle treated by total cavopulmonary connection. The PA radiograph reveals a boot-shaped heart caused by a greatly enlarged systemic right ventricle. The cardiac apex is directed upward. Note the mediastinum is very narrow, creating the "egg-on-string" appearance described in patients with D-TGA.

Right atrial enlargement (RAE) is almost always caused by tricuspid regurgitation, which also results in RV enlargement. Findings of RAE on the frontal view include increased convexity and elongation of the right cardiac border. RAE is difficult to identify on the lateral view.

Congestive Heart Failure

In congestive heart failure, both the left ventricle and the left atrium become enlarged because of the elevated LV end-diastolic volume (**see Chapters 21 and 23**). This enlargement may be exaggerated if the mitral annulus dilates and mitral regurgitation develops. As LA pressures increase, pulmonary venous hypertension (PVH) develops. Based on its severity, PVH can be divided into three grades: I or mild, II or moderate, and III or severe (see Classic References, Sharma). Each grade of PVH is associated with specific imaging findings (**Table 15.1**).

TABLE 15.1

Correlation of Pulmonary Venous Hypertension (PVH) with Mean Left Atrial (LA) Pressures and Imaging Findings on Chest Radiograph (CXR)

PVH Grade	MEAN LA PRESSURE (mm Hg)		Pulmonary Edema CXR Findings
	Acute Disease	Chronic Disease	
I	12-19	15-25	Mild pulmonary edema with vascular redistribution
II	20-25	25-30	Interstitial pulmonary edema with peribronchial cuffing and Kerley lines
III	>25	>30	Alveolar pulmonary edema with confluent air space opacities

The initial finding of PVH is redistribution of flow to the upper lung zones, resulting in equalization of the sizes of the vascular markings on an upright CXR. Over time the findings progress, with the upper lobe vessels larger than the lower lobe vessels. This phenomenon is known as *cephalization*, or pulmonary vascular redistribution (**Fig. 15.5A**).

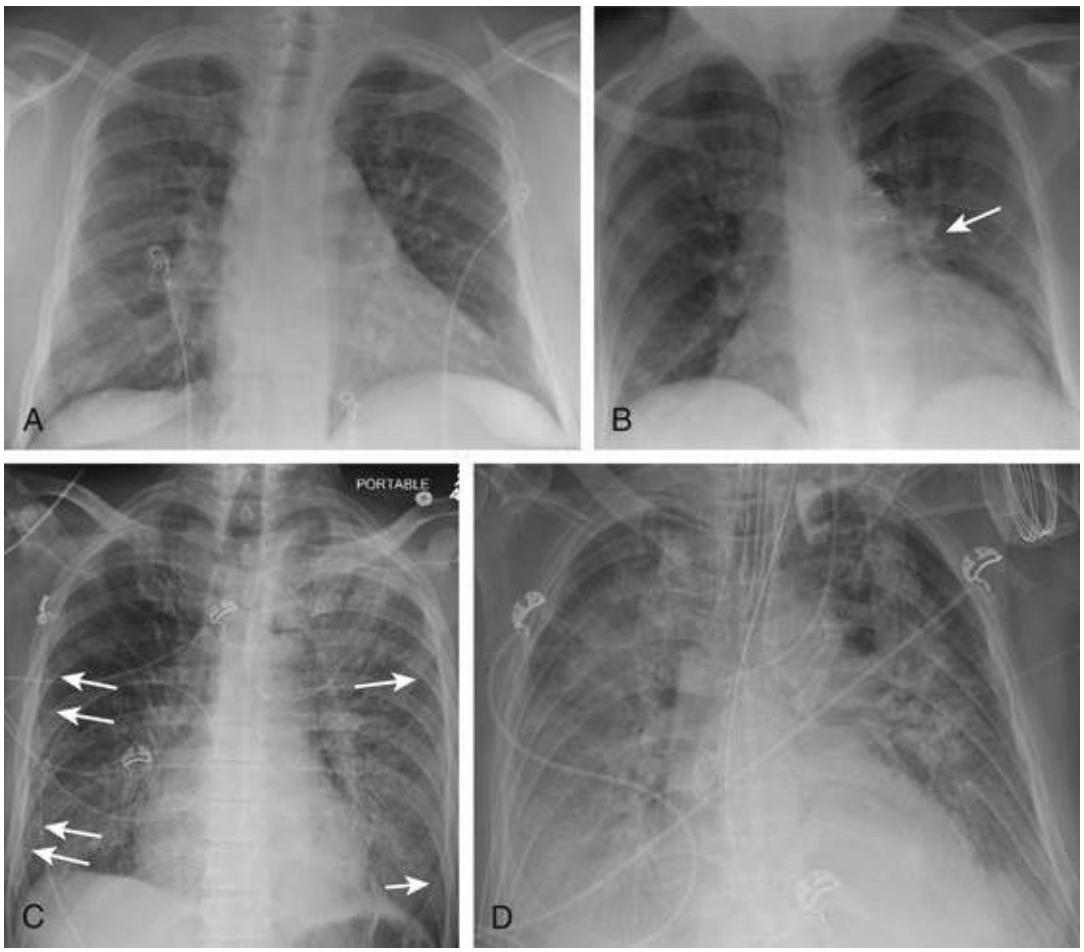


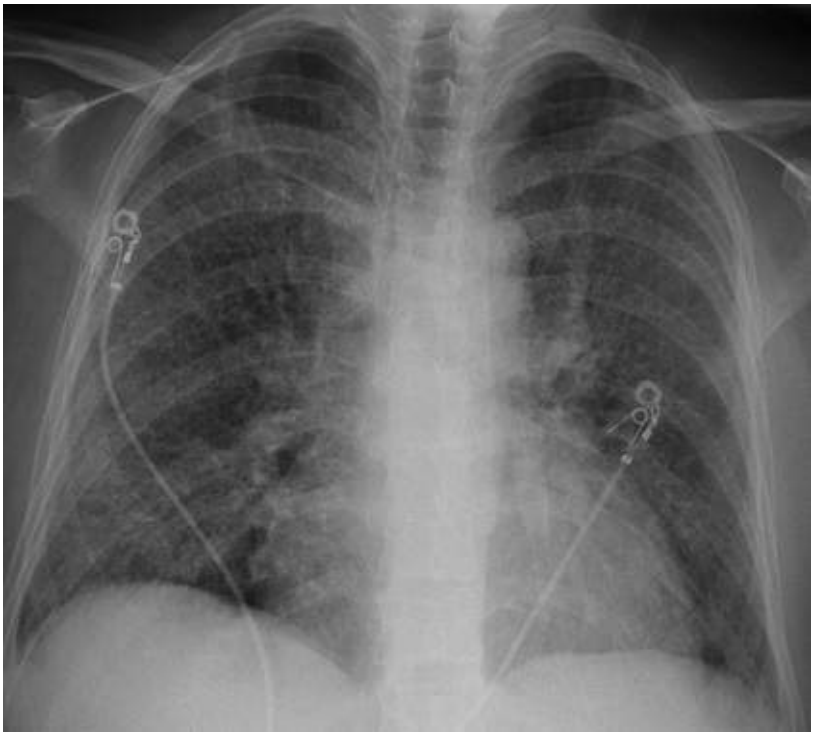
FIGURE 15.5 Pulmonary edema in four different patients with variable severity. **A,** Cephalization indicates pulmonary venous hypertension in which the upper lobe vessels are equal to or larger than the lower lobe vessels. At this point, pulmonary edema has not developed. **B,** With progression, mild pulmonary edema ensues; the vascular margins become indistinct, and peribronchial cuffing develops (*arrow*). Clothing clips project over the aorta and are external to this second patient. **C,** The third patient has left upper lobe pneumonia and suddenly developed worsening dyspnea. CXR shows moderate pulmonary edema with many interstitial lines, indicating fluid in the septa of the lung parenchyma (Kerley lines, *arrows*), superimposed on the left lobe pneumonia. **D,** The fourth patient has severe alveolar pulmonary edema that presents as bilateral air space opacities in both lungs on CXR. The bilateral pleural effusions are also caused by the congestive heart failure.

As the mean LA pressure increases, interstitial pulmonary edema develops from extravasation of fluid

into the lung interstitium surrounding the bronchovascular bundles and into the inter- and intralobular septa.[13] Such edema is manifest on a CXR with enlarged, poorly defined hilar vessels; thickening of the bronchial walls (peribronchial cuffing when viewed on end); fine central linear interstitial markings (Kerley A-lines), or peripherally appearing as parallel horizontal lines abutting the pleura (Kerley B-lines); and thickening of the fissural stripes, representing subpleural edema along the inner margin of the visceral pleura (**Fig. 15.5B**).

In severe pulmonary edema the fluid extends from the interstitium into the alveolar spaces, creating alveolar consolidations (or air space opacities), which tend to begin around the hila and progress in the middle and lower lung zones. Pleural effusions often develop in severe pulmonary edema (**Fig. 15.5C**). The distribution of findings is typically symmetric, creating a "bat wing" or "butterfly" appearance of the alveolar consolidations. If the patient has been lying on one side, the pulmonary edema tends to be more severe on that side because of the effect of gravity. Unilateral or focal pulmonary edema can result from central obstruction of a vein by a mass or surrounding mediastinal fibrosis or from a venous stricture, which can be a complication of LA ablation[14] (**see Chapter 38**).

It is important to distinguish cardiogenic from noncardiogenic pulmonary edema. Noncardiogenic pulmonary edema has many causes beyond heart failure, such as asphyxiation, drowning, intracranial hypertension, smoke and noxious fume inhalation, adult respiratory distress syndrome, and adverse reaction to certain drugs (e.g., diazepam, cocaine). In such patients the LA and pulmonary venous pressures are not significantly elevated, and heart size tends to be normal with no pleural effusions. The main cause of noncardiogenic pulmonary edema is diffuse alveolar damage with interruption of the alveolar-capillary membranes, leading to leakage of fluid into the alveolar spaces[15] (**eFig. 15.6**).



EFIGURE 15.6 Noncardiogenic pulmonary edema. Portable frontal chest radiograph of patient with multisubstance use demonstrates mixed interstitial and alveolar pulmonary edema. The heart size is normal. Echocardiography (not shown) demonstrated normal cardiac function.

Right heart failure is usually secondary to left heart failure. In such situations the azygos arch, SVC border, or IVC border can become enlarged, indicating systemic venous hypertension.[16]

Valvular Heart Disease

Knowing the location of cardiac valves is a key component of cardiac assessment on the CXR. To do this, on the lateral view an oblique line is drawn from the hilum to the cardiac apex. The expected location of the tricuspid valve is at the junction of the anterior and middle thirds of the line. The mitral valve is at the junction of the middle and posterior thirds, located just posterior to the line, and the aortic valve is located at that same location, but anterior to the line. On the frontal radiograph the tricuspid valve projects over the spine and has a vertical orientation. The mitral valve is located more cephalad and to the left of the spine[17] (**see Chapter 67**).

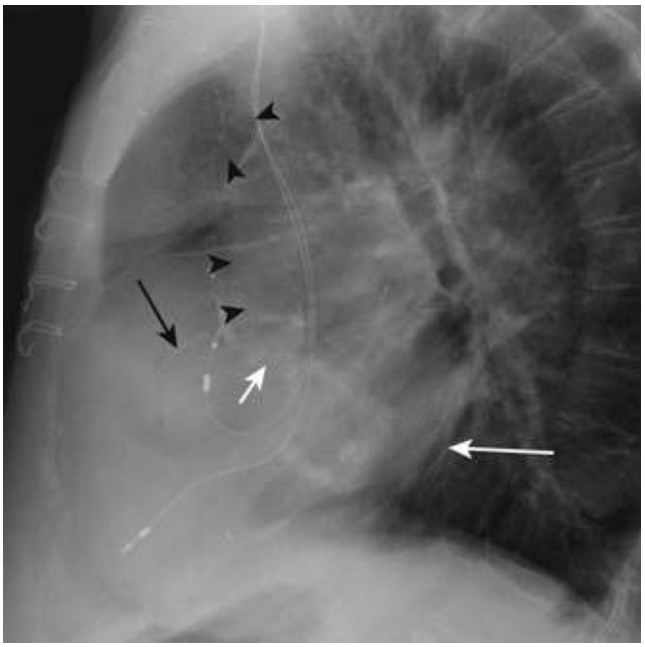
Valvular calcifications are only visible when very dense. Practically, only aortic valve and mitral annulus calcifications tend to be seen on CXRs. The lateral view is best for identifying calcifications of the valve leaflets and annulus. Manually adjusting the window setting of digital images can help reveal calcifications. In general, calcifications are best seen when oriented tangential to the x-ray beam.[18] **Table 15.2** provides the locations and appearance of various calcifications of the heart and vessels (**eFigs. 15.7 and 15.8**).

TABLE 15.2

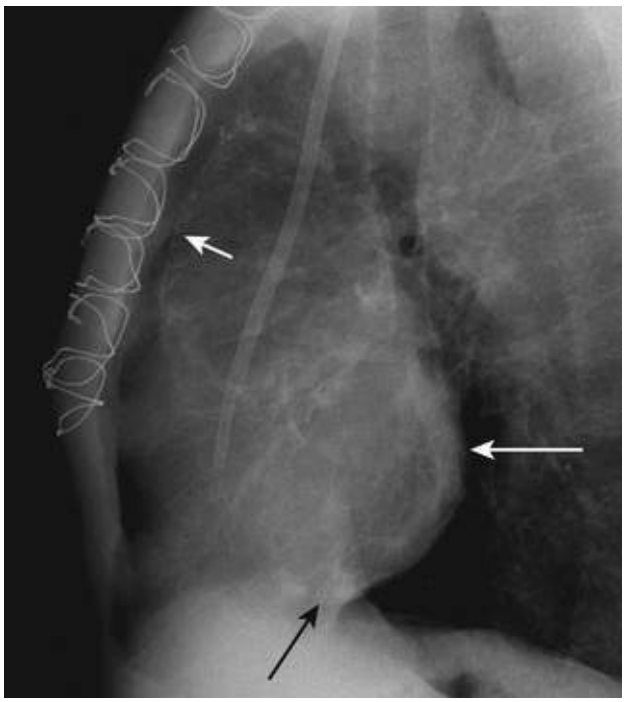
Cardiac Calcifications on a Chest Radiograph

LOCATION	EXAMPLE	LOCATION AND PATTERN OF CALCIFICATION
Myocardial wall	MI, left ventricular post-MI aneurysm	Apex or anterolateral walls of left ventricle
Left atrial wall	Longstanding mitral stenosis	Thin line roof of left atrium on lateral view
Pericardium	Calcific pericarditis	Most common in atrioventricular grooves and lateral to right atrial and right ventricular walls; not likely to involve the apex
Mitral annulus	Tumefactive calcification	Crescentic, reverse-C, or sometimes O-shaped coarse calcification
Mitral valve	Mitral stenosis	Lumplike mass in center of the expected location of mitral annulus
Aortic annulus and valve	Aortic stenosis	Irregular ring of dense calcification, which can also extend to the ring center when the leaflets are also calcified
Coronary artery	Atherosclerosis, aneurysms	Parallel lines (“train tracks”) when imaged along its length, and ring of calcification when imaged end on

MI, Myocardial infarction.



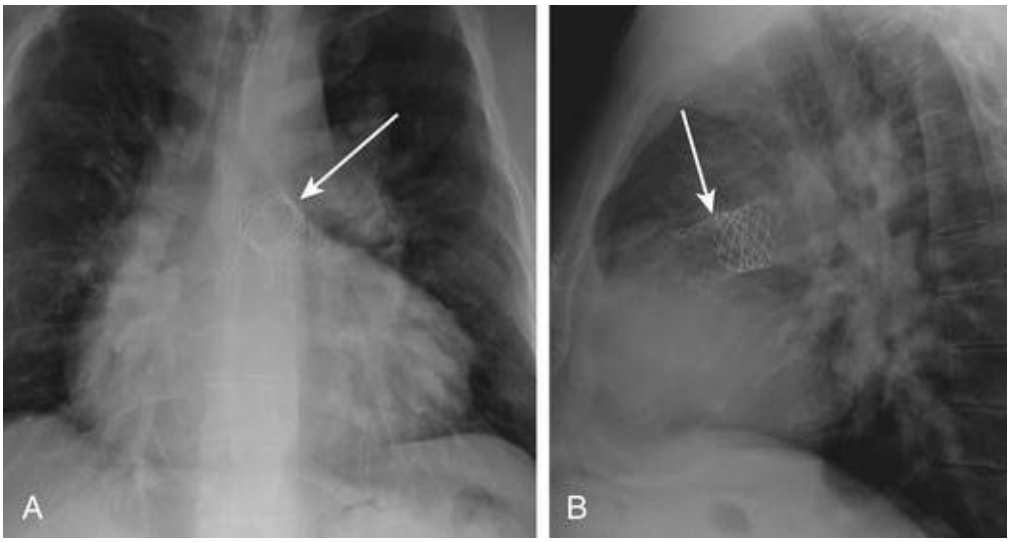
EFIGURE 15.7 Calcifications of the heart. Coned-down lateral chest radiograph of patient with known aortic stenosis shows nodular calcification in the expected location of the aortic valve (*short white arrow*), in addition to the reverse-C configuration of mitral annulus calcification (*long white arrow*). The *black arrowheads* depict atherosclerotic calcification of the anterior wall of the ascending aorta. A curvilinear calcific density crossing the aortic root and coursing anteriorly toward the apex (*black arrow*) represents calcification of the wall of the left anterior descending coronary artery.



EFIGURE 15.8 Calcifications of the heart. Coned-down lateral chest radiograph of patient with end-stage renal failure and heterotopic calcification of the myocardium. A dense, curvilinear, calcific density along the upper posterior cardiac border represents a densely calcified left atrial wall (*long white arrow*). This extends inferiorly also to involve the wall of the left ventricle (*black arrow*). Extensive atherosclerotic calcification of the ascending aorta is also present (*short white arrow*).

The aortic valve is located adjacent to the mitral valve, located slightly more anteriorly and superiorly, with a relatively more horizontal orientation. It projects over the spine on the frontal radiograph, making it difficult to visualize. The pulmonic valve is located superiorly above the expected location of the

RVOT, medial and caudal to the contour of the MPA (**eFig. 15.9**).



EFIGURE 15.9 Location of the right ventricular outflow tract. Frontal **(A)** and lateral **(B)** views of the chest show two Melody valves (*arrow*) placed in tandem in the pulmonary artery annulus and main pulmonary artery. This patient had a history of repaired tetralogy of Fallot and later developed moderately severe pulmonic regurgitation requiring placement of a Melody valve.

Diseases of the cardiac valves tend to cause specific cardiac chamber enlargement, instead of the global cardiomegaly typically seen with congestive heart failure. Stenotic valve diseases cause pressure overload of the chamber immediately proximal to the valve, leading to single-chamber enlargement. An example is mitral stenosis (MS), which causes marked LAE without LV dilation or hypertrophy (**see Chapter 69**). This is only true when complications of longstanding pressures have not yet developed, such as pulmonary hypertension from longstanding MS, in which the right ventricle also becomes enlarged. Moderate to severe regurgitation of a valve causes volume overload, which results in dilation of the cardiac chambers proximal and distal to the diseased valve.[18]

MS is responsible for the most severe enlargement of the LA on a chest radiograph, without significant LV enlargement. The left atrium can become so dilated that its lateral margin extends beyond the right atrial border. In such cases, on the frontal view the right cardiac border is created by the greatly enlarged let atrium. Chronic severe PVH combined with marked LAE can create the “Viking helmet” sign, with the enlarged vessels in the upper lobes representing the horns on the helmet (the heart) (**Fig. 15.6**). LA wall calcification is common in severe MS. This calcification appears linear and follows the expected contours of the left atrium, best seen on the lateral view [**see eFig. 15.7**]. Unlike MS, mitral regurgitation (MR) results in both LA and LV enlargement. The eccentric jet of regurgitation can be directed toward the ostium of the right superior pulmonary vein, leading to an asymmetric pulmonary edema in the right upper lobe[19] (**eFig. 15.10**).

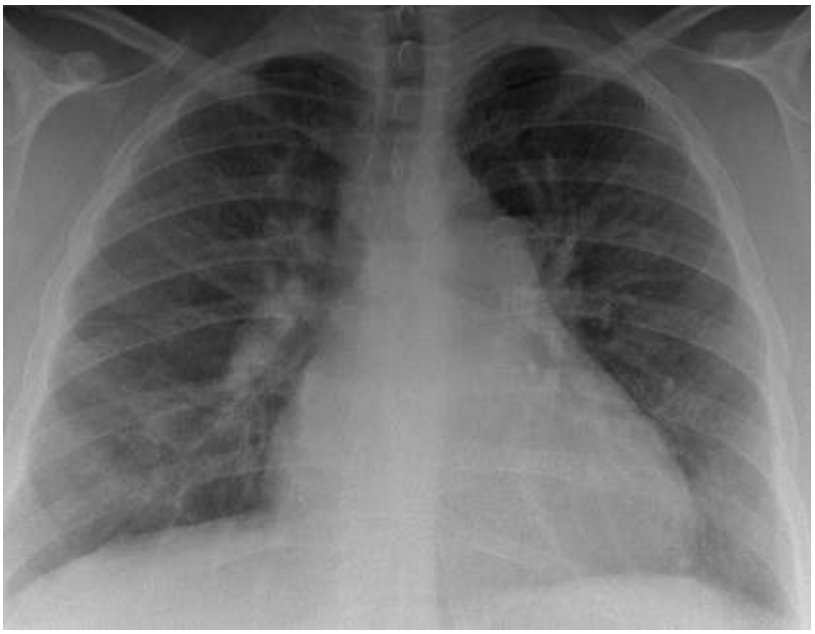
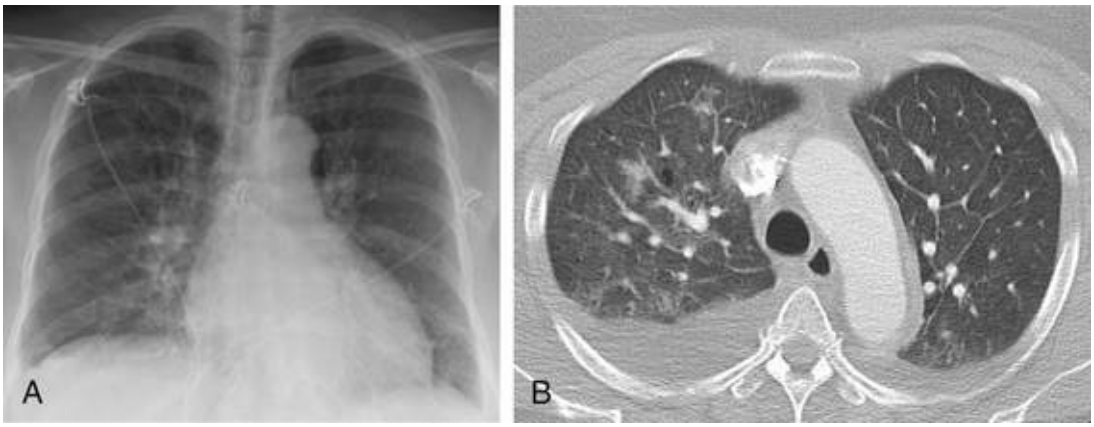


FIGURE 15.6 "Viking helmet" sign. PA radiograph of patient with known rheumatic heart disease and mitral stenosis shows cephalization of the upper lobe vessels, creating the Viking helmet sign. The left cardiac border is flattened because of left atrial enlargement, and the main pulmonary artery contour is enlarged from the ensuing pulmonary hypertension.

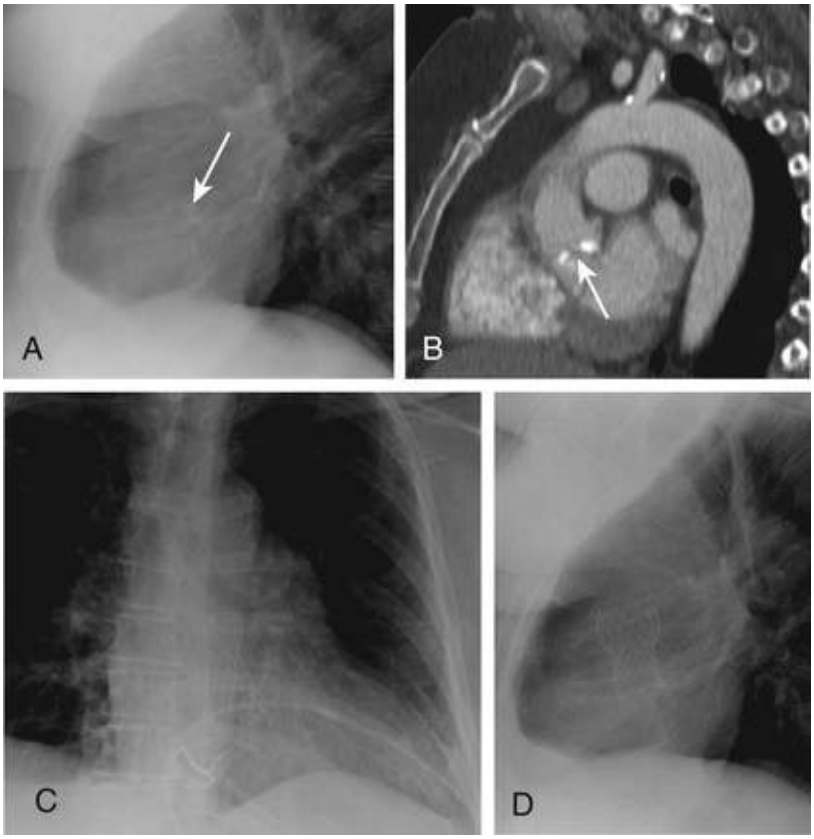


EFIGURE 15.10 Asymmetric pulmonary edema in 56-year-old woman with acute dyspnea was evaluated with CXR and CT to rule out pulmonary embolism. **A,** CXR showed mildly dilated, right upper lobe pulmonary vasculature, relative to that of the left upper lobe. **B,** CT image acquired 2 hours later revealed ground-glass opacities only involving the right upper lobe and representing early asymmetric pulmonary edema. There are also bilateral pleural effusions. Further laboratory workup excluded an infection and also revealed elevated troponin levels resulting from an acute myocardial infarction. Echocardiography showed mild to moderate mitral regurgitation and left ventricular ejection fraction of 30%.

Rarely, severe MR may present with fibrosis and areas of osseous metaplasia in the lungs from microhemorrhages secondary to elevated venous pressures. These tiny calcifications overlap calcified granulomas on CXR.[20]

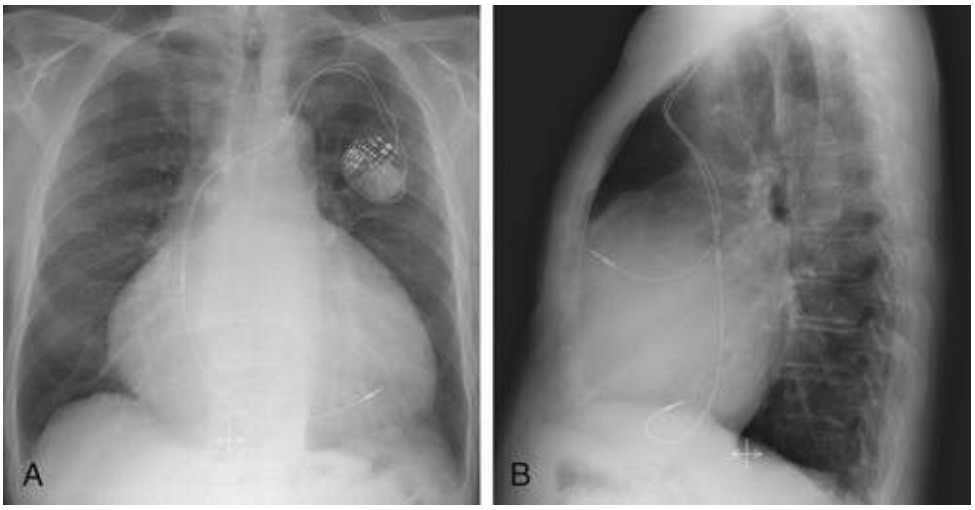
Chronic enlargement of the ascending aorta in the absence of systemic arterial hypertension, atherosclerotic aortic aneurysm, or type A aortic dissection should suggest aortic valve disease (**see Chapter 68**). If there is also LV dilation, aortic regurgitation should be the main consideration. However, if the LV size is normal, aortic stenosis (especially from a bicuspid aortic valve) should be suspected. Dilation of the ascending aorta on the PA view appears as an abnormal, smooth, convex contour superior to the expected location of the right atrium. On the lateral view the upper ascending aorta can be seen as

an upward convexity located posterior and slightly superior to the contour of the RVOT (**eFig. 15.11**). Severe calcification of the aortic valve leaflets in aortic stenosis is difficult to visualize on a chest radiograph and can sometimes be identified on the lateral view.[21]



EFIGURE 15.11 Aortic stenosis before and after repair. **A,** Lateral chest radiograph of elderly patient with severe aortic stenosis shows an irregular, ringlike calcification (*arrow*) in the expected location of the aortic valve. **B,** Corresponding CT image reconstructed in the sagittal plane across the valve shows densely calcified aortic valve leaflets (*arrow*), in keeping with patient history of stenosis. The location corresponds with the abnormality seen on the lateral chest radiograph. Coned-down images of the frontal **(C)** and lateral **(D)** chest radiographs obtained after transcatheter aortic valve replacement display the location of the valve replacement. Note that dark windowing of the images may be required to better visualize metallic hardware and calcifications.

Tricuspid valve stenosis (TS) is quite rare and only seen in congenital stenosis (**see Chapter 70**). Tricuspid regurgitation (TR) is much more common and may be seen in Ebstein anomaly (**Chapter 75**). In TS or TR the right atrium becomes extremely enlarged (**eFig. 15.12**). Acquired TS is seen with rheumatic heart disease and is frequently accompanied by valvular regurgitation caused by deformity of the leaflets. TR is most often encountered as a result of right heart failure secondary to left heart failure and from pulmonary hypertension. TR leads to both RA and RV enlargement on the CXR.[21,22]



EFIGURE 15.12 Right atrial and right ventricular enlargement in Ebstein anomaly. **A,** PA radiograph shows enlargement of the cardiac silhouette. The marked convexity of the right cardiac border is caused by the extremely dilated right atrium. The right ventricle is also much enlarged, as evidenced by the left lateral displacement of the right location of the tip of the ventricular lead of the cardiac pacemaker, which is located in the right ventricle. **B,** Lateral view reveals the long length of contact of the anterior cardiac border with the sternum, indicative of overall RV enlargement.

Pulmonic stenosis is most often a congenital anomaly and tends to manifest with RV enlargement accompanied by a very prominent MPA contour on the frontal view (**see Chapter 70**). The LPA also becomes enlarged, whereas the RPA size remains normal. The size of the RPA and LPA are best identified on the lateral chest radiograph[23] (**Fig. 15.7**).

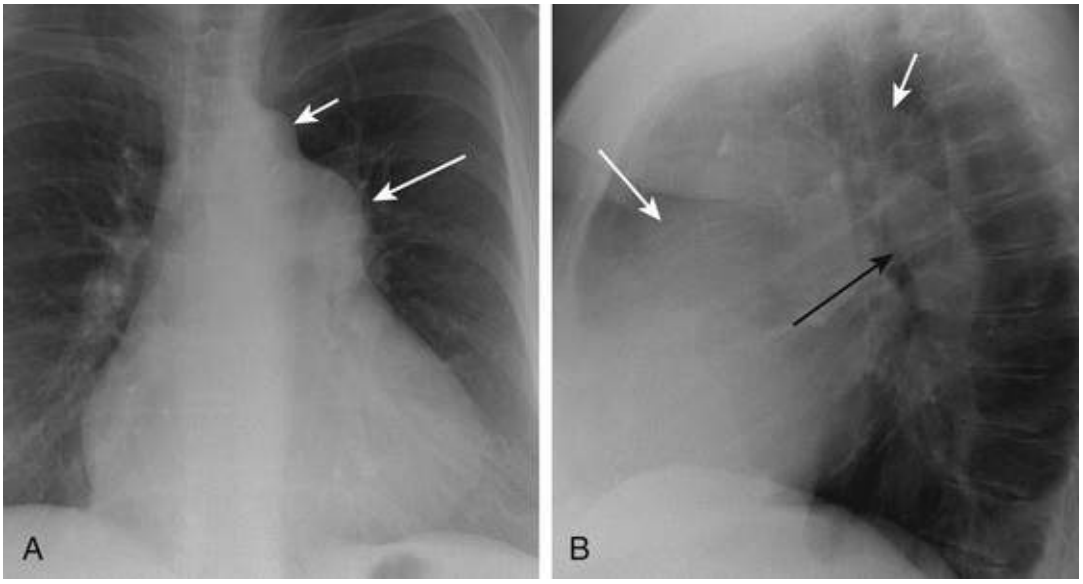


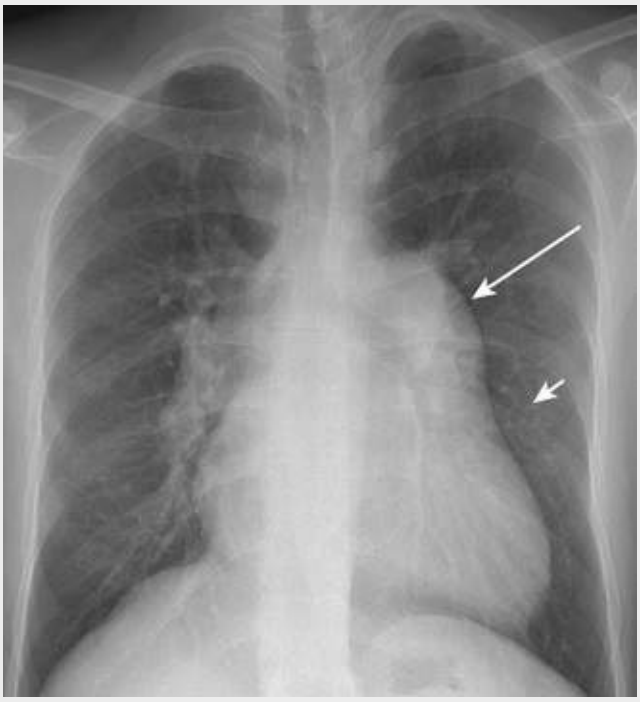
FIGURE 15.7 Congenital pulmonic stenosis. **A,** PA radiograph demonstrates marked enlargement of the main pulmonary artery (MPA) (*long white arrow*), such that it is larger the aorta (*short white arrow*). Note that the right pulmonary artery and its branches are normal sized, and the enlarged left pulmonary artery (LPA) is hidden behind the dilated MPA. **B,** On the lateral view the retrosternal space is filled by the enlarged right ventricle and the dilated MPA, which causes a masslike density with an upward convexity (*long white arrow*). Note dilated LPA (*long black arrow*) relative to the aorta (*short white arrow*).

Pulmonary Hypertension

Pulmonary hypertension (PH) may result from intrinsic conditions involving the pulmonary arterial wall

or may occur in the setting of other conditions, such as chronic left heart disease, interstitial lung disease, or chronic pulmonary thromboembolism (**see Chapter 85**). Regardless of the cause, PH will manifest with RV, RA, and MPA enlargement. The degree of central RPA and LPA enlargement is directly proportional to the severity of the PH.

CXR and CT examination of these patients is usually performed to help identify the cause of the PH. Evidence of severe mitral or aortic valve disease or underlying lung disease can be detected on CXRs. "Pruning" of the pulmonary vasculature, whereby the enlarged pulmonary arteries abruptly taper so that the outer 2 cm of the lung appears devoid of vasculature, can be seen in many causes of severe PH, most notably idiopathic PH, Eisenmenger syndrome, and chronic thromboembolic disease[24] (**eFig. 15.13**).



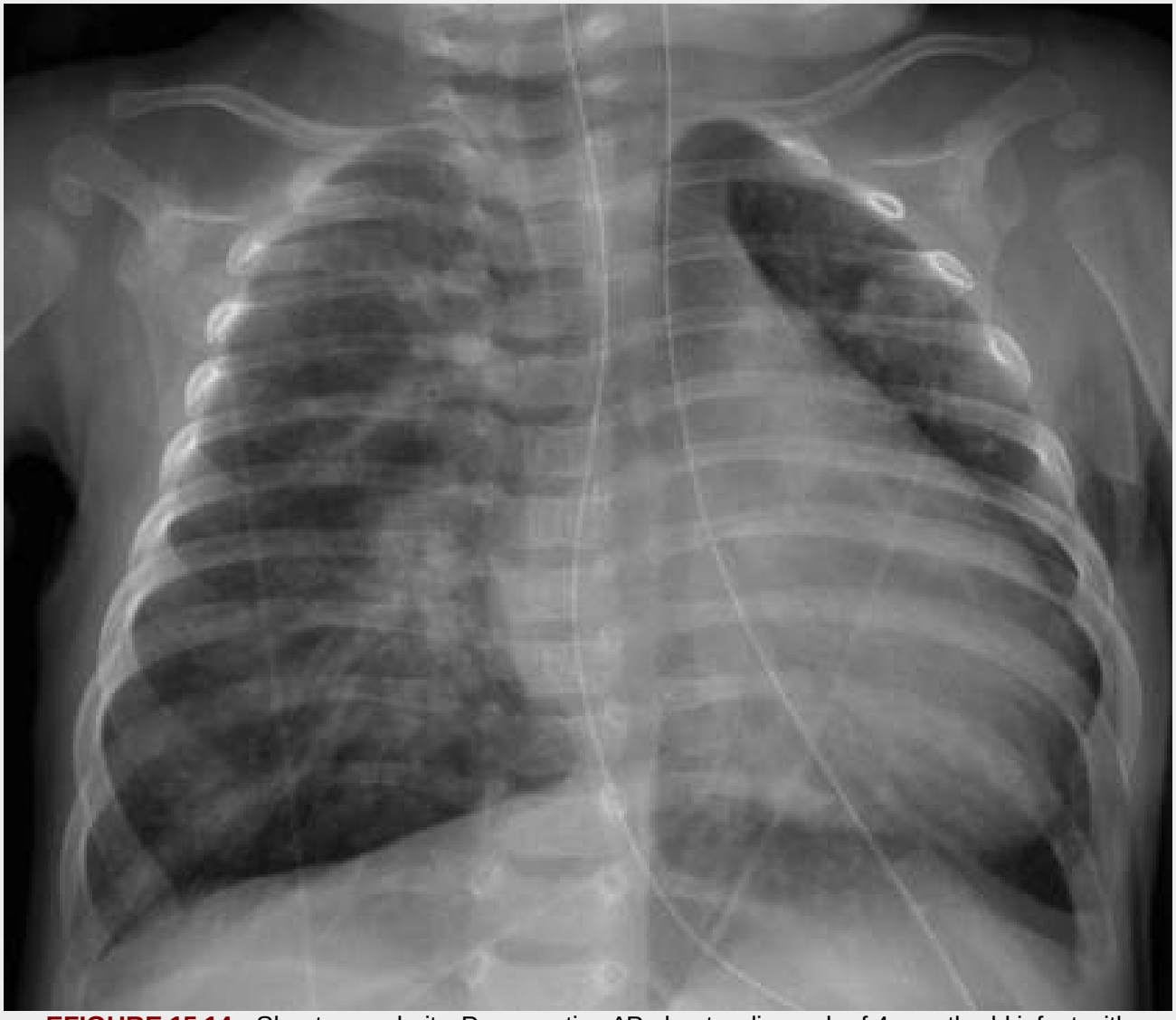
EFIGURE 15.13 Eisenmenger syndrome (phenomenon). PA chest radiograph of an adult patient with untreated ventricular septal defect and pulmonary hypertension caused by development of Eisenmenger syndrome. Marked enlargement of the main pulmonary artery contour (*long arrow*) and overall enlargement of the heart result from an enlarged right ventricle and right atrium, in keeping with the severe pulmonary hypertension. Central pulmonary arteries in the hila are enlarged, with multiple smaller arterial branches peripheral to the hila indicating shunt vascularity (*short arrow*). The inferior vena cava contour is displaced posteriorly because of the right atrial dilation. Crosshairs placed during acquisition of the radiograph project over the diaphragm and to the right of (which means posterior to) the IVC.

Congenital Heart Diseases

In the clinical evaluation of patients with congenital heart disease (CHD), it is important to know if the patient is cyanotic (indicative of a right-to-left shunt) or acyanotic (**see Chapter 75**). On the CXR, the clinician must determine if there is an enlarged cardiac silhouette and whether the pulmonary vascularity is normal, disorganized, decreased, or increased.[25,26] The specific imaging findings of some of the more common CHDs are discussed here.

Atrial and ventricular septal defects (ASDs and VSDs), partial anomalous pulmonary venous connections (PAPVCs), and patent ductus arteriosus (PDA) are acyanotic CHDs associated with a left-to-right shunt. This shunting increases the size and sometimes tortuosity of the pulmonary arterial branches, creating the characteristic "shunt vascularity" on a CXR. Unlike the pruning seen with PH, shunt vascularity does not taper and results in vessels that can be seen all the way to the pleural surface.

For this finding to become evident, a 2 : 1 shunt must exist (**eFig. 15.14**).

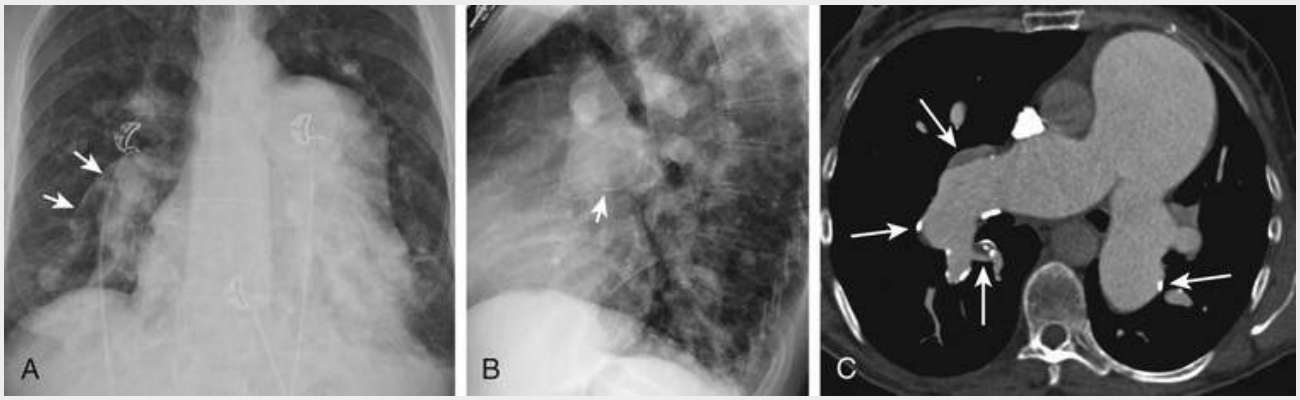


EFIGURE 15.14 Shunt vascularity. Preoperative AP chest radiograph of 4-month-old infant with ventricular septal defect. Dilated peripheral arterial branches extend to the pleura because of shunt vascularity. There is mild pulmonary edema. The left ventricle and left atrium are enlarged, resulting in an overall enlargement of the cardiac silhouette, displacement of the cardiac apex leftward and toward the diaphragm, and flattening of the upper left cardiac border. The internal and external portions of the nasogastric tube are noted.

In the setting of a shunt, the receiving cardiac chamber or vessel becomes enlarged. With an ASD, the right atrium, right ventricle, and MPA will be enlarged. VSDs tend to spare the right atrium to some degree but also result in LA dilation, unlike an ASD. In PAPVC a pulmonary vein drains into a systemic vessel (brachiocephalic vein, SVC, or IVC) leading to RA and RV enlargement. The aortic arch is not enlarged in ASDs, VSDs, or PAPVCs. Isolated PDA causes shunting from the proximal descending aorta into the MPA. This results in increased flow through the lungs and the left heart. Therefore, expected chest radiographic findings in addition to shunt vascularity are LA and LV enlargement. PDA is the only entity in this category where the aortic arch is enlarged.[27]

Longstanding shunting through the pulmonary arterial tree may eventually lead to pulmonary hypertension (Eisenmenger syndrome). Findings are similar to other causes of PH described earlier. One useful finding is calcification of the pulmonary arterial wall (similar to aortic atherosclerosis), which can be rarely seen when the shunting has been longstanding.[27,28] In fact, we have found that enlarged,

calcified pulmonary arteries on a CXR are almost secondary to a longstanding left-to-right shunt, usually an ASD (**eFig. 15.15**).



EFIGURE 15.15 Pulmonary arterial wall calcification caused by chronic shunting. Coned-down frontal **(A)** and lateral **(B)** chest radiographs of 45-year-old woman with newly discovered severe pulmonary hypertension resulting from a large untreated atrial septal defect. *Arrows* indicate the linear calcification of the right pulmonary artery wall. Note the greatly enlarged main pulmonary artery and the shunt vascularity in the lung parenchyma. **C,** Both calcified and noncalcified plaques along the walls of the very large pulmonary arteries (*arrows*) are well displayed by the contrast-enhanced CT image.

Tetralogy of Fallot is a cyanotic CHD in which the characteristic lesion of pulmonary or infundibular stenosis results in diminished pulmonary vascularity. The contour of the MPA may range from nearly normal to absent or very small. Even though the overall cardiac size is not enlarged, in tetralogy of Fallot the right ventricle is hypertrophied and dilated, pushing and rotating the heart into the left hemithorax. The right ventricle forms the cardiac apex, which is frequently directed upward, creating a boot-shaped heart (**see Fig. 15.4**). A right-sided aortic arch is present in up to 25% of patients, which appears as an absent left-sided aortic knob and an upper mediastinal outward bulge in the right paratracheal region.[29]

Coronary Artery Disease

Coronary artery abnormalities are best assessed by conventional angiography and contrast-enhanced CT angiography (**see Chapters 18 and 20**). In this section we discuss incidental coronary artery calcification, the role of a CXR after an acute myocardial infarction (MI), and the expected and unexpected radiographic findings after coronary artery bypass graft (CABG) surgery.

Atherosclerotic Calcification

Coronary artery calcifications are often discovered incidentally on a CXR. Cardiac motion blurs less dense calcification, while overlying soft tissues make the detection of subtle calcification impossible. Dual-energy subtraction chest radiography increases the sensitivity in detection of coronary artery calcification on CXR. This technique takes advantage of the differences between varying tissue attenuation of low- and high-energy photons, allowing for creation of calcium-only images.[30]

On the frontal CXR, the left main, left anterior descending (LAD), and left circumflex arteries and their proximal branches can be found at a site known as the “coronary artery calcification triangle.” This is best defined as a triangular area located in the left midheart immediately medial to the outer contour of the LA appendage, just below the level of the left main bronchus. This border forms the oblique side of the triangle. The other two sides are formed by the left border of the vertebral column and a horizontal line

drawn from the vertebral column to the left cardiac border, at approximately one-third the distance from the left bronchus to the diaphragm[31] (see Classic References, Souza). On the lateral radiograph, both the right coronary artery (RCA) and the LAD course anteriorly, curving downward toward the anterior margin of the heart (**see eFig. 15.7**). Generally, the RCA is anterior to the course of the LAD, which crosses the ascending aorta on the lateral projection.

Coronary artery *stents* can sometimes be mistaken for coronary artery calcifications. If the image is acquired with less motion blur, the clinician will be able to identify the higher metal attenuation of a stent relative to calcium and the parallel line of the stent (**Fig. 15.8**).

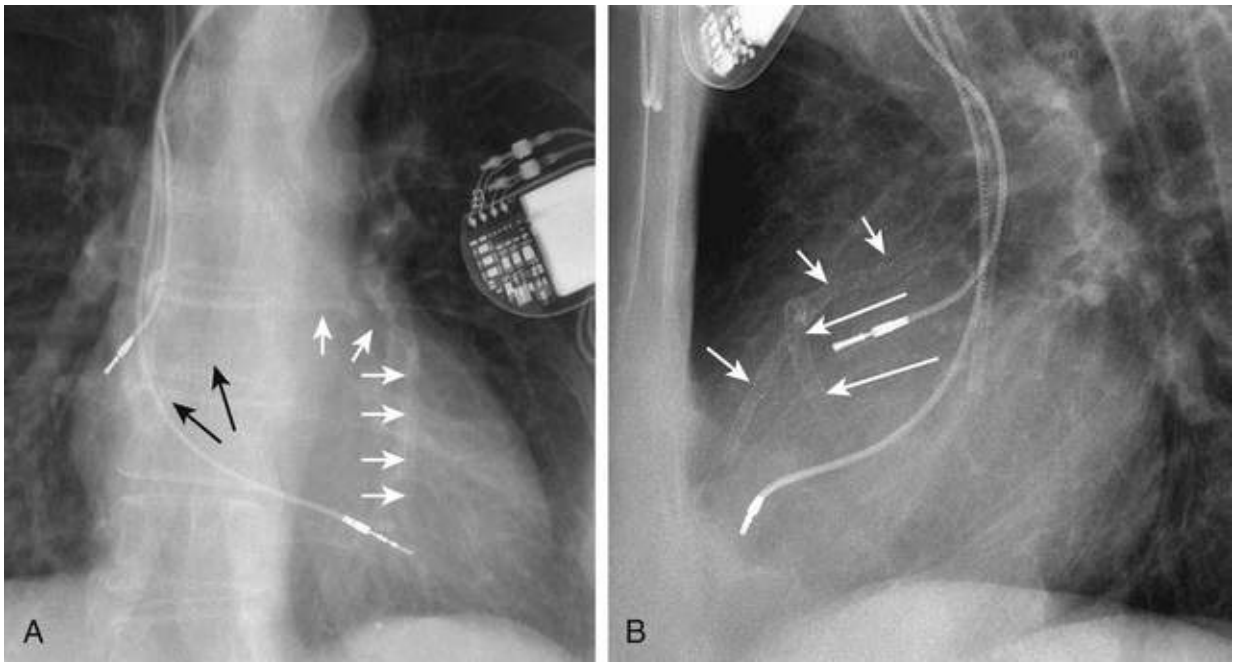


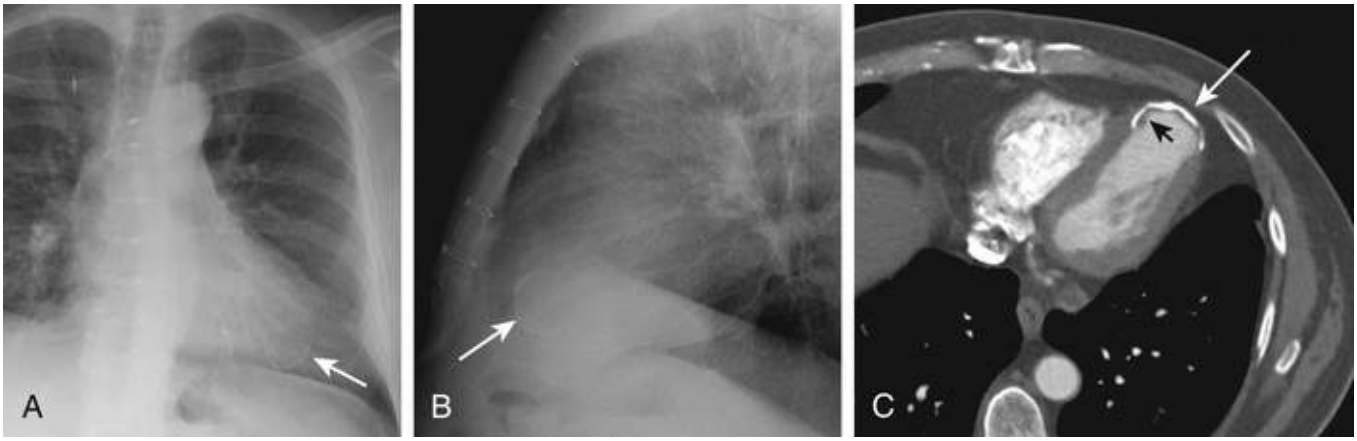
FIGURE 15.8 Coronary artery stents. Frontal **(A)** and lateral **(B)** views of the chest show coronary artery stents in a long length of the left anterior descending artery (LAD) (*short arrows*) and in the right coronary artery (RCA) (*long arrows*). On the frontal view the RCA is difficult to visualize because it projects over the spine. On the lateral view the courses of the LAD and RCA cross, such that the LAD extends more anteriorly toward the cardiac apex.

Coronary artery *aneurysms* tend to calcify and may be more easily appreciated on CXR than normal-sized calcified coronary arteries.[32] These coronary aneurysms are most often caused by atherosclerotic disease in Western countries and Kawasaki disease in the remainder of the world.

Acute Myocardial Infarction

Approximately half of patients presenting with an acute MI will have a normal CXR (see Classic References, Higgins).The abrupt dysfunction of the myocardium after an MI often leads to PVH and pulmonary edema. Unlike other causes of congestive heart failure, the heart size is usually normal, even with a large infarct. True and false aneurysms may develop after an MI. These may be recognized on CXR as a focal outpouching of the cardiac border on a chest radiograph, which may calcify. Other CXR findings include a double density sign at the expected locations of true and false LV aneurysms. True LV aneurysms are most often located at the LV apex and along the lateral wall and can present as a contour abnormality of the left cardiac border or a focal outpouching that could simulate a mass (**eFig. 15.16**). A false LV aneurysm is most frequently located along the inferolateral wall of the left ventricle and on the frontal view appears as a double density projecting over the heart, which would be more obvious on the

lateral view, where a saccular contour abnormality can be seen.[33]

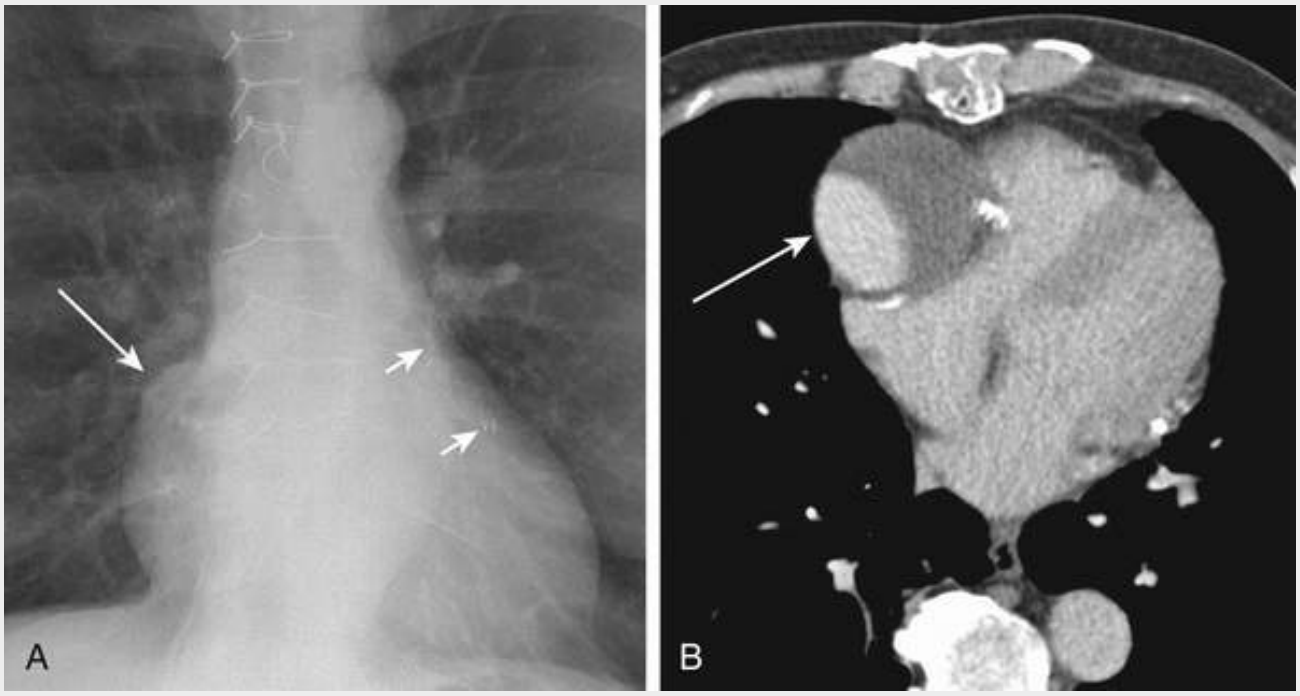


EFIGURE 15.16 True left ventricular aneurysm with myocardial calcification. Coned-down frontal **(A)** and lateral **(B)** chest radiographs demonstrate a curvilinear calcification in the region of the left ventricle (*arrows*). **C,** Coned-down contrast-enhanced axial CT image demonstrates the true aneurysm of the left ventricle apex (*arrow*) caused by a previous infarct. Its wall is calcified, with a thin margin of hypoattenuating thrombus along the luminal surface (*black arrow*).

Immediately after an acute MI, papillary muscle rupture can appear as sudden development of pulmonary edema as a result of MR (**see Chapter 58**). This edema is asymmetrically worse in the right upper lobe when the rupture is complete, similar to more chronic MR discussed previously. In the acute phase, cardiomegaly or LAE is not usually seen. Acute VSD has similar findings but is more often associated with mild cardiomegaly. If the patient survives these complications, the cardiomegaly could progress with development of both LA and LV enlargement.[34] Dressler syndrome most frequently occurs a few weeks to months after an MI and is caused by an autoimmune response to the antigens released by the dead myocytes. It presents as a late development of pericardial and pleural effusions.

Coronary Artery Bypass Grafts

The most common CABGs are saphenous vein grafts (SVGs) and internal mammary grafts. SVGs are anastomosed to the anterior wall of the ascending aorta above the level of the sinotubular junction of the aorta. A metallic ring or marker is usually placed, which helps identify the location of the ostium for future selective conventional coronary angiography. Shortly after CABG surgery, a pseudoaneurysm at the anastomosis site with the aorta can develop. Based on the size of the hematoma and pseudoaneurysm, this presents as a widened mediastinum on the frontal view and a masslike opacification in the retrosternal clear space on the lateral view. SVGs are more prone to intimal hyperplasia, wall calcification, and stenosis than their arterial counterparts and may develop true aneurysms anywhere along their course. These aneurysms tend to occur 10 to 20 years after bypass surgery. The calcification can be visible on chest radiography, and the aneurysms, which can be very large, may simulate a mass anywhere along the course of the SVG[35] (**eFig. 15.17**).



EFIGURE 15.17 Coronary artery bypass graft (CABG) aneurysm. **A,** Coned-down frontal view shows an abnormal budge along the upper margin of the cardiac border (*long arrow*) caused by an aneurysm of the saphenous vein CABG bypassing the right coronary artery. Surgical clips show the course of the left internal mammary artery CABG (*short arrows*) toward the left anterior descending coronary artery. **B,** Coned-down contrast-enhanced axial CT image demonstrates that this aneurysm (*arrow*) causes mass effect on the right atrium and right ventricle and contains an eccentric filling defect with a large amount of intraluminal thrombus.

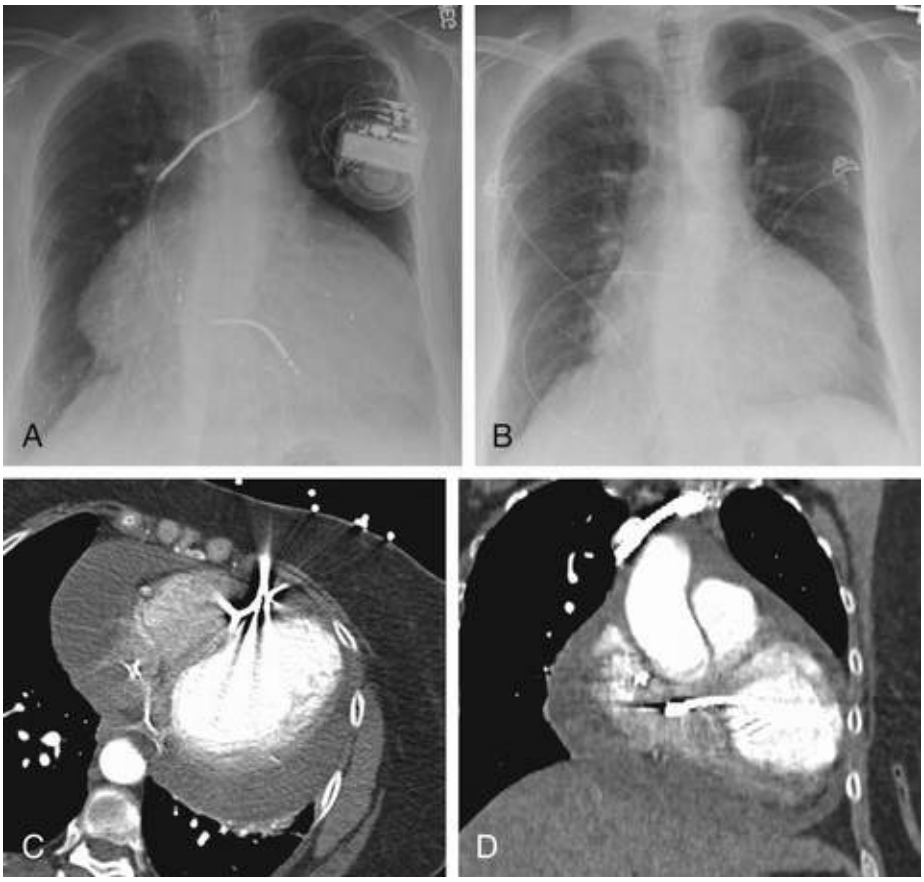
Internal mammary CABGs are more common on the left. Left internal mammary artery (LIMA) bypass grafts are anastomosed to the mid- to distal LAD or to a diagonal artery. The course of a LIMA graft can be followed on the frontal and lateral radiographs by the multiple metallic clips placed along its course. LIMA grafts have a vertical orientation on both PA and lateral views, coursing parallel to the mediastinum on the frontal view and posterior to the sternum on the lateral view. True aneurysms tend to be very unusual in LIMA grafts.

Pericardial Disease

Echocardiography is much more sensitive and specific in identifying pericardial disease than chest radiography (**see Chapters 14 and 83**).

Pericardial Effusion

The normal pericardium is composed of two layers, visceral and parietal, which form a thin sac containing 25 to 50 mL of fluid. With an increase in the amount of fluid, the overall size of the cardiac silhouette increases on CXR. This could be difficult to differentiate from global enlargement of the cardiac chambers, as seen with dilated cardiomyopathy. Any increase in the size of the cardiac silhouette (especially when acute) should suggest a pericardial effusion.[36] A large pericardial effusion may create a "water bottle" sign, where the right and lateral heart borders are straightened. Because the normal pericardial recesses become expanded by pleural fluid, this process may extend to the level of the aortic arch (**eFig. 15.18**).



EFIGURE 15.18 "Water bottle" sign of pericardial effusion. **A,** PA chest radiograph shows an extremely large cardiac silhouette, extending with the cardiac margins beginning higher than normal at the hilar level. **B,** Radiograph obtained 6 months earlier shows a more normal cardiac silhouette before the pericardial effusion developed. **C,** Contrast-enhanced CT axial image of the heart acquired at the time of the more recent radiograph shows a large pericardial effusion. **D,** On coronal reformatted image, the superior extent of the pericardial effusion into the pericardial recesses is displayed, creating the water bottle appearance.

On the lateral view a pericardial effusion may present as a vertical band of radiodensity (white or light gray) sandwiched by two radiolucent areas (dark gray). This is called the "fat pad" or "sandwich" sign and is visualized in the region of the cardiac apex close to the sternodiaphragmatic border. It is caused by separation of the epicardial and pericardial fat layers by the fluid in the pericardial sac (**Fig. 15.9**). Rarely a *variable density sign* can be seen, which appears as a band of greater lucency along the outer margin of the heart, parallel to the cardiac border. This sign is caused by decreased attenuation of the x-ray beam of the pericardial fluid compared with the more medial combination of pericardial fluid and myocardium (**eFig. 15.19**).

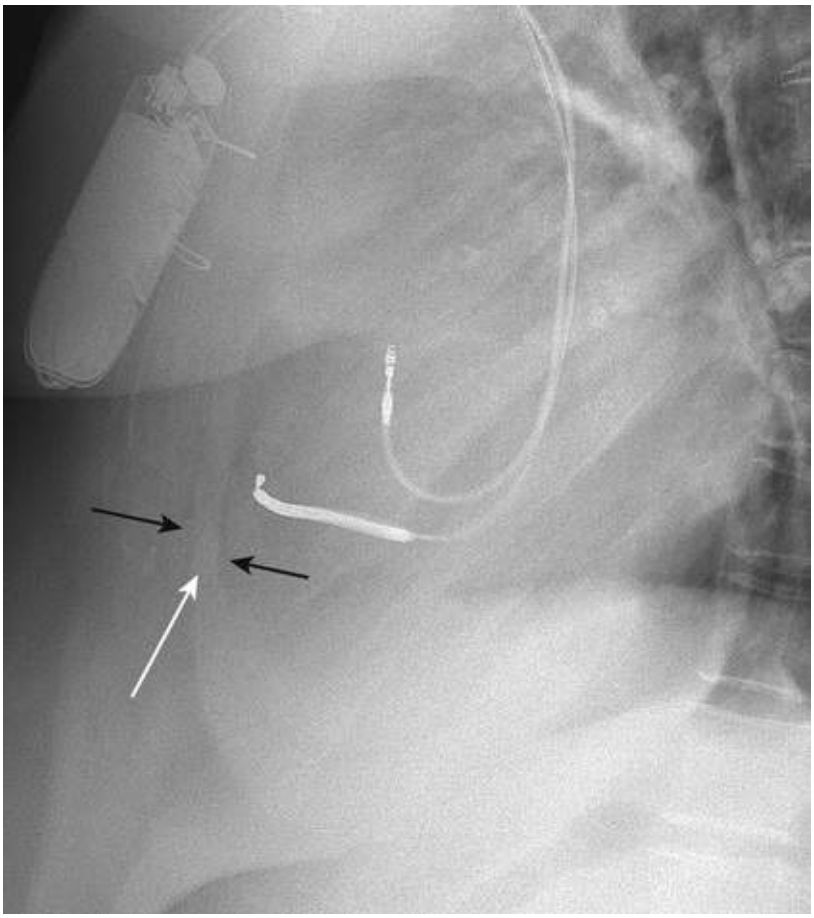
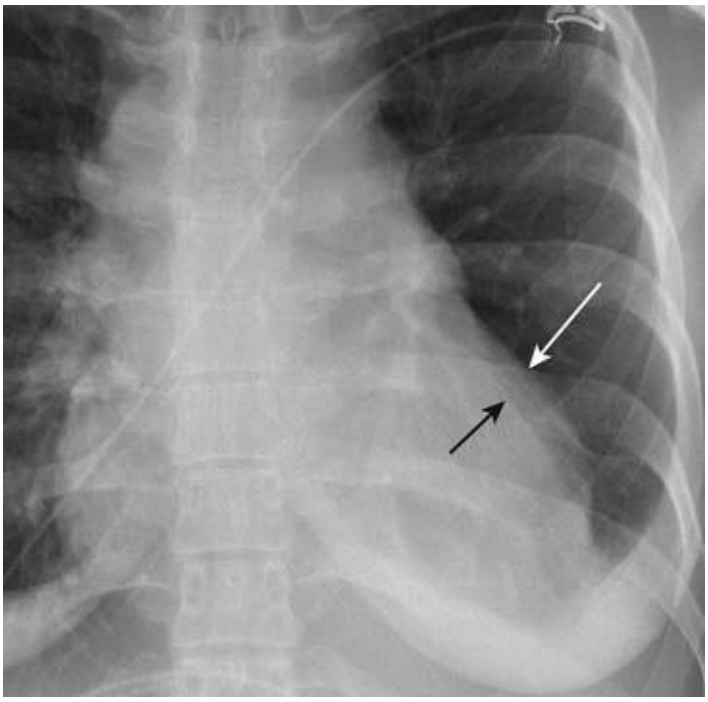


FIGURE 15.9 "Sandwich sign" of pericardial effusion. Coned-down lateral chest radiograph shows two dark bands of radiolucency (*black arrows*), separated by a band of radiodensity (*white arrow*), resulting from separation of the pericardial and epicardial fat pads by a moderate-sized pericardial effusion. The white band wraps around the inferior border of the heart, since the fluid tends to accumulate when standing.

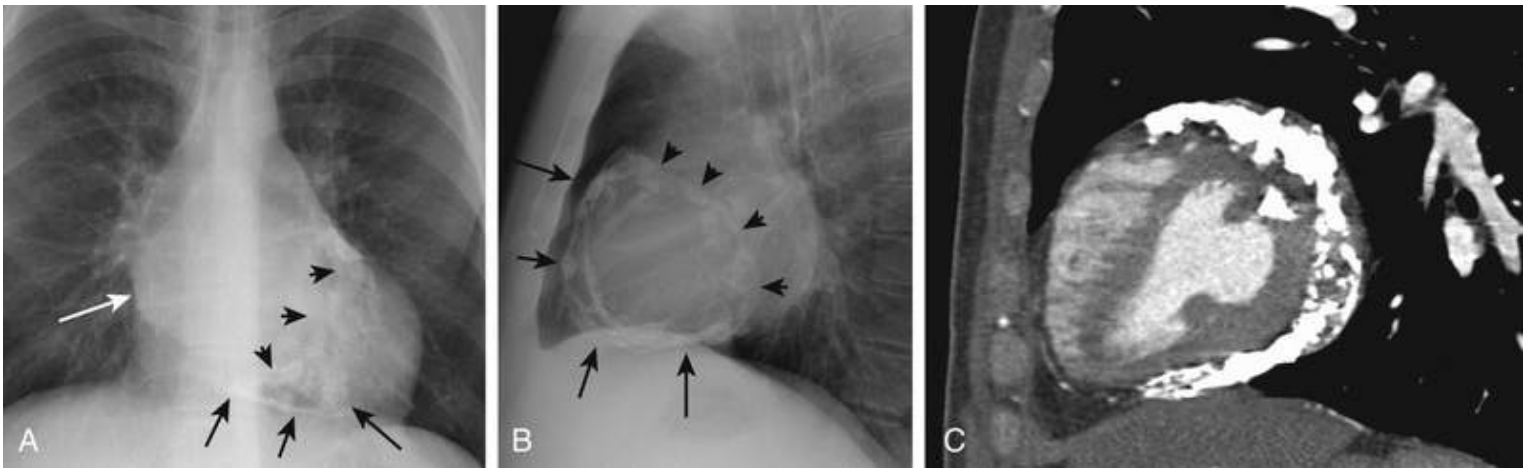


EFIGURE 15.19 Variable density sign of pericardial effusion. Coned-down PA radiograph shows a large cardiac silhouette caused by a known large pericardial effusion. There are two parallel lines along the left cardiac border; the medial line represents the margin of the myocardium (*black arrow*), and the lateral line represents the lateral margin of the visceral pericardium (*white arrow*). Note that patient also has a left pleural effusion.

Calcific Pericarditis

Calcific pericarditis may be associated with constrictive physiology. Pericardial calcification has a linear configuration and may be only visible on one view. It differs from LA calcification in that it is anteriorly located and often creates a ring along the expected location of the atrioventricular grooves.[37] **Table 15.2** compares various calcifications of the heart.

The most common site of pericardial calcification is along the atrioventricular (AV) groove and along the RV free wall. This pattern may impede diastolic relaxation of the right ventricle.[38] The overall heart size is normal on the CXR, even though on echocardiography, CT, and magnetic resonance imaging (MRI), dilation of the atria may be seen (**eFig. 15.20**). Other common sites of pericardial calcification and thickening include just anterior to the RVOT behind the sternum and along the LV free wall close to the left AV groove. In the latter situation, cephalization of the pulmonary vascularization and eventually edema and pleural effusions may be seen from increased left heart pressures.

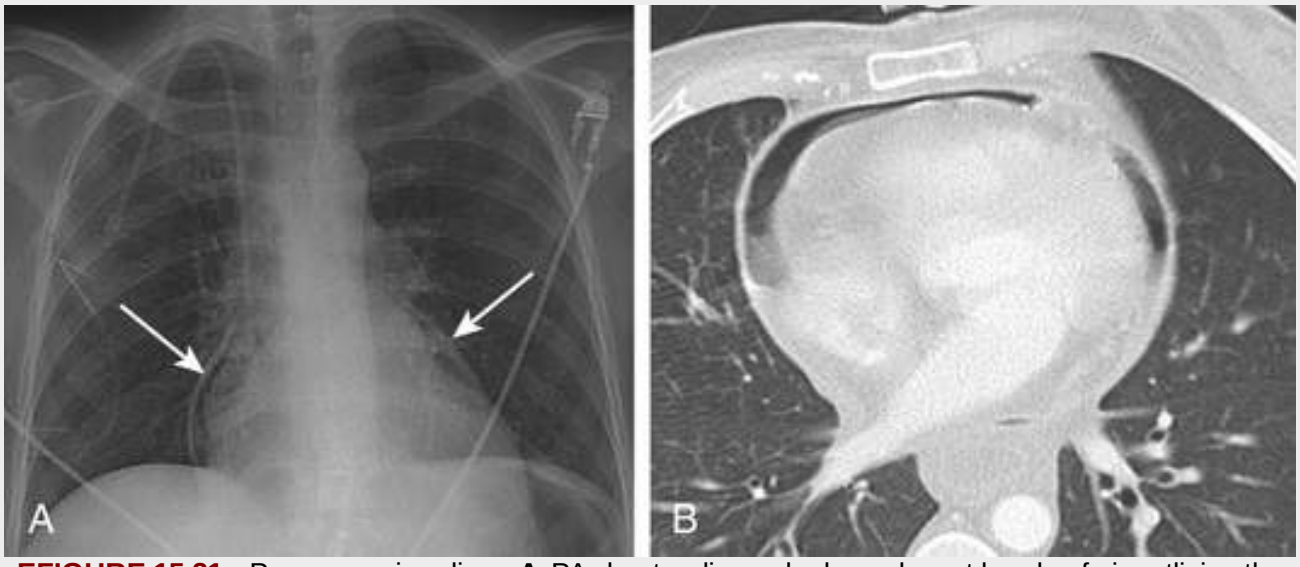


EFIGURE 15.20 Calcific pericarditis. **A,** Coned-down PA chest radiograph shows a nodular band of calcification (*black arrows*) projecting over the heart along the expected location of the left atrioventricular (AV) groove (*short black arrows*). There is also linear calcification along the inferior margin of the heart (*long black arrows*). Note the double density sign indicating left atrial dilation (*white arrow*). **B,** Lateral view shows a band of extensive calcification projecting over the heart, again in the AV groove (*black arrowheads*) and also around the apex and anterior and inferior walls of the right ventricle (*black arrows*). **C,** CT image depicts the extensive pericardial calcification.

Pneumopericardium

A pneumopericardium is most frequently seen after cardiac surgery or after placement of a surgical drain. It can rarely be caused by traumatic injury in which the pericardial space communicates with a pneumothorax. Other rare causes of pneumopericardium include infection and pericardial fistulas after esophageal dilation procedures or after ulceration of a hiatal hernia.

The CXR finding relies on the detection of gas along the cardiac border that does not extend above the aortic knob (where the pericardial recesses reflect). A pneumopericardium can accumulate along the anterior and inferior surface of the heart, appearing as a horizontal lucent (dark) line projecting over the lower heart close to diaphragm on the frontal radiograph[39] (**eFig. 15.21**).

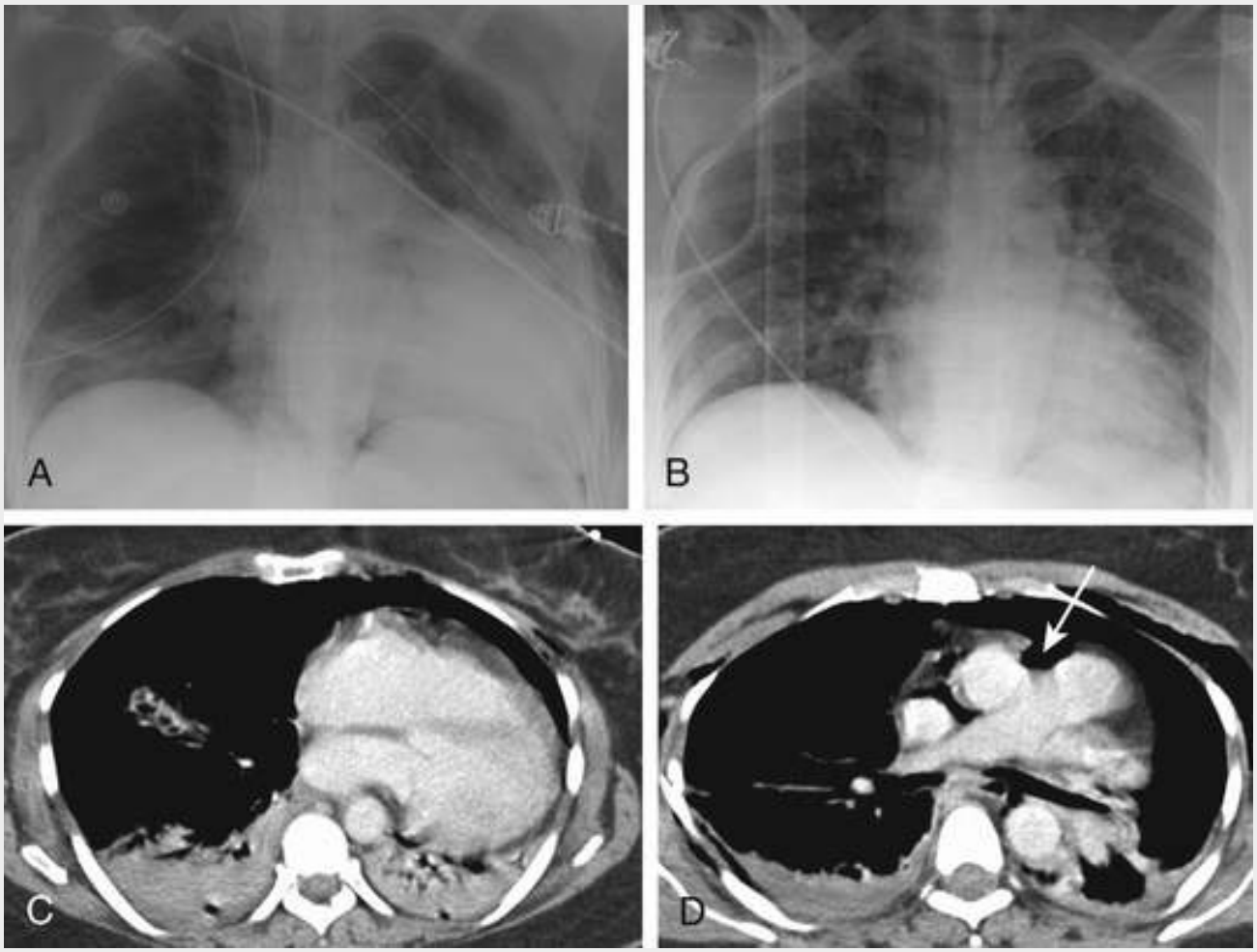


EFIGURE 15.21 Pneumopericardium. **A,** PA chest radiograph shows lucent bands of air outlining the right and left cardiac borders. A radiodense band outlining the pneumopericardium represents the thickening visceral pericardium (*arrows*). **B,** CT image obtained the same day demonstrates the small pneumopericardium, which developed after endoscopic balloon dilation of a distal esophageal stricture with a small fistula to the pericardium.

The pericardium is a true potential space, so gas within it tends to be uniformly lucent and moves with changes in patient positioning. These features are useful in distinguishing a pneumopericardium from a pneumomediastinum, which usually has thin strands of tissue from gas dissecting in the false space of the mediastinum and does not move with changes in positioning (e.g., lateral decubitus). When the gas extends above the aortic knob, it is also more typical of a pneumomediastinum than a pneumopericardium.

Congenital Absence of the Pericardium

Congenital absence of the pericardium is a rare condition that may involve absence of a portion of the pericardium, complete absence on one side, or bilateral absence. The ipsilateral medial pleura is usually also absent, resulting in direct communication between the pleural and pericardial spaces. Left complete absence is more common than right, and complete unilateral absence is more common than partial. Complete absence of the entire pericardium is rare. In absence of the entire left pericardium, the heart rotates into the left hemithorax and takes a somewhat tubular configuration. Another finding is separation of the aorta and MPA. This area is normally covered by the pericardium, which acts like a rubber band in keeping the two vessels together. In its absence the vessels separate, and lung insinuates into that space. Because of the rotation of the heart and separation of the aorta and the MPA, the frontal CXR will simulate a right anterior oblique projection despite the patient not being rotated (**eFig. 15.22**). In the era before widespread use of cardiac CT and MRI, diagnosis was confirmed by creating a small pneumothorax, which would extend around the heart through the absence. Another variant is absence of the diaphragmatic pericardium, in which the left lung could herniate under the rotated heart, creating a lucent band between the heart and the diaphragm.



EFIGURE 15.22 Partial absence of the pericardium. **A,** Portable AP chest radiograph of patient with multiple injuries from a motor vehicle accident shows leftward rotation of the heart (patient not rotated during imaging). **B,** AP radiograph obtained 4 hours earlier shows normal appearance of the heart, indicating that this is an acquired absence of the pericardium, with the heart herniating through the defect. CT images at the level of the ventricle **(C)** and the upper mediastinum **(D)** show marked leftward rotation of the heart, such that it drapes over the descending aorta **(C),** and no pericardium covering the space between the ascending aorta and the main pulmonary artery, allowing the lung to extend into that space (*arrow*).

Although partial absence of one side of the pericardium is not as common, it is potentially more dangerous. If a small portion of the heart, such as the atrial appendage, herniates through the defect, it may become strangulated. A change in the contour of the cardiac silhouette should raise concern for strangulation in a patient with known partial absence of the pericardium.[40]

Diseases of the Aorta

Aortic abnormalities of various causes have similar chest radiographic manifestations, making the clinical history and symptoms even more important in correctly diagnosing aortic conditions (**see Chapter 63**). In this section we discuss the specific radiographic findings of three groups: patients presenting after trauma, patients with acute chest pain because of an acute aorta syndrome, and patients with congenital aortic anomalies that may be discovered incidentally or from compressive symptoms.

Acute Traumatic Aortic Injury

Blunt acute traumatic aortic injury (ATAI) may result from rapid deceleration, as seen with motor vehicle crashes, falls, or direct crush injury. In these situations the aortic wall is disrupted, with development of a mediastinal hematoma of varying size. The injuries may range from a minimal intimal injury to complete

transection. The role of the CXR has continued to diminish in the multidetector CT era but is mainly to exclude a mediastinal hematoma in low-level trauma when the patient is asymptomatic (and able to verbalize the lack of symptoms). In the acute setting, radiographic findings are indicative of a mediastinal hematoma, which tends to be largest at the site of vascular wall injury. Most imaged aortic injuries occur at the level of the aortic isthmus (just distal to the left subclavian artery) because of the ligamentum arteriosum. Such injury presents with a mediastinum greater than 8 cm in width at the level of the top of the aortic arch (knob); an indistinct or enlarged contour of the aortic knob; an extra density extending from the left side of the mediastinum to the left lung apex (apical capping); rightward displacement of the trachea at the level of the third and fourth thoracic vertebral bodies; downward displacement of the left main bronchus to greater than 140 degrees from the trachea; and sometimes a left hemothorax (**Fig. 15.10**).

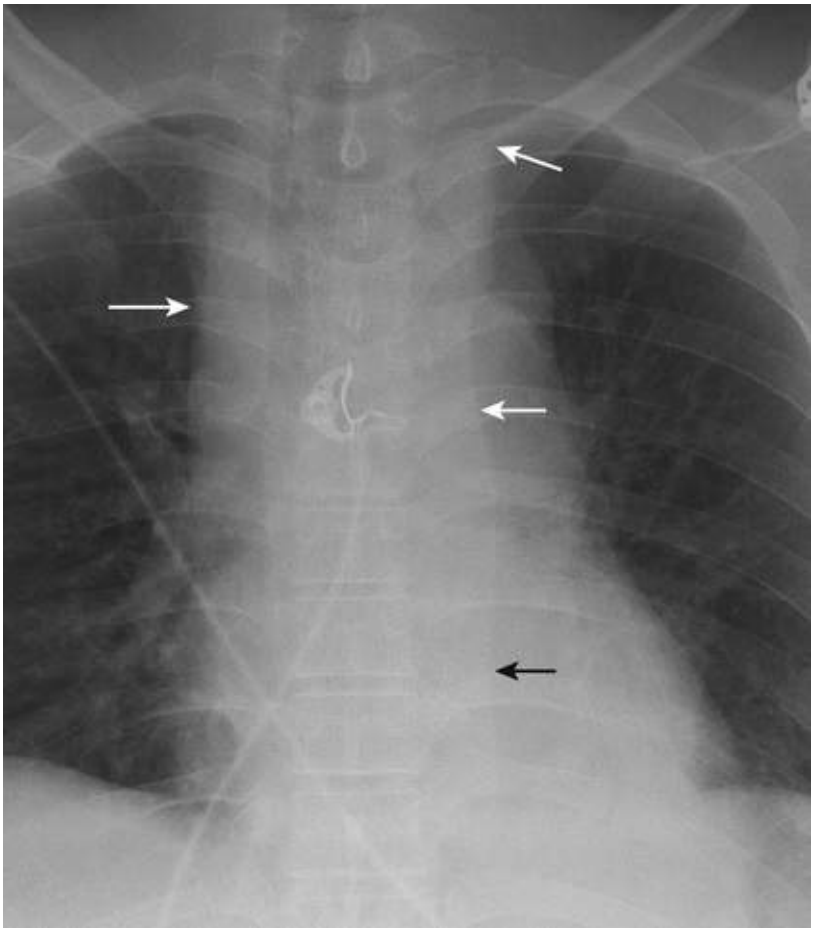


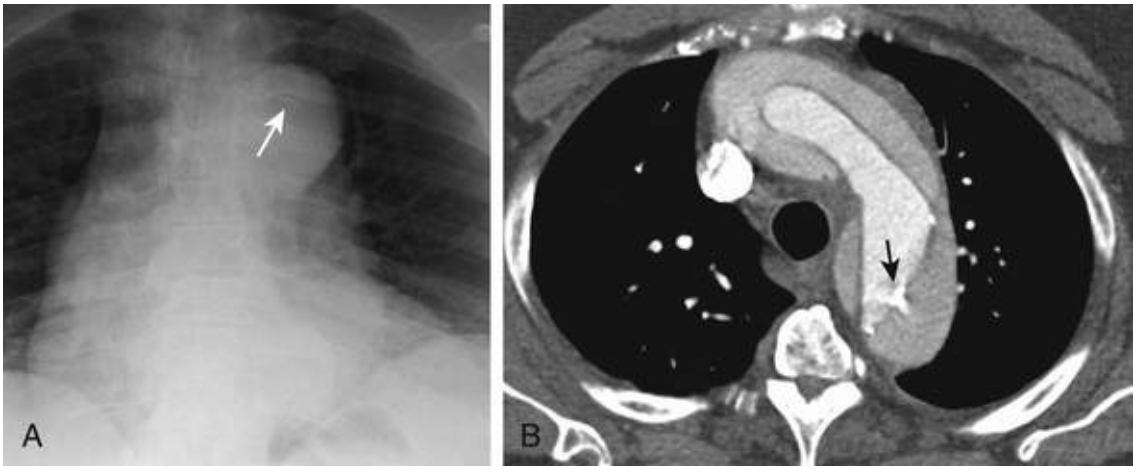
FIGURE 15.10 Mediastinal hematoma. Coned-down AP radiograph of young man who was a driver in a motor vehicle accident shows mediastinal widening (*arrows*) caused by acute traumatic aortic injury, which caused a large mediastinal hematoma. The displacement of the paravertebral line on the left extends to the left lung apex ("apical capping"). Note that the trachea is deviated to the right, and the left main bronchus is displaced inferiorly.

In the chronic setting where the ATAI has gone unrecognized and the mediastinal hematoma has resolved, an aortic *pseudoaneurysm* may be visible at the level of the isthmus. Although pseudoaneurysms can be subtle, they tend to have calcium along their undersurface; this allows them to be distinguished from atherosclerosis, which tends to be along the superior aspect of the aortic knob. If the ATAI results in traumatic injury to the great arterial branches of the aorta, there would be right-sided mediastinal widening, high-riding hematoma, and right apical capping.[41]

Aortic Aneurysm

Aneurysmal dilation of the aorta is most frequently caused by atherosclerotic disease but can also result from dissection, penetrating atherosclerotic ulcer, inheritable aortopathies (e.g., bicuspid aortopathy, Marfan disease), infectious aortitis, or vasculitis (e.g., Takayasu disease). The patient usually presents with acute chest pain when the aneurysm is unstable. Clearly, these patients will need full evaluation with cross-sectional imaging.

The radiographic findings include an enlarged contour or additional convexity along the expected course of the aorta in the mediastinum. On the frontal view, an aneurysmal ascending aorta presents as a widened right side of the mediastinum because of an additional convexity at the level of right cardiac border and just above it. On the lateral view, it appears as an additional convexity in the retrosternal space projecting over the MPA contour. Aneurysm of the aortic arch and descending aorta are easier to visualize on the PA and lateral views than aneurysm of the ascending aorta. A *saccular* aneurysm creates a masslike focal outpouching, whereas a *fusiform* aneurysm presents as alteration of a contour such as the aortic arch (knob). In situations where a mediastinal hematoma has developed, such as an acute aortic dissection or intramural hematoma, the imaging findings are similar to ATAI. An additional radiographic finding that can be seen with acute or chronic aortic dissection is the inward displacement of the calcified intima, which is most visible in the aortic arch when present[42] (**eFig. 15.23**).



EFIGURE 15.23 Displaced intimal calcification in aortic dissection. **A,** Frontal chest radiograph shows a curvilinear calcification (*arrow*) projecting over the aortic knob, located medial and parallel to the lateral contour of the aortic knob. **B,** Contrast enhanced CT obtained the same day shows an acute aortic dissection with a calcified intimal flap displaced medially toward the lumen (*arrow*).

Aortic Anomalies

Congenital anomalies of the aorta may present with stridor, dyspnea, and dysphagia, caused by compression of the trachea and esophagus. Many of these patients are asymptomatic and discovered incidentally. A *right-sided aortic arch* presents with an absent aortic contour on the left side of the mediastinum but with an abnormal contour on the right side. The trachea is deviated to the left by the right arch. This entity could be associated with tetralogy of Fallot, in which case a boot-shaped heart would also be present (**see Fig. 15.4**). A *double aortic arch* is a vascular ring in which the right arch is located more superiorly than the left arch.[43] The right arch is typically larger than the left (**Fig. 15.11**). *Aberrant right subclavian artery* (RSCA) is a common normal variant, in which the RSCA arises directly from the posterior aortic arch after the origin of the left subclavian artery. It ascends in the mediastinum after

passing between the spine and the esophagus. Aberrant RSCA is sometimes visible on a chest radiograph when there is a *diverticulum of Kommerell* at the origin of the aberrant RSCA. This diverticulum can become aneurysmal, in which case it appears as a poorly defined mass posterior to the trachea and superior to the aortic arch on the lateral view (**eFig. 15.24**).

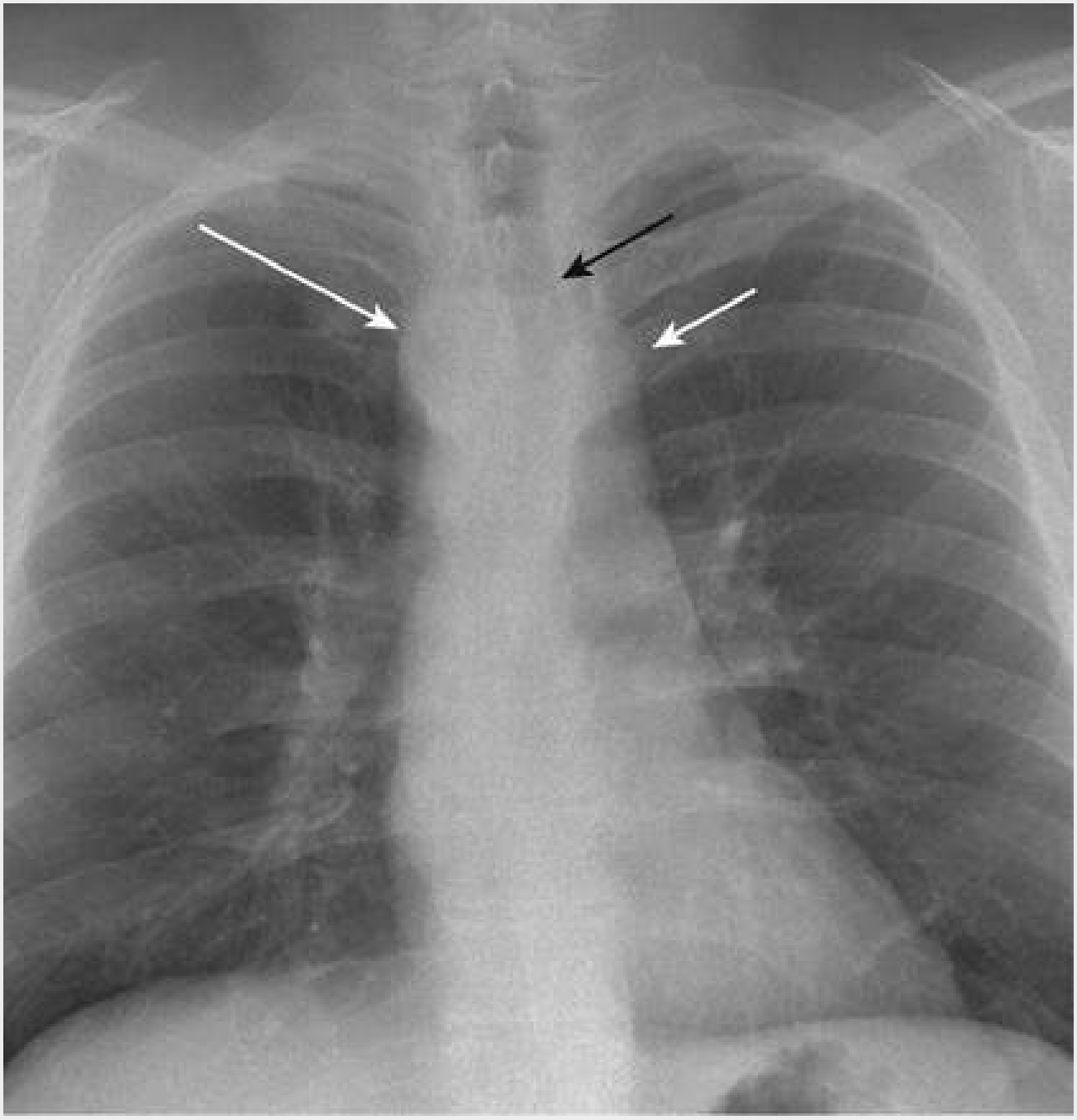
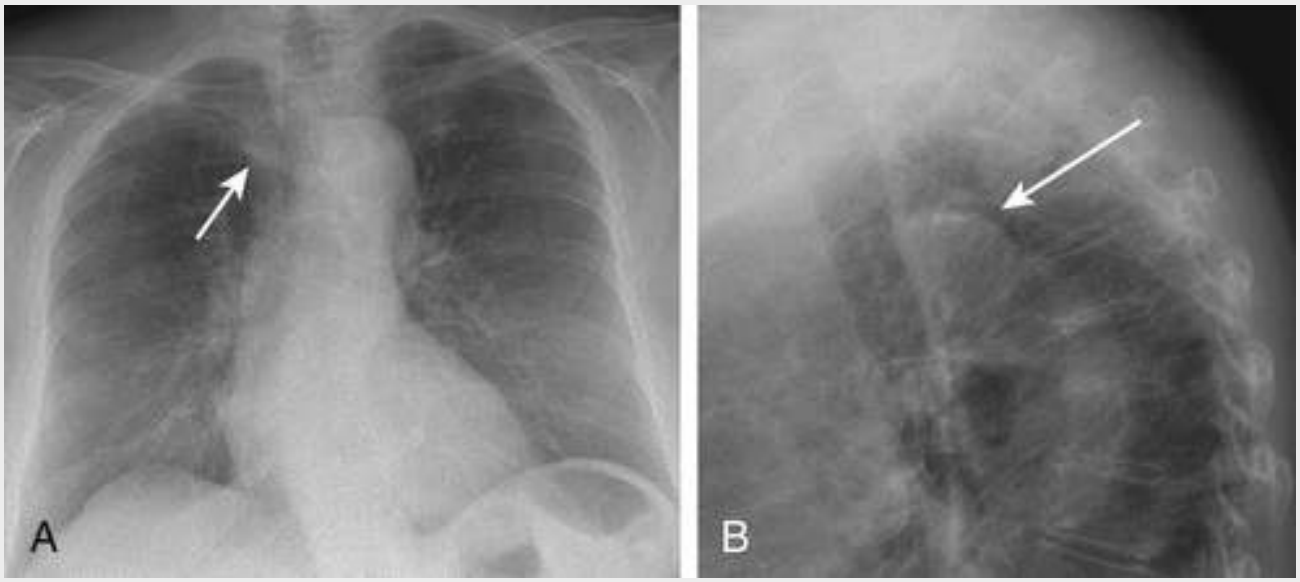
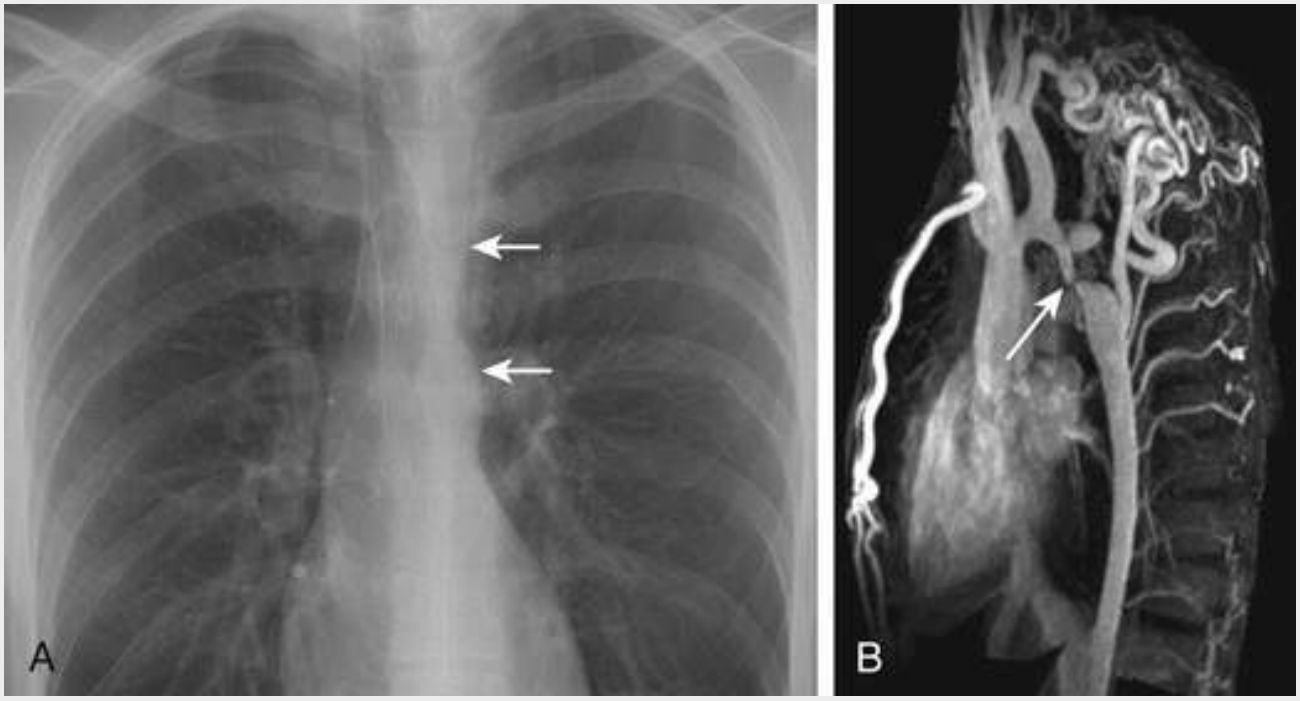


FIGURE 15.11 Double aortic arch. Coned-down PA chest radiograph shows right paratracheal budge representing the larger and higher right aortic arch (*long white arrow*), relative to the smaller and more inferiorly located left arch (*short white arrow*). Note that the trachea is deviated to the left by the right arch (*black arrow*).



EFIGURE 15.24 Aberrant right subclavian artery with diverticulum of Kommerell. **A,** Frontal view shows a focal convexity along the right paratracheal region of the superior mediastinum (*arrow*). **B,** Lateral view shows retrotracheal density just above the aortic arch and posterior to the trachea (*arrow*). Both represent a prominent diverticulum of Kommerell.

An *aortic coarctation* may appear as an additional convexity immediately above the aortic knob on the frontal view, with possible bilateral rib notching along the undersurface of the ribs. The left mediastinal contour has been dubbed the "figure of 3 sign" (**eFig. 15.25**). When an aortic anomaly is suspected, a CT or MR angiogram of the aorta is indicated to evaluate further the full nature of the anomaly and the extent of collateral arterial flow when coarctation is present.



EFIGURE 15.25 Coarctation of the aorta. **A,** Coned-down frontal chest radiograph demonstrates inferior rib notching in patient with severe coarctation of the aorta (*arrows*). Note straightening of a mild outward curvature above the aortic knob caused by the left subclavian artery as it takes a relatively more vertical course above the coarctation site. This bulge with the aortic knob created the "figure of 3 sign" of coarctation. **B,** Thick, maximum intensity projection image of magnetic resonance angiography of the aorta shows the coarctation site at the aortic isthmus (*arrow*), with extensive intercostal and internal mammary arterial collaterals, which are dilated and tortuous.

Conclusion

The chest radiograph still maintains a role in initial evaluation of patients presenting with chest pain and shortness of breath and helps diagnose alternative causes for such symptoms, such as pneumonia or a pneumothorax. It continues to play a strong role in the evaluation of patients who have had cardiac devices and central venous catheters and cannulas placed in the hospital. The CXR also can delineate the physiologic status of the cardiovascular system. A careful evaluation of the CXR using a systematic approach in the context of the clinical presentation, while comparing to prior images, is essential to maximizing the potential of this ubiquitous imaging study.

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16

Nuclear Cardiology

James E. Udelson, Vasken Dilsizian, Robert O. Bonow

The era of noninvasive radionuclide cardiac imaging in humans began in the early 1970s with the first reports of noninvasive evaluation of regional ventricular function at rest. Since that time, major advances have been achieved in the technical ability to image cardiac physiology and pathophysiology, including that of myocardial blood flow, myocardial metabolism, and ventricular function. Understanding how to apply the image information to the care of patients has also advanced, along with the effect of that information on clinical decision making. Ultimately, the role of information derived from any imaging procedure is to enhance the clinician's decision-making process for amelioration of symptoms and improvement of clinical outcomes.

Technical Aspects of Image Acquisition, Display, and Interpretation

Single-Photon Emission Computed Tomography of Perfusion and Function

The most common imaging procedure in nuclear cardiology is single-photon emission computed tomography (SPECT) *myocardial perfusion imaging* (MPI). After injection of the chosen radiotracer, the isotope is extracted from the blood by viable myocytes and retained within the myocyte for some time. Photons are emitted from the myocardium in proportion to the magnitude of tracer uptake, in turn related to perfusion. The standard camera used in nuclear cardiology studies, a gamma camera, captures the gamma ray photons and converts the information into digital data representing the magnitude of uptake and the location of the emission. The photoemissions collide along their flight path with a detector crystal. There, the gamma photons are absorbed and converted into visible light events (a *scintillation* event). Emitted gamma rays are selected for capture and quantitation by a collimator attached to the face of the camera detector system. Most often, parallel-hole collimators are used so that only photon emissions coursing perpendicular to the camera head and parallel to the collimation holes are accepted (**Fig. 16.1**). This arrangement allows appropriate localization of the source of the emitted gamma rays. Photomultiplier tubes, the final major component in the gamma camera, sense the light scintillation events and convert the events into an electrical signal to be further processed. The final result of SPECT imaging is the creation of multiple tomograms, or slices, of the organ of interest, composing a digital display representing radiotracer distribution throughout the organ.[1] With SPECT MPI, the display represents the distribution of perfusion throughout the myocardium.

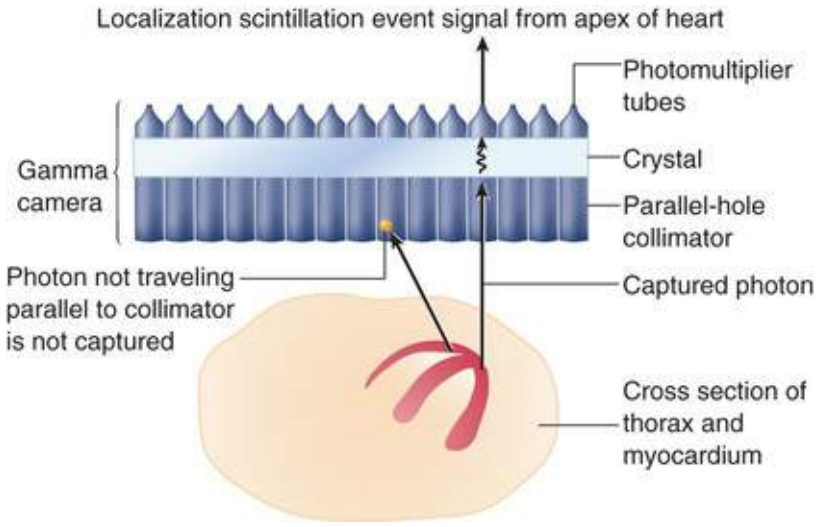


FIGURE 16.1 Capture of emitted photons by a gamma camera. Emissions are captured by a parallel-hole collimator, allowing photons to interact with a detector crystal, and are recorded as scintillation events. The event is localized on the basis of where the photon interacts with the crystal.

SPECT Image Acquisition

To construct the three-dimensional model of the heart from which tomograms are created, the myocardial perfusion data must be sampled from multiple angles over 180 or 360 degrees around the patient. Multiple images, each comprising 20 to 25 seconds of emission data, are collected. Each of the separate "projection" images constitutes a two-dimensional snapshot of myocardial perfusion from the angle at which the projection was acquired. Then the imaging information from each of the angles is back-projected onto an imaging matrix, creating a reconstruction of the organ of interest. Detailed reviews are available for more extensive information on the technical aspects of SPECT imaging and image reconstruction.[1]

SPECT Image Display

From the three-dimensional reconstruction of the heart, computer-processing techniques are used to identify the long axis of the left ventricle, and standardized tomographic images in three standard planes are derived. *Short-axis tomograms*, representing donutlike slices of the heart cut perpendicular to the long axis of the heart, are displayed beginning from the apex and moving toward the base. This tomographic orientation is similar to the short-axis view in two-dimensional echocardiography (**see Chapter 14**), although it is shifted counterclockwise (**Fig. 16.2A**). Tomographic slices cut parallel to the long axis of the heart and also parallel to the long axis of the body are termed *vertical long-axis tomograms* (**Fig. 16.2B**). Slices also cut parallel to the long axis of the heart but perpendicular to the vertical long-axis slices are known as *horizontal long-axis tomograms* (**Fig. 16.2C**). From all these tomographic planes, the entire three-dimensional myocardium is sampled and displayed, minimizing overlap of structures.

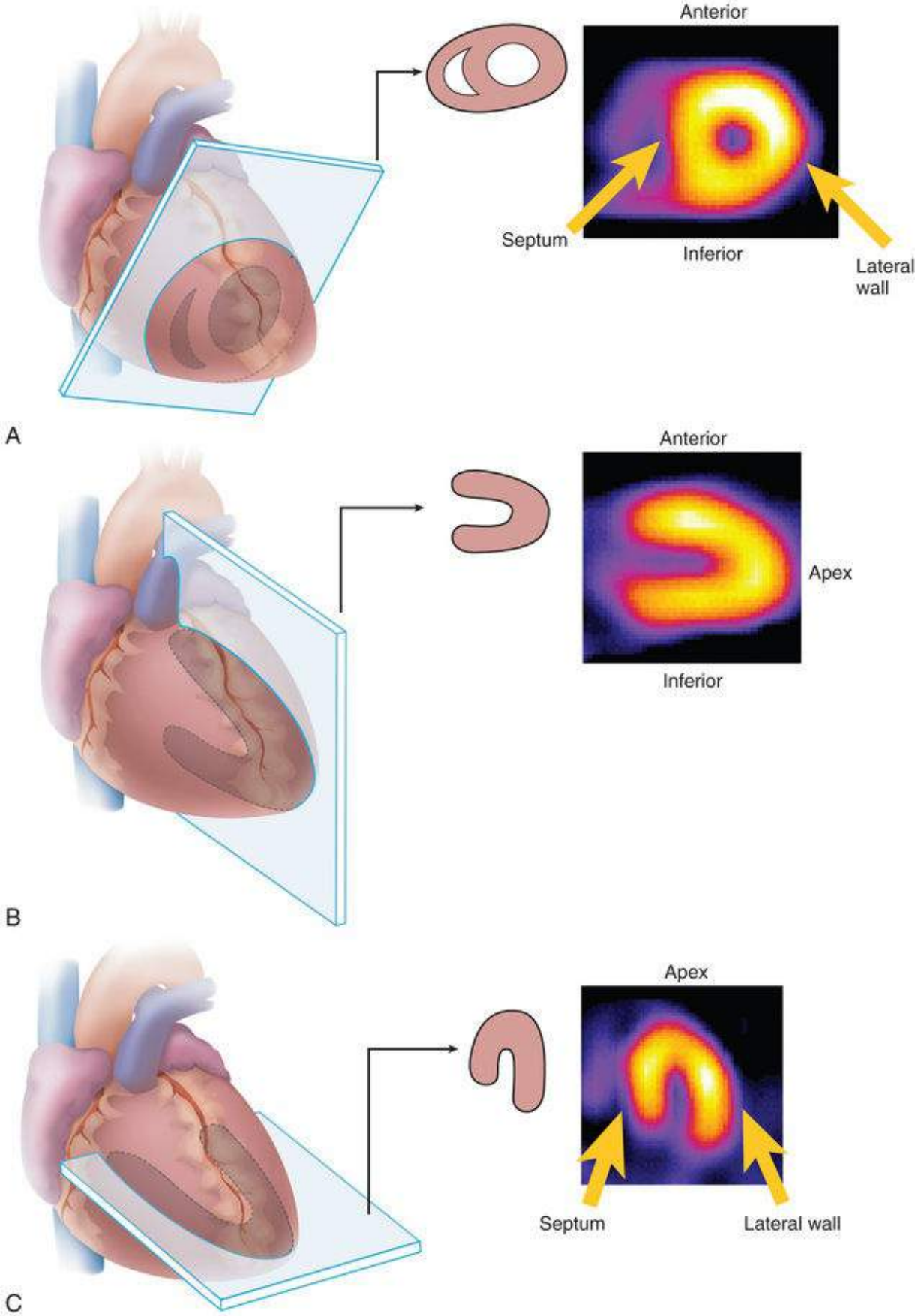


FIGURE 16.2 Standard SPECT imaging display. **A,** The short-axis images represent a portion of the anterior, lateral, inferior, and septal walls. **B,** Vertical long-axis images represent the anterior wall, apex, and inferior wall. **C,** Horizontal long-axis images represent the septum, apex, and lateral walls.

Basics of Quality Control.

The quality of SPECT MPI and the "accuracy" of the representation of regional myocardial perfusion depend on multiple quality control issues. Issues related to the patient and the organ being imaged include the stability of the tracer distribution in the organ of interest during the acquisition interval, the absence of motion of the patient or organ of interest or both during the acquisition, and the absence of overlying structures that would attenuate the photon emissions from one region relative to another region across the different projection images. Other quality control issues involve the camera and detector system, including the uniformity of photon detection efficiency across the camera face, as well as the stability of the camera across the entire orbit of acquisition.[2]

It is important in interpreting SPECT images to be aware of possible sources of image artifacts. Discrete motion of the patient, with consequent motion of the heart outside its original field, causes an abnormality in the final images that may be corrected with motion correction software. Imaging artifacts typically occur because of the effects of overlying structures that attenuate photon emissions. These artifacts include breast attenuation in women and attenuation of the inferobasal wall related to the diaphragm, usually seen in men. Strategies to overcome quality-specific problems such as attenuation are described subsequently.

High-Speed SPECT Imaging

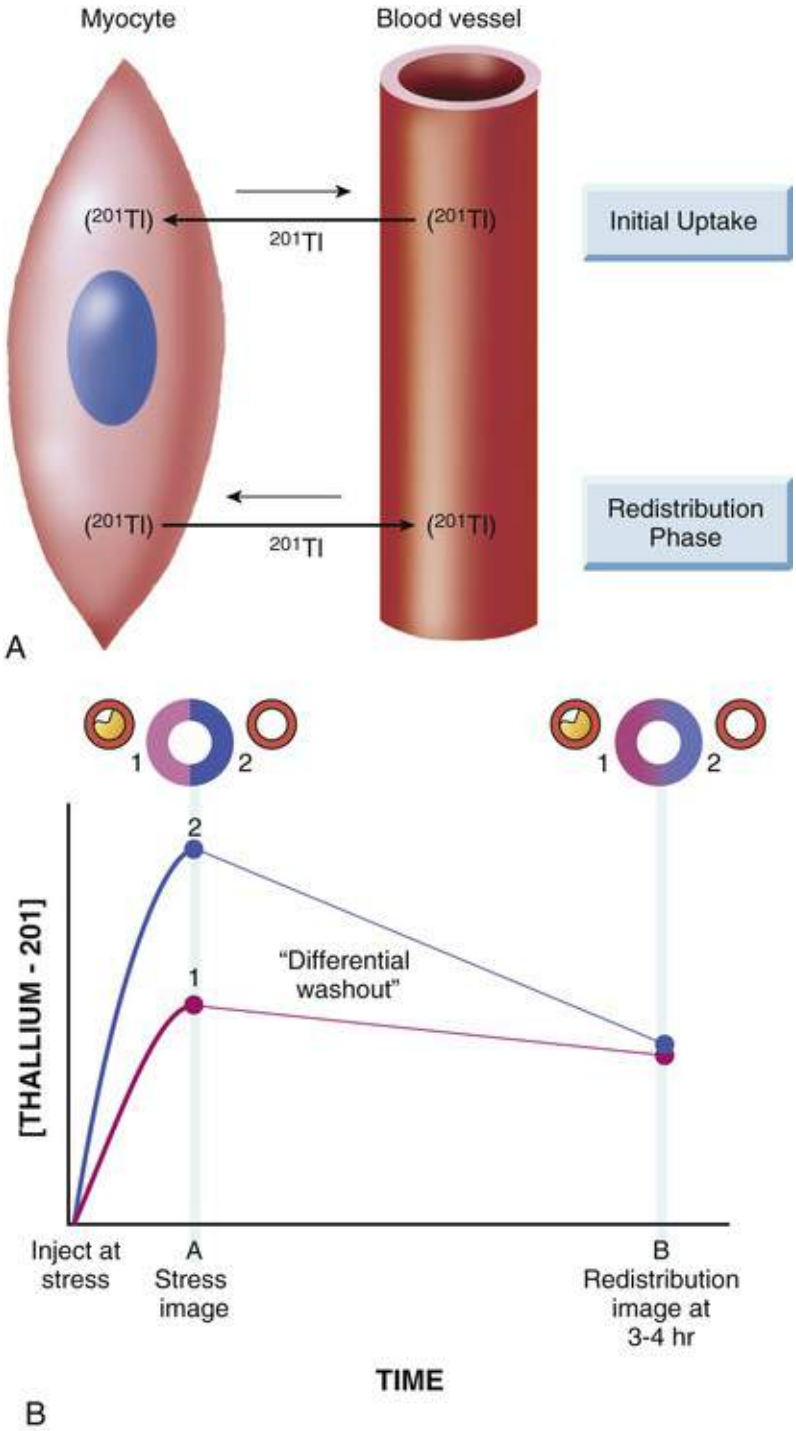
High-speed SPECT technology introduces an evolved design of SPECT in terms of both photon acquisition and reconstruction algorithms. Standard SPECT imaging with collimators using a parallel-hole design is inherently inefficient, because only a relatively small proportion of the camera and collimator surface area is used to capture photons emitted from the heart. Advances in camera and collimator technology have substantially increased the efficiency of count capture, by design features that allow much of the available detector area to image the cardiac field of view, increasing count sensitivity many-fold. One approach uses a series of small, pixilated, solid-state detector columns with cadmium zinc telluride or cesium iodide:thallium crystals, which provide considerably more information for each detected gamma ray. In addition, the design of the solid-state detector with wide-angle tungsten collimators combined with a novel image reconstruction algorithm provides true three-dimensional, patient-specific images localized to the heart.[3] Compared with the conventional SPECT cameras, the high-speed SPECT systems can provide up to an eightfold increase in count rates, thereby reducing imaging times significantly from 14 to 15 minutes with a conventional Anger gamma camera to 5 to 6 minutes with the newer solid-state cameras while achieving a twofold increase in spatial resolution.

In addition to advances in camera technology, software driving image reconstruction has also evolved. One technique, *resolution recovery,* improves spatial resolution while reducing noise in the images. Thus, studies acquired over a much shorter time, when reconstructed using these techniques, can yield images with the same signal-to-noise ratio as those using standard techniques and timing.[3] Reduced imaging times should translate to improved patient comfort and satisfaction, as well as less motion and fewer motion artifacts. An additional advantage of high-speed SPECT imaging is the potential for administration of lower doses of radiopharmaceuticals without sacrificing image resolution and quality, thereby reducing radiation dose to patients. The reduced imaging time in concert with reduced radiopharmaceutical doses may be cost-effective, with implications for future appropriateness of SPECT imaging.[3]

SPECT Perfusion Tracers and Protocols

Thallium-201

Thallium-201 (^{201}Tl) was introduced in the 1970s and propelled the clinical application of MPI as an adjunct to exercise treadmill testing. ^{201}Tl is a monovalent cation with biologic properties similar to those of potassium. Because potassium is the major intracellular cation in muscle and is virtually absent in scar tissue, ^{201}Tl is a well-suited radionuclide for differentiation of normal and ischemic myocardium from scarred myocardium.[4] Thallium-201 emits 80 keV of photon energy and has a physical half-life of 73 hours. The initial myocardial uptake early after intravenous injection of thallium is proportional to regional blood flow. First-pass extraction fraction (the proportion of tracer extracted from the blood as it passes through the myocardium) is high, in the range of 85%. It is transported across the myocyte cell membrane by the sodium/potassium ion (Na^+,K^+)–adenosine triphosphatase (ATPase) transport system and by facilitative diffusion. Peak myocardial concentration of thallium is achieved within 5 minutes of injection, with rapid clearance from the intravascular compartment. Although the initial uptake and distribution of thallium are primarily a function of blood flow, the subsequent redistribution of thallium, which begins within 10 to 15 minutes after injection, is unrelated to flow but is related to the rate of its clearance from myocardium, linked to the concentration gradient between myocyte levels and blood levels of thallium (**eFig. 16.1A**). Thallium clearance is more rapid from normal myocardium with high thallium activity than from myocardium with reduced thallium activity (ischemic myocardium), a process termed *differential washout* (**eFig. 16.1B**).



EFIGURE 16.1 Thallium-201 (^{201}Tl) redistribution. **A,** After initial uptake into the myocyte, an equilibrium is created between the intracellular and extracellular concentrations of thallium. After blood levels diminish during the redistribution phase, the equilibrium favors egress of thallium out of the myocyte. **B,** On the basis of that equilibrium, thallium concentration diminishes over time in zones of normal uptake while diminishing more slowly in zones with less initial thallium uptake, that is, those with diminished flow reserve or ischemia. In this example, segment 1 of the myocardial schematic is supplied by an artery with an 80% stenosis, and segment 2 is supplied by a normal artery. During peak stress, normal blood flow reserve is present in segment 2; blunted flow reserve, based on the presence of stenosis, is present in segment 1, and there is less initial thallium uptake into segment 1 (time point *A*). Thallium washout is more rapid from the territory with initially normal uptake and slower from the ischemic zone, creating the phenomenon of "differential washout." When redistribution imaging is done 3 to 4 hours later (time point *B*), thallium concentrations are equal in segments 1 and 2. Thus a reversible stress defect is seen in segment 1, based on the redistribution properties and differential washout. (Modified from Dilsizian V. SPECT and PET techniques. In Dilsizian V, Narula J, editors. Atlas of Nuclear Cardiology. Braunwald E, series editor. Philadelphia: Current Medicine; 2003, pp 19-46.)

Thallium studies can be divided into protocols in which ^{201}Tl is administered during stress and those in which it is given with the patient at rest.[4] After stress, the reversal of a thallium defect from the initial

peak stress to delayed 3- to 4-hour or 24-hour redistribution images is a marker of reversibly ischemic, viable myocardium. When thallium is injected in the resting state, the extent of thallium defect reversibility from the initial rest images to delayed redistribution images (at 3 to 4 hours) reflects viable myocardium with hypoperfusion at rest. When scarred myocardium is present, the initial rest or stress thallium defect persists over time; such deficits are termed *irreversible* or *fixed defects*. However, in some patients with coronary artery disease (CAD), the initial uptake of thallium during stress may be severely decreased, and tracer accumulation from the recirculating thallium in the blood during the redistribution phase may be slow or even absent because of rapid decline of thallium levels in the blood. The result is that some severely ischemic but viable regions may show no redistribution on either early (3- to 4-hour) or late (24-hour) imaging, even if viable myocardium is present. Viable myocardium in this situation can be revealed by raising blood levels of thallium by reinjection of a small dose (1 to 2 mCi) of thallium at rest. Thus, in some patients, thallium reinjection is necessary to identify viable myocardium when there are irreversible defects on stress-redistribution images.

Technetium 99m–Labeled Tracers

Technetium 99m (^{99m}Tc)–labeled myocardial perfusion tracers were introduced in the clinical arena in the 1990s.[4] ^{99m}Tc emits 140 keV of photon energy and has a physical half-life of 6 hours. Despite the excellent myocardial extraction and flow kinetic properties of ^{201}Tl, its energy spectrum of 80 keV is suboptimal for conventional gamma cameras (ideal photopeak in the 140-keV range). In addition, the long physical half-life of ^{201}Tl (73 hours) limits the amount of ^{201}Tl that may be administered to stay within acceptable radiation exposure parameters. Thus, ^{99m}Tc-labeled tracers improve on these two limitations of ^{201}Tl. Although three ^{99m}Tc-labeled tracers—sestamibi, teboroxime, and tetrofosmin—have received U.S. Food and Drug Administration (FDA) approval for detection of CAD, only sestamibi and tetrofosmin are available for clinical use at present.

Sestamibi and tetrofosmin are lipid-soluble cationic compounds with first-pass extraction fraction in the range of 60%. Myocardial uptake and clearance kinetics of both tracers are similar. They cross sarcolemmal and mitochondrial membranes of myocytes by passive distribution, driven by the transmembrane electrochemical gradient, and they are retained within the mitochondria.[4] Redistribution of these tracers is minimal compared with that for thallium. Consequently, myocardial perfusion studies with ^{99m}Tc-labeled tracers require two separate injections, one at peak stress and the second at rest.

Three basic protocols[5] with ^{99m}Tc-labeled tracers have been used: (1) a single-day study, in which myocardial blood flow is interrogated at rest and at peak stress, or in the reverse order, as long as the first injected dose is low (8 to 12 mCi) and the second injected dose is high (24 to 36 mCi); (2) a 2-day study (commonly performed in patients with large body habitus), in which higher doses of the tracer are injected (24 to 36 mCi) both at rest and at peak stress to optimize myocardial count rate; and (3) a dual-isotope technique, in which injection of ^{201}Tl at rest is followed by injection of a ^{99m}Tc tracer at peak stress. The last approach takes advantage of the favorable properties of each of the two tracers, including the high-quality gated SPECT images obtained with ^{99m}Tc and the potential to acquire redistribution images with ^{201}Tl (either at 4 hours before the stress study or at 24 hours after the ^{99m}Tc activity has decayed). **Table 16.1** compares the properties of the available isotopes for perfusion imaging.

TABLE 16.1

Properties of SPECT Tracers

TRACER	PHYSICAL HALF-LIFE	UPTAKE	MYOCARDIAL CLEARANCE	DIFFERENTIAL WASHOUT	MAXIMUM EXTRACTION
^{201}Tl	73 hours	Active	~50% at 6 hours	Yes	~0.70
^{99m}Tc-sestamibi	6 hours	Passive	Minimal	Minimal	0.39
^{99m}Tc-tetrofosmin	6 hours	Passive	Minimal	Minimal	0.24
^{99m}Tc-teboroxime	6 hours	Passive	~50% at 10 minutes	Yes	0.72

SPECT Image Interpretation and Reporting

SPECT myocardial perfusion images may be evaluated visually. The interpreter describes the perfusion pattern findings on stress and then visually interprets whether defects observed on the stress images are or are not reversible. Because the imaging data are digital, computer-aided quantitative analysis also may be used. Validated software programs for semiquantitative or fully automated quantitative analysis of SPECT myocardial perfusion images are now widely available.

General Principles of Interpretation and Reporting.

For any type of image interpretation, visual or quantitative, the key elements to be reported include the presence and location of perfusion defects and whether defects on stress images are reversible on the rest images (implying stress-induced ischemia) or whether stress perfusion defects are irreversible or fixed (often implying myocardial infarction) (**Fig. 16.3**). Moreover, substantial literature has documented that the extent and the severity of the perfusion abnormality are independently associated with clinical outcomes (risk of adverse events over time) and thus contribute importantly to the information on risk stratification to be conveyed to the ordering clinician.[6] The *extent* of perfusion abnormality refers to the amount of myocardium or vascular territory that is abnormal, and the *severity* refers to the magnitude of reduction in tracer uptake in abnormal zone relative to normal. **Figs. 16.4 to 16.6** provide examples of stress and rest SPECT myocardial perfusion abnormalities of varying extent and severity. These concepts imply that it is not sufficient to describe a stress perfusion imaging test as simply “abnormal.” Rather, a clinically relevant interpretation will include a description of the magnitude of abnormality as well as the extent of ischemia, extent of infarct, and localization to specific myocardial regions or vascular territories. The final report will incorporate all the clinical data, the stress testing result, and the imaging data to provide comprehensive information to the referring clinician, in a timely and clinically meaningful way. Guidelines for standardized reporting elements are available from professional societies.[7]

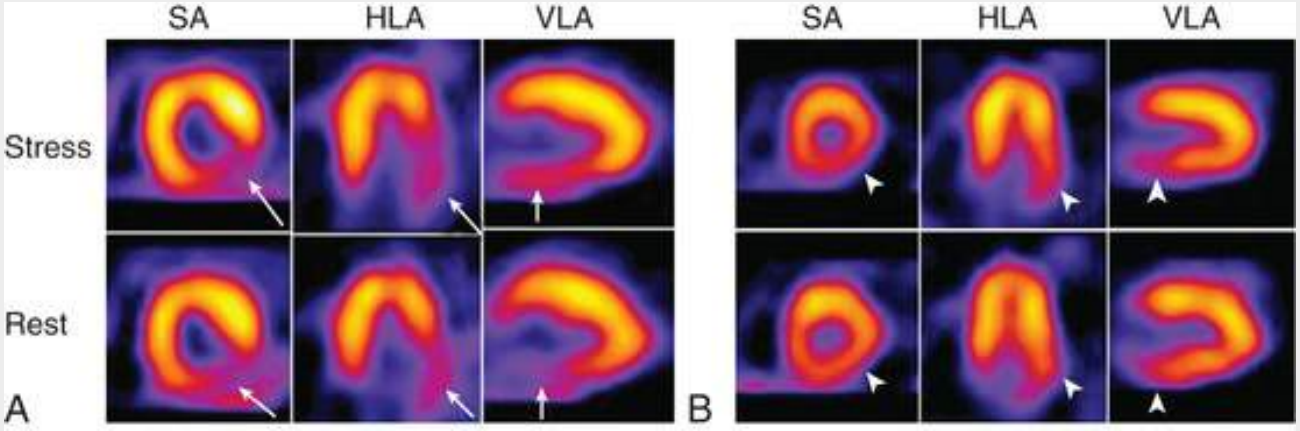


FIGURE 16.3 Examples of SPECT stress/rest perfusion imaging findings of infarct and ischemia. **A,** Fixed defect of the inferolateral wall (*arrows*), with similar reduction in tracer uptake in both stress and rest images in short-axis (SA), horizontal long-axis (HLA), and vertical long-axis (VLA) views, findings consistent with infarct. **B,** Reversible defect of the inferolateral wall (*arrowheads*), with relative reduction in tracer uptake in the inferolateral wall compared to the other walls in the stress images, with more homogeneous uptake in the rest images. These findings are consistent with blunted flow reserve in that area during stress, with normal perfusion at rest, identifying an area of stress-induced ischemia.

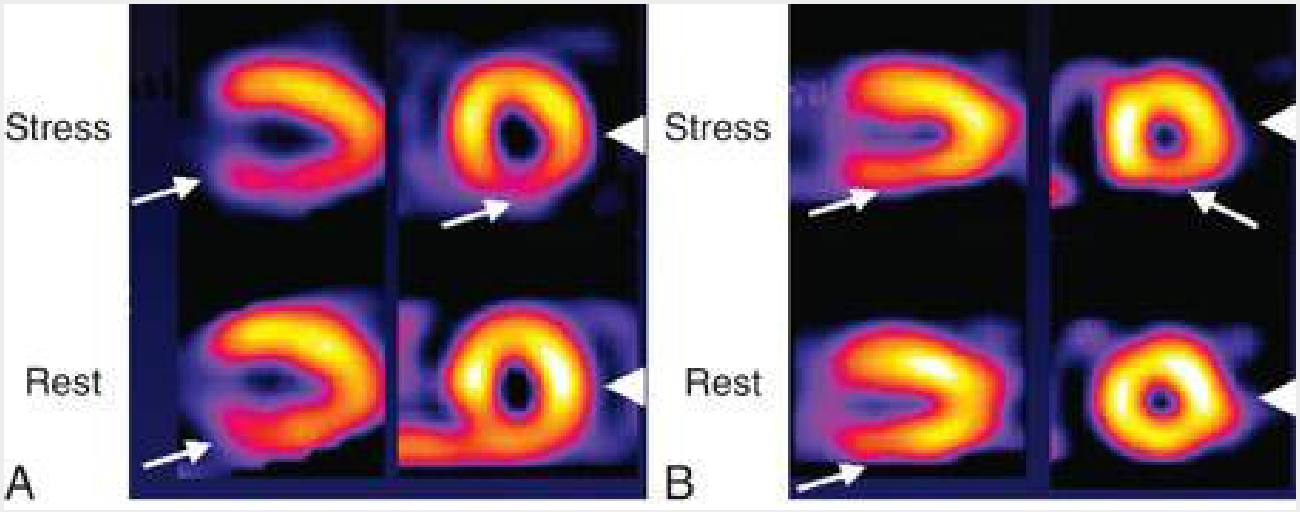


FIGURE 16.4 SPECT images of inferior wall abnormalities of differing extent and severity. **A,** Large, moderately severe, reversible inferior wall defect (*arrows*) reflecting a moderately severe flow reserve abnormality. **B,** Milder, reversible inferior wall defect (*arrows*) reflecting either a less severe stenosis or a severe stenosis with well-developed collaterals minimizing the defect severity. In both patients, a mild lateral wall reversible defect also is present (*arrowheads*). Note how the lateral wall brightens relative to the septum on the rest images compared with the stress images.

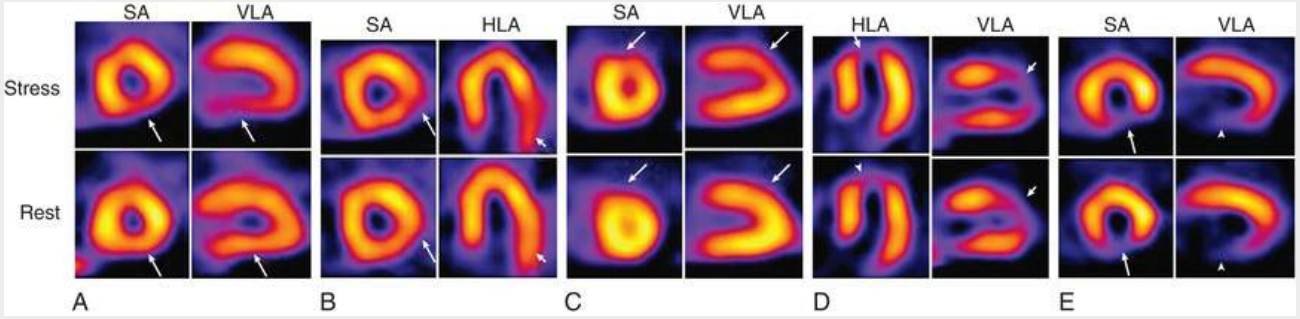
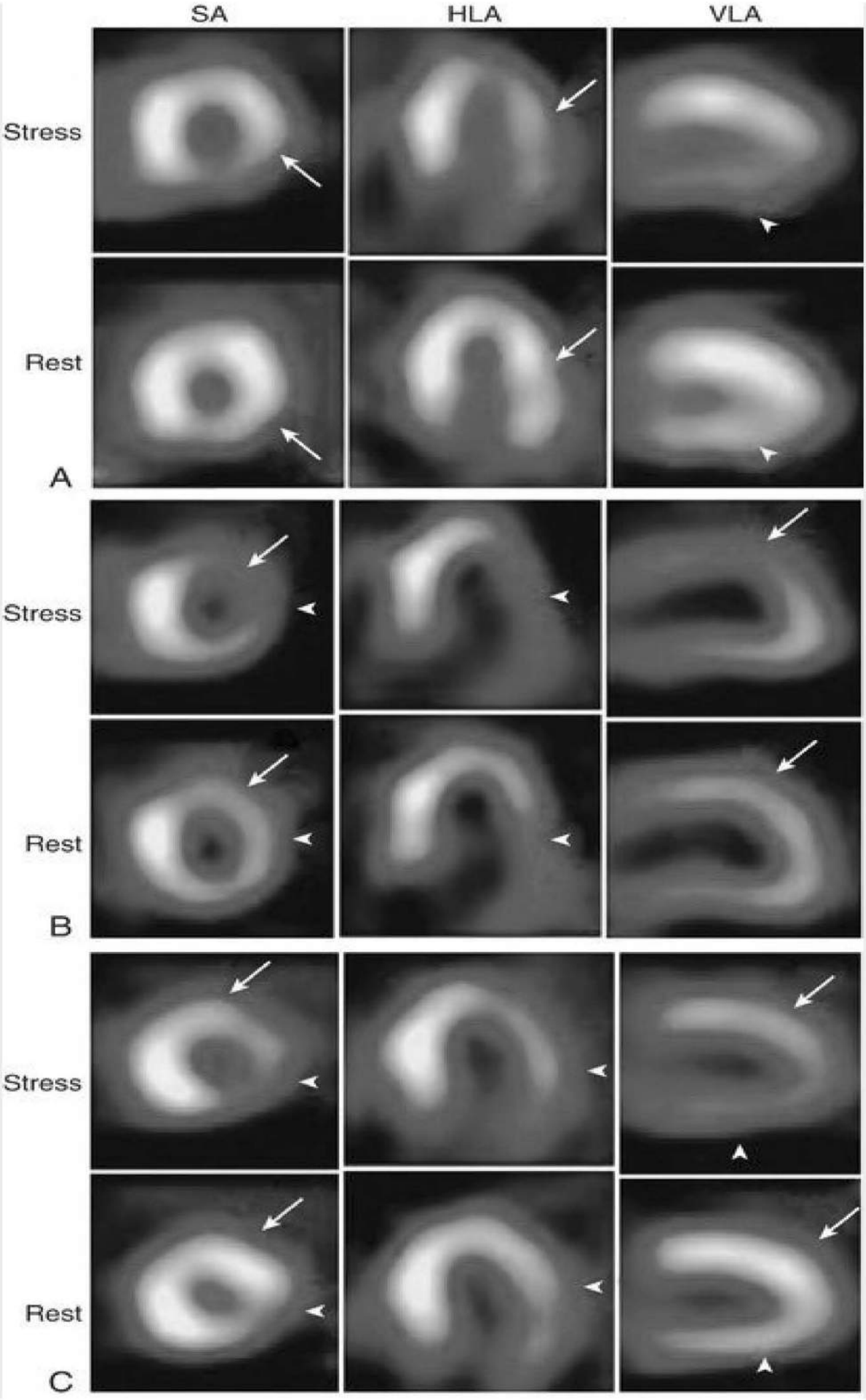


FIGURE 16.5 Examples of single vascular territory reversible defects. **A,** Reversible inferior wall defect (*arrows*) in short-axis (SA) and vertical long-axis (VLA) views, consistent with inducible ischemia in right coronary artery territory. **B,** Reversible lateral wall defect (*arrows*) in SA and horizontal long-axis (HLA) views (*arrows*), consistent with inducible ischemia in left circumflex coronary artery territory. **C,** Reversible anterior wall defect (*arrows*) in the SA and VLA views, consistent with inducible ischemia in left anterior descending (LAD) artery territory. **D,** Fixed perfusion pattern consistent with LAD artery territory infarct. There are fixed defects involving the apex in HLA view (*arrowheads*), and the anteroapical wall and apex in VLA view (*arrows*). **E,** Fixed perfusion defect pattern involving the inferior wall (*arrows*) in SA view and in VLA view (*arrowheads*), consistent with inferior infarct.


SA
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Stress
Rest
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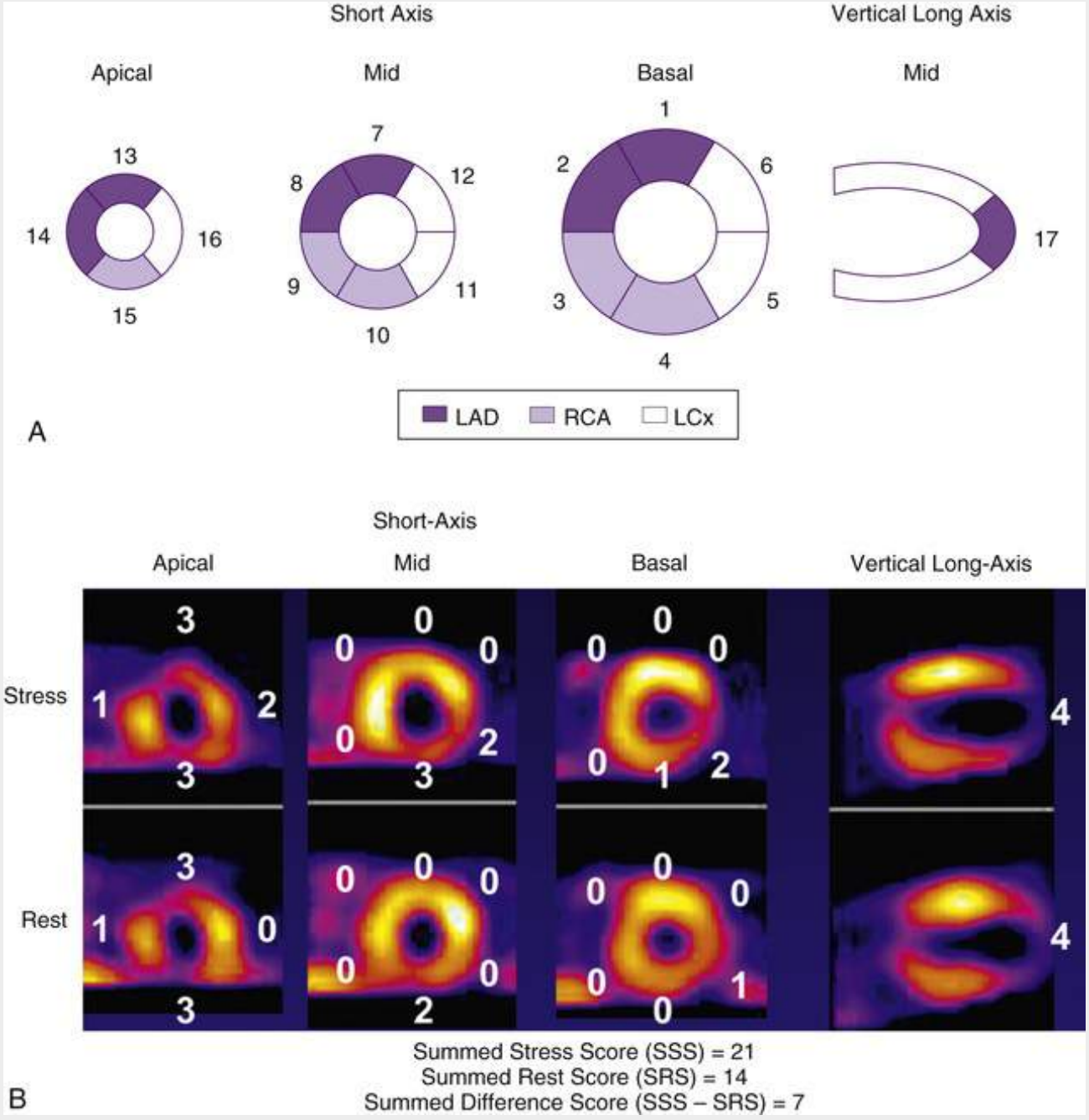
Stress
Rest
B
Stress
Rest
C

FIGURE 16.6 Examples of reversible defects in more than one vascular territory. **A,** Reversible lateral wall defect (*arrows*) in short-axis (SA) and horizontal long-axis (HLA) views, consistent with inducible ischemia in left circumflex (LCx) coronary artery territory, and a reversible inferior wall defect (*arrowheads*) in vertical long-axis (VLA) view, consistent with inducible ischemia in the right coronary artery (RCA) territory. **B,** Reversible anterior wall defect (*arrows*) in the SA and VLA views, consistent with inducible ischemia in the LAD artery territory, and a reversible lateral wall defect (*arrowheads*) in the SA and HLA views, consistent with inducible ischemia in LCx territory. **C,** Perfusion abnormalities in all three major vascular territories: reversible anterior wall defect (*arrows*) in SA and VLA views, consistent with inducible ischemia in LAD territory; reversible lateral wall defect (*arrowheads*) in SA and HLA views, consistent with inducible ischemia in LCx territory; and reversible inferior wall defect (*arrowheads*) in VLA view, consistent with inducible ischemia in RCA territory.

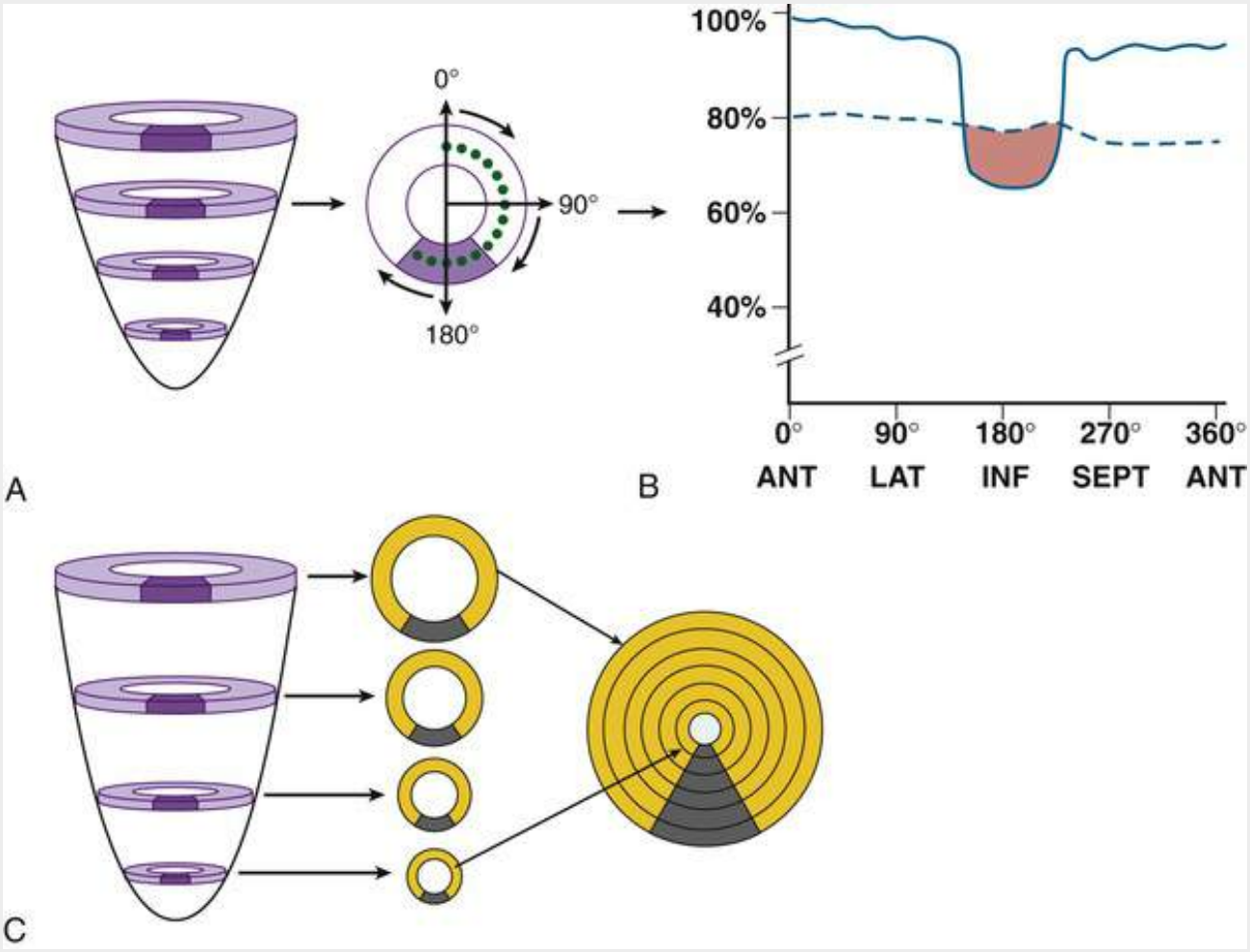
To minimize subjectivity in image interpretation, semiquantitative visual analysis or fully quantitative computer analysis may be applied to MPI data.[5] With semiquantitative visual analysis, a score is assigned to represent perfusion for each of multiple segments of the myocardium. A segmentation model has been standardized for this approach by dividing the myocardium into 17 segments[7] on the basis of three short-axis slices and a representative long-axis slice to depict the apex (**eFig. 16.2**). Perfusion is graded within each segment on a scale of 0 to 4, with 0 representing normal perfusion and 4 representing a very severe perfusion defect. Scores for all 17 segments are added to create a "summed" score. The sum of the segmental scores from the stress images, the *summed stress score* (SSS), represents the extent and severity of stress perfusion abnormality—the magnitude of perfusion defects related to both ischemia and infarction. The sum of the 17 segmental scores from the rest images, the *summed rest score* (SRS), represents the extent of infarction. The *summed difference score* (SDS) is derived by subtracting the SRS from the SSS and represents the extent and severity of stress-induced ischemia. The segmental scores can be assigned subjectively by the image interpreter or automatically by widely available software programs. As discussed later, a substantial literature has validated these summed scores, particularly the SSS, as predictors of natural history outcomes.



EFIGURE 16.2 **A,** Standard segmental myocardial display for semiquantitative visual analysis in a 16-segment model, with corresponding vascular territory schematic; *LAD,* left anterior descending artery; *LCx,* left circumflex coronary artery; *RCA,* right coronary artery. **B,** Segmental scoring of a patient whose stress and rest SPECT perfusion images show a severe apical fixed defect (in the vertical long axis), extending into the inferoapical and anteroapical walls (in the apical short axis), with evidence of reversible defects in the inferior and lateral walls (in the mid- and basal short axis). The summed stress score (SSS = 21) represents extensive perfusion abnormality at stress (reflecting ischemia and infarct); the summed rest score (SRS = 14) represents the extent of infarct; and the summed difference score (SDS = SSS − SRS = 7) represents the extent of ischemia.

Because SPECT MPI data are a digital representation of radiotracer distribution, the data can also be analyzed quantitatively. The most common technique involves creation of a circumferential profile of relative tracer activity around the tomogram of interest, such as a short-axis tomogram. With this technique, each short-axis tomogram is sampled at every 3 to 6 degrees for 360 degrees, along a ray extending from the center of the image (**eFig. 16.3**). The maximum counts at a picture element (pixel) along the ray, usually occurring in the midportion of the myocardium, are recorded for each angle. The data may be plotted to create a profile of the perfusion pattern of that tomogram relative to the most "normal" area of uptake, which is assigned a value of 100% uptake. Circumferential profiles for an

individual patient can be compared directly with a composite profile representing normal perfusion. The normal perfusion data are created from studies performed in normal individuals with a very low clinical probability of CAD or in those with known normal coronary arteries. A quantitative extent of abnormality can be derived for each tomogram of the individual patient (the total amount of myocardium that falls below the lower limit of normal) as well as a derivation of the severity of the perfusion abnormality (the depth of the patient's perfusion abnormality relative to the lower limit of normal).



EFIGURE 16.3 Quantitative analysis of SPECT imaging. **A,** Circumferential profile analysis of tracer uptake along rays emanating from the center of the short-axis tomogram. From this procedure, a circumferential profile of tracer uptake around the myocardium is developed for each short-axis tomogram. In this example, there is a perfusion defect in the inferior wall (*darker purple area*). **B,** The data are plotted relative to location around the myocardium (*x* axis) and "normalized" to the point of peak uptake, which is assigned a value of 100% (*y* axis). The patient's data (*solid line*) are compared with lower limits of normal (*dashed line*) derived from a group of participants without CAD of the same gender. From this comparison, the quantitative extent and severity of the perfusion abnormality can be derived (*red area*). *ANT,* Anterior; *INF,* inferior; *LAT,* lateral; *SEPT,* septal. **C,** Data from all the individual short-axis tomograms can be combined to create a bull's-eye polar plot, representing a two-dimensional compilation of all of the three-dimensional short-axis perfusion data. The extent of the inferior wall perfusion defect (*gray area* on individual profiles and polar plot) is seen on the two-dimensional map. (Images courtesy Ernest Garcia, PhD.)

Most contemporary computer systems and analysis programs create "bull's-eye" or polar maps representing perfusion of the entire three-dimensional myocardium in a two-dimensional plot (**Fig. 16.7; see eFig. 16.3**). Quantitative data may be derived on the extent of global perfusion abnormality, the abnormality within vascular territories, and the extent of reversible and fixed defects. These are often displayed as "blackout maps," in which any pixel values falling below a set number of standard

deviations below the normal limits is assigned the color black, and the extent of that abnormality is expressed as a percentage of the presumed vascular territory and as a percentage of the left ventricle (**Fig. 16.8**).

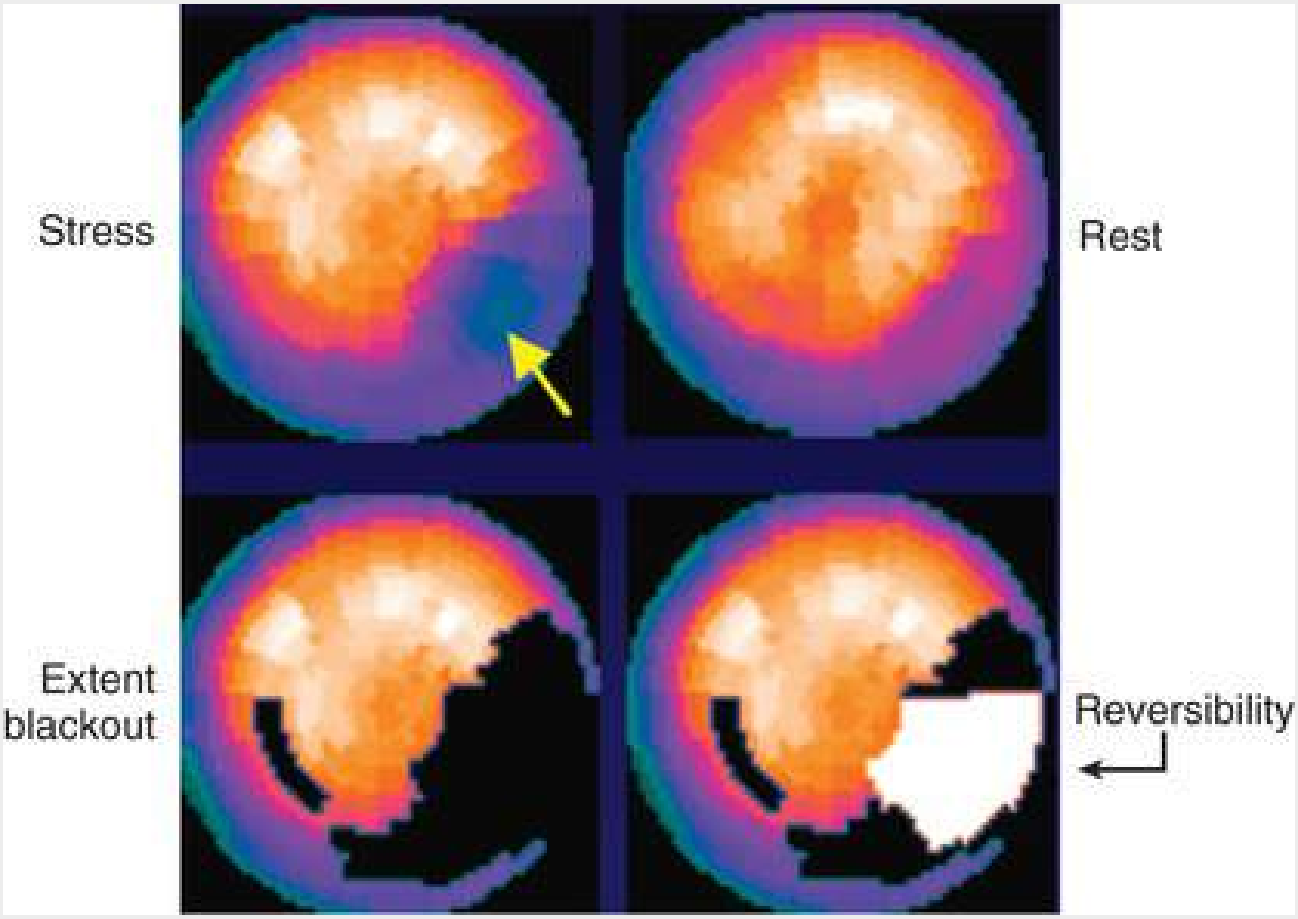


FIGURE 16.7 Example of bull's-eye polar plot for patient with reversible defect of inferolateral wall (*arrow* on stress bull's-eye plot, *upper left*). *Blackout area* (on extent blackout plot, *lower left*) represents the myocardium that falls below the lower limits of normal; in the reversibility plot (*lower right*); *white area* represents the extent of that abnormality that is reversible (ischemic) on rest imaging. (Images courtesy Ernest Garcia, PhD.)

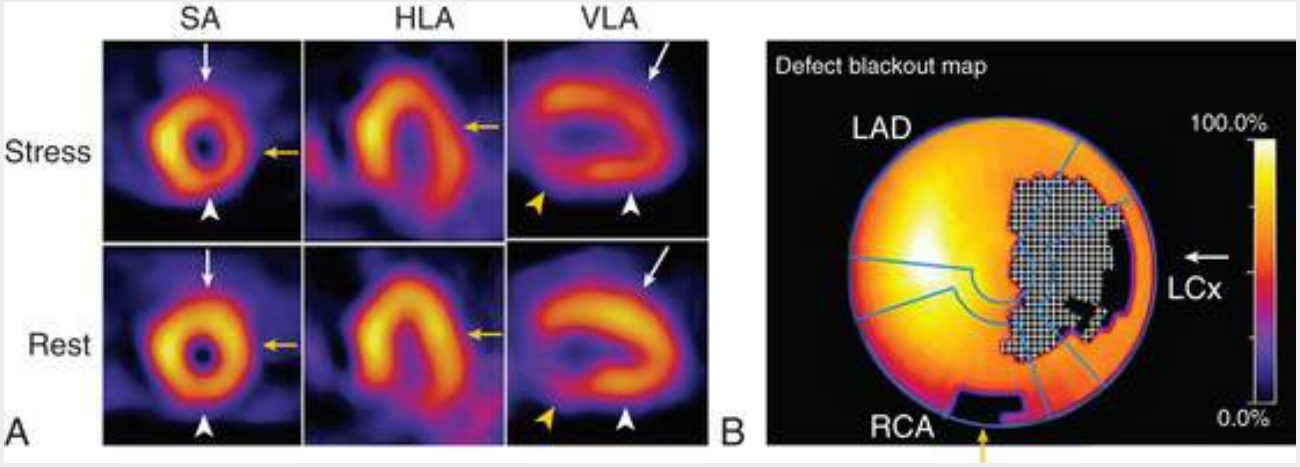
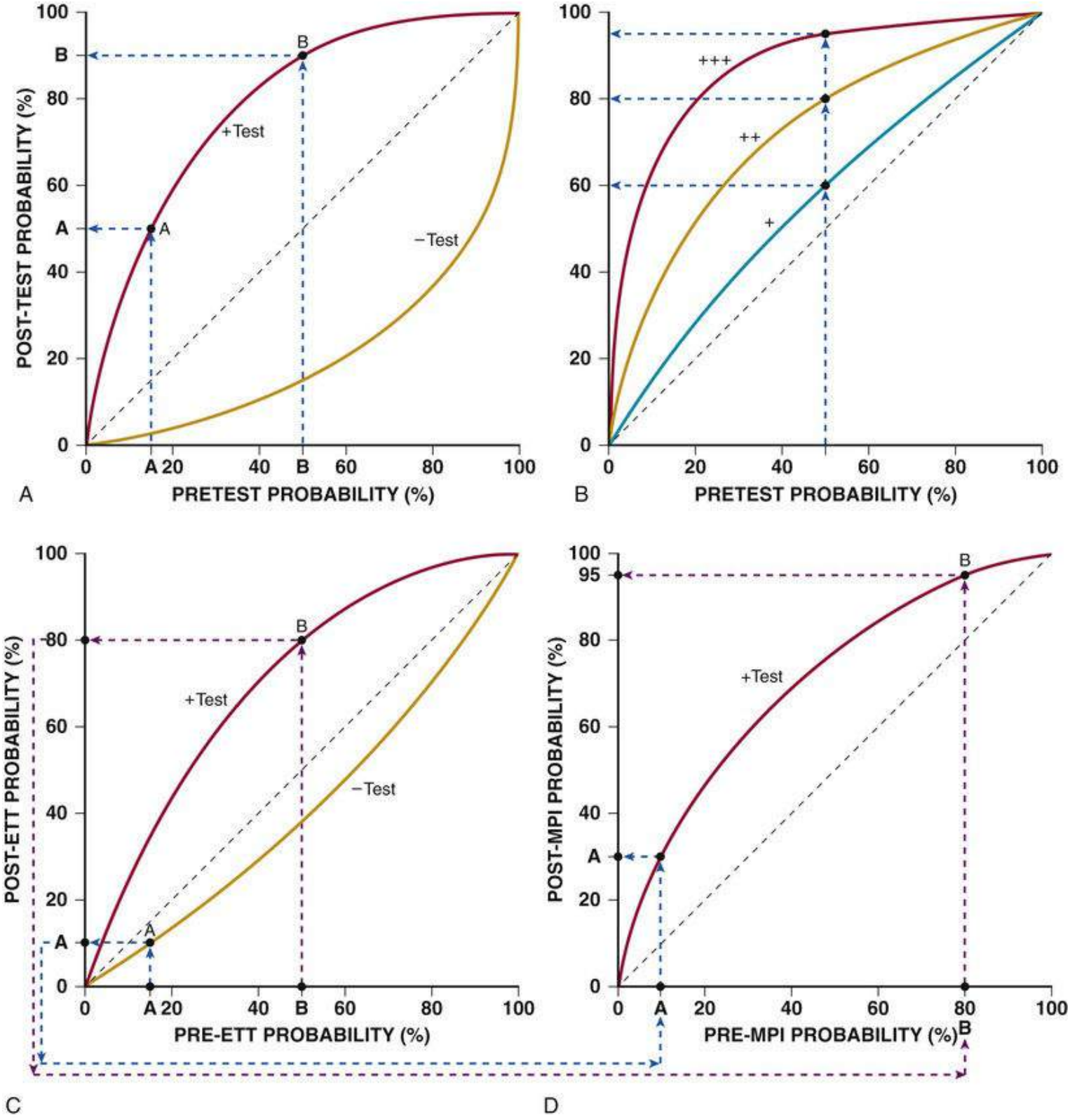


FIGURE 16.8 Examples of SPECT stress-rest perfusion imaging findings of extensive ischemia in all vascular territories and a small infarct. **A,** Reversible defects in the anterior wall and apex (*white arrows*), lateral wall (*yellow arrows*), and inferior wall (*white arrowheads*), consistent with inducible ischemia in all those territories. There is a small, fixed defect in the base of the inferior wall in the vertical long-axis (*VLA*) tomograms (*yellow arrowheads*), consistent with a small infarct. **B,** The polar map quantitation documents defects crossing into all vascular territories, with extensive reversibility (*white cross-hatched area, white arrow*), and a small irreversible area in the basal inferior wall (*blacked-out area, yellow arrow*). *SA,* Short-axis; *HLA,* horizontal long-axis view; *LAD,* left anterior descending artery; *LCx,* left circumflex artery; *RCA,* right coronary artery.

Reporting guidelines also outline the elements of a comprehensive reporting structure when semiquantitative and/or quantitative analysis are used.[7]

Incorporating Bayesian Principles Into Image Interpretation

Although it is possible to interpret MPI data in isolation and report only on what the images demonstrate, a more accepted interpretive methodologic principle is that the final interpretation should take into account the entirety of the data at hand. Therefore the image data build on the already-known clinical and stress test data, and the clinician should consider all this information when interpreting MPI data. An understanding of bayesian probability principles is useful in this regard. Bayes theorem posits that the post-test probability of disease (or risk of an event after a test) is influenced not only by the sensitivity and specificity of the test, but also by the pretest probability of disease (**see Chapter 13**). This principle is illustrated in **eFig. 16.4**. For a given positive test result, the post-test probability of disease may be distinctly lower in a patient with a very low pretest probability of disease compared with a different patient with a much higher pretest probability (**eFig. 16.4A**). In practice, MPI results are not simply positive or negative; rather, positive (i.e., abnormal) results can range from *borderline abnormal* (uncertainty whether the abnormality may be an artifact or a mild perfusion defect) to *strongly abnormal* (extensive and severe defects, highly likely to be real and unlikely to represent artifact). Thus the "test positive" curve in **eFig. 16.4A** can be thought of as a family of positivity curves, with distinct implications for post-test likelihood of disease (**eFig. 16.4B**).



EFIGURE 16.4 Influence of pretest probability on post-test interpretation and application of Bayes theorem. **A,** For patient with low pretest probability of disease (point *A* at 15% on *x* axis) with a positive test result, post-test probability of disease (point *A* at 50% on *y* axis) is lower than for a different patient with a higher pretest probability with the same positive test result (point *B* at 50% pretest probability on *x* axis, 90% post-test probability on *y* axis). In **B,** the "test positive" curve can be thought of as a family of curves influenced by how strongly positive the images can be. For a given pretest probability, the post-test probability becomes progressively higher as the image becomes more strongly abnormal. For a borderline abnormal study (+ curve), the post-test probability may be only slightly higher than the pretest value. For a strongly positive study (+++ curve), the post-test probability is very high no matter what the pretest probability. **C, D,** Sequential application of Bayes theorem. For a young patient with nonanginal chest pain, the pretest probability of coronary artery disease (CAD) is low (approximately 15%, point *A* on *x* axis in **C**). If the patient undergoes an exercise treadmill test (*ETT*) and exercises to a good workload with no symptoms and no electrocardiographic change, the post-ETT probability is even lower (10% on *y* axis in **C**). The post-ETT probability then becomes the pre-MPI probability, as seen in **D** (point *A* on *x* axis). A "positive" myocardial perfusion imaging (MPI) test result is still associated with a relative low post-test

probability of CAD (point *A* at 30% probability on *y* axis). If reported as positive, there is actually a greater chance that such a result represents a false-positive result (70%) as opposed to a true-positive result (30%). For an older patient with a history of chest pain (higher pretest probability, point *B* on *x* axis in **C**) in whom treadmill exercise reproduces those symptoms, with positive ECG changes, the post-ETT probability rises (point *B* on *y* axis in **C**), and that becomes the high pre-MPI probability (point *B* on *x* axis in **D**). Thus the same MPI results are much more likely to represent a true-positive finding (point *B* on *y* axis in **D**, 95%) and less likely to represent a false-positive study (5%).

The implication of incorporating these concepts for image interpretation can be illustrated by considering a mildly positive MPI study demonstrating a small, mild reversible inferobasal defect. Although this defect may represent a small area of inferior inducible ischemia, the image also may reflect diaphragm attenuation of the inferobasal wall predominantly affecting the stress image. The influence of the pretest probability data (i.e., pre-MPI) is illustrated in **eFig. 16.4C**. For a young patient with nonanginal chest pain, the pretest probability of CAD is low. If the patient undergoes an exercise treadmill test (ETT) as the stress portion of the MPI test and exercises to a good workload with no symptoms and no changes on the electrocardiogram (ECG), the post-ETT probability is even lower. The post-ETT probability then becomes the pre-MPI probability (**eFig. 16.4D**). A positive test result, especially a mildly positive result, is still associated with a relative low post-test probability of CAD. A result reported as positive is more likely to represent a false-positive than a true-positive finding. By contrast, for an older patient being evaluated for anginal chest pain in whom ETT reproduces those symptoms and who exhibits positive ECG changes, the pre-MPI probability is very high, so the same MPI results are much more likely to represent a true-positive than a false-positive finding (**eFig. 16.4C, D**). These examples illustrate how the clinical data may be incorporated into the MPI interpretation and also how bayesian probability principles may be incorporated sequentially so that the image reader conveys information to the referring clinician that reflects the post-test probability of disease (and risk), rather than simply reporting what the image data show in isolation.

Important Signs in SPECT Imaging Analysis Beyond Myocardial Perfusion

Other abnormal findings provide additional information beyond that indicated by the perfusion pattern alone, including lung uptake of tracer (particularly ^{201}Tl) and transient ischemic dilation of the left ventricle.

Lung Uptake

In some patients, substantial tracer uptake is apparent throughout the lung fields after stress that is not present at rest (**Fig. 16.9A**). Patients with lung uptake often have severe multivessel disease and exhibit elevation of pulmonary capillary wedge pressure and decreases in ejection fraction (EF) during exercise, all implying extensive myocardial ischemia.[4] It is likely that ischemia-induced elevation in left atrial and pulmonary pressures slows pulmonary transit of the tracer, allowing more time for extraction or transudation into the interstitial spaces of the lung, accounting for this imaging sign.

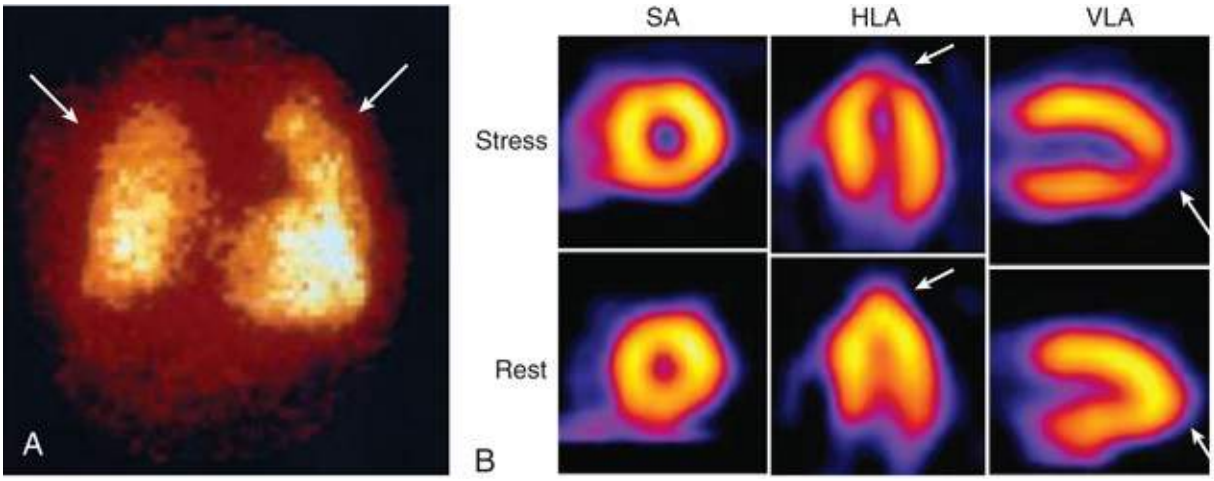


FIGURE 16.9 **A,** Increased lung uptake of ^{201}Tl (*arrows*) on planar imaging, viewed in the anterior projection. Lung uptake such as this pattern is associated with extensive CAD and an adverse prognosis. **B,** Apical reversible perfusion pattern consistent with ischemia (*arrows*) in the territory of the LAD artery. There is also transient ischemic dilation (TID), as the left ventricular cavity is larger (appears more dilated) in the stress images than in the rest images in all three tomographic views. The quantitative TID ratio was high at 1.49. Even though the perfusion pattern by itself suggests single-vessel LAD disease, the presence of TID makes the probability of multivessel disease more likely. *HLA,* Horizontal long-axis; *SA,* short-axis; *VLA,* vertical long-axis view.

Lung uptake of ^{201}Tl has been more extensively validated than lung uptake of the ^{99m}Tc tracers sestamibi and tetrofosmin. Splanchnic or background activity is minimal after thallium stress injection, allowing image acquisition earlier after stress. In addition, the redistribution properties of thallium mandate that imaging begin relatively early after stress, so lung uptake may be more apparent.

Transient Ischemic Dilation of the Left Ventricle

Transient ischemic dilation refers to an imaging pattern in which the left ventricle or left ventricular (LV) cavity appears larger on the stress images than on those obtained with the patient at rest[6] (**Fig. 16.9B**). For patients in whom the entire left ventricle appears larger during stress, the pathophysiology probably is related to extensive ischemia and prolonged postischemic systolic dysfunction, resulting in a dilated, dysfunctional left ventricle during the stress acquisition relative to the rest acquisition. In other patients the epicardial silhouette appears similar at stress and at rest, but with apparent dilation of the LV cavity. This pattern may represent diffuse subendocardial ischemia (relatively less tracer uptake in the subendocardium, creating the appearance of an enlarged LV cavity) and also is associated with severe and extensive CAD. Contemporary processing systems can automatically quantify transient ischemic dilation.

Both lung uptake and transient ischemic dilation provide clues to more extensive CAD than may have been suspected from the perfusion pattern alone. Both signs have been associated with angiographically extensive and severe CAD and with unfavorable long-term outcomes; accordingly, such changes are considered high-risk findings.

Common Normal Variations in SPECT Imaging.

Normal variations in perfusion images can be falsely interpreted as a defect. These perturbations from a completely homogeneous tracer pattern throughout the myocardium are related to structural variations of the myocardium as well as to technical factors associated with image acquisition.

One example is the “dropout” of the upper septum secondary to merging of the muscular septum with

the membranous septum (**Fig. 16.10A**). Apical thinning is another variation of normal that can be mistaken for a perfusion defect (**Fig. 16.10B**). The apex is anatomically thinner than other myocardial regions, creating this appearance. In normal SPECT images the lateral wall often may appear brighter than the contralateral septum (**Fig. 16.10C**). This difference is not caused by a disparity in lateral versus septal wall myocardial blood flow. Rather, during a SPECT acquisition, the camera is physically closer to the lateral myocardial wall (in proximity to the lateral chest wall) than to the septum through the course of the camera's orbit, so that the lateral wall emissions are subject to less soft tissue attenuation and the acquisition is associated with more efficient count capture from that region. A careful review of the data for a series of normal volunteers or patients with a low probability of CAD with one's own equipment is an important step in minimizing the influence of these normal variations on the sensitivity and specificity for detection of CAD.

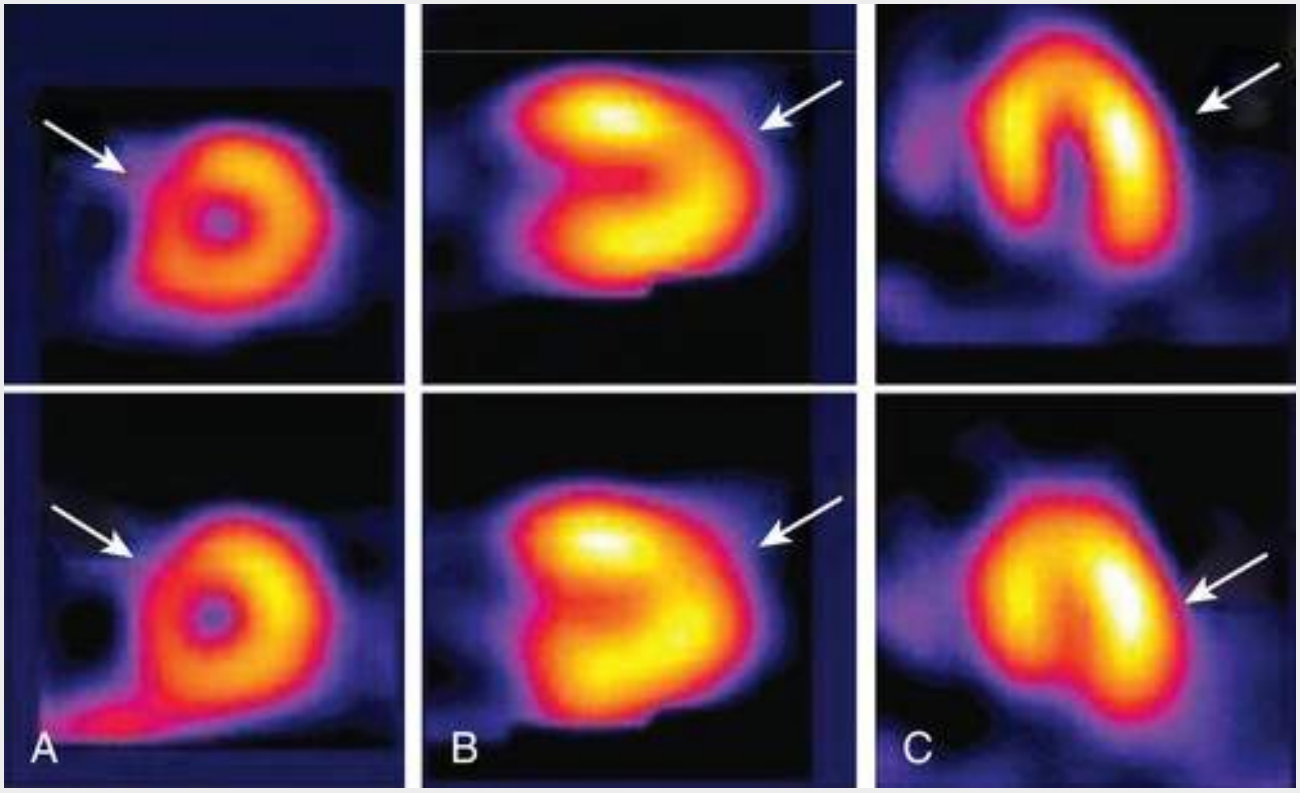


FIGURE 16.10 Normal variations in SPECT perfusion imaging. **A,** Normal "dropout" of the basal septum (*arrows*), which would be seen in the most basal short-axis tomograms. **B,** Normal apical thinning (*arrows*). **C,** The lateral wall often is slightly "hotter" than the septum, another normal variation.

Technical Artifacts Affecting Image Interpretation

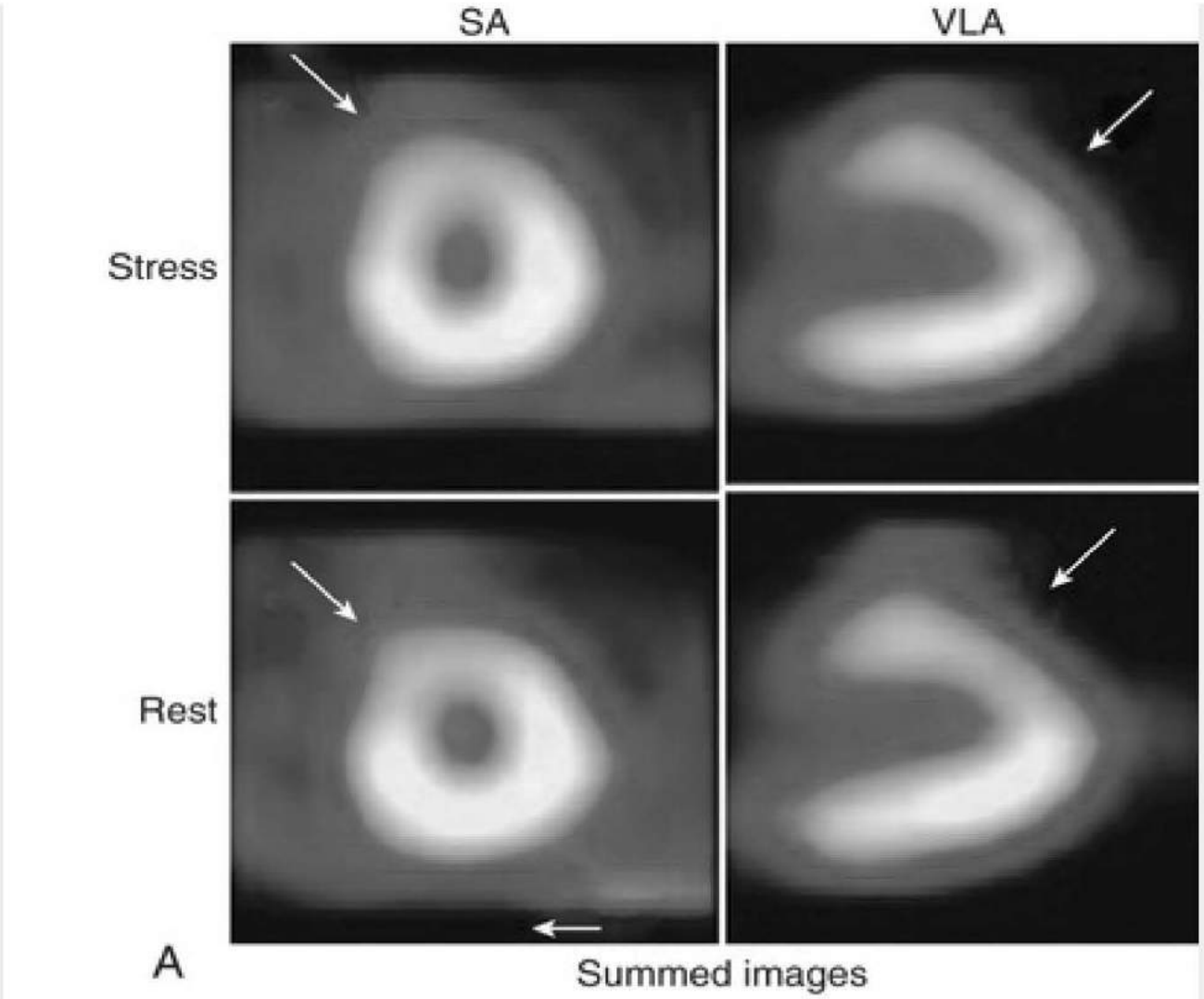
Photon Attenuation.

This refers to undetected events in the heart caused by interaction of photons with the intervening soft tissue, breast, or diaphragm. Attenuation of photons can produce artifactual defects in both positron emission tomography (PET) and SPECT cardiac imaging that mimic true myocardial perfusion defects, thereby reducing specificity (i.e., increasing false-positive findings).

Breast Attenuation.

In patients with large or dense breasts, significant attenuation may create artifacts varying considerably in their appearance and location (**Fig. 16.11**). A review of the cine display of the raw projection images may reveal the presence of potential breast attenuation.[5] The availability of gender-matched quantitative databases has had a favorable although modest impact on this issue, because such databases generally

consist of individuals of average body and breast size.


SA
VLA
Stress
Rest
A
Summed images

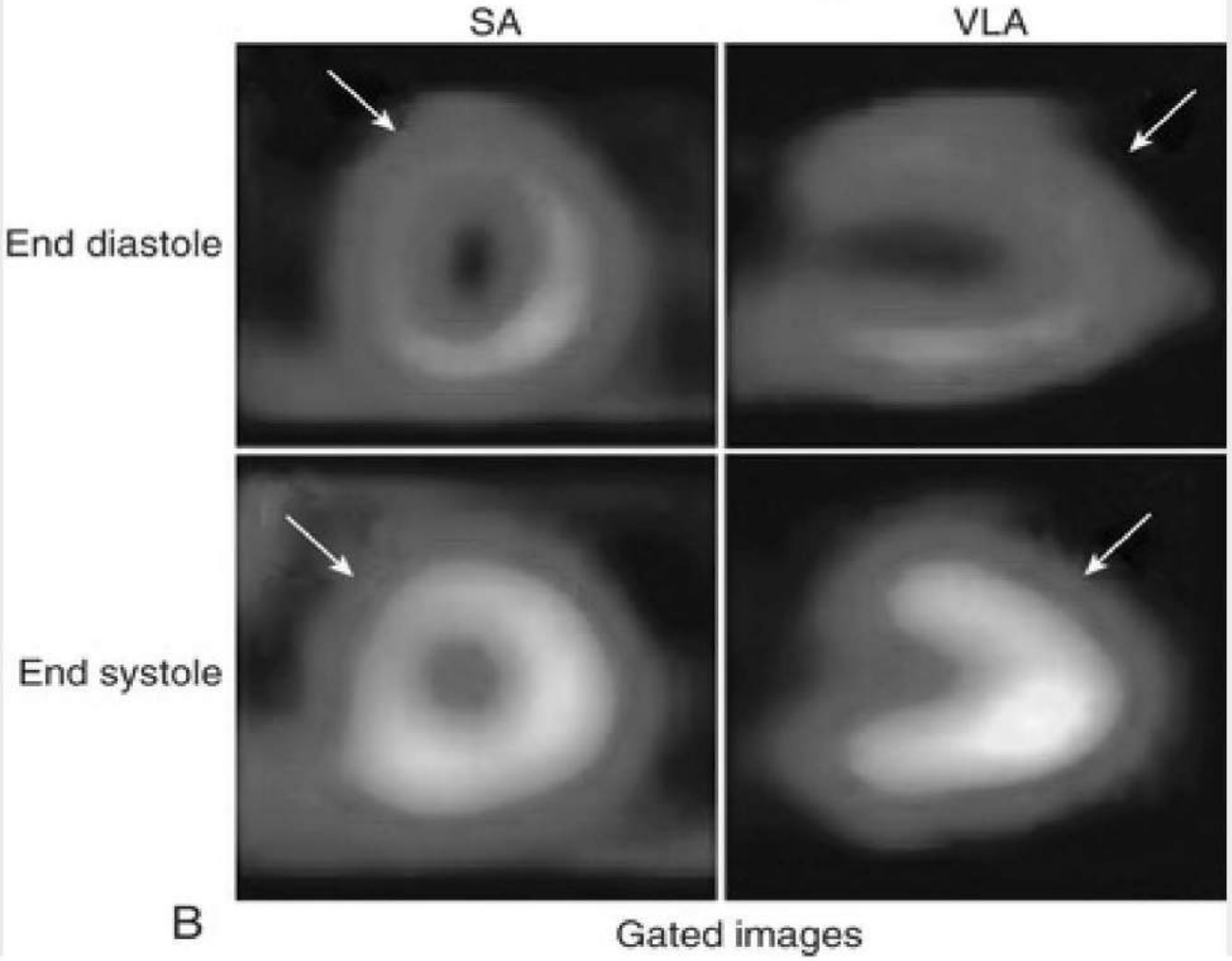

SA
VLA
End diastole
End systole
B
Gated images

FIGURE 16.11 Differential diagnosis of a mild fixed defect by incorporation of gated functional images. **A,** The summed images demonstrate a mild fixed anterior and anteroseptal defect in the short-axis (SA) and vertical long-axis (VLA) views (*arrows*). There was a suggestion of breast shadowing on review of the raw cine images (not shown). Thus this defect may represent either a nontransmural anterior infarct or an artifact consistent with breast attenuation. In such cases, the gated SPECT functional images are helpful in making this distinction. **B,** In the gated images, the same SA and VLA views are shown but frozen in end diastole and end systole. In both views, wall thickening from end diastole to end systole (*arrows*) appears normal. This appearance is most consistent with an attenuation artifact, because an infarct would be expected to result in abnormal wall thickening.

Several approaches to minimizing the impact of breast tissue have been taken to improve specificity (lowering the false-positive rate) in women. Most well validated is ECG-gated SPECT imaging with ^{99m}Tc-based agents (see later). The presence of preserved wall motion in the setting of a mildly to moderately severe fixed defect of the anterior or anterolateral wall suggests the absence of infarction and supports the interpretation of attenuation artifact (**Fig. 16.11**). Specificity for ruling out CAD in women has been improved significantly with this technique.[4]

Inferior Wall Attenuation.

Inferior wall attenuation artifacts are frequently encountered in SPECT imaging. This artifact may be caused by extracardiac structures, such as the diaphragm overlapping the inferior wall (**Fig. 16.12**). In addition, during a SPECT acquisition, the longer distance from the inferior wall to the camera means that photons must traverse a greater thickness of tissue before reaching the detectors, which may increase the degree of scatter and attenuation.

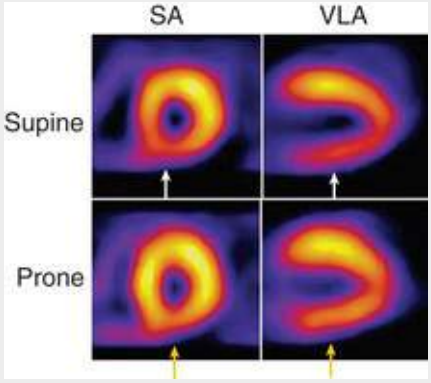


FIGURE 16.12 Example of the use of prone imaging to resolve diaphragm attenuation versus true defect. **Top row,** Standard supine images show an apparent inferior perfusion defect (*white arrow*). There was substantial diaphragm overlap of the inferior wall on the raw projection images (not shown), and the exercise stress test was very low risk, both suggesting that the defect was a false positive. **Bottom row,** The patient was reimaged in the prone position, which helps to create more separation between the diaphragm and the inferior wall. The prone images show normal perfusion of the inferior wall (*yellow arrows*), suggesting that the defect seen on the supine imaging was indeed a false positive. *SA,* Short-axis view; *VLA,* vertical long-axis view.

As with breast attenuation artifact detection, the demonstration of preserved wall thickening by gated SPECT imaging may be helpful in distinguishing attenuation artifact from infarct. The patient's positioning also may minimize the degree of attenuation. By imaging the patient in the prone position,[2,5] the inferior wall is shifted away from the diaphragm and is therefore less subject to attenuation (**Fig. 16.12**).

Artifacts Related to Extracardiac Tracer Uptake.

Tracer uptake in extracardiac structures can cause artifacts in SPECT images. When such a structure is near the heart, increased counts may reach the detector, falsely elevating the number of counts the system assigns to the nearby cardiac wall, so the cardiac region is displayed as falsely "hotter." A second possibility occurs when a nearby hot extracardiac structure causes a "ramp filter" or "negative lobe" artifact.[2] This artifact results from a hot extracardiac structure "stealing" counts from the heart during the calculation of the summed SPECT images. The adjacent myocardium appears falsely "cool." If substantial extracardiac uptake is noted, image acquisition can be repeated after waiting a longer time before imaging. Having the patient drink cold water may enhance clearance of tracer from visceral organs, particularly the bowel.

Attenuation Correction Methods

The 511-keV photons emitted by positron-emitting radiotracers in PET imaging are attenuated less per centimeter of soft tissue than are the lower-energy 80- to 140-keV photons typically emitted by SPECT radiotracers. In SPECT imaging, a single photon needs to travel from the heart to the camera; in PET imaging, two coincident photons (i.e., emitted simultaneously) need to travel across the entire body to reach their respective detectors (see later, Positron Emission Tomography). Although the total attenuation may actually be greater for PET than for SPECT, an important distinction in the case of PET is that the attenuation is the same along a projection line (the path the pair of photons traverse) independent of how deep in the body the annihilation took place. Thus, in PET, only the total attenuation through the whole body along a specific direction must be known. On the other hand, in SPECT, it is necessary to know the exact depth along a projection line where the radioactive decay took place in order to correct for attenuation. Therefore, attenuation correction for SPECT is theoretically more challenging. In recent years, several approaches to correct for attenuation in both PET and SPECT imaging have emerged, with the goal of "correcting" attenuation artifacts to minimize false-positive defects and to improve specificity.

PET Attenuation Correction.

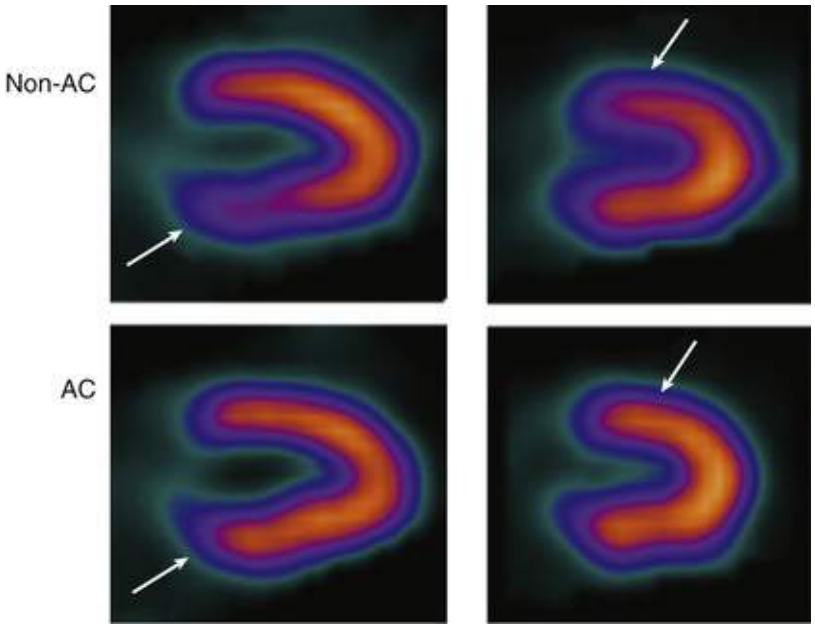
To measure the attenuation correction factor, a rod that rotates about the patient is filled with a relatively long-lived positron emitter, germanium-68, or a single-photon emitter, cesium-137. The rod is first made to rotate at a fixed speed in the gantry, and total coincident counts are measured without the patient (the blank scan) and repeated with the patient (the transmission scan). The ratio of coincident counts of blank scan and those of transmission scan yields the array of attenuation correction factors needed to correct each projection line. Once each projection line has been corrected for attenuation (and scatter), the emission data may be reconstructed into an attenuation-corrected emission image for clinical interpretation. As long as the patient does not move during the scanning procedure, cardiac PET images will be free from attenuation artifacts.

SPECT Attenuation Correction.

Approaches similar to PET attenuation correction have been attempted to correct attenuation artifacts in SPECT, but these methods have not been widely adopted because the problem of attenuation correction is fundamentally more challenging in SPECT than in PET. A number of commercially available SPECT gamma cameras have the ability to acquire transmission data and to perform attenuation correction. Several published studies suggest that incorporating attenuation correction into SPECT interpretation may increase the specificity of CAD diagnosis. However, the increased cost of SPECT attenuation correction systems and the additional time required to quality control, acquire, and process studies are factors that

have slowed the widespread deployment of this technology.

Despite these technical challenges, the application of attenuation correction in multicenter clinical trials, with different hardware and software approaches, has been shown to add to the diagnostic accuracy of stress myocardial perfusion SPECT, predominantly by improving specificity (**eFig. 16.5**). Guidelines suggest that incorporation of attenuation correction methodology into SPECT perfusion imaging studies is optional.[2] This recommendation presumes that, when it is performed, the attenuation correction methodology is applied by personnel highly knowledgeable about the technique and its stringent quality control.



EFIGURE 16.5 Impact of attenuation correction (*AC*). **Top row,** The non-AC images include examples of an inferior defect (*left column*) and an anterior defect (*right column*), which may represent diaphragmatic and breast attenuation, respectively, or may represent a true perfusion abnormality. **Bottom row,** With the application of AC, both images become normal in appearance, suggesting that the abnormalities in the non-AC images were highly likely to represent artifact. (Courtesy Ernest Garcia, PhD.)

Gated SPECT Imaging

An important advance in the use and application of SPECT MPI has been the incorporation of ECG-gated SPECT perfusion imaging for simultaneous assessment of LV function and perfusion. Before the use of gated SPECT, comprehensive information on both perfusion and function required separate testing modalities, such as SPECT MPI and separate radionuclide ventriculography (RVG) or echocardiography.

To assess parameters of cardiac function with echocardiography (**see Chapter 14**), LV endocardial borders are drawn over several beats to derive parameters such as ejection fraction (EF). With contrast left ventriculography, endocardial borders are drawn for either one beat or an average of several beats to calculate EF. In contrast, with MPI the number of counts recorded during any individual cardiac cycle is insufficient to create an interpretable image for assessment of ventricular function. This limitation is overcome with the use of a technique known as ECG *gating* (**Fig. 16.13**), in which an average cardiac cycle is created representing the average of several hundred beats acquired over 8 to 15 minutes.

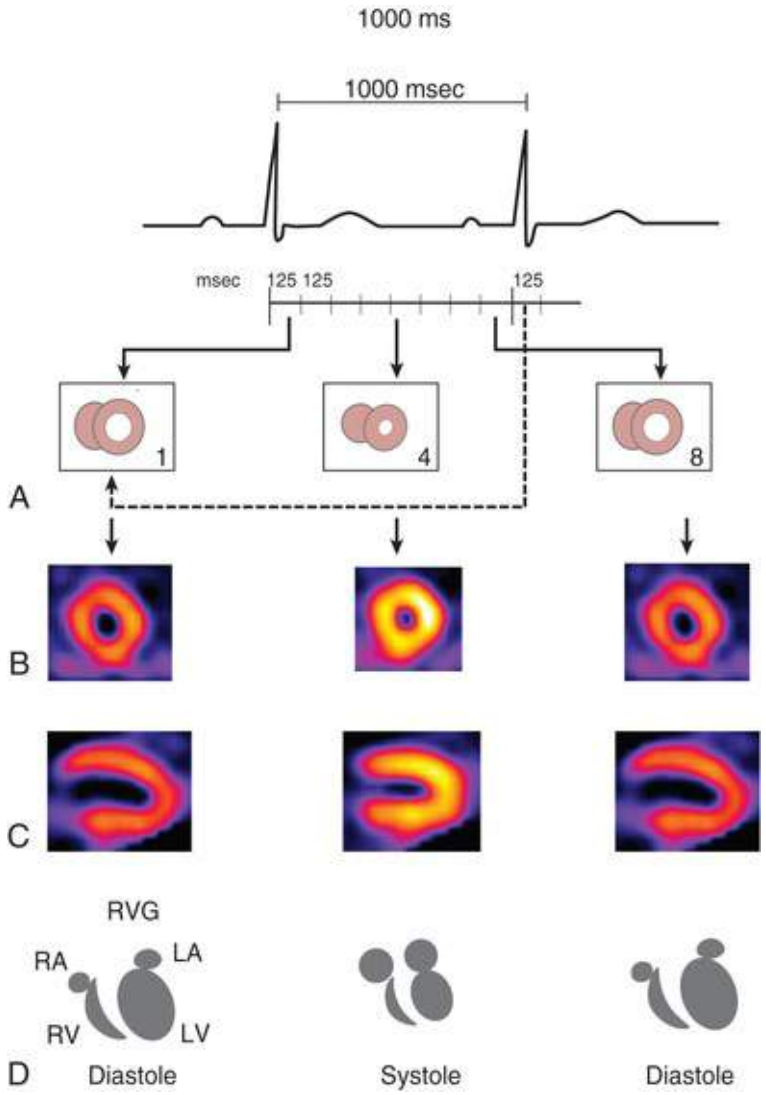


FIGURE 16.13 Basis for the technique of ECG gating. **A,** The scintigraphic acquisition data are collected in conjunction with the electrocardiogram. The R-R interval is divided into a prespecified number of "frames" (in this example, eight frames). At a heart rate of 60 beats/min (1000 msec/beat), each of the eight frames would comprise 125 milliseconds. For the first 125 milliseconds after the peak of the initial R wave, all imaging data are recorded in frame 1; the second 125 milliseconds are recorded in frame 2, and so on, until the peak of the next R wave is detected, and this is repeated for each beat in the acquisition. Frame 1 thus represents the end-diastolic events, and one of the frames in the middle of the acquisition (frame 4 in this example) represents end-systolic events. **B,** Examples of gated SPECT perfusion imaging. Short-axis images are seen at end diastole and at end systole. **C,** Similar timing with images displayed in the vertical long-axis orientation. Visually, wall thickening and brightening are seen across the course of systole. These events represent changes in regional and global function across the cardiac cycle. **D,** ECG-gated equilibrium radionuclide ventriculographic schematic images are shown at diastole and at end systole. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (Modified from Germano G, Berman DS. Acquisition and processing for gated SPECT: Technical aspects. In Germano G, Berman DS, editors. Clinical Gated Cardiac SPECT. Armonk, NY: Futura; 1999, pp 93-114.)

During an ECG-gated image acquisition, the patient's ECG is monitored simultaneously. As the peak of an R wave is detected, the "gate" opens, and a set number of milliseconds of imaging information is stored in a "frame." For a typical gated SPECT acquisition, each R-R interval is divided into eight frames. For example, if the patient's heart rate at rest is 60 beats/min (1000 milliseconds per beat), an eight-frame acquisition across the cardiac cycle comprises 125 milliseconds per frame. After the first 125 milliseconds of imaging data have been recorded in frame 1, the gate closes and then instantly reopens, allowing the second 125 milliseconds of information to be recorded in frame 2 (**Fig. 16.13A**). This sequence continues through the prespecified number of frames throughout the cardiac cycle. When the R wave of the next beat is detected by the ECG-gated system, the sequence is repeated, and so on, for each

of the many beats that occurs throughout the image acquisition.

When several hundred beats have been recorded, an average cardiac cycle representing all the recorded beats can be reconstructed by redisplaying the frames sequentially in a cine or movie format.[8] The first few frames represent systolic events, and the latter frames represent diastolic events (**Fig. 16.13A**).

High-quality ECG-gated images require that the cardiac cycles that are included have reasonably homogeneous beat lengths. This usually is accomplished by *beat-length windowing*, whereby the computer acquisition system is programmed to accept beats of only certain cycle lengths into the acquisition. Typically, cycles with the beat length represented by the average heart rate of the patient (1000 msec in the preceding example), along with cycles fluctuating up to 10% to 15% around the average beat length, are allowed into the acquisition. Cardiac cycles with cycle lengths above or below that limit are rejected. For example, the short cardiac cycle from the R wave of a normal beat to the R wave of a premature ventricular complex (PVC) would not be allowed into the acquisition, nor would the long cycle representing the post-PVC pause. This makes physiologic sense; the short pre-PVC beat and the more prolonged post-PVC beat have distinctly different systolic and diastolic characteristics from those of the beats occurring during normal sinus rhythm.

Gated SPECT Interpretation of Regional Wall Motion.

Normal regional systolic function is depicted as brightening of the wall during systole[2,8] (**Fig. 16.13B**). The wall appears to thicken, with apparent endocardial excursion. Assessment of regional LV function by gated SPECT imaging is based on an effect known in imaging physics as the *partial volume effect*, sometimes referred to as the recovery coefficient effect. When objects being imaged fall below a certain thickness threshold, count (or photon) recovery from the object is related not only to the tracer concentration within that object but also to the thickness of the object.[8] For SPECT imaging, usually all myocardial wall thicknesses fall below that threshold. Although tracer concentration within the myocardium is constant during a gated SPECT image acquisition, the recovery of counts (and thus the brightness of the object being imaged) is related to wall thickness. Thus, during systolic wall thickening, it appears that the LV wall becomes brighter and thicker, even though the isotope concentration per gram of myocardial tissue is actually unchanged. This principle forms the basis for gated SPECT imaging.

Regional myocardial function usually is assessed visually, in a manner similar to the analysis performed in echocardiography. Regions that brighten normally have normal regional systolic performance, and those with diminished but apparent brightening are labeled *hypokinetic*. Regions with slight brightening are interpreted as *severely hypokinetic*, and regions with no apparent brightening as *akinetic* (**Fig. 16.14**). Regional function also can be analyzed by quantitative techniques and displayed in a polar map format, although visual analysis is performed most often.

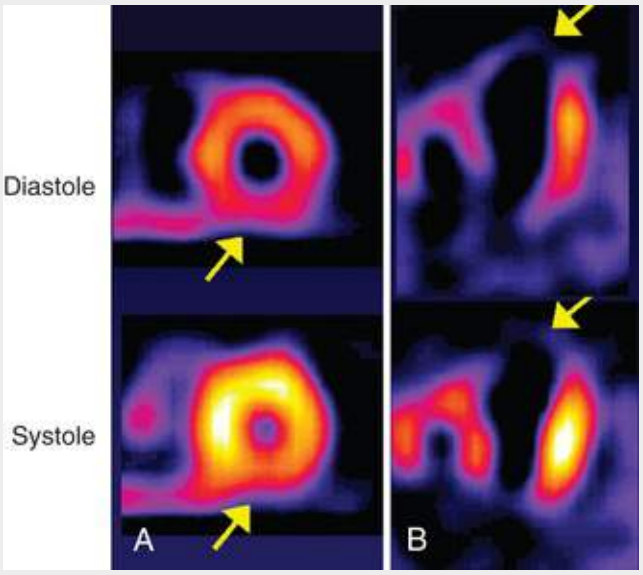


FIGURE 16.14 Examples of regional dysfunction detected by ECG-gated SPECT perfusion imaging. **A,** The severely hypokinetic inferior region appears to brighten less (*arrows*) than the other regions from diastole to systole. The lateral wall also brightens less than the normal septum and would therefore be interpreted as hypokinetic. **B,** The akinetic apex in the horizontal long axis (*arrows*) shows no apparent change from diastole to systole, in contrast to the normally thickening (brightening) lateral wall.

Gated SPECT Assessment of Global Left Ventricular Function.

All contemporary camera-computer systems have software capable of quantifying global LV function and computing the EF. These computer-based methodologies are fully automated and thus highly reproducible. The most common method involves automated interrogation of the apparent epicardial and endocardial borders of all the tomograms in all three orthogonal planes (**Fig. 16.15A**). These multiple two-dimensional contours are then reconstructed to create a surface-rendered three-dimensional display representing global LV function across the average cardiac cycle (**Fig. 16.15B**) that can be viewed from any direction by simple maneuvering of the computer display screen or cursor.[8] The three-dimensional display is accompanied by automated calculation of EF and LV volumes.

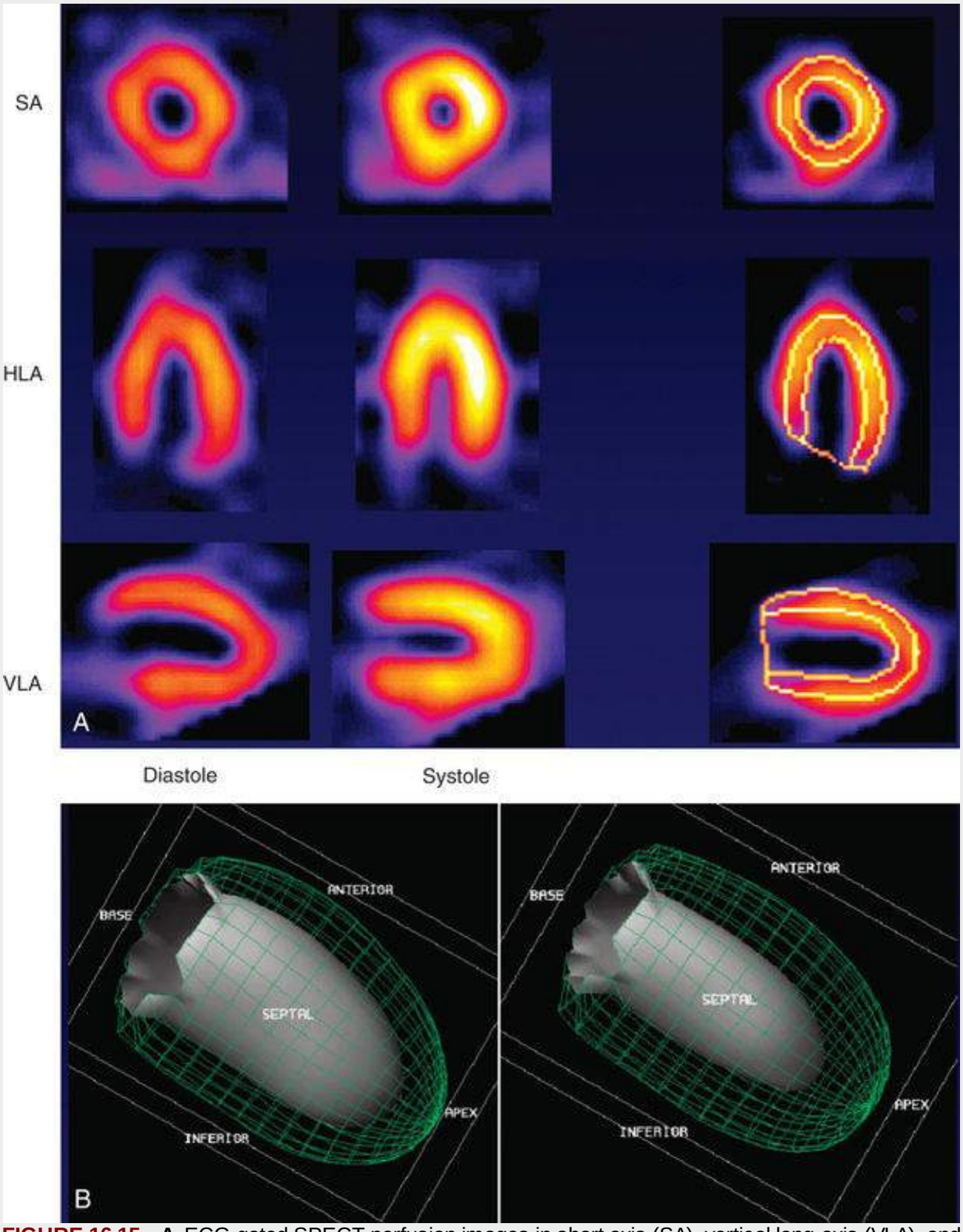


FIGURE 16.15 **A,** ECG-gated SPECT perfusion images in short axis (SA), vertical long-axis (VLA), and horizontal long-axis (HLA) views, shown frozen at end diastole (*left column*) and end systole (*middle column*). Endocardial and epicardial borders are shown on the diastolic frames as automatically assigned by the software analysis program (*right column*). **B,** From the contours that are created from all the two-dimensional tomograms, a three-dimensional surface-rendered image of the left ventricle can be created and displayed in multiple orientations, here frozen at end diastole (*left*) and end systole (*right*). The *green* "mesh" represents the epicardium, and the *gray* surface represents the endocardium. Ejection fraction (EF) is quantified from the volume change. During image interpretation, gated SPECT images are displayed in the cine format as an endless loop movie, rather than as the still frames depicted here.

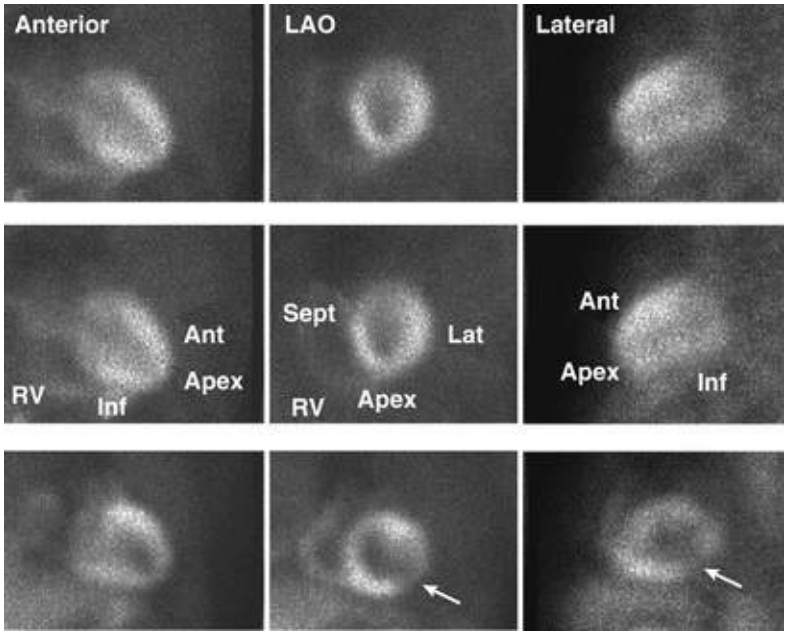
EF measurements from automated analysis of ECG-gated SPECT MPI have been extensively validated against those obtained using other quantitative techniques for assessing LV function, such as equilibrium

RVG, angiographic contrast left ventriculography, and cardiac magnetic resonance (CMR)[8] (**see Chapters 17 and 19**). Across a wide range of LV function, and even in the setting of severe perfusion defects, ECG-gated SPECT imaging provides robust, reproducible estimates of LVEF.

The incorporation of ECG-gated SPECT imaging into a SPECT acquisition is now routine in MPI and is recommended as standard by contemporary guidelines.[2,5] As discussed later, the addition of LV function data to the perfusion information provides incremental and independent prognostic information, in addition to its practical importance in management decisions. Gated SPECT imaging also has been an important advance in helping to differentiate attenuation artifacts from infarct, because regions with persistent low counts that show normal motion and thickening represent soft tissue artifacts rather than scar (**see Fig. 16.11**). Thus, gated SPECT has improved the specificity of perfusion imaging for ruling out CAD, particularly in women.[5]

Planar Myocardial Perfusion Imaging

Before the widespread application of tomographic (SPECT) perfusion imaging techniques, planar imaging was the standard acquisition and display methodology. In planar imaging, three separate two-dimensional images are obtained with the gamma camera after radiotracer injection and uptake into the myocardium.[2] The three standard views are an anterior, a left anterior oblique, and a more lateral view (**eFig. 16.6**).



EFIGURE 16.6 Examples of planar myocardial perfusion imaging (MPI). **Top row,** Normal stress planar perfusion study in the anterior, shallow left anterior oblique (*LAO*), and more lateral views. Tracer uptake is uniform throughout the myocardial walls. **Middle row,** The same normal planar stress perfusion images are shown, with the myocardial walls that are seen in each labeled view. The anterior wall (*Ant*), apex, and inferior (*Inf*) walls are seen in the anterior view, as well as right ventricle (*RV*). The septum (*Sept*), apex, and lateral walls (*Lat*) and the RV are seen in the shallow LAO view, and the anterior wall, apex, and inferior walls are seen in the lateral view. **Bottom row,** Abnormal planar study showing a lateral wall stress perfusion defect in the shallow LAO view (*arrow*), extending into the inferior wall in the lateral view (*arrow*). Rest images are not shown. (Courtesy Dr. Kim A. Williams.)

An advantage of planar imaging over SPECT imaging is its simplicity. Each of the three views can be acquired during 5 to 8 minutes with patients lying on a table with their arms by their sides. Planar imaging

is less affected by patient motion than is SPECT imaging. With planar imaging, extensive image processing is not required as with SPECT, so there are fewer sources of potential error and artifact. Because of its two-dimensional nature, however, planar imaging in each of the standard views generates substantial overlap of myocardial regions, with less differentiation of smaller and particularly milder perfusion abnormalities. The more standard orientation of SPECT imaging lends itself to easier understanding of the localization of perfusion abnormalities.

In contemporary practice, planar imaging may be used for patients who do not tolerate the position that must be maintained during a SPECT acquisition, those who have difficulty coping with presence of the larger SPECT camera so close to the body, or those with large body habitus that surpasses the weight and size limits of SPECT systems.[5]

Radionuclide Ventriculography or Angiography

Also known as radionuclide angiography or blood pool imaging, RVG may be performed using first-pass or by equilibrium-gated techniques.[8] The equilibrium technique often is referred to as *multiple gated acquisition* (MUGA) scanning. Although the two techniques each use specific tracers and data-recording methods, they provide similar results for global EF and chamber volumes. Both techniques provide a highly reproducible means to quantify global LV and right ventricular (RV) EF.

Equilibrium Radionuclide Angiography or Ventriculography (Gated Blood Pool Imaging)

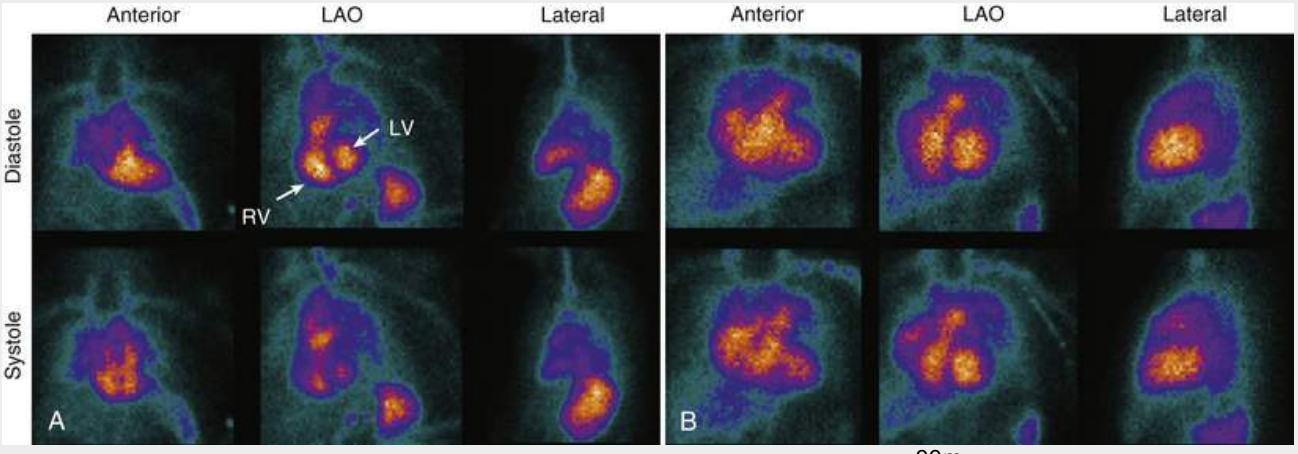
In equilibrium RVG studies, data are recorded in a computer system synchronized with the R wave of the patient's ECG, similar to ECG-gated SPECT (**see Fig. 16.13**). For labeling of the blood pool, ^{99m}Tc is bound to red blood cells (RBCs) or albumin. Image contrast usually is better with ^{99m}Tc-labeled RBCs, but ^{99m}Tc-labeled albumin is preferable in patients in whom RBC labeling may be difficult. Labeling of RBCs with ^{99m}Tc-pertechnetate requires a reducing agent, stannous pyrophosphate, which is administered 15 to 30 minutes before pertechnetate injection.

Image Acquisition.

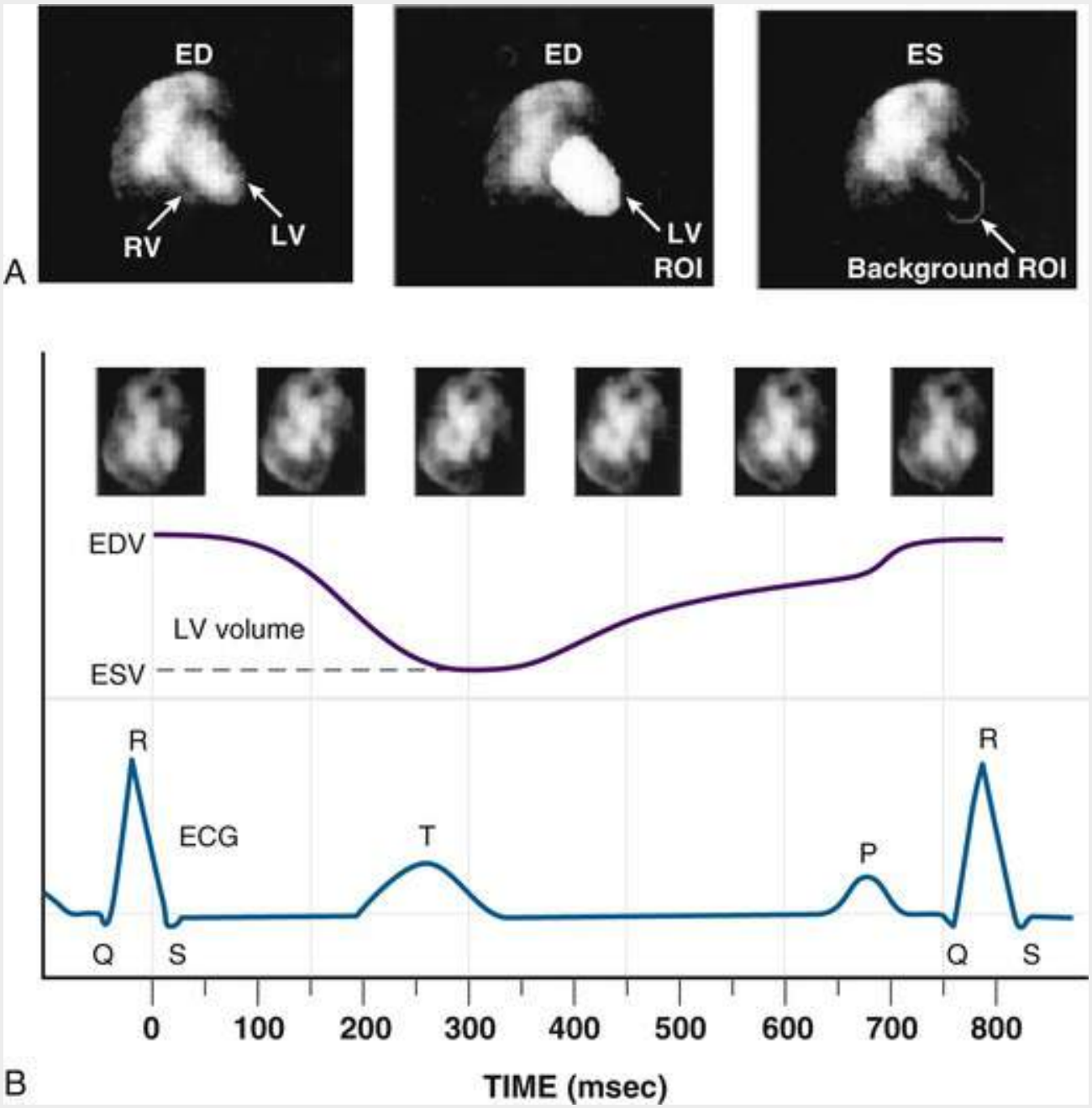
Although relatively few counts are recorded during a single ECG-gated cardiac cycle, the summation of counts from 800 to 1000 cardiac cycles produces an average cardiac cycle with high resolution. Images of the heart are usually acquired in three standard projections: anterior, “best septal” left anterior oblique (best separation of the left and right ventricles), and left lateral (or left posterior oblique). The minimum framing rate for a rest RVG study is 16 frames/cycle (approximately 50 msec/frame).[8] For quantitative assessment of diastolic indices and regional EF, the framing rate should be increased to 32 frames/cycle (approximately 25 msec/frame). For adequate counting statistics, images are acquired for a preset count of at least 250,000 per frame or count density of 300 counts per pixel, which corresponds to an acquisition time of 5 to 10 minutes per projection. For exercise studies, adequate counts can be obtained in the best septal view with a 2-minute acquisition using a high-sensitivity collimator. Arrhythmias such as multiple PVCs can adversely affect the study if these beats account for more than 10% of the total. In patients with atrial fibrillation, there may be considerable beat-to-beat variability, and the mean EF obtained during the period of acquisition may underestimate the actual LVEF.[8]

Image Display and Analysis.

Qualitative inspection of equilibrium studies as an endless cinematic loop of the cardiac cycle (**see Fig. 16.13D**) allows assessment of (1) size of heart chambers and great vessels; (2) regional wall motion; (3) global function (qualitative assessment) (**eFig. 16.7**); (4) ventricular wall thickness, pericardial effusion, pericardial fat pad, or paracardiac mass; and (5) extracardiac uptake, such as splenomegaly.
Quantification of systolic and diastolic indices and volumes is derived from the ventricular time-activity curve,[8] which is analogous to the angiographic time-volume curve (**eFig. 16.8**). In addition to the time-activity curve, functional images, such as amplitude and phase images, can be produced that have been useful in characterizing regional wall motion abnormalities and asynchrony.



EFIGURE 16.7 Equilibrium radionuclide ventriculography. The isotope (^{99m}Tc) is labeled to red blood cells, so the images represent the blood "pools" in the left ventricle (*LV*), the right ventricle (*RV*), the other cardiac chambers, and the great vessels as well as the spleen. Typically, three views are obtained, as shown. **A,** Normal LV function, with end-diastolic images in the *top row* and end-systolic images in the *bottom row.* LV and RV volumes diminish from diastole to systole. **B,** Images obtained in a patient with LV dysfunction. Significant LV and RV dilation is evident at both end diastole (*top*) and end systole (*bottom*), with severely diminished LV systolic function (i.e., much less volume change from end diastole to end systole compared with the study in **A**). *LAO,* Left anterior oblique.

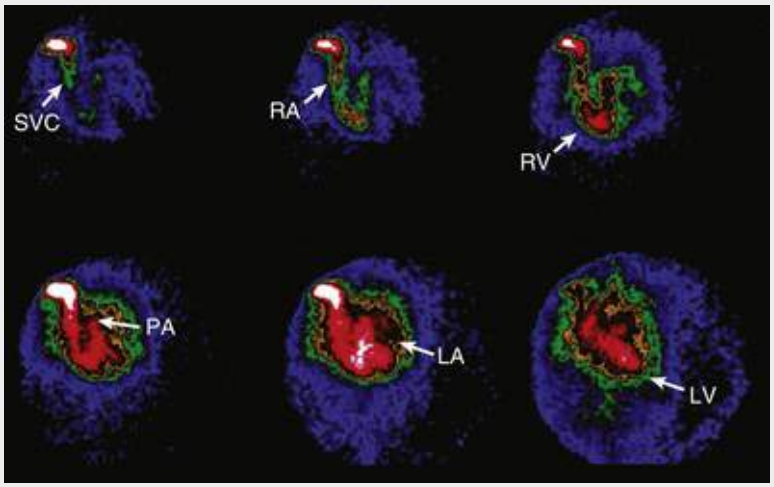


EFIGURE 16.8 Quantitative analysis of equilibrium electrocardiogram (ECG)-gated radionuclide ventriculography. **A,** Left anterior oblique view of the left ventricle (*LV*) and right ventricle (*RV*) is shown at end diastole (*ED*) **(left),** with a region of interest (*ROI*) identifying the LV contour at end diastole **(middle)** and a "background" ROI drawn at end systole (*ES*) **(right),** used to correct for count activity in front of and behind the LV. **B,** A time-activity curve illustrates the change in counts within the ROIs shown in **A** across a cardiac cycle. Because count activity is related to LV chamber volume, the time-activity curve represents the relative volume change of the LV chamber across a cardiac cycle, from end diastole to end systole and back to end diastole. *EDV,* End-diastolic volume; *ESV,* end-systolic volume. (From Green MV, Bacharach SL, Douglas MA, et al. The measurement of left ventricular function and the detection of wall motion abnormalities with high temporal resolution ECG-gated scintigraphic angiocardiography. IEEE Trans Nucl Sci 1976;23:1257.)

First-Pass Radionuclide Angiography or Ventriculography

In first-pass RVG studies, the bolus of radioactivity passes initially through the right chambers of the heart, then through the lungs, and finally through the left-sided chambers of the heart. Radiopharmaceuticals used for this purpose must produce adequate counts in a short time at an acceptably low radiation dose to the patient.[8]

Image Acquisition.
Images are acquired very rapidly as the tracer passes through the heart chambers. Separation of the right and left ventricles is achieved because of the temporal separation of the bolus. Image quality is related to the injection technique, which should be rapid (2 to 3 seconds) to achieve an uninterrupted bolus (**eFig. 16.9**). Images are acquired in the supine position after the rapid injection of 10 to 25 mCi of tracer (depending on type of camera/crystal) through an 18-gauge or larger intravenous catheter placed in the medial antecubital or external jugular vein. The shallow (20- to 30-degree) right anterior oblique projection is used, to optimize separation of the atria and great vessels from the ventricles and to view the ventricles parallel to their long axes. Although the right anterior oblique view maximizes overlap of the right and left ventricles, this is not a problem in most patients because the timing of tracer appearance reliably identifies each chamber sequentially. A 1-mCi tracer dose may be used to ensure proper positioning so that the right and left ventricles are in the field of view.



EFIGURE 16.9 First-pass radionuclide ventriculography. Individual frames from a first-pass acquisition, illustrating the path of the bolus isotope through the superior vena cava (*SVC*), right atrium (*RA*), right ventricle (*RV*), pulmonary outflow tract and lungs (pulmonary artery [*PA*]), left atrium (*LA*), and LV phase, from which the isotope bolus is then distributed systemically.

Image Analysis.
To identify the RV and LV phases, regions of interest are drawn around the right and left ventricles at end diastole.[8] Time-activity curves are generated, and cycles around and including the peak time-activity curve are used to calculate EFs. In general, two to five cardiac cycles are summed for the RV phase, and five to seven cycles are summed for the LV phase. From these data, quantitative analysis of LVEF and RVEF is performed.

Comparison of Equilibrium and First-Pass Techniques

Advantages of the first-pass technique are the high target-to-background ratio, more distinct temporal separation of the cardiac chambers, and rapidity of imaging. RVEF may be more readily assessed by the first-pass technique because of the more distinct separation of this structure from the other chambers with that technique. Advantages of equilibrium technique are the potential for repeated assessment of cardiac function during rapidly varying physiologic conditions, high count density, and acquisition of images in multiple projections. In contemporary practice, the equilibrium technique is performed much more

frequently.[2,5]

Positron Emission Tomography

Because of the quantitative capabilities of PET, measurement of myocardial perfusion and metabolism can be obtained with PET in absolute quantitative terms, a potential advantage compared with SPECT imaging. The radiotracers used in PET are labeled with positron-emitting isotopes that have chemical and physical properties identical to those of naturally occurring elements, such as carbon, oxygen, nitrogen, and fluorine. Incorporation of such elements allows interrogation of physiologically relevant processes in normal and diseased states.[4] Although most positron-emitting radiotracers are cyclotron produced with short half-lives, the development of generator-produced positron-emitting isotopes, such as rubidium-82 (^{82}Rb), makes it feasible for laboratories to perform cardiac PET studies without an on-site cyclotron.

Clinically available cardiac PET radiotracers fall within two broad categories: those that evaluate myocardial perfusion and those that evaluate myocardial metabolism (**Table 16.2**).[4] The perfusion tracers ^{82}Rb and ^{13}N-ammonia and the myocardial metabolic tracer 2-^{18}F-fluoro-2-deoxyglucose (FDG) have received FDA approval.

TABLE 16.2

Properties of Selected Positron Emission Tomography Tracers

TRACER	PRODUCED	HALF-LIFE	COMPOUND
Perfusion			
^{15}O	Cyclotron	2.1 minutes	H_2O
^{13}N	Cyclotron	10 minutes	NH_3
^{82}Rb	Generator	75 seconds	RbCl
Metabolism			
^{11}C	Cyclotron	20.4 minutes	Acetate, palmitate
^{18}F	Cyclotron	110 minutes	Deoxyglucose

Modified from Bergmann SR. Positron emission tomography of the heart. In Gerson MC, editor. Cardiac Nuclear Medicine. New York: McGraw-Hill; 1997, pp 267-300.

Image Acquisition.

PET employs camera systems designed to optimize the detection of positron-emitting radioisotopes. The process by which a positron-emitting radionuclide attempts to stabilize over time is termed *beta decay*, which occurs when the nucleus of an atom emits a positron, a positively charged beta particle (**Fig. 16.16**). After a high-energy positron is emitted from a nucleus, it travels a few millimeters in tissue and ultimately collides with an electron (a negatively charged beta particle). This collision results in complete annihilation of both the positron and the electron, with conversion to energy in the form of electromagnetic radiation composed of two high-energy gamma rays, each with 511-keV energy. The discharged gamma rays travel in perfectly opposite directions (180 degrees from each other). PET detectors can be programmed to register only events with temporal coincidence of photons that strike at directly opposing detectors. The outcome of such selective coincidence detection is an improvement in spatial and temporal resolution for PET over that achieved with SPECT imaging.[9] Unlike the procedure in SPECT, in which an extrinsic collimator is used to limit the direction at which photons enter the detector, the coincidence detection with PET provides “intrinsic” collimation and improves the sensitivity of the camera.

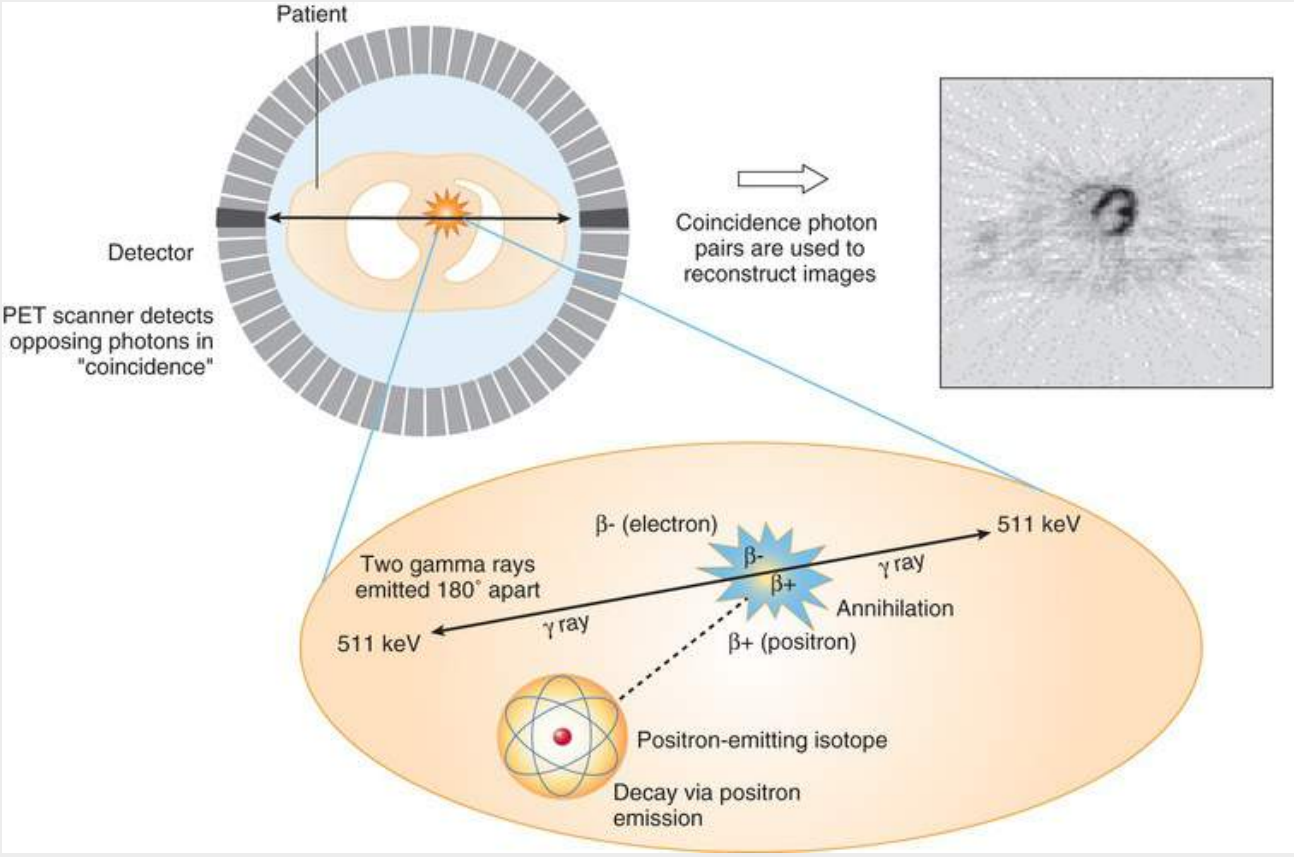


FIGURE 16.16 Schematic of positron and electron beta particle emission, with detection by a coincidence camera, as the basis of PET imaging.

In addition, an important distinction between PET and SPECT is in the ease of labeling primary substrates for energy metabolism and membrane receptor subtypes in the heart, allowing the interrogation of such physiologic pathways in vivo with PET. Moreover, dynamic-mode PET scanning permits potential analysis of the change in tracer content in a specific region of interest in the heart with time, allowing potential interrogation of the rate of change of a physiologic process.

Image Analysis.

Emission data are displayed as tomograms in the horizontal and vertical long-axis and short-axis views, as in SPECT display.[9] If the data are acquired in dynamic mode, with appropriate mathematical modeling, myocardial perfusion and metabolic data can be displayed in absolute terms: in milliliters per gram per minute for blood flow and moles per gram per minute for metabolism.

PET Perfusion Tracers

PET perfusion tracers can be divided into two types: (1) freely diffusible tracers, which accumulate and wash out from myocardial tissue as a function of blood flow, and (2) nondiffusible tracers, characterized by retention in myocardial tissue as a function of blood flow.[4,9] The rapid physiologic washout of the freely diffusible tracers, such as ^{15}O-water, makes it possible to repeat studies in rapid sequence. The images of the distribution of such tracers are usually not visually meaningful; mathematical modeling is done to arrive at flow values at each pixel. An advantage of freely diffusible tracers is that they do not depend on a metabolic trapping mechanism, which might change as a function of a changing metabolic environment.

The nondiffusible flow tracers are easier to image, because the tracer is retained in myocardium for a reasonable length of time. ^{82}Rb and ^{13}N-ammonia fall into this second category of flow tracers, the more microsphere-like flow tracers. ^{82}Rb is a cation, with biologic properties similar to those of potassium and

thallium, and uptake across the sarcolemmal membrane reflects active transport by the Na^+,K^+-ATPase pump. In experimental studies, its extraction fraction does not change significantly over a wide range of metabolic conditions. However, the very short half-life of 75 seconds for ^{82}Rb means that any trapped ^{82}Rb quickly disappears from the myocardium by physical decay. Despite its short half-life, ^{82}Rb is easily obtained, because it is generator produced, and it can be used clinically without the need for an on-site cyclotron.

^{13}N-ammonia is an extractable perfusion tracer, with a physical half-life of 10 minutes. Its transport across cell membranes may occur by passive diffusion or by the active Na^+-K^+ transport mechanism. Retention of ^{13}N-ammonia in the myocyte involves metabolic trapping. As with ^{82}Rb, myocardial uptake of ammonia reflects absolute blood flows up to 2 to 3 mL/g/min and plateaus at more hyperemic flows. The use of this tracer to assess myocardial blood flow has been extensively validated in both experimental and clinical studies.[9]

PET Perfusion Tracers: Research Directions.

^{18}F-labeled fluorobenzyl triphenyl phosphonium, originally developed for measurement of the mitochondrial membrane potential, has been introduced for MPI with PET.[10] The currently available PET myocardial perfusion tracers, ^{82}Rb-chloride and [^{13}N] ammonia, have short physical half-lives and require either an on-site cyclotron or generator, thereby limiting their widespread clinical application. The longer half-life of ^{18}F (110 minutes) allows the possibility of distribution as a single-dose unit on a daily basis, which may facilitate the clinical application of myocardial perfusion PET imaging. Moreover, the longer half-life of ^{18}F would allow assessment of perfusion during treadmill exercise, rather than with vasodilator stress alone, as is currently the case with ^{82}Rb PET.[10]

One such investigational agent, ^{18}F-flurpiridaz PET, has been studied in phase II and III clinical trials in comparison with ^{99m}Tc SPECT.[11] The high spatial resolution of PET imaging, along with high target-to-background ratios achieved with ^{18}F-flurpiridaz, allows the acquisition of very-high-quality electrocardiographic-gated PET images compared to SPECT, along with very good diagnostic accuracy in detection of significant CAD[10,11] (**Fig. 16.17**). In a human feasibility study where absolute quantitation of ^{18}F-flurpiridaz myocardial blood flow (MBF) was studied over a wide range of cardiac flow in the presence or absence of stress-inducible myocardial ischemia, there was a significant decrease in stress MBF in CAD territories, which allowed a clear distinction between vascular territories exhibiting stress-inducible myocardial ischemia and those with normal perfusion.[12] Further studies in larger numbers of patients will be needed to evaluate the clinical utility and diagnostic accuracy of ^{18}F-flurpiridaz absolute MBF, particularly in patients with multivessel CAD.

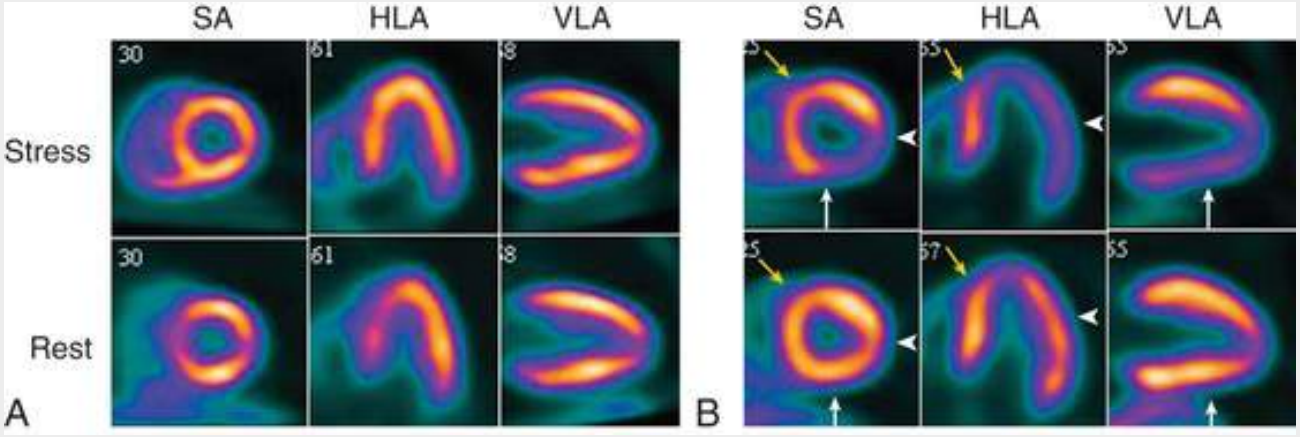


FIGURE 16.17 Representative examples of normal **(A)** and abnormal **(B)** ^{18}F-flurpiridaz PET myocardial perfusion images. **A,** Tomograms in the short-axis (SA), horizontal long-axis (HLA), and vertical long-axis (VLA) views of paired stress (*upper row*) and rest (*lower row*) images show normal distribution of the radiotracer in all myocardial regions. **B,** Paired stress and rest images show extensive reversible regional perfusion defects in all three coronary artery vascular territories: inferior wall reversible defect (*white arrows*), lateral wall reversible defect (*arrowheads*), and anteroseptal wall reversible defect (*yellow arrows*). (Modified from Dilsizian V, Taillefer R. Journey in evolution of nuclear cardiology: will there be another quantum leap with the F-18 labeled myocardial perfusion tracers? J Am Coll Cardiol Imaging 2012;5:1269-84.)

Clinical Application of PET Myocardial Perfusion Imaging

Advantages of PET perfusion imaging over SPECT include higher spatial resolution, improved attenuation and scatter correction, and potential for quantifying regional blood flow (**Fig. 16.18**). Although SPECT assessment of stress and rest myocardial perfusion has been firmly established as an important diagnostic and prognostic tool for the evaluation of myocardial ischemia and prior infarction, the interpretation of SPECT myocardial perfusion imaging studies has been primarily qualitative or semiquantitative in nature. The detrimental effects of soft tissue attenuation, which tends to degrade image quality, particularly in patients who are obese or have large body habitus, and increase interpretive errors, have long been recognized with SPECT. In concert with tracer-kinetic modeling and robust attenuation correction, PET permits the assessment of regional MBF of the left ventricle in absolute terms (mL/min/g tissue).[9,13] Quantitative absolute hyperemic MBF and flow reserve (representing the ratio of hyperemic and resting MBF)—derived from dynamic acquisition with measurements of resultant myocardial and blood pool time-activity curves—is a potentially powerful adjunct to PET perfusion imaging. As a result, a number of clinical studies with either ^{82}Rb or [^{13}N] ammonia PET have shown an improvement in either the sensitivity or specificity (as high as 95%) for detection of CAD compared with SPECT. However, the widespread use of PET myocardial perfusion studies in the clinical setting has been hampered by the requirement of an on-site cyclotron for [^{13}N] ammonia and the high cost of monthly generator replacement for ^{82}Rb. Moreover, the relatively short half-life of both ^{82}Rb and [^{13}N] ammonia limits the utility of PET perfusion studies to patients undergoing pharmacologic stress only. Because the exercise component of MPI studies has independent prognostic and diagnostic value, this represents an important limitation. On the other hand, the potential for quantifying MBF and blood flow reserve in absolute terms is highly desirable, with potential clinical applications. For example, patients with multivessel CAD may have uniform decrease in flow reserve, and the relative perfusion data from SPECT may fail to detect this “balanced” ischemia[13] (**Fig. 16.19**). At the other extreme, detection of mild abnormalities in MBF reserve with PET provides the potential for early identification of CAD characterized by endothelial dysfunction in asymptomatic patients with elevated cholesterol, smoking, hypertension, and insulin resistance.[14]

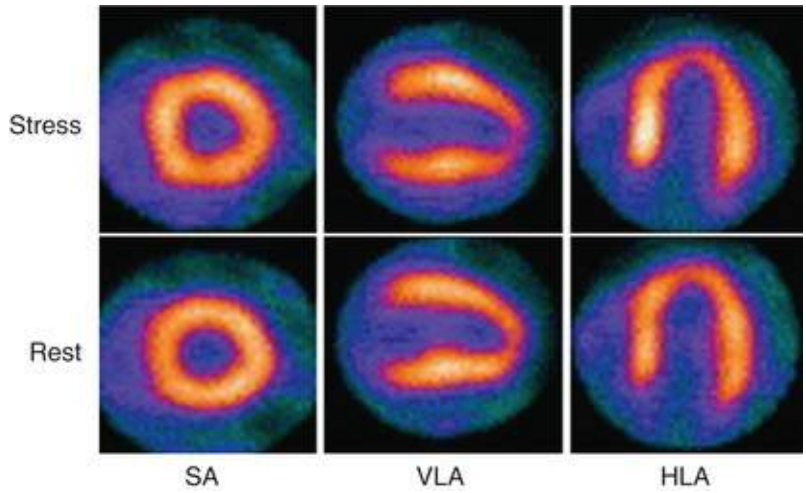


FIGURE 16.18 Example of high-quality stress **(top)** and rest **(bottom)** PET perfusion images, using ^{82}Rb as the perfusion tracer in the short axis (SA), vertical long axis (VLA), and horizontal long axis (HLA).

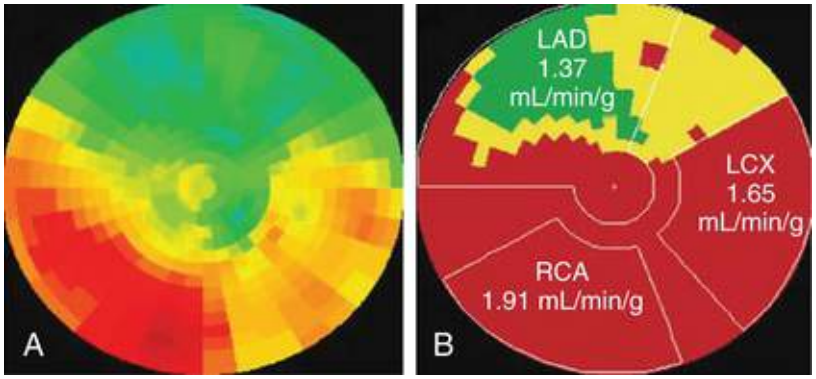


FIGURE 16.19 Polar maps of myocardial tracer uptake during adenosine vasodilation in patient with CAD. **A,** *Relative* distribution of tracer (as with SPECT studies) suggests single-vessel disease in left anterior descending artery (LAD) territory (*green* represents relatively reduced perfusion compared to the other territories). **B,** Quantitative assessment of adenosine-stimulated hyperemic myocardial blood flow reserve with ^{13}N-ammonia PET identifies abnormal flow reserve in all three vascular territories: LAD, left circumflex artery (LCX), and right coronary artery (RCA); normal hyperemic myocardial blood flow is approximately 3 mL/min/g. As such, the addition of the quantitative analysis of perfusion reserves suggests three-vessel disease instead of the single-vessel disease suggested by the standard analysis of relative distribution of flow. (Modified from Schindler TH, Schelbert HR. Quantitation of myocardial perfusion: absolute blood flow versus relative uptake. In Dilsizian V, Narula J, editors. Atlas of Nuclear Cardiology. 4th ed. New York: Springer; 2013, pp 145-194.)

Progress in PET Absolute Hyperemic Myocardial Blood Flow and Flow Reserve Assessment

An additional driver for cardiac PET comes from a potential paradigm shift in the evaluation and management of patients with CAD from an anatomic “gold standard” (coronary angiography) to a functional standard (fractional flow reserve).[15] PET absolute MBF provides a noninvasive alternative to invasive functional assessment of CAD, which may obviate the need for coronary angiography. Quantitative assessment of PET MBF in absolute terms is concurrent with the recent shift in the management of CAD.[16] Quantitative blood flow approaches offer an objective interpretation that is inherently more reproducible than visual analysis. Absolute quantification may aid in assessing the physiologic significance of known coronary artery stenosis, especially when of intermediate severity.

Moreover, noninvasive quantification of MBF extends the scope of conventional myocardial perfusion imaging from detection of end-stage, advanced, and flow-limiting epicardial CAD to balanced reduction of MBF in all three vascular territories, as well as early stages of atherosclerosis or microvascular dysfunction.[14] Adding quantification of hyperemic MBF and flow reserve to the visual interpretation of PET regional perfusion defects has been shown to improve the detection of CAD burden and accurately risk-stratify patients with varying clinical presentations.[17-19]

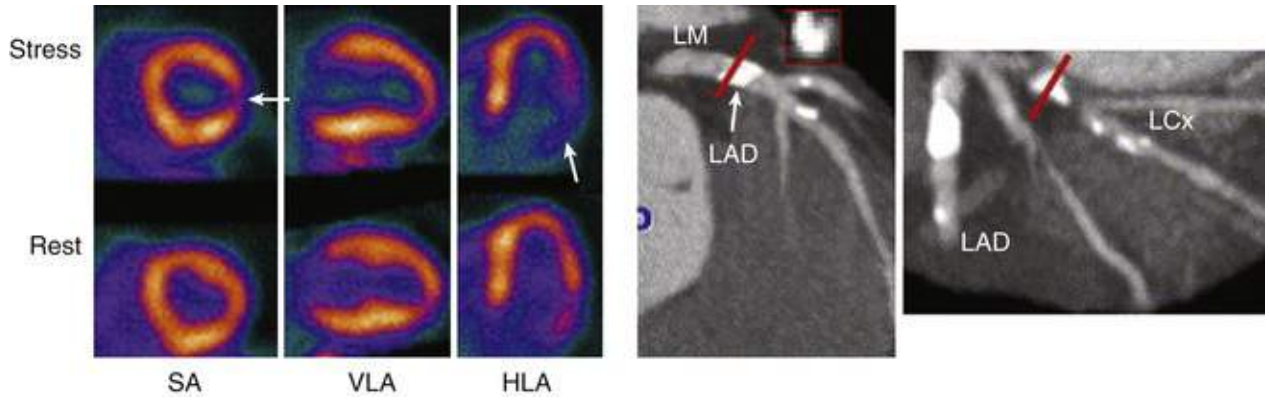
It is important to recognize, however, that myocardial flow reserve (MFR) ratio can be spuriously lowered by elevated resting blood flow in the denominator, as seen in patients with hypertension or high resting rate pressure product. Thus, it is important to interpret both hyperemic MBF and flow reserve in all patients. At present, quantitative absolute MBF measurements with PET appear most helpful in (1) patients without known prior history of cardiac disease who present with symptoms suspicious for myocardial ischemia, (2) patients with known CAD in whom more specific physiologic assessment is desired, (3) identification of an increased suspicion for multivessel CAD, (4) situations with a disparity between visual perfusion abnormalities and apparently normal coronary angiography to assess possible microvascular dysfunction, and (5) patients with heart transplant when vasculopathy may be present.[9]

PET Tracers of Myocardial Metabolism

PET is uniquely positioned to investigate alterations in myocardial metabolism and cellular physiology. Tracers for these applications are discussed in detail later (see Assessment of Myocardial Cellular Metabolism and Physiology).

Combined PET-CT and SPECT-CT Scanners

Scanners that combine PET or SPECT technology with radiographic computed tomography (CT) provide a tool for obtaining complementary anatomic and functional information in a single imaging session. CT angiography provides information on the presence and extent of luminal narrowing of epicardial coronary arteries with high sensitivity and specificity (**see Chapter 18**), whereas PET and SPECT provide information on the downstream functional consequences of anatomic lesions. Cardiac CT angiography is suited to determine whether an “obstructive” coronary artery stenosis is present, although the ability to accurately determine stenosis severity is limited with current-generation CT angiography systems. PET and SPECT, on the other hand, are more suited to determine if such a stenosis is physiologically significant regarding limitation of flow reserve. With the advent of hybrid PET-CT and SPECT-CT systems, such complementary information of anatomy and physiology can be realized immediately, at the same imaging session. The combination of these anatomic and functional modalities is particularly relevant in patients who have an intermediate finding on either SPECT-PET or CT angiography. The advantage afforded by the combined scanner is that the corresponding images are spatially aligned and can be acquired during a single imaging session (**eFig. 16.10**).



EFIGURE 16.10 Combined PET images of stress and rest perfusion **(left)** and cardiac CT angiography and calcium imaging **(right).** The PET images demonstrate a lateral wall reversible defect consistent with ischemia (*arrows* in short-axis [*SA*] and horizontal long-axis [*HLA*] images). *VLA,* Vertical long-axis view. However, the CT images demonstrate more extensive calcification and stenosis of the left main (*LM*), left anterior descending (*LAD*), and left circumflex (*LCx*) vessels. The combined information suggests that although the physiologic ischemia predominantly involves the lateral wall–LCx territory, more extensive CAD is present. *Red lines* represent planes for cross-sectional views of coronary arteries (not shown).

CT Attenuation Correction for PET

A subsidiary benefit of hybrid PET-CT and SPECT-CT imaging systems is in the potential to use the CT image to create the attenuation map for the MPI data.[9] This approach has allowed the replacement of germanium-68 or cesium-137 transmission scans with faster CT scans, reducing the overall duration of the PET procedure. One potential problem of using fast CT scans for attenuation correction, however, is the motion of the organs during respiration. The CT scanner "freezes" the heart, lungs, and liver at one point in the respiratory cycle, whereas the PET emission data are averaged over many respiratory cycles. Methods using respiratory gating to correct this problem are currently under investigation.

At present, the decision of whether a particular patient is a candidate for PET alone, CT angiography alone, or hybrid PET-CT depends on multiple factors. The age of the patient, underlying irregular heart rhythm, known coronary artery calcification or metallic implants, renal insufficiency, lung disease, or allergy to contrast medium will exclude a significant percentage of patients from being candidates for CT angiography. Because PET can be performed in a majority of these patients, and revascularization improves survival over medical therapy only in patients with a moderate to severe degree of inducible ischemia, most patients will not require simultaneous assessment of coronary artery anatomy and myocardial perfusion with hybrid PET-CT. The incremental radiation dose from performing two diagnostic studies also should be considered.

Patients with low-risk stress ECG or nuclear myocardial perfusion scans show no survival advantage from revascularization over medical therapy, regardless of the angiographic extent of coronary artery stenosis (**see Chapter 61**). On the other hand, among younger patients with strong family history or multiple risk factors for CAD, CT angiography may not only exclude significant coronary artery luminal narrowing but also detect early atherosclerosis by quantifying the extent of calcified plaques (**see Chapter 18**). The latter may have important implications for aggressive risk factor modification and medical therapy. Accordingly, hybrid PET-CT should be limited to only a small subset of patients in whom the knowledge of both coronary anatomy and physiology would be anticipated to have an impact on clinical management (e.g., anomalous coronary anatomy or myocardial bridging and chest pain).

All other applications, such as detection of endothelial dysfunction or microvascular disease and identification of soft plaques, remain experimental at this time, with limited clinical data to support widespread clinical application. In the future, with the potential development of new radiotracers that

target coronary artery plaque, hybrid PET-CT images that incorporate plaque anatomy with molecular imaging may provide valuable insights into differentiation of “vulnerable” from “nonvulnerable” plaque, which may be used to portend and potentially to prevent acute myocardial infarction.

Radiation Exposure Issues

Clinical decision making for the use of low-level ionizing radiation to obtain diagnostic nuclear cardiac studies must adhere to appropriate use criteria and encompass the broad range of the risk-benefit ratio, with the guiding principle to minimize exposure while obtaining the necessary high-quality diagnostic information. The prediction of risk of subsequent malignant transformation for an individual undergoing a medical diagnostic test or procedure employing ionizing radiation is a complex exercise with many uncertainties. Concerns about the late carcinogenic effects of exposure to low levels (<100 mSv) of ionizing radiation stem from extrapolation of exposure outcome data in survivors of atomic bomb explosions. Uncertainty remains, however, regarding the dose-response relationship in the lower range of exposure, adding complexity to assessment of the incremental risk to patients, as well as of tissue-specific reparative responses that also may be manifested at lower levels of exposure.[20] Nonetheless, exposure of the patient to ionizing radiation should be at the minimum dose consistent with obtaining a diagnostic examination. Each procedure is unique, and the methodology to achieve minimum exposure while maintaining diagnostic accuracy needs to be viewed in this light to ensure optimal patient care.

Myocardial Blood Flow, Myocardial Metabolism, and Ventricular Function

Assessment of Myocardial Blood Flow

Myocardial Blood Flow at Rest

The MBF at rest is tightly regulated to provide nutritive perfusion to viable, contractile myocytes (**see Chapter 57**). Although SPECT tracers to image MBF are commonly referred to as "perfusion tracers," they require viable myocyte cell membranes for uptake and retention.[4] Thus the uptake and retention of these tracers do reflect regional flow differences, but myocyte cell membrane integrity also is a prerequisite. Visualization of myocardial regions suggests the presence of working, viable cell membranes, but lack of visualization of myocardium does not necessarily indicate the absence of viable cells. Decreased regional myocardial tracer uptake at rest could reflect either lack of cell membrane integrity in an area of infarcted myocardium or reduced blood flow secondary to hibernating but viable myocardium. A severe reduction in tracer activity usually signifies infarction, but a more moderate reduction in regional activity of a blood flow tracer alone cannot always differentiate hibernating from partially scarred myocardium in patients with ischemic LV dysfunction. In these patients, techniques that assess intact cellular metabolic processes (e.g., FDG), the myocardial potassium space (e.g., ^{201}Tl redistribution), or the presence of some degree of uptake of the ^{99m}Tc tracers may be used as an adjunct to assessing viability of the myocardium.[4]

Imaging of Myocardial Infarction

In patients with previous myocardial infarction (MI), blood flow to the infarcted region is diminished, often severely, and few viable myocytes are present within the scarred territory.[4] Thus severely reduced uptake of a radionuclide perfusion tracer in a rest study is a good marker of presence, location, and extent of MI (**Fig. 16.20**).

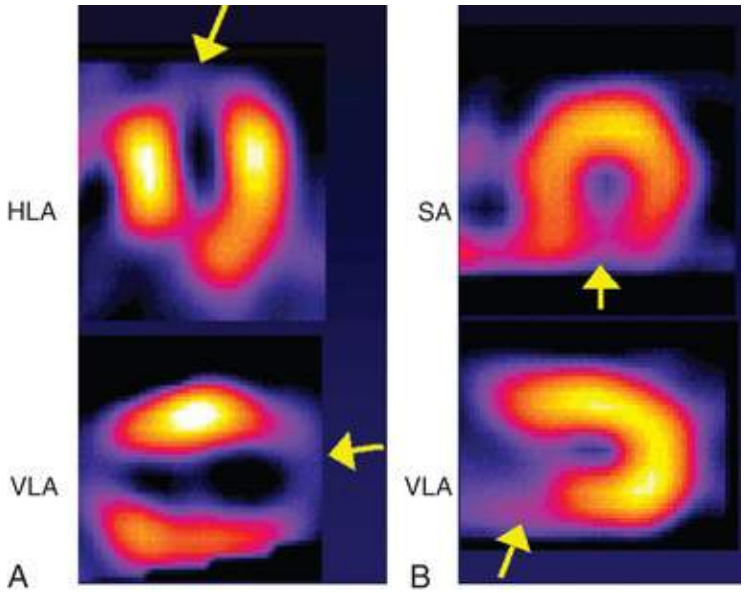


FIGURE 16.20 SPECT perfusion images demonstrating myocardial infarction in different locations. **A,** An apical infarction (*arrows*) in the horizontal long-axis (HLA) and vertical long-axis (VLA) views. **B,** An inferior infarction (*arrows*) in the short-axis (SA) and VLA views. In both studies, the severity of the defect suggests minimal myocyte viability within those territories.

Assessment of Infarct Size

Contemporary studies have used ^{99m}Tc-sestamibi to provide an assessment of infarct size.[21] Because clearance from the myocardium after initial uptake of this tracer is minimal, images acquired even hours after initial injection represent a "snapshot" of blood flow conditions and tracer uptake at the time of injection.

Infarct size as assessed by quantitative analysis of rest sestamibi uptake has been validated against many other measures of infarct size.[21] Moreover, a significant association between SPECT infarct size and death occurring during long-term follow-up has been demonstrated. Many clinical trials now use "final infarct size" as determined by sestamibi SPECT imaging as an early post-MI surrogate endpoint to assess new agents to reduce infarct size.

When a tracer such as sestamibi is injected during acute MI in the setting of an occluded infarct-related artery before reperfusion therapy, the resulting defect, even when imaged hours later after successful reperfusion, represents the "area at risk" of the occluded artery.[21] A second injection of sestamibi at rest with subsequent imaging can be done later during the post-MI course and represents final infarct size. The change in defect size between the initial image acquired in the acute stage and the later image represents the magnitude of salvaged myocardium from reperfusion. Therefore, SPECT imaging at rest in the early post-MI period can provide important information about final infarct size and infarct zone viability.

Assessment of Myocardial Perfusion During Stress

Coronary blood flow must respond rapidly to changing metabolic conditions and oxygen demand to meet the nutrient needs of myocytes being called on to contract more frequently and with more force. Oxygen extraction by the myocardium is nearly maximum at rest; thus any increase in oxygen demand can be met only through increasing coronary blood flow to deliver more oxygen per unit time (**see Chapter 57**). The major determinants of coronary blood flow include the perfusion pressure at the head of the system (principally aortic diastolic pressure) and the downstream resistance, residing predominantly in the coronary arteriolar bed. Because aortic diastolic pressure during exercise varies little from the value at

rest, the major mechanism responsible for increasing coronary blood flow during stress involves a reduction in coronary vascular resistance. During exercise stress, coronary blood flow can increase approximately two to three times above levels at rest. During pharmacologic stress to minimize coronary arteriolar resistance, using intravenous coronary arteriolar vasodilator agents such as dipyridamole, adenosine, or regadenoson (discussed later), coronary blood flow can increase up to four to five times above rest levels. The magnitude of blood flow increase secondary to any stress relative to flow values at rest is termed the *coronary blood flow reserve*.[22]

Perfusion Tracers and Coronary Blood Flow Reserve

The ideal perfusion tracer should track MBF across the entire physiologically relevant range achievable in animal models and in humans (**Fig. 16.21**). It should be extracted rapidly (from the blood into the myocyte), because the hemodynamic conditions during peak stress are not maintained for long periods. The ideal tracer also should be extracted as completely as possible out of the bloodstream, and it should be retained in myocardium for a sufficient period to be imaged. Moreover, perturbations in metabolic conditions, such as ischemia or common cardioactive drugs, should neither influence nor interfere with uptake so that the resulting regional tracer concentrations primarily reflect myocardial perfusion.[4]

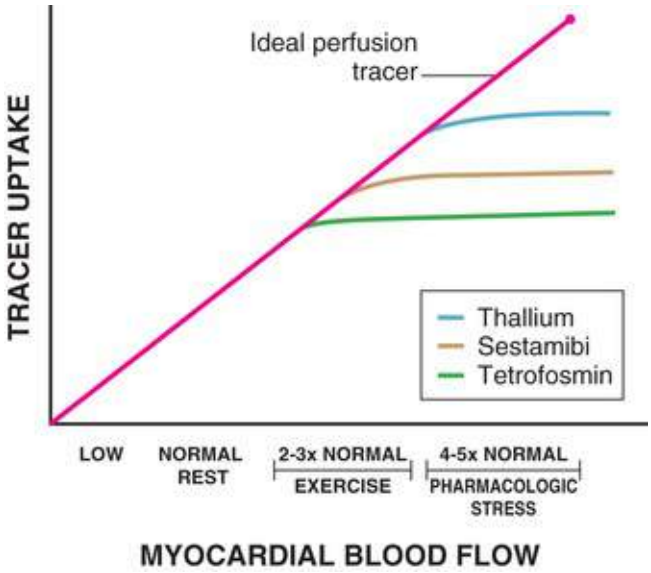


FIGURE 16.21 The relation between myocardial blood flow and perfusion tracer uptake. The ideal perfusion tracer would track myocardial blood flow across the entire range of physiologically relevant flows (*red line*). However, the available perfusion tracers "roll off" at higher levels of flow. The different tracers reach a plateau at different levels of myocardial blood flow, as demonstrated in this schematic example based on multiple studies in animal models.

Despite its excellent first-pass myocardial extraction (85%), the energy spectrum of ^{201}Tl is lower (69 to 80 keV) than optimum for current gamma cameras. The 140-keV energy spectrum of ^{99m}Tc perfusion tracers results in less scatter and soft tissue attenuation, with improved spatial resolution compared with thallium.[4] However, the first-pass myocardial extraction of both sestamibi and tetrofosmin is only in the 60% range with nonlinear extraction at high flows. Thus, none of the clinically available SPECT perfusion tracers has all the properties of an ideal perfusion tracer (**Fig. 16.21**). Nonetheless, regional differences in myocardial tracer uptake during exercise or pharmacologic stress have provided important diagnostic as well as prognostic information.[6]

The PET perfusion tracer ^{13}N-ammonia displays an extraction fraction exceeding 90%; ^{82}Rb has a

lower extraction fraction and reaches a plateau more rapidly at hyperemic range of flow. In the clinical setting, evaluation of regional MBF and flow reserve with ^{13}N-ammonia and ^{82}Rb has been validated for detection and localization of CAD.[9] As noted previously, most PET studies evaluating coronary flow reserve use pharmacologic rather than exercise stress.

Effect of a Coronary Stenosis on Coronary Blood Flow Reserve.

In animal models in which discrete coronary stenoses of varying degrees are induced, coronary blood flow at rest is maintained by autoregulatory dilation of the downstream arteriolar resistance vessels until a stenosis between 80% and 90% of vessel diameter is reached (**Fig. 16.22**). As stenosis severity increases further, the arteriolar vasodilatory capacity to maintain flow at rest is exhausted, at which point coronary blood flow at rest diminishes (**see Chapter 57**).

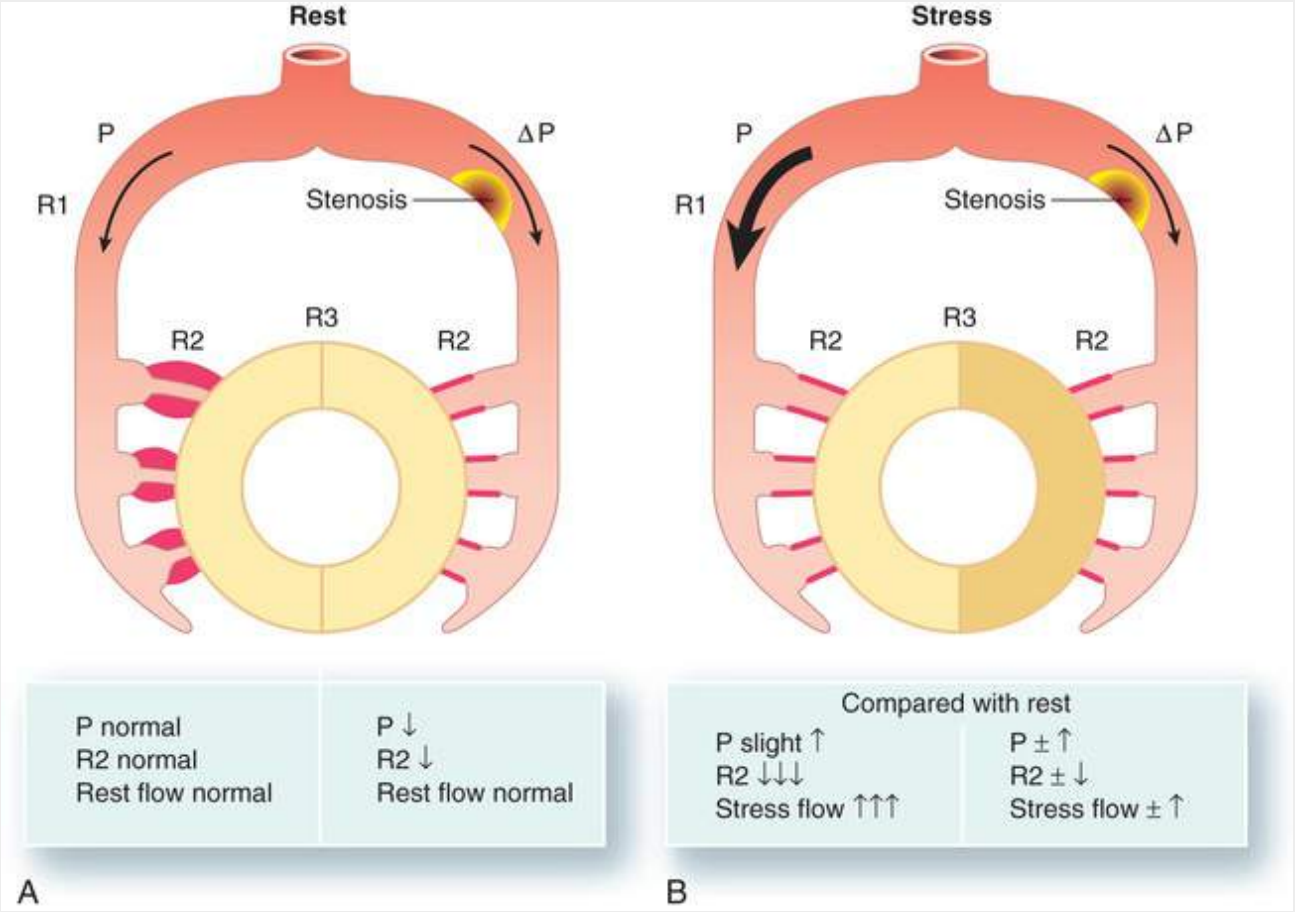


FIGURE 16.22 Effect of coronary resistance on coronary blood flow reserve. **A,** At rest, flow is driven by the pressure head (*P*) at the proximal end of the system. *R1* refers to resistance offered by the large epicardial conductance vessels. *R2* represents the coronary arteriolar resistance, which predominantly regulates coronary blood flow. *R3* represents the resistance provided by wall tension in the subendocardium. At rest in the normal vessel (*left vessel* on the drawing), some vasoconstrictor resistance is present. In the setting of an epicardial coronary stenosis (*right vessel*), blood flow at rest can be maintained, but at the expense of lowering of coronary resistance downstream (R2 decreased) by autoregulatory dilation of the arterioles. Thus, with lower resistance, flow at rest may be maintained despite the lower pressure head at the distal end of the stenosis. A perfusion tracer would show homogeneous uptake at rest. **B,** With demand stress or with administration of a coronary arteriolar vasodilator such as dipyridamole or adenosine, perfusion increases substantially in the area supplied by the normal epicardial artery (*left vessel* on the drawing) as resistance (R2) becomes minimal. However, blunted flow reserve is seen in the area supplied by the stenosis (*right vessel*), because most of the vasodilator reserve at the R2 level has been used to maintain flow at rest. Thus, heterogeneity of flow is established (based on presence of upstream stenosis) and can be imaged with a perfusion tracer as a defect in the territory supplied by the stenotic vessel.

By contrast, maximum coronary blood flow reserve begins to decrease when the upstream coronary stenosis reaches 50% diameter. Three levels of resistance influence coronary blood flow: that provided by the large-conductance epicardial vessels, designated R1; the coronary arteriolar resistance, R2; and the resistance in the subendocardium by wall tension from the ventricular chamber, R3 (**Fig. 16.22**). Under normal conditions, most of the resistance at rest is provided by R2, and most of the increase in coronary flow during heightened demand occurs through reduction of resistance at this level, potentially increasing flow as much as four times as demand increases. Normal epicardial vessels dilate slightly (R1 decreases slightly) in response to increased coronary flow as a consequence of normal endothelial cell function. Depending on the type of exercise performed, the R3 component may remain unchanged or may increase, with an increase in chamber radius and wall tension. Achieving maximal flow is predominantly dependent on the vasodilatory capacity of the downstream resistance vessels.[22] With a coronary stenosis, in which some vasodilatory reserve has been used to maintain flow at rest, less vasodilatory reserve is available to minimize resistance during stress. Thus, in a vessel with a moderate stenosis, coronary

blood flow reserve is blunted and detectable by a perfusion tracer (**Fig. 16.22**).

In contrast with animal models, human atherosclerotic CAD is more complex. Stenoses may not be discrete, the length and complexity of the stenosis may affect the coronary reserve, and impaired endothelial function plays a role (see Classic References, Gould). In patients with preserved endothelial function, the increased coronary flow during stress leads to coronary arterial and arteriolar vasodilation, contributing to maximal coronary flow reserve. Endothelial function often is abnormal, with early atherosclerosis or risk factors for atherosclerosis contributing to the blunting of coronary flow reserve. The development of collaterals to the distal perfusion bed of a myocardial territory with a severe upstream coronary stenosis also influences blood flow at rest and during stress.[22]

With SPECT imaging, relative regional differences of tracer uptake can be detected and quantified (**Fig. 16.23**), whereas with PET imaging, absolute regional coronary blood flow at rest and during stress (in milliliters per gram per minute) potentially can be quantified.[4,9]

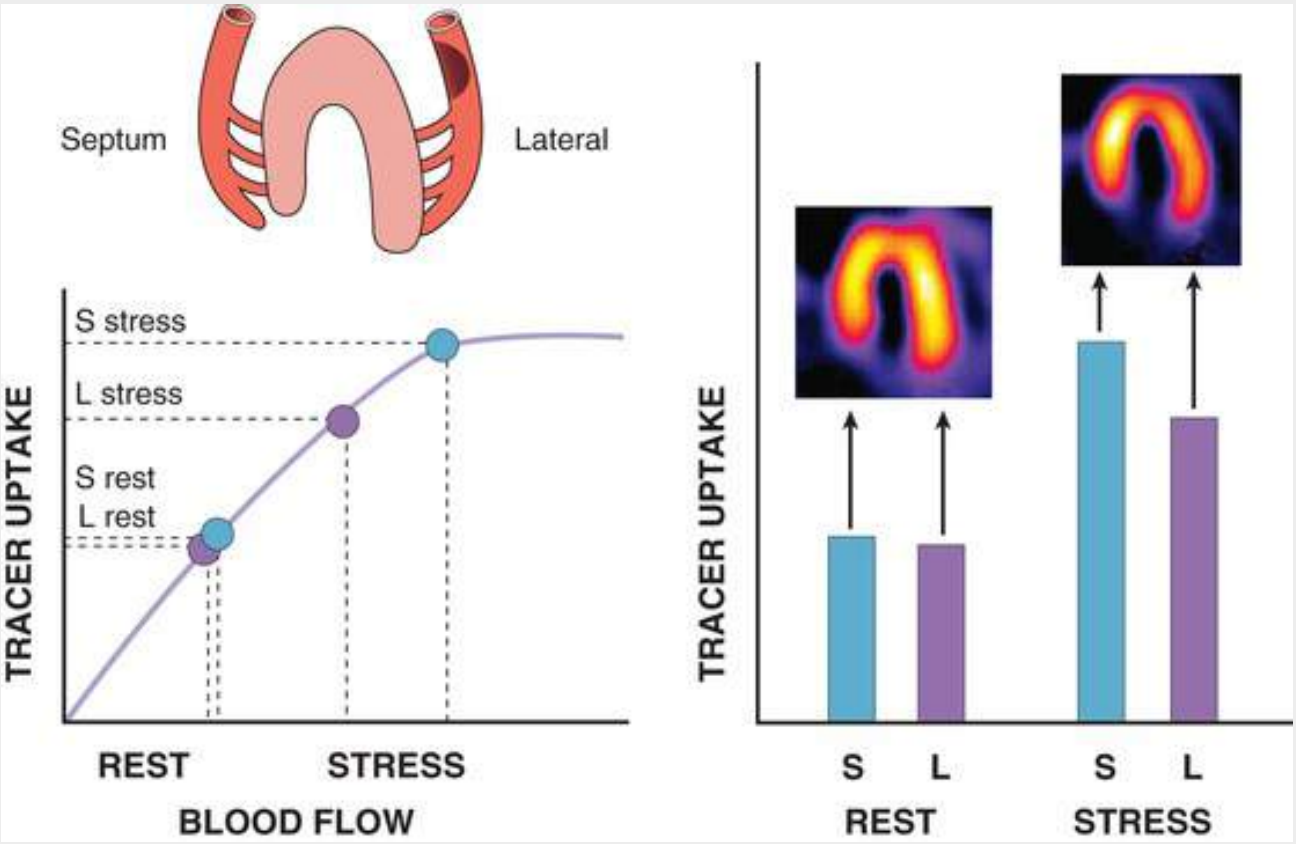


FIGURE 16.23 Graphs illustrating effect of coronary artery blood flow reserve abnormalities on perfusion tracer concentrations, with corresponding tomographic images. **Left,** Myocardial blood flow profiles at rest and stress of two myocardial regions, with region S (septum) supplied by a normal epicardial artery and region L (lateral wall) by an artery with significant epicardial coronary stenosis. Blood flow at stress is diminished in region L compared with S. **Right,** Perfusion tracer uptake profile is demonstrated with myocardial blood flow on the *y* axis. Tracer uptake is diminished in region L relative to S during stress. In the resulting perfusion images, a relative "defect" of tracer uptake is seen in the lateral wall compared with the septum, whereas both regions demonstrate similar tracer uptake at rest. The lateral wall thus demonstrates a reversible perfusion defect, reflecting the blunted coronary blood flow reserve and indirectly reflecting the presence of the coronary stenosis.

Detection of Stress-Induced Ischemia Versus Infarction

In standard practice, stress and rest myocardial perfusion images are compared to determine the presence,

extent, and severity of stress-induced perfusion defects and to determine whether such defects reflect regional myocardial ischemia or infarction.[2,5] Stress-induced perfusion abnormalities in regions that exhibit normal perfusion at rest are termed *reversible* perfusion defects, and such regions represent viable tissue with blunted coronary blood flow reserve (**Fig. 16.24A; see also Figs. 16.4 through 16.6 and 16.9B**). Strictly speaking, SPECT MPI demonstrates stress-induced reversible abnormalities in perfusion reserve, although these findings often are referred to as "ischemia." Regional myocardial tissue ischemia per se is not being demonstrated, although it is indeed often present, based on a mismatch between oxygen supply and demand. Perfusion abnormalities at stress that are *irreversible*, or fixed, as seen on rest images (unchanged from stress to rest), most often represent infarction, particularly if the defect is severe (**Fig. 16.24B; see also eFig. 16.2B**). When both viable myocardium and scarred myocardium are present, thallium redistribution or ^{99m}Tc tracer reversibility is incomplete, giving the appearance of partial reversibility on the delayed thallium or rest ^{99m}Tc images.

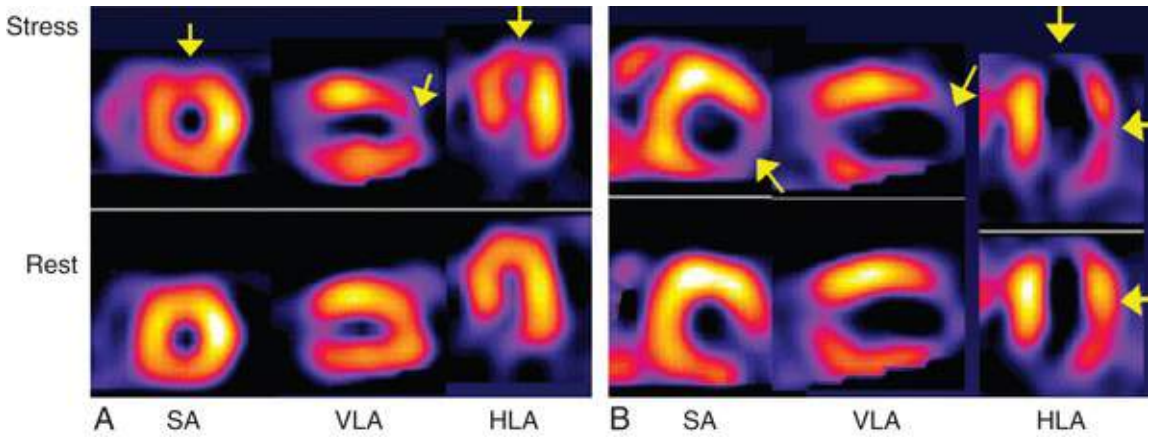


FIGURE 16.24 **A,** Example of SPECT anterior and apical reversible perfusion defects (*arrows*), representing inducible regional myocardial ischemia in short-axis (SA), vertical long-axis (VLA), and horizontal long-axis (HLA) views. **B,** Example of irreversible or fixed defects of inferolateral wall on SA images and of apex on VLA images (*arrows*), representing predominant myocardial infarction. On HLA image, evidence of a reversible lateral wall defect (*arrows*) representing lateral wall ischemia also is seen.

Exercise Stress to Induce Coronary Hyperemia

SPECT MPI frequently is performed with exercise stress to induce coronary hyperemia, particularly suitable for patients with exertional symptoms, because this provides the opportunity to link the symptoms induced during exercise to the location, extent, and severity of abnormal perfusion patterns.[5] Moreover, performing exercise stress in conjunction with MPI allows the opportunity to incorporate additional information on functional capacity, stress-induced electrocardiographic changes or arrhythmias, and use of heart rate reserve and heart rate recovery in the assessment of CAD probability or prognosis[23] (**see Chapter 13**).

Pharmacologic Stress to Induce Coronary Hyperemia

Exercise stress is the preferred modality to induce coronary hyperemia because it allows a correlation between exertional symptoms and the perfusion pattern and provides information on exercise duration, workload achieved, and presence and extent of ischemic electrocardiographic changes, all of which provide important diagnostic and prognostic information.[24] A substantial proportion of patients, however, are incapable of attaining a sufficient level of exercise. Patients with exertional symptoms may not

exercise adequately to reproduce these symptoms, and patients may not achieve more than 85% of the maximum predicted heart rate for age, considered the optimal level of exertion to achieve coronary hyperemic responses.[5,23] As the population ages and the prevalence of comorbid disease states such as peripheral vascular disease and diabetes increases, the proportion of patients referred for stress testing who are unable to achieve adequate levels of exercise will increase.

In such patients, pharmacologic stress testing can be used to induce coronary hyperemia. The most widely used agents for pharmacologic stress testing can be divided into those that act as coronary arteriolar vasodilators (adenosine, dipyridamole, and regadenoson) and adrenergic agents such as dobutamine.[5,24]

Mechanism of Coronary Arteriolar Vasodilator Pharmacologic Stress

Stimulation of adenosine A_{2a} receptors on the smooth muscle cells leads to enhanced production of adenylate cyclase, increased intracellular cyclic adenosine monophosphate (cAMP), and other effects that produce vasorelaxation. With maximal arteriolar vasodilation (maximal decrease in coronary resistance), coronary blood flow increases.

Adenosine is a powerful, endogenous molecule that acts as a regulator of blood flow in many organ beds, including the coronary circulation (**see Chapter 57**). It has many other effects mediated by different receptor subtypes. Adenosine A_1 receptors are present in the sinus node and atrioventricular (AV) node and mediate diminished heart rate and AV nodal conduction. Adenosine A_{2b} receptors are present in bronchioles and the peripheral vasculature, and stimulation may result in bronchial constriction and peripheral vasodilation.

Initial studies of adenosine demonstrated that a dose of 140 µg/kg/min induced maximal coronary hyperemia, with no further increase in maximum coronary blood flow at higher doses. After the onset of intravenous adenosine infusion, maximum coronary flow occurs at an average of 84 seconds, with a range of up to 125 seconds. Dipyridamole blocks the intracellular retransport of adenosine and inhibits adenosine deaminase, responsible for the intracellular breakdown of adenosine.[24] Thus, dipyridamole acts as an indirect coronary arteriolar vasodilator, increasing intracellular and interstitial concentrations of adenosine (**Fig. 16.25**). The newer agent regadenoson is similar to adenosine in that it directly interacts with the adenosine A_{2a} receptor.[24]

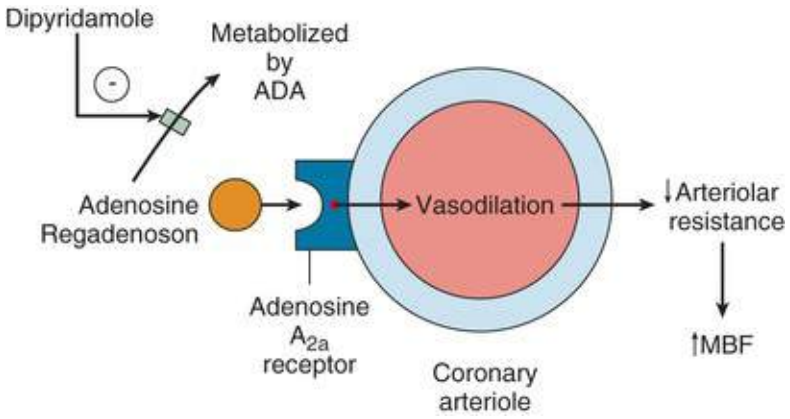


FIGURE 16.25 Schematic of the mechanism of action of dipyridamole, adenosine, and regadenoson. Exogenously administered adenosine acts directly on its receptor to result in coronary arteriolar vasodilation and a consequent increase in myocardial blood flow (MBF) as resistance is minimized. Regadenoson directly interacts with adenosine A_{2a} receptor. Adenosine A_{2a} receptor mediates coronary arteriolar vasodilation, which is the basis for pharmacologic stress testing. Dipyridamole blocks the intracellular retransport of adenosine and also inhibits adenosine deaminase (ADA), resulting in increased intracellular and interstitial concentrations of adenosine, which then interacts with its receptor.

Heterogeneity of Coronary Hyperemia with Pharmacologic Stress

With the administration of dipyridamole, adenosine, or regadenoson, the resistance vessels in the area subtended by a normal epicardial vessel dilate, diminishing coronary resistance and resulting in an increment in coronary blood flow four to five times above normal. Coronary resistance in a bed supplied by a stenotic epicardial vessel is diminished at rest (i.e., coronary vasodilator reserve has been used), and only minor or no further reductions can take place. Thus, MBF in that territory does not change or may even decrease slightly because of the peripheral vasodilation and drop in diastolic blood pressure characteristic of pharmacologic stress. The net result of these changes is heterogeneity in MBF, increased in the normal territory and relatively unchanged in the territory supplied by the stenotic epicardial vessel. Perfusion tracer administration in this setting demonstrates a defect in the area supplied by the stenotic vessel[24] (**see Fig. 16.22**).

During exercise stress, the increase in myocardial oxygen demand and limitation of oxygen supply create a supply-demand mismatch, often resulting in cellular ischemia. With pharmacologic stress, the perfusion defect may represent merely the heterogeneity in coronary flow reserve. “Demand” may change little during pharmacologic stress; there is often a reduction in blood pressure accompanied by a reflex but modest increase in heart rate, so that double product, reflecting oxygen demand, changes little during the vasodilator “stress.” Thus a supply-demand mismatch may not occur, and cellular ischemia may not be present, despite vasodilator-induced perfusion defects.[24]

Under certain conditions, true myocardial ischemia may indeed be present, related to development of a “coronary steal.” This phenomenon appears to occur when the myocardial perfusion bed supplied by a severe epicardial stenosis also is dependent on collateral vessels from remote coronary arteries. Blood flow through coronary collaterals depends on perfusion pressure, particularly if the collaterals are jeopardized (i.e., if the parent blood vessel is compromised by moderate coronary stenosis). In this setting, administration of a vasodilator stress agent diminishes the perfusion pressure supplying the collaterals, and collateral flow diminishes. Flow to the bed supplied by a severe epicardial stenosis may then decrease compared with flow at rest, and the diminished supply may create supply-demand mismatch and true myocardial ischemia, with ECG ST-segment depression.

Hemodynamic Effects of Vasodilator Pharmacologic Stress.

Administration of dipyridamole, adenosine, or regadenoson results in adenosine receptor–mediated systemic as well as coronary vasodilation, with an average reduction of 8 to 10 mm Hg in systolic and diastolic blood pressure, often accompanied by a reflex increase in heart rate.[24] The magnitude of the heart rate increase is variable, usually between 10 and 20 beats/min. A blunted heart rate response may be observed in patients who are taking beta blockers or in diabetic patients with underlying autonomic insufficiency.

Side Effects Associated With Vasodilator Pharmacologic Stress.

The side effects associated with pharmacologic vasodilator stress are the result of stimulation of the adenosine A_1, A_{2b}, and A_3 receptors and are common. After dipyridamole stress, approximately 50% of patients experience some side effect, and with adenosine more than 80% of patients experience untoward side effects, most commonly flushing, chest pain, or shortness of breath.[2,24] In the pivotal clinical trials of regadenoson, the prevalence of side effects was similar to that seen with adenosine, though a composite severity score was slightly lower.

As a result of adenosine's effect on the conduction system, AV block may develop during adenosine administration. Approximately 10% of patients manifest first-degree AV block, with 5% developing either second- or third-degree AV block. AV block is more common in patients who are studied while they are taking beta blockers or heart rate–lowering calcium channel blockers. Patients with baseline evidence of second- or third-degree AV block in the absence of a pacemaker should not receive adenosine. However, patients with first-degree AV block or left bundle branch block (LBBB) appear to tolerate adenosine infusion well, without an exacerbation of conduction abnormalities.[5,24]

Ischemic ST-segment depression is observed in 10% to 15% of patients undergoing pharmacologic vasodilator stress, probably representing the physiologic consequence of induction of a coronary steal and regional myocardial ischemia. Such patients often have extensive and severe perfusion defects on imaging and more often have collateralized multivessel disease on angiography.

Chest pain, even typical angina pectoris, frequently develops during pharmacologic vasodilator stress testing. Although it may reflect regional myocardial ischemia based on a coronary steal, chest pain also may occur in patients with no ischemic ECG changes and with normal perfusion studies because of involvement of adenosine A_1 receptors in the nociceptive pathway influencing the sensation of chest pain.[24] Thus, chest pain by itself is a nonspecific finding during vasodilator pharmacologic stress.

In early reports of dipyridamole testing, infrequent but severe episodes of bronchospasm occurred, possibly related to a nonspecific adenosine receptor–mediated mechanism. Thus, patients with a significant history of reactive airways disease should not undergo vasodilator stress testing.[5,24] Patients with chronic obstructive pulmonary disease (COPD) without a reactive airways component, however, generally tolerate the procedure well. Regadenoson has been studied in patients with mild to moderate asthma and in patients with moderate COPD. In a randomized trial the incidence of a greater than 15% decrement in forced expiratory volume in 1 second (FEV_1) from baseline was similar in regadenoson- and placebo-treated patients, although dyspnea was more common in the regadenoson patients.[25] No cases of severe bronchospasm occurred. These data suggest that regadenoson may be used in such patients, although with caution and after preparation to treat dyspnea.

Reversal of Effects of Vasodilator Pharmacologic Stress.

Methylxanthine compounds such as theophylline and caffeine act as competitive antagonists of adenosine at the receptor level, and infusion of intravenous (IV) aminophylline antagonizes the effects of the

vasodilator stress agents.[5] Because adenosine has a very short half-life (approximately 20 to 30 seconds), administration of aminophylline is rarely required during adenosine testing; simply stopping the infusion results in cessation of symptoms within 20 to 30 seconds. After IV dipyridamole or regadenoson, infusion of aminophylline at approximately 1 to 2 mg/kg over 30 seconds reverses side effects (as well as coronary vasodilator effects), usually within 1 to 2 minutes. Because the coronary vasodilator effects will be reversed as well, reversal of the vasodilator effect should be delayed until at least 1 to 2 minutes after radionuclide administration if it is clinically safe; otherwise, the true stress perfusion pattern may not be evident. In general, side effects from vasodilator pharmacologic stress, although common, may be tolerated for this time. However, with more severe side effects, such as severe shortness of breath or bronchospasm, or with more dramatic ST-segment abnormalities, more rapid reversal of the vasodilator effect is prudent. Because caffeine is a methylxanthine compound and antagonizes the effect of adenosine at its receptor, it is critical that patients be instructed to withhold caffeine, ideally for 24 hours before vasodilator pharmacologic stress testing.

In some patients, myocardial ischemia provoked during vasodilator stress testing triggers a cascade of events that maintains ischemia even after reversal of the vasodilator effect with aminophylline. The sensation of chest pain may drive a heightened sympathetic response, with an elevation of heart rate and blood pressure. In this setting, when aminophylline has been given to reverse the effects of the vasodilator, it is safe to administer sublingual nitroglycerin or other measures to relieve myocardial ischemia. It is not safe to give sublingual nitroglycerin before aminophylline to treat signs of myocardial ischemia. Because systemic vasodilation is present during vasodilator stress testing, administration of nitroglycerin before aminophylline may result in substantial systemic hypotension.

Protocols for Vasodilator Pharmacologic Stress Testing

Table 16.3 lists the accepted protocols for performing vasodilator pharmacologic stress testing.[5,24] Since the original descriptions of these protocols, iterations have been studied, with the goal of shortening the test procedure, minimizing side effects, or both, by shortening the duration of the adenosine infusion or adding low-level exercise.

TABLE 16.3
Pharmacologic Stress Protocols

AGENT	DOSE	DURATION	ISOTOPE INJECTION
Dipyridamole	142 μg/kg/min	4 minutes by hand infusion or pump	3 minutes after completion of infusion
Adenosine	140 μg/kg/min	6-minute infusion by pump	At 3 minutes into infusion
Regadenoson	0.4 mg (5 mL) rapid IV injection, followed by 5 mL saline flush	Bolus	10-20 seconds after the saline flush

Handgrip exercise may be used to raise peripheral blood pressure and thus coronary perfusion pressure. Reports are mixed on whether image quality is improved. This approach may be useful in patients with borderline low blood pressure before the test to avoid significant hypotension.

Low-level treadmill exercise has been increasingly applied in combination with vasodilator stress testing. Although no clear advantage in diagnostic performance has been shown, a reduction in side effects of pharmacologic stress testing has been consistently demonstrated, as well as a reduction in extracardiac tracer uptake with consequent improvement in image quality.

Differences Between Vasodilator and Exercise Stress

The perfusion images obtained by vasodilator pharmacologic stress are generally concordant with those

obtained with maximal exercise stress in the same patient, but with several important differences: Higher levels of coronary flow are achieved during vasodilator pharmacologic stress compared with exercise, possibly because of the increased resistance to flow with exercise caused by higher subendocardial pressures. Although theoretically this difference should result in increased sensitivity for detection of CAD with pharmacologic stress, such heightened sensitivity has not been clearly demonstrated. The failure to demonstrate increased sensitivity may result from the inability of the radionuclide tracers to reflect MBF adequately at the highest levels of flow[4] (**see Fig. 16.21**).

Vasodilator pharmacologic stress is less "physiologic" than exercise, and symptoms during testing (or lack thereof) cannot be as clearly linked to the perfusion pattern, as can be done with exercise stress. Optimal diagnostic performance of MPI during exercise often depends on the patient achieving a maximal level of stress, which does not always occur.

Anti-ischemic medications may significantly affect the results of MPI during exercise.[5] The extent and severity of myocardial perfusion defects also may be affected in an important way by background medication during pharmacologic stress. Antianginal medications should therefore be withheld if possible before the study.

Dobutamine Stress to Induce Coronary Hyperemia.

In some patients, vasodilator pharmacologic stress is contraindicated because of reactive bronchospastic airways disease or background methylxanthines. In such cases, IV dobutamine may be used to induce coronary hyperemia.[5] Dobutamine has a relatively rapid onset of action, with a half-life of approximately 2 minutes. This agent is given starting at a dose of 5 µg/kg/min and increased in a stepwise fashion by 5 µg/kg/min every 3 minutes, to a maximum dose of 40 µg/kg/min (**see Chapter 14**). Dobutamine is a broad adrenergic receptor agonist, at varying doses stimulating the $beta_1$, $beta_2$, and $alpha_1$ receptors. At relatively low doses, the predominant effect is an increase in contractility mediated through adrenergic receptors. As the dose is increased beyond 10 µg/kg/min, heart rate rises steadily, and the increase in oxygen demand stimulates an increase in MBF.

The hemodynamic response to dobutamine generally involves a modest increase in systolic blood pressure with a modest decrease in diastolic blood pressure through doses up to 20 µg/kg/min, with only small further changes after that point. Because the increase in MBF depends on the increase in oxygen demand, optimal sensitivity for MPI based on optimizing heterogeneity of flow depends on achieving an adequate heart rate response, often requiring a high dose of dobutamine.

The increment in MBF during maximal doses of dobutamine appears to be less than that achieved during vasodilator pharmacologic stress, so the degree of heterogeneity of coronary flow with a coronary stenosis also is less. Thus, vasodilator stress is the preferred pharmacologic modality for MPI in patients who cannot exercise adequately. Dobutamine stress is reserved for patients in whom vasodilator stress is contraindicated or cannot be performed because of background medications.[5,24]

Side effects of dobutamine are frequent and can be bothersome. The most common side effects include palpitations and chest pain, and arrhythmias including PVCs and nonsustained ventricular tachycardia may be encountered. Hypotension occurs in approximately 10% of patients, possibly as a result of myocardial mechanoreceptor stimulation during increased contractility with resulting withdrawal of peripheral constrictor tone. Hypotension during dobutamine stress does not have the same prognostic implications as exercise-induced hypotension. Because of the relatively short half-life, side effects generally resolve within a few minutes of stopping the infusion and can be aborted more quickly with IV

beta-adrenergic blockade.[5,24]

Assessment of Myocardial Cellular Metabolism and Physiology

Myocardial Ischemia and Viability

Programmed Cell Survival

Imbalance between oxygen supply and demand results in myocardial ischemia. If the imbalance is transient (i.e., triggered by exertion), it represents reversible ischemia. However, if supply-demand imbalance is prolonged, high-energy phosphates are depleted, and regional contractile function progressively deteriorates. If the supply-demand balance is sufficiently prolonged, cell membrane rupture with cell death follows.

The myocardium has several mechanisms of acute and chronic adaptation to a temporary or sustained reduction in coronary blood flow (**Fig. 16.26**), known as *stunning*, *hibernation*, and *ischemic preconditioning* (**see Chapter 57**). These responses to ischemia preserve sufficient energy to protect the structural and functional integrity of the cardiac myocyte. In contrast with programmed cell death, or *apoptosis*, the term *programmed cell survival* has been used to describe the commonality among myocardial stunning, hibernation, and ischemic preconditioning despite their distinct pathophysiology.[26]

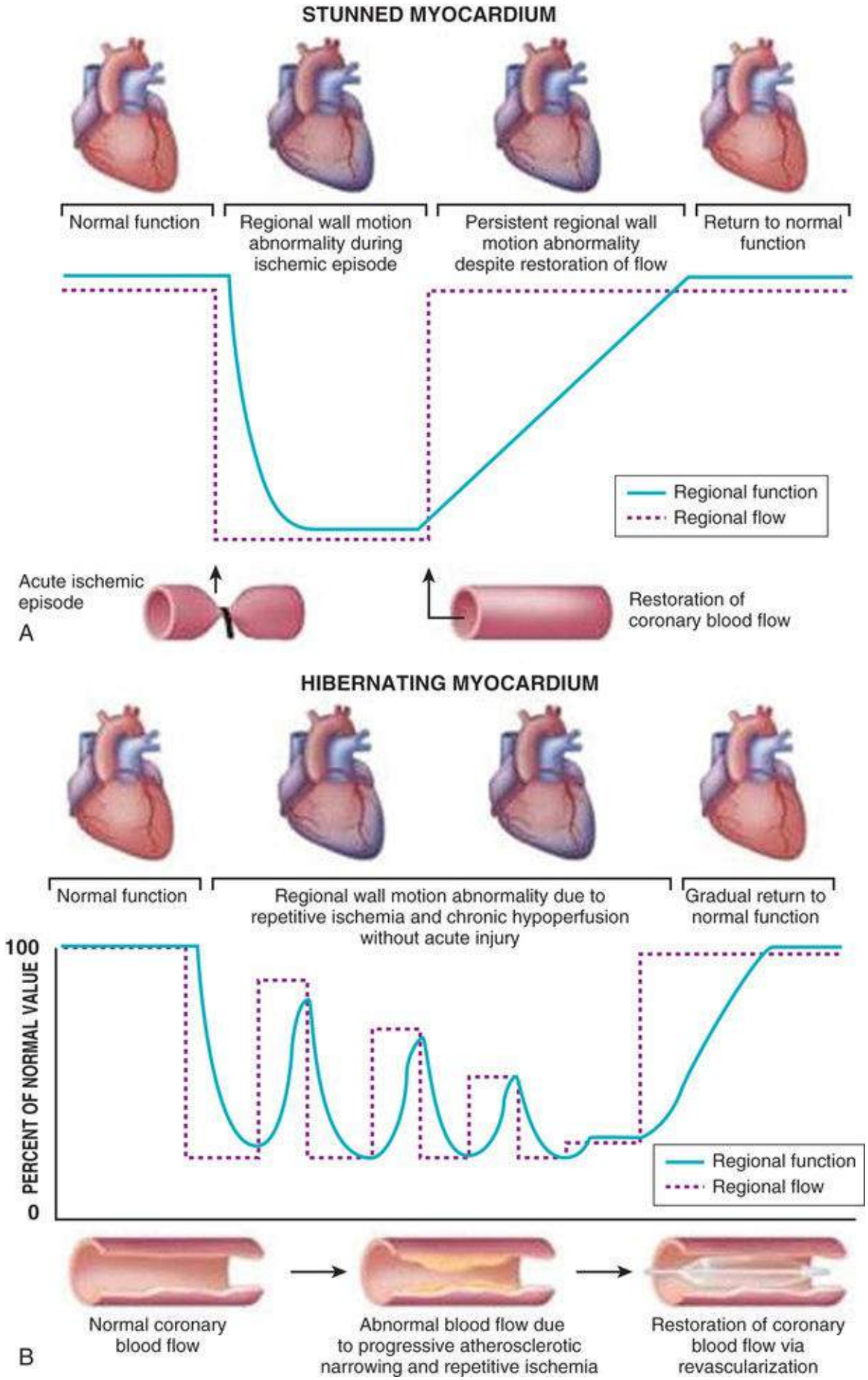


FIGURE 16.26 Pathophysiology of stunning **(A)** and hibernation **(B)**, representing different mechanisms of acute and chronic reversible left ventricular dysfunction. (Modified from Dilsizian V. Myocardial viability: Reversible left ventricular dysfunction. In Dilsizian V, Narula J, Braunwald E, editors. Atlas of Nuclear Cardiology. Philadelphia: Current Medicine; 2006.)

Stunned and Hibernating Myocardium

In stunned and hibernating myocardium, myocardial function is depressed at rest, but myocytes remain viable. Although LV dysfunction may be reversible in both stunning and hibernation, these states differ in the relationship between myocardial perfusion and function. *Stunned* myocardium is most often observed after a transient period of ischemia followed by reperfusion (depressed function at rest but preserved perfusion). The ischemic episodes can be single or multiple, brief or prolonged, but never severe enough to result in injury. This state is typically observed soon after coronary occlusion and reperfusion in the setting of acute MI. *Hibernating* myocardium refers to adaptive responses of the myocardium to repetitive episodes of ischemia resulting in myocardial hypoperfusion at rest[26] (depressed function and perfusion at rest). In clinical practice, it is likely that the adaptive responses of hibernation and stunning coexist.

Myocardial Viability

Requirements for cellular viability include (1) sufficient myocardial blood flow, (2) cell membrane integrity, and (3) preserved metabolic activity. MBF must be adequate to deliver substrate to the myocyte for metabolic processes and to remove the end products of metabolism. If MBF is severely reduced, metabolites accumulate, causing inhibition of the enzymes of the metabolic pathway, depletion of high-energy phosphates, cell membrane disruption, and cell death. Thus, with severe reduction in blood flow, perfusion tracers alone provide information about myocardial viability or absence of viability.[4] However, in regions in which the MBF reduction is less severe, perfusion information alone may be an insufficient signal to identify clinically relevant viability, and additional data, such as metabolic indices, may be important.

Because cell membrane integrity, another requisite for cell survival, is dependent on preserved intracellular metabolic activity to generate high-energy phosphates, tracers that reflect cation flux (e.g., ^{201}Tl), electrochemical gradients (sestamibi or tetrofosmin), or metabolic processes (FDG) provide insight into myocardial viability[4,26] (**Fig. 16.27**).

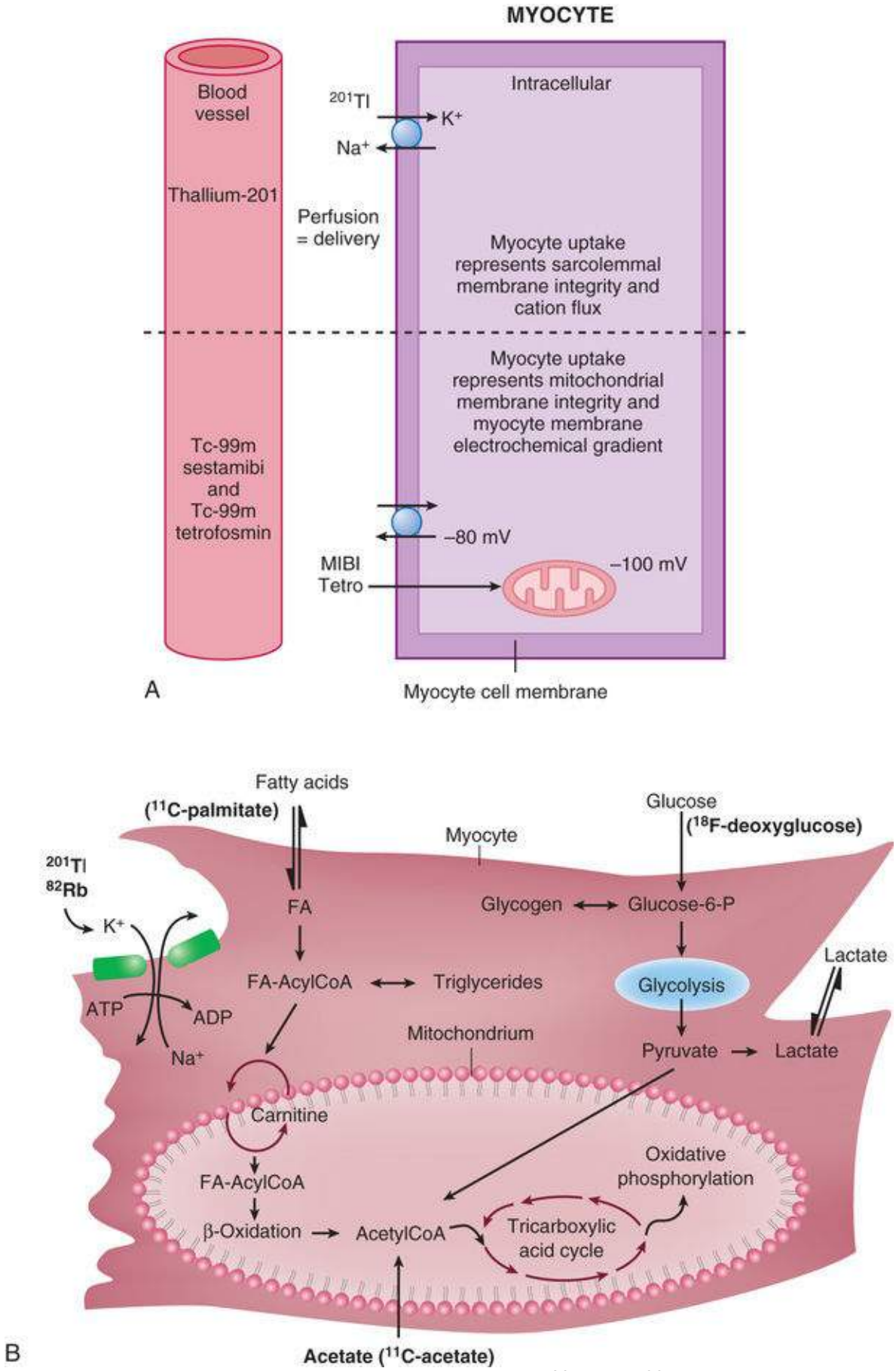


FIGURE 16.27 **A,** Mechanisms of uptake and retention of ^{201}Tl and ^{99m}Tc perfusion tracers. **B,** Mechanism of uptake and retention of PET agents tracing perfusion (^{82}Rb) and oxidative and anaerobic metabolism (^{11}C-acetate, ^{11}C-palmitate, and ^{18}F-deoxyglucose). *ADP,* Adenosine diphosphate; *ATP,* adenosine triphosphate; *CoA,* coenzyme A; *FA,* fatty acid; *Glucose-6-P,* glucose-6-phosphate. (Modified from Dilsizian V. SPECT and PET techniques. In Dilsizian V, Narula J, Braunwald E, editors. Atlas of Nuclear Cardiology. Philadelphia: Current Medicine; 2006.)

Major Myocardial Fuels and Energetics in Normal and Ischemic Myocardium

High-energy phosphates, such as adenosine triphosphate (ATP), provide the fuel that powers the myocyte contractile proteins (**see Chapter 22**). ATP is generated in the myocardium by two different but integrated metabolic processes: oxidative phosphorylation and glycolysis.[9,26] Fatty acids, glucose, and lactate are the major sources of energy in the heart, and depending on the arterial concentration of each and the physiologic condition, any one of these three can be the principal substrate (**Fig. 16.27B**). Increased uptake and use of one substrate will lead to a decreased contribution by the others.

In the fasting state, long-chain free fatty acids are the preferred source of energy in the heart, with glucose accounting for only 15% to 20% of the total energy supply. When the oxygen supply is normal, high levels of ATP and tissue citrate formed by breakdown of fatty acids suppress the oxidation of glucose. When the oxygen supply is decreased, ATP and citrate levels fall, and the rate of glycolysis is accelerated. Anaerobic glycolysis can be maintained only if lactate and hydrogen ion (the byproducts of glycolysis) are removed and do not accumulate. In the setting of severe hypoperfusion, these end products of the glycolytic pathway accumulate, causing inhibition of the glycolytic enzymes and depletion of high-energy phosphates, resulting in cell membrane disruption and cell death.[26] Thus, even to maintain anaerobic glycolysis, minimally sufficient blood flow is necessary.

Imaging of Alterations in Myocardial Metabolism

Imaging of Fatty Acid Metabolism.

Because fatty acids are the primary source of myocardial energy production in the fasting state, early PET studies focused on characterizing the kinetics of long-chain fatty acids, such as ^{11}C-palmitate.[4]

^{11}C-Palmitate.

Measurement by dynamic PET imaging allows determination of tracer inflow (by regional perfusion), peak accumulation, and release within a region of interest. Once in the cell, the tracer either enters the endogenous lipid pool or moves to the mitochondria, where rapid degradation by beta oxidation results in the generation of carbon dioxide. Depending on demand, approximately 80% of extracted ^{11}C-palmitate is activated for transport from the lipid pool into the mitochondria for breakdown by beta oxidation. Because of its complicated kinetic modeling and numerous confounding effects, ^{11}C-palmitate imaging has not gained wide clinical acceptance.

^{123}I-Bmipp.

Fatty acid imaging with radioiodine-labeled fatty acid analogues, such as iodine-123–labeled beta-methyliodopentadecanoic acid (BMIPP) with SPECT, is an investigational area for the assessment of ischemic memory.[4] After an ischemic episode, fatty acid metabolism may be suppressed for a prolonged period, and BMIPP imaging can demonstrate a regional metabolic defect even if perfusion has returned to normal. This metabolic signal of recent ischemia has been termed *ischemic memory* and theoretically may be clinically useful in patients who report to the emergency department (ED) with chest pain that resolved hours earlier. Although approved for clinical use in Japan, BMIPP has not yet received approval by the FDA.

Imaging of Glucose Metabolism.

Although fatty acids are the primary source of fuel in the fasting state, increased arterial glucose

concentration in the fed state results in an increase in insulin levels, stimulating glucose metabolism while inhibiting lipolysis. The result is a switch in myocardial metabolism from predominant use of fatty acids to glucose.

The principle of using a metabolic tracer that tracks glycolysis is based on the concept that glucose utilization may be preserved or increased relative to flow in hypoperfused but viable (hibernating) myocardium, termed *metabolism-perfusion mismatch*.[4,9,26] Myocardial glucose use is absent in scarred or fibrotic tissue, represented by metabolism-perfusion match (**Fig. 16.28**). Although the amount of energy produced by glycolysis may be adequate to maintain myocyte viability and to preserve the electrochemical gradient across the cell membrane, it may not be sufficient to sustain contractile function.[26]

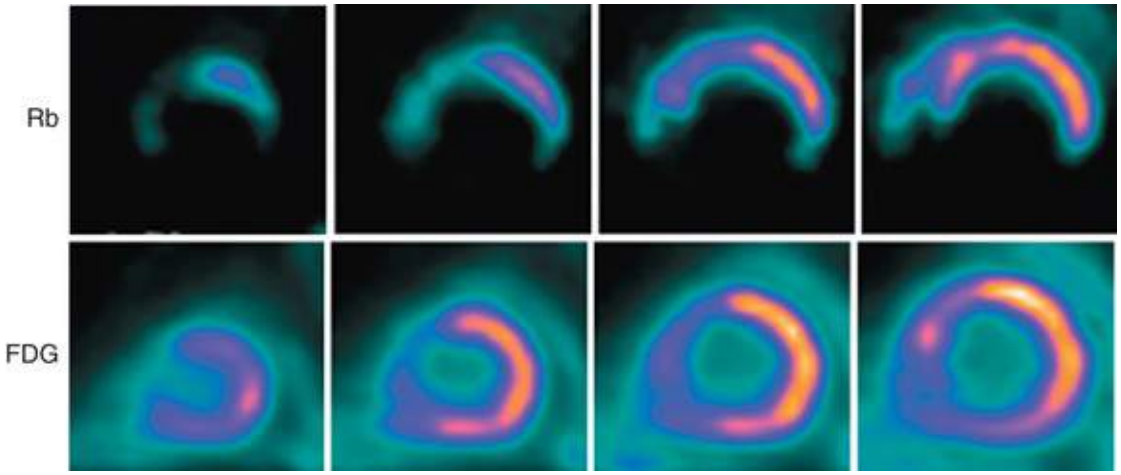


FIGURE 16.28 Assessment of viability by positron emission tomography (PET) imaging. **Top row,** Rubidium-82 (^{82}Rb) is used as a tracer of myocardial blood flow at rest in these short-axis images starting toward the apex (*left*) and moving toward the base of the heart (*right*). Myocardial perfusion is markedly decreased in the apical, inferior, inferolateral, and septal regions. **Bottom row**, ^{18}F-fluorodeoxyglucose (FDG) is used as a tracer of myocardial glucose metabolism. FDG uptake is enhanced relative to blood flow, demonstrating a pattern of perfusion-metabolism mismatch in most abnormally perfused myocardial regions, indicative of viable or hibernating myocardium. An exception is the anteroseptal region, which demonstrates a matched perfusion-metabolism pattern, indicative of nonviable or scarred myocardium. (From Taegtmeyer H, Dilsizian V. Imaging myocardial metabolism and ischemic memory. Nat Clin Pract Cardiovasc Med 2008;5[Suppl 2]:S42.)

2-^{18}F-Fluoro-2-Deoxyglucose.

FDG is a glucose analogue used to image myocardial glucose use with PET.[4,9,26] After injection of 5 to 10 mCi, FDG rapidly exchanges across the capillary and cellular membranes. It is phosphorylated by hexokinase to FDG-6-phosphate (**see Fig. 16.27B**) and not metabolized further or used in glycogen synthesis. Because its dephosphorylation rate is slow, FDG becomes trapped in the myocardium, permitting PET or SPECT imaging of regional glucose use. FDG uptake may be increased in dysfunctional but viable myocardium, and FDG uptake in asynergic myocardial regions with reduced blood flow at rest has become a scintigraphic marker of hibernation.

Diagnostic quality of FDG imaging is critically dependent on hormonal milieu and substrate availability. Most clinical FDG studies are performed after 50 to 75 g of glucose loading in the form of oral dextrose approximately 1 to 2 hours before the FDG injection, to increase glucose metabolism, to maximize FDG uptake, and to improve image quality.[4,9,26] Although 90% of FDG images are of diagnostic quality in nondiabetic patients, the quality of FDG images after glucose loading alone is less certain in

patients with clinical or subclinical diabetes, because the increase in plasma insulin levels may be attenuated, tissue lipolysis may not be inhibited, and free fatty acid levels may remain high. Standardization schemes to optimize FDG image quality in diabetic patients include (1) IV insulin injections after glucose loading, (2) hyperinsulinemic-euglycemic clamping, and (3) use of nicotinic acid derivative.[4,9]

Imaging of Oxidative Metabolism and Mitochondrial Function

^{11}C-Acetate.

All oxidative fuels are metabolized in the tricarboxylic acid cycle after conversion to acetyl coenzyme A (CoA). ^{11}C-acetate is avidly extracted by the myocardium and metabolized predominantly by conversion to ^{11}C-acetyl-CoA in the cytosol and by oxidation via the tricarboxylic acid cycle in the mitochondria to ^{11}C-carbon dioxide and water. Thus the rapid myocardial turnover and clearance of ^{11}C-acetate in the form of ^{11}C-carbon dioxide may reflect myocardial oxidative metabolism and provide insight into mitochondrial function.[4] Despite encouraging data in the literature, ^{11}C-acetate remains an investigational tracer.

Assessment of Left Ventricular Function

The EF as an index of global systolic LV performance is influenced by many factors, including the intrinsic state of contractility, preload, and afterload as well as neurohormonal and inotropic influences (**see Chapter 22**). Despite its load dependence, EF has proved to be clinically useful as a marker of LV performance. The radionuclide techniques used to image ventricular function, including RVG, gated SPECT, and gated PET imaging, have provided substantial insight into the physiology of LV function and the response to disease states (Videos 16.1 and 16.2).

Assessing the Left Ventricular Response to Exercise.

Equilibrium-gated RVG and first-pass RVG can evaluate ventricular performance during exercise. Most often, this is accomplished by imaging of the patient during bicycle exercise, supine or semisupine for equilibrium RVG and upright for first-pass RVG. EF measurements during exertion can then be compared with EF values at rest.[8]

The relative ease with which the EF response to exercise may be studied by RVG techniques led to many reports in the late 1970s and throughout the 1980s. However, evaluation of LV function during exercise by RVG has now been largely replaced by exercise echocardiography (**see Chapter 14**).

Evaluation of Left Ventricular Volumes.

With the RVG technique, the counts detected from the LV region of interest are proportional to LV volume. The proportional relation can be estimated from a blood sample of known volume, in which the quantitative relationship between counts and volume can be determined after correction for attenuation.[8]

The major advantage of the RVG technique for evaluation of ventricular volumes (and function) over contrast ventriculographic and echocardiographic methods is that the radionuclide techniques do not require assumptions about ventricular geometry. With use of RVG techniques, volumes are calculated from count rates over a region of interest (ROI) involving the left or right ventricle, or both, and are based on photon emissions from the ROI.[8] Thus the radionuclide techniques are not dependent on any assumption of ventricular geometry and are suitable for the study of ventricular volumes when ventricular geometry is abnormal.

LV volumes also may be calculated using gated SPECT perfusion imaging, and volumetric data have been validated against those obtained using other quantitative techniques.[5,8] At present, the accumulated experience with gated SPECT perfusion imaging for serial evaluation of LV volumes is less than that with equilibrium RVG volumetric techniques. Nonetheless, the ability to evaluate simultaneously LV function, perfusion, and volumes demonstrates the clinical versatility of gated SPECT MPI.

Serial Evaluation of Left Ventricular Function.

The quantitative nature of radionuclide analysis of ventricular function and the high reproducibility of the measurement make ECG-gated RVG or ECG-gated SPECT imaging well suited for serial follow-up evaluation of changes in LV systolic performance. Serial changes in LV function are clinically relevant in many clinical situations, such as in patients with heart failure,[27] those observed with valvular heart disease,[28] and those receiving cardiotoxic chemotherapy[29] (**see Chapters 25, 67, and 81**). Serial RVG studies demonstrating diminution in EF suggested that the early onset of myocardial dysfunction can herald the onset of a higher-risk clinical course directing clinical management decisions.

Disease Detection, Risk Stratification, and Clinical Decision Making

Stable Chest Pain Syndromes

Application of Radionuclide Imaging: Answering the Clinical Questions

For patients with stable symptoms of suspected CAD (**see Chapter 61**) who are referred for noninvasive testing, the two major goals of testing are to ascertain whether CAD is present or absent—the *diagnostic construct*—and to determine the longer-term prognosis or the risk for an adverse outcome over time—the *prognostic construct*. These goals of testing are linked to the two main treatment goals for patients with suspected or known CAD: (1) amelioration of symptoms in everyday life and (2) improvement in outcome.

Establishment of the presence or absence of CAD is an important goal of testing. The performance characteristics of radionuclide imaging for this purpose often are based on an angiographic definition of stenosis of 50% or greater, or 70% stenosis in an individual epicardial vessel. This definition of CAD is based in part on seminal studies in animal models showing that a 50% stenosis begins to blunt coronary flow reserve (**see Chapter 57**). Over time, however, a view has emerged that CAD is a more complex process than can be simply defined dichotomously by a 50% or even a 70% luminal stenosis. Throughout the progression of plaque growth, there is a risk of transformation from a stable plaque to an unstable plaque, with the potential for an acute coronary syndrome (ACS) that abruptly alters the natural history of the disease process[30] (**see Chapters 44 and 58**). Plaque encroachment of the lumen occurs later in the process but has a potentially important impact on the patient's everyday quality of life by causing symptoms related to exertional ischemia.

Patient-Related Outcomes as a “Gold Standard”

The evolution of preventive therapies such as 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins) to reduce cardiovascular risk has focused attention on the ability of global risk scores or noninvasive testing to assess risk of future events so that strategies to prevent future cardiac events can be instituted[31] (**see Chapter 45**). Thus, from the perspective of improving natural history, knowledge of

whether a stenosis greater than 50% is present in a patient with stable anginal symptoms becomes less important than knowledge of the patient's risk for a cardiovascular event (cardiac death or nonfatal MI). After initial investigations of the performance of radionuclide imaging to detect or to rule out CAD (sensitivity and specificity), the trajectory of the literature has been toward gaining more understanding of how noninvasive imaging results assess prognosis and stratify the risk of future cardiac events. This trend has occurred in parallel with similar directions in primary prevention efforts, such as the use of a Framingham risk score or the current "pooled cohort equation," leading to lifestyle and treatment interventions to lower that risk.[31] In much the same way, risk stratification and assessment of prognosis by noninvasive imaging will inform clinical management decisions geared toward reducing risk of MI and cardiac death and optimizing the selection of patients for revascularization and medical therapies.

Risk Stratification in Stable Chest Pain Syndromes

Definitions for Understanding the Literature.

For prognostic assessment, an important goal is to detect patients at risk for "hard" cardiac events. This definition includes nonfatal MI as well as cardiac death or all-cause mortality, irreversible events important to prevent.[32] "Soft" cardiac events include revascularization and hospital admission for management of ACS or heart failure. Such events occur more often than the hard cardiac events and thus contribute to a larger number of endpoints for data analysis. These events, however, are not as important in terms of natural history and may be driven by subjective changes in symptoms and, in the case of revascularization, by the results of the imaging tests themselves.

Risk categories as described in the American College of Cardiology/American Heart Association (ACC/AHA) stable angina guidelines are *low risk,* defined as a less than 1%/yr risk of hard cardiac events; *intermediate risk,* defined as a 1% to 3%/yr risk; and *high risk,* defined as a greater than 3%/yr risk.[32] These definitions are conceptually linked to implied treatment strategies. Patients with greater than 3%/yr risk would be most likely to benefit from a revascularization strategy, whereas those at low risk would be least likely to benefit from revascularization, in terms of natural history, and thus could be treated medically, with treatment directed against symptoms as well as risk factor modification.

Relation Between Extent of Perfusion Defect and Outcomes

Seminal studies in the 1980s demonstrated that the extent of perfusion abnormality by stress MPI has an important relationship with the subsequent likelihood of an adverse outcome (cardiac death or nonfatal MI). In patients presenting with chest pain and suspected CAD (without any previous known CAD-related history, such as MI or revascularization), the risk of cardiac death or MI increased as the number of reversible perfusion defects (i.e., the extent of inducible ischemia) increased. This concept has been confirmed many times by investigators worldwide. Moreover, this robust concept not only applies to exercise stress MPI but also extends across the spectrum of procedural variables in nuclear cardiology, including different stressors (vasodilator pharmacologic stress, dobutamine stress), isotopes (^{201}Tl and ^{99m}Tc agents), and imaging protocols.[5]

Fig. 16.29 provides an example of data on risk stratification implying therapeutic management strategies; in two older men with typical exertional angina, it would be predicted that the probability of CAD is high, according to established guidelines. What is not established from the clinical information, however, is the risk of cardiac events. This example demonstrates that patients presenting with similar

symptoms might be identified as having distinct natural history trajectories on the basis of perfusion imaging data, with distinct implications for subsequent management.

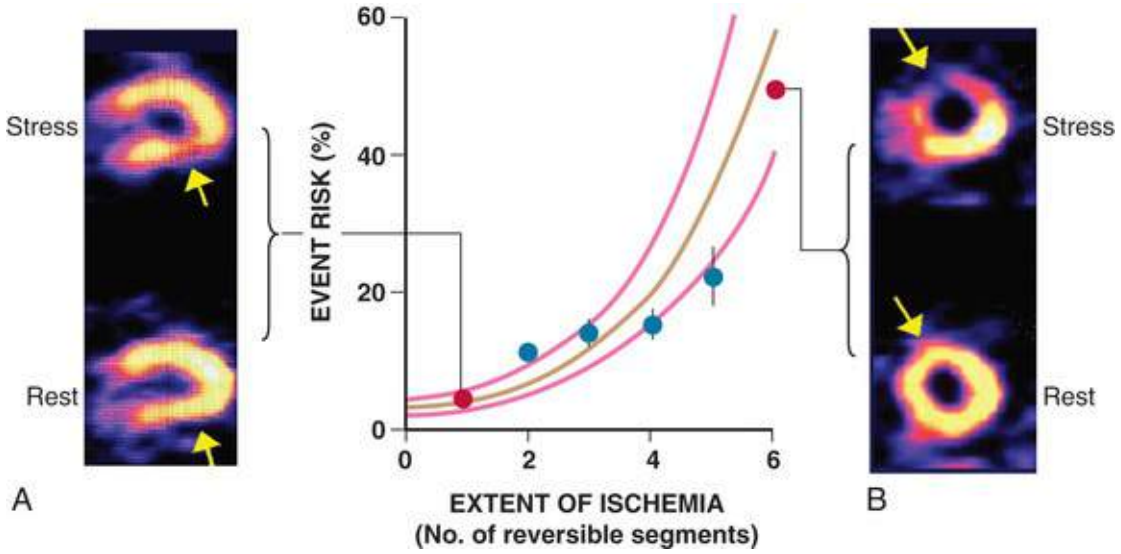
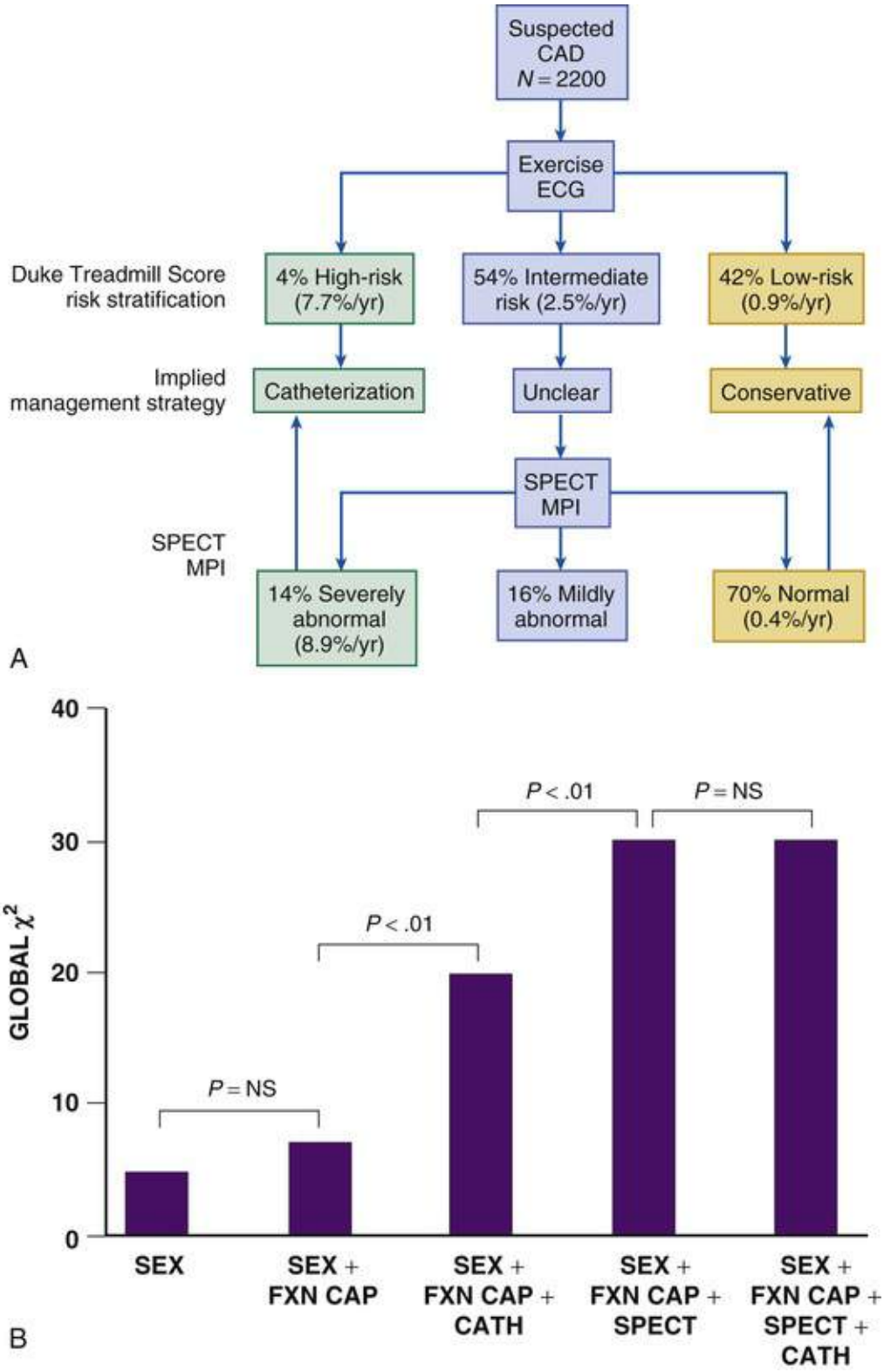


FIGURE 16.29 Prognostic implications of myocardial perfusion imaging (MPI). **Middle panel,** Cardiac event rate (risk of cardiac death or MI) during long-term follow-up plotted as a function of the extent of inducible ischemia (the number of reversible perfusion defects). An exponential relationship exists between the extent of ischemia and the risk of a cardiac event. The *brown line* represents modeling of data points; *magenta lines* represent confidence limits. **A, B,** SPECT perfusion images in two patients with stable anginal symptoms. **A,** Small area of inferoapical ischemia (*arrows*). When this extent of ischemia is plotted on the graph (line to *red circle* at *left* within graph), the patient is placed in a low-risk category. **B,** By contrast, the large, markedly affected area representing severe anterior and septal ischemia in a second case places the patient in a high-risk group (line to *red circle* at *right* within graph). (**A, B,** Modified from Ladenheim ML, Pollock BH, Rozanski A, et al. Extent and severity of myocardial hypoperfusion as predictors of prognosis in patients with suspected coronary artery disease. J Am Coll Cardiol 1986;7:464.)

Incremental Value of Perfusion Imaging

The term *incremental value* implies that MPI data provide information on natural history risk and outcomes that are additive to (incremental to) information from more available or less expensive tests, such as clinical data and stress ECG findings.

Stress MPI data have been shown to have incremental prognostic value when added to prognostic stress ECG instruments such as the Duke treadmill score (DTS), a well-validated instrument incorporating symptoms, treadmill performance, and stress ECG findings to predict natural history outcomes (**see Chapter 13**). In a group of 2200 patients with suspected CAD referred for nuclear testing, the DTS was used to place patients in subgroups according to the risk of a hard event (**eFig. 16.11**). When information from stress MPI studies was incorporated, incremental value to predict outcome was demonstrated within each of the three DTS risk categories.



EFIGURE 16.11 Incremental value of SPECT perfusion imaging. **A,** Comparison with the Duke treadmill score (DTS). A large group of patients with suspected CAD initially were risk-stratified using the well-validated DTS. Figures in *parentheses* are the observed annual event rates. A majority of the population is classified as "intermediate risk" by DTS, and management strategy is not clear. High-risk patients may be managed aggressively, and low-risk patients may be managed conservatively. Among patients originally determined to be in the intermediate-risk category by the DTS, almost 70% demonstrated normal findings on SPECT perfusion study, associated with a very low event rate. After SPECT MPI, more patients are classified at the "extremes" of risk (low or high), for whom management is more clearly implied by the risk prediction. Thus the imaging data allowed further stratification and had incrementally better value compared with the DTS information. **B,** The incremental value of imaging data may be expressed as the incremental chi-square value, a statistical measure of the strength of the association of clinical, demographic, stress, or imaging factors to risk stratification. Among patients with known CAD who had undergone catheterization (*CATH*), clinical information is added on the *x* axis, with the global chi-square value associated with the information depicted on the *y* axis. The larger the chi-square value, the stronger the relation between the combination of factors on the *x* axis and the natural history outcome of cardiac

death or myocardial infarction. Even when anatomic information is available, the physiologic information provided by SPECT MPI adds significantly to risk prediction ability. *FXN CAP,* Functional capacity. (**A,** Modified from Hachamovitch R, Berman DS, Kiat H, et al. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. Circulation 1996;93:905; **B,** modified from Iskandrian AS, Chae SC, Heo J, et al. Independent and incremental prognostic value of exercise single-photon emission computed tomography (SPECT) thallium imaging in coronary artery disease. J Am Coll Cardiol 1993;22:665.)

The importance of this information in driving management decisions for patients can be illustrated by considering how clinicians would manage patients on the basis of certain amounts of information. With use of the DTS information alone, the management of low-risk patients probably would be conservative, and the management of high-risk patients would likely involve revascularization. The optimal management of intermediate-risk patients is unclear, but many probably would be referred for catheterization. In almost 70% of the patients in the intermediate DTS category, however, stress perfusion study findings were normal (**eFig. 16.11A**), associated with a very-low-risk natural history, implying that conservative management would be a safe and effective strategy.

Another method used to demonstrate the incremental value of MPI data over that of clinical, stress, and even angiographic data involves the creation of a multivariable model to measure the strength of association of individual factors with the natural history outcomes (Classic References, Beller). This often is illustrated by assessing the incremental chi-square value, measuring the strength of the association of the factor with subsequent cardiac death and nonfatal MI (**eFig. 16.11B**). Contemporary studies might also use analytic techniques such as net reclassification index to assess the value of an additional increment of information in classifying prognostic risk.[33]

Identification of Treatment Benefit After Risk Stratification

Although numerous studies intimate that the extent and severity of perfusion abnormality are related to subsequent natural history risk, few studies have documented reduction in that risk associated with a particular therapy. Current information suggests that more extensive ischemia determined by MPI identifies patients in whom revascularization may lead to an improvement in outcome. In a group of more than 10,000 patients with suspected CAD studied by stress MPI, the extent of ischemic myocardium predicted reduction in the risk of death with revascularization compared with medical therapy (**Fig. 16.30**), beginning at just over 10% of ischemic myocardium.[6] As the percentage of ischemic myocardium increased, the magnitude of benefit of revascularization increased as well. Thus, MPI data appear to predict the magnitude of a potential treatment benefit from revascularization, helping to guide management decisions. These observational data were developed using techniques to account and correct for differences in the populations treated with revascularization versus medical therapy, but such techniques cannot account for all possible differences between groups. The concept that revascularization may improve outcome in stable outpatients with extensive inducible ischemia is currently being prospectively tested in the randomized, controlled International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial.[34]

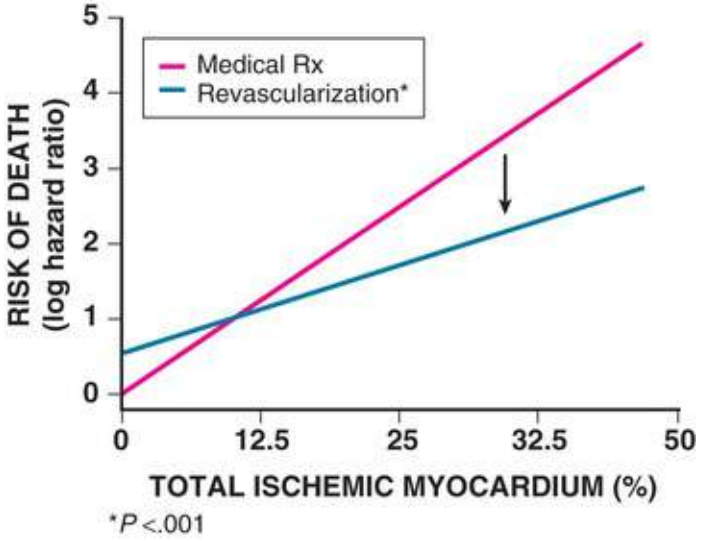


FIGURE 16.30 Predicting the magnitude of treatment benefit by revascularization. Risk of death is plotted as a function of the percentage of ischemic myocardium by SPECT perfusion imaging. The *lines* represent patients treated with medical therapy (Medical Rx) or revascularization. When the magnitude of ischemia exceeds approximately 12%, a potential survival benefit accrues to revascularization. (Modified from Hachamovitch R, Hayes SW, Friedman JD, et al. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation 2003;107:2900.)

Prognostic Value of Normal Myocardial Perfusion Imaging.

A consistent finding in studies assessing prognosis has been the benign outcome associated with a normal stress MPI study. As summarized in the American Society of Nuclear Cardiology (ASNC) imaging guidelines,[5] data on outcomes associated with normal findings on a stress SPECT MPI study involve almost 21,000 patients. In patients with a normal study result, the hard event rate (i.e., rate of cardiac death or nonfatal MI) occurring during an average follow-up period of 2 years is 0.7%/yr. This concept applies across a broad spectrum of isotopes, protocols, and stressors.[5] The prediction of low-risk outcome after a normal MPI study extends approximately 2 years after testing (i.e., the "warranty period").[6] Patients who at baseline represent higher-risk subsets (i.e., those with diabetes) are at slightly higher risk for an adverse outcome after normal results of a stress MPI study, consistent with Bayes theorem; that is, for a certain MPI finding, the post-test probability (outcome risk) is related in part to the pretest risk.

Even when angiographic CAD is present with a stable symptom complex, a normal stress MPI study result is associated with a low-risk outcome (approximately 0.9%/yr).[5] The mechanism for a normal MPI study result despite established CAD may involve preserved endothelial function, allowing appropriate flow-mediated vasodilation during stress, reducing the impact of an angiographic stenosis on downstream myocardial perfusion. If this is true, such preserved endothelial function may identify a decreased susceptibility to plaque fissuring or rupture and a greater likelihood of a stable clinical course. Another mechanism may involve the presence of robust collaterals, allowing normal stress perfusion in the setting of a stenosis, and protecting against infarction should the stenosis become completely occluded.

Detecting the Presence and Extent of CAD

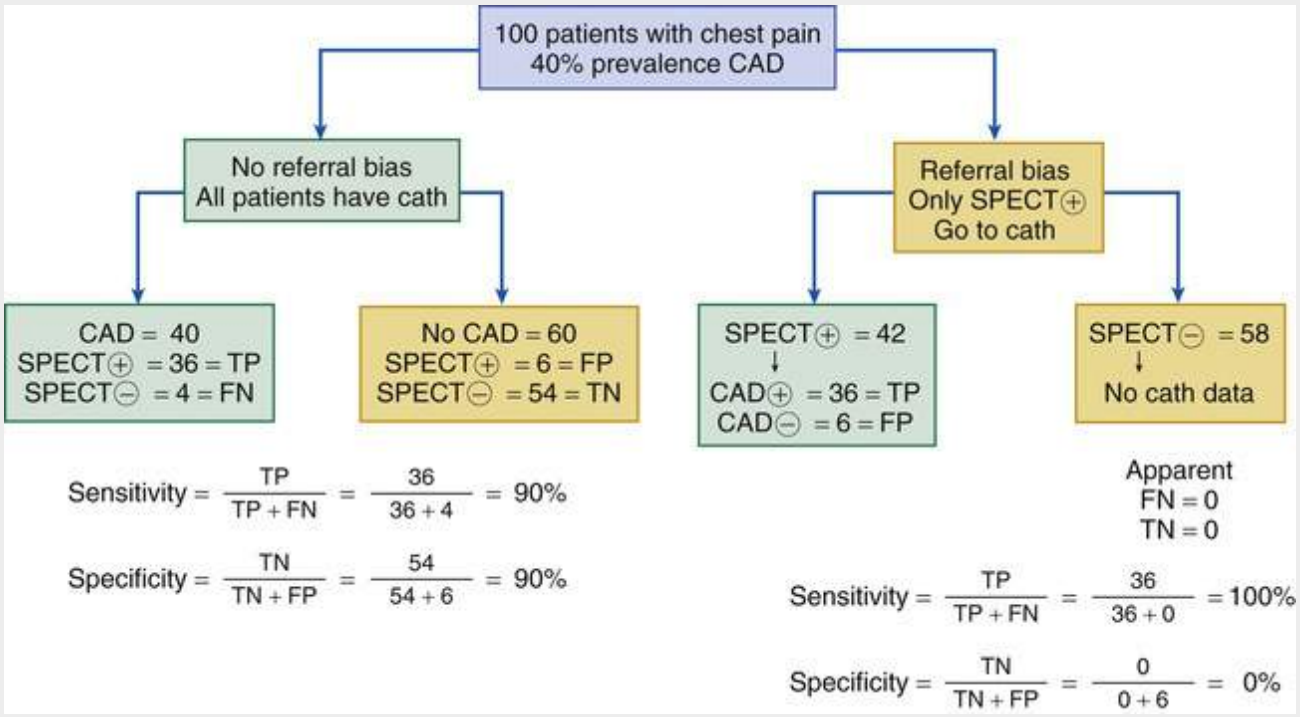
Noninvasive testing in patients with suspected CAD is typically performed to determine the presence or absence of angiographic CAD. In this paradigm, angiography is the gold standard to define the presence or absence of CAD, and performance of the noninvasive test is measured by its sensitivity (percentage of

true-positive test results among those with CAD, as defined by angiography) as well as by its specificity (percentage of true-negative test results among patients without CAD).[5] Published values of sensitivity to detect CAD and specificity to rule out CAD vary widely. An appreciation of the many methodologic or physiologic factors that may influence these performance characteristics is necessary for imaging data to be incorporated appropriately into clinical decision making.

Methodologic Influences on Sensitivity and Specificity

Referral Bias.

The apparent accuracy of any noninvasive test to detect CAD depends on the indications for coronary angiography. Accuracy of a new diagnostic test usually is determined initially in patients who are undergoing coronary angiography. As the test becomes implemented in routine diagnostic strategies, its results determine which patients are to be referred for coronary angiography (**eFig. 16.12**). For example, patients with abnormal MPI findings are more likely to undergo coronary angiography than those with normal MPI findings. This inherent selection process results in a phenomenon termed *post-test referral bias*, in which the specificity of a diagnostic test declines over time as it is accepted into clinical practice and plays a gatekeeper role in determining which patients undergo angiography.[5] In its extreme form, in which only patients with an abnormal test result are referred for angiography (as in **eFig. 16.12**), post-test referral bias drives the specificity to zero (all patients with normal coronary arteriograms have false-positive MPI results, and there are no true negatives). The same phenomenon artificially increases the sensitivity of the test and in its extreme drives the sensitivity to 100% (all patients with abnormalities on coronary arteriograms have true-positive findings on MPI, with no false negatives). This concept holds not only for MPI but also for any diagnostic test that might determine the indications for angiography.



EFIGURE 16.12 The effect of referral bias on specificity calculation. If the test being evaluated is used as the "gatekeeper" to coronary angiography, many patients in whom testing yields true negatives (i.e., those with a normal test result and no have CAD) will not undergo angiography, so their data will not be included in the specificity calculations (*right*). This has an effect of artificially reducing the apparent specificity of the noninvasive test in question. *FN,* False-negative; *FP,* false-positive; *TN,* true-negative; *TP,* true-positive value. (Modified from Rozanski A, Diamond GA, Berman D, et al. The declining specificity of exercise radionuclide ventriculography. N Engl J Med 1983;309:518.)

The concept of "normalcy rate" has been developed in an attempt to compensate for this referral bias. Normalcy is calculated in the same manner as for specificity but includes only the imaging test results of patients with a clinically low or very low pretest likelihood of having CAD, whether or not they are referred for cardiac catheterization. Normalcy rates tend to be higher than specificity.

Angiography as the Gold Standard.

In humans, coronary atherosclerosis is a complex disease most often involving the coronary arteries diffusely and not merely focally. Moreover, whether a given discrete stenotic lesion, imaged at rest during coronary angiography, results in a perfusion abnormality during stress is dependent on a number of factors besides the percentage degree of stenosis. These factors include the dilatory or constrictor response of the vessel during stress (mediated by endothelial function) and the presence or absence of collaterals. For example, a vessel with 70% stenosis but with preserved endothelial function and a well-developed collateral supply may not be associated with an abnormality on stress MPI. In a diagnostic construct, such a result would be categorized as a false-negative finding, reducing MPI sensitivity. However, the MPI data may be providing the correct physiologic information about the functional significance of the angiographic finding, demonstrating that collateral flow during exercise or normal endothelial function, or both, is associated with preserved coronary blood flow reserve despite the coronary stenosis. This example illustrates the limitation of using angiography as a gold standard in evaluation of a physiologic modality.

Many studies define CAD as 50% or greater stenosis, whereas others use a threshold of 70% or greater stenosis.[4,12] Use of ≥50% would decrease sensitivity (because some 50% to 70% stenoses are not hemodynamically significant) and increase specificity. By contrast, use of ≥70% would increase sensitivity (because more such stenoses are likely to be associated with a perfusion abnormality), but decrease specificity, because any positive scan result with 50% to 70% stenosis would be considered

false positive.

Physiologic Influences on Sensitivity and Specificity.

A number of disease processes involving the coronary vasculature or the myocardium may result in abnormalities in myocardial perfusion in the absence of a discrete coronary stenosis. In a diagnostic construct for CAD, such abnormalities would be labeled false positive, reducing specificity (i.e., the test result is positive in the absence of epicardial CAD). However, MPI may actually be providing correct information about perfusion physiology.

Left Bundle Branch Block.

Isolated reversible perfusion defects of the septum in patients with LBBB may be seen in the absence of stenosis of the left anterior descending (LAD) coronary artery.[5] This phenomenon may represent true heterogeneity of flow between the LAD and left circumflex arterial territories, related to delayed relaxation of the septum in LBBB leading to reduced coronary flow reserve in early diastole, or reduced oxygen demand as a result of late septal contraction, when wall stress is decreasing. Accordingly, the specificity and predictive value of a septal perfusion defect with LBBB are low. However, apical or anterior involvement in septal perfusion defects increases the specificity for CAD. Because a septal defect in LBBB most often is seen at high heart rates, pharmacologic stress improves specificity, and vasodilator stress is recommended in the setting of LBBB.[5]

Hypertrophic Cardiomyopathy.

The asymmetric septal hypertrophy in many patients with HCM can lead to the appearance of a greater amount of tracer uptake in the hypertrophied septum relative to the lateral wall, creating the impression of a mild lateral wall perfusion defect, especially when polar maps are employed (**see Chapter 78**). Many reports have demonstrated myocardial perfusion abnormalities in patients with HCM in the absence of epicardial CAD.[35] Such findings have important pathophysiologic relevance: patients with fixed perfusion defects are likely to have thinned akinetic walls on echocardiography and diminished EF (**Fig. 16.31**). Of asymptomatic patients with HCM, approximately 50% have inducible, reversible perfusion abnormalities in the absence of CAD, typically involving the septum. Thus, inducible perfusion defects in HCM that represent inducible myocardial ischemia, possibly related to microvascular abnormalities, have low specificity for CAD in patients with HCM. The blunted coronary flow reserve in patients with HCM is associated with a more unfavorable natural history.[35]

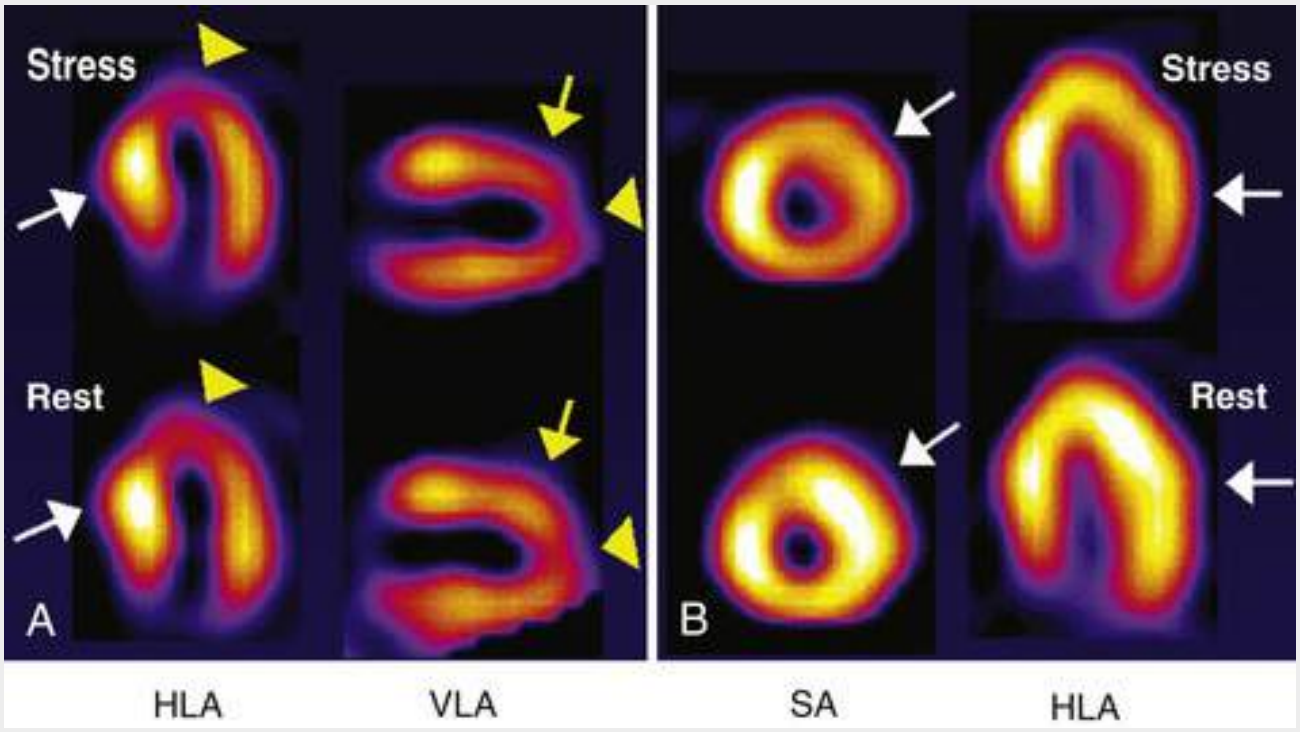


FIGURE 16.31 SPECT perfusion imaging in hypertrophic cardiomyopathy in young asymptomatic patients with normal coronary arteries. **A,** Fixed perfusion defect of the apex consistent with infarction, indicated by *yellow arrowheads* in the horizontal (HLA) and vertical (VLA) long-axis images, with a reversible defect of the anterior wall (*yellow arrows* in VLA images). The hypertrophied septum is evident (*white arrows* in HLA images). **B,** Extensive inducible silent ischemia in the anterior, lateral, and inferior walls (*white arrows*). Transient ischemic cavity dilation also is present, possibly related to subendocardial ischemia. (Based on data from O'Gara PT, Bonow RO, Maron BJ, et al. Myocardial perfusion abnormalities in patients with hypertrophic cardiomyopathy: assessment with thallium-201 emission computed tomography. Circulation 1987;76:1214; and Udelson JE, Bonow RO, O'Gara PT, et al. Verapamil prevents silent myocardial perfusion abnormalities during exercise in asymptomatic patients with hypertrophic cardiomyopathy. Circulation 1989;79:1052.)

Dilated Cardiomyopathy.

Abnormalities in myocardial perfusion are common in patients with DCM despite normal epicardial coronary arteries.[5] Several studies have demonstrated abnormal coronary flow reserve in these patients (**see Chapter 77**). An important diagnostic consideration in patients with LV systolic dysfunction involves distinguishing those whose cardiomyopathy may be primarily caused by CAD (many of whom have potentially reversible LV dysfunction) from those with idiopathic DCM. Although many patients with DCM may have perfusion abnormalities detected on MPI, the absence of perfusion abnormalities virtually excludes CAD as the cause of the cardiomyopathy[36] (**Fig. 16.32**). Extensive perfusion abnormalities in the setting of LV dysfunction are virtually always associated with CAD rather than with DCM, especially when the perfusion defects are segmental.

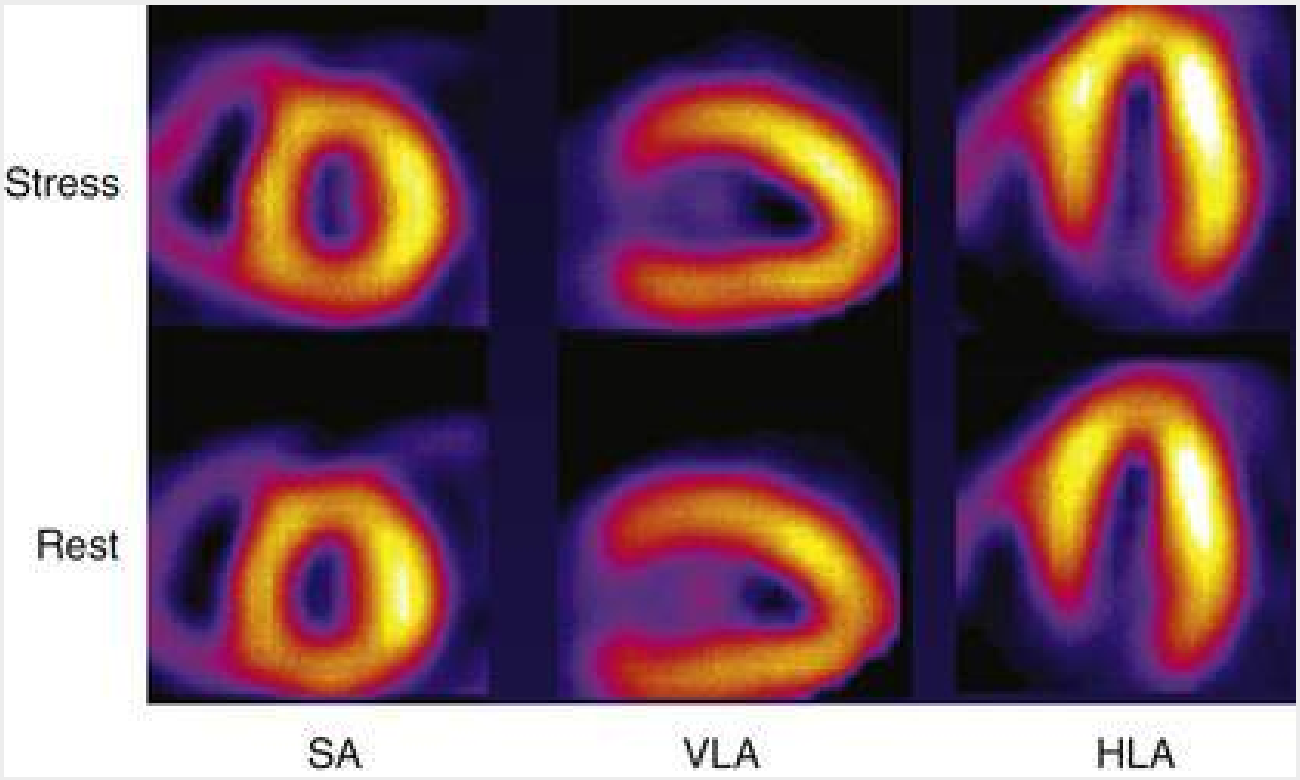


FIGURE 16.32 SPECT perfusion images obtained during stress and at rest in a patient with heart failure. The images depict a dilated left ventricle but with normal perfusion patterns, suggesting a low likelihood that CAD is the cause of heart failure. *HLA,* Horizontal long axis; *SA,* short axis; *VLA,* vertical long axis.

Endothelial Dysfunction.

Abnormalities in myocardial perfusion detected by SPECT MPI have been demonstrated in patients with coronary endothelial dysfunction, in the absence of "significant" epicardial vessel stenosis. That these perfusion findings represent true abnormalities in coronary flow reserve is supported by studies showing improvement in perfusion on follow-up MPI after treatment with medical therapies directed at improving endothelial function.[5] Further support for this concept comes from CMR studies demonstrating blunted subendocardial coronary flow reserve in patients with angina and normal coronary arteries[37] (**see Chapter 17**).

Sensitivity and Specificity of Myocardial Perfusion Imaging

ASNC imaging guidelines summarize sensitivity and specificity data from many studies involving patients undergoing exercise SPECT imaging.[5] Sensitivity to detect CAD was 87% (range, 71% to 97%) in this pooled analysis, and specificity to rule out CAD was 73% (range, 36% to 100%). Few if any of these studies incorporated ECG-gated SPECT imaging of regional function or attenuation correction, techniques that appear to enhance specificity. For example, in one study of women undergoing coronary angiography, specificity was improved from 76% to 96% when gated SPECT ^{99m}Tc-sestamibi imaging was used compared with nongated SPECT ^{201}Tl imaging.[5]

Influence of Perfusion Tracer on CAD Detection

Despite the expectation of improved diagnostic accuracy with use of ^{99m}Tc-based agents, on the basis of more favorable attributes as a radioisotope for gamma camera imaging compared with ^{201}Tl, studies comparing the widely used agents have not shown significant improvement in sensitivity or specificity. An exception is the improved specificity in women using ^{99m}Tc-sestamibi compared with ^{201}Tl. Thus the choice of radiotracer for MPI does not notably affect the discrimination between the presence and

absence of CAD. Studies often include participants who may not fully represent those most challenged by imaging. The ^{99m}Tc-based agents, with their greater photon energy, would be expected to offer improved performance in obese patients and those with large breasts, as well as allowing the option of higher-quality gated images.

Influence of Automated Quantitation of Myocardial Perfusion Images on CAD Detection

Both intra- and interobserver variability in the visual analysis of myocardial perfusion images may be significant. Several methods of quantitative analysis of MPI have been developed[1,5] to reduce the variability in reading by "objectifying" image analysis, comparing regional uptake values against a database of normal values. Automated quantitative analysis systems are incorporated into most SPECT camera computer equipment. Some of the most common are Emory Toolbox, Cedars QPS, and 4D-MSPECT[1] (**Fig. 16.33**). Although published data do not clearly demonstrate improved sensitivity or specificity of these programs over visual analysis for CAD detection, such data arise from expert centers, often where the quantitative software was developed, and the visual analysis data are derived from experienced readers in laboratories with excellent quality control. In practice, use of contemporary quantitative programs can improve image acquisition quality as well as interpretation. Some programs incorporate motion-sensing algorithms that interrogate the raw data and alert the technologist that motion correction may be needed.

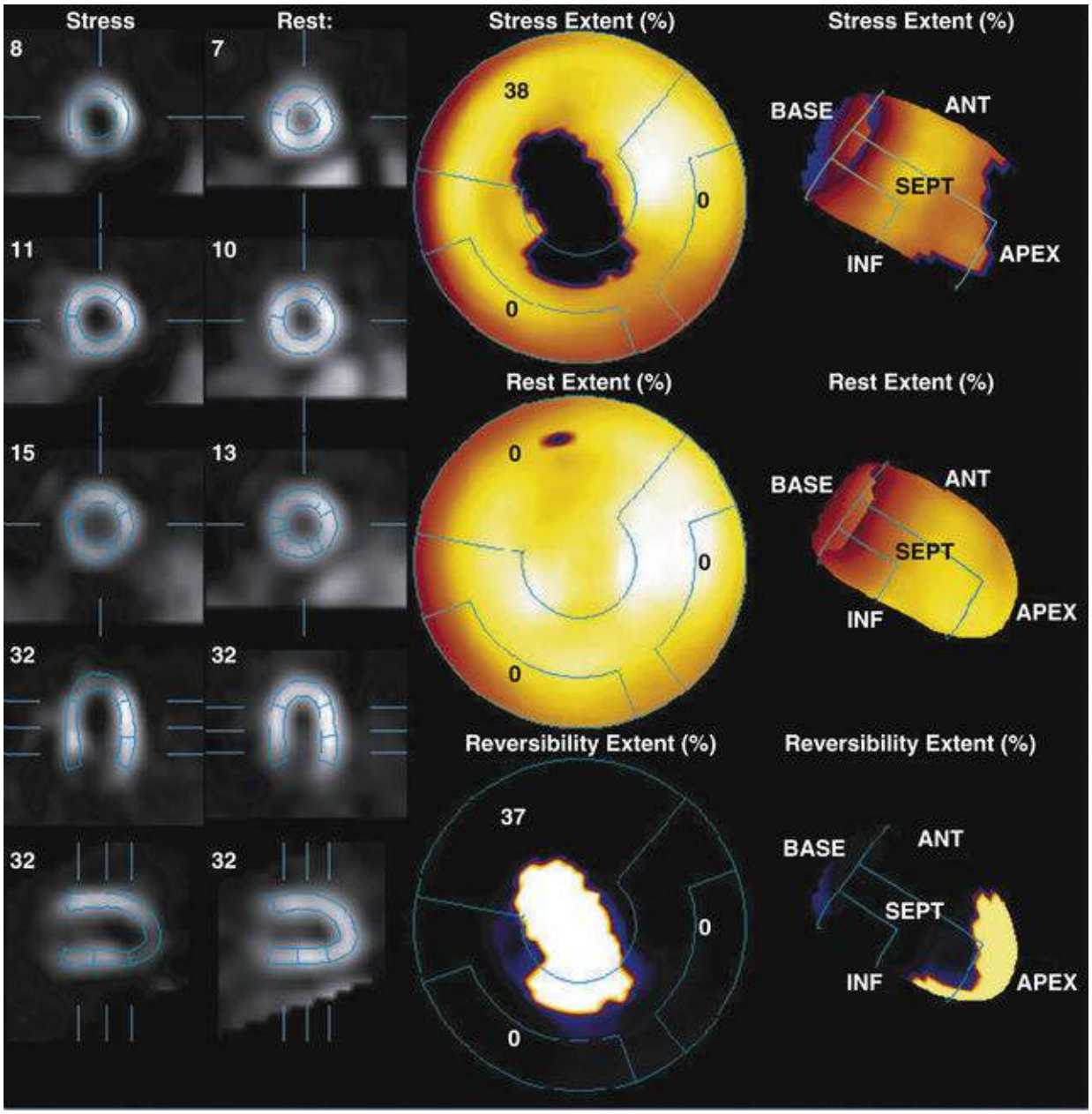


FIGURE 16.33 Automated quantitative analysis software display. Selected short- and long-axis tomograms from stress and rest studies (*two left columns*) are automatically segmented and scored. Bull's-eye plots are created (*third column*) representing the stress (*top*) and rest (*middle*) data and demonstrate a large apical reversible defect. The *bottom* bull's-eye plot displays the extent of ischemic myocardium (*white area*), which measures 23% of the total myocardium. The bull's-eye information also is displayed in a three-dimensional format (*right column*, *top*, *middle*, and *bottom*). Numbers on the bull's-eye maps represent the percentage of the vascular territory that is abnormal. *ANT,* Anterior; *INF,* inferior; *SEPT,* septal. (Images courtesy Guido Germano, PhD.)

Pharmacologic Stress Testing for Detecting CAD

Reports examining the sensitivity and specificity of vasodilator pharmacologic stress combined with MPI for the detection of CAD have achieved results similar to those reported with exercise stress. A pooled analysis involving 2465 catheterized patients in 17 studies[5] demonstrated sensitivity of 89% and specificity of 75%, similar to values from exercise SPECT MPI studies.

The more powerful hyperemic stress response achieved with vasodilator stress versus exercise might be expected to result in improved sensitivity to detect CAD, particularly more moderate stenoses. Such improvement has not been demonstrated, however, possibly because of the "roll-off" property of the common perfusion tracers, caused by diffusion limitation at hyperemic blood flow levels[4] (**see Fig.**

16.21). Thus the more favorable hyperemic stress achieved with pharmacologic stress is offset by the lack of linear tracer uptake in the areas with the highest flow.

The diagnostic ability of dobutamine stress imaging appears to be generally similar to that of other pharmacologic and exercise stress modalities for the detection of CAD.[5] However, because maximal coronary flow reserve is not achieved as often as with vasodilator pharmacologic stress, and side effects are substantial, dobutamine is recommended only when adenosine, dipyridamole, or regadenoson is contraindicated, such as in a patient with important reactive airways disease.

Effect of Submaximal Exercise Performance on CAD Detection

The sensitivity of MPI to detect CAD is optimized by achieving the highest possible level of oxygen demand to stimulate the greatest increment in coronary flow reserve. In exercise ECG testing, sensitivity to detect CAD falls significantly if greater than 85% of maximum predicted heart rate for age is not achieved[23] (**see Chapter 13**). Because perfusion heterogeneity usually develops at a lower degree of supply-demand mismatch than ECG changes, the sensitivity of MPI to detect CAD is maintained at somewhat lower workloads.[5] However, the extent and severity of reversible perfusion defects may be diminished at submaximal versus maximal workloads, which may affect the prognostic value of the test.

Thus the selection of a stress protocol can be summarized as follows. Exercise is the preferred stressor because it allows the optimal potential association of symptoms with perfusion abnormalities. The use of exercise also allows incorporation of validated stress test criteria such as the DTS, heart rate reserve, or heart rate recovery with the MPI data.[23] For patients who cannot exercise adequately, vasodilator stress with adenosine, dipyridamole, or regadenoson is the procedure of choice; dobutamine is used for patients with a contraindication to the vasodilators.[24] For patients who begin exercise but do not reach 85% of maximum predicted heart rate for age, or who do not reach an appropriate symptomatic endpoint, isotope injection at stress can be withheld, the exercise portion of the test terminated, and vasodilator stress performed to optimize diagnostic and risk stratification information.

Defining the Extent of CAD

In formulating a management strategy for patients, it is important to determine the *extent* of disease rather than only the presence or absence of disease. The term *extensive CAD* refers to angiographic patterns of CAD that have prognostic significance and suggest treatment benefit from revascularization, such as left main or severe three-vessel CAD involving the proximal LAD coronary artery.

Detecting Multivessel CAD

SPECT MPI is limited by the *relative* nature of the perfusion information: If all areas are hypoperfused in the presence of three-vessel CAD, the least hypoperfused area appears normal, and the true extent of CAD may be underestimated. However, incorporation of other findings, including regional functional abnormalities, can be used to estimate more correctly the probability of disease extent.

Wall motion abnormalities on poststress gated SPECT images may be of benefit in the detection of extensive CAD. Incorporating the finding of poststress wall motion abnormality on gated SPECT imaging with the degree of perfusion abnormality allows improved sensitivity for detection of proximal severe LAD stenoses or multivessel disease related to 90% or greater proximal stenoses.[5] Numerous reports suggest that nonperfusion signs such as lung uptake of ^{201}Tl after stress or transient ischemic dilation raise the probability of multivessel CAD for any given extent of perfusion abnormality.[5]

Another approach with increasing validation is measurement of myocardial flow reserve (MFR, the

ratio of stress to rest MBF) using PET technology. This can be done using available perfusion tracers such as ^{82}Rb. In a study of 120 patients undergoing stress ^{82}Rb perfusion imaging and coronary angiography, the MFR data were more powerful than the stress perfusion pattern at discriminating between the presence and absence of three-vessel CAD, and this measure was an independent predictor of the presence of three-vessel CAD.[38]

Findings unrelated to imaging also are useful in enhancing the diagnosis of left main or three-vessel CAD. The development of greater than 2 mm of ST-segment depression or hypotension on ECG treadmill testing increases the likelihood of left main or three-vessel CAD.[23]

Detection of CAD in Women

The detection of CAD by exercise ECG testing can be challenging in women[32] (**see Chapter 89**). The use of ^{201}Tl for detecting CAD in women is limited by potential artifacts associated with breast attenuation, resulting in false positives and reduced specificity. The use of ^{99m}Tc-labeled tracers should improve specificity because these agents are associated with slightly less tissue attenuation, as demonstrated in a study comparing ^{201}Tl SPECT with ^{99m}Tc-sestamibi–gated SPECT for the detection of angiographic CAD.[4] Incorporation of gated SPECT sestamibi imaging resulted in a specificity of 92%, versus 67% with ^{201}Tl (**see Fig. 16.11**).

Detection of CAD in Valvular Heart Disease

Several studies have evaluated the use of MPI in the assessment of concomitant CAD in patients with valvular heart disease; most involved patients with aortic stenosis. Sensitivity of MPI has ranged from 61% to 100%, with specificity of 64% to 77%.[5] Although it is potentially useful in select patients to assist in symptom evaluation, these performance characteristics are not sufficient to preclude the use of coronary angiography to define the presence of CAD in patients being considered for surgery (**see Chapters 67 to 69**).

Patients with Established Coronary Artery Disease

Several potential roles for SPECT MPI in patients with established CAD are recognized. Clinical questions may remain after angiography regarding the “physiologic significance” of stenotic lesions. The results of stress-rest SPECT MPI correlate generally with invasive measures of coronary flow reserve. Moreover, improvement of ischemia on SPECT imaging is a common finding after successful percutaneous coronary intervention (PCI), suggesting that SPECT MPI can identify the “culprit” ischemic lesion.[5]

Imaging After Coronary Artery Bypass Surgery.
In patients in whom recurrent symptoms develop after coronary artery bypass graft (CABG) surgery, SPECT MPI can accurately detect the presence and location of graft stenoses, even if the symptoms are atypical for ischemia. In symptomatic post-CABG patients, such information can guide the need for catheterization and intervention.

A number of studies have concordantly demonstrated the value of SPECT MPI in risk stratification of patients after CABG surgery, especially late, even in the absence of symptoms.[5] The extent of perfusion abnormality is related to the subsequent risk of cardiac death and nonfatal MI, and SPECT information

has incremental predictive value over clinical and stress data. Because the risk of cardiac events generally is low in the early years after CABG, routine stress MPI for detection of ischemia in an asymptomatic patient is considered a “rarely appropriate” indication for testing within 5 years after CABG by appropriate use criteria.[39]

Imaging After Percutaneous Coronary Intervention.

Exercise MPI is superior for detecting the presence and location of restenosis after PCI compared with exercise ECG, and current guidelines consider stress imaging in symptomatic patients after PCI as appropriate.[39] The extent of SPECT MPI abnormality in patients studied after PCI is associated with the subsequent risk of cardiac death or MI on long-term follow-up, even late after PCI, and this appears to hold true in patients even in the absence of symptoms. Thus, although routine assessment of asymptomatic patients after PCI with SPECT MPI is considered “rarely appropriate” within 2 years after PCI, or is considered “may be appropriate” more than after 2 years after PCI,[39] important information may be gleaned by imaging in symptomatic patients to guide decisions for reintervention.

Very early after PCI, SPECT MPI may demonstrate a mild reversible defect in the territory of the treated vessel (although less severe than before PCI).[5] This defect may be caused by delayed return of full coronary flow reserve after PCI, representing a true physiologic phenomenon.

Detection of Preclinical CAD and Risk Stratification in Asymptomatic Patients

Because sudden cardiac death is too often the first manifestation of CAD, interest in screening populations for CAD or for CAD risk is considerable. On the basis of Bayesian principles, the low prevalence of CAD in the general asymptomatic population results in low predictive value for a positive test result, although negative predictive value (NPV) is high. Current guidelines and appropriate use criteria do not recommend routine stress MPI in asymptomatic populations.[5,39]

A key question in considering testing such as SPECT MPI in asymptomatic populations is how the information will be used to manage or to reduce risk. Current guidelines suggest aggressive risk factor reduction therapy in those at high clinical risk for the development of vascular disease.[31] Whether further intensification of risk factor reduction in the patient with an abnormal imaging test, or diminished aggressiveness of risk factor reduction with a normal MPI study, results in improved outcomes is unproven and worthy of study.

Patients with diabetes are at significant risk for CAD development and cardiac events. An emerging body of literature suggests that a substantial proportion of asymptomatic diabetic patients have abnormal SPECT MPI studies, and that such patients may be at even higher risk for events over time. Studies suggest that results of SPECT MPI studies are abnormal in 20% to 40% of asymptomatic diabetic patients, often with evidence of inducible, silent ischemia.[40] SPECT MPI demonstrates substantial risk value in stratification in patients with diabetes, with risk being higher for any given perfusion abnormality than in nondiabetic patients. However, a randomized trial of screening asymptomatic diabetic patients with stress SPECT MPI showed no differences in outcomes during long-term follow-up between those who were screened and those not screened, with event rates low in both groups.[40] Thus, appropriate use criteria at present do not suggest the need for routine screening in asymptomatic diabetic patients with stress SPECT MPI.[39]

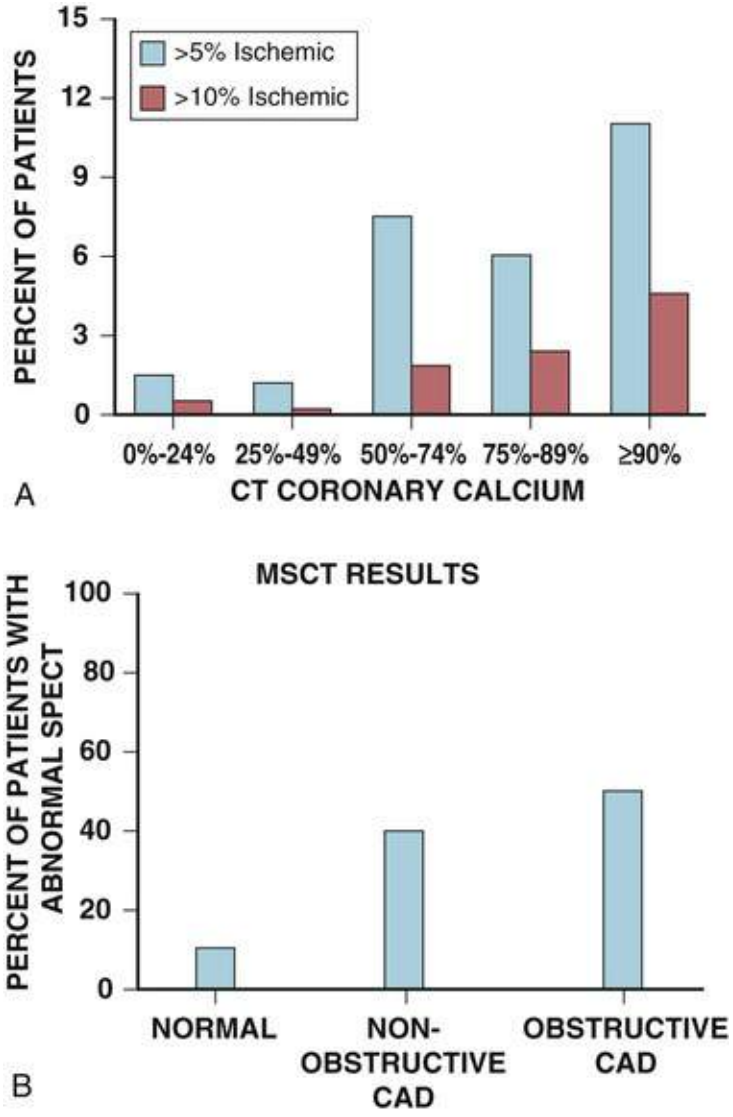
Myocardial Perfusion Imaging After CT Coronary Calcium Imaging or CT

Angiography

With the growing availability and use of noninvasive CT cardiac imaging (**see Chapter 18**), clinicians now often see patients with substantial coronary artery calcium (CAC), raising the possibility of multivessel CAD, or with apparent moderate or even severe stenoses seen on CT coronary angiography, raising questions about physiologic significance and risk stratification.

SPECT MPI and Coronary Calcium Imaging

Although extensive CAC and a high CAC score are indicative of atherosclerosis, studies to date have suggested that even extensive CAC is associated with important myocardial perfusion abnormalities in only a minority of patients. In one study of more than 1000 patients (approximately 50% of whom were asymptomatic),[41] only 10% of those with the highest CAC scores (Agatston score >400) had abnormal perfusion on stress SPECT MPI, and only 5% had "high-risk" SPECT MPI perfusion patterns warranting consideration of the potential benefit of revascularization (**eFig. 16.13**). Thus, although the extensive CAC on CT is well validated to represent subclinical atherosclerosis deserving of aggressive risk factor modification, it does not always indicate obstructive stenoses resulting in reduction in coronary flow reserve. On the basis of this concept, stress SPECT MPI is considered to be an appropriate test to determine the need for and potential benefit of catheterization and potential revascularization after CT demonstration of CAC, when baseline coronary heart disease risk is high and the Agatston score is greater than 100.[39] With lower baseline risk and lower Agatston scores, SPECT MPI is considered rarely appropriate.[39]



EFIGURE 16.13 **A,** In a study of 1195 patients without known CAD who underwent both SPECT perfusion imaging and assessment of coronary calcium by computed tomography (CT), the *x* axis categorizes patients by the age-corrected percentile of coronary calcium. Even when coronary calcium at a level greater than 90% for age is present, only 11% of patents had ischemia involving more than 5% of the left ventricle on SPECT, and only approximately 5% of such patients had ischemia involving more than 10% of the left ventricle. **B,** Prevalence of an abnormal SPECT perfusion study based on results of multislice CT (MSCT) angiography. Even when "obstructive" CAD (stenosis >50%) is confirmed by CT angiography, abnormal perfusion is present in only approximately 50% of patients. (**A,** Modified from Berman DS, Wong ND, Gransar H, et al. Relationship between stress-induced myocardial ischemia and atherosclerosis measured by coronary calcium tomography. J Am Coll Cardiol 2004;44:923; **B,** modified from Schuijf JD, Wijns W, Jukema JW, et al. Relationship between noninvasive coronary angiography with multi-slice computed tomography and myocardial perfusion imaging. J Am Coll Cardiol 2006;48:2508.)

Refining Risk Stratification by Incorporating Both CT Calcium Imaging and SPECT MPI.
Substantial literature now documents that patients with CAC, especially if extensive, are at higher risk for cardiac events over time compared with those with no CAC. However, many with extensive CAC exhibit normal stress perfusion on MPI, a finding that extensive data suggest is associated with low risk. How can these seemingly contradictory bodies of literature be reconciled? It is important to understand that "high risk" is a relative term; that is, patients with extensive CAC are at higher risk than those without CAC, but among those with extensive CAC, most will still not experience cardiac events. For example, in the Multi-Ethnic Study of Atherosclerosis (MESA), there was a clear gradient of risk as

CAC scores increased, but the absolute risk of events was low (approximately 1%/yr even among persons with high calcium scores)[42] (**see Chapter 18**). Therefore, combining data from CAC and SPECT MPI may provide a refinement of risk stratification. Conceptually, those patients with no CAC and normal SPECT MPI findings should have the lowest risk, and those patients with both evidence of CAC and abnormal findings on SPECT MPI the highest risk. Patients with either CAC or SPECT MPI abnormalities should have an intermediate risk. Thus, information from the two testing modalities may be complementary in refining the risk assessment of future coronary events, thereby curtailing the aggressiveness of primary prevention. Studies are ongoing in this regard.

SPECT MPI After CT.

With the growing availability and technical evolution of multidetector CT angiography, clinicians may now be faced with new questions about the physiologic significance of noninvasively detected coronary stenoses. Whereas CT angiography data demonstrate high sensitivity and moderate specificity to detect or to rule out obstructive stenoses, the spatial resolution is still not of a caliber such that accurate determination of the severity of an individual stenosis is consistently reliable or quantifiable, particularly in the intermediate range. Moreover, in a coronary segment that is heavily calcified, stenoses are particularly difficult to detect, to rule out, or to quantitate. SPECT MPI can assess the physiologic significance of a stenosis during stress and potentially link the perfusion abnormality to the patient's symptoms. This concept gives pause to moving directly to invasive angiography (and potential PCI) after CT angiography and suggests that assessment of the physiologic significance of CT angiography–defined stenoses may be important for clinical decision making. The development of noninvasive assessment of fractional flow reserve using fluid dynamic concepts and CT angiography is attempting to address this issue (**see Chapter 18**).

Selection of Initial Testing Strategy for Patients with Suspected CAD

CT angiography has evolved substantially, is a relatively rapid test to perform with modest radiation exposure using contemporary techniques, and has a very high NPV to rule out CAD. A fundamental question emerges as to whether it is optimal initially to evaluate a patent with symptoms suggestive of CAD with an anatomic strategy (CT angiography), to identify the presence/extent or absence of anatomic CAD, or with a functional stress test strategy, to identify the presence/extent or absence of stress-induced ischemia. This question was addressed by the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial, in which over 10,000 patients with symptoms suggestive of CAD/ischemia were randomized to an initial assessment by either CT angiography or functional stress testing (ECG, MPI, or echocardiography) and followed for an outcome composite incorporating death from any cause, MI, hospitalization for unstable angina, and major complication of procedures or testing.[43] PROMISE was a “pragmatic effectiveness” trial, in that the results were provided to the referring clinician to inform clinical decisions (i.e., decision making was not driven by protocol). After an average of approximately 2 years of follow-up, there was essentially no difference in the primary endpoint outcome composite, suggesting that the initial assessment strategies were associated with similar outcomes. Some differences did emerge among the secondary outcomes. The CT angiography strategy was associated with fewer downstream catheterizations with normal coronary results, suggesting fewer false positives, leading to what would be an unnecessary catheterization compared to functional testing. However, CT angiography was also associated with substantially more downstream invasive catheterization procedures and almost twice as many revascularization procedures, with the previously noted absence of outcome difference.

The results of PROMISE do suggest that an anatomic strategy using CT angiography is an acceptable alternative to functional stress testing. In practice, choice of an initial testing strategy should be informed

not only by results of trials such as PROMISE, but also by local expertise and quality as well as by the appropriateness of any testing given the clinical scenario.

Acute Coronary Syndromes

Application of Radionuclide Imaging: Answering the Clinical Questions

For patients with suspected ACS, radionuclide imaging techniques can play a diagnostic role (is the clinical presentation caused by ischemia and CAD?) and can also provide prognostic information. Among patients who present with an ACS and ST-segment depression or elevation (**see Chapters 59 and 60**), the typical role of imaging is in the stabilized patient after angiography and PCI, to provide risk stratification information to drive management strategies aimed at improving natural history.

Suspected Acute Coronary Syndromes in Emergency Department

Many patients presenting to the ED with symptoms suggestive of ACS, but with nondiagnostic findings on initial ECG and biomarker assays, are admitted to an observation unit for serial biomarker studies and possible stress testing. ^{99m}Tc-based perfusion agents may be administered to a patient in the ED at rest, with images acquired 45 to 60 minutes later,[5] and because redistribution is minimal, images reflect MBF at injection. In this setting, NPV for ruling out MI is high in all observational series.[5] Patients with positive MPI have a higher risk of cardiac events during the index hospitalization as well as during follow-up (**Fig. 16.34**). Thus, rest SPECT MPI can provide information to assist triage decisions for or against hospital admission from the ED.

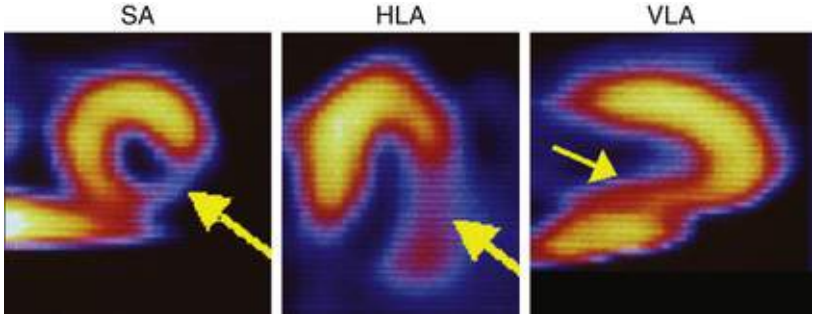


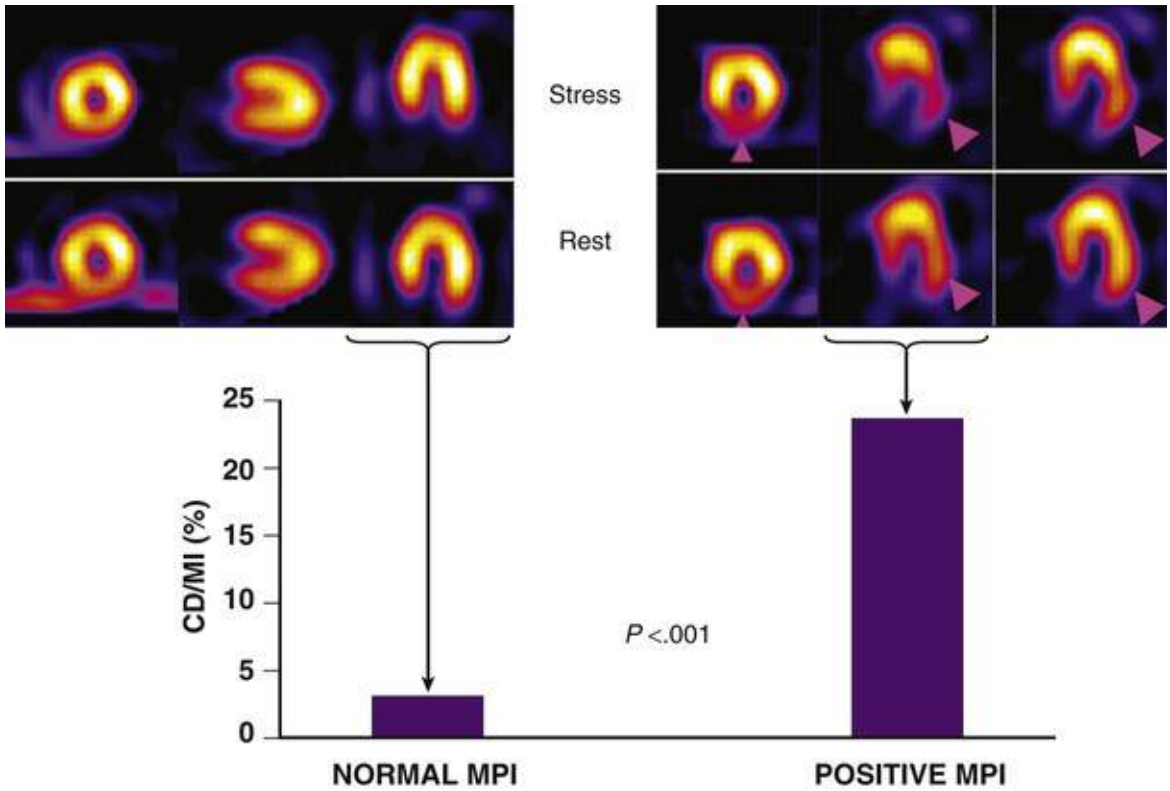
FIGURE 16.34 Example of rest SPECT images in a patient evaluated in the ED with chest pain and nondiagnostic initial electrocardiographic findings. A severe inferolateral resting perfusion defect (*arrow*, all images) suggests ischemia at rest or infarction in that territory. Subsequent emergent angiography demonstrated an occluded left circumflex artery. *HLA,* Horizontal long axis; *SA,* short axis; *VLA,* vertical long axis.

The Emergency Room Assessment of Sestamibi for Evaluation of Chest Pain (ERASE Chest Pain) trial in 2475 patients with symptoms suggestive of ACS randomly assigned them to receive an MPI strategy or usual ED care. A significant 20% relative reduction in unnecessary hospital admission was reported for patients ultimately found not to have ACS of those assigned to MPI (see Classic References, Udelson). The imaging data were among the most powerful factors associated with the decision to discharge the patient appropriately from the ED.

Thus, evidence from randomized controlled trials (RCTs) suggests that incorporation of SPECT MPI in ED evaluation of patients with suspected ACS but no definitive ECG changes can improve triage decisions. Rest MPI in these patients may be appropriate.[44]

Non–ST-Segment Elevation Myocardial Infarction and Unstable Angina

Guidelines recommend that patients with high-risk clinical characteristics in the setting of unstable angina undergo direct catheterization[30] (**see Chapter 60**). Contemporary clinical trials suggest that patients with positive biomarker assays or with a high-risk Thrombolysis in Myocardial Infarction (TIMI) score benefit in terms of outcome from an "invasive" strategy.[30] For patients with intermediate or low clinical risk (i.e., with "medically stabilized" unstable angina), stress MPI has been shown to have substantial risk stratification value and is considered an appropriate test.[44] Patients without ischemia or infarction, especially in the presence of preserved LV function, have a low-risk outcome, suggesting that such patients can be managed conservatively without catheterization, whereas patients with significant inducible ischemia are at high risk and thus are selected for intervention (**eFig. 16.14**).



EFIGURE 16.14 SPECT perfusion imaging in patients after medical stabilization of unstable angina. **Upper left,** Normal study findings, associated with a low risk of cardiac events during follow-up, suggesting that such a patient can be managed conservatively without catheterization but with aggressive secondary preventive strategies. The *bottom graph* is a summary of predictive values of SPECT imaging in the aftermath of unstable angina from multiple studies. Similar to the concepts in populations with stable chest pain, abnormal perfusion imaging after unstable angina is associated with a substantial increase in the risk of cardiac death or myocardial infarction (CD/MI) during follow-up. **Upper right,** Example of a high-risk stress-rest SPECT myocardial perfusion imaging (MPI) study result in the aftermath of unstable angina. Despite the stabilization of symptoms, extensive reversible perfusion abnormalities in the inferior and lateral walls suggest high risk of cardiac death or myocardial infarction, or both, during follow-up. This patient would therefore be managed more aggressively with catheterization and intervention. (Modified in part from Brown KA. Management of unstable angina: the role on noninvasive risk stratification. J Nucl Cardiol 1997;4:S164.)

Although the results of randomized clinical trials, such as Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)–TIMI 18, suggest slight superiority of an invasive approach in patients with unstable angina or non–ST-segment elevation MI (NSTEMI), subgroup analyses indicate that an important proportion of patients may be well managed by the conservative strategy of risk stratification by MPI, followed by more selective catheterization and

intervention. Moreover, a large randomized trial of patients with ACS and positive troponin T reported no difference in outcomes between an invasive strategy and a more selective invasive strategy in which patients were examined for ischemia before proceeding with catheterization while receiving contemporary aggressive medical therapy.[30] Therefore, patients without elevation of troponin or high TIMI risk score may be managed by a more conservative approach with risk stratification using imaging techniques.[30]

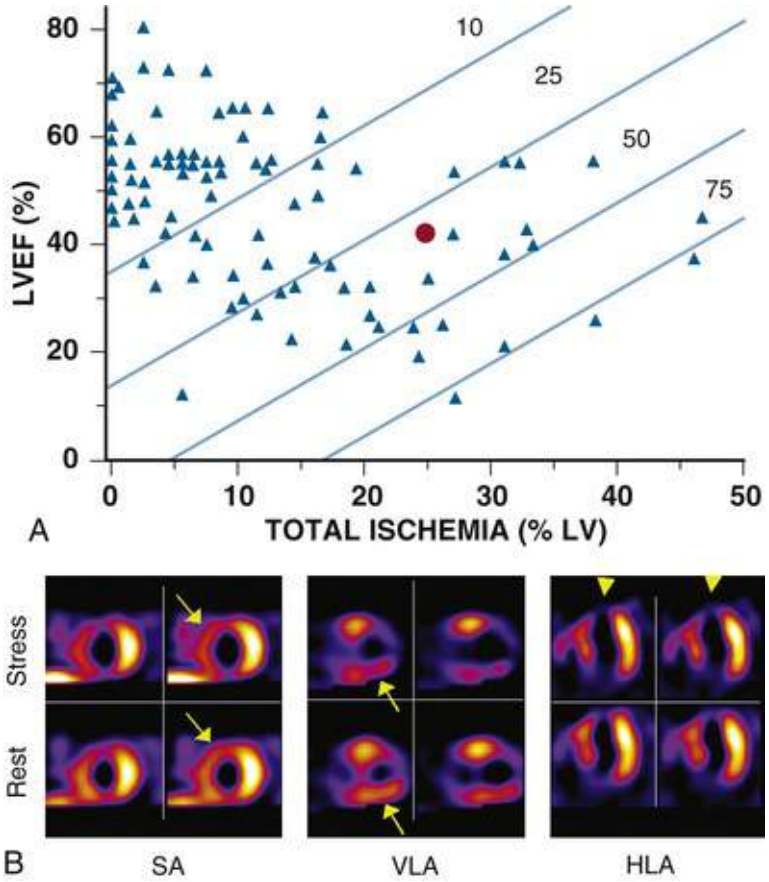
ST-Segment Elevation Myocardial Infarction

Clinical variables such as recurrent ischemia, heart failure, and nonacute arrhythmias during hospitalization for acute ST-segment elevation MI (STEMI) identify a subgroup of patients at high risk in whom catheterization and intervention are indicated, and who have not already undergone primary PCI as the initial approach for their STEMI[44] (**see Chapter 59**).

Assessment of Inducible Ischemia After Acute Myocardial Infarction

Three major determinants of risk after an acute MI are the residual LV function at rest, the extent of ischemic jeopardized myocardium, and the susceptibility to ventricular arrhythmias. Gated SPECT MPI can provide much of this information comprehensively and thus may be an important test in the stable patient after STEMI. Contemporary guidelines suggest that noninvasive assessment of the presence and extent of inducible ischemia is indicated (class I recommendation) for patients who have not already had coronary angiography and do not have other high-risk features that would drive a decision to perform angiography.[45]

Studies in the reperfusion era have reported generally similar results regarding the relation of stress-induced ischemia to post-MI outcomes. In a study of 134 consecutive patients tested within 14 days of an uncomplicated MI, the extent of ischemia on SPECT MPI was the only significant variable associated with a future cardiac event on Cox regression analysis (**eFig. 16.15**). The extent of SPECT ischemia remained strongly correlated with cardiac events in those who received thrombolytic therapy. The quantitated extent of ischemia on adenosine SPECT MPI also has been shown to be an important predictor of cardiac events in post-MI risk stratification. Post-MI patients with extensive inducible ischemia are at high risk for future cardiac events, and interventional management is likely to result in improved outcome.

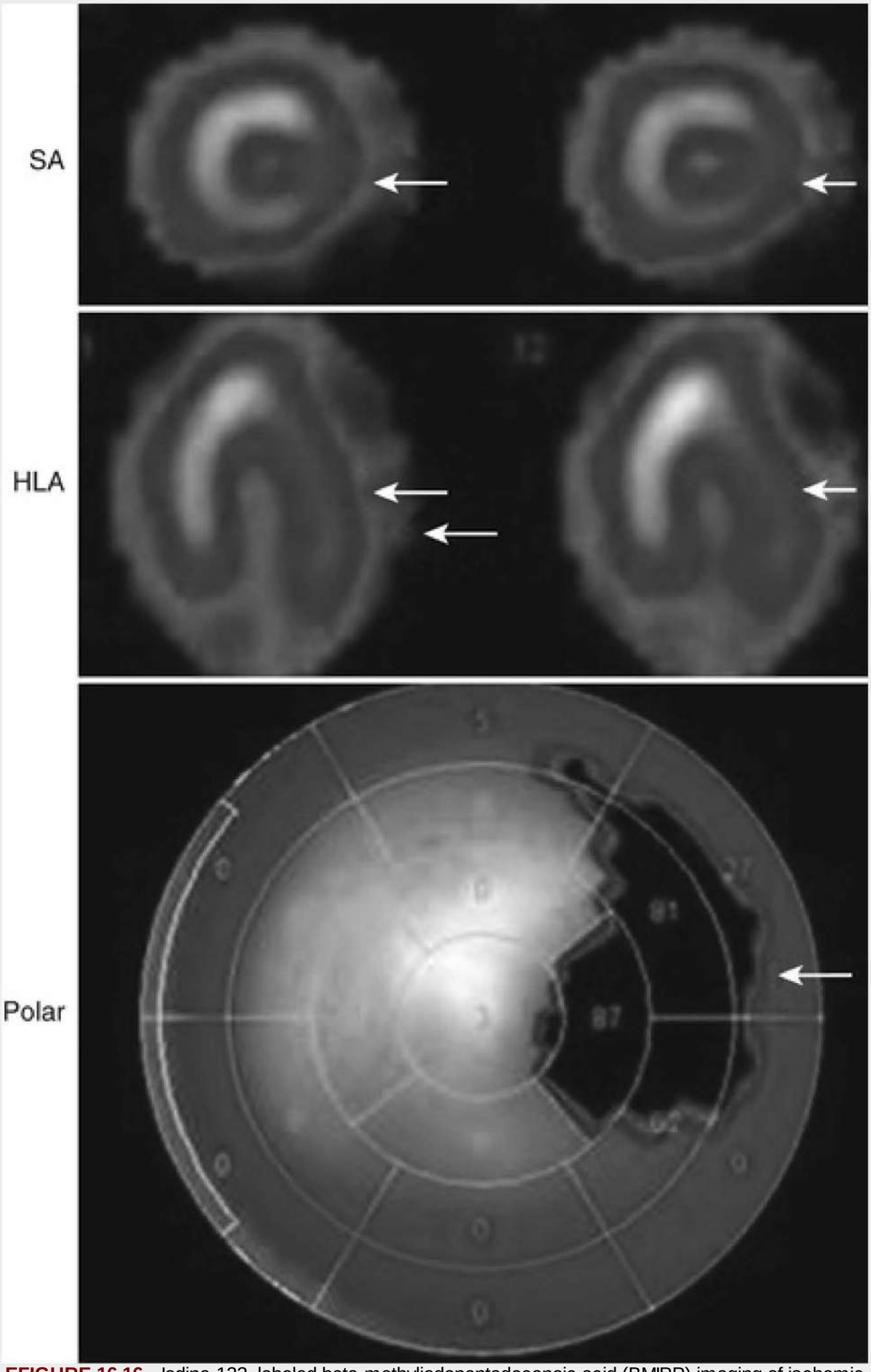


EFIGURE 16.15 **A,** Risk of cardiac event during long-term follow-up after myocardial infarction (MI) is predicted by the combination of infarct size (represented by LVEF) and the extent of reversible ischemia. As the extent of inducible ischemia increases (*x* axis) and the left ventricular ejection fraction (LVEF) decreases (*y* axis), the outcome risk increases. The *blue lines* represent isobars of 10%, 25%, 50%, and 75% risk of an adverse event during post-MI follow-up. (*Large red circle* refers to images in **B**.) **B,** SPECT images obtained in patient studied several days after acute ST-segment elevation MI and medical stabilization. Besides the fixed defect representing the infarct in the anterior wall and apex (*arrowheads*), extensive inducible ischemia is evident both within and remote from the infarct territory (septum and inferior walls, *arrows*), involving 25% of the ventricle. Gated SPECT EF was 38%. On the basis of the data in **A,** there is an approximately 25% risk of a post-MI adverse event (*large red circle* in **A**). *HLA,* Horizontal long axis; *SA,* short axis; *VLA,* vertical long axis. (Modified from Mahmarian JJ, Mahmarian AC, Marks GF, et al. Role of adenosine thallium-201 tomography for defining long term risk in patients after acute myocardial infarction. J Am Coll Cardiol 1995;25:1333.)

Radionuclide Imaging in Acute Coronary Syndromes: Research Directions

Imaging of Ischemic Memory.

A possible future approach to risk stratification in patients with suspected ACS involves the imaging of fatty acid metabolism. As noted earlier, after a regional ischemic insult, abnormalities in fatty acid metabolism may persist long after perfusion has returned to normal, a finding termed ischemic memory. Imaging of fatty acid metabolism may therefore allow assessment of recent ischemia. Uptake of the radiolabeled fatty acid analogue BMIPP has been imaged with SPECT 1 to 5 days after presentation in patients with suspected ACS. SPECT imaging of fatty acid metabolism in patients presenting to the ED with suspected ACS adds incremental value to initial clinical information for assessment of the presence or absence of an ACS[46] (**eFig. 16.16**). Future studies will determine whether such techniques can help guide management decisions.



EFIGURE 16.16 Iodine-123–labeled beta-methyliodopentadecanoic acid (BMIPP) imaging of ischemic

memory in a patient presenting to emergency department with a suspected acute coronary syndrome. **Top row,** Short-axis (SA) tomograms demonstrate a significant lateral wall defect (*arrows*), suggesting prolonged postischemic suppression of fatty acid metabolism, referred to as ischemic memory. **Middle row,** Horizontal long-axis (HLA) images also demonstrate the defect (*arrows*), as does the polar map **(bottom row).** Subsequent angiography demonstrated a severe stenosis of the left circumflex coronary artery. (Modified from Kontos MC, Dilsizian V, Weiland F, et al. Iodofiltic acid I 123 [BMIPP] fatty acid imaging improves initial diagnosis in emergency department patients with suspected acute coronary syndromes: a multicenter trial. J Am Coll Cardiol 2010;256:290.)

Imaging in Heart Failure

Is Coronary Artery Disease the Cause of Heart Failure?

Determination of whether LV dysfunction represents the consequences of CAD or is caused by one of the many other disorders of nonischemic etiology is a critical early step in the management of patients with heart failure (HF). Because CAD is the most common cause of HF in developed countries, noninvasive assessment of myocardial ischemia and viability would identify the subgroup of HF patients who have a potentially reversible degree of LV dysfunction and may benefit from revascularization. Therapeutic interventions that improve dysfunctional but viable myocardium may significantly affect global LVEF, LV remodeling, and survival. The identification of CAD in patients with HF also has implications in secondary prevention strategies, because recurrent MI is a common mechanism of death in HF patients.

Normal stress MPI in a patient with HF and LV dysfunction is highly predictive of the absence of CAD. Studies of MPI for detection of CAD in patients with LV dysfunction have shown high sensitivity but modest specificity[36] (**Fig. 16.35; see also Fig. 16.32**). The modest specificity of MPI to rule out CAD is explained in part by pathologic and CMR studies[47] demonstrating patchy or larger confluent territories of fibrosis or scarring (**see Chapter 17**), manifested as fixed defects on SPECT MPI, in patients with nonischemic cardiomyopathy.

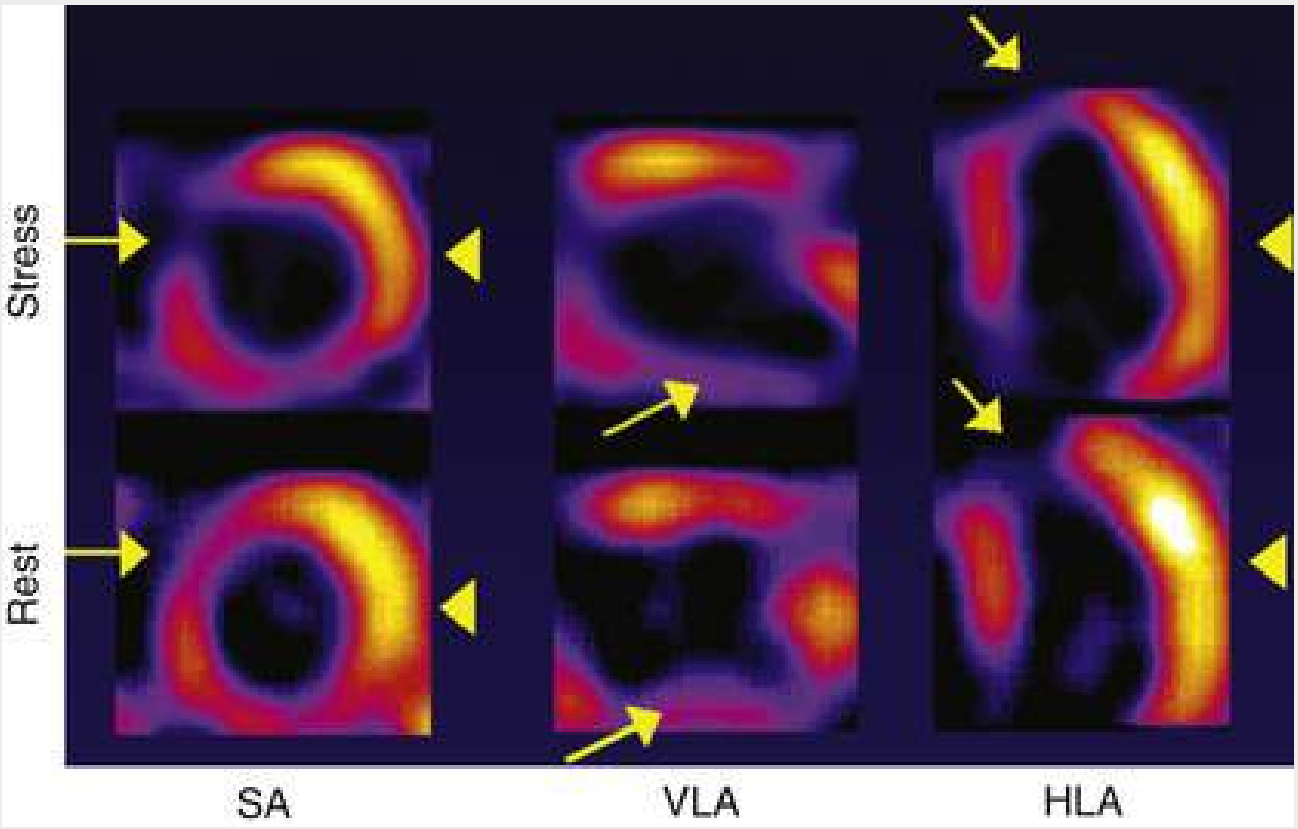


FIGURE 16.35 SPECT perfusion image demonstrating extensive severe fixed defects of the septum, apex, and inferior wall (*arrows*) suggestive of extensive previous myocardial infarction, as well as extensive inducible ischemia of the lateral wall (*arrowheads*). This set of findings strongly suggests that CAD is the cause of the heart failure syndrome observed in this patient. *HLA,* Horizontal long axis; *SA,* short axis; *VLA,* vertical long axis.

Although the presence of any perfusion abnormality is not specific for ruling out CAD, the pattern of perfusion abnormality may assist in the differentiation between CAD and nonischemic etiology of HF. More extensive or more severe perfusion defects, or both, are more likely to represent CAD and ischemic cardiomyopathy, whereas smaller and milder defects are more likely in patients with nonischemic cardiomyopathy.[36,47]

Assessment of Myocardial Viability and the Potential Benefit of Revascularization

A goal in assessing viability is to optimize selection of patients with HF whose symptoms and natural history may improve after revascularization. Data suggest that hibernation and stress-induced ischemia are common in patients with stable HF and LV dysfunction, even in the absence of angina.[47]

The potential for decreased HF symptoms after revascularization correlates with the magnitude of the PET mismatch pattern (i.e., enhanced FDG uptake relative to perfusion).[5] In a meta-analysis of outcome studies after viability imaging, patients with evidence of preserved myocardial viability[48] who underwent revascularization had a substantial reduction in the risk of cardiac death during long-term follow-up compared with those treated medically (**Fig. 16.36**). Revascularization conferred no advantage in patients without substantial myocardial viability. These data suggest that noninvasive imaging of viability and ischemia can potentially play a role in selecting patients for revascularization, with the expectation of ameliorating symptoms and improving natural history. However, this analysis was based on 24 retrospective studies in which there may have been inadequate adjustment for comorbidity and in which the medical management would not be considered adequate in terms of current guidelines recommendations. For example, few if any patients received beta blockers in these cohort studies. This

factor created the equipoise for the prospective STICH (Surgical Treatment of Ischemic Heart Disease) viability substudy, examining the influence of viability (determined by SPECT or dobutamine echocardiography) on outcomes associated with randomization to surgical or medical therapy.[49] In this study of more than 600 patients, viability status did not influence the intervention effect on outcome. This may result from better background medical therapies for patients with HF compared with those used in the older literature.

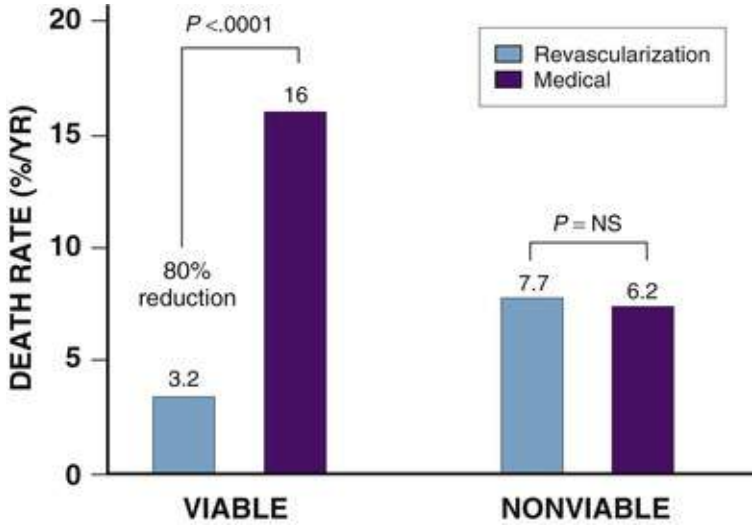


FIGURE 16.36 Data derived from a meta-analysis evaluating outcomes in patients with ischemic left ventricular dysfunction after viability testing. Among patients determined to have predominantly viable myocardium, treatment with medical therapy is associated with a 16% annual risk of cardiac death. Similar patients treated with revascularization have only a 3.2% annual risk of cardiac death, representing an 80% reduction in risk with revascularization. By contrast, patients with predominantly nonviable myocardium exhibit no difference in outcome whether they are treated with medical therapy or with revascularization. These data suggest that noninvasive interrogation of myocardial viability can identify treatment strategies associated with more favorable long-term outcomes. (Modified from Allman K, Shaw L, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. J Am Coll Cardiol 2002;39:1151.)

On the basis of all these data, current HF guidelines consider revascularization as a class IIa indication (level of evidence B) to improve survival in patients with mild to moderate LV systolic dysfunction and significant multivessel CAD or proximal LAD stenosis when viable myocardium is present.[50]

Principles of Assessing Myocardial Viability by Radionuclide Techniques

The radionuclide tracers and techniques most often used to assess viability have been evaluated for their relation to preserved tissue viability by correlation of tracer uptake with histologically confirmed extent of tissue viability.[48] Quantitative analysis of tracer uptake correlates directly with the magnitude of preservation of tissue viability, and tracer uptake represents a continuous variable—that is, the magnitude of tracer uptake directly reflects the magnitude of preserved tissue viability. For a dysfunctional segment or territory, the probability of functional recovery after revascularization is related to the magnitude of tracer uptake, representing the degree of preserved myocardial viability (extent of hibernation or stunning) within that territory. A dysfunctional territory with normal or only mildly reduced tracer uptake thus has a high likelihood of improved function after revascularization. By contrast, a territory with a severe reduction in tracer uptake would represent predominant infarction, and the likelihood of improved function after revascularization would be low (**Figs. 16.37 and 16.38**). The magnitude of potential improvement of global LV function after revascularization is in turn determined by the extent of viable

dysfunctional myocardium.

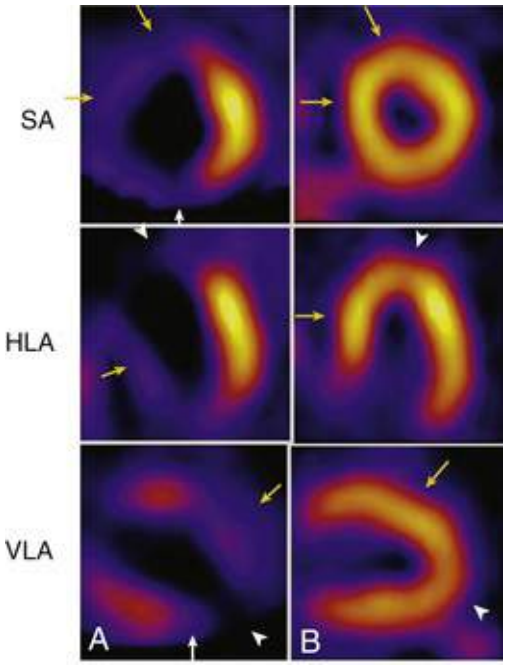


FIGURE 16.37 Resting SPECT perfusion imaging to assess myocardial viability. In column **A,** there are severe resting perfusion defects in the anterior wall and septum (*yellow arrows*), the apex (*arrowheads*), and the inferior wall (*white arrows*), all consistent with predominant infarct, in a patient with extensive CAD and severe LV dysfunction. It is not likely that revascularization would improve outcome or symptoms. In contrast, column **B** demonstrates images from a patient with an occluded proximal left anterior descending artery and severe hypokinesis of the subtended territories, with symptoms of heart failure and some angina. There is normal uptake throughout the anterior wall and septum (*yellow arrows*) as well as in the apex (*arrowheads*), consistent with completely retained viability. The images suggest that revascularization of the territory would be associated with improved regional function and likely improvement in symptoms. *HLA,* Horizontal long axis; *SA,* short axis, *VLA,* vertical long axis.

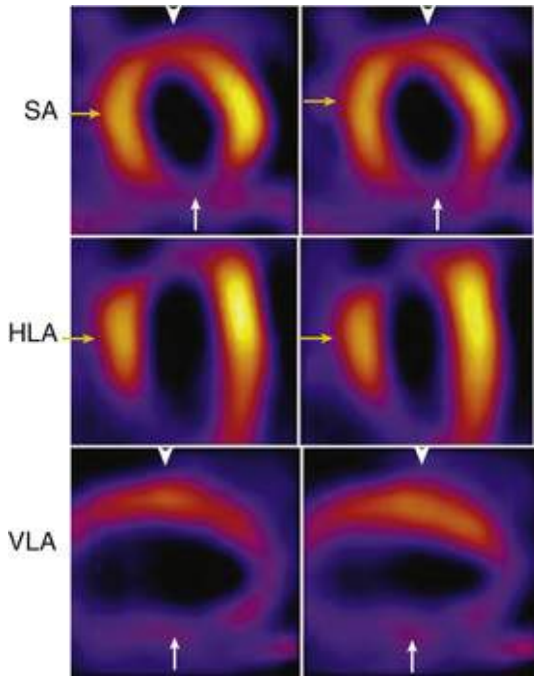
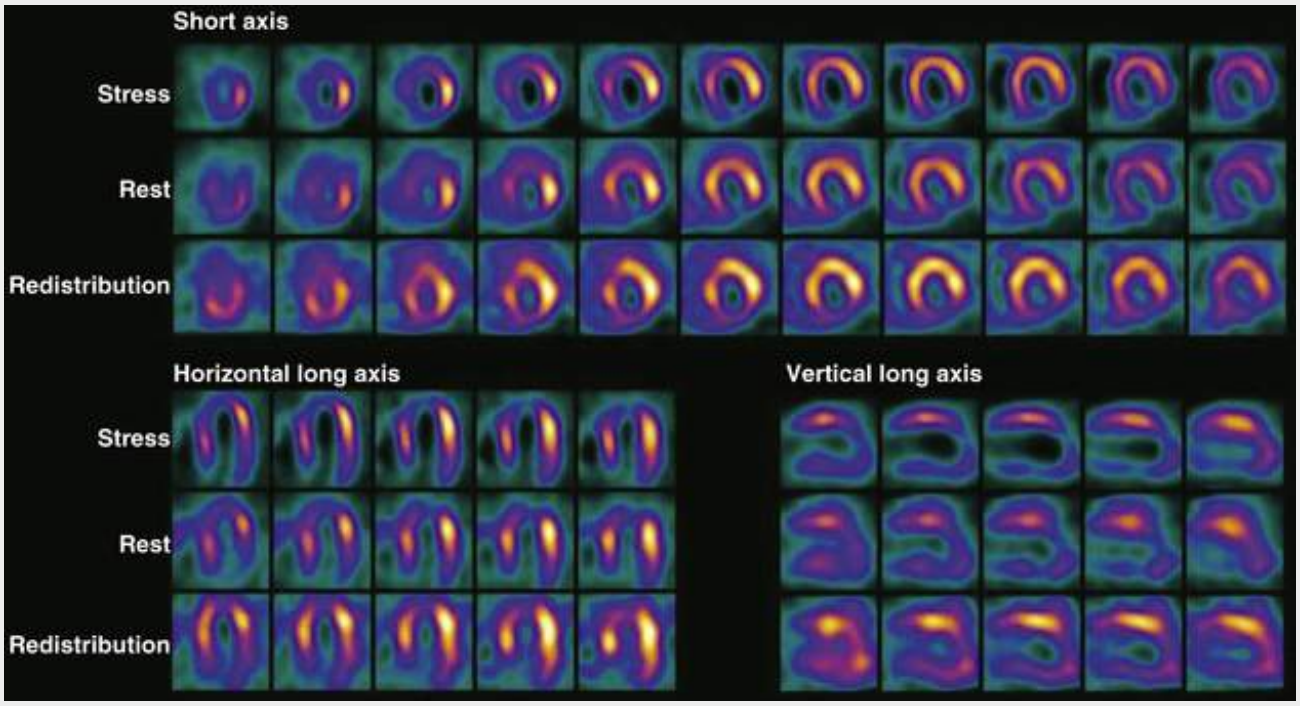


FIGURE 16.38 Resting ^{99m}Tc perfusion imaging to assess myocardial viability. Studies correlating tracer uptake with biopsy specimens have shown that the magnitude of uptake is related to the degree of retained myocyte viability within each territory. In this example, from a patient with multivessel CAD and significant LV dysfunction being considered for revascularization, different territories manifest distinct patterns of uptake and viability in these contiguous slices from the three orthogonal tomographic planes. There is a severe defect in the inferior wall (*white arrows*), consistent with predominant infarct. There is a moderately severe defect in the anterior wall (*white arrowheads*), in which there is clearly more uptake compared to the inferior wall. This would be consistent with an admixture of viable myocardium and infarct in that territory. There is only very mild reduction in tracer activity in the septum (*yellow arrows*), consistent with predominantly retained viability. Uptake in the lateral wall is normal, consistent with retained viability. *HLA,* Horizontal long axis; *SA,* short axis; *VLA,* vertical long axis.

Imaging Protocols for Assessment of Myocardial Viability

Thallium-201.

The presence of ^{201}Tl after redistribution implies preserved myocyte cellular viability. Because the absence of ^{201}Tl uptake on the redistribution images is not a sufficient sign of the absence of regional viability, however, iterations of the standard ^{201}Tl protocol have been investigated[4] to optimize the assessment of regional viability (**eFig. 16.17**). After ^{201}Tl reinjection, approximately 50% of regions with fixed defects on stress-redistribution imaging show significant enhancement of ^{201}Tl uptake, predictive of improvement in regional LV function.[48] The presence of a severe ^{201}Tl defect after reinjection identifies areas with a very low probability of improvement in function.



EFIGURE 16.17 Rest-redistribution thallium imaging performed as part of a dual-isotope technetium-thallium stress imaging protocol in 55-year-old patient with severe heart failure and left ventricular dysfunction (ejection fraction 30%). The initial thallium images demonstrate several areas of reduced blood flow at rest involving the septum, anteroapical wall, and inferior wall. Thallium redistribution imaging 4 hours later demonstrates substantial redistribution of thallium in the septal, anteroapical, and inferior regions of the left ventricle, indicating myocardial viability, with only the basal portion of the inferolateral wall representing irreversibly damaged myocardium. After the thallium redistribution image acquisition, stress imaging with ^{99m}Tc-sestamibi demonstrates inducible ischemia in the septum and anterior wall. However, without the redistribution images, routine stress-rest imaging would have given misleading information about viability because of the apparently irreversible defects in the inferior and anteroapical walls. (From Holly TA, Bonow RO. Assessment of myocardial viability with thallium-201 and technetium-based agents. In Zaret BL, Beller GA, editors. Nuclear Cardiology: State of the Art and Future Directions. 4th ed. Philadelphia: Mosby; 2010, pp 594-607.)

Late redistribution imaging, 24 to 48 hours after the initial stress ^{201}Tl injection, allows more time for redistribution to occur and has good positive predictive value (PPV) for improvement in function. Even with late redistribution imaging, the NPV is suboptimal, because redistribution does not occur in some patients even after a prolonged period, and in addition, image quality may be poor.[4,5] In such patients, ^{201}Tl reinjection after late redistribution imaging may provide further insight into defect reversibility and thus viability.

With *rest-redistribution* ^{201}Tl imaging, images are obtained 15 to 20 minutes after tracer injection at rest, reflecting regional blood flow at rest, and images obtained 3 to 4 hours after redistribution reflect myocyte viability. The finding of a reversible resting defect may identify areas of myocardial hibernation (**eFig. 16.17**). This finding appears to be an insensitive but specific sign of potential improvement in regional function.[4,51]

^{99m}Tc Sestamibi and Tetrofosmin.

The performance of the ^{99m}Tc agents in predicting improvement in regional function after revascularization is similar to that of ^{201}Tl.[5] The key finding to evaluate is the magnitude of tracer uptake in a dysfunctional region. *Normal* uptake is consistent with preserved viability; only *mild* reduction in uptake is consistent with predominantly preserved viability; *moderate* reduction in uptake is consistent with an admixture of viable and infarcted tissue; and a *severe* defect is consistent with predominant infarct. Administration of nitrates to improve blood flow at rest before injection of sestamibi appears to improve slightly the ability of these tracers to detect myocardial viability.[4,51]

PET Blood Flow–Metabolism Mismatch.

The extent of the PET mismatch pattern (enhanced FDG uptake relative to blood flow; **see Fig. 16.28**) correlates with improvement in LV function after revascularization as well as with the clinical course, magnitude of improvement in HF symptoms, and survival after revascularization.[51] Patients with HF and an extensive PET match pattern (diminished blood flow and severe reduction in FDG uptake), representing predominant infarction, are unlikely to benefit clinically from revascularization.

Comparison of Imaging Techniques for Viability Assessment.

On the basis of a meta-analysis evaluating the ability of the various radionuclide techniques to predict improvements in regional function and EF, all the radionuclide techniques (as well as low-dose dobutamine echocardiography; **see Chapter 14**) perform in a relatively similar manner regarding PPV and NPV for improvements in regional function.[48] SPECT techniques appear to be slightly more sensitive, dobutamine echocardiography appears to be slightly more specific, and PET techniques appear to have better accuracy. A randomized trial of patients with moderate LV dysfunction being considered for revascularization randomly allocated to have viability information supplied by either PET imaging or SPECT stress-rest sestamibi imaging found no difference in outcomes during long-term follow-up.[48]

All these data suggest that differences between the imaging approaches to assess viability are small, and that choice of modality should be driven by the available expertise and experience. For patients with more severe LV dysfunction, in whom thinner myocardial walls are often present, an advantage of PET and CMR is their better spatial resolution for imaging thinner objects.

Selection of Patients with Heart Failure for Viability Assessment

Guidelines recommend that patients with HF and active angina benefit from revascularization and thus should be referred directly for angiography.[50] In some situations, subsequent noninvasive definition of regional viability and ischemia may be important to plan the revascularization strategy when the anatomy is known.

For patients with HF and no angina, studies suggest that ischemia and viability may be present in a significant proportion of such patients[51] who have potential benefit from revascularization. For most such patients with HF, a search for underlying ischemia and viability would be an appropriate clinical strategy at some point in their evaluation.[47] The imaging data can be used in decision making to help balance the risks and benefits of revascularization in a patient with HF and LV dysfunction by supplying information on potential benefit of a revascularization strategy.

Assessment of Left Ventricular Function in Heart Failure

For patients with the clinical syndrome of HF, the distinction between those with preserved and those with impaired systolic function has important clinical relevance. Clinical trials evaluating the use of such therapeutic agents as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and beta blockers have focused on the subpopulation of HF patients with impaired systolic function[50] (**see Chapter 25**). Thus accurate determination of LV function in a patient with HF defines the evidence-based therapeutic approach that should be undertaken.

On the basis of the quantitative and reproducible nature of the EF results, equilibrium RVG techniques have been used in large clinical trials to identify systolic dysfunction.[5,51] In contemporary practice, ECG-gated SPECT is often used for determination of systolic function. The simultaneous assessment of LV systolic function as well as stress and rest perfusion by gated SPECT MPI can provide a range of information relevant to the care and clinical decision making for patients with HF, including the state of

LV function, the probability of CAD as the cause of HF, and the presence and extent of viability and ischemia.

Imaging in Inflammatory and Infiltrative Cardiomyopathies

Myocarditis

Inflammatory injury to the myocardium by infective agents, postinfective immune processes (e.g., Chagas disease, rheumatic carditis), hypersensitivity, and autoimmune conditions can cause myocardial dysfunction. The clinical manifestation of such an inflammatory process is acute myocarditis and cardiac allograft rejection (**see Chapters 27 and 79**). Because myocyte necrosis is an obligatory component of myocarditis (cellular infiltrates, predominantly lymphocytes and macrophages, clustered around necrotic myocytes), radionuclide-labeled agents that target some component of the damaged myocyte have been investigated. Indium-111 (^{111}In)–labeled antimyosin antibody, which specifically targets myosin heavy chain, has been used for the detection of necrosis associated with myocarditis and heart transplant rejection. In patients with biopsy-positive myocarditis, the sensitivity of an antimyosin scan is approximately 95%, with NPV of approximately 95%. However, the specificity and PPV of antimyosin imaging are modest, in the 50% range.[52]

Cardiac Sarcoidosis

Cardiac involvement with clinical manifestations occurs in about 5% of patients with sarcoidosis, but contemporary imaging studies suggest that clinically silent myocardial involvement appears to involve approximately 25% of patients with extracardiac sarcoidosis.[53,54] (**see Chapter 77**). Clinical manifestations may include AV block, ventricular tachycardia, HF, and sudden cardiac death. SPECT perfusion imaging studies have reported that both fixed and reversible defects may be seen, possibly secondary to focal fibromuscular dysplasia found in the small coronary arteries. Perfusion defects involving the left ventricle have been associated with AV block and HF, and defects involving the right ventricle on SPECT have been associated with ventricular tachycardia of RV origin.[53] Gallium-67 scintigraphy is a nonspecific marker of inflammation and has been used in the past to identify patients with active inflammation. It has essentially been replaced by FDG PET imaging, which has superior sensitivity and spatial resolution characteristics.[55]

In contemporary practice, CMR is often used to evaluate patients with suspected cardiac sarcoidosis (**see Chapter 17**). Late gadolinium enhancement and T2-weighted imaging can identify areas of scarring, inflammation, and edema with much higher prevalence than clinical features suggestive of cardiac involvement. CMR imaging cannot distinguish areas of active inflammation from scar,[56] a distinction with important implications for treatment.

FDG PET imaging (with or without anatomic colocalization with CT or CMR) has gained interest for diagnosis and potential follow-up of cardiac sarcoidosis.[55] Because inflammatory cells (e.g., macrophages) contain increased membrane glucose transporters and significantly high hexose monophosphate shunt pathway activity, FDG can accumulate within areas of granulomatous inflammation and cannot diffuse out or be metabolized further (**Fig. 16.39**). As a granuloma matures, the number of macrophages and inflammatory cells decreases, with subsequent fibrous replacement. FDG PET imaging is not highly sensitive for identifying any myocardial involvement, because areas of scarring without inflammation will not be identified by FDG-PET. Nonetheless, the presence of active inflammation identified by FDG PET appears to be associated with an increased incidence of adverse events during

follow-up after imaging.[55]

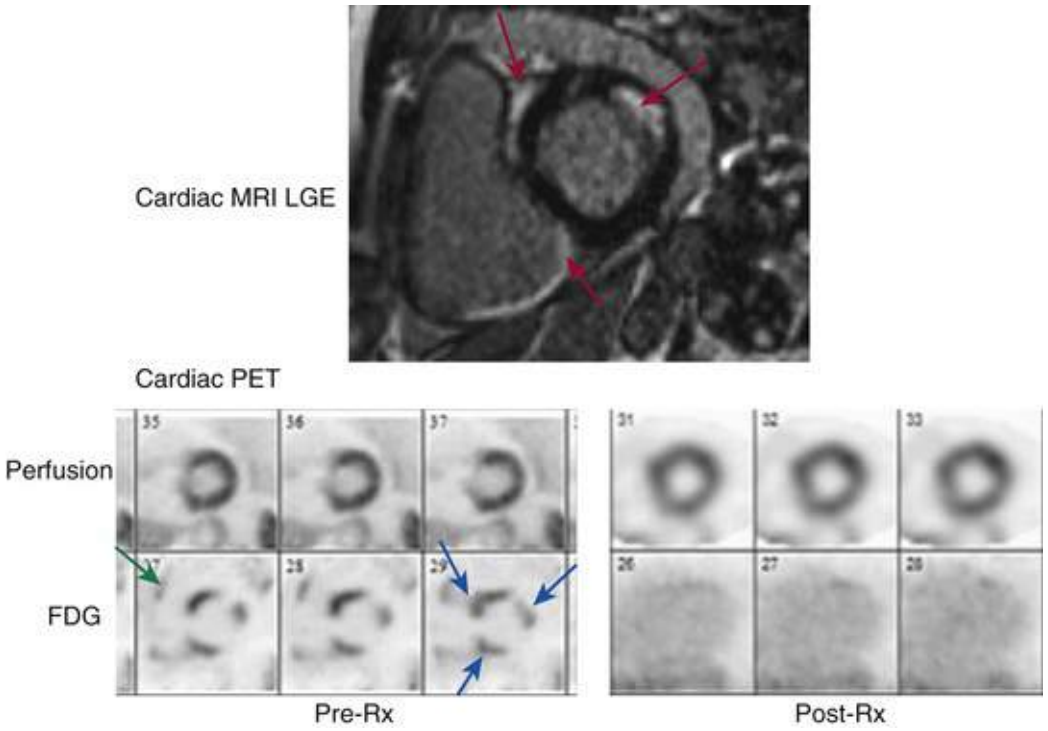


FIGURE 16.39 Example of cardiac MRI and PET findings consistent with cardiac sarcoidosis as well as a reduction in myocardial inflammation following immunosuppressive therapy. In a patient with a history of ventricular tachycardia referred for evaluation, cardiac MRI demonstrates a large amount of subepicardial late gadolinium enhancement (LGE) involving the basal anteroseptum and inferoseptum, most prominently at the RV insertion points, as well as subendocardial LGE involving the basal anterolateral wall. (*red arrows*). Note LGE along the basal inferoseptum extending across into the right ventricle. Because these features were strongly suggestive of cardiac sarcoidosis, the patient was subsequently referred for a rest PET scan. After a high-fat diet to suppress ^{18}F-fluorodeoxyglucose (FDG) uptake from the myocardium, there was intense FDG uptake involving the basal anteroseptum, inferoseptum, and anterolateral segments (*blue arrows*), as well as focal uptake of FDG by the right ventricle (*green arrow*). The rest perfusion images show a perfusion defect along the septum, in part corresponding to the areas of FDG uptake involving the septum. The patient was treated with oral corticosteroids, and follow-up PET 1 year later (*bottom right panel*) shows complete resolution of the myocardial inflammation. Notably, the resting perfusion defect also improved because of less inflammation compression on the microvasculature.
(Images courtesy Dr. Ron Blankstein.)

In concert with either CMR or CT, FDG PET may be optimal for monitoring the efficacy of therapy directed at the active inflammation in cardiac sarcoidosis and for detecting recurrence. In a study using serial FDG PET in patients with cardiac sarcoid undergoing corticosteroid therapy, reduction in FDG uptake after anti-inflammatory therapy was associated with an improvement in EF[55] (**Fig. 16.39**), suggesting potential clinical use to guide magnitude and duration of therapy.

Currently applicable guidelines for the diagnosis of cardiac sarcoidosis suggest two pathways to diagnosis, one involving direct endomyocardial biopsy evidence, but a second pathway that can utilize noninvasive imaging results. A diagnosis of cardiac sarcoid is said to be probable if there is histologic evidence of extracardiac sarcoid, accompanied by abnormal CMR, FDG PET, or gallium-67 imaging.[53]

Cardiac Amyloidosis

Our understanding of the cardiac amyloidosis syndromes has expanded substantially in recent years. Older classification schemes have now evolved to thinking of patients as having either AL amyloid, as part of a light chain protein proliferative disorder, or transthyretin (TTR) amyloid, which can have

several subtypes. Clinical trials of therapeutic agents are underway for both syndrome subtypes. The potential for a specific therapy, coupled with the evolution of cardiac imaging tools such as CMR (**see Chapter 17**), has brought new urgency to making a diagnosis of cardiac amyloid in a patient with the clinical syndrome of HF with preserved EF or unexplained LV hypertrophy.

In the past, ^{99m}Tc-labeled bone-avid tracers such as ^{99m}Tc-pyrophosphate (PYP) were used for diagnosis and localization of MI, even before the availability of the initially used cardiac enzymes such as creatine phosphokinase (CPK). Once serum enzyme diagnostics for MI became widely available, the use of PYP imaging for MI disappeared quickly. At that time. however, case series showed that these bone-avid tracers could also show uptake, sometimes quite substantial, in patients later found to have cardiac amyloidosis. The numbers of patients were modest, however, and patients were highly selected with varying degrees of rigor regarding the gold standard diagnosis. With the increasing use of tissue biopsies for diagnosis, the use of ^{99m}Tc tracers for this purpose remained infrequent.

Recent single-center studies have reexamined the use of ^{99m}Tc-PYP and other bone-avid tracers and suggested that this type of imaging can identify TTR amyloid with high sensitivity and specificity, noninvasively distinguishing that entity from AL amyloid[57] (**Fig. 16.40**).

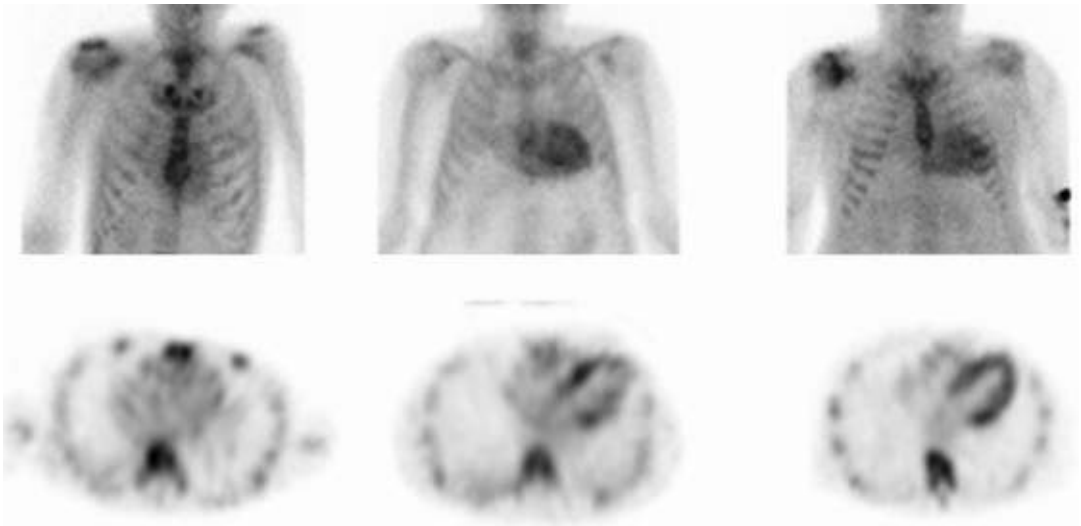


FIGURE 16.40 Sections of whole-body planar **(top row)** and chest SPECT **(bottom row)** ^{99m}Tc-pyrophosphate images. *Left panels,* Grade 0 uptake (no myocardial uptake), effectively excluding transthyretin cardiac amyloidosis. *Middle panels,* Grade 2 uptake (myocardial uptake equal to bone uptake). *Right panels,* Grade 3 uptake (myocardial uptake greater than bone uptake). Uptake of this tracer marks the myocardial deposition of TTR amyloid. (Images courtesy Sharmila Dorbala, MD.)

In a pooled analysis from multiple referral centers in the United States and Europe of almost 1500 patients with suspected cardiac amyloid, more than 800 of whom had a diagnosis of cardiac amyloid established, the sensitivity of any apparent ^{99m}Tc uptake to detect TTR amyloid was greater than 99%, with a specificity of 86%; false positives were most often caused by mild uptake in AL patients. The combination of a more than mildly positive ^{99m}Tc scan and the absence of a monoclonal spike on serum or urine testing was highly specific and predictive for TTR amyloid. Thus a combination of bone scintigraphy and monoclonal gammopathy testing may obviate the need for endomyocardial biopsy in many patients with suspected cardiac amyloid and may allow a “nonbiospy” diagnosis.[58]

Newer radionuclide agents are being developed that specifically bind to amyloid deposits in the heart. ^{18}F-florbetapir can be imaged with PET technology and in early studies shows promise to detect both AL and TTR cardiac amyloid[59] (**Fig. 16.41**).

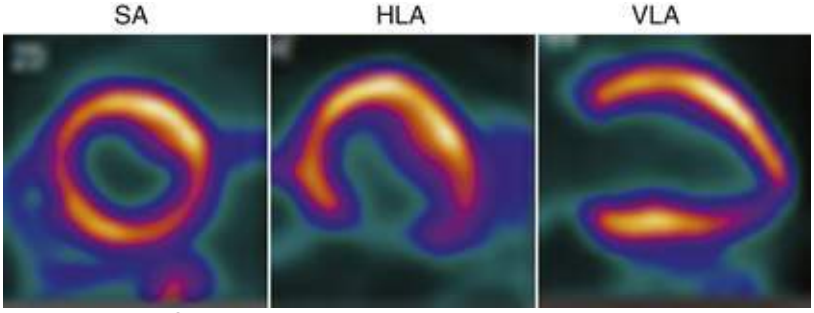


FIGURE 16.41 Myocardial ^{18}F-florbetapir images of patient with light chain cardiac amyloidosis. Standard short-axis (SA), horizontal long-axis and vertical long-axis (VLA) projections show uniform and intense ^{18}F-florbetapir uptake throughout the left ventricle, marking extensive myocardial amyloid deposition. (Images courtesy Sharmila Dorbala, MD.)

Imaging for Assessment of Arrhythmias in Heart Failure

Assessment of Cardiac Sympathetic Innervation.

An emerging area of risk stratification involves the use of ^{123}I-metaiodiobenzylguanidine (MIBG) imaging of cardiac sympathetic innervation in HF. ^{123}I-MIBG shares its reuptake mechanism and endogenous presynaptic storage with norepinephrine. ^{123}I-MIBG is taken up into presynaptic terminal via uptake-1, but as a false neurotransmitter, ^{123}I-MIBG is not catabolized, thereby localizing in high concentration in nerve terminals, allowing for external imaging. The highest density of sympathetic nerves is in the RV and LV myocardium, which can be imaged with single-photon-emitting radiotracer ^{123}I-MIBG, or positron-emitting radiotracers such as ^{11}C-hydroxyephedrine and ^{18}F-fluorobenzylguanidine.[60] PET provides higher-resolution images than planar or SPECT imaging with ^{123}I-MIBG, allowing for regional analysis of the innervation signal and kinetic modeling for true quantification.

In the post-MI setting, the territory of abnormal ^{123}I-MIBG uptake often exceeds the final infarct size, and such patients are at higher risk for subsequent ventricular arrhythmias.[61] In two multicenter prospective phase III studies comprising more than 900 patients with HF and systolic dysfunction, 2-year event-free survival was significantly higher for patients with more preserved ^{123}I-MIBG uptake (i.e., more preserved functional sympathetic innervation) than for patients who showed evidence of more advanced functional denervation on ^{123}I-MIBG imaging.[62] The ^{123}I-MIBG uptake was quantified using the ratio of counts/pixel in whole-heart (H) and in upper mediastinum (M) regions in 4-hour delayed anterior planar images of the chest (**Fig. 16.42**), referred to as the heart-to-mediastinum ratio (H/M). Adverse events were defined as symptomatic progression, potentially life-threatening arrhythmic event, or cardiac death. Two-year event-free survival was 85% in patients with more preserved ^{123}I-MIBG uptake (H/M ratio ≥1.6), compared with 63% in those with an abnormal imaging result (H/M <1.6; hazard ratio [HR]: 0.40; $P < 0.001$). These findings contributed to FDA approval of ^{123}I-MIBG for imaging sympathetic innervation of the myocardium in HF patients to assess risk of mortality. Additional clinical studies may define the role of this agent in optimizing selection of post-MI patients or those with HF who may (or may not) benefit from a defibrillator.

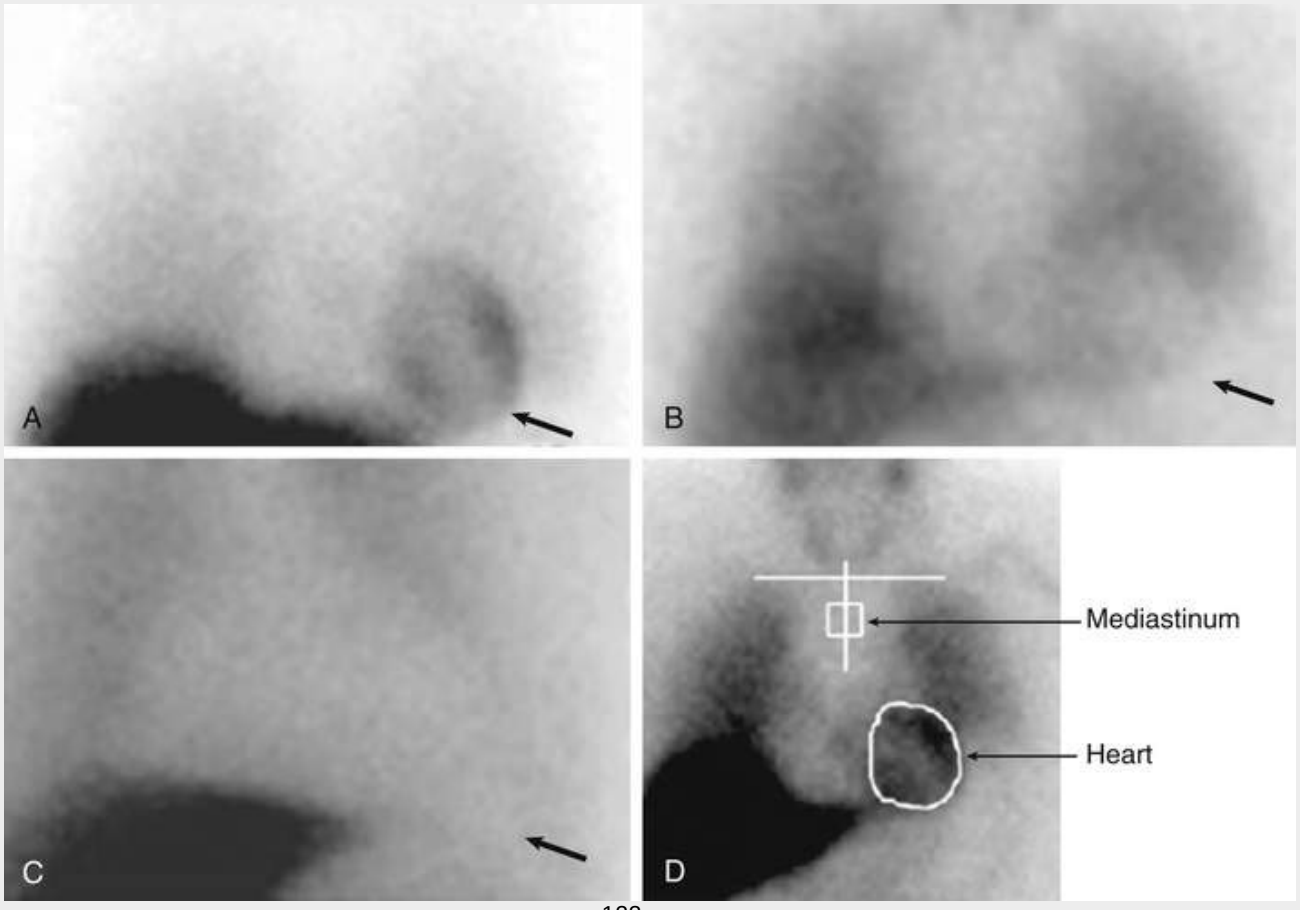


FIGURE 16.42 Examples and quantification of ^{123}I-MIBG imaging of cardiac sympathetic innervation. In these anterior planar images, *arrows* denote area of the heart. **A,** Normal cardiac uptake of MIBG, with uptake in the heart clearly greater than in the lungs or mediastinum. **B,** Abnormal uptake, similar to that in the lungs or mediastinum. **C,** Apparent absence of cardiac uptake, consistent with severe functional denervation. **D,** Method for quantification of MIBG uptake. Region of interest (ROI) is drawn around the cardiac epicardial border, as well as a region within the mediastinum, and a ratio of the counts/pixel in heart ROI and mediastinal ROI (H/M ratio) is calculated. (Modified from AdreView Prescribing Information. http://medlibrary.org/lib/rx/meds/adreview-1/page/3/. Accessed March 14, 2017.)

^{123}I-MIBG Neurocardiac and ^{18}F-FDG Metabolism: Cardiac Imaging to Guide Ventricular Tachycardia Ablation in Heart Failure.

The cornerstone of current techniques for identifying successful ablation sites of ventricular tachyarrhythmias in patients with structural heart disease and HF is the localization of abnormal or scarred myocardium. This tissue usually contains areas of slow conduction, which are critical for maintaining reentrant arrhythmias. Electroanatomic mapping performed in the electrophysiology laboratory identifies the presence of anatomic scar by decreased bipolar voltages measured with roving, steerable catheters. Given the inherent limitations of this technique, such as falsely low voltage recording due to poor catheter contact, the inability to detect intramural scar, and limited mapping density, imaging modalities such as magnetic resonance imaging (MRI), CT, PET, and SPECT have been used to assess scar by demonstrating gadolinium enhancement, thinned walls, and perfusion/metabolic abnormalities. The advantage of PET or PET-CT ^{18}F-FDG metabolic imaging[63] and ^{123}I-MIBG planar and SPECT[64] for scar imaging is that they are not affected by some of the patient restrictions with MRI or CT alone. Although delayed enhanced MRI has been well established to visualize scar tissue, the defibrillators, metal artifacts, and association with nephrogenic systemic sclerosis limit its use in the ventricular tachycardia (VT) patient population. Similarly, although scar imaging with delayed enhanced CT has been described, its applicability in chronic human infarcts is still evolving. The use of three-dimensional scar fusion models with ^{18}F-FDG and ^{123}I-MIBG allows accurate assessment of LV scar and its border

zone. The integration of a three-dimensional scar map into a clinical mapping system is feasible and allows supplementary scar characterization that is not available from endocardial voltage maps (**Fig. 16.43**). This difference could significantly facilitate substrate-based VT ablations.

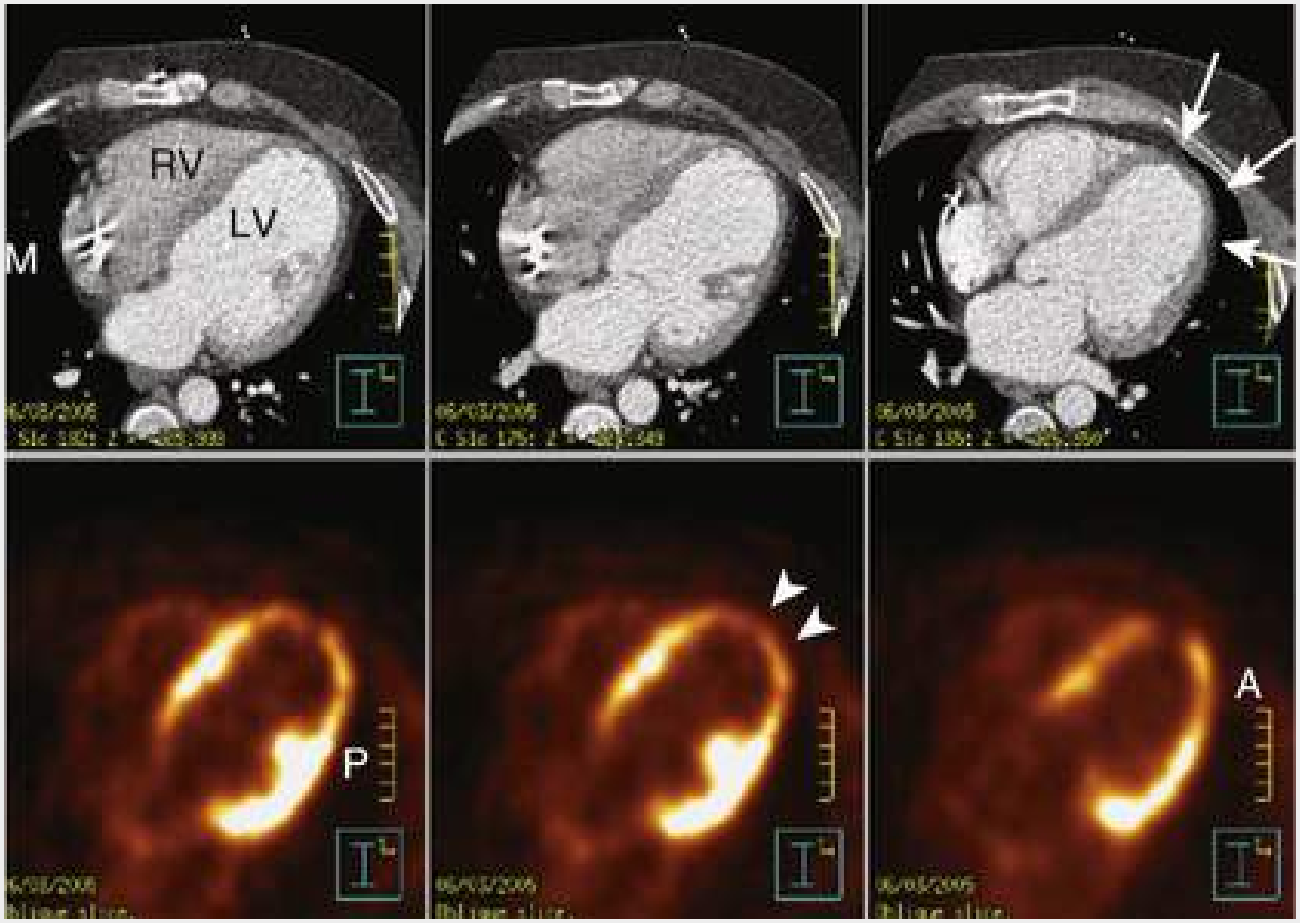


FIGURE 16.43 ^{18}F-FDG PET and CT imaging to identify substrate for ventricular arrhythmias in heart failure. **Top row,** Contrast-enhanced CT demonstrates all cardiac chambers. *RV,* Right ventricle; *LV,* left ventricle; *M,* metal artifact of internal defibrillator lead in right atrium. Significant wall thinning (*arrows*) is noted in the apical and lateral LV wall, consistent with myocardial infarction. **Bottom row,** FDG PET images show a matching decrease in signal intensity in apical and lateral wall segments (*arrowheads*). Preserved metabolism of papillary muscle (*P*) was noted. Note the areas of partially preserved metabolic activity (*A*) within the lateral wall, which appears uniformly thinned on CT images and may represent surviving myocardium within the infarcted area. (Modified from Dickfeld T, Lei P, Dilsizian V, et al. Integration of three-dimensional scar maps for ventricular tachycardia ablation with positron emission tomography-computed tomography. J Am Coll Cardiol Imaging 2008;1:73-82.)

Imaging to Assess Risk Before Noncardiac Surgery

The clinical role of MPI for evaluation of patients before elective noncardiac surgery is important in selected cases, because CAD constitutes a major perioperative and long-term risk in such patients (**see Chapter 11**). The ischemic burden from the stress of surgery and postoperative recovery can result in MI or cardiovascular death. Prospective identification of such patients has important prognostic and preventive implications. Initial cardiac assessment of patients undergoing noncardiac surgery should be based on (1) the urgency of the surgery; (2) the presence or absence of any active cardiac conditions, such as decompensated HF; (3) the type of surgical procedure (low or elevated risk); and (4) the patient's functional capacity.[65]

For patients having non–low-risk surgery who also have limited or unknown functional capacity, current guidelines recommend imaging for risk stratification based on "revised cardiac risk index" factors, which include history of CAD, previous HF, diabetes, renal insufficiency, and cerebrovascular disease. Noninvasive testing may be considered in patients with such risk factors for perioperative events, if this will change management. Asymptomatic patients with known CAD who have had revascularization within the past 5 years generally require no further evaluation.[65]

Normal MPI using pharmacologic stress uniformly predicts a low likelihood (approximately 1%) for perioperative or longer-term postoperative cardiac events.[65] Reversible perfusion defects predict an increased risk of cardiac events, and the magnitude of risk is related to the extent of ischemia. Although fixed perfusion defects (infarct) portend a lower risk than ischemia for perioperative cardiac events, the risk is higher than that with a normal scan, and patients with infarct or LV dysfunction are at higher long-term risk for death or HF.

In clinical practice, most patients in whom extensive ischemia is demonstrated preoperatively undergo catheterization with expectation of revascularization. Clinical trial evidence supporting this practice provides conflicting evidence,[65] however, and the threshold of ischemia extent above which revascularization might reduce short- or long-term cardiac risk is not known. In the contemporary era of PCI, the potential need for prolonged dual-antiplatelet therapy after stenting, and the attendant risk of perioperative bleeding, must also must be factored into the complex benefit-risk ratio in considering whether to pursue stress testing and potential catheterization with subsequent revascularization.

Molecular Imaging of the Cardiovascular System

During the past several decades, radionuclide cardiac imaging has focused primarily on "organ-level" assessment of physiology and pathophysiology, such as myocardial perfusion and ventricular function. However, advances in radiochemistry and imaging technology have enabled the interrogation of many more processes at the cellular and molecular level. Such techniques have the potential to refine the current understanding of mechanisms involved in cardiovascular diseases, such as instability of atherosclerotic plaque in a patient, with the promise of more targeted, individualized therapy.

Imaging of Potentially Unstable Atherosclerotic Plaque and Platelet Activation

Vulnerable atherosclerotic plaques typically have a necrotic lipid core with a thin, fibrous cap and contain a large amount of macrophages (**see Chapter 44**). When such vulnerable plaques rupture, they may cause MI, sudden death, or stroke. Thus the biologic composition and inflammatory state of an atherosclerotic plaque, rather than its size or degree of luminal stenosis, may be the major determinants of the conversion from a stable to an unstable plaque and the precipitation of acute ischemic clinical events.[66] Therefore, development of noninvasive imaging techniques that target plaque inflammation and other processes leading to plaque vulnerability is an area of intense investigation.[67]

Accordingly, recent studies have focused on noninvasive molecular imaging probes that target plaque composition, such as inflammation and microcalcification, using PET-CT technology. ^{18}F-FDG is an excellent probe to target macrophage infiltration as a marker of plaque inflammation, and another molecular probe, ^{18}F–sodium fluoride (^{18}F-NaF), targets active microcalcifications in atherosclerotic plaques.[68] Correlative studies between arterial plaque inflammation (by ^{18}F-FDG), active mineral

deposition (by ^{18}F-NaF), and vascular calcification (by CT) in major arteries (aorta and its major branches including carotid) have shown the ability of these two molecular probes to visualize these distinct biologic processes in atherosclerotic plaque.[69] The feasibility of ^{18}F-NaF PET for the detection of coronary microcalcification in humans was shown in a prospective cohort of healthy volunteers and patients with aortic sclerosis and stenosis.[70] Coronary ^{18}F-NaF uptake was higher in patients with coronary atherosclerosis than the controls and correlated with the CAC score. Similarly, in a study of patients with recent MI and those with stable angina, the highest coronary ^{18}F-NaF uptake was observed in the culprit plaque compared with the nonculprit plaque in the patients with recent MI[71] (**Fig. 16.44**). Among those with stable angina, almost half the patients had plaque with focal evidence of increased ^{18}F-NaF uptake, and these plaques had more high-risk features of plaque vulnerability on intravascular ultrasound (**see Chapter 20**) than plaques without ^{18}F-NaF uptake. These data suggest the potential of imaging to identify plaques and patients at risk of future ACS, paving the way for prevention trials.

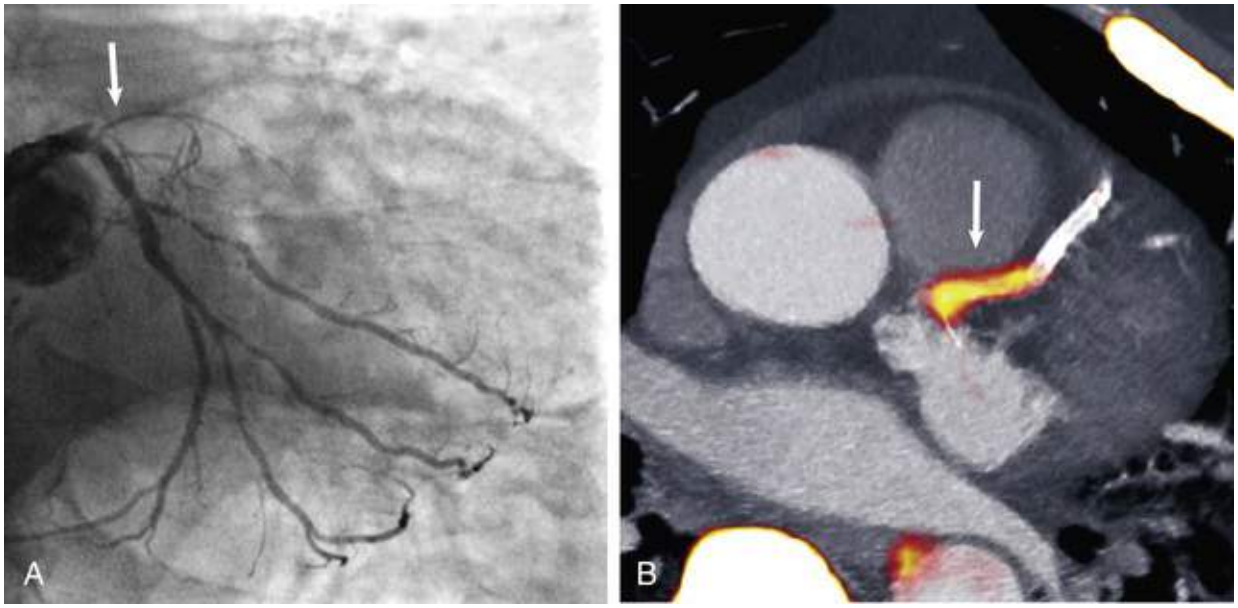


FIGURE 16.44 Uptake of ^{18}F-NaF in high-risk atherosclerotic plaque. **A,** *Arrow* indicates site of acute occlusion of proximal left anterior descending artery in patient with STEMI. **B,** PET-CT imaging performed several days later demonstrates intense focal uptake of tracer at plaque site (*arrow*), consistent with high-risk plaque features. (Modified from Joshi NV, Vesey AT, Williams MC, et al. ^{18}F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. Lancet 2014;383:705.)

The integrin αvβ3, which has been investigated for tumor neovascularization, also plays an important role in plaque vasa vasorum neoangiogenesis. An ^{18}F-labeled PET radiotracer that images αvβ3-integrin expression (^{18}F-galacto-RGD) targets both macrophages and intraplaque neovasculature (both implicated in progression and rupture of atherosclerotic lesions) that may be directly involved in the degradation of the protective fibrous cap of atherosclerotic plaques.[72] Whether this agent can ultimately be used to evaluate atherosclerotic lesions in patients remains untested.

It is important to recognize that most of the studies using these molecular imaging probes for atherosclerosis are restricted to larger arterial beds such as those for the carotid arteries and aorta, rather than the coronary arteries. Because of the limitations of the partial volume effect of small plaques, low target-to-background ratio of tracer uptake, and cardiac motion, direct visualization of atherosclerotic plaques in coronary arteries with current PET-CT technology is challenging.[67,68] Whether molecular imaging of noncoronary vascular beds is useful in predicting coronary plaque rupture and acute MI has not been ascertained. If successful, such molecular probes could provide new insights into the complex

development and progression of atherosclerosis, facilitate current understanding of mechanisms of plaque rupture, stimulate development of new medications to prevent or regress atherosclerosis, and provide a noninvasive tool to monitor the treatment effect.

Imaging of Cell- or Gene-Based Regenerative Therapy

Local targeted gene delivery or implantation of skeletal myoblasts, bone marrow–derived stem cells, mesenchymal stem cells, circulating progenitor cells, embryonic stem cells, and cardiac resident cells are all being investigated for potentially revitalizing scarred, noncontractile myocardial regions (**see Chapter 30**). Clinical trials to date, however, have demonstrated only marginal benefits of cell-based therapy in ischemic cardiomyopathy and chronic HF and after acute MI.[73,74]

Molecular imaging tools that can identify the optimal cell type, delivery route, dosing regimen, and timing of cell delivery may be the key to understanding and advancing cardiac stem cell therapy.[75] Imaging can be accomplished by direct labeling of the therapeutic cells (e.g., ^{99m}Tc or ^{111}In radionuclides) or "reporter gene" imaging that allows observation of intracellular or genomic events by PET, SPECT, PET-CT, or optical imaging. In animal studies, transplanted cardiomyoblasts expressing a PET reporter gene have been imaged longitudinally to gain insight into the pattern of cell survival.[75] In an experimental mouse model of MI that included intramyocardial injection of human cardiac progenitor cells, initial cell retention assessed by cardiac micro-PET predicted long-term myocardial functional improvement by CMR[76] (**Fig. 16.45**). Such molecular imaging techniques that track and localize stem cells may provide mechanistic insight into the success (or failure) of future trials.

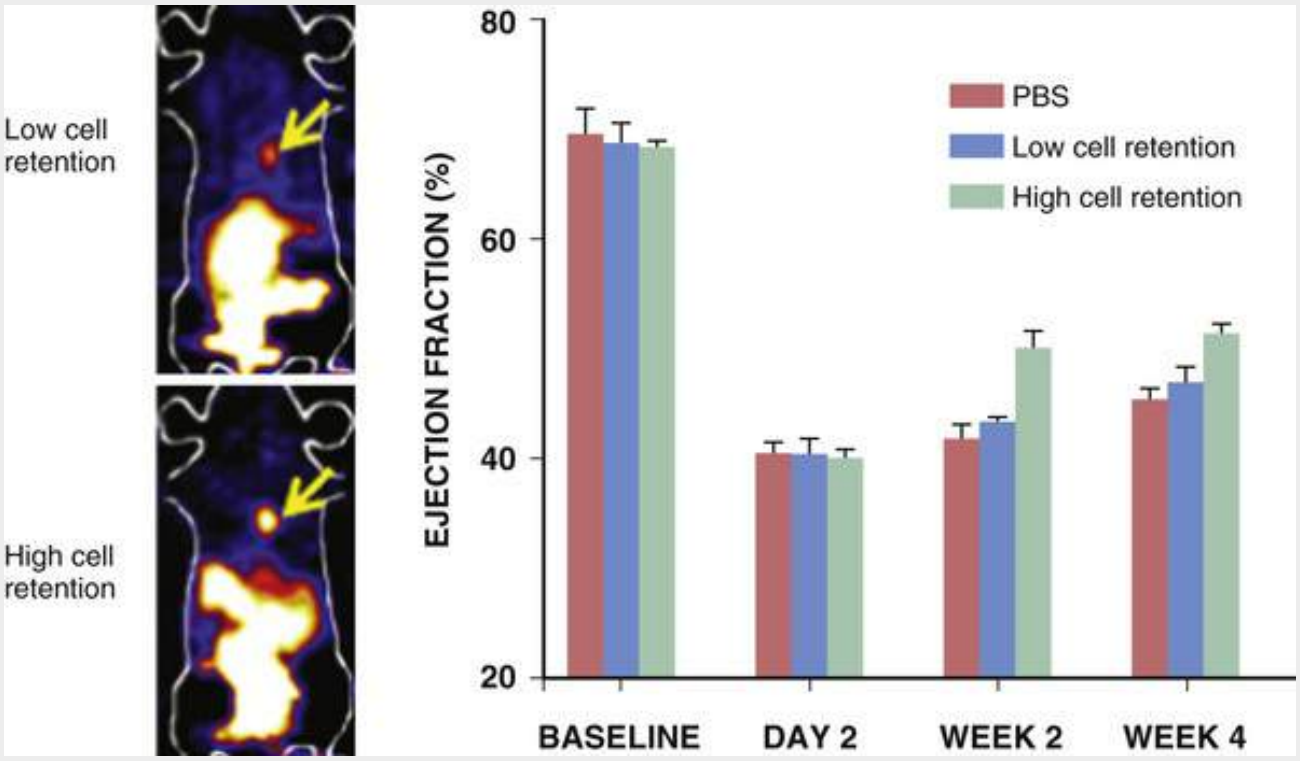


FIGURE 16.45 Early cell retention identified by molecular imaging predicts long-term myocardial functional improvement. Mice underwent experimental myocardial infarction followed by intramyocardial injection of human cardiac progenitor cells expressing a mutant thymidine kinase reporter gene tagged to a PET radionuclide. Serial PET and CMR studies were later performed to assess cell engraftment and LV function. **Left,** Representative coronal PET image is shown for a mouse with low cell retention on day 1 (*top*), compared with that of a mouse with high cell retention (*bottom*). **Right**, Average CMR-derived ejection fraction is greater at both week 2 and week 4 for mouse cohort with high initial cell retention than for cohort with low cell retention or injection of placebo solution (*PBS*). (Modified from Liu J, Narsinh KH, Lan F, et al. Early stem cell engraftment predicts late cardiac functional recovery: preclinical insights from molecular imaging. Circ Cardiovasc Imaging 2012;5:481.)

Imaging of Interstitial Fibrosis and Left Ventricular Remodeling

Activation of the renin-angiotensin-aldosterone system (RAAS), particularly its autocrine and paracrine components within the tissues, occupies a central place in the pathogenesis and progression of LV remodeling, interstitial fibrosis, and HF (**see Chapter 23**). Myocardial fibrosis in chronic HF is a dynamic process that is determined by a balance between collagen synthesis and its degradation by matrix metalloproteinases. In addition, local tissue synthesis of aldosterone appears to be mainly angiotensin II driven and may participate in a positive feedback loop, because aldosterone upregulates the angiotensin type 1 receptor (AT1R) and ACE expression in cardiac cells.

Investigations in animal models and also in humans have shown that radionuclide imaging of the RAAS can be used in experimental systems to study the human tissue ACE and AT1R directly. Use of ^{18}F-fluorobenzyl-lisinopril in human explanted hearts has shown a relationship between ACE and collagen replacement, because ACE was absent in the collagen-stained areas and was increased in the juxtaposed areas of replacement fibrosis.[51] These data suggest that increased ACE may be a stimulus for collagen replacement and remodeling. A subsequent study with ^{99m}Tc-lisinopril in transgenic rats overexpressing human ACE-1 established the specificity of the radioisotope probe to myocardial ACE-1 and demonstrated close correlation between quantitative uptake of ^{99m}Tc-lisinopril and enzyme activity.[77] Moreover, the signal intensity was sufficiently high to allow external imaging by hybrid micro-SPECT-CT (**Fig. 16.46**). Recently, AT1R also was targeted for imaging the human heart.[78] This first-in-human application of receptor ligand ^{11}C-KR31173 combined with PET-CT confirmed the presence of local tissue RAAS in human hearts, proved to be safe, and showed that the signal was high enough to allow

external imaging with PET. However, the myocardial retention of KR31173 was significantly lower in these healthy humans than that observed in normal healthy pigs, with a limited specificity: only 54% of the signal targeted the AT1R.[78,79]

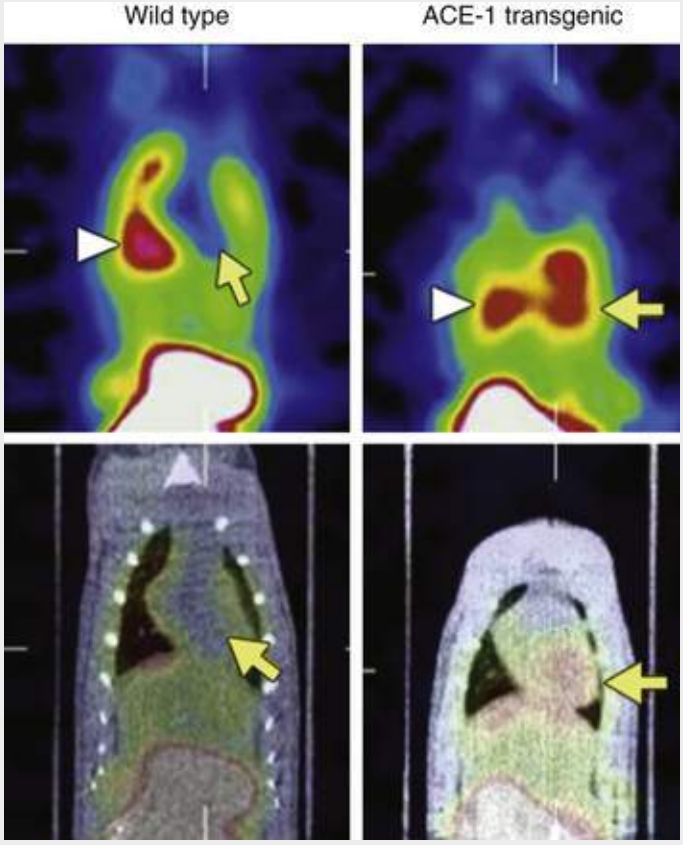


FIGURE 16.46 Noninvasive micro-SPECT-CT imaging of angiotensin-converting enzyme (ACE)-1 activity. **Top row,** Micro-SPECT-CT imaging provides simultaneous scintigraphic and morphologic localization of ^{99m}Tc-labeled lisinopril uptake, 60 minutes after tracer administration, in control animal (*left*) and in ACE-1–overexpressing transgenic animal (*right*). *White arrowheads* indicate intense lung uptake; *yellow arrows,* myocardial ACE-1 activity. ACE-1–overexpressing model shows much higher-intensity uptake in the myocardial region. **Bottom row,** Micro-SPECT data are superimposed on CT data for better myocardial localization in the overexpressing model. (Modified from Dilsizian V, Zynda TK, Petrov A, et al. Molecular imaging of human ACE-1 expression in transgenic rats. J Am Coll Cardiol Imaging 2012;5:409.)

In the future, noninvasive radionuclide imaging in HF patients may allow monitoring of changes in ACE expression patterns in vivo, possibly reflecting progression of disease and the effect of therapies before collagen replacement ensues.

Imaging of Cardiac Valvular Inflammation and Calcification

Beyond imaging vascular atherosclerosis, FDG and ^{18}F-NaF techniques also may identify patients with early valvular inflammation and microcalcification, before progression to severe, calcified stenosis is detectable by echocardiographic and CT imaging (**see Chapter 68**). In oncology patients with echocardiography-defined degenerative aortic stenosis (AS) who had undergone FDG PET–CT, the relationship between aortic valve inflammation and AS was investigated at the leaflet coaptation point.[80] Patients with mild and moderate AS on echocardiography or calcification on CT had significantly increased aortic valve FDG signal compared to controls. Patients with severe AS or calcification did not show increased FDG signal, suggesting an end stage of the inflammatory process. In a subset of patients

with serial echocardiographic studies over a 1- to 2-year period, 82% who exhibited high FDG valve signal intensity demonstrated progression of AS, compared with only 22% with low FDG signal intensity. This observational study suggests a potential role for FDG PET–CT in identifying patients at risk for more rapid progression of AS.

In a subsequent study, in which both FDG and ^{18}F-NaF were administered to assess valvular inflammation and calcification, 91% of patients with AS exhibited increased ^{18}F-NaF uptake.[81] The correlation between the degree of AS and the PET signal was significantly higher with ^{18}F-NaF than with FDG, suggesting different biologic processes of inflammation and microcalcification during the progression of valvular stenosis.

Imaging of Cardiac Device and Prosthetic Valve Infections

Cardiac Pacemaker or ICD Infection

There has been a significant increase in cardiac pacemaker or implantable cardioverter-defibrillator (ICD) implantation worldwide, which has been accompanied by an increase in the absolute number of device infections (**see Chapter 73**). All-cause 12-week mortality could be as high as 35% with cardiac pacemaker or ICD infection, especially for those with methicillin-resistant *Staphylococcus aureus* infection.[82] The 1-year mortality after removal of an infected device has been reported as 12% in patients with pocket infections and 17% in those with endovascular infections.[82] Accurate diagnosis of cardiac device infection is therefore critical for clinical decision making, such as antibiotic therapy alone or device extraction, but represents a challenge for current diagnostic methods. Among patients with suspected cardiac pacemaker or ICD infections, FDG PET-CT can accurately localize the site and extent of the infection.[83] A potential advantage of FDG PET-CT is in its detection of inflammatory cells early in the infection process, before morphologic damage ensues.[84] In contrast to its reported high accuracy in detecting cardiac device pocket infection, FDG PET-CT appears less reliable for lead infection or vegetation evaluation, which may be attributed to the small size of the lead and vegetation or ongoing antibiotic treatment.[85]

Cardiac Prosthetic Valve Infection

Almost half of prosthetic valve endocarditis cases are complicated by periannular extensions and require urgent surgical intervention (**see Chapter 73**). Transesophageal echocardiography (TEE) may fail to recognize this potentially fatal complication. Although ECG-gated CT angiography can improve the diagnostic accuracy in some patients, it is also a purely anatomic technique. The incremental value of FDG PET-CT to the findings on TEE or CT angiography has been shown in observational case series[86] (**Fig. 16.47**). Although these results are encouraging, FDG PET-CT is not advocated as a first-line or confirmatory imaging study for detecting prosthetic valve endocarditis.[87] Rather, it should be reserved for patients with clinical and microbiologic suspicion of endocarditis but indeterminate or negative TEE.

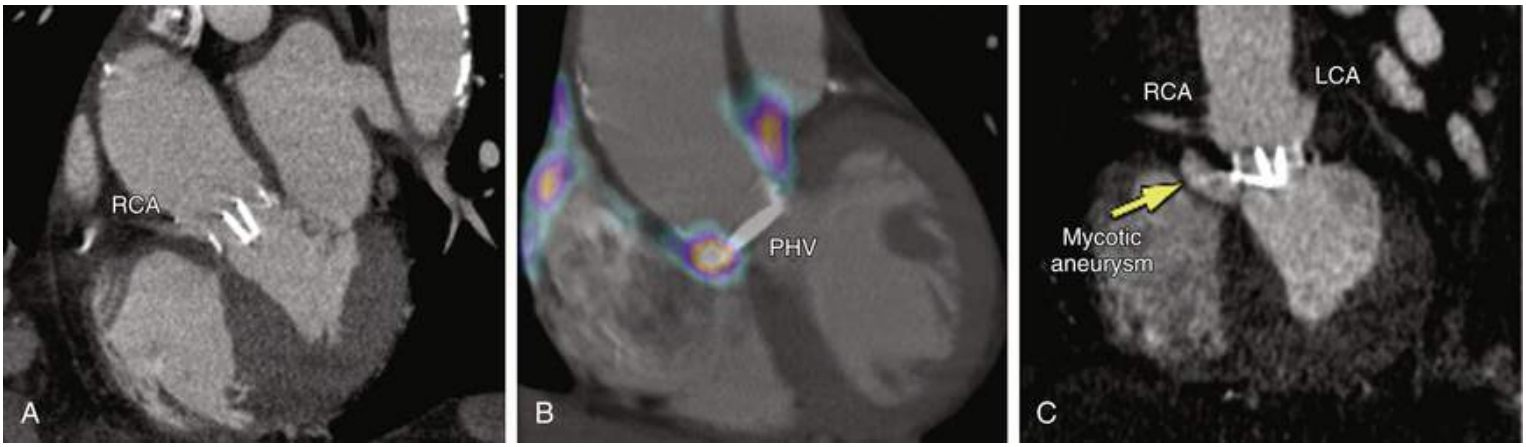


FIGURE 16.47 Periannular prosthetic valve endocarditis detected by FDG PET. Patient with bileaflet mechanical aortic prosthetic heart valve (PHV), placed 20 years earlier, presented with fever and blood cultures positive for *Staphylococcus aureus*. Despite a high degree of clinical suspicion for endocarditis, findings on transthoracic echocardiography and TEE, as well as CT **(A)**, were unremarkable for evidence of infection. **B,** FDG PET–low-dose CT fused image revealed high uptake around aortic PHV (*arrows*), near the proximal right coronary artery (RCA). **C,** Subsequently, CT revealed a mycotic aneurysm beneath the RCA origin, confirmed by urgent operation. In this case, only FDG PET–CT detected these abnormalities at a very early stage. LCA, Left coronary artery. (**A, B,** Modified from Tanis W, Scholtens A, Habets J, et al. Fusion of cardiac computed tomography angiography and ^{18}F-fluorodesoxyglucose positron emission tomography for the detection of prosthetic heart valve endocarditis. J Am Coll Cardiol Imaging 2013;6:1008.)

Left Ventricular Assist Device Infection

Because of the constant shortage of donor hearts, the role of the left ventricular assist device (LVAD) has been expanding in the management of end-stage HF patients both as a bridge to transplantation and as a destination therapy (i.e., alternative to transplantation). Although lifesaving, the LVAD is often complicated with infections. The percutaneous driveline that exits the abdomen can become disrupted by normal activities such as showering, which introduces bacteria. Once bacteria infect the driveline and then the bloodstream, eradication of infection is difficult. Bacteria can infect all areas of the LVAD, including driveline, pump, cannula, and tissues surrounding the pump. Treatment modalities include long-term antibiotics, LVAD replacement, debridement, and urgent transplant. FDG PET-CT imaging of the LVAD is a potential tool to make an early and accurate diagnosis of LVAD infection[88] (**Fig. 16.48**). FDG PET-CT imaging may allow earlier detection of LVAD infection and its extent, as well as evaluation of response to therapy.

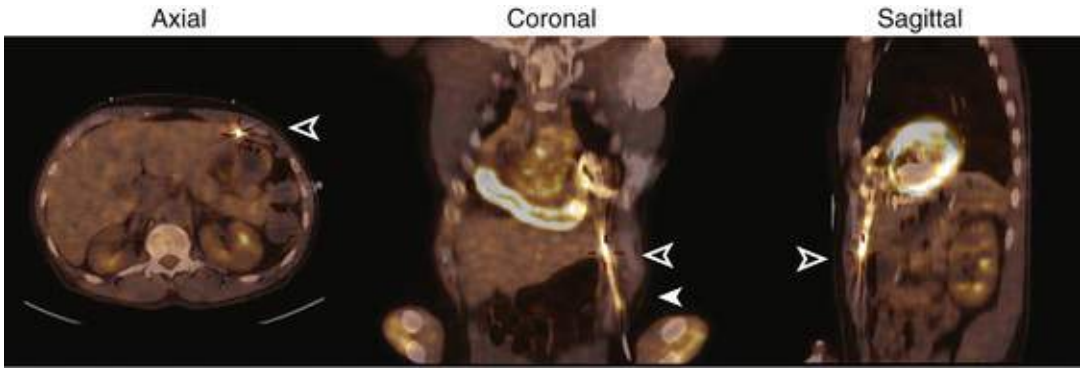


FIGURE 16.48 Fused CT and FDG-PET imaging of driveline left ventricular assist device (LVAD) infection. With a history of LVAD implantation, patient presented with symptoms of pain, purulent discharge, and nonhealing at driveline exit site 6 months after implant. The driveline culture revealed coagulase-negative *Staphylococcus aureus* and yeast. PET-CT images show intense linear FDG uptake along the driveline (*open arrowheads*) and percutaneous exit (*white arrowhead*), compatible with driveline LVAD infection. (Modified from Kim J, Feller ED, Chen W, Dilsizian V. FDG PET-CT imaging for LVAD-associated infections. J Am Coll Cardiol Imaging 2014;7:839-42.)

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17

Cardiovascular Magnetic Resonance Imaging

Raymond Y. Kwong

The multicomponent imaging capability of cardiovascular magnetic resonance (CMR) provides morphologic, structural, and physiologic information relevant to a broad array of cardiovascular diseases. CMR offers technical advantages of unrestricted tomographic imaging fields and various types of tissue characterization, without the need for ionizing radiation. This chapter reviews the current cardiac clinical applications of CMR.

Basic Principles of Magnetic Resonance Imaging

Magnetic Field and Gradient Coil System

Magnetic resonance imaging (MRI) is based on imaging of the abundant hydrogen nuclei in the human body. When a patient is placed inside the scanner magnet, producing a static magnetic field (called B_0), the ^1H nuclei, which have a spin magnetic moment, partially align with the direction of the B_0 field. (The degree of alignment depends on the influence of random effects such as thermal motion, which generally cannot be controlled in biologic systems.) The net magnetization produced by the small fraction of nuclear moments aligned along the B_0 direction (the *z* axis in the magnet's coordinate system) is termed the *equilibrium magnetization,* before irradiation of the nuclear spins of any radiofrequency (RF) pulse. An RF pulse can tip the nuclear spins away from the *z* axis, which leaves the ^1H nuclear magnetic moments precessing at a characteristic frequency, called the *Larmor frequency* (ω_0), which is related to the magnetic field strength and the nucleus's gyromagnetic ratio by $\omega_0 = \gamma B_0$, where γ is the gyromagnetic ratio (a constant for protons of hydrogen at a given field strength). The RF pulse should have a frequency that matches the Larmor frequency to have a “resonance” effect on the nuclear spins; otherwise, in terms of reorienting the nuclear spins, the effect is generally negligible.

B_0 is designed to be spatially uniform inside the CMR magnet bore; thus it is a homogeneous magnetic field. The homogeneity of B_0 is fine-tuned by the computer-controlled adjustments of currents in small coils mounted within the magnet, known as “active shimming.” For imaging, the clinician applies so-called magnetic field gradients that introduce a linear variation of B_0 in the direction of the gradient. B_0 gradients along *x, y,* or *z* direction are produced by a different set of coils, and gradients in arbitrary directions can be created by linear superposition of *x, y,* and *z* gradients. When a gradient is switched on, the ^1H nuclei precess at frequencies that depend linearly on the position along the direction of the magnetic field gradient. This means that the Larmor frequency of the nuclear spins is dependent on position, and excitation of the nuclear spins by an RF pulse has an effect only for a range of positions where the excitation frequency approximately matches the Larmor frequency. This center position, as well as the surrounding range where the RF pulse has a noticeable effect, depends on the center frequency and bandwidth of the RF pulse.

Generation of Magnetic Resonance Signal, Contrast, and Image Formation

To create an image, an RF pulse with a frequency matching the Larmor frequency will tip at least partially the net nuclear magnetization from the direction along B_0 into a plane transverse to B_0 (*x-y* plane), where transverse magnetization is left precessing at the Larmor frequency. The key to the generation of a detectable signal is that the nuclear spins precess coherently; that is, at least initially, all have at any moment the same phase in the transverse plane to yield a net transverse magnetic moment, which can induce a voltage in an external antenna. The extent to which the magnetization vector is tipped away from the direction of B_0 (*z* axis) defines the *flip angle,* reflects the amount of energy deposition in tissue, and is a function of the strength and duration of the RF pulse. The magnitude of the transverse magnetization will determine the amplitude of the detected signal, which is received by a set of surface coils surrounding the patient. To image a specific slice plane through the body, a magnetic field gradient is applied perpendicular to the slice plane, which results in a linear variation of the Larmor frequency perpendicular

to the prescribed slice plane. An RF pulse will then only excite the slice plane with magnetic spins precessing at frequencies approximately matching the center frequency of the RF pulse.

The absorbed electromagnetic energy will be released by two coexisting mechanisms, longitudinal magnetization recovery and transverse magnetization decay. *Longitudinal magnetization recovery*, also called T1 relaxation, corresponds to the recovery of the longitudinal component (*z* direction) along B_0 and is generally characterized by an exponential dependence on time after excitation with a time constant, *T1*. T1 is a physical characteristic of tissue and is affected by the field strength of the scanner, with values progressively longer at higher field strengths (in tesla, T). T1 characterization therefore allows generation of images that reflect the differences of T1 between tissue types (e.g., fat with short T1, muscle with longer T1). A T1-weighted scan will keep the time between delivery of two successive flip angles (repetition time) short; thus tissues with different T1 values will demonstrate different signal intensities because they have recovered to different degrees after an RF excitation.

Transverse magnetization decay results from B_0 field inhomogeneities and interactions between neighboring spins (spin-spin interaction), leading to exponential loss of the transverse component of the net magnetization vector, defined by the time constant *T2*. T2 is also a tissue-specific parameter and is defined as the time to lose 63% of the transverse magnetization. The choice of signal contrast weighting of the imaging method is partly dictated by the physiologic characteristics of the tissue being studied. For qualitative interpretation, signal enhancement (from T1 effects) generally is preferred over signal loss (T2*; see later, Imaging Methods) effects; thus most pulse sequences used in CMR are T1-weighted techniques. T2-weighted and T2*-weighted CMR are primarily for imaging of myocardial edema and iron content, respectively. Iron has a strong magnetic moment that disturbs the local magnetic field and speeds up the loss of phase coherence of the transverse magnetization and thus its decay (i.e., shortens T2). With the application of magnetic field gradients in any of the three orthogonal directions, the MR signal can carry spatial localization information, produced by encoding steps known as *slice select*, *phase encoding*, and *frequency encoding*. All relevant information of the MR signal is stored in a data matrix called the *k-space*, from which images can be reconstructed by so-called Fourier transformation.

Contrast Agents

Currently, only gadolinium-based contrast agents (GBCAs) are used clinically in CMR imaging. When injected as an intravenous (IV) bolus, the GBCA transits through cardiac chambers and coronary arteries over 15 to 30 seconds (*first-pass phase*) before it diffuses into the extracellular space. At approximately 10 to 15 minutes after injection, a transient equilibrium between contrast washing into the extracellular space and washing out to the blood pool is reached. Myocardial perfusion CMR and most magnetic resonance angiography (MRA) scans are performed during the first-pass phase, whereas late gadolinium enhancement images are obtained during the equilibrium phase.

GBCA use in CMR is very safe; approximately 1% of patients experience mild reactions (nausea, mild skin rash), and severe reactions are extremely rare. All GBCAs are chelated to render them nontoxic and to facilitate renal excretion. In patients with severe renal dysfunction, GBCA use exposes the patient to the toxic, nonchelated free gadolinium (Gd^{3+}), which can lead to *nephrogenic systemic fibrosis* (NSF), an interstitial inflammatory reaction that can lead to severe skin induration, contracture of the extremities, fibrosis of internal organs, and death. Risk factors for developing NSF include estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2, need for hemodialysis, acute renal failure, and presence of concurrent proinflammatory events. With the use of weight-based dosing and avoidance of

GBCA use in patients with eGFR less than 30 mL/min/1.73 m^2, NSF from GBCA now has a near-zero incidence.

Imaging Methods

CMR imaging uses a range of strategies to overcome cardiac, respiratory, and blood flow motion. To overcome blurring from cardiac motion, data acquisition is synchronized to the electrocardiogram (ECG) signal (cardiac gating), which can be either *prospective* (triggering by an ECG waveform followed by a fixed period of acquisition during all cardiac cycles) or *retrospective* (continuous data acquisition with subsequent reconstruction based on ECG timing). For cine imaging, retrospective gating is preferred because it covers the entire cardiac cycle. Many CMR techniques (pulse sequences) fractionate the data acquisition of an image to occur within a narrow window of the cardiac cycle over a few heartbeats (segmented approach). To overcome blurring from respiratory motion, a combination of patient breath-holding, navigator-based techniques (tracking of diaphragmatic motion to control respiratory motions), and respiratory motion averaging are now used clinically. In patients who cannot breath-hold or who have irregular heart rhythms, static single-shot and real-time cine imaging (both involve rapid acquisition of whole images within a cardiac cycle) can achieve diagnostic studies at reduced temporal and spatial resolutions.

Table 17.1 summarizes the most common clinical CMR pulse sequence techniques at our center, Brigham and Women's Hospital in Boston. CMR uses bright-blood cine imaging or dark-blood *fast spin-echo* (FSE) imaging to assess cardiac morphology and structure. Cine *steady-state free precession* (SSFP) is the standard pulse sequence for quantifying cardiac volumes and functions. It can acquire a cine movie at a high temporal resolution of 30 to 45 milliseconds during a breath-hold of less than 10 seconds (**Fig. 17.1**), thus capturing the whole heart in motion volumetrically in 3 to 5 minutes (Video 17.1). For dark-blood techniques, T1-weighted FSE is used for morphology of cardiac chambers, vascular structures, pericardium, and imaging of fat. T2-weighted FSE with fat suppressed is used for imaging of myocardial edema. Tagging assesses myocardial strain by marking the myocardium with parallel dark lines or a grid so that myocardial deformation can be visualized or quantified. Circumferential and radial strain can also be calculated and displayed over a colored scale. *Late gadolinium enhancement* (LGE) involves T1-weighted imaging that detects accumulation of GBCA in the myocardium from infarction, infiltration, or fibrosis. LGE is detected 5 to 15 minutes after IV injection of GBCA (0.1 to 0.2 mmol/kg) (thus the term “late” enhancement). LGE data can be captured in two or three dimensions. *Phase-sensitive inversion recovery* (PSIR) reconstruction is routinely used in LGE imaging to enhance myocardial tissue contrast. In patients who cannot perform breath-holding, LGE imaging can be acquired using either single-shot method or navigator guidance.

TABLE 17.1

Summary of Common Clinical Cardiac Magnetic Resonance (CMR) Pulse Sequence Techniques at Brigham and Women's Hospital

CMR TECHNIQUES	PULSE SEQUENCE OPTIONS	DARK/BRIGHT BLOOD	CONTRAST WEIGHTING	TYPICAL IN-PLANE SPATIAL/TEMP. RESOLUTIONS; OTHER PARAMETERS	BREATH-HOLD REQUIRED	Gd CONTRAST REQUIRED	RELATIVE MERITS OF PULSE SEQUENCE OPTIONS	IMAGE EX
Cine cardiac structure and ventricular	Cine SSFP¥ Cine FGRE Real-time	Bright	T2/T1W for cine SSFP and real-time cine SSFP;	1.5-2.5 mm/30-45 msec per phase	Yes for ECG-gated cine SSFP	No	Cine SSFP has higher SNR and CNR (between	

function	cine SSFP		T1W for FGRE	Adjust number of lines of k-space per cardiac cycle (segments) to balance temporal resolution and duration of patient breath-holds 2.3-3.2 mm/~60 msec for real-time cine	and FGRE Optional for real-time cine		endomyocardium and blood) than FGRE but is sensitive to field inhomogeneity (especially at 3 T), giving rise to banding artifact. FGRE has weaker endocardial definition than cine SSFP but is an alternative when severe artifact exists in cine SSFP. Good shimming or frequency scout would be needed at 3 T to eliminate banding artifact. Real-time cine SSFP: use in patients with significant arrhythmia or difficulty breath-holding; it has lowest spatial and temporal resolution.	 Cine SSFP
Quantitative regional myocardial strain	Myocardial tagging (newer but less widely available techniques for regional strain exist; see text)	Bright	T1W	Tag spacing 5-10 mm Temporal resolution ~50 msec Low flip angle, on order of 10 degrees to limit tag fading	Yes	No	Tissue-tracking quantitation of intramyocardial motion Disadvantages: tag lines fade near end of cardiac cycle, and time-consuming strain analysis (postprocessing)	
Structure, morphology, and fat imaging	Standard FSE[¥] SS FSE (or HASTE)	Dark	T1W ± fat suppression	0.8-1.5 mm/every cardiac cycle	Yes for standard fast SE No for SS FSE	No	Standard FSE has better image quality but relatively long scan time. Fat suppression can be achieved by fat saturation pulse (more specific) or by suppressing tissues with short T1 (STIR, which is less specific for fat, in particular after Gd contrast). SS FSE covers the whole heart quickly and is useful in patients with arrhythmia or limited breath-holding	
Myocardial scar by LGE imaging	Standard 2D segmented FGRE[¥] 2D SS SSFP technique 3D whole-heart techniques (breath-hold or navigator guided) Segmented or SS PSIR	Bright	T1W (10-30 min after 0.1-0.2 mmol/kg GBCA injection)	1.5-2.0 mm/150-200 msec (for standard 2D) Adjust inversion time and time delay after ECG detection to null "normal" myocardium and to image in diastole, respectively	Yes for standard 2D technique No for SS technique	Yes	Standard 2D technique has higher spatial and temporal resolutions than SS technique. 2D SS technique covers the whole heart quickly and is useful in patients with arrhythmia or difficulty breath-holding. PSIR is less inversion time sensitive and gives improved contrast	 2D segmen

							when normal myocardium is not perfectly nulled. New 3D application using navigator guidance yields higher SNR than 2D and can achieve spatial resolution of <1 mm without the need for breath-holding. Refer to **Table 17.2** for patterns of LGE in various cardiomyopathies.	
Myocardial perfusion imaging	Saturation-prepared gradient echo (GE)–based 2D techniques: FGRE[¥], hybrid GE-echoplanar (EPI), and SSFP	Bright	T1W	2.0-3.0 mm 130-180 msec/slice 3-4 locations every cardiac cycle or 6-8 locations every 2 cardiac cycles during vasodilator stress and rest 0.05-0.1 mmol/kg IV GBCA injected at 4 or 5 mL/sec (qualitative assessment only)	No, but breath-hold is preferable	Yes	Breath-holding is useful to track contrast-enhancement in specific segments. Parallel-imaging acceleration and sparse sampling to reduce acquisition time per slice and extend slice coverage of the heart, but carries SNR penalty	
Myocardial edema imaging	T2W FSE[¥] STIR FSE T1W EGE_r T2-prepared SSFP T2 map (SSFP readout)	Dark (FSE based) Bright (SSFP based)	T2W + fat suppression (for T2W techniques) T1W (for EGE_r technique)	In-plane spatial and temporal resolutions similar to standard FSE Slice thickness 7-10 mm to improve SNR For qualitative assessment, algorithm needed to correct for distance of heart from receiver surface coils T2 map for quantification (insensitive to signal nonuniformity)	Yes	No/yes for EGE	Myocardial edema appears as transmural area of high SI on T2W images. In FSE techniques, beware of artifacts from slow flow, especially adjacent to regional wall motion abnormality or LV apex, which may mimic edema. Regional myocardial signal variation from phase array coils may mimic edema. In absence of LGE, T2W edema reflects reversible myocardial injury. Using T2W FSE techniques, SI ratio of myocardium over skeletal muscle >1.9 reported as abnormal in myocarditis. EGE_r between myocardium and skeletal muscle of ≥4 or absolute myocardial SI increase of 45% after contrast are considered abnormal in myocarditis. Bright-blood SSFP-based technique has improved CNR and is less susceptible to slow	

							flow artifact. T2 map is insensitive to surface coil–related signal inhomogeneity and slow-flowing blood–related artifact.	
Myocardial iron content imaging	T2*W multiple echo times FGRE	Bright	T2*W	2.0-3.0 mm/~100-150 msec One short-axis midventricular location Series of images with 6-8 echoes from ~2 to 35 msec Axial ungated acquisition of the liver for comparison	Yes	No	Measurement is most accurate and reproducible in the midseptum. T2* value describes exponential decay of myocardial SI as echo time increases. At 1.5 T, T2* value <20 msec with LV dysfunction (without other obvious cause) indicates iron-overload cardiomyopathy.	
Cardiac thrombus	LGE with long inversion time EGE imaging	Bright	T1W	In-plane spatial and temporal resolutions similar to LGE imaging EGE acquired within first 5 minutes after Gd injection	Yes	Yes	LGE imaging with inversion time set at ≥600 msec or EGE imaging can detect thrombus, indicated by intense “black” regions. Look for thrombus in locations of stagnant flow.	
Cardiac blood flow	Phase-contrast imaging cine GE	Bright	Velocity-related signal phase shift	1.5-2.5 mm/50 msec per phase Keep number of lines of k-space per cardiac cycle (segments) low to improve temporal resolution during free-breathing studies.	No (multiple signal averages used)	No	Multiple averages can reduce ghosting artifacts from respiratory motion during free breathing. Should keep velocity encoding strength slightly above the highest expected flow velocity to avoid velocity aliasing while maximizing accuracy. Background phase correction may be needed for accurate results.	
Coronary MRA	3D whole-heart volume using SSFP or FGRE[¥] Target-vessel approach	Bright	T2-prepared 3D SSFP or FGRE technique	~0.6-1.0 mm in-plane Free-breathing navigator-guided 3D technique is currently most widely used.	No, *but* Yes for target-vessel approach	Yes at 3 T or optional at 1.5 T (no need for contrast with SSFP-based technique)	Compared to target-vessel approach, 3D coronary MRA has higher SNR and provides volumetric whole-heart coverage. T2-prepared SSFP sequence with suppression of adjacent epicardial fat provides strong blood vessel contrast. Contrast-enhanced FGRE-based technique is used in 3 T.	
Anatomy for electrophysiologic mapping of pulmonary vein	3D FGRE MRA of left atrial volume and pulmonary	Bright	T1W FGRE	1.5-2.5 mm isotropic volume Timing bolus is required to	Yes	Yes	Subtraction mask scan is necessary to enhance the MRA images.	

	veins			achieve proper timing of imaging during first-pass transit of contrast bolus. Gating is optional but may improve border definition at expense of prolonging breath-hold. Free-breathing navigator-guided 3D technique is increasingly used.			Coronal (more common) or axial 3D MRA of entire left atrium and pulmonary vein is generated for electrophysiologic mapping. Use same parameters as in the subtraction mask scan.	
T1 mapping for assessment of extracellular volume expansion and diffuse fibrosis	Look-Locker (LL), or modified Look-Locker 2D GE	Varying (depending on TI	GRE LL or SS SSFP (MOLLI)	1.5-2.0 mm in-plane resolution LL requires complete relaxation between repetitions MOLLI has lower TI resolution	Yes	Yes (measurements before and after contrast required)	MOLLI acquires all images during single cardiac phase, to allow calculation of T1 maps. MOLLI requires SSFP readouts. LL can provide high TI resolution for short TIs	

¥More commonly used option.

Note: Dark-blood techniques and myocardial iron content by T2* imaging should be performed before administration of gadolinium contrast.

CNR, Contrast-to-noise ratio; *ECG,* electrocardiogram; $EGE_{(r)}$, early gadolinium enhancement (ratio); *FGRE,* fast gradient-recalled echo; *FSE,* fast spin echo; GBCA, gadolinium-based contrast agent; *Gd,* gadolinium; *HASTE,* half-Fourier acquisition single-shot turbo spin echo; *TI,* inversion time; *LGE,* late gadolinium enhancement; *LV,* left ventricular; *MRA,* magnetic resonance angiography; *PSIR,* phase-sensitive inversion recovery; *SI,* signal intensity; *SNR,* signal-to-noise ratio; *SS,* single-shot; *SSFP,* steady-state free precession; *STIR,* short T1 inversion recovery; *T,* tesla; *T1W,* T1-weighted; *T2W,* T2-weighted.

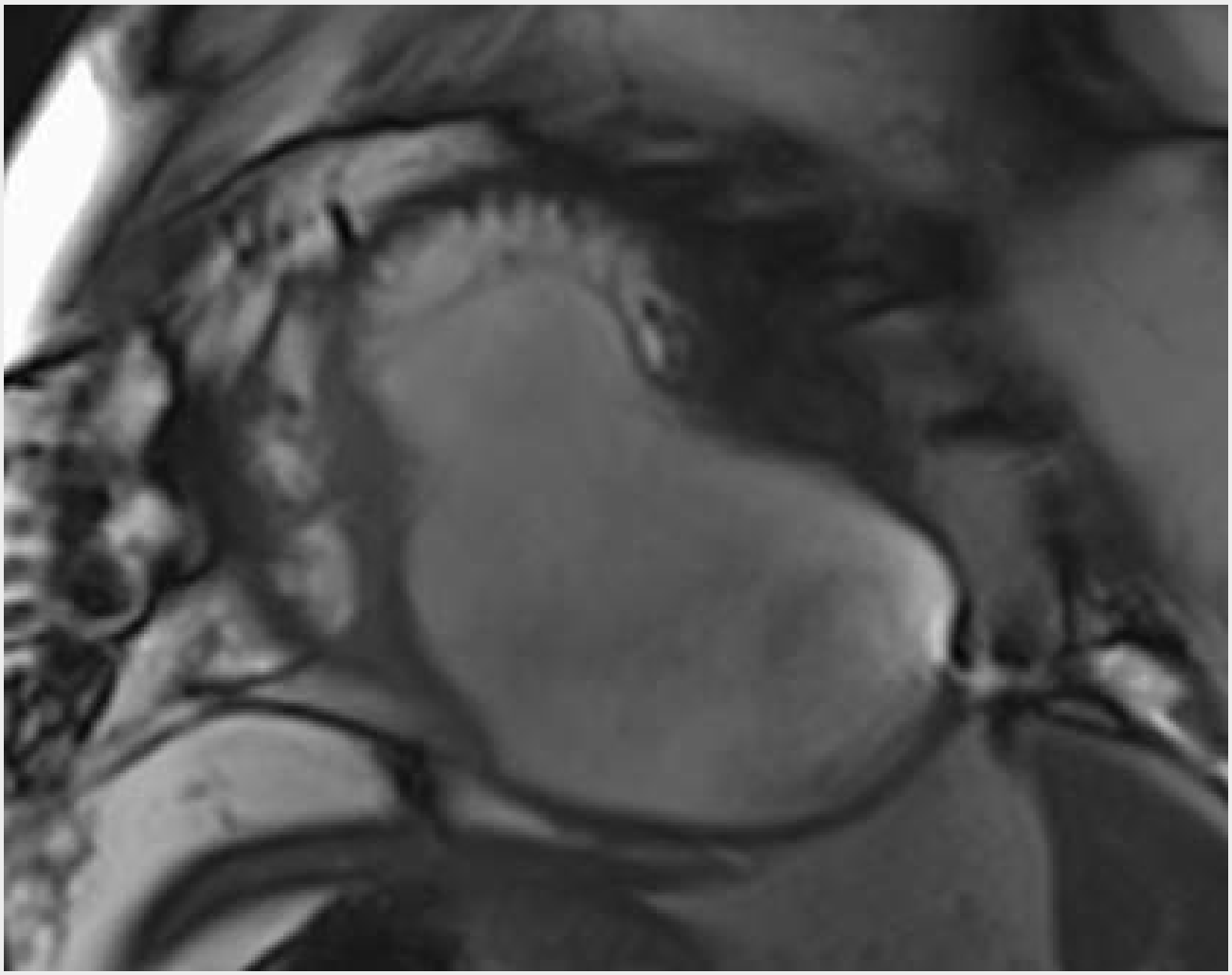


FIGURE 17.1 Massive inferior wall ventricular aneurysm complicating a chronic myocardial infarction. Note the wide neck of the aneurysm and extremely stagnant flow in the left ventricular cavity.

CMR perfusion imaging examines the first-pass transit of an IV bolus of GBCA as it travels through the coronary circulation. Several perfusion techniques are available; fast bright-blood gradient-echo imaging acquires three to five short-axis slices of the heart every cardiac cycle during injection of a GBCA bolus. Gadolinium provides strong signal enhancement in well-perfused regions compared to hypoenhancement (dark regions) in poorly perfused myocardium. At a spatial resolution of approximately 2 mm in-plane, CMR perfusion can provide information on myocardial blood flow at the endocardial/epicardial level or at a segmental level (Video 17.2). T2-weighted imaging detects myocardial edema from ischemic injury or inflammation, and it has been shown to have high correlation to the area at risk after acute myocardial infarction (MI). It also complements LGE in determining the chronicity of an MI and allowing for accurate measurement of *salvageable myocardium*. The pulse sequence options for T2-weighted imaging include black-blood *short T1 inversion recovery* (STIR) FSE and the newer SSFP methods, and their merits are listed on **Table 17.1**.

T2* is a transverse relaxation parameter and well-validated method for measuring tissue iron content. A T2* of less than 20 milliseconds (normal myocardium, approximately 40 to 50 msec) is diagnostic of myocardial iron overload, and a T2* of less than 10 milliseconds is evidence of severe iron overload (Video 17.3). Despite challenges from small luminal size and cardiac and respiratory motion, technical advances in coronary MRA have favored the use of whole-heart three-dimensional acquisition (with or without navigator-guidance), with promising preliminary clinical results.[1] Phase-contrast imaging allows quantitation of velocities of blood flow and myocardial motion and intravascular flow rates. Parallel imaging involves techniques that speed up CMR data acquisition by coordinating data obtained from

different components of the surface receiver coils, now routinely used to reduce acquisition time, improve temporal resolution, or even eliminate artifacts.

T1 and T2 Mapping

T1 mapping estimates in quantitative terms the expansion of the extracellular space in the myocardium where GBCA distributes. This method has demonstrated good correlation with collagen content of the interstitial space in conditions where diffuse fibrosis or infiltration occurs and can serve as a noninvasive method in monitoring disease progression or treatment response. Using both pre- and postcontrast T1 measurements, one determines the change of R1 (= 1/T1) between pre- and postcontrast states in myocardium relative to the change of R1 in blood. This ratio estimates the tissue volume fraction filled by extracellular GBCA. Compared to T1-weighted imaging such as LGE, T1 mapping provides quantitation of the spectrum of extracellular volume expansion from fibrosis or infiltration. T1 mapping techniques in early clinical studies have characterized significant changes in the myocardium not visible by LGE imaging.[2,3] Myocardial T2 mapping, which involves acquisition of a series of images with different T2 weighting, provides a quantitative measurement of regional fraction of free water in the myocardium. Compared to T2-weighted imaging, T2 mapping renders the detection of myocardial edema more reliable and is less prone to artifacts caused by motion or arrhythmia.

Patient Safety

All clinical CMR scanners depend on maintenance of a strong magnetic field that cannot be removed except in emergency situations. Common implants hazardous to CMR scanning include cochlear implants, neurostimulators, hydrocephalus shunts, metal-containing ocular implants, pacing wires, and metallic cerebral aneurysm clips. A full list is available at www.mrisafety.com. However, sternal wires, mechanical heart valves, annuloplasty rings, coronary stents, nonmetallic catheters, and orthopedic or dental implants are safe. Most claustrophobic patients can be managed with oral sedation alone or use of a scanner with large bore size. There are now pacemakers and implantable cardioverter-defibrillators (ICDs) approved by the U.S. Food and Drug Administration (FDA) that allow implanted patients to undergo MRI safely under specific imaging settings.

Standardization of Imaging Acquisitions and Reporting.
Several aspects of CMR imaging are key to delivery of a high-quality clinical service. The Society for Cardiovascular Magnetic Resonance (SCMR) has published guidelines for image interpretation and postprocessing techniques.[4] Normal values of various cardiac functions and chamber sizes can be pulse sequence specific, and recent updates have been published.[5] Furthermore, it is important to be aware of established criteria to assess CMR image quality,[6] as well as common CMR artifacts.[7]

Application in Specific Disorders and Conditions

This section discusses clinical applications of CMR imaging. **eTable 17.1** summarizes the CMR protocols used at our center. **Table 17.2** describes typical CMR findings of common conditions. A detailed description of CMR protocols endorsed by the SCMR can be found at www.scmr.org.

TABLE 17.2

Cardiac Magnetic Resonance Imaging (CMR) Findings That Differentiate Among Causes of Cardiomyopathy

CMR STUDY INDICATION	CINE CARDIAC STRUCTURE/FUNCTION	MYOCARDIAL EDEMA	MYOCARDIAL PERFUSION	LGE MAPPING	ASSOCIATED CMR FINDINGS
Acute myocardial stunning	RWMA	Positive	Normal (at rest)	Normal	Stress perfusion may show perfusion defect during peak vasodilation (if significant residual coronary stenosis exists). Coronary MRA may show luminal stenosis.
Chronic myocardial hibernation	RWMA, regional wall thinning possible	Negative	Usually shows resting subendocardial perfusion defect in a coronary distribution	Normal	Stress perfusion shows larger extent of perfusion defect than at rest (reversible defect) in regions without LGE. Intracavitary thrombus may exist in areas of stagnant flow.
Acute myocardial infarction	RWMA	Usually, transmural bright region in segments subtended by infarct-related artery	Subendocardial perfusion at rest (given revascularization of infarct-related artery) represents "no-reflow" zone of infarction	Subendocardial or transmural LGE in coronary distribution	Microvascular obstruction in "no-reflow" zone may be seen by LGE or myocardial perfusion imaging. Evidence of myocardial hemorrhage by T2 and T2* imaging has been described. Intracavitary thrombus may exist in areas of stagnant flow.
Chronic myocardial infarction	RWMA, chronic remodeling changes	Negative	Subendocardial defect at rest matching thinned infarcted region, but can be normal in small infarcts after coronary revascularization	Thinned subendocardial or transmural LGE in a coronary distribution	Intracavitary thrombus may exist in areas of stagnant flow.
Myocardial ischemia	Normal or RWMA	Negative	Reversible subendocardial perfusion defect in a coronary distribution	Normal	Subendocardial perfusion defect from significant coronary stenosis should persist beyond peak myocardial enhancement during first-pass transit of GBCA bolus. Coronary MRA may show luminal stenosis.
Idiopathic dilated cardiomyopathy	Dilated hypocontractile LV/RV	Negative	Normal	Midwall LGE often in the septum	Mitral regurgitation secondary to dilated ventricle and mitral annulus may be present.
Hypertrophic cardiomyopathy (HCM)	Increased ventricular mass Asymmetric septal hypertrophy in some cases with or without LV outflow obstruction Spade-shaped LV chamber in apical HCM	Often abnormal	Abnormality in thickened myocardial segments may represent abnormal microcirculation.	LGE at RV insertion into LV or patchy midwall involvement in hypertrophied segments	Outflow or midventricular obstruction by phase-contrast imaging Systolic anterior motion of mitral leaflet with or without mitral regurgitation May show reduced intramyocardial motion in hypertrophic regions Reversible perfusion defect may indicate abnormality of coronary microcirculation.
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	RV dilated/aneurysmal	Negative	Normal	RV often full-thickness LGE matching location of RV aneurysm with or without LV focal LGE	Fatty infiltration of RV and LV focally may be seen by T1W FSE imaging and confirmed by fat suppression techniques. "Nulling" of normal myocardium of RV and LV needs different inversion time (TI).
Acute myocarditis	RWMA and/or hypocontractile LV	Usually, transmural bright regions are seen; can be patchy or diffuse.	Normal	Epicardial and midwall LGE involving inferolateral wall or septum	Pericardial involvement or effusion possible
Cardiac sarcoidosis	RWMA and/or hypocontractile LV/RV	Bright regions representing myocardial edema are variable.	Normal	Multifocal intense LGE often involving septum, inferolateral wall of LV, right atrium, and RV free wall	Mediastinal lymphadenopathy
Cardiac amyloidosis	Restrictive morphology, reduction of systolic thickening in LGE segments	Negative	Diffuse perfusion defect common	Diffuse circumferential (often subendocardial) LGE	Rapid gadolinium washout from LV blood pool after injection Difficulty in finding right TI in "nulling" normal myocardium during LGE imaging Low endocardium/blood T1 ratio several minutes after contrast injection Thickened atrial walls with atrial

					LGE, loss of atrial contraction
Iron overload cardiomyopathy	Hypocontractile LV with dark myocardium	Negative	Normal	Normal	Very low hepatic T2* value
LV noncompaction	Hypocontractile LV with spongelike trabeculae often in lateral wall and apex	Negative	Normal	Midwall or focal LGE	May see intracavitary thrombi
Apical ballooning syndrome	Circumferential ballooning and RWMA of all apical segments	Bright regions primarily involve apical segments	Normal	Normal or only minimal subendocardial LGE	Patchy intermediate-intensity LGE without loss of wall thickness and T2W evidence of myocardial edema can be seen. Reversal of abnormal findings after stressful events helps diagnosis.
Endomyocardial disease	Dilated hypocontractile LV and/or RV	Negative	Normal	Diffuse subendocardial LGE of LV or RV with or without thrombus	Cavitary thrombus can be seen on cine SSFP or LGE imaging with long TI. May be extensive to obliterate LV or RV apex
Fabry disease	Concentrically thickened LV ± RWMA with wall thinning	Negative	Normal	Midwall LGE often in inferolateral wall	Associated evidence of CAD possible
Chagas disease	Often presents as dilated and severe hypocontractile LV during latent period of the disease	Negative in latent period; positive if presented acutely	Normal	Resembles pattern of healed viral myocarditis, with epicardial LGE often involving inferolateral wall Apical aneurysmal changes have been described.	—
Acute pericarditis	Often normal; pericardial effusion	Positive if myocardial involvement	Normal	Often normal but may see diffuse pericardial enhancement	Pericardial thickness often normal CMR is better than echocardiography in assessing extent and loculation of pericardial effusion.
Chronic pericardial constriction	Small heart, large atria, and abnormal septal motion with respiratory variation during real-time cine imaging	Negative	Normal	Diffuse pericardial enhancement Myocardial involvement possible	Diffuse thickening (>3 mm) of pericardium seen by T1W FSE Constrictive tricuspid inflow pattern by phase contrast Bilateral pleural effusions Enlarged venae cavae and tubular-shaped RV
Cardiac mass	Proximity to RWMA or catheter, atrial fibrillation, and recent endovascular procedure are associated with thrombus.	Thrombus is dark on T2W imaging. High SI may indicate edema with tumor mass.	Thrombus is dark on first-pass perfusion imaging. Cardiac tumors have variable degree of enhancement on first-pass perfusion.	Mural thrombus may have an “etched” appearance on LGE imaging. May see LGE within tumor mass from fibrosis	Most malignancy is metastatic rather than primary. Recognize common normal structures: eustachian valve, Chiari network, crista sagittalis or terminalis, RV moderator band, and interatrial septal aneurysm. Beware of “pseudotumors”: coronary or aortic aneurysm, lipomatous hypertrophy of interatrial septum, hiatal hernia, catheters, etc.

ARVC, CAD, coronary artery disease; *FSE,* fast spin echo; *LGE,* late gadolinium enhancement; *LV,* left ventricle/ventricular; *MRA,* magnetic resonance angiography; *RV,* right ventricle/ventricular; *RWMA,* regional wall motion abnormality; *SI,* signal intensity; *SSFP,* steady-state free precession; *T1W,* T1-weighted; *T2W,* T2-weighted.

ETABLE 17.1

Typical Cardiac Magnetic Resonance (CMR) Protocols at Brigham and Women's Hospital

CMR STUDY INDICATIONS	CMR TECHNIQUES OF HIGH RELEVANCE	TYPICAL SCAN PLANES	OPTIONAL TECHNIQUES
Myocardial viability for benefit from coronary revascularization	Cine cardiac structure/function Low-dose dobutamine cine (may depend on local expertise) Myocardial perfusion at rest LGE imaging for myocardial scar	Short-axis stack and selected long-axis locations Cine and LGE locations should match each other.	Stress myocardial perfusion Phase contrast for coexisting valvular heart disease Imaging for cardiac thrombus
Myocardial ischemia Vasodilating stress Dobutamine stress Exercise stress	Cine cardiac structure/function Myocardial perfusion at peak vasodilating stress and at rest LGE imaging for myocardial scar Cine function at baseline, during escalating stages of dobutamine infusion ± atropine, and recovery LGE imaging for myocardial scar	Short-axis stack and selected long-axis locations 3 short-axis and 2 or 3 long-axis locations for stress cine	Myocardial perfusion during dobutamine stress
Acute myocardial infarction	Cine cardiac structure/function Myocardial edema imaging Myocardial perfusion at rest LGE imaging for myocardial scar	Short-axis stack and selected long-axis locations	Imaging for cardiac thrombus and microvascular obstruction (no-reflow)
Detecting ACS or other causes of myocardial injury	Cine cardiac structure/function Myocardial edema imaging Myocardial perfusion at rest LGE imaging for myocardial scar	Short-axis stack and selected long-axis locations	Stress myocardial perfusion
Assessing etiology of undiagnosed CMP or specific CMP	Cine cardiac structure/function Myocardial edema imaging (if acute myocarditis, ACS, or infiltrative CMP suspected) Myocardial perfusion at rest LGE imaging for myocardial scar	Short-axis stack and selected long-axis or axial locations	Myocardial and hepatic iron content (if cardiac hemochromatosis suspected): myocardial T2* map Stress myocardial perfusion (if CAD suspected) FSE with and without fat suppression (if ARVC suspected) Phase-contrast flow imaging (if outflow obstruction suspected in HCM) Myocardial T1 quantitation (amyloidosis)
Pericardial disease	Cine cardiac structure/function T1W FSE without fat suppression to assess pericardium (low-intensity linear structure that lies between high-intensity mediastinal and epicardial fat) Myocardial edema imaging (if acute myocarditis, ACS, or infiltrative CMP suspected) LGE imaging for myocardial scar	Short-axis stack and selected long-axis or axial/oblique locations	Myocardial tagging to assess perimyocardial adhesions in region of reduced strain Imaging for sizes of venae cavae Real-time cine SSFP (to see septal motion) and phase-contrast flow across tricuspid valve for pericardial constriction T1W and T2W techniques to assess fluid content of significant pericardial effusion; transudative effusion is gray or dark on T1W and bright on T2W images; exudative effusion is bright and subacute hemorrhage is inhomogeneous on T1W images.
Valvular heart disease	Cine cardiac structure/function Phase-contrast flow of dysfunctional valve of interest. Use appropriate encoding velocity (V_{ENC}) strengths to obtain peak velocity (valvular stenosis) and forward/regurgitant flows (valvular insufficiency) Imaging of the great vessels (FSE, MRA, others) for anatomy	Short-axis stack and selected long-axis or axial/oblique locations	LGE for myocardial scar (e.g., severe aortic stenosis)
Cardiac mass or thrombus	Cine cardiac structure and function (size, attachment, motion pattern of mass) T1W FSE without and with fat saturation to assess fat content and structure T2W FSE to look for tissue edema or simple cyst T1W imaging before and after contrast to assess vascularity of mass	Short-axis stack and selected long-axis or axial/oblique locations	EGE or LGE with long inversion time to assess for thrombus First-pass perfusion to assess mass with high vascularity LGE to detect necrosis
CMR for left atrial mapping and pulmonary vein ablation	Cine cardiac structure/function 3D FGRE MRA imaging of left atrial volume and pulmonary veins	Short-axis stack and selected long-axis locations Coronal 3D locations for MRA	Phase-contrast imaging prescribed as cross section of origin of pulmonary veins from coronal MRA images; use encoding velocity of 30 cm/sec for normal flow, and increase if pulmonary stenosis suspected or aliasing detected. High-resolution LGE imaging of left atrial scar (with navigator guidance) reported by experienced centers in patients with radiofrequency ablation of left atrium

ACS, Acute coronary syndrome; *ARVC,* arrhythmogenic right ventricular cardiomyopathy; *CAD,* coronary disease; *CMP,* cardiomyopathy; *EGE,* early gadolinium enhancement; *FGRE,* fast gradient-recalled echo; *FSE,* fast spin echo; *HCM,* hypertrophic obstructive cardiomyopathy; *LGE,* late gadolinium enhancement; MRA, magnetic resonance angiography; *SSFP,* steady-state free precession; *T1W,* T1-weighted; *T2W,* T2-weighted.

Coronary Artery Disease

Myocardial Infarction

CMR provides a comprehensive assessment of the spectrum of coronary artery disease (CAD) using cine imaging for cardiac structure and function, perfusion imaging for myocardial blood flow, LGE for infarction, and in patients with acute coronary syndrome, T2-weighted or mapping imaging for myocardial edema. At a spatial resolution of 1.5 to 2 mm and a high contrast-to-noise ratio, LGE imaging detects subendocardial infarction of either the left or the right ventricle at a higher sensitivity than any other current cardiac imaging techniques, and its tissue contrast capability allows visualization of necrotic and non-necrotic myocardium. Infarct size determined by LGE imaging has been well validated against histologic pattern, and commercial software is available to perform infarct size quantification. CMR is valuable in assessing complications from MI (**Fig. 17.2**).

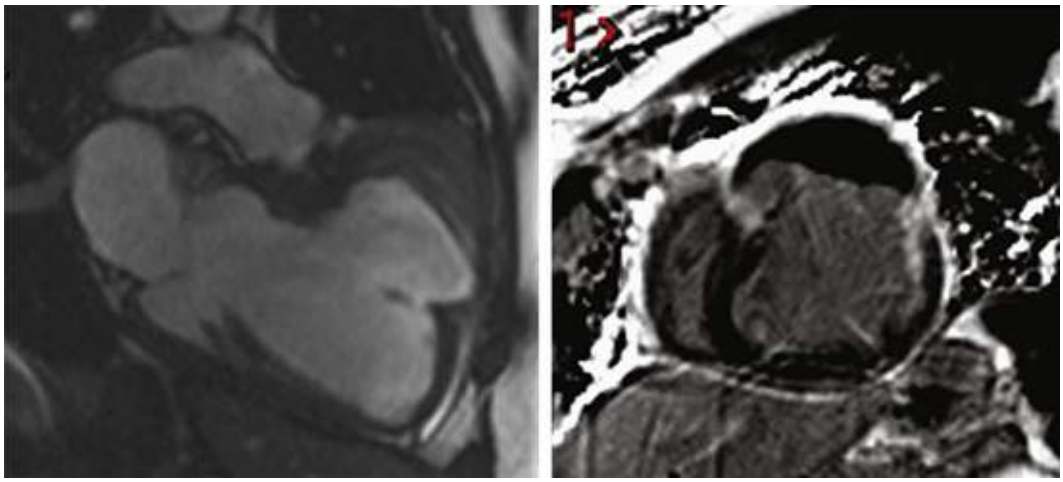


FIGURE 17.2 **Left,** Two-chamber long-axis steady-state free precession (SSFP) cine image at end-diastole in patient 5 years after anterior myocardial infarction (MI) demonstrates a chronic anterior pseudoaneurysm. Note narrowed neck of the pseudoaneurysm. **Right,** Short-axis phase-sensitive inversion recovery (PSIR) late gadolinium enhancement (LGE) image from same patient shows enhancement of fibrous outer layer of the pseudoaneurysm, which is lined with thrombus that appears black. (Courtesy Drs. Christopher Kramer and Michael Salerno, University of Virginia Health System.)

In patients with an acute reperfused MI, ischemic areas at risk (using either T2-weighted or precontrast T1 mapping) that surround an endocardial infarction and microvascular obstruction (no reflow) within an infarction are often seen and can be quantified (**Fig. 17.3** and Video 17.4). T2* imaging detects intramyocardial hemorrhage after acute MI (**Fig. 17.4**). These measurements along with right ventricular (RV) infarction may provide prognostic values incremental to clinical risk scores, left ventricular (LV) infarct size, and LV ejection fraction (EF).[8,9] More recently, characterization of remote myocardial fibrosis using serial T1 mapping has been shown to provide insights in post-MI cardiac remodeling and assess response to novel therapies.[10] In community-based studies that used CMR, MI detected by LGE imaging but unrecognized by either clinical examination, including ECG (thus untreated), was found in 6% to 17% of patients, with a marked increase in mortality consistently reported in these patients with unrecognized MI.[11,12] An interpretive algorithm incorporating various CMR imaging components can classify the age of an infarction as less than 1 month, 1 to 6 months, or more than 6 months.[13]

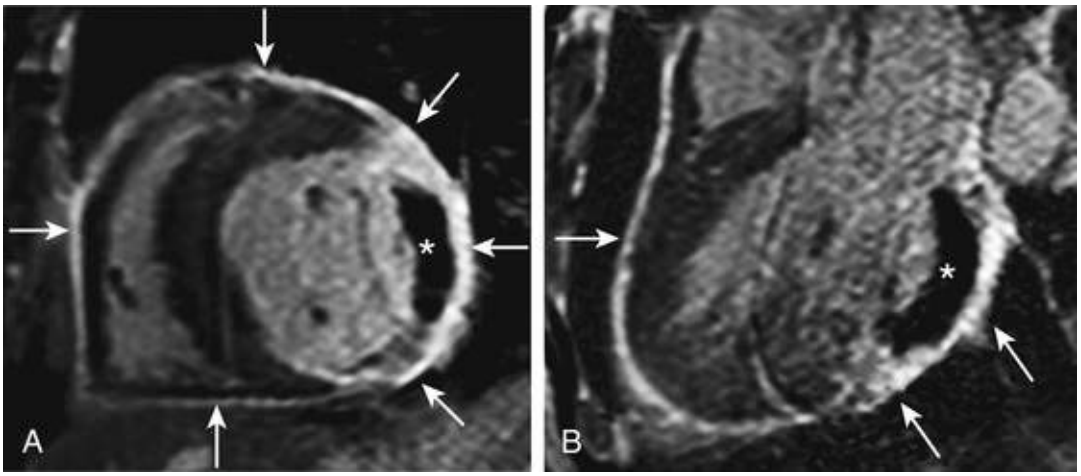


FIGURE 17.3 Acute pericarditis associated with transmural lateral MI. Short-axis **(A)** and long-axis **(B)** LGE views demonstrate a large transmural infarct with microvascular obstruction (*asterisks*) associated with severe acute pericarditis with diffuse LGE within the pericardium (*arrows*). (Courtesy Dr. Otávio Coelho Filho, University of Campinas, São Paulo, Brazil.)

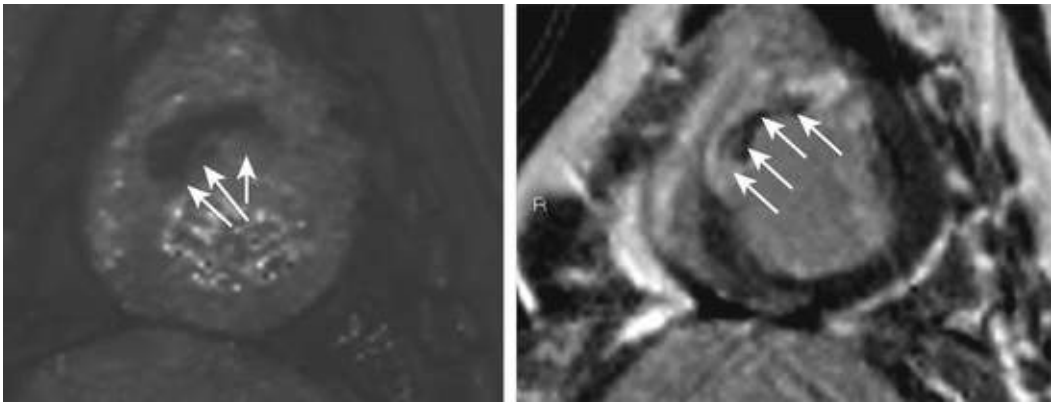


FIGURE 17.4 **Left,** Short-axis T2*-weighted image from a porcine model of reperfused MI demonstrates intramyocardial hemorrhage in anteroseptum. **Right,** Short-axis PSIR LGE image (*right*) in the same animal shows transmural LGE with a midwall region of intramyocardial hemorrhage. (Courtesy Drs. Christopher Kramer and Michael Salerno, University of Virginia Health System.)

Assessment of Myocardial Viability and Benefit from Coronary Revascularization

CMR imaging offers a multicomponent assessment of structure and physiology to evaluate myocardial viability. From early cine CMR studies, end-diastolic wall thickness of 5.5 mm or more and dobutamine-induced systolic wall thickening of 2 mm or more have excellent sensitivity and specificity in the prediction of segmental contractile recovery after revascularization. In addition, the transmural extent of myocardial scar detected by LGE imaging accurately depicts a progressive stepwise decrease in functional recovery despite successful coronary revascularization, especially in myocardial regions of akinesia or dyskinesia. Compared with dobutamine cine CMR, LGE is easy to perform and interpret, and a 50% transmurality cutoff is sensitive in detecting segmental contractile recovery. On the other hand, low-dose dobutamine cine imaging provides a highly specific physiologic assessment of the midmyocardial and subepicardial contractile reserve and early after acute MI, when tissue edema is prominent.

Detecting Acute Coronary Syndromes and Differentiating from Noncoronary Causes

CMR imaging has high sensitivity and specificity for detecting acute coronary syndromes and risk-stratifying patients presenting with acute chest pain. Specifically, CMR is a valuable diagnostic tool in patients who present with acute elevation of serum biomarkers consistent with myocardial injury but with nonobstructive coronary arteries, because it may provide diagnostic information to direct therapy and improve prognosis.[14] T2-weighted imaging (or T2 mapping) can detect the extent of the salvageable myocardium days after emergent restoration of coronary flow by percutaneous coronary intervention (PCI). Furthermore, CMR can capture various noncoronary abnormalities used to diagnose the causes of chest pain.

Detecting and Quantifying Myocardial Ischemia

Stress CMR imaging is performed using pharmacologic stress agents (vasodilating or positive inotropic) in many centers, and less often using treadmill exercise in highly specialized centers. As summarized by the recent AHA/ACCF guidelines for stable ischemic heart disease, vasodilating stress CMR *myocardial perfusion imaging* (MPI) is an effective clinical tool in diagnosing CAD and risk-stratifying patients with suspected myocardial ischemia.[15] Many single-center studies have shown that a negative CMR MPI predicts an annualized cardiac event rate of less than 1% in patients with an intermediate pretest likelihood of CAD. In addition, multiple clinical studies and a meta-analysis demonstrated excellent correlation of CMR MPI assessment of ischemia with invasive measurement of fractional flow reserve, illustrating the high accuracy of CMR in determining the physiologic significance of coronary stenosis[16] (**Fig. 17.5**).

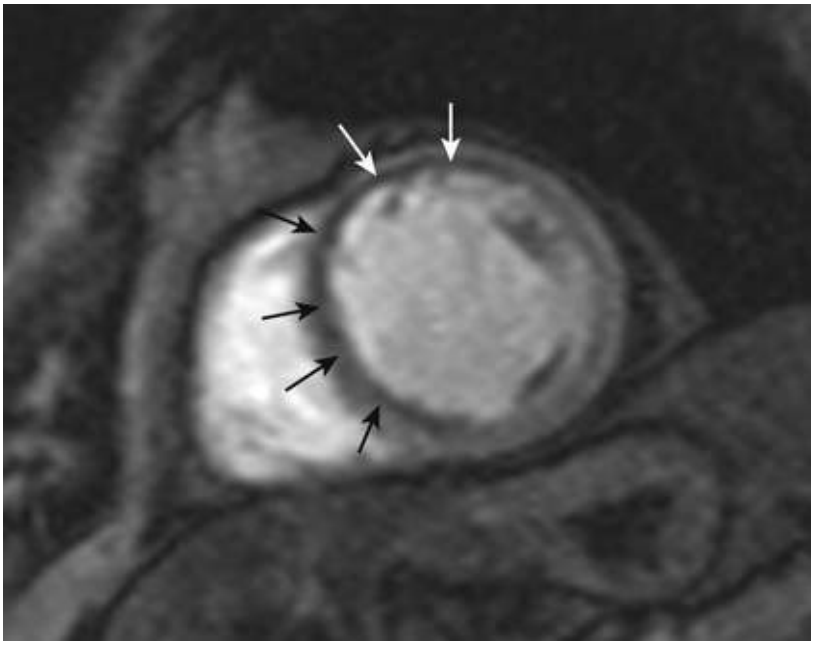


FIGURE 17.5 Patient who presented with chest pain underwent stress CMR perfusion with pharmacologic vasodilating stress. Note large subendocardial perfusion defect involving the anterior, septal, and inferior walls (*arrows*). On angiography, there is a critically stenosed proximal left anterior descending artery and right coronary artery.

Compared to single-photon emission tomography (SPECT) imaging (**see Chapter 16**), CMR MPI has several technical advantages: It is not limited by attenuation artifacts, is free from ionizing radiation, and

has a three- to fourfold higher spatial resolution than SPECT (Video 17.5). A stress CMR study that includes stress and rest perfusion imaging, cine cardiac function, and myocardial viability takes 35 to 45 minutes (versus >2 hours for dual-isotope SPECT). CMR MPI also can characterize the dynamic range of myocardial blood flow without being limited by plateau effect of counts at high flow rates, as seen in some nuclear tracers. Several clinical studies have reported that CMR MPI performed better than SPECT in detecting single- or multivessel CAD (area under curve, 86% to 89% versus 67% to 70%).

Dobutamine stress CMR (both perfusion and cine function) has excellent sensitivity and specificity in detecting CAD and is superior to dobutamine stress echocardiography (**see Chapter 14**). Such favorable results were consistent and maintained despite the presence of underlying resting wall motion abnormality. Multiple clinical studies have shown that dobutamine cine CMR provides strong prognostic value in risk assessment of patients. Accelerated real-time cine CMR imaging can eliminate the need for patient breath-holding or ECG gating during dobutamine stress in selected patients.

There are several promising technical developments in CMR MPI. First, quantitative CMR MPI is becoming the standard of care in some experienced CMR centers, with its potential advantages over qualitative methods including minimization of reader's bias and improved diagnostic accuracy, especially in patients with possible multivessel CAD.[17] Second, dynamic three-dimensional perfusion can provide larger myocardial coverage, can improve image quality, and has shown promising preliminary clinical results compared with invasive fractional flow reserve (FFR).[18] At a more investigational level, CMR can image for the change in myocardial oxygenation at rest and stress without the need for GBCA injection; deoxygenated hemoglobin in blood can act as an intrinsic contrast agent, changing proton signals in a way that can be imaged to reflect the level of blood oxygenation.[19]

Imaging of Atherosclerotic Plaques.

MRI of the carotid artery and the descending aorta remains the most comprehensive noninvasive method to characterize plaque structure and activity. Most studies used a standardized protocol of multiple contrast-weighted imaging sequences to identify carotid plaque fibrous cap, hemorrhage, calcifications, and loose matrix. Gadolinium-enhanced T1-weighted imaging helps to discriminate fibrous cap from necrotic or lipid core. Carotid plaque neovascularization can be assessed with contrast-enhanced dynamic MRI by measuring the transfer constant between blood and the extracellular space and may provide prognostic information. Ultrasmall superparamagnetic particles of iron oxide (USPIO) may target macrophage activity based on histologic and electron microscopic analyses of atherosclerotic plaques, and this may be imaged using T2*-weighted MRI. Similar to assessment of carotid plaque contents, CMR offers accurate quantitation of plaque size and extent and composition of thoracic aortic plaques and can complement plaque imaging with three-dimensional MRA over a large thoracic volume. Common to all modalities, imaging of the coronary plaque is challenged by both cardiac and respiratory motion and the small vessel size, but future technical improvements using exogenous targeted contrast agents, intravascular coils, and high-field CMR may offer promise.

Cardiomyopathy

Overall Approach

CMR imaging is an invaluable tool for assessing various cardiomyopathies given its multifaceted interrogation of ventricular structure and myocardial physiology in matching arbitrary scan planes. **Table**

17.2 summarizes the CMR features using rest and stress myocardial perfusion, regional function, LGE, and T2-weighted CMR, in differentiating causes of cardiomyopathies and severity of the conditions. In patients with valvular disease, volumetric cine CMR can assess the loading impact onto the heart and the resultant ventricular compensation, which determines appropriateness of surgery. Tissue tagging may help to resolve any suspected regional wall motion abnormality at rest or stress or when myocardial adhesion from pericardial diseases becomes part of the assessment. Current investigational CMR may offer unique guidance for cardiac resynchronization therapy in heart failure patients by demonstrating LV dyssynchrony, scar extent, and coronary venous anatomy in a single study.

Hypertrophic Cardiomyopathy

Compared to echocardiography, CMR provides a more precise three-dimensional pattern of LV hypertrophy and tissue characteristics in patients with hypertrophic cardiomyopathy (HCM) (**Fig. 17.6**) (**see Chapter 78**). Echocardiography missed hypertrophic segments and underestimated the magnitude of hypertrophy in the basal anterolateral wall by as much as 33% compared to CMR. In addition, 40% of apical aneurysms are missed by echocardiography. In HCM patients with severe septal hypertrophy and symptomatic dynamic LV outflow tract obstruction, CMR has the advantage over echocardiography of assessing the reduction in septal thickness from surgical myectomy or alcohol septal ablation (Video 17.6). LV mass index varies widely with maximal LV wall thickness because of the heterogeneity of the HCM phenotype. Markedly elevated LV mass index (males >91g/m^2 and females >69g/m^2) was sensitive (100%), whereas maximal wall thickness greater than 30 mm was specific (91%) for cardiac deaths. Presence of LGE is indicative of heterogeneous fibrosis and myofibril disarray and has been associated with ventricular arrhythmias and progressive ventricular dilation. Its extent provides prognostic value to patient risk beyond cardiac structures and function, particularly in patients considered at low clinical risk.[20] The multifaceted approach by CMR may allow an individualized characterization of abnormal myocardial pathophysiology secondary to coronary microvascular dysfunction (Video 17.7), fibrosis, and hypertrophy.

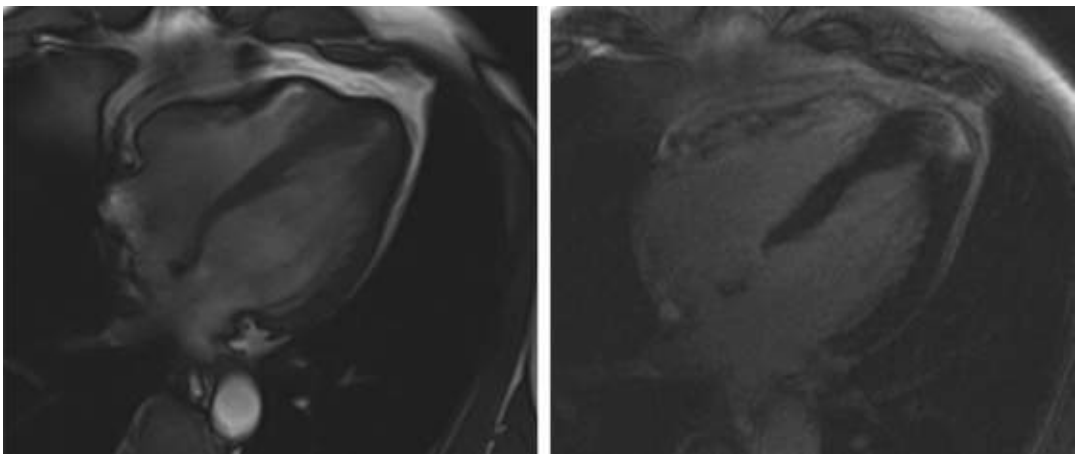


FIGURE 17.6 CMR images in 58-year-old man with history of palpitations and abnormal ECG shows evidence of apical increased wall thickness **(left)** and LGE involving apical inferior wall and true apex, consistent with fibrosis **(right).** These morphologic features are diagnostic of apical hypertrophic cardiomyopathy.

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) distinguishes itself from other cardiomyopathies by (1) a predisposition toward ventricular arrhythmia that precedes overt morphologic abnormalities and even histologic substrate and (2) diverse phenotypic manifestations despite the success in isolating the causative desmosomal mutations (**see Chapter 77**). CMR offers advantages over echocardiography with its quantitative and volumetric assessment of RV function and its fibrofatty tissue characterization of myocardium. Recent evidence indicates that early and predominant LV disease exists in variant groups. Enthusiasm in CMR was somewhat curbed by a lack of standardized imaging protocol in the past and inherent subjectivity in interpreting myocardial fat and wall motion abnormality of the thin-walled crescent-shaped right ventricle. Recent efforts in standardization of CMR protocols have nonetheless affirmed the value of CMR as an integral component in the workup of ARVC. Currently, task force guidelines consider localized aneurysms, severe global dilation with systolic dysfunction, and severe segmental dilation of the right ventricle as major criteria for ARVC (Video 17.8). These abnormalities are typically observed in predilection areas, including the subtricuspid region, basal RV free wall, and LV posterolateral wall.[21] Fat-suppressed LGE imaging of RV fibrosis has shown a high correlation with endomyocardial biopsy and the inducibility of ventricular arrhythmias. However, fat infiltration of the right ventricle as an isolated finding is of limited specificity for diagnosing ARVC. In patients suspected to have ARVC, CMR had a sensitivity of 96% and a specificity of 78% in detecting ARVC, according to diagnostic criteria that included genotype. This approach suggested that CMR potentially detected patients with early disease not characterized by task force guidelines.

Myocarditis

CMR targets the three main pathophysiologic components of myocarditis: myocardial edema by T2-weighted imaging, regional hyperemia and capillary leak by early gadolinium enhancement ratio (EGE_r), and myocardial necrosis or fibrosis by LGE imaging (**see Chapter 79**). **Table 17.1** and a published expert consensus summarize the diagnostic criteria of these techniques for acute myocarditis. From pooled data of the single-center studies, T2-weighted imaging, EGE_r, and LGE have sensitivity and specificity of 70% and 71%, 74% and 83%, and 59% and 86%, respectively. A combined approach using T2-weighted images and LGE provides high diagnostic accuracy for acute myocarditis (**see Table 17.2**). The subepicardium and midmyocardium of the inferolateral walls are usually involved, and *Parvovirus* has been implicated in these cases, but septal involvement is associated with human herpesvirus 6 with potentially more serious sequelae (**Fig. 17.7**). In recent studies, T1 mapping appears to offer promising improvement to the current diagnostic criteria. A proposed diagnostic algorithm using native (precontrast) T1 mapping has demonstrated higher diagnostic consistency than T2-weighted imaging in sizing the inflammatory myocardial region and staging disease activity.[22] Assessing the expansion of extracellular volume (ECV) using T1 mapping combined with LGE imaging can provide higher diagnostic accuracy than the current published criteria.[23]

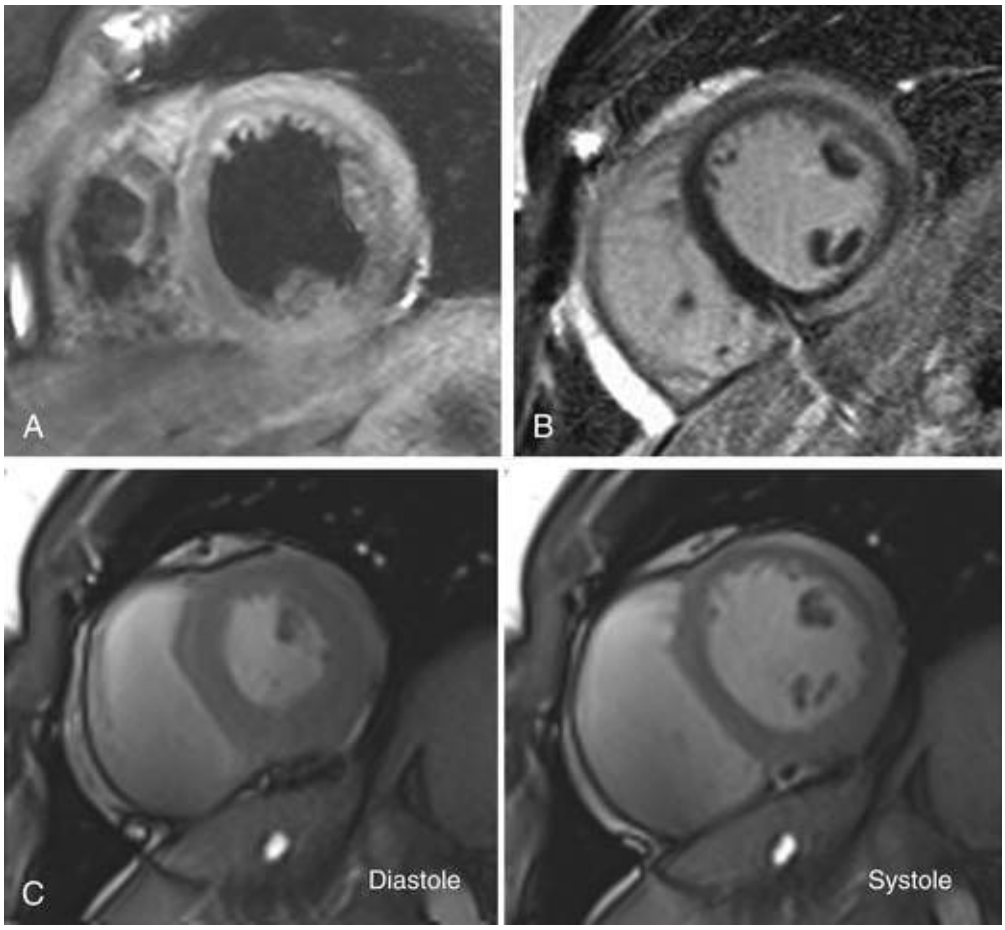


FIGURE 17.7 In 30-year-old man presenting with fever and pleuritic chest pain, troponin T was mildly elevated and serum C-reactive protein greatly elevated. **A,** CMR image show T2 enhancement involving basal and midanterior, anterolateral, inferolateral, and midinferior walls of LV myocardium, in subepicardial and midmyocardial distribution with sparing of subendocardium, suggestive of myocardial edema from a noncoronary inflammatory condition. **B,** Postcontrast LGE image shows LGE of corresponding segments in epicardial lateral wall segments. **C,** On cine images in diastole and systole, LV function globally and regionally was not impaired. These findings are characteristic of acute viral myocarditis. Patient was treated with ibuprofen with improvement of symptoms.

Cardiac Sarcoidosis

The CMR techniques and corresponding findings in cardiac sarcoidosis are listed in **Table 17.2 and eTable 17.1** (**see Chapter 77**). CMR may enhance disease detection through the successive histologic stages of disease: tissue edema, noncaseating granulomatous infiltration, and patchy myocardial fibrosis. LGE imaging has been reported to identify myocardial abnormalities caused by sarcoidosis at a higher sensitivity than the modified Japanese Ministry of Health guidelines. Most often, cardiac infiltration based on LGE imaging is seen in multiple locations involving the septum and basal anterior part of the right ventricle (**Fig. 17.8**). In cases where septal LGE are seen, CMR may also guide sampling during endomyocardial biopsy and increase tissue yield. LGE-positive patients had a ninefold increase in the risk of death or major dysrhythmic events. In patients with extracardiac sarcoidosis, LGE and RV dysfunction are high-risk markers for cardiac death or serious ventricular arrhythmias independent of LVEF.[24,25]

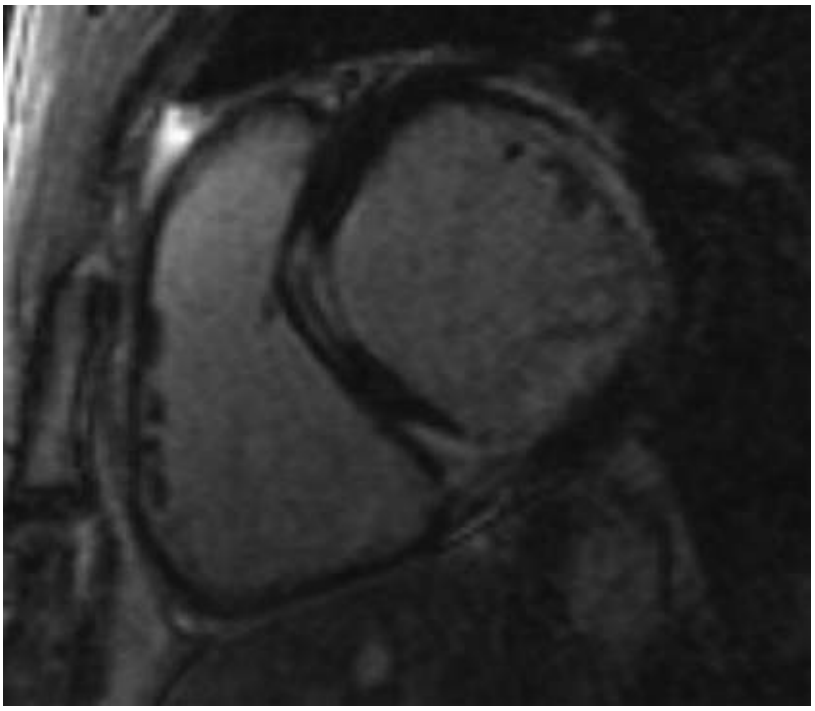


FIGURE 17.8 A 38-year-old man with no past medical history presented to hospital with syncope and was found to have runs of nonsustained ventricular tachycardia. His regional and global LV function was normal on echocardiography. On CMR, multiple regions of LGE are seen involving the septum (epicardial and midlateral wall). Focal expansion of the inferoseptal wall thickness is seen in this segment with LGE, consistent with myocardial infiltration. These patterns are characteristic of cardiac sarcoidosis.

Cardiac Amyloidosis

The typical features of CMR techniques in cardiac amyloidosis are summarized in **Table 17.2** (**see Chapter 77**). This characteristic circumferential pattern of LGE involving the LV and even the RV subendocardium had been reported to have high diagnostic accuracy and in some cases even to obviate the need for endomyocardial biopsy (**Fig. 17.9**). Furthermore, the pattern of LGE may differentiate the subtype of amyloidosis: cardiac amyloidosis caused by ATTR is more likely to show transmural LGE and RV involvement than the AL subtype.[26] The transmurality and extent of LGE represent advanced cardiac amyloidosis, and these findings are associated with patient mortality incremental to common risk markers, including systolic and diastolic function.[27] LGE is easy to interpret for diagnosing cardiac amyloidosis, but myocardial ECV may become a part of the standard diagnostic algorithm because it offers a more complete quantitation of the regional and global severity of amyloid infiltration, as well as in monitoring treatment response. Recent reports indicated that native myocardial T1 value is prolonged from amyloid protein of either AL or ATTR subtype,[28] and this measurement may be useful in diagnosing early cases of cardiac amyloidosis.[29]

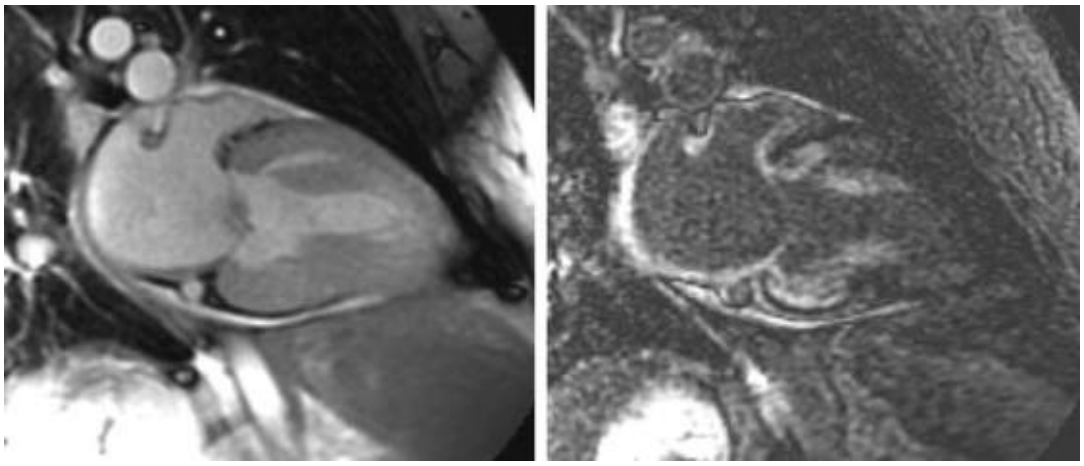


FIGURE 17.9 End-diastolic cine imaging **(left)** and a matching LGE image **(right)** of a patient with cardiac amyloidosis. Note the increase atrial wall thickness, which enhances on LGE imaging. Blood pooling is also remarkably dark after contrast injection, indicative of rapid blood pool washout caused by contrast sequestration into other organs.

Idiopathic Dilated Cardiomyopathy

Major advantages of CMR in evaluating suspected idiopathic dilated cardiomyopathy include ruling out ischemic cardiomyopathy; characterizing the LGE pattern, which has diagnostic and prognostic implications; and monitoring treatment response and disease progression (**see Chapter 77**). In up to 13% of patients diagnosed with nonischemic dilated cardiomyopathy on the basis of nonobstructive coronary angiography, subendocardial or transmural LGE consistent with infarction was seen. On the other hand, current evidence indicates that in the absence of LGE, an ischemic cause of LV dysfunction is highly unlikely. In a prospective randomized study, CMR using a combination of LGE and coronary MRA had a sensitivity of 100% and specificity of 96% in diagnosing ischemic etiology of new-onset heart failure and provided substantial cost-savings when used as a gatekeeper to invasive investigation. Furthermore, in patients with cardiomyopathy but without angiographic coronary stenosis, 28% had patchy or linear midwall striae on LGE most often seen in the basal septum. LGE extent is associated with a lack of response to medical therapy[30] and has been associated with sudden death and inducible ventricular tachycardia, independent of LV size and function.

Iron Overload Cardiomyopathy.

Iron overload cardiomyopathy is either inherited or acquired. In patients with transfusion-dependent thalassemia major, cardiac death as a result of myocardial iron toxicity occurs in 50% of patients. Global systolic LV function is usually preserved, especially in anemic thalassemic patients, until severe cardiac toxicity has developed, and thus provides little if any guidance to use of chelation therapy. The CMR T2* technique for quantifying myocardial iron is summarized in **Table 17.1**. CMR T2* quantitation has been shown to improve delivery of iron chelation therapy and has led to a substantial reduction in mortality for patients with thalassemia major. In patients with reduced ventricular function, a T2* less than 20 milliseconds is consistent with iron overload. Patients with a myocardial T2* less than 10 milliseconds are at the highest risk of developing heart failure within 1 year.

Other Cardiomyopathies.

Chagas disease is a myocarditis caused by infection from the protozoan *Trypanosoma cruzi* endemic in Central and South American countries. Most cases have a self-limiting course, but about 30% of patients

will have persistent parasitemia and latent infection that manifest years later as a dilated cardiomyopathy, often associated with ventricular arrhythmias. CMR is useful in diagnosing (**see Table 17.2**) and monitoring patients infected during the latent period. A diastolic noncompacted-to-compacted thickness ratio of more than 2.3 measured in a long-axis view was reported to be diagnostic for LV noncompaction. However, given the low specificity of this finding alone for genetic cardiomyopathy or adverse outcomes, it remains unclear whether the myocardial morphology is representative of LV noncompaction or merely an epiphenomenon associated with increased cardiac preload[31] (**Fig. 17.10**). Concurrent evidence of clinical heart failure, family history of cardiomyopathy, neuromuscular disorders, embolic events, or ventricular arrhythmias should be considered before diagnosing LV noncompaction.

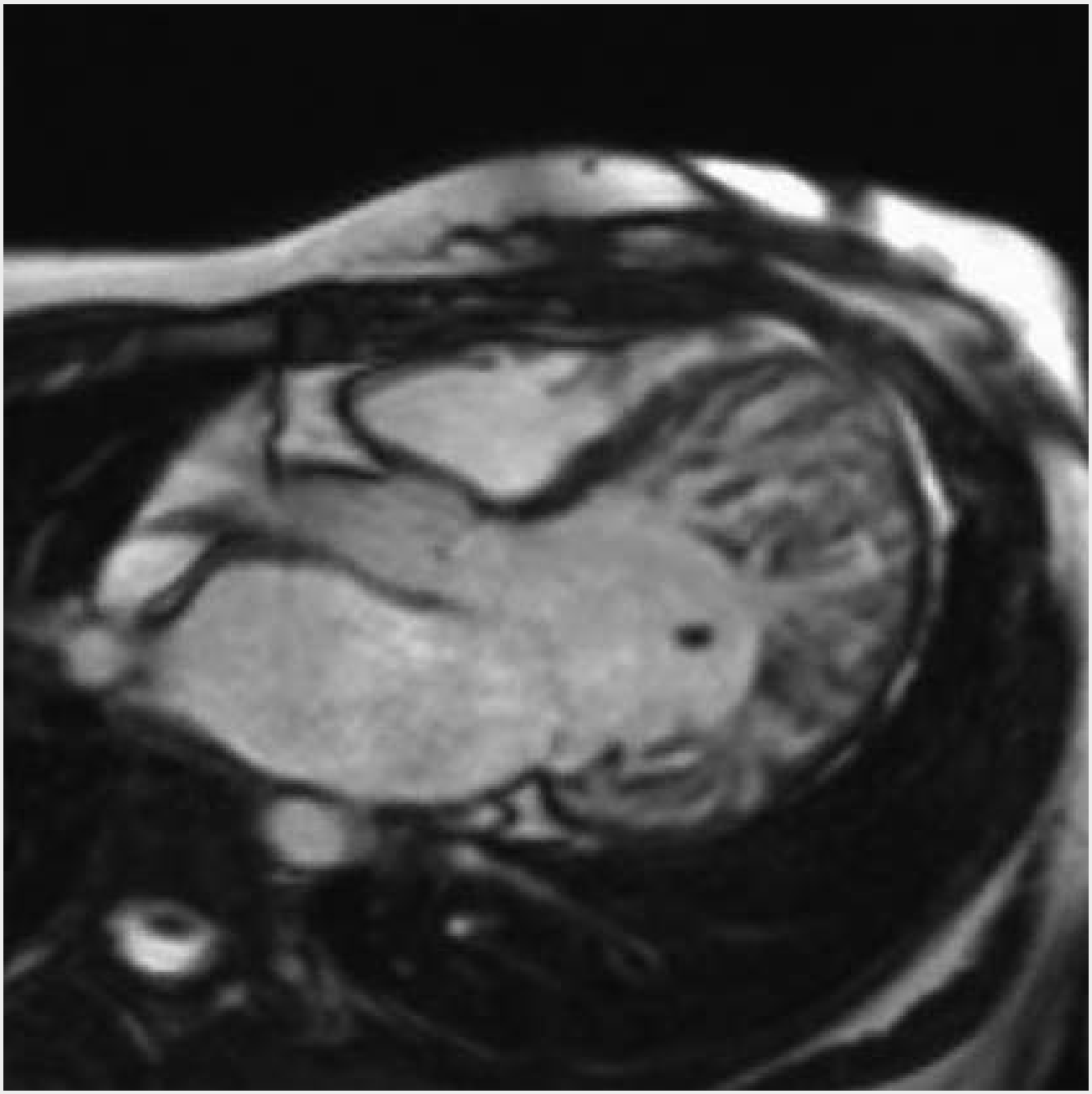


FIGURE 17.10 Left ventricular noncompaction in patient diagnosed with clinical heart failure. Note the pattern of the extensive spongelike appearance of the myocardium.

Transient LV apical ballooning syndrome, or *takotsubo cardiomyopathy*, is characterized by a transient contractile dysfunction of the apex, caused by elevated catecholamines from severe emotional or physical stress (Video 17.9). CMR can be useful in differentiating apical ballooning syndrome from

an acute coronary event. Endomyocardial disease is a restrictive cardiomyopathy that consists of two variants, *endomyocardial fibrosis* and *Löffler endocarditis*, both considered the result of direct toxic effects of eosinophils on the myocardium. Hypereosinophilia, regardless of its cause, has been suggested to lead to cardiomyopathy in three stages: necrosis, thrombosis, and fibrosis. Hypereosinophilia is the hallmark of Löffler endocarditis, whereas it is variable in endomyocardial fibrosis, which has characteristic features on CMR (**see Table 17.2**).

Arrhythmias

Imaging of Patients Before Electrophysiologic Procedures

CMR is helpful in planning electrophysiologic procedures given its ability to identify the potential site of ablation or scar and to provide three-dimensional volume mapping of the atria or ventricles. For patients with atrial fibrillation (AF) undergoing pulmonary venous isolation (PVI), left atrial emptying function and evidence of LV fibrosis on CMR are strong markers of AF recurrence[32,33] (**see Chapter 38**). In addition, in patients with recurrent AF after an ablation attempt, LGE of the atrial walls from prior ablation can guide repeated PVI procedures by identifying and localizing gaps and may reduce procedural duration and radiofrequency application time.[34] In a multicenter trial of patients with AF undergoing catheter ablation, a proprietary commercial LGE method was reported to successfully quantify native atrial tissue fibrosis and predict recurrent arrhythmia.[35] The validity of this method remains to be tested in other centers.

Although still early in development, CMR offers promise for characterizing mechanical dyssynchrony in heart failure patients[36] and providing information relevant to placement of the LV pacing lead, such as coronary venous anatomy and LV scan location. In both ischemic and nonischemic ventricular tachycardia (VT), critical isthmus sites are typically located in peri-infarct regions identifiable by LGE. These findings suggest that CMR can provide guidance to critical isthmus sites during VT ablation.[37]

Risk Stratification of Patients at Risk of Sudden Cardiac Death

CMR contributes to assessment of patients at risk of sudden cardiac death (SCD) by quantitation of LVEF and RV pathology, detection of myocardial scar using LGE, identification of anomalous coronary arteries, and less frequently, use of T2* mapping for iron overload.[38] LV structures and LGE pattern in combination differentiate most patients in this setting as having ischemic, nonischemic, or infiltrative disease, which provides clinical guidance and a patient risk profile. In one study of patients who presented with SCD, LGE identified unexpected myocardial scar and a potential arrhythmic substrate in more than 70%.[39] For patients with CAD, multiple single-center studies report that LGE size is a robust risk marker for SCD independent of LVEF. More than 5% of LV mass has been reported to be a risk marker in both ischemic and nonischemic cardiomyopathies.[40] In addition, it appears that heterogeneity in the scar tissue, characterized by LGE core and peri-infarct signal intensities, may further define the risk of SCD in patients who do not have an indication for ICD therapy.[41] In nonischemic cardiomyopathy, a midwall septal LGE pattern has been noted in many patients with dilated cardiomyopathy, and its size has been associated with inducibility of ventricular arrhythmias and SCD. LV LGE in patients with systemic sarcoidosis has been associated with a high risk of SCD. More research is needed to define how the LGE extent can improve the current practice guidelines, specifically for ICD therapy.

Pericardial Disease

At our center, a typical CMR assessment includes cine SSFP imaging, T1- and T2-weighted double-inversion black-blood FSE (half-Fourier acquisition single-shot turbo spin-echo, HASTE), and LGE imaging of the whole heart to assess for pericardial changes (**see eTable 17.1**). Real-time cine SSFP and phase-contrast flow across the tricuspid valve are often added to the examination to enhance the detection of cardiac constriction (Video 17.10). First-pass perfusion and pre- and postcontrast T1-weighted techniques may also be necessary to determine vascularity of a pericardial mass (e.g., differentiate tumor from thrombus). Cine myocardial tagged (dark lines or grids) imaging may be useful to identify any regional concordance caused by perimyocardial adhesions. Pericardial thickness is easily assessed by either black-blood FSE or cine imaging, and up to 3 mm is accepted as normal. The transverse sinus (lies dorsal to the ascending aorta) and the superior pericardial recess (a curvilinear space to the right of the ascending aorta) may be mistaken for an aortic dissection or a mediastinal mass. The oblique sinus behind the left atrium may be misinterpreted as an esophageal lesion or bronchogenic cyst. Enhancement of the thickened pericardium after administration of GBCA suggests active inflammation or pericardial fibrosis.

CMR is the current test of choice in differentiating constrictive pericarditis from restrictive cardiomyopathy, based on assessing pericardial thickness and constrictive physiology from pericardial disease and the pattern of any myocardial infiltration from restrictive cardiomyopathy (**see Fig. 17.3**). Computed tomography can demonstrate pericardial calcifications but is inferior to CMR because of limited hemodynamic data and tissue characterization. Pericardial cysts usually have thin, smooth walls without internal septa. Their homogeneous transudative contents appear dark on T1-weighted images and bright on T2-weighted images, with no enhancement from GBCA (**Fig. 17.11**). Proteinaceous cysts appear very bright on T1-weighted images. Pericardial metastases are much more common (from lung, breast, and lymphomas) than primary pericardial tumors. Malignant invasion of the pericardium often shows focal obliteration of the pericardial line and a pericardial effusion. Most neoplasms appear dark or gray on noncontrast T1-weighted images, except metastatic melanoma, because its paramagnetic metals are bound by melanin. Partial absence of the pericardium is usually left sided and may be associated with other congenital defects. Absence of pericardium is suspected when lung tissue is seen interposed between the aorta and pulmonary artery or between the heart and diaphragm (**see Chapter 83**).

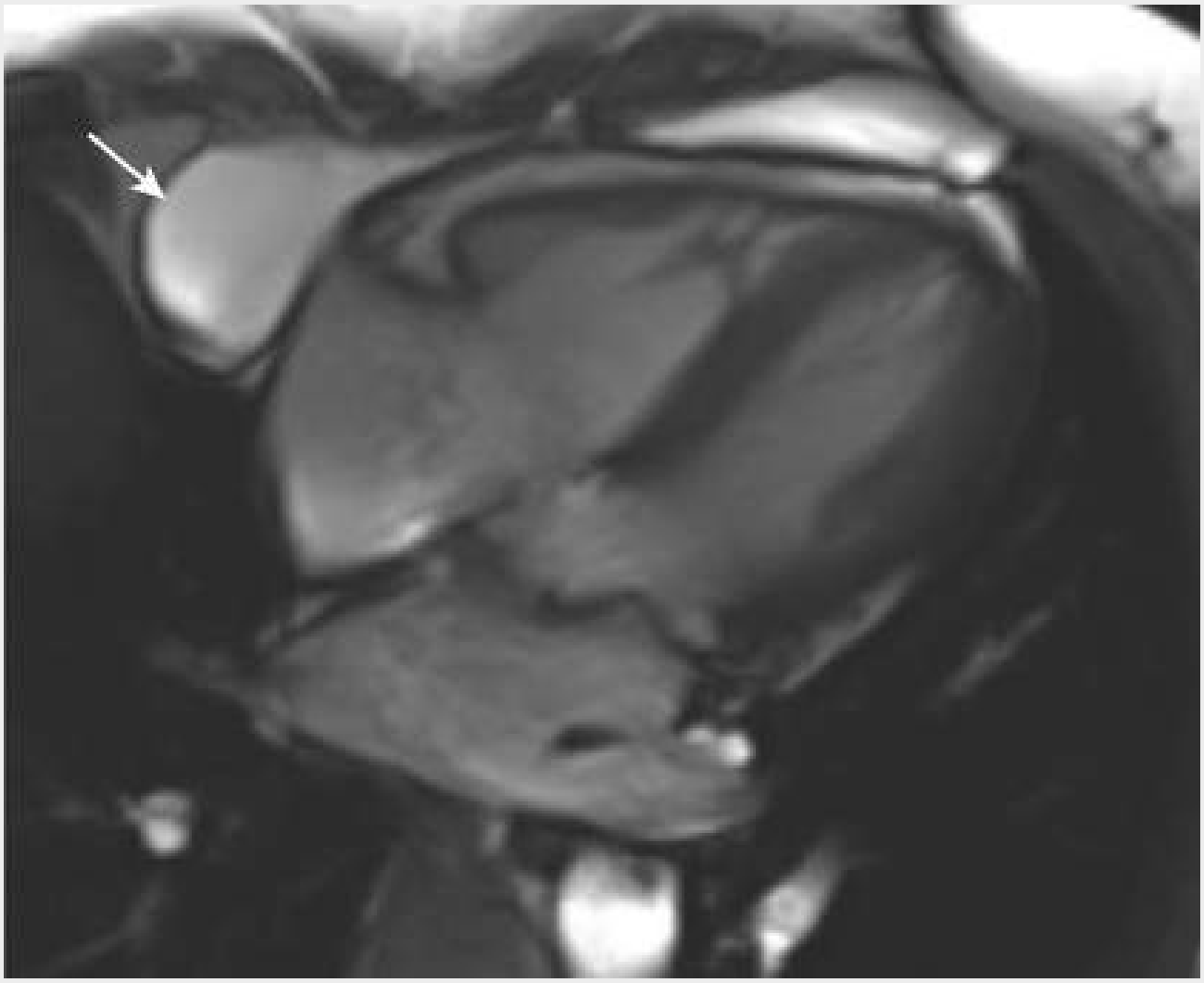
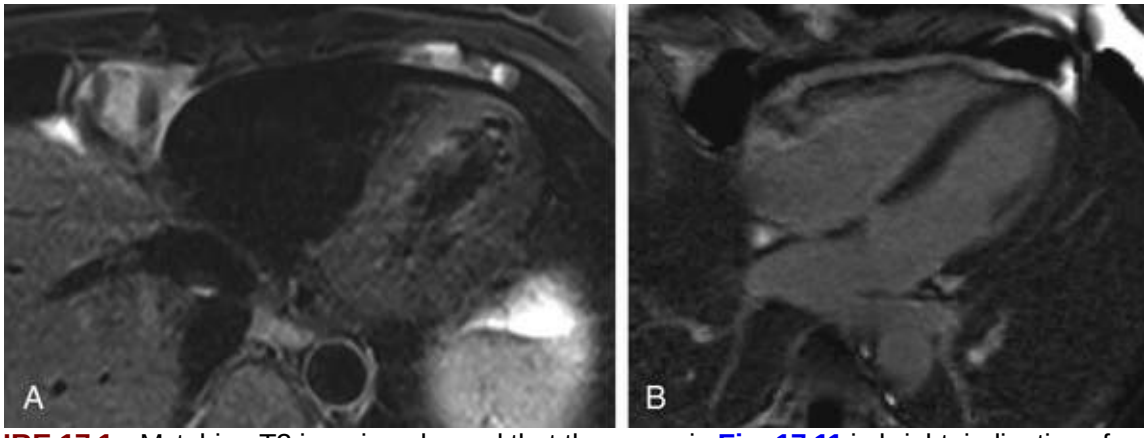


FIGURE 17.11 Pericardial cyst in 47-year-old woman presenting with a history of shortness of breath and palpitations and found to have a mass next to the right atrium on chest radiograph and then referred for CMR. Homogeneous mass (*arrow*) is seen abutting the right atrium and upper right ventricle without significant mass effects. Matching T2 images showed that this mass is bright, indicative of a simple fluid content (**see eFig. 17.1A**), which does not enhance after contrast (**eFig. 17.1B**).



EFIGURE 17.1 Matching T2 imaging showed that the mass in **Fig. 17.11** is bright, indicative of a simple fluid content **(A),** which does not enhance after contrast **(B).**

Adult Congenital Heart Disease

CMR can provide key additive data beyond other imaging methods in assessment of congenital heart disease based on (1) no need for ionizing radiation, (2) three-dimensional tomographic imaging of thoracic structures and anatomy (versus more limited echocardiographic windows with body growth), and (3) correlation of complex anatomy with blood flow and physiology (**see Chapter 75**).

Atrial and Ventricular Septal Defects

CMR offers a less invasive alternative to transesophageal echocardiography (TEE) and even diagnostic catheterization for patients presenting with right-sided volume overload from a suspected left-to-right shunt. A CMR study can detect the presence of an atrial septal defect (ASD) (**Figs. 17.12 and 17.13**; Video 17.11), assess suitability for transcatheter ASD closure, quantify right heart size and function by cine SSFP, determine pulmonary-to-systemic shunt ratio (Qp/Qs) using velocity-encoded phase contrast, and identify any coexisting anomalous pulmonary venous return using three-dimensional contrast-enhanced MRA. Phase-contrast imaging positioned in a plane parallel to the atrial septum and set at a low-velocity range (100 cm/sec) can visualize the ASD en face with good correlation with defect size measured invasively. Phase-contrast imaging of the tricuspid regurgitation can estimate the pulmonary artery systolic pressure. Since most closure devices are MRI compatible, CMR can be used to assess for residual shunt and proper device deployment. Patients with a ventricular septal defect (VSD) can be assessed using similar CMR techniques. In addition, LGE imaging may help to determine if a VSD developed as a complication of MI.

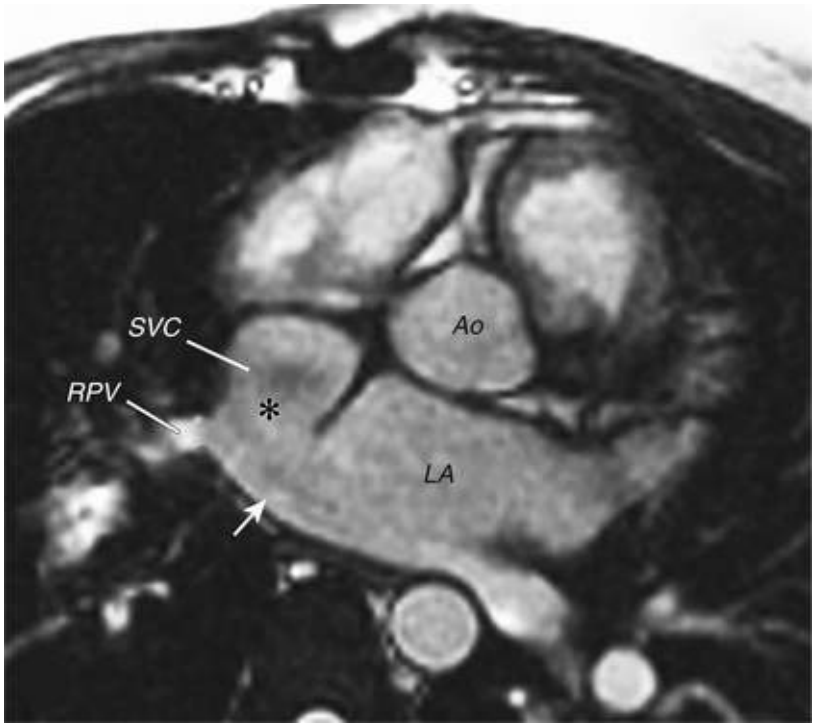


FIGURE 17.12 ECG-triggered SSFP cine CMR in the axial plane showing the defect (*) between the right upper pulmonary vein (*RPV*) and superior vena cava (*SVC*). Left-to-right shunt results from drainage of the RUPV to the SVC and from left atrial blood entering the right atrium through the orifice of the RUPV (*arrow*) and the unroofed wall between RPV and SVC (*). *Ao,* Ascending aorta; *LA,* left atrium.

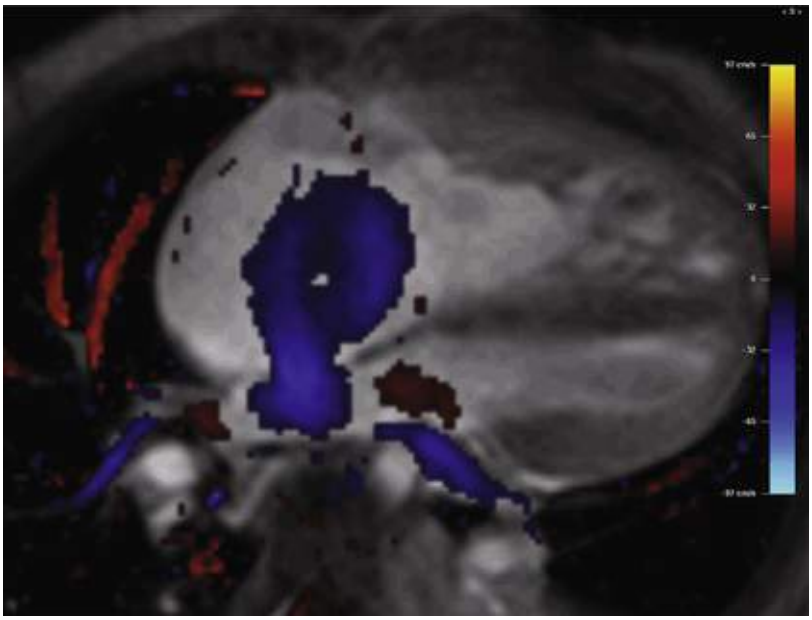


FIGURE 17.13 Patient with secundum atrial septal defect. Color-coded phase-contrast imaging demonstrates extensive left atrial–to–right atrial flow with resultant right atrial and ventricular dilation. (See Video 17.11.) (Courtesy of Drs. Andrew J. Powell and Rahul H. Rathod, Boston Children's Hospital.)

Anomalous Pulmonary Venous Connection

Using a large field of view, three-dimensional MRA can capture abnormal intrathoracic structures and vascular dynamics in anomalous pulmonary venous return. Near-isotropic in-plane resolution can be achieved, allowing reformatting in any plane to detect anomalous venous structures as small as 1 mm (**Fig. 17.14**). The magnitude of any left-to-right shunt can be assessed by either direct blood flow measurement in the anomalous pulmonary vein or by Qp/Qs ratio described previously, which generally is more accurate than invasive oximetry measurements because of the errors from mixed venous return in the right atrium.

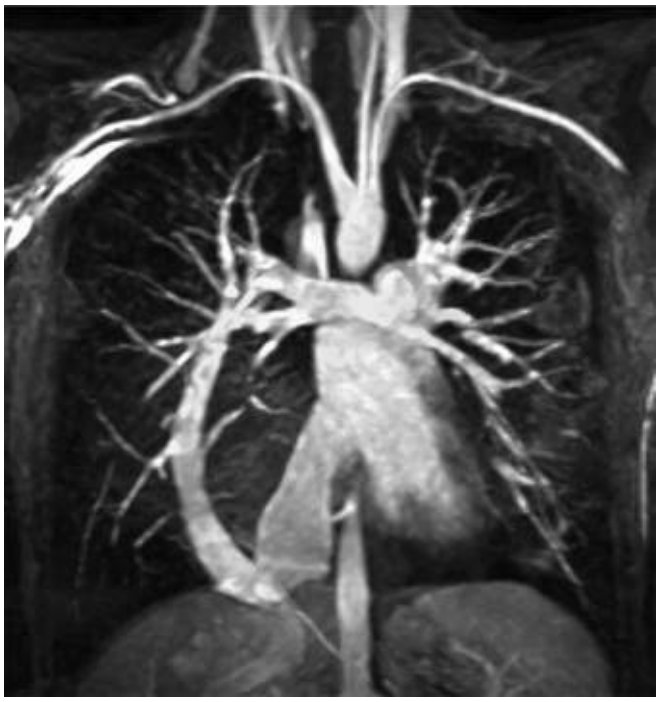


FIGURE 17.14 Gadolinium-enhanced 3D MRA (oblique coronal subvolume maximal intensity projection) in an adult with scimitar syndrome. Notice the partial anomalous pulmonary venous connection of the right lung (the curvilinear structure) to the inferior vena cava. (Courtesy of Drs. Andrew J. Powell and Rahul H. Rathod, Boston Children's Hospital.)

Coarctation of the Aorta

Gadolinium-enhanced three-dimensional MRA is sufficient in defining the site of aortic narrowing in most cases (**Fig. 17.15**). Cine SSFP in a long-axis "candy cane" view can further delineate the aortic anatomy, the degree of obstruction, and aortic valvular dysfunction. Cine SSFP is the gold standard for LV size, LV function, and myocardial mass. Black-blood FSE is useful to evaluate the entire aorta, particularly since it is affected less by metallic artifacts from implanted endovascular stent than gradient-echo techniques. Phase-contrast imaging can characterize the descending-to-ascending aorta flow ratio and estimate pressure gradient across the coarctation and collateral formation.

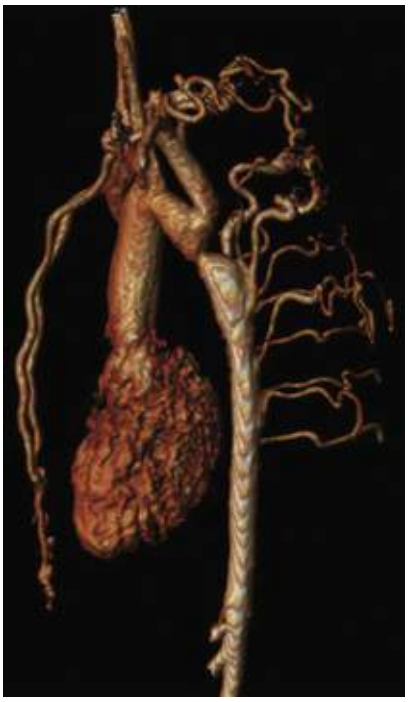


FIGURE 17.15 Volume-rendered gadolinium-enhanced three-dimensional MRA in a patient with aortic coarctation revealing several tortuous collateral vessels and dilated internal mammary arteries. (See Video 17.15.) (Courtesy of Drs. Andrew J. Powell and Rahul H. Rathod, Boston Children's Hospital.)

Conotruncal Anomalies

Tetralogy of Fallot (TOF) is an increasingly common referral. In patients planned for surgical repair, key elements provided by CMR include depiction of all sources of pulmonary blood flow (e.g., pulmonary artery, aortopulmonary collateral, ductus-arterial) in the presence of RV outflow obstruction, quantitation of the severity of infundibular or pulmonary stenosis, assessment of RV function, and ruling out a coexisting anomalous coronary artery. In patients who have undergone surgery for TOF, CMR provides relevant assessment of any RV outflow aneurysm, pulmonary regurgitation fraction (patients who underwent patching of pulmonic valve with postoperative pulmonary regurgitation), biventricular size and function, and any residual shunt. LGE imaging has been proposed for detection of myocardial fibrosis, which is associated with ventricular dysfunction, exercise intolerance, and arrhythmias. The principal physiologic abnormality in dextro- ("D-loop") transposition of the great arteries (D-TGA, the most common TGA) is profound hypoxemia caused by a ventriculoarterial discordant connection where systemic venous blood flows to the aorta and oxygenated pulmonary venous blood returns to the lung. Survival depends on systemic-pulmonary circulatory mixing through a ductus arteriosus, an ASD, or a VSD. An *arterial switch* operation is now the most common corrective surgery, although many adult patients have undergone an *atrial switch* procedure. CMR is useful in monitoring these patients after surgical correction by serially assessing ventricular size and function, flow across the postoperative LV and RV outflow tracts, and aortopulmonary collaterals. Systemic RV LGE is strongly associated with an adverse clinical outcome, especially arrhythmia in TGA. Thus LGE CMR should be incorporated in risk stratification of these patients.[42]

Valvular Heart Disease

With the capability to quantify cardiac volumes, valvular and great vessel flow hemodynamics, and angiography in three dimensions, CMR is complementary to echocardiography by being more sensitive to

changes in cardiac volume and structure. For aortic stenosis (**see Chapter 68**), CMR can visualize and achieve direct planimetry of the aortic valve orifice at high spatial resolution. Aortic valve area on CMR correlates well with TEE, although the reliability of CMR decreases when the aortic valve is heavily calcified. For aortic regurgitation, CMR phase-contrast imaging has higher reproducibility than echocardiography in quantifying the regurgitant volume and is more suitable for serial monitoring.[43] CMR quantification of aortic regurgitation has high accuracy and complements LV volumes in characterizing the progression of the regurgitant disease toward clinical need for surgery.[44] The ability of CMR to provide high-quality imaging of structure and physiology of the great vessels complements the assessment of valvular dysfunction (Videos 17.12 and 17.13). Four-dimensional flow imaging can identify a vortical (swirling) blood flow pattern in the pulmonary artery and estimate mean pulmonary artery pressures noninvasively. In addition, in patients with bicuspid aortic valve, visualization of vascular "vector" flow can determine vascular wall shear stress and systolic flow eccentricity, potentially predicting development of bicuspid aortic valvular aortopathy[45] (**Fig. 17.16**).

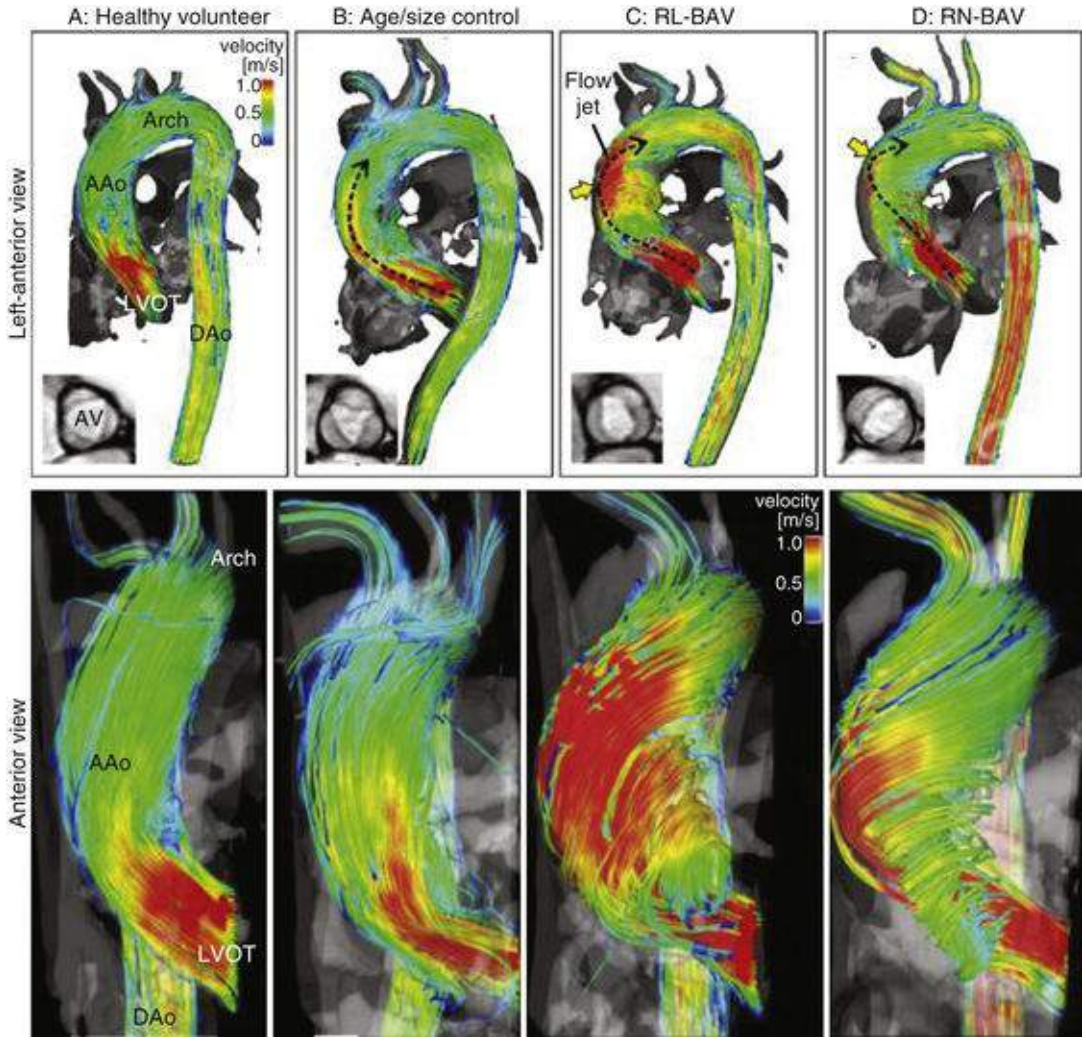


FIGURE 17.16 **Top row,** Three-dimensional (3D) streamline visualization of peak systolic blood flow in patients with bicuspid aortic valve (*BAV*) **(C, D)** compared to an aorta size–matched control **(B)** and a healthy volunteer **(A).** Note the presence of distinctly different 3D outflow flow jet patterns (*black dashed arrows*) in the ascending aorta (*AAo*) for patients **B** and **C. Bottom row,** 3D flow patterns in the left ventricular outflow tract (*LVOT*) and AAo distal to the aortic valve. Note the different systolic atrioventricular outflow flow jet patterns (*red* indicates high velocities >1 m/sec) and wall impingement zones, which correspond to variable exertion of high wall shear forces between different valve groups **(C, D)** and aorta size–matched controls **(B)** and healthy volunteers **(A).** *DAo,* Descending aorta. (From Mahadevia R, Barker AJ, Schnell S, et al. Bicuspid aortic cusp fusion morphology alters aortic three-dimensional outflow patterns, wall shear stress, and expression of aortopathy. Circulation 2014;129:673-82.)

CMR is a useful tool in assessing patients before or after transcatheter aortic valve replacement (TAVR) (**see Chapter 72**). Compared to transthoracic echocardiography (TTE), CMR is more accurate in sizing the aortic annulus before the procedure, which predicts the severity of aortic regurgitation after TAVR. CMR has also been shown to be more sensitive in detecting significant paravalvular aortic regurgitation at TAVR.[46] New ischemic-type myocardial LGE after TAVR has been observed in subsets of patients and is assumed to be of coronary embolic origin, which has clinical implications because it is associated with a decrease in LV function after TAVR.[47]

Cardiac Thrombus and Mass

The differential diagnoses of an intracardiac mass includes a thrombus, tumor, and vegetation. LGE imaging can detect thrombus at a higher sensitivity than echocardiography by depicting high contrast between the dark thrombus and its adjacent structures and by imaging in three dimensions. Mural

thrombus does not enhance on first-pass perfusion and often has a characteristic “etched” appearance on LGE imaging, thus providing higher diagnostic specificity than anatomic information alone. Multiple pulse sequences can be used to detect vascularity of tumor after contrast injection and allow differentiation from thrombus (Video 17.14). One study found that a pattern of hyperintensity/isointensity (compared with normal myocardium) with short TI and hypointensity with long TI was common in thrombi (94%), rare in tumors (2%), and had the highest accuracy (95%) for the differentiation of both entities[48] (**Fig. 17.17**). Common benign cardiac tumors include atrial myxoma, rhabdomyoma, fibroma, and endocardial fibroelastoma. Atrial myxomas are often seen as a round or multilobar mass in the left atrium (75%), right atrium (20%), or ventricles or mixed chambers (5%). They typically have inhomogeneous brightness in the center on cine SSFP imaging due to gelatinous contents and may have a pedunculated attachment to the fossa ovalis. Metastatic cardiac malignancy is much more common than primary cardiac malignancy. Malignant lesions include cardiac involvement from direct invasion (lung and breast), lymphatic spread (lymphomas and melanomas), and hematogenous spread (renal cell carcinoma) (**Fig. 17.18**). Primary cardiac malignancies occur more often in children or young adults and include angiosarcoma, fibrosarcoma, rhabdomyosarcoma, and liposarcoma. CMR in a multicenter trial correctly diagnosed 97% of these cases, although a differential diagnosis was necessary in 42%.

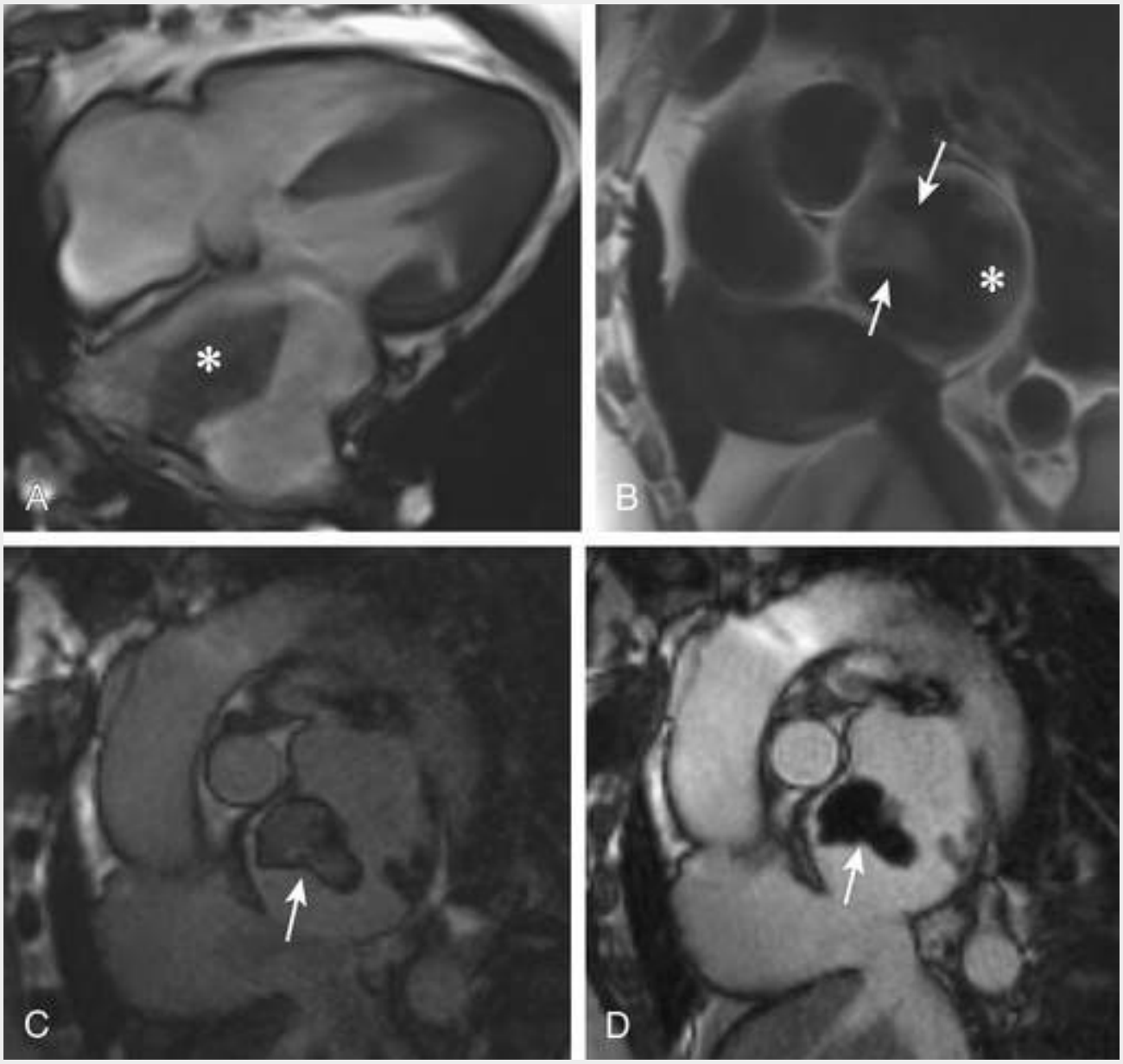


FIGURE 17.17 A 66-year-old woman with factor V Leiden mutation and antiphospholipid syndrome was found to have a mass on echocardiography and was then referred for CMR evaluation. **A,** SSFP image, four-chamber view, demonstrates an isointense mass in the left atrium posterior wall (*asterisk*). **B,** T1-weighted double–inversion recovery (DIR) image, short-axis view, shows an isointense mass attached to the left atrial wall *(arrows).* There is another small mass in the posterior wall of the atrium *(asterisk)*. **C,** On LGE image, short-axis view, the mass appears to be heterogeneously hyperintense. **D,** However, on LGE, long inversion time (TI) image (600 msec), short-axis view, the mass was nulled completely, suggesting lack of enhancement. These findings are consistent with an intracardiac thrombus.

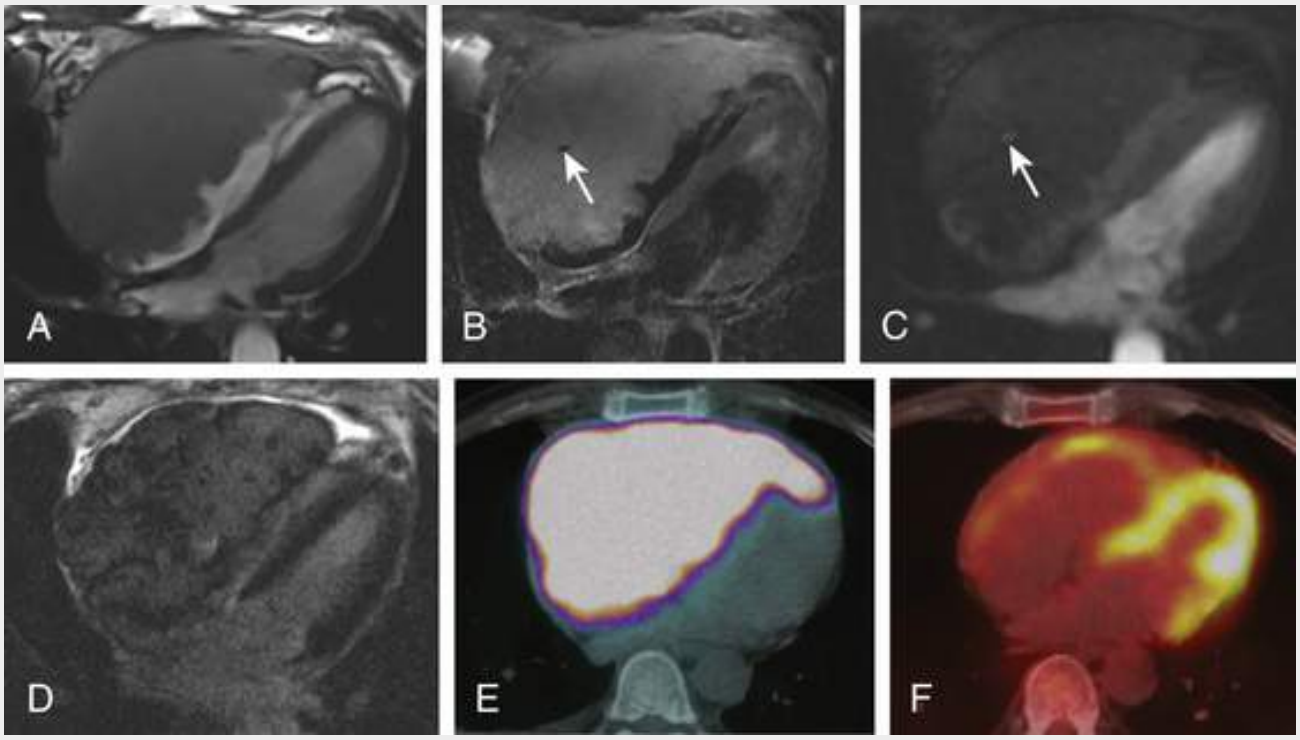


FIGURE 17.18 A 55-year-old man presented with chest pain and shortness of breath. Echocardiography revealed a large mass arising from the right ventricular free wall. **A,** SSFP image, four-chamber view, demonstrates a large, isointense mass along the right ventricular and atrial wall. **B,** Mass is hyperintense on fat-suppressed, T2-weighted DIR image, four-chamber view, and right coronary artery (RCA) appears to be patent, which can be seen as a flow void (*arrow*). **C,** Early cycle of first-pass perfusion (FPP) image, four-chamber view, demonstrates the patent RCA (*arrow*) as well. **D,** Heterogeneous enhancement on LGE. Histopathology of the mass revealed a large B cell lymphoma with high-grade features. **E,** Pretreatment PET-CT image demonstrates intensely FDG-avid mass, which is completely resolved on post-treatment image **(F)**. (Courtesy of Drs. Michael Steigner and Ayaz Aghayev, Brigham and Women's Hospital, Boston.)

Detection of Subclinical Cardiovascular Disease in Systemic Conditions

Subclinical cardiovascular disease is common in rheumatoid arthritis (**see Chapter 94**), including focal and diffuse myocardial fibrosis and inflammation, which are associated with impaired strain and right atrial disease activity.[49] Comprehensive cardiac imaging revealed cardiac steatosis, alterations in cardiac function, and a high prevalence of myocardial fibrosis in a contemporary group of asymptomatic HIV-infected patients undergoing combination antiretroviral therapy (**see Chapter 82**). Cardiac steatosis and fibrosis may underlie cardiac dysfunction and increased cardiovascular morbidity and mortality in patients with human immunodeficiency virus (HIV) infection.[50] Patients with systemic lupus erythematosus (SLE) and no cardiac symptoms show evidence of subclinical perimyocardial impairment. By using T1 mapping, subclinical myocardial involvement in patients with SLE may be detected.

Novel CMR Imaging Techniques

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) provides information regarding cellular metabolism. Free energy in adenosine triphosphate (ATP) is produced and stored primarily in mitochondria and carried to sites of energy consumption (e.g., myofibrils or ion channels) as phosphocreatine (PCr) through diffusion. Phorphorus-31 MRS assesses energy metabolism and thus the integrity of cellular function by quantifying the ratio of PCr to ATP. MRS is currently limited by the low signal-to-noise ratio caused by low

concentration of the high-energy phosphate molecules resulting in a limited sensitivity in detecting viable myocardium beyond the anterior left ventricle. However, ^{1}H MRS has up to 20-fold improved sensitivity than ^{31}P MRS and thus can quantify both phosphorylated and unphosphorylated creatine in any part of the left ventricle. Myocardial triglyceride, quantified by ^{1}H MRS, increased with an increasing amount of hepatic fat and visceral adiposity and has been associated with subtle systolic LV dysfunction.[51]

Molecular CMR Imaging

Molecular CMR imaging can theoretically provide dramatic improvement of sensitivity and specificity of disease detection by characterizing cellular process and allowing preclinical disease detection. Gadolinium chelates combined with a fibrin-specific peptide ligand can detect thrombi in the left atrium and coronary stents under experimental conditions. Other examples include the use of nanoparticles to target the adhesion molecule αvβ3-integrin as a marker of angiogenesis in atherosclerosis, USPIO particles to detect macrophages in inflamed carotid plaques, and tracking of intramyocardial transplanted mesenchymal stem cells in experimental infarction. Hyperpolarization results in a substantially increased signal that overcomes the sensitivity limitations of some multinuclear CMR applications. When combined with the metabolic tracers [$^{1\text{-}13}$C] and [$^{2\text{-}13}$C] pyruvate, this has resulted in unparalleled real-time imaging of myocardial substrate metabolism in vivo.[52]

Future Perspectives

Further technological advances in CMR will likely focus on improving the study throughput, protocol consistency, and patient tolerability. Combining rapid data collection using parallel imaging and better surface coil designs can eliminate the need for patient breath-holding and reduce CMR scan time. As a result, time-resolved techniques such as cine imaging may be replaced by real-time imaging. Data undersampling from parallel imaging leads to a reduction of signal-to-noise ratio, but three-dimensional pulse sequence and increased field strength at 3 T compensate for the signal/noise loss and are already in selected clinical use, replacing some two-dimensional methods (**Fig. 17.19** and Video 17.15). Automated motion correction reduces blurring from cardiac motions and has become standard in many pulse sequences because it not only improves qualitative visual displays, but also facilitates quantitative measurements. Semiautomated cardiac localization and scanning algorithms have been developed to reduce the time required in training physicians and technologists. New contrast agents hold promise in improving the assessment of myocardial or vascular physiology. For example, blood pool contrast agents may improve delineation of coronary stenosis by whole-heart coronary MRA and assessment of myocardial perfusion. Further development is needed in interventional instrumentation and MRI hardware, but CMR-guided interventions, especially for electrophysiologic applications, hold promise in improving ablative procedures.

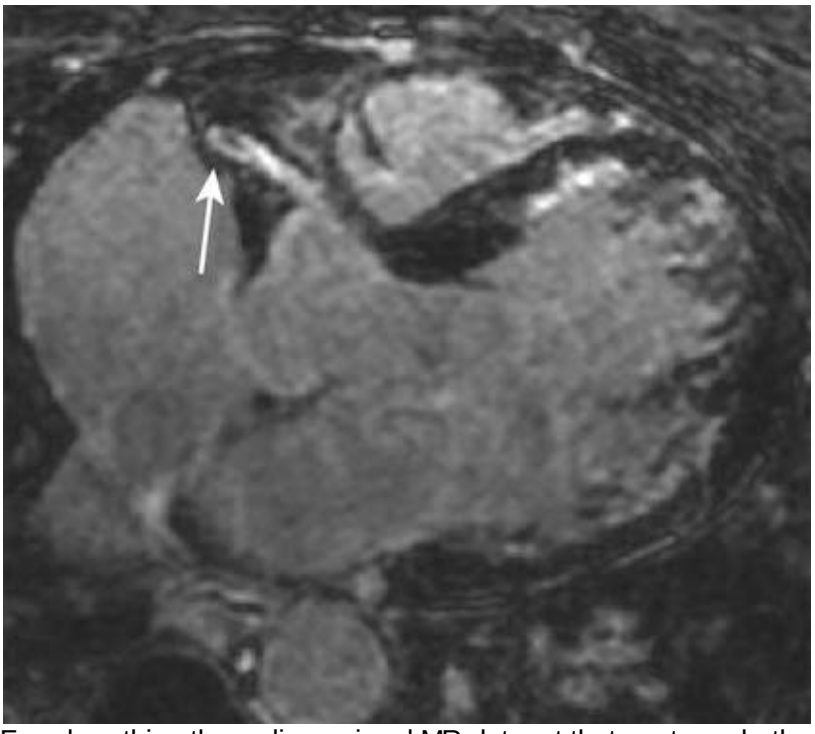
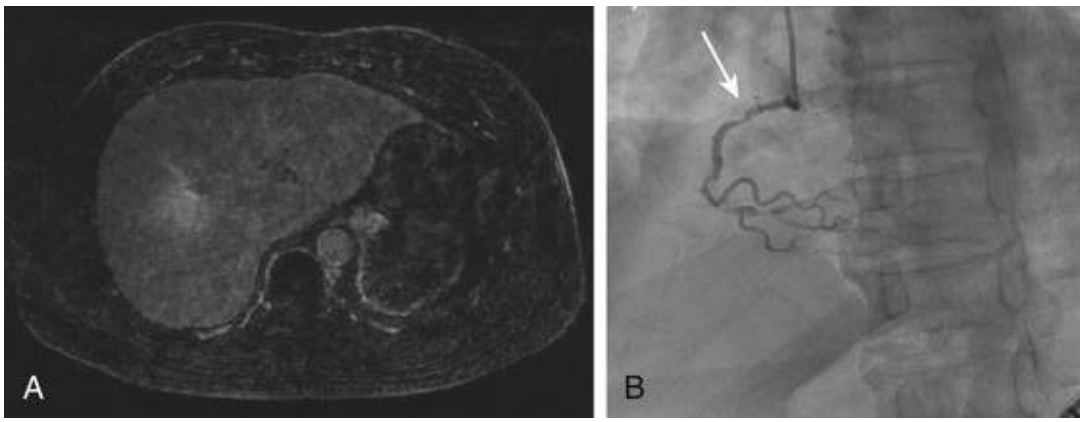


FIGURE 17.19 Free-breathing three-dimensional MR dataset that captures both coronary anatomy (*arrow*) and anteroseptal and apical myocardial infarction. Compressed sensing data acquisition and reconstruction were used to shorten the scan time. (**See also eFig. 17.2.**) (Courtesy of Dr. Reza Nazafat, Beth Israel Deaconess Medical Center, New York.)



EFIGURE 17.2 **A,** Free-breathing three-dimensional MR dataset that captures both coronary anatomy and anteroseptal and apical myocardial infarction. Compressed sensing data acquisition and reconstruction were used to shorten the scan time. **B,** Stenoses in the proximal coronary arteries (*arrow*) are confirmed on invasive angiography. (Courtesy Dr. Reza Nazafat, Beth Israel Deaconess Medical Center.)

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18

Cardiac Computed Tomography

James K. Min

Since the advent of computed tomography (CT) by Sir Godfrey Hounsfield in 1971, technological advances of CT systems have generated vast improvements in the detection and exclusion of anatomic and physiologic pathology in virtually all body systems. One such improvement was the 64–detector row CT scanner in 2005, which afforded the necessary temporal and spatial resolution for capturing almost

motion-free studies of the heart and coronary arteries that, when coupled with adequate volume coverage, reduced breath-hold times such that a cardiac CT study was achievable by most patients. In the last decade, further iterative improvements in CT have been introduced, which allow for comprehensive assessment of coronary and cardiac structure and function. This chapter provides an overview of the applications of CT for such indications.

Basics of Cardiac and Coronary Computed Tomography

At its core, CT is a relatively simple imaging modality that consists of an x-ray tube that emits photons directionally toward a patient, with photon attenuation occurring as a likelihood function of differential organ-specific densities within a patient (**Fig. 18.1**) (see Classic References, Kalender). These differences result in higher tissue densities generating higher attenuation coefficients, whereas higher photon energies will result in lower attenuation coefficients. In short, the combination of organ density and photon energy determines the number of photons that pass through a patient, which can then be quantified by a series of detector arrays located 180 degrees across from the x-ray tube. After being struck by photons, a scintillation reaction occurs at the level of the detector that encourages light formation from x-rays. The resultant scintillation pattern becomes digitized to a string of binary numbers that can be reconstructed to two-dimensional (2D) and three-dimensional (3D) images and that may be visualized for medical use on an imaging computer workstation. To enable 3D imaging, x-rays must be emitted from a series of angles. At a minimum, a 180-degree rotation of the gantry with x-ray emission is required to generate a 3D image, a process known as *half-scan integral reconstruction.* Important for optimal image generation are the CT *tube potential,* measured in kilovolt peaks (kVp), and *photon counts,* measured in milliamperes (mA). Higher tube potential (kVp) allows for greater tissue penetration, whereas higher photon count (mA) increases the total number of photons that ultimately reach the detector elements. Both higher kVp and higher mA increase the radiation dose associated with cardiac CT imaging.

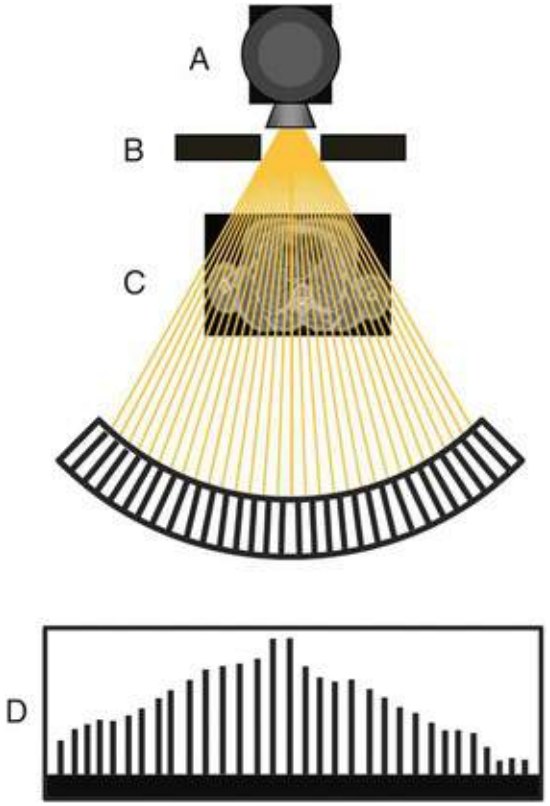

FIGURE 18.1 Computed tomography (CT) imaging requires an x-ray source (*A*) that directs photons past a collimator (*B*). Photons are attenuated by organs in a differential pattern related to their material densities. Photons not attenuated reach multiple detectors (*C*) at which a scintillation reaction occurs. At each detector, a photon flux is generated that is a product of the number of photons emitted from the x-ray tube (milliamperes, mA), the photon energy (kilovolts, kV), and the organ tissue properties. These are calculated for every detector element (*D*).

Three elements are required for acquisition of high-fidelity cardiac and coronary CT images: spatial resolution, temporal resolution, and volume coverage. When released, 64–detector row scanners across vendor platforms were generally similar, with in-plane (*x* and *y* directions) resolution of 0.5 to 0.8 mm, temporal resolution of approximately 160 to 220 milliseconds for 180-degree rotation of the gantry, and 2 to 3 cm of volume coverage. This corresponds to a spatial resolution approximately two to four times lower and a temporal resolution approximately four times worse than cineangiography (**see Chapter 20**). Since the introduction of 64–detector row CT scanners, spatial resolution, temporal resolution, and volume coverage have been improved individually across different vendor platforms, although a CT scanner that integrates all three advancements into a single scanner is currently lacking.

Spatial resolution, which depends on both the size of the detector elements and the material properties of the detector, has been improved by addressing the latter. Exchanging traditional CT detector materials made of gadolinium oxysulfate with garnet and phosphor elements, typically used in surgical lasers and xenon automobile headlights, improves spatial resolution to approximately 230-micron (μ) in-plane resolution. This is achieved by two basic advantages: improvements in the primary speed of the scintillation reaction and reduction of the "afterglow," or the recovery time of the scintillation response, which reduces light artifacts.

Temporal resolution improvements have been achieved by improved gantry rotational speed, dual-source CT (DSCT) scanning, and combined image- and projection-based solutions for motion correction. Improved gantry rotational speeds have resulted in half-scan temporal resolution to 100 to 140 milliseconds. In addition to a faster gantry rotation, DSCT scanners now effectively allow for image acquisition at twice the speed of single-source CT scanners. DSCT scanners comprise two x-ray sources and two detector arrays that are 90 degrees perpendicular to one another. By this method, gantry rotation

needs to occur only through one-fourth (rather than one-half) the gantry revolution to generate a 3D image, and this method has achieved temporal resolution rates as low as 67 milliseconds. Software-based postprocessing techniques for selective reduction of coronary motion, also known as intracycle motion correction algorithms, are used to correct coronary motion artifacts by exploiting the trajectory data across time and "backtracking" to create motion-free images.

Improvements in volume coverage by imaging greater lengths in the *z* axis, or craniocaudal direction, have been achieved by increases in the number of detector rows. This has been termed *volumetric* CT imaging, because with enough detector elements to cover its entire length, the heart can be imaged in a single gantry rotation in less than 1 second. At present, 320– and even 640–detector row CT scanners are now available for commercial use.

New Technologies

In addition to the CT hardware improvements previously described, other advances allow for enhanced CT image acquisition and reconstruction parameters. *Iterative reconstruction* (IR) has been introduced as an improvement over traditional filtered backprojection (FBP) methods used in CT and employs system statistics to reconstruct high-quality, noise-reduced images. Compared to FBP, an inverse method of image reconstruction, IR methods attain images by iterative forward steps, a method dependent on intense computational power.[1] IR improves image quality by accentuating signal-to-noise (SNR) and contrast-to-noise (CNR) ratios without increased radiation. An IR image can be acquired at a much lower radiation dose and can still achieve similar quality to images reconstructed by FBP.

Dual-energy computed tomography (DECT) techniques have also been recently introduced to improve material discrimination. This method acquires simultaneous, or near-simultaneous, imaging at a low and high kVp.[2] The use of widely disparate energies allows for harnessing two polychromatic spectra (e.g., 80 and 140 kVp) to discriminate between the material densities of two basic materials by examining their attenuation characteristics at different x-ray energies. Methods of DECT acquisition have used DSCT (one detector array offering a low-energy spectra and the other a high-energy spectra), fast kVp switching (with microsecond changes in polychromatic spectra from low and high kVp), and energy-dependent dual detectors. From each of these methods, tissues can be reconstructed into a single monochromatic energy (in kiloelectron volts, keV), which may be used to improve current coronary and cardiac imaging interpretation. For example, the use of a monochromatic single energy, such as 40 keV, is closer to the k-edge of iodinated contrast, enabling a higher signal that cannot be achieved by traditional polychromatic spectral single-energy CT imaging, potentially allowing for more accurate assessment of contrast-enhanced structures (e.g., coronary arteries). In addition, two materials that have sufficient differences in their attenuation patterns, iodinate and water, can be fully separated for absolute quantification of their material properties, unlike the relative separation of attenuation densities conferred by single-energy CT. Absolute quantification of material densities allows any given material to be "subtracted" from an image. One potential application of this is myocardial perfusion, in which contrast enhancement of the heart may exhibit different kinetic uptake in normal, ischemic, and infarcted myocardium. Because most tissues, including the myocardium, are composed primarily of water, reconstruction of water-free images from DECT will allow for absolute quantification of iodinated contrast and, in theory, absolute quantification of myocardial perfusion.

Image Acquisition Optimization

Prior to scanning, proper patient preparation is essential to a high-quality cardiac CT scan.[3] With the

constant movement of the heart and coronary arteries, coupled with the fixed temporal resolution of the CT scanner, a low heart rate permits less motion contamination of images, which improves diagnostic interpretation. Most often, beta-blocking agents such as metoprolol or atenolol are used. In our laboratory, metoprolol is given by both oral and intravenous (IV) administration. On the night before the CT, metoprolol is administered in oral form. At the CT scan, IV metoprolol is administered for "rescue" in individuals with heart rates greater than 65 beats/min. In my experience the use of other heart rate–lowering agents, such as calcium channel blockers, are generally ineffective in further lowering heart rate in individuals not reacting to metoprolol. A newer sinoatrial nodal–blocking agent, ivabradine, has been used with moderate efficacy in heart rate lowering.[4] Recommendations to abstain from caffeine and nicotine in the hours before CT scanning are also prudent.

Because the opacification of the coronary arteries requires the administration of contrast, any contraindication to iodinated contrast should be carefully ascertained. These include chronic kidney disease, elevated serum creatinine levels, and increased risk of contrast-induced nephropathy (CIN). Even among individuals not at risk of CIN, it is generally common practice to encourage ample hydration after CT scanning.

Other patient-specific factors that may degrade CT image quality include very high levels of coronary artery calcium (CAC), which can obfuscate visualization of the coronary arteries because of the "blooming," or partial volume, effects of highly attenuating structures such as calcium. Some laboratories refrain from cardiac CT if a greatly elevated CAC level is noted, although with the aforementioned improvements in CT technology, this practice is less common. To maximize visualization of the coronary artery lumen, 0.4 to 0.8 mg of sublingual nitroglycerin is often administrated for its coronary vasodilatory effects at CT scanning. Contraindications to nitroglycerin administration include low blood pressure or use of phosphodiesterase inhibitors (e.g., sildenafil, tadalafil) within 48 hours of CT scanning.

Electrocardiographic Gating Techniques

Electrocardiographic (ECG) gating is a requirement for cardiac CT scanning to allow for functional assessment of the heart, as well as image acquisition at a motion-free period within the cardiac cycle that optimizes visualization of the coronary arteries.[5] Traditionally, two ECG gating techniques have been applied to cardiac CT for synchronization of image acquisition to the proper phase of the cardiac cycle: retrospective helical gating and prospective axial triggering (**Fig. 18.2**). *Retrospective gating* allows for redundant imaging of the structure of interest. For cardiac CT imaging, this offers two advantages. First, the continuous overlapping sample of data enables gap-free imaging. Second, because this method is performed by continual scanning through the cardiac cycle, it allows four-dimensional (4D) imaging for volumetric assessment of heart motion over time. A disadvantage of retrospective gating is that it requires a generally low scan *pitch*, defined by the table feed per gantry rotation divided by the volume coverage in the *z* axis, which significantly increases the radiation dose of the examination.

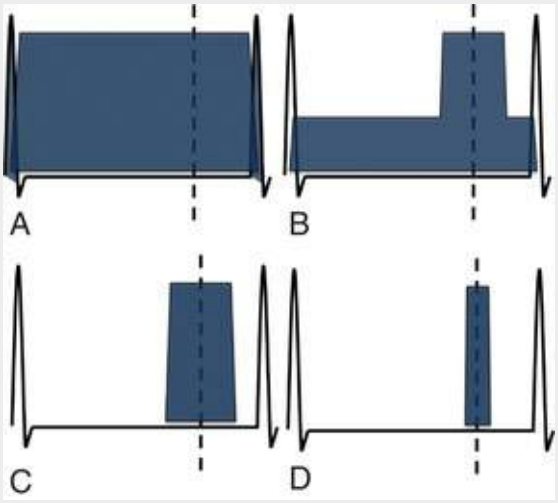

FIGURE 18.2 Electrocardiographic (ECG) gating of coronary CT angiography (CCTA). **A,** Retrospective helical acquisition imparts radiation (*dark area*) at a constant dose during the entire R-R interval. **B,** Retrospective helical gating with dose modulation imparts radiation throughout the cardiac cycle but reduces radiation doses during systole. **C,** Prospective ECG triggering is an axial imaging method that imparts radiation only during diastole, where motion-free coronary imaging is most often identified. **D,** Prospective ECG triggering with a narrow window imparts radiation at a single point within diastole. Prospective ECG triggering methods are associated with an 80% reduction in CCTA radiation dose.

In contrast to retrospective gating, *prospective triggering* allows for selective radiation exposure during only a brief period of the cardiac cycle. This technique images the heart during the mid-diastolic phase of the cardiac cycle, at a point when coronary motion is generally the least. In this mode, image acquisition relies on the prior R-R interval to estimate the present R-R diastolic period for scanning; thus, images are acquired every other heartbeat. Historically, this mode has been called “step and shoot” because the CT scanner table will move, and the image acquisition will then occur with no overlap. The advantage of prospective triggering is the profound reduction in radiation dose, which is 80% lower than that of retrospective gating methods. A disadvantage of this technique is the loss of 4D data. Importantly, for patients with higher heart rates, prospective triggering is often avoided, given the lower rate of coronary quiescence in the diastolic period. For these patients, retrospective gating techniques are more useful for evaluating the coronary arteries at every phase of the cardiac cycle, including the end-systolic period, another common period of coronary stillness.

A third method of ECG-gated CT scanning, known as *fast-pitch* (high-pitch) *helical scanning*, has been recently introduced on DSCT scanners. Historically, the pitch for cardiac CT imaging has ranged between 0.15 and 0.3, which results in high radiation dose because of overlapping image acquisition of body structures. In contrast, high-pitch helical scanning uses a very fast table movement, which allows for helical imaging of the *z* axis of the heart (i.e., direction of table movement) without overlap and thus rapid scanning at very low radiation dose. The rapid movement of the table enables cardiac CT imaging within a single heartbeat.

Image Interpretation

Once acquired, cardiac CT images can be viewed and interpreted in a variety of ways, including axial methods, oblique methods, multiplanar reformats, maximum and minimum intensity projections, and volume-rendered viewing (**Fig. 18.3**). Before 3D reconstruction methods, CT images were evaluated solely on *axial* imaging, with each image viewed in sequence of acquisition in the *z* axis. In cardiac imaging the heart is not typically located in the axial plane, and 3D oblique views are often constructed to align the heart for optimal viewing. Similarly, the coronary arteries are often tortuous and unaligned to the

axial plane. One technique to visualize the coronary arteries comprehensively is a *multiplanar reformat* technique that combines the multiple planes of the coronary artery into a single view that allows visualization of the entire artery in a single image. This technique helps to identify the spatial relationship of coronary stenoses or atherosclerosis within any given vessel and is particularly useful for coronary CT scans when the degree of stenosis is unclear in oblique images, for coronary stent assessment, and for very calcified coronary artery segments. *Volume-rendered* images depict structures in a surface-shaded view using 3D data in a cartesian manner where scalar values are assigned to points in the image space. Volume-rendered images are less often used for diagnostic purposes but can be useful when spatial orientations are important, such as for coronary artery anomalies, coronary artery bypass graft (CABG), and complex congenital heart disease.

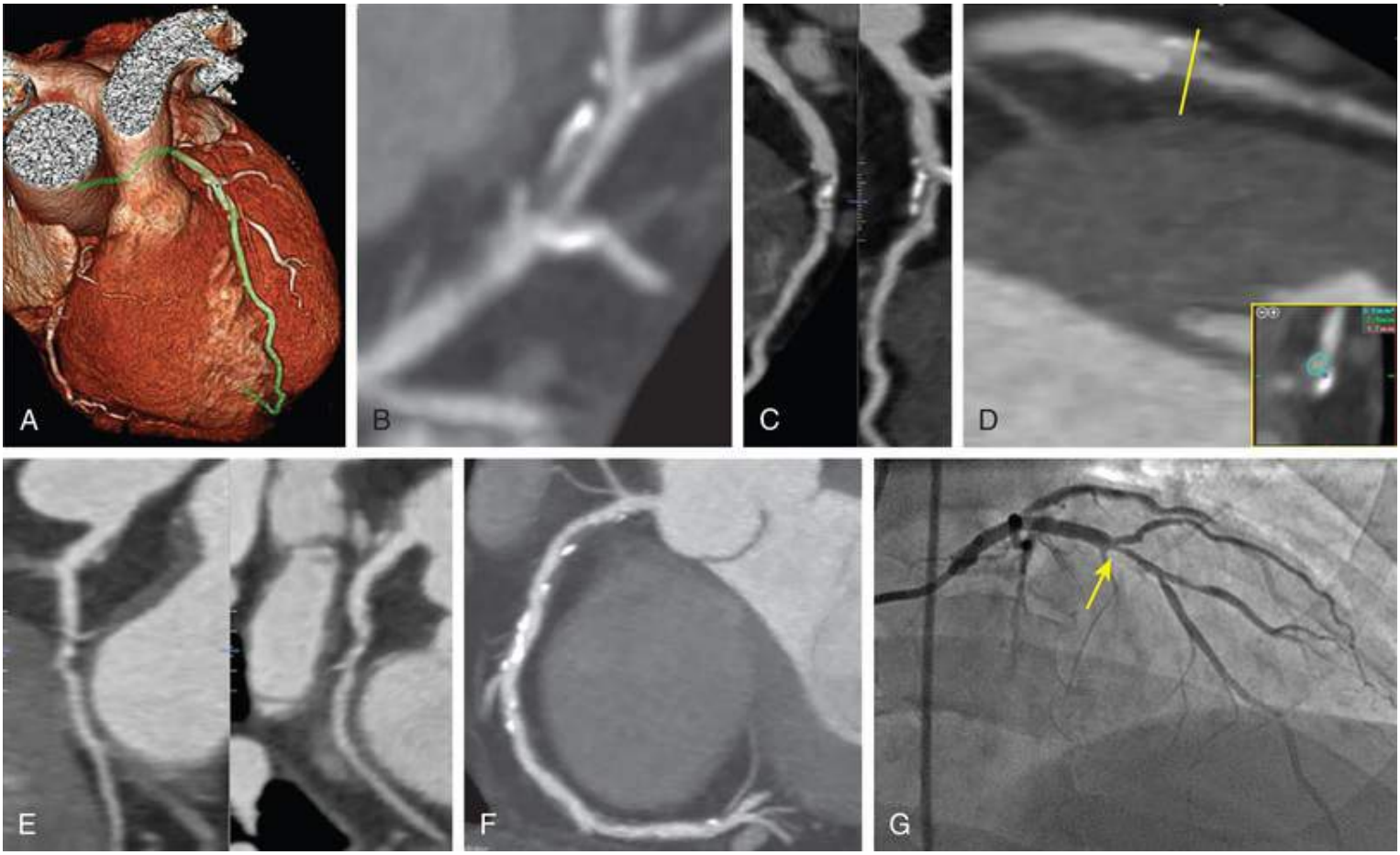

FIGURE 18.3 Common image postprocessing techniques for CCTA. Beyond 2D axial images, CCTA allows for 3D visualization of the coronary arteries by a number of different postprocessing formats. **A,** Cartesian view can be seen in a surface-shaded display of the volume-rendered technique. The left anterior descending artery can be visualized by **B,** maximum intensity projection (MIP) view; **C,** two curved multiplanar reformat views 180 degrees from each other to enable whole-vessel imaging; and **D,** curved multiplanar reformat view with orthogonal cross section of the vessel (*yellow line, inset*). **E,** The left circumflex artery in this patient is viewed in curved multiplanar format, whereas **F,** the right coronary artery is visualized as an oblique MIP. **G,** The corresponding invasive coronary angiogram confirms the high-grade stenosis visualized by the CCTA (*yellow arrow*).

Although high spatial resolution is valuable for detecting fine structures such as a coronary stenosis in a small artery, it is often so fine as not to allow concurrent visualization of a sufficient volume of data of the coronary artery to render an accurate diagnosis. To address this, a common technique is a “thin” maximum intensity projection (MIP) view of 3 to 5 mm. This postprocessing technique is done by increasing the thickness of the observed image by combining multiple 3D pixels, or *voxels*, of data into a larger single

cube. Within this larger cube, the most intense attenuation, or the “brightest” voxel, would be projected as the attenuation density of the entire cube. While commonly used for coronary artery visualization, the MIP technique can lead to diagnostic errors because it can obfuscate lower-attenuation-density materials, such as noncalcified coronary artery atherosclerosis. Similar to the generation of MIP, one can reconstruct cubic data as averages (AverageIP) as well as minimum attenuations (MinIP). The latter is particularly useful when trying to visualize data that are less bright than the iodinated contrast used in the examination. For example, in cardiac valve imaging, MinIP allows for accentuation of the valve structures.

Patient Safety

One major concern of cardiac CT imaging has been the effective dose of radiation required.[6] Potential harm from radiation can be considered in the type of risk it confers, which can be either deterministic or stochastic. *Deterministic risk* is a threshold measure, above which harm can occur and below which it does not. An example of a deterministic risk is a skin burn, which can occur at very high radiation doses. In contrast, *stochastic risk*—a concern expressed for cardiac CT imaging—is the potential of radiation to increase risk at any level of exposure. Potential future fatal and nonfatal cancer development is the primary concern of the stochastic risk of radiation, and approaches to reduce radiation to as low as reasonably achievable (ALARA) are considered highly important in cardiac CT imaging.

The units of measurement of radiation in cardiac CT imaging have varied.[6] On any given CT scanner, measures of radiation are often reported as the *dose-length product* (DLP) or the *CT dose index* (CTDI). The latter is a measurement of the total radiation dose absorbed by a patient's body and is typically reported in gray (Gy) or radiation absorbed dose (rad) units. In contrast, the DLP represents the CTDI multiplied by the scan length, reported as Gy × cm or rad × cm. In the literature, radiation from cardiac CT has usually been reported as the *effective dose*, measured in sieverts (Sv). This unit represents the biologic effects of imparted radiation weighted relative to the organ that is exposed to radiation. For cardiac CT scans, the organ weight used is from the thoracic density weight conversion constant of 0.014, with cardiac CT radiation calculated as DLP × 0.014.

At its introduction, 64–detector row cardiac scanning was associated with high radiation doses and with high variability among practice sites. From large-scale studies during the early period of cardiac CT, radiation doses were as high as 20 millisieverts (mSv).[6] These doses contrast unfavorably with the average annual background radiation dose experienced by an individual living at sea level, which is approximately 3 mSv and occurs primarily from radon exposure. Since 2005, advances in cardiac CT imaging have significantly reduced radiation doses,[5] including the following:

1. ECG dose modulation for retrospective helical scanning, in which full radiation doses are imparted only during diastole, with lower radiation doses throughout the remainder of the cardiac cycle
2. Prospective axial triggering, which constrains radiation exposure to only a short period during diastole and imparts no additional radiation throughout the remainder of the cardiac cycle
3. Reduction of the “padding” in prospective axial triggering, in which the heart is imaged at only a single point in diastole (rather than a range)
4. Minimization of the *z* axis only to the field of view of the heart
5. Reduction of tube current to reduce exposure to the total number of x-ray photons
6. Reduction of tube voltage, using lower kVp (e.g., 100 or 80)
7. Increasing scan pitch to avoid overlapping images, as done for high-pitch helical techniques

8. Applying IR techniques to achieve similar image quality to FBP methods while using lower radiation doses

Collectively, these techniques allow for significantly reduced radiation doses, with recent reports demonstrating the feasibility of cardiac CT imaging with less than 1 mSv radiation. In clinical practice, routine imaging using these methods can reliably reproduce radiation doses less than 3 mSv.

CIN is a serious complication in patients with preexisting kidney disease or those at risk for kidney disease. In two large single-center studies, 0.2% and 1.75% patients experienced CIN, defined by a greater than 25% increase in serum creatinine. For both of these studies, no requirement for hemodialysis was required.[7,8]

In addition to the heart, cardiac CT scanning also images portions of the thoracic cavity, which may result in the identification of important (or potentially irrelevant) noncardiac imaging findings (**Table 18.1**). A recent meta-analysis of 19 studies that included 12,922 patients found the pooled prevalence of incidental findings was 13%. There was large interstudy variability in these findings, and no outcomes were reported.[9] Whether these findings should be routinely reported remains unclear. To reduce the number of incidental findings, many cardiac CT laboratories have narrowed the visualized field of view (FOV) to limit evaluation to only the heart and its immediately adjacent structures. It is important to note, however, that the *direct* FOV in this case is not the same as the *scanned* FOV, which includes all structures that pass through the CT gantry. Thus, although the remaining thoracic cavity may not be reconstructed for cardiac CT image evaluation purposes, it has nevertheless been scanned and is able to be reconstructed. Future studies are required to determine the optimal approach to image reconstruction and reporting of incidental findings.

TABLE 18.1

Prevalence of Clinically Significant Extracardiac Findings Derived from Cardiac Computed Tomography (CT)

AUTHOR (YEAR)	PATIENTS (*n*)	NO. OF SLICES	SLICE THICKNESS (mm)	FOV	MEAN AGE	MALE (%)	SMOKERS (%)	EXTRACARDIAC FINDINGS* (%)	CLINICALLY SIGNIFICANT EXTRACARDIAC FINDINGS (%)	PATIENTS WITH PULMONARY NODULES (%)	P W C S P N ('
Multidetector CT-Based Studies											
Kim[136] (2010)	11,654	16/64	5	Full	58	58	56	—	—	—	—
Johnson[137] (2010)	6920	16/64	5	Full	54	65	52	24	15	6	3
Lee[138] (2010)	151	16/64	0.75-1.5	Full	57	70	7	43	22	17	11

*Extracardiac findings were defined as any finding outside the pericardium, including aortic and pulmonary arterial abnormalities.

FOV, Field of view; EBT, electron-beam tomography.

Coronary Artery Calcium Scoring

History and Overview

Before the advent of multidetector row CT (MDCT) scanners, electron beam CT (EBCT) scanners offered another method for cardiac evaluation. These CT scanners achieved 40-millisecond temporal resolution, image acquisition speeds similar to cine-angiography and significantly faster than current MDCT scanners. However, spatial resolution of EBCT scanners was 2 to 3 mm, which did not provide adequate characterization of the coronary arteries. Therefore, EBCT scanners have become largely extinct. In 1990, Agatston and Janowitz first demonstrated the use of ECBT scanners for the quantification of coronary artery calcium, extending the importance of the CAC concept to define coronary artery disease (CAD) risk, as previously observed using x-ray fluoroscopy (see Classic References). CAC findings on cardiac CT have been shown to be a strong, reliable marker of coronary atherosclerosis. In a study of coronary specimens imaged by CAC scanning and subject to histopathologic analysis, CAC on CT correlated strongly to the overall atherosclerotic plaque area. CAC represented one fifth of the overall plaque burden and demonstrated high linear correlation to the square root of the sum of pathologic plaque areas ($r = 0.90$; $P < 0.001$) (see Classic References, Rumberger). In this regard, it is often suggested that CAC may be a more sensitive and specific determinant of CAD risk than traditional CAD risk factors that may both over- and underdiagnose manifest coronary atherosclerosis.

CAC scanning is a non–contrast-enhanced image acquisition technique that is performed during a single breath-hold. Current guidelines recommend prospective ECG-triggered scanning from the bifurcation of the main pulmonary artery to the apex of the heart, with a 2.5- to 3-mm slice thickness and a tube voltage 120 kVp. No beta blockade is required, and the scan time is 3 to 5 seconds.[10] Both MDCT and EBCT scanners allow for adequate CAC scoring, although MDCT CAC imaging is the predominant method for contemporary CAC testing.

To date, almost every large-scale clinical study evaluating the clinical utility of CAC has relied on the *Agatston score,* which quantifies CAC as a function of CAC surface area and density (**Fig. 18.4**). This weighted sum of CAC is defined by areas within coronary arteries with Hounsfield unit (HU) values greater than 130 comprising three or more adjacent pixels. Each calcified voxel is then multiplied by a weighting factor from 0 to 4 based on the maximum HU within the calcified area. Standardized CAC categories have been established based on prior studies, and it is generally agreed that a CAC score of 0 indicates the absence of calcified plaque and that scores of 1 to 10, 11 to 100, 101 to 400, and greater than 400 indicate minimal, mildly elevated, moderately elevated, and severely elevated CAC level, respectively. In some studies a CAC score of 300 or greater has been used as an alternative threshold to describe severely elevated CAC level. Alternative scores, such as the volume score and mass score, have been proposed to reduce interstudy and interscanner variability but lack the prognostic evidence of the Agatston score for translation into clinical practice and are not typically reported[11,12] (see Classic References, Callister).

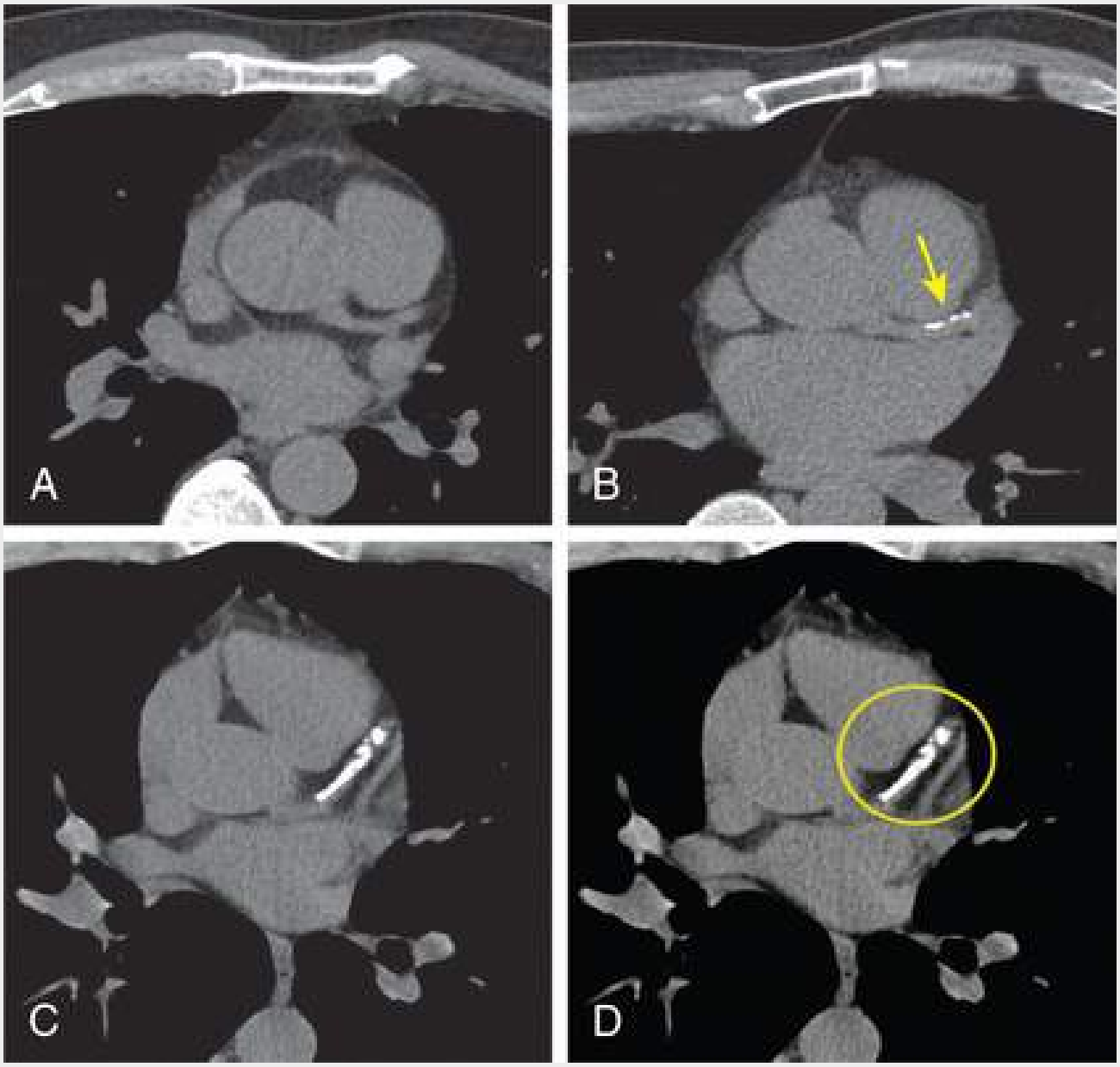

FIGURE 18.4 Examples of coronary artery calcium (CAC) imaging. Representative axial slices of a CAC CT scan demonstrate **A,** no evident calcium; **B,** mild coronary calcium; and **C,** severe coronary calcium. **D,** Method of quantification of the Agatston CAC score, in which the surface area of the coronary calcium is multiplied by the Hounsfield unit (HU) density conversion factor: a value of 1 = 139 to 199 HU, 2 = 200 to 299 HU, 3 = 300 to 399 HUs, and 4 = >400 HU.

Prognostic Implications

The prognostic value of CAC has been demonstrated consistently across many cohorts worldwide, most notably in the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based prospective cohort study of asymptomatic U.S. adults. Risk of incident adverse events for individuals with a CAC score of 0 was very low, with a major adverse cardiovascular event (MACE) rate of 0.5% over 4 years. However, higher levels of CAC showed a correspondingly higher risk of MACE; patients with a CAC score of 400 or higher experienced events more than 10% of the time, a rate exceeding the traditional definitions of a "coronary heart disease equivalent."[13] This prognostic value of CAC is incremental to clinical CAD risk factors, increasing the discrimination of future adverse clinical events (area under the receiver operating characteristic [ROC] curve 0.77 versus 0.82; $P < 0.001$).[14] The MESA study demonstrated higher CAC in Caucasians and Hispanics, male sex, and advancing age and also importantly provided population-based reference standards by which individual scores may be compared.[15] A CAC score greater than the 75th

percentile for age, sex, and ethnicity may be considered “high risk,” irrespective of the absolute score; however, the prognostic value of the absolute CAC score demonstrates uniformity across ethnic groups and by sex, and thus it has been suggested that absolute CAC rather than CAC percentiles be used for prediction of events.[13,16] The Heinz-Nixdorf Recall study similarly showed in an older population-based cohort that the upper quartile of CAC had an event rate 11.1 times that of the lowest quartile in men and 3.2 times that of the lowest quartile in women ($P < 0.01$ for both).[17]

In evaluating individuals without evident CAC, a long-term “warranty period” appears to be present. In a single-center study, 422 individuals with a baseline CAC score of 0 underwent annual CAC for 5 consecutive years and were compared to a matched cohort of 621 individuals with a baseline CAC greater than 0. In those without CAC, conversion to CAC greater than 0 occurred in 25% at an average of 4 years, suggesting no need for repeat imaging until at least this point. Evaluation of the matched cohort with CAC at baseline demonstrated CAC greater than 0 to be the strongest predictor of CAC progression (hazard ratio [HR] >12).[18] The slow conversion of 0 score to a CAC greater than 0 appears to translate to predictability of clinical outcomes. In a large study of 4864 participants with a baseline CAC of 0, the warranty period, defined by less than 1% mortality per year, extended to 15 years for individuals at low and intermediate risk for CAD events, as defined by the National Cholesterol Education Program and Adult Treatment Panel III (NCEP/ATP IIII) risk categories, regardless of age or sex. For individuals considered at high clinical risk, the warranty period extended only to 5 years and was 14 years for individuals older than 60[19] (**Fig. 18.5**).

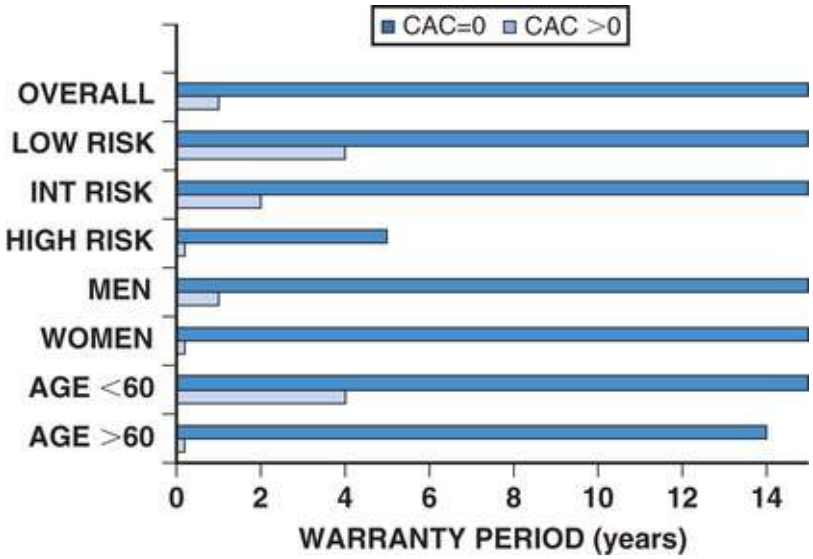

FIGURE 18.5 “Warranty” period of normal coronary artery calcium (CAC) study. Comparison of warranty period of individuals with (*dark blue*) versus without (*light blue*) CAC, as defined by a <1% annual mortality rate in 9715 individuals undergoing CAC scoring. *INT,* Intermediate. (Modified from Valenti V, O'Hartaigh B, Heo R, et al. A15-year warranty period for asymptomatic individuals without coronary artery calcium: a prospective follow-up of 9,715 individuals. JACC Cardiovasc Imaging 2015;8:900-9.)

In addition to improving prognostication and discrimination of risk, as evaluated by ROC curves, CAC improves accurate risk reclassification beyond risk scoring alone, either with older risk scores such as the Framingham Risk Score (FRS) or newer ones such as the American College of Cardiology and American Heart Association (ACC/AHA) 2013 Guideline Pooled Cohorts Equation.[14,20] Most notably, in the intermediate-risk population, CAC correctly reclassifies risk estimates from 52% to 66%, with less impact on the high- and low-risk groups.[17] Compared with other risk markers, such as brachial flow–mediated dilation, carotid intimal-media thickness, high-sensitivity C-reactive protein (CRP), and family

history, CAC provides superior discrimination and risk classification for CAD events.[21]

Notably, CAC is a measure of not only coronary atherosclerotic burden but also overall vascular atherosclerotic burden. In this regard, CAC is useful to predict cerebrovascular disease events. In the MESA study, among participants followed for almost 10 years, CAC was an independent predictor of cerebrovascular risk, even after accounting for traditional cerebrovascular disease events, and improved discrimination as well.[22] CAC is also associated with other adverse future clinical events, including atrial fibrillation, cancer, stroke, and congestive heart failure.[22-26]

One notable finding of CAC is the relationship of CAC density and incident risk. In a MESA analysis of 3398 patients followed for almost 8 years, the log-normalized CAC volume score was highly predictive for incident CAD events. However, higher CAC density demonstrated a protective influence, with CAC density scores associated with lower CAD risk. These contemporary data suggest that the integrated metric of the surface area and density of calcium, as is the case for the Agatston CAC score and for which higher density results in higher CAC scores, may require reexamination in prognostic studies.[27]

Although the negative predictive value of a CAC score of 0 has been consistently demonstrated with an event rate in asymptomatic patients, with an annualized event rate of 0.5% over 5 years in recent meta-analyses, it should not be considered similarly in symptomatic patients.[28] Recent data from the multinational CONFIRM registry showed that 4% of symptomatic patients with CAC of 0 had obstructive CAD of 50% stenosis or more, and CAC offered no incremental discriminatory utility above CCTA. Similarly, in the ROMICAT study, a CAC of 0 in acute chest pain patients did not adequately exclude acute coronary syndrome.[29,30]

The role of serial imaging of CAC is not well defined. Although progression of CAC is associated with an increased risk for future CAD events, prior studies have revealed no effect on CAC by statin treatment, thus raising the question of what information a follow-up CAC scan will offer[31] (see Classic References, Callister). In addition, the proper therapeutic course of action remains to be definitively determined for CAC visualized on noncardiac CT scans. CAC is frequently observed on myocardial perfusion imaging (MPI) as part of the attenuation correction scan (**see Chapter 16**). Although the likelihood of ischemic MPI is more than 2% with CAC less than 100, risk for future adverse events increases with higher CAC scores, and more than one third of patients with CAC greater than 400 have an abnormal MPI.[32,33] Similarly, CAC visualized on screening CT images for lung cancer also portend adverse prognosis, although no study to date has evaluated the effect of treatment of this CAC.

Clinical Trials and Professional Guidelines

To date, no adequately powered randomized clinical trial has been performed to assess the effects of a CAC-guided strategy compared to a clinical risk factor–guided strategy for event-free survival. Two prospective randomized trials provide new information on the potential effects of CAC treatment. In the St. Francis Heart Study, 1005 patients with CAC greater than 80th percentile were randomized to atorvastatin (20 mg), vitamin C (1 g), and vitamin E (1000 units) daily and compared to those receiving placebo.[34] At a 4.3-year follow-up, no differences were observed in the composite cardiovascular disease (CVD) endpoint (6.9% versus 9.9%; $P = 0.08$). Notably, for patients with a baseline CAC score greater than 400, there was a significantly lower event rate (8.7% versus 15.0%; $P = 0.046$). These study results, in the context of the new 2013 ACC/AHA cholesterol and risk guidelines, require updating with the more contemporary approaches to treatment.

In the single-center Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging

Research (EISNER) study of 2137 volunteers randomized to CAC scoring versus no CAC scoring, those receiving CAC scoring experienced near-complete cessation of FRS progression compared to those not receiving CAC scoring (**Fig. 18.6**). This cessation of FRS progression resulted from achieving lower systolic blood pressure, low-density lipoprotein (LDL) levels, abdominal girth, and weight. In an economic analysis, the CAC group experienced similar costs and medical testing as those not undergoing CAC scanning.[35,36]

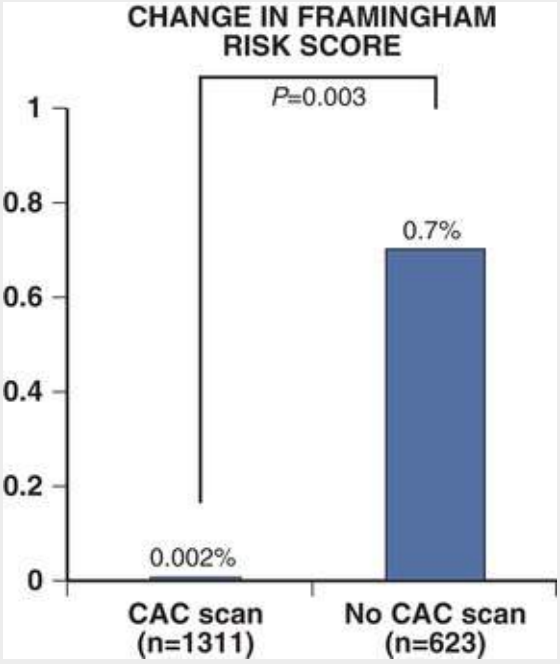

FIGURE 18.6 Primary outcome of randomized open-label EISNER trial of individuals who underwent coronary artery calcium (CAC) scanning versus those who did not. Framingham risk scores for individuals undergoing CAC scans (*left*) were unchanged over the 4-year follow-up period, whereas individuals who did not undergo CAC scan (*right*) experienced progression of Framingham risk scores. CAC scans were associated with improvement in systolic and diastolic blood pressure ($P < 0.001$), low-density lipoprotein level ($P < 0.001$), and reduced body weight ($P < 0.001$). (From Rozanski A, Gransar H, Shaw LJ, et al. Impact of coronary artery calcium scanning on coronary risk factors and downstream testing the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) prospective randomized trial. J Am Coll Cardiol 2011;57:1622-32.)

The 2013 ACC/AHA cholesterol and risk guidelines utilizing the new pooled cohort equations dramatically increased the number of people recommended to receive statins[37] (**see Chapter 45**). CAC evaluation is a class IIB recommendation for performance that is reserved for adults age 40 to 75 with no atherosclerotic cardiovascular disease, LDL of 70 to 189 mg/dL, and 10-year cardiovascular disease risk less than 7.5%. Among this population, CAC of 300 or more or 75th or greater percentile for age, sex, and ethnicity may be considered with other high-risk markers for determining the need for statins.[38] In the 2013 ACC multimodality imaging appropriate use criteria (AUC; see end of chapter), CAC scoring is considered inappropriate for performance in asymptomatic patients with low global CAD risk and may be appropriate in those with intermediate to high global CAD risk.[39] Application of these criteria to population-based CAC cohorts reveals that among intermediate-risk patients who would be considered appropriate for CAC scanning in the MESA study, 57% had a CAC of 0, with an atherosclerotic CVD event rate of 1.5 per 1000 person-years. However, among statin-recommended patients who would not have been considered appropriate for CAC evaluation by guidelines, 41% had CAC of 0, with only 5.2 CVD events per 1000 person-years, far below their risk estimate by the pooled cohort equations.[24] Among adults with CVD risk less than 7.5%, the number needed for screening to identify a statin-eligible

candidate was 14.7, superior to other high-risk measures (e.g., high-sensitivity CRP and ankle-brachial index).[40] Similarly, among statin-eligible patients in the Framingham Heart Study, a CAC = 0 identifies one-third of them as low-risk patients with a CVD rate of 1.6% over 9.4 years.[41]

Randomized controlled trials (RCTs) using CAC, informed by current guidelines and the AUC, will be needed to determine the appropriate patient population and follow-up treatment strategy that may benefit from CAC screening.

Coronary Computed Tomographic Angiography

Diagnostic Accuracy

Since its introduction, the primary interest in the clinical use of coronary CT angiography (CCTA) has been as a noninvasive alternative to coronary angiography (**Fig. 18.7**). An array of single-center studies and three prospective multicenter studies evaluated the diagnostic performance of CCTA, primarily compared to an invasive coronary angiography (ICA) reference standard (**Table 18.2**). Of the three multicenter studies, with a CAD prevalence of 25% to 68%, the Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography (ACCURACY) trial[42] and the study by Meijboom and colleagues[43] enrolled only patients without known CAD, observing a sensitivity of 95% and 99% and specificity of 83% and 64%, respectively. In contrast, the Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography (CORE64) study enrolled a heterogeneous group of patients with and without known CAD with a CAC score less than 600, noting the sensitivity and specificity to be 85% and 90%, respectively.[44] Based on these results, it is usually noted that CCTA is an excellent imaging modality for the exclusion of CAD. Further, its specificity for detection of coronary artery stenosis is similar or superior to more traditional stress testing methods, with or without imaging (**see Chapters 13, 14, and 16**).

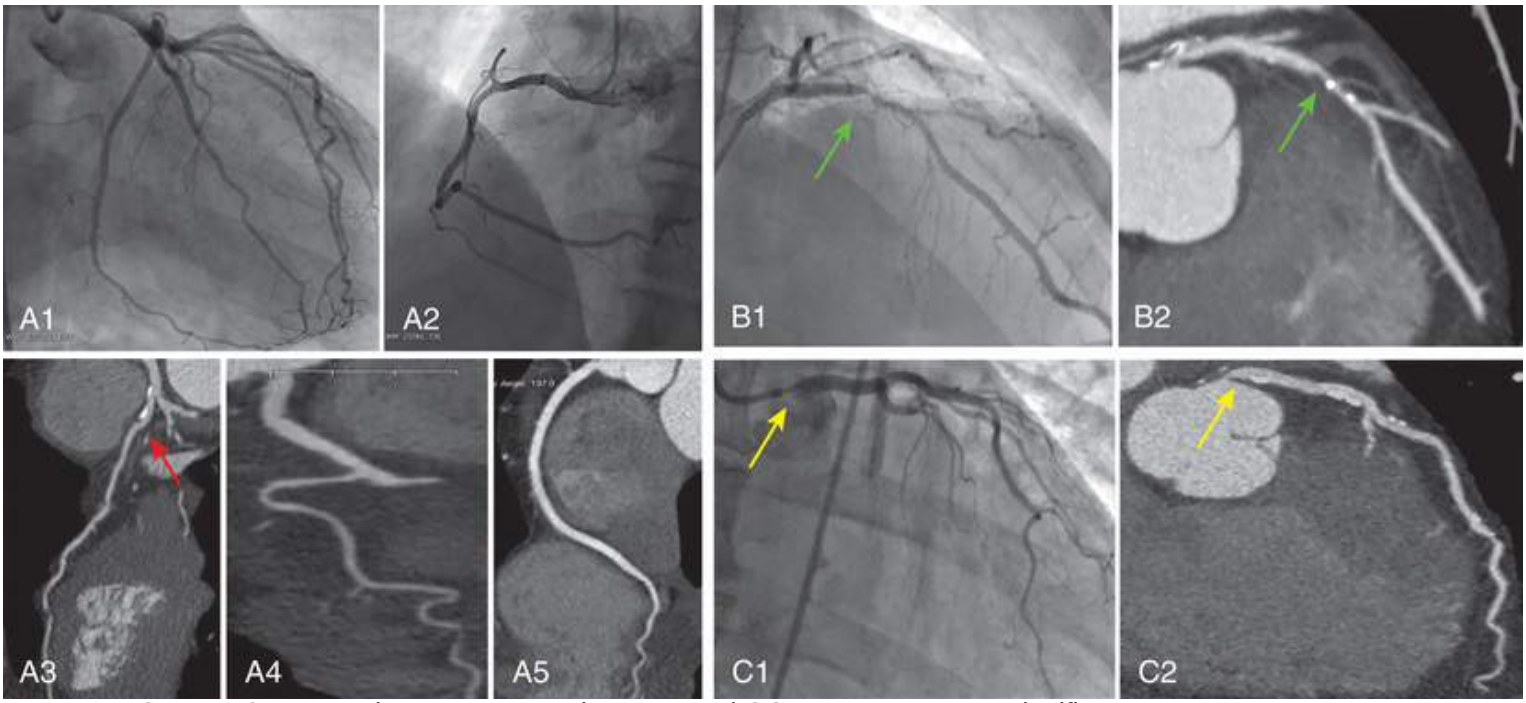

FIGURE 18.7 Invasive coronary angiograms and CCTAs: **A1** to **A5,** no significant coronary artery stenoses; **B1** and **B2,** moderate coronary artery stenosis; and **C1** and **C2,** severe coronary artery stenosis. **A1, A2,** Left and right invasive coronary angiograms demonstrate no significant stenosis. CCTA demonstrates mild, nonobstructive calcified plaque in the left anterior descending artery (LAD) **(A3)** (*red arrow*) and no stenosis in the left circumflex artery **(A4)** or right coronary artery **(A5).** Invasive angiogram of the LAD **(B1)** demonstrates moderate coronary stenosis in the midportion of the vessel, which is similar to the CCTA (*green arrows*) **(B2).** Left main artery angiogram reveals very-high-grade stenosis of the ostium **(C1),** which is identified also by the CCTA **(C2)** (*yellow arrows*).

TABLE 18.2

Diagnostic Accuracy of Coronary CT Angiography for Patient- and Vessel-Based Detection of Obstructive Coronary Stenosis

	BUDOFF[42]		MILLER[44]		MEIJBOOM[43]
Study name	ACCURACY*		CORE64†		—
Year published	2008		2008		2008
Study design	Prospective multicenter		Prospective multicenter		Prospective multicenter
Population	≥18 years of age, typical or atypical chest pain. No known history of CAD		At least 40 years of age, suspected symptomatic CAD, CACS of 600 or less		Patients with stable or unstable chest pain between the age of 50 and 70 years
Patients (*n*)	230		291		360
Vessels (*n*)	910		866		1440
Per-Patient Basis					
	≥50% STENOSIS	**≥70% STENOSIS**	**QUANTITATIVE MDCT**	**VISUAL MDCT**	
Disease prevalence (%, ≥50% stenosis)	25	14	52	50	68
Sensitivity (%)	95	94	85	83	99
Specificity (%)	83	83	90	91	64
PPV (%)	64	48	91	92	86
NPV (%)	99	99	83	81	97
Per-Vessel Basis					
	≥50% STENOSIS	**≥70% STENOSIS**	**QUANTITATIVE MDCT**	**VISUAL MDCT**	
Disease prevalence (%, ≥50% stenosis)	10	4	29	28	26
Sensitivity (%)	84	84	75	75	95
Specificity (%)	90	92	93	93	77
PPV (%)	51	36	82	83	59
NPV (%)	99	99	89	89	98

*Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography trial.

†Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography study.

CAD, coronary artery disease; *CACS,* coronary artery calcium score; *MDCT,* multidetector computed tomography; *PPV,* positive predictive value; *NPV,* negative predictive value.

With each improvement of CT technology, diagnostic performance of CCTA has been evaluated in smaller single-center studies of 30 to 160 patients. The sensitivity and specificity of CCTA versus ICA—both a per-patient and a per-vessel basis—have generally been observed to be higher than those using conventional 64–detector row CCTA, with both values generally above 90% (**Table 18.3**).

TABLE 18.3

Diagnostic Accuracy of Coronary CT Angiography with Prospective ECG Gating Based on Step-and-Shoot, Flash, and Volume Modes For Patient- and Vessel-Based Detection of Significant Coronary Stenosis Exceeding 50%

Author	Year	Patients	Vessels	Scanner	ECG Gating	NO. of Slices	DIAGNOSTIC ACCURACY, %							
							PER-PATIENT BASIS				PER-VESSEL BASIS			
							Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV
Pelliccia[139]	2013	118	375	Toshiba	Volume	320	98	91	93	98	93	95	92	96
Maffei[140]	2012	160	637	Siemens	Flash	128	100	83	72	100	98	91	61	100
Van Velzen[141]	2011	106	255	Toshiba	Volume	320	100*	87*	93*	100*	99*	95*	92*	99*
Stolzmann[142]	2011	100	-	Siemens	SAS	64	100	93	95	100	99	97	95	99
Bamberg[143]	2011	33	96	Siemens	Flash	128	100†	18†	71†	100†	91	69	79	85
Achenbach[144]	2011	50	200	Siemens	Flash	128	100	82	72	100	100	94	74	100
Scheffel[145]	2010	43	129	Siemens	SAS	64	100	93	97	100	96	89	90	95
Nasis[146]	2010	63	260	Toshiba	Volume	320	94	87	88	93	89	95	82	97
Husmann[147]	2010	61	244	GE	SAS	64	100	86	89	100	93	86	73	97
De Graaf[148]	2010	64	177	Toshiba	Volume	320	100	88	92	100	94	92	83	97
Carrascosa[149]	2010	50	210	Philips	SAS	64	100	75	81	100	96	94	83	99
Alkadhi[150]	2010	50	199	Siemens	SAS	128	94	91	85	99	97	98	88	99
Alkadhi[150]	2010	50	245	Siemens	Flash	128	94	94	89	97	96	97	83	99

*Excluding nondiagnostic segments vessels and patients.

†Hemodynamically significant coronary artery stenosis ≤0.75.

ECG, Electrocardiogram; *Sens,* sensitivity; *Spec,* specificity; *PPV,* positive predictive value; *NPV,* negative predictive value; *SAS,* step and shoot.

Studies directly comparing CCTA to traditional stress testing methods are less common but have been evaluated in a single, large-scale multicenter trial. Contemporary evidence to date suggests a value to CCTA over other imaging methods for the diagnosis of high-grade coronary stenoses. In the prospective multicenter Evaluation of Integrated Cardiac Imaging in Ischemic Heart Disease (EVINCI) study of 475 patients across several European centers, patients underwent CCTA, MPI by single-photon emission computed tomography (SPECT), or positron emission tomography (PET) and left ventricular wall motion analysis by stress echocardiography (SE) or cardiac magnetic resonance (CMR) imaging.[45] Significant CAD, as defined by greater than 70% luminal stenosis, was observed in 29% of patients. Among all the imaging modalities, CCTA demonstrated the highest diagnostic accuracy, with a sensitivity and specificity of 91% and 92%, respectively, and an area under ROC curve of 0.91. In contrast, MPI was observed to have a sensitivity and specificity of 74% and 73%, respectively, and area under ROC curve of 0.74. Wall motion analysis by SE or CMR demonstrated a higher specificity but lower sensitivity at 92% and 49%, respectively.

To date, no prospective multicenter study has been performed to evaluate the diagnostic performance of CCTA for in-stent restenosis (ISR) imaging, which may differ from native coronary artery examination due to the blooming artifacts of metallic stents that may preclude the ability to accurately assess the presence or absence of ISR (**Fig. 18.8**). It is commonly believed that stent size is the only factor that influences the visualization of stents by CCTA, but CT scan parameters and stent alloy type also play a significant role. Comparatively, current-generation drug-eluting stents are better visualized than older stents with different metallic makeup. Several meta-analyses report high diagnostic performance for stent imaging by CCTA, with sensitivity and specificity of 82% to 91% and 91% to 93%, respectively.[46-49] Notably, improvements in coronary stent technology may enhance the evolution of CCTA. Bioabsorbable drug-eluting vascular scaffolds comprised of poly-L-lactide and poly-D,L-lactide particularly accommodate CCTA visualization with little to no blooming artifacts. These revascularization methods, if

proven effective, may allow for more routine assessment of patency by CCTA.

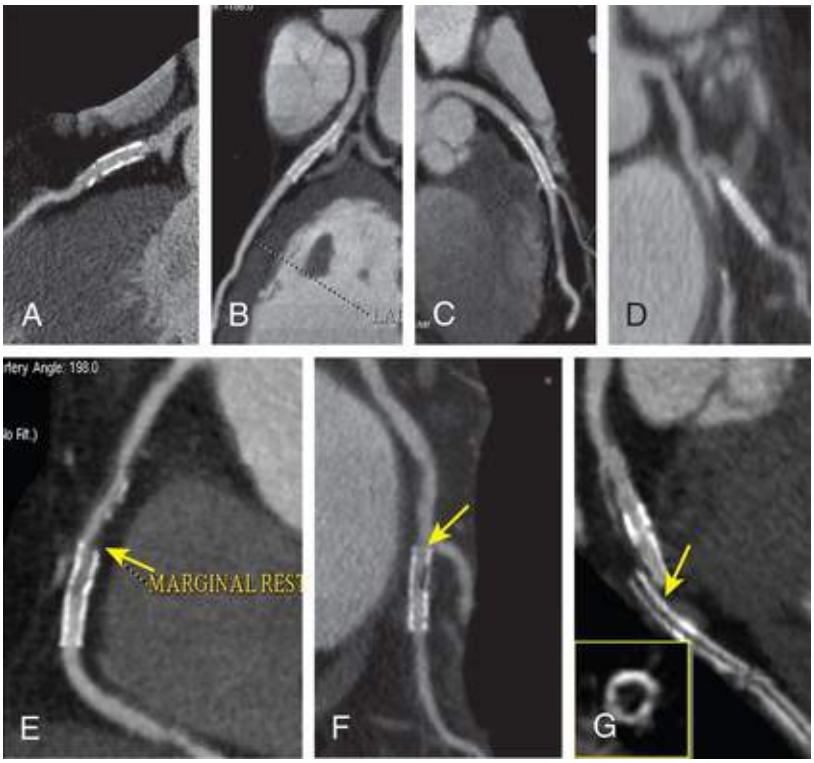

FIGURE 18.8 CCTA imaging of intracoronary stents: **A,** 4.0 mm; **B,** 3.5 mm; **C,** 3.0 mm; **D,** 2.25 mm. Note the smaller diameter of the 2.25-mm stent **(D)** exhibits "blooming" artifact that renders it difficult to visualize the coronary lumen within the stent. **E,** Mild; **F,** moderate; and **G,** severe in-stent restenosis (*yellow arrows*). In **G** there is malapposition of two stents, with a 100% occlusion of the stent (*yellow arrow, inset*).

Similarly, no large-scale trial has ever been conducted to examine the diagnostic performance of CCTA for evaluation CABG patency (**Fig. 18.9**). Contemporary studies evaluating CCTA have reported very high diagnostic accuracy for both stenosis and occlusion in CABGs. In a meta-analysis that combined the assessment of CABGs with stenosis and occlusion, sensitivity and specificity of CCTA was 96.1% and 96.3%, respectively.[50] In another study that separately categorized the two, CCTA demonstrated a sensitivity and specificity of 99% and 99%, respectively, for occlusion, and 98% and 98% for stenosis. Despite its high performance to identify and exclude CABG disease, such patients often have extensive native CAD. No study to date has evaluated the accuracy of CCTA for those undergoing CABG on a per-patient basis, in which the accuracy is evaluated for both CABG and native coronary arteries.

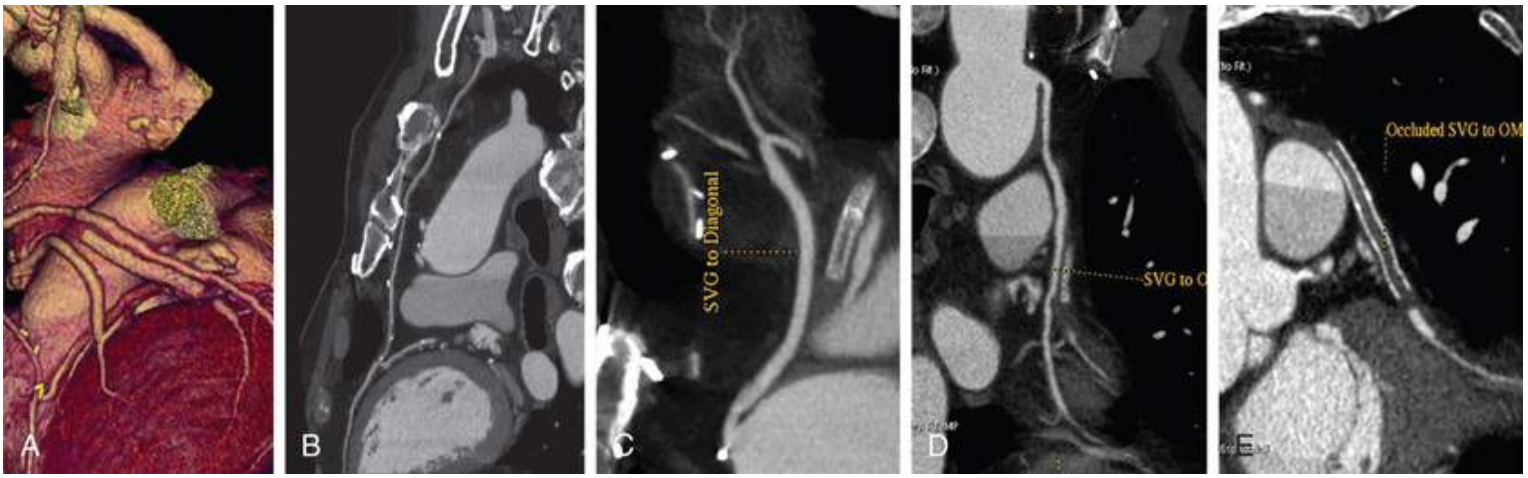

FIGURE 18.9 Patient with multiple coronary artery bypass grafts. **A,** The topology of the grafts can be appreciated well in a volume-rendered view. Curved reformat views demonstrate **B,** patency of left internal mammary artery graft to left anterior descending artery (LAD); **C,** patency of saphenous vein graft (SVG) to first diagonal branch of LAD; and **D,** patency of SVG to second obtuse marginal graft of left circumflex artery. **E,** Total occlusion of SVG to first obtuse marginal graft can be seen in the native graft as well as the portion of the graft containing a stent.

Prognostic Implications

Numerous potential coronary artery and cardiac characteristics observable by CCTA beyond luminal stenosis severity offer prognostic utility for risk stratification of patients with suspected CAD. These features include extent, severity, and location of CAD, as well as atherosclerosis measures of plaque composition, plaque burden, high-risk plaque features, and arterial remodeling.

To date, the largest study evaluating the prognostic value of these CAD findings is the Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter Registry (CONFIRM) study[51] (**eTable 18.1**). At its inception, this dynamic observational cohort study comprised 27,125 stable patients with suspected CAD who underwent CCTA and were followed for all-cause mortality, nonfatal myocardial infarction (MI), and other MACE events. The first published study from CONFIRM examined differences in all-cause mortality rates based on CCTA CAD findings, as stratified by single-, double-, and triple-vessel CAD.[52] In a 2.3-year follow-up, a 2.6-fold increased risk of death was observed for patients with any stenosis greater than 70%, as well as a 1.6-fold increased risk of death for those with milder stenoses (<50%). Increasing risk of mortality was observed for patients with greater numbers of coronary artery distribution involved for one-vessel (hazard ratio [HR] 2.00), two-vessel (HR 2.92), and three-vessel or left main CAD (HR 3.7) ($P < 0.01$ for all). A gender-CAD relationship was observed, with women experiencing greater risk of mortality than men for three-vessel CAD (HR 4.21 versus 3.27). Importantly, incident rates of all-cause death were very low in the absence of CAD by CCTA, with an annualized rate of 0.28%. Subsequent studies have validated this very low rate of events and suggest a warranty period of CCTA to extend beyond 5 years for patients with no evident stenosis or atherosclerosis by CCTA. These prognostic findings of CCTA have been subsequently evaluated within the CONFIRM study in many clinically important subgroups for both all-cause mortality and MACE, including for women and men, elderly patients, patients with a CAC score of 0, asymptomatic patients, diabetic patients, obese patients, patients of different ethnicities, individuals with no modifiable CAD risk factors, patients with impaired renal function, patients with low and high lifetime CAD risk, asymptomatic diabetic patients, patients with impaired left ventricular systolic function, smokers, patients with left coronary dominance, and patients with metabolic syndrome.[53-70] Beyond traditional statistical

techniques that employ logistic or linear regression methods, machine learning has now been employed to improve the prognostic ability of CCTA findings in CONFIRM.[71] Among 10,030 patients followed after CCTA for 5 years, boosting method–based machine learning proved superior to clinical- or clinical/image-based evaluation alone, demonstrating a higher area under the ROC curve of 0.61 and 0.64 and 0.79, respectively.

ETABLE 18.1

Prognostic Value of CAD Severity Assessed by CCTA in Various Population (CONFIRM Registry)

STUDY	POPULATION	SAMPLE SIZE (*n*)	CLINICAL OUTCOME	FOLLOW-UP PERIOD	STUDY OBJECTIVE	HAZARD RATIO (HR) BY CATEGORY	CLINICAL EVENT RATE	PRINCIPAL FINDING
Villines[53]	Symptomatic with no prior CAD	10,037	ACM, nonfatal MI and late revascularization	Median 2.1 years	Impact of CAD severity in patients with zero CACS	In patients with zero CACS Nonobstructive CAD: 1 Obstructive CAD: 5.7 (2.5-13.1)	Overall with zero CAC: 0.9% No CAD: 0.6% Nonobstructive CAD: 2.0% Obstructive CAD: 3.9%	In symptomatic patients with CACS zero, severity of CAD is associated with increased cardiovascular events
Chow[151]	No prior CAD, enable to assess FRS	14,064	ACM	Median 2.0 years	Impact of LVEF and CAD severity over FRS	No CAD: 1 Nonobstructive CAD: 2.8 (1.9-4.0) Obstructive CAD with nonhigh FRS: 3.3 (2.2-5.0) Obstructive CAD with high FRS: 4.9 LVEF<50%: 2.7 (2.1-3.5)	No CAD: 0.7% Nonobstructive CAD: 2.0% Obstructive CAD with nonhigh FRS: 3.0% Obstructive CAD with high FRS: 5.2% LVEF <50% : 4.8%	CCTA measures of CAD severity and LVEF have independent prognostic value
Min[51]	No prior CAD	24,775	ACM	Median 2.1 years	CAD severity by age and sex	No CAD: 1 Male vs. female 3-VD/LM: 3.27 (1.9-5.5) for male; 4.21 (2.5-7.2) for female: <65 vs. ≥65 3-VD/LM: 6.19 (3.4-11.2) for age <65 3.10 (1.9-4.9) for age ≥65	N/A	CAD severity by CCTA are associated with higher mortality rates, with risk profiles differing for age and sex
Rana[54]	Patients with and without diabetes	3370 vs. 6740 matched DM vs. non-DM	ACM	Median 2.2 years	CAD severity in DM patient	No CAD in non-DM: 1 In DM patients No CAD: 3.63 (1.7-7.9) Nonobstructive CAD: 5.25 (2.6-10.8) 1-VD: 6.39 (2.9-13.7) 2-VD: 12.33 (5.6-27.1) 3-VD: 13.25 (6.2-28.6)	DM patients: 3.2%, Non-DM patients: 1.7%	DM individuals experience higher risk of mortality compared with non-DM individuals
Cho[54]	Asymptomatic with no prior CAD	7590	ACM, nonfatal MI	Median 2 years	CAD severity in asymptomatic patients	No CAD: 1 Nonobstructive CAD: 1.7 1-VD: 2.1 2-VD: 5.9 3-VD or LM: 7.1	Overall rate: 2.2% No or nonobstructive CAD: 1.6% Obstructive CAD: 4.6%	Prognosis for asymptomatic individuals is stratified by CAD severity by CCTA
Labounty[59]	No prior CAD, enable to assess risk factors and BMI collected	16,291	ACM, nonfatal MI	Mean 2.4 years	ACM and MI event across 5 BMI categories (<20.0, 20.0-24.9, 25.0-29.9, 30.0-34.9, and ≥35 kg/m^2)	N/A	Annualized mortality event rate: <20.0: 1.2%; 20.0-24.9: 0.4%; 25.0-29.9: 0.4%; 30.0-34.9: 0.4%; ≥35: 0.4% Annualized mortality and MI rate: <20.0: 0.3%; 20.0-24.9: 0.3%;	A higher BMI is independently associated with increased risk of myocardial infarction

							25.0-29.9: 0.5%; 30.0-34.9: 0.7%; ≥35: 1.2%	
Min[55]	No prior CAD, enable to assess ICA or revascularization information	15,223	ACM	Median 2.1 years	ACM between medical therapy vs. coronary revascularization	Revascularization vs. medical therapy: In high-risk CAD: 0.4 (0.2-0.8) In low risk CAD: 3.2 (0.8-13.9)	In low risk of CAD: 0.97% for medical therapy, 2.06% for revascularization In high risk of CAD: 5.34% for medical therapy, 2.28% for revascularization	Coronary revascularization is associated with survival benefit in patients with high-risk CAD by CCTA, with no apparent benefit of revascularization in patients with low-risk CAD
Dwivedi[57]	Enable to assess creatinine value, LVEF assessment	5864	ACM	Median 1.6 years	ACM according to renal function	Impaired renal function: HR 2.3 (1.7-3.2) Obstructive CAD: HR 1.8 (1.3-2.5) Abnormal LVEF: 4.2 (2.5-7.1)	No CAD: 0.33% Nonobstructive disease: 1.82% Obstructive disease: 2.43%	CAD severity and LVEF by CCTA provide effective risk stratification across renal function
Hadamitzky[58]	Enable to assess plaque characteristics and risk factors	17,793	ACM	Median 2.3 year	Prognostic value of plaque composition and plaque location	Number of segment with any plaque: 1.2 (1.03-1.4) Number of segment with stenosis >50%: 1.2 (1.1-1.3) Number of segment with stenosis >70%: 1.3 (1.1-1.5) Number of proximal segment with calcified or mixed plaque: 1.4 (1.1-1.7) Number of proximal segment with stenosis: 1.5 (1.2-1.9)	N/A	Both plaque burden and stenosis, particularly in proximal segments, carry incremental prognostic value
Otaki[61]	Young patients (men age <55 and women age <65)	6308	ACM, nonfatal MI	Mean 2 years	ACM and MI event by family history in young patients	Without family history of CAD: 1 With family history of CAD: 2.6 (1.4-4.8)	Annual rate of MI Without family history of CAD: 0.2% With family history of CAD: 0.5%	Positive family history in young patients is strong clinical predictor of MI
Leipsic[60]	Exclude patients with modifiable risk factor	5262	ACM, nonfatal MI and late revascularization	Mean 2.3 years	CAD severity in patients with no medically modifiable risk factors	No CAD In symptomatic patients Obstructive CAD: 11.9 (4.8-29.6) In asymptomatic patients Obstructive CAD: 6.3 (2.4-16.7)	Overall without modifiable risk factor No CAD: 0.48% Nonobstructive CAD: 0.53% Obstructive CAD: 8.0%	Among individuals suspected of having CAD but without modifiable risk factors, CAD is significantly increased hazard for MACE and mortality
Hulten[152]	Patients with ethnicity data	16,451	ACM, nonfatal MI	Median 2.0 years	Impact of obstructive CAD for MACE according to ethnicity	Nonobstructive CAD: 1 Obstructive CAD: Caucasian: 2.8 (1.7-4.4) Africans: 6.3 (1.1-35.0) East Asians: 4.8 (2.2-10.9)	Annualized incidence of MACE Nonobstructive CAD Caucasian/Africans/East Asians: 0.7%/1.1%/0.1% Obstructive CAD Caucasian/Africans/East Asians: 2.2%/4.8%/0.8%	Presence and severity of CAD visualized by CCTA predict death or MI across 3 large ethnicities
Leipsic[64]	No prior CAD history, nonobstructive CAD	11,462	ACM, nonfatal MI	Mean 2.3 years	Gender difference MACE rate	No CAD: 1 Nonobstructive CAD Men: 1.8 (1.1-2.9) Women: 2.0 (1.2-3.3)	Annualized MI and death event rate MI rate: men, 0.2%; women, 0.2% ACM rate: men, 0.6%; women, 0.6%	Women and men experience comparable rates of incident mortality and MI in age, risk factor matched
Hulten[63]	Asymptomatic patients age 20-60 without diabetes or prior CAD	1863	ACM, nonfatal MI and late revascularization	Median 2.0 years	MACE by FRS and lifetime risk	N/A	Patients with low FRS Low lifetime risk: 0.32% High lifetime risk: 0.28%	Prognosis of MACE did not differ between low lifetime risk vs. high lifetime risk due to low number of

								events
Nakazato[66]	No prior CAD, enable to assess per-segment data	15,178	ACM, nonfatal MI and late revascularization	Median 2.1 years	CAD severity for MACE by age (<65 and ≥65)	<65 vs. ≥65 years No CAD in <65 years: 1 Nonobstructive CAD: 2.7 (1.8-4.0) vs. 6.2 (4.2-9.1) 1-VD: 11.4 (7.7-16.9) vs. 19.9 (13.6-29.1) 2-VD: 17.4 (10.9-27.9) vs. 36.1 (23.7-54.8) 3-VD or LM: 47.6 (28.5-79.7) vs. 48.1 (30.1-76.8)	N/A	Nonobstructive, and obstructive CAD are associated with higher MACE rates, with different risk profiles based on age
Min[65]	Asymptomatic diabetes with no prior CAD	400	ACM, nonfatal MI and late revascularization	Mean 2.4 years	CAD severity in asymptomatic DM patient	Per-patient maximal stenosis per grade: 1.8 (1.2-2.8) Number of obstructive vessels: 1.9 (1.3-2.7) Segment stenosis score: 1.1 (1.05-1.2)	33 MACE occurred (13 deaths, 8 MI, 12 revascularization) in asymptomatic DM patients: 8.25%, annualized rate 3.4%	CAD severity by CCTA associated with high MACE rate in asymptomatic DM patients
Arsanjani[62]	No prior CAD, enable to assess LVEF	7758	ACM	Mean 2.0 years	Impact of gradation measurement of LVEF	Normal LVEF: 1 45% ≤LVEF <55%: 1.4 (0.9-2.1) 35% ≤LVEF<45%: 3.14 (2.0-4.9) LVEF<35%: 5.2 (3.4-7.9)	Normal LVEF: 1.8% 45% ≤LVEF <55%: 2.9% 35% ≤LVEF <45%: 7.5% LVEF <35%: 12.8%	LV dysfunction and volumes measured with cardiac CT angiography augment risk prediction
Chow[68]	Nonobstructive CAD and no prior CAD and enable to assess medication history	10,418	ACM	Median 27months	Statin treatment and mortality event	Baseline statin treatment: Overall: 0.4 (0.3-0.7) Nonobstructive CAD: 0.3 (0.2-0.6) No CAD: 0.7 (0.3-1.4)	Nonobstructive CAD: Statin treatment: 1.0% Nonstatin treatment: 2.2% No CAD: Statin treatment: 0.6% Nonstatin treatment: 0.8%	Baseline statin therapy was associated with a significant reduction in mortality for individuals with nonobstructive CAD but not for individuals without CAD
Schulman-Marcus[153]	Patients with obstructive CAD by CCTA	1637	ACM, nonfatal MI	3 years	Effects of cardiac medication in patients with obstructive CAD	Cardiac medications Statin: 0.6 (0.4-0.9) Aspirin: 0.7 (0.5-1.1) Beta-blocker: 1.1 (0.7-1.6) ACE inhibitor: 1.4 (0.9-2.1)	N/A	In patients with obstructive CAD by CCTA, baseline use of statins was associated with improved clinical outcomes
Gebhard[69]	No prior CAD and enable to assess coronary dominance information	6382	ACM, nonfatal MI, and late revascularization	Median 2.1 years	Impact of coronary dominance for prognosis	Left dominance: 1 Right dominance: No CAD: 1.04 (0.7-1.6) Nonobstructive CAD: 1.0 (0.4-2.2) Obstructive CAD: 0.5 (0.2-1.3)	Cumulative event rate: Left dominant: 18.8% Right dominant: 19.1%	MACE did not differ significantly between patients with left or right coronary dominance.
Ahmadi[67]	Patients with metabolic syndrome	690	ACM, nonfatal MI and late revascularization	Median 2.5 years	Prognosis of CCTA in metabolic syndrome	Mortality event: 2.4 (1.2-4.7) MI: 0.8 (0.2-4.0) MACE 2.2 (1.3-3.7)	Metabolic syndrome: 1.9% No metabolic syndrome: 0.8%	Metabolic syndrome was associated with high incidence of MACE
Nakanishi[70]	No prior CAD with enable to assess smoking status	9456	ACM, nonfatal MI	Mean 2.8 years	Impact of current/past smoking for cardiac event	Never smoker: 1 Past smoker: 1.2 (0.8-1.6) Current smoker: 1.9 (1.4-2.6)	Never smoker: 2.8% Past smoker: 2.9% Current smoker: 4.8%	Compared with never smokers, higher MACE risk was observed only in current smokers, not past smokers
Cherubu[73]	Exclude patients with modifiable	1184	ACM, nonfatal MI and late	Mean 5.6 years	Long-term prognosis of CAD	No CAD: 1 Nonobstructive	No CAD: 5.6% Nonobstructive CAD:	CAD severity by CCTA provide long-

	risk factor		revascularization		severity in patients with no modifiable risk factors	CAD: 2.2 (1.3-3.7) Obstructive CAD: 6.6 (3.9-11.3)	13.2% Obstructive CAD: 36.3%	term (5-year) prognostic information in patients with no modifiable risk factors
Schulman-Marcus[154]	No prior CAD, enable to assess plaque severity information	5632	ACM, nonfatal MI	5 years	Sex difference in MACE risk and CAD severity	No CAD: 1 Nonobstructive CAD Men: 2.6 (1.6-4.0) Women: 2.2 (1.4-3.3) 1-VD Men: 2.7 (1.7-4.3) Women: 3.7 (2.4-5.8) 2-VD Men: 3.6 (2.2-5.8) Women: 3.9 (2.2-6.9) 3-VD/LM Men: 4.4 (2.7-7.2) Women: 5.9 (3.5-10.2)	N/A	There is no sex interaction for association between MACE risk and increased per-vessel extent of obstructive CAD
Blanke[155]	Patients with DM with no prior CAD	1823	ACM, nonfatal MI, and late revascularization	Mean 5.5 years	Long-term prognosis of CAD severity in DM patients	No CAD: 1 Nonobstructive CAD: 5.1 (2.9-8.9) 1-VD: 8.2 (4.6-14.5) 2-VD: 9.0 (4.8-17.1) 3-VD/LM: 24.8 (13.5-45.5)	Annualized MACE rate Overall DM patients: 6.8% No CAD: 1.3%	Among patients with DM, nonobstructive and obstructive CAD according to CCTA were associated with higher rates of MACE at 5 years

CCTA, Coronary CT angiography; *CAD,* coronary artery disease; *DM,* diabetes mellitus; *ACM,* all-cause mortality; *MI,* myocardial infarction; *MACE,* major adverse cardiovascular event; *LVEF,* left ventricular ejection fraction; *N/A,* nonapplicable; *VD,* vessel disease.

One potential benefit of CCTA imaging is its ability to discern nonobstructive CAD stenoses that can be present even in the setting of high overall atherosclerotic plaque burden. Prior studies have demonstrated that the majority of individuals experiencing their first unheralded MI do not in fact possess obstructive CAD stenosis. This was demonstrated first in a two-center prospective CCTA study of 2583 patients with suspected CAD.[72] At a 3.1-year follow-up, this population, limited only to those with maximum per-patient stenoses less than 50%, demonstrated differential outcomes based on the number of epicardial coronary artery distributions with any nonobstructive atherosclerosis, which were associated with a nearly twofold increased risk of mortality. A nearly fivefold increased risk of mortality was observed for individuals with nonobstructive CAD in all three epicardial vessel distributions.

One potential utility of CCTA is to identify at-risk individuals who do not meet conventional definitions as such by clinical risk scoring. In a 2.3-year follow-up study of 5262 patients without known CAD who were free from any modifiable CAD risk factor (e.g., smoking, hypertension, dyslipidemia, diabetes), the presence of any stenosis of 50% or more was associated with a 6.64-fold increase in the risk of MACE events, a finding independent of symptomatic state.[60] These findings persisted to almost 6 years, with increased mortality rates observed for individuals with one- or two-vessel obstructive CAD (HR 1.70) and three-vessel of left main CAD (HR 2.87).[73] Importantly, the presence of nonobstructive CAD alone was associated with increased risk of death in a manner similar to obstructive one- or two-vessel CAD (HR 1.73). Even among symptomatic individuals with a CAC score of 0, CCTA appears to offer incremental prognostic value for future mortality, nonfatal MI, or late coronary revascularization

more than 90 days after CCTA performance.[63] Among 8907 symptomatic patients undergoing both CCTA and CAC scoring, those with a CAC of 0 but a noncalcified plaque causing a 50% or greater stenosis experienced a more than fivefold increase in the rates of the composite endpoint.

Early reports of atherosclerosis findings were limited to classifications of noncalcified, calcified, and "mixed" plaques. In general, a cutoff point of 130 HU has been historically defined as calcified plaque, with values below this threshold interpreted as noncalcified plaque. Categorizations of noncalcified plaque can represent an admixture of fibrous, fibrofatty, and fatty plaques that, because of their significant overlap in HU by CCTA, are generally combined into a single group. Atherosclerotic plaques exhibiting a lower HU density (e.g., <70 HU) tend toward more lipoid plaques, with fibrous plaques manifesting higher HU densities (e.g., 70 to 130 HU). Recent studies have elicited some important imaging markers of atherosclerosis by CCTA based on HU densities that are associated with adverse clinical events and coronary ischemia.[74] More specifically, an atherosclerotic plaque with HU density less than 30 has been highly correlative on invasive ultrasound to plaques with lipid-laden necrotic cores found in "vulnerable" plaques.

In addition to atherosclerotic plaque composition, measures of arterial wall remodeling are quantifiable by CCTA. Similar to studies with intravascular ultrasound and histopathology, in which vulnerable plaques exhibit high rates of positive arterial remodeling, in an extreme compensatory response to CAD, the external elastic membrane area at the site of a coronary plaque is greater than that at an adjacent reference site (**see Chapter 44**). This ratio, when greater than 1.10, is generally considered positive remodeling. An additional atherosclerotic plaque feature on CCTA examined for its prognostic value is "spotty calcifications," defined as distinct calcifications 3 mm or less in length and circumscribing a 90-degree or less arc in cross section. This term, taken from the histopathology literature, is considered as the *microcalcifications* often present in a ruptured coronary artery. However, current-generation CT scanners do not have the spatial resolution to image these atherosclerotic characteristics, and thus the spotty calcifications on CT are actually *macrocalcifications*, and extrapolation of their findings to pathology-confirmed microcalcifications should be done with caution.

In the initial large-scale study evaluating the prognostic utility of atherosclerotic plaque characteristics, low-attenuation plaques with HU less than 30 and positive arterial remodeling were assessed for their ability to risk-stratify 1059 stable patients who underwent CCTA and were followed for acute coronary syndrome (ACS) occurrence to 27-month follow-up[75] (**Fig. 18.10**). Atherosclerotic plaques were categorized as having no high-risk features, one-feature positive, or two-feature positive plaques. Compared to patients with no high-risk features, significantly higher rates of ACS occurred in patients with one- and two-feature positive plaques (0.49% versus 3.7% versus 22.2%, respectively; $P < 0.001$). In a follow-up study of 3158 patients, CCTA-defined high-risk plaque was an independent predictor of future ACS incremental to high-grade stenosis.[76] In this study, for the 449 patients who underwent serial CCTA imaging, atherosclerotic plaque progression was also strongly associated with future ACS. These findings supporting the additive value of atherosclerotic plaque burden and plaque composition are also seen in patients presenting with non–ST-segment elevation MI (NSTEMI). In an evaluation of 312 patients presenting with NSTEMI or stable angina, lesions responsible for events demonstrated lower attenuation patterns by CCTA in those with NSTEMI.

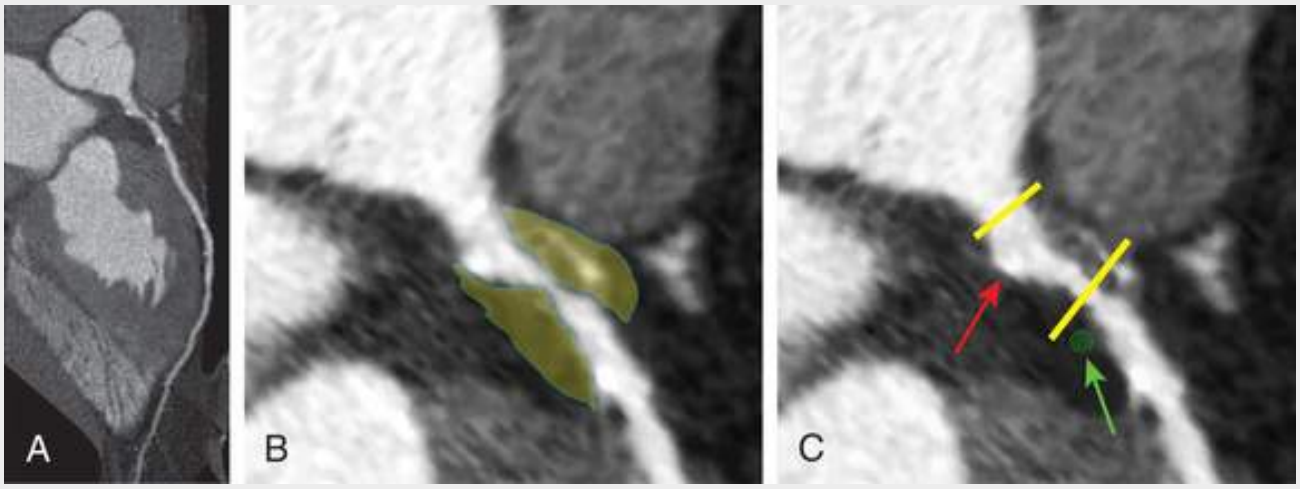

FIGURE 18.10 Atherosclerotic plaque that exhibits adverse plaque characteristics. **A,** Curved multiplanar reformat view demonstrates high-grade plaque in proximal portion of left anterior descending (LAD) artery, with smaller plaques in midportion of LAD. **B,** Close-up view reveals a stenosis with high atherosclerotic plaque burden. **C,** Three adverse plaque characteristics, including positive arterial remodeling *(yellow lines),* spotty calcifications *(red arrow),* and low attenuation plaque <30 Hounsfield units *(green arrow and circle)*. In this case the *remodeling index,* or the ratio between the external elastic membrane at the site of the greatest diameter within the stenosis to the external elastic membrane at the proximal reference vessel, is 1.14. A ratio >1.10 is considered positive arterial remodeling.

One potentially important clinical question arising from a normal CCTA without evidence of stenosis or atherosclerosis is its relatively benign nature. Prior studies have observed a very low risk of future mortality or MACE in individuals with normal CCTA. Annualized event rates have been reported at 0.01% to 0.24%.[77] These data emphasize the importance of the negative predictive value of CCTA not only to exclude the presence of CAD, but also to effectively rule out the risk of future events. At present, a normal CCTA appears to confer at least a 5-year warranty period. Given these propitious findings, prior studies have evaluated whether CCTA as a screening test offers incremental prognostic role over CAC in asymptomatic individuals. In a study of 7590 patients without chest pain syndrome who were followed for 24 months, CCTA added no prognostic value for future death or MACE (C-statistic, 0.75 versus 0.77), with no significant net reclassification of patients to higher or lower risk groups.[54] As such, routine performance of CCTA in asymptomatic individuals appears to have no tangible clinical benefit and, as per contemporary ACC multimodality imaging appropriate use criteria, should be avoided.[39]

In addition to native coronary artery findings, CCTA has also been evaluated for other cardiovascular findings that may offer incremental prognostic utility and that can be visualized on CCTA. Factors proven useful in this regard include determination of left ventricular systolic function and wall motion abnormalities, epicardial and pericardial adipose tissue, aortic calcifications, and nonalcoholic steatohepatitis.[62,78] Further, coronary findings include measures of plaque for prediction of no flow at the time of percutaneous intervention,[79] as well as future adverse event rates following CABG surgery.[80]

Relationship of Findings to Ischemia

A common question is to what degree CCTA findings coincide with coronary or myocardial ischemia. Traditional image-based decisions about coronary revascularization have relied heavily on “physiologic” measures of ischemia and blood flow, with prior studies suggesting that anatomic-based revascularization strategies do not affect event-free survival. CCTA has been compared to a host of physiologic stress tests, including SPECT, PET, and fractional flow reserve (FFR) for the correlation of anatomic stenoses to myocardial perfusion deficits (**see Chapters 16, 57, 61, and 62**). These studies have been generally small in sample size, 42 to 110 patients.[81-83] In the largest study comparing CCTA findings to rubidium-82

PET, CCTA was associated with myocardial perfusion defects, but only to a moderate degree. With worsening coronary stenosis on CCTA, as defined by less than 50%, 50% to 70%, and more than 70% stenosis, the positive predictive value (PPV) was only 29%, 44%, and 77%, respectively, at the per-patient level (**Fig. 18.11**). Conversely, the negative predictive value (NPV) to exclude myocardial ischemia was remarkably high, at 92%, 91%, and 88%, respectively. Similarly, using FFR in 79 patients with stable symptomatic CAD, CCTA showing 50% or more stenosis identified less than half of lesions that demonstrated coronary pressure differences.[84] The findings are generally consistent across studies and have raised the concern that CCTA findings will provoke higher rates of ICA and ad hoc coronary revascularization.

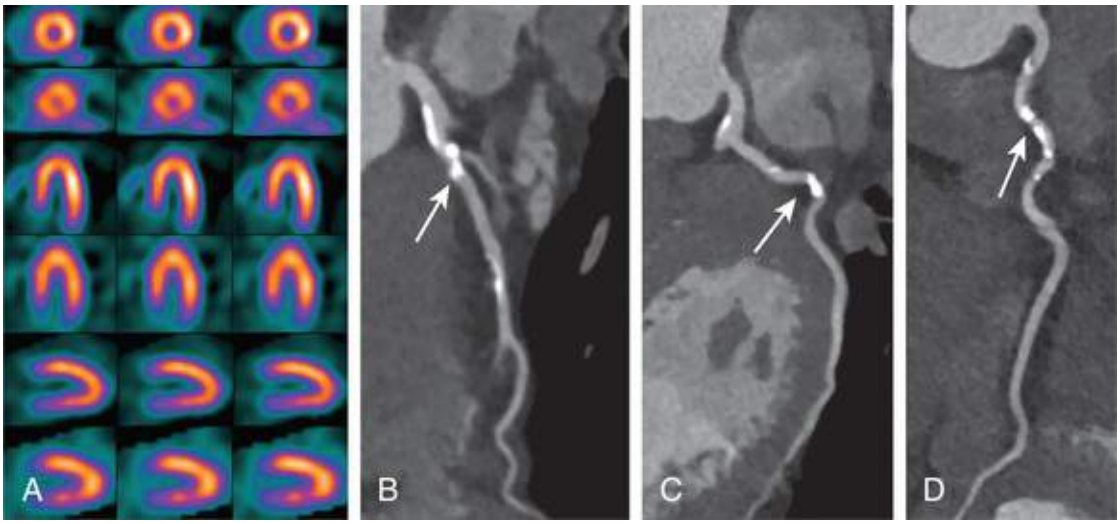

FIGURE 18.11 Example of discordance between physiologic and anatomic testing. **A,** Stress-rest single-photon emission computed tomography (SPECT) study of 66-year-old diabetic man with atypical chest pain shows no myocardial perfusion defect. During the stress test, patient exercised for 8 minutes and 30 seconds on Bruce treadmill protocol. CCTA demonstrates severe calcified plaque that precludes visualization of **B,** left anterior descending artery; **C,** left circumflex artery; and **D,** right coronary artery (*arrows*).

To offset the potential for increased rates of ICA, some have advocated for a hybrid approach in which CCTA is combined with SPECT, PET, or CT perfusion testing for improvements in identification of hemodynamically significant coronary artery stenoses.[85] One such method is the acquisition of CAC during SPECT or PET using information derived from the CT attenuation correction scans (**see Chapter 16**). This has proved useful in improving the sensitivity of SPECT (76% versus 86%) for identification of coronary stenoses, but had minimal effect on specificity (91% versus 86%).[86] Another hybrid method is simply to combine CCTA with SPECT.[82] This method has proved generally superior to the CAC approach whereby a hybrid approach was superior to SPECT for measures of specificity (53% versus 75%), with no decrement in sensitivity (95% versus 95%). Concerns remain for the routine use of the hybrid imaging approach that these procedures may increase radiation exposure to patients as well as potentially result in increased diagnostic workup costs.

Beyond simply luminal diameter stenosis, CCTA has also been evaluated for other measures of CAD to identify hemodynamically-significant CAD. In the Functional Imaging Criteria for Guiding Review of Invasive Coronary Angiography, Intravascular Ultrasound, and Coronary Computed Tomographic Angiography (FIGURE-OUT) study of 181 lesions of intermediate stenosis severity, minimum luminal area appeared to be superior to percent-diameter stenosis for identifying FFR-verified coronary ischemia (area under ROC curve, 0.712 versus 0.657).[87] Further, a recent prospective multicenter study of 252

patients from 17 centers evaluated the role of atherosclerotic plaque characteristics (APCs), including positive arterial remodeling (PR), low-attenuation plaque (LAP), and spotty calcifications (SC), for identification of ischemia-causing coronary artery lesions[88] (**Fig. 18.12**). A dose-response relationship was noted for increasing numbers of APCs and ischemia, with two or more APCs associated with a 12-fold increase in the rate of ischemia. This improvement for identification of ischemia existed only for PR (odds ratio [OR] 5.3) and LAP (OR 2.1), with no improvement noted for SC. Importantly, arteries exhibiting PR were useful for diagnosis of lesion-specific ischemia for stenoses of 50% or greater as well as 50% or less, the latter being present in almost 17% of ischemic lesions. One additional APC available by CCTA imaging is the percent aggregate plaque volume (%APV), which is the sum of the entire plaque volume within a vessel divided by the sum of the vessel volume from the artery ostium to the distal end of the coronary lesion. In a study of 58 lesions, %APV demonstrated high discriminatory capacity to identify vessel ischemia beyond traditional diameter stenosis alone (0.85 versus 0.68), with %APV enabling significant net reclassification over stenosis alone (net reclassification index [NRI] 0.77)[89] (**Fig. 18.13**).

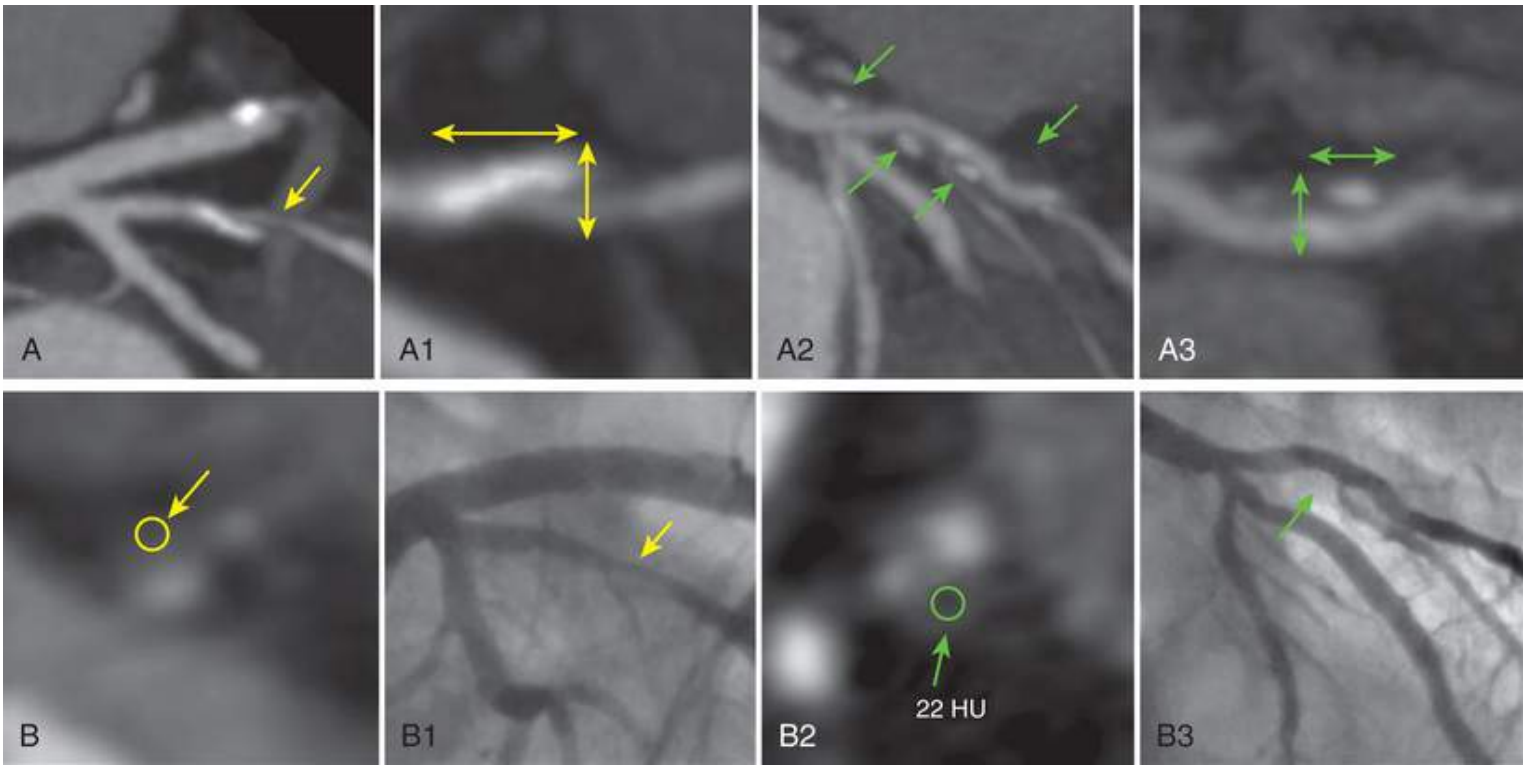

FIGURE 18.12 Relationship of atherosclerotic plaque characteristics (APCs) and coronary ischemia in two patients **(A, B)** undergoing CCTA, invasive coronary angiography (ICA), and atherosclerotic plaque evaluation. Patient **A** has high-grade stenosis from a single calcified plaque **(A1),** with no positive arterial remodeling **(A2)** and no low-attenuation plaque (Hounsfield unit [HU] density >30) **(A3).** Despite the severity of the stenosis confirmed by ICA, fractional flow reserve (FFR) demonstrates no ischemia with a value >0.80. In contrast, patient **B** demonstrates no significant stenosis but numerous atherosclerotic plaques with spotty calcifications **(B1)** that display positive arterial remodeling **(B2),** and low attenuation (HU <30) **(B3).** ICA confirms the absence of high-grade coronary stenoses. Despite this, coronary ischemia is present by an invasive FFR value of 0.76. (Modified from Park HB, Heo R, O'Hartaigh B et al. Atherosclerotic plaque characteristics by CT angiography identify coronary lesions that cause ischemia: a direct comparison to fractional flow reserve. JACC Cardiovasc Imaging 2015;8:1-10.)

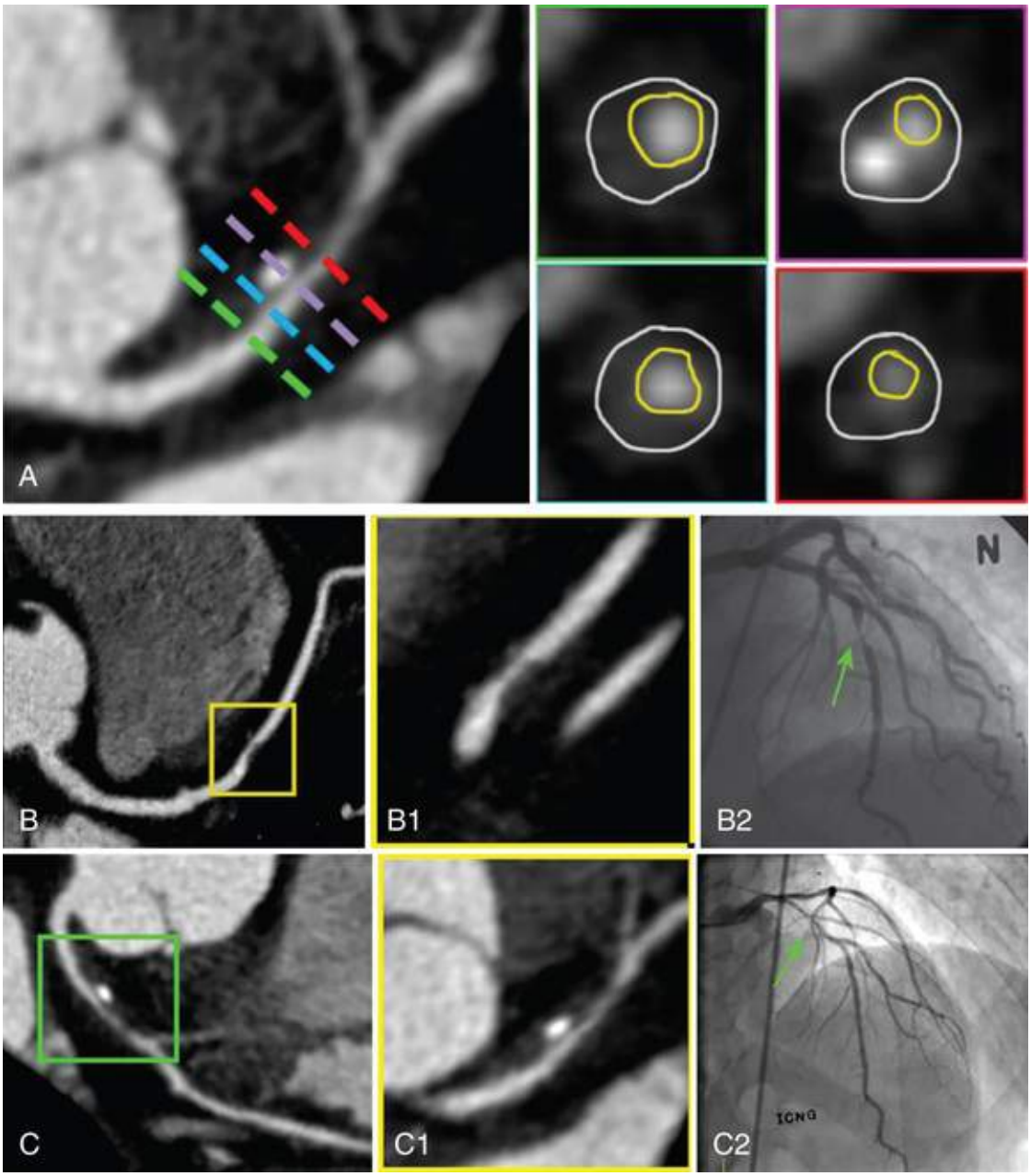

FIGURE 18.13 Relationship of aggregate plaque volume and coronary artery ischemia. **A,** Aggregate plaque volume percent (%APV) can be calculated by the ratio of the plaque area over the vessel area to the length of a coronary vessel; 1-mm cross-sectional areas are traced for vessel, lumen, and plaque areas. **B,** High-grade stenoses (*yellow box*) that are associated with low %APV **(B1)** are less likely to cause ischemia **(B2). C,** In contrast, stenoses (*green box*) that are associated with high %APV **(C1)** are more likely to produce ischemia **(C2)**. (Modified from Nakazato R, Shalev A, Doh JH, et al. Aggregate plaque volume by coronary computed tomography angiography is superior and incremental to luminal narrowing for diagnosis of ischemic lesions of intermediate stenosis severity. J Am Coll Cardiol 2013;62:460-7.)

Use in Patients with Acute Chest Pain

Each year, in the United States alone, almost 8 million patients present to the emergency department (ED) with complaints consistent with possible ACS, representing the second most common cause of ED visit.[90] This accounts for up to $15 billion of health care costs, although less than 1% of these patients are ultimately diagnosed with ACS. Workup patterns used at different medical centers include observational "chest pain" units, in-patient admission to exclude ACS by troponin markers, stress tests to diagnose hemodynamically significant CAD, and, most recently, CCTA to identify or exclude high-grade coronary stenoses.

A recent meta-analysis examined the relative diagnostic performance of CCTA versus other diagnostic

methods, including stress echocardiography and SPECT, when using ICA or ACS as a reference standard. In this analysis, CCTA demonstrated favorable diagnostic performance that was superior to stress echocardiography and SPECT (CT sensitivity/specificity, 95%/99%; stress echocardiography, 84%/94%; SPECT, 85%/86%).[91] Based on these favorable diagnostic findings, several observational cohort studies —both from research initiatives as well as site-specific clinical care—have attempted to determine the natural clinical outcomes of patients with low to intermediate acute chest pain (as defined primarily by the Thrombolysis in Myocardial Ischemia [TIMI] risk score) who present with suspected ACS.[90] In the largest observational study to date, the Rule-Out Myocardial Infarction Using Computed Assisted Tomography (ROMICAT), 368 patients with negative initial myocardial necrosis biomarkers and a nondynamic ECG underwent CCTA for diagnosis and exclusion of ACS.[92] In this population of individuals undergoing evaluation, 31 patients (8.4%) were diagnosed with ACS. CCTA identified approximately half these individuals as having no stenosis or atherosclerosis and 20% who had high-grade coronary stenosis. On discharge, none of those individuals without stenosis or atherosclerosis experienced ACS. Similarly, patients with nonobstructive CAD enjoyed a 98% NPV for ACS. In contrast, the PPV of CCTA for those with CCTA-identified obstructive coronary stenosis was only 35%, suggesting an overdiagnosis phenomenon in which CCTA may identify stenoses that are ultimately not the cause of the acute chest pain syndrome. In a low-risk population of 600 patients presenting with acute chest pain, more than four of five patients could be effectively discharged with a 30-day ACS rate of 0%.

Both these studies have raised concerns that the rates of ACS are low, and it remains unstudied whether less costly methods can be substituted for CCTA to achieve similar clinical outcomes. To assess this, several prospective randomized trials sought to determine the differential clinical and economic outcomes of a CCTA-based ACS evaluation versus the standard of care (**Table 18.4**). These trials differed in their inclusion criteria as well as mode of evaluation in the standard-of-care arms. In the ROMICAT II and CT Coronary Angiography Compared to Exercise ECG (CT-COMPARE) studies, low- to intermediate-risk patients were enrolled, whereas the American College of Radiology Imaging Network (ACRIN-PA) and Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment (CT-STAT) studies enrolled low-risk patients.[93-96] Uniform to these trials was a high NPV for ACS that was safe (i.e., with few reported adverse cardiovascular outcomes in a follow-up of 30 days to 6 months). Other important clinical, workflow, and resource utilization parameters were evaluated, including time to diagnosis, length of stay, rates of ED discharge, total and ED costs, and rates of downstream ICA. In both ACRIN-PA and ROMICAT II trials, a CCTA-based strategy resulted in immediate discharge of approximately half of patients, which was approximately two to four times the rate of standard-of-care practice. Among these large-scale trials, only ROMICAT II observed no ED cost-savings, whereas the other studies observed a 15% to 38% reduction. These cost-savings were in part the result of shorter lengths of stay but were offset by higher rates of ICA and coronary revascularization. Consistently, the latter is observed and evokes unease about the potential for CCTA findings to provoke unnecessary procedures in these low-risk or low- to intermediate-risk individuals.

TABLE 18.4

Primary and Secondary Diagnostic Findings of CT-STAT, ROMICAT-II, ACRIN/PA, and PROSPECT Trials

STUDY	CT-STAT[96] (2011)		ROMICAT-II[95] (2012)		ACRIN/PA[94] (2012)		PROSPECT[100] (2015)	
Design	Multicenter randomized		Multicenter randomized		Multicenter randomized		Single-center randomized	
No. of patients	699		1000		1370		400	
Patient presentation	Troponin (−), normal ECG		Troponin (−), normal ECG		Troponin (−), normal ECG		Troponin (−), normal ECG	
Controls	MPI		Standard evaluation		Standard evaluation		MPI	
Index Visit								
	CCTA	**Control**	**CCTA**	**Control**	**CCTA**	**Control**	**CCTA**	**Control**
Length of stay (hr) Median (IQR)	—	—	8.6 (6.4-27.6)	26.7 (21.4-30.4)	18 (7.6-27.2)	24.8 (19.2-30.5)	28.9 (11.0-48.4)	30.4 (23.9-51.3)
Time to diagnosis (hr) Median (IQR)	2.9 (2.1-4.0)	6.2 (4.2-19.0)	5.8 (4.0-9.0)	21.0 (8.5-23.8)	—	—	—	—
Direct ED discharge (%)	—	—	47	12	50	23	—	—
Total ED costs (USD) Median (IQR)	2137 (1660-3077)	3458 (2900-4297)	1937 (1504-4057)	2742 (1755-3832)	—	—	—	—
Radiation dose (mSv)	11.5* (6.8-16.8)	12.8* (11.6-13.9)	14.3 ±10.9**	5.3 ±9.6**	—	—	9.6* (6.2-23.0)	27* (19.0-27.0)
Index Visit + Follow-up								
Follow up duration	**6 Months**		**28 Days**		**30 Days**		**1 Year**	
ACS diagnosis (%)	1	3	9	6	1	1	—	—
ICA (%)	8	7	12	8	5	4	15	16
Revascularization (%)	4	3	6	4	3	1	8	6
MACE (%)	0.8	0.4	0.4	1	1	1	5	8

*Median value reported.

**Mean value reported.

ECG, Electrocardiogram; *MPI,* stress myocardial perfusion imaging; *CCTA,* coronary computed tomographic angiography; *IQR,* interquartile range; *ED,* emergency department; *USD,* United States Dollars; *ACS,* acute coronary syndrome; *ICA,* invasive coronary angiography; *MACE,* major adverse cardiac events.

MACE definitions:

CT-STAT: ACS, cardiac death or revascularization 6 months in patients who had normal or near-normal index testing.

ROMICAT-II: death, myocardial infarction, unstable angina, or urgent coronary revascularization within 28 days.

ACRIN/PA: cardiac death or myocardial infarction within 30 days.

PROSPECT: all-cause death, myocardial infarction, cardiac arrest and cerebrovascular accident.

The Cardiac CT in the Treatment of Acute Chest Pain (CATCH) trial aimed to determine the prognostic utility of CCTA compared to the standard of care in 299 patients presenting with acute chest pain and normal ECG and blood biomarkers.[97] For a primary composite MACE endpoint, there was a 19-month reduction in the CCTA group versus the standard-of-care group (HR 0.62; $P = 0.04$), with no modest differences when events were limited only to those experiencing cardiac death of nonfatal MI ($P = 0.06$). These results are consistent with a recent meta-analysis of four randomized trials and three case-control studies totaling more than 3300 patients. CCTA-based care resulted in a 74% reduction in downstream events and a 42% reduction in repeat ED visits.[98]

The most contemporary RCT, the Better Evaluation of Acute Chest Pain with Computed Tomography Angiography (BEACON), evaluated the use of a CCTA-based strategy versus the standard of care at seven sites where high-sensitivity troponins were used for early diagnosis of ACS.[99] The 500 patients were evaluated for a primary endpoint of coronary revascularization within 30 days following the index ED visits, for which there was no difference between strategies. Although a CCTA-based strategy did not increase ED discharge rates or change lengths of stay, CCTA patients did incur lower medical costs and less outpatient testing after ED discharge.

CCTA versus MPI stress testing was evaluated in the Study Comparing CT Scan and Stress Test in Diagnosing Coronary Artery Disease in Patients Hospitalized for Chest Pain (PROSPECT) trial.[100] The

400 patients represented an ethnically diverse population of more than 50% Hispanic and 37% African American patients of low socioeconomic status and were stratified to either CCTA or MPI testing at the index ED visit. The primary outcome—the rate of ICA without revascularization within 1 year—was no different between testing groups. At a median average follow-up of 40 months, no differences were observed for MACE in this underpowered study, although radiation exposure was lower for patients undergoing CCTA over MPI, and CCTA was regarded with higher patient satisfaction.

Some have advocated for a "triple rule out" (TRO) in which a long *z*-axis scan length is used to acquire images of the entire chest cavity to exclude the presence of CAD, pulmonary embolism, and aortic dissection (**see Chapters 63 and 84**). In a study of 12,834 patients from the Advanced Cardiovascular Imaging Consortium, patients undergoing TRO CT were compared to those undergoing CCTA alone.[101] The rates of diagnosis of significant disease pathology were similar for both TRO and CCTA (17.4% and 18.3%), with pulmonary embolism and aortic dissection more often observed in the TRO group (1.1% versus 0.4% and 1.7% versus 1.1%). However, nondiagnostic CT images were observed at a significantly higher rate with TRO than CCTA (9.4% versus 6.5%), which somewhat negates the uniform performance of TRO in patients with acute chest symptoms.

Use in Patients with Stable Suspected Coronary Artery Disease

At present, almost 10 million CAD imaging tests are performed each year in the United States, which annually represents 25% of the total number of individuals diagnosed with CVD.[102] The vast majority of these tests are stress tests with imaging, typically by SPECT MPI. Given the relatively recent introduction of CCTA, there is an intense interest to determine whether anatomic imaging by CCTA versus physiologic imaging by stress MPI offers any relative advantage in the care of stable patients with CAD. To this end, numerous large-scale observational cohort registries and randomized trials have been performed to determine the efficacy of each of these modes of workup (**Table 18.5**).

TABLE 18.5

Primary and Secondary Diagnostic Outcome Findings from PROMISE and SCOT-HEART Trials

	PROMISE103 (2015)				SCOT-HEART[107] (2015)			
Study design	Prospective multicenter				Prospective multicenter			
Population	Symptomatic patients without diagnosed CAD				Recent-onset chest pain, suspected CAD			
Patients (*n*)	10,003				4146			
Disease prevalence (%, >50% stenosis)	11				42			
Modalities (Population, *n*)	CCTA (4996)	Functional testing* (5007)	HR† (95% CI)	*P* value	Standard care plus CCTA (2073)	Standard care (2073)	HR‡ (95% CI)	*P* value
Primary composite endpoint	164	151	1.04 (0.83-1.29)	0.75	—	—	—	—
Death from any cause	74	75	—	—	17	20	0.86 (0.45-1.64)	0.65
Nonfatal MI	30	40	—	—	22	35	0.63 (0.37-1.07)	0.09
Hospitalization for unstable angina	61	41	—	—	76	69	1.12 (0.81-1.55)	0.51
Major procedural complication	4	5	—	—	—	—	—	—
Primary endpoint plus catheterization showing no obstructive CAD	332	353	0.91 (0.78-1.06)	0.22	—	—	—	—
Death or nonfatal MI	104	112	0.88 (0.67-1.15)	0.35	—	—	—	—
Death, nonfatal MI, or hospitalization for unstable angina	162	148	1.04 (0.84-1.31)	0.70	—	—	—	—
CAD death**	—	—	—	—	4	7	0.57 (0.17-1.97)	0.38
CAD death** and MI	—	—	—	—	26	42	0.62 (0.38-1.01)	0.05
CAD death,** MI, and stroke	—	—	—	—	31	48	0.64 (0.41-1.01)	0.06
Nonfatal stroke	—	—	—	—	5	7	0.73 (0.23-2.32)	0.59
Noncardiovascular death	—	—	—	—	13	13	1.01 (0.47-2.17)	0.99
Invasive catheterization showing no obstructive CAD	170	213	—	0.02	—	—	—	—
Coronary revascularization	—	—	—	—	233	201	1.20 (0.99-1.45)	0.06
PCI	—	—	—	—	184	160	1.19 (0.96-1.47)	0.11
CABG	—	—	—	—	54	45	1.22 (0.82-1.81)	0.33
Hospitalization for noncardiac chest pain	—	—	—	—	183	208	0.86 (0.71-1.05)	0.15

*Functional testing included exercise electrocardiogram, nuclear stress testing, or stress echocardiography.

†Hazard ratios were adjusted for age, sex, CAD risk equivalent (i.e., history of diabetes, peripheral arterial disease, or cerebrovascular disease), and the prespecification of the intended functional test if patients were randomly assigned to the functional-testing group.

‡Hazard ratios were adjusted for study center and minimization variables, excluding baseline diagnosis.

**CAD death was defined as death due to myocardial infarction in all cases.

PROMISE, Prospective Multicenter Imaging Study for Evaluation of Chest Pain; SCOT-HEART, Scottish Computed Tomography of the HEART; *CAD,* coronary artery disease; *CCTA,* coronary computed tomography angiography; *HR,* hazard ratios; *CI,* confidence interval; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention; *CABG,* coronary artery bypass graft surgery.

In the large-scale Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) randomized trial, 10,003 patients underwent either CCTA or “functional” testing, which included not only SPECT MPI but also stress echocardiography and stress ECG testing without imaging.[103] At a median-follow-up of 25 months, the primary endpoint—defined as all-cause mortality, nonfatal MI, unstable angina hospitalization, or procedural complication—was no different for the CCTA group than for the functional testing group (HR 1.04). Median average radiation exposure was lower for CCTA patients than those in the functional assessment arm (10.0 versus 11.3 mSv). CCTA was associated with a higher rate of

ICA within the 90 days following the index test (12.2% versus 8.1%), although those undergoing ICA in the CCTA arm were observed to have a higher rate of high-grade coronary stenosis. Despite higher rates of ICA, 3-year costs for CCTA were similar to functional testing, with $254 higher costs for CCTA at 90 days and similar costs at 1 and 3 years of follow-up.[104] Similarly, quality-of-life measures, as determined by the Duke Activity Status Index and Seattle Angina Questionnaire, were consistently similar during the entire follow-up period.[105] These nonsignificant differences in quality-of-life and clinical outcomes occurred despite significantly higher rates of prescribed primary prevention medical therapies for patients undergoing CCTA over functional testing for aspirin (11.8% versus 7.8%) and statins (12.7% versus 6.2%).[106] Compared with patients undergoing functional testing, CCTA patients were more likely to adopt a heart-healthy diet and achieve weight loss. Prognostically, compared with functional testing, CCTA was associated with greater predictive abilities for future adverse clinical outcomes when an abnormal test was reported (HR 5.86 versus 2.27).

In contrast to the clinical outcomes-based endpoint of the PROMISE trial, the Scottish Computed Tomography of the Heart (SCOT-HEART) trial examined an endpoint of diagnostic certainty of angina caused by CAD at a 6-week endpoint.[107] "Diagnostic certainty" was defined by the caring physician and categorized by presence versus absence, as well as unlikely versus probable angina. Importantly, this study was not a direct comparison of anatomic versus functional testing, but rather a test of standard of care (SOC) plus CCTA versus SOC alone, which included clinical evaluation plus symptom-limited exercise testing if considered clinically necessary. For the primary endpoint, there was a significant increase in the diagnostic certainty (relative risk [RR] 3.76) among imaging physicians, associated with a lower frequency of angina diagnosis (RR 0.78). A similar pattern emerged for the attending clinician, whose certainty rose by 1.75-fold with negligible effects on frequency of diagnosis. Increases in diagnostic certainty resulted in significant changes in downstream planned diagnostic evaluations in the SOC plus CCTA group versus SOC alone (15% versus 1%). Contrary to the PROMISE trial, average median radiation doses of CCTA were significantly lower (4.1 mSv).

In the 6-week follow-up of patients in the SCOT-HEART study, marginal differences were observed for near-term death or MI (1.3% versus 2.0%; $P = 0.053$). At 20 months' follow-up, however, when prognostic evaluations began at initiation of preventive therapy, those undergoing CCTA experienced a 50% reduction in fatal and nonfatal MI compared to SOC alone.[108] These findings were associated with similar rates of ICA between CCTA and SOC groups, but higher rates of confirmation of obstructive CAD in CCTA patients as well as higher rates of preventive medical therapies (HR 4.03).

The precise reasons for the improvement in clinical outcomes after CCTA have yet to be proved in an RCT. Large-scale observational evidence suggests the clinical outcomes benefit following CCTA may result from efficacy of primary preventive medical therapies. In 10,418 patients from the CONFIRM registry followed for 27 months with no or nonobstructive CAD, defined by a maximal per-patient coronary stenoses between 1% and 50%, those with evident mild coronary stenoses experienced a 56% reduction in mortality.[68] Independent of NCEP/ATP III guidelines, statins conferred a clinical benefit only for patients with evident CAD on CCTA. A subsequent study from CONFIRM evaluated the effects of primary versus secondary medical therapy on outcomes in patients with obstructive CAD of 50% or greater stenosis on CCTA. In this cohort, statins were similarly associated with a 43% reduction in the risk of MACE, with no decrement in this risk for patients prescribed aspirin, beta blockers, and ACE inhibitors. A further analysis of 15,223 stable patients without known CAD followed for 2.1 years revealed significant clinical outcomes differences for patients undergoing medical therapy versus medical therapy plus coronary revascularization based on extent and severity of CAD on CCTA.[59] CAD was categorized as high risk versus non–high risk based on the Duke CAD index, a metric that integrates the

degree of stenosis severities with the location of the stenoses. Patients with high-risk CAD undergoing medical therapy alone fared worse than patients who underwent revascularization (5.34% versus 2.28% mortality), whereas patients with non–high risk CAD or no CAD experienced higher rates of death if they were treated with coronary revascularization over medical therapy alone (2.06% versus 0.97%). These findings were corroborated in a follow-up study of 15,207 intermediate-likelihood patients at 2.3 years. Revascularization for patients with obstructive CAD resulted in a reduced mortality risk (HR 0.61) and, conversely, a more than twofold increase in mortality risk for patients without obstructive CAD.[109]

Given the potential increase in health care costs associated with CCTA, the recent Comprehensive Cardiac CT versus Exercise Testing in Suspected Coronary Artery Disease (CRESCENT) RCT examined the safety and efficacy of a tiered CT approach where the less costly CAC scan was performed as the initial test, followed by CCTA only if the CAC score was between 1 and 400.[110] These patients were randomized against a functional testing arm and followed for 1 year for clinical adverse events, angina symptoms, time to diagnosis, downstream testing rates, and health care costs. Compared with functional testing, patients undergoing CCTA experienced a higher rate of CAD event-free survival (96.7% versus 89.8%) with fewer angina symptoms. Time to diagnosis was more rapid with a CCTA approach compared with functional testing, a strategy associated with more than 50% lower rates of downstream testing and approximately 20% lower health care costs.

Physiologic Evaluation of Coronary Artery Disease

The sine qua non of CAD diagnostic imaging is the concomitant diagnosis of anatomic and physiologically significant CAD from a single test for identification and exclusion of actionable CAD that may benefit from revascularization. By invasive standards, FFR at the time of ICA has emerged as such an approach by pinpointing coronary stenoses that cause ischemia in a lesion-specific fashion (**see Chapters 57, 61, and 62**). Fractional flow reserve, defined as the ratio of pressure distal to a coronary stenosis to the pressure proximal to the coronary stenosis at maximum flow conditions, is considered both a diagnostic and a prognostic "gold standard."[111] To date, FFR represents the only method of ischemia evaluation that results in improved event-free survival over angiographic stenosis-guided revascularization or medical therapy alone.

FFR derived from CCTA (FFR_{CT}) is a method for deriving three-vessel FFR values using typically acquired CCTA (**Fig. 18.14**). In this regard, FFR_{CT} requires no additional testing or radiation and no medications, but can be performed on any acquired CCTA. As with invasive FFR, FFR_{CT} enables precise localization of ischemia-causing coronary stenoses. The concept of lesion-specific ischemia is new for the field of noninvasive imaging, which has previously relied on myocardial perfusion evaluation as an indirect measure of flow-limiting CAD. These stress testing methods have significant limitations for guiding decisions of referral to ICA and/or revascularization, given the almost two thirds of ICAs that reveal nonobstructive CAD at angiography.[112]

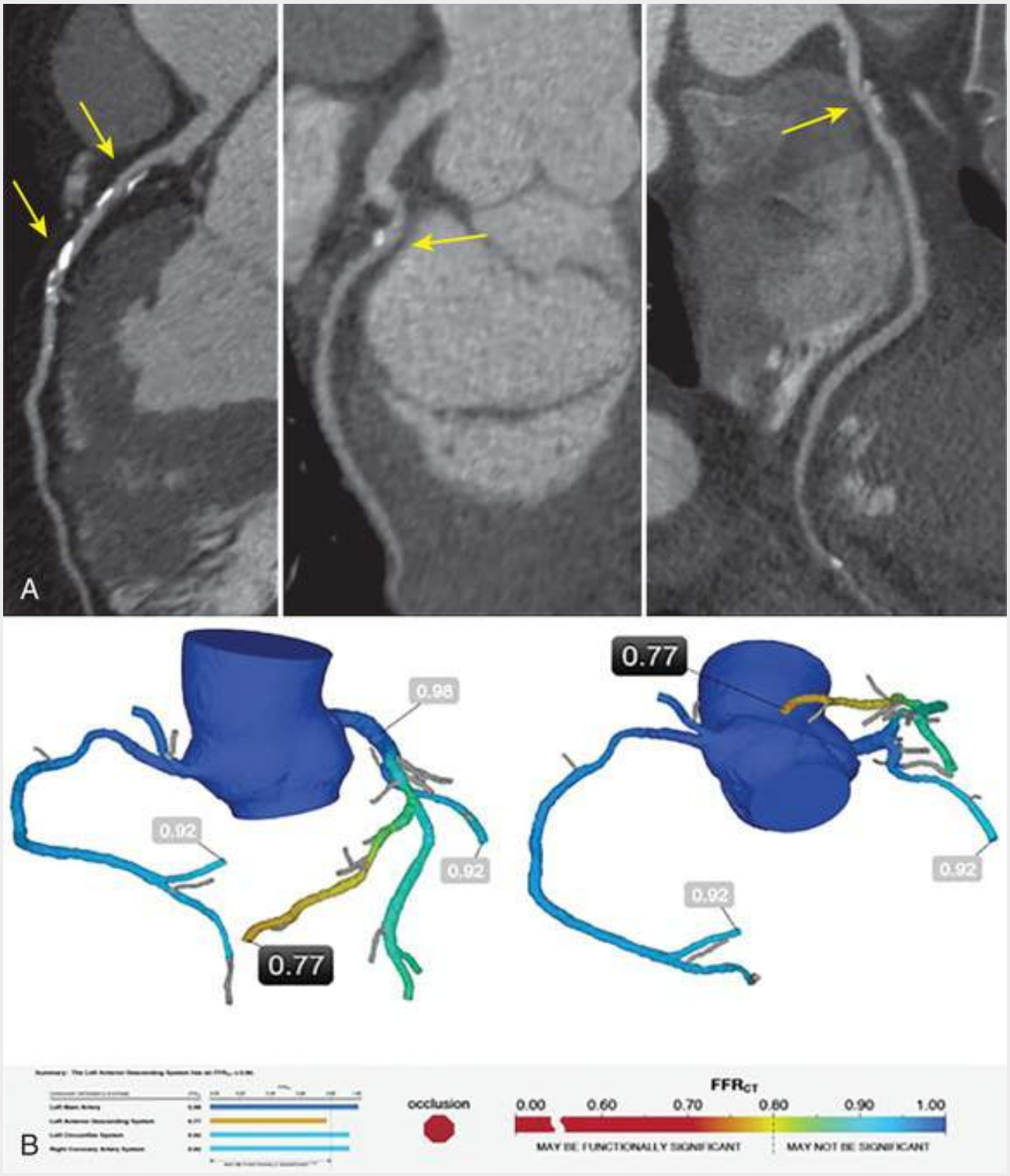

FIGURE 18.14 Fractional flow reserve derived from CCTA (FFR_{CT}). **A,** CCTA demonstrates moderate stenosis in proximal portion of left anterior descending artery (LAD). Midportion of LAD cannot be adequately visualized due to severe calcified plaque. Mild nonstenotic plaque is noted in left circumflex artery and moderate stenosis in midportion of right coronary artery. **B,** FFR_{CT} demonstrates significant ischemia in LAD (FFR_{CT} 0.77) that spares the diagonal branch (FFR_{CT} 0.92). Note that FFR_{CT} allows for interrogation of ischemia at all points in the coronary artery tree.

The advent of FFR_{CT} was coincident with the introduction of 64–detector row CCTA, because of the need for high-fidelity patient-specific coronary arterial geometry in its calculation.[113] At its core, FFR_{CT} calculations are based on the application of computational fluid dynamics (CFD) to CCTA to calculate coronary fluid pressure, velocity, and flow. Ubiquitous in nearly every field of engineering (e.g., automotive, aerospace), CFD principles rely on the laws of mass conservation and momentum balance. In the steps to calculate FFR_{CT}, coronary arteries and left ventricular myocardium are segmented with

subvoxel resolution. Based on form-function relationships, rest coronary flow for each artery is calculated as a function of the myocardial mass it subtends. To ensure correct FFR_{CT} values, allometric scaling laws are employed to calculate distal intramyocardial microcirculatory resistance. Hyperemia is then modeled using a response of coronary arteries to adenosine, the agent used in invasive FFR, and for which maximal reductions in coronary resistance occur at a predictable threshold. The final step in the calculation of FFR_{CT} is the distribution of several million tetrahedral meshes through each artery and its branch, then solving the fluid dynamic equations to obtain FFR values at every point in the coronary vascular bed.

The diagnostic performance of FFR_{CT} has been evaluated in three prospective multicenter trials: Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve (DISCOVER-FLOW), Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO), and Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT)[114-116] (**Table 18.6**). Each trial represented an improved generation over the last, with the NXT trial most recently reported. In this study of 254 patients referred for clinically indicated ICA, CCTA and FFR_{CT} were performed, with 484 vessels directly interrogated by invasive FFR. The primary endpoint of this study was the area under ROC curve for FFR_{CT}, 0.90 and 0.93 on a per-patient and per-vessel basis, respectively, which corresponded to an overall per-vessel diagnostic accuracy of 86%. These performance characteristics compared favorably to anatomic evaluation alone by ICA or CCTA, which revealed modest accuracies for diagnosis of invasive FFR-determined ischemia (77% versus 53%). A recent meta-analysis of diagnostic imaging modalities evaluated the comparative diagnostic performance of FFR_{CT} to SPECT, SE, CMR, and ICA. For invasive FFR-verified ischemia, highest sensitivities of testing modalities were observed for CCTA (90%), CMR (90%), and FFR_{CT} (90%), with more moderate specificities observed for FFR_{CT} (71%).

TABLE 18.6

Diagnostic Accuracy of Ffr_{ct} Versus Invasive FFR

ASSESSMENT	DISCOVER-FLOW[114] (2011)	DEFACTO[115] (2012)	NXT[116] (2014)	Renker[156] (2014)	Coenen[157] (2015)	De Geer[158] (2015)
Per Patient	*n* = 103	*n* = 252	*n* = 254	*n* = 53	—	*n* = 21
Sensitivity (%)	93	90	86	94	—	83
Specificity (%)	82	54	79	84	—	80
PPV (%)	85	67	65	71	—	63
NPV (%)	91	84	93	97	—	93
Accuracy (%)	87	73	81	—	—	81
AUC	0.92	0.81	0.90	0.91	—	—
Per Vessel	*n* = 159	*n* = 407	*n* = 484	*n* = 67	*n* = 189	*n* = 23
Sensitivity (%)	88	83	84	85	88	83
Specificity (%)	82	78	86	85	65	76
PPV (%)	74	—	61	71	65	56
NPV (%)	92	—	95	93	88	93
Accuracy (%)	84	—	86	—	75	78
AUC	0.90	—	0.93	0.92	0.83	—

FFR_{CT}, Fractional flow reserve computed tomography; *PPV,* positive predictive value; *NPV,* negative predictive value; *AUC,* area under the receiver operating characteristic (ROC) curve.

The combination of FFR_{CT} findings with APCs, including PR, LAP, and SC, for the diagnosis of lesion-specific ischemia as referenced by invasive FFR has been studied in 252 patients enrolled in the DeFACTO trial. In this study of 407 vessels directly interrogated by invasive FFR, only PR added incremental discriminatory value to FFR_{CT} alone for diagnosis of ischemia-causing coronary lesions

(area under ROC curve, 0.87 versus 0.83). In a subsequent study of the NXT population, coronary artery atherosclerotic plaque volumes were studied for their ability to provide incremental diagnostic value to FFR_{CT}. Overall plaque volumes were separated into noncalcified, low-density noncalcified, and calcified plaque. Aggregate plaque volumes were inversely correlated with ischemia in a manner independent of high-grade stenosis severity, with low-density noncalcified plaque plus FFR_{CT} yielding an area under the ROC curve of 0.90 for discrimination of lesion-specific ischemia.[117]

FFR_{CT} has been assessed for its ability to alter the clinical management of patients undergoing noninvasive and invasive testing. In the crossover-design Prospective Longitudinal Trial of FFR_{CT} Outcome and Resource Impacts (PLATFORM), 584 symptomatic patients with suspected CAD were assigned to either usual care or a CCTA-FFR_{CT}–based evaluation, to determine the rates of no obstructive CAD of 50% or greater stenosis at ICA.[118] Two separate cohorts were studied, referred for invasive assessment and for noninvasive stress testing. Compared with a CCTA-FFR_{CT}–based approach, usual care resulted in a significantly lower rate of obstructive CAD at ICA (12% versus 73%) and also resulted in 61% of ICAs being canceled after CCTA-FFR_{CT} findings were known. These cancellations were associated with 32% lower costs and similar quality-of-life measures by a CCTA-FFR_{CT} algorithm compared to usual care, a finding that extended to the 1-year follow-up. In contrast, among patients referred to noninvasive imaging, the rates of nonobstructive CAD at ICA were not statistically different (13% versus 6%). For these patients undergoing noninvasive imaging, quality-of-life measures were higher with a CCTA-FFR_{CT}–based strategy than with usual care, although with higher costs ($2766 versus $2137).[119]

Early investigations of the potential of FFR_{CT} to guide clinical decisions of coronary revascularization have been recently studied.[120] In a pilot study of 44 patients, CFD was applied to calculate FFR_{CT} values with subsequent computational modeling of coronary stenting for ischemia-causing lesions. Before and after "virtual stenting" FFR_{CT} moderately correlated with the invasive FFR at a mean difference of 0.006 and 0.024, respectively, and a diagnostic sensitivity and specificity of 85% and 57%.

CCTA is advocated by the ACC Multimodality Appropriate Use Criteria for the Detection and Risk Assessment of Stable Ischemic Heart Disease as appropriate for several clinical indications that are largely classified on the basis of symptoms suggestive of CAD or prior test results[39] (see end chapter, **Tables 18G.1** and **18G.2**). Appropriate symptom-based indications include those with intermediate pretest probability of CAD with an uninterpretable ECG or who are unable to exercise, new or worsening symptoms after a normal exercise ECG test, or newly diagnosed systolic heart failure. Prior testing within 90 days for abnormal or uncertain results after exercise ECG or stress imaging is considered appropriate for performance, with no appropriate indications for asymptomatic individuals.

Assessment of Cardiovascular Structure and Function

Beyond coronary artery stenosis and atherosclerosis, ECG-gated CT allows for comprehensive assessment of cardiac structure and function. Because cardiac function evaluation requires retrospective ECG helical gating, with significantly greater amounts of radiation exposure, cardiac CT functional evaluation is less frequently performed. In specific cases, however, it may be useful, and techniques to acquire optimal image acquisition and measurements should be known.

Left ventricular (LV) assessment can be determined by continuous image acquisition throughout the cardiac cycle in an array of patient subsets[121] (**Table 18.7**). In most cases, image reconstruction is performed at every 5% or 10% increment of the R-R interval, which enables cardiac motion assessment. Although 4D cardiac function evaluation at 5% increments appears "smoother" in motion than 10% increments, it is important to note that these images do not differ with respect to temporal resolution, which is fixed by the model of the CT scanner. Techniques to acquire these measurements vary and have historically been aimed to replicate echocardiography and SPECT planes, including short-axis and two-, three-, and four-chamber views, and are useful for correct sizing of cardiac chambers. However, current software algorithms allow for semiautomated segmentation with manual correction of LV cavities, which offers ease of volumetric measurement. LV volumes have been reported using prospectively triggered axial CT scans, which are acquired at variable points in mid-diastole. Because this phase of the cardiac cycle is not typically acquired by other imaging methods, care should be taken not to compare these CT findings to normal values, which have been detailed in normal individuals free of cardiovascular pathology.

TABLE 18.7

Comparison of Left Ventricular Volumetric Assessment According to Cardiac CT and Echocardiography*

		EDV			ESV			LVEF (%)		
Author	**Patients (*n*)**	**CT**	**ECC**	**$P_{difference}$**	**CT**	**ECC**	**$P_{difference}$**	**CT**	**ECC**	**$P_{difference}$**
Nasis[159] (2011)	Suspected or known CAD (139)	124 ±36	110 ±33	<0.001	52 ±27	47 ±24	<0.001	60 ±9	59 ±9	<0.001
Chang[160] (2010)†	Healthy adults (30)	134.8 ±18.7	124.0 ±16.5	<0.01	51.9 ±12.2	47.1 ±8.4	<0.01	61.2 ±6.4	62.0 ±4.8	<0.01
Chang[160] (2010)‡	Healthy adults (30)	134.8 ±18.7	132.6 ±18.9	<0.01	51.9 ±12.2	50.2 ±10.4	<0.01	61.2 ±6.4	62.0 ±5.8	<0.01
Maffei[161] (2010)	Suspected CAD (450)	78 ±38	—	—	41±35	—	—	52 ±15	55 ±13	<0.05
Ko[162] (2010)	Patients with CAD (126)	—	—	—	—	—	—	59.2 ±11	57.9 ±10	—

*Similar comparison between computed tomography and echocardiography for the measurement of right ventricular volumetric assessments are currently unavailable in literature to date.

†2D echocardiography.

‡3D echocardiography.

EDV, End-systolic volume; *ESV,* end-diastolic volume; *LVEF,* left ventricular ejection fraction; *ECC,* echocardiography; *CAD,* coronary artery disease; *IHD,* ischemic heart disease.

Despite current CT temporal resolution being significantly poorer than other imaging modalities, CT has generally demonstrated high correlation with other methods. Using a CMR gold standard, cardiac CT quantification demonstrated *r* values for comparison of LV ejection fraction (EF), end-systolic volume, and end-diastolic volume and mass: 0.93, 0.95, 0.93, and 0.86, respectively.[122] Partly because of these findings, cardiac CT is considered appropriate for use by recent multimodality AUC to be useful to differentiate etiologies of congestive heart failure (CHF). Regional wall motion assessment can be determined with high specificity and, when coupled with coronary angiographic findings, may help determine ischemia as a cause for impaired function and wall motion. Additional information can be gleaned by quantitation of attenuation patterns in myocardial tissue, with low attenuation suggestive of resting perfusion deficits that are sequelae of prior MI. Repeat contrast injection after initial performance of cardiac CT, typically 10 minutes later, may be useful for identification of areas of delayed hyperattenuation suggestive of nonviable myocardial scar.[123] For patients with preexisting chronic kidney disease, a CAC score of 0 can exclude high-risk CAD and may be considered as an alternative to CCTA.

Other specific etiologies of CHF are elicited through interpretation of cardiac CT.[121,124] These include

hypertrophic cardiomyopathy through measurements of LV wall thickness, systolic anterior motion of the mitral leaflets, and myocardial hyperattenuation pattern inconsistent with the angiographic CAD (**see Chapter 78**). Similarly, diagnosis of infiltrative cardiomyopathies such as sarcoidosis can be augmented by visualization of noncardiac structures such as mediastinal lymphadenopathy. LV myocarditis, noncompaction, arrhythmogenic right ventricular cardiomyopathy, constrictive pericarditis, and amyloidosis have also been reported as being diagnosable by cardiac CT (**see Chapters 77 and 83**). Other important pathologies, such as LV apical thrombus, ventricular aneurysms, and pseudoaneurysms, are easily diagnosed and serve as an added diagnostic benefit of cardiac CT.

With limitations, valvular assessment can be performed by cardiac CT.[125] Given current contrast protocols that aim to selectively opacify the LV cavity over the right, the general focus for valvular evaluation by cardiac CT has been on left-sided valves. Aortic stenosis is generally accurately diagnosed by cardiac CT (**see Chapter 68**). Double-oblique localization of the aortic valve at the level of the leaflet insertions can be easily performed by initial start planes in the left sagittal oblique and left coronary oblique axes, which allows visualization of the phasic motion of the valve throughout the cardiac cycle. Although some have suggested cardiac phases of 10% to 30% of the R-R interval as the optimal time for evaluation of the aortic valve area (AVA), this is variable among individuals and should instead be measured at the largest valve orifice area irrespective of the phase. Meta-analytic data from 14 studies suggest an overestimation of AVA by cardiac CT compared to transthoracic echocardiography (TTE), with better correlation to transesophageal echocardiography (TEE). One potential caveat is in AVA assessment in the case of low-flow, low-gradient aortic stenosis, where the lack of augmentation of LV contractile function may significantly reduce the perceived anatomic AVA by cardiac CT. Numerous other aortic valvular conditions are easily visualized by cardiac CT, including congenital bicuspid or quadricuspid aortic stenosis and extent and severity of aortic valve calcium.

In contrast to aortic stenosis, which relies on retrospective gating, aortic regurgitation (AR) can be assessed with moderate accuracy during prospective triggered cardiac CT. Among 53 patients with AR, compared to 29 patients without AR, undergoing cardiac CT and TTE, cardiac CT demonstrated a sensitivity and specificity of 98% and 98% to grade AR severity.[126] The utility of cardiac CT for AR evaluation is for moderate to severe cases, since cardiac CT misses more than one fourth of mildly regurgitant valves. Aortic regurgitant volume can be quantified when cardiac CT is performed by retrospective helical gating methods. Calculation of LV and right ventricular (RV) end-systolic and end-diastolic volumes enables calculation of their respective stroke volumes. RV stroke volumes subtracted from LV stroke volumes represent the aortic regurgitant volume.

Mitral valve (MV) evaluation can be more challenging than for the aortic valve because of its complex anatomic structure and highly mobile valvular apparatus[127] (**see Chapter 69**). MV scallops and chordae tendineae are very thin structures, and high-intensity opacification of the left ventricle and atrium with iodinated contrast can often obfuscate their visualization. Improved visualization of the MV and its related structures may occur with postprocessing techniques using a MinIP, which will enhance the relatively hypoattenuated valve tissue over the contrast-filled cavities.

Cardiac CT may also be useful for diagnosis of mitral stenosis when the MV is visualized by double-oblique short-axis methods.[125] Although prospective axial triggering methods allow for diastolic evaluation at 75% of the R-R interval, inspection of each diastolic phase should be carefully performed for the greatest MV area if retrospective helical gating is performed. At its greatest area, short-axis planimetry will offer measurements of the anatomic regurgitant orifice in a manner highly correlative to TTE for the diagnosis of moderate or severe mitral stenosis. Comparisons to TEE reveal a general overestimation of the MV area by cardiac CT.

Mitral regurgitation on cardiac CT can be quantified by two methods: calculation of the regurgitant volume and measurement of the anatomic regurgitant orifice area (ROA). Measurement of mitral regurgitant volume by differences in LV and RV stroke volumes shows high correlation to TTE (r = 0.95) with no significant biases.[128] Importantly, planimetry of the MV by cardiac CT provides only the *anatomic* ROA, which may differ from the hemodynamically dependent *effective* ROA. Numerous other MV pathologies can be readily interpreted on cardiac CT scans and may offer assistance in diagnosis of mitral regurgitation, including prolapse, flail leaflet, paravalvular abscess, endocarditis, or in the case of prosthetic valves, thrombus formation or dehiscence.

Structural Heart Disease Interventions

Given the anatomic and physiologic data afforded by cardiac CT, coupled with recent advances in complex percutaneous therapies for structural heart disease, CT has evolved to become an important imaging modality for preprocedural guidance and postprocedural follow-up for many of these interventions. These include imaging for transcatheter heart valve replacement, left atrial appendage occlusion, and arrhythmia ablation (**Chapter 38**).

Since its demonstrated superiority over conservative therapy and similar outcomes to surgical therapy in high-risk patients with severe aortic stenosis, transcatheter aortic valve replacement (TAVR) is finding expanding clinical utility in patients with less severe aortic valvular disease[129-131] (**see Chapter 72**). Almost coincident with this has been the examination of the potential of cardiac CT findings to provide information that may improve procedural TAVR outcomes or prevent unnecessary complications.[132] Specific to TAVR, cardiac and vascular CT scans are routinely performed and provide information related to (1) aortic annular size and calcifications, (2) prediction of TAVR deployment angles, (3) coronary ostial heights, (4) aorto-iliac size and atherosclerotic burden, and (5) postprocedural evaluation of TAVR devices for evidence of leaflet thickening suggestive of thrombosis (**Fig. 18.15**).

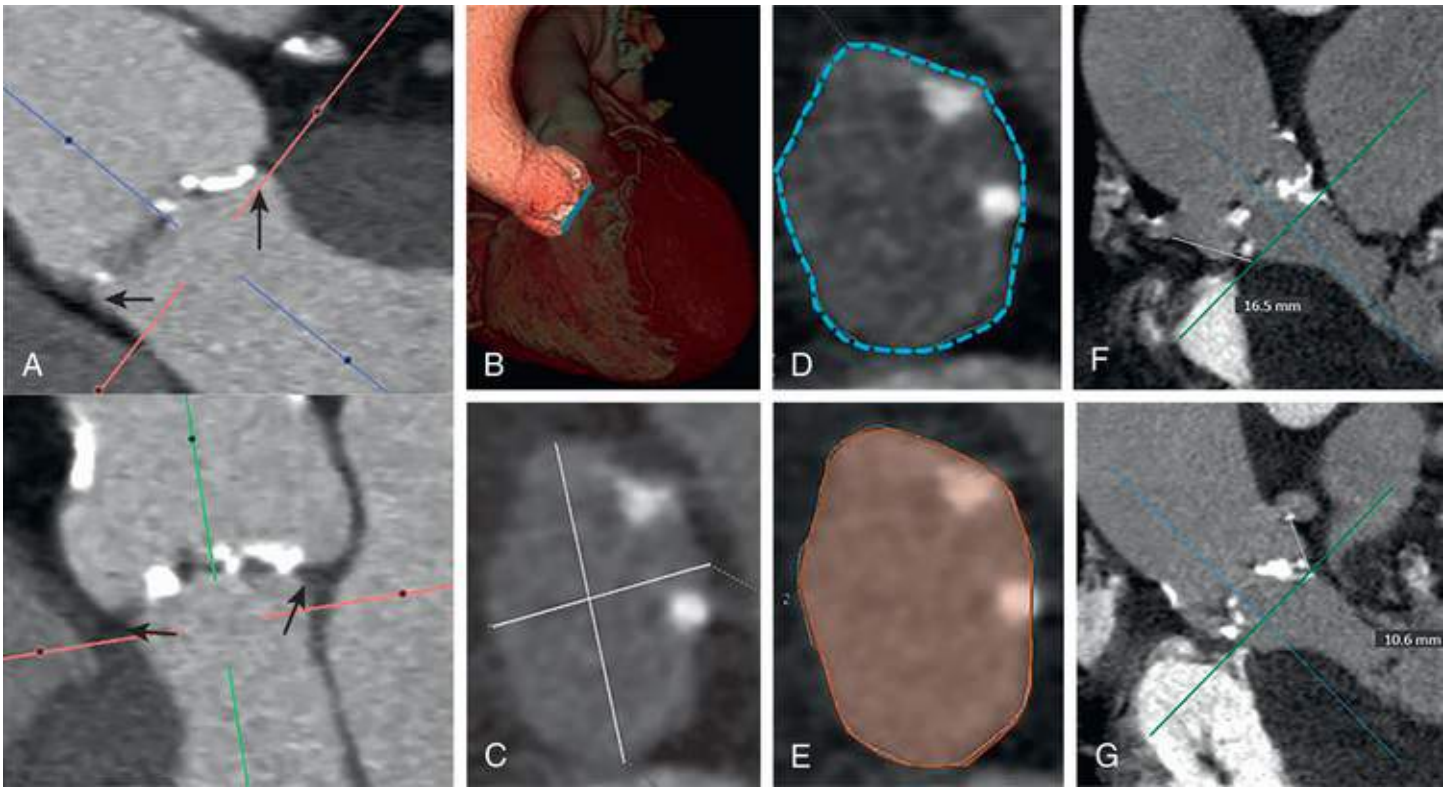

FIGURE 18.15 Cardiovascular CT for preprocedural planning of transcatheter aortic valve replacement (TAVR). **A,** Double-oblique approach to identifying aortic annular plane before TAVR (*black arrows*). Aortic annuli should be measured at the leaflet insertions rather than in the valve plane. **B,** Volume-rendered imaging of the aorta, aortic annulus, and aortic valve. *Blue line* indicates the plane of the aortic annulus. When all points in the aortic annular plane are aligned (as indicated by *blue line*), these CT projection angles can be helpful to proceduralists as a guide to which angles may be useful at the time of the TAVR procedure. Diameter **(C)**, area **(D)**, and, perimeter **(E)** measurements of the aortic annulus for proper sizing of the TAVR prostheses. Measurement of the right coronary ostial height **(F)**, and left coronary ostial height **(G)**, to ensure that the TAVR will not occlude the coronary ostia.

Cardiac CT scanning for TAVR is largely performed with retrospective helical gating. Patients undergoing TAVR are generally elderly, and the need for dynamic assessment of the aortic annulus often outweighs the risk of radiation from a cardiac CT. On CT the aortic annulus is localized by a double-oblique method that aligns the plane of insertion of the left, right, and noncoronary cusp leaflets. This plane is generally asymmetric to the plane of the left ventricular outflow tract (LVOT) and proximal ascending aorta, with the right coronary cusp leaflet generally inserting more inferior than its counterparts. The left-right, craniocaudal angles that define the aortic annular plane can aid in the determination of the fluoroscopic angles for coaxial deployment of TAVR at the time of the procedure. CT assessment of the aortic annulus reveals a structure that is elliptoid in shape, is often calcified, and exhibits dynamism throughout the cardiac cycle. Rather than report the uneven diameters of the elliptical aortic annulus, area measurements are preferred because they can be better applied to correctly size the circular-shaped TAVR devices. Given the larger annular area at the end of systole, it is during this phase of the cardiac cycle that aortic annular measurements should be reported. Proper TAVR sizing by CT reduces rates of postprocedural paravalvular aortic regurgitation (PAR), whose incidence increases with greater TAVR device diameter (or area) minus CT annular diameter (or area), respectively.[133] Appropriate device sizing is also important to prevent oversizing compared to aortic annular measurements, which can lead to aortic rupture. The calcifications of the aortic annulus, valve, and proximal aorta are important to note. Severity of aortic valve calcification at the level of the aortic wall, valve edge, or valve commissures by CT increases risk of PAR as well as rupture.

Several additional pre-TAVR CT findings are noteworthy. Given the generally high-profile TAVR stent

devices, it is important to measure the distance between the aortic annular plane and the coronary ostia. Catastrophic cases have occurred where TAVR deployment resulted in acute coronary occlusion and sudden death. Measurements of the coronary height should be done from the aortic leaflet insertions to the inferior portion of the left and right coronary ostia. This is generally an oblique plane and should not be substituted for a measurement perpendicular to the annular plane, which may underestimate the coronary height. Further, in candidates of TAVR, aortoiliac angiography is often simultaneously performed to assess the dimensions of the vasculature for planned transfemoral approaches. Several important imaging features can predict periprocedural complications, including minimum aortoiliac artery diameter less than diameter of external sheath, severe calcifications in femoral and superficial femoral arteries, “horseshoe” calcifications, and severe aortic atheromatous plaque. Patients undergoing TAVR who have underlying renal insufficiency may undergo low-dose iodinated contrast protocols, which have included use of monochromatic DECT imaging and selective aortoiliac angiography.

In the emerging field of transcatheter mitral valve replacement (TMVR), cardiac CT will likely play a similarly important role[127] (**see Chapter 72**). As with TAVR procedures, double-oblique methods of CT image reconstruction can be useful to assess the MV anatomy, which is a complex D-shaped structure with a saddle-shaped morphology. CT can be useful to quantify the mitral annular size, extent and location of calcifications, and 3D geometry. Similar to TAVR, CT will allow for depiction of fluoroscopic angles coplanar to the mitral annulus to help guide device deployment. Because TMVR prosthesis deployment will often extend into the LVOT, it will create a “neo-LVOT” after the procedure. Coupled with information related to the type and size of the TMVR device, CT allows for determination of the degree of LVOT obstruction that may result from TMVR.

For patients with atrial fibrillation (AF) being considered for pulmonary vein isolation (**see Chapter 38**), cardiac CT can be useful for detailed morphologic characterization of the left atrium, left atrial appendage (LAA), and pulmonary veins (PVs).[134] Left atrial measurements by CT are generally reported volumetrically and at end-systole, with values consistent with those derived by CMR. LAAs are easily appreciated on cardiac CT, which has been used to exclude LAA thrombus in patients with AF. Thrombus in the LAA will appear as an area of hypoattenuation with a generally distinct border. This contrasts with “thrombus in formation” (or very low LAA velocities), which possesses a hazier appearance. For individuals with suspected LAA thrombus on CT, a follow-up noncontrast study approximately 45 to 60 seconds after the contrast-enhanced CT is helpful. Loss of the hypoattenuation signal within the LAA at this second CT will exclude the diagnosis of LAA thrombus, whereas its persistence will establish the diagnosis (**Table 18.8**).

TABLE 18.8

Diagnostic Accuracy of CT for Left Atrial Appendage Thrombus

AUTHOR	PATIENTS (*n*)	PRESENCE OF THROMBUS (%)	ACCURACY (%)	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)
Kapa[163] (2010)	255	2	89	100	88	12	100
Maltagliati[164] (2011)	171	2	92	100	92	22	100
Dorenkamp[165] (2013)	329	2	96	29	98	20	98
Choi[166] (2013)	106	25	89	100	85	69	100
Homsi[167] (2016)	124	22	90	82	97	88	95
Lazoura[168] (2016)	122	16	86	100	86	15	100

PPV, Positive predictive value; *NPV,* negative predictive value.

The interindividual variations of LAA shape and size are considerable, but attempts have been made to

categorize LAA types into morphologies that represent a cactus, a chicken wing, a windsock, and a cauliflower. For AF patients who cannot tolerate anticoagulation, these findings may contribute to the determination of their suitability for percutaneous LAA occlusion.[135] LAA morphologies may have prognostic utility; a chicken-wing LAA shape may be associated with a lower risk of thromboembolic events for patients undergoing catheter ablation for AF. Given their high anatomic variability, the left atrium and PVs are often reconstructed by CT postprocessing methods and co-registered with left atrial electrical information obtained at the PV isolation procedure. This integrated electroanatomic map can offer improved localization of arrhythmogenic foci, as well as reduce complications such as PV stenosis or atrio-esophageal fistulas. 2D-3D image co-registration techniques also exist to fuse cardiac CT image data with x-ray fluoroscopy data for improved spatial orientation during the procedure.

Appropriate Use Criteria

Multimodality Imaging in Stable Ischemic Heart Disease and Heart Failure

James E. Udelson, Vasken Dilsizian, and Robert O. Bonow

Beginning in 2005, the America College of Cardiology (ACC) along with other professional societies published appropriate use criteria (AUC), a set of recommendations for the use of diagnostic and therapeutic procedures keyed to clinical situations. With respect to diagnostic imaging, since the initial document on single-photon emission tomography (SPECT) imaging in 2005, each AUC document considered an individual imaging test or procedure (e.g., SPECT, echocardiography), across numerous clinical indications. The AUC recommendations are meant to inform clinical decision making for the optimal use of cardiac imaging.

The most recent AUC documents provide recommendations for the appropriate use of imaging in clinical syndromes rather than focusing on one specific imaging modality alone. The documents encompass patients with stable ischemic heart disease, that is, those with suspected or known coronary artery disease[1] (**Table 18G.1**) and patients with heart failure[2] (**Table 18G.2**). The documents recommend criteria for the use of numerous testing modalities within each of those clinical syndromes, including exercise electrocardiography and all widely used imaging modalities, such as SPECT perfusion imaging, echocardiography, coronary computed tomographic angiography (CCTA) and calcium imaging, and cardiac magnetic resonance imaging (CMR). Testing is rated based on the published literature as well as expert opinion, in a well-defined process. Tests are rated using the current nomenclature as "appropriate," "may be appropriate," or "rarely appropriate."[3]

Table 18G.1

Multimodality Appropriate Use Criteria for the Detection and Risk Assessment of Stable Ischemic Heart Disease

INDICATION	EXERCISE ECG	STRESS RNI	STRESS ECHO	STRESS CMR	CALCIUM SCORING	CCTA	INVASIVE CORONARY ANGIOGRAPHY
Section 1. Detection of CAD/Risk Assessment							
1.1 Symptomatic							
1. Low pretest probability of CAD	A	R	M	R	R	R	R

	ECG interpretable AND able to exercise							
2.	Low pretest probability of CAD ECG uninterpretable OR unable to exercise	—	A	A	M	R	M	R
3.	Intermediate pretest probability of CAD ECG interpretable AND able to exercise	A	A	A	M	R	M	R
4.	Intermediate pretest probability of CAD ECG uninterpretable OR unable to exercise	—	A	A	A	R	A	M
5.	High pretest probability of CAD ECG interpretable AND able to exercise	M	A	A	A	R	M	A
6.	High pretest probability of CAD ECG uninterpretable OR unable to exercise	—	A	A	A	R	M	A
1.2. Asymptomatic (Without Symptoms or Ischemic Equivalent)								
7.	Low global CHD risk Regardless of ECG interpretability and ability to exercise	R	R	R	R	R	R	R
8.	Intermediate global CHD risk ECG interpretable AND able to exercise	M	R	R	R	M	R	R
9.	Intermediate global CHD risk ECG uninterpretable OR unable to exercise	—	M	M	R	M	R	R
10.	High global CAD risk ECG interpretable AND able to exercise	A	M	M	M	M	M	R
11.	High global CAD risk ECG uninterpretable OR unable to exercise	—	M	M	M	M	M	R
1.3. Other Cardiovascular Conditions								
Newly Diagnosed Heart Failure (Resting LV Function Previously Assessed but No Prior CAD Evaluation)								
12.	Newly diagnosed systolic heart failure	M	A	A	A	R	A	A
13.	Newly diagnosed diastolic heart failure	M	A	A	A	R	M	M
Evaluation of Arrhythmias Without Ischemic Equivalent (No Prior Cardiac Evaluation)								
14.	Sustained VT	A	A	A	A	R	M	A
15.	Ventricular fibrillation	M	A	A	A	R	M	A
16.	Exercise-induced VT or nonsustained VT	A	A	A	A	R	M	A
17.	Frequent PVCs	A	A	A	M	R	M	M
18.	Infrequent PVCs	M	M	M	R	R	R	R
19.	New-onset atrial fibrillation	M	M	M	R	R	R	R
20.	Prior to initiation of antiarrhythmia therapy in high global CAD risk patients	A	A	A	A	R	M	R
Syncope Without Ischemic Equivalent								
21.	Low global CAD Risk	M	M	M	R	R	R	R
22.	Intermediate or high global CAD risk	A	A	A	M	R	M	R
Section 2. Prior Testing or Procedure								
Section 2.1. Prior Testing Without Intervening Revascularization (If Intervening Revascularization Since Most Recent Test, Refer to Section 2.2)								
2.0. Sequential Testing (≤90 Days): Abnormal Prior Test/Study)								
23.	Abnormal rest ECG findings (potentially ischemic in nature such as LBBB, T wave inversions) Low global CAD risk	—	A	A	M	R	M	R
24.	Abnormal rest ECG findings (potentially ischemic in nature such as LBBB, T wave inversions) Intermediate to high global CAD risk	—	A	A	A	R	M	M
25.	Abnormal prior exercise ECG test	—	A	A	A	R	A	A
26.	Abnormal prior stress imaging study (assumes not repeat of same type of stress imaging)	R	M	M	M	R	A	A
27.	Obstructive CAD on prior CCTA study	M	A	A	A	—	—	A
28.	Obstructive CAD on prior invasive coronary angiography	M	A	A	A	R	R	—
29.	Abnormal prior CCT calcium (Agatston score >100)	A	A	A	M	—	M	R
2.1. Sequential or Follow-Up Testing (≤90 Days): Uncertain Prior Results								
Equivocal, Borderline, or Discordant Prior Noninvasive Evaluation Where Obstructive CAD Remains a Concern								
30.	Prior exercise ECG test	—	A	A	A	R	A	M
31.	Prior stress imaging study (assumes not repeat of same type of stress imaging)	R	M	M	M	R	A	A
32.	Prior CCTA	M	A	A	A	—	—	A
Prior Coronary Angiography (Invasive or Noninvasive)								
33.	Coronary stenosis or anatomic abnormality of unclear significance found on cardiac CCTA	M	A	A	A	—	—	A
34.	Coronary stenosis or anatomic abnormality of unclear significance on previous coronary angiography	M	A	A	A	R	R	—
2.2. Follow-Up Testing (>90 Days): Asymptomatic or Stable Symptoms								
Abnormal Prior Exercise ECG Test, Asymptomatic or Stable Symptoms								
35.	Last test <2 years ago	R	R	R	R	R	R	R
36.	Last test ≥2 years ago	M	M	M	R	R	R	R
Abnormal Prior Stress Imaging Study, Asymptomatic or Stable Symptoms								
37.	Last study <2 years ago	R	R	R	R	R	R	R
38.	Last study ≥2 years ago	R	M	M	M	R	R	R
Obstructive CAD on Prior Coronary Angiography (Invasive or Noninvasive), Asymptomatic (Without Ischemic Equivalent) or Stable Symptoms								
39.	Last study <2 years ago	R	R	R	R	R	R	R
40.	Last study ≥2 years ago	M	M	M	M	R	R	R
Prior Coronary Calcium Agatston Score, Asymptomatic (Without Ischemic Equivalent) or Stable Symptoms								
41.	Agatston score <100	R	R	R	R	R	R	R
42.	Low to intermediate global CAD risk Agatston score between 100 and 400	M	M	M	R	R	R	R

43.	High global CAD risk Agatston score between 100 and 400	M	M	M	M	R	R	R
44.	Agatston score >400	A	M	M	M	R	R	R
Normal Prior Exercise ECG Test, Asymptomatic (Without Ischemic Equivalent)								
45.	Low global CAD risk	R	R	R	R	R	R	R
46.	Intermediate to high global CAD risk Study <2 years ago	R	R	R	R	R	R	R
47.	Intermediate to high global CAD risk Study ≥2 years ago	M	M	M	M	R	R	R
Normal Prior Stress Imaging Study OR Nonobstructive CAD on Angiogram (Invasive or Noninvasive), Asymptomatic (Without Ischemic Equivalent)								
48.	Low global CAD risk	R	R	R	R	R	R	R
49.	Intermediate to high global CAD risk Study <2 years ago	R	R	R	R	R	R	R
50.	Intermediate to high global CAD risk Study ≥2 years ago	M	M	M	M	R	R	R
Normal Prior Exercise ECG Test, Stable Symptoms								
51.	Low global CAD risk	R	R	R	R	R	R	R
52.	Intermediate to high global CAD risk Study <2 years ago	R	R	R	R	R	R	R
53.	Intermediate to high global CAD risk Study ≥2 years ago	M	M	M	M	R	R	R
Normal Prior Stress Imaging Study OR Nonobstructive CAD on Angiogram (Invasive or Noninvasive), Stable Symptoms								
54.	Low global CAD risk	R	R	R	R	R	R	R
55.	Intermediate to high global CAD risk Study <2 years ago	R	R	R	R	R	R	R
56.	Intermediate to high global CAD risk Study ≥2 years ago	M	M	M	M	R	R	R
2.3. Follow-Up Testing: New or Worsening Symptoms								
57.	Normal exercise ECG test	M	A	A	A	R	A	M
58.	Nonobstructive CAD on coronary angiography (invasive or noninvasive) OR normal prior stress imaging study	M	A	A	A	R	R	M
59.	Abnormal exercise ECG test	R	A	A	A	R	A	A
60.	Abnormal prior stress imaging study	R	M	M	M	R	A	A
61.	Obstructive CAD on CCTA study	M	A	A	A	R	R	A
62.	Obstructive CAD on invasive coronary angiography	A	A	A	M	R	R	A
63.	Abnormal CCTA calcium (Agatston score >100)	A	A	A	A	R	M	A
Section 2.2. Post-Revascularization (PCI or CABG)								
2.4. Symptomatic (Ischemic Equivalent)								
64.	Evaluation of ischemic equivalent	M	A	A	A	R	M	A
2.5. Asymptomatic (Without Ischemic Equivalent)								
65.	Incomplete revascularization Additional revascularization feasible	M	A	A	M	R	R	R
66.	Prior left main coronary stent	M	M	M	M	R	M	M
67.	<5 years after CABG	R	R	R	R	R	R	R
68.	≥5 years after CABG	M	M	M	M	R	R	R
69.	<2 years after PCI	R	R	R	R	R	R	R
70.	≥2 years after PCI	M	M	M	M	R	R	R
Section 3. Preoperative Evaluation for Noncardiac Surgery								
3.1. Moderate-to-Good Functional Capacity (≥4 METs) OR No Clinical Risk Factors								
71.	Any surgery	R	R	R	R	R	R	R
3.2. Asymptomatic AND <1 Year After Normal CT or Invasive Angiogram, Normal Stress Test for CAD, or Revascularization								
72.	Any surgery	R	R	R	R	R	R	R
3.3. Poor or Unknown Functional Capacity (<4 METs)								
73.	Low risk surgery ≥1 clinical risk factor	R	R	R	R	R	R	R
74.	Intermediate risk surgery ≥1 clinical risk factor	M	M	M	M	R	R	R
75.	Vascular surgery ≥1 clinical risk factor	M	A	A	M	R	R	R
76.	Kidney transplant	M	A	A	M	R	R	M
77.	Liver transplant	M	A	A	M	R	R	M
Section 4. Determine Exercise Level Prior to Initiation of Exercise Prescription or Cardiac Rehabilitation								
4.1. Exercise Prescription								
78.	No prior revascularization	A	R	R	R	R	R	R

Appropriate Use Key: A = Appropriate; M = May Be Appropriate; R = Rarely Appropriate.

CABG, Coronary artery bypass graft; *CAD,* coronary artery disease; *CCT,* coronary computed tomography; *CCTA,* coronary computed tomography angiography; *CHD,* coronary heart disease; *CMR,* cardiac magnetic resonance imaging; *ECG,* electrocardiogram; *Echo,* echocardiography; *LBBB,* left bundle branch block; *LV,* left ventricular; *METs,* metabolic equivalents; *PCI,* percutaneous coronary intervention; *PVC,* premature ventricular complex; *RNI,* radionuclide imaging; *VT,* ventricular tachycardia.

TABLE 18G.2

Appropriate Use of Cardiovascular Imaging in Heart Failure

	Indication	REST ONLY					REST + STRESS				CCT	Cath
		Echo	RNV	SPECT	PET	CMR	Echo	SPECT	PET	CMR		
1. Initial Evaluation of Cardiac Structure and Function for Newly Suspected or Potential Heart Failure												
Newly Suspected or Potential Heart Failure												
1.	Symptoms of heart failure Shortness of breath OR Decreased exercise tolerance OR Symptoms of fluid retention AND Findings of heart failure Abnormal chest radiograph (e.g., enlarged silhouette, pulmonary venous congestion) OR Abnormal biomarker(s) (e.g., BNP, pro-BNP) OR Signs of heart failure Evidence of impaired perfusion OR Evidence of volume overload	A	A	M	R	A	R	R	R	R	M	R
2.	Malignancy Current or planned cardiotoxic therapy AND No prior imaging evaluation	A	A	R	R	A	R	R	R	R	R	R
3.	Familial or genetic dilated cardiomyopathy in first-degree relative	A	M	R	R	A	R	R	R	R	R	R
4.	Known adult congenital heart disease	A	M	R	R	A	R	R	R	R	M	M
5.	Acute myocardial infarction Evaluation of LV function during initial hospitalization	A	M	M	R	A	M	M	R	R	R	A
2. Evaluation for Ischemic Etiology												
6.	Angina/ischemic equivalent syndrome	M	R	R	M	M	A	A	A	A	A	A
7.	WITHOUT angina/ischemic equivalent syndrome	M	R	R	M	M	A	A	A	A	M	A
3. Viability Evaluation (After Ischemic Etiology Determined) Known to Be Amenable to Revascularization With or Without Angina												
8.	Severely reduced ventricular function (EF <30)	M	R	A*	A	A	A	A	A	A	M	R
9.	Moderately reduced LV function (EF 30%-39%)	M	R	M*	A	A	A	A	M	A	M	R
10.	Mildly reduced LV function (EF 40%-49%)	M	R	M*	M	A	A	A	A	A	M	R
4. Consideration and Follow-Up for Implantable Cardioverter-Defibrillator (ICD)/Cardiac Resynchronization Therapy (CRT)												
Implantable Cardioverter-Defibrillator Therapy												
11.	Evaluation determine patient candidacy Meets published clinical standards for device eligibility Candidacy requires assessment of EF and/or other structural information	A	A	M	R	A	R	R	R	R	M	R
12.	Routine follow-up after placement No deterioration in clinical status AND No change in arrhythmia status	R	R	R	R	R	R	R	R	R	R	R
13.	Follow-up after placement Change in arrhythmia status Appropriate ICD discharge (e.g., VT/VF)	A	R	M	R	R	R	R	R	R	M	R
14.	Follow-up after placement Change in arrhythmia status Inappropriate ICD discharge (e.g. rapid AFib)	A	R	M	R	R	R	R	R	R	R	R
Cardiac Resynchronization Device Therapy												
15.	Initial evaluation to determine patient candidacy Meets published clinical standards for device eligibility Candidacy requires assessment of EF	A	A	M	R	A	R	R	R	R	M	R
16.	Procedure planning: considerations Patient meets all published clinical standards for device Evaluation of myocardial fibrosis/scarring, coronary vein variations, and intracavitary thrombus (for dyssynchrony evaluation)	A	R	R	R	A	R	R	R	R	A	R
17.	Follow-up early (<6 months) after implantation No improvement in symptoms OR No improvement functional capacity	A	M	M	R	R	R	R	R	R	M	R
18.	Follow-up late (>6 months) after implantation Improved symptoms (i.e., from class III, IV to class I, II) OR Improved functional capacity	M	R	R	R	R	R	R	R	R	R	R
5. Repeat Evaluation of Heart Failure												
19.	New angina or ischemic equivalent syndrome	A	M	M	M	M	A	A	M	M	M	A
20.	New or increasing heart failure symptoms (e.g., shortness of breath, exertional dyspnea) AND Adherent to medical therapy	A	M	M	R	M	A	A	M	M	M	M
21.	No new symptoms AND No other change in clinical status <1 year since prior imaging	R	R	R	R	R	R	R	R	R	R	R
22.	No new symptoms AND No other change in clinical status ≥1 year since prior imaging	M	R	R	R	R	R	R	R	R	R	R

*SPECT rest/redistribution.

Appropriate Use Key: A = Appropriate; M = May Be Appropriate; R = Rarely Appropriate.

AFib, Atrial fibrillation; *BNP,* brain natriuretic peptide; *Cath,* catheterization; *CCT,* coronary computed tomography; *CMR,* cardiac magnetic resonance; *Echo,* echocardiography; *EF,* ejection fraction; *LV,* left ventricular; *PET,* positron emission tomography;

RNV, radionuclide ventriculography; *SPECT,* single-photon emission tomography; *VT/VF,* ventricular tachycardia/ventricular fibrillation.

The recommendations in these newer documents supersede those in prior AUC documents on each of the individual modalities. Moreover, a strength of these multimodality documents is that the writing panels had as one of its goals to "identify any and all tests that are considered reasonable for a given clinical indication."[1] The panel did not attempt to define which test might be "best" for each indication, but rather identified the range of testing that could be appropriate (or not) for a given clinical indications within the specific clinical syndrome. Importantly, it is acknowledged that local expertise and quality of testing are additional critical factors in determining test selection.

The AUC documents have been important in identifying for imaging laboratories and hospital systems that approximately 15% of tests that are ordered appear to fall into the category "rarely appropriate," providing clinicians with a guide to optimize case selection for testing, as well as test selection. The multimodality imaging AUC documents comprehensively compile the recommendations for all imaging modalities and are important guides to clinical practice.

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19

Cardiac Catheterization

Joerg Herrmann

Cardiac catheterization refers to all forms of direct invasive and catheter-based assessments of the heart. In clinical practice, a distinction is often made between coronary angiography (**see Chapter 20**) and hemodynamic (right ± left) heart catheterization, given the different aspects of these procedures. This chapter focuses on cardiac catheterization in general and hemodynamic catheterization in particular.

The first cardiac catheterization has been accredited to Reverend Stephen Hales, who used brass pipes inserted into the venous and arterial systems of a horse to perform a biventricular catheterization in 1711.[1] (See also Classic References, Mueller.) Animal catheterization procedures became common practice thereafter, and its inapplicability to humans a common assumption for two centuries. In 1929, however, German surgery resident Werner Forssmann, aiming to find better approaches for delivering drugs directly into the heart, advanced a well-oiled 4 French (4F) ureteral catheter via the left cubital vein for a total length of 65 cm into his own heart, walked the stairs to the radiology department, and documented a right atrial catheter position by a chest x-ray film.[2] The American physician-physiologists André Cournand and Dickinson Richards redesigned Forssmann's catheter and advanced the technique in the 1940s. This allowed for a safer procedure, longer indwell times, and easy, repeated collection of true mixed venous blood and thus the calculation of cardiac output by the use of the direct Fick principle for the first time in humans.[1] All three physicians were awarded the Nobel Prize in Physiology and Medicine in 1956. Cardiac catheterization has continued to evolve in many aspects, and currently more than 80% of all U.S. hospitals offer this service.[3]

Cardiac catheterization is not to be understood in isolation but rather as part of the continuum of the evaluation of patients with various cardiac conditions. It is to be pursued with the knowledge of noninvasive test results, and appropriately so, when these do not suffice to direct management decisions. The invasive examination therefore is to provide definitive guidance and needs to be adapted to the presentation and disease processes of the individual patient. **Fig. 19.1** provides an overview of the main indications, illustrating the scope of cardiac catheterization and its appropriate use criteria (AUC).[4] Performing the right procedure on the right patient for the right reason in the right way for the right outcome is becoming increasingly important, especially in a changing health care environment. **eTable 19.1** lists clinical scenarios in which cardiac catheterization is rarely appropriate.

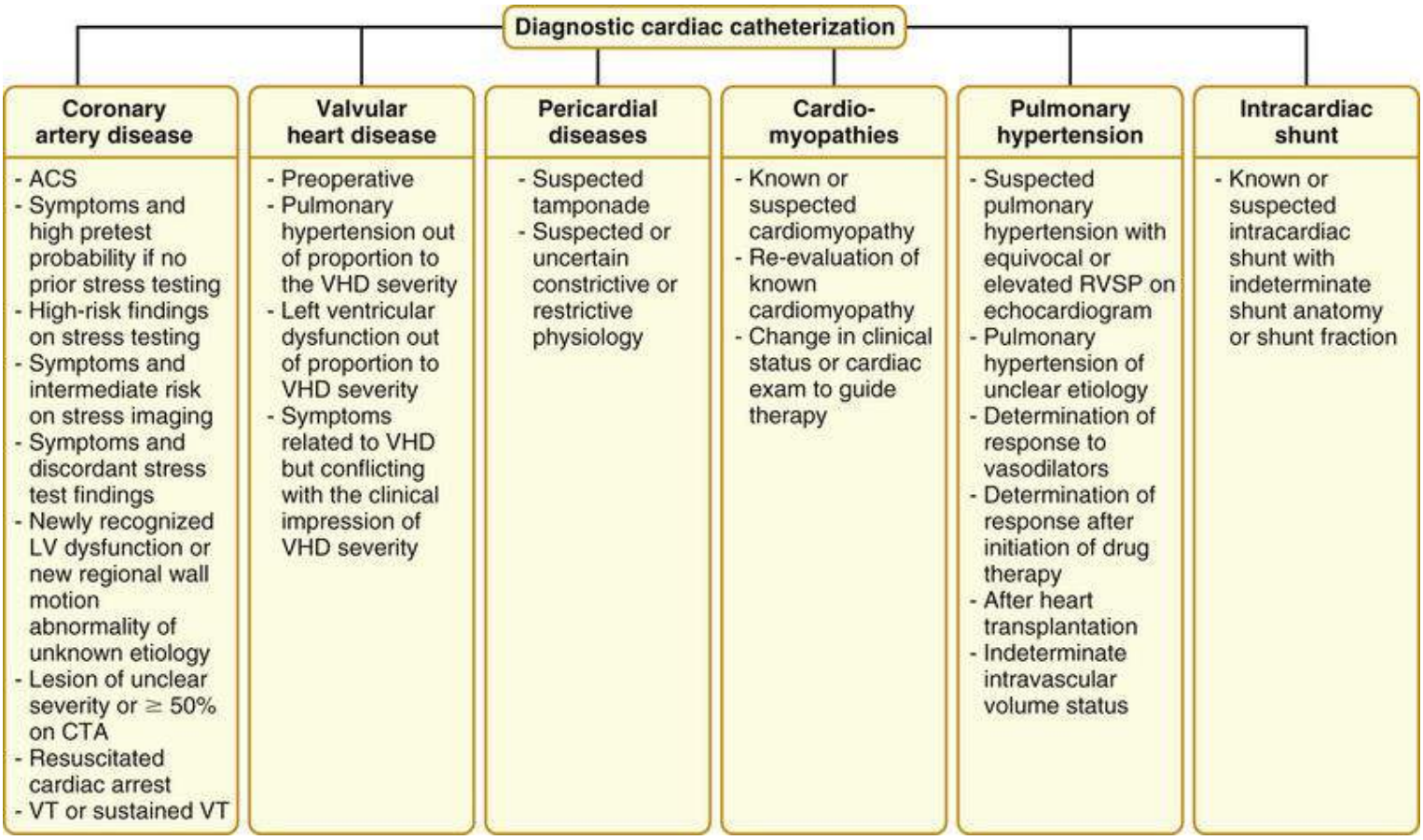


FIGURE 19.1 Overview of the main appropriate use indications for cardiac catheterization. *ACS,* Acute coronary syndrome; *CTA,* computed tomographic angiography; *LV,* left ventricular; *RVSP,* right ventricular systolic pressure; *VT,* ventricular tachycardia.

ETABLE 19.1

Overview of Clinical Scenarios Considered Rarely Appropriate for Cardiac Catheterization

Suspected Coronary Artery Disease (CAD)
No Prior Noninvasive Stress Imaging (No Prior PCI, CABG, or Angiogram Showing ≥50% Angiographic Stenosis)
Low global CAD risk, asymptomatic
Intermediate global CAD risk, asymptomatic
Low pretest probability, symptomatic
Prior Noninvasive Testing (No Prior PCI, CABG, or Angiogram Showing ≥50% Angiographic Stenosis)
Low-risk findings (e.g., Duke treadmill score ≥5), asymptomatic
Low-risk findings (e.g., <5% ischemic myocardium on stress SPECT MPI or stress PET, no stress-induced wall motion abnormalities on stress echo or stress CMR), asymptomatic
Coronary Calcium Score
Any calcium score, asymptomatic
Coronary Computed Coronary Angiography
Lesion <50% non–left main, asymptomatic
Cardiac Magnetic Resonance Imaging (CMR)
Area of delayed gadolinium myocardial enhancement of unknown etiology, asymptomatic
Patients with Known Obstructive CAD (e.g., Prior MI, PCI, or CABG, or Obstructive Disease on Invasive Angiography)
Medically Managed Patients
Low-risk noninvasive findings, asymptomatic/controlled symptoms or unchanged findings
Postrevascularization (PCI or CABG)
Asymptomatic or stable symptoms
Arrhythmias and No Prior Noninvasive Assessment of Ischemia with Normal Systolic Function
Syncope, low CHD risk
New-onset atrial fibrillation or flutter, low or intermediate CHD risk
Heart block (e.g., second-degree type II or third-degree AV block) OR symptomatic bradyarrhythmias, low or intermediate CHD risk
Preoperative Coronary Evaluation for Noncardiac Surgery in Stable Patients
Low-risk surgery, 4 METs functional capacity without symptoms
Intermediate-risk surgery, no risk or 1 to 2 risk factors
Vascular surgery, no risk factors
Chronic Native or Prosthetic Valvular Disease
Asymptomatic related to valvular disease and non-severe mitral stenosis, mitral regurgitation, aortic stenosis, or aortic regurgitation
Symptomatic related to valvular disease and noninvasive imaging for valvular disease concordant with clinical impression of severity

METs, Metabolic equivalents.

This chapter reviews cardiac catheterization within the framework of operational aspects (pre-, intra-, and postprocedural assessment), technical aspects and procedural performance, and clinical aspects and integration into patient care.

Operational Aspects of Cardiac Catheterization

Initial guidelines for the cardiac catheterization were published by the American College of Cardiology (ACC) and the American Heart Association (AHA) in 1991 (see Classic References, Pepine). These have since been supplemented by expert consensus statements on best practice standards for cardiac catheterization by the ACC and the Society for Cardiac Angiography and Interventions (SCAI) in 2001 with updates in 2012 and 2016.[3,5] These documents provide the necessary foundation for the operational aspects.

The Cardiac Catheterization Laboratory

There are four basic types of catheterization laboratories: hospital-based laboratories with full support services including cardiovascular surgery, hospital-based laboratories without cardiovascular surgical capability, freestanding laboratories, and mobile laboratories. To qualify for a full–support service facility, all the following on-site support services must be available: cardiovascular surgery, cardiovascular anesthesia, mechanical circulatory support services, vascular services, endovascular surgery/interventions, intensive care unit, nephrology consultative service and dialysis, neurology consultation services, hematologic consultative and blood bank services, and advanced imaging services (echocardiography with Doppler, computed tomography [CT], magnetic resonance imaging [MRI]; **see Chapters 14, 17, and 18**).[3] If offered, similar services should be available for pediatric patients. Even though cardiovascular surgery is the critical differentiating service, the catheterization laboratory requires all the listed services to provide catheterization services to the full spectrum of case complexities.

Approximately one fourth to one third of catheterization laboratories do not have cardiovascular surgery backup.[3] One may argue that almost all diagnostic procedures that do not involve additional risks could be performed safely without any surgical backup. Indeed, given the favorable safety and quality reports over time, the 2012 ACC/SCAI cardiac catheterization laboratory standards document lifted several (historic) restrictions. Accordingly, the only patient groups not recommended to undergo diagnostic cardiac catheterization without cardiovascular surgery backup are those with pulmonary edema caused by ischemia, those with class 4 symptoms from severe valvular dysfunction with reduced ejection fraction, those with complex congenital heart disease, those with acute coronary syndromes unless percutaneous coronary intervention (PCI; **see Chapter 62**) is possible, and patients at risk of vascular complications unless vascular services are available.[3] Even among non–high-risk patients, complications may arise that require surgical intervention. Moreover, some advanced diagnostic procedures should be performed only by experienced operators who are capable of managing any possible complications. This pertains to transseptal puncture, fractional flow reserve (FFR; **see Chapters 57, 61, and 62**), intravascular ultrasound or optical coherence tomography, and any PCI procedure. Minimum requirements for the performance of invasive cardiovascular procedures in a setting without on-site cardiovascular surgical services are outlined in a SCAI expert consensus, which pertains mainly to the pursuit of PCI.[6] Freestanding and mobile cardiac catheterization facilities fall into this category as well. For obvious reasons, this service is only for properly selected low-risk patients.

With the advanced structural heart interventions now available, especially transcatheter aortic valve replacement (TAVR; **see Chapter 72**), there has been increasing interest in hybrid cardiac catheterization laboratories.[7] These laboratories combine high-resolution imaging with the standards and capabilities of the operating room (OR). In practice, either catheterization laboratory imaging elements will be integrated into the OR or catheterization laboratories will be expanded to accommodate the OR requirements. Thus, these rooms are typically larger than usual and are operated by a team trained in and comfortable with both aspects.

Cardiac Catheterization Equipment

The key elements of the cardiac catheterization laboratory are the control room, the anesthesia cart and vital signs monitoring system, the imaging system, the data-processing/archiving system, and the data review and report station.

Imaging Equipment.

Imaging is an essential component of the catheterization procedure. Although not required for access, it is necessary for maneuvering the catheter. X-ray imaging remains the standard even though alternatives have

been tested, such as MRI, especially in children. The standard high-resolution x-ray imaging system operates in two modes: fluoroscopy and cine mode (cinefluorographic system). It consists of an x-ray tube that generates x-rays from electrical power under control of an x-ray generator, and a flat-panel x-ray detector, which produces a digital video image. This image is then processed, displayed, and stored. A feedback circuitry from the digital video processor to the x-ray generator enables adaptation of the x-ray output to imaging demands.[8] The frame rate and energy output are the corresponding determinates for radiation exposure and can be set by the operator. Furthermore, modern imaging systems allow for fluoroscopy storage, image processing, and road mapping as a standard tool to reduce exposure. Iodine-based contrast material serves as a positive contrast for x-ray imaging. It is injected either manually by a free syringe or manifold or in an automated manner. The volume of the individual contrast administration is usually limited to 10 mL based on the syringes typically used; however, 20-mL syringes have been used. For larger volumes (e.g., for filling of cardiac chambers), power injectors have been used.

Radiation Safety.

As low as reasonably achievable (ALARA) radiation has become the governing principle for the use of radiation to reduce both deterministic and stochastic effects. Even applying this principle, the radiation dose for cardiac catheterization is in the range of 1 to 10 millisieverts, typically 3 to 5 mSv, which is equivalent to 2 to 3 years of natural background radiation.

Deterministic effects are dose related, increasing in severity with increasing dose, typically once a threshold is exceeded. Cataracts and hair loss are examples, but skin injury is the most common deterministic effect, ranging from skin erythema, which can develop in hours, to desquamation and skin necrosis, developing over days to weeks. A reference point for the dose at the patient's skin level has thus been defined, termed the *interventional reference point,* when isocentric interventional equipment is used, and is located 15 cm (6 inches) from the x-ray tube on the central axis of the x-ray beam.[8]

Stochastic effects such as neoplasms and genetic defects are related to probability and not dose, although the likelihood increases with increasing exposure. An approximation of the total x-ray energy delivered to the patient therefore serves as a measure of the risk for stochastic effects. This is expressed as the *dose-area product*, which is the absorbed dose to air (air kerma) multiplied by the cross-sectional area of the x-ray beam at the point of measurement.[8]

Best practices to minimize radiation exposure include minimization of fluoroscopic beam time, use of beam collimation, application of the least magnification possible, and optimal positioning of the x-ray tube-image receiver unit with avoidance of extreme angles and rotation of the radiographic projection during long procedures. The estimated patient dose is continuously recorded, and warnings can be issued when certain levels are reached. State regulations vary but may state that procedures with an air kerma of 6000 milligray (mGy) or higher require reporting to an institutional radiation safety committee with documented patient follow-up.[9]

Similarly, all laboratory personnel exposed to radiation are required to record their exposure. It is recommended that at least two film badges be worn: one on the outside of the apron at the neck and the other under the apron at the waist. The latter monitors the effectiveness of the lead apron. The maximum allowable whole-body radiation dose per year for those working with radiation is 5 roentgen-equivalents-man (rem = 50 mSv), or a maximum of 50 rem in a lifetime.[8] Exposure reduction is accomplished by maximizing the distance from the x-ray source and scatter using appropriate shielding, lead aprons, thyroid collars, lead eyeglasses, and movable leaded barriers. Avoiding severely angulated views decreases radiation exposure to the operator as well by reducing scatter. The highest-risk angulation in this regard is the left anterior oblique (LAO) projection.

Physiologic Monitors.
All patients are adequately prepared for continuous monitoring of vital signs, including cardiovascular and respiratory status. Respiratory rate and oxygen saturation are tracked continuously by peripheral pulse oximetry. Cardiac rhythm is likewise continuously monitored with a surface electrocardiogram (ECG), mostly the three Einthoven leads. Systemic blood pressure is measured in regular intervals of only a few minutes by an automated system using an upper arm cuff. Once access is obtained, blood pressure measurement is supplemented by the use of fluid-filled catheter-tubing system connected to strain gauge pressure transducers and transmitted to a monitor. Catheterization laboratories performing hemodynamic evaluations furthermore need analyzers to measure arterial blood gases (ABGs) and the coagulation status by activated clotting time (ACT).

Accreditation

To gain proficiency in catheterization, the Accreditation Council for Graduate Medical Education set the requirements for level 1 at a minimum of 100 procedures over 4 months and for level 2 at 200 procedures over 8 months. For level 3, interventional catheterization, a total of 250 procedures over 20 months is required.

Thereafter, for proficiency to be maintained, cardiac catheterization laboratories for adults should perform a minimum of 300 procedures per year. The minimum volume for practicing physicians, however, has not been established. This is in distinction from PCI, even though a shift in focus has occurred toward quality. Regular quality assessments are recommended, and publically available outcome reports are now available. The laboratory director should have at least 5 years of catheterization experience and should be board-certified in interventional cardiology if PCIs are performed. The director is responsible for credentialing of physicians; review of laboratory, physician, and ancillary personnel performance; and provision of necessary training.

Catheterization Laboratory Protocol

Preprocedural Preparation of Patient

Every cardiac catheterization procedure needs to be properly planned. It begins with the referring physician, who should consider identifying the right patient for the right procedure, which is to be performed in the right manner for the right outcome.[4] AUC are in place to guide this process, and in general, the lower the level of appropriateness rating, the more documentation needs to be provided justifying the procedure. The benefits of the procedure relative to its risks need to be clearly explained. This equation varies by type of procedure and clinical status of the patient. In general, the risk of major complications and mortality related to cardiac catheterization is less than 0.5% and 0.08%, respectively (**Table 19.1**). For this reason, it is thought that the procedure can be performed with a relatively low risk even in the most critically ill patient. Most contraindications are currently viewed as “relative” (**Table 19.2**), except for inadequate equipment or catheterization facility. As outlined in the 1999 ACC/AHA coronary angiography guidelines, it is also a contraindication to perform a catheterization in patients who would not want further actions to be taken or in patients in whom nothing is to be gained in terms of management decisions, quality of life, or life expectancy. Accordingly, it is important to outline not only the potential risks and complications but also the potential benefits. Patients are ready to dismiss misconceptions once the correct information is provided with important implications for their choice of modes of therapy.[10] Shared decision making has thus been emphasized in the most current guidelines for

the management of patients with stable ischemic heart disease and remains an important principle in general.[11] Informed consent needs to be documented, as does code status and potential advance directives.

TABLE 19.1

Diagnostic Catheterization-Related Complications in Patients Without ST-Elevation Myocardial Infarction*

COMPLICATION	%
Any adverse event	1.35
Cardiogenic shock	0.24
Heart failure	0.38
Pericardial tamponade	0.03
Stroke (% of total hemorrhagic)	0.17 (9.16)
New requirement for dialysis	0.14
Non–risk adjusted in-hospital mortality	0.72
Non–risk adjusted in-hospital mortality, excluding CABG patients	0.60
CABG performed during admission	7.47
Salvage/emergency CABG	0.01/0.27
Urgent/elective CABG	5.27/1.92
Any bleeding event within 72 hours of the procedure	0.49
Any other vascular complication requiring treatment	0.15

*N = 1,091,557.

CABG, Coronary artery bypass graft surgery.

Modified from Dehmer Get al. A contemporary view of diagnostic cardiac catheterization and percutaneous coronary intervention in the United States. J Am Coll Cardiol 2012;60:2017.

TABLE 19.2

Relative Contraindications to Diagnostic Cardiac Catheterization

- Acute gastrointestinal bleeding
- Severe hypokalemia
- Uncorrected digoxin toxicity
- Anticoagulation with INR >1.8 or severe coagulopathy
- Previous anaphylactoid reaction to contrast media
- Acute stroke
- Acute renal failure or severe chronic non–dialysis-dependent kidney disease
- Unexplained fever or untreated active infection
- Severe anemia
- Recent cerebrovascular event (<1 month)
- Uncooperative patient
- Pregnancy

From Davidson CJ, Bonow RO. Cardiac catheterization. In Mann DL et al, editors. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed. Philadelphia: Elsevier; 2012.

Once an appropriate shared decision has been made, the preprocedural evaluation should confirm or dismiss any relative contraindications and prepare the patient and the team. Vital elements are history of present illness (chief complaint/health issue to be addressed in the current care session of the patient) and past medical history, with particular emphasis of prior cardiac and vascular events and procedures. Comorbidities such as diabetes mellitus, chronic kidney disease, liver disease, hematologic diseases (e.g., heparin-induced thrombocytopenia), and infectious diseases (e.g., HIV, hepatitis) need to be recorded as well as the related medications. Any prior allergic reactions to drugs, latex, or contrast material need to be reviewed, as well as any prior problems with anesthesia. The physical examination should document heart, lung, and vascular access status as well as the volume and neurologic status. Laboratory tests should include complete blood count with platelets, serum electrolyte determinations with creatinine, and estimated glomerular filtration rate (eGFR). A time frame of 2 to 4 weeks of the procedure is sufficient unless a change in clinical status has occurred. Prothrombin time (PT) with

international normalized ratio (INR) is now recommended only for patients receiving warfarin or with hepatic or hematologic disease, and a partial thromboplastin time (PTT) for those receiving heparin. Women of childbearing age should have a pregnancy test. A 12-lead ECG is recommended.

Patients in atrial fibrillation receiving anticoagulation need to be advised to discontinue warfarin approximately 3 days before the procedure. The INR should be less than 1.8 for a femoral approach and less than 2.2 for a radial approach to minimize risk for bleeding.[3] The direct thrombin inhibitor dabigatran should be discontinued 24 hours before catheterization in those with eGFR of 80 mL/min or greater, 36 hours if eGFR is 50 to 79 L/min, and 48 hours if 30 to 49 mL/min. If PCI is likely to be performed (in addition to diagnostic catheterization), these timelines should be extended by a factor of 2. Direct Xa inhibitors (rivaroxaban, apixaban, or edoxaban) should be discontinued 24 hours before the procedure if the eGFR is 30 mL/min or higher, otherwise at least 36 hours. In case PCI is a possibility, the timeline for discontinuation is at least 48 hours. Aspirin and other oral antiplatelet agents are continued before the procedure. Patients taking metformin should hold the medication the morning of the procedure and not resume until renal function is stable for at least 48 hours after the procedure.[3]

All patients but especially those with diabetes and chronic kidney disease (CKD) should receive periprocedural hydration to reduce the risk of contrast-induced nephropathy (CIN). It is a class I indication to estimate the risk of CIN in patients who may undergo PCI, and validated risk calculators are available.[12] Diabetes mellitus and baseline renal function impairment are the strongest patient-related risk factors (**see Chapters 51 and 98**). No intervention other than fluid volume has been shown to be effective, but the definite amount depends on baseline fluid status and cardiac function. If tolerated, a total of 1 liter of normal saline should be administered from start to completion of the procedure. It is also important to perform biplane angiography and to limit the amount of contrast material (as a general rule, <3.7 times eGFR).[3]

Patients with a history of anaphylactoid reaction to contrast (angioedema, flushing, pruritus, urticaria, bronchospasm, arrhythmia, shock) or atopic conditions are at highest risk for acute hypersensitivity reactions to contrast and should be adequately prepared to avoid this complication, even though this is less common with arterial than with venous contrast administration.[3] The most common premedication regimens are 60 mg of prednisone the night before and the morning of the procedure; 50 mg of prednisone 12 hours, 7 hours, and 1 hour before the procedure; 100 mg of hydrocortisone 12 hours and immediately before the procedure; or 200 mg of hydrocortisone 2 hours before the procedure. Cimetidine (300 mg by intravenous push or by mouth), a nonselective histamine antagonist, and diphenhydramine (25 to 50 mg by IV push) may also be given just before the procedure. Patients with medication and food allergies might have a predisposition, but they are usually not premedicated, and no special preparation is required for those with a shellfish allergy. In addition to acute reactions, it is important to be aware of possible delayed hypersensitivity reactions, presenting with fever and rash up to 48 hours after the procedure. Acute hemodynamic and electrophysiologic complications during the catheterization are less common with the current use of low- and iso-osmolar contrast material.

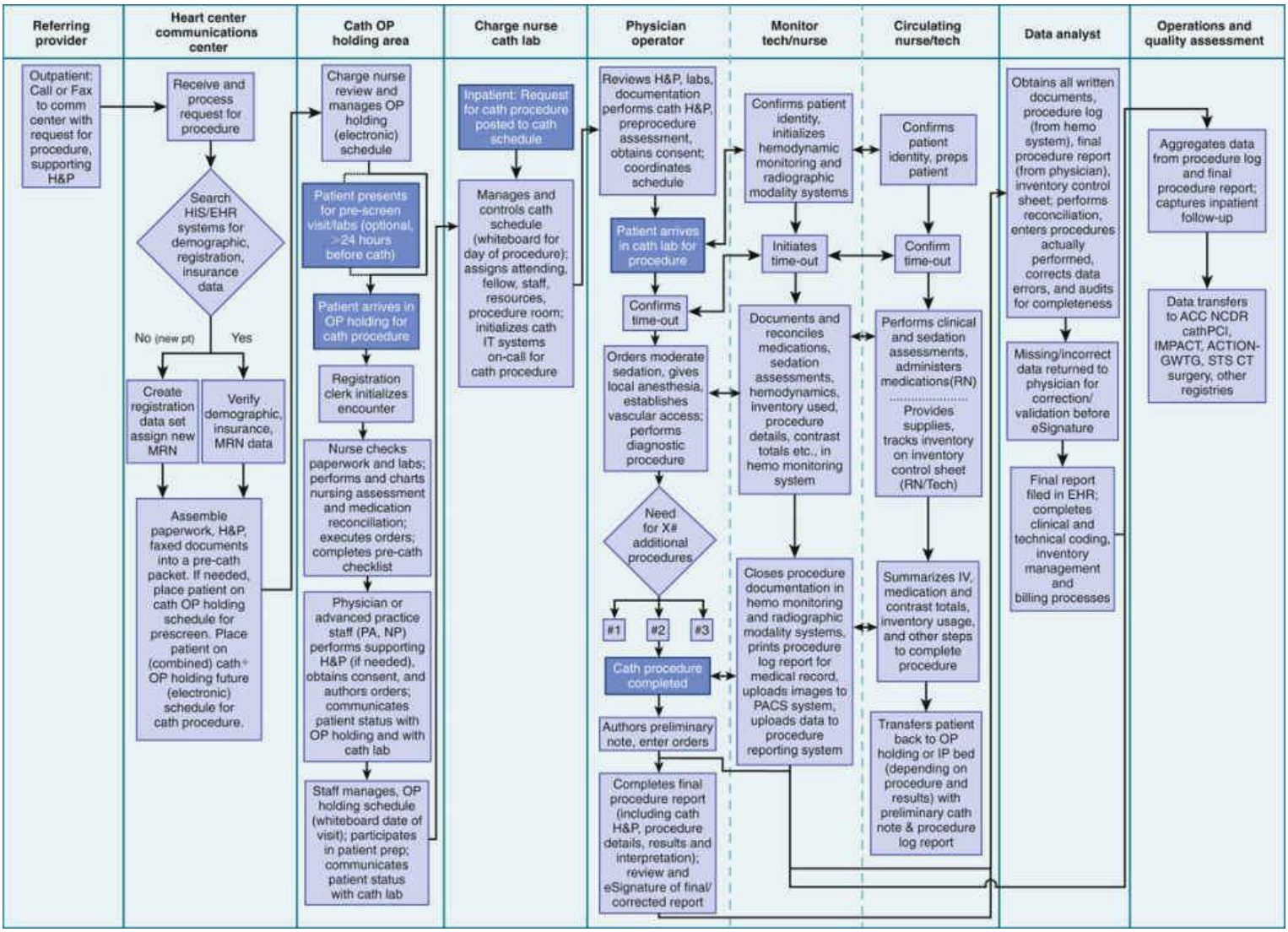
Although some institutions have opted away from a strict fasting policy, it is still recommendable to have patients fast before the procedure: no liquids up to 2 hours before and no solid food up to 6 hours before the procedure.[3] The fasting status and vital status are assessed in the cath lab preparation area along with a number of other parameters. IV access for hydration and drug administration is placed as well as ECG telemetry and pulse oximetry.

In contrast to its early beginnings, cardiac catheterization is no longer tied to hospitalization, and the vast majority of cases are performed as (hospital-based) outpatient practice. Patient groups that may benefit from preprocedural hospitalization for preparation for diagnostic catheterization include those

with severe congestive heart failure, those with stage 4 CKD requiring additional preprocedural hydration, and those receiving oral anticoagulation who need to but cannot be bridged by low-molecular-weight heparin (e.g., mechanical heart valve patients).

Intraprocedural Care

Only patients who are fully ready should be transferred to the catheterization laboratory; **eFig. 19.1** provides a sequence algorithm.[13] Once all monitoring is in place, the patient is draped in a sterile manner, and with all team members present, a procedural briefing should be performed. This should include the patient's name and medical record number, the procedure to be performed, the need and availability of necessary equipment, patient's allergies and premedications, renal and anticoagulation status, antiplatelet therapy status if intervention might become a consideration, and signed informed consent. Some institutions have also started to document the AUC preprocedurally. Comprehensive preprocedural checklists have also been used and are recommendable to maintain a uniform standard.[5]



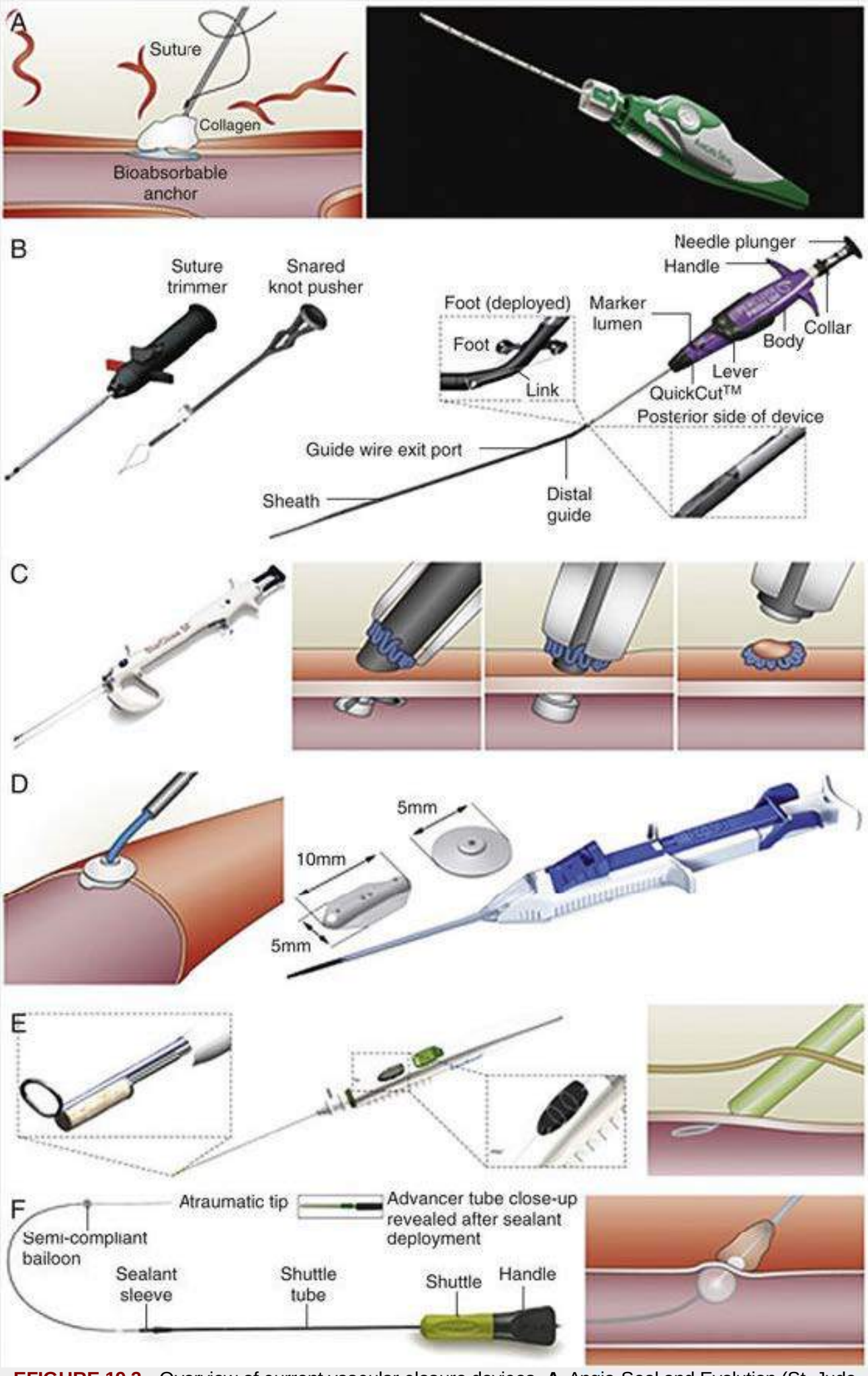
EFIGURE 19.1 Sequence diagram for cardiovascular catheterization procedures. ACC NCDR, American College of Cardiology National Cardiovascular Data Registry; ACTION-GWTG, Acute Coronary Treatment and Intervention Outcomes Network–Get with the Guidelines (registry); Cath Lab, catheterization laboratory; CathPCI, Cardiac Catheterization and Percutaneous Coronary Intervention (registry); H&P, history and physical; Hemo, hemodynamic; HER, electronic health record; HIS, hospital information system; IMPACT, Improving Pediatric and Adult Congenital Treatment (registry); IP, inpatient; IT, information technology; IV, intravenous; MRN, medical record number; NP, nurse practitioner; OP, outpatient; PA, physician assistant; PACS, picture archiving and communication system; RN, registered nurse; STS CT Surgery, Society of Thoracic Surgeons Cardiothoracic Surgery (registry); Tech, technologist. (From ACC/AHA/SCAI 2014 health policy statement on structured reporting for the cardiac catheterization laboratory: a report of the American College of Cardiology Clinical Quality Committee. J Am Coll Cardiol 2014;63:2591.)

If a hemodynamic catheterization is requested, this should be done before any contrast exposure, which could otherwise influence measurements given its vasoreactive properties. Similarly, one may obtain radial access but should avoid further manipulation and need for vasodilatory drugs until all hemodynamic measurements are complete. Leg elevation is another variable to consider, sometimes done to facilitate internal jugular venous access. Depending on the clinical presentation, the outlined sequence may change, as in patients with ST-segment elevation myocardial infarction (STEMI) or in cardiogenic shock; coronary angiography and intervention should be performed first, and any additional hemodynamic catheterization as needed thereafter.

Postprocedural Care

After completion of the procedure, the patient is transferred to a monitored bed and the postcare area. If only a diagnostic cardiac catheterization was performed, most patients can be discharged within 2 to 6 hours after the procedure unless some high-risk features are present, complications occurred, or supportive care is needed such as hydration or anticoagulation. In some instances, patients may also transfer directly to hospital services, such as those with heart failure and Swan-Ganz catheter placement for invasive monitoring. Any catheters other than those for hemodynamic monitoring are removed before the patient leaves the laboratory. The same applies to radial access sheaths, using an inflatable wristband for hemostasis and a deflation protocol thereafter. With femoral access, either a vascular closure device or manual compression is used. The latter is most often done in the postprocedural area. Firm pressure is applied approximately 2.5 to 5 cm (1 to 2 inches) above the skin incision point for 10 minutes, followed by bed rest for 2 hours in case of 4F-6F sheaths and 3 to 4 hours for sheaths greater than 6F. Venous sheaths are removed either in the catheterization laboratory or in the postprocedural area and require approximately 5 to 10 minutes of firm compression.

Vascular closure devices may be of benefit for patients who do not tolerate long periods of bed rest after femoral arterial access or those receiving anticoagulation (**eFig. 19.2**). These devices have not proved superior to manual compression in general, and may in fact be inferior in multiple vascular access attempts.[14] Vascular closure devices do play an important role in cases of large-bore access, which have become relatively common now in the era of TAVR with sheath sizes of 18F to 24F.



EFIGURE 19.2 Overview of current vascular closure devices. **A,** Angio-Seal and Evolution (St. Jude

Medical). **B,** Perclose Proglide (Abbot Vascular). **C,** Starclose (Abbot Vascular). **D,** FemoSeal (St. Jude Medical). **E,** Exoseal (Cordis EMEA). **F,** Mynx (AccessClosure). (From Byrne RA et al. Vascular access and closure in coronary angiography and percutaneous intervention. Nat Rev Cardiol 2013;10:27.)

Bleeding remains the most common complication and reason for postprocedural hospitalization. A distinction is made between access site and non–access site bleeds. The latter type can reflect underlying comorbidity unmasked by the anticoagulation and antiplatelet therapy of the procedure (e.g., peptic ulcer disease) or a complication of the procedure (e.g., pericardial bleed). Importantly, although often not as apparent initially, non–access site bleeds are often more relevant in terms of prognosis.[15] The anatomic location and severity of the bleed are important determinants of overall outcome. While more common after therapeutic than diagnostic catheterization, vigilance in terms of prevention, recognition, and management is still mandatory.

Access-site bleeds can present as minor oozing, more brisk bleeding, ecchymosis, or hematoma formation. The latter is considered a major vascular complication and is captured as a quality metric in registries such as the CathPCI registry of the ACC. Local hematoma larger than 5 cm, although likewise more common after PCI, are still noted in about 1 in 20 patients after diagnostic catheterization.[16,17] As a preventive effort, all sheaths should be removed as soon as possible, in case of anticoagulation with heparin once the activated clotting time is below 160 to 180 seconds and after 2 hours in case of bivalirudin and normal renal function. Protocols for sheath removal and after care should be in place, including distal extremity and blood pressure evaluation.

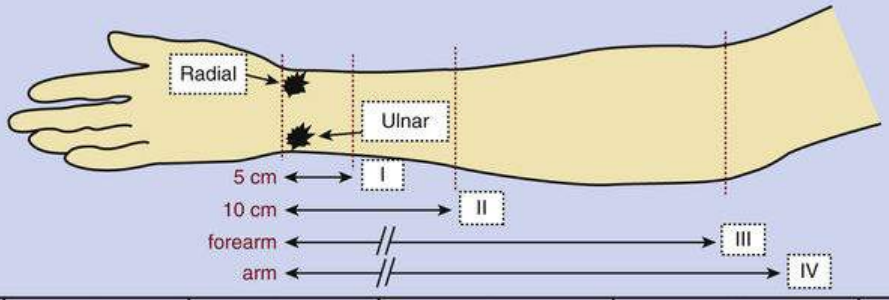
Other major vascular complications include retroperitoneal bleeding, pseudoaneurysm, arteriovenous fistula formation, and occlusion requiring arterial repair or thrombectomy, as well as infection. The incidence of major vascular complications combined is approximately 0.20% in the current era.[18] Related to the shift from the femoral to the radial access route, these complications have become less common with PCI but remain of concern with femoral access for structural cases. Historically, the rate of retroperitoneal hematoma was as high as 6%, whereas more recently it is 0.5%. Female gender, lower body mass index, and higher femoral arterial puncture site (above the upper third of femoral head) are the main risk factors. A retroperitoneal hematoma should be suspected in patients with unexplained hypotension and tachycardia, the latter being a distinguishing feature from vagal reactions, even though bradycardia may occur as well. In decreasing order, the most common presenting symptoms of retroperitoneal hematoma are hypotension (92%), diaphoresis (58%), groin pain (46%), abdominal pain (42%), back pain (23%), and bradycardia (31%). Some patients present with urinary or bowel urgency, peritoneal signs/irritation, and/or femoral neuropathy.[19] A hemoglobin drop on serial complete blood counts usually lags behind, and the interpretation may be confounded by the administration of fluid (and sometimes other blood losses) during the procedure. Thus, CT of the pelvis and abdomen should be performed as clinical suspicion demands. Thereafter, or even as a first step, an angiographic approach might be taken to visualize the vascular injury site and either aim to occlude it percutaneously or direct toward surgery. The risk of surgical repair is higher in patients of advanced age, with congestive heart failure, or a larger body surface area.

Ultrasound is the test of choice with concern for vascular complications more local to the access site, such as pseudoaneurysms. These communications between the artery and the overlying fibromuscular tissue result in a blood-filled cavity. They are classically seen with a low or lateral femoral artery puncture, excessive anticoagulation at the time of sheath removal, or inadequate compression of the puncture (access) site. The acceptable incidence is less than 0.2%, but studies have indicated an incidence as high as 3%.[20] The typical presentation is groin tenderness, a palpable pulsatile mass, and a systolic bruit. Sizes less than 2 cm represent a low likelihood of rupture and may be followed clinically

with serial ultrasound to document spontaneous thrombosis. For pseudoaneurysms larger than 2 cm in size, ultrasound-guided manual compression with or without thrombin or collagen injection is the treatment of choice. Covered stent placement or surgery are rarely required.

Arteriovenous (AV) fistulas have been reported to occur at an incidence of 0.25% to 1%, likewise more common with low femoral accesses (i.e., below the femoral head). Pain, swelling, and bruit are signs and symptoms similar to pseudoaneurysms, and ultrasound is again diagnostic. Most fistulas are very small and go undetected. Intervention is required only if significant shunting occurs (stent graft or vascular surgery).

After radial artery catheterization, vascular complication and access-related bleeding can be more subtle, and unnoticed and untreated hematoma can progress to the point of forearm compartment syndrome. Pain and paresthesia should serve as warning signs, and protocols for easy recognition and management have been developed (**eFig. 19.3**). Adequate hemostasis is important, but it is also critical to maintain patency of the radial artery, especially at sheath removal and shortly thereafter. Compression of the ipsilateral ulnar artery limited to this acute phase has sufficed to reduce radial artery occlusion.[21] Additional administration of vasodilators and adequate anticoagulation are important interventions. Otherwise, radial artery occlusion rates can be as high as 15% acutely and 3% to 5% chronically.



GRADE	I	II	III	IV	V
INCIDENCE	≤5%	<3%	<2%	≤0.1%	<0.01%
DEFINITION	Local hematoma, superficial	Hematoma with moderate muscular infiltration	Forearm hematoma and muscular infiltration, below the elbow	Hematoma and muscular infiltration extending above the elbow	Ischemic threat (compartment syndrome)
TREATMENT	Analgesia Additional bracelet Local ice	Analgesia Additional bracelet Local ice	Analgesia Additional bracelet Local ice Inflated BP cuff	Analgesia Additional bracelet, Local ice Inflated BP cuff	Consider surgery
NOTES		Inform physician	Inform physician	Inform physician	STAT call to physician
REMARKS	- Control blood pressure (BP) (importance of pain management) - Consider interruption of any anticoagulation and/or antiplatelet infusion - Follow forearm and arm diameters to evaluate requirement for additional bracelet and/or BP cuff inflation - Additional bracelet(s) can be placed alongside artery anatomy - Ice cubes in a plastic bag or washcloth are placed on the hematoma - Finger O_2 saturation can be monitored during inflated blood pressure cuff - To inflate blood pressure cuff, select a pressure of 20 mm Hg < systolic pressure and deflate every 15 minutes - After bracelet removal, use "Velpeau bandage" around forearm/arm for a few hours to maintain mild positive pressure				

EFIGURE 19.3 EASY trial hematoma grading scale with corresponding treatment strategies. (From Rao SV, Bernat I, Bertrand OF. Clinical update: remaining challenges and opportunities for improvement in percutaneous transradial coronary procedures. Eur Heart J 2012;33:2521-6.)

Overall, minor complications occur in approximately 1 in 25 patients undergoing routine cardiac catheterization, with the most common being transient hypotension and brief episodes of chest discomfort. The differential diagnostic considerations for hypotension, besides vasovagal reactions and severe (retroperitoneal) bleeds, should also include a contrast reaction, even though other manifestations should be present. Hives are less common with low-osmolar contrast agents and intra-arterial

administration; anaphylactoid reactions are very rare. IV corticosteroid and diphenhydramine are the main agents. Epinephrine is reserved for severe reactions, such as anaphylactic shock. Patients with severe allergic reactions and anaphylaxis should be observed at least overnight.

In patients with chest pain, the differential diagnosis is broad. If coronary angiography was performed, a dissection should be ruled out as well as embolization, especially if the aortic valve was crossed. The risk of myocardial infarction is 0.05%.[18,22]

If a right-heart catheterization was performed, the differential should include pulmonary embolism, pulmonary infarction, and pulmonary artery or right ventricular (RV) perforation. The most common complications of right-heart catheterization, however, are minor, nonsustained atrial or ventricular arrhythmias. Any patient with chest pain should have a 12-lead ECG, and those with significant changes, especially ST-segment elevation and after coronary angiography, should be taken back to the catheterization laboratory.

The risk of neurologic complications is 0.03% to 0.2%.[18,22] Those with severe aortic atherosclerosis and aortic stenosis are at higher embolic risk. After retrograde crossing of a stenotic aortic valve, neurologic deficits may be clinically apparent in as many as 3% of patients, and the incidence of focal acute cerebral embolic events may be as high as 22% by MRI.[23] Neurologic deficits can be noted at the time of or within a few hours after the procedure, and it is not clear whether the mechanisms differ by time of presentation.[24] The length of the procedure, volume of contrast material, urgent indications, and use of intra-aortic balloon pumps (IABPs) are known to increase the risk for stroke. Patient-related risk factors include diabetes mellitus, hypertension, previous stroke, and renal failure.[25] *Transient cortical blindness* needs to be distinguished from true stroke events. It is characterized by loss of perceived vision in conjunction with a normal neurologic examination occurring from minutes to 12 hours after angiography. Headaches, memory loss, and mental status changes can be present. Resolution begins within a few hours but it may take days to fully return to normal.[26] Furthermore, strokes should be distinguished from other conditions, including seizure, migraine, hypoglycemia, and encephalopathy. Standard stroke management with a multidisciplinary team is important to improve prognosis.

Death related to diagnostic cardiac catheterization is rare (0.08% to 0.75%) and mainly predicted by the clinical presentation. The strongest predictors are heart failure (especially advanced stages), hypotension and shock, acute coronary syndrome, severe aortic or mitral valve disease, renal failure, and moribund state. Patients with these conditions, especially in their complicated stage, are often referred to the cardiac catheterization laboratory as part of their hospital care. Other patient groups, such as those with critical coronary artery disease (e.g., severe left main stenosis), may need to be admitted to the hospital in response to the diagnostic findings for further management planning.

Technical Aspects and Procedural Performance

Arterial Access

Percutaneous Femoral Artery Technique

The standard access for many years has been the common femoral artery (CFA), also known as the Judkins technique. Familiarity with the anatomy is important, and the point of entry is 1 to 3 cm (1 to 2 fingerbreadths) below the inguinal ligament, in line with the palpable course of the CFA (**Fig. 19.2**). The inguinal crease can be misleading in obese as well as very thin individuals. In clinical practice the optimal point of skin entry over the inferior edge of the femoral head is therefore often identified under

fluoroscopy using a hemostatic clamp. Alternatively, ultrasound can be used to define the anatomy (**eFig. 19.4**). Ultrasound has been shown to improve first-pass success rates, reduce vascular complications in general, and might be useful particularly in patients with a diffuse pulse caused by scarring after multiple prior procedures.[27] The critical importance of the right location cannot be overemphasized, because too high of a location increases the risk of retroperitoneal hematoma, and too low increases the risk of pseudoaneurysm, AV fistula formation, and cannulation of the superficial femoral artery with sizes too small to accommodate any larger-sized sheaths or vascular closure devices. Further, a position off the femoral head does not leave an optimally firm backboard for hemostatic compression.

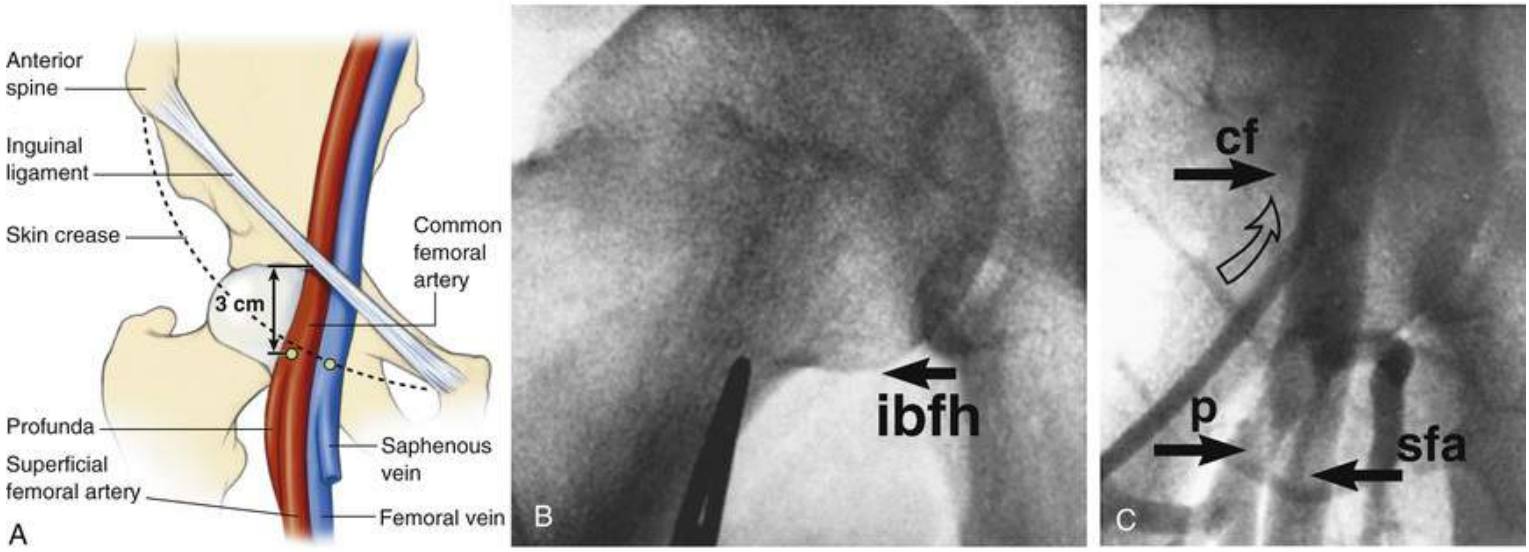
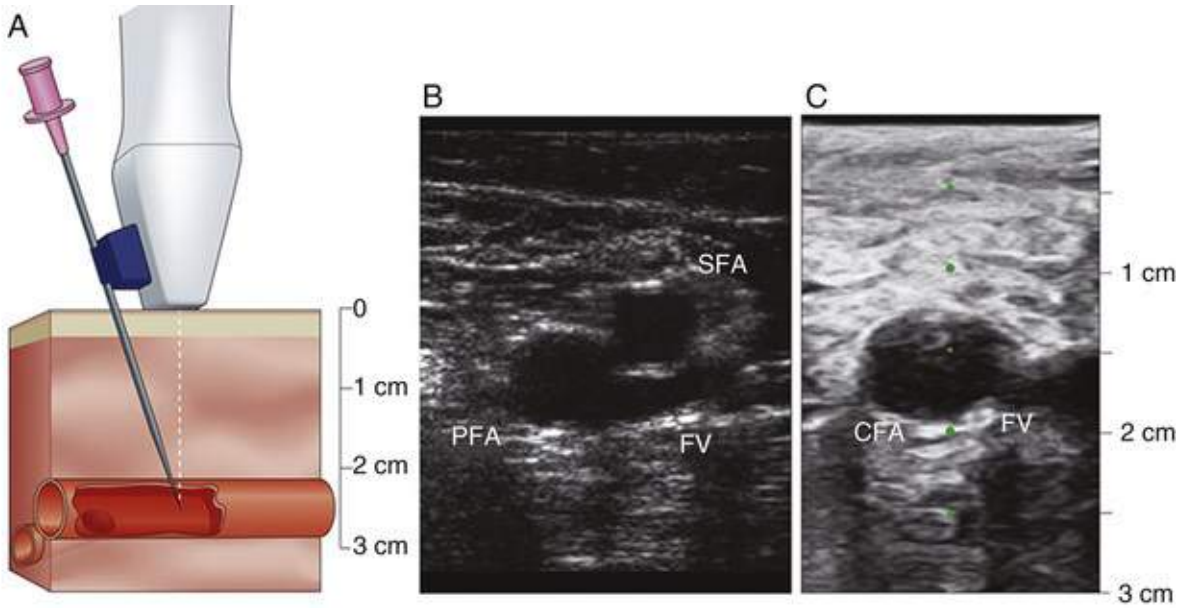


FIGURE 19.2 **A,** Schematic diagram showing the femoral artery and vein anatomy. The arterial skin nick should be placed approximately 3 cm below the inguinal ligament and directly over the femoral arterial pulsation; the venous skin nick should be placed at the same or lower level but approximately one fingerbreadth more medially. **B,** Localization of the skin nick by fluoroscopy and use of a hemostat, the top of which should point to the inferior border of the femoral head (*ibfh*). **C,** Catheter insertion (*open arrow*) into the common femoral artery (*cf*), above the bifurcation into the superficial femoral artery (*sfa*) and profunda (*p*) branches. (From Baim DS, Grossman W. Percutaneous approach, including transseptal and apical puncture. In Baim DS, Grossman W, editors. Cardiac Catheterization, Angiography, and Intervention. 7th ed. Philadelphia: Lea & Febiger; 2006, p 81.)



EFIGURE 19.4 Ultrasound-guided femoral artery access. **A,** The attached needle guide fixes the needle's angle of entry to intersect the vessel at the imaging plane 1.5 cm, 2.5 cm, or 3.5 cm below the skin, depending on the guide chosen. The vessel bifurcation is kept inferior to the probe at the time of insertion. **B,** The right femoral artery bifurcation is imaged in the axial plane, identifying the separation of the profunda femoral artery (*PFA*) and superficial femoral artery (SFA). Compression is used to differentiate arteries from the femoral vein (*FV*). **C,** The probe is moved superiorly until the common femoral artery (*CFA*) is visualized. During needle advancement, the anterior wall of the vessel is kept under the central target line, which indicates the path of the needle. (From Seto A et al. Real-time ultrasound guidance facilitates femoral arterial access and reduces vascular complications: FAUST (Femoral Artery Access with Ultrasound Trial). JACC Cardiovasc Interv 2010;3:751.)

Once conscious sedation and local anesthesia with 1% lidocaine (Xylocaine) are accomplished, a small transverse skin incision is made, and using the modified Seldinger technique (**Fig. 19.3**), an 18-gauge thin-walled needle is inserted at a 30- to 45-degree angle into the CFA. The backflow of blood should be solid and pulsatile; if not, one should suspect that the needle is either not freely or not at all in the lumen of the CFA. Once in the correct position, a 0.035- or 0.038-inch J-tip polytetrafluoroethylene (Teflon)–coated guidewire is advanced through the needle into the artery. The wire should pass freely, and if not, and particularly if the patient expresses any pain, the location of the wire needs to be defined carefully. Symptoms usually indicate vascular trauma such as dissections or perforations, which should be recognized immediately. Thus, while the advantages of the Judkins technique are the relative ease, speed, and reliability, experience and vigilance are still required to ensure quality and safety.

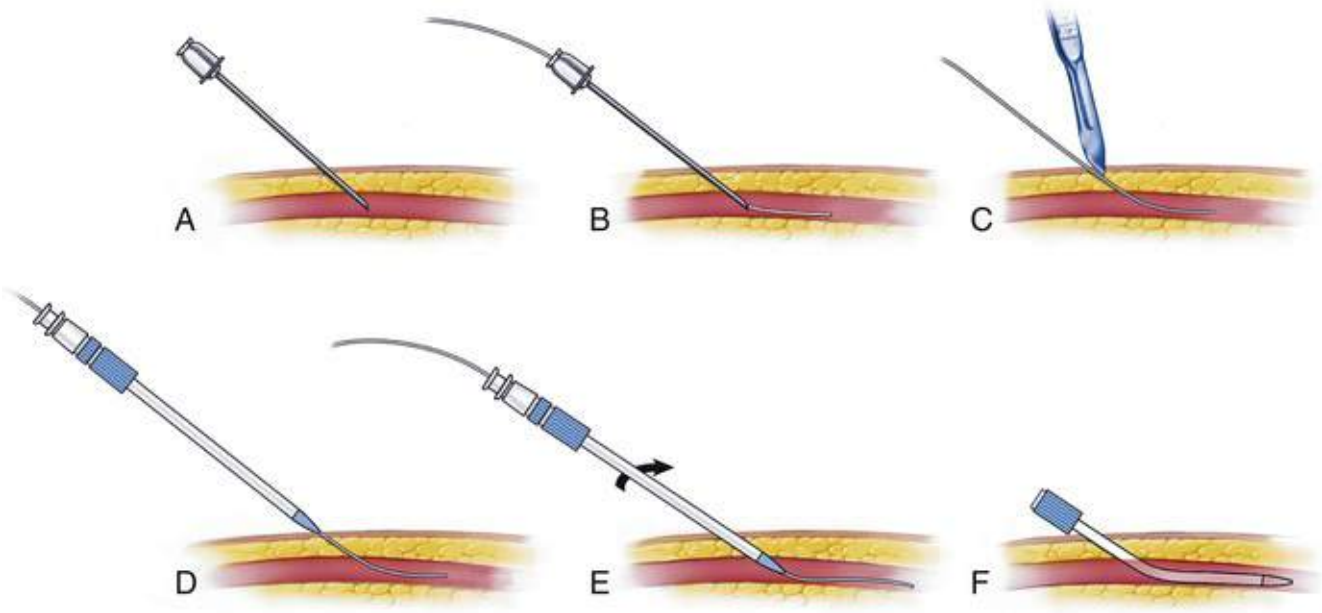


FIGURE 19.3 Modified Seldinger technique for percutaneous introduction of the catheter sheath. **A,** Vessel punctured by the needle. **B,** Flexible guidewire placed into the vessel through the needle. **C,** Needle removed, guidewire left in place, and hole in skin around wire enlarged with a scalpel. **D,** Sheath and dilator placed over guidewire. **E,** Sheath and dilator advanced over guidewire and into the vessel. **F,** Dilator and guidewire removed while sheath remains in the vessel. (From Hill JA, Lambert CR, Vlietstra RE, Pepine CJ. Review of general catheterization techniques. In Pepine CJ, Hill JA, Lambert CR, editors. Diagnostic and Therapeutic Cardiac Catheterization. 3rd ed. Baltimore: Williams & Wilkins; 1998, p 107.)

The femoral artery technique is disadvantageous for patients unable to endure long bed rest times, those with high bleeding risk, and those with peripheral artery disease (PAD). Patients with bleeding risk and PAD require careful assessment to ascertain that distal limb perfusion is adequate still during sheath placement and even once catheters are advanced, because some stenoses can be of a critical degree. Even if not of critical degree, iliofemoral stenoses may pose challenges to the retrograde passage of catheters, as does tortuosity. In fact, it might become necessary to opt early for a long sheath (>20 cm) to overcome tortuosity because it opposes catheter manipulation and can be of such a degree that the approach needs to be aborted as friction eliminates torquability, kinks compress the lumen, or length does not suffice. Any long sheath needs to be carefully placed under fluoroscopy. Similarly under careful fluoroscopic guidance, torquable floppy-tipped wires (e.g., Glidewire) may need to be used to advance to the aorta. A Judkins right or multipurpose catheter can be used to provide support, kept within short distance from the guidewire tip. On occasion, an extrastiff Amplatz-type guidewire is needed but may cause discomfort due to vessel folding and kinking. Long exchange-length wires are recommended in these difficult cases for any subsequent catheter exchanges. The dwell time of any wire should be kept to 2 to 3 minutes in consideration of the risk of thrombus formation (despite anticoagulation).

The sheath size should be at least equal to the catheter size used. Unfractionated heparin is no longer routinely given for diagnostic cardiac catheterization; however, for those with anticipated prolonged procedures, 2000 to 3000 units may be administered by IV push. In patients arriving on heparin, an ACT should be obtained after access and any further anticoagulation directed accordingly. Even though often mentioned, routine administration of protamine after the procedure to reverse the effect of heparin is not recommended. Hypotensive reactions can occur, especially in patients with diabetes and insulin use. Femoral sheaths should not be removed until the ACT is less than 160 to 180 seconds, unless a vascular closure device is being used.

Patients with a history of PAD require particular attention to history and physical examination. Before the procedure, one should carefully review what types of interventions were performed in the past (e.g.,

balloon angioplasty, patch endarterectomy, arterial conduits, prosthetic grafts). The anatomy should be defined, and additional mapping might become necessary. Suitability at the access point as well as patency to accommodate the equipment proximally is important. Prosthetic peripheral vascular grafts are likely the most problematic, not necessarily because they cannot be penetrated, but rather because of the aftercare to avoid lack of closure as well as thrombotic occlusion. For this reason, these grafts are usually avoided unless no other option is available, in which case the smallest possible access is taken and the procedural extent minimized. Complications arising from femoral access are outlined in the postprocedural care section.

Percutaneous Radial Artery Technique

Radial access has gained popularity in recent years as associated with a lower risk of bleeding and the ease on the patient postprocedurally. Documentation of adequate dual blood supply to the hand by either the Allen or the Barbeau test is recommended. The Allen test entails manual compression of the radial and the ulnar artery during fist clenching until blanching of the hand, at which point the pressure over the ulnar artery is released. Under normal conditions, normal color returns within 10 seconds, and significant reactive hyperemia is absent on release of pressure over the radial artery. The Barbeau test is performed similarly, only with the use of pulse oximetry; it has higher accuracy and reproducibility[28] (**Fig. 19.4**).

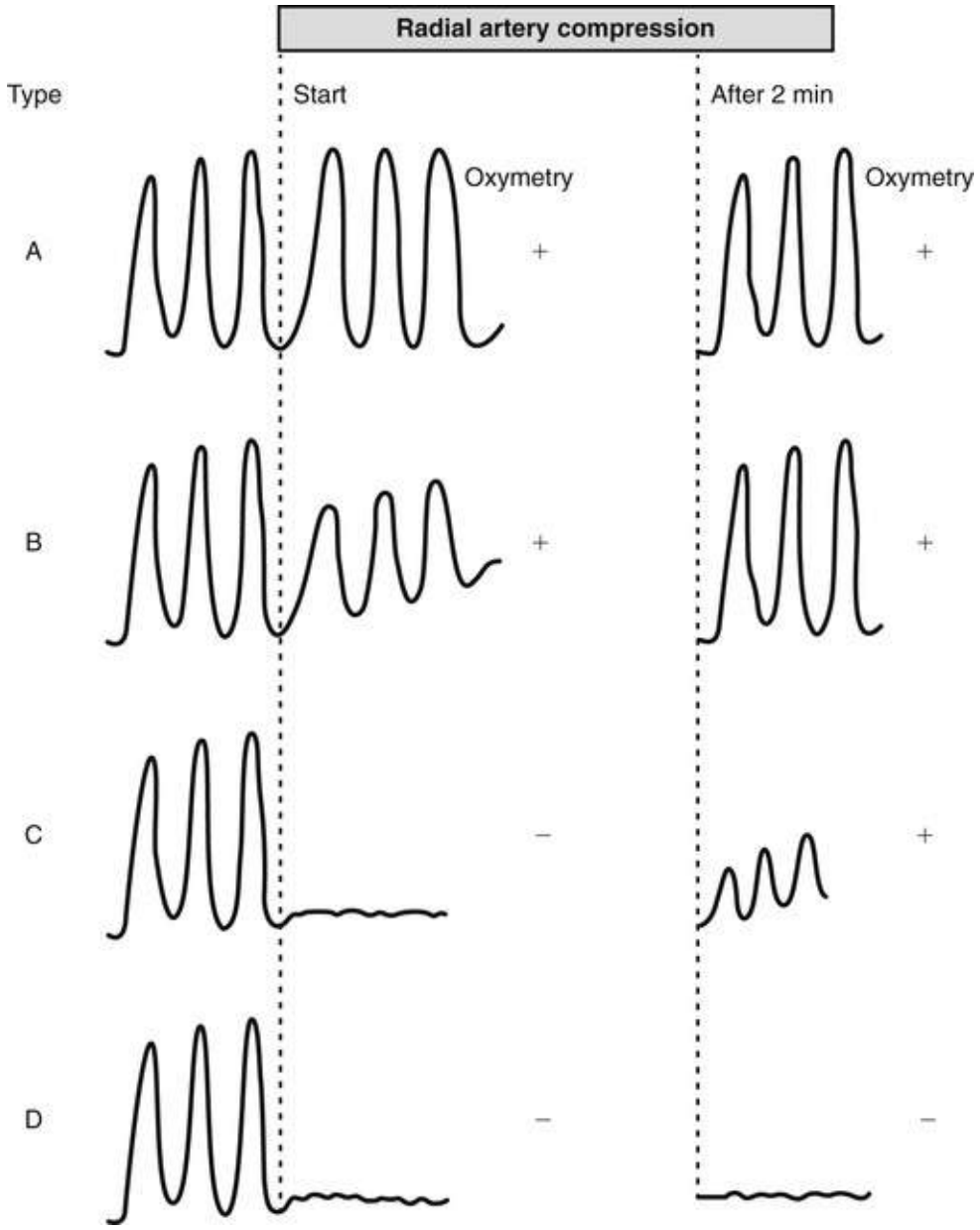
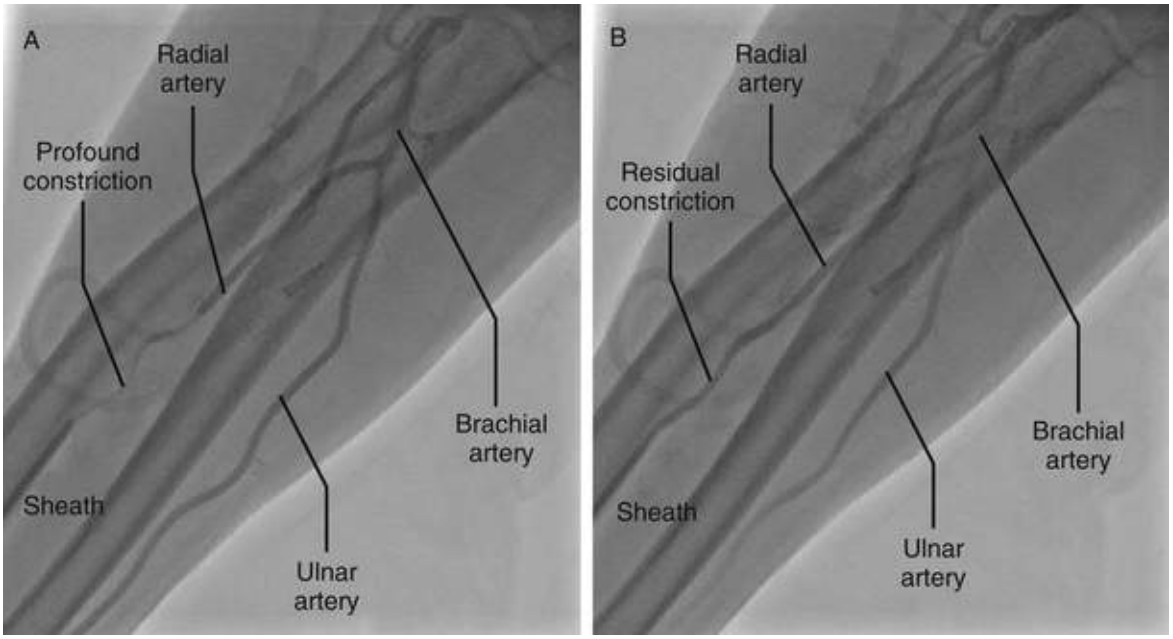


FIGURE 19.4 Four types of ulnopalmar arch patency findings based on plethysmography and oximetry, as recorded with the finger clamp applied on the thumb. Patients with a type **D** response should not undergo transradial catheterization of that wrist. (From Barbeau GR, Arsenault F, Dugas L, et al. Evaluation of the ulnopalmar arterial arches with pulse oximetry and plethysmography: comparison with the Allen's test in 1010 patients. Am Heart J 2004;147:489-93.)

In preparation for radial access, the arm should be placed on an appropriate board and abducted at a 30- to 45-degree angle, and the wrist should be hyperextended over a gauze roll. Unless prompted by anatomy or demand (e.g., left internal mammary artery injection), the right radial artery is used. Its distal course can be mapped by palpation or ultrasound; the latter has been shown to improve first-pass rates here as well.[29] Only up to 1 mL of 1% lidocaine is injected at the skin entry site, which should be approximately 1 to 2 cm (1 inch) proximal to the styloid process of the radius. The radial artery is accessed by either a micropuncture needle (anterior wall technique) or a 20-gauge angiocath needle (posterior wall technique) at a 30- to 45-degree angle. Thereafter, a 0.025-inch wire is introduced very carefully, and one should not proceed if any resistance is felt similar to the femoral access technique. Once a wire is placed safely, a sheath is introduced, again very carefully. Practices differ, but one should consider smaller sizes for women (4F to 5F) but larger sizes (6F; maximum 7F in men) if PCI is likely. Overstretching of the artery is to be avoided because it leads to higher postprocedural occlusion rates. A longer sheath has been considered to protect more against vasospasm at the level of the forearm.[30]

However, other studies suggest that it is the hydrophilic coating rather than the length of the sheath that reduces spasms.[31]

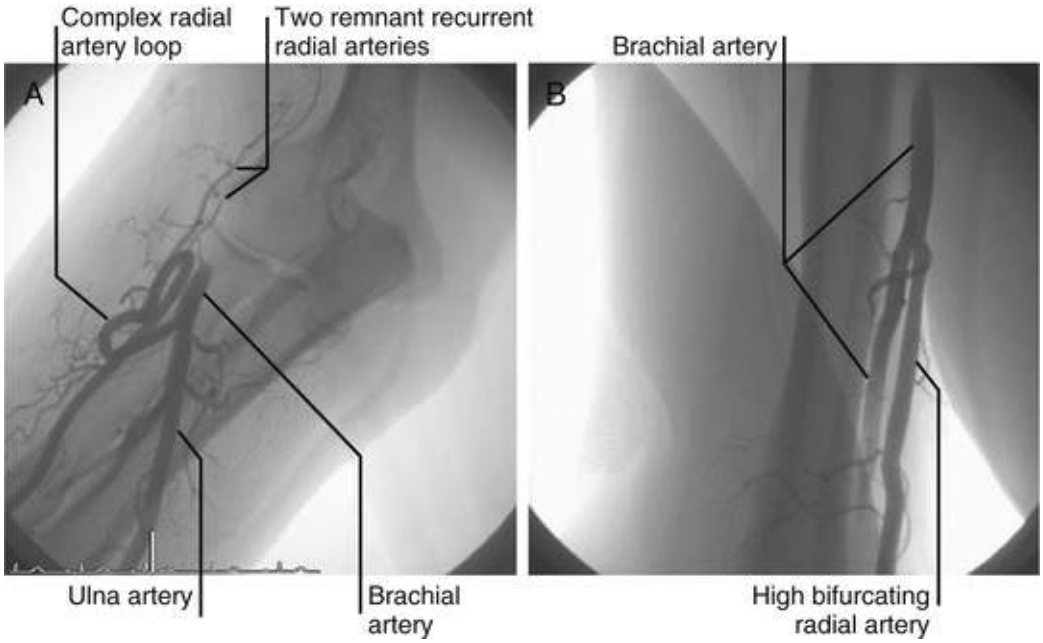
Typical sheath dimensions used for radial access are 4F to 6F in size and 7 to 16 cm in length. Once the sheath is in place, typically 5000 units of unfractionated heparin is given as a bolus, or weight adjusted (50 units/kg), preferably intravenously to prevent postprocedural radial artery occlusion. Arterial vasospasm is a complicating factor and is prevented by adequate sedation, avoidance of limb cooling, and administration of vasodilators (**eFig. 19.5**). Most often, nitroglycerin (100 to 200 µg) and verapamil (2.5 mg) are given. Other approaches are sublingual nitroglycerin and intra-arterial (local) administration of diltiazem or nicardipine. With these preparations, catheters can be advanced over a standard 0.035-inch J-tip wire into the ascending aorta.



EFIGURE 19.5 **A,** Right radial angiogram illustrating profound vasoconstriction directly after the access sheath. **B,** Resolution with administration of 2.5 mg of verapamil and 400 µg of nitroglycerin through the sheath.

Since the anatomic course may not be as straight, the J-tip wire and catheter should only be gently advanced[32] (**eFig. 19.6**). Challenges in advancement can often be overcome by a Glidewire or a Runthrough coronary guidewire (both Terumo Interventional Systems). These wires tend to cannulate not only the main lumen but also side branches more easily and should be exchanged once the catheter is advanced to the brachiocephalic level. In case of radial artery or brachial artery dissection, the procedure can often still be continued because the catheter itself will serve to tamponade. Closure, however, should be documented, as with its initial recognition, with angiography using a 50/50 mix of saline and contrast material. Injection of contrast material is also useful to visualize tortuosity, which can pose major challenges not only distally but also for engagement of the ascending aorta. In these cases the catheter might need to guide the wire around the origin of the brachiocephalic artery rather than vice versa. Deep inspiration can also be helpful under these circumstances. For difficult cases, it is recommended not to lose position and to use an exchange-length 0.035-inch J-tip wire for any additional catheter exchange. The use of diagnostic catheters designed for radial approaches and both coronary ostia (e.g., Tiger catheter) can ease the procedure. Once complete, the equipment is removed, including sheath, and a wristband with an inflatable balloon cuff is used to achieve hemostasis. To avoid thrombotic occlusion,

the site is allowed to bleed back before the cuff is inflated to 2 cc over hemostasis level. Practices should have protocols that guide the deflation process and monitoring of the pulse and perfusion status. “Patent hemostasis” is the key term for care after radial artery access.



EFIGURE 19.6 Anatomic variations of the radial artery. **A,** Large complex radial loop and remnant (recurrent) radial artery. **B,** High bifurcation of radial artery at the level of the midhumerus. (From Rao SV, Stone GW. Arterial access and arteriotomy site closure devices. Nat Rev Cardiol 2016. doi:10.1038/nrcardio.2016.133.)

While the main advantages are reduced risk of bleeding and lack of bed rest requirements, potential disadvantages include, besides propensity for vasospasm and thrombotic radial artery occlusion, dissections and compartment syndrome, limited catheter stability, and poor coronary engagement. Also, the radial artery is not the best approach if larger sheath sizes are required (e.g., for bifurcation interventions). Presentation and management of complications from radial access are summarized in the postprocedural care section (see **eFig. 19.3**).

Randomized controlled trial (RCT) comparisons between the radial versus the femoral approach have been made primarily in cohorts with STEMI. A meta-analysis of 12 studies with 5000 patients showed that a radial approach was associated with a nearly 50% decrease in mortality and major bleeding risk.[33] These primary benefits were confirmed subsequently in 8400 patients with acute coronary syndrome (ACS), with or without STEMI, randomized to a radial or femoral access for coronary angiography and PCI; radial access was associated with a 30% reduction in major bleeding and all-cause mortality.[34]

Percutaneous Brachial Artery Technique

The brachial artery approach is similar to the femoral artery approach but rarely used, as replaced by the radial technique. Using the Seldinger method, a 4F to 6F sheath is placed into the brachial artery and flushed with 3000 to 5000 units of heparin. Subsequent maneuvers are similar to those previously described. Proficient hemostasis after removal of the sheath is critical; the arm should be maintained straight on an arm board for 4 to 6 hours, with close observation of the radial and brachial pulses, access site, and upper arm size.

The main advantage of the brachial artery for percutaneous access is the larger luminal size than the radial artery and accessibility when other access options have failed. This includes access for patients

with severe peripheral arterial disease or such a degree of vascular tortuosity or body size that even with the use of extra-long coronary catheters, the coronary ostia cannot be reached. The percutaneous approach is easier than the cutdown of the brachial artery, which was in fact the first technique introduced for coronary artery catheterization by Sones and colleagues. Given the anatomic location, the access site is very close to the x-ray generator tube or image intensifier, depending on the angle. It may therefore lead to greater x-ray exposure and restriction of angiographic views.

Venous Access

With any concomitant procedure involving the femoral artery, the femoral vein is used most often for venous access. However, when the right-heart catheter is left in place after the procedure, the internal jugular approach is preferable (Videos 19.1 and 19.2). This approach improves patient comfort and allows the patient to sit up in bed. The internal jugular is preferred over the subclavian approach to lessen the risk for pneumothorax. Use of a micropuncture kit with a 21-gauge needle and introducer can minimize potential trauma from inadvertent puncture of the carotid artery or lung. When the jugular vein has been entered, the micropuncture assembly can be exchanged for any larger sheath (e.g., 7F) often used for right-heart catheterization or right ventricular biopsy. In addition, routine adjunctive use of portable vascular ultrasound probes can help to locate and verify the patency of the jugular vein.

For femoral venous access, the femoral artery is the anatomic landmark. The femoral vein is located 1 cm medial to the femoral artery, which is the distance to be taken from the arterial pulse in the horizontal plane, and another 1 cm caudal in the vertical plane. In patients with severe tricuspid regurgitation, venous pulsations should not be mistaken for arterial pulsations. Local anesthesia and the modified Seldinger technique are applied as described earlier. Typically, 7F sheaths are used, which accommodate standard right-heart catheters. Some procedures, however, may require a larger-sized access.

The internal jugular vein is located lateral to the carotid artery access in the anatomic triangle of the two heads of the sternocleidomastoid muscle and the clavicle. For access, the patient is instructed to lie supine with the head turned 30 degrees to the contralateral side. Any pillow should be removed. Patients with low venous pressure may require leg elevation to increase filling. The use of ultrasound is recommended to guide access; it has been shown to reduce the overall risk of complications by 70%, carotid artery puncture in particular.[35] A so-called high anterior approach is taken from the top of the outlined anatomic triangle, and the skin incision should not be lower than two fingerbreadths above the clavicle, to decrease the risk of pneumothorax. In patients with larger-sized necks, the anatomy can be difficult to define. Under these circumstances, it is advisable to palpate the suprasternal notch and then move the finger laterally. The first hump is the medial and the second hump the lateral head of the sternocleidomastoid muscle. The inner edge of the second hump is followed in a superior direction to the top of the triangle.[36] Under local anesthesia and using the modified Seldinger technique, venous access is obtained. “Mini access” or small needle kits have been used to increase procedural safety. These kits consist of a 21-gauge needle, a 0.018-inch floppy-tipped guidewire, and a two-piece dilator. Patients who have undergone multiple procedures (e.g., after heart transplantation) may require the use of multiple dilators sequentially progressive in size. The use of hydrophilic sheaths further helps in these scenarios.

Patent Foramen Ovale Cannulation.

Access to the left atrium can be accomplished via a foramen ovale that is patent to a probe, which is the

case in 20% to 30% of adults. For this approach, a multipurpose catheter is used and advanced to the high right atrium/superior vena cava (SVC) junction. With the tip directed medially and slightly posteriorly, the catheter is then slowly withdrawn until a slight forward and medial motion is observed into the foramen ovale. The catheter should then prolapse further into the left atrium with gentle pressure, and the position can be confirmed by the pressure waveform, blood samples demonstrating arterial saturation, or manual injection of contrast medium. If left atrial access cannot be obtained with this technique, transseptal catheterization should be undertaken.

Transseptal Catheterization.

First described by Brockenbrough, Ross, and Braunwald more than half a century ago (see Classic References), transseptal catheterization more than ever has become an essential element in the current era because of the demands for the evaluation and intervention of structural heart diseases and arrhythmias (**Fig. 19.5**).

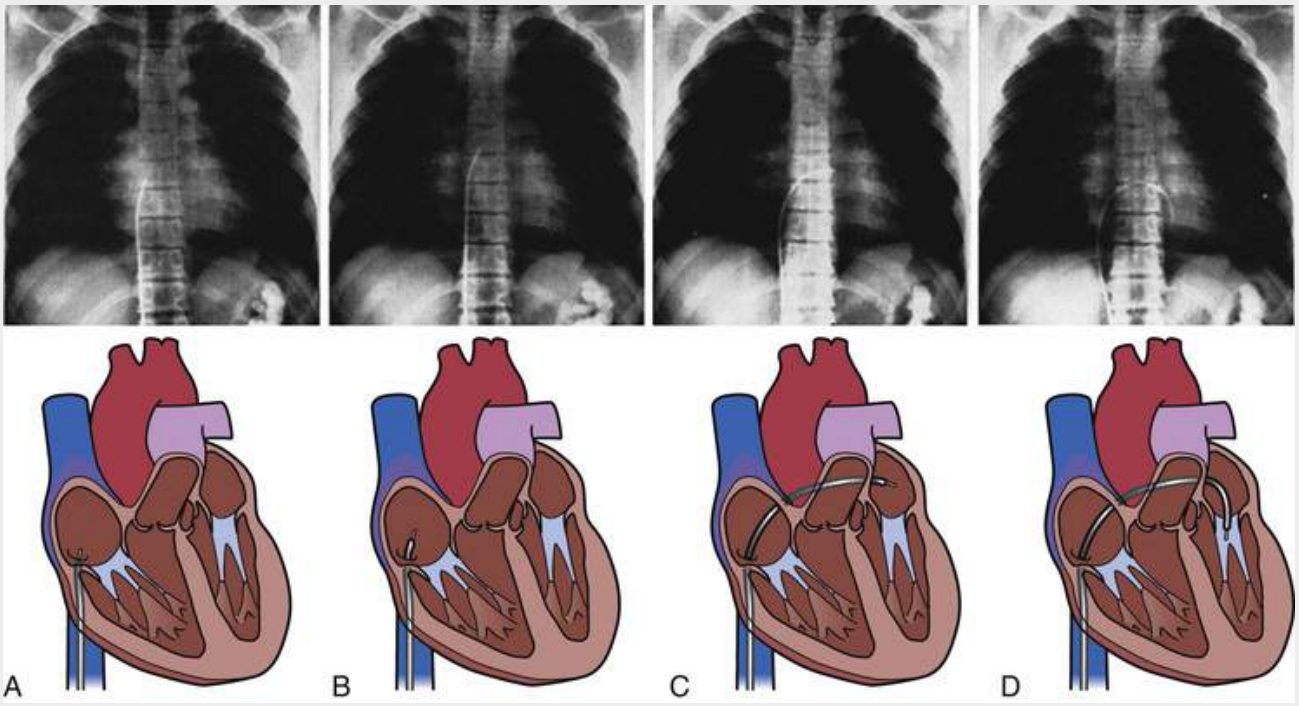
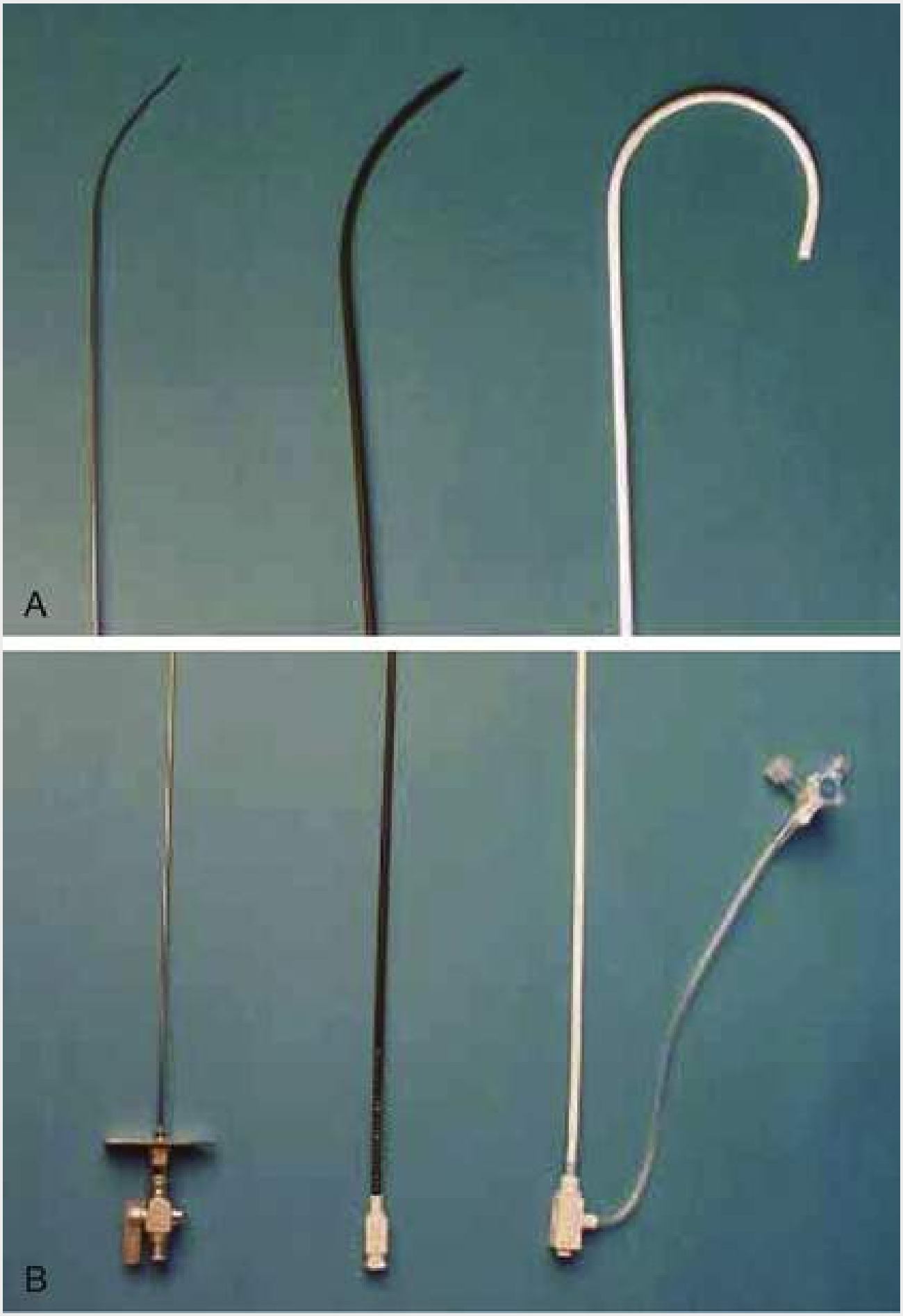


FIGURE 19.5 Steps of transseptal puncture as originally outlined by Brockenbrough and colleagues using a needle that has subsequently become known as the "Brockenbrough needle." **A,** In the first step, a catheter is advanced into the right atrium with the aid of the stylet, which is then withdrawn and replaced by the transseptal needle. **B,** After confirmation of needle tip position in the left atrium, the needle tip is turned from a posteromedial to a medial direction, and the catheter is advanced with the needle until both lie freely within the left atrial cavity. **C,** As the catheter is slipped over the end of the needle, the needle is withdrawn to the point of puncture. **D,** With the needle in place, the tip of the catheter is then advanced into the left ventricle and the needle withdrawn. (From Brockenbrough EC, Braunwald E, Ross J Jr. Transseptal left heart catheterization: a review of 450 studies and description of an improved technic. Circulation 1962;25:15-21.)

A femoral venous sheath is placed and a 0.032-inch guidewire advanced via the inferior vena cava (IVC) and right atrium into the SVC. Next, an 8F Mullins or transseptal sheath and dilator are advanced into the SVC. The guidewire is then replaced with a Brockenbrough needle, which is an 18-gauge needle that tapers to 21 gauge at the distal tip and whose distal port connects to a pressure manifold (**eFig. 19.7**). The tip of the needle is advanced just proximal to the tip of the Mullins sheath. The entire catheter system is then drawn back into the right atrium and simultaneously rotated from a 12 to a 5 o'clock position. Two abrupt rightward movements should be noted. The first reflects the descent of the catheter

from the SVC into the right atrium, and the second reflects the catheter passing over the limbic edge into the fossa ovalis. Steady gentle pressure may suffice to advance the dilator and needle as a unit through the fossa ovalis into the left atrium. If not, the sheath is held in place toward the fossa ovalis and directs the advancement of the needle across the interatrial septum. Transesophageal or intracardiac echocardiography (**see Chapter 14**) can be helpful, especially in difficult cases (e.g., large right atrium, postsurgical condition, anatomic variant). Once left atrial position in confirmed by the overall increase in pressure, contrast injection, or measurement of oxygen saturation, the unit is rotated toward the 3 o'clock position, and the dilator and sheath are safely advanced 2 to 3 cm into the left atrium. While holding the sheath firmly, the dilator and needle are removed. If pressure measurement or left ventriculography is necessary, the catheter can be advanced into the left ventricle with slight counterclockwise rotation.



EFIGURE 19.7 Transseptal catheters. **A,** Distal catheters. **B,** Proximal catheter. *Right,* Mullins transseptal sheath. *Middle,* Introducer (dilator) placed inside the sheath to add stiffness to the catheter. *Left,* Brockenbrough transseptal needle that is placed inside the sheath and used to penetrate the septum.

The major risk of transseptal catheterization is the puncture of structures within or adjacent to the left

atrium, such as atrial free wall, left atrial appendage, coronary sinus, aortic root, or pulmonary artery. The complication rate in experienced centers is no higher than 1%, with success rates of about 90%.[37] The risk for pericardial tamponade is limited in patients who have previously undergone cardiac surgery because mediastinal fibrosis is present.

Direct Transthoracic Left Ventricular Puncture

This approach is used only if pressure measurement or left ventriculography is necessary and the patient has mechanical prosthetic valves in both the mitral and the aortic position. Mechanical (tilting disc) valves should not be crossed with a catheter because of the risk for catheter entrapment, occlusion of the valve, or possible dislodgment and embolization of the disc[38,39] (**see Chapter 71**).

After localization of the left ventricular (LV) apex by echocardiography and administration of local anesthesia, an 18- or 21-gauge 6-inch Teflon catheter system is inserted at the upper rib margin and directed slightly posteriorly and toward the right second intercostal space until tactile contact with the apical impulse is made. At that point, the needle and sheath are advanced into the left ventricle, the stylet and needle are removed, and the sheath is connected for pressure measurement. For the transapical approach, an intercostal incision is made, and the LV apex is directly exposed for apical puncture using the Seldinger technique. The risks of this procedure include cardiac tamponade, hemothorax, pneumothorax, laceration of the left anterior descending coronary artery, embolism of LV thrombus, vagal reactions, and ventricular arrhythmias.

Left-Heart Catheterization

As in most cases, catheters will not simply advance into the left ventricle; crossing the aortic valve requires careful technique (**Fig. 19.6**). A common approach is the use of a straight pigtail catheter, advanced over a 0.035-inch J-tip guidewire to the level of the aortic valve. The wire is then pulled back into the catheter, allowing its tail to take a “figure 6” configuration in the right anterior oblique (RAO) projection. The catheter is subsequently pushed against the aortic valve to form a U shape. With deep inspiration or under pullback and clockwise rotation, the tip usually falls into the left ventricle. Inside the left ventricle, the catheter resumes again a “6” configuration in the RAO projection with the loop directed toward the apex. The catheter is positioned in front of the mitral valve, but not to interfere with its function or become entangled in the chordae. Repeated repositioning may be required to eliminate ventricular ectopy. The Halo catheters represent an alternative to the pigtail catheters (see Classic References, Caracciolo). They possess a tip with a perpendicular helix, inwardly and upwardly directed, and do not have 6 to 12 side holes along the shaft as do pigtail catheters. These features allow for less ectopy during injections and superior ventricular pressure measurements in hypertrophic cardiomyopathy (HCM).

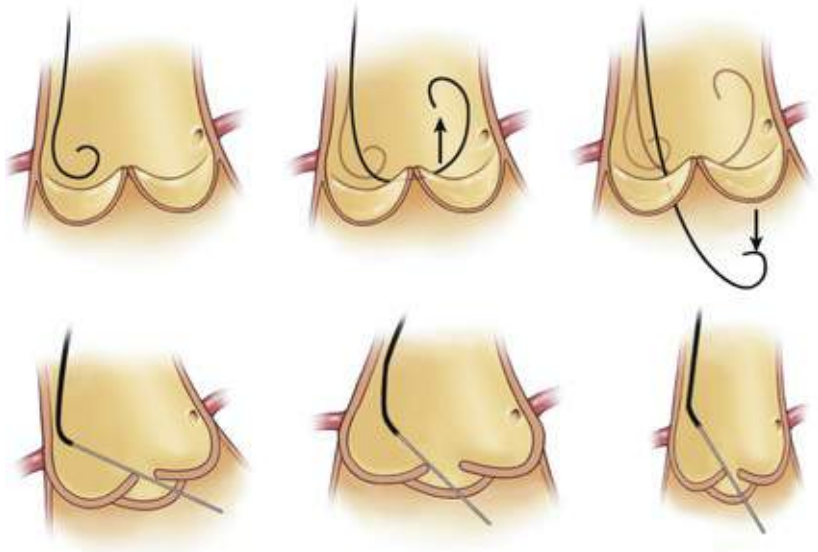


FIGURE 19.6 Technique for retrograde crossing of an aortic valve by a pigtail catheter. **Upper row,** Technique for crossing a normal aortic valve. **Bottom row: Left,** Use of a straight guidewire and pigtail catheter in combination. Increasing the length of the protruding guidewire straightens the curve of the catheter and causes the wire to point more toward the right coronary ostium; reducing the length of the protruding wire restores the pigtail contour and deflects the tip of the guidewire toward the left coronary artery. When the correct length of wire and the correct rotational orientation of the catheter have been determined, repeated advancement and withdrawal of the catheter and guidewire together allow retrograde passage across the valve. **Middle,** In a dilated aortic root an angled pigtail catheter is preferable. **Right,** In a small aortic root a right coronary Judkins catheter may have advantages. In patients with bicuspid valves an Amplatz left catheter is often used because it directs the wire more superiorly.
(From Baim DS, Grossman W. Percutaneous approach including transseptal and apical puncture. In Baim DS, Grossman W, editors. Cardiac Catheterization, Angiography, and Intervention. 6th ed. Philadelphia: Lea & Febiger; 2006, p 93.)

With dilated aortic roots or horizontally oriented hearts, an angled pigtail catheter is preferable, whereas small aortic roots may require a right coronary Judkins for initial wiring and subsequent replacement with a pigtail catheter. In patients with bicuspid valves, a left Amplatz catheter might be useful for placement of a guidewire into the left ventricle, which directs more superiorly. A left Amplatz is also useful in patients with aortic stenosis, or a multipurpose catheter, depending on the angulation of the aortic valve from left ventricle into ascending aorta (more horizontal or more vertical). On occasion, straight rather than J-tipped guidewires have been used, which facilitates probing of the stenotic aortic valve, but also has greater potential for dislodging material from the aortic valve or aorta.

For pressure measurements and contrast injections in the left ventricle, a pigtail catheter should be used because the risk of damaging the wall is reduced and the risk of entrapment of the mitral valve apparatus is low. The gradient across the aortic valve should be measured by simultaneous recording of pressure in the ascending aorta and left ventricle; pullback gradients do not suffice. Pigtail catheters with a dual lumen (distal and proximal) allow for this measurement, but the concordance of pressure should be verified in the aortic root before and after measurement. An alternative is the use of a multipurpose catheter through which a pressure wire is advanced into the left ventricle while the catheter remains in the aorta. A single multipurpose catheter with an end hole is desirable when an intraventricular or LV outflow tract gradient is in question and differentiation of location is needed (intraventricular, subvalvular, and/or transvalvular). For gradients across the mitral valve, LV and wedge or left atrial pressures are recorded simultaneously with two transducers. LV measurements include systolic, diastolic, and end-diastolic pressure; dP/dt can also be calculated.

Left Ventriculography

Once considered an integral part of every cardiac catheterization, a left ventriculogram is infrequently

performed in the current era given the advances in availability and quality of echocardiography (**see Chapter 14**) and concerns for complications. A left ventriculogram is still indicated for the assessment of LV function, ventricular septal defect (VSD), or quantification of mitral regurgitation (MR). It is, however, not encouraged for patients with severe, decompensated heart failure, if the LV end-diastolic pressure (EDP) is greater than 35 mm Hg, or in those at high risk for CIN.

Ideally, left ventriculography should be performed in two planes, and biplane x-ray systems are therefore of great value. The main projection is a 30-degree RAO, which covers the high lateral, anterior, apical, and inferior wall (Video 19.3). Higher views might be required in the setting of MR to separate retrograde contrast ejection from the spine or descending aorta. The axillary projection of 45- to 60-degree left anterior oblique (LAO)/20-degree cranial covers the lateral and septal walls and is of great benefit for assessing the extent of regurgitant contrast volume in the setting of MR (Video 19.4). It is also the best projection to visualize a VSD (Video 19.5), as well as an atrial septal defect (ASD), although the contrast injection then is into the pulmonary artery. The pulmonary artery would also be the site of injection for the evaluation of pulmonic regurgitation. As a general rule, contrast is injected just distal to the valve that is to be evaluated.

After the catheter is appropriately placed, it is connected to the power injector with high-pressure tubing, tight and air free. A test injection 5 to 8 mL is advised to confirm proper, free catheter position. The power injector is then programmed to deliver 20 to 50 mL of contrast at 10 to 15 mL/sec. For smoother delivery and so that maximum pressure (900 to 1200 psi) is not reached instantly but more slowly, a 0.2- to 0.5-second rise can be programmed. To facilitate lower contrast volumes, power injections can also be operator controlled and stopped once the ventricle is satisfactorily opacified. Frame rates of 30/sec suffice for heart rates of less than 95 beats/min. Every effort should be made to avoid ectopy because even one or two premature beats can result in over- or underestimation of the severity of MR and in unreliable measures of cardiac function. The same is true for underfilling, which also leads to underestimation of the degree of MR.

The main complications of left ventriculography are cardiac arrhythmias (both supraventricular and ventricular). Intramyocardial contrast staining during power injection can occur but is not clinically relevant if transient. If it persists, however, perforation needs to be ruled out. This is a concern when end-hole catheters such as the multipurpose catheter are used for power injections into the left ventricle, which should never be done. Embolism and contrast-related complications also may be encountered. Transient hypotension of 15 to 30 seconds was relatively common with the use of ionic high-osmolar contrast media but is not typically seen in the current era.

The wall motion pattern ranges from normokinesis to hypokinesis, akinesis, and dyskinesis. The degree of MR is scored by Sellers class and degree of VSD by calculation of the shunt extent.

Ascending Aortography

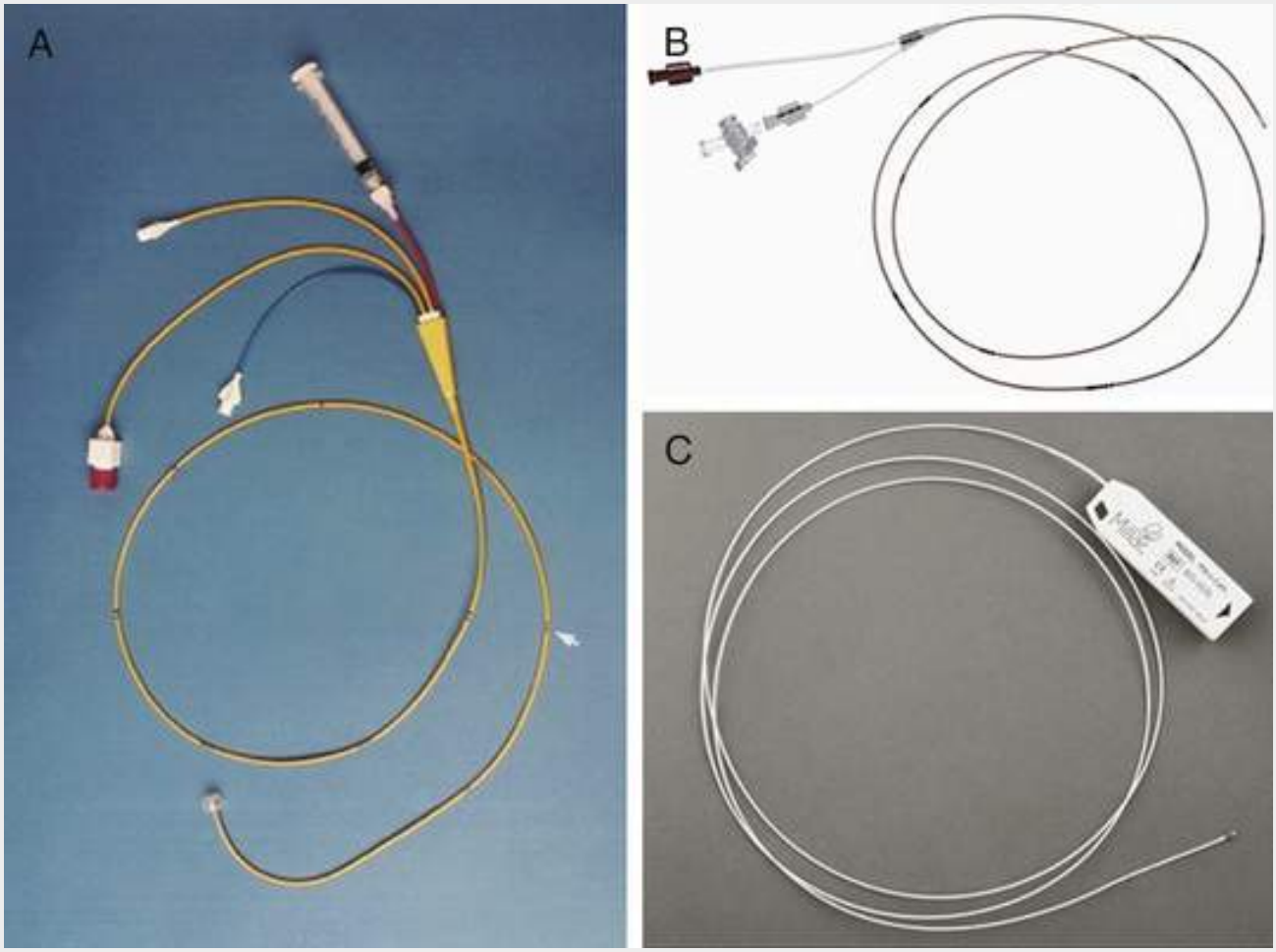
Aortic angiograms are indicated to determine the size of an ascending aortic aneurysm, the presence of aortic dissection, the severity of aortic regurgitation (AR), and the presence of bypass grafts. A side-hole (pigtail) catheter should be used to reduce the risk of aortic injury. In the case of concerns for aortic dissection, one must ascertain that the catheter is not entrapped in the false lumen. The position may be checked with a manual injection of contrast. For dissection, the optimal position is just above the suspected proximal tear, for the aortic valve just above the leaflets. Standard RAO and LAO projections suffice for aortic valve evaluation, and caudal or cranial angulation is of no additional benefit (Video 19.6). The severity of AR is best evaluated in the RAO projection (Video 19.7). The LAO projection is best for the assessment of the ascending aorta, aortic arch, and arch vessels. The typical setup for

power injections is 40 to 60 mL at 15 to 20 mL/sec. Frame rates of 15 frames/sec are adequate.

Right-Heart Catheterization

The right-heart catheterization is one of the central elements in the hemodynamic evaluation in the catheterization laboratory. Percutaneous venous access is accomplished via the internal jugular vein or femoral vein, or less frequently the subclavian or antecubital vein, as previously outlined. The choice of catheter depends on the access approach and clinical scenario.

The Swan-Ganz catheter is the catheter of choice for the internal jugular approach (**eFig. 19.8A**), whereas a so-called pulmonary hypertension Swan is advisable for the femoral approach and for patients with pulmonary hypertension or severe tricuspid valve regurgitation (TR) because it is stiffer and more torquable. End-hole catheters, or "balloon wedge catheters," are equally good for this purpose, with similar rigidity, less catheter whip artifact, and thus higher fidelity (**eFig. 19.8B**), although they lack the capacity to determine cardiac output by thermodilution.



EFIGURE 19.8 **A,** Typical Swan-Ganz catheter. The proximal ports, *left to right,* are the proximal injection hub, thermistor connector, distal lumen hub, and balloon inflation valve with syringe. The distal end of the catheter has a balloon and a distal end hole. The proximal injectate port exits 30 cm from the distal end of the lumen (*arrow*). The thermistor lies just proximal to the balloon. **B,** Example of a balloon wedge catheter (Arrow, Teleflex, Morrisville, NC), which has only one port besides the balloon inflation valve. **C,** Example of a diagnostic pressure catheter (Mikro-Cath, Millar, Houston, Texas). (**A,** From Davidson CJ, Bonow RO. Cardiac catheterization. In Mann DL et al, editors. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed. Philadelphia: Elsevier; 2012, p 367.)

Using the internal jugular venous approach, the standard Swan-Ganz catheter can be advanced relatively easily into the right atrium and then, with the balloon inflated, into the right ventricle, and on into the pulmonary artery and pulmonary capillary wedge position. Although one can orientate oneself with pressure tracings only, fluoroscopy is advisable, especially if there are any preknown structural and functional difficulties (e.g., severe right atrial enlargement, severe TR, severe right ventricular [RV] dilation). Some maneuvering of the catheter may be required especially in these cases.

The femoral venous approach is technically more demanding because of the acute angle from the IVC into the right ventricle. On occasion, the catheter can be advanced directly through the right atrium and across the tricuspid valve. Once in the right ventricle, the catheter is rotated clockwise so that it points superiorly and directly into the RV outflow tract. Once in the outflow tract, the tip of the balloon usually allows flotation into the pulmonary artery and wedge positions. Deep inspiration or cough can facilitate this maneuver and assist in crossing the pulmonic valve. In patients with high pulmonary artery pressure, a guidewire can be used to stiffen the catheter and allow advancement into the wedge position. However, the operator must use caution to prevent perforation of the pulmonary artery. If the catheter continues to point inferiorly toward the RV apex, another technique should be used because further advancement can risk perforation of the RV apex.

One alternative technique of right-heart catheterization via the femoral approach is to direct the balloon catheter to the lateral right atrial wall and then, by clockwise rotation, posteriorly and up into the SVC (**Fig. 19.7**). The catheter is then pulled back into the right atrium and with another clockwise rotation turned anteromedially, which allows the catheter to face and cross the tricuspid valve. Once the catheter is advanced into the right ventricle with the tip taking a horizontal course, additional clockwise rotation allows the catheter to point up toward the RV outflow tract. The catheter is then advanced into the pulmonary artery and wedge position.

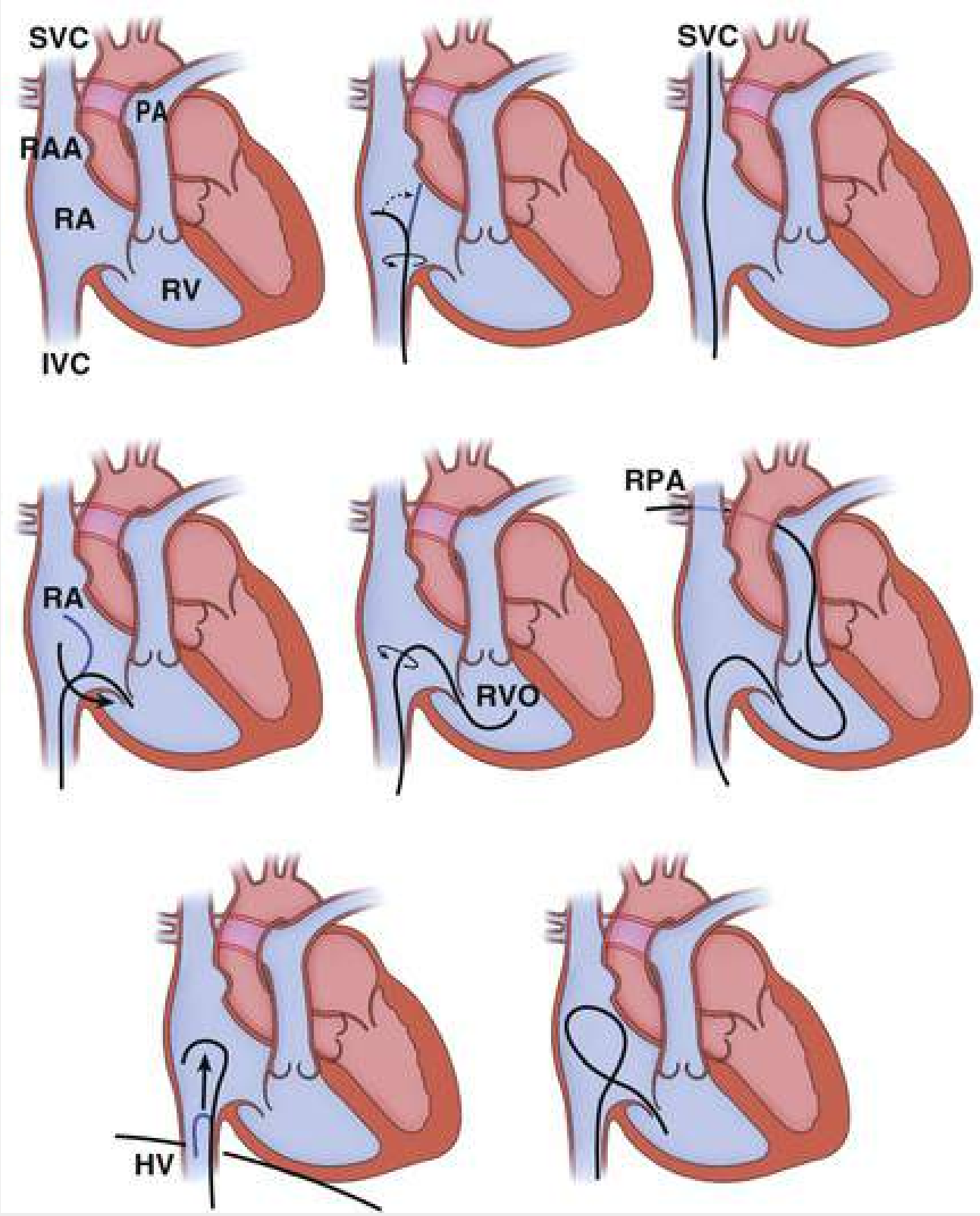


FIGURE 19.7 Right-heart catheterization via the femoral venous approach. **Top row,** The right-heart catheter is initially placed in the right atrium (*RA*) aiming at the lateral atrial wall. Counterclockwise rotation then directs the catheter posteriorly and allows advancement into the superior vena cava (*SVC*). Although it is not evident in the figure, clockwise catheter rotation into an anterior orientation would lead to advancement into the right atrial appendage (*RAA*) and thereby preclude SVC catheterization. *IVC,* Inferior vena cava; *PA,* pulmonary artery; *RA,* right atrium; *RV,* right ventricle. **Center row,** The catheter is withdrawn back into the RA and aimed laterally. Clockwise rotation causes the tip of the catheter to sweep anteromedially and cross the tricuspid valve. With the catheter tip in a horizontal orientation just beyond the spine, it is positioned below the RV outflow (*RVO*) tract. Additional clockwise rotation causes the catheter to point straight up and allows advancement into the main PA and from there into the right PA (*RPA*). **Bottom row,** Two maneuvers useful in catheterization of a dilated right heart. A larger loop with a downward-directed tip may be required to reach the tricuspid valve and can be formed by catching the tip of the catheter in the hepatic vein (*HV*) and advancing the catheter quickly into the RA. The reverse-loop technique **(right)** gives the tip of the catheter an upward direction, aimed toward the outflow tract. (From

Baim DS, Grossman W. Percutaneous approach, including transseptal and apical puncture. In Baim DS, Grossman W, editors. Cardiac Catheterization, Angiography, and Intervention. 7th ed. Philadelphia: Lea & Febiger; 2006, p 86.)

Another technique for the femoral venous approach is to create a loop in the right atrium by hooking the catheter tip on the hepatic vein or by advancing it against the lateral wall of the right atrium. With the loop in place, the catheter is advanced further, and with the tip facing inferiorly and medially, the tricuspid valve is passed and the pulmonary artery and wedge positions are reached. The redundant loop is then removed by slow catheter withdrawal, even into pulmonary artery position, at which point the balloon can be carefully inflated and wedged.

Hemodynamic Data.

The right-heart catheterization allows the measurement of flow (cardiac output), pressures, and vascular resistance. These three central parameters are connected by the Ohm's law: $Q = \Delta P/R$; that is, blood flow is a function of the pressure difference and resistance in the circulatory bed.

Right Ventriculography.

A right ventriculogram is indicated for the assessment of right-to-left ventricular shunts, TR, RV dysplasia, abnormalities of the RV outflow tract (RVOT), and pulmonary stenosis (Video 19.8). A 7F Berman balloon-tipped catheter is used, which has no end hole but eight side holes proximal to the balloon. The anteroposterior (AP) cranial or AP lateral projection is used to visualize the septum and RVOT. Typically, 20 to 30 mL of contrast material is injected at 8 to 10 mL/sec (but if enlarged, could be up to 40 to 50 mL at 12 to 18 mL/sec).

Hemodynamic Measurements

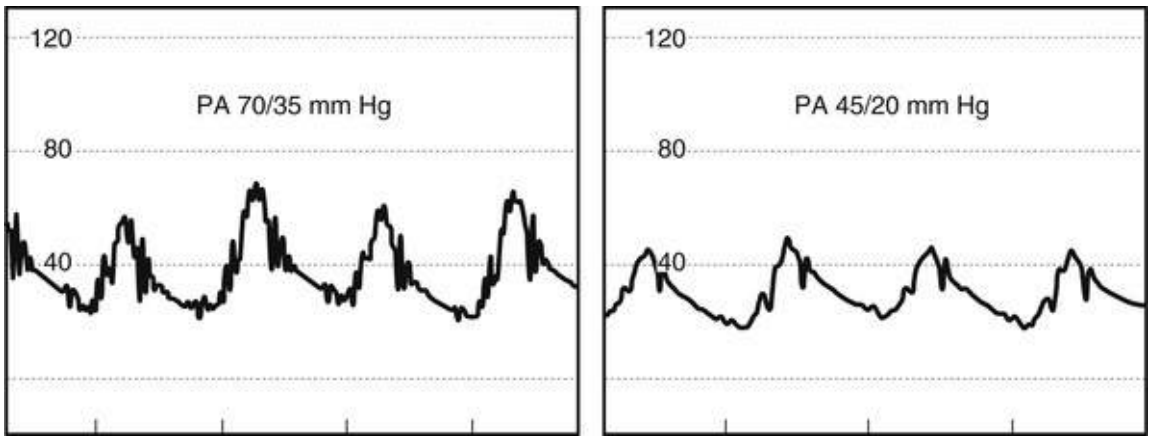
Pressure Measurements

Accurate recording of pressure waveforms and correct interpretation of the physiologic data derived from these waveforms are major goals of the cardiac catheterization. A *pressure wave* is the cyclic force generated by cardiac muscle contraction, and its amplitude and duration are influenced by various mechanical and physiologic parameters. The pressure waveform from a particular cardiac chamber is influenced by the force of the contracting chamber and its surrounding structures, including the contiguous chambers of the heart, pericardium, lungs, and vasculature. Physiologic variables of heart rate and the respiratory cycle also influence the pressure waveform. An understanding of the components of the cardiac cycle is essential for correct interpretation of hemodynamic data obtained in the catheterization laboratory.

Fluid-Filled Systems

Catheter-based pressure recording in the cardiac catheterization laboratory is most frequently accomplished by transducing the force of the pressure wave from the tip of the catheter to the transducer via a fluid-filled system (catheter plus tubing). Within the transducer, the pressure wave leads to the distortion of a diaphragm or wire, and this force is converted to an electrical and then analog signal. Various factors can influence this signal, undermining its accuracy, in which case the output amplitude is not a true representation of the input amplitude. An output-to-input ratio less than 1 represents *damping* (dissipation of energy), as by friction. This cause of error can be reduced by using a short, wide-bore, noncompliant tubing system that is directly connected to the transducer. Air leaks and air bubbles should be removed, and measurement should be taken without the catheter being filled with contrast material.

The higher the density of the liquid within the catheter, the greater is the damping effect. Furthermore, any luminal compromise ("kink") of the catheter-tubing system is a source of damping and needs to be considered with any unexpected and otherwise unexplained pressure drop (e.g., during extensive catheter manipulation or thrombus formation; **eFig. 19.9**). Another explanation of such a scenario is catheter tip obstruction by small vessels or orifices or by engagement against anatomic structures such as walls.



EFIGURE 19.9 Pressure artifacts leading to erroneous pressure measurements. The initial pulmonary artery (*PA*) pressure was 70/35 mm Hg **(left)** but fell to 45/20 mm Hg during the procedure in the absence of any other hemodynamic changes **(right)** because of the formation of a small thrombus in the small distal lumen of a thermodilution catheter. Constant monitoring of the pressure contour and intermittent frequent flushing of the lumen with heparinized saline are recommended to avoid this artifact. Using larger-bore catheters may be necessary to overcome this problem if damping of pressures continues despite the use of these techniques. (From American Heart Association; Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century. Circulation 2012;125:2138.)

Other sources of error are related to motion or impulses on the catheter (*noise*). This includes tapping on any of the connected catheter-tubing system elements and the "whip artifact" (motion of the tip within the chamber). The "impact artifact" can be noted when the catheter is struck by the walls or valves of the cardiac chambers. The operator also needs to be aware of an artificially elevated pressure caused by streaming or high velocity of the pressure wave when using an end-hole catheter, the "end-pressure artifact."

A critical prerequisite for all measurements is the correct calibration of the pressure transducer against a known pressure, or *zeroing*. This is done by placing the transducer at the level of the atria, which is approximately midchest, and if more than one transducer is used, all should be calibrated simultaneously. To address the risk of *drifting*, all transducers should be rebalanced immediately before any simultaneous recordings.

Micromanometer Catheters

Micromanometer catheters allow for superior pressure recording because they have the pressure transducer mounted at the tip (e.g., 3.5F Mikro-Cath, Millar, **eFig. 19.8C**). This eliminates the interposing fluid column and its damping effect as well as the 30- to 40-millisecond delay. The pressure waveform is less distorted and the whip (motion) artifact is greatly reduced. Thus it provides a true pressure reading at any height in fluid. These high-fidelity catheters, although more expansive, have been used to assess the rate of rise in ventricular pressure (dP/dt), wall stress, rate of decay in ventricular pressure (−dP/dt), time constant of relaxation (τ), and ventricular pressure-volume relationships. Catheters with two transducers separated by a short distance allow for accurate determination of gradients within chambers

(e.g., intraventricular gradient in HCM; **see Chapter 78**) and across structures (e.g., stenotic aortic valve). Some of the high-fidelity micromanometer systems allow for over-the-wire insertion and angiography.

Normal Pressure Waveforms.

There are two basic elements in the interpretation of pressure waveforms in a two-dimensional scale: the individual absolute values (*y* dimension) and the contour of the aggregated values over time (*x* dimension). Normal reference values are defined for all hemodynamic parameters (**Table 19.3**).

TABLE 19.3

Normal Pressure and Vascular Resistance Values

PRESSURE	MEAN (mm Hg)	RANGE (mm Hg)
Right Atrium		
a wave	6	2-7
v wave	5	2-7
Mean	3	1-5
Right Ventricle		
Peak systolic	25	15-30
End-diastolic	4	1-7
Pulmonary Artery		
Peak systolic	25	15-30
End-diastolic	9	4-12
Mean	15	9-19
Pulmonary Capillary Wedge		
Mean	9	4-12
Left Atrium		
a wave	10	4-16
v wave	12	6-21
Mean	8	2-12
Left Ventricle		
Peak systolic	130	90-140
End-diastolic	8	5-12
Central Aorta		
Peak systolic	130	90-140
End-diastolic	70	60-90
Mean	85	70-105
VASCULAR RESISTANCE	**MEAN (DYNE-SEC • CM^{-5})**	**RANGE (DYNE-SEC • CM^{-5})**
Systemic vascular resistance	1100	700-1600
Total pulmonary resistance	200	100-300
Pulmonary vascular resistance	70	20-130

The basic principle for the interpretation of pressure waveforms is that the removal of fluid from a compartment leads to a decrease in pressure and the addition of fluid to a compartment leads to an increase in pressure, depending on the confinement and compliance of the system. In the early phase of LV diastolic filling, the normal left ventricle relaxes to such a degree that LV pressure does not rise; in fact, it decreases despite an increase in LV volume after mitral valve opening. Accordingly, the lack of this pattern indicates an abnormal relaxation pattern of the ventricle (also known as diastolic dysfunction). **Fig. 19.8** shows examples of normal pressure waveforms.

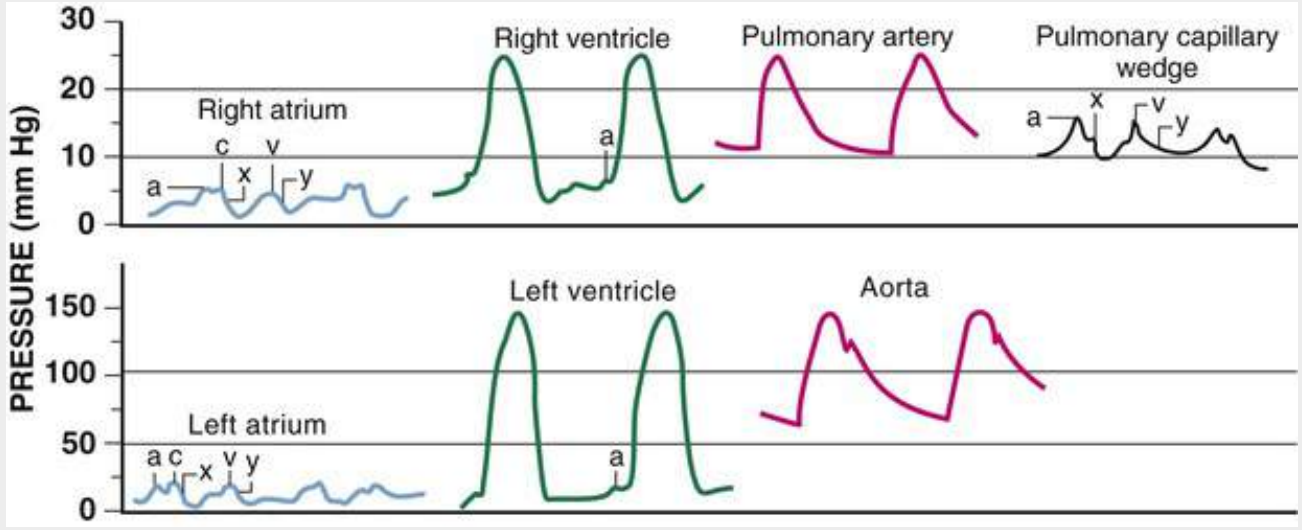


FIGURE 19.8 Normal right- and left-sided heart pressures recorded from fluid-filled catheter systems in a human. (From Pepine C, Hill JA, Lambert CR, editors. Diagnostic and Therapeutic Cardiac Catheterization. 3rd ed. Baltimore: Williams & Wilkins; 1998.)

Atrial Pressure.

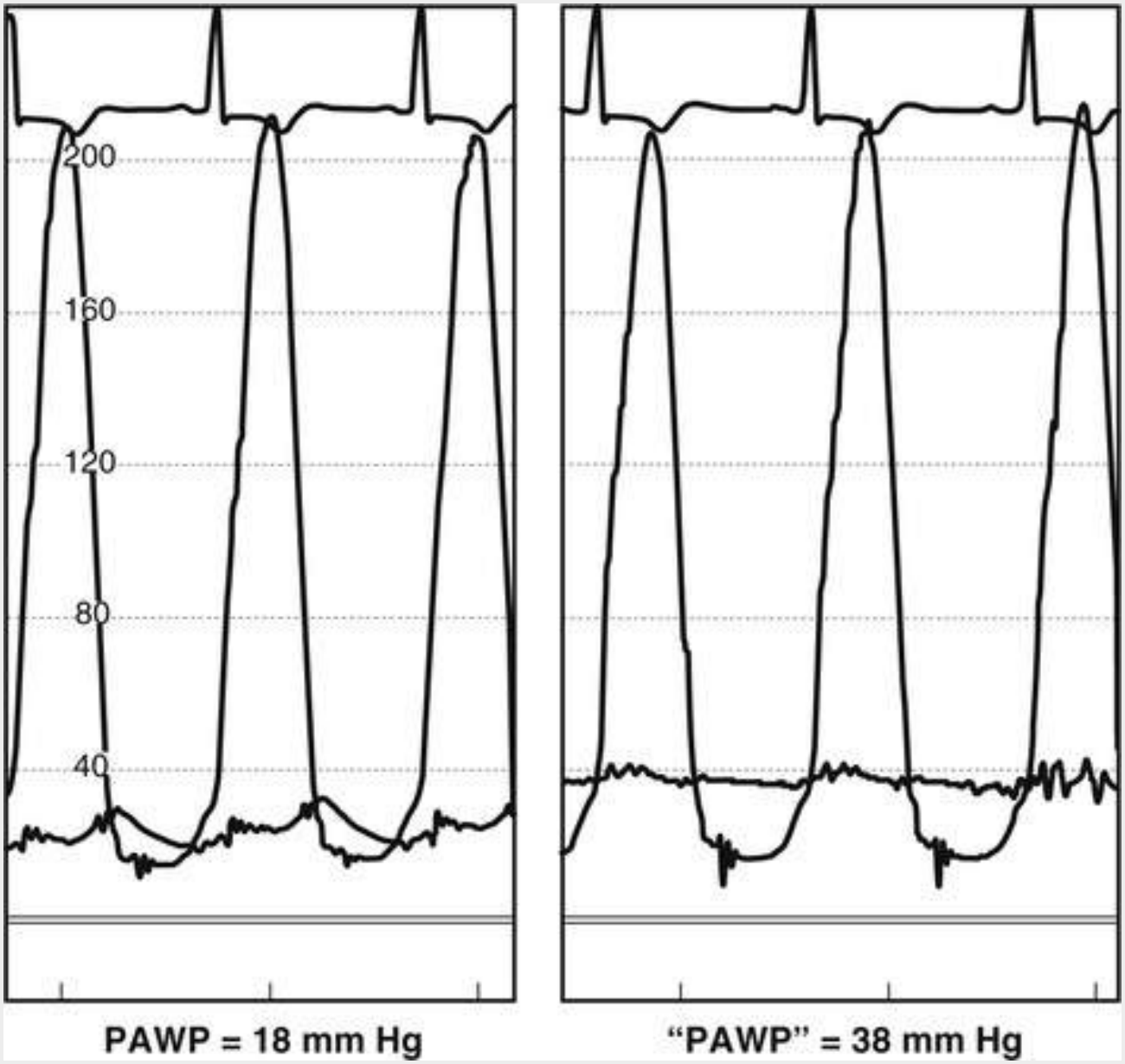
The right atrial pressure waveform has three positive deflections or waves (*a*, *c*, and *v*) and two negative deflections or descents (*x* and *y*). The *a* wave follows the P wave on the ECG and reflects atrial contraction, and atrial contractility and downstream resistance determine its height. It is followed by the *x* descent, which represents atrial relaxation and downward pulling of the tricuspid annulus as the right ventricle contracts. The *x* descent is interrupted as pressure increases again due to protrusion of the closed tricuspid valve into the right atrium with RV contraction: the *c* wave. Passing atrial filling finally terminates the *x* descent, and atrial pressure peaks in (right) ventricular systole: the *v* wave, which follows the R wave on the ECG. Atrial filling and compliance determine the height of the *v* wave, and under normal conditions, the *v* wave is smaller than the *a* wave. With subsequent opening of the tricuspid valve and emptying of the right atrium into the right ventricle, atrial pressure drops again: the *y* descent. Intrathoracic pressure and respiration influence these values. Inhalation leads to a drop in intrathoracic and right atrial pressure, and exhalation has the opposite effect. The reverse is true for patients on mechanical ventilation.

While overall similar, the left atrial pressure is generally higher, with a higher *v* than *a* wave. This occurs because the right atrium can easily decompress through the SVC and IVC, whereas the left atrium is constrained posteriorly by the pulmonary veins.

Pulmonary Capillary Wedge Pressure.

The PCWP waveform represents a slightly damped and delayed reflection of the left atrial pressure waveform, and *c* waves may not be seen. With the normally low resistance of the pulmonary circulation, pulmonary artery diastolic pressure matches mean PCWP. This is not the case under circumstances of elevated pulmonary vascular resistance (hypoxemia, pulmonary embolism, chronic pulmonary hypertension). Also, PCWP may not reflect left atrial pressure as accurately as needed for mitral valve surgery. In general, “overwedging” of the balloon catheter leads to falsely low values, whereas “underwedging” leads to falsely high pressure readings. These two scenarios can be recognized by the pressure waveform lacking its desired atrial waveform configuration: noticeably flat with overwedging and appearing as a dampened pulmonary artery pressure tracing with underwedging (**eFig. 19.10**). True wedge position of the catheter should always be confirmed by a blood sample documenting systemic oxygen saturation (normally near 100%). To avoid collapse of the vasculature distal to the inflated balloon, the blood should be aspirated slowly and gently, or if a larger-bore (balloon wedge) catheter is

used, simply by letting the blood bleed back into an ABG tube.



EFIGURE 19.10 For pulmonary artery wedge pressure (*PAWP*) readings, a large-bore end-hole catheter is recommended as well as confirmation of correct position by proper contour and respiratory variations of the pressure waveform and a >95% oxygen saturation. **Left,** PAWP was taken with a large-bore 7F balloon wedge catheter with appropriate respiratory variation and a proper contour as well as 98% saturation confirmation. **Right,** PAWP determination with a small-lumen thermodilution catheter, most likely representing a damped pulmonary artery pressure, no confirmation by saturation. (From Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century. Circulation 2012;125:2138.)

Ventricular Pressure.

Although similar in morphology, the magnitude of the LV waveform is higher than that of the RV waveform. Duration of systole, isovolumic contraction, and relaxation are longer, and the ejection period is shorter in the left than in the right ventricle. In the early, rapid filling phase of diastole, ventricular pressure initially drops quickly and then increases again, reaching a plateau. This plateau is extended over the slow filling phase but ended by a slow rise due to atrial contraction. The EDP is taken at the *C point*, that is, at the onset of isovolumic contraction and thus just before the notable sudden rise in ventricular pressure. If it cannot be well visualized, the C point can be estimated by drawing a line from the R wave on the simultaneous ECG to the ventricular pressure waveform.

Aortic and Pulmonary Artery Pressure.

The three key elements of the pressure waveform in the great vessels are the *systolic wave* (the ejection of the stroke volume through the open semilunar valves), the *incisura* (the closure of the semilunar valves), and the *diastolic phase* of gradual decline in pressure. The difference between the systolic and diastolic pressure, also known as pulse pressure, is a reflection of the stroke volume and the compliance of the arterial system. Mean pressure more accurately reflects peripheral resistance. As the pressure wave travels distally, an increase in systolic amplitude can be noted, whereas the diastolic amplitude decreases initially up to midthoracic level, then increases again.

The greater the peripheral vascular compliance (e.g., younger patients), the higher the peripheral (femoral, brachial, or radial artery) systolic pressure and the greater the difference in relation to the central aorta. These differences can impact important measurements such as those of aortic gradients. Accordingly, in general, it is advisable to measure the central aortic pressure at the level of the coronary arteries. This also avoids interference with the effect of pressure recovery, which can become relevant in patients with mild to moderate aortic stenosis, particularly when the aorta is small.

Abnormal Pressure Characteristics.

Abnormal pressure waveforms may be diagnostic of specific pathologic conditions. **eTable 19.2** summarizes the more commonly encountered waveforms.

ETABLE 19.2

Pathologic Waveforms

I. Right atrial pressure waveforms
A. Low mean atrial pressure
Hypovolemia
Improper zeroing of the transducer
B. Elevated mean atrial pressure
Intravascular volume overload states
RV failure caused by valvular disease (tricuspid or pulmonic stenosis or regurgitation)
RV failure caused by myocardial disease (RV ischemia, cardiomyopathy)
RV failure caused by left-sided heart failure (mitral stenosis or regurgitation, aortic stenosis or regurgitation, cardiomyopathy, ischemia)
RV failure caused by increased PVR (pulmonary embolism, chronic obstructive pulmonary disease, primary pulmonary hypertension)
Pericardial effusion with tamponade physiology
Obstructive atrial myxoma
C. Elevated *a* wave (any increase in ventricular filling)
Tricuspid stenosis
Decreased ventricular compliance as a result of ventricular failure, pulmonic valve stenosis, or pulmonary hypertension
D. Cannon *a* wave
Atrial-ventricular asynchrony (atria contract against a closed tricuspid valve, as during complete heart block, following premature ventricular contraction, during ventricular tachycardia, with a ventricular pacemaker)
E. Absent *a* wave
Atrial fibrillation, flutter, or atrial standstill
F. Elevated *v* wave
Tricuspid regurgitation
RV heart failure
Reduced atrial compliance (restrictive myopathy)
G. *a* wave equal to *v* wave
Tamponade
Constrictive pericardial disease
Hypervolemia
H. Prominent *x* descent
Tamponade
Subacute constriction and possibly chronic constriction
RV ischemia with preservation of atrial contractility
I. Prominent *y* descent
Constrictive pericarditis
Restrictive myopathies
Tricuspid regurgitation
J. Blunted *x* descent
Atrial fibrillation
Right atrial ischemia
K. Blunted *y* descent
Tamponade
RV ischemia
Tricuspid stenosis

L. Miscellaneous abnormalities
Kussmaul sign (inspiratory rise or lack of decline in right atrial pressure): constrictive pericarditis, right ventricular ischemia
Equalization (≤5 mm Hg) of mean right atrial ventricular diastolic, pulmonary artery diastolic, pulmonary capillary wedge, and pericardial pressures in tamponade
M or W patterns: RV ischemia, pericardial constriction, congestive heart failure
Ventricularization of right atrial pressure: severe tricuspid regurgitation
Sawtooth pattern: atrial flutter
Dissociation between pressure recording and intracardiac ECG: Ebstein anomaly

II. Left atrial pressure–pulmonary capillary wedge pressure waveforms
A. Low mean pressure
Hypovolemia
Improper zeroing of the transducer
B. Elevated mean pressure
Intravascular volume overload states
LV failure caused by valvular disease (mitral or aortic stenosis or regurgitation)
LV failure caused by myocardial disease (ischemia or cardiomyopathy)
LV failure caused by systemic hypertension
Pericardial effusion with tamponade physiology
Obstructive atrial myxoma
C. Elevated *a* wave (any increased resistance to ventricular filling)
Mitral stenosis
Decreased ventricular compliance because of LV failure, aortic valve stenosis, or systemic hypertension
D. Cannon *a* wave
Atrial-ventricular asynchrony (atria contract against a closed mitral valve, as during complete heart block, following premature ventricular contraction, during ventricular tachycardia, or with a ventricular pacemaker)
E. Absent *a* wave
Atrial fibrillation, flutter, or atrial standstill
F. Elevated *v* wave
Mitral regurgitation
Ventricular septal defect
LV heart failure
Reduced atrial compliance (restrictive myopathy)
G. *a* wave equal to *v* wave
Tamponade
Constrictive pericardial disease
Hypervolemia
H. Prominent *x* descent
Tamponade
Subacute constriction and possibly chronic constriction
Right ventricular ischemia with preservation of atrial contractility
I. Prominent *y* descent
Constrictive pericarditis
Restrictive myopathies
Mitral regurgitation
J. Blunted *x* descent
Atrial fibrillation
Atrial ischemia
K. Blunted *y* descent
Tamponade
LV ischemia
Mitral stenosis
L. Pulmonary capillary wedge pressure not equal to LV end-diastolic pressure
Mitral stenosis
Left atrial myxoma
Cor triatriatum
Pulmonary venous obstruction
Decreased ventricular compliance
Increased pleural pressure

III. Pulmonary artery pressure waveforms
A. Elevated systolic pressure
Primary pulmonary hypertension
Mitral stenosis or regurgitation
Congestive heart failure
Restrictive myopathies
Significant left-to-right shunt
Pulmonary disease (pulmonary embolism, hypoxemia, chronic obstructive pulmonary disease)
B. Reduced systolic pressure
Hypovolemia
Pulmonary artery stenosis
Subvalvular or supravalvular stenosis
Ebstein anomaly
Tricuspid stenosis
C. Reduced pulse pressure
Right heart ischemia
RV infarction
Pulmonary embolism
Tamponade
D. Bifid pulmonary artery waveform
Large left atrial *v* wave transmitted backward (i.e., mitral regurgitation)
E. Pulmonary artery diastolic pressure higher than pulmonary capillary wedge pressure
Pulmonary disease
Pulmonary embolus
Tachycardia

IV. Ventricular pressure waveforms

A. Systolic pressure elevated
Pulmonary or systemic hypertension
Pulmonary valve or aortic stenosis
Ventricular outflow tract obstruction
Supravalvular obstruction
RV pressure elevation with significant atrial or ventricular septal defect
RV pressure elevation because of factors that increase PVR (see factors that increase right atrial pressure)
B. Systolic pressure reduced
Hypovolemia
Cardiogenic shock
Tamponade
C. End-diastolic pressure elevated
Hypervolemia
Congestive heart failure
Diminished compliance
Hypertrophy
Tamponade
Regurgitant valvular disease
Pericardial constriction
D. End-diastolic pressure reduced
Hypovolemia
Tricuspid or mitral stenosis
E. Diminished or absent a wave
Atrial fibrillation or flutter
Tricuspid or mitral stenosis
Tricuspid or mitral regurgitation when ventricular compliance is increased
F. Dip and plateau in diastolic pressure wave
Constrictive pericarditis
Restrictive myopathies
Right ventricular ischemia
Acute dilation associated with tricuspid or mitral regurgitation
G. LV end-diastolic pressure higher than RV end-diastolic pressure
Restrictive myopathies

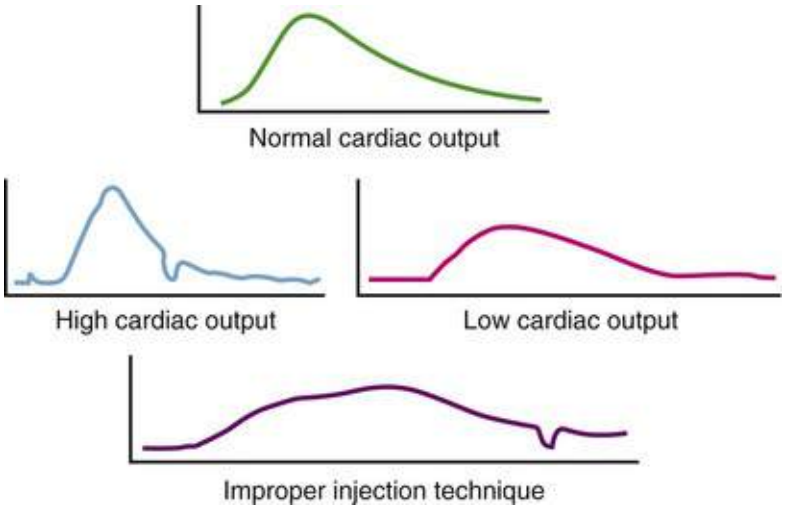
V. Aortic pressure waveform
A. Systolic pressure elevated
Systemic hypertension
Arteriosclerosis
Aortic insufficiency
B. Systolic pressure reduced
Aortic stenosis
Heart failure
Hypovolemia
C. Widened pulse pressure
Systemic hypertension
Aortic insufficiency
Significant patent ductus arteriosus
Significant rupture of sinus of Valsalva aneurysm
D. Reduced pulse pressure
Tamponade
Congestive heart failure
Cardiogenic shock
Aortic stenosis
E. Pulsus bisferiens
Aortic insufficiency
Obstructive hypertrophic cardiomyopathy
F. Pulsus paradoxus
Constrictive pericarditis
Tamponade
Obstructive airway disease
Pulmonary embolism
G. Pulsus alternans
Congestive heart failure
Cardiomyopathy
H. Pulsus parvus et tardus
Aortic stenosis
I. Spike-and-dome configuration
Obstructive hypertrophic cardiomyopathy

Cardiac Output Measurements

Although extremely important, often requested and tested, cardiac output measurements represent only estimates of the true cardiac output on the basis of several assumptions. Three methods are used in the catheterization laboratory: thermodilution, Fick, and ventriculography.

Thermodilution Method

Thermodilution is based on the principle of washout of a temperature change induced by injection of a defined fluid volume cooler than the body temperature. The faster the circulation or flow (i.e., cardiac output), the quicker the neutralization of the temperature change. In practice a bolus of liquid (usually 10 mL of normal saline kept at room temperature) is injected into the proximal port of the catheter, and the change in temperature from baseline is measured by a thermistor at the distal end of the catheter and displayed as a function over time. Cardiac output correlates inversely with the area under the curve and can be calculated when the temperature and specific gravity of the injectate and the blood as well as the volume of the injectate are known (**eFig. 19.11**).



EFIGURE 19.11 Display of a normal cardiac output reading by the thermodilution method **(top),** which plots temperature change over time; the area under the curve is converted into flow L/min by the Stewart-Hamilton formula. Configurations of thermodilution curves in high and low cardiac output states **(middle)** and with improper injection technique **(bottom).** (Modified from Davidson CJ and Bonow RO: Cardiac Catheterization. In Mann DL, et al. [eds]: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed. Philadelphia, Elsevier, 2012: p 364.)

The advantage of this method is the relative ease of use and results. However, thermodilution is less accurate in patients with significant tricuspid or pulmonic regurgitation, intracardiac shunts, low cardiac output, or irregular rhythms.

Fick Method

The Fick method relies on the principle that blood flow is proportional to the difference in the concentration of oxygen between arterial and venous blood and the rate of oxygen uptake in the lungs (**Fig. 19.9**) and the assumption that pulmonary blood flow (PBF) is equal to systemic blood flow (SBF) in the absence of an intracardiac shunt. In other words, the same number of red blood cells (RBCs) that enter the lung must leave the lung in the absence of an intracardiac shunt. Therefore, if the number of oxygen molecules attached to RBCs entering the lung, the number of oxygen molecules attached to RBCs leaving the lung, and the number of oxygen molecules consumed during travel through the lung are known, the rate of RBC flow through the lung can be determined. This can be expressed in the following terms:

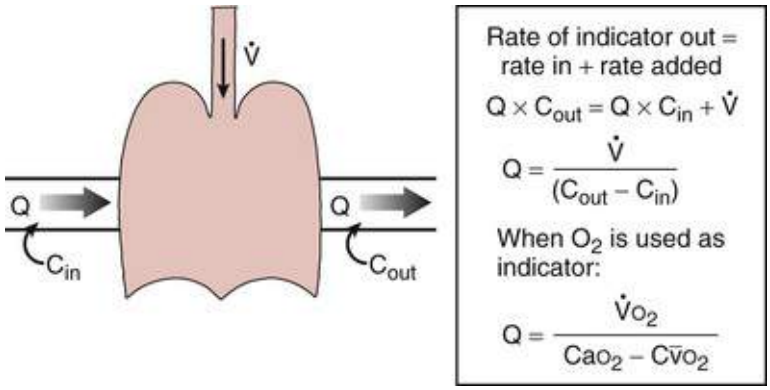


FIGURE 19.9 Schematic illustration of flow measurement by the Fick principle. Fluid containing a known concentration of an indicator (C_{in}) enters a system at a given flow rate, adding to the concentration of the indicator already present and thereby raising the concentration of the indicator in the outflow (C_{out}). In a steady state, the rate of indicator leaving the system must equal the rate at which it enters plus the rate at which it is added. When oxygen is used as the indicator, cardiac output can be determined by measuring oxygen consumption (V), arterial oxygen content (CaO_2), and mixed venous oxygen content ($C\bar{v}O_2$). (From Winniford MD, Kern MJ, Lambert CR. Blood flow measurement. In Pepine CJ, Hill JA, Lambert CR, editors. Diagnostic and Therapeutic Cardiac Catheterization. 3rd ed. Baltimore: Williams & Wilkins; 1998, p 400.)

$$\text{Fick cardiac output (L/min)} = \frac{\text{Oxygen consumption (mL/min)}}{\text{A-V}O_2 \times 1.36 \times \text{Hb} \times 10}$$

where A-VO_2 is the arterial-venous oxygen saturation difference, Hb is the hemoglobin concentration, and 1.36 the constant to adjust for the oxygen carrying capacity of hemoglobin.

Although the oxygen content in blood samples can be reliably measured, measurement of oxygen consumption may represent a source of variability, especially if steady-state conditions are difficult to establish. It is determined by a polarogram, which is connected to the patient by a plastic hood or mouthpiece and tubing and relates the difference between the oxygen concentration in the expired air and the known concentration of oxygen in room air.

The Fick method retains accuracy in patients with low cardiac output and TR. However, the Fick method should not be used in patients with significant MR or AR and is not suitable under conditions of rapid changes in flow. Also, patients should not be on supplemental oxygen.

An “assumed Fick” is often calculated; the oxygen consumption index is assumed based on the patient's age, sex, and body surface area or is estimated (125 mL/m^2) based on the body surface area. This can lead to large errors, however, as much as 40% in cardiac output estimates, compared with the measured oxygen consumption.[40]

Ventriculographic Method

As a third method, the cardiac output can be calculated based on determination of the stroke volume multiplied by the heart rate. The stroke volume equals the difference between end-diastolic and end-systolic volumes. The borders of the contrast-filled left ventricle are traced in end diastole and end systole, and these two-dimensional (2D) values are converted into three-dimensional (3D) volumes based on calibration algorithms with grids and phantoms.

Inaccuracies can easily be introduced in the calibration and tracing steps as well as heartbeat irregularities (e.g., atrial fibrillation, ventricular ectopy). The ventriculographic method, however, is

preferred in patients with significant aortic or mitral regurgitation.

Determination of Vascular Resistance

The analogy with Ohm's law defines *vascular resistance* as the ratio of the decrease in pressure over flow in a vascular segment. Even though it represents an oversimplification of the complex cardiovascular hemodynamics, it has proved very useful in clinical practice. Accordingly, the pressures at the proximal and the distal ends of a vascular bed are measured, and the difference is divided by the cardiac output: mean pressure gradient (mm Hg)/mean flow (L/min). For the systemic vascular resistance (SVR), this is mean aortic minus mean right atrial pressure divided by systemic blood flow (cardiac output), and for the pulmonary vascular resistance (PVR), mean pulmonary arterial pressure minus mean left atrial (mean pulmonary capillary wedge, although not always the same) pressure divided by pulmonary blood flow (in the absence of an intracardiac shunt equal to cardiac output). The corresponding values are in Woods units, which multiplied by 80 yield vascular resistance in the SI units dyne-sec • cm^{-5}.

Omitting the left atrial or PCWP yields the total pulmonary resistance. However, it is a less accurate means to assess the severity of pulmonary vascular disease. PVR, as described, reflects the pressure across the entire pulmonary circulation (main arteries, precapillary arterioles, and pulmonary capillaries).

An additional assessment often performed in the catheterization laboratory is whether any resistance elevation can be induced, as by exercise, or reduced, as by sodium nitroprusside systemically or inhalation of nitric oxide in the pulmonary circulation. Whether any resistance elevation is fixed or reversible, however, is an important question in various clinical scenarios (e.g., heart transplantation).

A more accurate measure to describe the dynamic relationship between pressure and flow is *vascular impedance*, which accounts for blood viscosity, pulsatile flow, reflected waves, and arterial compliance. However, it requires simultaneous measurement of pressure and flow data and is not easy to obtain. Thus, vascular impedance has not gained widespread acceptance as a routinely reported variable.

Clinical Aspects and Integration Into Patient Care

Evaluation of Valvular Stenosis

The cardiac catheterization takes an important part in the evaluation of patients with valvular stenoses, especially if there is discordance in the degree of severity by physical examination and noninvasive tests such as echocardiography. For a number of cases, determination of the pressure gradient will suffice, but the valve should be calculated as well.

Determination of Pressure Gradients

Aortic Valve Stenosis (see Chapter 68)

Although easily accessible, the femoral artery pressure, recorded through the access sheath, should not be used for the calculation of the gradient across the aortic valve because it is unreliable, for various reasons (**Fig. 19.10A**). The best location to measure the poststenotic valve pressure is on the level of the coronary arteries, and the LV pressure can be simultaneously recorded using a double-lumen pigtail catheter with

proximal lumen on the aortic side and distal lumen on the ventricular side of the aortic valve. Another option is to use a multipurpose catheter, which is kept in ideal aortic position, and a pressure wire that is advanced through the catheter just across the aortic valve. With either catheter type, it is important to validate that the side holes (pigtail catheter) or end holes (coronary catheter) are in proper position to avoid erroneous readings (**Fig. 19.10B**). The smaller aortic lumen of the dual lumen pigtail catheter should be continually flushed to avoid damping, and before and after the measurement of the gradient it should be verified that the pressure is identical in both lumina. Pullback recordings from the left ventricle into the aorta with one single catheter should be taken only as a screening technique. Importantly in patients with aortic valve area less than 0.7 cm^2, pullback of a 7F or 8F catheter can lead to an increase in peak arterial pressure of 5 mm Hg or more that has been related to partial obstruction of an already narrowed aortic valve by the retrograde catheter and relief of this obstruction with catheter withdrawal, the “Carabello sign.”[46]

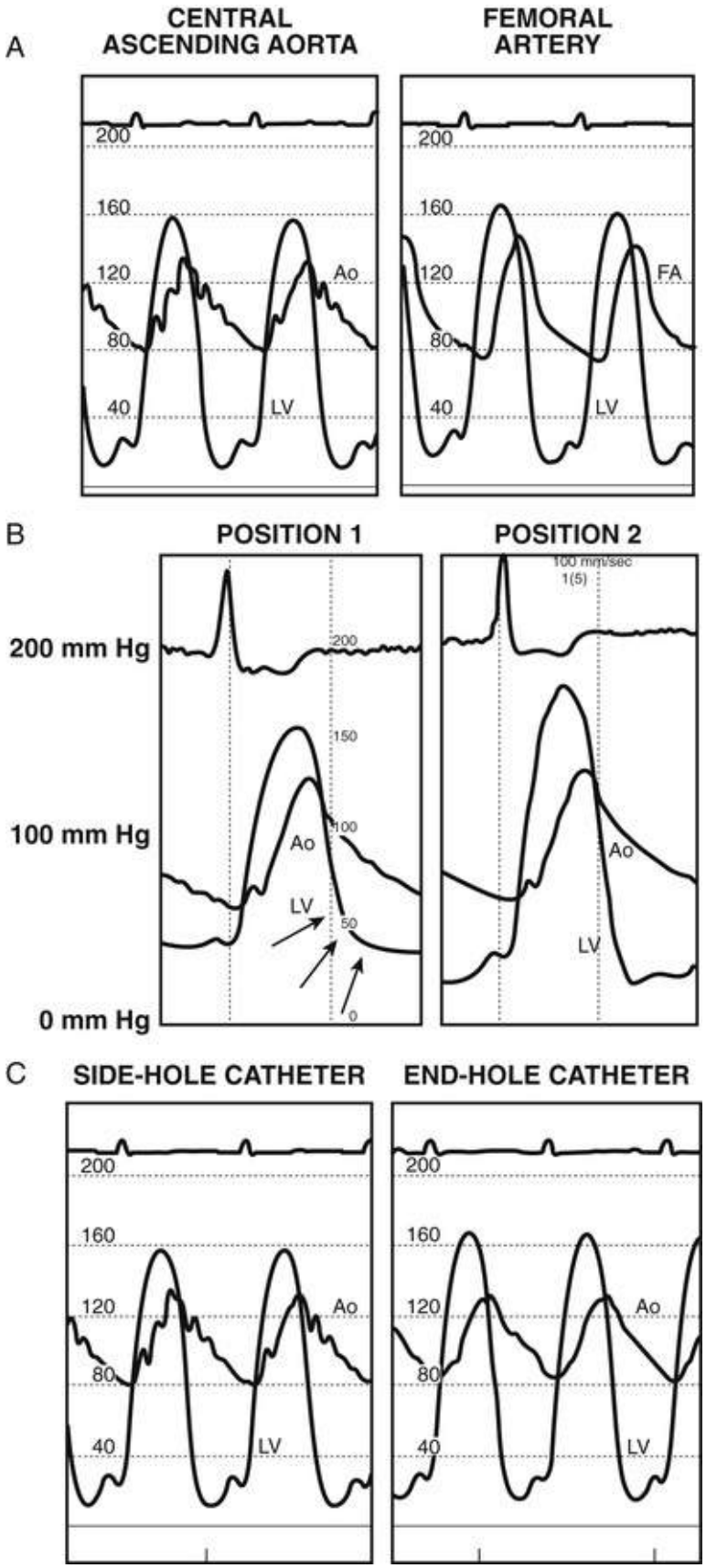


FIGURE 19.10 Examples of erroneous measurements of the transaortic gradient. **A,** The simultaneous left ventricular (*LV*) and femoral artery (*FA*) pressures may yield a falsely low gradient due to peripheral amplification and a falsely high gradient due to peripheral artery stenosis, in addition to the temporal delay that will affect the calculation of the mean gradient. **B,** Incomplete advancement of a pigtail catheter into the LV cavity leads to a marked delay in the fall of pressure during early diastole on the LV waveform due to straddling of some of the multiple side holes in the pigtail catheter at the level of the aortic valve, resulting in a fusion of LV and aortic pressure (*Ao*) (position 1), which is subsequently corrected (position 2). **C,** Typical damping of the aortic pressure (*Ao*) when an end-hole catheter is used instead of a sidehole catheter. (From American Heart Association; Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century. Circulation. 125:2138, 2012.)

The mean pressure gradient is the best parameter for the determination of the severity of aortic stenosis, which is the integrated gradient between the left ventricle and aortic pressure curve throughout the entire systolic ejection period (**Fig. 19.11**). The peak-to-peak gradient should not be used because it does not represent a physiologic measure of the difference at the same point in time. This is different from the peak instantaneous gradient on echocardiography (**see Chapter 14**), which represents a true measure of the maximum difference in pressure between the left ventricle and aorta when both are measured simultaneously.

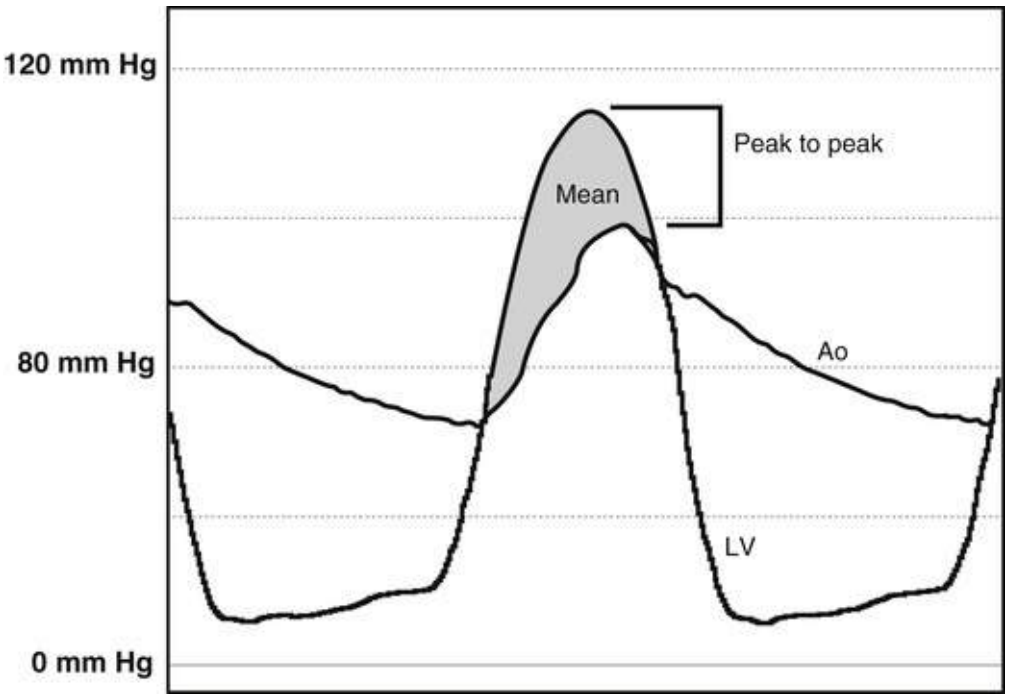


FIGURE 19.11 The optimal way to measure the gradient in a patient with aortic stenosis is to use simultaneous left ventricular (*LV*) and central aortic (*Ao*) pressure and to calculate the mean pressure gradient (the integrated gradient between LV and Ao pressure throughout the entire systolic ejection period). The peak-to-peak gradient, which is the difference between the peak LV and peak Ao pressures, should not be used because it represents a nonphysiologic measurement because of the temporal difference in peak pressures. (From Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century. Circulation 2012;125:2138.)

In patients with low-gradient severe aortic stenosis (i.e., valve area <1 cm^2 but mean gradient <40 mm Hg), pharmacologic maneuvers can be helpful (**see Chapter 68**). This includes dobutamine in patients with a reduced ejection fraction (**Fig. 19.12A, B**) and nitroprusside in those with a preserved ejection fraction (**Fig. 19.12C**) (see later, Physiologic and Pharmacologic Maneuvers). In patients with nonsevere aortic stenosis, the valve area should increase by more than 0.2 cm^2 with minimal or no change in the transvalvular gradient in response to low-dose dobutamine and an increase in contractility. Patients who lack an adequate contractile reserve (stroke volume increase <20%) do poorly with or without surgery. In patients with low-gradient severe aortic stenosis, preserved ejection fraction, relaxation abnormalities, and impaired ventriculovascular coupling, lowering of the peripheral resistance with nitroprusside should lead to an increase in aortic valve gradient without a change in valve area.

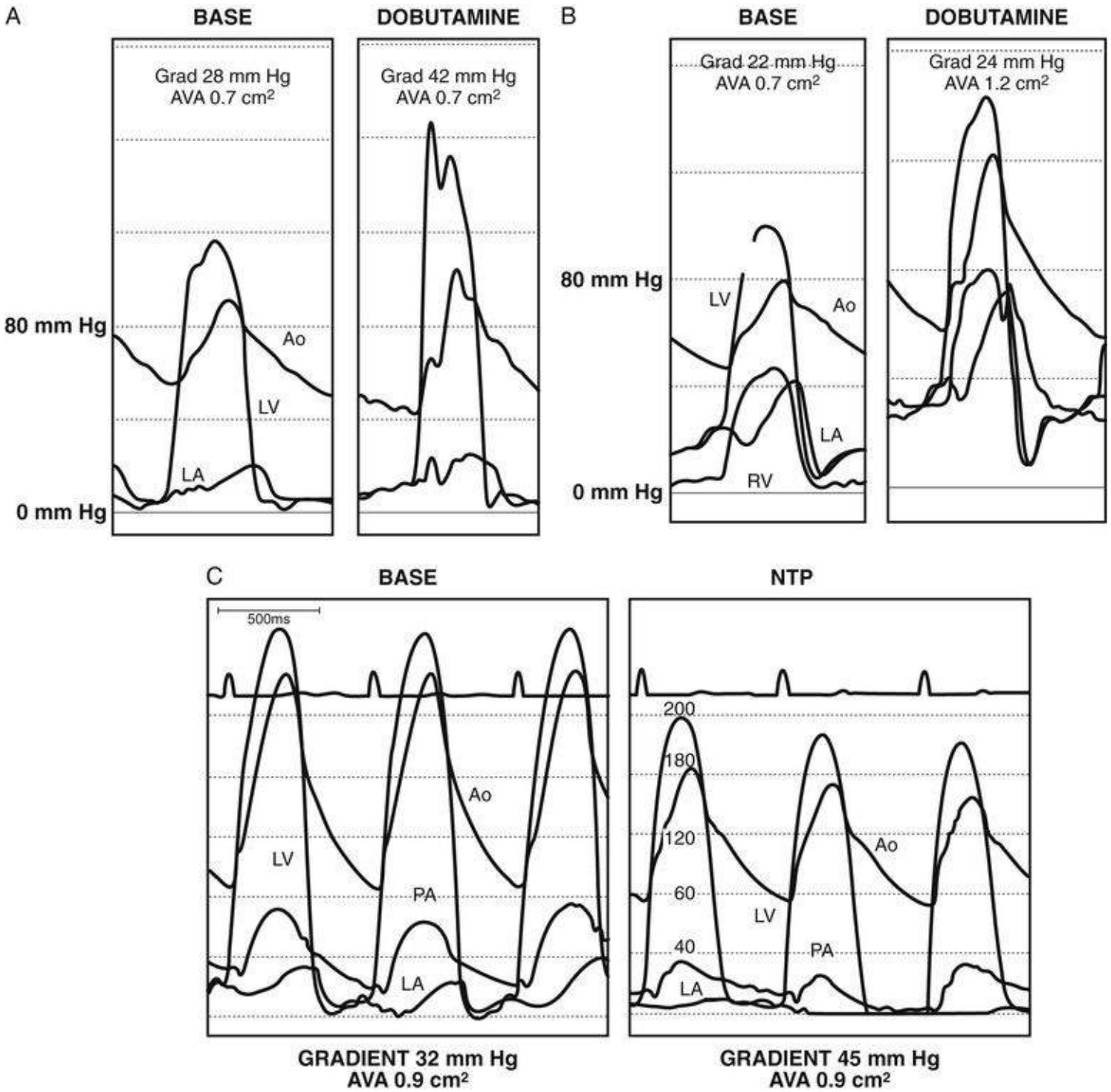


FIGURE 19.12 Pharmacologic testing in low-output, low-gradient (*Grad*) states for differentiation between true aortic stenosis (AS) and pseudo-AS. **A,** In a patient with reduced ejection fraction (EF), increase in contractility with dobutamine stimulation leads to an increase in the gradient from 28 to 42 mm Hg while the valve area remains small at 0.7 cm^2, indicating severe fixed valvular stenosis. **B,** While resting hemodynamics are similar, no increase in the gradient with dobutamine infusion can be noted in this patient, whereas the valve area increases to 1.2 cm^2; this exemplifies pseudo-AS, in which the valve area is small at baseline because of the lack of force generated by the ventricle to fully open a mildly stenotic aortic valve. **C,** Example of a patient with low-gradient AS in the presence of a preserved EF due to a high additional afterload from a noncompliant aortic system. In this case, lowering of the peripheral resistance with sodium nitroprusside (*NTP*) unmasks true AS by demonstrating an increase in aortic valve gradient and a fixed valve area. *Ao,* Central aortic pressure; *AVA,* aortic valve area; *LA,* left atrial; *LV,* left ventricular pressure; *PA,* pulmonary artery pressure. (From Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century. Circulation 2012;125:2138.)

Mitral Valve Stenosis (see Chapter 69)

Similar to the aortic valve, the mitral valve gradient is best measured by direct and simultaneous measurement of left atrial and LV pressure over several cardiac cycles and integral quantification of the pressure difference in diastole (**Fig. 19.13**). To avoid the transseptal puncture and its inherent risks, PCWP rather than left atrial pressure is typically used, carefully realigned with the LV tracing for accurate determination of the mean gradient. Although a satisfactory estimate, PCWP may overestimate left atrial pressure by 2 to 3 mm Hg and thus the mitral valve gradient. This applies even more to the case when the balloon catheter is overwedged, resulting in more profound damping and lower pressure recordings. Attention to technique and detail is especially important if the goal of the evaluation is to define how much mitral valve stenosis is contributing to a patient's clinical presentation. In some patients, it might become necessary to perform provocation maneuvers such as exercise to unmask the abnormality (**eFig. 19.12**). Occasionally, a transseptal approach might be required to measure the left atrial pressure directly and to define the transvalvular gradient more definitively. A simplified formula for the estimation of the mean mitral valve gradient (MVG) has become known as the Cui formula: MVG = Mean left atrial pressure – LVEDP/2.[41]

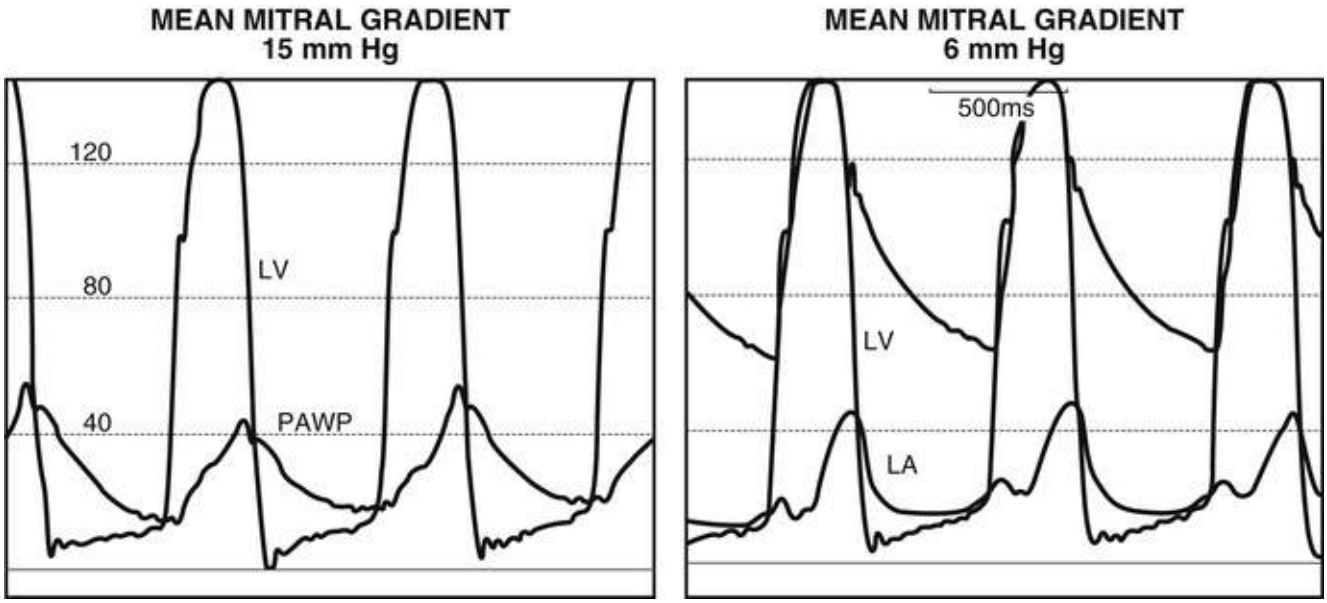
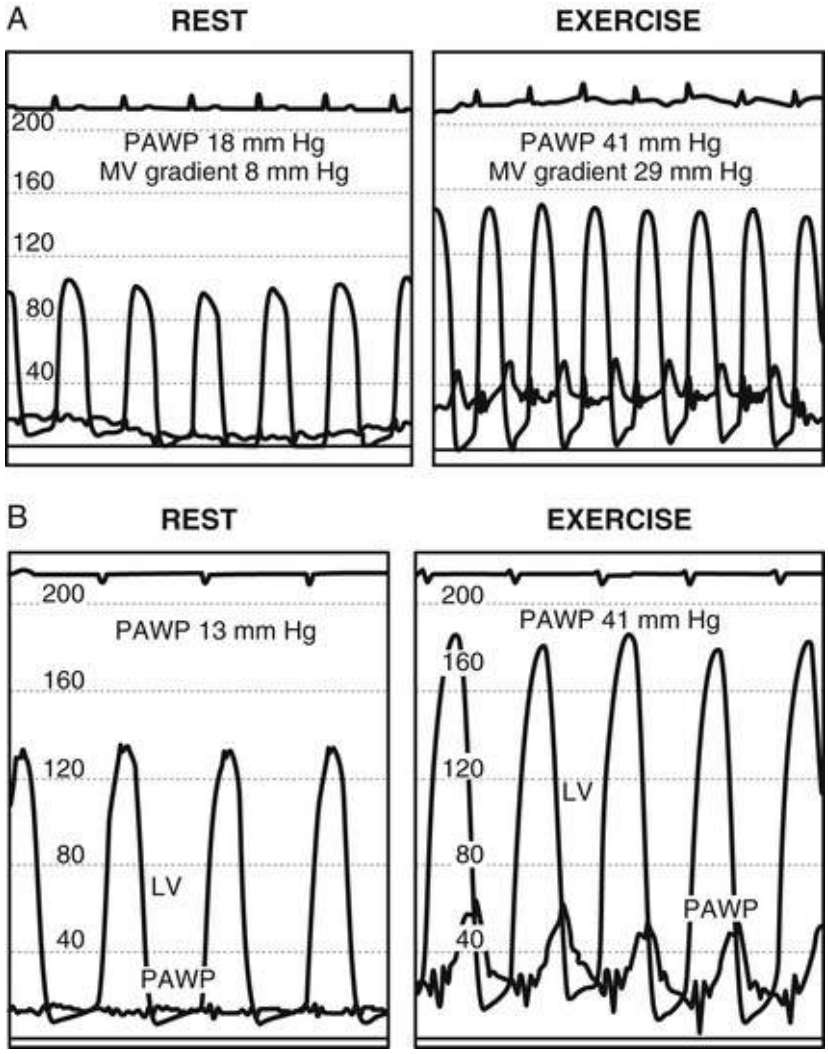


FIGURE 19.13 Overestimation of the transmitral gradient using pulmonary artery wedge pressure (*PAWP*) readings. **Left,** Simultaneous left ventricular pressure (*LV*) and PAWP in a patient with mitral stenosis. The measured mean gradient is 15 mm Hg. **Right,** In the same patient, the transmitral gradient is measured with a left ventricular and direct left atrial pressure (*LA*). The true mean transmitral gradient is only 6 mm Hg. (From Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century. Circulation 2012;125:2138.)



EFIGURE 19.12 Effects of exercise to unmask abnormalities not present in the resting state. **A,** Patient with mitral stenosis and significant symptoms out of proportion to the resting hemodynamics, which showed a mean resting mitral valve (*MV*) gradient of only 8 mm Hg and pulmonary artery wedge pressure (*PAWP*) of only 18 mm Hg. With supine bicycle exercise, the mean gradient rose to 29 mm Hg and PAWP to 41 mm Hg, indicating that the mitral stenosis was hemodynamically significant and clinically relevant. **B,** Patient with significant dyspnea on exertion but no significant valve disease and normal left ventricular (*LV*) systolic function. In the resting state, PAWP was only 13 mm Hg but increased to 41 mm Hg, with a large V wave at low levels of supine bicycle exercise. Mitral regurgitation was not present on simultaneous echocardiography, indicating that these symptoms were caused by noncompliance of the left atrium and left ventricle. (From Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century. Circulation 2012;125:2138.)

Pulmonary and Tricuspid Valve Stenosis (see Chapter 70)

The same principles and techniques apply for right-sided valves, using simultaneous pressure recordings. This can be done using multilumen catheters or two separate catheters. For the pulmonic valve, the gradient may be obtained on catheter pullback from the pulmonary artery to the right ventricle, although ideally it should be measured simultaneously.

Calculation of Stenotic Valve Orifice Areas.

The orifice area of a valve can be calculated based on hydraulic principles. The volume of flow (F) across an orifice equals the area of the orifice (A) times the velocity of flow (V): $F = A \times V$, and accordingly, the orifice area can be calculated as $A = F/V$. F equals the cardiac output, and V can be calculated from the transvalvular gradient based on Toricelli's law: $V = \sqrt{2gh}$, whereby g is the gravity-

related acceleration of velocity and h the pressure gradient.[40]

Gorlin and Gorlin refined this equation in 1951, which has become known as the "Gorlin formula" for the calculation of valve areas: $A = F/(C_c \times C_v \times \sqrt{2gh})$ (see Classic References). C_c is the coefficient of orifice contraction, which accounts for the fact that fluids tend to move through the center of an orifice, generating a physiologic orifice that is smaller than the anatomic orifice. C_v is the velocity coefficient, which allows for the pressure gradient not being fully converted to flow because some of the velocity is lost to friction. Neither of these two coefficients has ever been determined. Instead, an empiric value has been used to align the calculated area with the actual area on autopsy or surgery in 11 patients with mitral valve disease. The maximal discrepancy between the actual mitral valve area and calculated values was just 0.2 cm^2 for a constant C of 0.85. Importantly, such direct comparison data were never obtained for any of the other three valves, and not even empiric constants were developed for these. Rather, a constant of 1.0 has been assumed for any valve other than the mitral valve, which points out that the areas derived are best estimates only.

To derive a more accurate aortic valve area, because flow across the aortic valve occurs only during systole, the cardiac output often is divided by the actual systolic ejection period (SEP: the period from opening to closure of the aortic valve) times the heart rate (HR). In agreement with the Gorlin formula and factoring in a combined constant of 44.3 for C_c and C_v, the aortic valve area (AVA) can be calculated as follows:

$$\text{AVA } (cm^2) = [\text{Cardiac output } (mL/min) \div (\text{SEP} \times \text{HR})] \div [44.3 \times \sqrt{\text{Mean gradient}}]$$

The normal aortic valve area is 2.6 to 3.5 cm^2 in adults. Valve areas less than 1.0 cm^2 represent severe aortic stenosis (**see Chapter 68**).

The calculation is similar for the mitral valve area (MVA). Because mitral flow occurs only during diastole, cardiac output is corrected for the diastolic filling period (DFP; the period of opening to closure of the mitral valve), yielding the following formula:

$$\text{MVA } (cm^2) = [\text{Cardiac output } (mL/min) \div (\text{DFP} \times \text{HR})] \div [37.7 \sqrt{\text{Mean gradient}}]$$

The normal mitral valve area is 4 to 6 cm^2, and severe mitral stenosis is present with valve areas smaller than 1.0 cm^2 (**see Chapter 69**).

A simplified formula has been proposed by Hakki and colleagues (see Classic References). The effects of SEP and DFP are relatively constant at normal heart rates, which leads to the following equation:

$$\text{AVA } (cm^2) = \text{Cardiac output } (L/min) \div \sqrt{\text{Peak-to-peak or Mean gradient}}$$

Of note, mean aortic transvalvular gradient and peak-to-peak gradient yield similar correlation with the Gorlin formula and thus can be used in this formula. For the MVA, only the mean gradient was validated:

$$\text{MVA (cm}^2\text{)} = \text{Cardiac output (L/min)} \div \sqrt{\text{Mean gradient}}$$

The valve area using the Hakki formula can differ by almost 20% from the valve area using the Gorlin formula in patients with bradycardia or tachycardia.

Accurate measurements of pressure gradient and cardiac output are crucial because major management decisions rely on these. This is even more relevant in patients with borderline or low-pressure gradients. For this reason, it is essential to know the potential sources of error.

Because the square root of the mean gradient is used, miscalculation of the cardiac output leads to more erroneous valve areas than miscalculation of the gradient. Ironically, the imprecision in calculating the cardiac output is greatest in patients with a low cardiac output, in whom the pressure gradient is often inappropriately low and the severity of stenosis relies even more on accurate valve area determinations. In these patients, as well as in those with TR, the Fick method should be used. Neither thermodilution nor the Fick method should be used in patients with mixed valvular disease (stenosis and regurgitation) of the same valve because it overestimates stenosis severity in this setting. In patients with AR or MR, cardiac output is best measured by left ventriculography. If both AR and MR are present, accurate assessment of either the aortic or the mitral valve area is not possible.

Inherent to the Gorlin formula is the dependence of the calculated valve area on transvalvular flow. Although greater flow could lead to greater opening pressure and thus greater valve area, correlation studies with planimetry by transesophageal echocardiography (TEE) argue against it. Accordingly, even under increasing flow conditions, the aortic valve area by planimetry remains unchanged, whereas it increases with use of the Gorlin formula.

Intraventricular Pressure Gradients.

An outflow gradient can be present not only at the valvular level of the aortic valve but also at the subvalvular level of the ventricle. Whereas the aortic type is structural in nature, the LV type is caused by dynamic functional obstruction by hypertrophic myocardium (**see Chapter 78**). The aortic and LV waveforms display characteristics that are uniquely different (**Fig. 19.14A**). An easy assessment for any intracavitary gradient is by pullback of a multipurpose end-hole catheter from the LV apex to a posterior position just beneath the aortic valve. Even though a straightforward assessment, entrapment of the catheter by hypertrophic myocardium should be avoided because it leads to erroneous values. The level of loss of the aortic-LV gradient defines the gradient level, which is just slightly below. Accordingly, for any intracavitary gradient, the pressure difference between aorta and left ventricle is lost when the catheter is pulled back just below the aortic valve, and a LV waveform should still be present.

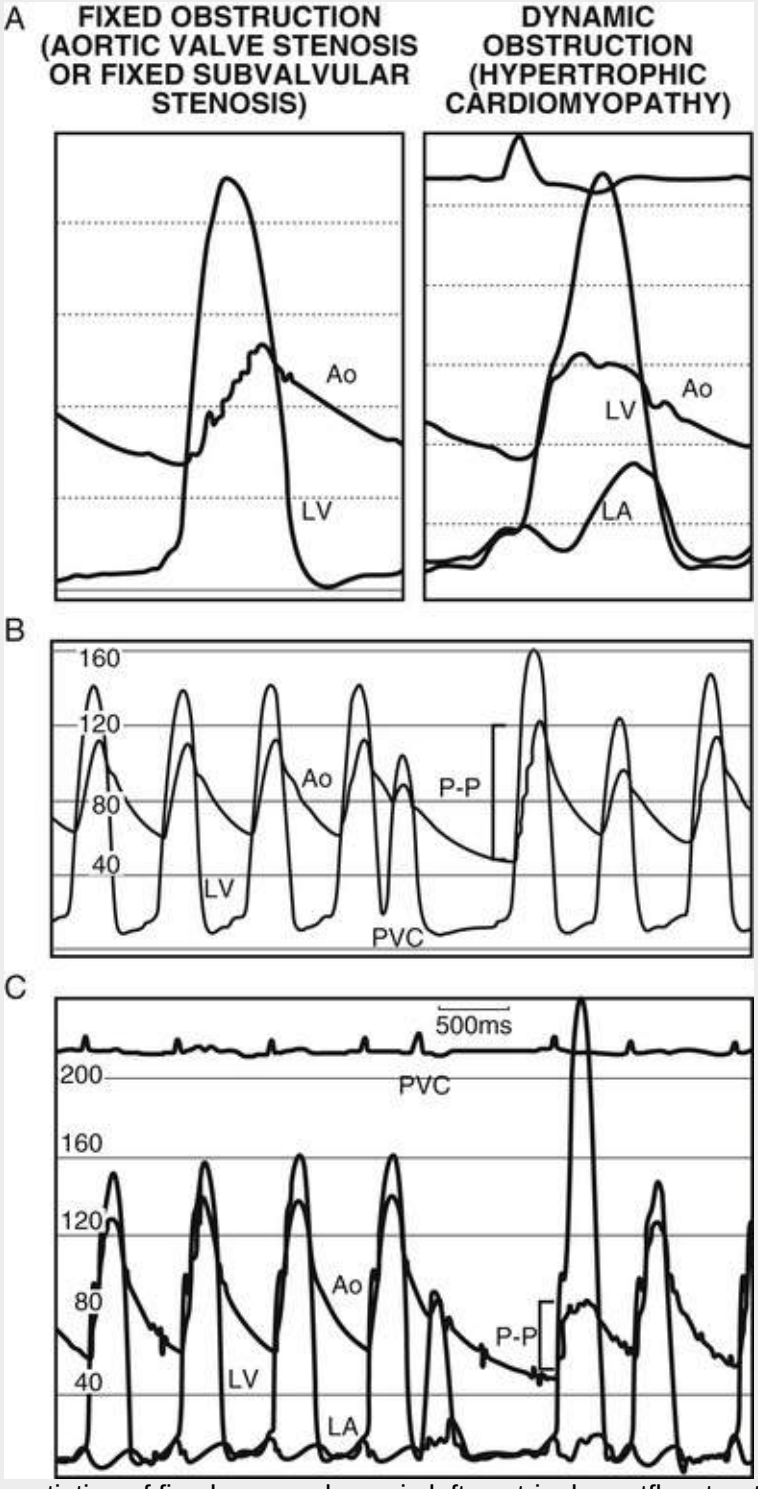
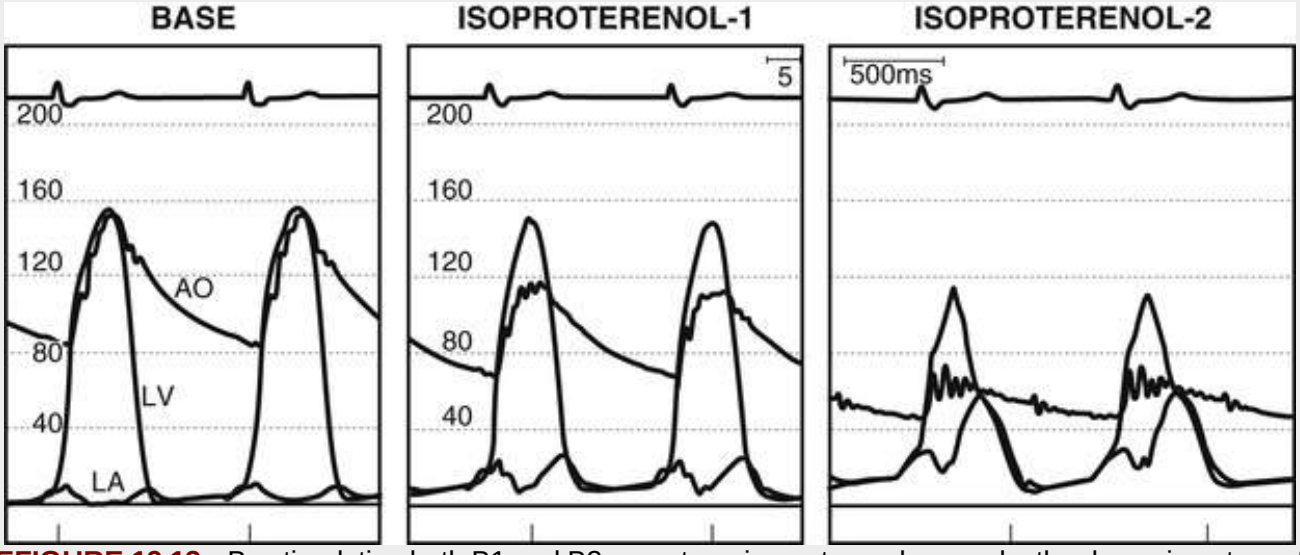


FIGURE 19.14 Differentiation of fixed versus dynamic left ventricular outflow tract obstruction. **A,** Fixed obstruction (either valvular stenosis or fixed subvalvular stenosis) typically leads to a parvus and tardus upstroke of the aortic pressure. Dynamic obstruction, however, such as related to hypertrophic cardiomyopathy (HCM), leads to a rapid rise of the aortic pressure (*Ao*) at the onset of aortic valve opening, which is subsequently blunted into a spike-and-dome contour as obstruction evolves in late systole. The left ventricular pressure (*LV*) also has a late peak because of the mechanism of this dynamic obstruction. **B,** In valvular aortic stenosis, pulse pressure (*P-P*) is increased on the first beat after the premature ventricular complex (*PVC*). **C,** In HCM, the opposite is observed. *LA,* Left atrial pressure. (From Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century. Circulation 2012;125:2138.)

Alternative methods for the assessment of intracavitary gradients are based on simultaneous pressure recordings in two different locations by use of a dual-lumen catheter, a double-sensor micromanometer catheter, or an end-hole catheter in the LV outflow tract and a second catheter in the left ventricle, placed by transseptal puncture. Provocation maneuvers to aid in the diagnostic evaluation of intracavitary

gradients include the introduction of a premature ventricular beat (subsequent drop in aortic pulse pressure is indicative of HCM, “Braunwald-Brockenborough-Morrow sign”; **Fig. 19.14B, C**), Valsalva maneuver, inhalation of amyl nitrate, or infusion of dobutamine or isoproterenol (**eFig. 19.13**).



EFIGURE 19.13 By stimulating both B1 and B2 receptors, isoproterenol unmasks the dynamic nature of the left ventricular (*LV*) outflow tract gradient in hypertrophic cardiomyopathy. **Left,** Absent LV outflow gradient at rest. *Middle,* Development of a 40 mm Hg gradient across the LV outflow tract with initial infusion of isoproterenol. *Right,* Progression to a 65 mm Hg LV outflow gradient with greater infusion of isoproterenol,. *AO,* Central aortic; *LA,* left atrial pressure. (From Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century. Circulation 2012;125:2138.)

Valvular Regurgitation.

The determination of the severity of valvular regurgitation in the cardiac catheterization laboratory is usually done by visual assessment and occasionally by calculation of the regurgitant fraction. Moreover, a complete hemodynamic evaluation by right-heart catheterization might provide very valuable information. In particular, pulmonary artery and PCWP at rest and with exercise are important parameters. With severe MR, a prominent *v* wave is characteristic, and the hemodynamic consequence is postcapillary pulmonary hypertension, especially under conditions of increased workload (**see Chapter 69**). It is a class I ACC/AHA guideline recommendation to perform a hemodynamic evaluation of either AR or MR when pulmonary artery pressures are disproportionate to regurgitation severities on noninvasive testing or when clinical and noninvasive findings are inconsistent.

Visual Assessment of Regurgitation.

The visual assessment relies on the injection of radiographic contrast material distal to the valve in question and the subsequent grading of opacification intensity and washout rapidity in the chamber proximal to it. It is important to be cognizant that the results are influenced by catheter position, volume of contrast, and chamber size and contractility, not regurgitant volume alone. Nevertheless, the semiquantitative classification scheme by Sellers and colleagues remains the reporting standard:

+	Minimal regurgitant jet seen. Clears rapidly from the proximal chamber with each beat.
++	Moderate opacification of the proximal chamber and clearing with subsequent beats.
+++	Intense opacification of the proximal chamber that becomes equal to that of the distal chamber.
++++	Intense opacification of the proximal chamber that becomes more dense than that of the distal chamber. Opacification often persists over the entire series of images obtained.

Regurgitant Fraction.

As a more quantitative measure, the regurgitant volume can be calculated, which is the fraction of the stroke volume that does not contribute to net cardiac output:

$$\text{Regurgitant stroke volume} = \text{Angiographic stroke volume} - \text{Forward stroke volume}$$

The angiographic stroke volume is calculated by the cardiac output measurement on the left ventriculogram, and the forward stroke volume by Fick or thermodilution cardiac output measurements; either value is then divided by the heart rate. Prerequisites to relate these output measurements to each other are similar heart rates, stable hemodynamic states between measurements, and the presence of only a single regurgitant valve.

The regurgitant stroke volume can also be determined in relation to the overall stroke volume, which is the regurgitant fraction:

$$\text{Regurgitant fraction (RF)} = \text{Regurgitant stroke volume} \div \text{Angiographic stroke volume}$$

The approximate correlation between RF and the visual grade of regurgitation severity is as follows: 1+ regurgitation is approximately equivalent to an RF of 20% or less, 2+ to an RF of 21% to 40%, 3+ to an RF of 41% to 60%, and 4+ to an RF of greater than 60%.

Shunt Determinations

The systemic and pulmonary circulations operate in series, and thus normally their output is the same. Any abnormal communication between them then generates a circuit shortcut or shunt. This can be from the systemic circulation to the pulmonary circulation (left-to-right shunt), from the pulmonary circulation to the systemic circulation (right-to-left shunt), or in both directions (bidirectional shunt). Given its ease, most shunt assessments in the cardiac catheterization laboratory are made by determination of the oxygen content in the blood at different levels of the circuit, given the normally very well-defined and distinct oxygenation values in the systemic and pulmonary circulations.

Even when using thermodilation, it is advisable to always obtain a pulmonary artery oxygen saturation. Values exceeding 80% should raise the suspicion for a left-to-right shunt. On the other hand, systemic arterial oxygen saturation less than 93% that persists after several deep breaths to counteract alveolar hypoventilation (as seen with oversedation or pulmonary venous congestion) should raise suspicion for a right-to-left shunt.

Oximetric Method

In addition to pulmonary artery sampling, a screening oxygen saturation should also be obtained from the SVC routinely with right-heart catheterization, possibly to detect even small left-to-right shunts. If the difference in oxygen saturation between these two samples is 8% or greater, a left-to-right shunt may be

present, and the oximetry run should be extended to include samples from the IVC, right atrium, and right ventricle. In fact, if an interatrial shunt is suspected, samples should be obtained at the level of the low, middle, and high right atrium, and for an interventricular shunt from the RV inflow tract, apex, and outflow tract. An absolute increase in oxygen saturation by 5% or more defined a significant step-up and the location of the shunt.

A small left-to-right shunt might be missed if the right atrium is used for screening purposes because of incomplete mixing of blood in the right atrium from the SVC, IVC, and coronary sinus. The coronary sinus blood has one of the lowest oxygen saturations, and the catheter should always be directed away from the coronary sinus when taking right atrial samples. However, oxygen saturation in the IVC is higher than in the SVC because oxygen extraction of the internal organs and lower extremity muscles is lower in a fasting and resting state than that of the brain. The best method for determination of the mixed venous saturation is by the Flamm formula, which is based on IVC and SVC samples (see below).

A full saturation run entails samples from the high and low IVC; high and low SVC; high, middle, and low right atrium; RV inflow, midcavity, and outflow tract; main pulmonary artery; left or right pulmonary artery; pulmonary vein and left atrium, if possible; left ventricle; and distal aorta. Right-to-left shunt assessments require samples from the pulmonary veins, left atrium, left ventricle, and aorta. A decrease (step-down) in oxygen saturation is expected in these cases.

Sampling error is reduced by obtaining multiple samples at each location, but this is rarely done in clinical practice because of cost and time restraints. Even with single samples and not being a very sensitive method in general, clinically significant shunts are still usually detected with oximetry runs. Balloon-tipped fiberoptic catheters have been developed that allow continuous registration of oxygen saturation during right-heart catheterization but are rarely used.

Shunt Quantification

To quantify the extent of a shunt, PBF and SBF need to be calculated, which is simply oxygen consumption divided by the difference in oxygen content across the pulmonary or systemic bed. The effective blood flow (EBF) is the fraction of mixed venous return received by the lungs without contamination by shunt flow. Under normal conditions, PBF, SBF, and EBF are equal.

The equations are as follows:

$$PBF = Vo_2 \div [(Pvo_2 - Pao_2) \times Hb \times 1.36 \times 10]$$

$$SBF = Vo_2 \div [(Sao_2 - Mvo_2) \times Hb \times 1.36 \times 10]$$

$$EBF = Vo_2 \div [(Pvo_2 - Mvo_2) \times Hb \times 1.36 \times 10]$$

Vo_2 (oxygen content) is determined as outlined previously. Pvo_2, Pao_2, Sao_2, and Mvo_2 are oxygen saturation of pulmonary venous, pulmonary arterial, systemic arterial, and mixed venous blood,

respectively.

MvO_2 is calculated by the Flamm formula:

$$MvO_2 = [3 \times (SVC\ O_2 \times Hb \times 1.36 \times 10) + 1 \times (IVC\ O_2 \times Hb \times 1.36 \times 10)] \div 4$$

Systemic arterial oxygen saturation may be substituted for pulmonary venous sampling, if at least 95%. Otherwise, in the absence of a right-to-left shunt, systemic arterial oxygen content is used. If a right-to-left shunt is present, pulmonary venous oxygen content is calculated as 98% of the oxygen capacity.

The size of an isolated left-to-right shunt is:

$$L \rightarrow R\ shunt = PBF - SBF$$

If an additional right-to-left shunt is present (bidirectional shunt), the approximate size of the left-to-right shunt is:

$$L \rightarrow R\ shunt = PBF - EBF$$

The approximate size of the right-to-left shunt is:

$$R \rightarrow L\ shunt = SBF - EBF$$

Clinically, the ratio of PBF to SBF (or Qp/Qs) is often used to express shunt significance. A ratio less than 1.5 indicates a small left-to-right shunt, a ratio of 1.5 to 2.0 a moderate-sized shunt, and a ratio greater than 2.0 a large left-to-right shunt. A flow ratio less than 1.0 indicates a net right-to-left shunt.

If oxygen consumption is not measured, the PBF/SBF ratio may be calculated as follows:

$$PBF/SBF\ ratio = (SaO_2 - MvO_2) \div (PvO_2 - PaO_2)$$

where SaO_2, MvO_2, PvO_2, and PaO_2 are systemic arterial, mixed venous, pulmonary venous, and pulmonary arterial blood oxygen saturation, respectively.

Physiologic and Pharmacologic Maneuvers

Not infrequently, potentially significant cardiac abnormalities are absent under resting conditions and require unmasking by physiologic and/or pharmacologic provocation maneuvers.

Dynamic Exercise.

Dynamic exercise is still the most physiologic way of testing. In the catheterization laboratory, this is

performed with a supine bicycle ergometry. Once a balloon flotation catheter is inserted in a sterile manner via an antecubital or internal jugular vein, even an upright bicycle and treadmill exercise can be performed under hemodynamic monitoring outside the catheterization laboratory.

Under normal conditions, the increased oxygen demand induced by exercise is met by an increase in cardiac output and peripheral oxygen extraction. Cardiac dysfunction impairs the increase in cardiac output, and the demands of exercise can only be met by increased peripheral oxygen extraction, leading to often profound drops in mixed venous oxygen saturation and thus profound increases in arteriovenous oxygen difference. The fact that cardiac output and oxygen consumption are in linear correlation allows for a prediction of the cardiac index at a given level of oxygen consumption. The exercise index represents the ratio of the actually observed to the predicted cardiac index. A value of 0.8 or greater reflects a normal cardiac output response to exercise. Another way of expressing the same relationship is the *exercise factor*, defined as the increase in cardiac output divided by the increase in oxygen consumption. An exercise factor of 6 or higher is normal; that is, for every 100-mL/min increase in oxygen consumption, cardiac output should increase by at least 600 mL/min with exercise.

Although the most suitable approach for the catheterization laboratory, there are important nuances to supine exercise. In the early phase, there is increased venous return, augmenting LV end-diastolic volume and stroke volume. However, at progressively higher levels of exercise, LV end-systolic volume and LV end-diastolic volume decrease, minimizing stroke volume increase. The augmentation in cardiac output with this form of stress testing is therefore accomplished primarily by an increase in heart rate. It can therefore remain low, for instance, because of chronotropic incompetence alone.

However, this type of invasive hemodynamic exercise testing still is very useful for the diagnostic workup of patients with presumed heart failure with preserved ejection fraction (HFpEF) and valvular heart disease of no or borderline significance in the resting state[42] (**see Chapter 26**). Exercise increases LVEDP, PCWP, and pulmonary artery pressure in patients with HFpEF. It increases transvalvular mitral gradient and pulmonary artery pressure in mitral stenosis. In patients with clinically relevant valvular regurgitation, exercise increases LVEDP, PCWP, and SVR in conjunction with a reduced exercise index (<0.8) and abnormal exercise factor (<6). Simultaneous echocardiographic evaluation of valvular regurgitation and invasive hemodynamic assessment is also useful in equivocal cases (**see Chapter 14**).

Pacing Tachycardia.

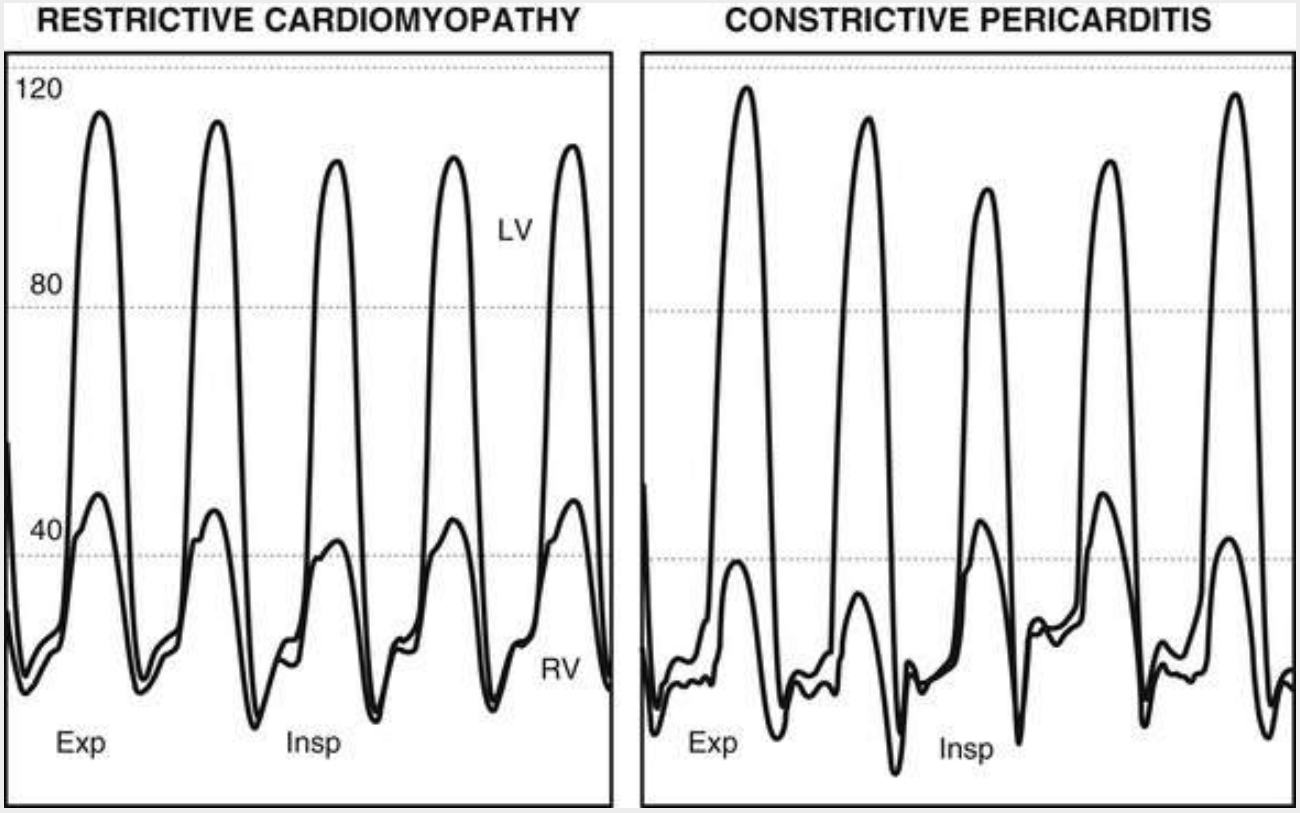
Rapid atrial or RV pacing increases myocardial oxygen consumption and myocardial blood flow, LV end-diastolic volume decreases, and there is little change in cardiac output. It can be a useful method to define the severity of mitral valve stenosis. The immediate on-and-off effect is of benefit.

Physiologic Stress.

Various forms of physiologic stresses can be used, all of which alter the filling conditions of the heart. For example, the Valsalva maneuver in the strain phase decreases venous return and thus LV preload, which increases the systolic LV outflow tract pressure gradient in patients with HCM. In these patients, induction of a premature ventricular beat (Brockenbrough maneuver) paradoxically decreases the pulse pressure and accentuates the spike-and-dome configuration on the aortic pressure waveform of the subsequent ventricular beat as the outflow gradient increases.

Another very useful physiologic challenge is rapid volume loading, which may unmask and/or distinguish pericardial constriction from myocardial restriction (**see Chapter 83**). Both conditions share early rapid filling dynamics and equalization of LV and RV pressure at end-expiration. One of the distinguishing features of constriction, however, is that the pericardial restraint does not allow any overall volume expansion of the cardiac chambers. Accordingly, any volume expansion of the right

ventricle will be at the cost of volume contraction of the left ventricle, and vice versa, so-called exaggerated ventricular interdependence. On inspiration, therefore, because of increased venous return, there is an increase in RV filling, volume, and pressure, reflected in an increase in the systolic pressure-time area on the RV pressure tracing. Concomitantly, LV volume and pressure decrease, reflected in a decrease in the LV systolic pressure-time area on the simultaneous LV pressure tracing (**eFig. 19.14**). The ratio of the RV to the LV systolic pressure–time area in inspiration versus expiration, the *systolic area index*, is positive in constriction but not in restriction (1.4 ±0.2 versus 0.92 ±0.019; $P < 0.0001$).[51] A systolic area index greater than 1.1 has a sensitivity of 97% and predicted accuracy of 100% for identifying constriction.[43] In real time, ventricular interdependence is often assessed in the catheterization laboratory by visual assessment of the LV and RV waveform dynamics relative to each other over the course of multiple respiratory cycles. It shows dyssynchrony in constriction and synchrony in restriction (**eFig. 19.14**).



EFIGURE 19.14 **Left,** In restrictive cardiomyopathy, there is a drop in left ventricular (*LV*) pressure and a drop in right ventricular (*RV*) pressure during inspiration (*Insp*). This indicates that the elevation of ventricular filling pressures is caused by a myocardial restrictive disease. *Right,* In constrictive pericarditis, there is ventricular discordance, with an increase in RV pressure and a decrease in LV pressure during inspiration. This is caused by the enhancement of ventricular interaction and dissociation of intrathoracic and intracardiac pressures. *Exp,* Expiration. (From Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century. Circulation 2012;125:2138.)

A rapid *y* descent is indicative of rapid early diastolic filling and corresponds to the dip of the square root sign on the diastolic ventricular pressure tracing. It is present in both restriction and constriction, but a rapid *y* descent is absent in patients with tamponade. The patients usually have a marked pulsus paradoxus, which is a greater than 10 mm Hg drop in systemic systolic blood pressure during inspiration. It can also be present in constrictive pericarditis and is an expression of the ventricular interdependence. The lack of decline or more obvious increase in atrial (venous) pressure during inspiration (Kussmaul sign) reflects impaired compliance of either the pericardium or myocardium and thus is not a

distinguishing feature between constriction and restriction.

Pharmacologic Maneuvers

A number of drugs are used in the cardiac catheterization laboratory. One of the most common indications is the determination of reversibility of pulmonary hypertension either by nitric oxide or sodium nitroprusside (**see Chapter 85**).

Nitric oxide is an endothelium-derived vasodilator, and if administered by inhalation, it is rapidly inactivated. Thus it can be used safely without causing systemic hypotension and effectively to assess a pulmonary vasodilator response, which is a fairly accurate predictor of the response to medical therapy. The dose can be doubled in 5- to 10-minute intervals from 10 to 80 ppm, but a single uniform dose of 80 ppm is equally feasible. Cardiac output, pulmonary artery pressure, and PCWP are the key study parameters, allowing calculation of PVR. A positive vasodilator response (reversibility) is defined as a decrease in mean pulmonary artery pressure of at least 10 mm Hg to an absolute mean pulmonary artery pressure of less than 40 mm Hg without a decrease in cardiac output.

If PCWP is elevated at baseline, inhaled nitric oxide is not to be used as a reduction in PVR would lead to increased forward flow through the pulmonary vasculature and thus increased filling of left-sided heart chambers that have already reached their maximum compliance, precipitating further increase in PCWP with the risk of pulmonary edema.

With elevated PCWP, sodium nitroprusside is to be used to document if reduction in afterload and LV filling pressure lowers pulmonary artery pressure and possibly improves cardiac output. This holds true in cases of MR, dilated cardiomyopathy, and HFpEF. A typical protocol is to commence the infusion at 0.25 to 0.5 µg/kg/min following acquisition of baseline hemodynamic data and to uptitrate at the same dose range in 3- to 5-minute intervals until PCWP is less than 18 mm Hg, systemic blood pressure less than 90 mm Hg, or development of symptoms (e.g., lightheadedness).[44,45] Hemodynamic measurements are then repeated, and a positive response is usually defined as a drop in PVR of at least 20%. This intervention can also be useful to define the degree of aortic stenosis in those with a severely narrowed valve area but low gradient and systemic hypertension[46] (**see Chapter 68**).

Up to one third of patients with low-flow, low-gradient aortic stenosis—a mean aortic gradient below 30 mm Hg and low cardiac output/low ejection fraction (<40%)—may be incorrectly defined as having severe aortic stenosis by the Gorlin formula. In order to differentiate true from pseudo–severe aortic stenosis, dobutamine can be infused at 5 µg/kg/min and increased by 3 to 10 µg/kg/min every 5 minutes. The test is ended once a maximum dose of 40 µg/kg/min is reached, the heart rate is greater than 140 beats/min, and/or cardiac output is increased by 50%, or the mean gradient increased to more than 40 mm Hg. Patients with a final aortic valve area smaller than 1.2 cm^2 and mean gradient greater than 30 mm Hg are considered to have severe aortic stenosis. A coronary angiogram is advised before dobutamine infusion in those at high risk for severe coronary artery disease as an explanation for the reduced cardiac function.

In patients with HCM, various manipulations can be performed to confirm the dynamic nature of the outflow tract gradient (**see Chapter 78**). The gradient is increased by isoproterenol due to increased inotropy and chronotropy, and by nitroglycerin or amyl nitrate due to decreased preload and afterload. Phenylephrine, by increasing afterload (SVR), is used to reduce the dynamic outflow tract gradient in obstructive HCM.

Endomyocardial Biopsy

The technique of percutaneous endocardial and myocardial biopsy is more than 50 years old with only slight refinements over time (**Fig. 19.15**). Currently it is mainly used to monitor for rejection after cardiac transplantation (**see Chapter 28** and Classic References, Konno). For native hearts, there are two class I indications, both directed toward giant cell myocarditis (**see Chapter 79**), amenable to immunosuppressive therapy and heart transplantation (**Table 19.4**). The first class I indication is new-onset heart failure of less than 2 weeks' duration associated with either normal or enlarged LV size and hemodynamic compromise, in essence fulminant myocarditis. The second class I indication is new-onset heart failure of up to 3 months' duration complicated by LV dilation, new ventricular arrhythmias, advanced heart block, or failure to respond to treatment within 2 weeks. The use of biopsy for suspected anthracycline toxicity (**see Chapter 81**) or restrictive disease is considered a class IIa indication.[47]

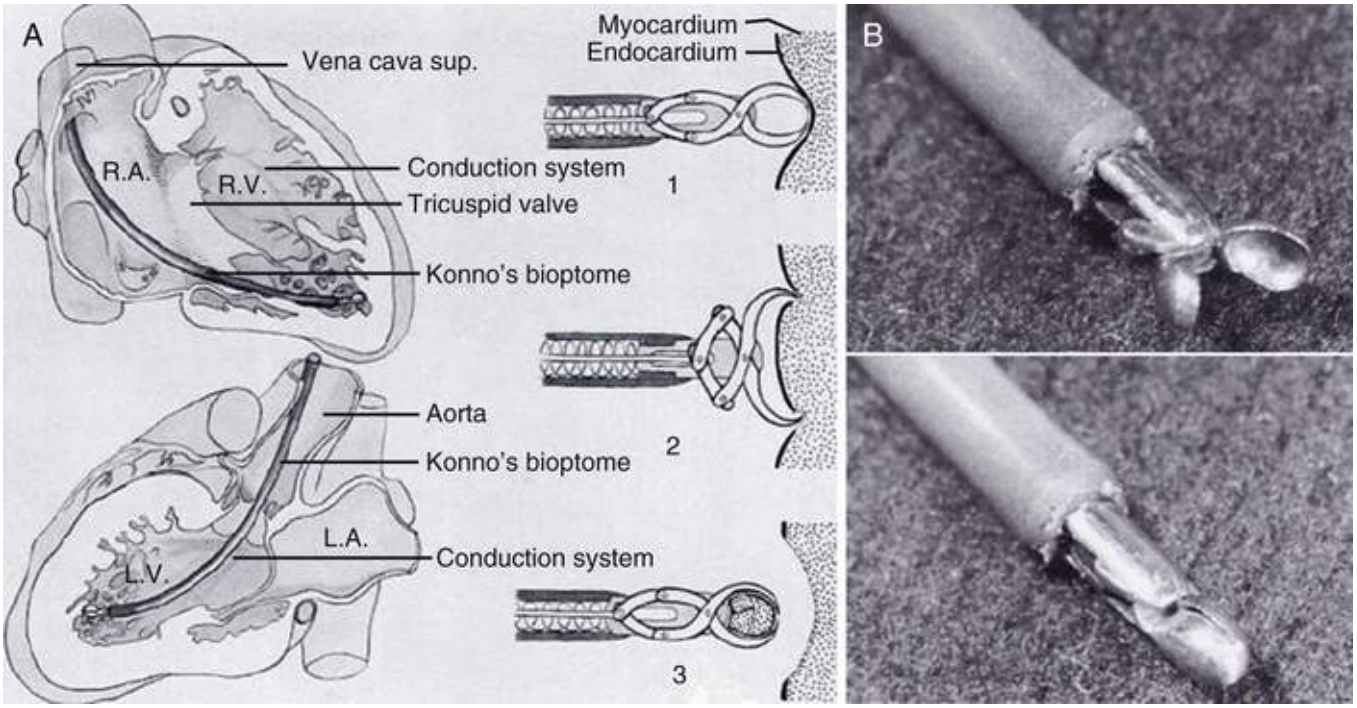


FIGURE 19.15 **A,** Original illustration by Konno and Sakakibara of the percutaneous technique of endocardial and myocardial specimen collection by use of a bioptome. **B,** Biopsies are taken by opening and closing the cutting claw at the tip of the catheter. (From Konno S, Sakakibara S. Endo-myocardial biopsy. Dis Chest 1963;44:345.)

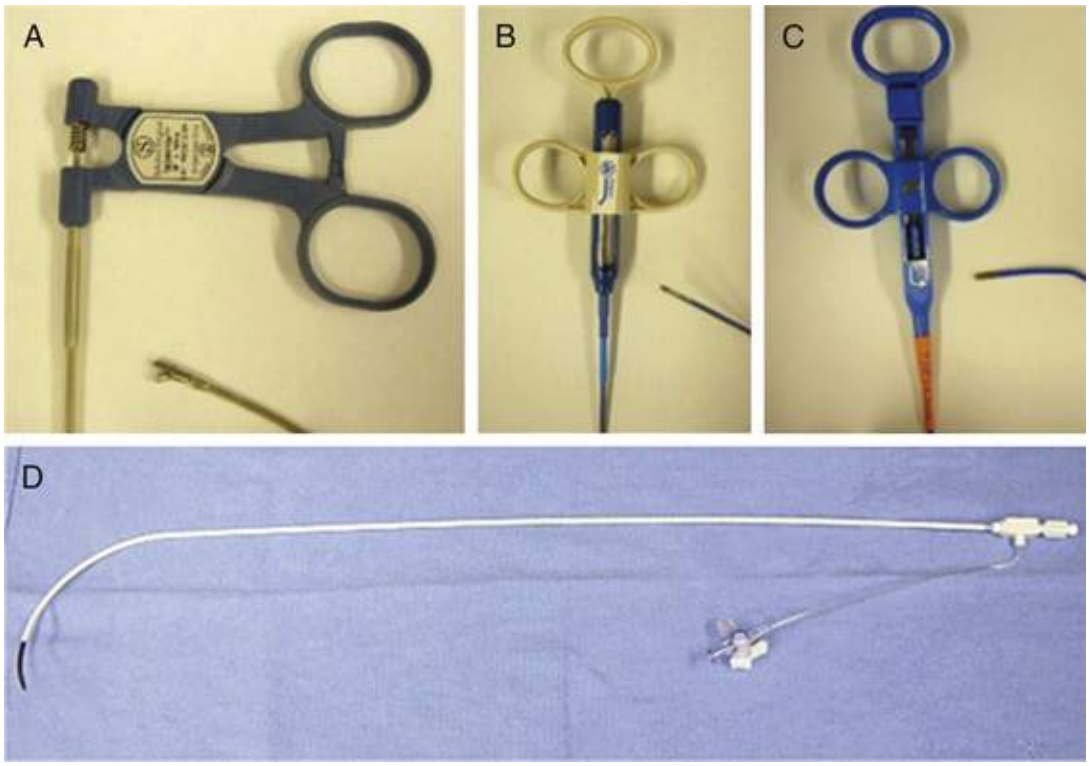
TABLE 19.4

Endomyocardial Biopsy Recommendations

CLINICAL SCENARIO	CLASS OF RECOMMENDATION	LEVEL OF EVIDENCE
New-onset heart failure of <2 weeks' duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise	I	B
New-onset heart failure of 2 weeks' to 3 months' duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 2 weeks	I	B
Heart failure >3 months' duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 2 weeks	IIa	C
Heart failure associated with dilated cardiomyopathy of any duration and suspected allergic reaction and/or eosinophilia	IIa	C
Heart failure associated with suspected anthracycline-induced cardiomyopathy	IIa	C
Heart failure associated with unexplained restrictive cardiomyopathy	IIa	C
Suspected cardiac tumors	IIa	C
Unexplained cardiomyopathy in children	IIa	C
New-onset heart failure of 2 weeks' to 3 months' duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 2 weeks	IIb	B
Heart failure >3 months' duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 2 weeks	IIb	C
Heart failure associated with unexplained hypertrophic cardiomyopathy	IIb	C
Suspected arrhythmogenic RV dysplasia	IIb	C
Unexplained ventricular arrhythmias	IIb	C
Unexplained atrial fibrillation	III	C

From Cooper LT et al. The role of endomyocardial biopsy in the management of cardiovascular disease. J Am Coll Cardiol 2007;50:1914.

Endomyocardial biopsy is performed mainly with disposable bioptomes, most often preshaped 50-cm bioptomes, delivered through the right internal jugular vein[48] (**eFig. 19.15**). To overcome potential sources of complications, as in the case of chronic, adherent thrombus or difficult atrial suture lines, it is advisable to use a long sheath. With a right internal jugular vein occlusion, one may consider a left internal jugular vein approach with a long catheter sheath to overcome the resistance of the two acute angles along this approach (1) into the left innominate/brachiocephalic vein and (2) into the SVC. Another alternative is the right subclavian vein approach, but it still needs to be addressed beforehand if the occlusion extends into the SVC. Often, a femoral venous approach is thus taken. LV biopsies are performed on rare occasions by the femoral arterial approach.[49,50]



EFIGURE 19.15 Commonly used bioptomes. **A,** Single-use 50-cm Novatome (Sholten Surgical Instruments, Lodi, Calif) with a 2.3-mm tip that requires a 9F sheath. **B,** Argon endomyocardial biopsy forceps (Argon Medical Devices, Athens, Texas) with a 1.8-mm tip that requires a 6F sheath or a 2.3-mm tip that requires a 7F sheath. **C,** Bipal 7 bioptome, 50 cm and 104 cm (Cordis, Miami Lakes, Fla) with a 2.3-mm tip that requires a 7F sheath. **D,** 8F Transseptal Mullens (Medtronic, Minneapolis, Minn) sheath when using the longer Bipal 7 bioptome through right femoral vein access to improve tip control and placement. (From AM, Maleszewski JJ, Rihal CS. Current status of endomyocardial biopsy. Mayo Clin Proc 2011;86:1095.)

For the right internal jugular venous approach, a 7F short straight sheath or long curved sheath (e.g., FastCath 45-cm introducer sheath with 30-degree curve type; St. Jude Medical, St. Paul, Minnesota) is introduced in Seldinger technique, ideally under ultrasound guidance and using a micropuncture kit for initial access. If a short sheath is used, the atrial suture line may be felt as a ridge that is passed as a 7F bioptome is advanced under fluoroscopic guidance. Any resistance or unusual deviation of the bioptome to the side should prompt reorientation to avoid perforation. Within the right atrium, a slight counterclockwise rotation usually allows the device to advance across the tricuspid valve, maintaining the torque unto the interventricular septum. Again, the lateral wall of the right atrium should be avoided, and force should never be used since perforations can occur. A too-medial orientation and associated risk of probing into the coronary sinus should also be avoided. The same general maneuvers apply to the placement of long preshaped sheaths, which are advanced through a 0.035-inch J-tip wire into the right ventricle and are positioned against the RV septum. The sheath should be aspirated and flushed to avoid thrombus formation, and RV pressure monitoring should exclude damping from engagement against the wall. The bioptome is then passed through the sheath directly onto the septum. However, this needs to be confirmed visually. For all these aspects of the procedure, 2D echocardiography can be of superior guidance than fluoroscopy. For the latter, both the 30-degree RAO and the 40-degree LAO view are advisable. The RAO view is to confirm that the device is in the midventricle away from the apex, the LAO view that the tip is oriented toward the interventricular septum. If long sheaths are used, infusion of contrast material through the side port can help confirm position.

For the femoral venous approach, a long 7F sheath (e.g., Mullins-style introducer sheath) is introduced and under fluoroscopy directed toward the septum. The conventional sheath has a 45-degree angle on its distal end; however, specifically designed sheaths have dual curves: the usual 180-degree curve and an

additional distal perpendicular septal plane curve of 90 degrees. This allows for improved manipulation and positioning toward the interventricular septum. With long sheaths, and especially if the Mullins sheath is used, continuous slow flush is recommended given the predisposition of this sheath to thrombus formation.

Regardless of access, contact of the bioptome with the myocardium is confirmed by induction of premature ventricular complexes (PVCs), resistance to further advancement, and device transmission of the RV impulse. The bioptome is then, under imaging, drawn back slightly from the septum, the jaws are opened, and the bioptome is readvanced to make contact with the myocardium; thereafter the jaws are closed. In good position, a slight tug is usually felt on removal of the device. Four to five biopsy samples, each at least 1 mm in size, often suffice for pathologic analysis. Preprocedural consultation with a pathologist or transplant cardiologist may be required to ensure appropriate biopsy sampling and processing. This includes addressing whether a global or a focal process is being addressed. For example, in patients with suspected sarcoidosis (**see Chapter 77**), the biopsy should be directed to areas that were identified as active on noninvasive imaging. Special cases may even require electromechanical mapping to orient the bioptome to the right location.

If an LV biopsy is to be performed, a long sheath is advanced from the common femoral artery into the left ventricle just below the mitral apparatus and away from the posterobasal wall over a wire and supported by an interior multipurpose or pigtail catheter, which forms the tip. Once in position, the sheath is advanced, and the catheter is exchanged for a long LV bioptome. Directing the LV bioptome by appropriate imaging is key again. As previously outlined, a constant slow infusion through the sheath minimizes the chances of thrombus formation and air embolism, which is even of greater risk with LV biopsies.

Potential complications of endomyocardial biopsy include cardiac perforation with tamponade (usually free wall sampling); emboli of air, tissue, or thrombus; arrhythmias; electrical conduction disturbances; injury to the tricuspid valve; vasovagal reactions; and pneumothorax (upper chest access complication). Another complication is the generation of coronary to LV or RV (coronary-cameral) fistula.[51] Overall, the cited complication rate may be as high as 6%, but the risk for cardiac perforation with tamponade is less than 0.1%. Importantly, endomyocardial biopsy is the most common cause of severe TR after heart transplantation.[48] This risk can be reduced with the use of longer sheaths and/or echocardiographic assistance at the time of biopsy to direct away from the tricuspid valve apparatus. Echocardiography is also useful to direct away from the moderator band, the disruption of which can cause a right bundle branch block (BBB); this is of greater significance in those with left BBB. In general, echocardiography, and more recently 3D echocardiography, has been found to improve positioning of the sheath and bioptome tip in one half and one third of the patients, respectively[52] (**see Chapter 14**).

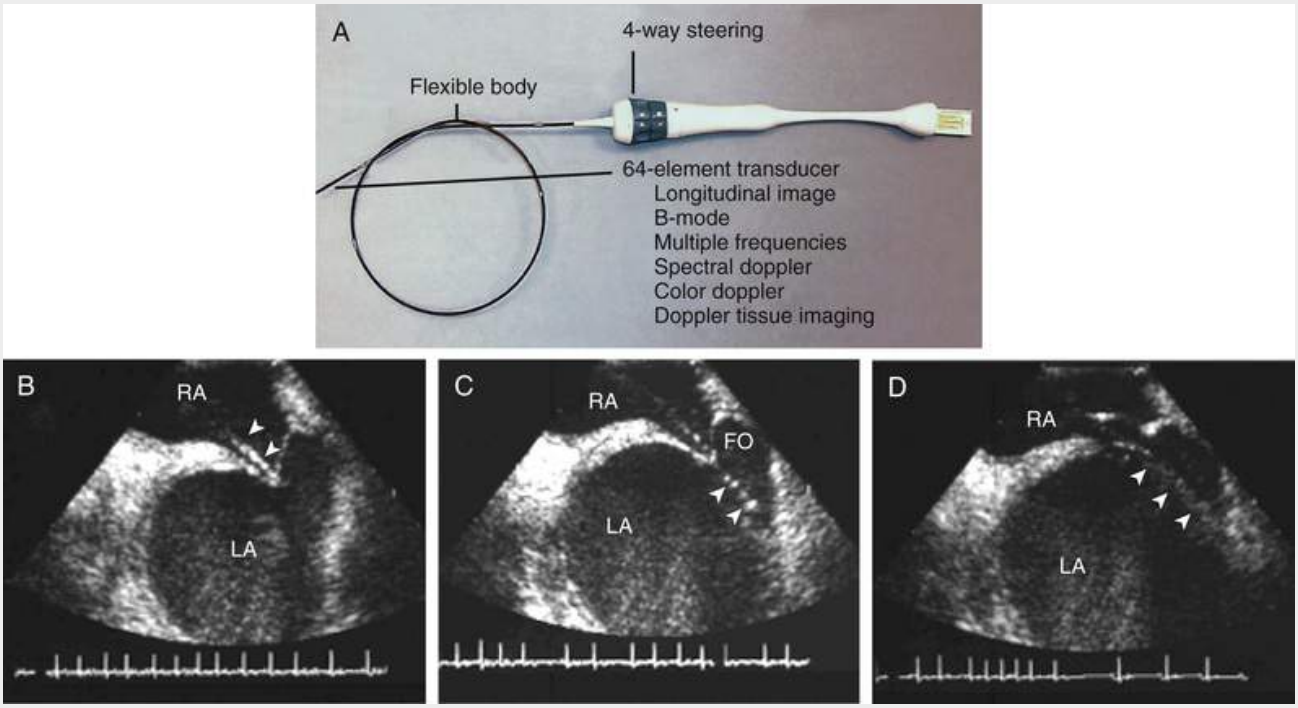
Systemic embolization and ventricular arrhythmias are more common with LV biopsy. LV biopsy should generally be avoided in patients with right bundle branch block because of potential for the development of complete atrioventricular block, as well as in patients with known LV thrombus.

Adjunctive Diagnostic and Therapeutic Techniques

Intracardiac Echocardiography

Intracardiac echocardiography (ICE) provides excellent imaging of the interatrial or interventricular

septum and left-sided heart structures from either the right atrium or ventricle. It is thus used to guide procedures, which are performed mainly at the atrial level, including transseptal puncture or percutaneous closure of atrial septal defects (ASDs) and patent foramen ovale. ICE has also been used in electrophysiologic procedures to identify structures difficult to view with fluoroscopy, such as pulmonary veins. A great advantage is the mitigation of the need for TEE and anesthesia (**eFig. 19.16**).



EFIGURE 19.16 **A,** ICE disposable transducer (Acuson) with a steering apparatus on proximal end and a flexible body with a transducer on distal tip of the catheter. **B,** Tenting of membranous fossa by dilator-needle assembly. Transseptal needle assembly (*arrowheads*) is advanced to indent fossa membrane. **C,** Advancement of transseptal needle across membranous fossa. Here the needle (*arrowheads*) is seen near posterosuperior left atrial wall. The membrane remains tented because the dilator has not yet crossed the septum. **D,** Passage of dilator and sheath across interatrial septum. The dilator and sheath assembly has now advanced into the left atrium, thereby releasing the tenting of the membranous fossa. *FO,* Fossa ovalis; *LA,* left atrium; *RA,* right atrium. (From Johnson SB, Seward JB, Packer DL. Phased-array intracardiac echocardiography for guiding transseptal catheter placement: utility and learning curve. Pacing Clin Electrophysiol 2002;25:402.)

The ICE imaging probe's catheter is available in 8F or 10F size and in 90- or 110-cm length and has two steering planes: anterior-posterior and left-right. The transducer operates at frequencies of 5 to 10 MHz and allows for 2D, color, and spectral Doppler echocardiographic imaging. The penetration length is up to 15 cm. The ICE probe is introduced by femoral venous access in the usual way, using an adequately sized sheath. The catheter has a stiffness that matches standard right-heart catheters and thus operates as such (short access sheath and careful advancement under fluoroscopy).

Percutaneous Hemodynamic Support

For patients with significant hemodynamic compromise, four main modalities of support are available in the catheterization laboratory: intra-aortic balloon pump (IABP), Impella, TandemHeart, and extracorporeal membrane oxygenation (ECMO)[53] (**Fig. 19.16** and **Table 19.5**).

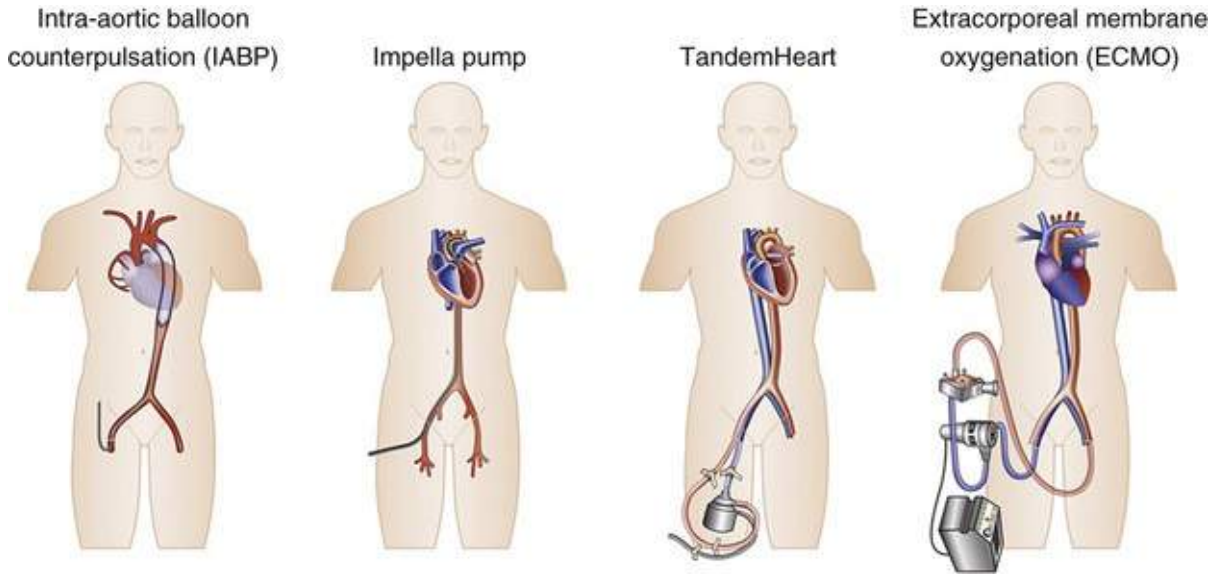


FIGURE 19.16 Percutaneous assist devices in cardiogenic shock. Intra-aortic balloon counterpulsation (IABP); Impella pump; TandemHeart; extracorporeal membrane oxygenation (ECMO). (From Werdan K, Gielen S, Ebelt H, Hochman JS. Mechanical circulatory support in cardiogenic shock. Eur Heart J 2014;35:156.)

TABLE 19.5

Currently Available, FDA-Approved Percutaneous Mechanical Support Devices

	IABP	IMPELLA 2.5	IMPELLA 5.0	TANDEMHEART	ECMO
Technical Aspects					
Pump mechanism	Pneumatic	Axial flow	Axial flow	Centrifugal	Centrifugal
Cannula size	7.9F	13F	22F	21F inflow; 15F-17F outflow	18-21F inflow;15F-22F outflow
Insertion technique	Descending aorta via the femoral artery	12F catheter placed retrograde across aortic valve via femoral artery	21F catheter placed retrograde across aortic valve via surgical cutdown of femoral artery	21F inflow cannula into left atrium via femoral vein and transseptal puncture and 15F-17F outflow cannula into femoral artery	Inflow cannula into right atrium via femoral vein, outflow cannula into descending aorta via femoral artery
Implantation time	+	++	++++	+++	++
Risk of limb ischemia	+	++	++	+++	+++
Anticoagulation	+	+	+	+++	+++
Hemolysis	+	++	++	++	++
Postimplantation management complexity	+	++	++	++++	+++
Duration of use	7 days	10 days	10 days	14 days	14-21 days
Relative costs	+	+++	++++	++++++	++++++
Hemodynamic Aspects					
Hemodynamic support	0.5-1.0 L min^{-1}	2.5 L min^{-1}	5.0 L min^{-1}	4 L min^{-1}	>4.5 L min^{-1}
Peripheral tissue perfusion	No significant increase	Improved	Improved	Improved	Improved
Coronary perfusion	Slight increase	Unknown	Unknown	Unknown	Unknown
LV stroke volume	Slight increase	Reduced	Reduced	Reduced	Reduced
LV preload	Slightly reduced	Slightly reduced	Slightly reduced	Reduced	Reduced
Afterload	Reduced	Neutral	Neutral	Increased	Increased
PCWP	Slightly reduced	Slightly reduced	Slightly reduced	Reduced	Reduced
Recommendations					
Indications	Cardiogenic shock (incl. RV failure), severe heart failure, MI, refractory arrhythmias, bridge to transplant/LVAD	Cardiogenic shock (no RV failure), perioperative support, bridge to transplant/LVAD	Cardiogenic shock (no RV failure), perioperative support, bridge to transplant/LVAD	Cardiogenic shock (no RV failure), perioperative support, bridge to transplant/LVAD	Cardiogenic shock (incl. RV failure), massive pulmonary embolus, cardiac arrest, bridge to transplant or LVAD/BiVAD, support after cardiac surgery
Contraindications	AR, severe PAD, aortic aneurysms, severe thrombocytopenia, inability to anticoagulate	AS, AR, significant aortic valve calcification, severe PAD, VSD, LV thrombus	AS, AR, significant aortic valve calcification, severe PAD, VSD, LV thrombus	Predominant RV failure, VSD, severe PAD	AS, AR, significant aortic valve calcification, severe PAD, VSD, LV thrombus

AR, Aortic regurgitation; *AS,* aortic stenosis; *ECMO,* extracorporeal membrane oxygenation; *F,* French; *LVAD,* Left ventricular assist device; *PAD,* peripheral artery disease; *PCWP,* pulmonary capillary wedge pressure; *VSD,* ventricular septal defect.

Intra-Aortic Balloon Pump

The IABP operates by inflation of a balloon (30 to 50 mL in volume) with a helium gas in diastole and deflation in systole gated by the surface ECG or the pressure tracing.[53] This action of "counterpulsation" augments diastolic perfusion pressure in the coronary arteries and reduces LV afterload stress for the myocardium. There is also a reduction in LV preload, LVEDP, and PCWP. The volume shift by the balloon pump increases LV stroke volume by 15% to 30% and cardiac output by 1 L/min. The greatest benefit is seen in patients with severely reduced cardiac output. However, these patients may need greater augmentation in cardiac output than provided under most optimal conditions with an IABP. Furthermore, such patients may have poor RV function and possibly even poor oxygenation and may require more extensive biventricular and cardiopulmonary support.

IABPs have been traditionally used for patients with refractory angina, severe left main disease, cardiogenic shock, or mechanical complications of myocardial infarction (including severe MR and VSD) (**see Chapter 58**). An IABP may also be valuable at the time of MI and even after primary PCI, depending on the hemodynamics. It has been used as a support tool for patients undergoing high-risk PCI.

Randomized controlled trials (RCTs) and meta-analyses, however, argue against a general benefit in terms of morbidity and mortality. Despite an increase in coronary perfusion pressure, coronary blood flow may not be augmented significantly once severe coronary artery stenosis or acute coronary syndrome is present. The ACC/AHA STEMI guidelines give a class IIa indication for the use of IABP for patients with acute MI with cardiogenic shock, whereas the European Society of Cardiology (ESC) gives a class IIb indication. Contraindications include moderate or severe AR, aortic dissection, aortic aneurysm, patent ductus arteriosus, severe PAD, bleeding disorders, and sepsis.

The IABP is placed through the femoral artery in the standard Seldinger technique using 7F or 8F sheaths and a 0.025-inch wire. The size of the balloon is based on the patient's height. Under fluoroscopy, the tip is placed 2 to 3 cm below the level of the left subclavian artery. Chest radiographs should be obtained daily thereafter, and the optimal position is 2 cm above the carina.[54] Timing of the balloon inflation is adjusted in the 1 : 2 mode (every other beat inflation) using the ECG or pressure tracing. The optimal timing of inflation coincides with the dicrotic notch on the aortic pressure waveform and of deflation immediately before systole, which ensures maximal diastolic flow augmentation and maximal systolic unloading (**Fig. 19.17**). All patients should undergo anticoagulation, even though heparin-free use of IABP has been reported.

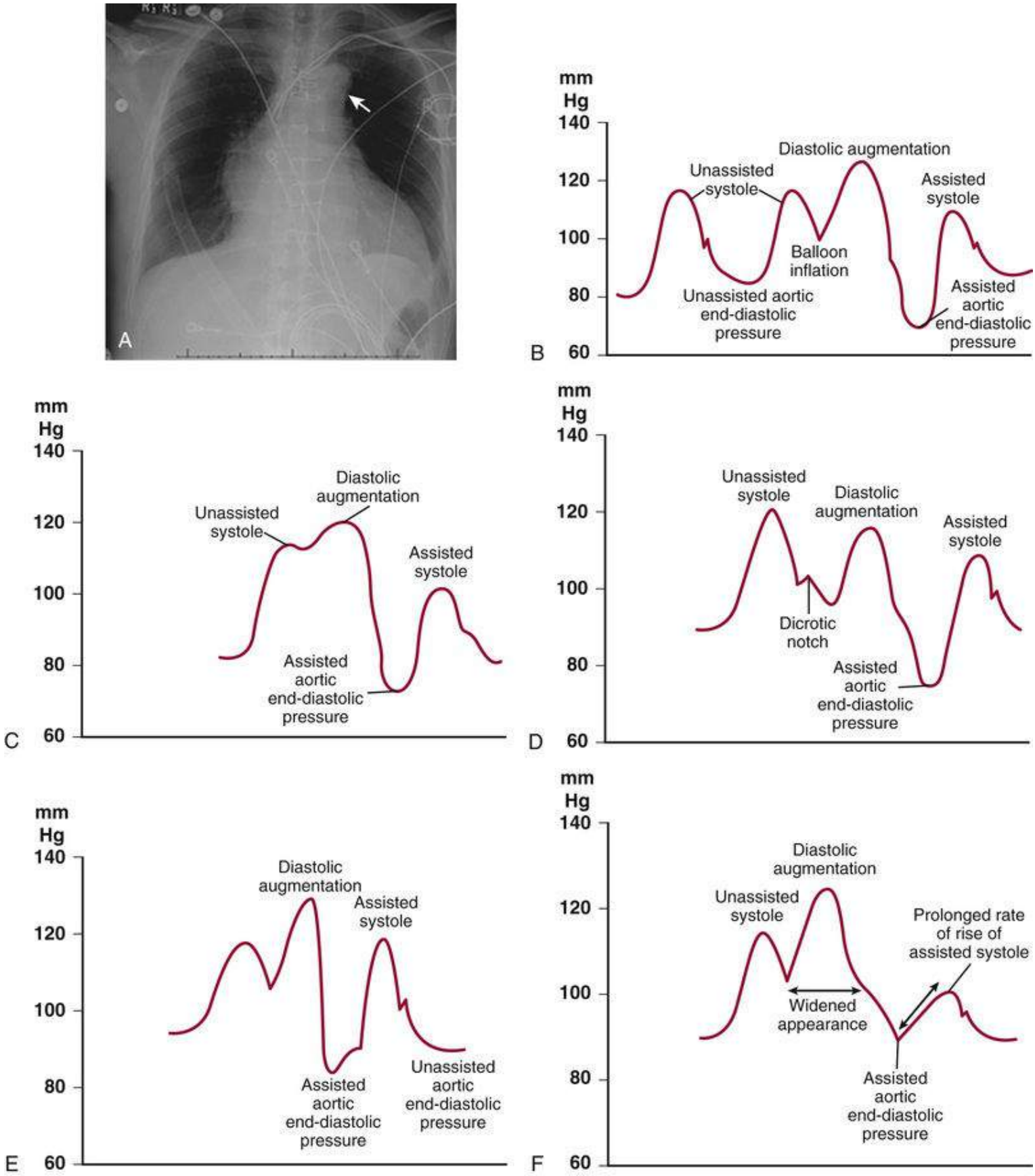


FIGURE 19.17 Intra-aortic balloon pump (IABP) position and arterial waveforms. **A,** Anteroposterior chest radiograph showing the proximal IABP marker (*arrow*) in proper position 2 cm above the carina. **B,** Normal systemic arterial pressure waveform with the IABP device programmed in 1 : 2 mode (i.e., to inflate during every other cardiac cycle). With the first beat, aortic systolic and end-diastolic pressures are shown without IABP support and are therefore unassisted. With the second beat, the balloon inflates with the appearance of the dicrotic notch, and peak-augmented diastolic pressure is inscribed. With balloon deflation, assisted end-diastolic pressure and assisted systolic pressure are observed. To confirm that the IABP is producing maximal hemodynamic benefit, the peak diastolic augmentation should be greater than the unassisted systolic pressure, and the two assisted pressures should be less than the unassisted values. **C,** Systemic arterial pressure waveform from a patient in whom balloon inflation occurs too early,

before aortic valve closure. Consequently, the left ventricle is forced to empty against an inflated balloon; the corresponding increase in afterload may increase myocardial oxygen demand and worsen systolic function. **D,** Systemic arterial pressure waveform from a patient in whom balloon inflation occurs too late, well after the beginning of diastole, thereby minimizing diastolic pressure augmentation. **E,** Systemic arterial pressure waveform from a patient in whom balloon deflation occurs too early, before the end of diastole. This may shorten the period of diastolic pressure augmentation. A corresponding transient decrease in aortic pressure may promote retrograde arterial flow from the carotid or coronary arteries and possibly induce cerebral or myocardial ischemia. **F,** Systemic arterial pressure waveform from a patient in whom balloon deflation occurs too late, after the end of diastole, thereby producing the same deleterious consequences as early balloon inflation (increased LV afterload with a resultant increase in myocardial oxygen demand and worsening of systolic function). (**A,** From American Heart Association; Tabit CE et al. Positional obstruction of the superior mesenteric artery by an intra-aortic balloon pump through subclavian artery approach. Circ Heart Fail 2014;7:864-7; **B-F,** From Trost JC, Hillis LD. Intra-aortic balloon counterpulsation. Am J Cardiol 2006;97:1391.)

Complications such as balloon rupture or entrapment are rare. The risk of infection increases with the acuity and the trauma of the placement, the initial and daily site care, as well as the duration of placement. Bleeding complications at the site are uncommon as long as no multiple access attempts have been made. The greater concern relates to limb ischemia, which may occur in 10% to 40% of patients. Patients with PAD (postinsertion ankle-brachial index <0.8), diabetes, and smaller-caliber vessels (women) are at higher risk. In at-risk populations, smaller catheters (7F) should be used. In case ischemia develops, the key is prompt recognition and prompt removal of the IABP, which usually suffices to resolve ischemia. Surgical intervention (thrombectomy, vascular repair, fasciotomy, or amputation) is rarely required.

Impella.

The Impella device is an axial flow pump in form of a pigtail catheter placed across the aortic or pulmonic valve, so that the inlets/outlets are positioned in the left ventricle/ascending aorta and right ventricle/pulmonary artery. Four versions are currently available: Impella 2.5, Impella CP, Impella 5.0, and Impella RP, providing up to 2.5, 4, 5, and 4 L/min in output, respectively. Because of the larger size, placement of the Impella 5.0 device requires surgical cutdown of the femoral or axillary artery, whereas the other types can be placed percutaneously through 13F, 14F, and 23F sheaths. The direct assist and mechanical unloading of the left ventricle with the Impella reduces end-diastolic wall stress and PCWP; myocardial oxygen consumption is reduced as well. The increased output improves coronary perfusion pressure and coronary blood flow. The right-sided Impella improves pulmonary perfusion and LV filling.

In patients with cardiogenic shock enrolled in the ISAR-SHOCK trial, the Impella 2.5 device led to greater increase in cardiac index and mean arterial pressure and lower lactate levels at no higher risk of complications than with the IABP.[55] Mortality outcomes were nevertheless similar. A lower mortality rate than with IABP, however, has been reported for the Impella 5.0 device in patients with postcardiotomy low-output syndrome. It has therefore been argued that greater levels of support may be required in patients in cardiogenic shock. Even so, as outlined next, even with greater levels of hemodynamic support, survival may not be improved. While the Impella device is safe, hemolysis caused by the high rotational speed of the axial flow pump, access bleeding, and limb ischemia are known complications.

The AHA/ACC and ESC guidelines for the management of STEMI give a class IIb recommendation for the use of left ventricular assist devices in refractory cardiogenic shock (especially those deteriorating on IABP). This includes Impella, TandemHeart, and ECMO.[53]

TandemHeart.

The TandemHeart involves the continuous centrifugal pump circulation of oxygenated blood from the left

atrium (via transseptal cannula placement) into the lower abdominal aorta or iliac arteries (via cannula placement through common femoral artery).[56] In comparison with IABP, it provides greater increase in cardiac output (up to 4 L/min) and mean arterial pressure and greater decrease in PCWP, central venous pressure, and pulmonary artery pressure. LV and RV filling pressures are reduced as is cardiac workload and oxygen demand.

Complications remain a concern and argue for suitable device experience. Indeed, performing a fluoroscopy-guided transseptal puncture and to advance a 21F inflow cannula into the left atrium in a patient in cardiogenic shock requires courage and skill. Registry data indicate that approximately 0.8% of patients may sustain a wire-related perforation of the left atrium after transseptal puncture, and a similar number with common femoral artery dissection. More common complications are groin hematomas (5.1%), bleeding around cannula site (29.1%), device-related limb ischemia (3.4%), sepsis/SIRS (29.9%), gastrointestinal bleeding (19.7%), coagulopathy (11%), and stroke (6.8%), as well as blood transfusions in 71%. Taken together, while conceptually intriguing, the challenges of the insertion of the TandemHeart may limit its use.

Extracorporeal Membrane Oxygenation.

The ECMO system consists of a centrifugal pump, a heat exchanger, and a membrane oxygenator. Deoxygenated blood is aspirated from the right atrium into the centrifugal pump by a cannula placed through a common femoral venous approach. The oxygenated blood is then returned into the descending aorta by an outflow cannula placed through a common femoral artery. ECMO generates full circulatory support with up to 4.0 L/min and reduces LV preload. However, it does not reduce, and in fact may increase, LV afterload and thus oxygen demand. Complications include systemic inflammatory response syndrome (SIRS), renal failure, limb ischemia, and bleeding. Despite these adverse effects, ECMO has been successfully used in cardiogenic shock patients with STEMI, myocarditis, and postcardiotomy syndrome. It has also been used in the cardiac catheterization laboratory for patients who developed cardiorespiratory arrest during interventional procedures.

In single-center retrospective comparisons with historic controls, 30-day survival was almost twofold higher in the ECMO group. It is particularly useful for patients with pulmonary oxygenation impairment. Disadvantages are potential bleeding complications, limb ischemia, and the need for specialized care, including the availability of perfusionists.

Acknowledgment

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20

Coronary Angiography and Intravascular Imaging

Roxana Mehran, George D. Dangas

Coronary angiography consists of the visualization of the coronary anatomy under fluoroscopy, facilitated by direct injection of contrast media into the epicardial coronary arteries through a catheter advanced from a peripheral artery to the aortic root and into the coronary ostia.

The history of coronary angiography starts in the 19th century with the discovery of x-rays by Roentgen in 1895. One month later, Haschek and Lindenthal injected a mixture of calcium carbonate in the blood vessels of an amputated hand and were able to visualize the vascular bed using a roentgenogram. Meanwhile, Frédérick Cournand and Dickinson Richards at Columbia University performed the first experiments on cardiac catheterization in animals, which led to the description of heart hemodynamics and the development of crucial techniques and principles, such as the Fick method to measure cardiac output and pressure manometry (**see Chapter 19**). Forssmann performed the first human cardiac catheterization on himself in 1928, advancing a catheter through an antecubital vein into his right atrium, and acquired roentgenograms to document it.

Selective coronary angiography was first attempted in 1958 by Mason Sones, who cannulated a right coronary artery with a catheter inserted through a brachial artery.[1] In the 1960s, angiographic studies for the determination of coronary artery disease (CAD) were performed in extremely ill patients in the few tertiary care centers in the United States with the necessary resources. Coronary angiography remained a purely diagnostic technique until 1977, when Gruentzig performed the first percutaneous transcatheter coronary angioplasty (see Classic References, Ryan). In the early 1990s the field of coronary angiography entered a period of explosive growth, such that by 2010, an estimated 1,029,000 inpatient diagnostic cardiac catheterizations procedures and 954,000 inpatient percutaneous coronary intervention (PCI) procedures (**see Chapter 62**) were performed per year in the United States alone.[2] Recent years have seen rapid development and maturation of the field, with continuous introduction of new materials, techniques, and innovations for coronary angiography and intracoronary interventions.

Despite the availability of noninvasive imaging techniques such as computed tomographic coronary angiography (CTCA) and magnetic resonance coronary angiography (MRCA) that allow visualization of

the coronary anatomy without the risks related to an invasive percutaneous procedure (**see Chapters 17 and 18**), selective coronary angiography remains the “gold standard” to determine the extent of CAD because it is the only technique that can simultaneously provide both functional and anatomic information for the estimation of ischemic burden of CAD. Although coronary angiography technique is well established, it is important to keep in mind that it is an invasive procedure with potential complications. Therefore, indications for coronary angiography are clearly defined in the current American Heart Association and American College of Cardiology (AHA/ACC) clinical practice guidelines.[3,4] In this chapter, we review the indications for coronary angiography, the basic technique, and interpretation of angiographic images, with an overview of the available intravascular imaging techniques.

Indications for Coronary Angiography

Selection of candidates for invasive coronary angiography is based on the pretest probability of CAD, which is estimated on the basis of the clinical evaluation of the patient, the patient's clinical presentation, and the results of noninvasive diagnostic testing such as electrocardiography, echocardiography, blood tests, stress test, and CTCA or MRCA if performed[5,6] (**see Chapters 13, 14, and 16 to 18**). Current guidelines and indications for coronary angiography by clinical presentation are summarized in **Chapters 59, 60, and 61** (**see also eTable 20.1**).[3,7]

ETABLE 20.1

Current Clinical Practice Guidelines on the Indications for Coronary Angiography in Stable CAD, UA/NSTEMI, and STEMI

CLASS I	CLASS IIA	CLASS IIB	CLASS III
Stable CAD			
1. Patients with SIHD who have survived sudden cardiac death or potentially life-threatening ventricular arrhythmia. (*LOE: B*) 2. Patients with SIHD who develop symptoms and signs of HF should be evaluated to determine whether coronary angiography should be performed for risk assessment. (*LOE: B*) 3. Patients whose clinical characteristics and results of noninvasive testing indicate a high likelihood of severe IHD and in whom the benefits are deemed to exceed risk. (*LOE: C*) 4. Patients with presumed SIHD who have unacceptable ischemic symptoms despite optimal medical therapy and who are amenable to, and candidates for, coronary revascularization. *(LOE: C)*	1. Patients with suspected SIHD whose clinical characteristics and results of noninvasive testing (exclusive of stress testing) indicate a high likelihood of severe IHD and who are amenable to, and candidates for, coronary revascularization. *(LOE: C)* 2. Patients with suspected symptomatic SIHD who cannot undergo diagnostic stress testing, or have indeterminate or nondiagnostic stress tests, when there is a high likelihood that the findings will result in important changes to therapy. *(LOE: C)* 3. Patients with SIHD who have depressed LV function (EF <50%) and moderate-risk criteria on noninvasive testing with demonstrable ischemia. (*LOE: C*) 4. Patients with SIHD and inconclusive prognostic information after noninvasive testing or patients for whom noninvasive testing is contraindicated or inadequate. (*LOE: C*) 5. Patients with SIHD who have unsatisfactory quality of life due to angina, have preserved LV function (EF >50%), and have intermediate-risk criteria on noninvasive testing. (*LOE: C*)	1. Patients with stress test results of acceptable quality that do not suggest the presence of CAD when clinical suspicion of CAD remains high and there is a high likelihood that the findings will result in important changes to therapy. *(LOE: C)*	1. Patients with SIHD who elect not to undergo revascularization or who are not candidates for revascularization because of comorbidities or individual preferences. (*LOE: B*) 2. Patients with SIHD who have preserved LV function (EF >50%) and low-risk criteria on noninvasive testing. (*LOE: B*) 3. Patients who are at low risk according to clinical criteria and who have not undergone noninvasive risk testing. (*LOE: C*) 4. Coronary angiography is not recommended to assess risk in asymptomatic patients with no evidence of ischemia on noninvasive testing. (*LOE: C*)
ACS—UA and NSTEMI			
1. An urgent/immediate invasive strategy (diagnostic angiography with revascularization if appropriate) is indicated in patients with NSTE-ACS who have refractory angina or hemodynamic or electrical instability (without serious comorbidities or contraindications to such procedures). *(LOE: A)* 2. An early invasive strategy (diagnostic angiography with revascularization if appropriate) is indicated in initially stabilized patients with NSTE-ACS (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events. *(LOE: B)*	1. It is reasonable to choose an early invasive strategy (within 24 hours of admission) over a delayed invasive strategy (within 25 to 72 hours) for initially stabilized high-risk patients with NSTE-ACS. For those not at high/intermediate risk, a delayed invasive approach is reasonable. *(LOE: B)*	1. An ischemia-guided strategy may be considered for initially stabilized patients with NSTE-ACS (without serious comorbidities or contraindications to this approach) who have an elevated risk for clinical events. *(LOE: B)* 2. An ischemia-guided strategy in initially stabilized patients (without serious comorbidities or contraindications to this approach) may be reasonable after considering clinician and patient preference. *(LOE: C)*	1. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is not recommended in patients with: a. Extensive comorbidities (e.g., hepatic, renal, or pulmonary failure; cancer), in whom the risks of revascularization and comorbid conditions are likely to outweigh the benefits of revascularization. *(LOE: C)* b. Acute chest pain and a low likelihood of ACS who are troponin negative *(LOE: C)*, especially women *(LOE: B)*.
ACS—STEMI			
1. Immediate angiography and PCI when indicated should be performed in resuscitated out-of-hospital cardiac arrest patients whose initial ECG shows STEMI. (*LOE: B*) 2. Primary PCI should be performed in patients with STEMI and ischemic symptoms of less than 12 hours' duration. (*LOE: A*) 3. Primary PCI should be performed in patients with STEMI and ischemic symptoms of less than 12 hours' duration who have contraindications to fibrinolytic therapy, irrespective of the time delay from first medical contact. (*LOE: B*) 4. Primary PCI should be performed in patients with STEMI and cardiogenic shock or acute severe HF, irrespective of time delay from MI onset. (*LOE: B*)	1. Primary PCI is reasonable in patients with STEMI if there is clinical and/or ECG evidence of ongoing ischemia between 12 and 24 hours after symptom onset. (*LOE: B*)		1. PCI should not be performed in a noninfarct artery at the time of primary PCI in patients with STEMI who are hemodynamically stable. (*LOE: B*)

ACS, Acute coronary syndrome; *CAD,* coronary artery disease; *ECG,* electrocardiogram; *EF,* ejection fraction; *HF,* heart failure; *IHD,* ischemic heart disease; *LOE,* level of evidence; *LV,* left ventricular; *MI,* myocardial infarction; *NSTE-ACS,* non–ST-segment elevation acute coronary syndrome; *NSTEMI,* non–ST-segment elevation myocardial infarction; *PCI,* percutaneous coronary intervention; *SIHD,* stable ischemic heart disease; *STEMI,* ST-segment elevation myocardial infarction; *UA,* unstable angina.

In patients with low pretest probability of CAD, first-line noninvasive assessment of cardiovascular

risk is necessary to decide whether to proceed to coronary angiography. Traditionally, stress test findings can be defined as low, intermediate, or high risk, which are associated with a cardiac mortality of less than 1%, 1% to 3%, and greater than 3% per year, respectively. For patients with intermediate-risk pretest probability, coronary angiography may be considered, whereas for patients with high-risk pretest probability, angiography should be performed without delay and with no need for further testing. Patients presenting with acute coronary syndrome (ACS), unstable angina (UA), or non–ST-segment elevation myocardial infarction (NSTEMI) with hemodynamic instability, or who are at high clinical risk (as determined by the presence of any of the risk factors listed in **eTable 20.2**) should undergo early invasive evaluation. For hemodynamically stable UA/NSTEMI patients without high clinical risk, a delayed invasive strategy may be justified, although an initially noninvasive risk stratification may be practiced outside the United States. Patients presenting with ST-segment elevation myocardial infarction (STEMI) should generally undergo urgent invasive intervention as soon as possible after symptom onset.[7] Patients with delayed cases may be treated conservatively, as described in other chapters.

ETable 20.2

Risk Factors That Support Early Invasive Evaluation of Patients Presenting with ACS

Significant troponin increase
Diagnostic ST or T wave changes
GRACE score >140
Diabetes mellitus
Reduced LV function (ejection fraction <40%)
Early postinfarction angina
Recent PCI
Prior CABG
Intermediate to high GRACE risk score

ACS, Acute coronary syndrome; *CABG,* coronary artery bypass graft surgery; *GRACE,* Global Registry of Acute Coronary Events; *LV,* left ventricular; *PCI,* percutaneous coronary intervention.

Appropriate Use Criteria

In 2012 the appropriate use criteria (AUC) for diagnostic coronary angiography were released.[4] This and a more recent focused update document provide a classification schema for procedures into *appropriate*, *may be appropriate*, and *rarely appropriate care* based on specific criteria. The proportion of "inappropriate" nonacute PCI has been reduced overall.[8] Clinical indications for PCI are beyond the scope of this chapter, but the AUC for diagnostic catheterization are mentioned here to highlight the appropriate selection of patients referred for coronary angiography for diagnostic purposes, since coronary angiography itself may be an unnecessary invasive procedure that could trigger an inappropriate coronary intervention in some cases.[9] The rate of angiographically normal or minimally diseased coronary arteries in patients undergoing elective procedures is approximately 39%.[10] In particular, the use of coronary angiography and PCI in asymptomatic patients is uncertain. A recent study showed that among a sample of 300,000 patients receiving coronary angiography in the United States, 25% were asymptomatic at the time of the elective coronary angiography. Furthermore, the rate of angiographic procedures in asymptomatic patients directly correlated with the number of inappropriate PCI procedures performed.[9] Therefore, strategies to verify the correct referral of patients for diagnostic coronary angiography are required to avoid unnecessary procedures, reduce health care costs, and prevent the therapeutic cascade that may lead from diagnostic angiography to inappropriate PCI.

Contraindications to Coronary Angiography

There are no absolute contraindications to coronary angiography listed in the clinical practice guidelines. However, specific conditions should be taken into account when weighing risks and benefits of the procedure. Based on the patient's cardiovascular risk and the clinical presentation, a decision should be made whether to avoid or postpone the procedure or proceed with coronary angiography using prophylactic measures to reduce the probability of periprocedural complications. Relative contraindications that should be taken into account are known anaphylactoid reaction to contrast media, moderate to severe kidney impairment, decompensated heart failure and pulmonary edema that prevent the patient from lying down during the procedure, uncontrolled hypertension, active infection, coagulopathy, and gastrointestinal bleeding.[12] In addition, coronary angiography requires the use of radiation to visualize the wires and catheters advanced through the blood vessels and to obtain images of the coronary arteries. Therefore, pregnant women should not undergo angiography unless strictly necessary and on exhaustive explanation of the risks related to radiation exposure, medications, and contrast media for both the mother and the fetus.[13] The presence of comorbidities that can increase the risk of complications should be critically considered before referring patients for coronary angiography.[14]

Complications of Coronary Angiography

Complications during coronary angiography are rare, occurring in approximately 2% of patients, with serious complications such as cerebrovascular accident (CVA, stroke) or myocardial infarction (MI) accounting for less than 1% of all patients. Mortality rate is lower than 0.1%.[14] Complications during PCI are more common (**see Chapter 62**). **Table 20.1** lists complications that may be encountered during coronary angiography.

TABLE 20.1

Risks Associated with Coronary Angiography

COMPLICATION	RISK (%)
Mortality	0.11
Myocardial infarction	0.05
Cerebrovascular accident	0.07
Arrhythmias	0.38
Vascular complications	0.43
Contrast agent reaction	0.37
Hemodynamic complications	0.26
Perforation of heart chamber	0.03
Other complications	0.28
Total of major complications	1.70

Modified from Scanlon P, Faxon D, Audet A, et al. ACC/AHA guidelines for coronary angiography. J Am Coll Cardiol 1999;33:1756.

Although rare, the most common complications are allergic reactions to contrast, vascular complications, and worsening of kidney function (see next section). Vascular complications at the access site include hematoma, pseudoaneurysm, aneurysm, and dissection. The risk of a vascular complication increases with the diameter of the sheath used, age of the patient, and degree of local calcifications. Iatrogenic coronary dissection or perforation occurs infrequently but is potentially life threatening and could require urgent coronary stenting[15] (**Fig. 20.1**). Ventricular and atrial arrhythmias are relatively common. Intracoronary injection of contrast media itself can induce arrhythmias. In particular, during injection of contrast media into the right coronary artery (RCA), one should take care to avoid deep

cannulation of the RCA and injection of contrast media directly into the conus branch, because this can result in ventricular fibrillation (VF).[16] In addition, when performing ventriculography, the mechanical stress of the catheter on the ventricular walls can trigger ventricular arrhythmias ranging from isolated premature ventricular complexes (PVCs) to runs of ventricular tachycardia (VT). Usually, these arrhythmias are self-resolving with catheter relocation and do not require medical intervention. Embolic events are rare but can occur and may involve the coronary arteries, central nervous system, or peripheral arteries.[17] Highly calcific axillary or subclavian arteries can increase the likelihood of embolization.

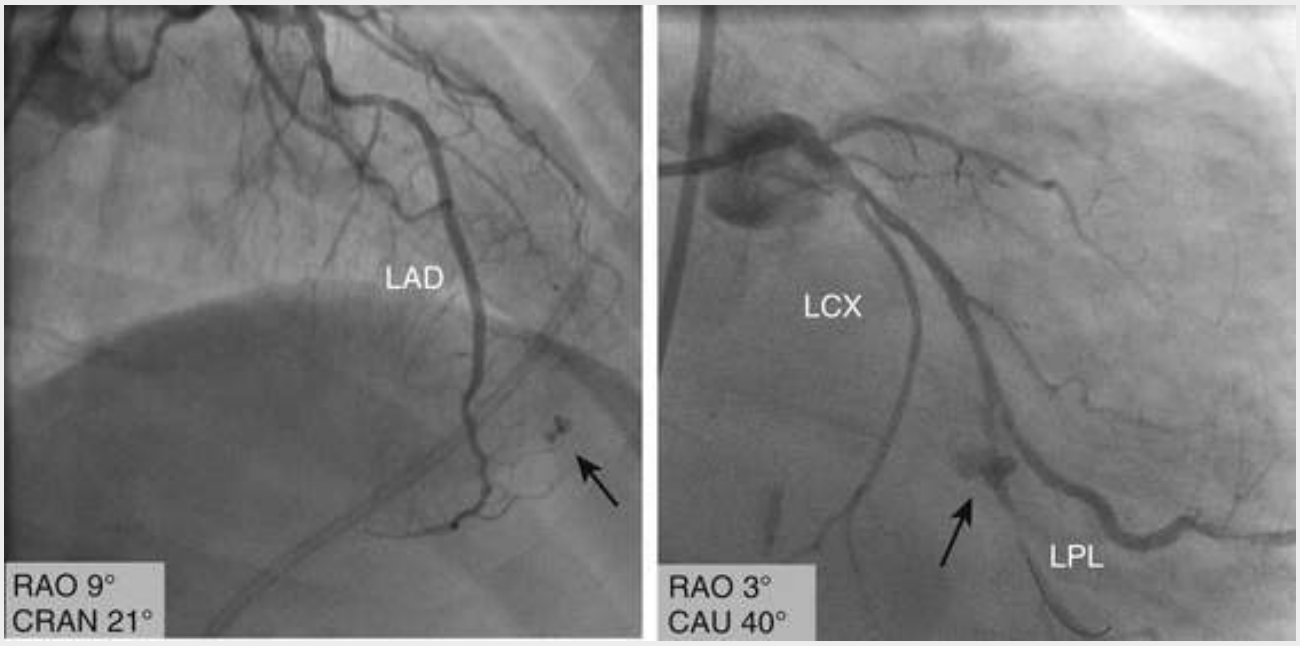

FIGURE 20.1 Iatrogenic coronary perforations. **Left,** Wire perforation of distal left anterior descending artery (*LAD*). **Right,** Perforation of a left posterolateral branch (*LPL*) after rotational atherectomy. *Black arrows* indicate contrast media extravasation. *LCX,* Left circumflex artery. RAO, Right anterior oblique; CRAN, cranial; CAU, caudal. (Angiographic images courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York City, NY.)

In addition, advanced age, diabetes mellitus, emergency coronary angiography, prior stroke, renal failure, and congestive heart failure (CHF) have been reported as risk factors for periprocedural stroke.[17] Infections are exceptionally rare in immunocompetent patients, and prophylactic antibiotic therapy is not usually required. Bleeding is usually minor, except when precipitated by vascular complications. In general, the use of anticoagulation during diagnostic angiography should be dosed based on the length of the procedure, weight of the patient, and presence of comorbidities such as kidney impairment, to avoid the risk of bleeding when the sheath is removed from the access site. Use of radial access rather than femoral access has significantly reduced the rate of vascular and bleeding complications[18] (**see Chapter 19**).

Contrast-Induced Acute Kidney Injury

Contrast-induced acute kidney injury (CI-AKI) is defined as an acute deterioration of renal function, defined as an increase in creatinine of 0.5 mg/dL or more, or 25% or greater compared to baseline. It generally develops 24 to 72 hours after administration of an intravascular contrast agent in the absence of other identifiable causes (see Classic References, Goldenberg). This complication significantly impacts the duration of hospital stay and related health care costs. CI-AKI also has marked repercussions on

short- and long-term morbidity and mortality.[19] In particular, studies in patients with moderate to severe renal dysfunction (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) undergoing coronary angiography or angioplasty show that the development of CI-AKI in such patients is a negative prognostic factor of clinical outcome both short and long term.[20] The incidence of CI-AKI ranges from 2% in low-risk patients to 12% to 50% in patients with diabetes and known chronic kidney disease (CKD) (**see Chapters 51 and 98**). The mechanisms of CI-AKI are only partially understood. Certainly, toxic damage caused by the passage of iodine molecules in the interstitial kidney is one of the causes. Another mechanism is related to the redistribution of flow in the kidney tissue secondary to contrast administration. In particular, after injection of contrast media, blood flow increases in the cortex and decreases in the medulla. Unfortunately, the medulla is particularly vulnerable to ischemic injury for the basal hypoxic condition (P_{O_2} = 20 mm Hg) because of high metabolic activity (e.g., sodium transporter channels). Therefore, blood flow reduction in the medulla after contrast injection further decreases oxygen tension, leading to endothelial dysfunction. Other important elements affecting kidney function are the physical and chemical characteristics of the contrast agents, in particular osmolality and viscosity. Contrast agents with a high osmolality and viscosity significantly increase hypoxemia and tubular stress. The downstream effect consists of an increase of free radicals, a reduction of nitric oxide (NO) bioavailability, and an increase in cellular death.[19,20]

The risk of CI-AKI depends largely on baseline renal function. The eGFR is a valid index to describe the level of renal function. Patients with an eGFR value below 60 mL/min are at high risk of CI-AKI. However, eGFR is not able to identify subclinical or latent forms of renal dysfunction. Therefore, a careful assessment of CI-AKI risk is essential, particularly before interventional procedures that may require high contrast medium volume (**Fig. 20.2**) (see Classic References, Mehran). Risk of CI-AKI can be stratified using a risk score model that includes patients' baseline and procedural characteristics.[21]

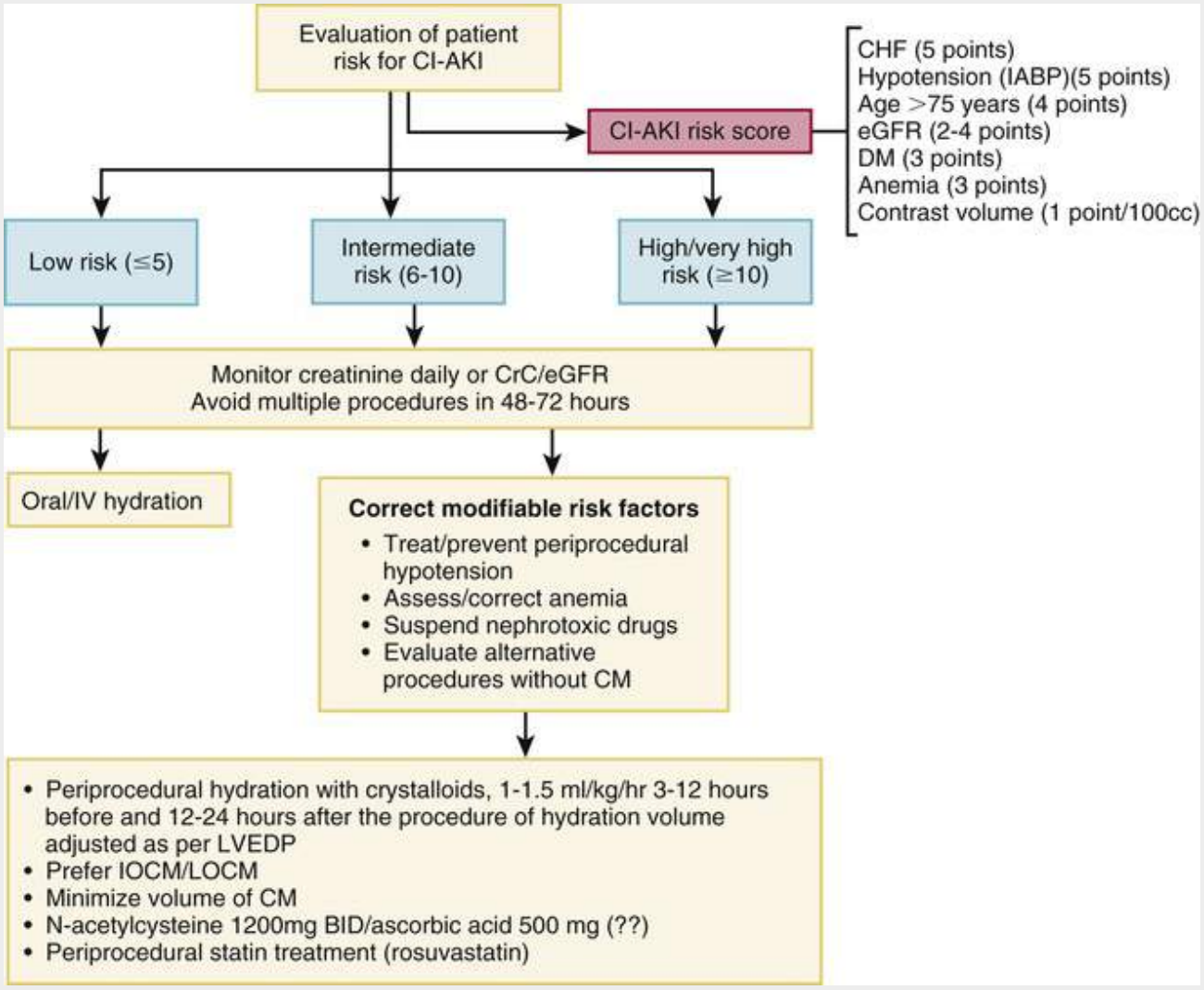

FIGURE 20.2 Risk score to determine the probability of contrast induced acute kidney injury. CHF, Congestive heart failure; CI-AKI, contrast-induced acute kidney injury; CM, contrast media; CrC, creatinine clearance; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IOCM, iso-osmolar contrast media; IV, intravenous; LVEDP, left ventricular end-diastolic pressure; LOCM, low-osmolar contrast media; BID, twice daily.

In high-risk patients, prevention is crucial and consists of pharmacologic and nonpharmacologic measures. Individual risk/benefit ratios should be carefully estimated for each patient, and the utility of an alternative noninvasive diagnostic test should be evaluated. If the use of contrast medium is necessary for diagnostic purposes, the volume used should be minimized, and the use of monomeric low- or iso-osmolality contrast agents is recommended. Hydration plays a pivotal role in reducing the incidence of CI-AKI. Depending on the clinical condition (e.g., CHF), the Contrast-Induced Nephropathy (CIN) Consensus Working Panel recommendations state that an infusion of 1.0 to 1.5 mL/kg/hr of isotonic saline solution, from 3 to 12 hours before until 6 to 24 hours after the procedure, is suitable to minimize the incidence of CIN.[22] Recently, a clinical trial specifically investigated the efficacy and safety of a left ventricular (LV) end-diastolic pressure–guided hydration protocol with good results; thus filling pressure–guided fast hydration may be employed in the catheterization laboratory.[23] Moreover, to obtain effective hydration, devices have been developed that balance the volume of infusion and fluids lost through diuresis.[24] *N*-Acetylcysteine has been considered for the prevention of CI-AKI for years. In animal models of ischemia-reperfusion injury, the use of *N*-acetylcysteine significantly limited kidney damage mainly through its antioxidant properties.[25] However, the efficacy of *N*-acetylcysteine in humans in clinical studies remains unclear, given the high heterogeneity in study protocols and populations.[26] Similarly, some studies report that the use of isotonic sodium bicarbonate is associated with a higher

reduction in the incidence of CI-AKI than saline solution. These findings were attributed to a potential reduction in the production of reactive oxygen species in the renal parenchyma. However, recent meta-analyses did not show superiority of sodium bicarbonate over saline solution.[27,28] For this reason, both *N*-acetylcysteine and sodium bicarbonate have minimal roles in the latest guidelines on prevention (i.e., no benefit) and the routine prevention of CIN in patients undergoing percutaneous coronary angiography and interventions.

Risks Related to Radiation Exposure

Coronary catheterization may result in radiation-related injury, which although infrequent may be potentially serious. Radiation injury may be *deterministic* (i.e., dose dependent), which can present weeks after exposure, or *stochastic*, which is genetically determined and not dose dependent. Stochastic injury can result in cancer, pregnancy complications, and inheritable diseases. Deterministic injury may result in skin injury, hair loss, and lens injury. However, the most common location of radiation-induced lesions in cardiac catheterization is the skin of the back, and common patterns include erythema, telangiectasia, and plaques.[29] The sensitivity of the skin to radiation exposure is differentiated by site; areas at risk in decreasing order of sensitivity include anterior neck, antecubital and popliteal areas, flexor extremities, chest and abdomen, face, back, extensors, nape of the neck, scalp, palms, and soles.[30] Although uncommon in contemporary practice, early reports from coronary catheterization indicate deep and extensive skin rashes and burns at the site of radiation exposure, some requiring skin grafting.

PCI procedures may result in 10-fold higher radiation exposure compared to diagnostic catheterization (**see Chapter 62**). An average PCI results in 150 times more exposure than a chest radiograph and five times the annual radiation exposure received as environmental background radiation.[31] Measures used to assess patient dose include dose-area product (DAP, the absorbed dose multiplied by the area irradiated), air kerma (AK, *k*inetic *e*nergy *r*eleased per unit *ma*ss of air), and fluoroscopy time (FT), which are routinely measured and documented.[32] All procedures should be performed using the ALARA (as low as reasonably achievable) principle.[33] Exposure can be minimized in several ways: reduced FT and acquisition time, use of multiple angles rather than a single working camera position, reduced fluoroscopy dose, avoidance of high magnification, use of collimator beams and filters, avoidance of high angulation, and reduction in the flat-panel image detector as much as possible. For exposures of absorbed radiation greater than 5 Gy, patients should be advised to watch for areas of erythema; for those greater than 10 Gy, a medical physicist should be consulted to calculate the peak dose in 2 to 4 weeks; greater than 15 Gy is regarded as a hospital risk management event. Similarly, in the event that FT exceeds 60 minutes, physicians must be vigilant for late radiation effects.

From the perspective of occupational radiation exposure, operators should be cognizant of the need to wear protective personal equipment during catheterization procedures, including a lead apron, thyroid drape, lead eyeglasses, and dosimeters.[33] Table height and distance from the x-ray source are important, and radiation risk decreases as the inverse square of distance from the source. Operators should also optimally position lead shields and skirts and should be compliant with use of radiation dosimeters for monitoring exposure to the whole body (chest) and eye. Novel dosimeters providing real-time monitoring and alerts can serve to decrease operator radiation exposure.[34] Monitoring, reporting, and audit of radiation exposure can promote improved awareness and practice in the operator and catheterization laboratory staff.

Coronary Arteriography Technique

Patient Preparation

Patients should receive a comprehensive explanation of the diagnostic angiographic procedure and of the coronary intervention potentially required. Risks of angiography should be discussed in-depth and weighed against both the clinical benefit and the risks related to refusal of the procedure. Patients are required to provide written informed consent before coronary angiography. Women of childbearing age should be questioned on their pregnancy status and advised on the additional risks of radiation exposure for pregnant women. A thorough medical history, including comorbidities, current medications, and allergies, needs to be obtained before the procedure. In the event of an emergency procedure, as with a STEMI presentation, a brief evaluation of the patient history with particular attention to known CKD and known allergies to contrast media should be obtained if possible. In patients with prior coronary artery bypass graft (CABG) procedure, a report stating the type, arterial or venous graft(s), and position of the graft(s) should be attained if available to facilitate the cannulation and subsequent imaging of the grafts. Patients may receive mild sedation with a benzodiazepine before the procedure according to the hospital standard practice.[35] In case of hemodynamic instability or respiratory distress, anesthesiologist support might be necessary. In most patients, however, general anesthesia and deep sedation are unnecessary for coronary angiography. Conscious sedation with short-term agents such as midazolam or fentanyl is most common. Constant monitoring of the patient's ECG, heart rate, blood pressure, respiratory rate, and oxygen saturation is required periprocedurally. A venous access line should be readily available for the infusion of fluids or medications. Local anesthesia with topical anesthetic cream or subcutaneous injection of 1% lidocaine or mepivacaine (0.5 to 1 mL for radial access and 2 to 5 mL for femoral access) should be performed in all patients before puncturing the peripheral artery and introducing the sheath.[36] An adequate local anesthetic will not only make the patient more comfortable but, by reducing the pain during the arterial cannulation, also reduce the risk of peripheral artery spasm.

Access Sites

Possible access sites for coronary angiography are the femoral artery and the radial artery. Although the radial access approach is associated with fewer vascular and bleeding complications, femoral access remains the most commonly used in the United States. Femoral access allows for larger-diameter equipment that could be necessary in case of PCI. In addition, accessing from the femoral artery usually grants an easier advancement of the catheter to the aortic root due to the lack of tortuosity in the descending aorta. After disinfection and appropriate local anesthesia at the access site, the common femoral artery (CFA) is punctured with a base-metal needle approximately 1 cm below the inguinal line with a 45- to 60-degree angulation.[35] In obese patients, the ideal puncture site is sometimes difficult to determine. The head of the femur, visualized under fluoroscopy, can be used as a landmark (**see Chapter 19**, **Fig. 19.2**). Puncture should be performed with the needle leveled at half the head of the femur. Multiple punctures should be avoided to reduce the risk of bleeding and vascular damage. A J-tip flexible guide is inserted through the needle into the CFA. The needle is then removed and a sheath advanced around the wire into the artery (**see Fig. 19.3**). Once the sheath is fully advanced in the artery, the dilator and wire are removed, and the sheath is flushed with saline.[37] Usually, a 6 French (6F) sheath (French units: F = 0.33 mm) is used for coronary angiography and coronary interventions. Verification of the correct position of the sheath in the vessel can be ascertained simply by drawing blood from the sheath.

Radial access should always be considered first, before resorting to the femoral approach, especially for diagnostic coronary angiography.[38] The procedure for the sheath insertion is similar to that described

for the femoral artery. However, when using radial access, a modified Allen test should be performed on both hands (**see Chapter 19**). The modified Allen test is performed by applying pressure on both the ulnar and the radial artery of one wrist to occlude them while the patient keeps the hand elevated with the fist clenched for approximately 30 seconds. Once opened, the hand appears pale. The compression on the ulnar artery is then removed while pressure is maintained on the radial artery. If the ulnar artery supply to the hand is adequate, the color quickly returns to the hand and the test is normal. Conversely, if color does not return, the ulnar artery supply is insufficient, meaning that the radial artery supports the entire circulation of the hand. In this case the radial artery should not be punctured, because this may compromise the blood flow to the hand. This rule may be bypassed if an oximeter is placed in the thumb during radial artery occlusion, and resurgence of pulsation and oxygenation is documented after its initial disappearance ("Barbeau method").

When both radial arteries are acceptable access sites, the patient's right, closer to the operator, is preferred for technical reasons. However, the left subclavian artery may be less tortuous than the innominate artery. The ideal puncture site is 1 to 2 cm proximal to the radial styloid with the wrist slightly hyperextended. After local anesthesia, usually 0.5 to 1 mL of 1% lidocaine, the needle is advanced angled 30 to 45 degrees to the skin until a flashback of blood is visualized. A straight-tip wire is gently inserted through the needle. After removing the needle, a 5F or 6F sheath is inserted in the radial artery over the wire. A small incision 1 mm long can be made on the skin to facilitate advancement of the sheath. Because the radial artery is extremely vasoactive, the risk of spasm is high, especially in women; therefore, as soon as access is obtained, an intra-arterial spasmolytic agent such as nitroglycerin (100 to 200 µg) or verapamil (2.5 mg) diluted into 10 mL of saline should be administered.[35] A hydrophilic-coated sheath can further reduce the likelihood of spasm and regional pain. To prevent thromboembolic events and radial artery occlusion, weight-adjusted unfractionated heparin (UFH), 40 to 70 U/kg up to 5000 U, is administered either intravenously or intra-arterially.[39]

Radial access appears associated with fewer periprocedural events and should be preferred whenever possible. It should be noted, however, that the axillary-subclavian axis can be tortuous and calcific, particularly in elderly patients, and it can therefore be technically difficult to advance the catheter to the aortic root. Brachial access is very uncommon, but unlike radial access, avoids the small-caliber arteries in the forearm, and therefore may be required in the event that radial access is not available or fails. Brachial access can be obtained with a percutaneous or cutdown approach. On the other hand, there is no alternative blood supply to the forearm in case of closure.

Basic Technique

Coronary angiography is an invasive procedure based on the intravascular advancement of angiographic guidewires and catheters from a percutaneous access using the Seldinger technique. After a valved sheath is inserted into the access site artery (see Access Sites), a flexible metallic J-tipped guidewire is inserted through the sheath and advanced slowly under fluoroscopic imaging through the arterial axis until the aortic root is reached. A fluid-filled catheter is then advanced over the angiographic guidewire, while the wire itself is maintained in place. Once the catheter is in the aortic root, the wire is fully extracted from the sheath, and the catheter is flushed and connected to the contrast media injection apparatus. Under fluoroscopic imaging, and with the help of small injections of contrast, the coronary ostium is engaged with the tip of the catheter.[40] At this point, the x-ray tube is positioned appropriately (see projection section), and angiographic images are obtained while injecting contrast directly into the cannulated coronary artery.

Catheters for Diagnostic Procedures

There are several types of diagnostic catheters, characterized by differing lengths, diameters, and shapes. In general, catheters are composed of an external layer, which is not thrombogenic or lubricious, and by a lubricious inner layer. These two layers include a fine metallic core required to confer stability, improve maneuverability, and reduce the risks of kinking. Lengthwise, the catheter is divided into three parts: hub, body, and tip. Through a female Luer-Lok, the *hub* connects the catheter to the contrast injection system and facilitates the catheter grip and rotation with winged tips. The *body*, mostly strong and rigid, transmits to the tip the movements impressed on the hub by the operator. The *tip* can be divided, starting from the distal end, into three curves: primary, secondary, and tertiary, which allows the best possible fit to the aortic root curvature. The size of the catheter is another important characteristic. Compared to guiding catheters used for PCI (**see Chapter 62**), diagnostic catheters have a thicker wall, which considerably reduces their internal lumen. 5F catheters allow an optimal balancing between contrast flow and satisfactory catheter manipulation, particularly for the radial approach. Catheter length can vary from 80 to 110 cm (32 to 44 inches), depending on the anatomic characteristics and the access site (radial, brachial, or femoral). However, the standard length for adult left-heart catheterization by both the radial and the femoral approach is 100 cm (40 inches), while 80 cm is suitable for brachial access.

Among the diagnostic catheters, the most commonly used are the Judkins and the Amplatz catheters. *Judkins catheters* can be used both for the femoral and for the right/left radial approach. A preformed left Judkins (JL) presents a primary curve of 90 degrees and a secondary curve of 180 degrees, whereas the right Judkins (JR) presents a primary curve of 90 degrees and secondary curve of 30 degrees (**Fig. 20.3**). Since the JL is preformed, after removing the angiographic guide, it automatically engages the ostium of the left coronary artery (LCA). The JR, in contrast, once positioned in the right coronary sinus, requires a clockwise rotation to engage the ostium of the RCA from any vascular approach. In both JL and JR catheters, the distance between the primary and secondary curves (termed *arm*) is variable; for example, JL4 has a 4.2-cm length arm, JL5 and JL6 have 5.2- and 6.2-cm-long arms, respectively (**see Fig. 20.3**). Catheter selection depends on the approach (radial or femoral), the height of the patient, and the aortic diameter and curvature. For example, when using a femoral access, the JL4 is the most adaptable catheter for the LCA, whereas for the radial access, the JL3.5 catheter may be more suitable. Moreover, the presence of a dilated aortic root or the anatomy of particularly tall patients (>180 cm [72 inches]) may increase the length required between the primary and secondary curves and might require the selection of a catheter with a longer arm. In addition to their conventional use, JR catheters may be used for saphenous vein graft (SVG) and left internal mammary artery graft study through femoral and left radial approach.

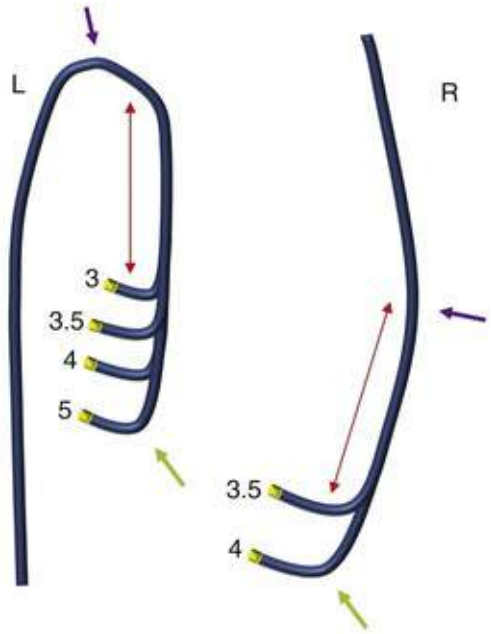

FIGURE 20.3 Judkins catheters. *Left* (L). Judkins for left coronary artery. *Right* (R), Judkins for right coronary artery. *Green arrows* indicate the primary curve. *Purple arrows* show the secondary curve. *Red arrows* indicate the distance between the primary and the secondary curve. To determine the correct catheter's tip, the operator should evaluate the approach (femoral or radial), the patient's height, and diameter of the aortic root. In particular, it would be helpful to add 0.5 cm for a femoral approach and for a dilated or horizontal aorta.

Amplatz catheters for the LCA (AL) and RCA (AR) represent a valid alternative to Judkins catheters (**Fig. 20.4**). The available lengths and sizes are the same as for the Judkins catheters, but the tip morphology of the left Amplatz (AL) catheter differs, allowing for easier coronary engagement in specific settings, such as short left main ostium, separate ostium of circumflex (Cx)–left anterior descending artery (LAD) branches, and RCA with anterior-high origin. Conversely, the right Amplatz (AR) catheter allows engagement of RCAs with inferior orientation. Amplatz catheters may also be used with confidence for the study of SVGs. *Multipurpose* (MP) *catheters* present a single bend (MPA 1 and 2 have a 45- to 60-degree primary curve, while MPB 1 and 2 have approximately an 80-degree primary curve) and may be used for the cannulation of coronary ostia that are difficult to reach with other catheters, as well as for engagement of SVGs. *Internal mammary artery* (IMA) *catheters* have a high angulated primary curve tip (80 degrees), to facilitate the engagement of the IMA either through the femoral or the radial approach. These catheters can also be used to engage the upward-pointing RCA (**Fig. 20.4**). It should be specified that the catheters just described are the ones most frequently used to perform diagnostic coronary angiography. Additional catheter types are available, although less frequently used, in case of specific coronary anatomic variables.

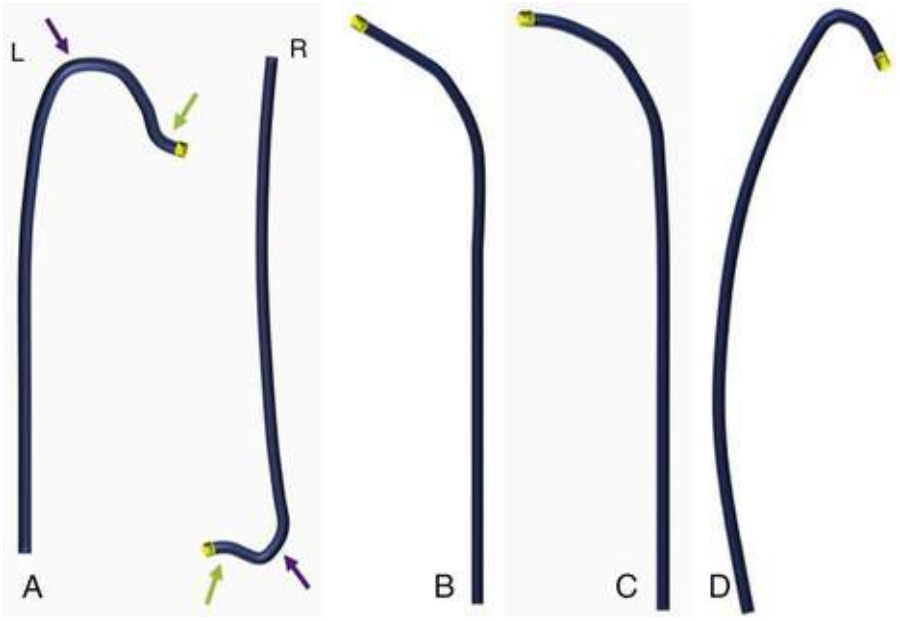

FIGURE 20.4 **A,** Amplatz catheters, left (L), Judkins for left coronary artery; right (R), Judkins for right coronary artery. *Green arrows* indicate the primary curve. *Purple arrows* show the secondary curve. **B,** Multipurpose A catheter. **C,** Multipurpose B catheter. **D,** Internal mammary artery catheter.

Selective Coronary Artery Cannulation

Left Coronary Artery.

The JL4.0 coronary catheter is used most often to engage the LCA (**Fig. 20.5**). The catheter is advanced over the guidewire until it reaches the aortic root. There, the catheter is rotated clockwise to direct it toward the left sinus of Valsalva. Once in position, the wire is removed, and the catheter regains its primary bent and should engage the ostium of the LCA. When the ascending aorta is dilated or the aortic arch is unfolded, advancement of the JL4.0 or JL5.0 might be necessary. If the tip of the JL catheter advances beyond the ostium of the LCA without engaging the ostium, the catheter can be advanced farther until the tip enters the left sinus and the catheter body assumes an acute angle. At that point, prompt withdrawal of the catheter should allow the tip to “pop” into the ostium of the LCA.

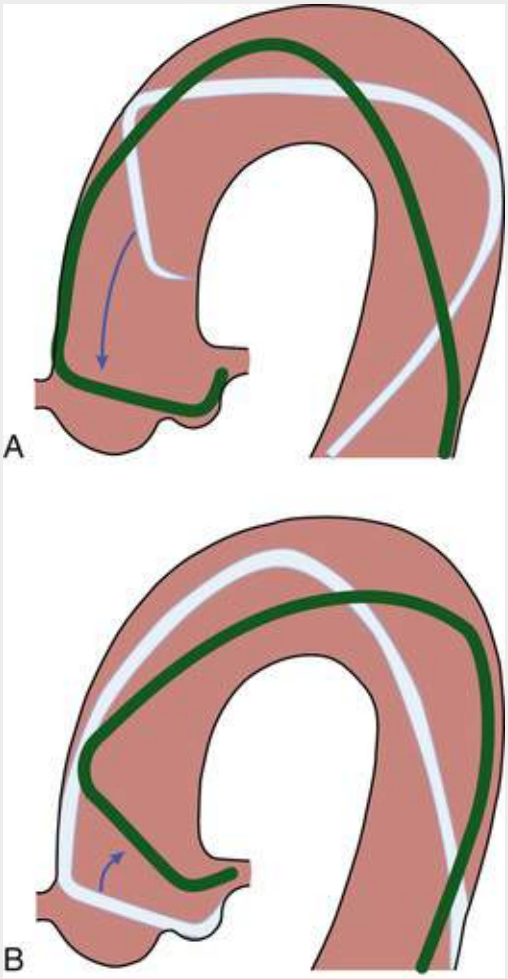

FIGURE 20.5 **A,** Push-pull technique for catheterization of the left coronary artery (LCA) with the Judkins left catheter. In the LAO view, the coronary catheter is positioned in the ascending aorta over a guidewire, and the guidewire is removed. The catheter is advanced so that the tip enters the left sinus of Valsalva. **B,** If the catheter does not selectively engage the ostium of the LCA, further slow advancement into the left sinus of Valsalva creates a temporary acute angle at the catheter. Prompt withdrawal of the catheter allows easy entry into the artery. (From Popma JJ, Kinlay S, Bhatt DL. Coronary angiography and intracoronary imaging. In Mann D, et al, editors. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed. Philadelphia: Elsevier Science; 2014.)

Right Coronary Artery.

The RCA is cannulated in the left anterior oblique (LAO) position (see later, Angiographic Projections). Once the JR or modified Amplatz catheter reaches the aortic root, it must be rotated clockwise to engage the vessel. The height of the catheter during the rotation may need to be adjusted by gently withdrawing the catheter to engage the ostium.

In patients with prior CABG, cannulation might be challenging because the locations of graft ostia are more variable, even when surgical clips or ostia markers are used. Whenever possible, the number, type, and course of the bypass grafts should be obtained before the procedure.

Saphenous Vein Grafts.

SVGs from the aorta to the distal RCA or posterior descending artery (PDA) originate from the right anterolateral aspect of the aorta approximately 5 cm (2 inches) superior to the sinotubular ridge. SVGs to the LAD artery (or diagonal branches) originate from the anterior portion of the aorta approximately 7 cm superior to the sinotubular ridge (**Fig. 20.6**). SVGs to the obtuse marginal branches arise from the left anterolateral aspect of the aorta 9 to 10 cm superior to the sinotubular ridge. In most patients, all SVGs can be engaged with a single catheter, such as a JR4.0 or a modified Amplatz right 1 or 2.

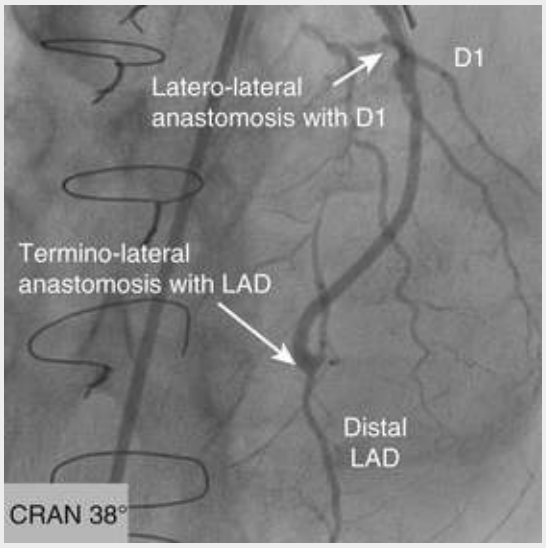

FIGURE 20.6 Sequential saphenous vein graft to the first diagonal branch (*D1*) and left anterior descending artery (*LAD*) with latero-lateral anastomosis to D1 and termino-lateral anastomosis to the distal LAD. CRAN, Cranial. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

Viewed in the LAO projection, the catheter should be rotated anteriorly from the leftward position as it is rotated in a clockwise direction. This movement should be repeated with the catheter at various heights in the ascending aorta, 5 to 10 cm above the sinotubular ridge, and with various degrees of rotation. Small test injections of contrast media can be used to verify that the catheter is in the SVG. If the graft is occluded, usually it is possible to visualize a "stump" during contrast injection. The surgical clips can be used to verify that all the grafts have been visualized. If one or more SVGs cannot be visualized, it can be useful to perform an ascending aortogram (preferably in biplane) to visualize all SVGs and their course to the coronary arteries. When visualizing an SVG, it is important to evaluate the ostium and the anastomotic site for irregularities or stenosis. It is also important to evaluate the flow distal to the anastomosis. *Sequential grafts* are those that supply two different epicardial branches in a side-to-side fashion (for the more proximal epicardial artery) and terminate in an end-to-side anastomosis (for the more distal epicardial artery). A Y graft is characterized by a proximal anastomosis in an end-to-side fashion to another saphenous vein or arterial graft, with two distal end-to-side anastomoses to the two epicardial grafts from these two grafts. It should be noted that with severe calcifications of the ascending aorta, the SVG could depart from the descending aorta to reach lateral wall branches.

Internal Mammary Artery Grafts.

The left IMA (LIMA) can be cannulated with a specially designed J-tip IMA catheter. The catheter is advanced into the aortic arch distal to the origin of the left subclavian artery, then rotated counterclockwise and gently withdrawn with the tip pointing in a cranial direction, allowing entry into the left subclavian artery. The right anterior oblique (RAO) or anteroposterior (AP) projections can be used to visualize the IMA (**Figs. 20.7 and 20.8**). For the right IMA (RIMA), first the innominate artery is entered with the guidewire in the LAO projection, then the IMA catheter is advanced to a point distal to the expected origin of the RIMA. The catheter is withdrawn slowly in the LAO view and rotated to cannulate the RIMA. Small injections of contrast are used to assess the position and the cannulation of the IMA. If the IMA cannot be selectively engaged and arteriography of the subclavian artery can be used, this usually allows for the opacification of all or most of the IMA, although weak (**Fig. 20.9**). The IMA can also be visualized with semiselective contrast injection; to avoid injury of the ostium, the catheter can simply be oriented toward the IMA without cannulating it. The correct orientation can be obtained by advancing a guidewire in the IMA to stabilize the position of the catheter during injection.

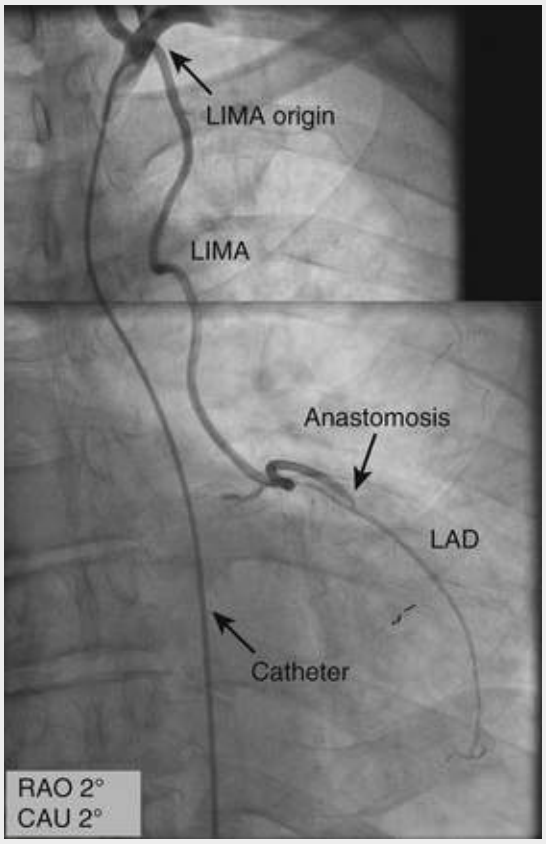

FIGURE 20.7 Arterial graft of left internal mammary artery (*LIMA*) to the left anterior descending artery (*LAD*). RAO, Right anterior oblique; CAU, caudal. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

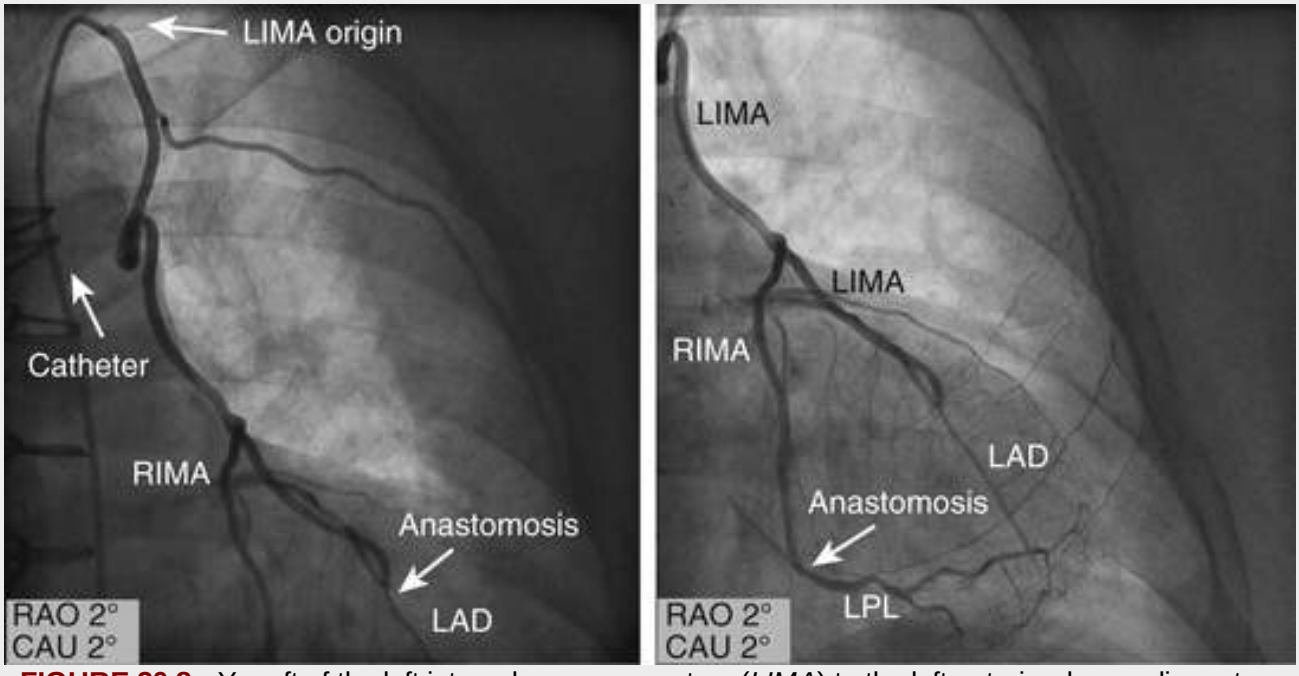

FIGURE 20.8 Y graft of the left internal mammary artery (*LIMA*) to the left anterior descending artery (*LAD*) and the right internal mammary artery (*RIMA*) to the left posterolateral branch (*LPL*). RAO, Right anterior oblique; CAU, caudal. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

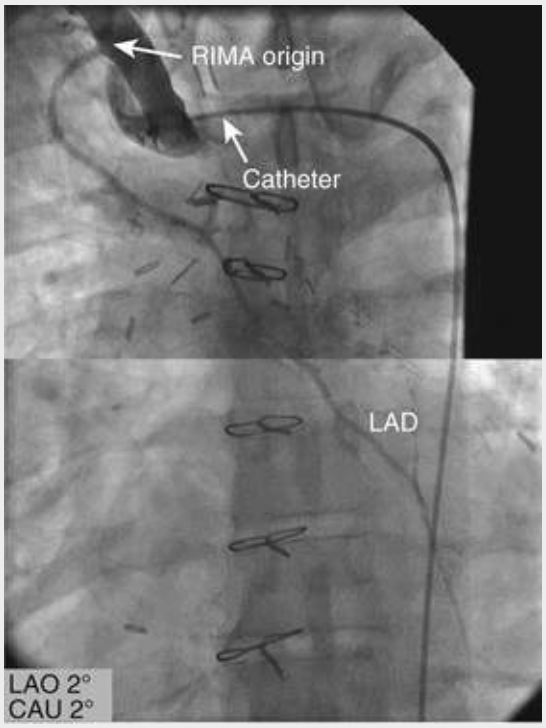

FIGURE 20.9 Nonselective cannulation of the right internal mammary artery (*RIMA*) anastomosed to the left anterior descending artery (*LAD*). LAO, Left anterior oblique; CAU, caudal. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

Radial Grafts.

Radial artery (RA) grafts represent the most popular arterial grafts after the LIMA and RIMA. Similar to SVGs, radial grafts require a double anastomosis, one on the aorta and one on the coronary vessel. Because of potential early spasm, RA grafts were abandoned in the 1970s and 1980s. In the 1990s, however, this procedure was rediscovered, and with specific surgical techniques and pharmacologic prophylaxis, it has safely been used with good short- and long-term results (**Fig. 20.10**).

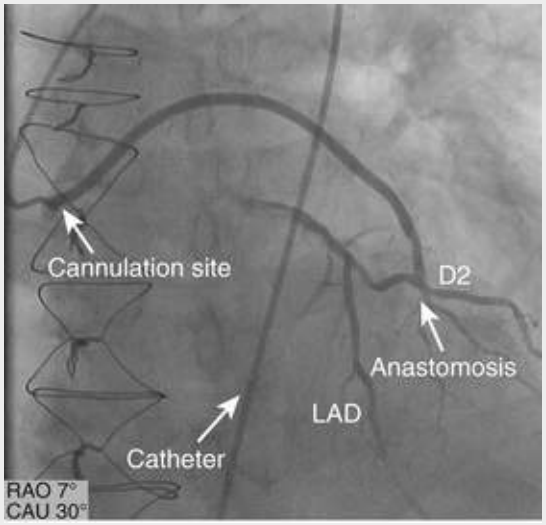

FIGURE 20.10 Free radial graft to large diagonal branch. *LAD,* Left anterior descending artery; *D2,* second diagonal branch. RAO, Right anterior oblique; CAU, caudal. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

Gastroepiploic Artery.

Rarely the right gastroepiploic artery (GEA) can be used for CABGs. To cannulate the GEA, first a

special catheter called the “cobra” is inserted into the common hepatic artery. Next, a hydrophilic-coated guidewire is advanced to the gastroduodenal artery and then to the right GEA. The cobra catheter is then exchanged for an MP or JR catheter, which is used for the selective cannulation of the GEA (**Fig. 20.11**).

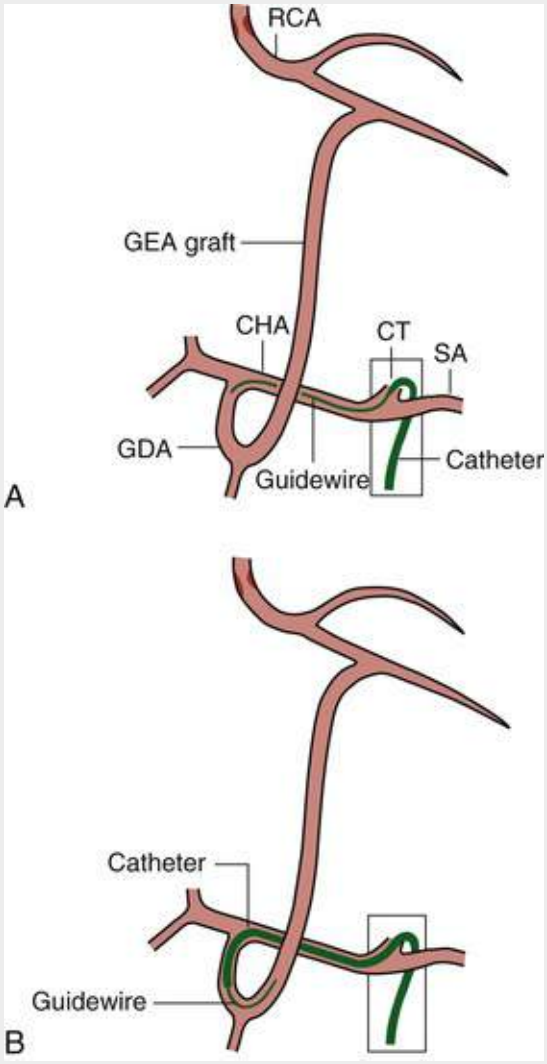

FIGURE 20.11 Catheterization of right gastroepiploic artery (*GEA*) graft. **A,** The celiac trunk (*CT*) is selectively engaged with a cobra catheter, and a guidewire is gently advanced to the gastroduodenal artery (*GDA*) and the GEA. **B,** The catheter is advanced over the guidewire for selective arteriography of the GEA graft. *CHA,* Common hepatic artery; *SA,* splenic artery. (From Popma JJ, Kinlay S, Bhatt DL. Coronary angiography and intracoronary imaging. In Mann D et al, editors. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed. Philadelphia: Elsevier Science; 2014.)

Selection of Contrast Media

Since the introduction of intravascular contrast agents (ICAs) in the 1950s, clinical practice has become increasingly dependent on their use, particularly as the use of computed tomography (CT) and cardiac catheterization procedures has expanded exponentially in recent years. All currently used ICAs are classified on the basis of their physical and chemical structure, specifically, osmolality, iodine content, ionization in solution, and viscosity (**Table 20.2**). The most useful classification in clinical practice divides available ICAs into high-osmolar (HOCA), low-osmolar (LOCA), and iso-osmolar (IOCA) contrast agents. The HOCAs have an osmolality four to five times higher than the blood (300 Osm). LOCAs have an osmolality twice as high as blood. The latest-generation IOCAs have the same osmolality

as blood. Ionic high-osmolality ICAs were the first class of ICA used. However, the high osmolality and calcium-chelating proprieties often resulted in heart rhythm disorders (sinus bradycardia, AV blocks, QRS prolongation, long QT, ST-T, giant T wave inversion, and extremely rarely, VT and VF) and altered LV contractility. Therefore, in recent decades, new-generation ICAs have been developed, with low osmolality and neutral chemical characteristics that allow a significant reduction of adverse events.[41] In large cohort studies, the incidence of all types of adverse reactions to contrast was approximately 12% with a high-osmolality agent, compared to only 3% with a low-osmolality ICA (see Classic References, Katayama). For this reason, LOCAs and IOCAs are now considered the safest ICAs to use for vascular diagnostic procedures.

TABLE 20.2

Intravascular Iodinated Contrast Agents: Characteristics

	GENERIC NAME	OSMOLALITY RANGE (mOsm/kg H_2O)	VISCOSITY RANGE (cp or mPa.s) 37°C	IONICITY
High osmolarity	Diatrizoate/meglumine Diatrizoate/sodium	1500-2000	4.1-10.5	Ionic
	Iothalamate	600-1400	1.5-4	
Low osmolarity	Ioxaglate	600	7.5	
	Iodipamide	664	5.6	
	Iohexol	322-844	1.5-10.4	Nonionic
	Iopamidol	413-796	3.0-9.4	
	Iopromide	330-770	1.5-10	
	Ioversol	502-792	3-9	
	Ioxilan	610-721	5.1-8.1	
Iso-osmolarity	Iodixanol	270-320	6.3-11.8	

Modified from Manual on Contrast Media of the American College of Radiology (ACR) Committee on Drugs and Contrast Media. Version 10.2, 2016.

Automatic and Manual Injection of Contrast Media

Manual contrast injection with a manifold permits a constant modulation of the pressure of the injection and allows the operator to feel the resistance of the vessel to the injection. However, careful evaluation of the line should be performed before the injection to ensure the absence of air bubbles in the system. Manual injection was the only technique used to deliver contrast media until 10 years ago, when power injections were introduced. These automatic systems can detect air bubbles in the tubes and stop the injection accordingly. The maximum volume of contrast delivered, as well as the maximum pressure, can be preset to reduce the risk of iatrogenic artery dissection. Current systems also allow for operator touch–sensitive, variable–volume and pressure injections. For the RCA, 4 to 6 mL/sec is usually injected to optimally visualize the entire vessel, with a maximal pressure of 450 psi. For the LCA, a volume of 6 to 8 mL/sec is injected at a pressure of 450 to 600 psi.

The use of automatic injection systems is now preferred in most catheterization laboratories in Europe, whereas in the United States, 50% of sites still use manual injection. Automatic injections can significantly reduce the volume of contrast used for coronary procedures, and some studies report that they might reduce the risk of contrast-induced acute kidney injury.[42,43]

Adverse Reactions to Contrast Media and Prophylactic Therapy

Adverse reactions after injection of ICA may be acute or delayed and can further be classified as allergic

or allergic-like (physiologic). *Allergic reactions* can present with a variety of clinical symptoms, ranging from itching to skin rash, local edema, asthma, and full-blown anaphylactoid reaction. The pathophysiologic mechanisms hinge on the activation of different components of the immune system. *Allergic-like reactions* have a similar clinical presentation as the classic allergic response but are independent of immune system activation. Allergic-like reactions revolve around a physiologic response to contrast (e.g., nausea, vomiting, vasovagal reaction, hypertension, flushing).[44] The incidence of acute adverse reactions is related to the chemical and physical characteristics of ICAs (**Table 20.3**). In particular, as previously described, high-osmolar ICAs have approximately a 12% rate of acute adverse events, whereas that of low- or iso-osmolality ICAs is significantly lower (see Classic References, Katayama). In a cohort of 545 patients undergoing CT, the use of nonionic ICAs led to an allergic reaction rate of only 0.6%, of which only 23% were graded moderate-severe.[45]

TABLE 20.3

Classification of Acute Adverse Reactions After Injection of Intravascular Iodinated Contrast Agents

MILD*	MODERATE†	SEVERE‡
Allergic-Like		
Urticaria or pruritus (+) Cutaneous edema (+) Throat discomfort (“itching”) Nasal congestion Sneezing, conjunctivitis, rhinorrhea	Urticaria or pruritus (++) Diffuse erythema (++) Facial edema (++) Wheezing or bronchospasm (++) Throat discomfort (“tightness or hoarseness”)	Diffuse edema (+++) Facial edema and dyspnea (+++) Diffuse erythema and hypotension (+++) Wheezing or bronchospasm and hypoxia (+++) Anaphylactic shock
Physiologic		
Nausea or vomiting (+) Self-limiting vasovagal reaction (+) Hypertension (+) Flushing or warmth (+) Headache or dizziness Altered sense of taste Anxiety	Nausea or vomiting (++) Vasovagal reaction (++) Hypertension urgency (++) Chest pain	Vasovagal reaction, resistant to treatment (+++) Hypertension emergency (++) Arrhythmia Convulsion

*Self-limited adverse effects without evidence of progression.

†More pronounced adverse effects that require medical therapy.

‡High risk of permanent morbidity and mortality if not adequately treated.

Modified from Manual on Contrast Media of the American College of Radiology (ACR) Committee on Drugs and Contrast Media. Version 10.2, 2016.

Temporally, acute reactions occur within seconds or minutes of contact with the ICA. Delayed reactions, on the other hand, may develop from 30 minutes up to 1 week after injection of ICA and usually present with cutaneous manifestations (**Table 20.4**). A prospective study of 539 patients by Loh and colleagues demonstrated that the percentage of delayed adverse events with the use of the dimeric low-molecular group (iohexol) is 14.3%, compared to 2.5% observed in the no-contrast group.[45a] Moreover, among the different types of ICA, nonionic dimeric agents show a higher percentage of delayed events than nonionic monomer agents. Because the rate of true allergic reaction to contrast is so low, prophylactic therapy is indicated only in patients with a history of allergic adverse events. In elective patients at risk for allergic reactions, in particular those with a history of anaphylactic reaction, prophylactic treatment must include prednisone, 50 mg by mouth (PO), or hydrocortisone, 200 mg intravenously (IV), at 13 hours, 7 hours, and 1 hour before ICA injection, plus diphenhydramine, 50 mg IV, intramuscularly (IM), or PO, 1 hour before ICA administration (see Classic References, Lasser). Methylprednisolone, 32 mg PO, 12 hours and 2 hours before ICA injection, plus an antihistamine can also be used. In addition, careful selection of ICA in addition to prophylactic therapy can help to further

reduce the risk of adverse reactions, which are very uncommon (0.2% to 1.6%). Reactions to contrast agents may be more difficult to manage in patients receiving beta-blocker therapy. Recurrence rates may approach 50% on repeat exposure to contrast agents, and prophylactic use of H_1 and H_2 histamine receptor–blocking agents and aspirin therapy has been recommended.

TABLE 20.4

Classification of Delayed Adverse Reactions After Injection of Intravascular Contrast Agents

MOST FREQUENT	RARE
Urticaria	Severe cutaneous reactions in patients with systemic lupus erythematosus (SLE)
Persistent rash	Cutaneous reactions in sun-exposed areas of body
Maculopapular exanthema	Inflammation and swelling of salivary glands (parotitis or mumps)
Exanthema pustulosis	Acute polyarthropathy
Urticaria or pruritus	Nausea or vomiting
Angioedema or pruritus	Fever
Pruritus alone	Drowsiness
	Headache
	Severe hypotension*
	Cardiopulmonary arrest*

*Extremely rare (only in part referable to administration of contrast agents).

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Angiographic Projections

To identify and interpret the severity of coronary lesions, proper visualization of every segment of the main epicardial vessels and their branches is crucial. Although the coronary anatomy has a certain degree of variability, specific angulations of the x-ray tube are typically used during coronary angiography to ensure that vessel segments are not foreshortened or overlapping. The projections depend on the position of the x-ray tube and image intensifier. The AP view is obtained with the image intensifier in perpendicular position above the patient, with the x-ray beam traveling back to front. The intensifier can then be angled toward the patient's left or right side to obtain LAO and RAO views. The beam can be angulated cranially if the intensifier is tilted toward the head of the patient, and caudally if it is moved toward the patient's feet. The degree of angulation can be changed to prevent overlapping of vessels or obstruction of vessel segments caused by superimposition of implantable devices or other structures, such as spine bone or diaphragm. As a general rule, in LAO views, the LAD is visible on the right side of the spinal column. Conversely, in RAO projections, the LAD is on the left side of the spinal column. Cranial and caudal tilting is used to “open” overlapped segments. Caudal views are mostly used for the proximal segment of the LCA, whereas cranial views avoid foreshortening and allow for the evaluation of the mid- and distal portion of the vessel and its bifurcations. **Table 20.5** lists common projections for every coronary artery, and **Figs. 20.12 and 20.13** provide examples for the LCA and RCA, respectively.

TABLE 20.5

Standard Angiographic Projections

PROJECTION/DEGREES	ANATOMIC DESCRIPTION
Right Coronary Artery	
LAO 45	Vessel engagement projection Ostium and RCA along AV sulcus
LAO10-30, CRAN 30	PDA, PL branches, and RCA after crux
RAO 30	PDA ostium, PDA septal branches, right ventricular branches, acute margin branches
Left Coronary Artery	
Anteroposterior, CAUD 10	LMCA engagement projection
LAO 20-45, CAUD 30-45	"Spider projection": LMCA and proximal segment of LAD, Cx, and ramus (if present)
LAO 20-45, CRAN 30-60	Mid- and distal LAD and its branches, Cx PDA, and Cx PL branches if present
RAO 15-30, CAUD 10-30	All LAD and branches, Cx and OM branches
RAO 15-30, CRAN 10-30	Mid- and distal LAD and branches, mid-Cx and branches

LAO, Left anterior oblique; *CRAN,* cranial; *RAO,* right anterior oblique; *CAUD,* caudal; *RCA,* right coronary artery; *AV,* atrioventricular; *PDA,* posterior descending artery; *PL,* posterolateral; *LMCA,* left main coronary artery; *Cx,* circumflex artery; *OM,* obtuse marginal.

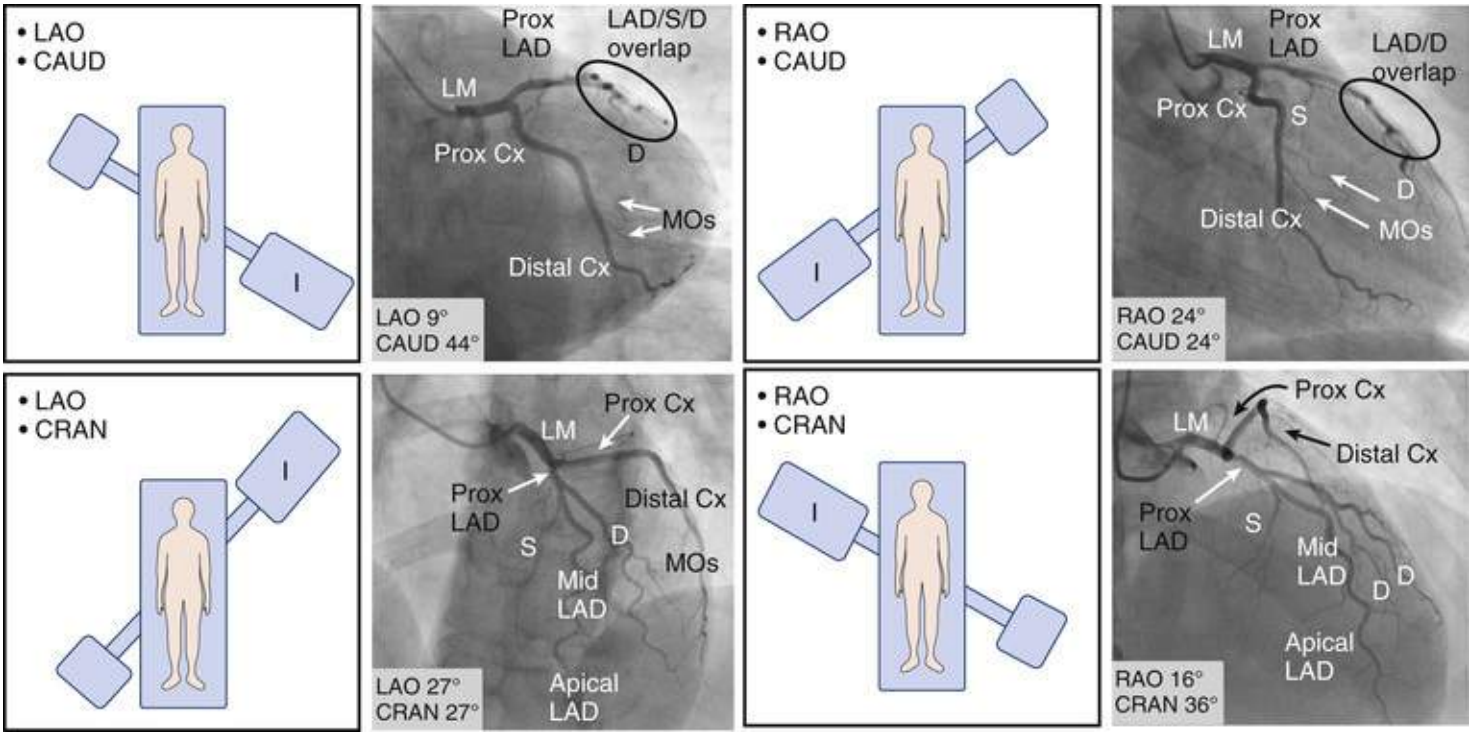

FIGURE 20.12 Angiographic projection for the left coronary artery and anatomic evaluation. *LM,* Left main coronary artery; *LAD,* left anterior descending artery; *Cx,* circumflex artery; *D,* diagonal branch(es); *S,* septal branch(es); *MO,* obtuse marginal branch(es); *prox,* proximal. LAO, Left anterior oblique; RAO, right anterior oblique; CAUD, caudal; CRAN, cranial; I, intensifier. (Angiographic images courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

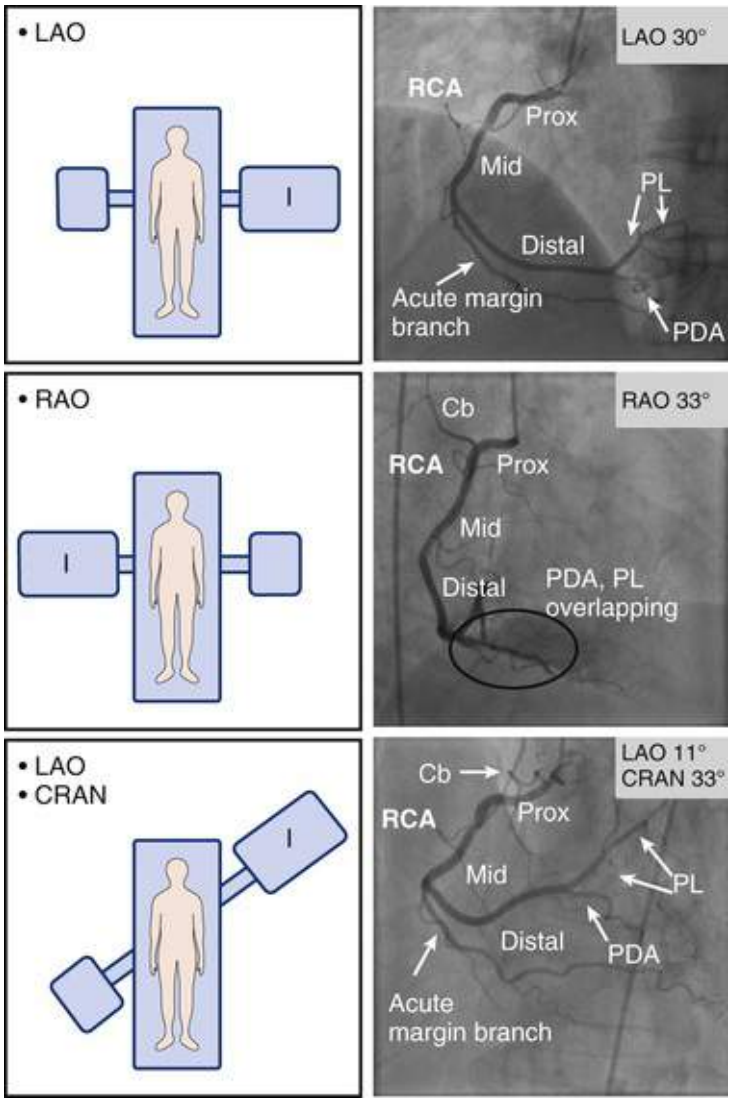

FIGURE 20.13 Angiographic projection for the right coronary artery (*RCA*) and anatomic evaluation. *Cb,* Conus branch; *PDA,* posterior descending artery, *PL,* posterolateral branches; *prox,* proximal. LAO, Left anterior oblique; RAO, right anterior oblique; CRAN, cranial; I, intensifier. (Angiographic images courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

Coronary Anatomy

The heart vasculature comprises three main epicardial arteries that divide into smaller, thinner branches that eventually form the arterioles. The arterioles have a muscular wall and are the main site of vascular resistance that can modulate the blood pressure reaching the capillary net downstream (**see Chapter 57**). This section reviews the coronary anatomy of the main epicardial vessels that can be visualized with coronary angiography.

The main epicardial vessels are the left main coronary artery (LMCA) and the RCA. The LMCA originates from the left sinus of Valsalva and divides into the LAD and the Cx arteries. Occasionally, a third branch can originate from the LMCA, the ramus intermedius (RI), usually attributed to the Cx artery.

The LAD artery runs along the anterior interventricular sulcus and provides circulation for the anterior and anterolateral wall of the left ventricle with diagonal vessels and the anterior two thirds of the interventricular septum with the septal branches. The number of diagonal and septal branches may vary greatly, and for the purpose of coronary description, they are simply numbered sequentially (D1, D2 … S1, S2, S3). Based on the length of the vessel, the LAD can be classified into type 1 if it does not reach the LV apex, type 2 if it reaches the LV apex, and type 3 if it reaches and wraps around the LV apex,

supplying also the posterior apex. The Cx artery courses along the left atrioventricular (AV) groove and provides branches for the left atrium, occasionally giving rise to the sinoatrial (SA) branch (40% of cases). The Cx also supplies the LV lateral and posterior walls with branches called *obtuse marginal* (OM) branches, which are numbered sequentially similar to the diagonal branches (**see Fig. 20.12**). There is high anatomic variability in the number of diagonal, septal, and OM branches present in the LCA.

The RCA originates from the right sinus of Valsalva and courses across the right AV groove. The proximal branches provided by the RCA are atrial branches for the right atrium, the SA node in 60% of cases, and the branch to the conus that supplies the right ventricular outflow tract. Once it reaches the acute margin of the ventricle, the RCA provides the acute margin branch. The RCA then continues to the crux cordis (where the AV groove intersects the posterior interventricular sulcus), where it branches into the PDA and the posterolateral (PL) branches (**see Fig. 20.13**). This anatomy is the most common and is termed *right coronary dominance*. Dominance can also be left or balanced, based on the origin of the PDA and the PL branches. Approximately 80% of the population displays a right dominance, meaning both the PDA and the PL branches are supplied by the RCA, while 10% of the population has a *left coronary dominance*, with PDA and PL branches deriving from the Cx artery. The remaining 10% display *codominance*, or *balanced coronary dominance*, with the PDA arising from the RCA and the PL branches arising from the Cx[1] (**Fig. 20.14**).

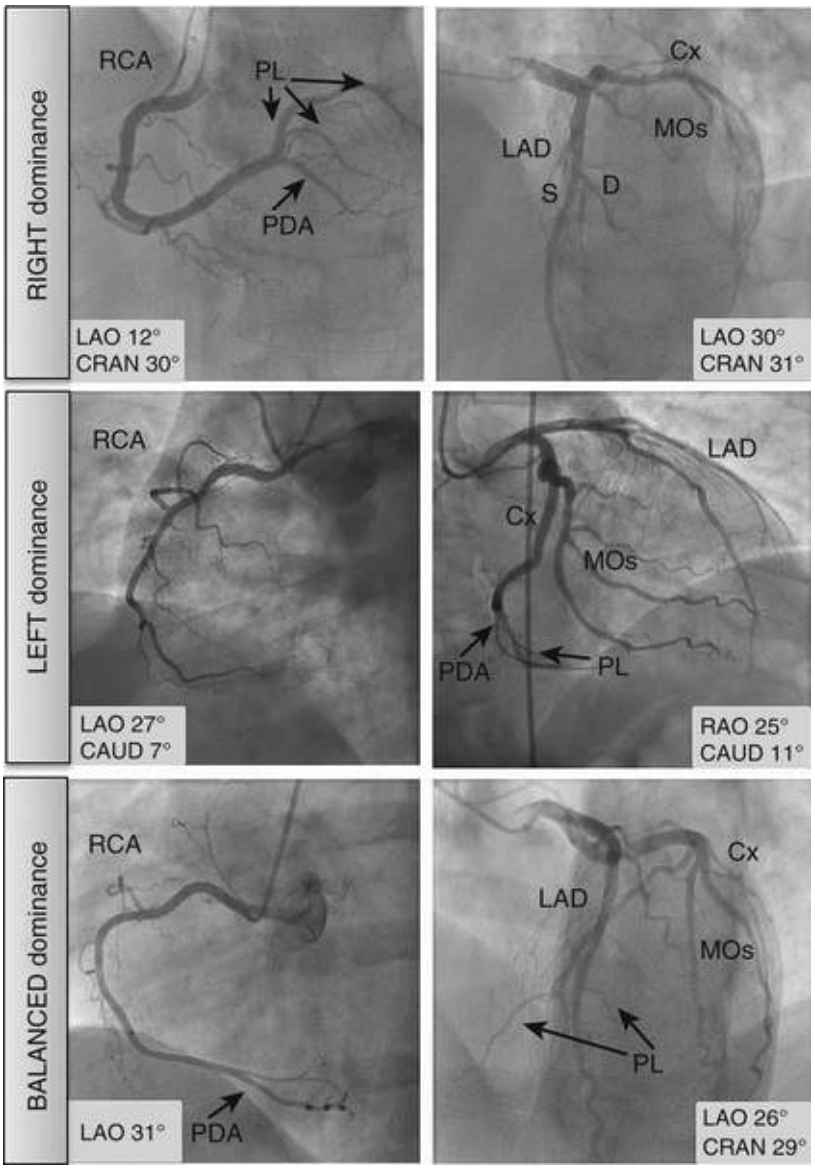

FIGURE 20.14 Coronary artery dominance. **Upper panels,** Example of right coronary dominance. **Middle panels,** Left coronary dominance. **Bottom panels,** Balanced dominance. *LAD,* Left anterior descending artery; *Cx,* circumflex artery; *RCA,* right coronary artery; *D,* diagonal branch(es); *S,* septal branch(es); *MO,* obtuse marginal branch(es); *PDA,* posterior descending artery, *PL,* posterolateral branches. LAO, Left anterior oblique; RAO, right anterior oblique; CAUD, caudal; CRAN, cranial. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

The subdivision of the coronary arteries into segments is crucial to describe the localization of lesions during angiography. **Table 20.6** lists the definitions of the coronary segments adapted from the SYNTAX Trial, with the corresponding CASS (coronary artery surgery study) number.

TABLE 20.6

Classification of Coronary Segments from SYNTAX Score

SEGMENT	DESCRIPTION	CASS NUMBER
Left main	From ostium of LCA until bifurcation into LAD and left Cx branches.	11
LAD proximal	Proximal to, and including, first major septal branch.	12
LAD middle	LAD immediately distal to origin of first septal branch and extending to the point where LAD forms an angle (RAO view). If this angle is not identifiable, this segment ends at one-half the distance from the first septal to the apex of the heart.	13
LAD distal	Terminal portion of LAD, beginning at end of previous segment and extending to or beyond apex	14
Major diagonal branches	LAD branches, sequentially numbered	15 first diagonal 16 second diagonal 29 third diagonal
Intermediate ramus	Branch from trifurcating left main other than proximal LAD or Cx; belongs to Cx territory.	28
Proximal Cx	Main stem of Cx from its origin from left main to and including origin of first OM branch.	18
Distal Cx	Stem of Cx distal to origin of most distal OM branch and running along posterior left atrioventricular grooves. Caliber may be small or artery absent.	19
OM branches	Cx branches, sequentially numbered	20 first OM 21 second OM 22 third OM
PL branches from Cx	PL branch originating from distal Cx	24 first PL 25 second PL 26 third PL
RCA proximal	From ostium to one-half the distance to acute margin of heart.	1
RCA mid	From end of first segment to acute margin of heart.	2
RCA distal	From acute margin of heart to origin of posterior descending artery.	3
Posterior descending	Branch running in the posterior interventricular sulcus	4 if from RCA 27 if from Cx
PL branches from RCA	Posterolateral branch originating from distal coronary artery distal to crux.	6 first PL 7 second PL 8 third PL

CASS, Coronary artery surgery study; *LAD,* left anterior descending artery; *RCA,* right coronary artery; *Cx,* circumflex artery; *RAO,* right anterior oblique; *OM,* obtuse marginal; *PL,* posterolateral.

Modified from www.syntaxscore.com.

Coronary Artery Anomalies

The prevalence of coronary artery anomalies (CAAs) in patients undergoing coronary angiography averages 1% to 5%[46] (**Table 20.7**). Despite being rare in the general population, CAAs are the second most common cause of sudden cardiac death (SCD) among young athletes.[47]

TABLE 20.7

Incidence of Coronary Anomalies in 1950 Angiograms

VARIABLE	NUMBER	FREQUENCY (%)
Coronary anomalies	110	5.64
Split RCA	24	1.23
Ectopic RCA (right cusp)	22	1.13
Ectopic RCA (left cusp)	18	0.92
Fistulas	17	0.87
Absent left main coronary artery	13	0.67
LCx arising from right cusp	13	0.67
LCA arising from right cusp	3	0.15
Low origin of RCA	2	0.1
Other anomalies	3	0.15

LCA, Left coronary artery; *RCA,* right coronary artery; *LCx,* left circumflex artery.

From Angelini P, editor. Coronary Artery Anomalies: A Comprehensive Approach. Philadelphia: Lippincott Williams & Wilkins; 1999, p 42.

There are many ways to classify CAAs. From a clinical standpoint, CAAs can be divided based on the presence of myocardial ischemia, into anomalies without ischemia, anomalies with episodic ischemia, and anomalies with obligatory ischemia (**Table 20.8**). Despite this important functional assessment, physicians often categorize CAAs based on anatomic characteristics. Use of CTCA and MRCA have increased the capability to detect and characterize anatomic abnormalities and help to determine optimal management of patients with a CAA. The most common anatomic classification of CAAs includes anomalies of ostium, anomalous origin of coronary artery, anomalous termination, congenital absence, and hypoplasia.[47]

TABLE 20.8

Classification of Coronary Anomalies Based on Ischemia

ISCHEMIA	CLASSIFICATION
Absence of ischemia	Most anomalies (split RCA, ectopic RCA from right cusp; ectopic RCA from left cusp)
Episodic ischemia	Anomalous origin of a coronary artery from the opposite sinus (ACAOS); coronary artery fistulas; myocardial bridge
Typical ischemia	Anomalous left coronary artery from the pulmonary artery (ALCAPA); coronary ostial atresia or severe stenosis

Congenital Atresia of Coronary Ostium.

Coronary ostial hypoplasia or atresia can occur as an isolated lesion or as a concomitant anomaly with other CAAs. The life expectancy of patients with coronary ostial hypoplasia or atresia depends on the presence of collateral circulation from other vessels that can supply the distal coronary bed.

Anomalous Origin of Coronary Artery.

Anomalous origin of coronary arteries is a common type of CAA. Coronary arteries with ectopic origin can arise either from the wrong sinus of Valsalva (e.g., the Cx artery arising from the right coronary sinus) (**Figs. 20.15 and 20.16**) or from a different structure, including the pulmonary artery (PA), a branch of another coronary artery, or even a ventricular chamber.[48] The course of the anomalous coronary arteries can be assessed by angiography in the RAO view. The LCA arising from the right aortic sinus usually follows one of these four courses: prepulmonic, retroaortic, interarterial, or transseptal (**Fig. 20.17**). The interarterial course of an anomalous LCA from the right sinus is associated with SCD during or shortly after exercise in young individuals. The hemodynamic mechanism underlying the risk of SCD remains unclear. Some authors hypothesize that distention of the aortic root and the pulmonary trunk

during exercise or stress might exacerbate the preexisting angulation of the anomalous coronary artery, resulting in compression of the coronary artery lumen. In other cases the vessel might have an aberrant course within the aortic wall that favors compression of the coronary artery. Similarly, origin of the RCA from the left aortic sinus with an interarterial course is associated with myocardial ischemia and SCD. Once this anomaly is diagnosed, CABG is recommended, although a stenting strategy has also been reported. A benign variation of the RCA origin is represented by the high anterior origin. This variation has no hemodynamic significance but might result in a challenging cannulation.

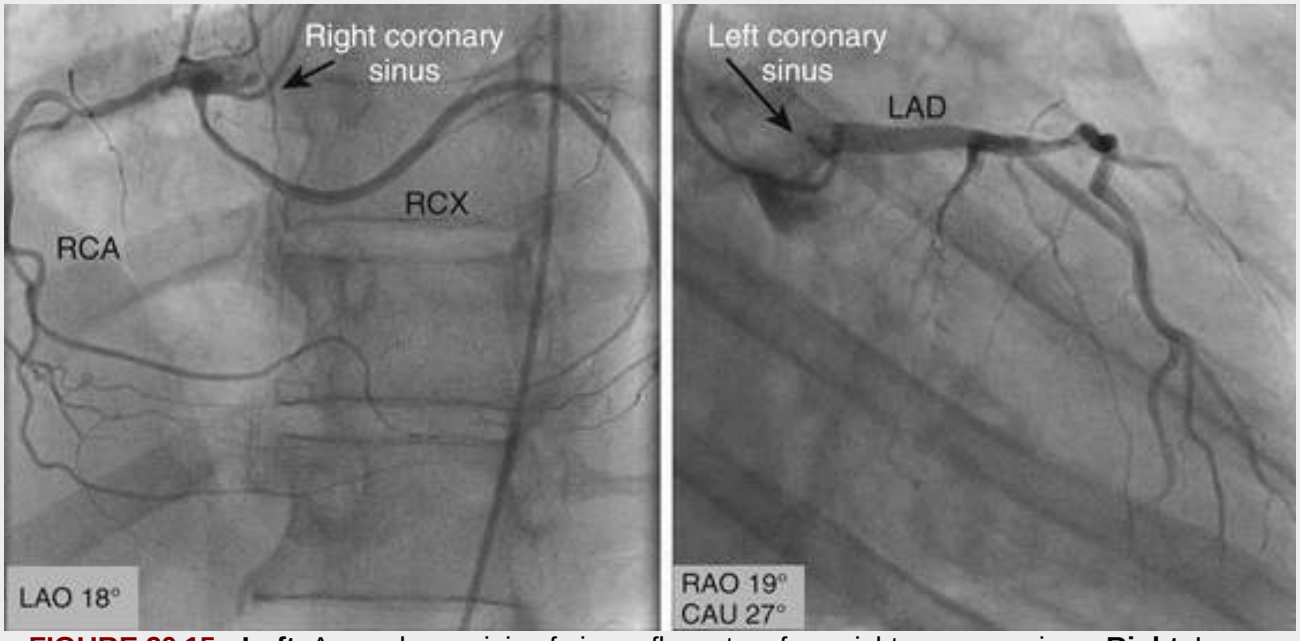

FIGURE 20.15 **Left,** Anomalous origin of circumflex artery from right coronary sinus. **Right,** Image shows that only the left anterior descending artery (LAD) arises from the left coronary sinus. *RCA,* Right coronary artery; *RCX,* right circumflex artery. LAO, Left anterior oblique; RAO, right anterior oblique; CAU, caudal. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

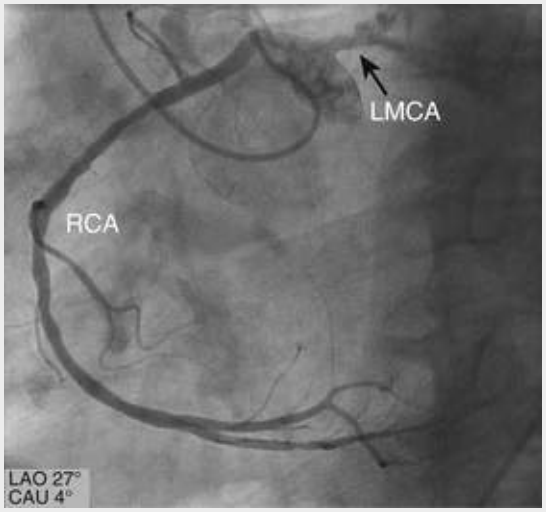

FIGURE 20.16 Anomalous origin of right coronary artery (*RCA*) from left coronary sinus. The left main coronary artery (*LMCA*) has a separate ostium in the left coronary sinus and can be seen in the upper right corner. LAO, Left anterior oblique; CAU, caudal. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

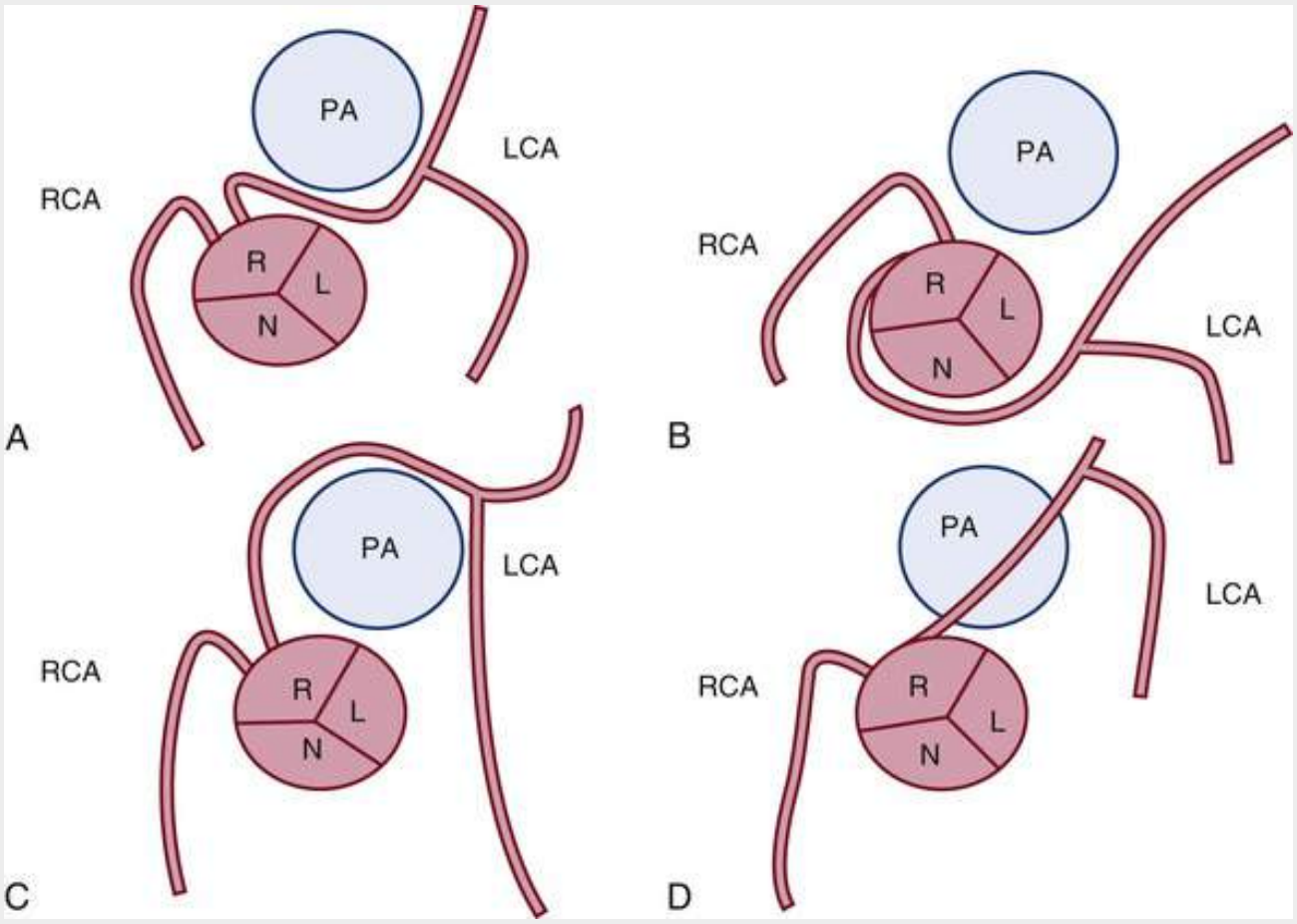

FIGURE 20.17 Four possible courses of the anomalous left coronary artery (*LCA*) arising from the right coronary sinus: **A,** interarterial; **B,** retroaortic; **C,** prepulmonic; **D,** transseptal. *PA,* Pulmonary artery; *RCA,* right coronary artery; *R,* right sinus of Valsalva; *L,* left sinus of Valsalva; *N,* noncoronary sinus.

Anomalous pulmonary origin of any coronary artery (APOCA) is a very rare occurrence (**Fig. 20.18**). If all three coronary arteries arise from the PA, prognosis is poor; patients with this anomaly usually die within the first month of life (see Classic References, Yamanaka). Anomalous origin of the LCA from PA (ALCAPA), also known as Bland-White-Garland syndrome, was reported for the first time in 1956 and represents the most common APOCA. Almost 90% of patients with this CAA die during the first year of life. Only very few, with extensive collateral circulation from the RCA, survive into adulthood. If diagnosed in time, the preferred treatment for APOCA is CABG.[49]

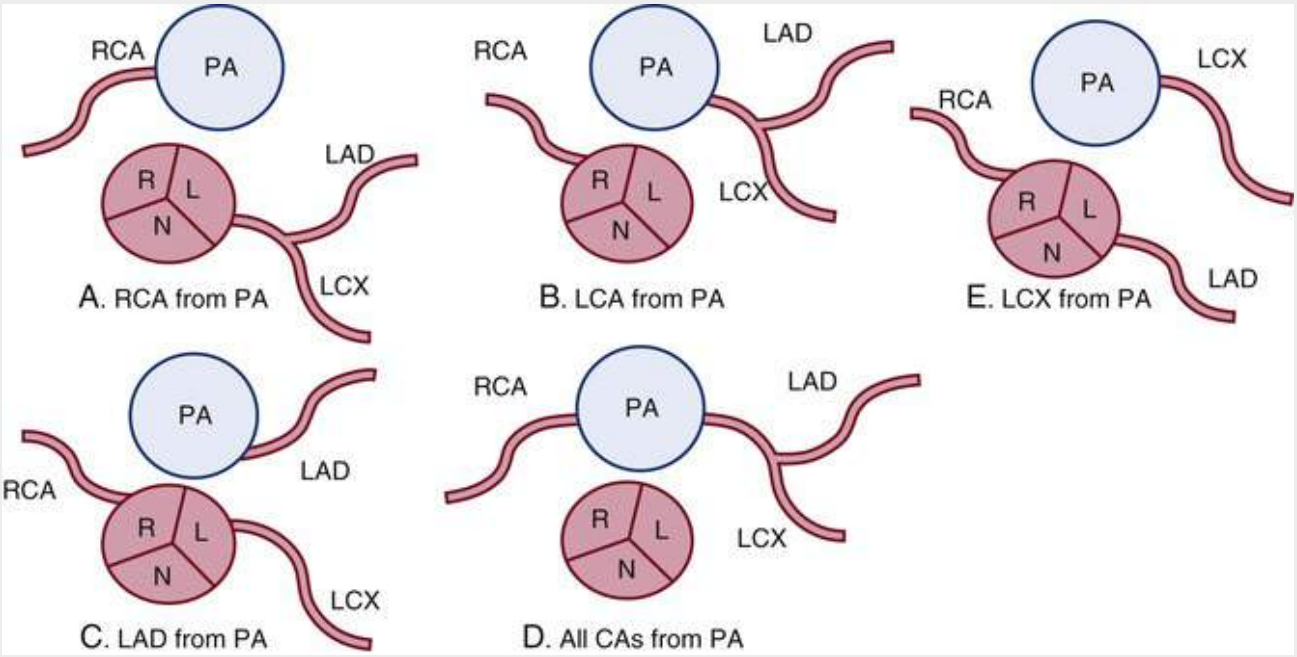

FIGURE 20.18 **A** to **E,** Anomalies of origin from pulmonary artery (*PA*). *RCA,* Right coronary artery; *LAD,* left anterior descending artery; *LCX,* left circumflex; *LCA,* left coronary artery; *CAs,* coronary arteries; *R,* right sinus of Valsalva; *L,* left sinus of Valsalva; *N,* noncoronary sinus.

Congenital Absence.

Lack of an LMCA is the most common form of congenital coronary absence, with a rate of 0.41% to 0.67% in the general population. In the absence of LMCA, the LAD and Cx arteries simply arise directly from the left sinus of Valsalva with separate origins. This anomaly is considered a benign condition and is an occasional finding during coronary angiography. The congenital absence of either the Cx or RCA have been reported and associated with a benign prognosis.[50]

Hypoplasia.

Hypoplasia of a coronary artery is defined as the maldevelopment of at least one of the major epicardial arteries or its branches. One, two, or all three coronary territories can be involved. Hypoplastic coronary arteries usually have a small diameter and a shortened course. A luminal diameter of less than 1.5 mm in a major epicardial vessel, with no nearby compensatory branches, has been proposed as the threshold for diagnosis. The prognosis of single-vessel hypoplasia of the Cx or RCA is relatively good, but SCD can occur in two-vessel hypoplasia.

Anomalous Termination.

Congenital coronary artery fistulas (CAFs) are rare anomalies, with an estimated incidence in the general population of approximately 0.002%. As an incidental finding, CAFs are reported in 0.3% to 0.8% of patients undergoing coronary angiography for any indication. CAFs are defined as abnormal direct communication between one or more coronary arteries with another major vessel or a chamber, such as the vena cava, left or right ventricle, pulmonary vein, or PA (**Fig. 20.19**).

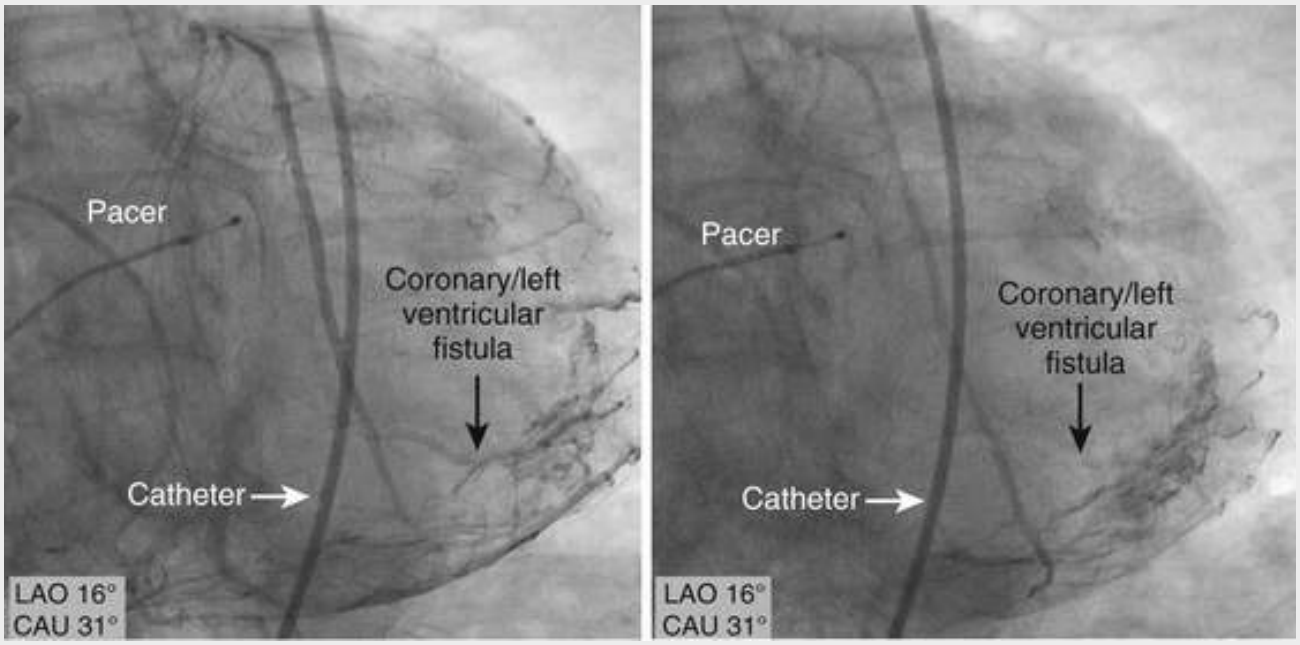

FIGURE 20.19 Coronary fistula with the left ventricle. LAO, Left anterior oblique; CAU, caudal. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

CAFs can originate from any of the major epicardial vessels and involve the RCA in 33% to 55%, the LAD in 35% to 49%, and the Cx in 17% to 18% of cases. Simultaneous involvement of both the left and the right coronary system exists in about 4% to 18% of CAFs.[51,52] Most of the fistulas drain into low-pressure structures, such as the right ventricle (40%), right atrium (26%), PA (17%), coronary sinus (7%), and superior vena cava (1%). Although possible, drainage of CAFs into left-sided chambers is less frequent (left atrium 5%, left ventricle 3%).[51-53]

Coronary angiography is the gold standard for the diagnosis of CAFs. However, in clinical practice, most CAFs are incidental findings during CTCA in low-risk patients. The clinical presentation of patients with CAF depends on size and volume of the shunt, location of the shunt, and concomitance with other cardiac disease. Approximately 50% of patients with CAF are asymptomatic. When present, common symptoms are dyspnea, fatigue, palpitation, and chest pain. The first manifestation of CAF can also include CHF, arrhythmias, SCD, and infective endocarditis. Symptomatic patients with large fistulas should be treated with surgical closure or interventional closure.

Pitfalls of Coronary Angiography

Improper interpretation of angiographic images can result from the use of inadequate projection views, CAAs, vessel foreshortening or superimposition of branches (**Fig. 20.20**), and deep engagement of the catheter into the vessel, potentially resulting in oversight of ostial lesions. In addition, obesity or instrument malfunctioning can lead to low image quality and erroneous image interpretation. Inadequate vessel opacification because of enhanced blood flow or competitive flow from a bypass graft might result in oversight of stenosis in collateral branches or in overestimation of the degree of thrombosis in a vessel. Also, when reading coronary angiograms, borderline lesions may require multiple views and potentially intracoronary imaging or evaluation of the fractional flow reserve (FFR) to adequately assess the severity of the lesion. **Fig. 20.21** shows an example of an eccentric lesion of the proximal LAD that is not visible in the LAO 34-degree, cranial 28-degree projection but becomes evident in the RAO 24-degree, caudal 21-degree projection. Moreover, a myocardial bridge or a coronary spasm can result in a minus defect in the coronary artery that can be misinterpreted as atherosclerotic disease, leading to unnecessary treatment

(see next section). In the case of ostial occlusion of a vessel, especially for primary or secondary branches of main epicardial vessels, it can be challenging to notice the missing vessel unless a collateral perfusion is present that allows for partial visualization of the downstream portion of the occluded vessel.[54]

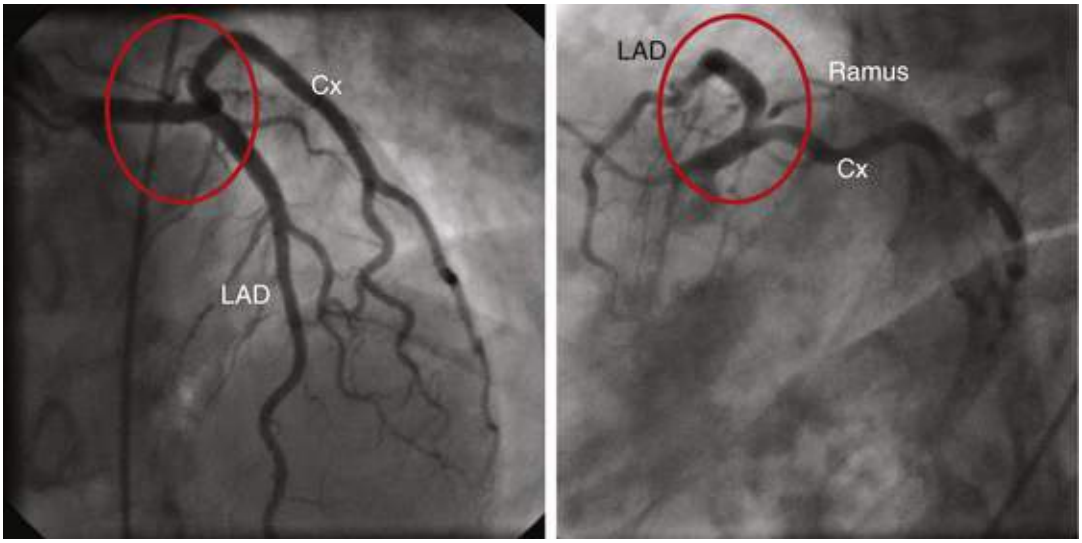

FIGURE 20.20 **Left,** Erroneous projection with overlapping of coronary vessels. **Right,** With a different projection, the trifurcation of the left main coronary artery becomes visible and can be evaluated for the presence of coronary stenosis. *LAD,* Left anterior descending artery; *Cx,* circumflex artery. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

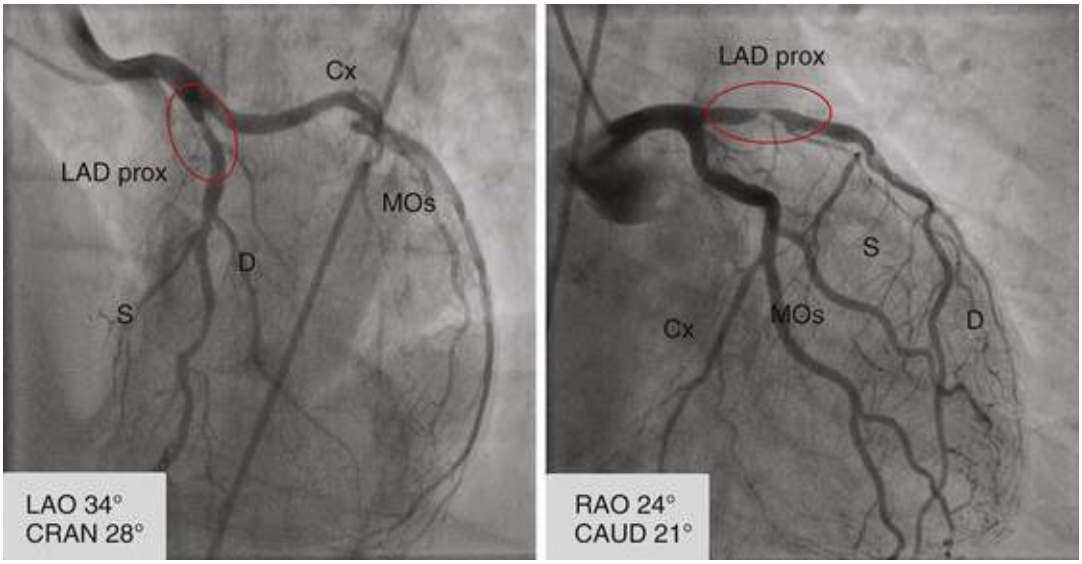

FIGURE 20.21 Example of eccentric coronary lesion in the proximal LAD, uncovered with the use of different angiographic projections. *LAD prox,* Proximal segment of left anterior descending artery; *Cx,* circumflex artery; *D,* diagonal branch(es); *S,* septal branch(es); *MO,* obtuse marginal branch(es). (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

Myocardial Bridging

Myocardial bridging is not a coronary lesion per se, although in the long term it can lead to local coronary

damage. It can also be mistaken for a coronary stenosis because bridging might cause filling defects. Myocardial bridging consists of a segment of an epicardial artery that descends into the myocardium for a variable distance (**Fig. 20.22**). It occurs in approximately 5% to 10% of patients and usually involves the LAD. As it runs in the myocardium, during systole the arterial segment is constricted by the muscle fibers and appears as a narrowing on the angiogram. However, these segments are usually easily identifiable because the narrowing disappears during diastole. Although bridging is not thought to be of any hemodynamic significance in most cases, myocardial bridging has been associated with angina, arrhythmia, depressed LV function, myocardial stunning, early death after cardiac transplantation, and SCD.[55] Treatment with beta blockers can be considered. Alternatively, surgical treatment can be attempted in selected cases.

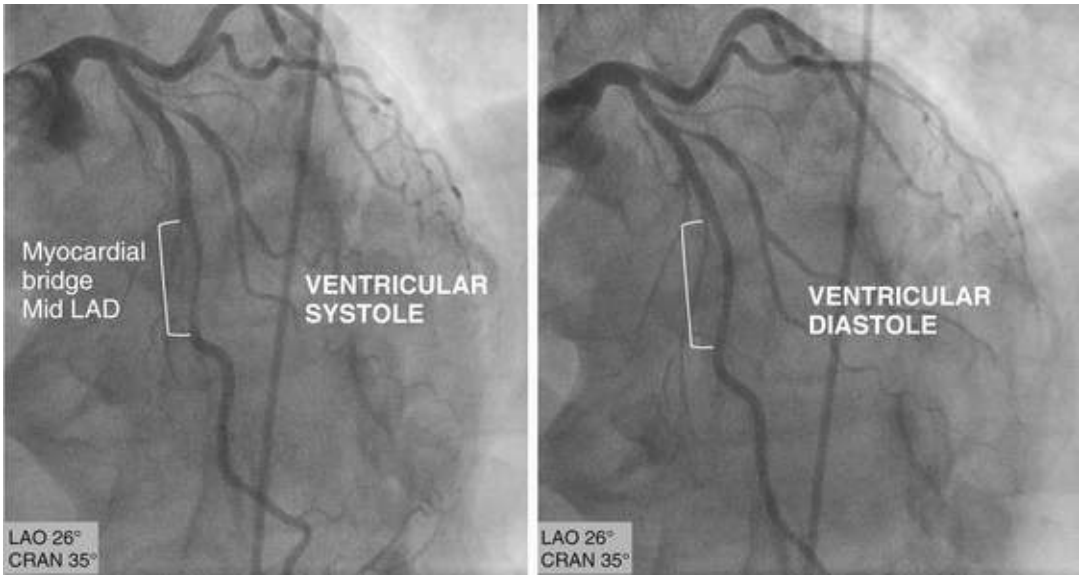

FIGURE 20.22 Myocardial bridge. **Left,** Narrowing of the middle left anterior descending artery (*LAD*) can be observed during the ventricular systolic phase. **Right,** The vessel diameter returns to normal during the ventricular diastolic phase. LAO, Left anterior oblique; CRAN, cranial. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

Coronary Artery Spasm

Coronary spasm is a dynamic reversible focal restriction or occlusion of a coronary artery caused by the constriction of the smooth muscle cells in the vessel wall (**Fig. 20.23**) (**see Chapter 57**). Coronary spasm, when prolonged, can cause Prinzmetal angina and lead to transitory ECG changes. Cigarette smoking, cocaine use, alcohol, intracoronary irradiation, and administration of catecholamines can promote coronary artery spasm. If a coronary spasm is suspected, a diagnosis can be made with several provocative tests, most often intravenous (IV) ergonovine maleate, IV acetylcholine, and hyperventilation. The physiologic response to ergonovine is a diffuse coronary vasoconstriction in all epicardial vessels. In patients with coronary spasm, however, ergonovine can induce focal coronary spasm often associated with chest pain and ECG changes. Intracoronary nitroglycerin is used to relieve the spasm. Acetylcholine (ACh) is a vasodilator acting on the muscarinic receptors of the vascular smooth muscle cells. Incremental doses of ACh (20, 30, and 50 µg) are injected directly into the coronary artery. In the presence of endothelial dysfunction, cells cannot produce NO in response to ACh, resulting in local vasoconstriction. Adverse reactions to ACh include hypotension, bradycardia, dyspnea, and flushing.

Also, hyperventilation during coronary angiography can elicit spasm, although it is a much less sensitive test compared to the others. If no spasm can be documented, the diagnosis relies instead on clinical features and the response to treatment with nitrates and calcium channel blockers.

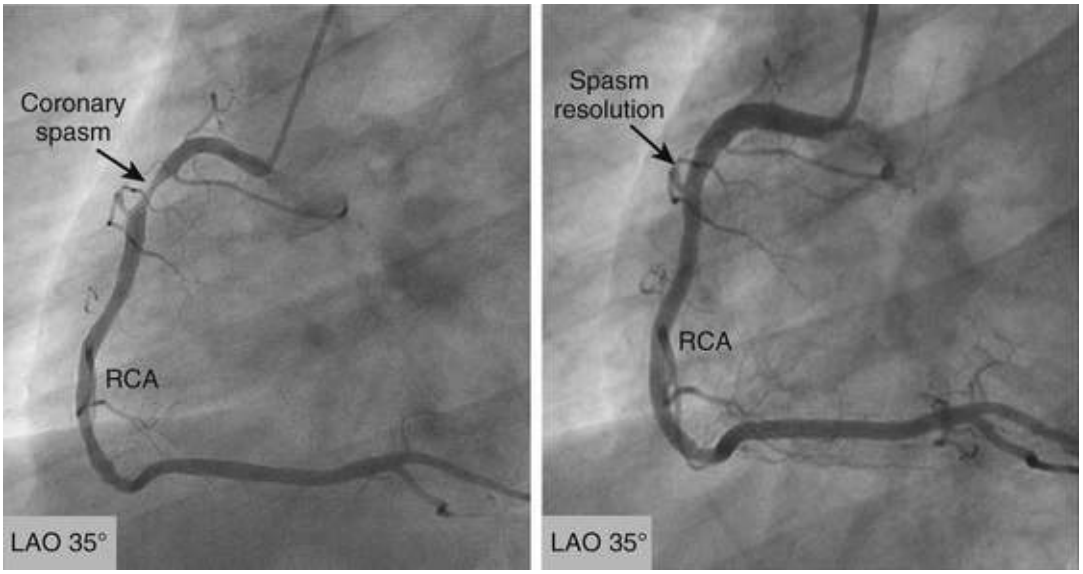

FIGURE 20.23 **Left,** Coronary spasm in the proximal segment of the right coronary artery (*RCA*). **Right,** Resolution of the spasm. LAO, Left anterior oblique. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

Angiogram Evaluation

When reading coronary angiograms, the entire extension of every coronary artery and its branches should be carefully evaluated in all the acquired views. First, the coronary dominance can be assessed. Next, the presence of abnormalities in the course of the coronary arteries should be investigated. The following elements should be part of the evaluation of diseased coronary vessels: (1) extension and localization of the lesion, (2) severity of the stenosis, (3) morphologic characteristics of the lesion, (4) evaluation of the downstream flow, (5) presence of collateral blood vessel circles, and (6) changes compared to previous angiograms, if available (**Fig. 20.24**).

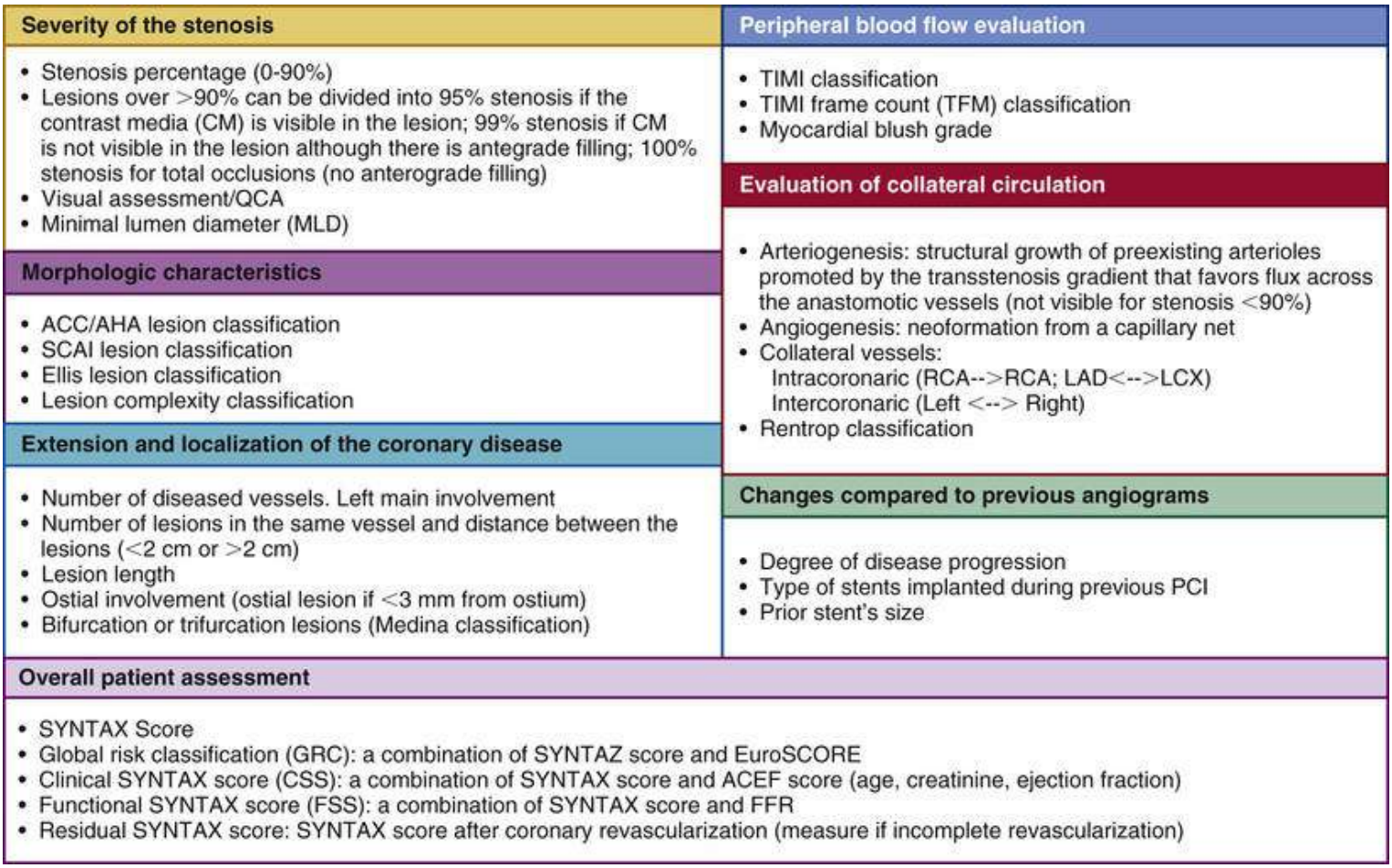

FIGURE 20.24 Evaluation of coronary stenosis.

Quantification of the Stenosis

A coronary stenosis is a reduction of the caliber of the vessel that is not caused by the progressive thinning of the vessel along its course but rather by pathologic local conditions. The degree of the stenosis can be evaluated by comparing the minimum diameter of the vessel at the level of the lesion to the diameter of the adjacent segment upstream of the stenosis. The degree of stenosis is usually underestimated compared to postmortem evaluation or intravascular ultrasound (IVUS) because the adjacent healthy lumen to which the stenosis is compared might present with vasospasm or diffuse atherosclerosis despite appearing normal on the angiogram. This often leads to underestimation of the stenosis. In addition, it is particularly difficult to evaluate long lesions since the arteries physiologically narrow during their course, and there might be a marked mismatch between the diameters of the normal segment upstream and downstream of a long stenosis.

Stenoses are defined as *minimal* if the narrowing is less than 50%, *moderate* between 50% and 70%, and *severe* or *significant* for a diameter reduction of 70% or more.[54] Evaluation of stenosis severity can be estimated visually by the interventional cardiologist reading the angiogram, or it can be measured with quantitative coronary angiography (QCA) methodologies based on the selection of the area of interest and vessel diameter measurements, which can be automatic, semiautomatic, or manual. Most programs can be calibrated using the diameter of the catheter and can automatically detect the edge of the vessel across its length and measure the minimum diameter of the stenosis and the length of the stenosis. Alternatively, rather than edge detection, densitometric methodology can be used. This technique avoids the errors of edge detection caused by geometric assumptions required for software calculations. Densitometry measures the stenosis based on the area containing ICA when the vessel is fully opaque. There is usually

good agreement between edge detection and densitometry techniques. QCA reduces interoperator variability of reading, which is estimated at ±20%.[56]

When evaluating a coronary lesion, the diameter and length of the stenosis are only two of many characteristics to consider. Also important are morphologic characteristics of the lesion, including the presence of thrombus, extent of calcification, and tortuosity of the vessel involved. The AHA has classified coronary artery lesions into three main types based on easily identifiable characteristics on the angiogram. This classification has predictive value for the success of a PCI procedure (**see Chapter 62**). Type A lesions have a procedural success rate of 92% and a low complication rate, type B lesions have a 72% success rate with a 10% rate of complications, and type C lesions have only a 61% success rate and a 21% rate of complications (**Table 20.9**). Additional classifications of lesion severity are the Society for Cardiovascular Angiography and Interventions (SCAI) and the Ellis systems.[57]

TABLE 20.9

AHA/ACC Lesion Classification

Type A	Length <10 mm Discrete Concentric readily accessible <45-degree angle Smooth contour	Little or no calcification Less than totally occluded Not ostial No major side branch involvement Absence of thrombus.
Type B B1 if only one characteristic is present B2 if two or more characteristics are present	Length 10-20 mm Eccentric Moderate tortuosity of proximal segment Irregular contour Presence of any thrombus grade	Moderate or heavy calcification Total occlusion <3 months old Ostial lesion Bifurcation lesion requiring two guidewires
Type C	Length >20 mm Diffuse Excessive tortuosity of proximal segment Total occlusion >3 months old and/or bridging collaterals' inability to protect major side branches Degenerated vein graft with friable lesions	

Evaluation of Microvascular Blood Flow

Evaluation of the downstream flow provides additional information not only on the severity of the stenosis, but also on the status of the microcirculation in the affected territory. It has been proved that often the microcirculation is impaired in the territory affected by epicardial vessel lesions. Prognostic information can be obtained from the degree of blood flow through the lesion. The most common classification is the Thrombolysis in Myocardial Ischemia/Infarction (TIMI) flow grade[35] (**Table 20.10**). In the presence of good blood flow in the coronary artery (TIMI 3) after PCI, patients can additionally be stratified using the TIMI frame count (TFC) score based on the number of angiographic frames necessary for the contrast to reach a standardized distal point in the vessel. The angiographic film should be acquired at 30 frames per second and contrast injection performed with a 6F catheter to measure TFC. The first frame is where the origin of the vessel appears fully opacified. The last frame is predefined for each coronary vessel: for the LAD and Cx arteries, it is the most distal bifurcation, whereas for the RCA, it is the emergence of the first PL branch. For the LAD, the apical segment is the milestone for the TFC. Because the LAD is usually longer than the other vessels, a correction factor needs to be used when calculating this score in the LAD by dividing TFC in the LAD by 1.7. Normal TFCs are 36 ±3 (or 21 ±2 if corrected) for the LAD, 22 ±4 for the Cx, and 20 ±3 for the RCA.[37] This score provides quantitative information on the status of the microcirculation in the infarcted areas and is a predictor of functional recovery and clinical outcomes after primary PCI. In fact, while most primary PCIs obtain patency of the epicardial flow and a TIMI flow grade 3, the tissue-level perfusion will determine the extent of the

myocardial damage or the muscle recovery. Similarly, the *myocardial blush* score provides a semiquantitative measure of peripheral perfusion (**Table 20.11**). It represents the arrival of the contrast in the capillaries and therefore can be appreciated only with angiographic acquisitions prolonged after the contrast has washed out of the main epicardial vessel. The myocardial blush grade is superior to TIMI flow grade for predicting postprocedural cardiac death and major adverse cardiac events (MACE).[58]

TABLE 20.10

Thrombolysis in Myocardial Ischemia/Infarction (TIMI) Flow Rate

TIMI 0 Flow	No penetration of contrast beyond the stenosis (100% stenosis, occlusion)
TIMI 1 Flow	Penetration of contrast beyond the stenosis but no perfusion of the distal vessel (99% stenosis, subtotal occlusion)
TIMI 2 Flow	Contrast reaches the distal vessel but at reduced rate of filling or clearing compared to other coronary arteries (partial perfusion)
TIMI 3 Flow	Contrast reached the distal vessel and clear at the same rate as the other coronary arteries

TABLE 20.11

Myocardial Blush Score

Grade 0	No myocardial blush or contrast density
Grade 1	Minimal myocardial blush or contrast density
Grade 2	Moderate myocardial blush but less than that obtained from the ipsilateral non–infarct-related coronary artery
Grade 3	Normal myocardial blush or contrast density comparable to that obtained during angiography of a contralateral or ipsilateral non–infarct-related artery

Collateral Vessel Circulation

The coronary arteries represent the end circulation of the heart, and thus there is very little redundancy in the vascularization of each myocardial territory. However, collateral vessels can form under specific circumstances. Collateral blood vessels are anastomotic connections between two segments of the same artery or between different native coronary arteries. They function as natural bypasses and represent an alternative source of blood supply for a coronary territory. Clearly, collateral circulation becomes very important in the event that the main vessel serving the territory becomes occluded. There are two main mechanisms by which collateral vessels can be formed: arteriogenesis and angiogenesis. *Arteriogenesis* is the growth of preexisting arterioles that transform into functional collateral arteries, as a muscular layer forms and viscoelastic and vasomotor properties are acquired. Arteriogenesis is promoted by the pressure gradient across the stenosis that favors the blood flow through the small, preexisting anastomotic vessels upstream of the stenosis. *Angiogenesis*, on the other hand, involves the de novo formation of vessels starting from primitive postcapillary venules. The process is favored by hypoxic stimuli such as local production of vascular endothelial growth factor (VEGF) and hypoxia-inducible factors (HIFs)[59] (**see Chapter 57**). The collateral vessel net can be intracoronary, if it connects different segments of the same coronary artery or the two LCAs, and intercoronary if it connects the RCA with one or both of the LCAs.

When evaluating coronary stenosis, it is important to take into account the presence of collateral vessels that may have formed over time. Collateral flow can allow visualization of an occluded vessel by retrograde opacification of the vessel downstream of the occlusion. Based on the presence of contrast in the collateral vessels and the degree of retrograde opacification of the epicardial vessel, collateral circulation can be classified with the Rentrop grade (see Classic References). Grade 0 represents no collateral circulation, grade 1 indicates presence of minor collateral vessels with no retrograde

visualization of the epicardial vessel, and grades 2 and 3 represent partial and complete retrograde opacification, respectively, of the epicardial vessel (**Figs. 20.25 and 20.26**).

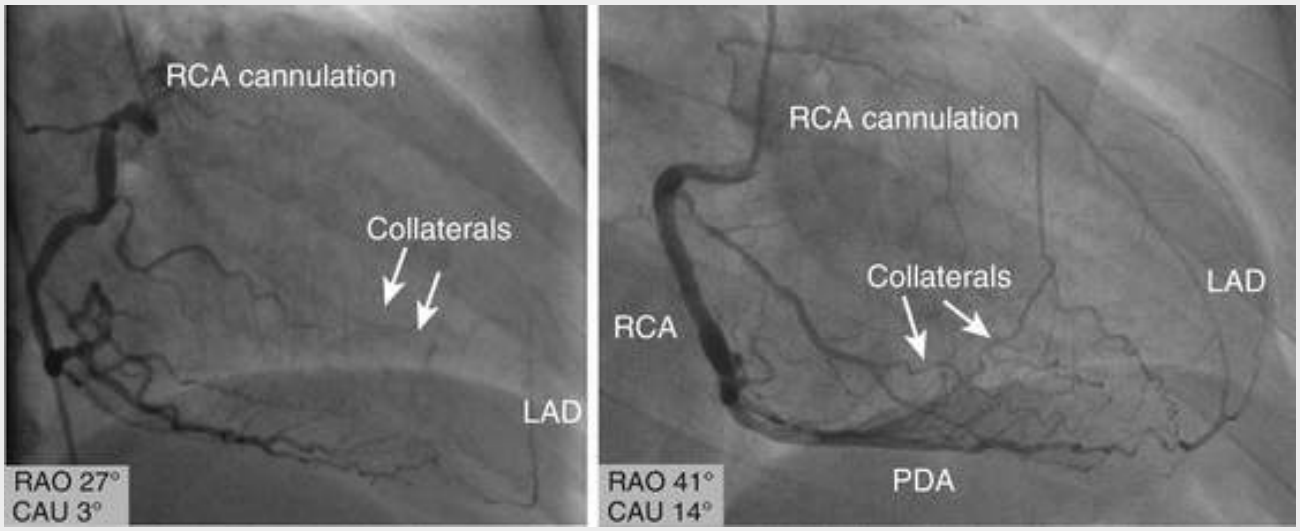

FIGURE 20.25 Collateral circulation from the right coronary artery to the left coronary artery. **Left,** Rentrop 2. **Right,** Rentrop 3. *LAD,* Left anterior descending coronary artery; *PDA,* posterior descending artery, *RCA,* right coronary artery. RAO, Right anterior oblique; CAU, caudal. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

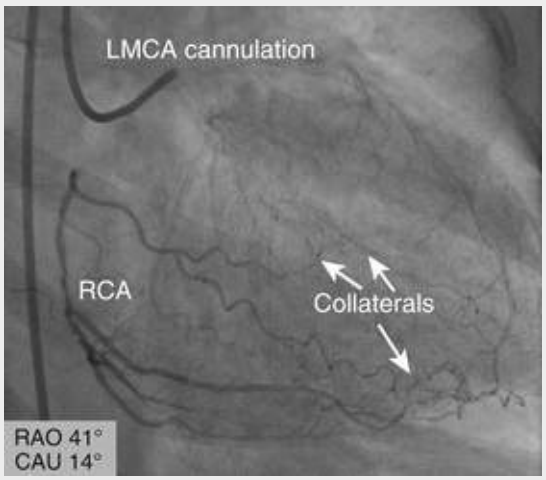

FIGURE 20.26 Rentrop 3 collaterals. The left coronary artery provides collateral vessels to the right coronary artery (*RCA*); *LMCA,* left main coronary artery. RAO, Right anterior oblique; CAU, caudal. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

Special Lesion Considerations

Chronic Total Occlusion

A chronic total occlusion (CTO) is the complete or almost-complete blockage of a coronary artery for 30 or more days. It can be an incidental finding in patients referred for diagnostic angiography. To visualize the vessel downstream to the CTO, a retrograde technique can be used by injecting the patent coronary artery; if collateral vessels are present between the two arteries, the vessel downstream of the CTO can

be visualized (see Rentrop classification for collateral vessels previously described). CTOs are considered very complex lesions and contribute greatly to the SYNTAX score (**see Chapters 61 and 62**); less than 50% of CTO lesions in the SYNTAX trial were successfully treated by PCI. A specific score, the J-CTO, has been developed to predict the probability of successful guidewire CTO crossing within 30 minutes; independent predictors were previously failed lesion, blunt stump type, vessel bending, presence of calcification, and occlusion length of 20 mm or more. For the purpose of CTO angioplasty, another way to visualize the vessel distal to the CTO is the preprocedural use of CTCA. Using co-registration software, the vessel portion that is "missing" in the coronary angiogram is integrated with the CT image, thus providing guidance for the advancement of the intracoronary guidewire.

Calcific Lesions

Atherosclerotic calcifications are an important predictor of successful PCI. Although invasive coronary angiography can detect calcific coronary lesions, it has a low sensitivity for calcium and can only detect moderate to severe calcifications[60] (**Figs. 20.27 and 20.28**). The gold standard for the evaluation of calcific lesions is CTCA (**see Chapter 18**). The extent of CAC correlates with the plaque burden (**Table 20.12**), and because of the high sensitivity of CT scan for calcium, this imaging modality can detect plaque burden at a very early stage As an alternative to CTCA, IVUS has been shown to have significantly higher sensitivity to detect coronary calcification than standard angiography, especially for milder calcifications.[60] Presence of a calcific arc greater than 180 degrees by IVUS is considered a severe calcification.[61]

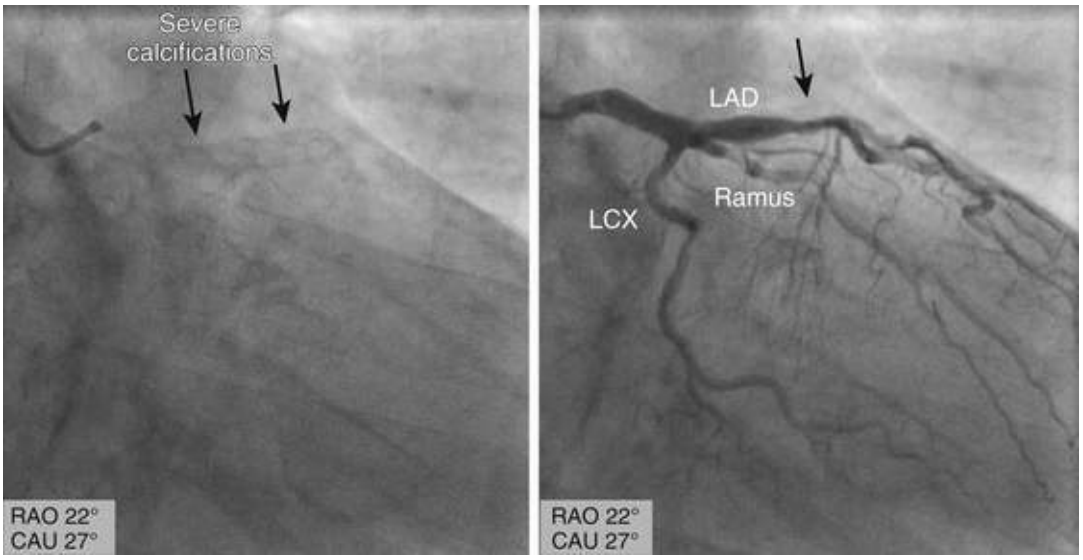

FIGURE 20.27 Severe calcifications in the proximal and middle left anterior descending artery (*LAD*). **Left,** Calcifications can be seen before contrast injection. **Right,** Marked irregularities of the vessel diameter in the segments with severe calcifications. *LCX,* Left circumflex artery. RAO, right anterior oblique; CAU, caudal. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

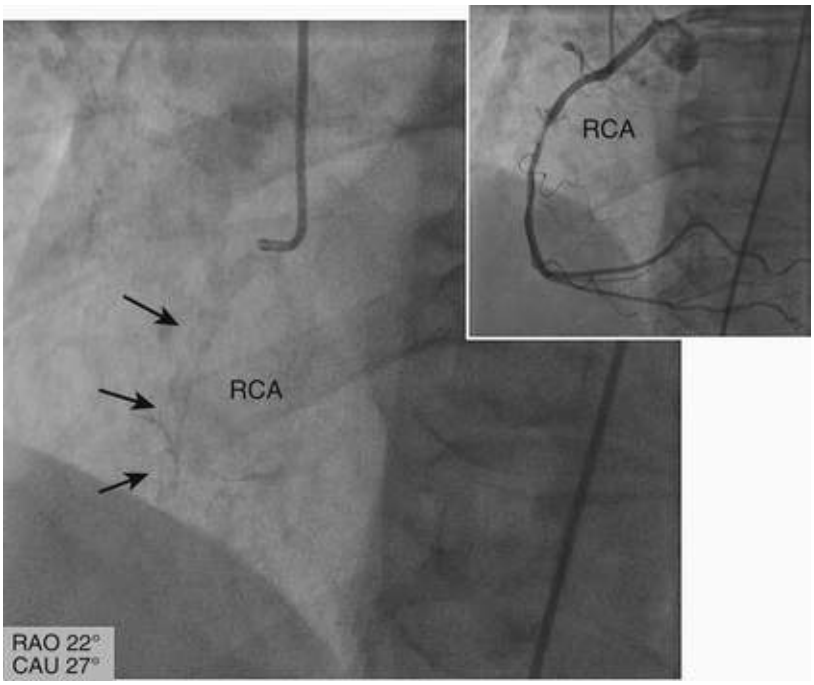

FIGURE 20.28 Severe calcifications in the right coronary artery (*RCA*). **Left,** Calcification can be seen before contrast injection. **Right inset,** Marked irregularities of the vessel diameter in the segments with severe calcifications. RAO, Right anterior oblique; CAU, caudal. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

TABLE 20.12

Coronary Artery Calcium (CAC) Score

SCORE (AGASTON)	PLAQUE BURDEN	DESCRIPTION/PROBABILITY OF CORONARY ARTERY DISEASE
0	Nonidentified	Negative test: very low risk of having a cardiovascular event in the next 10 years (<5%).
1-10	Minimal	Minimal atherosclerosis is present. Findings are consistent with a low risk of having a cardiovascular event in the next 10 years (<10%)
11-100	Mild	Mild coronary atherosclerosis is present. Mild or minimal coronary stenosis is likely.
101-400	Moderate	Moderate calcium is detected in the coronary arteries. There is a moderate risk of having a cardiovascular event within 10 years.
>400	Extensive	High risk of having at least one significant coronary stenosis (>90%). Significant risk of having a cardiovascular event within the next 10 years.

The correct assessment of the calcium burden of a coronary lesion is important to determine the most appropriate treatment strategy. Highly calcific lesions are not compliant, and despite dilation before stent deployment, the risk of suboptimal stent apposition is high. Vessel dissection and distal embolization with aggressive vessel dilation before or after stent deployment are also possible complications. CABG might not be a valid alternative to PCI with extensive calcifications that do not allow for graft insertion on the native coronary artery, particularly in multivessel calcific disease. Atherectomy (rotational or orbital) may specifically treat calcific lesions during PCI (**see Chapter 62**).

Thrombotic Lesions

Presence of thrombus is usually associated with plaque rupture observed during acute coronary syndromes (**see Chapters 58 and 59**). However, patients with generalized prothrombotic states can develop thrombus in the absence of plaque rupture. Thrombi are associated with higher rates of periprocedural complications. Thrombus load has been graded with the TIMI score as follows:

Grade 0, no cineangiographic characteristics of thrombus present

Grade 1, images suggestive but not diagnostic for thrombus: reduced contrast density, haziness, and irregular lesion contour

Grade 2, small thrombus present that is one-half or less the vessel diameter

Grade 3, moderate-size thrombus present with greatest linear dimension more than one-half the vessel diameter but less than two vessel diameters (**Fig. 20.29**)

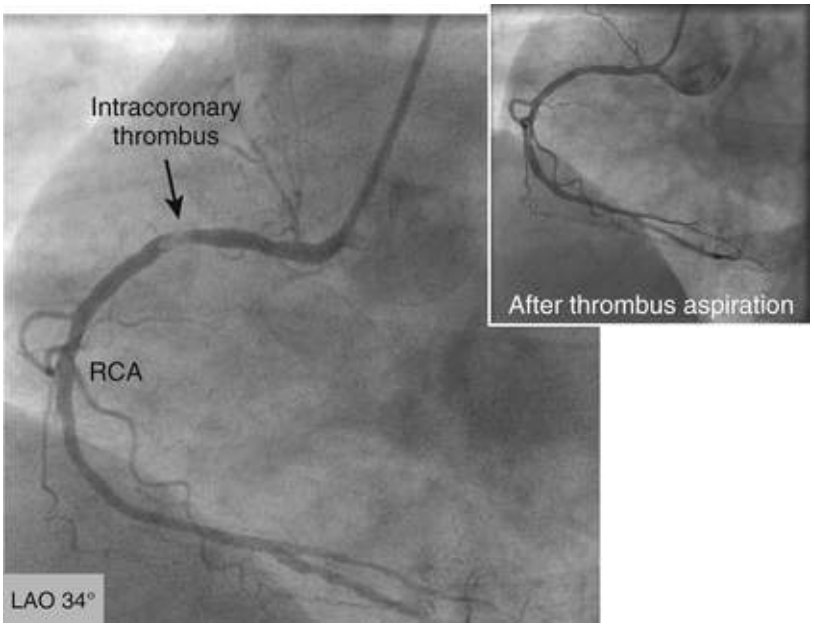

FIGURE 20.29 Grade 3 intracoronary thrombus in the proximal segment of the right coronary artery (*RCA*). **Right inset,** Absence of visible thrombus after aspiration. LAO, Left anterior oblique. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

Grade 4, large thrombus present with a largest dimension that is two vessel diameters or greater

Grade 5, recent total occlusion, which can involve some collateralization but usually does not involve extensive collateralization and tends to have a "beak" shape and a hazy edge or appearance of distinct thrombus

Grade 6, chronic total occlusion (CTO), which usually involves extensive collateralization, tends to have a distinct, blunt cutoff or edge, and will generally clot to the nearest proximal side branch.

Bifurcation Lesions

Bifurcation lesions account for approximately 15% of lesions requiring PCI. Bifurcation lesions are difficult to assess and treat because they may require intervention not only on the main vessel but on the side branch as well. Thus, these lesions are associated with increased complications during and after PCI. During coronary angiography, bifurcations are evaluated according to the Medina classification, a three-digit system based on the evaluation of three distinct vessel segments in the following order: main artery in the segment proximal to the bifurcation, main artery in the segment distal to the bifurcation, and the side branch. To each segment, the operator can assign 0 if no significant CAD or 1 if a significant stenosis is present.

Coronary Dissections

Coronary artery dissection can be a life-threatening complication during PCI or a spontaneous event. Iatrogenic dissections can be caused by the advancement of the guidewire into the coronary artery or by

plaque fracture after intracoronary balloon inflation. Based on their angiographic appearance, dissections can be classified (**Table 20.13 and Fig. 20.30**). Not all dissections require treatment. Type A and B dissections are usually considered benign and might not require intervention, whereas types C and F are often major dissections associated with morbidity and mortality. Whenever necessary, the management of coronary dissection is stent deployment.

TABLE 20.13

Classification of Coronary Dissections

Type A	Minor radiolucent areas within the coronary lumen during contrast injection with no persistence of the contrast after dye has cleared from the lumen
Type B	Dissections are parallel tract or double lumen separated by a radiolucent area during contrast injection with minimal or no persistence after dye clearance
Type C	Presence of contrast outside the coronary lumen ("extraluminal cap") with persistence of contrast after dye has cleared from the lumen
Type D	Spiral ("barbershop pole") luminal filling defects frequently with excessive contrast staining in the dissected false lumen
Type E	Dissection appears as new, persistent filling defects within the coronary lumen
Type F	Dissection that leads to total occlusion of the coronary lumen without distal antegrade flow

Modified from the National Heart, Lung and Blood Institute (NHLBI) classification system for intimal tears.

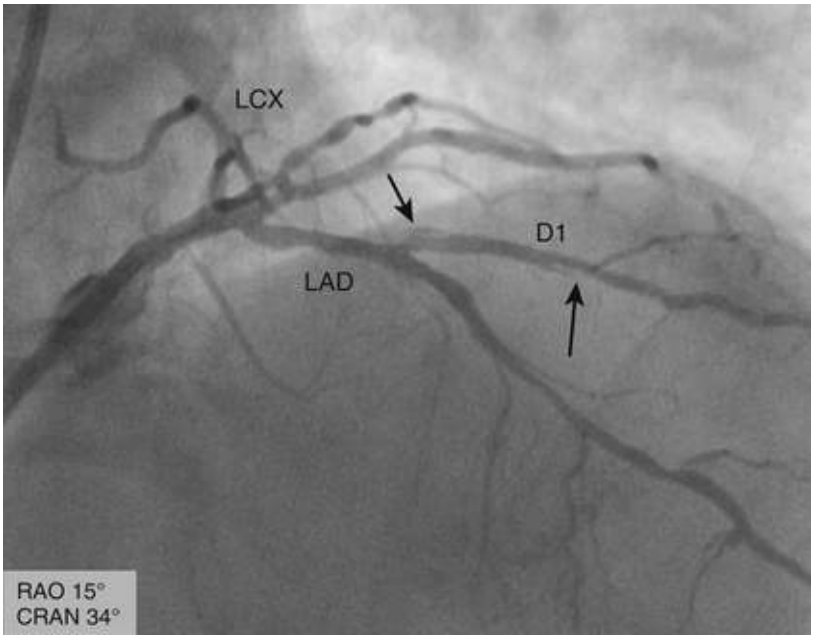

FIGURE 20.30 Type B coronary dissection. The *arrows* show two dissection sites in the diagonal branch. RAO, Right anterior oblique; CRAN, cranial. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

Spontaneous coronary artery dissections (SCADs) are rare. Their pathophysiology is not clear, but since they are more common in young women age 40 to 50 without any other cardiovascular risk factors, the etiology of SCAD has been associated with steroid hormones (**see Chapter 89**). In accordance with this theory, SCADs are more common within 2 weeks postpartum, when marked changes in hormonal levels are usually observed. Another possible explanation is the presence of undetected fibromuscular dysplasia (FMD), an arteriopathy that can involve different vascular districts, including renal arteries and coronary arteries (**see Chapter 64**). FMD can cause intramural hematomas that may result in SCADs. For example, in a study of 50 patients with SCAD, 86% were found to have FMD.[62]

Fractional Flow Reserve

Myocardial revascularization with PCI is recommended for coronary lesions with greater than 80% diameter stenosis. However, assessment of the hemodynamic significance of intermediate severe stenoses (those with diameter stenosis of 50% to 80%) might require more sophisticated methods to verify whether the lesion warrants an intervention. Application of FFR has been investigated intensively during the last decade (**see Chapters 57 and 62**).

FFR measures the pressure proximal to (aortic pressure) and distal to (guidewire pressure) a stenotic lesion during maximal hyperemia. Commercially available devices for detection of vessel physiology use 0.014-inch guidewires with a sensor on the tip (high-fidelity pressure transducer) to measure pressure, temperature, and flow. The application of FFR measurement is subject to certain technical necessities (**Table 20.14**). Coronary hyperemia can be induced by administration of adenosine (either IV or intracoronary). Each approach has its own limitations and benefits (**Table 20.15**). Several alternative drugs for induction of hyperemia are available, including papaverine (10 mg), nitroprusside (50 to 100 µg), adenosine triphosphate (ATP, 50 to 100 µg), or even contrast media.[89]

TABLE 20.14

Technical Approach for Fractional Flow Reserve (FFR) Measurement

1. Connect the FFR wire to systemic pressure analyzer. Calibration and zeroing should be performed outside the body.
2. It is necessary to use intravenous anticoagulation (heparin, 40 U/kg).
3. Advance the transducer into the guiding catheter until the transition zone is at the tip of the catheter. Pressure wire signal and guide pressure should be equalized before crossing the desired coronary lesion after flushing with saline.
4. Advance the FFR wire across the lesion (about 2 cm distal to the lesion).
5. Induce maximal hyperemia with adenosine (intravenous or intracoronary).
6. Estimate the pressure ratio proximal to distal of the lesion.
7. Finally, pull back the FFR wire into the guiding catheter to confirm equal pressure.

TABLE 20.15

Comparison of Intravenous and Intracoronary Adenosine Administration

	INTRAVENOUS	INTRACORONARY
Dose	140 µg/kg/min continuous infusion *or* Incremental dose until 160-180 µg/kg/min	Bolus injection of 20.30 µg/kg for RCA and 60-100 µg/kg for LCA
Effect peak	≤2 minutes after administration via central vein	<10 seconds
Effect duration	<2 minutes	<20 seconds
Side effect	AV block (rare) Bronchospasm (especially in patients with asthma) Decrease in blood pressure Increase in heart rate Angina-like symptoms and chest sensations	AV block, especially when administered in RCA
Benefit/limitation	Pullback is possible. Patient should avoid Valsalva maneuvers. Avoid kinking of punctured vein. In 8% of patients, only suboptimal hyperemia is inducible, resulting in implausible FFR values. Underestimation of values after caffeine or theophylline intake.	Does not allow pullback. In 10%-15% of patients, only suboptimal maximal hyperemia is possible. Underestimation of values after caffeine or theophylline intake.

AV, Atrioventricular; *FFR,* fractional flow reserve; *LCA,* left coronary artery; *RCA,* right coronary artery.

FFR is the ratio of maximal myocardial perfusion behind a stenotic lesion divided by maximal hyperemic flow in that same region in the hypothetical case that the lesion was not present. FFR is expressed as the reciprocal of normal maximal flow through a stenotic artery (**Fig. 20.31**). The normal value of FFR is unequivocally 1 for every coronary artery regardless of size. FFR values less than 0.80 in patients with stable CAD are considered hemodynamically significant and strongly correlate with inducible myocardial ischemia using noninvasive stress testing.

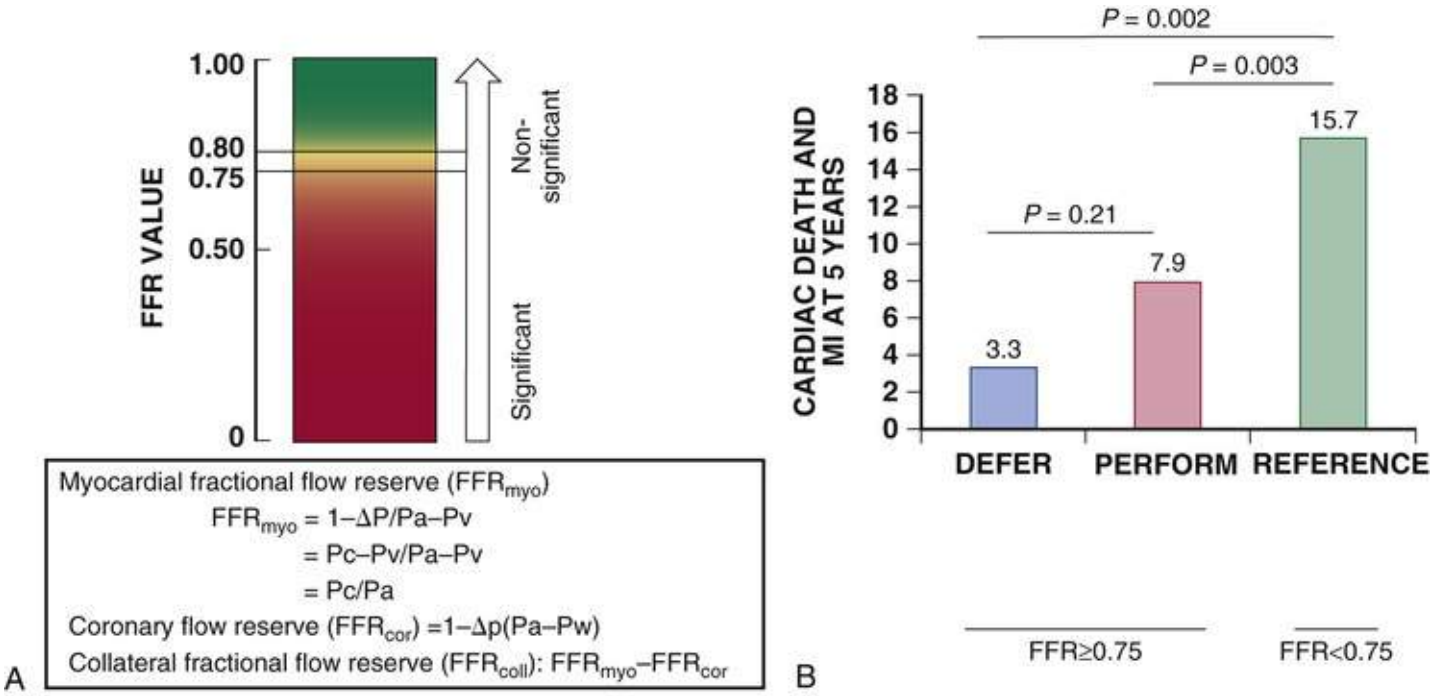

FIGURE 20.31 **A,** Calculation of fractional flow reserve (FFR) and normal and pathologic values for FFR. **B,** Cardiac death and myocardial infarction (*MI*) at follow-up of 5 years comparing defer vs. perform PCI in lesions with FFR ≥0.75 in comparison to reference group (FFR <0.75). (From Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol. 2007;49:2105-2111.)

In contrast to FFR, *coronary flow reserve* (CFR) measures the ability to increase resting flow to a normal maximal level (**see Chapter 57**). CFR estimates the capacity of major resistance components (epicardial vessel and supplied vascular bed). CFR, unlike FFR, is influenced by changes between basal and hyperemic blood flow, which in turn are influenced by heart rate, blood pressure, ventricular loading, and contractility. Therefore, CFR values should be interpreted with caution in particular patients (e.g., those with tachycardia, hypertension, LV hypertrophy, or heart failure). The most appropriate application of CFR is to identify coronary microvascular dysfunction.[63]

Several aspects during catheterization and measurement of FFR should be considered. The operator should avoid using catheters with side holes because a proximal pressure gradient will occur, thereby jeopardizing the measurement of distal gradient. Also, use of a larger guiding catheter might result in occlusion of the coronary ostium, leading to impairment of maximal flow. In numerous scenarios, a nonischemic FFR can be detected despite an apparently severe stenosis (**Table 20.16**).

TABLE 20.16

Reasons for Nonischemic Fractional Flow Reserve (FFR) Despite Apparently Severe Stenosis

Physiologic Reasons
Small perfusion territory
Myocardial infarction scar
Little viable tissue
Small vessel
Abundant collaterals
Severely diseased microcirculation
Interpretational Reasons
Other culprit lesion
Diffuse disease, not focal stenosis
Chest pain of noncardiac origin
Technical Reasons
Insufficient hyperemia
Guiding catheter too large, resulting in ostial occlusion
Electrical drift
True False-Negative FFR
Transmural myocardial infarction (small viable tissue area)
Severe left ventricular hypertrophy (imperfect hyperemia due to myocardial hypertrophy)
Exercise-induced spasm (resolution of lesion with hyperemia)

From Koolen JJ, Pijls NH. Coronary pressure never lies. Cath Cardiovasc Interv 2008;72:248-56.

Clinical Application

International clinical guidelines recommend the use of FFR in several clinical settings (**Table 20.17**) (**see Chapter 62**). Several CAD lesion subsets and clinical manifestation necessitate the measurement of FFR.

TABLE 20.17

International Guideline Recommendations for Measurement of Fractional Flow Reserve (FFR)

2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention (PCI)
FFR is reasonable to assess angiographic intermediate coronary lesions (50%-70% diameter stenosis) and can be useful for guiding revascularization decisions in patients with stable ischemic heart disease (SIHD). (Class IIA, level of evidence A)
2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline*
Measurement of FFR to determine whether PCI of a specific coronary lesion is warranted.
2014 European Society of Cardiology†
FFR to identify hemodynamically relevant coronary lesion(s) in stable patients when evidence of ischemia is not available. (Class I, level of evidence A) FFR-guided PCI in patients with multivessel disease (Class IIA, level of evidence B)

*Fihn SD, Gardin JM, Abrams, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation 2012;126:e354-471.

†Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541-2619.

Intermediate or Severe Lesions.

In almost 50% of angiographies, intermediate or severe lesions (defined as stenosis greater than 50% but less than 80%) are present. The Deferral vs. Performance of Percutaneous Coronary Intervention of

Functionally Non-Significant Coronary Stenosis (DEFER) Study investigated 325 patients undergoing PCI in three groups: FFR ≥0.75, FFR <0.75 treated with PCI, and FFR <75 with medical therapy[64] (**see Fig. 20.31B**). The prognosis of lesions with FFR >75 was excellent regardless of whether PCI was performed, whereas lesions with FFR <75 had the worst prognosis.

Multivessel Disease PCI.

The FAME (Fractional Flow Reserve vs. Angiography for Multivessel Evaluation) Trial compared a physiologic-guided PCI approach (FFR-PCI) to a conventional angiographic-guided PCI in 1005 patients with multivessel CAD. In FFR-PCI patients, PCI was performed if FFR was ≤0.80. At 1 year, there was a significantly lower rate of MACE (a composite of death, nonfatal MI, and revascularization) in the FFR-guided PCI group.[65] Similarly, the FAME 2 (Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease) Trial investigated patients in whom at least one stenosis was functionally significant (FFR ≤0.80) and randomly assigned them to FFR-guided PCI plus the best available medical therapy (PCI group) or optimal medical therapy alone (medical therapy group).[66] The trial was halted prematurely because of an excess of MACE (composite of death, myocardial infarction, and urgent revascularization) in the medical therapy group compared to the PCI group.[66] Hence, FFR ≤0.80 is the currently used cutoff for clinical purposes.

Left Main Stenosis.

Stenosis of the LMCA is associated with a high rate of false angiographic interpretation. Estimation of LMCA stenosis, in combination with the SYNTAX Score assigned to the coronary arteriogram as a whole, might lead to referral of the patient to a CABG procedure. Therefore, application of FFR is critical for decision making. Alternatively, IVUS or optical coherence tomography (OCT) can be used.

Ostial and Side Branch Lesions.

Lesions with side branch involvement may result in a “jailed” side branch after PCI. Estimating the need for PCI of the involved side branch is crucial eventually to reduce the need for risky and more complex interventions of the side and main branches. FFR may be used in the side branch to assess its significance for possible treatment. Functional SYNTAX Score might be used in lesions with nonsignificant FFR.

Saphenous Vein Graft Lesions.

In SVGs the FFR is the sum of competing flow in the native vessel, the SVG itself, and collateral circulation induced by longstanding occlusion of the native artery. Therefore the FFR will represent a net response indicating potential ischemia in that region. Small studies reported a high incidence of graft closure when placed on arteries with a preoperative FFR greater than 0.80.[67] Similar evidence was provided for arterial conduits from a retrospective evaluation.[68]

Acute Coronary Syndromes.

Measurement of FFR in patients with acute MI may lead to false-negative results because of a transient microcirculatory dysfunction in the infarcted area.

Multiple Lesions in One Vessel.

Serial lesions in one vessel constitute a challenge for estimation of an accurate FFR. Approximately expressed, if the distance between two consecutive lesions is more than six times the vessel diameter, each lesion can be considered independently. Otherwise, the FFR measured distal to the last lesion gives a sum of the flow across these serial lesions. In clinical practice, a pullback recording can be applied to identify the specific regions of a vessel with the highest pressure gradient. After treatment of these lesions, a reassessment should be done to estimate whether the gradient is residually high or not.

Postprocedural FFR Measurement.

Measurement of FFR after PCI might identify residual stenosis of a lesion requiring further intervention. In a study including 750 patients treated with PCI who underwent FFR immediately after stent implantation, positive post-PCI FFR was independently associated with adverse events at 6 months (**Fig. 20.32**). Noninvasive methods to determine FFR are under investigation.

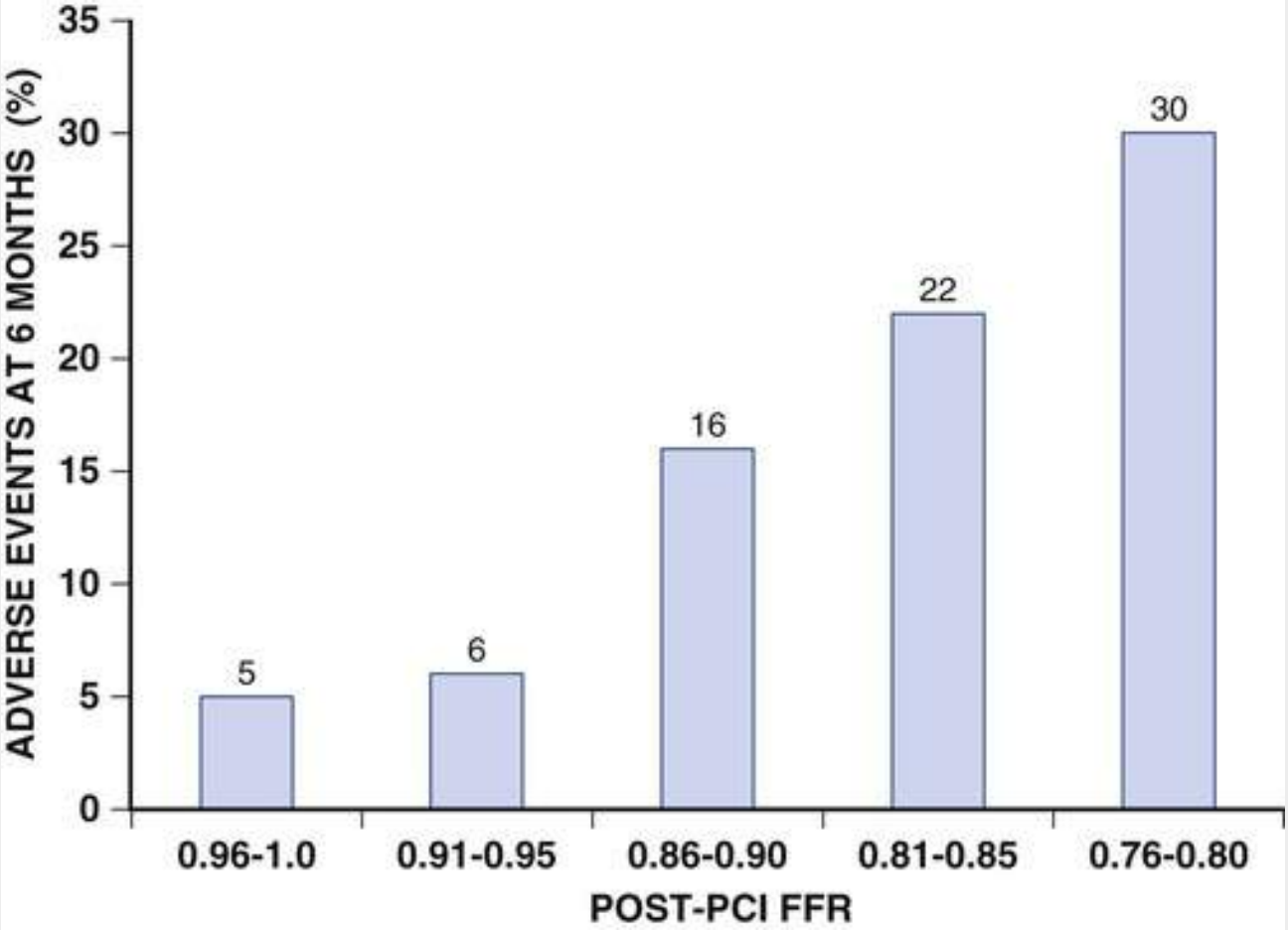

FIGURE 20.32 Increase in adverse events with lower post–percutaneous coronary intervention (PCI) fractional flow reserve (FFR). (From American Heart Association; Pijls NH, Klauss V, Siebert U, et al. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. Circulation. 2002;105:2950-4.)

Instantaneous Wave-Free Ratio

FFR requires maximal arteriolar vasodilation by administering a pharmacologic agent, most often adenosine. However, many physicians are reluctant to use adenosine because of patient-related discomfort and contraindications. Therefore, several catheterization laboratories have adopted the instantaneous wave-free ratio (iFR), a new physiologic index for assessment of the hemodynamic severity of a coronary stenosis.[69] Recently, randomized trials have demonstrated that the use of iFR compared with FFR is more feasible and reliable.[69-73]

The pressure gradient across a stenosis is related to the coronary flow velocity and microcirculatory resistance. To evaluate the severity of a stenosis, one must know constant coronary flow velocity and minimum microcirculatory resistance. During the wave-free period, the proximal-originating compression wave and microcirculatory-originating compression wave are quiescent, while microcirculatory resistance is the lowest and most stable throughout the cardiac cycle. Coronary pressure and flow are

linearly related.[69] Using conventional pressure guidewires, the process of measuring iFR is similar to that of FFR, except it does not require vasodilators. Measurement of iFR is based on a specific period in diastole called the *wave-free period,* during which resistance at rest is stable. This resting state occurs spontaneously in each cardiac cycle, without hyperemic stimulation, beginning 25% into diastole and ending 5 milliseconds before the end of diastole, representing almost 75% of diastole during which evaluation of pressure can be made[69] (**Fig. 20.33**). iFR is calculated as the mean pressure distal to the stenosis during the diastolic wave-free period divided by the mean aortic pressure during the diastolic wave-free period.

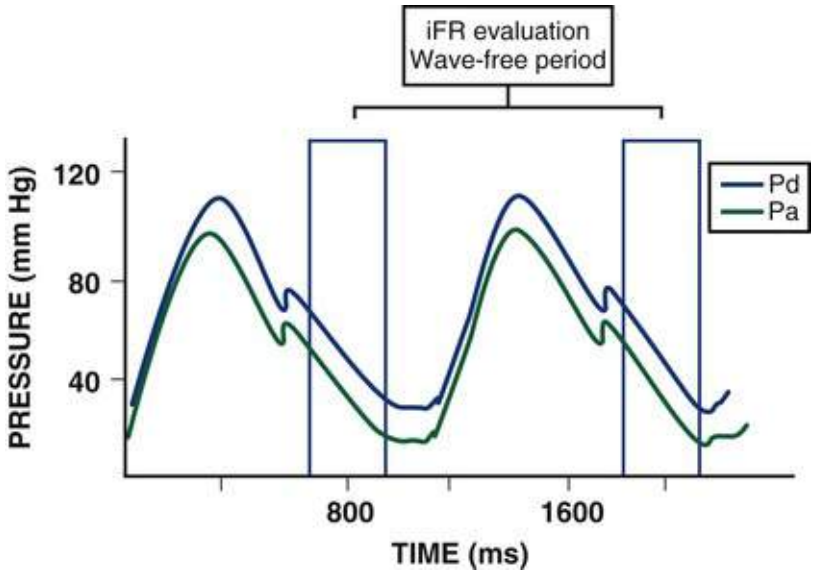

FIGURE 20.33 Illustration of wave-free period in the cardiac cycle. Instantaneous wave-free ratio (iFR) value of wave-free period in the cardiac cycle is demonstrated by the pressure distal to the stenosis lesion (Pd) divided by aortic pressure (Pa).

Comparison with Fractional Flow Reserve

In the first clinical study, iFR showed a good correlation with FFR ($r = 0.9$; $P < 0.001$) and also showed excellent diagnostic performance. Several studies recently reported various degrees of agreement between iFR and FFR, ranging from 80% to 90% depending on the severity of the investigated lesion. To match an FFR of 0.80 or less, the best iFR cutoff seems to be 0.89 to 0.90.[70-72]

Recently, iFR versus FFR approaches were compared in a randomized fashion.[73,74] The iFR strategy correlated with more deferral of PCI and overall similar ischemic outcomes to FFR. Further research on cost-effectiveness is ongoing.

Coronary Intravascular Imaging

The diffusion of techniques for intravascular imaging has advanced the understanding of coronary atherosclerotic disease and has provided additional information to angiography for the guidance of intracoronary stenting. IVUS and OCT are the main imaging modalities currently available in the catheterization laboratory for intravascular imaging.

Intravascular Ultrasound

An invasive coronary angiogram is a luminogram with poor specificity. Vascular imaging such as IVUS and OCT can facilitate detailed assessment and characterization of CAD and aid optimization of revascularization with stent implantation. Although OCT provides better definition of the vascular endothelium and fibrous cap of atheromas,[75] IVUS has higher vessel wall penetration that ensures a more detailed characterization of the atheroma core.

Principles.

IVUS employs an intracoronary catheter with a transducer at the tip, which generates sound waves by converting electrical energy into acoustic energy.[76] The waves are reflected off arterial vessel walls, returned to the transducer, and subsequently converted into a working image for qualitative and quantitative evaluation. Contemporary IVUS catheters include transducers emitting sound waves at frequencies of 20 to 45 MHz, which provide high penetration (5 to 10 mm) for accurate assessment of vessel size and plaque burden. However, the low resolution (70 to 200 μ; 100-μ micron axial resolution parallel to radius and 200-μ lateral resolution perpendicular to radius) of gray-scale IVUS results in imperfect plaque characterization.[77] Virtual histology IVUS (VH-IVUS) overcomes the drawback of gray-scale IVUS and allows detailed interpretation of plaque morphology in the different stages of phenotypic plaque evolution, namely, pathologic intimal thickening, fibrotic plaque, thick- and thin-cap fibroatheroma, and fibrocalcific plaque.[78] VH-IVUS also clearly demonstrates necrotic core, dense calcium, and areas of plaque rupture. Comparatively, OCT using light wave technology permits a higher resolution of 5 to 10 μ, although with low penetration for optimal assessment of plaque morphology, as well as differentiation between thrombus and plaque.[79] Finally, near-infrared spectroscopy (NIRS) technology promotes understanding of coronary plaque lipid burden and may be used in conjunction with IVUS or OCT.[80]

Technology.

There are two types of IVUS systems: single-element transducers and phased array transducers with multiple crystals arranged around the end of the delivery catheter.[76] A single-element transducer uses one element that generates and receives sound waves; a phased array system uses multiple transducers, which can be pulsed separately. The single-element type of catheter is commercially available with a transducer frequency of 40 to 45 MHz and a crossing profile of 2.9F to 3.2F compatible with 5F and 6F guides. Two such catheters are the Revolution (Volcano, California) and the Opticross (Boston Scientific). In contrast, the Eagle Eye Platinum catheter (Volcano) employs a phased array transducer with 20-MHz frequency and 2.9F crossing profile compatible with 5F guides. This catheter combines gray-scale and radiofrequency VH-IVUS assessment. The working length of the catheter is 150 cm (60 inches), and the proximal end is connected to the IVUS console for image reconstruction, which may be operated within the catheterization laboratory by radiation scientists. A console connected to the angiography table permits the operator to obtain measurements online during the procedure.

Indications for Use.

Current ACC/AHA guidelines[81] recommend IVUS use for assessment of indeterminate lesions in the LMCA (class IIA, level of evidence B) and non-LMCA (IIB, B) coronary arteries to determine the need for revascularization. IVUS is also recommended for optimization of stent implantation, particularly in the LMCA (IIA, B). Indeed, the use of IVUS in observational data has been associated with implantation

of larger and longer stents and higher pressures for postprocedural dilation.[82] After PCI, IVUS is recommended for the investigation of stent failure, to determine the mechanism of both in-stent restenosis (IIA, C) and stent thrombosis (IIB, C). Some investigators have also advocated IVUS use for the assessment and diagnosis of SCAD to visualize the tissue flap, true and false lumens, and intramural hematoma, thereby facilitating more accurate diagnoses.[83]

Procedure

Similar to a standard PCI procedure, IVUS examination is performed through a coronary guide catheter system over a 0.0014-inch guidewire using standard techniques with adequate anticoagulation for thrombus prevention. The crossing profile of the IVUS catheter varies from 2.9F to 3.2F, which is compatible with a 5F to 6F guide catheter. It is conventional to give a bolus dose of intracoronary nitroglycerin to prevent arterial spasm and allow better imaging assessment.[29] Once at the desired location distal to the lesion, pullback of the catheter is initiated, which may be automated or manual, with a typical pullback rate of 0.5 mm/sec. IVUS-related complications are rare and usually self-resolving. The risk of coronary dissection or perforation with IVUS use is estimated at 1.6%.[84] Complications with IVUS catheter use may be related to size of the vessel and force used to advance the catheter.

Interpretation

IVUS identifies three layers in normal vessel architecture, including the intima, media, and adventitia (**Fig. 20.34**). The *intima* is an echogenic, bright inner layer. The *media* is a hypoechoic, homogeneous area between the intima and adventitia composed of smooth muscle cells, collagen, elastic tissue, and proteoglycans. The *adventitia* is the outer reflective layer.[76] In the presence of atherosclerosis, there is evidence of medial thinning and deposition of plaque in the intima. This is typically noted to be heterogeneous due to variable impedance of the different plaque components (**Fig. 20.35**). Thrombus in the lumen may appear similar to plaque and cannot be clearly differentiated on gray-scale IVUS in the absence of a distinct interface between thrombus and plaque. Occasionally, IVUS may indicate the presence of blood flow through luminal thrombus. VH-IVUS identifies different plaque morphologies in a color-coded manner, and necrotic core, dense calcification, and fibrous and fibrofatty areas are all clearly noted.[78]

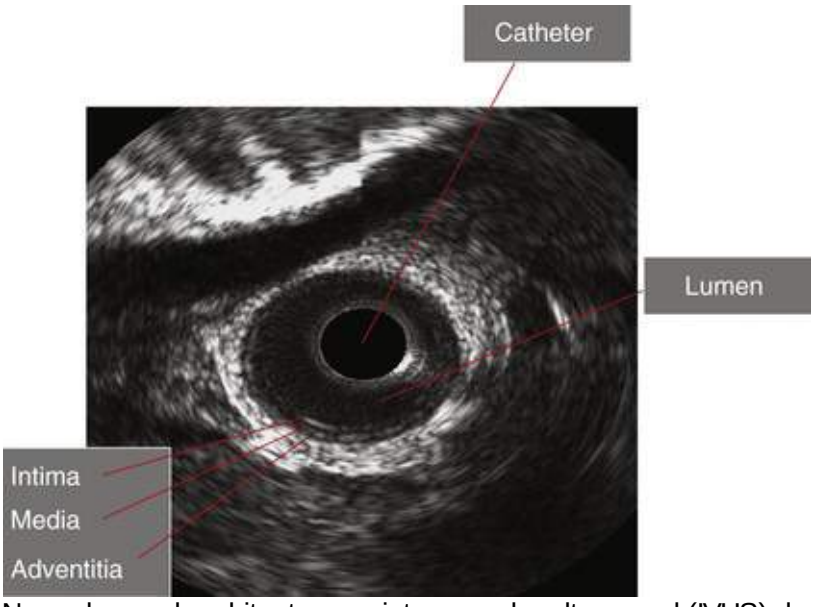

FIGURE 20.34 Normal vessel architecture on intravascular ultrasound (IVUS) demonstrating three layers: intima, media, and adventitia. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

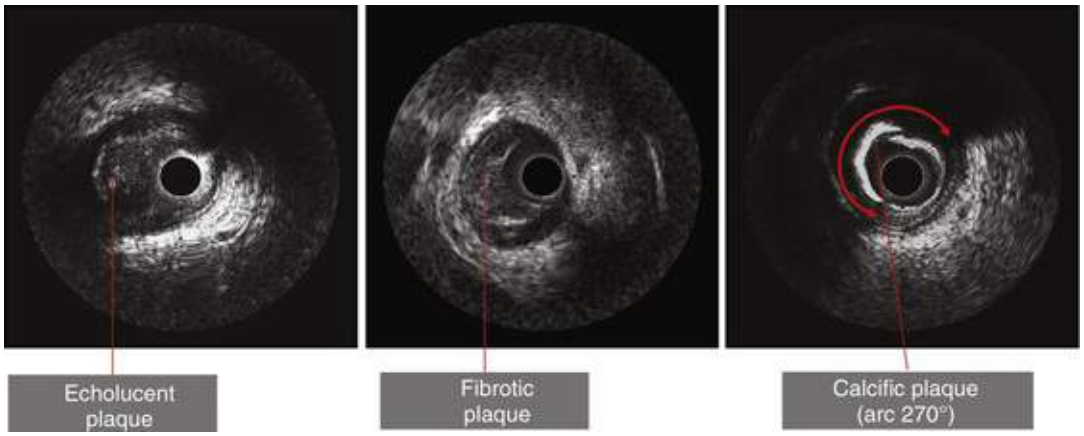

FIGURE 20.35 Heterogeneous nature of different plaque components caused by variable impedance on IVUS. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

A coronary dissection may be diagnosed on IVUS with documentation of tissue flap, true and false lumens, and intramural hematoma.[85] Implanted coronary stents can be assessed using IVUS for both expansion and apposition. A gap between the stent struts and the vessel wall indicates malapposition; the greater the distance between the stent strut and the vessel wall, the worse the malapposition. Stent underexpansion and malapposition are correlated with long-term adverse outcomes, including stent thrombosis. Real-time assessment of stent apposition and the need for post-dilation can be made online to allow specific management during PCI. Post-PCI neointimal hyperplasia caused by in-stent restenosis can be assessed using IVUS and appears as a hypoechoic area within the stent.[76]

In addition to immediate qualitative assessment of images for nature and extent of CAD, automated software analysis is available for both online and offline quantitative measurement of plaque burden and vessel size. Several validated measurements may be taken for evaluation of minimum lumen area, minimum lumen diameter, external elastic membrane (EEM) area, EEM diameter, plaque and media area (EEM area– lumen area), and plaque burden (plaque and media area/EEM area)[77] (**Fig. 20.36**). General criteria for significant obstructive disease include minimum lumen area less than 6 mm^2 in the LMCA or

less than 4 mm^2 in the proximal LAD and other major vessels.[87]

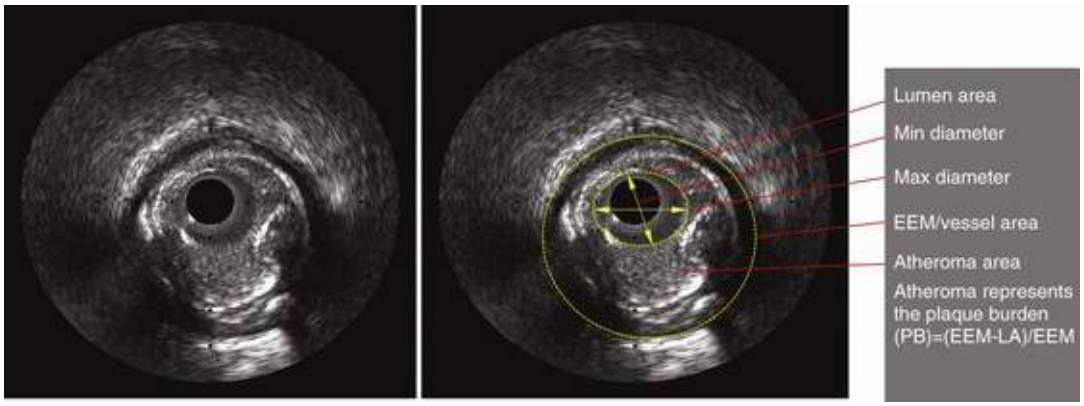

FIGURE 20.36 IVUS quantitative measurements for evaluation of lumen diameter and lumen area (LA), external elastic membrane (EEM) area, and plaque burden (PB). (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

For VH-IVUS, the gray-scale IVUS images recorded during pullback are combined with raw radiofrequency data captured on top of the R wave and reconstructed in a color-coded map by the IVUS-VH data recorder. The color-coded map identifies necrotic core (red), dense calcium (white), fibrofatty tissue (light green), and fibrous tissue (dark green). Thin-cap fibroatheroma on VH-IVUS is diagnosed in the presence of a greater than 30-degree arc of necrotic core abutting the lumen in three consecutive slices.[77]

Clinical Data

Several observational datasets have shown long-term benefit from IVUS use for PCI attributed to greater minimum stent area and lower MACE. In the Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents (ADAPT-DES) Study, IVUS was used in 39% of cases and was associated with longer stents, larger stent diameters, and higher inflation pressures in 74% of IVUS-guided cases.[82] IVUS-guided PCI was also associated with lower MACE, stent thrombosis, and target lesion revascularization after propensity-adjusted multivariable analysis. The MATRIX (Comprehensive Assessment of Sirolimus-Eluting Stents in Complex Lesions) registry compared patients undergoing IVUS guided versus non-IVUS guided PCI. Both short- and long-term outcomes were significantly reduced with IVUS use.[86] Similarly, a meta-analysis has shown that IVUS is associated with lower MACE, mortality, MI, stent thrombosis, and target lesion revascularization than angiography-guided PCI.[88] Nevertheless, these outcomes are from observational, not randomized data. Several randomized trials have been rather small in size and negative for routine use of IVUS imaging to improve PCI "hard outcomes."

In the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study, almost 700 patients presenting with ACS underwent three-vessel coronary angiography and IVUS after PCI. The study showed that non–culprit lesion–related MACE (composite of all-cause death, cardiac arrest, MI, or rehospitalization due to unstable or progressive angina) was associated with plaque burden of 70% or more, minimum lumen area of 4 mm^2 or less, and thin-cap fibroatheroma less than 65 μ.[84] However, at 3 years, MACE was equally related to culprit and nonculprit vessel lesions. Use of intracoronary imaging may facilitate early detection and treatment of vulnerable plaque in nonculprit lesions and decrease long-term MACE.

An important limitation of IVUS interpretation is the need for coaxial catheter position during image

acquisition.[89] The low resolution prevents clear differentiation between thrombus and plaque burden. In regard to applicability to the workflow of a busy catheterization laboratory, routine IVUS use is perceived to be expensive, time-consuming, and limited by operator skill. Further, IVUS does not allow visualization of the plaque lipid content, which might have important prognostic repercussions. To overcome this limitation, near-infrared spectroscopy (NIRS) can be used.

Plaque Lipid Core Detection

The NIRS catheter emits near-infrared waves with a wavelength of 0.8 to 2.5 µ. Based on differences in absorption pattern of the light, different components of plaque and lipid are demonstrated in a map or chemogram of lipid deposition along the coronary artery.[90] The TVC Insight Catheter (Infraredx, Massachusetts) combines NIRS and IVUS (40 MHz), with a crossing profile of 3.2F compatible with 6F guide catheter systems. The TVC composite system allows superimposed imaging from NIRS-IVUS, which can provide information on vessel size, plaque burden, and areas of lipid-rich plaque.[91]

Hybrid catheters are also available, combining FFR-IVUS and IVUS-OCT to provide complementary data from these dual technologies. NIRS can be used before PCI to identify lipid-rich plaques that might be at risk of periprocedural myonecrosis and distal embolization, to evaluate the necessity of distal protection filters.[92] The Coronary Assessment by Near-infrared of Atherosclerotic Rupture-prone Yellow (CANARY) Trial was a randomized clinical study on 57 patients undergoing coronary angiography and NIRS-IVUS imaging. Patients were randomized to angioplasty with or without a distal embolic protection device. The results showed that lipid-rich plaques identified by NIRS are associated with higher rates of periprocedural MI. However, the use of a distal protection filter did not prevent myonecrosis after PCI at lipid-rich plaques.[93]

Optical Coherence Tomography

Cardiovascular OCT is a catheter-based imaging technique that uses light and its reflection to create images of the coronary wall. Initially developed to perform imaging of the retina, OCT technology rapidly expanded to various biomedical and clinical applications.

Principles.

OCT is based on a fiberoptic wire with a rotating lens that emits near-infrared light (approximately 1300 nm) and records the light reflected from the analyzed tissue. One of the most valuable properties of OCT is its high resolution, up to 10 µ for axial resolution and 20 µ for lateral resolution. Although resolution is high, tissue penetration ranges from 1.0 to 3.5 mm.

The images created by OCT are derived from the delay that results from the light traveling to the target tissue and back to the lens. Images are generated by measuring the echo time delay and the intensity of reflected light. The speed of light does not allow direct measurement of the echo time delay, so a technique known as *interferometry* has been developed to analyze the reflected light signal. With this technique the light reflected from target tissue is measured by correlating it with light that has traveled a known reference distance. Cross-sectional images of the vessel are created by obtaining multiple axial scans as the fiberoptic wire is simultaneously rotating and pulled back rapidly along the vessel.

Two types of OCT imaging systems have been developed: *time-domain* OCT (TD-OCT) and Fourier-domain OCT, also known as *frequency-domain* OCT (FD-OCT). Using a novel wavelength-swept laser

as a light source, FD-OCT imaging systems provide superior signal-to-noise ratio and allow significantly faster imaging speed compared to the earlier time-domain technology. Recent FD-OCT imaging systems are capable of acquiring images at a rate of 180 frames/sec at a pullback speed of up to 36 mm/sec. One single pullback allows imaging of up to 75 mm of the vessel.

Early OCT technology required a complete displacement of blood from the viewing field to generate high-quality images. An over-the-wire low-pressure occlusion balloon catheter with distal flush ports to infuse saline or Ringer lactate can be used to remove erythrocytes from the viewing field. However, the accelerated pullback speed provided by FD-OCT no longer requires occlusion of the vessel, with a shift toward a nonocclusive approach with flushing of contrast.

Clinical Applications

OCT can be used to guide diagnosis during coronary angiography as well as procedure planning and assessment of PCI, as indicated in an initial clinical study.[94]

Normal Vessel Wall

In a healthy vessel, OCT visualizes the coronary artery wall as a layered structure (**Fig. 20.37**). The intima appears as a thin, highly reflective, and signal-rich layer, while the media occurs as a dark, low-reflective band. The latter is delimited by the internal elastic lamina, an adluminal signal-rich line, and the external elastic lamina, an abluminal signal-rich line. The adventitia appears as a signal-rich, heterogeneously textured outer layer.

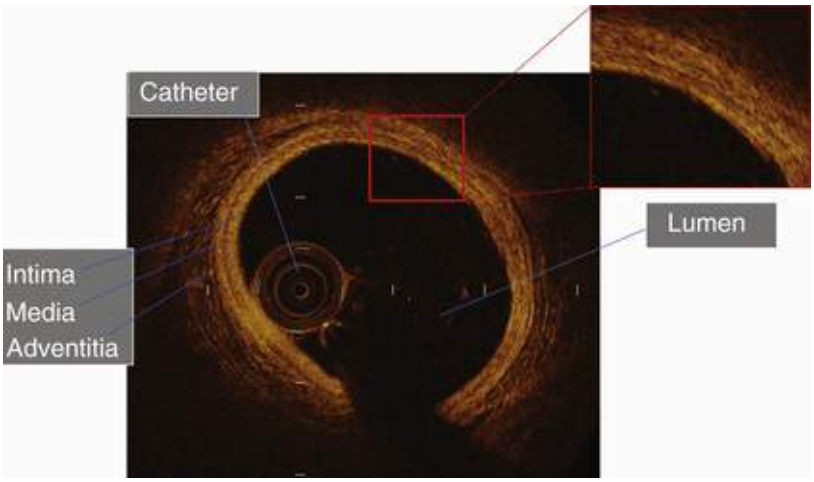

FIGURE 20.37 Optical coherence tomography (OCT) of a healthy vessel: The coronary artery wall is visualized as a layered structure. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

Stable Coronary Artery Disease

In patients with stable CAD, OCT imaging is used for quantitative assessment of the lesion by measuring the minimal lumen area (MLA). For the identification of hemodynamically severe coronary stenosis, OCT was shown to have only moderate diagnostic efficiency, when using the “gold standard” FFR as a reference, and similar accuracy compared to IVUS.[95]

Plaque Morphology

OCT provides the possibility to distinguish between fibrotic, lipid-rich, and calcified lesions (**Table 20.18**). High-risk features of plaques, including a thin fibrous cap, large lipid core, and increased macrophage infiltration, can be detected by OCT.[96]

TABLE 20.18

General Characteristics of Tissue Types by Optical Coherence Tomography (OCT)

TISSUE TYPE	BACKSCATTERING	ATTENUATION	GENERAL ASPECTS
Calcium	+	+	Sharp borders, low signal, with heterogeneous regions
Lipid	++	+++	Irregular borders, superficial high signal followed by very low signal
Fibrotic	++	+	Homogeneous bright tissue
Red thrombus	+++	+++	Superficial signal rich, low penetration, signal-free shadowing
White thrombus	+++	+	Signal rich, more penetration than for red thrombus
Media layer	+	+	Low signal region, limited by two signal-rich lines (IEL/EEL)
IEL/EEL	+++	+	High signal lines (20 μ)

IEL/EEL, Internal/external elastic lamina; +, low; ++, moderate; +++, high.

Modified from Bezerra HG, Costa MA, Guagliumi G, et al. Intracoronary optical coherence tomography: a comprehensive review clinical and research applications. JACC Cardiovasc Interv 2009;2:1035-46.

Acute Coronary Syndrome

In patients with ACS, OCT has not only high sensitivity to detect intraluminal thrombus, but also the capability of discriminating between red and white thrombus (**Fig. 20.38**). Furthermore, OCT has higher sensitivity in detecting fibrous cap rupture (**Fig. 20.39**) and fibrous cap erosion compared to IVUS.[97] The capability of OCT to discriminate the underlying mechanism of ACS has direct impact on further treatment strategy. In SCAD (**Fig. 20.40**), one of the non-CAD related causes that can be detected by OCT, unnecessary stent implantation can be avoided.

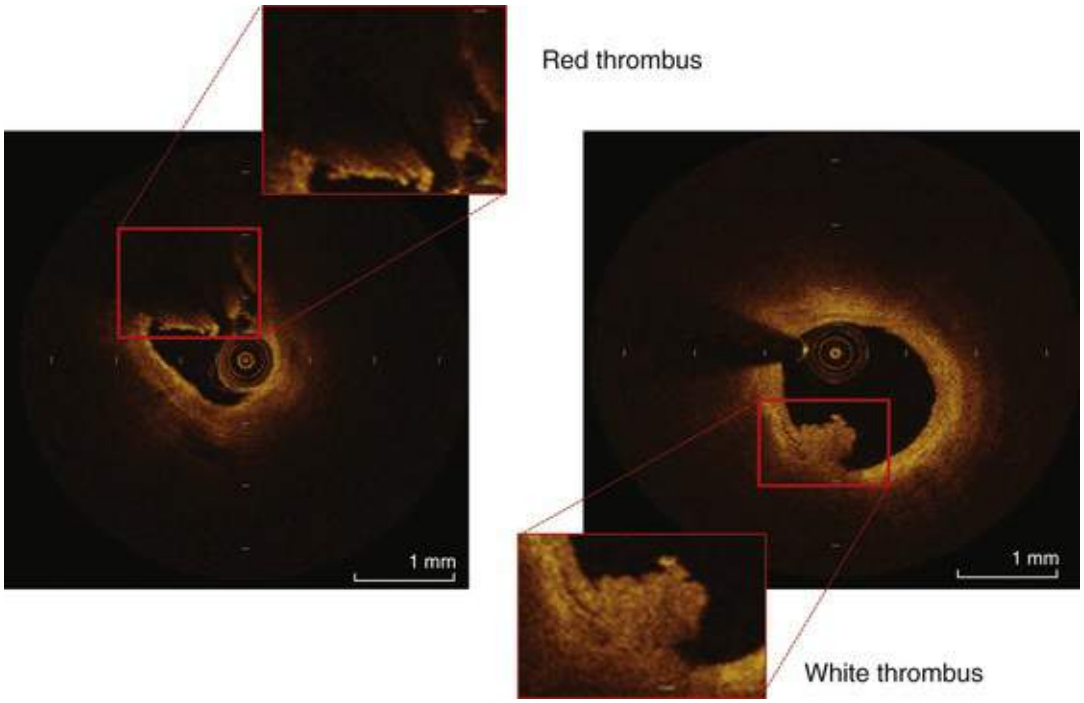

FIGURE 20.38 OCT is capable of discriminating between red **(left)** and white **(right)** thrombus. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

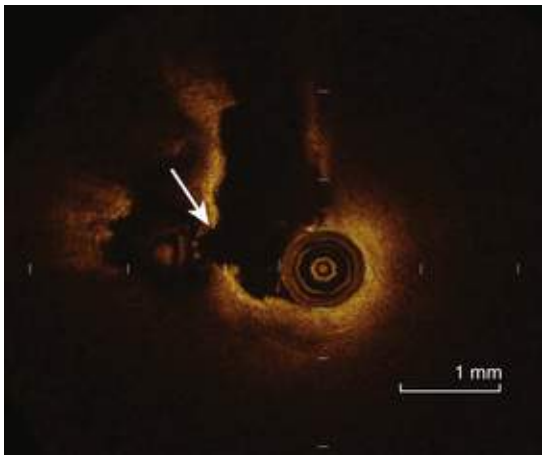

FIGURE 20.39 OCT of a ruptured fibrous cap. *Arrow* indicates the rupture site. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

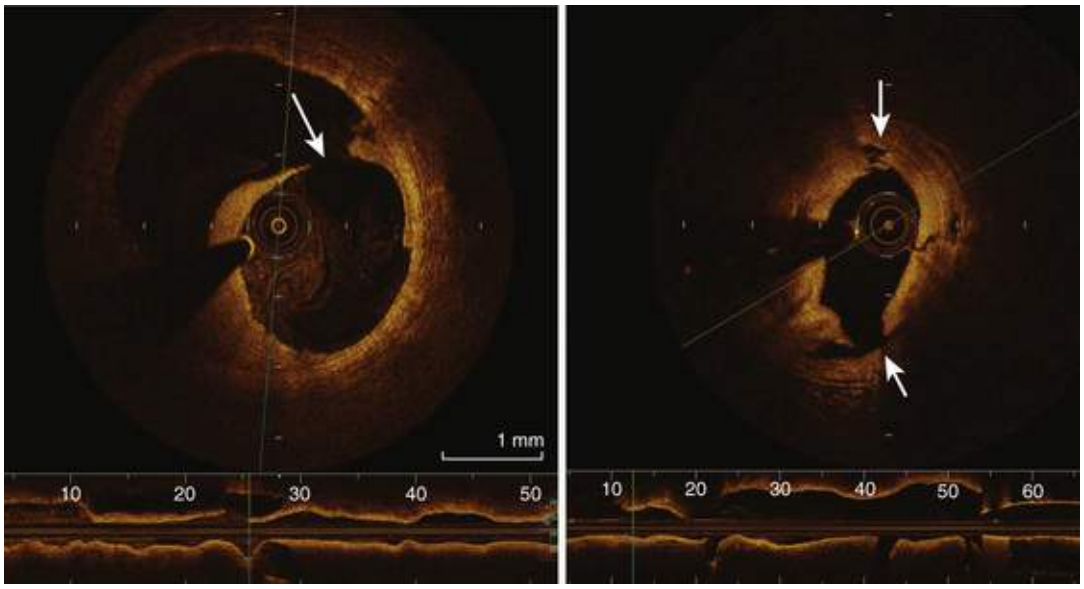

FIGURE 20.40 OCT of a dissected vessel. **Left,** Spontaneous coronary artery dissection (SCAD). **Right,** Dissection after balloon predilation. *Arrows* indicate the sites of rupture. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

Procedure Planning and Lesion Preparation

In procedural planning for PCI, OCT is a valuable tool for assessing the landing zone and especially for measuring calcium thickness. Concentric but thin calcium allows the use of regular or scoring balloons, whereas thicker concentric calcium may require atherectomy[98] (**Fig. 20.41**). OCT imaging can guide adequate lesion preparation, which is crucial for optimal stent deployment, but it can also be helpful for stent selection. Stent diameter, as well as length, can be chosen according to measurements of the reference vessel diameter both proximal and distal to the target lesion, as well as the lesion length. The fast-pullback acquisition of images makes FD-OCT less susceptible to artifacts resulting from heart motion, and therefore an optimal tool for accurate measurement of lesion length.

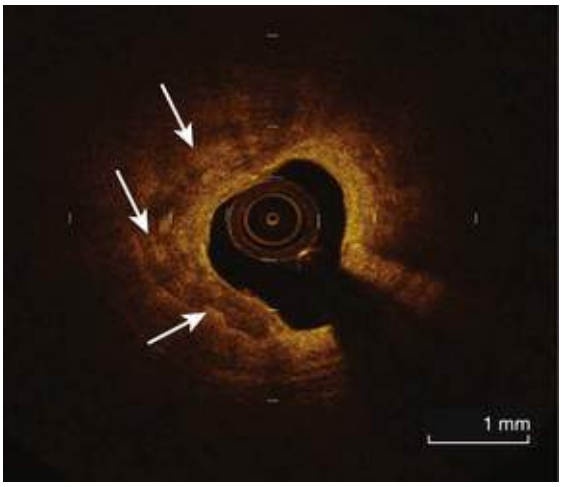

FIGURE 20.41 OCT of a severely calcified lesion. *Arrows* indicate some of the calcifications. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

Assessment After Percutaneous Coronary Intervention

Post-PCI OCT offers the possibility to detect postprocedural complications (**Fig. 20.40**) and to provide information on the potential need for further procedural steps. OCT is used for ensuring appropriate stent expansion and evaluating apposition of the stent with the vessel wall (**Fig. 20.42**). Stent underexpansion, associated with small minimal stent area measured by OCT, was shown to be an independent predictor of device-oriented clinical endpoints, including cardiac death, target vessel–related MI, target lesion revascularization, and stent thrombosis.[99] By allowing the determination of the distance of each stent strut from the vessel wall, OCT is capable of detecting the percentage of malapposed stent struts, which were shown to be associated with delayed neointimal coverage.[100] The presence of uncovered stent struts detected by OCT was proposed as an independent predictor of late stent thrombosis in drug-eluting stents.[101] In particular, for bioresorbable scaffolds, the rate of stent thrombosis seems to increase significantly in malapposition. Therefore, use of OCT is strongly recommended after deployment of such a stent. *Stent edge dissection* (SED) is another post-PCI complication that is detectable by OCT which has been shown to be associated with adverse clinical outcomes.[102] However, the vast majority of SEDs diagnosed by OCT heal without further treatment, and additional stenting should be reserved for the presence of intramural hematoma, as recently suggested.[98] Deployment of stent edges within the normal vessel wall and appropriate selection of stent diameter may help to avoid SED.[102] Compared to SED, tissue protrusion is a less investigated post-PCI complication. Irregular tissue protrusion was shown to be associated with device-related clinical endpoints, which were primarily driven by target lesion revascularization.[99] However, the further management of tissue protrusion detected by OCT is not yet clear.

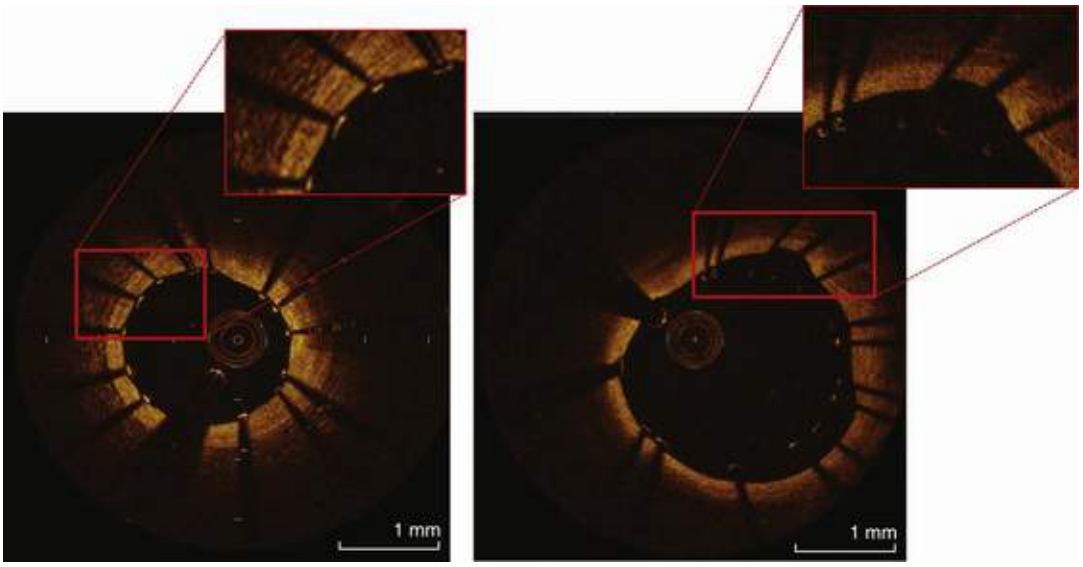

FIGURE 20.42 OCT is capable of evaluating apposition of a stent. **Left,** Good stent apposition. **Right,** Stent malapposition. (Courtesy Dr. Annapoorna Kini, Icahn School of Medicine at Mount Sinai, New York.)

Classic References

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PART IV
Heart Failure

OUTLINE

21

Approach to the Patient with Heart Failure

James L. Januzzi Jr, Douglas L. Mann

Definition and Epidemiology

Heart failure (HF) is a complex clinical syndrome resulting from structural and functional impairment of ventricular filling or ejection of blood. Although the clinical syndrome of HF may result from abnormalities or disorders involving all aspects of cardiac structure and function, most patients have impairment of myocardial function, ranging from normal ventricular size and function to marked dilation and reduced function. Symptoms of HF frequently depend on the presence of elevated left- or right-sided heart filling pressures, but the term “congestive heart failure” is no longer preferred, because many patients do not have overt congestion at evaluation, and their symptoms may be caused by other factors, such as reduced cardiac output.

The global incidence and prevalence rates of HF are approaching epidemic proportions, as evidenced by the relentless increase in the number of HF hospitalizations, the growing number of HF deaths, and the spiraling costs associated with the care of HF patients. The overall prevalence of HF is thought to be increasing, in part because current therapies for cardiac disorders (e.g., myocardial infarction, valvular heart disease, arrhythmias) are allowing patients to survive longer. Worldwide, HF affects almost 23 million people. In the United States the most recent epidemiologic data suggest that 5.7 million Americans have HF, and it is estimated that by 2030 the prevalence will increase 25% from current estimates.[1] Estimated prevalence of symptomatic HF in the general European population is similar to that in the United States and ranges from 0.4% to 2%.[2]

The prevalence of HF rises exponentially with age and affects 4% to 8% of people older than 65 (**Fig. 21.1A**). Although the relative incidence of HF is lower in women than men for all age groups, women constitute at least half the cases of HF because of their longer life expectancy, and the overall prevalence of HF is greater in women than men age 80 or older.[3] The U.S. National Institutes of Health (NIH)–funded Multi-Ethnic Study of Atherosclerosis (MESA) showed that blacks had the highest risk for development of HF, followed by Hispanic, white, and Chinese Americans[4] (**Fig. 21.1B**). In North America and Europe, lifetime risk of developing HF is approximately one in five for a 40-year-old. Risk factors for HF include ischemic heart disease, incident or prevalent myocardial infarction, myocarditis, valvular heart disease, tachycardia, diabetes mellitus, structural heart disease related to congenital heart disease, sleep apnea, excessive drug or alcohol use, and obesity. A significant percentage (30% to 40%) of nonischemic HF is thought to be caused by genetic factors (**see Chapter 7**). In addition, certain medications may increase the risk for HF, including nonsteroidal anti-inflammatory drugs (NSAIDs) and cancer chemotherapy.

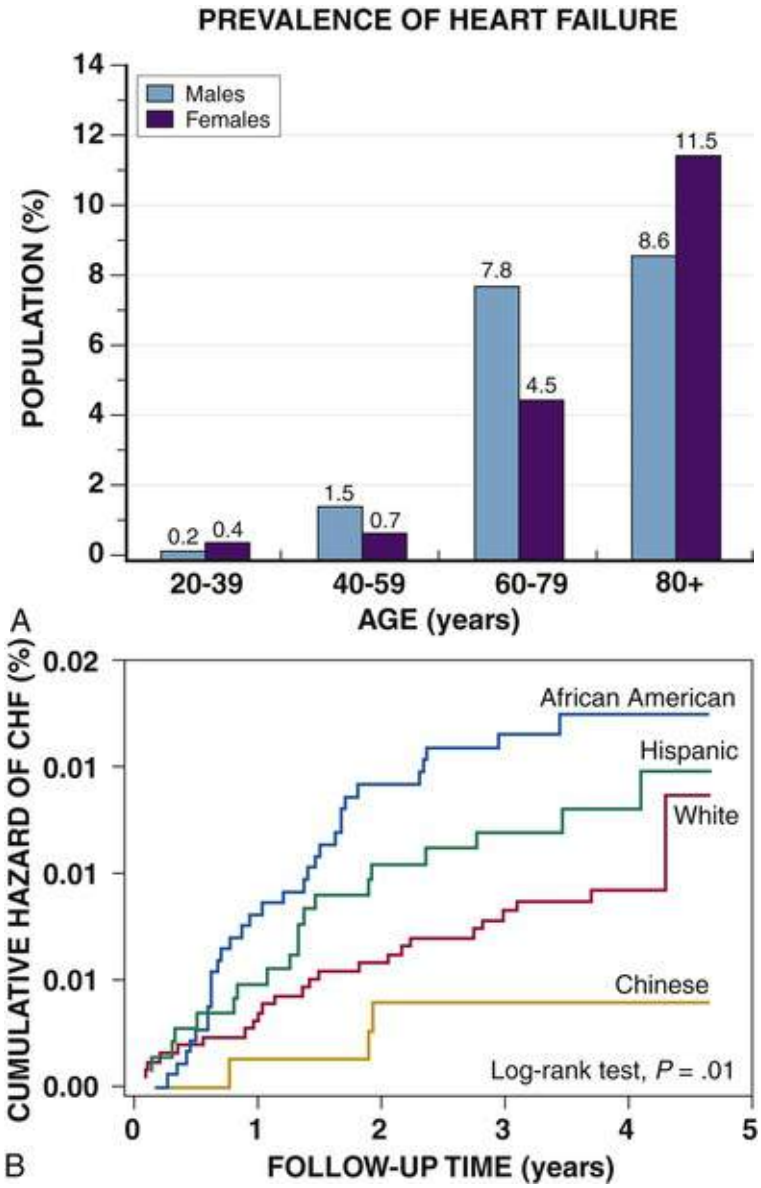


FIGURE 21.1 Prevalence and outcomes of heart failure (HF) in the United States. **A,** Prevalence of HF by sex and age (National Health and Nutrition Examination Survey: 2007–2010). **B,** Neslon-Aalen plots of cumulative hazard ratios for the development of congestive heart failure (CHF) by racial or ethnic group, in the Multi-Ethnic Study of Atherosclerosis (MESA) study. (**A,** Modified from Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation 2013;127:e6-245; **B,** From Bahrami H, Kronmal R, Bluemke DA, et al. Differences in the incidence of congestive heart failure by ethnicity: the Multi-Ethnic Study of Atherosclerosis. Arch Intern Med 2008;168:2138-45.)

The distribution of ejection fraction (EF) across unselected populations of HF patients is bimodal, with peaks centered around 35% and 55%.[3] Approximately half of patients have HF with preserved EF (HFpEF; **Chapter 26**), and the balance have HF with reduced EF[3] (HFrEF; **Chapter 25**). HFpEF is generally defined as a left ventricular EF of 50% or greater, whereas HFrEF is generally defined as an EF less than 40%. Treatment strategies for treating HF are based on these two categories, so these distinctions are critical. Recent interest has focused on those with HF and an EF between 40% and 50%[5]; these patients do not yet have consensus regarding their best management, because they are often excluded from clinical trials. The prevalence of HFpEF increases dramatically with age and is much more common in women than in men at any age.[4] The prevalence of HFpEF appears to be increasing, perhaps as a function of the aging population and increased recognition of HFpEF. These data further emphasize that HFpEF is an important cause of the HF syndrome.

Classification of Heart Failure

Patients with HF are classified according to symptomatology and the stage of the disease. The American College of Cardiology and American Heart Association (ACC/AHA) HF staging approach emphasizes the importance of development and progression of disease,[6] whereas the New York Heart Association (NYHA) functional classification focuses more on exercise tolerance in those with established HF (**Table 21.1**). Although considerably subjective, the NYHA functional classification is widely used. Use of both systems in conjunction provides a reasonable framework for clinician communication and patient prognostication. The NYHA classification is also used to determine eligibility for certain therapies (e.g., mineralocorticoid receptor antagonists, cardiac resynchronization).

TABLE 21.1

American College of Cardiology/American Heart Association (ACC/AHA) Stages of Heart Failure (HF) Compared to the New York Heart Association (NYHA) Functional Classification

ACC/AHA STAGES		NYHA FUNCTIONAL CLASSIFICATION	
A	At high risk for HF but without structural heart disease or symptoms of HF.	None	
B	Structural heart disease but without signs or symptoms of HF.	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF.	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
D	Refractory HF requiring specialized interventions.	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

When the diagnosis of HF is suspected, the goals of the clinical assessment is to determine whether HF is present, define the underlying etiology and the type of heart failure (HFrEF versus HFpEF), assess the severity of HF, and identify comorbidities that can influence the clinical course and response to treatment. Although the diagnosis of HF can be straightforward when the patient presents with a constellation of the classic signs and symptoms in the appropriate clinical setting (**Tables 21.2** and **21.3**), no sign or symptom alone can define the presence or severity of HF. Furthermore, detection of diagnostic physical findings of HF is imprecise, often requiring other diagnostic tools. Thus, as depicted in **Fig. 21.2**, the clinical assessment of HF most often depends on information that is gleaned from a variety of sources, including the history (both past and present), physical examination, laboratory tests, cardiac imaging, and functional studies.

TABLE 21.2

Using the Medical History to Assess the Heart Failure Patient

Symptoms Associated with HF Include:
Fatigue
Shortness of breath at rest or during exercise
Dyspnea
Tachypnea
Cough
Diminished exercise capacity
Orthopnea
Paroxysmal nocturnal dyspnea
Nocturia
Weight gain/weight loss
Edema (of extremities, scrotum, or elsewhere)
Increasing abdominal girth or bloating
Abdominal pain (particularly if confined to right upper quadrant)
Loss of appetite or early satiety
Cheyne-Stokes respirations (often reported by family rather than patient)
Somnolence or diminished mental acuity
Historical Information Helpful in Determining if Symptoms Are Caused by HF
A past history of HF
Cardiac disease (e.g., coronary artery disease, valvular or congenital disease, previous myocardial infarction)
Risk factors for heart failure (e.g., diabetes, hypertension, obesity)
Systemic illnesses that can involve the heart (e.g., amyloidosis, sarcoidosis, inherited neuromuscular diseases)
Recent viral illness or history of HIV infection or Chagas disease
Family history of HF or sudden cardiac death
Environmental and/or medical exposure to cardiotoxic substances
Substance abuse
Noncardiac illnesses that could affect the heart indirectly, including high-output states (e.g., anemia, hyperthyroidism, arteriovenous fistulas)

TABLE 21.3

Physical Findings of Heart Failure

Tachycardia
Extra beats or irregular rhythm
Narrow pulse pressure or thready pulse*
Pulses alternans*
Tachypnea
Cool and/or mottled extremities*
Elevated jugular venous pressure
Dullness and diminished breath sounds at one or both lung bases
Rales, rhonchi, and/or wheezes
Apical impulse displaced leftward and/or inferiorly
Sustained apical impulse
Parasternal lift
Third and/or fourth heart sound (either palpable and/or audible)
Tricuspid or mitral regurgitant murmur
Hepatomegaly (often accompanied by right upper quadrant discomfort)
Ascites
Presacral edema
Anasarca*
Pedal edema
Chronic venous stasis changes

*Indicative of more severe disease.

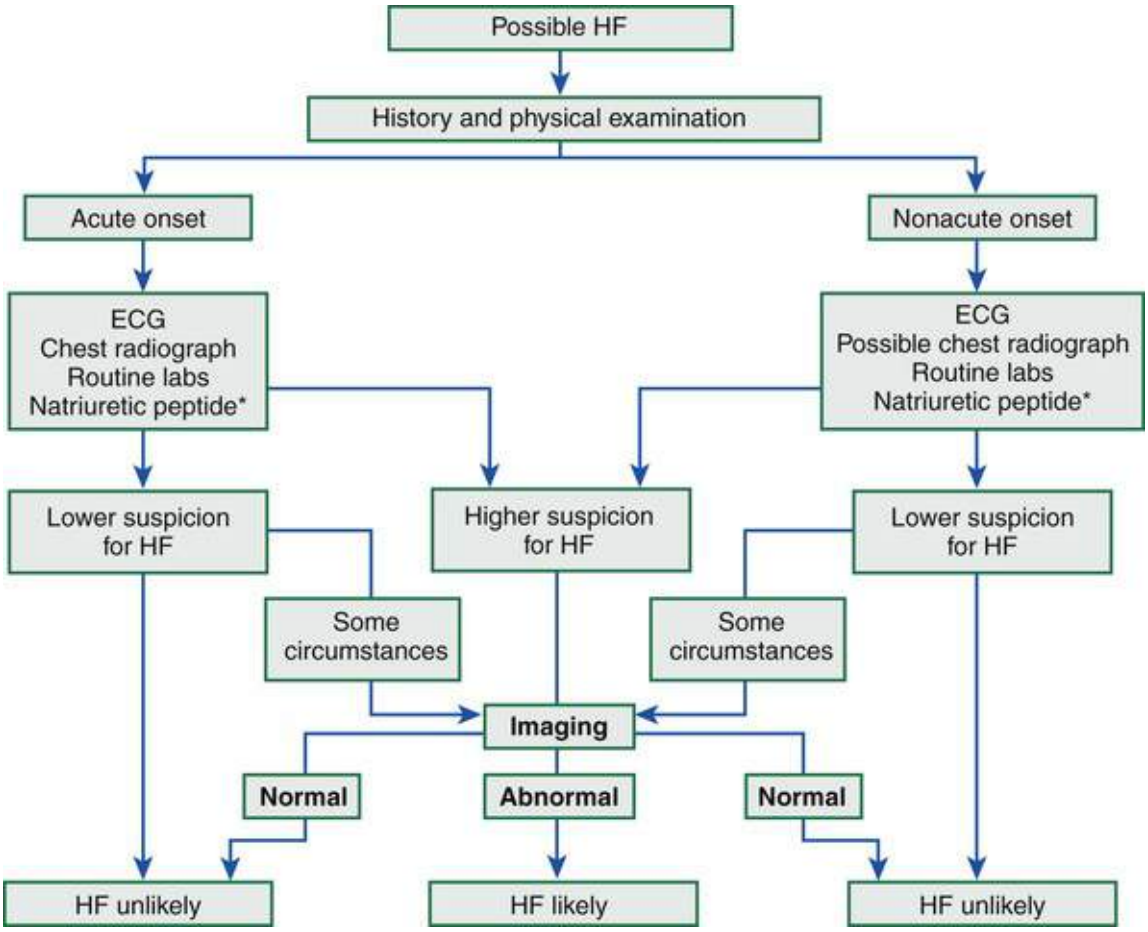


FIGURE 21.2 Flow chart for the evaluation of patients with HF. Appropriate cutoff values for natriuretic peptide testing (*asterisk*) to identify or exclude HF are provided in **ETable 21.1**. The diagnosis of HF is made using a combination of clinical judgment and initial and subsequent testing. Following thorough history and physical examination together with initial diagnostic testing, imaging (e.g., with echocardiography) may still be necessary in ambiguous cases to identify definitively or to exclude the diagnosis.

The Medical History and Physical Examination

A complete medical history and carefully focused physical examination are the foundation of the assessment in HF patients, providing important information regarding etiology of HF, identifying possible exacerbating factors, and lending pivotal data for proper management (**see Chapter 10**). The information obtained guides the further direction of the patient's evaluation and enables the clinician to make the most judicious use of additional tests. Further, the history helps to evaluate incongruent results that may emerge during the diagnostic process, and it can obviate the need for needless further testing.

Heart Failure Symptoms and Signs

Patients with HF may complain of a vast array of symptoms, the most common of which are listed in **Table 21.2**. None of these is entirely sensitive or specific for identifying the presence of severe congestion (**Table 21.4**), but some are more reliable than others for this indication. Importantly, none is specific to HFpEF versus HFrEF.

TABLE 21.4

Sensitivity and Specificity of History and Physical Examination (H&P) Components for Diagnosis of Elevated Filling Pressures in Patients with Heart Failure*

H&P FINDING	FREQUENCY	SENSITIVITY	SPECIFICITY	PREDICTIVE VALUE		LR		OR (95% CI)
				Positive	Negative	Positive	Negative	
Rales (≥1/3 lung fields)	26/192	15	89	69	38	1.32	1.04	1.4 (0.6, 3.4)
S3	123/192	62	32	61	33	0.92	0.85	0.8 (0.4, 1.5)
Ascites (moderate/massive)	31/192	21	92	81	40	2.44	1.15	2.8 (1.1, 7.3)
Edema (≥2+)	73/192	41	66	67	40	1.20	1.11	1.3 (0.7, 2.5)
Orthopnea (≥2 pillows)	157/192	86	25	66	51	1.15	1.80	2.1 (1, 4.4)
Hepatomegaly (>4 fingerbreadths)	23/191	15	93	78	39	2.13	1.09	2.3 (0.8, 6.6)
Hepatojugular reflux	147/186	83	27	65	49	1.13	1.54	1.7 (0.9, 3.5)
JVP ≥12 mm Hg	101/186	65	64	75	52	1.79	1.82	3.3 (1.8, 6.1)
JVP <8 mm Hg	18/186	4.3	81	28	33	0.23	0.85	0.2

*Values expressed as percentages unless otherwise indicated; *LR,* likelihood ratio; *OR,* odds ratio; *CI,* confidence interval.

Worsening *dyspnea* is a cardinal symptom of HF and is typically related to increases in cardiac filling pressures, but also may represent restricted cardiac output.[7] The absence of worsening dyspnea, however, does not necessarily exclude the diagnosis of HF, since patients may accommodate symptoms by substantially modifying their lifestyle. Probing more deeply into the current level of activity may uncover a decline in exercise capacity that is not immediately apparent. Dyspnea at rest is often mentioned by patients hospitalized with HF and has a high diagnostic sensitivity and significant prognostic ramifications in this population. However, it is also cited by patients with many other medical conditions, so that the specificity and positive predictive value (PPV) of dyspnea at rest alone are low. Patients may sleep with their heads elevated to relieve dyspnea while recumbent (orthopnea); additionally, dyspnea while lying on the left side (trepopnea) may occur. *Paroxysmal nocturnal dyspnea,* shortness of breath developing while recumbent, is one of the most highly reliable indicators of HF.

Cheyne-Stokes respiration (also referred to as periodic or cyclic respiration) is common in advanced HF and is usually associated with low cardiac output and sleep-disordered breathing (**see also Chapters 25 and 87**). The presence of Cheyne-Stokes respiration is generally indicative of an adverse prognosis.[8] Nocturnal cough is a frequently overlooked symptom of HF.

These symptoms all typically reflect pulmonary congestion, whereas a history of weight gain, increasing abdominal girth, early satiety, and the onset of edema in dependent organs (extremities or scrotum) indicate right-sided heart congestion. However, nonspecific, right upper quadrant pain caused by congestion of the liver is common in patients with significant right-sided HF and may be incorrectly attributed to other conditions.

Another cardinal symptom of HF is *fatigue,* generally held to be reflective of reduction in cardiac output as well as abnormal skeletal muscle metabolic responses to exercise.[9] Other causes of fatigue in HF may include major depression, anemia, renal dysfunction, endocrinologic abnormalities, and side effects to medications. Unintended weight loss, often leading to cachexia, may be prominent and is a major prognostic indicator.[10]

Other Historical Information

Information about a patient's past and current medical problems and a multigenerational family history as well as social history provides the background on which symptoms are interpreted and a management plan is designed. The presence of hypertension, coronary artery disease, and diabetes is particularly

helpful since these conditions account for approximately 90% of the population attributable risk for HF in the United States.[11]

The medical history should also focus on the drugs taken by the patient. Agents associated with incident HF include cancer chemotherapy,[12] diabetes drugs (e.g., thiazolidinediones), ergot-based antimigraine drugs, appetite suppressants, certain antidepressants and antipsychotic agents (notably including clozapine), decongestants such as pseudoephedrine (due to its ability to trigger severe hypertension), and anti-inflammatory agents such as the antimalarial hydroxychloroquine (infrequently associated with infiltrative cardiomyopathy) and NSAIDs. The NSAIDs are well-recognized to lead to HF through their ability to worsen renal function, trigger hypertension, and lead to fluid retention, particularly in elderly patients. Although selective and nonselective cyclooxygenase (COX) 2 inhibitors can provoke HF, the use of celecoxib has not been associated with increased risk of HF.

A history of use of herbal remedies and dietary supplements should be obtained. Environmental or toxic exposures, including alcohol or drug abuse, should be carefully sought. A multigenerational family history should be taken for prior HF or sudden cardiac death. Information about the presence of comorbidities (as described later) is essential in devising management plans. Although most etiologies of HF are cardiac, it is worth remembering that some systemic illnesses (e.g., anemia, hyperthyroidism) can cause this syndrome without direct cardiac involvement (**see Chapter 92**).

Physical Examination

The physical findings listed in **Table 21.2** complement information from the medical history in defining the presence and severity of HF. The signs of HF have been extensively described, and much as with the history of patients with heart failure, components of the physical examination have variable sensitivity and specificity for the diagnosis[13] (**see Table 21.4**), in part because of the subtlety of some physical findings, as well as variability in the physical diagnostic skills of the examiner. No physical finding in HF is absolutely pathognomonic for HFpEF versus HFrEF.[13]

An evaluation for the presence and severity of HF should include consideration of the patient's general appearance, measurement of vital signs in the seated and standing position, examination of the heart and pulses, and assessment of other organs for evidence of congestion, hypoperfusion, or indications of comorbid conditions. The patient's general appearance conveys vital information. The examiner should assess the patient's body habitus and state of alertness, as well as whether the patient is comfortable, short of breath, coughing, or in pain. The skin examination may show pallor or cyanosis resulting from underperfusion, stigmata of alcohol abuse (e.g., spider angiomata, palmar erythema), erythema nodosum from sarcoidosis, bronzing from hemachromatosis, or easy bruising from amyloidosis. Additional findings supporting amyloidosis include deltoid muscle infiltration (leading to the “shoulder pad sign”), tongue hypertrophy, and bilateral thenar wasting from carpal tunnel syndrome. The details of inspection and palpation of the heart are discussed in **Chapter 10**. By observing or palpating the apical impulse, the examiner can rapidly determine heart size and quality of the point of maximal impulse. In cases of severe HF, a palpable impulse corresponding to a third heart sound may be present. Cardiac auscultation is a crucial part of HF evaluation.

A characteristic holosystolic murmur of mitral regurgitation is heard in many HF patients. Tricuspid regurgitation, which is also common, can be differentiated from mitral regurgitation by the location of the

murmur at the left sternal border, an increased intensity of the murmur during inspiration, and the presence of prominent “V” waves in the jugular venous waveform. Both mitral and tricuspid regurgitation murmurs may become softer as volume overload is treated, and a reduction in ventricular size (with corresponding reduction in annular diameter) improves valve coaptation and competency. Aortic stenosis is an important cause of HF because its presence greatly alters management. The presentation of aortic stenosis may be subtle, however, since the intensity of the murmur depends on blood flow across the valve, which may be reduced as HF develops. The presence of a third heart sound is a crucially important finding and suggests increased ventricular filling volume; while difficult to identify, a third heart sound is highly specific for heart failure and carries a substantial prognostic meaning. A fourth heart sound usually indicates reduced ventricular compliance. In advanced HF the third and fourth heart sounds may be superimposed, resulting in a summation gallop.

A key objective of the examination in HF patients is to detect and quantify the presence of volume retention, with or without pulmonary and systemic congestion. As with symptoms, evidence of congestion does not always indicate with certainty that HF is present, and the absence of manifest congestion does not definitively exclude the diagnosis. Patients with HFpEF and HFrEF do not generally show significant differences in frequency or significance of the stigmata of volume overload.[14]

The most definitive method for assessing a patient's volume status by physical examination is by the measurement of jugular venous pressure (JVP). An elevated JVP has good sensitivity (70%) and specificity (79%) for elevated left-sided filling pressure[13] (**see Table 21.4**). The sensitivity and specificity of the JVP in detecting congestion can be considerably improved by exerting pressure on the right upper quadrant of the abdomen while assessing venous pulsations in the neck (hepatojugular reflux). Changes in JVP with therapy usually parallel changes in left-sided filling pressure. Limitations of JVP assessment include difficulties in its evaluation because of body habitus as well as significant interobserver variability in its estimation. Increase in the JVP may lag behind left-sided heart filling pressures, or it may not rise at all if pulmonary artery pressure is increased to the extent that right ventricular failure or tricuspid regurgitation occur. Conversely, the JVP may be elevated without an increase in left ventricular filling pressures in patients with pulmonary arterial hypertension, in those with isolated right ventricular pressure, or when isolated severe tricuspid regurgitation is present.

Although pulmonary congestion is exceedingly common in HF, physical findings indicating its presence are variable, and many are nonspecific. Dullness to percussion and diminished breath sounds at one or both lung bases suggest the presence of a pleural effusion. Bilateral pleural effusions are most common, but when an effusion is present unilaterally, it is usually right sided, with only approximately 10% occurring exclusively on the left side. Leakage of fluid from pulmonary capillaries into the alveoli can be manifest as rales or rhonchi, and wheezing may result from reactive bronchoconstriction. Pulmonary rales caused by HF are usually fine in nature and extend from the base upward, whereas those from other causes (e.g., pulmonary fibrosis) tend to be coarser. Importantly, rales or rhonchi may be absent in congested patients with advanced HF; this may reflect compensatory increases in local lymphatic drainage. “Cardiac asthma” is caused by the physical presence of fluid in the bronchial wall as well as secondary bronchospasm.[15] It can result in an incorrect diagnosis of “obstructive airways disease exacerbation,” with consequent mistriage and incorrect therapy with bronchodilators; such mismanagement may be associated with increased risk for mortality.[16]

Lower extremity edema is a common finding in volume-overloaded HF patients but may be the result of venous insufficiency (particularly after saphenous veins have been harvested for coronary artery bypass grafts) or as a side effect of medications (e.g., calcium channel blockers). Careful inspection of the JVP

helps improve the specificity of pedal edema for HF.

Detecting reduced cardiac output and systemic hypoperfusion are key components of the examination. Patients with poor systemic perfusion usually have low systolic and narrow pulse pressures as well as weak and thready pulses, but this relationship is not exact. Many patients with systolic blood pressure in the range of 80 mm Hg (or even lower) may have adequate perfusion, whereas others with reduced cardiac output may maintain blood pressure in the normal range at the expense of tissue perfusion by greatly increasing systemic vascular resistance. Findings suggesting reduced cardiac output include poor mentation, reduced urine output, mottled skin, and cool extremities. Of these, cool extremities are the most broadly useful.

Assessment for systemic congestion taken together with evaluation for reduced cardiac output may be useful to categorize patients into "dry/warm" (uncongested with normal perfusion), "wet/warm" (congested with normal perfusion, the most common combination found in decompensated heart failure), "dry/cold" (uncongested but hypoperfused), and "wet/cold" (cardiogenic shock),[17] as discussed in **Chapter 24**. These categories not only are prognostic, but also inform treatment decision making (**Fig. 21.3**).

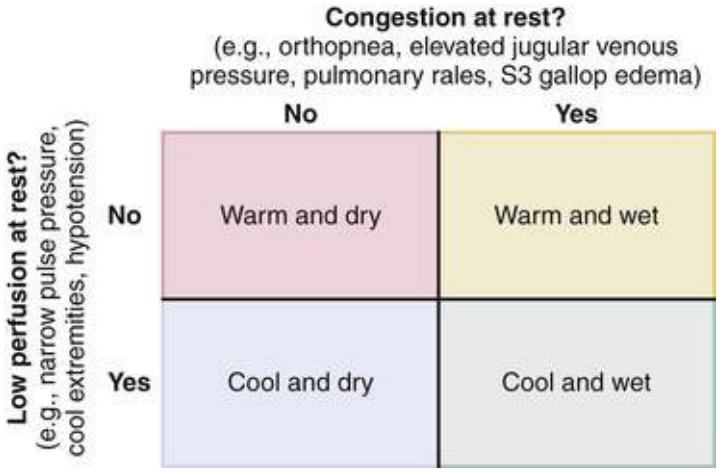


FIGURE 21.3 Schema for categorizing patients with HF on the basis of perfusion (warm versus cold) and presence of congestion (dry versus wet). The four categories of HF identified in this schema have different treatment strategies. (Based on data from Nohria A, Tsang SW, Fang JC, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol 2003;41:1797.)

Routine Laboratory Assessment

A suggested algorithm for the diagnostic evaluation of HF is presented in **Fig. 21.2**. The laboratory testing and imaging modalities described here provide important information for the diagnosis and management of patients with suspected or proven HF.

Chest Radiography

Despite advances in other imaging technologies, the chest x-ray film remains a useful component of the assessment, particularly when the clinical presentation is ambiguous. Results of chest radiography are additive to clinical variables from history and physical examination and similarly complement the results of biomarker testing. Accordingly, chest radiography should be a routine part of the early evaluation of

patients presenting with symptoms suggestive of acutely decompensated HF (**see Chapter 15**).

The classic chest x-ray pattern in patients with pulmonary edema is a “butterfly” pattern of interstitial and alveolar opacities bilaterally fanning out to the periphery of the lungs. Many patients, however, present with subtler findings, in which increased interstitial markings, including *Kerley B lines* (thin horizontal linear opacities extending to the pleural surface caused by accumulation of fluid in the interstitial space), peribronchial cuffing, and evidence of prominent upper lobe vasculature (indicating pulmonary venous hypertension) are the most prominent findings. Pleural effusions and fluid in the right minor fissure may also be seen. In many cases, particularly in patients with advanced heart failure, the chest radiograph may be entirely clear, despite significant symptoms of dyspnea; the negative predictive value (NPV) of chest radiography is too low to definitively exclude HF.[18]

Electrocardiography

The electrocardiogram (ECG) is a standard part of the initial evaluation of a patient with suspected HF. It may provide important clues regarding incident heart failure while assisting in understanding when previously diagnosed patients experience an episode of decompensation. In HF patients the ECG is infrequently normal, but it may only show nonspecific findings; thus, similar to the chest radiograph, the PPV of the ECG greatly surpasses the NPV in this setting (**see Chapter 12**).

Sinus tachycardia caused by sympathetic nervous system activation is seen with advanced HF or during episodes of acute decompensation. In addition to increasing the likelihood for the diagnosis, an elevated heart rate is also a prognostic finding in HF. The presence of atrial arrhythmia on the ECG as well as the ventricular response may provide clues as to the cause of HF, as well as explain why a patient may have developed decompensated symptoms; identifying atrial arrhythmia with a rapid ventricular response also provides a target for therapeutic interventions. Increased ventricular ectopy identifies a patient at risk for sudden death, particularly when the EF is very low (e.g., <30%).

The presence of increased QRS voltage may suggest left ventricular hypertrophy. In the absence of a prior history of hypertension, such a finding might be caused by valvular heart disease or by hypertrophic cardiomyopathy, particularly if bizarre repolarization patterns are noted. If right ventricular hypertrophy is present, primary or secondary pulmonary hypertension should be considered. Low QRS voltage suggests the presence of an infiltrative disease or pericardial effusion. The presence of Q waves suggests that HF may be caused by ischemic heart disease, and new or reversible ST changes identify the presence of acute coronary ischemia, even when chest pain is absent. Indeed, since acute coronary ischemia is a leading cause of acutely decompensated HF, a 12-lead ECG should be immediately obtained in this patient, to exclude acute myocardial infarction (AMI).

The intervals on the ECG may provide important information on causes of HF as well as for treatment strategy. Prolongation of the PR interval is common in patients in this setting and may result from intrinsic conduction disease, but it may also be seen in patients with infiltrative cardiomyopathy such as amyloidosis. With the advent of cardiac resynchronization therapy (CRT; **see Chapter 27**), evaluation of the QRS complex has become a critical part of the clinical assessment, providing important information on the cause of HF and regarding the therapeutic approach. The QT interval is often prolonged in patients

with HF and may be caused by electrolyte abnormalities, myocardial disease, and effects of common drugs, such as antiarrhythmics. A lengthened QT interval may identify patients at risk for torsades de pointes and is thus an important variable to consider when using therapeutic agents with effects on ventricular repolarization.

Measurement of Blood Chemistry and Hematologic Variables

Patients with new-onset HF and those with acute decompensation of chronic HF should have a panel of electrolytes, blood urea nitrogen (BUN), serum creatinine, hepatic enzymes, fasting lipid profile, thyroid-stimulating hormone, transferrin saturation, uric acid, complete blood count, and urinalysis. As discussed later, the natriuretic peptides may be exceedingly useful for diagnosis as well as for prognostication. A test for HIV or further screening for hemachromatosis is reasonable in select patients, and diagnostic tests for rheumatologic diseases, amyloidosis, or pheochromocytoma are reasonable when suspicion exists for these diseases.

Abnormalities of sodium are common in HF patients, particularly during periods of acute decompensation, and have substantial prognostic meaning. Studies have shown that hyponatremia (defined as serum sodium values <135 mmol/L) may be found in up to 25% of patients with acute HF, and hyponatremia may also be seen in patients with indolently worsening HF without obvious decompensation.[19] Low sodium concentrations in HF may result from worsening volume retention or may be related to the use of diuretics, including thiazides. Hyponatremia is associated with impaired cognitive and neuromuscular function, and when present and persistent, low sodium is strongly prognostic for longer hospital stay, as well as a high risk for mortality.[20] Despite this fact, strategies to correct serum sodium levels have not been shown clearly to improve the clinical course[21] (**see Chapter 24**). Hypernatremia, although uncommon, is also prognostic for mortality in patients with HF. Hypokalemia occurs frequently in HF patients who are treated with diuretics. In addition to increasing the risk of cardiac arrhythmias, low potassium may also lead to leg cramps and muscle weakness. Conversely, hyperkalemia is less common but is most often caused by effects of medications such as angiotensin-converting enzyme (ACE) inhibitors or mineralocorticoid inhibition.

Abnormalities of renal function are common in HF patients and result from renal congestion, inadequate cardiac output, or comorbid conditions.[22] In addition, HF therapies such as diuretics and ACE inhibitors or angiotensin receptor blockers can increase BUN and creatinine. In this regard, abnormalities of renal function may have substantial effects on the ability to treat HF patients aggressively. Furthermore, abnormal renal function represents one of the more powerful prognostic variables gleaned from routine laboratory testing in HF patients. For these reasons, assessment of renal function should be performed as part of the initial evaluation of HF, then periodically repeated during follow-up.

In patients hospitalized with acutely decompensated HF, registry data suggest that 60% to 70% have a reduced estimated glomerular filtration rate.[23] In such patients the initial BUN and serum creatinine concentrations are independently predictive of death.[24] After admission, approximately 30% of patients with acute HF may also develop an increase in serum creatinine by 0.3 mg/dL or greater, which is similarly prognostic for mortality.[22,23] The causes of this “cardiorenal” syndrome are complex but include the severity of right-sided heart congestion, increased intra-abdominal pressure, and renal hypoperfusion

from inadequate cardiac output. On the other hand, worsening renal function may also occur from aggressive decongestion strategies; such a decline in renal function has been linked to improved (rather than worse) prognosis because it presumably indicates a more thorough treatment for congestion, the trigger for acute HF hospitalization.[25] Accordingly, when faced with worsening renal function, the clinician must perform a careful examination to assess volume status and tissue perfusion and decide on appropriate therapies to manage the situation. Lastly, improvement in renal function may follow therapies that reduce the severity of congestion; such a finding is still associated with poor long-term prognosis.

Diabetes mellitus is common in HF patients, and hyperglycemia has emerged as a possible risk factor for adverse outcome in affected patients. Since diuretics can cause gout, measuring uric acid levels can help in patient management; elevated serum uric acid levels have been noted to be prognostic, and therapies to lower their concentration are now being studied to improve HF outcomes. Abnormalities in aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), bilirubin, or lactate dehydrogenase (LDH) may occur in HF patients because of either hemodynamic derangements leading to hepatic congestion or medications, and it is important to follow levels periodically. An unexpected increase in prothrombin time (PT) in patients receiving warfarin therapy may be an early harbinger of decompensation since it may reflect impaired synthetic capacity of a congested liver. Albumin levels are an indication of the patient's nutritional status and may be depressed because of poor appetite or impaired absorption across an engorged bowel wall; hypoalbuminemia is prognostic for mortality in acute and chronic HF.

Hematologic abnormalities are exceedingly common in HF, affecting almost 40% of affected patients. Low hemoglobin levels have been associated with more severe HF symptoms, reduced exercise capacity and quality of life, and increased mortality.[26] Although anemia may be a consequence of chronic disease in HF patients, a low hemoglobin level should trigger an evaluation to detect treatable causes, particularly iron deficiency. Increasing attention has also been given to the red blood cell distribution width as a prognostic variable in both acutely decompensated and chronic HF.[27] The white blood cell count with differential is helpful in detecting the presence of an infection responsible for destabilizing a previously well-compensated patient and could provide a clue that HF has an uncommon cause, such as eosinophilic infiltration of the myocardium.

Biomarkers

Beyond standard laboratory testing, the measurement of newer biomarkers has emerged over the past decade as an important adjunct to the initial and subsequent evaluation of patients with suspected or proven HF. Biomarkers are now routinely used to distinguish HF from other conditions, establish severity of the diagnosis, and provide useful prognostic information in HF patients. There is also considerable interest in determining the ability of biomarkers to guide therapy, in both acute and chronic settings. As shown in **Table 21.5**, Braunwald[28] has proposed that HF biomarkers be divided into six distinct categories, with an additional category reserved for biomarkers not yet classified.

TABLE 21.5

Biomarkers Used in Assessing Patients with Heart Failure

Inflammation[*†‡]
C-reactive protein
Tumor necrosis factor
Fas (APO-1)
Interleukins 1, 6, and 18
Oxidative Stress[*†§]
Oxidized low-density lipoproteins
Myeloperoxidase
Urinary biopyrrins
Urinary and plasma isoprostanes
Plasma malondialdehyde
Extracellular Matrix Remodeling[*§]
Matrix metalloproteinases
Tissue inhibitors of metalloproteinases
Collagen propeptides
Propeptide procollagen type I
Plasma procollagen type III
Neurohormones[*†§]
Norepinephrine
Renin
Angiotensin II
Aldosterone
Arginine vasopressin
Endothelin
Myocyte Injury[*†§]
Cardiac-specific troponins I and T
Myosin light-chain kinase I
Heart-type fatty acid protein
Creatine kinase MB fraction
Myocyte Stress[†‡§¶]
B-type and N-terminal pro–B-type natriuretic peptide
Midregional proadrenomedullin
ST2
New Biomarkers[†]
Chromogranin
Galectin 3
Osteoprotegerin
Adiponectin
Growth differentiation factor-15

[*]Biomarkers in this category aid in elucidating the pathogenesis of HF.

[†]Biomarkers in this category provide prognostic information and enhance risk stratification.

[‡]Biomarkers in this category can be used to identify patients at risk for HF.

[§]Biomarkers in this category are potential targets of therapy.

[¶]Biomarkers in this category are useful in the diagnosis of HF and in monitoring therapy.

As articulated,[29] clinically useful biomarkers of HF should be easily measured with high analytic precision, should reflect important processes involved in HF presence and progression, should not recapitulate clinical information already available at the bedside, and must provide clinically useful information for caregivers to establish or reject a diagnosis more swiftly and reliably, to estimate prognosis more accurately, or to inform more successful therapeutic strategies. Only the natriuretic peptides have met these requirements, although other promising biomarkers exist for use in HF assessment.

Natriuretic Peptides

The natriuretic peptides are useful biomarkers for HF diagnosis, estimation of HF severity and prognosis, and possibly for management of HF as well. The most frequently measured natriuretic peptides are B-type natriuretic peptide (BNP) and its amino-terminal (N-terminal) cleavage propeptide equivalent, NT-proBNP. These two biomarkers are released from cardiomyocytes in response to stretch, and highly

precise assays exist for their detection in blood (**see Chapter 23**). Given the preponderance of myocardium in the ventricles, BNP and NT-proBNP are held to reflect ventricular stretch and synthesized in response to wall stress. Atrial natriuretic peptide (ANP) is another member of this class and is synthesized and secreted from atrial tissue. A midregional (MR) pro-ANP assay is now available and appears to deliver comparable results to BNP and NT-proBNP in HF,[30] although data remain limited.

Because of the differences in their clearance, BNP and NT-proBNP have considerably different half-lives (BNP: 20 minutes; NT-proBNP: 90 minutes), and thus they circulate with very different concentrations. Both natriuretic peptides have become an important part of the HF assessment; however, as with any diagnostic test, clinicians must always remember the broad array of structural and functional reasons for BNP or NT-proBNP release to interpret these values correctly.[31] Natriuretic peptide levels tend to increase progressively with worsening NYHA functional class and tend to be higher in HFrEF than HFpEF, despite independent contributions of diastolic function to their concentrations. Patients with acute HF more often have higher values for BNP and NT-proBNP than stable patients with chronic HF, although this is not a universal finding. Knowledge of an individual's natriuretic peptide value when stable may be useful to better interpret a change in symptoms when it occurs.

When using BNP or NT-proBNP, the clinician should remember that beyond left ventricular systolic and diastolic dysfunction, concentrations of both peptides are higher in patients with valvular heart disease, pulmonary hypertension, ischemic heart disease, atrial arrhythmias, and even pericardial processes such as constriction.[31] Additionally, numerous relevant medical covariates with effects on natriuretic peptide values must also be kept in mind. For example, both BNP and NT-proBNP concentrations increase with age, thought to identify accumulating structural heart disease in older patients. Both natriuretic peptides are higher in patients with renal failure, partially reflective of slower clearance, but also similarly identifying heart disease in these patients with prevalent cardiovascular risk factors. Elevated natriuretic peptide values can also be seen in hyperdynamic states, including sepsis. Patients who have right ventricular dysfunction as a result of pulmonary embolus may have elevated natriuretic peptide concentrations. It is also important to recognize that angiotensin receptor neprilysin inhibitors (ARNIs; **see Chapter 25**) will lead to elevated levels of BNP but will not affect the circulating levels of NT-proBNP. Obesity is strongly linked to lower-than-expected BNP or NT-proBNP values, despite comparable or higher wall stress in heavier patients. Given the common effect on BNP, NT-proBNP, and MR-proANP, this is not likely to be a clearance effect (because each is cleared differently), but rather more likely to represent suppression of natriuretic peptide gene expression or post-translational modification.

Results of BNP or NT-proBNP, although useful, should always be interpreted in the context of sound clinical judgment and integrated with results of history, physical examination, and other testing. These important biomarkers strongly supplement clinical judgment but should not replace it. Keeping this in mind, the natriuretic peptides have been shown to be quite useful to identify and exclude acutely decompensated HF in the emergency department, as well as more indolent HF in the outpatient setting. Suggested cutoff values for use of natriuretic peptides are shown in **ETable 21.1**.[32]

ETABLE 21.1

Suggested Cutoff Values for Clinical Applications of Natriuretic Peptides

PEPTIDE	CUTOFF VALUE	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)
To Exclude Acutely Decompensated Heart Failure					
BNP	<30-50 pg/mL	97	*	*	96
NT-proBNP	<300 pg/mL	99	*	*	99
MR-proANP	<57 pmol/L	98	*	*	97
To Identify Acutely Decompensated Heart Failure					
Single Cut-Point Strategy					
BNP	≥100 pg/mL	90	76	79	89
NT-proBNP	≥900 pg/mL	90	85	76	94
MR-proANP	≥127 pmol/mL	87	79	67	93
Multiple Cut-Point Strategy					
BNP, "gray zone" approach	< 100 pg/mL to exclude	90	73	75	90
	100-400 pg/mL, "gray zone"	*	*	*	8
	>400 pg/mL, to rule in	63	91	86	74
NT-proBNP, "age-stratified" approach	≥450 pg/mL for age <50 yr	90	84	88	66
	≥900 pg/mL for age 50-75 yr				
	≥1800 pg/mL for age >75 yr				
MR-proANP, "age-stratified" approach	≥104 pmol/L for age <65 yr	82	86	75	91
	≥214 pmol/L for age ≥65 yr				
Outpatient Application					
BNP	<20 pg/mL (asymptomatic) or <40 pg/mL (symptomatic)	*	*	*	96
NT-proBNP, "age stratified" approaches	<125 pg/mL for age <75 yr	*	*	*	98
	<450 pg/mL for age ≥75 yr *or*	*	*	*	91
	<50 pg/mL for age <50 yr	*	*	*	98
	<75 pg/mL for age 50-75 yr	*	*	*	98
	<250 pg/mL for age >75 yr	*	*	*	93
MR-proANP	Unknown	Unknown	Unknown	Unknown	

*Not applicable.

PPV, Positive predictive value; *NPV,* negative predictive value.

Pivotal data for BNP and NT-proBNP testing to diagnose acute HF came from the Breathing Not Properly study and the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study, respectively. In the Breathing Not Properly, a BNP concentration of 100 pg/mL was highly accurate for the diagnosis of acutely decompensated HF; in PRIDE an NT-proBNP cutoff value of 900 pg/mL provided comparable performance to a BNP of 100 pg/mL. Subsequently, the International Collaborative of NT-proBNP (ICON) investigators subsequently showed that age stratification improved PPV of NT-proBNP in acutely dyspneic patients. An NT-proBNP concentration less than 300 pg/mL was also useful to exclude acutely decompensated HF.[31]

Knowledge of natriuretic peptide levels in the emergency department (ED) is associated with more rapid diagnosis, lower admission rate, shorter length of hospital stay and reduced cost. As clinical uncertainty in acute dyspnea is associated with worse prognosis, it is reassuring to note that natriuretic peptide testing is particularly useful in this complex situation.

For patients with less acute presentations of dyspnea in settings other than the ED, values of BNP or NT-proBNP are most often considerably lower. When used for evaluation of the dyspneic ambulatory patient, therefore, the optimized cutoff values from ED studies should not be used; lower values are mandatory and optimized for their NPV to exclude (rather than identify) HF[32] (**ETable 21.1**). Age stratification again improves diagnostic accuracy in this setting, because older patients are expected to have generally higher concentrations of BNP or NT-proBNP in the absence of clinical HF. If a patient is found to have values higher than such cutoffs, further diagnostic testing (e.g. echocardiography) is likely

needed. Causes of falsely low BNP or NT-proBNP in the outpatient setting are comparable to those found with acute dyspnea.

Natriuretic peptide levels provide useful prognostic information across all ACC/AHA stages of HF, even when adjusted for important variables from history, physical examination, echocardiography, or even cardiopulmonary exercise testing. One natriuretic peptide measurement is prognostically meaningful, but serial follow-up measurements add incrementally important prognostic information. For example, in patients with acute HF, those who do not show a robust reduction in BNP or NT-proBNP by the time of hospital discharge tend to have considerably higher rates of morbidity and mortality.[33] It has thus been suggested that a BNP or NT-proBNP decrease of 30% or more by hospital discharge is desirable. Similarly, in ambulatory HF patients, chronically elevated or rising natriuretic peptide values identify a particularly high-risk population. HF therapies may lower BNP and NT-proBNP concentrations, and when this finding occurs, prognosis is improved.

Other Biomarkers

Other promising biomarkers for use in patients with HF have been identified, and some are clinically available (see **Table 21.5**). In general, newer biomarkers for HF have been developed to supplement the natriuretic peptides for prognostication. Although most have not yet achieved the prerequisite data to justify their widespread use, a few promising biomarkers bear mention.

Soluble concentrations of *ST2*, a member of the interleukin receptor family, have been shown to be strongly linked to progressive HF and death in patients across the four ACC/AHA stages of HF.[34] Originally identified in a basic science model of mechanotransduction, ST2 plays a pivotal role in the formation of fibrosis in the heart; elevated concentrations of ST2 are thus associated with progressive cardiovascular dysfunction, remodeling, and risk of death. Soluble ST2 concentrations are additive to natriuretic peptides for prognostication, are useful in both HFrEF and HFpEF, and are similarly dynamic to natriuretic peptides in their changes after HF therapies. In patients with both acutely decompensated and chronic heart failure, a chronically elevated or rising ST2 value strongly predicts adverse outcome. Notably, among apparently normal patients in a population-based analysis, ST2 values predicted future HF, beyond other biomarkers such as BNP as well as echocardiographic parameters.[35] This implies that the biochemical changes of ventricular remodeling may be detectable well before conventional biomarkers or imaging are abnormal. Recent data suggest ST2 concentrations also indicate vascular remodeling and may therefore predict future arterial hypertension. Whether this mediates risk for future HF is uncertain.

Galectin 3 is another novel biomarker of tissue fibrosis. It is produced by activated macrophages involved in response to tissue injury and is strongly associated with increased myocardial collagen formation. When measured clinically, elevated galectin 3 values not only predict adverse outcomes in HF patients with both HFrEF and HFpEF, but also predict onset of HF in apparently normal patients, similar to ST2.[34]

The myofibrillar proteins *troponin T and I* are indicators of cardiomyocyte injury and may be elevated in HF patients in the absence of an acute coronary syndrome or even significant coronary artery disease (CAD). With the emergence of highly sensitive troponin assays, even more patients may be found to have elevated concentrations of these important predictors of risk.[36] Although an elevated troponin value does

not specifically identify myocardial necrosis caused by CAD per se, given the importance of AMI in the triggering of acute HF, a troponin should always be measured in this setting, but interpreted with caution. Elevated troponin concentrations in community-based normal individuals are prognostic for onset of HF (particularly if rising in serial measurement). Troponin is independently predictive of increased mortality risk across the HF spectrum.

Other novel biomarkers are emerging and may have a role in the comprehensive evaluation of the patient with HF. Many of these novel markers reflect systemic stress or disarray of organs outside the heart. For example, the midregional fragment of proadrenomedullin is a biomarker reflective of vascular and systemic stress and is powerfully prognostic for short-term adverse outcome[30] (**see Chapter 23**). Similarly, growth differentiation factor-15, another marker of cardiovascular stress, not only strongly predicts outcomes in established HF, but also may be prognostic for new-onset HF in apparently well persons.[35] The C-terminal fragment of provasopressin (also known as copeptin) provides an indirect means by which to measure the biologically unstable parent hormone from which it is derived; values of copeptin are prognostic in HF but are not directly associated with serum sodium values in this setting. Lastly, novel biomarkers of renal dysfunction are emerging as strong predictors of cardiovascular risk beyond the standard measures of BUN and serum creatinine. Cystatin C, a ubiquitous protein found in all nucleated cells whose clearance is directly related to glomerular filtration, and beta trace protein are two renal function markers whose values are tightly related to outcomes in HF. Neutrophil gelatinase-associated lipocalin, *N*-acetyl-β-D-glucosaminidase, and kidney injury molecule-1 are promising biomarkers of acute renal injury whose values rise well before renal function is perceived to be worsening and impart important prognostic information in HF patients.[37]

Ultimately, for the comprehensive evaluation of HF, it seems likely that a combination or panel of biomarkers will prove to be the most useful way of assessing prognosis.

Risk Scoring for Prognosis

During initial and subsequent evaluation of the patient with HF, the clinician should routinely assess the potential for adverse outcome. Besides biomarker testing, a number of validated methods for risk stratification in HF exist, including a variety of multivariable clinical risk scores for use in both ambulatory and hospitalized patients. One well-validated risk score, the Seattle Heart Failure model, is available in an Internet-based application (www.seattleheartfailuremodel.org) and has been shown to provide robust information regarding risk of mortality in ambulatory HF patients.[38] For patients hospitalized with acute symptoms, the model developed by the Acute Decompensated Heart Failure National Registry (ADHERE) incorporates three routinely measured variables on hospital admission (systolic blood pressure, BUN, and serum creatinine) and partitions patients into categories with a 10-fold difference in risk (2.1% to 21.9%).[38] Importantly, clinical risk scores have not performed as well in estimating risk of hospital readmission. For this purpose, biomarkers may be of more use before discharge, particularly when measured after treatment.

Right-Heart Catheterization

Measurement of intracardiac pressures and hemodynamics as part of the diagnostic workup or for guiding therapy is less frequently performed now than in the past, since biomarkers and noninvasive imaging

techniques provide much of the information that was previously available only by heart catheterization. Nonetheless, right-heart catheterization affords unequivocal assessment of hemodynamics and filling pressures, so it is particularly useful when uncertainty exists about the cause of a patient's symptoms and in situations where precise measurements are required to guide therapy or decision making (e.g., selection of patients for heart transplantation). Right-heart catheterization also is of value (and should be considered) in those with HF complicated by clinically significant hypotension, systemic hypoperfusion, dependence on inotropic infusions, or persistently severe symptoms despite adjustment of recommended therapies (**see Chapter 19**).

An invasive assessment with right-heart catheterization is important to assess the pulmonary vascular resistance, a necessary part of the evaluation for heart transplantation. When pulmonary artery pressures are found to be elevated, response to pulmonary arterial vasodilators can be determined in this context and provides important information on whether a patient with pulmonary hypertension will be acceptable for cardiac transplantation. Also, the pulmonary artery wedge pressure is useful for assessing volume status and usually estimates the left ventricular end-diastolic pressure if no obstruction to flow between the left atrium and left ventricle exists. Although determination of hemodynamic variables at rest suffices in most patients, exercise helps to reveal the presence or magnitude of abnormal intracardiac pressures and flow in some patients. Pulmonary hypertension, for example, can be highly dynamic, and exercise measurements may be needed.

Use of hemodynamic monitoring to guide therapy was evaluated in patients with advanced HF in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial.[39] The results showed no clear benefit on morbidity or mortality of pulmonary artery–guided management compared to careful clinical assessment. The failure to affect postdischarge outcomes appears to be related to the hemodynamic improvements affected during hospitalization reverting toward baseline within a relatively short time. Consequently, “tailored therapy” of HF is used less often now than in the past, although it has a role particularly in patients with HF complicated by hypotension, systemic hypoperfusion, or end-organ dysfunction.

Endomyocardial Biopsy

The role of endomyocardial biopsy for evaluating patients with HF is discussed in **Chapter 79**. In general, biopsy of the myocardium is performed if a disorder with a unique prognosis is suspected, or if the patient might benefit from a specific treatment regimen, and the diagnosis cannot be made by conventional methods. The incremental diagnostic, therapeutic, and prognostic benefit offered by the information obtained from a biopsy must be weighed against the risks of the procedure. The sensitivity of endomyocardial biopsy may vary, depending on the cause of HF; for example, sensitivity is higher in more diffuse disease states such as myocarditis or amyloidosis, whereas more patchy disease states such as sarcoidosis may be less easily detected using biopsy.

Detection of Comorbid Conditions

The incidence of HF rises sharply from the sixth decade on, coincident with the ages when other chronic diseases begin to manifest. In addition, many of the conditions leading to the development of HF (e.g.,

diabetes, hypertension, atherosclerosis) affect organs other than the heart. Thus, comorbidities are quite common in HF patients and have a profound effect on the course; in fact, a substantial percentage of hospitalizations in patients with HF are non-HF related and are not precipitated by a cardiac condition in more than half of cases.[40] Comorbidities not only complicate the course of patients with concomitant HF, but also have a substantial impact on ability to manage patients with HF; for example, chronic kidney disease may limit application of agents blocking the renin-angiotensin-aldosterone system. In addition, the presence of comorbidities reduces the prognostic benefits of guideline-directed medical therapy; for example, atrial fibrillation reduces the benefit of many therapies, including beta blockers and CRT. With recent data suggesting that both aggressive management of hypertension and use of sodium-glucose cotransporter-2 inhibitors for diabetes mellitus care may reduce HF events,[41,42] detection and management of comorbidities is a particularly relevant exercise.

Assessment of Quality of Life

Heart failure has a profound effect on quality of life, and poor health-related quality of life is a powerful predictor of adverse prognosis in HF patients. Determinants of poor quality of life in HF include female sex, younger age, higher body mass index, worse symptoms, and the presence of depression and sleep apnea.[43] Improved quality of life has been reported after CRT or in disease management programs with aggressive care. Given its importance, at the initial and subsequent visits, consideration should be given for quality-of-life assessment, whether through standard history or through the use of validated tools for its estimation, such as the Kansas City Cardiomyopathy Questionnaire or Minnesota Living with Heart Failure Questionnaire.

Cardiopulmonary Exercise Testing

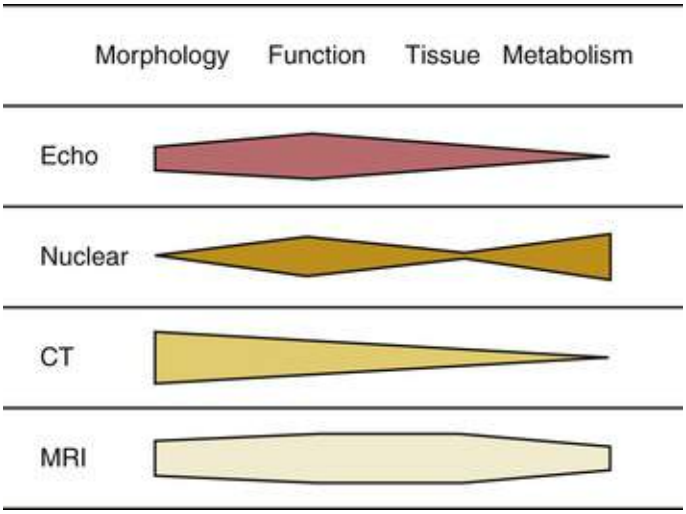
Exercise intolerance is a prime symptom of HF (**see Chapter 13**). Despite this fact, quantification of exercise tolerance is imprecise; standard approaches such as the NYHA criteria or the 6-minute walk test are subjective and insensitive measures of functional capacity. Additionally, the 6-minute walk test does not reveal how close the patient may be to her or his maximal capacity for exercise, does not discriminate between the causes of impaired exercise capacity (e.g., cardiac, pulmonary, orthopedic) or poor motivation, and does not account for the effects of conditioning and age; older age may undermine accuracy of the 6-minute walk test. When more precise information is needed, cardiopulmonary exercise testing (CPX) is often used because it allows for identification of causes of exercise intolerance, quantification of exercise capacity, and delivery of important physiologic information not routinely available from standard stress testing.[44] Use of CPX is a standard part of the routine evaluation before heart transplantation; moderate to severely reduced maximal oxygen uptake (V_{O_2}) values (e.g., <14 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) are often used as a prognostic threshold in this setting, whereas maximal V_{O_2} values less than 10 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ are considered severe and particularly prognostic when the V_E/V_{CO_2} slope is 45.0 or greater.

Imaging Modalities

Noninvasive cardiac imaging serves a vital role in the assessment of patients with HF and is essential for

determining whether the patient should be classified as HFpEF or HFrEF. Imaging may help confirm the diagnosis of HF by assessing the presence and severity of structural and functional changes in the heart, provide clues about the etiology of cardiac dysfunction (congenital heart disease, valvular abnormalities, pericardial disease, coronary artery disease), risk-stratify patients, and possibly guide treatment strategies. Imaging modalities can also be used to help assess the efficacy of therapeutic interventions, provide ongoing prognostic information, and further guide treatment.

The primary noninvasive cardiac imaging modalities used to evaluate HF patients are echocardiography (**Chapter 14**), magnetic resonance imaging (MRI; **Chapter 17**), computed tomography (CT; **Chapter 18**), and nuclear imaging, including single-photon emission computed tomography (SPECT) and positron emission tomography (PET) techniques (**Chapter 16**). Imaging modalities often provide complementary data, and each has the capacity to provide unique information in individual patients. Although the initial evaluation of a patient with newly diagnosed HF should include a transthoracic echocardiogram, further imaging with MRI, CT, and/or nuclear techniques may be considered depending on the need to further address questions regarding cardiac structure and function, etiology, and issues such as the potential for reversibility of systolic dysfunction with revascularization. The specific indications and advantages for each of these imaging modalities are summarized in **EFig. 21.1** and **ETable 21.2**.



EFIGURE 21.1 Relative strengths of noninvasive imaging modalities. (Modified from Friedrich MG. Tissue characterization of acute myocardial infarction and myocarditis by cardiac magnetic resonance. JACC Cardiovasc Imaging 2008;1:652.)

ETABLE 21.2

Comparative Values of Echocardiography, Magnetic Resonance Imaging (CMR), Nuclear Imaging, Computed Tomography (MDCT), and PET Imaging in Heart Failure Patients

		ECHO	CMR	MDCT	SPECT	PET
Remodeling/Dysfunction						
LV	Volumes	++	+++	++	++	++
	Ejection fraction	++	+++	++	++	–
	Mass	++	+++	++	–	–
RV	Volume	++	+++	++	–	–
	Ejection fraction	++	+++	++	–	–
	Mass	++	+++	++	–	–
LV diastolic dysfunction		+++	+	–	–	–
Dyssynchrony		++	+	–	+	–
Etiology						
CAD	Ischemia	+++	+++	–	+++	+++
	Hibernation	+++	+++	–	+++	+++
	Scar	++	+++	–	++	++
	Coronary anatomy	–	–	+++	–	–
Valvular:	Stenosis	+++	+	++	–	–
	Regurgitation	+++	++	–	–	–
Myocarditis		+	+++	–	–	–
Sarcoidosis		+	+++	–	–	++
Hypertrophic CMP	HCM	+++	++	–	–	–
	Amyloidosis	++	+++	–	–	–
Dilated CMP	Myocarditis	+	+++	–	–	–
	Eosinophilic syndromes	+	+++	–	–	–
	Hemochromatosis	+	+++	–	–	–
ARVC		++	+++	+	–	–
Restrictive CMP	Pericarditis	++	++	++	–	–
	Amyloidosis	++	+++	–	–	–
	Endomyocardial fibrosis	+	+++	–	–	–
	Anderson-Fabry	+	+	–	–	–
Unclassified CMP	Takotsubo CMP	++	++	–	–	–
Main Advantages						
		Wide availability	Good-quality images	Reasonable availability	Good availability	Good-quality images
		Portability	No radiation			
		No radiation		High-quality images		
		Relatively low cost		High-quality images		
Main Disadvantages						
		Echo window	Limited availability	Radiation	Radiation	Radiation
			Image quality may be limited if arrhythmia	Image quality may be limited if arrhythmia		Limited availability
			Renal function limits use	Renal function limits use		

PET, Positron emission tomography; *SPECT,* single-photon emission computed tomography; *LV,* left ventricle, *RV,* right ventricle; *CAD,* coronary artery disease; *CMP,* cardiomyopathy; *HCM,* hypertrophic cardiomyopathy; *ARVC,* arrhythmogenic right ventricular cardiomyopathy.

Modified from McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology (ECS). Developed in collaboration with the Heart Failure Association (HFA) of the ESC, Eur J Heart Fail 2012;14:803.

Echocardiography and Lung Ultrasound

Transthoracic echocardiography is an important part of the evaluation of HF,[45] can be performed without risk to the patient and at the bedside if necessary, and does not involve radiation exposure. Increasing use of handheld echocardiography has facilitated evaluation at the point of care, such as in the ED with an acute presentation.

Echocardiography is particularly well suited for evaluating the structure and function of both the myocardium and the heart valves and providing information about intracardiac pressure and flow. For patients with HFrEF, left ventricular (LV) volumes and systolic function can be assessed semiquantitatively or can be quantified using the biplane method and the modified Simpson's rule. Information about the morphology and relative sizes of the cardiac chambers may suggest specific diagnoses. For example, concentric LV hypertrophy with severe biatrial enlargement suggests that HF is caused by an infiltrative process such as amyloidosis, particularly in the absence of a prior diagnosis of hypertension. Diastolic function is assessed using Doppler measurements, including analyses of the mitral valve inflow pattern (early [E] and atrial [A] waveforms), tissue velocities at the mitral valve annulus, pulmonary vein flow, and the left atrial volume indexed to body surface area (**see Chapter 14**). Diastolic dysfunction can be further classified as grades I to III based on these measurements, with incremental prognostic importance in HF as worsening grades of diastolic dysfunction are noted. Ratio of early mitral valve inflow to mitral valve annulus velocity determined using tissue Doppler (E/e′) is particularly helpful to determine presence and severity of diastolic dysfunction; a ratio of 15 or greater is abnormal. Pulmonary hypertension in patients without significant systolic dysfunction or pulmonary disease suggests that diastolic dysfunction may be present. Another advantage of echocardiography is the ability to estimate right-sided heart pressures noninvasively. For example, right atrial (RA) pressures are estimated by the inferior vena cava (IVC) diameter and the relative change in diameter on inspiration. Normal IVC diameter and inspiratory collapse of at least 50% are associated with normal RA pressures, whereas increased IVC diameter and smaller inspiratory changes indicate elevated RA pressure.

Lung ultrasound (LUS) has become increasingly used to evaluate patients presenting to the ED. LUS has been found to be useful to diagnose interstitial pulmonary edema and fluid overload through the detection of vertical reverberation artifacts, known as Kerley B lines, created at the acoustic interface between two structures with differing acoustic impedances, such as fluid-filled structures and alveolar air. Also known as “comets” in the appropriate setting, Kerley B lines may be highly sensitive and specific for presence of HF, particularly when incorporated with clinical judgment and other tools, such as chest radiography and natriuretic peptide testing.

Magnetic Resonance Imaging

MRI provides high-quality imaging of the heart and involves no radiation, which is a significant advantage over CT. Diagnostic images can be obtained in almost all patients, and unlike echocardiography, images can be obtained in arbitrary tomographic planes. MRI is excellent for evaluating cardiac morphology, chamber sizes, and cardiac function. Using different pulse sequences with and without gadolinium contrast, MRI can characterize myocardial tissue and assess myocardial viability. Cardiac MRI can distinguish ischemic from nonischemic cardiomyopathies based on the pattern of delayed gadolinium enhancement from T1-weighted images; ischemic cardiomyopathies usually show characteristic subendocardial enhancement at sites of prior infarction, whereas nonischemic dilated cardiomyopathies typically have no enhancement, midwall enhancement, or other patterns, depending on the etiology (**Fig. 21.4**). Additionally, MRI is extremely useful to identify the presence of myocarditis and may be similarly helpful in the diagnosis of specific cardiomyopathies, such as infiltrative processes or LV noncompaction. A major limitation is that the current implantable pacemakers or defibrillators are not safe for the patient to undergo MRI, although this limitation may be overcome with greater use of MRI-compatible devices (**see Chapter 17**).

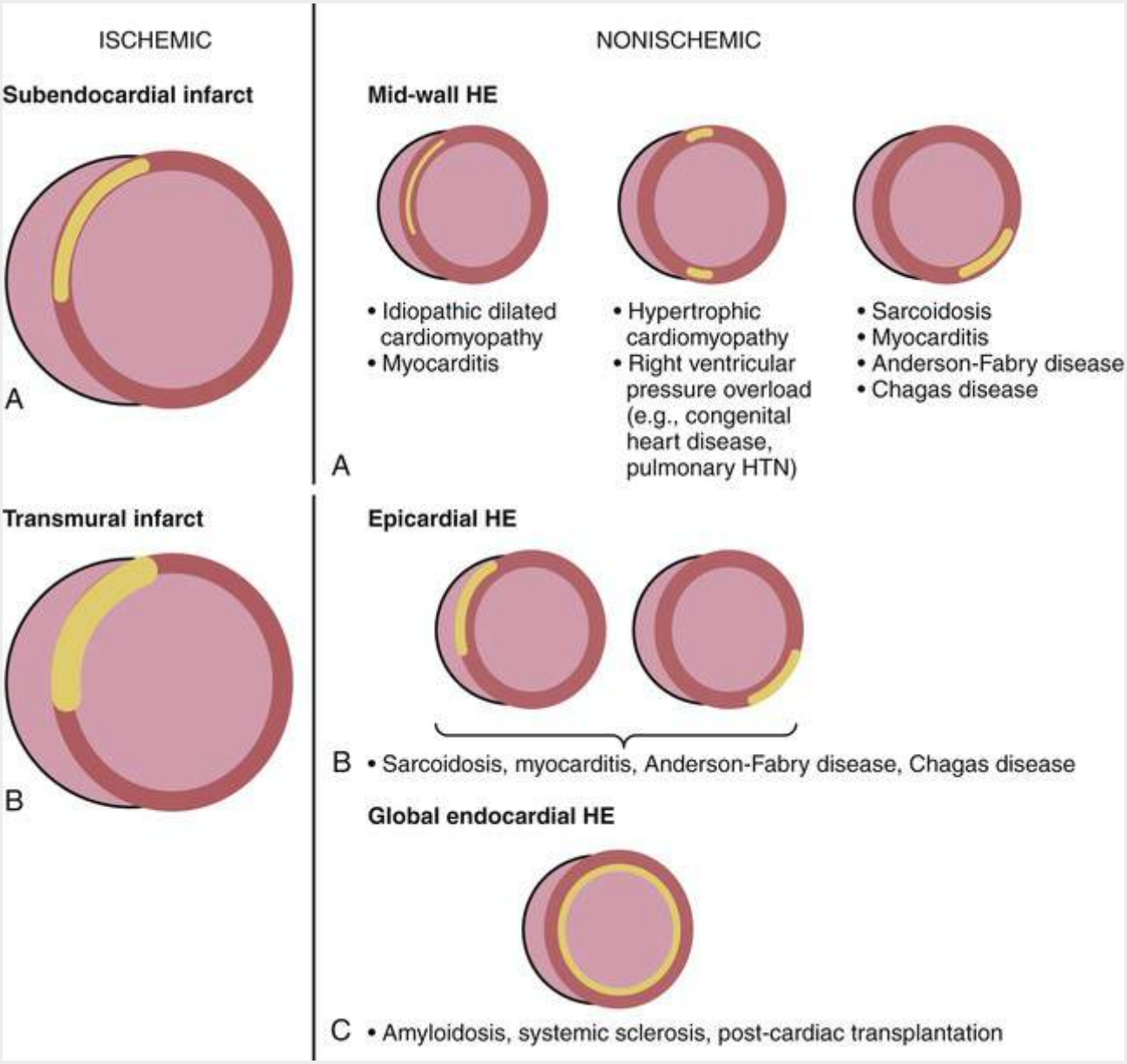


FIGURE 21.4 Patterns of hyperenhancement (*HE*) with MRI in various disease states; *HTN,* hypertension. (Modified from Mahrholdt H, Wagner A, Judd RM, et al. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. Eur Heart J 2005;26:1461.)

Cardiac Computed Tomography

The current role of cardiac CT in HF is mainly to help determine whether or not obstructive CAD is present through the use of CT angiography, an important application particularly for patients with lower likelihood for CAD. Emerging applications of CT angiography may be to assist in assessment of coronary venous anatomy before CRT lead placement. Recent advances in CT technology have led to less radiation exposure, but cardiac CT angiography still involves administering iodinated contrast, a concern in patients at risk for developing nephrotoxicity (**see Chapter 18**).

Nuclear Imaging

A wide array of nuclear imaging techniques have been developed for the assessment of HF. In particular, SPECT and PET technologies are well suited for assessing myocardial ischemia and viability and for evaluating myocardial function. The use of nuclear imaging to determine myocardial viability is discussed in **Chapter 16**. Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET scanning may be particularly helpful for diagnosis prognosis, and management of cardiac sarcoidosis[46]; a characteristic heterogeneous uptake pattern in the myocardium may be seen in patients with cardiac sarcoidosis, in contrast to diffuse

uptake seen in dilated cardiomyopathy and normal individuals. After successful treatment with immunosuppressive medication, ^{18}F-FDG uptake may normalize. Technetium-99m pyrophosphate (^{99m}Tc-PYP) scanning shows promise in diagnosing transthyretin (TTR) amyloidosis (**Fig. 21.5**). Although more frequently positive in patients with TTR amyloidosis, ^{99m}Tc-PYP scans can also be positive in patients with AL amyloidosis[47] (**see Chapter 77**). Lastly, cardiac scans using iodine-123 (^{123}I) metaiodobenzylguanidine (MIBG) may provide objective evaluation of cardiac sympathetic function and may predict risk for sudden death from arrhythmia in NYHA Class II or III HFrEF when the heart-to-mediastinum ratio of ^{123}I-MIBG is low[48] (**EFig. 21.2**).[48]

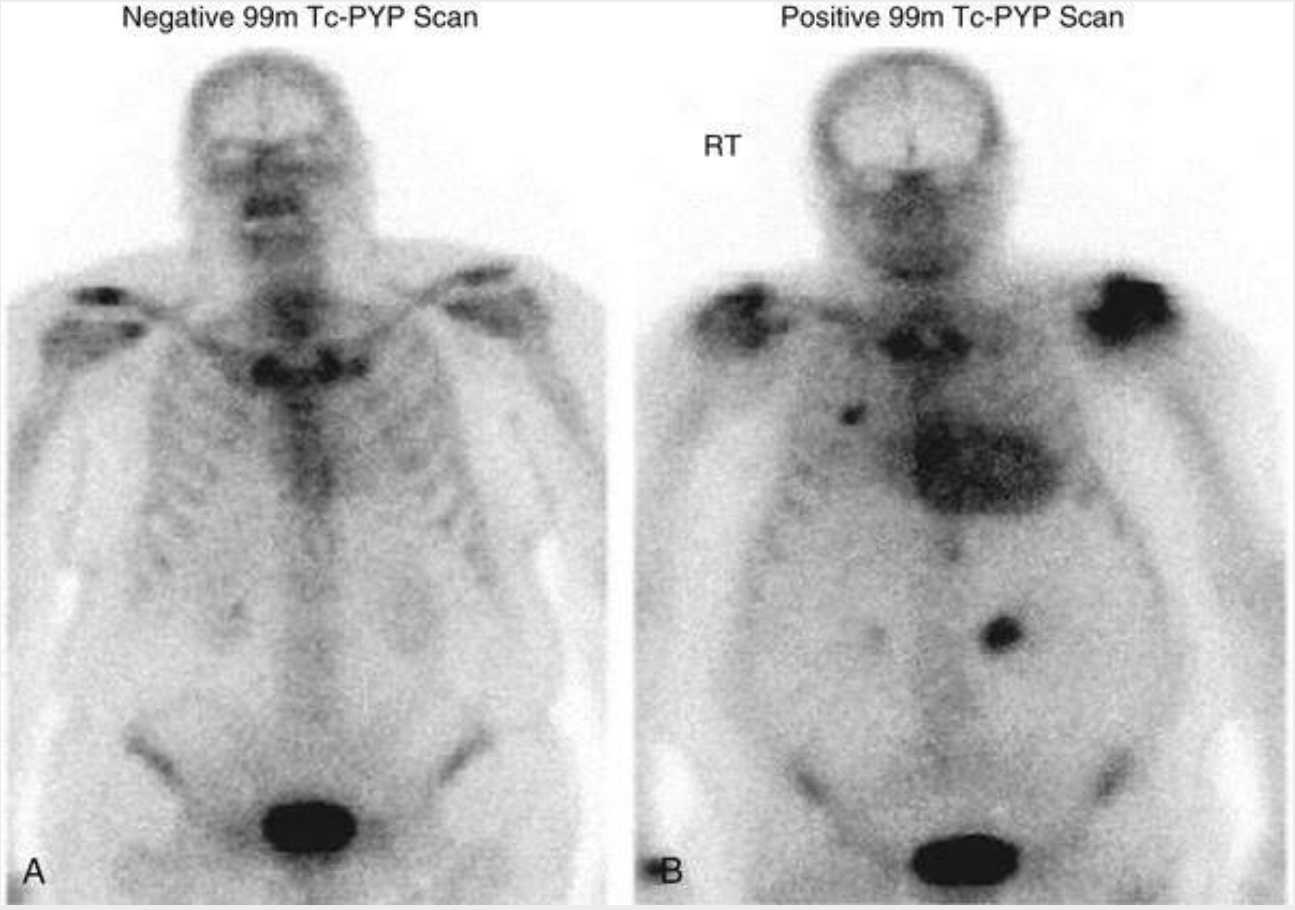
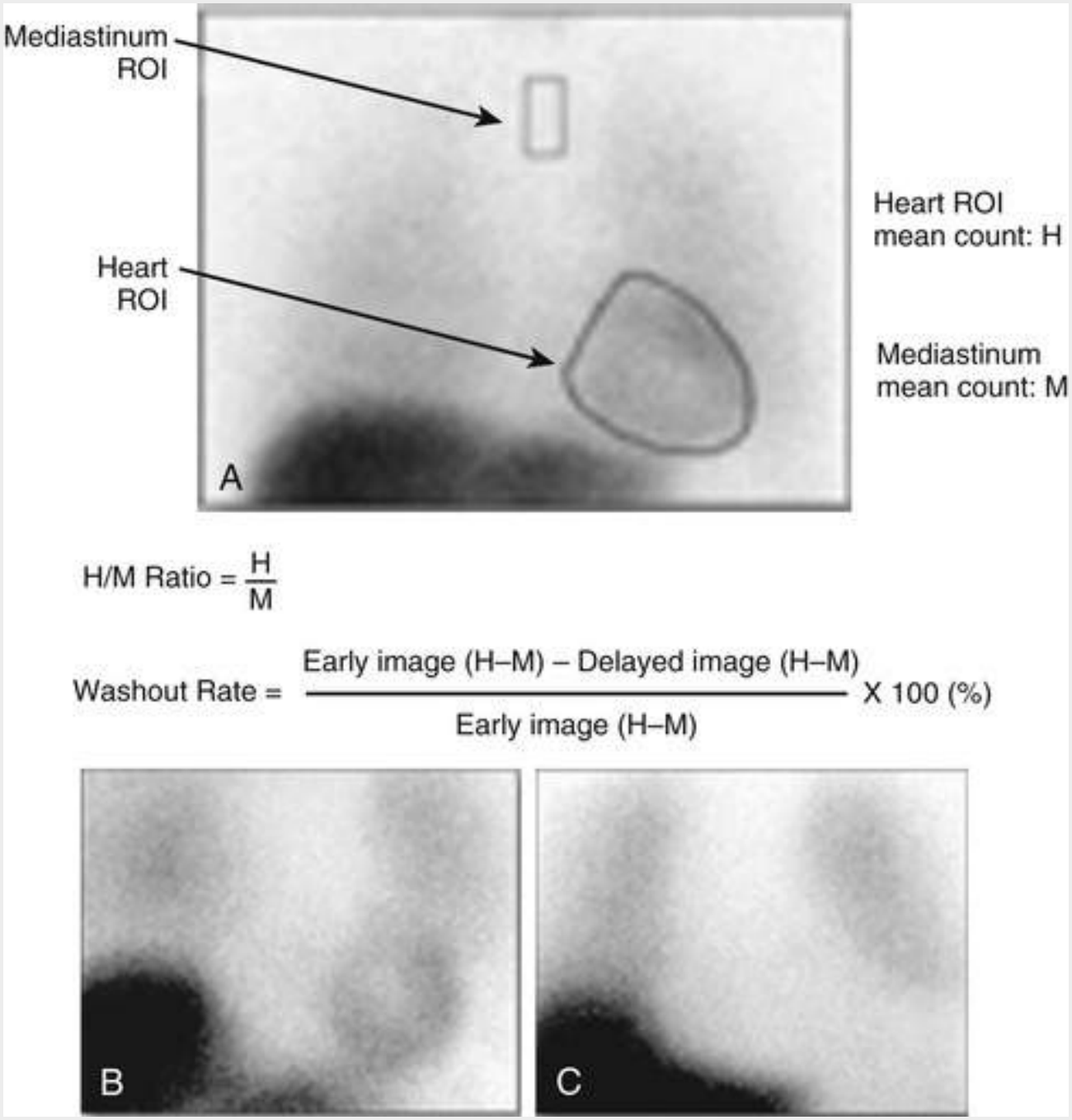


FIGURE 21.5 Technetium 99m pyrophosphate imaging in two patients with heart failure with preserved ejection fraction for diagnosis of transthyretin (TTR) amyloidosis. Compared to the control patient on the left **(A),** the patient on the right has radiotracer (*RT*) uptake **(B),** consistent with a diagnosis of TTR amyloidosis



EFIGURE 21.2 Metaiodobenzylguanidine (MIBG) imaging to determine the severity of heart failure. **A,** Calculation the MIBG heart (*H*)/mediastinum (*M*) ratio and washout rate on an anterior view of the thorax. Regions of interest (*ROI*) are drawn over the heart and mediastinum. **B,** Normal cardiac MIBG activity in a patient with H/M ratio of 1.80. **C,** Severely decreased cardiac MIBG activity in patient with H/M ratio of 1.10. (From Carrio I, Cowie MR, Yamazaki J, et al. Cardiac sympathetic imaging with mIBG in heart failure. JACC Cardiovasc Imaging 2010;3:92.)

Future Perspectives

As treatment options for heart failure continue to evolve, there will be increased emphasis on more rapid, accurate, and cost-effective assessment of patients, with the goal of providing unambiguous information about the presence, severity, and cause of HF. New insights into the biology of cardiac dysfunction are likely to lead to the development of therapeutic approaches that are specific to the underlying etiology. Continued advances in the use of biomarkers and imaging techniques to diagnose, stage, and determine etiology of HF will be needed to meet these future demands. Even as these diagnostic modalities increase in their precision and accuracy, the information obtained through the history and physical examination will

remain at the core of our ability to understand how to employ these tests most judiciously and to treat patients most effectively.

Guidelines

Initial Evaluation of the Patient with Heart Failure

James L. Januzzi Jr and Douglas L. Mann

A joint task force of the American College of Cardiology and the American Heart Association (ACC/AHA) published updated comprehensive guidelines for the evaluation and management of heart failure (HF) in 2013.[1] These were updated in two sequential "focused" guidelines in 2016[2] and 2017[3] that provided several recommendations regarding new medical therapies for HF with reduced ejection fraction (HFrEF), but did not provide new guidelines for devices for monitoring or treating HF. Beginning in 2016 and for all subsequent guidelines thereafter, the Heart Failure Society of America (HFSA) has partnered with the ACC and the AHA to provide coordinated recommendations about HF guidelines. The European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of chronic HF were published 2016,[4] which superseded previous complete guidelines in 2012.[5] Guidelines for the initial evaluation of the patient with HF are reviewed in this chapter; guidelines for the management of the hospitalized patient are reviewed in **Chapter 24**, for patients with a reduced ejection fraction in **Chapter 25**, for heart failure with a preserved ejection fraction in **Chapter 26**, and for the use of devices for managing heart failure in **Chapter 27**.

As discussed in **Chapters 21 and 25**, the ACC/AHA guidelines classify patients according to the following four stages:

Stage A: patients at high risk for developing heart failure but without structural disorders of the heart
Stage B: patients with a structural disorder of the heart but no symptoms of heart failure
Stage C: patients with past or current symptoms of heart failure associated with underlying structural heart disease
Stage D: patients with end-stage disease who require specialized treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation, or hospice care

The guidelines are organized into recommendations for each stage. As with other ACC/AHA guidelines, these recommendations classify interventions into one of three classes of recommendation (COR), including two levels for the class II (intermediate) group and two levels for the class III (no benefit or harm) group:

Class I (Strong): Procedure/Treatment/Diagnostic Testing **is recommended/indicated** (Benefit > Risk)
Class IIa (Moderate): Procedure/Treatment/Diagnostic Testing **is reasonable/can be useful** (Benefit Risk)
Class IIb (Weak): Procedure/Treatment/Diagnostic Testing **might be reasonable/considered** (Benefit ≥ Risk)

Class III: No Benefit (Moderate): Treatment/Diagnostic Testing **is not recommended/indicated/useful** (Benefit = Risk) *or*
Class III: Harm (Strong): Treatment/Diagnostic Testing **is potentially harmful/causes harm/is associated with excess morbidity/mortality/ should not be performed** (Risk > Benefit)

The ACC/AHA/HFSA guidelines also adopt a convention for rating levels of evidence on which recommendations have been based, as follows:

Level A recommendations are derived from data from multiple populations with data from multiple randomized clinical trials and/or meta-analyses.
Level B recommendations are derived from data from limited populations with data from a single randomized clinical trial or nonrandomized studies
B-R = moderate-quality evidence from one or more randomized clinical trials
B-NR = moderate-quality evidence from one or more nonrandomized clinical trials
Level C recommendations are based on very limited populations or the consensus opinion of experts or case studies or standard of care
C-LD = randomized or nonrandomized observational/registry studies or a meta-analysis
C-EO = consensus of expert opinion

The term *guideline-directed medical therapy* (GDMT) represents optimal medical therapy as defined by the ACC/AHA guideline–recommended therapies (primarily class I).

Initial Patient Evaluation

The ACC/AHA guidelines state that a complete history and physical examination should be the first step in the evaluation of patients with HF (**Table 21G.1**). This evaluation may provide insight into the cause of the patient's HF and the presence or absence of structural cardiovascular abnormalities. Other issues to be addressed include presence or absence of history of diabetes, rheumatic fever, chest radiation, exposure to cardiotoxic drugs, and use or abuse of alcohol, illicit drugs, or alternative therapies. The patient's functional and volume status should also be evaluated to assess prognosis and guide management. New recommendations include a three-generational family history for patients with dilated cardiomyopathy (DCM) and the use of validated multivariable risk models for assessing subsequent mortality risk.

TABLE 21G.1

ACC/AHA Guidelines for Initial and Serial Evaluation of Heart Failure

CLASS	INDICATION: HISTORY, PHYSICAL EXAMINATION, AND RISK SCORING	LEVEL OF EVIDENCE
I	A thorough history and physical examination should be obtained/performed in patients presenting with HF to identify cardiac and noncardiac disorders or behaviors that might cause or accelerate the development or progression of HF.	C
	In patients with idiopathic DCM, a three-generational family history should be obtained to aid in establishing the diagnosis of familial DCM.	C
	Volume status and vital signs should be assessed at each patient encounter. This includes serial assessment of weight, as well as estimates of jugular venous pressure and the presence of peripheral edema or orthopnea.	B
IIa	Validated multivariable risk scores can be useful to estimate subsequent risk of mortality in ambulatory or hospitalized patients with HF.	C
INDICATION: DIAGNOSTIC TESTS AND BIOMARKERS (ALSO SEE BELOW)		
I	Initial laboratory evaluation of patients presenting with HF should include complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone.	C
	Serial monitoring, when indicated, should include serum electrolytes and renal function.	C
	A 12-lead ECG should be performed initially on all patients presenting with HF.	C
	In ambulatory patients with dyspnea, measurement of BNP or N-terminal pro-B-type natriuretic (NT-proBNP) is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty, and measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF.	A
IIa	Screening for hemochromatosis or HIV is reasonable in select patients who present with HF.	C
	Diagnostic tests for rheumatologic diseases, amyloidosis, or pheochromocytoma are reasonable in patients presenting with HF in whom there is a clinical suspicion of these diseases.	C
	BNP-guided or NT-proBNP–guided HF therapy can be useful to achieve optimal dosing of GDMT in select, clinically euvolemic patients followed in a well-structured HF disease management program.	B
IIb	The usefulness of serial measurement of BNP or NT-proBNP to reduce hospitalization or mortality in patients with HF is not well established. The measurement of other clinically available tests, such as biomarkers of myocardial injury or "fibrosis," may be considered for additive risk stratification in patients with chronic HF.	B
INDICATION: NONINVASIVE CARDIAC IMAGING		
I	Patients with suspected or new-onset HF, or those presenting with acute decompensated HF, should undergo a chest radiograph to assess heart size and pulmonary congestion and to detect alternative cardiac, pulmonary, and other diseases that may cause or contribute to the patient's symptoms.	C
	A two-dimensional echocardiogram with Doppler should be performed during initial evaluation of patients presenting with HF to assess ventricular function, size, wall thickness, wall motion, and valve function.	C
	Repeat measurement of EF and measurement of the severity of structural remodeling are useful to provide information in patients with HF who have had a significant change in clinical status; who have experienced or recovered from a clinical event; who have received treatment, including GDMT, that might have had a significant effect on cardiac function; or who may be candidates for device therapy.	C
IIa	Noninvasive imaging to detect myocardial ischemia and viability is reasonable in patients presenting with de novo HF who have known CAD and no angina, unless the patient is not eligible for revascularization of any kind.	C
	Viability assessment is reasonable in select situations when planning revascularization in HF patients with CAD.	B
	Radionuclide ventriculography or MRI can be useful to assess LVEF and volume when echocardiography is inadequate.	C
	MRI is reasonable when assessing myocardial infiltrative processes or scar burden.	B
III: no benefit	Routine repeat measurement of LV function assessment in the absence of clinical status change or treatment interventions should not be performed.	B
INDICATION: INVASIVE EVALUATION		
I	Invasive hemodynamic monitoring with a pulmonary artery catheter should be performed to guide therapy in patients who have respiratory distress or clinical evidence of impaired perfusion in whom the adequacy or excess of intracardiac filling pressures cannot be determined from clinical assessment.	C
IIa	Invasive hemodynamic monitoring can be useful for carefully selected patients with acute HF who have persistent symptoms despite empiric adjustment of standard therapies and (a) whose fluid status, perfusion, or systemic or pulmonary vascular resistance is uncertain; (b) whose systolic pressure remains low, or is associated with symptoms, despite initial therapy; (c) whose renal function is worsening with therapy; (d) who require parenteral vasoactive agents; or (e) who may need consideration for mechanical circulatory support or transplantation.	C
	When ischemia may be contributing to HF, coronary arteriography is reasonable for patients eligible for revascularization.	C
	Endomyocardial biopsy can be useful in patients presenting with HF when a specific diagnosis is suspected that would influence therapy.	C
III: no benefit	Routine use of invasive hemodynamic monitoring is not recommended in normotensive patients with acute decompensated HF and congestion with symptomatic response to diuretics and vasodilators.	B
III: harm	Endomyocardial biopsy should not be performed in the routine evaluation of patients with HF.	C

ACC, American College of Cardiology; *AHA,* American Heart Association; *BNP,* B-type natriuretic peptide; *CAD,* coronary artery disease; *DCM,* dilated cardiomyopathy, *EF,* ejection fraction; *GDMT,* guideline-directed medical therapy; *HIV,* human immunodeficiency virus; *LVEF,* left ventricular ejection fraction; *MRI,* magnetic resonance imaging.

The guidelines recommend that the initial evaluation should include a complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone, and that serial monitoring of electrolytes should be performed when indicated. The guidelines also recommend a chest radiograph and a 12-lead electrocardiogram; two-dimensional echocardiography with Doppler to assess left ventricular function and detect underlying myocardial, valvular, or pericardial disease was considered a more valuable initial test than radionuclide ventriculography or magnetic resonance imaging. Screening tests for hemochromatosis, amyloidosis, the human immunodeficiency virus, sleep-disturbed breathing, connective tissue diseases, amyloidosis, or pheochromocytoma are also reasonable in select patients.

Screening for and assessment of coronary artery disease in HF patients are given less weight in the 2013 ACC/AHA guidelines than in previous guidelines. When ischemia may be contributing to HF, the guidelines indicate that coronary arteriography is reasonable for patients eligible for revascularization (class IIa, level of evidence C). The guidelines also support noninvasive imaging to detect myocardial ischemia and viability in patients presenting with de novo HF who have known CAD and no angina, unless the patient is not eligible for revascularization of any kind, as well as viability testing in select patients when planning revascularization (class IIa, level of evidence B or C). Although the guidelines support the use of endomyocardial in patients presenting with HF when a diagnosis that would influence therapy is suspected (class IIb, level of evidence C), the routine use of endomyocardial biopsy is not recommended (class III: harm). The guidelines do not support serial measurement of left ventricular function in the absence of change in clinical status. The updated ACC/AHA guidelines now give a class I (level of evidence C) recommendation the use of invasive hemodynamic monitoring with a pulmonary artery catheter to guide therapy in patients who have respiratory distress or clinical evidence of impaired perfusion in whom the adequacy or excess of intracardiac filling pressures cannot be determined from clinical assessment (**see Chapter 24** guidelines).

Indications for the Use of Biomarkers

The updated ACC/AHA/HFSA and ESC guidelines reflect recent research on biomarkers, including B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP)[3,4] (**Fig. 21G.1** and **Table 21G.2**). Clinical assays for natriuretic peptide biomarkers, including BNP and NT-proBNP, have been used reliably to establish the diagnosis and prognosis of HF. In general, both natriuretic peptide biomarker values track in a similar fashion, and either can be used in patient care settings, with the understanding that their respective absolute values and cutoffs are different and cannot be used interchangeably. Importantly, the type of natriuretic peptide assay performed must be considered during interpretation of natriuretic peptide biomarker levels in patients receiving angiotensin receptor neprilysin inhibitors (ARNIs; **see Chapter 25**). Use of ARNIs will lead to elevated levels of BNP but will not falsely affect the circulating levels of NT-proBNP. Indeed, in clinical studies with ARNIs, NT-proBNP levels were reduced, and in one analysis, reduction in NT-proBNP levels was associated with improved clinical outcomes.

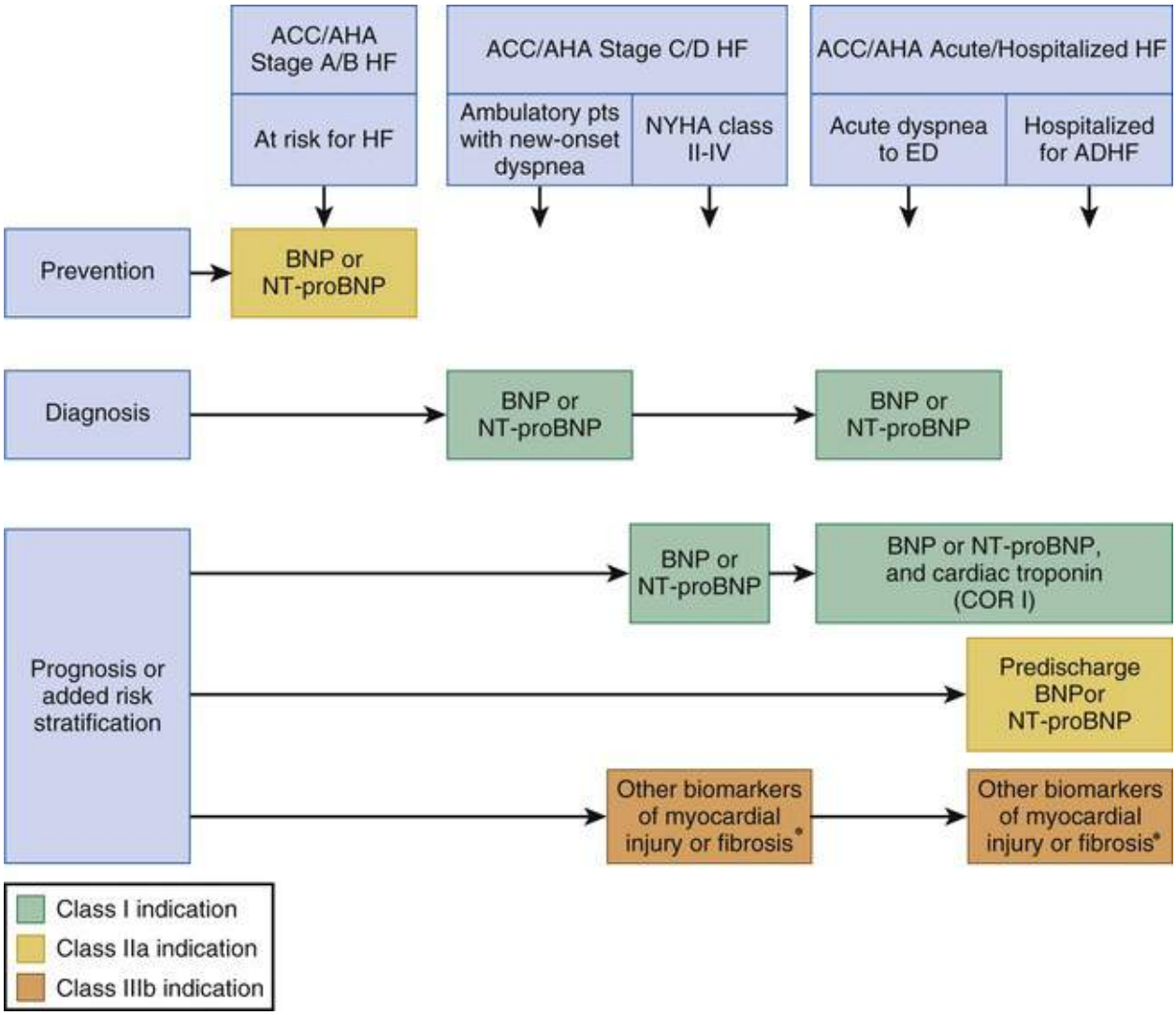


FIGURE 21G.1 Indications for the use of biomarkers in heart failure. *Other biomarkers of injury or fibrosis include soluble ST2 receptor, galectin-3, and high-sensitivity troponin. *ACC,* American College of Cardiology; *AHA,* American Heart Association; *ADHF,* acute decompensated heart failure; *BNP,* B-type natriuretic peptide; *COR,* class of recommendation; *ED,* emergency department; *HF,* heart failure; *NT-proBNP,* N-terminal pro-B-type natriuretic peptide; *NYHA,* New York Heart Association; *pts,* patients.
(Modified from Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. J Am Coll Cardiol 2017;70(6):776.

TABLE 21G.2

ACC/AHA/HFSA Guidelines for Use of Biomarkers in Heart Failure

CLASS	BIOMARKERS FOR PREVENTION OF HF	LEVEL OF EVIDENCE
IIa	For patients at risk of developing HF, natriuretic peptide biomarker–based screening can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF.	B-R
BIOMARKERS FOR DIAGNOSIS		
I	In patients presenting with dyspnea (acute or chronic), measurement of natriuretic peptide biomarkers is useful to support a diagnosis or exclusion of HF.	A
BIOMARKERS FOR PROGNOSIS OR ADDED RISK STRATIFICATION		
I	Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF.	A
I	Measurement of baseline levels of natriuretic peptide biomarkers and/or cardiac troponin on admission to the hospital is useful to establish a prognosis in acutely decompensated HF.	A
IIa	During a HF hospitalization, a predischarge natriuretic peptide level can be useful to establish a postdischarge prognosis.	B-NR
IIb	In patients with chronic HF, measurement of other clinically available tests, such as biomarkers of myocardial injury or fibrosis, may be considered for additive risk stratification.	B-NR

The 2017 ACC/AHA guidelines give a class I (level of evidence A) recommendation for the use of

BNP or NT-proBNP to evaluate patients with acute and chronic dyspnea, and a class I (level of evidence A) recommendation for the use of BNP or NT-proBNP for establishing prognosis or disease severity in acute or chronic HF. In addition, the guidelines recognized the additive prognostic value of a predischarge measurement of BNP or NT-proBNP for patients with acute HF with a class II (level of evidence A) recommendation. Other biomarkers may be useful for prognosticating HF, including troponin (class I) and "fibrosis" markers such as soluble ST2 (class IIb). Lastly, based on the results of the STOP-HF trial (**see Chapter 25**),[6] the updated guidelines give a class IIa recommendation (level of evidence B-R) for the use of natriuretic peptide–based screening in conjunction with team-based care to optimize GDMT to prevent the development of systolic and diastolic dysfunction or new-onset HF.

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22

Mechanisms of Cardiac Contraction and Relaxation

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Microanatomy of Contractile Cells and Proteins

Ultrastructure of Contractile Cells

The major function of cardiac muscle cells (*cardiomyocytes* or *myocytes*) is to execute cardiac excitation-contraction-relaxation that depends on the electrical calcium ion (Ca^{2+}) transport and contractile properties.[1,2] Cardiomyocytes constitute approximately 75% of total ventricular volume and weight, but only one third of the total number of cells there.[1-4] Approximately half of each ventricular myocyte is occupied by myofibrils of the myofibers and 30% by mitochondria (**Fig. 22.1 and Table 22.1**). A *myofiber* is a group of cardiomyocytes held together by surrounding collagen connective tissue, the latter being a major component of the extracellular matrix. Further strands of collagen connect myofibers to each other.

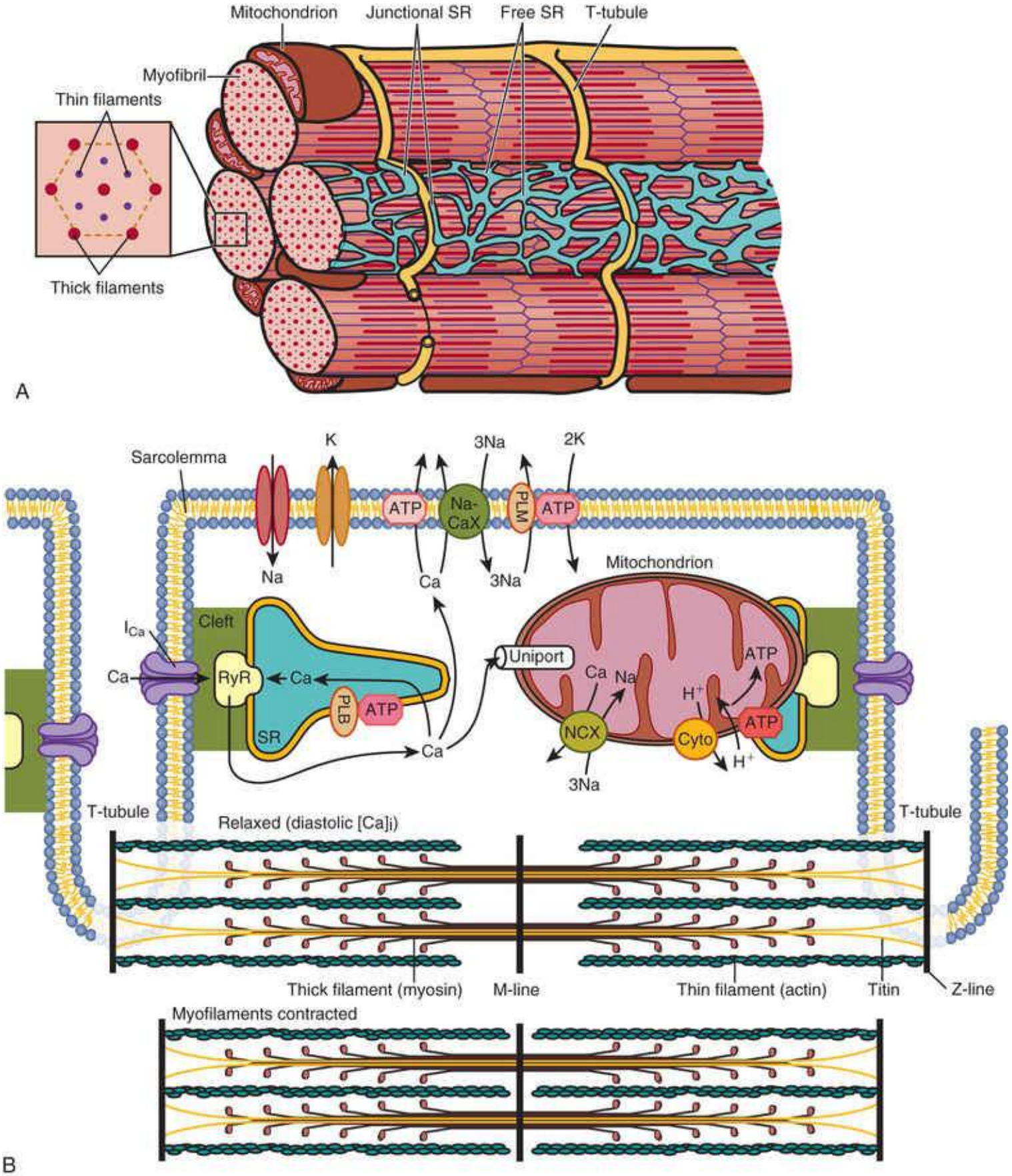

FIGURE 22.1 Ultrastructural components of excitation-contraction coupling in ventricular myocytes, viewed anatomically (**A,** with *inset* showing an end-on view of thick and thin filament organization) and schematically **(B).** The action potential is conducted along the surface sarcolemma and sarcolemma that extends into the T tubules. Ca^{2+} current (I_{Ca}) at sites of junctional SR clefts trigger local Ca^{2+} release, and the Ca^{2+} diffuses throughout the cytosol to activate myofilament contraction. The $[Ca^{2+}]_i$ quickly declines at each beat because of Ca^{2+} uptake via the SR Ca^{2+}-ATPase (ATP/PLB), extrusion via sarcolemmal Na^+/Ca^{2+} exchange (NCX) and Ca^{2+}-ATPase (and mitochondrial Ca^{2+} uniport), allowing relaxation (diastole) to proceed. The myofibrils are bundles of contractile proteins that are organized into a regular

sarcomeric array, bounded longitudinally by Z-lines that are immediately adjacent to T tubules that run in parallel. In diastole (*bottom*) the thin filaments (containing mainly actin) create a cage around the thick filaments (containing mainly myosin) that have cross-bridges (myosin heads) that extend toward the thin filament. Myosin molecule tails all face the center of the sarcomere, creating a zone around the M-line devoid of myosin heads. During systole, the myosin cross-bridges pull the thin filament "cage" toward the M-line, thus shortening the sarcomere length (additional details are in subsequent figures). (**A,** Redrawn, based on a classic sketch by Fawcett and McNutt [J Cell Biol 1969;42:1-45].)

TABLE 22.1

Characteristics of Cardiac Cells, Organelles, and Contractile Proteins

MICROANATOMY OF HEART CELLS			
	Ventricular Myocyte	**Atrial Myocyte**	**Purkinje Cells**
Shape	Long and narrow	Elliptical	Long and broad
Length (μm)	75-170	20-100	150-200
Diameter (μm)	15-30	5-6	35-40
Volume (μm^3)	15,000-100,000	400-1500	135,000-250,000
T tubules	Plentiful	Rare or none	Absent
Intercalated disc	Prominent end-to-end transmission	Side-to-side as well as end-to-end transmission	Very prominent abundant gap junctions Fast; end-to-end transmission
General appearance	Mitochondria and sarcomeres very abundant Rectangular branching bundles with little interstitial collagen	Bundles of atrial tissue separated by wide areas of collagen	Fewer sarcomeres, paler

COMPOSITION AND FUNCTION OF VENTRICULAR CELL		
Organelle	**Percentage of Cell Volume**	**Function**
Myofibril	≈50-60	Interaction of thick and thin filaments during contraction cycle
Mitochondria	16 in neonate 33 in adult rat 23 in adult man	Provide ATP chiefly for contraction
T-system	≈1	Transmission of electrical signal from sarcolemma to cell interior
SR	10 in neonate 2-3 in adult	Takes up and releases Ca^{2+} during contraction cycle
SR terminal cisternae	0.33 in adult	Site of calcium storage and release
Rest of network of SR	Rest of volume	Site of calcium uptake en route to cisternae
Sarcolemma	Very low	Control of ionic gradients, channels for ions (action potential), maintenance of cell integrity, receptors for drugs and hormones
Nucleus	≈3	Transcription
Lysosomes	Very low	Intracellular digestion and proteolysis
Sarcoplasm (= cytoplasm) (includes myofibril but not mitochondria or SR)	~60	Cytosolic volume within which $[Ca^{2+}]_i$ rises and falls

ATP, Adenosine triphosphate; *SR,* sarcoplasmic reticulum.

Ventricular myocytes are roughly brick shaped, typically 150 × 20 × 12 μm (**Table 22.1**), and are connected at the long ends by specialized junctions that mechanically and electrically couple the myocytes with each other (**Fig. 22.2**). Atrial myocytes are smaller and more spindle shaped (<10 μm in diameter and <100 μm in length). When examined under a light microscope, atrial and ventricular myocytes have cross striations and are often branched. Each myocyte is bounded by a complex cell membrane, the *sarcolemma* (*sarco*, "flesh"; *lemma*, "thin husk"), and is filled with rodlike bundles of *myofibrils* containing the contractile elements. The sarcolemma invaginates to form an extensive transverse tubular network (*T tubules*) that extends the extracellular space into the interior of the cell (**see Figs. 22.1 and 22.2**). Ventricular myocytes are typically binucleate, and these nuclei contain most of the cell's genetic information. Some myocytes have one or three to four nuclei. Rows of mitochondria are located between the myofibrils and also immediately beneath the sarcolemma. Mitochondria function mainly to generate the energy, in the form of adenosine triphosphate (ATP), that is needed to maintain cardiac contractile function and the associated ion gradients. The *sarcoplasmic reticulum* (SR) is a specialized form of

endoplasmic reticulum that is critical for calcium (Ca^{2+}) cycling, which is the on-off switch for contraction. When the wave of electrical excitation reaches the T tubules, voltage-gated Ca^{2+} channels open to provide relatively small entry of Ca^{2+}, which triggers additional release of Ca^{2+} from the SR via closely apposed Ca^{2+} release channels. This is the Ca^{2+} that initiates myocardial contraction. Ca^{2+} sequestration by the SR and extrusion from the myocyte causes relaxation (diastole).

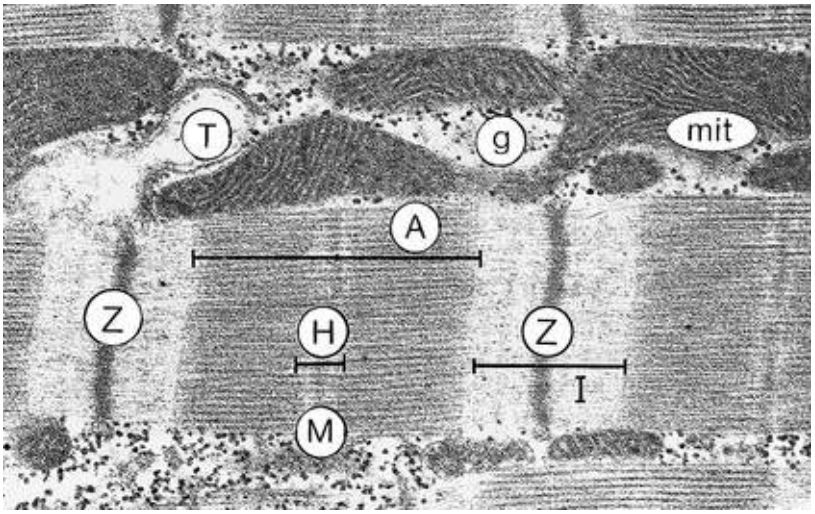

FIGURE 22.2 The sarcomere is the distance between the two Z-lines. Note the presence of numerous mitochondria (*mit*) sandwiched between the myofibrils and the presence of T tubules (*T*), which penetrate into the muscle at the level of the Z-lines. This two-dimensional picture should not disguise the fact that the Z-line is really a "Z-disc," as is the M-line (*M*), also shown in **Fig. 22.1**. *A,* Band of actin-myosin overlap; *g,* glycogen granules; *H,* central clear zone containing only myosin filament bodies and the M-line; *I,* band of actin filaments, titin, and Z-line (rat papillary muscle, 32,000×). (Courtesy Dr. J. Moravec, Dijon, France.)

Anatomically, the SR is a lipid membrane–bounded, fine interconnected network spreading throughout the myocytes. The *Ca^{2+} release channels* (or *ryanodine receptors* [RyRs]) are concentrated at the part of the SR that is in very close apposition to the T tubular Ca^{2+} channel. These are called *terminal cisternae* ("boxes" or "baskets," Latin) or the *junctional sarcoplasmic reticulum* (jSR). The second part of the SR, the *longitudinal*, *free*, or *network sarcoplasmic reticulum*, consists of ramifying tubules that surround the myofilaments (**see Fig. 22.1**) that take Ca^{2+} back up into the SR and thus drive relaxation. Such Ca^{2+} uptake is achieved by the ATP-consuming Ca^{2+} pump known as *SERCA* (sarcoendoplasmic reticulum Ca^{2+}–adenosine triphosphatase, or SR Ca-ATPase). The Ca^{2+} taken up into the SR is then stored at high concentration, in part bound to Ca^{2+}-buffering proteins, including *calsequestrin*, before being released again in response to the next wave of depolarization. *Cytoplasm* or *sarcoplasm* refers to the intracellular fluid and proteins therein, but excludes the contents of organelles such as the mitochondria, nucleus, and SR. The cytoplasm is crowded with myofilaments, but this is the fluid within which the concentration of Ca^{2+} rises and falls to cause cardiac contraction and relaxation.

Subcellular Microarchitecture

The molecular signal systems that convey messages from surface receptors to intracellular organelles may be directed to specific sites by molecules that "anchor" components of the signaling cascades to specific loci, such as around beta-adrenergic receptors and Ca^{2+} channels at the T tubule–SR junction and *caveolae* (small, flask-shaped sarcolemmal invaginations). *Scaffolding proteins* such as caveolin or the RyR itself bring interacting molecules closely together at these locations. These complexes can also release components that translocate and signal elsewhere in the cell, such as the nucleus, where they can

signal for myocyte growth. Another type of subcellular shuttling is involved in transporting the ATP produced in mitochondria to sites where it is used (e.g., myofilaments), which is facilitated by the location of creatine kinase, an enzyme that converts creatine phosphate to ATP.

Mitochondrial Morphology and Function

The typical ventricular myocyte has approximately 8000 mitochondria, each of which is ovate with a long axis measuring 1 to 2 μm and short axis of 300 to 500 nm. Mitochondria have two membranes: outer and inner mitochondrial membranes (OMM and IMM; **Fig. 22.3**). The IMM is "crumpled" into folds called *cristae,* which provide a large surface area within a small volume. The IMM also contains the cytochrome complexes that make up the respiratory chain, including F_0-F_1 ATP synthase. The space within the IMM, the mitochondrial matrix, contains enzymes of the tricarboxylic acid (TCA) cycle and other key metabolic components. These components provide reducing equivalent protons that are pumped out of the matrix by the cytochromes, and it is this proton pumping that creates the very negative voltage with respect to cytosol (Ψ_m = −180 mV). The proton pumping out of the matrix also creates a trans-IMM [H^+] gradient, which together with the very negative Ψ_m creates a strong electrochemical gradient for protons to enter the matrix. The energy from this "downhill" proton flux is used by the F_0-F_1 ATP synthase to make ATP. However, in the absence of the normal proton and Ψ_m, this elegant F_0-F_1 ATP synthase runs backward, consuming ATP. The ATP produced in the matrix is transported across the IMM by an adenine nucleotide transporter that exchanges mitochondrial ATP for cytosolic adenosine diphosphate (ADP). This system is exquisitely regulated to maintain cytosolic [ATP] and [ADP] [concentration] constant during dramatic changes in cardiac workload.[5] The multiple control mechanisms involved in this process are not fully understood, but one is relevant to excitation-contraction coupling. Increased cardiac work in a physiologic setting is usually driven by higher-amplitude and/or more frequent Ca^{2+} transients. This elevation in average intracellular [Ca^{2+}] ($[Ca^{2+}]_i$) also increases mitochondrial matrix [Ca] ($[Ca^{2+}]_m$), which activates key dehydrogenases in the TCA cycle and also pyruvate dehydrogenase to restore levels of reduced nicotinamide adenine dinucleotide (NADH), which drives cytochrome activity and helps restore [ATP] toward normal.

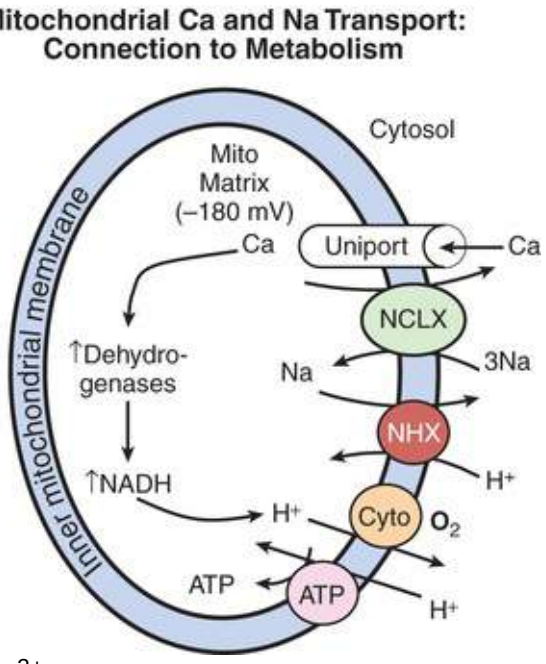

FIGURE 22.3 Mitochondrial Ca^{2+} regulation. The intramitochondrial matrix is very negative with respect to the cytosol (−180 mV). Ca^{2+} enters mitochondria via the Ca^{2+} uniporter in the inner mitochondrial membrane and is extruded by Na^+/Ca^{2+} exchange (*NCLX*). Na^+ is extruded via Na^+/H^+ exchange (*NHX*). Protons (H^+) are pumped out of mitochondria by the cytochrome (*Cyto*) systems, thereby allowing H^+ to enter via F_0-F_1 ATP synthase (*ATP*). When mitochondrial $[Ca^{2+}]$ is increased, it activates mitochondrial dehydrogenases, which increase NADH levels and provide additional reducing equivalent protons to the electron transport chain. (Modified from Bers DM. Excitation-Contraction Coupling and Cardiac Contractile Force. Dordrecht, Netherlands: Kluwer Academic; 2001.)

This raises the issue of how mitochondria regulate $[Ca^{2+}]_m$, because there is also a huge electrochemical gradient favoring entry of Ca^{2+} into mitochondria.[2] Indeed, $[Ca^{2+}]_m$ is typically similar to $[Ca^{2+}]_i$ and is kept at that level by a mitochondrial Na/Ca exchanger (NCLX), which uses the also steep Na^+ electrochemical gradient to pump Ca^{2+} out of the mitochondria.[2] However, this would load the mitochondria with Na^+, so Na^+ must also be extruded from the mitochondria. This is accomplished by the mitochondrial Na/H exchanger in the IMM, but a consequence is that this influx of H^+ costs energy. That is, these protons could have entered the mitochondria via the F_0-F_1 ATP synthase making ATP, but instead they were used to extrude Na^+ and Ca^{2+}. Thus in a sense the mitochondrion can make ATP or extrude Ca^{2+}. This becomes important when myocytes (or other cells) experience Ca^{2+} overload. In the short term, mitochondria can take up large amounts of Ca^{2+} to protect the cell from short-term Ca^{2+} overload, but chronic high $[Ca^{2+}]_i$ has dire consequences. First, this Ca^{2+} uptake can diminish Ψ_m and occurs at the expense of ATP production (as noted), thus hampering energetic recovery from such stress. Second, elevated $[Ca^{2+}]_i$ and $[Ca^{2+}]_m$ can facilitate opening of the mitochondrial permeability transition pore, which immediately wipes out Ψ_m and allows the matrix contents to be released to the cytosol. This can be the death knell for individual mitochondria, as well as the cells that rely on their function.

Thus, mitochondria can rapidly become agents of cell death as just described, as well as by producing excessive reactive oxygen species (ROS), which can promote necrotic cell death through the mitochondrial permeability transition pore and release of proapoptotic proteins[6] (**see Chapter 23**). Mitochondria can also induce mitochondrial autophagy, or *mitophagy*, which selectively and adaptively clears damaged mitochondria. Increased oxidative stress and apoptotic proteases can inactivate mitophagy and thereby cause cell death.[7]

Contractile Proteins

The two chief contractile proteins are the motor protein *myosin* on the thick filament and *actin* on the thin filament (**see Figs. 22.1 and 22.2**). Ca^{2+} initiates the contraction cycle by binding to the thin filament regulatory protein *troponin C* to relieve the inhibition otherwise exerted by this troponin complex (**Fig. 22.4**). The thin actin filaments are connected to the *Z-lines* (Z for German *Zuckung*, "contraction") at either end of the *sarcomere*, which is the functional contractile unit that is repeated through the filaments. The sarcomere is limited on either side by a Z-line, which with the thin filaments creates a "cage" around the thick myosin filament that extends from the center of the sarcomere outward toward, but not reaching, the Z-line. During contraction, the myosin heads grab onto actin and pull the actin filaments toward the center of the sarcomere. The thin and thick filaments can thus slide over each other to shorten the sarcomere and cell length, without the individual actin or myosin molecules actually changing length (**Fig. 22.1B**). The interaction of the myosin heads with actin filaments that is switched on when Ca^{2+} arrives is called *cross-bridge cycling*. As the actin filaments move inward toward the center of the sarcomere, they draw the Z-lines closer together so that the sarcomere length shortens. The energy for contraction is provided by breakdown of ATP (myosin is an ATPase).

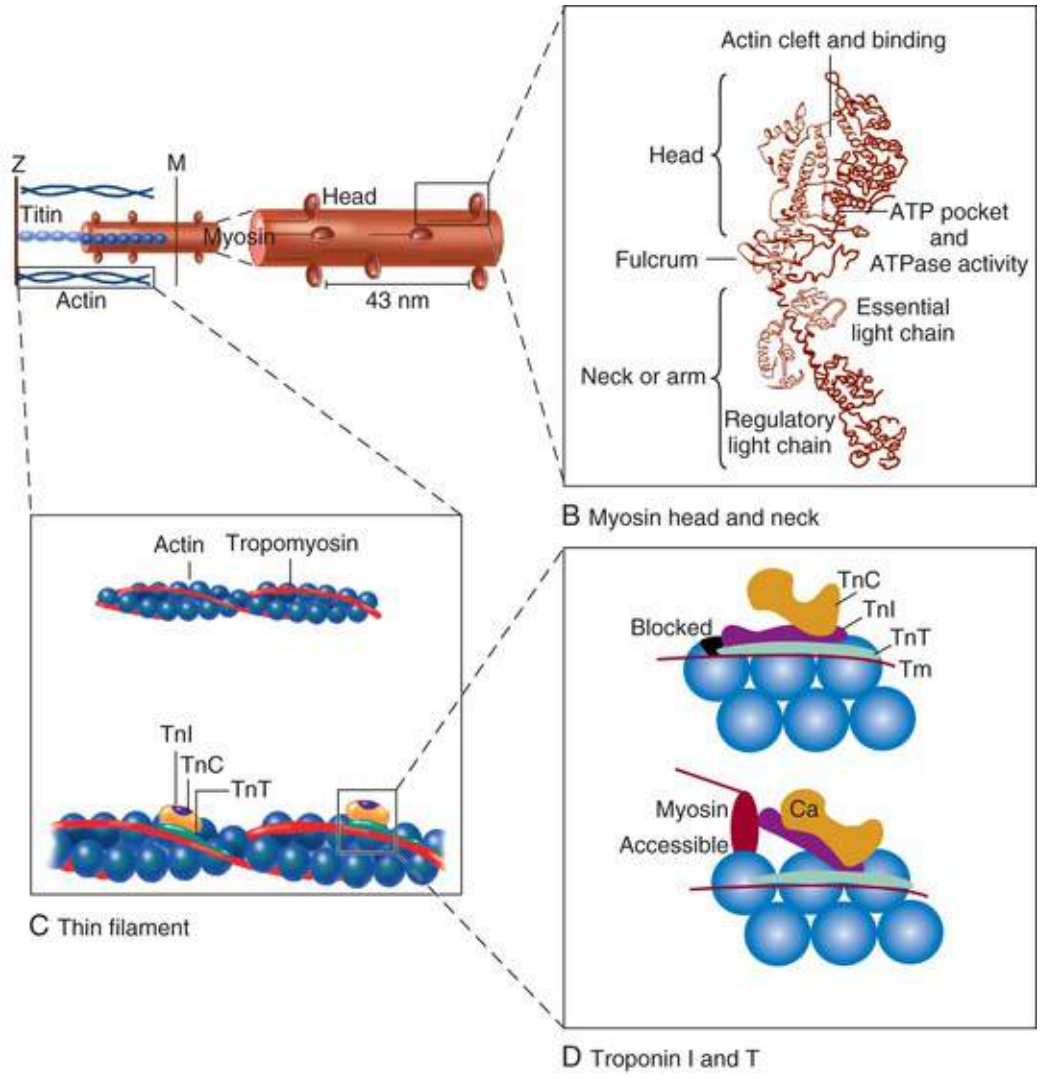

FIGURE 22.4 Key contractile protein interactions. The thin actin filament **(A)** interacts with the myosin head **(B)** when Ca^{2+} ions arrive at troponin C (*TnC*) **(C).** This causes troponin-tropomyosin shifts to expose the actin site to which a myosin head can attach. **A,** The thin actin filament contains TnC and its Ca^{2+} binding sites. When TnC is not activated by Ca^{2+}, troponin I (*TnI*) stabilizes troponin T (*TnT*) and tropomyosin (*Tm*) along the actin filament to block myosin cross-bridge binding **(D). B,** The molecular structure of the myosin head, based on Rayment and colleagues,[8] is composed of heavy and light chains. The heavy head chain in turn has two major domains: one of 70 kDa (i.e., 70,000 molecular weight) that interacts with actin at the actin cleft and has an ATP binding pocket. The "neck" domain of 20 kDa, also called the "lever," is an elongated alpha helix that extends and bends and has two light chains surrounding it as a collar. The essential light chain is part of the structure. The other regulatory light chain may respond to phosphorylation to influence the extent of the actin-myosin interaction. **C,** TnC with sites in the regulatory domain for activation by calcium and for interaction with TnI. **D,** Binding of calcium to TnC causes TnI to shift binding from TnT to TnC, allowing the TnT-Tm complex to shift deeper into the actin groove and expose the myosin binding domain on actin. (Modified from Opie LH. Heart Physiology, from Cell to Circulation. Philadelphia: Lippincott Williams & Wilkins; 2004. Figure copyright L. H. Opie, © 2004. **D,** Modified from Solaro RJ, Van Eyk J. Altered interactions among thin filament proteins modulate cardiac function. J Mol Cell Cardiol 1999;28:217.)

Titin and Length Sensing

Titin is a giant molecule, the largest protein yet described. It is extraordinarily long, elastic, and slender (**Fig. 22.5**). Titin extends from the Z-line into the thick filament, approaching the M-line, and connects the thick filament to the Z-line (**see Fig. 22.1**). Titin has two distinct segments: an inextensible anchoring segment and an extensible elastic segment that stretches as sarcomere length increases. Thus the titin molecule can stretch between 0.6 and 1.2 μm in length and has multiple functions. First, it tethers myosin and thick filaments to the Z-line, thereby stabilizing sarcomeric structure. Second, as it stretches and

relaxes, its elasticity contributes to the stress-strain relationship of cardiac and skeletal muscle. At short sarcomere lengths, the elastic domain is coiled up on itself to generate restoring force (**Fig. 22.5**), similar to a spring, helping to relengthen the sarcomere and aid early diastolic filling. These changes in titin help explain the *series elastic element* that was inferred from mechanics studies as elasticity in series with the myosin filaments. Third, the increased diastolic stretch of titin as the length of the sarcomere in cardiac muscle is increased causes the enfolded part of the titin molecule to straighten. This stretched molecular spring then limits overstretching of sarcomeres and end-diastolic volume and returns some potential energy during systole as the sarcomeres shorten during cardiac ejection.[4] Fourth, titin may transduce mechanical stretch into growth signals. Sustained diastolic stretch, as in volume overload, can cause titin-dependent signaling to muscle LIM protein (MLP) attached to the Z-line end of titin.[8] MLP is proposed to be a stretch sensor that transmits the signals that result in the myocyte growth pattern characteristic of volume overload, and it may be defective in a subset of human dilated cardiomyopathy.[9]

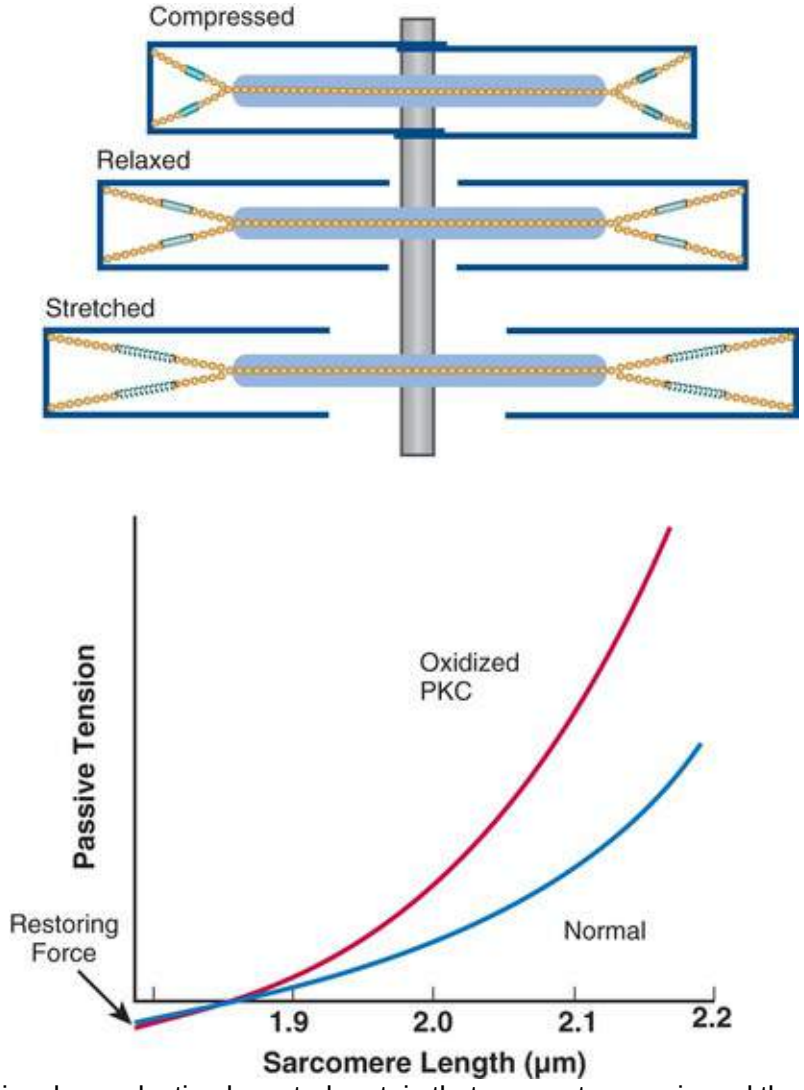

FIGURE 22.5 Titin is a huge elastic elongated protein that connects myosin and the M-line to the Z-line. It is a bidirectional spring that develops passive force in stretched sarcomeres and resting force in shortened sarcomeres. **Upper panel,** As the sarcomere is stretched to its maximum physiologic diastolic length of 2.2 μm, titin stretches and increases passive force generated (contributing to end-diastolic pressure). At short lengths (*top*), which may reflect end-systole, substantial restoring force is generated **(lower panel).** (Modified with permission of the American Heart Association, from Lewinter MM, Granzier HL. Titin is a major human disease gene. Circulation 2013;127:938-44.)

Molecular Basis of Muscular Contraction

Although the molecular level details underlying the cross-bridge cycle are complex, cross bridges appear to exist in either a strong or a weak binding state. During diastole, myosin heads normally have ATP bound (**Fig. 22.6B**) and hydrolyzed to ADP plus inorganic phosphate (P_i), although ADP-P_i is not yet released and the energy of ATP is not yet fully consumed (**Fig. 22.6C**). Thus the cross bridges are poised and ready to bind to actin. This interaction is permitted when Ca^{2+} arrives and binds to troponin C, shifting the position of the troponin-tropomyosin complex on the actin filament (**see Fig. 22.4C, D**). This enables the poised myosin heads to form strong binding cross bridges with actin molecules (**Fig. 22.6D**) and use the energy stored in myosin-ADP-P_i to rotate the myosin head while bound to actin in the *power stroke* (and release P_i) while still in the strong binding state (**Fig. 22.6D, E**). Once a particular cross bridge proceeds through the power stroke (using the energy previously stored in the ATP molecule), it will remain in the strong binding or *rigor* state (**Fig. 22.6A**) until ATP binds again to myosin, causing a shift back to the weak binding state and allowing cross-bridge detachment and ATP hydrolysis (**Fig. 22.6C**). As long as $[Ca^{2+}]_i$ and [ATP] remain high, the cycle can continue with myosin-ADP-P_i binding to a new actin molecule. The weak binding state predominates when $[Ca^{2+}]_i$ falls and Ca^{2+}dissociates from troponin C, allowing relaxation during diastole. If intracellular [ATP] declines too far (e.g., during ischemia), ATP cannot bind and disrupt the rigor linkage, leaving cross bridges locked in the strong binding state (as in rigor mortis).

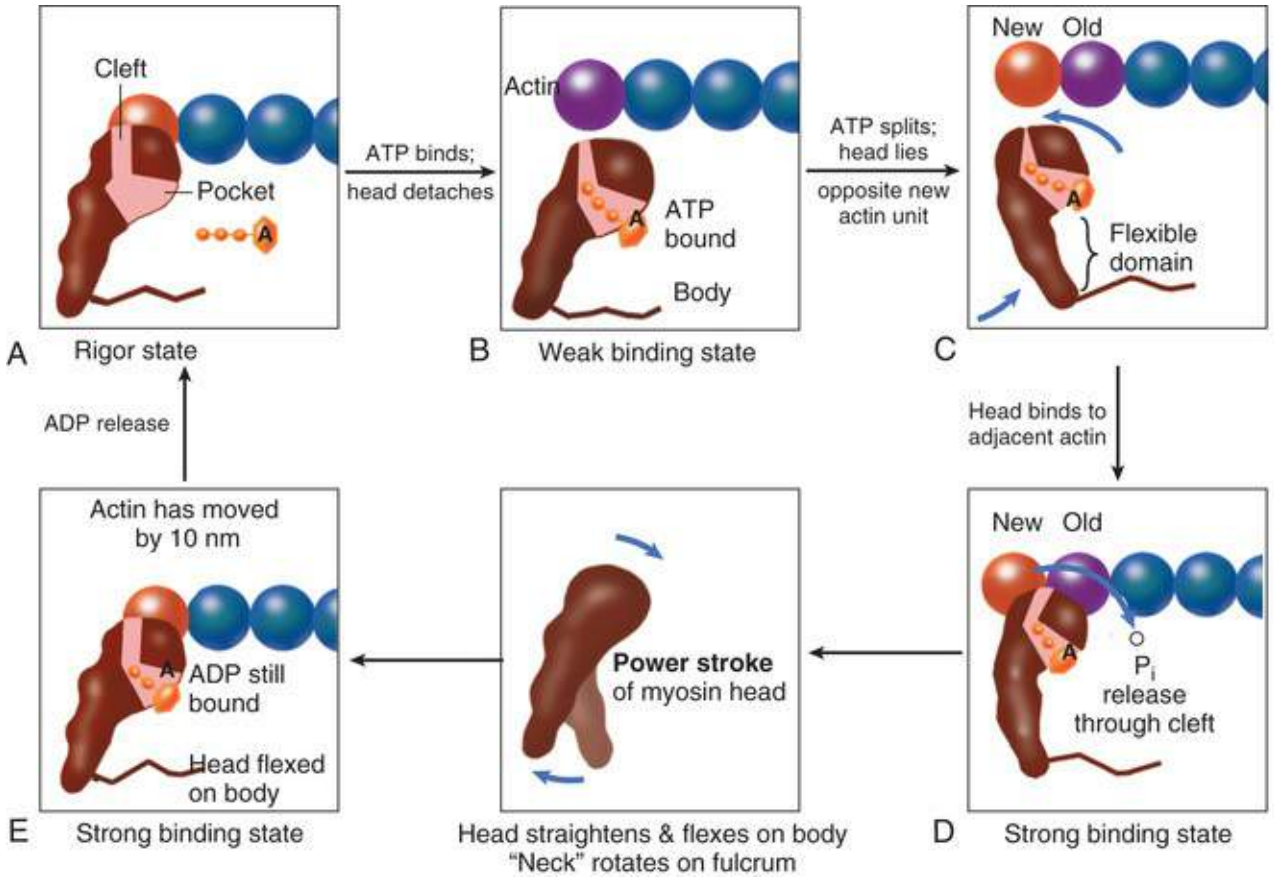

FIGURE 22.6 Cross-bridge cycling molecular model. The cross-bridge (only one myosin head depicted) is pear shaped, and the catalytic motor domain interacts with the actin molecule and is attached to an extended alpha helical "neck region," which acts as a lever arm. The nucleotide pocket that binds ATP is in the catalytic domain. The actin binding cleft bisects the catalytic motor domain. Starting with the rigor state **(A),** binding of ATP to the pocket **(B)** is followed by ATP hydrolysis **(C)**, which alters the actin binding domain, favoring release from actin. The binding to actin is enhanced when phosphate is released, and the myosin head strongly attaches to actin to induce the power stroke **(D, E).** During the power stroke the head rotates around the head-neck fulcrum. As the head flexes, the actin filament can be displaced by ~10 nm **(E),** causing shortening (although during isometric contraction the neck region stretches and bears force). In this process, ADP is also released, so the binding pocket becomes vacant, resulting in the rigor state again **(A)** until ATP binds to release the cross bridge.

Actin and Troponin Complex

The Ca^{2+} on-switch of cross-bridge cycling is mediated by a series of interactions within the troponin, tropomyosin, and actin complex (**see Fig. 22.4C, D**). Thin filaments are composed of two helical intertwining actin filaments, with a long tropomyosin molecule that spans seven actin monomers located in the groove between the two actin filaments. Also, at every seventh actin molecule (38.5 nm along this structure) there is a three-protein regulatory *troponin complex:* troponin C (Ca^{2+} binding), I (inhibitory), and T (tropomyosin binding).

When $[Ca^{2+}]_i$ is low, the position of tropomyosin blocks the myosin heads from interacting effectively with actin. As a result, most cross bridges are in the "blocked position," with a few visiting the weak binding state. Ca^{2+} binding with troponin C causes troponin C to bind more tightly to troponin I (**see Fig. 22.4D**), which allows tropomyosin to roll deeper into the thin filament groove,[1] thereby opening access to allow myosin binding to actin. This allows the cross-bridge cycle to proceed (**see Fig. 22.6**). As they form, strong cross bridges can nudge tropomyosin deeper into the actin groove, allowing cross-bridge attachment at one site to enhance actin-myosin at its "nearest-neighbor" sites. This cooperatively spreads activation farther along the myofilaments.[1,4]

Myosin Structure and Function

Each myosin head is the terminal part of the myosin heavy chain molecule. The other ends of two myosin molecules (tails) intertwine as a coil that forms the bulk of the thick filament. Also, a short "neck" leads to the myosin head that protrudes out from the filament (**see Fig. 22.4**). According to the Rayment model, the base of the head and/or neck region changes configuration during the power stroke previously described.[8] Each head has an *ATP-binding pocket* and a narrow cleft that extends from the base of this pocket to the actin-binding face[10] (**see Fig. 22.6**). During the power stroke when there is no mechanical load on the muscle, the myosin head flexes and can move the actin filament by approximately 10 nm.[1] When the pocket releases ADP and binds ATP, the cross bridge releases back to an orientation more perpendicular to the direction of the thin and thick filaments. During isometric (or isovolumic) contraction, the cross bridges rotate but cannot fully move the actin filament, and the stretched strong binding cross bridges bear force. During shortening (ejection), the actin filament moves during the power stroke, accompanied by decreases in sarcomere length and ventricular volume.

Note that myosin heads stick out from the thick filament in six directions in an organized array to allow interactions with each of six actin filaments that surround each thick filament (**see Fig. 22.1**). The myosin molecules are also oriented in reversed longitudinal directions on either side of the M-line (which itself contains only myosin tails), such that each side is trying to pull the Z-lines toward the center. That is, when cross bridges are in the strong binding or rigor linkages, they form "chevrons" (or arrows) pointing toward the Z-line on that side of the M-line.

Each cycle of the cross bridge consumes one molecule of ATP, and this *myosin ATPase activity* is the major site of ATP consumption in the beating heart. Thus, when the heart is more strongly activated, the level of ATP consumption is similarly increased. The two myosin heads that stick out from an intertwined pair of myosin molecules seem to work through a hand-over-hand action such that the myosin dimer never fully releases the thin filament during the activation period.[11] There are also two main myosin isoforms in cardiac myocytes, alpha and beta, which have similar molecular weight but exhibit substantially different cross-bridge cycle and ATPase rates. The beta-myosin heavy chain (β-MHC) isoform exhibits a slower ATPase rate and is the predominant form in adult humans. In small mammals (rats and mice), the faster α-MHC form normally predominates but shifts to the β-MHC pattern during chronic stress and heart failure.[4]

Each myosin molecule neck also has two light chains (**see Fig. 22.4A**). The *essential myosin light chain* (MLC-1) is more proximal to the myosin head and may limit the contractile process by interaction with actin. The *regulatory myosin light chain* (MLC-2) is a potential site for phosphorylation (e.g., in response to beta-adrenergic stimulation) and may promote cross-bridge cycling.[12] In vascular smooth muscle, which lacks the troponin-tropomyosin complex, contraction is activated by the Ca^{2+}-dependent *myosin light chain kinase* (MLCK) rather than by Ca^{2+} binding to troponin C (as in striated muscle). Myosin-binding protein C appears to traverse the myosin molecules in the A-band, thereby potentially tethering the myosin molecules and stabilizing the myosin head with respect to the thick and thin filaments. Defects in myosin, myosin-binding protein C, and several other myofilament proteins are genetically linked to familial hypertrophic cardiomyopathy.[13]

Graded Effects of $[Ca^{2+}]_i$ on Cross-Bridge Cycle

The myofilaments are activated in a graded rather than all-or-none manner as a function of $[Ca^{2+}]_i$ (**Fig. 22.7**). The dynamics and regulation of Ca^{2+} transients in cardiac myocytes are discussed in the following section, but a major physiologic mechanism for regulating cardiac contractility (e.g., during sympathetic

activity) is to increase peak $[Ca^{2+}]_i$ and more fully activate the myofilaments. The higher the $[Ca^{2+}]_i$, the more fully saturated are the Ca^{2+} binding sites on troponin C, and consequently, more sites are available for cross bridges to form. When more cross bridges are working in parallel, the myocyte (and heart) can develop greater force. There is high cooperativity in this process, in large part because of the "nearest-neighbor" effect mentioned earlier. That is, Ca^{2+} bound to a single troponin C molecule encourages local cross-bridge formation, and both Ca^{2+} binding and cross-bridge formation directly enhance the likelihood of cross-bridge formation in the seven actin molecules controlled by one tropomyosin molecule. Furthermore, the openness of that domain directly enhances that of the neighboring domain with respect to both Ca^{2+} binding and cross-bridge formation. This cooperativity means that a small change in $[Ca^{2+}]_i$ can have a great effect on the strength of contraction.

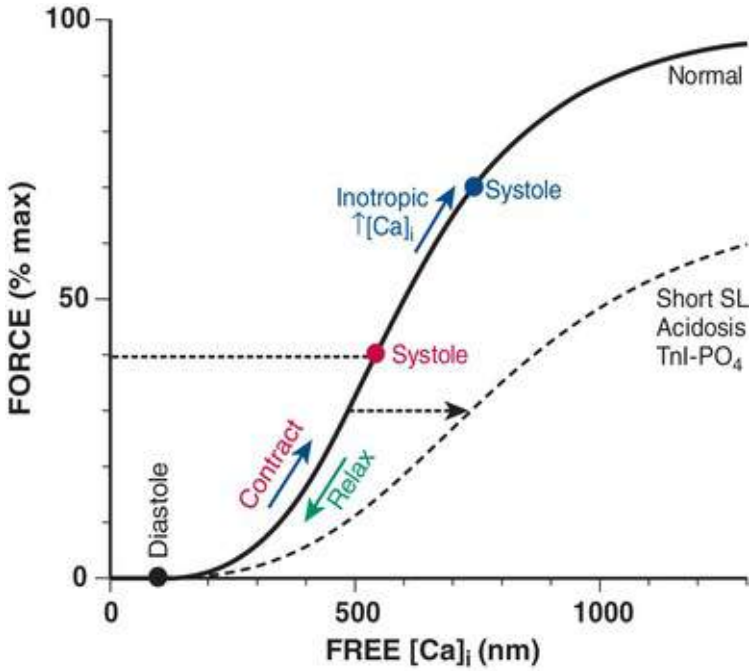

FIGURE 22.7 Myofilament Ca^{2+} sensitivity. Active force development in cardiac muscle depends on the cytosolic free $[Ca]_i$. As $[Ca]_i$ rises during systole, force develops as dictated by the sigmoidal myofilament Ca^{2+} sensitivity curve (*solid curve*; Force = 100/(1+ [600 nm]/$[Ca]_i)^4$). As $[Ca]_i$ declines relaxation ensues and force declines. If peak $[Ca]_i$ increases (as in inotropy) the peak force can reach a higher value. At shorter sarcomere length (SL), acidosis, and troponin I (TnI) phosphorylation, the myofilament Ca^{2+} sensitivity is reduced, and the former two also decrease maximal force (*dashed curve*).

Length-Dependent Activation and the Frank-Starling Effect

Besides $[Ca^{2+}]_i$, the other major factor influencing the strength of contraction is *sarcomere length* at the end of diastole (preload), just before the onset of systole. Both Otto Frank and Ernest Starling observed that the more the diastolic filling of the heart, the greater the strength of the heartbeat. The increased heart volume translates into increased sarcomere length, which acts by a length-sensing mechanism. A part of this *Frank-Starling effect* has historically been ascribed to increasingly optimal overlap between the actin and myosin filaments. Clearly, however, there is also a substantial increase in myofilament Ca^{2+} sensitivity with an increase in sarcomere length (**Fig. 22.7**).[1] A plausible mechanism for this regulatory change may reside in the decreasing interfilament spacing as heart muscle is stretched. That is, the myocyte is at constant volume (over the cardiac cycle), so as the cell shortens, it must thicken, and

conversely, when it is stretched, the cell becomes thinner and filament spacing becomes narrower. This attractive lattice-dependent explanation for the Frank-Starling relationship has been challenged by careful x-ray diffraction studies,[4] which found that reducing sarcomere lattice spacing by osmotic compression failed to influence myofilament Ca^{2+} sensitivity. Although several mechanisms could contribute to myofilament Ca^{2+} sensitization at longer sarcomere length, the issue is unresolved.

When changes in diastolic length (or preload) are the cause of altered contractile strength, it is said to be a Frank-Starling (or Starling) effect. Conditions in which contraction is strengthened independent of sarcomere length (e.g., typically by increased Ca^{2+} transient amplitude) are referred to as positive *inotropic states* or enhanced *contractility*. The distinction between these heterometric (Starling) and homeometric (inotropic) mechanisms of altered cardiac strength is functionally and therapeutically important.

Cross-Bridge Cycling Differs From Cardiac Contraction-Relaxation Cycle

The cardiac cycle of Wiggers (see later) must be distinguished from the cross-bridge cycle. The cardiac cycle reflects the overall changes in pressure in the left ventricle, whereas the cross-bridge cycle is the repetitive interaction between myosin heads and actin. During isovolumic contraction (before aortic valve opening), the sarcomeres do not shorten appreciably, but cross bridges are developing force, although not all simultaneously. That is, at any given moment, some myosin heads will be flexing or flexed (resulting in force generation), some will be extending or extended, and some will be attached weakly to actin and some detached from actin. Numerous such cross-bridge cycles, each lasting microseconds, are integrated to produce the resulting force (and pressure). When ventricular pressure (sum of cross-bridge forces) reaches aortic pressure (afterload), ejection begins and is associated with the cross bridges actively moving the thin actin filaments toward the central of the sarcomere (M-line), thereby shortening the sarcomere. Note that as ejection proceeds (and sarcomeres shorten), myofilament Ca^{2+} sensitivity declines (**see Fig. 22.7**). Thus, both $[Ca^{2+}]_i$ decline and shortening cause a progressive decline in the contractile state as systole gives way to diastole. Both the Ca^{2+} transient properties and the myofilament Ca^{2+} sensitivity and cross-bridge cycling rate are altered under physiologic conditions, such as sympathetic stimulation and local acidosis or ischemia, as discussed later.

Force Transmission

Volume and pressure overload may have different effects on myocardial growth because of different patterns of force transmission.[4] Whereas increased diastolic force is transmitted longitudinally by titin to reach MLP, the postulated sensor (see earlier), increased systolic force may be transmitted laterally (i.e., at right angles) by the Z-disc and cytoplasmic actin to reach the cytoskeletal proteins and cell-to-matrix junctions, such as the focal adhesion complex. This mechanical force is translated into signals that activate the growth pathways, such as those leading to mitogen-activated protein kinase (MAPK) and altered gene regulation and cell size and shape, as addressed in other chapters.

Contractile Protein Defects and Cardiomyopathy.
Genetic-based hypertrophic and dilated cardiomyopathies not only produce hearts that look and behave very differently but also have diverse molecular causes. These cardiomyopathies in general are linked to mutant genes that cause abnormalities in the force-generating system, such as β-MHC, MLCs, myosin-binding protein C, troponin subunits, and tropomyosin (**see Chapter 77**). One hypothesis is that

mutations that increase myofilament calcium sensitivity, contractility, and energy demand result in concentric hypertrophy,[14] whereas mutations that reduce myofilament calcium sensitivity or force generation or that result in non–force-generating cytoskeletal proteins (e.g., dystrophin, nuclear lamin, cytoplasmic actin, titin) lead to a dilated cardiomyopathy. Although useful, such broad distinction between the two types of cardiomyopathy is oversimplified, with several examples of overlapping mechanisms.

Calcium Ion Fluxes in Cardiac Contraction-Relaxation Cycle

Calcium Movements and Excitation-Contraction Coupling

Ca^{2+} is a central regulator of cardiac contraction and relaxation. Details of the associated Ca^{2+} fluxes that link contraction to the wave of excitation (*excitation-contraction coupling*) are now reasonably well clarified and accepted.[1,2] Relatively small amounts of Ca^{2+} (*trigger* Ca^{2+}) enter and leave the cardiomyocyte during each cardiac cycle, with larger amounts being released and taken back up by the SR (**Fig. 22.8**). Each action potential depolarization traveling down the T tubules opens the voltage-gated L-type Ca^{2+} channels that are physically near the junctional SR, which is mainly in the T tubule, and activates SR Ca^{2+} release channels (RyRs). In this *Ca^{2+}-induced Ca^{2+} release* mechanism, a smaller amount of Ca^{2+} entering via the calcium current (I_{Ca}) triggers the release of a larger amount of Ca^{2+} into the cytosol.[1,4] In the human ventricle and large mammals, SR Ca^{2+} release is three to four times higher than Ca^{2+} influx by I_{Ca}. In rat and mouse myocytes, however, SR Ca^{2+} cycling is more than 10 times greater than sarcolemmal Ca^{2+} flux.[1] The combined Ca^{2+} release and influx elevates $[Ca^{2+}]_i$ and promotes binding of Ca^{2+} to troponin C and thus contractile activation.

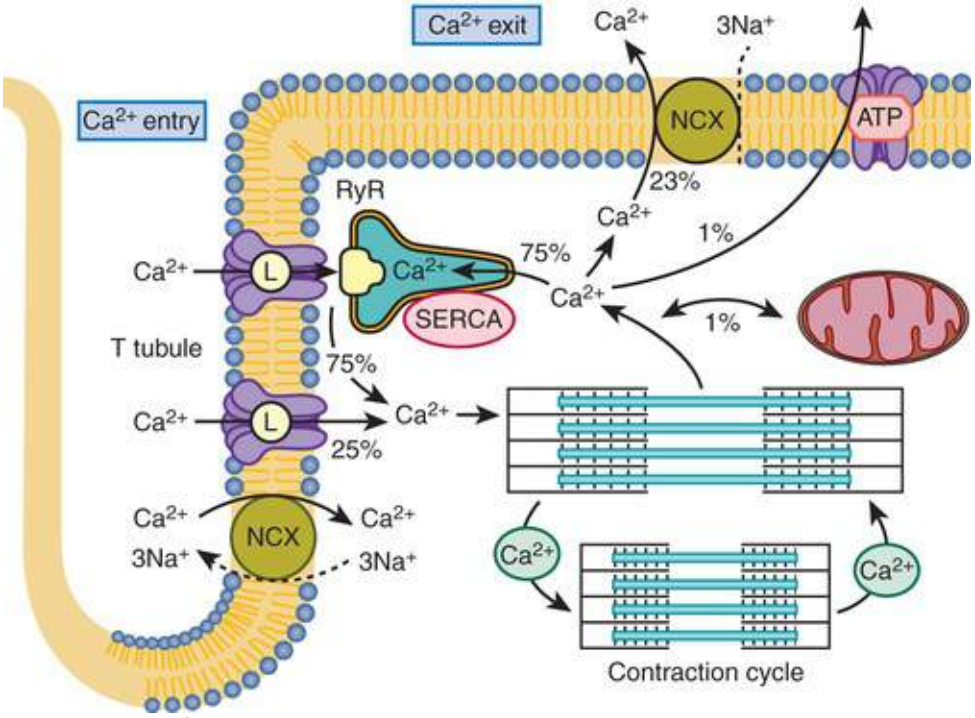

FIGURE 22.8 Myocyte Ca^{2+} fluxes during excitation-contraction (E-C) coupling. Crucial features are (1) Ca^{2+} entry via the voltage-activated L-type Ca^{2+} channels, which triggers release of more Ca^{2+} from the SR; (2) a tiny amount of Ca^{2+} may enter via Na^+/Ca^{2+} exchange early in the action potential; and (3) removal of Ca^{2+} ions from the cytosol is mainly via the SR Ca-ATPase (SERCA; 75%) and Na^+/Ca^{2+} exchange (24%), with tiny amounts transported by mitochondrial Ca^{2+} uniport and the sarcolemmal Ca-ATPase (1%). The sodium pump (Na^+/K^+-ATPase) extrudes the Na^+ ions that entered during Na^+ current and Na^+/Ca^{2+} exchange action. Note that extracellular and intra-SR [Ca^{2+}] (1-2 mm) is much higher than diastolic $[Ca^{2+}]_i$ (0.10 µm). Mitochondria can act as a buffer against excessive changes in cytosolic Ca^{2+}.
(Modified from diagram by Bers DM: Cardiac excitation-contraction coupling. Nature 2002;415:198.)

Calcium Release and Uptake by Sarcoplasmic Reticulum

Sarcoplasmic Reticulum Network and Ca^{2+} Movements

Electron and fluorescence microscopy studies show that the SR is a continuous network surrounding the myofilaments with connections across Z-lines and transversely between myofibrils. Moreover, the lumens of the entire SR network and nuclear envelope are connected in adult cardiac myocytes. This allows relatively rapid diffusion of Ca^{2+} within the SR to balance free [Ca^{2+}] within the SR ($[Ca^{2+}]_{SR}$).[15,16] The total SR Ca^{2+} content is the sum of $[Ca^{2+}]_{SR}$ plus Ca^{2+} bound to intra-SR Ca^{2+} buffers (especially calsequestrin). SR Ca^{2+} content is critical to normal cardiac function and electrophysiology, and its abnormalities contribute to systolic and diastolic dysfunction and arrhythmias. $[Ca^{2+}]_{SR}$ dictates the SR Ca^{2+} content and driving force for Ca^{2+} release and also regulates RyR release channel gating.[16]

Junctional Sarcoplasmic Reticulum and Ryanodine Receptor

The RyR channels that mediate SR release Ca^{2+} are mainly located in the jSR membrane at the junctions with the T tubule.[1] Each junction has 50 to 250 RyR channels on the jSR that are directly under a cluster of 20 to 40 sarcolemmal L-type Ca^{2+} channels across a 15-nm junctional gap (that is crowded with protein). RyR2 (the cardiac isoform) functions both as a Ca^{2+} channel and as a scaffolding protein that localizes numerous key regulatory proteins to the jSR.[1,4] On the large cytosolic side, these include proteins that can stabilize RyR gating (e.g., *calmodulin* [CaM], FK-506 binding protein [FKBP-12.6]);

kinases that can regulate RyR gating by phosphorylation (e.g., protein kinase A [PKA], *Ca^{2+}/CaM-dependent protein kinase II* [CaMKII]); and the protein phosphatases PP1 and PP2A, which dephosphorylate the RyR. Inside the SR, the RyR also couples to several proteins (e.g., junctin, triadin, and via these, calsequestrin) that similarly regulate RyR gating and, in the case of calsequestrin, provides a local reservoir of buffered Ca^{2+} close to the release channel. The actual RyR channel is made up of a symmetric tetramer of RyR molecules, each of which may have the aforementioned regulatory proteins associated with it. Thus the RyR receptor complex is very large (>7000 kDa; **Fig. 22.8**).[17] When the T tubule is depolarized, one or more L-type Ca^{2+} channels open, and local cleft [Ca^{2+}] increases sufficiently to activate at least one local jSR RyR (multiple channels here ensure high-fidelity signaling). The Ca^{2+} released from these first openings recruit additional RyRs in the junction through Ca^{2+}-induced Ca^{2+} release to amplify release of Ca^{2+} into the junctional space. The Ca^{2+} diffuses out of this space throughout the sarcomere to activate contraction. Each of the approximately 20,000 jSR regions in the typical ventricular myocyte seems to function independently in response to local activation by I_{Ca}. Thus the global Ca^{2+} transient in the myocyte at each beat is the spatiotemporal summation of SR Ca^{2+} release events from thousands of jSR regions, synchronized by the upstroke of the action potential and activation of I_{Ca}.

Turning Off Ca^{2+} Release: Breaking Positive Feedback

Ca^{2+}-induced Ca^{2+} release is a positive feedback process, but it is now known that SR Ca^{2+} release turns off when $[Ca]_{SR}$ drops by approximately 50% (i.e., from a diastolic value of 1 mM to a nadir of 400 µM).[14] Elegant studies have documented how I_{Ca} is inactivated by high local [Ca^{2+}], and this robust calcium-dependent inactivation is mediated by binding of Ca^{2+} to the CaM that is already associated with that channel. When Ca^{2+} binds to CaM, it alters channel conformation such that I_{Ca} inactivation is favored. I_{Ca} is also subject to voltage-dependent inactivation during the action potential plateau, and thus inactivation limits further entry of Ca^{2+} into the cell.

As for Ca^{2+}-dependent RyR activation, several mechanisms may contribute to breaking its inherent positive feedback. Although not necessarily most compelling, one mechanism is analogous to Ca^{2+}/CaM-dependent inactivation of I_{Ca}. That is, binding of Ca^{2+} to CaM that is prebound to RyR2 favors closure of RyR channels and inhibits reopening[18] (**Fig. 22.9**). A second mechanism, undoubtedly important, is that RyR2 gating is also sensitive to luminal $[Ca^{2+}]_{SR}$ such that high $[Ca^{2+}]_{SR}$ favors opening and low $[Ca^{2+}]_{SR}$ favors closure.[19] Indeed, release of Ca^{2+} from the SR during normal Ca^{2+} transients is robustly turned off when $[Ca^{2+}]_{SR}$ falls to approximately half its normal value (400 µM, which is still 500 times higher than bulk $[Ca^{2+}]_i$), almost regardless of the rate of SR Ca^{2+} release.[14,15] A third and related mechanism is that as Ca^{2+} release proceeds and $[Ca^{2+}]_{SR}$ declines, Ca^{2+} flux through the RyR falls and junctional [Ca^{2+}] also falls, all of which tend to disrupt the positive feedback. That is, the RyR is less sensitive to activating Ca^{2+} (because $[Ca^{2+}]_{SR}$ is low) and lower [Ca^{2+}] on the cytosolic side also activates more weakly.[20]

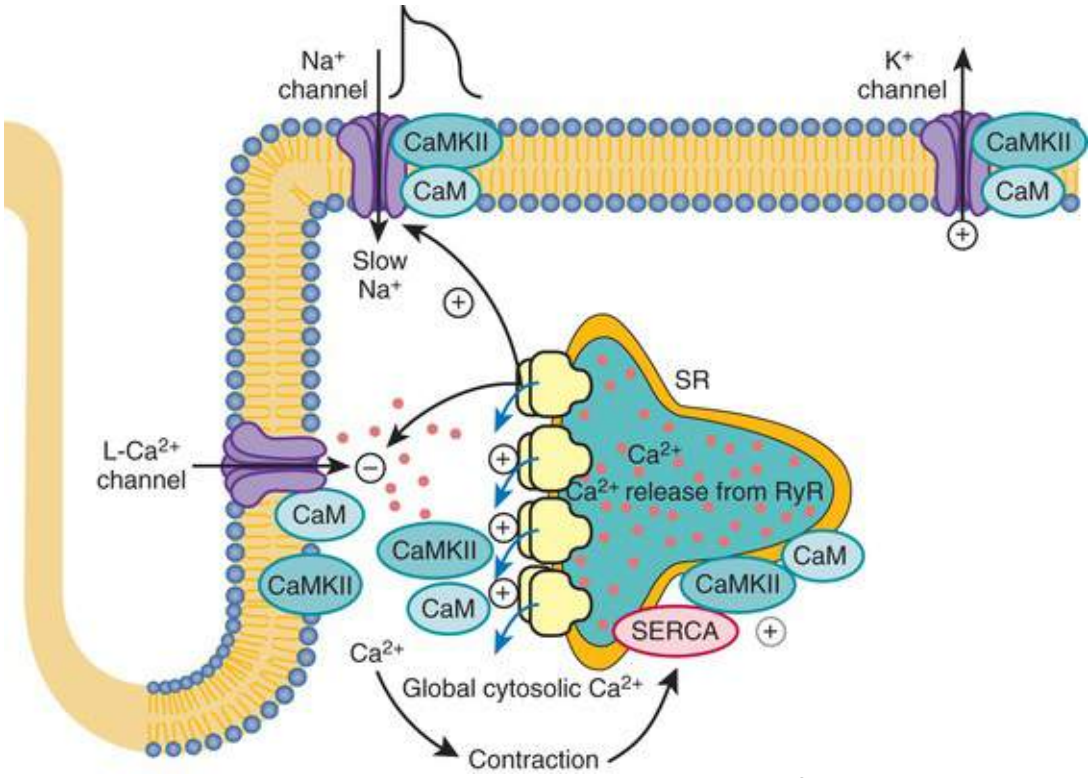

FIGURE 22.9 Role of CaM and CaMKII in regulating intracellular [Ca^{2+}]. The rising cytosolic Ca^{2+} concentration in systole activates the Ca^{2+} regulatory system whereby Ca^{2+}-CaM causes inactivation of L-type Ca^{2+} current and RyR release. This negative feedback system limits cellular Ca^{2+} gain. The effects of CaMKII can also modulate these systems.[21] For example, (1) CaMKII limits the extent of Ca^{2+}-dependent inactivation and enhances Ca^{2+} current amplitude, (2) it increases the fraction of SR Ca^{2+} released from the RyR in response to the Ca^{2+} current trigger (which can be arrhythmogenic), (3) it phosphorylates PLB to enhance SR Ca^{2+} uptake by SERCA, and (4) it can modulate Na^+ and K^+ channel gating in ways that are also proarrhythmic.[21,22]

Calmodulin: Versatile Mediator of Ca^{2+} Signaling.

CaM has four Ca^{2+}-binding sites, resembles troponin C, and participates in many different cellular pathways, from ion channels to transcriptional regulation.[18] In many cases (e.g., L-type Ca^{2+}, Na^+, and some K^+ channels; RyR and inositol 1,4,5-triphosphate receptors), CaM is already prebound or "dedicated" such that elevation of local $[Ca^{2+}]_i$ can rapidly induce Ca^{2+}-CaM effects on their targets[21,22] (**Fig. 22.9**). Indeed, more than 90% of the CaM in myocytes is already bound to cellular targets before Ca^{2+} binds to and activates it. Nevertheless, many myocyte CaM targets (e.g., CaMKII, calcineurin, nitric oxide synthase [NOS]) compete for this limited pool of "promiscuous" CaM. Thus, CaM signaling in myocytes is complex and is further complicated by the effects of CaMKII, which influences some of the same targets and processes as CaM itself does.[18,22]

Calcium Sparks and Waves.

In addition to SR Ca^{2+} release triggered by I_{Ca} during normal excitation-contraction coupling, there is a finite probability that a given RyR will open stochastically. Because of local Ca^{2+}-induced Ca^{2+} release in the junctional cleft, this can lead to spontaneous local SR Ca^{2+} release events known as Ca^{2+} *sparks*.[20,23] Under normal resting conditions, these Ca^{2+} sparks have a low probability (approximately 10^{-4}), which means that at any moment there might be one or two Ca^{2+} sparks per myocyte. Because local $[Ca^{2+}]_i$ declines rapidly as Ca^{2+} diffuses away from the initiating cleft, the resulting local $[Ca^{2+}]_i$ at the

next cleft (1 to 2 μm away) is normally too low to trigger that neighboring site. Thus, Ca^{2+} sparks are very local events (within 2 μm in the cell). However, the probability of Ca^{2+} sparks is greatly enhanced when $[Ca^{2+}]_i$ or $[Ca^{2+}]_{SR}$ is elevated or under conditions in which the RyR is otherwise sensitized (e.g., by oxidation or CaMKII). These conditions can greatly enhance the likelihood that SR Ca^{2+} release from one junction will be sufficient to trigger neighboring junctions 1 to 2 μm away and result in propagating Ca^{2+} waves throughout the whole myocyte. These Ca^{2+} waves can be arrhythmogenic. The Ca^{2+} wave can activate substantial inward current through Na^+/Ca^{2+} exchange (NCX; see later), which can depolarize the membrane potential and contribute to both early and delayed afterdepolarizations (EADs and DADs) during the action potential plateau or during diastole, respectively. EADs result in prolongation of the action potential duration, and DADs can initiate premature ventricular complexes (PVCs).

Calcium Uptake into Sarcoplasmic Reticulum by SERCA

Ca^{2+} is transported into the SR by SERCA, which constitutes almost 90% of the SR protein. Its molecular weight is 115 kDa, with 10 transmembrane domains and large cytosolic and small SR-luminal domains. Three isoforms exist, but in cardiac myocytes the dominant form is SERCA2a. For each molecule of ATP hydrolyzed by this enzyme, two calcium ions are taken up into the SR (**Fig. 22.10**; **see also Fig. 22.9**). SR Ca^{2+} uptake is the primary driver of cardiac myocyte relaxation, and reuptake starts as soon as $[Ca^{2+}]_i$ begins to rise. Because Ca^{2+} removal is slower than Ca^{2+} influx and release, a characteristic rise and fall in $[Ca^{2+}]_i$ called the Ca^{2+} *transient*, takes place. As $[Ca^{2+}]_i$ falls, Ca^{2+} dissociates from troponin C, which progressively switches off the myofilaments. A reduction in SERCA expression or function (as seen in heart failure or energetic limitations) can thus directly result in slower rates of cardiac relaxation. In addition, the strength of SR Ca^{2+} uptake directly influences the diastolic SR Ca^{2+} content and $[Ca^{2+}]_{SR}$, which dictates both the sensitivity of the RyR and the flux rate of SR Ca^{2+} release. Thus, SR Ca^{2+} uptake and release are an integrated system.

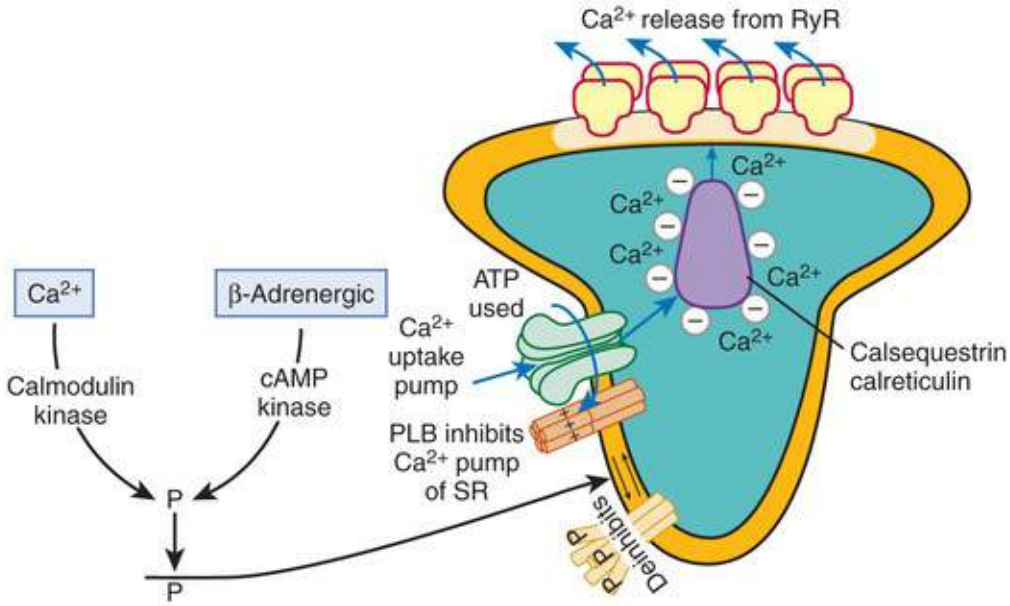

FIGURE 22.10 Ca^{2+} uptake into the SR by SERCA2a. An increased rate of uptake of Ca^{2+} into the SR enhances the rate of relaxation (*lusitropic effect*). PLB, when phosphorylated (*P*), removes the inhibition exerted on the Ca^{2+} pump by its dephosphorylated form. Thereby, Ca^{2+} uptake is increased either in response to enhanced cytosolic [Ca^{2+}] or in response to beta-adrenergic agonists or CaMKII activation (which can be secondary to the beta-adrenergic system).[1,22,31]

Phospholamban (PLB) was so named by its discoverers Tada and Katz[24] to mean "phosphate receiver." PLB is a single-transmembrane pass protein that binds directly to SERCA2a. Under basal conditions, this reduces the affinity of SERCA for cytosolic Ca^{2+}, which results in weaker SR Ca^{2+} uptake at any given $[Ca^{2+}]_i$. However, when PLB is phosphorylated by either PKA or CaMKII (at Ser16 or Thr17, respectively), the inhibitory effect is relieved, thereby resulting in increased rates of SR Ca^{2+} uptake, cardiac relaxation (*lusitropic effect*), and increased SR Ca^{2+} content, which drives stronger contraction (*inotropic effect*; **Fig. 22.10**).

The Ca^{2+} taken up into the SR is stored within the SR before further release. The highly charged, low-affinity Ca^{2+} buffer (K_d approximately 600 µM) *calsequestrin* is found primarily at the jSR and enhances the local availability of Ca^{2+} for release by the nearby RyR. *Calreticulin* is another Ca^{2+}-storing protein that is similar in structure to calsequestrin and probably similar in function. There is also evidence that calsequestrin and two other proteins located in the SR membrane (junctin and triadin) may regulate the properties of the RyR and may be part of the mechanism by which higher $[Ca]_{SR}$ enhances RyR opening.[19] Reuptake by SERCA occurs everywhere in the SR membrane in the network that surrounds the myofilaments. Diffusion of Ca^{2+} within the SR is relatively fast, which allows restoration of $[Ca^{2+}]_{SR}$ at the jSR to occur quickly because Ca^{2+} is taken back up everywhere.[25] Indeed, during normal Ca^{2+} release, intra-SR Ca^{2+} diffusion is rapid enough to limit Ca^{2+} gradients between SR release sites in the jSR and the Ca^{2+} uptake sites. This diffusion also ensures that $[Ca^{2+}]_{SR}$ is relatively uniform throughout the myocyte, which facilitates the uniformity of SR Ca^{2+} release and myofilament activation throughout the cell.

Sarcolemmal Control of Ca^{2+} and Na^{+}

Calcium and Sodium Channels

Excitation-contraction coupling is initiated by voltage-induced opening of the sarcolemmal L-type Ca^{2+} channels. The channels are pore-forming macromolecular proteins that span the sarcolemmal lipid bilayer

to allow a highly selective pathway for transfer of ions into the heart cell when the channel changes from a closed to an open state. Ion channels have two major properties: gating and permeation. Ca^{2+} and Na^{+} channels have two functional "gates," activation and inactivation. At the normal resting membrane potential, the activation gate is closed and the inactivation gate is open, so the channels are available to open on depolarization in their characteristic *voltage-gated* manner. On activation, the inactivation gate starts to close, and the kinetics of inactivation depends on voltage, time, and local $[Ca^{2+}]_i$. Recovery from inactivation (which makes the channels available for activation again) is also time, voltage, and Ca^{2+} dependent. Thus, after the action potential ends, time is required for the Ca^{2+} and Na^{+} channels to recover from inactivation.

Permeation (or conductance) refers to the actual flow of ions or current through the open channel. Ca^{2+} and Na^{+} channels are highly selective for Ca^{2+} and Na^{+}, respectively, relative to other physiologic ions. However, nonphysiologic ions can also permeate; barium (Ba^{2+}) and strontium (Sr^{2+}) readily permeate Ca^{2+} channels, and lithium (Li^{+}) permeates Na^{+} channels, and these ions are sometimes used experimentally to study I_{Ca} and I_{Na}. The concentration of the permeant ion influences the conductance, and in simple Ohm's law terms ($I_{Ca} = g_{Ca}[E_m - E_{Ca}]$), current is the product of conductance (g_{Ca}; which depends on gating and permeation) times the electrochemical driving force ($E_m - E_{Ca}$), which is the difference between the membrane potential (E_m) and the potential that exactly counterbalances the transmembrane $[Ca^{2+}]$ gradient (E_{Ca}, typically +120 mV but changes as $[Ca]_i$ changes). Thus, depolarization activates both Ca^{2+} and Na^{+} channels but also decreases the driving force for the currents.

Molecular Structure of Ca^{2+} and Na^{+} Channels

Both Ca^{2+} and Na^{+} channels contain a major alpha subunit with four transmembrane domains (I to IV), each of which has six transmembrane helices (S1 to S6) and a pore loop between S5 and S6. Each channel also has associated auxiliary subunits (α2δ, β, and γ for Ca^{2+} channels) that may influence trafficking and gating.[1] Activation is now understood in molecular terms as outward movement of the charged S4 transmembrane segment (called the *voltage sensor*) in each of the four domains of Na^{+} and Ca^{2+} channels. This S4 voltage dependence differs among channels, and Na^{+} channels are activated at more negative E_m than are Ca^{2+} channels. *Inactivation* is more complex and involves multiple channel domains, and channels accumulate in this state during prolonged depolarization. The open state is typically the last of a sequence of multiple molecular closed conformations. However, there is typically a binary switch between closed and open such that the single-channel conductance is either near zero or at a constant open conductance. This stochastic nature means that it is often better to speak of the *probability of channel opening* for a single channel, while the whole-cell current integrates flux through all the stochastic channels.

T- Versus L-Type Ca^{2+} Channels

The cardiovascular system has two major types of sarcolemmal Ca^{2+} channels, T-type and L-type channels. T (transient)–type channels open at a more negative voltage, have short bursts of opening, and do not interact with conventional Ca^{2+} antagonist drugs.[1] In adult ventricular myocytes, there does not seem to be appreciable T-type I_{Ca} (except under pathophysiologic conditions). Even when expressed in ventricular myocytes, T-type channels do not seem to target the regions where RyRs are, and consequently they do not participate in excitation-contraction coupling per se. However, measurable T-type I_{Ca} is present in neonatal ventricular myocytes, Purkinje fibers, and some atrial cells (including pacemaker

cells). In these locations the negative activation voltages may allow T-type I_{Ca} to contribute to pacemaker function. Thus, in ventricular myocytes, L-type currents predominate.

L-Type Ca^{2+} Channel Localization and Regulation

L (long-lasting)–type Ca^{2+} channels are concentrated in the T tubules at jSR sites, where they are positioned for Ca^{2+}-induced Ca^{2+} release from the RyR. A fraction of L-type Ca^{2+} channels are also localized in caveolae, where they may participate in local Ca^{2+} signaling, which is somewhat distinct from triggering of SR Ca^{2+} release. L-type Ca^{2+} channels are inhibited by Ca^{2+} channel blockers such as verapamil, diltiazem, and the dihydropyridines. I_{Ca} is rapidly activated during the rising phase of the action potential, but the combination of Ca^{2+} influx via I_{Ca} itself and local SR Ca^{2+} release causes rapid Ca^{2+}-dependent inactivation of I_{Ca}. Voltage-dependent inactivation also contributes to I_{Ca} decline during the action potential, but I_{Ca} continues at low levels throughout the action potential.[26] Inward I_{Ca} is an important contributor to the plateau phase of the cardiac action potential, and excess I_{Ca} or failure of inactivation can prolong the duration of the action potential.

During beta-adrenergic stimulation, cyclic adenosine monophosphate (cAMP) and PKA activity increases and results in phosphorylation of the Ca^{2+} channel and alteration of its gating properties. Notably, most of the molecular components of this beta-adrenergic receptor–cAMP-PKA and phosphatase pathway are localized directly at the L-type Ca^{2+} channel, which facilitates rapid sympathetic activation of changes in I_{Ca}. PKA-dependent phosphorylation of the channel shifts activation (and inactivation) to more negative voltages and increases the open time of the channel. This combination can greatly increase I_{Ca}, which increases both the fraction of SR Ca^{2+} release and the Ca^{2+} load of the cell and SR (to enhance further the Ca^{2+} transient amplitude and inotropic state).

Sodium Channels

Voltage-gated cardiac Na^+ current is carried mainly by the Nav1.5 *cardiac* isoform, but a minor component is attributed to several other, *neuronal* isoforms. The Nav1.5 channels seem to be especially concentrated at the ends of the myocyte near intercalated discs, but the overall density of I_{Na} is relatively uniform between the T tubule and surface membrane.[27] Depolarization activates I_{Na}, and peak I_{Na} is very large and drives the upstroke of the cardiac action potential. Voltage-dependent inactivation of I_{Na} is very rapid, and under normal conditions, Na^+ channels inactivate within a few milliseconds of depolarization. However, a small number of Na^+ channels remain open (or reopen), thereby creating a small but persistent influx of Na^+ throughout the plateau of the action potential. This so-called late sodium current (I_{NaL}) is characterized by ultraslow, voltage-independent inactivation and reactivation.[28] Although the amplitude of I_{NaL} is small (<1% of peak I_{Na}), because peak I_{Na} is so large, this I_{NaL} still constitutes a significant inward current during the plateau phase of the action potential. Under pathophysiologic conditions, the amount of I_{NaL} can increase significantly, which can result in acquired long-QT (LQT) syndrome and also cause Na^+ and Ca^{2+} loading of myocytes, which carries additional arrhythmogenic potential. Thus, I_{NaL} has emerged as a potentially important therapeutic target.[21,29]

Ca^{2+}/Calmodulin-Dependent Protein Kinase II Alters Gating of I_{Na}, I_{Ca}, and Other Channels.

CaMKII is known to be upregulated and chronically activated in numerous pathophysiologic conditions

(e.g., ischemia-reperfusion, heart failure, ROS). Also, CaMKII-dependent Na^+ channel phosphorylation causes increased I_{NaL}, which may produce an acquired form of LQT3 syndrome in patients with genetically normal Na^+ channels[21,29] (**see Fig. 22.9**). At the same time, CaMKII also shifts Na^+ channel availability to more negative voltages, enhances intermediate inactivation, and slows recovery from inactivation, all loss-of-function effects that could cause an acquired Brugada syndrome–like condition. Indeed, this can foster both phenotypes, depending on the heart rate: LQT syndrome at a lower heart rate and Brugada syndrome at a higher heart rate.[21] CaMKII also modulates Ca^{2+} and potassium (K^+) channel currents, which can further promote arrhythmogenesis through EADs and enhanced transmural dispersion of repolarization.[21]

Ion Exchangers and Pumps

To maintain steady-state Ca^{2+} and Na^+ balance, the amount of Ca^{2+} and Na^+ entering during each action potential must be exactly balanced by efflux before the next beat. This is the definition of steady state. For Ca^{2+}, Na^+/Ca^{2+} exchange (NCX) is responsible for extruding most of the Ca^{2+} that entered by I_{Ca} and NCX, whereas a minor fraction is extruded by the plasma membrane Ca^{2+}-ATPase (PMCA). NCX uses the inward $[Na^+]$ electrochemical gradient from 3 Na^+ ions to pump each Ca^{2+} ion into the extracellular space against a large electrochemical gradient (and PMCA uses 1 ATP to pump each Ca^{2+} ion). The main mechanism for extruding Na^+ from the cell is Na^+,K^+-ATPase, which pumps 3 Na^+ ions out for each ATP consumed. Note that NCX also indirectly uses the energy from Na^+,K^+-ATPase to perform its function.

Sodium-Calcium Exchanger

During relaxation, SR Ca^{2+}-ATPase and NCX compete for the removal of cytosolic Ca^{2+}, with the SR pump normally being dominant.[1,4] NCX is reversible, so the direction of Ca^{2+} flux depends on the membrane potential and $[Na^+]$ and $[Ca^{2+}]$ on both sides of the sarcolemma. The E_m at which the inward electrochemical potential is the same for 3 Na^+ ions as for 1 Ca^{2+} ion to enter is the reversal or equilibrium potential (E_{NCX}, similar to that for ion channels). When E_m is higher than this voltage, entry of Ca^{2+} is favored, whereas for E_m below E_{NCX}, the Ca^{2+} efflux mode is thermodynamically favored. During diastole (E_m = −80 mV), NCX normally extrudes Ca^{2+}, but because $[Ca^{2+}]_i$ is low during diastole, the Ca^{2+} flux rate is low (low substrate concentration). As the action potential rises to a peak, E_m normally exceeds E_{NCX} and Ca^{2+} influx is favored, but this occurs only briefly because the high local $[Ca^{2+}]_i$ near the membrane drives NCX back into the Ca^{2+} extrusion mode. When the action potential repolarizes, the negative E_m further enhances the Ca^{2+} extrusion flux, and at this time, $[Ca^{2+}]_i$ is above the diastolic level, so NCX can transport Ca^{2+} effectively. Note that if SR Ca^{2+} release is small and/or I_{Ca} is small or $[Na^+]_i$ is abnormally high (as occurs in heart failure), NCX can continue to bring Ca^{2+} into the cell during much of the action potential duration and in that sense can partially compensate for the lack of I_{Ca} or SR Ca^{2+} release.[1] NCX is also allosterically activated by increasing $[Ca^{2+}]_i$.[30] Although such regulation is time dependent, it may provide a mechanism to enhance the cell's ability to extrude Ca^{2+} when $[Ca^{2+}]_i$ is chronically high, as well as to keep NCX from driving $[Ca^{2+}]_i$ and indirectly $[Ca^{2+}]_{SR}$ to inappropriately low levels when cytosolic Ca^{2+} is in short supply.

Under normal conditions in human or rabbit ventricular myocytes, the steady-state condition occurs when the relative Ca^{2+} removal from the cytosol by SERCA and NCX is 70% to 75% and 20% to 25%, respectively, with PMCA contributing 1% or less (**see Fig. 22.8**). In heart failure, in which SERCA is

downregulated and NCX may be upregulated, the SERCA and NCX contributions are closer to the same. In the mouse and rat ventricle, the difference is larger (92% SERCA, 7% NCX). This steady state involves all the various Ca^{2+} transport systems dynamically, but the relative rates of Ca^{2+} flux by SERCA and NCX at physiologic $[Ca^{2+}]_i$ provide a good estimate. These removal fluxes must also pertain to the integrated Ca^{2+} fluxes into the cytosol. That is, the combination of Ca^{2+} entry by I_{Ca} and NCX in human and mouse ventricle would be 25% and 8%, respectively. In other words, amplification of the Ca^{2+} transient by SR Ca^{2+} release is only approximately fourfold for human or rabbit ventricle (and less in heart failure) but approximately 12-fold for mouse or rat ventricle.

Heart Rate and Na^+/Ca^{2+} Exchange.

NCX participates in the force-frequency relationship (treppe or Bowditch phenomenon).[1] An increasing heart rate (independent of sympathetic activation) increases the amount of Na^+ and Ca^{2+} entry per unit time and also diminishes the time available for extrusion of Na^+ and Ca^{2+}. This will tend to increase the amount of Ca^{2+} in the SR simply because of more frequent I_{Ca} pulses and less time for removal of Ca^{2+} from the cell. However, the same happens for Na^+, and the elevation in $[Na^+]_i$ also limits the ability of NCX to extrude Ca^{2+}, which further increases the amount of Ca^{2+} in the myocyte and SR when the cell achieves a new steady state. This NCX effect (once referred to as the “sodium pump lag” hypothesis) thus amplifies the intrinsic inotropic effect of an increase in heart rate.

Sodium Pump (Na^+,K^+–Adenosine Triphosphatase)

During the normal heartbeat, Na^+ enters the myocyte mainly by Na^+ channels and NCX, with NCX being quantitatively most important.[31] Na^+/H^+ exchange also mediates significant Na^+ influx, particularly when cells are acidotic. In the steady state, this Na^+ influx is matched by an equal Na^+ efflux, mediated mainly by sarcolemmal Na^+,K^+-ATPase, or the Na^+ pump. The Na^+ pump is activated by internal Na^+ or external K^+ and transports 3 Na^+ ions out and 2 K^+ ions in per ATP molecule used. During this process, one positive charge leaves the cell, and thus Na^+,K^+-ATPase is electrogenic and carries an outward current.[31] Na^+,K^+-ATPase in the heart is modulated by the endogenous accessory protein *phospholemman* (PLM), which works in a manner analogous to the PLB-SERCA2a mechanism. That is, at baseline, PLM reduces the intracellular Na^+ affinity of Na^+,K^+-ATPase, but when it is phosphorylated (by either PKA or protein kinase C [PKC]), that inhibitory effect is relieved.[31] Thus, during sympathetic activation, Na^+,K^+-ATPase activity is increased at any given $[Na^+]_i$ to keep up better with the higher rates of Na^+ influx that occur under this condition.

Digitalis glycosides inhibit Na^+,K^+-ATPase and have been used for more than 200 years as a cardiac inotropic drug for the treatment of heart failure, although their use has diminished in recent years (**see also Chapter 25**). Partial inhibition of Na^+,K^+-ATPase causes an increase in $[Na^+]_i$ in myocytes, which limits the ability of NCX to extrude Ca^{2+}, resulting in enhanced myocyte and SR Ca^{2+} loading and release. A limitation with this approach is the narrow therapeutic range, and too much inhibition can lead to myocyte Ca^{2+} overload and trigger arrhythmias. However, this emphasizes the close interrelationship between Na^+ and Ca^{2+} regulation mediated by the powerful NCX present in cardiac myocytes.

Adrenergic Signaling Systems

Physiologic Fight-or-Flight Response

During the classic adrenergic fight-or-flight response, cardiac myocyte beta-adrenergic receptors are activated, which leads to increased cAMP production and PKA activation and consequent phosphorylation and altered function of numerous myocyte targets. This results in an increased heart rate (*positive chronotropy*), increased contractility (*positive inotropy*), faster cardiac relaxation (*positive lusitropy*), and enhanced conduction velocity through the conduction system (*positive dromotropy*). These events enhance cardiac output by enhancing the heart rate, stroke volume, and diastolic filling. Thus the adrenergic response is a key physiologic mechanism for increasing cardiac output in response to increased metabolic and hemodynamic demands.

During the adrenergic response, norepinephrine is released by sympathetic neurons at small swellings on small end-branches, or *varicosities*, into the local myocyte environment (**Fig. 22.11**), analogous to synaptic transmission. Norepinephrine is synthesized in the varicosities from dopa and dopamine and the amino acid tyrosine. The norepinephrine thus synthesized is stored within the terminals in *storage granules* (or *vesicles*) to be released on stimulation by an adrenergic nervous impulse. Thus, when central stimulation increases during excitement or exercise, an increased number of sympathetic nerve impulses liberate an increased amount of norepinephrine from the terminals into the synaptic cleft. Most of the norepinephrine released is taken up again by the nerve terminal varicosities to reenter the storage vesicles or to be metabolized. The norepinephrine in these *synaptic clefts* interacts with both alpha- and beta-adrenergic receptors on myocytes and also alpha-adrenergic receptors in arterioles (**Table 22.2**). The beta-adrenergic effects on the sinoatrial (SA) node and conduction system contribute to the chronotropic and dromotropic effects mentioned earlier, whereas those on myocytes are responsible mainly for the inotropic and lusitropic effects. These effects can also be modulated by coactivation of myocyte alpha-adrenergic receptors. Increased alpha-adrenergic activity causes arteriolar constriction and increased vascular impedance, although local metabolic control of arteriolar resistance is strong in the heart and dominates coronary resistance in arterioles. Parasympathetic (vagal) innervation is strongest in the conduction system, where local release of acetylcholine (ACh) activates muscarinic receptors and tends to slow the heart rate and conduction velocity (**Fig. 22.11**). In these conditions the heart rate and blood pressure fall. The influence of these main effector pathways is also modulated by numerous other signaling factors, such as local adenosine and nitric oxide (NO) and the powerful neuromodulator angiotensin II, which can also potentiate release of norepinephrine and vasoconstriction. Both alpha- and beta-adrenergic receptors are part of the family of seven–transmembrane domain G protein–coupled receptors (GPCRs).

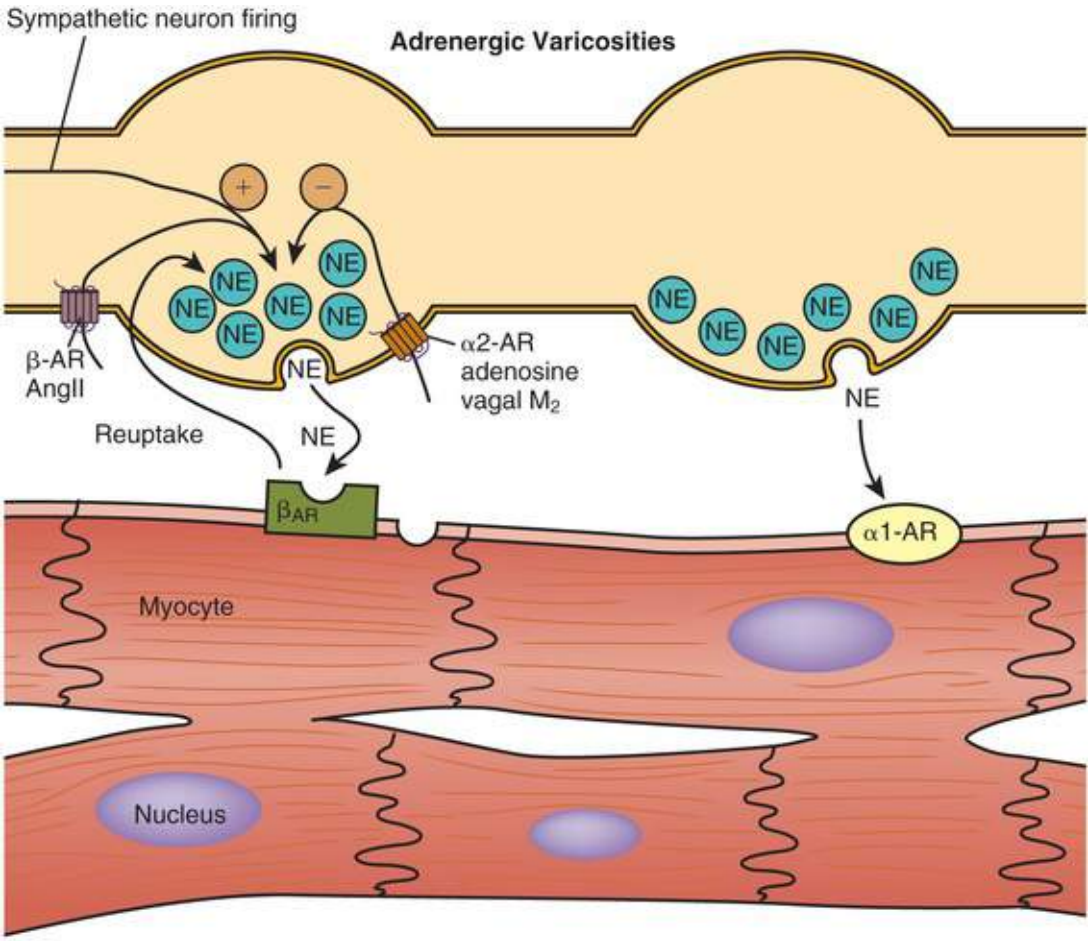

FIGURE 22.11 Norepinephrine (NE) release from sympathetic neurons**.** NE is released from storage granules in adrenergic varicosities into narrow, synapse-like spaces near its receptors in the sarcolemma of the cardiac and smooth muscle myocytes of the heart and arterial walls. In cardiomyocytes, beta-adrenergic receptor (AR) activation increases heart rate (chronotropy), contractile force (inotropy) and relaxation (lusitropy), and conduction (dromotropy). However, NE also activates cardiac myocyte $alpha_1$-adrenergic receptors, which can further modulate contractility and myocyte signaling cascades. In arterioles, NE predominantly causes vasoconstriction via postsynaptic $alpha_1$ receptors. NE also stimulates presynaptic $alpha_2$ receptors to invoke feedback inhibition that can limit its own release. Circulating epinephrine stimulates vascular vasodilatory $beta_2$ receptors but also presynaptic receptors on the nerve terminal, which promotes NE release. Angiotensin II (AngII) is also powerfully vasoconstrictive and acts both by stimulation of NE release (presynaptic receptors, as indicated schematically) and directly on arteriolar AngII receptors. M_2 is muscarinic receptor, subtype two.

TABLE 22.2

Comparative Cardiovascular Effects of Alpha- and Beta-Adrenergic Receptor Stimulation

	ALPHA$_1$ MEDIATED	BETA MEDIATED
Electrophysiologic effects	±	++
		Conduction
		Pacemaker
		Heart rate
		− AP duration
Myocardial mechanics	±	++
		Contractility, lusitropy
		Stroke volume
		Cardiac output
Myocardial metabolism	±	++
	Glycolysis	O_2 uptake ↑
		ATP
Signal systems	GPCR, can activate PKC and MAPK	GPCR, activates cAMP and PKA
Coronary arterioles	++	+ Direct dilation
	Constriction	+++ Indirect dilation (metabolic)
Peripheral arterioles	+++	+
	Constriction	Dilation
	SVR ↑	SVR ↓
	SBP ↑	SBP ↓

AP, Action potential; *GPCR,* G protein–coupled receptor; *MAPK,* mitogen-activated protein kinase; *PK,* protein kinase; *SBP,* systolic blood pressure; *SVR,* systemic vascular resistance.

Modified from Opie LH. Heart Physiology, from Cell to Circulation. 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2004.

Beta-Adrenergic Receptor Subtypes

Cardiac beta-adrenergic receptors are chiefly the beta$_1$ subtype, whereas most noncardiac receptors are beta$_2$. Beta$_2$ receptors constitute approximately 20% of the total beta receptor population in the left ventricle. Whereas beta$_1$ receptors are linked to the stimulatory G protein G_s, a component of the G protein–adenylyl cyclase system, beta$_2$ receptors are linked to both G_s and the inhibitory protein G_i (**Fig. 22.12**), so their signaling pathway bifurcates at the first postreceptor step.[4] In humans the positive inotropic response to beta$_2$ stimulation by salbutamol (albuterol) occurs, at least in part, through beta$_2$ receptors on the terminal neurons of cardiac sympathetic nerves, thereby releasing norepinephrine, which in turn exerts dominant beta$_1$ effects.[4] Indirect evidence suggests that the G_i pathway is relatively augmented in heart failure, whereas the strength of the G_s path is lessened because of uncoupling of G_s from the beta receptor (**see Chapter 23**). There also appear to be a small number of beta$_3$-adrenergic receptors in cardiac myocytes that seem to produce more G_i-mediated negative inotropic signaling, mediated in part by NO, but this pathway is not as well understood. The beta-adrenergic receptor site is highly stereospecific, the best fit among catecholamines being achieved with the synthetic agent isoproterenol rather than with the naturally occurring catecholamines norepinephrine and epinephrine. In the case of beta$_1$ receptors, the order of agonist activity is isoproterenol > epinephrine = norepinephrine, whereas in the case of beta$_2$ receptors, the order is isoproterenol > epinephrine > norepinephrine. Human beta$_1$ and beta$_2$ receptors have both been cloned and studied extensively.[4] The transmembrane domains are the site of agonist and antagonist binding, whereas the cytoplasmic domains interact with G proteins.

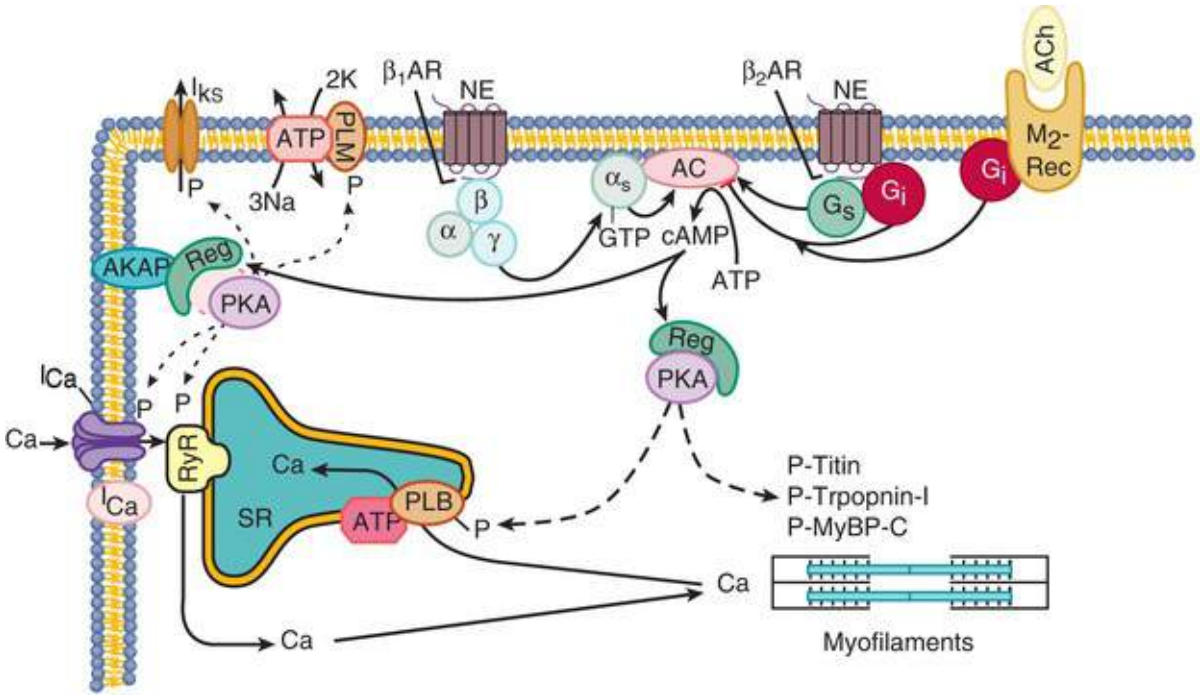

FIGURE 22.12 Beta-adrenergic and muscarinic activation in cardiac myocytes interact. Activation of beta$_1$-adrenergic receptors (β_1*AR*) activate adenylyl cyclase (*AC*) via G_s (via the activated alpha subunit (α_s) dissociation from the beta and gamma subunits (β and γ). AC produces cAMP, which activates protein kinase A (*PKA*), which phosphorylates (*P*) several key functional targets (*broken arrows*). β_2-AR activate both G_s and G_i, which activate or inhibit AC, respectively. Activation of muscarinic M_2 receptors (*M_2-Rec*) by acetylcholine (*ACh*) from parasympathetic neurons inhibits AC via G_i. *Reg,* Regulatory subunit of PKA; *PLM,* phospholemman; *PLB,* phospholamban. (Modified from Bers DM. Excitation-Contraction Coupling and Cardiac Contractile Force. Dordrecht, Netherlands: Kluwer Academic; 2001.)

Alpha-Adrenergic Receptor Subtypes

The two alpha-adrenergic receptor isoforms are alpha$_1$ and alpha$_2$. Those on the sarcolemma of vascular smooth muscle are vasoconstrictor alpha$_1$ receptors, whereas those situated on the terminal varicosities are alpha$_2$-adrenergic receptors that feed back (**see Fig. 22.11**) to inhibit release of norepinephrine. Pharmacologically, an alpha$_2$-adrenergic receptor mediates a response in which the effects resemble those of the pharmacologic agent phenylephrine. Among catecholamines, the relative potencies of alpha$_1$-agonists are norepinephrine > epinephrine > isoproterenol. Physiologically, norepinephrine liberated from nerve terminals is the chief stimulus to vascular alpha$_1$-adrenergic activity. Both alpha$_1$ and alpha$_2$ receptors are also found in cardiac myocytes, where their activation can fine-tune Ca^{2+} transients, ionic currents, and myofilament properties acutely, but they are also known to be important modulators of cardiac remodeling (in both adaptive and maladaptive contexts).[32]

G Proteins

G proteins are a superfamily of proteins that bind guanine triphosphate (GTP) and other guanine nucleotides. G proteins are crucial in carrying the signal onward from the agonist and its receptor to the activity of the membrane-bound enzyme system that produces the second messenger cAMP (**Fig. 22.13**; **see also Fig. 22.12**).[4] Thus the combination of the beta receptor, G protein complex, and adenylyl cyclase is the crux of beta-adrenergic signaling.

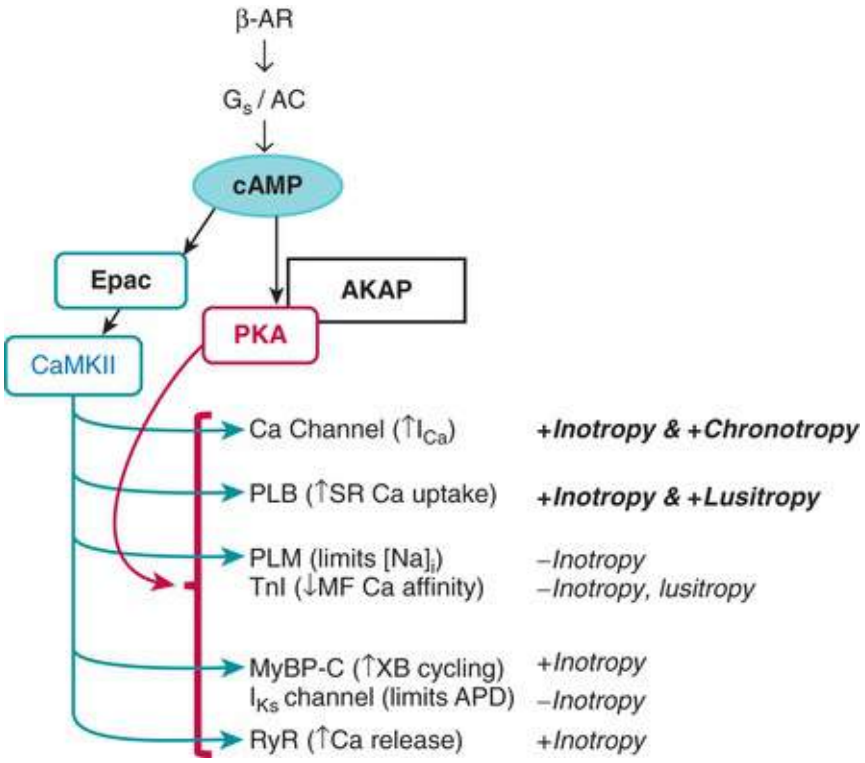

FIGURE 22.13 Key roles of PKA (and CaMKII) in beta-adrenergic responses. Major intracellular effects of beta-agonist catecholamines are via the formation of cAMP, which increases the activity of PKA and also Epac (exchange protein activated by cAMP). PKA is localized by A-kinase anchoring proteins (AKAPs) that target PKA function to local nanodomains. Epac also activates CaMKII which can phosphorylate and modulate function of some of the same targets as PKA (often by phosphorylation at different amino acids).

The Stimulatory G Protein G_s.

The G protein itself is a heterotrimer composed of G_α, G_β, and G_γ, which on receptor stimulation splits into the alpha subunit that is bound to GTP and the beta-gamma subunit. Either of these subunits may regulate different effectors such as adenylyl cyclase, phospholipase C, and ion channels. The activity of adenylyl cyclase is controlled by two different G protein complexes, namely, G_s, which stimulates, and G_i, which inhibits. The alpha subunit of G_s (α_s) combines with GTP and then separates from the other two subunits to enhance the activity of adenylyl cyclase. The beta and gamma subunits (beta-gamma) appear to be linked structurally and functionally.

The Inhibitory G Protein G_i.

In contrast, a second trimeric GTP-binding protein, G_i, is responsible for inhibition of adenylyl cyclase.[4] During stimulation of muscarinic and some $beta_2$-adrenergic receptors, GTP binds to the inhibitory alpha subunit α_i. The latter then dissociates from the other two components of the G protein complex, which are, as in the case of G_s, the combined beta-gamma subunits. The beta-gamma subunits act as follows. By stimulating the enzyme guanosine triphosphatase (GTPase), they break down the active α_s subunit (α_s-GTP) such that less activation of adenylyl cyclase occurs in response to alpha stimulation. Furthermore, the beta-gamma subunit activates the K_{ACh} channel, which can slow SA node firing and thereby contribute to the bradycardic effect of cholinergic stimulation. The α_i subunit may also activate another potassium channel (K_{ATP}) that stabilizes the diastolic potential. The major physiologic stimulus for G_i is thought to be vagal muscarinic receptor stimulation (although $beta_2$-adrenergic receptors may contribute as well). In

addition, adenosine, by interaction with A_1 receptors, couples to G_i to inhibit contraction and heart rate. The adenosine A_2 receptor paradoxically increases cAMP. The latter effect, only of ancillary significance in the myocardium, is of major importance in vascular smooth muscle, where it induces vasorelaxation. Pathologically, G_i is increased in experimental postinfarct heart failure[4] and in donor hearts before cardiac transplantation.[4]

A Third G Protein, G_q.

This protein links a group of GPCRs, including the alpha-adrenergic receptor and those for angiotensin II and endothelin-1, to another membrane-associated enzyme, phospholipase C, and then to PKC and PKD (and IP_3-induced Ca^{2+} mobilization). G_q has at least four isoforms, two of which have been found in the heart. This G protein, unlike G_i, is not susceptible to inhibition by pertussis toxin. Overexpression of G_q in mice induces a dilated cardiomyopathy,[4] which is of interest because angiotensin II and endothelin, which act through G_q, are overactive in human heart failure. Conversely, when the activity of G_q is genetically inhibited, the hypertrophic response to pressure overload is attenuated, wall stress increases, but cardiac function is relatively well maintained.

Cyclic Adenosine Monophosphate and Protein Kinase A

Adenylyl Cyclase

Adenylyl cyclase (also called adenylate or adenyl cyclase) catalyzes formation of the second messenger cAMP. Several isoforms exist, but AC5 and AC6 are most prominent in cardiac myocytes, and these isoforms are partially inhibited by high $[Ca^{2+}]_i$. Adenylyl cyclase, when stimulated by G_s, produces cAMP, which acts through multiple intracellular signals (including importantly PKA) to mediate the chronotropic, inotropic, lusitropic, and dromotropic effects of cardiac beta-adrenergic agonists. In contrast, cholinergic (and vagal) stimulation can inhibit adenylyl cyclase through G_i, to slow heart rate, but also limit cAMP formation downstream of G_s activation.

Adenylyl cyclase is the only enzyme that produces cAMP, using low concentrations of Mg^{2+}-ATP as substrate. It is a transmembrane enzyme, with most mass on the cytoplasmic side where G proteins interact. Cyclic guanosine monophosphate (cGMP) is a related second messenger that often antagonizes cAMP effects. cAMP has very rapid turnover as a result of a constant dynamic balance between its formation by adenylyl cyclase and conversion to AMP by phosphodiesterases (PDEs). Several major PDE isoforms have different substrate specificity (cAMP versus cGMP) and are differentially regulated by cyclic nucleotides and Ca^{2+}/calmodulin.[33] In general, directional changes in the tissue content of cAMP can be related to directional changes in cardiac contractile activity, but local subcellular domains may have differential cAMP and PKA regulation that depends in part on PDE isoform localization. For example, while beta-adrenergic stimulation increases both cAMP and PKA target phosphorylation, differences may occur at ion channel and myofilament target sites.[34] *Forskolin* is a potent direct adenylyl cyclase activator, and isobutyl methylxanthine (*IBMX*) is a PDE inhibitor that inhibits all PDE isoforms. These are widely used agents experimentally, but isoform-specific PDE inhibitors are being explored as more targeted therapeutic strategies. A number of hormones or peptides can couple to myocardial adenylyl cyclase independent of the beta-adrenergic receptor. These include glucagon, thyroid hormone, prostacyclin, and calcitonin gene–related peptide.

There is also a GTP *e*xchange *p*rotein directly *a*ctivated by *c*AMP (*Epac*) that is activated in parallel to cAMP-dependent PKA activation. This allows additional parallel signaling downstream of beta-

adrenergic activation. For example, beta-adrenergic activation of SR Ca^{2+} release is mediated by cAMP-Epac–dependent signaling to CaMKII and consequent RyR2 phosphorylation,[35] and not by PKA activation.

Protein Kinase A

PKA occurs in two isoforms, but PKA-II predominates in cardiac cells. It is now clear that many key cAMP effects are mediated by activation of PKA and phosphorylation of key proteins.[36] Each PKA complex is composed of two regulatory (R) and two catalytic (C) subunits, the latter of which transfers the terminal phosphate of ATP to serine and threonine residues of the protein substrates. When cAMP interacts with the inactive protein kinase, it binds to the R subunits, causing partial release and activation of the C subunits. A former dogma was that the C subunits were completely released from the R subunits, but more recent evidence suggests that a loose tethering remains when PKA is active. The R subunits are in turn bound to specific *A-kinase anchoring proteins* (AKAPs) that target PKA-dependent phosphorylation at specific subcellular targets.[37] This helps to explain the local compartmentalization of cAMP and PKA signaling. Indeed, there is good evidence that beta-adrenergic receptors, G proteins, adenylyl cyclase, PKA, AKAP, PDE, and phosphatases can all complex on targets such as the L-type Ca^{2+} channel and RyR2 to facilitate local PKA-dependent signaling[15,38,39] (**Fig. 22.13**).

$Beta_1$-Adrenergic and PKA Signaling in Ventricular Myocytes

The sequence of events for PKA activation is as follows (**see Fig. 22.12**): catecholamine stimulation → beta receptor → molecular changes → binding of GTP to the α_s subunit of G protein → GTP-α_s subunit stimulating adenylyl cyclase → formation of cAMP from ATP → activation of cAMP-dependent PKA, locally bound by an AKAP → phosphorylation of the target proteins. The L-type Ca^{2+} channel is rapidly phosphorylated by this cascade, which results in both a large increase in the amount of peak I_{Ca} and a shift in the activation voltage to more negative potentials. This increases the amount of Ca^{2+} that enters the cell at each beat and also enhances excitability (including in pacemaker cells). In addition, the higher I_{Ca} triggers more SR Ca^{2+} release, but the higher peak I_{Ca} and SR Ca^{2+} release also enhance Ca-dependent inactivation of I_{Ca}, which limits the total amount of Ca^{2+} entry during the action potential. This contributes to an increased Ca^{2+} transient amplitude, the inotropic effect, and also the chronotropic and dromotropic effects of PKA in heart (**Figs. 22.12 to 22.14**).

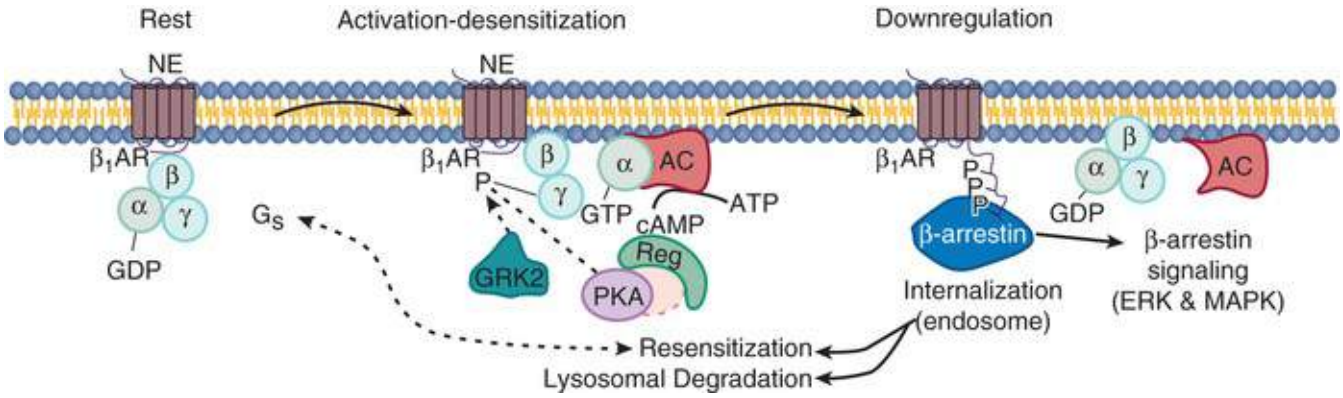

FIGURE 22.14 Beta$_1$-adrenergic receptor (β_1AR) activation, desensitization, downregulation, and recycling. Prolonged β_1AR activation causes recruitment of a G-protein receptor kinase (GRK2) that phosphorylates the receptor and favors recruitment of beta-arrestin (β-arrestin). β-arrestin promotes its own signaling cascades (e.g. via extracellular receptor and MAP kinase (ERK and MAPK) as well as internalization of the β_1AR into endosomes. From there β_1AR can either be degraded or recycled to the cell surface. (Modified from Bers DM. Excitation-Contraction Coupling and Cardiac Contractile Force. Dordrecht, Netherlands: Kluwer Academic; 2001.)

Another major contributor to the inotropic effect of PKA in the heart is phosphorylation of phospholamban. PLB is associated with SERCA2 and at baseline inhibits the Ca^{2+} pump by reducing its affinity for Ca^{2+}. On phosphorylation of PLB by PKA (or CaMKII), the inhibitory effect is relieved and the Ca^{2+} pumping function greatly enhanced. This allows more Ca^{2+} to accumulate inside the SR during the cardiac cycle, which enhances the amount that can then be released (thereby contributing to inotropy). The faster rate of SR Ca^{2+} uptake is also the major factor in accelerating relaxation, the lusitropic effect of PKA. This occurs because twitch $[Ca^{2+}]_i$ decline is faster, which allows faster Ca^{2+} dissociation from the myofilaments.

Phosphorylation of troponin I by PKA also contributes to the enhanced lusitropic effect of beta-adrenergic agonists (**see Fig. 22.13**). PKA-dependent troponin I phosphorylation reduces myofilament sensitivity for calcium, which is intrinsically negatively inotropic, but has the benefit of faster dissociation of Ca^{2+} from myofilaments, which hastens relaxation and diastolic filling. In addition, myosin-binding protein C is also a target for PKA, and its phosphorylation appears to be responsible for accelerating the cross-bridge turnover rate. This effect also serves largely to offset the negative inotropic effect of troponin I phosphorylation and may also hasten the rate of sarcomere shortening at a given $[Ca^{2+}]$ and mechanical load, which could enhance stroke volume.[40]

PKA also phosphorylates the RyR, although the impact of this effect is controversial.[41] One group has suggested that this displaces the immunophilin FKBP-12.6 from its binding to RyR2, thereby activating RyR openings, and that this is an important part of the beta-adrenergic inotropy and cardiac dysfunction in heart failure.[42] However, this idea has been strongly challenged by extensive mechanistic experimental data and theoretical arguments from numerous groups worldwide.[41] Even though the effects of PKA on the cardiac RyR may enhance the rate of RyR activation during excitation-contraction coupling, it does not seem to increase the amount released (for a given I_{Ca} trigger and SR Ca^{2+} load),[43] nor does it directly enhance the likelihood of spontaneous SR Ca^{2+} release events.[44] Moreover, even when the RyR is sensitized, it causes enhanced SR Ca^{2+} release only for several beats, which then drives greater efflux of Ca^{2+} from the cell (by NCX) and reduces the SR Ca^{2+} content such that it cannot explain the enhanced Ca^{2+} transients during beta-adrenergic activation.[45]

PKA also phosphorylates PLM, a small PLB-like protein that regulates Na^+,K^+-ATPase (see earlier).[31] This is actually a sensible integral part of the fight-or-flight response because the increase in heart rate

incurs more frequent I_{Na} pulses and Ca^{2+} influx (by I_{Ca}) that causes more Na^+ influx by NCX, resulting in a major increase in $[Na^+]_i$. This Na^+,K^+-ATPase activation limits the rise in $[Na^+]_i$ during sympathetic activation and thus allows NCX to remain functional in removing Ca^{2+} from the myocyte. The increase in Na^+,K^+-ATPase function thus is somewhat negatively inotropic (by limiting $[Na^+]_i$). This is opposite the effect mediated by inhibition of Na^+,K^+-ATPase by digitalis cardiac glycosides. Notably, digitalis toxicity is associated with cellular Ca^{2+} overload and arrhythmogenesis. Consequently, Na^+,K^+-ATPase stimulation may limit these arrhythmogenic consequences associated with higher Ca^{2+} loading.

Beta-Adrenergic Receptor Desensitization.
There is a potent and rapid feedback mechanism whereby beta-adrenergic receptor stimulation can be muted so that the signal can be turned off (**Fig. 22.14**). Physiologically, this mechanism of beta-adrenergic receptor *desensitization* occurs within minutes**.** Sustained beta-agonist stimulation recruits a G protein–coupled receptor kinase (GRK2; also called beta-adrenergic receptor kinase 1 [βARK1]). GRK2 phosphorylates a site on the carboxyl-terminal of the beta-adrenergic receptor, which by itself does not switch off signaling. However, GRK2 activity increases beta receptor affinity for *arrestins*, which uncouple receptor signaling. Beta-arrestin is a scaffolding and signaling protein that links to one of the cytoplasmic loops of the beta-adrenergic receptor and lessens activation of adenylyl cyclase, thereby inhibiting receptor function. Furthermore, beta-arrestin can switch agonist coupling from G_s to G_i and also lead to internalization of the beta-adrenergic receptor.[4] *Resensitization* of the receptor occurs if the phosphate groups are removed by a phosphatase, and the receptor then more readily linked to G_s (or by recycling the internalized receptor to the surface). Beta-arrestin signaling can also evoke an alternative protective path by activating the epidermal growth factor receptor (EGFR), which leads to the protective extracellular signal–related kinase (ERK)/MAPK pathway[46] (**Fig. 22.14**). Although the GRK2-arrestin effects are best described for the $beta_2$ receptor, they also occur with the $beta_1$ receptor. Prolonged beta receptor stimulation, as in hyperadrenergic conditions, is linked to adverse end results in that it both impairs contractile function and enhances adverse signaling. As discussed in **Chapter 23**, this mechanism also plays a role in long-term desensitization of the beta-adrenergic receptor as in heart failure, and transgenic mice overexpressing GRK2 are protected from heart failure.[47]

Ca^{2+}/Calmodulin-Dependent Protein Kinase II

CaMKII is a serine/threonine-specific protein kinase that is regulated by the Ca^{2+}/CaM complex. CaMKII is involved in many signaling cascades in the heart, and several of the key proteins that are phosphorylated by PKA are also phosphorylated by CaMKII (**see Fig. 22.13**), typically at different amino acids. Moreover, there is good evidence that CaMKII is activated during beta-adrenergic stimulation.[22] Thus, CaMKII signaling is often coactivated with PKA and can synergize at downstream targets.[22] CaMKII activates L-type Ca^{2+} channels (I_{Ca} facilitation), which results in increased peak I_{Ca} and also slows down inactivation, thereby boosting total Ca^{2+} influx by I_{Ca}. CaMKII also phosphorylates PLB at Thr17 (versus at Ser16 by PKA) and, by the same mechanism as for PKA, can enhance SR Ca^{2+} uptake. However, the CaMKII effects on I_{Ca} and SERCA/PLB are typically smaller in magnitude than the effects of PKA activation, so PKA is probably dominant physiologically at these targets. CaMKII can also phosphorylate RyR2 at Ser2814, close to a recognized PKA target site (2808). In contrast to PKA, it is

more universally agreed that CaMKII strongly activates the RyR and that this effect may be important in causing a diastolic SR Ca^{2+} leak, which can both reduce the SR Ca^{2+} content (contributing to both systolic and diastolic dysfunction) and contribute to triggered arrhythmias.[21,22,41] CaMKII can also phosphorylate cardiac Na^+ and K^+ channels and lead to arrhythmogenic consequences.[21,22] CaMKII-dependent activation of the late Na^+ current may also lead to elevated intracellular [Na^+] and [Ca^{2+}], which can create Ca^{2+} overload and trigger arrhythmias. Myofilament proteins are also targets for CaMKII (e.g., myosin-binding protein C),[48] but the relative functional importance of this effect is not yet fully resolved. The chronic activation of CaMKII in pathologic states such as heart failure makes these pathways important to keep in mind.

Cholinergic and Nitric Oxide Signaling

Cholinergic Signaling

Parasympathetic stimulation reduces the heart rate and is negatively inotropic. As in adrenergic signaling, there is an extracellular messenger (ACh), a GPCR (the *cholinergic* muscarinic receptor), and a sarcolemmal signaling system (G protein system, specifically G_i). The *myocardial* muscarinic receptor (M_2) is a GPCR (**see Fig. 22.12**). Receptor stimulation produces a negative chronotropic response that is inhibited by atropine. NO, also formed by $beta_3$-adrenergic signaling,[49] facilitates cholinergic signaling at two levels, the nerve terminal and the activity of the enzyme system that produces the second messenger cGMP. *Neuregulins* are growth factors that maintain the activity of the muscarinic receptor, thereby indirectly helping to balance the normal parasympathetic modulation of excess beta-adrenergic stimulation.[50,51]

Muscarinic G_i activation also inhibits adenylyl cyclase, which functionally integrates the input from activating G_s (e.g., from $beta_1$-adrenergic and other receptors) and the inhibitory effects of G_i (from M_2 muscarinic and other receptors; **Fig. 22.12**). As a result, vagal stimulation also limits [cAMP] resulting from ambient sympathetic tone. The net effect is slowing of the heart rate. Vagal activity has less strong effects on atrial or ventricular myocyte electrophysiology, Ca^{2+} transients, or contractility than on conduction system cells, in part because of the lower density of vagal innervation at myocytes, but also because of the intrinsic properties of the cells (e.g., lacking major pacemaker function). Nevertheless, vagal activation can shorten the action potential duration in the atria and, to a lesser degree, in the ventricles (primarily by $I_{K(Ach)}$ activation). Similarly, vagal stimulation can cause antiadrenergic effects in myocytes by effects on adenylyl cyclase that limit cAMP levels (see earlier) and the consequent downstream effects associated with a physiologic level of sympathetic tone (**see Figs. 22.12 and 22.13**).

Vagal innervation in the heart is highest in the SA and atrioventricular (AV) nodes, with lower density in atrial myocardium and the lowest density in ventricular myocardium. Activation of M_2 receptors results in activation of the coupled G_i and consequent limitation of cAMP signaling. ACh also directly activates $I_{K(ACh)}$, by a K^+ channel thought to result from heterotetramers of inward rectifier K^+ channel protomers Kir3.1 and Kir3.4. This increased K^+ conductance causes more negative diastolic potential in pacemaker cells and also impairs the rate of diastolic depolarization (in the same way that I_{K1} stabilizes the diastolic potential of atrial and ventricular myocytes). These factors slow the rate of SA node pacemaker firing and thus the heart rate.

Cyclic Guanosine Monophosphate Signaling in the Heart

The second messenger cGMP typically has negative inotropic effects in the heart, in contrast to its cyclic nucleotide cousin cAMP. Cyclic GMP is produced from GTP in cardiac myocytes mainly by soluble and particulate guanylyl cyclases, which are activated downstream of NO and natriuretic peptide receptor activation, respectively (**Fig. 22.15**), and possibly by cholinergic effects. Local subcellular regions in which NO and cGMP signaling take place are also likely to exist.[38] Of note, cell-permeable analogues of cGMP have antiadrenergic effects. When local [cGMP] is elevated, it can stimulate protein kinase G (PKG), which results in inhibitory cardiac effects such as a decreased heart rate and negative inotropic response. These effects are largely achieved by modulation of Ca^{2+} entry through L-type Ca^{2+} channels and through alteration of internal Ca^{2+} cycling.[51,52] PKG has also been suggested to be a critical suppressor of pathophysiologic hypertrophy.[53]

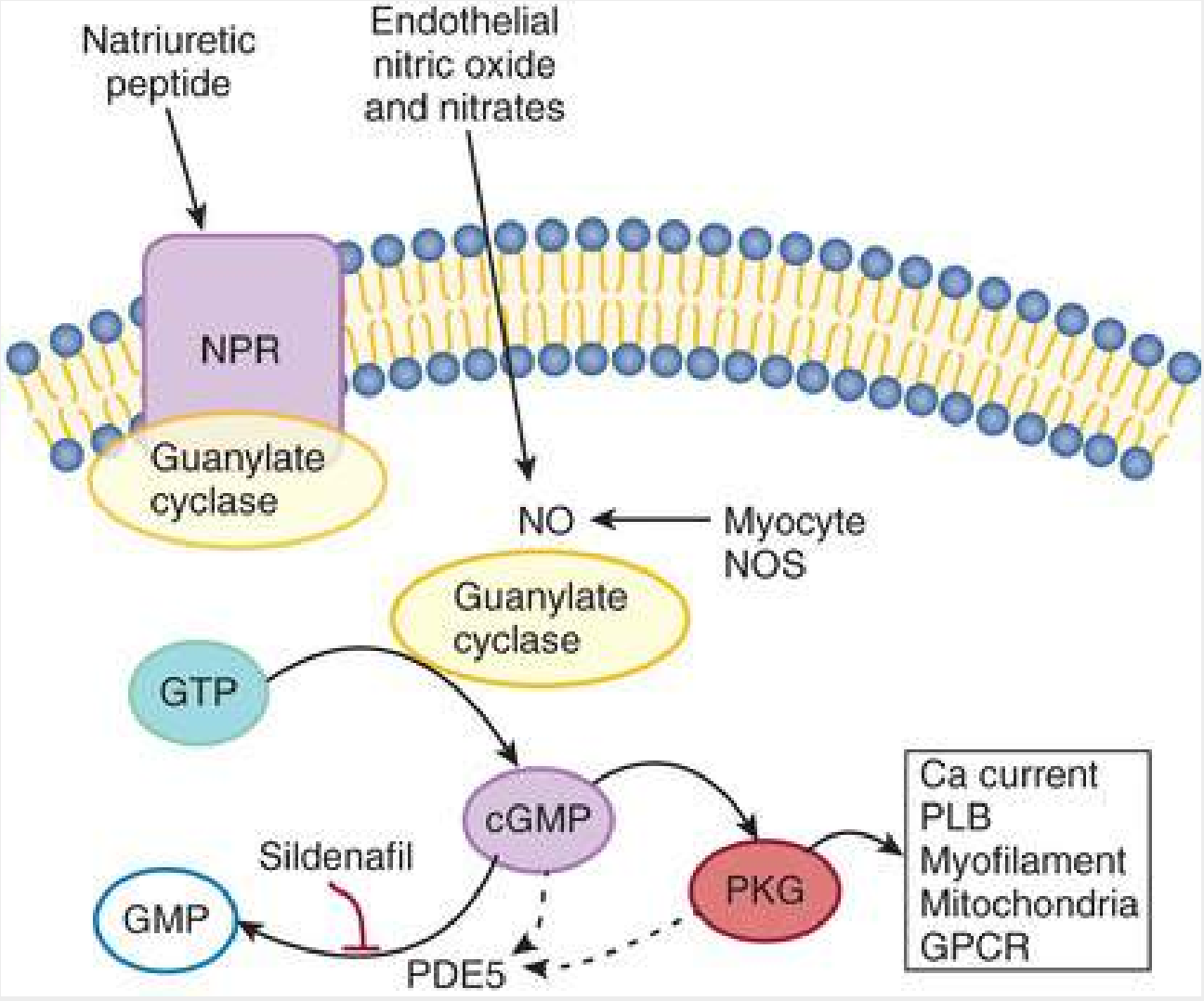

FIGURE 22.15 Nitric oxide (NO) and the natriuretic peptide receptor (NPR) activate guanylate cyclase (via particulate and soluble cyclases, respectively), resulting in production of cGMP and activation of protein kinase G (PKG). PKG can phosphorylate numerous myocyte targets that tend to counteract cAMP and PKA effects at some targets (with some exceptions). Phosphodiesterase 5 (PDE5) breaks down cGMP, and PDE5 inhibitors (e.g., sildenafil) can thus increase cGMP levels. Notably, high cGMP and PKG levels promote vasodilation and negative inotropic effects, and antianginal nitrates promote vasodilation by this mechanism.

cGMP is broken down by PDE, and seven PDE isoforms are expressed in the heart, some of which

break down both cAMP and cGMP (PDE1 to PDE3) whereas PDE4 is cAMP specific and PDE5 is cGMP specific.[52] PDE5 has achieved prominence as a result of its inhibition by sildenafil and related compounds that all enhance penile vasodilation. Emerging data show wider therapeutic potential. Thus sildenafil, by accumulation of cGMP, combats the harmful excessive adrenergic stimulation of contractile function. Furthermore, through cGMP, sildenafil can inhibit excess left ventricular growth in response to aortic constriction.[54] Conversely, in human cardiac hypertrophy and heart failure, PDE5 is more highly expressed, which may exacerbate adverse remodeling. The key target of cGMP, PKG, as with its counterpart PKA, colocalizes with its targets to control substrate phosphorylation.[55] The anchoring protein for PKG may be the same AKAP as for PKA, thus allowing tight subcellular colocalization and regulation of the counterpoised activities of cAMP and cGMP and of their respective upstream signaling cascades.[52]

Nitric Oxide

The focus of the Nobel Prize Award for 1998, NO is a unique messenger in that it is formed in so many tissues, is a gas, and is a physiologic free radical. NO is generated in the heart by one of three isoenzymes.[51] All three isoforms are present in the heart, including NOS1 (nNOS, or neuronal NOS), NOS2 (iNOS, or inducible NOS), and NOS3 (eNOS, or endothelial NOS).[56,57] NO signaling is reviewed in **Chapter 23**.

Contractile Performance of Intact Hearts

There are five main determinants of ventricular mechanical performance: preload (or Frank-Starling mechanism), afterload, contractility, lusitropy (diastolic function), and heart rate. This section describes the cardiac cycle and then the determinants of left ventricular (LV) function.

The Cardiac Cycle

The cardiac cycle, fully assembled by Lewis[58] but first conceived by Wiggers,[59] yields important information on the temporal sequence of events (**Fig. 22.16**). The three basic events with respect to the left ventricle are LV contraction, LV relaxation, and LV filling (**Table 22.3**). Similar mechanical events occur in the right ventricle.

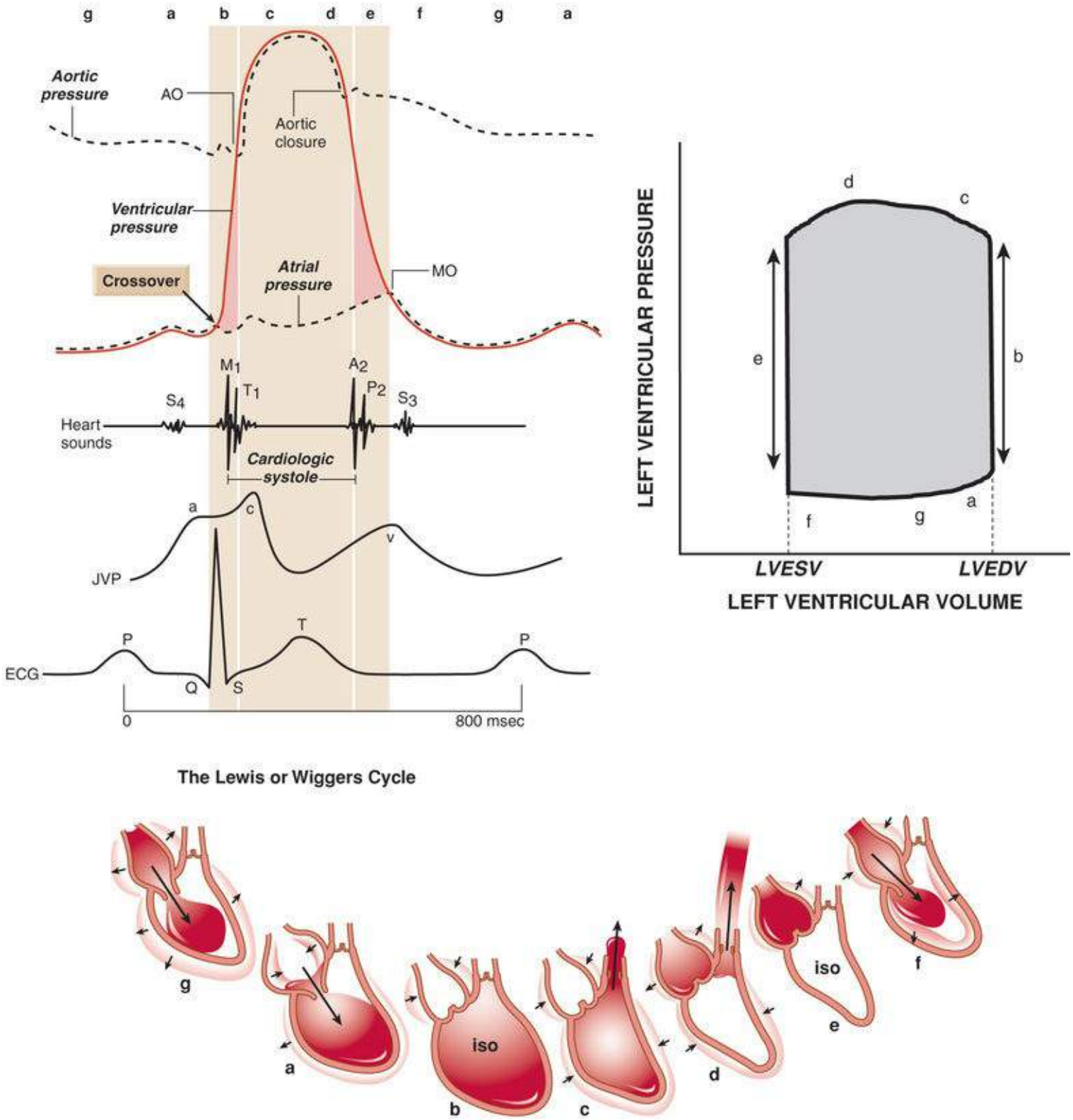

FIGURE 22.16 Mechanical events in the cardiac cycle depicted as pressure versus time **(upper left)** and left ventricular pressure versus volume **(upper right).** The visual phases of the ventricular cycle are shown in the **bottom panel.** For an explanation of phases a to g in upper right and bottom panels, **see Table 22.3**. *ECG,* Electrocardiogram; *JVP,* jugular venous pressure; M_1, mitral component of the first sound at the time of mitral valve closure; T_1, tricuspid valve closure, second component of the first heart sound; *AO,* aortic valve opening, normally inaudible; A_2, aortic valve closure, aortic component of the second sound; *MO,* mitral valve opening, may be audible in mitral stenosis as the opening snap; P_2, pulmonary component of the second sound, pulmonary valve closure; S_3, third heart sound; S_4, fourth heart sound; a, wave produced by right atrial contraction; c, carotid wave artifact during the rapid LV ejection phase; v, venous return wave, which causes pressure to rise with the tricuspid valve closed, *LVESV,* left ventricular end-systolic volume; *LVEDV,* left ventricular end-diastolic volume. (Modified from Opie LH: Heart Physiology, from Cell to Circulation. Philadelphia, Lippincott, Williams & Wilkins, 2004. Figure copyright L.H. Opie, © 2004. **Bottom panel,** Modified from Shepherd JT, Vanhoutte PM. The Human Cardiovascular System. New York: Raven Press;

1979, p 68.)

TABLE 22.3
The Cardiac Cycle

Left Ventricular Contraction
Isovolumic contraction (b)
Maximal ejection (c)
Left Ventricular Relaxation
Start of relaxation and reduced ejection (d)
Isovolumic relaxation (e)
LV filling: rapid phase (f)
Slow LV filling (diastasis) (g)
Atrial systole or kick (a)

The letters a to g refer to the phases of the cardiac cycle shown in Wiggers' diagram (**see Fig. 22.16**). These letters are arbitrarily allocated so that atrial systole (a) coincides with the A wave and (c) with the C wave of jugular venous pressure.

Left Ventricular Contraction

LV pressure increases as Ca^{2+} arrives at the contractile proteins after cellular depolarization triggers actin-myosin interaction.[4] This occurs shortly after the upstroke of the ventricular action potential, indicated by the QRS complex of the electrocardiogram (ECG; **Fig. 22.16**). When LV pressure exceeds that in the left atrium (normally 8 to 15 mm Hg), the mitral valve closes, causing the mitral component of the first sound, M_1. Right ventricular (RV) pressure changes are usually slightly delayed because of electrical conduction, such that tricuspid valve closure (T_1), follows M_1. The phase of LV contraction after mitral closure and before aortic opening when the LV volume is fixed is referred to as *isovolumic contraction*. As more myofibers become activated, LV pressure proceeds to increase until it exceeds aortic pressure, causing the aortic valve to open (usually a clinically silent event). Opening of the aortic valve is followed by the phase of *rapid ejection*. The rate of ejection is determined by the pressure gradient across the aortic valve, as well as the elastic properties of the aorta and the arterial tree, which undergo systolic expansion. LV pressure rises to a peak and then starts to fall.

Left Ventricular Relaxation

As myocyte $[Ca^{2+}]_i$ starts to decline because of SR Ca^{2+} uptake, Ca^{2+} dissociates from troponin C, thereby preventing further cross-bridge formation.[4] As this state of relaxation progresses, the rate of LV ejection of blood into the aorta falls (*phase of reduced ejection*). During this phase, blood flow from the left ventricle to the aorta rapidly diminishes but is maintained by aortic recoil—the Windkessel effect.[4] When the pressure in the aorta significantly exceeds the falling LV pressure, the aortic valve closes, which creates the first component of the second sound, A_2 (the second component, P_2, results from closure of the pulmonic valve as pulmonary artery pressure exceeds RV pressure). Thereafter, the ventricle continues to relax. Because the mitral valve is still closed during this phase after aortic closure, LV volume cannot change (*isovolumic relaxation*). The rate of pressure decay during isovolumic relaxation is related to the magnitude of systolic shortening in the preceding contraction, similar to a spring compressed below its unstressed slack length.[60] When LV pressure falls to below that in the left atrium, the mitral valve opens (normally silent), and the filling phase of the cardiac cycle restarts (**Fig. 22.16**).

Left Ventricular Filling Phases

Following mitral valve opening, the phase of rapid or early filling occurs and accounts for most of the ventricular filling.[4] Under normal circumstances, this is caused by a negative pressure gradient from atrium to the LV apex, creating a suction effect, especially during exercise, when LV filling rates must be augmented to increase cardiac output.[60] Such rapid filling may cause the physiologic third heart sound (S_3), when there is a hyperkinetic circulation or a pathologic S_3 when left atrial and LV diastolic pressures are elevated in congestive heart failure.[4] As pressures in the atrium and ventricle equalize, LV filling virtually stops (diastasis, separation). Renewed filling requires that atrial pressure exceed LV pressure. This is achieved by atrial systole (or the "left atrial kick"), which is especially important at a high heart rate, as during exercise, or when the left ventricle fails to relax normally, as in LV hypertrophy.[4]

Definitions of Systole and Diastole.
In Greek, *systole* means "contraction" and *diastole* means "to send apart." The start of systole can be regarded as the beginning of isovolumic contraction, when LV pressure exceeds the atrial pressure, or as mitral valve closure (M_1). *Physiologic systole* lasts from the start of isovolumic contraction to the peak of the ejection phase (**see Fig. 22.16 and Table 22.3**). *Physiologic diastole* commences as Ca^{2+} is taken back into the SR, so that myocyte relaxation dominates over contraction, and as the LV pressure starts to fall, as shown on the pressure-volume curve. In contrast, *cardiologic systole* is longer than physiologic systole and is demarcated by the interval between the first heart sound (M_1) to the closure of the aortic valve (A_2). The remainder of the cardiac cycle automatically becomes *cardiologic diastole*. For the cardiologist, *protodiastole* is the early phase of rapid filling, the time when S_3 can be heard. This sound probably reflects ventricular wall vibrations during rapid filling and becomes audible with an increase in LV diastolic pressure, wall stiffness, or rate of filling.

Contractility Versus Loading Conditions

Contractility

Contractility, or the *inotropic state*, is the inherent capacity of the myocardium to contract independently of changes in preload or afterload.[60] These are key terms in cardiologic language. At the molecular level, an increased inotropic state is usually explained by either enhanced Ca^{2+} transients or enhanced myofilament Ca^{2+} sensitivity and typically means a greater rate of contraction to reach a greater peak force. Frequently, increased contractile function is associated with enhanced rates of relaxation, or a lusitropic effect (e.g., as during beta-adrenergic activation). Contractile function is an important regulator of myocardial oxygen (O_2) uptake. Factors that increase contractility include exercise, adrenergic stimulation, digitalis, and other inotropic agents.

Preload

It is important to stress that any change in the contractility should be independent of the loading conditions. The preload describes the degree of myocardial stretch or distention before contraction has started and is best represented at the chamber level by the LV end-diastolic volume (EDV). Because volume is difficult to measure accurately and precisely in practice, preload is often estimated by LV end-diastolic pressure (EDP), but it is important to remember that the relationship between EDP and EDV varies between patients, especially when diastolic dysfunction or ventricular interdependence are

present.

Afterload

Afterload refers to the forces opposing LV ejection.[4,60] Afterload is often oversimplified as being equal to aortic blood pressure, but is more accurately described as aortic *impedance* or *elastance*, which incorporates steady and oscillatory components of cardiac load. LV afterload can also be expressed by the wall stress that exists during systole. When preload increases, the stroke volume rises according to Starling's law, if all other factors are held constant. Conversely, when afterload increases, stroke volume drops.

Starling's Law of the Heart

Venous Filling Pressure and Heart Volume

In 1918, Starling related the venous pressure in the right atrium to the heart volume in a dog heart-lung preparation.[4] He proposed that, within physiologic limits, the larger the volume of the heart, the greater the energy of its contraction and the amount of chemical change at each contraction. Starling did not, however, measure sarcomere length. He could only relate *LV volume* to cardiac output. In practice the LV volume is not often measured, rather making use of a variety of surrogate measures, such as LVEDP or the pulmonary capillary wedge pressure (PCWP). The relation between LVEDV and LVEDP is curvilinear, with the slope reflecting LV compliance (bottom portion of pressure-volume loop, **Fig. 22.16**). The venous filling pressure can be measured in humans, although indirectly by Swan-Ganz catheterization, as can the stroke volume.

Frank and Isovolumic Contraction

If a larger heart volume increases the initial length of the muscle fiber, to increase stroke volume and thus cardiac output, diastolic stretch of the left ventricle (and increased sarcomere length) increases the force of contraction.[4] In 1895, Frank had already reported that the greater the initial LV volume, the more rapid the rate of rise, the greater the peak pressure reached, and the faster the rate of relaxation. He described both a positive *inotropic effect* (*ino*, “fiber”; *tropus*, “move”) and an increased lusitropic effect. These complementary findings of Frank and Starling are often combined into the *Frank-Starling law*. Thus an increase in the strength of contraction can generally be categorized as either a *Frank-Starling effect* (increased sarcomere length) or an inotropic effect (altered Ca^{2+} transient or myofilament Ca^{2+} sensitivity), although both effects can occur simultaneously, as with physical exercise. Being able to parse effects mechanistically in this way can be helpful in selecting therapeutic interventions.

Preload and Afterload Are Interlinked

Although the previous distinctions between preload and afterload are useful, one can influence the other. By the Frank-Starling law, an increased LV volume leads to increased contractile function, which in turn will increase the systolic aortic pressure and thus the afterload in the subsequent contraction cycle. During LV ejection, sarcomere length progressively declines, decreasing both myofilament Ca^{2+} sensitivity and maximal force, which along with progressive $[Ca^{2+}]_i$ decline, reduces contractile force. Afterload also dynamically changes during ejection and declines as ejection wanes.

Preload and Diastolic Pressures May Become Uncoupled in Diseased Hearts.
LV pressure and volume are nonlinearly related because of myocardial compliance variations. In patients with reduced diastolic LV compliance, a higher EDP is required to achieve a similar EDV (preload). While the left and right ventricles influence each another in series (right ventricle pumps blood to left ventricle), factors in the right heart and pericardium also may influence LV pressure when there is enhanced ventricular interdependence, for example, with RV dilation from acute infarction or pulmonary embolism, or pericardial restraint caused by fibrotic constrictive pericarditis. In these situations, EDP may be high even when EDV is normal or low, because the right heart and pericardium are applying "external pressure" that uncouples pressure from preload volume.

The true "distending" pressure that determines LV preload volume is referred to as the *left ventricular transmural pressure* and can be calculated by EDP minus the external pericardial pressure. Pericardial pressure is approximated by right atrial pressure; thus transmural pressure can be estimated by the difference between EDP (or PCWP) and right atrial pressure.

Force-Length Relationships and Ca^{2+} Transients

Acute changes in sarcomere length do not alter the Ca^{2+} transient appreciably. Thus the favored explanation for the steep length-tension relationship of cardiac muscles is enhanced myofilament Ca^{2+} sensitivity as the initial sarcomere length increases[4] (**Fig. 22.17**).

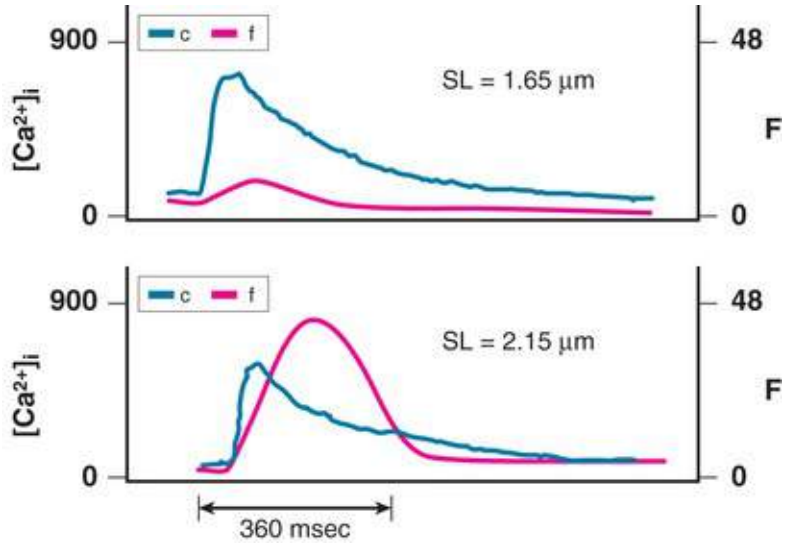

FIGURE 22.17 Length-dependent enhancement of myofilament Ca sensitivity. In the **top panel,** sarcomere length (*SL*) is 1.65 µm, which produces modest developed force (*f*). In the **bottom panel,** at near-maximal sarcomere length (2.15 µm), the Ca^{2+} transient (*c*) is almost unchanged, but causes much greater force development. (Modified from Backx PH, ter Keurs HEDJ. Fluorescent properties of rat cardiac trabeculae microinjected with fura-2 salt. Am J Physiol 1993;264:H1098.)

Anrep Effect: Abrupt Increase in Afterload

When the aortic pressure is elevated abruptly, it limits ejection and tends to increase EDV, which acutely increases force and pressure at the next beat by the Frank-Starling effect. However, in a slower adaptation that takes seconds to minutes, the inotropic state of the heart increases (and Ca^{2+} transients are larger). Both phases of this can be readily recapitulated in isolated muscle strips from the heart. This slow force

response or adaptation is referred to as the *Anrep effect*. Extensive study has implicated stretch-induced activation of several important autocrine/paracrine myocyte signaling pathways in this slowly developing inotropic effect.[59,61]

Wall Stress

Wall stress develops when tension is applied to a cross-sectional area, and the units are force per unit area (**Fig. 22.18**). According to Laplace's law, wall stress = (pressure × radius)/(2 × wall thickness). This equation, although an oversimplification, emphasizes two points. First, the larger the LV size and radius, the higher is the wall stress.[4] Second, at any given radius (LV size), the greater the pressure developed by the left ventricle, the greater is the wall stress. An increase in wall stress achieved by either of these two mechanisms (LV size or intraventricular pressure) will increase myocardial O_2 uptake, because a greater rate of ATP use is required for the myofibrils to develop more tension.

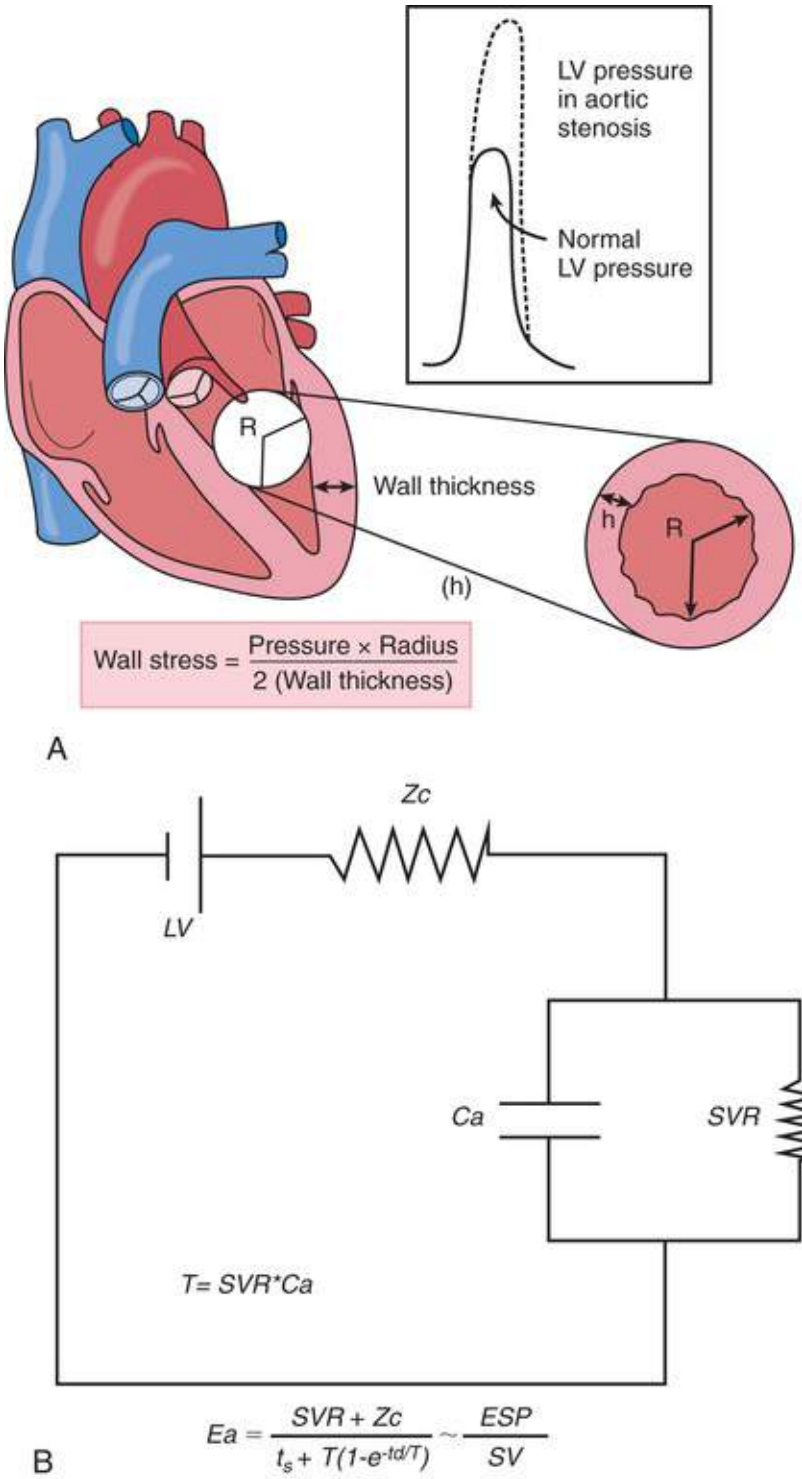

FIGURE 22.18 **A,** Wall stress increases as afterload increases**.** The formula shown is derived from Laplace's law. The increased LV pressure in aortic stenosis is compensated for by LV wall hypertrophy, which decreases the denominator on the right side of the equation. **B,** Electrical circuit analog of the arterial system as it relates to LV afterload, based on the three-element Windkessel model. The LV generates current (flow, cardiac output) that is ejected through an upstream impedance in the proximal aorta (characteristic impedance, *Zc*) upstream of total arterial compliance (*Ca*) and systemic vascular resistance (*SVR*) that arranged in parallel. Effective arterial elastance (*Ea*) is a lumped measure of net arterial "stiffness" that is related to each of these components and can be estimated by the ratio of end-systolic LV pressure (*ESP*) to stroke volume (*SV*). Ea (and thus arterial afterload) increases as Zc or SVR increases or as Ca decreases. *R,* Radius. (From Opie LH. Heart Physiology, from Cell to Circulation. Philadelphia: Lippincott Williams & Wilkins; 2004. Figure copyright L.H. Opie, © 2004.)

In cardiac hypertrophy, Laplace's law explains the effects of changes in wall thickness on wall stress (**Fig. 22.18**). The increased wall thickness from hypertrophy balances the increased pressure, and wall stress remains unchanged during the phase of compensatory hypertrophy.[4] The concept that this change is compensatory and beneficial has been challenged by a mouse model in which the process of hypertrophy

was genetically inhibited so that wall stress increased in response to a pressure load, yet these mice had better cardiac mechanical function than did the wild-type mice in which compensatory hypertrophy developed.[4] Another clinically useful concept is that in congestive heart failure, the heart dilates so that the increased radius elevates wall stress. Furthermore, because ejection of blood is inadequate, the radius stays too large throughout the contractile cycle, and both end-diastolic and end-systolic wall stress is higher. This decreases LV efficiency, increases myocardial O_2 demand, and augments release of natriuretic peptide levels. The overall reduction in heart size decreases wall stress and improves LV function.[4]

Wall Stress, Preload, and Afterload.

This definition brings in both the volume and the fiber length that define the radius.[4] *Preload* can be defined as the wall stretch at the end of diastole, and therefore at the maximal resting length of the sarcomere (**Fig. 22.18**). Measurement of wall stress in vivo is difficult because use of the radius of the left ventricle (see the preceding sections) neglects the confounding influence of the complex LV anatomy. Surrogate preload indices include LVEDP or dimensions (the latter being the major and minor axes of the heart in a two-dimensional echocardiographic view). *Afterload*, being the load on the contracting myocardium, is also the wall stress during LV ejection. Increased afterload means that increased intraventricular pressure has to be generated first to open the aortic valve and then during the ejection phase. These increases will translate into increased myocardial wall stress, which can be measured either as an average value or at end-systole.

Peak systolic wall stress reflects the three major components of afterload: peripheral resistance, arterial compliance, and peak intraventricular pressure.[4] Decreased arterial compliance and increased afterload can be anticipated with aortic remodeling and dilation, as in severe systemic hypertension or in elderly patients. The systolic timing of the afterload can also influence LV relaxation. In experimental and human studies, a late systolic load, as when the aorta has stiffened, is associated with impaired LV systolic shortening and diastolic relaxation.[62,63] This is why it is crucial to consider both afterload and preload when evaluating indices of LV function based on the velocity or extent of tissue motion using echocardiography.[63]

Aortic impedance or *elastance* gives another accurate measure of LV afterload (**Fig. 22.18**). The advantage of impedance/elastance compared to wall stress is that this measure is totally independent of heart size or wall thickness. The aortic impedance reflects the ratio of aortic pressure to flow across different frequency harmonics. During systole, when the aortic valve is open, an increased afterload will communicate itself to the ventricles by increasing wall stress. In LV failure, aortic impedance is augmented not only by peripheral vasoconstriction (high systemic vascular resistance), but also by decreases in aortic compliance (ability of aorta to “yield” during systole), especially with aging. The problem with the clinical measurement of aortic impedance is that it is expressed in the frequency domain, which is cumbersome to relate to time-domain measures of LV function. An alternative index of LV afterload is the *arterial elastance* (Ea), estimated by the relationship between end-systolic LV pressure and stroke volume (**Fig. 22.18**). Ea is derived from the Windkessel model of the arterial system, which includes upstream characteristic impedance (Zc) and a downstream resistance and capacitor that are situated in parallel. Thus, Ea incorporates both mean resistive components of load along with heart rate and aortic compliance.

Heart Rate and Force-Frequency Relationship

Treppe or Bowditch Effect

An increased heart rate progressively enhances the force of ventricular muscle contraction, even in isolated papillary muscle preparations and isolated myocytes, the *Bowditch staircase phenomenon.*[4] Alternative names are the *treppe* (German, “steps”) phenomenon, positive inotropic effect of activation, or force-frequency relationship (**Fig. 22.19A**). Conversely, a decreased heart rate has a negative staircase effect. However, at a very high heart rate, force progressively decreases. These effects at the myocyte level are largely attributable to changes in Na^+ and Ca^{2+} in the myocyte. At a higher heart rate, there is more Na^+ and Ca^{2+} entry per unit time and less time for the cell to extrude these ions, which results in higher $[Na^+]_i$ and cellular and SR Ca^{2+} content.[1] The increase in SR Ca^{2+} content increases the amount of Ca^{2+} released during the action potential, the primary cause of the increase in contractility at higher heart rates. The elevation in $[Na^+]_i$ also further reduces the efficacy of NCX in extruding Ca^{2+} during the cardiac cycle, thereby leading to further gains in cellular (and SR) Ca^{2+}. A new steady-state Ca^{2+} load will be achieved when the increased Ca^{2+} transients cause Ca^{2+} extrusion by NCX to match the amount of Ca^{2+} influx at each beat (and similarly when Na^+,K^+-ATPase extrudes the amount of Na^+ that enters per beat). This is the definition of steady state, with no net gain or loss of cellular Ca^{2+} (or Na^+) from beat to beat.

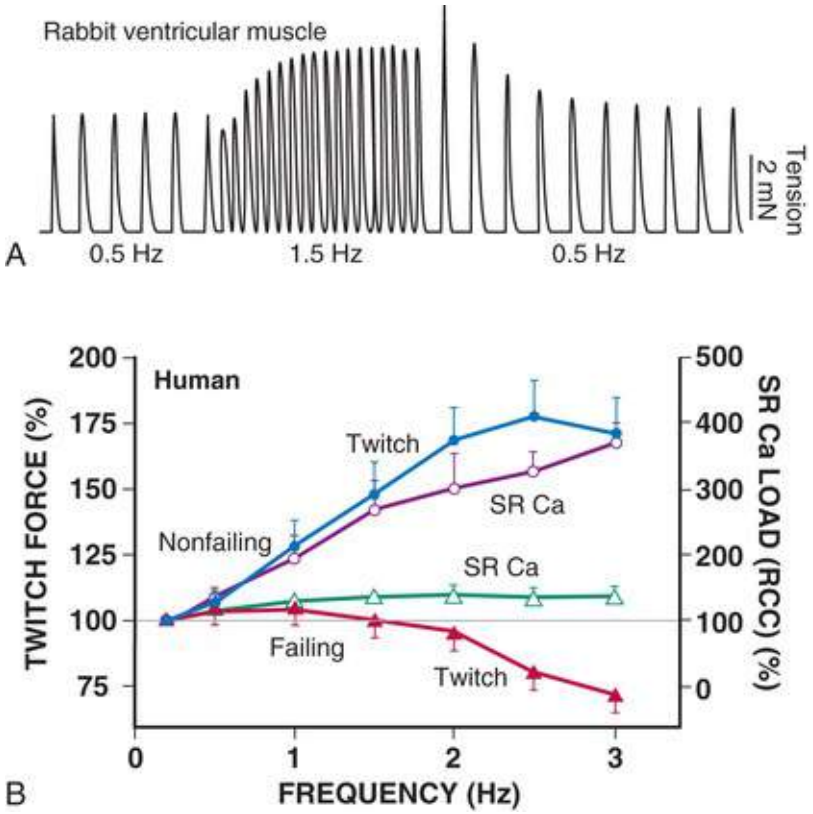

FIGURE 22.19 Heart rate dependence on contraction: Bowditch staircase or *treppe* phenomenon. **A,** An increased stimulation rate increases the force of contraction. The tension developed by rabbit ventricular muscle is shown in mN. During the first shortened diastolic interval the first beat is smaller, an effect caused mainly by refractoriness of the SR Ca^{2+} release channel. As the 1.5-Hz stimulation approaches a steady state, the contraction is progressively increased, an effect attributable to the gain in myocyte Na^{+} and Ca^{2+} and enhanced SR Ca^{2+} content. When the diastolic interval is prolonged (first beat at 0.5 Hz), the first beat is especially large because the SR Ca^{2+} load is still elevated and there is more time for the RyR to recover from refractoriness. The larger Ca^{2+} transient then drives higher extrusion of Ca^{2+} from the cell as the initial 0.5-Hz steady state is eventually achieved. **B,** With an increasing heart rate, normal nonfailing ventricular muscle exhibits a progressive increase in SR Ca^{2+} content (*SR Ca*) and a positive force-frequency relationship that peaks at approximately 2.5 Hz. The decline at 3 Hz is caused by reduced fractional SR Ca^{2+} release. In failing human ventricular muscle, the SR fails to increase its Ca^{2+} content appreciably at higher heart rates; this results in a negative force-frequency relationship (which is dominated by the refractoriness, but here is not compensated by increased SR Ca^{2+}). SR Ca^{2+} in these experiments was assessed by rapid-cooling contractures (*RCC*). (From Bers DM. Excitation-Contraction Coupling and Cardiac Contractile Force. Dordrecht, Netherlands: Kluwer Academic; 2001.)

To the extent that the SR can take up this extra Ca^{2+} load at a higher heart rate, diastolic $[Ca^{2+}]_i$ and stiffness remain low. This is helped by an increase in the rate of SR Ca^{2+} uptake at a higher heart rate (known as “frequency-dependent acceleration of relaxation”) mediated by faster SR Ca^{2+} uptake function (although the mechanism is not fully resolved). However, if SR Ca^{2+}-ATPase and NCX are unable to remove Ca^{2+} sufficiently from the cytoplasm during the time between beats, an increase in diastolic $[Ca^{2+}]_i$ and force/stiffness will occur. Systolic function is also limited at increasing heart rates. The primary reason at physiologic heart rates is that the SR Ca^{2+} release process has refractoriness that is reminiscent of that seen with voltage-gated Na^{+} and Ca^{2+} channels. Thus, at higher heart rates, even when a normal action potential and Ca^{2+} current signal occur, the fraction of SR Ca^{2+} released can be reduced (**Fig. 22.19B**). In a sense, the resulting Ca^{2+} transient and contraction at increasing heart rates can be seen as the product of the increasing SR Ca^{2+} content times the declining fractional SR Ca^{2+} release, with the former factor being dominant (especially at more moderate heart rate) but the latter being progressively limiting.

In the intact heart this scenario is complicated by alterations in filling time and consequent changes in

preload. That is, at higher heart rates there will also be a reduced filling time that will limit preload (EDV), and thus a negative Frank-Starling effect will modulate the positive and negative inotropic effects to limit the overall strength of LV contraction. In addition, higher aortic elastance (Ea) at increased heart rates will also increase cardiac afterload and limit the ability of the left ventricle to eject blood. Thus, both fundamental myocyte and hemodynamic properties combine to influence net cardiac function at increased heart rates.

Premature ventricular complexes (PVCs) or *extrasystoles* can also modulate contraction in understandable ways. When a PVC occurs during the time when SR Ca^{2+} release is partially refractory and the left ventricle has not been refilled, the strength of that PVC will be very weak and may even fail to open the aortic valve. However, because the PVC had low SR Ca^{2+} release, less Ca^{2+} current inactivation and less Ca^{2+} extrusion from the cell occur and result in much higher SR Ca^{2+} release at the next (postextrasystolic) beat following the usual compensatory pause (because of AV node refractoriness during the next sinus node beat). Similarly, by the time the postextrasystolic beat occurs, the much smaller LV ejection and continued LV filling result in greater preload, reduced afterload, and a larger Ca^{2+} transient. These cellular and hemodynamic effects combine to cause an extremely strong, postextrasystolic potentiation beat that a person can often sense as the heart "skipping a beat."

Physiologic Force-Frequency Relationship and Optimal Heart Rate

When the heart rate increases under physiologic conditions, it is usually accompanied and partially mediated by sympathetic beta-adrenergic activation at myocytes throughout the heart. As discussed earlier, this will increase Ca^{2+} current influx, the rate of SR Ca^{2+} uptake, and the amount of SR Ca^{2+} released during the beat, which greatly amplifies the inotropic and lusitropic effects associated with alteration of the heart rate without sympathetic activation. However, the beta-adrenergic system also enhances Na^+,K^+-ATPase activity to limit the rise in $[Na^+]_i$ that occurs at the higher heart rate, and this would temper the overall inotropic effect. Normally, peak contractile force at a fixed muscle length (isometric contraction) increases, and a peak is reached at about 150 to 180 beats/min[1,4] (**Fig. 22.19B**). In situ, the optimal heart rate is also dependent on the previous hemodynamic factors and a functioning sympathetic system, so the exact value of the heart rate when cardiac output starts to decrease rather than increase is more difficult to specify and likely varies among people. Pacing rates of up to 150 beats/min can be tolerated, whereas higher rates cannot because of the development of AV block. In contrast, during exercise, indices of LV function still increase up to a maximum heart rate of about 170 beats/min, presumably because of enhanced contractile function and peripheral vasodilation.[4] The critical heart rate associated with a fall-off in LV function likely occurs at lower values in diseased hearts, but this is not well understood.

Myocardial Oxygen Uptake

Myocardial O_2 demand can be increased by the heart rate (HR), preload, or afterload (**Fig. 22.20**), factors that can all precipitate myocardial ischemia in those with coronary artery disease (CAD). Because myocardial O_2 uptake ultimately reflects the rate of mitochondrial metabolism and thus ATP production, any increase in ATP requirement will be reflected in increased O_2 uptake. In general, factors increasing wall stress will increase O_2 uptake. Increased afterload causes increased systolic wall stress, which requires greater O_2 uptake. Increased diastolic wall stress, resulting from increased preload (EDV), will also require more oxygen because the greater stroke volume must be ejected against the afterload. In

states of enhanced contractile function, the rate of change in wall stress is increased. Because systolic blood pressure (SBP) is an important correlate of afterload, a practical index of O_2 uptake is SBP × HR, the *double product*. The concept of wall stress in relation to O_2 uptake also explains why heart size is such an important determinant of myocardial O_2 uptake (because a larger radius increases wall stress).

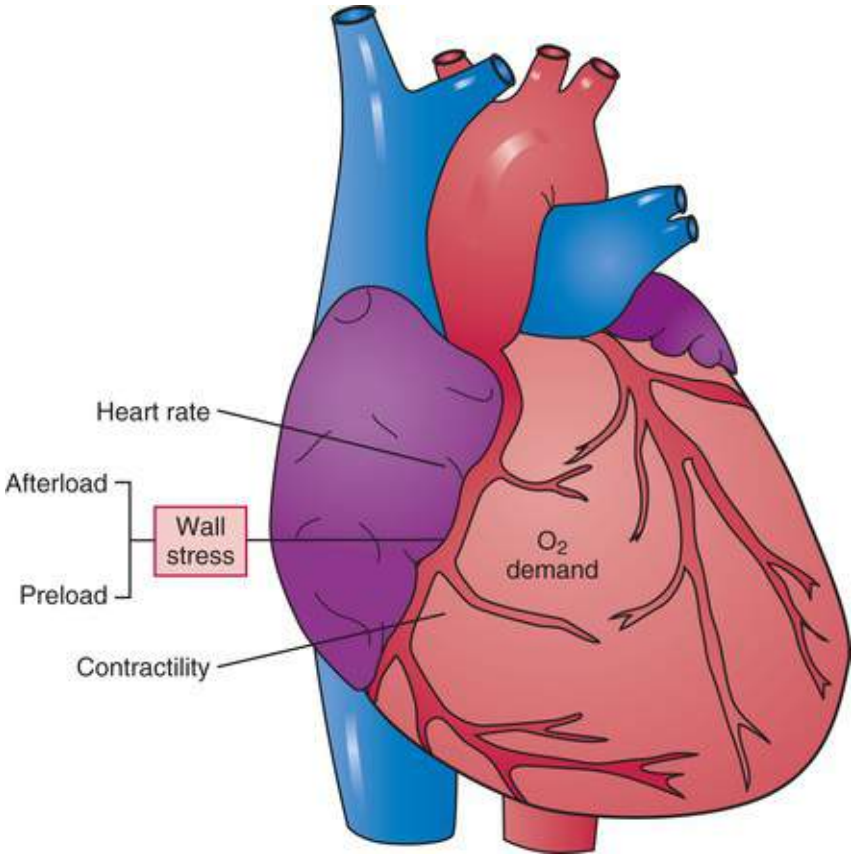

FIGURE 22.20 Major determinants of the O_2 demand of the normal heart: heart rate, wall stress, and contractile function. (Modified with permission from Opie LH. Heart Physiology, from Cell to Circulation. Philadelphia: Lippincott Williams & Wilkins; 2004. Figure copyright L.H. Opie, © 2004.)

Work of the Heart

External work (pressure × volume) is done by the heart, with stroke volume (or cardiac output) being the volume moved against arterial blood pressure. *Volume work* (associated with increased stroke volume) requires less oxygen than *pressure work* does (increased pressure or heart rate), and one might suppose that external work is not an important determinant of myocardial O_2 uptake. However, three determinants of myocardial O_2 uptake are involved: preload (because this helps determine stroke volume), afterload (in part determined by blood pressure), and heart rate. *Minute work* can be defined as the product of systolic blood pressure, stroke volume, and heart rate (SBP × SV × HR). Not surprisingly, heart work is related to O_2 uptake. This *pressure-work index* takes into account both the double product (SBP × HR) and HR × SV (i.e., cardiac output). The *pressure-volume area* is another index of cardiac work or O_2 uptake, but requires invasive monitoring for accurate measurements (**see Fig. 22.18**). External cardiac work can account for up to 40% of the total myocardial O_2 uptake.

Internal Work (Potential Energy).

Total O_2 consumption is related to the total work of the heart (area *abcd* in **Fig. 22.21**), which means that both external work (area *abce*) and the volume-pressure triangle joining the end-systolic volume-pressure point to the origin (area *cde*; marked PE).[64] Although this area has been called internal work, more strictly it should be called the "potential energy" that is generated within each contraction cycle but not converted to external work. Such potential energy at the end of systole (point *c*) may be likened to the potential energy of a compressed spring.

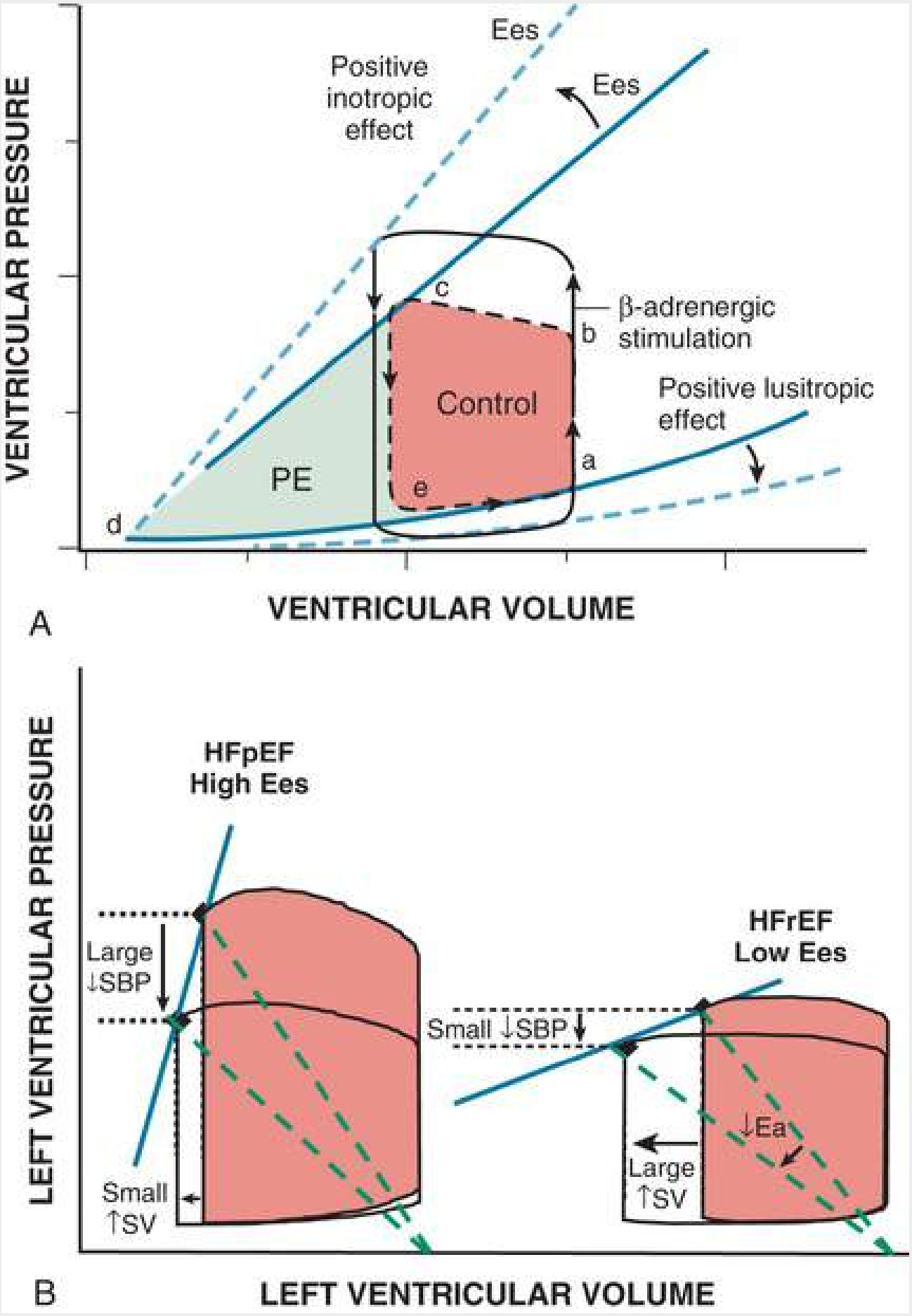

FIGURE 22.21 Pressure-volume loop of the left ventricle. **A,** Note the effects of beta-adrenergic catecholamines with both positive inotropic (increased slope of line *Ees*) and increased lusitropic (relaxant) effects. *Ees* is slope of the pressure-volume relationship. The total pressure-volume area (for the control area, see *abcd*) is closely related to myocardial O_2 uptake. The area *cde* is the component of work spent in generating potential energy (*PE*). **B,** Representative LV pressure-volume loops in a patient with heart failure and preserved ejection fraction (HFpEF, left) and heart failure with reduced ejection

fraction (HFrEF, right) demonstrating the differential effects of vasodilator therapy. In HFpEF, the end-systolic pressure volume relationship is steep, Ees is high, and reductions in arterial afterload or elastance (*Ea*) from acute vasodilator therapy (in this case, nitroprusside infusion) lead to dramatic reductions in systolic blood pressure (*SBP*) and modest increases in stroke volume (*SV,* defined by the width of the pressure-volume loop). In the patient with HFrEF, contractility is depressed, Ees is low, and the end-systolic pressure volume relationship is accordingly shallow. Thus the same degree of vasodilation (reduction in Ea) causes much less reduction in SBP and much more increase in forward SV. (**A**, Modified from Opie LH. Heart Physiology, from Cell to Circulation. Philadelphia: Lippincott, Williams & Wilkins; 2004. Figure copyright L.H. Opie, © 2004; **B,** modified from Schwartzenberg S et al. J Am Coll Cardiol 2012; PMID 22281246.)

Efficiency of work is the relationship between the work performed and myocardial O_2 uptake.[4] Metabolically, efficiency is increased by promotion of glucose rather than fatty acids as the major myocardial fuel. Conversely, heart failure decreases the efficiency of work, although the basis is not fully understood. Because as little as 12% to 14% of O_2 uptake may be converted to external work,[4] it is probably the "internal work" that becomes less demanding. Ion fluxes ($Na^+/K^+/Ca^{2+}$) account for approximately 20% to 30% of the ATP requirement of the heart, so most ATP is spent on actin-myosin interaction and much of that on the generation of heat rather than on external work. An increased initial muscle length sensitizes the contractile apparatus to Ca^{2+}, thereby theoretically increasing the efficiency of contraction by diminishing the amount of Ca^{2+} flux required.

Measurements of Contractile Function

Force-Velocity Relationship and Maximum Contractile Function in Muscle Models

If contractility is truly independent of load and the heart rate, unloaded heart muscle stimulated at a fixed rate should have a maximum value of contractile function for any given magnitude of the cytosolic Ca^{2+} transient. This value, the V_{max} of muscle contraction, is defined as the *maximal velocity of contraction* when there is no afterload to prevent maximal rates of cardiac ejection.[4] Beta-adrenergic stimulation increases V_{max}, and converse changes are found in failing myocardium. V_{max} is also termed V_0 (maximum velocity at zero load). As the load increases, the velocity of shortening decreases. A limitation of this relatively simple concept is that V_{max} cannot be measured directly but must be extrapolated from the *force-velocity relationship* to the velocity axis intercept. The other extreme condition is zero muscle shortening, with all the energy going into the development of pressure (P_0) or force (F_0). This situation is an example of *isometric shortening*.

Isometric Versus Isotonic Contraction

Data for P_0 are obtained under isometric conditions (length unchanged). When muscle is allowed to shorten against a steady load, the conditions are *isotonic* (*tonic,* "contractile force").[4] Thus the force-velocity curve may be a combination of initial isometric conditions followed by isotonic contraction and then abrupt and total unloading to measure V_{max}. Although isometric conditions can be found in the whole heart (e.g., during isovolumic contraction), isotonic conditions are rare because afterload is constantly changing during the ejection period, and complete unloading is impossible. However, as shortening progresses during ejection, the maximal P_0 declines. and velocity is lower for any given nonzero load. Therefore the force-velocity relationship is heuristically useful, but measurements in vivo are limited.

Pressure-Volume Loops

Accordingly, measurements of pressure-volume loops are among the best of the current approaches for assessment of the contractile behavior of the intact heart (**see Figs. 22.18 and 22.21**). A crucial measurement is the *end-systolic elastance* (Ees) from the pressure-volume relationship.[4] When the loading conditions are changed, alterations in the slope of this line joining the different E_s points (the end-systolic pressure-volume relationship) are generally a good load-independent index of the contractile performance of the heart. In clinical practice, the need to change the loading conditions and the requirement for invasive monitoring for the full pressure-volume loop lessen the usefulness of this index. Measurement of LV volume adequately and continuously throughout the cardiac cycle is not easy. During a positive inotropic intervention, the pressure-volume loop reflects a smaller end-systolic volume and a higher end-systolic pressure, so the slope of the pressure-volume relationship (E_s) has moved upward and to the left (**Fig. 22.21**). When the positive inotropic intervention consist of beta-adrenergic stimulation, the enhanced relaxation (lusitropic effect) results in a lower pressure-volume curve during ventricular filling than in controls.

Ventricular Function in Heart Failure (see also Chapter 23).
In patients with heart failure and reduced ejection fraction (HFrEF), the ventricle is dilated, EF is low, and contractility is severely depressed.[65] As such, the pressure-volume loop is shifted to the far right on the volume axis, and the end-systolic pressure-volume relationship (ESPVR, contractility) is very shallow (**Fig. 21.21**). In this setting, a reduction in arterial afterload (Ea) produces modest reductions in blood pressure despite often dramatic increases in stroke volume. This heightened "afterload dependence" of the LV in HFrEF serves as the hemodynamic basis for aggressive use of vasodilators in this disease. In contrast, patients with heart failure and preserved EF (HFpEF) display an increased Ees (steep ESPVR). In this patient, the same degree of afterload reduction (decrease in Ea) using a vasodilator causes a much more dramatic drop in blood pressure, with little improvement in forward stroke volume.

Limitations of the Concept of Contractility

Despite all the previous procedures that can be adopted in an attempt to measure true contractility (or the inotropic state), the concept has at least two serious defects: (1) the absence of any noninvasive index that can be measured unequivocally and (2) the impossibility of separating the cellular and chamber-level mechanisms of changes in contractile function from those of load or the heart rate.[4] Thus an increased heart rate, by the changes in Na^+ and Ca^{2+} handling noted earlier, gives rise to increased cytosolic Ca^{2+} transients, and contraction is clearly an inotropic effect. However, the simultaneous changes in preload and afterload also involve Frank-Starling effects, which complicates this picture in the clinical setting. Similarly, increased preload involves increased fiber stretch, which in turn causes enhanced myofilament Ca^{2+} sensitivity, a factor that in a sense is built into the Frank-Starling effect. However, additional changes in myofilament Ca^{2+} sensitivity (e.g., during acidosis or alpha-adrenergic activation) would be attributed to inotropic changes. *So there is a clear overlap between contractility, which should be independent of load or heart rate, and the effects of load and heart rate on the cellular mechanisms.*[3,4] Even though this does not undermine the importance of the intrinsic mechanistic distinctions between contractility/inotropy and Frank-Starling mechanisms, the distinction can be blurred by the clinical context and available measurements. For example, in humans with atrial fibrillation and constantly

varying ventricular frequency, contractility inferred from pressure-volume loops constantly changes from beat to beat. It is then more difficult to infer a “true” change in LV contractility versus operation of the Frank-Starling mechanism because of varying diastolic filling times.[4]

Left Ventricular Relaxation and Diastolic Dysfunction

Normal diastolic function allows the ventricle to fill adequately during rest and exercise, without an abnormal increase in LA pressure.[60] The phases of diastole are isovolumic pressure decline and filling. The filling phase is divided into early rapid filling, diastasis, and atrial systole. Early rapid filling contributes 70% to 80% of LV filling in normal individuals. Early diastolic filling is driven by the LA-to-LV pressure gradient, which is dependent on a complex interplay of factors, including myocardial relaxation, LV elastic recoil, LV diastolic stiffness, left atrial (LA) pressure, ventricular interaction, pericardial constraint, pulmonary vein properties, and mitral orifice area. Diastasis occurs in mid-diastole when LA and LV pressure is usually almost equal. It contributes less than 5% of LV filling, and its duration shortens with tachycardia. In normal persons, atrial systole contributes 15% to 25% of LV diastolic filling without raising mean LA pressure. This contribution depends on the PR interval, atrial inotropic state, atrial preload, atrial afterload, autonomic tone, and heart rate. **Chapter 26** further details the basic mechanisms of LV relaxation, as well as measurements of LV relaxation. In addition to being important in heart failure, abnormalities in diastolic relaxation and stiffness develop as part of normal aging, and this cardiac aging process seems to be accelerated in the presence of obesity.[66]

Right Ventricular Function

Most of the forgoing principles and discussions also apply to the right ventricle, and the differences are not discussed in any detail here. RV myocytes are fundamentally the same as those in the left ventricle, with some minor, mainly quantitative differences in their ion channel, electrophysiology, Ca^{2+} handling, and myofilament properties. The most important functional differences are in the chamber geometry related to Laplace's law and the normal levels of pressure developed (lower pressure in the right ventricle and pulmonary circulation).[67] The right ventricle has a larger radius of curvature, which would tend to increase wall tension, but it normally develops much lower pressure, which greatly reduces wall tension (wall tension = [radius × pressure]/[2 × thickness]). RV wall thickness is also lower such that the normal characteristics of RV shape and size are functionally matched to the different prevailing conditions on the right ventricle. The right ventricle is poorly suited to eject against high pressures, as in pulmonary hypertension, and this heightened afterload-dependence is further accentuated in patients with heart failure.[68]

Atrial Function

The left atrium has five main functions.[4,69] First and best known, the left atrium functions as a blood-receiving reservoir chamber. Second, it also is a contractile chamber that by presystolic contraction helps complete LV filling with an atrial kick. Third, the left atrium functions as a conduit that empties its contents into the left ventricle down a pressure gradient after the mitral valve opens. Fourth, it is a *blood volume sensor* in the heart and releases atrial natriuretic peptide (ANP) in response to stretch so that ANP-induced diuresis can help restore blood volume to normal. Notably, in congestive heart failure, when the renin-angiotensin system causes fluid retention and exacerbates the elevation in LA pressure and

volume, ANP secretion is elevated. Fifth, the left atrium contains receptors for the afferent arms of various reflexes, including mechanoreceptors that increase the sinus discharge rate, thereby contributing to the tachycardia of exercise as venous return increases (Bainbridge reflex).[3,4]

The atrial pressure-volume loop is very different in shape from that of the ventricles in that it resembles a figure 8. During atrial pacing, preload is increased and the atria are distended, so the volume part of the loop is small, and the pressure part of the loop is much enlarged.[67] The atria have a number of differences in structure and function from the ventricles, including smaller myocytes with fewer T tubules, a shorter action potential duration, and more fetal myosin isoforms (both heavy and light chains).[70] The more rapid atrial repolarization is caused by increased outward potassium currents, such as I_{to}, and also has faster Ca^{2+} transient kinetics. In general, these histologic and physiologic changes might be related to the decreased need for the atria to generate high intrachamber pressures, rather than being sensitive to changes in volume while retaining enough contractile action to help with LV filling and to respond to inotropic stimuli. *Atrial remodeling* refers to a variety of ionic, structural, contractile, and metabolic changes that are induced by insults such as chronic atrial tachyarrhythmias, including atrial fibrillation,[70] or by left atrial stretch and enlargement. Cellular mechanisms include decreased L-type Ca^{2+} channel activity,[70] increased abnormal collagen,[71] and probably adverse stretch-induced signaling. The results include poor contractile performance and increased initiation and perpetuation of atrial fibrillation. Atrial remodeling and deterioration in left atrial function lead to worsening pulmonary hypertension and secondary right ventricular dysfunction in patients with heart failure.[72]

Future Perspectives

During the last 20 years we have gained tremendous molecular and cellular insight into a much richer, quantitatively detailed understanding of the individual steps in the overall excitation-contraction-relaxation process. In addition, there is a greatly enhanced understanding about how all these processes interact at the cellular and tissue level, how they are regulated by numerous interacting signaling pathways, and what goes wrong during certain cardiac pathologies. This is a very complex system, and diseases such as heart failure are also extremely complex. In the coming 5 years we can expect further clarification of all these systems, likely with a better understanding of signaling in local microdomains and protein complexes. At present, however, we must use this rich mechanistic knowledge to test novel therapeutic strategies for heart failure (e.g., SERCA2 overexpression, RyR inhibitors, GRK2 inhibitors, myofilament enhancers). This work may provide novel effective therapies but will also help us better understand how the fundamental systems impacted by these approaches integrate into the behavior of the whole system. This emphasizes how critical it is to integrate our knowledge of these many systems that dynamically regulate contraction and relaxation over multiple physical scales (molecules to cell to heart to animal) and time scales (milliseconds to seconds, minutes, hours, days, and years), as well as in multiple disciplinary and methodologic perspectives, to help bring the entire system to a higher level of understanding. In this way the therapeutic strategies that we must also continue to test are likely to improve.

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23

Pathophysiology of Heart Failure

Gerd Hasenfuss, Douglas L. Mann

Overview

Despite repeated attempts to discover a unique pathophysiologic mechanism that precisely explains the clinical syndrome of heart failure (HF), no single conceptual paradigm has withstood the test of time. Although clinicians initially viewed HF as a problem of excessive salt and water retention that was caused by abnormalities of renal blood flow (the so-called cardiorenal model) and/or abnormal pumping capacity of the heart (the cardiocirculatory or hemodynamic model),[1] these models do not adequately explain the relentless disease progression that occurs in this syndrome.

This chapter focuses on the molecular and cellular changes that underlie heart failure with a reduced ejection fraction (HFrEF), with an emphasis on the role of neurohormonal activation and left ventricular (LV) remodeling as the primary determinants for disease progression in HF. The hemodynamic, contractile, and wall motion disorders in HF are discussed in the chapters on echocardiography (**see Chapter 14**), cardiac catheterization (**Chapter 19**), radionuclide imaging (**Chapter 16**), and clinical assessment of the patient with HF (**Chapter 21**). **Chapter 26** discusses the pathogenesis of HF with preserved ejection fraction.

Pathogenesis

As shown in **Fig. 23.1A**, heart failure may be viewed as a progressive disorder that is initiated after an *index event* either damages the heart muscle, with a resultant loss of functioning cardiac myocytes or,

alternatively, disrupts the ability of the myocardium to generate force, thereby preventing the heart from contracting normally. This index event may have an abrupt onset, as in the case of a myocardial infarction (MI); it may have a gradual or insidious onset, as in the case of hemodynamic pressure or volume overloading, or it may be hereditary, as in the case of many of the genetic cardiomyopathies. Regardless of the nature of the inciting event, the feature that is common to each of these index events is that they all, in some manner, produce a decline in pumping capacity of the heart. In most instances, patients will remain asymptomatic or minimally symptomatic after the initial decline in pumping capacity of the heart, or symptoms develop only after the dysfunction has been present for some time. Although the precise reasons why patients with LV dysfunction remain asymptomatic have not been established with certainty, one potential explanation is that a number of compensatory mechanisms that become activated in the setting of cardiac injury or depressed cardiac output appear to modulate LV function within a physiologic/homeostatic range, such that the patient's functional capacity is preserved or is depressed only minimally. With progression to symptomatic HF, however, the sustained activation of neurohormonal and cytokine systems leads to a series of end-organ changes within the myocardium referred to collectively as *left ventricular remodeling*. As discussed later, LV remodeling is sufficient to lead to disease progression in HF independent of the neurohormonal status of the patient.

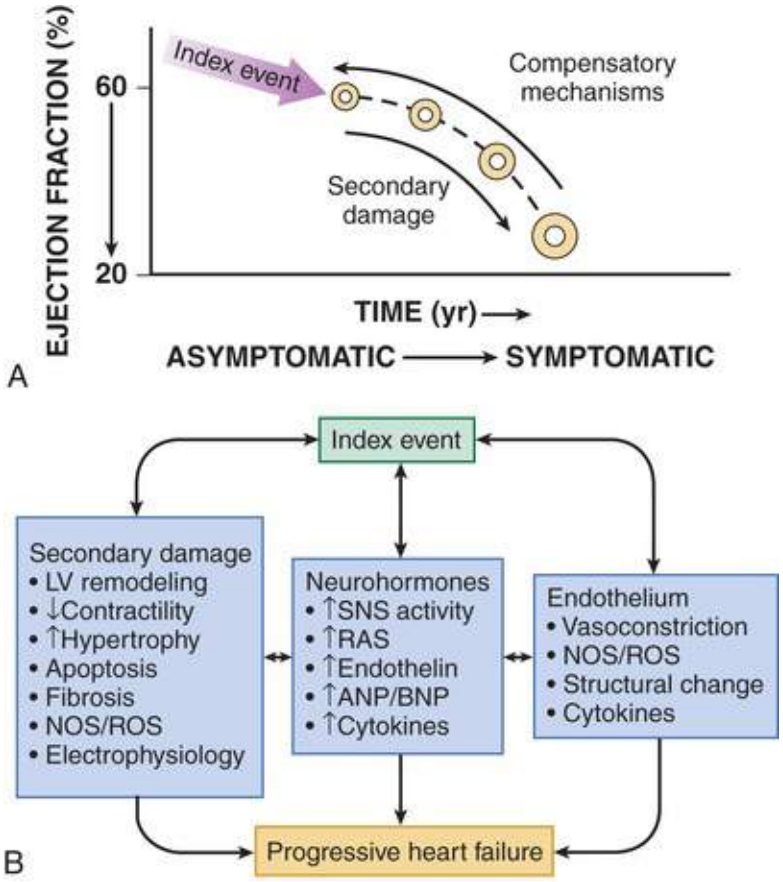


FIGURE 23.1 Pathogenesis of heart failure. **A,** Heart failure begins after a so-called index event produces an initial decline in pumping capacity of the heart. **B,** After this initial decline in pumping capacity, a variety of compensatory mechanisms are activated, including the adrenergic nervous system, the renin-angiotensin system (RAS), and the cytokine systems. In the short term, these systems are able to restore cardiovascular function to a normal homeostatic range, with the result that the patient remains asymptomatic. With time, however, the sustained activation of these systems can lead to secondary end-organ damage within the ventricle, with worsening LV remodeling and subsequent cardiac decompensation. As a result of these changes, patients undergo the transition from asymptomatic to symptomatic heart failure. ANP/BNP, Atrial/brain-type natriuretic peptide; NOS, nitric oxide synthase; ROS, reactive oxygen species; SNS, sympathetic nervous system. (From Mann DL: Mechanisms and models in HF: a combinatorial approach. Circulation 199;100:99; and Kaye DM, Krum H. Drug discovery for heart failure: a new era or the end of the pipeline? Nat Rev Drug Discov 2007;6:127.)

Heart Failure as a Progressive Model

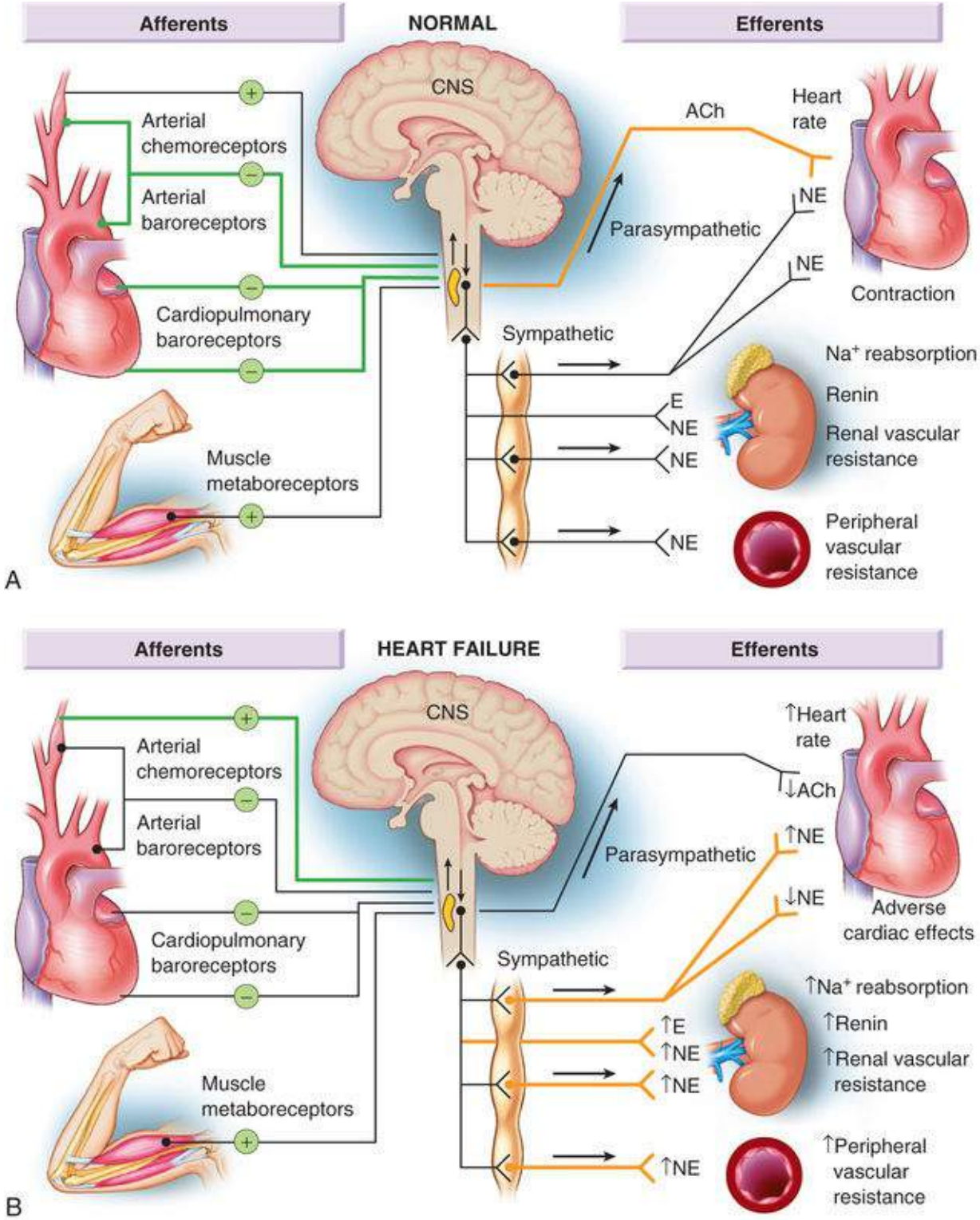
Neurohormonal Mechanisms

A growing body of experimental and clinical evidence suggests that HF progresses as a result of the overexpression of biologically active molecules that are capable of exerting deleterious effects on the heart and circulation[2] (**Fig. 23.1B**). The portfolio of compensatory mechanisms that have been described thus far includes activation of the adrenergic nervous systemic system and the renin-angiotensin system (RAS), which are responsible for maintaining cardiac output through increased retention of salt and water; peripheral arterial vasoconstriction and increased contractility; and inflammatory mediators that are responsible for cardiac repair and remodeling. It bears emphasis that *neurohormone* is largely a historical term, reflecting the original observation that many of the molecules that were elaborated in HF were produced by the neuroendocrine system and thus acted on the heart in an endocrine manner. It has since become apparent, however, that a great many of the so-called classic neurohormones such as norepinephrine (NE) and angiotensin II are synthesized directly within the myocardium by myocytes and

thus act in an autocrine and paracrine manner. Nonetheless, the important unifying concept that arises from the neurohormonal model is that the overexpression of portfolios of biologically active molecules contributes to disease progression by virtue of the deleterious effects these molecules exert on the heart and circulation.

Activation of Sympathetic Nervous System

The decrease in cardiac output in HF activates a series of compensatory adaptations that are intended to maintain cardiovascular homeostasis. One of the most important adaptations is activation of the sympathetic (adrenergic) nervous system (SNS), which occurs early in the course of HF. Activation of the SNS in HF is accompanied by a concomitant withdrawal of parasympathetic tone (**eFig. 23.1**). Although these disturbances in autonomic control initially were attributed to loss of the inhibitory input from arterial or cardiopulmonary baroreceptor reflexes, increasing evidence indicates that excitatory reflexes also may participate in the autonomic imbalance that occurs in HF.[3] In healthy persons, “high-pressure” carotid sinus and aortic arch baroreceptors and “low-pressure” cardiopulmonary mechanoreceptors provide inhibitory signals to the central nervous system (CNS) that repress the sympathetic outflow to the heart and peripheral circulation. Under normal conditions, inhibitory inputs from high-pressure carotid sinus and aortic arch baroreceptors and the low-pressure cardiopulmonary mechanoreceptors are the principal inhibitors of sympathetic outflow, whereas discharge from the nonbaroreflex peripheral chemoreceptors and from muscle *metaboreceptors* are the major excitatory inputs to sympathetic outflow. The vagal limb of the baroreceptor heart rate reflex also is responsive to arterial baroreceptor afferent inhibitory input. Healthy persons display low sympathetic discharge at rest and have a high heart rate variability. In patients with HF, however, inhibitory input from baroreceptors and mechanoreceptors decreases and excitatory input increases, with the net result of a generalized increase in sympathetic nerve traffic and blunted parasympathetic nerve traffic, leading to loss of heart rate variability and increased peripheral vascular resistance.[3]



EFIGURE 23.1 Compensated and decompensated heart failure (HF), as indicated by the presence or absence of urinary sodium retention, together with symptoms and signs of expanded intravascular and extravascular volume. **A,** In compensated HF with mild to moderate reductions in renal perfusion, natriuretic peptides, such as atrial natriuretic peptide (ANP) released by distended atria, stimulate sodium excretion (decreasing reabsorption, *minus sign*) so that the urinary sodium-potassium (Na^+/K^+) ratio is greater than 1.0. **B,** In decompensated HF, moderate to severe reductions in renal perfusion activate the renin-angiotensin-aldosterone system (RAAS), overriding the action of natriuretic peptides to stimulate nearly complete urinary sodium reabsorption (*plus sign*), resulting in a urinary sodium-potassium ratio less than 1.0. *Ach,* Acetylcholine; *CNS,* central nervous system; *E,* epinephrine; *NE,* norepinephrine. (From Weber KT. Aldosterone in congestive heart failure. N Engl J Med 2001;345:1689; and Weber KT, Villareal D. Aldosterone and antialdosterone therapy in congestive heart failure. Am J Cardiol 1993;71[suppl 3A]:11A.)

As a result of the increase in sympathetic tone, there is an increase in circulating levels of NE, a potent adrenergic neurotransmitter. The elevated levels of circulating NE result from a combination of increased

release of NE from adrenergic nerve endings and its consequent “spillover” into the plasma, as well as reduced uptake of NE by adrenergic nerve endings. In patients with advanced HF, the circulating levels of NE in resting patients are two to three times those found in normal persons. Indeed, plasma levels of NE predict mortality in patients with HF. Whereas the normal heart usually extracts NE from the arterial blood, in patients with moderate HF the coronary sinus NE concentration exceeds the arterial concentration, indicating increased adrenergic stimulation of the heart. However, as HF progresses there is a significant decrease in the myocardial concentration of NE. The mechanism responsible for cardiac NE depletion in severe HF is not clear and may relate to an “exhaustion” phenomenon resulting from the prolonged adrenergic activation of the cardiac adrenergic nerves in HF. In addition, there is decreased activity of myocardial tyrosine hydroxylase, which is the rate-limiting enzyme in the synthesis of NE. In patients with cardiomyopathy, iodine 131 (^{131}I)–labeled metaiodobenzylguanidine (MIBG), a radiopharmaceutical that is taken up by adrenergic nerve endings, is not taken up normally, suggesting that NE reuptake is also depressed.

Increased sympathetic activation of the beta$_1$-adrenergic receptor results in increased heart rate and force of myocardial contraction, with a resultant increase in cardiac output (**see Chapter 22**). In addition, the heightened activity of the adrenergic nervous system leads to stimulation of myocardial alpha$_1$-adrenergic receptors, which elicits a modest positive inotropic effect, as well as peripheral arterial vasoconstriction (**Fig. 23.2**). Although NE enhances both contraction and relaxation and maintains blood pressure, myocardial energy requirements are augmented, which can intensify ischemia when myocardial oxygen (O_2) delivery is restricted. The augmented adrenergic outflow from the CNS also may trigger ventricular tachycardia or even sudden cardiac death, particularly in the presence of myocardial ischemia. Thus, activation of the SNS provides short-term support that has the potential to become maladaptive over the long term. Moreover, increasing evidence suggests that apart from the deleterious effects of sympathetic activation, parasympathetic withdrawal also may contribute to the pathogenesis of HF. Withdrawal of parasympathetic nerve stimulation has been associated with decreased nitric oxide (NO) levels, increased inflammation, increased sympathetic activity, and worsening LV remodeling. Several clinical trials with vagal nerve stimulation did not meet their primary endpoint but have shown encouraging trends in several secondary endpoints.[4]

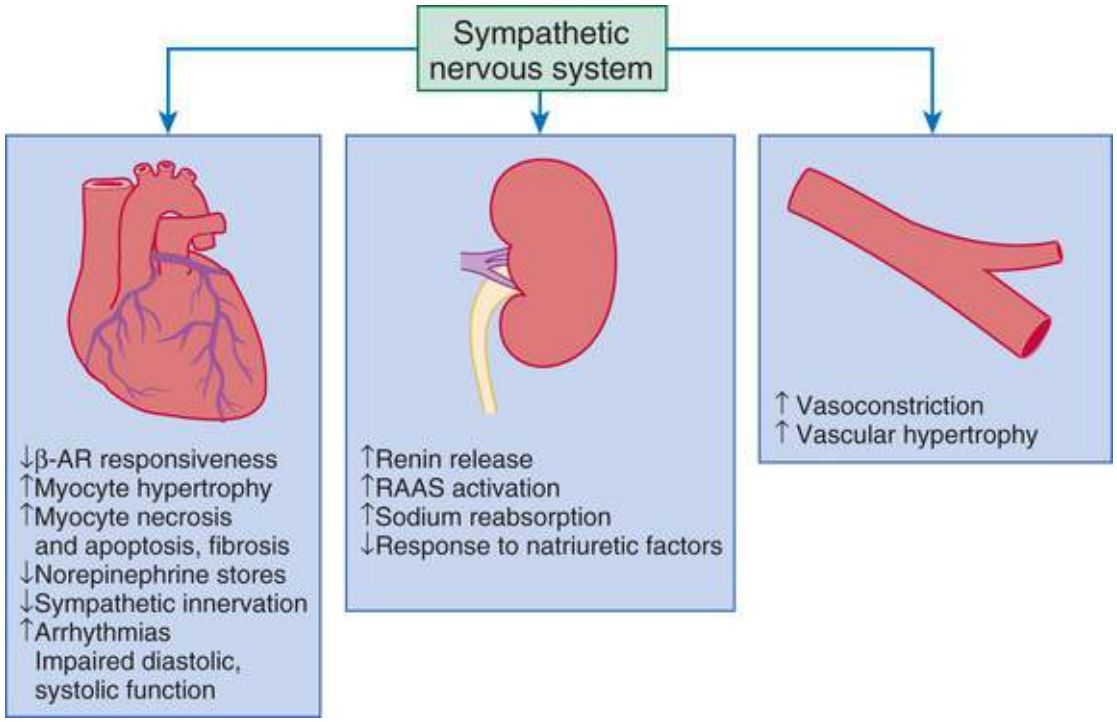


FIGURE 23.2 Activation of the sympathetic nervous system. Increased sympathetic nervous system (SNS) activity may contribute to the pathophysiology of congestive heart failure by multiple mechanisms involving cardiac, renal, and vascular function. In the heart, increased SNS outflow may lead to desensitization beta-adrenergic receptors (β-ARs), myocyte hypertrophy, necrosis, apoptosis, and fibrosis. In the kidneys, increased SNS activation induces arterial and venous vasoconstriction, activation of the renin-angiotensin-aldosterone system (RAAS), increase in salt and water retention, and an attenuated response to natriuretic factors. In the peripheral vessels, neurogenic vasoconstriction and vascular hypertrophy are induced by increased SNS activity. (From Nohria A, Cusco JA, Creager MA. Neurohormonal, renal and vascular adjustments in heart failure. In Colucci WS, editor. Atlas of Heart Failure. 4th ed. Philadelphia: Current Medicine; 2008, p 106.)

Activation of the Renin-Angiotensin System

In contrast with the SNS, the components of the RAS are activated comparatively later in HF. The presumptive mechanisms for RAS activation in HF include renal hypoperfusion, decreased filtered sodium reaching the macula densa in the distal tubule, and increased sympathetic stimulation of the kidney, leading to increased renin release from juxtaglomerular apparatus. As shown in **Fig. 23.3**, renin cleaves four amino acids from circulating angiotensinogen, which is synthesized in the liver, to form the biologically inactive decapeptide angiotensin I. Angiotensin-converting enzyme (ACE) cleaves two amino acids from angiotensin I to form the biologically active octapeptide (1-8) angiotensin II. Most ACE activity (approaching 90%) in the body is found in tissues; the remaining 10% is found in a soluble (non–membrane-bound) form in the interstitium of the heart and vessel wall. The importance of tissue ACE activity in HF is suggested by the observation that ACE messenger RNA (mRNA) and ACE-binding sites and ACE activity are increased in explanted human hearts.[5] Angiotensin II also can be synthesized using renin-independent pathways through the enzymatic conversion of angiotensinogen to angiotensin I by kallikrein and cathepsin G (**Fig. 23.3A**). The tissue production of angiotensin II also may occur along ACE-independent pathways, through the activation of chymase. This latter pathway may be of major importance in the myocardium, particularly when the levels of renin and angiotensin I are increased by the use of ACE inhibitors. Angiotensin II itself can undergo further proteolysis to generate three biologically active fragments: angiotensin III (2-8) angiotensin IV (3-8) and angiotensin 1-7 (**Fig. 23.3B**).

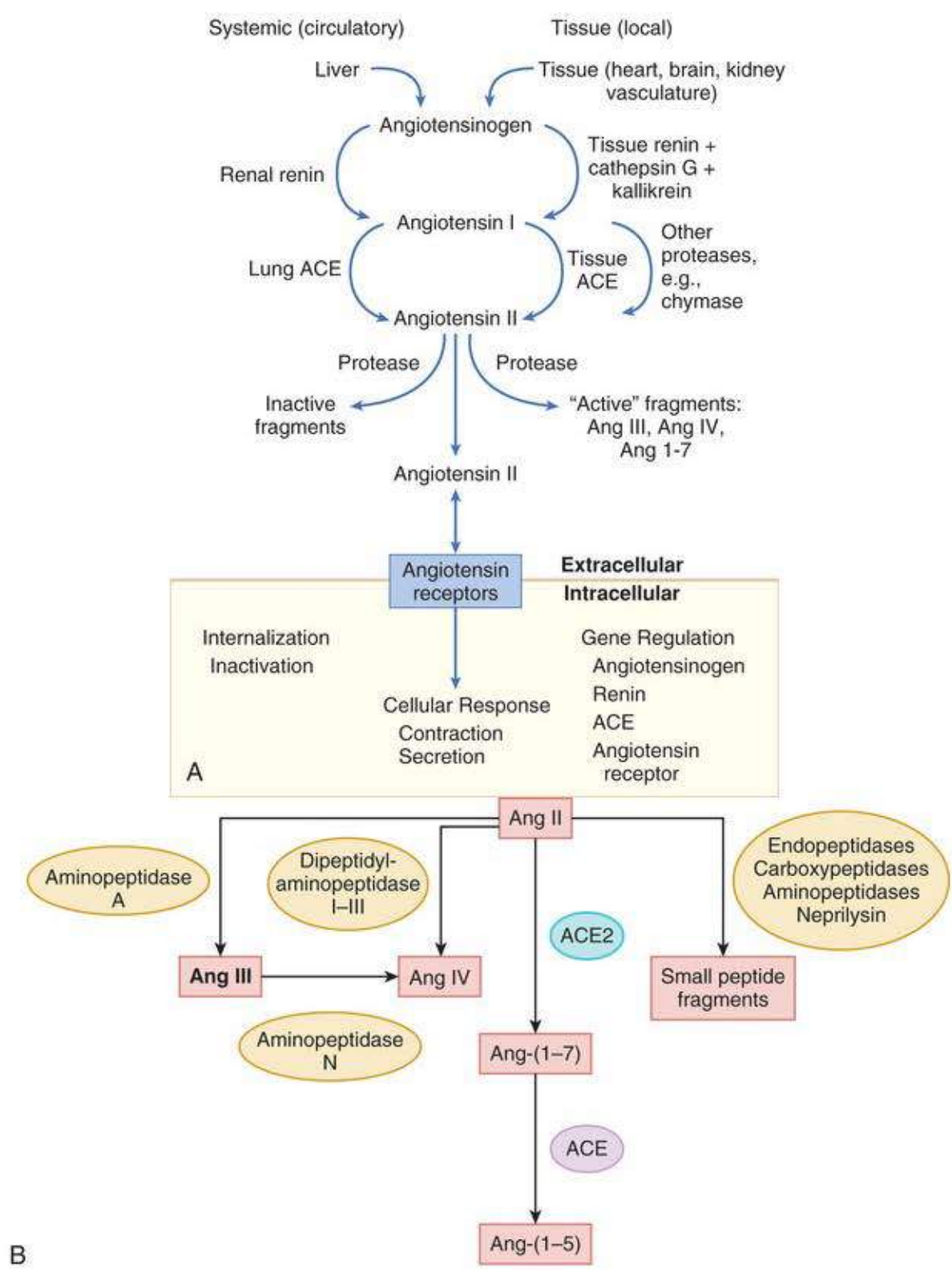

Systemic (circulatory)
Tissue (local)
Liver
Tissue (heart, brain, kidney vasculature)
Angiotensinogen
Renal renin
Tissue renin + cathepsin G + kallikrein
Angiotensin I
Lung ACE
Tissue ACE
Other proteases, e.g., chymase
Angiotensin II
Protease
Protease
Inactive fragments
"Active" fragments: Ang III, Ang IV, Ang 1-7
Angiotensin II
Angiotensin receptors
Extracellular
Intracellular
Internalization
Inactivation
Gene Regulation
Angiotensinogen
Renin
ACE
Angiotensin receptor
Cellular Response
Contraction
Secretion
A
Ang II
Aminopeptidase A
Dipeptidyl-aminopeptidase I–III
Endopeptidases
Carboxypeptidases
Aminopeptidases
Neprilysin
ACE2
Ang III
Ang IV
Small peptide fragments
Aminopeptidase N
Ang-(1–7)
ACE
Ang-(1–5)
B
Angiotensin II
Angiotensin-(1–7)
AT1 Receptor
AT2 Receptor
MAS receptor
• Vasoconstriction
• Na/H2O reabsorption
• Inflammatory response
• Hypertrophy/hyperplasia
• Cell proliferation
• Oxidative stress
• Vasodilation
• Antiinflammation
• Apoptosis
• Anticell proliferation
• Antioxidative stress
• Vasodilation
• Diuresis and natriuresis
• Antihypertrophy
• Antiproliferation
• Antifibrosis
• Stimulation of bradykinin and NO release
C

FIGURE 23.3 **A,** The systemic and tissue components of the RAS. Several tissues, including myocardium, vasculature, kidney, and brain, have the capacity to generate angiotensin II independent of the circulating RAS. Angiotensin II produced at the tissue level may play an important role in the pathophysiology of heart failure. ACE, Angiotensin-converting enzyme; Ang, angiotensin. **B,** Angiotensin II degradation pathways. Angiotensin II is degraded by angiotensin-converting enzyme 2 (ACE2) to form Ang-(1–7), which subsequently can be degraded by ACE to form Ang-(1–5). Other pathways of angiotensin II degradation include aminopeptidase A to Ang-(2–8), dipeptidyl-aminopeptidase I–III to Ang IV, and neprilysin and various peptidases to other small peptide products. Ang-(2–8) and Ang IV may also be reversibly interchanged via aminopeptidase N. **C,** Action of angiotensin II type 1 (AT_1) and type 2 (AT_2) receptors and MAS-mediated signaling. NO, Nitric oxide. (**A,** Modified from Timmermans PB et al. Angiotensin II receptors and angiotensin II receptor antagonists. Pharmacol Rev 1993;45:205; **B,** modified from Batlle D et al. Angiotensin-converting enzyme 2: enhancing the degradation of angiotensin II as a potential therapy for diabetic nephropathy. Kidney Int 2012;81:520-8; **C,** modified from Iwai M, Horiuchi M. Devil and angel in the renin-angiotensin system. Hypertens Res 2009;32:533-6.)

Angiotensin II exerts its effects by binding to two G protein–coupled receptors (GPCRs), the angiotensin type 1 (AT_1) and angiotensin type 2 (AT_2) receptors. The predominant angiotensin receptor in the vasculature is the AT_1 receptor. Although both AT_1 and AT_2 receptor subtypes are present in human myocardium, the AT_2 receptor predominates in a 2 : 1 molar ratio. Cellular localization of the AT_1 receptor in the heart is most abundant in nerves distributed in the myocardium, whereas the AT_2 receptor is localized more specifically in fibroblasts and the interstitium. Activation of the AT_1 receptor leads to vasoconstriction, cell growth, aldosterone secretion, and catecholamine release, whereas activation of the AT_2 receptor leads to vasodilation, inhibition of cell growth, natriuresis, and bradykinin release (**Fig. 23.3C**). Studies have shown that the AT_1 receptor and mRNA levels are downregulated in failing human hearts, whereas AT_2 receptor density is increased or unchanged, so that the ratio of AT_1 to AT_2 receptors decreases.[6] The MAS receptor is a GPCR that is expressed primarily in the brain and testes but also in the heart (**Fig. 23.3C**).

Angiotensin II has several important actions that are critical to maintaining short-term circulatory homeostasis. The sustained expression of angiotensin II is maladaptive, however, leading to fibrosis of the heart, kidneys, and other organs. Angiotensin II can also lead to worsening neurohormonal activation by enhancing the release of NE from sympathetic nerve endings, as well as stimulating the zona glomerulosa of the adrenal cortex to produce aldosterone. Analogous to angiotensin II, aldosterone provides short-term support to the circulation by promoting the reabsorption of sodium in exchange for potassium, in the distal segments of the nephron. However, the sustained expression of aldosterone may exert harmful effects by provoking hypertrophy and fibrosis within the vasculature and the myocardium, contributing to reduced vascular compliance and increased ventricular stiffness. In addition, aldosterone provokes endothelial cell dysfunction, baroreceptor dysfunction, and inhibition of NE uptake, any of which may lead to worsening HF. The mechanism of action of aldosterone in the cardiovascular system appears to involve oxidative stress, with resultant inflammation in target tissue. Although the exact role of angiotensin III (2-8) angiotensin IV (3-8) and angiotensin 1-7 in HF are not known, experimental studies suggest that angiotensin 1-7 counteracts the effects of angiotensin II, and attenuates LV remodeling.[2] In contrast, angiotensin III directly stimulates the zona glomerulosa of the adrenal glands to produce aldosterone,[2] which promotes sodium resorption in the distal collecting duct of the kidney. Angiotensin III also has an important role in vasopressin release in the brain, which controls water retention in the distal collecting duct of the kidney. Angiotensin III in the brain can also modulate cardiac nervous sympathetic hyperactivity, as well as LV remodeling after MI.[2]

Oxidative Stress.

Reactive oxygen species (ROS) are a normal byproduct of aerobic metabolism. In the heart, the potential sources for ROS include the mitochondria, xanthine oxidase, and nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase (**Fig. 23.4**). ROS can modulate the activity of a variety of intracellular proteins and signaling pathways, including essential proteins involved in myocardial excitation-contraction coupling, such as ion channels, sarcoplasmic reticulum (SR) calcium release channels, and myofilament proteins, as well as signaling pathways that are coupled to myocyte growth.[7] "Oxidative stress" occurs when the production of ROS exceeds the buffering capacity of antioxidant defense systems, leading to an excess of ROS within the cell. Substantial evidence indicates that the level of oxidative stress is increased both systemically and in the myocardium of patients with HF. Oxidative stress in the heart may be caused by reduced antioxidant capacity and increased production of ROS, which may arise secondary to mechanical strain of the myocardium, neurohormonal stimulation (angiotensin II, alpha-adrenergic agonists, endothelin-1 [ET-1]), or inflammatory cytokines (tumor necrosis factor [TNF], interleukin [IL]-1). Excessive mitochondria-derived ROS in cardiac myocytes have been demonstrated in experimental models of HF and may contribute to contractile dysfunction in advanced HF. Increased xanthine oxidase expression and activity have been reported in canine rapid pacing–induced HF and patients with end-stage HF. Moreover, increased expression and activity of myocardial NADPH oxidases have been demonstrated in both experimental and human HF.[7] In cultured cardiac myocytes, ROS stimulate myocyte hypertrophy, reexpression of fetal gene programs, and apoptosis. ROS also can modulate fibroblast proliferation and collagen synthesis and trigger increased matrix metalloproteinase (MMP) abundance and activation. ROS also can affect the peripheral vasculature in HF by decreasing the bioavailability of NO. These and other observations have led to the suggestion that strategies to reduce ROS may be of therapeutic value in patients with HF. However, xanthine oxidase inhibition with allopurinol to reduce oxidative stress in hyperuremic patients with HF did not improve clinical status or cardiac function in a recent trial.[8]

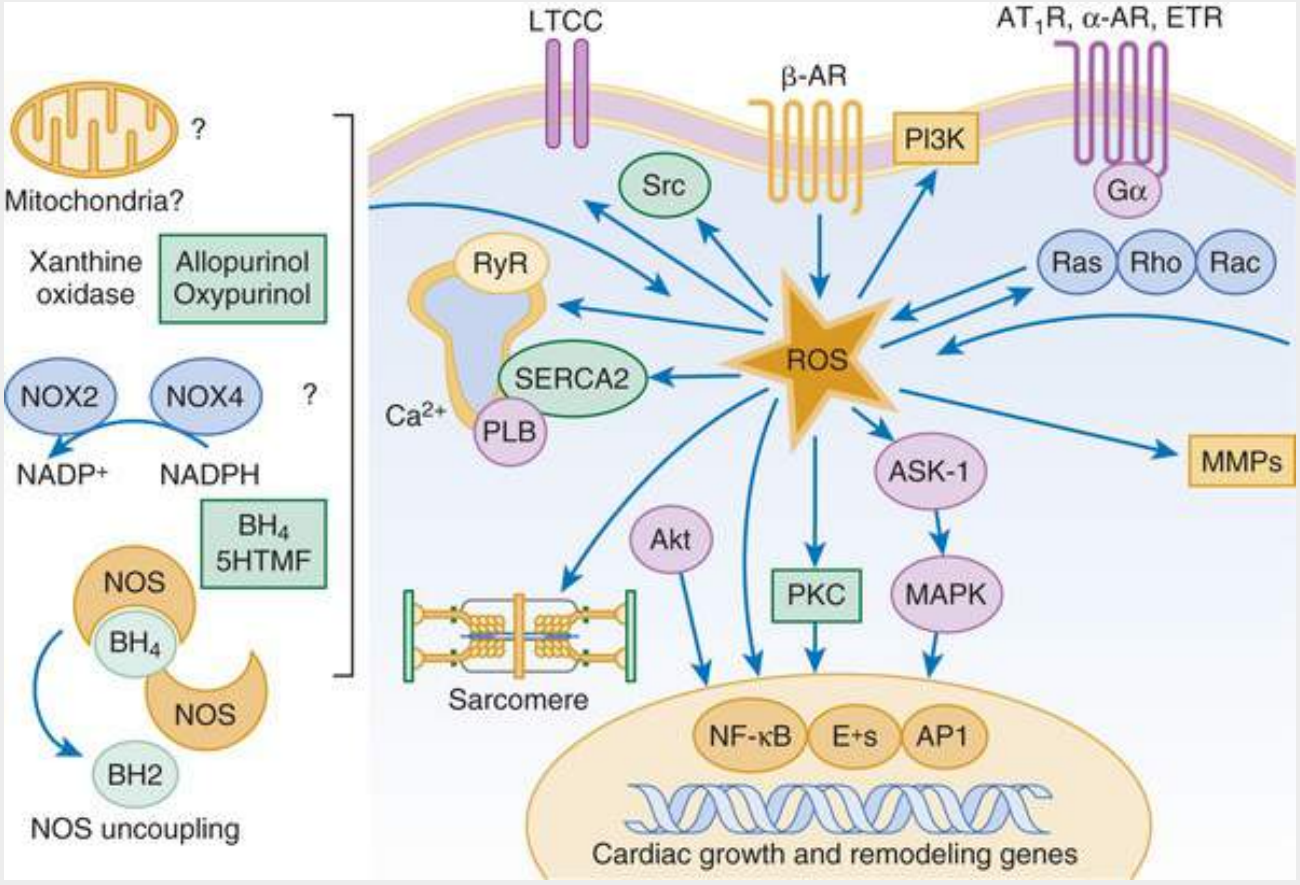


FIGURE 23.4 Cellular sources of ROS and ROS signaling in cardiac hypertrophy. ROS-generating systems are shown on the *left* and include xanthine oxidase, NADPH oxidases (NOX2, NOX4), NOS, and mitochondrial complexes. ROS activation has protean effects on calcium handling, myofilament function, matrix activation, kinase and phosphatase stimulation, and transcriptional regulation of matrix metalloproteinases (MMPs). *Akt,* Protein kinase B; *ASK-1,* apoptosis signal-regulating kinase 1; *ETR,* endothelin receptor; *5HTMF,* 5-hydrotetramethylpholate; *LTCC,* L-type calcium channel; *MAPK,* mitogen-activated protein kinase; *NF-κB,* nuclear factor-kappaB; *PKC,* protein kinase C; *PI3K,* phosphatidylinositol 3-kinase; *PLB,* phospholamban; *RyR,* ryanodine receptor; *SERCA2,* sarcoendoplasmic reticulum Ca^{2+}-ATPase. (Modified from McKinsey TA, Kass DA. Small-molecule therapies for cardiac hypertrophy: moving beneath the cell surface. Nat Rev Drug Discov 2007;6:617.)

The importance of aldosterone, independent of angiotensin II, has been demonstrated by clinical trials (**see Chapter 25**) showing that low-dose spironolactone increased the survival of patients with New York Heart Association (NYHA) Class II to IV systolic HF, as well as improved survival after MI, independent of changes in volume or electrolyte status.[9]

Neurohormonal Alterations of Renal Function

One of the signatures of advancing HF is increased salt and water retention by the kidneys. Traditional theories have ascribed this increase to either “forward” failure, which attributes sodium retention to inadequate renal perfusion as a consequence of impaired cardiac output, or “backward” failure, which emphasizes the importance of increased venous pressure in favoring transudation of salt and water from the intravascular to the extracellular compartment. These mechanisms have largely been supplanted by the concept of decreased *effective arterial blood volume*, which postulates that despite blood volume expansion in HF, inadequate cardiac output sensed by baroreceptors in the vascular tree leads to a series of compensatory neurohormonal adaptations that resemble the homeostatic response to acute blood loss.[2] As illustrated in **Fig. 23.5**, a falling cardiac output or redistribution of the circulating blood volume is sensed by baroreceptors in the left ventricle, aortic arch, carotid sinus, and renal afferent arterioles. The

loss of inhibitory input from arterial or cardiopulmonary baroreceptor reflexes leads to sustained activation of the SNS and the RAS. An implantable barostimulation device that activates the carotid baroreceptors to decrease sympathetic activation and increase vagal tone improved quality of life and exercise capacity in patients with symptomatic HF.[4] The ongoing BeAT-HF (Barostim Therapy for Heart Failure) trial will determine whether baroreceptor activation therapy will favorably impact cardiovascular mortality and HF mortality at study completion (efficacy endpoint) and major adverse neurologic and cardiovascular events at 6 months.

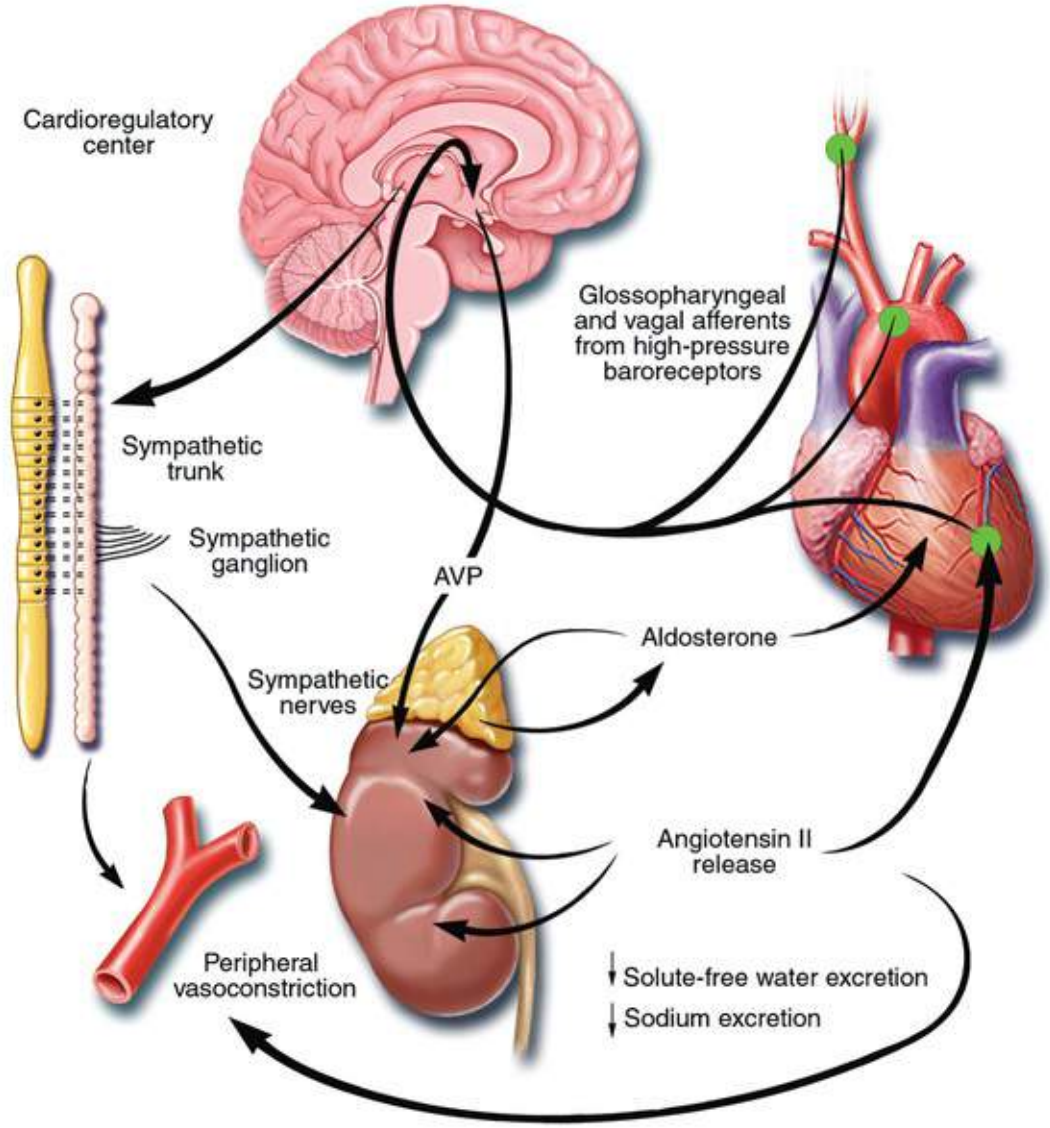


FIGURE 23.5 Unloading of high-pressure baroceptors (*circles*) in the left ventricle, carotid sinus, and aortic arch generates afferent signals that stimulate cardioregulatory centers in the brain, resulting in the activation of efferent pathways in the sympathetic nervous system. The SNS appears to be the primary integrator of the neurohumoral vasoconstrictor response to arterial underfilling. Activation of renal sympathetic nerves stimulates the release of arginine vasopressin (*AVP*). Sympathetic activation also causes peripheral and renal vasoconstriction, as does angiotensin II. Angiotensin II constricts blood vessels and stimulates the release of aldosterone from the adrenal gland, and it also increases tubular sodium reabsorption and causes remodeling of cardiac myocytes. Aldosterone also may have direct cardiac effects, in addition to increasing the reabsorption of sodium and the secretion of potassium (K^+) and hydrogen ($H^{+)}$ ions in the collecting duct. The *black arrows* designate circulating hormones. (Modified from Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med 1999;341:577.)

There is little evidence to suggest that a primary renal abnormality is responsible for the initial sodium

retention in heart; however, there is mounting evidence that secondary changes in the kidney contribute importantly to volume overload as HF progresses. Volume overload in HF is multifactorial and is secondary, at least in part, to several factors that have the potential to cause increased sodium reabsorption, including activation of the SNS, activation of RAS, reduced renal perfusion pressures, and blunting of renal responsiveness to natriuretic peptides. Increased renal sympathetic nerve–mediated vasoconstriction leads to decreased renal blood flow, as well as increased renal tubular sodium and water reabsorption throughout the nephron. Renal sympathetic stimulation also can lead to the nonosmotic release of arginine vasopressin (AVP) from the posterior pituitary, which reduces the excretion of free water and contributes to worsening peripheral vasoconstriction, as well as increased endothelin (ET) production.[2] Increased renal venous pressure can also lead to renal interstitial hypertension, with the development of tubular injury and renal fibrosis.

Arginine Vasopressin.
AVP is a pituitary hormone that plays a central role in the regulation of free water clearance and plasma osmolality (**see Fig. 23.5**). Under normal circumstances, AVP is released in response to an increase in plasma osmolality, leading to increased retention of water from the collecting duct. Of note, circulating AVP is elevated in many patients with HF, even after correction for plasma osmolality (i.e., nonosmotic release),[2] and may contribute to the hyponatremia that occurs in HF. The cellular effects of AVP are mediated mainly by interactions with three types of receptors, termed V_{1a}, V_{2a}, and V_2. The V_{1a} receptor, the most widespread subtype, is found primarily in vascular smooth muscle cells. The V_{1b} receptor has a more limited distribution and is located mainly in the CNS. The V_2 receptors are found primarily in the epithelial cells in the renal collecting duct and the thick ascending limb. AVP receptors are members of the GPCRs. The V_{1a} receptors mediate vasoconstriction, platelet aggregation, and stimulation of myocardial growth factors, whereas V_{1b} modulates adrenocorticotropic hormone (ACTH) secretion from the anterior pituitary. The V_2 receptor mediates antidiuretic effects by stimulating adenyl cyclase to increase the rate of insertion of water channel−containing vesicles into the apical membrane. Because the vesicles contain preformed functional water channels, termed *aquaporins*, their localization in the apical membranes in response to V_2 stimulation increases the water permeability of the apical membrane, leading to water retention. The “vaptans,” vasopressin receptor antagonists with V_{1a} (relcovaptan) or V_2 (tolvaptan, lixivaptan) selectivity or nonselective V_{1a}/V_2 activity (conivaptan), have been shown to reduce body weight and reduce hyponatremia in clinical trials (**see Chapters 24 and 25**).

Increased renal sympathetic activity leads to increased renin production by the kidneys, with a resultant sustained activation of RAS, despite an expanded extracellular volume. Angiotensin II facilitates retention of sodium and water by multiple renal mechanisms, including a direct proximal tubular effect, as well as through activation of aldosterone, which leads to increased sodium resorption in the distal tubule. Angiotensin II also stimulates the thirst center of the brain and provokes the release of AVP and aldosterone, both of which can lead to further dysregulation of salt and water homeostasis.

A number of counterregulatory neurohormonal systems become activated in HF in order to offset the deleterious effects of the vasoconstricting neurohormones (**eTable 23.1**). Metabolites of vasodilatory prostaglandins, including prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2), are elevated in patients with HF. In addition to being a vasodilator, PGE_2 enhances renal sodium excretion and modulates the

antidiuretic action of AVP. One class of the most important counterregulatory neurohormonal systems that become activated in HF are the natriuretic peptides, including atrial natriuretic peptide (ANP) and brain (B-type) natriuretic peptide (BNP). Under physiologic conditions, ANP and BNP function as natriuretic hormones that are released in response to increases in atrial and myocardial stretch, often secondary to excessive sodium intake. Once released, these cardiac peptides act on the kidney and peripheral circulation to unload the heart, through increased excretion of sodium and water, while inhibiting the release of renin and aldosterone (**Fig. 23.6**). In the setting of RAS activation, the release of ANP and BNP may serve as an important counterregulatory mechanism that maintains sodium and water homeostasis. However, for reasons that are not entirely clear, the renal effects of the natriuretic peptides appear to become blunted with advancing HF, leaving the effects of RAS unopposed.[10] Potential reasons for this blunting include low renal perfusion pressure, relative deficiency or altered molecular forms of the natriuretic peptides, and decreased levels of natriuretic peptide receptors.

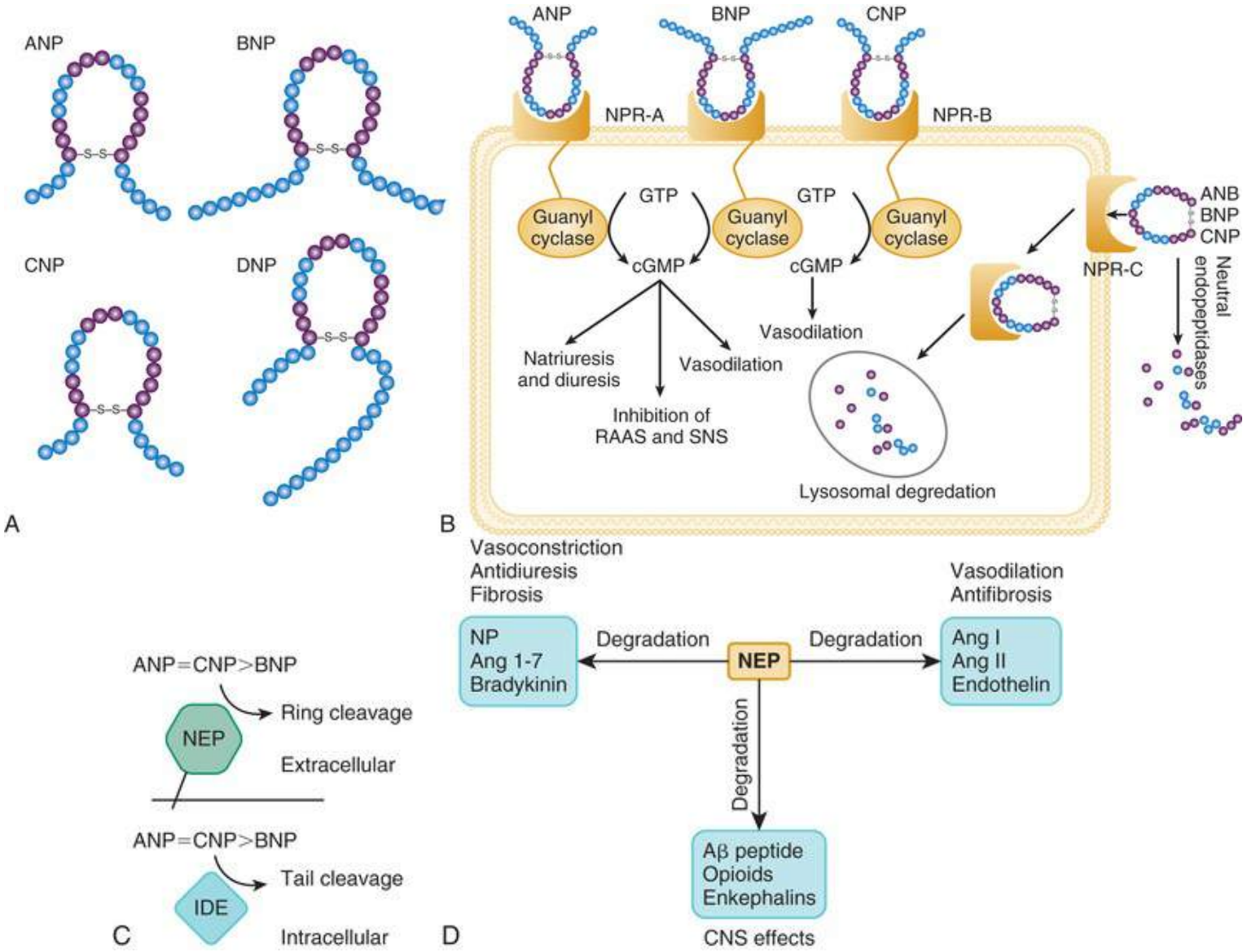


FIGURE 23.6 Natriuretic peptides. **A,** The similar 17–amino acid disulfide ring in natriuretic peptides A, B, C, and D. Identical amino acid sequences are marked in *purple*. **B,** Action and clearance of the natriuretic peptides. **C,** Enzymatic degradation of natriuretic peptides extracellularly by neutral endopeptidase (*NEP*) 24.11 (neprilysin), or intracellularly by insulin-degrading enzyme (*IDE*). **D,** Neutral endopeptidases (*NEP*) degrade a variety of different peptides. *ANP,* Atrial natriuretic peptide; *BNP,* B-type natriuretic peptide; *CNP,* C-type natriuretic peptide; *DNP,* dendroaspis natriuretic peptide; *GTP,* guanosine triphosphate; *NPR,* natriuretic peptide receptor; *RAAS,* renin-angiotensin-aldosterone system. (**B,** Modified from Gardner RS, Chong KS, McDonagh TA. B-type natriuretic peptides in heart failure. Biomark Med 2007;1:243; **C,** Modified from Volpe M, Carnovali M, Mastromarino V. The natriuretic peptides system in the pathophysiology of heart failure: from molecular basis to treatment. Clin Sci (Lond) 2016;130:57.)

ETABLE 23.1

Neurohormonal Regulation of Vascular Tone

Vasoconstrictors
Catecholamine
Norepinephrine: peripheral alpha$_1$-adrenergic stimulation
Peptide
Angiotensin II Arginine vasopressin Endothelin Neuropeptide Y Urotensin II
Lipid
Thromboxane A_2
Vasodilators
Catecholamine
Norepinephrine: central alpha$_2$-adrenergic stimulation Epinephrine: beta$_2$-adrenergic stimulation Dopamine
Peptide
Bradykinin Adrenomedullin Apelin
Gas
NO (i.e., “endothelium-derived relaxing factor” [EDRF])
Lipid
Prostacyclin (PGI_2) Prostaglandin E_2 (PGE_2)

Modified from Katz AM. Physiology of the Heart. Philadelphia: Lippincott Williams & Wilkins; 2001.

Natriuretic Peptides.

The natriuretic peptide system consists of five structurally similar peptides: ANP, urodilatin (an isoform of ANP), BNP, C-type natriuretic peptide (CNP), and dendroaspis natriuretic peptide (DNP) (**Fig. 23.6A**).[11] ANP, a 28–amino acid peptide hormone, is produced principally in the cardiac atria, whereas BNP, a 32–amino acid peptide originally isolated from porcine brain, was later identified as a hormone that was primarily produced in the cardiac ventricles.[11] Both ANP and BNP are secreted in response to increasing cardiac wall tension; however, other factors such as neurohormones (e.g., angiotensin II, ET-1, catecholamines) or physiologic factors (e.g., age, sex, renal function) may also play a role in their regulation. The biosynthesis, secretion, and clearance of BNP differs from ANP, suggesting that these two natriuretic peptides have discrete physiologic and pathophysiologic roles. Whereas ANP is secreted in short bursts in response to acute changes in atrial pressure, the activation of BNP is regulated transcriptionally in response to chronic increases in atrial/ventricular pressure. ANP and BNP initially are synthesized as prohormones that are subsequently proteolytically cleaved, respectively, by corin and furin, to yield large, biologically inactive N-terminal fragments (NT-ANP and NT-BNP) and smaller, biologically active peptides (i.e., ANP and BNP). ANP has a relatively short half-life of approximately 3 minutes, whereas BNP has a plasma half-life of approximately 20 minutes. CNP, which is located primarily in the vasculature, also is released as a prohormone that is cleaved into biologically inactive form (NT-CNP) and a 22–amino acid, biologically active form (i.e., CNP).

Fig. 23.6B illustrates the signaling pathway of the natriuretic peptide system. The natriuretic peptides stimulate the production of the intracellular second-messenger cyclic guanosine monophosphate (cGMP), via binding to the natriuretic peptide A receptor (NPR-A), which preferentially binds ANP and BNP, and the natriuretic peptide B receptor (NPR-B), which preferentially binds CNP. Both NPR-A and NPR-B

are coupled to particulate guanylate cyclase. Activation of NPR-A and NPR-B results in natriuresis, vasorelaxation, inhibition of renin and aldosterone, inhibition of fibrosis, and increased lusitropy. The natriuretic peptide C receptor (NPR-C) is not linked to cGMP and serves as a clearance receptor for the natriuretic peptides.

All three natriuretic peptides are degraded by two major mechanisms: NPR-C–mediated internalization, followed by lysosomal degradation and enzymatic degradation by neutral endopeptidase (NEP) 24.11 (neprilysin), which is widely expressed in multiple tissues, where it often is colocalized with ACE. Both ACE and NEP are membrane-bound zinc-containing metallopeptidases involved in the metabolism of a variety of biologic peptides[12] (**Fig. 23.6C**). NEP preferentially cleaves small peptides on the N-terminal side of hydrophobic residues. It has a wide range of tissue distribution, including vascular endothelium, smooth muscle cells, myocytes, fibroblasts, kidney tubule cells, and nerve cells. NEP degrades multiple peptides, including natriuretic peptides (**Fig. 23.6D**), angiotensin I, angiotensin II, ET-I, adrenomedullin, opioids, bradykinin, chemotactic peptides, enkephalins, and amyloid-β peptide (Aβ). NEP inhibition of degradation of natriuretic peptides results in vasorelaxation, natriuresis, inhibition of hypertrophy, and fibrosis. On the other hand, inhibition of degradation of other vasoactive peptides, such as angiotensin II, angiotensin 1-7, and ET, opposes the vasodilatory effects of natriuretic peptides. Accordingly, NEP inhibition has variable effects on blood pressure. NEP inhibition increases urinary kinin levels, which may contribute to its natriuretic effects. NEP plays an important role in clearance of amyloid peptides in the brain. In particular, NEP is of major relevance for degrading the amyloid-beta peptides (Aβ), which play a significant role in neurotoxicity, and formation of amyloid plaques from Aβ aggregates in complex with other proteins is a hallmark of Alzheimer disease. Overexpression of neprilysin ameliorated the development of Alzheimer disease, and disruption of the neprilysin gene induces cognitive dysfunction in a mouse model of Alzheimer disease. Because of the potentially beneficial effects of natriuretic peptides in HF, NEP inhibition was pursued as a rational approach for HF therapy. The early use of omapatrilat, a dual vasopeptidase inhibitor that inhibits both ACE and NEP, was not shown to be more effective than ACE inhibition alone in HF patients.[12] However, the use of a combined AT_1 receptor antagonist and a neprilysin inhibitor (valsartan/sacubitril, LCZ696) was shown to have a favorable impact on HF outcome, including quality of life, exercise capacity, and more importantly, HF hospitalization and total mortality, in the PARADIGM-HF trial (**see Chapter 25**).

The biologic importance of the natriuretic peptides in renal sodium handling has been demonstrated in multiple studies employing NPR antagonists, as well as overexpression of ANP or BNP. In experimental HF models, either acute blockade of NPR-A and NPR-B or chronic genetic disruption of NPR-A blunts the renal natriuretic response to acute volume expansion, demonstrating the renal protective action of natriuretic peptide activation. The infusion of a recombinant human ANP and BNP exerts beneficial hemodynamic effects, characterized by decreases in arterial and venous pressures, increase in cardiac output, and suppression of neurohormonal activation in humans, resulting in their clinical development as therapeutic agents for human HF (**see Chapter 24**). In addition to their important biologic role, the natriuretic peptides have provided important diagnostic and prognostic information in HF (**see Chapter 21**).

Neurohormonal Alterations in the Peripheral Vasculature

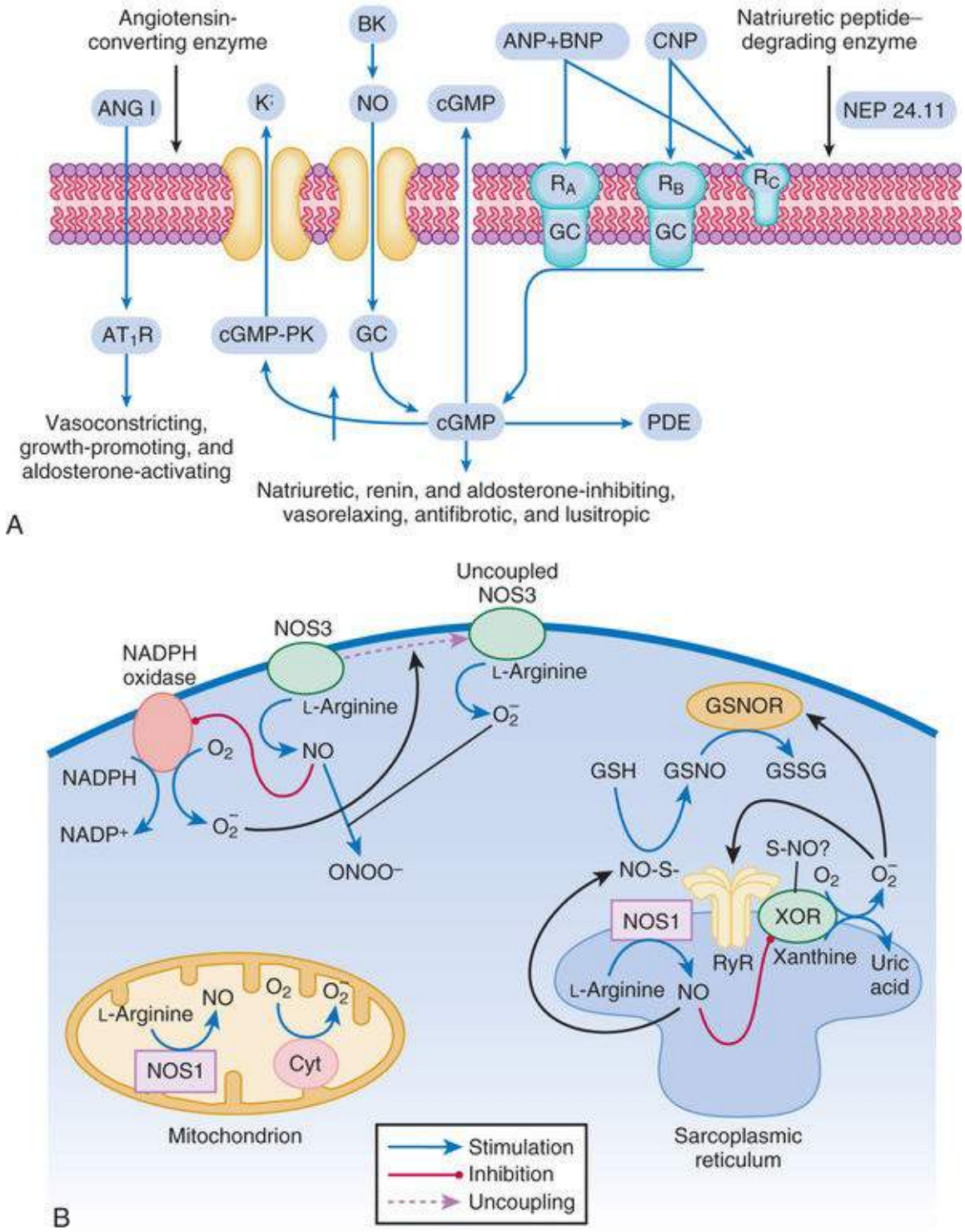
In patients with heart failure, the complex interactions between the autonomic nervous system and local autoregulatory mechanisms tend to preserve circulation to the brain and heart while decreasing blood flow to the skin, skeletal muscles, splanchnic organs, and kidneys. This intense visceral vasoconstriction

during exercise helps to divert the limited cardiac output to exercising muscle but contributes to hypoperfusion of the gut and kidneys. The most powerful stimulus for peripheral vasoconstriction is sympathetic activation, which releases the potent vasoconstrictor NE. Other vasoconstrictors that contribute to maintaining circulatory homeostasis include angiotensin II, ET, neuropeptide Y, urotensin II, thromboxane A_2, and AVP (**see eTable 23.1**). The increased sympathetic adrenergic stimulation of the peripheral arteries and the increased concentrations of circulating vasoconstrictors contribute to the arteriolar vasoconstriction and to the maintenance of arterial pressure. The sympathetic stimulation of the veins contributes to an increase in venous tone, which helps to maintain venous return and ventricular filling and to support cardiac performance by Starling's law of the heart (**see Chapter 22**). Additional content on this topic is presented in the online supplement for this chapter (Vasoconstricting Peptides in Heart Failure).

As noted, the vasoconstricting neurohormones activate counterregulatory vasodilator responses, including release of natriuretic peptides, NO, bradykinin, adrenomedullin, apelin, and vasodilating PGI_2 and PGE_2 (**see eTable 23.1**). Under normal circumstances, the continuous release of NO (endothelium-derived relaxing factor) from the endothelium counteracts the vasoconstricting factors and allows for appropriate vasodilatory responses during exercise. As HF advances, however, the endothelial cell–mediated vasodilatory responsiveness is lost, which contributes to the excessive peripheral arterial vasoconstriction that is emblematic of advanced HF. Of interest, the vasodilator response can be restored by the administration of L-arginine, a precursor of endothelium-derived NO.

Nitric Oxide

The free radical gas NO is produced by three isoforms of NO synthase (NOS). All three isoforms are present in the heart, including NOS1 (neuronal NOS [nNOS]), NOS2 (inducible NOS [iNOS]) and NOS3 (so-called endothelial-constitutive NOS [eNOS]). NOS1 has been detected in cardiac conduction tissue, in intracardiac neurons, and in the SR of cardiac myocytes. NOS2 is an inducible isoform that is not normally expressed in the myocardium but is synthesized de novo in virtually all cells in the heart in response to inflammatory cytokines. NOS3 is expressed in coronary endothelium and endocardium and in the sarcolemma and T-tubule membranes of cardiac myocytes. NOS1 and NOS3 can be activated by calcium or calmodulin, whereas the induction of NOS2 is calcium independent. NO activates soluble guanylate cyclase (**see eFig. 23.2A**). Under normal circumstances, the continuous release of NO (endothelium-derived relaxing factor) from the endothelium counteracts the vasoconstricting factors and allows for appropriate vasodilatory responses during exercise. This activation leads to the production of cyclic guanosine monophosphate (cGMP), which in turn activates protein kinase G (PKG) and cascade of different signaling events. In normal persons, NO released by endothelial cells mediates vasodilation in the peripheral vasculature through cGMP mediated relaxation of vascular smooth muscle. In patients with HF, endothelium-dependent NO-mediated dilation of the peripheral vasculature is blunted, which has been attributed to decreased NOS3 expression and activity.



EFIGURE 23.2 **A,** Cellular actions in signaling of the natriuretic peptide system; *Ang I,* Angiotensin I; *AT_1R,* angiotensin type 1 receptor; *BK,* bradykinin; *GC,* guanylate cyclase; *NEP,* neutral endopeptidase; *PDE,* phosphodiesterase; *PK,* protein kinase; *R_A*, *R_B,* and *R_C,* particulate guanylate cyclase A, B, and C receptors. **B,** Interaction of oxidative and nitrosative pathways in heart failure. The principal sources of ROS in the cardiomyocyte are xanthine oxidoreductase (*XOR*), NADPH oxidase, and the mitochondria. NO is produced by nNOS1, situated in the SR and in the mitochondria, and by eNOS (situated in the caveolae in the cell membrane). XOR and NOS1 colocalize in the SR, and this allows the inhibition of XOR by NOS1, possibly through *S*-nitrosylation In turn, XOR reduces *S*-nitrosoglutathione (*GSNO*), leading to the regeneration of glutathione (*GSH*), the enzyme that reduces SNO moieties in proteins and preserves the *S*-nitrosylation equilibrium. In SR, NOS1 regulates the activity of the ryanodine receptor (*RyR*) through *S*-nitrosylation; by contrast, XOR-generated superoxide (O_2^-) irreversibly activates RyR, precluding this regulatory action of NO. In the cell membrane, NOS3 suppresses NADPH activity, whereas NADPH-produced O_2^- can induce NOS3 uncoupling resulting in O_2^- production and reduced NO synthesis. O_2^- interacts with NO and generates peroxynitrite ($ONOO^-$). *Cyt,* Cytochrome; *GSSG,* oxidized GSH; *GSNOR,* GSNO reductase. (**A,** From Burnett JC, Costello-Boerrigter L, Boerrigter G. Alterations in the kidney in heart failure: the cardiorenal axis in the regulation of sodium homeostasis. In Mann DL, editor. Heart Failure: A

Companion to Braunwald's Heart Disease. Philadelphia: Elsevier; 2004, pp 279-89; **B,** from Tziomalos K, Hare JM. Role of xanthine oxidoreductase in cardiac nitroso-redox imbalance. Front Biosci 2009;14:2379.)

The actions of NO on the myocardium are complex and include both short-term alterations in function and energetics and longer-term effects on structure. NO modulates the activity of several key calcium channels involved in excitation-contraction coupling as well as mitochondrial respiratory complexes. This type of regulation is accomplished by spatial localization of different NOS isoforms in distinct cellular microdomains involved in excitation-contraction coupling. Specifically, NOS1 localizes to the SR in proximity to the ryanodine receptor (RyR) and sarcoendoplasmic reticulum calcium–adenosine triphosphatase (SR Ca^{2+}-ATPase, SERCA2a), and NOS3 is found in sarcolemmal caveolae compartmentalized with cell surface receptors and the L-type Ca^{2+} channel (**eFig. 23.2B**). NO also participates in mitochondrial respiration, the process that fuels excitation-contraction coupling. The different NOS isoforms also may participate in the process of cardiac remodeling. LV remodeling was ameliorated and survival improved after MI in transgenic mice deficient in NOS2.[13] By contrast, overexpression of NOS3 resulted in improved remodeling after MI. These contrasting effects of NOS2 and NOS3 may reflect the differences in amount of NO produced, which is much higher with NOS2. Emerging evidence indicates an imbalance between increasing free radical production and decreased NO generation in HF, which has been termed the "nitroso-redox imbalance".[13] NOS uncoupling secondary to a deficiency of tetrahydrobiopterin may further contribute to the nitroso-redox imbalance.[13] The nitroso-redox imbalance probably contributes to disease progression in HF secondary to increased oxidative stress, as well as loss of the peripheral vasodilatory effects of NO.

Bradykinin.

Kinins are vasodilators that are released from inactive protein precursors (kininogens) through the action of proteolytic enzymes termed *kallikreins*. The biologic actions of the kinins are mediated by binding to B_1 and B_2 receptors. Most cardiovascular actions are initiated by the B_2 receptor, which is distributed widely in tissues, where it binds bradykinin and kallidin. The B_1 receptor binds the metabolites of bradykinin and kallidin. Stimulation of the B_2 receptor leads to vasodilation, which is mediated by the activation of NOS3, phospholipase A_2, and adenylyl cyclase. Studies suggest that bradykinin plays an important role in the regulation of vascular tone in HF.[14] The breakdown of bradykinin is catalyzed by ACE and neprilysin, so these enzymes not only lead to the formation of a potent vasoconstrictor (angiotensin II) but also mediate the breakdown of a vasodilator (bradykinin). The augmentation of bradykinin levels likely contributes to the beneficial actions of ACE inhibitors and NEP inhibitors (**see Chapter 25**).

Adrenomedullin.

Adrenomedullin is a 52–amino acid vasodilatory peptide that originally was discovered in human pheochromocytoma tissue. Subsequently, high levels of adrenomedullin immunoreactivity were detected in cardiac atrium and adrenal and pituitary glands, with lower levels detected in the ventricle, kidney, and vasculature.[15] Adrenomedullin binds to a number of GPCRs, including the calcitonin receptor–like receptor and one specific for the adrenomedullin peptide. Adrenomedullin receptors are present in multiple tissue beds, as well as both endothelial and vascular smooth muscle cells. Circulating concentrations of adrenomedullin are elevated in cardiovascular disease and HF in proportion to the severity of cardiac and hemodynamic impairment. Increasing evidence suggests that adrenomedullin may

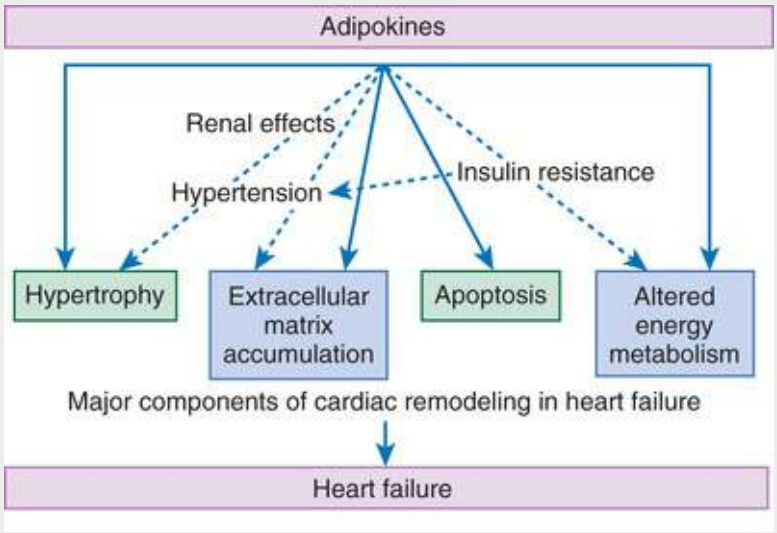
play a compensatory role in HF by offsetting the deleterious effects of excessive peripheral vasoconstriction. Plasma levels of adrenomedullin are elevated in chronic HF and are increased proportionally in response to disease severity. Immunoassays that detect the prohormone form of adrenomedullin have been shown to predict HF-related death in the Biomarkers in Acute Heart Failure (BACH) trial.[16]

Apelin.

Apelin is a vasoactive peptide that is an endogenous ligand for the GPCR APJ. The *APJ* gene encodes a receptor that most closely resembles the angiotensin receptor AT_1. However, the APJ receptor does not bind angiotensin II. In the cardiovascular system, apelin elicits endothelium-dependent, NO-mediated vasorelaxation and reduces arterial blood pressure. In addition, apelin demonstrates potent inotropic activity without stimulating concomitant cardiac myocyte hypertrophy. Apelin also produces diuresis by inhibition of arginine vasopressin activity. In experimental animals, apelin concentrations are significantly lower in failing hearts and are increased after treatment with an angiotensin receptor blocking agent. Furthermore, apelin levels are significantly reduced in patients with HF compared with controls and are significantly increased after cardiac resynchronization. The APJ receptor is a bifunctional GPCR that conveys cytoprotective signals after endogenous ligand stimulation and also acts a mechanosensor to delimit cardiac hypertrophy after hemodynamic pressure overload.[17] CLR325 is a apelin receptor agonist that is currently undergoing phase II clinical evaluation in patients with chronic HF.

Adipokines.

Although adipose tissue was once considered as a simple storage depot for fat, adipose tissue is now known to synthesize and secrete a family of proteins collectively referred to as *adipokines* (**see eFig. 23.3**). Adipokines include adiponectin, TNF, plasminogen activator inhibitor type 1 (PAI-1), transforming growth factor-β, and resistin. *Leptin* is a 16-kDa protein hormone that plays a key role in regulating energy intake and energy expenditure. The product of the ob gene, leptin is predominantly synthesized and secreted by adipocytes, although the heart is also a site of leptin synthesis. The initial role of leptin was thought to be decreasing appetite through hypothalamic stimulation and thus regulation of food intake. However, elevated circulating levels of leptin, which act via a family of receptor (ob.R) isoforms, appear to play an important role in hypertension, hypertrophy, and HF.[18] Leptin may affect myocardial function through direct peripheral effects or through secondary CNS-mediated responses. Lack of leptin and leptin resistance may lead to an accumulation of lipids in nonadipose peripheral tissues, resulting in a variety of “lipotoxic” effects, including cardiac myocyte apoptosis. Several studies suggest that leptin directly induces hypertrophy in both human and rodent cardiac myocytes.[18]



EFIGURE 23.3 Potential direct and indirect effects of adipokines on cardiac remodeling. Various circulating adipokines, the profile of which alters in obesity, may directly (*solid lines*) influence remodeling events known to occur in heart failure: hypertrophy, apoptosis, fibrosis, and metabolic alterations. Another potential mechanism whereby adipokines may influence cardiac structure and function is through indirect effects (*broken lines*) on parameters known to influence cardiac remodeling, such as hypertension, insulin resistance, and renal effects. (From Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. Physiol Rev 2008;88:389.)

Adiponectin is a 224–amino acid polypeptide that modulates a number of metabolic processes, including glucose regulation and fatty acid oxidation. Although adiponectin initially was thought to be exclusively produced by adipose tissue, recent studies have demonstrated adiponectin expression in the heart. Studies in adiponectin-deficient mice demonstrated progressive cardiac remodeling after hemodynamic pressure overloading, whereas administration of adiponectin diminished the infarct size, apoptosis, and TNF production after myocardial ischemia-reperfusion in both wild-type and adiponectin-deficient mice. Many studies have correlated decreased adiponectin levels with development of obesity-linked HF. Thus, adiponectin has been proposed as a potential biomarker of HF and therapeutic target in its treatment.[18]

Inflammatory Mediators.

The adult heart responds to tissue injury by synthesizing a series of proteins that promote homeostasis, either by activating mechanisms that facilitate tissue repair or, alternatively, by upregulating mechanisms that confer cytoprotective responses within the heart.[19] An ensemble of proinflammatory cytokines, including TNF, IL-1β, and IL-6, serve as the downstream "effectors" of the innate immune system by facilitating tissue repair within the heart. What has been less well understood, until recently, is how these myocardial innate immune responses are coordinated after tissue injury. The relatively recent discovery of a family of receptors termed *Toll-like receptors* (TLRs) and *NOD-like receptors* (NLRs) has greatly increased our understanding of the "upstream" molecular components that regulate the innate immune response.[20] Although the primary role for these molecules is to initiate repair of the injured myocardium, when expressed for protracted periods or at high levels, these molecules are sufficient to recapitulate virtually all aspects of the HF phenotype, by provoking deleterious changes in cardiac myocytes and nonmyocytes, as well as changes in the myocardial extracellular matrix (**summarized in Table 23.1**).[19] Moreover, in experimental models, substantial cross-talk takes place between proinflammatory cytokines and RAS, such that angiotensin II upregulates the expression of TNF through a nuclear factor-κB (NF-κB)–dependent pathway, and the expression of inflammatory mediators leads to upregulation of RAS though increased activation of myocardial ACE and chymase. Circulating levels of proinflammatory cytokines (e.g., TNF, IL-6) are increased in patients with HF and correlate with adverse patient

outcomes.[20] Conversely, the plasma concentrations of anti-inflammatory cytokines (e.g., IL-10) are reduced in patients with HF and are decreased more in direct relation to the severity of the degree of HF, suggesting that the imbalance between pro- and anti-inflammatory cytokine expression may contribute to progression of the disease process.

TABLE 23.1

Effects of Inflammatory Mediators on Left Ventricular Remodeling

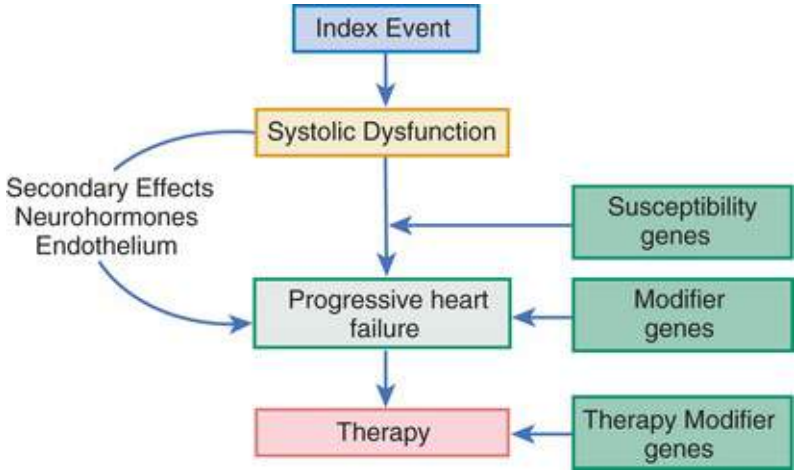
Alterations in the Biology of the Myocyte
Myocyte hypertrophy Fetal gene expression Negative inotropic effects Increased oxidative stress
Alterations in the Biology of Nonmyocytes
Conversion of fibroblasts to myofibroblasts Upregulation of AT_1 receptors on fibroblasts Increased MMP secretion by fibroblasts
Alterations in the Extracellular Matrix
Degradation of the matrix Myocardial fibrosis
Progressive Myocyte Loss
Necrosis Apoptosis

Left Ventricular Remodeling

Although the neurohormonal concept explains many aspects of disease progression in the failing heart, increasing clinical evidence suggests that current neurohormonal models fail to completely explain the basis for this progression. That is, although neurohormonal antagonists stabilize and in some cases reverse certain aspects of the disease process in HF, in the overwhelming majority of patients, it will progress, although at a slower rate. It has been suggested that the process of LV remodeling is directly related to future deterioration in LV performance and a less favorable clinical course in patients with HF (i.e. “biomechanical model”).[1] LV remodeling is influenced by hemodynamic, neurohormonal, epigenetic,[21] and genetic factors (**eFig. 23.4**), as well as by comorbid conditions. Although the complex changes that occur in the heart during LV remodeling have traditionally been described in anatomic terms, the process of LV remodeling also has an important impact on the biology of the cardiac myocyte, on changes in the volume of myocyte and nonmyocyte components of the myocardium, and on the geometry and architecture of the LV chamber (**Table 23.2**).

TABLE 23.2
Overview of Left Ventricular Remodeling

Alterations in Myocyte Biology
Excitation-contraction coupling
Myosin heavy chain (fetal) gene expression
Beta-adrenergic desensitization
Hypertrophy
Myocytolysis
Cytoskeletal proteins
Myocardial Changes
Myocyte loss
Necrosis
Apoptosis
Autophagy
Alterations in extracellular matrix
Matrix degradation
Myocardial fibrosis
Alterations in Left Ventricular Chamber Geometry
LV dilation
Increased LV sphericity
LV wall thinning
Mitral valve incompetence



EFIGURE 23.4 Role of genetics in the pathogenesis of heart failure. Gene polymorphisms may contribute to disease progression in HF through several mechanisms. Disease susceptibility genes may confer increased risk of disease progression after cardiac injury, whereas modifier genes can increase and/or decrease the impact of susceptibility genes. Finally, gene polymorphisms may modify the response to HF therapies (therapy modifier genes).

Alterations in Biology of Cardiac Myocyte

Numerous studies have suggested that failing human cardiac myocytes undergo a number of important changes that might be expected to lead to a progressive loss of contractile function. These include decreased alpha-myosin heavy chain gene expression with a concomitant increase in beta-myosin heavy chain expression, progressive loss of myofilaments in cardiac myocytes, alterations in cytoskeletal proteins, and alterations in excitation-contraction coupling and in energy metabolism, as well as desensitization of beta-adrenergic signaling (**Table 23.2**).

Cardiac Myocyte Hypertrophy

Two basic patterns of cardiac hypertrophy occur in response to hemodynamic overload (**Fig. 23.7**). In pressure overload hypertrophy (e.g., with aortic stenosis or hypertension), increased systolic wall stress

leads to the addition of sarcomeres in parallel, an increase in myocyte cross-sectional area, and increased LV wall thickening. This pattern of remodeling has been referred to as “concentric” hypertrophy (**Fig. 23.7A**) and has been linked with alterations in Ca^{2+}/calmodulin-dependent protein kinase II–dependent signaling[22] (**Fig. 23.8**). By contrast, in volume overload hypertrophy (e.g., with aortic and mitral regurgitation), increased diastolic wall stress leads to an increase in myocyte length with the addition of sarcomeres in series, thereby engendering increased LV ventricular dilation. This pattern of remodeling has been referred to as “eccentric” hypertrophy (because of the position of the heart in the chest), or a “dilated” phenotype (**see Fig. 23.7A**), and has been linked with protein kinase B (Akt) activation[22] (**see Fig. 23.8**). Patients with HF classically present with a dilated left ventricle with or without LV wall thinning. The myocytes from these failing ventricles have an elongated appearance that is characteristic of myocytes obtained from hearts subjected to chronic volume overload.

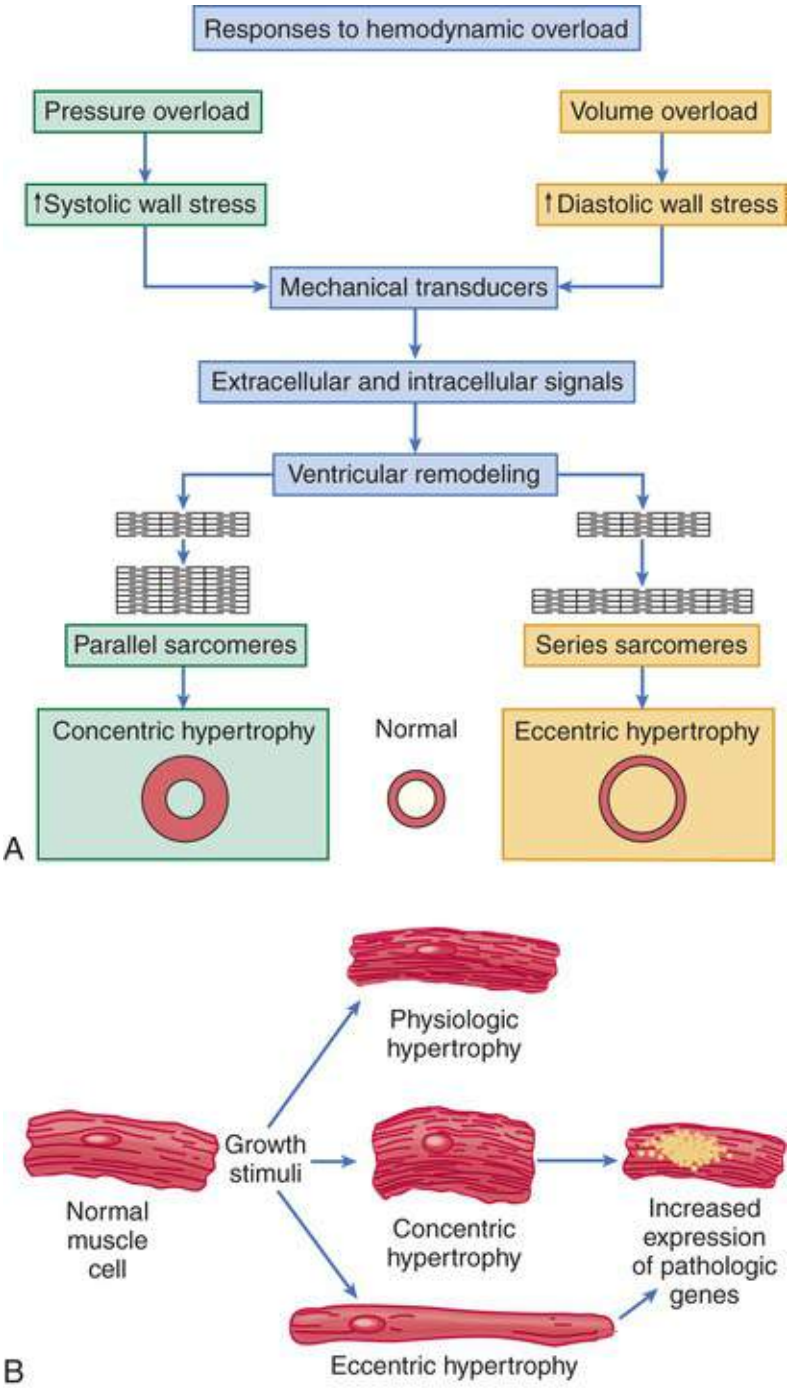


FIGURE 23.7 The pattern of cardiac and cellular remodeling that occurs in response to hemodynamic overloading depends on the nature of the inciting stimulus. **A,** When the overload is predominantly due to an increase in pressure (e.g., with systemic hypertension or aortic stenosis), the increase in systolic wall stress leads to the parallel addition of sarcomeres and widening of the cardiac myocytes, resulting in "concentric" cardiac hypertrophy. When the overload is predominantly due to an increase in ventricular volume, the increase in diastolic wall stress leads to the series addition of sarcomeres, lengthening of cardiac myocytes, and LV dilation, which is referred to as "eccentric" chamber hypertrophy. **B,** Phenotypically distinct changes occur in the morphology of myocytes in response to the type of hemodynamic overload that is superimposed. When the overload is predominantly due to an increase in pressure, the increase in systolic wall stress leads to the parallel addition of sarcomeres and widening of the cardiac myocytes. When the hemodynamic overload is predominantly due to an increase in ventricular volume, the increase in diastolic wall stress leads to the series addition of sarcomeres with consequent lengthening of cardiac myocytes. The expression of maladaptive embryonic genes is increased in both eccentric and concentric hypertrophy, but not in physiologic myocyte hypertrophy as occurs with exercise (see Table 23.2). (**A,** From Colucci WS, editor. Heart Failure: Cardiac Function and Dysfunction. 2nd ed. Philadelphia: Current Medicine; 1999, p 4.2. **B,** Modified from Hunter JJ, Chien KR. Signaling pathways for cardiac hypertrophy and failure. N Engl J Med 1999;341:1276.)

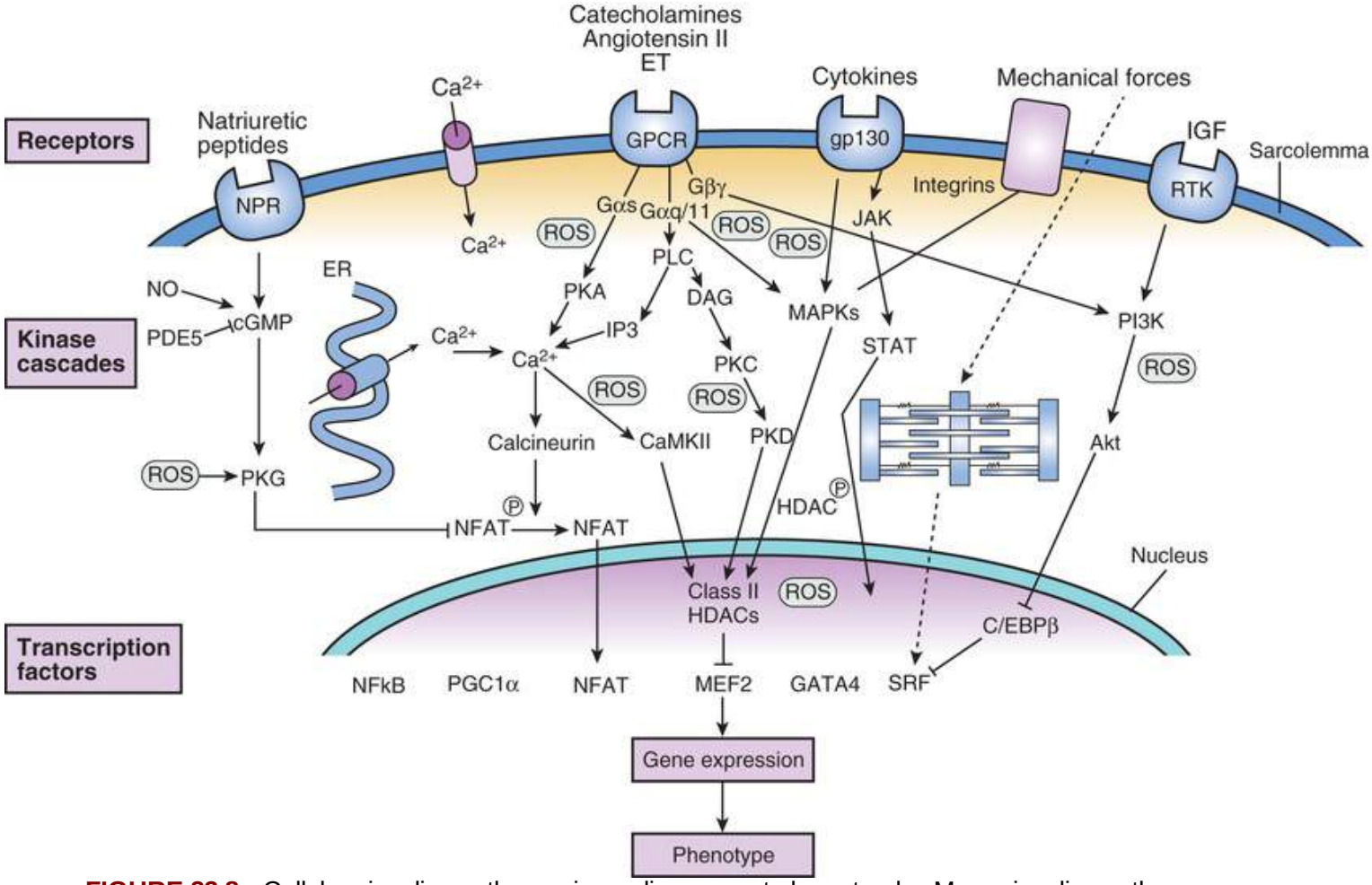


FIGURE 23.8 Cellular signaling pathways in cardiac myocyte hypertrophy. Many signaling pathways have the potential to regulate the growth of cardiac cells acting through an increasingly complex network of intracellular signaling cascades. Agonists for α-adrenergic, angiotensin, and endothelin (*ET*) receptors couple to phospholipase C (*PLC*) and calcium influx channels by way of G proteins. Activation of PLC results in the generation of two second messengers, inositol triphosphate (*IP3*) and diacylglycerol (*DAG*). IP3 causes the release of calcium from intracellular stores, and DAG activates protein kinase C (*PKC*). Changes in intracellular calcium stores can activate Ca^{2+}/calmodulin-dependent kinases (*CaCMKII*), as well as calcineurin, which can affect gene expression in multiple ways. PKC and G proteins can affect gene expression by activating mitogen-activated protein kinase (*MAPK*) cascades. Histone deacetylase complexes (*HDACs*) are emerging as important negative regulators of genes involved in cardiac hypertrophy. Cytokines and peptide growth factors, such as insulin-like growth factor (*IGF*), can be elaborated by various cells within the heart and may act in an autocrine or paracrine manner. These growth factors activate cellular receptors that usually possess receptor tyrosine kinase (*RTK*) activity and are coupled to a cascade of protein kinase. Mechanical deformation of cardiac myocytes through matrix-integrin interactions can lead to activation or modulation of several signaling pathways, at least in part through autocrine action of released agonists such as angiotensin. Both NO and oxidative stress may be induced after stimulation of signaling pathways and modulate the activity of kinase cascades and transcription factors leading to alterations in contractile phenotype, growth, and death in myocytes. *Akt,* Protein kinase B; *C/EBPβ,* CCAAT/enhancer binding protein-β; *ER,* endoplasmic reticulum; *GATA4,* GATA-binding protein; *gp130,* glycoprotein 130; *GPCR,* G protein–coupled receptor; *JAK,* Janus kinase; *MEF2,* myocyte enhancer factor; *NFAT,* nuclear factor of activated T cells; *NFκB,* nuclear factor-kappaB cells; *NPR,* natriuretic peptide receptor; *P,* phosphorylation; *PDE5,* phosphodiesterase type 5; PGC1α, peroxisome proliferator–activated receptor gamma, coactivator 1 alpha; *PKA, PKD, PKG,* protein kinases A, D, G; *STAT,* signal transducer and activator of transcription; *SRF,* serum response factor. (From Shah AM, Mann DL. In search of new therapeutic targets and strategies for heart failure: recent advances in basic science. Lancet 2011;378:704.)

Cardiac myocyte hypertrophy also leads to changes in the biologic phenotype of the myocyte that are secondary to reactivation of portfolios of genes normally not expressed postnatally. The reactivation of these fetal genes, the so-called fetal gene program, also is accompanied by decreased expression of a number of genes that are normally expressed in the adult heart. As discussed later, activation of the fetal

gene program may contribute to the contractile dysfunction that develops in the failing myocyte. As shown in **Fig. 23.8**, the stimuli for the genetic reprogramming of the myocyte include mechanical stretch/strain of the myocyte, neurohormones (e.g., NE, angiotensin II), inflammatory cytokines (e.g., TNF, IL-6), other peptides and growth factors (e.g., ET), and ROS (e.g., superoxide, NO). These stimuli occur both locally within the myocardium, where they exert autocrine/paracrine effects, and systemically, where they exert endocrine effects.

The early stage of cardiac myocyte hypertrophy is characterized morphologically by increases in the number of myofibrils and mitochondria, as well as enlargement of mitochondria and nuclei. At this stage, the cardiac myocytes are larger than normal, but with preservation of cellular organization. As hypertrophy continues, there is an increase in the number of mitochondria, as well as the addition of new contractile elements in localized areas of the cell. Cells subjected to longstanding hypertrophy show more obvious disruptions in cellular organization, such as extremely enlarged nuclei with highly lobulated membranes, accompanied by the displacement of adjacent myofibrils with loss of the normal registration of the Z-bands. The late stage of hypertrophy is characterized by loss of contractile elements (myocytolysis) with marked disruption of Z-bands and severe disruption of the normal parallel arrangement of the sarcomeres, accompanied by dilation and increased tortuosity of T tubules.

Alterations in Excitation-Contraction Coupling

As discussed in **Chapter 22**, excitation-contraction coupling refers to the cascade of biologic events that begins with the cardiac action potential and ends with myocyte contraction and relaxation (**see Fig. 22.1**). Impaired contraction and relaxation of the failing heart is most prominent at high heart rates, which results in a depressed force-frequency relationship. This has been demonstrated both in isolated strips of human myocardium and in clinical observations of patients (**Fig. 23.9**). Normally, higher contraction frequency increases cardiac performance because of a frequency-dependent augmentation of intracellular Ca^{2+} transients. By contrast, in the failing myocardium, a decline in force generation is seen with higher heart rates that is secondary to a decrease in amplitude of intracellular Ca^{2+}, a prolonged decline of the Ca^{2+} transient, and increased levels of diastolic calcium. The reduced intracellular Ca^{2+} transient is secondary to depletion of Ca^{2+} from the SR, the result of three major defects in calcium cycling that occur in the failing heart: (1) increased Ca^{2+} leak through ryanodine receptors (RyRs), (2) impaired sarcoplasmic reticulum (SR) Ca^{2+} uptake from reduced SERCA2a (SR calcium pump) protein levels and function, and (3) increased expression and function of the sarcolemmal Na^{+}/Ca^{2+} exchanger (NCX).

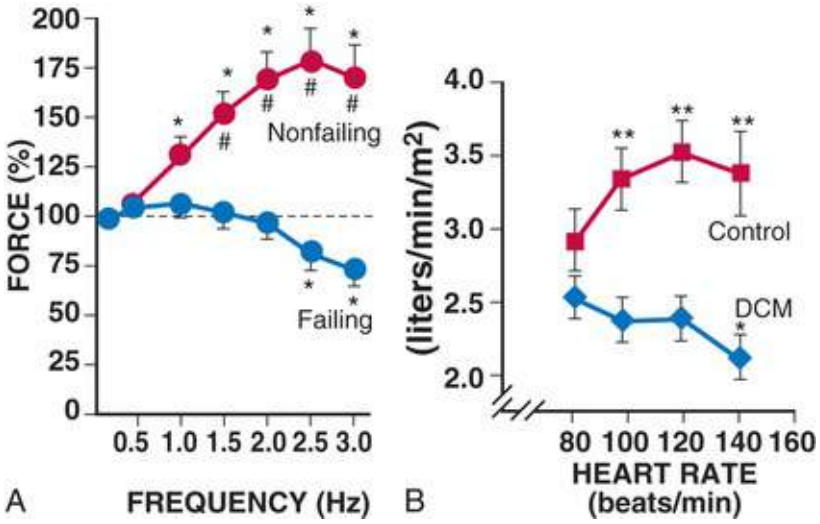


FIGURE 23.9 Relationship between contraction frequency and cardiac performance (force-frequency relation) in heart failure. **A,** Relationship between stimulation frequency and force generation of isolated muscle strip preparations from nonfailing and failing human hearts. In nonfailing myocardium, contractile force increases up to a stimulation rate of approximately 2.5 Hz (150 beats/min), whereas contractile force does not significantly increase in failing myocardium. (* indicates $P < 0.05$ versus 0.25 Hz; # indicates $P < 0.05$ between failing and nonfailing myocardium.) **B,** Cardiac index versus heart rate in patients with and without HF. Heart rate was changed by temporary pacing during cardiac catheterization, and cardiac output was measured by thermodilution. In patients without HF, cardiac index increases with higher heart rates up to 120 beats/min, but it declines continuously in patients with HF. (* indicates $P < 0.05$ and ** $P < 0.01$ versus lowest pacing rate.) *DCM,* Dilated cardiomyopathy. (**A,** Modified from Pieske B et al. Ca^{2+} handling and sarcoplasmic reticulum Ca^{2+} content in isolated failing and nonfailing human myocardium. Circ Res 1999;85:38; **B,** modified from Hasenfuss G et al. Influence of the force-frequency relationship on haemodynamics and left ventricular function in patients with non-failing hearts and in patients with dilated cardiomyopathy. Eur Heart J 1994;15:164.)

Increased Ca^{2+} Leak

Ca^{2+} enters the cell during the action potential through L-type calcium channels and triggers a release of a much larger amount of calcium from the SR through RyRs. Although controversy surrounds the expression levels of RyRs in HF, as well as the coupling of RyRs to L-type Ca^{2+} channels, there is general agreement that the diastolic Ca^{2+} leak in HF is the result of RyRs opening during diastole.[23] The resultant release of calcium from the SR event is referred to as a "Ca^{2+}-spark." The pathophysiologic mechanism underlying the diastolic Ca^{2+} leak in HF has been attributed to increased phosphorylation of the RyR by protein kinase A (PKA), Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), and decreased binding of the RyR stabilizing protein calstabin (FKBP12.6). Experimental studies suggest that PKA-dependent phosphorylation of the RyR may provoke Ca^{2+} leak by destabilizing the association between calstabin and FKB (**see Chapter 22**). Interestingly, in dogs, beta-adrenergic blockers prevent the development Ca^{2+} leak by restoring RyR stabilization by FKBP12.6.[24] This observation has led to the suggestion that the increase in contractile function following treatment with beta blockers is secondary to RyR stabilization. The role of excess PKA-dependent RyR phosphorylation in the etiology of HF appears somewhat paradoxical, in that the β-receptor is downregulated in HF. One current proposal is that there are microdomains in close proximity to the RyR where there is increased PKA phosphorylation and more cyclic adenosine monophosphate (cAMP) and decreased activity of the type 4 phosphodiesterase (PDE4D3).[25] Besides its contribution to reduced SR Ca^{2+} content, increased leak seems to be relevant for arrhythmias in HF. This results from activation of NCX: Ca^{2+} leaking out of the SR activates NCX to remove Ca^{2+} from the cytosol in exchange of Na^+. Since NCX is electrogenic (3 Na^+ versus 1 Ca^{2+}), this results in a net inward current generating the so-called delayed afterdepolarizations (DADs) as a trigger of arrhythmias. Drugs with the ability to bind to and stabilize the RyR (referred to as RYCALS), such as

the diltiazem derivative JTV 519, have been shown to attenuate experimental HF and arrhythmias[24] and are currently being developed as a novel therapeutic class of drugs in the treatment of HF.

Sarcoplasmic Reticulum Ca^{2+} Reuptake and Sarcolemmal Ca^{2+} Elimination

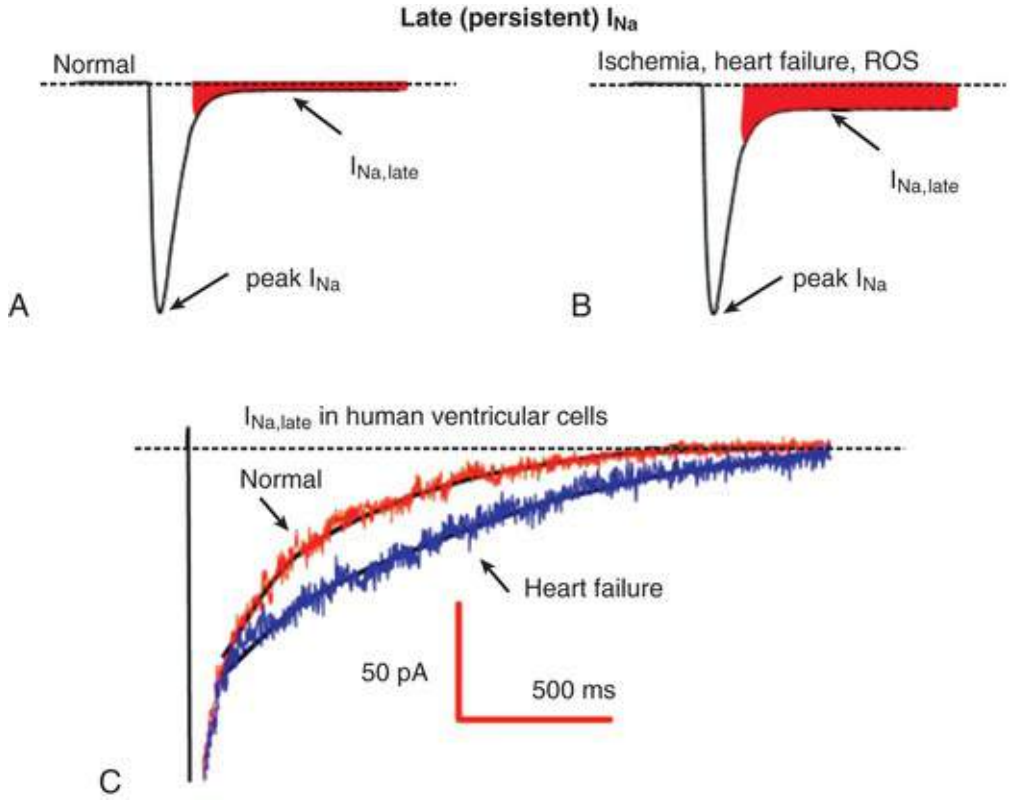
Relaxation of the contractile proteins occurs after dissociation of Ca^{2+} from troponin C and Ca^{2+} elimination from the cytosol. In the human heart, there are two main mechanisms responsible for elimination of Ca^{2+} from the cytosol: SR uptake of Ca^{2+} by the SERCA2a Ca^{2+} pump and transsarcolemmal Ca^{2+} elimination through NCX. Under normal conditions, approximately 75% of Ca^{2+} is taken up by the SR and 25% extruded from the cell through NCX. In HF there is decreased uptake of Ca^{2+} by the SR secondary to decreased SERCA2a protein levels and SERCA2a function. In addition, phosphorylation of phospholamban (PLB) is reduced in the failing heart, resulting in increased PLB-dependent inhibition of the SR Ca^{2+} pump.[24] The decrease of SR Ca^{2+} uptake in the failing heart results in a relative increase of transsarcolemmal Ca^{2+} elimination by the NCX, which is most likely secondary to increased expression of NCX protein.

Restoring deficient SERCA2a by gene transfer has been shown to improve contractile function and restore electrical stability experimentally. However, the recent CUPID trial failed to show clinical benefit of SERCA2a gene transfer in patients with HF, whereas the gene transfer procedure itself seems to be safe.[26] Although the increase in NCX activity may result in increased Ca^{2+} elimination from the myocyte, thereby preserving diastolic calcium levels and preventing diastolic dysfunction when SR calcium uptake is reduced, increased NCX activity may further reduce SR Ca^{2+} accumulation/content and may therefore reduce Ca^{2+} activation of contractile proteins.[24] As noted, electrogenic NCX activity induces DADs and arrhythmias.

Action Potential Duration and Sodium Handling

Several factors contribute to the prolongation of the action potential duration, which is a ubiquitous finding in failing hearts.[27] The transient outward potassium current (Ito) and the inward rectifier potassium current (Ik1) both are reduced in HF. In addition, the increased inward Na^+ current through the NCX and persistent activity of the sodium channel also may contribute to prolongation of the action potential. The latter mechanism, also termed the "late sodium current," may be important in the pathogenesis of cardiac arrhythmias in HF. As discussed in **Chapter 22**, the voltage-gated Na^+ channels are activated on depolarization of the cell membrane, leading to rapid influx of Na^+ that is responsible for the fast upstroke of the action potential (**see eFig. 23.5**). Under normal conditions, Na^+ channels inactivate a few milliseconds after depolarization. However, it is now recognized that some Na^+ channels remain open (or reopen), leading to a small but persistent influx of Na^+ throughout the plateau of the action potential, which generates a "late" sodium current (I_{Na}).[28] Late I_{Na} is sufficient to lead to a substantial influx of Na^+ into the cell in HF, with consequent prolongation of the action potential and early afterdepolarizations (EADs), which may be a significant source of increased arrhythmias in HF. High levels of intracellular Na^+ also may lead to cellular acidosis secondary to increased sodium-proton exchange activity. Increased intracellular Na^+ also influences the driving forces for the NCX, thereby reducing Ca^{2+} extrusion through the forward mode of the NCX, which when combined with reduced activity of the SERCA2a pump, may be a cause of the elevated diastolic cytosolic calcium levels and disturbed diastolic function in HF. Inhibition of the late Na^+ current with the inhibitor ranolazine can improve disturbed diastolic function in isolated myocardium from failing human hearts and also may exhibit antiarrhythmic properties.[29] Of note, the different contributions to altered Ca^{2+} handling may vary significantly from patient to patient, which

may explain the heterogeneity of different HF phenotypes. If SERCA2a expression is decreased and intracellular sodium is high, both systolic and diastolic function will be impaired. By contrast, higher NCX expression with moderately elevated intracellular Na^+ will result in excess transsarcolemmal calcium elimination, and diastolic function will rather be preserved. However, this may be associated with increased arrhythmias secondary to increased NCX activity.[24]

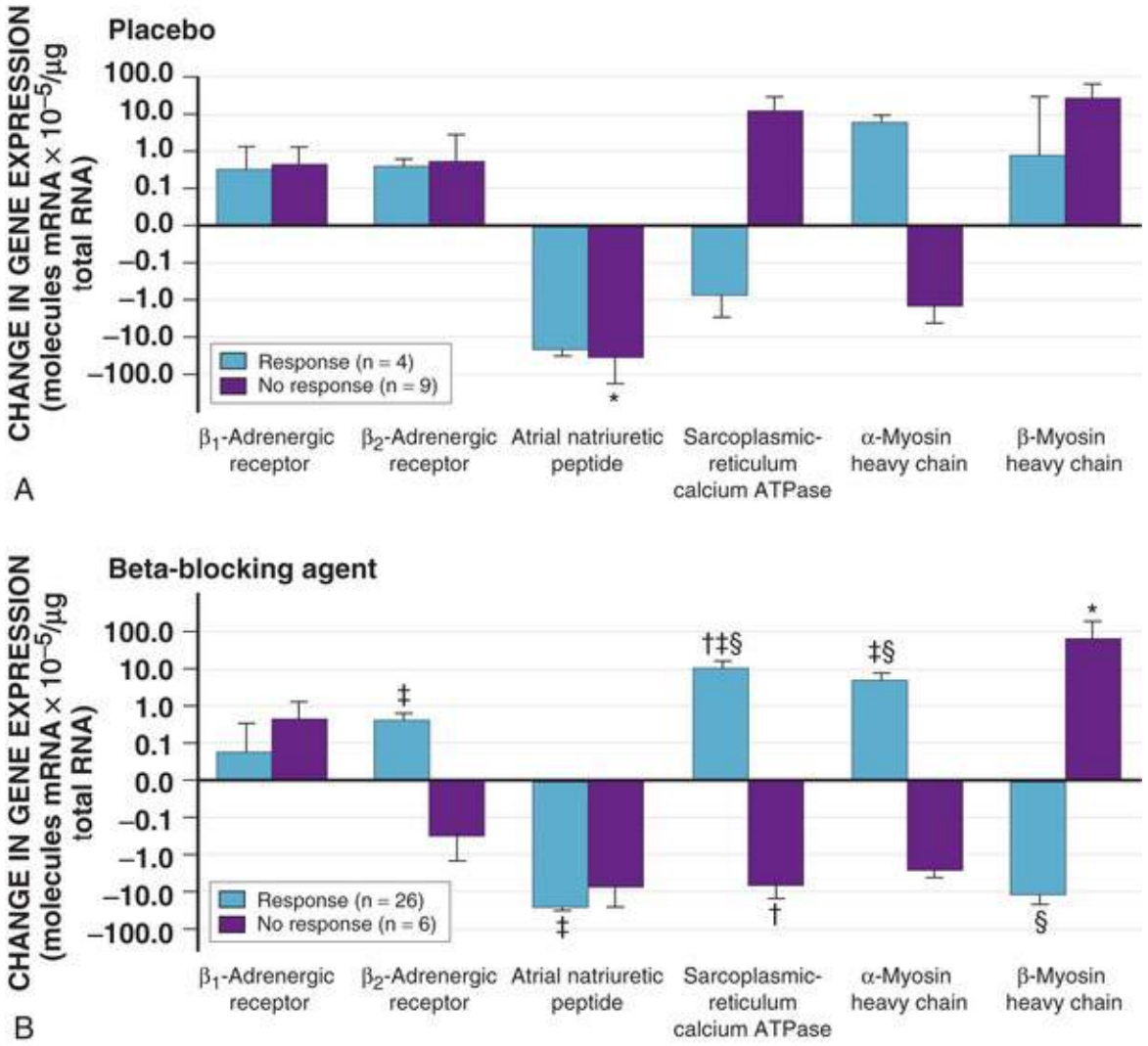


EFIGURE 23.5 Sodium current under normal and disease conditions. **A,** Depiction of Na^+ current in nonfailing myocardium. Under normal conditions, Na^+ channels inactivate a few milliseconds after depolarization and net Na^+ influx is small. **B,** Pathologic conditions (ischemia, HF, ROS) alter Na^+ current. Channels remain open (or reopen), and a persistent influx of Na^+ generates the so-called late Na^+ current ($I_{Na,late}$). This causes a substantial influx of Na^+, which contributes to elevated Na^+ concentrations under conditions of HF. **C,** Original recordings of Na^+ currents from human ventricular isolated cells. Persistent opening of Na^+ channels in the myocyte from a failing heart results in a larger Na^+ influx relative to that for the myocyte from the normal heart. (From Maltsev VA, Silverman N, Sabbah HN, et al. Eur J Heart Fail 2007;9:219.)

Abnormalities in Contractile and Regulatory Proteins

Early studies showed that the activity of myofibrillar ATPase was reduced in the hearts of patients who died of HF. Furthermore, reductions in the activity of myofibrillar ATPase, actomyosin ATPase, or myosin ATPase have been demonstrated in several animal models of HF. Subsequent studies showed that these abnormalities in ATPase activity could be explained by a shift to the fetal isoform of myosin heavy chain (MHC) in cardiac hypertrophy and failure. In rodents the predominant MHC is the “fast” V1 isoform (alpha-MHC [MYHC6]), which has high ATPase activity. With pressure-induced hypertrophy or after MI in rodents, reexpression of the “slow” V3 fetal isoform of MHC that has low ATPase activity (beta-MHC [MYHC7]) and decreased expression of the V1 isoform have been observed. Although translating this information to human HF proved to be more challenging, because the predominant MHC isoform in humans is the slower V3 isoform (MYHC7), polymerase chain reaction (PCR) techniques have shown

that MYHC6 accounts for approximately 33% of MHC mRNA in normal human myocardium, whereas MYHC6 mRNA abundance decreases to approximately 2% in failing hearts. Furthermore, when myocardial biopsy was performed in patients receiving beta blockers, reciprocal changes were observed in the levels of MYHC6 (increase) and MYHC7 (decrease) mRNA, and an increase in the MYHC6/MYHC7 ratio was noted in those who demonstrated an improvement in LV function. However, these changes in myosin isoform shifts did not occur in HF patients who showed no improvement in LV function with beta blockers (**eFig. 23.6**). Thus the decreased expression of MYHC6 may play a significant role in the pathophysiology of dilated cardiomyopathy (DCM).



EFIGURE 23.6 Changes in myocardial mRNA expression and beta-adrenergic receptor protein levels. **A, B,** Changes between baseline and the end of the 6-month study in the abundance of myocardial mRNA for six contractility-regulating or hypertrophy-regulating proteins in patients who received either placebo or a beta-blocking agent. The changes in patients who had an improvement in LV ejection fraction (a "response," defined as an increase by at least 5 ejection fraction [EF] units) were compared with the changes in patients who did not demonstrate such a response. Gene expression is shown as molecules of mRNA per microgram of total RNA on a logarithmic scale. The *asterisk* indicates $P < 0.10$ for the change between the baseline value and the value measured at 6 months by the paired *t*-test; †, $P < 0.05$ for the comparison with the placebo group by the test for interaction; ‡, $P < 0.05$ for the change between the baseline value and the value measured at 6 months by the paired *t*-test; and §, $P < 0.05$ for the comparison with patients who did not have a response. Each panel shows results for patients with complete data for the indicated mRNA and receptor protein measurements. (From Lowes BD et al. Myocardial gene expression in dilated cardiomyopathy treated with beta blocking agents. N Engl J Med 2002;346:1357.)

Another important modification of contractile proteins that contributes to contractile dysfunction is

proteolysis of the myofilaments themselves (myocytolysis). Myocardial biopsy samples from patients with advanced LV dysfunction show a significant reduction in the volume of myofibrils per cell, which may contribute to the development of cardiac decompensation.

Alterations in the expression and/or activity of myofilament regulatory proteins also have been proposed as a potential mechanism for the decrease in cardiac contractile function in HF (**Table 23.3**), including the myosin light chains, the troponin-tropomyosin complex, and titin. Changes in myosin light chain isoforms have been observed in the atria and ventricles of patients whose hearts have been subjected to mechanical overload. Although changes in the abundance and/or isoforms of troponins TnI and TnC have not been reported in HF, isoform shifts have been reported in TnT (**see Chapter 22**). In normal adult myocardium, TnT is expressed as a single isoform (cTnT3). In myocardium samples from patients with end-stage HF, however, both the fetal cTnT1 and the cTnT4 isoforms are expressed at increased levels, which might be expected to lead to a decrease in maximal active tension. Changes in the titin isoform from N2B, which is expressed postnatally and is stiffer, to N2BA, the more distensible fetal isoform, have been associated with increased compliance in hearts from patients with HF.[30]

TABLE 23.3

Changes in the Biology of the Failing Myocyte

PROTEIN	CHANGE IN HUMAN HEART FAILURE
Plasma Membrane	
L-type calcium channels	Decreased*†
Sodium/calcium exchanger	Increased*†
Sodium pump	Reexpression of fetal isoforms
$Beta_1$-adrenergic receptor	Decreased*†
$Beta_2$-adrenergic receptor	Increased*
$Alpha_1$-adrenergic receptor	Increased*
Contractile Proteins	
Myosin heavy chain (MHC)	Reversion to fetal isoform (↓MYHC6/MYHC7)
Myosin light chain (MLC)	Reversion to fetal isoform
Actin	Normal*
Titin	Isoform switch (↑N2BA/N2B), hypophosphorylated
Troponin I	Normal*, hypo- and hyperphosphorylated‡
Troponin T	Isoform switch, hyperphosphorylated‡
Troponin C	Normal*
Tropomyosin	Normal*
Sarcoplasmic Reticulum	
SERCA2a	Decreased*†
Phospholamban	Hypophosphorylated
Ryanodine receptor	Hyperphosphorylated†
Calsequestrin	Normal*
Calreticulin	Normal*

*Refers to protein level.

†Refers to functional activity.

‡Hyperphosphorylation results in decreased Ca^{2+} sensitivity.

Modified from Katz AM. Physiology of the Heart. Philadelphia: Lippincott Williams & Wilkins; 2001.

Abnormalities in Cytoskeletal Proteins

The cytoskeleton of cardiac myocytes consists of actin, the intermediate filament desmin, the sarcomeric protein titin (**see Chapter 22**), and alpha- and beta-tubulin, which form the microtubules by polymerization. Vinculin, talin, dystrophin, and spectrin constitute a separate group of membrane-associated proteins. In numerous experimental studies, a role for cytoskeletal and membrane-associated proteins has been implicated in the pathogenesis of HF. In patients with DCM, titin is downregulated, and

the cytoskeletal proteins desmin and membrane-associated proteins such as vinculin and dystrophin are upregulated. Proteolytic digestion of the dystrophin molecule has been identified as a possible reversible cause of HF. Loss of integrity of the cytoskeleton and its linkage of the sarcomere to the sarcolemma and extracellular matrix would be expected to lead to contractile dysfunction at the myocyte level, as well as at the myocardial level.

Beta-Adrenergic Desensitization

Ventricles obtained from HF patients demonstrate a marked reduction in beta-adrenergic receptor density, isoproterenol-mediated adenyl cyclase stimulation, and the contractile response to beta-adrenergic agonists.[31] The downregulation of beta-adrenergic receptors is likely mediated by increased levels of NE in the vicinity of the receptor (**see eFig. 23.6**). In patients with DCM, this reduction in receptor density involves primarily the $beta_1$-receptor protein and mRNA and is proportional to the severity of HF. In contrast, the level of $beta_2$-adrenergic receptor protein and mRNA are unchanged or increased. In addition, there are increases in the expression of beta-adrenergic receptor kinase 1 (βARK1, also called G protein–coupled receptor kinase 2 [GRK2]), a member of the family of GPCR kinases, in failing human hearts. As noted in **Chapter 22**, βARK phosphorylates the cytoplasmic loops of both $beta_1$- and $beta_2$-adrenergic receptors and increases the affinity of these receptors for a scaffolding protein termed *beta-arrestin* (**see Fig. 22.14**). The binding of beta-arrestins to the cytoplasmic tail of the beta receptor not only uncouples the receptor from heterotrimeric G proteins, but also targets the receptor for internalization in clathrin-coated vesicles. Although this internalization fosters receptor dephosphorylation and serves as a prelude to recycling the beta receptor to the surface for reactivation, at some point receptor entry via endocytosis is not followed by recycling, but rather leads to receptor trafficking to lysosomes and receptor degradation. Increased βARK (GRK2) activity may therefore contribute to the desensitization of both $beta_1$ and $beta_2$ receptors in patients with HF. Desensitization of the beta receptors can be both beneficial and deleterious in HF. By reducing LV contractility, desensitization may be deleterious. However, by reducing energy expenditure of the energy-starved myocardium and protecting the myocyte from the deleterious effects of sustained adrenergic stimulation, this adaptive response is beneficial. Interestingly, lymphocyte GRK2 protein levels were shown to be independent predictors of cardiovascular mortality in patients with HF and added prognostic and clinical value over demographic and clinical variables.[32]

Alterations in the Myocardium

The changes that occur in failing myocardium may be categorized broadly into those that occur in the volume of cardiac myocytes and those that occur in the volume and composition of the extracellular matrix. For changes in the myocyte component of the myocardium, increasing evidence suggests that progressive myocyte loss, through necrotic, apoptotic, or autophagic cell death pathways, may contribute to progressive cardiac dysfunction and LV remodeling. Myocardial regeneration is discussed in **Chapter 30**.

Necrosis.
Although necrosis initially was thought to be a “passive” form of cell death, emerging evidence indicates that necrotic cell death also is “regulated.”[33] The relative proportion of unregulated versus regulated

necrotic death in the heart is not currently known; however, regulated necrosis is an important component of MI, HF, and cerebrovascular accident (stroke). The hallmark features of necrosis are loss of plasma membrane integrity and depletion of cellular adenosine triphosphate (ATP). Dysfunction of the plasma membrane in necrotic cells leads to cell swelling and rupture. There is also swelling of organelles such as the mitochondria. In the heart, increased plasma membrane permeability allows Ca^{2+} to leak into the cell, exposing the contractile proteins to very high concentrations of this activator, which in turn initiates extreme interactions between the myofilaments (contraction bands), further contributing to disruption of the cellular membrane. Necrotic myocyte death occurs in ischemic heart disease, myocardial injury, toxin exposure (e.g., daunorubicin; **see Chapter 81**), infection, and inflammation. Neurohormonal activation also can lead to necrotic cell death. For example, concentrations of NE available within myocardial tissue, as well as circulating levels in patients with advanced HF, are sufficient to provoke myocyte necrosis in experimental model systems. Moreover, excessive stimulation with angiotensin II, ET, or TNF has been shown to provoke myocyte necrosis in experimental models.

In contrast with apoptosis, the rupture of cell membranes with cell necrosis releases intracellular contents, so-called danger-associated molecular patterns (DAMPS), which evoke an intense inflammatory reaction, leading to the influx of granulocytes, macrophages, and collagen-secreting fibroblasts into the area of injury. The final result is a fibrotic scar, which may alter the structural and functional properties of the myocardium.[34] The regulated cell death pathways that have been studied thus far include TNF signaling through the type 1 TNF receptor (TNFR1) and opening of the mitochondrial permeability transition pore (MPTP) in the inner mitochondrial membrane, resulting in loss of the electrical potential difference ($\Delta\psi m$) across the inner mitochondrial membrane, leading to ATP depletion (**Fig. 23.10A**).

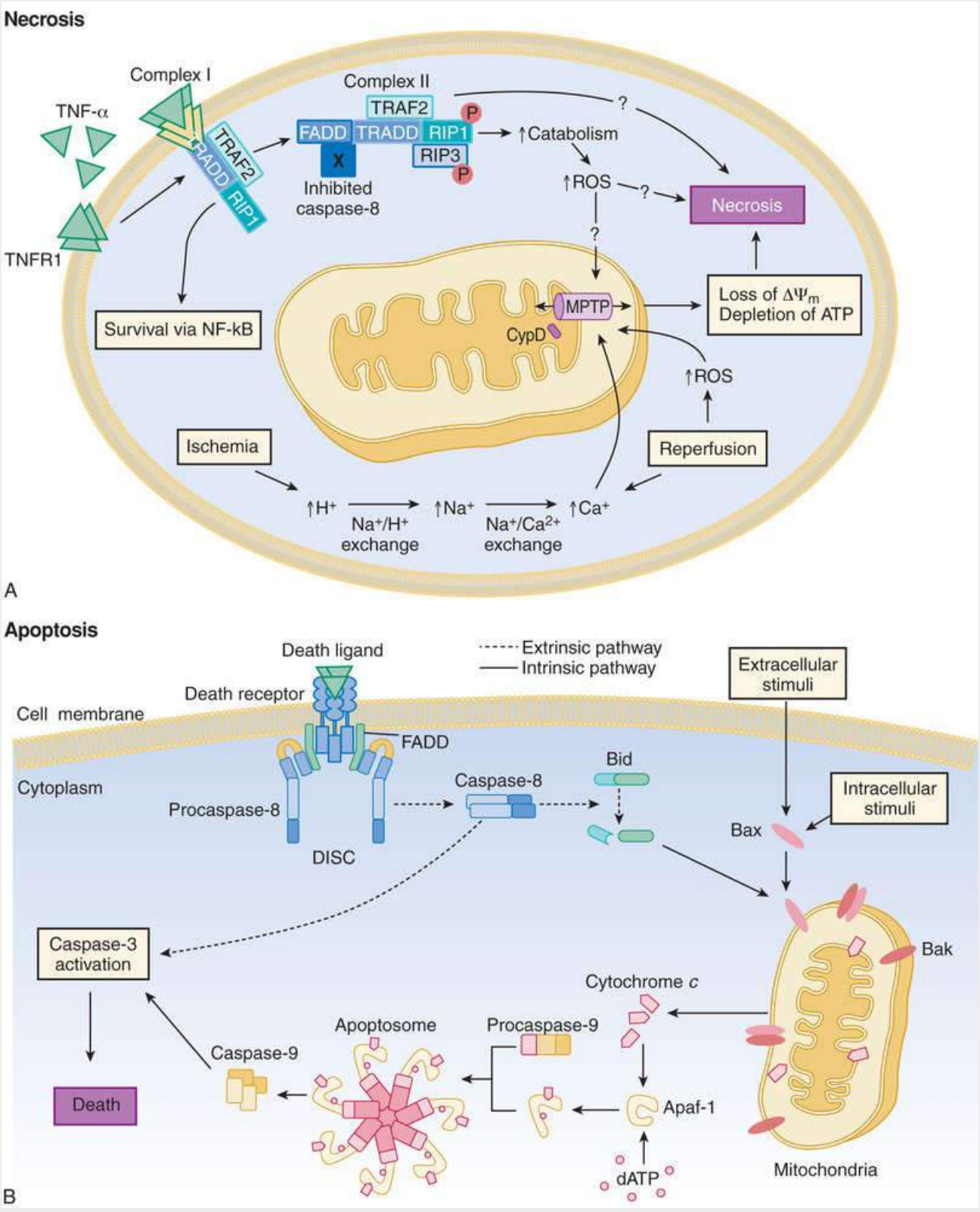


FIGURE 23.10 Apoptotic and necrotic cell death pathways. **A,** Necrosis. Information about regulated signaling in necrosis is currently limited to two pathways. The first involves death receptors, as exemplified by TNFR1 (tumor necrosis factor-α receptor 1). Depending on context, activation of TNFR1 can promote cell survival or either apoptotic or necrotic cell death. These choices are mediated by multiprotein complexes I and II. The binding of TNF-α to TNFR1 stimulates formation of complex I, which contains TNFR1, TRADD, RIP1, TRAF2, and cIAP1/2. Death effects of TNFR1 signaling are mediated via complex II, which forms after endocytosis of complex I, the dissociation of TNFR1, and the deubiquitination of RIP1 by CYLD and A20 (*not shown*). A second necrosis pathway involves the mitochondrial permeability transition pore (*MPTP*) in the inner mitochondrial membrane and its regulation by cyclophilin D (*CypD*). This pore may be opened by increased Ca^{2+}, oxidative stress, decreased ATP generation, and other stimuli that operate during ischemia-reperfusion and heart failure. Ischemia-reperfusion can lead to increased Ca^{2+} and ROS, as depicted. MPTP opening results in profound alterations in mitochondrial structure and function, which results in decreased ATP generation. **B,** Apoptosis is mediated by an extrinsic pathway involving cell surface death receptors and by an intrinsic pathway that uses the

mitochondria and endoplasmic reticulum (ER). The extrinsic pathway is activated by binding of death ligand to its receptor, which triggers formation of the DISC (death-inducing signaling complex). Caspase-8 is activated by forced proximity within the DISC and then cleaves and activates downstream procaspases. Caspase-8 also can cleave the BH3-only protein Bid, which translocates to the mitochondria to trigger apoptotic mitochondrial events. The intrinsic pathway is activated by diverse biologic, chemical, and physical stimuli. These signals are transduced to the mitochondria and ER (*not shown*) by proapoptotic Bcl-2 proteins: Bax (a multidomain protein) and BH3-only proteins. These death signals trigger the release of apoptogens from the mitochondria into the cytosol, including cytochrome *c*, which triggers the formation of a second multiprotein complex, the apoptosome, in which procaspase-9 undergoes activation. Caspase-9 then cleaves and activates downstream procaspases. Downstream caspases cleave several hundred cellular proteins to bring about the apoptotic death of the cell. *FADD,* Fas-associated protein with death domain; *RIP1, RIP3,* receptor-interacting proteins 1, 3; *TRADD,* tumor necrosis factor receptor type 1–associated death domain protein; *TRAF2,* TNF receptor–associated factor. (Modified from Whelan RS, KaplinskiyV, Kitsis RN. Cell death in the pathogenesis of heart disease: mechanisms and significance. Annu Rev Physiol 2010;72:19.)

Apoptosis.

Apoptosis, or programmed cell death, is an evolutionarily conserved process that allows multicellular organisms to selectively remove cells through a highly regulated program of cell suicide. Apoptosis is mediated by two pathways (**Fig. 23.10B**). The extrinsic pathway utilizes cell surface receptors, whereas the intrinsic pathway involves the mitochondria and endoplasmic reticulum (ER), and each of these pathways leads to caspase activation. In addition, connections between the pathways amplify signals, increasing the efficiency of killing. The intrinsic pathway is responsible for transducing most apoptotic stimuli, including those caused by inadequate nutrients or survival factors, hypoxia, oxidative stress, nutrient stress, proteotoxic stress, DNA damage, and chemical and physical toxins. These stimuli ultimately converge at the mitochondria to trigger the release of apoptogenic proteins, such as cytochrome *c*, and at the ER to stimulate the release of luminal Ca^{2+}.[35] Apoptosis plays important roles in development and in postnatal life, when it is critical for tissue homeostasis and surveillance for damaged or transformed cells. However, under pathologic circumstances, such as acute ischemia and in DCM, the apoptotic program can be triggered inappropriately, resulting in inadvertent cell death that can lead to organ failure. In contrast with the cell swelling that characterizes necrosis, during apoptosis the cell shrinks and eventually breaks up into small, membrane-surrounded fragments. The latter often contain bits of condensed chromatin referred to as *apoptotic bodies*. Maintenance of plasma membrane integrity until late in the apoptotic process allows the dying cell to be engulfed by macrophages, which prevents the release of the reactive intracellular contents, thereby preventing an inflammatory reaction.

Cardiac myocyte apoptosis has been shown to occur in failing human hearts.[36] Indeed, many of the factors implicated in the pathogenesis of HF, including catecholamines acting through $beta_1$-adrenergic receptor, angiotensin II, ROS including NO, inflammatory cytokines (e.g., TNF), and mechanical strain, have been shown to trigger apoptosis in vitro. Moreover, activation of either the extrinsic or the intrinsic cell death pathway provokes progressive LV dilation and decompensation in transgenic mice.[37] Nonetheless, the exact physiologic significance and consequence(s) of apoptosis in human HF have been difficult to determine because of the uncertainty about the actual rate of cardiac myocyte apoptosis in the failing human heart.[36] The aggregate clinical and experimental data, however, suggest that apoptosis is likely to play an important role in HF.

Autophagy.

Autophagy refers to the homeostatic cellular process of sequestering organelles, proteins, and lipids in a double-membrane vesicle inside the cell (*autophagosome*), where the contents are subsequently delivered to the lysosome for degradation. Unlike necrosis and apoptosis, autophagy is primarily a survival mechanism that regulates the quality and abundance of intracellular proteins and organelles. The

three types of autophagy are macroautophagy, microautophagy, and chaperone-mediated autophagy. The term *autophagy* generally refers to macroautophagy unless otherwise specified. When autophagy involves the total destruction of the cell, it is referred to as *autophagic cell death.* Recent studies have demonstrated the existence of autophagic cell death in hypertrophied, failing, and hibernating myocardium.[35] Approximately 0.3% of the cardiac myocytes in explanted hearts from patients with HF exhibited autophagic cell death,[38] whereas the predominant form of cell death in pressure-overloaded human hearts was mainly by autophagy and oncosis.[39] Recent studies, however, have clearly demonstrated that autophagy has a variety of physiologic roles in the heart, and that impaired clearance of autophagosomes (impaired autophagic flux) may be deleterious, rather than the process of autophagy per se.[40]

Although the distinction between necrosis and apoptosis is apparent in certain circumstances, it often is less clear in the failing heart. Indeed, similar mechanisms can operate in both types of cell death. Thus, instead of the existence of distinct types of cell death in HF, a more likely scenario is a continuum of cell death responses that contribute to progressive myocyte loss and disease progression.

Alterations in the extracellular matrix (ECM) constitute the second important myocardial adaptation that occurs during cardiac remodeling. The myocardial ECM consists of a basement membrane, a fibrillar collagen network that surrounds the myocytes, proteoglycans and glycosaminoglycans, and specialized proteins such as matricellular proteins. The major fibrillar collagens in the heart are types I and III, with a type I/III ratio of approximately 1.3 : 1 to 1.9 : 1. The organization of myocardial fibrillar type I and type III collagen ensures the structural integrity of adjoining myocytes and is essential for maintaining alignment of myofibrils within the myocyte through the interaction of collagen and integrins and the cytoskeletal proteins (**Fig. 23.11A**). *Matricellular proteins* are a class of nonstructural ECM proteins exerting regulatory functions, most likely through their interactions with cell surface receptors, the structural proteins, and soluble extracellular factors such as growth factors and cytokines. *Osteopontin* (OPN [Eta-1]) is a matricellular protein that is expressed in various cell types, including cardiac myocytes and fibroblasts and myofibroblasts (**Fig. 23.11B**). Because of its localization and molecular properties, OPN is likely to be involved in the communication between the ECM and cardiac myocytes, which implies a role in cardiac remodeling after hemodynamic overloading. OPN is markedly upregulated in animal models of cardiac hypertrophy and failure and myocardial ischemia and in the hearts of patients with DCM. OPN is elevated in the peripheral circulation of patients in direct relation to HF disease severity.[41]

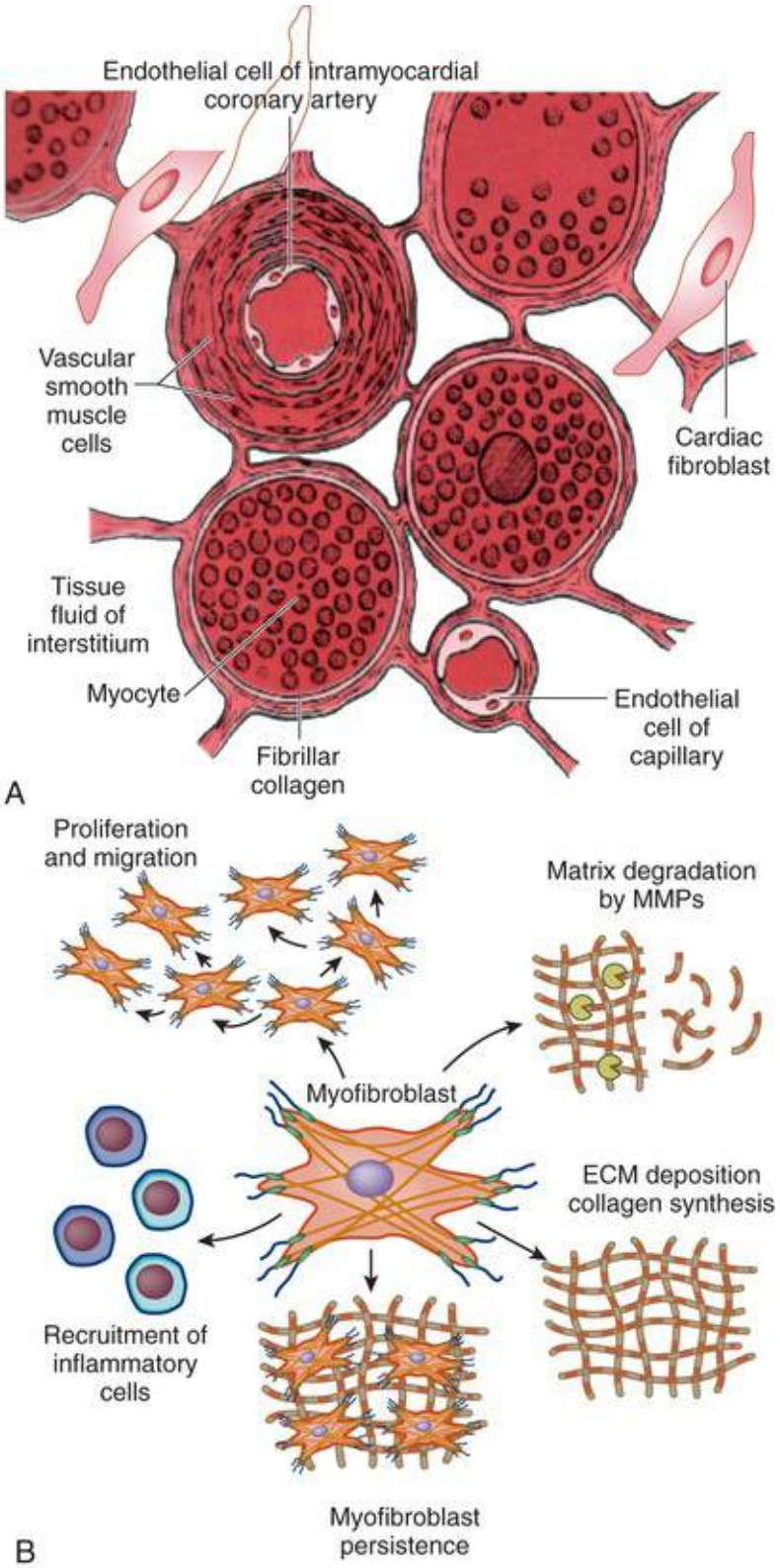


FIGURE 23.11 Extracellular matrix in heart failure. **A,** Although myocytes are the major components of heart on the basis of mass, they represent only a minority on the basis of number. Nonmyocyte cellular constituents of the myocardium include fibroblasts, smooth muscle cells, and endothelial cells. Myocytes and nonmyocytes are interconnected by a complex of connective tissue and extracellular matrix (ECM). Components of ECM include collagens, proteoglycans, glycoproteins (e.g., fibronectin), several peptide growth factors, and proteases (e.g., plasminogen activators) and collagenases (e.g., MMPs). **B,** Interactions among cardiac fibroblasts, myocytes, and ECM. In response to biomechanical stress, peptide growth factors in ECM and adjacent cardiac fibroblasts release an ensemble of peptide growth factors that activate hypertrophic signaling pathways in cardiac myocytes. Activated cardiac myofibroblasts express elevated levels of various proinflammatory and profibrotic factors that directly contribute to inflammatory cell infiltration and fibroblast proliferation, secrete high levels of matrix metalloproteinases (MMPs) and other ECM-degrading enzymes that facilitate fibroblast migration, and contribute to the deposition of collagen and other ECM proteins, leading to scar formation. (**A,** Modified from Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Circulation 1991;83:1849; **B,** from Travers JG et al. Cardiac Fibrosis: The Fibroblast Awakens. Circ Res 2016;118:1021-40. Copyright 2016 American Heart Association.)

During cardiac remodeling, important alterations in the ECM include changes in fibrillar collagen synthesis and degradation (**Fig. 23.12**) and in the degree of collagen cross-linking, as well as loss of collagen struts that connect the individual cardiac myocytes.[42] Markers of collagen turnover have been shown to be increased in patients with DCM compared with age-matched controls.[43] In patients with idiopathic or ischemic DCM, serum N-terminal peptide type III collagen propeptide (PIIINP) levels have been shown to be independent predictors of mortality.[44] In the RALES trial (**see Chapter 25**), serum C-terminal peptide type I collagen propeptide (PIP) and PIIINP were decreased in the spironolactone-treated patients but not in the placebo group, suggesting that aldosterone may play an important role in ECM synthesis. Moreover, it is becoming increasingly apparent that the three-dimensional organization of the ECM plays an important role in regulating cardiac structure and function in HF.[45]

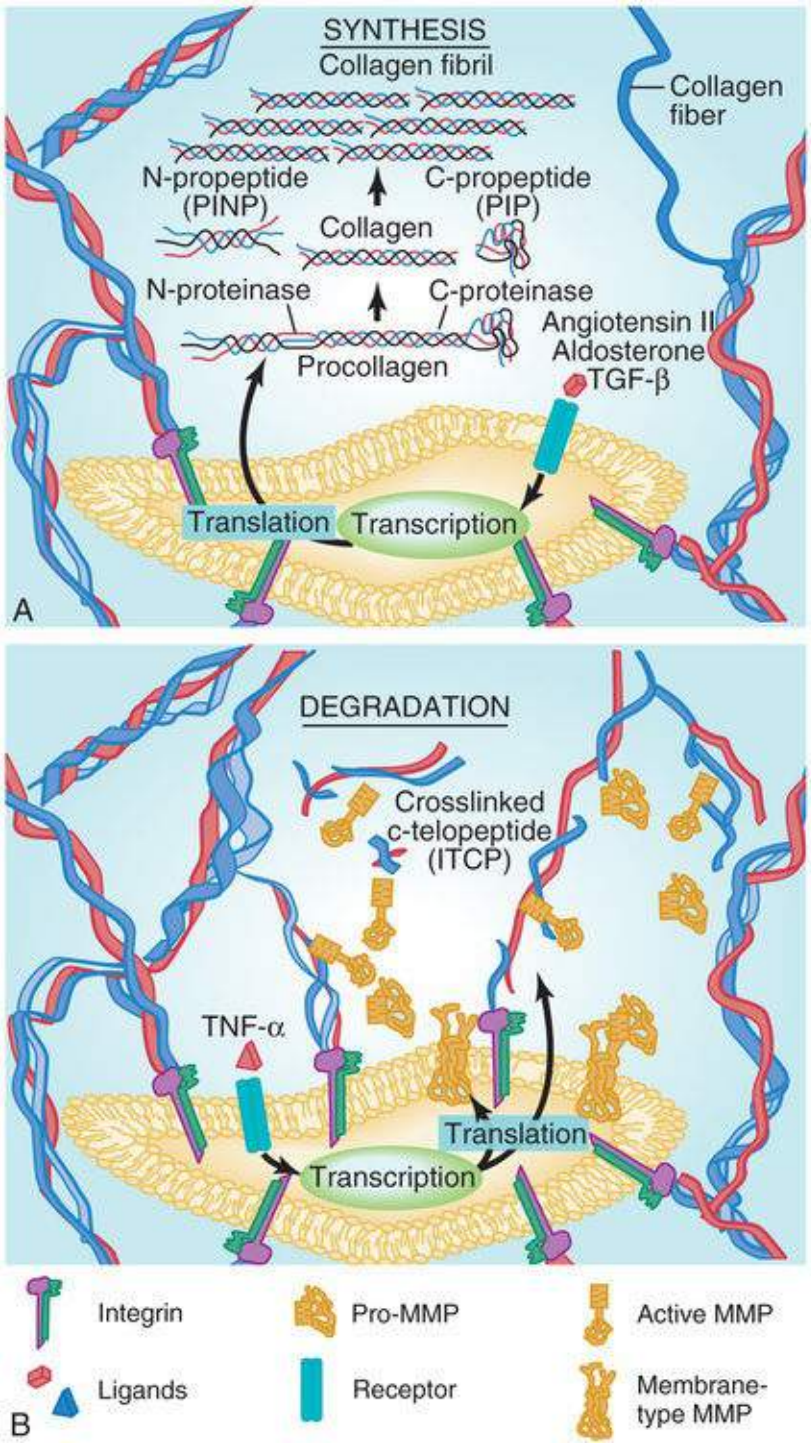


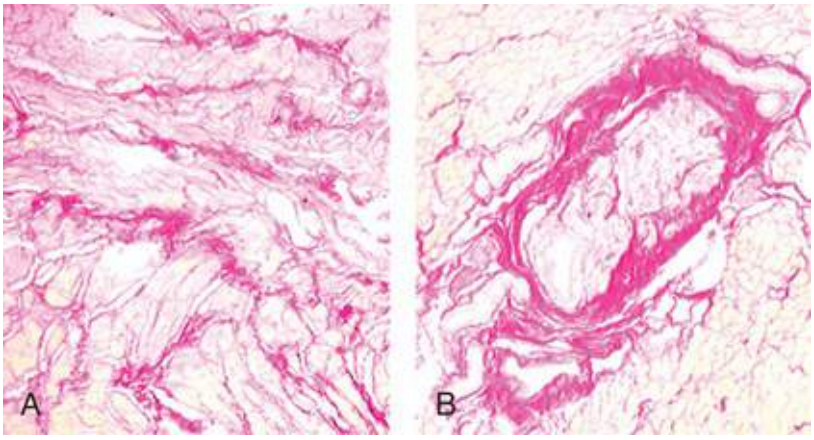
FIGURE 23.12 Collagen synthesis and degradation. **A,** Intracellular signals generated by neurohormonal and/or mechanical stimulation of cardiac fibroblasts results in transcription and translation of nascent collagen proteins containing aminoterminal (N-terminal) and carboxyl terminal (C-terminal) propeptides that prevent collagen from assembling into mature fibrils. Once secreted into the interstitium, these propeptides are cleaved by N- and C-proteinases, yielding two procollagen fragments and a mature triple-stranded collagen molecule. In the case of collagen type I, these propeptides are referred to as N-terminal peptide type I collagen propeptide (PINP) and C-terminal peptide type I collagen propeptide (PIP). Removal of the propeptide sequences allows the secreted collagen molecule to integrate into growing collagen fibrils, which can then further assemble into collagen fibers. After the collagen fibrils form in the extracellular space, their tensile strength is greatly strengthened by the formation of covalent cross-links between the lysine residues on the collagen molecules. **B,** The degradation of the collagen matrix within the myocardium entails a number of biochemical events involving several protease systems. Degradation of collagen fibrils occurs through catalytic cleavage of the three collagen alpha chains at a single locus by interstitial collagenase, yielding 36-kDa and 12-kDa collagen telopeptides that maintain their helical structure and thus are resistant to further proteolytic degradation. The large 36-kDa telopeptide spontaneously denatures into nonhelical gelatin derivatives, which in turn are completely degraded by interstitial gelatinases. The small 12-kDa pyridinoline cross-linked C-terminal telopeptide resulting from the cleavage of collagen type I (ICTP) is found in intact in blood, where it appears to be derived from tissues, with a stoichiometric ratio of 1 : 1 between the number of collagen type I molecules degraded and that of ITCP released. (From Deschamps AM, Spinale FG. Extracellular matrix. In Walsh RA, editor. Molecular Mechanisms of Cardiac Hypertrophy and Failure. Boca Raton, Fla: Taylor & Francis; 2005, pp 101-116.)

Cardiac Fibroblasts and Mast Cells.

The cardiac fibroblast, which accounts for almost 90% of nonmyocyte cells in the heart, is the primary cell type that is responsible for the secretion of a majority of ECM components in the heart, such as collagens I, III, and IV and laminin and fibronectin. In response to mechanical stress and neurohormonal activation, a subset of fibroblasts undergoes phenotypic conversion to myofibroblasts that are characterized by increased expression of α-smooth muscle actin and enhanced secretory activity. Recent studies have shown that myofibroblasts, which are responsible for the collagen secretion and contraction/realignment of the nascent collagen fibers, arises from tissue-resident fibroblasts that become activated after tissue injury.[46] Myofibroblasts migrate into the area surrounding tissue and play an important role in the final scar formation. Cardiac myofibroblasts also may regulate the phenotype of cardiac myocytes through multiple paracrine signaling pathways (**Fig. 23.11B**). Several lines of evidence suggest that that cardiac fibroblasts and myocytes release proteins that regulate neighboring cells.[47] The proteins that have been implicated thus far include transforming growth factor-β1 (TGF-β1), fibroblast growth factor-2 (FGF2), members of the IL-6 family, and the recently discovered cytokine IL-33. Increasing evidence also suggests that mast cells, which are bone marrow–derived cells that "home" to and reside in the myocardium, also play an important role in remodeling of the ECM. Myocardial mast cells are located mainly around blood vessels and between myocytes, where they are capable of releasing profibrotic cytokines and growth factors that influence ECM remodeling. In experimental studies, mast cells that are recruited to the heart during inflammation were responsible for TGF-β1–mediated fibroblast activation, myocardial fibrosis, and LV diastolic dysfunction.[48]

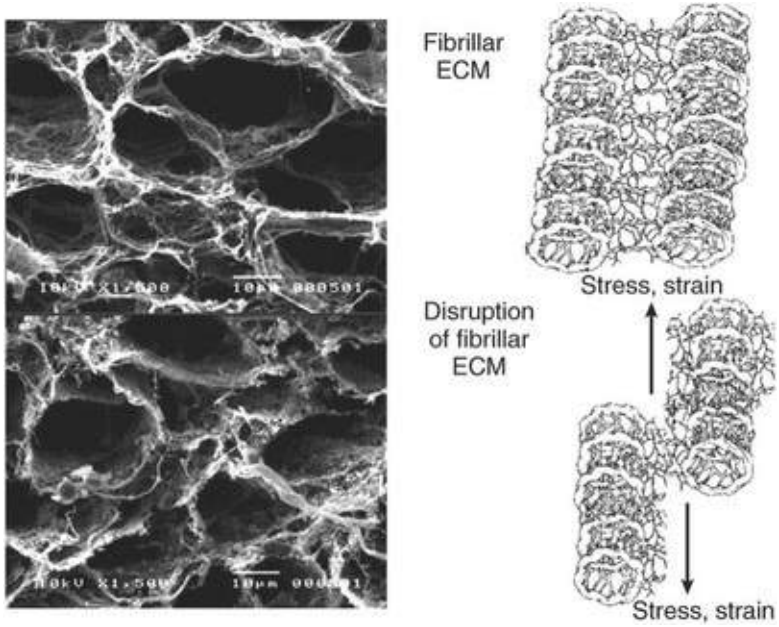
As noted earlier, one of the histologic signatures of advancing HF is the progressive increase in collagen content of the heart (myocardial fibrosis). Studies in failing human myocardium have shown a quantitative increase in collagen types I, III, VI, and IV, along with fibronectin, laminin, and vimentin, and a decrease in the type I/III collagen ratio in patients with ischemic cardiomyopathy. Moreover, clinical studies show a progressive loss of cross-linking of collagen in the failing heart, as well as loss of connectivity of the collagen network with individual myocytes, which would be expected to result in

profound alterations in LV structure and function. Furthermore, loss of cross-linking of the fibrillar collagen has been associated with progressive LV dilation after myocardial injury. The accumulation of collagen can occur on a “reactive” basis around intramural coronary arteries and arterioles (perivascular fibrosis) or in the interstitial space (interstitial fibrosis) and does not require myocyte cell death (**eFig. 23.7**). Alternatively, collagen accumulation can occur as a result of microscopic scarring, which develops in response to cardiac myocyte cell necrosis. This scarring or “replacement fibrosis” is an adaptation to the loss of parenchyma and is therefore critical to preserve the structural integrity of the heart. The increased fibrous tissue would be expected to lead to increased myocardial stiffness, which presumably would result in decreased myocardial shortening for a given degree of afterload. In addition, myocardial fibrosis may provide the structural substrate for atrial and ventricular arrhythmias, thus potentially contributing to inhomogeneous activation, bundle branch block, and dyssynchrony, as well as sudden death (**see Chapter 42**). Although the full complement of molecules responsible for fibroblast activation is not known, many of the classic neurohormones (e.g., angiotensin II, aldosterone) and cytokines (ET, TGF-β, cardiotrophin-1) that are expressed in HF are sufficient to provoke fibroblast activation. Indeed, the use of ACE inhibitors, beta blockers, and aldosterone receptor antagonists has been associated with a decrease in myocardial fibrosis in experimental HF models.[49]



EFIGURE 23.7 Myocardial fibrosis. Histologic section of a human myocardial biopsy specimen showing interstitial **(A)** and perivascular **(B)** fibrosis using picrosirius red staining. (Modified from Lopez B et al. Biochemical assessment of myocardial fibrosis in hypertensive heart disease. Hypertension 2001;38:1222.)

Although the fibrillar collagen matrix initially was thought to form a relatively static complex, it is now recognized that these structural proteins can undergo rapid turnover. A major development in understanding the pathogenesis of cardiac remodeling was the discovery that a family of collagenolytic enzymes, the *matrix metalloproteinases* (MMPs), is activated within the failing myocardium. Conceptually, ECM disruption would be expected to lead to LV dilation and wall thinning as a result of mural realignment of myocyte bundles and within the LV wall (**as depicted in eFig. 23.8**), as well as LV dysfunction as a result of dyssynchronous contraction of the left ventricle. Although the precise biochemical triggers responsible for activation of MMPs are not known, TNF and other cytokines and peptide growth factors expressed within the failing myocardium are capable of activating MMPs.



EFIGURE 23.8 Disruption of the fibrillar extracellular matrix (ECM). **Left,** Scanning electron micrographs of normal human myocardial ECM in which the myocardium has been subjected to corrosion digestion to provide full relief of the collagen ECM. The scaffolding around where the myocytes are positioned is evident and underscores the complexity of the fibrillar collagen matrix. **Right,** Schematic representation depicting the collagen matrix and the potential effects of mechanical load and proteolytic digestion of fibrillar collagen support. The geometric alignment of myocytes is disrupted, with loss of the rigid architecture of the matrix. (Electron micrographs from Rossi MA. Connective tissue skeleton in the normal left ventricle and in hypertensive left ventricular hypertrophy and chronic chagasic myocarditis. Med Sci Monit 2001;7:820; schematic representation of ECM disruption, courtesy Dr. Francis G. Spinale.)

However, the biology of matrix remodeling in HF is likely to be much more complex than the simple presence or absence of MMP activation, because degradation of the matrix also is controlled by glycoproteins termed *tissue inhibitors of matrix metalloproteinases*. TIMPs are capable of regulating the activation of MMPs by binding to and preventing these enzymes from degrading the collagen matrix of the heart. The TIMP family at present consists of four distinct members, TIMP-1, -2, -3, and -4, each of which is constitutively expressed in the heart by fibroblasts as well as myocytes. TIMPs are secreted proteins that act as the natural inhibitors of active forms of all MMPs, although the efficiency of MMP inhibition varies among the different members. The extant literature suggests that MMP activation can lead to progressive LV dilation, whereas TIMP expression favors progressive myocardial fibrosis. Additional content on this topic is presented in the online supplement for this chapter (Matrix Metalloproteinases and Tissue Inhibitors of Metalloproteinases).

Noncoding RNAs.

Once considered “transcriptional noise,” noncoding RNAs have emerged as potential biomarkers as well as therapeutic targets in HF. The noncoding portion of the genome is actively transcribed, generating thousands of regulatory short and long noncoding RNAs that are capable of regulating gene networks. Noncoding RNAs are classified based on their length. Small noncoding RNAs are less than 200 nucleotides in size and include both small interfering RNAs (siRNAs) and microRNAs (miRNAs). Transcripts larger than 200 nucleotides are called long noncoding RNAs (lncRNAs). MicroRNAs are involved in virtually all cellular processes. The lncRNAs also regulate gene and protein levels but through more complicated and diverse mechanisms.

Experimental studies have shown that microRNAs have a profound effect on cardiac remodeling.

MicroRNAs are noncoding RNAs that pair with specific “target” mRNAs and negatively regulate their expression through translational repression or mRNA degradation (gene silencing). The binding specificity of microRNAs depends on complementary base pairing of the approximately 6 nucleotide (nt) region at the 5′ end of the microRNA with the 3′ untranslated region (UTR) of the corresponding mRNA target. As shown in **Fig. 23.13A**, binding of microRNAs to their cognate target mRNAs typically leads to decreased expression of target genes. Individual microRNAs modulate the expression of collections of mRNA targets that often have related functions, thereby governing complex biologic processes. Recent studies have suggested that microRNAs contribute to adverse or pathologic remodeling in experimental HF models.[50] As shown in **Fig. 23.13B**, microRNAs regulate key components of the remodeling process, including cardiac myocyte biology, cell fate, ECM remodeling, and neurohormonal activation. Given that microRNAs are coordinately upregulated in response to stress signals, and that microRNAs regulate the expression levels of gene networks that determine the “heart failure phenotype,” it is tempting to speculate that microRNAs, acting singly or in combination, may be responsible for modulating the transition from adaptive to pathologic cardiac remodeling. Moreover, it is possible that certain microRNAs may themselves become therapeutic targets using chemically modified oligonucleotides to target specific microRNAs and disrupt the binding between a specific microRNA and a specific mRNA target.[50]

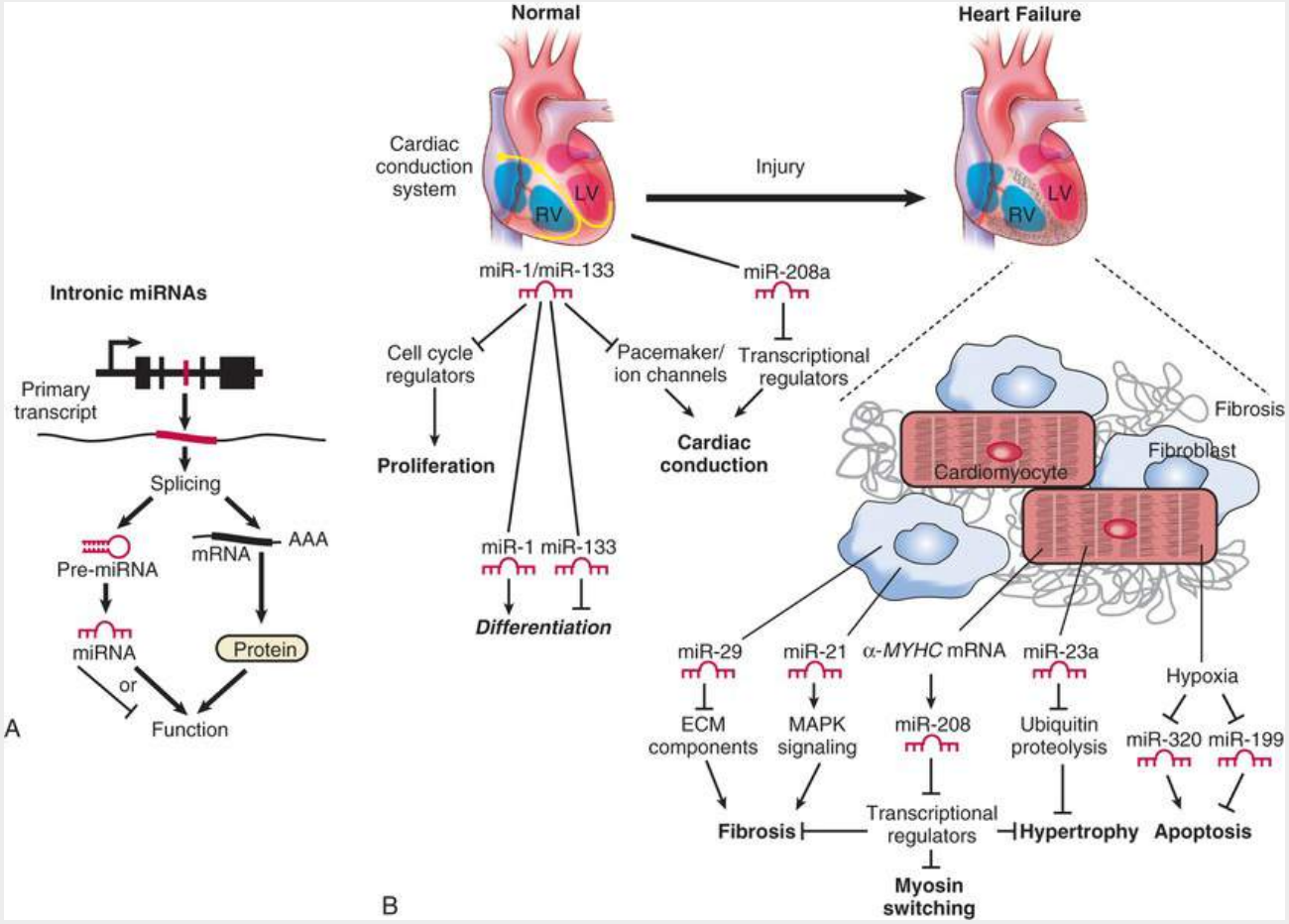


FIGURE 23.13 MicroRNAs (miRNAs) and the heart. **A,** The potential modes of miRNA-based regulation of gene expression are illustrated. Intronic microRNAs are encoded within an intron of a host gene. Messenger RNA splicing generates a protein coding transcript and a microRNA stem-loop. A common mechanism of miRNA function involves the modest repression of several mRNAs in a common biologic process by a single miRNA, most commonly through transcriptional silencing, or through enhanced mRNA degradation. Intronic miRNAs often regulate similar processes to that of the protein encoded by the host gene. *AAA,* Polyadenylated tail of the transcript; pre-miRNA, precursor miRNA. **B,** Functional role of miRNAs in the normal and failing heart. A normal heart and a hypertrophic/failing heart are shown in schematic form, depicting miRNAs that contribute to normal function or pathologic remodeling. All *arrows* denote the normal action of each component or process. The miRNAs miR-1 and miR-133 are involved in the development of a normal heart **(left)** by regulating proliferation, differentiation, and cardiac conduction. After cardiac injury **(right),** various miRNAs contribute to pathologic remodeling and the progression to heart failure: miR-29 blocks fibrosis by inhibiting the expression of ECM components, whereas miR-21 promotes fibrosis; miR-208 controls myosin isoform switching, cardiac hypertrophy, and fibrosis; and miR-23a promotes cardiac hypertrophy by inhibiting ubiquitin proteolysis, which itself inhibits hypertrophy. Hypoxia results in the repression of miR-320 and miR-199, which promote and block apoptosis, respectively. (Modified from Small EM, Olson EN. Pervasive roles of microRNAs in cardiovascular biology. Nature 2011;469:336.)

Long noncoding RNAs are mechanistically more complex than microRNAs and likely modulate the genome at multiple different levels. For example, lncRNAs may interact with RNAs, proteins, and DNA and can either activate or silence the interaction with other molecules through conformational switching. Recent studies have shown that the profile of myocardial lncRNAs is altered in human HF, and that several lncRNAs are responsible for regulating cardiac structure and function following hemodynamic overload.[51]

Alterations in Left Ventricular Structure

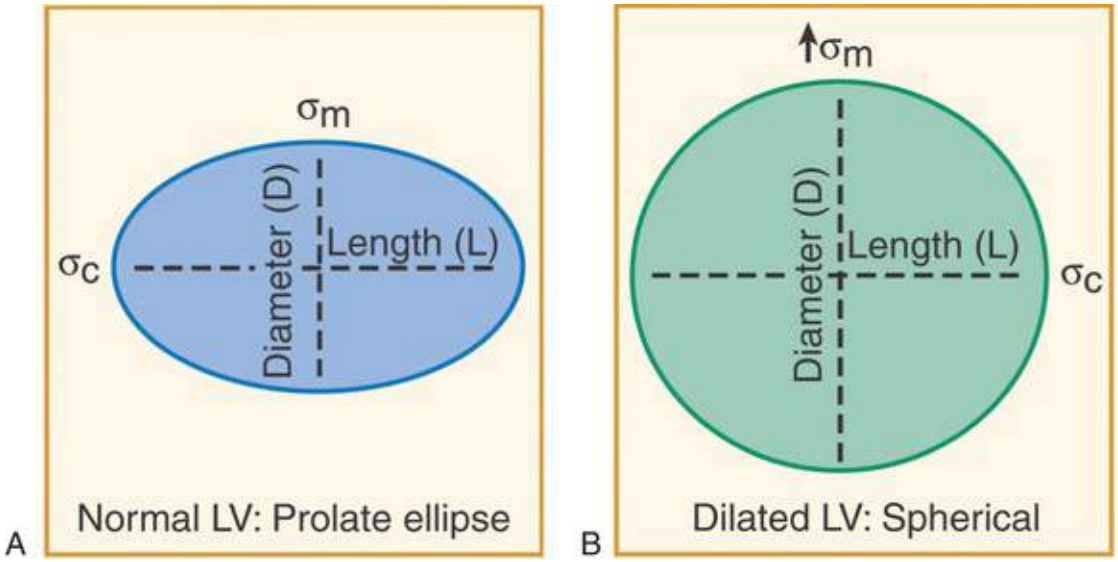
The alterations in the biology of the failing myocyte, as well as in the failing myocardium, are largely responsible for the progressive LV dilation and dysfunction that occur during cardiac remodeling. Many

of the structural changes that accompany LV remodeling may contribute to worsening HF (**eTable 23.2**). Indeed, one of the first observations regarding the abnormal geometry of remodeled ventricle was the consistent finding that the remodeled heart was not only larger but also more spherical in shape. An important point in this context is that a change in LV shape from a prolate ellipse to a more spherical shape results in an increase in meridional wall stress of the left ventricle, thereby creating a de novo energetic burden for the failing heart (**eFig. 23.9**). Since the load on the ventricle at end-diastole contributes importantly to the afterload on the ventricle at the onset of systole, LV dilation itself will increase mechanical energy expenditure of the ventricle, which exacerbates the underlying problems with energy utilization in the failing ventricle (**eFig. 23.10**).

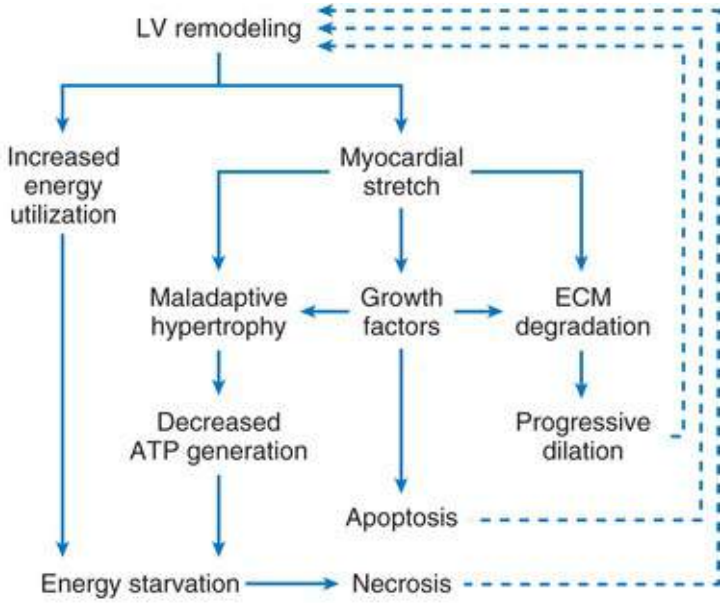
ETABLE 23.2

Mechanical Disadvantages Created by Left Ventricular Remodeling

Increased wall stress (afterload)
Afterload mismatch
Episodic subendocardial hypoperfusion
Increased oxygen utilization
Functional mitral regurgitation
Worsening hemodynamic overloading
A stretch-induced activation of maladaptive signal transduction pathways
Stretch-induced activation of maladaptive gene programs



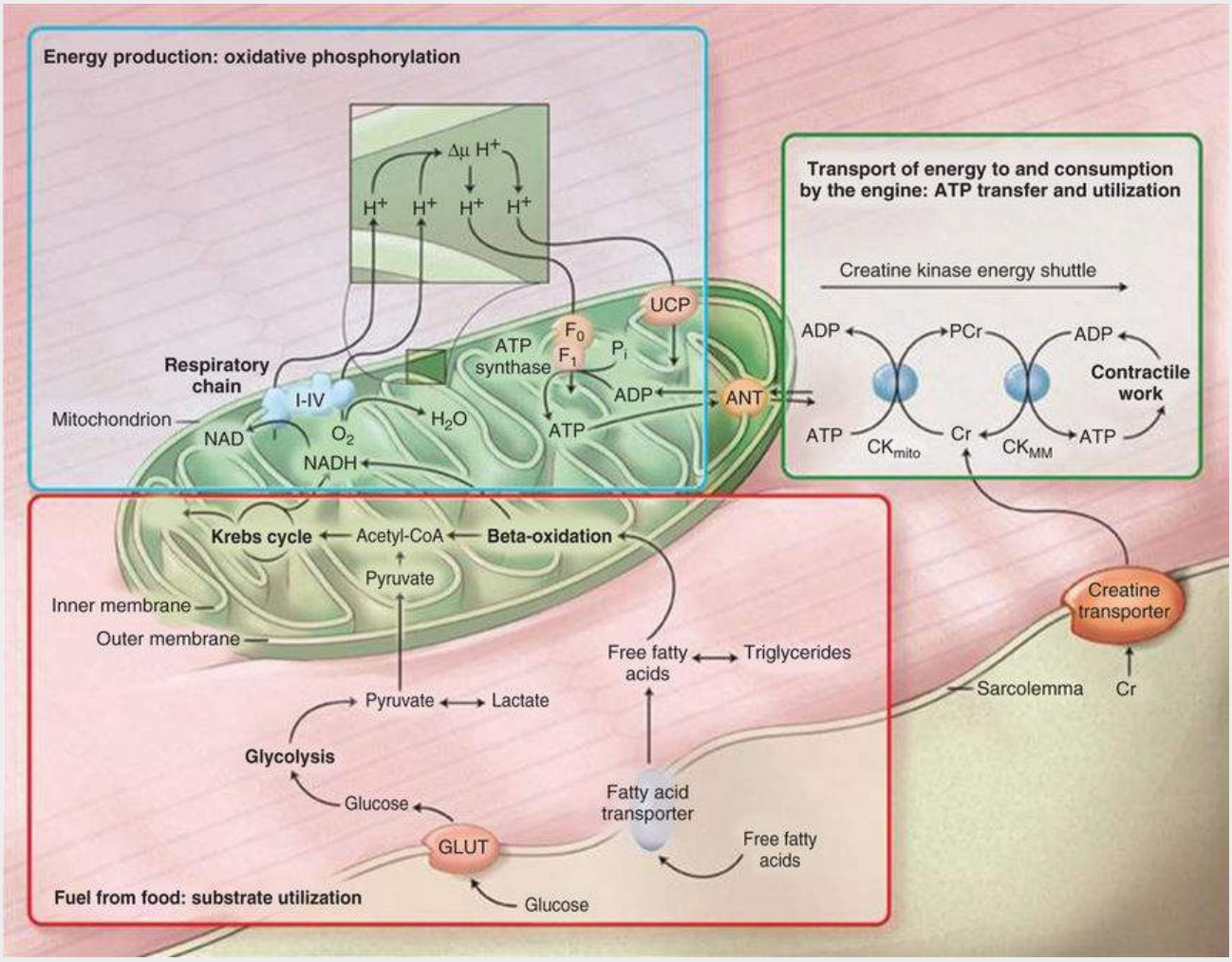
EFIGURE 23.9 Effect of changes in LV shape on LV wall stress. During LV remodeling, ventricle undergoes a change in LV shape from a prolate ellipse **(A)** to a more spherical shape heart **(B).** As shown in **B,** increase in short-axis dimension of ventricle as the heart becomes more spherical in shape leads to an increase in meridional wall stress of the ventricle, thereby creating a de novo mechanical burden for the heart. σ_c, Circumferential wall stress; σ_m, meridional wall stress. (From Mann DL. Left ventricular size and shape: determinants of mechanical signal transduction pathways. Heart Fail Rev 2005;10:95.)



EFIGURE 23.10 Self-amplifying nature of LV remodeling. LV remodeling results in increased afterload on the heart, which increases energy utilization and further stimulates cardiac growth through stretch-mediated activation of growth factors. The former contributes directly to a state of energy starvation, whereas the latter contributes to further cardiac remodeling, including increased myocyte hypertrophy and further matrix remodeling. The sustained activation of growth stimuli also promotes apoptosis and myocardial fibrosis, which contribute to LV dysfunction and LV remodeling. (Modified from Katz AM. Heart Failure. Philadelphia: Lippincott Williams & Wilkins; 2000.)

Cardiac Energetics and Mitochondrial Biology.

Energy transfer in the cardiac myocyte occurs in three stages: uptake and metabolism, energy production through oxidative phosphorylation, and energy transfer by means of the creatine kinase (CK) shuttle (**eFig. 23.11**). Each stage of this process can lead to contractile dysfunction of the heart. Studies in patients with end-stage cardiomyopathy have shown that myocardial ATP concentration, the total adenine nucleotide pool (ATP, ADP, and AMP), CK activity (required for synthesis of ATP), creatine phosphate (CrP) concentration, and CrP/ATP ratio are all decreased in HF. In addition, decreased levels of creatine phosphokinase have been reported, which would slow phosphocreatine shuttle, further exacerbating energy utilization in the failing heart.[52] Thus, in the failing heart, key components of the cardiac energetic system are downregulated. It is unclear at present, however, whether these energetic changes are biomarkers or drivers of LV dysfunction.



EFIGURE 23.11 Energy transfer in the cardiac myocyte occurs in three stages. Each stage may be the site of metabolic derangements causing or accompanying contractile dysfunction of the heart. The first stage is substrate uptake and metabolism (outlined in *red*). In this stage, substrates are broken down by β-oxidation and glycolysis to form acetyl-coenzyme A (acetyl-CoA), from which the Krebs cycle produces NADH and CO_2. The second stage is energy production through oxidative phosphorylation (outlined in *blue*). Respiratory chain complexes in the mitochondria transfer electrons from NADH to oxygen. This creates a proton electrochemical gradient ($\Delta\mu\ H^+$) across the inner mitochondrial membrane, in addition to water and NAD. This gradient drives ATP synthase. Uncoupling proteins (UCPs) use this electrochemical gradient to create heat instead of ATP. The third stage is energy transfer via the creatine kinase shuttle (outlined in *green*). ATP is transferred to and consumed by myofibrillar ATPase and other reactions. *ANT,* Adenine nucleotide translocase; CK_{mito}, mitochondrial creatine kinase isoenzyme; CK_{MM}, myofibrillar creatine kinase isoenzyme; *Cr,* free creatine; *GLUT,* glucose transporter; *PCr,* phosphocreatine; P_i, inorganic phosphate. (Modified from Neubauer S. The failing heart—an engine out of fuel. N Engl J Med 2007;356:11407.)

Although several mechanisms have been proposed to explain the fall in ATP content in HF, one mechanism that has received considerable attention relates to changes in substrate utilization in HF. Under normal conditions, the adult heart derives most of its energy through oxidation of fatty acids in mitochondria. The genes involved in this key energy metabolic pathway are transcriptionally regulated by members of the nuclear receptor superfamily, specifically the fatty acid–activated peroxisome proliferator–activated receptors (PPARs) and the nuclear receptor coactivator, PPAR-gamma coactivator-1α (PGC-1α). In experimental HF models, an initial decrease is seen in the oxidation of fatty acids secondary to downregulation of fatty acid–metabolizing genes, with a resultant shift toward glycolytic metabolism.[53] These observations have given rise to the suggestion that metabolic modulation may be beneficial in HF. Additional content on this topic is presented in the online supplement for this chapter (Metabolic Modulation). In addition to metabolic modulation, there are ongoing randomized phase II clinical trials in patients with HF with a preserved and with a reduced ejection fraction, using a

mitochondrial-targeting protein (elamipretide [MTP-13]) that enhances mitochondrial ATP synthesis.

In addition to loss of substrate, ATP generation may be impaired in the failing heart secondary to abnormalities in mitochondrial dynamics.[54] Studies in yeast have demonstrated that maintaining normal mitochondrial morphology and function depends on the dynamic balance of mitochondrial *fusion* and *fission* (division), collectively called "mitochondrial dynamics." The balance between mitochondrial fusion and fission determines the number, morphology, and activity of mitochondria in the heart. Fusion and fission modulate multiple mitochondrial functions, ranging from energy and ROS production to Ca^{2+} homeostasis and cell death. Although studies in HF are limited, data suggest that mitochondrial fusion may be reduced, which would be predicted to lead to reduced O_2 consumption and alterations in mitochondrial metabolism. Moreover, abnormalities in mitochondrial dynamics may contribute to the cell death through apoptotic and autophagic cell-signaling pathways.[55] Of note, abnormally small and fragmented mitochondria have been observed in end-stage DCM, myocardial hibernation, and congenital heart disease, suggesting that mitochondrial fusion/fission becomes dysregulated in cardiac disease. However, the contribution of abnormalities in mitochondrial fission/fusion in HF as a cause versus a consequence of myocardial injury remains unknown.

LV wall thinning also occurs as the ventricle begins to dilate and remodel. The increase in wall thinning along with the increase in afterload created by LV dilation leads to a functional "afterload mismatch" that may further contribute to a decrease in forward cardiac output. Increased LV wall stress also can lead to sustained expression of stretch-activated genes (angiotensin II, ET, TNF) and stretch activation of hypertrophic signaling pathways. Moreover, the high end-diastolic wall stress might be expected to lead to episodic hypoperfusion of the subendocardium with resultant worsening of LV function, as well as increased oxidative stress, with the resultant activation of gene families that are sensitive to free radical generation (e.g., TNF, IL-1β). Another important mechanical problem from progressive LV dilation is that the papillary muscles are pulled apart, resulting in incompetence of the mitral valve and development of "functional mitral regurgitation." In addition to the loss of forward blood flow, mitral regurgitation results in further hemodynamic volume overloading of the ventricle. Together, the mechanical burdens engendered by LV remodeling might lead to increased LV dilation, decreased forward cardiac output, and increased hemodynamic overloading (**see eFig. 23.10**), any of which is sufficient to contribute to worsening LV function independent of the patient's neurohormonal status.

Reversibility of Left Ventricular Remodeling

Clinical studies have shown that medical and device therapies that reduce HF morbidity and mortality also lead to decreased LV volume and mass and restore a more normal elliptical shape to the ventricle. These salutary changes represent the summation of a series of integrated biologic changes in cardiac myocyte size and function (**eTable 23.3**), as well as modifications in LV structure and organization that are accompanied by shifts of the LV end-diastolic pressure-volume relationship toward normal. For want of better terminology, these changes are collectively called "reverse LV remodeling." Interestingly, in recognized subsets of patients, the heart is undergoes reverse LV remodeling either spontaneously or after medical or device therapies. Importantly, the subsequent clinical course of these patients is associated with fewer future HF events.[56] This phenomenon has often been referred to as "myocardial recovery." Despite the frequent interchangeable use of the terms *myocardial recovery* and *reverse LV remodeling* to describe the reversal of various aspects of the HF phenotype with medical and device therapy, the literature suggests that important differences exist between these two phenomena and that they are not

synonymous. The term *reverse remodeling*, as currently used, describes the biologic process involving the reversal of the cellular, myocardial, and anatomic abnormalities seen in the remodeled ventricle. As shown in **Fig. 23.14**, patients whose hearts have undergone reverse remodeling may experience one of two potential outcomes: freedom from future HF events or recurrence of HF events. Based on the disparate clinical outcomes of reverse remodeling, it has been suggested that the term *myocardial recovery* should be used to describe the normalization of the molecular, cellular, myocardial, and LV geometric changes that are associated with freedom from future HF events. The term *myocardial remission* should be used to refer to the normalization of these changes that are associated with cardiac remodeling but that are insufficient to prevent the recurrence of HF in the face of normal or perturbed hemodynamic loading conditions.[56] Although the biologic differences between myocardial recovery and myocardial remission are not known, it has been suggested that myocardial remission represents reversal of the HF phenotype superimposed on hearts that have sustained irreversible damage, whereas myocardial recovery represents reversal of the HF phenotype superimposed on hearts that have not sustained irreversible damage.

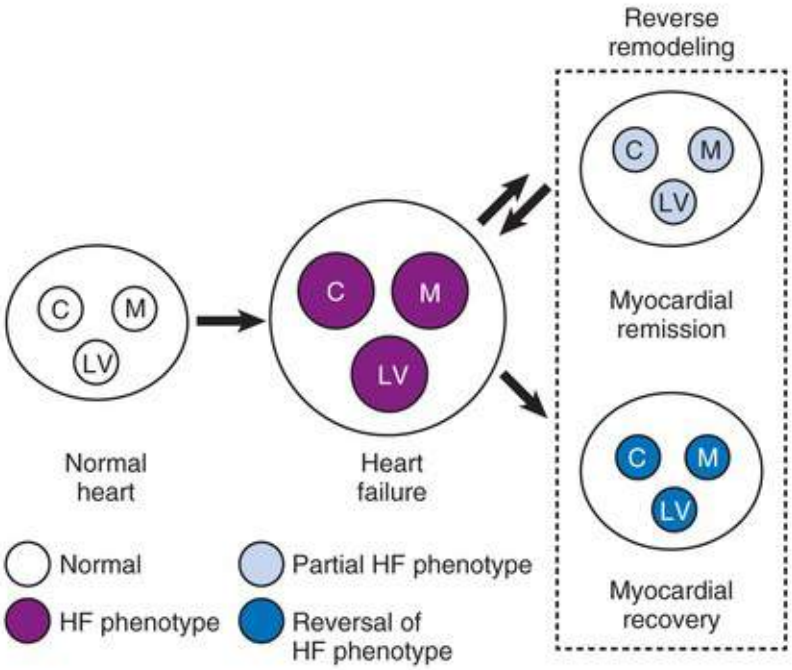


FIGURE 23.14 Reverse left ventricular remodeling and myocardial recovery in heart failure. Cardiac remodeling occurs secondary to abnormalities that arise in the biology of the cardiac myocyte (*C*), the myocardium (cardiocytes and extracellular matrix [*M*]), as well as left ventricular [*LV*] geometry, which have collectively been referred to as the "heart failure phenotype." During reverse remodeling, there is a reversal of the abnormalities in the cardiac myocyte, as well as the extracellular matrix, leading to normalization of LV geometry. Reverse remodeling can lead to two clinical outcomes: (1) myocardial recovery, characterized by freedom from future cardiac events; or (2) myocardial remission, characterized by recurrence of HF events. (Modified from Mann DL, Barger PM, Burkhoff D. Myocardial recovery: myth, magic or molecular target? J Am Coll Cardiol 2012;60:2465.)

ETABLE 23.3

Cellular and Molecular Determinants of Reverse Remodeling

COMPONENT	ACE INHIBITOR	BETA BLOCKER	LVAD	CSD
Myocyte Defects				
Hypertrophy	Decreased	Decreased	Decreased	Decreased
Myocytolysis	ND	Decreased	Decreased	ND
Excitation-contraction coupling	Increased	Increased	Increased	Increased
Fetal gene expression	Decreased	Decreased	Decreased	Decreased
Beta-adrenergic desensitization	Decreased	Decreased	Decreased	Decreased
Cytoskeletal proteins	ND	ND	Increased	ND
Myocyte contractility	ND	Increased	Increased	Increased
Myocardial Defects				
Myocyte necrosis	Decreased	Decreased	Decreased	ND
Myocyte apoptosis	Decreased	Decreased	Decreased	Decreased
MMP activation	Decreased	Increased	Decreased	Decreased
Fibrosis	Decreased	Decreased	Increased	Decreased
Other				
LV volume	Stabilized	Decreased	Decreased	Decreased

CSD, Cardiac support device; *LVAD,* left ventricular assist device; *ND,* not done.

Future Perspectives

The clinical syndrome of heart failure can be considered in terms of several different clinical model systems, including cardiorenal, hemodynamic, and neurohormonal. Each of the models has strengths and weaknesses in explaining the mechanisms responsible for HF, as well as in developing effective new therapies for HF. Nonetheless, current models for explicating the mechanisms for HF are inadequate and do not adequately describe disease progression in HF. Moreover, they do not provide an adequate scaffold for understanding newer device therapies that appear to work through neurohormonally independent mechanisms. This emphasizes the importance of cardiac remodeling as a mechanism of disease progression in HF. Future therapeutic advances are likely to require a more comprehensive understanding and analysis of the pathobiology of HF, particularly cell-cell interactions during LV remodeling, as well as the complex interactions that govern the process of reverse LV remodeling. In this regard, the emerging field of systems biology, which uses network theory to describe how the interrelationships between genes, proteins, and metabolites determine functional changes at the level of the cell, tissue, and organ, may allow investigators to accelerate the pace of novel target identification, as well as improve the likelihood of success in clinical trials.

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Heart Failure as a Progressive Model: Neurohormonal Mechanisms

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Heart Failure as a Progressive Model: Left Ventricular Remodeling

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Vasoconstricting Peptides in Heart Failure

Endothelin

The three endothelin (ET) peptides—ET-1, ET-2, and ET-3—all are potent vasoconstrictors. Although released primarily by endothelial cells, ET also can be synthesized and released by a variety of other cell types, such as cardiac myocytes. ET-1 is the predominant isoform of the ET peptide family and is ubiquitously expressed. ET-1 is synthesized as a protein precursor termed *preproET-1*. Preproendothelin-1 is processed by multiple proteases in a process that involves the proteolytic release of proendothelin-1 (“big endothelin”), followed by C-terminal trimming by a carboxypeptidase and further processing by endothelin-converting enzyme (ECE) to generate the biologically active 21–amino acid ET-1 peptide. However, studies in ECE-knockout mice have confirmed the presence of significant levels of mature ET-1, suggesting that there may be alternative ECE-independent (e.g., chymase, non-ECE metalloproteinases) pathways for generation of ET-1. At least two subtypes of ET receptors, designated A and B, have been identified in human myocardium. Endothelin ET(A) receptors mediate vasoconstriction, cell proliferation, pathologic hypertrophy, fibrosis, and increased contractility, whereas ET(B) receptors are involved in the clearance of ET-1 and the release of NO and prostacyclin. The release of ET from endothelial cells in vitro can be enhanced by several vasoactive agents (e.g., NE, angiotensin II, thrombin) and cytokines (e.g., TGF-β, TNF, IL-1). Several reports have documented an increase in circulating levels of ET-1 in patients with heart failure (HF) and have shown that ET levels correlate with patient outcomes. Furthermore, plasma ET concentrations correlate directly with pulmonary artery pressure and pulmonary

vascular resistance. Based on the biologic properties of ET, ET receptor antagonists were developed for the treatment of patients with HF. Although early experimental studies showed that ET(A) receptor antagonists inhibited myocardial hypertrophy in rats with pressure overload–induced hypertrophy caused by aortic banding and prevented cardiac remodeling in rats with myocardial infarction, and although early clinical studies confirmed the ability of these new agents to improve hemodynamics, the effect of chronic ET receptor antagonism has not been beneficial in clinical HF trials, and use of such agents has led to worsening outcomes in some settings.[1]

Neuropeptide Y

Neuropeptide Y (NPY) is a vasoconstricting peptide that is released together with NE from sympathetic nerve endings. NPY is abundant in cerebral cortex, hippocampus, thalamus, brainstem, and hypothalamus, where it is colocalized with agouti-related protein (AgRP), and positively modulates food intake. NPY is released from sympathetic nerves in the heart and influences coronary artery constriction and myocardial contraction. In addition, NPY potentiates the vasoconstrictor effects of other extracellular messengers, including alpha-adrenergic agonists and angiotensin II, and also inhibits acetylcholine release from parasympathetic nerve endings in the heart. Six NPY (NPY[1-6]) receptor subtypes have been identified thus far, of which NPY(1), NPY(2), and NPY(5) appear to be responsible for mediating functional responses in the heart.[1] Recent studies have suggested that NYP exerts important mitogenic and hypertrophic effects in endothelial and vascular smooth muscle cells, as well as cardiac myocytes. Although the role of NPY in HF is not known, circulating concentrations of NPY-like immunoreactivity are significantly increased in moderate to severe forms of HF and correlate with circulating levels of NE.[1]

Urotensin Ⅱ

Mammalian urotensin II is the most potent endogenous cardiostimulatory peptide identified thus far, with an 8- to 110-fold greater potency than that of ET-1. The effects of urotensin II are mediated by binding to the urotensin receptor. Urotensin II mediates vascular tone and increased contractile force in human atrium and ventricle. Analogous to ET-1, urotensin II provokes trophic and/or mitogenic actions in vascular smooth muscle cells, cardiac myocytes, and cardiac fibroblasts. However, unlike ET-1, which uniformly constricts most blood vessels, the vasoactive effects of urotensin II are both species- and vascular bed–dependent. Urotensin receptor (GPR14) expression is increased in cardiac myocytes, endothelial cells, and fibroblasts in the rat heart after coronary artery ligation. Urotensin II treatment increased collagen mRNA and protein levels in cardiac fibroblasts and augmented cardiac hypertrophy in cultured neonatal cardiomyocytes after transfection with recombinant urotensin II receptor.[2] Plasma levels of urotension II have been found to be elevated in some but not all studies in HF patients. Of interest, with iontophoresis of urotensin II into the skin, urotensin II mediated a dose-dependent vasodilator response in normal persons but a dose-dependent vasoconstrictor response in HF patients, suggesting that urotensin II may contribute to the increased peripheral vascular tone that occurs in HF.[2]

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Matrix Metalloproteinases and Tissue Inhibitors of Metalloproteinases

The matrix metalloproteinases (MMPs) represent a family of zinc-dependent proteases that play an important role in normal tissue remodeling, as well as in pathologic processes such as inflammation, tumor invasion, and metastasis. The MMPs are secreted as inactive zymogens that must be activated by cleavage of the N-terminal sequence of the propeptide domain, which allows the Zn^{2+} binding site of the catalytic domain to become exposed. The exception is membrane-type 1 MMP (MT-MMP1), which is cell surface–bound and is processed before cell surface localization by a furin-dependent mechanism. The MMPs can be classified into subgroups based on substrate specificity or structure, or both (**eTable 23.4**). This classification includes the collagenases (e.g. MMP-1 and MMP-13), the stromelysins (e.g., MMP-3), the gelatinases (e.g, MMP-9 and MMP-2), and the membrane-type MMPs (MT-MMPs). Once the activated, the MMPs are capable of degrading all the ECM components. Myocardial MMP abundance and activation have been assessed in end-stage human HF.[1] Although the majority of MMP species are increased in HF, the abundance of MMP-1 is significantly reduced in HF patients.[2] Furthermore, different levels of MMP-2 abundance and activity have been observed in congestive heart failure (CHF) myocardium of ischemic or nonischemic origin. Loss of tissue inhibitor of matrix metalloproteinases (TIMP)–mediated inhibitory control has been suggested as a reason for enhanced MMP activity in patients with dilated cardiomyopathy, in whom a reduction in relative myocardial levels of TIMP-1 and TIMP-3 and/or alterations in MMP/TIMP binding have been reported. This disparity between MMP and TIMP levels favors a persistent MMP activation, enhanced ECM proteolysis, and progressive LV dilation.[2] The role of MMP inhibition in the postinfarction setting was examined in humans in the PREMIER (Prevention of Myocardial Infarction Early Remodeling) trial, in which 253 patients with ST-segment elevation MI and an EF between 15% and 40% were randomized in 1 : 1 ratio to placebo or an MMP inhibitor (PG-116800) with high affinity for MMP-1, -3, -8, -9, -13, and -14. In this small study, MMP inhibition failed to reduce LV remodeling or improve clinical outcomes after MI. The failure to show a benefit may have been related to inadequate dosing of the MMP inhibitor.[3]

ETABLE 23.4

Classes of Matrix Metalloproteinases (MMPs) Identified in Human Myocardium

NAME	NUMBER	SUBSTRATE/FUNCTION	ABUNDANCE/ACTIVITY IN HEART FAILURE
Collagenase			
Interstitial collagenases	MMP-1	Collagens I, II, III, VII and basement membrane components	Decreased
Collagenase 3	MMP-13	Collagens I, II, III	Increased
Neutrophil collagenase	MMP-8	Collagens I, II, III and basement membrane components	
Gelatinase			
Gelatinase A	MMP-2	Gelatins, collagens, I, IV, V, VII and basement membrane components	Increased/Unchanged
Gelatinase B	MMP-9	Gelatins, collagens, IV, V, XIV and basement membrane components	Increased
Stromelysin			
Stromelysin 1	MMP-3	Fibronectin, laminin, collagens III, IV, IX and MMP activation	Increased
Membrane-Type MMP			
MT1-MMP	MMP-14	Collagens I, II, III, fibronectin, laminin-1, activates pro-MMP-2 and pro-MMP-13	Increased

Modified from Deschamps AM, Spinale FG. Extracellular matrix. In Walsh RA, editor. Molecular Mechanisms of Cardiac Hypertrophy and Failure. Boca Raton, Fla: Taylor & Francis; 2005, p 101.

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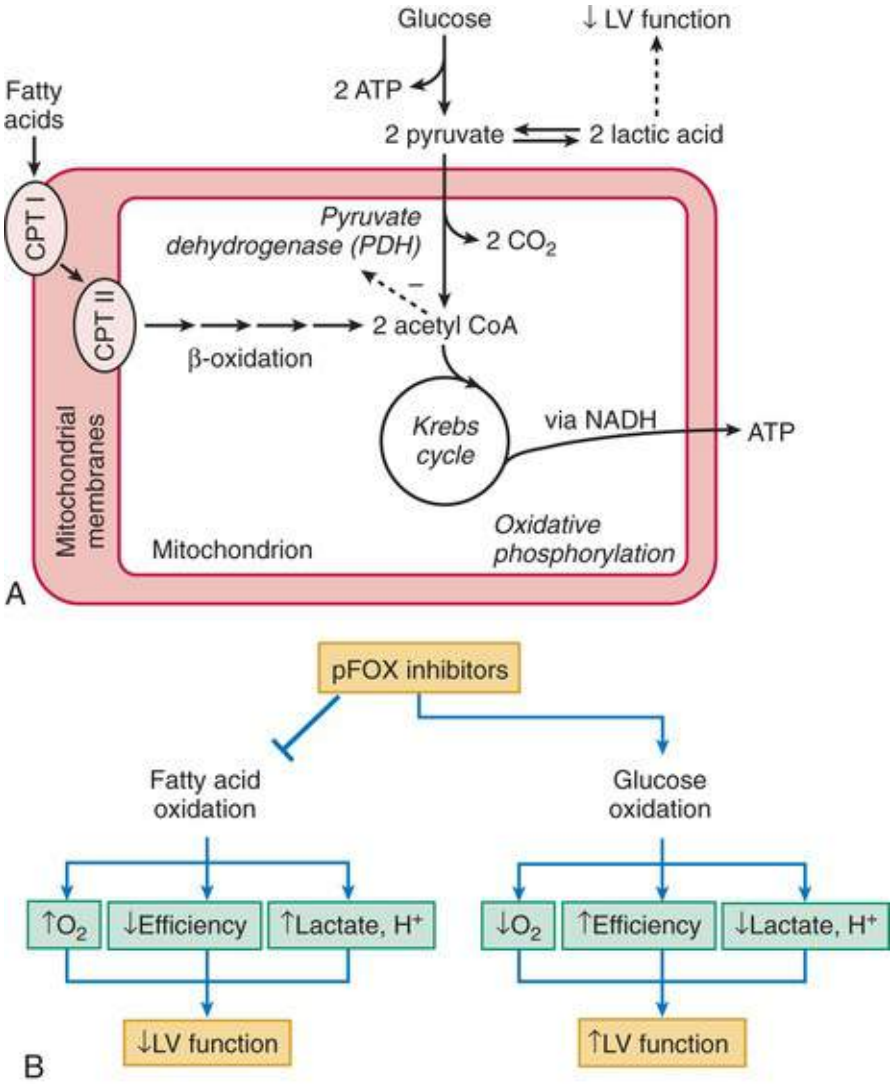
Metabolic Modulation

Optimization of myocardial energy utilization represents another unique approach for the treatment of HF. A number of derangements in myocardial metabolism may partly explain the decrease in high-energy phosphates and phosphocreatine that have been reported in the failing heart. In the normal heart, free fatty acids (FFAs) are the preferred fuel for the heart, producing approximately four times the ATP per mole of substrate utilized compared with glucose. However, FFA oxidation is less efficient than glucose oxidation, requiring 10% to 12% more O_2 consumption to produce equivalent amounts of ATP. Under conditions where O_2 is the limiting substrate, as occurs in the failing heart, glycolysis becomes the more efficient pathway, requiring less O_2 compared with FFA oxidation. Fatty acid oxidation is physiologically regulated at several levels, including the concentration of circulating FFA substrate, at the level of entry into the mitochondrion, and by the activity of several of the mitochondrial matrix enzymes that comprise the beta-oxidation pathway.[1] On the other hand, the rate of glucose oxidation is regulated primarily, although not exclusively, by the rate of FFA oxidation, which inhibits the pyruvate dehydrogenase complex (PDH), the activity of which is rate limiting for glucose oxidation (**eFig. 23.12**). Inhibition of PDH can lead to increased glucose utilization through conversion of pyruvate to lactate, resulting in progressive tissue acidosis, and impaired myocyte contractility (**eFig. 23.12A**). From a theoretical perspective, shifting energy utilization from FFAs to glucose would optimize metabolic efficiency, reverse abnormalities in the cellular milieu, and improve cardiac function (**eFig. 23.12B**). Although the results of the studies on substrate utilization in HF have often yielded conflicting results, the aggregate data support the concept that rates of FFA oxidation are normal or slightly increased in pathologic hypertrophy of early HF, whereas FFA oxidation is decreased during the latter stages of HF, accompanied by an absolute or relative increase in glucose utilization during late stages of HF.[2]



EFIGURE 23.12 Metabolism of free fatty acids and glucose. **A,** Metabolic pathway for glucose metabolism and fatty acid oxidation. **B,** Effects of switching metabolism from fatty acid beta-oxidation to glucose oxidation (under conditions in which oxygen supply is rate limiting) using partial inhibitors of fatty acid oxidation (*pFOX*). (From Dimmeler S, Mann DL, Zeiher AM. Emerging therapies and strategies in the treatment of heart failure. In Bonow RO, Mann DL, Zipes DP, Libby P, editors. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 9th ed. Philadelphia: Saunders; 2012, pp 627-43.)

The prototype partial inhibitors of fatty acid oxidation (pFOX), etomoxir, oxfenicine, and perhexiline, act by inhibiting carnitine palmityltransferase I (CPT I), the gatekeeper of FFA entry to the mitochondrion (**eFig. 23.12A**). These agents shift energy utilization from FFAs to glucose by decreasing oxidation of FFAs. However, since there is no apparent feedback from CPT I activity to sarcolemmal FFA import, CPT I inhibitors can lead to accumulation of unmetabolized lipids in cardiac myocytes, which may lead to lipotoxicity-induced cardiac myocyte cell death. *Etomoxir* is an oxirane carboxylic acid derivative that indirectly promotes increased glucose oxidation through inhibition of CPT I. In an open-label, uncontrolled trial conducted in 10 patients with NYHA Class II-III HF, treatment with etomoxir for 3 months was associated with a significant improvement in left ventricular ejection fraction (LVEF), cardiac output at peak exercise, and clinical status.[3] Subsequent phase II studies with etomoxir were halted because the compound did not have the expected efficacy in the treatment of HF (MediGene 2002 Annual Report, March 26, 2003). Although *oxfenicine* was shown to be beneficial in the canine rapid-pacing model of HF, in other animal models oxfenicine therapy resulted in a dose-related increase in cardiac mass, as well as an increase in liver and kidney weights. *Perhexiline* is currently in use clinically as an antianginal agent. Although there were early reports of hepatotoxicity with this agent, hepatotoxicity occurred in patients with a genetic variant of a cytochrome P-450 enzyme (slow hydroxylation), which

resulted in drug accumulation, as well as accumulation of phospholipids in the liver and nerves. The risk of toxic effects is virtually eliminated by maintaining plasma concentrations between 150 and 600 ng/mL, at which levels the drug still remains effective.[3] Perhexiline has shown promise as adjunctive therapy for HF in a small, short-term, randomized double-blind clinical trial in patients with ischemic and nonischemic cardiomyopathy. In this study, 8 weeks of treatment with perhexiline resulted in an increase in the combined primary endpoint of peak oxygen uptake and LVEF, and an improvement in quality of life (Minnesota Living with Questionnaire). Importantly, maximum O_2 uptake was increased significantly in both the ischemic and the nonischemic group, suggesting that the benefit of perhexiline was not entirely anti-ischemic.[4] Although there remains some optimism that CPT I inhibitors can be used as adjunctive therapy in HF, other pFOX inhibitors may have less side effects.

The pFOX inhibitors trimetazidine and ranolazine were also originally developed as antianginal agents. *Trimetazidine* is a piperazine compound that has been widely used outside the United States as an antianginal agent. Trimetazidine has no discernible vasodilator properties at rest or during dynamic exercise and has a very favorable side effect profile. The exact mechanism of action of trimetazidine is not known, but it appears to work, at least in part, through inhibition of long-chain 3-ketoacyl coenzyme A thiolase, a crucial enzyme in the terminal steps of mitochondrial beta-oxidation. Clinical trials have shown improvements in ejection performance, reverse cardiac remodeling, and NYHA functional class with trimetazidine.[3] Trimetazidine has been evaluated in a number of small clinical trials in patients with both ischemic and nonischemic cardiomyopathy.[1,3] Two months of treatment with trimetazidine resulted in significant improvement in LVEF at rest and enhanced LV wall motion during a dobutamine stress test compared with placebo in NYHA Class II and III HF patients.[1] In two recent small clinical studies, trimetazidine was shown to improve systolic LV function in patients with diabetes and ischemic cardiomyopathy compared with placebo.[1,5] In contrast, another study, which assessed the effects of trimetazidine in patients with HF who were diabetic, demonstrated no significant effect on exercise capacity and only minor effects on LV systolic function.[3] In a study that specifically enrolled elderly patients with CAD and LVEF less than 50%, the group that received 6 months of trimetazidine on top of standard therapy showed a significantly greater improvement in LVEF (7%), as well as smaller LV end-diastolic and end-systolic dimensions. In addition, the trimetazidine group had improved NYHA functional class and quality-of-life scores (Minnesota Living with Questionnaire). These findings have been confirmed in recent larger trials with longer-term follow-up (18 to 24 months), which have also shown improvements in LVEF, reduction in LV volumes, and improvement in NYHA functional class in patients with ischemic cardiomyopathy (LVEF <50%).[3] Given the antianginal effects of trimetazidine, it is not surprising that this agent led to improvements in LV function and NYHA functional class in patients with ischemic cardiomyopathy. However, a recent study with trimetazidine also included patients with nonischemic cardiomyopathy and showed similar increases in LVEF, reductions in LV end-systolic volume, and similar trends for improved quality of life and exercise capacity in both the ischemic and the nonischemic group.[6] Thus it appears that trimetazidine has both functional and physiologic benefits regardless of the HF etiology.

Ranolazine (Ranexa) is a novel anti-ischemic drug that prolongs the QT interval and is the first FDA-approved pFOX inhibitor for the treatment of angina. The principal mechanism of action for this drug as an antianginal remains controversial, although recent studies suggest that the antianginal effects of ranolazine may be related to decreased sodium entry into cells by inhibiting the rapid component of the delayed rectifier K^+ current [I_{kr}]. Ranolazine also increases the activity of pyruvate decarboxylase, a key regulator of glucose metabolism, most likely due to loss of inhibition of the end products of the beta-oxidation (NADH, acetyl-CoA). Although no clinical trials have yet been reported using ranolazine in

patients with dilated cardiomyopathy, there are studies with ranolazine in patients with a preserved ejection fraction (**see Chapter 26**).

Glucagon-Like Peptide 1

Sustained activation of the sympathetic nervous system (**Chapter 22**) in HF leads to increased lipolysis, with a subsequent rise in levels of circulating fatty acids with a resultant insulin resistance. Although the exact role of insulin resistance in HF is not known, studies with the incretin hormone glucagon-like peptide-1 (GLP-1), which increases postprandial insulin secretion and improves insulin sensitivity, have demonstrated improvements in contractility in both experimental and human HF. In a study of 12 patients with NYHA functional class III/IV HF, a continuous infusion of GLP-1 for 12 weeks improved LVEF (21% to 27%) and functional capacity, even in non-diabetic patients.[7] Similarly, in a study of 10 patients with acute myocardial infarction and LV systolic dysfunction (LVEF <40%), a 72-hour continuous infusion of GLP-1 was associated with a significant improvement in LVEF, as well as global and regional wall motion.[8] In contrast to these early encouraging findings, there was no improvement in cardiac index, LV ejection fraction or brain natriuretic peptides levels in a small study of 20 non-diabetic patients with NYHA class II-III HF, following a 48-hour infusion of GLP-1. Moreover, there was a small but potentially concerning rise in heart rate and diastolic blood pressure in this study.[9] Exenatide, a GLP-1 agonist, increased both heart rate and cardiac index in male NYHA Functional Class III/IV patients (n = 20) with type 2 diabetes, along with a decrease in pulmonary capillary wedge pressure in a crossover study with intravenous infusions for 2 consecutive days with either exenatide (0.12 pmol/kg/min) or placebo for 6 hours, followed by a washout period for 18 hours. There were no observed adverse effects in this short-term study.[10] A recent randomized placebo-controlled phase II study with the GLP-1 agonist liraglutide, in 300 patients with a reduced ejection fraction, showed that compared with placebo, liraglutide had no significant (P = 0.31) effect on the primary endpoint, which was a global rank score of time to death, time to rehospitalization for HF, and time-averaged proportional change in N-terminal pro-B-type natriuretic peptide level from baseline to 180 days.[11] Moreover, a prespecified subgroup analyses in patients with diabetes revealed no significant between-group differences. In the more recent LEADER trial in patients with type 2 diabetes and increased cardiovascular risk, liraglutide exhibited a significant reduction in time to first major cardiovascular event.[12]

Micronutrient Supplementation

The heart requires a continuous supply of energy-providing substrates and amino acids in order to maintain normal structure and function. In HF, alterations in substrate metabolism, the tricarboxylic acid cycle, or oxidative phosphorylation may contribute to contractile dysfunction. For example, deficiencies in coenzyme Q10 (CoQ10), L-carnitine, amino acids, thiamine, and other B vitamins have been documented in the failing heart, raising the interesting possibility that micronutrient supplementation might improve the abnormal energetic milieu of the failing heart. Although a number of clinical supplementation trials of key micronutrients involved in cardiac metabolism, including CoQ10, L-carnitine, thiamine, and taurine, have yielded promising results in patients with HF, none has yielded conclusive results. Because of the absence of definitive clinical trial data in this area, the ACC/AHA practice guidelines (**see Chapter 25**) do not recommend the use of nutritional supplements as a treatment for HF in patients with current or prior HF symptoms.

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24

Diagnosis and Management of Acute Heart Failure

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Acute heart failure (AHF) is among the most common causes for hospitalization in patients older than 65 years in the developed world. In the United States alone, 4 million patients are hospitalized each year with a primary or secondary diagnosis of heart failure (HF), and AHF contributes to more than 7 million hospital days annually.[1] AHF has a similar burden in Europe and is increasingly recognized as a as a global public health problem.[2] The prevalence of HF is projected to continue to increase over time because of a convergence of several epidemiologic trends: (1) the aging of the population, given the age-related incidence of HF; (2) the reduction in hypertension-related mortality and the greatly improved survival after myocardial infarction (MI), resulting in more patients living with chronic left ventricular (LV) dysfunction (**see Chapter 21**); and (3) the availability of effective therapy for prevention of sudden death (**see Chapters 27 and 42**). Previously considered part of the natural history of chronic HF, AHF is increasingly recognized as a distinct disorder with unique epidemiology, pathophysiology, treatments, and outcomes.

Epidemiology

Nomenclature and Definition

A variety of overlapping terms have been used to characterize AHF in the literature, including “acute heart failure syndrome” (AHFS), “acute decompensated heart failure” (ADHF), “acute decompensation of chronic heart failure” (ADCHF), and “hospitalization for heart failure” (HHF). Although none of these is universally accepted, we use the terminology “acute heart failure” in this chapter. Broadly speaking, AHF can be defined as the new onset or recurrence of symptoms and signs of HF requiring urgent or emergent therapy and resulting in unscheduled care or hospitalization. Although the word “acute” in the nomenclature suggests a sudden onset of symptoms, many patients may have a more subacute course, with gradual worsening of symptoms that ultimately reach a level of severity sufficient to seek unscheduled medical care.

Scope of the Problem

AHF represents a major burden in the developed world. In the United States, HF is the primary diagnosis for more than 1 million hospitalized patients annually, and a secondary diagnosis for an additional 3 million hospitalizations.[1] Similar numbers of hospitalizations are reported in Europe.[2] The direct and indirect costs associated with HF approach 40 billion U.S. dollars per year in the United States, and the majority of these expenditures are related to the costs of hospitalizations.[3,4] As noted, the overall prevalence of chronic heart failure continues to grow. However, recent data suggest that the age-adjusted rate of hospitalization for HF has begun to decrease. In a study using U.S. Medicare claims data from 1998 to 2008, age-related incidence of hospitalization for HF declined for all race and gender groups.[5] Other data suggest that while HF as a primary diagnosis may have decreased, the incidence of HF as a

secondary diagnosis has remained stable[6] (**eFig. 24.1**). Similar data have been published in several countries in Europe.[7] To what extent these changes are related to more effective treatments of chronic HF, or alternatively, changes in care to create alternative care pathways for avoiding hospitalization, is unknown. Changes in medical care (especially in the United States) have led to increased efforts to manage milder forms of HF decompensation without hospitalization, utilizing outpatient diuretic clinics and observation units, although available data suggest that even these milder forms of decompensation are still associated with adverse prognosis.[8,9] Despite these potentially encouraging trends, it appears likely that HF hospitalization will be a major clinical and economic problem for health care systems for the foreseeable future. A major development in the understanding of the epidemiology, clinical characteristics, and outcomes of patients with AHF has been the development of large, relatively unselected registries of AHF, which have provided a "real world" perspective on the epidemiology and outcomes of this clinical syndrome worldwide (**Table 24.1**).

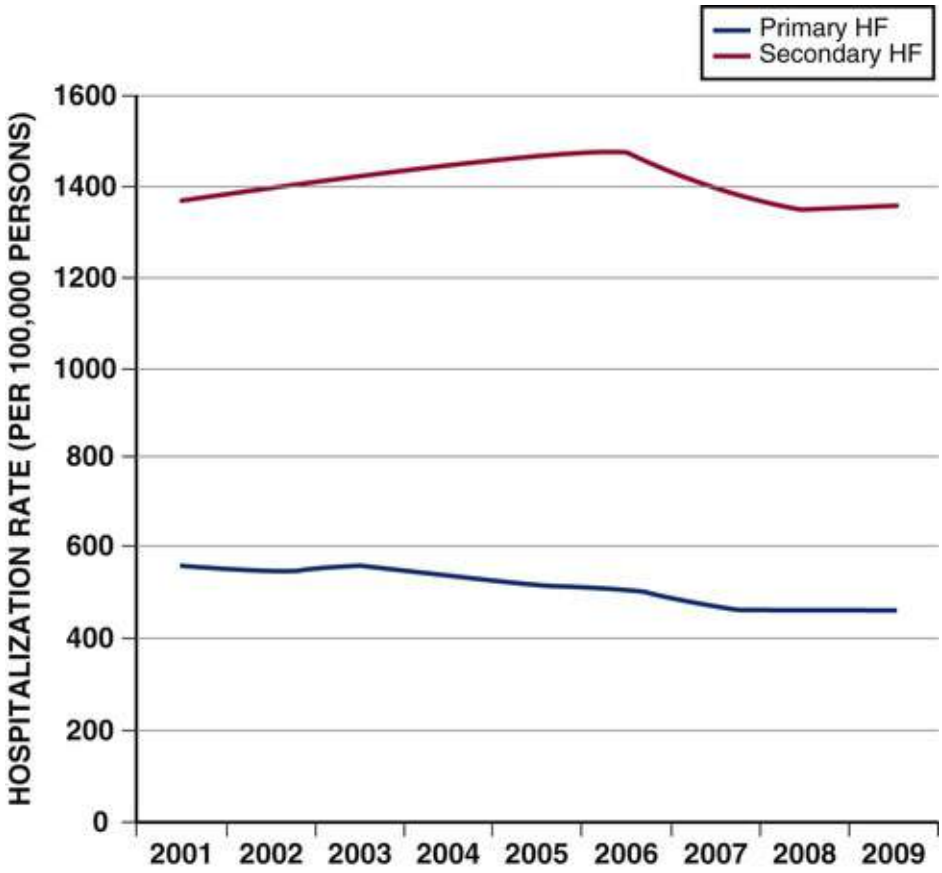
TABLE 24.1

Demographics and Comorbidities of Patients Hospitalized with Acute Heart Failure From Select Studies

	ADHERE (*n* = 187,565)	OPTIMIZE-HF (n = 48,612)	PERNA ET AL (*n* = 2974)	EHFS II (*n* = 3580)	EFICA (*n* = 599)	ITALIAN AHF (*n* = 2807)	ATTEND (*n* = 4841)	DAMASCENO (*n* = 1006)
Region	US	US	Argentina	Europe	France	Italy	Japan	Africa
Age (y)	75	73	68	70	73	73	73	52
Male (%)	48	48	59	61	59	60	58	49
Preserved EF (%)	53	51	26	52	45	34	47	25
Prior HF (%)	76	88	50	63	66	56	36	-
Medical History								
CAD	57	50		54	46		N/A	
MI	30	N/A	22		22	36	N/A	
Hypertension	74	71	66	62	60	66	69	56
AF or atrial flutter	31	31	27	39	25	21	40	18
Chronic renal insufficiency	30	20	10	17	10	25	N/A	8
Diabetes	44	42	23	33	27	38	34	11
COPD/asthma	31	34	15	19	21	30	12	

AF, Atrial fibrillation; *CAD,* coronary artery disease; *COPD,* chronic obstructive pulmonary disease; *MI,* myocardial infarction.

Data from ADHERE Scientific Advisory Committee. Acute Decompensated Heart Failure National Registry (ADHERE) core module Q1 2006 final cumulative national benchmark report. Scios; 2006; OPTIMIZE-HF: Gheorghiade M et al: Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA 2006;296:2217-2226; Argentina: Perna ER et al. Overview of acute decompensated heart failure in Argentina: lessons learned from 5 registries during the last decade. Am Heart J 2006;151:84-91; EHFS II: Nieminen MS et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients—description of population. Eur Heart J 2006;27:2725-2736; EFICA: Zannad F et al. Clinical profile, contemporary management and one-year mortality in patients with severe acute heart failure syndromes: the EFICA study. Eur J Heart Fail 2006;8:697-705; Italian AHF: Tavazzi L et al. Nationwide survey on acute heart failure in cardiology ward services in Italy. Eur Heart J 2006;27:1207-1215; ATTEND: Sato N et al. Hyponatremia and in-hospital mortality in patients admitted for heart failure (from the ATTEND registry). Am J Cardiol 2013;111:1019-25; and Dr. Naoki Sato. Personal communication; AFRICA: Damasceno A et al. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries: results of the sub-Saharan Africa survey of heart failure. Arch Intern Med 2012;172:1386-94.



EFIGURE 24.1 Rates of hospitalizations as the primary and secondary hospitalization for heart failure (HF) in the United States. (From Blecker S et al. Heart failure–associated hospitalizations in the United States. J Am Coll Cardiol 2013;61:1259-67.)

Preserved Versus Reduced Ejection Fraction

As with chronic HF, recent decades have seen increasing recognition of the epidemiologic importance of HF with normal or near-normal systolic function, “heart failure with preserved ejection fraction” (HFpEF). On the basis of available registry data, 40% to 50% of patients hospitalized have HFpEF. Important epidemiologic differences exist between “heart failure with reduced ejection fraction” (HFrEF) and HFpEF (**see Chapter 21**). The in-hospital mortality of patients with HFpEF appears to be lower compared with that of patients with HFrEF, but postdischarge rehospitalization rates are similarly high for both groups. Patients with AHF and HFpEF are more likely to be rehospitalized for and to die from noncardiovascular causes than patients with AHF and reduced EF, reflecting their more advanced age and greater burden of comorbidity. More recently, the concept of “midrange ejection fraction” (generally considered as EF of 40% to 49%) has been proposed as an additional refinement of the standard HFrEF versus HFpEF dichotomy, but specific data on AHF outcomes in this group are lacking.[10]

Age, Race, and Gender

There are significant differences in the epidemiology of AHF based on age, race, and gender. AHF disproportionally affects elderly people, with a mean age of 75 years in large registries. AHF affects men and women almost equally, but there are important differences by gender. In the ADHERE Registry, women admitted for AHF were older than men (74 versus 70 years) and more frequently had preserved systolic function (51% versus 28%).[11] Differences in ethnic groups have been studied most extensively in the United States and have focused primarily on differences between African American and white

patients. In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) Registry, African American patients admitted with AHF were younger (64 versus 75 years) and more likely to have LV systolic dysfunction (57% versus 51%) with a lower mean EF (35% versus 40%), hypertensive etiology for HF (39% versus 19%), renal dysfunction, and diabetes compared with the non–African American group.[12] Lower estimated mortality rates have been reported for African American than for non–African American patients, but when adjustments are made for these differences in comorbidities and age, mortality rates are similar.

Comorbidities

Concomitant diseases are common in patients admitted with AHF, reflecting the elderly population. These comorbidities not only represent diseases that are risk factors for the development of HF, but also can complicate diagnosis and management. Hypertension is the most prevalent of the concurrent conditions, present in approximately two thirds of AHF patients (**see Chapters 46 and 47**), whereas coronary artery disease (CAD) is present in about half and dyslipidemia in more than one third[13,14] (**Chapter 61**). Other conditions resulting from the vascular injury produced by these diseases, such as cerebrovascular accident (stroke), peripheral vascular disease, and chronic renal insufficiency, are also common in patients with AHF. Diabetes mellitus is present in more than 40% of U.S. patients with AHF, most likely related to increasing incidence of obesity, and ranges from 27% to 38% in Europe. Chronic obstructive pulmonary disease (COPD) is also present in approximately 25% to 30%, which confounds the presenting symptoms of dyspnea and is associated with lower utilization of evidence-based therapy. Atrial fibrillation (AF) appears to be more common in Europe (up to 42%, versus 31% in U.S. patients with AHF) and can both precipitate AHF and complicate its management.

Global Differences in AHF

Although most data continue to emerge from North America and Europe, AHF is increasingly recognized as a global issue, and important differences between regions of the world have emerged in terms of epidemiology, therapy, and outcomes.[15] Although there are various country- or region-specific registries (**see Table 24.1**), to date most available data highlighting these differences has come from large global outcome trials. Although these studies can provide important insight into regional differences, they do suffer from inherent limitations and may not be truly representative of the general population because of selection bias. The growth of less selected registries in other areas of the world will provide new insights into global burden of disease.

Pathophysiology

AHF is not a single disease but a heterogeneous clinical syndrome. As such, pathophysiology of AHF is complex and highly variable, with many overlapping pathogenic mechanisms that may be operative to a greater or a lesser degree. This fundamental heterogeneity complicates the attempt to create a simple and unified conceptual model. One potentially useful framework for understanding the pathophysiology of AHF is to consider it as the result of the interaction of underlying substrate, initiating mechanisms or triggers, and amplifying mechanisms, all of which contribute to a common set of clinical signs and symptoms (primarily related to congestion, end-organ dysfunction, or both) that define AHF (**Fig. 24.1**). In this context, *substrate* refers to underlying cardiac structure and function. The underlying substrate may be

one of normal ventricular function, for example, patients without a prior history of HF who develop AHF because of sudden changes in ventricular function from an acute insult such as MI or acute myocarditis (**see Chapter 79**). Alternatively, some patients may have no prior history of HF but abnormal substrate (e.g., stage B patients with asymptomatic LV dysfunction) with a first presentation of HF (de novo heart failure). Also, most patients with AHF have a substrate of chronic compensated HF, who then decompensate and present with AHF.

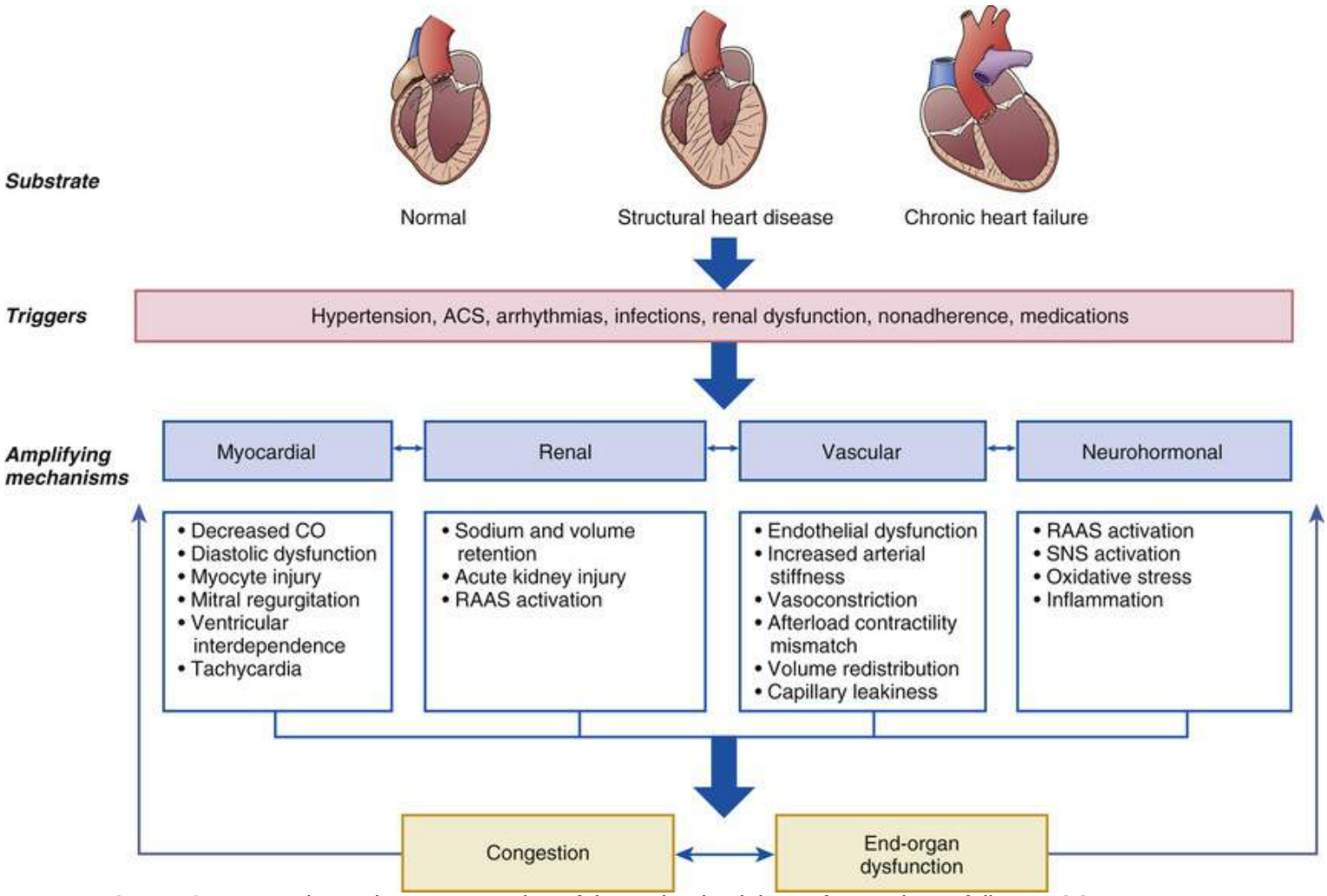


FIGURE 24.1 A schematic representation of the pathophysiology of acute heart failure. ACS, Acute coronary syndrome; CO, cardiac output; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

Initiating mechanisms vary according to, and interact with, the underlying substrate and may be cardiac or extracardiac. For patients with normal substrate (normal myocardium), a substantial insult to cardiac performance (e.g., acute myocarditis) is required to lead to the clinical presentation of AHF. For patients with abnormal substrate at baseline (asymptomatic LV dysfunction), smaller perturbations (e.g., poorly controlled hypertension, AF, or ischemia) may precipitate an AHF episode. For patients with a substrate of compensated or stable chronic HF, medical or dietary nonadherence, agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) or thiazolidinediones, and infectious processes are all common triggers for decompensation.

Regardless of the substrate or initiating factors, a variety of “amplifying mechanisms” perpetuate and contribute to the episode of decompensation. These include neurohormonal and inflammatory activation, ongoing myocardial injury with progressive myocardial dysfunction, worsening renal function, and

interactions with the peripheral vasculature, all of which may contribute to the propagation and worsening of the AHF episode.

Congestion

Systemic or pulmonary congestion, often caused by a high ventricular diastolic pressure, dominates the clinical presentation of most patients hospitalized for AHF. In this sense, congestion can be seen as a final common pathway producing clinical symptoms leading to hospitalization. A general view of AHF pathophysiology is that gradual increases in intravascular volume lead to symptoms of congestion and clinical presentation, and normalization of volume status with diuretic therapy results in restoration of homeostasis. Whereas this mechanism may be operative in some patients, this model is a vast oversimplification. Although some data suggest that increases in body weight often precede decompensation and hospitalization for HF, careful studies using implantable hemodynamic monitors suggest that increases in invasively measured LV filling pressures can occur without substantial changes in body weight.[16] These observations have led to increasing interest in the concept of *volume redistribution* and the dynamic role of the vasculature as a contributing mechanism to decompensation in HF (see later, Vascular Mechanisms).

One potentially important concept is the distinction between "clinical congestion" and "hemodynamic congestion." Although patients present with signs and symptoms of systemic congestion such as dyspnea, rales, elevated jugular venous pressure, and edema, this state is often preceded by *hemodynamic congestion*, defined as high ventricular diastolic pressures without overt clinical signs. Similarly, clinical congestion may resolve with treatment but hemodynamic congestion may persist, leading to a high risk of rehospitalization. It has been postulated that hemodynamic congestion may contribute to the progression of HF because it may result in increased wall stress as well as in renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) activation. This may trigger a variety of molecular responses in the myocardium, including myocyte loss and increased fibrosis. The natriuretic peptides (**see Chapter 23**), which are the intrinsic counterregulatory hormone in HF, may have abnormal processing that leads to diminished biologic activity in patients with advanced HF.[17] In addition, elevated diastolic filling pressures may decrease coronary perfusion pressure, resulting in subendocardial ischemia that may further exacerbate cardiac dysfunction. Increased LV filling pressures can also lead to acute changes in ventricular architecture (more spherical shape), contributing to worsening mitral regurgitation.

These mechanisms also play an important role in *pathologic remodeling of the ventricle*, a chronic process that may be accelerated by each episode of decompensation. Consistent with this paradigm is the well-established clinical observation that each hospitalization for AHF heralds a substantial worsening of the long-term prognosis, an effect that appears additive with recurrent hospitalizations.[18] Data from studies with implantable hemodynamic monitors have confirmed that chronically elevated filling pressures (i.e., hemodynamic congestion) are associated with increased risk of future events.[19] With the recognition of congestion as the most common aspect of AHF presentation, there has been a formal attempt to better assess and quantitate congestion in HF.[20]

Myocardial Function

Although a variety of extracardiac factors play important roles in AHF, impairments of cardiac function (systolic, diastolic, or both) remain central to our understanding of this disorder (**see Chapter 22**). Changes in systolic function and decreased arterial filling can initiate a cascade of effects that are

adaptive in the short term but maladaptive when elevated chronically, including stimulation of the SNS and RAAS. Activation of these neurohormonal axes leads to vasoconstriction, sodium and water retention, volume redistribution from other vascular beds, increases in diastolic filling pressures, and clinical symptoms. In patients with underlying ischemic heart disease, initial defects in systolic function may initiate a vicious cycle of decreasing coronary perfusion, increased myocardial wall stress, and progressively worsening cardiac performance. Increased LV filling pressures and changes in LV geometry can worsen functional mitral regurgitation, further decreasing cardiac output.

Although decreases in systolic function can clearly play a role in the pathophysiology of AHF, epidemiology data previously summarized show that approximately half of patients with AHF have relatively preserved systolic function. Importantly, abnormalities in diastolic function are present in HF patients regardless of EF. The impairment of the diastolic phase may be related to passive stiffness, abnormal active relaxation of the left ventricle, or both. Hypertension, tachycardia, and myocardial ischemia (even in the absence of CAD) can further impair diastolic filling. All these mechanisms contribute to higher LV end-diastolic pressures, which are reflected back to the pulmonary capillary circulation. Diastolic dysfunction alone may be insufficient to lead to AHF, but it serves as the substrate on which other precipitating factors (e.g., AF, CAD, hypertension) lead to decompensation. One underappreciated aspect of myocardial function in AHF relates to the interdependence of the left and right ventricles. Because of the constraints of the pericardial space, distention of either ventricle from increased filling pressures can result in direct impingement of diastolic filling of the other ventricle. This may be particularly operative in clinical scenarios leading to abrupt failure of the right ventricle (e.g., pulmonary embolism or right ventricular infarction), resulting in diminished filling of the left ventricle and arterial hypotension.

The availability of increasingly sensitive assays for circulating cardiac *troponins* has substantially advanced our understanding of the role of myocardial injury in the pathophysiology of HF. Data from both registries and clinical trial populations indicate that circulating cardiac troponins are elevated in a large proportion of patients with AHF, even in the absence of clinically overt myocardial ischemia.[21,22] In a representative analysis of data from the RELAX-AHF study using a highly sensitive assay, 90% of patients enrolled had a troponin T level above the 99th percentile upper reference limit (URL) at baseline, and troponin elevation was associated with postdischarge outcomes to 180 days[23] (**Fig. 24.2**).

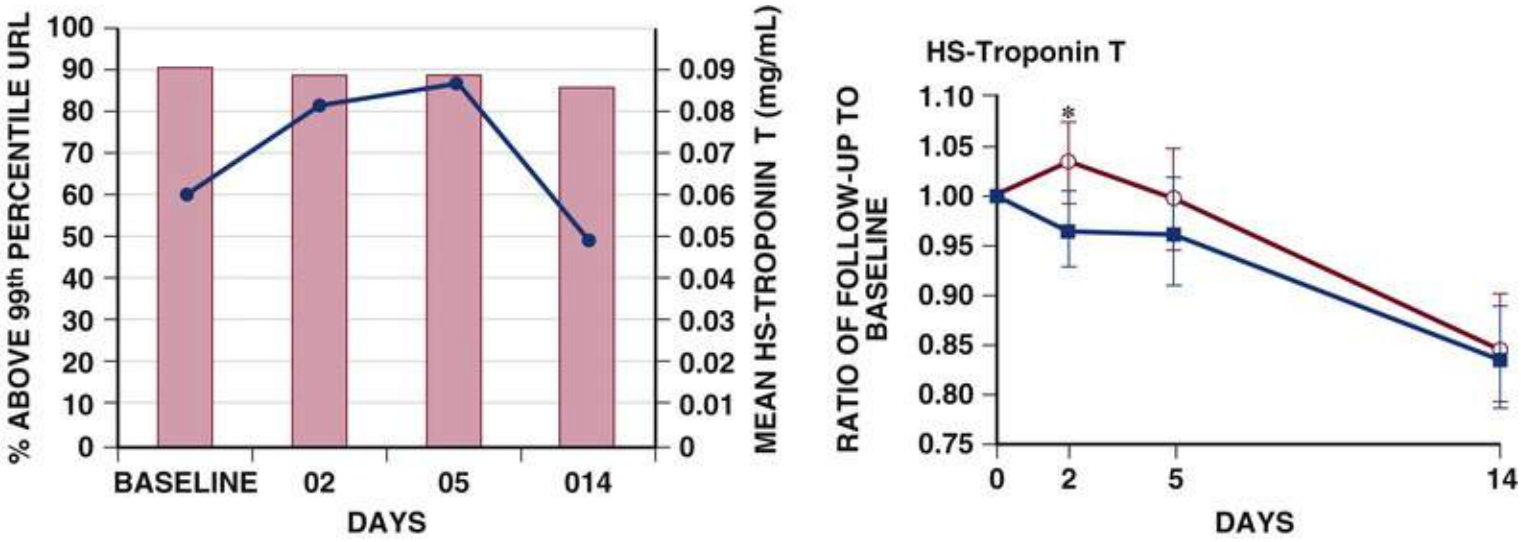


FIGURE 24.2 Incidence of elevated (above the 99th percentile upper reference limit [URL]) high-sensitivity (HS) troponin T in the RELAX-AHF study and effect of serelaxin therapy on troponin levels. (From Felker GM et al. Serial high sensitivity cardiac troponin T measurement in acute heart failure: insights from the RELAX-AHF study. Eur J Heart Fail 2015;17:1262-70; and Metra M et al. Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) Development Program: correlation with outcomes. J Am Coll Cardiol 2013;61:196-206.)

The precise mechanisms mediating myocardial injury in AHF are poorly defined, but increased myocardial wall stress, decreased coronary perfusion pressure, increased myocardial oxygen (O_2) demand, endothelial dysfunction, activation of the neurohormonal and inflammatory pathways, platelet activation, and altered calcium handling may all contribute to myocyte injury, even in the absence of epicardial CAD.[21] Specific therapeutic interventions that may increase myocardial O_2 demand (e.g., positive inotropic agents) or decrease coronary artery perfusion pressure (e.g., some vasodilators) may exacerbate myocardial injury and further contribute to the cycle of decompensation. Whether avoidance of myocardial injury is a specific target for therapy in AHF remains a subject of active investigation. Data from the RELAX-AHF study of serelaxin suggest that avoidance of myocardial injury (as demonstrated by less troponin elevation) may be an important mechanism of action underlying the observed treatment benefit[24] (**Fig. 24.2**).

Renal Mechanisms

The kidney plays two fundamental roles relative to the pathophysiology of HF: it modulates loading conditions of the heart by controlling intravascular volume and is responsible for neurohormonal outputs (i.e., the RAAS system). Abnormalities of renal function are extremely common in patients with AHF and may be underestimated by creatinine alone—64% of patients in the ADHERE Registry had a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2.[25] Baseline measures of renal function are well-established risk factors for poor outcomes in AHF (see later, Risk Stratification). Our understanding of the implications of changes in measures of renal function during HF decompensation and therapy has continued to evolve[26] (**see Chapter 98**).

The term *cardiorenal syndrome* has been increasingly used to describe pathologic interactions between the cardiac and renal axes in the setting of HF. Although specific definitions and nomenclature have varied, in the context of AHF the cardiorenal syndrome describes the clinical situation of worsening measures of renal function in the setting of persistent congestion. This clinical scenario has been associated with poor outcomes in a variety of observational studies. Multiple studies have investigated the pathophysiology and risk factors for this phenomenon, which is related to an intricate interplay of

patient characteristics (age), comorbidities (baseline renal function as assessed by GFR, diabetes mellitus, hypertension), neurohormonal activation (especially of RAAS and SNS), and hemodynamic factors (central venous congestion, and less frequently arterial underfilling with renal hypoperfusion), as well as other factors such as activation of inflammatory cascades and oxidative stress.[27] Although often assumed to be related to low cardiac output and renal blood flow, careful hemodynamic studies have repeatedly confirmed that the strongest predictor of worsening renal function (WRF) in HF patients relates to elevated central venous pressure**,** which is reflected back to the renal veins and leads directly to changes in GFR.[28] Importantly, recent data have emphasized the importance of evaluating changes in renal function in the context of the overall clinical picture. WRF in the setting of ongoing clinical improvement is generally reflective of successful decongestion and does not portend a poor prognosis[29] (**Fig. 24.3**). Although there has been substantial interest in the utility of newer biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), to identify episodes of frank kidney injury before changes in markers of renal function, the clinical utility of these markers remains uncertain. A detailed classification system for understanding the interplay between cardiac performance and renal function provides a framework for understanding the complex pathophysiology underlying the cardiorenal syndrome.[27]

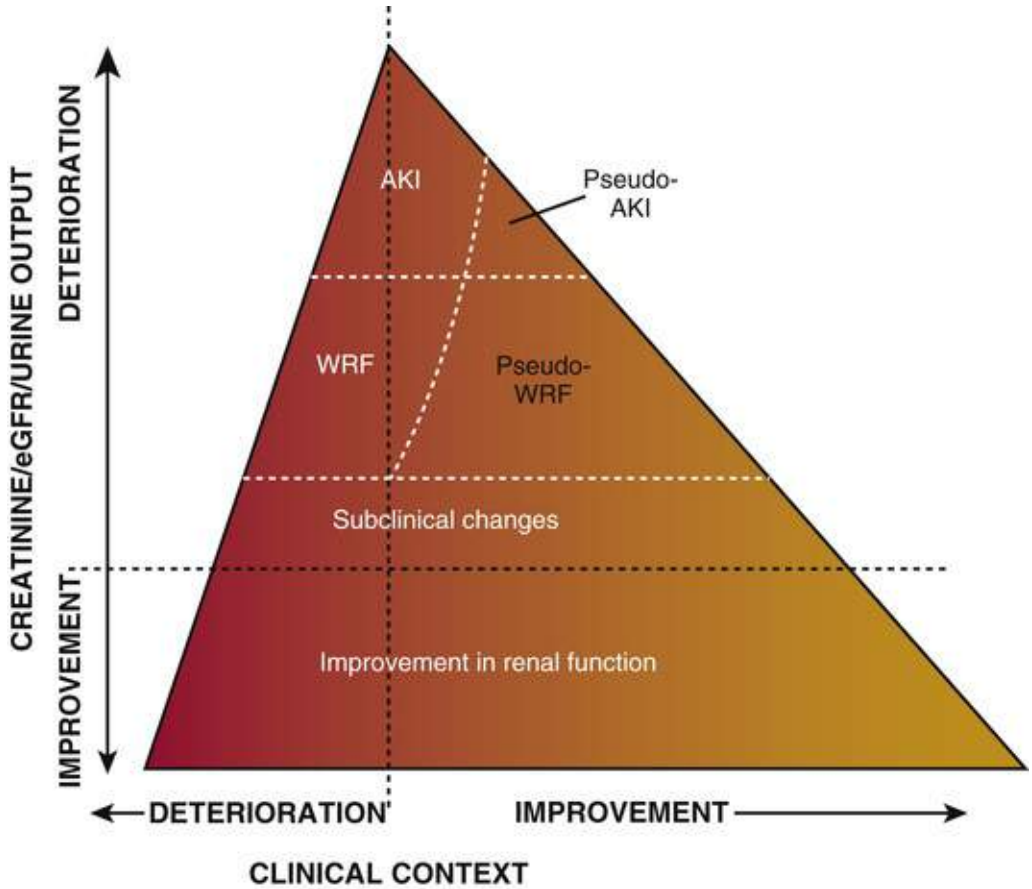


FIGURE 24.3 Schematic of changes in renal function within different clinical contexts in acute heart failure. *AKI,* Acute kidney injury; *eGFR,* estimated glomerular filtration rate; *WRF,* worsening renal failure.
(From Damman K, Testani JM. The kidney in heart failure: an update. Eur Heart J 2015;36:1437-44.)

Vascular Mechanisms

Although abnormalities in cardiac function are central to the pathogenesis of AHF, there is increasing appreciation for the importance of the peripheral vasculature in this disorder. Abnormalities of

endothelial function related to nitric oxide (NO)–dependent regulation of vascular tone are well described in HF.[30] Arterial stiffness, which is related to but distinct from blood pressure, increases cardiac loading conditions and is associated with incident HF and worse outcomes. Peripheral vasoconstriction in the setting of AHF redistributes blood centrally, increasing pulmonary venous congestion and edema. As noted, elevated central venous pressure reduces renal function, resulting in greater fluid retention that further elevates venous pressures. Peripheral arterial vasoconstriction increases afterload, LV filling pressures, and postcapillary pulmonary venous pressures, resulting in worsening of pulmonary edema and dyspnea. This increased afterload causes greater ventricular wall stress and increased myocardial ischemia and cardiac arrhythmias. Abnormal vascular compliance also predisposes these patients to marked blood pressure lability with relatively minor changes in intravascular volume, causing precipitous increases in afterload and ultimately in LV filling pressures resulting in pulmonary congestion. The effects of this vascular abnormality are amplified by LV diastolic dysfunction.

The clinical observation that vasodilator treatment can improve dyspnea in many acutely hypertensive patients without significant diuresis has led to the concept that afterload-contractility mismatch can lead to increased diastolic filling pressures in the setting of minimal total body volume changes. Similarly, the recognition of the large capacitance of the venous (in particular the splanchnic circulation) system has led to increased interest in volume shifts from the "venous reservoir" into the effective circulatory volume as a potentially important and underrecognized mechanism in AHF.[31] These shifts can be mediated by SNS activation, and this has been proposed as a potential explanation for the apparent disconnect between changes in filling pressures and changes in body weight during chronic hemodynamic monitoring. Whether fluid shifts involving this venous reservoir can be modulated by specific therapies is a subject of active investigation.

Neurohormonal and Inflammatory Mechanisms

Although elevations of circulating neurohormones are well documented in patients with AHF, the precise role of neurohormonal activation in the pathophysiology of AHF remains to be fully delineated. Increased plasma concentrations of norepinephrine, plasma renin activity, aldosterone, and endothelin (ET)-1 have all been reported in patients with AHF—all these axes are associated with vasoconstriction and volume retention, which could contribute to myocardial ischemia and congestion, thus exacerbating cardiac decompensation. Inflammatory activation and oxidative stress may also play a role. Proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6 are elevated in patients with AHF and have direct negative inotropic effects on the myocardium as well as increasing capillary permeability and inducing endothelial dysfunction.[32,33] In addition to direct effects, this activation stimulates the release of other factors, such as the potent procoagulant tissue factor and ET-1, which can lead to further myocardial suppression, disruption of the pulmonary alveolar-capillary barrier, and increased platelet aggregation and coagulation (potentially worsening ischemia). (**See also Chapter 23**.)

Evaluation of the Patient With Acute Heart Failure

The initial evaluation of the patient with acute HF focuses on the following critical aspects: (1) establishing a definitive diagnosis of AHF as rapidly and efficiently as possible; (2) emergent treatment for potentially life-threatening conditions (e.g., shock, respiratory failure); (3) identifying and addressing any relevant clinical triggers or other conditions requiring specific treatment (e.g., ACS, acute pulmonary

embolism); (4) risk stratification in order to triage patient to appropriate level of care (e.g., intensive care unit, telemetry unit, observation unit); and (5) defining the clinical profile of the patient (based on blood pressure, volume status, and renal function) in order to rapidly implement the most appropriate therapy. **Fig. 24.4** presents a proposed flow diagram for the initial evaluation of patients with suspected AHF from the most recent HF guidelines from the European Society of Cardiology (ESC).[10]

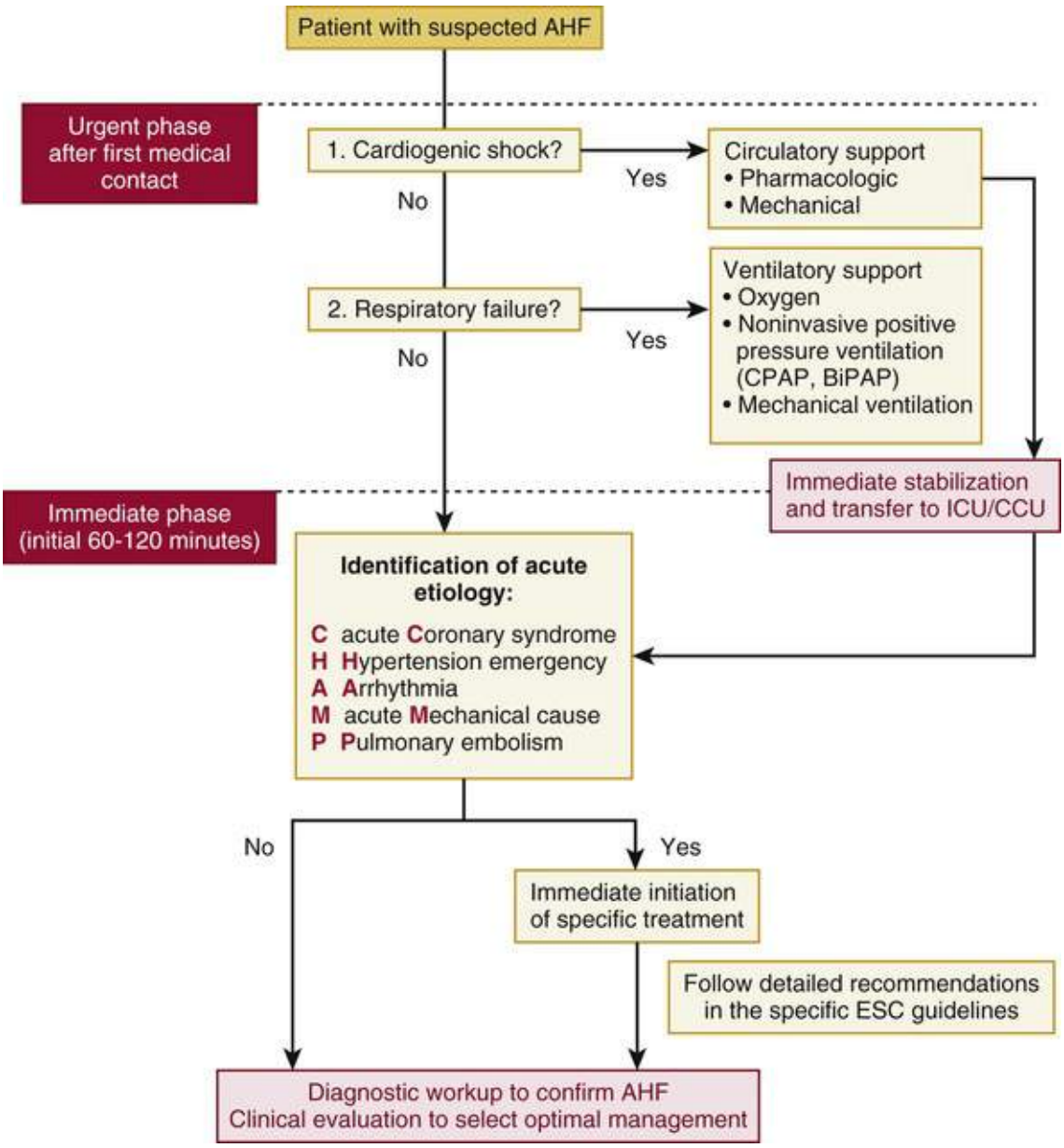


FIGURE 24.4 Algorithm for initial stabilization and management of patients with acute heart failure (AHF). (From Ponikowski P et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.)

Classification

The inherent heterogeneity of AHF makes the development of a comprehensive classification scheme difficult, and no single classification system has garnered universal acceptance. One potentially useful distinction is based on the presence or absence of a prior history of HF. New-onset or de novo HF makes up about 20% of hospitalizations for AHF.[14] These patients may have no prior history of cardiovascular

(CV) disease or risk factors (e.g., acute myocarditis), but more frequently, they have a background of risk factors for HF (stage A heart failure according to the ACC/AHA guidelines) or preexisting structural heart disease (stage B heart failure according to the ACC/AHA guidelines) (**see Chapters 21 and 25**). Many of these patients with de novo HF develop AHF in the setting of acute coronary syndrome (ACS). The vast majority of AHF patients, however, have a history of preexisting chronic HF. These patients usually have a less dramatic clinical presentation, since the chronic nature of the disorder has allowed for recruitment of compensatory mechanisms and remodeling (e.g., increased pulmonary lymphatic capacity). Additionally, these patients are typically already being treated with neurohormonal antagonists and loop diuretics, such that neurohormonal activation may be less profound but diuretic resistance more common. A simplified classification scheme defines three general groups of AHF patients (**Table 24.2**):

TABLE 24.2

Simplified Classification and Common Clinical Characteristics of Patients with Acute Heart Failure

CLINICAL CLASSIFICATION	SYMPTOM ONSET	TRIGGERS	SIGNS AND SYMPTOMS	CLINICAL ASSESSMENT	COURSE
Decompensated heart failure	Usually gradual	Noncompliance, ischemia, infections	Peripheral edema, orthopnea, dyspnea on exertion	SBP: variable CXR: often clear despite elevated filling pressures	Variable, high rehospitalization rate
Acute hypertensive heart failure	Usually sudden	Hypertension, atrial arrhythmias, ACS	Dyspnea (often severe), tachypnea, tachycardia, rales common	SBP: high (>180/100 mm Hg) CXR with pulmonary edema Hypoxemia common	High acuity, but patient often responds quickly to therapy with vasodilators, noninvasive ventilation. Postdischarge mortality is low.
Cardiogenic shock	Variable	Progression of advanced HF or major myocardial insult (e.g., large AMI, acute myocarditis)	End-organ hypo-perfusion; Oliguria, confusion, cool extremities	SBP: low or low normal LV function usually severely depressed RV dysfunction common Laboratory evidence of end-organ dysfunction (renal, hepatic)	High inpatient mortality Poor prognosis unless readily reversible cause or mechanical support, transplantation

ACS, Acute coronary syndrome; *AMI,* acute myocardial infarction; *CXR,* chest x-ray film; *LV,* left ventricular; *RV,* right ventricular; *SBP,* systolic blood pressure.

1. *Decompensated heart failure.* This group is composed of patients with worsening signs and symptoms of congestion on a background of chronic HF. The time course of worsening may be acute, subacute, or indolent, with gradually worsening symptoms over days to weeks. They may have either preserved or reduced EF, but cardiac output is generally preserved and blood pressure is within the normal range. Overall, this group represents the largest portion of patients hospitalized for AHF.
2. *Acute hypertensive heart failure.* Hypertension is increasingly recognized as a common feature of the AHF presentation, with 50% of patients presenting with systolic blood pressure (SBP) greater than 140 mm Hg and 25% with greater than 160 mm Hg.[34] In this group, hypertension may be triggered by a high sympathetic tone related to dyspnea and accompanying anxiety (*reactive hypertension*), or acute hypertension with accompanying changes in afterload may be a trigger for decompensation. Both these mechanisms may be operative in a given patient, and cause-and-effect relationships may be difficult to discern. Epidemiologically, patients in whom acute hypertensive HF are more likely to have preserved systolic function, more likely to be women,

and more likely to have sudden onset of symptoms. Frank pulmonary edema with evident rales and florid congestion on chest x-ray film is much more common in this group of patients than in those with more gradual onset of symptoms, likely related to difference in LV compliance, acuity of pressure changes, and pulmonary lymphatic capacity. Although often strikingly ill at the initial presentation with hypoxemia and the possible need for noninvasive ventilation or even intubation, this group tends to respond well to therapy and have lower in-hospital mortality.[14]

3. *Cardiogenic shock*. This group presents with signs and symptoms of organ hypoperfusion despite adequate preload. SBP is often (although not always) decreased, and evidence of frank or impending end-organ dysfunction (renal, hepatic, CNS) is common. This type of AHF is relatively uncommon (4% of AHFS presentations in EHFS II) in broad community registries but more common in tertiary care settings.

While this classification system does not fully capture some less common clinical scenarios (e.g., isolated right HF or high output HF), it usefully encompasses the vast majority of AHF patients likely to be seen in routine clinical practice. The management of several specific clinical scenarios in AHF patients is discussed in more detail later.

Symptoms

The most common reasons for patients to seek medical care for AHF are symptoms related to congestion (**Table 24.3**). Dyspnea is the most common symptom and is present in more than 90% of patients presenting with AHF. The duration and time course of symptom onset can vary greatly, from very acute onset over minutes to slow worsening of chronic symptoms until patients present to medical attention. The sensation of dyspnea is a complex phenomenon influenced by multiple physiologic, psychological, and social factors and can vary dramatically between patients.[35] Dyspnea is typically present at rest or with minimal exertion by the time the patient presents with AHF. Patients may also present with symptoms related to systemic venous congestion, including peripheral edema, weight gain, early satiety, and increasing abdominal girth. Importantly, atypical symptoms can predominate, especially in elderly patients, where fatigue, depression, altered mental status, and sleep disruptions may be the primary complaints.

TABLE 24.3

Common Presenting Symptoms and Signs of Decompensated Heart Failure

SYMPTOMS	SIGNS
Predominantly Related to Volume Overload	
Dyspnea (exertional, paroxysmal nocturnal dyspnea, orthopnea, or at rest), cough, wheezing	Rales, pleural effusion
Foot and leg discomfort	Peripheral edema (legs, sacral)
Abdominal discomfort/bloating; early satiety or anorexia	Ascites/increased abdominal girth; right upper quadrant pain or discomfort; hepatomegaly/splenomegaly; scleral icterus
	Increased weight
	Elevated jugular venous pressure, abdominojugular reflux
	Increasing S_3, accentuated P_2
Predominantly Related to Hypoperfusion	
Fatigue	Cool extremities
Altered mental status, daytime drowsiness, confusion, or difficulty concentrating	Pallor, dusky skin discoloration, hypotension
Dizziness, presyncope, or syncope	Pulse pressure (narrow) Proportional pulse pressure (low)
Other Signs/Symptoms of Acute Heart Failure	
Depression	Orthostatic hypotension (hypovolemia)
Sleep disturbances	S_4
Palpitations	Systolic/diastolic cardiac murmurs

Physical Examination

Despite advances in diagnostics technology, biomarkers, and imaging, heart failure remains a clinical diagnosis and the physical examination continues to play a fundamental role (**see Chapters 10 and 21**). A useful framework in the bedside evaluation of patients with AHF is that developed by Stevenson and colleagues, which focuses on the adequacy of perfusion ("cold" versus "warm") and congestion at rest ("wet" versus "dry"; **see Fig. 21.3**).[36] While this framework does not encompass all the heterogeneity of AHF, it does focus the evaluation on two critical aspects that will significantly influence both prognosis and choice of treatments.

Measuring the blood pressure is a critical part in the evaluation of patients with AHF; hypotension is one of the strongest predictors of poor outcomes and helps to define the clinical profile of the patient and appropriate therapeutic interventions. SBP is typically normal or elevated in patients with AHF, with almost 50% presenting with SBP greater than 140 mm Hg. The combination of underlying hypertension and the marked increase in sympathetic stimulation that accompanies AHF can result in elevations of SBP consistent with hypertensive urgencies or emergencies (12% of patients had SBP >180 mm Hg on admission). Patients with very low SBP are uncommon, with only 2% of patients in ADHERE presenting with an SBP less than 90 mm Hg. Although blood pressure is generally related to cardiac output and the state of organ perfusion, it is important to recognize that hypotension and hypoperfusion are not synonymous. Patients with systemic hypoperfusion may present with normal blood pressure, and likewise, patients with advanced forms of HF may have chronically low blood pressure not associated with acute hypoperfusion. *Pulse pressure* (the difference between systolic and diastolic blood pressure) is a useful measure that is an indirect marker of cardiac output. A low pulse pressure is a marker of a low cardiac output and confers an increased risk in patients admitted with AHF. A high pulse pressure may alert the physician to a high-output state, including the possibility of unrecognized thyrotoxicosis, aortic regurgitation, or anemia.

The *jugular venous pressure* (JVP) is literally a barometer of systemic venous hypertension and is the single most useful physical examination finding in the assessment of patients with AHF. The accurate assessment of the JVP is highly dependent on examiner skill. The JVP reflects the right atrial pressure,

which typically (although not always) is an indirect measure of LV filling pressures. JVP may not reflect LV filling pressures in isolated right ventricular (RV) failure (e.g., from pulmonary hypertension or RV infarct), and significant tricuspid regurgitation can complicate the assessment of the JVP since the large "CV wave" of tricuspid regurgitation can lead to its overestimation.

Rales or inspiratory crackles are the most common physical examination finding and have been noted in 66% to 87% of patients admitted for AHF. However, rales are often not heard in patients with a background of chronic HF and pulmonary venous hypertension, because of increased lymphatic drainage, reinforcing the important clinical pearl that the absence of rales does not necessarily imply normal LV filling pressures. Cool extremities with palpable peripheral pulses suggest decreased peripheral perfusion consistent with a marginal cardiac index, marked vasoconstriction, or both. Of note, the temperature should be assessed at the lower leg as opposed to the foot, and this assessment is relative to the temperature of the examiner's hands.

Peripheral edema is present in up to 65% of patients admitted with AHF and is less common in patients presenting with predominantly low-output HF or cardiogenic shock. As with rales, the presence of edema has a reasonable positive predictive value (PPV) for AHF but a low sensitivity, so its absence does not exclude that diagnosis. Edema caused by AHF is usually dependent, symmetric, and pitting. It is estimated that a minimum of 4 liters of extracellular fluid is accumulated to produce clinically detectable edema.

Other Diagnostic Testing

Biomarkers

The natriuretic peptides are a family of important counterregulatory hormones in HF with vasodilatory and other effects (**see Chapter 23**). In the context of AHF, both brain (B-type) natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) have been shown to play an important role in the differential diagnosis of patients presenting in the emergency department (ED) with dyspnea and are now strongly recommended by clinical practice guidelines.[37] For diagnostic natriuretic peptide (NP) testing in the setting of AHF, a critical point is that negative predictive value (NPV; i.e., the ability to rule out HF a as a cause of dyspnea) is generally greater than the PPV (i.e, the ability to definitively identify a diagnosis of HF as the cause of dyspnea). As with all biomarker testing, false positives (e.g., due to MI or pulmonary embolism) and false negatives (primarily due to obesity, which results in lower NP levels for a given degree of HF) may occur. Although NP levels tend to be lower in patients with HFpEF than those with reduced systolic function, NP testing cannot reliably distinguish HFpEF from systolic HF in an individual patient.

As noted previously, measurement of cardiac troponin is frequently elevated in patients presenting with AHF, and elevated levels are associated with worse in-hospital and postdischarge outcomes. The development of progressively more sensitive troponin assays has dramatically increased the proportion of patients presenting with AHF with elevations of circulating troponin. Assessment of cardiac troponin in patients with AHF is now recommended by current clinical practice guidelines and serves both to establish prognosis and to help gauge the likelihood of concurrent ACS.

Other Laboratory Testing

Assessment of renal function is a critical component in the management of patients with AHF. Estimated glomerular filtration rate (eGFR) should be calculated because serum creatinine may underestimate the

degree of renal dysfunction, especially in elderly patients. Blood urea nitrogen (BUN) is more directly related to the severity of AHF than creatinine and is typically elevated on admission in a large number of patients with AHF. In addition to reflecting intrinsic renal function, serum BUN is approximately proportional to neurohormonal activation in AHF. A wide variety of other biomarkers, including ST2, galectin 3, and GDF15, have been evaluated in patients with AHF, but none is currently recommended for routine use in patients with AHF. In patients in whom the diagnosis of AHF is uncertain, testing to establish alternative causes (e.g., D-dimer to evaluate for pulmonary embolism or procalcitonin to evaluate for evidence of infection) may be very useful.

Chest Radiograph, Electrocardiogram, and Echocardiogram

Chest radiography is usually performed at presentation in patients with dyspnea and is a fundamental test in the evaluation of patients with suspected AHF. In the ADHERE Registry, 90% of patients underwent chest radiography during hospitalization and there was evidence of congestion in more than 80% of these patients. In patients with a background of chronic HF and/or slow onset of symptoms, evidence of congestion on chest x-ray film may be subtle, and frank pulmonary edema is often absent despite substantially elevated filling pressures.

The electrocardiogram (ECG) is another standard diagnostic test that is appropriate in all patients presenting with AHF (**see Chapter 12**). Careful attention for ECG changes suggestive of ischemia is important, since troponin elevation is common in AHF regardless of etiology, and thus many not be a reliable marker of ACS. Arrhythmias are also a common trigger for AHF, and AF is present in 20% to 30%.

Utilization of echocardiography is very high in patients with AHF—more than 80% of patients in EHFS II had an echocardiogram performed during the index hospitalization[14] (**see Chapter 14**). An echocardiogram is generally the single most useful test in evaluating the etiology of the patient with AHF. Echocardiography can assess global systolic and diastolic function, regional wall motion abnormalities, valvular function, hemodynamics including estimates of filling pressures and cardiac output, and pericardial disease. The tissue Doppler ratio of peak early diastolic transmitral blood flow velocity (E) to the peak early-diastolic mitral annular tissue velocity (Ea) (E:Ea ratio) has been shown to be additive to BNP measures in diagnosing AHF patients presenting with dyspnea. An E:Ea ratio greater than 15 predicts a pulmonary capillary wedge pressure (PCWP) greater than 15 mm Hg and has been demonstrated to be accurate in the ED and intensive care settings.

Clinical Triggers

Whereas the preceding section focused on intrinsic mechanisms involved in the pathophysiology of AHF, a variety of specific identifiable clinical triggers may be identified as well. In the OPTIMIZE-HF registry, 61% of enrolled participants had an identifiable clinical precipitant, with pulmonary processes (15%), myocardial ischemia (15%), and arrhythmias (14%) being the most common[38] (**Fig. 24.5**). More than one precipitant was identified in a substantial minority of the study population. Of the identified triggers, worsening renal function was associated with the highest in-hospital mortality (8%), whereas nonadherence to diet or medication or uncontrolled hypertension had a much better prognosis (<2% in-hospital mortality for each).

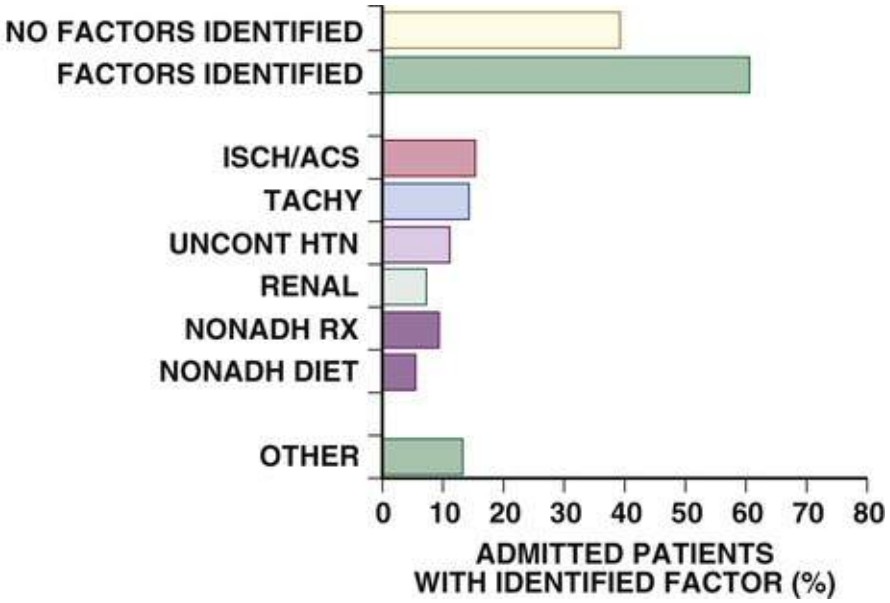


FIGURE 24.5 Identified triggers for acute heart failure hospitalization in the OPTIMIZE-HF Registry. ISCH/ACS, Myocardial ischemia/acute coronary syndrome; TACHY, tachycardia/tachyarrhythmia; UNCONT HTN, uncontrolled hypertension; NONADH Rx, nonadherence to medications; NONADH DIET, nonadherence to diet. (From Fonarow GC et al. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. Arch Intern Med 2008;168:847-54.)

Risk Stratification

Risk stratification can serve as important clinical tools by helping to identify those patients at both ends of the spectrum of risk; patients who are at very high risk may be observed more closely or treated more intensively, whereas patients at low risk may avoid hospitalization altogether or need less rigorous follow-up and monitoring. A variety of predictive models have been developed in AHF, which can generally be divided into two groups: those focused on in-hospital mortality and those focused on postdischarge events (death or rehospitalization).

Predictive Models of in-Hospital Mortality

Data from the ADHERE Registry have been used to develop a classification and regression tree (CART) analysis to identify the best predictors of in-hospital mortality and to develop a risk stratification model.[39] Of the 39 variables evaluated, the CART method identified elevated BUN, lower SBP, and higher serum creatinine at admission to be the best predictors of in-hospital mortality. These three variables allowed for discrimination of groups with very low (2%) or extremely high (22%) in-hospital mortality.

Predictive Models of Postdischarge Events

As noted, there is a substantial risk of mortality or rehospitalization in the first 60 to 90 days after discharge in AHF patients. Some variables may predict mortality but not rehospitalization, and vice versa. In general, models for prediction of mortality have performed better than models focused on the composite of death or rehospitalization, potentially because rehospitalization risk is influenced by a variety of social factors not easily captured in multivariable models. There has been intense focus on preventing rehospitalization in AHF, and as such, models for predicting rehospitalization have been of substantial interest. A few readily available markers have generally been associated with prognosis across multiple studies, as summarized next.

Blood Pressure.
SBP has been found to be an important predictor of outcomes in a variety of studies, with higher blood pressure consistently associated with lower risk. In a detailed analysis of SBP in patients from the OPTIMIZE-HF study, there was a relatively monotonic relationship between blood pressure and mortality across the spectrum of blood pressure, with no evidence of increased risk even at very high levels of blood pressure (>180 mm Hg).[34]

Blood Urea Nitrogen.
Renal function (estimated by BUN, creatinine, and GFR) is an important predictor of prognosis in patients with AHF.[39] Of note, BUN has consistently been shown to be a stronger predictor of outcome than creatinine. BUN appears to integrate a variety of important prognostic aspects, including intrinsic renal function and neurohormonal activation (due to impaired urea clearance).[40,41]

B-Type (Brain) Natriuretic Peptide and N-Terminal Pro-BNP.
BNP and NT-proBNP have been demonstrated to be powerful predictors of risk in HF. In the setting of AHF, natriuretic peptide levels at initial presentation are important predictors of both short-term and long-term outcomes. In the PRIDE study of patients presenting to the ED with unexplained dyspnea, a single NT-proBNP value at initial presentation was an independent predictor of mortality to 1 year.[42] In the ADHERE Registry, admission BNP level was a significant predictor of in-hospital mortality regardless of EF. Data from the OPTIMIZE Registry comparing admission BNP, discharge BNP, and change in BNP over the course of hospitalization identified discharge BNP as the having the greatest power for predicting postdischarge events.[43]

Management of the Patient With Acute Heart Failure

Phases of Management

A central aspect of AHF is the need for urgent care beyond that which may be given in the outpatient setting. The management of AHF patients may be considered in the context of four phases of treatment with distinct goals. To achieve these goals, a seamless integration of the various phases of management with a high level of coordination between the in-hospital and postdischarge caregivers is necessary. Different treatment strategies and a detailed description of various therapies are presented later.

Phase I: Urgent/Emergent Care

The initial goals in the management of a patient presenting with AHF are to expeditiously establish the diagnosis (as previously discussed), treat life-threatening abnormalities, initiate therapies to rapidly provide symptom relief, and identify the etiology and precipitating triggers for the episode of AHF.

Initial therapies may follow the algorithm in **Fig. 24.6**. Insofar as dyspnea is the most common complaint in AHF patients, the initial management of uncomplicated AHF usually targets this symptom.[44] In patients with severe hypoxemia (oxygen saturation [Sa_{O_2}] <90%), O_2 administration is recommended. Although Sa_{O_2} on presentation is inversely related to short-term mortality, inhaled oxygen (Fi_{O_2} ≥0.4) may cause adverse hemodynamic effects (e.g., hyperoxia-induced vasoconstriction) in patients with systolic dysfunction[45] and therefore is not routinely recommended for patients without hypoxemia.[46] In patients with COPD, high Fi_{O_2} concentrations should not be used, to avoid the risk of respiratory depression and

worsening hypercarbia.

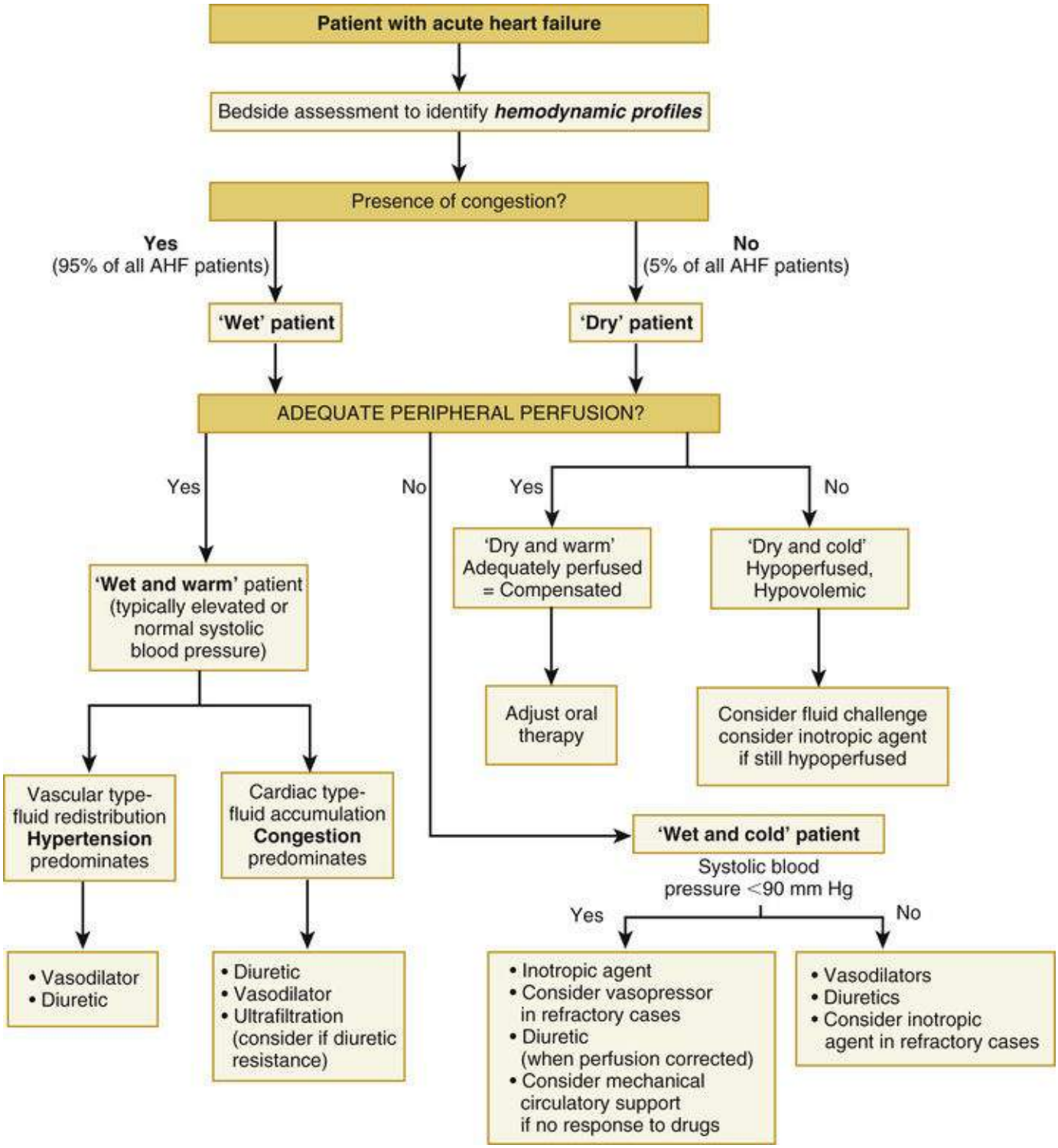


FIGURE 24.6 Algorithm for management of patients admitted with AHF based on degree of congestion and perfusion. (From Ponikowski P et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.)

Early clinical studies and meta-analyses suggest that in patients with cardiogenic pulmonary edema, treatment with continuous positive airway pressure (CPAP) or noninvasive intermittent positive-pressure ventilation (NIPPV) improves symptoms and physiologic variables and reduces the need for invasive ventilation and mortality.[47] The Three Interventions in Cardiogenic Pulmonary Oedema (3CPO) trial

enrolled 1069 patients with pulmonary edema who were randomized to standard O_2 therapy, CPAP, or NIPPV.[48] Noninvasive ventilation (NIV) with CPAP or NIPPV was associated with greater improvement in patient-reported dyspnea, heart rate, acidosis, and hypercapnia after 1 hour of therapy, although it was not associated with a 7-day mortality benefit or a decreased need for intubation compared with standard O_2 therapy. CPAP is typically initiated with a positive end-expiratory pressure (PEEP) of 5 to 7.5 cm H_2O and titrated to 10 cm H_2O as needed for dyspnea relief and improvement in Sa_{O_2}. Contraindications to the use of NIV include immediate need for endotracheal intubation (inability to protect the airways, life threatening hypoxia) and lack of patient cooperation (altered sensorium, unconsciousness, anxiety, inability to tolerate mask). Caution should be used in patients with cardiogenic shock, RV failure, and severe COPD. Potential side effects and complications include anxiety, claustrophobia, dry mucous membranes, worsening RV failure, hypercapnia, pneumothorax, and aspiration. Mechanical ventilation with endotracheal intubation is required in about 4% to 5% of all patients.[14,49] Morphine may be useful in patients with severe anxiety or distress but should be used cautiously or avoided, especially in the presence of hypotension, bradycardia, advanced atrioventricular (AV) block, or carbon dioxide (CO_2) retention. Morphine use has been associated with increased likelihood of mechanical ventilation, intensive care unit (ICU) admission, prolonged hospital stay, and mortality in some retrospective analyses.

Intravenous (IV) loop diuretics are the most frequently administered pharmacologic therapy for AHF; more than 75% of patients in the ED receive IV diuretics, with a mean time to first IV administration of 2.2 hours in ADHERE.[49] Although some patients with volume redistribution rather than hypervolemia may derive benefit from vasodilators alone, symptomatic patients with objective evidence of congestion consistent with pulmonary or systemic venous hypertension or edema should generally receive urgent diuretic therapy for relief of symptoms related to congestion. Initial therapy is typically a bolus injection with a dose between 1 and 2.5 times the patient's oral loop diuretic dose for those receiving chronic diuretic therapy (see later, Diuretics). In the absence of hypotension, vasodilators play an important role in the initial therapy of patients with pulmonary edema and poor oxygenation. A treatment strategy of early initiation of IV nitrate therapy in patients with severe cardiogenic pulmonary edema has been shown to reduce the need for mechanical ventilation and the frequency of MI.[50]

After the emergent care of the patient, evaluation for triage is performed, and a critical decision concerns whether to admit the patient to the hospital. Although low-risk patients may be discharged with careful follow-up, the vast majority who present to the ED with AHF are hospitalized.[51] Although fewer than 5% of HF patients are initially treated in an ED observation unit, these specialized care centers may be effective in decreasing hospitalizations, ICU and critical care unit (CCU) admissions, and related health care costs while maintaining the quality of patient care.[52] In general, hospitalization is recommended for patients with evidence of severe decompensated HF, including hypotension, WRF, or altered mentation; dyspnea at rest associated with either tachypnea or, less often, significant hypoxemia (Sa_{O_2} <90%); hemodynamically significant arrhythmia (usually AF either with rapid ventricular response or new onset); and ACS. Hospitalization should be considered in patients with worsened congestion, even in the absence of dyspnea and often reflected by significant weight gain (≥5 kg), other signs or symptoms of pulmonary or systemic congestion, newly diagnosed HF, complications of HF therapy (e.g., electrolyte disturbances, frequent ICD firings), or other comorbidities.[53]

Specific Clinical Presentations

Atrial Fibrillation with Rapid Ventricular Response (see Chapter 38).

AF with rapid ventricular response is the most common tachyarrhythmia requiring treatment in patients with AHF. It may be difficult to determine with certainty whether the AF was a trigger for AHF or whether progressive HF decompensation led to AF. Although the ventricular response frequently decreases in parallel with the relief of dyspnea, and consequent decreased sympathetic drive, additional therapy may be required. Immediate cardioversion is generally not indicated, except in the unstable patient, because while the patient remains significantly decompensated, cardioversion is associated with a high rate of recurrent AF. In patients with systolic dysfunction, IV digoxin (in the absence of an accessory pathway), cautious use of beta-adrenergic blocker therapy or amiodarone may be used. Diltiazem and other agents that suppress ventricular function should be avoided in patients with significant systolic dysfunction but may be effective in patients with preserved function.

Right Ventricular Heart Failure.

The most common cause of RV HF in AHF is left-sided failure. Isolated RV HF is relatively rare and is generally caused by acute RV infarction, acute pulmonary embolism, or severe pulmonary hypertension. Isolated RV HF caused by an acute RV infarction is best treated with early reperfusion, whereas hemodynamically significant pulmonary embolism may be treated with thrombolytics. Hemodynamic stabilization by optimizing central venous pressure (CVP) with carefully monitored fluid loading (target CVP, approximately 10 to 12 mm Hg), and increasing RV systolic function with IV inotropic support under invasive hemodynamic guidance may also be necessary.[54] Selective pulmonary artery vasodilation by inhaled (NO, prostacyclin analogues) or IV (prostacyclin analogues, sildenafil) agents may improve RV function through decreased afterload. If the patient is mechanically ventilated, normoxia and hypocarbia should be goals using moderate tidal volumes (approximately 8 mL/kg) and as low a PEEP as possible (<12 cm H_2O) to maintain moderate plateau pressures.

Acute Coronary Syndromes (see Chapters 58 and 59).

ACS may be the underlying trigger in patients presenting with AHF, but as previously noted, the diagnosis is confounded by the high prevalence of elevated troponins in AHF itself. These patients may present with chest discomfort, electrocardiographic changes consistent with ischemia, and elevated serum troponin. Aggressive therapy for ACS should be rapidly instituted. In the absence of cardiogenic shock, inodilators should be avoided in patients with ACS and with significant asymptomatic CAD because experimental data have shown that inodilators can cause necrosis of ischemic and hibernating myocardium.

Cardiogenic Shock (see Chapter 59).

Cardiogenic shock is characterized by marked hypotension (SBP <80 mm Hg) lasting more than 30 minutes, associated with severe reduction of cardiac index (usually <1.8 L/min/m^2) despite adequate LV filling pressure (PCWP >18 mm Hg), resulting in organ hypoperfusion. Cardiogenic shock is an unusual presentation of AHF, occurring in less than 4% of the patients in EHFS II,[14] most of whom had MI. Mechanical complications of AMI such a mitral regurgitation, cardiac rupture with ventricular septal defect or tamponade, and isolated RV infarct may also be causes in this setting. IV inotropes or even vasoconstrictors may be required in these patients, with mechanical circulatory support, such as intra-aortic balloon pump (IABP) or left ventricular assist device (LVAD), for critical refractory cases, as a bridge to heart transplant or other mechanical intervention. A variety of newer approaches to provide hemodynamic support are now available, which may permit temporary stabilization until decisions about the appropriateness of other therapies (e.g., durable mechanical support or transplantation) can be made (**see Chapter 29**).

Phase II: Hospital Care

The goals for the management of a patient with AHF during the hospitalization phase are to complete the diagnostic and acute therapeutic processes that were initiated at the initial presentation; to optimize the patient's hemodynamic profile, volume status, and clinical symptoms; and to initiate or optimize chronic HF therapy. Ideally, these goals would be met in a manner to minimize intensive care and total hospital length of stay (LOS). Monitoring of daily weights, fluid intake and output, and vital signs, including orthostatic blood pressure, as well as a daily assessment of symptoms and signs are crucial. Laboratory monitoring should include daily analysis of electrolytes and renal function. Diagnostic evaluations should include an echocardiogram, if not recently performed. Evaluation for myocardial ischemia may be needed if there is suspicion of ischemia as a trigger of decompensation. Dietary sodium restriction (2 g daily) and fluid restriction (2 L daily) may be useful to help treat congestion, although the utility of sodium and fluid restriction in this setting has increasingly been called into question.[55] The increased risk of venous thromboembolism in HF is exacerbated by the decreased mobility of hospitalized patients with AHF, and venous thromboembolism prophylaxis is indicated in all patients unless there is a clear contraindication.

Most outpatient medications should generally be continued during inpatient therapy at existing doses, and it should be recognized that AHF hospitalization represents an opportunity to review and optimize chronic HF therapy. Although changes in renal function may necessitate dose adjustment or temporary discontinuation of RAAS inhibitors, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), angiotensin receptor neprilysin inhibitors (ARNIs), and/or mineralocorticoid receptor antagonists, in general this should be avoided where possible. Patients admitted receiving beta blockers have a lower occurrence of ventricular arrhythmias, a shorter LOS, and reduced 6-month mortality than those not receiving them. Patients who had beta blockers withdrawn had significantly lower outpatient use of beta blockers and higher in-hospital mortality, short-term mortality, and combined short-term rehospitalization and mortality, even after adjustments for potential confounders.[56] Therefore, patients should continue beta-blocker therapy during the admission for AHF, unless significant hypotension or cardiogenic shock are present. Identification of other untreated targets (e.g., revascularization, consideration of CRT in appropriate candidates) should be performed during the hospitalization. The hospitalization phase of AHF management is also an opportunity to provide education and behavioral therapies to patients. Patients should receive specific and clear education about HF, including indications for specific drugs, outpatient monitoring of fluid status through daily weights, self-adjustment of diuretics, exercise programs, and nutritional counseling, as well as possible consultation with physical and occupational therapy. Comorbidities should be aggressively addressed because these often complicate HF management. The hospitalization is also a possible opportunity to enroll the patient in appropriate HF disease management programs.

The Cardiorenal Syndrome in Hospitalized Patients

The cardiorenal syndrome represents one of the greatest therapeutic challenges in the field of AHF (**see Chapter 98**). Although there is no consensus definition to date, in the context of AHF, cardiorenal syndrome is often described as the clinical state where the volume overload of HF is resistant or refractory to treatment due to progressive renal insufficiency. A commonly used practical definition is an increase in serum creatinine of more than 0.3 mg/dL (or 25% decreases in GFR) despite evidence of persistent clinical or hemodynamic congestion. Using this definition, the cardiorenal syndrome occurs in approximately 25% to 35% of the patients admitted with AHF, associated with longer LOS and higher postdischarge mortality.[26] This definition of the cardiorenal syndrome emphasizes the importance of

persistent congestion, because multiple studies have suggested that changes in renal function during successful decongestion therapy are usually transient and may not be associated with adverse outcomes.[29,57]

Although the diagnosis of the cardiorenal syndrome may be straightforward, the clinical management is a major challenge. Since absolute serum creatinine concentrations can be misleading, eGFR should be calculated in patients with AHF. As noted, arterial underfilling from overdiuresis or low cardiac output does not appear to be the most frequent primary cause of WRF, although hypotension can be an important factor.[58] Progressive deterioration of renal function (BUN >80 mg/dL and creatinine >3.0 mg/dL) or hyperkalemia may necessitate discontinuation of RAAS inhibitors, although use of other vasodilators should be considered, either IV (nitroglycerin or nitroprusside) or oral (isosorbide dinitrate and hydralazine). Increasing doses of diuretics are typically required, although diuretic resistance may be profound. The degree of diuretic resistance, sometimes quantified as diuretic efficiency, is known to be associated with increased LOS and adverse prognosis.[59] Although ultrafiltration is often considered in this scenario, clinical trial data have not supported the efficacy or safety of this approach.[60] Overall, the appropriate management of patients with cardiorenal syndrome remains a major unmet clinical challenge in AHF.

In-Hospital Worsening Heart Failure

Traditional assessments of the inpatient course of patients with AHF have generally lacked granularity and focused primarily on in-hospital mortality. However, there has been increasing emphasis from both a clinical and a research perspective on difference in the clinical “trajectory” of patients during inpatient AHF treatment. It is apparent that different patients may have markedly different clinical courses during inpatient therapy for AHF, from relatively uncomplicated courses marked by steady improvement in HF status, to those characterized by progressive deterioration in clinical status[8] (**Fig. 24.7**). Fundamentally, the concept of in-hospital worsening heart failure (WHF) encompasses clinical worsening (as manifest by worsening signs and/or symptoms of HF) that necessitates a significant intensification of therapy. Both terminology and specific definitions of WHF have varied between studies, leading to widely varying estimates of prevalence from 5% to 42% In general, the development of WHF during inpatient AHF therapy is associated with both longer LOS (by about 5 days in a recent pooled analysis), as well as adverse postdischarge outcomes (50% to 100% increase in 30- or 60-day mortality or HF rehospitalization).[61] As expected, different severity of WHF implies different risk, with WHF treated with increased diuretics alone associated with less increase in baseline risk than WHF requiring IV inotropes or mechanical circulatory or respiratory support. Although the definition of WHF continues to evolve, researchers and regulators have shown substantial interest in the concept of WHF as a clinical trial endpoint in AHF studies. WHF is a primary endpoint in two phase 3 AHF studies (TRUE-HF[62] and RELAX-AHF-2[63]; see later).

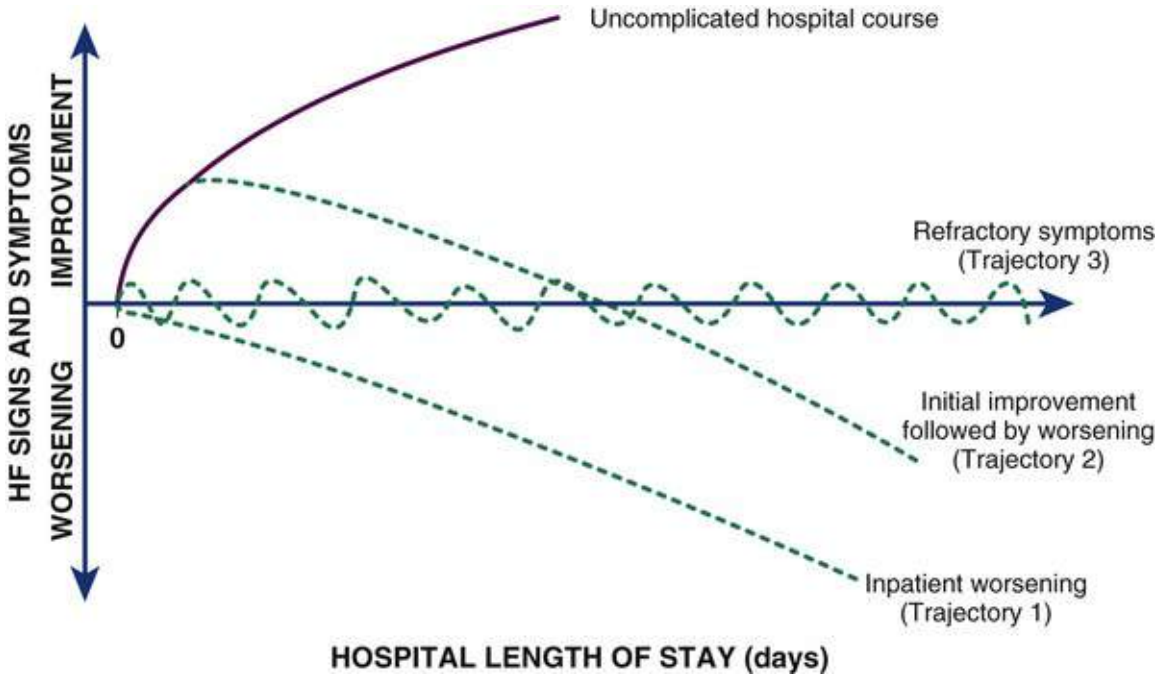


FIGURE 24.7 Various clinical trajectories of patients with acute heart failure during inpatient management. (From Butler J et al. In-hospital worsening heart failure. Eur J Heart Fail 2015;17:1104-13.)

Phase III: Predischarge Planning

The predischarge phase focuses on the goals of evaluating readiness for discharge, optimizing chronic oral therapy, minimizing the side effects of treatments, and ultimately preventing early readmission and improving symptoms and survival. Although there may be considerable pressures to discharge patients rapidly, particularly in the United States, careful optimization of medical regimen before discharge may reduce the risk of subsequent readmissions and improve long-term outcomes.[64] Despite that most patients present with congestion, many are discharged without significant weight loss, and available data demonstrate that persistent clinical congestion at discharge is associated with a high risk for rehospitalization.[65] Similarly, elevations of discharge BNP level have been associated with risk for rehospitalization after discharge.[43] Evaluation of functional capacity with simple maneuvers such as climbing one flight of stairs or walking down the corridor may be a simple and valuable tool to use before discharge.

Pharmacologic therapies known to improve long-term outcomes in chronic HF, such as beta blockers, ACE inhibitors or ARBs, and mineralocorticoid receptor antagonists, should be initiated as soon as reasonable during the hospitalization and before discharge in hemodynamically-stable, appropriate patients. The recent approval of two new therapies for chronic HF with reduced EF (sacubitril/valsartan and ivabradine) has created uncertainty about how to deal with these agents in the setting of AHF. In patients already treated chronically with these agents before this episode of AHF, they should generally be continued during hospitalization (similar to beta blockers and other RAAS inhibitors). To date, there are no data to support the new initiation of either of these agents in hospitalized AHF patients, although several studies are ongoing. Predischarge initiation of a beta blocker increases the proportion of patients receiving appropriate therapy at 60 days and may also reduce 60- to 90-day mortality. Clinical practice guidelines provide general criteria for considerations of hospital discharge, although substantial clinical judgment is still required[66] (**Table 24.4**).

TABLE 24.4

Considerations Before Discharge After Acute Heart Failure Hospitalization

Recommended for All Heart Failure (HF) Patients
Exacerbating factors addressed
Near-optimal volume status observed
Transition from intravenous to oral diuretic successfully completed
Patient and family education completed, including clear discharge instructions
LVEF documented
Smoking cessation counseling initiated
Near-optimal pharmacologic therapy achieved, including ACE inhibitor and beta blocker (for patients with reduced LVEF), or intolerance documented
Follow-up clinic visit scheduled, usually for 7 to 10 days
Should Be Considered for Patients with Advanced HF or Recurrent Admissions for HF
Oral medication regimen stable for 24 hours
No intravenous vasodilator or inotropic agent for 24 hours
Ambulation before discharge to assess functional capacity after therapy
Plans for postdischarge management (scale present in home; visiting nurse or telephone follow-up generally no longer than 3 days after discharge)
Referral for disease management, if available

ACE, Angiotensin-converting enzyme; *LVEF,* left ventricular ejection fraction.

Modified from Lindenfeld J et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. J Card Fail 2010;e1-194.

Phase IV: Postdischarge Management

Early recurrence of signs and symptoms of HF suggestive of worsening volume overload and/or neurohormonal activation are likely to contribute to the high rates of readmission that are observed in AHF.[67] Prompt interventions may therefore allow intervention to prevent the progression of volume overload and new admissions. At least some rehospitalizations for HF appear to be preventable.[68] A series of studies have also investigated the benefits of postdischarge support, especially patient-centered discharge instructions, transition coaches, follow-up telephone calls, and early physician follow-up, although results of these studies have been mixed in terms of impact on outcomes.[69,70] A follow-up appointment is optimally scheduled within 7 to 10 days after discharge, but closer follow-up (<1 week) should be considered for patients with high-risk features.

Treatment Strategies

Targeting Congestion

Treatment strategies for AHF have been largely empiric and limited by an incomplete understanding of its epidemiology and pathophysiology, as well as the relatively blunt nature of the available therapeutic tools (**see Fig. 24.6**). The current general approach focuses on the successful treatment of clinical and hemodynamic congestion, while limiting untoward effects on myocardial or end-organ function, identifying addressable triggers, and optimizing proven long-term therapies. This approach incorporates information from three main aspects of the patient's clinical presentation: blood pressure, volume status, and renal function.

Blood Pressure

Blood pressure (BP) reflects the interaction between vascular tone and myocardial pump function and is one of the most important prognostic indicators in AHF (see above). Most patients present with elevated BP and consequently will benefit from and safely tolerate vasodilator therapy. Vasodilators may decrease preload by reversing venous vasoconstriction and the related central volume redistribution from the peripheral and splanchnic venous systems, and reduce afterload by decreasing arterial vasoconstriction with a resultant improvement in cardiac and renal function. Vasodilators are the primary therapy for AHF

with pulmonary edema, and for nonhypotensive patients with low cardiac output (poor peripheral or central perfusion with SBP >85 to 100 mm Hg). A systematic review of clinical studies supported the ability of vasodilators to improve short-term symptoms and appear safe to administer, but revealed no data suggesting an impact on mortality.[71] However, in an international registry of 4953 patients admitted for AHF (ALARM-HF; 75% admitted to ICU/CCU care settings), analysis of a propensity-based matched cohort of 1007 matched pairs demonstrated improved in-hospital survival in patients treated with vasodilators and diuretics compared to patients treated only with diuretics of 7.8% compared to 11.0% in-hospital mortality, respectively ($P = 0.016$).[72] Interestingly, this difference in survival was particularly evident in patients with SBP less than 120 mm Hg (**Fig. 24.8**). The selection of agent depends on the clinical situation, local practice, and availability (see later, Specific Therapies).

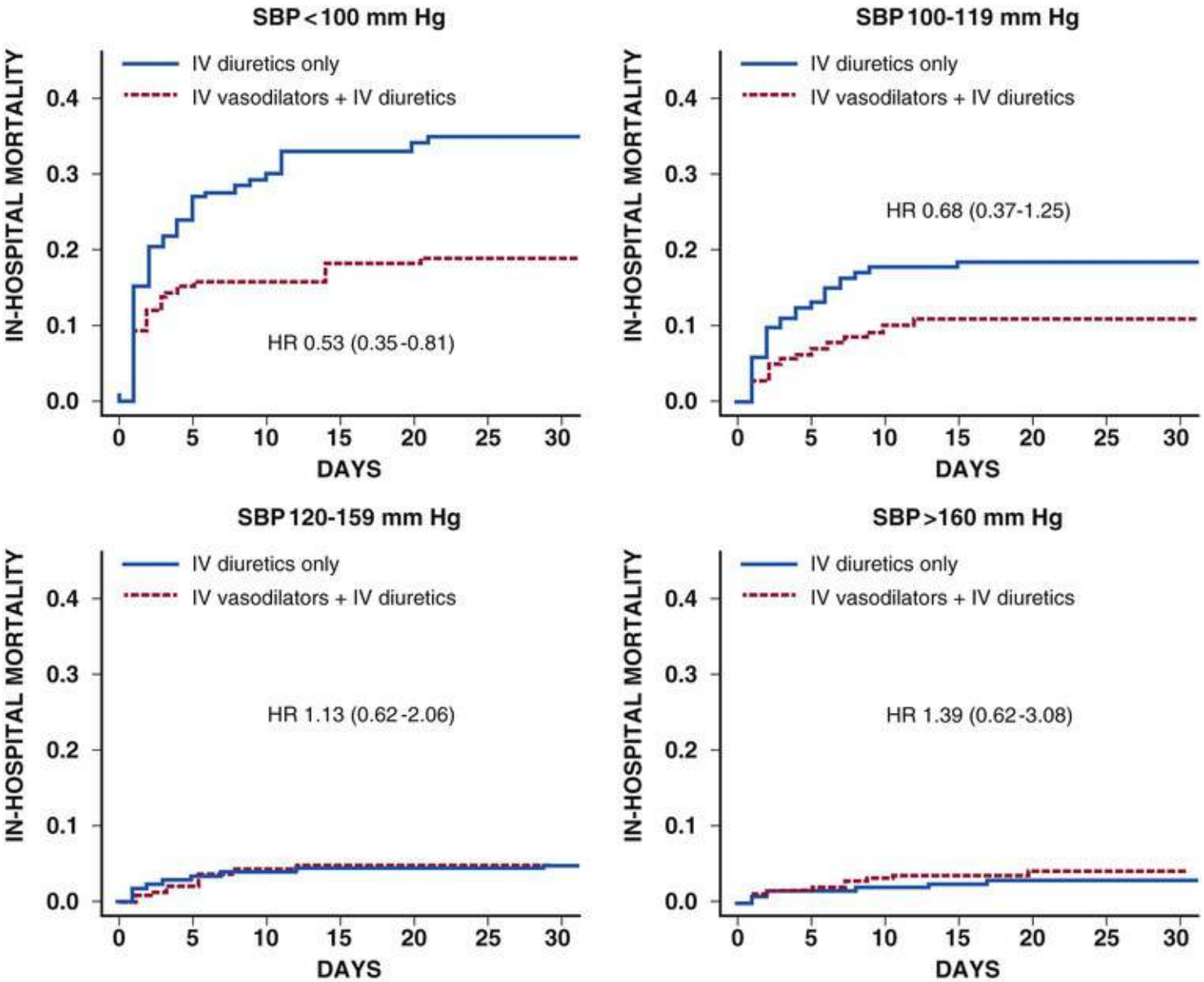


FIGURE 24.8 Effects of IV vasodilators on in-hospital mortality of patients with various levels of systolic blood pressure (SBP). SBP ranged from <100 to ≥160 mm Hg. The number of patients is 318, 334, 668, and 694 for SBP <100, 100-119, 120-159, and ≥160 mm Hg, respectively. HR, Hazard ratio. Values in parentheses are 95% confidence interval. (From Mebazaa A et al. Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods. Intensive Care Med 2011;37:290-301.)

Hypotension (SBP <85 to 90 mm Hg) or signs of peripheral hypoperfusion are poor prognostic signs in

patients with AHF. Treating the potentially reversible, underlying etiologies, such as ACS, pulmonary embolus, and (rarely) hypovolemia, is essential. Hypovolemic hypotension, usually related to overdiuresis, is unusual in patients presenting with symptomatic AHF, and unappreciated volume overload may be present, especially in obese patients in whom neck veins and ascites are difficult to assess. If there is clear evidence of hypovolemia, carefully monitored "fluid challenges" may be attempted, although rapid IV fluid boluses can precipitate congestive symptoms. Asymptomatic hypotension, as an isolated finding in the absence of congestion and poor peripheral or central perfusion, does not require emergent treatment. Inotropic therapy may be indicated for persistent symptomatic hypotension or evidence of hypoperfusion in the setting of advanced systolic dysfunction. An analysis of 954 propensity-matched pairs of patients from the ALARM-HF Registry suggested that IV catecholamine use was associated with 1.5-fold increase in in-hospital mortality for dopamine or dobutamine use and a more than 2.5-fold increase for norepinephrine (NE) or epinephrine use.[72] Specific inotropic agents vary by country and local clinical practice (see specific agents later). In most patients, invasive pulmonary artery catheter monitoring is not necessary, since the measures of urine output, BP, and end-organ function may be clinically evaluated. The use of vasoconstrictors, such as high-dose dopamine, phenylephrine, epinephrine, or NE, should generally be avoided unless absolutely necessary for refractory symptomatic hypotension or hypoperfusion. Rarely, overdosage of afterload-reducing agents can precipitate admissions for AHF with a clinical presentation similar to cardiogenic shock or "pseudosepsis," in which case careful administration of vasoconstrictors may be indicated.

Volume Status

Most patients with AHF have evidence of volume overload, and for patients in whom this is the dominant presenting feature, such as those with significant peripheral edema or ascites, IV diuretics remain the foundation of AHF therapy. Patients with clinically evident congestion typically have 4 to 5 liters of excess volume and amounts greater than 10 liters are not uncommon. The choice of diuretic regimen is influenced by the amount and rapidity of the desired fluid removal and the renal function (see next section). Diuresis addresses the underlying abnormality and frequently improves symptoms and signs of elevated filling pressures. However, IV vasodilator therapy may provide more rapid relief in highly symptomatic patients with evidence of pulmonary congestion. In fact, many patients with hypertensive AHF may require minimal diuretics. Surprisingly, in a study of 131,430 admissions for HF, 11% of the patients received a median of 1 liter of IV fluids, predominantly normal saline, during the first 2 days of hospitalization. Patients receiving IV fluids had increased rates of subsequent critical care admission, intubation, renal replacement therapy, and hospital death compared with those who received only diuretics.[73] Thus, careful attention to volume status is critical because patients' symptoms of congestion may resolve despite persistent hemodynamic congestion (i.e., elevated filling pressures). Hospital discharge before hemodynamic congestion is fully treated appears to be a common cause of rehospitalization.[74]

Renal Function

Renal function is the third main aspect of a contemporary approach to treatment of the patient with AHF (**see Chapter 98**). Treatment of AHF in the presence of normal renal function is generally uncomplicated. Diuretics may be given in standard doses, although renal function, electrolytes, and volume status must be carefully monitored. However, approximately two thirds of patients present with at least moderate renal insufficiency.[25] This may be from preexisting kidney disease or may be a manifestation of worsening HF.

Abnormal renal function is typically associated with some degree of diuretic resistance, and higher doses of diuretics or other strategies may be needed (see later, Diuretics). The important clinical problem of WRF during AHF therapy, the cardiorenal syndrome, is discussed earlier.

Invasive Hemodynamic Strategy

Invasive hemodynamic management with pulmonary artery catheterization (PAC) may be a useful strategy in the management of some patients with AHF. PAC is an invasive procedure that provides detailed hemodynamic data, including direct assessment of filling pressures and cardiac output, and calculation of pulmonary and systemic vascular resistance. Potential risks of PAC include bleeding, infection, arrhythmias, and rare catastrophic events, such as pulmonary artery (PA) rupture or infarction. The use of PAC in the routine management of AHF has been a subject of controversy. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) was a randomized controlled trial (RCT) of 433 patients with severe symptomatic HF despite recommended therapies randomized to receive therapy guided by clinical assessment and PAC or by clinical assessment alone.[75] In ESCAPE, use of PAC did not significantly affect the days alive and out of hospital during the first 6 months (133 versus 135 days), mortality (43 versus 38 deaths), or number of days hospitalized (8.7 versus 8.3 days) compared to clinical assessment alone. Based on the results of the ESCAPE trial, use of PAC in AHF management has declined; in EHFS II, only 5% of patients had a PAC during AHF hospitalization. Importantly, the ESCAPE study excluded patients in whom the treating clinician did not have equipoise about the need for invasive hemodynamic measurement. Invasive hemodynamic assessment with PAC may still play an important role in select patients, especially those with shock or other severe hemodynamic compromise, with oliguria or anuria, or with unclear hemodynamics and poor response to therapy. In patients with advanced HF in whom PAC are used to tailor therapy, an LV filling pressure (as approximated by PCWP) of less than 16 mm Hg, right atrial pressure less than 8 mm Hg, and a systemic vascular resistance between 1000 and 1200 dynes-sec/cm^{-5} are useful targets.

Process of Care, Outcomes, and Quality Assessment

The first point of contact at the admitting hospital for most patients (80%) is the emergency department.[76] Many patients with AHF may be effectively managed in and safely discharged from the ED, and specific algorithms for care and criteria for discharge are evolving.[77] Once the patient with AHF is hospitalized, there appear to be substantial geographic differences in process of care and hospital course worldwide. In the U.S. ADHERE Registry, 23% of patients were admitted to an ICU setting, whereas a substantially higher proportion (51%) had an ICU stay in a similar European registry (EHFS II). Median length of stay is also markedly different across geographic regions, with LOS in the United States being approximately 4 days, more than twice that in Europe (median of 9 days in EHFS II), and even higher in Japan (21 days in ATTEND Registry). These differences in LOS do not appear to be fully explained by differences in case mix or severity of illness. The longer LOS outside the United States is generally associated with lower rates of short-term rehospitalization, although a cause-and-effect relationship is not fully established. A focus on reducing LOS in the United States appears to have been accompanied by an increase in postdischarge events, both mortality and (in particular) rehospitalization.[78] In contrast, in U.S. Veterans Affairs hospitals, HF hospitalizations have increased slightly, whereas 30-day mortality has decreased significantly.[79]

In general, the natural history of AHF is characterized by relatively low in-hospital mortality but a high rate of recurrent postdischarge events (**Table 24.5**). Inpatient mortality in AHF ranges between 3% and

7%, with the notable exception of patients in cardiogenic shock, who have greatly increased in-hospital mortality (40% in EHFS II).[14] Although in-hospital mortality is low, hospitalization for AHF portends a substantial worsening of the clinical course in many patients. In the EVEREST study, despite careful attention to evidence-based care in the context of a large clinical trial, 26% of enrolled patients had died in a median follow-up period of 9.9 months. Of all deaths, 41.0% were caused by HF, 26.0% were sudden cardiac death, 2.6% resulted from acute MI, 2.2% from stroke, and 13.2% from noncardiovascular causes.[80]

TABLE 24.5

Outcomes in Patients with Acute Heart Failure from Select Trials and Registries

STUDY	PATIENTS (*n*)	REHOSPITALIZATION	MORTALITY	
			In-Hospital	Postdischarge
Trials				
ASCEND-HF	7141	6% at 30 days		13% at 6 mo
EVEREST	4133	12% at 30 days	3%	26% at 9.9 mo
RELAX-AHF	1161	9% at 60 days		9% at 6 mo
Registries				
Lee (Canada)	4031	N/A	8.7%	10.6% 30 days 31% 1 yr
ADHERE (US)	187,565	N/A	3.8%	N/A
OPTIMIZE-HF (US)	41,267	30% at 60-90 days	3.8%	8.0% at 60-90 days
Tavazzi (Italy)	2807	38.1% at 6 mo	7.3%	12.8% at 6 mo
EHFS II (EU)	3580	N/A	6.7%	N/A
ATTEND (Japan)	4837	N/A	6.3%	N/A
Damasceno (sub-Saharan Africa)	1006	9% at 60 days (all cause)	4.2%	18% at 6 mo

Data from O'Connor CM et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 2011;365:32-43; Konstam MA et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST outcome trial. JAMA 2007;297:1319-31; Teerlink JR et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet 2013;381:29-39; Lee DS et al. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA 2003;290:2581-7; ADHERE Scientific Advisory Committee. Acute Decompensated Heart Failure National Registry (ADHERE) core module Q1 2006 final cumulative national benchmark report. Paris: Scios; 2006; Gheorghiade M et al. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA 2006;296:2217-26; Tavazzi L et al. Nationwide survey on acute heart failure in cardiology ward services in Italy. Eur Heart J 2006;27:1207-15; Nieminen MS et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients—description of population. Eur Heart J 2006;27:2725-36; Sato N et al. Hyponatremia and in-hospital mortality in patients admitted for heart failure (from the ATTEND Registry). Am J Cardiol 2013;111:1019-25; Damasceno A et al. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries: results of the Sub-Saharan Africa Survey of Heart Failure. Arch Intern Med 2012;172:1386-94.

The Rehospitalization Problem

The high rates of rehospitalization after discharge from a HF hospitalization have become a major focus of clinicians, policymakers, and payers. Claims data using the U.S. Medicare sample suggest striking rate of rehospitalization in elderly patients, with a 30-day rehospitalization rate of 27%, although rates are substantially lower in younger non-Medicare cohorts.[81,82] Rates of rehospitalization within 6 months approach 50% in many cohorts, in particular the elderly. Of note, approximately half the rehospitalizations are not HF related, which underscores the total burden of comorbidity in HF patients as well as the challenges in affecting this event rate with HF-focused interventions. In EVEREST, careful adjudication of postdischarge hospitalizations showed that 46% were for HF, 15% for other CV causes, and 39% for non-CV causes.[80] These rehospitalizations represent a major driver of health expenditures, accounting for over $39 billion spent on HF care per year in the United States.[4] Although controversial, reducing rehospitalization rates for HF has been identified as a major focus of quality improvement and

cost containment by payers such as the U.S. Centers for Medicare and Medicaid Services. As a result, a variety of interventions and initiatives related to inpatient management, discharge planning, and transitions of care have been implemented in an attempt to decrease rehospitalization rates for HF, although the nature, implementation, and effectiveness of these practices have varied widely across health systems.[83] Despite these significant efforts, recent evidence suggests only a minor impact on rehospitalizations.[84] There is also uncertainty about what proportion of rehospitalizations are avoidable, although a systematic review suggests that a quarter or more may be preventable.[68] To date, only improved utilization of proven evidence-based therapies (e.g., beta blockers, ACE inhibitors) during acute hospitalization has been shown to improve postdischarge outcomes.[64] Hospital discharge before congestion is adequately treated appears to be a common cause of early readmission.[74] Early postdischarge follow-up has also been associated with lower rehospitalization rates in retrospective registry data.[70] A variety of other interventions centered on telemedicine, disease monitoring, and disease management remain under active investigation.

Specific Therapies

Diuretics

Loop diuretics are the primary pharmacologic treatment for volume overload in patients with AHF and typically result in rapid symptom relief in most patients[85] (**see Chapter 25**). Loop diuretics (furosemide, torsemide, bumetanide, and ethacrynic acid; **Table 24.6**) can lead to excretion of up to 25% of the filtered sodium, and IV administration avoids variable bioavailability and allows for rapid onset of action, typically within 30 to 60 minutes. Preliminary data suggest that genetic variants modulate the response to furosemide in patients with decompensated HF.[86] Based on the results of the DOSE study, initial doses of approximately 2.5 times the outpatient dose should be considered for patients receiving chronic oral diuretic therapy, with underlying renal dysfunction, or with severe volume overload. Given the steep dose-response curve of these agents, titration should be rapid, with doubling of the dose until an effective response is noted. If there is significant volume overload (>5 to 10 L) or diuretic resistance, a continuous IV infusion can be considered.

TABLE 24.6

Therapeutic Approaches for Volume Management in Acute Heart Failure (AHF)

SEVERITY OF VOLUME OVERLOAD	DIURETIC	DOSE (mg)	COMMENTS
Moderate	Furosemide, or	20-40, or up to 2.5 times oral dose	IV administration preferable in symptomatic patients
	Bumetanide, or	0.5-1.0	Titrate dose according to clinical response.
	Torsemide	10-20	Monitor Na^+, K^+, creatinine, BP
Severe	Furosemide, or	40-160, or 2.5 times oral dose 5-40 mg/hr infusion	Intravenously
	Bumetanide, or	1-4/0.5-2 mg/hr infusion (max, 2-4 mg/hr, limit 2-4 hr)	Bumetanide and torsemide have higher oral bioavailability than furosemide, but IV administration preferable in AHF.
	Torsemide	20-100/5-20 mg/hr	
	Ultrafiltration	200-500 mL/hr	Adjust ultrafiltration rate to clinical response; monitor for hypotension; consider hematocrit sensor.
Refractory to loop diuretics	Add HCTZ, *or*	25-50 twice daily	Combination with loop diuretic may be better than very high dose of loop diuretics alone.
	Metolazone, *or*	2.5-10 once daily	Metolazone more potent if creatinine clearance <30 mL/min
	Chlorothiazide, *or*	250-500 mg IV 500-1000 mg PO	
	Spironolactone	25-50 once daily	Spironolactone best choice if patient not in renal failure and normal or low serum K^+, although may not be very potent
In case of alkalosis	Acetazolamide	0.5	Intravenously
Refractory to loop diuretics and thiazides	Add dopamine (renal vasodilation), *or*		
	dobutamine or milrinone (inotropic agent)		
	Ultrafiltration, or hemodialysis if coexisting renal failure		

Despite their ubiquitous use in AHF, loop diuretics have generally not been tested in rigorously controlled clinical trials. Loop diuretics may lead to neurohormonal activation and electrolyte repletion and have been associated in observational studies with both increased WRF risk and decreased survival, although a recent analysis suggested no relationship between diuretic exposure and 30-day all-cause mortality or HF hospitalization.[87] DOSE, a randomized double-blind study, prospectively compared diuretic strategies in AHF.[88] Using a 2 × 2 factorial design, 308 patients were randomized to treatment with IV furosemide using either twice-daily bolus dosing or continuous infusion and to either a low-dose (equivalent to numerical value of oral outpatient dose given IV) or a high-dose (2.5 times the oral dose given IV) strategy. There was no significant difference in either of the co–primary endpoints of global assessment of symptoms and change in creatinine at 72 hours with administration by bolus compared to infusion or with the low- versus high-dose strategy. The high-dose strategy was associated with greater relief of dyspnea and net fluid loss at 72 hours, although more patients in the high-dose group had a transient increase in creatinine greater than 0.3 mg/dL, which resolved by hospital discharge (**eTable 24.1**). The significance of this finding is unclear; although there were no apparent differences in hospital LOS or days alive out of the hospital, the study was not powered for long-term clinical outcomes. Overall, there were no differences in results between the continuous infusion and intermittent bolus strategies in the clinical trial setting of DOSE, suggesting that whichever approach is most likely to reliably produce the desired diuresis in the particular local clinical practice should be used.

ETABLE 24.1

Results from DOSE Study of Furosemide Strategies in Acute Heart Failure

	Q12 *n* = 156	CONTINUOUS *n* = 152	*P* VALUE	LOW DOSE *n* = 151	HIGH DOSE *n* = 157	*P* VALUE
Primary Endpoints						
Patient Global Assessment VAS AUC at 72 hr	4236 (1440)	4373 (1404)	0.47	4147 (1436)	4430 (1401)	0.06
Change in creatinine at 72 hr (mg/dL)	0.05 (0.3)	0.07 (0.3)	0.45	0.04 (0.3)	0.08 (0.3)	0.21
Secondary Endpoints						
Dyspnea VAS AUC at 72 hr: mean (SD)	4456 (1468)	4699 (1573)	0.36	4478 (1550)	4668 (1496)	0.041
Free from congestion at 72 hr	14%	15%	0.78	11%	18%	0.091
Change in weight at 72 hr: mean (SD)	−6.8 lb (7.8)	−8.1 lb (10.3)	0.20	−6.1 lb (9.5)	−8.7 lb (8.5)	0.011
Net volume loss at 72 hr: mean (SD)	4237 mL (3208)	4249 mL (3104)	0.89	3575 mL (2635)	4899 mL (3479)	0.001
Change in NT-proBNP at 72 hr (pg/mL): mean (SD)	−1316 (4364)	−1773 (3828)	0.44	−1194 (4094)	−1882 (4105)	0.06
Worsening or persistent HF	25%	23%	0.78	26%	22%	0.40
Treatment failure	38%	39%	0.88	37%	40%	0.56
Creatine increase >0.3 mg/dL within 72 hr	17%	19%	0.64	14%	23%	0.041
Length of stay, days (median)	5	5	0.97	6	5	0.55

From Felker GM et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;264:797-805.

In the setting of diuretic resistance, administration of a thiazide-like diuretic that blocks the distal tubule can provide significant augmentation of the diuretic effect.[89] IV chlorothiazide (500 to 1000 mg) or oral metolazone (2.5 to 10 mg) given before the loop diuretic are effective agents, although care must be taken to monitor for hypotension, WRF, and electrolyte abnormalities, which may be profound. NSAIDs can greatly reduce the efficacy of diuretics by reducing renal synthesis of vasodilatory prostaglandins and should be avoided. If hypokalemia is a persistent problem with replacement requirements, administration of a potassium-sparing diuretic, such as spironolactone or eplerenone, should be considered and may also provide synergistic diuretic effects, especially at higher doses,[90] as well as long-term beneficial effects on outcomes (**see Chapter 25**).

Vasodilators

In the absence of hypotension, vasodilators can be used as first-line therapy in combination with diuretics in the management of AHF patients to improve congestive symptoms[91] (**Table 24.7**). As noted, in the ALARM-HF Registry using propensity-matching techniques, patients admitted with AHF and treated with diuretics and vasodilators had significantly better in-hospital survival than patients treated with diuretics alone or those treated with inotropes.[72] However, a more recent analysis of 11,078 patients admitted for AHF demonstrated no mortality benefit at 7, 30, or 365 days,[92] consistent with the findings of a systematic review.[71] After extensive review of these and other data, the UK National Institute for Health and Care Excellence found no evidence to support the routine use of vasodilators in patients with AHF.[93] In practice, however, vasodilators appear to provide symptom relief in these patients. Vasodilators can be classified as (1) predominantly venous dilators, with consequent reduction in preload; (2) arterial dilators, leading to a decrease in afterload; and (3) balanced vasodilators, with combined action on both the venous and the arterial system. Currently available vasodilators include the organic nitrates (nitroglycerin [NTG] and isosorbide dinitrate), sodium nitroprusside, and nesiritide. All these drugs act by activating soluble guanylate cyclase (sGC) in the smooth muscle cells, leading to higher intracellular concentrations of cyclic guanosine monophosphate (cGMP) and consequent vessel relaxation (**see Chapter 23**). These should be used with caution in patients who are preload or afterload dependent (e.g., severe diastolic dysfunction, aortic stenosis, CAD), since these drugs may cause severe hypotension. BP should be monitored frequently and the drug discontinued if symptomatic hypotension develops.

Table 24.7

Intravenous Vasoactive Agents for Treatment of Acute Heart Failure

INTRAVENOUS MEDICATION	INITIAL DOSE	EFFECTIVE DOSE RANGE	COMMENTS
Vasodilators			
Nitroglycerin; glyceryl trinitrate	20 µg/min	40-400 µg/min	Hypotension, headache Tolerance with continuous use after 24 hours
Isosorbide dinitrate	1 mg/hr	2-10 mg/hr	Hypotension, headache Tolerance with continuous use within 24 hours
Nitroprusside	0.3 µg/kg/min	0.3-5 µg/kg/min (usually <4 µg/kg/min)	Caution in patients with active myocardial ischemia Hypotension; cyanide side effects (nausea, dysphoria); thiocyanate toxicity; light sensitive
Nesiritide†††	2 µg/kg bolus with 0.010-0.030 µg/kg/min infusion*	0.010-0.030 µg/kg/min†	Uptitration: 1 µg/kg bolus, then increase infusion rate by 0.005 µg/kg/min no more frequently than every 3 hours, up to maximum of 0.03 µg/kg/min Hypotension, headache (less than with organic nitrates)
Inotropes			
Dobutamine	1-2 µg/kg/min	2-20 µg/kg/min	For inotropy and vasodilation; hypotension, tachycardia, arrhythmias; ?mortality
Dopamine	1-2 µg/kg/min	2-4 µg/kg/min	For inotropy and vasodilation; hypotension, tachycardia, arrhythmias; ?mortality
	4-5 µg/kg/min	5-20 µg/kg/min	For inotropy and vasoconstriction; tachycardia, arrhythmias; ?mortality
Milrinone	25-75 µg/kg bolus over 10-20 min* followed by infusion	0.10-0.75 µg/kg/min	For vasodilation and inotropy; hypotension, tachycardia, arrhythmias; renal excretion; ?mortality
Enoximone††	0.25-0.75 mg/kg	1.25-7.5 µg/kg/min	For vasodilation and inotropy; hypotension, tachycardia, arrhythmias; ?mortality
Levosimendan††	12-24 µg/kg bolus over 10 min followed by infusion	0.5-2.0 µg/kg/min	For vasodilation and inotropy; active metabolite present for ~84 hours; hypotension, tachycardia, arrhythmias; ?mortality
Epinephrine		0.05-0.5 µg/kg/min	For vasoconstriction and inotropy; tachycardia, arrhythmias, end-organ hypoperfusion; ?mortality
Norepinephrine		0.2-1.0 µg/kg/min	For vasoconstriction and inotropy; tachycardia, arrhythmias, end-organ hypoperfusion; ?mortality

*Some clinicians do not administer a bolus dose, to decrease the risk of hypotension. Bolus not recommended in patients with hypotension.

†Lower doses have also been effective in some small studies.

††Not approved for use in all countries.

Nitrates

Organic nitrates are one of the oldest therapies for AHF. These agents are potent venodilators, producing rapid decreases in pulmonary venous and ventricular filling pressures and improvement in pulmonary congestion, dyspnea, and myocardial O_2 demand at low doses. At slightly higher doses and in the presence of vasoconstriction, nitrates are also arteriolar vasodilators, reducing afterload and increasing cardiac output. Nitrates are relatively selective for epicardial, compared to intramyocardial, coronary arteries, resulting in increased coronary blood flow and making them useful for patients with concomitant active myocardial ischemia. The starting dose of nitroglycerin is usually 20 µg/min with rapid uptitration occurring every 5 to 15 minutes in either 20-µg/min increments or doubling of the dose. The dose may initially be titrated to the goal of immediate symptom relief, but a BP reduction of at least 10 mm Hg in mean arterial pressure with SBP greater than 100 mm Hg may be preferable. The nitrate dose may need to be reduced if SBP is 90 to 100 mm Hg and will often need to be discontinued with SBP less than 90 mm Hg. IV nitrates use appears to be more common in Europe than in the United States (38% in EHFS-II but only 9% in ADHERE).[14,49] Organic nitrates may also be administered orally, sublingually, or by spray, allowing for convenient emergent treatment before establishing IV access.

There is limited clinical trial experience with organic nitrates. Early administration of high-dose IV nitrates is beneficial in improving arterial oxygenation and potentially preventing some consequences of AHF (MI, need for mechanical ventilation), compared to furosemide alone[50] or noninvasive ventilation,[94]

although these studies were small and not blinded. In a study designed to evaluate nesiritide in patients with dyspnea at rest from decompensated HF, nitroglycerin treatment in 143 patients demonstrated nonsignificant, mild decreases in PCWP and no significant improvement in patient-assessed dyspnea within 3 hours, but the dose was remarkably low (42 µg/min).[95] In a small, single-site substudy [96] in which nitroglycerin was aggressively uptitrated to a mean dose of 155 µg/min by 3 hours, there were significant decreases in PCWP (4 to 6 mm Hg decrease from baseline) from 1 to 12 hours, but no difference at 24 hours. The major limitation of organic nitrates is the tolerance that typically develops within 24 hours. Headache is the most common adverse effect (20% within 24 hours[95]). Symptomatic hypotension (5%) may also be noted, but generally resolves when nitrate therapy is discontinued. Given the risk of severe hypotension with potentially catastrophic consequences, the recent use of phosphodiesterase 5 inhibitors (sildenafil, tadalafil, vardenafil) should be ruled out before administration of nitrates.

Sodium Nitroprusside

Sodium nitroprusside (SNP) induces a balanced reduction in afterload and preload that is exquisitely titratable, because of a very short half-life (seconds to a few minutes), and is particularly effective in the setting of markedly elevated afterload (e.g., hypertensive AHF) and moderate-severe mitral regurgitation. IV administration is usually monitored with an indwelling arterial line, although automated BP cuffs are now used in many centers. Titration of the SNP dose to rapidly improve symptoms and to achieve an SBP of 90 to 100 mm Hg are typical goals, and invasive PACs may assist in meeting other hemodynamic goals. Tapering the dose of SNP before discontinuation is advised to avoid the possibility of “rebound hypertension.” Physician discomfort with the cyanide metabolites and the historical institutional requirements for invasive arterial monitoring has limited the use of this highly effective therapy to fewer than 1% of patients with AHF in Europe and the United States.[14,49]

Nitroprusside, a prodrug that is rapidly metabolized to NO and cyanide, has no inherent arrhythmogenic properties, may improve myocardial O_2 demand by reducing afterload and wall stress, creates no significant electrolyte disturbances, and is rarely toxic. Despite its potency, severe hypotension is unusual and rapidly resolves. However, significant vasodilation of the intramyocardial vasculature has been noted, possibly producing a coronary steal phenomenon; and consequently, nitroprusside is not recommended for patients with active myocardial ischemia. The most common complaints with nitroprusside are related to the cyanide metabolite, including nausea, abdominal discomfort, dissociative feelings, and dysphoria. Cyanide rarely accumulates in patients, but impaired hepatic function and doses greater than 250 µg/min for more than 48 hours increase this risk. The thiocyanate metabolite can accumulate in patients with moderate to severe renal insufficiency when exposed to prolonged infusions of high doses (usually >400 µg/min) over days and is usually not relevant in the treatment of AHF. Cyanide levels may be measured but rarely return in a timely fashion to be useful.

There are no randomized studies of nitroprusside in patients with AHF, although multiple studies demonstrated dramatic reduction in PCWP (15 mm Hg) and marked increases in cardiac output, associated with increases in diuresis and natriuresis and decreased neurohormonal activation. In a contemporary analysis of 175 consecutive patients admitted for AHF, IV SNP was associated with greater hemodynamic improvement and lower rates of inotropic support or WRF during hospitalization and with lower rates of all-cause mortality after discharge than nitroprusside, despite a worse

hemodynamic profile at baseline.[97]

Nesiritide

Nesiritide (recombinant human BNP) is identical to endogenous BNP and causes potent vasodilation in the venous and arterial vasculatures, resulting in significant reductions in venous and ventricular filling pressures and mild increases in cardiac output. As with other vasodilators, nesiritide may reduce diuretic requirements, but in clinical studies, there is limited evidence for a significant direct “natriuretic” effect. Nesiritide may be used for treatment of patients with acutely decompensated congestive heart failure (CHF) who have dyspnea at rest or with minimal activity, but it should not be administered for the indication of replacing diuretics, enhancing diuresis, protecting renal function, or improving survival. An optional bolus of 2 µg/kg followed by a 0.01 µg/kg/min infusion is the recommended starting dose for nesiritide. There is limited clinical trial experience with uptitration of the drug, but for patients who remain symptomatic with evidence of volume overload and sufficient BP, uptitration may be considered. Nesiritide has clear effects on hemodynamics and has limited need for frequent dose adjustments and an absence of tolerance, but its high cost and lack of clear clinical benefit beyond other, less expensive, more readily titratable agents have limited its use.

The Vasodilation in the Management of Acute CHF (VMAC) trial randomized 489 patients with decompensated CHF and dyspnea at rest to placebo, nitroglycerin, or nesiritide.[95] After 3 hours, patients receiving nesiritide had a significantly greater decrease in PCWP compared to both nitroglycerin and placebo, and improvement in dyspnea compared to placebo (no difference from nitroglycerin). A pooled analysis of the RCT data suggested that nesiritide may be associated with an increased risk of WRF as well as increased mortality. To address these issues, the ASCEND-HF trial randomized 7141 patients with AHF to nesiritide or placebo for 24 to 168 hours.[98] At 30 days, there was no difference between the two groups with regard to the composite endpoint of death or rehospitalization for HF. The clinical effects on dyspnea were relatively modest and have generally not been regarded as clinically important compared to placebo (**Fig. 24.9**). Use of nesiritide had no impact on WRF but was associated with an increase in the rate of hypotension. Another small study (ROSE-AHF) enrolled 360 patients admitted for AHF specifically to assess the effect of low-dose nesiritide on congestion and renal function.[99] In this study, nesiritide had no beneficial effect on urine output or cystatin C or on any of the other secondary endpoints reflective of decongestion, renal function, or clinical outcomes, although it was associated with more symptomatic hypotension.

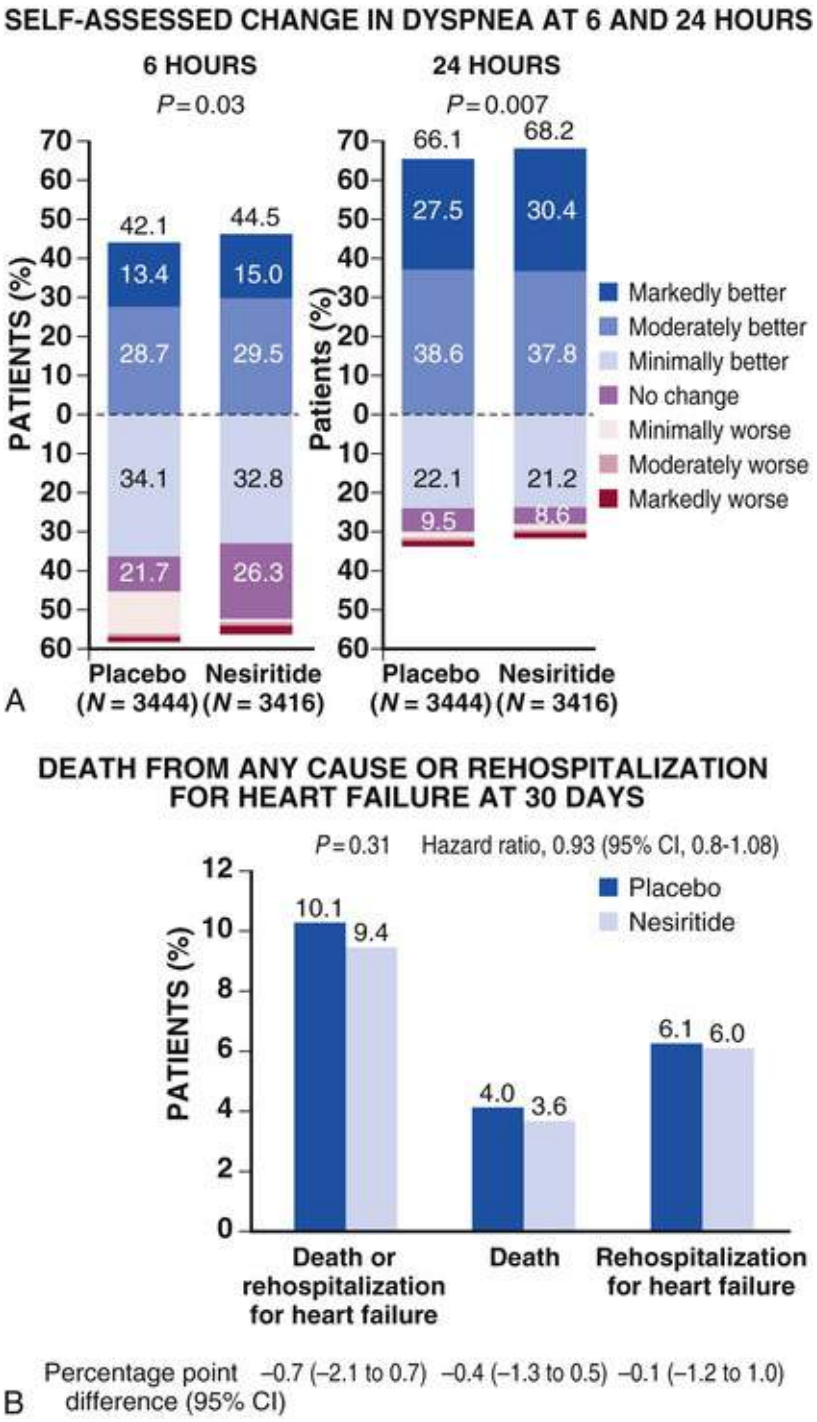


FIGURE 24.9 Changes in dyspnea at 6 and 24 hours **(A)** and the primary clinical endpoints at 30 days **(B).** In **A,** numbers above the bars indicate overall percentage of patients who reported being markedly or moderately better after receiving study treatment (i.e., those represented by percentages above *dashed line*). (From O'Connor CM et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 2011;365:32-43.)

Nesiritide exerts its activity via guanylyl cyclase–linked natriuretic peptide receptors (NPR A and B) causing cGMP-mediated vasodilation. Hypotension, at times prolonged (>2 hours)[95] despite the relatively short (18-minute) half-life of the peptide, is more common in patients with volume depletion, and consequently, nesiritide use should be limited to those with congestive signs and symptoms. Headache also occurs, but less often than with nitroglycerin. Other actions of nesiritide include neurohormonal antagonism with reduction in vasopressin, aldosterone, and sympathetic tone and alteration of intrarenal hemodynamics and glomerular filtration. Nesiritide did not improve urine output

or renal function in AHF patients with worsening creatinine.[99]

Inotropes and Inodilators

The inotropic drugs and inodilators (inotropic drugs with vasodilatory properties), increase cardiac output through cAMP-mediated inotropy and reduce PCWP through vasodilation.[100] (**Table 24.7**). However, retrospective data from both registries and trials of AHF patients suggest that even the short-term use (hours to few days) of IV inotropes (except for digoxin) is associated with significant side effects, such as hypotension, atrial or ventricular arrhythmias, and an increase in in-hospital[72] and possibly long-term mortality.[101] Patients with CAD may be at higher risk of adverse events due to reduced coronary perfusion and increased myocardial O_2 requirements with possible myocardial ischemia and injury. Therefore, these agents are reserved for use in select situations of hypoperfusion when other interventions are inappropriate or have failed. The use of these drugs should be limited to patients with reduced EF, who present with low SBP (<90 mm Hg) or low measured cardiac output in the presence of signs of congestion and organ hypoperfusion, such as decreased mentation or reduced urine output.[10,53] Despite these recommendations, inotropes are still frequently used in patients with HFpEF in some regions. Inotropic agents for AHF should be used with close hemodynamic and telemetry monitoring and stopped as soon as adequate organ perfusion is restored. All these agents may increase conduction through the AV node, causing a rapid ventricular response in patients presenting with AF. Additionally, IV inotropes may be employed in cardiogenic shock as a temporary therapy to prevent hemodynamic collapse or as a life-sustaining bridge to more definitive therapy for those patients awaiting mechanical circulatory support, ventricular assist devices (VADs), or cardiac transplantation. In North American and European registries, approximately 15% and 25% of patients were treated with inotropic agents, although given the minimal supportive clinical evidence, there is marked local variability in the use of these drugs.[102]

Dobutamine

Dobutamine is the most commonly used positive inotrope in Europe and the United States, despite evidence that it increases mortality.[103,104] Dobutamine at doses of 1 to 2 µg/kg/min may improve renal perfusion in patients with cardiogenic shock, although higher doses (5 to 10 µg/kg/min) may be necessary for more profound hypoperfusion. Tachyphylaxis may occur with infusions of more than 24 to 48 hours, partially because of receptor desensitization. In general, dobutamine (or dopamine) is the preferred inotrope in patients with significant hypotension and in the setting of significant renal dysfunction, given the renal excretion of milrinone. Concomitant beta-blocker therapy will result in competitive antagonism of the effects of dobutamine, and higher doses of dobutamine (10 to 20 µg/kg/min) may be required to obtain the desired hemodynamic effects. The lowest effective dose of dobutamine should be used in the context of continuous BP and rhythm monitoring. The patient should be gradually weaned off dobutamine and the clinical status reevaluated with each dose adjustment. Temporary adjustments to afterload-reducing agents or diuretics may assist in weaning.

As an agonist of both $beta_1$- and $beta_2$-adrenergic receptors with variable effects on the alpha receptors, dobutamine has multiple actions (**see Chapter 22**). Beta receptor stimulation results in increased inotropy and chronotropy through increases in intracellular cAMP and calcium, as well as by direct

activation of voltage-sensitive calcium channels. At low doses, stimulation of $beta_2$ and alpha receptors causes vasodilation, resulting in decreased aortic impedance and systemic vascular resistance with reduction in afterload and indirect increases in cardiac output. At higher doses, vasoconstriction can ensue with decreased venous capacitance and increased right atrial pressure. Adverse effects of dobutamine include tachycardia, increasing ventricular response to AF, increased atrial and ventricular arrhythmias, myocardial ischemia, and possibly cardiomyocyte necrosis from direct toxic effects and induction of apoptosis.[105]

Hemodynamic and other effects of dobutamine have been studied, but there has been only one placebo-controlled randomized trial in patients with AHF. Although some methodologic concerns exist, the Calcium Sensitizer or Inotrope or None in Low Output Heart Failure (CASINO) study demonstrated significantly increased mortality with dobutamine compared to placebo, consistent with the results of other studies of this class of drugs.[103]

Dopamine

In both the United States and Europe, dopamine is used as often as dobutamine, presumably as a vasoconstrictor and for its putative effects on renal vasodilation. As a precursor to the synthesis of NE, an agonist of both adrenergic and dopaminergic receptors, and an inhibitor of NE uptake, dopamine has complex effects that vary significantly with dose. Initiation of dopamine therapy causes a rapid release of NE that can precipitate tachycardia, as well as atrial and ventricular arrhythmias. In addition, intermediate to high doses can cause significant vasoconstriction, precipitating HF and poor perfusion. Patients should be gradually weaned from these doses down to 3 to 5 µg/kg/min and then discontinued, to avoid potential hypotensive effects of low-dose dopamine.

Low-dose dopamine (≤2 µg/kg/min) has been proposed to cause specific dilation of renal, splanchnic, and cerebral arteries, potentially increasing renal blood flow in a selective manner, as well as promoting natriuresis through direct distal tubular effects. The DAD-HF study of 60 patients admitted for AHF suggested that a combination of low-dose furosemide and low-dose dopamine resulted in comparable urine output and dyspnea relief, but improved renal function profile and potassium homeostasis, compared to high-dose furosemide.[106] However, the DAD-HF II study of 161 patients found no beneficial effect of the addition of low-dose dopamine to furosemide.[107] In the ROSE-AHF study of 360 patients hospitalized with AHF, low-dose dopamine did not increase urine volume during 72 hours, did not improve cystatin C concentrations, but did reduce hypotension and increased tachycardia compared to placebo.[99] Therefore, there appears to be no indication for low-dose dopamine therapy to improve renal function.

Intermediate-dose dopamine (2 to 10 µg/kg/min) results in enhanced NE release, stimulating cardiac receptors with an increase in inotropy and mild stimulation of peripheral vasoconstricting receptors. Since the positive inotropic effect is largely dependent on myocardial catecholamine stores, which are often depleted in patients with advanced HF, dopamine is a poor inotrope in patients with severe systolic dysfunction.

High-dose dopamine (10 to 20 µg/kg/min) causes peripheral and pulmonary artery vasoconstriction, mediated by direct agonist effects on $alpha_1$ receptors. These doses pose a significant risk of precipitating limb and end-organ ischemia and should be used cautiously.

Epinephrine

Epinephrine is a full beta receptor agonist and a potent inotropic agent with balanced vasodilator and vasoconstrictor effects. The direct effect of epinephrine on increasing inotropy independent of myocardial catecholamine stores makes epinephrine a useful agent in the treatment of transplant patients with denervated hearts.

Phosphodiesterase Inhibitors

Cyclic adenosine monophosphate (cAMP) is a ubiquitous signaling molecule that increases inotropy, chronotropy, and lusitropy in cardiomyocytes and causes vasorelaxation in vascular smooth muscle (**see Chapter 22**). Phosphodiesterase (PDE) IIIa is compartmentalized in the cardiac and vascular smooth muscle, where it terminates the signaling activity of cAMP by degrading it to AMP. Many specific inhibitors of PDE IIIa, such as milrinone and enoximone, have been developed to provide organ-specific improvements in hemodynamics through increasing myocardial and vascular smooth muscle cell cAMP concentrations. In theory, subcellular localization may allow stimulation of inotropy without increasing heart rate with low doses of highly specific PDE inhibitor. The independence of the mechanism from adrenergic receptors bypasses receptor downregulation, desensitization, and antagonism by beta blockers. Although studies have shown improved hemodynamic efficacy with PDE inhibitors compared to dobutamine in patients receiving beta-blocker therapy, such limitations of dobutamine's effects are not typically clinically relevant. In addition, this mechanism allows for synergistic effects with beta receptor agonists, such as dobutamine. Such combination therapy may be useful in patients with greatly reduced LV systolic function. PDE inhibitors cause significant peripheral and pulmonary vasodilation, reducing afterload and preload while increasing inotropy. These effects make PDE inhibitors well suited for patients with LV dysfunction and pulmonary hypertension or for post-transplant patients.

Milrinone.

Although the most frequently used PDE inhibitor, only 3% of patients in ADHERE[49] and less than 1% in EHFS II[14] received milrinone. Therapy may be initiated with a 25- to 75-µg/kg bolus over 10 to 20 minutes, although in clinical practice the bolus dose is usually omitted. Infusions are typically started at 0.10 to 0.25 µg/kg/min and may be uptitrated to hemodynamic effect. Given the elimination half-life of 2.5 hours and the pharmacodynamic half-life of more than 6 hours, effects from uptitration are delayed by at least 15 minutes after dosage adjustment. Also because of these pharmacodynamics, patients who have had prolonged administration of milrinone may have delayed deterioration, so they should be observed for at least 48 hours after cessation. Milrinone is renally excreted, necessitating dose adjustment in the presence of renal dysfunction or substitution with dobutamine. Milrinone has many side effects, including hypotension and atrial and ventricular arrhythmias. In OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure),[108] 951 patients admitted with exacerbation of systolic HF not requiring IV inotropic support were randomized to milrinone or placebo infusion. There was no difference in the primary endpoint of days hospitalized for cardiovascular causes with 60 days, but significant increases in sustained hypotension and new atrial arrhythmias were noted in the milrinone-treated patients. In addition, a post hoc subgroup analysis demonstrated increased mortality in patients with an ischemic etiology of HF who received milrinone.[101] This study reinforces the caution that must be exercised in selecting PDE inhibitors for the treatment of patients with AHF.

Enoximone.
This PDE IIIa inhibitor is available in Europe. Enoximone dosing is essentially one-tenth that of milrinone, with a bolus dose of 0.25 to 0.75 µg/kg over 10 to 20 minutes, followed by an infusion of 1.25 µg/kg/min. Enoximone is extensively metabolized by the liver into renally cleared active metabolites, so doses should be reduced in the setting of either renal or hepatic insufficiency. Otherwise, the previous comments apply to this PDE inhibitor as well.

Levosimendan

Levosimendan is a novel agent that increases myocardial contractility and produces peripheral vasodilation, through cardiac myofilament calcium sensitization by calcium-dependent (systolic) troponin C binding and activation of vascular smooth muscle potassium channels, respectively. Levosimendan also has some PDE inhibitor activity, which some contend is responsible for its inotropic activity in patients.[109] Levosimendan was administered to almost 4% of patients in EHFS II[14] and is available in more than 40 countries (although not in the United States), where it is used in patients with reduced LV systolic function and hypoperfusion in the absence of severe hypotension. Although it may be given with a bolus of 12 to 24 µg/kg over 10 minutes, many clinicians directly initiate a continuous infusion at 0.05 to 0.10 µg/kg/min, which may be uptitrated to 0.2 µg/kg/min. In clinical trials, levosimendan significantly increased cardiac output, reduced PCWP and afterload, and improved dyspnea. The potent vasodilating effects of levosimendan can cause significant hypotension, the risk of which may be reduced by maintaining filling pressures.[100] Levosimendan has an active, acetylated metabolite with a half-life longer than 80 hours, allowing it to have hemodynamic effects days after discontinuation of the infusion.

Initial clinical studies demonstrated reduced arrhythmias and improved survival with levosimendan compared to placebo and dobutamine. REVIVE-II (Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy Versus Placebo in the Short Term Treatment of Decompensated Heart Failure), a recent study of 600 patients, demonstrated significant improvement in the clinical status, serial BNP, and hospital LOS with levosimendan treatment compared to standard care, but there were also more episodes of hypotension, AF, and ventricular ectopy, as well as a nonsignificant increase in early mortality at 14 to 90 days.[110] SURVIVE (Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support trial) randomized 1327 patients with systolic dysfunction, evidence of low cardiac output, and dyspnea at rest despite diuretics and vasodilators to either levosimendan or dobutamine. An early reduction in mortality was not sustained through 180 days, but levosimendan was associated with a greater incidence of AF and lower incidence of worsening HF compared to dobutamine.[111]

Vasopressors

These agents should be reserved for patients with marked hypotension in whom central organ hypoperfusion is evident. Vasopressors will redistribute cardiac output centrally at the expense of peripheral perfusion and increased afterload. *Norepinephrine* is a potent agonist of the $beta_1$ and the $alpha_1$ receptors but is a weaker agonist of $beta_2$ receptors, resulting in marked vasoconstriction. In general, NE is the preferred vasopressor for cardiogenic shock.[10] In the SOAP II trial, 1679 patients with shock were randomized to either dopamine or NE with a nonstatistical difference increase in mortality with dopamine associated with a significant increase in arrhythmic events.[112] In a subgroup analysis

including the 280 patients with cardiogenic shock, NE had improved survival compared to dopamine. *Phenylephrine* is a selective alpha$_1$ receptor agonist with potent direct arterial vasoconstrictor effects. This agent may be used in patients with severe hypotension, particularly when the hypotension is related to systemic vasodilation, rather than to a decrease in cardiac output. As noted above, *dopamine* may also be used for its vasoconstrictor properties. All these agents may induce end-organ hypoperfusion and tissue necrosis.

Other Pharmacologic Therapies

Digoxin.

Digoxin rapidly improves hemodynamics without increasing heart rate or decreasing BP and may be considered in patients with a low BP caused by low cardiac output.[113] Digoxin may be used intravenously with an initial bolus of 0.5 mg. It should be given slowly because rapid administration may cause systemic vasoconstriction. The initial bolus should be followed by an oral or IV dose of 0.25 mg at least 12 hours after the initial dose. In patients who continue to have signs and symptoms of HF, digoxin therapy should be continued in addition to other therapies, with a dose resulting in a trough serum concentration less than 1 ng/mL. Ischemia, hypokalemia, or hypomagnesemia may increase the likelihood of developing digitalis intoxication, even at the therapeutic doses. Digoxin should not be used in patients with moderate to severe renal impairment, ongoing ischemia, or advanced AV block.

Arginine Vasopressin Antagonists.

Arginine vasopressin (AVP), also known as antidiuretic hormone, is the main regulator of plasma osmolality. Vasopressin levels are inappropriately high in both acute and chronic HF and are thought to have a major role in the pathophysiology of HF. In particular, vasopressin appears to be the major contributor to the development of the hyponatremia observed in patients with HF. In patients with AHF, volume overload, and persistent hyponatremia at risk for or having active cognitive symptoms, therapy with an AVP antagonist for short-term improvement in serum sodium concentration may be considered. Currently available AVP antagonists are *tolvaptan* (an oral, selective V_2 receptor antagonist) and *conivaptan* (V_{1a}/V_2 receptor antagonist for IV use). Although both agents have been approved for the treatment of clinically significant hypervolemic and euvolemic hyponatremia, they have not been shown to be improve long-term outcomes in HF and are not currently approved for this indication. The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) was an international trial that evaluated more than 4000 patients admitted with AHF and reduced EF. Tolvaptan added to standard therapy for AHF modestly improved signs and symptoms during hospitalization and modestly reduced body weight without affecting renal function, heart rate, or BP, but postdischarge survival and readmission rate were not affected by chronic postdischarge therapy with tolvaptan.[114,115] Two recent, small, double-blind studies of short-term therapy with tolvaptan compared to placebo in AHF did not show a clinically important benefit of tolvaptan therapy in this setting.[116] In patients with AHF, the addition of conivaptan to standard therapy increased urine output without a significant improvement in signs/symptoms or a decrease in body weight.[117]

Calcium Channel Blockers.

CCBs without significant myocardial depressant effects, such as *nicardipine* and *clevidipine*, may be potentially useful in patients with AHF presenting with severe hypertension refractory to other therapies. In a pilot study of 104 patients with hypertensive AHF who exhibited pulmonary congestion, clevidipine

rapidly provided significant BP control associated with improvement in dyspnea compared to standard of care.[118]

Other Nonpharmacologic Therapies

Ultrafiltration

Peripheral ultrafiltration is an available modality to remove sodium and water in hospitalized patients with HF. The theoretical advantage of ultrafiltration is the removal of isotonic fluid, resulting in greater and more reliable salt removal, potentially without the neurohormonal activation seen with diuretics.[85] Potential limitations of ultrafiltration include the need for large-bore venous access, systemic anticoagulation, and increased complexity of nursing care related to management of the device. Although theoretically attractive, the appropriate use of ultrafiltration in AHF remains uncertain.

The Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial randomized 200 patients with AHF to venovenous ultrafiltration or standard of care within 24 hours of initial presentation. Patients receiving ultrafiltration demonstrated a greater reduction in body weight at 48 hours, but no improvements in dyspnea or renal function.[119] Intriguingly, there was a reduction in postdischarge events at 90 days with ultrafiltration, although the number of events was small. Other recent studies have assessed the optimal use of ultrafiltration in HF. In an observational study of 63 patients with persistent congestion refractory to hemodynamically guided intensive medical therapy, slow continuous ultrafiltration resulted in improved hemodynamics, yet was associated with high incidence of subsequent transition to renal replacement therapy and high in-hospital mortality.[120] The Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS) randomized 188 patients with AHF, WRF, and persistent congestion to a strategy of stepped pharmacologic care (IV diuretics dosed by investigator to maintain urine output of 3 to 5 L/day plus IV vasodilators or inotropes if needed to achieve target urine output) or ultrafiltration (fluid removal rate, 200 mL/hr).[60] Ultrafiltration resulted in similar weight loss (approximately 12 pounds) but resulted in an increase in creatinine levels, compared to standard care, and was associated with more serious adverse events, especially kidney failure, bleeding complications, and IV catheter-related complications. CARRESS enrolled a high-risk population with a composite rate of death or rehospitalization at 60 days greater than 50%. The AVOID-HF study (Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure) was designed as an 810-patient trial that was terminated early after 224 patients were enrolled. Although underpowered, there were trends suggesting longer time to first HF event and fewer HF and cardiovascular events in the adjustable ultrafiltration group compared to those randomized to adjustable IV loop diuretics.[121] There was no difference in renal function, but more patients assigned to ultrafiltration experienced adverse events.

Hypertonic Saline.

Administration of hypertonic saline solution (HSS, 3%) along with high-dose furosemide and sodium and fluid restriction may be associated with greater diuretic and clinical response. The SMAC-HF study randomized 1771 patients hospitalized for AHF to a single-blind strategy of HSS (150 mL 3% normal saline [NS]) plus furosemide (250-mg IV bolus twice daily) and sodium restriction to 120 mmol/day versus furosemide (250-mg IV bolus twice daily) and sodium restriction to 80 mmol/day; both groups

received a fluid intake of 1000 mL/day.[122] After discharge, the HSS group continued with 120 mmol Na/day; the second group continued with 80 mmol Na/day. There was a shorter LOS, increased creatinine clearance at discharge, reduced readmission rate, and improved survival for patients in the HSS group. These hypothesis-generating data are intriguing, but they are limited by the unblinded study design and the potential confounding by postdischarge management. Larger, prospective, blinded trials are needed to evaluate this therapeutic approach further before adoption for clinical practice.

Novel Therapies

Most of the large clinical trials of new therapies for AHF have been negative in terms of efficacy and safety (**Table 24.8**). A variety of potential explanations have been proposed, including lack of drug efficacy, patient selection, timing of therapy, and endpoints.[123] Nonetheless, given the diverse pathophysiology of AHF, it may be unrealistic to expect that a single drug would exert beneficial effects in all patients with AHF. There remain areas of significant unmet need in the treatment of AHF, including vasodilators with proven clinical benefits, agents that improve myocardial performance without significant adverse effects, and agents that improve or protect renal function. There are a number of interesting compounds that are undergoing development and clinical evaluation.

Table 24.8

Select Clinical Trials for Patients with Acute Heart Failure

TRIAL	TREATMENT ARMS	POPULATION	RESULTS
VMAC (2002) *n* = 489	Nesiritide (Nes; 0.01-0.03 μg/kg/min with optional 2-μg/kg bolus; from 24 hr up to 7 days) vs. placebo (only during first 3 hr) vs nitroglycerin (NTG; from 24 hr up to 7 days)	Dyspnea at rest ≥2 signs of HF within 72 hours CXR with pulmonary edema	Change in PCWP, at 3 hr (1°): −5.8 mm Hg Nes, −3.8 mm Hg NTG, −2 mm Hg placebo ($P < 0.001$); at 24 hr: −8.2 mm Hg Nes, −6.3 mm Hg NTG ($P < 0.04$) Self-evaluation of dyspnea at 3 hr, Likert (1°): Nes vs. placebo, $P = 0.03$; Nes vs. NTG, $P = 0.56$; at 24 hr: NTG vs. Nes, $P = 0.13$ Self-evaluation of global clinical status, at 3 hr: Nes vs. placebo, $P = 0.07$; Nes vs. NTG, $P = 0.33$; at 24 hr: NTG vs. Nes, $P = 0.08$
OPTIME-HF (2002) *n* = 951	Milrinone (0.5 μg/kg/min, titratable to 0.75) vs. placebo, for 48-72 hr	Presenting within 48 hr Known systolic HF LVEF ≤40%	Days with CV hospitalization or dead in 60 days (1°): milrinone, 12.3 vs. placebo 12.5 ($P = 0.71$) Failure of therapy due to adverse event within 48 hr: milrinone 20.6% vs. placebo 9.2% ($P < 0.001$) Excess sustained hypotension ($P = 0.004$), new atrial fibrillation/flutter ($P < 0.001$), VT/VF ($P = 0.06$)
ESCAPE (2005) *n* = 433	Pulmonary artery catheter (PAC)–guided therapy vs. clinical assessment (CA)–guided therapy	LVEF ≤30% SBP ≤125 mm Hg ≥1 sign *and* ≥1 symptom of HF 3-mo duration of HF symptoms despite ACE inhibitor and diuretics	Days alive out of hospital during 6 mo (1°): PAC, 133 days vs. CA, 135 (HR 1.00; 95% CI 0.82-1.21; $P = 0.99$) Greater number of adverse events in PAC group
VERITAS (2007) *n* = 1435	Tezosentan (Tezo; 5 mg/hr for 30 min, followed by 1 mg/hr for 24-72 hr) vs. placebo	Presenting within 24 hr Persistent dyspnea Respiratory rate ≥24 bpm At least two of: elevated BNP/NT-proBNP, clinical pulmonary edema, CXR with congestion, LV systolic dysfunction	Change in dyspnea AUC, 24 hr (1°): VERITAS-1, Tezo −562 vs. placebo −550 mm/hr ($P = 0.80$); VERITAS-2, Tezo −367 vs. placebo −342 ($P = 0.60$) Death or worsening HF, 7 days: VERITAS-1 and -2, Tezo 26.3% vs. placebo 26.4 ($P = 0.95$)
SURVIVE (2007) *n* = 1327	Levosimendan (Levo; loading 12 μg/kg, followed 0.1-0.2 μg/kg/min; for 24 hr) vs. dobutamine (Dob; 5 μg/kg/min, titratable up to 40 μg/kg/min; for at least 24 hr)	LVEF ≤30% Requiring IV inotropic support At least one of following: dyspnea at rest, oliguria, PCWP ≥18 mm Hg or CI ≤2.2 L/min/m^2	All-cause mortality, 180 days (1°): Levo, 26% vs. Dob 28% (HR 0.91; 95% CI 0.74-1.13; $P = 0.40$) Change in BNP from baseline to 24 hr: Levo, −631 vs Dob, −397, $P < 0.001$ No change in dyspnea at 24 hr, days alive out of hospital at 180 days, all-cause mortality at 31 days, CV mortality at 180 days
EVEREST (2007) *n* = 4133	Tolvaptan (Tol; 30 mg PO qd) vs. placebo, for at least 60 days	Randomized within 48 hr NYHA III-IV symptoms LVEF ≤40% Signs of volume expansion	Composite of changes in global clinical status and body weight, 7 days (1°): $P < 0.001$, for Tol superiority; no difference in clinical status; change in body weight, 1 day: Tol, −1.76 kg vs. placebo, −0.97; $P < 0.001$ All-cause mortality (1°): Tol, 25.9% vs. placebo 26.3% (HR 0.98, 95% CI 0.87-1.11, superiority $P = 0.68$; noninferiority $P < 0.001$ CV death or HF hospitalization (1°): Tol, 42.0% vs. placebo 40.2% (HR 1.04, 95% CI 0.95-1.14, superiority $P = 0.55$

UNLOAD (2007) *n* = 200	Ultrafiltration (UF; fluid removal titrated by investigator up to 500 mL/hr) vs. diuretic (titrated by investigator, at least twice daily oral dose), for 48 hr	Randomized within 24 hr ≥2 signs of congestion	Weight loss, 48 hr (1°): UF, −5.0 kg vs. diuretics, −3.1, *P* = 0.001 Dyspnea score, 48 hr (1°): UF, 6.4 vs. diuretics, 6.1; *P* = 0.35 HF rehospitalization, 90 days: UF, 0.22 vs. diuretics, 046, *P* = 0.022; days rehospitalized: UF, 1.4 days vs. diuretics, 3.8; *P* = 0.022; unscheduled HF visits: UF, 21% of patients vs. diuretics, 44%, *P* = 0.009
3CPO (2008) *n* = 1069	Noninvasive positive-pressure ventilation (NIPPV) vs. continuous positive airway pressure (CPAP) vs. oxygen therapy (O_2)	Clinical diagnosis of cardiogenic pulmonary edema CXR with pulmonary edema Respiratory rate >20 bpm Arterial pH <7.35	All-cause mortality, 7 days (1°): NIPPV + CPAP 9.5% vs. O_2 9.8% (OR 0.97, 95% CI 0.63-1.48; *P* = 0.87) Composite death or intubation, 7 days (1°): NIPPV + CPAP, 11.1% vs. O_2 11.7% (OR 0.94, 95% CI 0.59-1.51; *P* = 0.81) NIPPV + CPAP better than O_2: change in arterial pH, 1 hr (*P* < 0.001); dyspnea score, 1 hr (*P* = 0.008)
DAD-HF (2010) *n*=60	Dopamine 5 μg/kg/min plus low-dose furosemide (5 mg/hr continuous infusion) vs. high-dose furosemide (20 mg/hr continuous infusion	Hospitalized for ADHF with evidence of volume overload and eGFR ≥30 mL/min/1.73 m^2	SCr increase >0.3 mg/dL within 24 hr (1°): 6.7% low-dose dopamine/low-dose furosemide vs. 30% high-dose furosemide, *P* = 0.042 >20% decrease in eGFR within 24 hr (1°): 10% low-dose dopamine/low-dose furosemide vs. 33.3% high-dose furosemide, *P* = 0.057
PROTECT (2010) *n* = 2033	Rolofylline 30 mg vs. placebo for up to 3 days	Randomized within 24 hr, persistent dyspnea at rest or with minimal activity, estimated CrCl 20-80 mL/min, BNP ≥500 pg/mL or NT-proBNP ≥2000 pg/mL, IV loop diuretic therapy	Clinical composite (1°): OR for rolofylline 0.92, 95% CI 0.78-1.09, *P* = 0.35
DOSE (2011) *n* = 308	Low-dose vs. high-dose furosemide Continuous vs. intermittent intravenous bolus 1 : 1:1 : 1 2 × 2 factorial design	Randomized within 24 hr ≥1 sign and ≥1 symptom of HF, history of chronic HF treated with furosemide 80-240 mg/day (or equivalent) for at least 1 mo	Global assessment of symptoms (1°): 4236 ±1440 AUC bolus vs. 4373 ±1404 AUC continuous infusion, *P* = 0.47; 4171 ±1436 AUC low dose vs. 4430 ±1401 AUC high dose, *P* = 0.06 Mean change in SCr (1°): 0.05 mg/dL bolus vs. 0.07 mg/dL continuous infusion, *P* = 0.45; 0.04 mg/dL low dose vs. 0.08 mg/dL high dose, *P* = 0.21
ASCEND-HF (2011) *n* = 7141	Nesiritide (Nes) 0.01 μg/kg/min with optional 2 μg/kg bolus (from 24 hr up to 7 days) vs. placebo)	Hospitalized for ADHF, dyspnea at rest, or with minimal activity, ≥1 sign and ≥1 objective measure of ADHF, randomized within 24 hr of first IV treatment for ADHF	Self-reported dyspnea moderately or markedly better at 6 hr: 42.1% placebo vs. 44.5% Nes, *P* = 0.03*; at 24 hr: 66.1% placebo vs. 68.2% Nes, *P* = 0.007* Death or rehospitalization for HF at 30 days: 10.1% placebo vs. 9.4% Nes (HR 0.93, 95% CI 0.8-1.08, *P* = 0.31)
CARRESS-HF (2012) *n* = 188	Ultrafiltration (UF) vs. stepped pharmacologic care (Pharm)	Develop cardiorenal syndrome before (within 6 wk) or after (within 7 days from admission) hospitalization	Change in creatinine level: UF +0.23 mg/dL vs. Pharm −0.04 ±0.53 mg/dL, *P* = 0.003 Weight loss: 5.5 ±5.1 kg [12.1 ±11.3 lb] in Pharm group vs. 5.7 ±3.9 kg [12.6 ±8.5 lb] in UF group, *P* = 0.58 Serious adverse events: 72% in UF group vs. 57% in Pharm group, *P* = 0.03
RELAX-AHF (2013) *n* = 1161	Serelaxin (Ser) 30 μg/kg/day vs. placebo for 48 hours	Patients with dyspnea at rest or on minimal exertion, congestion on chest x-ray, BNP ≥350 ng/L (or NT-proBNP ≥1400 ng/L), eGFR 30-75 mL/min/1.73 m^2, and SBP >125 mm Hg	Change in dyspnea by VAS AUC to day 5 (1°): 19% improvement by Ser compared to placebo by VAS AUC (448 mm/hr, 95% CI 120-775), *P* = 0.007 Proportion of patients with moderately or markedly improved dyspnea by Likert scale at all 3 early timepoints (6, 12, 24 h; 1°): Ser 27% vs. placebo 26%, *P* = 0.70 Days alive out of hospital up to day 60: Ser 48.3 vs. placebo 47.7, *P* = 0.37 180-day mortality: placebo 65 deaths vs. Ser 42, HR 0.63 (95% CI 0.43-0.93), *P* = 0.02
REVIVE-2 (2013) *n* = 600	Levosimendan (Levo; loading 12 μg/kg, followed by 0.1-0.2 μg/kg/min; for 24 hr) vs. placebo	Dyspneic at rest LVEF ≤35%	Clinical composite endpoint, 5 days (1°): Levo superior, *P* = 0.015 More frequent hypotension and cardiac arrhythmias, during the infusion period; numerically higher risk of death, 90 days (REVIVE-1 and -2: Levo, 49 deaths/350 patients; vs. placebo, 40/350, *P* = 0.29)
ROSE (2013) *n* = 360	Dopamine (2 μg/kg/min; *n* = 122) Nesiritide (0.005 μg/kg/min without bolus; *n* = 119) Pooled placebo group (*n* = 119)	Acute heart failure Renal dysfunction (eGFR 15-60 mL/min/1.73 m^2) Randomized within 24 hr of admission	Compared to placebo: Dopamine: no significant effect on 72-hr cumulative urine volume or on change in cystatin C level; increased tachycardia Nesiritide: no significant effect on 72-hr cumulative urine volume or on change in cystatin C level
DAD-HF II (2014) *n* = 161	8-hour continuous infusions of (a) high-dose furosemide (HDF, *n* = 50, 20 mg/hr), (b) low-dose furosemide and low-dose dopamine (LDFD, *n* = 56, 5 mg/hr and 5 μg kg^{-1} min^{-1}, respectively), or (c) low-dose furosemide (LDF, *n* = 55, furosemide 5 mg/hr)	Dyspnea on minimal exertion or rest dyspnea Oxygen saturation <90% on admission ABGs One or more of (a) signs of congestion, (b) interstitial congestion or pleural effusion on chest x-ray, and (c) elevated serum BNP levels	No significant differences in 60-day and 1-year all-cause mortality and hospitalization for HF, dyspnea relief (Borg index), worsening renal function, and LOS
AVOID-HF (2016) *n* = 224 (810 planned)	Adjustable ultrafiltration (AUF; *n* = 110)) Adjustable IV loop diuretics (ALD; *n* = 114).	Chronic daily oral loop diuretics Fluid overload Received ≤2 IV loop diuretic doses Randomized within 24 hr of admission	Estimated days to first HF event 62 for AUF group vs. 34 for ALD group, *P* = 0.106 At 30 days, fewer HF and CV events for AUF vs. ALD group Renal function changes similar More AUF patients with adverse events
ATOMIC-AHF (2016) *n* = 606	3 sequential cohorts (~200 patients per cohort): Cohort 1: Omecamtiv mecarbil (OM, target plasma concentration 115 ng/mL) vs. placebo Cohort 2: OM (target plasma concentration, 230 ng/mL) vs.	LVEF ≤40% Dyspnea at rest or with minimal exertion Elevated natriuretic peptides Randomized within 24 hr of initial IV diuretic.	Dyspnea relief: no significant difference vs. placebo (3 OM dose groups and pooled placebo: placebo, 41%; OM cohort 1, 42%; cohort 2, 47%; cohort 3, 51%; *P* = 0.33); increased dyspnea relief in cohort 3 at 48 hr (placebo, 37% vs. OM, 51%; *P* = 0.034) and through 5 days (*P* = 0.038) Plasma concentration-related increases in LVEF (*P* < 0.0001) and decreases in end-systolic dimension (*P* < 0.05).

	placebo Cohort 3: OM (target plasma concentration 310 ng/mL) vs. placebo		
BLAST-AHF (2016) *n* = 621	a. Placebo (*n* = 183) b. TRV027 1 mg/hr (*n* = 128) c. TRV027 5 mg/hr (*n* = 182) d. TRV027 25 mg/hr (*n* = 125)	History of HF Elevated natriuretic peptides ≥2 physical HF signs SBP ≥120 and ≤200 mm Hg eGFR (sMDRD) 20-75 mL/min/1.73 m^2 Excluded if use of ARBs 7 days prior, IV inotropes or vasopressors within 2 hours prior, or IV nitrates within 1 hr prior to randomization	1° endpoint (multiple outcomes, analyzed as composite z-score), including (1) time from baseline to death through day 30, (2) time from baseline to HF rehospitalization through day 30, (3) first assessment timepoint after worsening HF through day 5, (4) change in dyspnea VAS AUC representing change from baseline over time from baseline through day 5, and (5) initial LOS (in days) from baseline: no difference in any group
TACTICS (2016) *n* = 257	a. Placebo (*n* = 128) b. Tolvaptan (Tol) (*n* = 129)	Acute HF within 24 hr of presentation Elevated natriuretic peptides + 1 additional sign or symptom of congestion Serum sodium ≤140 mmol/L	Dyspnea relief by Likert scale similar between Tol and placebo at 8 hr (25% moderately or markedly improved for Tol vs. 28% placebo, *P* = 0.59) and at 24 hr (50% Tol vs. 47% placebo, *P* = 0.80); proportion defined as responders at 24 hr (1°) 16% for Tol and 20% for placebo, *P* = 0.32; Tol resulted in greater weight loss and net fluid loss vs. placebo, but Tol patients more likely to experience worsening renal function during treatment
TRUE-AHF (2017) *n* = 2157	a. Placebo (*n* = 1069) b. Ularitide (Ula) (*n* = 1088)	Men or women, age 18-85 Unplanned hospitalization or ED visit for acutely decompensated HF Dyspnea at rest, worsening within past week Evidence of HF on CXR BNP >500 pg/mL or NT-proBNP >2000 pg/mL Persistence of dyspnea at rest despite ≥40 mg of IV furosemide (or equivalent) Systolic BP ≥116 and ≤180 mm Hg Start of study drug infusion within 12 hr after initial clinical assessment	Cardiovascular death (1°): Ula 235 deaths, placebo 225; HR = 1.03 (96% CI 0.85-1.25); *P* = 0.75; hierarchical clinical composite at 48 hr (1°): *P* = 0.82 2°: Intensive care LOS during first 120 hours, hospital length of stay during first 30 days, episodes of in-hospital WHF during first 120 hours, proportion with WHF during first 120 hours, rehospitalization for HF within 30 days of hospital discharge, duration (hr) of IV therapy for HF during index admission, all-cause mortality or CV hospitalization at 6 months: all NS; change in NT-proBNP at 48 hr: 47% decrease with Ula, *P* < 0.001; change in serum creatinine during first 72 hr: increased with Ula, *P* = 0.005 Adverse events: hypotension: placebo 10.1% vs. Ula 22.4%; no difference in renal events
RELAX-AHF-2 (2017) *n* = 6545	a. Placebo (*n* = 3271) b. Serelaxin (Ser) (*n* = 3274)	Patients with dyspnea at rest or on minimal exertion, congestion on CXR, BNP ≥500 ng/L (or NT-proBNP ≥2000 ng/L), eGFR >25-75 mL/min/1.73 m^2, SBP >125 mm Hg	Cardiovascular death (1°): Ser 285 deaths, placebo 290; HR = 0.98 (95% CI:0.83-1.15); *P* = 0.39; WHF through day 5 (1°): Ser 6.9%, placebo 7.7%, HR = 0.89 (95% CI 0.75-1.07); *P* = 0.097

*Did not meet prespecified U.S. regulatory requirement of significance.

1°, Primary endpoint; 2°, secondary endpoint(s); *ADHF,* acute decompensated heart failure; *ABGs,* arterial blood gases; *BNP,* B-type natriuretic peptide; *CV,* cardiovascular; *CXR,* chest x-ray film; *eGFR,* estimated glomerular filtration rate; *HF,* heart failure; *LOS,* length of stay; *LVEF,* left ventricular ejection fraction; *PCWP,* pulmonary capillary wedge pressure; *VAS AUC,* visual analog scale score calculated as area under curve; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia; *WHF,* worsening heart failure.

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Vasodilating Agents.

A variety of novel molecules with vasodilator properties are in development as therapeutics for AHF.[91]

Serelaxin.

Relaxin was first identified as a major hormone of pregnancy with powerful systemic and renal vascular effects, as well as beneficial effects on cardiac preconditioning and ischemia, inflammation, fibrosis, and apoptosis. Serelaxin (recombinant human relaxin-2) demonstrated encouraging effects in a dose-finding pilot study of 234 patients with AHF.[124] The Phase III RELAX-AHF (Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure) trial enrolled 1161 patients within 16 hours of presentation who had dyspnea, congestion, mild to moderate renal insufficiency, and SBP greater than 125 mm Hg and randomized them to standard of care with a 48-hour infusion of either serelaxin (30 µg/kg/day) or placebo.[125] The trial demonstrated efficacy of serelaxin in improving dyspnea as quantified by the area under the curve of the change from baseline dyspnea visual analog scale over 5 days, which was associated with improvements in signs of congestion, decreased in-hospital WHF, shorter LOS, and both CV and all-cause mortality at 180 days. There were no significant changes in the dyspnea score, as assessed by the 7-level Likert scale over the first 24 hours, and no endpoint related to HF rehospitalization. Serelaxin treatment was also associated with improved markers of end-organ damage or dysfunction, including cardiac, renal, and hepatic markers.[24] There were no serious adverse events of hypotension or other safety signals in the serelaxin-treated patients. Mechanistic studies have confirmed serelaxin's beneficial effects on hemodynamics[126] and renal function.[127] Based on the promising results of RELAX-AHF, the RELAX-AHF-2 trial enrolled more than 6600 patients admitted for AHF and evaluated the effects of serelaxin compared to placebo on the independently powered primary endpoints of WHF through 5 days and 180-day CV mortality.[63] In this large global outcomes study, serelaxin did not improve either the primary endpoint of CV mortality at 180 days or WHF through day 5 compared to placebo.[128]

Ongoing analyses of data from RELAX-AHF-2 and prior studies of serelaxin may provide additional insights into these results, but at present the data do not support a role for the routine use of serelaxin in patients with AHF.

Natriuretic Peptides.

Multiple different natriuretic peptides continue to be developed and investigated for the treatment of AHF, including naturally-occurring and alternatively spliced peptides and chimeric designer peptides. *Urodilatin*, a modified version of pro-ANP, is a 32–amino acid hormone synthesized and secreted from the distal tubules of the kidney that regulates renal sodium absorption and water homeostasis via binding to NPR1 receptors and increasing intracellular cGMP levels. *Ularitide*, a synthetically produced urodilatin, has demonstrated beneficial effects on hemodynamics and symptom relief in two studies of patients with AHF.[129] The TRUE-AHF trial enrolled 2157 patients with symptomatic AHF and randomized them to a 48-hour infusion of either ularitide (15 ng/kg/min) or placebo. Ularitide did not significantly improve either primary endpoint of clinical composite through 5 days or CV mortality during the course of the study. Ularitide had no beneficial effect on any secondary endpoint without evidence of end-organ protection and increased creatinine associated with a doubling of hypotension.[130]

Neurohormonal Antagonists.

Direct renin inhibitors (DRIs) block the first enzymatic step in the RAAS cascade, leading to a profound suppression of this neurohormonal system (**see Chapters 23 and 25**). Given the role of RAAS in the pathogenesis and complications of HF, as well as the improved survival associated with its inhibition, further blockade of this system may confer additional survival benefits. *Aliskiren* is the first oral DRI on the market and currently approved for the treatment of hypertension. The ASTRONAUT trial enrolled 1639 hemodynamically stable patients at a median 5 days after admission for AHF with EF less than 40%, elevated natriuretic peptides, and signs or symptoms of fluid overload who were randomized to daily oral aliskiren or placebo.[131] Aliskiren treatment was associated with higher rates of hyperkalemia, hypotension, and renal impairment/failure compared to placebo after a median follow-up of 11.3 months, but there was no difference in CV death or HF rehospitalization at 6 or 12 months.

Endothelin receptor antagonists block the actions of ET-1, the most powerful endogenous vasoconstrictor produced by the vascular endothelial cells. It exerts its effects by binding to two receptors, ET_A and ET_B, located on the vascular smooth muscle cells, resulting in significant systemic arterial vasoconstriction. *Tezosentan*, a nonselective ET_{A-B} antagonist, has been shown to improve hemodynamics in patients with AHF. The Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Study (VERITAS) studied more than 1400 patients admitted with AHF in a large international trial. The addition of IV tezosentan to standard therapy did not improve symptoms nor decrease worsening HF or mortality at 7 days after randomization.[132] Another approach to neurohormonal antagonism in AHF included the angiotensin II type I receptor beta-arrestin–biased ligand *TRV027*, which increases signaling of the beta-arrestin–mediated pathways stimulating inotropy while simultaneously antagonizing the classic G-protein angiotensin II–signaling pathways. The BLAST-AHF study enrolled 621 patients admitted with AHF in a dose-ranging study of a 48- to 96-hour infusion of TRV027 compared to placebo.[133] TRV027 conferred no benefit over placebo at any dose with regard to the primary composite endpoint or any of the individual components, although there were no significant safety issues.

Soluble Guanylate Cyclase Activators and Stimulators.

Cinaciguat is the first compound in a new class of vasodilators. Their mechanism of action is similar to that of organic nitrates (and their end product NO), since both classes of drugs activate the soluble form of guanylate cyclase (sGC) in smooth muscle cells, thus leading to the synthesis of cGMP and subsequent vasodilation. Cinaciguat has been shown to improve hemodynamics in patients with AHF; at high doses, however, it has been associated with significant hypotension, which resulted in the termination of early

clinical studies.[134] *Vericiguat* is an oral sGC stimulator studied in patients enrolled within 4 weeks of a WHF event. In the SOCRATES-Reduced study of 456 patients, vericiguat did not significantly improve log-transformed NT-proBNP concentrations compared to placebo, but there was a suggestion of a dose-response effect.[135]

Inotropic Agents

Cardiac Myosin Activators.

A new mechanistic class of agents designed to increase myocardial contractility, cardiac myosin activators increase the transition rate from the weakly bound to the strongly bound state necessary for initiation of a force-generating power stroke. Unlike current inotropes, these agents increase the systolic ejection time without altering the rate of LV pressure development, resulting in increased stroke volume and cardiac output without increases in intracellular cAMP or calcium. *Omecamtiv mecarbil* is the first agent of this class to undergo human testing. In both healthy volunteers and patients with chronic stable HF with reduced EF, administration of omecamtiv mecarbil produced dose-dependent increases in systolic ejection time, fractional shortening, stroke volume, and EF and was well-tolerated over a broad range of plasma concentrations.[136] In a phase IIb dose-finding study of 606 patients with AHF (ATOMIC-AHF), IV omecamtiv mecarbil did not meet the primary endpoint of dyspnea improvement compared to the pooled placebo, but it was generally well tolerated, increased systolic ejection time, and improved dyspnea in the high-dose group.[137]

Istaroxime.

The prototype of a new class of drugs, istaroxime exerts its actions on the myocyte in two ways: by stimulation of the membrane-bound Na^+,K^+-ATPase pathway and by enhancing the activity of the sarcoendoplasmic reticulum Ca^{2+}-ATPase type 2a (SERCA2a). These two distinct mechanisms result, respectively, in increased cytosolic calcium accumulation during systole, with positive inotropic effects, and in rapid sequestration of cytosolic calcium into the sarcoplasmic reticulum during diastole, leading to an enhanced lusitropic effect. The HORIZON-HF study evaluated 120 patients admitted with AHF and decreased EF. The addition of istaroxime to standard therapy lowered PCWP and heart rate and increased SBP. The higher infusion dose increased cardiac index and reduced LV end-diastolic volume. There were no changes in neurohormones, renal function, or troponin I levels during the short, 6-hour infusion.[138,139]

Renoprotective Agents.

Therapeutics to prevent or treat acute kidney injury (AKI) and maintain or improve renal function in the setting of AHF are an important unmet need. *Adenosine A_1 receptor antagonists* have been developed to increase renal blood flow and enhance diuresis without activating the tubuloglomerular feedback. *Rolofylline* is a highly selective adenosine A_1 receptor antagonist that has been studied in patients with HF. Despite the positive trends seen in the PROTECT-Pilot study, the Phase III PROTECT trial failed to show any clinical benefit, including renal protection,[140] and was associated with more seizure and stroke events compared to placebo. Given these results, it is doubtful that these agents will undergo further evaluation in AHF.

Future Perspectives

Acute heart failure remains one of the most challenging cardiovascular problems, with unacceptably high postdischarge rehospitalization and mortality rates. The development of new therapies has been a

persistent challenge over recent decades, and most patients are still treated primarily with intravenous loop diuretics. Current management consists primarily of treating the manifestations of the syndrome rather than central pathophysiologic derangements. Improvement in understanding of underlying pathophysiology and better targeting of treatments to specific patient groups most likely to benefit will potentially provide greater success in developing efficacious new therapies for AHF. Given the heterogeneity of the AHF population, it is unlikely that a “one therapy fits all” approach will lead to an improvement in outcomes. While new therapies are sought, continued efforts to improve and standardize the use of “best practices” in terms of process of care, transitions of care, and postdischarge follow-up, will potentially allow us to better utilize currently available therapies to improve outcomes from this highly morbid condition.

Guidelines

The Hospitalized Patient

G. Michael Felker and John R. Teerlink

The most significant addition to the 2009 American College of Cardiology and American Hospital Association (ACC/AHA) updated guidelines was inclusion of specific new recommendations regarding the hospitalized patient (**Table 24G.1**). Although there were a number of new class I indications involving the diagnosis of heart failure, the use of B-type natriuretic peptide and N-terminal pro-B natriuretic peptide (NT-proBNP), recognition of acute coronary syndromes, recognition of potential precipitating factors, use of supplemental oxygen, use of intravenous inotropic or pressure agents in patients with clinical evidence of hypotension with hypoperfusion, use of pulmonary artery catheters, and transition of intravenous to oral diuretics, the level of evidence supporting each of these recommendations was based on consensus opinion or standard use of care (i.e., level of evidence, C). Stronger class I recommendations (level of evidence, B) were provided for the use of intravenous diuretics to decongest patients, initiation of ACE inhibitors/ARBs, and beta blockers before hospital discharge, as well as the importance of postdischarge systems of care.

TABLE 24G.1

ACC/AHA Recommendations for the Hospitalized Patient with Heart Failure (HF)

CLASS	INDICATION	LEVEL OF EVIDENCE*
I	Thorough history and physical examination to evaluate for adequacy of systemic perfusion, volume status, contribution of precipitating factors and/or comorbidities, and whether HF is associated with preserved ejection fraction.	C
	Concentrations of B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) to evaluate dyspnea if the contribution of heart failure is not known.	A
	Acute coronary syndrome should be promptly identified by electrocardiogram and cardiac troponin testing, and treated, as appropriate to the overall condition and prognosis of patient.	C
	Oxygen therapy should be administered to relieve symptoms related to hypoxemia.	C
	Improve systemic perfusion in patients who present with rapid decompensation and hypoperfusion associated with decreasing urine output and other manifestations of shock.	C
	Treatment of significant fluid overload with intravenous loop diuretics. The diuretic dose should be titrated to relieve symptoms and to reduce extracellular fluid volume excess.	B, C
	Monitored the effects of therapy with careful measurement of fluid intake and output; vital signs; body weight, and symptoms of systemic perfusion and congestion.	C
	Intensify the diuretic regiment when the diuresis is inadequate to relieve congestion.	C
	Intravenous inotropic or vasopressor drugs should be administered to maintain systemic perfusion and preserve end-organ performance in patients with clinical evidence of hypotension associated with hypoperfusion and elevated cardiac filling pressures.	C
	Invasive hemodynamic monitoring to guide therapy in patients who are in respiratory distress or with clinical evidence of impaired perfusion if filling pressures cannot be determined from clinical assessment	C
	Medications should be reconciled and adjusted as appropriate on admission to and discharge from the hospital.	C
	Maintenance treatment with oral therapies known to improve outcomes (ACE inhibitors or ARBs and beta-blocker therapy) in the absence of hemodynamic instability or contraindications.	C
	Initiation of treatment with oral therapies known to improve outcomes (ACE inhibitors or ARBs and beta-blocker therapy) in stable patients prior to hospital discharge.	B
	During transition from intravenous to oral diuretic therapy, patient should be monitored carefully for supine and upright hypotension, worsening renal function, and HF signs/symptoms.	C
	Comprehensive written discharge instructions for patients and their caregivers is strongly recommended.	C
	Postdischarge systems of care, if available, should be used to facilitate the transition to effective outpatient care.	B
IIa	Urgent cardiac catheterization and revascularization in patients with acute HF with known or suspected acute myocardial ischemia due to occlusive coronary disease when there are signs and symptoms of inadequate systemic perfusion and revascularization is likely to prolong meaningful survival.	C
	Intravenous nitroglycerin, nitroprusside, or nesiritide for patients with evidence of severely symptomatic fluid overload in the absence of systemic hypotension.	C
	Ultrafiltration for patients with refractory congestion not responding to medical therapy.	B
IIb	Intravenous inotropic drugs (dopamine, dobutamine, or milrinone) for patients presenting with documented severe systolic dysfunction, low blood pressure, and evidence of low cardiac output, with or without congestion, to maintain systemic perfusion and preserve end-organ performance.	C
III	Use of parenteral inotropes in normotensive patients with acute decompensated HF without evidence of decreased organ perfusion.	B
	Routine use of invasive hemodynamic monitoring in normotensive patients with acute decompensated HF and congestion with symptomatic response to diuretics and vasodilators.	B

*See guidelines text for definition of level of evidence categories.

ACC, American College of Cardiology; *AHA,* American Heart Association.

The updated guidelines offer qualified support (class IIa) for the use of urgent catheterization and revascularization, the use of vasodilators (intravenous nitroglycerin, nitroprusside, nesiritide), invasive hemodynamic monitoring, and ultrafiltration. More muted support (class IIb) was given for the use of inotropic agents (dopamine, dobutamine, or milrinone) in patients with severe left ventricular dysfunction, low blood pressure, and evidence of low cardiac output. In contrast, the use of inotropic agents in patients without evidence of decreased organ perfusion, as well as the routine use of invasive hemodynamic monitoring, was not recommended (class III indication).

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Management of Heart Failure Patients with Reduced Ejection Fraction

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The epidemiology and clinical assessment of patients with heart failure (HF) are reviewed in **Chapter 21**. The diagnosis and management of patients with acute HF are discussed in **Chapter 24**. This chapter focuses on the management of HF patients with a reduced ejection fraction (HFrEF). **Chapter 26** discusses he management of HF patients a preserved ejection fraction (HFpEF).

Etiology

Any condition that leads to an alteration in left ventricular (LV) structure or function can predispose a patient to developing HF (**Table 25.1**). Although the etiology of HF in patients with HFrEF differs from that of patients with HFpEF, there is considerable overlap between the etiologies of these two conditions. In industrialized countries, coronary artery disease (CAD) is the predominant cause in men and women and is responsible for 60% to 75% of cases of HF. Hypertension contributes to the development of HF in a significant number of patients, including most patients with CAD. Both CAD and hypertension interact to augment the risk of HF. Rheumatic heart disease remains a major cause of HF in Africa and Asia, especially in the young population. Hypertension is an important cause of HF in the African and African American population. Chagas disease is still a major cause of HF in South America.[1] As developing nations undergo socioeconomic development, the epidemiology of HF is becoming similar to that of Western Europe and North America, with CAD emerging as the single most common cause of HF.

TABLE 25.1

Risk Factors for Cardiac Failure (Olmstead County)

RISK FACTOR	ODDS RATIO (95% CI)	*P* VALUE	POPULATION-ATTRIBUTABLE RISK (95% CI)		
			Overall	Women	Men
Coronary heart disease	3.05 (2.36-3.95)	<.001	0.20 (0.16-0.24)	0.16 (0.12-0.20)	0.23 (0.16-0.30)
Hypertension	1.44 (1.18-1.76)	<.001	0.20 (0.10-0.30)	0.28 (0.14-0.42)	0.13 (0.00-0.26)
Diabetes	2.65 (1.98-3.54)	<.001	0.12 (0.09-0.15)	0.10 (0.06-0.14)	0.13 (0.08-0.18)
Obesity	2.00 (1.57-2.55)	<.001	0.12 (0.08-0.16)	0.12 (0.07-0.17)	0.13 (0.07-0.19)
Ever smoker	1.37 (1.13-1.68)	.002	0.14 (0.06-0.22)	0.08 (0.00-0.15)	0.22 (0.07-0.37)

From Dunlay SM, Weston SA, Jacobsen SJ, et al. Risk factors for heart failure: a population-based case-control study. Am J Med 2009;122:1023-8.

In 20% to 30% of HFrEF cases, the exact etiologic basis is not known. These patients are referred to as having dilated or “idiopathic” cardiomyopathy if the cause is unknown (**see Chapter 77**). Prior viral infection (**Chapter 79**) or toxin exposure (e.g. alcohol [**Chapter 80**] or use of chemotherapeutic agents [**Chapter 81**]) may also lead to a dilated cardiomyopathy (DCM). Although excessive alcohol consumption can promote cardiomyopathy, alcohol per se is not associated with increased risk for HF and may protect against the development of HF when consumed in moderation.[2] It is also becoming increasingly clear that a large number of DCM cases are secondary to specific genetic defects, most notably those in the cytoskeleton. Most of the forms of familial DCM are inherited in an autosomal dominant manner. Mutations of genes encoding cytoskeletal proteins (desmin, cardiac myosin, vinculin) and nuclear membrane proteins (lamin) have been identified thus far. DCM is also associated with Duchenne, Becker, and limb-girdle muscular dystrophies (**see Chapter 97**). Conditions that lead to a high cardiac output (e.g., arteriovenous fistula, anemia) are seldom responsible for the development of HF in a normal heart. However, in the presence of underlying structural heart disease, these conditions often lead to overt congestive heart failure.

Prognosis

Although several recent reports have suggested that the mortality for HF patients is improving, the overall mortality rate remains higher than for many cancers, including those involving the bladder, breast, uterus, and prostate. In the Framingham Study, the median survival was 1.7 years for men and 3.2 years for women, with only 25% of men and 38% of women surviving 5 years. European studies have confirmed a similar poor long-term prognosis (**Fig. 25.1**).[3] More recent data from the Framingham Study have examined long-term trends in the survival of HF patients and shown improved survival in both men and women, with an overall decline in mortality of approximately 12% per decade from 1950 to 1999. Moreover, recent reports from Scotland, Sweden, and the United Kingdom also suggested that survival rates may be also improving following hospital discharge.[3] Of note, HF mortality in epidemiologic studies is substantially higher than that reported in clinical HF trials involving drug and device therapies, in which the mortality figures are often deceptively low because the patients enrolled in trials are younger, are more stable clinically, and tend to be followed more closely clinically.

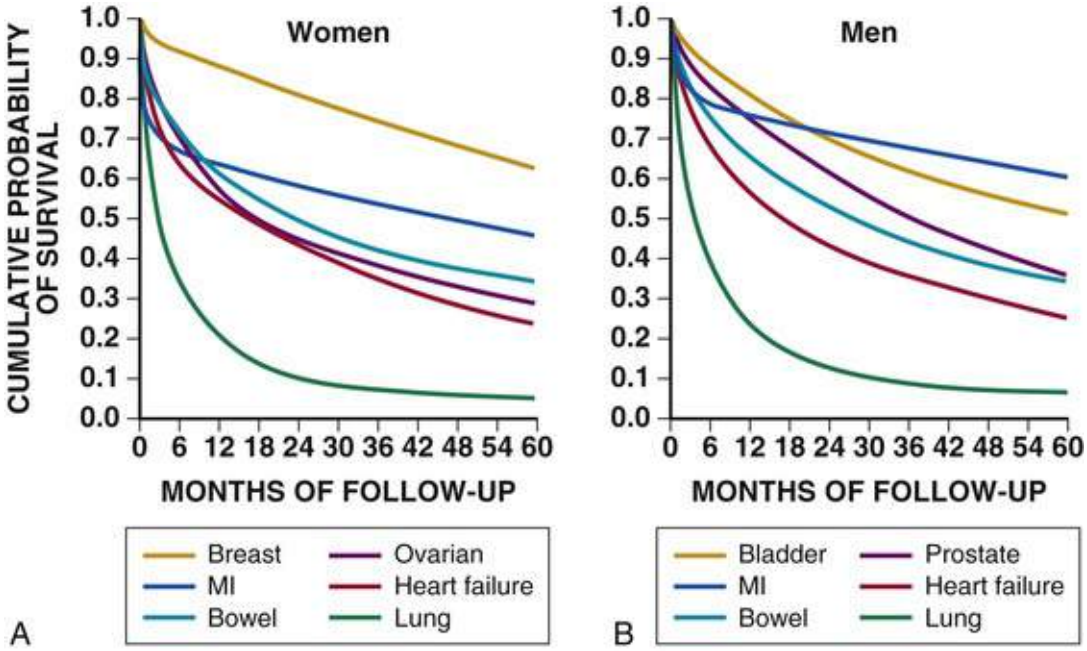


FIGURE 25.1 Survival in HF patients compared to cancer. Five-year survival following a first admission to any Scottish hospital in 1991 for heart failure, myocardial infarction (MI), and the four most common sites of cancer specific to men and women. (Modified from Stewart S, MacIntyre K, Hole DJ, et al. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail 2001;3:315-22.)

The role of gender and HF prognosis remains a controversial issue with respect to HF outcomes. Nonetheless, the aggregate data suggest that women with HF have a better overall prognosis than do men.[4] However, women appear to have a greater degree of functional incapacity for the same degree of left ventricular (LV) dysfunction and also have higher prevalence of HF with a normal ejection fraction (EF) (**see Chapter 26**). Controversy has also arisen regarding the impact of race on outcome, with higher mortality rates being reported in blacks in some but not all studies. In the United States, HF affects approximately 3% of blacks, whereas in the general population, the prevalence is about 2%.[5] Blacks with HF present at an earlier age and have more advanced LV dysfunction and a worse New York Heart Association (NYHA) class at diagnosis. Although the reasons for these differences are not known, as previously noted, differences in HF etiology might explain some of these observations. Additional socioeconomic factors may influence outcomes in black patients, such as geographic location and access to health care. Age is one of the stronger and most consistent predictors of adverse outcome in HF[6] (see later, Special Populations).

Many other factors have been associated with increased mortality in HF patients (**Table 25.2**). Most of the factors listed as outcome predictors have withstood univariate analysis at least, with many standing out independently when multifactorial analysis techniques are employed. Nonetheless, it is extraordinarily difficult to determine which prognostic variable is most important to predict individual patient outcome in either clinical trials or, more importantly, during the day-to-day management of an individual patient. To this end, several multivariate models for predicting the HF prognosis has been developed and validated. The Seattle Heart Failure Model was derived by retrospectively investigating predictors of survival among HF patients in clinical trials. This model provides an accurate estimate of 1-, 2-, and 3-year survival with the use of easily obtained clinical, pharmacologic, device, and laboratory characteristics and is accessible free of charge to all health care providers as an interactive Internet-based program (http://depts.washington.edu/shfm).

TABLE 25.2

Etiology of Chronic Heart Failure

Myocardial Disease
Coronary artery disease
Myocardial infarction*
Myocardial ischemia*
Chronic pressure overload
Hypertension*
Obstructive valvular disease*
Chronic volume overload
Regurgitant valvular disease
Intracardiac (left-to-right) shunting
Extracardiac shunting
Nonischemic dilated cardiomyopathy
Familial/genetic disorders
Infiltrative disorders*
Toxic/drug-induced damage
Metabolic disorder*
Viral or other infectious agents
Disorders of Rate and Rhythm
Chronic bradyarrhythmias
Chronic tachyarrhythmias
Pulmonary Heart Disease
Cor pulmonale
Pulmonary vascular disorders
High-output states
Metabolic Disorders
Thyrotoxicosis
Nutritional disorders (beriberi)
Excessive Blood Flow Requirements
Systemic arteriovenous shunting
Chronic anemia

*Conditions that can also lead to HF with a preserved ejection fraction.

Biomarkers and Prognosis

The observation that the renin-angiotensin-aldosterone (RAAS), adrenergic, and inflammatory systems are activated in HF has prompted the examination of the relationships between a variety of biochemical measurements and clinical outcomes (**Table 25.3**) (**see Chapters 21 and 23**). Strong inverse correlations have been reported between survival and plasma levels of norepinephrine, renin, arginine vasopressin, aldosterone, atrial (ANP) and brain (B-type) (BNP and NT-proBNP) natriuretic peptides, endothelin (ET)-1, and inflammatory markers such as tumor necrosis factor (TNF), soluble TNF receptors, C-reactive protein, galactin-3, pentraxin-3, and soluble ST2. Markers of oxidative stress, such as oxidized low-density lipoprotein, and serum uric acid, have also been associated with worsening clinical status and impaired survival in patients with chronic HF. Cardiac troponin T and I, sensitive markers of myocyte damage, may be elevated in patients with nonischemic and predict adverse cardiac outcomes. The association between a low hemoglobin/hematocrit (Hb/Hct) and adverse HF outcomes has also long been recognized, with recent renewed attention after several reports illustrated the independent prognostic value of anemia in patients with HF with either reduced or normal EF.[7]

TABLE 25.3

Prognostic Variable in Heart Failure Patients

Demographics	**Exercise Testing**
Gender	Metabolic assessment
Race	BP response
Age	Heart rate response
Heart Failure Etiology	6-min walk
CAD	Peak VO_2
IDCM	Anaerobic threshold
Valvular heart disease	VE/VCO_2
Myocarditis	Oxygen uptake slope
Hypertrophy	**Metabolic**
Alcohol	Serum sodium
Anthracyclines	Thyroid dysfunction
Amyloidosis	Anemia
Hemochromatosis	Acidosis/alkalosis
Genetic factors	**Chest Radiograph**
Comorbidities	Congestion
Diabetes	Cardiothoracic ratio
Systemic hypertension	**Electrocardiogram**
Pulmonary hypertension	Rhythm (atrial fibrillation or arrhythmias)
Sleep apnea	Voltage
Obesity/cachexia (body mass)	QRS width
Renal insufficiency	QT interval
Hepatic abnormalities	Signal-average ECG (T wave alternans)
COPD	HR variability
Clinical Assessment	**Biomarkers**
NYHA class (symptoms)	NE, PRA, AVP, aldosterone
Syncope	ANP, BNP, NT-proBNP, endothelin
Angina pectoris	TNF, sTNFR 1,2, galectin-3, pentraxin-3, sST2
Systolic vs. diastolic dysfunction	Cardiac troponins, hematocrit
Hemodynamics	**Endomyocardial Biopsy**
LVEF	Inflammatory states
RVEF	Degree of fibrosis
PAP	Degree of cellular disarray
PCWP	Infiltrative processes
CI	
PAP-PCWP	
Exercise hemodynamics	

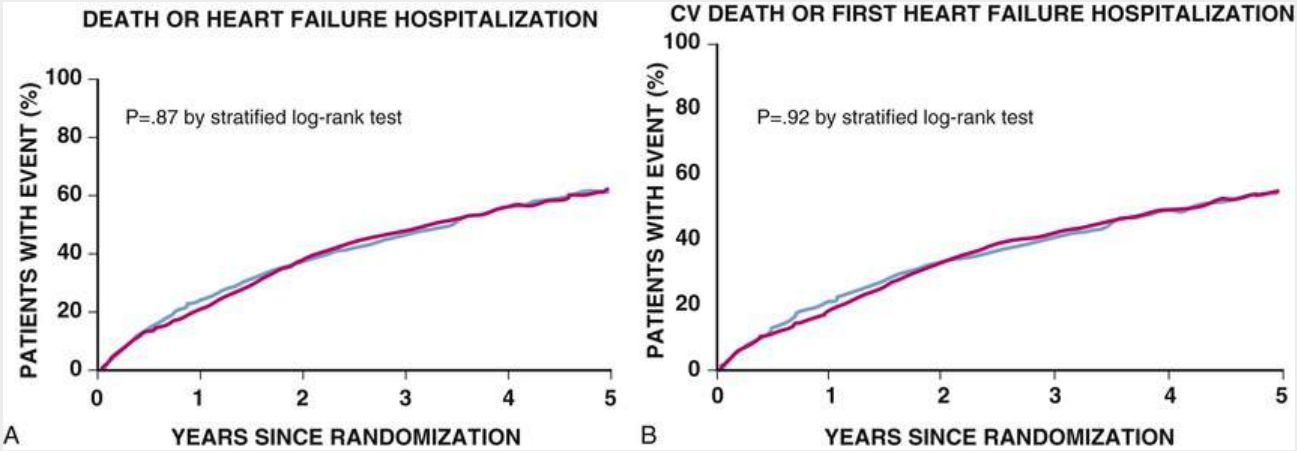
AVP, Arginine vasopressin; *BP,* blood pressure; *CAD,* coronary artery disease; *CI,* cardiac index (width); *COPD,* chronic obstructive pulmonary disease; *CRP,* C-reactive protein; *ESR,* erythrocyte sedimentation rate; *IDCM,* idiopathic dilated cardiomyopathy; *IL,* interleukin; *LVEF,* left ventricular ejection fraction; *NE,* norepinephrine; *NYHA,* New York Heart Association; *PAP,* pulmonary artery pressure; *PAP-PCWP,* gradient across lung; *PCWP,* pulmonary capillary wedge pressure; *RVEF,* right ventricular ejection fraction; *TNF,* tumor necrosis factor.

Modified from Young JB. The prognosis of heart failure. In Mann DL, editor. Heart Failure: A Companion to Braunwald's Heart Disease. Philadelphia: Elsevier; 2004, pp 489-506.

Published estimates of the prevalence of anemia (defined as Hb concentration <13 g/dL in men and <12 g/dL in women) in HF patients vary widely, ranging from 4% to 50% depending on the population studied and definition of anemia used. In general, anemia is associated with more HF symptoms, worse NYHA functional status, greater risk of HF hospitalization, and reduced survival.[8] However, it is unclear whether anemia is a cause of decreased survival or simply a marker of more advanced disease. The underlying cause for anemia is likely multifactorial, including reduced sensitivity to erythropoietin receptors, presence of a hematopoiesis inhibitor, and defective iron supply for erythropoiesis.

A standard diagnostic workup should be undertaken in anemic HF patients, recognizing that no definite etiology is identified in many of these patients. Correctable causes of anemia should be treated according to practice guidelines. The role for blood transfusions in patients with cardiovascular (CV) disease is controversial. Although a “transfusion threshold” for maintaining the Hct above 30% in patients with CV disease has been generally been accepted, this clinical practice has been based more on expert opinion

rather than on direct evidence that documents the efficacy of this form of therapy. Given the risks and costs of red blood cell transfusion, the evanescent benefits of blood transfusions in patients with a chronic anemia, coupled with the unclear benefit in HF patients, the routine use of blood transfusion cannot be recommended for treating the anemia that occurs in stable HF patients. Treatment of anemic HF patients with mild to moderate anemia (Hb level 9.0 to 12.0 g/dL) with the erythropoietin analogue darbepoetin alpha was evaluated in the RED-HF (Reduction of Events with Darbepoetin Alfa in Heart Failure) trial. As shown in **eFig. 25.1**, there was no significant difference in the primary outcome variable of death from any cause or hospitalization for worsening HF (hazard ratio [HR] in darbepoetin alfa group, 1.01; 95% confidence interval [CI] 0.90 to 1.13; *P* = 0.87), nor the secondary outcome (**eFig. 25.1B**) of CV death or time to first hospitalization for worsening HF (HR in darbepoetin alfa group, 10.01; 95% CI 0.89 to 1.14; *P* = 0.2). The lack of effect of darbepoetin alfa was consistent across all prespecified subgroups. Importantly, treatment with darbepoetin alfa led to an early (within 1 month) and sustained increase in Hb level throughout the study.



EFIGURE 25.1 Effect of treatment with darbepoetin alfa on clinical outcomes in patients with HF and mild-to-moderate anemia. **A,** Kaplan-Meier estimate of the probability of the death or heart failure hospitalization (primary endpoint). **B,** Kaplan-Meier estimate of death from cardiovascular (CV) causes or first hospitalization for heart failure (secondary endpoint). (Modified from Swedberg K, Young JB, Anand IS, et al. Treatment of anemia with darbepoetin alfa in systolic heart failure N Engl J Med 2013;368:1210.)

Iron deficiency is a common comorbidity in patients with HFrEF and has been associated with increased mortality and a poorer quality of life, regardless of whether there is concomitant anemia.[9] Correction of iron deficiency in anemic and nonanemic patients with HFrEF (EF <30% to 45%) has been studied in several clinical trials.[9] Two of the three randomized trials conducted thus far have used intravenous (IV) ferric carboxymaltose (FCM). Studies with FCM have shown improvement in symptoms, exercise capacity, and health-related quality of life; however, the effects on major clinical events remain uncertain.[8] The one randomized clinical trial that used an oral iron polysaccharide (Oral Iron Repletion Effects on Oxygen Uptake in Heart Failure [IRONOUT]; NCT02188784), did not show an improvement in peak VO_2 by cardiopulmonary exercise testing at 16 weeks. Based on the results of the randomized trials with IV iron supplementation, the current American College of Cardiology, American Heart Association, and Heart Failure Society of America (ACC/AHA/HFSA) guidelines recommend (class IIb, level of evidence B-R) that IV iron replacement might be reasonable in patients with NYHA Class II and III HF and iron deficiency (ferritin <100 ng/mL or 100 to 300 ng/mL if transferrin saturation <20%) to improve functional status and quality of life.[10]

Renal Insufficiency

Renal insufficiency is associated with poorer outcomes in patients with HF; however, some uncertainty remains whether renal impairment is a simply a marker for worsening HF or whether renal impairment might be causally linked to worsening HF. Although more common in patients hospitalized for HF, at least some degree of renal impairment is still present in about half of stable HF outpatients. Patients with renal hypoperfusion or intrinsic renal disease show an impaired response to diuretics and angiotensin-converting enzymes inhibitors (ACEIs) and are at increased risk of adverse effects during treatment with digitalis. In a recent meta-analysis the majority of HF patients had some degree of renal impairment. These patients represented a high-risk group with an approximately 50% increased relative mortality risk compared with patients who had normal renal function.[11] Similar findings were observed in ADHERE (Acute Decompensated Heart Failure National Registry) (**see Chapter 24**). In the Second Prospective Randomized Study of Ibopamine on Mortality and Efficacy, impaired renal function was a stronger predictor of mortality than impaired LV function and NYHA class in patients with advanced HF (**Fig. 25.2**). Thus, renal insufficiency is a strong, independent predictor of adverse outcomes in HF patients.

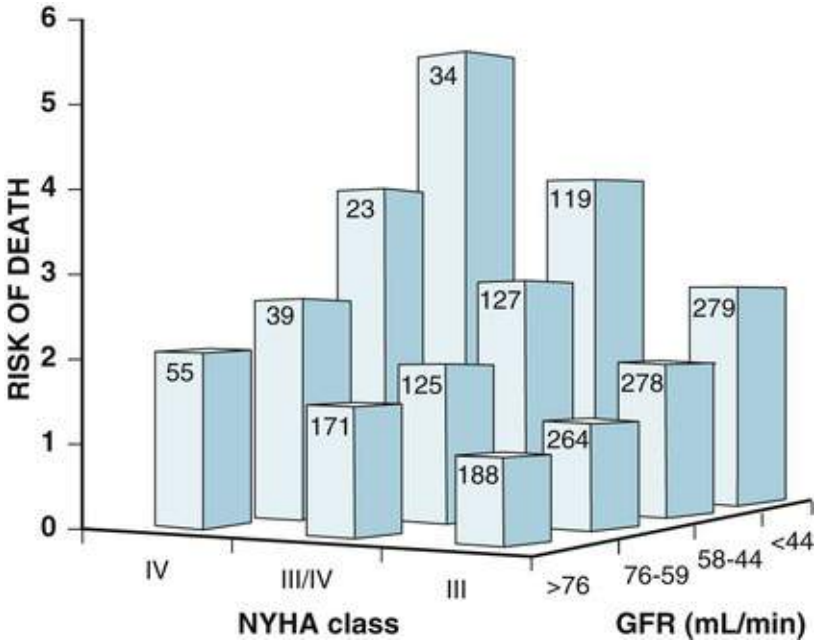


FIGURE 25.2 Effect of renal function on outcomes in heart failure patients. Three-dimensional bar graph showing risk of mortality (*vertical axis*) in relation to decreasing New York Heart Association (NYHA) class (*horizontal axis*) and decreasing quartiles of glomerular filtration rate (GFR; *diagonal axis*). (From Hillege HL, Girbes AR, de Kam PJ, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation 2000;102:203-10.)

Approach to the Patient

HFrEF should be viewed as continuum comprising four interrelated stages[12] (**Fig. 25.3**). Stage A includes patients at high risk for developing HF, but without structural heart disease or symptoms of HF (e.g., patients with diabetes or hypertension). Stage B includes patients who have structural heart disease but without symptoms of HF (e.g., patients with previous myocardial infarction and asymptomatic LV dysfunction). Stage C includes patients who have structural heart disease who have developed symptoms of HF (e.g., patients with previous MI with shortness of breath and fatigue). Stage D includes patients

with refractory HF requiring special interventions (e.g., patients with refractory HF awaiting cardiac transplantation). **Fig. 25.4** provides a simplified algorithm for approaching patients with HF. **Chapter 21** discusses the clinical assessment of patients with HFrEF, and **Chapter 26** discusses the diagnosis and management of patients with HFpEF.

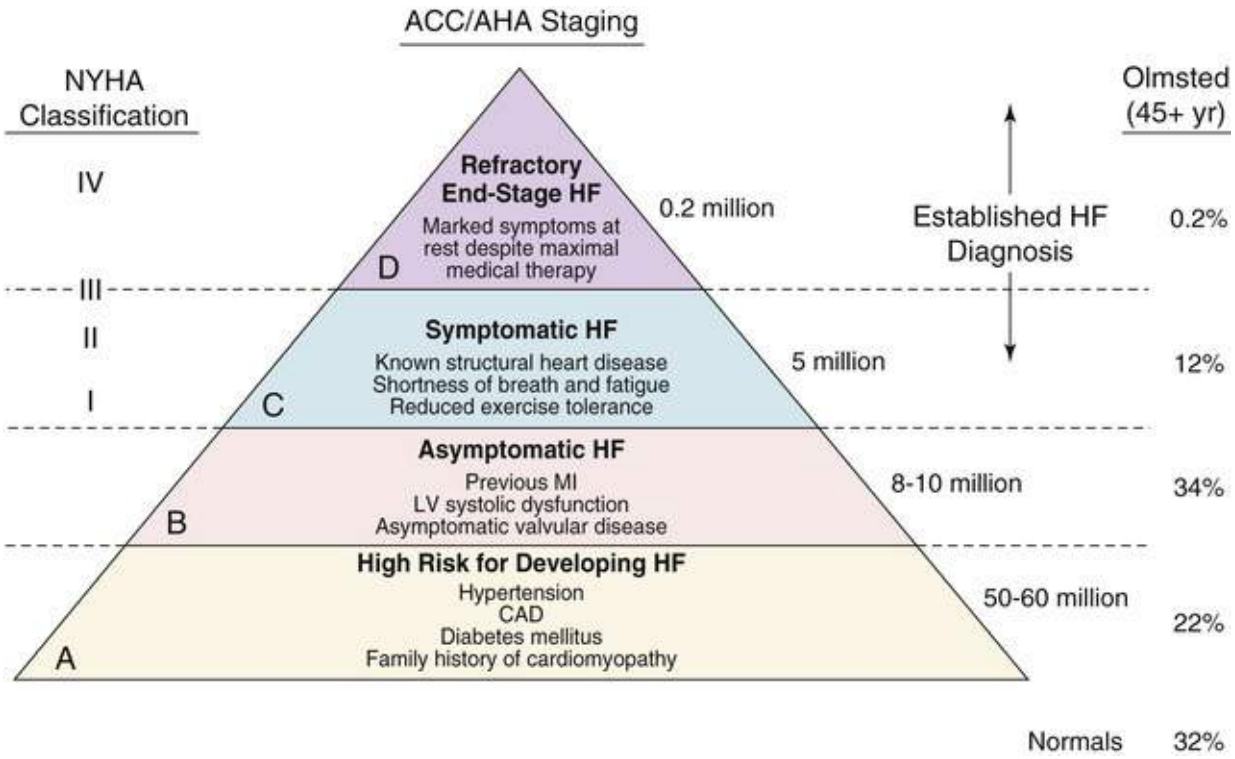


FIGURE 25.3 Stages of heart failure (HF) and prevalence of stages (data from the Olmstead County Epidemiology Study). Patients with stage A HF are at high risk for HF but do not have structural heart disease or symptoms of HF. This group includes patients with hypertension, diabetes, coronary artery disease (CAD), previous exposure to cardiotoxic drugs, or a family history of cardiomyopathy. Patients with stage B HF have structural heart disease but have no symptoms of HF. This group includes patients with left ventricular (LV) hypertrophy, previous myocardial infarction (MI), LV systolic dysfunction, or valvular heart disease, all of whom would be considered to have New York Heart Association (NYHA) Class I symptoms. Patients with stage C HF have known structural heart disease and current or previous symptoms of HF. Their symptoms may be classified as NYHA Class I, II, or III. Patients with stage D HF have refractory symptoms of HF at rest despite maximal medical therapy, are hospitalized, and require specialized interventions or hospice care. All such patients would be considered to have NYHA Class IV symptoms. AHA. American Heart Association; ACC, American College of Cardiology. (Modified from Ammar KA, Jacobsen SJ, Mahoney DW, et al. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. Circulation 2007;115:1563-70.)

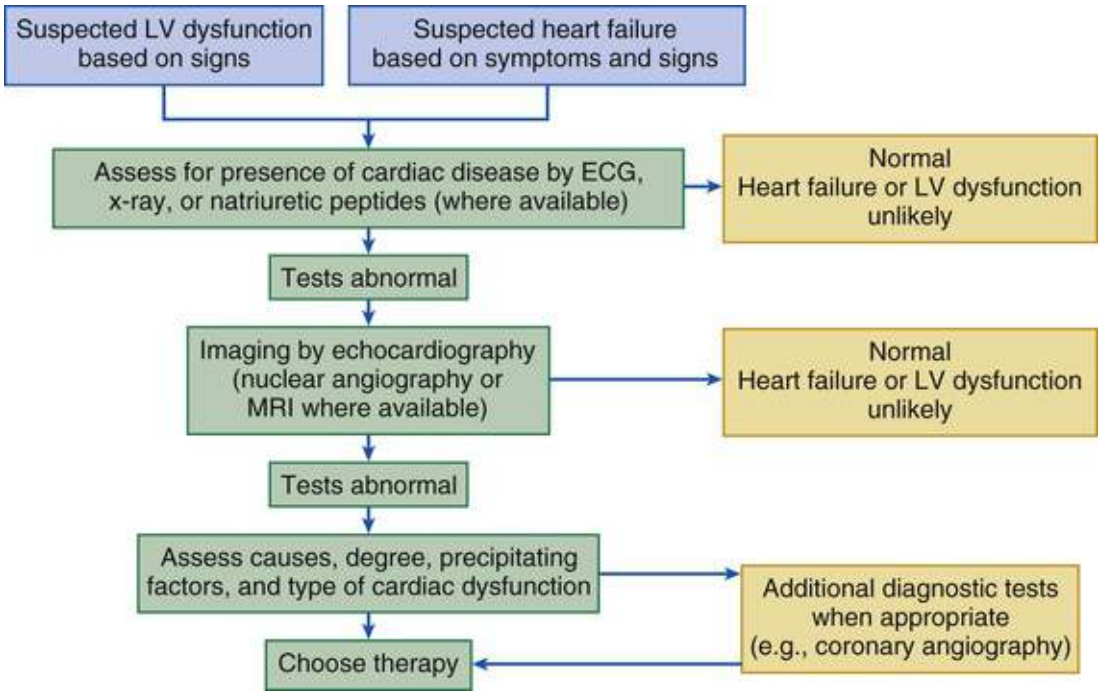


FIGURE 25.4 Algorithm for the diagnosis of heart failure or left ventricular (LV) dysfunction. ECG, Electrocardiogram; MRI, magnetic resonance imaging. (From Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:1115-40.)

Patients at High Risk for Developing Heart Failure (Stage A)

For patients at high risk of developing HFrEF, every effort should be made to prevent HF, using standard practice guidelines to treat preventable conditions that are known to lead to HF, including hypertension (**see Chapter 46**), hyperlipidemia (**Chapter 48**), and diabetes (**Chapter 51**). In this regard, ACEIs are particularly useful in preventing HF in patients who have a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated CV risk factors.

Population Screening.

At present, there is limited information available to support screening broad populations to detect undiagnosed HF and/or asymptomatic LV dysfunction. Although initial studies suggested that determination of BNP or N-terminal (NT) pro-BNP levels might be useful for screening, the positive predictive value (PPV) for these tests in a low-prevalence and asymptomatic population to detect cardiac dysfunction varies among studies, and the possibility of false-positive results has significant cost-effectiveness implications.

Patients who are at very high risk of a developing cardiomyopathy (e.g., those with a strong family history of cardiomyopathy or those receiving cardiotoxic interventions; **see Chapters 80 and 81**) are appropriate targets for more aggressive screening such as two-dimensional echocardiography to assess LV function. The STOP-HF (St. Vincent's Screening To Prevent Heart Failure) showed that, in patients with known CV risk factors, screening with BNP testing followed by collaborative care between internists and CV specialists resulted in a significant reduction in LV dysfunction (odds ratio [OR], 0.55; 95% CI, 0.37 to 0.82; P = .003). Although there was no significant reduction in clinical HF events, there was a significant decrease in the incidence rates of emergency hospitalization for major CV events.[13]

However, the routine periodic assessment of LV function in low-risk patients is not currently recommended. Several sophisticated clinical scoring systems have been developed to screen for HF in population-based studies, including the Framingham Criteria, which screen for HF on the basis of clinical criteria, and the National Health and Nutrition Examination Survey (NHANES), which uses self-reporting of symptoms to identify HF patients (**Table 25.4**). However, as discussed in **Chapter 21**, additional laboratory testing is usually necessary to make a definitive diagnosis of HF when these methodologies are used.

TABLE 25.4

Diagnostic Criteria for Heart Failure (HF) in Population-Based Studies

FRAMINGHAM CRITERIA		
Major Criteria	**Minor Criteria**	**Major or Minor Criteria**
Paroxysmal nocturnal dyspnea or orthopnea Neck vein distention Rales Cardiomegaly Acute pulmonary edema S_3 gallop Increased venous pressure >16 cm H_2O Hepatojugular reflux	Ankle edema Night cough Dyspnea on exertion Hepatomegaly Pleural effusion Vital capacity decreased One-third from maximal capacity Tachycardia (rate >120/min)	Weight loss >4.5 kg in 5 days in response to treatment

NHANES CRITERIA		
Category	**Criteria**	**Score**
History	*Dyspnea:*	
	When hurrying on a hill	1
	When walking at an ordinary pace	1
	Do you stop for breath when walking at an ordinary pace?	2
	Do you stop for breath when after 100 yards on flat ground?	2
Physical examination	*Heart rate:*	
	91-110 beats/min	1
	>110 beats/min	2
	Jugular venous pressure (> 6 cm H_2O):	
	Alone	1
	PLUS hepatomegaly or edema	2
	Rales:	
	Basilar crackles	1
	Crackles more than basilar crackles	2
Chest radiograph	Upper zone flow redistribution	1
	Interstitial pulmonary edema	2
	Interstitial edema plus pleural fluid	3
	Alveolar fluid plus pleural fluid	3

The diagnosis of HF using the Framingham criteria requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria. Minor criteria are acceptable only if they cannot be attributed to another medical condition (e.g., pulmonary hypertension, chronic lung disease, cirrhosis, ascites, nephrotic syndrome). NHANES-1 criteria: diagnosis of HF is score ≥3 points.

NHANES, National Health and Nutrition Survey.

Modified from Ho KK et al. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993;22:6A-13A; and Schocken DD et al. Prevalence and mortality rate of congestive heart failure in the United States. J Am Coll Cardiol 1992;20:301-6.

Management of Patients with Symptomatic and Asymptomatic Heart Failure

Transient Left Ventricular Dysfunction

As noted in **Chapter 23**, the clinical syndrome of HF with reduced EF begins after an initial index event

produces a decline in ejection performance of the heart. However, it is important to recognize that LV dysfunction may develop transiently in a variety of different clinical settings that may not invariably lead to development of the clinical syndrome of HF. **Fig. 25.5** illustrates the important relationship between LV dysfunction (transient and sustained) and the clinical syndrome of HF (asymptomatic and symptomatic). LV dysfunction with pulmonary edema may develop acutely in patients with previously normal LV structure and function. This most frequently occurs after cardiac surgery, in the setting of severe brain injury, or after a systemic infection. The general pathophysiologic mechanism involved is either some form of "stunning" of functional myocardium (**see Chapter 67**) or activation of proinflammatory cytokines capable of suppressing LV function. Emotional stress can also precipitate severe, reversible LV dysfunction accompanied by chest pain, pulmonary edema, and cardiogenic shock in patients without CAD (takotsubo syndrome). In these patients, LV dysfunction is thought to result from the deleterious effects of catecholamines after heightened sympathetic stimulation.[14] It is also important to note that exercise-induced LV dysfunction, usually caused by myocardial ischemia, may lead to symptoms by causing an increase in LV filling pressure and a decrease in cardiac output in the absence of discernible LV dysfunction at rest. If LV dysfunction persists after the initial cardiac injury, patients may remain asymptomatic for months to years; however, the weight of epidemiologic and clinical evidence suggests that at some point, these patients will undergo the transition to overt symptomatic HF.

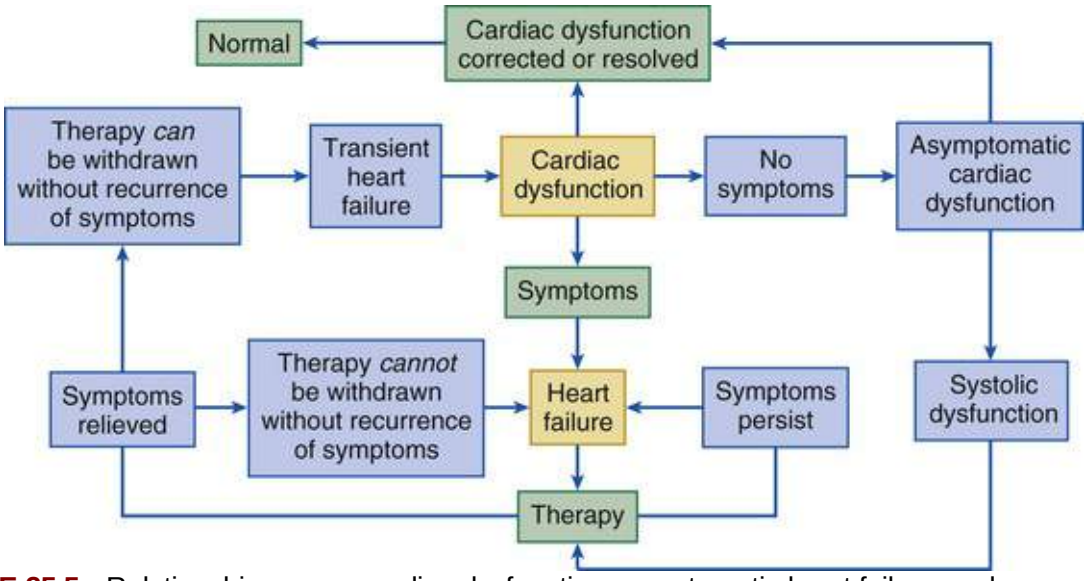


FIGURE 25.5 Relationship among cardiac dysfunction, symptomatic heart failure, and asymptomatic heart failure following appropriate treatment. (From Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:1115-40.)

Defining the Appropriate Strategy

The main goals of treatment for are to reduce symptoms, prolong survival, improve the quality of life, and prevent disease progression. As discussed later, the current pharmacologic, device, and surgical therapeutic armamentarium for the management of HF patients with a reduced EF permit health care providers to achieve each of these goals in the great majority of patients. Once patients have developed structural heart disease (stage B to D), the choice of therapy for patients with HFrEF depends on their NYHA functional classification (**see Chapter 21**, **Table 21.1**). Although this classification system is

notoriously subjective and has large interobserver variability, it has withstood the test of time and continues to be widely applied to patients with HF. For patients who have developed LV systolic dysfunction but who remain asymptomatic (NYHA Class I), the goal should be to slow disease progression by blocking neurohormonal systems that lead to cardiac remodeling (**see Chapter 23**). For patients who have developed symptoms (NYHA Class II to IV), the primary goal should be to alleviate fluid retention, lessen disability, and reduce the risk of further disease progression and death. As discussed subsequently, these goals generally require a strategy that combines diuretics (to control salt and water retention) with neurohormonal interventions (to minimize cardiac remodeling).

General Measures

Identification and correction of the condition(s) responsible for the cardiac structural and functional abnormalities are critical (**see Table 25.2**), because some conditions that provoke LV abnormalities are potentially treatable or reversible. Further, clinicians should aggressively screen for and treat comorbidities such as hypertension and diabetes that are believed to underlie the structural heart disease. In addition to seeking reversible etiologies and comorbidities that contribute to HF development, it is equally important to identify factors that provoke worsening HF in stable patients (**Table 25.5**).

TABLE 25.5

Factors That May Precipitate Acute Decompensation in Patients with Chronic Heart Failure (HF)

Dietary indiscretion
Inappropriate reduction in HF medications
Myocardial ischemia/infarction
Arrhythmias (tachycardia or bradycardia)
Infection
Anemia
Initiation of medications that worsen the symptoms of HF
Calcium antagonists (verapamil, diltiazem)
Beta blockers
Nonsteroidal anti-inflammatory drugs
Thiazolidinediones
Antiarrhythmic agents (all class I agents, sotalol [class III])
Anti-TNF antibodies
Alcohol consumption
Pregnancy
Worsening hypertension
Acute valvular insufficiency

From Mann DL. Heart failure and cor pulmonale, In Kasper DL, Braunwald E, Fauci AS, et al. Harrison's Principles of Internal Medicine. 17th ed. New York: McGraw-Hill; 2007, p 1448.

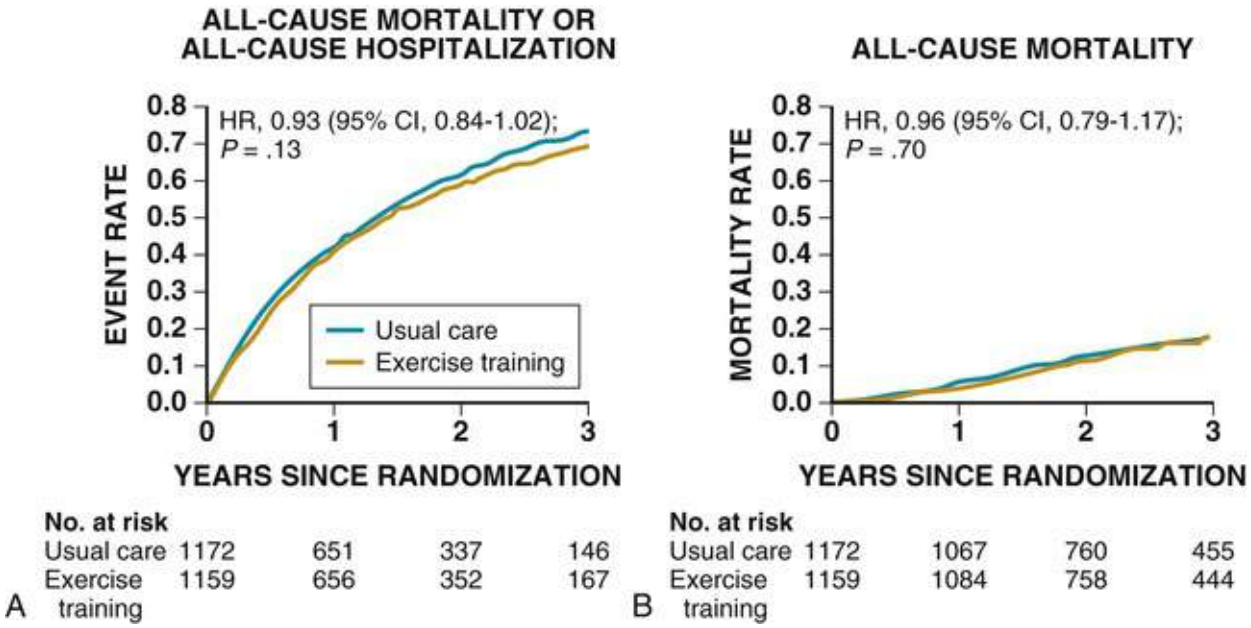
Among the most common causes of acute decompensation in a previously stable patient are dietary indiscretion and inappropriate reduction of HF therapy, either from patient self-discontinuation of medication or from physician withdrawal of effective pharmacotherapy (e.g., because of concern over azotemia). HF patients should be advised to stop smoking and to limit alcohol consumption to two standard drinks per day in men or one standard drink per day in women. Patients suspected of having an alcohol-induced cardiomyopathy should be advised to abstain from alcohol consumption indefinitely. Excessive temperature extremes and heavy physical exertion should be avoided. Certain drugs are known to make HF worse and should also be avoided. For example, nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase 2 (COX-2) inhibitors, are not recommended in patients with chronic HF because the risk of renal failure and fluid retention is greatly increased in the setting of reduced renal function and ACEI use. Patients should be advised to weigh themselves regularly to monitor weight gain and to alert a health care provider or adjust their diuretic dose in the event of a sudden unexpected weight

gain of more than 3 to 4 pounds over a 3 day period.

Although there is no documented evidence of the effects of immunization in HF patients, they are at high risk of developing pneumococcal infection and influenza. Accordingly, clinicians should consider recommending influenza and pneumococcal vaccines to their HF patient to prevent respiratory infections. The clinician should also educate the patient and family about HF and the importance of proper diet and compliance with the medical regimen. Supervision of outpatient care by a specially trained nurse or physician assistant and at specialized HF clinics has been found to be helpful, particularly in patients with advanced disease (see later, Disease Management Approach to Heart Failure).

Activity

Although heavy physical labor is not recommended in HF patients, routine modest exercise has been shown to be beneficial in selected patients with NYHA Class I to III HF. HF-ACTION (A Controlled Trial Investigating Outcomes of Exercise Training) was a large, multicenter, randomized controlled trial (RCT) with the primary endpoint of a composite of all-cause mortality and all-cause hospitalization. Secondary endpoints included all-cause mortality, all-cause hospitalization, composite of CV mortality or CV hospitalization, and composite of CV mortality or HF hospitalization. HF-ACTION failed to show a significant improvement in all-cause mortality or all-cause hospitalization (HR, 0.93; 95% CI 0.84 to 1.02; $P = 0.13$) in patients who received a 12-week (three times/week) exercise training program followed by 25- to 30-minute, 5 days/week, home-based, self-monitored exercise workouts on a treadmill or stationary bicycle (**eFig. 25.2A**). Moreover, there was no difference in all-cause mortality (HR, 0.96; 95% CI 0.79 to 1.17; $P = 0.70$) (**eFig. 25.2B**). However, there was a trend toward decreased CV mortality or HF hospitalization (HR, 0.87; 95% CI 0.74 to 0.99; $P = 0.06$), and quality of life was significantly improved in the exercise group.[15] For euvolemic patients, regular isotonic exercise such as walking or riding a stationary-bicycle ergometer may be useful as an adjunctive therapy to improve clinical status after patients have undergone exercise testing to determine suitability for exercise training (patient does not develop significant ischemia or arrhythmias). Exercise training is not recommended, however, in HF patients with a reduced EF who have had a major CV event or procedure within the last 6 weeks, in patients receiving cardiac devices that limit the ability to achieve target heart rates, and in patients with significant arrhythmia or ischemia during baseline cardiopulmonary exercise testing.



EFIGURE 25.2 Kaplan-Meier analysis of the effect of exercise versus usual care on heart failure morbidity and mortality. **A,** Time to all-cause mortality or all-cause hospitalization, and **B,** time to all-cause mortality in the HF-ACTION trial. (From O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439-50.)

Diet

Dietary restriction of sodium (2 to 3 g daily) is recommended in all patients with the clinical syndrome of HF and preserved or depressed EF. Further restriction (<2 g daily) may be considered in moderate to severe HF. Fluid restriction is generally unnecessary unless the patient is hyponatremic (<130 mEq/L), which may develop because of activation of the renin-angiotensin system (RAS), excessive secretion of arginine vasopressin (AVP), or loss of salt in excess of water from prior diuretic use. Fluid restriction (<2 L/day) should be considered in hyponatremic patients (<130 mEq/L), or for those patients whose fluid retention is difficult to control despite high doses of diuretics and sodium restriction. Caloric supplementation is recommended for patients with advanced HF and unintentional weight loss or muscle wasting (cardiac cachexia); however, anabolic steroids are not recommended for these patients because of the potential problems with volume retention. The measurement of nitrogen balance, caloric intake, and prealbumin may be useful in determining appropriate nutritional supplementation. The use of dietary supplements ("nutriceuticals") should be avoided in the management of symptomatic HF because of the lack of proven benefit and the potential for significant interactions with proven HF therapeutics.

Management of Fluid Retention

Many of the clinical manifestations of the syndrome of HF result from excessive salt and water retention that leads to an inappropriate volume expansion of the vascular and extravascular space. The use of implantable devices to monitor HF is discussed in **Chapter 27**. This section focuses on the use of diuretics in chronic HFrEF. Although both digitalis and low doses of ACEIs enhance urinary sodium excretion, few volume-overloaded HF patients can maintain proper sodium balance without the use of diuretic drugs. Indeed, attempts to substitute ACEIs for diuretics have been shown to lead to pulmonary edema and peripheral congestion. As shown in **Fig. 25.6**, diuretic-induced negative sodium and water balance can decrease LV dilation, functional mitral insufficiency, mitral wall stress, and subendocardial ischemia. In short-term clinical trials, diuretic therapy has led to a reduction in jugular venous pressure

(JVP), pulmonary congestion, peripheral edema, and body weight, all of which were observed within days of initiation of therapy. In intermediate-term studies, diuretics have been shown to improve cardiac function, symptoms, and exercise tolerance in HF patients.[16] To date, there have been no long-term studies of diuretic therapy in HF; thus their effects on morbidity and mortality are not clearly known. Although retrospective analyses of clinical trials suggest that diuretic use is associated with worse clinical outcomes,[16] a meta-analysis (Cochrane Review) suggested that treatment with diuretic therapy produced a significant reduction in mortality (OR, 0.24; 95% CI 0.07 to 0.83; $P = 0.02$) and worsening HF (OR 0.07; 95% CI 0.01 to 0.52; $P = 0.01$).[16] However, given the retrospective nature of this review, this analysis cannot be used as formal evidence to recommend the use diuretics to reduce HF mortality.

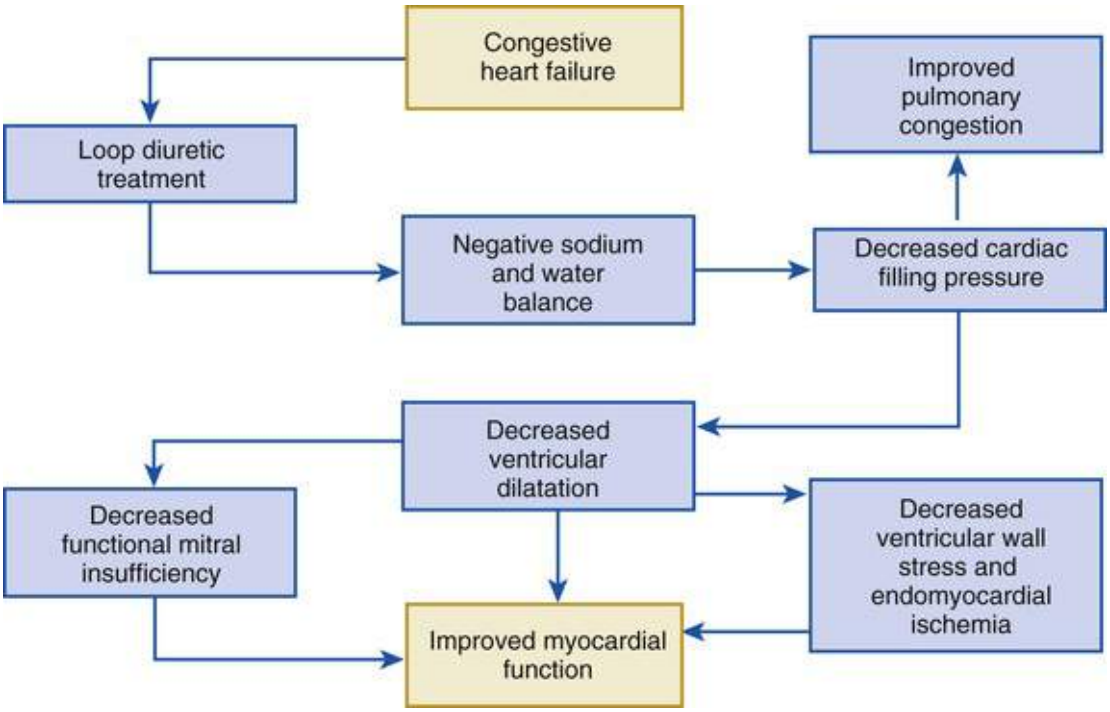


FIGURE 25.6 Potential beneficial effects of diuretics on myocardial function. Diuretic-induced negative sodium and water balance can decrease LV dilation, functional mitral insufficiency, mitral wall stress, and subendocardial ischemia. However, treatment with diuretics can also lead to deterioration of renal function and worsening neurohormonal activation. (Modified from Schrier RW. Use of diuretics in heart failure and cirrhosis. Semin Nephrol 2011;31:503-12.)

Diuretic Classes

A number of classification schemes have been proposed for diuretics on the basis of their mechanism of action, their anatomic locus of action within the nephron, and the form of diuresis that they elicit ("solute" versus "water diuresis"). The most common classification for diuretics employs an admixture of chemical (e.g., *thiazide* diuretic), site of action (e.g., *loop* diuretics), or clinical outcomes (e.g., *potassium-sparing* diuretics). The loop diuretics increase sodium excretion by up to 20% to 25% of the filtered load of sodium, enhance free water clearance, and maintain their efficacy unless renal function is severely impaired. In contrast, the thiazide diuretics increase the fractional excretion of sodium to only 5% to 10% of the filtered load, tend to decrease free water clearance, and lose their effectiveness in patients with impaired renal function (creatinine clearance <40 mL/min). Consequently, the loop diuretics have emerged as the preferred diuretic agents for use in most patients with HF. Diuretics that induce a water

diuresis (“aquaretics”) include demeclocycline, lithium, and vasopressin V_2 receptor antagonists, each of which inhibits the action of AVP on the collecting duct through different mechanisms, thereby increasing free water clearance. Drugs that cause solute diuresis are subdivided into two types: *osmotic* diuretics, which are nonresorbable solutes that osmotically retain water and other solutes in the tubular lumen, and drugs that selectively inhibit ion transport pathways across tubular epithelia, which constitute the majority of potent, clinically useful diuretics. **Table 25.6** lists the classes of diuretics and individual class members, and **Fig. 25.7** shows their renal sites of action.

TABLE 25.6

Diuretics for Treating Fluid Retention in Chronic Heart Failure

DRUG	INITIAL DAILY DOSE(S)	MAXIMUM TOTAL DAILY DOSE	DURATION OF ACTION
Loop Diuretics*			
Bumetanide	0.5-1.0 mg once or twice	10 mg	4-6 hours
Furosemide	20-40 mg once or twice	600 mg	6-8 hours
Torsemide	10-20 mg once	200 mg	12-16 hours
Ethacrynic acid	25-50 mg once or twice	200 mg	6 hours
Thiazide Diuretics**			
Chlorothiazide	250-500 mg once or twice	1000 mg	6-12 hours
Chlorthalidone	12.5-25 mg once	100 mg	24-72 hours
Hydrochlorothiazide	25 mg once or twice	200 mg	6-12 hours
Indapamide	2.5 mg once	5 mg	36 hours
Metolazone	2.5-5.0 mg once	5 mg	12-24 hours
Potassium-Sparing Diuretics			
Amiloride	5.0 mg once	20 mg	24 hours
Triamterene	50 to 100 mg twice	300 mg	7-9 hours
AVP Antagonists			
Satavaptan	25 mg once	50 mg once	NS
Tolvaptan	15 mg once	60 mg once	NS
Lixivaptan	25 mg once	250 mg twice	NS
Conivaptan (IV)	20 mg IV loading dose followed by	100 mg once	7-9 hours
	20 mg continuous IV infusion/day	40 mg IV	
Sequential Nephron Blockade			
Metolazone	2.5-10 mg once PLUS loop diuretic		
Hydrochlorothiazide	25-100 mg once or twice PLUS loop diuretic		
Chlorothiazide (IV)	500-1000 mg once PLUS loop diuretic		

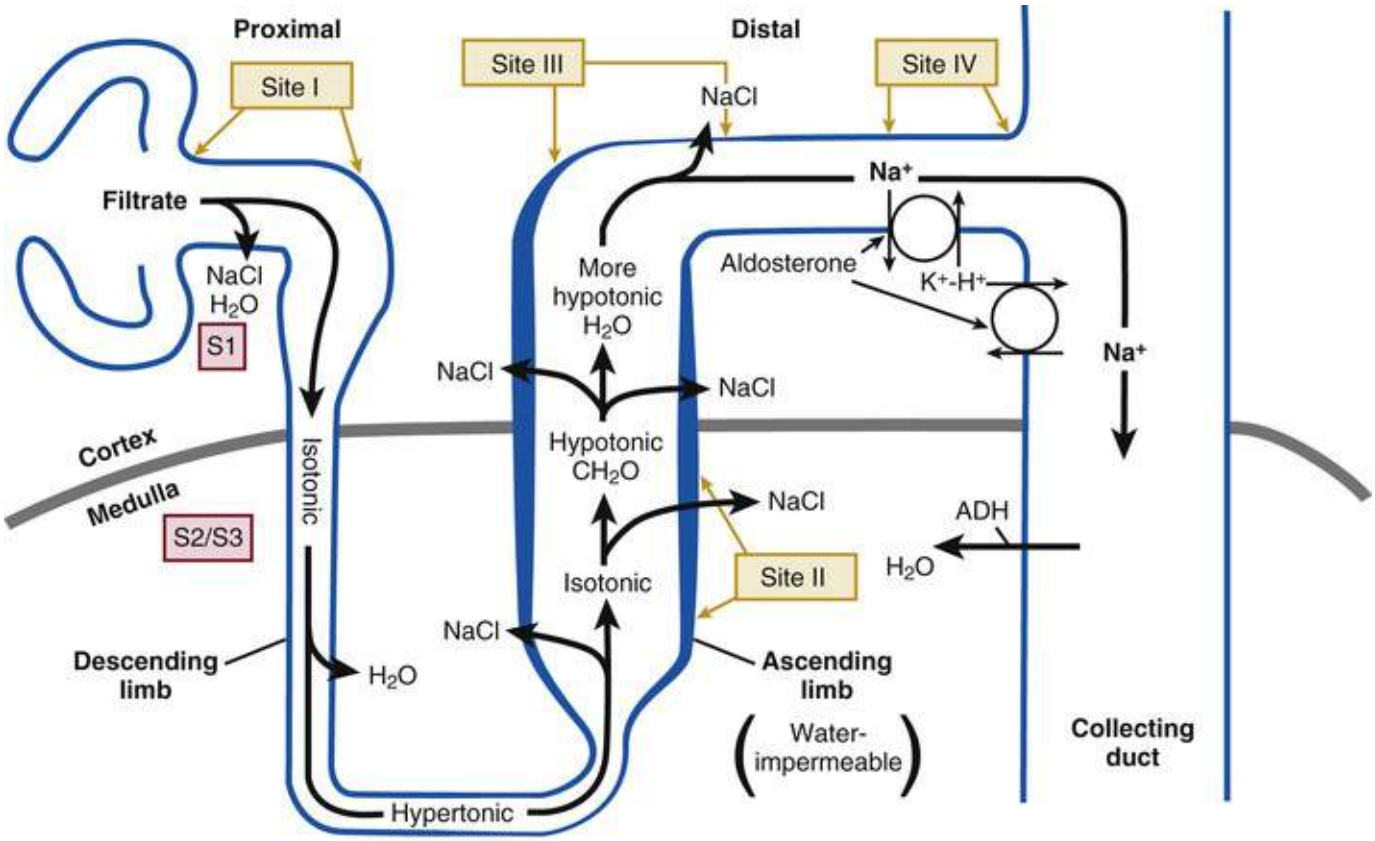
*Equivalent doses: 40 mg furosemide = 1 mg bumetanide = 20 mg torsemide = 50 mg of ethacrynic acid.

**Do not use if estimated glomerular filtration rate is <30 mL/min, or with cytochrome 3A4 inhibitors.

Unless indicated, all doses are for oral diuretics.

IV, Intravenous(ly); *NS,* not specified.

Modified from Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult–summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2005;46(6):1116.



Site I (proximal convoluted tubule): carbonic anhydrase inhibitors, SGLT2 inhibitors
Site II (ascending loop of Henle): loop diuretics
Site III (distal convoluted tubule): thiazide and thiazide-like diuretics
Site IV (late distal tubule and collecting duct): potassium-sparing diuretics, MRAs

FIGURE 25.7 Sites of action of diuretics in the kidney. (Modified from Wile D. Diuretics: a review. Ann Clin Biochem 2012;49:419-31.)

Loop Diuretics

The agents classified as loop diuretics, including *furosemide*, *bumetanide*, and *torsemide*, act by reversibly inhibiting the Na^+-K^+-$2Cl^-$ symporter (cotransporter) on the apical membrane of epithelial cells in the thick ascending loop of Henle (site II, **Fig. 25.7**). Because furosemide, bumetanide, and torsemide are bound extensively to plasma proteins, delivery of these drugs to the tubule by filtration is limited. However, these drugs are secreted efficiently by the organic acid transport system in the proximal tubule and thereby gain access to their binding sites on the Na^+-K^+-$2Cl^-$ symporter in the luminal membrane of the ascending limb. Thus the efficacy of loop diuretics depends on sufficient renal plasma blood flow and proximal tubular secretion to deliver these agents to their site of action. Probenecid shifts the plasma concentration-response curve for furosemide to the right by competitively inhibiting furosemide excretion by the organic acid transport system. The bioavailability of furosemide ranges from 40% to 70% of the oral dose. In contrast, the oral bioavailability of bumetanide and torsemide exceeds 80%. Accordingly, these agents may be more effective in patients with advanced HF or right-sided HF, although at considerably greater cost. Agents in a second functional class of loop diuretics, typified by ethacrynic acid, exhibit a slower onset of action and have delayed and only partial reversibility. Ethacrynic acid may be safely used in sulfa-allergic HF patients.

Mechanisms of Action.

Loop diuretics are believed to improve symptoms of congestion by several mechanisms. First, loop diuretics reversibly bind to and reversibly inhibit the action of the Na^+-K^+-$2Cl^-$ cotransporter, thereby preventing salt transport in the thick ascending loop of Henle. Inhibition of this symporter also inhibits Ca^{2+} and Mg^{2+} resorption by abolishing the transepithelial potential difference that is the driving force for absorption of these cations. By inhibiting the concentration of solute within the medullary interstitium, these drugs also reduce the driving force for water resorption in the collecting duct, even in the presence of AVP (**see Chapter 23**). The decreased resorption of water by the collecting duct results in the production of urine that is almost isotonic with plasma. The increase in delivery of Na^+ and water to the distal nephron segments also greatly enhances K^+ excretion, particularly in the presence of elevated aldosterone levels.

Loop diuretics also exhibit several characteristic effects on intracardiac pressure and systemic hemodynamics. Furosemide acts as a venodilator and reduces right atrial and pulmonary capillary wedge pressure (PCWP) within minutes when given intravenously (0.5 to 1.0 mg/kg). Similar data, although not as extensive, have accumulated for bumetanide and torsemide. This initial improvement in hemodynamics may be secondary to the release of vasodilatory prostaglandins, because animal and human studies have demonstrated that the venodilatory actions of furosemide are inhibited by indomethacin. There have also been reports of an acute rise in systemic vascular resistance in response to loop diuretics, which has been attributed to transient activation of the systemic or intravascular RAS. The potentially deleterious rise in LV afterload reinforces the importance of initiating vasodilator therapy with diuretics in patients with acute pulmonary edema and adequate blood pressure (**see Chapter 24**).

Thiazide and Thiazide-Like Diuretics.

The benzothiadiazides, also known as thiazide diuretics, were the initial class of drugs that were synthesized to block the Na^+-Cl^- transporter in the cortical portion of the ascending loop of Henle and the distal convoluted tubule (site III, **Fig. 25.7**). Subsequently, drugs that share similar pharmacologic properties became known as “thiazide-like diuretics,” even though they were technically not benzothiadiazine derivatives. *Metolazone,* a quinazoline sulfonamide, is a thiazide-like diuretic that is used in combination with furosemide in patients who become resistant to diuretics (see later). Because thiazide and thiazide-like diuretics prevent maximal dilution of urine, they decrease the kidney's ability to increase free water clearance and may therefore contribute to the development of hyponatremia. Thiazides increase Ca^{2+} resorption in the distal nephron (**see Fig. 25.7**) by several mechanisms, occasionally resulting in a small increase in serum Ca^{2+} levels. In contrast, Mg^{2+} resorption is diminished, and hypomagnesemia may occur with prolonged use. Increased delivery of NaCl and fluid into the collecting duct directly enhances K^+ and H^+ secretion by this segment of the nephron, which may lead to clinically important hypokalemia.

Mechanisms of Action.

The site of action of thiazide diuretics within the distal convoluted tubule has been identified as the Na^+-Cl^- symporter of the distal convoluted tubule. Although this cotransporter shares about 50% amino acid homology with the Na^+-K^+-$2Cl^-$ symporter of the ascending limb of the loop of Henle, it is insensitive to the effects of furosemide. This cotransporter (or related isoforms) is also present on cells within the vasculature and many cell types within other organs and tissues and may contribute to other actions of these agents, such as their utility as antihypertensive agents. Similar to the loop diuretics, the efficacy of

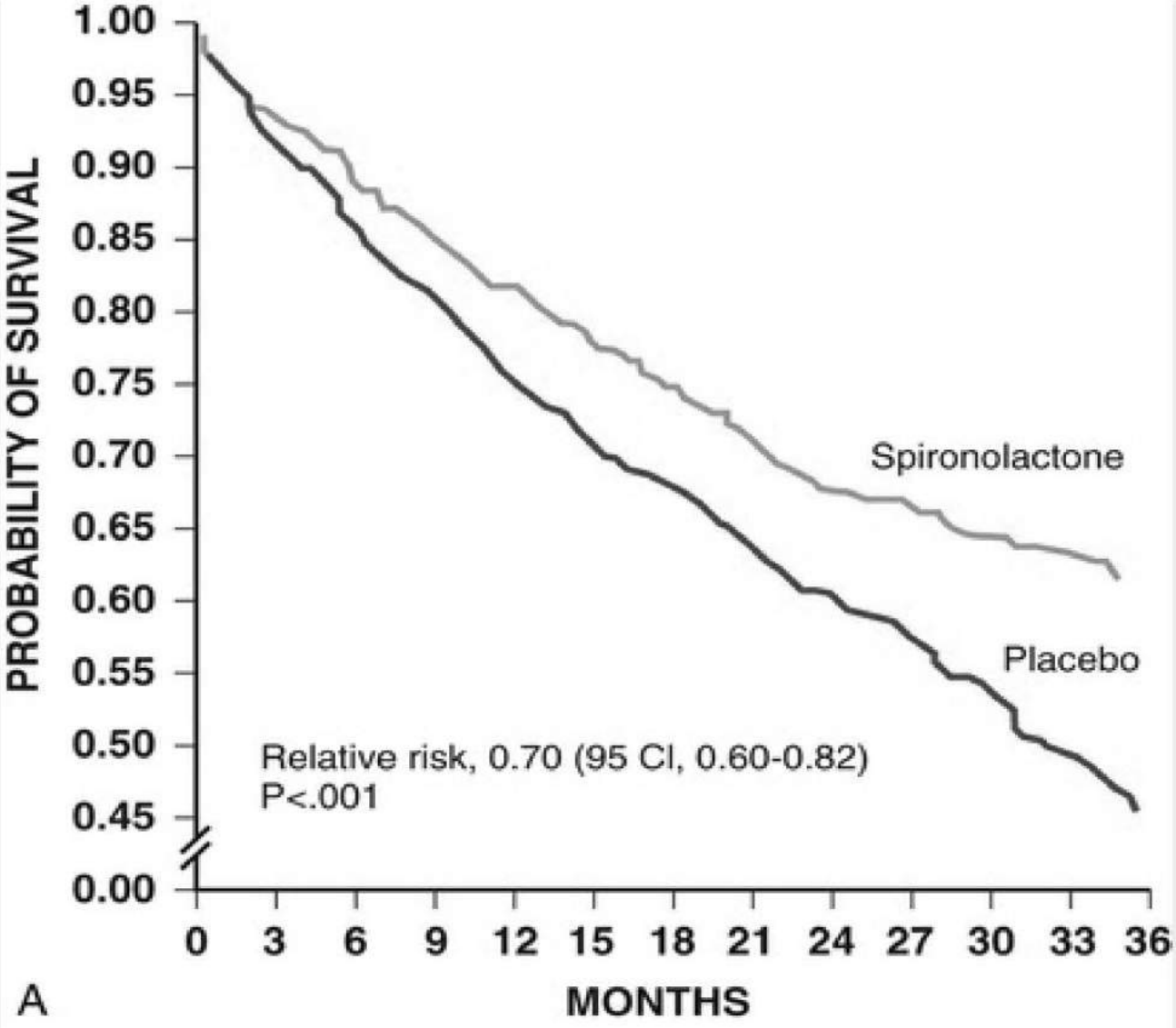
thiazide diuretics depends, at least in part, on proximal tubular secretion to deliver these agents to their site of action. Unlike the loop diuretics, however, the plasma protein binding varies considerably among the thiazide diuretics; accordingly, this parameter will determine the contribution of glomerular filtration to tubular delivery of a specific diuretic.

Mineralocorticoid Receptor Antagonists

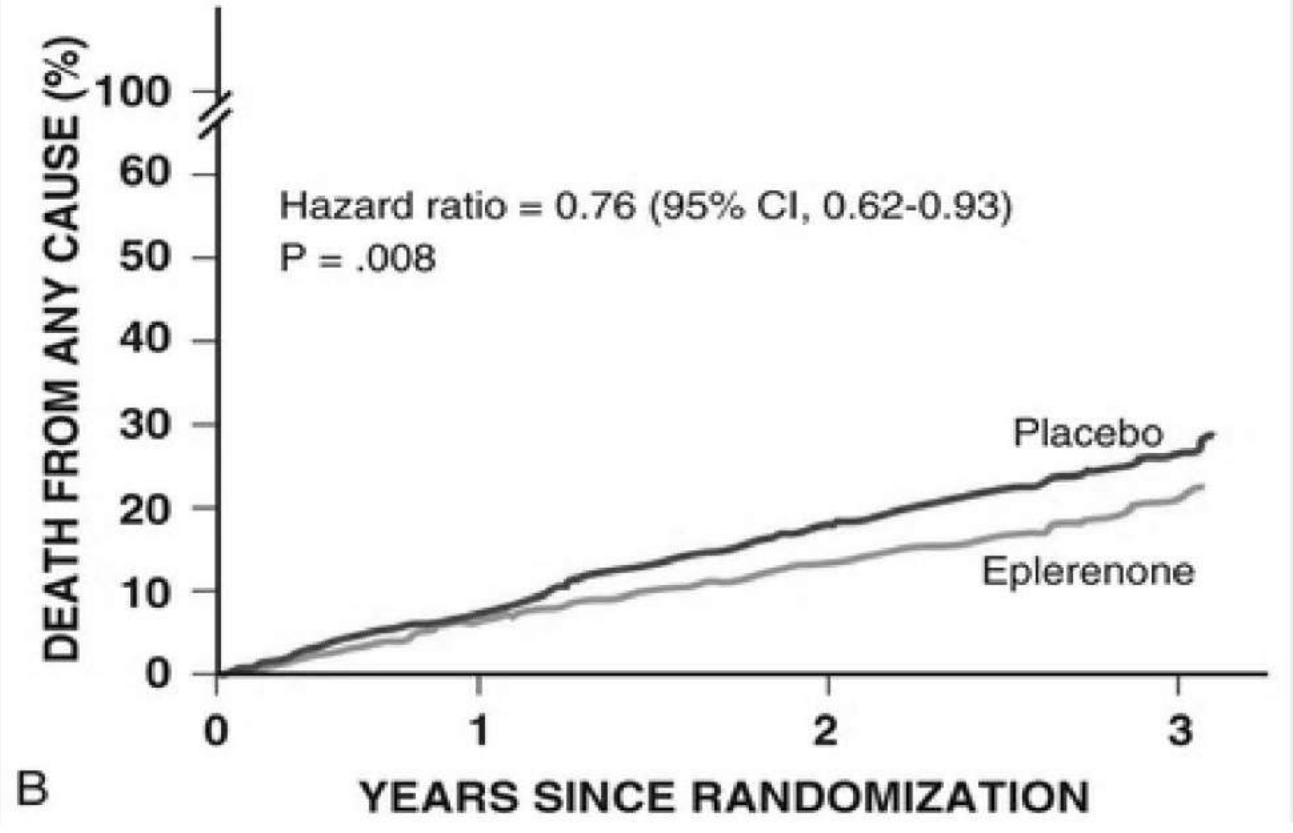
Mineralocorticoids such as *aldosterone* cause retention of salt and water and increase the excretion of K^+ and H^+ by binding to specific mineralocorticoid receptors. *Spironolactone* (first-generation MRA) and *eplerenone* (second-generation MRA) are synthetic mineralocorticoid receptor antagonists (MRAs) that act on the distal nephron to inhibit Na^+/K^+ exchange at the site of aldosterone action (**see Fig. 25.7**).

Mechanisms of Action.

Spironolactone has antiandrogenic and progesterone-like effects, which may cause gynecomastia or impotence in men and menstrual irregularities in women. To overcome these side effects, eplerenone was developed by replacing the 17α-thioacetyl group of spironolactone with a carbomethoxy group. As a result, eplerenone has greater selectivity for the mineralocorticoid receptor than for steroid receptors and has less sex hormone side effects than spironolactone. Eplerenone is further distinguished from spironolactone by its shorter half-life and having no active metabolites. Although spironolactone and eplerenone are both weak diuretics, clinical trials have shown that both have profound effects on CV morbidity and mortality by virtue of their ability to antagonize the deleterious effects of aldosterone in the CV system (**Fig. 25.8**) (**see Chapter 23**). Therefore, these agents are used in HF for their ability to antagonize the RAAS (see later) rather than for their diuretic properties. Spironolactone (**see Table 25.6**) and its active metabolite, canrenone, competitively inhibit the binding of aldosterone to mineralocorticoid or type I receptors in many tissues, including epithelial cells of the distal convoluted tubule and collecting duct. These cytosolic receptors are ligand-dependent transcription factors, which on binding of the ligand (e.g., aldosterone), translocate to the nucleus, where they bind to hormone response elements present in the promoter of some genes, including several involved in vascular and myocardial fibrosis, inflammation, and calcification.


PROBABILITY OF SURVIVAL
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.00
Spironolactone
Placebo
Relative risk, 0.70 (95 CI, 0.60-0.82)
P<.001
0 3 6 9 12 15 18 21 24 27 30 33 36
MONTHS

A


DEATH FROM ANY CAUSE (%)
100
60
50
40
30
20
10
0
Hazard ratio = 0.76 (95% CI, 0.62-0.93)
P = .008
Placebo
Eplerenone
0 1 2 3
YEARS SINCE RANDOMIZATION

B

FIGURE 25.8 Kaplan-Meier analysis of the probability of survival among patients in the placebo and treatment groups in the RALES trial **(A)** with spironolactone and the EMPHASIS trial **(B)** using eplerenone. (Modified from Pitt B et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709-17, and Zannad F et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11-21.)

Although first- and second-generation steroid-based MRAs have been shown to reduce HF mortality rates, the broader use of these agents in HF patients has been limited by significant side effects, most notably hyperkalemia. Novel, potent, and selective "third-generation" nonsteroidal MRAs that combine the potency and efficacy of spironolactone with the selectivity of eplerenone, and that have less hyperkalemia, have recently entered clinical trials (**Fig. 25.9**). *Finerenone* (BAY 94-8862) is a nonsteroidal MRA that was compared to eplerenone in patients with worsening chronic HF and type 2 diabetes mellitus and/or chronic kidney disease in the phase IIb ARTS-HF (Mineralocorticoid-Receptor Antagonist Tolerability Study).[17] ARTS-HF was a randomized, double-blind, comparator-controlled multicenter trial in 1066 patients with heart failure (LVEF ≤40%). The primary endpoint was the percentage of individuals with a decrease of more than 30% in plasma NT-proBNP from baseline to day 90. When compared to eplerenone, finerenone was well tolerated and resulted in a 30% or greater decrease in NT-proBNP levels, which was similar to the proportion of patients observed in the eplerenone group. The composite clinical endpoint of death from any cause, CV hospitalizations, or emergency presentation for worsening HF until day 90, which was a prespecified secondary endpoint, occurred less frequently in all finerenone groups except for the lowest doses.

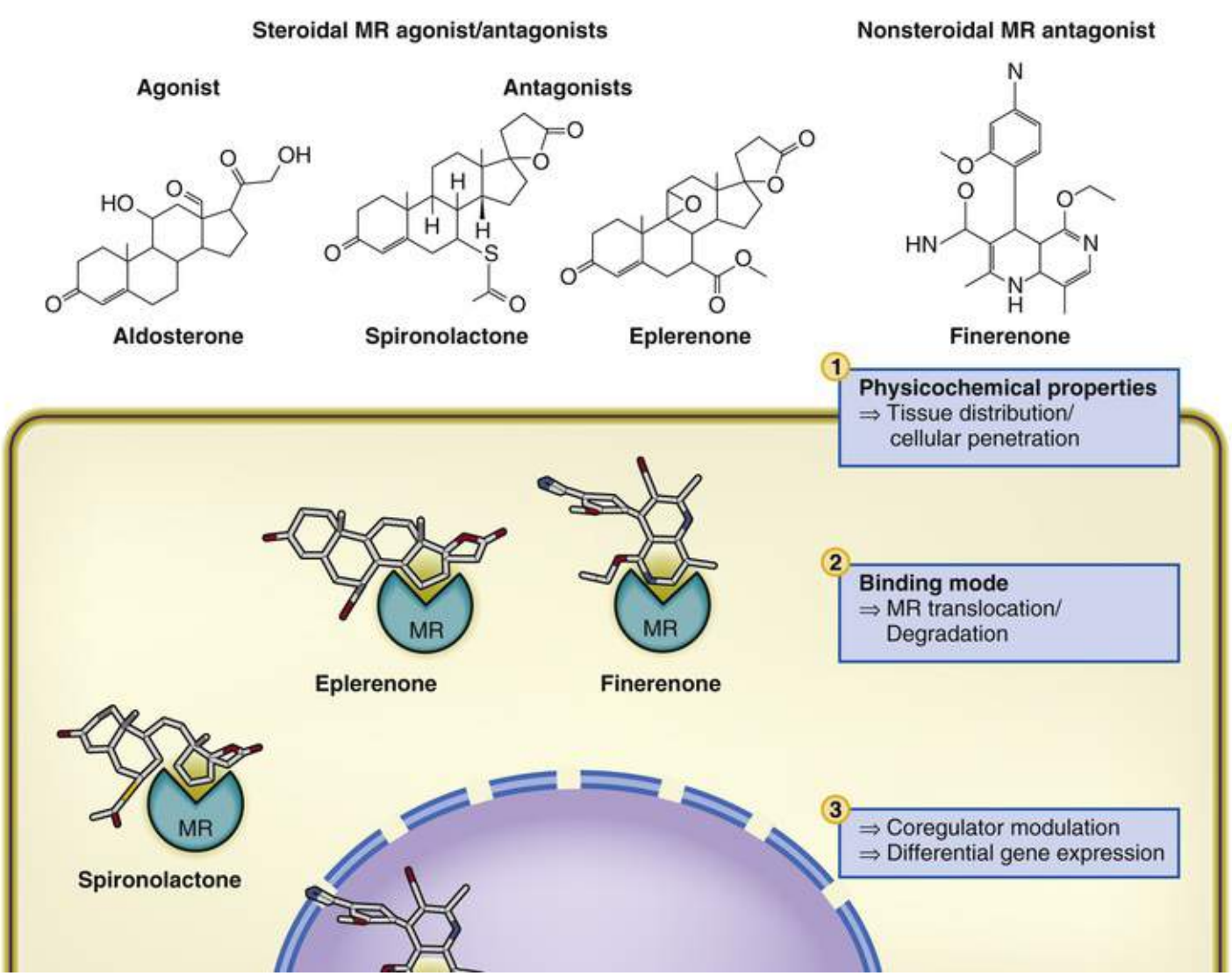


FIGURE 25.9 Nonsteroidal mineralocorticoid receptor antagonists (MRAs). The nonsteroidal MRA finerenone has a unique pharmacodynamic profile considered to be a consequence of several individual key differences compared with steroidal MRAs, including physicochemical properties, tissue distribution, mode of mineralocorticoid receptor inactivation, and differential regulation of downstream antihypertrophic gene expression. Differential modes of action exist between the steroidal MRAs and the nonsteroidal finerenone. The steroidal MRA aldosterone and antagonists spironolactone and eplerenone are structurally distinct from the nonsteroidal MRA finerenone, as shown at the top of the figure. The key cellular localizations, which determine the final pharmacologic profile of steroidal MRAs and finerenone, are as follows: first, the extracellular space and plasma membrane (determination of tissue distribution and cellular penetration); second, the cytoplasm (binding mode determines the nuclear translocation of mineralocorticoid receptor or its degradation); and third, the nucleus (ligand-dependent coregulator modulation determines differential gene expression). (From Kolkhof P, Nowack C, Eitner F. Nonsteroidal antagonists of the mineralocorticoid receptor. Curr Opin Nephrol Hypertens 2015;24:417-24.)

Potassium-Sparing Diuretics

Triamterene and *amiloride* are referred to as potassium-sparing diuretics and share the common property of causing a mild increase in NaCl excretion, as well as having anti-kaliuretic properties. Triamterene is a pyrazinoylguanidine derivative, whereas amiloride is a pteridine. Both drugs are organic bases that are transported into the proximal tubule, where they block Na^+ reabsorption in the late distal tubule and collecting duct (site IV, **Fig. 25.7**). However, since Na^+ retention occurs in more proximal nephron sites in HF, neither amiloride nor triamterene is effective in achieving a net negative Na^+ balance when given alone in HF patients. Both amiloride and triamterene appear to share a similar mechanisms of action. Considerable evidence suggests that amiloride blocks Na^+ channels in the luminal membrane of the

principal cells in the late distal tubule and collecting duct, perhaps by competing with Na^+ for negatively charged areas within the pore of the Na^+ channel. Blockade of Na^+ channels leads to hyperpolarization of the luminal membrane of the tubule, which reduces the electrochemical gradient that provides the driving force for K^+ secretion into the lumen. Amiloride and its congeners also inhibit Na^+/H^+ antiporters in renal epithelial cells and in many other cell types, but only at concentrations that are higher than those used clinically.

Carbonic Anhydrase Inhibitors

The zinc metalloenzyme carbonic anhydrase plays an essential role in the $NaHCO_3$ resorption and acid secretion in the proximal tubule (site I, **Fig. 25.7**). Although weak diuretics, carbonic anhydrase inhibitors (**see Table 25.6**) such as acetazolamide potently inhibit carbonic anhydrase, resulting in near complete loss of $NaHCO_3$ resorption in the proximal tubule. The use of these agents in patients with HF is confined to temporary administration to correct the metabolic alkalosis that occurs as a "contraction" phenomenon in response to the administration of other diuretics. When used repeatedly, these agents can lead to metabolic acidosis as well as severe hypokalemia.

Sodium-Glucose Transporter-2 Inhibitors

The sodium-glucose cotransporter-2 (SGLT-2) is a high-capacity, low-affinity transporter located in the S_1 and S_2 segments of the proximal tubule in the kidneys (**see Fig. 25.7**). SGLT-2 accounts for 90% of glucose reabsorption by the kidney, whereas the lower-capacity higher-affinity sodium-glucose transporter-1 (SGLT-1), located in the S_3 segment of the proximal tubules, accounts for the remaining 10% of glucose absorption. SGLT-2 is also responsible for proximal tubular reabsorption of sodium and the passive absorption of chloride that is driven by the resulting electrochemical gradient in the proximal tubule lumen. The increased absorption of sodium and chloride in the proximal tubule results in lower chloride concentration delivered to the distal tubule, which in turn results in dilation of the afferent arteriole and increase glomerular filtration through "tubuloglomerular feedback." SGLT-2 inhibitors result in a 1 : 1 stoichiometric inhibition of sodium and glucose uptake in the proximal tubule of the kidney. This leads to increased concentration of chloride in the distal tubule, and a resetting of the tubulo-glomerular feedback mechanism, that results in a contraction of the plasma volume without activation of the sympathetic nervous system. Agents in the SGLT-2 class of inhibitors include *canagliflozin*, *dapagliflozin*, and *empagliflozin*.

The landmark EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) showed that empagliflozin reduced death from CV causes by 38%, hospitalization for HF by 35%, and progression to end-stage kidney disease in patients with type 2 diabetes and established CV disease[18] (**see Chapter 51**). Although the precise mechanism(s) that resulted in the striking reduction in HF hospitalization in the empagliflozin treatment arm is not known, it is likely more than simply glucose lowering and may be secondary to additional mechanisms of action, including renal-protective effects, enhanced diuretic efficiency, improved cardiac metabolism, and improved vascular stiffness.[19] Based on these promising results, there are a number of planned or ongoing clinical trials with SGLT-2 inhibitors in heart failure (NCT02653482, NCT02862067, NCT02920918).

Vasopressin Antagonists

Increased circulating levels of the pituitary hormone arginine vasopressin contribute to the increased

systemic vascular resistance and positive water balance in HF patients (**see Chapter 23**). The cellular effects of AVP are mediated by interactions with three types of receptors, V_{1a}, V_{1b} and V_2. Selective V_{1a} antagonists block the vasoconstricting effects of AVP in peripheral vascular smooth muscle cells, whereas V_2-selective receptor antagonists inhibit recruitment of *aquaporin* water channels into the apical membranes of collecting duct epithelial cells, reducing the ability of the collecting duct to resorb water (**see Fig. 25.12**). Combined V_{1a}/V_2 antagonists lead to a decrease systemic vascular resistance and prevent the dilutional hyponatremia that occurs in HF patients.[20]

The AVP antagonists or "vaptans" (**see Table 25.6**) were developed to selectively block the V_2 receptor (e.g., *tolvaptan, lixivaptan, satavaptan*) or nonselectively block both the V_{1a} and the V_2 receptor (e.g., *conivaptan*). All four AVP antagonists increase urine volume, decrease urine osmolarity, and have no effect on 24-hour sodium excretion.[20] Long-term therapy with the V_2-selective AVP antagonist tolvaptan did not improve mortality but appears to be safe in patients with advanced HF.[21] Currently, two AVP antagonists are approved by the U.S. Food and Drug Administration (FDA), conivaptan and tolvaptan, for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum $Na^+ \leq 125$) that is symptomatic and resisted correction with fluid restriction in patients with HF; however, neither of these agents is currently specifically approved for the treatment of HF. Use of these agents is appropriate after traditional measures to treat hyponatremia have been tried, including water restriction and maximization of medical therapies such as ACEIs or ARBs, which block or decrease angiotensin II. The use of vaptans in hospitalized HF patients is discussed in **Chapter 24**.

Diuretic Treatment of Heart Failure

Patients with evidence of volume overload or a history of fluid retention should be treated with a diuretic to relieve their symptoms. In symptomatic patients, diuretics should be always used in combination with neurohormonal antagonists that are known to prevent disease progression. When patients have moderate to severe symptoms or renal insufficiency, a loop diuretic is generally required. Diuretics should be initiated in low doses (**see Table 25.6**) and then titrated upward to relieve signs and symptoms of fluid overload. A typical starting dose of furosemide for patients with systolic HF and normal renal function is 40 mg, although doses of 80 to 160 mg are often necessary to achieve adequate diuresis. Because of the steep dose-response curve and effective threshold for loop diuretics, it is critical to find an adequate dose of loop diuretic that leads to a clear-cut diuretic response (**Fig. 25.10A**). One common method for finding the appropriate dose is to double the dose until the desired effect is achieved, or until the maximum dose of diuretic is reached. Once patients have achieved an adequate diuresis, it is important to document their "dry weight" and make certain that patients weigh themselves daily to maintain their dry weight.

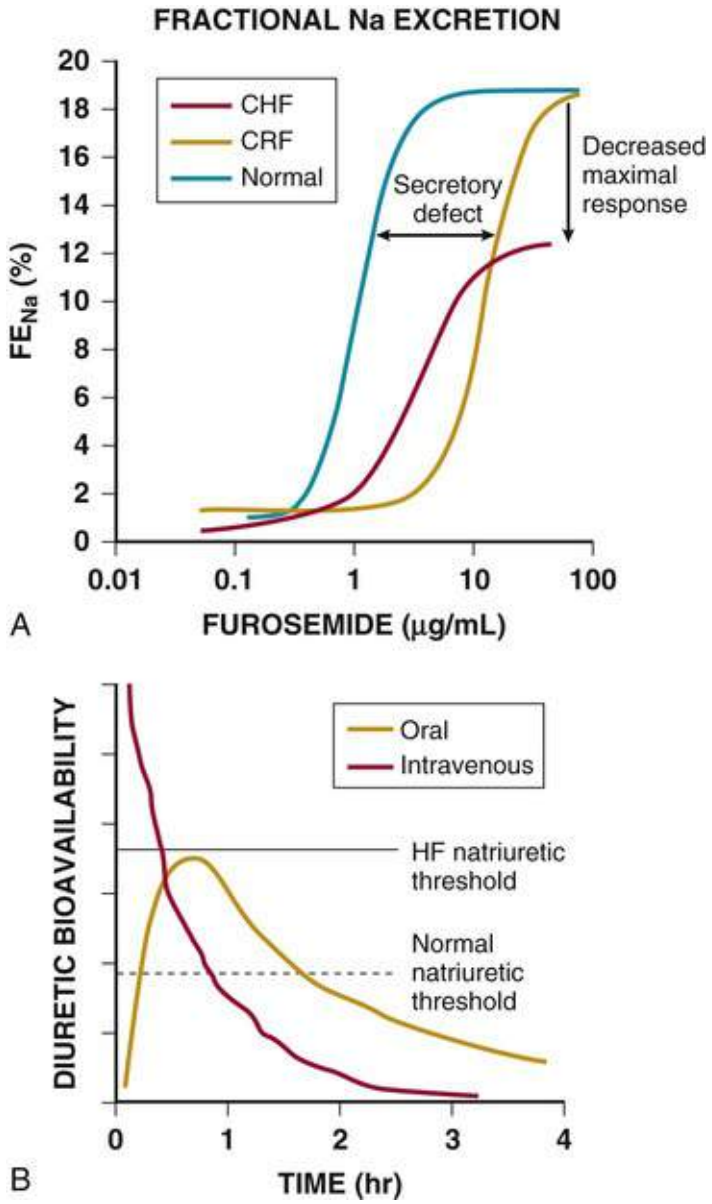


FIGURE 25.10 Dose-response curves for loop diuretics. **A,** Fractional sodium (Na) excretion (FE_{Na}) as a function of loop diuretic concentration. Compared with normal patients, patients with chronic renal failure (CRF) show a rightward shift in the curve because of impaired diuretic secretion. The maximal response is preserved when expressed as FE_{Na}, but not when expressed as absolute Na excretion. Patients with chronic heart failure (CHF) demonstrate a rightward and downward shift, even when the response is expressed as FE_{Na}, and thus are relatively diuretic resistant. **B,** Comparison of the response to intravenous and oral doses of loop diuretics in normal individuals and HF patients. Diuretic bioavailability is shown for normal patients and HF patients. The natriuretic threshold necessary to produce a diuresis in shown for normal individuals (*dotted line*) and for HF patients (*solid line*). In a normal individual, an oral dose may be as effective as an IV dose because the diuretic bioavailability (area under the curve) that is above the natriuretic threshold for IV and oral diuretics is approximately equal. However, if the natriuretic threshold increases in a patient with HF, the oral dose may not provide a high enough serum level to elicit a significant natriuresis. (Modified from Ellison DH. Diuretic therapy and resistance in congestive heart failure. Cardiology 2001;96:132-43.)

Although furosemide is the most frequently used loop diuretic, the oral bioavailability of furosemide is approximately 40% to 79%. Therefore, bumetanide or torsemide may be preferable because of their increased bioavailability. With the exception of torsemide, the common loop diuretics are short-acting (<3 hours). For this reason, loop diuretics usually need to be given at least twice daily. Some patients may develop hypotension or azotemia during diuretic therapy. While the rapidity of diuresis should be slowed in these patients, diuretic therapy should be maintained at a lower level until the patient becomes euvolemic, since persistent volume overload may compromise the effectiveness of some neurohormonal

antagonists. IV administration of diuretics may be necessary to relieve congestion acutely and can be done safely in the outpatient setting (**Fig. 25.10B**) (**see Chapter 24**). After a diuretic effect is achieved with short-acting loop diuretics, increasing administration frequency to twice or even three times per day will provide more diuresis with less physiologic perturbation than larger single doses. Once the congestion has been relieved, treatment with diuretics is continued to prevent the recurrence of salt and water retention in order to maintain the patient's ideal dry weight.

Complications of Diuretic Use

Patients with HF who are receiving diuretics should be monitored regularly for complications. The major complications of diuretic use include electrolyte and metabolic disturbances, volume depletion, and worsening azotemia. The interval for reassessment should be individualized based on severity of illness and underlying renal function, use of concomitant medications such as ACEIs, angiotensin receptor blockers (ARBs), and aldosterone antagonists, past history of electrolyte imbalances, and need for more aggressive diuresis.

Electrolyte and Metabolic Disturbances

Diuretic use can lead to potassium (K^+) depletion, which can predispose the patient to significant cardiac arrhythmias. Renal K^+ losses from diuretic use can be also exacerbated by the increase in circulating levels of aldosterone observed in patients with advanced HF, as well by the marked increases in distal nephron Na^+ delivery that follow use of either loop or distal nephron diuretics. The level of dietary salt intake may also contribute to the extent of renal K^+ wasting with diuretics.

In the absence of formal guidelines with respect to the level of maintenance of serum K^+ levels in HF patients, many experienced HF clinicians have advocated that the serum K^+ should be maintained between 4.0 and 5.0 mEq/L, because HF patients are often treated with pharmacologic agents that are likely to provoke proarrhythmic effects in the presence of hypokalemia (e.g., digoxin, type III antiarrhythmics, beta agonists, phosphodiesterase inhibitors). Hypokalemia can be prevented by increasing the oral intake of potassium chloride (KCl). The normal daily dietary K^+ intake is approximately 40 to 80 mEq. Therefore, to increase this by 50% requires an additional 20 to 40 mEq K^+ supplementation daily. However, in the presence of alkalosis, hyperaldosteronism, or Mg^{2+} depletion, hypokalemia is quite unresponsive to increased dietary intake of KCl, and more aggressive replacement is necessary. If supplementation is necessary, oral potassium supplements in the form of KCl extended-release tablets or liquid concentrate should be used whenever possible. IV potassium is potentially hazardous and should be avoided except in emergencies. Where appropriate, the use of an MRA may also prevent the development of hypokalemia.

The use of aldosterone receptor antagonists is often associated with the development of life-threatening hyperkalemia, particularly when combined with ACEIs, ARBs, or angiotensin receptor neprilysin inhibitors (ARNIs).[22] Potassium supplementation is generally stopped after the initiation of aldosterone antagonists, and patients should be counseled to avoid high–potassium-containing foods. The management of acute hyperkaliemia (>6.0 mEq/L) may require a short-term cessation of potassium-retaining agents and/or RAAS inhibitors; however, RAAS inhibitors should be carefully reintroduced as soon as possible while monitoring K^+ levels. Two new K^+ binders, patiromer and sodium zirconium cyclosilicate, have

been studied in HF patients with hyperkalemia. *Patiromer* is a nonabsorbed, cation-exchange polymer that contains a calcium-sorbitol counterion and works by binding K^+ in the lumen of the gastrointestinal tract, resulting in a reduction of serum K^+ levels within 7 hours of the first dose. Patiromer is FDA approved for the treatment of hyperkalemia but should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action. The initial clinical studies in patients with HF have shown that these therapies reduce serum K^+ and prevent recurrent hyperkalemia in HF patients with chronic kidney disease who were receiving RAAS inhibitors.[23]

Diuretics may be associated with multiple other metabolic and electrolyte disturbances, including hyponatremia, hypomagnesemia, metabolic alkalosis, hyperglycemia, hyperlipidemia, and hyperuricemia. Hyponatremia is usually observed in HF patients with very high degrees of RAAS activation and high AVP levels. Aggressive diuretic use can also lead to hyponatremia. Hyponatremia can typically be treated by more stringent water restriction. Both loop and thiazide diuretics can cause hypomagnesemia, which can aggravate muscle weakness and cardiac arrhythmias. Magnesium replacement should be administered for signs or symptoms of hypomagnesemia (arrhythmias, muscle cramps) and can be routinely given (with uncertain benefit) to all patients receiving large doses of diuretics or requiring large amounts of K^+ replacement. The modest hyperglycemia or hyperlipidemia produced by thiazide diuretics is not usually clinically important, and blood glucose and lipids are usually easily controlled using standard-practice guidelines. Metabolic alkalosis can generally be treated by increasing KCl supplementation, lowering diuretic doses, or transiently using acetazolamide.

Hypotension and Azotemia

The excessive use of diuretics can lead to a decreased blood pressure, decreased exercise tolerance, and increased fatigue, as well as impaired renal function. Hypotensive symptoms usually resolve after a decrease in the dose or frequency of diuretics in patients who are volume depleted. In most patients, however, use of diuretics is associated with decreased blood pressure and mild azotemia, which do not lead to patient symptoms. In these cases, reductions in the diuretic dose are not necessary, particularly if the patient remains edematous. In some patients with advanced, chronic HF, elevated blood urea nitrogen (BUN) and creatinine concentrations may be necessary to maintain control of congestive symptoms.

Neurohormonal Activation

Diuretics may increase the activation of endogenous neurohormonal systems in HF patients, which can lead to disease progression unless patients are receiving treatment with a concomitant neurohormonal antagonist (e.g., ACEI, beta blocker).

Ototoxicity

Ototoxicity, which is more frequent with ethacrynic acid than the other loop diuretics, can manifest as tinnitus, hearing impairment, and deafness. Hearing impairment and deafness are usually, but not invariably, reversible. Ototoxicity occurs most frequently with rapid IV injections and least frequently with oral administration.

Diuretic Resistance

One of the inherent limitations of diuretics is that they achieve water loss through excretion of solute at the expense of glomerular filtration, which in turn activates a set of homeostatic mechanisms that ultimately

limit their effectiveness. In normal patients the magnitude of natriuresis following a given dose of diuretic declines over time as a result of the "braking phenomenon" (**Fig. 25.11**). Studies have shown that the time-dependent decline in natriuresis for a given diuretic dose is critically dependent on reduction of the extracellular fluid (ECF) volume, which leads to an increase in solute and fluid reabsorption in the proximal tubule. In addition, contraction of the ECF volume can lead to stimulation of efferent sympathetic nerves, which reduces urinary Na^+ excretion by reducing renal blood flow, stimulating renin (and ultimately aldosterone) release, which in turn stimulates Na^+ reabsorption along the nephron (**see Chapter 23**). The magnitude of the natriuretic effect of potent loop diuretics may also decline in HF patients, particularly as HF progresses. Although the bioavailability of these diuretics is generally not decreased in HF, the potential delay in their rate of absorption may result in peak drug levels within the tubular lumen in the ascending loop of Henle that are insufficient to induce maximal natriuresis. The use of IV formulations may obviate this problem (**see Chapter 24**). However, even with IV dosing, a rightward shift of the dose-response curve is observed between the diuretic concentration in the tubular lumen and its natriuretic effect in HF (**see Fig. 25.10A**). Moreover, the maximal effect (ceiling) is lower in HF. This rightward shift has been referred to as "diuretic resistance" and is likely caused by several factors in addition to the braking phenomenon.

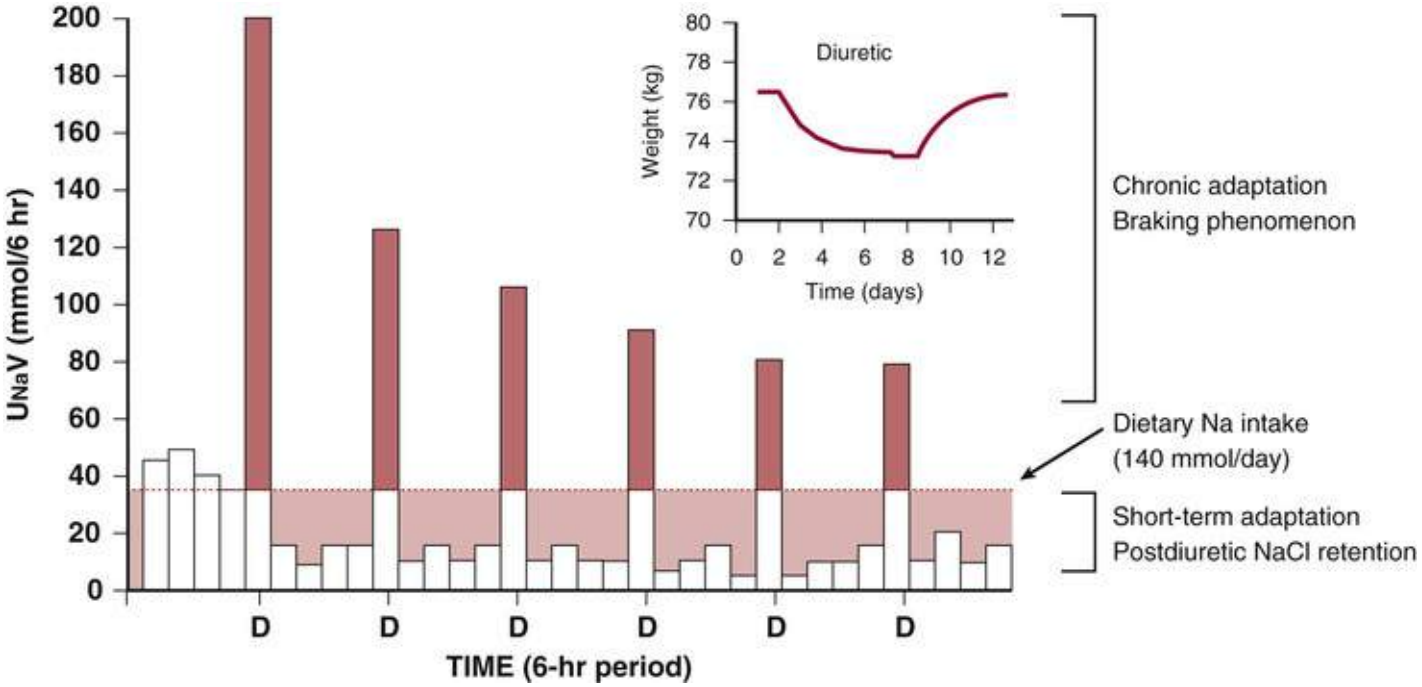


FIGURE 25.11 Effects of diuretics on urinary sodium (Na) excretion and extracellular fluid (ECF) volume. **Main graph,** Effects of a loop diuretic on urinary Na excretion ($U_{Na}V$). Bars represent 6-hour periods before (in Na balance) and after doses of loop diuretic (*D*). The *dotted line* indicates dietary Na intake. The *solid red* portion of the *open bars* indicates the amount by which Na excretion exceeds intake during natriuresis. The *hatched areas* indicate the amount of positive Na balance after the diuretic effect has worn off. Net Na balance during 24 hours is the difference between the *shaded area below the stippled line* (postdiuretic NaCl retention) and the *solid areas within the bars* (diuretic-induced natriuresis). Chronic adaptation is indicated by progressively smaller peak natriuretic effects (the braking phenomenon) and is mirrored by a return to neutral balance. **Inset,** Effect of a diuretic on body weight, taken as an index of ECF volume. Note that steady state is reached within 6 to 8 days despite continued diuretic administration.
(Modified from Ellison DH. Diuretic therapy and resistance in congestive heart failure. Cardiology. 2001;96:132-143.)

First, most loop diuretics, with the exception of torsemide, are short-acting drugs. Accordingly, after a period of natriuresis, the diuretic concentration in plasma and tubular fluid declines below the diuretic threshold. In this situation, renal Na^+ reabsorption is no longer inhibited, and a period of antinatriuresis or

postdiuretic NaCl retention ensues. If dietary NaCl intake is moderate to excessive, postdiuretic NaCl retention may overcome the initial natriuresis in patients with excessive activation of the adrenergic nervous system and RAS. This observation forms the rationale for administering short-acting diuretics several times per day to obtain consistent daily salt and water loss. Second, there is a loss of renal responsiveness to endogenous natriuretic peptides as HF advances (**see Chapter 23**). Third, diuretics increase solute delivery to distal segments of the nephron, causing epithelial cells to undergo both hypertrophy and hyperplasia. Although the diuretic-induced signals that initiate changes in distal nephron structure and function are not well understood, chronic loop diuretic administration increases the Na^+,K^+-ATPase activity in the distal collecting duct and cortical collecting tubule, as well as increases the number of thiazide-sensitive Na^+-Cl^- cotransporters in the distal nephron, which increases the solute resorptive capacity of the kidney as much as threefold.

In patients with HF, an abrupt decline in cardiac and/or renal function or patient noncompliance with the diuretic regimen or diet may lead to diuretic resistance. Apart from these more obvious causes, it is important to query the patient with regard to concurrent use of drugs that adversely affect renal function, such as NSAIDs and COX-2 inhibitors (**see Table 25.5**), and certain antibiotics (trimethoprim and gentamicin). The relative risk of increased HF hospitalization varies between individual NSAIDs; including a 1.16 (95% CI 1.07 to 1.27) increase for naproxen, a 1.18 (1.12 to 1.23) increase for ibuprofen, a 1.19 (1.15 to 1.24) increase for diclofenac and a 1.51 (1.33 to 1.71) increase for indomethacin. The use of the COX-2 inhibitors etoricoxib and rofecoxib was also associated with increased risk of hospitalization.[24] The insulin-sensitizing thiazolidinediones (TZDs) have also been linked to increased fluid retention in patients with HF, although the clinical significance of this finding is not known. It has been suggested that TZDs activate proliferator-activated receptor-gamma expression in the renal collecting duct, which enhances expression of cell surface epithelial Na^+ channels. Moreover, studies in healthy men have shown that pioglitazone stimulates plasma renin activity, which may contribute to increased Na^+ retention. Rarely, drugs such as probenecid or high plasma concentrations of some antibiotics may compete with the organic ion transporters in the proximal tubule responsible for the transfer of most diuretics from the recirculation into the tubular lumen. The use of increasing doses of vasodilators, with or without a marked decline in intravascular volume as a result of concomitant diuretic therapy, may lower renal perfusion pressure below that necessary to maintain normal autoregulation and glomerular filtration in patients with renal artery stenosis from atherosclerotic disease. Therefore, a reduction in renal blood flow may occur despite an increase in cardiac output, thereby leading to a decrease in diuretic effectiveness.

A patient with HF may be considered to be resistant to diuretic drugs when moderate doses of a loop diuretic do not achieve the desired reduction of the ECF volume. In outpatients, a common and useful method for treating the diuretic-resistant patient is to administer two classes of diuretic concurrently. Adding a proximal tubule diuretic or a distal collecting tubule diuretic to a regimen of loop diuretics is often dramatically effective. As a general rule, when adding a second class of diuretic, the dose of loop diuretic should not be altered because the shape of the dose-response curve for loop diuretics is not affected by the addition of other diuretics, and the loop diuretic must be given at an effective dose for it to be effective. The combination of loop and distal collecting tubule diuretics has been shown to be effective through several mechanisms.[25] One is that distal collecting tubule diuretics have longer half-lives than

loop diuretics and may thus prevent or attenuate postdiuretic NaCl retention. A second mechanism by which distal collecting tubule diuretics potentiate the effects of loop diuretics is by inhibiting Na^+ transport along the proximal tubule, since most thiazide diuretics also inhibit carbonic anhydrase, as well as by inhibiting NaCl transport along the distal renal tubule, which may counteract the increased solute resorptive effects of the hypertrophied and hyperplastic distal epithelial cells.

The selection of distal collecting tubule diuretic to use as second diuretic is a matter of choice. Many clinicians choose metolazone because its half-life is longer than that of some other distal collecting tubule diuretics, and because it has been reported to remain effective even when the glomerular filtration rate (GFR) is low. However, direct comparisons between metolazone and several traditional thiazides have shown little difference in natriuretic potency when they are included in a regimen with loop diuretics in HF patients.[26] Distal collecting tubule diuretics may be added in full doses (50 to 100 mg/day hydrochlorothiazide or 2.5 to 10 mg/day metolazone; **see Table 25.6**) when a rapid and robust response is needed. However, such an approach is likely to lead to excessive fluid and electrolyte depletion if patients are not followed extremely closely. One reasonable approach to combination therapy is to achieve control of fluid overload by initially adding full doses of distal collecting tubule diuretic on a daily basis and then decreasing the dose of the distal collecting tubule diuretic to three times weekly to avoid excessive diuresis. An alternative strategy in hospitalized patients is to administer the same daily parenteral dose of a loop diuretic by continuous IV infusion, which leads to sustained natriuresis because of the continuous presence of high drug levels within the tubular lumen (**see Chapter 24**) and avoids postdiuretic ("rebound") resorption of Na^+ (**see Fig. 25.11**). This approach requires the use of a constant-infusion pump but permits more precise control of the natriuretic effect achieved over time, particularly in carefully monitored patients. It also diminishes the potential for too rapid a decline in intravascular volume and hypotension as well as the risk of ototoxicity in patients given large-bolus IV doses of a loop diuretic. A typical continuous furosemide infusion is initiated with a 20- to 40-mg IV loading dose as a bolus injection, followed by a continuous infusion of 5 to 10 mg/hr for a patient who had been receiving 200 mg of oral furosemide per day in divided doses. The DOSE (Diuretic Optimal Strategy Evaluation in Acute Heart Failure) study showed that there was no significant difference in symptoms or renal function when patients with acute decompensated heart failure (ADHF) were treated by an IV bolus of furosemide compared to IV infusion of furosemide, suggesting that whichever approach is most likely to reliably produce the desired dieresis should be used.

Another common reason for diuretic resistance in advanced HF is the development of the *cardiorenal syndrome* (see also **Chapters 24 and 98**), which is recognized clinically as worsening renal function that limits diuresis in patients with obvious clinical volume overload.[27] In patients with advanced HF, the cardiorenal syndrome is frequently present in those who have repeated HF hospitalizations, and in whom adequate diuresis is difficult to obtain because of worsening indices of renal function. This impairment in renal function often is dismissed as "pre-renal"; however, when measured carefully, neither cardiac output nor renal perfusion pressure have been shown to be reduced in diuretic-treated patients who develop the cardiorenal syndrome. Importantly, worsening indices of renal function contribute to longer hospital stays and predict higher rates of early rehospitalization and death[28] (**see Fig. 25.2**). The mechanisms for and treatment of the cardiorenal syndrome remain poorly understood.

Device-Based Therapies

Mechanical methods of fluid removal may be needed to achieve adequate control of fluid retention, particularly in patients who become resistant and/or refractory to diuretic therapy(**see Chapter 24**). *Extracorporeal ultrafiltration* (UF) removes salt and water isotonically by driving the patient's blood through a highly permeable filter via an extracorporeal circuit in an arteriovenous or venovenous mode. Alternative extracorporeal methods include continuous hemofiltration, hemodialysis, or hemodiafiltration. With slow, continuous UF, the patient's intravascular fluid volume remains stable as fluid shifts from the extravascular space into the intravascular space, with no deleterious activation of neurohormonal systems. UF has been shown to reduce right atrial and pulmonary artery wedge pressures and increase cardiac output, diuresis, and natriuresis without changes in heart rate, systolic blood pressure, renal function, electrolytes, or intravascular volume.[29]

The Relief for Acutely Fluid-Overloaded Patients with Decompensated Congestive Heart Failure (RAPID-CHF) trial, which was the first RCT of ultrafiltration for ADHF, enrolled 40 patients who were randomized to receive usual care (diuretic) or a single 8-hour period of UF therapy (using a proprietary device) in addition to usual care. The primary endpoint was weight loss 24 hours after enrollment. Fluid removal after 24 hours was approximately twofold greater in the UF group.[29] The Ultrafiltration versus IV Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) study compared the long-term safety and efficacy of UF therapy (using a proprietary device) to IV diuretics in a multicenter trial involving 200 patients, who were assessed at entry and at intervals to 90 days. The primary endpoint was total weight loss during the first 48 hours of randomization and the change in dyspnea score during the first 48 hours of randomization. Although the two treatments were similar in ability to relieve dyspnea, UF was associated with significantly greater fluid loss over 48 hours and a lower rate of rehospitalization during the next 90 days.[29] The use of UF in high-risk patients developing the cardiorenal syndrome was explored in CARRESS (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) trial, which showed that UF resulted in similar weight loss, but an increase in creatinine levels, compared to standard care, and was associated with more serious adverse events and IV catheter–related complications.[29]

Given the cost, need for venous access, and the nursing support necessary to implement UF, additional studies are needed to determine its role in the management of volume overload in HF patients. In addition to extracorporeal methods for relieving volume overload, peritoneal dialysis can be used as a viable alternative therapy for the short-term management of refractory congestive symptoms for patients in whom vascular access cannot be obtained, or for whom appropriate extracorporeal therapies are not available.

Prevention of Disease Progression

Drugs that interfere with the excessive activation of renin-angiotensin-aldosterone system (RAAS) and the adrenergic nervous system can relieve the symptoms of HF with a depressed EF by stabilizing and/or reversing cardiac remodeling (**see Fig. 25G.1**). In this regard, ACEIs/ARBs and beta-adrenergic blockers have emerged as cornerstones of modern HF therapy for patients with a depressed EF (**Table 25.7**).

TABLE 25.7

Drugs for the Prevention and Treatment for Chronic Heart Failure

AGENT	INITIATING DOSE	MAXIMAL DOSE
Angiotensin-Converting Enzyme Inhibitors		
Captopril	6.25 mg 3 times	50 mg 3 times
Enalapril	2.5 mg twice	10 mg twice
Lisinopril	2.5-5.0 mg once	20 mg once
Ramipril	1.25-2.5 mg once	10 mg once
Fosinopril	5-10 mg once	40 mg once
Quinapril	5 mg twice	40 mg twice
Trandolapril	0.5 mg once	4 mg once
Angiotensin Receptor Blockers		
Valsartan	40 mg twice	160 mg twice
Candesartan	4-8 mg once	32 mg once
Losartan	12.5-25 mg once	50 mg once
Angiotensin Receptor Neprilysin Inhibitor		
Sacubitril/valsartan	24 mg/26 mg twice	97 mg/103 mg twice
Beta-Adrenergic Receptor Blockers		
Carvedilol	3.125 mg twice	25 mg twice (50 mg twice if >85 kg)
Carvedilol-CR	10 mg once	80 mg once
Bisoprolol	1.25 mg twice	10 mg once
Metoprolol succinate CR	12.5-25 mg qd	Target dose 200 mg qd
Mineralocorticoid Receptor Antagonists		
Spironolactone	12.5-25 mg once	25-50 mg once
Eplerenone	25 mg once	50 mg once
Other Agents		
Combination of hydralazine/isosorbide dinitrate	10-25 mg/10 mg 3 times	75 mg/40 mg 3 times
Fixed dose of hydralazine/isosorbide dinitrate	37.5 mg/20 mg (one tablet) 3 times	75 mg/40 mg (two tablets) 3 times
Digoxin*	0.125 mg qd	≤0.375 mg/once†
Ivabradine	5 mg twice daily	7.5 mg twice‡

*Dosing should be based on ideal body weight, age, and renal function; *qd,* every day.

†Trough level should be 0.5 to 1 ng/mL, although absolute levels have not been established.

‡Approved in the European Union for the treatment of heart failure but is not FDA approved.

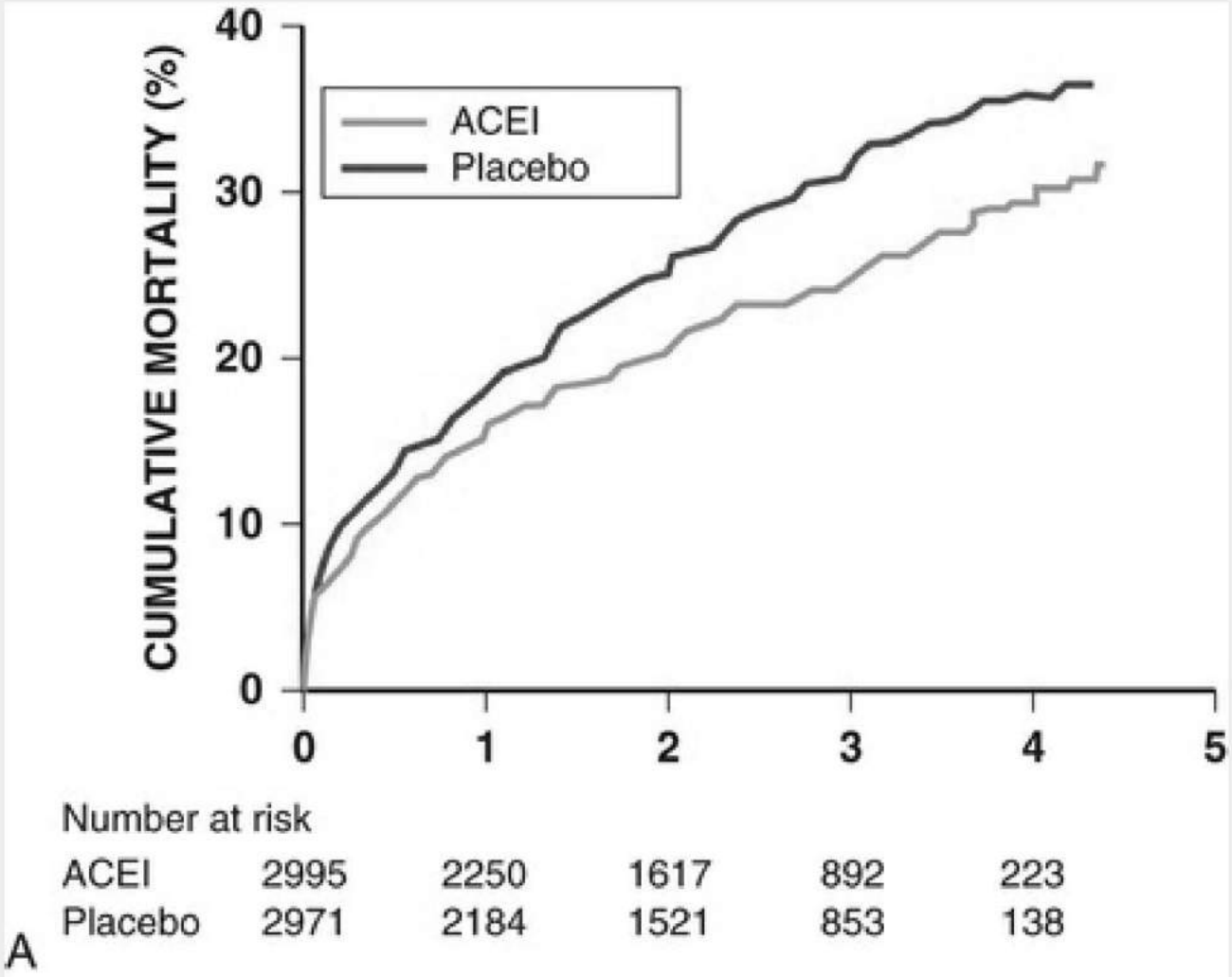
Modified from Mann DL. Heart failure and cor pulmonale. In Kasper DL, Braunwald E., Fauci AS, et al. Harrison's Principles of Internal Medicine. 17th ed. New York: McGraw-Hill; 2007, p 1449.

Angiotensin-Converting Enzyme Inhibitors

There is overwhelming evidence that ACEIs should be used in symptomatic and asymptomatic patients with a reduced EF (<40%). ACEIs interfere with the RAS by inhibiting the enzyme that is responsible for the conversion of angiotensin I to angiotensin II (**see Chapter 23**). However, because ACEIs also inhibit kininase II, they may lead to the upregulation of bradykinin, which may further enhance the effects of angiotensin suppression. ACEIs stabilize LV remodeling, improve patient symptoms, prevent hospitalization, and prolong life. Because fluid retention can attenuate the effects of ACEIs, it is preferable to optimize the dose of diuretic first, before starting the ACEI. However, it may be necessary

to reduce the dose of diuretic during the initiation of an ACEI, to prevent symptomatic hypotension. ACEIs should be initiated in low doses, followed by increments in dose if lower doses have been well tolerated. Titration is generally achieved by doubling doses every 3 to 5 days. The dose of ACEI should be increased until the doses used are similar to those that have been shown to be effective in clinical trials (**Table 25.7**). Higher doses are more effective than lower doses in preventing hospitalization. For stable patients, it is acceptable to add therapy with beta-blocking agents before full target doses of either ACEIs are reached. Blood pressure (including postural changes), renal function, and potassium should be evaluated within 1 to 2 weeks after initiation of ACEIs, especially in patients with preexisting azotemia, hypotension, hyponatremia, or diabetes mellitus or taking potassium supplements. Abrupt withdrawal of treatment with an ACEI may lead to clinical deterioration and therefore should be avoided in the absence of life-threatening complications (e.g., angioedema, hyperkalemia).

The efficacy of ACEIs has been consistently demonstrated in clinical trials with patients with asymptomatic and symptomatic LV dysfunction[8,12] (**Fig. 25.12**). These trials recruited a broad variety of patients, including women and the elderly, as well as patients with a wide range of causes and severity of LV dysfunction. The consistency of data from the Studies on Left Ventricular Dysfunction (SOLVD) Prevention Study, Survival and Ventricular Enlargement (SAVE), and the Trandolapril Cardiac Evaluation (TRACE) has shown that asymptomatic patients with LV dysfunction will have less development of symptomatic HF and fewer hospitalizations when treated with an ACEI. ACEIs have also consistently shown benefit for patients with symptomatic LV dysfunction (**Table 25.8**). All placebo-controlled chronic HF trials have demonstrated a reduction in mortality. Further, the absolute benefit is greatest in patients with the most severe HF. Indeed, the patients with NYHA Class IV HF in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS I) had a much larger effect size than the SOLVD Treatment Trial, which in turn had a larger effect size than the SOLVD Prevention Trial.



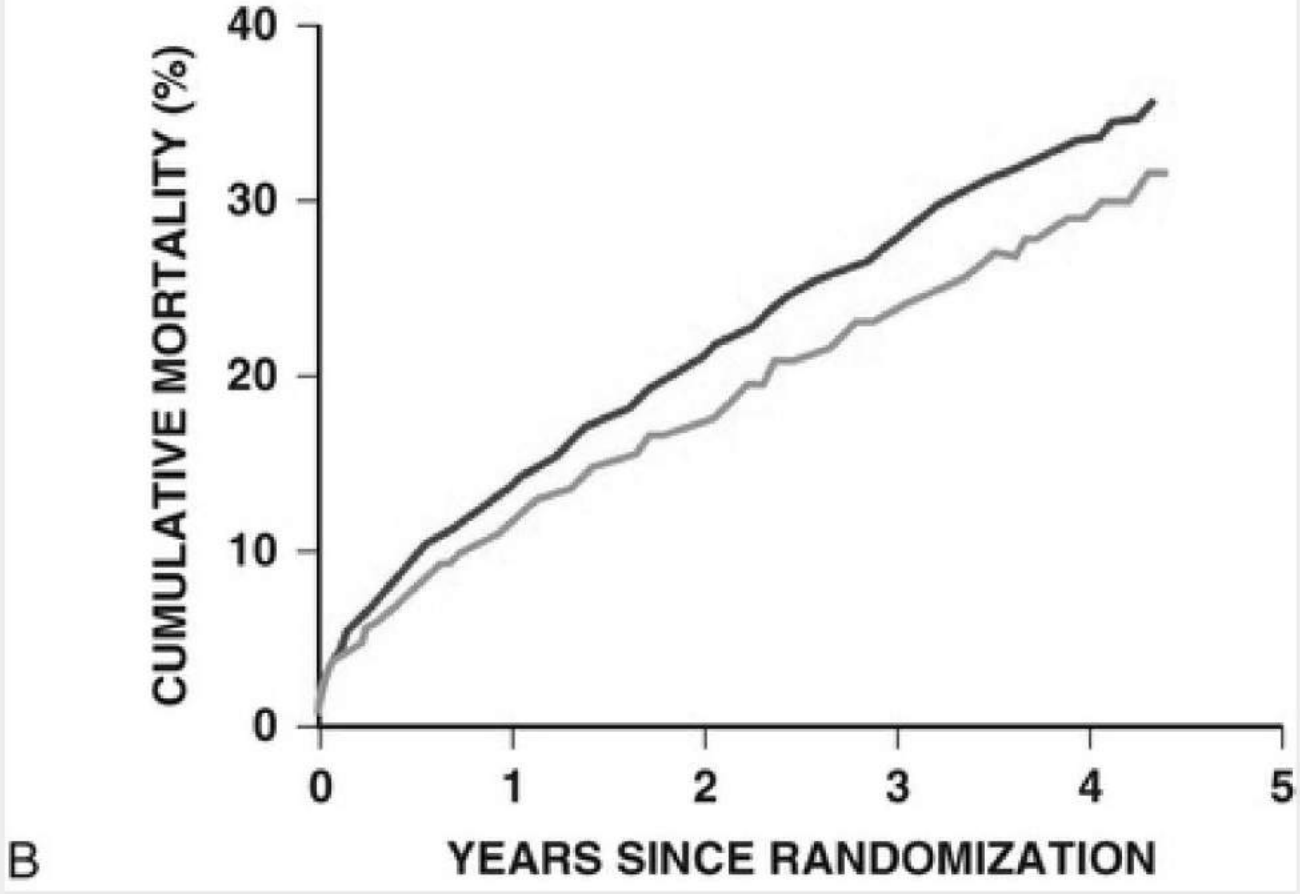


FIGURE 25.12 Meta-analysis of angiotensin-converting enzyme inhibitor (ACEI) in HFrEF. **A,** Kaplan-Meier curves for mortality for patients with HF with a depressed ejection fraction (EF) treated with an ACEI

following acute myocardial infarction (three trials). **B,** Kaplan-Meier curves for mortality for patients with HF with a depressed EF treated with an ACEI in five clinical trials, including postinfarction trials. The benefits of ACEI were observed early and persisted long term. (Modified from Flather MD et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet 2000;355:1575-80.)

TABLE 25.8

Mortality Rates in Placebo-Controlled Trials Conducted in Patients with Chronic Heart Failure (EF <40%) or Patients with Acute Myocardial Infarction or at Risk for Heart Failure

TRIAL NAME	AGENT	NYHA CLASS	NO. OF PATIENTS ENROLLED	12-MONTH PLACEBO MORTALITY (%)	12-MONTH EFFECT SIZE (%)	*P* VALUE 12 MONTHS (Full F/U)
Angiotensin-Converting Enzyme Inhibitors						
Heart Failure						
CONSENSUS-1	Enalapril	IV	253	52	↓31	0.01 (0.0003)
SOLVD-Rx	Enalapril	I-III	2569	15	↓21	0.02 (0.004)
SOLVD-Asx	Enalapril	I, II	4228	5	0	0.82 (0.30)
Post–Myocardial Infarction						
SAVE	Captopril	—	2231	12	↓18	0.11 (0.02)
AIRE	Ramipril		1986	20	↓22	0.01 (0.002)
TRACE	Trandolapril		1749	26	↓16	0.046 (0.001)
Angiotensin Receptor Blockers						
Heart Failure						
VAL-HeFT	Valsartan	II-IV	5010	9	0	NS (0.80)
CHARM-Alternative	Candesartan	II-IV	2028	NS	NS	NS (0.02)
CHARM-Added	Candesartan	II-IV	2547	NS	NS	NS (0.11)
HEAAL	Losartan	II-IV	3846	NS	NS	NS (0.24)
Angiotensin Receptor Neprilysin Inhibitors						
PARADIGM	Sacubitril/Valsartan	II-IV	8442	NS	NS	NS (<0.001)
Mineralocorticoid Receptor Antagonists						
Heart Failure						
RALES	Spironolactone	III, IV	1663	24	↓25	NS (<0.001)
EMPHASIS	Eplerenone	II	2737	9	NS	NS (<0.01)
Post–Myocardial Infarction						
EPHESUS	Eplerenone	I	6632	12	↓15	NS (0.005)
Beta-Adrenergic Blockers						
Heart Failure						
CIBIS-I	Bisoprolol	III, IV	641	21	↓20*	NS (0.22)
U.S. Carvedilol	Carvedilol	II, III	1094	8	↓66*	NS (<0.001)
ANZ - Carvedilol	Carvedilol	I, II, II	415	NS	NS	NS (>0.1)
CIBIS-II	Bisoprolol	III, IV	2647	12	↓34*	NS (0.001)
MERIT-HF	Metoprolol CR	II-IV	3991	10	↓35*	NS (0.006)
BEST	Bucindolol	III, IV	2708	23	↓10*	NS (0.16)
COPERNICUS	Carvedilol	Severe	2289	28	↓38*	NS (0.0001)
Post–Myocardial Infarction						
CAPRICORN	Carvedilol	I	1959	NS	↓23*	NS (0.03)
BEAT	Bucindolol	I	343		↓12*	NS (0.06)

*Effect size at the conclusion of the trial.

NOTE: Twelve-month mortality rates were taken from the survival curves when data were not directly available in published material.

F/U, Follow-up; *NS,* Not specified; *NYHA,* New York Heart Association.

AIRE, Acute Infarction Ramipril Efficacy; BEAT, Bucindolol Evaluation in Acute Myocardial Infarction Trial; BEST, Beta Blocker Evaluation of Survival Trial; CAPRICORN, Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; CHARM, Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; MERIT-HF, Metoprolol CR/XL Randomized Interventional Trial in Congestive Heart Failure; PARADIGM, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial; RALES, Randomized Aldactone Evaluation Study; SAVE, Survival and Ventricular Enlargement; SOLVD, Studies of Left Ventricular Dysfunction; TRACE, Trandolapril Cardiac Evaluation; Val-HeFT, Valsartan Heart Failure Trail.

Modified from Bristow MR, Linas S, Port DJ. Drugs in the treatment of heart failure. In Zipes DP et al, editors: Braunwald's Heart Disease. 7th ed. Philadelphia: Elsevier; 2004, p 573.

Although only three placebo-controlled mortality trials have been conducted in patients with chronic

HF, the aggregate data suggest that ACEIs reduce mortality in direct relation to the degree of severity of chronic HF. The Vasodilator in Heart Failure II (V-HeFT-II) trial provided evidence that ACEIs improve the natural history of HF through mechanisms other than vasodilation. Participants treated with enalapril had significantly lower mortality than those treated with the vasodilatory combination of hydralazine plus isosorbide dinitrate (which does not directly inhibit neurohormonal systems). Although enalapril is the only ACEI that has been used in placebo-controlled mortality trials in chronic HF (**see Table 25.8**), multiple ACEIs have proved to be more or less equally effective when administered orally within the first week of the ischemic event in myocardial infarction (MI) trials. ACEIs markedly enhance survival in patients with signs or symptoms of HF after MI. In addition to these effects on mortality, ACEIs improve the functional status of patients with HF. In contrast, ACEIs only produce small benefits in exercise capacity. Taken together, these observations support the conclusion that the effects of ACEIs on the natural history of chronic HF, the incidence of post-MI LV dysfunction, or patients at high risk of developing HF represent “class effects” of these agents. Nonetheless, it should be emphasized that patients with a low blood pressure (<90 mm Hg systolic), or impaired renal function (serum creatinine >2.5 mg/mL) were not recruited or represent a small proportion of patients who participated in these trials. Thus the efficacy of these agents for this latter patient population is less well established.

Side Effects of ACEI Use

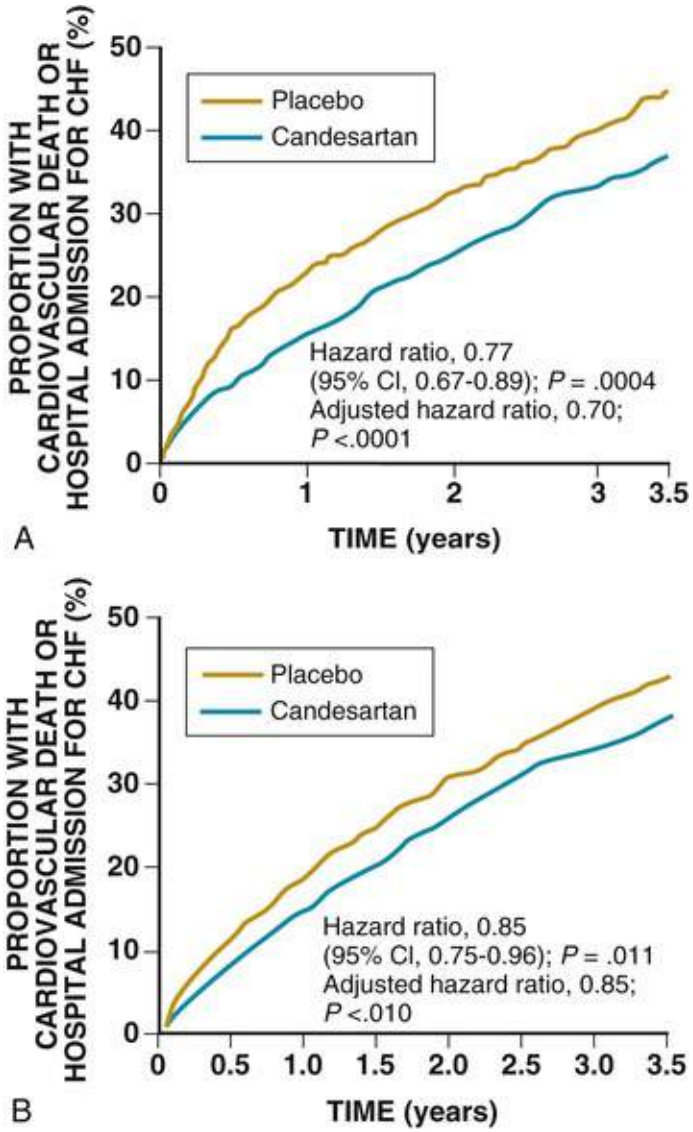
The majority of the adverse effects of ACEIs are related to suppression of the RAS. The decreases in blood pressure and mild azotemia often seen during initiation of therapy are generally well tolerated and do not require a decrease in ACEI dose. However, if hypotension is accompanied by dizziness or if the renal dysfunction becomes severe, it may be necessary to decrease the dose of the diuretic if significant fluid retention is not present, or alternatively decrease the ACEI dose if significant fluid retention is present. Potassium retention may also become problematic if the patient is receiving potassium supplements or a potassium-sparing diuretic. Potassium retention that is not responsive to these measures may require a reduction in ACEI dose. The side effects of ACEIs related to kinin potentiation include a nonproductive cough (10% to 15% of patients) and angioedema (1%). In patients who cannot tolerate ACEIs because of cough or angioedema, ARBs are the next recommended line of therapy. Patients intolerant to ACEIs because of hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. The combination of hydralazine and an oral nitrate should be considered for these latter patients (**see Table 25.7**).

Angiotensin Receptor Blockers

ARBs are well tolerated in patients who are intolerant of ACEIs because of cough, skin rash, or angioedema and therefore should be used in symptomatic and asymptomatic patients with an EF less than 40% who are ACE intolerant for reasons other than hyperkalemia or renal insufficiency (**see Table 25.7**). Although ACEIs and ARBs inhibit the RAAS, they do so by a different mechanism. Whereas ACEIs block the enzyme responsible for converting angiotensin I to angiotensin II, ARBs block the effects of angiotensin II on the angiotensin type 1 receptor, the receptor subtype responsible for virtually all the adverse biologic effects relevant to angiotensin II on cardiac remodeling (**see Chapter 22**). Multiple ARBs approved for treatment of hypertension are now available to clinicians. Three of these, *losartan*, *valsartan*, and *candesartan*, have been extensively evaluated in the setting of HF (**see Table 25.8**). Several studies have shown that there is added modest therapeutic benefit for the addition of ARB to an

ACEI in patients with chronic HF. ARBs should be initiated with the starting doses shown in **Table 25.7**, which can be uptitrated every 3 to 5 days by doubling the dose of ARB. As with ACEIs, blood pressure, renal function, and potassium should be reassessed within 1 to 2 weeks after initiation and followed closely after changes in dose.

In symptomatic HF patients intolerant to ACEIs, the aggregate clinical data suggest that ARBs are as effective as ACEIs in reducing HF morbidity and mortality. Candesartan significantly reduced all-cause mortality, CV death, or hospital admission in the Candesartan Heart Failure: Assessment of Reduction in Mortality and Morbidity trial (CHARM-Alternative)[8,12] (**eFig. 25.3**). Importantly, candesartan reduced all-cause mortality, irrespective of background ACEI or beta-blocker therapy. Similar findings were shown with valsartan in the small subgroup of patients not receiving an ACEI in the Valsartan Heart Failure Trial (Val-HeFT). A direct comparison of ACEIs and ARBs was assessed in the Losartan Heart Failure Survival Study (ELITE-II), which showed that losartan was not associated with improved survival in elderly HF patients compared to captopril but was significantly better tolerated. Two trials have evaluated ARBs compared to ACEIs in post-MI patients who developed LV dysfunction or signs of HF. The direct comparison of losartan with captopril indicated that losartan was not as effective as captopril on all-cause mortality, whereas valsartan was noninferior to captopril on all-cause mortality in the Valsartan in Acute Myocardial Infarction Trial (VALIANT).[8,12] The combination of captopril and valsartan produced no further reduction in mortality in VALIANT, although the number of adverse events increased. When given in addition to ACEIs in general cohorts of patients with symptomatic HF, the effects of ARBs were shown to have a modest beneficial effect in the CHARM-Added trial.[8,12] However, the addition of valsartan to ACEIs had no beneficial effect on mortality in Val-HeFT, although the combined endpoint of mortality and morbidity was significantly (13.2%) lower with valsartan than with placebo because of a reduction in the number of patients hospitalized for HF.[12] The question of high-dose versus low-dose angiotensin receptor antagonism on clinical outcomes was evaluated in the Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan (HEAAL) trial.[8,12] This study showed that high-dose losartan was not associated with a significant reduction in the primary endpoint of all-cause death or admission for HF (HR 0.94; 95% CI 0.84 to 1.04; $P = 0.24$) compared to low-dose losartan, but was associated with a significant reduction in HF admissions (HR 0.94; 95% CI 0.84 to 1.04; $P = 0.24$), suggesting that uptitration of ARBs may confer clinical benefit.



EFIGURE 25.3 Effect of candesartan on cardiovascular mortality or hospital admission for congestive heart failure (CHF) in the CHARM-Alternative **(A)** and CHARM-Added **(B)** trials. Two groups of patients who were randomized to candesartan or placebo are depicted: **A,** patients who were not receiving an angiotensin-converting enzyme (ACE) inhibitor, and **B,** patients who were receiving an ACE inhibitor. The effect size of candesartan was reduced in the group of patients receiving an ACEI. (Modified from Granger CB et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003;362:772-6, and McMurray JJ et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362:767-71.)

Although one meta-analysis suggests that ARBs and ACEIs have similar effects on all-cause mortality and HF hospitalizations,[30] and although ARBs may be considered as initial therapy rather than ACEIs following MI, the general consensus is that ACEIs remain first-line therapy for the treatment of HF, whereas ARBs were recommended for ACEI-intolerant patients.[8,12]

Side Effects of ARB Use

Both ACEIs and ARBs have similar effects on blood pressure, renal function, and potassium. Therefore the problems of symptomatic hypotension, azotemia, and hyperkalemia will be similar for both these agents. Although less frequent that with ACEIs, angioedema has also been reported in some patients who receive ARBs. In patients intolerant of ACEIs and ARBs, the combined use of hydralazine and isosorbide dinitrate may be a therapeutic option (**see Table 25.7**). However, compliance with this combination has generally been poor because of the large number of tablets required and the high incidence of adverse

reactions.

Angiotensin Receptor Neprilysin Inhibitors

A new therapeutic class of agents that antagonizes RAAS and inhibits the neutral endopeptidase system has been recently developed. The first agent is a molecule that combines valsartan (an AT1 receptor antagonist) with sacubitril (a neprilysin inhibitor) in a 1 : 1 mixture. The combination of an angiotensin receptor neprilysin inhibitor (ARNI) slows the degradation of natriuretic peptides, bradykinin, and adrenomedullin, thereby enhancing diuresis, natriuresis, and myocardial relaxation. It also inhibits renin and aldosterone secretion, while selectively blocking the angiotensin type 1 (AT1) receptor reduces vasoconstriction, sodium, and water retention and myocardial hypertrophy[31] (**see Chapter 23**).

In the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF),[32] the use of fixed-dose sacubitril/valsartan resulted in striking reductions in all-cause mortality, CV mortality, and HF hospitalizations compared with an ACEI (enalapril) alone in patients with mild to moderate HF (NYHA Class II to IV; LVEF 35%) (**Fig. 25.13**). This was characterized by either mildly elevated natriuretic peptide levels (BNP >150 pg/mL or NT-proBNP ≥600 pg/mL) or hospitalization in the preceding 12 months and elevated natriuretic peptide levels (BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL) in patients who were also able to tolerate both a target dose of enalapril (10 mg twice daily) and then subsequently sacubitril/valsartan (200 mg twice daily). ARNIs should be administered in low doses (sacubitril 24 mg/valsartan 26 mg twice daily) in ACEI/ARB-naive patients or moderate doses (sacubitril 49 mg/valsartan 51 mg twice daily) in patients tolerant of ACEIs/ARBs. The target dose of sacubitril/valsartan in PARADIGM-HF was 97 mg/103 mg twice daily. Although the most recent update of the ACC/AHA/HFSA guidelines do not recommend starting HFrEF patients on ARNIs (**see Fig. 25G.1** and **Table 25G.3**), in patients with HFrEF NYHA Class II or III who are tolerating an ACEI or ARB, ARNIs are recommended as a replacement for ACEI/ARB to further reduce morbidity and mortality.[10]

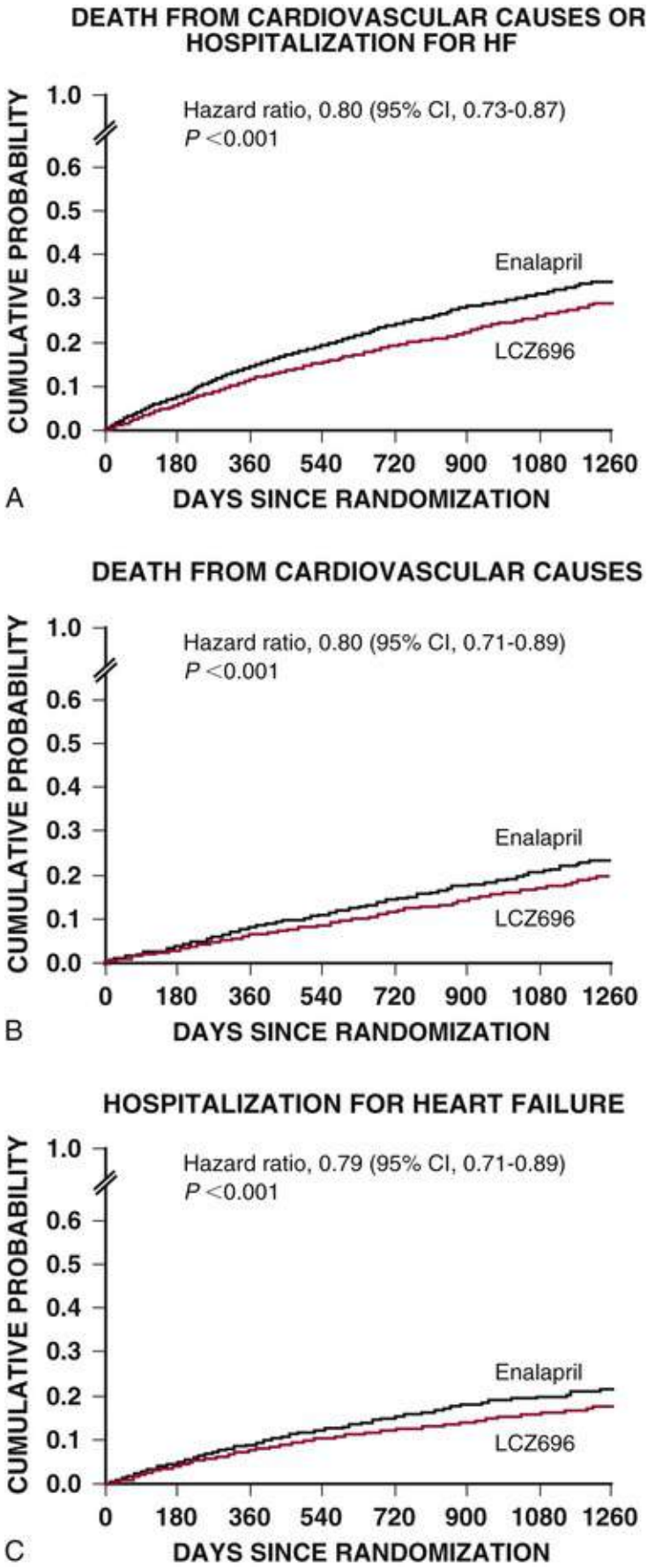


FIGURE 25.13 Kaplan-Meier analysis of outcomes in the PARADIGM trial. **A,** Death from cardiovascular causes or hospitalization for heart failure (the primary endpoint). **B,** Death from cardiovascular cause. **C,** Hospitalization for heart failure. (Modified from McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;317:993-1004.)

Side Effects of ARNIs

The use of an ARNI is associated with hypotension (approximately 18% of patients), hyperkalemia (12%), cough (5%), and extremely low incidence of angioedema. Oral neprilysin inhibitors, used in combination with ACEIs, can lead to angioedema; thus the concomitant use of ACEIs and ARNIs is contraindicated (class III recommendation). For patients who are switching from ACEIs to sacubitril/valsartan, the ACEI should be withheld for at least 36 hours before initiating sacubitril/valsartan, to minimize the risk of angioedema caused by overlapping ACE and neprilysin inhibition. There are additional concerns about effects of sacubitril/valsartan on the degradation of beta-amyloid peptide in the brain, which could theoretically accelerate amyloid deposition. The optimal titration and tolerability of ARNIs, particularly with regard to blood pressure and adjustment of concomitant HF medications, will require addition clinical experience.

Beta Blockers

Beta-adrenergic blocker therapy represents a major advance in the treatment of HF patients with a depressed EF. Beta blockers interfere with the harmful effects of sustained activation of the central nervous system by competitively antagonizing one or more alpha- and beta-adrenergic receptors (α_1, β_1, and β_2). Although there are a number of potential benefits to blocking all three receptors, most of the deleterious effects of sympathetic activation are mediated by the β_1-adrenergic receptor. When given in concert with ACEIs, beta blockers reverse the process of LV remodeling, improve patient symptoms, prevent hospitalization, and prolong life. Therefore, beta blockers are indicated for patients with symptomatic or asymptomatic HF and a depressed EF less than 40%. Three beta blockers have been shown to be effective in reducing the risk of death in patients with chronic HF: *bisoprolol* and sustained-release *metoprolol succinate* both competitively block the β_1 receptor, and *carvedilol* competitively blocks the α_1, β_1, and β_2 receptors.

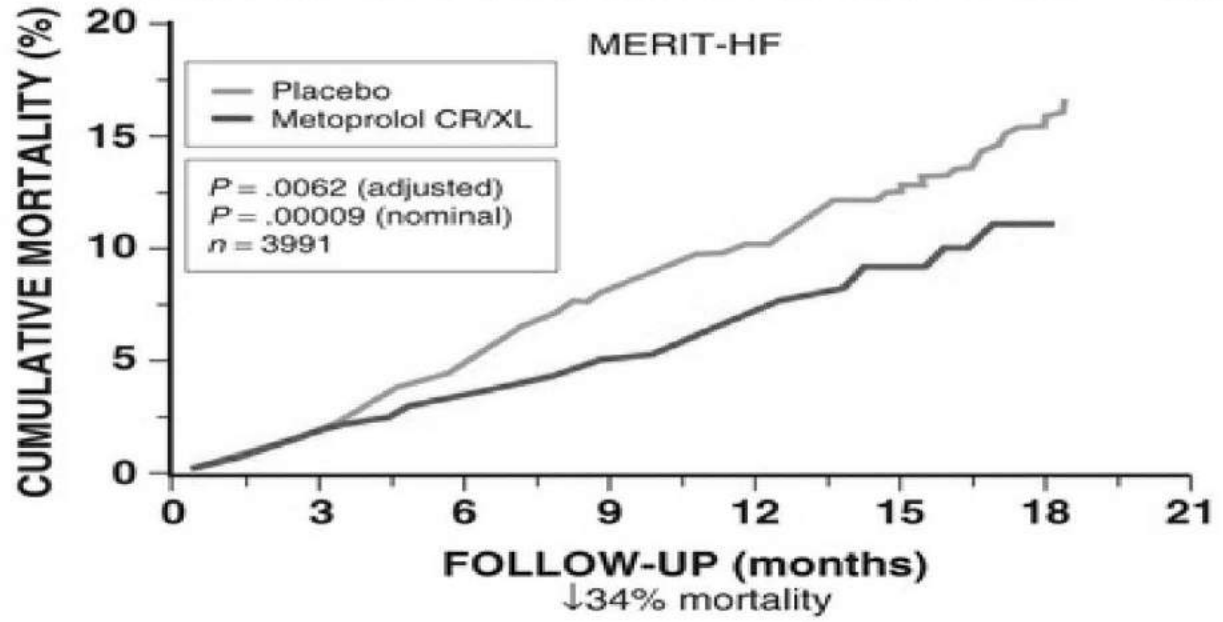
Analogous to the use of ACEIs, beta blockers should be initiated in low doses, followed by gradual increments if lower doses have been well tolerated. The dose of beta blocker should be increased until the doses used are similar to those reported to be effective in clinical trials (**see Table 25.7**). However, unlike ACEIs, which may be uptitrated relatively rapidly, the dose titration of beta blockers should proceed no sooner than 2-week intervals, since the initiation and increased dosing of these agents may lead to worsening fluid retention because of the abrupt withdrawal of adrenergic support to the heart and circulation. Therefore, it is important to optimize the dose of diuretic before starting therapy with beta blockers. If worsening fluid retention does occur, it is likely to be within 3 to 5 days of initiating therapy and to manifest as increased body weight or symptoms of worsening HF. The increased fluid retention can usually be managed by increasing the diuretic dose. Patients need not be taking high-dose ACEIs before being considered for treatment with a beta blocker, because most patients enrolled in the beta-blocker trials were not taking high doses of ACEIs. Furthermore, in patients taking a low-dose ACEI, the addition of a beta blocker produces a greater improvement in symptoms and a further reduction in mortality risk than an increase in the ACEI dose. Recent data show that beta blockers can be safely started before discharge even in patients hospitalized for HF, provided that the patient is stable and does not require IV HF therapy.

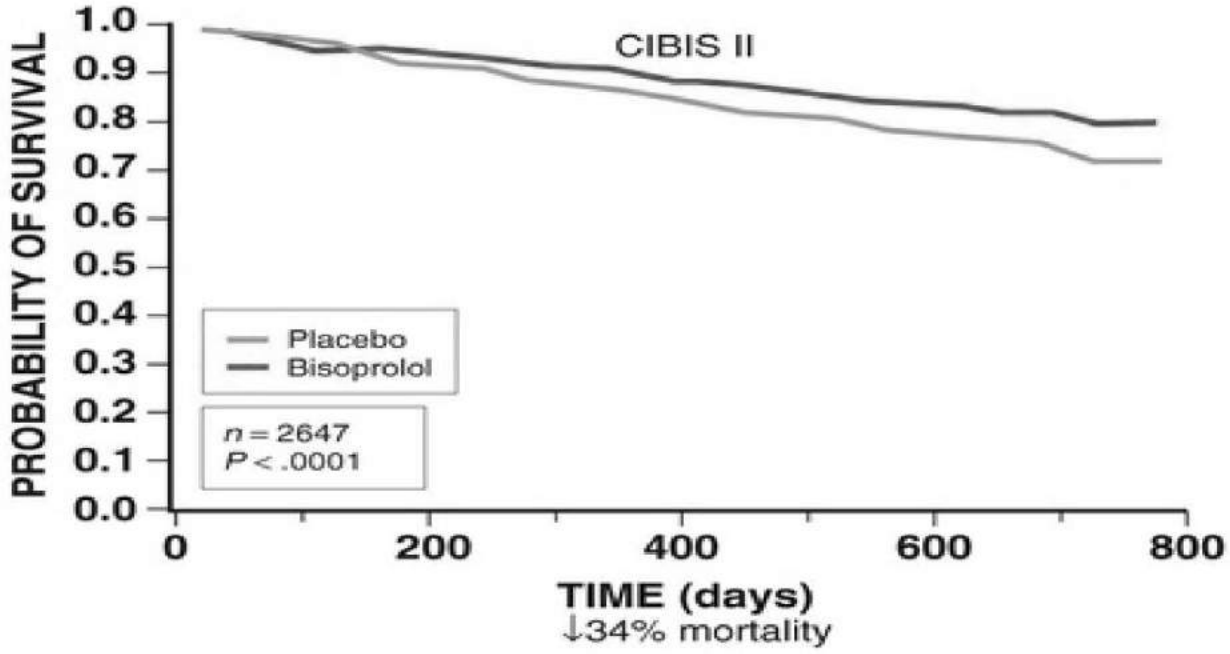
Contrary to early reports, the aggregate results of clinical trials suggest that beta-adrenergic blocker therapy is well tolerated by the great majority of HF patients (>85%), including patients with comorbidities such as diabetes mellitus, chronic obstructive lung disease, and peripheral vascular disease. Nonetheless, a subset of patients (10% to 15%) remain intolerant to beta blockers because of

worsening fluid retention or symptomatic hypotension.

The first placebo-controlled multicenter trial with a beta-blocking agent was the Metoprolol in Dilated Cardiomyopathy (MDC) trial, which used the shorter-acting tartrate preparation at a target dose of 50 mg three times a day in symptomatic HF patients with idiopathic DCM. Metoprolol tartrate at an average dose of 108 mg/day reduced the prevalence of the primary endpoint of death or need for cardiac transplantation by 34%, which did not quite reach statistical significance ($P = 0.058$). The benefit resulted entirely from a reduction by metoprolol in the morbidity component of the primary endpoint, with no favorable trends in the mortality component. A more efficacious formulation of metoprolol was subsequently developed, metoprolol (succinate) CR/XL, which has a better pharmacologic profile than metoprolol tartrate because of its controlled-release (CR) profile and longer half-life. In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), metoprolol CR/XL provided a significant relative risk reduction of 34% reduction in mortality in patients with mild to moderate HF and moderate to severe systolic dysfunction compared with the placebo group[8,12] (**Fig. 25.14**). Importantly, metoprolol CR/X reduced mortality from both sudden death and progressive pump failure. Further, mortality was reduced across most demographic groups, including older versus younger subjects, nonischemic versus ischemic etiology, and lower versus higher EFs.

EFFECT OF BETA BLOCKADE ON MORTALITY IN CHF





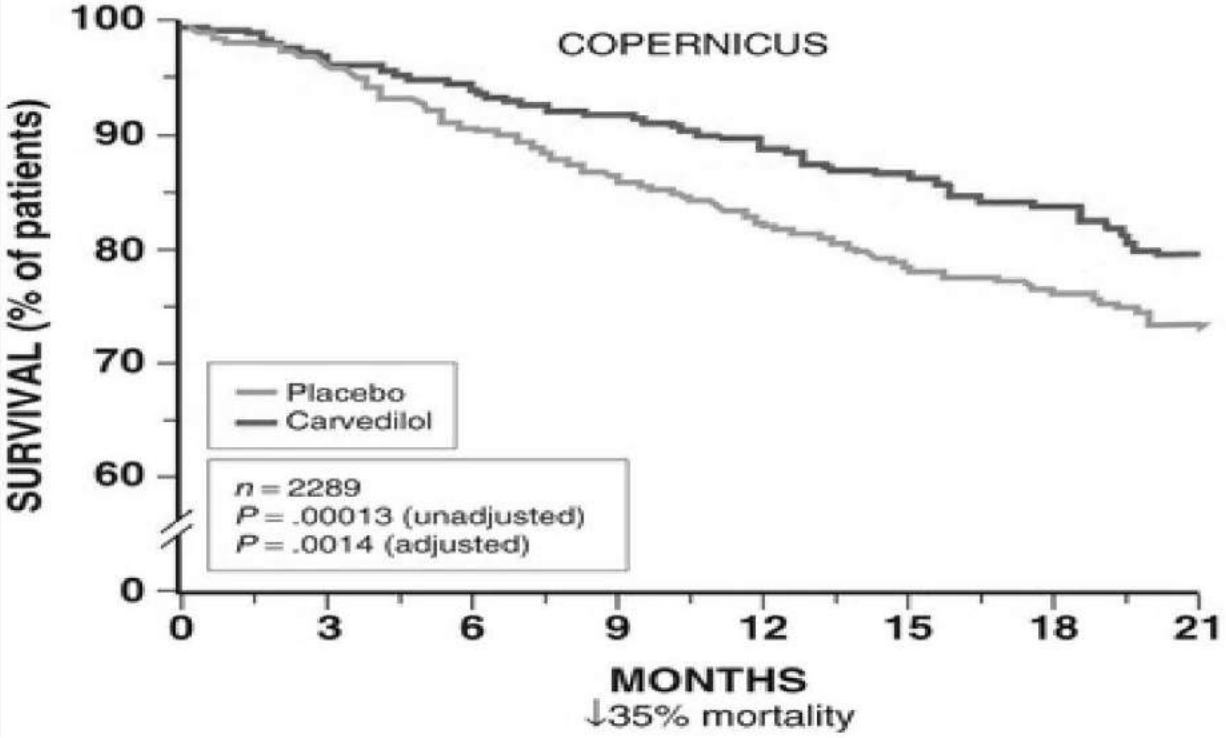


FIGURE 25.14 Kaplan-Meier analysis of the probability of survival among patients in the placebo and beta-blocker groups in the MERIT-HF **(top),** CIBIS II **(middle),** and COPERNICUS **(bottom)** trials. *CHF,* Chronic heart failure; *CI*, confidence interval. (Data from The Cardiac Insufficiency Bisoprolol Study II [CIBIS II]. Lancet 1999;353:9-13; Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure [MERIT-HF]. Lancet 1999;353:2001-7; and Packer M et al, for The Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651-8.)

Bisoprolol is a second-generation β_1 receptor–selective blocking agent with approximately 120-fold higher affinity for human β_1 versus β_2 receptors. The first trial performed with bisoprolol was the Cardiac Insufficiency Bisoprolol Study I (CIBIS-I), which examined the effects of bisoprolol on mortality in patients with symptomatic ischemic or nonischemic cardiomyopathy. CIBIS-I showed a nonsignificant ($P = 0.22$) 20% risk reduction for mortality at 2 years' follow-up. Because the sample size for CIBIS-I was based on an unrealistically high expected event rate in the control group, a follow-up trial with more conservative effect size estimates and sample size calculations was conducted. In CIBIS-II, bisoprolol reduced all-cause mortality by 34% (11.8% bisoprolol versus 17.3% placebo; $P = 0.002$), sudden cardiac death by 45% (3.6% versus 6.4%; $P = 0.001$), HF hospitalizations by 30% (11.9% versus 17.6%; $P < 0.001$), and all-cause hospitalizations by 15% (33.6% versus 39.6%; $P = 0.002$) (**Fig. 25.14**). The CIBIS-III trial addressed the important question of whether an initial treatment strategy using the beta blocker bisoprolol was noninferior to a treatment strategy of using an ACEI (enalapril) first, among patients with newly diagnosed mild to moderate HF. The two strategies were compared in a blinded manner with regard to the combined primary endpoint of all-cause mortality or hospitalization, as well as with regard to each of the components of the primary endpoint individually. Although the per-protocol primary endpoint analysis of death or rehospitalization did not meet the prespecified criteria for noninferiority, the intent-to-treat analysis showed that bisoprolol was noninferior to enalapril (HR, 0.94; 95% CI 0.77 to 1.16; $P = 0.019$ for noninferiority). Although CIBIS-III did not provide clear-cut evidence to justify starting with a beta blocker, the overall safety profile of the two strategies was similar. Current guidelines continue to recommend starting with an ACEI, followed by the addition of a beta blocker.

Of the three beta blockers approved for the treatment of HF, carvedilol has been studied most extensively (**see Table 25.8**). The phase III U.S. Trials Program, composed of four individual trials managed by single Steering and Data and Safety Monitoring Committee, was stopped prematurely because of a highly significant ($P < 0.0001$) 65% reduction in mortality by carvedilol that was observed across all four trials. This was followed by a second study, the Australia-New Zealand Heart Failure Research Collaborative Group Carvedilol Trial (ANZ-Carvedilol), which showed there was a significant improvement in LVEF ($P < 0.0001$) and a significant ($P = 0.0015$) reduction in LV end-diastolic volume index in the carvedilol-treated group at 12 months, as well a significant relative risk reduction of 26% in the clinical composite of death or hospitalization for the carvedilol group at 19 months. Rates of hospitalization were also significantly lower for patients treated with carvedilol (48%) compared to placebo (58%). The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study extended these benefits to patients with more advanced HF; patients with advanced HF symptoms needed to be clinically euvolemic and to have an LV EF less than 25%. When compared with placebo, carvedilol reduced the mortality risk at 12 months by 38% and the relative risk of death or HF hospitalization by 31% (**Fig. 25.14**). Carvedilol has also been evaluated in a post-MI trial in which patients had to exhibit LV dysfunction. The Carvedilol Post-Infarct Survival Controlled Evaluation (CAPRICORN) trial was an RCT designed to test the long-term efficacy of carvedilol on

morbidity and mortality in patients with LV dysfunction after MI already treated with ACEIs. Although carvedilol did not reduce the prespecified primary endpoint of mortality plus CV hospitalization, it did significantly reduce total mortality by 23% ($P = 0.03$), CV mortality by 25% ($P < 0.05$), and nonfatal MI by 41% ($P = 0.014$). Lastly, in the Carvedilol or Metoprolol European Trial (COMET), carvedilol (target dose, 25 mg twice daily) was compared with immediate-release metoprolol tartrate (target dose, 50 mg twice daily) with respect to the primary endpoint of all-cause mortality. Carvedilol was associated with a significant 33% reduction in all-cause mortality compared with metoprolol tartrate (33.9% versus 39.5%; HR, 0.83; 95% CI 0.74 to 0.93; $P = 0.0017$).[8,12] Based on the results of the COMET trial, short-acting metoprolol tartrate is not recommended in the treatment of HF. The results of COMET emphasize the importance of using doses and formulations of beta blockers that have been shown to be effective in clinical trials. There have been no trials to ascertain whether the survival benefits of carvedilol are greater than those of metoprolol (succinate) CR/XL when both drugs are used at the appropriate target doses.

Not all studies with beta blockers have been universally successful, suggesting that their effects should not necessarily be viewed broadly as a class effect. Indeed, early studies with the first-generation of nonspecific β_1 and β_2 receptors without ancillary vasodilating properties (e.g., propranolol) resulted in significant worsening of HF and death. The Beta-blocker Evaluation of Survival Trial (BEST) evaluated the third-generation beta-blocking agent *bucindolol,* which is a completely nonselective β_1 and β_2 blocker with some α_1 receptor blockade properties. Although BEST showed that there was a nonsignificant ($P = 0.10$) 10% reduction in total mortality in the bucindolol-treated group, there as a statistically significant ($P = 0.01$) 19% reduction in mortality in white patients. The differential response of bucindolol in white patients has been suggested to be secondary to a polymorphism (Arginine 389) in the β_1-adrenergic receptor that is more prevalent in white patients (see online supplement, Pharmacogenomics in Heart Failure). *Nebivolol* is a selective β_1 receptor antagonist with ancillary vasodilatory properties that are mediated, at least in part, by nitric oxide (NO). In the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS), nebivolol significantly reduced the composite outcome of death or CV hospitalizations (HR, 0.86; 95% CI 0.74 to 0.99; $P < 0.04$), which was the primary endpoint of the trial, but did not but did not reduce mortality. Although approximately 35% of the patients in SENIORS had an LVEF greater than 35%; more than half these patients had an EF ranging from 35% to 50%, and thus would not be considered as HFpEF patients. Nebivolol is not FDA approved for the treatment of HF.

Side Effects of Beta Blockers

The adverse effects of beta blockers are generally related to the predictable complications that arise from interfering with the adrenergic nervous system. These reactions generally occur within several days of initiating therapy and are generally responsive to adjusting concomitant medications, as previously described. The problem of fluid retention is discussed earlier. Treatment with a beta blocker can be accompanied by feelings of general fatigue or weakness. In most patients, the increased fatigue spontaneously resolves within several weeks or months; in some, however, it may be severe enough to limit the dose of beta blocker or require the withdrawal or reduction of treatment. Therapy with beta blockers can lead to bradycardia and can exacerbate heart block. Moreover, beta blockers (particularly those that block the α_1 receptor) can lead to vasodilatory side effects. Thus the dose of beta blockers should be decreased if the heart rate decreases to less than 50 beats/min and/or second- or third-degree heart block develops, or symptomatic hypotension develops. Continuation of beta blocker treatment

during an episode of acute decompensation is safe, although dose reduction may be necessary.[33] Beta blockers are not recommended for patients with asthma who have active bronchospasm.

Mineralocorticoid Receptor Antagonists

Although classified as potassium-sparing diuretics, MRAs that block the effects of aldosterone (e.g., spironolactone) have beneficial effects that are independent of their effects on sodium balance (**see Fig. 25.8**). Although ACEIs may transiently decrease aldosterone secretion, with chronic therapy there is a rapid return of aldosterone to levels similar to those before ACEI therapy, referred to as "aldosterone breakthrough."[34] The administration of an MRA is recommended for patients with NYHA Class II to IV HF who have a depressed EF (≤35%) and who are receiving standard therapy, including diuretics, ACEIs, and beta blockers.[35] The dose of aldosterone antagonist should be increased until the doses used are similar to those shown to be effective in clinical trials (**see Table 25.7**). *Spironolactone* should be initiated at a dose of 12.5 to 25 mg daily and uptitrated to 25 to 50 mg daily, whereas *eplerenone* should be initiated as doses of 25 mg/day and increased to 50 mg daily (**see Table 25.7**). As previously noted, potassium supplementation is generally stopped after the initiation of aldosterone antagonists, and patients should be counseled to avoid high–potassium-containing foods. Potassium levels and renal function should be rechecked within 3 days and again at 1 week after initiation of an aldosterone antagonist. Subsequent monitoring should be dictated by the general clinical stability of renal function and fluid status but should occur at least monthly for the first 6 months.

The first evidence that MRAs could produce a major clinical benefit in HF was demonstrated by the Randomized Aldactone Evaluation Study (RALES) trial,[8,12] which evaluated spironolactone (25 mg/day initially, titrated to 50 mg/day for signs of worsening HF) versus placebo in NYHA Class III or IV HF patients with LVEF less than 35% being treated with an ACEI, a loop diuretic, and in most cases, digoxin. As shown in **Fig. 25.8A**, spironolactone led to a 30% reduction in total mortality compared with placebo ($P = 0.001$). The frequency of hospitalization for worsening HF was also 35% lower in the spironolactone group than in the placebo group. Although the mechanism for the beneficial effect of spironolactone has not been fully elucidated, prevention of extracellular matrix remodeling (**see Chapter 23**) and prevention of hypokalemia levels are plausible mechanisms. Although spironolactone was well tolerated in RALES, gynecomastia was reported in 10% of men treated with spironolactone, compared with 1% in the placebo group ($P < 0.001$). The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial, performed in patients with NYHA Class II HF with EF less than 30% (or 35% if the QRS width was >130 msec), demonstrated that eplerenone (titrated to 50 mg/day) led to a significant 27% decrease in CV death or HF hospitalization (HR, 0.63; 95% CI 0.54 to 0.74; $P < 0.001$) (**Fig. 25.8B**).[8,12] There were also significant decreases in all-cause death (24%), CV death (24%), all-cause hospitalization (23%), and HF hospitalizations (43%). Importantly, the effect of eplerenone was consistent across all prespecified subgroups. In contrast to the RALES trial, which was conducted prior to the widespread adoption of beta blockers, the background therapy for EMPHASIS-HF included ACEIs or ARBs and beta blockers. The findings in RALES and EMPHASIS-HF are consistent with findings in randomized clinical trials in patients with acute MI and LV dysfunction. The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) evaluated the effect of eplerenone (titrated to a maximum of 50 mg/day) on morbidity and mortality among patients with

acute MI complicated by LV dysfunction and HF. Treatment with eplerenone led to a 15% decrease in all-cause death (RR, 0.85; 95 CI 0.75 to 0.96; *P* = 0.008). Based on the results of the RALES and EMPHASIS-HF trials,[8,12] aldosterone antagonists are currently recommended for all patients with persistent NYHA Class II to IV symptoms and an EF of 35% or less, despite treatment with an ACEI (or ARB if ACEI not tolerated) and a beta blocker.

Side Effects of MRAs

The major problem with the use of aldosterone antagonists is the development of life-threatening hyperkalemia, which is more prone to occur in patients who are receiving potassium supplements or who have underlying renal insufficiency. Aldosterone antagonists are not recommended when the serum creatinine is greater than 2.5 mg/dL (or creatinine clearance <30 mL/min) or the serum potassium is greater than 5.5 mmol/L. The development of worsening renal function should lead to consideration of stopping aldosterone antagonists because of the potential risk of hyperkalemia. Painful gynecomastia may develop in 10% to 15% of patients who use spironolactone, for whom eplerenone may be substituted.

Combination of Hydralazine and Isosorbide Dinitrate

The combination of hydralazine and isosorbide dinitrate is recommended for blacks with NYHA Class III or IV HFrEF who remain symptomatic despite concomitant use of ACEIs, beta blockers, and aldosterone antagonists. There is no evidence to suggest that the combination of hydralazine and isosorbide dinitrate is beneficial as a first-line therapy in nonblacks with HFrEF, although this has never been formally tested in a clinical trial.[12] Nonetheless, the combination of hydralazine and isosorbide dinitrate has been shown to reduce mortality in symptomatic HFrEF patients who tolerate an ACEI or ARB because of drug intolerance, hypotension, or renal insufficiency.

I_f Channel Inhibitor

Ivabradine is a heart rate–lowering agent that acts by selectively blocking the cardiac pacemaker I_f ("funny") channel current that controls the spontaneous diastolic depolarization of the sinoatrial node. Ivabradine blocks I_f channels in a concentration-dependent manner by entering the channel pore from the intracellular side, and thus it can only block the channel when it is open. The magnitude of I_f inhibition is directly related to the frequency of channel opening and would therefore be expected to be most effective at higher heart rates. Initially developed and approved as an antianginal agent in Europe, ivabradine was also shown to improve outcomes in The Systolic Heart Failure Treatment with the I_f inhibitor Ivabradine Trial (SHIFT), which enrolled symptomatic patients with and an LV EF of 35% or less who were in sinus rhythm with heart rate of 70 beats/min or more and receiving standard medical therapy for HF (including beta blockers). SHIFT showed that ivabradine (uptitrated to maximum dose of 7.5 mg twice daily) reduced the primary composite outcome of CV death or HF hospitalization by 18% (HR, 0.82; 95% CI 0.75 to 0.90; *P* < 0.0001) (**Fig. 25.15**). The composite endpoint was driven primarily by reducing hospital admissions for worsening HF (HR, 0.74; CI 0.66 to 0.83; *P* < 0.0001), since there was no decrease in CV deaths (HR, 0.91; 95% CI 0.80 to 1.03; *P* = 0.13) or all-cause death.[36] Given that ivabradine lowered heart rate by approximately 10 beats/min, and that only 26% of patients in the trial were taking optimal doses of beta blockers, it is possible that titrating beta blockers to recommended doses may have reduced the HF hospitalizations to a similar degree. Additional safety evidence for ivabradine comes from the

morbidity-mortality evaluation of the I_f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL) trial, in which more than 10,000 patients with coronary heart disease and an EF less than 40% were randomized to treatment with ivabradine, 7.5 mg twice daily. Although this trial did not meet its primary endpoint of reducing CV death, MI, or HF hospitalization, ivabradine was well tolerated in this patient population.[37]

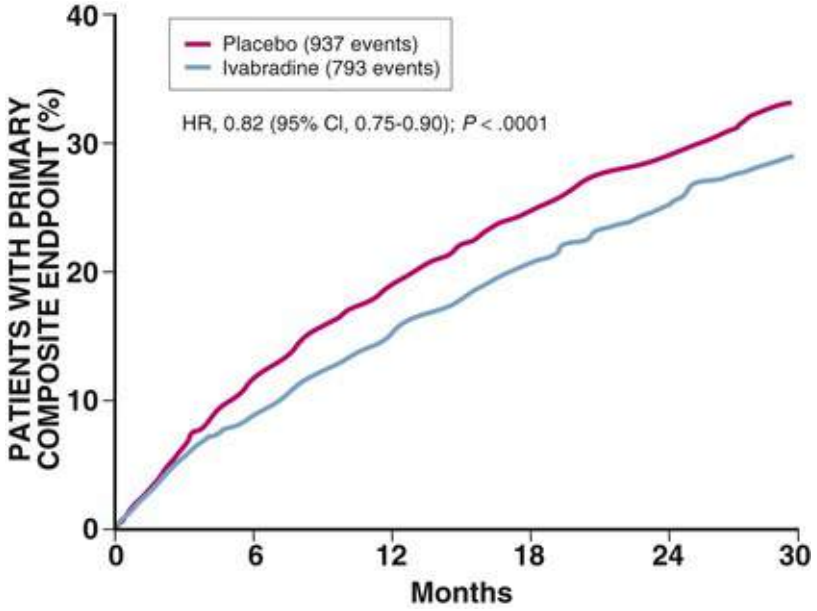


FIGURE 25.15 Kaplan-Meier cumulative event curves for the primary composite endpoint of cardiovascular death or hospitalization for worsening HF in patients treated with ivabradine compared to placebo. (Modified from Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010;376:875-85.)

Renin Inhibitors

Aliskiren is an orally active direct renin inhibitor that appears to suppress RAS to a similar degree as ACEIs.[38] Although the benefits of ACEIs and ARBs in HF have been clearly established, these agents provoke a compensatory increase in renin and downstream intermediaries of the RAAS that may attenuate the effects of ACEIs and ARBs (aldosterone breakthrough). Aliskiren is a nonpeptide inhibitor that binds to the active site (S_1/S_3 hydrophobic binding pocket) of renin, preventing the conversion of angiotensinogen to angiotensin I (**see Chapter 23, Fig. 23.3**). In the Aliskiren Observation of Heart Failure Treatment (ALOFT) trial, aliskiren was shown to decrease significantly ($P < 0.01$) NT-proBNP in urinary aldosterone excretion.[39] Based on these promising early results, several large pivotal outcomes trials were initiated to determine whether adding aliskiren to standard HF therapy would improve clinical outcomes. However, both the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT)[40] and the Efficacy and Safety of Aliskiren and Aliskiren/Enalapril Combination on Morbidity-Mortality in Patients with Chronic Heart Failure (ATMOSPHERE)[41] clinical trials failed to improve outcomes in HFrEF patients, and renin inhibitors such as aliskiren are not presently recommended as an alternative to an ACEI or ARB or in combination with ACEIs.

Management of Patients Who Remain Symptomatic

As noted earlier, an ACEI/ARB or ARNI, a beta blocker, and an MRA should be standard background therapy for patients with HFrEF. However, the addition of an ARB to the combination of an ACEI and an MRA is not recommended in HFrEF patients because of the risk of hyperkalemia. Moreover, the combination of ARNI with an ACEI is not recommended because of the risk of angioedema. Additional pharmacologic therapy (polypharmacy) or device therapy (see later) should be considered in patients who have persistent symptoms or progressive worsening despite optimized therapy with evidence-based medical and device therapies. Digoxin is recommended for patients with symptomatic HFrEF to reduce hospitalizations despite receiving standard therapy, including ACEIs (or ARBs), ARNIs, beta blockers, and MRAs.

Cardiac Glycosides

Digoxin and *digitoxin* are the most frequently used cardiac glycosides. Given that digoxin is used most often and is the only glycoside evaluated in placebo-controlled trials, there is little reason to prescribe other cardiac glycosides for the management of patients with chronic HF. Digoxin exerts its effects by inhibiting the Na^+,K^+-ATPase pump in cell membranes, including the sarcolemmal pump of cardiac myocytes (**see Chapter 22**). Inhibition of the Na^+,K^+-ATPase pump results in increased intracellular Ca^{2+} and thus increased cardiac contractility, which led to the suggestion that beneficial effects of digoxin were secondary to its inotropic properties. However, the more likely mechanism of digoxin in HF patients is to sensitize Na^+,K^+-ATPase activity in vagal afferent nerves, leading to an increase in vagal tone that counterbalances the increased activation of the adrenergic system in advanced HF. Digoxin also inhibits Na^+,K^+-ATPase activity in the kidney and therefore may blunt renal tubular resorption of sodium. Therapy with digoxin is usually initiated and maintained at a dose of 0.125 to 0.25 mg daily. For the great majority of patients, the dose should be 0.125 mg daily and the serum digoxin level less than 1.0 ng/mL, especially in elderly patients, patients with impaired renal function, and patients with a low lean body mass. Higher doses (e.g., digoxin >0.25 mg/day) are rarely used and or not recommended for the management of HF patients in sinus rhythm or who have atrial fibrillation. Further details about digitalis, including mechanism of action, pharmacokinetics, and interaction with other common drugs, can be found in the online supplement for this chapter (Digoxin).”

Although clinicians have used cardiac glycosides to treat patients with chronic HF for more than 200 years, there is still considerable despite debate regarding the effectiveness of the cardiac glycosides in HF patients. Whereas small and medium-sized trials conducted in the 1970s and 1980s yielded equivocal results, two relatively large digoxin withdrawal studies in the early 1990s, the Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) and the Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin (PROVED), provided strong support for clinical benefit from digoxin.[12] In these studies, worsening HF and HF hospitalizations developed in more patients who were withdrawn from digoxin than in patients who were maintained on digoxin. Because withdrawal studies are difficult to interpret with respect to efficacy of a given therapeutic agent, the Digoxin Investigator Group (DIG) trial was conducted to address prospectively the role of digitalis in chronic HF. Although the DIG trial showed that digoxin had a neutral effect on the primary endpoint of mortality, digoxin reduced hospitalizations (including 30-day readmission for HF)[12] and favorably affected the combined endpoints of death or hospitalization due to worsening HF. Data from the DIG trial

indicated a strong trend ($P = 0.06$) toward a decrease in deaths secondary to progressive pump failure, which was offset by an increase in sudden and other non–pump failure cardiac deaths ($P = 0.04$). One of the most important findings to emerge from the DIG trial was that mortality was directly related to the digoxin serum level.[12] In men, trough levels between 0.6 and 0.8 ng/mL were associated with decreased mortality, suggesting that trough levels of digitalis should be maintained between 0.5 and 1.0 ng/mL. There is also evidence that digoxin may be potentially harmful in women. In a post hoc multivariable analysis of the DIG trial, digoxin was associated with a significantly higher risk (23%) of death from any cause among women, but not men, possibly because of the relatively lower body weight in women, who were prescribed doses of digoxin on the basis of a nomogram rather than trough levels.[12] The DIG trial was conducted before the widespread use of beta blockers, and no large trial of digoxin in addition to therapy with both ACEIs and beta blockers is available.

Complications of Digoxin Use

The principal adverse effects of digoxin are (1) cardiac arrhythmias, including heart block (especially in elderly patients) and ectopic and reentrant cardiac rhythms; (2) neurologic complaints, such as visual disturbances, disorientation, and confusion; and (3) gastrointestinal (GI) symptoms such as anorexia, nausea, and vomiting. As noted, these side effects can generally be minimized by maintaining trough levels of 0.5 to 1.0 ng/mL. In patients with HF, overt digitalis toxicity tends to emerge at serum concentrations greater than 2.0 ng/mL; however, digitalis toxicity may occur with lower digoxin levels, particularly if hypokalemia or hypomagnesemia coexist. Oral potassium administration is often useful for atrial, atrioventricular (AV) junctional, or ventricular ectopic rhythms, even when the serum K^+ is in the normal range, unless high-grade AV block is also present. However, serum K^+ levels must be monitored carefully to avoid hyperkalemia, especially in patients with renal failure or those taking aldosterone receptor antagonists. Potentially life-threatening digoxin toxicity can be reversed by antidigoxin immunotherapy using purified Fab fragments (see online supplement). The concomitant use of quinidine, verapamil, spironolactone, flecainide, propafenone, and amiodarone can increase serum digoxin levels and may increase the risk of adverse reactions. Patients with advanced heart block should not receive the digitalis unless a pacemaker is in place.

n-3 Polyunsaturated Fatty Acids

A large body of experimental evidence suggests that n-3 polyunsaturated fatty acids (PUFAs) have favorable effects on inflammation, including a reduction of endothelial activation and production of inflammatory cytokines, platelet aggregation, autonomic tone, blood pressure, heart rate, and LV function. The GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca–Heart Failure) showed that long-term administration of 1 g/day of omega-3 PUFAs resulted in a significant reduction in both all-cause mortality (adjusted HR, 0.91; 95.5% CI 0.83 to 0.99; $P = 0.041$) and all-cause mortality and CV admissions (adjusted HR, 0.92; 99% CI 0.849 to 0.999; $P = 0.009$), in all the predefined subgroups, including HF patients with nonischemic cardiomyopathy.[42] The most recent European Society of Cardiology (ESC) guidelines endorse the use of PUFAs as adjunctive therapy for HFrEF patients who are receiving optimal evidence-based medical therapy.[8]

Pharmacogenomics and Personalized Medicine

As discussed in **Chapter 8**, *pharmacogenomics* is the study of how genetic variations affect drug response, including genetic variants of enzymes that metabolize drugs, variants in drug receptors or drug transporters, and variants in drug targets. These variations can result in gain or loss of therapeutic efficacy, can influence optimal drug dosing, or can favor alternative drug treatment. Given the tremendous heterogeneity in HF patients, genetic variations likely play a significant role in determining drug metabolism, disposition, and functional activity in HF patients. Recent advances in the field of pharmacogenetics suggest an analysis of underlying gene polymorphism in disease-causing pathways may enable clinicians to develop personalized therapeutic regimens for HF patients. Indeed, polymorphisms have been identified in the genes that appear to influence the therapeutic efficacy of ACEIs, beta blockers, nitrates, and diuretics. An overview of the major genetic variations in these pathways and the proposed functional impact of these polymorphisms is presented in the online supplement for this chapter (Pharmacogenomics in Heart Failure).

Personalized medicine seeks to use genetic information to "personalize" and improve diagnosis, prevention, and therapy. The personalized management of HF patients involves a large spectrum of potential applications, from diagnosis of monogenic disorders (**see Chapters 77 and 78**) to prevention and management strategies based on modifier genes, as well as to pharmacogenomics. However, the major challenge in applying pharmacogenomics to everyday clinical practice in patients with HFrEF is the absence of robust clinical data that support the differential use of neurohormonal antagonists in the management of HFrEF patients with specific gene polymorphisms.[43] Indeed, all the extant pharmacogenomic analyses in HFrEF have come from post hoc retrospective analyses of clinical trial data or from observational patient series studies, rather than prospective outcomes studies that randomized HFrEF patients to pharmacogenomic-guided therapy versus standard of care. Of note, the ongoing GENETIC-AF (Genetically Targeted Therapy for the Prevention of Symptomatic Atrial Fibrillation in Patients with Heart Failure [NCT01970501]) will prospectively compare the effects of bucindolol to metoprolol succinate on the recurrence of symptomatic atrial fibrillation/atrial flutter in HF patients (LVEF <0.50) who have a specific genotype for the β_1-adrenergic receptor (β1389 Arg/Arg genotype).

Management of Atherosclerotic Disease

The clinical evaluation of atherosclerotic cardiovascular heart disease in HF patients is discussed in **Chapter 21**. In patients with a prior MI and HF without angina, the use of ACEIs and beta blockers has been shown to decrease the risk of reinfarction and death. Although the role of *aspirin* in HF patients of ischemic etiology has not been clearly established in randomized trials and remains controversial because of the concern that aspirin may attenuate the beneficial effects of ACEIs, long-term treatment with an antiplatelet agent, including aspirin (75 to 81 mg), is recommended for patients with HF due to ischemic etiology, regardless of whether they are receiving ACEIs.[44] Alternative antiplatelet agents (e.g., clopidogrel) may not interact adversely with ACEIs and may have superior effects in preventing clinical events; however, their ability to favorably affect outcomes in HF has not been demonstrated. Both beta blockers and ivabradine (in selected patients) are effective for controlling angina in HFrEF patients.[45]

Coronary artery bypass grafting (CABG) has not been shown to improve cardiac function or symptoms or to prevent reinfarction or death in HF patients without angina. In contrast, CABG has been shown to improve symptoms and survival in patients with modestly reduced EF and angina, although patients with clinical HF or markedly depressed ventricular function have generally been excluded from

most studies. The STICH (Surgical Treatment for Ischemic Heart Failure) trial showed that CABG did not reduce all-cause death (HR, 0.86; 95% CI 90.7to 1.04; *P* = 0.12), which was the primary endpoint of the trial. However, CABG did reduce the composite endpoint of CV death, death from any cause, or hospitalization for CV causes (HR for CABG, 0.74; 95% CI 0.64 to 0.85; *P* < 0.001), which was a prespecified secondary analysis. The 10-year follow-up to the original STICH trial demonstrated a significantly lower mortality in patients who underwent CABG compared to medical therapy (**see Chapter 28**, **Fig. 28.2**). The results of STICH suggest that CABG is beneficial in HF patients of ischemic etiology who are otherwise suitable for surgery (**see Table 25G.6**). Although the data are less robust, percutaneous coronary intervention (PCI) may be considered as an alternative to CABG in patients unsuitable for surgery. The surgical management of patients with CAD and HF is discussed in **Chapter 28**.

Special Populations

Women

Although women account for a significant proportion of the growing heart failure epidemic, they have been poorly represented in clinical trials. Women with HF are more likely to be older (**see Fig. 21.1**), have a preserved EF (**see Chapter 26**), and have a nonischemic etiology for their HF. Although some studies have reported that HF outcomes are worse for women than men, the aggregate data suggest that women have a survival advantage when they develop HF. Although the explanation for this is unclear, it may be related to gender differences in etiology for HF. Nonetheless, although women appear to have a survival advantage after the diagnosis of HF, they experience increased morbidity, with worse quality of life, and have increased depression. Moreover, women are at increased risk of developing HF after acute MI.[46] Pooled analysis of several large-scale prospective clinical trials with beta blockers and ACEIs suggest that these agents provide similar survival benefits in women with reduced EF as in men.[46] (See also **Chapter 89**.)

Race/Ethnicity

Epidemiologic and clinical trial data have raised awareness of potential areas of concern regarding the evaluation and treatment of HF in specific racial and ethnic groups (**see Chapter 21**). The efficacy of pharmacologic treatments in such subgroups is somewhat controversial because so few randomized clinical trials of HF treatment have prespecified a subgroup analysis of outcomes stratified by race or ethnicity and had sufficient participants for meaningful statistical analysis. Several retrospective analyses have highlighted that differences between African American and white populations in response to some standard HF therapies. Unfortunately, few data exist for Hispanic and Asian HF populations. Retrospective analyses from SOLVD and the Vasodilator in Heart Failure Trial (V-HeFT) trials suggested that African Americans do not benefit from ACEIs. In contrast, post hoc analysis of studies with approved beta blockers have shown that African American patients benefit from beta-blocker therapy, although the magnitude of the effect appears to be diminished.[47] The African American Heart Failure Trial (A-HeFT) compared the adjunctive use of a proprietary formulation of isosorbide dinitrate and hydralazine to a standard HF regimen of ACEIs, beta blockers, and diuretics in African Americans with NYHA Class III or IV HF.[12] The primary endpoint was a composite score of weighted values for death from any cause, first hospitalization for HF, and change in quality of life. The study was terminated early because there

was a significant 43% reduction in the rate of death from any cause and a significant 33% relative reduction in the rate of first hospitalization for HF (**Fig. 25.16**). The mechanism for the beneficial effect of the hydralazine/isosorbide regimen may be related to an improvement in NO bioavailability; however, the combination therapy group also had a small (but significant) effect on blood pressure lowering. The effect of the hydralazine/isosorbide combination in other HF patients receiving standard therapy is not known because the population studied in A-HeFT was limited to African Americans. However, there is no reason to believe that this benefit is limited to blacks. The results of the A-HeFT trial have led to the suggestion that the addition of isosorbide dinitrate and hydralazine to a standard medical regimen for HF, including ACEIs, ARNIs, beta blockers, and MRAs, is reasonable and can be effective in African Americans with NYHA Functional Class III or IV HF.

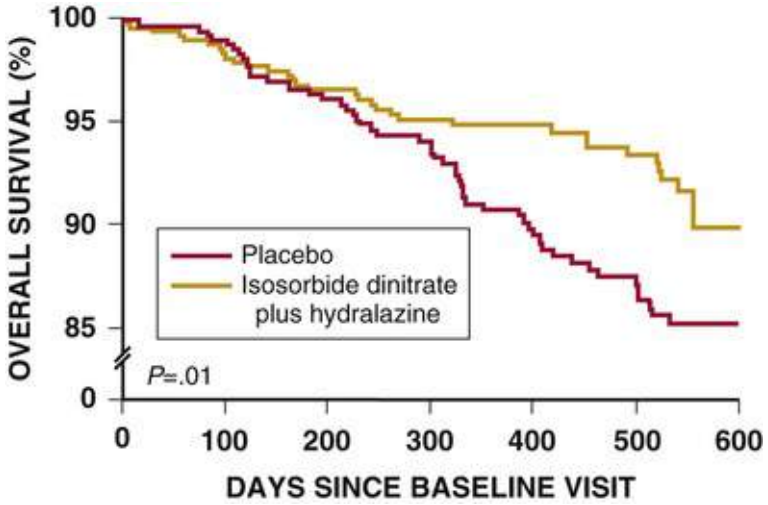


FIGURE 25.16 Kaplan-Meier analysis of the probability of survival among patients in the placebo and isosorbide dinitrate plus hydralazine treatment arms of the A-HeFT study. (Modified from Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351:2049-57.)

Elderly Persons

Prevalence of HF increases with age (**see Fig. 21.1**) and is the most common reason for hospitalization in elderly patients. Of note, the presentation of HF may differ in elderly patients with HF. Although they typically present with the classic symptoms of dyspnea and fatigue, elderly are more likely than younger patients to present with atypical symptoms such as altered mental status, depression, or poor executive functioning.[6] The therapeutic approach to HF with a reduced EF in elderly patients should be, in principal, identical to that in younger patients regarding the choice of pharmacologic therapy. However, altered pharmacokinetic and pharmacodynamic properties of CV drugs in the elderly population may require that these therapies be applied more cautiously, with reductions in drug dosages when appropriate (**see Chapter 88**). Other complicating factors may include blunting of baroreceptor function and orthostatic dysregulation of blood pressure, which may make it difficult to use target doses of some neurohormonal antagonists. Multidisciplinary HF programs have been successful in decreasing the rate of readmission and associated morbidity in elderly patients (see later).

Patients with Cancer

Patients with cancer are particularly predisposed to the development of HF as a result of the cardiotoxic effects of many cancer chemotherapeutic agents. The management of these patients is discussed in **Chapter 81**.

Anticoagulation and Antiplatelet Therapy

Patients with HF have an increased risk for arterial or venous thromboembolic events. In clinical HF trials the rate of cerebrovascular accident (stroke) ranges from 1.3% to 2.4% per year. Depressed LV function is believed to promote relative stasis of blood in dilated cardiac chambers with increased risk of thrombus formation. Thromboembolism prophylaxis in patients with HF and atrial fibrillation (AF) should be individualized and based on an assessment of the risk of stroke versus the risk of bleeding on an anticoagulant. In general, most patients with HFrEF will have an increased risk of stroke, as assessed by a variety of risk scores (e.g., *c*ardiac failure, *h*ypertension, *a*ge ≥75 (doubled), *d*iabetes, *s*troke (doubled), *v*ascular disease, *a*ge 65-74, and *s*ex category (female) [CHA2DS2-VASc]; **see Chapter 38**). A recent meta-analysis of clinical trials in patients with nonvalvular AF suggests that, compared to warfarin, novel oral anticoagulants (NOACs) have a favorable risk-benefit profile, with significant reductions in stroke, intracranial hemorrhage, and mortality and with similar major bleeding as for warfarin, but increased GI bleeding.[48] Other studies have suggested comparable efficacy but fewer major bleeding events. On the basis of these studies, the ESC heart failure guidelines recommend NOACs, recognizing that their safety in older patients and those with impaired renal function is not known.[8] Anticoagulation is also recommended for all patients with a history of systemic or pulmonary emboli, including stroke or transient ischemic attack (TIA). Patients with symptomatic or asymptomatic ischemic cardiomyopathy and documented recent, large, anterior MI, or recent MI with documented LV thrombus should be treated with warfarin (goal INR, 2.0 to 3.0) for the initial 3 months after MI unless there are contraindications. The question of whether HF patients who are in sinus rhythm should be treated with anticoagulants to reduce stroke was addressed in the WARCEF (Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction) trial, which showed that treatment with warfarin compared with aspirin did not reduce the composite outcome of time to ischemic stroke, intracerebral hemorrhage, or death from any cause (HR, 0.93; 95% CI 0.79 to 1.10; $P = 0.40$).[49] Although treatment with warfarin was associated with a significant reduction in the rate of ischemic stroke (HR, 0.52; 95% CI 0.33 to 82; $P = 0.005$), this benefit was offset by a significant increase in the rate of major hemorrhage. Interestingly, the rates of intracerebral and intracranial hemorrhage did not differ significantly between the two treatment groups. Based on the results of the WARCEF trial, there is no compelling reason to use warfarin rather than aspirin in HF patients with a reduced LVEF who are in sinus rhythm.

Management of Cardiac Arrhythmias

Atrial fibrillation is the most common arrhythmia in HF and occurs in 15-30% of patients (**see Chapters 37 and 38**). AF may lead to worsening HF symptoms (**see Table 25.5**) and increases the risk of thromboembolic complications, particularly stroke. The AF-CHF (Atrial Fibrillation and Congestive Heart Failure) trial tested rate control versus rhythm control in patients with chronic HFrEF (EF <35%) and a history of AF. A strategy of rhythm control (pharmacologic or electrical cardioversion) was not shown to be superior to a strategy of controlling ventricular rate with respect to reducing death from CV causes (HR rhythm control group, 1.06; 95% CI 0.86 to 1.30; $P = 0.59$).[50] Secondary outcomes were also

similar in the rate and rhythm control groups, including death from any cause, stroke, worsening HF, and the composite of death from CV causes, stroke, or worsening HF.[50] Therefore a rhythm control strategy is best suited for patients with a reversible secondary cause of AF or in patients who cannot tolerate AF symptoms after optimization of rate control and HF therapy.

For control of heart rate in HF AF patients, beta blockers are preferred over digoxin because digoxin does not provide rate control during exercise. Although the effectiveness of beta blockers in HFrEF patients with coexisting AF was cast in doubt by a patient-level meta-analysis, a recent substudy of the AF-CHF trial showed that the use of beta blockers was associated with significantly lower mortality but no difference in CV and non-CV hospitalizations in patients with HFrEF and AF. The mortality reduction was not altered by the type of AF (i.e., paroxysmal or persistent) or the proportion of time spent in AF.[51] Importantly, the combination of digoxin and a beta blocker is more effective than a beta blocker alone in controlling the ventricular rate at rest. When beta-adrenergic blockers cannot be used, amiodarone has been used by some physicians, but chronic use has potentially significant risks, including thyroid disease and lung toxicity (see later). The short-term IV administration of diltiazem or amiodarone has been used for the acute treatment of AF patients with very rapid ventricular response; however, the negative inotropic effects of nondihydropyridine calcium channel blockers such as diltiazem and verapamil must be considered if these agents are used.

The optimum control of ventricular rate in patients with HF and AF is unclear at present. Although a resting ventricular response of 60 to 80 beats/min and a ventricular response of 90 to 115 beats/min during moderate exercise have been suggested, the RACE II study (Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II) did not show a difference in a composite of clinical outcomes when a strategy of strict rate control (<80 beats/min at rest and <110 beats/min during 6 minute walk) was compared with lenient rate control.[52] Recognizing that sustained tachycardia can lead to a cardiomyopathy, AV node ablation and cardiac resynchronization therapy (CRT) have been suggested for control of ventricular rate (<100 to 110 beats/min) in extreme cases of a rapid ventricular response in patients with AF.[8]

Most antiarrhythmic agents, with the exception of amiodarone and dofetilide, have negative inotropic effects and are proarrhythmic. *Amiodarone* is a class III antiarrhythmic that has little or no negative inotropic or proarrhythmic effects and is effective against most supraventricular arrhythmias (**see Chapter 38**). Amiodarone is the preferred drug for restoring and maintaining sinus rhythm and may improve the success of electrical cardioversion in patients with HF. Amiodarone increases the level of phenytoin and digoxin and will prolong the international normalized ratio (INR) in patients taking warfarin. Therefore, it is often necessary to reduce the dose of these drugs by as much as 50% when initiating therapy with amiodarone. The risk of adverse events, such as hyperthyroidism, hypothyroidism, pulmonary fibrosis, and hepatitis, are relatively low, particularly when lower doses of amiodarone are used (100 to 200 mg/day).

Dronedarone is a novel antiarrhythmic drug that reduces the incidence of AF and atrial flutter and has electrophysiologic properties similar to those of amiodarone but does not contain iodine and thus does not cause iodine-related adverse reactions. Although dronedarone was significantly more effective than placebo in maintaining sinus rhythm in several studies, the ANDROMEDA trial (European Trial of Dronedarone in Moderate to Severe Congestive Heart Failure) had to be terminated prematurely because of a twofold increase in mortality (HR, 2.13; 95% CI 1.07 to 4.25; $P = 0.167$) in the dronedarone-treated

HF patients.[53] The excess mortality was predominantly related to worsening HF. As a result of this study, dronedarone is contraindicated in patients with NYHA Class IV HF or those with Class II or III HF who have had a recent HF decompensation.

Because of the risk of proarrhythmic effects of antiarrhythmic agents in patients with LV dysfunction, it is preferable to treat ventricular arrhythmias with implantable cardioverter-defibrillators (ICDs), either alone or in combination with amiodarone (**see Chapter 26**).

Device Therapy

Cardiac Resynchronization Therapy

CRT is discussed in detail in **Chapters 27 and 41**. When CRT is added to optimal medical therapy in patients in sinus rhythm there is a significant decrease in patient mortality and hospitalization, a reversal of LV remodeling, as well as improved quality of life and exercise capacity (**see Chapter 27**).[8,12] CRT should be considered for patients NYHA Class II-IV HF with a depressed EF <30% to 35% and a wide QRS (**see Table 27.G1** for details), who are already on optimal background therapy including an ACEI/ARB, beta-blocker, and an MRA for several months, and may be considered in select patients with NYHA class I HF with a wide QRS (**see Table 27G.1**). For eligible patients, consideration should be given for implantation of CRT with an ICD (CRT-ICD).

Implantable Cardioverter-Defibrillators

ICDs are discussed in detail in **Chapters 27, 41, and 44**. Briefly, the prophylactic implantation of ICDs in patients with mild to moderate HF (NYHA Class II or III) has been shown to reduce the incidence of sudden cardiac death (SCD) in patients with ischemic or nonischemic cardiomyopathy. Thus, implantation of an ICD should be considered for patients NHA Class II or III HF with a depressed EF less than 30% to 35% who are already receiving optimal background therapy, including an ACEI/ARB, beta blocker, and MRA for several months, and who have a reasonable expectation of survival with a good functional status for more than 1 year. CRT-ICD should be considered for NYHA Class IV patients.

Sleep-Disordered Breathing

The general topic of sleep disorders in CV disease is discussed in **Chapter 87**. HF patients with a reduced EF (<40%) typically exhibit sleep-disordered breathing; approximately 40% exhibit central sleep apnea (CSA), commonly referred to as “Cheyne-Stokes breathing” (**see Chapter 21**); whereas another 10% exhibit obstructive sleep apneas (OSA). CSA associated with Cheyne-Stokes respiration is a form of periodic breathing in which central apneas and hypopneas alternate with periods of hyperventilation that have a waxing-waning pattern of tidal volume. Risk factors for the development of CSA in HF patients include male gender, age older than 60 years, presence of AF, and hypocapnia.[54] **Fig. 25.17** illustrates the proposed mechanisms that underlie periodic oscillations in ventilation in HF, including heightened sensitivity to arterial partial pressure and long circulation time. The main clinical significance of CSA in HF is its association with increased mortality. Whether this is simply because Cheyne-Stokes respiration with CSA is a reflection of advanced disease with poor LV function, or whether its presence constitutes a separate and additive adverse influence on outcomes, is not clear. Regardless, multivariate analyses suggest that CSA remains an independent risk factor for death or

cardiac transplantation, even after controlling for potentially confounding risk factors. The potential mechanism(s) for adverse outcomes in HF patients with CSA may be attributed to marked neurohumoral activation (especially norepinephrine). Studies have suggested that Cheyne-Stokes respirations can resolve with proper treatment of HF. However, if the patient continues to have symptoms related to sleep-disordered breathing for the treatment of nocturnal hypoxemia in OSA despite optimization of HF therapies, a comprehensive overnight sleep study–polysomnography is indicated.

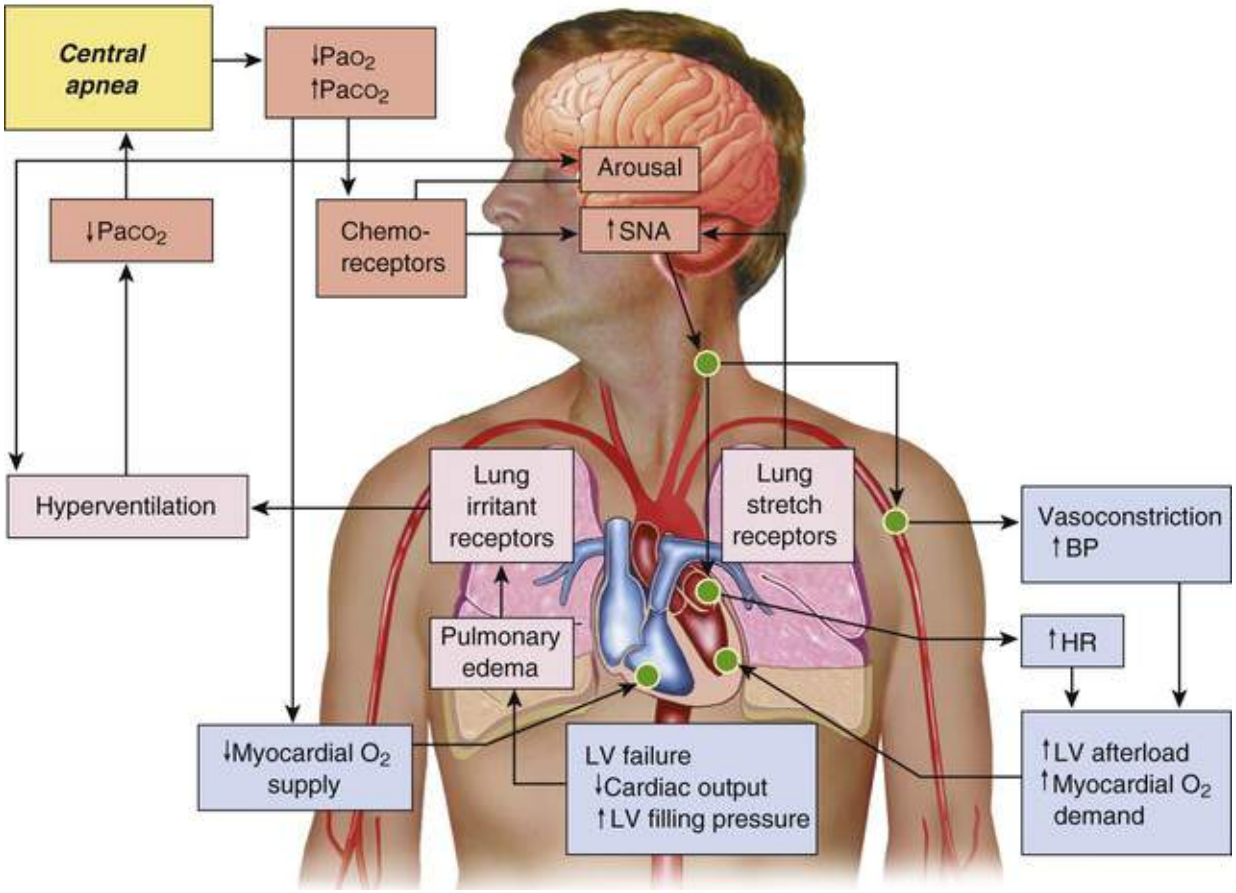


FIGURE 25. 17 Pathophysiology of central sleep apnea and Cheyne-Stokes respiration in heart failure (HF). HF leads to increased LV filling pressure. The resulting pulmonary congestion activates lung vagal irritant receptors, which stimulate hyperventilation and hypocapnia. Superimposed arousals cause further abrupt increases in ventilation and drive the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) below the threshold for ventilation, triggering a central apnea. Central sleep apneas are sustained by recurrent arousal resulting from apnea-induced hypoxia and the increased effort to breathe during the ventilatory phase because of pulmonary congestion and reduced lung compliance. Increased sympathetic activity causes increases in blood pressure (*BP*) and heart rate (*HR*) and increases myocardial oxygen (O_2) demand in the presence of reduced supply. *SNA,* Sympathetic nervous system activity; PaO_2, partial pressure of oxygen in arterial blood. (Redrawn from Bradley TD, Floras JS: Sleep apnea and heart failure. Part II. Central sleep apnea. Circulation 2003;107:1822.)

Although current guidelines recommend that continuous positive airway pressure (CPAP) may be reasonable to improve sleep quality and daytime sleepiness in patients with OSA,[10] there is no consensus as to how CSA should be treated. Since CSA is to some extent a manifestation of advanced HF, the first consideration is to optimize drug therapy, including aggressive diuresis to lower cardiac filling pressure, along with the use ACEIs/ARBs, ARNIs, beta blockers, and MRAs, which may lessen the severity of

CSA. In some cases, however, metabolic alkalosis arising from diuretic use may predispose to CSA by narrowing the difference between the circulating arterial carbon dioxide partial pressure ($PaCO_2$) and the $PaCO_2$ threshold that is necessary for apnea to develop. The use of nocturnal oxygen and CPAP devices has been reported to alleviate CSA, abolish apnea-related hypoxia, and decrease nocturnal norepinephrine levels, as well as produce symptomatic and functional improvement in HF patients when used in the short term (up to 1 month). However, the effects of supplemental O_2 on CV endpoints over more prolonged periods have not been assessed. Although there is no direct evidence that treatment of sleep-disturbed breathing prevents the development HF, treatment with CPAP breathing has been shown to improve LV structure and function in patients with OSA or CSA disturbed-breathing syndrome.[54]

Despite these objective measurements of improvement with CPAP, this treatment modality did not lead to a prolongation of life in the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) trial,[54] which was discontinued early after concerns about the early divergence of transplantation-free survival favoring the control group. There was no difference in the primary endpoint of death or transplantation ($P = 0.54$) and no significant difference in the frequency of hospitalization between groups (0.56 versus 0.61 hospitalizations per patient year; $P = 0.45$). However, a post hoc analysis of the CANPAP study suggested that adequate suppression of CSA by CPAP was associated with improved heart transplant–free survival.[54]

The role of adaptive servo-ventilation (ASV), which alleviates CSA by delivering servo-controlled inspiratory pressure support on top of expiratory positive airway pressure was evaluated in the SERVE-HF trial (Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure).[55] In patients with HFrEF (LVEF ≤45%) who predominantly had CSA, ASV had no effect on the primary end point, which was a time-to-event analysis of the first event of death from any cause, lifesaving CV intervention (cardiac transplantation, implantation of ventricular assist device, resuscitation after sudden cardiac arrest, or appropriate lifesaving shock), or unplanned hospitalization for worsening HF. However, all-cause mortality (HR, 1.28; 95% CI 1.06 to 1.55; $P = 0.01$) and CV mortality (HR, 1.34; 95% CI 1.09 to 1.65; $P = 0.006$) were significantly higher in the ASV group than in the control group. Therefore, ASV is not recommended in patients with NYHA Class II to IV HFrEF and predominantly CSA (level III: harm).[10]

Thus the data remain unclear whether elimination of apnea will lead to improved clinical outcomes. Other therapies proposed for sleep-disordered breathing in HF include nocturnal O_2, CO_2 administration (by adding dead space), theophylline, and acetazolamide and diaphragmatic pacing, but have not yet been systematically studied in outcome-based, prospective randomized trials.[56]

Disease Management Approach to Heart Failure

Despite the compelling scientific evidence that ACEIs/ARBs, beta blockers, and aldosterone antagonists reduce hospitalizations and mortality in patients with HF, these life-prolonging therapies continue to be underutilized outside of the highly artificial environment of clinical trials. Indeed, numerous studies in a variety of different clinical settings have documented that a significant proportion of patients with HF are not receiving treatment with guideline-recommended, evidence-based therapies. The failure to deliver optimal medical care to HF patients is almost certainly multifactorial, as it is with other complex chronic conditions that have substantial morbidity and mortality. Further, the elderly status of many HF patients, who often have a myriad of comorbidities, also presents a special challenges to health care providers. Optimal HF care includes a trained network of health care providers involved in the delivery of HF

management and interventions, including nurses, case managers, physicians, pharmacists, caseworkers, dietitians, physical therapists, psychologists, and information systems specialists; a method for communicating this knowledge to the patient, including patient education, education of caregivers and family members, medication management, peer support, or some form of post–acute care, as well as a method of ensuring that the patient has received and understood the knowledge; and a system for encouraging adherence to the recommended regimen and patient compliance (**Fig. 25.18**). Numerous studies have shown that many of the challenges to delivering optimal care to HF patients can be met through an integrated specialized HF clinic approach that uses nurse and physician extenders to deliver and ensure the implementation of care. Technology-driven strategies that employ low-cost telemonitoring also appear promising in terms of improving HF management and outcomes[57] (**see Chapter 27**). However, the optimum approach to noninvasive remote monitoring is uncertain, and the data from randomized clinical trials have been inconsistent and are not recommended by current practice guidelines.

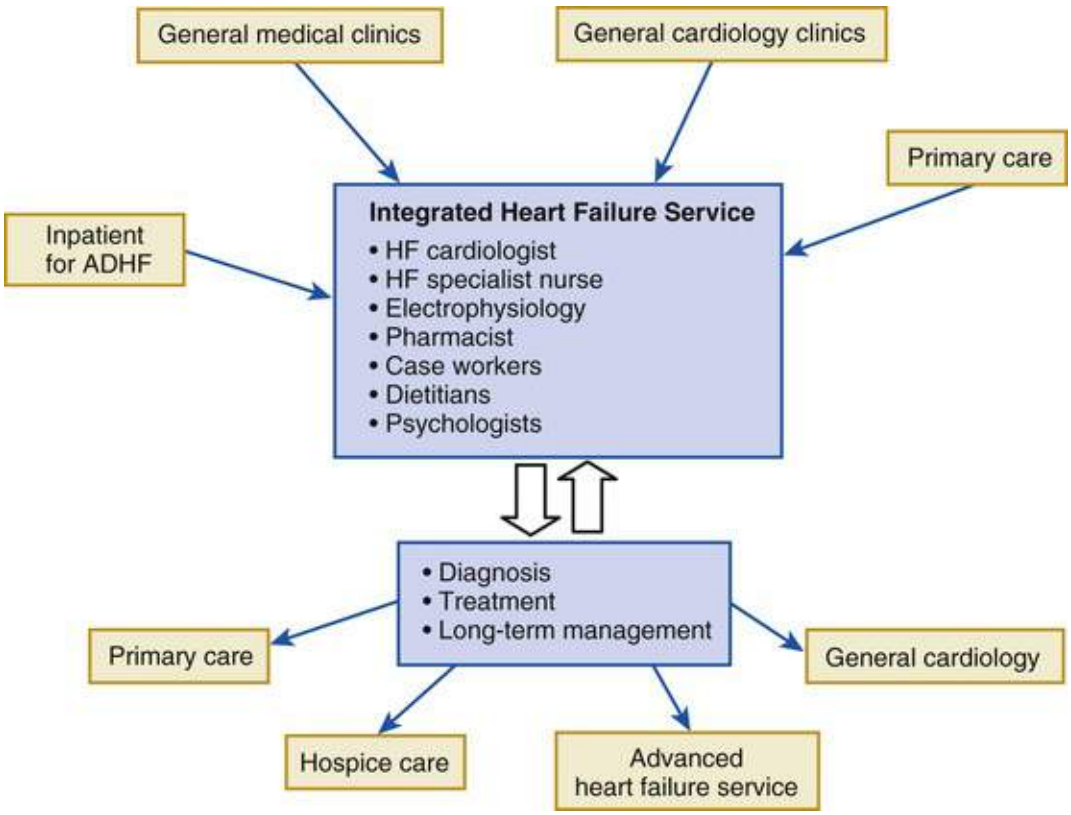


FIGURE 25.18 Integrated disease management program in heart failure. *ADHF,* Acute decompensated heart failure. (Modified from McDonagh TA. Lessons from the management of chronic heart failure. Heart 2005;91(Suppl 2):ii24-7.)

A disease management approach to HF has been shown to reduce hospitalizations and increase the percentage of patients receiving ideal, guideline-recommended therapy. Recent studies demonstrate that disease management programs need not be confined to the outpatient setting, and that hospital-based disease management systems can also improve medical care and education of hospitalized HF patients and accelerate use of evidence-based, guideline-recommended therapies by administering them before hospital discharge.[35] Although disease management strategies can lead to improved survival, it is not clear that these strategies are necessarily more cost-effective. Accordingly, the greatest challenge to disease management programs will be to determine how to support the additional personnel required in this model of care.

Patients With Refractory End-Stage Heart Failure (Stage D)

Most patients with HF caused by reduced LVEF respond well to evidenced-based pharmacologic and nonpharmacologic treatments and enjoy a good quality of life with a meaningful prolongation of life. However, for reasons that are not clear, some patients do not improve or will experience a rapid recurrence of symptoms despite optimal medical and device therapies. These individuals represent the most advanced stage of HF (stage D) and should be considered for specialized treatment strategies, such as mechanical circulatory support (**see Chapter 29**), continuous IV positive inotropic therapy, or referral for cardiac transplantation (**see Chapter 28**). However, before a patient is considered to have refractory HF, physicians should identify any contributing conditions (**see Table 25.5**) and ensure that all conventional medical strategies have been optimally employed. When no further therapies are appropriate, careful discussion of the prognosis and options for end-of-life care should be initiated (**see Chapter 31**).

Future Perspectives

Treatment with ACEIs/ARBs, beta blockers, MRAs, and cardiac devices has substantially improved quality and quantity of life for patients with HFrEF. Moreover, the recent success with the use of ARNIs offers the possibility of combining traditional neurohormonal approaches with drugs such as neprilysin inhibitors, whose mode of action is not completely understood. Ongoing approaches with small molecules that modulate contractility and gene therapy (**see Chapter 30**), accompanied by growing appreciation of the role of pharmacogenomics (**Chapter 8**), may lead to further advances in the field.

Guidelines

Management of Heart Failure with a Reduced Ejection Fraction

Douglas L. Mann

Guidelines for the initial evaluation of the heart failure patient are reviewed in **Chapter 21**, whereas this chapter reviews guidelines for the management of patients with a reduced ejection fraction (HFrEF). A joint task force of the American College of Cardiology and the American Heart Association (ACC/AHA) published updated comprehensive guidelines for the evaluation and management of heart failure (HF) in 2013.[1] These were updated in two sequential guidelines in 2016[2] that focused on changes in medical therapies but did not provide new guidelines for devices in diagnosing and treating heart failure.[2] The Heart Failure Society of America (HFSA) has partnered with the ACC and the AHA to provide coordinated recommendations about the 2016 and 2017 guidelines. The European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of chronic HF were published 2016,[3] which superseded guidelines in 2012.[4] The ACC/AHA updated guidelines for management of patients with heart failure with a preserved ejection fraction (HFpEF) are reviewed in **Chapter 26**, and the use of devices for managing heart failure in **Chapter 27**.

As reviewed in this chapter and **Chapter 21**, the ACC/AHA guidelines classify patients according to four stages:

Stage A: patients at high risk for developing heart failure but without structural disorders of the heart
Stage B: patients with a structural disorder of the heart but no symptoms of heart failure
Stage C: patients with past or current symptoms of heart failure associated with underlying structural heart disease
Stage D: patients with end-stage disease who require specialized treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation, or hospice care

The following guidelines are organized into recommendations for each stage. As with other ACC/AHA guidelines, these recommendations classify interventions into one of three classes of recommendation (COR), including two levels of the "intermediate" group and two of the "no benefit" (NB) group. The term *guideline-directed medical therapy* (GDMT) represents optimal medical therapy as defined by the ACC/AHA guideline–recommended therapies.

Treatment of Patients at High Risk of Developing Heart Failure (Stage A)

The 2013 ACC/AHA guidelines for stage A patients are simplified from previous guidelines and continue to provide strong recommendations (class I) for treating hypertension and lipid disorders in accordance with contemporary guidelines in order to lower the risk of HF (**Table 25G.1**). The guidelines also suggest that other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided. For the first time, the updated ACC/AHA/HFSA 2017 guidelines provide a class IIa recommendation (level of evidence B-R) for the use of screening natriuretic peptide biomarker to prevent HF.

TABLE 25G.1

ACC/AHA Guidelines for Treating Patients at High Risk of Developing Heart Failure (Stage A)

CLASS	INDICATION	LEVEL OF EVIDENCE
I	Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines to lower the risk of HF.	A
I	In patients at increased risk, stage A, the optimal blood pressure in those with hypertension should be less than 130/80 mm Hg.	B-R
I	Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided.	C
II	For patients at risk of developing HF, natriuretic peptide biomarker–based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF.	B-R

GDMT, Guideline-directed medical therapy; *HF,* heart failure.

Treatment of Patients With Left Ventricular Dysfunction Who Have Not Developed Symptoms (Stage B)

The goal of therapy in stage B HF is to reduce the risk of further damage to the heart and to minimize the rate of progression of LV dysfunction (**Table 25G.2**). In the absence of contraindications, beta blockers

and angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor antagonists (ARBs) in those intolerant of ACEIs, are recommended for all patients with histories of myocardial infarction (MI), regardless of ejection fraction (EF), and for all patients with diminished EF, regardless of history of MI (class I, level of evidence A-C). In contrast, the guidelines discourage use of calcium channel blockers with negative inotropic action in this population. The guidelines also support the use of an ICD (class IIb, level of evidence B) in patients with asymptomatic ischemic cardiomyopathy who have had a recent (>40 days) MI with and EF of 30% or less, who are on appropriate medical therapy, and who have a reasonable expectation of life longer than 1 year (**see Chapter 27** for review of ICD guidelines).

TABLE 25G.2

ACC/AHA Guidelines for Treatment of Asymptomatic Left Ventricular Systolic Dysfunction (Stage B)

CLASS	INDICATION	LEVEL OF EVIDENCE
I	In all patients with a recent or remote history of MI or ACS and reduced EF, ACE inhibitors should be used to prevent symptomatic HF and reduce mortality. In patients intolerant of ACE inhibitors, ARBs are appropriate unless contraindicated.	A
	In all patients with a recent or remote history of MI or ACS and reduced EF, evidence-based beta blockers should be used to reduce mortality. Beta blockade and ACE inhibition should be used in all patients with a recent or remote history of MI regardless of EF or presence of HF.	B
	In all patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and cardiovascular events.	A
	Blood pressure should be controlled in accordance with clinical practice guidelines for hypertension to prevent symptomatic HF.	A
	ACE inhibitors should be used in all patients with a reduced EF to prevent symptomatic HF.	A
	Beta blockers should be used in all patients with a reduced EF to prevent symptomatic HF.	C
IIa	To prevent sudden death, placement of an ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 days post-MI, have an LVEF of 30% or less, are on appropriate medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year.	B
III: Harm	Nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low LVEF and no symptoms of HF after MI.	B

ACE, Angiotensin-converting enzyme; *ACS,* acute coronary syndrome; *ARB,* angiotensin receptor antagonist; *EF,* ejection fraction; *ICD,* implantable cardioverter-defibrillator; *LVEF,* left ventricular ejection fraction; *MI,* myocardial infarction.

Treatment of Patients With Left Ventricular Dysfunction and Current or Prior Symptoms (Stage C)

Fig. 25G.1 and **Table 25G.3** summarize the 2017 ACC/AHA/HFSA recommended approach to the treatment of stages C and D HFrEF.[5] Application of the same measures recommended for preventing or minimizing progression of LV dysfunction for stage A and B patients is supported for stage C patients, who have current or prior symptoms attributable to LV dysfunction (**Table 25G.3**). Physical activity and cardiac rehabilitation are recommended for stage C patients. The updated guidelines also reflect the results of the recent HF-ACTION trial (**see Chapter 25**), in which exercise training did not have a favorable impact on all-cause mortality or HF hospitalization. Maximal exercise testing with or without measurement of respiratory gas exchange to facilitate an appropriate exercise program, which was a class IIa indication in 2009, is not recommended in the 2013 ACC/AHA guidelines, although it is still recommended in the 2016 ESC guidelines.

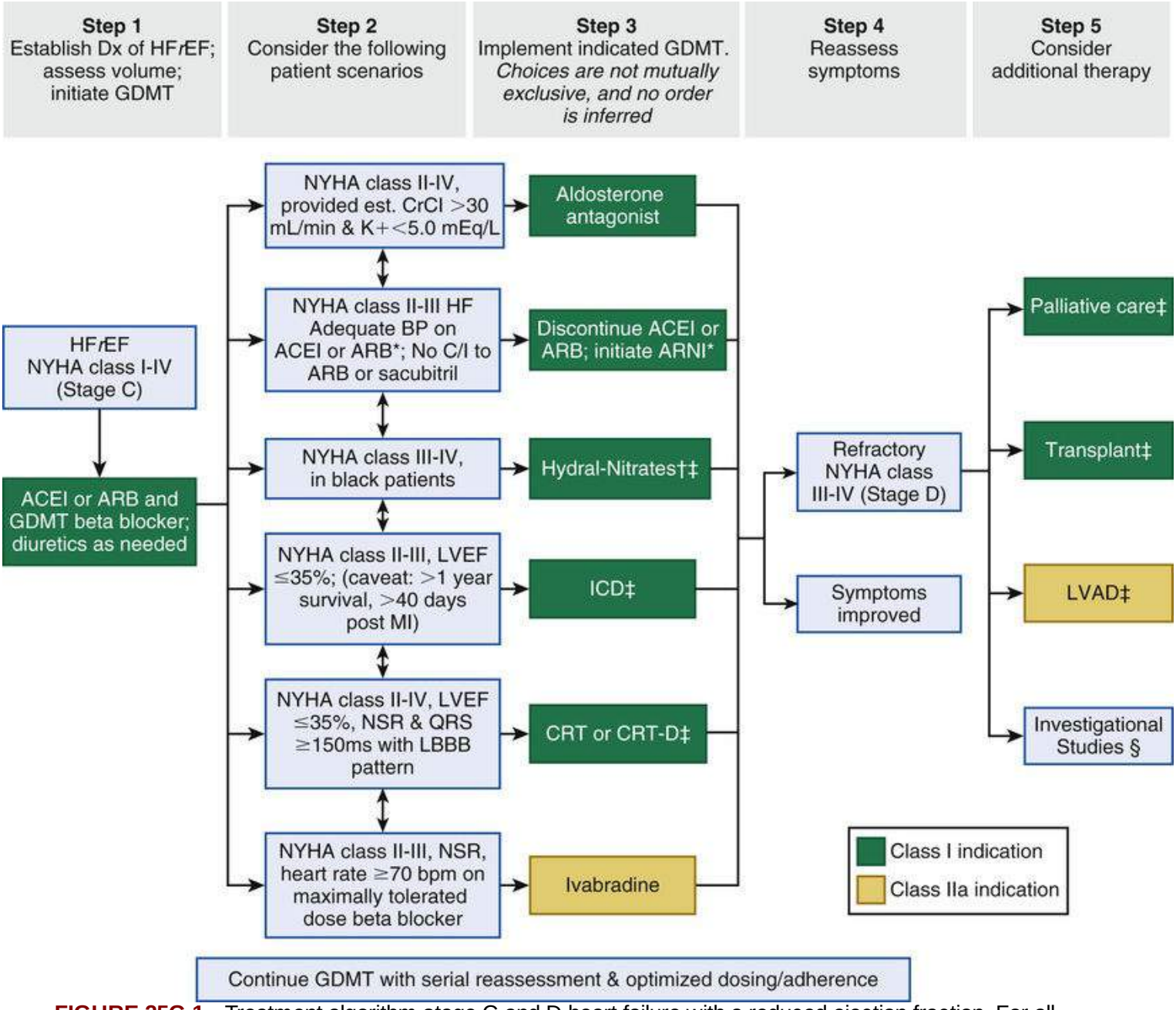


FIGURE 25G.1 Treatment algorithm stage C and D heart failure with a reduced ejection fraction. For all medical therapies, dosing should be optimized and serial assessment exercised. (See text in Chapter 25 for details.) *See text for important treatment directions. †Hydral-Nitrates *green box*: The combination of ISDN/HYD with ARNI has not been robustly tested. BP response should be carefully monitored. ‡See 2013 ACC/AHA heart failure guidelines.[1] §Participation in investigational studies is also appropriate for stage C, NYHA Class II and III HF. ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor-blocker; ARNI, angiotensin receptor neprilysin inhibitor; BP, blood pressure; bpm, beats per minute; C/I, contraindication; CrCl, creatinine clearance; CRT-D, cardiac resynchronization therapy–device; Dx, diagnosis; GDMT, guideline-directed management and therapy; HF, heart failure; HF*r*EF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; ISDN/HYD, isosorbide dinitrate hydral-nitrates; K^+, potassium; LBBB, left bundle-branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSR, normal sinus rhythm; NYHA, New York Heart Association. (Modified from Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017 Apr 28; doi: 10.1161. [Epub ahead of print.].)

TABLE 25G.3

ACC/AHA Guidelines for Treatment of Patients with Prior or Current Symptoms of Chronic HFrEF (Stage C)

CLASS	INDICATION	LEVEL OF EVIDENCE
	Nonpharmacologic Interventions	
I	Patients with HF should receive specific education to facilitate HF self-care.	B
	Exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional status.	A
IIa	Cardiac rehabilitation can be useful in clinically stable patients with HF to improve functional capacity, exercise duration, health-related quality of life, and mortality.	B
	Sodium restriction is reasonable for patients with symptomatic HF to reduce congestive symptoms.	C
	Continuous positive airway pressure (CPAP) can be beneficial to increase LVEF and improve functional status in patients with HF and sleep apnea.	B
	Pharmacologic Interventions	
I	Measures listed as class I recommendations for patients in stages A and B are recommended where appropriate.	A,B,C
	GDMT as depicted in should be the mainstay of pharmacologic therapy for HFrEF.	A
	Diuretics	
I	Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms.	C
	ACEIs/ARBs/ARNIs	
I	The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HFrEF, to reduce morbidity and mortality.	A
	The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HFrEF who are intolerant of ACE inhibitors because of cough or angioedema.	A
I	ARNIs are recommended in patients with HFrEF unless contraindicated, to reduce morbidity and mortality.	B-R
I	ARNIs are recommended in patients with HFrEF NYHA Class II-III who are tolerant of an ACE inhibitor or ARB; replacement by a ARNI is recommended to further reduce morbidity and mortality.	B-R
IIa	ARBs are reasonable to reduce morbidity and mortality as alternatives to ACE inhibitors as first-line therapy for patients with HFrEF, especially for patients already taking ARBs for other indications, unless contraindicated.	A
IIb	Addition of an ARB may be considered in persistently symptomatic patients with HFrEF who are already being treated with an ACE inhibitor and a beta blocker in whom an aldosterone antagonist is not indicated or tolerated.	A
IIa	Ivabradine can be beneficial to reduce HF hospitalizations in patients with NYHA Class II-III HFrEF (LVEF <35%) who are receiving GDMT, including a beta blocker, and who are in sinus rhythm with a heart rate of ≥70 beats/min.	B-R
III: harm	Routinely combining an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended.	C
III: harm	ARNI should not be administered concomitantly with ACE inhibitors or within the last dose of an ACE inhibitor.	B-R
III: harm	ARNI should not be administered to patients with a history of angioedema.	C-EO
	Beta-Adrenergic Blockers	
I	Use of one of the three beta blockers proven to reduce mortality (i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality.	A
	Aldosterone Receptor Antagonists	
I	Aldosterone receptor antagonists (or MRAs) are recommended in patients with NYHA Class II-IV and who have LVEF ≤35%, unless contraindicated, to reduce morbidity and mortality.	A
I	Aldosterone receptor antagonists are recommended to reduce morbidity and mortality following an acute MI in patients who have LVEF ≤40% who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated.	B
III: harm	Inappropriate use of aldosterone receptor antagonists is potentially harmful because of life-threatening hyperkalemia or renal insufficiency when serum creatinine is >2.5 mg/dL in men or >2.0 mg/dL in women (or estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2), and/or potassium >5.0 mEq/L.	B
	Hydralazine and Isosorbide Dinitrate	
I	The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA Class III-IV HFrEF receiving optimal therapy with ACE inhibitors and beta blockers, unless contraindicated.	A
IIa	A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated.	B
	Digoxin	
IIa	Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF.	B
	Anticoagulation	
I	Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age) should receive chronic anticoagulant therapy.	A
I	The selection of an anticoagulant agent (warfarin, dabigatran, apixaban, or rivaroxaban) for permanent/persistent/paroxysmal AF should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in the international normalized ratio (INR) therapeutic range if the patient has been taking warfarin.	C
IIa	Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal AF but are without an additional risk factor for cardioembolic stroke.	B
III: no benefit	Anticoagulation is not recommended in patients with chronic HFrEF without AF, a prior thromboembolic event, or a cardioembolic source.	B
	Statins	
III: no benefit	Statins are not beneficial as adjunctive therapy when prescribed solely for HF.	A
	Omega-3 Polyunsaturated Fatty Acids	
IIa	Omega-3 polyunsaturated fatty acid (PUFA) supplementation is reasonable to use as adjunctive therapy in patients with NYHA Class II-IV symptoms and HFrEF or HFpEF, unless contraindicated, to reduce mortality and cardiovascular hospitalizations.	B
	Drugs of Unproven Value or that May Cause Harm	
III: no benefit	Nutritional supplements as treatment for HF are not recommended in patients with current or prior symptoms of HFrEF.	B
	Hormonal therapies other than to correct deficiencies are not recommended for patients with current or prior symptoms of HFrEF.	C
III: harm	Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HFrEF are potentially harmful and should be avoided or withdrawn whenever possible (e.g., most antiarrhythmic drugs, most calcium channel blockers except amlodipine, NSAIDs, thiazolidinediones).	B
	Long-term use of infused positive inotropic drugs is potentially harmful for patients with HFrEF, except as palliation for patients with end-stage disease who cannot be stabilized with standard medical treatment (see recommendations for stage D).	C
	Calcium Channel Blockers	
III: no benefit	Calcium channel blocking drugs are not recommended as routine therapy for patients with HFrEF.	A

ACEIs, Angiotensin-converting enzyme inhibitors; *ARBs,* angiotensin receptor blockers; *ARNIs,* angiotensin receptor neprilysin

inhibitors; *GDMT,* guideline-directed medical therapy; *HFpEF,* heart failure with preserved ejection fraction; *HFrEF,* heart failure with a reduced ejection fraction; *LVEF,* left ventricular ejection fraction; *NYHA,* New York Heart Association.

The 2017 ACC/AHA/HFSA updated guidelines support the use of beta blockers (bisoprolol, carvedilol, sustained-release metoprolol succinate) and ACEIs (ARBs for patients who cannot tolerate ACEIs) for all stage C patients, in the absence of contraindications, and use of diuretics for patients with fluid overload. New for the 2017 guidelines is the class I recommendation (level B-R) to replace an ACE inhibitor/ARB by a ARNI to further reduce morbidity and mortality in patients with NYHA Class II-III heart failure. When stopping an ACEI and starting an ARNI, it is important to wait at least 36 hours, to avoid the risk of angioedema (class III: harm; level of evidence EO). Of note, the 2016 ESC guidelines do not recommend the routine replacement of an ACEI/ARB by an ARNI unless the patient remains symptomatic after an ACEI (equivalent to 10 mg twice daily of enalapril) or ARB, a beta blocker, and a mineralocorticoid receptor antagonist (MRA), and had elevated levels of plasma natriuretic peptides (BNP ≥150 pg/mL or plasma NT-proBNP ≥600 pg/mL), or if there was a HF hospitalization within the past 12 months with an elevated plasma level of natriuretic peptides (BNP ≥100 pg/mL or plasma NT-proBNP ≥400 pg/mL).[3] The class IIa recommendation for the use of ivabradine in symptomatic patients in sinus rhythm and a heart rate of 70 beats/min or higher (at rest) is also new for the 2017 AHA/ACC/HFSA guidelines.

Based on the results of the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), MRAs are now recommended for all NYHA Class II-IV HF patients with an EF of 35% or less, to reduce morbidity and mortality, unless contraindicated (class I, level of evidence A). As with the 2009 guidelines, the use of hydralazine and isosorbide remains a class I indication for self-identified African Americans who remain symptomatic in NYHA Class III-IV HF despite optimal therapy. The combination of hydralazine and isosorbide is recommended in patients who are intolerant of an ACEI or ARB. Digitalis remains a reasonable approach to decrease hospitalizations in symptomatic patients. Based on the results of the WARCEF (Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction), anticoagulation is not recommended in patients with chronic HF without atrial fibrillation, a prior embolic event, or a cardioembolic source (class III: no benefit). However, anticoagulation continues to be recommended for patients with chronic HF and permanent/persistent/paroxysmal atrial fibrillation who have an additional risk factor for cardioembolic stroke (class I, level of evidence B). The guidelines explicitly discourage the routine use of a combination of an ACEI with an ARB and MRA because of the risk of hyperkalemia; use of an ACEI with an ARNI because of the risk of angioedema; calcium channel blockers, long-term infusion of positive inotropic drugs (except as palliation in patients with end-stage disease, **see Table 25G.3**), use of nutritional supplements, statins as adjunctive therapy for HF, and hormonal therapies other than those needed to replete deficiencies. The recommendations regarding the use of implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) are reviewed in **Chapter 26**.

Treatment of Patients With Refractory End-Stage Heart Failure (Stage D)

The 2009 ACCF/AHA HF guidelines define stage D as patients with truly refractory HF who might be eligible for specialized advanced treatment strategies such as mechanical circulatory support (MCS; **see Chapter 29**), procedures to facilitate fluid removal, continuous inotropic infusions, or cardiac transplantation (**Chapter 28**) or other innovative or experimental surgical procedures, or for end-of-life care, such as hospice (**Chapter 31**). The guidelines provide clear indications for the use of inotropic

agents and MCS in stage D patients (**Table 25G.4**). The guidelines endorse the use of continuous IV inotropic support until definitive therapy can be performed (e.g., MCS, heart transplantation) and/or to maintain systemic perfusion and preserve end-organ performance until the acute precipitating problem is resolved (class I, level of evidence C). The guidelines also support inotropic support as "bridge therapy" to guideline-directed medical therapy (GDMT) and/or device therapy (class IIa, level of evidence B), as well as short-term continuous IV inotropic in hospitalized patients with documented severe systolic dysfunction who present with low blood pressure and significantly depressed cardiac output, in order to maintain systemic perfusion and preserve end-organ performance, or as palliative therapy for symptom control (class IIb, level of evidence B). The guidelines regard long-term use of either continuous or intermittent, IV parenteral positive inotropic agents, in the absence of specific indications or for reasons other than palliative care, as potentially harmful (class III: harm, level of evidence B)

TABLE 25G.4

ACC/AHA Guidelines for Treatment of Patients with End-Stage Heart Failure (Stage D)

CLASS	INDICATION	LEVEL OF EVIDENCE
	Nonpharmacologic Interventions	
IIa	Fluid restriction (1.5-2 L/day) is reasonable in stage D, especially in patients with hyponatremia.	B
	Inotropic Support	
I	Until definitive therapy (e.g., coronary revascularization, MCS, heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary IV inotropic support to maintain systemic perfusion and preserve end-organ performance.	C
IIa	Continuous IV inotropic support is reasonable as "bridge therapy" in patients with stage D refractory to GDMT and device therapy who are eligible for and awaiting MCS or cardiac transplantation.	B
IIb	Short-term, continuous IV inotropic support may be reasonable in those hospitalized patients presenting with documented severe systolic dysfunction who present with low blood pressure and significantly depressed cardiac output, to maintain systemic perfusion and preserve end-organ performance.	B
	Long-term, continuous IV inotropic support may be considered as palliative therapy for symptom control in select patients with stage D despite optimal GDMT and device therapy who are not eligible for either MCS or cardiac transplantation.	B
III: Harm	Long-term use of either continuous or intermittent, IV parenteral positive inotropic agents, in the absence of specific indications or for reasons other than palliative care, is potentially harmful in the patient with HF.	B
	Use of parenteral inotropic agents in hospitalized patients without documented severe systolic dysfunction, low blood pressure, or impaired perfusion, and evidence of significantly depressed cardiac output, with or without congestion, is potentially harmful.	B
	Mechanical Circulatory Support (MCS)	
IIa	MCS is beneficial in carefully selected patients with stage D HFrEF in whom definitive management (e.g., cardiac transplantation) or cardiac recovery is anticipated or planned.	B
	Nondurable MCS, including the use of percutaneous and extracorporeal ventricular assist devices (VADs), is reasonable as a "bridge to recovery" or "bridge to decision" for carefully selected patients with HFrEF with acute, profound hemodynamic compromise.	B
	Durable MCS is reasonable to prolong survival for carefully selected patients with stage D HFrEF.	B
	Cardiac Transplantation	
I	Evaluation for cardiac transplantation is indicated for carefully selected patients with stage D HF despite GDMT, device, and surgical management	C

GDMT, Guideline-directed medical therapy; *HFrEF,* heart failure with reduced ejection fraction; *IV,* intravenous; *MCS,* mechanical circulatory support.

The 2013 ACC/AHA guidelines provide qualified support for MCS in carefully selected patients with stage D HF with a reduced ejection fraction (HFrEF), in whom definitive management (e.g., cardiac transplantation) or cardiac recovery is anticipated or planned, and also indicate that percutaneous and extracorporeal ventricular assist devices (VADs) are reasonable as a "bridge to recovery" or "bridge to decision" for carefully selected patients with HFrEF with acute profound hemodynamic compromise (class IIb, level of evidence B). The guidelines also provide qualified support for the use of durable VADs to prolong survival in carefully selected patients with stage D HFrEF. As in previous guidelines, cardiac transplantation remains a class I indication (level of evidence C) for carefully selected patients with stage D HFrEF despite GDMT, device, and surgical management.

Comorbidities in Heart Failure Patients

The 2013 ACC/AHA practice guidelines recognize the importance of comorbidities in the heart failure

patient, including hypertension, anemia, diabetes, arthritis, chronic kidney disease, and depression, but did not provide specific recommendations. However, the 2017 ACC/AHA/HFSA focused guideline update did provide specific recommendations for the treatment of hypertension, anemia, and sleep-disordered breath (**Table 25G.5**).

TABLE 25G.5

ACC/AHA/HFSA Guidelines for Treatment of Comorbidities in Heart Failure

CLASS	INDICATION	LEVEL OF EVIDENCE
	Hypertension	
I	Patients with HFrEF and hypertension should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg.	C-EO
	Anemia	
IIb	In patients with NYHA Class II and III HF and iron deficiency (ferritin <100 ng/mL or 100-300 ng/mL if transferrin saturation is <20%), intravenous iron replacement might be reasonable to improve functional status and quality of life.	B-R
III: No Benefit	In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality.	B-R
	Sleep-Disordered Breathing	
IIa	In patients with NYHA Class II-IV HF and suspicion of sleep-disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable.	C-LD
IIb	In patients with cardiovascular disease and obstructive sleep apnea, CPAP may be reasonable to improve sleep quality and daytime sleepiness.	B-R
III: Harm	In patients with NYHA Class II-IV HFrEF and central sleep apnea, adaptive servo-ventilation causes harm.	B-R

CPAP, Continuous positive airway pressure; *NYHA,* New York Heart Association.

The Hospitalized Patient

The updated 2010 HFSA, 2012 ESC, and 2013 ACC/AHA guidelines included specific recommendations regarding the hospitalized patient and are reviewed in **Chapter 24** (**Table 24G.1**).

Heart Failure With Preserved Ejection Fraction

The updated 2010 HFSA, 2012 ESC, and 2013 ACC/AHA guidelines included specific recommendations regarding management of patients with HFpEF and are reviewed in **Chapter 26** (**Table 26G.1**).

Surgical/Percutaneous/Transcatheter Interventional Treatment of Heart Failure

The 2013 ACC/AHA guidelines reviewed surgical therapies and percutaneous interventions that are commonly integrated in the management of HF patients, including coronary revascularization (e.g., CABG, angioplasty, stenting); aortic valve replacement, mitral valve replacement, and LV surgical reconstruction (**Table 25G.6**). The revised guidelines recommend coronary artery revascularization via CABG or percutaneous intervention for patients on GDMT with angina and suitable coronary anatomy, especially for a left main stenosis (>50%) or left main equivalent disease (class I, level of evidence C). CABG was also recommended to improve survival in mild to moderate LV dysfunction (EF 35% to 50%) and significant (≥70% diameter stenosis) multivessel CAD or proximal left anterior descending coronary artery stenosis when viable myocardium is present, as well as to improve morbidity and cardiovascular mortality for patients with severe LV dysfunction (EF <35%), HF, and significant CAD (class IIa, level of evidence B). Qualified support was provided for a survival benefit for CABG (class IIb, level of evidence B) in patients with ischemic heart disease with severe LV systolic dysfunction (EF <35%) and operable coronary anatomy irrespective of whether viable myocardium was present. The new guidelines

provided a class IIa (level of evidence B) recommendation for surgical aortic valve replacement in patients with a predicted surgical mortality of less than 10% and a class IIa (level of evidence B) recommendation for transcatheter aortic valve replacement in inoperable patients with critical aortic valve disease. The guidelines offer qualified support for transcatheter mitral valve repair or mitral valve surgery for functional mitral insufficiency and recommend that this approach should be considered after careful candidate selection and in addition to GDMT (class IIb, level of evidence B). A similar level of qualified support was given for surgical reverse remodeling or LV aneurysmectomy for intractable HF and ventricular arrhythmias.

TABLE 25G.6

ACC/AHA Guidelines for Surgical/Percutaneous/Transcatheter Interventional Treatments for Heart Failure

CLASS	INDICATION	LEVEL OF EVIDENCE
I	Coronary artery revascularization via CABG or percutaneous intervention is indicated for patients (HFpEF and HFrEF) on GDMT with angina and suitable coronary anatomy, especially for a left main stenosis (>50%) or left main equivalent disease.	C
IIa	CABG to improve survival is reasonable in patients with mild to moderate LV systolic dysfunction (EF 35%-50%) and significant (≥70% diameter stenosis) multivessel CAD or proximal left anterior descending coronary artery stenosis when viable myocardium is present in the region of intended revascularization.	B
	CABG or medical therapy is reasonable to improve morbidity and cardiovascular mortality for patients with severe LV dysfunction (EF <35%), HF, and significant CAD.	B
	Surgical aortic valve replacement is reasonable for patients with critical aortic stenosis and a predicted surgical mortality of no greater than 10%.	B
	Transcatheter aortic valve replacement after careful candidate consideration is reasonable for patients with critical aortic stenosis who are deemed inoperable.	B
IIb	CABG may be considered with the intent of improving survival in patients with ischemic heart disease with severe LV systolic dysfunction (EF <35%) and operable coronary anatomy whether or not viable myocardium is present.	B
	Transcatheter mitral valve repair or mitral valve surgery for functional mitral insufficiency is of uncertain benefit and should only be considered after careful candidate selection and with a background of GDMT.	B
	Surgical reverse remodeling or LV aneurysmectomy may be considered in carefully selected patients with HFrEF for specific indications, including intractable HF and ventricular arrhythmias.	B

CABG, Coronary artery bypass grafting; *CAD,* coronary artery disease; *EF,* ejection fraction; *GDMT,* guideline-directed medical therapy; *HFpEF,* heart failure with preserved ejection fraction; *HFrEF,* heart failure with reduced ejection fraction; *LV,* left ventricular.

Coordinating Care for Patients With Chronic Heart Failure

The guidelines recognize that systems of care designed to support patients with HF and other cardiac diseases can produce significant improvement in outcomes, but indicate that the quality of evidence is mixed for specific components of HF clinical management interventions, such as home-based care, disease management, and remote telemonitoring programs. Thus the guidelines recommend that interventions should focus on improving adherence to GDMT (**Table 25G.7**). The updated guidelines advocate patient education and involvement of patients with HF and their families, especially during transitions of care, to ensure effective care that is designed to achieve GDMT and prevent hospitalizations (class I, level of evidence B). The guidelines also recommend that every patient with HF should have a clear, detailed, and evidence-based plan of care that ensures the achievement of GDMT goals, effective management of comorbid conditions, timely follow-up with the health care team, appropriate dietary and physical activities, and compliance with secondary prevention guidelines for cardiovascular disease (class I, level of evidence C). The guidelines recommend that the HF and palliative care teams are best suited to help patients and families decide when end-of-life care (including hospice) is appropriate (class I, level of evidence C). The core elements of comprehensive palliative care for HF include expert symptom assessment and management, including symptom control, psychosocial distress, health-related quality of life, preferences about end-of-life care, caregiver support,

and assurance of access to evidence-based disease-modifying interventions.

TABLE 25G.7

Coordinating Care for Patients with Chronic Heart Failure

CLASS	INDICATION	LEVEL OF EVIDENCE
I	Effective systems of care coordination with special attention to care transitions should be deployed for every patient with chronic HF, to facilitate and ensure effective care designed to achieve GDMT and prevent hospitalization.	B
	Every patient with HF should have a clear, detailed, and evidence-based plan of care that ensures the achievement of GDMT goals, effective management of comorbid conditions, timely follow-up with the health care team, appropriate dietary and physical activities, and compliance with secondary prevention guidelines for cardiovascular disease. This plan of care should be updated regularly and made readily available to all members of each patient's health care team.	C
	Palliative and supportive care is effective for patients with symptomatic advanced HF to improve quality of life.	B

GDMT, Guideline-directed medical therapy.

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Pharmacogenomics in Heart Failure

Current heart failure (HF) practice guidelines (**see Chapter 25** heart failure guidelines) recommend titrating angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), angiotensin receptor neprilysin inhibitors (ARNIs), aldosterone antagonists, and beta blockers to doses that have been shown to be beneficial in clinical trials. Although this approach tends to work well for most patients, it has two major shortcomings. Most importantly, basing drug dosing on the doses selected in clinical trials does not allow for dose optimization in patients who may metabolize and/or distribute drugs differently. The second problem is that clinical trials are generally designed to yield "binary" results. That is, a drug under investigation is either deemed beneficial or not beneficial because the patients in the treatment arm have, or have not, reached a prespecified endpoint (e.g., death or hospitalization). A beneficial effect in a positive clinical trial implies that all patients will receive the same degree of benefit from the drug that is given. However, a more likely outcome is that a given therapy will have a markedly positive impact for some patients, a more modest effect in others, and may be completely ineffective or perhaps even harmful in a smaller group of treated patients. Thus, even though a drug is deemed beneficial in a clinical trial, there is no guarantee that an individual patient will benefit from the treatment. For example, beta blockers have been shown consistently to reduce the risk of death in HF patients by approximately 35% (**see Fig. 25.14**); however, clinical trials have also shown that beta blockers will need to be discontinued in 8% to 25% of HF patients because of significant adverse effects, including worsening HF.[1] Recent advances in the field of pharmacogenetics suggest that a careful analysis of underlying gene polymorphisms within a given patient may enable clinicians to develop personalized therapeutic regimens for HF patients. Given the central role of the renin-angiotensin-aldosterone system (RAAS) and adrenergic systems in the pathophysiology (**see Chapter 23**) and treatment of HF, it is perhaps not surprising that polymorphisms in the genes that regulate these pathways appear to influence the therapeutic efficacy of ACEIs and beta blockers.

Genetic Variations in the Renin-Angiotensin Aldosterone System

One of the most widely studied genetic variants is the ACE insertion/deletion polymorphism (I/D) that involves a 287–base pair insertion or deletion within intron 16 of the ACE gene. Although the clinical significance of this polymorphism remains controversial, the physiologic association with ACE enzymatic activity has consistently been demonstrated. Studies have shown that individuals with the DD genotype have the highest ACE activity and angiotensin II levels, heterozygotes (I/D) have intermediate levels, and individuals who are homozygous for the I allele (I/I) have the lowest levels of ACE activity. The relationship of ACE I/D has been explored with respect to numerous conditions, including atherosclerosis, myocardial infarction, left ventricular hypertrophy, hypertrophic cardiomyopathy, and HF. Although the current weight of evidence does not allow for definitive conclusions to be made with respect to the overall contribution of the ACE I/D polymorphism to the clinical outcome in these conditions, there is growing evidence that the ACE I/D polymorphism may predict drug responsiveness to both beta blockers and ACEIs in HF patients. In one study of patients with chronic HF, the ACE DD polymorphism was significantly associated with death or the need for transplantation compared to patients with II or ID genotypes. Within the ACE DD group, patients treated with beta blockers had significantly improved transplant-free survival compared to patients not receiving beta-blocker therapy, whereas beta-blocker treatment had no effect in clinical outcomes in the II or ID groups.[2] In a similar study, patients with the DD genotype had better clinical outcomes when receiving high-dose ACEI therapy compared to low-dose ACEI therapy, whereas the ACE dose had no effect on clinical outcomes in patients with the II or ID

genotype. In this study the regimen of high-dose ACE inhibitors and beta blockers had the greatest impact on transplant-free survival in patients with the DD variant.[2] Taken together, these studies suggest a differential clinical response to standard HF therapy based on the ACE I/D polymorphism.

While the impact of genetic heterogeneity on HF outcomes has been extensively studied in predominantly white cohorts, few studies have investigated the impact of genomic variation in blacks. In a genetic substudy of the African Americans in Heart Failure (A-HeFT) trial (**see Chapter 25**), a single-nucleotide polymorphism within the promoter region of the aldosterone synthase gene (C-to-T transition at position −344) was shown to predict responsiveness to the fixed combination of hydralazine and isosorbide dinitrate.[3] In A-HeFT treatment with the fixed combination of hydralazine/isosorbide was associated with a markedly improved clinical outcome (mortality, HF hospitalization, and change in quality of life at 6 months) in the TT homozygotes, but had no significant impact among subjects with the −344C allele, suggesting that genetic variations in aldosterone production may play an important role in disease progression in blacks with HF.

Genetic Variations in Beta-Adrenergic Receptor System

Beta-adrenergic blockers have been a mainstay of HF pharmacotherapy; however, there is great variation in response to beta-blocker therapy, including certain subsets of the HF population who do not receive the same mortality and morbidity benefit.[4] Single-nucleotide polymorphisms (SNPs) have been identified in the β_1-AR (*ADRB1)*, β_2-AR (*ADRB2)*, α_{2c} AR (*ADRA2C)*, and G-protein receptor kinase 5 (*GRK5)* genes of the adrenergic system and may partially explain the variable effects received from beta blockade. Patients with a common polymorphism of the beta$_1$-adrenergic receptor (AR) that results in either an arginine (Arg) or glycine (Gly) substitution at amino acid position 389 have different clinical responses to beta blockers. In the Bucindolol Evaluation of Survival trial (BEST), bucindolol-treated patients who were homozygous for the Arg 389 polymorphism (Arg389Arg) had improved clinical outcomes compared to “glycine carriers” (Arg389Gly and Gly389Gly) who were treated with bucindolol, suggesting that the therapeutic response to beta blockers differs by genotype.[5] The Arg389Arg genotype was also associated with significantly greater reductions in LV end-diastolic and end-systolic diameters following treatment with beta blockers compared to identically treated Gly389 carriers. In a substudy of the BEST trial that evaluated the effects of bucindolol in patients with atrial fibrillation, AF patients and sinus rhythm patients who achieved a resting heart rate of 80 beats/min or less on bucindolol showed beneficial treatment effect on cardiovascular (CV) mortality/CV hospitalization. The patients who were homozygous for the Arg389Arg genoty had nominally significant reductions in all-cause mortality/HF hospitalization and CV mortality/hospitalization, whereas the Gly389 carriers did not.[6]

The alpha$_{2c}$-adrenergic receptor inhibits norepinephrine release at cardiac presynaptic nerve endings through a negative feedback mechanism. The deletion of four consecutive amino acids in (aa 322-325) in the alpha$_{2c}$-adrenergic receptor results in loss of normal synaptic autoinhibitory feedback mechanism and thus enhanced presynaptic release of norepinephrine. There appears to be an increased risk of developing HF when the alpha$_{2c}$Del322-325 and the Arg389 beta$_1$-AR polymorphism are both present (i.e., a diplotype).[7] Although the impact of the alpha$_{2c}$Del322-325 and Arg389 beta$_1$-AR synergism on beta-blocker responsiveness is not known, it is likely that patients with this diplotype may have increased responsiveness to beta blockers, based on what has been reported thus far for the Arg389 polymorphism. Recently, a nonsynonymous polymorphism in which leucine (Leu) is substituted for glutamine (Gln) at amino acid position 49 of G-protein receptor kinase 5 (GRK5-Leu41), which desensitizes beta-AR

signaling, was shown to uncouple beta-AR signaling more effectively than the GRK5-Gln41 polymorphism. Human association studies showed a pharmacogenomic interaction between GRK5-Leu41 and beta-blocker treatment, in which the presence of the GRK5-Leu41 polymorphism was associated with decreased mortality in African Americans (in whom this polymorphism is more prevalent) with HF or cardiac ischemia. Subsequent studies showed that among patients not taking beta blockers, GRK5-Leu41 was associated with improved survival in African Americans, suggesting that GRK5-Leu41 provides a "genetic beta blockade" that improves survival in African Americans with HF.[8] In addition to contributing to the functional response to beta-blockers, genetic polymorphisms that affect drug metabolism may also influence the therapeutic response to beta blockers. For example, genetic variants in the cytochrome P-450 (CYP) 2D6 gene have a marked effect on plasma concentrations of metoprolol and carvedilol. In subjects with a nonfunctional CYP2D6 enzyme (poor metabolizers), the peak plasma concentration of metoprolol is sixfold higher than in subjects with a normally functioning enzyme.[1]

Genetic Variations in Response to Hydralazine and Isosorbide Dinitrate

The combination of hydralazine and isosorbide dinitrate is recommended for African Americans with NYHA Class III-IV HFrEF who remain symptomatic despite concomitant use of ACE inhibitors, beta blockers, and aldosterone antagonists. Polymorphisms in the G-protein $beta_3$ subunit (GNB3) influence $alpha_2$-adrenergic signaling. Specifically, the GNB3 C825T polymorphism is associated with enhanced adrenergic signaling. In the GRAHF (Genetic Risk Assessment of Heart Failure in African Americans) patients who were homozygous for the GNB3 TT allele had a greater therapeutic effect of fixed-dose hydralazine/isosorbide dinitrate with respect to the composite endpoint of death, hospital stay for heart failure, event-free survival, and change in quality of life (QoL).[9]

Genetic Variations in Response to Digoxin

Digoxin is recommended for patients with symptomatic HF, but only at doses that correlate with relatively low serum levels, due to increased mortality at higher levels. Given this narrow therapeutic range, factors that impact digoxin concentration may have important clinical implications. The P-glycoprotein encoded by the *ABCB1* gene plays a role in the elimination of digoxin.[10] Three SNPs in *ABCB1(*substitution of thymine at positions 1236, 2677, and 3435 [referred to as the TTT haplotype]) have been associated with increased digoxin serum levels in some, but not all studies.[11] Validation in a larger independent population will be necessary to establish if there is a genetic link between the TTT haplotype to digoxin levels and in HF patients who are receiving digoxin.

Genetic Variations in Response to Loop Diuretics

As noted, loop diuretics act by inhibiting sodium-potassium-chloride luminal transporters in the loop of Henle (**see Fig. 25.7**). Pharmacogenomic research has shown that changes in the response to diuretics is based, at least in part, on genetic variations in the solute carrier genes. In a pharmacogenomic study on furosemide, bumetanide, and torsemide, a polymorphism in *SLC12A3* (Ala26) gene, which encodes the renal thiazide-sensitive NaCl cotransporter and mediates Na^+ and Cl^- reabsorption in the distal nephron, was associated with increased excretion of Cl^- and K^+ compared to the SLC12A3 Gly264 polymorphism.[11] In a post hoc analysis of clinical trials from the NIH Heart Failure Network, a set of rare

variants in the *APOL1* gene, which codes for apolipoprotein L1, was associated with an increase in net fluid loss after 72 hours of loop diuretic treatment. Additionally, a common variant in the multidrug-resistant protein-4 coding gene (*ABCC4*) was associated with increased weight loss with furosemide use.[12] Further confirmatory work in HF patients will be necessary to understand the clinical utility of these studies.

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Digoxin

Cardiac glycosides are used to treat chronic HF in patients in sinus rhythm and to control the response of the ventricular rate to supraventricular arrhythmias, including atrial fibrillation.[1] Digoxin is the most

commonly prescribed cardiac glycoside because of its convenient pharmacokinetics, alternative routes of administration, and widespread availability of serum drug level measurements.

Mechanisms of Action

Digoxin is a complex agent in that its mode of action, inhibition of Na^+,K^+-ATPase, affects multiple cellular processes, including several critical to cardiac myocyte function.[1] Digoxin is also extremely toxic, not surprising in view of its apparent role in nature as a toxin evolved by plants to kill mammals. Cardiac glycosides bind to a specific high-affinity site on the extracytoplasmic face of the alpha subunit of Na^+,K^+-ATPase, the enzymatic equivalent of the cellular "sodium pump." The affinity of the subunit for cardiac glycosides varies among species and among the three known mammalian subunit isoforms, each of which is encoded by a separate gene.[1]

Cardiac glycoside binding to and inhibition of the Na^+,K^+-ATPase sodium pump are reversible and entropically driven. Under physiologic conditions, these drugs preferentially bind to the enzyme after phosphorylation of a beta-aspartate on the cytoplasmic face of the alpha subunit, thus stabilizing what is known as the E2P conformation.[1,2] Extracellular K^+ promotes dephosphorylation at this site, resulting in a decrease in the cardiac glycoside–binding affinity for the enzyme.[2] This action presumably explains why increased extracellular K^+ tends to reverse some manifestations of digitalis toxicity.

Positive Inotropic Effect

Cardiac glycosides increase the velocity and extent of shortening of cardiac muscle, thereby resulting in an upward and leftward shift of the ventricular function curve (Frank-Starling) relating cardiac performance to filling volume or pressure. This process occurs in normal as well as failing myocardium and in atrial as well as ventricular muscle. The effect appears to be sustained for weeks or months without evidence of desensitization or tolerance.[3]

The positive inotropic effect is caused by an increase in the availability of cytosolic Ca^{2+} during systole, thus increasing the velocity and extent of sarcomere shortening. The increase in intracellular $[Ca^{2+}]$ is a consequence of cardiac glycoside–induced inhibition of sarcolemmal Na^+,K^+-ATPase.[1,2] Inhibition of Na^+,K^+-ATPase causes an increase in intracellular Na^+, which is then exchanged for extracellular Ca^{2+} through the Na^+/Ca^{2+} exchanger. The net effect of these adjustments is to increase intracellular Ca^{2+} during systole, which increases systolic function.

In part because cardiac glycosides produce an increase in contractile function without increasing the heart rate, the positive inotropic effects are more energetically efficient than the effects of beta-adrenergic agonists and higher doses of phosphodiesterase inhibitors.[4] This difference may be one of the reasons why low-dose digoxin does not increase mortality in patients with HF.[5]

Sympatholytic Effects

Na^+,K^+-ATPase is involved in baroreflex afferent signaling and may be upregulated in the carotid sinus in HF.[6] Decreased baroreflex control is one of the mechanisms responsible for an increase in generalized and cardiac adrenergic activity in HF.[6] Inhibition of Na^+,K^+-ATPase by ouabain modulates baroreflex function toward normal in animal models of HF,[6] which is likely to be the mechanism by which cardiac glycosides inhibit adrenergic activity in HF.

Electrophysiologic Effects

Cardiac glycosides have complex electrophysiologic effects that are a combination of indirect, parasympathetic, and direct effects on specialized cardiac pacemaker and conduction tissues. At low to moderate therapeutic serum concentrations (0.5 to1.9 ng/mL), digoxin usually decreases automaticity and increases maximal diastolic resting membrane potential in atrial and atrioventricular (AV) nodal cells as a result of augmented vagal tone and decreased sympathetic nervous system activity. These effects are accompanied by prolongation of the effective refractory period and decreased AV nodal conduction velocity. At higher, toxic digoxin levels or in the presence of underlying disease, patients are susceptible to sinus bradycardia or arrest, prolongation of AV conduction, or heart block. At toxic levels, cardiac glycosides can also increase sympathetic nervous system activity, potentially contributing to the generation of arrhythmias.

Increased intracellular Ca^{2+} loading and increased sympathetic tone both contribute to an increased rate of spontaneous (phase 4) diastolic depolarization and also to delayed afterdepolarizations that may reach threshold and generate propagated action potentials. The combination of increased automaticity and depressed conduction in the His-Purkinje network predisposes to arrhythmias, including ventricular tachycardia and fibrillation. Data from the Digitalis Investigation Group (DIG) Trial[7] suggest that the increase in ventricular arrhythmia manifested in chronic HF as an increase in sudden death extends down to digoxin serum levels of 1.0 ng/mL, because higher concentrations were associated with an increase in mortality.

Pharmacokinetics and Dosing

Orally administered digoxin is variably absorbed, depending on the preparation, but Lanoxin is 60% to 80% absorbed. Digoxin is approximately 25% protein bound in plasma, has a large volume of distribution (4 to 7 L/kg), and crosses both the blood-brain barrier and the placenta. Digoxin is eliminated primarily by renal mechanisms, both glomerular filtration and tubular secretion. Tubular excretion is through the energy-dependent membrane-bound efflux pump/transport enzyme, P-glycoprotein, which is modulated by many other drugs. Digoxin is largely excreted in the urine unchanged, with a clearance rate proportional to the GFR, which results in the excretion of approximately one third of body stores daily. The half-life for digoxin elimination of 36 to 48 hours in patients with normal or near-normal renal function permits once-daily or every-other-day dosing.[8] In the presence of an elevated blood urea nitrogen/creatinine ratio (“prerenal azotemia”), digoxin clearance more closely parallels urea clearance, indicating that under these circumstances, some of the drug filtered through the glomerulus undergoes tubular reabsorption.[8] In patients with HF, increased cardiac output and renal blood flow in response to treatment with vasodilators or sympathomimetic agents may increase renal digoxin clearance and necessitate dosage adjustment.

Digoxin can be loaded at a dose of 0.75 to 1.25 mg orally (or intravenously at doses 25% lower) over a 24-hour period in three to four divided doses and then given at a maintenance dose, or a daily oral maintenance dose of 0.0625 to 0.25 mg can be started, depending on renal function, body size, and the presence or absence of co-administered drugs causing pharmacokinetic interactions. In the absence of loading doses, nearly steady-state blood levels are achieved in four to five half-lives, or about 1 week after initiation of maintenance therapy if normal renal function is present. If given intravenously, administration should be carried out over at least 15 minutes to avoid vasoconstrictor responses to a more rapid injection. Intramuscular digoxin is absorbed unpredictably, causes local pain, and is not recommended.

Patients with HF usually have a reduced volume of distribution and reduced renal function, and both

may be influenced by other treatment and by the ebb and flow of HF. Although nomograms on digoxin dosing have been published, these nomograms should not be used in patients with HF because of the narrow therapeutic index and the unpredictability of the numerous factors that can alter digoxin pharmacokinetics. Instead, patients should be started on a dose as just described and trough levels (see later) measured 1 to 2 weeks later and at frequent intervals (every 1 to 3 months) thereafter.

Drug Interactions with Digoxin

Multiple drugs interact with digoxin at multiple levels, including reduced renal tubular excretion by drugs inhibiting P-glycoprotein renal tubular transport,[9] induction of gut P-glycoprotein, alterations in gut flora by antibiotics causing less gut metabolism of digoxin before absorption, displacement from plasma protein-binding sites, or reduction in renal function. The accompanying table provides a partial list of these interactions. Among these interactions are drugs that are routinely used in patients with HF, including carvedilol and amiodarone, in whose presence digoxin doses should be lowered.

Partial List of Drugs Interacting with Digoxin

Drug	Effect on Serum Level	Mechanism
Amiodarone	Increases	?Renal clearance
Verapamil	Increases	?Renal clearance
Nifedipine	Increases	?Renal clearance
Diltiazem	Increases	?Renal clearance
Quinidine	Increases	Displacement of protein binding ?Renal clearance
Propafenone	Increases	?Renal clearance
Captopril	Increases	? Renal clearance
Carvedilol	Increases	?Oral bioavailability
Spironolactone	Increases	?Renal clearance
Amiloride	Increases	?Renal clearance
Triamterene	Increases	?Renal clearance
Salbutamol (albuterol)	Decreases	Unknown
Macrolide antibiotics	Increases	Altered gut flora ?Renal clearance
Tetracycline	Increases	Altered gut flora
Indomethacin	Increases	?Renal clearance
Alprazolam	Increases	?Renal clearance
Itraconazole	Increases	?Renal clearance
Rifampin	Decreases	Induction of gut P-glycoprotein
Sucralfate	Decreases	Decreased gut absorption
Cholestyramine	Decreases	Decreased gut absorption
Cyclosporine	Increases	?Renal clearance
St. John's wort	Increases	?Renal clearance

Therapeutic Drug Monitoring

Digoxin has an extremely low therapeutic index, and its use should be carefully monitored by serum blood levels. The various clinical conditions and drug interactions that can alter digoxin's pharmacokinetics are also reflected in the serum digoxin level. As discussed earlier, on the basis of the dose range of the positive inotropic effects,[10] the neurohormonal inhibition effects,[11] and the DIG trial mortality data,[7] the optimal trough digoxin serum level is 0.5 to 1.0 ng/mL. This concentration range also should be used to control the ventricular rate response to atrial fibrillation in patients with HF, particularly because digoxin is not a very effective agent in this regard in the setting of high amounts of adrenergic activity.[12] Blood samples for measurement of serum digoxin levels should be taken at least 6 to 8 hours following the last digoxin dose, and patients should be instructed to take their digoxin in the evening so that any level determined during the day is a trough measurement.

Digitalis Toxicity

In patients with HF, overt clinical toxicity tends to emerge at serum concentrations greater than 2.0 ng/mL, but substantial overlap in serum levels exists among patients exhibiting symptoms and signs of toxicity and those with no clinical evidence of intoxication. Disturbances in cardiac impulse formation, conduction, or both are the hallmarks of digitalis toxicity. Among the common electrocardiographic manifestations are ectopic beats of AV junctional or ventricular origin, first-degree AV block, an excessively slow ventricular rate response to atrial fibrillation, or an accelerated AV junctional pacemaker. These manifestations may require only dosage adjustment and monitoring. Sinus bradycardia, sinoatrial arrest or exit block, and second- or third-degree AV conduction delay often respond to atropine, but temporary ventricular pacing is sometimes necessary and should be available.

Management

Oral potassium administration is often useful for atrial, AV junctional, or ventricular ectopic rhythms, even when the serum potassium is in the normal range, unless high-grade AV block is also present. However, [K^+] must be monitored carefully to avoid hyperkalemia, especially in patients with renal failure. Magnesium may be useful in patients with atrial fibrillation in an accessory pathway in whom digoxin administration has facilitated a rapid accessory pathway–mediated ventricular response; again, careful monitoring is required to avoid hypermagnesemia.[13] Neurologic or gastrointestinal complaints can also be manifestations of digitalis toxicity. Occasionally, gynecomastia results from digoxin administration, apparently because of the similarity of the glycoside structure to that of estrogens.

Antidigoxin Immunotherapy

Potentially life-threatening digoxin or digitoxin toxicity can be reversed by antidigoxin immunotherapy. Purified Fab fragments from digoxin-specific antisera are available at most poison control centers and larger hospitals in North America and Europe. Clinical experience in adults and children has established the effectiveness and safety of antidigoxin Fab in treating life threatening digoxin toxicity, including cases of massive ingestion with suicidal intent.[14] Doses of Fab are calculated by using a simple formula based on either the estimated dose of drug ingested or the total body digoxin burden and are administered intravenously in saline over 30 to 60 minutes.

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26

Heart Failure with a Preserved Ejection Fraction

Michael R. Zile, Sheldon E. Litwin

Overview

Patients with heart failure can be divided into those with (1) heart failure with a *reduced* ejection fraction

(HFrEF) and (2) heart failure with a *preserved* ejection fraction (HFpEF). All these patients, regardless of ejection fraction status (EF value), have the clinical syndrome of heart failure (HF). In addition, many features are similar across the EF spectrum, including abnormal left ventricular (LV) filling dynamics, elevated LV diastolic pressure, LV systolic and diastolic dysfunction, neurohormonal activation, impaired exercise tolerance, frequent hospitalization, and reduced survival.[1-4] Patients with HFpEF have a devastating 5-year mortality rate (approaching 60%), costly morbidity (6-month hospitalization rate of 50%), and debilitating symptoms (reduced exercise capacity and maximum myocardial oxygen consumption [MVO_2; averaging 12 to 14 mL/g/min]).[5-9] Clear differences also are recognized between HFpEF and HFrEF. Compared to HF patients with a reduced EF, those with preserved EF are older and more likely to be female, although HFpEF occurs in both men and women throughout the fifth to ninth decades of life.[10] The most common antecedent disease leading to HFpEF is systolic hypertension, which is present in more than 85% of patients, whereas ischemic heart disease is less common than in HFrEF.[10] Differences in cardiovascular (CV) structure and function between HFpEF and HFrEF also are well recognized.[4,11-15] Patients with HFpEF have normal LV end-diastolic volume and normal (or near-normal) EF and stroke volume (at rest) and usually exhibit concentric remodeling of LV chamber and/or cardiomyocytes. Differences also are evident in the effects of pharmacologic treatment in patients with HFrEF versus HFpEF. Standard HF therapy shown to be effective in HFrEF has not been found to reduce morbidity or mortality associated with HFpEF, leaving a substantial area of unmet need (**Table 26.1**). This chapter summarizes the current understanding of the clinical, prognostic, pathophysiologic, and therapeutic information about patients with HFpEF and suggests where future advances are likely to occur.

TABLE 26.1

Current Status: Management Success (RCTs) in Heart Failure*

TREATMENT	HFrEF	HFpEF	HFpEF STUDY
Beta blockers	Yes	No	SENIORS
ACEIs/ARBs	Yes	No	CHARM, I-Preserve PEP-CHF
Digitalis	Yes	No	DIG-PEF
PDE5-I	ND	No	RELAX
Aldo Antag (MRA)	Yes	"Yes"	TOPCAT
Hydralazine/N_2	Yes	No	NEAT-HFpEF
Endothelin Antag	No	Yes p II	Sitaxsentan
Sacubitril/valsartan	Yes	Yes p II	PARAMOUNT; PARAGON
CRT/ICD	Yes	ND	
Vagal/spinal cord stimulators	No	ND	
Baroreceptors	Yes p II	ND	HOPE4HF; BEAT-HF
Exercise	Yes	"Yes"	Meta-analysis
IHM	Yes	Yes	CHAMPION

**HFpEF,* Heart failure with preserved ejection fraction; *HFrEF,* heart failure with reduced ejection fraction.

ACEIs, Angiotensin-converting enzyme inhibitors; *ARBs,* angiotensin receptor blockers; *CRT,* chronic resynchronization therapy; *ICD,* implantable cardioverter-defibrillator; *IHM,* implantable hemodynamic monitor; *MRA,* mineralocorticoid receptor antagonist; *PDE5,* phosphodiesterase-5; *RCTs,* randomized controlled trials.

Terminology

A variety of terms have been used to describe patients with the condition currently called *heart failure with a preserved ejection fraction* (HFpEF), including heart failure with a normal EF, heart failure with normal systolic function, diastolic heart failure, and diastolic dysfunction heart failure. Heart failure

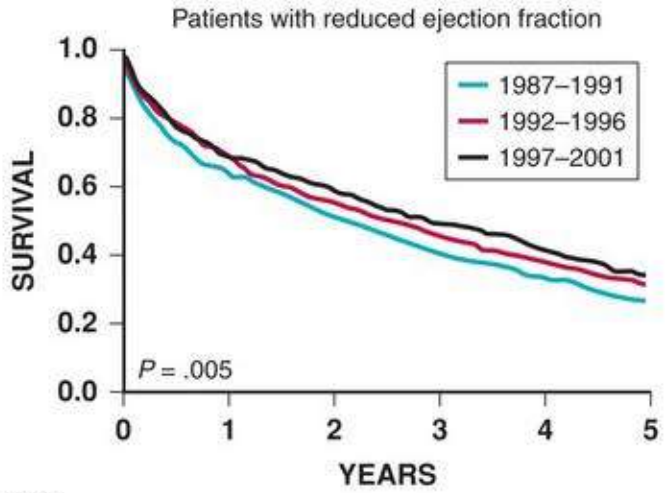
guidelines, recent publications, and this chapter use the term HFpEF. The rationale for this choice includes the following. The mean EF in normal populations depends somewhat on the method used to measure it, but this is generally agreed to be above 60%. The lower 95% confidence interval (CI) for EF is approximately 55%, whereas an EF greater than 50% often is used as a diagnostic criterion for HFpEF; the term HFpEF also has been applied to HF in some patients with EF in lower than normal range. For example, some randomized controlled trials (RCTs) have included patients with EF greater than 35%, 40%, or 45%. Therefore, because the term HFpEF has been applied to this broader spectrum of patients with HF, the term "heart failure with a normal EF" is less frequently used. Although patients with an EF below 50% clearly have significant abnormalities in systolic function, recent studies have shown that even patients with an EF above 50% may have midwall and/or longitudinal systolic dysfunction at rest and global systolic dysfunction during exercise. Therefore the term "heart failure with normal systolic function" is not an accurate description, even for patients with heart failure and EF above 50%.

Because patients with the clinical syndrome of HFpEF have abnormalities in LV diastolic function, systolic function, and vascular properties, the terms "diastolic heart failure" and "diastolic dysfunction heart failure," which single out the abnormalities in diastole, are now used less often. The term *diastolic dysfunction* refers to abnormalities in LV filling secondary to altered compliance, relaxation, and recoil. Abnormalities in diastolic function can occur in the presence or absence of a clinical syndrome of HF and with normal or abnormal systolic function. Whereas diastolic dysfunction describes abnormal LV performance, HFpEF describes a clinical syndrome of heart failure. The epidemiology of HFpEF is reviewed in **Chapter 21**.

Natural History

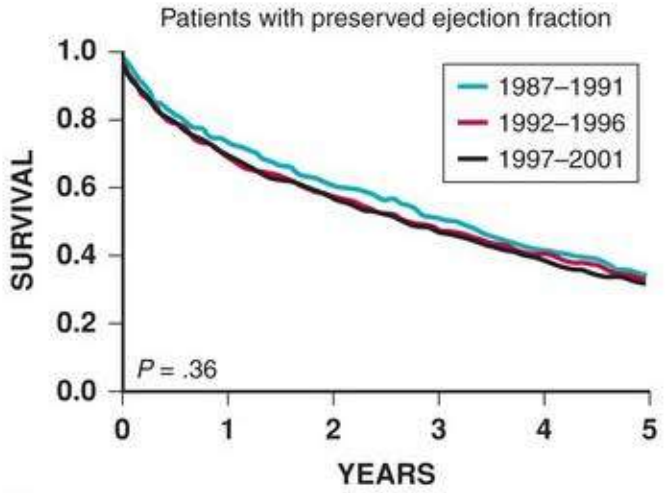
Mortality

The 5-year survival rate for all patients with heart failure, regardless of EF, is less than 50%. Although survival has improved over time for patients with HFrEF, it has not changed for patients with HFpEF[16] (**Fig. 26.1A, B**). Some epidemiologic studies have found that all-cause mortality for HFpEF is similar to that for HFrEF; other epidemiologic studies and RCTs suggest that all-cause mortality is somewhat lower in HFpEF than in HFrEF (**see Chapter 25**). For example, three RCTs have enrolled both patients with HFpEF and those with HFrEF, allowed direct comparisons, and demonstrated a lower mortality rate in HFpEF versus HFrEF.[17] Taken together, data from epidemiologic studies of HFpEF find that the annual mortality is approximately 10%, but RCTs in patients with HFpEF suggest that the annual mortality is about 5%. This apparent difference may be caused by the exclusion of patients with the comorbid conditions from the RCTs. However, the mortality rates found in patients with HFpEF are not caused solely by the comorbid diseases. In the RCTs, patients with HFpEF, who have antecedent and comorbid factors such as hypertension, coronary artery disease (CAD), and diabetes mellitus (DM), were found to have more than twice the mortality rate of patients with hypertension, CAD, or DM who do not have HFpEF[17] (**Fig. 26.1C, D**).



No. at risk

	1987-1991	819	525	424	336	274	220
	1992-1996	857	594	481	395	331	273
A	1997-2001	748	520	447	319	210	114



No. at risk

	1987-1991	510	377	313	263	216	117
	1992-1996	771	537	447	375	314	262
B	1997-2001	885	629	513	365	230	138

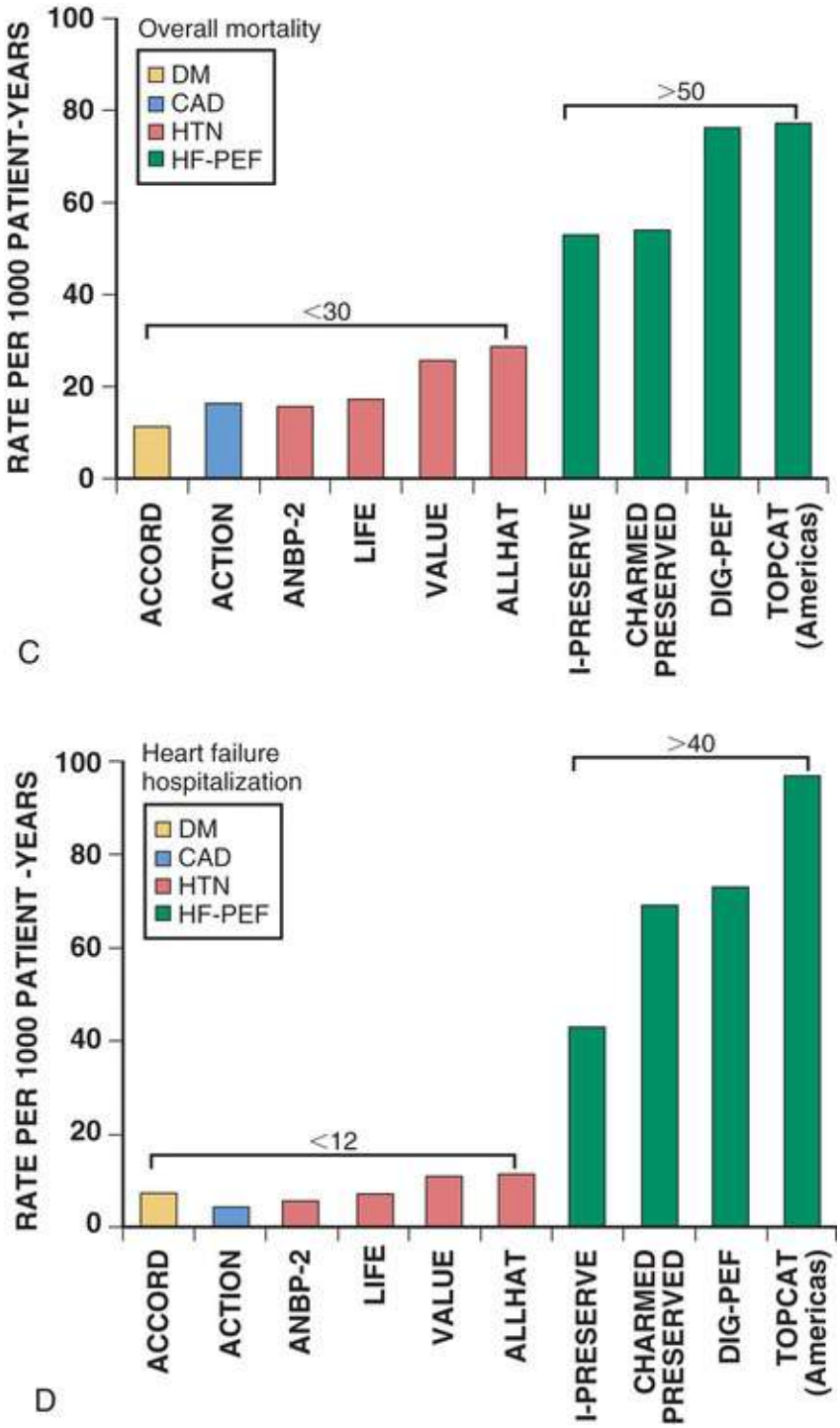


FIGURE 26.1 Mortality and morbidity in patients with HFrEF or HFpEF in epidemiologic studies versus randomized controlled trials (RCTs). **A, B,** In epidemiologic studies, 5-year survival rate for all patients with heart failure, regardless of EF, is less than 50%; survival has improved over time in HFrEF but has not changed in HFpEF. RCTs suggest that mortality is somewhat lower in HFpEF than in HFrEF. **C, D,** Mortality and morbidity in patients with HFpEF do not arise solely from the comorbid conditions. In the RCTs, among patients with HFpEF, who have antecedent and comorbid factors such as hypertension (HTN), coronary artery disease (CAD), and diabetes mellitus (DM), mortality rate and heart failure–related hospitalization rate are more than twice those in patients with HTN, CAD, or DM who do not have congestive heart failure. (**A, B,** From Owan TE et al: Trends in prevalence and outcomes of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251; **C, D,** from Campbell R et al. What have we learnt about patients with heart failure and preserved ejection fraction (HF-PEF) from DIG-PEF, CHARM-Preserved, and I-Preserve? J Am Coll Cardiol 2012;60:2349.)

Mode of Death

Most of the deaths (50% to 70%) in patients with HFpEF are cardiovascular in nature, with 20%

resulting from heart failure and 35% from sudden death[18] (**eTable 26.1**). This distribution of modes of CV death is similar to that for HFrEF. The incidence of noncardiovascular deaths is significantly higher for HFpEF (30% to 40%) than for HFrEF (15%), reflecting the higher age and increased comorbidity in patients with HFpEF.[19] Additional content on the morbidity of HFrEF and conversion from HFpEF to HFrEF are presented in an online supplement for this chapter (Morbidity of HFpEF).

ETABLE 26.1

Mode of Death Distribution in Randomized Controlled Trials

CATEGORY	HFpEF *n* (%)			HFrEF Mean % (range)		
	I-Preserve	CHARM-P	PEP-CHF	DIG-P	Drugs	Devices
Total	881	481	109	231		
Sudden death	231 (26)	134 (28)	NR	NR	42 (23-58)	28 (21-34)
Heart failure	125 (14)	102 (21)	NR	64 (28)	36 (27-56)	45 (34-63)
Myocardial infarction	44 (5)	13 (3)	NR	NR	7 (2-15)	6 (3-15)
Stroke	76 (9)	33 (7)	NR	NR	5 (3-6)	5 (3-6)
Cardiovascular procedure	13 (1)	13 (3)	NR	NR	2 (1-3)	2 (1-3)
Other cardiac	10 (1)	35 (7)	NR	NR	7 (2-11)	6 (3-10)
Other vascular	32 (4)	NR	NR	NR	NR	NR
Noncardiovascular	268 (30)	141 (29)	31 (28)	69 (30)	14 (4-20)	15 (5-17)
Unknown	81 (9)	NR	NR	NR	NR	NR

CV, Cardiovascular; *NR,* not reported.

From Zile MR, Gaasch WH, Anand IS, et al. Mode of death in patients with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-Preserve) trial. Circulation 2010;121:1393.

Pathophysiology

The pathophysiologic mechanisms that cause the development of HFpEF are reflected in changes in LV relaxation and filling, LV and left atrial (LA) structural remodeling and altered geometry, changes in LV and systemic and pulmonary vascular compliance, skeletal muscle and endothelial function, and proinflammatory and profibrotic signaling (**Table 26.2 and Figs. 26.2 and 26.3**).

TABLE 26.2

Mechanisms and Factors Contributing to Pathophysiology of Heart Failure with Preserved Ejection Fraction

Cardiovascular
Left Ventricular Structure
Concentric remodeling
Left ventricular hypertrophy
Left Ventricular Function
Diastolic dysfunction: abnormal relaxation, decreased recoil, abnormal filling, decreased distensibility, increased diastolic pressure
Systolic dysfunction: abnormal midwall and long-axis shortening, decreased twist
Hemodynamic load
Increased afterload and filling load
Heterogeneity
Dyssynergy, dyssynchrony
Left atrial structure and function
Increased LA volume and stiffness, decreased LA reservoir function, passive conduit function, and active booster pump function
Ischemia
Subendocardial and microvascular disease, impaired coronary, pulmonary, and peripheral flow reserve
Rate and rhythm abnormalities
Chronotropic incompetence, atrial fibrillation, supraventricular tachycardia
Vascular dysfunction
Arterial stiffening, endothelial dysfunction
Cardiomyocyte
Abnormal calcium homeostasis (↑ diastolic calcium or ↓ rate of calcium reuptake → incomplete or impaired relaxation)
Sarcolemmal calcium channels (Na^+/Ca^{2+} exchanger and calcium pump)
Sarcoendoplasmic reticulum Ca^{2+}-ATPase (SERCA) abundance and function
Proteins modifying SERCA activity: phospholamban, calmodulin, calsequestrin abundance, and phosphorylation state
Sarcoplasmic reticulum calcium release channels
Energetics (↓ ATP or ↑ ADP slows actin-myosin cross-bridge release)
ADP/ATP ratio, ADP and P_i concentration, phosphocreatine shuttle function
Proteins regulating cross-bridge formation and calcium sensitivity
Troponin C: calcium binding
Troponin I: phosphorylation state
Cytoskeletal proteins
Microtubules (increased density) → ↑ diastolic stiffness
Titin isoforms (↑ noncompliant isoform and phosphorylation state) → ↑ diastolic stiffness
Extracellular Matrix
Collagen structure, geometry, content, collagen I/III ratio
Collagen homeostasis, synthesis, postsynthetic processing, post-translational cross-linking, degradation
Basement membrane proteins
Bioactive proteins and peptides: MMP/TIMP, SPARC, TGF-β
Fibroblast structure, function, phenotype
Myofibroblast transdifferentiation
Extracardiac
Extrinsic forces (RV-LV interaction and pericardial constraint)
Peripheral muscle and ergoreflex dysfunction
Pulmonary hypertension (secondary to chronic pulmonary venous hypertension)
Neurohormonal activation
Comorbid conditions (renal dysfunction, anemia, chronic lung disease)

ADP, Adenosine diphosphate; *ATP,* adenosine triphosphate; *MMP,* matrix metalloproteinase; *RV-LV,* right ventricle–left ventricle; *SPARC,* secreted protein, acidic and rich in cysteine [osteonectin]; *TGF,* transforming growth factor; *TIMP,* tissue inhibitor of metalloproteinase.

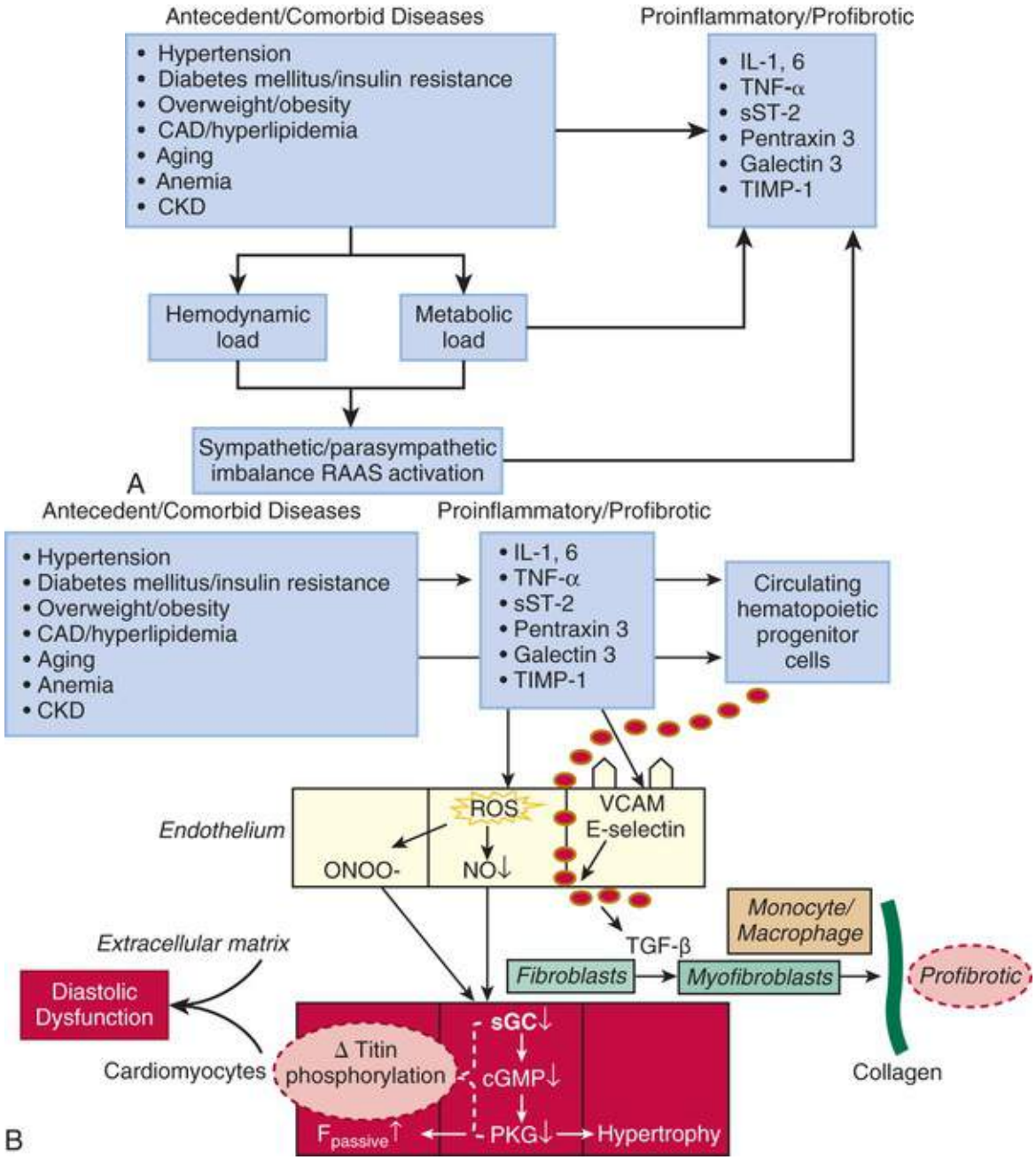


FIGURE 26.2 Pathophysiologic mechanisms underlying the development of HFpEF. **A,** Antecedent and comorbid diseases create both a hemodynamic and metabolic load that causes sympathetic and RAAS activation and parasympathetic suppression. These factors create a pro-inflammatory and profibrotic milieu as evidenced by changes in typical plasma biomarkers. CAD, Coronary artery disease; CKD, chronic kidney disease; TIMP, tissue inhibitor of metalloproteinase. **B,** Proinflammatory and profibrotic signaling effects recruitment of circulating hematopoietic progenitor cells, alters endothelial function, and increases reactive oxygen species, all of which in turn alters extracellular matrix (ECM) homeostasis that favors fibrosis and cardiomyocyte mechanisms including calcium and energetic regulation, myofilament structure and function, and intracellular signaling. In aggregate these changes in the ECM and cardiomyocyte result in abnormal diastolic function and promote the development of HFpEF. ROS, Reactive oxygen species; VCAM, vascular cell adhesion molecule. (Modified from Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013;62:263-71.)

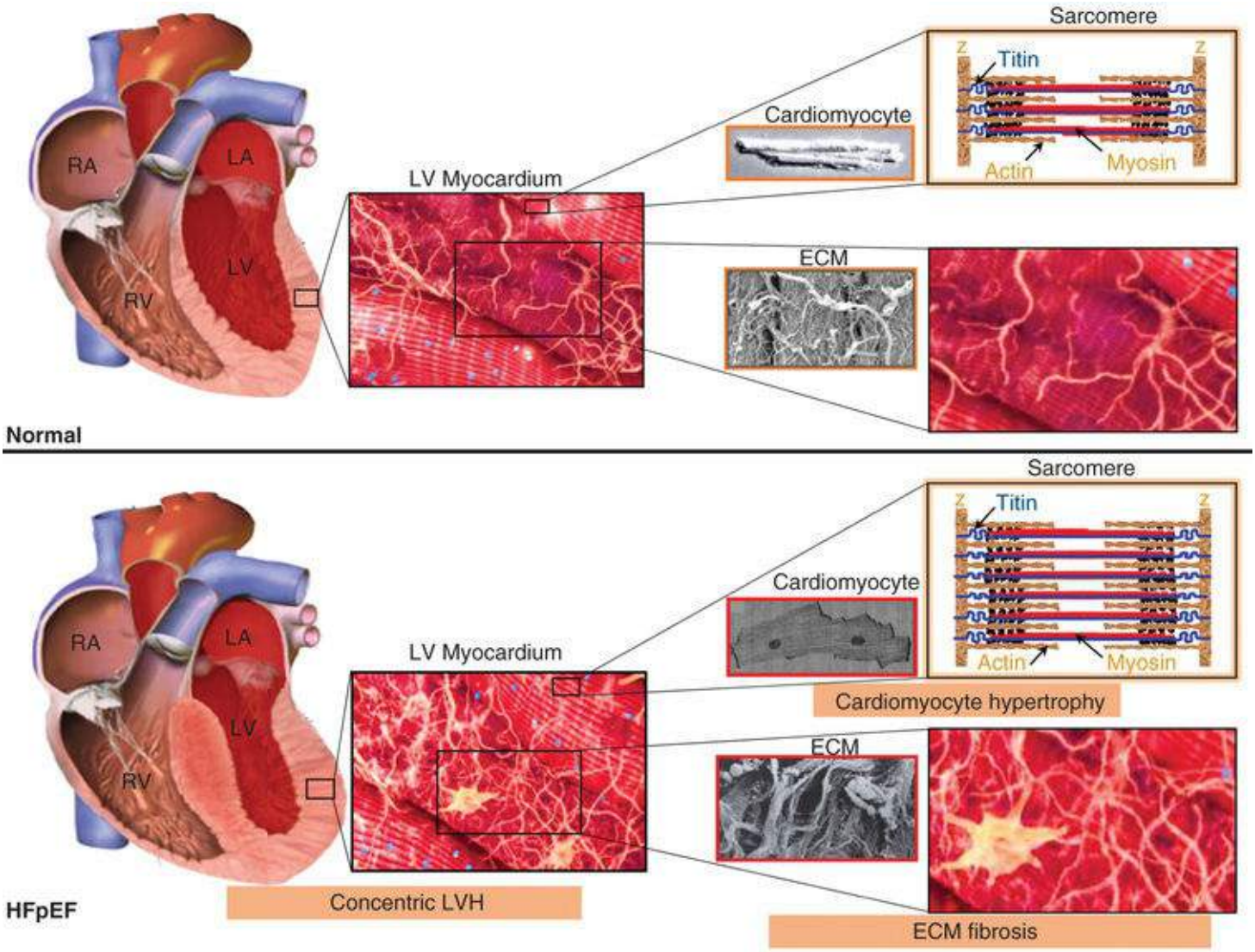


FIGURE 26.3 Ventricular, cellular, extracellular matrix (ECM), and molecular structural changes in patients with HFpEF. Compared with age- and gender-matched normal controls **(upper panel),** HFpEF patients **(lower panel)** are characterized frequently by concentric hypertrophy or remodeling at the LV and cardiomyocyte level. The left ventricle is increased in wall thickness with no change in volume; cardiomyocytes have increased diameter but no change in length. These structural cellular changes are accompanied by alterations in titin phosphorylation. In addition, there are structural changes in the ECM, including increased fibrillar collagen content, thickness, and number. These ECM structural changes are associated with alterations in fibroblast function that lead to interstitial fibrosis. *LVH,* Left ventricular hypertrophy. (Modified from Aurigemma GP, Zile MR, Gaasch WH. Contractile behavior in the left ventricle in diastolic heart failure: with emphasis on regional systolic function. Circulation 2006;113:296; and Zile MR et al. Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin. Circulation 2015;131:1247-59.)

Normal Diastolic Properties

Normal diastolic function allows the ventricle to fill adequately during rest and exercise, without an abnormal increase in LA pressure (**see Chapter 21**). The phases of diastole are *isovolumic pressure decline* and *filling*. The filling phase is divided into early rapid filling, diastasis, and atrial systole. *Early rapid filling* contributes 70% to 80% of LV filling in normal individuals. This contribution diminishes with age and various disease states. Early diastolic filling is driven by the LA-to-LV pressure gradient, which depends on a complex interplay of factors: myocardial relaxation, LV elastic recoil, LV diastolic stiffness, LA pressures, ventricular interaction, pericardial constraint, pulmonary vein properties, and mitral orifice area. *Diastasis* occurs in mid-diastole, when the LA and LV pressures usually are almost

equal. It contributes less than 5% of the LV filling, and its duration shortens with tachycardia. In normal individuals, *atrial systole* contributes 15% to 25% of LV diastolic filling without raising the mean LA pressure. This contribution depends on the PR interval, atrial inotropic state, atrial preload, atrial afterload, autonomic tone, and heart rate.

Left Ventricular Relaxation

LV relaxation is an active, energy-dependent process that begins with the decay of force-generating capacity, follows the completion of the ejection phase of systole, and continues through isovolumic pressure decline and the rapid filling phase. LV filling depends both on active relaxation and on the recoil/suction that results from the release of potential energy stored during systole by contraction. Thus, blood is effectively "pulled" into the left ventricle.[20] In normal hearts, over a range of normal heart rates, relaxation and recoil are adequate to allow LA pressures to remain normal. In addition, catecholamine-induced enhancement of relaxation and recoil during exercise lowers LV pressures in early diastole, thereby increasing the LA-to-LV pressure gradient without increasing LA pressures, as well as enhancing filling during exercise. By contrast, in patients with HFpEF, relaxation and recoil are abnormal at rest and are not enhanced during increased HR or exercise. As a result, filling can be maintained only by increased LA pressure; blood must be "pushed" into the left ventricle.

Isovolumic Pressure Decline.

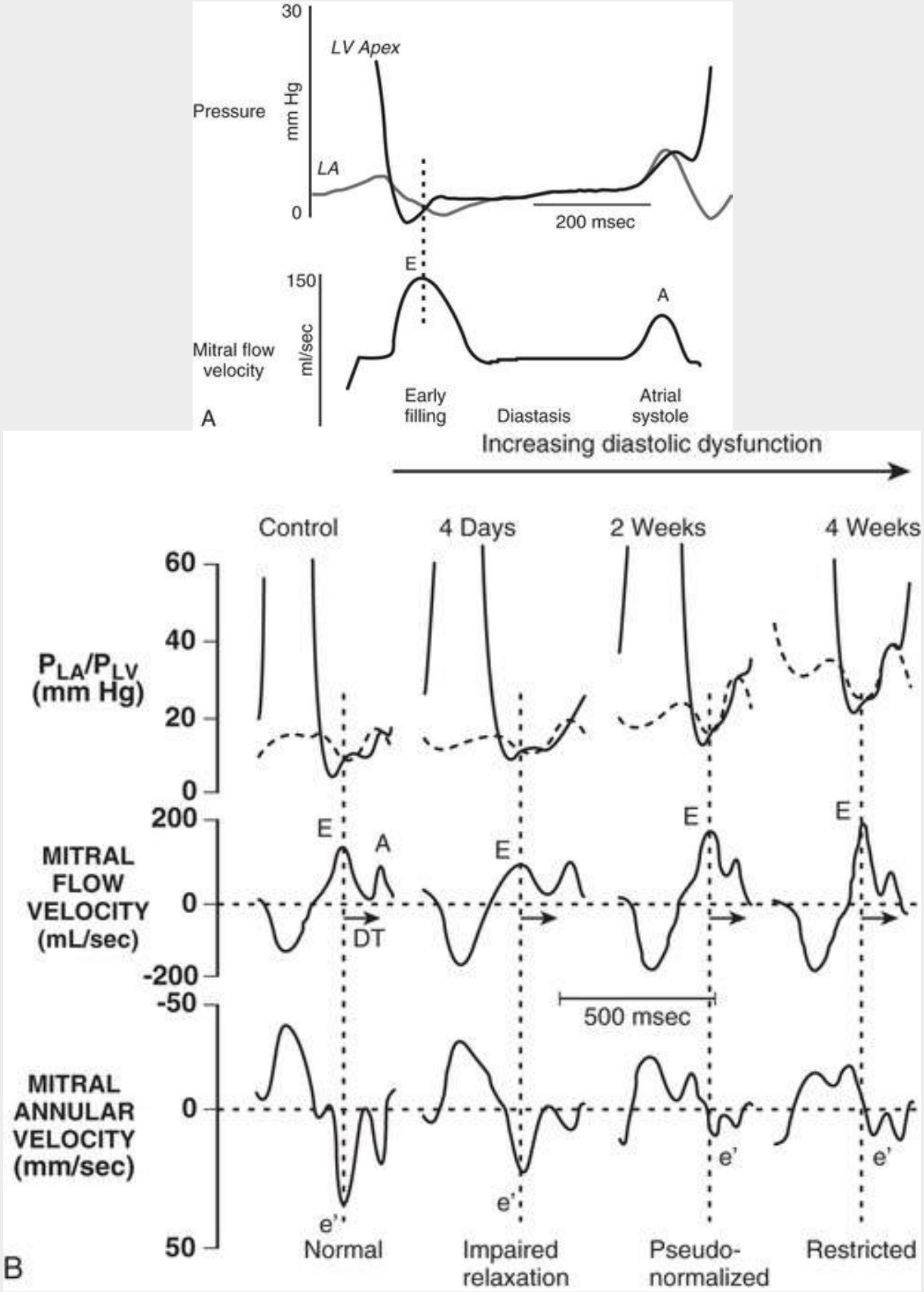
The time course of isovolumetric pressure decline has been quantitatively described by the peak rate of pressure fall (dP/dt_{min}) and the time constant τ (tau) of the exponential fall in LV isovolumetric pressure. Each of these requires that LV pressure be measured using a micromanometer-tipped catheter. dP/dt_{min} measures the rate of pressure decline at a single point in time, is strongly influenced by the LV pressure at the time of aortic valve closure, and therefore, as with all indices of diastolic function, is afterload dependent. Patients with HFpEF have a larger dP/dt_{min}, signifying that relaxation rate is decreased.

The time constant τ describes the rate of LV pressure decline throughout isovolumic relaxation. Pressure (P) and time (t) data during the period from end-systole (aortic valve closure) to the onset of LV filling (mitral valve opening) are fit to an exponential equation such as the following: LV pressure = $P_0 e^{-t/\tau}$, where P_0 is LV pressure at end-ejection and τ is the exponential time constant. The larger the value of τ, the longer it takes for the LV pressure to fall and the more impaired is relaxation. A normal value for τ is less than 40 milliseconds in most age-groups, suggesting that relaxation is nearly complete by 3.5 × τ (<140 milliseconds).

The *isovolumic relaxation time* (IVRT) also can be estimated by echo techniques as the time between aortic valve closure and mitral valve opening. Although less precise than τ, IVRT is useful in the noninvasive assessment of diastolic properties. However, IVRT depends not only on the rate of LV relaxation but also on the aortic pressure at the time of aortic valve closure and the LA pressure at mitral valve opening. Thus, IVRT can be increased by an elevation of aortic pressure or decreased by an increase in LA pressure. The time course of LV pressure decline during isovolumetric relaxation can also be characterized using noninvasive Doppler measurement of the velocity of a regurgitant jet across the mitral valve. In this method the modified Bernoulli equation is used to approximate LV pressure during isovolumetric relaxation, allowing calculation of the maximum rate of LV pressure decline and the exponential time constant.

Recoil and Left Ventricular Filling.

During systole, potential energy is stored in the elastic elements of the cardiomyocytes and extracellular matrix (ECM).[20] The elastic elements are compressed and twisted during systolic contraction. During relaxation, this potential energy is released as the elastic elements recoil and return to their original length and orientation. Recoil causes LV pressure to fall rapidly during isovolumetric relaxation. Furthermore, for the first 30 to 40 milliseconds after mitral valve opening, the relaxation of LV wall tension normally is rapid enough to cause LV pressure to continue to decline despite an increase in LV volume. This fall in LV pressure produces an early diastolic pressure gradient from the left atrium that extends to the LV apex (**eFig. 26.1A**). This accelerates blood out of the left atrium and produces rapid early diastolic flow that quickly propagates to the apex. Because the diastolic intraventricular pressure gradient pulls blood to the apex, it can be considered a measure of LV suction. It is reduced in both experimental models and in patients with ischemia, hypertrophic cardiomyopathy,[21] and heart failure, including HFpEF.[22-24] The intraventricular pressure gradient can be measured noninvasively from the diastolic spatial-temporal velocity map obtained using apical color M-mode echocardiography.



EFIGURE 26.1 **A,** LV filling dynamics recorded in a conscious animal. **B,** Recordings in a conscious animal of pressures in the apex of the left ventricle (P_{LV}) and left atrium (P_{LA}) and the mitral valve flow velocity. The late diastolic mitral flow velocity (A), peak early diastolic flow velocity (E), peak early mitral annular velocity (e'), and E deceleration time (DT) are shown. (From Little WC, Oh JK. Echocardiographic evaluation of diastolic function can be used to guide clinical care. Circulation 2009;120:802.)

Because the LV apex remains fixed during the cardiac cycle, the *mitral annular velocity* provides a measure of long-axis lengthening rate.[25] Under normal conditions, peak early diastolic mitral annular velocity (e′) occurs coincidentally with or before the mitral peak early diastolic flow velocity (E)[26,27] (**eFig. 26.1B**). This is a manifestation of the symmetric expansion of the left ventricle in early diastole as blood moves rapidly to the LV apex in response to a progressive pressure gradient from the left atrium to the LV apex. In addition, the rapid recoil of the mitral annulus and valve into the left atrium early in diastole relocates blood from the left atrium into the left ventricle. Under normal circumstances, both E and e′ respond to changes in the LA-to-LV pressure gradient. For example, both E and e′ normally increase in response to increased volume load and exercise.[27-29]

Determinants of Left Ventricular Relaxation

LV relaxation is under the control of multiple factors that include hemodynamic load (early diastolic load and afterload), myofiber inactivation (see later discussion of cellular determinants), and the uniformity of the distribution of load and inactivation in space and time (dyssynchrony, dyssynergy, treppe). Each of these determinants may affect indices of diastolic relaxation, recoil, and filling.

Hemodynamic Load

Both isovolumic pressure decline and early filling are affected by afterload (LV systolic stress). An increase in LV systolic stress results in a delay in and slowed rate of pressure decline and early filling. Increases in systolic load may have different effects, depending on when the load is imposed during systole. Increases in LV pressure late in systole hasten the onset of LV relaxation, but relaxation occurs at a slower rate (increased τ). Increases in LV pressure late in systole occur with aging because of age-related vascular stiffening, which alters the timing of reflected pressure wave in the vascular tree so that the reflected wave arrives in late systole rather than diastole. In clinical practice an acute increase in blood pressure either at rest or during exercise will impair ejection, slow pressure decline, prolong time to complete relaxation, and reduce recoil. These changes in relaxation decrease the LA-to-LV gradient, decrease early filling, and result in increased LV diastolic and LA pressure. In addition, the load present at mitral valve opening (LA-to-LV gradient, i.e., early diastolic load) affects early LV filling.

Heterogeneity

Synchrony (timing of relaxation of the different myocardial segments) and *synergy* (extent to which myocardial segments relax) will enhance LV relaxation, whereas *dyssynchrony* or *dyssynergy* (e.g., caused by infarction, ischemia, asymmetry of hypertrophy, or conduction abnormalities) will impair global LV relaxation. Dyssynchrony, measured using a variety of echocardiographic measurements, may be present in patients with HFpEF, particularly those with left bundle branch block (LBBB) or right ventricular (RV) pacing. Whether or not treatment aimed at resynchronization (i.e., cardiac resynchronization therapy [CRT]) will effect clinical improvement in patients with HFpEF has not been fully investigated.

Cellular Mechanisms

Myofiber inactivation refers to the many cellular processes that ultimately influence the process by which the left ventricle, its constitutive cardiomyocytes, and individual sarcomeres return to a normal end-diastolic length with minimum cross-bridge cycling and low force generation. To accomplish this state of

complete relaxation requires (1) calcium (Ca^{2+}) resequestration into the sarcoplasmic reticulum, followed by calcium extrusion into the extracellular space; (2) availability of sufficient adenosine triphosphate (ATP); (3) normal myofilament function; and (4) normal elastic properties of the cardiomyocyte and the ECM. Additional material on this topic is presented in an online supplement for this chapter (Cellular Mechanisms of Myocardial Relaxation).

Prevalence and Prognosis for Abnormal Relaxation

Impaired relaxation is present in HFpEF and contributes to the development of elevated LA pressure at rest. The rate of relaxation is further impaired during exercise and hemodynamic stress. Any factor that shortens the diastolic filling period (prolonged contraction or long PR interval) will worsen the effect of impaired relaxation on LV diastolic pressures during filling and thus affect the mean LA pressure needed to fill the left ventricle. Whether therapies to enhance relaxation directly and specifically can be developed, and whether such therapies will relieve symptoms, remains an area of active investigation.

Left Ventricular Diastolic Stiffness, Compliance, and Distensibility

Methods of Measurement

The passive characteristics of the left ventricle during diastole can be described by the passive *diastolic pressure-volume relationship* (DPVR).[20] Optimally, this relationship should be constructed from points that are obtained after relaxation is complete and at slow filling rates so that viscous effects are not present. In practice, this can be approximated using points obtained late in diastole, when relaxation is assumed to be complete, by correcting pressure data affected by incomplete relaxation or by using data from variably loaded beats at end-diastole. The resultant DPVR is nonlinear and can be approximated by an exponential function. *Left ventricular stiffness* is defined as the ratio of LV diastolic pressure and LV diastolic volume (LV dP/dV) at any given LV diastolic volume. *Left ventricular compliance* is the reciprocal of stiffness (LV dV/dP). Because the DPVR can be approximated as an exponential, stiffness will increase as the left ventricle fills to higher LV diastolic volumes; thus, as the left ventricle fills, it becomes stiffer. *Left ventricular diastolic distensibility* is defined as the end-diastolic pressure required to distend the left ventricle to an end-diastolic volume. Patients with HFpEF have reduced distensibility, indicated by a normal or reduced end-diastolic volume and an elevated end-diastolic pressure.[2,30] Because the DPVR can be approximated by an exponential function, its position and shape can be described by the constants within an equation such as $P = \alpha \times e^{\beta V}$, where α and β represent the "stiffness constants." It should be recognized that β does not indicate stiffness but instead describes how rapidly stiffness increased with increases in volume ($\beta = [dP/dV]/V$). The "stiffness constants" derived in this fashion can be used to compare passive diastolic properties in different patients or patient groups. The end-diastolic pressure-versus-volume ratio (instantaneous operative distensibility) also can be used in comparing patients or patient groups. Patients with HFpEF have abnormal DPVR with elevated β and abnormal distensibility (**Fig. 26.4**).

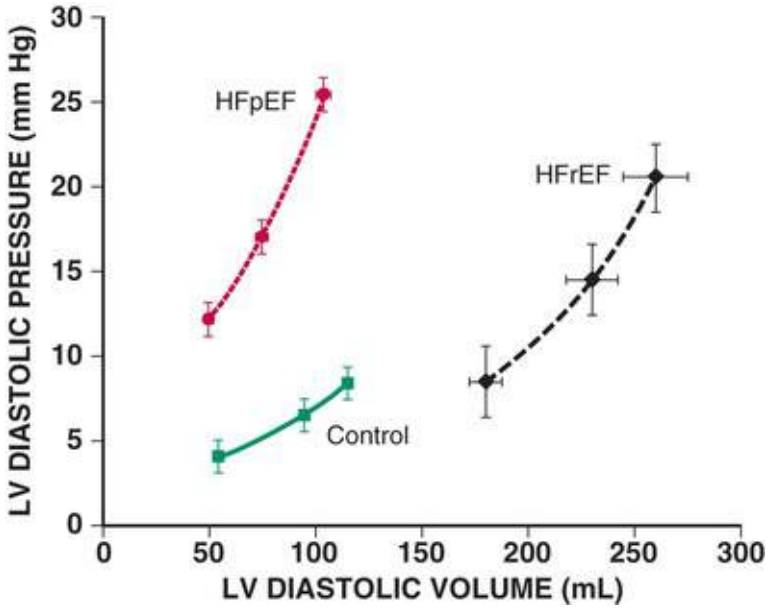


FIGURE 26.4 Difference in diastolic chamber distensibility in patients with HFpEF (in *red*) versus HFrEF (in *black*) versus age- and gender-matched referent controls (in *green*). Compared with that in the controls, the diastolic pressure-volume relationship (DPVR) in patients with HFpEF is shifted upward and to the left, such that for any given LV volume, pressure is higher in HFpEF, indicating decreased distensibility (increased stiffness). By contrast, in patients with HFrEF, the DPVR is shifted to the right, indicating increased distensibility. (From Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med 2004;350:1953; and Aurigemma GP, Zile MR, Gaasch WH. Contractile behavior in the left ventricle in diastolic heart failure: With emphasis on regional systolic function. Circulation 2006;113:296.)

Patients with HF and an increased LV diastolic pressure can be divided into four groups defined by patterns of DPVR (**Fig. 26.5**). DPVR in patients with HFrEF typically is characterized by the graphed curve D in the figure, in which eccentric remodeling results in a shift of the DPVR to the right, representing an increase in distensibility. It should be recognized that although the ventricle is more distensible, the LV end-diastolic volume in these patients typically is very large, and the end-diastolic stiffness in the operating region is high. DPVR in patients with HFpEF may be characterized by graphed curves A to C. In **Fig. 26.5C**, pericardial constraint causes a parallel upward shift in DPVR. In patients with HFpEF, when relaxation is markedly prolonged and diastole is abbreviated (**Fig. 26.5A**), LV diastolic pressure falls throughout diastole but remains increased. In the most prevalent pattern in HFpEF (**Fig. 26.5B**), DPVR is shifted upward and to the left, indicating reduced distensibility, where LV pressure is increased at any LV volume.

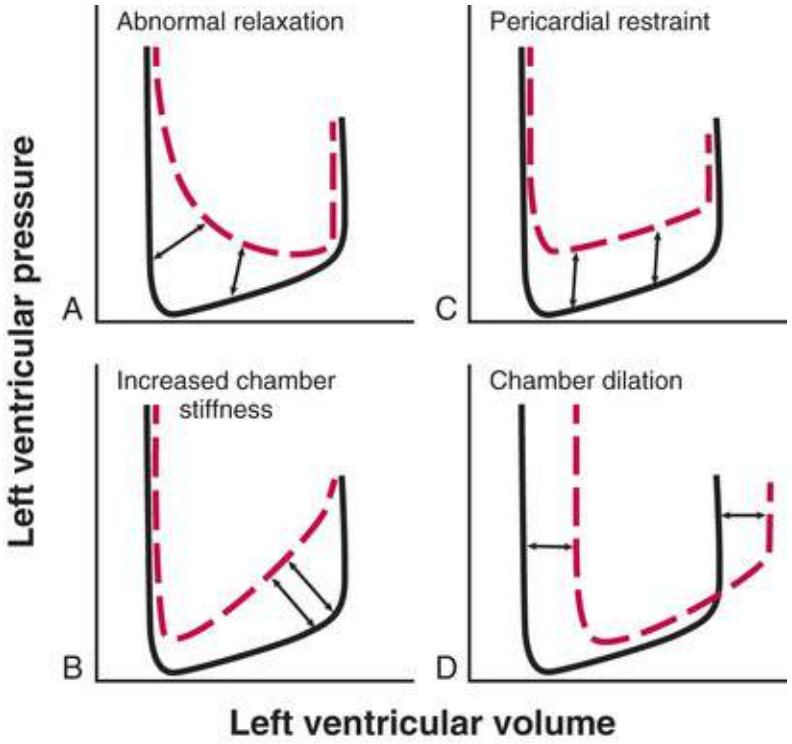


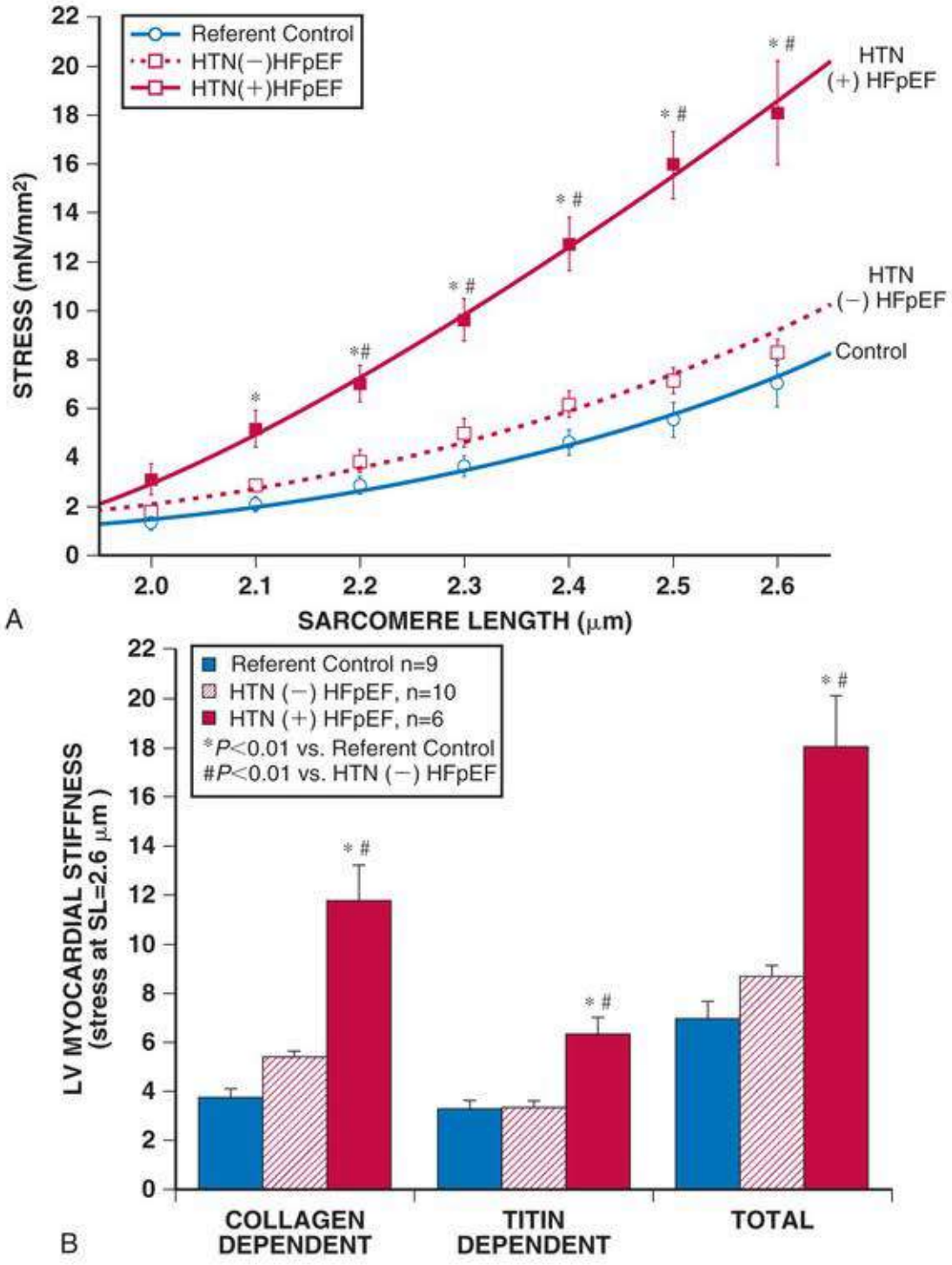
FIGURE 26.5 Mechanisms that result in increased LV diastolic pressure. Among patients with heart failure and an increased LV diastolic pressure, four patterns of diastolic pressure-volume relationship (DPVR) can be discerned. DPVR in patients with HFpEF may be characterized by graphed curves **A** and **B.** In the most prevalent pattern in HFpEF, represented by curve **B,** the DPVR is shifted upward and to the left, indicating reduced distensibility, where LV pressure is increased at any LV volume. In patients with HFpEF, when relaxation is markedly prolonged and diastole is abbreviated, as shown in curve **A,** LV diastolic pressure falls throughout diastole but remains increased. In curve **C,** pericardial constraint causes a parallel upward shift in the DPVR. DPVR in patients with HFrEF typically is characterized by curve **D,** in which eccentric remodeling results in a shift of the DPVR to the right, representing an increase in distensibility. It should be recognized that although the ventricle is more distensible, the end-diastolic volume in these patients typically is very large and the end-diastolic stiffness in the operating region is high. (From Carroll JD, Lang RM, Neumann AL, et al. The differential effects of positive inotropic and vasodilator therapy on diastolic properties in patients with congestive cardiomyopathy. Circulation 1986;74:815.)

Determinants of Left Ventricular Pressure-versus-Volume Relationship

Two of the determinants associated with an upward and leftward shift of the DPRV in patients with HFpEF are (1) the presence of LV and cardiomyocyte concentric remodeling and hypertrophy and (2) changes in the material properties of myocardial muscle itself (i.e., myocardial stiffness). *Myocardial diastolic stiffness* can be determined by assessing the myocardial diastolic LV stress-versus-strain relationship. The stress-strain relationship represents the resistance of the myocardium to *stretch* (increase in length) when subjected to *stress* (distending force). Calculation of stress requires the use of a geometric model of the left ventricle, and the calculation of strain requires assumption of the unstressed LV volume, which cannot be directly measured in the intact circulation. In addition to these potential theoretical limitations, these calculations require accurate measurements over a wide range of LV pressures, volumes, dimensions, and wall thicknesses. These challenges in determining myocardial stress-strain relationships have limited their clinical application, but they remain important to basic and translational research efforts.

Recently, techniques have been developed that allow assessment of myocardial stiffness and determination of the mechanisms that alter myocardial stiffness to be examined using LV myocardial biopsies in patients with clinical heart disease and patients with HFpEF. These translational studies examined the contribution that changes in the cardiac ECM such as fibrillar collagen, cardiomyocyte

cellular structure and processes such as calcium homeostasis and energetics, and myofilament and cytoskeletal proteins such as titin and microtubules make to the abnormalities in myocardial stiffness present in patients with HFpEF[31-33] (**Fig. 26.6**).



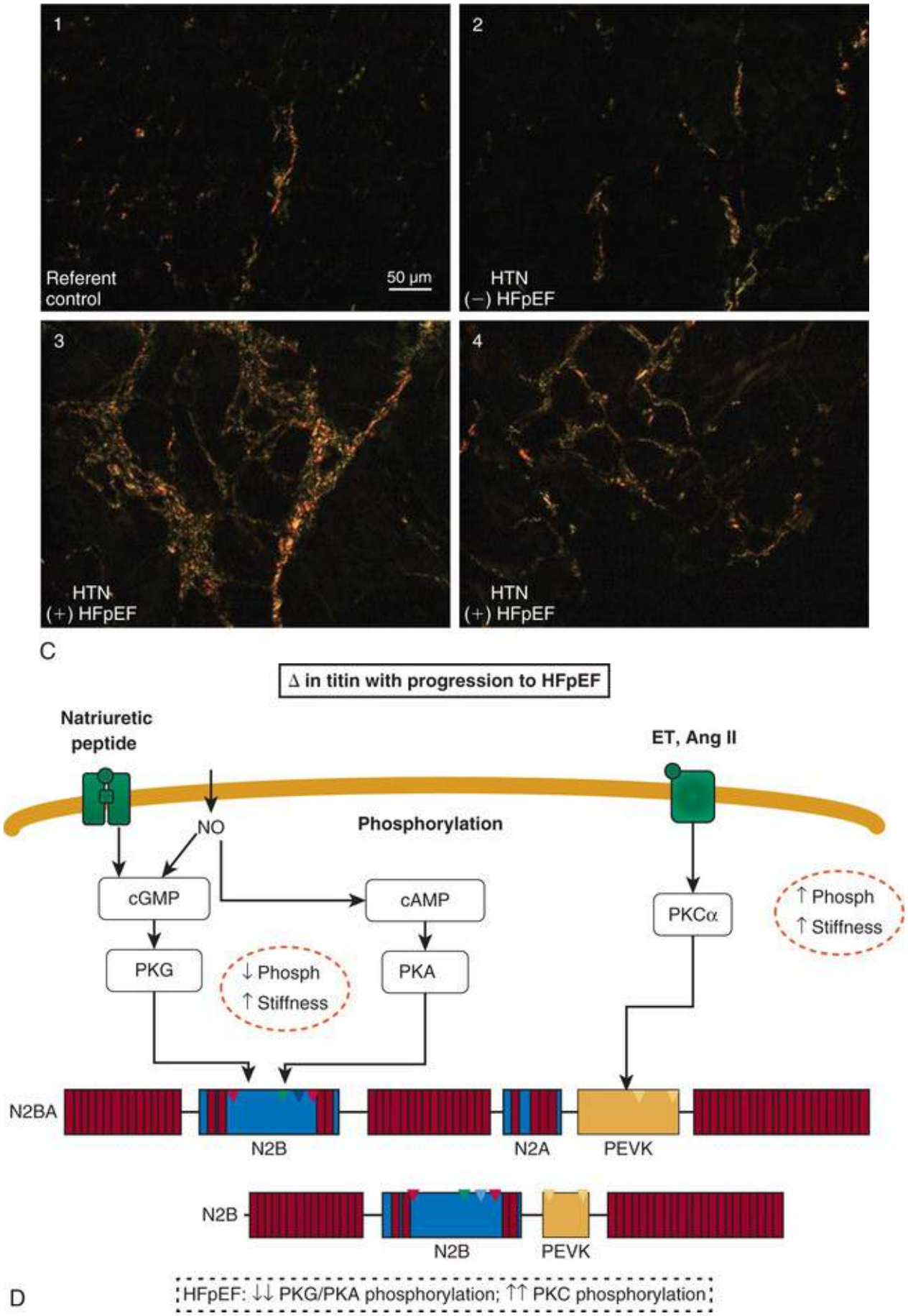


FIGURE 26.6 Contributions of changes in collagen and titin to the increased myocardial stiffness in HFpEF patients. **A,** Total myocardial stiffness expressed as the relationship between myocardial stress versus cardiomyocyte sarcomere length for referent control patients (*open circle, solid blue line*), patients with hypertension but without heart failure and a preserved ejection fraction (HTN(−)HFpEF, *closed circle, dashed red line*), and patients with hypertension and HFpEF (HTN(+)HFpEF, *closed squares, solid red line*). As sarcomere length increases, the slope increases most rapidly in the HTN(+)HFpEF group. Patients with HTN(+)HFpEF had an increase in total myocardial stiffness as indicated by a leftward shift in the stress vs. sarcomere length relationship. There were no significant differences between

HTN(−)HFpEF vs. referent control patients; hypertension in the absence of HFpEF, did not alter passive myocardial stiffness. *, # = $P < 0.01$ vs. referent control and HTN(−)HFpEF. **B,** Myocardial stiffness: Contribution of cellular vs. extracellular matrix (ECM) mechanism. Patients with HTN(+)HFpEF (*solid red bar*) had an increase in collagen-dependent myocardial stiffness and titin-dependent myocardial stiffness. There were no significant differences in HTN(−)HFpEF (*cross-hatched red bar*) or referent control patients (*solid blue bar*). *, # = $P < 0.01$ vs. referent control and HTN(−)HFpEF. **C,** Myocardial collagen content in patients with HTN(+)HFpEF **(panels 3 and 4)** vs. HTN(−)HFpEF **(panel 2)** and referent control **(panel 1).** Picrosirius-stained myocardial sections showed that P HTN(+)HFpEF had an increase in collagen; there were no significant differences between HTN(−)HFpEF or referent control patients. **D,** Change in titin phosphorylation with progression to HFpEF. Compared with referent control patients and patients with HTN(−)HFpEF, patients with HTN(+)HFpEF S11878(S26) and S12022(S170), sites known to be phosphorylated by protein kinase C (*PKC*) and S4185(S469), a site known to be phosphorylated by protein kinase A (*PKA*). Patients with HTN(+)HFpEF had an decreased phosphorylation on the PKG/PKA related N2B S4185(S469) site and increased titin phosphorylation on the PKCα-related PEVK S11878(S26); both of which lead to increased myocardial stiffness. *ET,* Endothelin. (**A-C,** from Zile MR, Baicu CF, Ikonomidis JS, et al. Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin. Circulation 2015;131:1247-59; **D,** from American Heart Association; LeWinter MM, Granzier HL. Titin is a major human disease gene. Circulation 2013;127:938-944.)

Extracellular Matrix

The ECM consists of fibrillar proteins such as collagen types I and III, elastin, and proteoglycans; basement membrane proteins such as collagen type IV, laminin, and fibronectin; and a large number of bioactive peptides and proteins such as matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs), signaling proteins such as transforming growth factor-β (TGF-β), and cytokines (**see Chapter 22**). The myocardial collagen network is composed of endomysial fibers surrounding individual myocytes and capillaries; perimysial fibers, which interweave muscle bundles; and epimysial fibers, which form a matrix adjacent to the epicardial and endocardial surfaces. ECM structure is dynamic and regulated by physical, neurohormonal, and inflammatory mediators. These modulate the four steps in collagen homeostasis: collagen synthesis, postsynthetic processing, posttranslational cross-linking, and degradation.[34-37] The ECM fibrillar collagen content is increased in patients with HFpEF. These changes in fibrillar collagen are not present in patients with antecedent disease processes such as hypertensive heart disease alone but develop only after patients make the transition to HFpEF[37] (**see Fig. 26.6**). Experimental studies have shown that acute degradation of collagen fibers by collagenase perfusion or activation of MMPs results in decreased LV stiffness. Animal models have demonstrated that interventions associated with increases or decreases in myocardial fibrosis are associated with increased or decreased LV diastolic stiffness. Thus, evidence that the ECM can contribute to diastolic dysfunction by increasing diastolic stiffness or contribute to impairment in relaxation by altering regional loading or uniformity is strong and supports the potential therapeutic strategy of preventing or reducing fibrosis in the therapy of HFpEF.

Myofilament and Extramyofilament Proteins

The giant myocardial protein *titin* spans the Z-lines and serves as a molecular spring that resists distention, thereby contributing to LV stiffness (**see Chapter 21**). A number of factors, including titin isoform switches (to a less compliant N2B isoform) and titin phosphorylation state, affect diastolic stiffness. Such alterations in titin phosphorylation are present in HFpEF contributing to increased LV diastolic stiffness.[38,39] These changes in titin phosphorylation are not present in patients with antecedent disease processes such as hypertensive heart disease alone, but develop only after patients make the transition to HFpEF[37] (**see Fig. 26.6**). Interaction of titin with other signaling molecules and with ion

channels also may contribute to diastolic stiffness. The role of alterations in titin and the interactions of titin with the ECM in patients with HFpEF constitute an important area of investigation. In addition to titin, other cardiomyocyte structural proteins and changes in their phosphorylation state may affect diastolic stiffness. These include changes in myosin-binding proteins, microtubules, and others.

Prevalence and Prognosis for Decreased Diastolic Distensibility

Measuring the DPVR in large series of patients with HFpEF, particularly in RCTs, is impractical. However, several studies using both invasive measurements and noninvasive estimates of LV stiffness have shown that LV diastolic stiffness is increased in patients with HFpEF compared with both age-matched control cohorts and patients with hypertensive LV hypertrophy but without HF.[2,30,40,41] The exact prevalence in either epidemiologic or pathophysiologic studies is not completely defined, but studies to date suggest that the prevalence of increased diastolic stiffness is high in HFpEF. Several studies using implantable hemodynamic monitors (IHMs) have shown that increased LV diastolic pressures (or their equivalents in pulmonary artery diastolic pressure, left atrial pressures, and thoracic impedance) in patients with HFpEF predict an increase in the frequency of subsequent acute decompensated heart failure and mortality.

Clinical Features

Diagnostic Criteria

The diagnosis of HFpEF can be made and confirmed using a combination of clinical and laboratory assessments (**Fig. 26.7**). Diagnostic criteria for HFpEF have been proposed by the AHA, ACC, HFSA, ESC, and other groups and share the following findings. First, the diagnosis of HFpEF requires the presence of signs and symptoms of HF. This clinical evaluation can be supported by objective measures of exercise intolerance and increased pulmonary extravascular fluid (**Fig. 26.7A**). Second, an EF greater than 50% and a normal LVEDV should be present (**Fig. 26.7B**). Third, expected antecedent or comorbid conditions should be present and all noncardiac causes of symptoms and signs excluded (**Fig. 26.7C**). The presence of these findings is sufficient to make the diagnosis of HFpEF. However, if these lead to ambiguous, borderline, or nonconcordant findings, further diagnostic clarification can be obtained with a fourth set of data (**Fig. 26.7D, E**). This objective noninvasive and invasive evidence of cardiac dysfunction should be used to further support, clarify, and provide specificity to the diagnosis of HFpEF.[42]

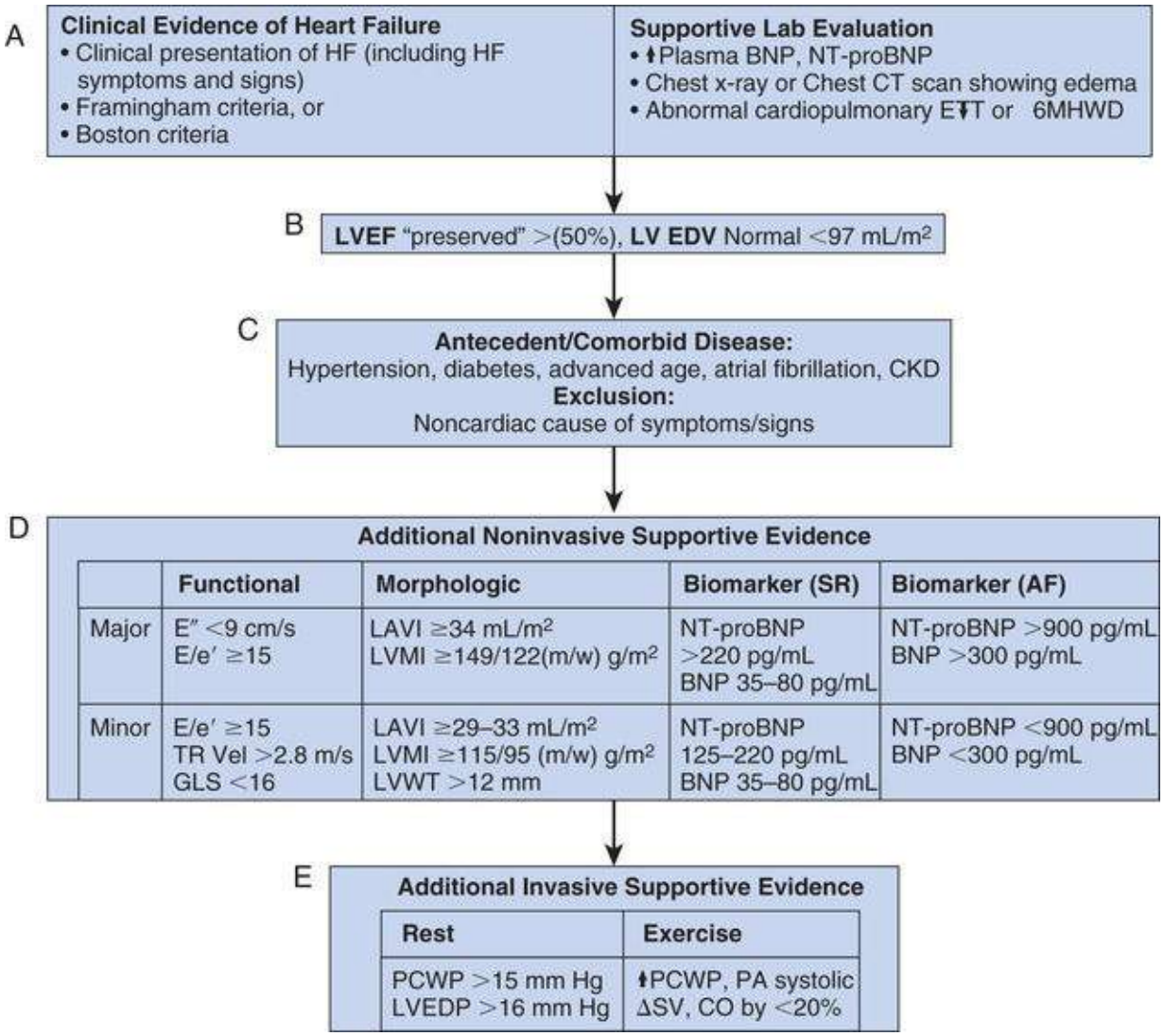
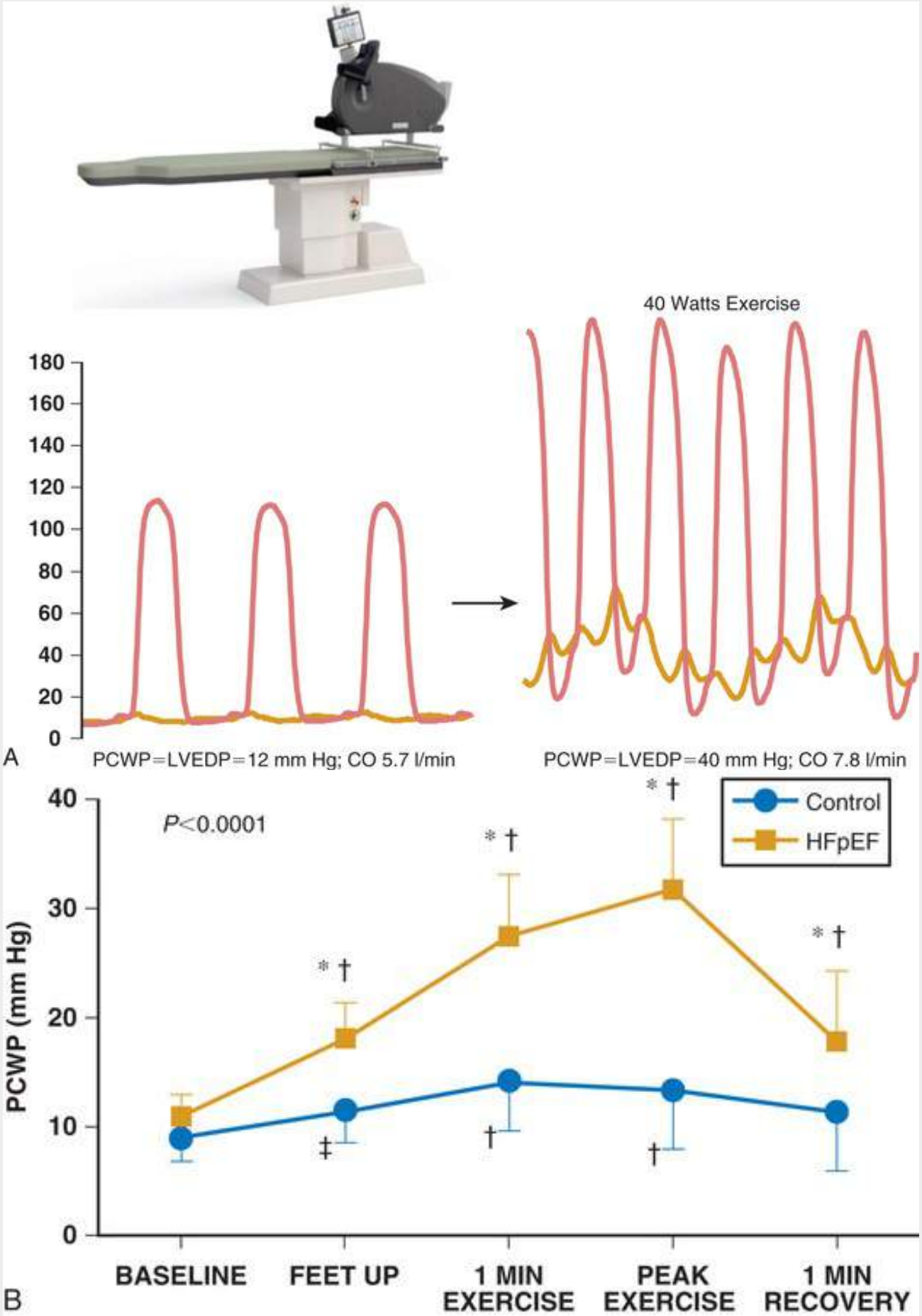


FIGURE 26.7 Diagnostic criteria for HFpEF. See text for discussion. 6MHW, 6-minute hall walk; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; LAVI, left atrial volume index; LVEDP, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; PCWP, pulmonary capillary wedge pressure. (Modified from Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.)

The clinical manifestations of HF are similar regardless of the EF. These include reduced exercise tolerance, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, and pulmonary congestion apparent on chest radiographs or computed tomography (CT) scans (**see Chapter 21**). Although a displaced LV apical impulse and pulsus alternans are presumed to be present only in HFrEF, no clinical features (symptoms, signs, or chest radiograph findings) can be used to reliably distinguish between HFpEF and HFrEF. Thus, determination of the EF and LV end-diastolic volume (usually by echocardiography) is required in patients being evaluated for HF. Furthermore, symptoms and signs common in HF can have other causes not related to HF. The diagnosis of HFpEF requires the exclusion of noncardiac causes of symptoms and signs. For example, exercise intolerance and dyspnea may be caused by obesity, pulmonary disease, anemia, or deconditioning. Edema may result from obesity or venous insufficiency. For these reasons, objective demonstration of CV dysfunction or remodeling is necessary to confirm the diagnosis of HF. A reduced EF provides this evidence in patients with HFrEF, but in HFpEF the EF is not abnormal (i.e., EF >50%) and the end-diastolic volume is not increased, so an elevation of the biomarker B-type natriuretic peptide (BNP) (or N-terminal pro-BNP), abnormal LV diastolic function (determined noninvasively or by direct measurement of LV diastolic pressure), or

elevated LA volume is required to support the diagnosis of HFpEF.

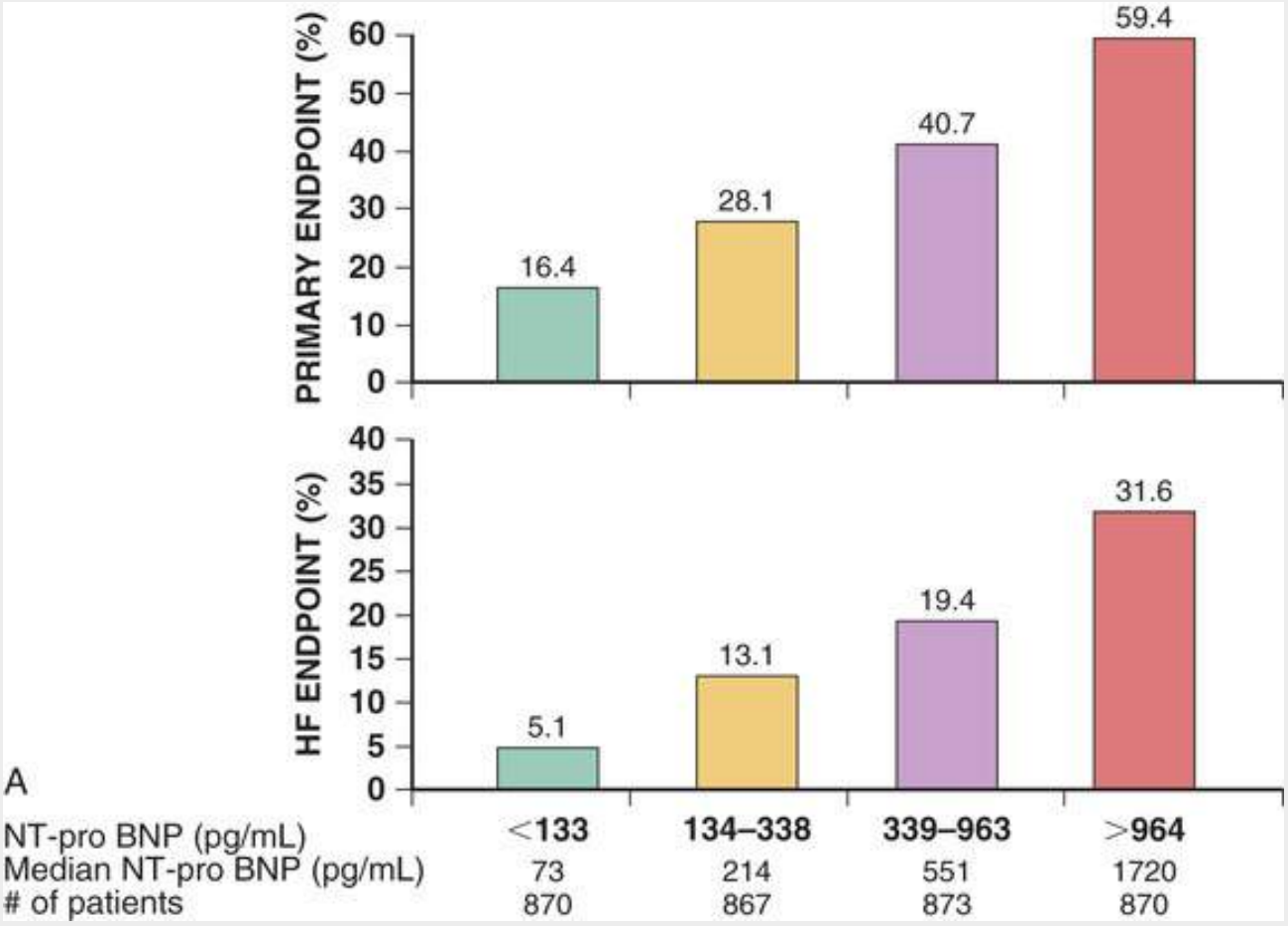
Biomarkers.
The best-characterized biomarkers in patients with HFpEF are the natriuretic peptides (NPs) BNP and NT-proBNP. The utility of NPs and other plasma/serum biomarkers in HFpEF have recently been reviewed in an AHA guideline document.[43] Circulating levels of these proteins are elevated in patients with HFpEF compared with persons without HF but are lower than in patients with HFrEF (**see Chapter 21**). In patients with HFpEF, increased BNP is directly related to LV diastolic filling pressure and end-diastolic wall stress. For any given LV diastolic filling pressure in patients with HFpEF, BNP levels are lower in obese patients and higher in women, older persons, and patients with concomitant pulmonary disease (chronic obstructive disease, pulmonary hypertension, pulmonary embolus) and renal dysfunction. Several methods have been suggested to allow "adjustment" of NP levels for these concomitant states, such as the adjustment for BMI: for every 1 kg/m^2 increase in BMI above 25, NP levels fall 4%.[44] Because patients with HFpEF have a smaller LV cavity and thicker LV walls, their end-diastolic wall stress is much lower than in HFrEF, even in the setting of high systolic and diastolic pressures, thus producing a lower stimulus for BNP production. On average, patients with HFpEF presenting with acute decompensation have a BNP value of 100 to 500 pg/mL, versus 500 to 1500 pg/mL in patients with HFrEF. The standard partition values for BNP of 100 pg/mL and for NT-proBNP of 400 pg/mL have been suggested to support the diagnosis of HFpEF. However, in a subset of patients with normal NPs but all the other characteristics typical of HFpEF, confirmation of the diagnosis should include invasive measures of diastolic function and assessment of response to exercise (**eFig. 26.2**).

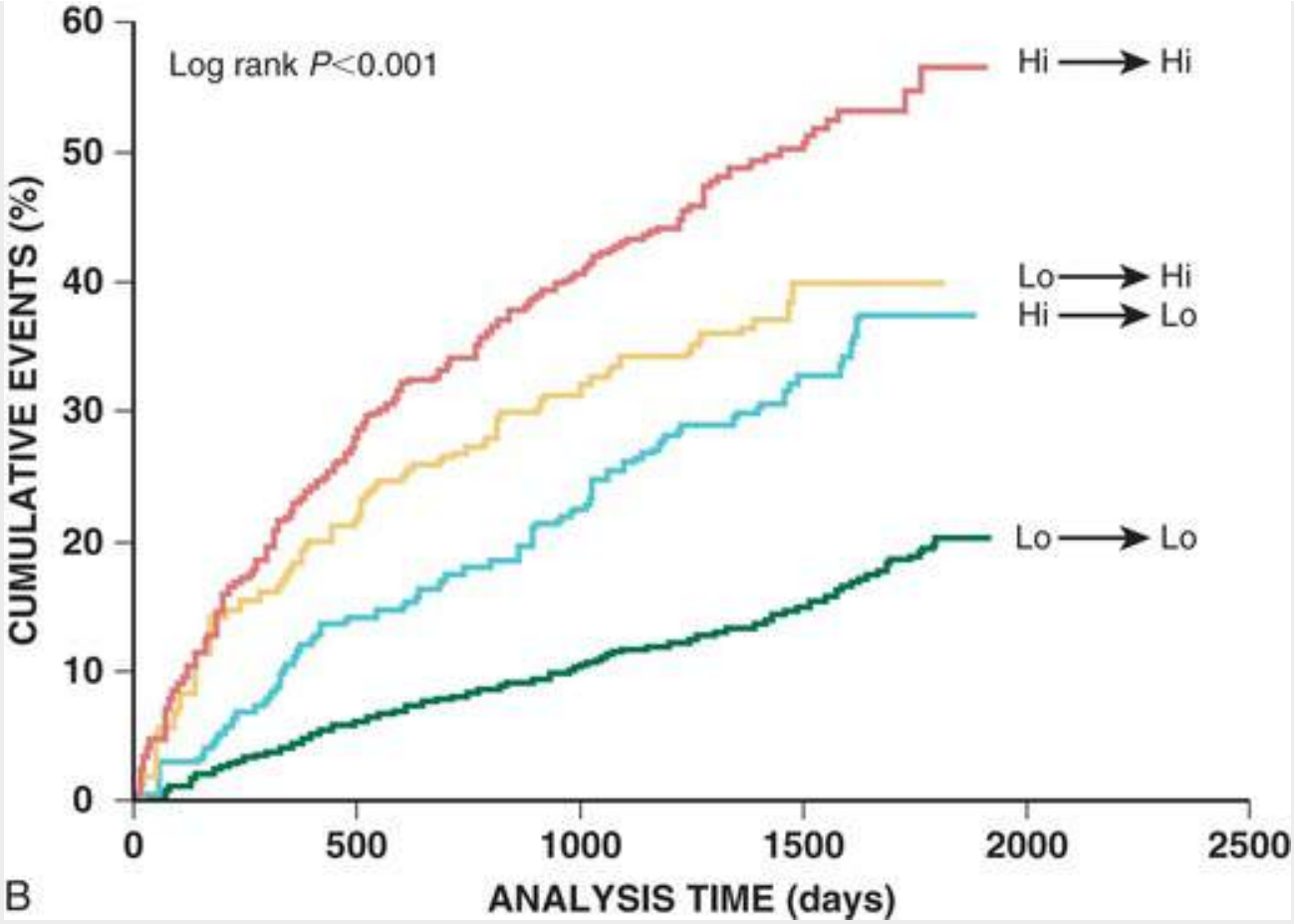


EFIGURE 26.2 Exercise-induced diastolic dysfunction in HFpEF patients using invasive measurement of diastolic function (bicycle ergometry in catheterization lab with right heart catheter in place). **A,** Example of 70-year-old patient with NYHA III symptoms of heart failure and clear decrease in 6MHWD and MVO_2 but BNP <60 pg/mL. At rest the PCWP and LVEDP were normal; however, with exercise both rose dramatically. **B,** Exercise response of PCWP in HFpEF patients (*yellow squares*) versus referent controls (*blue circles*). (**A,** Examples courtesy Barry Borlaug; **B,** From American Heart Association; Borlaug BA et al. Exercise

hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010;3:588-95.)

Both baseline values and change from baseline predict CV outcomes in patients with HFpEF (**eFig. 26.3**). Elevation of BNP also indicates increased risk for subsequent events, even in asymptomatic persons. Frequent measurement of BNP and NT-proBNP may be useful in the medical management of HFpEF. Other biomarkers to aid in the diagnosis, prognosis, and management of HFpEF include U.S. Food and Drug Administration (FDA)–approved biomarkers (e.g. soluble ST2, galectin 3), as well as others still under development (e.g., TIMP-1).[43]





EFIGURE 26.3 Baseline and change from baseline values of NT-proBNP have prognostic value in HFpEF patients. **A,** Baseline values of NT-proBNP have significant prognostic value and predict morbidity and mortality outcomes. The higher the baseline value of NT-proBNP, the higher the rate of the primary and heart failure endpoints in the I-Preserve study. **B,** Prognosis: NT-proBNP change from baseline. Change from baseline values of NT-proBNP have significant prognostic value and predict morbidity and mortality outcomes. Data from the I-Preserve study indicated that the directional change in NT-proBNP predicted primary and heart failure outcome rates. (**A,** From McKelvie RS et al. Baseline plasma NT-proBNP and clinical characteristics: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction trial. J Card Fail 2010;16:128; **B,** from Jhund PS et al. Changes in N-terminal pro-B-type natriuretic peptide levels and outcomes in heart failure with preserved ejection fraction: an analysis of the I-Preserve study. Eur J Heart Fail 2015;17:809-17.)

Demographic Features

The incidence of HFpEF increases with age, and the condition is more prevalent in women (**see Chapter 21**). These demographic features may differ in specific populations and are associated with differences in race, ethnicity, and geographic region. For example, African Americans may develop HFpEF at a younger age. This predilection may be a consequence of more severe comorbid disease, including hypertension, obesity, and diabetes. In addition, HFpEF is increased in Asians with a lean body mass and diabetes. The antecedent and comorbid conditions are different in HFrEF than HFpEF. A history of hypertension is present in a majority of patients with HFpEF (80% to 90%), and the disorder may have developed only later in life. Obesity is seen in 30% to 50%, diabetes in 20% to 30%, current atrial fibrillation (AF) in up to 20% to 30%, and a history of AF in about 50% of patients. There is a high prevalence of renal disease, which may be progressive. The prevalence of CAD is 20% to 40%. The presence of each of these comorbidities predicts higher morbidity and mortality.[45] Because medical therapy is aimed at these comorbid conditions both to treat existing HFpEF and prevent the development of HFpEF, the medications used by patients with HFpEF and those with HFrEF are similar. They include diuretics, digoxin, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta

blockers, calcium channel blockers, and various other vasodilators and antihypertensive and antiarrhythmic drugs. Although these agents are not being prescribed as part of a guidelines-based therapeutic approach, they do target the comorbid conditions and the congestive state present in HFpEF.

Comorbid Conditions

Patients with HFpEF and those with HFrEF both frequently have important comorbid diseases (**see Fig. 26.2**). Some of these conditions are antecedent diseases that contribute to the structural and functional changes underlying the pathophysiology of HFpEF or precipitate the development of acute decompensation and contribute to morbidity and mortality.[45] The frequency and severity of comorbid states appear to be higher in HFpEF, at least in part because of the older age of the patients. Because no treatment approaches specific to HFpEF have been proved to reduce morbidity and mortality, treatment suggestions have focused on comorbid states. Although comorbidity plays a pivotal role in both HFrEF and HFpEF, some investigators have raised the question of whether HFpEF represents a primary cardiac condition or just a collection of comorbid conditions with a secondary phenotype of HF.

A number of recent studies have provided data supporting the conclusion that HFpEF is an important, unique clinical syndrome of heart failure.[1] For example, the role of comorbidity in 386 patients with HFpEF was examined in a recent report.[46] Hypertension, obesity, diabetes, anemia, and renal dysfunction were present in many of these patients. However, even after accounting for age, sex, body size, and comorbidity, patients with HFpEF as a group showed larger LV mass, greater degree of systolic and diastolic dysfunction, more LA enlargement, and increased arterial stiffness. These observations indicate that the comorbid conditions contribute to the development of CV abnormalities of HFpEF, but the cardiac abnormalities are more than what might be expected with these conditions alone.[1] In addition, other recent analyses of data from RCTs indicated that the prognosis with HFpEF is much worse than that expected with a specific comorbidity alone. Thus, treating the comorbid diseases (especially hypertension) can be expected to delay or prevent the development of HFpEF but may not be adequate therapy for HFpEF once it develops. Therefore, although comorbid conditions are frequent and important, HFpEF is more than just a collection of such conditions.

The distribution and frequency of comorbid conditions have led some to characterize HFpEF as a “heterogeneous” clinical syndrome. However, all patients with HF, regardless of their EF or how they are grouped, can be characterized as heterogeneous. Using any metric of heterogeneity, HFrEF patients are just as heterogeneous as HFpEF patients. There are significant variabilities in demographics, comorbidities, CV structure and function, and other metrics in both HFrEF and HFpEF populations, and these measures of heterogeneity are equally pronounced in both groups of HF patients. Therefore the presence of heterogeneity alone should not prevent or impede studies in patients with HFpEF. One potential approach to overcoming the challenges intrinsic to the presence of heterogeneity in HF populations is to characterize HFpEF using phenotypic mapping.[47]

Aging.
The incidence of HFpEF increases with age, probably because of increased comorbidity in elderly patients and the adverse effects of normal aging on the cardiovascular system. LV diastolic function becomes abnormal with normal aging. This decrement is apparent as slower rates of LV relaxation, changes in the pattern of LV filling, and reduction in the early diastolic annular velocity that slowly

progress with age. Thus age correction is used for the normal values of these parameters. In addition, arterial, LV systolic, and LV diastolic stiffness increase with aging. Structural cardiac changes with aging (e.g., increased cardiomyocyte size, increased apoptosis with decreased cardiomyocyte number, altered growth factor regulation, focal collagen deposition) and functional changes at the cellular level involving blunted beta-adrenergic responsiveness, excitation-contraction coupling, and altered calcium-handling proteins also may contribute to diastolic dysfunction with normal aging.[12] Some evidence suggests that prolonged, sustained endurance training may slow or prevent some of the age-related changes.

Sex.

Female sex is a potent risk factor for HFpEF.[48] The reasons for the female prominence in HFpEF are not entirely clear, but women have more arterial and LV systolic and diastolic stiffness compared with men, and arterial and ventricular stiffness increases more dramatically with age in women. Women are shorter in stature than men, which may enhance the impact of reflected arterial waves on systolic pressure. These differences also may result from reproductive hormone effects on LV structure and function and response to alterations in load.[49]

Hypertension.

Hypertension is the most commonly associated cardiac condition in patients with HFpEF (**see Chapters 45 and 46**). Chronically increased systolic blood pressure is an important stimulus for cardiac structural remodeling and functional changes. The resultant hypertensive heart disease is characterized by concentric remodeling or overt LV hypertrophy, increasing arterial and ventricular systolic stiffness, impaired relaxation, and increased diastolic stiffness—all factors linked to the pathogenesis of HFpEF. In the presence of hypertensive heart disease, ischemia produces exaggerated increases in filling pressures, and hypertensive and ischemic heart disease often are present in combination in patients with HFpEF. Determining which factors mediate the transition from hypertensive heart disease to clinical HFpEF is an area of active investigation; however, recent studies have demonstrated that proinflammatory and profibrotic signaling lead to both fibroblast/monocyte-macrophage mediated changes in ECM collagen homeostasis and changes in cardiomyocyte myofilament phosphorylation states. These changes lead to increased myocardial fibrosis and alterations in titin phosphorylation, which in turn increase myocardial stiffness and play a causal role in the transition to HFpEF (**see Figs. 26.2 and 26.3**).

Coronary Artery Disease.

The reported prevalence of CAD or myocardial ischemia in patients with HFpEF varies widely (**see Chapter 61**). Although acute ischemia is known to cause diastolic dysfunction, the role of coronary artery disease and ischemia in contributing to chronic diastolic dysfunction and symptoms in patients with HFpEF remains speculative. In addition, even in the absence of atherosclerosis, changes in vascular endothelial function may contribute to the development of HFpEF (**see Fig. 26.2**). Despite uncertainty regarding the role of ischemia in the pathophysiology of HFpEF and a lack of data documenting that revascularization improves outcomes in patients with HFpEF, heart failure management guidelines recommend revascularization in those patients with HFpEF in whom “ischemia is felt to contribute to diastolic dysfunction.”[50]

Atrial Fibrillation and Other Rhythm Disturbances.

AF is recognized as a frequent precipitant of acute decompensation in patients with HFpEF. This is caused by both the loss of atrial contraction and the resulting tachycardia. Whereas AF may cause acute decompensation of HF in patients with diastolic dysfunction, diastolic dysfunction (even in the absence of HF) results in left atrial enlargement and increases the risk of AF. Thus, aging, diastolic dysfunction,

AF, and HFpEF are related conditions. (**See also Chapter 38**.)

Obesity.

Obesity is associated with an increased risk for HF regardless of EF. In general, patients with HFpEF are more often obese than patients with HFrEF, and the prevalence of diastolic dysfunction is increased in obese persons. Increased adiposity not only imposes an adverse hemodynamic and metabolic load on the heart, but also is a source of a large number of biologically active peptide and nonpeptide mediators, many linked to chronic inflammation. Increased body mass index (BMI) is a risk factor for hypertension, DM, CAD, and AF, all of which are associated with HFpEF. Studies using tissue Doppler imaging or invasive LV pressure measurement have reported an association among diastolic dysfunction, elevated filling pressures, and obesity, even in the absence of an HF diagnosis.[51] Dramatic weight loss with caloric restriction or bariatric surgery is associated with improved LV diastolic function.[52]

Diabetes Mellitus.

DM is a potent risk factor for HF, and the prevalence of diabetes is similar in patients with HFrEF and in those with HFpEF, suggesting that diabetes contributes to the pathophysiology of both forms of HF (**see Chapter 51**). DM predisposes to CAD, renal dysfunction, and hypertension. In addition, direct effects of diabetes and hyperglycemia on myocardial structure and function have been described. The morphologic changes in the diabetic heart include myocyte hypertrophy, increased ECM (fibrosis), and intramyocardial microangiopathy. Functional changes include impaired endothelium-dependent and endothelium-independent vasodilation, impaired LV relaxation, increased passive diastolic stiffness, and contractile dysfunction. Mechanisms contributing to structural and functional coronary vascular and myocardial changes include metabolic disturbances, activation of proinflammatory and profibrotic mediators, cardiac autonomic neuropathy, and increases in advanced glycation end products (AGEs), which promote increased collagen accumulation and stiffness. AGE accumulation may play a role in age-related CV stiffening. It appears that better control of blood glucose is associated with an improvement in LV diastolic function, as measured by noninvasive methods.[41]

Chronic Kidney Disease.

The critical impact of renal function on morbidity and mortality in HF is well established.[53] There is no clear difference in severity of renal dysfunction between patients with HFrEF and those with HFpEF.[14,54] Furthermore, the incidence of worsening renal function during HF therapy is similar in patients with HFrEF and in those with HFpEF. However, the presence of chronic kidney disease (CKD) in HFpEF makes the regulation of volume status with diuretics and nitrates more difficult. Although the prevalence of renal vascular disease in HF has been poorly delineated, evaluation of the renal arteries should be considered in patients presenting with the triad of hypertension, renal dysfunction, and HFpEF.

Sleep Apnea.

Obstructive sleep apnea is common in patients with HFpEF, can contribute to symptom severity, and is likely to promote progression of HF. Central sleep apnea can occur in association with severe HFpEF. (**See also Chapter 87**.)

Pulmonary Hypertension.

Most patients with HFpEF have at least some degree of pulmonary hypertension, with pulmonary artery systolic pressures typically greater than 40 mm Hg.[55] This is at least partly because of the elevated LV filling pressures, with resulting increased pulmonary venous pressure.[23] In addition, the pulmonary vascular resistance may be increased by reactive pulmonary arterial vasoconstriction. This reactive process may be most apparent during exercise. In some patients, chronic pulmonary venous hypertension causes pulmonary vascular remodeling (congestive pulmonary vasculopathy), leading to irreversible

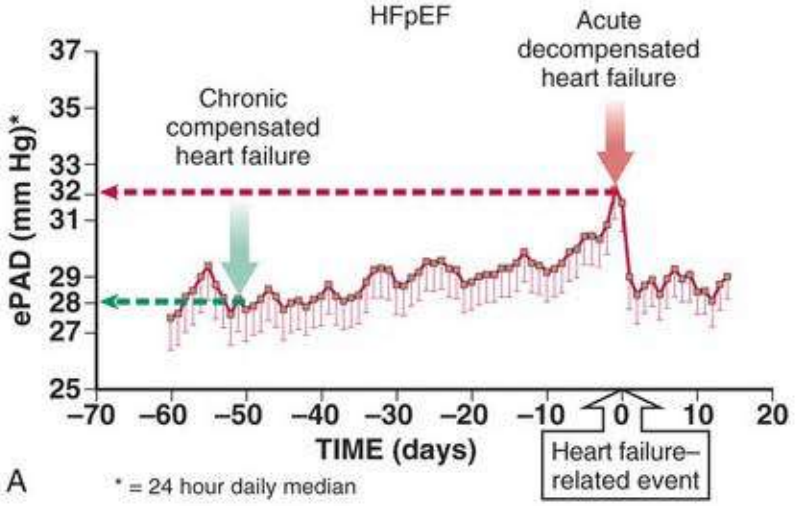
pulmonary hypertension. The presence of increased pulmonary artery pressures has prognostic implications and is associated with higher morbidity and mortality rates.

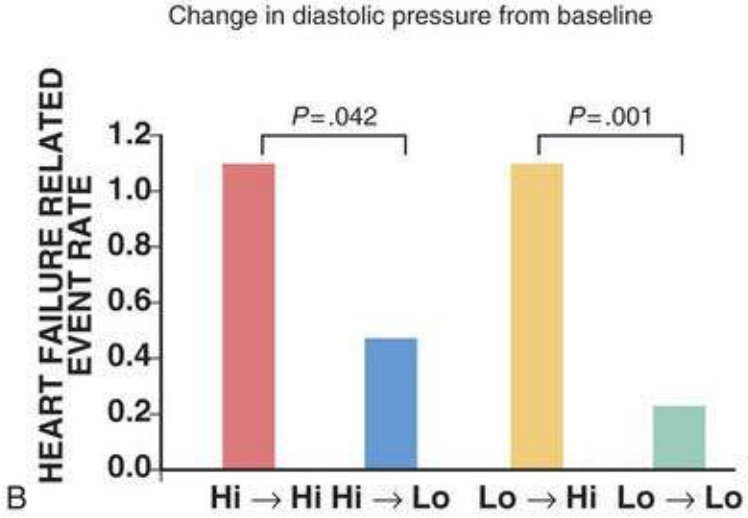
Rarer Causes of Heart Failure with Preserved Ejection Fraction

Hypertrophic cardiomyopathy (**see Chapter 78**), infiltrative cardiomyopathies such as amyloidosis (**Chapter 77**), valvular disease (**Chapters 68 to 70**), and constrictive pericarditis (**Chapter 83**) should always be considered in patients with HFpEF. However, these diseases account for a small minority of cases of HFpEF. The clinical presentation and echocardiographic appearance in older persons with HFpEF may be identical to those in patients previously diagnosed with restrictive cardiomyopathy. An important consideration in patients with previous malignancy treated with mediastinal irradiation is radiation-induced heart disease (**see Chapter 81**). Radiation can cause pericardial and concomitant myocardial damage, and persistent HF after pericardiectomy is common because of concomitant myocardial disease. Concomitant valvular disease and premature CAD also are common in patients with previous mediastinal irradiation and may contribute to the pathophysiology of HFpEF in patients with radiation-induced HF.

Acute Decompensated Heart Failure in Patients with HFpEF

Acute decompensated heart failure (ADHF) is a frequent outcome in patients with HF and may require urgent treatment in the hospital, emergency department (ED), or outpatient office setting (**see Chapter 24**). A majority of patients hospitalized for ADHF have preexisting HF; at least 50% of these patients have HFpEF. Rehospitalizations are frequent, but some patients with HFpEF may be minimally symptomatic between episodes of ADHF. In the vast majority, ADHF is caused by pulmonary congestion that accompanies increases in LV diastolic filling pressure[56] (**Fig. 26.8A**). Both baseline LV diastolic filling pressure and changes in filling pressure are sensitive predictors of future ADHF events (**Fig. 26.8B**); treatment and prevention of increased diastolic filling pressures have been shown to reduce HF hospitalization and CV mortality (**Fig. 26.8C, D**; see later discussion). ADHF in patients with HFpEF can result from increased filling pressure with or without significant changes in body weight, total blood volume, or LV diastolic volume.[57] In contrast, increased LV diastolic pressure and volume can result from increases in total intravascular volume or shifts of intravascular volume due to splanchnic vasoconstriction. The mechanisms responsible for these changes include worsening diastolic dysfunction, increased neurohormonal activation, and poorly controlled comorbid disease. In patients with HFpEF, arterial hypertension, myocardial ischemia, and DM can act on preexisting structural and functional abnormalities to cause deterioration in LV diastolic function and precipitate ADHF. Atrial arrhythmias can result in loss of atrial function and can stimulate compensatory increases in diastolic filling pressure to maintain LV filling and cardiac output. Decreased LV diastolic function and abnormal LA function can result in neurohormonal activation, which plays an important role in ADHF by increasing sodium and water retention, venous return, splanchnic tone, and arterial vasoconstriction. Even after normal volume status is restored and neurohormonal activation suppressed, the inciting comorbidity may remain and can influence the subsequent clinical course. This ongoing process may contribute to a high rate of non-HF–related rehospitalizations after an HF episode.[19,58]


HFpEF
Acute decompensated heart failure
Chronic compensated heart failure
ePAD (mm Hg)*
37
35
33
32
31
29
28
27
25
–70 –60 –50 –40 –30 –20 –10 0 10 20
TIME (days)
Heart failure–related event
A
* = 24 hour daily median


Change in diastolic pressure from baseline
HEART FAILURE RELATED EVENT RATE
P=.042
P=.001
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Hi → Hi
Hi → Lo
Lo → Hi
Lo → Lo
B

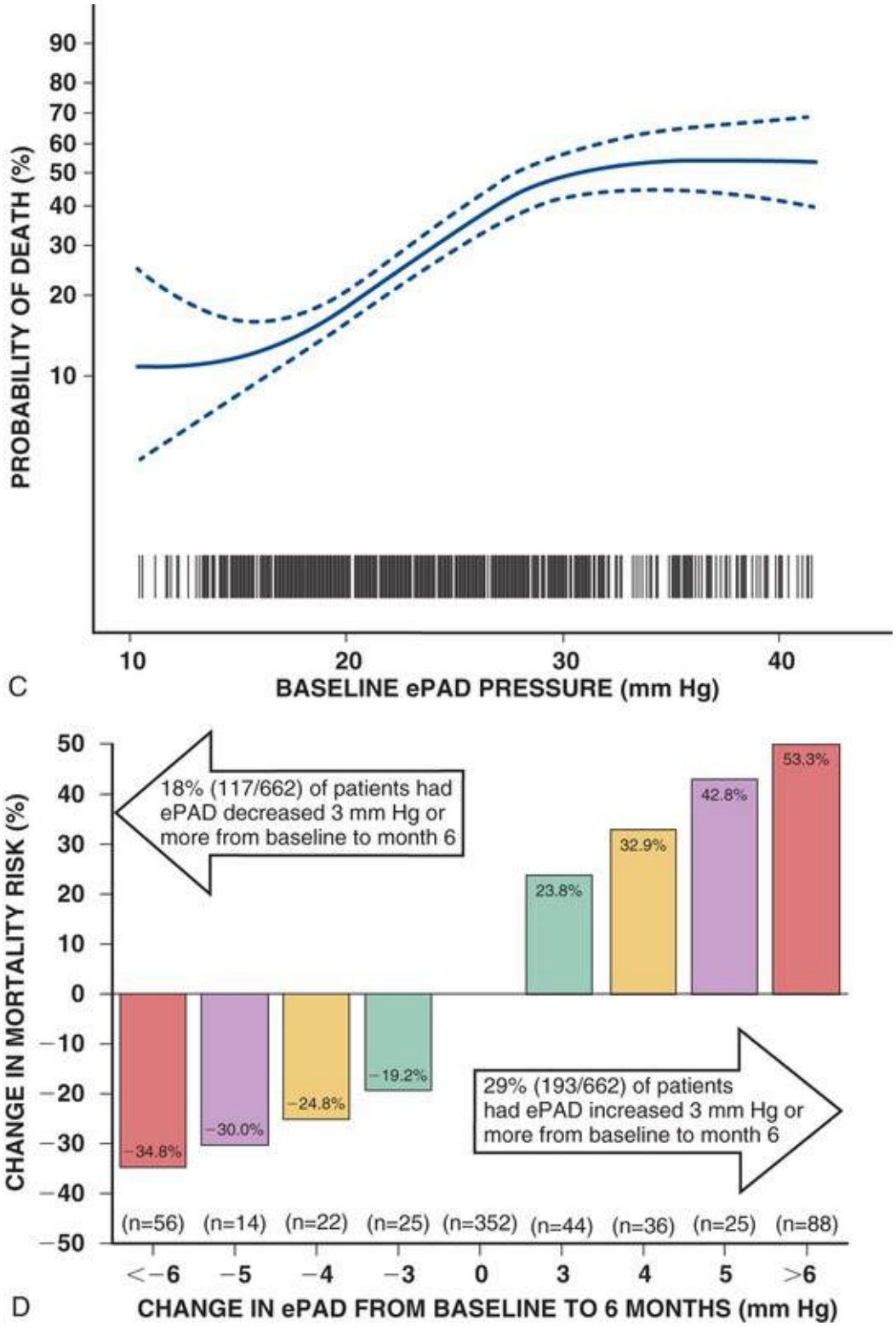


FIGURE 26.8 Left ventricular diastolic pressures in HFpEF patients predict mortal and morbid events. **A,** Patients with HFpEF have increased LV diastolic pressure (indexed here as *ePAD*) even when considered in good compensation by their physician and experience further increases in pressure with the development of acute decompensated heart failure (ADHF) necessitating hospital admission. **B,** Both baseline LV diastolic filling pressure and changes in filling pressure are sensitive predictors of future ADHF events. **C, D,** Both baseline LV diastolic filling pressure and changes in filling pressure are sensitive predictors of all-cause mortality. (**A,** From Zile MR et al. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. Circulation 2008;118:14331; **B,** from Stevenson LW et al. Chronic ambulatory intracardiac pressures and future heart failure events. Circ Heart Fail 2010;3:580; **C, D,** from Zile MR et al. Intracardiac pressures measured using an implantable hemodynamic monitor: relationship to mortality in patients with chronic heart failure. Circ Heart Fail 2017;10[1].)

Assessment of LV structure and function is an essential step in the clinical evaluation of patients with suspected HFpEF to establish diagnosis, assess prognosis, and monitor effectiveness of treatment.[25] In addition, changes in structure and function contribute to the pathophysiologic mechanisms that underlie the development of HFpEF. Although echocardiography remains the most widely used noninvasive clinical imaging technique, evaluation may be supplemented or enhanced by magnetic resonance imaging (MRI) and computed tomography (CT). As in patients with HFrEF, the structural and functional characteristics of patients with HFpEF have some features that all (or nearly all) patients share and others that demonstrate some variability in prevalence.

Left Ventricular Structure

Left Ventricular Volume

Most (>90%) patients with HFpEF have normal LV chamber dimension, area, and volume; up to 5% of patients have a mild increase in LV volume above the upper normal partition value of 75 mL/m^2.[10,59,60] In addition, in many patients with HFpEF, LV volumes are small, contributing to a limitation in stroke volume and cardiac output response to exercise. An LV volume less than 75 mL/m^2 is one of the guidelines-based diagnostic criteria for HFpEF.

Left Ventricular Mass

LV mass is increased and reaches criteria for LV hypertrophy in 30% to 50% of patients with HFpEF.[8] Some evidence suggests that the prevalence of LV hypertrophy may be higher among African American patients and women with HFpEF.[61,62] When present, LV hypertrophy is associated with significantly worse prognosis. Even in those patients who do not meet criteria for LV hypertrophy, structural remodeling may have developed, evidenced as concentric remodeling and cardiomyocyte hypertrophy (**see Fig. 26.3**).

Left Ventricular Geometry

The ratio of LV mass to volume (M/V), or of LV wall thickness to LV internal dimension (relative wall thickness [RWT]), describes the geometry of the left ventricle.[9] When mass or thickness is increased relative to (or out of proportion with) volume or dimension, the resultant changes are termed *concentric remodeling*. Concentric remodeling can occur even in the absence of frank LV hypertrophy in approximately 20% to 30% of patients with HFpEF and is associated with a 25% to 35% higher risk of HF events.[19]

Left Ventricular Function

Diastolic Properties

Patients with HFpEF may have abnormalities in all aspects of diastolic function, including a delayed and slow relaxation, decreased recoil, slow and incomplete early filling, increased filling during atrial contraction, and decreased distensibility. The methods necessary to quantify these abnormalities and the causative mechanisms are described earlier (see Pathophysiology). However, echocardiographic techniques can be used to assess these properties in a combinatorial fashion in order to characterize a diastolic function grade of 0 (normal), 1 (abnormal relaxation), 2 (pseudonormalized), 3a (reversible restrictive), or 3b (irreversible restrictive)[25] (**Fig. 26.9**). This echocardiographic and Doppler echo–based grading scale is the most common clinical method of assessing severity of diastolic dysfunction.

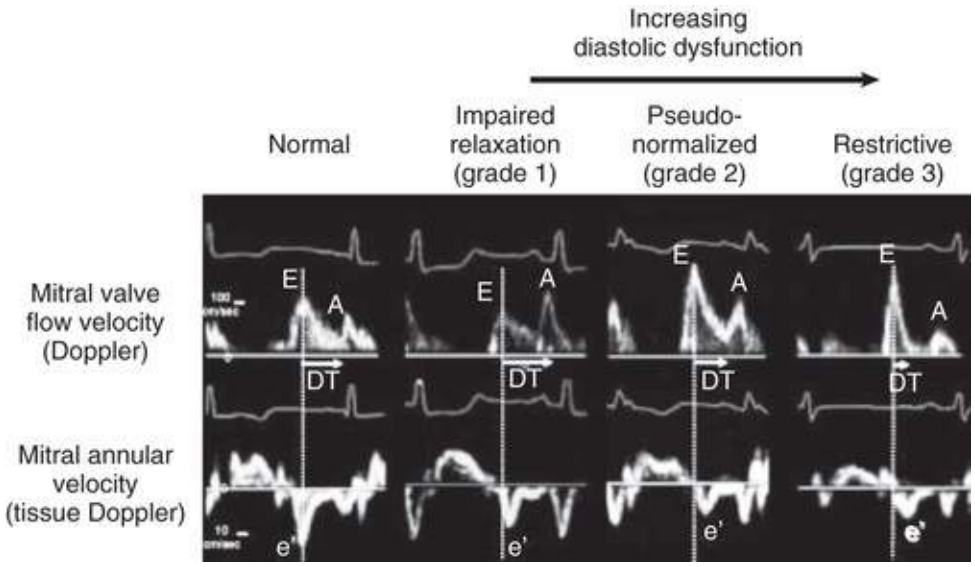


FIGURE 26.9 Evaluation of diastolic function based on the left ventricular filling dynamics determined by Doppler measurement of mitral valve flow velocity and tissue Doppler measurement of mitral annular velocity. Normally, the early diastolic mitral flow velocity (*E*) and the mitral annular velocity (*e′*) are brisk and occur almost simultaneously. With mild diastolic dysfunction (impaired relaxation pattern—grade 1) the mitral E velocity is reduced and is less than the late diastolic mitral flow velocity (*A*). The E deceleration time (*DT*) is increased. With more severe diastolic dysfunction (grades 2 and 3), E is increased and the DT is reduced. In these patterns, e′ is reduced and delayed relative to the mitral E. (From Little WC, Oh JK. Echocardiographic evaluation of diastolic function can be used to guide clinical care. Circulation 2009;120:802.)

Grade 1 diastolic dysfunction is characterized by the presence of mild diastolic dysfunction with slow LV relaxation. The early diastolic pressure gradient between the left ventricle and the left atrium that accelerates transmitral flow into the left ventricle is decreased because there is no increase in LA pressure, and early LV diastolic pressure is higher because of abnormal relaxation.[25] This results in a decrease in both the early transmitral flow velocity (E) and the early tissue velocity (e′) and an increase in the importance of late diastolic mitral flow velocity (A), the transmitral velocity resulting from atrial contraction, producing an E/A ratio less than 1. The delayed relaxation results in a prolongation of E wave deceleration time (DT) and may be associated with a mid-diastolic peak of mitral flow (L wave).[63] The contribution to LV filling produced by atrial contraction is increased. This filling pattern has been termed an "impaired relaxation pattern" (abnormal relaxation) or grade 1 diastolic dysfunction.[64] In most patients with impaired relaxation pattern, the mean LA pressure is not elevated despite an increased LV end-diastolic pressure, which is maintained by a vigorous atrial contraction.

Grade 2 diastolic dysfunction occurs when progressive worsening of diastolic dysfunction is associated with an increase in LA pressure and there is restoration of the early diastolic pressure gradient despite increased early diastolic LV pressures. These changes result in a return of the E wave to the normal range (pseudonormal mitral inflow pattern). Displacement of the left ventricle onto a steeper portion of the pressure-volume curve results in a shortening of the DT. With slower relaxation, the e′ is delayed, occurring after the E. This indicates that the left ventricle is not expanding symmetrically in diastole, but that propagation of filling to the apex and longitudinal expansion occur slowly after the left ventricle is filled by the movement of blood from the left atrium into the LV inflow tract. In the presence of slow relaxation, e′ does not occur during the time of the LA-to-LV pressure gradient, so e′ is reduced and becomes almost independent of LA pressure.[26] Both the low mitral annular e′ and the delay in e′ relative to E correlate with increased time constant of LV isovolumetric pressure decline.[26] Thus the

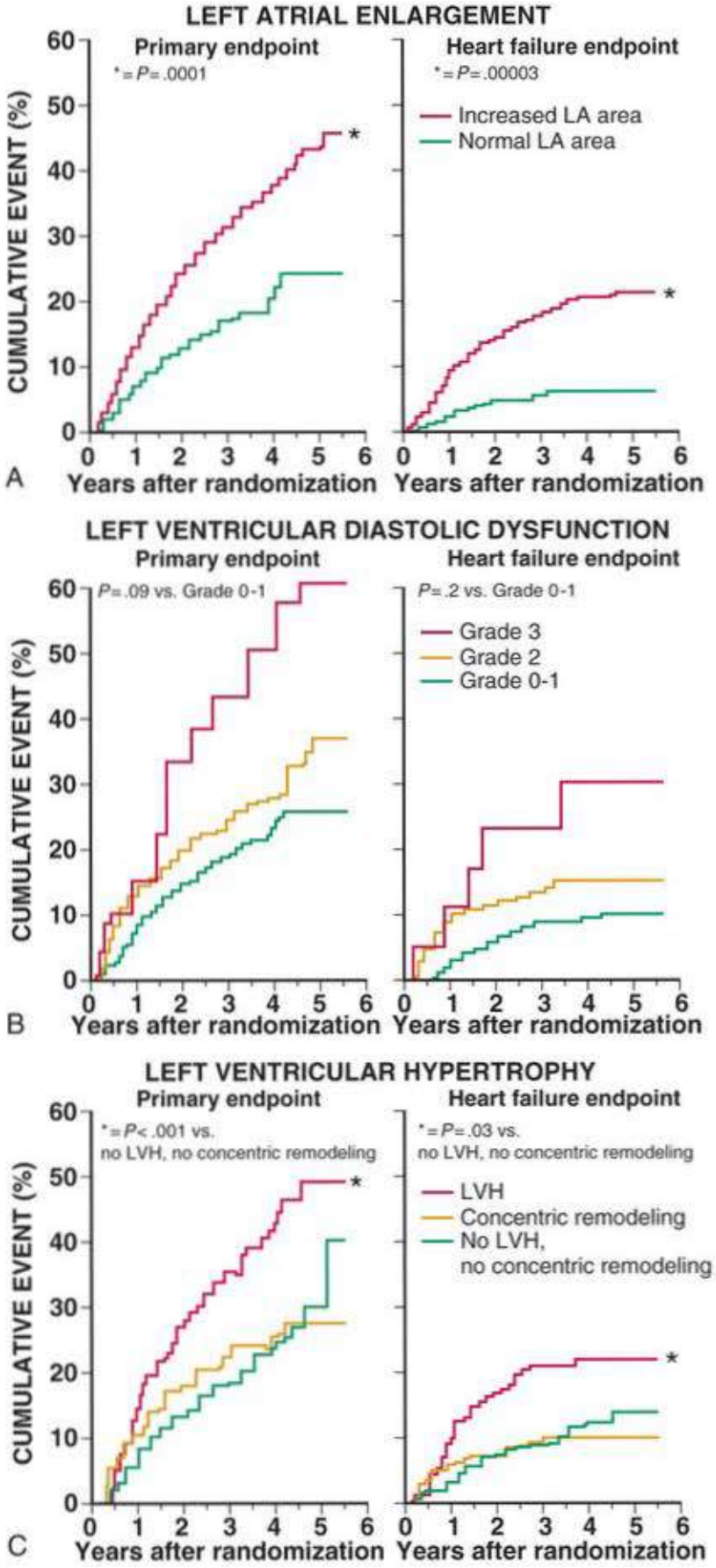
pseudonormal mitral inflow pattern is distinguished from normal by a reduced and delayed e′ and increase in the E/e′ ratio.

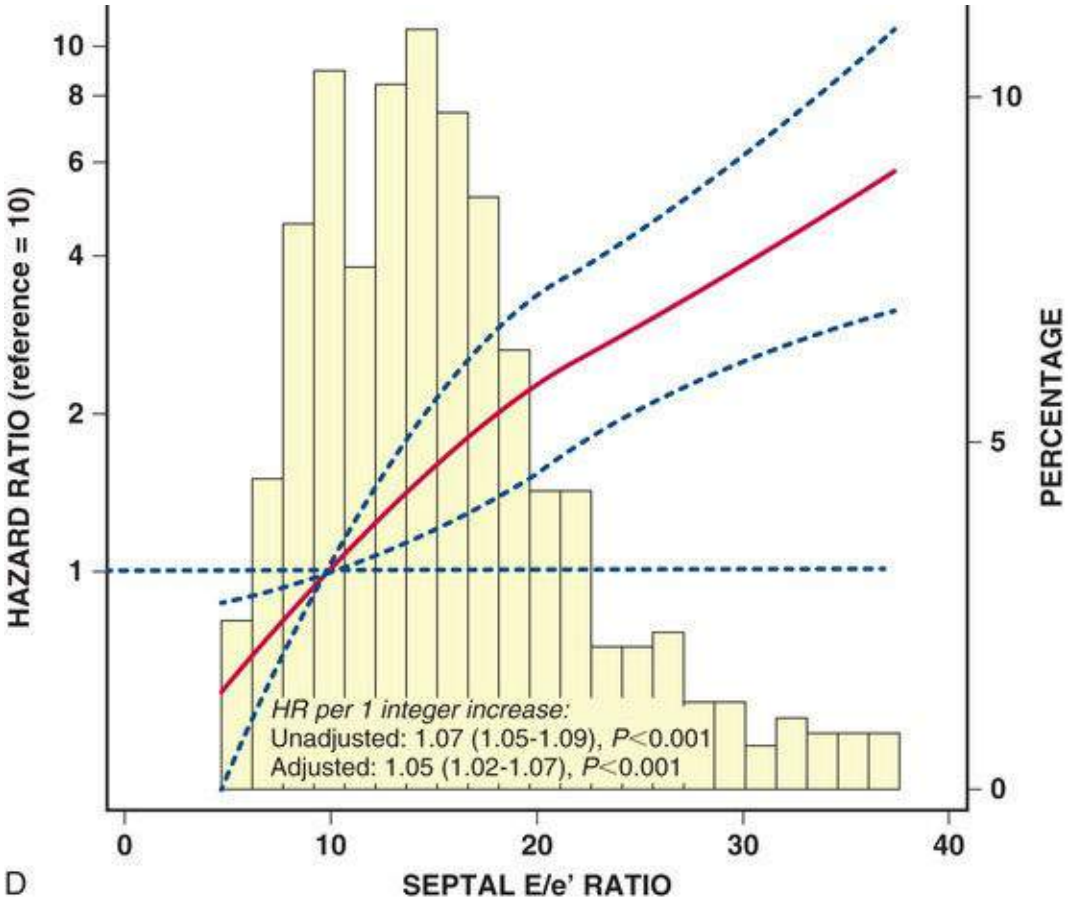
Grade 3 diastolic dysfunction occurs when severe diastolic dysfunction causes a markedly slowed relaxation and elevated LA pressure; the E increases further, DT becomes very short, and e′ is further reduced and delayed resulting in a marked elevation of E/e.[27] With severe diastolic dysfunction, the late diastolic annular velocity (a′) also may be reduced, and pulmonary venous systolic forward flow velocity is reduced as well, to less than diastolic forward flow velocity. With grade 3 diastolic dysfunction, if a Valsalva maneuver causes a reduction of E wave velocity, the condition is designated *reversible* (grade 3a); if Valsalva does not change E, it is designated *irreversible* (3b).

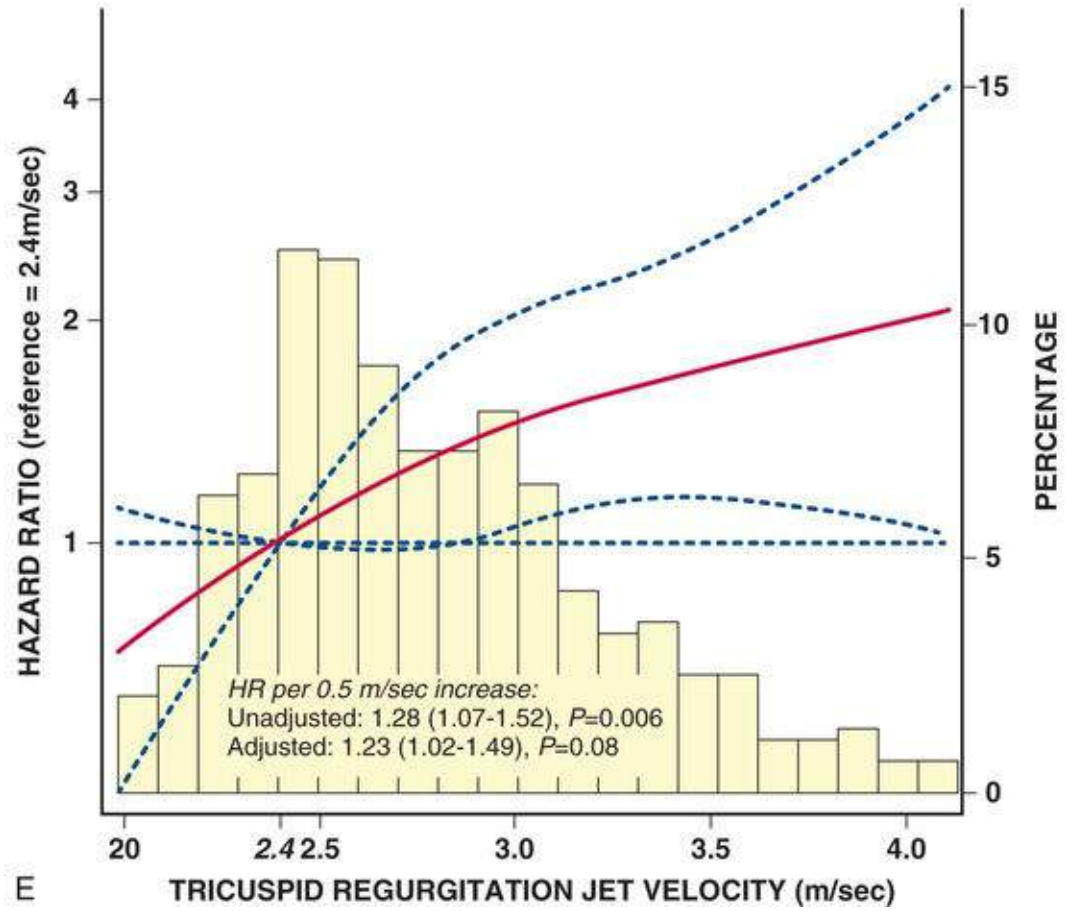
Noninvasive Estimation of Left Ventricular Diastolic Filling Pressure.

Knowledge of LV diastolic pressure in patients with known or suspected HFpEF is important for establishing diagnosis, predicting prognosis, and directing therapy. However, because direct measures of diastolic pressure are invasive and not suitable for repeated measures, noninvasive echocardiographic and echo-Doppler measurements have been developed and clinically applied. The measurements used in the diastolic grading system also can be used to estimate LV diastolic filling pressures and to follow progression of disease and response to therapy. Pseudonormalized and restricted filling patterns indicate the presence of both diastolic dysfunction and elevated LA pressure.[27] By contrast, the impaired relaxation pattern indicates diastolic dysfunction without a marked elevation in LA pressure.

Additional echo-Doppler measurements that may reflect diastolic filling pressures include estimation of peak right ventricular systolic pressure (PRVSP) from the tricuspid regurgitation velocity and LA volume.[23] The most common cause of increased pulmonary artery systolic pressure in HFpEF is an elevation of LA pressure, and the echocardiographic parameters best correlated with PRVSP are DT and E/e′.[55] Diastolic dysfunction grade and PRVSP estimate instantaneous diastolic pressure. Changes in LA volume reflect longer-term changes in LV filling pressures.[2,55,62] LA volume is dependent on the product of diastolic pressure and time, so the longer pressures are increased and the higher they are increased, the larger the LA volume. Abnormal diastolic dysfunction grade, increased PRVSP, and increased LA volume are highly prevalent in patients with HFpEF and have significant prognostic value (**eFig. 26.4**).


LEFT ATRIAL ENLARGEMENT
Primary endpoint
*=P=.0001
Heart failure endpoint
*=P=.00003
Increased LA area
Normal LA area
CUMULATIVE EVENT (%)
Years after randomization
A
LEFT VENTRICULAR DIASTOLIC DYSFUNCTION
Primary endpoint
P=.09 vs. Grade 0-1
Heart failure endpoint
P=.2 vs. Grade 0-1
Grade 3
Grade 2
Grade 0-1
CUMULATIVE EVENT (%)
Years after randomization
B
LEFT VENTRICULAR HYPERTROPHY
Primary endpoint
*=P<.001 vs.
no LVH, no concentric remodeling
Heart failure endpoint
*=P=.03 vs.
no LVH, no concentric remodeling
LVH
Concentric remodeling
No LVH,
no concentric remodeling
CUMULATIVE EVENT (%)
Years after randomization
C





EFIGURE 26.4 Prognostic significance of alterations in cardiac structure and function in patients with HFpEF in the I-Preserve and TOPCAT studies. **A,** Left atrial (LA) enlargement; **B,** higher diastolic dysfunction grade; **C,** left ventricular hypertrophy (LVH). **D,** increased E/e′ ratio; and **E,** increased estimated peak RV systolic pressure as evidenced by increased tricuspid regurgitant (TR) jet velocity increased the risk of heart failure hospitalization and cardiovascular (CV) mortality. (**A-C,** from Zile MR, Gottdiener JS, Hetzel SJ. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. Circulation 2011;124:2491; **D, E,** from Shah AM et al. Cardiac structure and function

and prognosis in heart failure with preserved ejection fraction: findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial. Circ Heart Fail 2014;7:740-51.)

All the previous measures are useful in identifying patients with or without elevations of LA pressure. However, the most frequently used and easily interpretable parameter to estimate LA pressure is the E/e′ ratio.[25] E/e′ has been found to correlate with pulmonary capillary wedge pressures (PCWPs) in a wide range of patients studied in multiple laboratories.[64,65] An E/e′ greater than 15 has been found clearly to indicate elevated PCWP, whereas E/e′ less than 8 is associated with normal LA pressure[64] (**see Fig. 26.4**). The cutoff value for E/e′ of 15 to recognize elevated LA pressure was obtained using e′ velocity from the medial mitral annulus. Because e′ velocity from the lateral annulus usually is higher than the medial e′ velocity, the cutoff value should be adjusted to 12 if the lateral annular velocity is used. An average of the medial and lateral annular velocities has been recommended.[64] In some situations, however, E/e′ may not provide an accurate assessment of PCWP. The clinical settings in which this application of E/e′ may be inaccurate are described in an online supplement for this chapter (Limitations in Use of E/e′ Ratio).[25]

Prevalence and Prognosis for Diastolic Dysfunction in HFpEF.

The frequency distribution of diastolic dysfunction grade, increased PRVSP, and LA volume varies according to the characteristics of the population studied, that is, the patient's level of hemodynamic compensation and severity of disease. A truly normal diastolic function profile, however, is uncommon in patients with HFpEF.[66] For example, an abnormal diastolic dysfunction grade was found in 60% to 70% of the patients enrolled in the TOPCAT, I-Preserve, and CHARM studies; LA enlargement was present in 66%, and either diastolic dysfunction of grade II to IV or LA enlargement was found in 85%.

Echocardiographic findings related to diastolic function provide important prognostic information in a wide variety of patient populations. A normal filling pattern in community-dwelling patients indicates an excellent prognosis.[67] By contrast, an abnormal filling pattern along with progressively worsening abnormalities of LV filling pattern (impaired relaxation versus pseudonormalized and restricted filling) indicates patients with a progressively increased risk of subsequent mortality. The stage of diastolic dysfunction correlates with the impairment of exercise capacity in patients without myocardial ischemia, whereas LV EF does not.[68] In patients with HF, the stage of diastolic dysfunction is a stronger predictor of mortality than EF.[69]

A short DT indicates an increased LV operating stiffness, is a hallmark of restrictive filling pattern, and connotes poor prognosis in patients with a history of myocardial infarction (MI), those with dilated cardiomyopathy (DCM), heart transplant recipients, and patients with hypertrophic or restrictive cardiomyopathy.[64] Both pseudonormalized and restricted filling patterns are associated with a fourfold increase in the risk of death in HF patients withCAD.[70] Similarly, an elevated E/e′ indicates a poor prognosis in a wide variety of patients.[64] Lastly, in patients with HFpEF, abnormal diastolic function measured as diastolic dysfunction grade, LA enlargement, or increased PRVSP also predicts marked increase in morbidity and mortality events (**eFig. 26.4**).

Systolic Properties

Global LV systolic chamber properties are normal at rest in patients with HFpEF. By definition, patients with HFpEF have a normal (or near-normal) EF. In addition, at rest, patients with HFpEF have normal dP/dt_{max}, stoke volume, stroke work, and preload-recruitable stroke work. Furthermore, indices of chamber contractility such as LV end-systolic elastance are actually increased in HFpEF, matching the

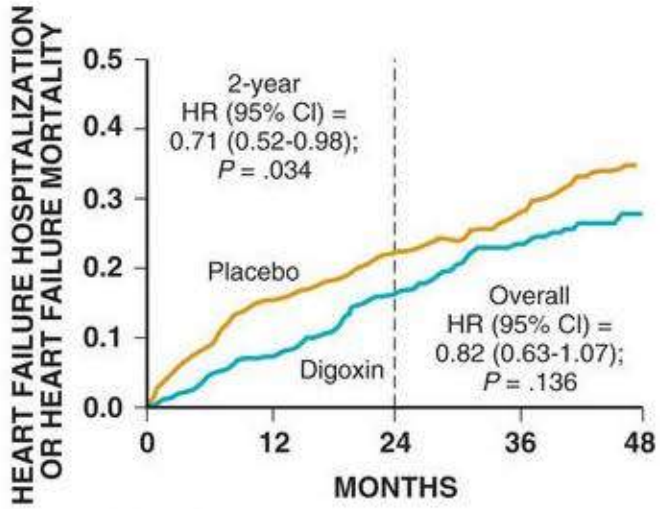
increased arterial elastance, so that the coupling between these properties is preserved.[71,72] By contrast, in HFrEF, LV systolic elastance is reduced and arterial elastance is elevated so that ventricular-vascular coupling is impaired. In fact, the presence of a normal EF indicates that the coupling of the left ventricle and arterial system is almost optimal to convert the energy of contraction into the stroke work.[73] Thus, arterial vasodilation improves LV systolic performance in HFrEF but not in HFpEF.[74] Because indices of end-systolic elastance are altered by remodeling, chronic changes in chamber contractility should be normalized to the LV mass/end-diastolic volume ratio. With this adjustment, elastance measurements in patients with HFpEF are normal in the resting state. (See the online supplement for this chapter, Indices of Myocardial Contractile Function and Assessment of Exercise Capacity in Heart Failure with Preserved Ejection Fraction).

Therapy

Many prospective RCTs have been conducted in patients with HFrEF, with findings used to guide evidence-based therapy. By contrast, such evidence is lacking for patients with HFpEF: No treatment has yet been shown, convincingly, to reduce morbidity or mortality in patients with HFpEF.[75] Therapies with proven benefit in HFrEF, including pharmacologic regimens of ACE inhibitors, ARBs, beta blockers, or hydralazine/nitrates, as well as placement of implantable defibrillators and cardiac resynchronization, have not shown any clear benefit in HFpEF, or data from RCTs are not available for HFpEF. Nevertheless, the practical clinical approach presented in this section will reduce symptoms, prevent acute decompensation, and improve exercise tolerance.

Summary of Randomized Controlled Trials

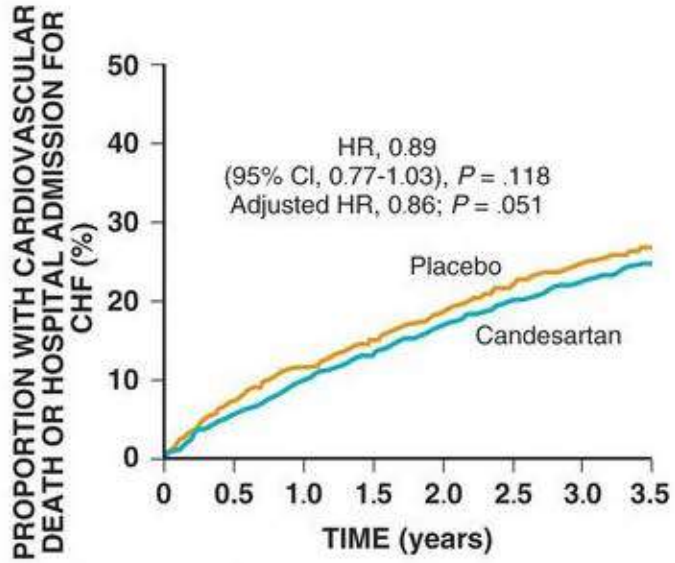
Eight large RCTs have enrolled patients with HFpEF (with EF entry criteria ranging from >35% to >50%), six had HF hospitalization or CV death as the primary endpoint, two had exercise or activity level endpoints. Six of these RCTs had a clearly neutral outcome; in a post hoc analysis, one demonstrated a reduction in HF hospitalization or CV death in patients who actually had HFpEF and were treated with spironolactone, and one demonstrated that therapy could be facilitated using an implantable hemodynamic sensor (**Fig. 26.10**; **see Table 26.1**).



Number of patients at risk

Placebo	496	408	366	240	84
Digoxin	492	440	387	248	98

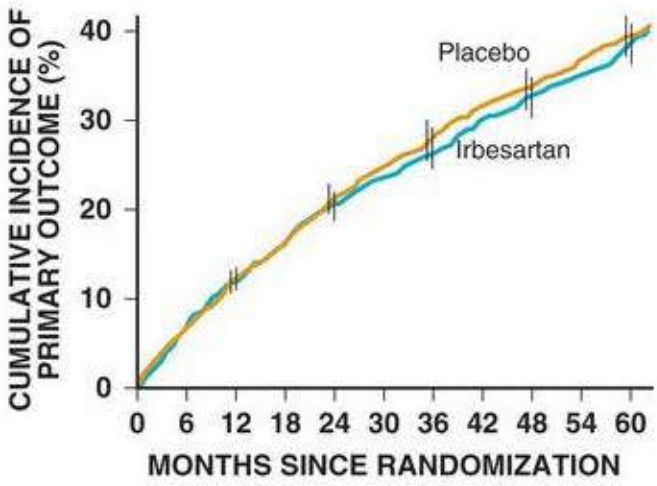
A



Number of patients at risk

Candesartan	1514	1458	1377	833	182
Placebo	1509	1441	1359	824	195

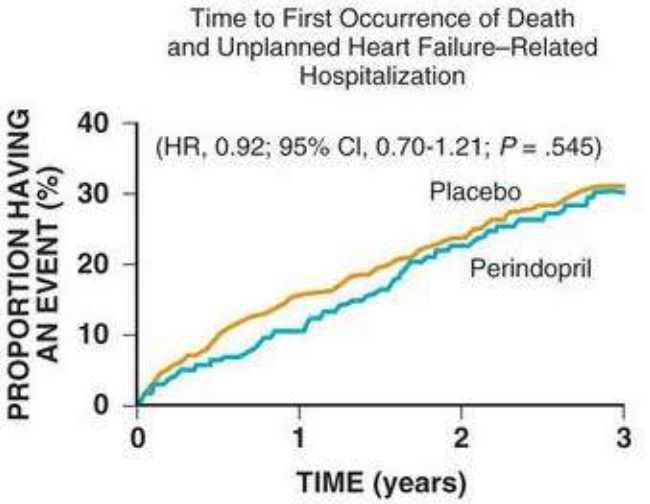
B



Number of patients at risk

Irbesartan	2067	1929	1812	1730	1640	1569	1513	1291	1088	816	497
Placebo	2061	1921	1808	1715	1618	1539	1466	1246	1051	776	446

C



Number of patients at risk

Perindopril	424	374	184	70
Placebo	426	356	186	69

D

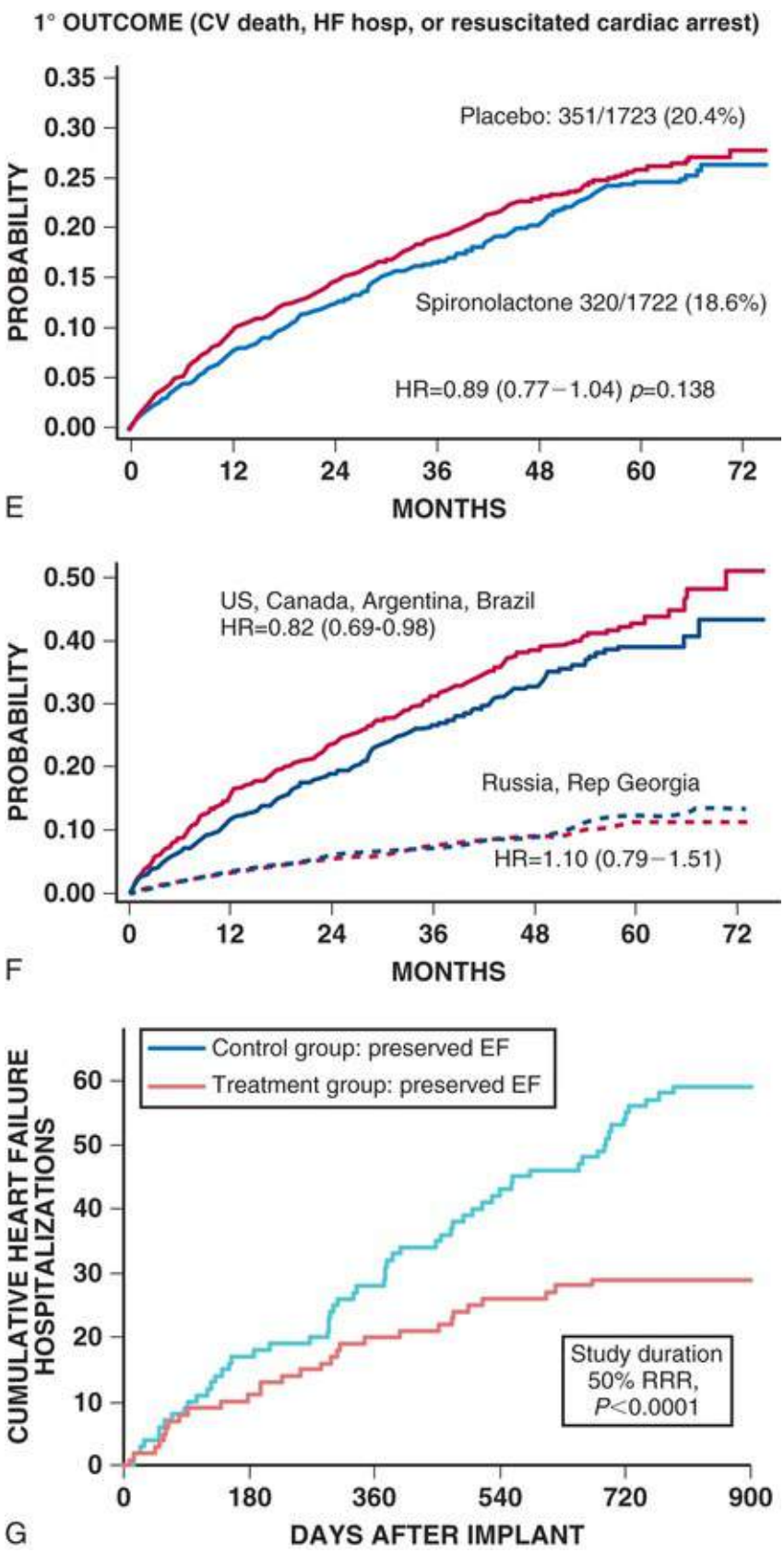


FIGURE 26.10 Kaplan-Meier survival curves for the primary endpoint in **A,** Digitalis Investigators Group (DIG) trial substudy of patients with heart failure with normal ejection fraction (HFnlEF); **B,** Candesartan in Heart Failure: Assessment of Reduction in Morbidity and Mortality (CHARM)-Preserved trial; **C,** Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction (I-Preserve) trial; **D,** Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial. **E** and **F,** Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trail; and **G,** CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial. See text for discussion. CV, Cardiovascular; CI, confidence interval; EF, ejection fraction; HR = hazard ratio. (**A,** From Ahmed A et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: The Ancillary Digitalis Investigation Group Trial. Circulation 2006;114:397; **B,** from Yusuf S et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. Lancet 2003;362:777; **C,** from Massie BM et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456; **D,** from Cleland JG et

al. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study. Eur Heart J 2006;27:2338; **E**, from Pitt B et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370:1383; **F**, from American Heart Association; Pfeffer MA et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial. Circulation 2015;131:34; **G**, from American Heart Association; Adamson PB et al. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. Circ Heart Fail 2014;7:935.)

DIG Trial.

The Digitalis Investigators Group (DIG) Trial included a separate cohort of 988 patients with ambulatory HFpEF (EF >45%) in normal sinus rhythm. In this HFpEF group, digoxin did not alter the primary endpoint of HF-related hospitalization or CV mortality but did reduce the number of such hospitalizations. Total CV hospitalizations were not reduced, however, because of an increased rate of admissions for unstable angina, which completely negated the benefit of reduced HF hospitalizations.[76]

Charm.

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program of trials evaluated the ARB candesartan in HF patients. In the CHARM-Preserved arm,[77] HF patients with an EF above 40% were randomly assigned to receive candesartan or placebo in addition to standard therapy. Fewer patients in the candesartan group than in the placebo group reached the primary endpoint of CV death or HR-related hospitalization, a finding that reached statistical significance only after adjustment for small differences in baseline characteristics. Furthermore, there was no impact on mortality.

PEP-CHF.

In the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial, patients older than 70 with HFpEF (EF >0.45) with echocardiographic evidence of diastolic dysfunction were randomly assigned to receive perindopril (an ACE inhibitor) or placebo.[78] The primary endpoint was a composite of all-cause mortality or unplanned HF-related hospitalization. Both enrollment and event rates were lower than anticipated, and a high rate of cessation of blinded therapy, with crossover to open-label ACE inhibitor use, was reported for both groups. These factors limited the power of the study, which did not show significant reduction in the primary endpoint. Some trends toward benefit, primarily driven by reduction in HF-related hospitalizations, were observed in a post hoc analysis of the results at 1 year, when crossover therapy rates were lower.

I-Preserve.

The Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-Preserve) tested the ARB irbesartan in 4128 patients who were at least age 60 and had New York Heart Association (NYHA) Class II, III, or IV HF, with an EF above 45%.[79] The primary outcome was death from any cause or hospitalization for a CV cause (HF, MI, unstable angina, arrhythmia, or stroke). Secondary outcomes included death from HF or hospitalization for HF, death from any cause and from CV causes, and impaired quality of life. Irbesartan had no effect on any of the prespecified outcomes.

Seniors.

The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) trial tested the effect of the $beta_1$-selective blocking agent nebivolol in HF

patients without an EF requirement.[80] Nebivolol also has vasodilator properties thought to be related to its effects on nitric oxide (NO) release. A modest but significant reduction was observed in the primary endpoint of all-cause mortality or CV hospitalizations, driven primarily by the effect on hospitalizations. Prespecified subgroup analysis in patients with EF above versus below 35% did not detect any trends toward reduced benefit in those with higher EF. Unfortunately, very few patients with EF above 50% were included in the trial. Thus it is not possible to draw conclusions about the benefit of beta blockers in HFpEF from this study. However, analysis of a large observational study found no mortality benefit of treatment with a beta blocker after a hospitalization for HF in patients with EF above 40%. By contrast, in patients with EF below 40%, a clear mortality benefit was found, consistent with the results of randomized trials of beta blockers with HFrEF.

Topcat.

Mineralocorticoid receptor antagonists (MRAs) have been shown to improve measures of diastolic function and exercise capacity in HFpEF patients. Furthermore, MRAs have shown favorable effects on LV load (both preload and afterload) and myocardial fibrosis. The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trail was performed to determine whether treatment with spironolactone would improve clinical outcomes in patients with symptomatic HFpEF. TOPCAT was a randomized, double-blind trial; 3445 patients with symptomatic HFpEF (EF ≥45%) were assigned to receive either spironolactone (15 to 45 mg daily) or placebo. The primary outcome was a composite of death from CV causes, aborted cardiac arrest, or hospitalization for the management of HF. With a mean follow-up of 3.3 years, the primary outcome occurred in 18.6% of the spironolactone group and 20.4% of the placebo group (hazard ratio [HR], 0.89; 95% CI 0.77 to 1.04; P = 0.14).[81] Although the primary endpoint of the TOPCAT trial was not significant statistically, hospitalization for HF, which was one of the components of the primary endpoint, was significantly lower in the spironolactone group than the placebo group (12.0% versus 14.2%; HR, 0.83; 95% CI 0.69 to 0.99, P = 0.04). Further analysis of TOPCAT found that (1) patients enrolled from Russia and Georgia had rates of HF hospitalization and CV mortality roughly equivalent to age- and gender-matched controls, suggesting that they did not have symptomatic HFpEF, and (2) enrolled patients from Russia and Georgia who were treated with spironolactone had no significant changes in blood pressure, creatinine, or potassium, and the metabolic product of spironolactone was low or undetected, suggesting that these patients were likely not compliant with drug therapy. A non-prespecified post hoc analysis of TOPCAT that excluded patients enrolled in Russian and Georgian sites showed that there was a clear and significant reduction in the primary study endpoint (HR, 0.82; 95% CI 0.69 to 0.98).[82]

Champion.

See discussion later, Remote Monitoring Systems to Help Tailor Management.

Relax.

Because phosphodiesterase-5 (PDE5) metabolizes the NO and NP systems' second-messenger cyclic guanosine monophosphate, it was hypothesized that PDE5 inhibition may increase NO and NP actions in the heart, vasculature, and kidneys and improve clinical status in HFpEF. Early phase II and single-center studies suggested that the PDE5 inhibitor sildenafil would have salutary effects in patients with HFpEF, but the Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction (RELAX) trial showed that sildenafil did not improve exercise capacity or clinical status.[83] This was a moderate-sized (216 patients), short-term (24 weeks) study performed by

the National Heart, Lung and Blood Institute (NHLBI)–sponsored Heart Failure Clinical Research Network (HFCRN).[83]

NEAT-HFpEF.

Because the hemodynamic effects of nitrates might attenuate pulmonary congestion with exertion and improve exercise capacity in HFpEF, the Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT-HFpEF) trial was performed to test the hypothesis that extended-release isosorbide mononitrate would enhance the daily activity level in patients with HFpEF, as assessed by patient-worn accelerometers. This was a moderate-sized (110 patients), short-term (6 weeks) study also performed by the NHLBI-sponsored HFCRN. HFpEF patients who received isosorbide mononitrate were less active and did not have better quality of life or submaximal exercise capacity than patients who received placebo.[84] Current studies are now focused on the potential use of organic nitrites in oral and inhaled preparations that target the nitrate-nitrite-NO pathway.

Phase II Studies of Novel Management Strategies for HFpEF

Several novel approaches to the management of HFpEF are being developed and examined in phase II and phase III trials. These include treatment with the angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan (Entresto), oral and inhaled nitrites, serelaxin, soluble guanaline cyclase agonists, and placement of atrial septostomy device. Sacubitril/valsartan has progressed to a full phase III trial.

Prospective comparison of ARNI versus ARB on Management of Heart Failure with Preserved Ejection Fraction (PARAMOUNT) was a phase II, randomized, parallel-group, double-blind, multicenter trial in patients with NYHA Class II or III HFpEF (EF >45%) and NT-proBNP level greater than 400 pg/mL.[85] The ARNI sacubitril/valsartan appears to have antifibrotic effects.[85] A cohort of 149 patients were assigned to receive therapy with sacubitril/valsartan (200 mg twice daily) and another 152 patients to receive valsartan (160 mg twice daily) for 36 weeks. The primary endpoint was change in NT-proBNP from baseline to 12 weeks. At 12 weeks, sacubitril/valsartan significantly reduced NT-proBNP by approximately 15%, compared with valsartan (no significant change; for difference in response, $P = 0.005$). At 36 weeks, sacubitril/valsartan significantly reduced LA volume by approximately 5% compared with valsartan (no significant change; for difference in response, $P = 0.003$). Sacubitril/valsartan improved NHYA functional class versus valsartan ($P = 0.05$). Sacubitril/valsartan was well tolerated, with adverse effects similar to those for valsartan. Whether these findings will translate into improved outcomes is being tested in a large randomized trial, PARAGON-HF.

Management of Heart Failure Patients with Preserved Ejection Fraction

The practical clinical management of HFpEF has three main components. The first aspect of management is reduction and prevention of pulmonary and peripheral venous congestion. These objectives can be accomplished with fluid and sodium restriction, judicious use of diuretics and nitrates, selective application of neurohormonal modulation, and appropriate remote monitoring–based tailored care. The second component is aggressive treatment of antecedent and comorbid diseases. Strategies include controlling blood pressure at rest and modifying blood pressure response to exercise, controlling glucose, treating and preventing ischemia, maintaining adequate renal function, and treating obesity with medical

and surgical weight loss management and exercise training. The third component of management is optimization of cardiac functional status—to prevent excessive tachycardia or bradycardia, to match heart rate to metabolic needs, to maintain or restore normal sinus rhythm, and to control ventricular response rate during atrial arrhythmias.

Nonpharmacologic Therapy

General measures that may be used in the management of patients with HFpEF include attention to diet and lifestyle, avoidance or reversal of obesity, increase in exercise, adherence to management strategies, daily monitoring of weight, patient education, and close medical follow-up using facilitated home management. Sodium restriction to less than 2 g/day may be effective. Excessive fluid volume intake should be avoided but balanced with respect to renal function (see later). If sodium and fluid restriction together with diuretic use results in decreased glomerular filtration rate (GFR), optimal volume status may be characterized by some amount of permissive peripheral edema. Modest-sized randomized studies have demonstrated that exercise training in patients with HFpEF improves exercise tolerance, although the effects on indices of diastolic function have been variable.[86,87]

Treatment of Comorbid Conditions

Patients with HFpEF frequently have important antecedent and comorbid diseases that can contribute to the development of HFpEF, affect its clinical severity, and precipitate decompensation. Accordingly, treating comorbid illnesses is an important element of management of patients with HFpEF. The most important and frequent comorbid conditions include arterial hypertension, obesity, diabetes, chronic kidney disease, obstructive sleep apnea, and anemia.

Most patients (>85%) with HFpEF have either current or previous hypertension. Untreated hypertension is a strong risk factor for the development of HF. Treatment of systolic hypertension in elderly patients (who have the highest risk for development of HFpEF) is associated with a more than 50% reduction in HF frequency.[86] Evidence-based therapy of HFpEF therefore includes control of systolic hypertension. The goal of therapy is systolic arterial pressure below 140 mm Hg and diastolic blood pressure below 90 mm Hg. However, recent large RCTs on hypertension suggest that even lower blood pressure targets less than 120 mm Hg systolic pressure may reduce the incident development of HFpEF.[88,89] Because of the arterial stiffening present in many patients, especially the elderly, adequate blood pressure control may be difficult to achieve. These patients also are prone to the development of orthostatic hypotension. Adequate treatment of patients with hypertensive heart disease includes not only control of the blood pressure but also prevention of LV hypertrophy or measures to induce regression of the hypertrophy, which will lead to reduced morbidity and mortality, improved exercise tolerance, and improved diastolic function.[90]

Diabetes and obstructive sleep apnea are common in HFpEF and are associated with worse outcomes. The available data suggest that treatment of diabetes and sleep apnea improves diastolic function and clinical status in patients with HFpEF. Thus, use of proven therapies for these conditions is an important component of managing patients with HFpEF.

Obesity is highly prevalent among patients with HFpEF. For example, the large ADHERE Registry found that more than half of patients weigh more than 172 pounds, and one quarter weigh more than 213 pounds. This is an impressive finding, because a majority of the patients are elderly women.[91] Obesity

itself impairs exercise intolerance but also contributes to the development of hypertension, diabetes, and sleep apnea. BMI is an important predictor of outcomes in patients with HFpEF. Weight loss produced by bariatric surgery, caloric reduction, and exercise improves indices of diastolic function. Thus, weight loss through diet, bariatric surgery, or appetite-suppressant drugs may represent an important management strategy for obese patients with HFpEF.

Chronic kidney disease frequently accompanies HFpEF and contributes to decompensations. GFR is an important predictor of outcomes in patients with HFpEF, with decreasing estimated GFR predicting increased event rates. Finally, anemia is common in HFpEF and is associated with a worse prognosis.

Sensor-Based Strategies

A number of novel sensor-based management strategies are being developed that provide facilitated management of HFpEF using remote monitoring–based tailored therapy. These include both implantable hemodynamic monitors (IHMs), subcutaneous and cutaneous sensors, noninvasive monitors (to assess measures of volume status, heart rate, rhythm, sympathetic tone, and activity), and serum/plasma-measured biomarkers.

Remote Monitoring Systems to Help Tailor Management

In the Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) trial, 70 patients with HFpEF (with EF >50%) were studied using an IHM that measured an estimated pulmonary artery diastolic pressure (ePAD), a measurement that in the absence of pulmonary vascular disease approximates PCWP. This study demonstrated that (1) patients with HFpEF demonstrated significantly increased filling pressures even while they were considered to be in a compensated state by their physicians; (2) these pressures rose further when they became decompensated; and (3) both baseline pressures and change from baseline pressures predicted outcomes, including the rates of HF hospitalization and CV mortality.[92-95] Additional measurements that reflect diastolic pressure and interstitial volume, such as baseline and change from baseline measures of thoracic impedance, also have been shown to predict outcomes, including rates of HF hospitalization and CV mortality.[96] The investigators hypothesized that modifying treatment based on data obtained from remote monitoring using an IHM would decrease baseline pressure, prevent an increase in pressure, and lower HF events in HFpEF. This hypothesis was tested in the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial. One half of the 152 enrolled patients with HFpEF were managed using pulmonary artery diastolic pressure information from an IHM; the other half received standard medical therapy without knowledge of the IHM data. Those in the active treatment arm demonstrated a 152% decrease in pulmonary artery diastolic and systolic pressures and a 52% decrease in HF-related events (both $P < 0.0001$ and control) and a decrease in CV mortality rate. In addition to IHM systems, noninvasive systems measuring indices of impedance and heart rate variability, rhythm, and activity are being developed and tested[96-99] (**see Fig. 26.8**).

Future Perspectives

Evidence-based guidelines for the treatment of symptomatic patients with HFrEF include the use of multiple drugs and devices. Thus, patients with HFrEF (EF <30%) and NYHA Class III status may be receiving a beta blocker, ACE inhibitor, or ARB; aldosterone antagonist; digitalis; diuretics; CRT; and implantable cardioverter-defibrillator (ICD) treatment. Each of these treatments targets a number of

different underlying pathophysiologic mechanisms that have been demonstrated to be operative in the development or progression of HFrEF. To date, when beta-blocker, ACE inhibitor, ARB, and digitalis treatments have been applied in HFpEF, outcomes have not been successful. These facts should inform the development of novel and effective management strategies for HFpEF in the following manner. First, the difference in outcomes of RCTs using the same agents in HFrEF versus HFpEF provides evidence of important and fundamental differences between these two heart failure syndromes. These differences include distinct underlying pathophysiologic targets for treatment. Novel and effective management of HFpEF must target these pathophysiologic mechanisms, including treatments that alter LV, myocardial, cellular/extracellular, and molecular structure and function. For example, treatments that restore calcium homeostasis, change the phosphorylation state of titin, reduce ECM fibrosis, and normalize natriuretic peptide levels may each contribute to improved outcomes in HFpEF. Second, comprehensive treatment will require multiple drugs and devices that individually target multiple independent mechanisms. This multitargeted approach is necessary because each mechanism, independent of other mechanisms, probably contributes to disease progression. Therefore, as in HFrEF patients, who often require five drugs and two devices for effective treatment, HFpEF patients will require a similar multitargeted approach with components that act synergistically to reduce morbidity and mortality in HFpEF.[100]

Guidelines

Heart Failure with a Preserved Ejection Fraction

Michael R. Zile and Sheldon E. Litwin

A joint task force of the American College of Cardiology and the American Heart Association (ACC/AHA) published updated comprehensive guidelines for the evaluation and management of heart failure with a preserved ejection fraction (HFpEF) in 2013.[1] An ACC/AHA/Heart Failure Society of America (HFSA)–focused update in 2017 made several important new recommendations to the guidelines (**Table 26G.1**).[2] The European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of heart failure with a preserved ejection fraction (HFpEF) were published 2016.[3] Most notably, the 2017 ACC/AHA/HFSA guidelines provide qualified support (class IIb, level of evidence B-R) for the use of aldosterone receptor antagonists to decrease hospitalizations. The 2017 guidelines also provide a class III: no benefit recommendation for the routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HFpEF.

TABLE 26G.1

ACC/AHA/HFSA Guidelines for Treatment of Patients with Stage C Heart Failure and Preserved Left Ventricular Ejection Fraction (HFpEF)

CLASS	INDICATION	LEVEL OF EVIDENCE
I	Systolic and diastolic blood pressure should be controlled in accordance with published clinical practice guidelines to prevent morbidity.	B
	Diuretics should be used for relief of symptoms due to volume overload.	C
IIa	Coronary revascularization is reasonable in patients with coronary artery disease in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic heart failure.	C
	Management of atrial fibrillation according to published clinical practice guidelines is reasonable to improve symptomatic heart failure.	C
	The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure.	C
IIb	In appropriately selected patients with HFpEF (with EF ≥45%, elevated BNP levels or heart failure admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations.	B-R
IIb	The use of ARBs might be considered to decrease hospitalizations.	B
III: no benefit	The routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HFpEF is ineffective.	B-R
III: no benefit	Routine use of nutritional supplements is not recommended.	C

ACE, Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *BNP,* B-type (brain) natriuretic peptide.

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Morbidity of HFpEF

Among patients with HFpEF, morbidity rates are comparable to those with HFrEF; heart failure (HF)–related hospital readmission rates approximate 50% at 6 months for both HFrEF and HFpEF. The lifetime burden for all-cause hospitalization is high and nearly equivalent for patients with HFpEF and those with HFrEF. All patients with heart failure (both HFpEF and HFrEF) have many comorbid conditions that

influence both morbidity and mortality. Like mortality, the HF hospitalization rates in patients with HFpEF are not based solely on the presence of antecedent or comorbidities themselves. Data from RCTs have shown that the HF hospitalization rates in patients with HFpEF (who have antecedent and comorbid factors such as hypertension, coronary artery disease, and diabetes mellitus) are more than twice those in patients with hypertension, CAD, or DM who do not have HFpEF (**Fig. 26.3D**).[1] Rates of progressive functional decline after hospital admission for HF also are similar in patients with HFpEF and those with HFrEF. In addition to HF-related hospitalizations, abnormalities in exercise tolerance, maximum myocardial oxygen consumption (MVO_2), and quality-of-life assessment are similar for HFrEF and HFpEF.

Conversion From Heart Failure with Preserved Ejection Fraction to Heart Failure with Reduced Ejection Fraction

Conversion from HFpEF to HFrEF is uncommon and generally is associated with an incident injury (e.g., myocardial ischemia, viral infection, alcohol abuse, cancer chemotherapy).[2-6] For example, in one study, 1233 patients with HF had serial echocardiograms to determine the time course of changes in the left ventricular ejection fraction (LVEF) over a 5-year observation period.[5] On average, the LVEF decreased by approximately 0.06 over 5 years in the HFpEF group, whereas it increased by nearly 0.07 in the HFrEF group. These rates should be interpreted in light of the following limitations: HFpEF and HFrEF were divided on the basis of an EF of 50%; this value is an arbitrary cutoff. Clearly, patients with EF of 51% and those with EF of 49% are not substantially different and are likely to cross back and forth across the threshold. In addition, no uniform deterioration in EF occurred in patients with HFpEF. Some experienced no fall in EF, and a majority (>60%) did not demonstrate a decline in EF below 50%. Another prospective study of 343 patients with concentric LV remodeling (but no HF) found that over 7 years, only 7% developed eccentric remodeling with LV dilation and a fall in EF.[6] Thus, although treatment of HFrEF may result in normalization of EF, a decline in EF in HFpEF appears usually to be caused by an intercurrent event, most frequently ischemic injury.

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Cellular Mechanisms of Myocardial Relaxation

The detachment of actin from myosin requires prompt decreases in cytosolic calcium concentrations during diastole. There are several causes for prolongation of the calcium transient (**see Chapter 24**), but particularly by reduced reuptake of calcium (Ca^{2+}) into the sarcoplasmic reticulum (SR) because of decreases in the amount or activity of the sarcoendoplasmic reticulum Ca^{2+}-ATPase (SERCA).[1] Beta-adrenergic stimulation activates protein kinase A (PKA), which phosphorylates phospholamban and removes its tonic inhibition of SERCA activity, hastening calcium reuptake and left ventricular (LV) relaxation. Beta-adrenergic/PKA-mediated phosphorylation of troponin I also hastens relaxation by decreasing calcium sensitivity, and reduced troponin I phosphorylation may accentuate afterload-induced changes in relaxation.[2] Impaired beta-adrenergic signaling is well established in HFrEF (**see Chapter 25**), in animal models of pressure overload with relevance to HFpEF, and with increasing clinical evidence in patients with HFpEF.[3] Chronic catecholamine activation contributes to beta-adrenergic receptor downregulation and desensitization, and catecholamine levels are elevated in HFpEF, suggesting that impaired beta-adrenergic signaling may contribute to relaxation impairment in HFpEF. More recently, chronotropic incompetence and impaired systolic and lusitropic reserve function have been reported in HF with normal (nl) EF, findings that further support a role for impaired beta-adrenergic signaling in HFpEF.[4-9] Phospholamban phosphorylation may also be reduced by increases in protein kinase C (PKC) through effects on protein phosphatases.[10] PKC activity is increased in HF with reduced EF and in animal models of pressure overload relevant to HFpEF. In addition, transsarcolemmal extrusion of calcium, while only 5% of all calcium movement in normal patients, is increased in animal models of pressure overload with relevance to HFpEF and appears to fail during decompensation. Therefore, impaired beta-adrenergic/PKA signaling, reduced SERCA amount and activity, increased PKC activity, and decreased Na-Ca exchanger function all contribute to the development of abnormal diastolic function and may provide potential novel therapeutic targets for HFpEF therapies.

Energy (ATP) supply influences relaxation by regulating calcium reuptake via SERCA and by influencing cross-bridge detachment at the myosin heads, where the phosphocreatine shuttle mechanism ensures delivery of adenosine triphosphate (ATP) from the mitochondria and removal of adenosine diphosphate (ADP) and inorganic phosphate (P_i) from the site of cross-bridge formation (**see Chapter 24**). Inadequate ATP and increased levels of ADP at the cross-bridge sites impair cross-bridge detachment and slow relaxation. Impaired relaxation is the first functional abnormality to occur during acute ischemia and with persistent ischemia is accompanied by parallel upward shifts of the diastolic pressure-volume relationship (decreased distensibility) due to rigor bonds. Both features may contribute to the elevated filling pressures with ischemia. Hypertrophied hearts are more sensitive to ischemia, with greater increases in filling pressures resulting from ischemia. Impaired creatinine kinase ATP kinetics have been described in patients with HFpEF and linked to impaired relaxation and systolic reserve function.[7]

Changes in myofilament proteins such as titin and extramyofilament proteins such as microtubules may also affect the elastic properties of the cardiomyocyte and alter diastolic function in patients with HFpEF. Changes in titin isoforms and phosphorylation state affect cardiomyocyte distensibility, as does microtubule polymerization state. These proteins, along with calcium homeostasis, myofilament function, and energetics, determine the elastic properties of the cardiomyocyte (and as a result the left ventricle) and determine the distending force necessary to achieve an adequate end-diastolic volume (EDV) and resultant stroke volume (SV).

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Limitations in Use of E/e′ Ratio

There are several situations where E/e′ may not provide an accurate assessment of pulmonary capillary wedge pressure (PCWP).[1] First, in a normal heart, e′ (early tissue velocity) occurs coincidentally with E (early transmitral flow velocity) and responds to changes in LA pressure. For example, E/e′ was not increased, but may decrease in response to massive fluid loading in normal experimental animals.[2] However, left atrial (LA) pressure is rarely elevated in patients with a normal heart.[3] Thus the failure of E/e′ to recognize elevated LA pressure in normal individuals is of little clinical importance. Second, E/e′ does not increase in patients with constrictive pericarditis despite elevated PCWP.[4] In fact, the medial e′ increases as constriction becomes worse, which results in a decrease in E/e′ as constriction becomes more severe and diastolic filling pressure increases (annulus paradoxus). If a patient has clinical signs of HF, especially with increased jugular venous pressure, a normal or increased medial e′ velocity strongly suggests constrictive pericarditis. Third, E/e′ may not provide an estimate of LA pressure in patients with mitral stenosis or mitral regurgitation, especially without a reduction in EF.[5,6] The mitral annular velocity should not work as well in patients with aortic or mitral valve replacement and mitral annulus calcification. However, this issue has not been systematically evaluated. Fourth, although E/e′ correlates with LA pressure in patients with hypertrophic cardiomyopathy, there is substantial scatter, limiting its use

alone in an individual patient.[7]

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Indices of Myocardial Contractile Function and Assessment of Exercise Capacity in Heart Failure with Preserved Ejection Fraction

Indices of Myocardial Contractile Function

Although global left ventricular (LV) systolic performance at rest is normal in HFpEF, indices of myocardial contractile function such as midwall shortening, long-axis shortening, global longitudinal strain (GLS) and strain rate, and reduced apical systolic torsion may be reduced.[78] These regional abnormalities on LV ejection performance appear to be offset by concentric remodeling or hypertrophy, and enhanced circumferential shortening offsets the impact. Although these abnormalities of regional performance occur during systole, their greatest impact may occur during diastole. Decreased long-axis shortening and torsion lessen the diastolic recoil of elastic elements compressed during ejection, thereby diminishing the ability of the left ventricle to function as a suction pump, so LV filling becomes more dependent on left atrial (LA) pressure. Thus these regional systolic abnormalities result in significant increases in pulmonary venous filling pressures and symptoms of congestion and volume overload.

During exercise, patients with HFpEF have a decreased ability to augment indices of LV chamber systolic performance, function, and contractility. This decrement in adaptability to the demands of exercise may result from abnormalities in diastolic function, chronotropic incompetence, decreased response to sympathetic and renin-angiotensin-aldosterone system (RAAS) stimulation, or exaggerated increase in afterload. For example, decreased diastolic distensibility prevents the left ventricle from recruiting Starling forces in patients with HFpEF; thus abnormal diastolic function limits augmentation of systolic properties. In addition, because hypertensive heart disease is common in HFpEF, many patients with HFpEF have limited exercise tolerance because of the exaggerated increase in blood pressure that accompanies exercise; this increased afterload prolongs relaxation and decreases diastolic distensibility. Finally, because systolic and arterial elastances are increased in HFpEF, exercise-induced increases in

RAAS and sympathetic stimulation are unable to augment systolic properties sufficiently to maintain adequate stroke volume.[79]

Assessment of Exercise Capacity

Patients with HFpEF have a symptomatic disability that is evident by a reduction in their exercise tolerance. This disability can be objectively assessed by a 6-minute hall walk (6MHW), standard exercise treadmill, and cardiopulmonary exercise testing. These tests have important diagnostic utility in HFpEF patients, particularly if the cause of the exercise intolerance is unclear or the diagnosis is uncertain. In addition, cardiopulmonary exercise testing can identify poor motivation, deconditioning, and pulmonary disease as alternate explanations for dyspnea (**see Chapter 13**). These objective measures of exercise tolerance are similarly impaired in HFpEF and HFrEF, with equivalent decreases in time and distance on the treadmill and decreases in maximum myocardial oxygen consumption (MVO_2). Exercise testing can identify factors that contribute to the clinical syndrome of HFpEF and that potentially can be modified. For example, an exaggerated increase in systolic arterial pressure during exercise can cause load-dependent diastolic dysfunction. Pharmacologic reduction of this response can improve exercise tolerance in HFpEF. Because augmentation of the stroke volume is limited in HFpEF, the cardiac output is very dependent on increased heart rate. In HFpEF patients with an inadequate increase in heart rate with exercise (chronotropic incompetence), limiting beta-adrenergic blockers or even rate-responsive pacing may improve exercise tolerance. Finally, exercise training improves exercise tolerance in HFpEF by reversing some of the effects of deconditioning. Exercise training may also improve indices of diastolic function. Changes in exercise capacity that limit functional capacity can be assessed by a variety of quality of life (QOL) measurements. A number of QOL surveys have been validated and used in studies in HFpEF. These include Quality of Life in Severe Heart Failure Questionnaire (QLSHFQ), the Chronic Heart Failure Questionnaire (CHQ), the Left Ventricular Dysfunction Questionnaire (LVD), and the Minnesota Living with Heart Failure Questionnaire (MLHFQ). The three most commonly used are the QLSHFQ, CHQ, and MLHFQ.[1]

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27

Devices for Monitoring and Managing Heart Failure

William T. Abraham

The U.S. Food and Drug Administration (FDA) approval of the first cardiac resynchronization therapy (CRT) device in 2001 initiated a new era of implantable device therapies for the management of heart failure (HF). Since then, implantable cardioverter-defibrillators (ICDs) and combined CRT-ICD devices have also received FDA approval for the management of HF. ICDs became indicated for the primary prevention of all-cause mortality through a reduction in the incidence of sudden cardiac death (SCD) in patients with heart failure and reduced ejection fraction (HFrEF). Combined CRT-ICD devices were shown to reduce morbidity and mortality in HF patients with ventricular dyssynchrony, with a suggestion of additive benefit over a CRT device alone. In acknowledgment of the evidence-based benefits of these

devices, the 2005 update to the American College of Cardiology/American Heart Association (ACC/AHA) heart failure guideline strongly supported, with class I indications, the use of ICD and CRT devices in the management of eligible HF patients[1]; these indications were updated in 2013[2] (**see Table 27G.1**).

In addition to these therapeutic devices, implantable devices that monitor physiologic parameters such as patient activity level, heart rate variability, intrathoracic impedance, and hemodynamics have been developed. In some cases these data are already available in currently implantable CRT and ICD devices. The utility of such device-based diagnostic or monitoring information is unknown and currently under investigation. This chapter reviews the use of CRT and ICDs for the management of heart failure and discusses the potential utility of implantable HF-monitoring devices. The medical management of HF is discussed in **Chapters 25 and 26**.

Ventricular Dyssynchrony: the Target of Cardiac Resynchronization Therapy

Several conduction abnormalities are commonly seen in association with chronic heart failure. Among these are abnormalities of ventricular conduction, such as bundle branch blocks, that alter the timing and pattern of ventricular contraction so as to place the already failing heart at a further mechanical disadvantage. These ventricular conduction delays produce suboptimal ventricular filling, a reduction in left ventricular (LV) contractility, prolonged duration of mitral regurgitation, and paradoxical septal wall motion.[3,4] Taken together, these mechanical manifestations of altered ventricular conduction have been termed *ventricular dyssynchrony*. Ventricular dyssynchrony has been defined by a prolonged QRS duration, generally greater than 120 milliseconds, on the surface electrocardiogram (ECG). By this definition, about one third of patients with systolic HF have ventricular dyssynchrony. In addition to reducing the ability of the failing heart to eject blood, ventricular dyssynchrony has also been associated with increased mortality in HF patients.

Ventricular dyssynchrony may now be addressed with pacing therapy, through the implantation of pacing leads to both right and left ventricles. This form of pacing therapy is now known as *cardiac resynchronization therapy*. Favorable single-case experiences with CRT in the mid-1990s lead to small observational studies evaluating the acute effects of CRT on hemodynamics and other measures of cardiac performance.[5] These studies provided additional proof of concept supporting the use of CRT. Several uncontrolled or unblinded studies soon followed to evaluate further the acute and longer-term effects of CRT on clinical status in HF patients.[5] The results of these trials were equally encouraging, with patients demonstrating consistent, sustained improvement in exercise tolerance, quality of life, and New York Heart Association (NYHA) functional class. Finally, large-scale randomized controlled trials (RCTs) confirmed the beneficial effects of CRT on functional status and outcomes, leading to the initial indications for this therapy. More recent trials have both expanded and limited the indications for CRT.

Randomized Controlled Trials of CRT in NYHA Class III and IV Patients

More than 4000 patients have been evaluated in RCTs of CRT in NYHA Functional Class III and IV heart failure. The following RCTs are considered among the landmark studies of CRT in this patient population: the Multisite Stimulation in Cardiomyopathy (MUSTIC) studies,[6,7] Multicenter InSync

Randomized Clinical Evaluation (MIRACLE) trial,[8,9] MIRACLE ICD trial,[10] CONTAK CD trial,[11] Cardiac Resynchronization in Heart Failure (CARE HF) trial,[12,13] and Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial.[14,15] To understand the clinical benefits, risks, and limitations of CRT with or without an ICD, these studies are reviewed.

Multisite Stimulation in Cardiomyopathy Trials

The MUSTIC trials were designed to evaluate the safety and efficacy of CRT in patients with advanced HF, ventricular dyssynchrony, and either normal sinus rhythm[6] or atrial fibrillation (AF).[7] They represent the first randomized single-blinded trials of CRT for HF. The first study involved 58 randomized patients with NYHA Class III HF, normal sinus rhythm, and a QRS duration of at least 150 milliseconds. All patients were implanted with a CRT device, and after a run-in period, patients were randomized to either active pacing or no pacing. After 12 weeks, patients were crossed-over and remained in the alternate study assignment for 12 weeks. The second MUSTIC study involved fewer patients (only 37 completers) with AF and a slow ventricular rate (either spontaneously or from radiofrequency ablation). A VVIR biventricular pacemaker and leads for each ventricle were implanted, and the same randomization procedure described above was applied; however, biventricular VVIR pacing versus single-site right ventricular VVIR pacing (rather than no pacing) were compared in this group of patients with AF.

The primary endpoints for MUSTIC were exercise tolerance assessed by measurement of peak oxygen consumption (VO_2) or the 6-minute hall walk distance (6MHWD) test and quality of life determined using the Minnesota Living with Heart Failure (MLWHF) questionnaire. Secondary endpoints included rehospitalizations and/or drug therapy modifications for worsening HF. Results from the normal sinus rhythm arm of MUSTIC provided strong evidence of benefit. The mean 6MHWD was 23% greater with CRT than without CRT ($P < 0.001$). Significant improvement was also seen in quality of life and NYHA functional class ranking. There were fewer hospitalizations during active resynchronization therapy. The AF cohort evaluated in MUSTIC demonstrated similar improvements, although the magnitude of benefit was slightly less.

Multicenter InSync Randomized Clinical Evaluation

MIRACLE was the first prospective, randomized, double-blind, parallel-controlled clinical trial designed to evaluate the benefits of CRT.[8,9] Primary endpoints were NYHA class, quality of life score (using the MLWHF questionnaire), and 6MHWD. Secondary endpoints included assessments of a composite clinical response, cardiopulmonary exercise performance, cardiac structure and function, a variety of measures of worsening HF, and combined morbidity and mortality.

The MIRACLE trial was conducted between 1998 and 2000. It included 453 patients with moderate to severe symptoms of HF associated with a left ventricular ejection fraction (LVEF) of 35% or less and a QRS duration of at least 130 milliseconds. They were randomized (double-blind) to CRT ($n = 228$) or to a control group ($n = 225$) for 6 months, while conventional therapy for HF was maintained. Compared with the control group, patients randomized to CRT demonstrated a significant improvement in quality of life score (–18.0 versus –9.0 points; $P = 0.001$), 6MHWD (+39 vs. +10 meters [m]; $P = 0.005$), NYHA functional class ranking (–1.0 vs. 0.0 class; $P < 0.001$), treadmill exercise time (+81 vs. +19 sec; $P = 0.001$), peak VO_2 (+1.1 vs. 0.1 mL/kg/min; $P < 0.01$), and LVEF (+4.6% vs. –0.2%; $P < 0.001$). Patients randomized to CRT demonstrated a highly significant improvement in a composite clinical HF response endpoint, compared to controls, suggesting an overall improvement in HF clinical status (**Fig. 27.1**). In addition, when compared with the control group, fewer patients in the CRT group required hospitalization

(8% vs. 15%) or intravenous medications (7% and 15%) for the treatment of worsening HF (both $P < 0.05$). In the CRT group, the 50% reduction in hospitalization was accompanied by a significant reduction in length of stay, resulting in a 77% decrease in total days hospitalized over 6 months compared to the control group. The major limitation of the therapy resulted from unsuccessful implantation of the device in 8% of patients. The results of this trial led to FDA approval of the InSync system in August 2001, the first approved CRT system in America, allowing the introduction of CRT into clinical practice.

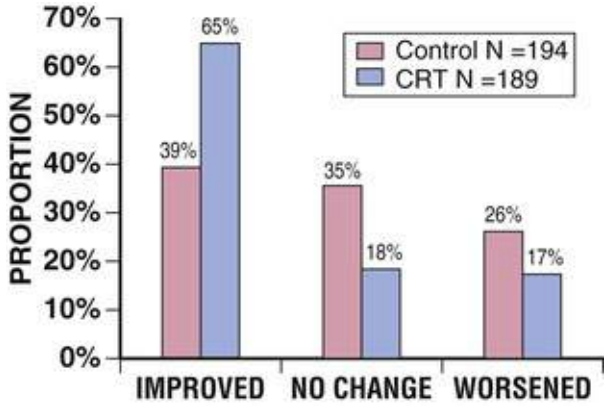

FIGURE 27.1 Effect of cardiac resynchronization therapy (CRT) on a composite clinical response endpoint in the MIRACLE trial. *Worsened:* Patient dies; or is hospitalized due to or associated with worsening heart failure; or demonstrates worsening in NYHA class at last observation carried forward (LOCF) or moderate-marked worsening of patient global assessment score at LOCF. *Improved:* Patient has not worsened (as defined above) and demonstrates improvement in NYHA class at LOCF and/or moderate-marked improvement in patient global assessment score at LOCF. *Unchanged:* Patient is neither improved nor worsened. $P < 0.001$ for chi-square analysis. (Modified from Abraham WT, Fisher WG, Smith AL, et al, for the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Investigators and Coordinators. Double-blind, randomized controlled trial of cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845-53.)

The MIRACLE trial also provided persuasive evidence supporting the occurrence of reverse LV remodeling with chronic CRT. Serial Doppler echocardiograms were obtained at baseline, 3 months, and 6 months in a subset of 323 patients. CRT for 6 months was associated with reduced end-diastolic and end-systolic volumes (both $P < 0.001$), reduced LV mass ($P < 0.01$), increased LVEF ($P < 0.001$), reduced mitral regurgitant blood flow ($P < 0.001$), and improved myocardial performance index ($P < 0.001$), compared with controls. These effects are similar to those seen with beta-adrenergic blockade in HF but were seen in MIRACLE in patients already receiving beta-blocker therapy.

Multicenter InSync–Implantable Cardioverter-Defibrillator Randomized Clinical Evaluation

The MIRACLE ICD study was designed to be almost identical to the MIRACLE trial. MIRACLE ICD was a prospective, multicenter, randomized, double-blind, parallel-controlled clinical trial intended to assess the safety and efficacy of a combined CRT-ICD system in patients with dilated cardiomyopathy (LVEF ≤35%; left ventricular end-diastolic dimension [LVEDD] ≥55 mm), NYHA Class III or IV HF, ventricular dyssynchrony (QRS ≥130 msec), and an indication for an ICD.[10] Primary and secondary efficacy measures were essentially the same as those evaluated in the MIRACLE trial, but also included measures of ICD function.

Of 369 patients receiving devices and randomized, 182 were controls (ICD activate, CRT inactive), and 187 were in the resynchronization group (ICD activate, CRT active). At 6 months, patients assigned to active CRT had a greater improvement in median quality-of-life score (–17.5 vs. –11.0; $P = 0.02$) and

functional class (–1 vs. 0; $P = 0.007$) than controls, but were no different than controls in the change in distance walked in 6 minutes (55 vs. 53 m; $P = 0.36$). Peak $\dot{V}O_2$ increased by 1.1 mL/kg/min in the resynchronization group, versus 0.1 mL/kg/min in controls ($P = 0.04$), while treadmill exercise duration increased by 56 seconds in the CRT group and decreased by 11 seconds in controls ($P = 0.0006$). The magnitude of improvement was comparable to that seen in the MIRACLE trial, suggesting that HF patients with an ICD indication benefit as much from CRT as those without an indication for an ICD. The combined CRT-ICD device used in this study was approved by the FDA in June 2002 for use in NYHA Class III and IV systolic HF patients with ventricular dyssynchrony and an ICD indication.

CONTAK CD

The CONTAK CD trial enrolled 581 symptomatic HF patients with ventricular dyssynchrony and malignant ventricular tachyarrhythmias, who were all candidates for an ICD.[11] Following unsuccessful implant attempts and withdrawals, 490 patients were available for analysis. The study did not meet its primary endpoint of a reduction in disease progression, defined by a composite endpoint of HF hospitalization, all-cause mortality, and ventricular arrhythmia requiring defibrillator therapies, although the trends were in a direction favoring improved outcomes with CRT. However, the CONTAK CD trial did demonstrate statistically significant improvements in peak $\dot{V}O_2$ and quality of life in the resynchronization group compared to controls, although quality of life was improved only in NYHA Class III and IV patients without right bundle branch block. LV dimensions were also reduced, and LVEF increased, as seen in other trials of CRT. Importantly, the improvement seen in peak $\dot{V}O_2$ with cardiac resynchronization was again comparable to that observed in the MIRACLE trial. Improvements in NYHA functional class were not observed in this study. The CONTAK CD device was approved by the FDA for use in NYHA Class III and IV systolic HF patients with ventricular dyssynchrony and an ICD indication in May 2002.

Cardiac Resynchronization in Heart Failure Trial

The CARE HF trial was designed to evaluate the effects of CRT without an ICD on morbidity and mortality in patients with NYHA Class III or IV HF and ventricular dyssynchrony.[12,13] In this unblended RCT, 819 patients with an LVEF of 35% or less and ventricular dyssynchrony (defined as QRS duration ≥150 msec or 120-150 msec, with echocardiographic evidence of dyssynchrony) were followed for an average of 29.4 months; 404 patients were assigned to receive optimal medical therapy alone, and 409 were randomized to optimal medical therapy plus CRT. The primary endpoint, risk of death from any cause or unplanned hospitalization for a major cardiac event, analyzed as time to first event, was significantly reduced by 37% in the treatment group compared to the control group (hazard ratio [HR], 0.63; 95% confidence interval [CI] 0.51 to 0.77; $P < 0.001$). In the CRT group, 82 patients (20%) died during follow-up compared to 120 patients (30%) in the medical group, yielding a significant 36% reduction in all-cause mortality with CRT (HR, 0.64; 95% CI 0.48 to 0.85; $P < 0.002$; **Fig. 27.2**). CRT also significantly reduced the risk of unplanned hospitalization for a major cardiac event by 39%, all-cause mortality plus HF hospitalization by 46%, and HF hospitalization by 52%.

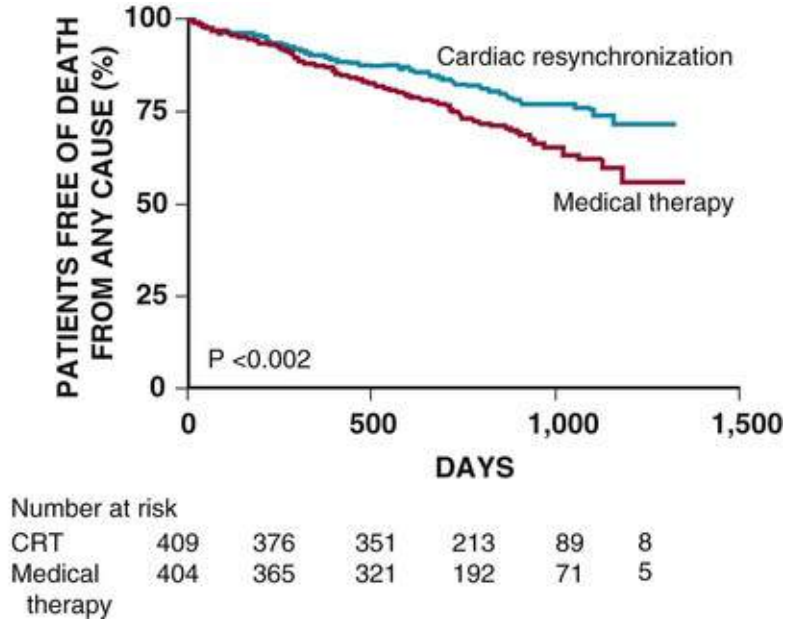

FIGURE 27.2 Kaplan-Meier estimates of survival in patients randomized to CRT compared to conventional medical therapy in the CARE-HF trial. (Modified from Cleland JGF, Daubert JC, Erdmann E, et al, for the Cardiac Resynchronization–Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49.)

Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure

Begun in early 2000, COMPANION was a multicenter, prospective RCT designed to compare drug therapy alone to drug therapy combined with CRT in patients with dilated cardiomyopathy, an intraventricular conduction defect (IVCD), NYHA Class III or IV HF, and no indication for a device.[14,15] The COMPANION trial randomized 1520 patients into one of three treatment groups in a 1 : 2:2 allocation: group I (308 patients) received optimal medical care only, group II (617 patients) received optimal medical care and the Guidant CONTAK TR (biventricular pulse generator), and group III (595 patients) received optimal medical care and the CONTAK CD (combined HF/bradycardia-tachycardia device). The primary endpoint was a composite of all-cause mortality and all-cause hospitalization, measured as time to first event, beginning from time of randomization. Secondary endpoints included all-cause mortality and a variety of measures of CV morbidity. Compared to optimal medical therapy alone, the combined endpoint of mortality or HF hospitalization was reduced by 35% for patients receiving CRT and 40% for patients receiving CRT-ICD (both $P < 0.001$). For the mortality endpoint alone, CRT patients had a 24% risk reduction ($P = 0.060$), and CRT-ICD patients experienced a risk reduction of 36% ($P < 0.003$), compared to optimal medical therapy (**Fig. 27.3**). COMPANION confirmed the results of earlier CRT trials in improving symptoms, exercise tolerance, and quality of life for HF patients with ventricular dyssynchrony. In addition, COMPANION showed for the first time the impact of CRT-ICD in reducing all-cause mortality and suggested incremental benefit from combined device therapies.

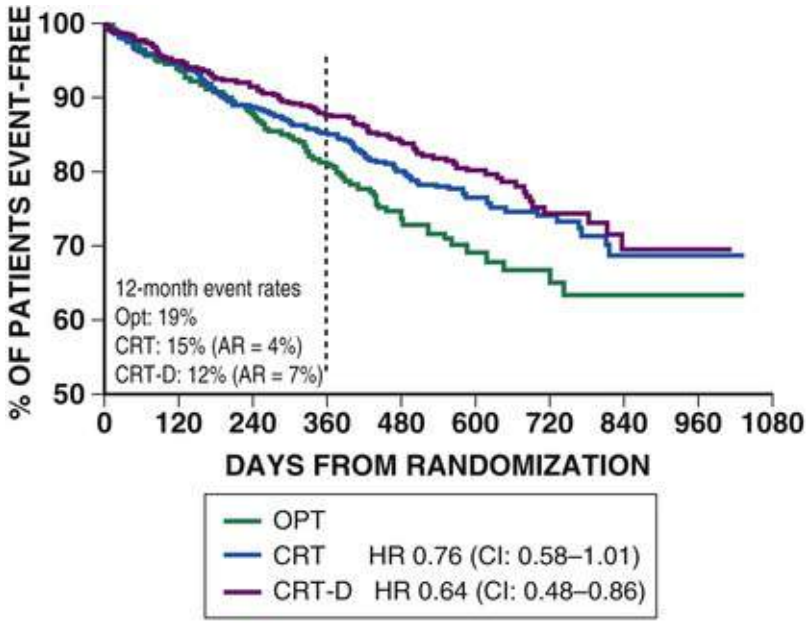

FIGURE 27.3 Kaplan-Meier estimates of the time to death from any cause in patients randomized to optimal medical therapy (OPT) alone versus OPT with CRT alone versus OPT with a combined CRT-ICD device in the COMPANION trial; AR, absolute risk; HR, hazard ratio; RR, relative risk. (Modified from Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-50.)

Guideline Recommendation

These trials in NYHA Class III and IV HF patients established the initial guideline recommendation for CRT: “Patients with LVEF less than or equal to 35%, sinus rhythm, and NYHA Functional Class III or ambulatory Class IV symptoms despite recommended optimal medical therapy and who have cardiac dyssynchrony, which is currently defined as a QRS greater than or equal to 0.120 seconds, should receive CRT, with or without an ICD, unless contraindicated (Level of Evidence: A).”[1] These guidelines have been updated and are discussed later under indications for CRT.

More recent clinical trials in CRT have focused on delaying progression of HF in asymptomatic or less symptomatic patients. The MIRACLE-ICD II trial suggested such a benefit in a small cohort of NYHA Class II patients,[16] leading to subsequent large-scale trials in this population.

Randomized Controlled Trials of CRT in NYHA Class I and II Patients

More than 4500 patients have been evaluated in trials of CRT in NYHA Functional Class I and II heart failure. The following RCTs are considered among the landmark studies of CRT in this patient population: the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial,[17,18] Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT),[19,20] and Resynchronization/defibrillation for Ambulatory Heart Failure Trial (RAFT).[21]

Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction Trial

The REVERSE trial was a double-blinded RCT designed to address the benefit of CRT on heart failure morbidity in patients with mild HF compared to optimal medical therapy alone;[17,18] 610 patients with NYHA Class I and II HF (QRS ≥120 msec, LVEF ≤40%, LVEDD ≥55 mm) were randomized. All patients received a CRT device with or without an ICD, and 191 were assigned to the control of optimal medical therapy alone (CRT off) and 419 to the CRT group combined with optimal medical therapy. The primary endpoint was a clinical composite HF score. The study goal was to determine the effect on preventing disease progression, so a "worsened" status was considered a negative outcome.

While the percent worsened in the clinical composite response endpoint was not significantly reduced in the CRT compared to control group (16% vs. 21%; $P = 0.10$), a significant benefit of CRT was seen in improvement in ventricular structure and function and in HF morbidity, which was also significantly improved with a 53% relative risk reduction (RRR) in the time to first HF hospitalization (HR, 0.47; $P = 0.03$). Thus, REVERSE was the first large, randomized, multicenter trial to demonstrate the potential for CRT to slow progression of disease through reverse remodeling in NYHA Class I and II HF patients with ventricular dyssynchrony.

Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy

The MADIT-CRT trial was a multicenter RCT designed to address the potential survival and morbidity benefit of CRT in NYHA Class I and II HF patients by assessing the reduction in risk of death and nonfatal HF events in this population.[19] Prophylactic CRT combined with an ICD was compared to ICD only in 1820 patients (LVEF ≤30%, QRS ≥130 msec) with either an ischemic (Class I patients) or any (Class II patients) cause. The study was not blinded; the treating physicians were aware of the study group assignments.

During the average follow-up of 2.4 years, the primary endpoint of death from any cause or nonfatal HF event occurred in 17.2% of the CRT-ICD group versus 25.2% of the ICD-only group, with RRR of 34% (HR, 0.66; 95% CI 0.52 to 0.84; $P = 0.001$). This significant benefit was driven by a 41% reduction in HF events (13.9% vs. 22.8%; HR, 0.59; 95% CI 0.47 to 0.74; $P < 0.001$). In terms of prespecified subgroups, both ischemic and nonischemic groups showed benefit with CRT; however, a greater benefit was noted for women versus men and in patients with QRS of 150 milliseconds or longer. Another factor predicting CRT responsiveness in this trial was QRS morphology; patients benefiting most had left bundle branch block (LBBB).[22] The MADIT-CRT trial led the FDA to expand the indication for CRT to NYHA Class II or ischemic Class I patients, with LVEF less than 30%, QRS duration longer than 130 milliseconds, and LBBB, for the devices evaluated in this study.

Resynchronization/Defibrillation for Ambulatory Heart Failure Trial

The RAFT trial differed from the REVERSE and MADIT-CRT trials in that, initially, patients in NYHA Class II and III were included. However, after data from the CARE HF trial showed a clear reduction in mortality for patients in NYHA Class III, the protocol was revised to include only patients in Class II. Importantly, the RAFT trial was the first to show a mortality benefit of combined CRT-ICD over an ICD alone, and a mortality reduction with the addition of CRT in patients in NYHA Class II HF.[21] The primary outcome of all-cause mortality or hospitalization for HF occurred in 40% and 33% of the ICD and CRT-ICD groups, respectively, with a significant delay to time of occurrence of the primary outcome in the CRT-ICD group. Overall, 23.5% of the patients died. The 5-year actuarial death rate was lower (28.6% vs. 34.6%) and the time to death longer in the CRT-ICD patients than in the ICD group. On the basis of

these results, 14 patients would need to be treated with a CRT-ICD for 5 years to prevent one death, compared to those treated with an ICD alone. These benefits were at the expense of an increased rate of procedure-related adverse events.

Nevertheless, the results from RAFT and REVERSE resulted in the FDA expanding the indication for certain CRT devices to include patients with mildly symptomatic HF (NYHA Class II, with LVEF ≤30%, LBBB, and QRS ≥130 msec).

CRT in Patients with Narrow QRS Complex

Mechanical dyssynchrony occurs in patients with a narrow QRS complex, suggesting the potential usefulness of CRT in HF patients with narrow QRS and imaging-identified (usually echocardiographic) ventricular dyssynchrony. Preliminary studies suggested the benefits of CRT in such patients; however, a definitive trial, Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT), did not confirm these benefits.[23] The EchoCRT trial evaluated the effect of CRT in patients with NYHA Class III or IV HF, LVEF of 35% or less, QRS duration less than 130 milliseconds, and echocardiographic evidence of LV dyssynchrony. All patients underwent device implantation and were randomly assigned to have CRT turned on or off. The primary efficacy outcome was the composite of death from any cause or first hospitalization for worsening HF. The study was stopped for futility on the recommendation of the Data and Safety Monitoring Board. Of the 809 randomized patients followed for a mean of 19.4 months, the primary outcome occurred in 116 of 404 patients in the CRT group, versus 102 of 405 in the control group (28.7% vs. 25.2%; HR, 1.20; 95% CI 0.92 to 1.57; *P* = 0.15) (**Fig. 27.4**). There were 45 deaths in the CRT group and 26 in the control group (11.1% vs. 6.4%; HR, 1.81; 95% CI 1.11 to 2.93; *P* = 0.02), demonstrating the potential for harm in using CRT in narrow-QRS patients. Thus, CRT is considered contraindicated in these patients.

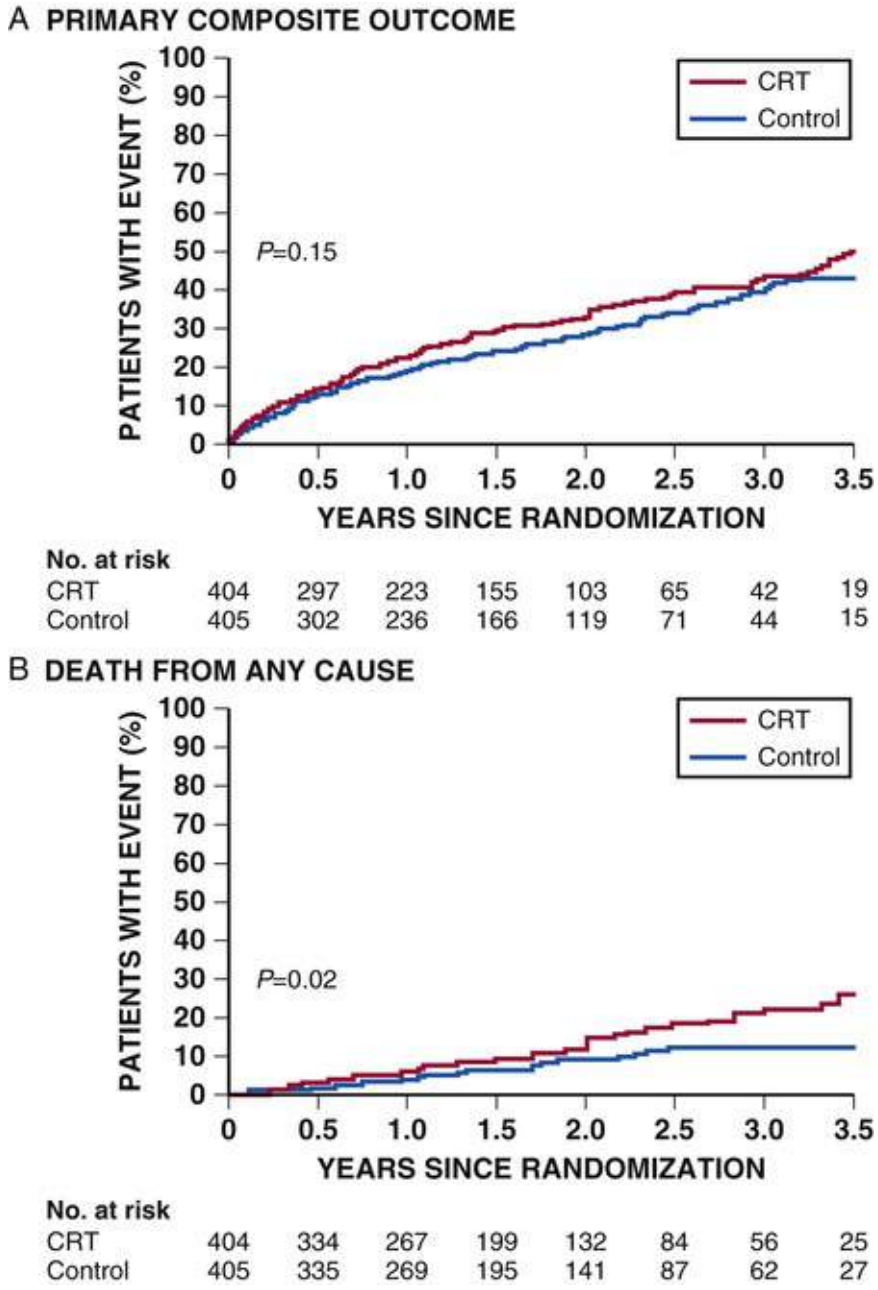

FIGURE 27.4 Effect of CRT on morbidity and mortality in heart failure patients with narrow QRS complex and echocardiographic ventricular dyssynchrony. **A,** Kaplan-Meier curves for the primary composite outcome of death from any cause or hospitalization for heart failure. **B,** Kaplan–Meier curves for death from any cause. (From Ruschitzka F, Abraham WT, Singh JP, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med 2013;369:1395-405.)

Indications for CRT in Patients with Heart Failure

Since the original 2005 guideline recommendation for CRT, the indications for CRT have been expanded to less symptomatic patients, but also limited on the basis of QRS morphology and QRS duration.[2,24] Current guideline recommendations define ventricular dyssynchrony by QRS duration, rather than by imaging (echocardiography)–assessed ventricular dyssynchrony. Subgroup analyses from REVERSE, MADIT-CRT, and RAFT suggest that patients with QRS duration of 150 milliseconds or more and/or with LBBB morphology benefit most from CRT. Based on these observations, the recommendations for the use of CRT were substantially revised in 2012 (**see Table 27G.1**).[24]

According to these revised CRT guidelines, indications for CRT include patients who have an LVEF of 35% or less, sinus rhythm, LBBB with QRS of 120 milliseconds or longer, and NYHA Class II, III, or

ambulatory IV symptoms while receiving optimal medical treatment. Although the level of indication is somewhat stronger for patients fulfilling these criteria with QRS of 150 milliseconds or greater, CRT should generally be offered to all HF patients with a reduced EF and LBBB. In patients with more advanced HF (i.e., NYHA Class III or ambulatory Class IV patients), those fulfilling the aforementioned criteria with a QRS duration of at least 150 milliseconds and non-LBBB morphology should also be considered for CRT.

Limitations of CRT

The success rate for placement of a transvenous cardiac resynchronization system has ranged from about 88% to 92% in clinical trials, although in contemporary clinical experience it is as high as 97% to 98% in some centers (e.g., Ohio State University experience). Thus, some patients undergoing an implant procedure will not receive a functioning system using this approach. Implant-related complications are similar to those seen with standard pacemakers and defibrillators, with the additional risk of dissection or perforation of the coronary sinus. This is a rare event but may lead to substantial morbidity and even mortality in HF patients

Despite the results of randomized controlled CRT trials, some patients do not respond to this therapy. The nonresponder rate for cardiac resynchronization therapy appears to be about 25%, a rate that is similar to the nonresponder rate for HF drug therapies. Factors proposed as contributing to the nonresponder rate associated with CRT include suboptimal LV lead placement, suboptimal AV and VV timing, ventricular scar, and HF disease progression.

Sudden Cardiac Death in Heart Failure

Patients with heart failure and left ventricular systolic dysfunction are at increased risk for sudden cardiac death[25-27] (**see also Chapter 42**). SCD is the leading cause of mortality in patients with HF and occurs at a rate six to nine times that seen in the general population. Given this high incidence of SCD in HF patients, it was easy to hypothesize that an ICD used as prophylactic therapy would reduce total mortality by reducing the incidence of SCD. A series of studies have tested this hypothesis.

Randomized Controlled Trials of Implantable-Cardioverter Defibrillators for Heart Failure

Several early studies supported the benefit of prophylactic ICD implantation, but none of them proved this conclusively. The landmark trials establishing a role for ICDs as primary prevention of mortality in HF patients are the Multicenter Automatic Defibrillator Implantation II (MADIT II),[28] Prophylactic Defibrillator Implantation in Patients with Nonischemic Dilated Cardiomyopathy (DEFINITE),[29] and the National Institutes of Health (NIH)–sponsored Sudden Cardiac Death–Heart Failure Trial (SCD-HeFT).[30] A more recent study, the Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) trial, has raised questions regarding the efficacy of prophylactic ICD use in nonischemic HF patients.[31]

Multicenter Automatic Defibrillator Implantation II Trial

MADIT II was prospectively designed and powered to assess the survival benefit of ICDs in a population

of post–myocardial infarction (MI) patients with reduced EF (<30%). Importantly, this trial included no arrhythmic markers, such as nonsustained or inducible ventricular tachycardia, for inclusion. The 1232 patients were randomly assigned in a 3 : 2 ratio to receive an ICD (742 patients) or conventional medical therapy (490 patients).[28] During an average follow-up of 20 months, the all-cause mortality rates were 19.8% in the conventional therapy arm and 14.2% in the ICD group (31% RRR; *P* = 0.016). The effect of ICD therapy on survival was similar in subgroup analyses stratified according to age, gender, EF, NYHA class, and QRS duration. Moreover, beta-blocker use was 72% in these patients and was well balanced between the ICD and conventional therapy groups.

Of note, the majority of patients enrolled in MADIT II were NYHA Class II or III. Class IV patients were excluded, and the Class I cohort was relatively small. The average LVEF was 23%. These findings suggest that HF patients with mild to moderate symptoms and moderate to severe reductions in LVEF may benefit the most from a prophylactic ICD. Moreover, the survival benefit observed in MADIT II began approximately 9 months after the device was implanted. This observation may be important when considering the timing of device placement in eligible patients.

Prophylactic Defibrillator Implantation in Patients with Nonischemic Dilated Cardiomyopathy Trial

Whereas MADIT II enrolled exclusively post-MI patients with an ischemic cause of LV systolic dysfunction and HF, the DEFINITE trial was the first RCT of primary prevention therapy with an ICD in nonischemic cardiomyopathy patients.[29] Such patients also exhibit high rates of SCD; until recently, however, there has been little consensus regarding the management of SCD risk in such patients, partly because of limitations in objective risk assessment, in that no invasive or noninvasive testing procedure has been shown to determine accurately which nonischemic HF patient is likely to die suddenly. Also, clouding the picture were older observations suggesting that the prophylactic administration of an antiarrhythmic agent, amiodarone, might prolong survival in nonischemic cardiomyopathy patients.

The DEFINITE trial was a prospective evaluation of 458 patients with nonischemic dilated cardiomyopathy. Entry criteria included EF of 35% or less, history of symptomatic HF, and presence of ambient arrhythmias, defined as an episode of nonsustained ventricular tachycardia (VT) or at least 10 premature ventricular complexes (PVCs) per 24-hour period on continuous ambulatory electrocardiographic monitoring. The 229 patients were randomized to each study arm to receive either an ICD and standard medical therapy or standard medical therapy alone. Compliance with medical therapy was excellent and included an angiotensin-converting enzyme inhibitor (ACEI) in 86% of the cohort and a beta blocker in 85%. The patients were followed for a mean of 29.0 ±14.4 months, with a primary endpoint of all-cause mortality.

There were 68 deaths reported in DEFINITE, 28 in the ICD group and 40 in the standard therapy group. The implantation of an ICD yielded a nonsignificant 35% reduction in death from any cause (HR, 0.65; 95% CI 0.40 to 1.06; *P* = 0.08) and significantly reduced the risk of SCD by a remarkable 80% (HR, 0.20; 95% CI 0.06 to 0.71; *P* = 0.006). In the subgroup of NYHA Class III patients, all-cause mortality was significantly decreased in the ICD arm (HR, 0.37; 95% CI 0.15 to 0.90; *P* = 0.02). Although this study was underpowered and did not reach statistical significance with respect to the primary endpoint of all-cause mortality for the entire randomized cohort, the results demonstrated a strong trend toward a survival advantage for patients receiving an ICD.

Sudden Cardiac Death–Heart Failure Trial

The results of the SCD-HeFT trial were published in 2005 and have had a substantial impact on current practice guidelines for ICDs.[30] This landmark RCT enrolled 2521 patients between 1997 and 2001. Patients with NYHA Class II (70%) or III (30%) HF and reduced LVEF (≤35%; mean ≈ 25%) of either ischemic or nonischemic etiology were eligible for the study. SCD-HeFT was a three-arm trial, comparing treatment with an ICD to amiodarone and placebo. Thus, SCD-HeFT addressed at least two important issues in HF management: (1) whether or not empiric amiodarone therapy saved lives in well-treated NYHA Class II and III HF patients with no arrhythmic indication for the drug, and (2) whether or not a prophylactic ICD saved lives in such patients with HF from either an ischemic or a nonischemic cause.

In SCD-HeFT, patients received standard HF therapy, if tolerated, which included an ACEI or angiotensin receptor blocker (ARB) in 85%, beta blocker in 69%, and aldosterone antagonists in 19%, compatible with then-current guideline recommendations. The median follow-up was 45.5 months. Importantly, the cohort was equally divided between ischemic and nonischemic causes of HF, allowing an important subgroup analysis of these cohorts. Mortality rates in the ICD, amiodarone, and placebo groups were, respectively, 17.1%, 24%, and 22.3% at 3 years and 28.9%, 34.1%, and 35.9% at 5 years (**Fig. 27.5**). The ICD was associated with a statistically significant 23% reduction in all-cause mortality compared to placebo (HR, 0.77; 97.5% CI 0.62 to 0.96; $P = 0.007$). Mortality in the amiodarone arm was not significantly different from placebo across all subgroups (HR, 1.06; 97.5% CI 0.86 to 1.30). Similar degrees of benefit with the ICD were noted in patients with ischemic (21% mortality reduction) and nonischemic (27% mortality reduction) HF, thus confirming the findings of MADIT II and DEFINITE, respectively.

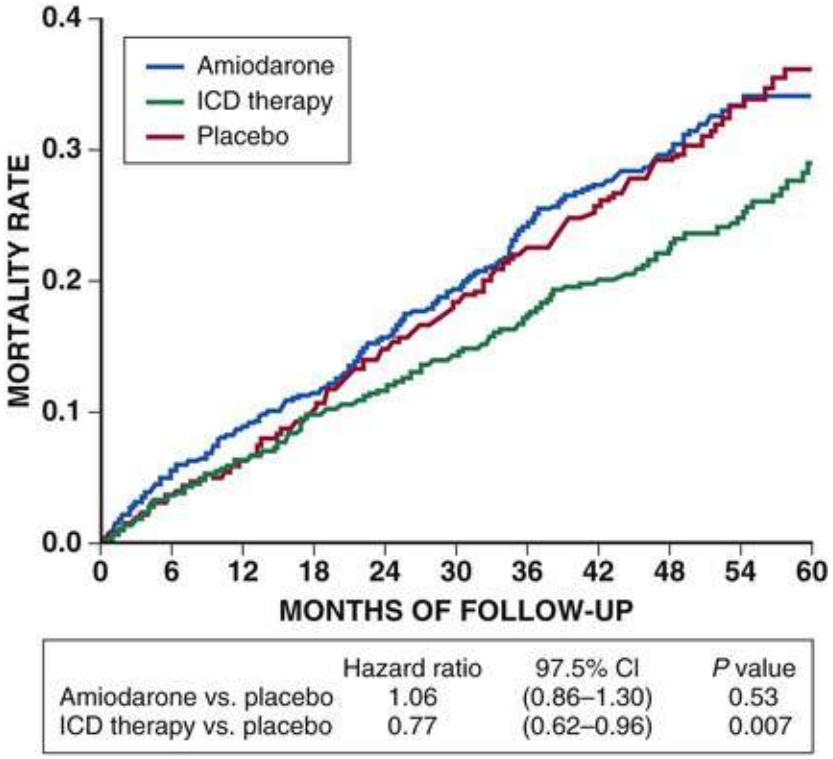

FIGURE 27.5 Kaplan-Meier estimates of survival in patients randomized to an implantable cardioverter-defibrillator (ICD) compared to conventional medical therapy or conventional medical therapy plus amiodarone in the SCD-HeFT Trial. (Modified from Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-37.)

The SCD-HeFT trial provides the most robust evidence to date supporting the prophylactic use of an

ICD in patients with NYHA Class II and III systolic HF.

Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Systolic Heart Failure on Mortality (DANISH)

The DANISH trial randomly assigned 1116 patients with systolic HF not caused by coronary artery disease (CAD; i.e., nonischemic cardiomyopathy) to receive an ICD (556 patients) versus usual care (560 patients).[31] In both groups, 58% of patients received CRT. Results showed that at after 5.6 years, the primary outcome of death from any cause occurred in 120 patients in the ICD group compared to 131 patients in the usual-care group (HR, 0.87; 95% CI 0.68 to 1.12; *P* = 0.28) (**Fig. 27.6**). The secondary endpoint of SCD occurred in 24 patients in the ICD group versus 46 patients in the usual-care group (*P* = 0.005). The authors concluded “prophylactic ICD implantation in patients with symptomatic systolic heart failure not caused by coronary artery disease was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care.” These results and this conclusion questioned the routine use of prophylactic ICDs in the treatment of such patients.

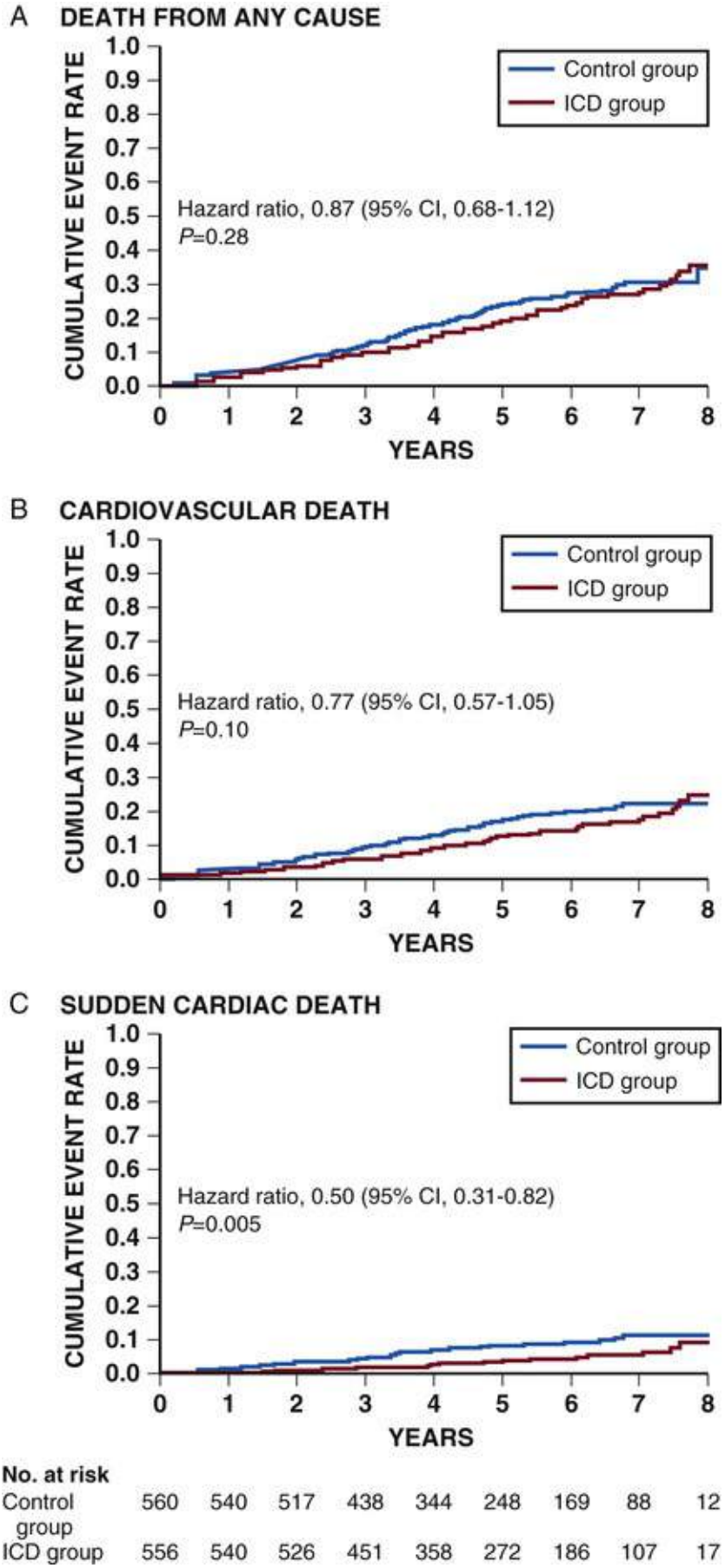

FIGURE 27.6 Effect of prophylactic ICD in heart failure patients with nonischemic cardiomyopathy. Kaplan-Meier estimates for **A,** all-cause mortality; **B,** cardiovascular mortality; and **C,** sudden cardiac death. (From Kober L, Thune JJ, Nielsen JC, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med 2016;375:1221-30.)

However, an updated meta-analysis supports the efficacy of ICD use for nonischemic cardiomyopathy, despite the results of the DANISH trial.[32] This analysis identified six RCTs enrolling 2970 patients with

nonischemic cardiomyopathy to study the efficacy of ICDs for primary prevention. Pooled analysis demonstrated a statistically significant 23% risk reduction (RR) in all-cause mortality in favor of ICD therapy (HR, 0.77; 95% CI 0.64 to 0.91). Thus it is unlikely that current guideline recommendations for ICDs will change, despite the negative result of the DANISH trial.

Indications for Prophylactic ICD Implantation in Heart Failure Patients

The 2013 ACC/AHA heart failure guidelines provided strong (level I) recommendations for prophylactic ICDs in patients with HF and reduced EF.[2] ICD therapy is recommended for primary prevention of SCD to reduce total mortality in select patients with nonischemic dilated cardiomyopathy or ischemic heart disease at least 40 days after MI and with LVEF of 35% or less and NYHA Class II or III symptoms receiving chronic guideline-directed medical therapy (GDMT), who have reasonable expectation of meaningful survival for more than 1 year (level of evidence A). ICD therapy is also recommended for NYHA Class I patients with ischemic heart disease at least 40 days post-MI with LVEF of 35% or less, who have reasonable expectation of meaningful survival for more than 1 year (level of evidence B). Of note in the context of these recommendations, a recent study showed the importance of ICD programming in minimizing inappropriate shocks and improving patient outcomes.[33] This trial demonstrated that programming of ICD therapies for tachyarrhythmias of 200 beats/min or higher or with a prolonged delay in therapy for tachyarrhythmias of 170 beats/min or higher, compared to conventional programming, was associated with reductions in inappropriate therapy and all-cause mortality during an average follow-up of 1.4 years.

Implantable Devices to Monitor Heart Failure

Device-Based Heart Failure Diagnostics

Implantable devices can provide substantial physiologic information about HF patients. Such information may be useful in evaluating HF clinical status and in predicting episodes of HF decompensation. If these devices are reliable in the latter sense, the use of this information may improve HF outcomes by reducing the risk of worsening heart failure (WHF). For example, many implantable CRT and ICD devices can provide information on atrial heart rate and rhythm, ventricular heart rate and rhythm, patient activity level, heart rate variability, and in some cases intrathoracic impedance, proposed as a measure of lung "wetness." Many implantable devices record an activity trend, providing an objective record of the number of hours per day that patients are physically active. The activity level may serve as a useful teaching and reinforcement tool for both patient and family about the importance and level of activity. Because exercise intolerance is a manifestation of WHF, a decrease in patient activity level may provide one objective clue to disease progression or decompensation.

Heart rate variability (HRV) reflects the balance between sympathetic and parasympathetic nervous system activity in the heart; a decrease in HRV is as a marker of increased sympathetic and decreased parasympathetic tone (**see Chapter 99**). Adamson and colleagues[34] showed that HRV fell in the days to weeks leading up to a hospitalization for WHF, suggesting that decreases in HRV may predict episodes of WHF. Given our understanding of the changes in the neurohormonal milieu that occur as HF worsens, this approach to HF monitoring may ultimately prove useful.

Since most patients with decompensation exhibit pulmonary congestion caused by an elevated LV

filling pressure, indirect measurement of lung water or direct measurement of LV filling pressure or its surrogate may be useful in managing HF patients on an outpatient basis. Implantable devices can monitor fluid status by assessing changes in intrathoracic impedance. In 33 patients, intrathoracic impedance changes demonstrated the ability to predict hospitalization for decompensated HF 10 to 14 days in advance of the event.[35] A larger study confirmed this observation and demonstrated the superiority of intrathoracic impedance versus daily weight monitoring in predicting WHF events.[36]

Moreover, it appears that changes in device-based HF diagnostic parameters, using an algorithm based on combined parameters, can stratify patients into high-risk and low-risk subgroups. The Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients with Heart Failure (PARTNERS-HF) trial showed that patients with a positive combined HF device diagnostics score had a 5.5-fold increased risk of HF hospitalization within 1 month of the assessment.[37] Despite this apparent utility of device-based diagnostics, to date no RCT has demonstrated a reduction in HF hospitalization on the basis of this technology. One attempt to do so, the Diagnostic Outcome Trial in Heart Failure (DOT-HF), demonstrated an expected increase in outpatient HF clinic visits and an unexpected increase in HF hospitalizations.[38]

Implantable Hemodynamic Monitors

A new generation of even more sophisticated implantable hemodynamic monitors (IHMs) is under investigation. These devices allow continuous or intermittent assessment of hemodynamics, generally focused on the assessment of intracardiac or pulmonary artery pressures. Early observations supported the utility of these devices,[39-42] and a large RCT confirmed these observations.

The CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial randomized 550 patients, regardless of LVEF, to two groups; clinicians used a novel wireless monitoring system for daily measurement of pulmonary artery pressure (PAP) in addition to standard of care (treatment group; $n = 270$) versus standard of care alone (control group; $n = 280$).[43] The CHAMPION trial differed from prior studies of IHMs in that specific pressure targets and treatment algorithms were mandated by protocol to ensure adequate testing of the hypothesis. The primary endpoint of the trial was the rate of HF hospitalization over 6 months, and long-term outcomes were also prospectively evaluated.

Over a 6-month period, significantly fewer HF hospitalizations occurred in the treatment group (83) than in the control group (120). During the entire single-blinded follow-up averaging 15 months, the treatment group had a 37% RRR in HF hospitalizations compared with the control group (**Fig. 27.7**). The majority of pressure-based medication changes (≈75%) involved, as expected, diuretics and long-acting nitrates. All four prespecified and statistically powered secondary endpoints were met favoring the treatment group, including PAP reduction, proportion of patients hospitalized for HF, days alive and out of the hospital for HF, and quality-of-life score. Freedom from device- or system-related complications was 98.6%, and overall freedom from pressure-sensor failures was 100%. Subsequent subgroup analyses demonstrated the efficacy of PAP-guided HF management in patients with heart failure and a preserved ejection fraction (HFpEF),[44] and a report on long-term effects of this approach demonstrated sustained benefits.[45]

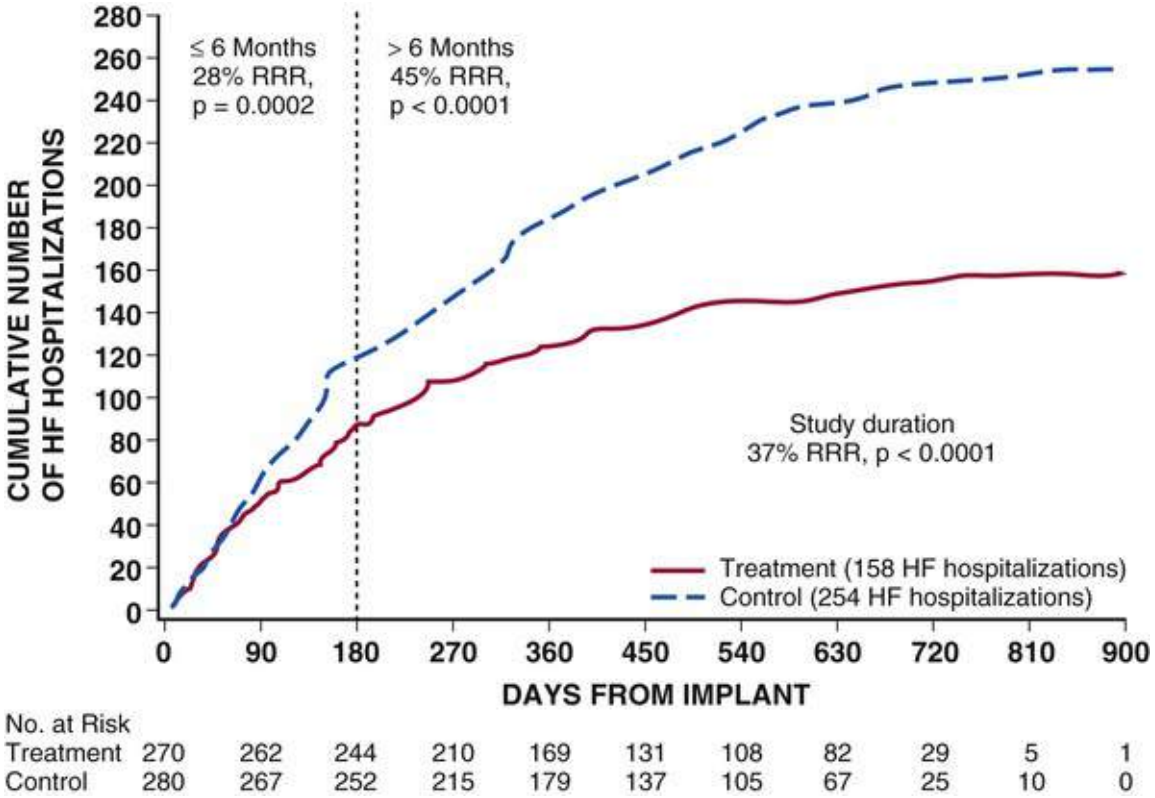

FIGURE 27.7 Primary (6-month) and extended results of the CHAMPION trial for the primary endpoint of heart failure (HF) hospitalization rate; RRR, relative risk reduction. (Modified from Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 2011;377:658-66.)

The results of the CHAMPION trial led to the FDA approval of the first implantable hemodynamic monitoring system in May 2014, for use in HF patients with NYHA Class III symptoms and a history of HF hospitalization within the past 12 months. Other IHMs are currently in development.

Conclusion

Cardiac resynchronization therapy offers a therapeutic approach for treating patients with ventricular dyssynchrony and heart failure. Substantial experience suggests that CRT is safe and effective, with patients demonstrating significant improvement in both clinical symptoms and multiple measures of functional status, exercise capacity, and outcomes. Recommendations for CRT are now based not only on QRS duration but also on morphology. Prophylactic implantation of an ICD is also of proven benefit in HF patients. Implantable hemodynamic monitoring technologies improve the clinician's ability to avoid episodes of HF decompensation and may improve the natural history of the disease.

Guidelines

Cardiac Resynchronization and Implantable Cardioverter-Defibrillators in Heart Failure with a Reduced Ejection Fraction

William T. Abraham

In 2012, the American College of Cardiology, American Heart Association, and Heart Rhythm Society (ACC/AHA/HRS) updated the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities.[1] These revised guidelines were incorporated into the 2013 ACCF/AHA heart failure guidelines.[2] The revised guidelines include a comprehensive revision of cardiac resynchronization therapy (CRT) indications, based on all available studies through 2013 (**Table 27G.1**). The guidelines expand the indications for CRT to some NYHA Class II and very selected Class I patients, limit CRT indications by QRS morphology and QRS duration, and attempt to harmonize indications across NYHA classes when possible. The most certain indications are for those patients who have a left ventricular ejection fraction (LVEF) of 35% or less, sinus rhythm, left bundle branch block with a QRS duration of 150 milliseconds or longer, and NYHA Class II, III, or ambulatory IV symptoms and who are receiving optimal medical treatment.

TABLE 27G.1

ACCF/AHA Guidelines for Cardiac Resynchronization Therapy (CRT)

CLASS	INDICATION	LEVEL OF EVIDENCE
I	CRT is indicated for patients who have LVEF of 35% or less, sinus rhythm, LBBB with QRS duration of 150 msec or greater, and NYHA Class II, III, or ambulatory IV symptoms on GDMT.	A for NYHA Class III/I B for Class II
IIa	CRT can be useful for patients who have LVEF of 35% or less, sinus rhythm, non-LBBB pattern with QRS duration of 150 msec or greater, and NYHA Class III/ambulatory Class IV symptoms on GDMT.	A
	CRT can be useful for patients who have LVEF of 35% or less, sinus rhythm, LBBB with QRS duration of 120 to 149 msec, and NYHA Class II, III, or ambulatory IV symptoms on GDMT.	B
	CRT can be useful in patients with atrial fibrillation and LVEF of 35% or less on GDMT if (a) the patient requires ventricular pacing or otherwise meets CRT criteria and (b) atrioventricular nodal ablation or pharmacologic rate control will allow near-100% ventricular pacing with CRT.	B
	CRT can be useful for patients on GDMT who have LVEF of 35% or less and are undergoing placement of new or replacement device with anticipated requirement for significant (>40%) ventricular pacing.	C
IIb	CRT may be considered for patients who have LVEF of 35% or less, sinus rhythm, non-LBBB pattern with QRS duration of 120 to 149 msec, and NYHA Class III/ambulatory Class IV on GDMT.	B
	CRT may be considered for patients who have LVEF of 35% or less, sinus rhythm, non-LBBB pattern with QRS duration of 150 msec or greater, and NYHA Class II symptoms on GDMT.	B
	CRT may be considered for patients who have LVEF of 30% or less, ischemic etiology of HF, sinus rhythm, LBBB with QRS duration of 150 msec or greater, and NYHA Class I symptoms on GDMT.	C
III: no benefit	CRT is not recommended for patients with NYHA Class I or II symptoms and non-LBBB pattern with QRS duration less than 150 msec.	
	CRT is not indicated for patients whose comorbidities and/or frailty limit survival with good functional capacity to less than 1 year.	

GDMT, Guideline-directed medical therapy; *LBBB,* left bundle-branch block; *LVEF,* left ventricular ejection fraction; *NYHA,* New York Heart Association.

Patients with reduced LVEF are at increased risk for ventricular tachyarrhythmias leading to sudden cardiac death (SCD). Patients who have had sustained ventricular tachycardia, ventricular fibrillation, unexplained syncope, or cardiac arrest are at highest risk for recurrence. Indications for implantable cardioverter-defibrillator (ICD) therapy as secondary prevention of SCD is also discussed in the 2013 American College of Cardiology Foundation and American Heart Association (ACCF/AHA) guidelines for heart failure (**Table 27G.2**),[2] as well as the ACCF/AHA/HRS device-based therapy guidelines.[3]

TABLE 27G.2

ACCF/AHA Guidelines for Indications for Implantable Cardioverter-Defibrillators (ICDs)

CLASS	INDICATION	LEVEL OF EVIDENCE
I	ICD therapy is recommended for primary prevention of SCD in selected patients with HFrEF at least 40 days post-MI with LVEF less than 35% and NYHA Class II or III symptoms receiving chronic GDMT, who are expected to live more than 1 year.	A
I	ICD therapy is recommended for primary prevention of SCD in selected patients with HFrEF at least 40 days post-MI with LVEF less than 30% and NYHA Class I symptoms receiving GDMT, who are expected to live more than 1 year.	B
IIa	To prevent SCD, placement of ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 days post-MI, have an LVEF of 30% or less, are on appropriate medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year.	B
IIb	ICD therapy to prevent SCD in patients with nonischemic cardiomyopathy who are at least 40 days post-MI, have LVEF less than 35%, with NYHA Class II or III symptoms while undergoing chronic optimal medical therapy, and have reasonable expectation of survival for more than 1 year with good functional status.	B
	Usefulness of implantation of ICD is of uncertain benefit to prolong meaningful survival in patients with high risk of non-SCD, as predicted by frequent hospitalizations, advanced frailty, or comorbidities such as systemic malignancy or severe renal dysfunction.	B

HFrEF, Heart failure with reduced ejection fraction; *MI,* myocardial infarction; *SCD,* sudden cardiac death; see **Table 27G.1** for other abbreviations.

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28

Surgical Management of Heart Failure

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In the current era of management of heart failure associated with a reduced left ventricular ejection fraction (HFrEF), clinicians frequently encounter optimally treated patients who remain symptomatic. Indeed, despite the variety of available medical therapies and electrophysiologic interventions, such as placement of biventricular pacemakers and implantable cardioverter-defibrillators (**see Chapter 27**), many patients who have been so treated are still left with a reduced quality of life and a poor prognosis. In a subpopulation of these patients, surgical intervention may be appropriate to alleviate ischemia, to

attenuate valvular dysfunction, to reduce mechanical disadvantages caused by ventricular remodeling, or, when all other treatment options have failed, to perform cardiac transplantation or implantation of a permanent ventricular assist device (VAD). This chapter describes the surgical management of patients with heart failure secondary to a decreased left ventricular ejection fraction (LVEF). The medical management of patients with a reduced ejection fraction is discussed in **Chapter 25** and the role of circulatory assist devices in **Chapter 29**.

Coronary Artery Revascularization

Selection of Patients

Until the design, completion, and publication of the original STICH (Surgical Treatment of Ischemic Heart Failure) trial[1] and now the 10-year follow-up of this trial,[2] no randomized clinical trials had evaluated the outcomes of revascularization in patients with ischemic cardiomyopathy. The term *ischemic cardiomyopathy* is used to describe the myocardial dysfunction that arises secondary to occlusive or obstructive coronary artery disease (**see Chapter 61**). Although ischemic cardiomyopathy was considered the second most common cause (after hypertension) of heart failure (HF) in the Framingham Study (**see Chapter 21**), ischemic cardiomyopathy is now recognized as the most common cause of HF in clinical trials of patients with HFrEF.

Ischemic cardiomyopathy is composed of three interrelated pathophysiologic processes that may overlap: *myocardial hibernation*, defined as persistent contractile dysfunction at rest, caused by reduced coronary blood flow that can be partially or completely restored to normal by myocardial revascularization; *myocardial stunning*, wherein the viable myocardium may demonstrate prolonged but reversible postischemic contractile dysfunction caused by the generation of oxygen-derived free radicals on reperfusion and by a loss of sensitivity of contractile filaments to calcium; and irreversible *myocyte cell death*, leading to ventricular remodeling and contractile dysfunction.

The three major historical, randomized clinical trials that have compared coronary artery bypass grafting (CABG) with medical management—the Veterans Administration Cooperative Study, the European Coronary Surgery Study, and the Coronary Artery Surgery Study—all had excluded patients with HF or severe left ventricular (LV) dysfunction. Several clinical factors have traditionally played a major role in the decision-making process with respect to selection of suitable candidate patients with HF to undergo coronary artery revascularization, including the presence of angina, severity of HF symptoms, LV dimensions, degree of hemodynamic compromise, and presence and severity of comorbid conditions. Other major technical issues to be considered are the adequacy of target vessels for revascularization and an adequate conduit strategy. The most important determinant remains the extent of jeopardized but still-viable myocardium (**see Chapters 14, 16, and 17**). Studies have suggested that for a significant reduction in HF symptoms and improvement in LV function, as well as in survival after coronary revascularization, at least 25% of the myocardium should be viable. Of interest, in the STICH trial, the presence of viable myocardium was associated with a greater likelihood of survival in patients with coronary artery disease (CAD) and LV dysfunction, regardless of treatment. The assessment of myocardial viability, however, did not identify patients with a differential survival benefit with CABG versus medical therapy alone. The

role of viability testing in the decision-making process is still evolving after this STICH trial substudy.[3] The impact of viability on decision making for revascularization is discussed separately in **Chapter 16**.

Risks of Coronary Artery Bypass Grafting

The perioperative risks in patients with severe LV dysfunction range from 2% to almost 10%, depending on the availability of targets and their viability, right ventricular dysfunction, advanced HF symptoms (New York Heart Association [NYHA] Class IV), increased LV end-diastolic pressure, comorbidities of advanced age, peripheral vascular disease, renal dysfunction, mitral regurgitation, and chronic obstructive pulmonary disease.[4,5] The Society of Thoracic Surgeons (STS)–predicted risk of death in 2006 for a 70-year-old patient with no comorbid conditions but with a 20% LVEF was 1.3%; for a man of the same age with a normal LVEF, this risk was 0.5%. Mortality rates increase substantially when the LVEF is below 20% or when HF is severe (NYHA Class IV).

Studies show that for patients with clinical heart failure, perioperative mortality rates range from approximately 2.6% to 8.7%, depending on age and presence of one or more comorbid conditions. A recent study investigating CABG in patients with HF with either preserved or reduced ejection fraction (EF) found HF to be an independent predictor of mortality within 30 days either with reduced EF (hazard ratio [HR], 2.52; 95% confidence interval [CI] 1.99 to 3.19; 4.0% 30-day mortality) or preserved EF (HR, 1.83; 95% CI 1.26 to 2.66; 2.8% 30-day mortality).[6] Pocar and associates[7] found a 30-day mortality rate of 4.4% in 45 consecutive angina-free patients with NYHA Class III or IV, LVEF below 35%, and significant viability by positron emission tomography (PET). Predictors of death included LV end-diastolic pressure above 25 mm Hg, age older than 70 years, and significant peripheral vascular disease. In the CABG Patch trial, patients without angina or HF had a perioperative mortality of 1.3%. The mortality increased to 4.8% for patients with no angina and mild HF, NYHA Class I or II, and 7.4% with no angina and NYHA Class III or IV HF. For cardiogenic shock after myocardial infarction, the results of emergent CABG are poor but still better than medical therapy. The SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial gave 30-day and 6-month mortality rates after CABG of 47% and 50%, respectively, for patients in cardiogenic shock. These rates were 56% and 63% with medical therapy alone.[8]

The STICH trial was a prospective, randomized, intention-to-treat study of 2800 patients from 100 centers.[1] Patients on an optimal medical regimen with LV dysfunction and CAD amenable to CABG were randomly assigned to one of three different treatment strategies: CABG, CABG plus surgical ventricular reconstruction (SVR), or medical therapy alone (MED) (**Fig. 28.1**). This trial was powered to address two primary hypotheses: (1) CABG combined with medical therapy improves long-term survival over that achieved with MED, and (2) SVR provides additional long-term survival benefit when combined with CABG and medical therapy. Between July 2002 and May 2007, a total of 1212 patients with an LVEF of 35% or less and CAD amenable to CABG were randomly assigned to receive medical therapy alone (602 patients) or medical therapy plus CABG (610 patients). The primary outcome was the rate of death from any cause. Major secondary outcomes included the rates of death from cardiovascular (CV) causes and of death from any cause or hospitalization for CV causes. Of the 610 patients randomly assigned to CABG, 555 (91%) underwent CABG before the end of the study. A concurrent mitral valve

operation was performed in 63 patients (11%). The all-cause death rate within 30 days of assignment to treatment, which is an approximate estimation of perioperative mortality, was 4% in the medical treatment plus CABG arm, compared with 1% 30-day mortality rate in the MED group. A 10-year follow-up to the original STICH trial demonstrated a significantly lower mortality in patients who underwent CABG (58.9%) compared to medical therapy (66.1%)[2] (**Fig. 28.2**).

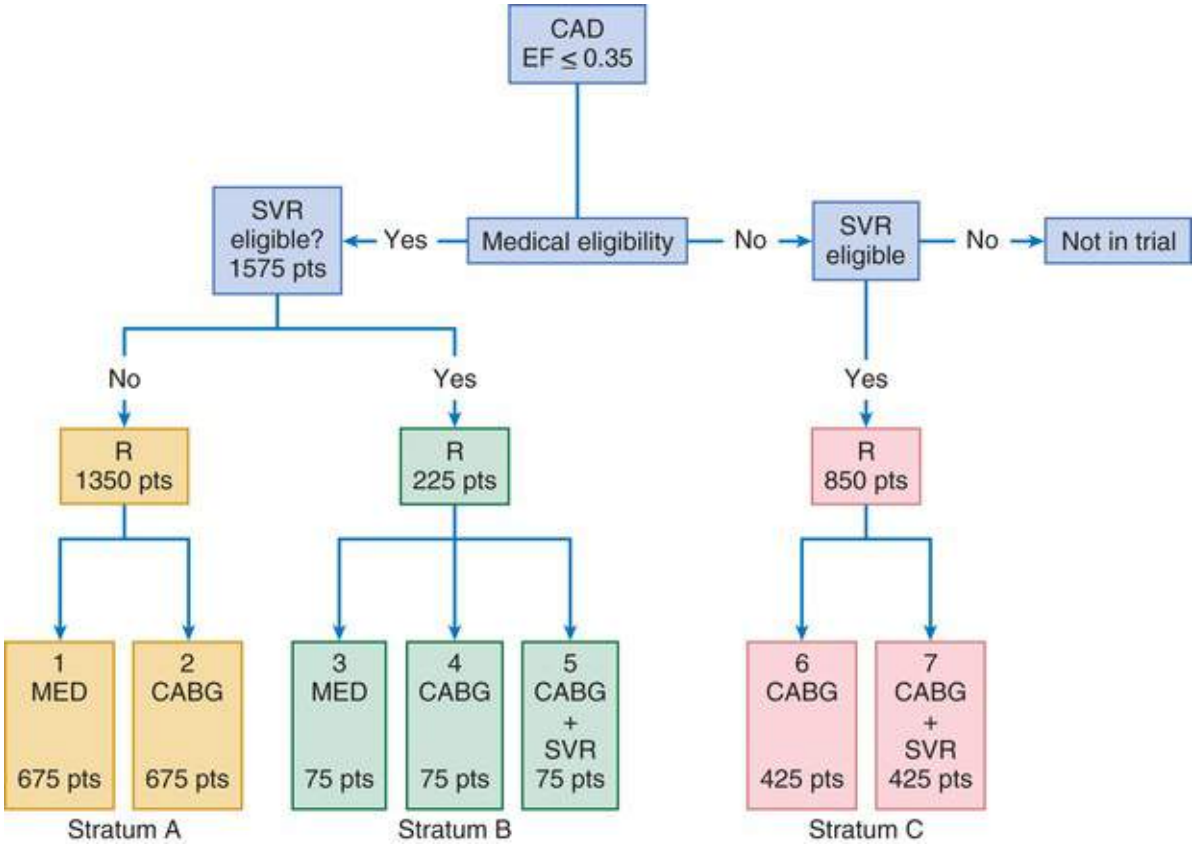

FIGURE 28.1 Treatment strata in the STICH trial. CAD, Coronary artery disease; EF, ejection fraction; MED, medical therapy; pts, patients; R, randomized; SVR, surgical ventricular reconstruction.

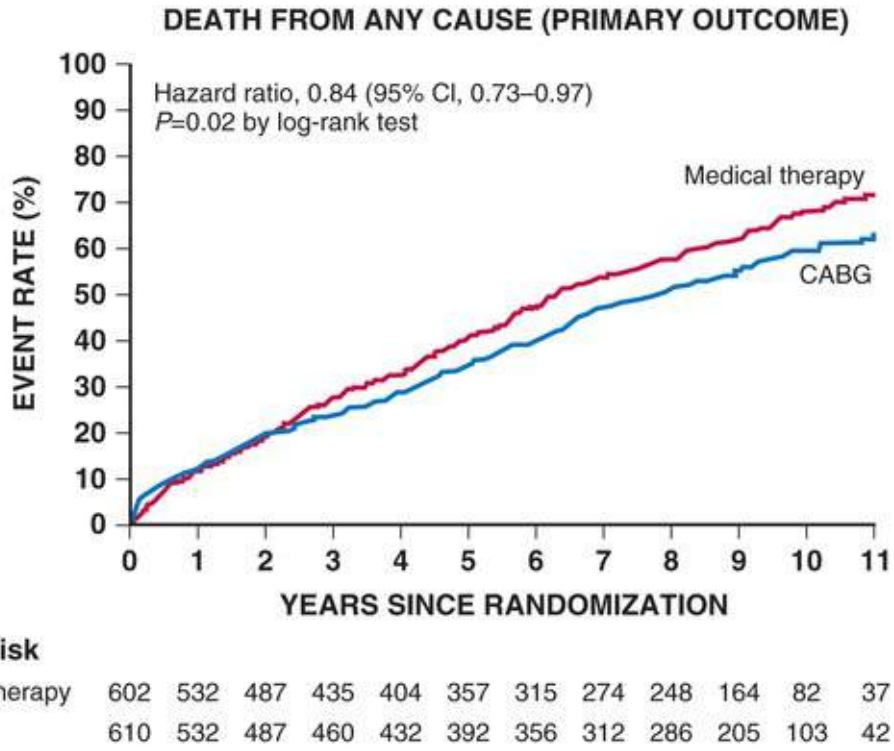

FIGURE 28.2 Kaplan-Meier curves for the probability of death from any cause in the STICHES study. CABG, Coronary artery bypass surgery. (From Velazquez EJ, Lee KL, Jones RH, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. N Engl J Med 2016;374:1511.)

Benefits of Coronary Artery Bypass Grafting

The beneficial effect of revascularization should theoretically result from improved blood flow to hypoperfused but viable myocardium (hibernating myocardium), with a subsequent improvement in LV function and clinical outcomes. Alleviation of ischemia also may lessen the tendency toward proarrhythmias, thereby reducing the incidence of sudden cardiac death (SCD). Accordingly, coronary artery revascularization has the potential to relieve symptoms of HF, improve LV function, and enhance survival.

In the STICH trial the intention-to-treat analysis found no statistically significant difference in death from any cause between the medical and the surgical groups (HR for CABG, 0.86; 95% CI 90.7 to 1.04; $P = 0.12$), whereas the prespecified secondary analysis found a significant difference between the medical and surgical groups with respect to the combined endpoints of CV death, death from any cause, and hospitalization for CV causes (HR for CABG, 0.74; 95% CI 0.64 to 0.85; $P < 0.001$). The HR for CV death was 19% lower in the CABG arm (0.81; 95% CI 0.66 to 1.00) and for the composite of death or CV hospitalization was 16% lower in the CABG arm (0.84; 95% CI 0.71 to 0.98). These findings were consistent across several prespecified subgroups.

The updated 10-year follow-up of the STICH cohorts (STICHES) has further confirmed these findings, with a clear improvement in the primary outcome of all-cause mortality, with improved median survival in the CABG group compared to medical therapy (7.73 versus 6.29 years).[2] The prespecified secondary outcomes included death from CV causes, combined death from any cause or hospitalization for HF, death from any cause or hospitalization for any cause, death from any cause or revascularization, and death from any cause or nonfatal stroke. Beneficial improvements in all secondary outcomes were noted in the CABG cohort compared to medical management (**Table 28.1**). Furthermore, given the significant crossover of medically managed patients into the CABG arm (17%) within the first year of

randomization, the overall outcomes in the CABG group were likely adversely affected, limiting the real overall impact of CABG on survival. Based on the long-term follow-up data, the authors concluded that a significant benefit of CABG plus medical therapy over medical therapy alone with respect to the rate of death from any cause could be achieved among patients with ischemic cardiomyopathy. A follow-up study utilizing the original STICH dataset focused on the anatomic variables associated with improved outcomes in patients with reduced EF undergoing CABG. Three prognostic criteria were evaluated: EF less than the median (27%), end-systolic volume index (ESVI) above the median (79 mL/m^2), and the presence of three-vessel CAD. A net benefit to CABG with medical management compared to medical management alone was noted in patients with two or three of these criteria (HR, 0.53; 95% CI 0.37 to 0.75; $P < 0.001$), but not those with only one criterion (HR, 0.88; 95% CI 0.59 to 1.31; $P = 0.535$).

TABLE 28.1

The STICH Study Outcomes

OUTCOME	NO. OF SUBJECTS (%)		HAZARD RATIO WITH CABG (95% CI)	*P* VALUE*
	CABG (*n* = 610)	Medical Therapy (*n* = 602)		
Primary Outcome				
Death from any cause	359 (58.9)	398 (66.1)	0.84 (0.73-0.97)	0.02
Secondary Outcomes				
Death from cardiovascular causes	247 (40.5)	297 (49.3)	0.79 (0.66-0.93)	0.006
Death from any cause or hospitalization for cardiovascular causes	467 (76.6)	524 (87.0)	0.72 (0.64-0.82)	<0.001
Death from any cause or hospitalizations for heart failure	404 (66.2)	450 (74.8)	0.81 (0.71-0.93)	0.002
Death from any cause of hospitalizations for any cause	506 (83.0)	538 (89.4)	0.81 (0.71-0.91)	0.001
Death from any cause or revascularization†	388 (63.6)	478 (79.4)	0.63 (0.55-0.73)	<0.001
Death from any cause or nonfatal myocardial infarction‡	376 (61.6)	409 (67.9)	0.86 (0.74-0.98)	0.03
Death from any cause of nonfatal stroke‡	367 (60.2)	406 (67.4)	0.85 (0.74-0.98)	0.03

*Hazard ratios (CABG vs. medical therapy) are based on the Cox model, and the associated *P* values are based on the long-rank test. All assessments were adjusted for patient stratum (A vs. B; patients who met the eligibility criteria for random assignment to the coronary artery bypass grafting (CABG) group or medical therapy group but did not meet the criteria for eligibility for surgical ventricular reconstruction were enrolled in stratum A; patients who did meet the criteria for eligibility for surgical ventricular reconstruction were enrolled in stratum B).

†The method of revascularization was either percutaneous coronary intervention or CABG.

‡Death or nonfatal myocardial infarction and death or nonfatal stroke were not prespecified outcomes.

From Velazquez EJ, Lee KL, Jones RH, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. N Engl J Med 2016;374:1511.

Several studies have reported marked reduction in HF symptoms after revascularization. A 1999 study from Verona followed 167 patients with angina and HF symptoms and an average LVEF of 28% and demonstrated significant freedom from angina after surgery, 98% and 81%, and from HF, 78% and 47%, at 1 and 5 years, respectively.[9] Only 54% of patients were symptom free of both angina and HF at follow-up evaluation. Di Carli and colleagues[10] studied 36 patients with LVEF of 28% by PET imaging and found a significant correlation between the total extent of a PET blood flow–metabolism mismatch and percentage improvement in functional class after CABG. A mismatch of more than 18% was associated with a sensitivity of 76% and a specificity of 78% for predicting a change in functional status after revascularization. A substantial objective improvement in physical activity was noted in patients with presurgical mismatches that occupied at least 20% of the ventricular myocardium. Thus, patients with large perfusion-metabolism mismatch exhibited the greatest clinical benefit after revascularization.

The impact of the CABG strategy on subsequent symptoms of patients in the STICH trial has further demonstrated benefits in both angina (odds ratio [OR], 0.70; 95% CI 0.55 to 0.90; $P < 0.01$),[11] as well as quality of life as measured with the Kansas City Cardiomyopathy Questionnaire.

A reasonable management strategy for patients who present with HF secondary to CAD (i.e., ischemic cardiomyopathy) includes coronary angiography (**see Chapter 20**), especially if patients have any component of angina pectoris. Viability studies may be appropriate for patients with severe disease and adequate surgical targets. The weight of currently available clinical evidence suggests that CABG may be superior to medical therapy alone in outcome measures of survival and quality of life. Current American and European guidelines for CABG in patients with HF include various strengths of recommendation for surgery (**Table 28.2**).

TABLE 28.2

Surgery for Management of Heart Failure (HF): Guideline Recommendations

2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure
Recommendations for Myocardial Revascularization in Patients with Chronic HF
• Myocardial revascularization is recommended when angina persists despite antiangina drugs; *class I, level of evidence A.* The choice between CABG and PCI should be made by the heart team after careful review. CABG is recommended for patients with angina and significant LM or LM-equivalent stenosis to improve prognosis. CABG is recommended for patients with HFrEF, significant CAD (LAD or multivessel disease), and LVEF <35%.
2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease*
• A heart team approach to revascularization is recommended in patients with diabetes mellitus and complex multivessel CAD; *class 1, level of evidence C.* • CABG is generally recommended in preference to PCI to improve survival in patients with diabetes mellitus and multivessel CAD for which revascularization is likely to improve survival (3-vessel CAD or complex 2-vessel CAD involving the proximal LAD); *class 1, level of evidence B.*
2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease†
Indications for Aortic Valve Surgery in Aortic Stenosis (as) with Left Ventricular Dysfunction
• AVR is recommended for asymptomatic patients with severe AS and LVEF <50%; *class I, level of evidence B.* • AVR is reasonable in symptomatic patients with low-flow/low-gradient severe AS with reduced LVEF with a low-dose dobutamine stress study that shows an aortic velocity ≥4.0 m/sec or mean pressure gradient ≥40 mm Hg with a valve area of ≤1.0 cm^2; *class IIa, level of evidence B.* • AVR is reasonable for patients with moderate AS who are undergoing other cardiac surgery; *class IIa, level of evidence C.* • TAVR is recommended in patients who meet an indication for AVR for AS and who have a prohibitive surgical risk and post-TAVR survival >12 mo; *class I, level of evidence B.* • TAVR is a reasonable alternative to surgical AVR in patients who meet an indication for AVR and who have a high surgical risk; *class IIa, level of evidence B.*
Indications for Aortic Valve Surgery in Aortic Regurgitation (AR) with LV Dysfunction
• AVR is recommended for symptomatic patients with severe AR; *class I, level of evidence B.* • AVR is indicated for patients with severe AR and LV systolic dysfunction; *class I, level of evidence B.*
Indications for Mitral Valve Surgery in Functional Mitral Regurgitation (MR)
• Mitral valve surgery is reasonable for patients with chronic severe functional MR who are undergoing CABG or AVR; *class IIa, level of evidence C.* • Mitral valve surgery may be considered for severely symptomatic patients (NYHA Class III/IV) with chronic severe functional MR; *class IIb, level of evidence B.* • Mitral valve repair may be considered for patients with chronic moderate functional MR who are undergoing other cardiac surgery; *class IIb, level of evidence C.*
ESC/EACTS Guidelines on the Management of Valvular Heart Disease (Version 2012)‡
Indications for Mitral Valve Surgery in Chronic Secondary Mitral Regurgitation (MR)
• Surgery is indicated in patients with severe MR undergoing CABG and LVEF >30%; *class I, level of evidence C.* • Surgery should be considered in patients with moderate MR undergoing CABG; *class IIa, level of evidence C.* • Surgery should be considered in symptomatic patients with severe MR, LVEF <30%, option for revascularization, and evidence of viability; *class IIa, level of evidence: C.* • Surgery may be considered in patients with severe MR, LVEF >30%, who remain symptomatic despite optimal medical management (including CRT if indicated) and have low comorbidity, when revascularization is not indicated; *class IIb, level of evidence C.*

*Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation 2014;130:1749-67.

†Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease. J Thorac Cardiovasc Surg 2014;148:E1-E132.

‡Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J 2012;33:2451-96. *ESC/EACTS,* European Society of Cardiology/European Association for Cardio-Thoracic Surgery;

AVR, Aortic valve replacement; *CABG,* coronary artery bypass grafting; *CAD,* coronary artery disease; *CRT,* cardiac resynchronization therapy; *HFrEF,* heart failure with reduced ejection fraction; *LAD,* left anterior descending coronary artery; *LCx,* left circumflex coronary artery; *LM,* left main coronary artery; *LVEF,* left ventricular ejection fraction; *LVESV,* left ventricular end-systolic volume; *NYHA,* New York Heart Association; *PCI,* percutaneous coronary intervention; *TAVR,* transcatheter aortic valve replacement.

Valve Surgery in Patients With Left Ventricular Dysfunction

Mitral Valve

As discussed in **Chapter 69**, the surgical treatment of primary valvular heart disease that leads to LV dysfunction or HF is now widely accepted. However, patients who have valvular dysfunction *secondary* to, or in association with, a primary cardiomyopathy pose a much more difficult management problem. The following discussion focuses on the impact and outcome of valve repair or replacement for patients

with a dilated cardiomyopathy and secondary mitral regurgitation (MR). However, much of the same controversy relates to the decision to repair or replace the regurgitant mitral valve in the patient with an ischemic cardiomyopathy and a low LVEF who is undergoing CABG.

MR is frequently observed in patients with HF and is associated with a poor prognosis. Progressive LV remodeling, characterized by increasing LV dilation with change to a more spherical shape, can result in functional MR secondary to annular dilation, papillary muscle displacement, and chordal tethering. The functional MR leads to an increased preload, increased wall tension, and increased LV workload, all of which contribute in a positive feedback loop to progressive HF. The presence of MR itself is an independent risk factor for poor outcome, in both nonischemic and ischemic forms of the disorder. Even uncorrected mild MR, as well as moderate to severe MR associated with ischemic cardiomyopathy, is associated with reduced long-term survival. In addition, MR is a progressive disorder in which the regurgitation-related LV volume overload promotes further LV remodeling, leading to worsening of the problem.

Mitral valve repair or replacement to restore valve competency is a well-established procedure when symptoms of HF are present and the primary disease is of the valve leaflets (**see Chapter 69**). More recently, however, interest has focused on functional or secondary mitral insufficiency, in which the valve leaflets are anatomically normal but do not fully coapt because of annular dilation and restricted leaflet motion secondary to increased ventricular size and sphericity. Such remodeling of the ventricle often is associated with an LVEF of 40% or less and HF symptoms of NYHA Class III or IV. Surgery in this situation is controversial, because the MR is the consequence and not the cause of LV dysfunction, and the prognosis is therefore more specifically related to the underlying cardiomyopathic process.

Although it is clear that the advent of secondary mitral insufficiency is associated with a worse prognosis, it is unclear whether the worse outcomes arise from the MR itself or whether MR is simply a marker for worsening HF, in which case the correction of MR might not improve symptoms or survival. The historical point of view was that surgical correction of MR in patients with advanced HF patients and poor LV function is associated with prohibitive operative mortality. This view was challenged by Bolling in the mid-1990s, ushering in the era of both mitral valve repair and other surgical procedures for the failing heart. The traditional hypothesis held that the mitral valve functions as a “pop-off” mechanism for the failing ventricle and that surgical correction results in prohibitive mortality. The Bolling hypothesis is that there is an “annular solution for a ventricular problem … such that reconstruction of the mitral valve annulus' geometric abnormality by an undersized ring restores valvular competency, alleviates excessive ventricular workload, improves ventricular geometry and improves ventricular function.”[12] Subsequent studies in an ischemic sheep model of MR showed that reducing the annulus with a small ring reduces the radius of curvature of the left ventricle at the base equatorial and apical level, supporting the concept that a small ring can restore a more elliptical ventricular shape. It is now recognized that the surgical mortality for mitral valve replacement observed in the past probably resulted from the loss of the subvalvular apparatus, underscoring the paramount importance of maintaining annular and subvalvular continuity during mitral valve surgery.

In degenerative mitral valve disease, the repair of the mitral valve has been demonstrated to provide superior long-term outcomes in regard to survival and ventricular function compared to mitral valve replacement. Unfortunately, in the case of functional MR, multiple studies suggest that the rate of

recurrence of MR after repair is approximately 30% to 40%, bringing into question the appropriate surgical management strategy for severe functional MR: repair versus replacement. The landmark Cardiothoracic Surgical Trials Network (CTSnet), a randomized, prospective, multi-institutional study evaluating either mitral valve (MV) repair or chordal-sparing MV replacement for severe ischemic MR, provided insight into this complicated question. The study randomized 251 patients with severe ischemic MR to either MV repair with a rigid, complete, downsized annuloplasty (126 patients) or MV replacement with complete preservation of the subvalvular apparatus (125 patients). The primary endpoint of the initial study was LV remodeling as assessed by left ventricular end-systolic volume index (LVESI) at 12 months.[13] Secondary endpoints included mortality, a composite of adverse cardiac or cerebrovascular events (death, stroke, subsequent MV surgery, hospitalization for HF, or increase in NYHA class), serious adverse events, recurrent MR, quality of life, and rehospitalization. No difference in LVESI between groups was identified at 12 months. The mortality rate, rate of composite adverse events, functional status, and quality of life were noted to be equivalent at 12 months. The ensuing study followed this patient cohort for 2 years using clinical and echocardiographic endpoints.[14] At 2 years, the LVESI among survivors was not statistically significant ($P = 0.19$) between the two groups: 52.6 ±27.7 mL/m^2 for MV repair and 60.6 ±39.0 mL/m^2 for MV replacement. The 2-year mortality was 19.0% in the repair group and 23.2% in the replacement group (HR, 0.79; 95% CI 0.46 to 1.35; $P = 0.39$). As shown in **Fig. 28.3**, the rate of recurrence of moderate or severe MR over 2 years was markedly higher in the repair group than the replacement group (58.8% vs. 3.8%; $P < 0.001$). There was no significant difference in rates of serious adverse events and overall readmissions. However, patients in the repair group had more serious adverse events related to HF recurrence ($P = 0.05$) and CV readmissions ($P = 0.01$). Data from this trial support MV replacement over repair for severe ischemic MR. Similarly, a large, contemporaneous, retrospective, propensity-matched study (ISTIMIR) from Lorusso and colleagues[15] evaluating MV replacement and repair for severe ischemic MR demonstrated no difference in short- or long-term mortality between patients cohorts. They noted no difference in late LV function, cardiac and valve-related death, or functional capacity. MV repair was noted to be the strongest predictor of need for valve-related reoperation. In a subgroup analysis, patients who underwent MV repair without recurrent MR had significantly greater LV reverse remodeling than patients who underwent replacement. In the case of MV replacement, it is important to ensure complete chordal preservation of both anterior and posterior chords to limit myocardial remodeling.

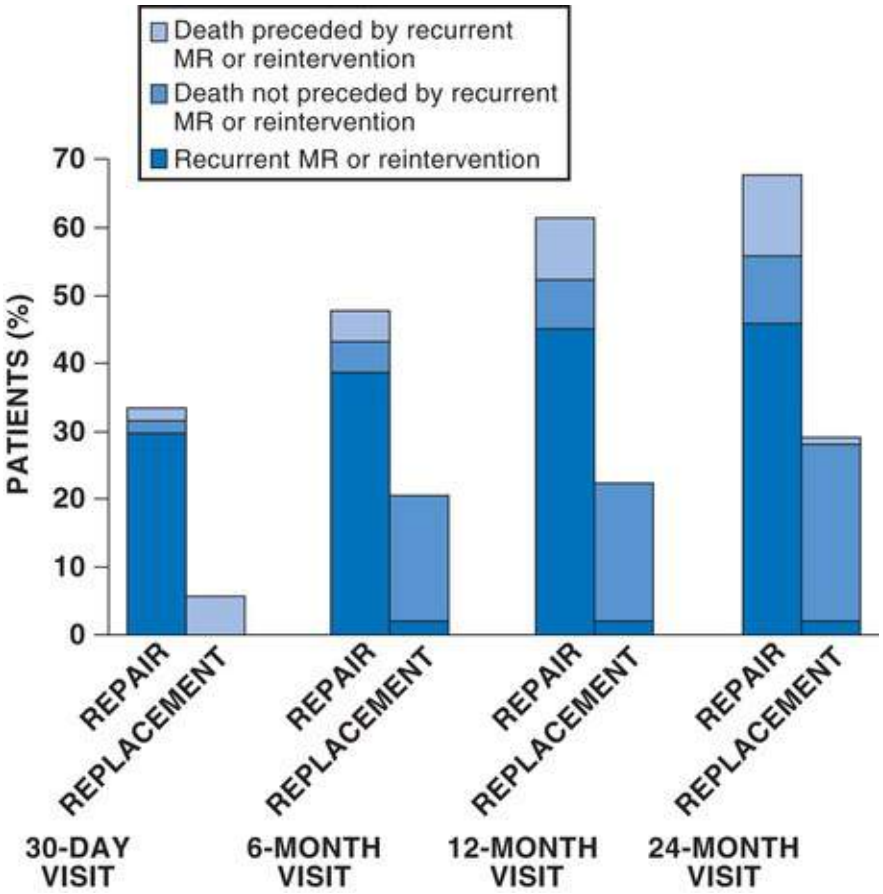

FIGURE 28.3 Results of CTSnet severe ischemic mitral regurgitation trial showing the cumulative failure of mitral valve repair or replacement at 2 years. Failure of the intervention was defined as death, moderate or severe mitral regurgitation (MR) as seen on transthoracic echocardiography, or mitral valve reintervention. (From Goldstein D, Moskowitz AJ, Gelijns AC, et al. Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. N Engl J Med 2016;374:344.)

Another common clinical scenario is the management of moderate ischemic MR in patients undergoing CABG. Proponents of MV repair have argued for the potential benefits of long-term reverse LV remodeling and symptomatic relief. The countervailing point of view is that revascularization alone will improve the MR and that MV repair will not have a long-term durable benefit. A randomized, prospective, multi-institutional CTSnet study evaluating the surgical treatment of moderate ischemic MR at the time of CABG addressed this clinical dilemma.[16] Patients with moderate ischemic MR were randomly assigned to either CABG alone (n = 151) or CABG plus MV repair (n = 150). The primary endpoint was the degree of LV remodeling by means of the LVESI. Secondary endpoints included a composite of major adverse cardiac or cerebrovascular events, mortality, serious adverse events, residual MR, functional status, quality of life, and rehospitalization. Assessment of LVESI at 1 year demonstrated no difference (z score = 0.50; P = 0.61). Moreover, the 2 year follow-up showed that the mean LVESI was 41.2 ±20.0 mL/m^2 in the CABG group, compared to 43.2 ±20.6 mL/m^2 in the CABG plus MV repair group (z score = 0.38; P = 0.71).[17] The mortality rate was similar for CABG (10.6%) and CABG plus MV repair (10.0% [HR, 0.90; 95% CI 0.45 to 1.83; P = 0.78]). Although the rate of moderate or severe MR was higher in the CABG group (32.3% vs. 11.2%; P < 0.001), the overall rates of hospital readmission and serious adverse events were similar between groups (**Fig. 28.4**). The authors concluded that in patients with moderate ischemic MR undergoing CABG, the addition of MV repair did not lead to significant differences in LV remodeling at 2 years.

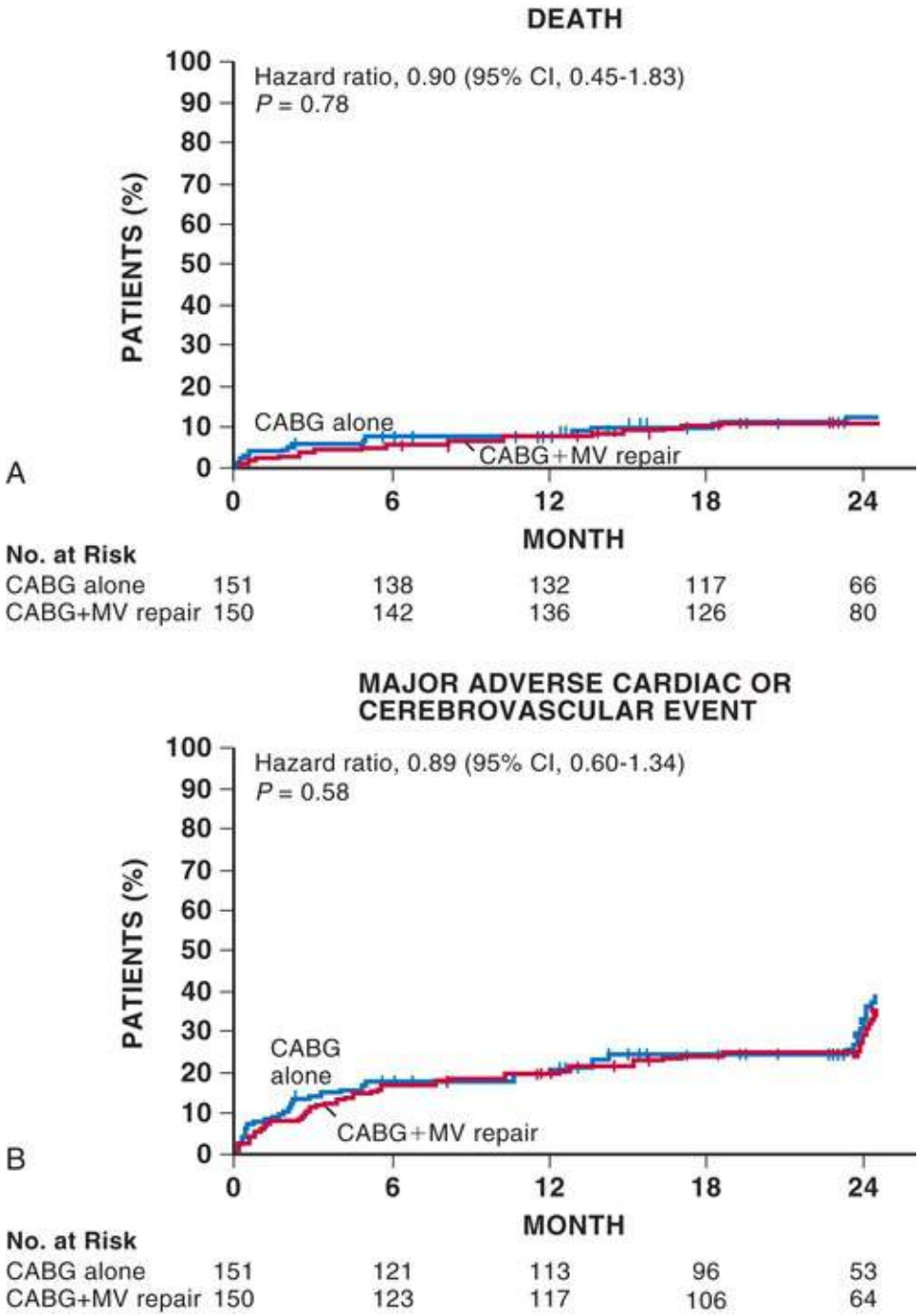

FIGURE 28.4 Results of CTSnet moderate ischemic mitral regurgitation trial showing mortality and cardiovascular events at 2 years. **A,** Rates of death, and **B,** a composite of major adverse cardiac and cerebrovascular events (defined as death, stroke, subsequent mitral valve surgery, hospitalization for heart failure, or worsening New York Heart Association class) among patients undergoing either coronary artery bypass grafting (CABG) or CABG plus mitral valve (MV) repair. (From Michler RE, Smith PK, Parides MK, et al. Two-year outcomes of surgical treatment of moderate ischemic mitral regurgitation. N Engl J Med 2016;374:1932.)

A subgroup analysis of the patients in the CTSnet trial who underwent MV repair identified the presence of a basal aneurysm or dyskinesis as the strongest predictor of repair failure. Additional predictors of recurrence include an anterior leaflet angle greater than 25 to 39.5 degrees, an LV end-diastolic diameter greater than 65 mm, and increased LV sphericity. The 2015 American Association for Thoracic Surgery guidelines support MV replacement in the presence of basal aneurysm/dyskinesis, significant leaflet tethering, or moderate to severe remodeling (LVEDD >65 mm) (class IIa, level of evidence A). In the absence of these findings, consideration of MV repair with an undersized, complete rigid ring should be considered (class IIb, level of evidence B).[18] **Table 28.2** summarizes recent guideline statements about surgery for MR in patients with HF. Additional content on this topic is presented in the

online supplement for this chapter (Mitral Valve Repair for Mitral Regurgitation in Ischemic Cardiomyopathy).

In summary, in experienced centers, MV repair for patients with LV dysfunction and MR may be appropriate for those undergoing CABG as well as for selected patients with idiopathic dilated cardiomyopathy who remain symptomatic despite optimal medical therapy. The current literature suggests that functional mitral insufficiency in patients with advanced HF and LV dysfunction can be corrected with a low operative mortality in either ischemic or nonischemic cardiomyopathies. Both randomized and nonrandomized series suggest a symptomatic benefit as well as a remodeling benefit in patients with idiopathic dilated cardiomyopathy who undergo MV repair. No randomized studies have compared surgical correction of severe MR with optimal medical management. Currently, no evidence indicates that elimination of mitral insufficiency in HF patients conveys a survival benefit, but rather that this is symptomatic therapy. Percutaneous MV repair is discussed in **Chapter 69**.

Aortic Valve

The indications for valve replacement in aortic stenosis (AS) and aortic regurgitation (AR) are discussed in **Chapter 68**. The focus here is on aortic valve replacement (AVR) for patients with aortic valve disease and significant ventricular dysfunction, typically causing HF. Patients with AS may develop ventricular dysfunction with a low gradient across the aortic valve. AVR is warranted in these patients if the LV dysfunction is secondary to the AS. Accordingly, it is important to differentiate between pseudo-obstruction, with poor ventricular function leading to reduced opening of the aortic valve, and true AS. In true AS, a primary valve obstruction leads to LV dysfunction in patients with AS and a low cardiac output. Dobutamine echocardiography is useful to make this determination (**see Chapter 14**).

Although patients with true AS and LV dysfunction have been deemed inoperable in the past because of the concern of perioperative mortality, the prognosis for these patients, if they do not receive an AVR, is extremely poor, with 1-, 5-, and 10-year survival rates of 62%, 32%, and 18%, respectively.[19] No definitive trials have been conducted to demonstrate that concomitant pharmacotherapy has any impact on survival. Conversely, studies have indicated that this population of patients can undergo surgery safely, with better outcomes than with medical therapy alone. In a study from the Cleveland Clinic, the in-hospital mortality for this group of patients was 8%, with a 1-year survival rate of 82%, versus 41% for those treated with medical therapy alone; 4-year survival rates of 78% and 15% were noted for those treated with AVR and medical therapy alone, respectively.[20] Assuming that the patient has true AS with a depressed cardiac output and a low gradient, the risk-to-benefit ratio would favor surgical intervention in patients who are otherwise healthy enough to undergo surgery. In the current era, *transcatheter aortic valve replacement* (TAVR) allows a further reduction in perioperative morbidity and mortality in treating patients with HF and AS (**see Chapter 68**). Analysis of the PARTNER trial data has demonstrated TAVR to be a safe treatment strategy in high-risk patients with LV dysfunction.[21] Midterm follow-up has demonstrated a significant improvement in EF (35.7 ±8.5% to 48.6 ±11.3% at 1 year). In another common clinical scenario, the patient undergoing CABG is found to have some degree of AS as well. Studies and guideline recommendations suggest that in many situations, a dual procedure of CABG and AVR can be safely performed with better long-term outcomes.

The management of patients with severe AR and LV dysfunction poses a different problem. Some patients develop advanced HF and have been considered for cardiac transplantation because the LV dysfunction was considered to be irreversible. Although the operative mortality in this group has been high historically, a study from the Brigham and Women's Hospital has demonstrated that surgical AVR for

patients with pure AR and LV dysfunction (LVEF <35%) is safe with negligible mortality.[22] In this series, positive ventricular remodeling with improvements in LV diameter, volume, and function were observed after AVR surgery. A recent study suggests that LV remodeling after AVR for chronic AR is greatest in patients with higher global longitudinal strain indexed for end-diastolic volume,[23] correlating improved outcomes with preserved ventricular dimensions. Although late survival may not be as good in the presence of LV dysfunction compared to patients with normal preoperative LV function with severe aortic insufficiency, the outcomes may be better than with cardiac transplantation or continued medical therapy. Although a number of series have examined the prognostic variables after aortic valve surgery, patients with both low LVEF and significant aortic insufficiency are included only in small numbers.[24] For many years, guidelines have encouraged the surgical management of patients with significant AR before the onset of significant HF symptoms or severe LV dilation. More recently, newer surgical procedures have used aortic valve repair or aortic root replacement as better procedures than AVR alone in the patient with primary AR.

In summary, aortic valve surgery can be performed safely, although at higher operative risk, in patients with severe LV dysfunction and HF, and it appears to have a better clinical outcome than that achieved with current medical therapy in observational studies.

Left Ventricular Reconstruction

Revascularization and valve operations lead to clinical improvement in many patients, but in others, ventricular dilation and dysfunction are so severe that direct ventricular surgery has been proposed to optimize cardiac function. Patients who have a transmural myocardial infarction (MI) may develop ventricular dilation and remodeling that lead to changes in increased LV wall stress and LV dysfunction. A host of adverse events are initiated, including increased myocardial oxygen consumption secondary to increased wall stress, increased neurohormone and cytokine levels, afterload mismatch, and subendocardial hypoperfusion. The stated goals of ventricular reconstruction are to remove or to exclude the infarcted segment to restore an elliptical ventricular chamber, to diminish remote wall stress, to promote helical fiber orientation and increase thickening of the akinetic or dyskinetic portion of the chamber, to reduce end-systolic volume, to diminish mitral insufficiency, and to eliminate residual ischemia. Concomitant CABG often is necessary, and if more than moderate MR is present, this should be corrected separately.

This type of operation is variously named *surgical ventricular reconstruction* (SVR) or the *Dor procedure* (after Vincent Dor), in which the aneurysm or akinetic segment is reconstructed, typically with a patch (endoventricular patch plasty).[25] The operation is performed through the area of scar. A pursestring suture is placed between the infarcted and normal myocardium. An endoventricular Dacron patch usually is used to exclude the infarcted segment, with closure of the aneurysm sac over the patch. A mandrel often is used to ensure that adequate ventricular volume is maintained. This operation typically is reserved for patients who have had a large anterior-apical infarct that involves the apex, anterior wall, and septum with resulting LV remodeling. Ideally, the operation was designed to reduce end-systolic volumes by at least 30% while ensuring adequate size of the ventricle.

The RESTORE (Reconstructive Endoventricular Surgery Returning Torsion Original Radius Elliptical Shape to the Left Ventricle) multicenter study investigated various techniques for LV reconstruction in a

registry of 1198 patients with post–anterior infarction HF operated on between 1998 and 2003. Concomitant procedures included CABG in 95% and MV repair in 22%. The operative mortality rate in patients who underwent LV reconstruction was 5.3%. At 5 years the overall survival rate was 68% ±2.8%, and freedom from hospital readmission for HF was confirmed in 78%. Logistic regression analysis identified LVEF of less than 30%, LV end-systolic volume index (LVESI) of 80 mL/m^2 or higher, advanced NYHA functional class, and age older than 75 years as risk factors for death. LV reconstruction resulted in a significant decrease in LVESI (from 80.0 ±5.1 to 56.0 ±34.3 mL/m^2) and a significant increase in LVEF (from 29% ±11.0% to 39% ±12.3%).[25] Clinicians worldwide embraced this reconstructive surgery, and one arm of the STICH trial further explored the usefulness of this operative procedure for patients with ischemic cardiomyopathy.

The SVR arm of the STICH trial (hypothesis 2) tested whether adding SVR to CABG in ischemic HF patients would decrease death from any cause or cardiac rehospitalization compared with CABG alone. This substudy included 1000 patients (operated on between 2002 and 2006) with HF who had concomitant CAD, LVEF of less than 35%, and anterior LV wall scar amenable to SVR. Bypass surgery alone was performed in 499 patients and CABG plus SVR in 501 patients. They were studied for a median follow-up of 48 months. No significant difference was found in the primary outcome endpoint of death from any cause or hospitalization for cardiac causes (HR for SVR plus CABG, 0.99; 95% CI, 0.84 to 1.17; $P = 0.90$) during the 5 years of the study (**Fig. 28.5**). The results have been criticized because the average percentage reduction in end-systolic volume after CABG plus SVR was only 19%—below the accepted criterion for successful LV reconstruction, which requires a 30% (minimum) reduction in end-systolic volume. In addition, the absolute LVESI in the STICH patients undergoing CABG plus SVR was 67 mL/m^2. The results of Oh and colleagues[26] demonstrated that patients who were left with a residual LVESI greater than 60 mL/m^2 had a worse survival than that achieved in those with a more optimal LVESI of less than 30 mL/m^2. An additional limitation of the STICH trial is that 13% of patients did not have an infarct before development of LV dysfunction. A final criticism is that with an ongoing selection bias, the study did not include patients thought to clearly benefit from SVR. Many surgeons think that because of these possible shortcomings in the trial, STICH did not prove or disprove the original hypothesis. Certainly, ongoing investigations are examining predictors of success using the SVR operation in other cohorts outside of the STICH trial.

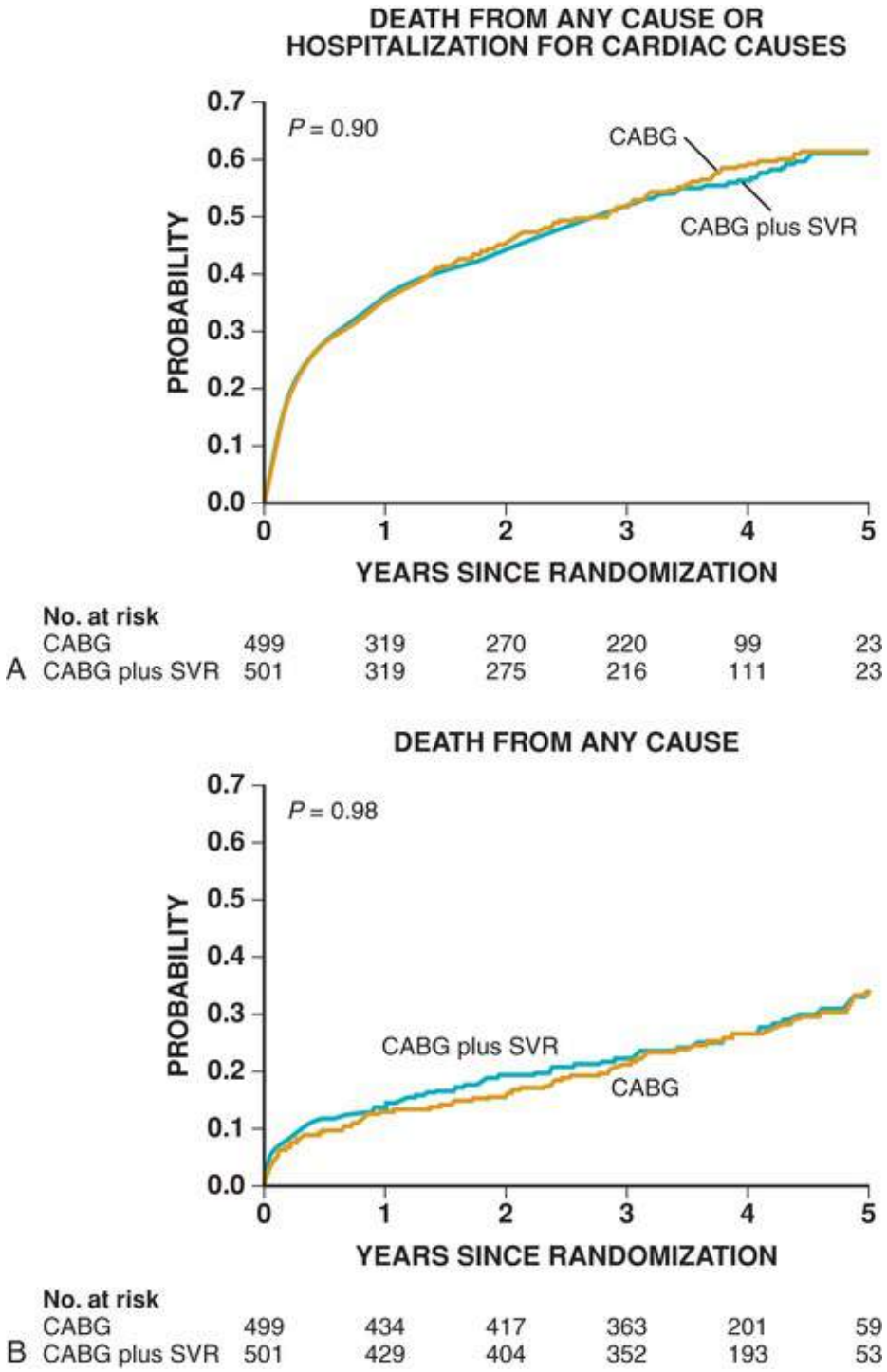

FIGURE 28.5 Results of STICH trial showing no benefit for surgical ventricular reconstruction (SVR) and CABG over CABG alone. (From Jones RH, Velazquez EF, Michler RE, et al. Coronary bypass surgery with or without surgical ventricular reconstruction. N Engl J Med 2009;360:1705.)

In addition to direct surgical ventricular reconstruction of the failing heart, a number of novel surgical approaches have also been studied to inhibit or to reverse LV remodeling, including passive cardiac support devices developed from original observations with dynamic cardiomyoplasty, which initially was intended to act as an auxiliary pump for the failing heart. Additional content on this topic is presented in the online supplement for this chapter (Passive Cardiac Support Devices).

Cardiac Transplantation

Donor Allocation System

In the United States, the allocation of donor organs is accomplished under the supervision of the United Network of Organ Sharing (UNOS), a private organization under contract to the federal government. The United States is divided geographically into 11 regions for donor heart allocation. Under UNOS policy, thoracic organs are distributed on the basis of blood type, medical urgency, and time on the waiting list. The physiologic limit of approximately 4 to 5 hours of ischemic out-of-body time for hearts precludes a national sharing of donor hearts. Currently, the highest priority for patients to receive donor organs is assigned according to the severity of illness. Each candidate awaiting heart transplantation is assigned a status corresponding to the medical urgency for that candidate. For a candidate who is 18 years of age or older at the time of listing, medical urgency is assigned according to UNOS policies[27] (**Table 28.3**). A candidate who is listed as "status 7" is considered temporarily unsuitable to receive a thoracic organ transplant. In the current system, there is marked regional variability in waitlist time across the United States[28,29]; a revised allocation proposal is under evaluation.[30,31]

TABLE 28.3

United Network of Organ Sharing (UNOS) Allocation of Hearts

Adult Heart Status 1A Requirements	
If Candidate Meets This Condition:	**Adult Status 1A Is Valid For:**
Candidates (at least 18 years old) Currently Hospitalized in Transplant Hospital	
Has a mechanical circulatory support device: Total artificial heart Intra-aortic balloon pump Extracorporeal membrane oxygenation	14 days, recertified every 14 days
Requires continuous mechanical ventilation	14 days, recertified every 14 days
Requires continuous infusion of a single high-dose IV inotrope or multiple IV inotropes and continuous hemodynamic monitoring of LV pressures	7 days, may be renewed for 7 days
Candidates (at least 18 years old), Current Hospitalization Not Required	
Has a mechanical circulatory support device: Left ventricular assist device (LVAD) Right ventricular assist device (RVAD) Left and right ventricular assist device (BiVAD)	30 days at any point after implantation
Has mechanical circulatory support, and there is medical evidence of significant device-related complication	14 days, recertified every 14 days
Adult Heart Status 1B Requirements	
If Candidate Meets This Condition:	**Adult Status 1B Is Valid For:**
Left ventricular assist device (LVAD) Right ventricular assist device (RVAD) Left and right ventricular assist device (BiVAD) Continuous infusion of IV inotrope	Unlimited time
Adult Heart Status 2 Requirements	
If Candidate Meets This Condition:	**Adult Status 2 Is Valid For:**
Registered for listing, not 1A or 1B	Unlimited time

Worldwide, patients waiting for a donor heart greatly exceed availability.[32] In the United States, as many as 40% of patients listed and waiting for a heart transplant are implanted with a mechanical circulatory support (MCS) device (**see Chapter 29**), typically a left ventricular assist device (LVAD), to maintain end-organ integrity, reduce pulmonary vascular resistance, and improve functional capacity. Serious debate has emerged concerning the additional cost of MCS to transplant and the outcomes for these patients compared with transplant recipients without a LVAD during the waiting period. Other transplant centers have chosen a strategy of accepting marginal donors for critically ill patients rather than using MCS as a bridge to transplant.

Evaluation of the Potential Recipient

Fig. 28.6 outlines the questions that must be answered to evaluate a potential patient for cardiac transplantation. Patients estimated to have less than a 1-year life expectancy are the usual candidates because the considerable risks of the transplant procedure must be taken into account; transplant

guidelines underscore this point.[33] Typically, patients for consideration have (1) cardiogenic shock requiring mechanical support or high-dose inotropic or vasopressor drugs (in which case the irreversibility of their course is usually clear); (2) chronic progressive, refractory, or stage D heart failure symptoms despite optimal therapy; (3) recurrent life-threatening arrhythmias despite maximal interventions, including implanted defibrillators; or, rarely, (4) refractory angina without potential for revascularization. Moreover, adult patients with repaired congenital heart disease, especially those with failing-Fontan physiology, are being increasingly considered for heart transplantation.

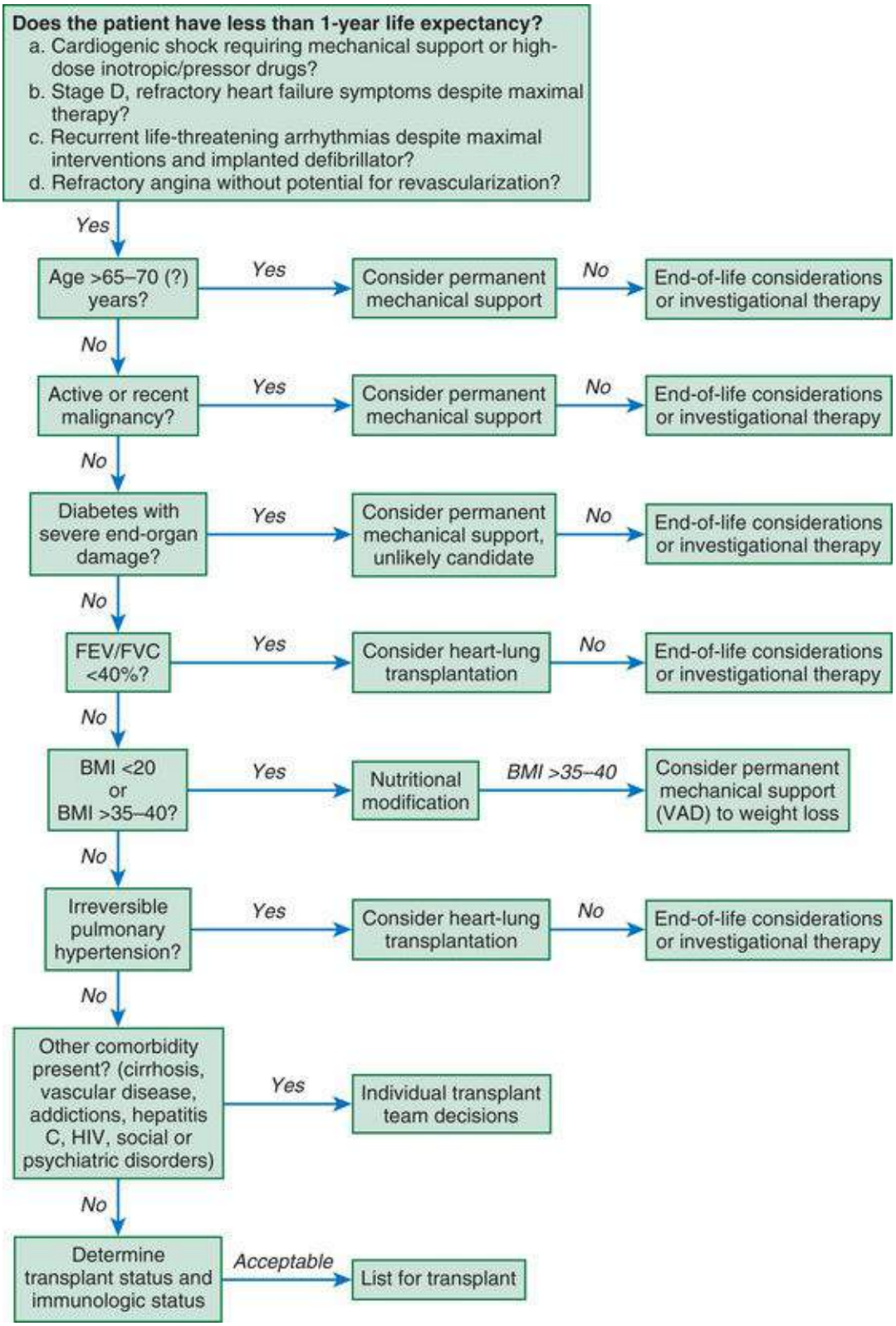

FIGURE 28.6 Algorithm for evaluation of the potential heart transplant recipient. BMI, Body mass index; FVC, forced vital capacity; FEV, forced expiratory volume; HIV, human immunodeficiency virus; VAD, ventricular assist device.

Several models have been proposed to assist in the risk stratification of HF patients with biomarkers using invasive and noninvasive methods. Models to assess the prediction of risk in a patient who will undergo transplantation also have been proposed[34-36] (**Fig. 28.7**). The most potent predictor of outcome in ambulatory patients with HF is a symptom-limited metabolic stress test to calculate peak oxygen consumption (Vo_2). A peak Vo_2 of less than 12 mL/kg/min indicates a poor prognosis, with likelihood of survival less than that with transplantation.[33] The lack of applicability of Vo_2 in patients too sick to exercise, however, has necessitated the use of other methods of risk assessment. Nonambulatory patients

requiring continuous intravenous (IV) inotropic support who cannot be weaned or who require mechanical support to maintain adequate cardiac index are more obviously at risk for a poor outcome without transplantation, but signs and symptoms of end-organ failure of the pulmonary, hepatic, and renal systems, which may signal an ominous prognosis even with a transplant procedure, are often manifested.[37,38]

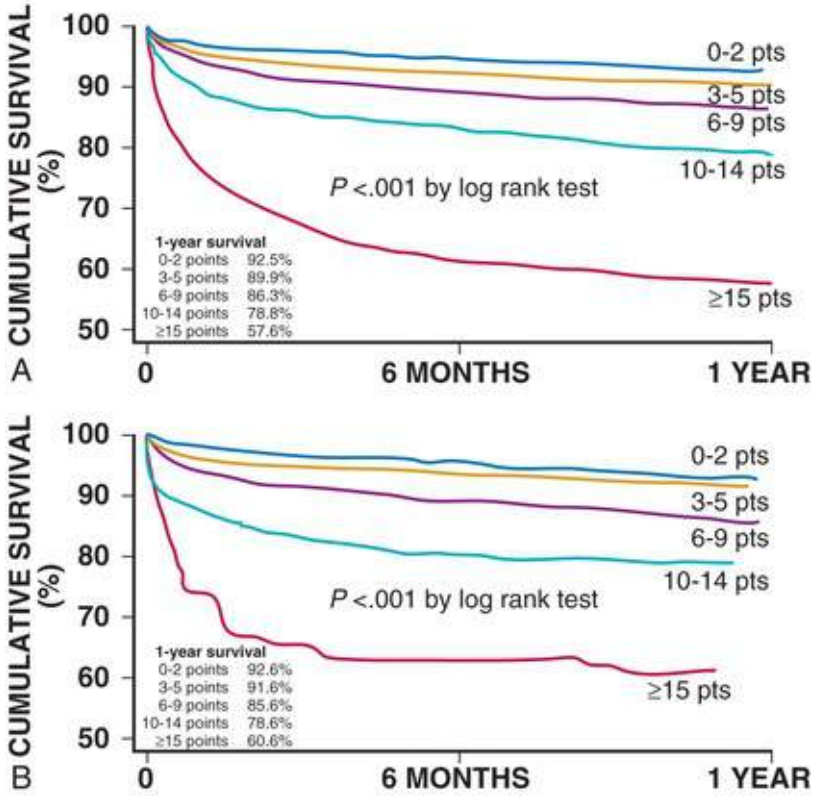

FIGURE 28.7 Kaplan-Meier cumulative 1-year survival of recipients in the derivation cohort **(A)** and validation cohort **(B)** as stratified by three-point increments of risk in the IMPACT score used to predict risk of death for patients undergoing orthotopic heart transplantation. (From Weiss ES, Allen JG, Arnaoutakis GJ, et al. Creation of a quantitative recipient risk index for mortality prediction after cardiac transplantation (IMPACT). Ann Thorac Surg 2011;92:914.)

Each patient must then undergo an extensive medical and psychosocial evaluation by the transplant team to exclude contraindications to transplantation, to further efforts at prognosis, to determine the urgency of transplantation, and to determine immunologic status.[39,40] A number of relative contraindications to heart transplantation are recognized; one of the most debated and variable among centers is the upper age limit for consideration. In general, patients older than 70 years are ineligible and more often are assigned to high-risk reparative surgery, permanent cardiac assist devices, or investigational therapies, such as cell transplantation, or to receive hearts from an alternate list of less-than-optimal donors. Nevertheless, some transplant centers maintain that carefully selected patients older than 70 can achieve outcomes equivalent to those obtained in younger patients. An active or recent malignant neoplasm, diabetes with severe end-organ damage, and other metabolic abnormalities that may limit life expectancy after transplantation are common reasons to exclude potential recipients. Significant lung disease complicates postoperative management and precludes the possibility of normal physical functioning; extremes of weight, as measured by body mass index (BMI), also have been shown to worsen post-transplantation prognosis. Patients with advanced HF associated with renal dysfunction generally are excluded from heart transplantation, because abnormal renal function increases morbidity after

transplantation. Alternatively, some centers have successfully performed simultaneous heart and kidney transplants in patients with advanced kidney disease, using organs from the same donor. Thus it is important to distinguish patients with potentially reversible renal failure from those in whom renal dysfunction is associated with advanced, irreversible end-stage renal disease.

Pulmonary arterial hypertension in a patient with pulmonary vascular resistance greater than 6 Wood units that cannot be reduced by medical therapy, or after placement of a VAD, is considered an absolute contraindication to cardiac transplantation. In the setting of fixed pulmonary hypertension, the donor right ventricle often will fail, leading to a high rate of early postoperative mortality.[41] In patients with irreversible pulmonary pressures, some centers may consider individual patients for a combined heart-lung transplant procedure. Other comorbid conditions that may have a negative impact on a transplant team's decision to further consider a potential recipient include peripheral or cerebral vascular disease, advanced neuropathy, human immunodeficiency virus (HIV) status, addictions to alcohol or illicit drugs, and social or psychiatric disorders. In selected patients with cirrhosis, a combined heart-liver transplant has been done.[42]

An increasingly sophisticated immunologic evaluation of each patient is done for ABO blood typing and antibody screening, panel-reactive antibody (PRA) level determination, and human leukocyte antigen (HLA) typing. The PRA test can identify the presence of circulating anti-HLA antibody but not the specificity or strength of antibody. Enzyme-linked immunoassay and flow cytometry can also determine PRA level and are more sensitive than the cytotoxic test.[43] Virtual crossmatch methods, in which flow cytometry–based single-antigen bead assays allow the clear identification of antibody specificities, are now widely used. Prospective donors with these antigens can be avoided, and a compatible donor can be selected without the need for a prospective crossmatch. This approach allows an increased rate of donor matching outside the geographic area of the local organ procurement organization.

The Cardiac Donor

In light of an inadequate number and increasing organ demand, efficacious donor management and selection are crucial in maintaining excellent transplant volumes and outcomes. It is critical to obtain a complete medical history for the donor, including any relevant cardiovascular disorders before brain death. All donors are screened for communicable diseases, including viral disorders such as hepatitis and HIV infection. Specific information that is relevant for the assessment of cardiac donor suitability also includes the presence or absence of thoracic trauma, disseminated cancer, donor hemodynamic stability, pressor and inotropic requirements, duration of cardiac arrest, and need for cardiopulmonary resuscitation. In some cardiac donors, hemodynamic deterioration may be caused by brain death. Cardiac echocardiography is required for all donors, and coronary arteriography is required to evaluate the presence of CAD in donors older than 45 to 50 years, depending on other risk factors.

The acceptable cold ischemia time for cardiac transplantation is approximately 4 to 5 hours; systems of ex vivo heart perfusion of human donors are under investigation.[44] Prolonged ischemic time has been shown to be a significant risk factor for death after cardiac transplantation, especially when coupled with other risk factors, such as older donor age. Donors up to age 60 to 65 years are currently considered, depending on transport distance and other donor risk factors. The final decision to accept a heart for transplantation is made at the time of harvesting, after direct examination of the heart for coronary calcification, as well as LV hypertrophy or dilation. Many regions have instituted a process of systematically reviewing donor turndown events to reduce variability and increase confidence in expanded criteria for donors. These outcome reviews have resulted in improved donor organ utilization

and transplant volumes.[45]

Surgical Considerations

The two most common surgical approaches for the implantation of the donor heart are the biatrial and the bicaval anastomoses. The *bicaval anastomosis* technique was introduced with the intention to reduce right atrial size, minimize distortion of the recipient heart, preserve atrial conduction pathways, and decrease tricuspid regurgitation. This alternative procedure entails five anastomoses: left atrium, pulmonary artery, aorta, inferior vena cava, and superior vena cava. Although no prospective trial has been conducted to establish the superiority of either technique, the bicaval technique is now being done most often in the United States, primarily because it appears to decrease the need for permanent pacemakers in transplant recipients.[46] Most important, the number of patients coming to transplantation with a VAD in place has steadily increased, so that transplant procedures are riskier and result in more device-related complications.

The most common reason for failure to wean a heart transplant recipient from cardiopulmonary bypass is right-sided heart failure, evidenced by a low cardiac output despite a rising central venous pressure. The right side of the heart can be seen in the surgical field to dilate and to contract poorly. Intraoperative transesophageal echocardiography shows a dilated, poorly contracting right ventricle and an underfilled, vigorously contracting left ventricle. Right ventricular function may be enhanced with inotropes and pulmonary vasodilators, but the prognostic importance of preoperative pulmonary vascular resistance becomes obvious in these first few hours after surgery.[41]

Immunosuppression

Immunosuppressive regimens begin with the simultaneous use of three classes of drugs: glucocorticoids, calcineurin inhibitors (CNIs), and antiproliferative agents.[47] In a subset of patients, transplant teams use a variety of drugs for induction therapy to rapidly enhance immune tolerance.[48] In the immediate postoperative period, immunosuppressive agents are given parenterally, with a quick transition to oral formulations.

Corticosteroids are nonspecific anti-inflammatory agents that work primarily by lymphocyte depletion. Patients initially receive high doses of IV and then oral corticosteroids, which are gradually tapered during the next 6 months; the goal often is to withdraw corticosteroid therapy completely. At many centers, corticosteroids are given several hours before the transplant surgery. Side effects include cushingoid appearance, hypertension, dyslipidemia, weight gain with central obesity, peptic ulcer formation and gastrointestinal bleeding, pancreatitis, personality changes, cataract formation, hyperglycemia progressing to corticosteroid diabetes, and osteoporosis with avascular necrosis of bone. The well-appreciated adverse side effect profile of the corticosteroids has led to a number of innovative strategies to eliminate them as early as possible after the transplant surgery. Corticosteroids usually are the agents of first choice to treat acute rejection as well.

There are two CNIs, *cyclosporine* and *tacrolimus*. Their main mechanism of action involves binding to specific proteins to form complexes that block the action of *calcineurin*, a key participant in T cell activation. The CNIs serve to block the signal transduction pathways responsible for T cell and B cell activation and therefore act specifically on the immune system and do not affect other, rapidly proliferating cells. Critical and often limiting adverse effects include nephrotoxicity in as many as 40% to 70% of patients and hypertension with the development of LV hypertrophy; both drugs cause

approximately equivalent numbers of these untoward events. Hirsutism, gingival hyperplasia, and hyperlipidemia are more frequent with cyclosporine, and diabetes and neuropathy are more common with tacrolimus. In addition, an increased incidence of deep vein thrombosis, tremor, headache, convulsions, and paresthesias of the limbs has been reported with both drugs.

Antiproliferative agents work to either directly or indirectly inhibit the expansion of alloactivated T cell and B cell clones. *Azathioprine* was the earlier agent used in this class and served as the mainstay of immunosuppression even before the routine use of cyclosporine. In the past decade, *mycophenolate mofetil* (MMF) has replaced azathioprine as the first-line antiproliferative agent, with several randomized trials demonstrating superiority compared with azathioprine.[49] MMF is hydrolyzed to mycophenolic acid, which inhibits de novo purine synthesis. Both azathioprine and MMF cause leukopenia as their major adverse effect; the use of MMF can be limited by debilitating diarrhea or nausea. The combination of MMF and tacrolimus likely potentiates their individual adverse effects.

Sirolimus (often called *rapamycin*) and *everolimus* are two newer agents that block activation of T cells after autocrine stimulation by interleukin-2 (IL-2). They also are known to inhibit proliferation of endothelial cells and fibroblasts. Their action is complementary to that of CNIs, and both sirolimus and everolimus have been used as maintenance immunosuppression, as alternatives to standard immunosuppression, and as rescue drugs for rejection. Sirolimus, an m-TOR inhibitor, has been shown to slow progression of *cardiac allograft vasculopathy* (CAV) with established disease,[50] and everolimus has been demonstrated to reduce both acute rejection and CAV. Because the drugs inhibit the proliferation of fibroblasts, they may cause significant difficulties with wound healing, and many centers do not use them for initial therapy immediately after the transplant surgery. The drugs have been associated with the development of significant pericardial effusions. Several investigators have explored using sirolimus as a primary immunosuppressive agent as an alternative to a CNI.[51] Sirolimus and everolimus have been used to replace CNIs as a strategy to improve renal dysfunction or to reverse LV hypertrophy.

With improved immunosuppression, the incidence of any cardiac rejection from donor heart implantation to 1 year has decreased from 30% in 2004 to 2006 to 25% in 2010 to 2012,[52] underscoring the efficacy of current immunosuppression. The TICTAC (Tacrolimus in Combination, Tacrolimus Alone Compared) trial reported that the addition of MMF to single-agent immunosuppression with tacrolimus did not provide an advantage over single-agent immunosuppression in terms of rejection, CAV, or 3-year survival.[53] Corticosteroids were successfully discontinued in all patients. The statistical power of the trial, which included only 150 patients, has been questioned, but these findings have led the heart transplant community to explore a strategy of even less immunosuppression in select patients.

Rejection

Rejection involves cell- or antibody-mediated cardiac injury resulting from recognition of the cardiac allograft as non-self. By histologic and immunologic criteria, this process is categorized into three major types of rejection: hyperacute, acute, and chronic. *Hyperacute* rejection results when an abrupt loss of allograft function occurs within minutes to hours after circulation is reestablished in the donor heart and is rare in modern-day transplantation. The phenomenon is mediated by preexisting antibodies to allogeneic antigens on the vascular endothelial cells of the donor organ, which is now avoided with current HLA typing techniques. These antibodies fix complement, which promotes intravascular thrombosis. Subsequently, rapid occlusion of graft vasculature occurs, followed by swift and overwhelming failure of the cardiac graft.

Acute cellular rejection or cell-mediated rejection is a mononuclear inflammatory response,

predominantly lymphocytic, directed against the donor heart. It is most common from the first week to several years after transplantation and occurs in up to 30% of patients during the first year after surgery. The key event in both the initiation and the coordination of the rejection response is T cell activation, moderated by IL-2, a cytokine. IL-2 is produced by $CD4^+$ cells and to a lesser extent by $CD8^+$ cells and exerts both an autocrine and a paracrine response. Unlike in renal and liver transplants, no reliable serologic markers for rejection in the cardiac transplant have been identified, although several reports have explored the utility of using high-sensitivity cardiac troponin I for this purpose. Therefore the endomyocardial biopsy remains the "gold standard" for the diagnosis of acute rejection (**see Chapter 79**). Biopsies are performed using a transjugular approach weekly and then every other week for several months; monthly biopsies continue for 6 to 12 months in many programs and for years thereafter in others. There is ongoing scrutiny of the cost-effectiveness of routine or surveillance biopsies after 1 year.[54]

Cell-mediated rejection is graded according to a universally agreed-on system[55] (**Table 28.4**). Endomyocardial biopsies are invasive and painful and may cause serious adverse events such as pericardial tamponade or tricuspid insufficiency. Accordingly, efforts continue to develop a serologic assay composed of gene expression or transcriptional factors that are significantly regulated during cardiac rejection. The largest trial to date, IMAGE (Invasive Monitoring Attenuation through Gene Expression), demonstrated that among select patients who had received a cardiac transplant more than 6 months before entering the study, and who were at a low risk for rejection, a strategy of monitoring for rejection that involved gene-expression profiling, compared with use of routine biopsies, was not associated with an increased risk of serious adverse outcomes and resulted in the performance of significantly fewer biopsies.[56] It is not clear how readily this assay has been adopted in the United States, although the study seems to have resulted in a lower rate of endomyocardial biopsies done for surveillance only. Cardiac magnetic resonance imaging has also been investigated as a modality to detect rejection.

TABLE 28.4

Current Grading System for Cell-Mediated Rejection in Heart Transplantation Compared with an Earlier System

2004 SYSTEM		1990 SYSTEM	
Grade 0 R	No rejection	Grade 0	No rejection
Grade 1 R, mild	Interstitial and/or perivascular infiltrate with up to one focus of myocyte damage	Grade 1, mild	
		A—focal	Focal perivascular and/or interstitial infiltrate without myocyte damage
		B—diffuse	Diffuse infiltrate without myocyte damage
Grade 2 R, moderate	Two or more foci of infiltrate with associated myocyte damage	Grade 2, moderate (focal)	One focus of infiltrate with associated myocyte damage
Grade 3 R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage, ± vasculitis	Grade 3, moderate	
		A—focal	Multifocal infiltrate with myocyte damage
		B—diffuse	Diffuse infiltrate with myocyte damage
		Grade 4, severe	Diffuse, polymorphous infiltrate with extensive myocyte damage ± hemorrhage ± vasculitis

Modified from Stewart S, Winters GL, Fishbein MC, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant 2005;24:1710.

Risk factors for early rejection include younger recipient age, female sex, female donor, positive cytomegalovirus (CMV) serologic test results, prior infections, black recipient race, and number of HLA mismatches; a risk score predictive for rejection has been developed.[57] Most important, patients who fail to take or to tolerate their immunosuppressant drugs, especially early in the postoperative course, are at very high risk for severe or recurrent cellular rejection. The occurrence of one or more episodes of treated rejection during the first year is a risk factor for both failure to attain 5-year survival and

development of transplant-related CAD. Likewise, treatment of acute rejection in the first 6 months after transplantation contributes to a slower overall rehabilitation of the patient.

The aggressiveness of treatment for cell-mediated rejection depends on the biopsy grade, clinical correlation, patient risk factors, rejection history, length of time after transplantation, and whether or not target levels of the immunosuppressant drugs are achieved. For example, an asymptomatic, early moderate rejection occurring soon after transplantation in a patient in whom immunosuppressants are at or above target levels, or who has one or more risk factors for early rejection, would be treated more aggressively than a low-risk patient with no previous history of cell-mediated rejection.

Another form of acute rejection is acute humoral rejection, or *antibody-mediated rejection,* which occurs days to months after transplantation and is initiated by antibodies rather than by T cells. The alloantibodies are directed against donor HLA or endothelial cell antigens. Antibody-mediated rejection is a serious complication after heart transplantation and is manifested as "graft dysfunction" or hemodynamic abnormalities in the absence of cellular rejection on biopsy. Antibody-mediated rejection is now recognized as a distinct clinical entity, and strict histopathologic and immunologic criteria for its diagnosis have been established (**eTable 28.1**).[58] Patients at greatest risk for antibody-mediated rejection are women and patients with a high PRA level or a positive crossmatch. It is estimated that significant antibody-mediated rejection occurs in about 7% of patients, but the rate may be as high as 20%. Because antibody assays are becoming more precise, more antibody-mediated rejection probably will be recognized, with a correlating need for newer treatment algorithms.

ETABLE 28.1

Findings in Acute Antibody-Mediated Rejection (AMR) of Cardiac Transplants

	REQUIRED FINDINGS	OPTIONAL
1. Clinical evidence of acute graft dysfunction		Recommended in combination with other evidence to support diagnosis of AMR
2. Histologic evidence of acute capillary injury (a and b required)	a. Capillary endothelial changes b. Macrophages in capillaries	c. Neutrophils in capillaries (severe) d. Interstitial edema hemorrhage (severe)
3. Immunopathologic evidence for antibody-mediated injury (a or b or c required)	a. IgG, IgM, and/or IgA + C3d and/or C4d or Clq (2-3+ intensity) by IF b. CD 68 for macrophiages in capillaries (CD31 or CD34) and/or C4d (2-3+ intensity) in capillaries by paraffin IH c. Fibrin in vessels (severe)	
4. Serologic evidence of anti-HLA or antidonor antibodies		Anti-HLA class I and/or class II or other antidonor antibody at biopsy (supportive of clinical and/or morphologic findings)

IF, Immunofluorescence; *IH,* immunohistochemistry.

Modified From Reed EF, Demetris AJ, Hammond E, et al. Acute antibody-mediated rejection of cardiac transplants. J Heart Lung Transplant 2006;25:153-9.

Chronic rejection, or late graft failure, is an irreversible gradual deterioration of graft function that occurs in many allografts months to years after transplantation. Current concepts suggest that donor heart dysfunction in the chronic stages of maintenance immunosuppression is related to chronic rejection, is mediated by antibodies, or is a result of progressive graft loss from ischemia. The latter process is characterized by intimal thickening and fibrosis, leading to luminal occlusion of the graft vasculature, and is often referred to as CAV or transplant CAD.[59]

Infection

Despite the advances in immunosuppressive management, a major untoward consequence remains the occurrence of life-threatening infections. Infections cause approximately 20% of deaths within the first year after transplantation and continue to be a common contributing factor in morbidity and mortality

throughout the recipient's life. The most common infections in the first month after surgery are nosocomial bacterial and fungal infections related to mechanical ventilation, catheters, and the surgical site; the use of MCS as a bridge to transplant has increased the overall infectious rate. Mortality is highest for fungal infections, followed by protozoal, bacterial, and viral infections. Aspergillosis and candidiasis are the most common fungal infections after heart transplantation. Viral infections, especially those caused by CMV, can enhance immunosuppression, potentially resulting in additional opportunistic infections. Accordingly, patients typically are given a prophylactic regimen against CMV, *Pneumocystis jiroveci*, and herpes simplex virus infections and oral candidiasis, to be used during the first 6 to 12 months after transplantation. Prophylactic IV ganciclovir or oral valganciclovir generally is given for variable periods in CMV-seronegative recipients of a transplant from a CMV-positive donor.

Medical Complications and Comorbid Conditions

The complications that follow heart transplantation reflect in part the premorbid status of a majority of transplant recipients, who have vascular disease and other significant medical conditions.[38] After 5 years, more than 90% of recipients have hypertension, at least 80% have hyperlipidemia, and more than 30% have diabetes[60] (**Table 28.5**). Each year after transplantation, clinically significant CAV—which is the major limitation to long life after transplantation—will develop in a large number of patients. By 5 years, almost 30% of recipients will have CAV, and at least half will be so afflicted at 10 years. Cardiac allograft vasculopathy is the most common reason why retransplant is undertaken in the United States (**Fig. 28.8**). Likewise, progressive renal insufficiency is an insidious problem that has only recently been addressed by substitution protocols to limit the administration of CNIs.

TABLE 28.5

Cumulative Post–Heart Transplant Morbidity Rates for Adult Patients*

OUTCOME	WITHIN 5 YEARS	TOTAL NO. OF PATIENTS WITH KNOWN RESPONSE	WITHIN 10 YEARS	TOTAL NO. OF PATIENTS WITH KNOWN RESPONSE
Hypertension	92%	13,023	N/A	N/A
Renal dysfunction	52%	15,769	68%	5428
Abnormal creatinine <2.5 mg/dL	33%		39%	
Creatinine >2.5 mg/dL	15%		20%	
Chronic dialysis	2.9%		6.0%	
Renal transplantation	1.1%		3.6%	
Hyperlipidemia	88%	14,372	N/A	N/A
Diabetes	38%	15,458	N/A	N/A
Cardiac allograft vasculopathy	30%	11,511	50%	3146

*Cumulative prevalence in survivors at 5 and 10 years after transplantation (January 1995 to June 2013). N/A, Not available.

Modified from Lund LH, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-first Official Adult Heart Transplant Report—2014. Focus theme: retransplantation. J Heart Lung Transplant 2014;33:996-1008.

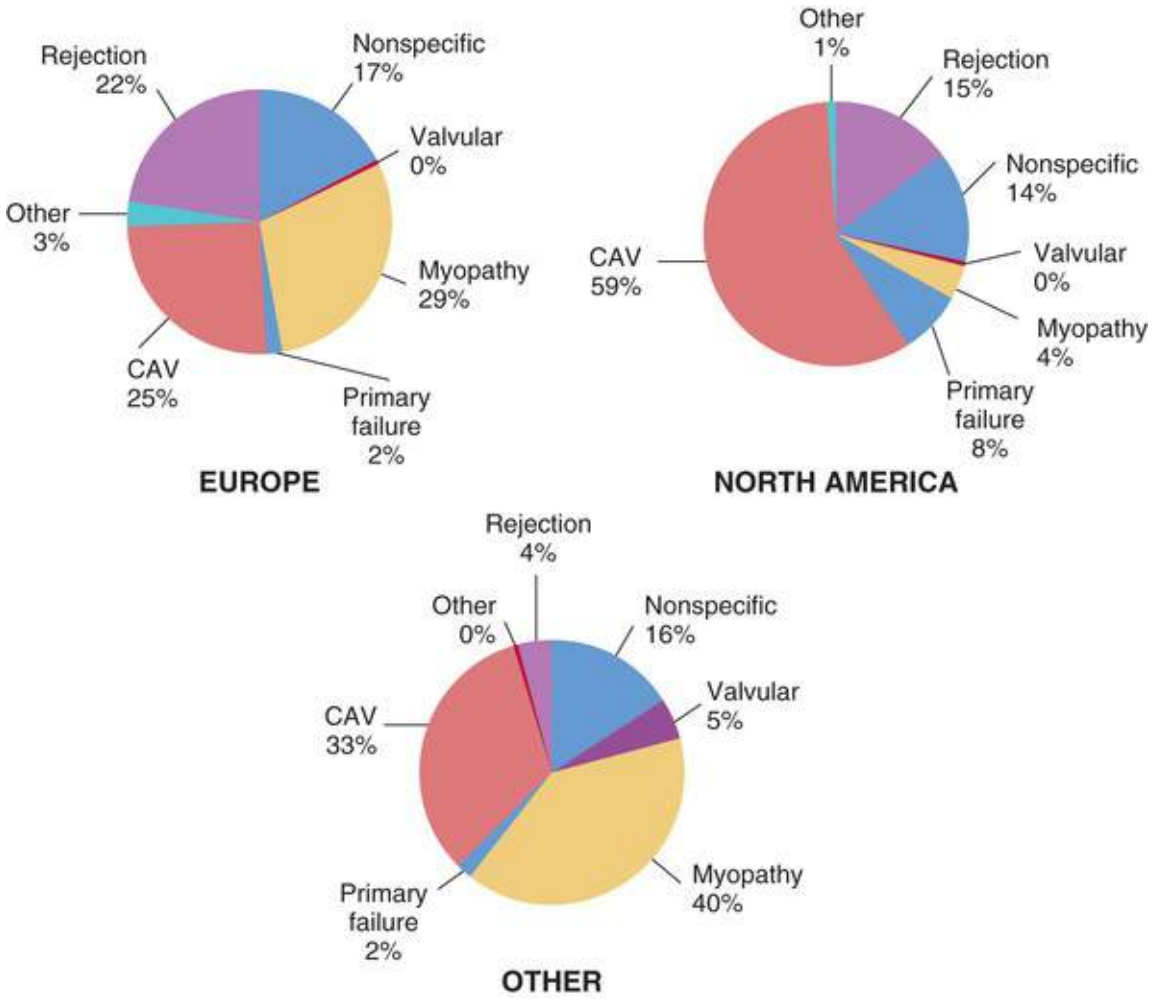

FIGURE 28.8 Indication for retransplantation by geographic location for adult heart retransplantation (2006 to June 2013). CAV, Cardiac (coronary) allograft vasculopathy. (From Lund LH, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-first Official Adult Heart Transplant Report—2014. Focus theme: retransplantation. J Heart Lung Transplant 2014;33:996-1008.)

Malignant Neoplasia

The magnitude of overimmunosuppression in many transplant recipients is illustrated by the prediction of a 30% to 40% incidence of neoplasia in these patients during the past 30 years. The risk of fatal malignant disease progressively increases in the years after transplantation, and there is a substantially higher risk in immunosuppressed patients than in the normal population.[61] Post-transplantation lymphoproliferative disease and lung cancer are the most common fatal malignant neoplasms (**Table 28.6**).

TABLE 28.6

First Malignancy Occurring after Adult Heart Transplant*

TYPE/LOCATION	TOTAL	MALES	FEMALES
	n (%)	*n* (%)	*n* (%)
Lung carcinoma	111 (21)	87 (21)	24 (23)
PTLD/lymphoma	88 (17)	76 (18)	12 (11)
Prostate carcinoma	81 (15)	81 (19)	—
Melanoma	35 (6.7)	32 (7)	3 (2.9)
Colon carcinoma	26 (4.9)	18 (4.5)	7 (6.7)
Breast carcinoma	22 (4.2)	—	21 (20)

*Excludes basal cell and squamous cell skin cancer.

PTLD, Post-transplant lymphoproliferative disease.

Adapted from Higgins RS, Brown RN, Chang PP, et al. A multi-institutional study of malignancies after heart transplantation and a comparison with the general United States population. J Heart Lung Transplant 2014;33:478-85.

Diabetes Mellitus

Patients in whom new-onset diabetes mellitus (DM) develops after transplantation are at increased risk for morbidity and mortality. Accumulating evidence suggests that long-term outcomes, including patient survival and graft survival, may be adversely affected. Much of the diabetes that occurs is attributed to the high-dose corticosteroids used early after transplant surgery, but it is now appreciated that the CNIs play an important role as well. Impaired B cell function appears to be the primary mechanism of CNI-induced new-onset DM.

The risk factors for the development of DM after transplantation include obesity, increased age, family history of DM, abnormal glucose tolerance, and African American or Hispanic descent. Changing trends in the demographics of transplant patients, such as increased age and increased BMI, suggest that these patients may now be at a greater risk for new-onset DM than in the past.[40] Increased BMI increases risk of insulin resistance, and corticosteroids can cause glucose intolerance, insulin resistance, and frank hyperglycemia. African Americans are more likely to develop new-onset DM regardless of the immunosuppression used but are particularly susceptible after treatment with tacrolimus.

Hypertension

The excess risk of hypertension is related primarily to the use of CNIs because of both direct effects of the drugs on the kidney and the associated renal insufficiency that also is highly prevalent. The incidence of hypertension may be lower with tacrolimus than with cyclosporine. Post-transplantation hypertension is difficult to control and often requires a combination of several antihypertensive agents.

Renal Insufficiency

The risk for the development of chronic renal failure after heart transplant is approximately 10% to 15% by 5 years.[62] Moreover, acute kidney failure complicates the early postoperative course in as many as 40% to 70% of patients. The various postulated causes of CNI-associated early renal insufficiency include direct CNI-mediated renal arteriolar vasoconstriction, increased levels of endothelin-1 (a potent vasoconstrictor), decreased nitric oxide production, and alterations in the kidney's ability to adjust to changes in serum tonicity. Once early renal insufficiency occurs, progressive renal failure has appeared to be inexorable, until recently. Investigators continue to evaluate the effects on renal function, as well as on rejection episodes, of substituting an m-TOR inhibitor (sirolimus or everolimus) for a CNI.[51,63]

Hyperlipidemia

Hyperlipidemia is common after transplantation, as it is in the general population. The concern has been that many studies have demonstrated an association of hyperlipidemia with the development of CAV and cerebrovascular and peripheral vascular disease, with the attendant morbidity and mortality of these vascular disorders. Typically, total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides increase by 3 months after transplantation and then generally fall somewhat after the first year. A number of drugs commonly used after transplantation contribute to the hyperlipidemia observed. Corticosteroids may lead to insulin resistance, increased free fatty acid synthesis, and increased very-low-density lipoprotein production. Cyclosporine increases serum LDL cholesterol and binds to the LDL receptor, decreasing its availability to absorb cholesterol from the bloodstream; tacrolimus probably causes less hyperlipidemia. Sirolimus and MMF also have unfavorable effects on lipids. Sirolimus in escalating doses has been shown to result in prominent elevation of triglyceride levels.

Lipid-lowering therapy with any statin, or HMG-CoA reductase inhibitor, was strongly associated with a marked improvement in 1-year survival in the Heart Transplant Lipid Registry. In heart transplant recipients, pravastatin and simvastatin have been associated with outcome benefits in survival, severity of rejection, incidence of CAV, and even malignancies.[64]

Cardiac Allograft Vasculopathy

The development of transplant vasculopathy remains the most prominent long-term complication of heart transplantation, with an annual incidence rate of 5% to 10%. The prognosis for heart transplant recipients is largely determined by the occurrence of CAV; after the first postoperative year, CAV becomes increasingly important as a cause of death. CAV can develop as early as 3 months after transplantation and is detected angiographically in 20% of grafts at 1 year and in 40% to 50% at 5 years. In contrast with eccentric lesions seen in atheromatous disease, CAV results from neointimal proliferation of vascular smooth muscle cells, so that it is a generalized process. The condition typically is characterized by concentric narrowing that affects the entire length of the coronary tree, from the epicardial to the intramyocardial segments, leading to rapid tapering, pruning, and obliteration of third-order branch vessels. A majority of patients will not experience anginal symptoms because of denervation of coronary arteries. The first clinical manifestation of CAV may be myocardial ischemia and infarction, HF, ventricular arrhythmia, or SCD.

The causes of transplant vasculopathy are multifactorial. The risk for CAV increases as the number of HLA mismatches and the number and duration of rejection episodes increase. Various nonimmunologic factors, including CMV infection of the recipient,[65] donor or recipient factors (e.g., age, sex, pretransplantation diagnosis), and factors related to surgery (e.g., ischemia-reperfusion injury), have been associated with development of CAV and increase the risk for CAV. Classic risk factors for vascular disease, such as smoking, obesity, diabetes, dyslipidemia, and hypertension, also contribute to development of CAV.

In an effort to detect CAV, transplant teams must devise an approach to screen for the disease and, when it is found, to control its progression. Coronary angiography is limited by the fact that CAV produces concentric lesions that affect the distal and small vessels, often before it becomes apparent in the main epicardial vessels. Intravascular ultrasound (IVUS) is the most sensitive imaging technique to study early transplant vasculopathy. IVUS provides quantitative information on vessel wall morphology and lumen dimensions. An increase in intimal thickness of at least 0.5 mm in the first year after transplantation is a reliable indicator of both CAV development and 5-year mortality. However, the inherent invasiveness of

IVUS and the cost of the procedure preclude its widespread application. Dobutamine stress echocardiography has been described as having high sensitivity (83% to 95%) and specificity (53% to 91%) compared with angiographic evaluation of CAV but has been challenged in preference to coronary computed tomographic angiography. Most transplant centers do either coronary angiography or another screening test on an annual basis to assess the risk of new CAV.

A number of trials have been undertaken to examine the efficacy of sirolimus or everolimus in preventing the development or progression of CAV in heart transplant recipients. The precise role of the two drugs in maintenance immunosuppression has not yet been determined, but they are used frequently, with promising results for reduction of coronary intimal thickening once CAV has been detected.[66] Percutaneous coronary intervention with or without coronary stents has been used, with some success.

Outcomes after Heart Transplantation

Survival

Fig. 28.9 depicts the latest data from the International Society for Heart and Lung Transplantation on overall transplant survival, grouped by age at transplant.[52] During the first year after transplantation, early causes of death are graft failure, infection, and rejection, with an overall survival rate at 1 year of 82%. Of interest, although worldwide approaches to the management of the cardiac transplant recipient are substantially different from center to center, the outcomes are surprisingly similar in high-volume programs. Indeed, this phenomenon of similar outcomes despite marked differences in programmatic management may be regarded as a testament to the overall antirejection strategy; institutional and recipient factors determine survival as well.[67-69] Nonspecific graft failure contributes to approximately 35% of deaths during the first 30 days after transplantation, whereas non-CMV infection was the primary cause of death during the first year. After 5 years, CAV and late graft failure (approximately 30% together), malignant neoplasia (25%), and non-CMV infection (10%) are the most prominent causes of death.[52,70] Management of this challenging group of patients has been enhanced by specialty-trained nurses and the development of a multidisciplinary care team.[70]

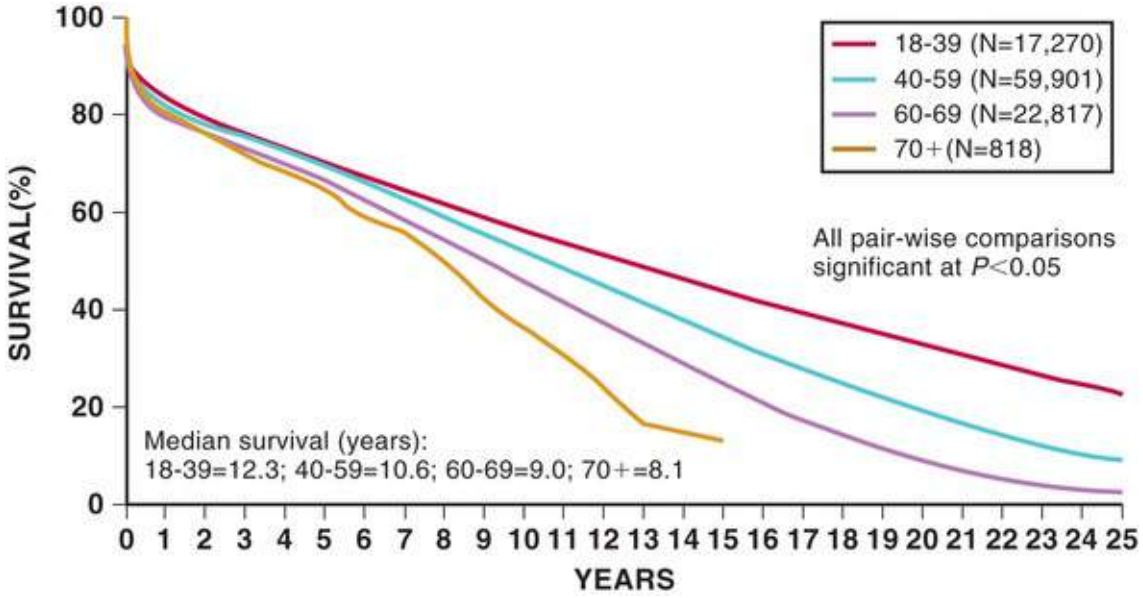

FIGURE 28.9 Kaplan-Meier long-term survival by age at transplant. (Transplants done between January 1982 and June 2013.) (From Lund LH, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-second Official Adult Heart Transplantation Report—2015. Focus theme: early graft failure. J Heart Lung Transplant 2015;34:1244-54.)

Functional Outcomes

By the first year after transplantation surgery, 90% of surviving patients report no functional limitations, and approximately 35% return to work. These figures may change as the demographics of cardiac transplant recipients evolve. Numerous challenges to ensure optimal functional outcomes have been identified, including inadequate access to cardiac rehabilitation programs. Some U.S. employers are reluctant to hire the transplant survivor.

The heart transplant procedure greatly reduces cardiac filling pressures observed in the recipient before transplantation and augments cardiac output. Abnormal maximal cardiac output during exercise may be secondary to denervation, limited atrial function, decreased myocardial compliance from rejection or ischemic injury, and donor-recipient size mismatch. Much of this hemodynamic abnormality may be normalized with regular exercise. Immediately after surgery, a restrictive hemodynamic pattern frequently is observed that gradually lessens over a few days to weeks. Some 10% to 15% of recipients develop a chronic cardiac restrictive-type response during exercise that may produce fatigue and breathlessness. In the absence of parasympathetic innervation, which normally lowers the heart rate, the resting heart rate of a recipient typically is 90 to 115 beats/min. Likewise, beta blockers may further impair exercise response in the transplant recipient and should not be given as first-line agents for treatment of hypertension in this group.[71]

Future Perspectives

There are many potential reasons why surgery may be considered in patients with heart failure, especially those with ischemic cardiomyopathy. The most widely used surgical procedure for heart failure is coronary artery bypass grafting; the long-term results of the STICH trial results may impact the frequency of CABG in the future. Clearly, the immediate perioperative mortality for all surgical procedures has dropped remarkably over the past two decades. The availability of ventricular assist devices (VADs; **Chapter 29**) and less invasive procedures such as transcatheter aortic valve replacement (TAVR;

Chapter 72) will undoubtedly change the scope of HF surgery in the future. For the patient with advanced HF, a true comparative effectiveness trial between heart transplant and permanent VAD may be difficult, but the concept and the research required to undertake such a trial are often debated.

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Mitral Valve Repair for Mitral Regurgitation in Ischemic Cardiomyopathy

Proponents of mitral valve repair (MVR) for functional mitral regurgitation (MR) argue that in appropriately selected patients, durable MVR will result in greater reverse left ventricular (LV) remodeling. Data to support this claim is also provided by several studies that evaluated MVR either alone or in combination with coronary artery revascularization for patients with ischemic disease. Braun and colleagues[1] showed that the combination of MVR and CABG resulted in a significant decrease in LV end-diastolic volume up to 4 years after surgery as a result of MVR. Fattouch and associates,[2] in a randomized study of coronary artery bypass grafting (CABG) versus CABG and MVR, demonstrated that the addition of MVR improves postoperative NYHA functional class and ventricular remodeling, decreases pulmonary artery pressure, and leads to a decrease in hospitalization for heart failure.[2] Although these studies are in contrast to the findings of the CTSnet prospective trial findings, they provide evidence to support the benefits of MVR in a subgroup of appropriately selected patients.

Several investigators have evaluated the combination of subvalvular repair techniques in addition to traditional restrictive annuloplasty to reduce recurrence of MR in the case of severe MR, including papillary muscle slings, papillary muscle relocation, anterior leaflet augmentation, and chordal cutting.[3,4] A recent randomized prospective trial evaluating the repair of severe ischemic MR ($n = 96$) with either isolated restrictive mitral annuloplasty or restrictive annuloplasty with papillary muscle reapproximation found a significant improvement in ventricular remodeling (LVEDD change, −5.8 ±4.1 mm vs. −0.2 ±2.3 mm; $P < 0.001$) and improvement in ejection fraction (mean change, +8.8 ±5.9% vs. 2.5 ±4.3%; $P < 0.001$) with the combination annuloplasty and papillary muscle reapproximation compared to restrictive

annuloplasty alone.[5] Interestingly, the authors noted only 15.0% and 13.2% recurrence of moderate to severe MR at 2 years, respectively, for the annuloplasty and annuloplasty and papillary muscle reapproximation groups. These reports provide further evidence for the role of MVR in severe functional MR that remains to be elucidated.

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Passive Cardiac Support Devices

Novel surgical approaches have been undertaken to inhibit or to reverse LV remodeling, including passive cardiac support devices, which were developed from original observations with dynamic cardiomyoplasty, intended to act as an auxiliary pump for the failing heart.[1] Subsequent hemodynamic assessments in animals and humans have suggested that much of the observed benefit of dynamic cardiomyoplasty appeared to be derived from the passive girdling effect of the muscle wrap, which limits ventricular dilation, reduces LV wall stress, and prevents LV remodeling. These early experiences with dynamic cardiomyoplasty and the insights into its biologic effects led to the development of surgical therapies specifically aimed at inhibiting LV remodeling. Unfortunately, the two different cardiac support devices that have undergone clinical trials (Acorn Pivotal Trial and PEERLESS-HF) either were stopped for futility (PEERLESS-HF) or failed to show a convincing risk-to-benefit profile (Acorn Pivotal Trial), despite a long-term follow-up evaluation of the patients that did not identify any safety concerns and demonstrated apparently favorable outcomes. At present, no U.S. Food and Drug Administration (FDA)–approved cardiac support devices are available in the United States.

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29

Mechanical Circulatory Support

Keith D. Aaronson, Francis D. Pagani

Mechanical circulatory support (MCS) devices are mechanical pumps designed to assist or replace the function of either the left or the right ventricle, or both ventricles, of the heart. Important characteristics of MCS devices include (1) location of the pumping chamber, (2) specific ventricle(s) supported, (3) pumping mechanism, and (4) indicated duration of support, for either temporary (days to weeks) or long-term (months to years) use (**Table 29.1**). Typically, short-term devices are *extracorporeal* (or *paracorporeal*) pumps (pump located outside the body), whereas durable devices are implantable (*intracorporeal*) systems.

TABLE 29.1

Terminology Describing Characteristics of Mechanical Circulatory Support (MCS) Devices

Pump Location
Extracorporeal: Pump located outside the body *Paracorporeal*: Pump located outside but adjacent to the body *Intracorporeal*: Pump implanted within the body *Orthotopic*: In the normal position of the heart (TAH)
Ventricle Supported
LV support (LVAD) RV support (RVAD) Biventricular support (BiVAD) Biventricular replacement (TAH)
Intended Use
Short-term: Days to weeks (BTR indication) 1. Patient remains hospitalized 2. Patient tethered to pump *Long-term*: Months to years (BTT or DT indication) 1. Patient discharged with untethered, "hands-free" mobility
Pump Mechanism[6,7]
Pulsatile flow, volume displacement with: 1. Pneumatic actuation, *or* 2. Electrical actuation *Continuous-flow* rotary pump with *axial design* (flow of blood is along axis of symmetry of pump) *and* 1. Bearing support of impeller (mechanical pivot), *or* 2. Magnetic or hydrodynamic levitation of impeller (bearingless design) *Continuous-flow* rotary pump with *centrifugal design* (flow of blood from center to periphery of pump) *and* 1. Bearing support of impeller, *or* 2. Magnetic or hydrodynamic levitation of impeller (bearingless design)

BiVAD, Biventricular support; *BTR,* bridge to recovery; *BTT,* bridge to transplantation; *DT,* destination therapy; *LVAD,* left ventricular assist device; *RVAD,* right ventricular assist device; *TAH,* total artificial heart.

Indications and Device Selection

Three indications for MCS are approved by the U.S. Food and Drug Administration (FDA) and reimbursed by the Centers for Medicare and Medicaid Services (CMS): bridge to recovery, bridge to transplantation, and destination therapy.

Bridge to Recovery

Bridge to recovery (BTR) refers to the use of MCS devices in patients with acute cardiogenic shock or acute decompensated heart failure that is refractory to optimal medical management (OMM), also characterized by a reasonable expectation that the myocardial injury is reversible and that myocardial function will recover during a short period of temporary MCS. The short-term use of MCS for BTR is the most common application of this modality in the United States. Examples of reversible forms of myocardial injury are acute myocardial infarction (AMI), acute myocarditis, and postcardiotomy cardiogenic shock resulting from ischemic myocardial stunning. Several types of devices can provide temporary circulatory support in these circumstances, including intra-aortic balloon pumps (IABP) (**Fig. 29.1**), surgically and percutaneously placed extracorporeal/paracorporeal ventricular assist devices (VADs) (**Figs. 29.2 to 29.4**), and systems for extracorporeal life support (**Fig. 29.5**), previously called extracorporeal membrane oxygenation, which provide both cardiac and pulmonary support. Typically, temporary MCS devices (e.g., IABP; Impella 2.5, CP, and 5.0; TandemHeart) are placed percutaneously to facilitate rapid initiation of cardiac support and ease of removal when cardiac function recovers. Some types of extracorporeal VAD systems require major operative procedures with sternotomy for access and

placement of the outflow and inflow cannulas and more frequently are initiated in the operating room for postcardiotomy heart failure (**Fig. 29.2**).

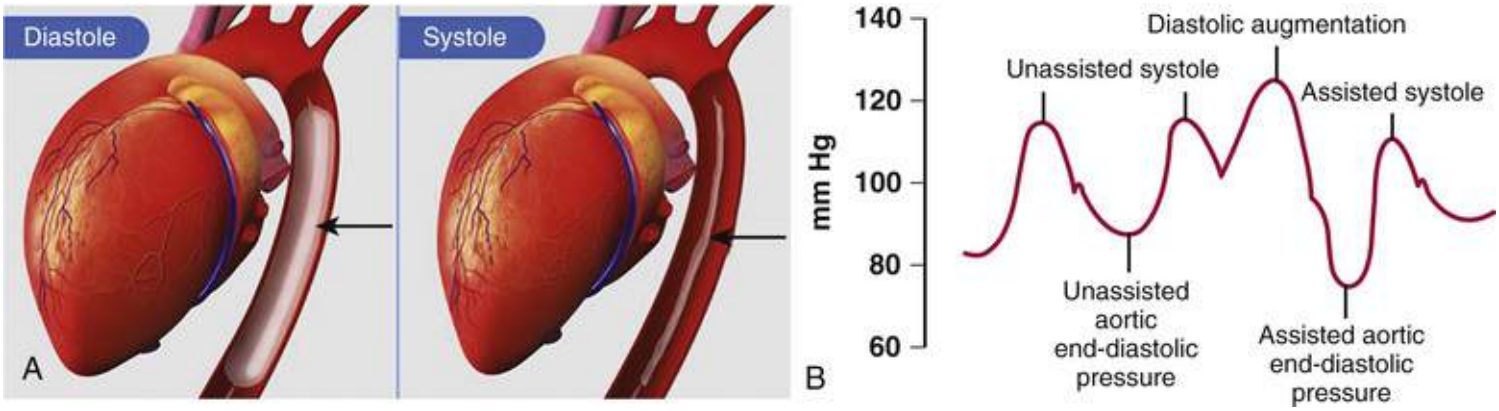

FIGURE 29.1 **A,** Intra-aortic balloon pump (IABP) positioned in descending aorta and inflated during diastole (increasing diastolic blood pressure and coronary perfusion) and deflated during systole (reducing ventricular afterload). **B,** Aortic pressure tracing during IABP support. Balloon counterpulsation is occurring after every other heartbeat (1 : 2 counterpulsation). With correct timing, balloon inflation begins immediately after aortic valve closure, signaled by the dicrotic notch of the arterial waveform. Compared with unassisted ejection, the pump augments diastolic blood flow by increasing peak aortic pressure during diastole. Balloon deflation before systole decreases ventricular afterload, with lower aortic end-diastolic pressure and lower peak systolic pressure.

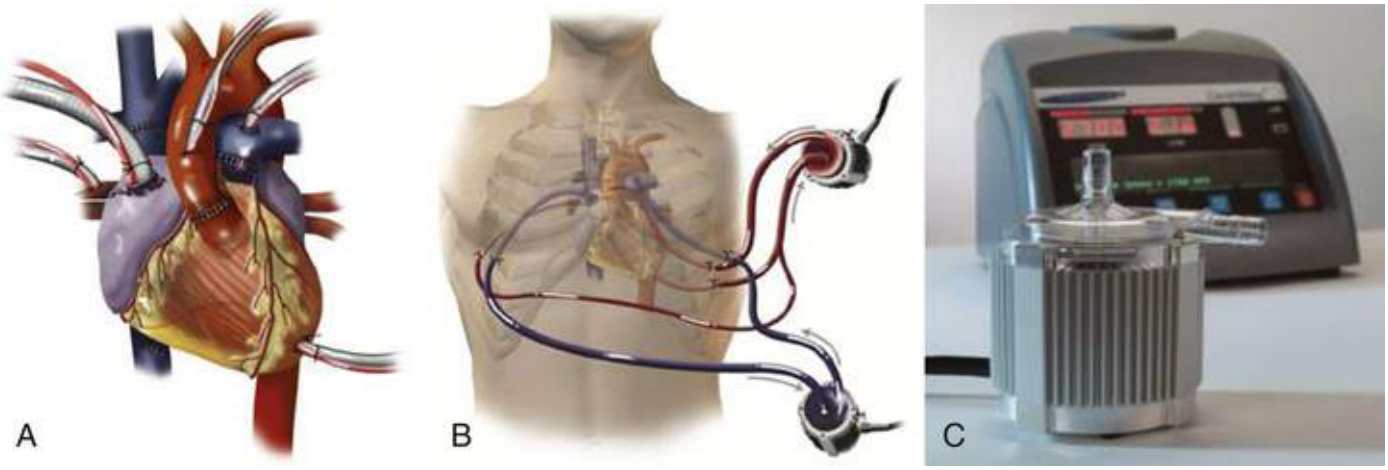

FIGURE 29.2 Temporary extracorporeal mechanical circulatory support—CentriMag Ventricular Assist System (St. Jude Medical, Minneapolis, Minn). **A,** Surgically implanted cannula for biventricular support configuration. *Left ventricular support*: A cannula is positioned in the right superior pulmonary vein and drains blood from the left atrium and pumps it back to the aorta. *Right ventricular support*: A cannula positioned in the right atrial appendage drains blood from the right atrium and pumps it to the main pulmonary artery. **B,** Cannula connected to external blood pumps (extracorporeal pumps). **C,** The CentriMag is a continuous-flow rotary pump with centrifugal design and full magnetic levitation of the internal rotor.

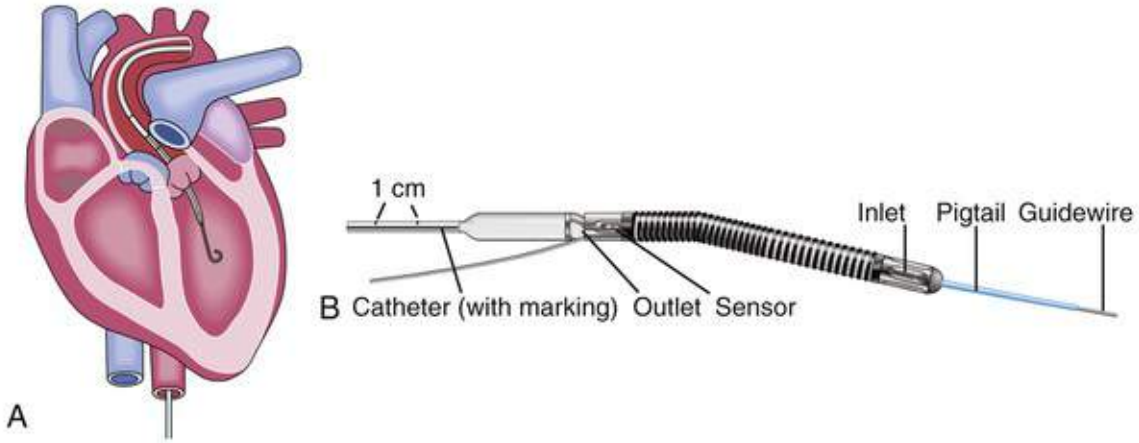

FIGURE 29.3 Temporary mechanical circulatory support—Impella (Abiomed, Danvers, Mass). **A,** The Impella is a continuous-flow, microaxial pump designed to propel blood from the left ventricle into the ascending aorta, in series with the left ventricle. The tip is positioned within the left ventricle, and blood is pumped from the left ventricle into the ascending aorta. **B,** The tip of the catheter is a flexible pigtail loop that stabilizes the device within the left ventricle. The catheter connects to a 12F (Impella 2.5), 14F (Impella CP), or 21F (Impella 5.0) cannula that contains the pump inlet and outlet areas, motor housing, and pump-pressure monitor. The proximal end of the catheter is connected to the external pump. (From Thunberg CA, Gaitan B, Arabia FA, et al. Ventricular assist devices today and tomorrow. J Cardiothorac Vasc Anesth 2010;24:656.)

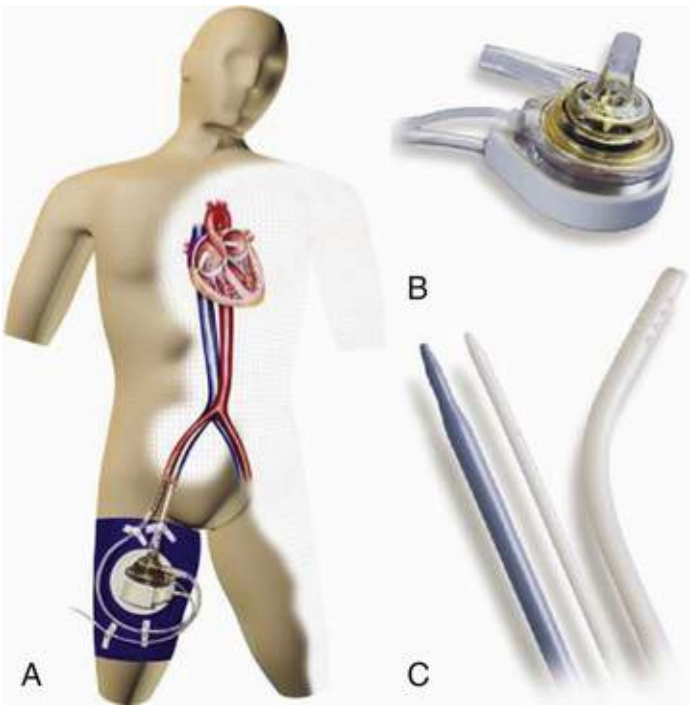

FIGURE 29.4 Temporary mechanical circulatory support—TandemHeart pVAD (CardiacAssist, Pittsburgh). **A,** The TandemHeart has four components: a centrifugal pump with hydrodynamic levitation of the internal rotor positioned on the right thigh **(B),** a 21F transseptal cannula **(C),** a femoral arterial cannula, and a control console.

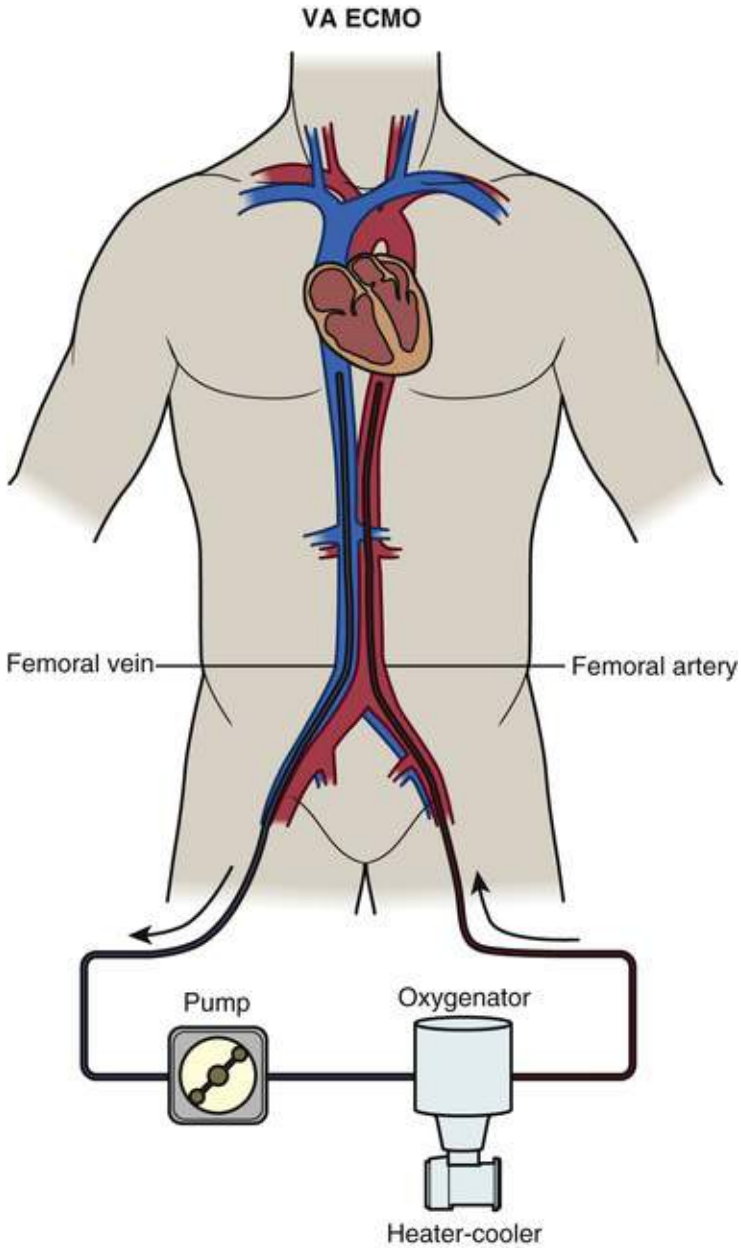

FIGURE 29.5 Extracorporeal life support (ECLS) or extracorporeal membrane oxygenation (ECMO) circuit. The ECMO circuit is used to establish rapid initiation of mechanical circulatory support. The circuit consists of a pump (typically a centrifugal pump system), oxygenator, and heater-cooler element. A typical configuration for emergent application of ECMO is percutaneous placement of cannulas in the femoral vein and femoral artery.

The assumption that the mechanism of myocardial injury is reversible may not be applicable in all clinical situations where the patient presents with significant hemodynamic compromise and significant organ injury. Temporary MCS may be instituted with good expectation of clinical improvement, with subsequent recognition that myocardial recovery is unlikely to occur or has not occurred despite an extended period of support. In such situations, temporary MCS can be continued as a bridge to placement of a long-term, implantable VAD (*bridge to bridge* [BTB] application), or as a bridge to heart transplantation. The use of temporary MCS in this way is not an approved indication but occasionally may be appropriate because of the inherent difficulties in accurately assessing the potential for myocardial recovery in all clinical settings. As a rule, *patients should be excluded from consideration for temporary MCS if myocardial recovery is unlikely and the option of heart transplantation or implantation of a long-term, durable VAD is not feasible*. In these patients, MCS generally is considered futile and should not be instituted.

Bridge to Transplantation

The second indication for MCS applies to patients presenting with cardiogenic shock or decompensated advanced heart failure (HF) refractory to OMM in whom myocardial function is unlikely to recover (e.g., longstanding ischemic, valvular, or idiopathic cardiomyopathy; severe AMI or myocarditis), and who are considered eligible for heart transplantation. Durable, implantable MCS devices designed for long-term use that permit untethered patient mobility and discharge from the hospital are appropriate devices for bridge to transplantation (BTT) indication (**Figs. 29.6 to 29.8**). A major operative procedure, including cardiopulmonary bypass (CPB), is required for placement in most patients, although newer, small-device designs permit less invasive implant techniques without CPB. These devices ideally are placed in patients with significant symptoms of HF who are either receiving intravenous (IV) inotropes or who are not on inotropes but have limiting symptoms at rest, and in whom hemodynamics are stable and end-organ function is preserved or slowly deteriorating. Select patients with acutely unstable hemodynamics and compromised organ function may be better served by a BTB strategy consisting of temporary MCS, followed by placement of a durable MCS device only for those who respond with improvements in hemodynamics and organ function.

FIGURE 29.6 Implantable durable left ventricular assist device—HeartMate 3 (HM3, St. Jude Medical). **A,** The HM3 LVAD is a continuous-flow rotary pump with centrifugal design and complete magnetic levitation of the internal rotor. The blood pump is positioned within the pericardial space, with its integral inflow conduit in the left ventricle and outflow graft (*not shown*) attached to the ascending aorta. The percutaneous power cable is tunneled through the abdominal wall and is attached to the system controller that receives power from two lithium-ion batteries. The implanted components include the inflow cannula, pump housing, motor, control electronics, outflow graft and bend relief, and percutaneous driveline. The HM3 uses a centrifugal flow pump that has a capacity to pump blood up to 10 L/min. LV blood is drawn into the inflow cannula along a central axis and is expelled at right angles by and between the impeller blades of a rotor rotating about the central axis. Blood is angularly accelerated and travels around a volute before it is diffused to a desired pressure and flow rate by being directed tangentially into the outflow graft. The pump rotor is fully supported by magnetic levitation, obviating mechanical or fluid bearings and essentially eliminating mechanical wear as a reliability factor. Both drive (i.e., rotation) and levitation of the rotor is accomplished using a single stator comprising iron pole pieces, a back-iron, copper coils, and position sensors. Measuring the position of a permanent magnet in the rotor and controlling the current in the drive and levitation coils enables active control of the radial position and rotational speed of the rotor. Because the permanent magnet is attracted to the iron pole pieces, the rotor passively resists excursion in the axial direction, whether translating or tilting. The electronics and software necessary to control motor drive and levitation are integrated into the lower housing with the stator; these components plus the rotor comprise the motor. **B,** Cross section of an implantable durable continuous-flow rotary pump with centrifugal design and complete magnetic levitation of the internal rotor. The rotor (*R*) is magnetically levitated by electromagnetic coils (*C*) and rotated by motor drive coils (*D*). The levitated rotor produces wide recirculation passages radially (*P1*) and axially (*P2*). A second axial passage beneath the rotor is hidden in this view. Motor electronics (*E*) are incorporated into the implantable pump. (From Heatley G, Sood P, Goldstein D, et al. Clinical trial design and rationale of the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3) investigational device exemption clinical study protocol. J Heart Lung Transplant 2016;35:528.)

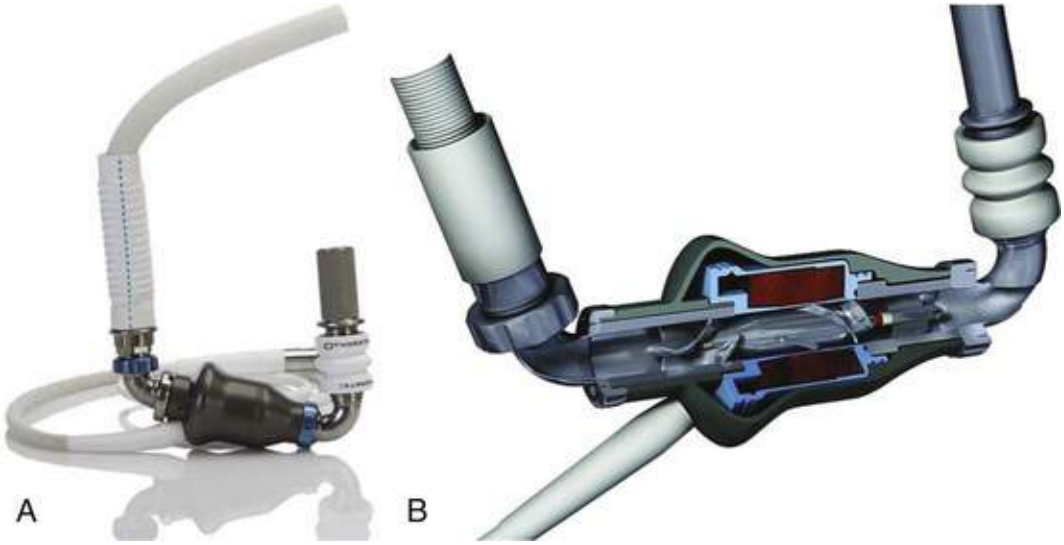

FIGURE 29.7 Implantable durable left ventricular assist device—HeartMate II (St. Jude Medical, Minneapolis, Minn). **A,** The HeartMate II LVAD is a continuous-flow rotary pump with axial design and mechanical support of the internal rotor. The device is positioned outside the pericardial space in a preperitoneal pump pocket. The inlet cannula is inserted into the apex of the left ventricle, and the outflow graft is attached to the ascending aorta. **B,** Internal view of the HeartMate II device demonstrating blood flow path with internal rotor containing a magnet suspended by mechanical pivots (stators) and external wiring (coils), creating a rotating magnetic field that spins the rotor (and internal magnet).

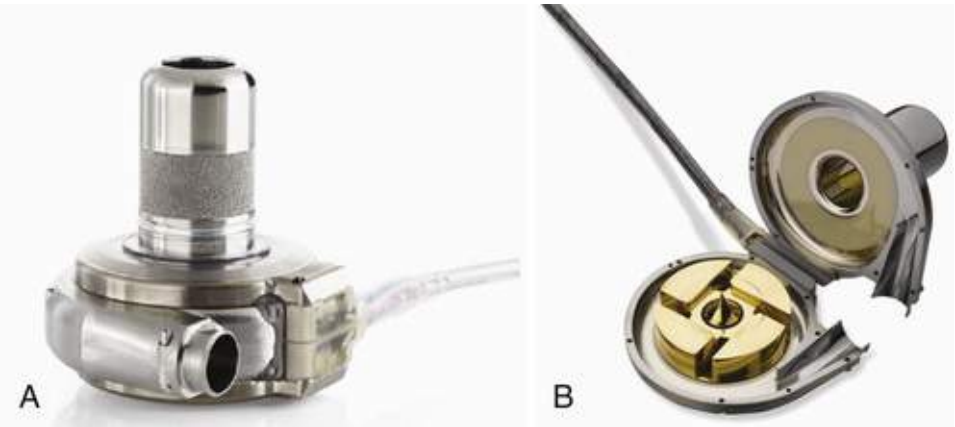

FIGURE 29.8 Implantable durable left ventricular assist device—HVAD (Medtronic, Minneapolis, Minn). **A,** The HVAD LVAD is a continuous-flow rotary pump with centrifugal design and hydrodynamic and magnetic levitation of the internal rotor. The pump is positioned within the pericardial space with the integrated inlet cannula positioned within the apex of the left ventricle and the outflow graft (*not shown*) sewn to the ascending aorta. The percutaneous driveline traverses the skin and attaches to an external controller and power source (batteries). **B,** Internal view of the pump demonstrating internal rotor that is levitated by magnets (passive magnetic field) positioned in the impeller and central post. Hydrodynamic forces generated by the top surface of the impeller stabilize impeller position.

Destination Therapy

The feasibility of durable, implantable MCS devices to provide long-term support demonstrated through the BTT experience prompted further expansion of indications for durable, implantable MCS devices as a permanent alternative to heart transplantation. Destination therapy (DT) is the application of MCS in patients with chronic refractory symptoms of advanced HF that result from irreversible forms of either nonischemic or ischemic cardiomyopathy and who are ineligible for heart transplantation. Use of durable, implantable devices that permit untethered “hands-free” patient mobility at home is appropriate in this

clinical situation. A major operative procedure is required for placement of these implantable pumps, which, as in the setting of BTT, are ideally used in patients with significant symptoms of advanced HF but stable hemodynamics and no manifestations of significant organ injury, frailty, or cachexia. The benefits of MCS for DT, in terms of survival, function, and quality of life, for the treatment of chronic advanced HF were established in a prospective, randomized trial known as REMATCH (Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure).[1] REMATCH evaluated the use of an implantable left ventricular assist device (LVAD) compared with OMM for refractory chronic advanced HF. LVAD therapy halved (relative risk [RR], 0.52; 95% confidence interval [CI] 0.34 to 0.78) the mortality seen in the control population (92% at 2 years) treated with OMM. Despite serious adverse events (e.g., stroke, infection, bleeding, device malfunction) attributable to MCS, LVAD recipients experienced a better quality of life than those in the OMM group.

Patients evaluated for DT must meet specific criteria for reimbursement from CMS that include (1) ineligibility for heart transplantation; (2) significant functional limitations consistent with New York Heart Association (NYHA) Class IIIB or IV symptoms for 45 of the preceding 60 days, despite the use of maximally tolerated doses of drugs outlined in guidelines for heart failure treatment; (3) left ventricular ejection fraction (LVEF) less than 25%; and (4) a peak exercise oxygen consumption (peak VO_2) of 14 mL/kg/min or less, unless the patient is dependent on IV inotropes for 14 days or IABP for 7 days.[2] Although the current reimbursement framework requires determination of DT or BTT status, it is often not possible when assessing VAD candidacy to accurately determine future transplant eligibility. Many patients present with hemodynamic compromise, significant pulmonary hypertension, organ injury, cachexia, or debilitation, all of which represent relative contraindications to heart transplantation but may be reversible with a period of MCS.

The terms *bridge to candidacy* (BTC) and *bridge to decision* (BTD) reflect the unknown efficacy of MCS therapy to reverse the clinical conditions that represent relative barriers to heart transplantation. In a similar vein, patients receiving MCS for BTT indication may experience significant complications after implantation of an MCS device that could adversely affect transplantation candidate status. Although BTC or BTD more accurately reflects the dynamic state of transplant eligibility, BTC and BTD are not recognized by the FDA as an approved indication for use of MCS therapy (nor by CMS as eligible for coverage). Recent clinical trials investigating new devices for durable VAD therapy have attempted to reframe VAD candidacy without reference to transplant candidacy by using patient characteristics and physiologic parameters to define an indication for "long-term support."[3] In the future, this unifying indication of long-term support with coverage determination likely will encompass MCS therapy with durable devices for long-term support independent of transplant eligibility.

The decision to initiate MCS must include an analysis of the intended use and clinical setting, patient variables and conditions, the type of MCS devices available for the selected indication, medical society guidelines for use of the device, and financial considerations.

Design of Ventricular Assist Devices

An MCS pump or pumps may be positioned extracorporeally (outside the body) (**see Figs. 29.1 to 29.5**) or intracorporeally (contained within the body) (**see Figs. 29.6 to 29.8**) as a biventricular assist device

(BiVAD), a right ventricular assist device (RVAD), or more often an LVAD. The pump's flow characteristic further substratifies it as *pulsatile flow* or *continuous flow*. The older-generation, pulsatile-flow, volume-displacement pumps, such as the HeartMate XVE and Novacor LVAS, were large, preload dependent, and associated with decreased durability and are now of only historical interest.[4] Newer-generation continuous-flow pumps are smaller, capable of a similar degree of pumping support (6 to 10 liters per minute [L/min]), more durable, and functionally dependent on both preload and afterload. These include the HeartMate 3 (HM3; **Fig. 29.6**), the HeartMate II (**Fig. 29.7**), and HVAD (**Fig. 29.8**).[5-9] Additional content on this topic is presented in the online supplement for this chapter (Engineering Designs of Ventricular Assist Devices) (**Fig. 29.9**). The improvements in design attributes of the newest continuous-flow pump (HM3) with centrifugal design, including complete magnetic levitation of the internal rotor, decreased mechanical wear, operation at low flow, and perceived improved potential for hemocompatibility, are currently under investigation in the MOMENTUM clinical trial.[8,9]

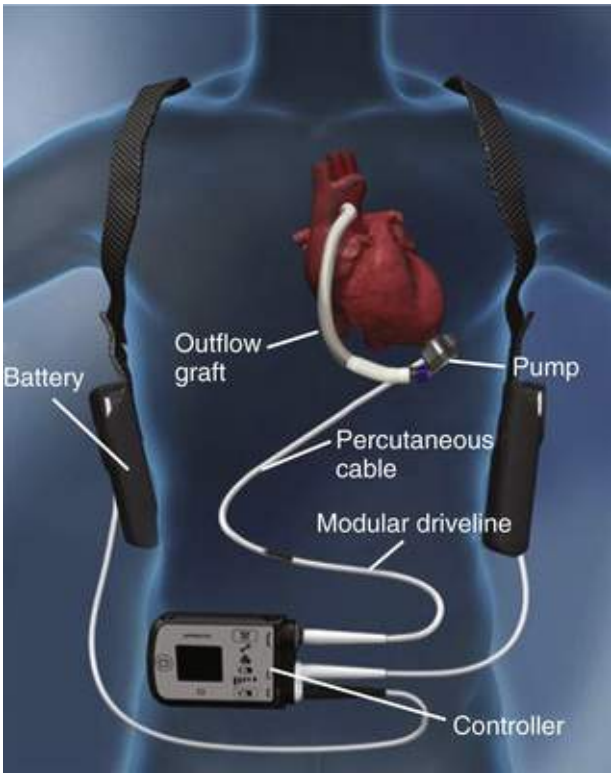

FIGURE 29.9 Typical configuration for a wearable durable LVAD. The pump is attached to the apex of the left ventricle, and the outflow graft is attached to the ascending aorta. The power supply for implantable pumps is delivered through a percutaneous lead (also referred to as driveline) that traverses the skin and connects the external power system (batteries or stationary power unit) with the internal pump. The external components of an implantable system generally consist of a power source (i.e., batteries or an AC power unit) and a small, portable computer (controller) that controls device speed and monitors device function.

Patient Selection, Comorbidity, and Timing of Intervention

Appropriately timing the initiation of MCS is crucial to obtaining good patient outcomes. There are no absolute hemodynamic criteria to meet in order to initiate MCS for any indication. Generally, patients presenting with acute forms of myocardial injury exhibit recognizable changes in hemodynamics. A

cardiac index less than 1.8 to 2.2 L/min/m^2, systolic blood pressure less than 90 mm Hg, pulmonary capillary wedge pressure (PCWP) greater than 20 mm Hg, and evidence of poor tissue perfusion, reflected by oliguria, rising creatinine and liver transaminases, mental status changes, or cool extremities, despite the use of OMM, constitute general guidelines for initiation of MCS.[10] Patient history and overall clinical setting also need to be considered in the decision. When the patient reaches this degree of hemodynamic compromise, the risk of death is substantial, more than 50% at 30 days, despite the availability of OMM, invasive circulatory monitoring, thrombolysis, and IABP support.[11]

More subtle indications to initiate MCS may be present, particularly in patients with chronic advanced HF who are being evaluated for BTT or DT. These indications include resting tachycardia, progressive organ dysfunction, and persistent significant HF symptoms resulting in limited functional capacity and poor quality of life despite OMM, with or without inotrope therapy. In chronic HF patients who had previously maintained good end-organ function and functional performance despite substantially compromised hemodynamics, deterioration in end-organ function or progressive decline in functional performance may occur in the absence of any significant change in hemodynamic parameters. Ambulatory patients with NYHA Class IIIB or IV symptoms who do not tolerate OMM for advanced HF, or who experience renal insufficiency or hypotension with optimal dosages of angiotensin-converting enzyme (ACE) inhibitors or beta blockers, may need evaluation for MCS therapy. Patients who require inotrope therapy or who do not tolerate inotrope therapy as a result of refractory ventricular arrhythmias, or those who have life-threatening coronary anatomy and unstable angina not amenable to revascularization and are at risk of imminent death (hours, days, or weeks), may be considered for MCS without necessarily meeting hemodynamic criteria.

Renal Function

Renal dysfunction has consistently been one of the greatest risks for morbidity and mortality with the use of MCS.[12] Renal dysfunction often is secondary to decreased perfusion of the kidney in cardiogenic shock or advanced HF but also may be caused by nephrotoxic effects of drugs used for HF therapy, intrarenal hemodynamic derangements reflecting overactivity of the renin-angiotensin-aldosterone (RAAS) and sympathetic nervous systems in advanced HF, and immune-mediated nephrotoxicity or complications of noncardiac comorbidity. In patients with shock or advanced HF, it is difficult to assess the reversibility of renal dysfunction. Acute onset of renal failure requiring renal replacement therapy is not necessarily a contraindication to initiate short-term MCS but may be a greater obstacle to successful long-term support with implantable devices for BTT and in particular, DT. In the setting of cardiogenic shock with acute renal failure, establishing normal hemodynamics with MCS may resolve the renal failure in a relatively short period. However, a preimplant creatinine clearance of less than 30 mL/min/m^2 is associated with a 22% 3-month mortality in recipients of a continuous-flow LVAD, and this constitutes a contraindication to durable LVAD implantation at most centers.[12] Thus the degree and duration of cardiogenic shock, along with the patient's baseline renal function, must be considered in estimating the probability of recovery of renal function.

Pulmonary Function

Heart failure may be associated with a restrictive pattern on pulmonary function testing. However, this often improves with removal of interstitial fluid and pleural effusions after placement of an MCS device and resolution of lung congestion. Patients with a long history of smoking or a history of other intrinsic lung disease with significant abnormalities on pulmonary function testing—for example, less than 50% of

predicted normal value for forced vital capacity (FVC), forced expiratory volume at 1 second (FEV_1), or diffusion capacity for carbon monoxide (DL_{CO})—should undergo high-resolution computed tomography (CT). Patients with low oxygen saturation (<92%) on room air also require evaluation with echocardiography to rule out a right-to-left shunt from an atrial septal defect or patent foramen ovale; if results are negative, spiral (helical) CT or radionuclide scanning (in patients without pulmonary abnormalities on chest radiography) is warranted to rule out thromboembolic disease. Patients with severe pulmonary disease may have an elevated pulmonary vascular resistance (PVR) that is fixed (not responsive to pulmonary artery vasodilators). High fixed PVR (thresholds vary from 3 to 6 Wood units) represents a contraindication to heart transplantation and consequently to use of LVAD for BTT indication. Moderate elevations in PVR can be encountered in patients with cardiogenic shock and especially in those with long-established HF and does not preclude successful use of LVAD, if lowering of PVR (reversibility) is achieved with inotropes or pulmonary vasodilators. PVR frequently declines a few months after LVAD implantation, so patients deemed not transplantable because of elevated PVR at the time of implant may later become eligible. Perioperative hypoxia secondary to significant underlying lung disease also may contribute to pulmonary vasoconstriction, leading to right ventricular (RV) failure after institution of VAD support. Sleep apnea is present in a significant number of patients with HF, which may contribute to pulmonary hypertension.

Hepatic Function

Preoperative total bilirubin level and hepatic cellular enzyme levels more than three times normal are independent risk factors for RV failure and reduced survival following LVAD implantation. The etiology of the hyperbilirubinemia may be multifactorial, including congestive hepatopathy, cirrhosis, or a combination of causative disorders. Abnormal liver function often is associated with abnormal coagulation factors, as well as low serum albumin. Attempts should be made to normalize all indices of liver function and the cause(s) of any abnormalities preoperatively. The presence of portal hypertension with liver cirrhosis is a contraindication to initiating MCS support. A history of significant alcohol use should be ruled out in all potential candidates for MCS therapy, especially those with abnormal liver function. Patients also should be tested for previous infection with hepatitis A, B, or C virus or others. Ultrasound visualization of the liver is a good screening test in patients with significant hepatomegaly to rule out infiltrative disease, mass, or other pathologic condition that may warrant biopsy. Decrease in hepatic congestion and recovery of synthetic functions can occur with institution of MCS.

Right Ventricular Function

Patients with advanced HF frequently have coexisting RV failure. This entity may be a major contributor to mortality or morbidity after initiation of MCS.[13-16] RV failure in most patients is a result of LV failure. Patients with a nonischemic etiology often present with significant RV failure and may have a three- to fourfold increased risk of requiring both LV and RV support. Patients who require BiVAD support have significantly higher preoperative creatinine and total bilirubin levels and a greater need for mechanical ventilation before MCS device insertion than patients requiring LVAD support only. The need for BiVAD support is associated with substantially worse survival with both short-term and long-term MCS devices because of a greater degree of compromised preoperative organ function.[13] RV failure is a prominent factor leading to renal dysfunction after LVAD implantation, because significantly elevated right atrial (RA) pressures lead to changes in glomerular filtration from cortical to medullary nephrons, with secondary reduction in urine output and resistance to diuretic therapy. Preoperative optimization of RV function with a goal RA pressure ideally at 10 mm Hg is important in reducing the need for postoperative RV support. The higher the left atrial (LA) pressure or PCWP at device implantation, the greater is the

benefit to the right ventricle and pulmonary artery pressure when the left ventricle is totally unloaded and LA pressure falls. Postoperative recovery of RV function, however, may lag for several days, because total decompression of the left ventricle allows a significant shift of the interventricular septum toward the left ventricle, with further distention and dysfunction of the right ventricle.[16-19]

Coagulation

Coagulopathy is a significant risk factor and a common abnormality noted in patients with refractory HF. An abnormal international normalized ratio (INR) in the absence of warfarin use is of added concern, because it may reflect chronically high RA pressures, leading to hepatic congestion and, ultimately, to hepatic fibrosis and cirrhosis. Prolonged abnormal INR and low platelet count combined with use of anticoagulation or antiplatelet therapy are associated with significant perioperative bleeding, requiring multiple transfusions, leading to increased PVR, RV failure, decline in renal function, hemodynamic instability, and multiple-organ failure. In addition, patients with severe HF typically have a nutritional basis for abnormal coagulation because of depletion of several specific coagulation factors, such as factor VII. The minimum preoperative screen for coagulation abnormalities should include prothrombin time (PT), partial thromboplastin time (PTT), INR, platelet count, and in view of the high likelihood of previous heparin exposure, a heparin-induced thrombocytopenia (HIT) assay. The presence or development of HIT is associated with a high risk of bleeding, as well as thrombosis of MCS devices.

Other Medical Considerations

Other important medical considerations in instituting MCS include the presence or absence of significant aortic, mitral, or tricuspid valve disease, coronary artery disease, and atrial and ventricular arrhythmias, as well as intracardiac shunts. Additional content on this topic is presented in the online supplement for this chapter (Important Medical Conditions in Instituting Mechanical Circulatory Support).

Patient Outcomes

Temporary Mechanical Circulatory Support

Temporary MCS is indicated in patients with cardiogenic shock refractory to medical therapy when *rapidly achieved* augmentation of cardiac output and reduction of ventricular filling pressures are required to sustain life.[20] When used in the setting of medically refractory myocarditis or takotsubo cardiomyopathy, temporary MCS may provide time for spontaneous recovery and discontinuation of MCS. When cardiogenic shock complicates longstanding HF, temporary MCS can provide the time needed for patients, family members, and physicians to make critical decisions about long-term MCS and heart transplantation. Patients with HF severe enough to warrant long-term MCS but with reversible clinical characteristics (e.g., coagulopathy from hepatic congestion, acute renal failure from low cardiac output and high RA pressure, hypoalbuminemia resulting from cardiac cachexia and bowel edema) that put them at high risk for perioperative death with a long-term device may benefit from temporary MCS, if their risk profile could be substantially improved with temporary MCS to the extent that they would become good candidates for a durable MCS device. The clinical evaluation of temporary MCS devices for treatment of cardiogenic shock generally has not involved randomized clinical trials but rather has relied on the use of prospective, single-arm observation studies to validate device design, safety, and efficacy. **Table 29.2** summarizes extracorporeal assist devices and their characteristics.

TABLE 29.2

Temporary Mechanical Circulatory Support (MCS) Devices*

DEVICE	PUMP MECHANISM	PUMP ENERGY SOURCE	METHOD OF PLACEMENT	VENTRICLE SUPPORTED	DEGREE OF SUPPORT†
Intra-aortic balloon pump (IABP) (several manufacturers)	Counterpulsation	Pneumatic	Percutaneous placement via femoral artery or operative placement in ascending aorta or axillary artery	Principal effect: reduction of LV afterload and increase in coronary perfusion	Partial-support device
Extracorporeal life support (ECLS) (several manufacturers depending on pump selected)	Continuous-flow rotary pump with centrifugal design	Variable; depends on pump used for ECLS circuit (most frequently a continuous-flow rotary pump with centrifugal design)	Percutaneous or operative placement	Venous-arterial configuration Partial unloading of right and left ventricles by reduction in preload with oxygenation of blood	Full-support device (4-6 L/min)
CentriMag VAD (St. Jude Medical, Minneapolis)	Continuous-flow rotary pump with centrifugal design (magnetic levitation; no bearing)	Electric motor	Operative placement	Right, left, or biventricular support	Full-support device (4-6 L/min)
TandemHeart pVAD (CardiacAssist, Pittsburgh)	Continuous-flow rotary pump with centrifugal design (hydrodynamic support of impeller)	Electric motor	Percutaneous placement Requires transseptal placement of cannula for left atrial drainage Arterial return to femoral artery	LV support‡	Partial-support device (2-4 L/min)
Impella 2.5, CP, 5.0, or RP (Abiomed Corp., Danvers, Mass)	Continuous-flow rotary pump with microaxial design (bearing support of impeller)	Electric motor	Percutaneous via femoral artery (Impella 2.5, CP, or 5.0) or operative placement via aorta or axillary artery depending on device size (Impella 5.0, CP) Placement across aortic valve (Impella 5.0, CP) Inflow from left ventricle and outflow in ascending aorta	LV support or RV support (Impella RP)‡	Partial-support device 1-3 L/min for Impella 2.5 or full-support device 3.5-4 L/min for Impella CP 5 L/min for Impella 5.0

*The table includes representative MCS devices and is not meant to be an exhaustive listing of all devices currently available in the United States or internationally.

†Values of cardiac support represent approximate ranges and capabilities of the device.

‡Impella RP designed specifically for right ventricular support. Provides 4 liters or greater of flow.

Intra-Aortic Balloon Pump

The intra-aortic balloon pump remains the most commonly used MCS device (**see Fig. 29.1**). The IABP consists of a balloon catheter and a pump console to control the timing of balloon inflation and deflation. The catheter is a double-lumen, 7.5- to 8.0 French (F) catheter with a polyethylene balloon attached at its distal end, with one lumen of the catheter attached to the pump and used to inflate the balloon with gas. Helium is used because its low viscosity facilitates rapid transfer in and out of the balloon, and because it absorbs very rapidly in blood if the balloon ruptures. Timing of balloon inflation and deflation is based on electrocardiogram (ECG) or pressure triggers. The balloon inflates with the onset of diastole, which roughly corresponds with electrophysiologic repolarization or the middle of the T wave on the surface ECG, or just after the dicrotic notch on the aortic pressure tracing. Following diastole, the balloon rapidly deflates at the onset of LV systole, which is timed electrocardiographically to the peak of the R wave on the surface ECG. The IABP increases diastolic blood pressure, decreases afterload, decreases myocardial oxygen consumption, increases coronary artery perfusion, and modestly enhances cardiac output. The IABP provides modest ventricular unloading but does increase mean arterial pressure and

coronary blood flow. Patients must have some level of LV function and electrical stability for an IABP to be effective, because any increase in cardiac output depends on the work of the heart itself. Optimal hemodynamic effect from the IABP depends on several factors, including the balloon's position in the aorta, the blood displacement volume, the balloon diameter in relation to aortic diameter, the timing of balloon inflation in diastole and deflation in systole, and the patient's own heart rate, blood pressure, and vascular resistance.

The efficacy of IABP counterpulsation was recently evaluated in SHOCK II, a randomized, prospective, open-label, multicenter trial comparing IABP therapy with best available medical therapy for treatment of AMI complicated by cardiogenic shock.[21] All patients were expected to undergo early revascularization (by means of percutaneous coronary intervention or bypass surgery). At 30 days, 119 patients in the IABP group (39.7%) and 123 patients in the control group (41.3%) had died (RR with IABP, 0.96; 95% CI 0.79 to 1.17; $P = 0.69$). No significant differences were found in secondary endpoints or in process-of-care measures, including the time to hemodynamic stabilization, the length of stay in the intensive care unit, serum lactate levels, dose and duration of catecholamine therapy, and renal function. The use of IABP counterpulsation did not significantly reduce 30-day mortality in patients with AMI complicated by cardiogenic shock for whom an early revascularization strategy was planned. There have not been adequately powered randomized clinical trials of IABP to assess for a mortality benefit in cardiogenic shock occurring outside the context of an AMI.

Extracorporeal Life Support and Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) provides cardiopulmonary support for patients whose heart and/or lungs can no longer provide adequate physiologic support[22-24] (**Fig. 29.5**). ECMO can be either venovenous (VV) for oxygenation only or venoarterial (VA) for oxygenation and circulatory support. In cases of biventricular failure, VA ECMO is the MCS of choice for patients in cardiogenic shock and impaired oxygenation, since it provides full cardiopulmonary support. ECMO may be placed at the bedside without fluoroscopic guidance. ECMO is similar to a CPB circuit used in cardiac surgery. VA ECMO involves a circuit composed of a continuous-flow centrifugal pump for blood propulsion and a membrane oxygenator for gas exchange. A venous cannula drains deoxygenated blood into a membrane oxygenator for gas exchange, and oxygenated blood is subsequently infused into the patient through an arterial cannula. VA ECMO provides systemic circulatory support with flows sometimes exceeding 6 L/min depending on cannula size. Because of the increase in systemic afterload, however, VA ECMO alone may not significantly reduce ventricular wall stress and may result in LV distension in cases where residual LV function is inadequate to eject against the increase in systemic afterload. This may result in high myocardial oxygen demand (secondary to high filling pressures and volume). This may have negative consequences on myocardial recovery unless the left ventricle is unloaded by concomitant IABP, an LV vent, atrial septostomy, or use of a percutaneous LV-to-aorta VAD.

Numerous large clinical series have reported successful use of extracorporeal life support (ECLS) for cardiac and respiratory support in adult, pediatric, and neonatal patients.[22,24] In the largest series to date, Bartlett and colleagues[24] at the University of Michigan reported on outcomes for 1000 patients supported with ECLS from 1980 through 1998. Cardiac failure was the indication for support in 146 cases. Survival to hospital discharge occurred in 33% of adult patients (31 cases) and in 48% of pediatric patients (105 cases). Survival in adult patients was improved by using ECLS as a bridge to placement of longer-term implantable devices in patients who did not demonstrate early recovery of myocardial function. However, the availability of long-term implantable devices has extended the use of ECLS to situations where recovery of myocardial function is unlikely.

Left Atrium to Aorta Assist Device

The TandemHeart paracorporeal ventricular assist device (pVAD) is a percutaneously inserted extracorporeal left atrial–aorta assist device that pumps blood from the left atrium to the femoral artery through a transseptally placed LA cannula, thereby bypassing the left ventricle entirely (**see Fig. 29.4**). The TandemHeart system includes a 21F transseptal cannula, a centrifugal pump, a femoral arterial cannula, and a control console. The TandemHeart is approved by FDA to incorporate an oxygenator to the circuit, allowing for concomitant LV unloading and oxygenation. The centrifugal blood pump contains a hydrodynamic bearing that supports a spinning impeller. The impeller is powered by a brushless direct-current (DC) electromagnetic motor, rotating between 3000 and 7500 rpm. The external console controls the pump and provides battery backup in case of power failure. A continuous infusion of heparinized saline flows into the lower chamber of the pump, which provides lubrication and cooling, and prevents thrombus formation. The redirection of blood from the left atrium reduces LV preload, LV workload, filling pressures, wall stress, and myocardial oxygen demand. The increase in arterial blood pressure and cardiac output supports systemic perfusion. The flow through the TandemHeart is additive to LV output through the aortic valve (parallel circulation). However, the contribution from the native heart is typically reduced as MCS support is increased due to changes in LV loading conditions (i.e., decrease in preload and increase in afterload). Coronary flow is driven by the perfusion pressure (diastolic pressure − right atrial pressure). With a parallel circulation, the aorta is perfused and pressured by both the left ventricle and the TandemHeart. Not infrequently, LV contraction (native heart output) may be negligible, and systemic perfusion is pump dependent, with a flat mean arterial pressure curve. This situation can result in stasis of blood within the aortic root, resulting in thrombus formation and stroke.

In a randomized comparison of IABP with the TandemHeart, Thiele and colleagues[25] reported a more effective improvement in cardiac power index as well as other hemodynamic and metabolic variables with the TandemHeart pVAD compared with the IABP. Complications such as severe bleeding and limb ischemia, however, were encountered more frequently after VAD support. Thirty-day mortality rates were similar between the groups, but the study was underpowered to compare mortality between groups.

Left Ventricle to Aorta Assist Device

The Impella is a continuous flow micro-axial pump designed to pump blood from the LV into the ascending aorta, in series with the LV (**see Fig. 29.3**). Three versions are available for LV assist and include the 12F (Impella 2.5) and 21F (Impella 5.0), which provide maximal flow rates of 2.5 and 5.0 L/min, respectively, and the 14F device (Impella CP), with an intermediate level of support of 3.0 to 4.0 L/min. A device specifically designed for RV support, the Impella RP, is also available. The devices for LV assist are designed to be placed via the femoral artery, either percutaneously (Impella 2.5 and CP) or with a surgical cutdown (Impella 5.0). Alternate access sites such as the subclavian artery have been described but are not routinely used. The tip of the catheter is a flexible pigtail loop that stabilizes the device in the LV with a low likelihood of perforation. The pigtail connects to the cannula that contains the pump inlet and outlet areas, motor housing, and pump-pressure monitor. The 9F catheter shaft proximal to the pump houses the motor power leads and purge and pressure measurement lumens. The catheter's proximal end consists of a hub for attachment of a console cable and side arms for attachment of purge solution and pressure-measurement tubing. The Impella CP device has just recently become available in the United States, so the most experience to date has been with the Impella 2.5 device. The Impella pumps blood from the left ventricle into the ascending aorta, thereby unloading the LV and increasing forward flow. It reduces myocardial oxygen consumption, increases coronary perfusion, improves mean arterial

pressure, and reduces PCWP. The Impella 2.5 provides a greater increase in cardiac output than the IABP but less than the TandemHeart device. The more powerful Impella CP and 5.0 devices are comparable to the TandemHeart device in terms of support. Similar to the TandemHeart, adequate RV function or concomitant RVAD is necessary to maintain LV preload and hemodynamic support during biventricular failure or unstable ventricular arrhythmias.

In a prospective, randomized clinical trial comparing the Impella 2.5 to the IABP, cardiac index was significantly increased in patients with the Impella 2.5 compared with patients supported with an IABP.[26] Overall mortality rates at 30 days were similar in both groups, but the study was not adequately powered to assess for a mortality difference.

Despite the absence of suitably powered randomized clinical trials demonstrating a mortality benefit over IABP therapy (which itself has no proven mortality benefit), the use of temporary MCS devices in patients with cardiogenic shock is likely to continue. In comparison with an IABP, these devices provide a much larger increment in cardiac output and superior LV unloading.

Devices Intended for Long-Term Mechanical Circulatory Support

The introduction of continuous-flow technology into clinical practice was a milestone in the field of MCS therapy and led to significant improvements in survival and reduction of serious major adverse events, especially in the area of device malfunction. Compared with pulsatile-flow devices, continuous-flow technology provides functionally equivalent hemodynamic support improvement of kidney and liver function. Long-term survival with continuous-flow technology is significantly better with half the rate of stroke and infection and one-third the rate of device malfunction compared to pulsatile-flow technology. **Table 29.3** summarizes the characteristics of durable MCS devices intended for long-term use.

TABLE 29.3

Long-term Durable Mechanical Circulatory Support (MCS) Devices*

DEVICE	PUMP MECHANISM	PUMP ENERGY SOURCE	METHOD OF VENTRICLE PLACEMENT SUPPORTED		INDICATION
HeartMate 3† (St. Jude Medical, Minneapolis)	Continuous-flow rotary pump with centrifugal design and magnetic levitation of internal impeller	Electric motor Power to pump delivered via percutaneous lead with external power source and computer controller	Operative	Left ventricle Implantable pump with intrapericardial placement	Long-term support (intended for BTT and DT indication)
HeartMate II (St. Jude Medical)	Continuous flow rotary pump with axial design with mechanical pivot support of internal impeller	Electric motor Power to pump delivered via percutaneous lead with external power source and computer controller	Operative	Left ventricle Implantable pump requiring preperitoneal pocket	BTT, DT
HVAD (Medtronic, Minneapolis)	Continuous flow rotary pump with centrifugal design with magnetic and hydrodynamic levitation of internal impeller	Electric motor Power to pump delivered via percutaneous lead with external power source and computer controller	Operative	Left ventricle Implantable pump with intrapericardial placement No preperitoneal pocket required	BTT DT‡
Syncardia TAH-t (SynCardia Systems, Tucson, Arizona)	Pulsatile, volume displacement (50-cc and 70-cc displacement devices)	Pneumatic Patient tethered to portable drive unit	Operative	Biventricular support Orthotopic placement with removal of both ventricles	BTT DT§

*The table includes representative MCS devices and is not meant to be an exhaustive list of all devices currently available in the United States or internationally.

†Currently under clinical investigation in the United States for long-term support (inclusive of BTT and DT indication) in the MOMENTUM 3 Pivotal trial.

‡Undergoing clinical evaluation in the United States for DT indication in the ENDURANCE and ENDURANCE Supplemental Pivotal Trials.

§Currently under clinical evaluation for DT indication.

BTT, Bridge to transplantation; *DT,* destination therapy.

Durable Implantable Left Ventricular Assist Devices

HeartMate 3

The HM3 is intended for long-term support of patients with advanced HF (**see Fig. 29.5**). HM3 is currently in clinical evaluation for long-term support indication in the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM) trial. MOMENTUM is a multicenter randomized clinical trial evaluating the HM3 to the HeartMate II pump. Initial results of a short-term cohort (6-month follow-up) have been reported.[9] Of 294 patients, 152 were assigned to the HM3 centrifugal-flow pump group and 142 to the HeartMate II axial-flow pump group. In the intention-to-treat population, the primary endpoint (disabling stroke-free survival at 6 months while supported on original device, or transplanted or explanted for myocardial recovery) occurred in 131 patients (86.2%) in the HM3 group and in 109 (76.8%) in the HeartMate II group (absolute difference, 9.4 percentage points; 95% lower confidence boundary, −2.1; $P < 0.001$ for *noninferiority*; hazard ratio [HR], 0.55; 95% CI 0.32 to 0.95; two-tailed P = 0.04 for superiority). There were no significant between-group differences in the rates of death or disabling stroke, but reoperation for pump malfunction occurred less in the HM3 than in the HeartMate II group (1 [0.7%] vs. 11 [7.7%]; HR, 0.08; 95% CI 0.01 to 0.60; $P = 0.002$). Suspected or confirmed pump thrombosis did not occur in the centrifugal-flow pump group but was experienced by 14 patients (10.1%) in the axial-flow pump group (**Table 29.4 and eTable 29.1**).

TABLE 29.4

Clinical Trials of Durable, Implantable Continuous-Flow Rotary Devices for MCS in United States

CLINICAL TRIAL	PATIENTS (*n*)	FOLLOW-UP DURATION	STUDY DEVICE SURVIVAL (6 mo/1 yr/2 yr)	COMPARATOR GROUP (Patients, Device Used)	TRIAL DESIGN	COMPARATOR GROUP SURVIVAL (6 mo/1 yr/2 yr)
HeartMate II Pivotal BTT trial[5]	133	Median duration of support: 126 days	75%/68%/—	None	Observational Single arm	N/A
HeartMate II Pivotal BTT trial and CAP[27]	281	Median duration of support: 155 days	82%/73%/72% (18 mo)	None	Observational Single arm	N/A
HVAD* Pivotal BTT trial[31]	140	Duration of follow-up: 89.1 patient-years	94%/86%/—	499 Commercially implanted devices for BTT (INTERMACS)	Observational Contemporaneous control group	90%/85%/—
HVAD Pivotal BTT trial and CAP[32]	332	—	91%/84%/—	None	Observational Single arm	N/A
HeartMate II Postapproval BTT study[30]	169	Median duration of support: 386 days	90%/85%/—	169 HeartMate XVE or Thoratec pVAD or IVAD (INTERMACS)	Observational Contemporaneous control group	79%/70%/—
HeartMate II Pivotal DT trial—original cohort[28]	134	Median duration of support: 1.7 years	—/68%/58%	66 HeartMate XVE	Randomized clinical trial	—/55%/24%
HeartMate II Pivotal DT trial—CAP[29]	281	Median duration of support: 1.7 years	—/73%/63%	None	Observational Single arm	N/A
HeartMate 3† Pivotal trial[3,9]	151	Complete follow-up to 6 months	89%/—/—	138 HeartMate II	Randomized clinical trial	88%/—/—

*Undergoing clinical evaluation in United States for DT indication in the ENDURANCE and ENDURANCE Supplemental Pivotal Trials.

†Undergoing clinical evaluation in United States for long term support indication (inclusive of BTT and DT) in the MOMENTUM 3 Pivotal Trial.

CAP, Continued access protocol; *N/A,* not applicable.

ETABLE 29.1

Adverse Events in Major Clinical Trials of Durable Mechanical Circulatory Support Devices in the United States*

CLINICAL TRIAL	PATIENTS (*n*)	CUMULATIVE DURATION OF DEVICE SUPPORT (patient-years)	ADVERSE EVENT: No. of Patients (%), Occurrence Rate (patient-years)						
			Bleeding Requiring Surgery	Device Infection: Percutaneous Lead	Device Infection: Pump Pocket	Right-Sided HF: Need for RVAD	Stroke–ICVA	Stroke–HCVA	Device Replacement
HeartMate II Pivotal BTT Trial[5]	133	61.7	41 (31%)	18 (14%)	0 (0%)	5 (4%)	8 (6%)	3 (2%)	5 (4%)
			0.78	0.37	0	0.08	0.13	0.05	0.08
HeartMate II Pivotal BTT Trial and CAP[27]	281	181.8	72 (26%)	41 (14%)	5 (2%)	17 (6%)	15 (5%)	9 (3%)	12 (4%)
			0.45	0.31	0.03	0.09	0.09	0.05	0.07
HeartWare HVAD pivotal BTT Trial[31]	140	89.1	20 (14.3%)	17 (12.1%)	0† (0%)	4 (2.9%)	10 (7.1%)	8 (5.7%)	10 (7%)
			0.26	0.29	0	0.04	0.11	0.09	0.10
HeartMate II Postapproval BTT Study[30]	169	142	75‡ (44.4%)	30 (17.8%)	3 (1.8%)	5‡ (3%)	8 (4.7%)	2 (1.2%)	2 (1.2%)
			1.44	0.32	0.03	—	0.06	0.01	0.01
HeartMate II Pivotal DT Trial (original cohort)[28]	133	211	40 (30%)	42 (32%)	12§ (9%)	5§ (4%)	11 (8%)	15 (11%)	12 (9%)
			0.23	0.38	0.09	0.02	0.06	0.07	0.06
HeartMate II Pivotal DT Trial and CAP[29]	281	498	55 (20%)	75 (27%)	20 (7%)	17 (6%)	22 (8%)	13 (5%)	22 (8%)
			0.14	0.22	0.05	0.03	0.05	0.03	0.04
HeartMate 3 Pivotal Trial[3,9]	151	To 6 mo¶	15 (9.9%)	18 (11.9%)	N/A	4 (2.6%)	8 (5.3%)	4 (2.6%)	1 (0.7%)

*Adverse events are displayed for investigative device only. Adverse events are not reported for the comparator arm if applicable.

†The HeartMate 3 and HVAD are positioned within the pericardium and do not require preperitoneal pocket for placement.

‡INTERMACS definitions were used for the HeartMate II Postapproval BTT Study. Bleeding definition incorporates bleeding requiring surgery and other types of bleeding. Right-heart failure definition incorporates need for RVAD and lesser degrees of right-heart failure requiring prolonged inotrope use. The number of patients requiring RVAD use was reported, but without the cumulative patient incidence.

§Data obtained from HeartMate II pivotal DT TRIAL and CAP.[29] Individual rates of percutaneous lead infection and pump pocket infection were not reported in the HeartMate II pivotal DT trial—original cohort.[28]

¶Complete follow-up to 6 months (data for occurrence rates not available).

CAP, Continued access protocol; *HCVA,* hemorrhage cerebrovascular accident; *HF,* heart failure; *ICVA,* ischemic cerebrovascular accident; *RVAD,* right ventricular assist device.

HeartMate II

The HeartMate II (**see Fig. 29.7**) is intended for long-term support of patients with advanced HF and is the most evaluated MCS device to date, with more than 13,000 implantations worldwide. Patient outcomes after implantation of the HeartMate II have been extensively evaluated in five major scientific reports on its use for BTT and DT indications within the context of pre- and postapproval clinical trials[5,27-30] (**Table 29.4 and eTable 29.1**). Additional content on this topic is presented in the online supplement for this chapter (Clinical Trials with the HeartMate II Device).

HVAD

The HVAD has undergone clinical evaluation in the United States for BTT indication in a prospective, nonrandomized clinical trial, ADVANCE[31,32] (**Table 29.4 and eTable 29.1**). The unique feature of ADVANCE was the use of a contemporaneous, observational control arm derived from registrants entered into INTERMACS. The primary outcome in ADVANCE was success defined as survival on the originally

implanted device, transplantation, or explantation for ventricular recovery at 180 days and was evaluated for both noninferiority and superiority. A total of 140 patients received the investigational pump, and 499 patients received a commercially available pump (the HeartMate II in at least 95% of cases) implanted contemporaneously. Success was achieved in 90.7% of patients on the investigational pump and in 90.1% of controls, establishing the noninferiority of the investigational pump ($P < 0.001$; 15% noninferiority margin). At 6 months, median 6-minute walk distance increased by 128.5 meters, and both disease-specific and global quality-of-life scores improved significantly. The HVAD was approved for use in the United States for the BTT indication in 2012 and currently is completing clinical evaluation in the United States for the DT indication; the ENDURANCE and ENDURANCE Supplemental Trials are multicenter randomized clinical trials comparing the HVAD to the HeartMate II.

Total Artificial Heart

SynCardia Total Artificial Heart–Temporary (TAH-t)

Another option for MCS is the total artificial heart (TAH). The 70-mL stroke volume version of the SynCardia CardioWest Total Artificial Heart–Temporary (TAH-t; **Fig. 29.10**) was evaluated in a large, prospective, nonrandomized trial conducted in five centers for BTT indication in 81 patients at risk for imminent death from irreversible biventricular cardiac failure.[33] The study cohort was compared with a nonrandomized, observational control cohort of 35 patients. The primary study endpoints included the rates of survival to heart transplantation and survival after transplantation. The rate of survival to transplantation was 79% (95% CI 68% to 87%). Of the 35 patients in the control cohort who met the same entry criteria but did not receive the TAH-t, 16 (46%) survived to transplantation ($P < 0.001$). Overall, the 1-year survival rate among the patients who received the TAH was 70%, compared with 31% among the controls ($P < 0.001$). After transplantation, 1-year and 5-year survival rates among patients who had received the TAH were 86% and 64%.[33] The SynCardia TAH-t was approved by the FDA for BTT in 2007. The TAH-t is currently being evaluated in the United States for DT indication. A smaller version of the device (50-cc ventricle) is also being evaluated in U.S. clinical trials.

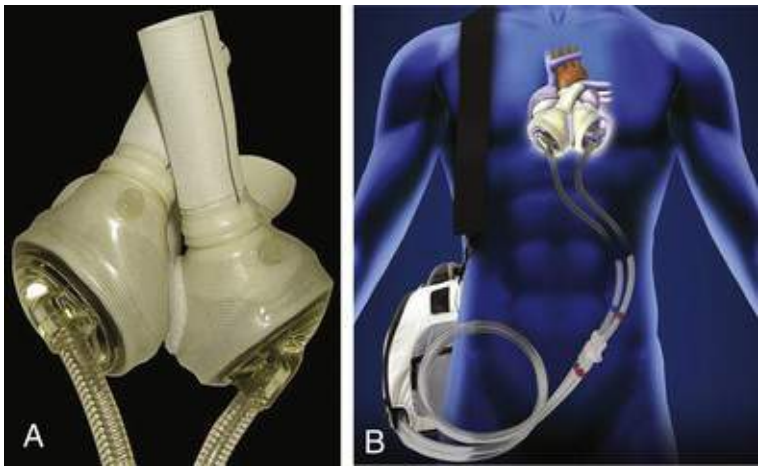

FIGURE 29.10 Syncardial Total Artificial Heart-Temporary (Syncardia Systems, Tucson, Arizona). **A,** The TAH-t consists of a right and left prosthetic ventricle. The prosthetic ventricles, made of biocompatible polyurethane, have a capacity of 70 mL. A 50-cc prosthetic ventricle is currently being evaluated in clinical studies in the United States to permit use in patients with small body habitus. The ventricles are pneumatically driven with four flexible polyurethane diaphragms positioned between the blood surface and the air sac. When compressed air is forced into the air sacs simultaneously, compression is effected onto the blood sac and ejection occurs in simulation of cardiac systole. Cardiac ejection in the TAH-t thus occurs in parallel from the left and right sides. As the air sac is deflated, the blood sac is filled passively from the atrial connection. Two mechanical valves are situated along the prosthetic ventricle to provide unidirectional inflow and outflow. The prosthetic ventricles are connected by quick-connect silicone cuffs to two atrial connectors on the cuffs (*not shown*), and two connectors on the end of the grafts are sewn to the aorta and pulmonary artery. The compressed air is delivered by an external console (*not shown*) through two separate air tubes connected to the right and left prosthetic ventricles. The console has two independent controllers that allow redundancy for emergency backup. Compressed air cylinders inside the console can be used to mobilize the patient. **B,** Portable drive unit to permit hospital discharge and improve patient mobility is also available.

Interagency Registry of Mechanically Assisted Circulatory Support

An important milestone in the advance of MCS therapy has been the development of the National, Heart, Lung and Blood Institute (NHLBI)–sponsored national registry, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). INTERMACS is the largest available data repository for the study of durable MCS outcomes.[34] INTERMACS represents a collaboration between the NHLBI, the FDA, the CMS, device manufacturers, and the professional community and began prospective patient enrollment and data collection in June 2006. In March 2009, CMS and the U.S. Department of Health and Human Services mandated that all U.S. hospitals approved for use of MCS for DT enter MCS patient data into INTERMACS for all noninvestigative MCS devices approved by FDA. Although mandated data entry was discontinued by CMS in October 2013, the number of DT implants entered annually into INTERMACS has increased. Since the inception of INTERMACS, the ongoing evolution of strategies for device application and the types of available devices has continued to refine the landscape of MCS. The major limitation of INTERMACS is the inability to enter patient information on investigative devices currently in evaluation in the United States, as well as the need for informed consent, which represents a barrier for capture of all patients receiving MCS therapy. To date, data on more than 15,000 patients receiving durable MCS therapy have been reported to INTERMACS.[34] The overall survival rate for all patients undergoing primary implantation of a durable MCS device is approximately 80% at 1 year and 70% at 2 years[34] (**Fig. 29.11**). Survival for patients undergoing primary implantation with an LVAD was

superior to survival with bilateral VAD or TAH.

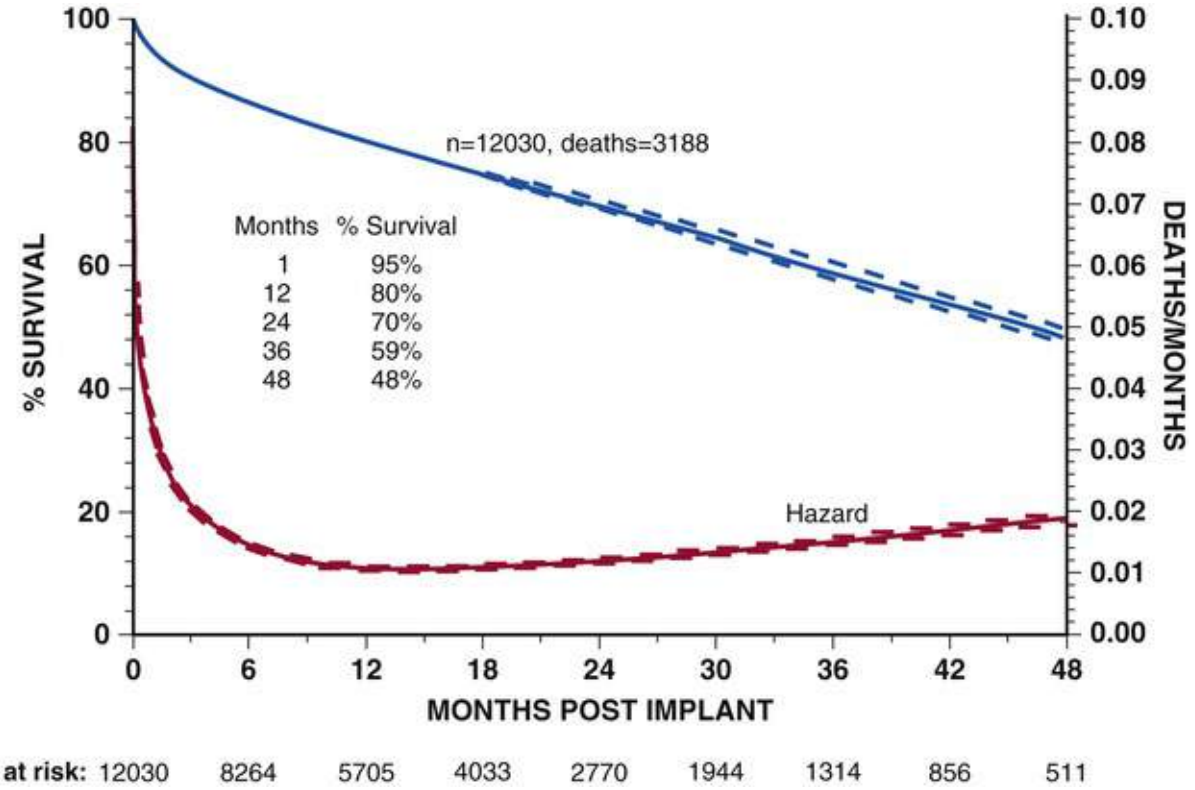

FIGURE 29.11 Actuarial and parametric modeling of survival after implantation of primary continuous-flow LVADs with or without concomitant RVAD support. The *upper curve* displays the Kaplan-Meier survival estimates over time. The *lower curve* indicates the hazard function, or instantaneous risk, over time. The *dashed lines* indicate the 70% confidence limits. (Data from Kirklin JK, Naftel DC, Pagani FD, et al. Seventh INTERMACS annual report: 15,000 patients and counting. J Heart Lung Transplant 2015;34:1495.)

One of the most important contributions to the MCS field has been the development of a subjective classification system based on severity of illness, termed "INTERMACS Patient Profiles," which range from Profile 1 (critical cardiogenic shock) to Profile 7 (advanced NYHA Class III HF)[35] (**Table 29.5**). This classification system has added enhanced resolution of patient outcomes in the advanced stages of HF or cardiogenic shock beyond that offered by the NYHA classification system. INTERMACS patient profiles are associated with short-term survival following LVAD implantation and are used to inform appropriate timing of intervention with durable, implantable MCS devices. Patients undergoing implantation of an MCS device who have critical cardiogenic shock (INTERMACS Patient Profile 1) have worse long-term outcomes than patients with more stable forms of advanced HF (INTERMACS Patient Profile levels 2 through 7).[34] Patients with significant organ dysfunction at MCS device implantation, accompanied by a greater degree of hemodynamic compromise, are significantly more likely to require BiVAD support and are at higher risk for major adverse events and at significantly higher risk for death during use of MCS devices.

TABLE 29.5

INTERMACS Patient Profiles

PROFILE	DEFINITION	DESCRIPTION
1	"Crashing and burning"	Life-threatening hypotension and rapidly escalating inotropic pressor support, with critical organ hypoperfusion confirmed by worsening acidosis and lactate levels.
2	"Inotrope dependent and worsening"	Shows signs of continuing deterioration in nutrition, renal function, fluid retention, or other major status indicator *or* refractory volume overload, ± evidence of impaired perfusion, with inotropic infusion intolerance due to tachyarrhythmias, clinical ischemia, or other.
3	"Stable on inotropes"	Clinically stable on mild-moderate doses of IV inotropes (or has a temporary MCSD) after repeated failures to wean without symptomatic hypotension, worsening symptoms, or progressive organ dysfunction. May be either at home or in the hospital.
4	"Frequent flyer/resting symptoms"	At home on oral therapy but frequently has symptoms of congestion at rest or with ADLs. May have orthopnea, SOB during ADLs, GI symptoms, disabling ascites, or severe lower extremity edema.
5	"Exercise intolerant"	Comfortable at rest but unable to engage in any activity, living predominantly within the house or housebound. No congestive symptoms, but may have chronically elevated volume status, frequently with renal dysfunction, and may be characterized as exercise intolerant.
6	"Walking wounded"	Comfortable at rest without evidence of fluid overload, but able to do some mild activity. ADLs are comfortable and minor activities outside the home can be performed, but fatigue results within a few minutes of any meaningful physical exertion. Occasional episodes of worsening symptoms; likely to have had a hospitalization for heart failure within the past year.
7	"Advanced NYHA Class III"	Clinically stable with a reasonable level of comfortable activity, despite history of previous decompensation that is not recent. Usually able to walk more than a block. Any decompensation requiring IV diuretics or hospitalization within the previous month should make this person a Patient Profile 6 or lower.

ADLs, Activities of daily living; *GI,* gastrointestinal; *IV,* intravenous; *MCSD,* mechanical circulatory support device; *NYHA,* New York Heart Association; *SOB,* shortness of breath.

From Stevenson LW, Pagani FD, Young JB, et al. INTERMACS profiles of advanced heart failure: the current picture. J Heart Lung Transplant 2009;28:535-41.

Future Perspectives

Recent rapid technological advancements and successful clinical application of mechanical circulatory support have provided a major impetus to extending the use of this modality. Important initiatives that will contribute significantly to future directions in MCS therapy include (1) introduction of new MCS devices that focus on miniaturization and biventricular support applications; (2) implementation of partial-support MCS devices and regimens; (3) design of fully implantable MCS devices, with elimination of the percutaneous lead and introduction of wireless energy transfer; (4) specific developments in the field of pediatric MCS, including appropriately designed MCS devices, clinical trials, and national registry development; (5) evaluation of MCS therapy in patients with less advanced HF; and (6) harmonization of the global MCS experience through international registry initiatives. A number of new MCS devices are under development. The MVAD (Medtronic) is a small, implantable continuous-flow rotary pump with axial design.[6,36] The pump uses hydromagnetic levitation of the impeller that eliminates the need for an internal bearing for impeller support. The small size of the pump facilitates applications to minimally invasive surgical implantation, biventricular support applications, and different inflow and outflow configurations.[36]

The percutaneous lead has been a significant source of morbidity and adversely influences quality of life for patients on MCS support.[37] The introduction of wireless energy transfer will allow MCS systems to receive energy transcutaneously without the need for the percutaneous lead.[38] The entire MCS system will be implantable, with an internal power source providing short periods of support, allowing the patient to pursue activities that are restricted with current technology, such as swimming and bathing. The incorporation of this type of technology, if successful, can be expected to increase patient satisfaction and quality of life significantly.

To date, a majority of MCS devices have been designed to provide complete cardiac output or full support. As MCS therapy moves into populations of patients with less advanced HF, the concept of small,

partial-assist MCS devices has been developed to reverse HF symptoms with only limited assist of cardiac function. The C-Pulse is a counterpulsation device similar in concept to the IABP but is implanted around the ascending aorta, rather than being placed into the circulation.[39,40] The major feature of the device is the reduction in potential risk of stroke, because the device is not incorporated into the circulation and can be turned on and off without risk of device thrombosis (nonobligatory). The Intravascular Ventricular Assist System (iVAS; NuPulse CV, Raleigh, NC) is a small IABP for partial circulatory support that is placed with a minimally invasively approach in the descending aorta via subclavian artery access. As with the C-Pulse, the iVAS is designed to be nonobligatory. A small, wearable pneumatic driver allows full ambulation.

Important developments in the pediatric field include the PumpKIN Trial (Pumps in Kids, Infants and Neonates).[41] PumpKIN is an NHLBI initiative to investigate the use of several novel pump designs and ECLS systems for pediatric MCS application. The trial is investigating two unique miniaturized ECLS systems and an implantable pump design based on the Jarvik 2000 VAD.[41] The initiative is a collaboration among industry, clinical centers, and the New England Research Institutes (NERI), designated as the data-coordinating center for the trial. Two national registries will serve as contemporary observational control arms for the new devices studied in PumpKIN. PediMACS, an INTERMACS initiative dedicated to pediatric patients, will serve as the contemporary observational arm for the PumpKIN trial using the FDA-approved pediatric device Berlin Heart Excor Pediatric VAD. Data for the MCS devices designed for ECLS in the PumpKIN trial will be compared against contemporaneous outcomes for ECLS in the Extracorporeal Life Support Organization (ELSO) Registry.

Widespread interest in MCS therapies has resulted in global adoption and clinical application of this technology. An understanding of international outcomes based on uniform definitions of outcomes and adverse events is essential to the sustainability of MCS therapy and to foster efficient device development and clinical evaluation. IMACS is an international registry collaboration supported by the International Society of Heart and Lung Transplantation and INTERMACS that was initiated to achieve international cooperation on reporting of MCS outcomes.[42] Efforts to create uniform registration and reporting requirements worldwide constitute an important initiative of the FDA to facilitate clinical device evaluation in the United States.[43]

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Future Perspectives

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Engineering Designs of Ventricular Assist Devices (VADs)

General Characteristics

VADs share a number of basic components despite the differences in design and indications for use. All systems for left-sided support (arterial system), whether temporary or designed for long-term use, consist of an inflow cannula that drains blood from the heart (most often directly from the left ventricular (LV) apex or from the left atrium via the right superior pulmonary vein or transseptal approach) to the pump and an outflow cannula that carries blood back to the arterial system by way of the aorta or femoral, axillary, or carotid artery, depending on the particular MCS device. For right ventricular (RV) support systems, cannulas usually are positioned to drain blood from the right atrium (most common) or right ventricle and return blood to the pulmonary artery. Temporary devices typically have long cannulas that attach to the heart, traverse the skin, and then connect to the pump. Although the actual pump may reside in the body, as with the Impella device (**see Fig. 29.3**), the motor to drive the pump for temporary MCS devices is located outside the body (in an extracorporeal position) (**Figs. 29.2 to 29.5**). Long-term, implantable MCS devices generally are designed with very short inflow cannulas, as with the HeartMate II (**Fig. 29.7**), or have incorporated the inflow cannula into the pump, as with the HeartMate 3 (**Fig. 29.6**) and HVAD (**Fig. 29.8**). The power supply for implantable pumps is delivered through a percutaneous lead

that traverses the skin and connects the external power system with the internal pump. The external components of an implantable system generally consist of a power source (i.e., batteries or alternating-current [AC] power unit) and a small, portable computer (controller) that controls device speed and monitors device function (**see Fig. 29.9**).

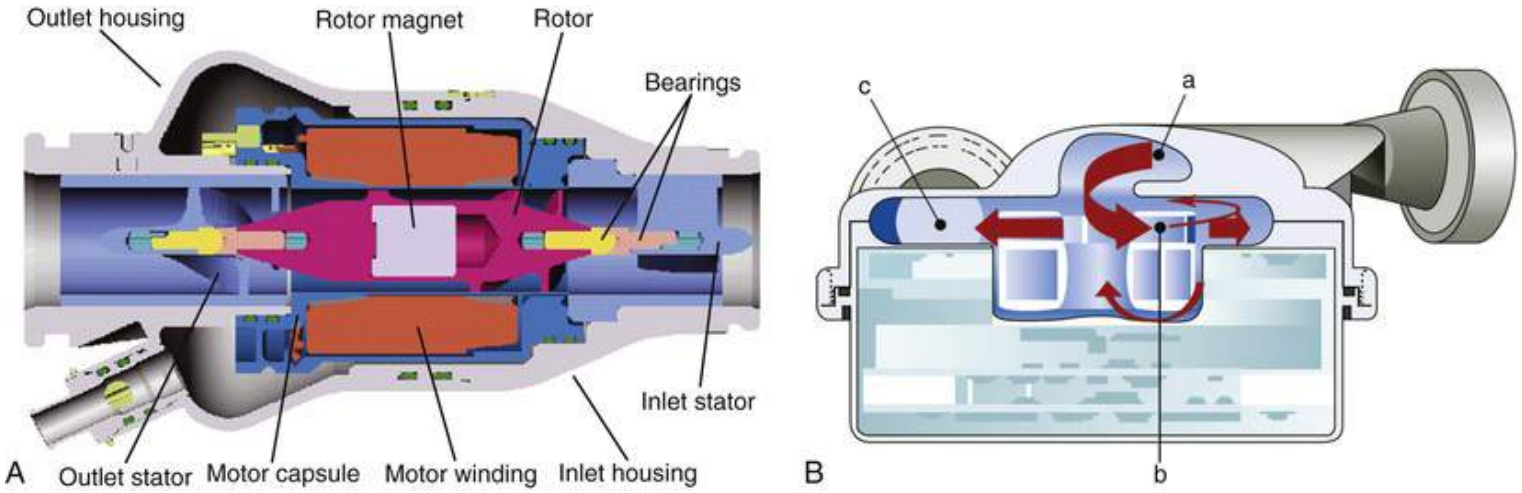
Pulsatile-Flow, Volume-Displacement Pumps

Early MCS devices were based on a volume-displacement design with pulsatile flow that mimicked the phasic contractions of the human heart, but are now largely of historical interest, and are no longer commercially available for adult patients. The major feature of these pulsatile, paracorporeal or implantable pulsatile systems that contributed to their use was the flexibility to provide biventricular support. Today, the use of pulsatile pumps is restricted to temporary MCS support as extracorporeal pumps for bridge to recovery (BTR) or as paracorporeal pumps for bridge to transplantation (BTT) indication in pediatric patients who do not have other options for implantable, durable pumps.

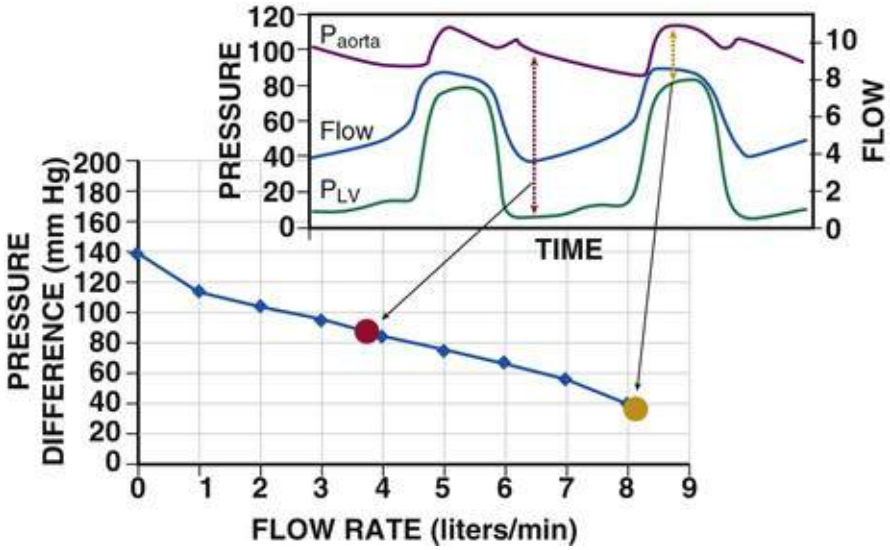
Continuous-Flow Rotary Pumps

The field of MCS has significantly evolved from volume-displacement pulsatile pumps to continuous-flow rotary pumps. This trend has continued for both short- and long-term MCS device designs. Continuous-flow rotary pumps offer several advantages over pulsatile-flow, volume-displacement pumps. These advantages include smaller size, fewer moving parts (resulting in greater durability and reliability), limited blood contacting surfaces, and reduced energy requirements.

A continuous-flow pump consists of blood inlet and outlet ports and a single rotating impeller suspended within a tube that propels blood forward by spinning the internal impeller at high speeds, thereby imparting significant kinetic energy to the blood (**eFig. 29.1**). The spinning of the impeller is accomplished by actuating an electrical current and magnetic field around the impeller, which contains internal magnets. Although continuous flow through the pump occurs throughout the cardiac cycle, there are also superimposed phasic changes in pump flow. Pump flow is greater during native cardiac systole than during native cardiac diastole because native LV contraction raises intracardiac pressure, thereby lowering the pressure gradient (the difference between aortic and LV pressures) the pump must overcome to generate forward flow (**eFig. 29.2**). These phasic changes in blood flow with a rotary pump impart a pulse to the native circulation. The magnitude of pulse pressure typically is diminished compared with that generated with a native heart contraction or pulsatile-flow pump. Under normal circumstances (pump working in conjunction with the native heart contraction), the aortic flow pattern with a rotary pump is more accurately described as being *continuous*, rather than using the description of “nonpulsatile flow.” In circumstances where native heart contraction is absent (e.g., ventricular fibrillation), the flow through a continuous-flow rotary pump is nonpulsatile.



EFIGURE 29.1 Axial and centrifugal pump designs. **A,** Continuous-flow rotary pump with axial flow design. The internal impeller is supported by outflow and inflow stators (mechanical pivot design) with bearings. The internal impeller contains a magnet. Rotation of the impeller is achieved by an alternating magnetic field generated from the motor and electrical coils surrounding the impeller. **B,** Continuous-flow rotary pump with centrifugal design. Internal impeller supported by magnetic levitation. Bearings are eliminated. The impeller rotation is achieved by motor stators that are magnetically coupled to the impeller. Schematic diagram demonstrates the blood flow path from the inflow section (*a*), blood flow path through the impeller and the backflow paths above the shroud and between the rotor and the motor (*b*), and outflow path (*c*). (From Farrar DJ, Bourque K, Dague CP, et al. Design features, developmental status, and experimental results with the HeartMate III centrifugal LV assist system with a magnetically levitated rotor. ASAIO J 2007;53:310.)



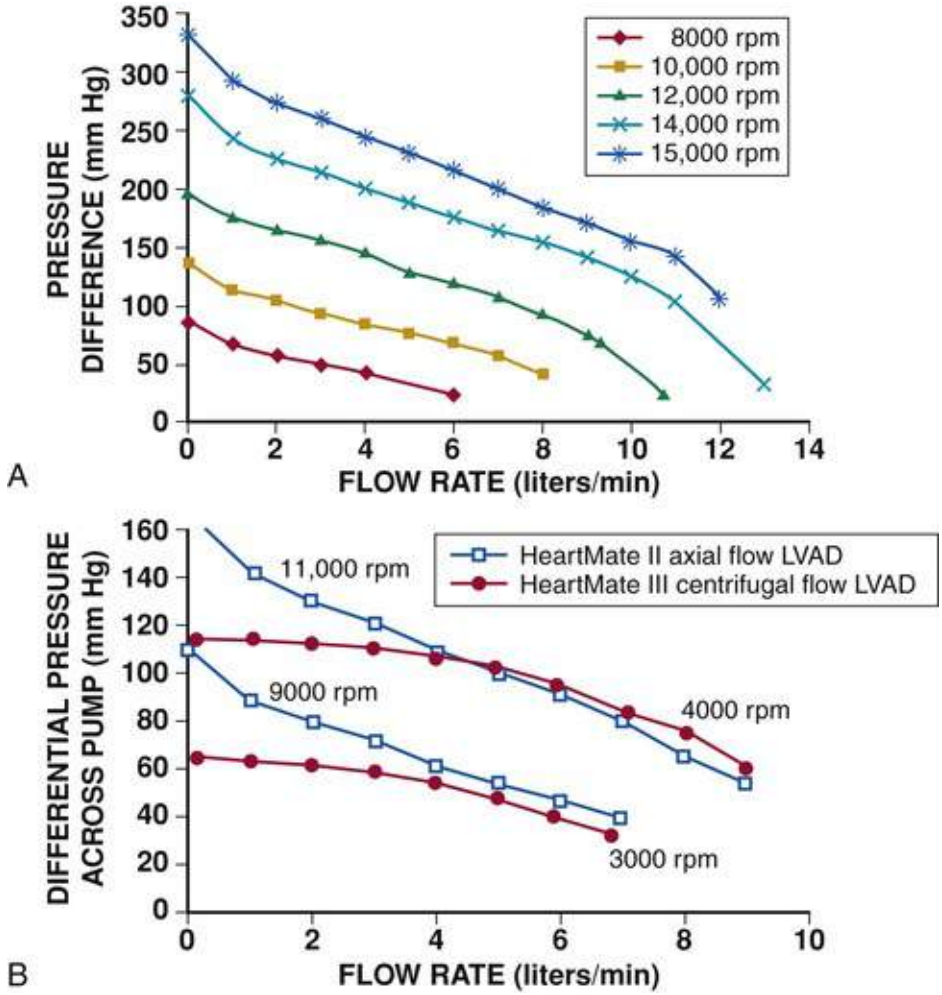
EFIGURE 29.2 Blood flow in a continuous-flow rotary pump is both continuous during the entire cardiac cycle and phasic (more flow through the pump is observed during native cardiac systole than during native cardiac diastole because of the interaction between native heart contraction and hydrodynamic properties of pump). These phasic changes in blood flow with a rotary pump are caused by a change in pressure gradients across the pump resulting from changes in native diastolic and systolic pressures. During diastole, the pressure gradient across the pump (the difference between aortic [P_{aorta}] and left ventricular [P_{LV}] pressures) is greatest, resulting in less flow. During systole, the pressure gradient across the pump (difference between P_{aorta} and P_{LV}) is less, resulting in more flow. These pressure changes induce corresponding changes in flow that impart a pulse to the native circulation.

Other important distinguishing characteristics of continuous-flow pumps are the flow pattern and the mechanism of impeller support (**see eFig. 29.1**). A distinguishing feature of continuous-flow pumps is the method by which the internal impeller is supported. The internal impeller in axial or centrifugal designs may or may not be supported by mechanical bearings (mechanical pivot design). Levitation systems

utilized in more advanced rotary pumps suspend the moving impeller within the blood field without any mechanical contact. Magnetic forces may be *passive* without the consumption of power (permanent magnet) or *active* (induction of magnetic field with electricity) in design. Hydrodynamic levitation depends on fluid forces generated by the rotating impeller. Pump designs can be further distinguished by the use of hydrodynamic levitation only, hydrodynamic levitation working in synergy with magnetic levitation for suspension, or variations of active and/or passive magnetic levitation. Active magnetic levitation of the impeller typically uses complex position sensing and control systems that increase requirements for a larger pump size. Hydrodynamic suspension does not use position sensors, resulting in a less complicated electronic design and ability to miniaturize pump size. However, in circumstances of low rotational speeds or if the pump were to stop, hydrodynamic forces may be inadequate to prevent the impeller from coming into contact with the outer device housing, potentially causing impeller damage or heat generation and leading to thrombus formation.

There are theoretical benefits to incorporation of a bearingless design into pumps. Having bearings present in the blood path to suspend the impeller constitutes a potential point of frictional wear and of heat generation. Frictional wear of the bearing may result in device failure and subsequent need for device exchange. Bearings also may represent a potential site for thrombus formation at the interface of the impeller and bearing if the bearing design does not permit adequate blood “washing” of the bearing surfaces and creates localized areas of blood stasis. Heat generated by the contact of the impeller and bearing is dissipated by blood flow through the pump. Periods of low flow through a pump can result in inadequate heat transfer from the bearing and result in denaturation and deposition of proteins on the bearing. This deposition could contribute to future thrombus formation or hemolysis. Additionally, the presence of stators that support the bearings and act to redirect blood flow in second-generation pumps also represents an obstruction within the blood flow path and a potential site for thrombus deposition.

Blood flow through continuous-flow pumps, both axial and centrifugal, is directly proportional to pump speed and inversely related to the pressure difference across the inlet (LV pressure) and outlet (aortic pressure) orifices of the pump. Centrifugal devices are generally more efficient at energy transfer and provide continuous flow at rotational speeds that are much slower, approximately 2000 to 6000 rpm, compared with 8000 to 15,000 rpm for pumps with axial-flow designs. The relationship between pressure and flow can be displayed in a series of so-called H-Q curves, reflecting blood flow (Q) over varying pressure gradients (H, for pressure head) at specific pump speeds, the pressure-flow relationship (**eFig. 29.3**).



EFIGURE 29.3 Hydrodynamic properties of a continuous-flow rotary pump. **A,** Blood flow through a continuous-flow rotary pump is inversely related to pressure gradient (the difference between aortic and LV pressures) across the pump and directly related to pump speed. This pressure-flow relationship is visualized by a series of pressure-flow curves at different pump speeds. **B,** In this example the pressure-flow relationship for the axial flow pump is steeper than for the centrifugal flow pump. The less steep pressure-flow relationship of the centrifugal flow pump elicits greater variation in pump flows during the cardiac cycle, that is, larger changes. LVAD, Left ventricular assist device.

The relationship between flow and pressure with axial pumps differs from that of centrifugal pumps. With centrifugal blood pumps, the pressure-flow relationship generally tends to be less steep (this may not be the case with all pumps), such that small changes in pressure across a centrifugal pump produce larger changes in blood flow compared with those occurring with an axial pump (**eFig. 29.3**). The more responsive pressure-flow relationship in centrifugal pumps results in a greater degree of flow variability across the cardiac cycle (less flow in diastole and more flow in systole). In theory, the benefits of centrifugal versus axial pumps are a greater aortic pulse pressure and less propensity to create LV collapse or a “suction event” resulting from the greater drop in pump flow as LV end-diastolic pressures decrease. LV collapse or suction events elicited by a VAD may cause ventricular arrhythmias or may increase the propensity for thrombus formation on bearings because of low flow or on the endocardium because of trauma.

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Important Medical Conditions in Instituting Mechanical Circulatory Support (MCS)

Valvular Heart Disease

Abnormalities of the cardiac valves have important adverse consequences in patients being considered for MCS and may require repair or replacement to initiate successful MCS or achieve weaning from support. Mild to moderate aortic stenosis (AS) in the absence of insufficiency is not a contraindication to placement of a ventricular assist device (VAD). Severe AS should be corrected before placement of a VAD, preferably with a bioprosthetic valve, to facilitate future weaning or to optimize native heart function in the event of device failure.

The presence of moderate aortic insufficiency can have a significant impact on the effectiveness of MCS therapy. In patients in whom LV assistance is initiated with LA-to-aortic cannulation, aortic insufficiency will result in LV distention in the presence of significant LV dysfunction. LV distention adversely affects subendocardial blood flow and can prevent weaning from MCS. In patients in whom MCS support is initiated with devices that require LV apical-to-aortic cannulation, reductions in LV pressure elicited by MCS increase the pressure gradient across the aortic valve and increase the degree of aortic insufficiency. Blood pumped into the aorta by the LVAD will flow backward across the incompetent aortic valve (aortic insufficiency), decreasing net forward flow and compromising end-organ perfusion. Mild to moderate aortic insufficiency may become more severe with initiation of MCS from an LVAD, because the elevated LV end-diastolic pressure will be significantly reduced by emptying of the LV cavity by the device, and the aortic root pressure will be elevated above baseline because of device flow.

The presence of significant aortic insufficiency can be confirmed by echocardiography, and significant aortic insufficiency (moderate or greater) should be addressed with either aortic valve repair, replacement, or closure of the aortic outflow with a patch sewn to the annulus of the aortic valve. A comparison of techniques (repair versus replacement versus patching) to address aortic insufficiency identified a higher mortality for those who underwent patch closure of the aortic valve annulus, suggesting repair or replacement are more appropriate techniques to resolve aortic insufficiency.[1] Patients with a mechanical valve prosthesis in the aortic valve position should have the mechanical valve replaced with a bioprosthetic valve before institution of LV assistance. During complete unloading of the left ventricle by a VAD, the aortic valve may not open, and the mechanical valve may be prone to thrombus formation. Placing a patch over the mechanical valve may be another alternative, but this may increase thromboembolic risk.

Patients with significant mitral stenosis (MS) at initiation of device support may require correction of the valvular problem before implantation of a device, depending on device selection and site of cannulation. In the setting of significant MS, LV filling is impaired. VADs that use apical ventriculotomy for cannula placement for ventricular drainage may experience limitations in device filling resulting from MS. This problem can be circumvented by correcting the underlying valvular pathologic abnormality (mitral valve repair or replacement with a bioprosthetic valve). The impact of mitral regurgitation on limiting forward flow through a VAD is not well understood, and data to suggest routine repair or replacement of the mitral valve for insufficiency are lacking. However, in patients in whom weaning from MCS may be feasible, correction of the mitral pathologic condition, either stenosis or regurgitation, is

necessary to optimize ventricular function.

Adequate RV function is extremely important for maintaining LVAD flow in the early postoperative period. Severe tricuspid regurgitation (TR) can significantly impair the forward flow of blood from the right ventricle, particularly in situations of high pulmonary vascular resistance (PVR). Severe TR contributes to elevated central venous pressure, hepatic congestion, and renal dysfunction. Severe TR may be present preoperatively in the setting of volume overload and biventricular failure or may develop after institution of LVAD support because of RV dilation from leftward shift of the interventricular septum.[2-4] If severe TR is present during the initiation of LVAD support, tricuspid valve repair should be performed to improve RV performance.

Coronary Artery Disease (CAD)

Patients with significant obstructive CAD or patients with postcardiotomy shock following failed coronary bypass operations may experience angina during MCS. Generally, CAD does not have adverse hemodynamic consequences during the period of MCS. However, the presence of obstructive coronary disease with ongoing ischemia may limit the degree of myocardial recovery and affect the ability to wean from temporary MCS.

Perioperative ischemia of the right ventricle may be of hemodynamic significance during institution of LVAD support. RV ischemia causing myocardial stunning or infarction that occurs during or soon after implantation of an LVAD can elicit RV failure, resulting in decreased flow to the LVAD. In patients who have had coronary bypass surgery and are candidates for MCS, patent bypass grafts, particularly to the right coronary artery (RCA) or left anterior descending coronary artery (LAD), should be preserved to reduce the risk of perioperative RV failure and arrhythmias. In select patients it may be important to perform a coronary artery bypass to the RCA or LAD systems to optimize RV function in the perioperative period if significant obstructive coronary lesions amenable to bypass are present in the distribution of the these arteries.

Arrhythmias

Atrial and ventricular arrhythmias are common in patients with cardiogenic shock and underlying ischemic or idiopathic cardiomyopathies. These arrhythmias generally persist in the immediate postoperative period and subsequently resolve with time as the patient's hemodynamic condition improves and inotropic therapy is weaned. Some patients will have persistent arrhythmias as a result of their underlying pathology (e.g., giant cell myocarditis). Severe ventricular arrhythmias have traditionally been thought to be a contraindication to univentricular support. However, the hemodynamic consequences in patients in whom these arrhythmias develop in the late postoperative period generally are not life threatening. In the absence of pulmonary hypertension and elevated PVR in the postoperative period, patients maintain adequate LVAD flows during ventricular fibrillation (VF). This situation is analogous to a Fontan (systemic vein to pulmonary artery) circulation. In the early perioperative period, some patients with refractory ventricular arrhythmias may require biventricular support until the PVR drops and a Fontan circulation is tolerated. The addition of RV support for hemodynamic compromise because of refractory ventricular arrhythmia is unusual. In patients with elevated PVR, sustained ventricular tachycardia (VT) and VF will result in reduced LVAD flows and may precipitate thrombus formation within the pump. VAD-specific considerations when VT or VF occur include confirmation of proper inflow-cannula position and pump-speed adjustment to reduce suction events. Therapy directed at control

of ventricular arrhythmia must be pursued, including correction of underlying metabolic abnormalities, consideration of antiarrhythmic drug therapy, and in rare cases, radiofrequency ablation for VT. In patients for whom weaning from MCS is feasible or planned, elimination of the ventricular arrhythmias with antiarrhythmic therapy is essential.

Intracardiac Shunts

Intracardiac shunts, such as a patent foramen ovale (PFO) or atrial septal defect (ASD), should be closed at implantation of an LVAD to prevent right-to-left shunting. These anomalies should be identified before surgery using transesophageal echocardiography. During the initiation of LV assistance, left atrial pressure is reduced compared with right atrial pressure. In the presence of ASD or PFO, this gradient results in significant systemic hypoxemia as deoxygenated blood is shunted from the right to the left atrium.

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Clinical Trials with the HeartMate II Device

The HeartMate II Pivotal Trial for BTT was an FDA-approved, prospective, nonrandomized, multicenter study of 133 patients with end-stage heart failure (HF) who were on a waiting list for heart transplantation and received implantation of the HeartMate II device (**see Table 29.4**). The primary endpoint was a composite of the proportions of patients who, at 180 days, had undergone transplantation, were explanted for cardiac recovery, or had ongoing MCS with the HeartMate II while remaining eligible for transplantation. Of the 133 patients receiving support with the HeartMate II device, the principal outcomes were observed in 100 patients (75%).[1] At 3 and 6 months, device support with the HeartMate II was associated with significant improvement in functional status (NYHA functional class and 6-minute walk distance) and in quality of life (Minnesota Living with Heart Failure and Kansas City Cardiomyopathy questionnaires).[1] Major adverse events included postoperative bleeding, stroke, right-sided HF, percutaneous lead infection, and device malfunction (**see Table 29.5**). After this initial report of data for 133 patients, a follow-up evaluation was conducted through a continued access protocol (CAP) that included an additional 148 patients.[2] At 18 months, 222 patients (79%) met the primary endpoint, as defined previously for the pivotal trial.[2] The primary causes of death were sepsis, stroke, and right-sided HF. Episodes of bleeding requiring transfusion and surgery were the most common adverse events in the study, followed by stroke, localized infection not related to the device, infection associated with the percutaneous lead, preperitoneal pump pocket infection, and right-sided HF. There were no mechanical failures of the pumping mechanism. The freedom from device replacement for all causes,

including infection, device thrombosis, and percutaneous lead failure, was 92% (95% CI 88% to 97%) at 18 months.[2]

After completion of the FDA pivotal trial for evaluation of the HeartMate II for the bridge to transplantation (BTT) indication, a clinical study of the HeartMate II was performed for the first 169 consecutive patients enrolled in the postapproval phase, and results were compared with those for the first 169 consecutive patients who received another FDA-approved VAD (79% HeartMate XVE, 21% Thoratec IVAD) enrolled in INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) who were listed for transplantation or likely to be listed.[3] Kaplan-Meier survival at 12 months was significantly greater for HeartMate II recipients than for controls ($P = 0.001$), and this advantage was sustained after adjustment for significant baseline differences in creatinine, blood urea nitrogen, white blood cell count, heart rate, pump type, and aspartate transaminase (AST) ($P = 0.009$). A greater percentage of patients in the HeartMate II (90%; $n = 152$) versus the control (80%; $n = 130$) group reached the successful outcomes of survival to transplant, recovery of the heart, or ongoing support at 6 months ($P = 0.018$).

The HeartMate II DT Pivotal Trial randomly assigned 200 patients with New York Heart Association (NYHA) Class IIIB to IV symptoms and a left ventricular ejection fraction (LVEF) of 25% or less to receive a HeartMate II or a HeartMate XVE.[4] Eligible patients also needed a maximal oxygen consumption not exceeding 14 mL/kg/min, required treatment with intravenous inotropic agents for 14 days or longer, or had an intra-aortic balloon pump (IABP) for 7 days or longer. The primary endpoint was a composite of survival to 24 months without disabling stroke or the need for an operation to repair or replace the device. The patient population was predominantly male, with a mean age of 62 years. This was a severely ill population, as reflected by a mean LVEF of 17% and mean creatinine 1.6, relatively low use of baseline neurohormonal antagonists, and substantial use of inotropes (77%) and IABP (22%). There was a greater than fourfold increase in the percentage of HeartMate II patients who successfully reached the primary endpoint (46% versus 11%; $P < 0.001$)[5] (**see Table 29.3**). All adverse events were less frequent in the HeartMate II patients, with significant reductions in sepsis, device-related infections, right-sided HF, renal failure, and rehospitalizations. Changes in functional capacity, 6-minute walk distance, and quality-of-life scores were similar between groups, suggesting that the improvements seen in these metrics in VAD-supported patients are more closely linked to the favorable effects of increasing the cardiac output and lowering the left-sided filling pressures, rather than the characteristics of blood flow. The favorable results of the HeartMate II DT Pivotal Trial resulted in FDA approval of this device in 2010 as the second LVAD indicated for long-term support for the destination therapy (DT) indication.

A follow-up study reported the outcomes of patients entered into the HeartMate II Pivotal Trial for Destination Therapy through a CAP to those entered in the original cohort to determine if outcomes in the latter group were superior.[6] The 281 patients who underwent HeartMate II for DT from May 2007 to March 2009 (Mid-Trial group) were compared with the initial 133 HeartMate II patients from March 2005 to May 2007 (Early Trial group). Patient entry criteria were the same, and important baseline characteristics were similar for the two groups. **Table 29.4** provides Kaplan Meier survival data for the Early Trial and Mid-Trial experiences.[6] There were nominal improvements in survival, quality of life, and many adverse events, some of which achieved statistical significance.

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30

Cardiovascular Regeneration and Repair

Kiran Musunuru, Joseph C. Wu

A longstanding quest in cardiovascular medicine is to regenerate injured tissue or to correct fundamental defects in molecular pathways that cause organ dysfunction in the setting of heart disease. Depending on the specific etiologic disorder, the myocardium might comprise diseased cardiac myocytes, fibrous tissue that replaced permanently lost cardiac myocytes, and normal cardiac myocytes (**see Chapter 23**). As shown in **Fig. 30.1**, there are two general strategies to addressing myocardial disorders. The first is a *regenerative therapy* to replace permanently lost cardiac myocytes within the myocardium. A second strategy is to undertake *disease modeling* ex vivo to identify therapeutic strategies that can repair diseased cardiac myocytes or prevent myocytes from becoming diseased, which may entail the use of traditional small-molecule drugs or cutting-edge technologies such as gene therapy and genome editing. After decades of research, significant obstacles remain in translating these strategies into clinical practice, but recent scientific advances have improved the prospects for cardiovascular regeneration and repair to reach patients in the near future.

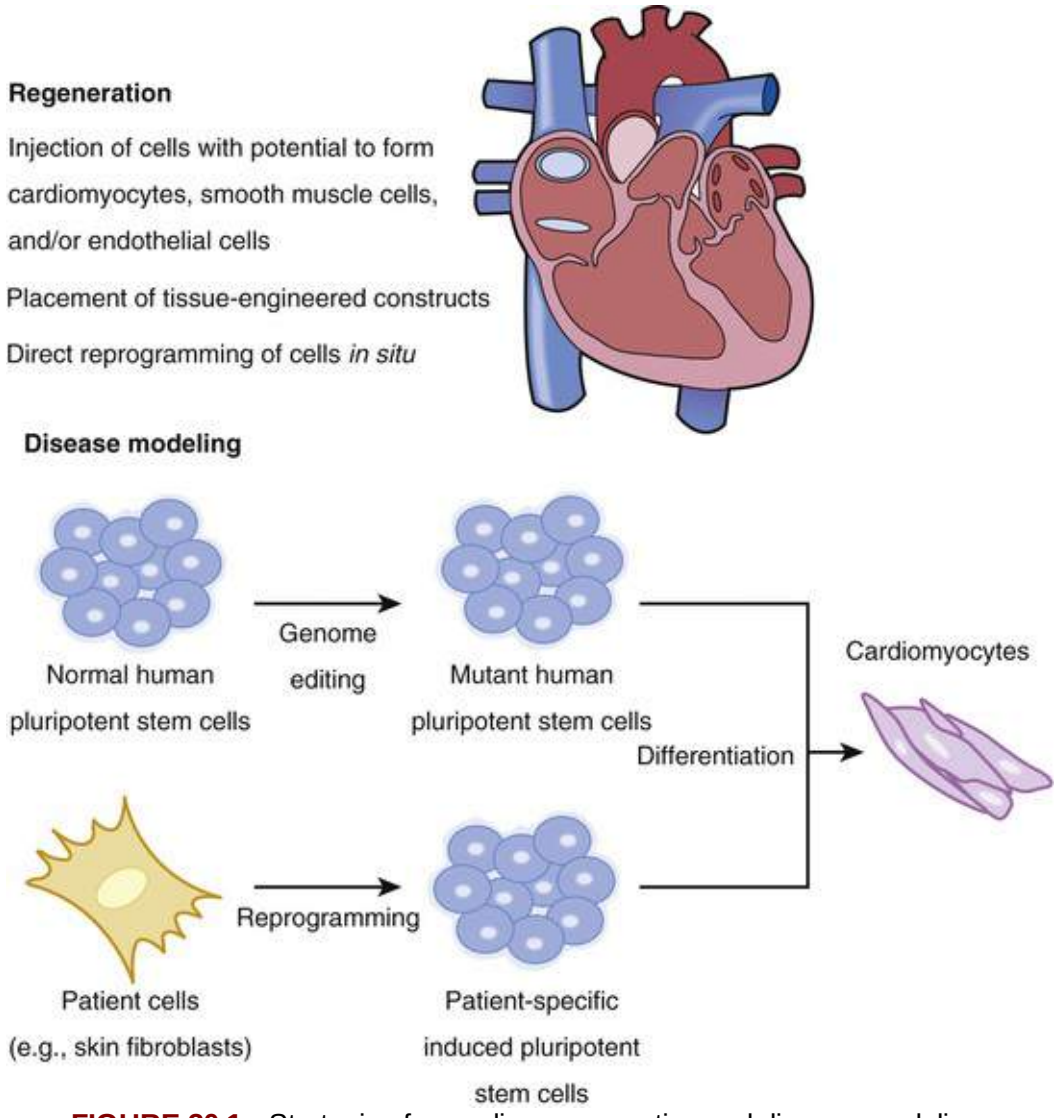

FIGURE 30.1 Strategies for cardiac regeneration and disease modeling.

Regeneration

A primary goal of cardiac cell-based therapy is to repopulate areas of damaged myocardium with three types of cells capable of engraftment: cardiac myocytes, vascular smooth muscle, and endothelium. Although a variety of cellular substrates have been proposed for cardiac regenerative therapy, including bone marrow mononuclear cells, skeletal myoblasts, mesenchymal stem cells, mesenchymal progenitor cells, endothelial precursor cells, and cardiac-derived stem cells, the ability of each of these substrates to productively supply one or more of the three key cardiac cell types within damaged myocardium remains to be firmly established, and initial clinical trials have had mixed results.[1] Rather than attempting to define how each of these cellular substrates might directly convert into, substitute for, or stimulate the growth of the three native cardiac lineages, it is more instructive to review what is known about the normal process of embryonic cardiac development giving rise to functioning myocardium.

Cardiac Development

Our knowledge of cardiac development was elucidated mostly in studies in mice and other model organisms and either has been replicated with human cell-based studies or is otherwise presumed to be relevant to humans.[2,3] Following gastrulation early in development, cardiac mesoderm progenitors migrate

from the primitive streak into the splanchnic mesoderm to form the first heart field and second heart field. These progenitors initially express the transcription factor Brachyury (Bry), which is encoded by a direct target gene of Wnt/β-catenin signaling. On traversal into the splanchnic mesoderm, the inhibition of canonical Wnt/β-catenin signaling and activation of both noncanonical Wnt signaling and eomesodermin signaling in the Bry^+ cells result in the downregulation of Bry and the expression of mesoderm posterior 1 (MesP1), committing these cells to cardiogenesis. The $MesP1^+$ cardiogenic progenitor cells give rise to multipotent cardiovascular progenitor cells within the first and second heart fields. The *first heart field* forms the cardiac crescent and then the heart tube, ultimately contributing most of the cells in the left ventricle. Although specific markers for the multipotent cardiovascular progenitor cells in the first heart field remain to be defined, the influence of bone morphogenetic protein (BMP) and fibroblast growth factor (FGF) signaling eventually gives rise to a population of cells expressing homeobox protein Nkx-2.5 and T-box 5 (Tbx5). These $Nkx\text{-}2.5^+/Tbx5^+$ cells are bipotent, producing both cardiomyocytes and smooth muscle cells.

The *second heart field* ultimately contributes more than two thirds of the cells in the heart, including the atrial and right ventricular chambers, the outflow tract myocardium, the proximal coronary arteries, and much of the conduction system. The multipotent cardiovascular progenitor cells in the first heart field are defined by expression of ISL LIM homeobox 1 (ISL-1), Nkx-2.5, and fetal liver kinase 1 (Flk-1), which are capable of giving rise to cardiomyocytes, smooth muscle cells, and endothelial cells, as determined by the influences of a variety of signaling pathways. Additional contributions to the developing heart, particularly the epicardium, cardiac fibroblasts in the myocardium, coronary arteries, aorta, and autonomic nerve cells, are provided by proepicardial progenitor cells and cardiac neural crest cells.

Understanding of the normal process of cardiac development and the central roles of multipotent cardiovascular progenitor cells in that process provides key insights into how initial attempts at cardiac regenerative therapy can be further improved. Optimal therapeutic approaches might entail either the recruitment, expansion, or differentiation of any rare multipotent cardiovascular progenitor cells still resident in the adult heart or, perhaps more realistically, by enhancing the ability to grow and differentiate large numbers of multipotent or pluripotent cells ex vivo, followed by transplantation.

Human Pluripotent Stem Cells

Human pluripotent stem cells (hPSCs) have several defining properties that are a major focus of interest in the field of regenerative medicine. First, they are human cells with normal human genomes and thus are more appropriate for therapeutic use in humans than transformed or immortalized human cultured cell lines with tumorigenic characteristics. Second, hPSCs are pluripotent and thus have the capacity to differentiate into any human cell types, including cardiac myocytes, smooth muscle, and endothelium. Third, as stem cells, hPSCs have an unlimited capacity for expansion and thus can serve as a renewable source of cells for regenerative therapy.

There are two major types of hPSCs, human embryonic stem cell (hESCs)[4,5] and human induced pluripotent stem cells (iPSCs).[6] (A third type of hPSCs, derived by somatic cell nuclear transfer, is currently too rare to be relevant for therapeutic applications.) hESCs are generated from human embryos, but because they typically entail the destruction of the source embryos, they are not used currently for therapy. By contrast, iPSCs are typically generated from adult cells from living donors. The potential source cells for iPSCs include skin fibroblasts, blood-derived T lymphocytes, and urine-derived renal tubular cells, all of which can be obtained in a minimally invasive manner. The source cells undergo a

process called *reprogramming*, in which a set of factors—classically, Oct3/4, Sox2, Klf4, and c-Myc—are transiently introduced into the differentiated cells, converting them into pluripotent cells. Aside from any mutations that may result from the reprogramming procedure, the iPSCs are perfectly matched to the donors. This is equally true of iPSCs from healthy individuals and those from patients with genetic disorders or genetic predisposition to disease. Because they represent an autologous source of cells, iPSCs are attractive substrates for regenerative therapy, in addition to being well suited for personalized disease modeling, as described later.

Differentiation Into Cardiac Lineages

In vitro differentiation of hPSCs into a desired cell type can be guided by knowledge of the process by which the cell type arises in the body during normal human development. Efforts to develop and optimize protocols to yield pure cardiomyocytes from hPSCs demonstrate this principle.[7,8] Initial attempts entailed the dispersion of hPSCs, culturing in suspension conditions, and formation of three-dimensional aggregates called *embryoid bodies*. Cells within embryoid bodies spontaneously differentiate into any of the three germ layers—endoderm, mesoderm, or ectoderm—resulting in a heterogeneous mix of cells of different lineages. Some proportion of the cells will have cardiomyocyte properties and in principle can be purified away from noncardiomyocyte cells. However, the exact proportion of cardiomyocyte-like cells in any given embryoid body is typically not large and is quite variable, limiting the usefulness of embryoid body–based protocols.

Taking a cue from normal cardiac development, subsequent attempts at cardiomyocyte differentiation explored the exposure of hPSCs to growth factors and signaling-pathway inhibitors thought to be important for cardiogenesis. Thus the differentiation would be directed toward reproducing what naturally occurs in vivo, rather than relying on the spontaneous products. Various protocols along these lines have greatly improved the efficiency and consistency of cardiomyocyte differentiation, particularly when the cells are differentiated in a two-dimensional monolayer format. A widely used protocol sequentially exposes hPSCs to a glycogen synthase kinase 3β inhibitor and then a Wnt inhibitor, with the effect of initially activating canonical Wnt/β-catenin signaling and then blocking it, mimicking the steps that occur in development as embryonic cells are induced into mesodermal progenitors and then transformed into cardiogenic progenitors.[9] The use of these inhibitors reproducibly yields proportions of cardiomyocytes as high as over 90%. As with cardiomyocytes, insights from normal human development have helped improve differentiation protocols for vascular endothelial and smooth muscle cells.

Despite these advances with respect to in vitro cardiomyocyte differentiation, as well as differentiation of other cell types, the lack of purity and lack of maturity remain obstacles. For therapeutic applications, highly pure cardiomyocyte preparations would be optimal. One approach is to sort the desired cells away from noncardiomyocyte cells using antibodies for cardiomyocyte-specific membrane proteins or cardiomyocyte-specific dyes.[10,11] Another approach is to genetically introduce antibiotic resistance cassettes into the hPSCs before differentiation, with the resistance only expressed in cardiomyocytes (e.g., through the use of a cardiac-specific promoter). The treatment with the antibiotic removes noncardiomyocyte cells while sparing the cardiomyocytes. Yet another approach is to exploit the ability of differentiated cardiomyocytes to metabolize lactate, with a prolonged exposure to a lactate-rich, glucose-poor medium that eliminates noncardiomyocyte cells.[12] Each of these approaches has been demonstrated to improve the yield of cardiomyocytes to almost 100%.

Although in vitro they have functional characteristics that are exclusive to cardiomyocytes, differentiated cardiomyocytes have important differences from the mature adult cardiomyocytes in the

human heart. In many respects, they resemble fetal cardiomyocytes, indicating a degree of immaturity that remains a significant obstacle for researchers to overcome.[13,14] Such differences are found in length and shape (smaller length-to-width ratio), in having single rather than multiple nuclei, in lacking well-developed sarcoplasmic reticulum and transverse tubules, and in having fewer mitochondria, higher resting membrane potentials, slower depolarization speeds, and differences in functional gene expression, particularly ion channel and calcium-handling genes (**Table 30.1**). Some of these signs of immaturity can be addressed by building the cardiomyocytes into engineered myocardial structures (e.g., with micropatterning techniques). Another challenge is that in vitro differentiated cardiomyocytes are typically a mix of ventricular-like, atrial-like, and nodal-like cardiomyocytes, although progress is being made in developing methods to direct the differentiation of cells to just one type of cardiomyocyte.[15]

TABLE 30.1

Differences Between Human Pluripotent Stem Cell (hPSC)–Derived Cardiomyocytes and Mature Adult Cardiomyocytes

	hPSC-DERIVED CARDIOMYOCYTES	ADULT CARDIOMYOCYTES
Morphology		
Shape	Round or polygonal	Rod and elongated
Size	20-30 pF	150 pF
Nuclei per cell	Mononucleated	~25% multinucleated
Multicellular organization	Disorganized	Polarized
Sarcomere appearance	Disorganized	Organized
Sarcomere length	Shorter (~1.6 μM)	Longer (~2.2 μM)
Sarcomeric protein: MHC	β > α	β α
Sarcomeric protein: titin	N2BA	N2B
Sarcomeric protein: troponin I	ssTnI	cTnI
Sarcomere units: H-zones and A-bands	Formed after prolonged differentiation	Formed
Sarcomere units: M-bands and T-tubules	Absent	Present
Distribution of gap junctions	Circumferential	Polarized to intercalated disks
Electrophysiology		
Resting membrane potential	Approx. –60 mV	–90 mV
Upstroke velocity	Approx. 50 V/s	Approx. 250 V/s
Amplitude	Small	Large
Spontaneous automaticity	Exhibited	Absent
Hyperpolarization-activated pacemaker (I_f)	Present	Absent
Sodium (I_{Na})	Low	High
Inward rectifier potassium (I_{K1})	Low or absent	High
Transient outward potassium current (I_{to})	Inactivated	Activated
ATP-sensitive K^+ current ($I_{K,ATP}$)	Not reported	Present
Conduction velocity	Slower (~0.1 m/s)	Faster (0.3–1.0 m/s)
Calcium Handling		
Ca^{2+} transient	Inefficient	Efficient
Amplitudes of Ca^{2+} transient	Small and decrease with pacing	Increase with pacing
Excitation-contraction coupling	Slow	Fast
Contractile force	~nN range/cell	~μN range/cell
Ca^{2+}-handling proteins: CASQ2, RyR2, PLN	Low or absent	Normal
Force-frequency relationship	Positive	Negative
Mitochondrial Bioenergetics		
Mitochondrial number	Low	High
Mitochondrial volume	Low	High
Mitochondrial structure	Irregular distribution, perinuclear	Regular distribution, aligned
Mitochondrial proteins: DRP1 and OPA1	Low	High
Metabolic substrate	Glycolysis (glucose)	Oxidative (fatty acid)
Adrenergic Signaling		
Responses to β-adrenergic stimulation	Lack of inotropic reaction	Inotropic reaction
Cardiac α-adrenergic receptor ADRA1A	Absent	Present

ATP, Adenosine triphosphate; *m/s,* meters per second; *nN,* nanonewtons; *μN,* micronewtons; *pF,* picofarads; *V/s,* volts per second.

From Sayed N, Liu C, Wu J. Translation of human-induced pluripotent stem cells: from clinical trial in a dish to precision medicine. J Am Coll Cardiol 2016;67:2161.

Tissue Engineering

The original concept of issue engineering was to provide living tissue grafts that could be used surgically to repair or replace dead or congenitally defective myocardium. Constructs of heart muscle can be generated using cell populations seeded within a matrix scaffold to form three-dimensionally engineered cardiac tissue. It has been challenging to generate tissue in vitro with sufficient contractile force and size to support the failing heart.[16] Various culture conditions have been used in combination with multiple cell mixtures (e.g., neonatal cardiomyocytes, fibroblasts, skeletal myoblasts, adult stem cells, in vitro differentiated cardiomyocytes) for creating a range of patches, strips, loops, and chambers of beating myocardial tissue in vitro. hESCs and iPSCs are potential sources for the generation of heart tissue in vitro. Although the survival of human engineered heart tissue implanted in the rat has been demonstrated, the maturation of specific tissue phenotype presents an important challenge, and the long-term engraftment followed by a meaningful functional improvement in the human heart remains an ambitious goal.[17] In addition, the size of typical avascular engineered heart tissue constructs is limited by oxygen diffusion. Accordingly, researchers have fused several individually cultured, single engineered tissue rings or sheets, and various strategies are under development to create vascularized constructs that can be perfused and integrated with the host circulation.

At the interface between tissue engineering and cell therapy, the development of novel biomaterials has seen increasing interest. Biodegradable matrix materials with sophisticated chemical and mechanical properties have been developed to be used as ventricular restraints and to provide scaffolds for in vitro tissue engineering.[18] In addition, the injection of new self-assembling nanomaterials and decellularized natural tissue matrix can modify the intramyocardial cellular microenvironments to augment functional integration of cells for in situ tissue engineering and subsequent cardiac regeneration.

In Vitro Differentiated Cardiomyocytes as Therapy

A number of barriers must be overcome before hPSC-derived cardiomyocytes or other cell types can be used successfully for regenerative therapy in human patients[19] (**Fig. 30.2**). Perhaps the greatest challenge is poor cell engraftment and survival in the heart after transplantation. Existing data suggest that only a small percentage of transplanted cells persist in the heart, limiting their contribution to myocardial regeneration. A related issue is the lack of standards for the tracking of cell fate after transplantation of cells. Labeling of cells before transplantation to allow tracking with imaging techniques after delivery into the body is critical not only for determining whether cells are engrafting in the heart, but also as a means to quantify which strategies to increase engraftment and regeneration (e.g., various routes of delivery into the heart, tissue engineering approaches, use of adjuvants to promote transplanted cell survival) are the most successful, rather than relying on relatively imprecise metrics such as ejection fraction.

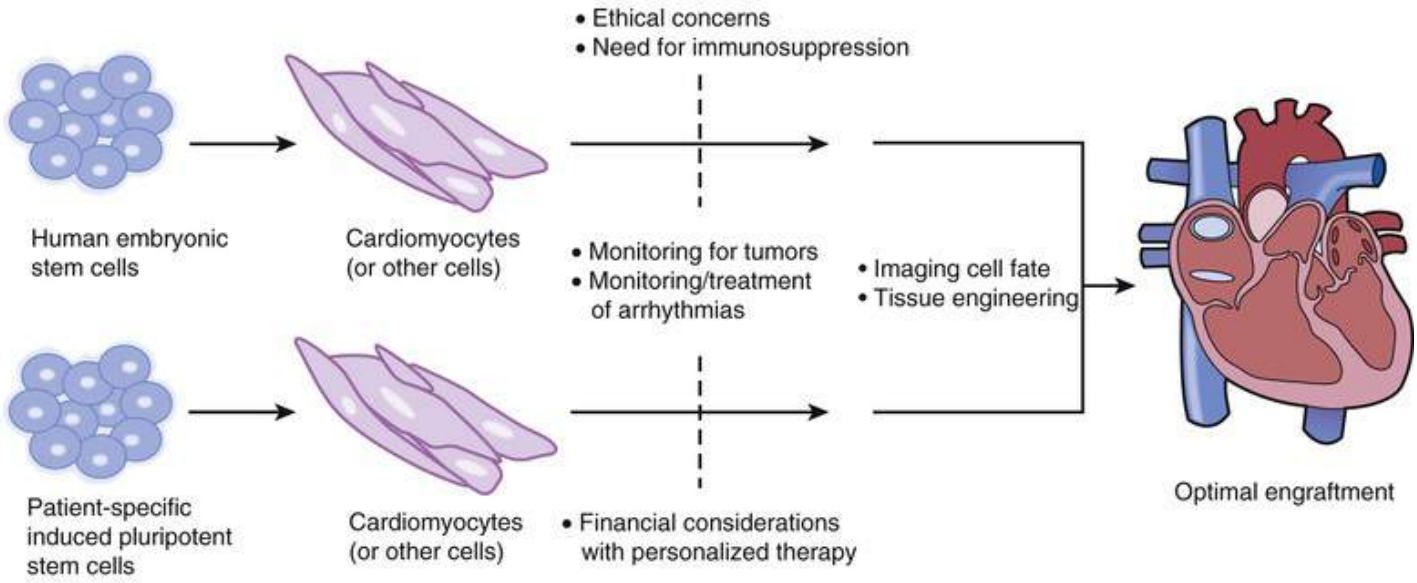

FIGURE 30.2 Obstacles to overcome and possible solutions in the use of human pluripotent stem cells for cardiac regenerative therapy.

As with any transplantation-based therapy, immunogenicity is a substantial concern. If the same standard-issue hPSC-derived cardiomyocytes or other cells are to be used in all patients (i.e., allogeneic therapy), patients will presumably need lifelong immunosuppression to tolerate the engrafted cells, with all the attendant risks. Simply speaking, the use of patient-specific iPSC-derived cardiomyocytes (i.e., autologous therapy) would avoid the risk of rejection. Good manufacturing practice (GMP) conditions would require generating iPSCs from a patient, performing the extensive quality control protocols needed, expanding the cells to large numbers, and differentiating the cells into cardiomyocytes to treat individual patients, an unrealistic prospect given the high costs involved using current technology. Possible solutions include the banking of several hundred prevalidated iPSC lines that are HLA antigen–matched to the majority of the population,[20] which could then be used on demand, or the use of genome-editing technology to engineer universal-donor hPSCs that could be tolerated by all patients.[21]

Other concerns include tumorigenicity and arrhythmogenicity. Tumorigenicity is a particular issue with hPSC-derived cardiomyocytes, because any hPSCs remaining after differentiation have the potential to form teratomas.[22] Although cardiomyocyte differentiation protocols have advanced tremendously in recent years (see earlier), special consideration will need to be given to the prevention of and monitoring for tumor formation in patients receiving hPSC-based therapies. Arrhythmogenicity is a concern for any cell type used for cardiac regenerative therapy. The failure of engrafted cells to integrate seamlessly into the myocardium could create foci for life-threatening ventricular arrhythmias, a risk that will require careful monitoring of patients after transplantation and perhaps even routine prophylactic placement of implantable cardioverter-defibrillators (ICDs).

Some of these concerns are highlighted by the preclinical studies of in vitro differentiated cardiomyocyte transplantation that have been performed to date. A succession of animal studies over many years culminated in the demonstration that hESC-derived cardiomyocytes or monkey iPSC-derived cardiomyocytes could develop extensive grafts in monkey hearts when they were administered after myocardial infarction.[23,24] At least half a billion transplanted cells per animal were needed to achieve these results, and frequent ventricular arrhythmias were observed in the recipients after transplantation. Although findings from these studies raised potential concerns about the clinical use of hPSC-derived cardiomyocytes, a phase 1/2 clinical study reported no adverse arrhythmias after transplantation of hESC-

derived cardiac progenitor cells embedded in a fibrin patch that was sutured directly onto the epicardium.[25] The results of these preclinical and early clinical studies to date indicate that cardiac regenerative therapy may be viable in human patients in the future, but much more work is needed to make this prospect a reality.

Directed Reprogramming

In principle, the process of generating autologous cells for regenerative therapy could be greatly accelerated if adult cells could be directly reprogrammed into expandable, multipotent cardiovascular progenitor cells in vitro. This would reduce the time and cost required to generate patient-specific iPSC lines and to differentiate them into cardiac lineages. Recent studies have established the feasibility of directed reprogramming of mouse fibroblasts into cardiovascular progenitor cells capable of differentiating into cardiomyocytes, smooth muscle cells, and endothelial cells, suggesting that the same will be possible with human fibroblasts.[26,27]

The concept of directed reprogramming of host fibroblasts in vivo has been demonstrated experimentally.[28,29] The expression of the transcription factors Gata4, Mef2c, and Tbx5 in cardiac fibroblasts resulted in conversion of some of the cells into cardiomyocyte-like cells. This raises an interesting new strategy of stimulating cardiac regeneration by inducing the differentiation of endogenous cardiac fibroblasts into cardiomyocytes in a diseased heart. If ultimately proven to be efficient enough to improve function substantially in the diseased heart in various preclinical models, directed reprogramming would be a viable therapeutic approach that avoids most of the difficulties in introducing exogenously produced cells into the myocardium for regeneration. However, difficulties associated with delivery vectors to the heart, specificity of transfecting only fibroblasts, and host immune response against foreign vector/gene products could make this a daunting prospect.

Disease Modeling

Whereas the basis of regeneration is to repopulate damaged areas within the heart with new cells, the basis of disease modeling is to understand the molecular mechanisms resulting in diseased cardiomyocytes in order to prevent heart disease or repair the compromised cells in the heart. Although important insights into disease pathogenesis can be obtained from model organisms, the physiology of the human heart is sufficiently different from that of other model species such that human-based models, if feasible, would be much more informative. hPSCs provide a platform with which to model the effects of patient-specific mutations as well as the effects of medications and other environmental exposures on the myocardium.

Induced PSCs with Patient-Specific Genotypes

The ability to reprogram somatic cells from living people into pluripotent stem cells provides a renewable source of differentiated cells, including cardiomyocytes, which can be genetically matched to individual patients. This makes iPSCs particularly useful for studying monogenic disorders in which single mutations have large phenotypic effects. Even when studying complex disorders that involve the contributions of multiple genes and environmental factors, iPSCs are advantageous because the reprogramming process largely resets any epigenetic changes resulting from environmental exposures during a person's lifetime, thus isolating and clarifying the genetic factors contributing to disease.

Potential disadvantages of iPSCs include the time and expense entailed in generating new lines—several months and thousands of U.S. dollars for each line—and the variability that can result from the reprogramming process, with iPSC lines generated even from the same person potentially showing distinct gene expression profiles. It appears that these issues can be at least partly addressed with automation techniques that allow for higher-throughput, more consistent production of iPSCs.[30] Another consideration is the choice of control iPSC lines against which to compare patient-specific iPSC lines. Confounding factors may result from differences in genetic background (particularly if the iPSC lines are not matched for sex and ethnicity), epigenetic background, the capacity for differentiation into the desired cell type for study, the type of somatic cell used to generate the iPSCs, the means of expressing the reprogramming factors in the source cells, and the passage numbers and adaptation of the iPSCs to a laboratory's cell culture conditions. These sources of confounding can be somewhat mitigated but not entirely eliminated by (1) choosing unaffected first-degree relatives of the affected individuals as the donors for control iPSC lines, with approximately 50% shared genetic background, and (2) using iPSC lines from a sizable number of patients with the disease of interest and iPSC lines from a similar number of control individuals, which sharpens the signal-to-noise ratio with respect to the phenotypic differences that are genuinely related to the disease.

Genome Editing of Human PSCs

Specific disease-associated mutations may be desirable to study, but they are sufficiently rare or unique that it is not possible locally to recruit individuals with the relevant mutations to generate iPSCs. Newly developed genome-editing tools permit the introduction of the mutations or other types of DNA alterations into hPSCs[31] (**Fig. 30.3**). They also permit the correction of pathogenic mutations in patient-derived iPSCs, which may be useful for therapeutic purposes.

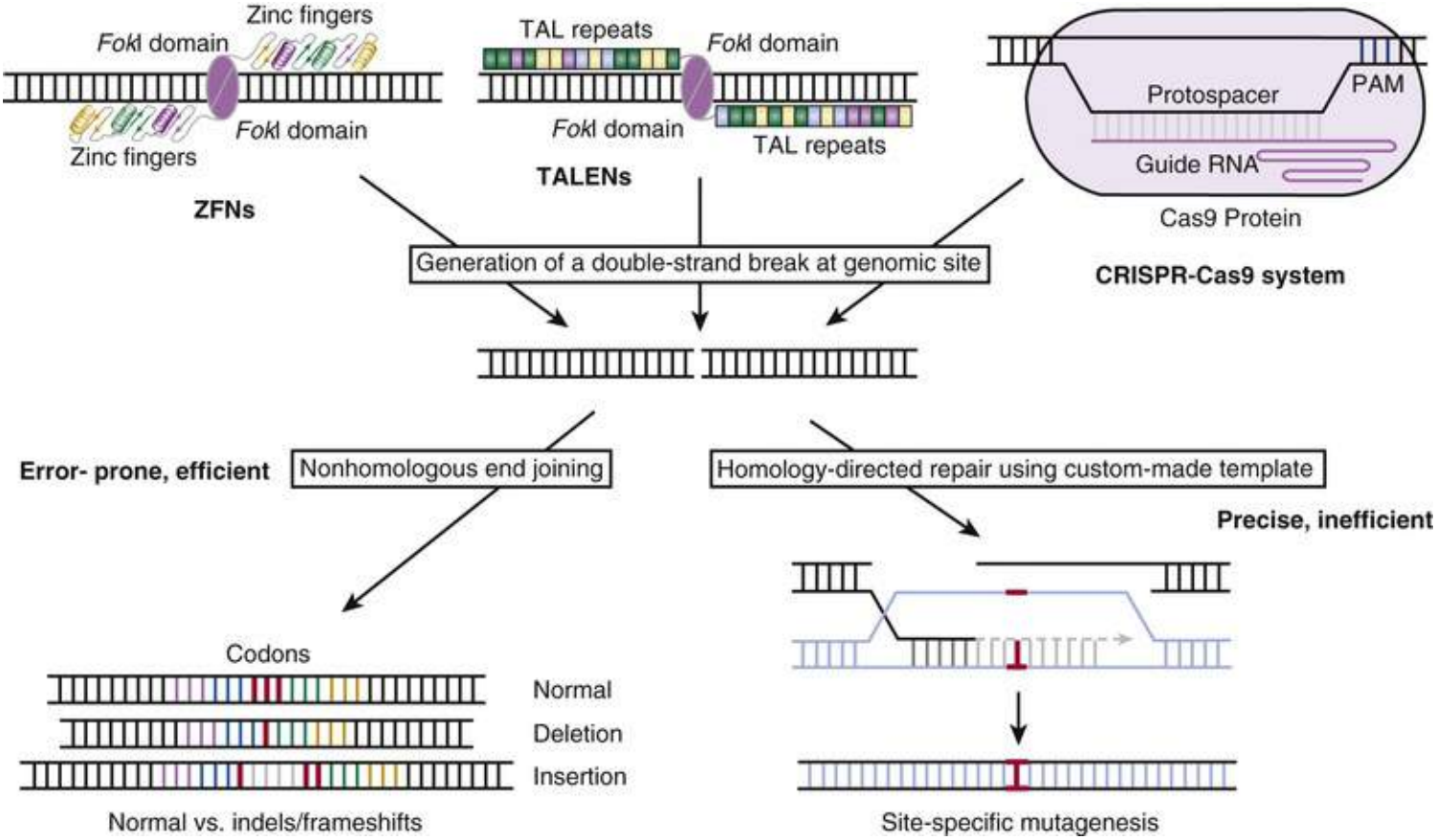

FIGURE 30.3 Genome editing with zinc-finger nucleases (*ZFNs*), transcription activator-like (*TAL*) effector nucleases (*TALENs*), and clustered, regularly interspaced, short palindromic repeats (*CRISPR*)–CRISPR-associated 9 (*Cas9*) by nonhomologous end-joining (NHEJ) or homology-directed repair (HDR). ZFNs use DNA-binding domains, called *zinc fingers,* that recognize three base pairs each, as well as *Fok*I nuclease domains (two are needed in combination to make double-strand breaks). TALENs use DNA-binding domains, called *TAL repeats,* that recognize one base pair each, as well as *Fok*I nuclease domains. CRISPR-Cas9 uses hybridization of part of the sequence of the guide RNA with one strand of DNA (protospacer) along with Cas9 protein recognition of a protospacer-adjacent motif (*PAM*) in the DNA sequence.

The most commonly used genome-editing tools are zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and clustered, regularly interspaced, short palindromic repeats (CRISPR)-CRISPR-associated 9 (Cas9).[32] Each represents a type of engineered nuclease that can be customized to recognize, bind, and cleave a specific sequence in the genome. Whereas ZFNs and TALENs are entirely protein based, CRISPR-Cas9 has both protein and RNA components. ZFNs and TALENs are modular proteins comprising an array of domains, each recognizing specific nucleotides, and a nuclease domain; for each new DNA sequence to be targeted, new proteins must be assembled from scratch. By contrast, for CRISPR-Cas9, the RNA component confers specificity for the target sequence. Approximately the first 20 nucleotides of the "guide RNA" direct the Cas9 nuclease protein to the target sequence through RNA-DNA hybridization of the sequence. For all three tools, the common consequence is the introduction of a double-strand break (DSB) at the site of the target sequence.

Cells have two major mechanisms for the repair of DSBs: nonhomologous end-joining (NHEJ) and homology-directed repair (HDR). NHEJ operates in all cells during all phases of the cell cycle, repairing the DSB in an error-prone manner that potentially introduces insertions or deletions (*indels*) at the break site. HDR uses a repair template, typically a sister chromatid, to accurately fix the DSB. HDR is typically active only in proliferating cells, during the S and G2 phases of the cell cycle. Whereas NHEJ can be used efficiently to knock out genes in cells through the introduction of frameshift mutations in coding sequences, HDR can be exploited to make specific alterations (e.g., introduction or correction of

mutations) if a researcher introduces into the cells a custom-made repair template that matches the break site but also contains the desired alteration.

ZFNs, TALENs, and CRISPR-Cas9 have all been demonstrated to be effective in hPSCs, although the efficiency varies widely depending on the tool used and the genomic locus to be targeted. Besides its ease of use, CRISPR-Cas9 is advantageous in that it generally works more efficiently in hPSCs than ZFNs and TALENs, and therefore it has become the tool of choice for most projects involving hPSCs.

With respect to disease modeling, genome-edited hPSC lines avoid some of the potential disadvantages of patient-specific iPSC lines. It is often quicker and cheaper to use genome editing to introduce mutations into preexisting hPSC lines than to generate new iPSC lines. Genome editing of an hPSC line results in well-matched control and mutant cell lines with a shared origin, genetic background, and epigenetic background, thus eliminating many possible confounders. Nonetheless, in cases when it is important that cell lines be perfectly genetically matched to patients, iPSCs generated directly from those patients will be preferred.

Modeling of Cardiovascular Genetic Disorders with Human PSCs

A variety of cardiovascular diseases have been modeled with hPSCs, including electrophysiologic disorders, familial cardiomyopathies, valvular and vascular disorders, and metabolic disorders[33] (**Table 30.2**). Some of the earliest diseases to be modeled with iPSCs were long-QT syndromes (LQTSs), monogenic disorders in which mutations in ion channel genes result in delayed repolarization of the heart, thereby placing patients at risk for fatal ventricular arrhythmias.[34,35] The three most commonly involved genes are potassium voltage-gated channel subfamily Q member 1 (*KCNQ1*) and subfamily H member 2 (*KCNQ2*) and sodium voltage-gated channel alpha subunit (*SCNA5*). Patient-specific iPSC-derived cardiomyocytes with mutations in any of these three genes have been reported to have increased action potential durations, abnormal ion currents depending on the affected channels, and in some cases, increased arrhythmogenicity. Similar findings have been reported in iPSC-derived cardiomyocytes from patients with other rare genetic rhythm disorders.

TABLE 30.2

Diseases Modeled with Human Induced Pluripotent Stem Cells or Human Embryonic Stem Cells

DISEASE MODELED	MUTATED GENE
Long-QT syndrome type 1	*KCNQ1*
Long-QT syndrome type 2	*KCNH2*
Long-QT syndrome type 3	*SCN5A*
Jervell and Lange-Nielsen syndrome	*KCNQ1*
Timothy syndrome	*CACNA1C*
Brugada syndrome	*SCN5A*
Catecholaminergic polymorphic ventricular tachycardia type 1	*RYR2*
Catecholaminergic polymorphic ventricular tachycardia type 2	*CASQ2*
Hypertrophic cardiomyopathy	*MYH7, MYBPC3*
Dilated cardiomyopathy	*TNNT2, RBM20, LMNA, DES, PLN, TTN*
Left ventricular noncompaction	*TBX20*
Arrhythmogenic right ventricular dysplasia	*PKP2*
Duchenne muscular dystrophy	*DMD*
Friedreich's ataxia	*FXN*
LEOPARD syndrome	*PTPN11*
Barth syndrome	*TAZ*
Pompe disease	*GAA*
Danon disease	*LAMP2*
Dyslipidemia	*SORT1, ABCA1*
Hypoinsulinemic hypoglycemia and hemihypertrophy	*AKT2*
Lipodystrophy	*PLN1*
Maturity-onset diabetes of the young type 2	*GCK*
Mitochondrial aldehyde dehydrogenase 2 deficiency	*ALDH2*
Hutchinson-Gilford progeria syndrome	*LMNA*
Williams-Beuren syndrome	*ELN* and others
Calcific aortic valve	*NOTCH1*

From Matsa E, Ahrens JH, Wu JC. Human induced pluripotent stem cells as a platform for personalized and precision cardiovascular medicine. Physiol Rev 2016;96:1093.

Patient-specific iPSCs have been particularly informative in modeling familial cardiomyopathies, including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and left ventricular noncompaction (LVNC). The most common mutant gene linked to familial HCM is myosin, heavy chain 7 (*MYH7*), with mutations in a number of other genes encoding sarcomere components also linked to HCM. In one study of an HCM-linked *MYH7* missense mutation, iPSC lines were generated from 10 affected and unaffected members of a single family.[36] iPSC-derived cardiomyocytes with the mutation showed cellular enlargement, contractile arrhythmia, and abnormal calcium handling at the single-cell level. In a separate study, iPSC-derived cardiomyocytes with a different *MYH7* mutation displayed similar defects.[37] In both studies the defects could be reversed by treatment with the calcium channel blocker verapamil. A large proportion of familial DCM cases are also linked to mutations in genes encoding sarcomere components, such as troponin T, cardiac muscle (*TNNT2*). In studies of a DCM-linked *TNNT2* missense mutation, iPSC lines were generated from several affected and unaffected family members.[38,39] iPSC-derived cardiomyocytes with the mutation showed myofibrillar disarray, reduced contractility, and abnormal calcium handling, which were accentuated with β-adrenergic stimulation. The DCM cells also had increased expression of the phosphodiesterase 2A and 3A genes (*PDE2A* and *PDE3A*) via epigenetic activation connected to the mutant troponin protein, resulting in blunted β-adrenergic signaling. In a study of an LVNC-linked T-box protein 20 (*TBX20*) nonsense mutation, iPSC-derived cardiomyocytes from affected family members compared to those from unaffected family members showed a proliferation defect and abnormal activation of TGF-β signaling, a finding that was reproduced in genetically modified mice.[40]

Genome editing of hPSCs has been useful in introducing or correcting mutations linked to disorders such as familial DCM, Barth syndrome, aortic valve disease, maturity-onset diabetes of the young (MODY), hypoinsulinemic hypoglycemia and hemihypertrophy (HIHGHH), dyslipidemia, and LQTS.

Various lines of evidence—including the discovery of an epidemiologic association between truncating mutations in the titin gene (*TTN*) and familial DCM, the insertion of *TTN* truncating mutations into normal iPSCs followed by differentiation of matched wild-type and mutant iPSCs into cardiomyocytes, and the recognition that mutant cells had sarcomere insufficiency, impaired responses to mechanical and β-adrenergic stress, and attenuated growth factor and cell-signaling activation—now unequivocally demonstrate that *TTN* truncating mutations can be both causal and sufficient for DCM.[41] Similarly, a primary causal relationship between *TAZ* mutations and the dilated-type cardiomyopathy observed in Barth syndrome has been established by evidence showing that the introduction of frameshift mutations into the tafazzin gene (*TAZ*) in wild-type iPSCs reproduced the mitochondrial defects, excess levels of reactive oxygen species, abnormal sarcomere assembly, and impaired contractility observed in iPSC-derived cardiomyocytes from patients with Barth syndrome.[42] Notably, in both the *TTN* and *TAZ* studies, the phenotyping was most informative when performed with engineered myocardial structures where more complex physiologic characteristics could be observed than in single cardiomyocytes.

Mutations in *NOTCH1* have been linked to an inherited form of bicuspid aortic valve with severe calcification of the valve. iPSCs from patients with *NOTCH1* mutations were subjected to genome editing to correct the mutations, followed by differentiation of the matched patient-specific and corrected iPSCs into endothelial cells.[43] When subjected to the in vitro equivalent of vascular shear stress, the mutant endothelial cells did not activate the antiosteogenic, anti-inflammatory, and antioxidant pathways that were observed in corrected endothelial cells, establishing that *NOTCH1* mutations can be both causal and necessary for valvular calcification.

Modeling of Cardiotoxicity with Human PSCs

An important goal during the process of drug development is to assess whether drug candidates have toxic effects that would prevent their clinical use.[33] Cardiotoxicity is a particular concern. Increased risk of ventricular arrhythmia has been involved in 28% of drug withdrawals from the U.S. market, showing that drug candidates that were apparently safe in preclinical models could prove to be unsafe when used by patients. This is clear evidence that standard preclinical models do not faithfully recapitulate some important aspects of human physiology, including cardiac electrophysiology.

Standard preclinical models used to test drug candidates for cardiotoxicity include Chinese hamster ovary (CHO) cells and human embryonic kidney (HEK) cells overexpressing the hERG channel, which is often implicated in drug-induced QT prolongation and ventricular arrhythmias. These cell lines are convenient to use for high-throughput drug screening, but they lack important characteristics of cardiomyocytes, including expression of cardiac ion channels (e.g., the hERG channel is heterologously expressed in the cells). Because of this lack of fidelity, the cell lines can yield incorrect assessments of drug toxicity. For example, verapamil has effects on both potassium channels and calcium channels, which together cancels their opposing effects on QT prolongation and render the drug nonarrhythmogenic. However, when tested in cell lines in which only the hERG potassium channel is expressed, verapamil is incorrectly interpreted as having toxic QT-prolonging activity, creating a false-positive result that could eliminate a safe and potentially valuable drug candidate. Conversely, alfuzosin is a QT-prolonging drug acting on sodium channels rather than hERG, and thus is incorrectly interpreted as nontoxic in hERG-overexpressing cell lines (i.e., false-negative result that “passes” an unsafe and potentially harmful drug candidate). Preclinical animal models also have shortcomings because of their differences in cardiac physiology with humans. For example, the mouse heart beats nine times more quickly than the human heart and has briefer action potentials. Moreover, the hERG channel does not play a major role in

repolarization in mouse cardiomyocytes, and expression of genes involved in sarcomere function and calcium handling differs significantly. Larger animals are more similar to humans with respect to cardiac physiology but can still differ substantially from humans in their drug responses.

hPSC-derived cardiomyocytes have several practical advantages as preclinical models for drug testing. Despite their immaturity compared to adult human cardiomyocytes, they appear to recapitulate drug responses faithfully; for example, they correctly determined verapamil to be nontoxic and alfuzosin to be toxic with respect to QT prolongation.[44] hPSC-derived cardiomyocytes have been used to test the toxicity of a liposomal formulation of doxorubicin, a chemotherapeutic agent known to cause cardiomyopathy in some patients. The finding that there was limited delivery of the drug into the cardiomyocytes and, as a result, no signs of toxicity, contributed to the decision to take the formulation forward into phase I clinical trials.[45] hPSC-derived cardiomyocytes can be produced in large quantities in formats amenable to high-throughput screening. In one study, they were used in a 384-well format to screen 131 different drugs at six concentrations.[46]

Cardiomyocytes can be obtained using patient-specific iPSCs, which potentially offer the ability to predict whether drugs will be toxic or nontoxic when administered to the patients from whom the iPSCs were obtained. For example, iPSCs were generated from breast cancer patients who either developed or did not develop cardiomyopathy on receiving doxorubicin.[47] When treated with doxorubicin, iPSC-derived cardiomyocytes from the cardiomyopathy patients had reduced viability, impaired mitochondrial and metabolic function, impaired calcium handling, decreased antioxidant pathway activity, and increased reactive oxygen species production compared to cardiomyocytes from the noncardiomyopathy patients. Thus, it may be feasible to use iPSCs prospectively to determine which patients are more or less likely to develop doxorubicin-induced cardiomyopathy and tailor their chemotherapeutic regimens appropriately. Similarly, iPSC-derived cardiomyocytes from more than 10 individuals have been used to screen more than 20 U.S. Food and Drug Administration (FDA)-approved *tyrosine kinase inhibitors* (TKIs) used to treat various types of cancer. The data generated allowed the researchers to generate a “cardiac safety index” to assess the cardiotoxicity of existing TKIs.[48] Furthermore, transcriptional profiling of iPSC-derived cardiomyocytes paired with bioinformatics analysis has been used to predict patient-specific drug-induced cardiotoxicity.[49] Also, iPSC-derived cardiomyocytes could potentially be used to assess a patient's risk of an adverse outcome from an environmental exposure other than a drug. For example, they have been used to provide an in vitro model for coxsackievirus B3–induced myocarditis.[50]

Cardiovascular Precision Medicine with Human PSCs

The U.S. National Institutes of Health (NIH) calls precision medicine “an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.” As avatars of people's genetic makeup, iPSCs could have an important role in the practice of precision medicine. As previously discussed, iPSCs offer an opportunity to test whether medications will produce pathology in a patient's cardiomyocytes or, conversely, whether they can repair cardiomyocytes that already are in a diseased state, without exposing the patient to risk. In principle, several alternative medications could be tested in vitro on iPSC-derived cardiomyocytes to help choose the optimal medication beforehand rather than testing each medication individually in the patient.

Early studies suggest that iPSCs may indeed be useful in matching the right treatments to the right patients. In one study, iPSC-derived cardiomyocytes from patients with HCM or LQTS were more vulnerable to the arrhythmogenic effects of cisapride, a drug previously withdrawn from the U.S. market when it was found to cause ventricular arrhythmias in patients with heart failure or preexisting QT

prolongation.[51] In another study, an LQTS patient with frequent ventricular arrhythmias was found to harbor possibly pathogenic mutations in two LQTS-associated genes, *KCNH2* and *SCN5A*; iPSC-derived cardiomyocytes from this patient clarified that the latter gene had the pathogenic mutation, because the cells had sodium channel but not potassium channel current defects.[52] The cells responded better to treatment with one sodium channel blocker, mexiletine, rather than a combination of two sodium channel blockers, mexiletine and flecainide, and the defects were also improved with increased pacing of the cells. Consistent with these findings, the patient's arrhythmias had been found by trial and error to be best controlled by using mexiletine alone and setting the patient's ICD to a high pacemaker rate. Although no examples have yet been reported, it is conceivable that a patient's iPSC-derived cardiomyocytes could be used to perform drug screening to identify a novel or tailored treatment for the patient's disease.

Besides being useful for determining the optimal treatments for patients, hPSCs could play an important role in predicting which individuals are at risk for certain diseases. Although much progress has been made in understanding the genetic basis of both monogenic and complex cardiovascular disorders (**see also Chapter 7**), risk prediction remains an enormous challenge. With clinical exome and genome sequencing now being performed in many patients, a related challenge is that of the "variant of uncertain significance." For example, a patient may be incidentally found to harbor a variant in a gene related to HCM (**Chapter 78**) or DCM (**Chapter 77**), raising the questions of whether the patient is genuinely at risk for cardiomyopathy, whether the patient should be prospectively managed as someone at risk of developing cardiomyopathy, and whether the patient should even be alerted to the finding of the variant. Complicating the issue, computational and population-based methods of discriminating among pathogenic and benign mutations have so far proved to be unreliable.

Human PSCs may be used in various ways to improve risk prediction for diseases such as the cardiomyopathies. For example, because they are genetically matched to patients, iPSC-derived cardiomyocytes could be phenotyped for characteristics that suggest the patients are susceptible for disease, including characteristics such as gene expression signatures, morphologic and functional properties, and pharmacologic responses. Another approach to addressing patient-specific variants of uncertain significance would employ genome editing in hPSCs to obtain functional readouts of the variants. For either strategy to be successful, extensive characterization and comparison of iPSC-derived cardiomyocytes from patients with diseases of interest versus healthy individuals would be needed to define criteria by which to properly classify pathologic versus normal cardiomyocytes—thus the need for large-scale disease-modeling efforts involving cohorts of iPSCs. Recent efforts by funding agencies to establish iPSC biobanks with hundreds of lines from patients with different disorders will be invaluable in this regard.

Future Perspectives and Prospects for Cardiac Repair

The goal of cardiac repair is to reverse the pathologic process in cardiomyocytes leading to heart disease. Currently, several therapeutic approaches have shown promising results in preclinical animal models, all of which must be validated before clinical use can commence (**Fig. 30.4**). The first is the use of traditional small-molecule therapeutics that modify protein activity in such a way as to mitigate the disease process. One example is the development of an inhibitor of myosin adenosine triphosphatase (ATPase) to reduce the contractility of cardiomyocytes, which was shown to halt and even partially reverse the progression of disease in a mouse model of HCM.[53] The second is gene therapy, which

introduces a therapeutic gene into cardiomyocytes via a viral vector based on either adenovirus or adeno-associated virus (AAV). One example is the delivery of sarcoendoplasmic reticulum calcium-ATPase (SERCA) 2a for the treatment of heart failure. This strategy has been tested with encouraging results in a variety of experimental models of heart failure,[54] although results from the recent CUPID 2 trial did not find evidence of improved patient outcomes.[55]

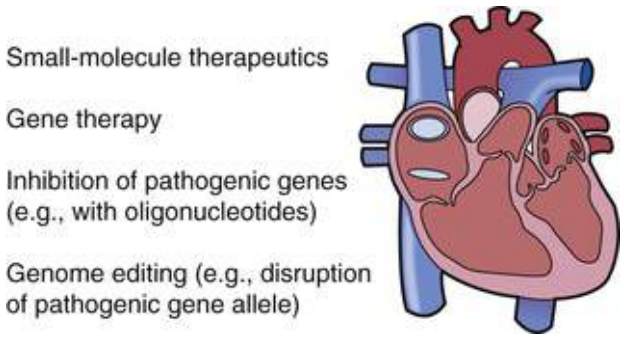

FIGURE 30.4 Possible therapeutic approaches to cardiac repair.

The third therapeutic approach is inhibition of a pathogenic gene in cardiomyocytes. One example is the use of RNA interference to specifically knock down the expression of the dominant mutant allele of *MYH6* responsible for disease in a mouse model of HCM; the therapy slowed the development of disease in mice.[56] The recent emergence of CRISPR-Cas9 genome editing offers a different approach to gene inhibition, creating permanent disruption or correction of the pathogenic gene allele. While gene disruption via NHEJ and gene correction via HDR have been demonstrated to occur at high efficiency in mouse liver in vivo,[57,58] which raises the possibility of addressing metabolic disorders such as dyslipidemia that contribute to cardiovascular diseases, it remains to be seen how efficiently genome editing will work in myocardium. Since HDR is typically only active in proliferating cells, gene repair may not be a viable option in the nonproliferative cardiomyocytes in the adult heart using current genome-editing techniques, although gene disruption by NHEJ may still be feasible.

The past few decades have witnessed extraordinary efforts to advance cardiovascular regeneration and repair. Progress toward the development of human clinical therapies has been slower than researchers and patients alike had hoped, but the next decade will surely see some important steps forward in this area.

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31

Management of Patients with Cardiovascular Disease Approaching End of Life

Larry A. Allen, Lynne Warner Stevenson

Thirty years ago, death in patients with cardiac disease often occurred unexpectedly and rarely followed a protracted period of refractory symptoms. Successful therapies have since rerouted the course of almost every cardiovascular disease (**Fig. 31.1**). Early coronary revascularization and secondary prevention have increased survival after acute myocardial infarction, with a parallel increase in the prevalence of

heart failure (**see Chapter 21**). Improved surgical techniques for congenital heart disease have created a growing population of adults with unique structural heart disease (**see Chapter 75**). Advances in cancer chemotherapy and radiation have left many survivors with new, life-threatening cardiac disease (**see Chapter 81**). Widespread use of neurohormonal blockade and implantable devices in patients with reduced left ventricular ejection fraction has contributed to a decrease in sudden death associated with prolongation of life and death with pump failure (**see Chapter 25**). The aging of the population yields an increasing number of patients with senile aortic stenosis and vascular pathology who may now be eligible for percutaneous procedures, but they remain limited by the multimorbidity and frailty that rendered them ineligible for open surgery in the first place[1] (**see Chapter 88**).

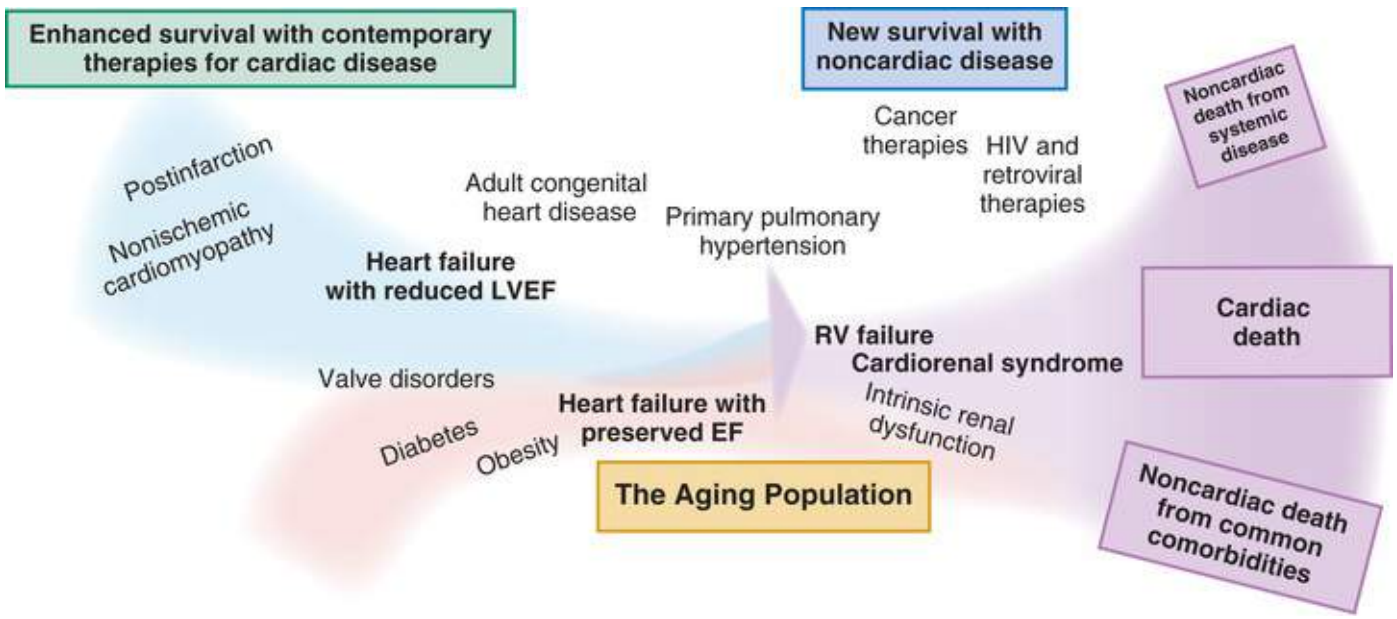


FIGURE 31.1 Complex contemporary pathways to death with cardiac disease. Patients with a history of myocardial infarction or dilated cardiomyopathy have extended survival with good quality of life, particularly because of decreases in ventricular remodeling and decreases in sudden death, as well as decreased reinfarction with coronary artery disease. With prolonged survival, right ventricular (RV) failure and the cardiorenal syndrome are more frequently seen in the late stages of heart failure not only with reduced left ventricular ejection fraction (LVEF), but also with preserved ejection fraction (EF) and in adult survivors with congenital heart disease. Successful therapy of cancer has created a population with cardiac disease resulting from chemotherapy and radiation, and long-term survival with human immunodeficiency virus (HIV) can be accompanied by cardiac disease due to infections and to retroviral therapies. Both heart failure and aortic stenosis are often diagnosed in the aging population, in whom the increased prevalence of diabetes and obesity also increase symptoms and death from noncardiac comorbidities.

Once prolongation of life no longer drives treatment, the focus of disease management shifts to palliation of symptoms. Unfortunately, in practice, this shift too often jolts patients and families as a sudden reversal of strategy from “do everything” to “do nothing,” rather than a gradual transition away from procedural intervention through a phase of care increasingly but not exclusively focused on quality of life. Guiding patients and families to understand prognosis and express goals of care is crucial for them to share in decisions about the intensity and timing of care. When a cardiac condition is likely to cause or accelerate death within the coming year, cardiac specialists may often have a good vantage point from which to survey the disease trajectory and steer the direction of care.[2] Ideally, patients continue to the end guided by health care providers who maintain longitudinal relationships with them and apply palliative care principles to smooth this journey. This chapter clarifies main concepts and provides practical approaches to the management of patients with cardiovascular disease nearing the end of life (**Table**

31.1).

TABLE 31.1

Key Messages for Managing Patients with Cardiovascular Disease Approaching End of Life

1. Worsening disease should trigger preparation with patients and families, but without specifically answering the question of how much time remains, which is usually bounded by wide uncertainty.
2. "What-if" conversations should be standard before any major intervention in the setting of advanced cardiac disease or other serious medical conditions, including frailty.
3. Difficult discussions now will simplify difficult decisions in the future.
4. Shared decisions include a broad spectrum of potential interventions beyond those relating to resuscitation preferences.
5. Deactivation of the defibrillation function of implantable cardioverter-defibrillators should be explained and offered regularly to patients with poor prognosis and must be done before transition to hospice.
6. Palliative care specialist consultation may be particularly helpful to facilitate decision making within challenging family dynamics and to improve relief of refractory symptoms.
7. Clinicians with existing relationships should shoulder the primary responsibility for presenting an end-of-life plan consistent with values and goals expressed by patient and family.
8. The transition separating "do everything" from hospice may be bridged through a phase of "quality survival" during which patients increasingly weigh the benefits, risks, and burdens of initiating or continuing life-sustaining treatments.
9. Revision of the medical regimen for symptom relief and quality of life may involve discontinuation of some recommended therapies and addition of therapies not usually recommended.
10. The end-of-life plan should honor patient preference for the site of death as feasible, with agreement on a "plan B" if that becomes unsupportable.

Integration of Palliative Care Into Cardiovascular Care

Palliative care is designed to improve quality of life for patients and their families through anticipation of declining health status and major events, clarification of goals of care, relief of physical symptoms, provision of psychosocial and spiritual support, coordination of care, and assistance with bereavement[3] (**Fig. 31.2**). Given the high prevalence, morbidity, and lethality of many cardiovascular (CV) diseases, they create a substantial need for palliative care at the end of life[4,5] (**eFig. 31.1**). However, many providers of cardiovascular care do not distinguish between palliative care and hospice or understand the indications for these services.[6] Palliative approaches to care should be integrated throughout the care of patients with CV disease, with intensification during major events and approaching the end of life[2] (**Fig. 31.3**).

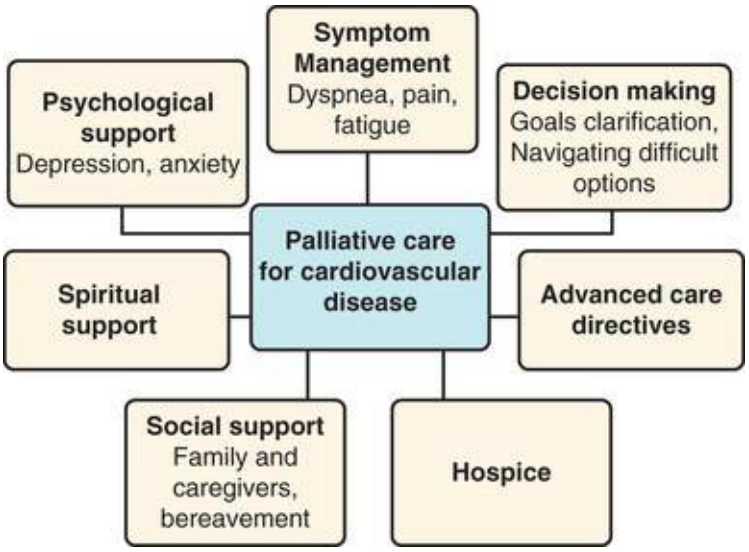


FIGURE 31.2 Components of palliative care for cardiovascular care.

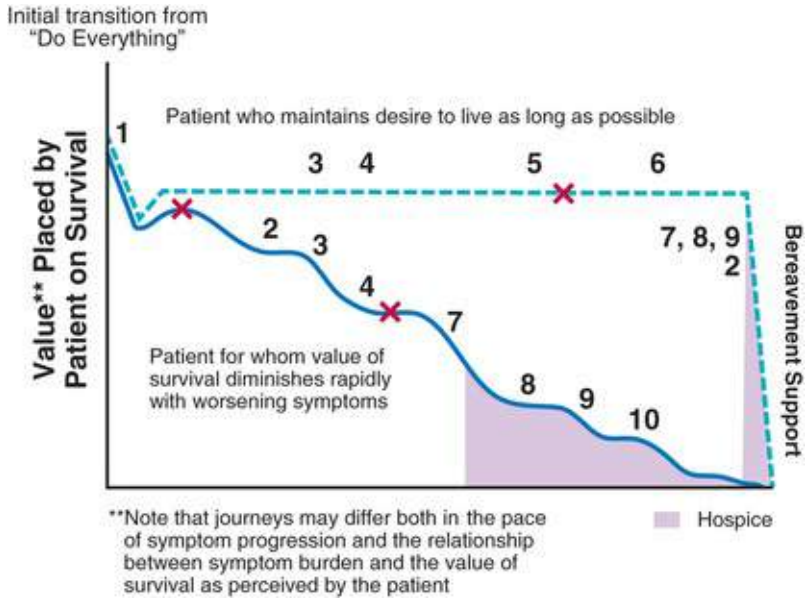
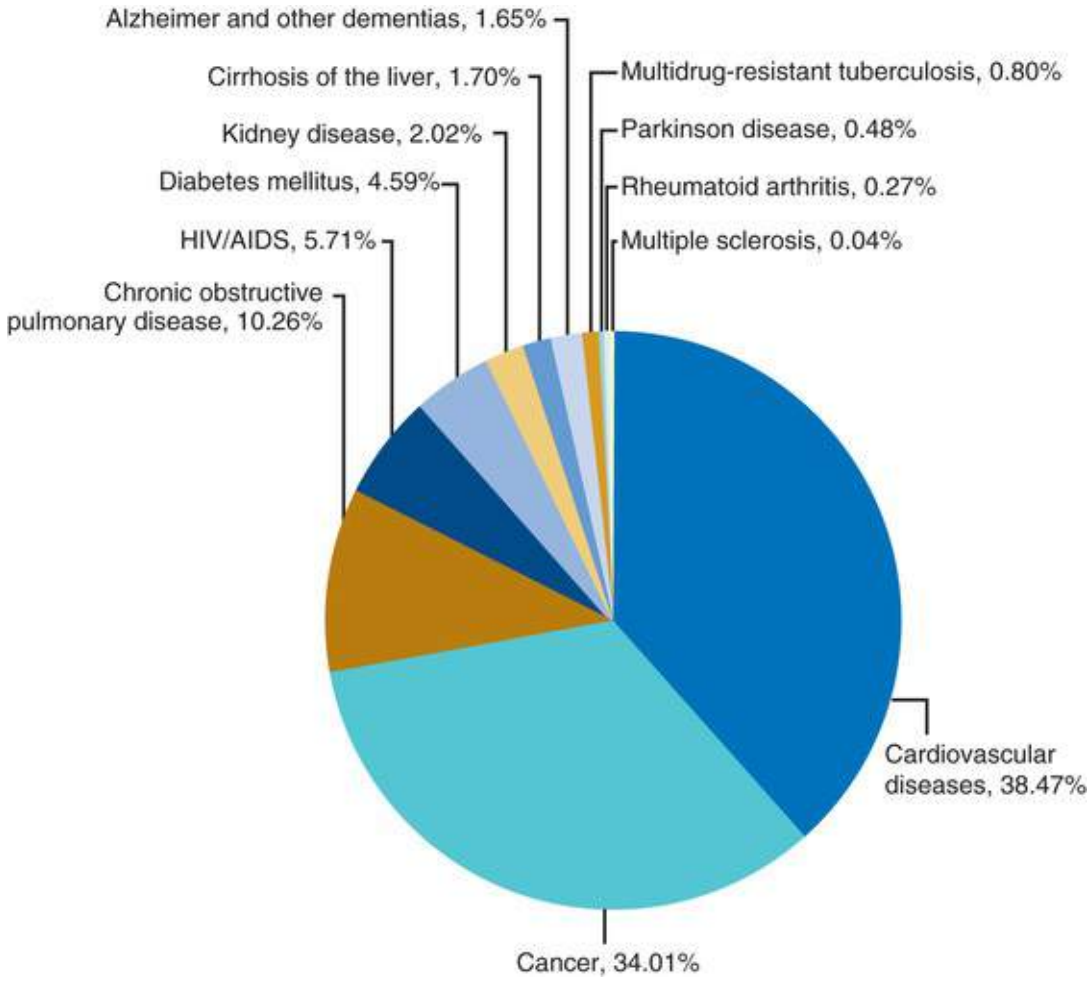


FIGURE 31.3 Examples of differing journeys through the phase of "quality survival" in patients nearing the end of life. *1,* Initial shift from "do everything" to limited intervention and prognosis. Examples of intervention: *2,* Inactivation of defibrillation function of implantable cardioverter-defibrillator. *3,* Screening colonoscopy canceled. *4,* Hospitalization for worsening heart failure symptoms. *5,* Transfusion for hypotension from gastrointestinal bleed (not appropriate for patient in hospice). *6,* Blood cultures to evaluate fever (not appropriate for patient in hospice). *7,* Palliative care nearing end of life can include initiation of opiates for refractory dyspnea whether or not patient is in hospice. *8,* Discontinuation of angiotensin-converting enzyme inhibitors and beta blockers for fatigue with systolic blood pressure less than 80 mm Hg. *9,* Discontinue blood tests. *10,* Benzodiazepines for anxiety. *x,* Possibility of death occurring during sleep or precipitous clinical decline at any point in this phase without time for hospice.



EFIGURE 31.1 Distribution of adults in need of palliative care at the end of life by disease, with cardiovascular diseases constituting the greatest need. (From http://www.who.int/nmh/Global_Atlas_of_Palliative_Care.pdf. Copyright World Health Organization, 2014.)

Primary Palliative Care

All clinicians caring for patients with advanced CV disease play a role to provide supportive and palliative interventions. This role is vital because (1) many of the therapies that improve symptoms and quality of life derive from treatment of the underlying CV disease; (2) prognosis and complex decisions are often best understood by the cardiovascular specialist; (3) integrated care is often preferable to further fragmentation through another consult team; and (4) there are not enough palliative care specialists to provide such services to everyone in need. Provision of supportive care by the usual care team has been designated as *primary* palliative care, to distinguish it from *secondary* or *subspecialty* palliative care.[5] Clinicians supervising inpatient or longitudinal care for patients with CV disease should regard expertise in providing palliative care as integral to their professional competence.

Secondary (Subspecialty) Palliative Care

Palliative care clinicians receive specific training in management of refractory symptoms and facilitation of difficult care planning in life-threatening illnesses. Hospice and Palliative Medicine is a recognized medical subspecialty in the United States,[7] Canada, England, Ireland, Australia, and New Zealand. Master's degree programs have been developed for physicians, nurse practitioners, physician assistants, and nurses who are interested in becoming community palliative care specialists, and specialty certifications are also available for nurses, social workers, and chaplains. In most jurisdictions, specialty

palliative care is provided by an interdisciplinary team who work with a patient's other clinicians to provide an “extra layer” of support.[8]

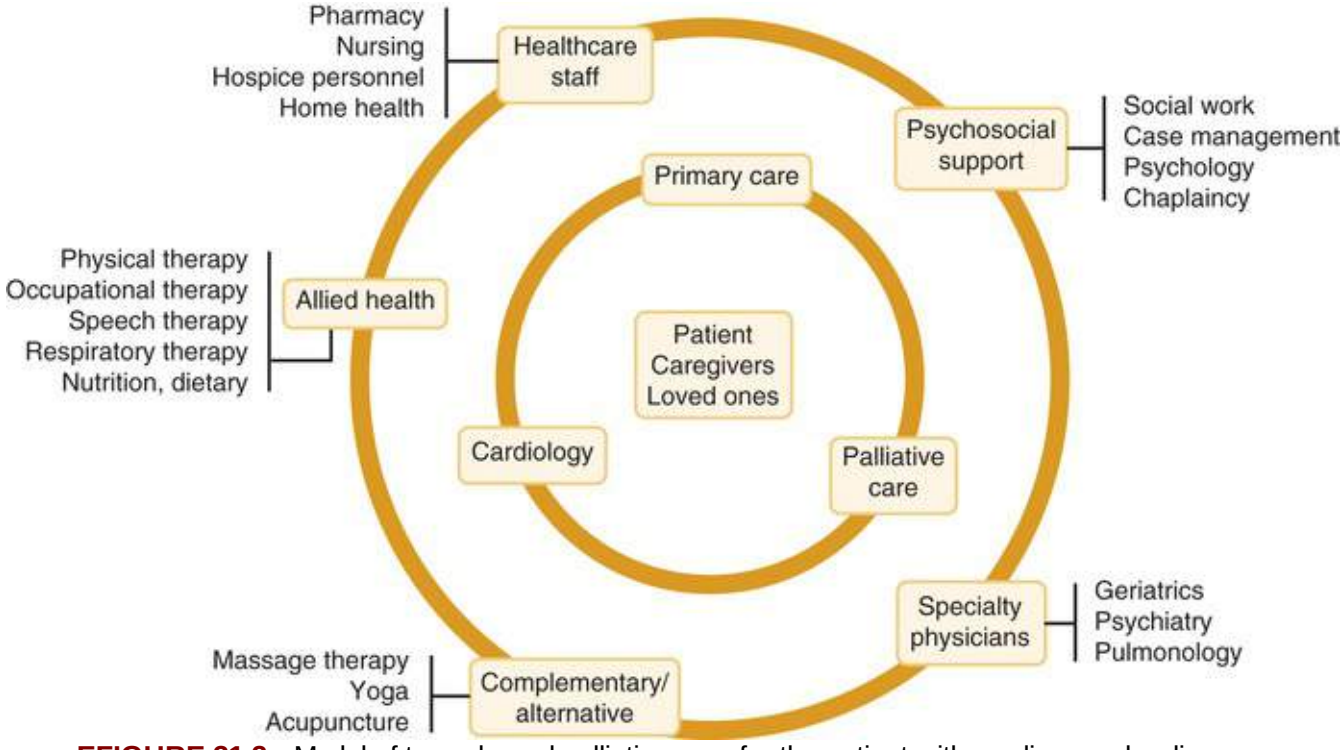
Hospice

The term *hospice* is used to describe a specific model of palliative care offered to patients who are at the end of life with a terminal disease when curative or life-prolonging therapy is no longer a focus of treatment. Historically, hospice was developed for patients with cancer, but it is increasingly used for patients with CV disease, with 14.7% of admissions to U.S. hospices in 2014 having a primary diagnosis of heart disease.[9] Referral is guided by the U.S. Centers for Medicare and Medicaid Services (CMS) hospice eligibility guidelines, which require that a physician estimate that life expectancy is 6 months or less.[10] The 6-month period is rarely reached, but patients who survive longer can usually continue to receive hospice benefits if the prognosis remains poor.

Palliative Care Consultation

Indications

Various specialties may assume the central role in coordination of patient care at different stages of disease progression, often with transition of leadership from primary care to cardiology to palliative care[11] (**eFig. 31.2**). Shared ownership and planning around palliative care needs can improve communication and understanding of patient goals and achieve better end-of-life experiences. Formal consultation may be particularly helpful when symptoms remain intolerable or when medical decision making is particularly challenging. For example, since 2013, national standards require centers that offer permanent mechanical circulatory support to include palliative care specialists as part of the team from evaluation through to death.[12] Similar mandates are anticipated for palliative consultation to review options and “what-ifs” for other major cardiac interventions with high mortality and morbidity.



EFIGURE 31.2 Model of team-based palliative care for the patient with cardiovascular disease.

Benefits

Data are mixed regarding effectiveness of specialty palliative care. Retrospective analysis of Medicaid patients in four New York hospitals from 2004 to 2007 indicated that palliative care consultation during hospitalization for exacerbation of chronic fatal illness, including heart failure, was associated with a $4000 lower cost for discharged patients and $7000 lower cost for patients dying during that hospitalization.[13] The Palliative Care in Heart Failure (PAL-HF), a single-center randomized trial of 150 patients with advanced heart failure, showed that randomization to a multidisciplinary palliative team intervention improved scores for quality of life and functional assessment of chronic illness therapy with palliative care (FACIT-Pal) at 6 months.[14] In a large randomized trial in intensive care settings, however, palliative care specialist supervision of at least two structured family meetings and written information did not decrease anxiety or depression and may have increased post-traumatic stress for families compared to similar intervention led by the intensive care unit teams.[15] To be effective, palliative care consultations need to be targeted to the right patients at the right time and integrated thoughtfully into the overall plan of medical care.

Having Difficult Conversations

High-quality communication is one of the most important interventions for patients with severe CV disease. When done well, such discussions can help to align therapy with patient goals, improve quality of life for both patients and caregivers, and enhance the quality of medical decisions and symptom palliation. End-of-life discussions are sensitive and time-consuming and may be further complicated by discordant priorities of patients and their families. Almost half of older Americans report they have not had any end-of-life planning discussion.[16] In 2016, CMS established specific reimbursement for two advance care planning sessions provided to Medicare beneficiaries by physicians or other practitioners,[17] which will diminish the financial disincentive to engage in these discussions. However, these discussions

are also avoided due to lack of training in palliative and communication techniques. In a multisite survey of 95 cardiology and primary care physicians, nurse practitioners, and physician assistants, almost one-third reported a low or very low level of confidence in initiating prognosis or end-of-life discussions, enrolling patients in hospice, or providing end-of-life care.[18]

Anticipating Disease Trajectory

The disease trajectory for individual patients is variable and characterized by considerable uncertainty. Guidelines recommend using validated scores to estimate mortality risk in cardiac disease.[19] Many cardiovascular risk models are well validated, available online, and increasingly used (e.g., http://www.heartfailurerisk.org, https://depts.washington.edu/shfm/, http://www.gracescore.org/website/WebVersion.aspx). These models may be useful to reduce unrealistic expectations and alert clinicians who have not recognized the need to discuss prognosis with a patient at high risk for adverse events, but cannot replace thoughtful review and recognition of uncertainty.

Timing of Discussions

It is clearly preferable to have these types of discussions prior to the need for urgent decisions. A routinely scheduled "annual review" has been proposed to help patients with significant disease understand their medical trajectory and potential future choices.[2] Then, clinical events and major decisions should trigger reevaluation of disease trajectory, goals, and treatment preferences (**Table 31.2**). These "milestones" include hospitalization for worsening CV disease, development of a new diagnosis such as cancer, or consideration of invasive procedures. Use of an algorithm during hospitalization to trigger palliative care consultation has increased the frequency of goals-of-care conversations.[20] However, it is important to reevaluate resuscitation decisions, because more than 20% of patients have been shown to change their preferences in the subsequent months.[21]

TABLE 31.2

Triggers for Formally Assessing Prognosis and Having Conversations about Goals of Care and Voluntary Advance Care Planning

Routine
"Annual Heart Failure Review" with a scheduled clinic visit
Event-Driven "Milestones" that Should Prompt Reassessment
Increased symptom burden and/or decreased quality of life
Significant decrease in functional capacity
Loss of activities of daily living
Falls
Transition in living situation (independent to assisted or long-term care)
Worsening heart failure prompting hospitalization, particularly if recurrent
Serial increases of maintenance diuretic dose
Symptomatic hypotension, azotemia, or refractory fluid retention necessitating neurohormonal medication withdrawal (renin-angiotensin-aldosterone system inhibitors and beta blockers)
First or recurrent implantable cardioverter-defibrillator shock for ventricular arrhythmias
Initiation of intravenous inotropic support
Consideration of renal replacement therapy
Other important change in comorbidities (e.g., new cancer)
Major "life events" (e.g., death of spouse)

Framing the Conversation.

Most patients and their families desire open, honest, and accurate information.[22] Yet, talking about the end

of life with patients who have CV disease is often an unexpected “bad news” conversation. The clinician should plan carefully before opening the discussion. Asking patients to describe how their activities and symptoms have changed over time often leads them to recognize the progression of their own illness, which can improve acceptance. Shaping discussion around “ask-tell-ask” can help:[23]

- Ask what the patient understands and what information the patient wants.
- Tell information that responds to the patient's questions, correct misunderstandings, and explain other factors important to the patient's decisions.
- Ask the patient to summarize what has been heard and what further questions the patient may have.

The clinician should expect that more than one period of discussion will usually be necessary.

Recognizing Emotion and Cognitive Biases.

During medical decision making for end-stage CV disease, emotion is heightened, and *mortality salience* (awareness that death will happen) is pushed to the front of consciousness.[24] Until emotions are recognized and acknowledged, people can have difficulty engaging in the more cognitive aspects of medical decision making. This can be done by using explicit language normalizing strong emotions and careful framing of information to minimize cognitive biases.

Discussing Prognosis While Recognizing Uncertainty

Multiple studies have shown that patients and clinicians tend to overestimate survival.[25] Particular care should be taken to avoid a numeric answer to the common question, “How long do I have to live?” For example, it has been demonstrated that for patients predicted to die at a certain time with late-stage cancer, about half will either die in less than half the predicted time or survive for more than twice as long.[26] It is better to focus on preparation for the end of life rather than prediction of when it will come. The palliative care motto of “hope for the best and prepare for the worst” can facilitate discussion of prognosis and care planning in all phases of disease.

Goals and Values.

After discussion of what and how the patient wants to know about prognosis, most conversations can pivot naturally to asking the patient about important goals as the overall health status worsens. The Serious Illness Conversation Guide provides one example of how this can be done.[20] Specific fears and worries are elicited from the patient about what might happen, as some may be allayed and others may direct choices that will need to be made. In a related question, patients consider what abilities are so critical to their lives that they could not imagine life without them. One of the most important aspects of patient preference is the answer to the question, “If you become sicker, how much are you willing to go through for the possibility of getting more time?” Studies of patients with advanced heart failure show a wide range of preferences around what they would be willing to endure to increase their likelihood of longer survival.

Decision Support Tools.

Shared decision making recognizes that there are often complex trade-offs in medical decisions and extends beyond the limited legal mandate to inform patients of risks and benefits of a treatment.[27] Patient

decision aids designed to facilitate patient participation in health care decisions can be helpful to convey critical information, elicit patient preferences, and encourage deliberation (https://decisionaid.ohri.ca/azinvent.php).[28] They are not substitutes for conversations with health care providers, but tools to help frame high-quality discussions. The use of decision aids generally improves patient knowledge and awareness of treatment choices.[29]

Medical Decision Making Near the End of Life

Is There Still a Definitive Treatment Option?

After recognizing that a patient may be nearing the end of life with cardiac disease, it is important for the medical team to devote final consideration to whether any major interventions could favorably alter the course of disease. Examples include valve replacement or coronary revascularization. If there is a feasible option to consider in a patient at high risk for procedural complications, it should be presented together with a clear alternative option of palliative care focused on quality of life. The elements of the conversation as previously described would help to determine whether the procedure is aligned with the patient goals and values. Unfortunately, current procedural outcome data often focuses only on survival, with limited objective data on the likelihood of adverse events, loss of independence, and caregiver burden, which are crucial components of decision making for many patients with serious illness. For patients who have chosen to undergo procedures with a high risk of adverse outcomes, preparation before surgery should include discussion about how they would translate their goals to the setting of "what-ifs" (e.g., ventilator dependence or stroke).

The Transition to End of Life Is Not a Point but a Process

The time and extent of transition away from "do everything" varies across diagnoses, patients, and families.[30] The acceptance of death within the near future may be unstable, and for some, may never be fully completed before the end. Usually, however, it is important to accept that there is a point after which major interventions, as exemplified earlier, will not be revisited. At the time of this major transition, it is generally appropriate and reassuring to continue all therapies that patients have been receiving for disease stabilization. However, the patient and family should understand that therapies can be added or removed for the goal of improving symptoms and quality of life, even if the change might shorten survival, unless maximizing the remaining survival remains the predominant goal for the patient. Additional content is available in the online supplement for this chapter (Removing Therapies and Futility).

Advance Care Planning Documentation

Advance care planning, defined as "planning for and about preference-sensitive decisions often arising at the end-of-life," is an ongoing process in which patients, families, and health care providers discuss current and future health care choices in the context of what is medically reasonable.[31] Such discussions can unfold in many ways but include a review with expression of preferences (**eTable 31.1**), resulting in various types of documentation (**Table 31.3**). The health care proxy should have been completed long before this stage of disease but should be confirmed at this time. The general principles guiding the completion of these documents are derived from the discussions of goals, values, and preferences (as outlined previously). An important distinction clarified in medical orders for life-sustaining treatment

(MOLST) forms is between the use of life-support interventions for an indefinite period versus a brief period, such as mechanical ventilation for chronic respiratory failure versus a pneumothorax, or dialysis for chronic renal failure versus iatrogenic hyperkalemia. Although the resuscitation decision in hospitals receives appropriate attention as a signpost for other decisions, the frequency of cardiopulmonary resuscitation was only 1.1% in a study of 1.4 million heart failure hospitalizations. Of those patients, 73% died before discharge, 10% were discharged to a skilled nursing facility, and only 16% were discharged home.[32]

TABLE 31.3

Types of Advance Care Directives and Documentation

- A **living will** is a signed, witnessed (or notarized) document called a "declaration" or "directive." A living will can be very specific or very general. Most declarations instruct an attending physician to withhold or withdraw medical interventions from its signer if he/she is in a terminal condition and is unable to make decisions about medical treatment.
- A **health care proxy** (Durable Power of Attorney for Health Care) is a legal document in which an individual designates another person to make health care decisions if he/she is rendered incapable of making their wishes known. The health care proxy has, in essence, the same rights to request or refuse treatment that the individual would have if capable of making and communicating decisions.
- A **combination advance directive** is a signed, witnessed (or notarized) document that contains specific written directions that are to be followed by a named agent (e.g., Five Wishes).
- **Medical orders for life-sustaining treatment** (MOLST, or physician orders, POLST) is a medical order form that tells others the patient's medical orders for life-sustaining treatment. MOLST is generally for patients with serious health conditions. All health care professionals must follow these medical orders as the patient moves from one location to another, unless a physician examines the patient, reviews the orders, and changes them.

ETABLE 31.1

Components of Advance Care and Preparedness Planning Discussion

Characterize clinical status.	Assess current functional ability, symptom burden, mental status, and quality of life. Review recent disease trajectory. Integrate impact of noncardiac diseases. Solicit perceptions from caregivers for corroboration.
Acknowledge prognosis and uncertainty.	Recognize uncertainty. Review different possible clinical courses and causes of death. Consider incorporating objective risk modeling data into qualitative messaging within wide time frames.
Solicit patient values and beliefs.	Clarify values as they relate to trade-offs (e.g., aggressive vs. nonaggressive care, quality versus quantity of life). Identify major life goals. Envision physical limitations that would be unacceptable. Elicit general care preferences.
Review treatments.	Evaluate indicated and contraindicated cardiac medications and devices. Consider overlap and interactions with comorbidities. Factor in declining relevance of routine preventive care.
Consider options.	Anticipate major treatment choices on the horizon.
Document.	Document in the medical record surrogate decision makers, resuscitation preferences, and preferences for and location of end-of-life care. Communicate "do-not" outside the hospital (e.g., Medic-Alert bracelet, posting on refrigerator).

Complex Treatment Decisions

Although advance care planning documents provide important guidance, many complex medical decisions may arise that are neither anticipated nor addressed by the specific details of the documents (**eTable 31.1**). Additional content is available in the online supplement for this chapter (Complex Treatment Decisions).

Treatment of Symptoms Approaching End of Life

Progressive symptoms are the most common reason for reduced health status in patients with CV disease.[33] Among patients with heart failure (HF)—the final common pathway for many heart diseases—symptom burden at the end of life is often greater than for patients with advanced lung or pancreatic

cancer.[34] Thus, design of the cardiovascular regimen and general palliative approaches are critical near the end of life.

Ongoing Role for Cardiovascular Treatments

The best treatment to relieve late-stage cardiac symptoms is often continuation of the regimen that was initiated to decrease progression from earlier stages of disease. For example, the treatment of angina at any stage of ischemic heart disease involves reducing myocardial oxygen supply/demand mismatch. The primary treatment of symptomatic congestion remains diuretic therapy. Supplementation with oral, sublingual, or topical nitrates can temporarily help redistribute volume when adequate diuresis cannot be achieved. If symptoms are related to diuretic resistance or hypotension, a decrease in or discontinuation of neurohormonal antagonists may improve comfort by enhancing diuretic response and increasing systemic blood pressure (**eTable 31.2**). Although discontinuation of these agents is associated with worsening HF over time in stable patients, it is unlikely to worsen cardiac function or symptoms in the final days of life. Caution is required in certain situations; for example, withdrawal of beta-adrenergic receptor blockers may worsen symptom burden in patients with frequent angina or tachyarrhythmias. Relaxation of chronic sodium and fluid restriction often worsens symptoms of congestion; however, favorite foods and beverages can be a major factor in quality of life and social interaction for some patients at a time when few other shared pleasures remain.

ETABLE 31.2

Common Cardiovascular Medications and Changing Indications at End of Life (EOL)

COMMON MEDICATIONS FOR CARDIAC DISEASE	USUAL INDICATIONS TO MODIFY DISEASE AND IMPROVE LONG-TERM OUTCOMES	POSSIBLE SHORT-TERM SYMPTOM BENEFIT OF CONTINUING AT EOL	POTENTIAL HEMODYNAMIC IMPACT DURING EOL	POSSIBLE DELETERIOUS EFFECT AT EOL	COMMENTS ON DISCONTINUATION AT EOL
ACEIs/ARBs	To prolong survival, prevent reinfarction, and improve ventricular function. Decrease HF hospitalizations. Treat HTN.	Not expected	Lower blood pressure	Symptoms of hypotension and declining diuretic response	Renal function likely to improve. Symptoms of hypotension may improve.
Beta blockers	As above. Decrease recurrence of ventricular tachycardia. Decrease ventricular rate of atrial fibrillation.	Decrease angina. Decrease tachyarrhythmias.	Higher filling pressures Lower cardiac output Lower blood pressure	Worsening dyspnea Worsening fatigue Symptoms of hypotension	Energy and symptoms of hypotension may improve. Renal function might improve. Be alert to exacerbation of angina or symptomatic arrhythmias.
Sacubitril/valsartan*	To prolong survival and decrease hospitalizations in chronic HF	May decrease dyspnea and edema.	Lower blood pressure	Symptoms of hypotension	Symptoms of hypotension may improve. Diuretic requirement may increase.
Mineralocorticoid Antagonist	Decrease fibrosis, improve survival, and decrease HF hospitalizations.	Weak synergy with other diuretics. Decreases need to take oral potassium.	Possible slightly lower filling pressures	Need for potassium binders if serum potassium is high	Renal function may improve. Less risk of hyperkalemia, but hypokalemia may cause cramps and muscle fatigue.
Loop diuretics†	Treat congestion and maintain fluid balance. Facilitate titration of neurohormonal antagonists.	Most effective treatment of dyspnea and edema through diuresis.	Most effective therapy to lower filling pressures and valvular regurgitation	Increased need to take potassium	Marked exacerbation of dyspnea and other congestive symptoms patients with fluid retention.
Nitrates†	Relief of angina. With hydralazine, to improve outcomes in African American patients. Treat HTN.	Decrease dyspnea. Decrease chest pain.	Lower blood pressure Lower filling pressures and valvular regurgitation	Can cause headaches	Relief of nitrate headaches Worsening of dyspnea Symptoms of hypotension may improve.
Hydralazine	With nitrates, to improve survival, symptoms, and decrease hospitalization in African American patients. Treat HTN.	Might decrease dyspnea or angina with severe mitral regurgitation	Modestly lower filling pressures and blood pressure if baseline vasoconstriction Less mitral regurgitation	Can cause nausea	Nausea may improve. Dyspnea might worsen if mitral regurgitation severe.
Statin therapy	Improve outcomes with atherosclerotic disease.	None		Can cause or aggravate myalgias	No known benefit at EOL
Digitalis glycosides	Decrease hospitalization in symptomatic HF. Decrease rate in atrial fibrillation.	Decrease rate in atrial fibrillation.	Modestly higher cardiac output	Nausea Visual disturbances Digoxin toxicity if declining renal function	Discontinuation known to exacerbate HF symptoms. May discontinue to avoid toxicity if progressive renal dysfunction.
Sodium (Na) and fluid restriction	Decrease fluid retention. Treat HTN.	Decrease dyspnea and edema.	Restriction is likely to decrease filling pressures and valvular regurgitation.	Diminished enjoyment of food and social contact Diminished quality of life May accelerate cachexia Family conflict regarding adherence	Relaxation of Na restriction may improve quality of life, nutrition, and social contact. Generally relaxed only for special occasions or when death anticipated within a few days. May reduce patient-family conflict related to adherence.
Nonsteroidal anti-inflammatory drugs contraindicated in HF	Contraindicated because of potential for worsening HF, fluid retention, and renal function	Use may diminish musculoskeletal pain, especially from gout.	May increase filling pressures and valvular regurgitation	Dyspnea and edema may increase with fluid retention and renal dysfunction.	Intermittent use may improve comfort and mobility. Benefit must be weighed against effects to decrease renal function and increase fluid retention.

*Insufficient experience to anticipate effects of withdrawal near end of life.

†Note alternative routes of administration for patients with difficulty swallowing medications.

ACEIs, Angiotensin-converting enzyme inhibitors; *ARBs,* angiotensin receptor blockers; *HF,* heart failure; *HTN,* hypertension.

Inotropic Infusion (see also Chapter 24).

Continuous inotropic infusions are selectively used to treat symptoms of refractory HF. Even when intended to be temporary, the decision to start inotropic therapy should be undertaken only after careful consideration of next steps. For patients discharged on home inotropic infusions, reported survival has improved from less than 50% at 6 months to approximately 50% at 1 year.[35] The decreased mortality may be related to lower dosing, increased presence of implantable cardioverter-defibrillators (ICDs), or use in patients with less advanced disease. Patients should not be discharged on intravenous inotropic infusions with the anticipation that death will occur peacefully at home, since many are readmitted with recurrent symptoms, infectious complications, or breaks in the indwelling catheters. The potential complications and the inconvenience for patients and families warrant repeated attempts to wean inotropic therapy before discharge, which can be facilitated by stopping neurohormonal antagonists, in some cases with substitution of hydralazine and nitrates and cautious use of digoxin. An additional concern is that many home nursing agencies are not able to offer the benefits of hospice care to patients receiving relatively costly continuous infusions.[36]

General Palliation for Refractory Symptoms.

Even with expert cardiovascular management, symptoms are rarely completely relieved and often worsen as the disease becomes increasingly refractory to CV-focused therapies.[30] The basic principles, strategies, and expected benefits of palliative care approaches to symptoms pertain to severely symptomatic and functionally limited patients with end-stage CV disease.[4] Furthermore, CV disease rarely occurs in isolation, so integrated approaches to care, which consider symptoms arising from multiple causes, apply to most patients with HF. A palliative care specialist is rarely needed to prescribe the interventions; most primary care or cardiology clinicians should learn to provide these services.

Joint and body pain is a common symptom in patients with end-stage CV disease, with prevalence rising to 40% to 75% among persons with advanced HF.[37] Clinicians should inquire about pain and develop strategies for management. When this appears to be musculoskeletal in nature, discontinuation of statin therapy is reasonable.[38] Arthritis is common in older persons, but the nonsteroidal anti-inflammatory drugs (NSAIDs) are relatively contraindicated in patients with significant HF and vascular disease.[39] Local treatments such as lidocaine patches, application of heat or cold, and physical therapy should be considered in an integrated approach to pain management. However, if joint pain at the end of life is particularly severe, particularly from episodic gout, consideration may be given to cautious intermittent use of NSAIDs with close monitoring for fluid retention and worsening renal function (if laboratory tests are still being performed).

Antiemetics should be considered for nausea. Lorazepam is less likely to prolong the QT interval than other antiemetics, although this is often not a major concern if the end of life is anticipated.[39] Weight loss from anorexia and the hypercatabolic state of end-stage cardiac disease may be treated with a variety of agents—progesterone analogues (e.g., megestrol acetate), cannabinoids (e.g., dronabinol), mirtazapine, corticosteroids, and anabolic agents (e.g., testosterone)—although use should be continued only when it improves symptoms and help meet goals of care.[40] For patients having difficulty swallowing pills and taking in oral nutrition and hydration, placement of feeding tubes or indwelling lines is rarely indicated at this stage and should be undertaken only after full consideration of the potential implications. The number and size of daily pills can often be decreased with thoughtful review.

Narcotics for Pain and Dyspnea

Pain at the end of life is most often treated with opioids, which are very effective for dyspnea as well as

pain. For patients with dyspnea refractory to hemodynamic interventions (diuretics, afterload reduction, inotropes) and oxygen, international guidelines recommend the use of opioids,[41] although not all studies have been positive.[42] Low dosages of opioids are often sufficient to achieve relief of dyspnea. Because the response may increase, only cautious dose increases should occur within the first week. Opioids must be accompanied by laxatives in time to prevent rather than reverse constipation. Renal function is impaired in many older patients with advanced CV disease, so oxycodone may be preferred to morphine (some metabolites of morphine can accumulate and cause confusion). Clinicians report fear of adverse respiratory effects and addiction as important barriers to opioid prescription, despite studies showing limited adverse effects and low rates of dependence and addiction in appropriately treated patients.[43] Scopolamine is occasionally used to decrease secretions but should not be used routinely because it often causes disorientation and confusion.

Psychosocial Support

The impact of HF on quality of life for both the patient and the family is complex and extends beyond physical symptoms.

Depression

Depression in symptomatic HF and after myocardial infarction has an estimated prevalence of 20% to 40%, is associated with worse clinical outcomes, and increases with worsening disease severity[44] (**see Chapter 96**). The first step is treat its causes, including pain and dyspnea. Unfortunately, limited data are available on pharmacologic, cognitive, and exercise therapy for depression in patients with advanced CV disease. A trial of 469 patients with symptomatic HF found no significant difference in depression or CV status in the treatment group compared with placebo.[45] In another trial of 158 HF patients, cognitive-behavioral therapy was effective in the treatment of depression compared with usual care (12.8 [10.6] versus 17.3 [10.7]; $P = 0.008$), but did not influence self-care.[46] Despite these mixed data, many clinicians continue to try pharmacologic therapy with selective serotonin reuptake inhibitors (SSRIs), psychostimulants (e.g., methylphenidate), or tricyclic antidepressants (e.g., nortriptyline, which has less significant anticholinergic effects such as orthostatic hypotension than other TCAs). Medication side effects that may warrant monitoring in some patients include QT prolongation with TCAs and hyponatremia with SSRIs.[39]

Emotional, Spiritual, and Social Support.
The loss of physical and social function is devastating. Patients with advanced CV diseases may fear dying, worry about burdening families, and experience hopelessness, isolation, disability, and uncertainty regarding their course. Clinicians should acknowledge patients' losses and sources of grief, screen for spiritual concerns, and engage chaplaincy and patients' religious communities when appropriate.[47]

Caregiver Burden, Bereavement, and Support.
Although most family and friends embrace the opportunity to help, they and informal caregivers report scheduling, financial, and family burdens. As patients approach the end of life, these burdens increase.[48] Advances in technology have also created challenging and even traumatic situations around death, as has been seen with left ventricular assist devices.[49] Health status and emotional well-being of family

caregivers can be impaired. Therefore, careful attention to family and other caregivers is an important part of the end-of-life process, including grief counseling services after bereavement.[50]

The Site for the End of Life

An important component of end-of-life care planning is to determine where the patient and family anticipate that the final days should occur. Patients most often prefer this to be at home. Hospice use is substantially lower in advanced HF patients than in those with advanced cancer, but rates are increasing, with more than 40% of Medicare patients with HF dying in hospice.[50] Home hospice care includes extended availability for calls and visits to help with symptoms and events at the end; however, dying at home requires continuous support from family or friends, which is not always possible or desired. Inpatient hospice is limited in most areas and usually entails substantial costs not covered by insurance. Alternatively, some end-of-life services can be provided in a long-term skilled nursing facility. Patients who are receiving high-intensity therapies are generally not eligible for home hospice or transfer to a skilled nursing facility. For example, intravenous inotropic infusions or dialysis can be substantial obstacles to peaceful end-of-life care. In these situations, the high level of support must usually be stopped before discharge, in full recognition that death may occur in the hospital. Regardless of the anticipated course, it is always prudent to have a “plan B” to implement if the patient planning to die in the hospital does not do so quickly, or if the patient planning to die at home or his family faces unanticipated difficulties.

Future Perspectives

The integration and quality of palliative care for patients with heart failure warrants substantive improvement, including changes in medical education and performance measures for advanced HF certification of clinicians and hospitals, as well as cultural acceptance of the end of life and end-of-life planning. Smoothing the transition between “do everything” and “do nothing except for comfort” requires attention to what happens in between, after recognition that survival is limited. If the shift in focus from maximizing survival to enhancing quality of life has been successful—minimizing symptom burden, enhancing meaningful interactions, and encouraging achievement of short-term goals—patients and families will often seek to prolong the duration of this phase of “quality survival” before hospice care is indicated. Additional content is available in the online supplement for this chapter (Changing the Culture of Palliative Care). As providers, we need to develop a responsive model of care that honors patient and family goals, as well as stewardship of finite resources, throughout their journey with cardiac disease.

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Psychosocial Support and the Site for the End of Life

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Removing Therapies and Futility

Deactivation of Cardiac Rhythm Devices

Decisions around withdrawal of therapies are often more complex than the decisions to start them is.[1] In end-stage heart disease, dilemmas arise around deactivation of cardiac implantable electronic devices. Providers rarely discuss implantable cardioverter-defibrillator (ICD) deactivation,[2] and many patients with ICDs are not aware of the option to deactivate them.[3] The result is that ICDs remain active until and sometimes during death; disturbingly, this can even happen in hospice.[4,5] Turning off the defibrillator function should be presented as a simple step that may be consistent with the goal of preserving quality of life during the dying process. Although this option relates to resuscitation preferences, patients often have strong and disparate views on external and internal defibrillation. In difficult situations, consultation with palliative care can help clarify the relationship of the device to goals of care.[6] Planned replacement of the

device generator at battery end of life should be carefully reviewed in the context of patient preferences, illness trajectory, and reliance on pacing and cardiac resynchronization therapy.

Futility

Certain therapeutic options may be considered unreasonable or become impossible for an individual patient and therefore are not provided, even if demanded by a patient or family. For example, cardiopulmonary resuscitation may not be appropriate in a patient with progressive cardiogenic shock without a reversible underlying etiology. Fortunately, situations of *medical futility*, where members of the health care team disagree with the patient and/or family about whether therapies have an acceptable likelihood of benefiting patient goals, are uncommon.[7] Referral to a specialty palliative care or involvement of a hospital ethics committee should be considered for assistance when there are disagreements about potentially futile care.

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Complex Treatment Decisions

Although advance care planning documents provide important guidance, many complex medical decisions may arise that are neither anticipated nor addressed by the specific details of the documents[1] (**eTable 31.1**). Some of these decisions may be whether to attempt cure or palliation of serious new diagnoses such as cancer, whereas others may be for symptomatic relief such as hip replacement. When decisions involve an elective procedure, particularly for surgery, there is time for shared discussion, which should include not only consideration of usual risks and benefits, but also the time frame in which such benefits would be enjoyed after procedural discomfort and recovery. There may be decisions that arise emergently about procedures to prevent death from a catastrophic event such as an intracranial hemorrhage or ruptured bowel; these should be guided strongly by the goals, values, and preferences previously elicited.

Standard care practices established for asymptomatic disease (e.g., surgery for a large abdominal

aortic aneurysm) or incidental findings (e.g., biopsy of a pulmonary mass) would not likely be performed in a patient with end-stage cardiac disease, but evaluation for these conditions may at times proceed farther than warranted. Perhaps the most common oversight, emblematic of the impact of computerized algorithms, is to perform routine screening for malignancy. The net benefit from routine colonoscopy is clearly negative in patients with end-stage cardiac disease, in whom the fluid and electrolyte shifts and the sedation pose some risk and even the minor discomforts are unwarranted.

Even though not definitive, some cardiac procedures may be reasonable to treat new or recurrent conditions in a patient still otherwise clinically stable. For example, cardioversion of atrial flutter or angioplasty for worsening angina could be considered in patients for whom some survival with improved quality is still anticipated. However, the decision for any such procedure should include careful review of the likelihood and response for the adverse "what-if" outcomes, such as cardiac arrest, coronary artery laceration, or acute stroke.

During hospitalization within months of anticipated death, initial triage and therapy often occur without appreciation of the disease trajectory. Although often begun with intent for temporary use, intravenous inotropic therapy, dialysis, and catheters for pleural or peritoneal fluid drainage may lead to difficult decisions about continuation. This becomes particularly important when the primary goal becomes discharge to home.

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Changing the Culture of Palliative Care

Policies Mandating for Palliative Care in Cardiovascular Care

The integration and quality of palliative care for patients with heart failure warrants substantive improvement, which may be triggered by a number of initiatives. The Accreditation Council for Graduate Medical Education now includes "interpersonal and communication skills" as one of its six core competencies, but how this will improve care for patients with severe illness is unclear.[1,2] The Joint Commission has introduced performance measures for advanced heart failure certification that include discussions of advance care planning and advance directive documentation, but few hospitals participate in such certification.[3] The Centers for Medicare and Medicaid Services plan to reimburse physicians for engaging patients in advance care planning discussions should ease the financial disincentive to schedule the time required,[4] but serious obstacles remain.[5] Change is symbolized by stronger mandates for shared decision making before high-risk device interventions, such as Medicare requirements for palliative care with left ventricular assist device (LVAD) teams[6] and "a formal shared decision-making interaction with an independent non-interventional physician using an evidence-based decision tool" before payment for a left atrial appendage closure device.[7] However, despite the details of how these mandates will be met for payment, the details of what each of these mandates means for payment are still being elaborated by the National Quality Forum and others.[8]

Death Not as Failure

Cultural acceptance of end-of-life planning requires cultural acceptance of the end of life, and both are vital. When death is viewed as a deviation or failure rather than as the inevitable outcome, patients and families will not be prepared when disease progresses beyond therapies. One example of how end-of-life culture can evolve is found in La Crosse, Wisconsin, where the Gundersen Health System implemented the Respecting Choices program for advance care planning and decision making in 1991,[9,10] which within the next 5 years enhanced the prevalence of advance directives and the understanding of preferences by families and physicians. A subsequent study 10 years later using the same advance care planning model showed further improvement in completion of advance directives and fewer treatments at the end of life.[11] There is hope that such efforts can be more widely disseminated for impact generalized to communities rather than isolated to specific diagnoses.

Respecting the "Quality Survival Phase" of Life

Smoothing the transition between "do everything" and "do nothing except for comfort" requires attention to what happens in between, after recognition that survival is limited. If the shift in focus to quality of life has been successful—minimizing symptom burden, enhancing meaningful interactions, and encouraging achievement of short-term goals—patients and families will often seek to prolong survival in this phase.

Although major procedural interventions are not usually warranted, benefit may yet be obtained from therapy directed beyond immediate symptom relief. This may be for new problems, such as intravenous antibiotics for pneumonia, or for intensification of therapy during heart failure hospitalization, which frequently increases toward the end of life. Symptoms and quality of life frequently improve after hospitalization, even in advanced disease,[12] so it is difficult to determine when hospitalization is not indicated. When surveyed before discharge, many patients close to the end of life describe their lives as continuing to have value.

Health care providers need to recognize, respect, and support this phase of "quality survival" nearing the end of life. However, it is an obvious target for reducing hospitalizations and avoidance of financial penalties. This may trigger increased efforts to persuade patients to enter hospice while they are still reluctant to give up the options of hospitalization and treatment such as antibiotics or intravenous inotropic therapy. We need to develop a new model of care responsive to the goals of this phase as well as to our stewardship of constrained resources.

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PART V
Arrhythmias, Sudden Death, and Syncope

OUTLINE

32

Approach to the Patient with Cardiac Arrhythmias

Gordon F. Tomaselli, Douglas P. Zipes

The evaluation of patients with suspected cardiac arrhythmias is highly individualized. However, two key features—the history and electrocardiogram (ECG)—are pivotal in directing the diagnostic evaluation and treatment. The physical examination is focused on determining whether there is cardiopulmonary disease that is associated with specific cardiac arrhythmias. The absence of significant cardiopulmonary

disease often, but not always, suggests a benign cause of a cardiac rhythm disturbance. The judicious use of noninvasive diagnostic tests is an important element in the evaluation of patients with arrhythmias, and the most important is the ECG, particularly if recorded at the time of symptoms.

An evidence-based approach to the history and physical examination is presented in **Chapter 10**. This chapter focuses on features most germane to the patient with cardiac rhythm disturbances. However, it is essential to understand that the general medical condition of the patient may profoundly influence the presentation of any cardiac arrhythmia. This chapter discusses the general approach to the patient with a suspected arrhythmia. Details of the diagnostic evaluation of such patients are presented in **Chapter 35**.

Signs and Symptoms

General Approach

Patients with cardiac arrhythmias exhibit a wide spectrum of clinical presentations, ranging from asymptomatic incidental ECG abnormalities to survival from sudden cardiac arrest (SCA). The presenting features may vary with circumstances, and arrhythmias are common in the setting of cardiovascular (CV) and medical diseases, leading to overlap of symptoms and signs. The history is key to directing the evaluation of patients. In general, the more severe the presenting symptoms, the more aggressive are the evaluation and treatment. Loss of consciousness believed to be of cardiac origin typically mandates an exhaustive search for the etiology and may require invasive, device-based diagnostic evaluation and treatment. The presence of structural heart disease and prior myocardial infarction (MI) often dictates a change in the approach to the management of syncope or ventricular arrhythmias. A family history of a significant cardiac arrhythmia may not directly inform the prognosis of a patient, but it should alert the practitioner to the possibility of a heritable trait that may increase susceptibility to development of an arrhythmia.

Palpitations

Palpitations are the awareness of the heartbeat that may be caused by a rapid heart rate, irregularities in heart rhythm, or an increase in the force of cardiac contraction, as occurs with a post–extrasystolic beat; however, this perception can also exist in the setting of a completely normal cardiac rhythm. Patients who complain of palpitations describe the sensation of an unpleasant awareness of a forceful, irregular, or rapid beating of the heart. Many patients are acutely aware of any cardiac irregularity, whereas others are oblivious, even to long runs of a rapid ventricular tachycardia or atrial fibrillation (AF) with rapid ventricular rates. The latter is particularly noteworthy because if untreated, it may be associated with stroke or may produce a tachycardia-induced cardiomyopathy. Patients may use terms such as a “pounding” or “flipping” sensation in the chest; a fullness or pounding in the throat, neck, or chest; or a pause in the heartbeat, or “skipped a beat.” The skip often results from the pause after a premature ventricular complex (PVC) or the resetting of sinus rhythm after a premature atrial complex (PAC). Usually, the premature beat, particularly if it is a ventricular extrasystole, occurs too early to permit sufficient ventricular filling to cause a sensation when the ventricle contracts. The ventricular systole that ends the compensatory pause is often responsible for the actual palpitation, the result of a more forceful contraction from prolonged ventricular filling or increased motion of the heart in the chest. Anxiety over such symptoms is usually the complaint that brings the patient to the physician's office.

Premature atrial or ventricular complexes constitute the most common causes of palpitations. If the

premature complexes are frequent, or particularly if a sustained tachycardia is present, patients are more likely to have additional symptoms, such as lightheadedness, syncope or near-syncope, chest discomfort, fatigue, or shortness of breath. The context and symptoms associated with palpitations can be diagnostically and prognostically informative. Low-risk features include isolated palpitations not induced by exercise, the absence of structural heart disease or symptoms such as syncope or chest pain, no family history of sudden cardiac death (SCD), and a normal 12-lead ECG. Associated symptoms, such as syncope or chest pain, the presence of structural heart disease, or a documented arrhythmia, and family history of SCD may be associated with a more ominous cause of palpitations.[1] In the setting of structural heart disease, the differential diagnosis is broad. The age of the patient and the presence of associated CV problems influence the nature of the symptoms. For example, a supraventricular tachycardia (SVT) at a rate of 180 beats/min can provoke chest pain in a patient with coronary artery disease (CAD) or syncope in a patient with aortic stenosis, but may result in mild breathlessness in an otherwise healthy young person.

The onset and offset of palpitations can suggest the etiology of the arrhythmia. A sudden, abrupt, onset, "like a light switch turning on," is consistent with a paroxysmal tachycardia such as atrioventricular nodal reentrant tachycardia (AVNRT; **see Chapter 37**), whereas gradual speeding and slowing are more consistent with atrial or sinus tachycardia. However, even tachycardias that start abruptly can begin and end with extra beats appearing to have a more gradual onset and offset. Termination by Valsalva maneuver or carotid sinus massage suggests a tachycardia incorporating nodal tissue in the reentrant pathway, such as sinus node reentry, atrioventricular reentrant tachycardia (AVRT), or AVNRT (**see Chapters 34 and 37**).

The rate of an untreated tachycardia often narrows diagnostic possibilities, and patients should be taught to count their radial or carotid pulse rate, noting whether it is regular or irregular. Ventricular rates of 150 beats/min should always suggest the diagnosis of atrial flutter with 2 : 1 atrioventricular (AV) block (**see Chapter 37**), whereas most SVTs, such as those caused by AVNRT or AVRT, usually occur at rates exceeding 150 beats/min. The rates of ventricular tachycardias (VTs) overlap with those of the SVTs.

Patients with bradyarrhythmias may have symptoms of low cardiac output, including fatigue, weakness, dizziness, dyspnea, and syncope (**see Chapter 40**). Palpitations can result from an increased force of contraction associated with longer ventricular filling times and may be prominent symptoms in bradycardias.

Syncope, Presyncope, and Altered Level of Consciousness

Syncope, commonly referred to as "fainting" or "passing out," is a transient, self-limited loss of consciousness and posture resulting from a drop in blood pressure with cerebral hypoperfusion and should always prompt a search for a cause (**see Chapter 43**). It is important to distinguish syncope from other causes of transient loss of consciousness, such as seizures, metabolic disorders (hypoglycemia, hypoxia [e.g., airline decompression]), intoxication, cataplexy, and pseudosyncope. The etiologies of true syncope are varied with similarly diverse prognoses. The unheralded loss of consciousness in any patient, even if benign from the cardiac perspective, can be dangerous depending on the circumstances (e.g., while driving a vehicle, at the top of a flight of stairs). However, because syncope can be a harbinger of SCD, it is important to identify cardiac from more benign causes of syncope[2] (**eTable 32.1**).

ETABLE 32.1

Syncope: Criteria for Immediate Evaluation*

Presence of Structural Heart Disease
Heart failure
Significant left ventricular dysfunction or hypertrophy
Prior myocardial infarction
Clinical Features
Exertional syncope
Syncope while supine
Palpitations associated with syncope
Family history of sudden death
Electrocardiographic Features
Ventricular tachycardia
Bifascicular block
Intraventricular conduction delay (QRS duration >120 msec)
Sinus bradycardia (heart rate <50 beats/min), sinoatrial block†
Preexcited QRS complex
Prolonged or short QT interval
Brugada pattern on ECG
T wave inversion and late potentials in right precordial leads‡
Significant Comorbidities
Anemia
Electrolyte disturbance

*Based on European Society of Cardiology (ESC) guidelines.

†In the absence of medications with negative chronotropic effects.

‡Suggestive of arrhythmogenic right ventricular dysplasia/cardiomyopathy.

When caused by a cardiac arrhythmia, the onset of syncope is rapid and the duration is brief, with or without preceding aura, and is not typically followed by a postictal confusional state. It can be associated with bodily injury if the patient falls while unconscious. Palpitations preceding syncope may support an arrhythmic cause of syncope but are often absent if the loss of consciousness is rapid. Seizure activity is uncommon and occurs mostly after prolonged asystole or a rapid ventricular arrhythmia. Therefore, the seizure does not begin with or anticipate the syncope, whereas in epileptic seizures, convulsive movements start within seconds of the onset of syncope. Tongue biting or incontinence is also uncommon in cardiac syncope. In summary, syncope with early seizure activity is frequently caused by epilepsy, whereas later seizure activity is more likely caused by a cardiac arrhythmia with cerebral hypoperfusion. The history of syncope should be elicited and interpreted carefully, because older people who have fallen might deny loss of consciousness during the event because of retrograde amnesia. Common arrhythmic causes of syncope include bradyarrhythmias caused by sinus node dysfunction or AV block and tachyarrhythmias, most often ventricular but on occasion supraventricular. Bradycardia can follow tachycardia in patients with the bradycardia-tachycardia syndrome, and treatment of both may be necessary.

Of the reflex syncopes—neurocardiogenic, carotid hypersensitivity, and situational—neurocardiogenic is the most common. It should be differentiated from syncope caused by orthostasis, which may be seen in autonomic failure (e.g., due to diabetes).[3] Vasodepressor and cardioinhibitory syncope usually unfold more slowly and can be preceded by manifestations of autonomic hyperactivity such as nausea, abdominal cramping, diarrhea, sweating, or yawning. In fact, palpitations are common in this setting. On recovery, the patient may be bradycardic, pale, sweaty, and fatigued, unlike the patient recovering from a Stokes-Adams attack or an episode of VT, who may be flushed and may have a sinus tachycardia, usually without persistent mental confusion. Palpitations and presyncope on standing can be symptoms of postural orthostatic tachycardia syndrome.

Drug-induced (orthostatic hypotension, bradyarrhythmia) and nonarrhythmic cardiac causes such as aortic stenosis, hypertrophic cardiomyopathy, pulmonary stenosis, pulmonary hypertension, and acute MI

can be excluded by the history, physical examination, ECG, echocardiography, and other laboratory tests. Noncardiac causes of syncope, such as hypoglycemia, transient ischemic attack, and psychogenic causes, often can be excluded by a careful history (**see Chapters 35 and 43**).

Sudden Cardiac Arrest and Aborted Sudden Cardiac Death

SCD is common, although estimates of the incidence are confounded by inadequate case identification and secular trends that have influenced both the rates and the etiologies of sudden death (**see Chapter 42**). SCD caused by cardiac arrhythmias is most often the result of VT or ventricular fibrillation (VF) but can result from profound bradycardia, as might be observed in complete heart block, or asystole. A variety of noncardiac conditions may be associated with life-threatening arrhythmias, including neurologic diseases (stroke, intracranial hemorrhage, epilepsy, neuromuscular disease, Parkinson disease), diabetes, obesity, cirrhosis, anorexia, and bulimia. In well-adjudicated cases, coronary heart disease (CHD) is the most common finding in SCD and can be the first and last manifestation. Up to 80% of cases of SCD occur in patients with some form of structural heart disease, such as CHD, cardiomyopathy, or congenital heart disease. Other cardiac causes of SCD, referred to as "autopsy negative," include primary electrical diseases such as long-QT syndrome (LQTS), Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), idiopathic ventricular fibrillation (IVF), and under some circumstances, Wolff-Parkinson-White (WPW) syndrome (**see Chapters 33 and 37**). The remaining sudden deaths are usually not cardiac in etiology.

For the purposes of evaluation, SCA should be considered as SCD that someone has survived. It is essential that patients who have SCA undergo a comprehensive evaluation to identify the cause and proper treatment. A history of cardiac disease is critically important in directing the evaluation and management, as is a family history of SCD or significant cardiac arrhythmias. The circumstances at the time of SCA are often informative. Cardiac symptoms that predate the SCD suggest preexisting structural heart disease. A variety of precipitating factors can provide clues to the etiology of SCA. Exercise, emotional upset, or stress may precipitate cardiac arrest in the setting of a variety of structural heart diseases, arrhythmogenic cardiomyopathy (arrhythmogenic right ventricular cardiomyopathy/dysplasia, ARVD/C), and primary electrical diseases such as LQTS (types 1 and 2) and CPVT. SCD in LQTS3 or Brugada syndrome is more likely to occur at rest or with sleep. Fever is common precipitant of the characteristic ECG abnormality (**Fig. 32.1**) and arrhythmias in Brugada syndrome. Medications and recreational drugs can increase the risk of lethal arrhythmias; patients should be asked about use of antiarrhythmics, stimulants, decongestants, psychotropics, antibiotics, alcohol, amphetamines, cocaine, and supplements, especially those used for weight loss and energy enhancement. Patients with LQTS and Brugada syndrome should be cautioned about the use of medications that may increase risk of arrhythmias. Drugs that should be avoided are listed on https://www.crediblemeds.org/ and http://www.brugadadrugs.org/, respectively. Structural heart diseases, such as dilated (DCM) or hypertrophic (HCM) cardiomyopathy are associated with delayed ventricular repolarization, an acquired form of LQTS, and the same drugs can produce life-threatening arrhythmias in these patients.

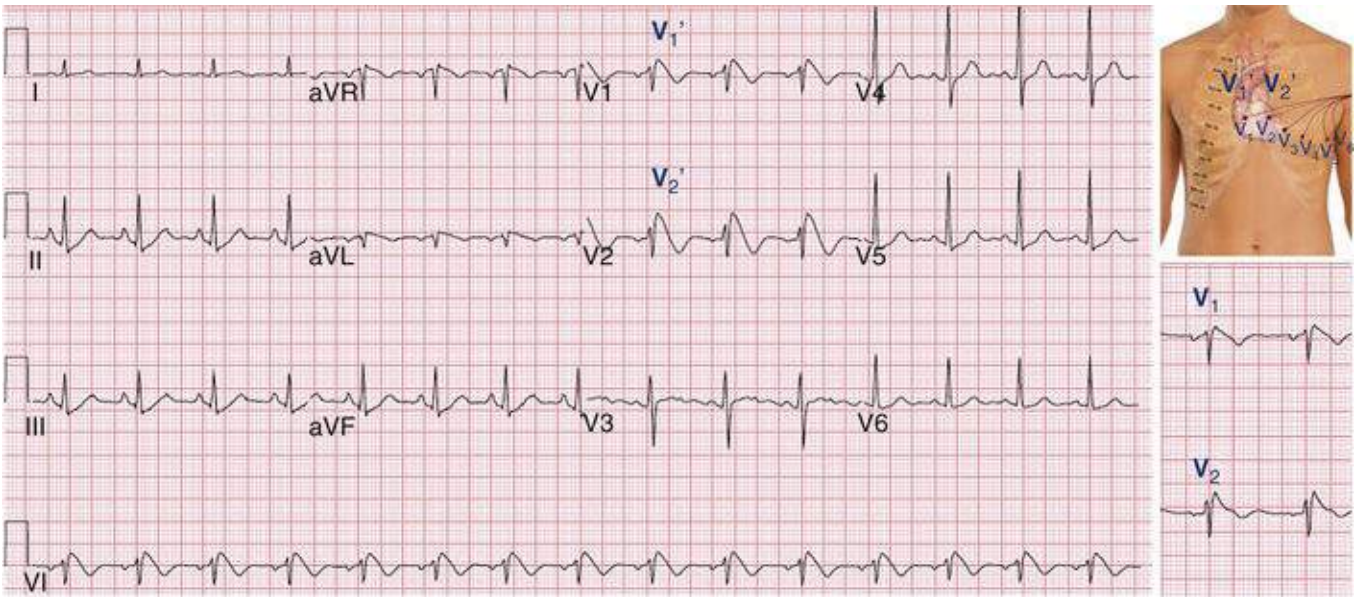


FIGURE 32.1 12-Lead electrocardiogram (ECG) with V_1' and V_2' recorded in the second intercostal space, as shown on the torso. *Inset,* Appearance of leads V_1 and V_2 in the standard positions in this patient.

The presence of a family history of serious ventricular arrhythmias, premature sudden death, stillbirths, sudden infant death syndrome (SIDS), unexplained motor vehicle and other accidents, and relatives with permanent pacemakers or implantable cardioverter-defibrillators (ICDs) may be relevant and will influence the evaluation of presumed heritable arrhythmias. If available, biologic materials from related decedents may be suitable for genetic testing or a molecular autopsy in suspected cases of heritable causes of SCD.

Physical Findings

The physical examination is focused on determining whether CV disease is present. The absence of significant cardiopulmonary disease often, but not always, suggests benignity of a rhythm disturbance. In contrast, palpitations, syncope, or near-syncope in the setting of significant heart or lung disease have a more ominous prognosis. In addition, the physical examination may reveal the presence of a persistent arrhythmia such as AF. The detailed approach to the CV physical examination is outlined in **Chapters 10 and 35**. The general physical examination is also important and can identify medical conditions associated with cardiac manifestations and arrhythmias. Inspection of the skin may reveal erythema chronicum migrans, the rash associated with Lyme disease; hair loss and exophthalmos may reflect the presence of thyroid disease; and ptosis and skeletal muscle wasting or myotonia may indicate the presence of neuromuscular disease (**see Chapter 97**).

If a tachycardia is present, the priority is to obtain a 12-lead ECG if the patient is hemodynamically stable. If it is not possible to obtain an ECG, several clues on the physical examination can help to make a diagnosis. The presence of regular cannon A waves in the jugular venous pulse would be consistent with a 1 : 1 retrograde ventriculoatrial activation, as in tachycardias such as AVRT, AVNRT, and some junctional tachycardias and VTs. In contrast, patients may have physical examination features of AV dissociation, such as intermittent cannon A waves, variable intensity of the first heart sound, and variable peak systolic blood pressure, consistent with arrhythmias, including VT and nonparoxysmal AV junctional tachycardia, without retrograde capture of the atria (**see Fig. 10.4**).

Carotid sinus massage (CSM) during the physical examination can be useful to interrupt arrhythmias

sensitive to autonomic tone and identify the patient with a hypersensitive carotid sinus reflex. The examiner first needs to listen carefully over both carotid arteries to be certain that no bruit is present, palpate lightly to determine that a normal carotid pulse is present, and then gently depress or rub the carotid sinus. Gentle massage is usually sufficient to terminate a sensitive tachycardia or produce significant periods of sinus arrest or AV block in susceptible patients. The most definitive responses to CSM are tachycardia termination, as may be observed in AVRT, AVNRT, sinus node reentry, adenosine-sensitive atrial tachycardia (AT), and idiopathic right ventricular outflow tract tachycardia. CSM can gradually slow a sinus tachycardia without termination and decrease the ventricular response to AT, atrial flutter, and AF without termination, allowing examination of atrial activity. CSM transiently terminates the permanent form of AV junctional reciprocating tachycardia, which then restarts when carotid massage ceases. CSM generally does not affect reentrant ventricular or junctional tachycardias (**Fig. 32.2**).

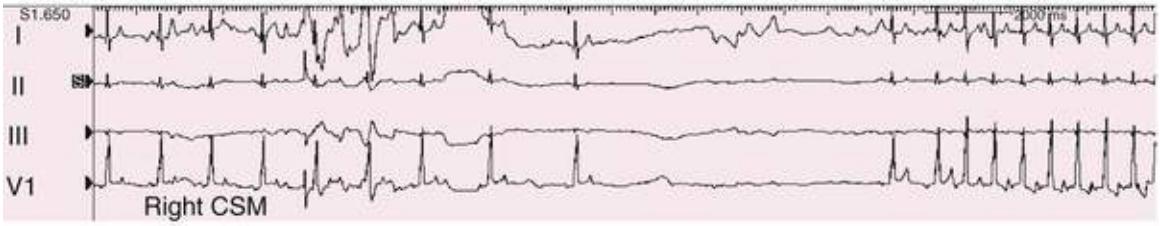


FIGURE 32.2 Right carotid sinus massage (CSM) produces sinus arrest and a 7.2-second pause in a patient with episodic dizziness. (Image courtesy Dr. Joseph Marine.)

Clinical and Laboratory Testing

The history, physical examination, and ECG are of paramount importance in the evaluation of patients with a suspected arrhythmia. A number of other studies, alone or in combination, may assist in the diagnosis and management of patients with cardiac arrhythmias.

Cardiac Imaging

The prognostic implications of a cardiac arrhythmia depend on context, most importantly the presence of structural heart disease. The presence of structural heart disease may be apparent from the history and physical examination, chest radiograph, and ECG itself. Cardiac imaging plays an important role in the detection and characterization of myocardial structural abnormalities that can render the heart more susceptible to arrhythmias. Ventricular tachyarrhythmias, for instance, occur more frequently in patients with ventricular systolic dysfunction and chamber dilation, in HCM, and in the setting of infiltrative diseases such as sarcoidosis. Supraventricular arrhythmias may be associated with particular congenital conditions, including AV reentry in the setting of Ebstein anomaly (**see Chapter 75**). Echocardiography (**see Chapter 14**) is frequently employed to screen for disorders of cardiac structure and function. Increasingly, magnetic resonance imaging (MRI) of the myocardium (**Chapter 17**) is being used to screen for scar burden, fibrofatty infiltration of the myocardium as seen in ARVC, and other structural changes that affect arrhythmia susceptibility. Both contrast-enhanced MRI and ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomographic transmission (^{18}F-FDG PET/CT) have been used in the diagnosis, management, and treatment response of cardiac sarcoidosis[4] (**Fig. 32.3**).

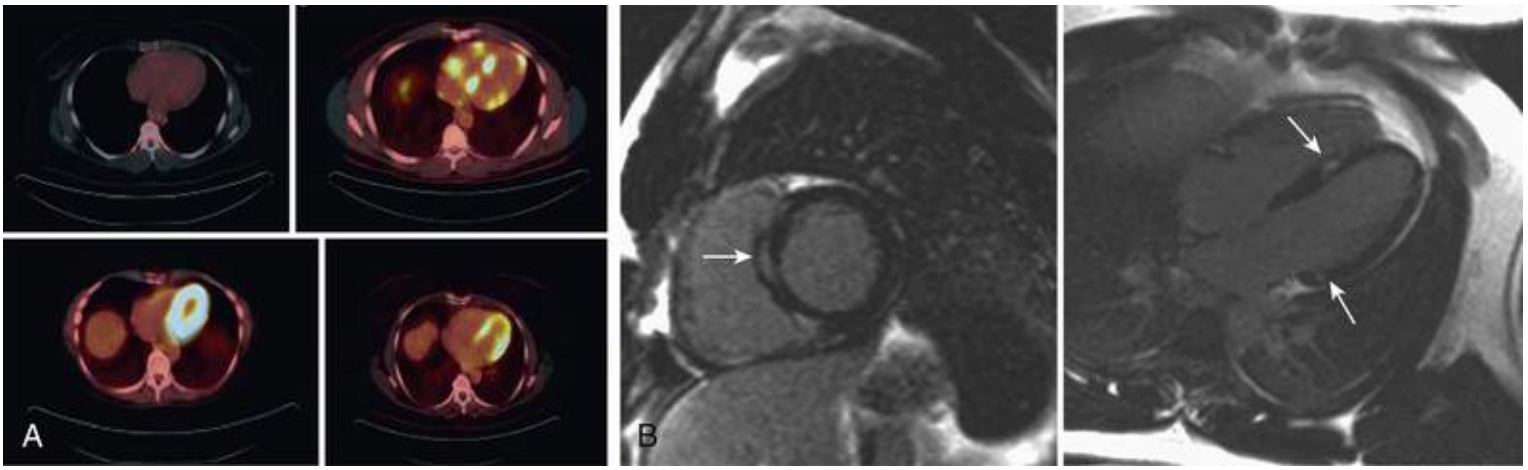


FIGURE 32.3 Sarcoidosis **A,** Four images show the pattern of ^{18}F-fluorodeoxyglucose uptake on positron emission tomography (PET) scan. **B,** Two cardiac magnetic resonance images show evidence of delayed gadolinium enhancement in the midwall of the left ventricle (*arrows*). (Modified from Hamzeh N, Steckman DA, Sauer WH, et al: Pathophysiology and clinical management of cardiac sarcoidosis. Nat Rev Cardiol 2015;12:278.)

Resting Electrocardiographic Recording

The judicious use of noninvasive diagnostic tests is an important element in the evaluation of patients with arrhythmias, and there is no test more important than the ECG (**see Chapter 12**). Uncommon but diagnostically important signatures of electrophysiologic disturbances may be unearthed on the *resting* ECG, such as delta waves in WPW syndrome, prolongation or shortening of the QT interval, right precordial ST-segment abnormalities characteristic of Brugada syndrome (**see Fig. 32.1**), and epsilon waves in ARVD/C.

Signal-averaged electrocardiography (SAECG) uses signal-averaging techniques to amplify small potentials in the body surface ECG that are associated with slow conduction in the myocardium (**see eFig. 35.1**). The presence of these small potentials, referred to as *late potentials* because of their timing with respect to the QRS complex, and prolongation of the filtered (or averaged) QRS duration are indicative of slowed conduction in the ventricle and have been associated with an increased risk of ventricular arrhythmias after MI (**see Chapter 35**).

Holter Monitoring and Event Recording

The fundamental diagnostic principle in managing patients with an undocumented cardiac rhythm disturbance is to record the ECG during a symptomatic episode and establish a causal relation between arrhythmia and symptoms. In patients not suspected of having a life-threatening arrhythmia, Holter monitoring and event recording, continuously or intermittently, record the ECG over longer periods, enhancing the possibility of observing the cardiac rhythm during symptoms (**eTable 32.2**). Continuous ECG recording may also be useful in assessing dynamic changes in ECG segments and intervals. Changes in the ST-T waves may signal the presence of myocardial ischemia and the dynamics of heart rate (HRV) and QT interval (QTv) variability may indicate arrhythmic risk. The type and duration of ECG monitoring depend on the frequency of symptoms. Most continuous recording systems are equipped with patient-triggered recording to enable correlation of the ECG with symptoms (**see Chapter 35**).

ETABLE 32.2

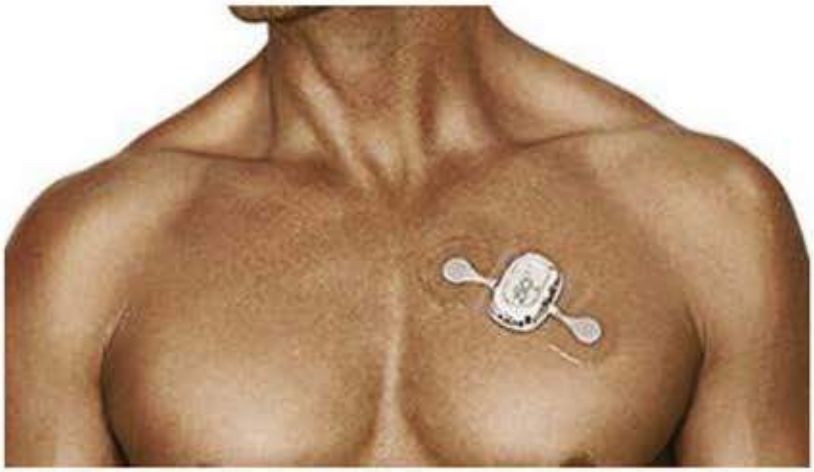
Wireless ECG Recording Systems

DEVICE	COMPANY	URL	DESCRIPTION
Continuous			
eMotion ECG mobile	Mega Electronics	http://www.megaemg.com/products/emotion-ecg/	3-Lead ECG transmitted via a wearable sensor to a mobile phone via Bluetooth; then over a mobile network to a server; data can be monitored in real time or stored and analyzed.
BodyGuardian	Preventice	http://www.preventice.com/	Patch monitor of ECG, activity, respirations, and body position
Zio XT Patch	iRhythm	http://www.irhythmtech.com/?utm_campaign=Listly&utm_medium=list&utmsource=lastly	14-day continuous ECG monitoring with a single adhesive chest wall patch; mailed to iRhythm for analysis
NUVANT Mobile Cardiac Telemetry System	Corventis	http://www.corventis.com/	Automatic and patient-triggered 30-day cardiac rhythm monitoring; transmits information wirelessly to the Corventis Monitoring Center
Ambulatory ECG	iHealth	http://ces.cnet.com/8301-35284_1-57616620/at-ces-2014-health-monitors-join-thewearables-parade/	Sensor attaches to chest and transmits ECG to smartphone
Intermittent			
Alivecor System	Alivecor	http://www.alivecor.com/	Application to skin records, analyzes, and prints ECGs as PDFs; ECG data sync between the application and online ECG hub.
ECG Check	Cardiac Designs	http://cardiacdesigns.com/	Application to skin records, analyzes, and prints ECGs as PDFs; ECG data sync between the application and online ECG hub.
EPI Mini (also EPI Life)	EPI Mobile Health Solutions	http://epimhealth.com.sg/	Device that transmits ECG to smartphone, which can forward it to a "health concierge" service for interpretation
12-Lead ECG	MobilECG	http://mobilecg.hu/	USB-based open-source 12-lead clinical ECG
Implantable			
Reveal LINQ Reveal XT	Medtronic	http://www.medtronicdiagnostics.com/us/cardiac-monitors/reveal-linq/index.htm	LINQ smaller than an AAA battery (1 cc), up to 3 years of monitoring; automated and patient-triggered data storage; magnetic resonance conditional data storage
SJM Confirm	St. Jude Medical	*	6.5 cc, 3 years of monitoring; automated and patient-triggered data storage; magnetic resonance conditional data storage

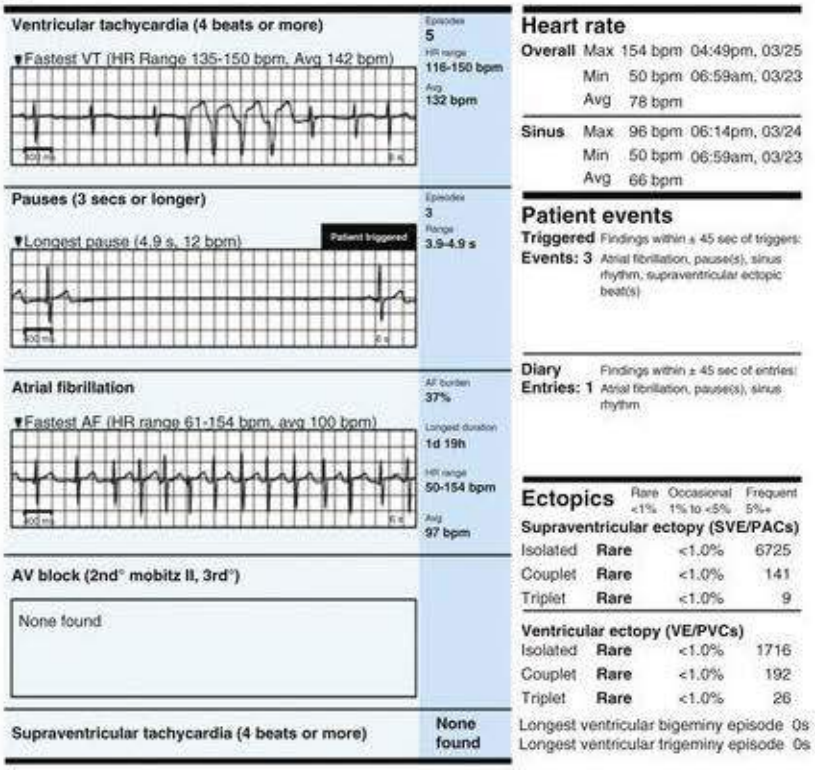
*https://www.sjm.com/en/professionals/featured-products/electrophysiology/recording-and-monitoring/implantable-cardiac-monitor/confirm-af-implantable-cardiac-monitor?alert=DeepLinkSoftAlert&clset=af584191-45c9-4201-8740-5409f4cf8bdd%3ab20716c1-c2a6-4e4c-844b-d0dd6899eb3a.

Modified from American Heart Association; Walsh JA III, Topol EJ, Steinhubl SR. Novel wireless devices for cardiac monitoring. Circulation 2014;130:573-81.

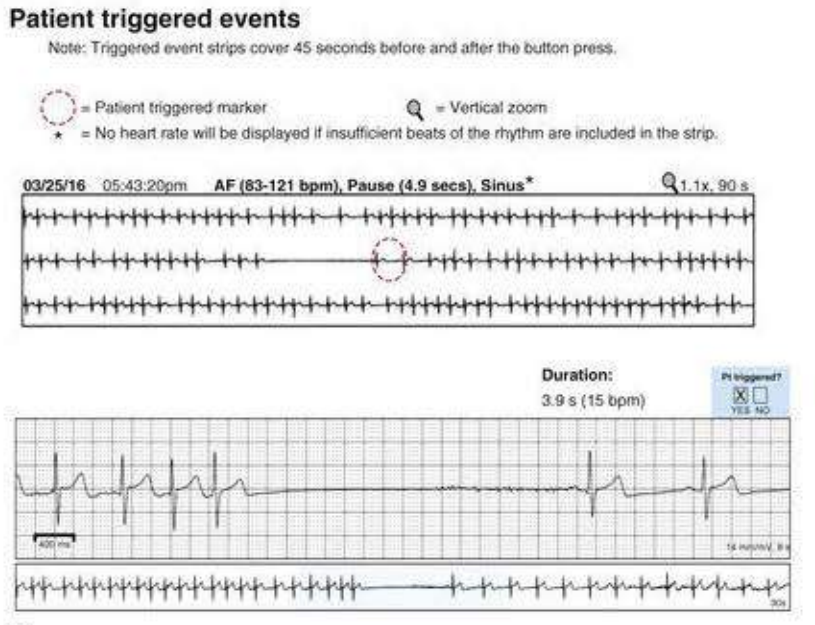
Short-term continuous Holter monitoring may be sufficient to adjudicate daily symptoms related to arrhythmias such as palpitations or presyncope, quantify a particular arrhythmia phenomenon (e.g., PVC burden, AF burden, variation in QT interval, ST-T changes in ischemia or Brugada syndrome), or assess response to therapy. If the arrhythmia does not occur with sufficient frequency, 24-hour, or even 48-hour, recording is not likely to be useful. A longer-term monitoring system is required for arrhythmias that occur less frequently. These systems also record the ECG continuously by chest electrodes attached to a pager-sized sensor. The sensor wirelessly transmits collected data to a portable monitor that analyzes the rhythm data. If an arrhythmia is detected, the monitor automatically transmits recorded data wirelessly via the Internet to a central monitoring station for subsequent analysis. Newer, more compact systems have been developed that contain all the components in a wearable patch (**eFig. 32.1**). Continuous recording systems do not require patient recognition of an arrhythmia but do allow for patient-activated ECG data transmission.



A



B



C

EFIGURE 32.1 **A,** Adhesive electrocardiographic patch that allows for long-term continuous recording of the ECG. **B,** Summary page illustrating three patient-triggered events: wide-complex rhythm during atrial

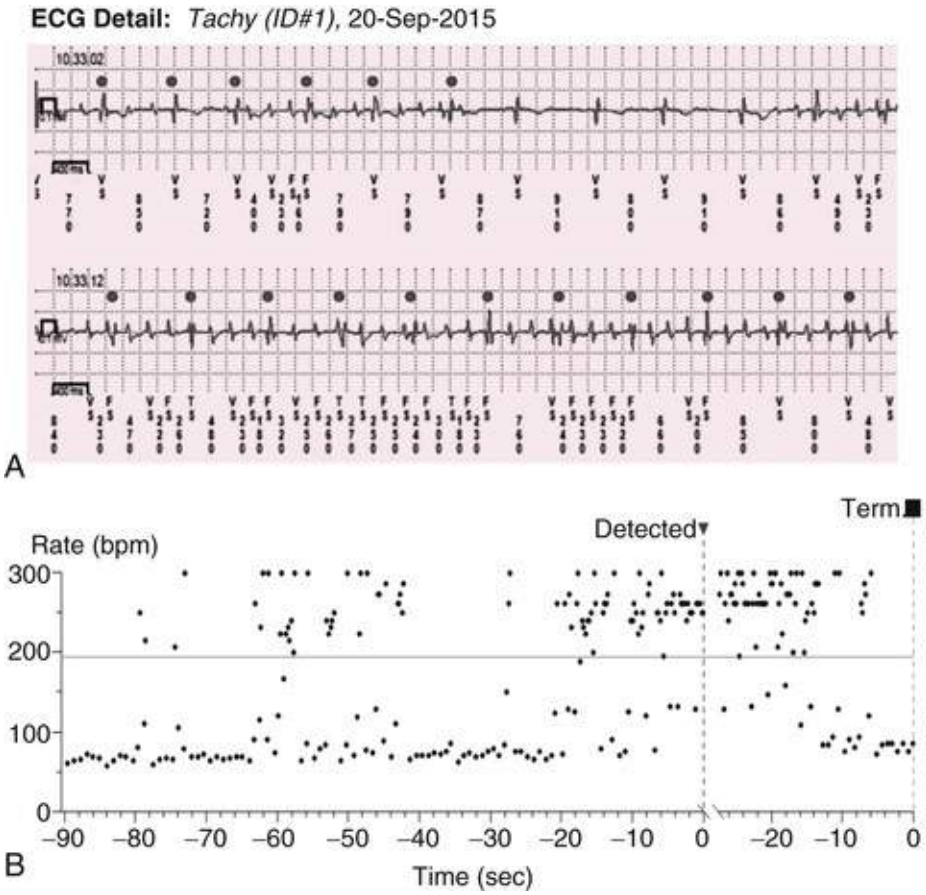
fibrillation (AF), a 4.9-second pause with termination of a paroxysm of AF, and AF with rapid ventricular response. **C,** Greater detail of the pauses; both are patient-triggered events. (**A,** From iRhythm Technologies, San Francisco.)

Event recorders are indicated when symptoms occur less frequently (e.g., several episodes per month), and because the monitors are typically patient-activated, are well-suited for correlating symptoms with rhythm disturbances. Event recorders can be continuous with auto-triggered or patient-activated recording. Discontinuous transtelephonic monitoring systems without looping memory require patient activation (**see Chapter 35**).

Mobile technology is ubiquitous, and anyone who has a smartphone or tablet carries an easily configured ECG monitoring system. Applications are available for real-time ECG monitoring in both iPhones and Android phones. These phones and tablets may use electrical recording systems or camera-based plethysmography to assess the cardiac rhythm and are accurate and easy to use. They are useful for on-demand arrhythmia diagnosis and monitoring arrhythmia burden and are being used as a phenotyping platform in population studies[5] (**eFig. 32.2**).

EFIGURE 32.2 Real-time monitoring of the ECG. Finger contact with electrodes on the case of a cellular phone (right) activates ECG recording of bipolar lead I and is transmitted to the smartphone (left). (From AliveCor, Mountain View, Calif.)

Implantable monitors or *implantable loop recorders* (ILRs) are typically used for the evaluation of suspected serious arrhythmias that occur infrequently and cannot be provoked at diagnostic electrophysiologic study. An ILR, a single-lead ECG monitoring device placed subcutaneously, monitors the cardiac rhythm for as long as 24 to 36 months. These devices have both auto-triggered and patient-activated arrhythmia-recording capabilities (**eFig. 32.3**). Use of such devices has been successful in recording tachyarrhythmias and, more often, bradyarrhythmias. ECG recordings can be sent to an analyzing center transtelephonically and then to physicians via the Internet. Interrogation of ILRs can also be performed remotely over a landline telephone. ILRs have primarily been used in the evaluation of syncope, but their use is increasing in monitoring arrhythmia density, especially AF. Technological advances have resulted in further reduction in size and ease of implantation of ILRs, with the likely increase in clinical deployment of these devices.[6]



EFIGURE 32.3 Implantable loop recorders (ILRs) are implanted subcutaneously and can continuously record a single-lead ECG for up to 36 months. The smallest ILRs are 45 × 7 × 4 mm, the length and width of a paper clip. **A,** Rhythms recorded by an ILR and interrogated remotely by landline telephone in a patient with Parkinson disease. Artifact from the movement disorder is interpreted as tachycardia; the *dots* identify the QRS complexes. **B,** A time series plot of the detected rates at the time of the artifact.

Dual-chamber pacemakers can record atrial and ventricular high-rate episodes and can be correlated with the arrhythmia (**see Chapter 41**). Apart from detecting and treating ventricular arrhythmias, a dual-chamber ICD also helps in identifying cycle length, duration, and frequency of atrial arrhythmias. Remote monitoring facilitates arrhythmia diagnosis in patients with implanted pacemakers and ICDs.

Stress Electrocardiography

Exercise electrocardiographic stress testing may be particularly useful in the evaluation of patients who experience symptoms with exertion (**see Chapter 13**). Exercise stress testing is important in determining the presence of myocardial demand ischemia and other arrhythmic substrates, such as alterations in repolarization and the dynamic behavior of the QT interval (**see Chapter 33**). Microscopic alterations in the T wave (T wave alternans; **see Chapter 35**) at low heart rates may identify patients at risk for ventricular arrhythmias. Altered heart rate recovery may indicate autonomic dysfunction associated with heightened arrhythmic risk.

It is important to recognize that not all arrhythmias induced by exercise have an ominous prognosis. Approximately one third of individuals without heart disease will have ventricular ectopy associated with exercise. Typically, this manifests as occasional uniform PVCs, more likely to occur at faster heart rates and not reproducible from one test to the next. Multiform PVCs, pairs of PVCs, and VT are an infrequent response to exercise in healthy individuals; thus the development of more complex ventricular arrhythmias during exercise testing should prompt a search for underlying structural heart disease.[7,8]

Ventricular ectopy occurs in about half of patients with CAD, generally appearing more reproducibility

and at lower heart rates (<130 beats/min) than healthy individuals and often in the early recovery period. Frequent PVCs (>10 per minute), polymorphic PVCs, and VT are more likely to occur in patients with CAD. PVCs at rest can be suppressed by exercise in patients with CAD; therefore this observation does not necessarily imply a benign prognosis or absence of underlying structural heart disease.

Exercise testing also has diagnostic or prognostic value in patients with primary electrical abnormalities such as LQTS, CPVT, and Brugada syndrome (**see Chapter 33**). Since the QT interval can be normal in up to one quarter of patients with genetically proven LQTS, exercise testing can stress repolarizing reserve and can be useful to expose ECG abnormalities in these patients. An abnormal response of the QT interval to the heart rate acceleration produced by standing is seen in patients with LQTS compared with normal patients. Exercise testing can unmask polymorphic PVCs and VT in CPVT patients (**Fig. 32.4**). In patients with Brugada syndrome, significant ST-segment elevation with coving of the ST segment during recovery phase predicts arrhythmic events during follow-up.[9,10]

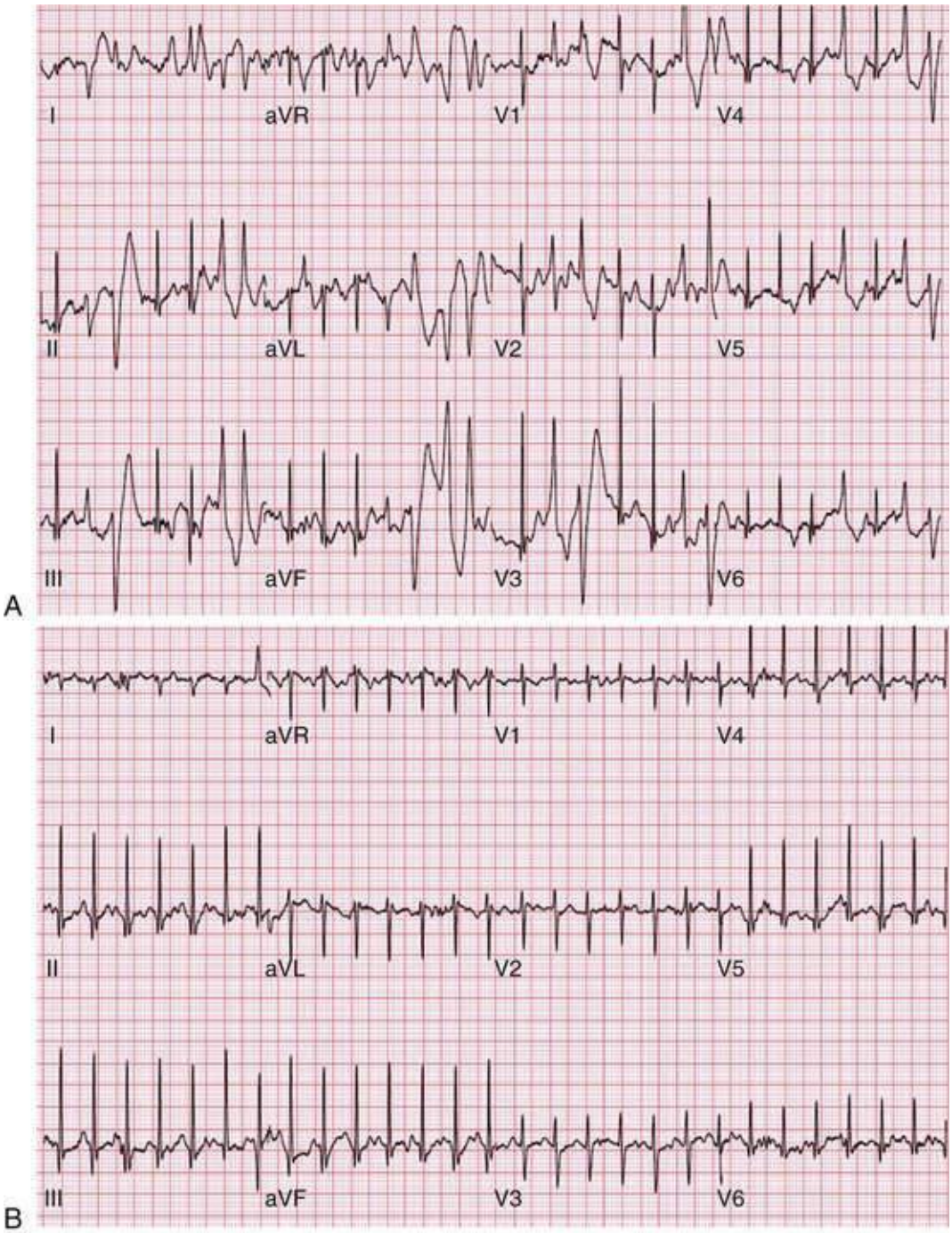


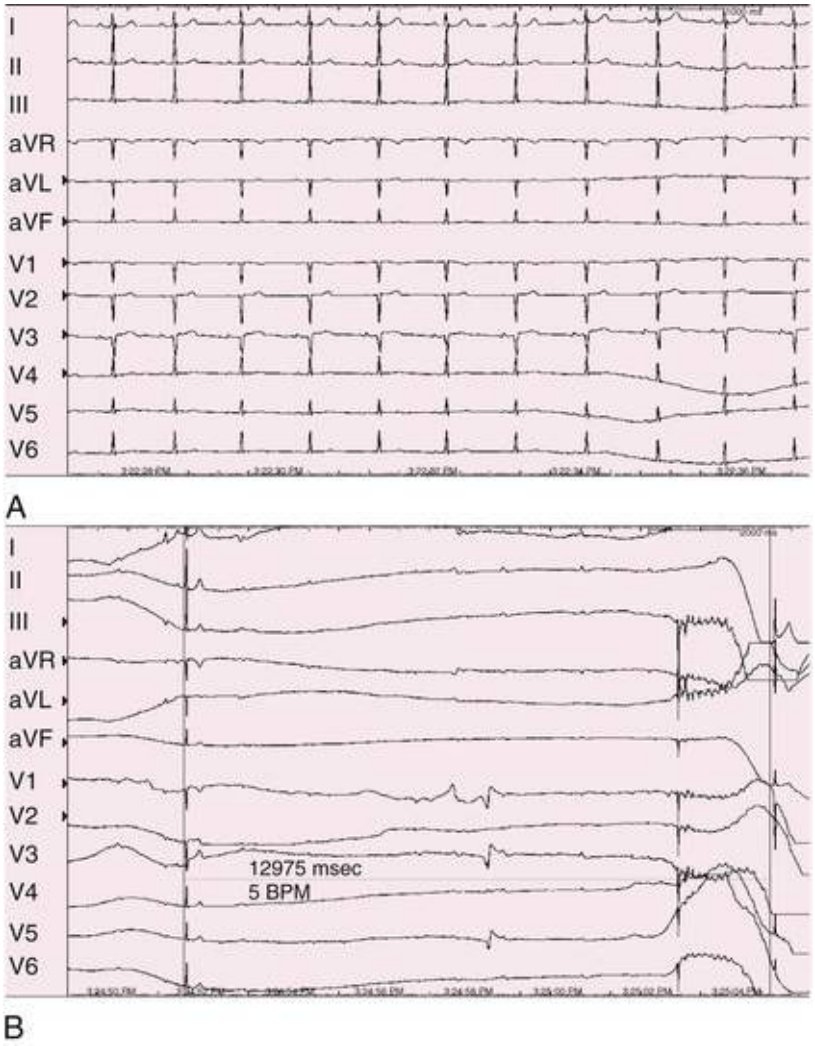
FIGURE 32.4 Exercise-induced polymorphic premature ventricular complexes (PVCs) and ventricular tachycardia (VT) in a young woman with presyncope; palpitations caused by a ryanodine receptor (RyR2) mutation producing catecholaminergic polymorphic VT. **A,** ECG at peak exercise before treatment. **B,** ECG while receiving treatment with nadolol and flecainide.

Head-Up Tilt-Table Testing

Tilt-table testing (TTT) is useful in the evaluation of patients with syncope in whom there is a suspicion that exaggerated vagal tone producing cardioinhibitory and/or vasodepressor responses may play a causal role. The physiologic response to TTT is incompletely understood; however, redistribution of blood volume and increased ventricular contractility occur consistently. Exaggerated activation of a central reflex in response to TTT produces a stereotypic response of an initial increase in heart rate, followed by drop in blood pressure and then a reduction in heart rate characteristic of neutrally mediated hypotension. Varied responses to TTT can be observed in which either cardioinhibitory or vasodepressor responses predominate. In patients with orthostatic hypotension and autonomic insufficiency, blood pressure will

drop with only a minimal increase in heart rate. *Postural orthostatic tachycardia syndrome* (POTS) is a variant of neurocardiogenic intolerance characterized by the inability to tolerate the upright posture and a dramatic increase (>30 beats/min) in heart rate (>120 beats/min) within 10 minutes of assuming an upright posture. A wide array of symptoms complicates the diagnosis of POTS, which is often confused with anxiety disorder, inappropriate sinus tachycardia, chronic fatigue syndrome, and fibromyalgia.[11] Data from an international registry suggest that endurance- and strength-training programs may be useful in managing POTS.[12]

TTT is used most often in patients with recurrent syncope, although it may be useful in patients with a single syncopal episode with associated injury, particularly in the absence of structural heart disease (**eFig. 32.4**). In patients with structural heart disease, TTT may be indicated in those with syncope in whom other causes (e.g., asystole, tachyarrhythmias) have been excluded. TTT has been suggested as a useful tool in the diagnosis of and therapy for recurrent idiopathic vertigo, chronic fatigue syndrome, recurrent transient ischemic attacks, and repeated falls of unknown etiology in elderly patients (**see Chapter 35**). Importantly, TTT is relatively contraindicated in the presence of severe CAD with proximal coronary stenoses, known severe cerebrovascular disease, severe mitral stenosis, and obstruction to left ventricular outflow (e.g., aortic stenosis).



EFIGURE 32.4 Head-up tilt-table response in a patient with syncope in the absence of structural heart disease. **A,** 12-Lead ECG immediately before syncope. **B,** Sinus bradycardia and atrioventricular block produce hypotension and syncope 15 minutes after head-up tilt-table test. (Images courtesy Dr. Joseph Marine.)

Invasive Electrophysiologic Testing

The electrophysiologic study (EPS) is central to the understanding and treatment of many cardiac arrhythmias (**see Chapter 35**). The indications for EPS fall into several broad categories: to define the mechanism of an arrhythmia, to deliver catheter-based ablative treatment, and to determine the etiology of symptoms that may be caused by an arrhythmia (e.g., syncope, palpitations). An EPS is performed by introducing a number of multipolar electrode catheters into specific regions of the heart. Positioning of these catheters is guided by complementary imaging modalities, including fluoroscopy, intracardiac echocardiography (ICE), and electroanatomic mapping (EAM), often using MRI and CT to merge cardiac images with the EAM information.

The components of the EPS are baseline measurements of conduction under resting and stressed (rate or pharmacologic) conditions and maneuvers, both pacing and pharmacologic, to induce arrhythmias. A number of electrical mapping and catheter-guidance techniques have been developed to facilitate catheter-based therapeutics in the electrophysiology laboratory. EPS is most effective in the evaluation and management of SVTs and VTs that have occurred spontaneously and can be induced in the laboratory. However, a number of conditions present during EPS (e.g., sedation, differences in autonomic tone or hemodynamics, ischemia) may prevent the induction of a clinically relevant arrhythmia. Failure to induce an arrhythmia does not exclude the possibility that it is present clinically and is responsible for the patient's symptoms.

Ideally, the EPS would induce a clinical and prognostically important arrhythmia in only patients who are at risk for a spontaneous arrhythmia. Unfortunately, this is not the case, and depending on the aggressiveness (e.g., number and coupling interval of extra stimuli) of programmed electrical stimulation nonspecific tachyarrhythmias, in particular flutter and fibrillation in both atria and ventricles, are typically induced.

Approach to Specific Symptoms/Conditions

SCA Survivors, SCD Risk

In patients who have survived and recovered from SCA that is not associated with acute transmural MI, or who are deemed to be at risk for arrhythmic SCD, should undergo an evaluation with the goal of defining a susceptible myocardial substrate and arrhythmic triggers (**see Chapter 42**). The approach to primary or secondary prevention of SCD is defined by the presence of underlying structural heart disease and the reversibility of the initiating events. The history and physical examination as well as structural and functional imaging of the heart are essential. Significant CAD may require revascularization in addition to specific antiarrhythmic therapies that may include drugs, devices, or surgery. Other structural abnormalities of the heart associated with SCA may require directed therapy to improve function (DCM, HCM) or reduce inflammation (e.g., myocarditis, sarcoidosis) but generally mandate ICD placement because of the high risk of recurrence of SCA.

Survivors of SCA who have structurally normal hearts often require defibrillator implantation because of the unpredictability of their clinical course. Often, these ICDs can be completely extravascular (S-ICD) (**see Chapter 41**). SCA deemed to result from AF in the presence of ventricular preexcitation in WPW syndrome can be managed with catheter ablation of the accessory pathway alone.

Patients with heritable arrhythmia syndromes (LQTS, SQTS, CPVT, ARVD, Brugada syndrome) who survive SCA should have an ICD placed. However, the proper management of patients with these

conditions and no history of SCA continues to evolve (**see Chapter 33**). In many cases, pharmacotherapy such as beta blockers in CPVT or LQTS types 1 and 2, and in some patients lifestyle modifications alone, may be sufficient.

Syncope (see Chapter 43)

The majority of patients with syncope have a noncardiac cause, with more than one third having neurocardiogenic syncope and up to one fourth with orthostatic hypotension.[13] A key challenge for the physician is identifying patients with potentially lethal causes of syncope. Initial evaluation includes careful history taking and ECG. If a cardiac cause is suspected, echocardiography and ambulatory ECG monitoring is indicated. EPS can occasionally define the mechanism of syncope (**see Chapter 35**). Evaluation of patients suspected of neurocardiogenic causes often includes TTT. Patients who have syncope from a noncardiac cause usually have an excellent prognosis, whereas those who have syncope from a cardiac cause have a greater risk of SCD. Although it is important to establish the cause and risk-stratify patients with syncope, currently available tools are not sufficiently discriminating.[2]

Bradyarrhythmias (see Chapter 40)

Resting and ambulatory ECG recording is a cornerstone in the management of patients with bradyarrhythmias. Many patients have asymptomatic bradyarrhythmias; in most circumstances it is important to establish that the bradycardia produces symptoms before assuming that therapy is required. Patients that present with a symptomatic bradyarrhythmia may require no further diagnostic testing. Certain electrocardiographic and electrophysiologic findings may define therapeutic decisions in patients without symptoms. For example, in patients who have type II second-degree AV block, the demonstration of His-Purkinje block, even in the absence of symptoms, may be sufficient to justify pacemaker implantation because of the risk for progression to complete AV block. It is important to keep in mind that asymptomatic sinus bradycardia in patients with heart rates of 35 to 40 beats/min, sinus arrhythmia with pauses of 2 to 3 seconds, Wenckebach second-degree AV block (particularly during sleep), wandering atrial pacemaker, and junctional escape complexes can be completely normal, especially in young people and in well-conditioned athletes.

EPS is indicated when a causal relation between the appearance of the bradycardia and the patient's symptoms cannot be established or to exclude a tachyarrhythmia as the cause of symptoms. In patients with AV block the site of block, which often dictates the clinical course and the need for pacemaking, can usually be determined from analysis of the ECG. Exercise, atropine, or isoproterenol can shorten the PR interval and increase the ratio of conducted P waves during type I (Wenckebach) AV nodal block, whereas these maneuvers can increase the number of blocked P waves in type II second-degree AV block, and thus may help to define the level of AV block, prognosis, and management.

Tachyarrhythmias (see Chapters 37-39)

A 12-lead ECG recording during tachycardia is invaluable. A QRS morphology that is identical to that present during sinus rhythm, even if abnormal, suggests that the tachycardia is supraventricular. Wide-complex tachycardias without a typical right or left bundle branch block configuration of the QRS, particularly if different from the QRS in sinus rhythm, and especially in patients with a history of MI, are almost always VT (**see Chapter 39**).

Supraventricular tachycardias can be classified based on the temporal relationship of the P wave and R wave. When a P wave occurs closer to the preceding R wave (i.e., in the first half of the R-R interval), the tachycardia is called a *short* RP′ tachycardia, whereas if a P wave occurs in the second half of the RR cycle, the arrhythmia is called a *long* RP′ tachycardia. The differential diagnosis of a short RP′ tachycardia includes AVNRT, AVRT, junctional tachycardia, and AT with a markedly prolonged PR interval. If no P waves or other evidence of atrial activity are apparent, and the R-R interval is regular, AVNRT is the most likely cause. If a retrograde P wave is apparent in the ST segment, AVRT is most likely. Long RP′ tachycardias include sinus tachycardia, atypical AVNRT, permanent junctional reciprocating tachycardia, and AT. Regardless of the RP′ interval, the P waves of sinus and atrial tachycardias do not exhibit consistent coupling with the preceding R wave. The presence of conduction over an accessory pathway during sinus rhythm or during tachycardia suggests that WPW syndrome with its associated accessory pathway is responsible for the arrhythmia.

Evaluation and Management of Athletes with Arrhythmias

Highly trained athletes often exhibit remodeling of the heart. *Cardiomegaly* is an adaptation to generate the sustained increase in cardiac output required for regular high-intensity exercise. Endurance training such as long-distance running or cycling produces a sustained volume load to the heart, resulting in four-chamber enlargement and increased stroke volume at rest and exercise. Strength training such as weightlifting presents a pressure load to the heart that may be accompanied by a concentric increase in left ventricular (LV) wall thickness. Some sports, such as basketball, present a combination of both types of loads. At times the physiologic increases in heart size may be difficult to distinguish from early manifestations of cardiomyopathy.[14] The ECG will often reflect this structural remodeling and may reveal left ventricular hypertrophy (LVH, approximately 40% of athletes), T wave inversion in precordial leads V_1 to V_4 (14% of African American athletes), QT prolongation, frequent PVCs, and sinus bradycardia as well as various degree of AV block due to increased vagal tone. These ECG changes can mimic ARVD/C, Brugada syndrome, or LQTS and may confound diagnostic decisions in athletes.

Arrhythmias occur with increased frequency in competitive athletes. The most devastating is arrhythmic SCD/SCA. The most common medical cause of death in a study of National Collegiate Athletic Association (NCAA) athletes was SCD (1 in 53,703 athlete-years), with autopsy-negative SCD the most common.[15] Similarly, a national registry of the use of automated external defibrillators (AEDs) in high schools with 4.1 million student-years of follow up demonstrated a SCA rate of 1.14/100,000 in student-athletes, about a 3.65-fold increased risk compared to nonathletes.[16]

In some cases, intense exercise can trigger arrhythmogenic SCD in an athlete with occult cardiac disease. Risk assessment for serious arrhythmias or SCD during athletic activity is challenging, and the proper pre-participation evaluation continues to be debated. A particular controversy concerns the routine use of 12-lead ECG screening.[17] Several countries, such as Italy and Israel, have mandated ECG-based screening, whereas others, such as Denmark, have rejected this approach, citing extremely low event rates. The elements that are generally agreed on are a comprehensive understanding of the athletic endeavor and the role of the athlete. Guidelines from the American Heart Association (AHA) and American College of Cardiology (ACC) advocate the use of a 14-point preparticipation history and physical examination acknowledging that athletes with underlying CV disease may manifest warning signs and symptoms elicited by a careful history and physical examination.[18] The 14-point evaluation includes elements of the personal history: chest discomfort, unexplained syncope or near-syncope, excessive and unexplained fatigue/dyspnea or palpitations with exercise, prior recognition of a heart murmur, elevated

blood pressure, prior restriction from sport, or prior cardiac testing ordered by a physician. Components of the family history include premature sudden and unexpected death in a family member less than 50 years old, disability from heart disease in a family member less than 50 years old, and family history of a heritable heart disease, cardiomyopathy, or primary electrical disease. The elements of the physical examination in the evaluation include heart murmurs, evaluation of the femoral pulses, the presence of stigmata of Marfan syndrome, and brachial blood pressure measurement.[17] Any of these findings should trigger a referral for further evaluation. A number of ECG findings in athletes should also prompt further evaluation. These include significant bradycardia, pauses, AV and intraventricular conduction system disease, SVT, and VT[19] (**eTable 32.3**).

ETABLE 32.3

Indications for Referral or Workup of Arrhythmias in Athletes

ARRHYTHMIA	INDICATION
Severe sinus bradycardia	Heart rate ≤30 beats/min, *or* Bradycardia sinus pause >3 seconds while awake, *or* Signs/symptoms of sinus node disease
First-degree AV block	Does not resolve with hyperventilation or exercise, *or* Cardiac symptoms, *or* Family/personal history suggestive of heart disease, *or* Physical examination indicative of heart disease
Second-degree type I AV block	Does not resolve with hyperventilation or exercise, *or* Cardiac symptoms, *or* Family/personal history suggestive of heart disease, *or* Physical examination indicative of heart disease
Second-degree type II AV block	All cases
Third-degree AV block	All cases
Incomplete RBBB	Cardiac symptoms, *or* Family/personal history suggestive of heart disease, *or* Physical examination indicative of heart disease
Complete RBBB	All cases
LBBB	All cases
LVH by voltage criteria	ECG markers of pathologic LVH, *or* Cardiac symptoms, *or* Family/personal history suggestive of heart disease, *or* Physical examination indicative of heart disease
Repolarization abnormalities	Early repolarization in inferior and/or lateral leads, *or* Cardiac symptoms, *or* Family/personal history suggestive of heart disease, *or* Physical examination indicative of heart disease
Atrial fibrillation	All cases
Atrial flutter	All cases
AVRT/AVNRT	All cases
WPW	All cases
Premature ventricular complexes (PVCs)	2 or more PVCs on screening ECG, *or* Increased PVC frequency during exercise, *or* Cardiac symptoms, *or* Family/personal history suggestive of heart disease, *or* Physical examination indicative of heart disease

AV, Atrioventricular; *AVRT,* AV reentrant (reciprocating) tachycardia; *AVNRT,* AV nodal reentrant (reciprocating) tachycardia; *LBBB,* left bundle branch block; *LVH,* left ventricular hypertrophy; *RBBB,* right bundle branch block; *WPW,* Wolff-Parkinson-White syndrome.

From McClaskey D, Lee D, Buch E. Outcomes among athletes with arrhythmias and electrocardiographic abnormalities: Implications for ECG interpretation. Sports Med 2013;43:979.

Other recommendations included standardization of questionnaires for examiners of athletes and potential athletes and utilization of electrocardiography and other noninvasive testing in the context of a history and physical examination suggestive of underlying cardiac disease, but not universal screening.[18] Recommendations regarding sports participation in individuals with established cardiac disease are specific to those diseases and are covered in other chapters.

Physical activity in patients with ICDs is often a question. Recent registry data suggest that patients

with ICDs can safely participate in some athletic activities without the development of inappropriate or appropriate shocks, personal injury, or failed-device therapies. With some restrictions on the type of activity, physical activity and sports are safe for defibrillator patients.[20]

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33

Genetics of Cardiac Arrhythmias

David J. Tester, Michael J. Ackerman

Potentially lethal and inheritable arrhythmia syndromes involve electrical disturbances with the propensity to produce fatal arrhythmias in the setting of a structurally normal heart. Collectively called the “cardiac channelopathies,” these often-unassuming electrical abnormalities have the capacity to cause the heart of an unsuspecting individual to develop a potentially lethal arrhythmia, leading to the sudden and early demise of an otherwise healthy individual. In fact, it is now recognized that almost one third of autopsy-negative sudden unexplained death (SUD) in young persons and approximately 10% of sudden infant death syndrome (SIDS) stem from these genetically inherited cardiac channelopathies.[1]

Molecular advances in the field of cardiovascular genetics have uncovered the underlying genetic basis responsible for many inherited cardiac arrhythmia syndromes, and for others, their underlying genetic substrates are on the cusp of discovery. Over the past decade a particular set of themes, including extreme genetic heterogeneity, reduced or incomplete penetrance, and variable expressivity, have proved to be common among the cardiac channelopathies. For some disorders, however, important genotype-phenotype correlates have been recognized and have provided diagnostic, prognostic, and therapeutic impact.

Given the potentially devastating impact that these genetic disorders can have on families and their communities, this chapter provides the clinical description, genetic basis, and genotype-phenotype correlates associated with these inherited arrhythmia syndromes. Specifically, we focus first on the subset of "QT-opathies"—long QT syndrome (including calmodulin mediated), triad in knockout syndrome, Andersen-Tawil syndrome, Timothy syndrome (TS), cardiac-only Timothy syndrome, short-QT syndrome, and drug-induced torsade de pointes—and then discuss the other channelopathies, including Brugada syndrome, early repolarization syndrome, idiopathic ventricular fibrillation, progressive cardiac conduction disease, sick sinus syndrome, catecholaminergic polymorphic ventricular tachycardia, "ankyrin-B syndrome," and familial atrial fibrillation.

The QT-Opathies

Long-QT Syndrome

Clinical Description and Manifestations

Congenital long-QT syndrome (LQTS) comprises a distinct group of cardiac channelopathies characterized by delayed repolarization of the myocardium, QT prolongation (QTc >480 msec as the 50th percentile among individuals with genetically confirmed LQTS), and increased risk for syncope, seizures, and sudden cardiac death (SCD) in the setting of a structurally normal heart and otherwise healthy individual. The incidence of LQTS may exceed 1 in 2500 persons.[2] Individuals with LQTS may or may not manifest QT prolongation on a resting 12-lead surface electrocardiogram (ECG). This repolarization abnormality almost always is without consequence; rarely, however, triggers such as exertion, swimming, emotion, auditory stimuli (e.g., alarm clock), or during the postpartum period, can cause the heart to become electrically unstable and develop potentially life-threatening and sometimes lethal arrhythmia of torsade de pointes (**see Chapter 39**). Although the cardiac rhythm most often spontaneously returns to normal, resulting in only a transient episode of syncope, 5% of untreated and unsuspecting LQTS individuals succumb to a fatal arrhythmia as their sentinel event. However, it is estimated that almost half of individuals experiencing SCD, stemming from this treatable arrhythmogenic disorder, may have exhibited prior warning signs (i.e., exertional syncope, family history of premature sudden death) that went unrecognized. LQTS may explain approximately 20% of autopsy-negative SUD in young persons and 10% of SIDS cases.[1]

Genetic Basis.

LQTS is a genetically heterogeneous disorder largely inherited in an autosomal dominant pattern, previously known as "Romano-Ward syndrome." Rarely, LQTS is inherited as the recessive trait first described by Jervell and Lange-Nielsen and is characterized by a severe cardiac phenotype and sensorineural hearing loss. Spontaneous or sporadic germline mutations can account for approximately

5% to 10% of LQTS cases. To date, hundreds of mutations have now been identified in 14 LQTS susceptibility genes responsible for a nonsyndromic "classic" LQTS phenotype. In addition, two extremely rare, multisystem disorders associated with marked QT prolongation (Timothy syndrome, formerly annotated as LQT8) and prolonged QU intervals (Anderson-Tawil syndrome, formerly annotated as LQT7), as well as LQT4, which is better classified as "ankyrin-B syndrome," have also been described.

Approximately 75% of patients with a clinically robust diagnosis of LQTS host either loss-of-function or gain-of-function mutations in one of three major LQTS genes (**Table 33.1**): *KCNQ1*-encoded I_{Ks} ($K_v7.1$) potassium channel (LQT1, approximately 35%; loss of function), *KCNH2*-encoded I_{Kr} ($K_v11.1$) potassium channel (LQT2, 30%; loss of function), and *SCN5A*-encoded I_{Na} ($Na_v1.5$) sodium channel (LQT3, 10%; gain of function). These genes are responsible for the orchestration of the cardiac action potential (**Fig. 33.1**). Approximately 5% to 10% of patients have multiple mutations in these genes, and patients with multimutation LQTS present at a younger age and with greater expressivity.[1]

TABLE 33.1

Summary of Heritable Arrhythmia Syndrome Susceptibility Genes

GENE	LOCUS	PROTEIN
Long-QT Syndrome (LQTS)		
Major LQTS Genes		
KCNQ1 (LQT1)	11p15.5	I_{Ks} potassium channel alpha subunit (KVLQT1, $K_v7.1$)
KCNH2 (LQT2)	7q35-36	I_{Kr} potassium channel alpha subunit (HERG, $K_v11.1$)
SCN5A (LQT3)	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
Minor LQTS Genes (listed alphabetically)		
AKAP9	7q21-q22	Yotiao
CACNA1C	12p13.3	Voltage-gated L-type calcium channel ($Ca_v1.2$)
CALM1	14q32.11	Calmodulin 1
CALM2	2p21	Calmodulin 2
CALM3	19q13.2-q13.3	Calmodulin 3
CAV3	3p25	Caveolin-3
KCNE1	21q22.1	Potassium channel beta subunit (MinK)
KCNE2	21q22.1	Potassium channel beta subunit (MiRP1)
KCNJ5	11q24.3	Kir3.4 subunit of I_{KACH} channel
SCN4B	11q23.3	Sodium channel $beta_4$ subunit
SNTA1	20q11.2	Syntrophin-$alpha_1$
Triadin Knockout (TKO) Syndrome		
TRDN	6q22.31	Cardiac triadin
Andersen-Tawil Syndrome (ATS)		
KCNJ2 (ATS1)	17q23	I_{K1} potassium channel (Kir2.1)
Timothy Syndrome (TS)		
CACNA1C	12p13.3	Voltage-gated L-type calcium channel ($Ca_v1.2$)
Cardiac Only Timothy Syndrome (COTS)		
CACNA1C	12p13.3	Voltage-gated L-type calcium channel ($Ca_v1.2$)
Short-QT Syndrome (SQTS)		
KCNH2 (SQT1)	7q35-36	I_{Kr} potassium channel alpha subunit (HERG, $K_v11.1$)
KCNQ1(SQT2)	11p15.5	I_{Ks} potassium channel alpha subunit (KVLQT1, $K_v7.1$)
KCNJ2 (SQT3)	17q23	I_{K1} potassium channel (Kir2.1)
CACNA1C (SQT4)	12p13.3	Voltage-gated L-type calcium channel ($Ca_v1.2$)
CACNB2 (SQT5)	10p12	Voltage-gated L-type calcium channel $beta_2$ subunit
CACN2D1 (SQT6)	7q21-q22	Voltage-gated L-type calcium channel 2 $delta_1$ subunit
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)		
RYR2 (CPVT1)	1q42.1-q43	Ryanodine receptor 2
CASQ2 (CPVT2)	1p13.3	Calsequestrin 2
KCNJ2 (CPVT3)	17q23	I_{K1} potassium channel (Kir2.1)
CALM1	14q32.11	Calmodulin 1
CALM3	19q13.2-q13.3	Calmodulin 3
TRDN	6q22.31	Cardiac triadin
Brugada Syndrome (BrS)		
SCN5A (BrS1)	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
Minor BrS Genes (listed alphabetically)		
ABCC9	12p12.1	ATP-binding cassette, subfamily C member 9

CACNA1C	2p13.3	Voltage-gated L-type calcium channel ($Ca_v1.2$)
CACNA2D1	7q21-q22	Voltage-gated L-type calcium channel 2 $delta_1$ subunit
CACNB2	10p12	Voltage-gated L-type calcium channel $beta_2$ subunit
FGF12	3q28	Fibroblast growth factor 12
GPD1L	3p22.3	Glycerol-3-phosphate dehydrogenase 1–like
KCND3	1p13.2	Voltage-gated potassium channel (I_{to}) subunit $K_v4.3$
KCNE3	11q13.4	Potassium channel $beta_3$ subunit (MiRP2)
KCNJ8	12p12.1	Inward rectifier K^+ channel Kir6.1
HEY2	6q	Hes-related family BHLH transcription factor with YRPW motif 2
PKP2	12p11	Plakophilin-2
RANGRF	17p13.1	RAN guanine nucleotide release factor 1
SCN1B	19q13	Sodium channel $beta_1$
SCN2B	11q23	Sodium channel $beta_2$
SCN3B	11q24.1	Sodium channel $beta_3$
SCN10A	3p22.2	Sodium voltage-gated channel $alpha_{10}$ subunit ($Na_v1.8$)
SLMAP	3p14.3	Sarcolemma associated protein
Early Repolarization Syndrome (ERS)		
ABCC9	12p12.1	ATP-binding cassette, subfamily C member 9
CACNA1C	2p13.3	Voltage-gated L-type calcium channel ($Ca_v1.2$)
CACNA2D1	7q21-q22	Voltage-gated L-type calcium channel 2 $delta_1$ subunit
CACNB2	10p12	Voltage-gated L-type calcium channel $beta_2$ subunit
KCNJ8	12p12.1	Inward rectifier K^+ channel Kir6.1
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
SCN10A	3p22.2	Sodium voltage-gated channel $alpha_{10}$ subunit ($Na_v1.8$)
Idiopathic Ventricular Fibrillation (IVF)		
ANK2	4q25-q27	Ankyrin B
CALM1	14q32.11	Calmodulin 1
DPP6	7q36	Dipeptidyl-peptidase-6
KCNJ8	12p12.1	Inward rectifier K^+ channel Kir6.1
RYR2	1q42.1-q43	Ryanodine receptor 2
SCN3B	11q23	Sodium channel $beta_3$ subunit
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
Progressive Cardiac Conduction Disease/Defect (PCCD)		
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
TRPM4	19q13.33	Transient receptor potential cation channel, subfamily M, member 4
Sick Sinus Syndrome (SSS)		
ANK2	4q25-q27	Ankyrin B
HCN4	15q24-q25	Hyperpolarization-activated cyclic nucleotide–gated channel 4
MYH6	14q11.2	Myosin, heavy chain 6, cardiac muscle, alpha
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
“Ankyrin-B Syndrome”		
ANK2	4q25-q27	Ankyrin B
Familial Atrial Fibrillation (FAF)		
ANK2	4q25-q27	Ankyrin B
GATA4	8p23.1-p22	GATA-binding protein 4
GATA5	20q13.33	GATA-binding protein 5
GJA5	1q21	Connexin 40
KCNA5	12p13	I_{Kur} potassium channel ($K_v1.5$)
KCNE2	21q22.1	Potassium channel beta subunit (MiRP1)
KCNH2	7q35-36	I_{Kr} potassium channel alpha subunit (HERG, $K_v11.1$)
KCNJ2	17q23	I_{K1} potassium channel (Kir2.1)
KCNQ1	11p15.5	I_{Ks} potassium channel alpha subunit (KVLQT1, $K_v7.1$)
NPPA	1p36	Atrial natriuretic peptide precursor A
NUP155	5p13	Nucleoporin 155 KD
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)

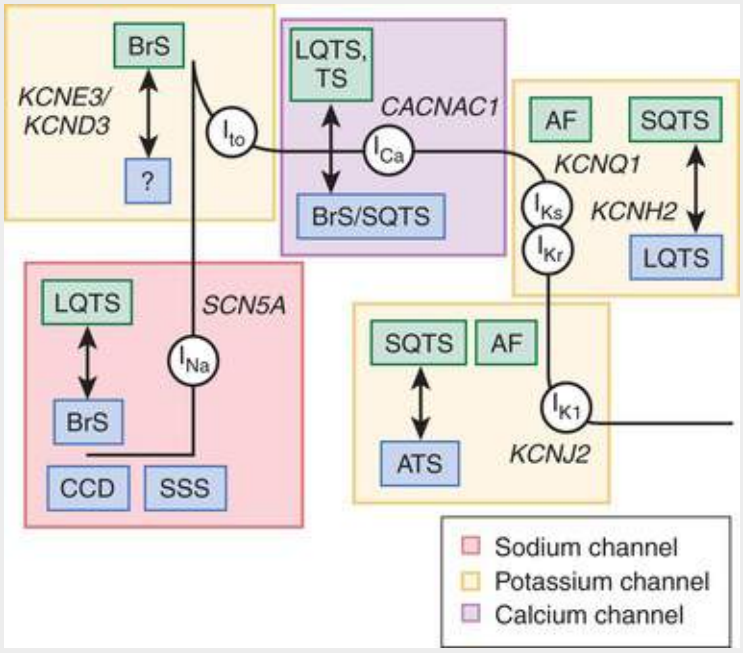

FIGURE 33.1 Cardiac action potential disorders. Illustrated are the key ion currents (*white circles*) along the ventricular cardiocyte's action potential that are associated with potentially lethal cardiac arrhythmia disorders. Disorders resulting in gain-of-function mutations are shown in *green rectangles* and those with loss-of-function mutations in *blue rectangles.* For example, gain-of-function mutations in the *SCN5A*-encoding cardiac sodium channel responsible for I_{Na} lead to long-QT syndrome (*LQTS*), and loss-of-function *SCN5A* mutations result in Brugada syndrome (*BrS*), cardiac conduction disorder (*CCD*), and sick sinus syndrome (*SSS*). *AF,* Atrial fibrillation; *ATS,* Andersen-Tawill syndrome; *SQTS,* short-QT syndrome.

In 2012, Boczek and colleagues,[3] following their whole-exome sequencing, genomic triangulation, and systems biology approach, identified a novel genetic substrate (P857R-*CACNA1C*) for a large, 15-member (8 affected) multigenerational pedigree with autosomal dominant "classic" LQTS. Functional characterization of the mutation using whole-cell patch-clamp technique revealed a gain-of-function mutation in peak $I_{Ca,L}$ consistent with cardiac action potential prolongation and the clinical phenotype of LQTS. Their subsequent mutational analysis of 102 unrelated patients with robust clinical evidence of LQTS has indicated that 3% to 5% of genetically elusive LQTS may be attributed to *CACNA1C* mutations, making *CACNA1C* potentially the fifth most common genetic substrate for nonsyndromic LQTS. The majority of the mutations identified reside in the *CACNA1C*-encoded L-type calcium channel (LTCC) critical PEST domain, which signals for rapid protein degradation. These mutations presumably result in a biogenic increase in LTCCs at the cell surface membrane. In addition, Fukuyama and colleagues[4] in 2014 and Wemhöner and colleagues[5] in 2015 identified gain-of-function *CACNA1C* missense mutations in 4 of 278 (1.4%) and 6 of 540 (1.1%) patients with LQTS, respectively.

The remaining seven minor LQTS susceptibility genes encode for either cardiac ion channels or key cardiac channel interacting proteins (ChIPs) that generally regulate the native ion channel current and collectively explain perhaps 5% of LQTS cases. The most recent ChIP to be implicated in LQTS is calmodulin. In 2013, Crotti and colleagues[6] performed a parent-child trio, whole-exome sequencing strategy to elucidate the underlying genetic cause for two unrelated sporadic cases of infantile LQTS with recurrent cardiac arrest and extreme QT prolongation. Both infants hosted sporadic de novo mutations (D130G-CALM1 and D96V-CALM2) in genes (*CALM1* and *CALM2*) that encode for *calmodulin,* a ubiquitously expressed and essential calcium signaling protein that is critically involved in many physiologic functions, including as a Ca^{2+} sensor for Ca^{2+}-dependent inactivation of the LTCC ($Ca_v1.2$), inactivation of the cardiac sodium channel ($Na_v1.5$), and activation of the voltage-gated potassium

channel (K_v7.1).

The calmodulin genes represent an interesting and rare phenomenon in human biology. There are three distinct calmodulin genes with distinct loci: *CALM1*, Chr.14q32.11; *CALM2*, Chr.2p21; and *CALM3*, Chr.19q13.2-q13.3. Although they share 76% homology at the DNA nucleotide level, these three genes encode for an identical 149–amino acid protein called calmodulin. All three genes are expressed in cardiac myocytes, with transcript expression levels highest for *CALM3*, followed by *CALM2* and *CALM1*.[6] Since the initial report by Crotti and colleagues,[6] mutations in all three of the *CALM* genes have been implicated in LQTS.[7,8] These calmodulin missense mutations localize to critical EF-hand calcium-binding motifs, reduce calmodulin's calcium-binding affinity, and attenuate Ca_v1.2 inactivation through loss of calcium-dependent inactivation of the LTCC.[8,9]

Calmodulin-positive LQTS patients exhibit the common cardiac features of life-threatening ventricular arrhythmias occurring very early in life, frequent T wave alternans, greatly prolonged QT intervals (QTc >600 msec), and intermittent 2 : 1 atrioventricular (AV) block (3 of 4 patients).[6] Ventricular fibrillation is often triggered by adrenergic activation occurring either spontaneously or preceded by a short episode of torsade de pointes that is not pulse dependent.[6,8] Additionally, patients often have some degree of neurodevelopmental delay, ranging from mild delay in language development to severe cognitive or motor development.[8]

The vast majority of LQTS susceptibility mutations are coding-region single-nucleotide substitutions or small insertions/deletions resulting in nonsynonymous missense (amino acid substitution for another amino acid), nonsense (amino acid substitution for a termination codon), splice-site alterations (resulting in exon skipping or intron inclusion), or frameshift mutations (altered normal amino acid coding resulting in early termination). Recently, a few large gene rearrangements involving hundreds to thousands of nucleotides and resulting in single or multiple whole-exon deletions/duplications have been described.[1] Importantly, there is no quintessential mutational “hot spot” within these genes, because the vast majority of unrelated families have their own unique, “private” mutation. In 2017 it is important to note that almost 20% of clinically definite cases of LQTS remain genetically elusive.

In contrast to rare, pathogenic LQTS-associated channel mutations, present in less than 0.04% (1 : 2500) of persons and in 75% of clinically robust LQTS cases, comprehensive genetic testing of *KCNQ1*, *KCNH2*, and *SCN5A* for more than 1300 ostensibly healthy volunteers has revealed that approximately 4% of Caucasians and up to 8% among non-Caucasians host rare nonsynonymous genetic variants (<0.5% allelic frequency) in these specific cardiac channel genes.[10] In fact, a total of 79 distinct channel variants were detected among these healthy individuals, including 14 variants in *KCNQ1*, 28 in *KCNH2*, and 37 in *SCN5A*.[10] This has enabled a case-control mutational analysis of the properties and localization of case-associated mutations compared to the compendium of presumably innocuous variants.[10] The probabilistic rather than binary nature of genetic testing is depicted in **Fig. 33.2**, showing that rare mutations other than missense mutations (approximately 20% of the LQTS spectrum of mutations) are high-probability LQTS-associated mutations, whereas the probability of pathogenicity for the most common mutation type, missense mutations (i.e., single amino acid substitutions), is strongly location dependent. For example, missense mutations localizing to the transmembrane spanning/pore domains of the LQT1- and LQT2-associated potassium channels are high-probability disease mutations, whereas a similarly rare missense mutation that localizes to the domain I-II linker of the Nav1.5 sodium channel is indeterminate, a variant of uncertain significance (VUS). Without cosegregation or functional data, such a mutation has a point estimate for probability of pathogenicity of less than 50%.

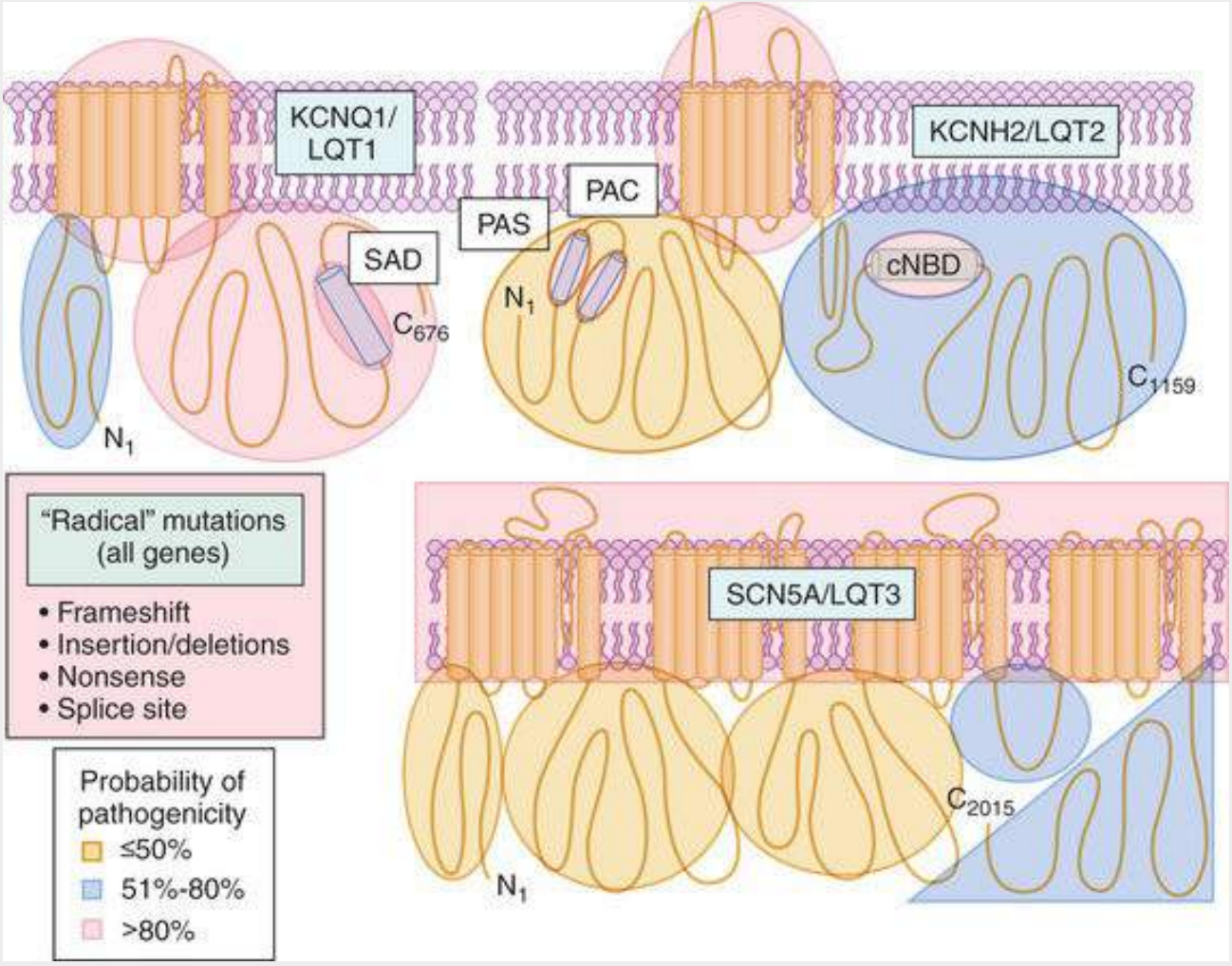

FIGURE 33.2 Probabilistic nature of LQTS genetic testing. Depicted are the three major ion channels causative for LQTS with areas of probability of pathogenicity shown for mutations localizing to these respective areas. Although "radical" mutations have a greater than 90% probability of being a true pathogenic mutation, the level of probability for missense mutations vary depending on their location for each channel protein. Missense mutations residing in *red-shaded areas* have a high probability (>80%) of being pathogenic, those in *blue* are possibly (51% to 80%) pathogenic, and those in *yellow-shaded areas* truly represent variants of uncertain significance (VUS, ≤50% probability) clinically.

Besides this background frequency (4% to 8%) of rare variants in health, 15 unique common polymorphisms (allelic frequency >0.5%) have been identified in the four potassium channel subunit genes (*KCNQ1*, *KCNH2*, *KCNE1*, and *KCNE2*), and eight common polymorphisms have been identified in the sodium channel gene (*SCN5A*). Many of these rare and common polymorphisms represent innocent bystanders; however, a layer of complexity is added to the genetics of these channelopathies and the management of patients when otherwise apparently innocuous variants can modify disease. For example, the most common sodium channel variant, H558R with a minor allelic frequency of approximately 29% in African Americans, 20% in Caucasians, 23% in Hispanics, and 9% in Asians, can provide a modifying effect on the disease state through "intragenic complementation" (the interaction of two mutations within the same gene that produce a novel functional effect) of other *SCN5A* mutations.[11] In fact, several studies indicate that some of these common polymorphisms may be clinically informative and relevant to the identification of those at risk for cardiac arrhythmias, particularly in the setting of torsade de pointes–inducing drugs or other environmental factors, as discussed later.

Phenotypic Correlates for the Three Canonical LQTS Genotypes

Specific genotype-phenotype associations in LQTS have emerged, suggesting relatively gene-specific

triggers, ECG patterns, and response to therapy[1] (**Fig. 33.3**). Swimming- and exertion-induced cardiac events are strongly associated with mutations in *KCNQ1* (LQT1), whereas auditory triggers and events occurring during the postpartum period most often occur in patients with LQT2. Exertion- or emotional stress–induced events are most common in LQT1, and events occurring during periods of sleep/rest are most common in LQT3. Using a study population of 721 LQT1 and 634 LQT2 genetically confirmed patients from the U.S. portion of the international LQTS registry, a multivariate analysis was used to assess the independent contribution of clinical and mutation-specific factors to the occurrence of a first triggered event associated with exercise, arousal, or sleep/rest.[12,13] Among the 221 symptomatic LQT1 patients, their first cardiac event was most often associated with exercise (55%), followed by sleep/rest (21%), arousal (14%), and nonspecific (10%) triggers, whereas the 204 symptomatic LQT2 patients most often had their first event associated with either arousal triggers (44%) or nonexercise/nonarousal triggers (43%), and only 13% of the symptomatic LQT2 patients had an exercise-induced first event. In addition, LQT1 male patients younger than 13 years had an almost threefold increase in risk for exercise-triggered events, whereas LQT1 females age 13 and older had a 3.5-fold increase in risk for sleep/rest nonarousal events. For LQT2 patients, the rate of arousal-triggered events was similar between male and female children, whereas there was a significant higher rate in women than in men (26% versus 6%, at age 40) after the onset of adolescence. Characteristic gene-suggestive ECG patterns have been described previously. LQT1 is associated with a broad-based T wave LQT2 with a low-amplitude notched or biphasic T wave, and LQT3 with a long isoelectric segment followed by a narrow-based T wave.

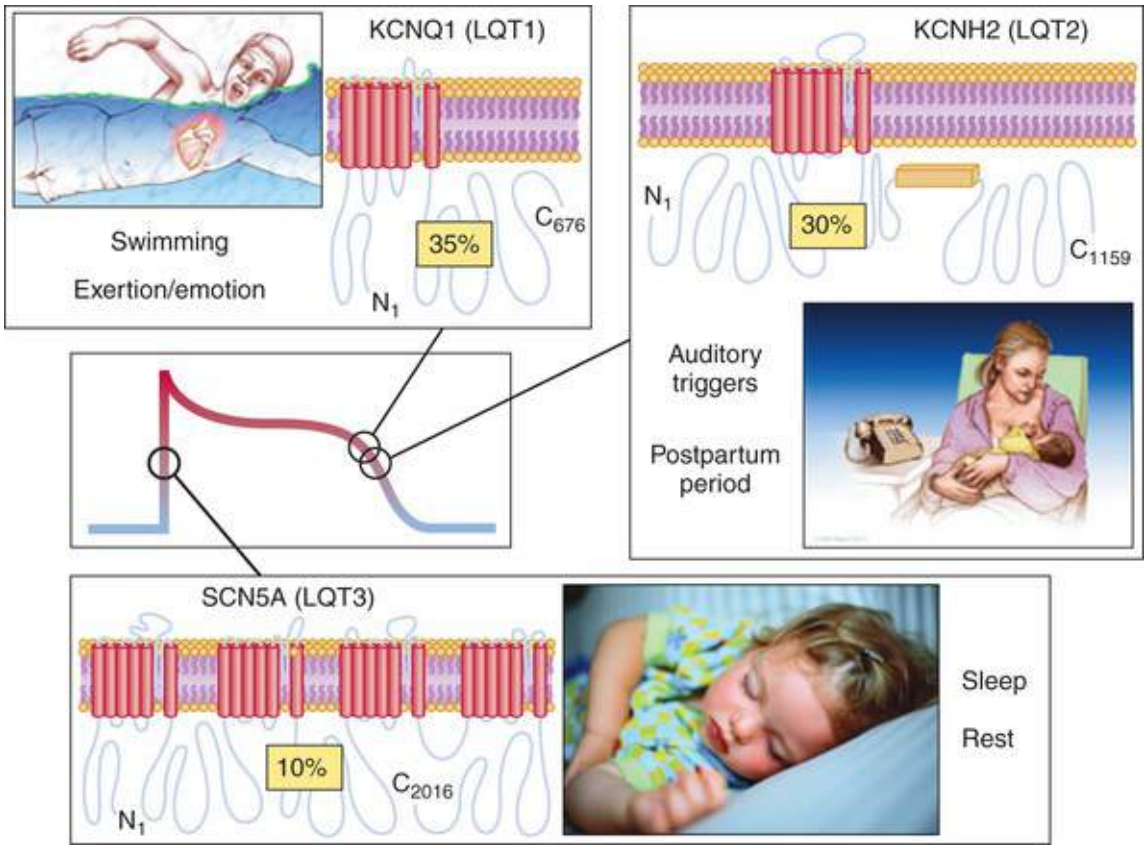

FIGURE 33.3 Genotype-phenotype correlations in LQTS. Seventy-five percent of clinically strong LQTS is caused by mutations in three genes (35% *KCNQ1*, 30% *KCNH2*, and 10% in *SCN5A*) encoding for ion channels that are critically responsible for the orchestration of the cardiac action potential. Genotype-phenotype correlations have been observed, including swimming/exertion/emotion and LQT1, auditory triggers/postpartum period and LQT2, and sleep/rest and LQT3.

However, exceptions to these relatively gene-specific T wave patterns exist, and due caution must be

exercised with making a pre–genetic test prediction of the particular LQTS subtype involved because the most common clinical mimicker of the LQT3-looking ECG is seen among patients with LQT1. This is key to keep in mind because importantly, the underlying genetic basis heavily influences the response to standard LQTS pharmacotherapy with beta blockers, which are extremely protective in LQT1 patients and moderately protective for patients with LQT2 and LQT3. Additionally, targeting the pathologic LQT3-associated late sodium current with agents such as mexiletine, flecainide, and ranolazine may represent a gene-specific therapeutic option for LQT3.[14,15] Attenuation in repolarization with clinically apparent shortening in the QTc has been demonstrated with such a strategy, with a reduction in LQT3-triggered events using this strategy.[14-16] The generalization that beta-blocker efficacy is genotype dependent has been well accepted, whereas the effectiveness of beta-blocker therapy may be largely trigger specific. For both LQT1 and LQT2 patients, beta blockade was associated with a pronounced 71% (LQT2 patients) to 78% (LQT1 patients) reduction in the risk for exercise-triggered cardiac events, but had no statistically significant effect on the apparent risk for arousal- or sleep/rest-triggered events.[12,13] However, many symptomatic LQT1 and LQT2 patients experience a subsequent cardiac event associated with a different trigger. For example, an LQT2 patient first presenting with an arousal event or event during sleep may present subsequently with an exercise-triggered event. Therefore beta-blocker therapy still remains first-line therapy even for patients experiencing a non–exercise-associated first event.

In addition, intragenotype risk stratification has been realized for the two most common subtypes of LQTS based on mutation type, mutation location, and cellular function.[1] Patients with LQT1 secondary to K_v7.1 missense mutations localizing to the transmembrane-spanning domains clinically have a twofold greater risk of a LQT1-triggered cardiac event than LQT1 patients with mutations localizing to the C-terminal region. In addition, missense mutations localizing to the so-called cytoplasmic loops (C-loops) within the transmembrane-spanning domains, an area of the protein involved in adrenergic channel regulation, are associated with the highest rate of both exercise- and arousal-triggered events, but were not associated with an increase rate of sleep/rest-associated events.[13] C-loop K_v7.1 missense mutations were consistently associated with a greater than sixfold increase in risk for exercise-triggered events compared to nonmissense mutations and a nearly threefold increase compared to N- and C-terminal missense mutations.[13]

Patients with mutations resulting in a greater degree of K_v7.1 loss of function at the cellular in vitro level (i.e., dominant negative) have a twofold greater clinical risk than those mutations that damage the biology of the K_v7.1 channel less severely (haploinsufficiency). Adding to the traditional clinical risk factors, molecular location and cellular function are independent risk factors used in the evaluation of patients with LQTS.[1]

Similar to molecular risk stratification in LQT1, patients with LQT2 secondary to K_v11.1 pore region mutations have a longer QTc and more severe clinical manifestation of the disorder and experience significantly more arrhythmia-related cardiac events at a younger age than LQT2 patients with non–pore-related mutations in K_v11.1. Similarly, in a Japanese cohort of LQT2 patients, those with pore mutations had a longer QTc, and although not significant among probands, nonprobands with pore mutations experienced their first cardiac event at an earlier age than those with a non–pore-related mutation. Most recently, additional information suggests that LQT2 patients with mutations involving the transmembrane pore region had the greatest risk for cardiac events, those with frameshift or nonsense mutations in any region had an intermediate risk, and those with missense mutations in the C terminus had the lowest risk for cardiac events. Interestingly, LQT2 patients with mutations in the pore loop region of the K_v11.1

channel have a greater than twofold increased risk for arousal-triggered events, and LQT2 patients with non–pore loop TM region mutations have an almost sevenfold increase in the risk for exercise-triggered cardiac events compared with patients with N-terminal or C-terminal (non-PAS domain) mutations.[12]

Incomplete penetrance and variable expressivity are clinical hallmark features of LQTS and it has been long thought that co-inheritance of a true disease-causing mutation and either a common or rare channel genetic variant may determine the expressed severity of the disorder. For example, the coexistence of the common K897T-KCNH2 polymorphism and the A1116V-KCNH2 mutation (on opposite alleles) led to a more severe clinical course in a single Italian LQTS family. The A1116V mutation by itself produced a subclinical phenotype of mild QT prolongation and an asymptomatic course, while the proband hosting both variants had clinically overt disease consisting of a diagnostic QT prolongation, presyncopal episodes, and cardiac arrest. Besides cardiac ion channels, SNPs of non–ion channel genes such as *NOS1AP* (the gene encoding the nitric oxide synthase 1 adapter protein), *ADRA2C* ($alpha_{2C}$-adrenergic receptor), and *ADRB1* ($beta_1$-adrenergic receptor) may modify disease severity in LQTS.[1]

In 2012, Amin and colleagues[17] provided compelling evidence for a strong, disease-modifying effect of a 3′ untranslated region (3′UTR) KCNQ1 allele–specific haplotype in LQT1 mutation–positive pedigrees; the magnitude of the effect on the QTc and the symptomatology go well beyond any other currently described genetic modifiers. The *KCNQ1* gene encodes for a single $K_v7.1$ ion channel alpha subunit. Following *KCNQ1* gene expression and post-translational modifications, four alpha subunits are assembled to create a pore-forming $K_v7.1$ tetrameric channel. Therefore, if a patient had a heterozygous *KCNQ1* mutation (i.e., one normal *KCNQ1* gene allele and one mutant allele), one would expect that if both the normal and the mutant gene alleles were expressed in equal amounts, $1/16$ of the channels would be a normal homomeric tetramer and $1/16$ of the channels would be mutant homomeric tetramer. The remaining channels would be hybrids containing both normal and mutant alpha subunits. One would predict that if the normal *KCNQ1* gene allele expression was somehow suppressed, there would be relatively more KCNQ1 mutant alpha subunits translated and ultimately assembled to provide more dysfunctional KCNQ1 channels, thus leading to a more severe manifestation of the disorder (**Fig. 33.4**). Simply put, there would be far more bad (mutant) channels than good (healthy) channels created. The opposite would be true if the mutation containing the *KCNQ1* allele were suppressed.

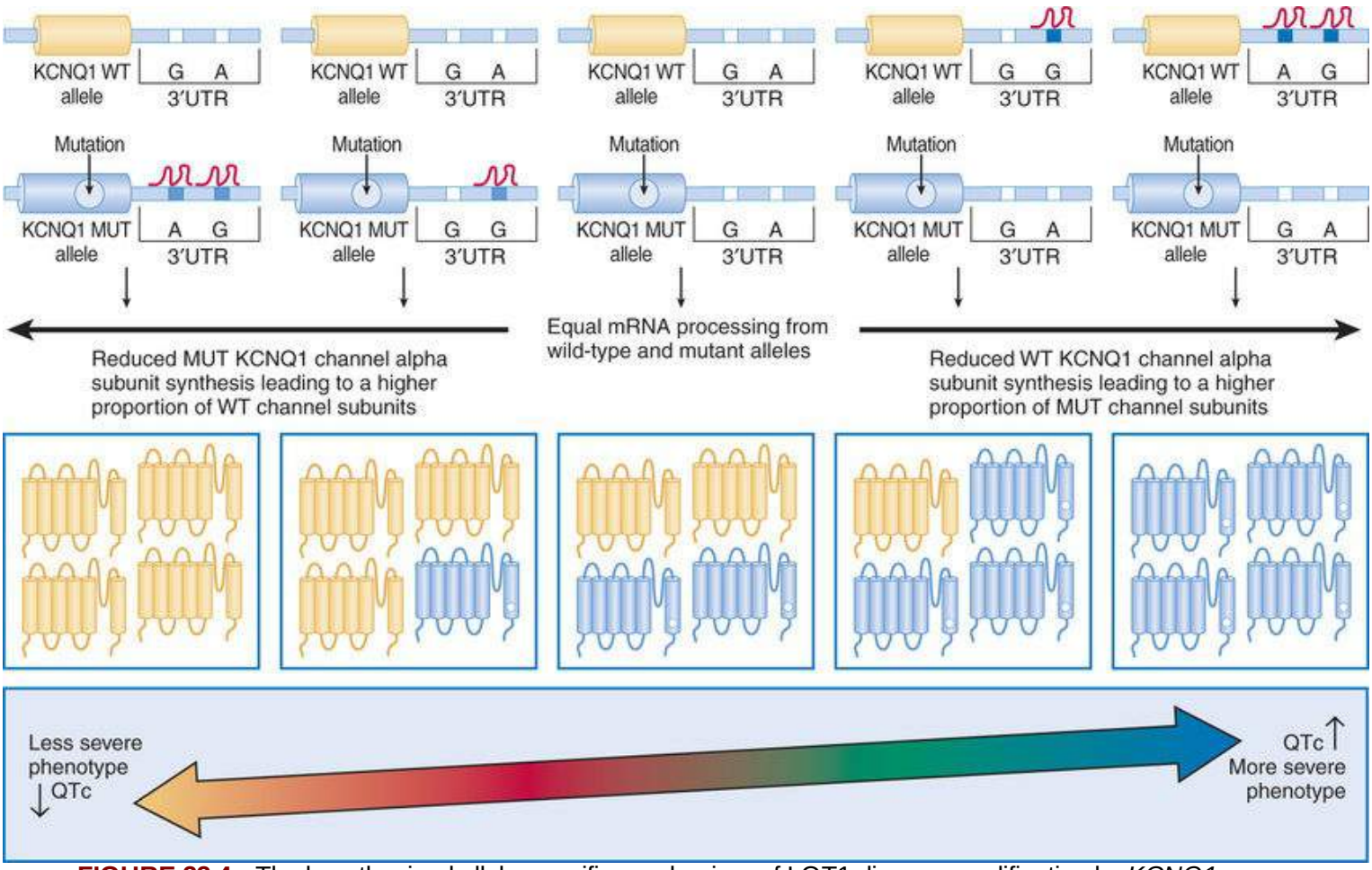

FIGURE 33.4 The hypothesized allele-specific mechanism of LQT1 disease modification by *KCNQ1* 3′UTR single-nucleotide polymorphisms (SNPs). Illustrated is the proposed microRNA-mediated allele-specific *KCNQ1* gene transcript–"suppressing" mechanism, supported by the existence of naturally occurring SNPs within the *KCNQ1* 3′UTR. Presence of the SNPs' minor alleles (A, G; *dark squares*) creates a "suppressive" haplotype by forming new microRNA (shown in *red*) binding sites that suppress the expression of the *KCNQ1* allele in which they reside, thus altering the stoichiometric assembly of wild-type (i.e., normal, shown in *yellow*) and mutant (shown in *gray*) $K_V7.1$ alpha subunits. (Modified from Amin AS, Giudicessi JR, Tijsen AJ, et al. Variants in the 3′ untranslated region of the KCNQ1-encoded Kv7.1 potassium channel modify disease severity in patients with type 1 long QT syndrome in an allele-specific manner. Eur Heart J 2012;33:714-23.)

Most genes have a 3′UTR that produces a messenger RNA (mRNA) transcript containing regions of *cis*-regulatory binding sites for small, noncoding microRNAs (miRNAs) that bind to the transcript and ultimately inhibit that gene's expression. Naturally occurring genetic variation within these 3′UTRs (miR-SNPs) can either abolish existing or create new miRNA-binding sites. Amin and colleagues[17] identified three naturally occurring, single-nucleotide polymorphisms (SNPs; rs2519184, rs8234, and rs10798) within the *KCNQ1* 3′UTR, whereby the presence of their minor alleles (A, G, G) create a "suppressive" haplotype by creating new miRNA-binding sites that suppress the expression of the *KCNQ1* gene allele in which they reside. In a cohort of 168 *KCNQ1* (LQT1) mutation–positive individuals from 41 families, the inheritance of the "suppressive" haplotype residing on the normal "healthy" allele produced a more severe LQT1 phenotype in regard to QTc and symptomatology, whereas the inheritance of the "suppressive" haplotype residing on the same allele as the *KCNQ1* mutation gave a less severe LQT1 phenotype (shorter QTc and fewer symptoms).[17] This intriguing discovery not only may explain a significant component of reduced penetrance and variable expressivity that is a common feature of arrhythmia syndromes, but also may represent a paradigm shift in our thinking about disease-modifying genetic-drivers of mendelian disorders, because one of the most important genetic determinants of disease severity in LQT1 appears to be the 3′UTR *KCNQ1* haplotype on the allele inherited from the unaffected

“non-LQTS” parent.

In 2011 the Heart Rhythm Society (HRS) and European Heart Rhythm Association (EHRA) released the first HRS/EHRA-sponsored guidelines for clinical genetic testing for LQTS and the other channelopathies.[18]

Triadin Knockout Syndrome

Recently, Altmann and colleagues[19] discovered *TRDN*-encoded triadin (Trdn) as a novel genetic basis for recessively inherited LQTS that they termed triadin knockout (TKO) syndrome. Almost 15% of their genetically elusive LQTS cohort overall and 50% of the children (≤10 years) with genetically elusive LQTS hosted homozygous or compound heterozygous *TRDN* frameshift mutations. However, because the cohort was small, the prevalence in this study may not be reflective of the general population of genetically elusive LQTS cases. A homozygous p.D18fs*13 mutation was identified in an African American girl; the same homozygous p.K147fs0* mutation was identified in three unrelated patients of either Indian or Arabic decent; and one Caucasian male was found to be compound heterozygous for two frameshift mutations (p.N9fs*5 and p.K147fs*0). Since frameshift mutations often result in nonfunctional proteins or immediate nonsense-mediated RNA decay, these patients are expectantly triadin null. Remarkably, all five triadin null children displayed the common electrocardiographic phenotype of extensive T wave inversions in precordial leads V_1 to V_4, with persistent or transient QT prolongation, severe disease expression of exercise-induced cardiac arrest in early childhood, and a recessive inheritance pattern, and required aggressive therapy. Patients often presented with sudden cardiac arrest (SCA) before age 5 years, and current therapeutic strategies (beta blockers and left cardiac sympathetic denervation [LCSD] surgery) have not been effective.[19] Importantly, the parents of these children, who are all heterozygous for a triadin null allele (i.e., triadin haploinsufficient), do not have an overt abnormal cardiac phenotype. Whether they may be predisposed to an environmentally induced and acquired ventricular arrhythmia is currently unknown.

In addition, *TRDN* mutations have been implicated previously in recessively inherited catecholaminergic polymorphic ventricular tachycardia (CPVT), as identified in 2 of 97 (2%) patients diagnosed with CPVT who were genotype negative for *RYR2* or *CASQ2* mutations.[20] Specifically, a homozygous p.D18fs*13 mutation was identified in a 2-year-old boy who experienced exertion-induced SCA, and compound heterozygous triadin null mutations (p.T59R and p.Q205X) were identified in a 26-year-old man who experienced recurrent exertion-induced syncope since infancy. Most recently, two additional case reports described children with compound triadin null alleles (p.N9fs*5/p.Q205X and p.D18fs*13/p.E168X).[21,22] Similar to previous observations, three of the six children described in these two case reports experienced SCA before age 5 years.

Triadin is a critical component of the cardiac calcium release unit (CRU), which mediates its calcium-sensing properties and governs excitation-contraction coupling (ECC) in the heart.[23,24] Specifically, cardiac triadin is responsible for stabilization of the T tubule junctional sarcoplasmic reticulum (jSR) association by linking calsequestrin 2 (Casq2), ryanodine receptor 2 (RyR2), and junctophilin-2 (JPH2) proteins together in proximity to the L-type calcium channel (LTCC), thus facilitating a proper negative feedback loop for Ca^{2+} handling. Ablation of cardiac triadin results in cardiac dyad structural remodeling and Ca^{2+} overload as a result of slower Ca^{2+}-dependent inactivation of the LTCC. Slower LTCC inactivation could lengthen the cardiac action potential and manifest as QT prolongation on the ECG.

Andersen-Tawil Syndrome

Clinical Description and Manifestations

Andersen-Tawil Syndrome (ATS), first described in 1971 in a case report by Andersen and later described by Tawil in 1994, is now recognized as a rare, multisystem disorder characterized by a triad of clinical features: periodic paralysis, dysmorphic features, and ventricular arrhythmias. ATS is a heterogeneous disorder that is either sporadically or autosomal dominantly derived and has a high degree of variable phenotypic expression and incomplete penetrance, with as much as 20% of mutation-positive patients being nonpenetrant. The mean age of onset for periodic paralysis has been reported to be 5 years (ranging from 8 months to 15 years) and slightly older, 13 years (range, 4 to 25 years), for cardiac symptoms.[1]

Electrocardiographic (ECG) abnormalities of ATS may include pronounced QTU prolongation, prominent U waves, and ventricular ectopy, including polymorphic ventricular tachycardia (VT), bigeminy, and bidirectional VT. Although ventricular ectopy is common and the ectopic density can be high in some patients, the majority of ATS patients are asymptomatic, and SCD is extremely rare. ATS1 was initially proposed as type 7 LQTS (LQT7) due to the observation of extreme prolongation of the QT interval; however, these measurements included the prominent U wave. As such, this complex clinical disorder, manifesting at times with only a modest prolongation of the QT interval, is probably best considered as its own clinical entity, referred to as ATS1, rather than as part of the LQTS regime. However, given the potential for false interpretation of the QT interval because of the prominent U wave and the probability of phenotypic expression of only cardiac-derived symptomatology (syncope, palpitations, ventricular rhythm disturbances), a considerable number of ATS patients are misdiagnosed, conceivably with classic LQTS. Similarly, the presence of bidirectional VT, an accepted hallmark of CPVT (see later), often leads to a misdiagnosis of ATS as the potentially lethal CPVT. Correctly distinguishing between ATS and CPVT is critical because the treatment strategies are quite different.[1]

Genetic Basis.

To date, more than 40 unique mutations in *KCNJ2* have been described as causative for ATS1. Mutations in *KCNJ2* account for approximately two thirds of ATS cases, while the molecular basis of the remaining third remains genetically and mechanistically elusive. However, the prevalence of *KCNJ2* mutations may be as high as 75% to 80% for patients with at least two ATS phenotypic features (i.e., typical ATS).[25,26] Most ATS-associated mutations in *KCNJ2* are inherited in an autosomal dominant inheritance pattern, but as many as one third of mutations in *KCNJ2* could be sporadic, de novo occurrences. In addition, somatic mosaicism has also been described in at least one *KCNJ2*-associated ATS family.[26] Localized to chromosome 17q23, *KCNJ2* encodes for Kir2.1, a small potassium channel alpha subunit expressed in brain, skeletal muscle, and heart, that is critically responsible for the inward rectifying cardiac I_{K1} current (**see Table 33.1 and Fig. 33.1**). In the heart, I_{K1} plays an important role in setting the heart's resting membrane potential, buffering extracellular potassium, and modulating the action potential waveform. Most *KCNJ2* mutations described in ATS are missense mutations that cause a loss of function of I_{K1} either through a dominant negative effect on Kir2.1 subunit assembly or through haploinsufficiency as a result of protein-trafficking defects.

Phenotypic Correlates in *KCNJ2*-Mediated Andersen-Tawil Syndrome

(ATS1)

Genotype-specific ECG features of ATS have emerged. Zhang and colleagues[27] examined the ECG T-U morphology and found that 91% of *KCNJ2* mutation–positive ATS1 patients had characteristic T-U wave patterns (including prolonged terminal T wave downslope, a wide T-U junction, and biphasic enlarged U waves), compared to none of the 61 unaffected family members or 29 genotype-negative ATS patients. In 2012, Kimura and associates[25] found that 88% of *KCNJ2* mutation–positive ATS patients had an abnormal U wave. Additionally, whereas the U wave is greatly abnormal in ATS1, it is typically normal in LQTS. Consequently, this *KCNJ2* gene–specific ECG feature of T-U morphology can be useful in differentiating ATS1 patients from *KCNJ2* mutation–negative ATS and LQT1 to LQT3 patients and may facilitate a cost-effective approach toward genetic testing of the appropriate disorder.[27] Interestingly, topologic location of *KCNJ2* mutations may influence the phenotypic expression of ATS features. The vast majority (approximately 90%) of *KCNJ2* mutations reside in either the N or the C terminus of this two-transmembrane single-pore channel. C-terminal mutations appear to be more often associated with typical ATS (more than two ATS features), dysmorphism, and periodic paralysis, whereas N-terminal mutations were more often observed in atypical ATS (only one ATS feature, predominately a cardiac phenotype only).[25]

Timothy Syndrome

Clinical Description and Manifestations

Timothy syndrome (TS, LQT8) is an extremely rare (<30 patients described worldwide), multisystem, highly lethal arrhythmia disorder associated with both cardiac and extracardiac abnormalities. The typical cardiac manifestations of TS include fetal bradycardia, extreme prolongation of the QT interval (QTc >500 msec) often with macroscopic T wave alternans and 2 : 1 AV block at birth.[28] These abnormalities often coincide with congenital heart defects or cardiomyopathies. Extracardiac abnormalities often consist of simple syndactyly (webbing of toes and fingers), dysmorphic facial features, abnormal dentition, immune deficiency, severe hypoglycemia, and developmental delay (including autism). Currently, the majority of TS patients die before reaching puberty. Although the majority of TS cases have been described as sporadic de novo occurrences, there have now been a few cases described with somatic mosaicism that is associated with a less severe phenotype.[1] For example, the *CACNA1C* mutation may be present in the patient's skeletal muscle, but only in minuscule amounts, or may even be completely absent, in other cell types of the human body (absent in heart, blood lymphocytes, etc.), and the patient may present with simple syndactyly but not an overt cardiac phenotype.

Genetic Basis.

In 2004, Splawski and colleagues[28] identified the molecular basis for this highly lethal arrhythmia disorder and named it Timothy syndrome after Katherine Timothy, Drs. Keating and Splawski's study coordinator, who meticulously phenotyped these cases. Remarkably, in all 13 unrelated patients where DNA was available, Splawski identified the same recurrent sporadic de novo missense mutation, G406R, in the alternatively spliced exon 8A of the *CACNA1C*-encoded LTCC ($Ca_v1.2$), which is important for excitation-contraction coupling in the heart and, as with the cardiac sodium channel *SCN5A*, mediates an inward depolarizing current in cardiomyocytes[28] (**see Table 33.1 and Fig. 33.1**). Through the mechanism of alternative splicing, the human LTCC consists of two mutually exclusive isoforms, one

containing exon 8A and the other exon 8. In 2005, Splawski and coworkers[29] described two cases of atypical TS (TS2) with similar features of TS but without syndactyly. As with other TS cases, these two atypical cases were identified as having sporadic de novo *CACNA1C* mutations not in exon 8A, but rather in exon 8. One case hosted a mutation analogous to the classic TS mutation, G406R, whereas the other case hosted a G402R missense mutation. All three mutations confer gain of function to the LTCCs through impaired channel inactivation[28,29] and reside near the end of the S6 transmembrane segment of domain 1 in the beginning of the intracellular loop between domains I and II of the Cav1.2 alpha subunit.

In 2012, Gillis and colleagues[30] identified a novel *CACNA1C* mutation A1473G in a single patient with a prolonged QT interval, dysmorphic facial features, syndactyly, and joint contractures consistent with TS. In 2015, Boczek and colleagues[31] identified a novel *CACNA1C* mutation I1166T in a patient exhibiting a TS phenotype with QT prolongation, patent ductus arteriosus, seizures, facial dysmorphism, joint hypermobility, hypotonia, hand anomalies, intellectual impairment, and tooth decay. Patch-clamp analysis of I1166T demonstrated a novel electrophysiologic phenotype distinct from the loss of inactivation seen with the previously established TS mutations. Instead, I1166T electrophysiologic studies illustrated a loss of current density and a gain-of-function shift in activation, leading to an increase in window current.[31] Interestingly, the topologic position of both I1166T and A1473G (a few amino acids away from the S6 transmembrane segment of domain III and IV, respectively) in the channel architecture is similar to that of the three original TS mutations (S6 segment of domain I).

Cardiac-Only Timothy Syndrome

In 2015, Boczek and colleagues[32] used whole-exome sequencing to identify a novel *CACNA1C* mutation R518C that was most likely responsible for the observed phenotype in a large pedigree with concomitant LQTS, hypertrophic cardiomyopathy (HCM), congenital heart defects, and SCD. None of the patients had extracardiac phenotypes, such as those observed with TS. A subsequent *CACNA1C* exon 12–specific analysis in five additional unrelated index cases with a similar phenotype of LQTS and a personal or family history of HCM identified two additional pedigrees with mutations at the same amino acid position, either R518C or R518H. Patch-clamp studies on both R518C and R518H revealed a complex $Ca_v1.2$ electrophysiologic phenotype consisting of loss of current density and inactivation in combination with increased window and late current. All three pedigrees hosting R518C/H–*CACNA1C* presented with this unique and atypical phenotypic sequela consistent with cardiac-only Timothy syndrome (COTS).[32]

Short-QT Syndrome

Clinical Description and Manifestations

Short-QT syndrome (SQTS), first described in 2000 by Gussak and associates, is associated with a short QT interval (usually ≤320 msec) on a 12-lead ECG, paroxysmal atrial fibrillation, syncope, and an increased risk for SCD. Giustetto and colleagues[33] analyzed the clinical presentation of 53 patients with SQTS from 29 families, the largest cohort studied to date, and found that 62% were symptomatic, with cardiac arrest being the most common symptom (31% of patients) and frequently the first manifestation of the disorder. One fourth of the patients had a history of syncope, and almost 30% had a family history of SCD. Symptoms, including syncope and cardiac arrest, most often occurred during periods of rest or sleep. Almost one-third presented with atrial fibrillation.[34] SCD was observed during infancy, suggesting the potential role for SQTS as a rare pathogenic basis for some cases of SIDS.[1,34,35]

Genetic Basis.
SQTS is most often inherited in an autosomal dominant manner; however, some de novo sporadic cases have been described. To date, mutations in six genes have been implicated in the pathogenesis of SQTS, including gain-of-function mutations in the potassium channel encoding genes *KCNH2* (SQT1), *KCNQ1* (SQT2), and *KCNJ2* (SQT3) and loss-of-function mutations in *CACNA1C* (SQT4), *CACNB2b* (SQT5), and *CACNA2D1* (SQT6) encoding for LTCC alpha, beta, and delta subunits, respectively (**see Table 33.1 and Fig. 33.1**). However, despite the identification of these six SQTS susceptibility genes, it remains unknown as to what proportion of SQTS is expected to be SQT1 to SQT6 genotype positive and what proportion awaits genetic elucidation. More than 75% of SQTS cases remain elusive genetically.

Genotype-Phenotype Correlates

Insufficient data exist to define genotype-phenotype correlations clearly in SQTS, since probably less than 60 cases have been described in the literature to date, but gene-specific ECG patterns have emerged. The typical ECG pattern consists of a QT interval of 320 milliseconds or less (QTc ≤340 msec) and tall, peaked T waves in the precordial leads with either no or a short ST segment present. The T waves tend to be symmetric in SQT1 but asymmetric in SQT2 to SQT4. In SQT2, inverted T waves can be observed. In SQT5, a Brugada syndrome–like ST elevation in the right precordial lead may be seen.[34]

Although perhaps premature because of a small sample size, a recent report has suggested that SQTS patients with *KCNH2* mutations have a shorter QT and a greater response to hydroquinidine therapy than patients with a non–*KCNH2*-mediated SQTS.[36] Based on a clinical variable analysis of 65 mutation-positive SQTS patients among 132 SQTS cases previously reported in the literature, Harrell and colleagues[37] indicated that patients with *KCNH2*-mediated SQTS (SQT1) exhibit a later age of onset of manifestation, whereas patients with *KCNQ1*-mediated SQTS (SQT2) have a higher prevalence of bradyarrhythmias and atrial fibrillation.

Drug-Induced Torsade de Pointes

Clinical Description and Manifestations

Drug-induced QT prolongation or drug-induced torsades de pointes (DI-TdP) is a constant concern for physicians prescribing particular drugs with the capacity for producing such unwanted and potentially life-threatening side effects (**see Chapters 8, 37, and 39**). The estimated incidence of antiarrhythmic drug–induced TdP has ranged from 1% to 8% depending on the drug and dose.[38] DI-TdP and subsequent sudden death are rare events, but the list of potential "QT liability" or "torsadegenic" drugs is extensive and includes not only antiarrhythmic drugs such as quinidine, sotalol, and dofetilide, but also many noncardiac medications, such as antipsychotics, methadone, antimicrobials, antihistamines, and the gastrointestinal stimulant cisapride[39] (see www.qtdrugs.org for a comprehensive list).

I_{Kr} Channel Blockers and the "Repolarization Reserve"

Besides their intended function and their intended target of action, the vast majority of medications with a potential unwanted TdP-predisposing side effect are $I_{Kr}/K_v11.1$ channel blockers (also referred to as HERG channel blockers). In effect, QT-prolonging drugs create an "LQT2-like" phenotype through reduced repolarization efficiency and subsequent lengthening of the cardiac action potential. However, I_{Kr}

drug blockade alone does not appear sufficient to provide the potentially lethal TdP substrate. One particular thesis centers on the observation that cardiac repolarization relies on the interaction of several ion currents that provide some level of redundancy in order to protect against extreme QT prolongation by "QT liability" drugs. This "repolarization reserve" may be reduced through anomalies in the repolarization machinery, as a result of common or rare genetic variants in critical ion channels that produce a subclinical loss of the repolarizing currents I_{Ks} and I_{Kr}.[38] In fact, studies revealed that 10% to 15% of patients with DI-TdP hosted rare ion channel mutations.[1] A recent smaller study found potential LQTS susceptibility mutations in 40% of cases of seemingly isolated, drug-induced LQTS.[40] Further, functional characterization suggested that these mutations were somewhat "weaker" than the loss-of-function mutations associated with classic, autosomal dominant LQTS, supporting the multihit hypothesis that underlies "reduced repolarization reserve."

Common Ion Channel Polymorphisms.

Among the common polymorphisms of the *KCNH2*-encoding I_{Kr} potassium channel, the K897T and R1047L polymorphisms have received the most attention (**see Chapter 8**). As reviewed by Fitzgerald and Ackerman,[39] Paavonen and coworkers observed that T897-KCNH2 channels exhibit slower activation kinetics with a higher degree of inactivation, an alteration expected to decrease channel function and perhaps alter drug sensitivity, since several common drugs inhibiting I_{Kr} channel function bind preferentially to the inactivated state of the channel. These data suggest that T897 channels may genetically "reduce repolarization reserve" and facilitate a proarrhythmic response that may be enhanced in the setting of I_{Kr} channel–blocking drugs, compared to wild-type K897 channels. In fact, K897T appears to affect the QTc response to ibutilide in a gender specific manner. In a study by Sun and colleagues reviewed by Schulze-Bahr,[11] among 105 atrial fibrillation patients treated with dofetilide, R1047L was overrepresented among those patients who developed drug-induced TdP compared with patients who were free of TdP. In addition to these common potassium channel alpha subunit polymorphisms, three common polymorphisms (D85N-KCNE1, T8A-KCNE2, and Q9E-KCNE2) involving auxiliary beta subunits have been implicated in drug-induced arrhythmia susceptibility.[39]

Along with genetic variants in major repolarizing channels, variants of the major depolarizing channel, Nav1.5, may provide a substrate for a proarrhythmic response in the setting of I_{Kr} channel–blocking drugs or in patients with other risk factors for DI-TdP. The most prominent channel polymorphism to confer arrhythmia susceptibility in an ethnic-specific manner is S1103Y-SCN5A (originally annotated as the Y1102 variant). This polymorphism, seen in 13% of African Americans but not observed in any Caucasian or Asian controls (>1000), was overrepresented in arrhythmia cases (56.5%) compared to controls (13%) involving African-Americans (odds ratio, 8.7).[38,39] S1103Y has very subtle alterations in channel kinetics in heterologous expression studies under basal conditions. However, functional and modeling studies supported the potential for QT prolongation, reactivation of calcium channels, early afterdepolarizations, and arrhythmias, particularly in the setting of concomitant exposure to I_{Kr}-blocking drugs.

Recent genome-wide association studies (GWAS) have associated common variants of the *NOS1AP*-encoded nitric oxide synthase 1 adapter protein with QT interval duration. NOS1AP is a regulator of the neuronal nitric oxide synthase (nNOS), which regulates intracellular calcium levels and myocyte contraction through its effect on the LTCCs. Common SNPs in the *NOS1AP* appear associated with drug-induced QT prolongation and ventricular arrhythmia.[41] This association was most pronounced in patients

taking amiodarone, currently one of the most common antiarrhythmic drugs. It has been hypothesized that genetic variants in *NOS1AP* that suppress the gene's expression may in turn result in increased LTCC currents and subsequent QT prolongation, and such individuals may be at increased arrhythmogenic risk while taking amiodarone.[41] However, although QT prolongation is observed routinely with amiodarone, DI-TdP attributed to amiodarone is exceedingly rare.

Additionally, genetic variation or individual differences in drug elimination or metabolism may contribute to individual risk for DI-TdP. For example, patients with genetically mediated reduction in cytochrome P-450 (CYP) 3A enzymatic activity could be vulnerable to DI-TdP in the setting of I_{Kr} blockers that depend on CYP3A for its metabolism.[11,39]

The Other Channelopathies

Catecholaminergic Polymorphic Ventricular Tachycardia

Clinical Description and Manifestations

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a heritable arrhythmia syndrome that classically manifests with exercise-induced syncope or sudden death, is predominantly expressed in young persons, and closely mimics the phenotypic byline of LQT1 but appears to be much more lethal.[42,43] As with LQT1, swimming is a potentially lethal arrhythmia-precipitating trigger in CPVT. In fact, both LQT1 and CPVT have been shown to underlie several cases of unexplained drowning or near-drowning in young, healthy swimmers. However, CPVT is associated with a completely normal resting ECG (perhaps bradycardia and mild U waves) and is suspected on ECG after exercise or catecholamine stress testing that demonstrates significant ventricular ectopy, occasionally with CPVT's pathognomonic arrhythmia of bidirectional VT.[1]

Clinically, a presentation of exercise-induced syncope and a QTc less than 460 milliseconds should always prompt first consideration of and need to rule out CPVT rather than “concealed” or “normal QT interval” LQT1. Further, exercise-induced premature ventricular complexes in bigeminy is much more likely than the more specific but less sensitive finding of bidirectional VT.[44] CPVT is associated with a structurally normal heart. Once thought to manifest only during childhood, more recent studies have suggested that the age of first presentation can range from infancy to 40 years. CPVT's potential lethality is illustrated by mortality rates of 30% to 50% by age 35 and the presence of a positive family history of young (<40 years) SCD for more than one third of CPVT individuals and in as many as 60% of families hosting *RYR2* mutations.[43] Moreover, approximately 15% of autopsy-negative SUD in young persons and some cases of SIDS have been attributed to CPVT.[1,45,46]

Genetic Basis.

Perturbations in key components of intracellular calcium–induced calcium release from the sarcoplasmic reticulum serve as the pathogenic basis for CPVT (**see Chapter 34**). Inherited in an autosomal dominant manner, mutations in the *RYR2*-encoded cardiac ryanodine receptor/calcium release channel represent the most common genetic subtype of CPVT (CPVT1), accounting for 60% of clinically “strong” cases of CPVT (**Fig. 33.5; see Table 33.1**). Gain-of-function mutations in *RYR2* lead to leaky calcium release channels and excessive calcium release, particularly during sympathetic stimulation that can precipitate calcium overload, delayed depolarizations, and ventricular arrhythmias.[42] Again, most unrelated CPVT

families are identified with their own unique *RYR2* mutation, and about 5% of unrelated mutation-positive patients host multiple putative pathogenic mutations.[47]

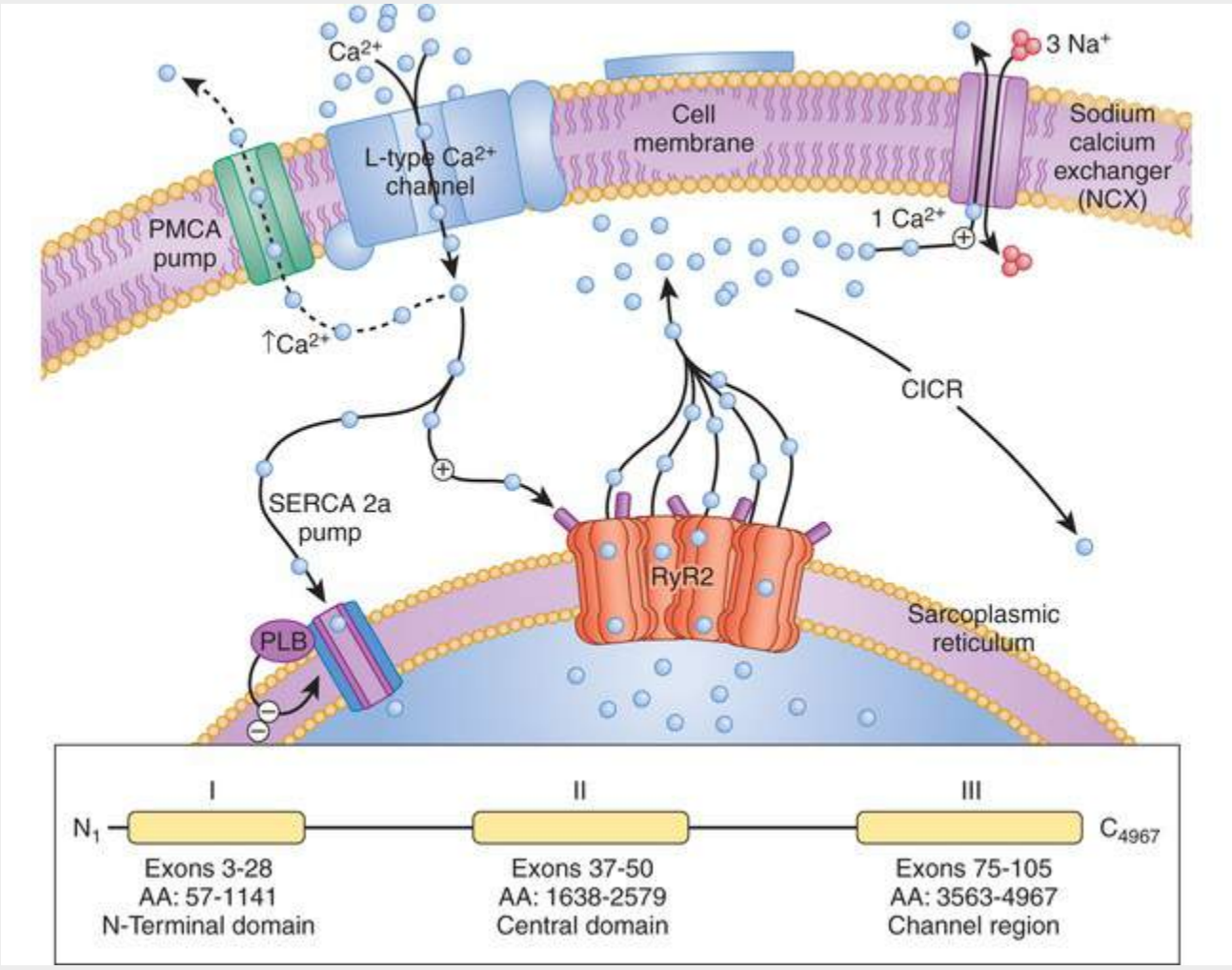

FIGURE 33.5 Catecholaminergic polymorphic ventricular tachycardia (CPVT), a disorder of intracellular calcium handling. Perturbations in key components of the calcium-induced calcium release (*CICR*) mechanism responsible for cardiac excitation-contraction coupling is the pathogenic basis for CPVT. At the center of this mechanism is the *RYR2*-encoded cardiac ryanodine receptor (RyR2)/calcium release channel located in sarcoplasmic reticulum membrane. Mutations in *RYR2* are clustered and distributed in three "hot spot" regions of this 4967–amino acid (*AA*) protein: domain I, or the N-terminal domain (AA: 57-1141); domain II, or the central domain (AA: 1638-2579); and domain III, or the channel region (AA: 3563-4967).

RYR2 is one of the largest genes in the human genome, with 105 exons that transcribe/translate one of the largest cardiac ion channel proteins comprising 4967–amino acid residues. There apparently are no specific mutation "hot spots," but there are three regional hot spots or "domains" where unique mutations reside (**Fig. 33.5**). Greater than 90% of *RYR2* mutations discovered to date represent missense mutations. However, as many as 5% of unrelated CPVT patients may host large gene rearrangements consistent with large whole-exon deletions, similar to that observed in LQTS.[47] Although genotype-phenotype correlations have been limited, a more recent study has suggested that family members hosting C-terminal (ion channel–forming domain) *RYR2* mutations may have a higher ventricular arrhythmia burden of nonsustained ventricular tachycardia (NSVT) than individuals hosting N-terminal or central domain *RYR2*-localizing mutations.[48]

Strikingly, almost one third of patients with "possible/atypical" LQTS (QTc <480 msec) who have exertion-induced syncope have also been identified as *RYR2* mutation positive.[47] In fact, almost 30% of

patients with CPVT have been misdiagnosed as having “LQTS with normal QT intervals” or “concealed LQTS,” indicating the critical importance of properly distinguishing between CPVT and LQTS at the clinical level, because risk assessment and treatment strategies of these unique disorders may vary. Similarly, some patients diagnosed with CPVT based on the presence of bidirectional VT on exercise have been identified with *KCNJ2* mutations, which are associated with the rarely lethal ATS.[1] The misdiagnosis of ATS as the potentially lethal disorder CPVT may lead to more aggressive prophylactic therapy (i.e., ICD implantation) than necessary. Two autosomal recessive forms of CPVT have been identified involving mutations in either *CASQ2*-encoded calsequestrin-2 protein or *TRDN*-encoded triadin.[1,21] Recently, mutations in *CALM1* and *CALM3* have been implicated as a cause of autosomal dominant CPVT[49,50] (**see Table 33.1**).

Brugada Syndrome

Clinical Description and Manifestations

Brugada syndrome (BrS) is an heritable arrhythmia syndrome characterized by an ECG pattern consisting of coved-type ST-segment elevation (≥2 mm) followed by a negative T wave in the right precordial leads V_1 through V_3 (often referred to as type 1 Brugada ECG pattern) and an increased risk for SCD resulting from episodes of polymorphic ventricular tachyarrhythmias.[51] The penetrance and expressivity of the disorder are highly variable, ranging from lifelong asymptomatic individuals to SCD during the first year of life. BrS is generally considered a disorder involving young male adults, perhaps greatest among Southeast Asian men, with arrhythmogenic manifestation first occurring at an average age of 40 years, with SCD typically occurring during sleep. However, BrS has been demonstrated in children and infants. In a 2007 population study of 30 children (<16 years) affected by BrS from 26 families, fever represented the most common precipitating factor for arrhythmic cardiac events, including syncope and SCD.[1]

Genetic Basis.

BrS is inherited as an autosomal dominant trait, although more than half of BrS cases may be sporadic. Approximately 20% to 30% of BrS cases result from loss-of-function mutations in the *SCN5A*-encoded cardiac sodium channel (**see Table 33.1 and Fig. 33.1**) and are classified as Brugada syndrome type 1 (BrS1). In 2009 an international compendium of *SCN5A* mutations in patients referred for BrS genetic testing reported almost 300 distinct mutations in 438 of 2111 (21%) unrelated patients, and the mutation detection yield ranged from 11% to 28% across nine centers.[52] The yield of mutation detection may be significantly higher among familial forms than in sporadic cases. Schulze-Bahr and colleagues[53] identified *SCN5A* mutations in 38% of their familial BrS cases, compared to none in 27 sporadic cases ($P = 0.001$). The majority of the mutations were missense (66%), followed by frameshift (13%), nonsense, (11%), splice site (7%), and in-frame deletions/insertions (3%). Approximately 3% of the genotype-positive patients host multiple putative pathogenic *SCN5A* mutations, and as in the genotype-phenotype observations in LQTS, patients hosting multiple *SCN5A* mutations tend to be younger at diagnosis (29.7 ±16 years) than those with a single mutation (39.2 ±14.4 years).[52] Again, as in LQTS, there is no particular mutational “hot spot” because almost 80% of the BrS-related *SCN5A* mutations occur as “private,” single-family mutations.

However, almost 10% of the 438 unrelated, *SCN5A* mutation–positive patients hosted one of four mutations: E1784K (14 patients), F861WfsX90 (11 patients), D356N (8 patients), and G1408R (7

patients).[52] Interestingly, the most common BrS1 mutation, E1784K, has also been reported as the most frequently seen LQT3-associated *SCN5A* mutation, illustrating how the same DNA alteration in a given gene can lead to two distinct cardiac arrhythmia syndromes, most likely as a result of other environmental or genetic modifying factors. In fact, E1784K represents the quintessential example of a cardiac sodium channel mutation with the capacity to provide for a mixed clinical phenotype of LQT3, BrS, and conduction disorders.[54]

In addition to pathogenic mutations in *SCN5A*, common polymorphisms may have a modifying effect on the disorder. Bezzina and others described an Asian-specific haplotype of six *SCN5A* promoter polymorphisms in near-complete linkage disequilibrium that occurred with an allelic frequency of 22% and was comparatively absent in Caucasians and blacks.[1] These promoter region polymorphisms may modulate the variability in cardiac conduction and in part contribute to the observed higher prevalence of BrS in the Asian population. Brugada and colleagues[55] provided data supporting the common polymorphism H558R as a modulator of the BrS phenotype, where the minor allele R558 provided a less severe clinical course in their 75 genotyped Brugada patients. Patients homozygous for H558 had longer QRS complex duration in lead II, higher J point elevation in lead V_2, higher "aVR sign," and trended toward more symptoms than H558R heterozygotes or R558 homozygotes. In 2013, Bezzina and associates[56] conducted a GWAS of 312 individuals with BrS and 1115 controls and detected three common genetic variants at three loci within or near the *SCN5A*, *SCN10A*, and *HEY2* genes that had a significant association with the BrS phenotype. These three loci had a cumulative dose-dependent, oligogenetic effect on disease risk, with an estimated odds ratio reaching 21.5 in the presence of more than four risk alleles compared to less than two alleles.

In addition to *SCN5A*, mutations have now been discovered in 17 other BrS susceptibility genes (**see Table 33.1**). Mechanistically, either decreases in the inward sodium or calcium currents or increases in the outward $K_v4.3$ potassium current produce the BrS phenotype through perturbations of the respective channel alpha subunits or channel interacting proteins[51] (**see Fig. 33.1**). For example, mutations in the glycerol-3-phosphate dehydrogenase 1–like protein encoded by *GPD1L* affect trafficking of the sodium channel to the plasma membrane, thus reducing overall sodium current and giving rise to the BrS phenotype, whereas mutations involving the LTCC alpha and beta subunits encoded by the *CACNA1C* and *CACNB2b* genes, respectively, were implicated in approximately 10% of BrS cases. However, on closer examination of this seminal discovery, a tight link between calcium channel–mediated disease and the clinical phenotype of BrS with concomitant short QT interval is evident, in which 50% of patients with BrS/short QT interval hosted a mutation in the LTCC subunit. In fact, in 2012, Crotti and associates[57] performed the first comprehensive mutational analysis in a large cohort of unrelated BrS patients. They identified *SCN5A* mutations in 16% of their cohort, but only 1.5% of their BrS cases had a mutation in one of the LTCC subunit genes, in the absence of a short QT interval.

To date, 18 genes have been implicated in BrS pathogenicity, but only *SCN5A* shows a significant contribution to the disease. In fact, extreme caution must be used when interpreting rare genetic variants identified within the minor BrS genes.[58,59] Importantly, the genetic cause of more than two thirds of clinically diagnosed BrS remains elusive, suggesting a high degree of genetic heterogeneity. This degree of genetic elusiveness also begs the question of whether most BrS is a genetically heterogeneous monogenic disorder or in fact a congenital heart defect or developmental disorder involving the epicardial right ventricular outflow tract,[60] or as anticipated, a mixture of monogenic-mediated BrS, oligogenic-mediated BrS, and non–genetic-mediated BrS.[56]

Phenotypic Correlates of *SCN5A*-Mediated Brugada Syndrome (BrS1)

Because the majority of BrS cases are elusive genetically, genotype-phenotype correlations in BrS have not been analyzed to the same degree as in LQTS. *SCN5A* mutations are associated with a higher incidence of conduction abnormalities in BrS patients, and the presence of a long PQ interval may be indicative of *SCN5A*-mediated BrS1, whereas the presence of a short QT interval (QTc <350 msec) may be indicative of LTCC-mediated BrS pathology. Crotti and colleagues[57] reported that compared to a less than 10% yield for a positive *SCN5A* genetic test in patients with a PQ interval shorter than 200 milliseconds, the yield was almost 40% among patients with a PQ interval of 200 milliseconds or longer.[57] Interestingly, young BrS males (<20 years, 83%) had a significantly higher *SCN5A* mutation detection rate than men age 20 to 40 (21%) and those over 40 (11%; $P < 0.0001$). In addition, BrS1 patients with nonsense, frameshift, or premature truncation–inducing mutations exhibit a more severe phenotype.[61] Unlike LQTS genetic testing, in which the triad of diagnostic, prognostic, and therapeutic impact has been fulfilled, BrS genetic testing is currently limited by its lower yield (25%, versus 75% for LQTS) and relative absence of a therapeutic contribution from knowing the genotype.[1,18,51,62]

Early Repolarization Syndrome

Clinical Description and Manifestations

The early repolarization (ER) pattern is characterized by the ECG finding of an elevation (≥1 mm above baseline) of the QRS-ST junction (the "J point") manifesting as QRS slurring (at transition of QRS to ST segment) or notching (positive deflection inscribed on terminal S wave), ST-segment elevation with upper concavity, and prominent T waves in two or more contiguous leads. The prevalence of the ER pattern in the general population has been reported to range from less than 1% to 13%, depending on age, sex, race, and the criteria for J point elevation.[63] This ECG phenomenon has long been considered an innocuous variant in healthy individuals. However, Haissaguerre and colleagues[64] have noted that J point elevation (≥1 mm above baseline) on inferolateral ECG leads was overrepresented significantly (31%) and was greater in magnitude among 206 case participants who experienced cardiac arrest caused by idiopathic ventricular fibrillation (IVF) than in 412 controls (5%; $P < 0.001$) matched for age, sex, race, and level of physical activity. Those patients with ER were more often males and have a personal history of syncope or cardiac arrest during sleep than those without ER pattern. Similarly, Rosso and colleagues[65] noted an overrepresentation of J point elevation in their 45 IVF patients compared to controls (45% versus 13%; $P = 0.001$), with the same observation of male predominance among those with ER. Therefore, according to the 2016 J wave syndromes expert consensus conference report, early repolarization syndrome (ERS) is typically diagnosed in patients who display ER in the inferior and/or lateral leads and present with aborted cardiac arrest, documented ventricular fibrillation, or polymorphic ventricular tachycardia. The Proposed Shanghai Scoring System for the diagnosis of ERS was presented in the 2016 consensus document.[51]

In community-based general population of 10,864 middle-aged (30 to 59 years 52% male) Finnish individuals, Tikkanen and colleagues[66] identified 630 persons overall (5.8%) with a J point elevation of at least 0.1 mV. This overall prevalence of ER pattern was reduced to only 0.33% when considering a J point elevation of 0.2 mV or greater. A 30-year follow-up with the endpoint of cardiac death showed that compared to participants without a J point elevation, those with ER (J point ≥0.1 mV) in the inferior leads had an increased risk of both cardiac death (adjusted relative risk [ARR] = 1.28; 95% confidence interval [CI] = 1.04 to 1.59; $P = 0.03$) and arrhythmias (ARR = 1.43; 95% CI = 1.06 to 1.94; $P = 0.03$), and this

risk was further increased (cardiac death ARR = 2.98; 95% CI = 1.85 to 4.92; $P < 0.001$; arrhythmia ARR = 2.92; 95% CI = 1.45 to 5.89; $P < 0.001$) with increasing elevation (≥0.2 mV) of the J point. However, an ER pattern localizing to only the lateral leads did not show a statistically significant association with increased risk for arrhythmic cardiac death.[66] The clinical conundrum with respect to this inferolateral ERS is distinguishing the potentially lethal ERS from the frequently observed juvenile ER pattern seen in healthy individuals, particularly healthy athletes.

Genetic Basis.

The indication for a genetic basis of ERS stems from the observation that 16% of IVF patients with an ER pattern had a family history of unexplained sudden death.[64] In 2009, Haissaguerre and colleagues[67] described the first gene to be implicated in ERS, a rare, functionally uncharacterized, missense mutation (S422L) in the *KCNJ8*-encoding pore-forming subunit Kir6.1 of the adenosine triphosphate (ATP)–sensitive potassium channel in a 14-year-old girl with IVF. Since then, this same mutation has been described in additional cases of BrS and ERS and has been shown to have a gain of function in electrophysiologic phenotype.[68,69] However, despite its abnormal in vitro functional phenotype, it is now appreciated that S422L-*KCNJ8* is far more common than once thought, thus questioning its pathogenic status. In fact, since its implication in disease, S422L-*KCNJ8* is now known to have heterozygous frequency of 0.5% (168 of 33,363) among European Caucasians in the Exome Aggregation Consortium (ExAC) and as high as 4% among the Ashkenazi Jewish population, thus suggesting that this variant may be a functional polymorphism rather than a pathogenic mutation.[70] In 2010, Burashnikov and colleagues[71] implicated the LTCC alpha$_1$ (*CACNA1C*), beta$_2$ (*CACNB2b*), and alpha$_2$delta (*CACNA2D1*) subunit encoding genes in the pathogenesis of ERS with their identification of mutations in 4 of 24 (16.6%) ERS index cases.[71] However, not all these genetic variants have been characterized functionally, and some may represent rare variants of uncertain significance. In addition, rare variants in *ABCC9*, *SCN5A*, and *SCN10A* have been implicated in ERS.[51]

Idiopathic Ventricular Fibrillation

Clinical Description and Manifestations

Ventricular fibrillation (VF) is a major cause of SCD and ultimately is the “final common arrhythmic pathway” for all the aforementioned channelopathies. In the absence of identifying structural or genetic abnormalities to explain the VF or the out-of-hospital cardiac arrest, the VF is termed “idiopathic” ventricular fibrillation (IVF). In essence, as in SIDS, IVF is a diagnosis of exclusion and can stem from several underlying mechanisms. IVF may account for up to 10% of sudden deaths, especially in the younger population. About 30% of IVF-labeled individuals will have recurrent episodes of VF. About 20% have a family history of sudden death or IVF, suggesting a hereditary component in some cases.[72] Unfortunately, most IVF cases are often only recognized after their first out-of-hospital cardiac arrest.

Genetic Basis.

IVF may be clinically, genetically, and mechanistically related most closely to BrS. As many as 20% of IVF patients have been diagnosed subsequently with BrS, depending on the criteria used.[1] As with BrS,

loss-of-function *SCN5A* mutations have been identified in IVF patients who have no ECG stigmata at rest, or with provocation for BrS. However, some case reports of IVF have identified mutations in other arrhythmia susceptibility genes, such as *ANK2*, which encodes for ankyrin B; *RYR2*, which encodes for the cardiac ryanodine receptor; and *CALM1*, which encodes for calmodulin 1.[35,73] These particular IVF cases ultimately represented atypical presentations of LQTS or CPVT. For most IVF cases, a genetic mechanism remains undefined.

However, Alders and associates[72] embarked on a genome-wide haplotype-sharing analysis involving three distantly related IVF pedigrees and identified a haplotype on chromosome 7q36 that was conserved among all affected individuals and in 7 of 42 independent IVF patients, suggesting a risk locus for IVF. This chromosome segment contains part of the *DPP6* gene, which encodes for dipeptidyl-peptidase-6, a putative component of the transient outward current (Ito, Kv4.3) in the heart. Further, the investigators showed a 20-fold increase in *DPP6* mRNA expression in the myocardium of haplotype carriers compared to controls, suggesting that *DPP6* may be a candidate gene for IVF. To date, however, no IVF-associated coding-region mutations have been identified in *DPP6*. Valdivia and colleagues[74] identified a mutation in the *SCN3B*-encoded sodium channel Na_v $beta_3$ subunit that precipitates intracellular retention of $Na_v1.5$, functionally mimicking a trafficking-defective *SCN5A* loss of function, in a 20-year-old man with IVF.

Progressive Cardiac Conduction Disease (Defect)

Clinical Description and Manifestations

Cardiac conduction disease (CCD) causes a potentially life-threatening alteration in normal impulse propagation through the cardiac conduction system. CCD can result from a number of physiologic mechanisms, ranging from acquired to congenital, and with or without structural heart disease. Progressive cardiac conduction disease or defect (PCCD), also known as *Lev-Lenègre disease*, is one of the most common cardiac conduction disturbances in the absence of structural heart disease. It is characterized by progressive (age-related) alteration of impulse propagation through the His-Purkinje system, with right or left bundle branch block and widening of the QRS complex, leading to complete AV block, syncope, and occasionally sudden death.[75]

Genetic Basis.

In 1999, Schott and colleagues further expanded the spectrum of loss-of-function *SCN5A* disease with the inclusion of familial PCCD, identifying a splice-site *SCN5A* mutation (c.3963+2 T>C) associated with an autosomal dominant inheritance pattern in a large French family, as reviewed by Ruan and associates.[75] Since then, investigators have identified more than 30 PCCD-associated mutations in *SCN5A*. In addition to *SCN5A*, mutations in *SCN1B* can cause BrS with conduction disease. These mutations present with a loss-of-function phenotype through reduced current density and enhanced slow inactivation of the channel. As with most loss-of-function *SCN5A* diseases, the phenotypic expression of PCCD can be complex and is often present with a concomitant BrS or BrS-like phenotype. In fact, Probst and associates[76] showed that PCCD is the prevailing phenotype in BrS-associated *SCN5A* mutation carriers, in whom the penetrance of conduction defects was 76%.

In 2009, Meregalli and colleagues[61] demonstrated that the *SCN5A* mutation type can have a profound effect on the severity of PCCD and BrS. Studying 147 individuals hosting one of 32 different *SCN5A*

mutations, they found that patients with either a premature truncation mutation (M_T; i.e., nonsense or frameshift) or a severe loss-of-function missense mutation ($M_{inactive}$, >90% reduction in peak I_{Na}) had a significantly longer PR interval compared with patients with missense mutations having less impairment to the sodium current (M_{active}, ≤90% reduction). Further, those patients with a truncation mutation had significantly more episodes of syncope than those with an "active" mutation (M_{active}). These data suggest that mutations with a more deleterious loss of sodium current produce a more severe phenotype of syncope and conduction defect, providing the first evidence for intragenotype risk stratification associated with *SCN5A* loss-of-function disease.

Most recently, gain-of-function mutations (E7K, R164W, A432T, and G844D) in the *TRPM4*-encoded transient receptor potential melastatin type 4 ion channel have been implicated as a cause of autosomal dominant, isolated cardiac conduction disease and progressive familial heart block type 1 (PFHBI) following linkage analysis and subsequent mutational analysis of *TRPM4* in four different large, multigenerational pedigrees, thus identifying an essential role for calcium-activated nonselective cation channel activity in the cardiac conduction system.[77,78]

When CCD is associated with concomitant phenotype of LQTS, the QRS is usually narrow, and the conduction defect is typically an intermittent 2 : 1 AV block. Patients with LQT2, TS1, or ATS1 may also have dysfunctional AV conduction.

Sick Sinus Syndrome

Clinical Description and Manifestations

Sinus node dysfunction (SND) or sick sinus syndrome (SSS), manifesting as inappropriate sinus bradycardia, sinus arrest, atrial standstill, tachycardia-bradycardia syndrome, or chronotropic incompetence, is the leading reason for pacemaker implantation and has been attributed to dysfunction of the sinoatrial (SA) node.[1] SSS usually occurs in the elderly population (1 in 600 cardiac patients over age 65) with acquired cardiac conditions, including cardiomyopathy, congestive heart failure, ischemic heart disease, and metabolic disease. However, a significant number of patients show no identifiable cardiac anomalies or cardiac conditions underlying SND ("idiopathic" SND), which can occur at any age, including in utero. Additionally, familial forms of idiopathic SND consistent with autosomal dominant inheritance with reduced penetrance and recessive forms with complete penetrance have been reported.[75]

Genetic Basis.

Mutational analysis of small cohorts and case reports of patients with idiopathic SSS have thus far implicated four genes: *SCN5A*, *HCN4*, *ANK2*, and *MYH6* (**see Table 33.1**). To date, 15 SSS-associated mutations have been reported in *SCN5A*.[75,79] The mutations either produced nonfunctional sodium channels through loss of expression or channels with mild to severe loss of function through an altered biophysical mechanism of the channel.[79] In 2003, based on prior observations of arrhythmias and conduction disturbances, Benson and coworkers examined *SCN5A* as a candidate gene for congenital SSS in 10 pediatric patients from seven families who were diagnosed during the first decade of life and identified compound heterozygote mutations (T220I + R1623X, P1298L + G1408R, and delF1617 + R1632H) in five individuals from three of the seven families, implicating *SCN5A* in autosomal recessive SSS.[75] Not surprisingly, many of the *SCN5A*-positive patients displayed a mixed phenotype consisting of SSS, BrS, and/or CCD. The expressivity of the mixed phenotype can be highly variable within affected

families. In 2007 a 12-year-old boy with SSS, CCD, and recurrent VT was identified with an L1821fsX10 frameshift mutation that displayed a unique channel phenotype of 90% reduced current density (consistent with BrS/SSS/CCD), but an increase in late sodium current relative to the peak current (consistent with LQT3) for those channels expressed. As illustrated by this family, in whom the mutation was present in six asymptomatic members, with two displaying only mild ECG phenotypes, this disorder is often associated with incomplete or low penetrance.

Two loss-of-function mutations in hyperpolarization-activated cyclic nucleotide-gated channel 4 gene, *HCN4*, have been identified in two cases of idiopathic SND. The *HCN4* gene encodes the so-called I_f or pacemaker current and plays a key role in automaticity of the sinus node. In one study a heterozygous single-nucleotide deletion (c.1631delC) creating a frameshift mutation (P544fsX30) with early truncation of the protein was identified in an idiopathic SND patient, and in a second study, another patient with idiopathic SND had a missense mutation (D553N) that resulted in abnormal trafficking of the pacemaker channel.[80] Interestingly, the frameshift mutation identified in a 66-year-old woman produced a mild phenotype associated with sinus rhythm during exercise, whereas the D553N missense mutation identified in a 43-year-old woman was associated with severe bradycardia, recurrent syncope, QT prolongation, and polymorphic ventricular tachycardia (torsade de pointes), suggesting the potential for lethality in *HCN4*-mediated disease. Whether or not the preliminary 10% to 15% yield for defective *HCN4*-encoded pacemaker channels in idiopathic SND is durable, as derived from the two small cohorts, will require further studies involving much larger cohorts.

In 2008, Le Scouarnec and colleagues[81] reported the genetic and molecular mechanism involving *ANK2* (also known as *ANKB*)-encoded ankyrin B in two large families with high-penetrant and severe SND. Ankyrin B is essential for normal membrane organization of the ion channels and transporters in the cardiocytes within the SA node and is required for proper physiologic cardiac pacing. Dysfunction of ankyrin B-based trafficking pathway causes abnormal electrical activity in the SA node and SND. As in the sodium channel, variants in *ANK2* cause a variety of cardiac dysfunctions.

In 2011, Holm and colleagues,[82] using a GWAS on 792 Icelandic individuals with SSS and 37,592 Icelandic population controls, identified a rare missense variant (c.2161C>T, p.R721W) in MYH6-encoded alpha heavy-chain 6 subunit of cardiac myosin that was significantly associated with SSS. Moreover, the lifetime risk of being diagnosed with SSS was only 6% for noncarriers of c.2161C>T compared to 50% for carriers of the *MYH6* variant. In 2015, Ishikawa and associates[83] identified a three–base pair in-frame deletion resulting in a single–amino acid deletion (p.delE933) in one of nine unrelated genotype-negative probands with SSS. The mutant slowed down action potential propagation when heterologously expressed in atrial myocardial HL-1 cells. Moreover, morpholino knockdown of *MYH6* in zebrafish lead to a reduced heart rate that could be restored when coexpressed with wild-type *MYH6*, but not when coexpressed with dE933-*MYH6*.

“Ankyrin-B Syndrome”

The *ANK2* gene encodes ankyrin B protein, a member of a large family of proteins that anchors various integral membrane proteins to the spectrin-based cytoskeleton. Specifically, ankyrin B is involved in anchoring the Na^+,K^+-ATPase, Na^+/Ca^+ exchanger, and InsP3 receptor to specialized microdomains in the cardiomyocyte transverse tubules. Loss-of-function mutations of *ANK2* were shown originally to cause a dominantly inherited cardiac arrhythmia, with an increased risk for SCD associated with a prolonged QT interval, and subsequently the label “type 4 long QT syndrome” (LQT4) was assigned to this *ANK2* pedigree. Since then, this disorder has been more correctly renamed “sick sinus syndrome with

bradycardia," or the "ankyrin-B syndrome."[84]

In 2007, Mohler and colleagues[84] described the first human *ANK2* mutation (E1425G) identified in a large, multigenerational French kindred presenting with "atypical LQTS" displaying a phenotype of prolonged QT interval, severe sinus bradycardia, polyphasic T waves, and atrial fibrillation. Following this sentinel discovery, significant loss-of-function ankyrin B variants of differing degrees of functionality have been identified in patients with various arrhythmia phenotypes, including bradycardia, SND, delayed cardiac conduction/conduction block, IVF, atrial fibrillation, drug-induced LQTS, exercise-induced VT, and even a CPVT phenotype. In addition, 2% to 4% of ostensibly healthy white controls and 8% to 10% of black controls (including the most common "black"-specific variant L1622I) also host rare variants in *ANK2,* underscoring the challenge in distinguishing pathogenic mutations that truly mediate an "ankyrin-B syndrome" from rare *ANK2* variants of uncertain significance. Individuals hosting *ANK2* variants displaying a more severe loss of function in vitro tend to have a more severe cardiac phenotype and may be at increased risk for SCD.[84]

Familial Atrial Fibrillation

Clinical Description and Manifestations

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with a prevalence of about 1% in the general population and 6% in people over age 65 years[85] (**see Chapter 38**). Most often, AF is associated with underlying cardiac pathology, including cardiomyopathy, valvular disease, hypertension, and atherosclerotic cardiovascular disease, and is responsible for more than one third of cardioembolic episodes. However, AF can present even at an early age without any identifiable cardiac anomalies and is termed *lone* AF, accounting for 2% to 16% of all AF cases.[85] Further, approximately one third of lone AF patients have a family history of AF, suggesting familial forms of the disease.[86]

Genetic Basis.

Although the majority of familial atrial fibrillation (FAF) cases remain genetically elusive, several genetic loci and causative genes have been described over the past decade. In 1996, Brugada and colleagues identified three families with autosomal dominant AF. The age of onset ranged from in utero to 45 years. Genetic linkage analysis of these families revealed a novel locus for AF on chromosome 10 (10q22). In 2003 a second locus was identified at 6q14-16, again associated with autosomal dominant inheritance. To date, the underlying causative genes for both loci remain unknown.

In 2003, however, an AF-associated locus on chromosome 11 in a large four-generation family and subsequent identification of a SQTS-like gain-of-function mutation, S140G-*KCNQ1*, in $K_v7.1$ (I_{Ks}) was identified, thus providing for the first time a causal link between a cardiac potassium ion channel mutation and FAF. Interestingly, a second de novo mutation involving codon 141 of *KCNQ1* was identified in a patient with a severe form of AF and SQTS presenting in utero.[85] An R27C mutation in *KCNE2,* which encodes for a $K_v7.1$ and $K_v11.1$ interacting protein, was discovered in two AF families and produced an I_{Ks} gain-of-function phenotype when coexpressed with wild-type *KCNQ1.* In 2005 a V93I mutation in *KCNJ2* in 1 of 30 unrelated Chinese AF families was identified. Whereas loss-of-function *KCNJ2* mutations yield ATS1, the AF-associated V93I mutation conferred gain-of-function biophysical properties to the Kir2.1 channels. Lastly, in 2006, a loss-of-function mutation in *KCNA5* responsible for the $K_v1.5$ potassium channel I_{Kur} was discovered in a family with AF.

Beside these potassium channels, $Na_v1.5$ has been implicated in lone and familial AF. In fact, AF is a fairly common arrhythmia among patients with loss-of-function *SCN5A*-opathies; in particular, up to 15% to 20% of BrS cases develop AF.[76] In 2008 a novel *SCN5A* mutation (M1875T) was described in a family characterized by juvenile-onset atrial arrhythmias that progressed to AF in the absence of structural heart disease or ventricular arrhythmias. Functional studies of this mutant channel produced an increased peak current density and a depolarizing shift of activation (gain of function). Additionally, Darbar[86] identified *SCN5A* channel mutations in approximately 3% of AF cases. In 2014, Hasegawa and colleagues[87] performed a mutational analysis of AF-related genes (*KCNQ1*, *KCNH2*, *KCNE1-3*, *KCNJ2*, and *SCN5*A) and identified three missense variants (*SCN5A*-M1875T, *KCNJ2*-M301K, and *KCNQ1*-G229D) in 3 of 30 (10%) consecutive patients with juvenile-onset AF.

Non–ion channel genes also have been implicated in familial and lone AF.[85] In 2008, Hodgson-Zingman and colleagues identified a frameshift mutation in the *NPPA* gene in a large pedigree with FAF.[88] *NPPA* encodes for the atrial natriuretic peptide, which modulates ionic currents in myocardial cells and may shorten atrial conduction time. The clinical phenotype of neonatal onset of AF, with an autosomal recessive inheritance pattern, was recently linked to a mutation in *NUP155*, which encodes for a member of the nucleoporins family of proteins. In 2006, Gollob and colleagues identified four heterozygote *GJA5* missense mutations in 4 of 15 patients with early-onset idiopathic AF.[89] Most interestingly, three of the four mutations were shown to be in cardiac tissue only (somatic) and not germline in origin. *GJA5* encodes for the cardiac gap-junction protein connexin 40, which is selectively expressed in atrial myocytes and mediates the finely orchestrated electrical activation of the atria. Most recently, Yang and colleagues[90,91] have identified either a *GATA4* (S70T and S160T) or *GATA5* (G184V, K218T, and A266P) missense mutation in 5 or 130 (3.8%) unrelated Han Chinese individuals with familial AF. *GATA4* and *GATA5* belong to a family of cardiac transcription factors critical for cardiogenesis.

Future Perspectives

The comparatively young discipline of the heritable arrhythmia syndromes and cardiac channelopathies has exploded over the past decade. The pathogenic insights into the molecular underpinnings for nearly all these syndromes have matured through the entire continuum of research from discovery, translation, and most recently, incorporation into clinical practice. This bench-to-bedside maturation now requires the learned interpretation of the available genetic tests for these syndromes, with a clear understanding of the diagnostic, prognostic, and therapeutic implications associated with genetic testing for these channelopathies.

The emergence of next-generation sequencing platforms and systems biology bioinformatics algorithms are providing new tools to efficiently interrogate an individual's entire genome or exome (entire amino acid–encoding region of the genome) in a single reaction. This highly proficient technology effectively provides a list of every single-nucleotide substitution and small insertion/deletion (common or rare, benign or pathogenic) for every gene in a patient's genome and is crucial to the current and next phase of new gene discovery. Current and forthcoming advanced sequencing technologies and systems biology bioinformatics algorithms will soon allow us to close the genetic gap in our understanding of these potentially lethal yet highly treatable cardiac arrhythmia syndromes. This will not only foster new disease-causing gene discovery, but also reveal novel genetic variants that may in part explain reduced penetrance and variable expressivity and help identify patients at greatest risk for a potentially tragic cardiac event. Continued exploration into the underlying genetic and molecular basis of these arrhythmia

syndromes will open the door for novel approaches to genotype-specific pharmacologic therapeutics.

In addition, recent advances in cellular programming have provided new avenues for understanding the etiology of complex diseases. The biomedical promise of human induced pluripotent stem (iPS) cell–generated cardiomyocytes, derived from a patient's own skin biopsy (fibroblast), venipuncture (lymphocytes), or urine sample, is enormous for cardiac research into disease models, personalized drug development, and key questions about the reduced penetrance and variable expressivity common among these cardiac channelopathies.

Despite that pharmacologic and invasive therapies for inherited cardiac arrhythmia disorders often achieve symptom reduction, there is still an urgent need for alternative therapeutics to effectively treat or even cure the most severe forms. With continued understanding of the genetic and molecular basis of these syndromes, as well as of “gene silencing” based on small interfering RNA (siRNA), microRNA (miRNA), and small hairpin RNA (shRNA), together with the development of novel RNA-guided nuclease-mediated CRISPER/Cas9 genome editing, sophisticated viral vectors such as adeno-associated virus 9 (AAV9), and novel gene delivery strategies, gene therapy may become a feasible option for some patients with difficult-to-manage, potentially life-threatening cardiac arrhythmias.[92]

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34

Mechanisms of Cardiac Arrhythmias

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Foundations of Cardiac Electrophysiology

Physiology of Ion Channels

Electrical signaling in the heart involves the passage of ions through ionic channels. The sodium, potassium, calcium, and chloride (Na^+, K^+, Ca^{2+}, and Cl^-) ions are the major charge carriers, and their movement across the cell membrane through channel pores creates a flow of current that generates excitation and signals in cardiac myocytes. Opening of ion channels allows selected ions to flow passively down the electrochemical activity gradient at a very high rate (>10^6 ions per second). The high transfer rates and restriction to “downhill” fluxes not stoichiometrically coupled to the hydrolysis of

energy-rich phosphates distinguish ionic channel mechanisms from those of other ion-transporting structures (pumps and exchangers), such as sarcolemmal Na^+,K^+–adenosine triphosphatase (ATPase), sarcoendoplasmic reticulum Ca^{2+}-ATPase (SERCA) or the Na^+/Ca^{2+} exchanger (NCX). Ion channels may be induced to open or close (gated) by extracellular and intracellular ligands, changes in transmembrane voltage, or mechanical stress (**Table 34.1**). Gating of single ion channels can best be studied by means of the patch-clamp technique.

TABLE 34.1

Synopsis of Transsarcolemmal Ionic Currents in Mammalian Cardiac Myocytes

CURRENT	SUBUNIT	FUNCTIONAL PROPERTIES
I_{Na}	Nav1.5, Nav1.1, Nav1.3, Nav1.6, Nav1.8 (alpha subunits)	TTX-resistant (Nav1.5, Nav1.8) and TTX-sensitive (Nav1.1, Nav1.3, Nav1.6) voltage-gated currents; Nav1.5 is the major cardiac isoform; neuronal Na^+ channel isoforms contribute to SA node pacemaking and ventricular repolarization
$I_{Ca.L}$	Cav1.2 (alpha subunit)	L-type (*l*ong lasting, *l*arge conductance) Ca^{2+} currents through voltage-gated Ca^{2+} (Cav) channels blocked by dihydropyridine antagonists (e.g., nifedipine), phenylalkylamines (e.g., verapamil), benzodiazepines (e.g., diltiazem), and various divalent ions (e.g., Cd^{2+}); activated by dihydropyridine agonists (e.g., Bay K 8644); responsible for phase 0 depolarization and propagation in SA and AV nodal tissue and contributing to the plateau of atrial, His-Purkinje, and ventricular cells; main trigger of Ca^{2+} release from the sarcoplasmic reticulum (Ca^{2+}-induced Ca^{2+} release); the noninactivating or "window" component underlies EADs
$I_{Ca.T}$	Cav3.1/alpha$_{1G}$ (alpha subunit)	T-type (*t*ransient current, *t*iny conductance) Ca^{2+} currents through Cav channels blocked by mibefradil and efonidipine but insensitive to dihydropyridines; may contribute an inward current to the later phase of phase 4 depolarization in pacemaker cells and action potential propagation in AV nodal cells; role in triggering Ca^{2+}-induced Ca^{2+} release uncertain
I_f	HCN4 (alpha subunit)	Hyperpolarization-activated "funny" current carried by Na^+ and K^+ in SA and AV nodal cells and His-Purkinje cells; involved in generating phase 4 depolarization; increases the rate of impulse initiation in pacemaker cells
I_{K1}	Kir2.1 (alpha subunit)	K^+ current through inwardly rectifying K^+ (Kir) channels, voltage-dependent block by Ba^{2+} at micromolar concentrations; responsible for maintaining resting the membrane potential in atrial, His-Purkinje, and ventricular cells; channel activity is a function of both membrane potential and $[K^+]_o$; inward rectification appears to result from depolarization-induced internal block by Mg^{2+} and neutral or positively charged amino acid residues in the cytoplasmic channel pore
$I_{K.G}$ ($I_{K.ACh}$, $I_{K.Ade}$)	Kir3.1/Kir3.4 (alpha subunit)	Inwardly rectifying K^+ current activated by muscarinic (M_2) and purinergic (type 1) receptor stimulation via GTP regulatory (G) protein signal transduction; expressed in SA and AV nodal cells and atrial cells, where it causes hyperpolarization and action potential shortening; activation causes negative chronotropic and dromotropic effects
I_{Ks}	KvLQT1 (alpha subunit)/minK (beta subunit)	K^+ current carried by a voltage-gated K^+ (Kv) channel (delayed rectifier K^+ channel); plays a major role in determining phase 3 of the action potential
I_{Kr}	hERG (alpha subunit)/MiRP1 (beta subunit)	Rapidly activating component of delayed rectifier K^+ current; I_{Kr} specifically blocked by dofetilide and sotalol in a reverse use–dependent manner; inward rectification of I_{Kr} results from depolarization-induced fast inactivation; plays a major role in determining the APD
I_{Kur}	Kv1.5 (alpha subunit)	K^+ current through a Kv channel with ultrarapid activation but ultraslow inactivation kinetics; expressed in atrial myocytes; determines the APD
$I_{K.Ca}$	SK2 (alpha subunit)	K^+ current through small-conductance Ca^{2+}-activated channels; blocked by apamin and expressed in human atrial and ventricular myocytes; determines the APD; upregulated in failing cardiomyocytes
I_{to} (I_{to1}, I_A)	Kv4.3 (alpha subunit)/KChIP2 (beta subunit)	Transient outward K^+ current through voltage-gated (Kv) channels; exhibits fast activation and inactivation and recovery kinetics; blocked by 4-aminopyridine in a reverse use–dependent manner; contributes to the time course of phase 1 repolarization; transmural differences in I_{to} properties contribute to regional differences in early repolarization
$I_{Cl.Ca}$ (I_{to2})	?	4-Aminopyridine–resistant transient outward current carried by Cl^- ions; activated by an increase in intracellular calcium level; blocked by stilbene derivatives (SITS, DIDS); contributes to the time course of phase 1 repolarization; may underlie spontaneous transient inward currents under conditions of Ca^{2+} overload; molecular correlate uncertain
$I_{Cl.cAMP}$	?	Time-independent chloride current regulated by the cAMP/adenylate cyclase pathway; slightly depolarizes resting membrane potential and significantly shortens the APD; antagonizes action potential prolongation associated with beta-adrenergic stimulation of $I_{Ca.L}$
$I_{Cl.swell}$ or $I_{Cl.vol}$	?	Outwardly rectifying, swelling-activated Cl^- current; inhibited by 9-anthracene carboxylic acid; activation causes resting membrane depolarization and action potential shortening
$I_{K.ATP}$	Kir6.2 (alpha subunit)/SUR	Time-independent K^+ current through Kir channels activated by a fall in intracellular ATP concentration; inhibited by sulfonylurea drugs, such as glibenclamide; activated by pinacidil, nicorandil, cromakalim; causes shortening of the APD during myocardial ischemia or hypoxia
$I_{Cir.swell}$	?	Inwardly rectifying, swelling-activated cation current; permeable to Na^+ and K^+; inhibited by Gd^{3+}; depolarizes resting membrane potential and prolongs terminal (phase 3) repolarization
$I_{Na/Ca}$	NCX1.1	Current carried by Na^+/Ca^{2+} exchanger; causes net Na^+ outward current and Ca^{2+} inward current (reverse mode) or net Na^+ inward and Ca^{2+} outward current (3 Na^+ for 1 Ca^{2+}); direction of Na^+ flux depends on membrane potential and intracellular and extracellular concentrations of Na^+ and Ca^{2+}; Ca^{2+} influx mediated by $I_{Na/Ca}$ can trigger SR Ca^{2+} release; underlies I_{ti} (transient inward current) under conditions of intracellular Ca^{2+} overload
$I_{Na/K}$	Alpha subunit/beta subunit	Na^+ outward current generated by Na^+,K^+-ATPase (stoichiometry: 3 Na^+ leave and 2 K^+ enter); inhibited by digitalis
I_{ti}	?	Transient inward current activated by Ca^{2+} waves; I_{ti} possibly reflects 3 Ca^{2+}-dependent components: I_{NCX}, $I_{Cl.Ca}$, and a *TRPM4* (transient receptor potential cation channel, member 4 gene)–mediated current
Electroneutral Ion-Exchanging Proteins		
Ca^{2+}-ATPase	SERCA2	Extrudes cytosolic calcium
Na/H	Cardiac myocytes express isoform NHE1	Exchanges intracellular H^+ for extracellular Na^+; specifically inhibited by the benzoylguanidine derivatives HOE 694 and HOE 642; inhibition causes intracellular acidification
Cl^--HCO_3^-		Exchanges intracellular HCO_3^- for external Cl^-; inhibited by SITS
Na^+-K^+-$2Cl^-$	Na-K-Cl NKCC1	Cotransporter blocked by amiloride

APD, Action potential duration; *AV,* atrioventricular; *DIDS,* 4,4′-diisothiocyanatostilbene-2,2′-disulfonic acid; *EADs,* early afterdepolarizations; *GTP,* guanosine triphosphate; *SA,* sinoatrial; *SITS,* 4-acetamido-4′-isothiocyanatostilbene-2,2′-disulfonic acid; *TTX,* tetrodotoxin.

The *permeability ratio* is a commonly used index of a channel's ionic selectivity, defined as the ratio of

the permeability of one ion type to that of the main permeant ion type. Permeability ratios of voltage-gated K^+ and Na^+ channels for monovalent and divalent (e.g., Ca^{2+}) cations are usually less than 1 : 10. Voltage-gated Ca^{2+} channels exhibit a more than 1000-fold discrimination against Na^+ and K^+ ions (e.g., P_K / P_{Ca} = 1/3000) and are impermeable to anions.

Because ions are charged, net ionic flux through an open channel is determined by both the concentration and the electrical gradients across the membrane (electrodiffusion). The potential at which the passive flux of ions resulting from the chemical driving force is exactly balanced by the electrical driving force is called the *equilibrium, reversal,* or *Nernst potential* of the channel. In a channel that is perfectly selective for one ion species, the reversal potential equals the thermodynamic equilibrium potential of that ion, E_S, which is given by the Nernst equation in the form:

$$E_S = (RT/zF) \ln([S_o]/[S_i])$$

where $[S_i]$ and $[S_o]$ are the intracellular and extracellular concentrations of the permeant ion, respectively, z is the valence of the ion, R is the gas constant, F is the Faraday constant, T is the temperature (kelvin), and ln is the natural logarithm. At membrane voltages more positive than the reversal potential of the channel, passive cation movement is outward, whereas it is inward at membrane potentials more negative than the Nernst potential of that channel. If the current through an open channel is carried by more than one permeant ion, the reversal potential becomes a weighted mean of all Nernst potentials.

Membrane voltages during a cardiac action potential vary over the range of approximately −90 to +30 mV (**eTable 34.1**). With physiologic external K^+ (4 mM), E_K is approximately −91 mV, and passive movement of K^+ during an action potential is out of the cell. On the other hand, because the calculated reversal potential of a cardiac Ca^{2+} channel is +64 mV (assuming that P_K/P_{Ca} = 1/3000, K_i = 150 mM, K_o = 4 mM, Ca_i = 100 nM, and Ca_o = 2 mM), passive Ca^{2+} flux is into the cell. With physiologic internal and external chloride concentrations, E_{Cl} is −83 to −36 mV, and passive movement of Cl^- ions through open chloride channels can be both inward and outward at membrane potentials typically occurring during a cardiac action potential. In more general terms, the direction and magnitude of passive ion flux through a single open channel at any given transmembrane voltage are governed by the reversal potential of that ion and its concentration gradient across the membrane.

ETABLE 34.1

Ion Concentrations and Reversal Potentials in Cardiac Muscle

ION	EXTRACELLULAR CONCENTRATION $[S]_o$ (mM)	INTRACELLULAR CONCENTRATION $[S]_i$ (mM)	RATIO $[S]_o/[S]_i$	E_S (mV)
Na^+	145	15	9.7	+60
K^+	4	150	0.027	−94
Cl^-	120	5-30	4-24	−83 to −36
Ca^{2+}	2	10^{-4}	2×10^4	+129

Ion Flux Through Voltage-Gated Channels.

Changes in transmembrane potential determine ion flux through voltage-gated channels, not only through

the voltage dependence of the electrochemical driving force on the permeant ion, but also through the voltage dependence of channel activation. The fraction of time that a channel is open and allows ionic flux is determined by the membrane voltage. Activation of cardiac Na^+ channels or voltage-dependent K^+ channels (see later discussions) increases with membrane depolarization. Note that channels do not have a sharp voltage threshold for opening. Rather, the dependence of channel activation on membrane potential is a continuous function of voltage and follows a sigmoidal curve (**Fig. 34.1A**, *blue curve*). The potential at which activation is half-maximal and the steepness of the activation curve determine the channel's activity during changes in membrane potential. Shifting the activation curve to potentials positive to the midpoint of activation and reducing the steepness of the channel's activation curve are two possible mechanisms by which ion channel blockers can inhibit ion channel activity.

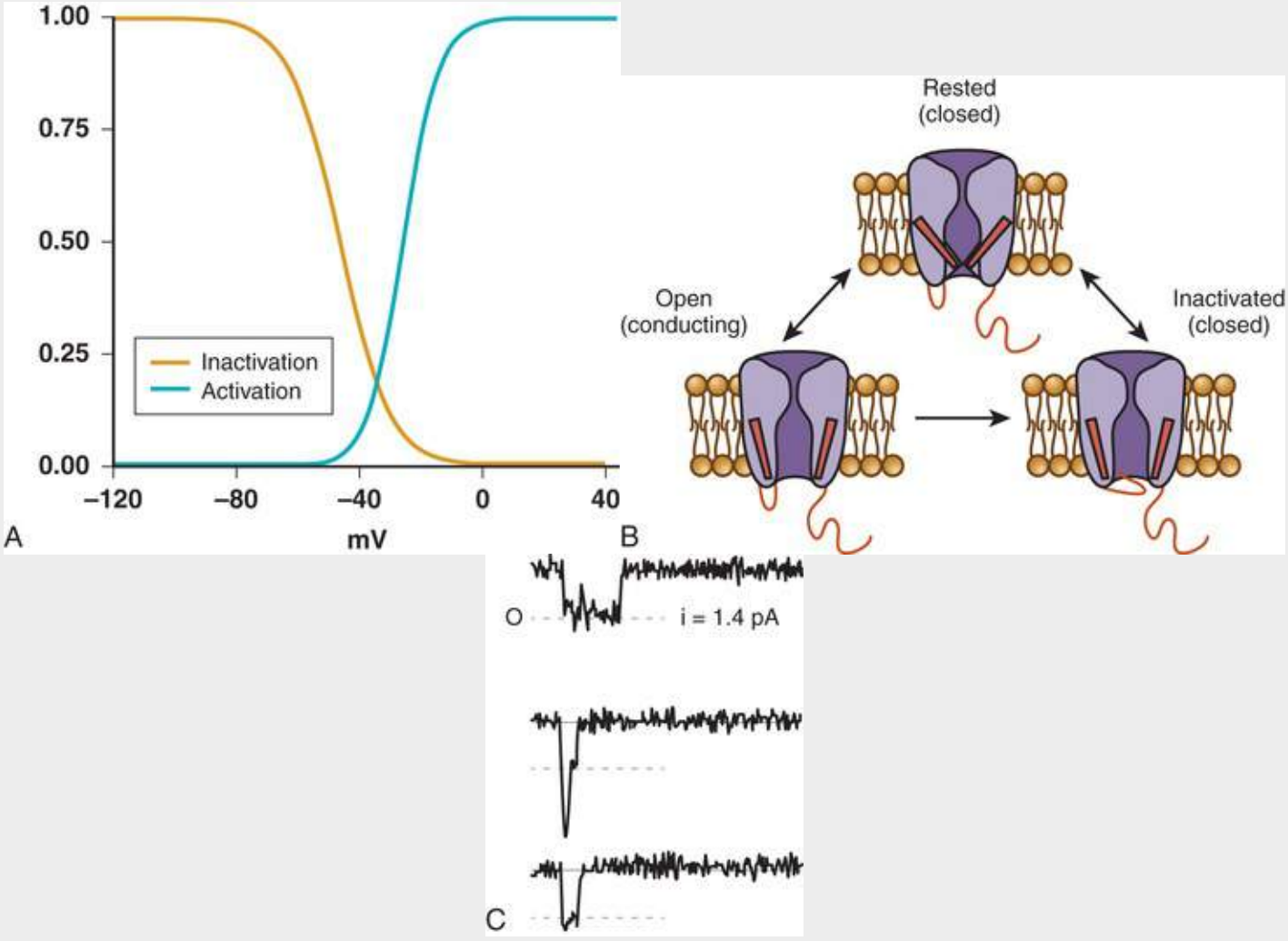


FIGURE 34.1 **A,** Curves that describe the voltage dependence of channel opening or the transition from the rested, closed to the open, conducting state (activation curve, *blue*) and channel availability (inactivation, *orange*). The inactivation or availability curve describes the voltage dependence of the occupancy of the inactivated state, and channels may transition to the inactivated state by way of the open or the rested, closed state. Generally, an inactivated channel must first return to the closed state in order to be available to open again. **B,** Schematic of the principal conformations of voltage-dependent channels. The position of the activation gate changes with the transition from closed to open, and the transition to the inactivated state is determined by the position of the inactivation gate. **C,** Single-channel current recordings showing the opening of sodium (Na) channels in response to a step change in voltage. The *middle tracing* reflects the activity of two channels, each with a single-channel amplitude of 1.4 pA.

As indicated in **Fig. 34.1B**, open channels enter a nonconducting conformation after a depolarizing change in membrane potential, a process termed *inactivation*. If membrane depolarization persists, the

channel remains inactivated and cannot reopen. This steady-state inactivation increases with membrane depolarization in a sigmoidal fashion (**see Fig. 34.1A**, *gold curve*). Inactivation curves of the various voltage-gated ion channels in the heart differ in their slopes and midpoints of inactivation. For example, sustained membrane depolarization to −50 mV (as may occur in acutely ischemic myocardium) causes almost complete inactivation of the fast voltage-gated Na^+ channel, whereas the L-type Ca^{2+} channel (see Voltage-Gated Ca^{2+} Channels) exhibits only little inactivation at this membrane potential. Activation and inactivation curves can overlap, in which case a steady-state or noninactivating current flows. The existence of such a "window" current has been verified for both the voltage-gated Na^+ and the L-type Ca^{2+} currents. The L-type Ca^{2+} current and the fast Na^+ window currents have been implicated in the genesis of triggered activity arising from early afterdepolarizations (EAD) and delayed afterdepolarizations (DAD).[1]

Channels recover from inactivation and then enter the closed state, from which they can be reactivated and open again (**see Fig. 34.1B**). Rates of recovery from inactivation vary among the different types of voltage-dependent channels and usually follow monoexponential or multiexponential time courses, with the longest time constants ranging from a few milliseconds, for example, as for the fast sodium current, to several seconds, as for some subtypes of K^+ currents. Together, the activity of voltage-dependent ion channels in cardiomyocytes over the course of an action potential is tightly regulated by the orchestrated interplay of a number of time- and voltage-dependent gating mechanisms, including activation, inactivation, and recovery from inactivation. All these mechanisms represent potential targets for pharmacologic intervention.

Principles of Ionic Current Modulation.

The whole-cell current amplitude I is the product of the number of functional channels in the membrane available for opening (N), the probability that a channel will open (P_o), and the single-channel current amplitude (i), or $I = N \cdot P_o \cdot i$. Modulation of current amplitudes in single cardiomyocytes therefore results from alterations in N, P_o, i, or any combination of these factors. Changes in the number of available channels in the cell membrane may result from alterations in the expression of ion channel–encoding genes. The magnitude of the single-channel current amplitude is dependent, among other factors, on the ionic concentration gradient across the membrane. Changes in channel activation (i.e., P_o) can result from phosphorylation or dephosphorylation of the channel protein. The channel's phosphorylation state may cause a shift in the membrane potential dependence of a channel's activation or availability curve, or both, or modification of the sensitivity of channel activation or inactivation to changes in membrane potential.

Phases of the Cardiac Action Potential

The cardiac transmembrane action potential consists of five phases: *phase 0,* upstroke or rapid depolarization; *phase 1,* early rapid repolarization; *phase 2,* plateau; *phase 3,* final rapid repolarization; and *phase 4,* resting membrane potential and diastolic depolarization (**Fig. 34.2 and eFig. 34.1**). These phases are the result of passive ion fluxes moving down their electrochemical gradients established by active ion pumps and exchange mechanisms. Each ion moves primarily through its own ion-specific channel. The following discussion explains the electrogenesis of each of these phases.

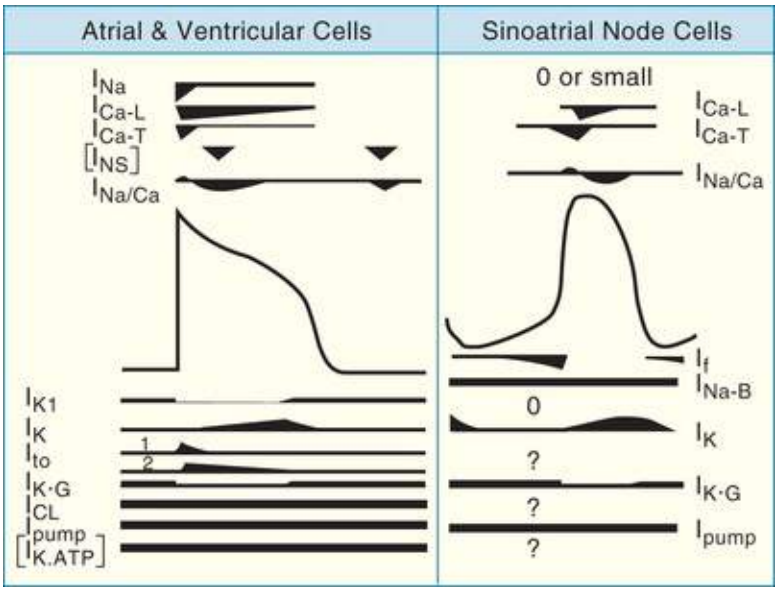
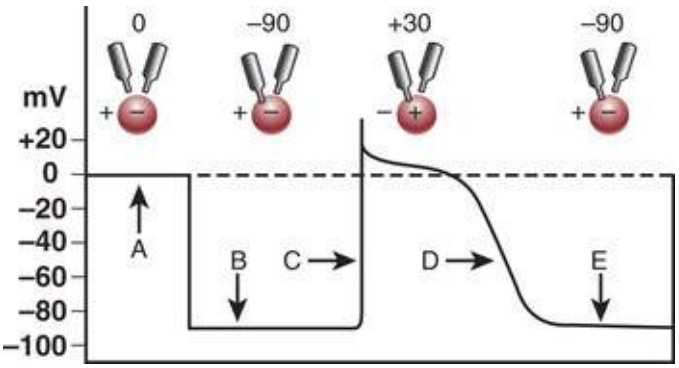


FIGURE 34.2 Currents and channels involved in generating resting membrane and action potentials. The time course of a stylized action potential of atrial and ventricular cells is shown on the **left,** and that of sinoatrial node (SAN) cells is on the **right.** Above and below are the various channels and pumps that contribute the currents underlying the electrical events. See **Table 34.1** for identification of the symbols and description of the channels or currents. Where possible, the approximate time courses of the currents associated with the channels or pumps are shown symbolically, without trying to represent their magnitudes relative to each other. I_K incorporates at least two currents, I_{Kr} and I_{Ks}. There appears to be an ultrarapid component as well, designated I_{Kur}. The *heavy bars* for I_{Cl}, I_{pump}, and $I_{K.ATP}$ indicate only the presence of these channels or pump, without implying magnitude of currents, because the magnitude would vary with physiologic and pathophysiologic conditions. The channels identified by *brackets* (I_{NS} and $I_{K.ATP}$) are active only under pathologic conditions. I_{NS} may represent a swelling-activated cation current. For the SAN cells, I_{NS} and I_{K1} are small or absent. *Question marks* indicate that experimental evidence is not yet available to determine the presence of these channels in SAN cell membranes. Although it is likely that other ionic current mechanisms exist, they are not shown here because their roles in electrogenesis are not sufficiently well defined. (From Members of the Sicilian Gambit. Antiarrhythmic Therapy: a Pathophysiologic Approach. Mount Kisco, NY: Futura; 1994, p 13.)



EFIGURE 34.1 Demonstration of action potentials recorded during impalement of a cardiac cell. **Upper row,** Shown are a cell (*circle*), two microelectrodes, and stages during impalement of the cell and its activation and recovery. Both microelectrodes are extracellular (*A*), and no difference in potential exists between them (0 potential). The environment inside the cell is negative, and the outside is positive, because the cell is polarized. One microelectrode has pierced the cell membrane (*B*) to record the intracellular resting membrane potential, which is −90 mV with respect to the outside of the cell. The cell has depolarized (*C*), and the upstroke of the action potential is recorded. At its peak voltage, the inside of the cell is approximately +30 mV with respect to the outside of the cell. The repolarization phase (*D*) is shown, with the membrane returning to its former resting potential (*E*).

General Considerations.

Ionic fluxes regulate membrane potential in cardiac myocytes in the following fashion. When only one type of ion channel opens, assuming that this channel is perfectly selective for that ion, the membrane potential of the entire cell would equal the Nernst potential of the permeant ion. By solving the Nernst equation for the four major ions across the plasma membrane, the following equilibrium potentials are obtained: sodium, +60 mV; potassium, −94 mV; calcium, +129 mV; and chloride, −83 to −36 mV (**Table 34.2**). Therefore, if K^+-selective channels open, such as the inwardly rectifying K^+ (Kir) channel (see later), the membrane potential approaches E_K (−94 mV). If Na^+-selective channels open, the transmembrane potential becomes E_{Na} (+60 mV). A quiescent cardiac myocyte (phase 4) has many more open potassium than sodium channels, and the cell's transmembrane potential is close to E_K. When two or more types of ion channels open simultaneously, each channel moves the membrane potential to the equilibrium potential of their respective permeant ions. The contribution of each ion type to the overall membrane potential at any given moment is determined by the instantaneous permeability of the plasma membrane to that ion. For example, deviation of the measured resting membrane potential from E_K (**see Table 34.2**) would predict that other ion types with equilibrium potentials positive to E_K are contributing to the resting membrane potential in cardiac myocytes. If it is assumed that Na^+, K^+, and Cl^- are the permeant ions at resting potential, their individual contributions to the resting membrane potential (V) can be quantified by the Goldman-Hodgkin-Katz (GHK) voltage equation:

TABLE 34.2

Properties of Transmembrane Potentials in Heart Cells

PROPERTY	SA NODAL CELL	ATRIAL MYOCYTE	AV NODAL CELL	HIS PURKINJE CELL	VENTRICULAR MYOCYTE
Resting potential (mV)	−50 to −60	−80 to −90	−60 to −70	−90 to −95	−80 to −90
Action Potential Features					
Amplitude (mV)	60-70	110-120	70-80	120	110-120
Overshoot (mV)	0-10	30	5-15	30	30
Duration (msec)	100-300	100-300	100-300	300-500	200-300
Vmax (V/sec)	1-10	100-200	5-15	500-700	100-200
Propagation velocity (m/sec)	<0.05	0.3-0.4	0.1	2-3	0.3-0.4
Fiber diameter (μm)	5-10	10-15	1-10	100	10-15

AV, Atrioventricular; *SA,* sinoatrial; *Vmax,* maximal rise of membrane potential.

Modified from Sperelakis N. Origin of the cardiac resting potential. In Berne RM, Sperelakis N, Geiger SR, editors. Handbook of Physiology: The Cardiovascular System. Bethesda, Md: American Physiological Society; 1979, p 190.

$$V = (RT/F)\ln[(P_K[Na]_o + P_{Cl}[Cl]_i)/P_K[K]_i + P_{Na}[Na]_P_c[Cl]_o$$

where the symbols have the meanings outlined previously. With only one permeant ion, V approximates the Nernst potential for that ion. With several permeant ion types, V is a weighted mean of all the Nernst potentials.

Resting Membrane Potential.

The intracellular potential during electrical quiescence in diastole is −50 to −95 mV, depending on the type of cell (**Table 34.2**). Therefore the inside of the cell is 50 to 95 mV negative relative to the outside of the cell because of the transmembrane gradients of ions such as K^+, Na^+, and Cl^-.

Because cardiac myocytes have an abundance of open K^+ channels at rest, the cardiac transmembrane potential (in phase 4) is close to $E_{K.}$ Outward potassium current through open, inwardly rectifying K^+ channels (I_{K1}) under normal conditions contributes to the resting membrane potential mainly in atrial and ventricular myocytes, as well as in Purkinje cells. Deviation of the resting membrane potential from E_K is the result of movement of ions with an equilibrium potential greater than the E_K, for example, Cl^- efflux through activated chloride channels, such as $I_{Cl.cAMP}$, $I_{Cl.Ca}$, and $I_{Cl.swell}$. Calcium does not contribute directly to the resting membrane potential, but changes in intracellular free calcium concentration $[Ca^{2+}]_i$ can affect other membrane conductance values. For example, an increase in sarcoplasmic reticulum (SR) Ca^{2+} load can cause spontaneous intracellular Ca^{2+} waves, which in turn activate the Ca^{2+} -dependent chloride conductance $I_{Cl.Ca}$ and thereby lead to spontaneous transient inward currents and concomitant membrane depolarization. Increases in $[Ca^{2+}]_i$ can also stimulate the Na^+/Ca^{2+} exchanger $I_{Na/Ca}$. This protein exchanges three Na^+ ions for one Ca^{2+} ion and thus generates a current; the direction depends on the $[Na^+]$ and $[Ca^{2+}]$ on the two sides of the membrane and the transmembrane potential difference (see Electrogenic Transporters). At the resting membrane potential and during a spontaneous SR Ca^{2+}-release event, this exchanger would generate a net Na^+ influx, possibly causing transient membrane depolarization.[2] Another transporter, the Na-K pump, electrogenically pumps Na^+ out of the cell and simultaneously pumps K^+ into the cell (three Na^+ outward and two K^+ inward) against their respective chemical gradients, keeping the intracellular K^+ concentration high and the intracellular Na^+ concentration low. The rate of Na^+-K^+ pumping to maintain the same ionic gradients must increase as the heart rate increases because the cell gains a small amount of Na^+ and loses a small amount of K^+ with each depolarization. Cardiac glycoside block of Na^+,K^+-ATPase increases contractility through an increase in intracellular Na^+ concentration $[Na^+]_i$, which in turn reduces Ca^{2+} extrusion through the Na^+/Ca^{2+} exchanger and thereby increases myocyte contractility.[3]

Phase 0: Upstroke or Rapid Depolarization.

A stimulus delivered to excitable tissues can evoke an action potential characterized by a sudden change in voltage caused by transient depolarization followed by repolarization. The action potential is conducted throughout the heart and is responsible for initiating each heartbeat. Electrical changes in the action potential follow a relatively fixed time and voltage relationship that differs according to specific cell types (**Fig. 34.3**). In neurons, the entire process takes several milliseconds, whereas action potentials in human cardiac fibers last several hundred milliseconds. Normally, the action potential is independent of the size of the depolarizing stimulus if the latter exceeds a certain threshold potential. Small, subthreshold depolarizing stimuli depolarize the membrane in proportion to the strength of the stimulus. However, when the stimulus is sufficiently intense to reduce membrane potential to a threshold value in the range of −70 to −65 mV for normal Purkinje fibers, an “all-or-none” response results. More intense depolarizing stimuli do not produce larger action potential responses; in contrast, hyperpolarizing pulses, or stimuli that render the membrane potential more negative, elicit a response proportional to the strength of the stimulus.

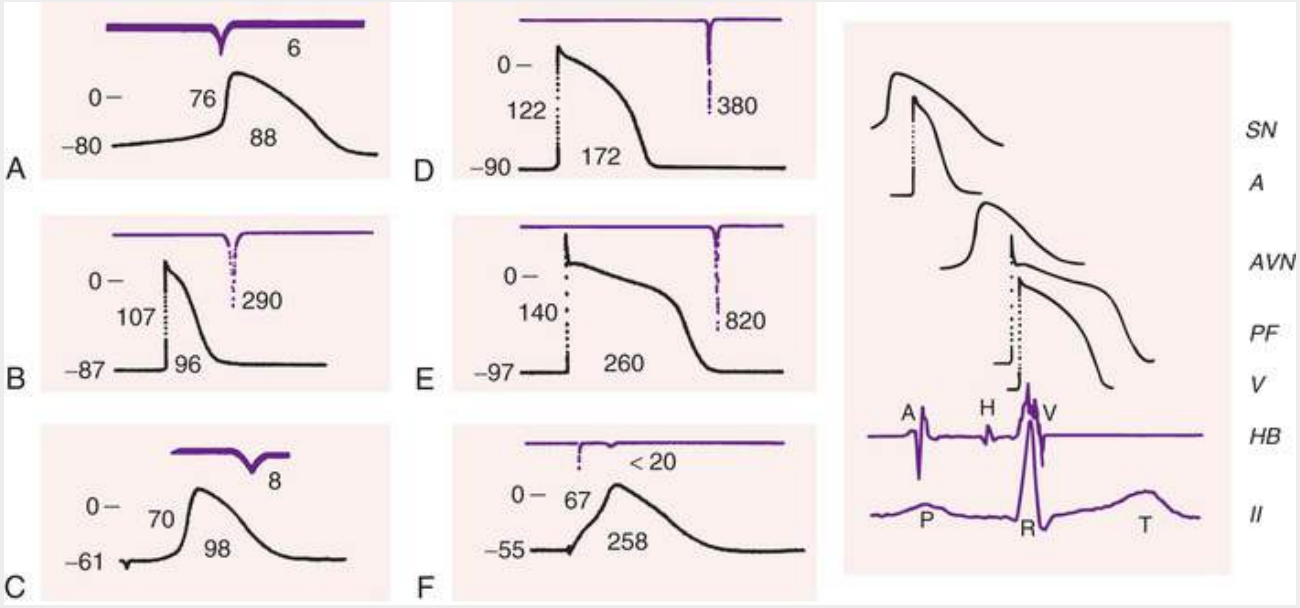


FIGURE 34.3 Action potentials recorded from different tissues in the heart **(left)** remounted along with a His bundle recording and scalar electrocardiogram from a patient **(right)** to illustrate the timing during a single cardiac cycle. In panels **A** to **F,** the top tracing is dV/dt of phase 0, and the second tracing is the action potential. For each panel, the numbers (from *left to right*) indicate maximum diastolic potential (mV), action potential amplitude (mV), action potential duration at 90% of repolarization (milliseconds), and rate of depolarization of phase 0 (V/sec). Zero potential is indicated by the *short horizontal line* next to the zero on the upper left of each action potential. **A,** Rabbit sinoatrial node. **B,** Canine atrial muscle. **C,** Rabbit AV node. **D,** Canine ventricular muscle. **E,** Canine Purkinje fiber. **F,** Diseased human ventricle. Note that the action potentials recorded in **A, C,** and **F** have reduced resting membrane potentials and amplitudes relative to the other action potentials. In the right panel, *A,* Atrial muscle potential; *AVN,* atrioventricular nodal potential; *HB,* His bundle recording; *II,* lead II; *PF,* Purkinje fiber potential; *SN,* sinus nodal potential; *V,* ventricular muscle potential. Horizontal calibration on the left: 50 milliseconds for **A** and **C,** 100 milliseconds for **B, D, E,** and **F;** 200 milliseconds on the right. Vertical calibration on the left: 50 mV; horizontal calibration on the right: 200 milliseconds. (Modified from Gilmour RF Jr, Zipes DP. Basic electrophysiology of the slow inward current. In Antman E, Stone PH, editors. Calcium Blocking Agents in the Treatment of Cardiovascular Disorders. Mount Kisco, NY: Futura; 1983, pp 1-37.)

Mechanism of Phase 0.

The upstroke of the cardiac action potential in atrial and ventricular muscle and His-Purkinje fibers is the result of a sudden increase in membrane conductance of Na^+. An externally applied stimulus or a spontaneously generated local membrane circuit current in advance of a propagating action potential depolarizes a sufficiently large area of membrane at an adequately rapid rate to open the Na^+ channels and depolarize the membrane further. When the stimulus activates enough Na^+ channels, Na^+ ions enter the cell down their electrochemical gradient. The excited membrane no longer behaves like a K^+ electrode, that is, exclusively permeable to K^+, but more closely approximates an Na^+ electrode, and the membrane voltage moves toward the Na^+ equilibrium potential (+60 mV).

The rate at which depolarization occurs during phase 0, that is, the maximum rate of change in voltage over time, is indicated by the expression dV/dt_{max} or Vmax (**see Table 34.2**), which is an approximation of the rate and magnitude of Na^+ entry into the cell and a determinant of conduction velocity for the propagated action potential. The transient increase in sodium conductance lasts 1 to 2 milliseconds. The action potential, or more properly the Na^+ current (I_{Na}), is said to be regenerative; that is, intracellular movement of a little Na^+ depolarizes the membrane more, which increases conductance of Na^+ more and allows more Na^+ to enter, and so on. As this process is occurring, however, $[Na^+]_i$ and positive intracellular charges increase and reduce the driving force for Na^+ flux into the cell. When the equilibrium potential for Na^+ (E_{Na}) is reached, the driving force acting on the ion to enter the cell

balances the driving force acting on the ion to exit the cell, and no current flows. Importantly, Na^+ conductance is time dependent, so when the membrane spends some time at voltages less negative than the resting potential, Na^+ conductance decreases (inactivation). Therefore an intervention that reduces membrane potential for a time (acute myocardial ischemia), but not to threshold, partially inactivates Na^+ channels, and if the threshold is now achieved, the magnitude and rate of Na^+ influx are reduced, which causes conduction velocity to slow.

In cardiac Purkinje fibers, sinoatrial cells, and to a lesser extent, ventricular muscle, different populations of Na^+ channels exist: the tetrodotoxin (TTX)-sensitive, neuronal Na^+ channel isoforms and the TTX-resistant Nav1.5 isoform, the latter being the predominant isoform in cardiac muscle.[4] Although the precise roles of TTX-sensitive Na^+ channels in ventricular or atrial cardiomyocytes have not been defined, these channels may be important modulators of sinoatrial node pacemaking, Purkinje myocyte action potential duration, and in arrhythmia production in some situations.[5] Neuronal Nav channels in the heart have been identified as regulators of contractility.[6]

Normal atrial and ventricular muscle cells and fibers in the His-Purkinje system exhibit action potentials with very rapid, large-amplitude upstrokes called *fast responses*. Action potentials in the normal sinoatrial (SA) and atrioventricular (AV) nodes and many types of diseased tissue have very slow, reduced-amplitude upstrokes and are called *slow responses* (**see Table 34.1 and Figs. 34.2 and 34.3**). Upstrokes of slow responses are mediated by a slow inward, predominantly L-type voltage-gated (Cav) Ca^{2+} current ($I_{Ca.L}$) rather than by the fast inward I_{Na} and are referred to as *slow response potentials* because the time required for activation and inactivation of $I_{Ca.L}$ is approximately an order of magnitude slower than that for the fast I_{Na}. The recovery of slow responses is delayed because of slow recovery of $I_{Ca,L}$ from inactivation. Recovery of $I_{Ca,L}$ slow-response channel requires establishment of the maximal diastolic potential (i.e., is voltage dependent) and more time before the channel can be activated again (i.e., time dependent), a phenomenon termed *postrepolarization refractoriness*. Moreover, calcium entry and $[Ca^{2+}]_i$ promote inactivation and delay recovery of slow-response channels.

The prolonged time for reactivation of $I_{Ca.L}$ probably accounts for the fact that SA and AV nodal cells remain refractory longer than the time that it takes for full voltage repolarization to occur. Thus, premature stimulation immediately after the membrane potential reaches full repolarization leads to action potentials with reduced amplitudes and upstroke velocities. Therefore, slow conduction and prolonged refractoriness are characteristic features of nodal cells. These cells also have a reduced "safety factor for conduction," which means that the stimulating efficacy of the propagating impulse is low, and conduction block occurs easily. The electrophysiologic changes accompanying acute myocardial ischemia may represent a depressed form of a fast response in the center of the ischemic zone and a slow response in the border area.

The threshold for activation of $I_{Ca.L}$ is about −30 to −40 mV. In fibers of the fast-response type, $I_{Ca.L}$ is normally activated during phase 0 by the regenerative depolarization caused by the fast I_{Na}. Current flows through both fast and slow channels during the latter part of the action potential upstroke. However, $I_{Ca.L}$ is much smaller than the peak I_{Na} and therefore contributes little to the action potential until the fast I_{Na} is inactivated after completion of phase 0. Thus, $I_{Ca.L}$ affects mainly the plateau of action potentials recorded in atrial and ventricular muscle and His-Purkinje fibers. In addition, $I_{Ca.L}$ may play a prominent role in partially depolarized cells in which fast I_{Na} has been inactivated, if conditions are appropriate for slow-channel activation.

Ca^{2+} entry through activated L-type Cav channels triggers release of Ca^{2+} from SR stores and is an

essential component of cardiac excitation-contraction coupling in atrial and ventricular myocardium (**see Chapter 22**). L-type Cav channels are expressed in SA and AV nodal cells, where they play a role in controlling automaticity and action potential propagation, respectively. Although T-type Cav channels have not been detected in human myocardium, experimental evidence in animals has suggested that these channels play an important role in determining SA node automaticity and AV nodal conduction.[7]

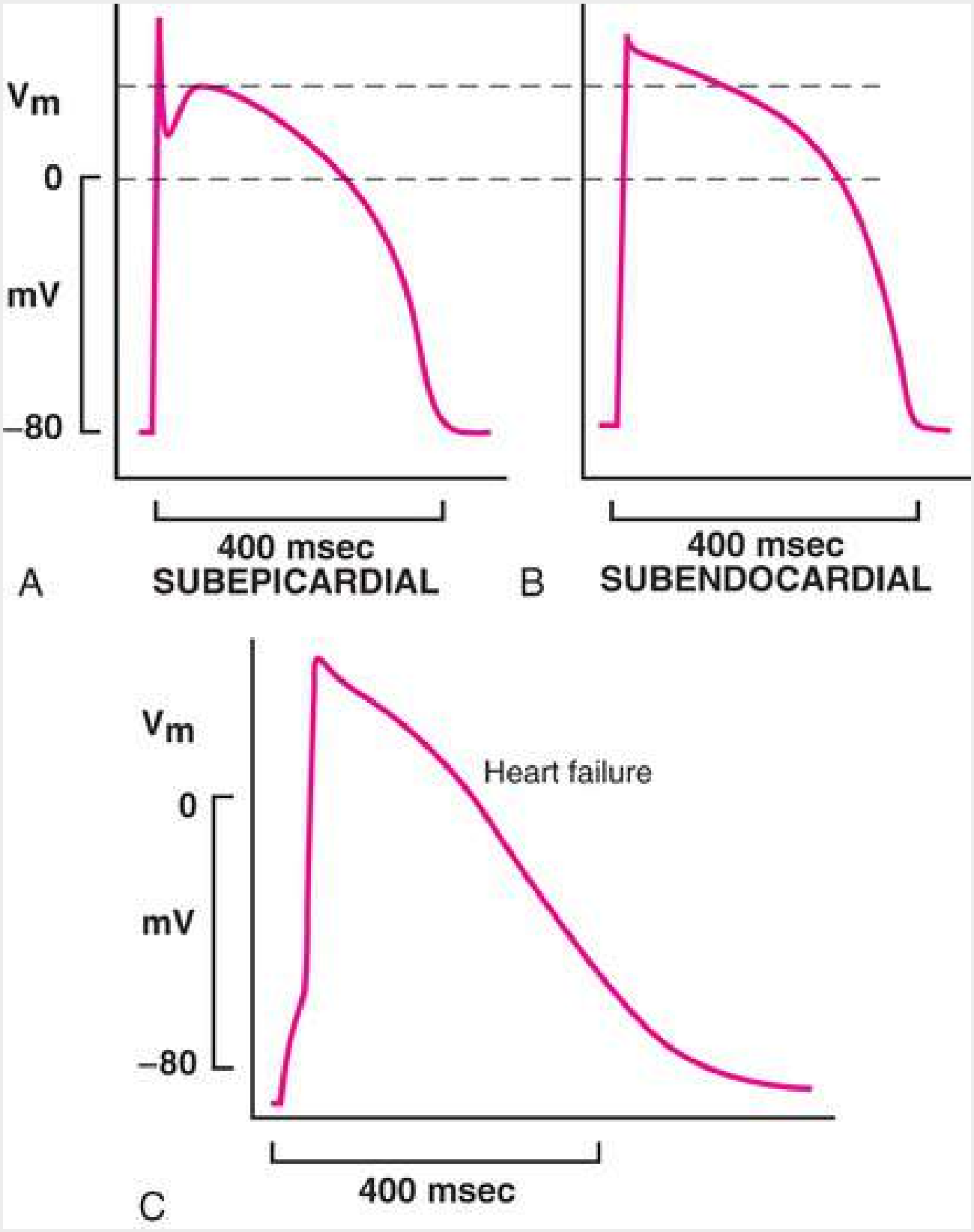
Other significant differences exist between the fast and slow channels. Drugs that elevate cyclic adenosine monophosphate (cAMP) levels, such as beta-adrenoceptor agonists, phosphodiesterase inhibitors such as theophylline, and the lipid-soluble derivative of cAMP, dibutyryl cAMP, increase $I_{Ca.L}$. Although Nav channels are sensitive to increases in cAMP, the net effect (decrease versus increase) appears to be species and condition dependent. Acetylcholine reduces $I_{Ca.L}$ by decreasing adenylate cyclase activity. However, acetylcholine stimulates the accumulation of cyclic guanosine monophosphate (cGMP). cGMP has negligible effects on basal $I_{Ca.L}$ but decreases the $I_{Ca.L}$ levels that have been elevated by beta-adrenoceptor agonists. This effect is mediated by cAMP hydrolysis through a cGMP-stimulated cyclic nucleotide phosphodiesterase.

Fast and slow channels can be differentiated on the basis of their pharmacologic sensitivity. Calcium channel antagonists that block the slow channel with a fair degree of specificity include verapamil, nifedipine, diltiazem, and D-600 (a methoxy derivative of verapamil). Antiarrhythmic agents such as lidocaine, quinidine, procainamide, and disopyramide affect the fast channel and not the slow channel (**see Chapter 36**).

Phase 1: Early Rapid Repolarization.

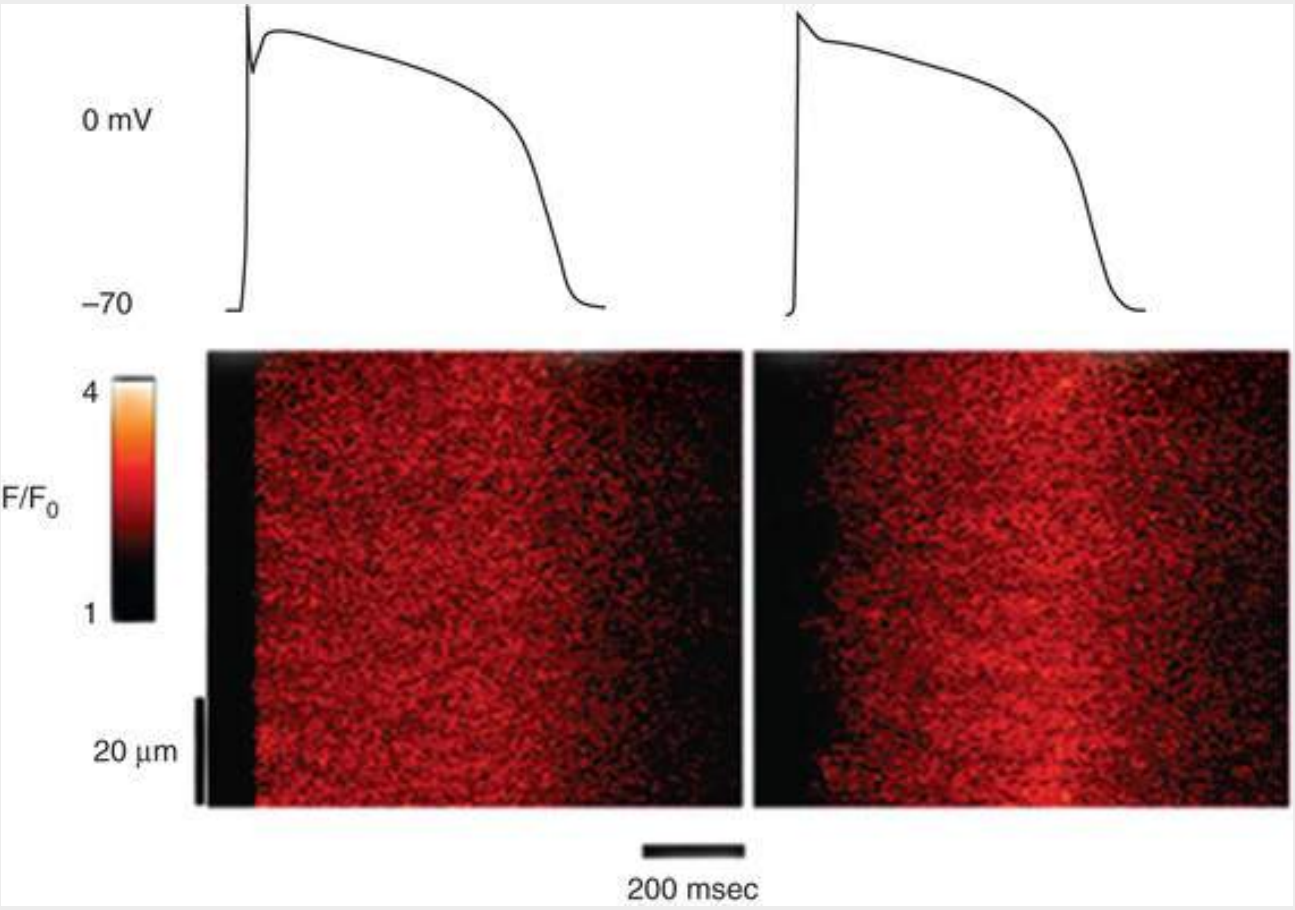
Following phase 0, the membrane repolarizes rapidly and transiently to almost 0 mV (early notch), partly because of inactivation of I_{Na} and concomitant activation of several outward currents.

The 4-aminopyridine–sensitive transient outward K^+ current, commonly termed I_{to} (or I_{to1}), is turned on rapidly by depolarization and then rapidly inactivates. Both the density and the recovery of I_{to} from inactivation exhibit transmural gradients in the left and right ventricular free wall, with the density decreasing and reactivation becoming progressively prolonged from epicardium to endocardium. Transmural differences in the expression of KChIP2, the auxiliary subunit to Kv4.3 pore-forming alpha subunits, may also contribute to the transmural gradient in I_{to} properties and densities in the human heart.[8] This gradient gives rise to regional differences in action potential shape, with increasingly slower phase 1 restitution kinetics and diminution of the notch along the transmural axis (**eFig. 34.2**).



EFIGURE 34.2 Action potential recordings demonstrating differences in the action potential shape of human ventricular myocytes of subepicardial **(A)** and subendocardial **(B)** origin. Subepicardial myocytes present a prominent notch during phase 1 repolarization of the action potential, most likely caused by a larger I_{to} in these cells. The notch is absent in subendocardial cells. The peak plateau potential is higher in subendocardial than in subepicardial myocytes, and the action potential duration tends to be shorter in subepicardial cells. **C,** Transmembrane action potential in a human ventricular cardiomyocyte from a failing heart. Note loss of the prominent phase 1 notch and delayed repolarization. Recording temperature = 35°C; $V_{m,}$ membrane potential. (**A, B,** From Näbauer M et al. Regional differences in current density and rate-dependent properties of the transient outward current in subepicardial and subendocardial myocytes of human left ventricle. Circulation 1996;93:168; **C,** from Priebe L, Beuckelmann DJ. Simulation studies of cellular electrical properties in heart failure. Circ Res 1998;82:1206.)

These regional differences might create transmural voltage gradients, thereby increasing dispersion of repolarization, a putative arrhythmogenic factor (Brugada syndrome; **see Chapters 33 and 39**). However, elimination of the physiologic repolarization gradient appears to be similarly arrhythmogenic. Downregulation of I_{to} is at least partially responsible for slowing of phase 1 repolarization in failing human myocytes. Studies have demonstrated that these changes in the phase 1 notch of the cardiac action potential cause a reduction in the kinetics and peak amplitude of the action potential–evoked intracellular Ca^{2+} transient because of failed recruitment and synchronization of SR Ca^{2+} release through $I_{Ca.L}$ (**eFig. 34.3**). Thus, modulation of I_{to} appears to play a significant physiologic role in controlling cardiac excitation-contraction coupling, and it remains to be determined whether transmural differences in phase 1 repolarization translate into similar differences in regional contractility.



EFIGURE 34.3 Diminution of phase 1 amplitude ("notch") causes asynchronous sarcoplasmic reticulum (SR) Ca^{2+} release. Normal cardiomyocytes were voltage-clamped, with action potential profiles having a normal or heart failure wave shape **(top),** and local changes in intracellular calcium were recorded simultaneously. When the myocyte was clamped with a normal action potential profile having the early phase 1 repolarization notch **(left),** there was uniform Ca^{2+} release, reflected in the rapid and synchronous increase in fluorescence. However, when a congestive heart failure action potential profile without early rapid phase 1 repolarization was used **(right),** Ca^{2+} release was dyssynchronous. This dyssynchrony causes slowing in the rate of rise of the Ca^{2+} transient and loss of spatial and temporal release uniformity. F/F_0, Fluorescence of the Ca^{2+} indicator normalized to its baseline fluorescence. (From Harris DM et al. Alterations in early action potential repolarization causes localized failure of sarcoplasmic reticulum Ca^{2+} release. Circ Res 2005;96:543. By permission of the American Heart Association.)

The 4-aminopyridine–resistant, Ca^{2+} -activated chloride current $I_{Cl.Ca}$ (or I_{to2}) also contributes a significant outward current during phase 1 repolarization.[1] This current is activated by the action potential–evoked intracellular Ca^{2+} transient. Therefore, interventions that augment the amplitude of the

Ca^{2+} transient associated with the twitch (e.g., beta-adrenergic receptor stimulation) also enhance outward $I_{Cl.Ca}$. It is not currently known whether human cardiac myocytes express Ca^{2+}-activated chloride channels. Other, time-independent chloride currents may also play a role in determining the time course of early repolarization, such as the cAMP- or swelling-activated chloride conductances $I_{Cl.cAMP}$ and $I_{Cl.swell}$.

A third current contributing to early repolarization is outward Na^+ movement through the Na^+/Ca^{2+} exchanger operating in reverse mode. Sometimes, a transient depolarization follows phase 1 repolarization altering the initial voltage of the plateau (**see eFig. 34.2**).

Phase 2: Plateau.

During the plateau phase, which may last several hundred milliseconds, membrane conductance of all ions falls to rather low values; this is a time of high membrane resistance. Less change in current is required near plateau voltages than near resting potential levels to produce the same changes in transmembrane potential. The plateau is maintained by competition between the outward current carried by K^+ and Cl^- ions and the inward current carried by Ca^{2+} moving through $I_{Ca,L}$ and Na^+ being exchanged for internal Ca^{2+} by the Na^+/Ca^{2+} exchanger operating in forward mode. After depolarization, I_{K1} conductance falls to plateau levels as a result of inward rectification, despite the large electrochemical driving force on K^+ ions.

Several potassium currents are activated during the plateau phase, including the rapid (I_{Kr}) and slow (I_{Ks}) delayed rectifier currents (see Voltage-Gated K^+ Channels). The mechanism underlying rectification of the rapid component of the delayed rectifier K^+ current (I_{Kr}) in cardiac cells is rapid inactivation that occurs during depolarizing pulses. More I_{Kr} channels enter the inactivated state with stronger depolarizations, thereby causing inward rectification. This fast inactivation mechanism is sensitive to changes in extracellular K^+ in the physiologic range, with inactivation being more accentuated at low extracellular K^+ concentrations. Thus, hypokalemia would decrease outward I_{Kr}, thereby prolonging the action potential duration (APD).

Outward K^+ movement carried by I_{Ks} also contributes to plateau duration. Mutations in the *KvLQT1* subunit, which in combination with the I_{Ks} ancillary subunit (*KCNE1* encoding minK) reconstitutes the cardiac I_{Ks} current, are associated with abnormally prolonged ventricular repolarization (LQTS type 1; **see Chapters 33 and 39**). Although I_{Ks} activates slowly compared to the APD, it is only slowly inactivated. Therefore, increases in heart rate can cause this activation to accumulate during successive depolarizations, increasing K^+ currents that are active during the plateau of the action potential and thus shortening the APD appropriately at higher heart rates.

In conditions of reduced intracellular adenosine triphosphate (ATP) concentration (e.g., hypoxia, ischemia), K^+ efflux through activated K_{ATP} channels is enhanced, thereby shortening the plateau phase of the action potential. Other ionic mechanisms that control plateau potential and duration include the kinetics of inactivation of the L-type Ca^{2+} current. Reduced efficiency of intracellular free Ca^{2+} in inducing Ca^{2+}-dependent inactivation, such as in myocytes from hypertrophic hearts, can result in delayed repolarization. Steady-state components of both I_{Na} and $I_{Ca.L}$ (window currents) also shape the plateau phase. Na^+,K^+ -ATPase generates a net outward current by electrogenic ion exchange. Noninactivating chloride currents, such as $I_{Cl.swell}$ and $I_{Cl.cAMP}$, may produce significant outward currents during the plateau phase under certain conditions, thereby significantly shortening the APD. A nonselective, swelling-induced cation current has been shown to cause prolongation of action potentials in myocytes from failing ventricles.[1]

Phase 3: Final Rapid Repolarization.
Repolarization of the terminal portion of the action potential proceeds rapidly in part because of two currents: time-dependent inactivation of I_{CaL}, with a decrease in the intracellular movement of positive charges, and activation of repolarizing K^+ currents, including I_{Ks} and I_{Kr} and the inwardly rectifying K^+ currents I_{K1} and I_{KACh}, which all cause an increase in the movement of positive charges out of the cell. The net membrane current becomes more outward, and the membrane potential moves to the resting potential. A small-conductance Ca^{2+} -activated K^+ current, I_{KCa}, expressed in human atrial myocytes, controls the time course of phase 3 repolarization.[9]

Loss-of-function mutations in the human ether-a-go-go–related or hERG gene (*KCNH2*), which encodes the pore-forming subunit of I_{Kr}, prolong phase 3 repolarization, thereby predisposing to the development of torsades de pointes. Macrolide antibiotics such as erythromycin, antihistamines such as terfenadine, several neurologically active agents, and antifungal drugs such as ketoconazole inhibit I_{Kr} and have been implicated in acquired forms of LQTS (**see Chapters 33 and 39**). Similarly, mutations in *KVLQT1*, which encodes the pore-forming subunit of I_{Ks}, will prolong repolarization and predispose to lethal ventricular arrhythmias. A decrease in I_{K1} activity, as is the case in left ventricular myocytes from failing hearts, causes prolongation of the action potential by slowing of phase 3 repolarization and resting membrane depolarization. A reduction in the outward potassium current through open inwardly rectifying K^+ channels renders the failing cardiomyocyte more susceptible to the induction of delayed afterdepolarizations triggered by spontaneous intracellular Ca^{2+}-release events and therefore plays a major role in arrhythmogenesis in the failing heart.[1]

Phase 4: Diastolic Depolarization.
Under normal conditions, the membrane potential of atrial and ventricular muscle cells remains steady throughout diastole. I_{K1} is the current responsible for maintaining the resting potential near the K^+ equilibrium potential and shuts off during depolarization in atrial, His-Purkinje, and ventricular cells. In other fibers found in certain parts of the atria, in the muscle of the mitral and tricuspid valves, in His-Purkinje fibers, and in the SA node and portions of the AV nodal tract, the resting membrane potential does not remain constant in diastole but gradually depolarizes (**see Figs. 34.2 and 34.3**). The property possessed by spontaneously discharging cells is called phase 4 diastolic depolarization, which leads to initiation of action potentials resulting in automaticity. The discharge rate of the SA node normally exceeds the discharge rate of other potentially automatic pacemaker sites and thus maintains dominance of the cardiac rhythm. The discharge rate of the SA node is usually more sensitive than the discharge rate of other pacemaker sites to the effects of norepinephrine and acetylcholine. Normal or abnormal automaticity at other sites can cause discharge at rates faster than the SA nodal discharge rate and can thus usurp control of the cardiac rhythm for one cycle or many (**see Chapter 35**).

Normal Automaticity

Two models of sinoatrial node pacemaking have been proposed. In the first model, HCN channels (see Cardiac Pacemaker Channels and **Table 34.1**) are activated by hyperpolarizations in the normal range of diastolic membrane potentials. During the hyperpolarized diastolic interval between consecutive action potentials, the probability of HCN channels being open increases. Open HCN channels conduct both Na^+ and K^+, but at these negative membrane potentials, Na^+ entry predominates. It is this inward Na^+ current through HCN channels (together with inflow of Ca^{2+} through voltage-activated Ca^{2+} channels, inward currents through Na^+/Ca^{2+} exchangers, and decaying outward K^+ currents; **see Fig. 34.4**) at diastolic

membrane potentials that is thought to depolarize the pacemaker cells to threshold and thus trigger the next action potential and generate a periodically firing pacemaker.[1]

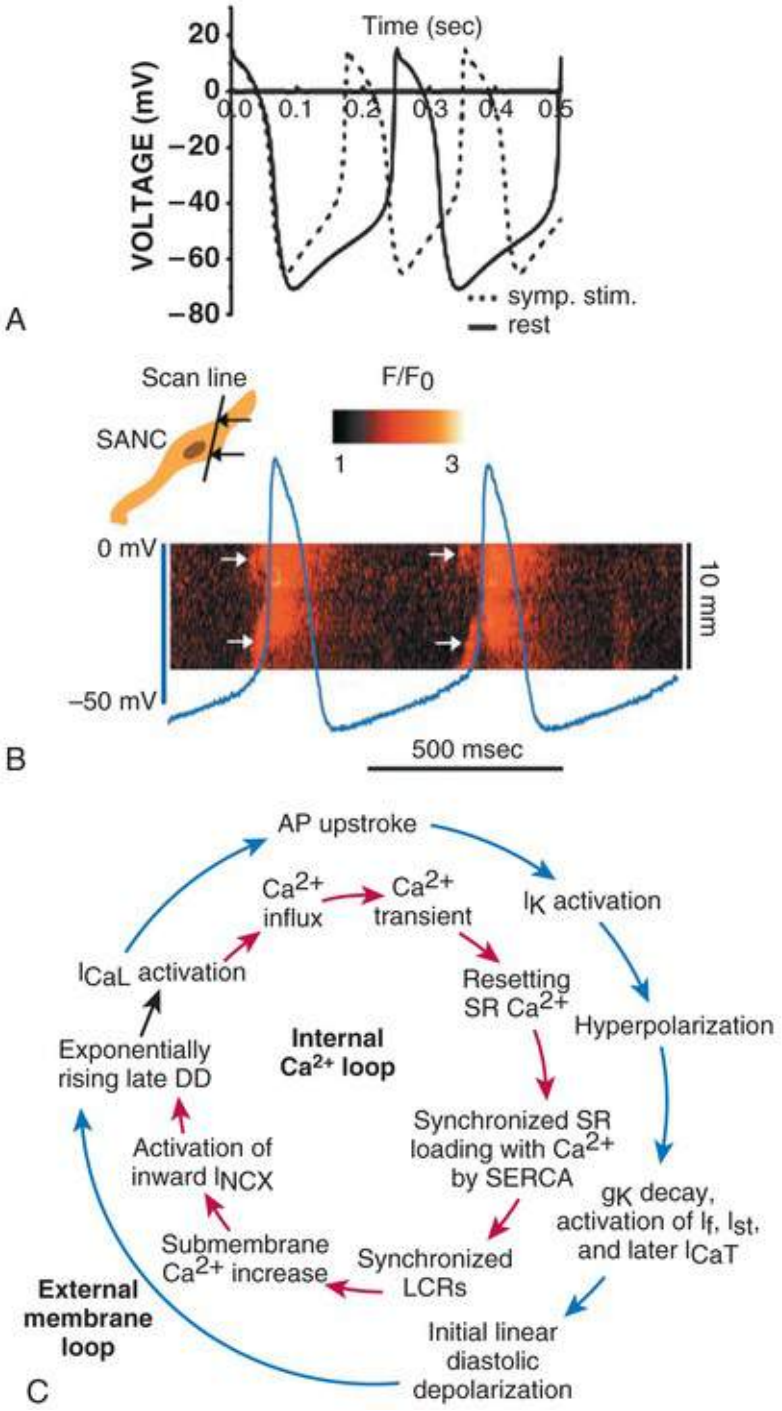
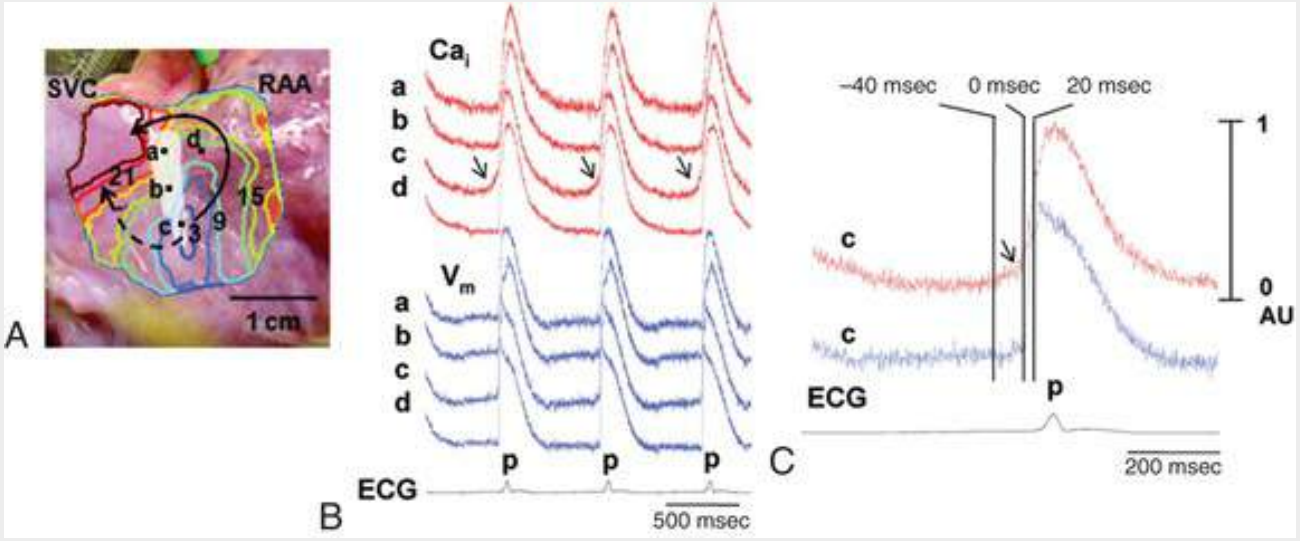


FIGURE 34.4 Sympathetic stimulation of heart rate in the sinoatrial node (SAN). **A,** Simulated SAN action potentials during baseline (*solid line*) and sympathetic stimulation (*dashed line*). Sympathetic stimulation increases the rate of diastolic depolarization and shifts the maximum diastolic potential to a less negative value, thereby accelerating action potential firing. **B, C,** Spontaneous sarcoplasmic reticulum (SR) Ca^{2+}-release events trigger membrane excitation in SAN myocytes. **B,** Confocal line scan images of Ca^{2+} signals measured in spontaneously beating rabbit sinoatrial node cells (SANC) with simultaneous recording (*blue lines*) of transmembrane action potentials; the orientation of the scan line is shown in the inset. *Arrows* in the confocal image show the local Ca^{2+} release in the submembrane space during late diastolic depolarization that precedes the rapid upstroke of the action potential. **C,** Model of sinoatrial node cell pacemaking, as suggested by Maltsev and coworkers. I_{NCX}, Na^+/Ca^{2+} exchange current; *DD,* diastolic depolarization; *LCR,* local Ca^{2+} release; *SERCA,* sarcoendoplasmic reticulum Ca^{2+}-ATPase. (**A,** From Larsson HP. How is the heart rate regulated in the sinoatrial node? Another piece to the puzzle. J Gen Physiol 2010;136:237; **B, C,** from Maltsev VA et al. The emergence of a general theory of the initiation and strength of the heartbeat. J Pharmacol Sci 2006;100:338.)

In the model proposed by proponents of Ca^{2+} oscillations operating as the primary pacemaking mechanism ("Ca^{2+} clock"), periodic increases in $[Ca^{2+}]_i$ serve as an internal generator ("calcium clock") of rhythmic signals that are transformed into changes in membrane voltage via modulation of calcium-sensitive ion channels and transporters in the outer membrane ("membrane clock"). This concept is illustrated in **Fig. 34.4**, in which simultaneous $[Ca^{2+}]_i$ and action potential measurements in isolated sinoatrial myocytes are used as an example. Local submembrane increases in $[Ca^{2+}]_i$ (denoted by the white arrows in **Fig. 34.4B**) occurring during the latter part of the spontaneous diastolic depolarization (transmembrane action potentials are shown in blue) precede the rapid upstroke of the action potential. The periodic SR Ca^{2+}-release events rhythmically activate the Na^+/Ca^{2+} exchange inward (i.e., depolarizing) current (I_{NCX}), which then results in an increase in membrane potential that prompts activation of surface membrane L-type Ca^{2+} channels to initiate an action potential. Thus the NCX operating in forward mode plays an essential role in converting the driver intracellular Ca^{2+} signals into membrane (i.e., voltage) signals. Once an action potential has been initiated, two highly interacting, concurrent series of events proceed during a normal SA node cell cycle (**Fig. 34.4C**). In a surface membrane delimited series of events, depolarization-induced activation of the delayed rectifier K^+ current I_K leads to membrane hyperpolarization, which is followed by slow diastolic depolarization via activation of a number of inward currents, including I_f and I_{CaT} (**see Table 34.1**). In a second, parallel cycle of events, action potential–induced SR Ca^{2+} release is followed by Ca^{2+} reuptake into the SR, which subsequently gives rise to multifocal, synchronized spontaneous Ca^{2+}-release events culminating in an increase in inward I_{NCX}. The role of late diastolic spontaneous SR Ca^{2+}-release events in triggering the SA node action potential has been demonstrated in canine hearts in situ (**eFig. 34.4**).



EFIGURE 34.4 Demonstration of late diastolic intracellular calcium elevations in the sinoatrial node in situ by simultaneous optical mapping of changes in intracellular calcium (Ca_i) and transmembrane voltage (V_m) in an isolated canine right atrial preparation. **A,** Isochronal map of atrial activation during sinus rhythm superimposed on a photograph of the endocardial surface of the sinoatrial node region. The number on each isochronal line indicates the time of activation in milliseconds. The *white shaded area* is the sinoatrial node. *SVC,* Superior vena cava; *RAA,* right atrial appendage. **B,** V_m (*blue*) and Ca_i (*red*) recordings from the superior (a), middle (b), and inferior (c) sinoatrial node, and right atrium (d). *Arrows* indicate late diastolic elevations in Ca_i. Note the presence of slow diastolic depolarization in the V_m tracings a through c, but not in d. **C,** Magnified views of Ca_i and V_m tracings of the inferior sinoatrial node. The late diastolic elevation in Ca_i (*arrow*) precedes rapid upstroke of the sinoatrial and atrial action potential and occurs much earlier than the P wave on the electrocardiogram (ECG). (From Joung B et al. Intracellular calcium dynamics and acceleration of sinus rhythm by β-adrenergic stimulation. Circulation 2009;119:788.)

The rate of SA node discharge can be varied by several mechanisms in response to autonomic or other influences. The pacemaker locus can shift within or outside the SA node to cells discharging faster or more slowly. If the pacemaker site remains the same, alterations in the slope of the diastolic depolarization, maximum diastolic potential, or threshold potential can speed or slow the discharge rate. For example, if the slope of diastolic depolarization steepens, and if the resting membrane potential becomes less negative or the threshold potential more negative (within limits), the discharge rate increases (e.g., **Fig. 34.4A**, dotted line). Opposite changes slow the discharge rate. The molecular mechanism that is primarily responsible for acceleration of the SA node discharge rate has been highly controversial. Proponents of the HCN pacemaker role consider an increase in inward HCN current via a shift of the HCN channel activation curve to more depolarized potentials as the primary regulatory mechanism.[1] In contrast, proponents of the Ca^{2+} clock model suggest protein kinase A (PKA)–mediated phosphorylation of Ca^{2+} -handling proteins (RyR, phospholamban [**see Chapter 22**], SERCA, voltage-gated Ca^{2+} channels) as the mechanism responsible for increased action potential firing: an increase in cAMP level (after beta-adrenergic receptor stimulation) augments PKA activity, which then increases the rate of spontaneous SR Ca^{2+} release and SR Ca^{2+} reuptake via synergistic activation of these proteins, whereas a reduction in cAMP levels (after muscarinic receptor stimulation) has the opposite effect. Acetylcholine (ACh) activates K^+ efflux through ACh-sensitive inward rectifier K^+ channels, which are expressed in both SA nodal and AV nodal cells, thereby shifting the maximum diastolic potential to more negative values. The same mechanism reduces input resistance at diastolic potentials, which means that a greater depolarizing current would be required to achieve the “threshold” for firing an action potential.

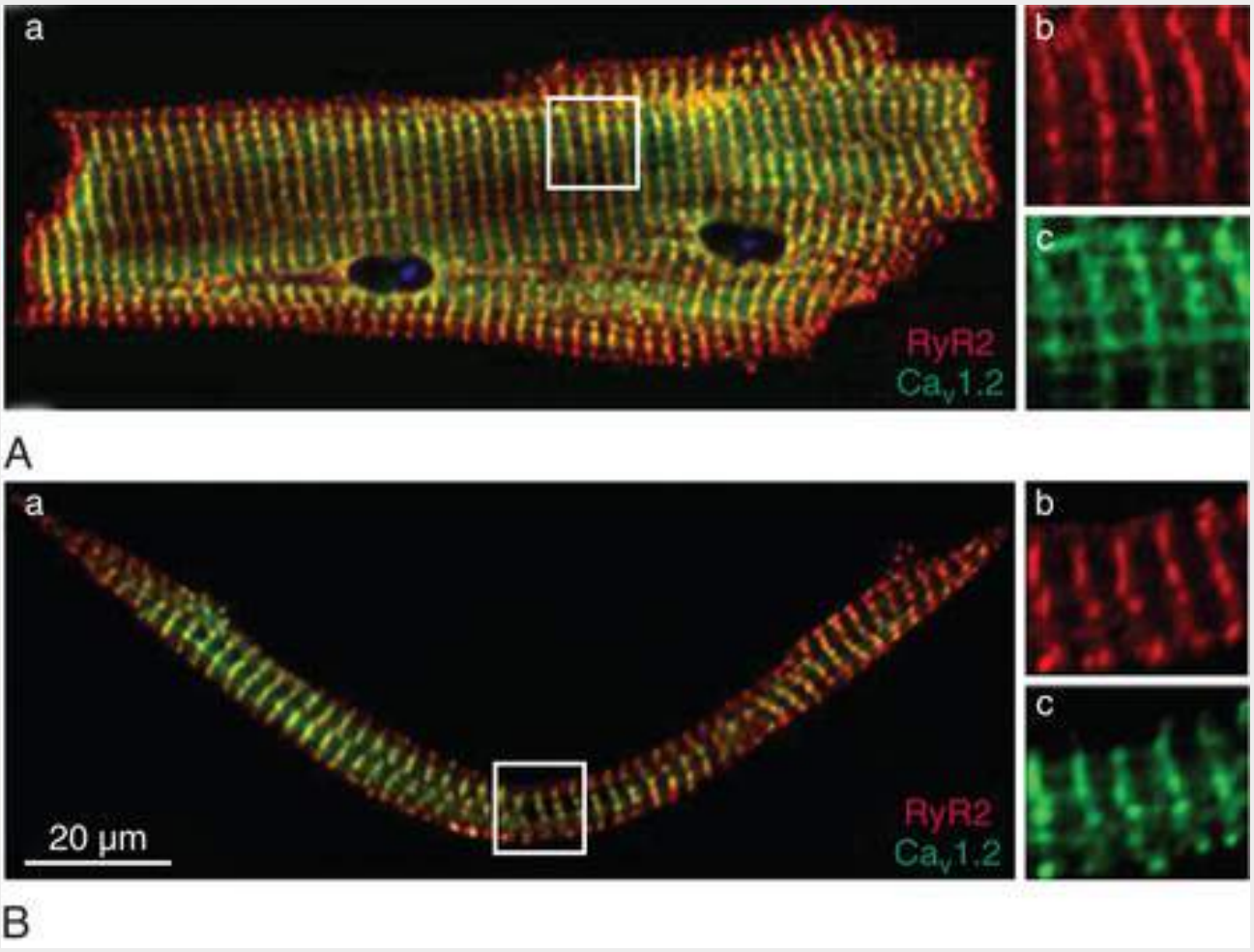
Passive Membrane Electrical Properties.

Passive membrane properties, including membrane resistance, capacitance, and cable properties, play an

important role in cardiac electrophysiology. Although the cardiac cell membrane is resistant to current flow, it also has capacitive properties, which means that it behaves like a battery and can store charges of opposite signs on its two sides—an excess of negative charges inside the membrane balanced by equivalent positive charges outside the membrane. These resistive and capacitive properties cause the membrane to take a certain amount of time to respond to an applied stimulus, rather than responding instantly, because the charges across the capacitive membrane must be altered first. A subthreshold rectangular current pulse applied to the membrane produces a slowly rising and decaying change in membrane voltage rather than a rectangular voltage change. A value called the *time constant* of the membrane reflects its capacitive property. The time constant tau (τ) is equal to the product of membrane resistance (R_m) and cell capacitance (C_m):

$$\tau = R_m \times C_m$$

This is the time taken by the membrane voltage to reach 63% of its final value after application of a steady current. The time course of changes in membrane potential after the application of a hyperpolarizing or depolarizing subthreshold current step is typically monoexponential in all myocyte types, thus indicating that the entire sarcolemma (including the T-tubular membrane; **see eFig. 34.5**) is generally charging uniformly.



EFIGURE 34.5 Subcellular colocalization of ryanodine receptors (RyR2) and L-type calcium channels ($Ca_V1.2$) in Purkinje cells (PCs) and ventricular myocytes (VMs). **A,** VM; **B,** PC; for each, subpanels (*b* and *c*) are enlarged regions of the boxed area. Colocalization RyR2 and $Ca_V1.2$ is shown in the T tubules and at the sarcolemma. T tubules are more heterogeneous and less well developed in PCs. *Red,* RyR2; *green,* $Ca_V1.2$. (From American Heart Association; Willis CB et al. Constitutive intracellular Na^+ excess in Purkinje cells promotes arrhythmogenesis at lower levels of stress than ventricular myocytes from mice with catecholaminergic polymorphic ventricular tachycardia. Circulation 2016;133:2348.)

When aligned end to end, cardiac cells, particularly the His-Purkinje system, behave similar to a long cable, in which current flows more easily inside the cell and to the adjacent cell across the gap junction than it does across the cell membrane to the outside. When current is injected at a point, most of it flows parallel to the long axis inside the cell, but some leaks out. Because of this loss of current, the change in voltage of a cell at a site distant from the point of applied current is less than the change in membrane voltage at the point where the stimulus was applied. A measure of this property of a cable is called the *space* or *length constant* lambda (λ), which is the distance along the cable from the point of stimulation at which the voltage at steady state is 1/e (37%) of its value at the point of stimulation.

Because the current loop in any circuit must be closed, current must flow back to its point of origin. Local circuit currents pass across gap junctions between cells and exit across the sarcolemmal membrane to close the loop and complete the circuit. Inward excitation currents in one area (carried by Na^+ in most regions) flow intracellularly along the length of the tissue (carried mostly by K^+), escape across the membrane, and flow extracellularly in a longitudinal direction. The outside local circuit current is the current recorded on an electrocardiogram (ECG). Through these local circuit currents, the transmembrane potential of each cell influences the transmembrane potential of its neighbor, because of the passive flow of current from one segment of the fiber to another across the low-resistance gap junctions (see Gap Junction Channels and Intercalated Discs and **Fig. 34.7**).

The speed of conduction in cardiac tissue depends on active membrane properties such as the magnitude of the Na^+ current, a measure of which is Vmax. Passive membrane properties also contribute to conduction velocity and include the *excitability threshold*, which influences the capability of cells adjacent to the one that has been discharged to reach threshold; the *intracellular resistance* of the cell, determined by free ions in the cytoplasm; the resistance of the gap junction; and the cross-sectional area of the cell. The direction of propagation is crucial because of the influence of *anisotropy*, in which conduction is faster parallel to the fiber axis compared to that across fibers.

Loss of Membrane Potential and Development of Arrhythmias

Many acquired abnormalities of cardiac muscle or specialized fibers that result in arrhythmias produce a loss of the resting membrane potential (less negative). This change should be viewed as a symptom of an underlying abnormality, analogous to fever or jaundice, rather than as a diagnosis in and of itself, because both the ionic changes resulting in cellular depolarization and the more fundamental biochemical or metabolic abnormalities responsible for the ionic alterations probably have a number of causative factors.

Cellular depolarization can result from elevated $[K^+]_o$ or decreased $[K^+]_i$, an increase in membrane permeability to Na^+ (P_{Na} increases), or a decrease in membrane permeability to K^+ (P_K decreases). Reference to the GHK equation for voltage (see earlier) illustrates that these changes alone or in combination make the transsarcolemmal diastolic voltage less negative.

Normal cells perfused by an abnormal milieu (e.g., hyperkalemia), abnormal cells perfused by a normal milieu (e.g., healed myocardial infarction), or abnormal cells perfused by an abnormal milieu (e.g., acute myocardial ischemia and infarction) can exist alone or in combination and reduce the resting membrane voltage. Each of these changes can have one or more biochemical or metabolic causes. For example, acute myocardial ischemia results in decreased $[K^+]_i$ and increased $[K^+]_o$, release of norepinephrine, and acidosis, which may be related to an increase in intracellular Ca^{2+} and Ca^{2+}-induced transient inward currents and accumulation of amphipathic lipid metabolites and oxygen free radicals. All these changes can contribute to the development of an abnormal electrophysiologic environment and arrhythmias during ischemia and reperfusion.

Effects of Reduced Resting Potential.

The reduced resting membrane potential alters the depolarization and repolarization phases of the cardiac action potential. For example, partial membrane depolarization causes a decrease in the steady-state availability of fast sodium channels, thereby reducing the magnitude of peak I_{Na} during phase 0 of the action potential. The subsequent reduction in action potential amplitude prolongs the conduction time of the propagated impulse, at times to the point of block.

Action potentials with reduced upstroke velocity resulting from partial inactivation of I_{Na} are called *depressed* fast responses. Their contours often resemble and can be difficult to distinguish from slow responses, in which upstrokes are caused by $I_{Ca.L}$ (**see Fig. 34.3F**). Membrane depolarization to levels of −60 to −70 mV can inactivate a substantial portion of the available voltage-gated Na^+ channels, and depolarization to −50 mV or less can almost completely inactivate all the Na^+ channels (**see Fig. 34.1A**). At membrane potentials positive to −50 mV, $I_{Ca.L}$ can be activated to generate phase 0 if conditions are appropriate. These changes in the action potential are likely to be heterogeneous, with unequal degrees of Na^+ inactivation that create areas with minimally reduced velocity, more severely depressed zones, and

areas of complete block. These inhomogeneous changes are conducive to the development of arrhythmias. Cells with reduced membrane potentials can exhibit postrepolarization refractoriness. Furthermore, if conduction block occurs in a fairly localized area without significant slowing of conduction proximal to the site of block, cells in this proximal zone exhibit short action potentials and refractory periods because unexcited cells distal to the block (still in a polarized state) electrotonically speed recovery in cells proximal to the site of block. If conduction slows gradually proximal to the site of block, the duration of these action potentials and their refractory periods can be prolonged.

Molecular Structure of Ion Channels

Ion channels are building blocks of biologic electricity in the heart, brain, skeletal muscle, and other excitable tissues. Ion channels are transmembrane glycoproteins that form ion-selective pores in cell membranes that open and close (*gating*) in response to an appropriate biologic signal. The most abundant ion channels in the heart gate in response to changes in transmembrane voltage. Other physiologically important channels respond to chemical ligands such as ACh, ATP, and calcium. Ion channels are typically named for the predominant permeant ion Na^+, Ca^{2+}, or K^+, and when appropriate, the ligand activator, ACh-dependent K channel. Electrophysiologic studies have detailed the functional properties of Na^+, Ca^{2+}, and K^+ currents in cardiomyocytes, and molecular cloning has revealed a large number of pore-forming (α) and auxiliary (β, γ, and δ) subunits thought to contribute to formation of ion channels. These studies have demonstrated that distinct molecular entities give rise to the various cardiac ion channels and shape the myocardial action potential. Mutations in the genes encoding subunits of cardiac ion channels are responsible for several inherited cardiac arrhythmias[10] (**see Chapter 33**). The expression and functional properties of myocardial ion channels also change in a number of acquired disease states, and these alterations can predispose to cardiac arrhythmias.[11]

Voltage-Gated Na^+ Channels.

Voltage-gated Na^+ (Nav) channel pore-forming (α) subunits have four homologous domains (I to IV), each of which contains six-transmembrane–spanning regions, and these four domains come together to form the Na^+-permeable pore[12] (**Fig. 34.5A**). Among the multiple Nav α subunits, Nav1.5 (which is encoded by the *SCN5A* gene) is the prominent one expressed in mammalian myocardium. The name of the voltage-gated sodium channel consists of the chemical symbol of the principal permeating ion (Na^+) and v, which indicates its principal physiologic regulator (voltage). The number following v indicates the gene subfamily (Nav1), and the number following the decimal point identifies the specific channel isoform (e.g., Nav1.1). An identical nomenclature applies to voltage-gated calcium and potassium channels. Mutations in *SCN5A*, which are associated with LQT3 syndrome, disrupt Nav channel inactivation and thereby give rise to a sustained inward Na^+ current during the plateau phase of the action potential and to prolongation of the action potential. Mutations in *SCN5A* are also linked to Brugada syndrome. Brugada syndrome mutations result in reduced Nav current amplitude, which leads to slowing of phase 0 action potential upstroke, reduced action potential amplitude, and altered phase 1 early repolarization.

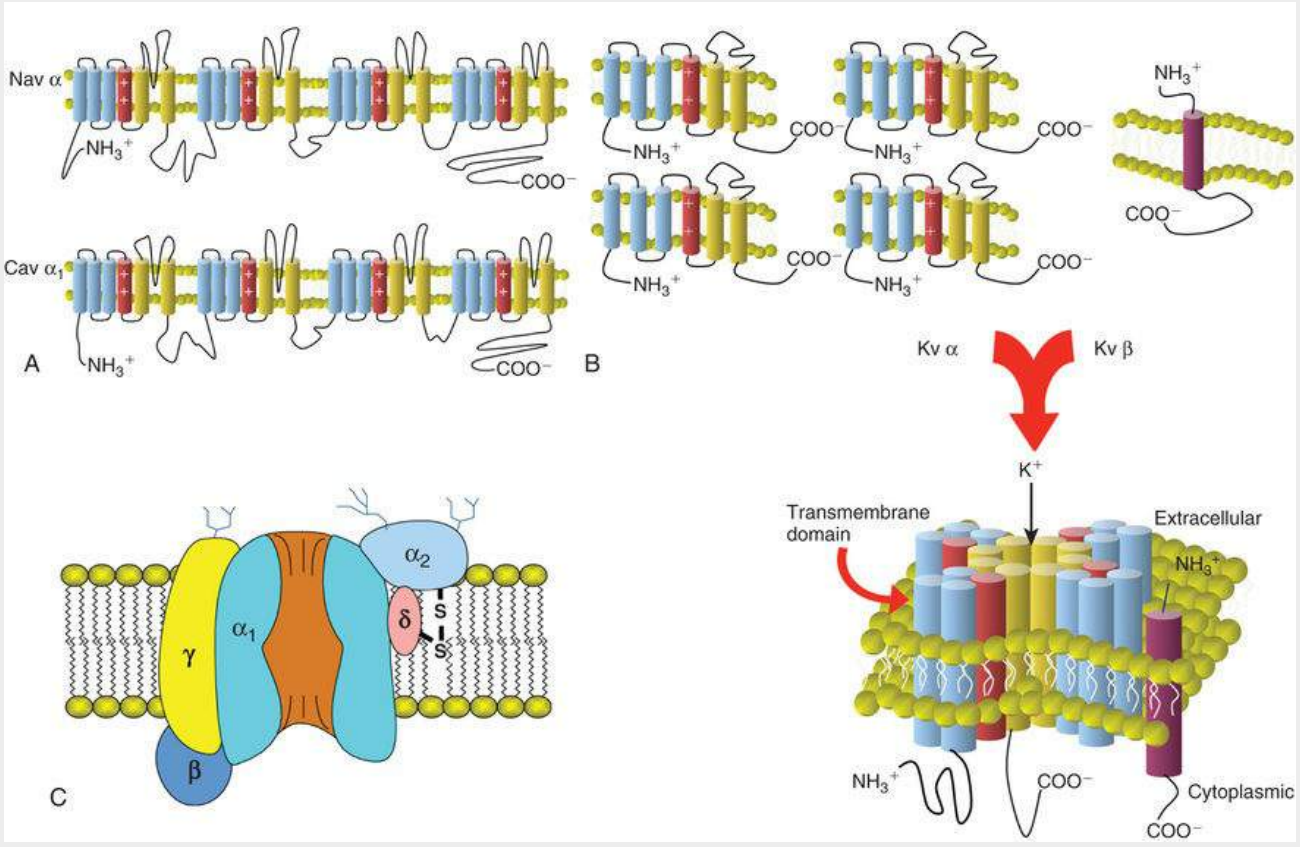


FIGURE 34.5 Transmembrane topology and schematic of the structure of ion channels. **A,** Voltage-gated Na^+ and Ca^{2+} channels are composed of a single tetramer consisting of four covalently linked repeats of the six-transmembrane–spanning motifs, whereas **B,** voltage-gated K^+ channels are composed of four separate subunits, each containing a single six-transmembrane–spanning motif. Inwardly rectifying K^+ channels are formed by inward rectifier K^+ channel pore-forming (alpha) subunits (Kir). In contrast to voltage-gated K^+ channel alpha subunits, the Kir alpha subunits have only two (not six) transmembrane domains. **C,** All ion channels are multisubunit proteins, as exemplified by the schematic subunit structure of L-type Ca channels.

Nav1.5 pore-forming α subunits coassemble with one to two auxiliary Nav β subunits to form functional cell surface Nav channels in cardiomyocytes. Nav β subunits appear to play an important role in anchoring ion channel proteins to the outer cell membrane. Subpopulations of Nav1.5 channels are present in different subcellular regions, such as the intercalated disc and T-tubular membranes.[13,14] As with many other ion channels, Nav1.5 channels are part of macromolecular complexes of channel and regulatory proteins.[15]

Voltage-Gated Ca^{2+} Channels.

As with Nav channels, cardiac voltage-gated Ca^{2+} (Cav) channels are assemblies of a pore-forming α_1 subunits and auxiliary Cav β or Cav α_2 -δ subunits (**Fig. 34.5C**). Among the various α subunits, Cav1.2, also known as α_{1C} encoded by the *CACNA1C* gene, is the prominent Cav α_1 subunit expressed in mammalian myocardium. Cav1.2 channels exhibit many of the time- and voltage-dependent properties and pharmacologic sensitivities of cardiac L-type Ca^{2+} currents (**see Table 34.1**). Accessory subunits modulate the functional properties of Cav channels.[16]

Cav3.1/α_1 G alpha subunits form a Ca^{2+} -selective channel with time- and voltage-dependent characteristics and pharmacologic sensitivities that resemble those of the low-voltage activated T-type Ca^{2+} channel. Disruption of the gene encoding Cav3.1 subunits (*CACNA1G*) in mice has been demonstrated to slow the sinus node rate and AV conduction, consistent with its role in SA and AV node function.[7]

Voltage-Gated K^+ Channels.

Voltage-gated K^+ channels (Kv) are the most diverse family of voltage-dependent channels in the heart. Kv channels are composed of four separate pore-forming (α) subunits, each containing six-membrane–spanning domains (S_1 through S_6)[17] (**see Fig. 34.5B**). Kv α subunits expressed in the human heart include members of the Kv1, Kv4, hERG (Kv7), and KvLQT (Kv11) subfamilies. In addition, Kv channel α subunit proteins interact with Kv channel accessory subunits, including minK, KChIP2, and MiRP1 (**see Table 34.1**), to form functional cell surface channels with distinct time- and voltage-dependent properties. Coassembly of the Kv4.3 α subunits and the accessory subunit KChIP2 gives rise to the cardiac transient outward Kv channel I_{to} (see Phase 1: Early Rapid Repolarization). hERG α subunits, together with MiRP1 accessory subunits, contribute to the generation of functional cardiac I_{Kr} channels. Mutations in the gene encoding hERG (*KCNH2*) have been shown to underlie congenital LQT2 syndrome. These LQT2 mutations are loss-of-function mutations that lead to reduced functional I_{Kr} channel expression or to alterations in channel processing or trafficking (**see Chapter 33**).

KvLQT1 α subunits associate with minK (encoded by *KCNE1*) accessory subunits to form functional channels that resemble slowly activating, noninactivating K^+ currents, referred to as I_{Ks}, in human myocardium. Mutations in the gene encoding KvLQT1 α subunits, *KCNQ1*, have been linked to LQT1 syndrome. Mutations in the minK-encoding gene *KCNE1* are associated with LQT5 syndrome. These mutations are all loss-of-function mutations that result in reduced expression of functional I_{Ks} channels in the outer membrane. Two missense mutations that cause familial atrial fibrillation (AF) are located on adjacent amino acid residues in the first membrane-spanning segment of *KCNQ1* and lead to altered physical interactions with the *KCNE1* subunits, which ultimately results in slowing of deactivation of I_{Ks} channels.[18]

Kv1.5 α subunits contribute to K^+-selective channels with time- and voltage-dependent characteristics that resemble the rapidly activating and slowly inactivating I_{Kur} in human atrial myocytes. I_{Kur} densities are greatly downregulated in the atria of patients with chronic AF.

Small-conductance, Ca^{2+}-sensitive K^+ channels are tetrameric assemblies of SK α subunits (encoded by *KCNN3*) and underlie a Ca^{2+}-activated K^+ current, $I_{KCa,}$ in human cardiomyocytes.[9] Common variants in *KCNN3* discovered in genome-wide analyses have been associated with AF.[19]

Inwardly Rectifying Cardiac K^+ Channels.

Kir channels in cardiac myocytes, as in other cells, conduct inward current at membrane potentials negative to E_K (see earlier, Physiology of Ion Channels) and smaller outward currents at membrane potentials positive to E_K. The activity of Kir channels is a function of both the membrane potential and the extracellular K^+ concentration ($[K^+]_o$) and are the major determinant of the resting membrane potential in working myocardium. As $[K^+]_o$ changes, the channel conducts inward current at potentials negative to the new E_K, whereas a small outward current within a certain potential range positive to the new E_K remains. Rectification simply means that membrane conductance changes with voltage. Specifically, inward rectification means that K^+ channels support ion flux at negative potentials but are closed or blocked at less negative or positive voltages. Membrane depolarization–induced internal block by intracellular magnesium and polyamine ions is thought to underlie inward rectification of cardiac I_{K1} channels.[17] Inwardly rectifying K^+ channels are formed by inward rectifier K^+ channel pore-forming α subunits. In contrast to Kv α subunits, Kir α subunits have only two (not six) transmembrane domains. Molecular studies have provided direct evidence that the α subunits Kir2.1 and Kir2.2 encoded by *KCNJ2* and *KCNJ3*, respectively, underlie the strongly inwardly rectifying Kir channel I_{K1} in

cardiomyocytes.

In cardiomyocytes, pore-forming Kir6.2 α subunits (encoded by *KCNJ11*) assemble with sulfonylurea receptor proteins (SUR1, SUR2 encoded by *ABCC8* and *ABCC9*, respectively) to form K^+-selective sarcolemmal $I_{K.ATP}$ channels. Kir6.1 protein (encoded by *KCNJ8*) also forms a channel, but its role in the heart is uncertain because sarcolemmal $I_{K.ATP}$ is abolished in SA nodal cells of Kir6.2 knockout mice. Based on activation of sarcolemmal $I_{K.ATP}$ by pinacidil and cromakalim, which are relatively specific for SUR2, the cardiac channel is suggested to be an octameric assembly of SUR2A/Kir6.2. However, different anatomic regions of the heart may express $I_{K.ATP}$ comprised of differing channel and SUR subunits. $I_{K.ATP}$ channels are thought to play a pivotal role in myocardial ischemia and preconditioning. For example, opening of cardiac sarcolemmal $I_{K.ATP}$ channels underlies electrocardiographic ST-segment elevation during acute myocardial ischemia. Drugs such as nicorandil and diazoxide open ATP-sensitive K^+ channels, whereas sulfonylurea compounds (e.g., glibenclamide) inhibit the activity of $I_{K.ATP}$.[20] Mutations in *ABCC9* have been associated with a rare multiorgan system disease, Cantu syndrome, characterized by craniofacial, dermal, and skeletal deformities, as well as congenital cardiac abnormalities such as bicuspid aortic valve, patent ductus arteriosus, biventricular hypertrophy pulmonary hypertension, and pericardial effusion.[21] It has been suggested that vasodilation by opening of vascular $I_{K.ATP}$ may be pathogenically involved.

In addition to the sarcolemmal channel an ATP-sensitive potassium conductance in mitochondrial (mitoK[ATP]) has been described that is involved in cardioprotection and arrhythmias. The molecular composition of this channel is uncertain but likely is composed of another type of inwardly rectifying K^+ channel.[22]

The molecular basis of the ACh-activated K^+ channel $I_{K.ACh}$ is a heteromultimer of two inwardly rectifying potassium channel subunits, Kir3.1 and Kir3.4.[17] Stimulation of $I_{K.ACh}$ by vagally secreted ACh decreases spontaneous depolarization in the SA node and slows conduction velocity in the AV node. Adenosine, through type 1 purinergic receptor–mediated G-protein activation, also increases $I_{K.ACh}$ activity (in this context referred to as $I_{K.Ado}$) in atrial, SA node, and AV node cells. Adenosine is useful for the acute termination of arrhythmias with the AV node as part of the reentry circuit, such as atrioventricular reentrant (AVRT) and atrioventricular nodal reentrant tachycardias (AVNRT) (see later, Mechanisms of Arrhythmogenesis).

Cardiac Pacemaker Channel.

The pacemaker (“funny”) current known as I_f of sinoatrial myocytes prominently contributes to diastolic depolarization. The current is found in many cell types but its features are variable. I_f activates slowly on hyperpolarization and deactivates rapidly with depolarization and supports a mixed monovalent cation (Na^+ and K^+) current. I_f is highly regulated; beta-adrenergic stimulation increases the probability of channel opening by shifting the channel's activation curve to more positive potentials, which leads to increased current availability for the generation of diastolic depolarization and thus steepens its rate. Cholinergic action, in general, exerts the opposite effect (see earlier). A family of genes topologically similar to voltage-dependent K^+ channels and related to cyclic nucleotide–gated channels in photoreceptors in the retina appears to encode I_f. Several isoforms of hyperpolarization-activated cyclic nucleotide–gated channels (HCN) have been cloned from heart. Of the four known HCN pore-forming α subunits, HCN4 is the most highly expressed in the mammalian myocardium. Mutation in the human *HCN4* gene has been linked to familial sinus bradycardia and inappropriate sinus tachycardia.[23,24]

Electrogenic Transporters

Na^+/Ca^{2+} Exchanger.

The NCX is an electrogenic ion transporter that exchanges three Na^+ ions for one Ca^{2+}, exhibiting the highest levels of activity in the mammalian heart. The cardiac NCX is a transmembrane glycoprotein proposed to have nine-transmembrane repeats based on hydropathy analysis (**Fig. 34.6A, B**). The intracellular loop contains domains that bind Ca^{2+} (CBD 1 and 2) and the endogenous NCX inhibitory domain, XIP.

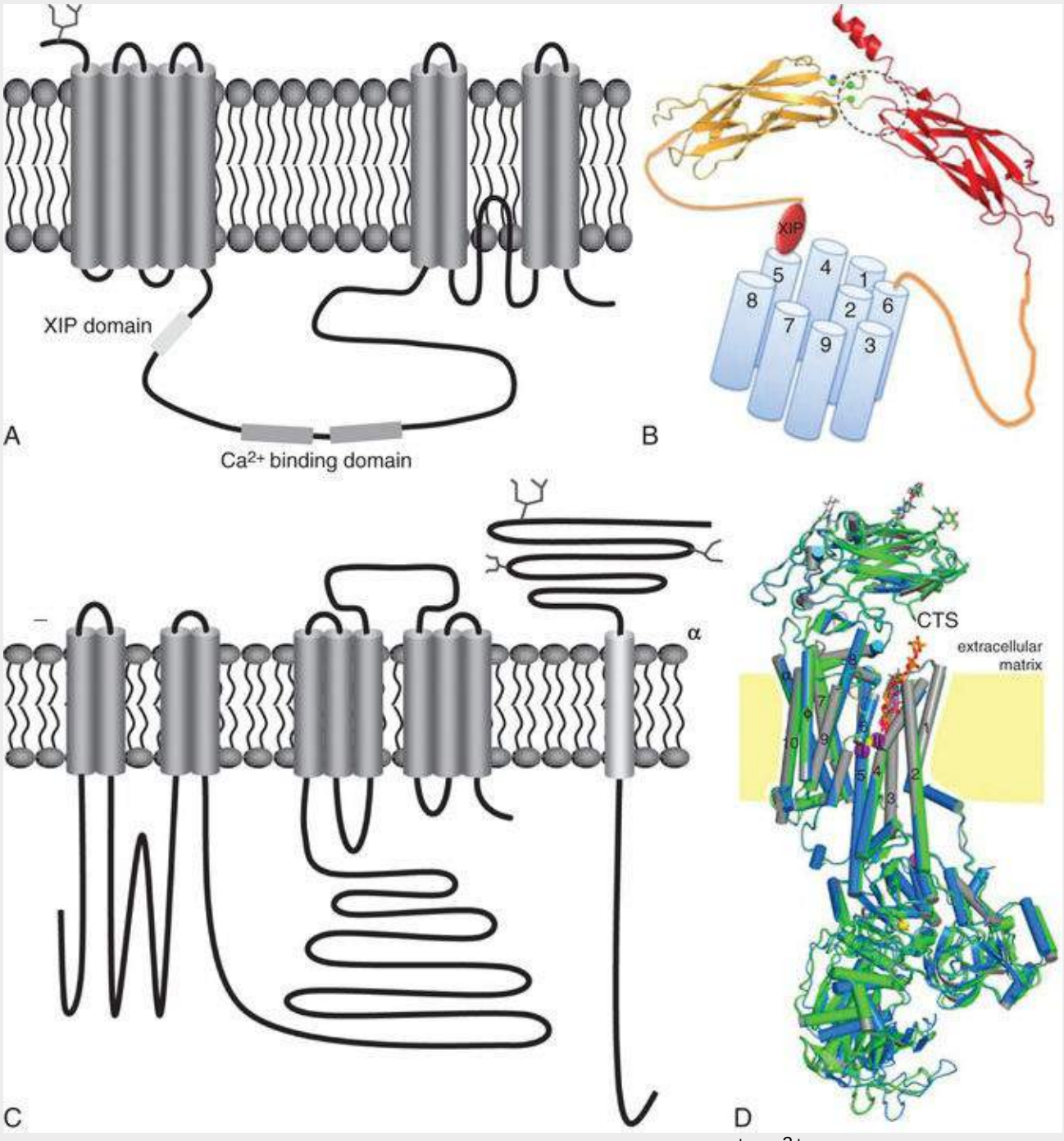


FIGURE 34.6 Transmembrane topology and predicted structures of Na^+/Ca^{2+} exchanger (NCX) and the Na^+,K^+-ATPase (Na pump). **A,** Predicted topology of NCX, the cytoplasmic segment includes an autoinhibitory domain (XIP) and two Ca^{2+}-binding domains. **B,** Predicted structure; the cytoplasmic surface is on top. **C,** Topologic structure of the α and β subunits of Na^+,K^+-ATPase. **D,** Overlapping structures of the Na pump bound to three different cardiotonic steroids. CTS, Cardiotonic steroid. (**B**, From Khaninshvilli. The SLC8 gene family of sodium-calcium exchangers (NCX) - structure, function, and regulation in health and disease. Mol Aspects Med 2013;34:220-35; **D,** from Laursen M et al. Structures and characterization of digoxin- and bufalin-bound Na^+,K^+-ATPase compared with the ouabain-bound complex. Proc Natl Acad Sci USA 2015;112:1755-60.)

Ion exchange through NCX can occur in either direction. With each heartbeat, cytosolic [Ca^{2+}] is released from SR stores primarily by the ryanodine release channel RyR2. Intracellular [Ca^{2+}] increases from the global resting level of less than 100 nM to approximately 1 μM with each cardiac cycle. Under normal physiologic conditions, outward Ca^{2+} flux through the NCX (generating an inward current) along with Ca^{2+} reuptake into the SR by the SR Ca^{2+}-ATPase (SERCA) are the major mechanisms of restoration of normal diastolic [Ca^{2+}]. NCX is sensitive to the cytoplasmic [Ca^{2+}] and [Na^+], which determine the exchanger activity and the membrane potential at which exchange current ($I_{Na/Ca}$) reverses direction. NCX

current is time independent and largely reflects changes in intracellular [Ca^{2+}] during the action potential. Thus, NCX plays an important role in determining the membrane voltage both at rest and during activation of the myocyte. At very depolarized potentials, reverse-mode Na^+/Ca^{2+} exchange (Ca^{2+} influx, net outward current) can occur; however, the role of reverse-mode exchange in initiating SR Ca^{2+} release and contraction is uncertain.[25]

NCX current may participate in the generation of arrhythmias in several ways. Increases in $[Ca^{2+}]_i$ shift the reversal potential of the NCX to more positive potentials and therefore increase the driving force for inward exchanger current. Inward NCX current will depolarize the membrane toward the threshold for firing an action potential and may be arrhythmogenic. NCX current is an important component of the inward current that underlies delayed afterdepolarizations (DADs). DADs are spontaneous membrane depolarizations from rest after complete repolarization of the action potential. DADs are usually not present under physiologic conditions but are favored by conditions that increase SR Ca^{2+} load, such as rapid firing rates, digitalis intoxication, and ischemia/reperfusion. Under these conditions, spontaneous SR Ca^{2+} release occurs, which then increases NCX and probably other Ca^{2+}-dependent currents, resulting in membrane depolarization.[2]

Na^+,K^+-*ATPase.*

Also called the Na pump, Na^+,K^+-ATPase establishes and maintains the major ionic gradients across the cardiac cell membrane. The Na pump belongs to the widely distributed class of P-type ATPases that transport a number of cations. The P-type designation refers to the formation of a phosphorylated aspartyl intermediate during the catalytic cycle. Na^+,K^+-ATPase hydrolyzes a molecule of ATP to transport two K^+ into the cell and three Na^+ out and thus is electrogenic, generating a time-independent outward current. The Na^+,K^+-ATPase is oligomeric, consisting of α and β subunits and a tissue-specific regulator phospholemman (PLM). PLM belongs to a family of single-membrane–spanning proteins called FXYD proteins, for a conserved FXYD motif in their extracellular domain. PLM (FXYD1) is expressed in heart and skeletal muscle. PLM in its unphosphorylated form inhibits Na^+,K^+-ATPase ion pumping.[26]

Na^+,K^+-ATPase isoforms are diverse and exhibit tissue-specific distributions. The structural diversity of the Na^+,K^+-ATPase comes from variations in α and β genes, splice variants of the α subunits and promiscuity of subunit associations, themes that also underlie the diversity of ion channels, particularly K channels. The α subunit is catalytic and binds digitalis glycosides in the extracellular linker between the first and second membrane-spanning region (**Fig. 34.6C, D**). In the heart, it has been suggested that the α_2 subunit preferentially regulates Na^+ in the dyadic cleft where α_1 seems to be engaged in regulating bulk $[Na^+]_i$.[3]

In heart failure, Na^+-K^+ ATPase function is compromised, and a number of studies have shown a reduction in expression in ventricular myocardium. The decrease occurs without a significant impact on the inotropic effect of digitalis glycosides, which exerts its predominant effect by blocking the Na pump. However, the reduction in the density of the Na pump may influence the electrophysiology of cardiac myocytes and their response to an extracellular K^+ load, as might occur in ischemia. The role of PLM in cardiac hypertrophy and failure has yet to be systematically characterized, and there is no consensus regarding the level of expression, phosphorylation, or functional role in the diseased heart.

Gap Junction Channels and Intercalated Discs

Another family of ion channel proteins is that containing the gap junctional channels. These dodecameric channels are found in the intercalated discs between adjacent cells (**Fig. 34.7A, B**). Three types of

specialized junctions make up each intercalated disc. The macula adherens or desmosome and the fascia adherens form areas of strong adhesion between cells and may provide a linkage for the transfer of mechanical energy from one cell to the next. The *nexus,* also called the tight or gap junction (**Fig. 34.7C-E**), is a region in the intercalated disc where cells are in functional contact with each other. Membranes at these junctions are separated by only about 10 to 20 Å and are connected by a series of hexagonally packed subunit bridges or gap junction channels that provide biochemical and low-resistance electrical coupling between adjacent cells, by establishing aqueous pores that directly link the cytoplasm of these adjacent cells. Gap junctions allow the movement of ions (e.g., Na^+, Cl^-, K^+, Ca^{2+}) and small molecules (e.g., cAMP, cGMP, inositol 1,4,5-triphosphate [IP_3]) between cells, thereby linking the interiors of adjacent cells.

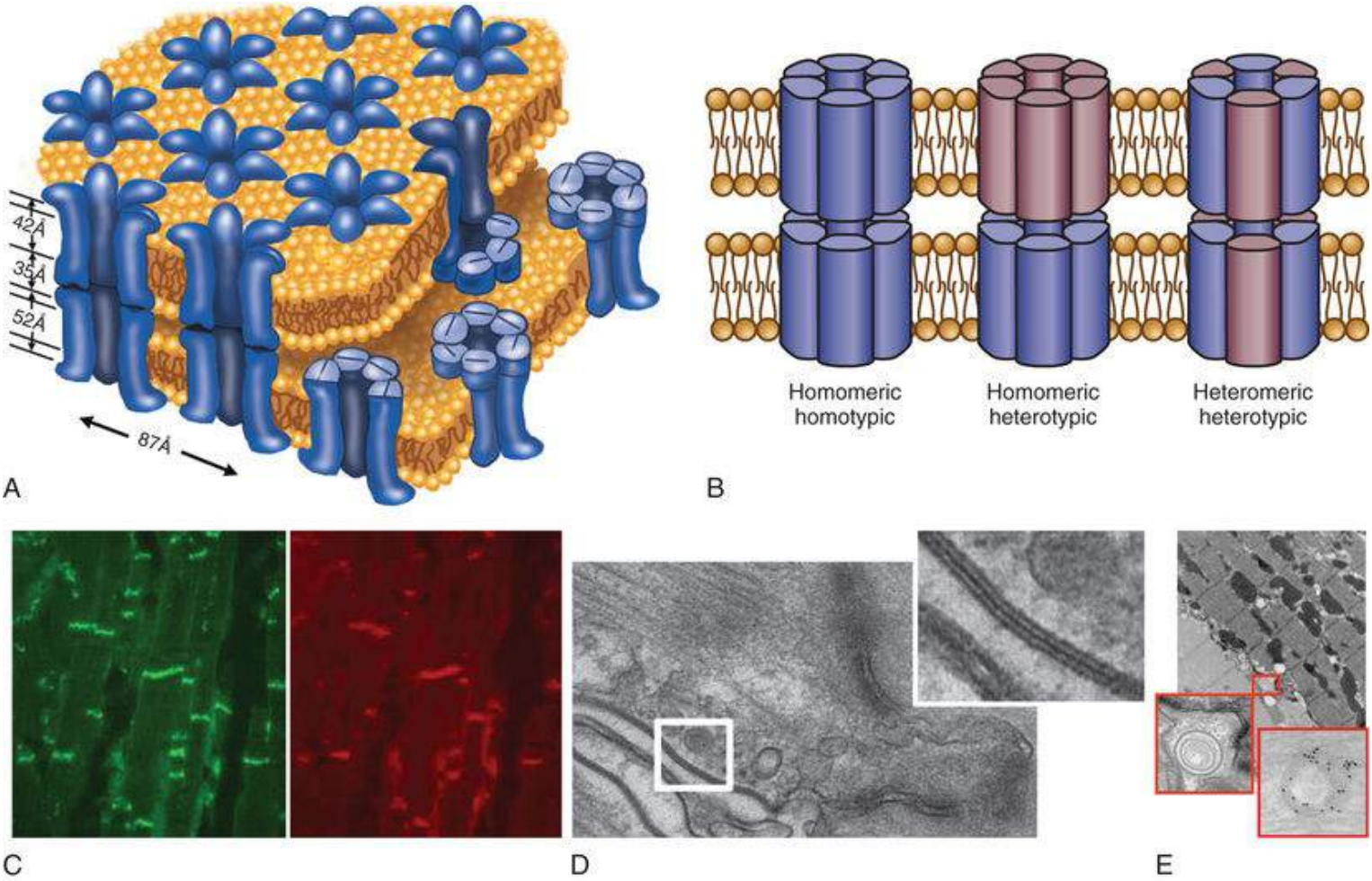


FIGURE 34.7 **A,** Model of the structure of a gap junction based on the results of x-ray diffraction studies. Individual channels are composed of paired hexamers that travel in the membranes of adjacent cells and adjoin in the extracellular gap to form an aqueous pore that provides continuity of the cytoplasm of the two cells; Å, ångstroms. **B**, Mixing of connexin subunits to form gap junction channels may occur at interfaces between tissue types in the heart. Homomeric, homotypic channels contain a single connexin isoform; homomeric heterotypic channels are composed of connexons (hemichannels) comprising a single connexin isoform; and heteromeric, heterotypic channels are made from connexons containing more than one connexin isoform. **C,** Connexin 43 (Cx43) is concentrated at the intercalated discs at cell ends in ventricular myocardium (*green*) and colocalizes with junctional proteins such as N-cadherin (*red*). **D,** Electron microscopic view of and intercalated from normal ventricular myocardium reveals a pentalaminar membrane (*inset*) characteristic of gap junctions. **E,** Remodeling of gap junctions in the failing heart. Immunoreactive Cx43 is increased along lateral cell borders, and annular gap junctions that label with anti-Cx43 immunogold antibodies (*insets*) can be observed. (**A,** From Saffitz JE. Cell-to-cell communication in the heart. Cardiol Rev 1995;3:86; **C, E,** modified from Hesketh et al. Ultrastructure and regulation of lateralized connexin43 in the failing heart. Circ Res 2010;106:1153-63.)

Gap junctions permit a multicellular structure such as the heart to function electrically as an orderly, synchronized, interconnected unit and are responsible in part for conduction in the myocardium being anisotropic; that is, its anatomic and biophysical properties vary according to the direction in which they are measured. Usually, conduction velocity is two to three times faster longitudinally, in the direction of the long axis of the fiber, than it is transversely, in the direction perpendicular to this long axis. Resistivity is lower longitudinally than transversely. Interestingly, the *safety factor for propagation* is greater transversely than horizontally. The *safety factor for conduction* determines the success of action potential propagation and has been defined as the ratio of electrical charge that is generated to charge that is consumed during the excitation cycle of a single myocyte in tissue. Conduction delay or block occurs more frequently in the longitudinal direction than it does transversely. Cardiac conduction is discontinuous because of resistive discontinuities created by the gap junctions, which have an anisotropic distribution on the cell surface. Because of anisotropy, propagation is discontinuous and can be a cause of

reentry.[1]

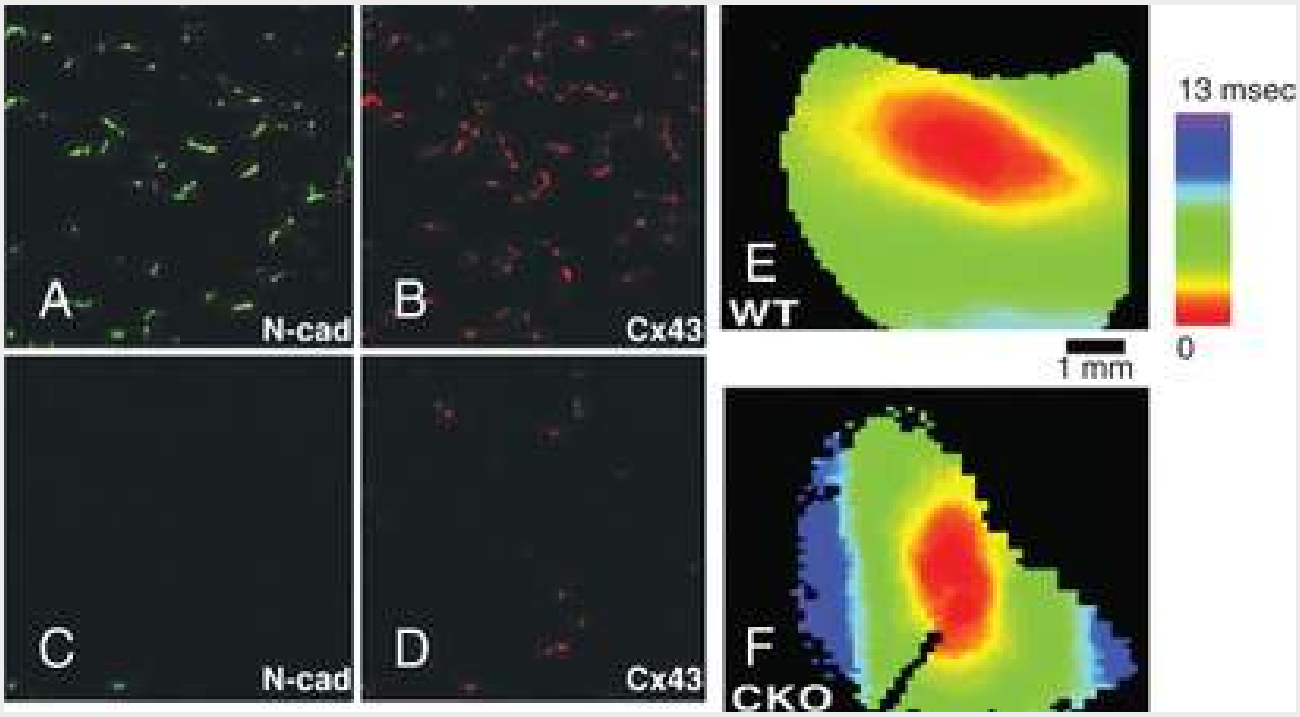
Gap junctions also provide “biochemical coupling,” which permits cell-to-cell movement of ATP (or other high-energy phosphates), cyclic nucleotides, and IP_3, the activator of the IP_3-sensitive SR Ca^{2+}-release channel. This demonstrates that diffusion of second-messenger substances through gap junctional channels constitutes a mechanism enabling coordinated responses of the myocardial syncytium to physiologic stimuli.[1]

Gap junctions can also change their electrical resistance. When the intracellular calcium level rises, as in myocardial infarction (MI), the gap junction may close to help seal off injured from noninjured cells. Acidosis increases and alkalosis decreases gap junctional resistance. Increased gap junctional resistance tends to slow the rate of action potential propagation, a condition that could lead to conduction delay or block. Cardiac-restricted inactivation of gap junctions decreases transverse conduction velocity to a greater degree than longitudinal conduction, thereby resulting in an increased anisotropic ratio, which may play a role in premature sudden death from ventricular arrhythmias.

Connexins are the proteins that form the intercellular channels of gap junctions. An individual channel is created by two hemichannels (*connexons*), each located in the plasma membrane of adjacent cells and composed of six integral membrane protein subunits (connexins). The hemichannels surround an aqueous pore and thereby create a transmembrane channel (**Fig. 34.7A**). *Connexin 43*, a 43-kDa polypeptide, is the most abundant cardiac connexin, with connexins 40 and 45 being found in smaller amounts. Ventricular muscle expresses connexins 43 and 45, whereas atrial muscle and components of the specialized conduction system express connexins 43, 45, and 40. Individual cardiac connexins form gap junctional channels with characteristic unitary conductances, voltage sensitivities, and permeabilities. Tissue-specific connexin expression and the spatial distribution of gap junctions determine the disparate conduction properties of cardiac tissue. The functional diversity of cardiac gap junctions is further enhanced by the ability of different connexin isoforms to form hybrid gap junctional channels with unique electrophysiologic properties (**Fig. 34.7B**). These channel chimeras appear to have a major function in controlling impulse transmission at the SA node–atrium border, the atrium–AV node transitional zone, and the Purkinje-myocyte border.[1]

Alterations in the distribution and function of cardiac gap junctions are associated with increased susceptibility to arrhythmias. Conduction slowing and arrhythmogenesis have been associated with redistribution of connexin 43 (Cx43) gap junctions from the end of cardiomyocytes to the lateral borders and with decreased phosphorylation of Cx43 in a dog model of nonischemic dilated cardiomyopathy (**Fig. 34.7C-E**). Adult mice genetically engineered to express progressively decreasing levels of cardiac Cx43 exhibited increased susceptibility to the induction of fatal tachyarrhythmias. Side-to-side electrical coupling between cardiomyocytes from the epicardial border zone of healing infarcts has been shown to be reduced, thereby exaggerating anisotropy and facilitating reentrant activity.[1] Lastly, mutations in the atrial-specific connexin 40 gene that exhibit altered function have been associated with AF.[27] Studies have suggested that normal electrical coupling of cardiomyocytes through gap junctions depends on normal mechanical coupling through cell-cell adhesion junctions. A defect in cell-cell adhesion or a discontinuity in the linkage between intercellular junctions and the cytoskeleton prevents normal localization of connexins in gap junctions, which in turn could contribute tachyarrhythmias causing sudden death. Mutations in *desmoplakin*, a protein that links desmosomal adhesion molecules to *desmin*, a filament protein of the cardiomyocyte cytoskeleton, and *plakoglobin*, a protein that connects N-

cadherins to actin and desmosomal cadherins to desmin, produce recessive variants of arrhythmogenic right ventricular cardiomyopathy (ARVC), Cavajal disease, and Naxos disease, respectively[28] (**see Chapter 77**). Notably, restoring plakoglobin (*JUP* gene) levels in a mouse model of Naxos disease caused by a truncation of plakoglobin prevented cardiac dysfunction, consistent with a loss of function defect of the truncated protein.[29] Approximately 40% of the pathogenic variants linked to familial ARVC are in the gene encoding the desmosomal protein plakophilin-2.[30] Demonstration of the important role of other adhesion proteins in stabilizing gap junctions comes from a study in which conditional loss of N-cadherin expression in mouse hearts resulted in a decrease in Cx43 gap junctions and changes in conduction velocity, with a concomitant increase in arrhythmogenicity (**eFig. 34.6**).



EFIGURE 34.6 Cardiac-restricted loss of N-cadherin leads to alteration in connexin 43 (Cx43) with conduction slowing. **A to D,** Anti–N-cadherin (**A, C**) and anti-Cx43 (**B, D**) immunoreactivity in a control mouse heart **(A, B)** and in a genetically manipulated mouse heart with knocked-out N-cadherin expression **(C, D).** N-cadherin was lost from intercalated disc in the knock-out heart, whereas Cx43 was significantly decreased. **E, F,** Optical mapping of electrical activation in the left ventricular epicardium of a control **(E)** and N-cadherin knocked-out heart **(F)** with a voltage-sensitive fluorescent dye. The heart was paced at the lateral wall, and activation maps were generated. Color-coded isochrone maps show that conduction was more impaired in the longitudinal than in the lateral direction, thereby increasing conduction anisotropy.
(From Li J et al. Cardiac-specific loss of N-cadherin leads to alteration in connexins with conduction slowing and arrhythmogenesis. Circ Res 2005;97:474.)

Structure and Function of the Cardiac Electrical Network

Sinoatrial Node

In humans, the sinoatrial node (SAN) is a spindle-shaped structure composed of a fibrous tissue matrix with closely packed cells. It is 10 to 20 mm long and 2 to 3 mm wide and tends to narrow caudally toward the inferior vena cava (IVC). It lies less than 1 mm from the epicardial surface, laterally in the right atrial sulcus terminalis at the junction of the superior vena cava (SVC) and right atrium. The proximity to the right phrenic nerve (RPN) is an important consideration when catheter ablation or modification of the SAN is contemplated (**Fig. 34.8**). The artery supplying the SAN branches from the right (55% to 60% of the time) or the left (40% to 45%) circumflex coronary artery and approaches the node from a clockwise or counterclockwise direction around the junction of the SVC and right atrium (**eFigs. 34.7 and 34.8**).

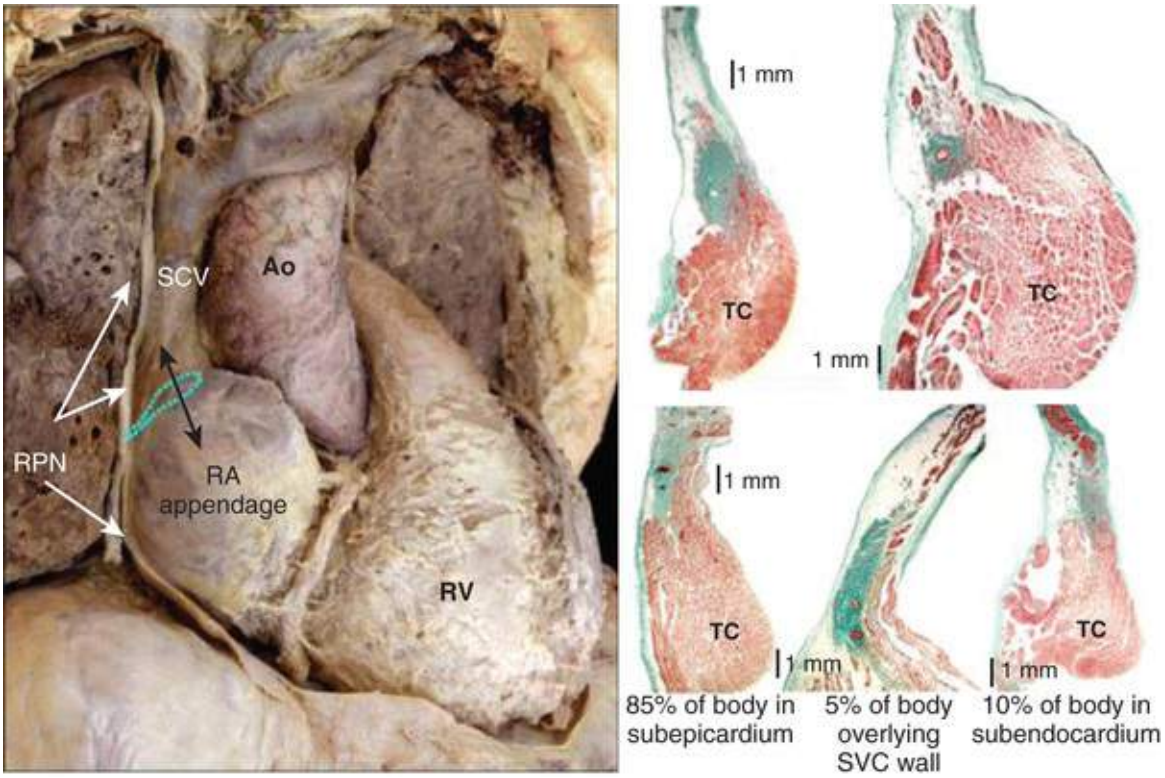
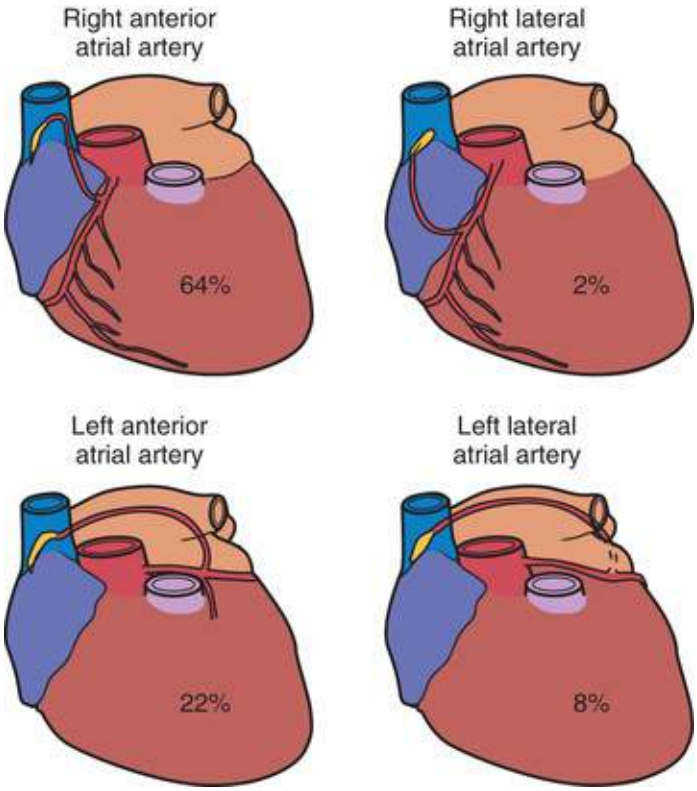
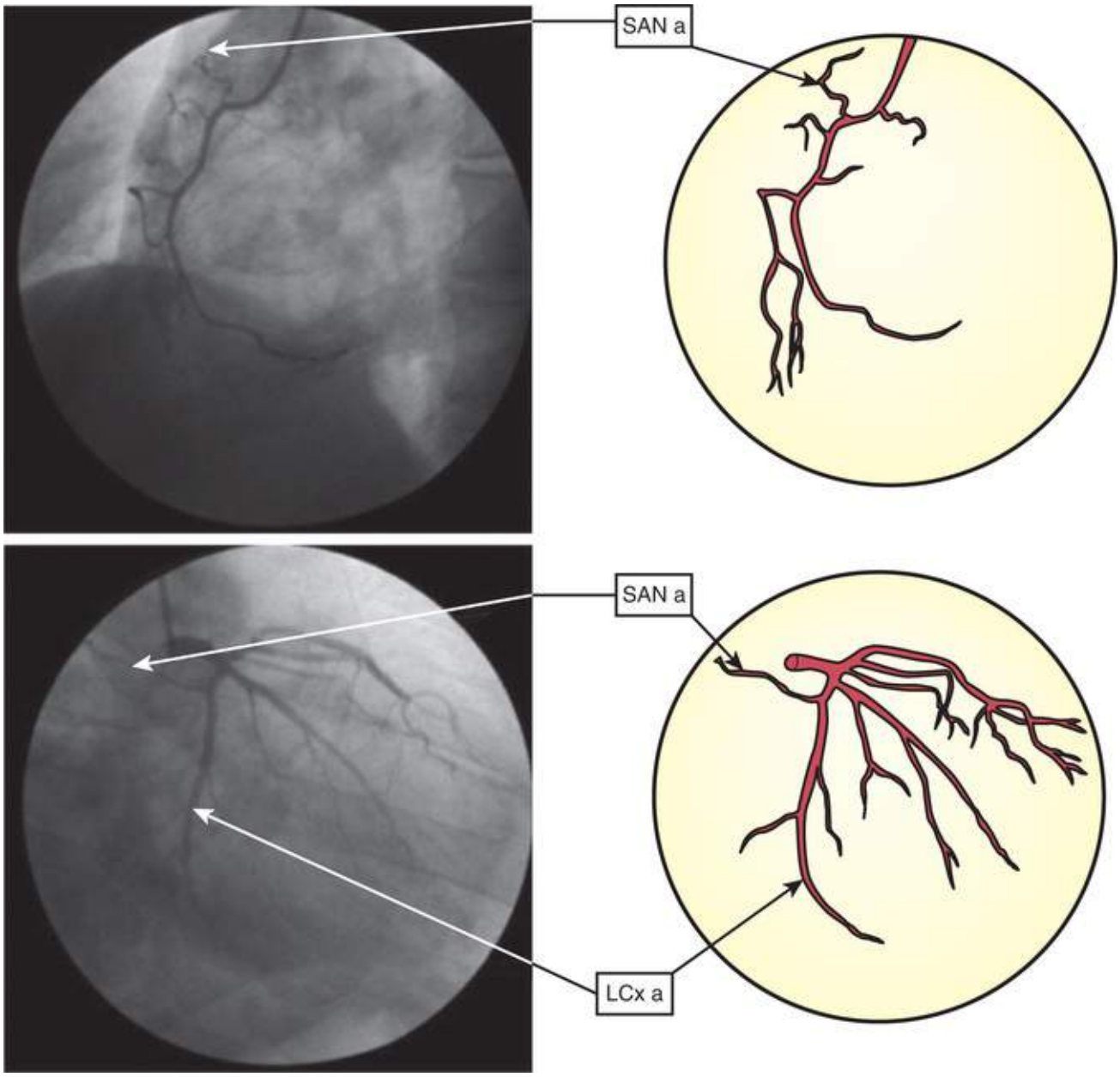


FIGURE 34.8 **Left,** Anterior view of the heart in a cadaver that has been dissected to show the course of the right phrenic nerve (*RPN*) relative to the right atrium (*RA*). The anticipated location of the sinus node outlined with the *dots*. The *double-headed arrow* represents the sectioning plane used for making the cross sections through the sinus node and the terminal crest (*TC*) shown in the histologic sections. *Ao,* Aorta; *RV,* right ventricle; *SCV,* superior caval vein. The histologic sections in the two **upper right panels** show variations in sizes of the sinus node cross section and the TC. With this stain (Masson trichrome), the node is recognizable by its fibrous matrix (*green*) and its artery. Two **lower right panels** show variations in nodal location relative to the epicardial and endocardial surfaces and to the SCV.; SVC, Superior vena cava. (From Ho SY, Sanchez-Quintana D. Anatomy and pathology of the sinus node. J Interv Card Electr 2016;46:3-8.)



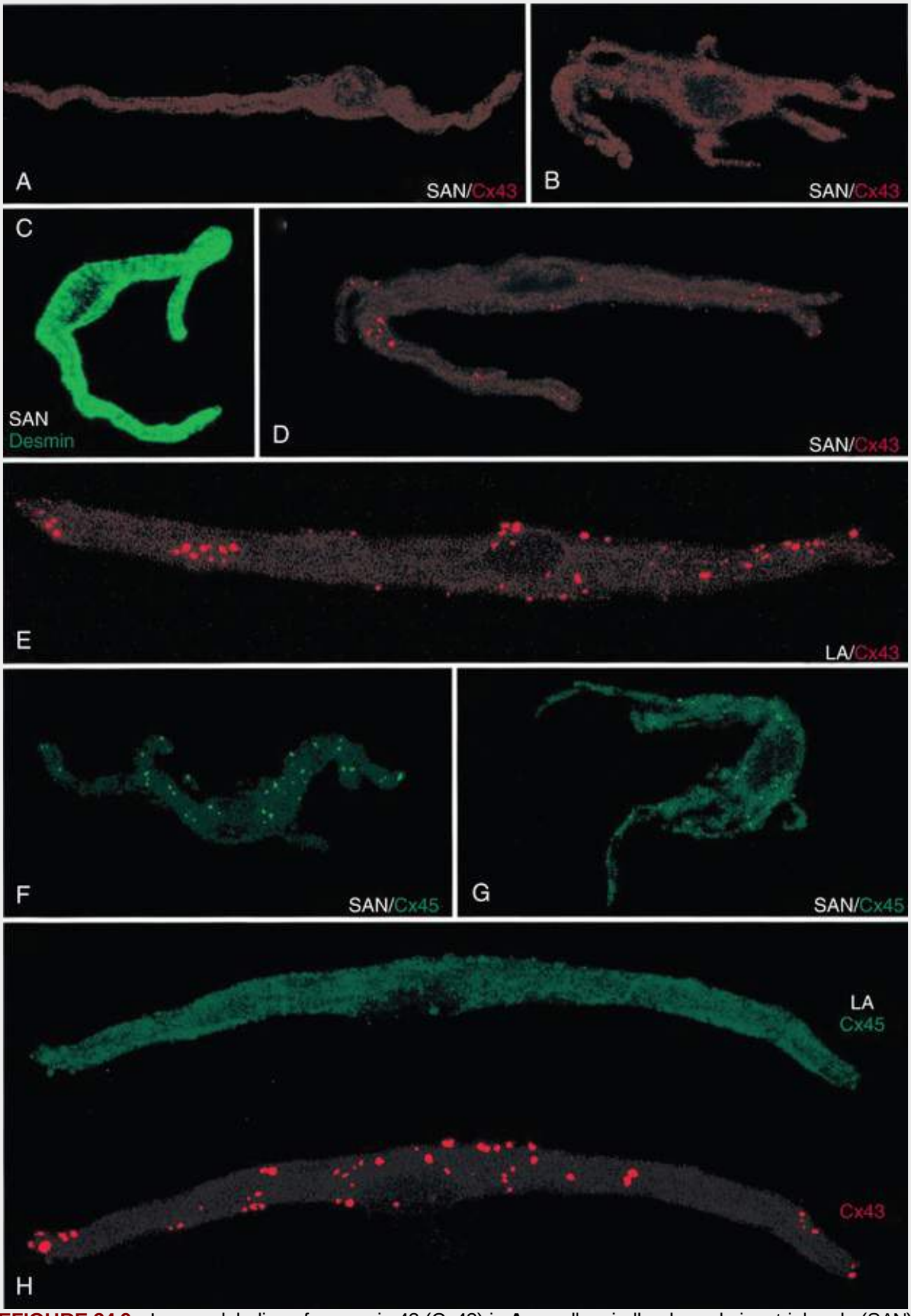
EFIGURE 34.7 Sinoatrial node (SAN) artery variations in the arterial supply of the sinus node (*yellow*). The SAN blood supply originates from a single coronary artery in 96% of cases and from both coronary arteries in 4 %. If the origin is from the left coronary artery, the nodal artery crosses the roof or the anterior wall of the left atrium. (From Ho SY, Sanchez-Quintana D. Anatomy and pathology of the sinus node. J Interv Card Electr 2016;46:3-8.)



EFIGURE 34.8 Angiographic view of the sinoatrial node blood supply. The sinoatrial node artery (SAN a) arises from the right coronary artery in a small majority of cases, but frequently is a branch of the left circumflex coronary artery (LCx a). (From Ramanathan L et al. Origin of the sinoatrial and atrioventricular nodal arteries in South Indians: an angiographic study. Arq Bras Cardiol 2009;92:342-8.)

Cellular Structure.

Cells from the SAN region exhibit a wide variety of morphologic features, including spindle- and spider-shaped cells, rod-shaped atrial cells with clear striations, and small, round cells corresponding to endothelial cells. The SAN cells stain for connexin 45 and in larger spindle-shaped cells, connexin 43 (**eFig. 34.9**). Only the spindle- and spider-shaped cells exhibit the typical electrophysiologic characteristics of pacemaker cells, including the hyperpolarization-activated current I_f and spontaneous beating under physiologic conditions.

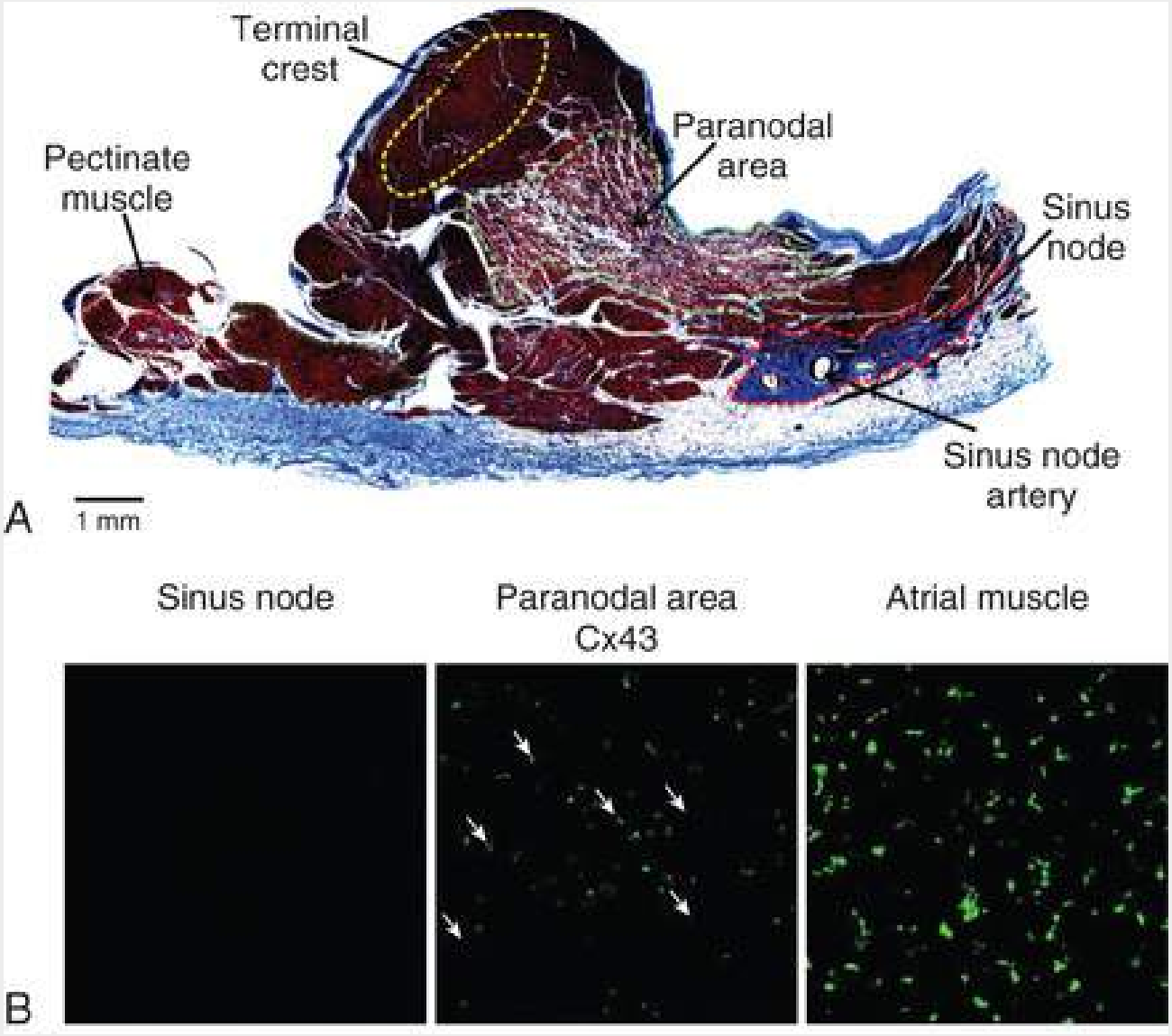


EFIGURE 34.9 Immunolabeling of connexin 43 (Cx43) in **A,** small, spindle-shaped sinoatrial node (SAN) cell, and **B,** spider-shaped SAN cell. **C,** Immunolabeling of desmin in small, spindle-shaped SAN cell. **D,** Immunolabeling of Cx43 in medium-sized, spindle-shaped SAN cell. **E,** Immunolabeling of Cx43 in left atrial (LA) cell. **F, G,** Immunolabeling of Cx45 in spider-shaped SAN cells. **H,** Immunolabeling of Cx45 (*top*) and Cx43 (*bottom*) in LA cell (cell *double-labeled*). Projection images shown in all panels. Scale bar = 20 μm. (From Honjo SY et al. Heterogeneous expression of connexins in rabbit sinoatrial node cells: correlation between

connexin isotype and cell size. Cardiovasc Res 2002;53:89.)

Function.

The ionic mechanism(s) underlying SAN cell automaticity has been controversial (see earlier, Normal Automaticity). Alternative models propose HCN channels in the surface membrane or intracellular Ca^{2+} oscillations affecting Ca^{2+}-sensitive ion channels and ion transporters in the cell surface membrane as the main regulators of the heart rate.[1] Similarly, the mechanism of *entrainment*, which enables synchronization of the electrical activity of multiple individual SAN cells to give rise to discharge of the SAN, has been uncertain. Most likely, no single cell in the SAN serves as the pacemaker. Rather, SAN cells function as electrically coupled oscillators that discharge synchronously. The interaction depends on the degree of coupling and the electrophysiologic characteristics of the individual SAN cell. The resulting rate is not just a simple average of each of the cells. With an individual pacemaker cell coupled to an average of five other cells, each likely with different electrophysiologic properties, the resulting discharge rate is not obvious. Functioning of the SAN as a pacemaker requires a delicate balance of intercellular electrical coupling. Excess electrical coupling depresses SAN automaticity because the SAN membrane potential is damped by the surrounding atrial myocardium to a more negative potential than the normal maximal diastolic potential, thereby inhibiting spontaneous diastolic depolarization. Insufficient coupling can prevent transmission of impulses to the adjacent atrial muscle. Restriction of the hyperpolarizing influence of the atrial muscle on the SAN while maintaining exit of impulses into the adjacent atrial myocardium is achieved by the composition and spatial organization of connexins, which form gap junction channels responsible for intercellular ion fluxes (see earlier). Connexins 40 and 45, but not connexin 43, are expressed in the central SAN (**eFig. 34.10B**). The major part of the crista terminalis–SAN border exhibits a sharply demarcated boundary of connexin 43–expressing atrial myocytes and connexin 40/45–expressing myocytes. On the endocardial side, a transitional zone (paranodal region; **eFig. 34.10A**) exists between the crista terminalis and the peripheral node where connexins 45 and 43 are colocalized. The colocalization of different connexin isoforms suggests that individual gap junctional channels in the transitional zone are formed by more than one connexin isoform.



EFIGURE 34.10 **A,** Masson trichrome–stained section through the human sinus node region. The node (*red dashed line*) is identified on the basis of the presence of the sinus node artery and the large amount of connective tissue (stained *blue*; myocytes stained *purple-pink*). The section also reveals the presence of a paranodal area (*green dashed line*) composed of loosely packed myocytes and sandwiched between the crista terminalis (*yellow dashed line*) and the sinus node. **B,** Cx43 is expressed prominently at cell ends in atrial muscle in the paranodal region and in the terminal crest. (From Chandler NJ et al. Molecular architecture of the human sinus node. Circulation 2009;119:1562.)

These disparate connexin phenotypes may create specific types of hybrid channels with rectifying electrical properties that ensure the maintenance of SAN pacemaker activity but diminish electrotonic interference from the atrial muscle. At the level of the intact SAN in situ, studies combining immunohistochemistry and high-resolution optical mapping of action potentials have provided structural and functional evidence of the existence of discrete exit pathways that electrically connect the SAN and atria. Electrical excitation during sinus rhythm originates in the central portion of the SAN and spreads slowly, bidirectionally (1 to 14 cm/sec) within the SAN, with failure to conduct laterally to the crista terminalis and interatrial septum. After a conduction delay of approximately 50 milliseconds within the SAN, the impulse reaches the atrial myocardium by two main superior or inferior exit pathways located a few millimeters from the leading pacemaker site. The ellipsoidal SAN is thus functionally insulated from the adjacent working myocardium. This insulation coincides with the lack of Cx43 expression and the presence of connective tissue and coronary arteries at the sinoatrial border (**eFig. 34.10**). The intranodal location of the primary pacemaking site is not fixed but rather appears to shift under varying conditions (e.g., sympathetic stimulation).

Several experimental studies have investigated the usefulness of gene delivery–based or cell-based approaches to generate biologic pacemakers in the mammalian heart. Gene-based techniques included transduction of in situ left ventricular cardiomyocytes with genes encoding a dominant-negative, inwardly rectifying potassium channel or isoforms of the HCN channel or somatic reprogramming of myocardial cells by expression of the appropriate transcription factors.[31] Cell-based approaches have used human induced pluripotent stem cell (iPSC)–derived pacemaker-like cardiomyocytes and mesenchymal stem cells ectopically expressing HCN isoforms.[32] Clinical translatability of these approaches will require additional experimental testing.[33]

Innervation.

The sinoatrial node is densely innervated by postganglionic adrenergic and cholinergic nerve terminals. Discrete vagal efferent pathways innervate both the sinoatrial (SA) and the atrioventricular (AV) region of the dog and nonhuman primate, as well as other species. Most efferent vagal fibers to the atria appear to converge first at a single fat pad between the medial portion of the SVC and the aortic root, superior to the right pulmonary artery; the fibers then project onto two other fat pads found at the junction of the IVC and left atrium and the junction of the right pulmonary vein and atrium and subsequently project to both atria. Vagal fibers to the SA and AV nodes also converge at the SVC–aortic root fat pad before projection to the right pulmonary vein and IVC fat pads. Although the SAN region contains amounts of norepinephrine equivalent to those in other parts of the right atrium, acetylcholine, acetylcholinesterase, and choline acetyltransferase (enzyme necessary for ACh synthesis) have been found in greatest concentration in the SAN, with the next highest concentration located in the right and then the left atrium. The ACh concentration in the ventricles is only 20% to 50% of that in the atria.[1]

Neurotransmitters modulate the discharge rate of the SAN by stimulation of beta-adrenergic and muscarinic receptors. Both $beta_1$- and $beta_2$-adrenoceptor subtypes are present in the SAN. Human sinoatrial nodes contain more than a threefold greater density of beta-adrenergic and muscarinic cholinergic receptors than adjacent atrial tissue. The functional significance of beta-adrenoceptor subtype diversity in the SAN is unclear. Binding of receptor agonists released from sympathetic nerve terminals causes a positive chronotropic response through a $beta_1$-receptor–activated pathway involving the stimulatory guanosine triphosphate (GTP) regulatory protein (G_s), activation of adenylyl cyclase, intracellular accumulation of cAMP, stimulation of cAMP-dependent PKA, and phosphorylation of ion-handling proteins, which ultimately results in an increased SAN discharge rate (see earlier, Phases of the Cardiac Action Potential). The negative chronotropic response of vagal stimulation is mediated by ACh binding to and ensuing activation of M_2 muscarinic receptors.[34,35]

In addition to its negative chronotropic effect, acetylcholine also prolongs intranodal conduction time, at times to the point of SAN exit block. ACh increases, whereas norepinephrine decreases refractoriness in the center of the SAN. The phase (timing) in the cardiac cycle at which vagal discharge occurs and the background sympathetic tone importantly influence vagal effects on the sinus rate and conduction (see earlier, Normal Automaticity). After cessation of vagal stimulation, SAN automaticity may accelerate transiently (postvagal tachycardia). The neurotransmitters neuropeptide Y (NPY) and vasoactive intestinal peptide (VIP) are localized in sympathetic and parasympathetic nerve terminals, respectively. VIP reversibly increases I_f, whereas NPY reversibly decreases I_f. The role of other peripheral neurotransmitters (e.g., calcitonin gene–related peptide, substance P) in controlling sinoatrial node electrophysiology is unclear.[1]

Atrioventricular Junctional Area and Intraventricular Conduction System

Atrioventricular Node

Based on histology and immunolabeling, the normal AV junctional area is composed of multiple distinct structures, including transitional tissue, inferior nodal extension, compact portion, penetrating bundle, His bundle, atrial and ventricular muscle, central fibrous body, tendon of Todaro, and valves[36] (**Fig. 34.9A and eFig. 34.11**).

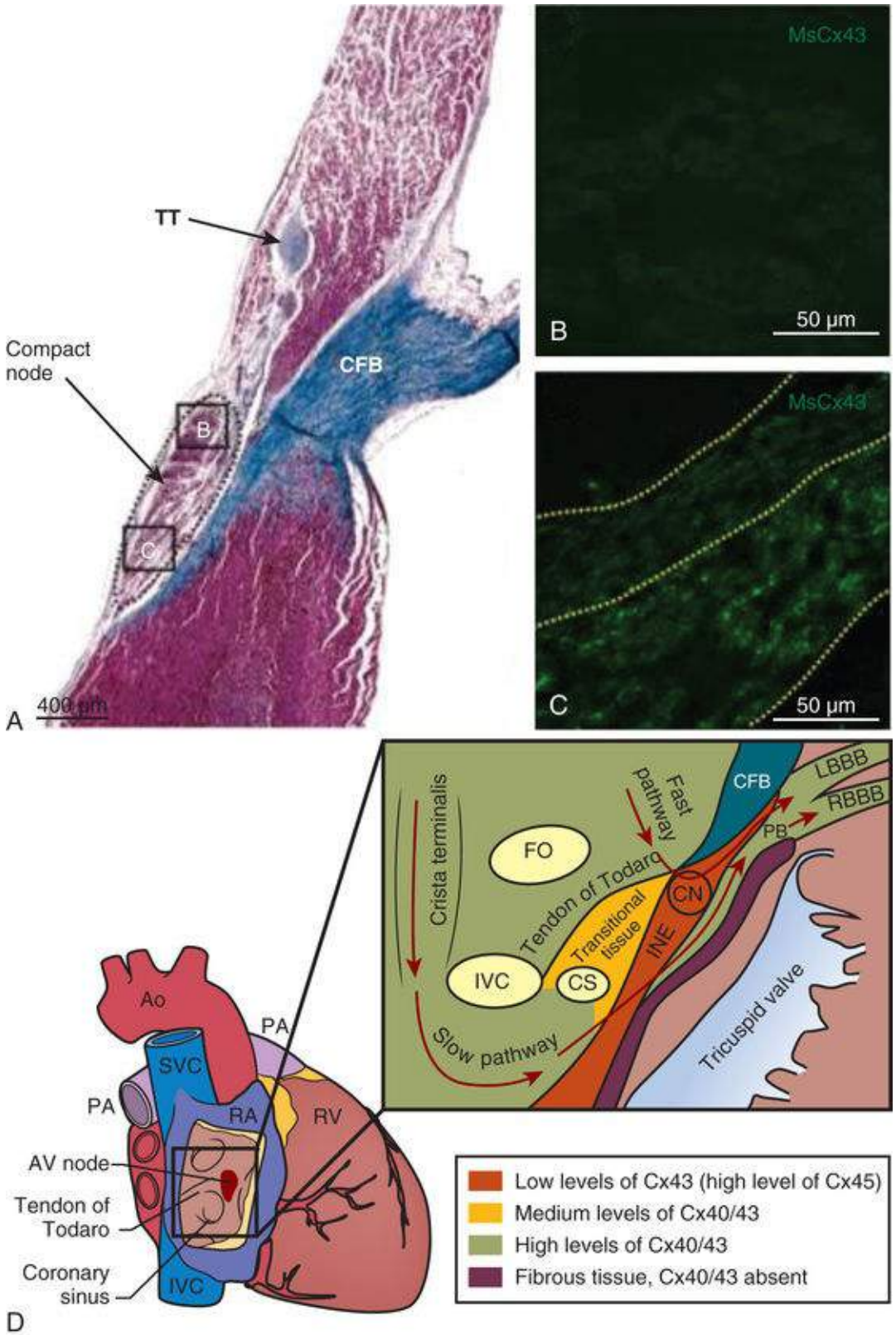
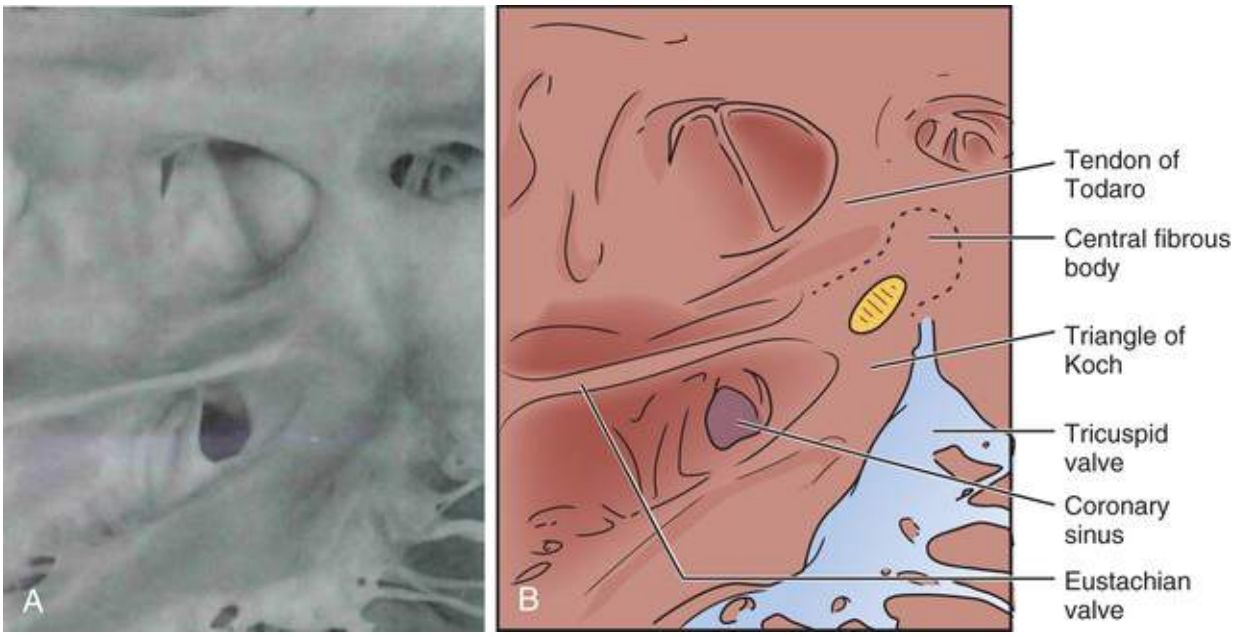
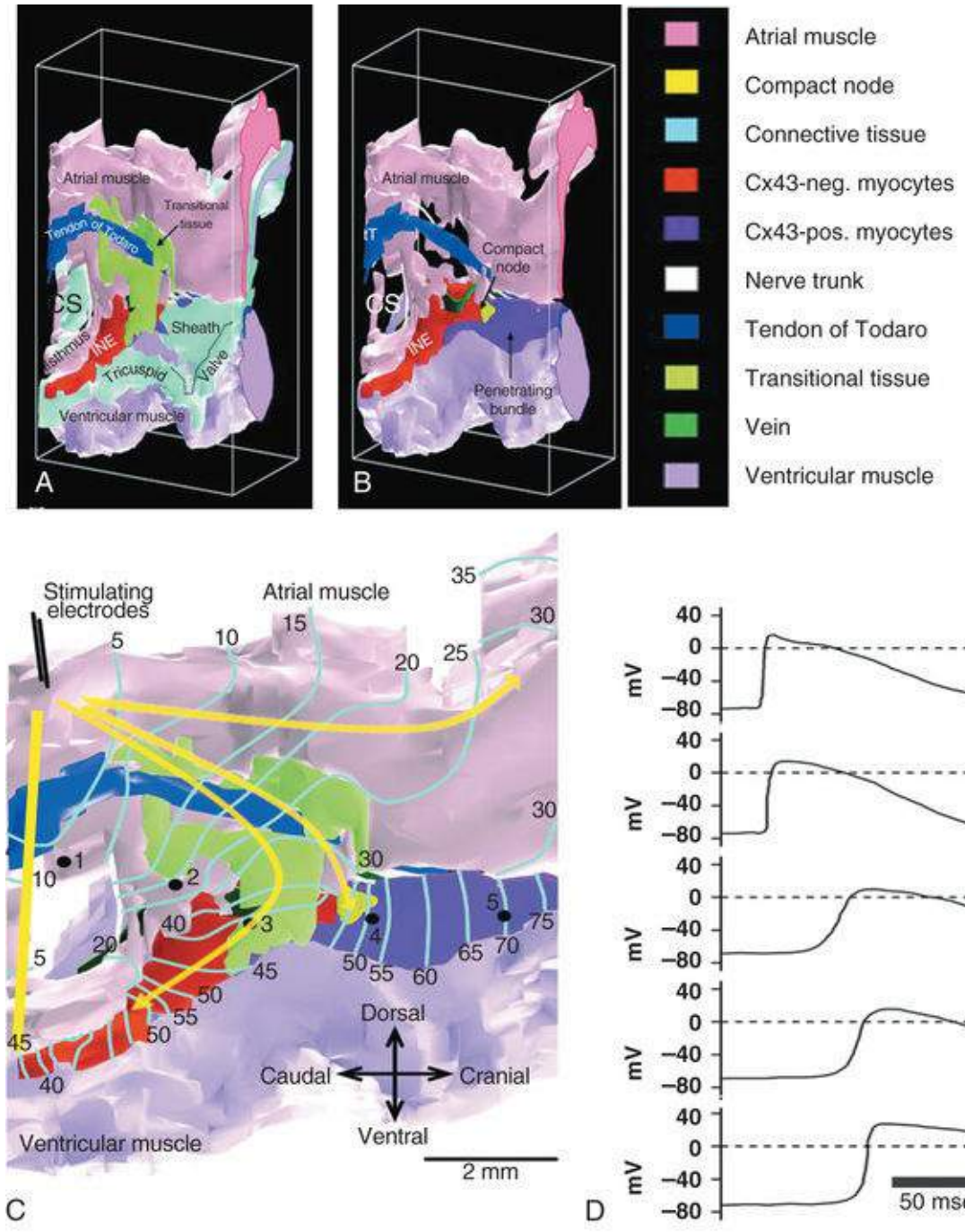


FIGURE 34.9 **A,** Masson's trichrome–stained section through the compact node of the rabbit heart (*red,* myocytes; *blue,* connective tissue). The compact node is enclosed with a *dashed line*. **B, C,** High-magnification images of boxed regions in **A** (**B** is the compact node; **C** is the lower nodal bundle) showing Cx43 expression (immunofluorescence, *bright-green* punctate spots). In **C,** *dotted yellow lines* divide tissue into Cx43-negative (*top*) and Cx43-positive (*bottom*) regions. (Modified from Dobrzynski et al. Site of origin and molecular substrate of atrioventricular junctional rhythm in the rabbit heart. Circ Res 2003;93:1102-10.) *CFB,* Central fibrous body; *TT,* tendon of Todaro. **D,** Color-coded map of the distribution of connexins (Cx) in the atrioventricular (AV) junction. *Ao,* Aorta; *CN,* compact AV node; *CS,* coronary sinus; *FO,* foramen ovale; *INE,* inferior nodal extension; *IVC,* inferior vena cava; *LBBB,* left bundle branch block; *PA,* pulmonary artery; *PB,* penetrating bundle; *RA,* right atrium; *RBBB,* right bundle branch block; *RV,* right ventricle. (From Temple IP et al. Connexins and the atrioventricular node. Heart Rhythm 2010;10:297.)



EFIGURE 34.11 **A,** Photograph of a normal human heart showing the anatomic landmarks of the triangle of Koch. This triangle is delimited by the tendon of Todaro superiorly, by the fibrous commissure of the flap guarding the openings of the inferior vena cava and coronary sinus, by the attachment of the septal leaflet of the tricuspid valve inferiorly, and by the mouth of the coronary sinus at the base. **B,** The *stippled area (orange)* adjacent to the central fibrous body is the approximate site of the compact atrioventricular node. (From Janse MJ et al. "AV nodal" reentry: I. "AV nodal" reentry revisited. J Cardiovasc Electrophysiol 1993;4:561.)

At the level of the AV junction, the tract of nodal tissue is divided into two major components, the inferior nodal extension and the penetrating bundle. The *inferior nodal extension* (INE) is located between the coronary sinus and the tricuspid valve, and the end of the INE is covered by transitional tissue (**Fig. 34.9D**). The small myocytes in the INE are dispersed among connective tissue and do not express connexin 43, whereas myocytes in the transitional zone do express Cx43; however, unlike the Cx43-positive atrial myocytes in the working myocardium, they are loosely packed between collagen septa (**Fig. 34.9B-C and eFig. 34.12**). The INE is continuous with the penetrating bundle, which penetrates the fibrous tissue separating the atria and ventricles and emerges in the ventricles as the bundle of His. Both structures are covered by connective tissue and are therefore enclosed. Myocytes in the *penetrating bundle* express Cx43 and are dispersed among connective tissue. A tract of Cx43-positive nodal tissue projects into the Cx43-negative INE.

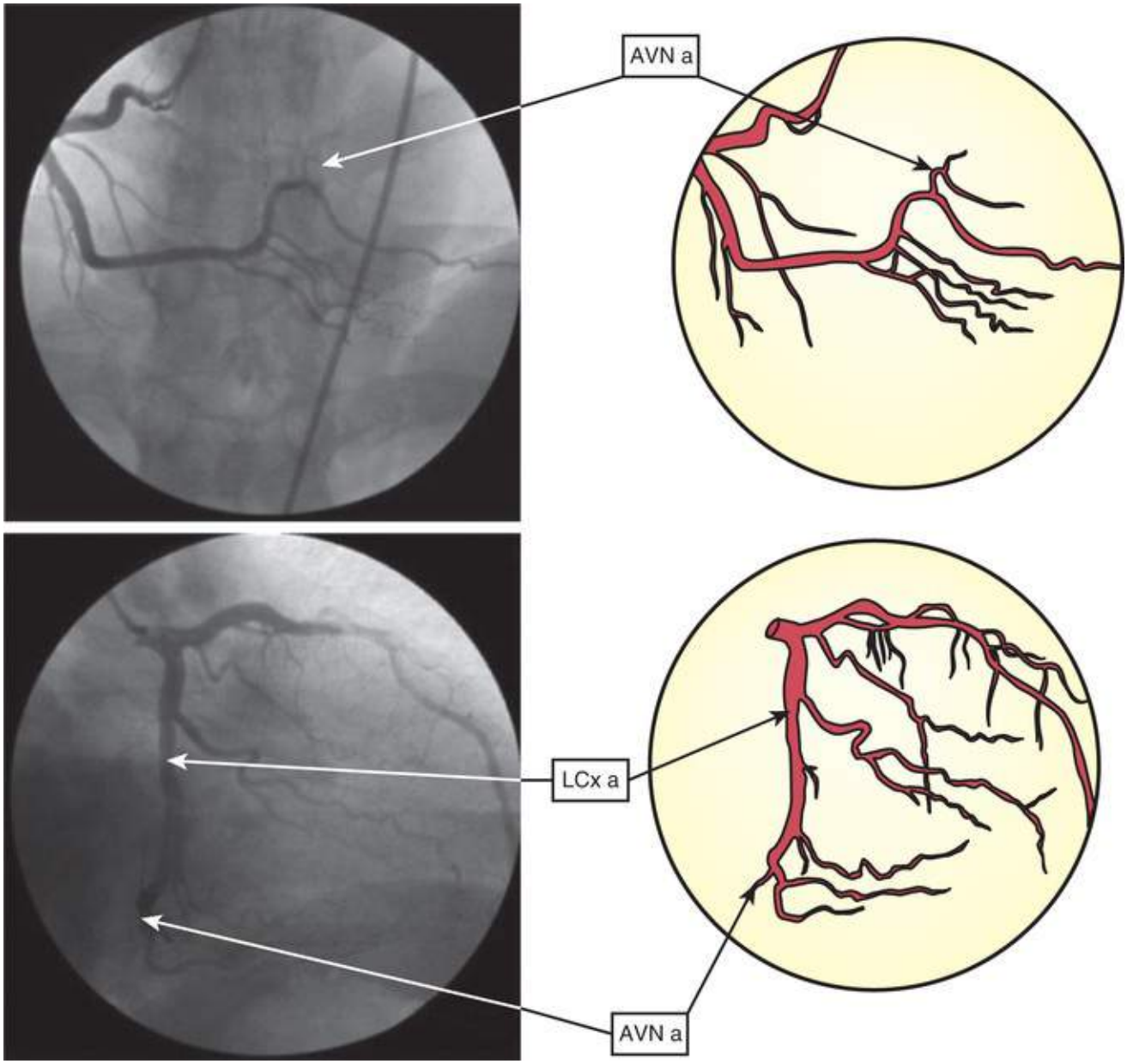


EFIGURE 34.12 **A, B,** Computer-generated three-dimensional anatomic model of the atrioventricular (AV) node as viewed from the right atrium-ventricle. **A** shows all cell types. **B** shows the model after removal of transitional and connective tissue. The inferior nodal extension (*INE*) is located between the coronary sinus (*CS*) and the tricuspid valve; the end of the INE is covered by transitional tissue; the penetrating bundle begins at the apex of the triangle of Koch (formed by CS, tendon of Todaro [*tT*], and tricuspid valve); and the penetrating bundle and His bundle are covered by connective tissue ("sheath"). After removal of the transitional and connective tissue, one sees protraction of a connexin 43 (Cx43)–positive portion of nodal tissue into the Cx43-negative INE. The compact node is located at the junction of Cx43-negative and Cx43-positive nodal tissue. **C, D,** Structure-function relationships of the AV node. **C,** Schematic representation of the sequence of anterograde AV conduction by using a combination of mathematical modeling and experimental mapping of action potential propagation. The preparation is electrically stimulated at the crista terminalis. The activation sequence is shown as isochrones at 5-millisecond intervals. *Yellow arrows* delineate the conduction pathways. (See also Video 34.1.) **D,** Transmembrane action potentials recorded at locations indicated by *black dots* in C (numbered *1* through *5*). (Modified from Li J et al. Computer three dimensional reconstruction of the atrioventricular node. Circ Res 2008;102:975.)

The compact portion of the AV node (**Fig. 34.9A**) is a superficial structure lying just beneath the right atrial endocardium, anterior to the ostium of the coronary sinus, and directly above the insertion of the septal leaflet of the tricuspid valve. It is at the apex of a triangle formed by the tricuspid annulus and the

tendon of Todaro (**Fig. 34.9D**), which originates in the central fibrous body and passes posteriorly through the atrial septum to continue with the eustachian valve. The term *triangle of Koch*, however, has to be used with caution because histologic studies of anatomically normal adult hearts have demonstrated that the tendon of Todaro, which forms one side of the triangle of Koch, is absent in about two thirds of hearts. The compact node is located at the junction where the Cx43-negative nodal tissue meets the Cx43-positive nodal tissue (**Fig. 34.9B-D**).

In 85% to 90% of human hearts, the arterial supply to the AV node is derived from a branch of the right coronary artery that originates at the posterior intersection of the AV and interventricular grooves (crux). A branch of the circumflex coronary artery provides the arterial supply to the AV node in the remaining hearts (**eFig. 34.13**).



EFIGURE 34.13 The atrioventricular node artery (AVN a) arises from the posterior descending branch of the right coronary artery in the large majority of cases. AVN artery arises from the left circumflex coronary artery (LCx a) in most of the remaining cases, although in some circumstances, there is dual blood supply. (From Ramanathan L et al. Origin of the sinoatrial and atrioventricular nodal arteries in South Indians: an angiographic study. Arq Bras Cardiol 2009;92:342-8.)

During normal anterograde AV conduction, the action potential propagates from the SAN through atrial working myocardium (the existence of specialized internodal conduction pathways has been controversial) and enters the tract of nodal tissue at two points (**Fig. 34.9D and eFig. 34.12**; see also Video 34.1). The first point is at the end of the INE (next to the penetrating bundle) via the transitional tissue. This conduction pathway most likely corresponds to the fast-pathway route previously observed in electrical mapping experiments.[36] Second, the action potential enters toward the beginning of the INE. This conduction pathway probably constitutes the slow-pathway route. The action potential cannot enter the nodal tissue at other tissue points because the nodal and atrial tissues are isolated from each other by a vein along this length of tissue. From the two entry points, the action potentials propagate both anterogradely and retrogradely along the INE and eventually annihilate each other. The action potential entering the nodal tract via the transitional zone also propagates into the compact node and then reaches the His bundle and propagates down the left and right bundle branches.

Transmembrane action potentials recorded from cardiomyocytes in situ at various locations within the nodal tract exhibit distinct shapes and time courses. Action potentials from extranodal atrial tissue and the His bundle have more hyperpolarized diastolic potentials and faster upstrokes (**Fig. 34.4B, E**) than do myocytes in the transitional zone and penetrating bundle (**Fig. 34.4C and eFig. 34.12D**). This smaller rate of depolarization results in slowing of conduction across the compact portion and penetrating bundle (conduction velocity <10 cm/sec versus 35 cm/sec in atrial working myocardium), thereby giving rise to the AV conduction delay.

Bundle of His (Penetrating Portion of Atrioventricular Bundle)

This structure is the continuation of the penetrating bundle on the ventricular side of the AV junction before it divides to form the left and right bundles. Myocytes in the His bundle are small and Cx43 positive (**see Fig. 34.9D**). However, large, well-formed fasciculoventricular connections between the penetrating portion of the AV bundle and the ventricular septal crest are rarely found in adult hearts. Branches from the anterior and posterior descending coronary arteries supply the upper muscular interventricular septum with blood, which makes the conduction system at this site more impervious to ischemic damage unless the ischemia is extensive.

Bundle Branches (Branching Portion of Atrioventricular Bundle)

The bundle branches begin at the superior margin of the muscular interventricular septum, immediately beneath the membranous septum, with cells of the left bundle branch (LBB) cascading downward as a continuous sheet onto the septum beneath the noncoronary aortic cusp (**Fig. 34.10A**). The AV bundle may then give off other LBBs, sometimes constituting a true bifascicular system with an anterosuperior branch, in other hearts giving rise to a group of central fibers, and in still others appearing more as a network without clear division into a fascicular system (**Fig. 34.10B, C**). The right bundle branch continues intramyocardially as an unbranched extension of the AV bundle down the right side of the interventricular septum to the apex of the right ventricle and base of the anterior papillary muscle. In some human hearts, the His bundle traverses the right interventricular crest and gives rise to a right-sided narrow stem origin of the LBB. The anatomy of the LBB system can be variable and may not conform to a constant bifascicular division. However, the concept of a trifascicular system remains useful to both electrocardiographers and clinicians (**see Chapter 12**).

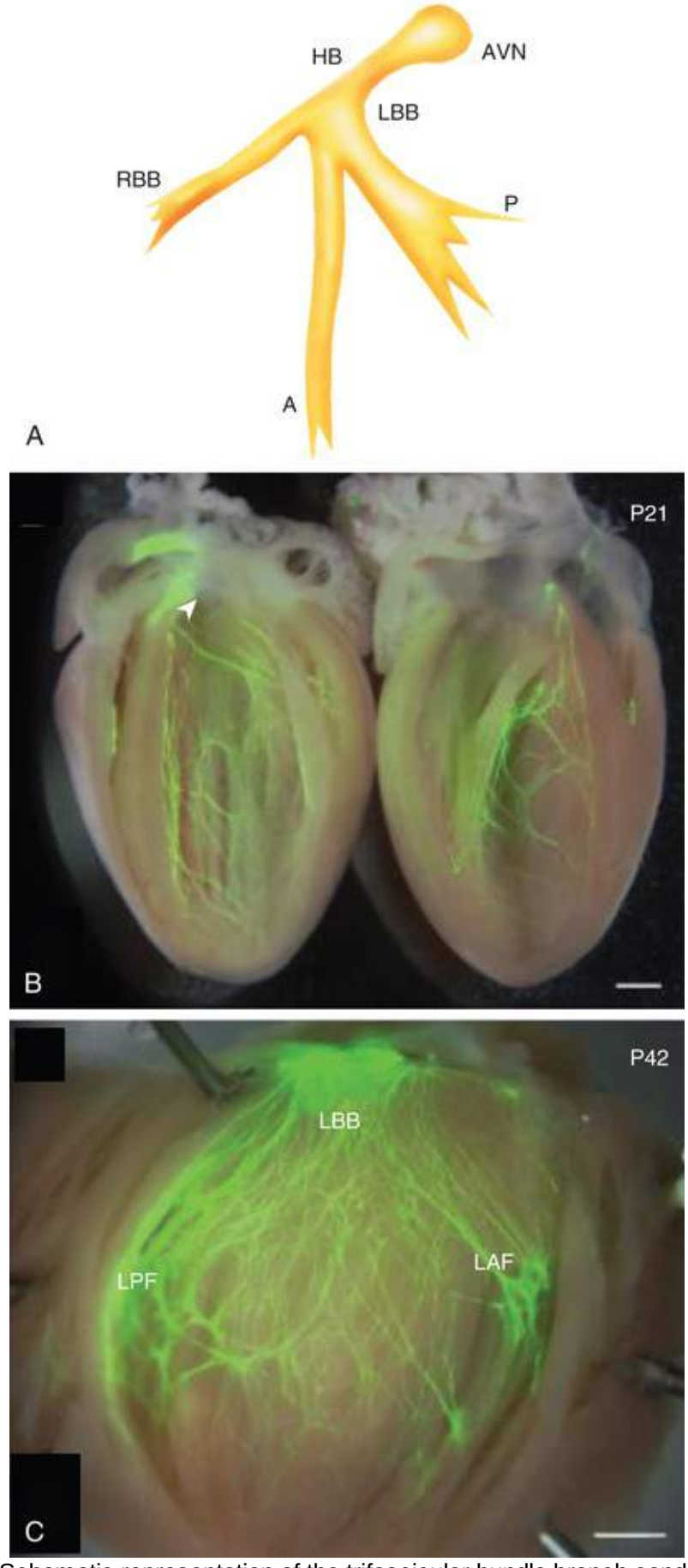


FIGURE 34.10 **A,** Schematic representation of the trifascicular bundle branch conduction system. **B, C,** Whole mount of murine hearts expressing contactin-2 eGFP reporter gene (Cntn2^{EGFP}) demonstrate the presence of Cntn2 throughout the cardiac conduction system. The hearts are from mice **(B)** 21 days (P21) and **(C)** and 42 days (P42) postpartum. There is robust expression of Cntn2 within the atrioventricular node (*AVN*) (*arrowhead*) His bundle (*HB*), bundle branches, and Purkinje network. Scale bars = 500 µm. *LAF,* Left anterior fascicle; *LBB,* left bundle branch; *LPF,* left posterior fascicle; *RBB,* right bundle branch. (**A,** Modified from Rosenbaum MB et al. The Hemiblocks. Oldsmar, Fla: Tampa Tracings; 1970, cover

illustration; **B, C,** from Maass K et al. Isolation and characterization of embryonic stem cell–derived cardiac Purkinje cells. Stem Cells 2015;33:1102-12.)

Terminal Purkinje Fibers

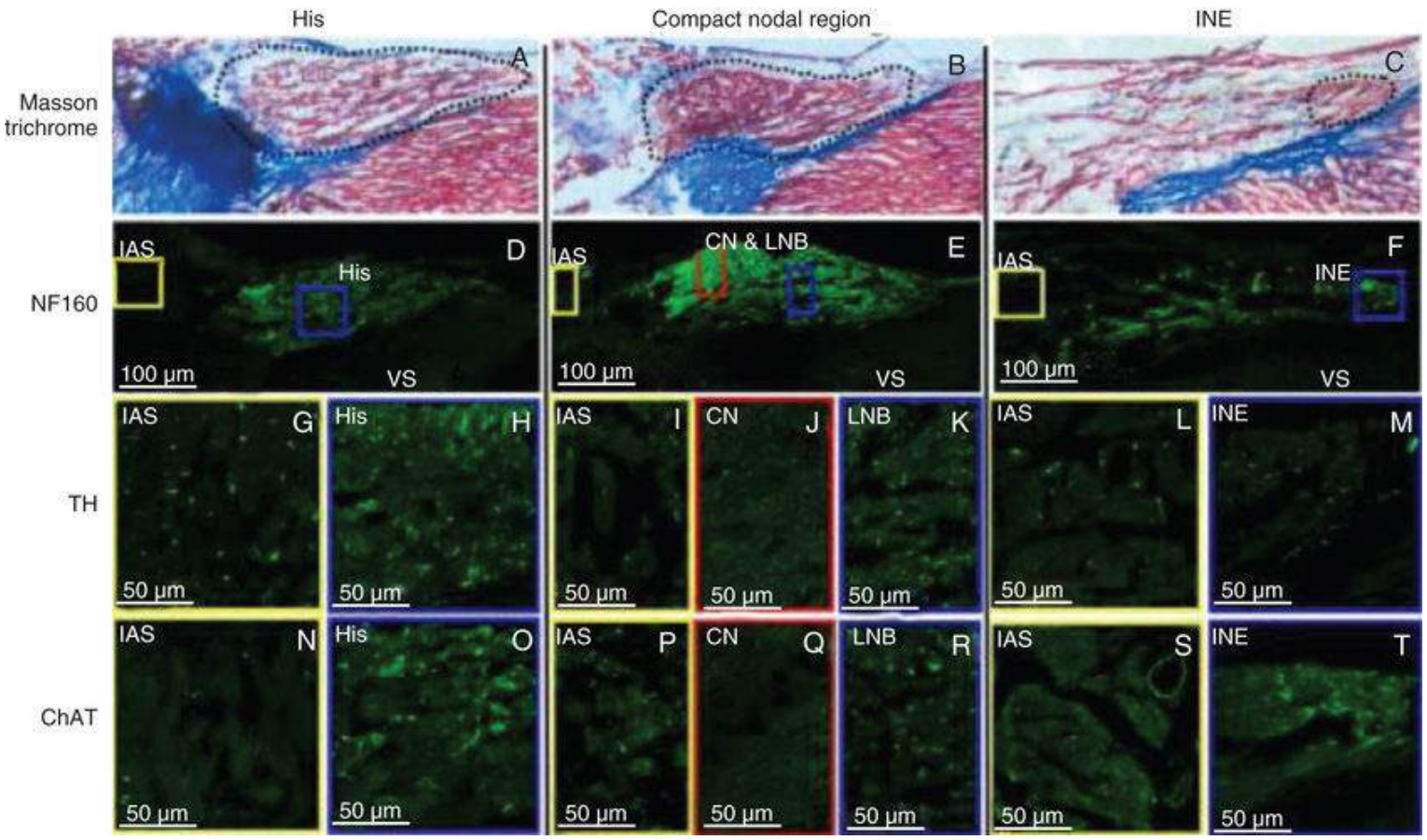
The Purkinje fibers connect with the ends of the bundle branches to form interweaving networks on the endocardial surface of both ventricles and transmit the cardiac impulse almost simultaneously to the entire right and left ventricular endocardium. Purkinje fibers tend to be less concentrated at the base of the ventricle and at the papillary muscle tips. They penetrate the myocardium for varying distances, depending on the species. In humans, Purkinje fibers apparently penetrate only the inner third of the endocardium, whereas in pigs, they almost reach the epicardium. Such variations could influence changes produced by myocardial ischemia, for example, because Purkinje fibers appear to be more resistant to ischemia than are ordinary myocardial fibers. Purkinje myocytes are found in the His bundle and bundle branches, cover much of the endocardium of both ventricles (**see Fig. 34.10B**), and align to form multicellular bundles in longitudinal strands separated by collagen. Although conduction of cardiac impulses appears to be their major function, free-running Purkinje fibers composed of many Purkinje cells in a series, sometimes called *false tendons*, are capable of contraction. Action potentials propagate within the thin Purkinje fiber bundles from the base to the apex before activation of the surrounding myocytes occurs. Purkinje myocytes have less well-developed transverse tubules (**see eFig. 34.5B**), which reduces membrane capacitance and thus accelerates action potential propagation. Propagation of action potentials within the His-Purkinje system and working myocardium is mediated by connexins. Ventricular myocytes express mainly Cx43, and Purkinje fibers express connexins 40 and 45. The molecular identity of the connexin type that enables transmission of impulses at the Purkinje fiber–myocyte junction (PMJ) is unclear. It is also still not clear how the small amount of depolarizing current provided by the thin bundle of Purkinje fibers can activate a much larger mass of ventricular muscle (current-to-load mismatch). It is possible that individual gap junctional channels at the PMJ are formed by more than one connexin isoform. These disparate connexin phenotypes may create specific types of hybrid channels with unique properties that ensure safe conduction at the PMJ. Because Purkinje cells have markedly longer repolarization times than surrounding myocytes (**see Fig. 34.3E**), these connexin hybrids could also decrease entrainment of repolarization at the PMJ and thereby increase repolarization gradients.

Innervation of Atrioventricular Node, His Bundle, and Ventricular Myocardium

Pathways of Innervation

The AV node and His bundle region are innervated by a rich supply of cholinergic and adrenergic fibers with densities exceeding those found in the ventricular myocardium.[1,34,35] Immunolabeling with markers for sympathetic and parasympathetic nerves revealed nonuniform innervation density in the AV junctional area. For example, the INE has been shown to exhibit a higher density of both nerve types than the working atrial myocardium, whereas the opposite is true for the compact node (**eFig. 34.14**). Ganglia, nerve fibers, and nerve nets lie close to the AV node. Parasympathetic nerves to the AV node region enter the canine heart at the junction of the IVC and the inferior aspect of the left atrium, adjacent to the entrance to the coronary sinus. Nerves in direct contact with AV nodal fibers have been observed, along with agranular and granular vesicular processes, which presumably represent cholinergic and adrenergic

processes.



EFIGURE 34.14 Innervation of atrioventricular node (AVN). **A to C,** Masson trichrome staining of the His bundle, compact AVN region, and inferior nodal extension (INE). **D to F,** Neurofilament 160 (NF160) staining of sections adjacent to those shown in **A, B,** and **C** showing that NF160 specifically marks the rabbit conduction system. **G to M,** Tyrosine hydroxylase (TH) staining of areas marked with boxes in **D to F. N to T,** Choline acetyltransferase (ChAT) staining of areas marked with boxes in **D to F.** Interatrial septum (IAS) staining was actually taken from areas 200 to 300 µm to the left of the areas marked with *yellow boxes* in **D, E,** and **F.** *LNB,* Lower nodal bundle. Other abbreviations as in previous figures. (From Hucker WJ et al. Autonomic control and innervation of the atrioventricular junctional pacemaker. Heart Rhythm 2007;4:1326-35.)

In general, autonomic neural input to the heart exhibits some degree of "sidedness," with the right sympathetic and vagal nerves affecting the sinoatrial node more than the AV node and the left sympathetic and vagal nerves affecting the AV node more than the SA node. The distribution of neural input to the SA and AV nodes is complex because of substantial overlapping innervation. Despite the overlap, specific branches of the vagal and sympathetic nerves can be shown to innervate certain regions preferentially. Supersensitivity to acetylcholine follows vagal denervation. Stimulation of the right stellate ganglion produces sinus tachycardia with less effect on AV nodal conduction, whereas stimulation of the left stellate ganglion generally produces a shift in the sinus pacemaker to an ectopic site and consistently shortens AV nodal conduction time and refractoriness but inconsistently speeds the SA nodal discharge rate. Stimulation of the right cervical vagus nerve primarily slows the SA nodal discharge rate, and stimulation of the left vagus primarily prolongs AV nodal conduction time and refractoriness when sidedness is present. Neither sympathetic nor vagal stimulation affects normal conduction in the His bundle. The negative dromotropic response of the heart to vagal stimulation is mediated by the activation of $I_{K.ACh}$, which results in hyperpolarization of the AV nodal cells and thereby influences the conductive

properties of the node. The positive dromotropic effect of sympathetic stimulation arises because of an increase in cytosolic cAMP levels and ensuing activation of the L-type Ca^{2+} current $I_{Ca.L}$.

Most efferent sympathetic impulses reach the canine ventricles over the ansae subclavia, branches from the stellate ganglia. Sympathetic nerves then synapse primarily in the caudal cervical ganglia and form individual cardiac nerves that innervate relatively localized parts of the ventricles. The major route to the heart is the recurrent cardiac nerve on the right side and the ventrolateral cardiac nerve on the left. In general, the right sympathetic chain shortens refractoriness primarily of the anterior portion of the ventricles, and the left affects primarily the posterior surface of the ventricles, although overlapping areas of distribution occur.

The intraventricular route of sympathetic nerves generally follows the coronary arteries. Functional data suggest that afferent and efferent sympathetic nerves travel in the superficial layers of the epicardium and dive to innervate the endocardium, and anatomic observations support this conclusion. Vagal fibers travel intramurally or subendocardially and rise to the epicardium at the AV groove (**Fig. 34.11A**). Sympathetic nerve density in the left ventricle appears to be higher in the epicardial than in the endocardial portion of the ventricle, which at least in part results from transmural gradients in the expression of cytokines during cardiac development that attract and repel, respectively, sympathetic nerve growth[1,34,35] (**Fig. 34.11B**).

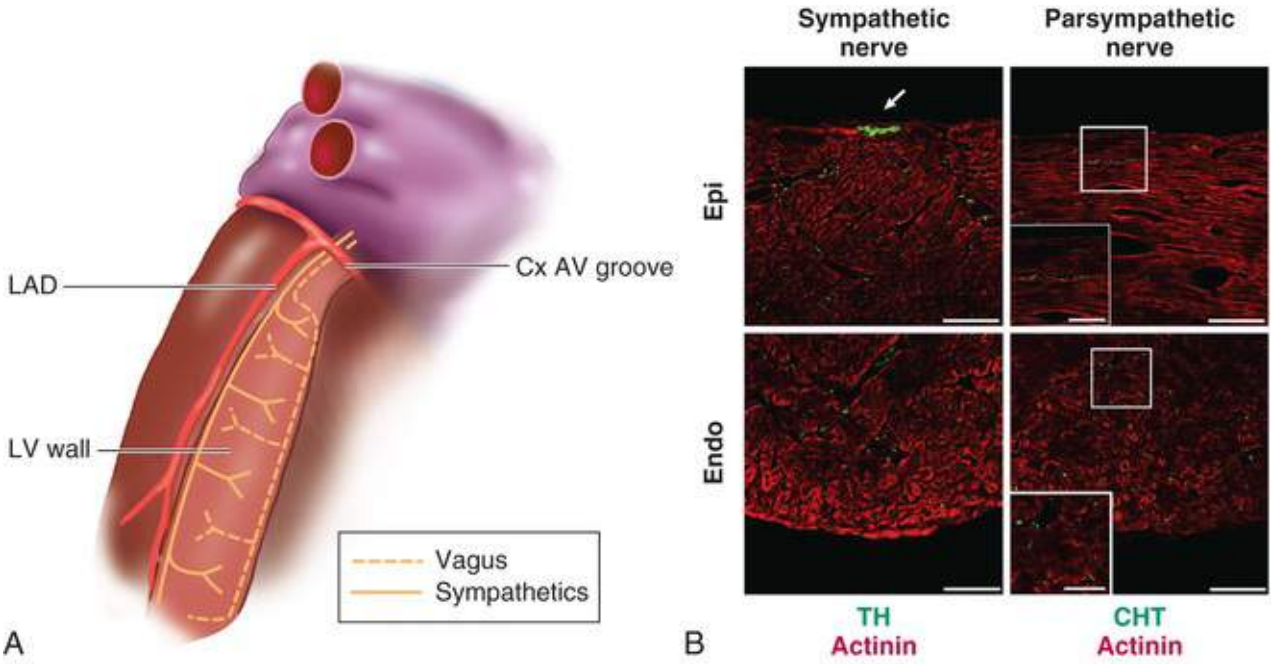
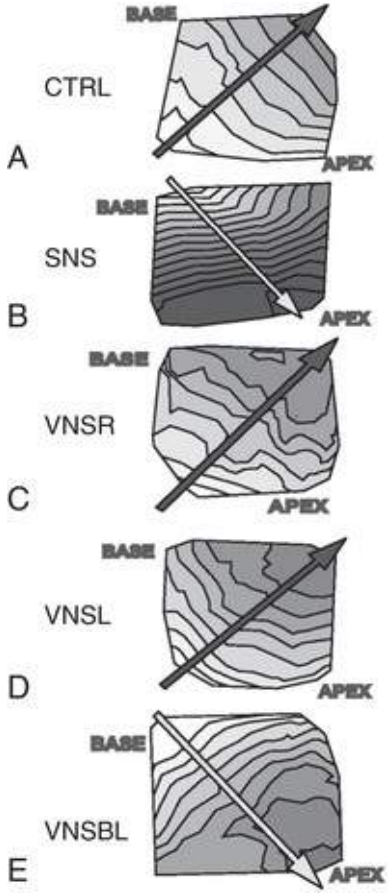


FIGURE 34.11 **A,** Intraventricular route of the sympathetic and vagal nerves to the left ventricle (*LV*); *LAD,* left anterior descending artery. **B,** Distribution of sympathetic and parasympathetic nerves in the mammalian heart. Immunofluorescence staining for the sympathetic and parasympathetic nerve markers tyrosine hydroxylase (*TH*) and choline transporter (*CHT*) is shown in the LV of a rat heart (*green,* nerves; *red,* alpha-actinin, a cardiomyocyte marker). TH-positive nerves are more abundant in the subepicardial (Epi) layer than in the subendocardial (Endo) layer. The *arrow* indicates sympathetic nerves at the epicardial surface. No CHT-positive nerves are present at the epicardial surface, and CHT-positive nerves are more abundant in the subendocardial layer. Higher magnification views of the boxed regions are shown in the *insets*. Scale bars = 100 µm. (**A,** From Ito M, Zipes DP. Efferent sympathetic and vagal innervation of the canine right ventricle. Circulation 1994;90:1459. By permission of the American Heart Association; **B,** from Kanazawa H et al. Heart failure causes cholinergic transdifferentiation of cardiac sympathetic nerves via gp130-signaling cytokines in rodents. J Clin Invest 2010;120:408.)

Effects of Vagal Stimulation

The vagus nerve modulates cardiac sympathetic activity at prejunctional and postjunctional sites by regulating the amount of norepinephrine released and by inhibiting cAMP-induced phosphorylation of cardiac proteins, including ion channels and calcium pumps. The latter inhibition occurs at more than one level in the series of reactions constituting the adenylate cyclase–cAMP-dependent protein kinase system. Neuropeptides released from the nerve fibers of both autonomic limbs also modulate autonomic responses. For example, NPY released from sympathetic nerve terminals inhibits cardiac vagal effects.

Tonic vagal stimulation produces a greater absolute reduction in the sinoatrial rate in the presence of tonic background sympathetic stimulation, a sympathetic-parasympathetic interaction termed *accentuated antagonism*. In contrast, changes in AV conduction during concomitant sympathetic and vagal stimulation are essentially the algebraic sum of the individual AV conduction responses to tonic vagal and sympathetic stimulation alone. Cardiac responses to brief vagal bursts begin after a short latency and dissipate quickly; in contrast, cardiac responses to sympathetic stimulation commence and dissipate slowly. The rapid onset and offset of responses to vagal stimulation allow dynamic beat-to-beat vagal modulation of the heart rate and AV conduction, whereas the slow temporal response to sympathetic stimulation precludes any beat-to-beat regulation by sympathetic activity. Periodic *vagal bursting*, as may occur each time that a systolic pressure wave arrives at the baroreceptor regions in the aortic and carotid sinuses, induces phasic changes in sinus cycle length and can entrain the sinus node to discharge faster or slower at periods identical to those of the vagal burst. In a similar phasic manner, vagal bursts prolong AV nodal conduction time and are influenced by background levels of sympathetic tone. Because the peak vagal effects on sinus rate and AV nodal conduction occur at different times in the cardiac cycle, a brief vagal burst can slow the sinus rate without affecting AV nodal conduction or can prolong AV nodal conduction time and not slow the sinus rate. Bilateral but not unilateral vagal nerve stimulation increases and reverses the spatial dispersion of ventricular repolarization as the direction of repolarization from the apex to the base in sinus rhythm shifts from the base to the apex. This effect is attributable to more pronounced prolongation of the action potential at the apex than at the base of the heart (**eFig. 34.15**).



EFIGURE 34.15 Reversal of the ventricular repolarization sequence during autonomic nerve stimulation in a rabbit heart. Each map represents the dispersion of repolarization for a single cardiac beat and is displayed as an isochronal map with lines 2 milliseconds apart. *Light to dark shades* represent early to late repolarization time points. *Arrows* point to the direction of the repolarization sequence. CTRL, Control; SNS, sympathetic nerve stimulation; VNSBL, bilateral vagal nerve stimulation; VNSL, left vagal nerve stimulation; VNSR, right vagal nerve stimulation.

Effects of Sympathetic Stimulation

Similar to bilateral vagal nerve stimulation, sympathetic nerve stimulation also increases and reverses the spatial gradients of ventricular repolarization as the direction of polarization from the apex to the base in sinus rhythm shifts from base to apex. This reversal results from a marked shortening of action potential duration at the base, with no or negligible effect on the repolarization time course at the apex of the heart (**eFig. 34.15**). Nonuniform distribution of sympathetic nerves—and thus norepinephrine levels—may in part contribute to some of the nonuniform electrophysiologic effects, because the ventricular content of norepinephrine is greater at the base than at the apex of the heart. In humans, both direct and reflex sympathetic stimulation increases regional differences in cardiac repolarization. The dispersion of repolarization is significantly enhanced in patients with ischemic cardiomyopathy.[37] Afferent vagal activity appears to be higher in the posterior ventricular myocardium, which may account for the vagomimetic effects of inferior MI.

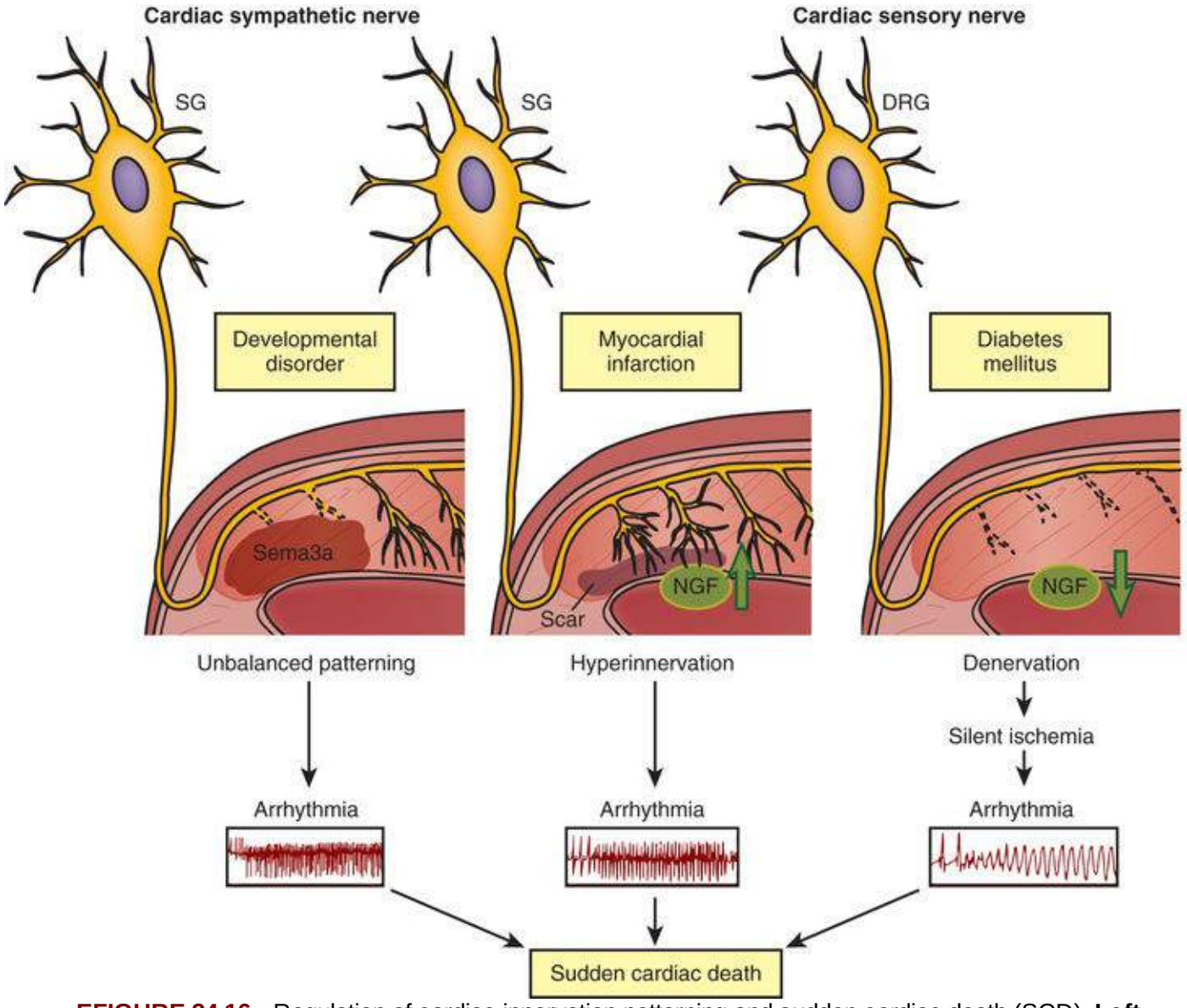
The vagi exert minimal but measurable effects on ventricular tissue; they decrease the strength of myocardial contraction and prolong refractoriness. Under some circumstances, acetylcholine can cause a positive inotropic effect. It is now clear that the vagus (ACh) can exert direct effects on some types of ventricular fibers, as well as indirect effects by modulating sympathetic influences.

Beyond the beat-to-beat regulation of rate and contractile force, sympathetic input to the heart, through both translational and post-translational modifications, also exerts long-term regulation of adrenergic receptor sensitivity and ionic channels. These long-term changes in autonomic responsiveness and cardiac

electrical properties appear to be mediated, at least in part, by highly localized signaling cascades involving neurally released molecules such as NPY.[1]

Arrhythmias and the Autonomic Nervous System

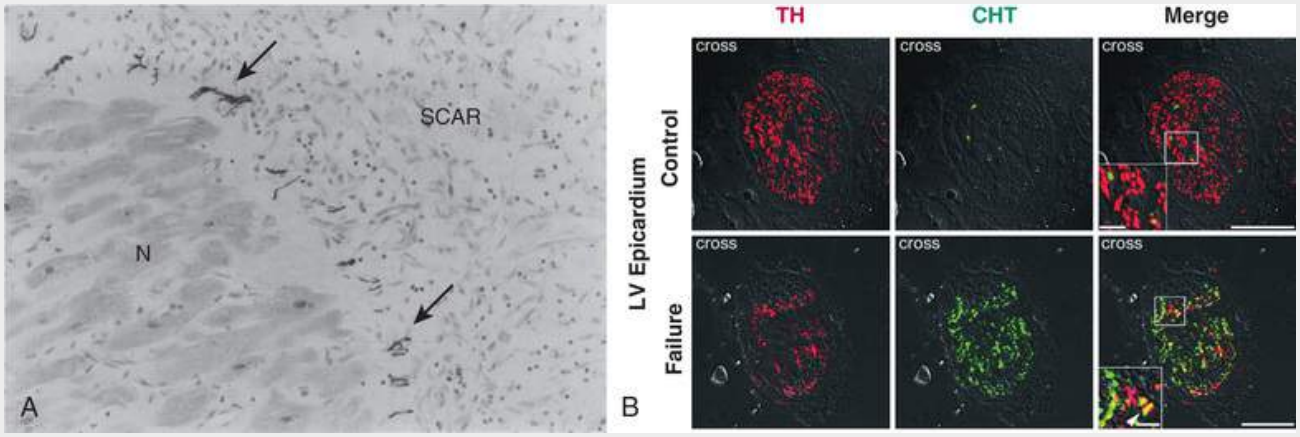
Alterations in vagal and sympathetic innervation (autonomic remodeling) can influence the development of arrhythmias and result in sudden cardiac death (SCD) from ventricular tachyarrhythmias.[34,35] Damage to nerves extrinsic to the heart, such as the stellate ganglia, and to intrinsic cardiac nerves from diseases that may affect primarily nerves, such as viral infections, or from diseases that secondarily cause cardiac damage may produce cardioneuropathy. Although the mechanisms by which altered sympathetic innervation modulates cardiac electrical properties are largely unknown, spatially heterogeneous sympathetic hyperinnervation could result in enhanced dispersion of myocardial excitability and refractoriness through patchy adrenergic stimulation of ionic currents, including $I_{Ca.L}$, I_{Ks}, and I_{Cl} (**see Table 34.1**). Sympathetic hypoinnervation has been shown to increase the sensitivity of adrenergic receptors to activation by circulating catecholamines (*denervation supersensitivity*) (**eFig. 34.16**).



EFIGURE 34.16 Regulation of cardiac innervation patterning and sudden cardiac death (SCD). **Left,** Overexpression or lack of semaphorin 3A (sema3A) in endocardium causes unbalanced patterning of sympathetic nerves, which alters the susceptibility to lethal arrhythmias. **Middle,** Upregulation of secreted nerve growth factor (*NGF*) from cardiomyocytes with hyperinnervation in diseased hearts may cause lethal arrhythmias and SCD. **Right,** Downregulation of NGF in diabetic hearts induces denervation of cardiac sensory nerves, which may lead to silent ischemia and lethal arrhythmias. *DRG,* Dorsal root ganglia; *SG,* stellate ganglia. (From Fukuda K et al. Cardiac innervation and sudden cardiac death. Circ Res 2015;116:2005.)

Numerous studies have suggested a primary role of altered cardiac sympathetic innervation in arrhythmogenesis. Chronic infusion of nerve growth factor (NGF) into the left stellate ganglion in dogs with chronic MI and complete AV block caused spatially heterogeneous sympathetic cardiac hyperinnervation (nerve sprouting) and dramatically increased the incidence of SCD from ventricular tachyarrhythmias. Ambulatory long-term recordings of left stellate ganglion nerve activity in these dogs revealed that most malignant ventricular arrhythmias were preceded by increased neuronal discharge, thus suggesting a causal role of sympathetic input in triggering arrhythmogenic SCD. A high-cholesterol diet was reported to result in cardiac sympathetic hyperinnervation in rabbits and a marked increase in the incidence of ventricular fibrillation (VF).[1] Explanted human hearts from transplant recipients with a history of arrhythmias exhibited a significantly higher and also more heterogeneous density of

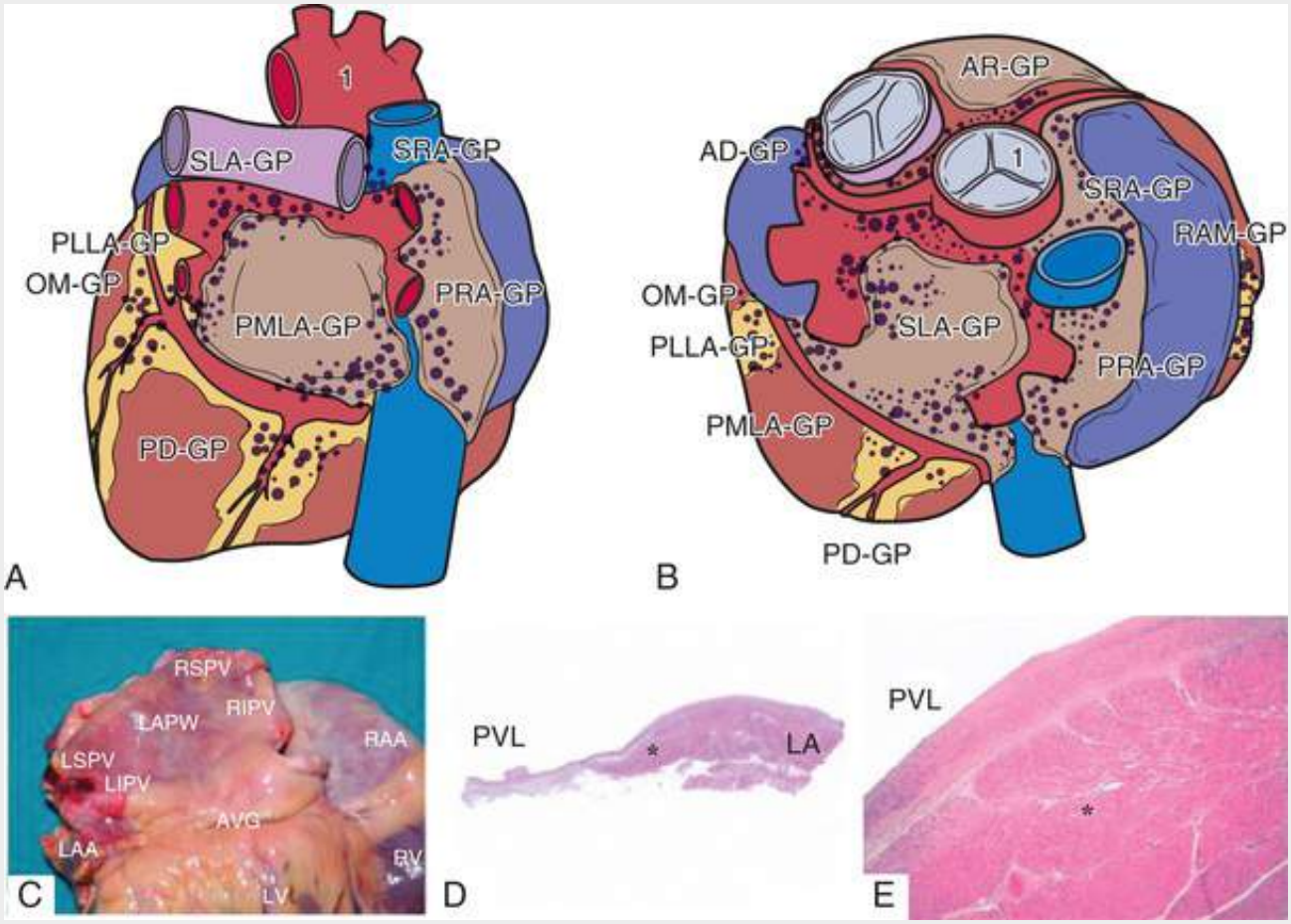
sympathetic nerve fibers than did those from patients without arrhythmias (**eFig. 34.17A**). Whether neural remodeling also involved parasympathetic nerve fibers in the heart was not examined in these studies. In a canine model of heart failure with dyssynchronous ventricular contraction, cardiac resynchronization therapy (CRT) restored sympathovagal balance by upregulation of cholinergic signaling with a reduction in arrhythmogenic afterdepolarizations.[38] In patients with congestive heart failure, sympathetic neural tone is upregulated, and excess activation of the sympathetic nervous system leads to adverse myocardial effects, including lethal arrhythmias, and also causes depletion of cardiac norepinephrine content. This depletion of norepinephrine has recently been shown to result, at least partially, from neurotransmitter switching and transdifferentiation from catecholaminergic into cholinergic neurons in the chronically failing heart (**eFig. 34.17B**). This process is induced by release of cholinergic differentiation factors from failing cardiomyocytes. It remains to be determined, however, whether neurotransmitter switching is an adaptive response to protect the heart from excess sympathetic stimulation and thus lethal arrhythmias.



EFIGURE 34.17 Sympathetic neural remodeling in the diseased heart. **A,** Regional hyperinnervation (*arrows*) at the junction between scar and surviving myocardium (*N*) in a patient with cardiomyopathy and ventricular tachyarrhythmias. **B,** Cholinergic transdifferentiation of cardiac sympathetic nerves in failing human hearts. Shown are representative cross sections of epicardial nerve bundles in the left ventricle (LV) of a nonfailing **(upper row)** and a failing human heart **(lower row).** Hearts were stained for tyrosine hydroxylase (TH; *red*) and choline transporter (CHT; *green*) as catecholaminergic and cholinergic nerve markers, respectively. The failing heart exhibits fewer TH-positive nerves and many more CHT-positive nerves than does the nonfailing heart, whereas overall nerve density appears to be similar. The **right panels** display merged images of the TH and CHT signal, which reveals that in the failing heart, some nerves coexpress TH and CHT (*yellow* because of overlap of *red* TH and *green* CHT fluorescence). Higher-magnification views of the boxed regions are shown in the *insets*. The *arrowhead* in the lower left corner of the lower right image denotes a nerve coexpressing TH and CHT. Scale bar = 10 µm; insets = 50 µm. (**A,** From Chen PS et al. Sympathetic nerve sprouting, electrical remodeling and the mechanisms of sudden cardiac death. Cardiovasc Res 2001;50:409; **B,** from Kanazawa H et al. Heart failure causes cholinergic transdifferentiation of cardiac sympathetic nerves via gp130-signaling cytokines in rodents. J Clin Invest 2010;120:408.)

The junctions between pulmonary veins and the left atrium are highly innervated structures. Both sympathetic and parasympathetic nerves are colocated and concentrated in “ganglionated plexuses” around the pulmonary veins. Selective ablation of ganglionated plexuses, as well as extensive regional ablation targeting anatomic areas containing ganglionated plexuses, has been shown to reduce the incidence of paroxysmal AF in some but not all clinical and experimental studies, thus further supporting a causal involvement of autonomic nerve activity in atrial arrhythmogenesis[35,39] (**eFig. 34.18**). On the other hand, spatially heterogeneous sympathetic denervation was similarly associated with an increased risk for atrial and ventricular arrhythmias. Mutations in genes encoding cardiac ion channel subunits also affect channel function in the central and peripheral autonomic nervous system and thereby result in

abnormal firing properties of affected neurons.[1,10] This observation may partially explain the clinical finding that SCD in some variants of LQTS (**see Chapters 33 and 39**) is typically preceded by sympathetic arousal. Also, the antiarrhythmic efficacy of surgical left cardiac sympathetic denervation has previously been demonstrated in young patients with catecholaminergic polymorphic ventricular tachycardia (CPVT, see later). Thus the cardiac sympathetic nervous system provides a potentially useful target for treating patients at risk for clinical arrhythmias.[34,35,40]



EFIGURE 34.18 **Top,** Diagrams showing the human atrial ganglionated plexuses. **A,** Posterior view. **B,** Superior view. AD-GP, Anterior descending ganglionated plexus; AR-GP, aortic root; OM-GP, obtuse marginal; PD-GP, posterior descending; PLLA-GP, posterolateral left atrial; PMLA-GP, posteromedial left atrial; PRA-GP, posterior right atrial; RAM-GP, right acute marginal; SLA-GP, superior left atrial; SRA-GP, superior right atrial. **Bottom: C,** Gross view of a human left atrial posterior wall with the distal tract of the four pulmonary veins: right and left superior (RSPV, LSPV) and right and left inferior (RIPV, LIPV). AVG, Atrioventricular groove; LAPW, left atrial posterior wall; LAA, RAA, left, right atrial appendage; LV, RV, left, right ventricle. **D,** Low-power longitudinal histologic section of the pulmonary venoatrial junction. The sleeves of atrial cardiomyocytes (*asterisk*) extend over the junction into pulmonary vein wall. **E,** Medium-power view of pulmonary vein wall 1 cm above the pulmonary venoatrial junction. The PV *tunica media* consists of multiple striated cardiac myocyte bundles (*asterisk*). LA, Left atrium; PVL, –. (From Corradi D et al. Morphology and pathophysiology of target anatomical sites for ablation procedures in patients with atrial fibrillation. Part II. Pulmonary veins, caval veins, ganglionated plexi, and ligament of Marshall. Int J Cardiol 2013;168:1769-78.)

Mechanisms of Arrhythmogenesis

The mechanisms responsible for cardiac arrhythmias are generally divided into disorders of impulse formation, disorders of impulse conduction, or combinations of both (**Table 34.3**). However, our currently available diagnostic tools do not permit unequivocal determination of the electrophysiologic mechanisms

responsible for many clinical arrhythmias or their ionic bases. This is especially true for ventricular arrhythmias. It is clinically difficult to separate microanatomic reentry from automaticity, and often one is left with the consideration that a particular arrhythmia is “most consistent with” or “best explained by” one or the other electrophysiologic mechanism. Some tachyarrhythmias can be started by one mechanism and perpetuated by another. An episode of tachycardia caused by one mechanism can precipitate another episode caused by a different mechanism. For example, a premature complex caused by abnormal automaticity can precipitate an episode of tachycardia sustained by reentry. However, entrainment can identify arrhythmias caused by macroreentry (see later and **Chapter 37**).

TABLE 34.3

Mechanisms of Arrhythmias

DISORDER	EXPERIMENTAL EXAMPLES	CLINICAL EXAMPLES
Disorders of Impulse Formation		
Automaticity		
Normal automaticity	Normal in vivo or in vitro in SA nodal, AV nodal, and Purkinje cells	Sinus tachycardia or bradycardia inappropriate for the clinical situation; possibly ventricular parasystole
Abnormal automaticity	Depolarization-induced automaticity in Purkinje myocytes	Possibly accelerated ventricular rhythms after myocardial infarction
Triggered activity		
EADs	Drugs (sotalol, *N*-acetylprocainamide, terfenadine, erythromycin), cesium, barium, low $[K^+]_o$	Acquired LQTS and associated ventricular arrhythmias
DADs	Gain-of-function mutations in the gene encoding RyR2	Catecholaminergic polymorphic ventricular tachycardia
Disorders of Impulse Conduction		
Block		
Bidirectional or unidirectional without reentry	SA, AV, bundle branch, Purkinje-muscle	Sinoatrial, AV, bundle branch block
Unidirectional block with reentry	AV node, Purkinje-muscle junction, infarcted myocardium	Reciprocating tachycardia in Wolff-Parkinson-White syndrome, AV nodal reentry tachycardia, ventricular tachycardia caused by bundle branch reentry
Reflection	Purkinje fiber with area of inexcitability	Unknown
Combined Disorders		
Interactions between automatic foci	Depolarizing or hyperpolarizing subthreshold stimuli speed or slow the automatic discharge rate	Modulated parasystole
Interactions between automaticity and conduction	Deceleration-dependent block, overdrive suppression of conduction, entrance and exit block	Similar to experimental

AV, Atrioventricular; *DADs,* delayed afterdepolarizations; *EADs,* early afterdepolarizations; *LQTS,* long-QT syndrome; *SA,* sinoatrial.

Disorders of Impulse Formation

Disorders of impulse formation are characterized by an inappropriate discharge rate of the normal pacemaker, the SA node (e.g., sinus rates too fast or too slow for physiologic needs of patient), or discharge of an ectopic pacemaker that controls the atrial or ventricular rhythm. Pacemaker discharges from ectopic sites, often called *latent* or *subsidiary* pacemakers, can occur in fibers located in several parts of the atria, coronary sinus and pulmonary veins, AV valves, portions of the AV junction, and His-Purkinje system. Usually kept from reaching the level of threshold potential because of overdrive suppression by the more rapidly firing sinus node or electrotonic depression from contiguous fibers, ectopic pacemaker activity at one of these latent sites can manifest when the sinus nodal discharge rate slows or block occurs at some level between the SA node and the ectopic pacemaker site, which permits *escape* of the latent pacemaker at the latter's normal discharge rate. A clinical example would be sinus bradycardia to a rate of 45 beats/min that permits an AV junctional escape complex to occur at a rate of 50 beats/min.

Alternatively, the discharge rate of the latent pacemaker can speed inappropriately and usurp control of

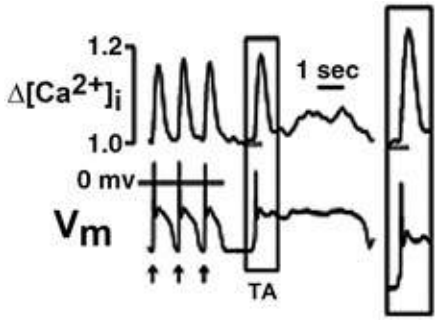
cardiac rhythm from the SA node, which has been discharging at a normal rate, such as may occur with a premature ventricular complex (PVC) or a burst of ventricular tachycardia (VT). Such disorders of impulse formation can be caused by speeding or slowing of a *normal* pacemaker mechanism (e.g., phase 4 diastolic depolarization that is physiologically normal for SA node or for ectopic site such as a Purkinje fiber, but occurs inappropriately fast or slow) or by a physiologically *abnormal* pacemaker mechanism.

A patient with persistent sinus tachycardia at rest or sinus bradycardia during exertion exhibits inappropriate sinus nodal discharge rates, but the ionic mechanisms responsible for sinus nodal discharge can still be normal, although the kinetics or magnitude of the currents can be altered. Conversely, when a patient experiences VT during acute MI, ionic mechanisms ordinarily not involved in the formation of spontaneous impulses for this fiber type can be operative and generate the tachycardia. For example, although pacemaker activity is not generally found in typical working myocardium, the effects of myocardial ischemia and infarction can depolarize these cells to membrane potentials at which inactivation of I_K and activation of $I_{Ca.L}$ cause automatic discharge. In vitro studies have demonstrated that myofibroblasts in infarct scars depolarize cardiomyocytes by heterocellular electrotonic interactions via gap junctions and also induce synchronized spontaneous activity in neighboring cardiomyocytes.[1]

Abnormal Automaticity

The mechanisms responsible for normal automaticity are described earlier (Phase 4: Diastolic Depolarization). Abnormal automaticity can arise from cells that have reduced maximum diastolic potentials, often at membrane potentials positive to −50 mV, when I_K and $I_{Ca.L}$ may be operative. Automaticity at membrane potentials more negative than −70 mV may be caused by I_f. When the membrane potential is between −50 and −70 mV, the cell may be quiescent. Electrotonic effects from surrounding normally polarized or more depolarized myocardium influence the development of automaticity.

Abnormal automaticity can be produced in normal muscle or Purkinje fibers by appropriate interventions, such as passage of current that reduces the diastolic membrane potential. An automatic discharge rate speeds up with progressive depolarization, and hyperpolarizing pulses slow the spontaneous firing. It is possible that partial depolarization and failure to reach normal maximal diastolic potential can induce automatic discharges in most if not all cardiac fibers. Although this type of spontaneous automatic activity has been found in human atrial and ventricular fibers, its relationship to the genesis of clinical arrhythmias has not been established. Abnormal automaticity in Purkinje cells can also originate secondary to spontaneous, submembrane Ca^{2+} elevations through activation of calcium-sensitive membrane conductances, a process identical to that previously identified in SA node myocytes. Indeed, Purkinje myocytes isolated from mice heterozygous for an arrhythmia-causing mutation in the gene encoding the cardiac ryanodine receptor Ca^{2+}-release channel (RyR2) display a greater propensity for the development of arrhythmogenic Ca^{2+}-handling abnormalities than do nonmutant ventricular cardiomyocytes. This proarrhythmic behavior is further exacerbated by catecholaminergic stimulation with the development of triggered beats (**eFig. 34.19**), thus supporting the concept that Purkinje cells are critical contributors to arrhythmic triggers in animal models and humans with RyR2 mutations that are linked to CPVT.[41]



EFIGURE 34.19 Arrhythmogenic spontaneous Ca^{2+} elevations in a Purkinje myocyte isolated from a mouse heterozygous for a gain-of-function mutation in the *RYR2* gene. Changes in intracellular free calcium ($\Delta[Ca^{2+}]_i$, *upper trace*) and transmembrane action potential (V_m) were simultaneously recorded in a mutant Purkinje myocyte during electrical field stimulation (*arrows*) and during a spontaneous elevation in Ca^{2+} (triggered action potential, TA). Note that the action potential upstroke is preceded by a low-amplitude elevation in Ca^{2+}, followed by a suprathreshold membrane depolarization that triggers a markedly prolonged action potential. (From Kang G et al. Purkinje cells from RyR2 mutant mice are highly arrhythmogenic but responsive to targeted therapy. Circ Res 2010;107:512.)

Rhythms resulting from abnormal automaticity may be slow atrial, junctional, or ventricular escape rhythms; certain types of atrial tachycardias (e.g., those produced by digitalis or perhaps those coming from pulmonary veins); accelerated junctional (nonparoxysmal junctional tachycardia) and idioventricular rhythms; and parasystole (**see Chapters 37 and 39**).

Triggered Activity

Automaticity is the property of a fiber to initiate an impulse spontaneously, without need for prior stimulation, so that electrical quiescence does not occur. Triggered activity is initiated by *afterdepolarizations,* which are depolarizing oscillations in membrane voltage induced by one or more preceding action potentials. Thus, triggered activity is pacemaker activity that results *as a consequence* of a preceding impulse or series of impulses, without which electrical quiescence occurs (**Fig. 34.12 and eFig. 34.20**). This triggering activity is not caused by an automatic self-generating mechanism, and the term "triggered automaticity" is therefore contradictory. These depolarizations can occur before or after full repolarization of the fiber and are best termed *early afterdepolarizations* (EADs) when they arise from a reduced level of membrane potential during phases 2 and 3 of the cardiac action potential (**Fig. 34.12C**) or *late afterdepolarizations* or DADs (**Fig. 34.12B**) when they occur after completion of repolarization (phase 4), generally at a more negative membrane potential than that from which EADs arise. Not all afterdepolarizations may reach the threshold potential, but if they do, they can trigger another afterdepolarization and thus self-perpetuate.

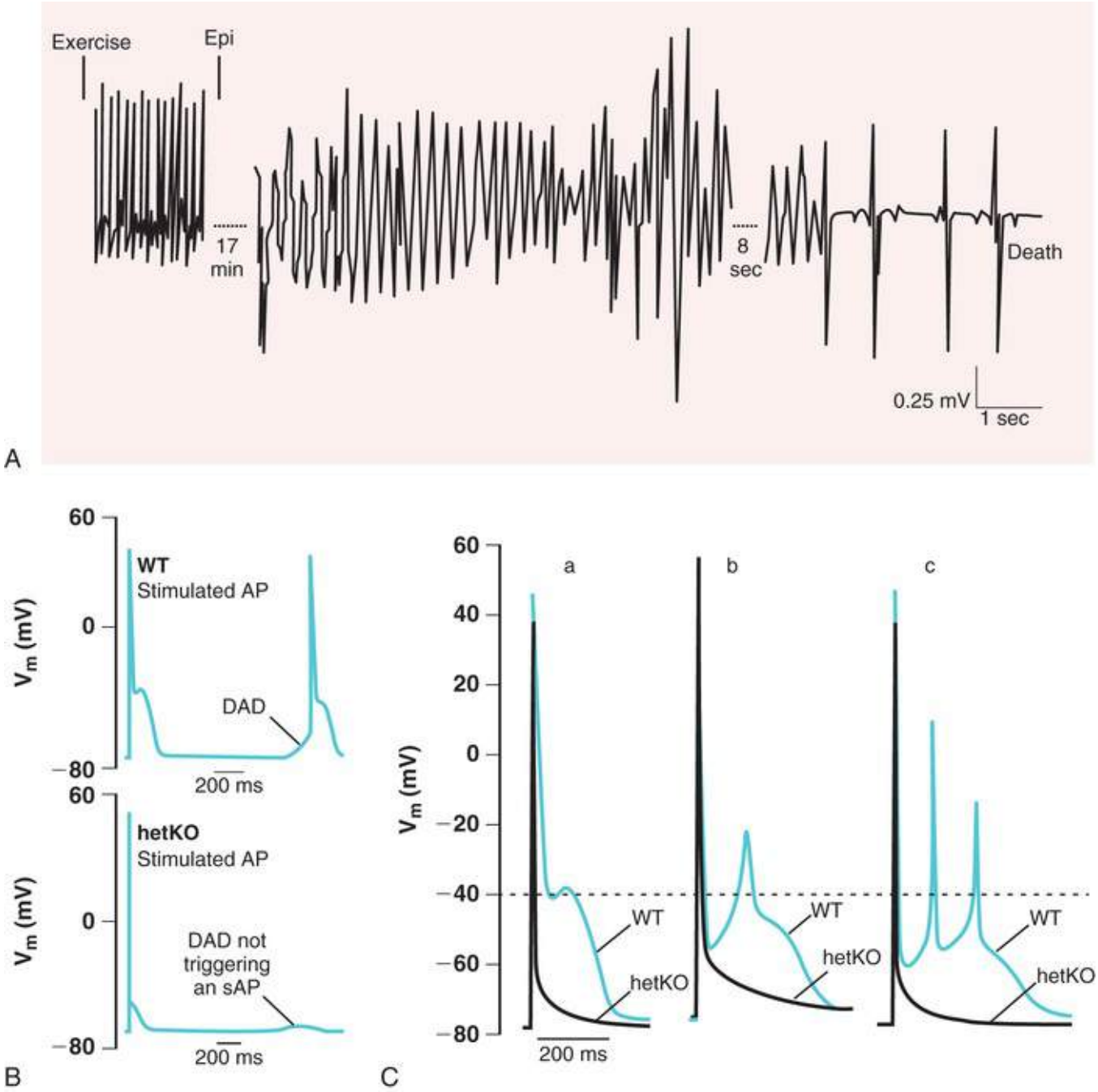
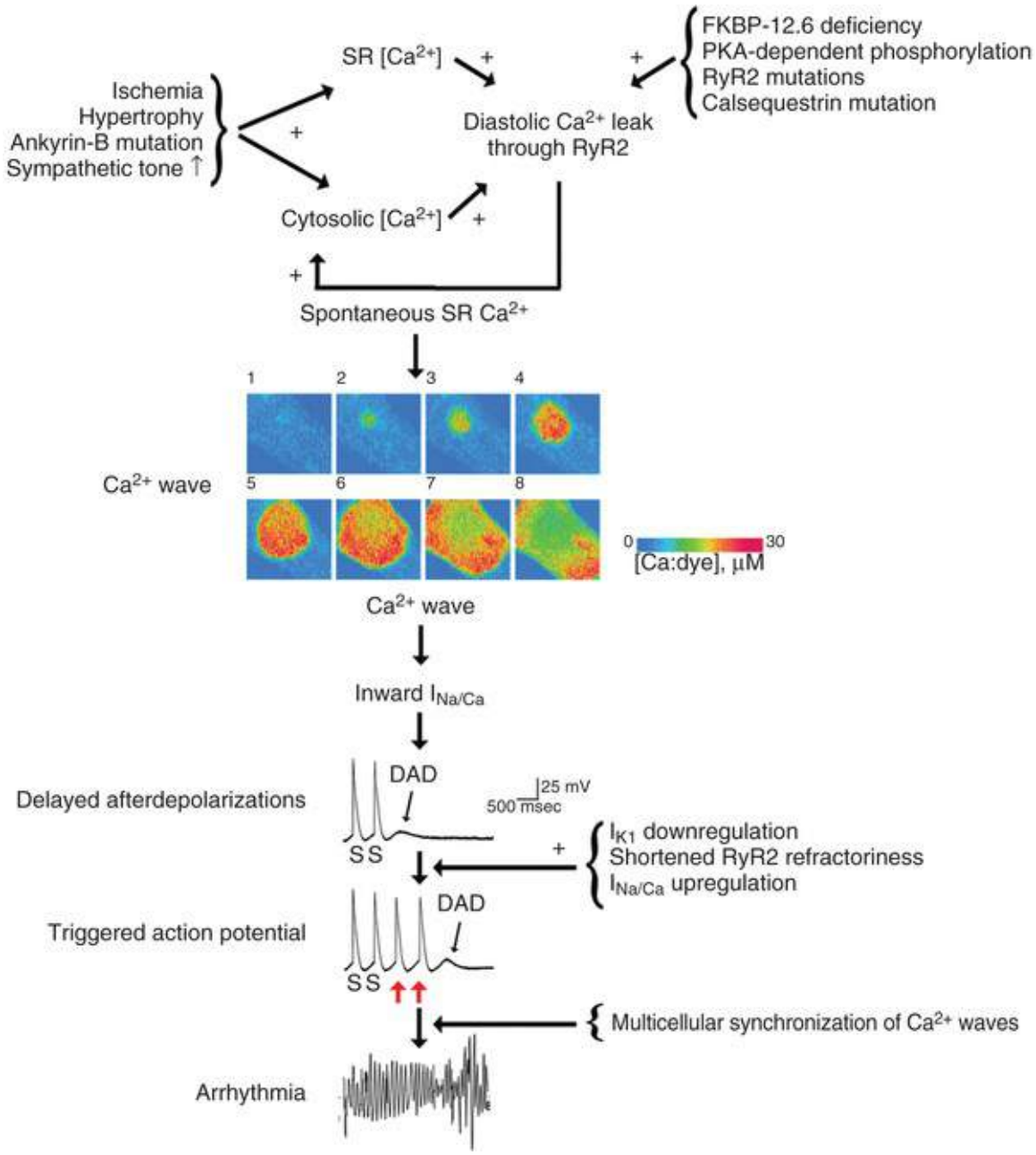


FIGURE 34.12 **A,** Electrocardiogram after exercise and administration of epinephrine in a mouse heterozygous for a loss-of-function mutation in the gene encoding ankyrin-B ($AnkB^{-/+}$). Polymorphic ventricular tachycardia (torsades de pointes) occurred within about 17 minutes of epinephrine administration, followed by marked bradycardia and death 2 minutes after the arrhythmia. **B,** Impaired translation of delayed afterdepolarizations (DADs) into spontaneous action potentials (APs) in heterozygous knockout of Na^+/Ca^{2+} exchanger (hetKO) versus wild-type (WT) exposed to isoproterenol and an arrhythmogenic pacing protocol. The first AP is initiated by current injection. The second AP in the **upper panel** is triggered by a DAD in the WT, it fails to generate an AP in the hetKO. **C,** Early afterdepolarizations (EADs) in WT and heterozygous knockout of Na^+/Ca^{2+} exchanger. The EAD shape varied between low-amplitude, slow-transient membrane fluctuations **(a),** spike-like depolarizations **(b),** and steep upstrokes **(c).** (**A,** From Mohler PJ et al. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. Nature 2003;421:634; **B** and **C,** from American Heart Association; Bögeholz N et al. Suppression of early and late afterdepolarizations by heterozygous knockout of the Na^+/Ca^{2+} exchanger in a murine model. Circ Arrhythm Electrophysiol 2015;8:1210.)



EFIGURE 34.20 Proposed scheme of events leading to delayed afterdepolarizations (DADs) and triggered tachyarrhythmia. **Top panel,** Congenital (e.g., gain-of-function mutations in the *RYR2* or *CASQ2* genes) or acquired factors (e.g., ischemia, hypertrophy, increased sympathetic tone, heart failure) will cause a diastolic Ca^{2+} leak through RyR2 that results in localized and transient increases in $[Ca^{2+}]_i$ in cardiomyocytes. **Middle panel,** Representative series of images showing changes in $[Ca^{2+}]_i$ during a Ca^{2+} wave in a single cardiomyocyte loaded with a Ca^{2+}-sensitive fluorescent dye. Images were obtained at 117-millisecond intervals. Focally elevated Ca^{2+} (*2*) diffuses to the adjacent junctional sarcoplasmic reticulum (SR), where it initiates more Ca^{2+} release events that result in a propagating Ca^{2+} wave (*frames 3-8*). **Bottom panel,** The Ca^{2+} wave, through activation of inward $I_{Na/Ca}$, will depolarize the cardiomyocyte (DAD). If of sufficient magnitude to overcome the source-sink mismatch, the DAD will depolarize the cardiomyocyte above threshold and result in a single or repetitive premature activations (*red arrows*), which can trigger an arrhythmia. Downregulation of the inwardly rectifying potassium current (I_{K1}), upregulation of $I_{Na/Ca}$, and shortened Ca^{2+} signaling refractoriness because of ryanodine receptor phosphorylation and/or oxidation can promote the generation of DAD-triggered action potentials. *S,* Stimulus. (Modified from Rubart M, Zipes DP. Mechanisms of sudden cardiac death. J Clin Invest 2005;115:2305. With permission from the Journal of Clinical Investigation.)

Delayed Afterdepolarizations

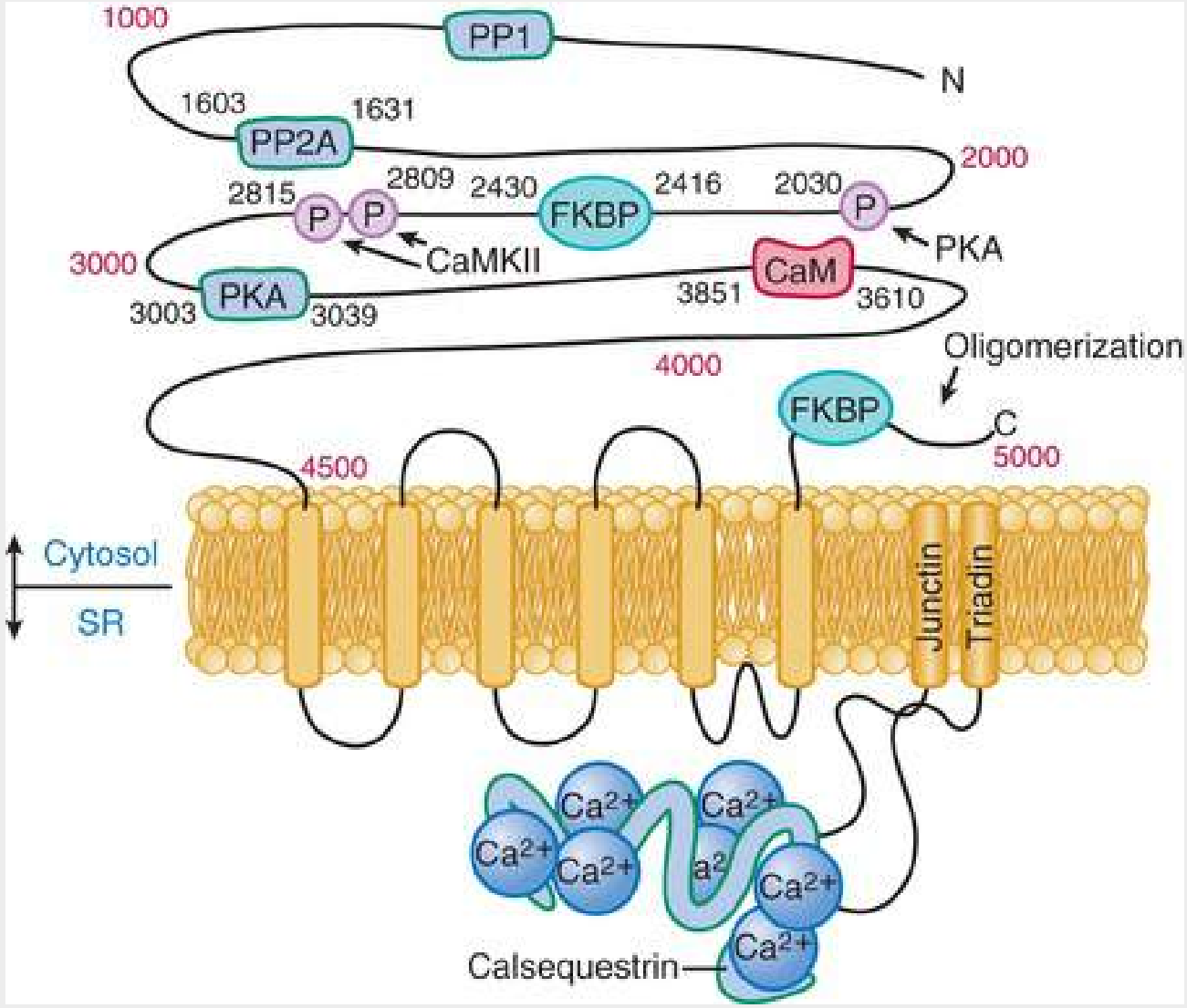
DADs and triggered activity have been demonstrated in Purkinje fibers, specialized atrial fibers and ventricular muscle fibers exposed to digitalis preparations, pulmonary veins, normal Purkinje fibers exposed to Na-free superfusates from the endocardium of the intact heart, ventricular myocardial cells from failing hearts and from mouse hearts with ankyrin-B mutations (**Fig. 34.12A**) during beta-adrenergic stimulation, and endocardial preparations 1 day after MI. When fibers in the rabbit, canine, simian, and human mitral valves and in the canine tricuspid valve and coronary sinus are superfused with norepinephrine, they exhibit the capability for sustained, triggered rhythmic activity.[1]

In vivo, atrial and ventricular arrhythmias apparently caused by triggered activity have been reported in the dog and possibly in humans. It is tempting to ascribe certain clinical arrhythmias to DADs, such as some arrhythmias precipitated by digitalis or some cases of AF arising from DADs in pulmonary veins. The accelerated idioventricular rhythm 1 day after experimental canine MI may be caused by DADs, and some evidence has suggested that certain ventricular tachycardias, such as those arising in the right ventricular outflow tract, may be caused by DADs, whereas other data suggest that EADs are responsible.[42]

Major Role of Intracellular Ca^{2+}-Handling Abnormalities in DAD Generation

It is well recognized that DADs result from the activation of a calcium-sensitive inward current elicited by spontaneous increases in the intracellular free calcium concentration. Acquired or inherited abnormalities in the properties of the SR calcium-release channels or SR calcium-binding proteins underlie these spontaneous calcium-release events.

Rapid mobilization of Ca^{2+} from the SR into the cytosol is mediated by the synchronous opening of ryanodine-sensitive Ca^{2+}-release channels (ryanodine receptors, RyRs). The cardiac RyR is composed of four equivalent subunits (homotetramer), each encoded by the *RYR2* gene. During cardiac systole, the small influx of calcium ions through L-type Cav channels triggers a massive release of Ca^{2+} from the SR via synchronous opening of RyR2 channels, a process called Ca^{2+}-induced Ca^{2+} release (**see Chapter 22**). During diastole, RyR2 channels close and Ca^{2+} is recycled into the SR via calcium pumps, thereby refilling SR Ca^{2+} stores for the next release cycle. The duration and amplitude of Ca^{2+} efflux from the SR are therefore tightly controlled by the gating of RyR2 channels. RyR2 interacts with a number of accessory proteins to form a macromolecular Ca^{2+}-release complex (**eFig. 34.21**). Proteins interact with RyR2 at multiple sites within the cytosolic domains of RyR2 and in the SR (e.g., calsequestrin, the major calcium-binding protein in the SR lumen). Among the cytosolic ligands, FKBP-12.6 (calstabin 2) has been implicated in stabilizing the closed state of the RyR2 channel and thus preventing diastolic Ca^{2+} leakage. [1]

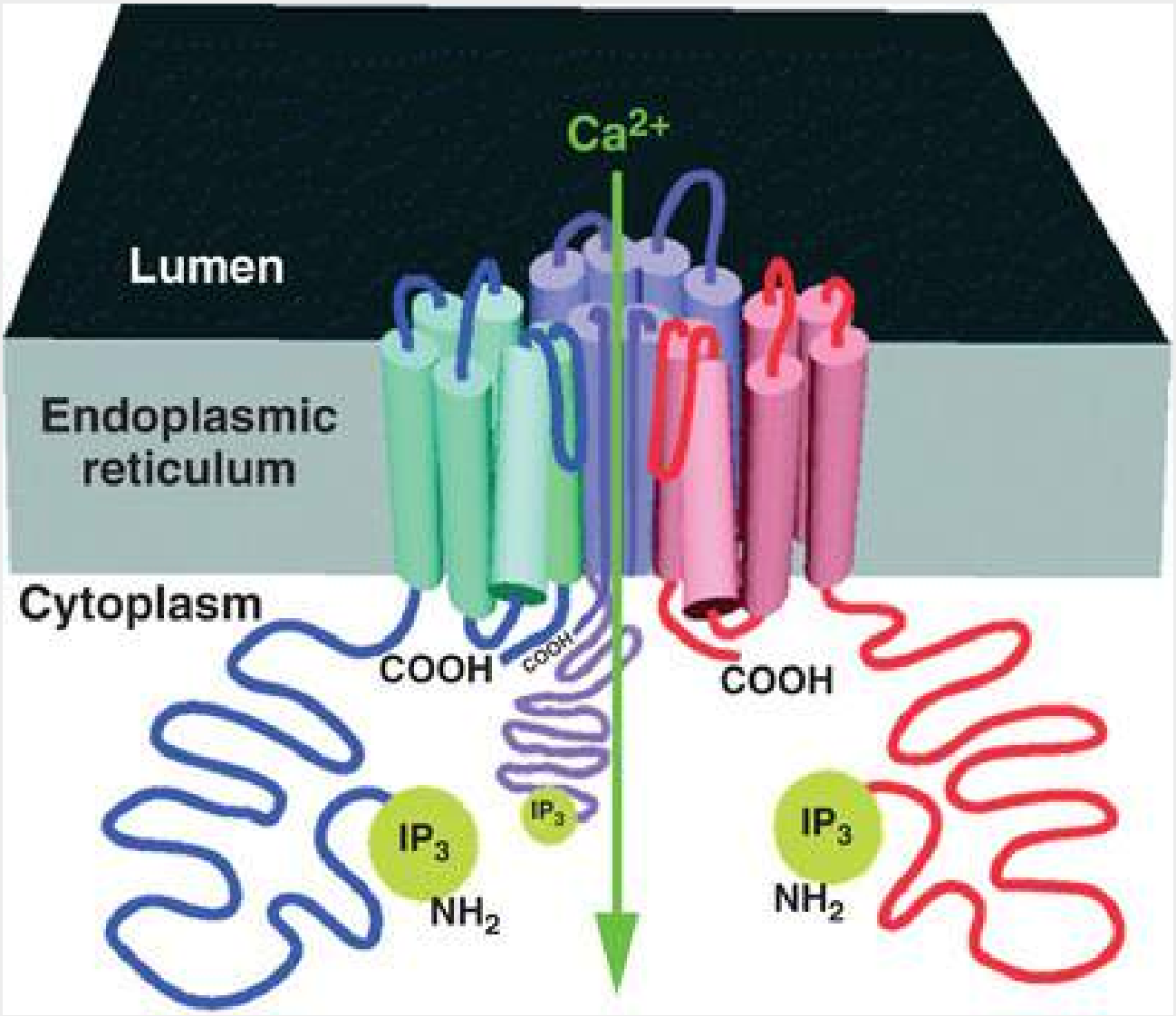


EFIGURE 34.21 Structure of the cardiac ryanodine receptor monomer subunit, RyR2, delineating the sites of interaction with auxiliary proteins and the phosphorylation sites (P). CaM, Calmodulin; CaMKII, calmodulin-dependent kinase II; FKBP, FK506-binding protein 12.6; PKA, protein kinase A; PP, protein phosphatase. Calsequestrin, junctin, and triadin are proteins that interact with RyR2 in the sarcoplasmic reticulum (SR). (From Bers DM. Macromolecular complexes regulating cardiac ryanodine receptor function. J Mol Cell Cardiol 2004;37:417.)

Mutations in the human *RYR2* gene and in *CASQ2*, which encodes calsequestrin, have been linked to CPVT. Experimental studies have revealed that the *RYR2* and *CASQ2* mutations that underlie CPVT cause an increase in the sensitivity of the RyR2 channel to luminal Ca^{2+} activation on adrenergic stimulation (e.g., from emotional or physical stress) and enhance the propensity for spontaneous, diastolic Ca^{2+} release from the SR and subsequent DAD-triggered arrhythmias. It is also possible that CPVT mutants exhibit reduced affinity for binding of the regulatory protein FKBP-12.6, thereby resulting in diastolic Ca^{2+} leakage from the SR. Reduced FKBP-12.6 binding caused by protein kinase A–mediated hyperphosphorylation has been implicated in cardiac arrhythmogenesis associated with heart failure. Polymorphic VT develops in FKBP-12.6–deficient mice on adrenergic stimulation. Treatment with the 1,4-benzothiazepine derivatives JTV519 and S107, which restore FKBP-12.6 affinity for RyR2, has been shown to suppress CPVT in FKBP-12.6–deficient mice.[1]

The IP_3 receptor (IP3R) is another Ca^{2+}-release channel in cardiomyocytes that is activated by binding of the second-messenger IP_3 and cytosolic Ca^{2+}. IP3R exists as a homotetramer or heterotetramer, each subunit encoded by the *ITPR1*, *ITPR2*, or *ITPR3* gene (**eFig. 34.22**). The type 2 IP3R is the predominant subtype in atrial myocytes, where they are located near RyR2 channels at the SR Ca^{2+}-release sites and

contribute to altered excitation-contraction coupling and arrhythmogenesis in the atria. In Purkinje myocytes, type 1 IP3Rs colocalize with type 3 RyR in the subsarcolemmal space to form a functional dyad that critically determines electrical excitability. IP_3-dependent Ca signaling has been implicated in cardiac arrhythmias attributable to ischemia and reperfusion injury, inflammation, and cardiac failure. IP3Rs are upregulated in heart failure and AF.[1,43] In atrial and Purkinje myocytes, IP_3 causes spontaneous $[Ca^{2+}]_i$ transients, Ca^{2+} waves, and Ca^{2+} alternans and facilitates the generation of afterdepolarizations.[44]



EFIGURE 34.22 Structure of the IP_3 receptor (IP3R). IP3Rs are intracellular membrane proteins that exist as homotetramers or heterotetramers. The Ca^{2+}-conducting pore is believed to be created at the central axis of the tetrameric structure. The drawing depicts three of four IP3R molecules (in different colors) in a single tetrameric channel structure. Part of the luminal loop (i.e., the loop facing the SR lumen) connecting transmembrane helices 5 and 6 of each monomer dips into the fourfold symmetric axis and creates the pathway for efflux of Ca^{2+} from the sarcoplasmic reticulum (SR) lumen. (From Foskett JK et al. Inositol trisphosphate receptor Ca^{2+} release channels. Physiol Rev 2007;87:593.)

The cascade of events linking cellular Ca^{2+}-handling abnormalities to cardiac arrhythmias is illustrated in **eFig. 34.20**. Ca^{2+} leaking through SR Ca^{2+}-release channels during diastole gives rise to localized increases in the cytosolic calcium level in a single cardiomyocyte. The focally elevated Ca^{2+} then causes a propagating Ca^{2+} wave that depolarizes the cardiomyocyte membrane and triggers a DAD through

transient activation of the inward Na^+/Ca^{2+}exchange current ($I_{Na/Ca}$). Inhibition of calmodulin kinase has a number of effects in the heart cell, including elimination of transient inward $I_{Na/Ca}$, indicating that activation of this enzyme plays an important role in cardiac arrhythmogenesis. In addition, drugs that reduce I_{Na} also reduce the transient inward current, relieve Ca^{2+} overload, and can abolish DADs. DADs most likely play a causative role in arrhythmogenesis in the failing heart, where upregulation of $I_{Na/Ca}$, in combination with downregulation of the inward rectifier K^+ current I_{K1}, facilitates DAD generation.[2]

Short coupling intervals and pacing at rates more rapid than the triggered activity rate (*overdrive pacing*) increase the amplitude and shorten the cycle length of the DAD after cessation of pacing (*overdrive acceleration*) rather than suppressing and delaying the escape rate of the afterdepolarization, as in normal automatic mechanisms. Premature stimulation exerts a similar effect: the shorter the premature interval, the larger the amplitude and the shorter the escape interval of the triggered event.

The clinical implication is that tachyarrhythmias caused by DAD-triggered activity may not be suppressed easily or indeed may be precipitated by rapid rates, either spontaneously, as with sinus tachycardia, or induced by pacing. Further, because a single premature stimulus can both initiate and terminate triggered activity, differentiation from reentry (see later) becomes difficult. The response to overdrive pacing may help separate triggered arrhythmias from reentrant arrhythmias.

Early Afterdepolarizations

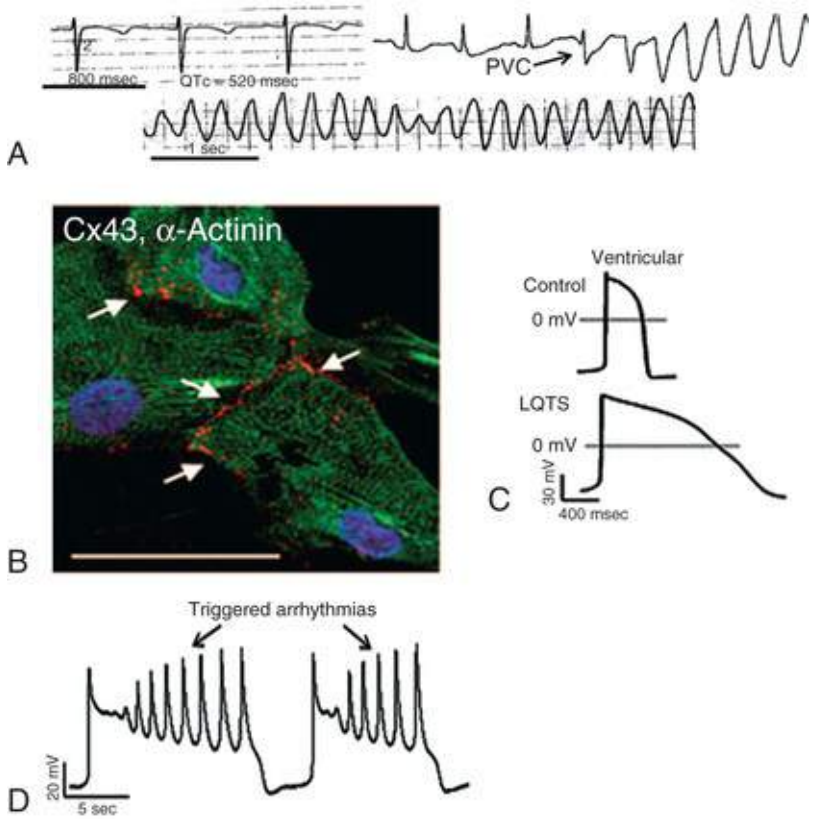
Various interventions, each of which results in an increase in intracellular positivity, can cause EADs. EADs may be responsible for the lengthened repolarization time and ventricular tachyarrhythmias seen in several clinical situations, such as the acquired and congenital forms of LQTS (**see Fig. 34.12 and Chapter 39**).

Long-QT Syndrome

Patients with heritable LQTS have an abnormally prolonged ventricular action potential duration and are at increased risk for SCD from ventricular tachyarrhythmias (**see Chapters 33 and 39**). The genesis of LQTS-associated VT or VF is uncertain. Evidence is mounting that an increased $[Ca^{2+}]_i$ related to spontaneous release of Ca^{2+} from the SR in cardiomyocytes, coupled with dispersion of repolarization, plays a causative role in LQTS-associated cardiac arrhythmia and SCD. Action potential prolongation may increase influx of Ca^{2+} through L-type Ca^{2+} channels during a cardiac cycle and cause excessive accumulation of Ca^{2+} in the SR and spontaneous release of Ca^{2+} from the SR. The ensuing elevation of intracellular free calcium can depolarize cardiomyocyte membrane potential by activation of Ca^{2+}-dependent chloride currents, the electrogenic Na^+/Ca^{2+} exchange current, or both, thereby evoking EADs. EADs can trigger a propagated response and thus elicit an extra beat, which can initiate a tachycardia.

Genetically modified mice have been used extensively to model congenital arrhythmogenic disorders, including LQTS. However, the usefulness of this approach is limited because of the profound differences in electrophysiologic properties between the murine and human heart. The ability to generate patient-specific human iPSCs offers a new paradigm for modeling human disease. Recently, several research groups have independently reported successful derivation of functional cardiomyocytes from LQTS patient–specific human iPSC lines. Electrophysiologic evaluation of LQTS cardiomyocytes demonstrated that they recapitulate the disease phenotype in vitro, including marked action potential prolongation and increased susceptibility to spontaneous or pharmacologically induced triggered activity.[45] A study of cardiomyocytes derived from LQTS patient–specific iPSCs is summarized in **eFig. 34.23**. Large-scale

production of human iPSC–derived cardiomyocytes has made it possible to generate sufficient numbers of uniform cardiac monolayers and higher-order three-dimensional models that can be used for the study of arrhythmia mechanisms in vitro.[46,47] Collectively, pluripotent stem cell technology now offers a unique platform to evaluate patient-specific arrhythmia mechanisms and to evaluate and optimize patient therapy.



EFIGURE 34.23 Recapitulation of long-QT syndrome (LQTS) via induced pluripotent stem cell (iPSC) technology. **A,** Surface ECG from a 28-year-old woman with familial type 2 LQTS as a result of a loss-of-function mutation in the *KCNH2* gene, which encodes the pore-forming subunit of the hERG potassium channel (see **Table 34.1**). Tracings were recorded during sinus rhythm (**upper left panel;** the QT interval corrected for heart rate is 520 milliseconds) and during initiation **(upper right panel)** and sustainment of torsades de pointes. **B,** iPSC-derived cardiomyocytes in culture express structural markers of the cardiac lineage. Dermal fibroblasts were obtained from the LQTS patient above and were reprogrammed to generate LQTS patient–specific human iPSCs via transduction with a cocktail of transcription factors. These iPSCs were then induced to differentiate into cardiomyocytes. Immunocytostaining revealed expression of sarcomeric alpha-actinin (*green*) and the gap junction protein connexin 43 (*red; arrows*) in LQTS cardiomyocytes. **C,** Transmembrane action potential recordings from LQTS ventricular cardiomyocytes revealed a markedly prolonged action potential duration relative to recordings obtained from healthy control patient iPSC–derived myocytes, consistent with a reduction in *KCNH2*-encoded I_{Kr} in the LQTS patient. **D,** Spontaneous development of repetitive early afterdepolarizations in LQTS cardiomyocytes. (From Itzhaki I et al. Modelling the long QT syndrome with induced pluripotent stem cells. Nature 2011;471:225.)

Experimental observations have also suggested an important role of transmural or longitudinal heterogeneity of repolarization. Marked transmural dispersion of repolarization can create a vulnerable window for the development of reentry. Direct experimental evidence of the existence of transmural dispersion in the action potential has been provided for the human heart. Normal hearts studied showed midmyocardial islands of cells that had distinctly long action potential durations (APDs) with steep local APD gradients. In contrast, failing hearts were observed to have significantly reduced transmural repolarization gradients and to lack islands of cells with delayed repolarization. The ionic mechanisms underlying transmural dispersion of repolarization in the human heart are currently unknown but may

involve spatial variations in expression of the transient outward potassium current I_{to} and the delayed rectifier potassium current I_{Ks} (**see Table 34.1**).[1]

Sympathetic stimulation, primarily left, can increase the EAD amplitude to provoke ventricular tachyarrhythmias. Alpha-adrenoceptor stimulation also increases the amplitude of cesium-induced EADs and the prevalence of ventricular tachyarrhythmias, both of which are suppressed by magnesium.

Acquired LQTS and torsades de pointes from drugs such as quinidine, *N*-acetylprocainamide, cisapride, erythromycin, and class III antiarrhythmic agents may be mediated by EADs (**see Chapters 8 and 36**). Such drugs easily elicit EADs experimentally and clinically, whereas magnesium suppresses them. Multiple drugs may additively prolong the action potential and provoke EADs and torsades de pointes in patients. Alternatively, drug-induced alterations in metabolism may increase the concentration of a compound that prolongs the action potential.[48] Activators of ATP-dependent potassium channels, such as pinacidil and nicorandil, can eliminate EADs.

Parasystole

Classically, parasystole has been likened to the function of a fixed-rate, asynchronously discharging pacemaker—its timing is generally not altered by the dominant rhythm, it produces depolarization when the myocardium is excitable, and the intervals between discharges are multiples of a basic interval (**see Chapters 35 and 39**). Complete *entrance block*, constant or intermittent, insulates and protects the parasystolic focus from surrounding electrical events and accounts for such behavior. On occasion, the focus can exhibit *exit block*, during which it may fail to depolarize excitable myocardium. In fact, the dominant cardiac rhythm may modulate parasystolic discharges to speed up or slow down its rate. Brief subthreshold depolarizations induced during the first half of the cardiac cycle of a spontaneously discharging pacemaker delay the subsequent discharge, whereas similar depolarizations induced in the second half of the cardiac cycle accelerate it.

Disorders of Impulse Conduction

Conduction delay and block can result in bradyarrhythmias or tachyarrhythmias. Bradyarrhythmias occur when the propagating impulse is blocked and is followed by asystole or a slow escape rhythm; tachyarrhythmias occur when the delay and block produce reentrant excitation (see later, Reentry). Various factors involving both active and passive membrane properties determine the conduction velocity of an impulse and whether conduction is successful. These factors include the stimulating efficacy of the propagating impulse, which is related to the amplitude and rate of rise of phase 0; the excitability of the tissue into which the impulse is conducted; and the geometry of the tissue.

Deceleration-Dependent Block

Diastolic depolarization has been suggested as a cause of conduction block at slow rates, so-called bradycardia- or deceleration-dependent block (**see Chapter 40**). However, excitability and the speed of impulse propagation *increase* as the membrane depolarizes until approximately −70 mV despite a reduction in action potential amplitude (*supernormal conduction*). This type of block has also been referred to as “phase 4 block,” but experiments in Purkinje fiber bundles have demonstrated that diastolic (phase 4) depolarization is not a necessary condition for the occurrence of deceleration-dependent block. Evidently, depolarization-induced inactivation of fast Na^+ channels is offset by other factors, such as a reduction in the difference between membrane potential and threshold potential and an increase in

membrane excitability.

Tachycardia-Dependent Block

More often, impulses are blocked at rapid rates or short cycle lengths as a result of incomplete recovery of refractoriness (postrepolarization refractoriness) caused by incomplete time- or voltage-dependent recovery of excitability. For example, such incomplete recovery is the usual mechanism responsible for a nonconducted premature P wave or one that conducts with a functional bundle branch block.

Decremental Conduction

"Decremental conduction" is a term commonly used in the clinical literature but is often misapplied to describe any Wenckebach-like conduction block, that is, responses similar to a block in the AV node during which progressive conduction delay precedes the nonconducted impulse. Correctly used, decremental conduction refers to a situation in which the properties of the fiber change along its length such that the action potential loses its efficacy as a stimulus to excite the fiber ahead of it. Thus the stimulating efficacy of the propagating action potential diminishes progressively, possibly as a result of its decreasing amplitude and slowed upstroke velocity.

Reentry

Electrical activity during each normal cardiac cycle begins in the sinoatrial node and continues until the entire heart has been activated. Each cell becomes activated in turn, and the cardiac impulse dies out when all fibers have been discharged and are completely refractory. During this absolute refractory period, the cardiac impulse has "no place to go." It must be extinguished and restarted by the next sinus impulse. If, however, a group of fibers not activated during the initial wave of depolarization recovers excitability in time to be reactivated before the impulse dies out, the fibers may serve as a link to reexcite areas that were just discharged and have now recovered from the initial depolarization. Such a process has been given various names—reentry, reentrant excitation, circus movement, reciprocal or echo beat, and reciprocating tachycardia—and all have approximately the same meaning.

Entrainment

Entraining a tachycardia (i.e., increasing the rate of the tachycardia by pacing), with resumption of the intrinsic rate of the tachycardia when pacing is stopped, establishes the presence of reentry (**Fig. 34.13A**). Entrainment represents capture or continuous resetting of the tachycardia by the pacing-induced activation. Each pacing stimulus creates a wavefront that travels in an anterograde direction (orthodromic) and resets the tachycardia to the pacing rate. A wavefront propagating retrogradely in the opposite direction (antidromic) collides with the orthodromic wavefront of the previous beat. As the right ventricular (RV) pacing rate is increased, the paced QRS morphology (**Fig. 34.13B-D**) changes, the result of more of the tachycardia circuit being captured by the anterograde activation wave, yet when pacing is stopped, the tachycardia is still present; this is referred to as *progressive fusion*. These wavefront interactions create electrocardiographic and electrophysiologic features that can be explained only by reentry. Therefore the criteria of entrainment can be used to prove the reentrant mechanism of a clinical tachycardia and form the basis for localizing the pathway traveled by the tachycardia wavefront. Such localization is essential for ablation therapy.

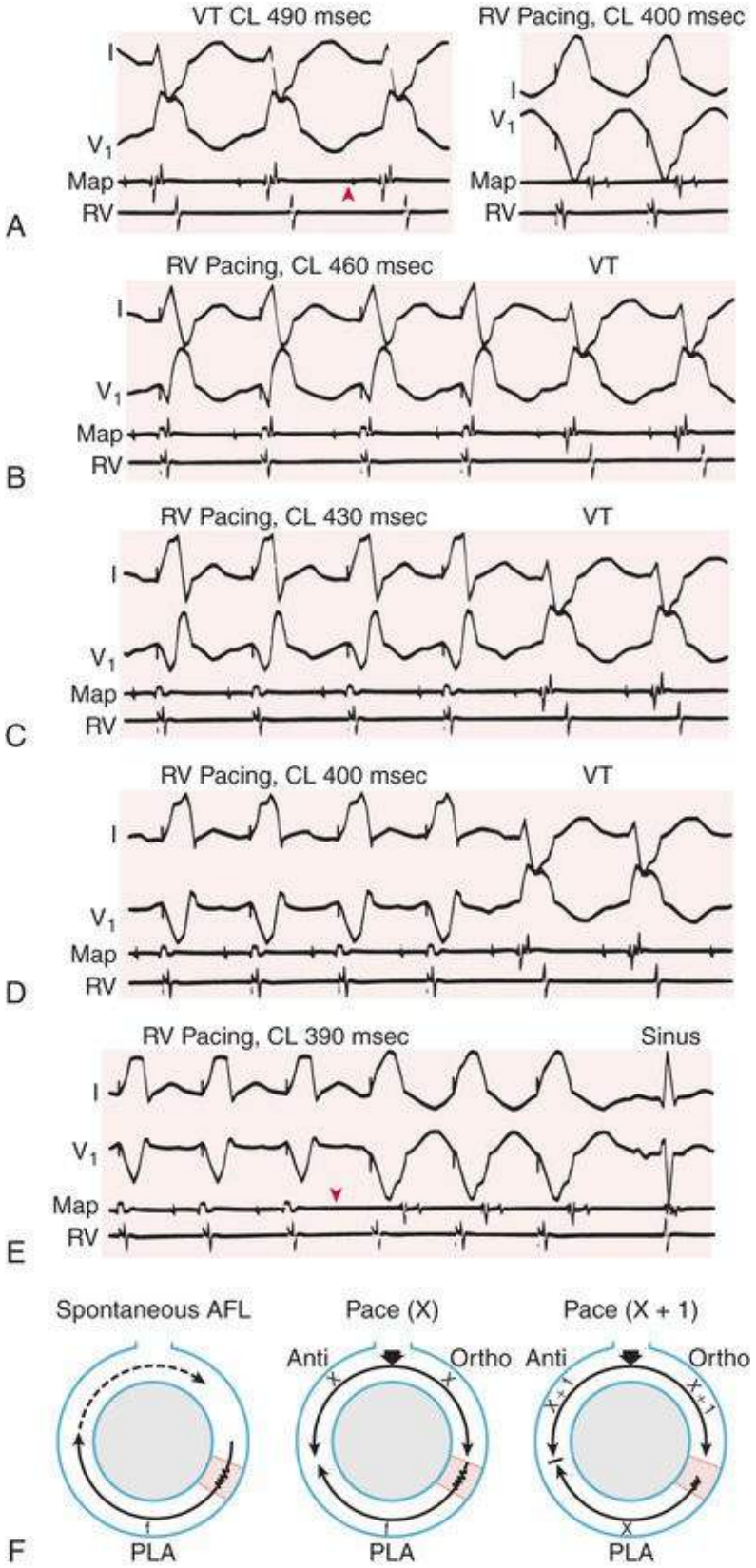


FIGURE 34.13 **A to E,** Criteria for entrainment exemplified in a case of postinfarction ventricular tachycardia (VT). **A, left,** Two leads of the ECG of a VT and intracardiac recordings from a mapping catheter (Map) at a left ventricular site critical for VT continuation, as well as from the right ventricular apex (RV). Note the diastolic potential (*red arrowhead*) during VT. Recordings are similarly arranged in all subsequent panels. **A, right,** RV pacing in the setting of sinus rhythm. **B,** RV pacing at a cycle length (CL) slightly shorter than VT produces a QRS complex that is a blend between fully VT and fully paced ("fusion") complexes. All recordings are accelerated to the paced CL, and after pacing ceases, the same VT resumes. Each fused QRS complex is identical, and the last beat is entrained, but surface fusion is absent. **C, D,** The same phenomena, but at shorter-paced CLs. Note that the fused QRS complex appears to be more similar to pacing than to VT as the pacing CL shortens. **B to D,** Progressive degrees of fusion on ECG. Map recording of **B, C,** and **D** also shows a progression of fusion, with both the morphology and timing of a portion of the electrogram changing with faster pacing. **E,** Finally, an even shorter-paced CL results in a sudden change in both map electrogram (block in small diastolic potential,

red arrowhead) and surface ECG, which is now fully paced. When pacing ceases, VT has been interrupted. **F,** Diagrammatic representation of the reentrant circuit during spontaneous atrial flutter (AFL) and transient entrainment of the AFL. **Left,** Reentrant circuit during spontaneous type I AFL; *f* = circulating wavefront of the AFL. **Center,** Introduction of the first pacing impulse (X) during rapid pacing from a high atrial site during AFL. The *black arrowhead* indicates entry of the pacing impulse into the reentrant circuit, where it is conducted orthodromically (Ortho) and antidromically (Anti). The antidromic wavefront of the pacing impulse (X) collides with the previous beat, in this case the circulating wave front of the spontaneous AFL (*f*), which results in an atrial fusion beat and, in effect, terminates the AFL. However, the orthodromic wavefront from the pacing impulse (X) continues the tachycardia and resets it to the pacing rate. **Right,** Introduction of the next pacing impulse (X + 1) during rapid pacing from the same high atrial site. The *black arrowhead* again indicates entry of the pacing impulse into the reentrant circuit, where it is conducted orthodromically and antidromically. Once again, the antidromic wavefront from the pacing impulse (X + 1) collides with the orthodromic wavefront of the previous beat. In this case, it is the orthodromic wavefront of the previous paced beat (X), and an atrial fusion beat results. The orthodromic wavefront from the pacing impulse (X + 1) continues the tachycardia and resets it to the pacing rate. In all three parts, *arrows* indicate the direction of spread of the impulses; the *serpentine line* indicates slow conduction through a presumed area of slow conduction (*stippled region*) in the reentrant circuit. (**A-E,** From Zipes DP. A century of cardiac arrhythmia: in search of Jason's golden fleece. J Am Coll Cardiol 1999;34:959; **F,** from Waldo AL. Atrial flutter: entrainment characteristics. J Cardiovasc Electrophysiol 1997;8:337.)

Anatomic Reentry

Studies on reentry have used models with anatomically defined separate pathways where it could be shown that they had an area of unidirectional block and recirculation of the impulse to its point of origin. An example of AV nodal reentry using different pathways is illustrated in **Fig. 34.14**. Because the two pathways have different electrophysiologic properties (e.g., shorter refractory period and slower conduction in one pathway versus a longer refractory period and faster conduction of the other), the impulse is first blocked anterogradely in the fast pathway with the longer refractory period and then propagates slowly in the adjacent slow pathway, whose refractory period is shorter (**Fig. 34.14A**). If conduction in this alternative route is sufficiently depressed, the slowly propagating impulse excites tissue beyond the blocked pathway and returns in the reverse direction along the pathway initially blocked, to reexcite tissue proximal to the site of block (**Fig. 34.14B**). A clinical arrhythmia caused by anatomic reentry is most likely to have a monomorphic contour (Video 34.2).

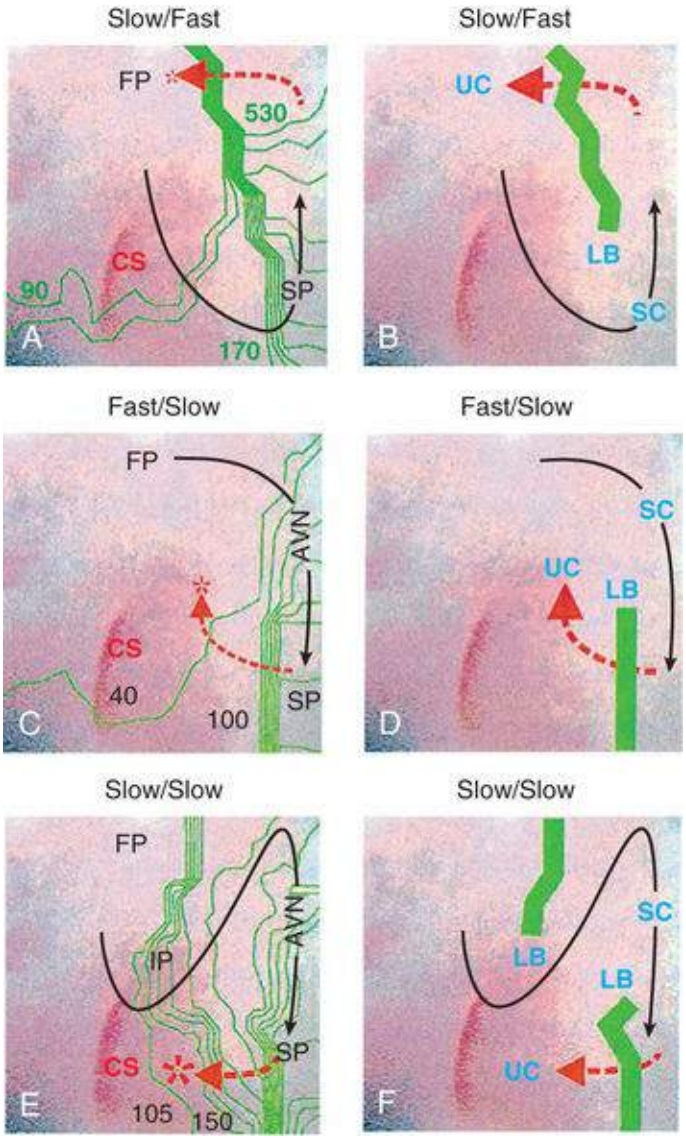


FIGURE 34.14 Reentrant circuits of different types of atrioventricular nodal reentrant tachycardia (AVNRT). Pictures of the optical activation maps of A_2 stimuli obtained from three different experiments at A_2 coupling intervals of 190, 220, and 190 milliseconds, respectively, were merged with the pictures of the mapping area to show the initiation of echo beats in **A** (Slow/Fast), **C** (Fast/Slow), and **E** (Slow/Slow) circuits. The numbers on the maps indicate the activation times in reference to the A_2 stimulus. The *black arrow* indicates anterograde conduction, and the *asterisk* and the *dashed red arrow* represent the site of earliest retrograde atrial activation. The corresponding locations of the lines of block (LB, *green*), slow anterograde conduction (SC, *black arrow*), and unidirectional conduction (UC, *red*) are shown in **B, D,** and **F,** respectively. *CS,* Coronary sinus; *FP,* fast pathway; *IP,* intermediate pathway; *SP,* slow pathway. (From Wu J, Zipes DP. Mechanisms underlying atrioventricular nodal conduction and the reentrant circuit of atrioventricular nodal reentrant tachycardia using optical mapping. J Cardiovasc Electrophysiol 2002;13:831.)

For anatomic reentry to occur, the time for conduction within the depressed but unblocked area and for excitation of the distal segments must exceed the refractory period of the initially blocked pathway and the tissue proximal to the site of block. Stated another way, continuous reentry requires the anatomic length of the circuit traveled to equal or exceed the reentrant wavelength (λ). The latter, λ, is equal to the mean conduction velocity of the impulse multiplied by the longest refractory period of the elements in the circuit. Both values can be different at different points along the reentry pathway, and thus a tachycardia does not have a single wavelength.

Conditions for Anatomic Reentry.

The length of the pathway is fixed and determined by the anatomy. Conditions that depress conduction velocity or abbreviate the refractory period promote the development of reentry in this model, whereas prolonging refractoriness and speeding conduction velocity can hinder it. For example, if conduction velocity (0.30 m/sec) and refractoriness (350 milliseconds) for ventricular muscle were normal, a pathway of 105 mm (0.30 m/sec × 0.35 sec) would be necessary for reentry to occur. However, under certain conditions, conduction velocity in ventricular muscle and Purkinje fibers can be very slow (0.03 m/sec), and if refractoriness is not greatly prolonged (600 milliseconds), a pathway of only 18 mm (0.03 m/sec × 0.60 sec) may be necessary. Such reentry frequently exhibits an *excitable gap*, that is, a time interval between the end of refractoriness from one cycle and the beginning of depolarization in the next, when tissue in the circuit is excitable. This condition results because the wavelength of the reentrant circuit is *less* than the length of the pathway. Electrical stimulation during this period can invade the reentrant circuit and reset its timing or terminate the tachycardia. Although "microanatomic" reentry (confinement of the reentrant circuit to a few adjacent myocytes) has been postulated to occur in fibrotic myocardium, its occurrence in intact heart muscle has not been demonstrated directly. This difficulty results from the inability unambiguously to distinguish microreentry from triggered activity with currently available techniques.

In reentrant circuits with an excitable gap, conduction velocity determines the revolution time of the impulse around the circuit and therefore the rate of the tachycardia. Prolongation of refractoriness, unless it is long enough to eliminate the excitable gap and make the impulse propagate in relatively refractory tissue, does not influence the revolution time around the circuit or the rate of the tachycardia. Anatomic reentry occurs in patients with Wolff-Parkinson-White (WPW) syndrome (**Fig. 34.15**), in AV nodal reentry, in some atrial flutters, and in some VTs.

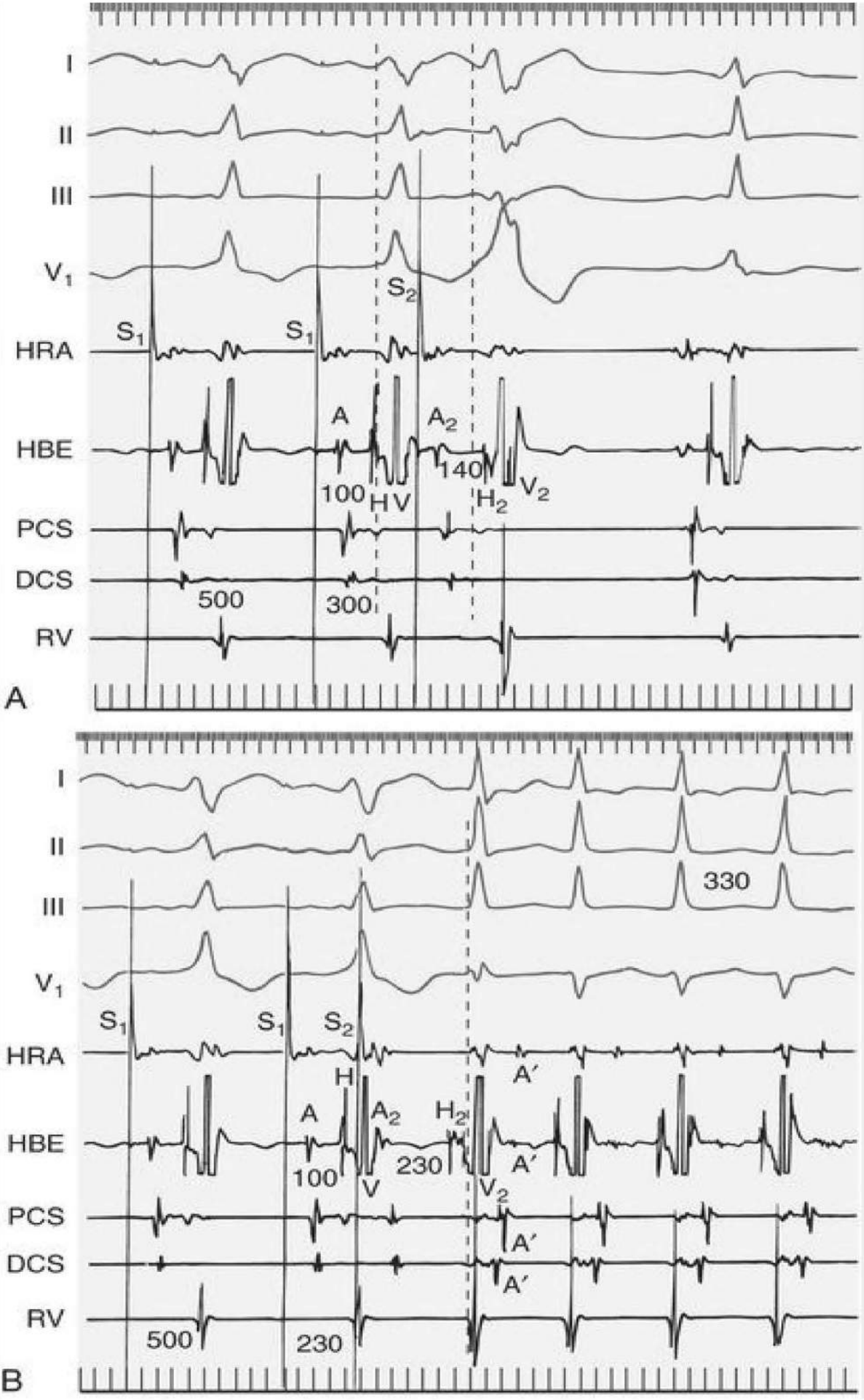
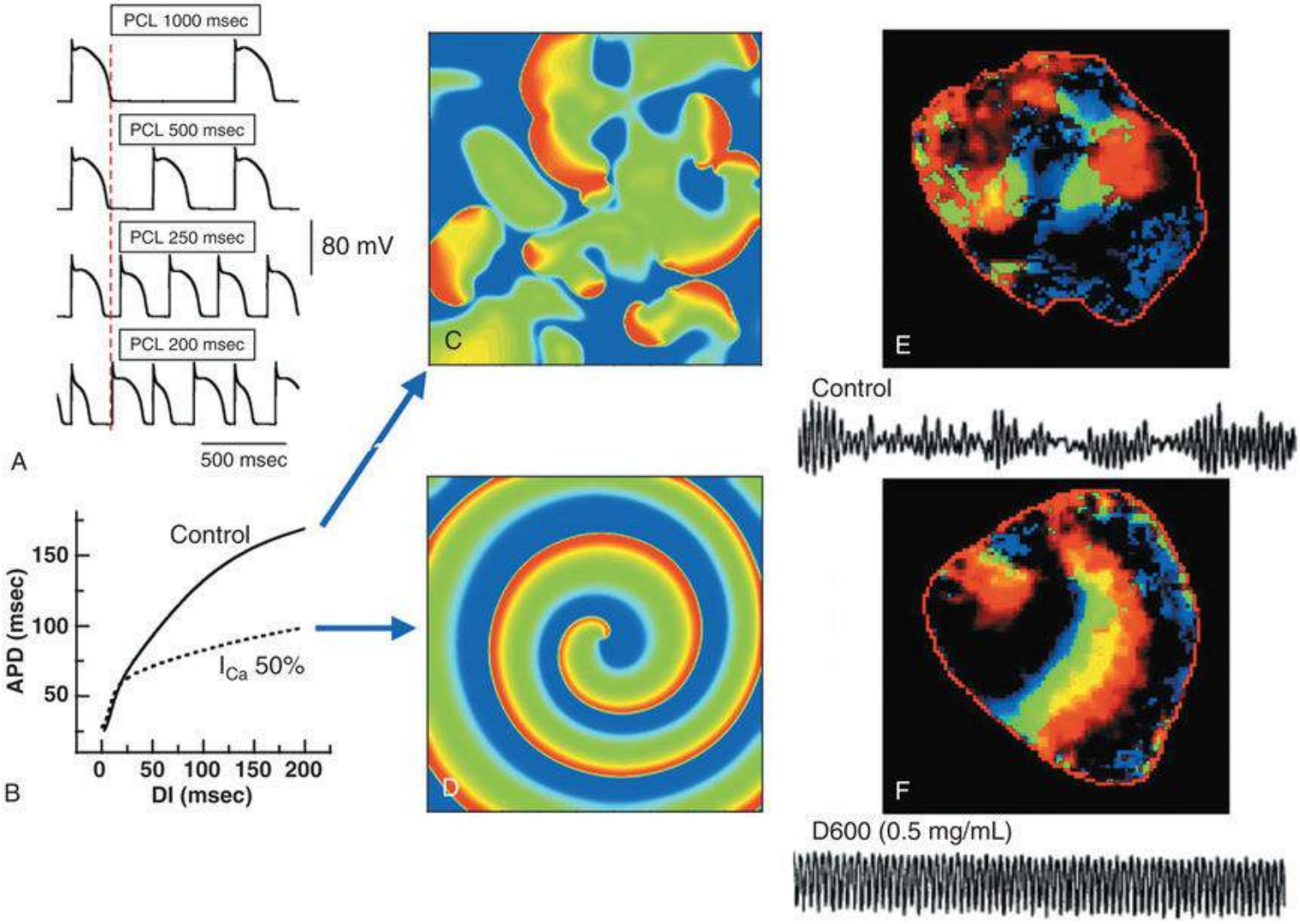

I
II
III
V1
S2
S1
S1
HRA
A
A2
HBE
140
100
HV
H2
V2
PCS
DCS
500
300
RV
A
330
S1
S1
S2
H
A′
A
A2
H2
HBE
100
V
230
V2
A′
PCS
A′
DCS
A′
RV
500
230
B

FIGURE 34.15 **A,** Wolff-Parkinson-White syndrome. Following high right atrial pacing at a cycle length of 500 milliseconds (S_1-S_1), premature stimulation at a coupling interval of 300 milliseconds (S_1-S_2) produces physiologic delay in AV nodal conduction, which results in an increase in the A-H interval from 100 to 140 milliseconds but no delay in the AV interval. Consequently, activation of the His bundle follows activation of the QRS complex (*second interrupted line*), and the QRS complex becomes more anomalous in appearance because of increased ventricular activation over the accessory pathway. **B,** Induction of reciprocating AV tachycardia. Premature stimulation at a coupling interval of 230 milliseconds prolongs the A_2-H_2 interval to 230 milliseconds and results in anterograde block in the accessory pathway and normalization of the QRS complex (a slight functional aberrancy in the nature of incomplete right bundle branch block occurs). Note that H_2 precedes onset of the QRS complex (*interrupted line*). Following V_2, the atria are excited retrogradely (A′) beginning in the distal coronary sinus, followed by atrial activation in leads recording from the proximal coronary sinus, His bundle, and high right atrium. A supraventricular tachycardia is initiated at a cycle length of 330 milliseconds. I, II, III, and V_1 indicate scalar electrocardiographic leads. A, H-V, atrial, His bundle, and ventricular activation during the drive train; A_2, H_2,V_2, atrial, His bundle, and ventricular activation during the premature stimulus; DCS, distal coronary sinus electrogram; HBE, His bundle electrogram; HRA, high right atrium; PCS, proximal coronary sinus electrogram; RV, right ventricular electrogram. Time lines are in 50- and 10-millisecond intervals. S_1, Stimulus of the drive train; S_2, premature stimulus. (From Zipes DP et al. Wolff-Parkinson-White syndrome: cryosurgical treatment. Indiana Med 1986;89:432.)

Functional Reentry

Functional reentry lacks confining anatomic boundaries and can occur in contiguous fibers that exhibit functionally different electrophysiologic properties caused by local differences in transmembrane action potential (e.g., Purkinje-myocyte transition). Dispersion of excitability, refractoriness, or both, as well as anisotropic distributions of intercellular resistance, permit initiation and maintenance of reentry. Functional heterogeneities in the electrophysiologic properties of the myocardium have been shown to contribute to the generation and maintenance of tachycardia and fibrillation. These heterogeneities can be fixed, as in the case of spatial redistribution of gap junctions in the failing heart or infarct border zone, or with spatial gradients in the magnitude of the background K^+ current I_{K1}. They can also change dynamically, as in an acutely ischemic myocardium or in the presence of repolarization-prolonging agents.[1,49] A very important determinant of the dynamically induced component of heterogeneity has been identified as *electrical restitution*, or variation of the action potential duration and conduction velocity with the diastolic interval. It has been proposed that the breakup of periodic waves is precipitated by oscillations in the APD (APD alternans) of sufficiently large amplitude to cause conduction block along a spiral wavefront[50] (**eFig. 34.24**).



EFIGURE 34.24 Action potential duration (APD) restitution slope and rotor stability. **A,** APD shortening and APD alternans as the pacing cycle length (PCL) decreases (computer simulations). **B,** APD restitution curves with a slope greater than 1 (*solid line*) or less than 1 (*dashed line*, obtained with 50% block of the calcium current). **C, D,** Spiral wave behavior several seconds after initiating a rotor in homogeneous two-dimensional tissue. All myocytes are assumed to be identical, with either a steep **(C)** or shallow **(D)** APD restitution slope. **E, F,** Conversion of multiple-wavelet ventricular fibrillation (VF) to mother rotor VF. Optically measured surface voltage maps were obtained from an intact Langendorff-perfused rabbit heart before **(E)** and after **(F)** partially blocking the L-type calcium current to flatten the APD restitution slope to less than 1. In **E,** multiple wavefronts move in a complex VF pattern. In **F,** VF has converted to ventricular tachycardia, manifested as a stable rotor. *Black tracings* below the color panels in **E** and **F** are corresponding electrograms. *DI,* Diastolic interval. (From Weiss JN et al. The dynamics of cardiac fibrillation. Circulation 2005;112:1232. By permission of the American Heart Association.)

Tachycardias Caused by Reentry

Reentry is probably the cause of many tachyarrhythmias, including various types of supraventricular and ventricular tachycardias, flutter, and fibrillation (**see Chapters 37 and 39**).

Atrial Flutter

Reentry is the most likely cause of the usual form of atrial flutter, with the reentrant circuit being confined to the right atrium in typical atrial flutter, where it usually travels counterclockwise in a caudocranial direction in the interatrial septum and in a craniocaudal direction in the right atrial free wall. An area of slow conduction is present in the posterolateral to posteromedial inferior area of the right atrium, along

with a central area of block that can include an anatomic (IVC) and functional component. This area of slow conduction is rather constant and represents the site of successful ablation of typical atrial flutter. Ablation results are consistent with a macroreentry circuit.

Different reentrant circuits exist in patients with other types of atrial flutter, such as those that occur after surgery or ablation or that are associated with an atrial septal defect (**see Chapter 75**).

Atrial Fibrillation

Spatiotemporal Organization and Focal Discharge

According to the multiple-wavelet hypothesis, AF is characterized by fragmentation of the wavefront into multiple daughter wavelets (**see Chapter 38**). They wander randomly throughout the atrium and give rise to new wavelets that collide with each other and are mutually annihilated or that give rise to new wavelets in a perpetual activity.

The randomness of the irregular electrical activity during AF has been disputed on the basis of both statistical methods and experimental studies. A combination of high-resolution video imaging, ECG recordings, and spectral analysis was used to demonstrate that reentry in anatomically or functionally determined circuits forms the basis of spatiotemporal periodicity during acute AF. The cycle length of the source in the left atrium determines the dominant peak in the frequency spectra. The underlying periodicity may stem from a repetitive focal source of activity propagated from an individual pulmonary vein or left atrial site to the remainder of the atrium as fibrillating waves. If a single repetitive focal source of activity that undergoes fractionated conduction underlies the maintenance of AF, ablation of this focal source should interrupt AF. Indeed, delivery of radiofrequency energy to discrete sites in the distal pulmonary veins in humans has been shown to eliminate or reduce recurrence of AF. Alternatively, ablation of a discrete focus that serves as a trigger for AF would also reduce arrhythmia recurrence. In a large animal model of inducible AF associated with heart failure, it was recently demonstrated that AF dynamics is characterized by rapid repetitive activation (resulting from either microanatomic reentry or triggered activity) revolving around fibrotic obstacles in the posterior left atrium or pulmonary vein ostia. Furthermore, fibrillatory activity was maintained by intramural reentry centered on fibrotic patches and appeared as *endocardial breakthroughs* at the posterior left atrium (endocardial breakthroughs are considered sudden and unexpected appearances of localized electrical activity not related to activation or slow conduction in the surrounding regions). In atria with heart failure, AF waves changed the origin and direction of propagation on a beat-to-beat basis, whereas in normal left atria, the breakthrough sites and direction of activation of AF wavefronts were highly recurrent from one AF wave to the next (Video 34.3).

Several experimental models have been used to study the structural and basic electrophysiologic properties of pulmonary veins that are thought to play a role in initiation and maintenance of AF. Morphologic studies have demonstrated the presence of complex anatomic structures and phenotypically different cardiomyocytes in pulmonary veins.[1,51] Electrophysiologic studies have shown that a combination of reentrant and nonreentrant mechanisms (automaticity and triggered activity) is the underlying arrhythmogenic mechanism for initiation of AF from the pulmonary veins. Abnormal intracellular calcium handling probably plays a pivotal role in the pulmonary vein electrical activity.

Ion Channel Abnormalities in Atrial Fibrillation

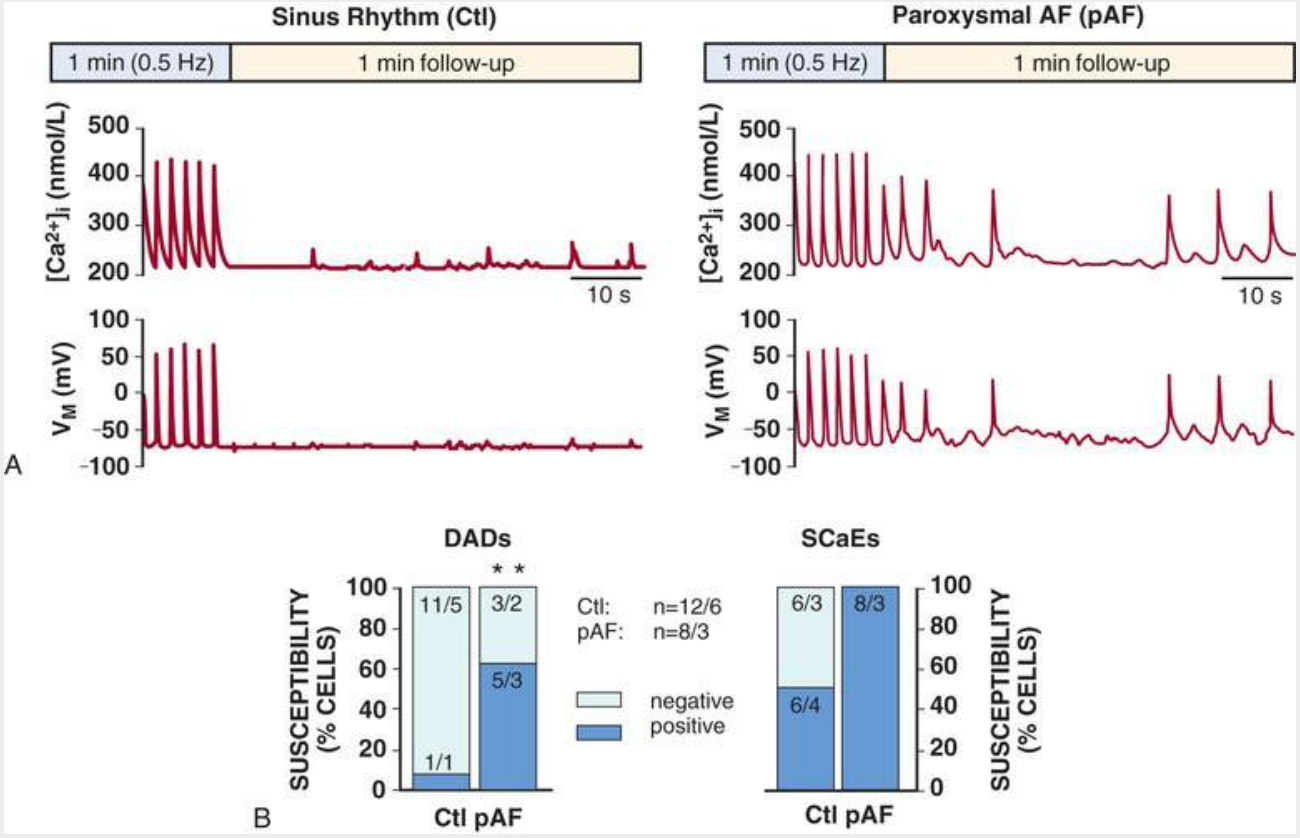
Monogenic (Familial) Atrial Fibrillation.

Although familial forms of AF are relatively rare, identification of mutations in AF kindreds has provided valuable insight into the molecular pathways underlying the arrhythmia. Most mutations linked to familial AF have been located in genes that encode sodium or potassium channel subunits. Functional analyses of these mutations have revealed either gain-of-function or loss-of-function effects. Mutations in genes encoding pore-forming alpha or auxiliary beta subunits of the delayed rectifier potassium channel and the voltage-gated sodium channel (I_{Ks} and I_{Na}, respectively; **see Table 34.1**) have been reported in familial AF. The mechanisms by which these mutations cause AF are not clearly understood. Gain-of-function mutations in I_{Ks} give rise to increased repolarizing currents, which then shorten the APD and atrial refractoriness, thereby facilitating fibrillatory activity. An augmented inward sodium current can induce triggered activity. Conversely, a reduced inward sodium current promotes reentry by abbreviating the action potential duration/refractoriness and thus the reentry wavelength. Other potassium channel mutations in the *KCNJ2* and *KCNA5* genes, which encode the inward rectifier and ultrarapid delayed rectifier potassium current, respectively, have been associated with AF (**see Table 34.1**). Finally, mutations in the *GJA5* gene, which encodes the gap junction channel subunit connexin 40, have been linked to familial AF. Functionally, abnormal intercellular electrical coupling can result in conduction heterogeneity and facilitate reentry.[52]

Genome-Wide Association Studies for Lone Atrial Fibrillation.

GWASs have identified variations in multiple genomic regions that are associated with lone AF. [19] These regions encode ion channels (e.g., calcium-activated potassium channel gene *KCNN3*, HCN channel gene *HCN4*), transcription factors related to cardiopulmonary development (e.g., homeodomain transcription factor PRRX1), and cell-signaling molecules (e.g., CAV1, a cellular membrane protein involved in signal transduction). The mechanistic links between these genetic variations and susceptibility to AF remain to be determined.

A number of experimental studies have probed the primary role of abnormalities in ion channel expression or properties in causing AF. In human tissue studies, diastolic Ca^{2+} leak and associated triggered activity in right atrial appendage myocytes were associated with paroxysmal AF[53] (**eFig. 34.25**). Genetically induced deficiency of Cav1.3 Ca^{2+} channels, or ablation of *KCNE1* (an auxiliary subunit of the pore-forming K^+ channel α subunit *KCNQ1*) or a small-conductance Ca^{2+}-dependent potassium (SK) channel impairs repolarization and increases atrial arrhythmias in mouse models.[1] SK channels participate in repolarization of human atrial myocytes and are dysregulated in chronic AF.[9]



EFIGURE 34.25 Atrial fibrillation (AF), delayed afterdepolarizations (DADs), spontaneous SR Ca^{2+}-release events (SCaEs) in human right atrial myocytes. **A,** Intracellular [Ca^{2+}] **(top)** and membrane potential **(bottom)** in control (Ctl) **(left)** and paroxysmal AF (pAF) **(right)** cardiomyocytes. SCaEs and DADs were assessed during a 1-minute follow-up after cessation of 0.5-Hz stimulation in 2.0-mmol/L extracellular [Ca^{2+}]. **B,** Prevalence of DADs exceeding 20 mV **(left)** and SCaEs **(right).** (From American Heart Association; Voigt N et al. Cellular and molecular mechanisms of atrial arrhythmogenesis in patients with paroxysmal atrial fibrillation. Circulation 2014;129:145.)

Electrical Remodeling of the Atria

Electrical remodeling of the atria appears to be a key determinant for maintenance of AF. Prolonged rapid atrial rates cause electrophysiologic alterations in the atria, including shortening and loss of the physiologic rate adaptation of refractoriness and a decrease in conduction velocity. Because abbreviation of the atrial refractory period is disproportionately larger than the reduction in conduction velocity, the wavelength of the reentrant wavelets shortens and thereby promotes reentrant activity.

The ionic basis of shortening of the refractory period and slowing of conduction may be a significant reduction in the density of the L-type Ca^{2+} and the fast Na^{+} currents. The electrophysiologic changes are paralleled by similar decreases in messenger RNA levels of Ca^{2+} and Na^{+} channel genes, which suggests alterations in gene expression as the underlying molecular mechanisms of atrial electrical remodeling. Changes in the density, spatial distribution, or both of various connexin types may also cause alterations in atrial impulse propagation. [54] In addition, autonomic remodeling appears to play a key role in both triggering and maintaining AF. Long-term selective vagal denervation of the atria and SA and AV nodes prevents induction of AF. Heterogeneous sympathetic denervation of the atria favors the development of sustained AF.[55]

Sinus Reentry

The SA node shares with the AV node electrophysiologic features such as the potential for dissociation of

conduction; that is, an impulse can be conducted in some nodal fibers but not in others, thereby permitting reentry to occur (**see Chapter 37**). The reentrant circuit can be located entirely within the SA node or may involve both the SA node and atrium. Supraventricular tachycardias caused by sinus node reentry are generally less symptomatic than other SVTs because of slower rates. Ablation of the SA node may occasionally be necessary for refractory tachycardia.

Atrial Reentry

Reentry within the atrium, unrelated to the SA node, can be a cause of SVT in humans. Distinguishing atrial tachycardia (AT) caused by automaticity or afterdepolarizations from AT sustained by reentry over small areas (i.e., microanatomic reentry) is difficult.

Atrioventricular Nodal Reentry

Differences in the electrical properties of the various tissue types that contribute to the AV node are responsible for AV nodal reentrant tachycardia (AVNRT; **see Fig. 34.9 and eFig. 34.12**). Optical mapping of AV nodal transmembrane action potentials during echo beats reveals the reentrant pathways underlying the various types of AVNRT (**see Fig. 34.14**). The reentrant pathway of the slow-fast type starts counterclockwise with block in the fast pathway (transitional zone; **see Fig. 34.9**), delay in conduction across the slow pathway (inferior nodal extension, INE) to the compact AV node (CN), exit from the AV node to the fast pathway, and rapid return to the slow pathway through atrial tissue located at the base of the triangle of Koch. The reentrant circuit of the fast-slow type is clockwise. In the slow-slow type, anterograde conduction is over the intermediate pathway and retrograde conduction is over the slow pathway. Because slow-pathway conduction is involved in each type of AVNRT, ablation of the slow pathway is effective for all types of AVNRT. These results also demonstrate that atrial tissue surrounding the triangle of Koch is clearly involved in all three types of AV nodal reentry described.

Preexcitation Syndrome

In most patients who have reciprocating tachycardias associated with WPW syndrome, the accessory pathway conducts more rapidly than the normal AV node but takes a longer time to recover excitability; that is, the anterograde refractory period of the accessory pathway exceeds that of the AV node at long cycles. Consequently, a premature atrial complex (PAC) that occurs sufficiently early is blocked anterogradely in the accessory pathway and continues to the ventricle over the normal AV node and His bundle. After the ventricles have been excited, the impulse is able to enter the accessory pathway retrogradely and return to the atrium. A continuous conduction loop of this type establishes the circuit for the tachycardia. The usual (orthodromic) activation wave during such a reciprocating tachycardia in a patient with an accessory pathway occurs anterogradely over the normal AV node–His-Purkinje system and retrogradely over the accessory pathway, which results in a normal-duration QRS complex (**see Fig. 34.15**).

Because the circuit requires both atria and ventricles, the term “supraventricular tachycardia” is not precisely correct, and the tachycardia is more accurately termed *atrioventricular reciprocating tachycardia* (AVRT). The reentrant loop can be interrupted by ablation of the normal AV node–His bundle pathway *or* the accessory pathway. On occasion, the activation wave travels in a reverse (antidromic) direction to the ventricles over the accessory pathway and to the atria retrogradely up the AV node. Two accessory pathways can form the circuit in some patients with antidromic AVRT. In some patients the accessory pathway may be capable of only retrograde conduction (“concealed”), but the circuit and

mechanism of AVRT remain the same. Less frequently, the accessory pathway can conduct only anterogradely. The pathway can be localized by ECG analysis. Patients can have AF as well as AVRT. Developmental studies in mice have demonstrated that myocardium-specific inactivation of T-box 2 (Tbx2), a transcription factor essential for AV canal patterning, leads to the formation of fast-conducting accessory pathways, malformation of the annulus fibrosus, and ventricular preexcitation in mice.[56]

Unusual accessory pathways with AV node–like electrophysiologic properties, that is, nodofascicular or nodoventricular fibers, can be part of the circuit for reciprocating tachycardias in patients who have variant forms of WPW syndrome. Tachycardia in patients with nodoventricular fibers can be caused by reentry, with these fibers being used as the anterograde pathway, and the His-Purkinje fibers and a portion of the AV node being used retrogradely. In the Lown-Ganong-Levine syndrome (short PR interval and normal QRS complex), conduction over a James fiber that connects the atrium to the distal portion of the AV node and His bundle has been proposed, although little functional evidence exists to support the presence of this entity.

Ventricular Tachycardia Caused by Reentry

Reentry in the ventricle, both anatomic and functional, as a cause of sustained VT has been supported by many animal and clinical studies (**see Chapter 37**). Reentry in ventricular muscle, with or without contributions from specialized tissue, is responsible for many or most VTs in patients with ischemic heart disease. The area of microreentry appears to be small, and less often a macroreentry circuit is found around the infarct scar. Surviving myocardial tissue separated by connective tissue provides serpentine routes of activation traversing infarcted areas that can establish reentry pathways. Bundle branch reentry, macroreentry using the specialized conduction system, can cause sustained ventricular tachycardia, particularly in patients with dilated cardiomyopathy.

Both figure-of-8 and single-circle reentrant loops have been described as circulating around an area of functional block in a manner consistent with the “leading circle” hypothesis or as conducting slowly across an apparent area of block created by anisotropy. When intramural myocardium survives, it can form part of the reentrant loop. Structural discontinuities that separate muscle bundles—as a result of the naturally occurring myocardial fiber orientation and anisotropic conduction, as well as collagen matrices formed from the fibrosis after MI—establish the basis for slowed conduction and fragmented electrograms, which can lead to reentry. After MI, the surviving epicardial border zone undergoes substantial electrical remodeling, including reduced conduction velocity and increased anisotropy associated with the occurrence of reentrant circuits and VT. Slowing of conduction arises from alterations in the spatial distribution and electrophysiologic properties of connexin 43 gap junctions, as well as from reduced voltage-gated sodium current. Whether myocyte depolarization secondary to electrotonic coupling to adjacent myofibroblasts (which typically have a much more depolarized potential) plays a role in electrical remodeling in postinfarction border-zone myocardium remains to be seen. During acute ischemia, various factors, including elevated $[K^+]_o$ and reduced pH, combine to create depressed action potentials in ischemic cells that impede conduction and can lead to reentry. Indeed, optical mapping studies in arterially perfused canine wedge preparations during global no-flow ischemia have demonstrated initiation of reentry during initial ischemia and subsequent reperfusion caused by the unidirectional block of conduction resulting from the spatiotemporal dispersion in tissue responses to stimulation. The rapidly changing combination of transmural dispersion in response to endocardial pacing stimuli and the velocity of conduction creates a dynamic substrate in which reentry can be initiated and sustained.

Brugada Syndrome

Phase 2 reentry has been implicated in the genesis of VT-VF associated with Brugada syndrome, which is characterized by ST-segment elevation (unrelated to ischemia, electrolyte abnormalities, or structural heart disease) in the right precordial (V_1 to V_3) leads of the ECG, often but not always accompanied by an apparent right bundle branch block. The hereditary nature of the syndrome is well established; however, it is apparent that simple mendelian transmission does not explain the phenotypic expression in many cases.[10] Brugada syndrome has been linked to loss-of-function mutations in *SCN5A*, which encodes the pore-forming cardiac sodium channel alpha subunit Nav1.5, and mutations in *SCN1B*, *SCN2B*, and *SCN3B*, which encode the function-modifying sodium channel beta subunits (**see Chapter 33**). Although Na^+ channel mutations are most common, mutations in the α and β subunits of the Ca^{2+} channel and several potassium channel genes have been found in some patients with Brugada syndrome, as have mutations in the glycerol-3-phosphate dehydrogenase 1–like (*GPD1L*) and other genes that encode proteins that regulate the functional expression of the Na^+ current I_{Na}. Brugada syndrome–associated gene defects cause a reduction or loss of sodium or calcium current in combination with altered functional properties of voltage-gated sodium channels.[57] Alterations in the sodium current can cause heterogeneous loss of the action potential dome during the plateau phase (phase 2) in the right ventricular epicardium, which leads to a marked dispersion of repolarization and refractoriness and the potential for phase 2 reentry. Ablation of RV epicardium eliminated ventricular arrhythmias in an animal model of pharmacologically induced Brugada syndrome. However, ablation in humans has been shown to eliminate the electrocardiographic changes but does not totally eliminate the risk of recurrent ventricular arrhythmias.[58]

Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT is an inherited arrhythmogenic syndrome characterized by stress-induced, adrenergically-mediated polymorphic ventricular tachycardia occurring in structurally normal hearts. Heterozygous missense mutations in the gene encoding the RyR2 have been reported in most patients with CPVT, although mutations in the calsequestrin gene can also cause CPVT. A common mechanism underlying RyR2-associated CPVT is increased leakage of Ca^{2+} from the SR during diastole, leading to intracellular Ca^{2+} waves and triggered activity. Carvedilol, a beta blocker used for prevention of ventricular tachyarrhythmias in heart failure, and flecainide, a blocker of voltage-gated sodium channels, have recently been shown to suppress CPVT by direct inhibition of cardiac ryanodine receptor–mediated Ca^{2+} release, thus indicating that these agents possess pharmacologic properties that can be exploited for the treatment of Ca^{2+}-dependent arrhythmias in the clinical setting.[1,59] Although the mechanism of action of flecainide in CPVT has been debated, some studies suggest block of a noncardiac Nav channel in the dyad.[5,60]

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited myopathy characterized by sustained monomorphic ventricular tachycardia and sudden death (**see Chapter 77**). Previous studies have linked ARVC with mutations in proteins of the cardiac desmosome, a component of the intercalated disc essential for mechanical coupling between cardiomyocytes. Mutations in multiple genes, including desmoplakin, desmoglein 2, desmocollin 2, plakophilin 2, plakoglobin (*JUP*, also called gamma-catenin), ryanodine receptor 2, laminin receptor 1, and transforming growth factor-beta 3, have been identified in patients with ARVC. Approximately 40% of the pathogenic mutations linked to ARVC are in the gene encoding plakophilin 2 (*PKP2*), which interacts with other cytoskeletal proteins to stabilize the

desmosome.[30] In vitro studies have demonstrated that loss of *PKP2* expression reduces the voltage-gated sodium current and connexin 43 expression at the intercalated disc and thus results in slowed action potential propagation. Shared phenotypic, genetic and functional features have suggested the possibility of pathogenic links between ARVC and Brugada syndrome.[28,61]

Ventricular Fibrillation: Initiation and Maintenance

Previous experimental and simulation investigations have suggested that VF is maintained solely by reentry (**see Chapter 39**). This reentry was thought to be unstable and to be maintained by wandering wavelets of activation following constantly changing paths of activation and exhibiting frequent conduction block caused by nonuniform dispersion of refractoriness. More recent investigations have suggested other mechanisms of maintenance of VF and have introduced the concepts of restitution kinetics, wavefront, wave break, focal discharge, and rotors as replacement for the classic reentry theory.[50,62] (For a demonstration of wavefront dynamics during fibrillation, see Video 34.4.)

The hallmark of cardiac fibrillation is ongoing wave break (or wave splitting). Wave break is caused by conduction block occurring at a specific site along the wavefront while the remaining portions of the front continue to propagate. This localized block, wave break, causes splitting of the mother wavefront into two daughter wavelets. Two hypotheses exist regarding the genesis of wave breaks during fibrillation. The “mother rotor” hypothesis states that VF is maintained by a single, stationary, intramural stable reentrant circuit (i.e., the mother rotor) in a dominant domain, which has the shortest refractory period from which activations propagate into the more slowly activating domains with longer refractory periods. Wave breaks result from Wenckebach-like conduction as high-frequency impulses emanating from the dominant domain are unable to sustain 1 : 1 conduction through heterogeneous tissue. In this case, the fastest activating (i.e., dominating) rotor rather than ongoing wave break is the engine driving cardiac fibrillation, and wave break occurs only secondarily. Evidence supporting this concept is that frequency domain analyses have shown (1) single, stable (both in space and time), dominant frequencies in the power spectra of membrane voltage signals obtained from various regions of the heart; (2) correlation of dominant frequencies and the frequency of reentry; (3) relative infrequency of reentry on the surface of the heart during fibrillation, with an intramural location of the mother rotor being favored, such as the Purkinje network; and (4) Wenckebach-like conduction at the borders between different dominant frequency domains. These borders can result from preexisting structural or functional heterogeneities. For example, high-resolution electrical mapping has suggested that fast activation during VF is driven by Purkinje fibers. Spatial heterogeneity in the magnitude of ionic currents has been implicated in the generation of spatial gradients in activation rates and in maintaining rotor stability in the fastest activating regions. For example, the magnitude of the inward rectifying K^+ current I_{K1} (**see Table 34.1**) was larger in the rapidly activating LV myocytes than in the slower activating RV myocytes. Furthermore, regions with larger I_{K1} had faster activation rates and more stable rotors than did regions with smaller I_{K1}.[1]

In contrast to the stable mother rotor theory, other experimental evidence has supported the idea that dynamic wave break plays a fundamental role in the initiation and maintenance of short-duration VF (“wandering wavelet” hypothesis).[1,62] According to this hypothesis, VF is maintained by wandering wavelets with constantly changing, evanescent, reentrant circuits. Experimental evidence favoring the multiple-wavelet hypothesis includes (1) an inability to detect a single dominant frequency in the power

spectra of mapping data from fibrillating hearts; (2) spatiotemporal instability of frequency domain distributions during VF, with the exception of anatomic borders, such as the Purkinje-myocyte transition; (3) failure to demonstrate stable intramural reentry at higher frequencies than at the surface; and (4) boundaries dynamically generated by wavelet behavior rather than by anatomic conduction block. To reproduce the dynamic spatiotemporal instability of dominant frequency domains, a combination of dynamically changing and fixed-tissue heterogeneity is required. The most important determinant of the dynamically induced component of heterogeneity has been identified as electrical restitution, or variation of the action potential duration and conduction velocity with the diastolic interval. For example, it has been proposed that the breakup of periodic waves is precipitated by APD alternans sufficiently large to cause conduction block along the spiral wavefront. Simulations have shown that a reentrant rotor becomes unstable and breaks down into multiple rotors when the slope of the restitution curve for the APD versus the diastolic interval is greater than 1. Pharmacologic blockade of the L-type calcium current can terminate VF by reducing the APD restitution slope (**see eFig. 34.24**). If it is occurring in a spatially discordant pattern, alternans is considered a key arrhythmogenic factor predisposing the heart to reentry and fibrillation.[1] At the cellular level, the origin of APD alternans appears to be determined primarily by alternations in cardiomyocyte calcium transient amplitude or duration (calcium alternans).[63]

During spatially discordant alternans, the APD alternates out of phase in different regions of the heart, thereby increasing dispersion of refractoriness so that ectopic beats have a high probability of inducing reentry. This mechanism is illustrated in **Fig. 34.16**; some regions of the heart alternate in a long-short-long pattern, whereas other regions at the same time alternate in a short-long-short pattern. These out-of-phase regions are separated by a nodal line in which no alternans is present, but spatial gradients in the APD are steepest along this line. Thus, spatially discordant alternans creates gradients in tissue refractoriness, which in turn favor the development of reentry by a premature beat (**Fig. 34.16B**). At the cellular level, the steepness of the APD restitution curve and intracellular calcium level ($[Ca^{2+}]_i$) dynamics cause the APD and $[Ca^{2+}]_i$ transient to alternate. Given the bidirectional coupling between changes in $[Ca^{2+}]_i$ and membrane potential—for example, the membrane potential determines the activity of L-type Ca channels, and conversely, the $[Ca^{2+}]_i$ transient amplitude strongly modulates the APD through its effects on Ca^{2+}-sensitive currents (e.g., $I_{Na/Ca}$ and I_{Ca}) during the action potential plateau—an alternation in $[Ca^{2+}]_i$ transient amplitude can cause a secondary alternation in the APD. Indeed, experimental evidence has strongly suggested that the onset of APD alternans is primarily attributable to instabilities in $[Ca^{2+}]_i$ cycling dynamics, thus defining a causal role of intracellular Ca^{2+}-handling abnormalities in initiating electrical instability. At the tissue level, alternans combines with instabilities in conduction velocity to cause alternans to become spatially discordant.

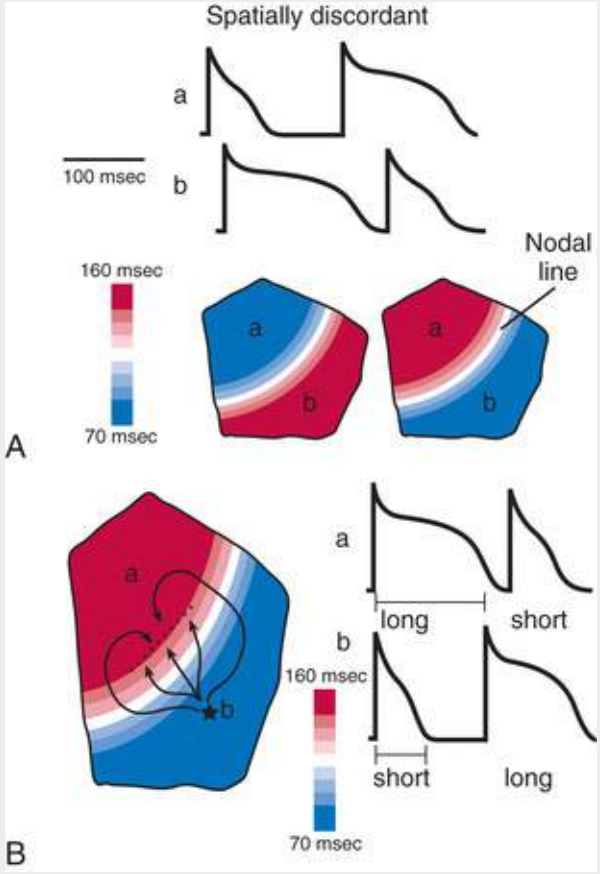


FIGURE 34.16 Initiation of reentry by a premature beat during spatially discordant alternans. **A, upper panel,** At rapid rates, action potentials at site **a** alternate short-long, whereas at the same time, action potentials at site **b** alternate long-short, thereby creating a steep gradient of action potential duration (APD) distribution with a nodal line that has no APD alternation separating the out-of-phase regions **a** and **b (lower panel). B,** A premature beat (*asterisk*) occurring in region **b** blocks (*dotted line*) as it propagates across the nodal line into the region with a long APD **(a).** The premature beat propagates laterally along the nodal line while waiting for the long APD region to repolarize and then reenters the blocked region to initiate figure-of-8 reentry. (From Weiss JN et al. From pulsus to pulseless: the saga of cardiac alternans. Circ Res 2006;98:1244.)

Ventricular Tachycardias Caused by Nonreentrant Mechanisms

In some VTs, especially in patients without coronary artery disease, nonreentrant mechanisms are important causes. In many patients, however, the mechanism of the VT remains unknown.

Triggered Activity

A group of VTs occurring in the absence of structural heart disease can be initiated and terminated by programmed stimulation. These are catecholamine dependent and can be terminated by the Valsalva maneuver, adenosine, or verapamil. These VTs are generally but not exclusively located in the RV outflow tract and may be caused by triggered activity, possibly DADs that are cAMP dependent. [42] EADs have been recorded in this VT as well. LV fascicular tachycardias can be suppressed by verapamil but not generally by adenosine, and some may be caused by triggered activity and others by reentry. EADs and triggered activity may be responsible for torsades de pointes.

Automaticity

Automatic discharge can be responsible for some VTs and does not appear to be suppressed by adenosine. Unless invasive studies are undertaken, mechanisms of VT can only be conjectured.

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Diagnosis of Cardiac Arrhythmias

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In managing clinical arrhythmias, physicians must evaluate and treat the entire patient, not just the rhythm disturbance.[1] Some arrhythmias are hazardous to the patient regardless of the clinical setting, such as

ventricular fibrillation, whereas others are hazardous because of the clinical setting, such as rapidly conducted atrial fibrillation (AF) in a patient with severe coronary artery stenoses. Some rhythm abnormalities, such as premature ventricular complexes (PVCs), may be highly symptomatic but not associated with any adverse outcomes, whereas other patients with PVCs may have no palpitations but develop heart failure related to the PVCs. Some patients with AF have no symptoms but may still be at significant risk for stroke or heart failure from the rapid ventricular rate, whereas others are highly symptomatic with palpitations but have low risk for stroke or heart failure. Evaluation of the patient begins with a careful history and physical examination and should usually progress from the simplest to the most complex test, from the least invasive and safest to the most invasive and risky, and from the least expensive out-of-hospital evaluations to those that require hospitalization and sophisticated, costly, and potentially risky procedures. On occasion, depending on the clinical circumstances, the physician may choose to proceed directly to an expensive procedure associated with some risk, such as an electrophysiologic study (EPS), before obtaining a 24-hour electrocardiographic recording. In most cases, management of arrhythmia has a dual purpose: evaluation and treatment must address not only the patient's symptoms, but also whatever risks the arrhythmia poses to the individual.

Patient History

Patients with disturbances in cardiac rhythm can have various complaints, but symptoms such as palpitations, syncope, presyncope, or dyspnea commonly cause them to seek a physician's help. Their awareness of palpitations and a regular or irregular cardiac rhythm varies greatly. Some patients perceive slight variations in their heart rhythm with uncommon accuracy, whereas others are oblivious to even sustained episodes of ventricular tachycardia (VT); still others complain of palpitations when they actually have regular sinus rhythm.

In assessing a patient with a known or suspected arrhythmia, several key pieces of information should be obtained that can help determine a diagnosis or guide further diagnostic testing. The *mode of onset* of an episode can provide clues about the type of arrhythmia or preferred treatment option. For example, palpitations that occur in the setting of exercise, fright, or anger are often caused by catecholamine-sensitive automatic or triggered tachycardias that may respond to adrenergic blocking agents (**see Chapter 36**); palpitations that occur at rest or that awaken the patient can be caused by vagal initiation, such as AF. Lightheadedness or syncope occurring in the setting of a tightly fitting collar, shaving the neck, or turning the head suggests carotid sinus hypersensitivity. The triggering event may help establish the presence of an inherited ion channel abnormality (**see Chapter 33**). The *mode of termination* of episodes can also be helpful: palpitations that are reliably terminated by breath-holding or by Valsalva or other vagal maneuvers probably involve the atrioventricular (AV) node as an integral part of a tachycardia circuit; on occasion, focal atrial tachycardias or VTs can be terminated with vagal maneuvers, as can VT originating in the right ventricular outflow tract. Patients should be asked about the frequency and duration of episodes and the severity of symptoms. In some women the features of their episodes vary according to the menstrual cycle. These features can help guide how aggressively and quickly the physician needs to pursue a diagnostic or therapeutic plan (a patient with daily episodes associated with near-syncope or severe dyspnea warrants a more expeditious evaluation than does one with infrequent episodes of mild palpitations and no other symptoms). Patients should be encouraged to report their heart rate during an episode (either rapid or slow, regular or irregular) by counting the pulse directly or by using an automatic blood pressure or heart rate monitor or smart phone application; these may or may not provide reliable

data. Characteristics of the mode of onset and frequency of episodes can guide the choice of diagnostic tests (see later).

A careful drug and dietary history should also be sought; some nasal decongestants can provoke tachycardia episodes, whereas beta-adrenergic blocking eye drops for the treatment of glaucoma can drain into tear ducts, be absorbed systemically, and precipitate syncope secondary to bradycardia. Dietary supplements, particularly those containing stimulants such as ephedrine (generally removed from the market), can cause arrhythmias. A growing list of drugs can directly or indirectly affect ventricular repolarization and produce or exacerbate long-QT interval–related tachyarrhythmias (**see Chapter 8**). The patient should be questioned about the presence of systemic illnesses that may be associated with arrhythmias, such as chronic obstructive pulmonary disease, thyrotoxicosis (**see Chapter 86**), pericarditis (**Chapter 83**), and chronic heart failure (**Chapters 24 and 25**), as well as previous chest injury, surgery, or radiation therapy or chemotherapy. A family history of rhythm disturbances is often present in those with long-QT syndrome, AF or other inherited arrhythmia syndromes, hypertrophic cardiomyopathy (**see Chapter 78**), and muscular or myotonic dystrophy (**Chapter 97**).

Physical Examination

Examination of a patient during an arrhythmia episode can be revealing. Heart rate and blood pressure should be evaluated, as well as how ill the person appears. Assessment of jugular venous pressure and waveform can disclose the rapid oscillations of atrial flutter or “cannon” A waves indicative of contraction of the right atrium against a closed tricuspid valve in patients with AV dissociation, such as in complete heart block or VT. Variations in the intensity of the first heart sound and systolic blood pressure have the same implications.

Physical maneuvers during tachycardia can have diagnostic and therapeutic value. As noted, the Valsalva maneuver[2] (as well as carotid sinus massage) causes a transient increase in vagal tone; tachyarrhythmias that depend on the AV node for continuation can terminate or slow with these maneuvers but may also show no change. Even though focal atrial and VTs occasionally terminate in response to vagal stimulation, sinus tachycardia slows slightly but returns to its original rate soon thereafter; the ventricular response during atrial flutter and AF and other atrial tachycardias can decrease briefly. During wide-QRS tachycardias with a 1 : 1 relationship between P waves and QRS complexes, vagal influence can terminate or slow a supraventricular tachycardia (SVT) that depends on the AV node for perpetuation; on the other hand, vagal effects on the AV node can transiently block retrograde conduction and thus establish the diagnosis of VT by demonstrating AV dissociation. Because the effect of either of these physical maneuvers typically lasts only seconds, clinicians must be ready to observe or record any changes in rhythm on an electrocardiogram (ECG) when the maneuver is performed or the response may be missed.

Carotid massage is performed with the patient supine and comfortable and the head turned slightly away from the side being stimulated.[3] Careful auscultation for carotid bruits must always precede any attempt at carotid massage (embolic events have been associated with massage). The area of the carotid sinus, at the artery's bifurcation, is palpated with two fingers at the angle of the jaw until a good pulse is felt. Even this minimal amount of pressure can induce a hypersensitive response in susceptible individuals. If no initial effect is noted, a side-to-side or rotating motion of the fingers over the site is performed for up to 5 seconds. A negative response is lack of effect on the ECG after 5 seconds of pressure adequate to cause mild discomfort. Because responses to carotid massage may differ on the two

sides, the maneuver can be repeated on the opposite side; however, both sides should never be stimulated simultaneously. Findings may not be readily reproducible, even within minutes of a prior attempt.

Physical findings can suggest the presence of structural heart disease (and thus generally a clinically more serious situation with a worse overall prognosis), even in the absence of an arrhythmia episode. For example, a laterally displaced or dyskinetic apical impulse, a regurgitant or stenotic murmur, or a third heart sound in an older adult can denote significant myocardial or valvular dysfunction or damage (**see Chapter 10**). Even facial features may suggest an associated rhythm disorder (e.g., cataracts and early balding with myotonic dystrophy, micrognathia and low-set ears in Andersen-Tawil syndrome).

Electrocardiogram

The ECG is the primary tool for analysis of arrhythmias (**see Chapter 12**); an EPS, in which intracardiac electrode catheters are used to record activity from several regions of the heart at one time, is more definitive but not always immediately available. Initially, a 12-lead ECG is recorded. In addition, a long continuous recording with use of a lead that shows distinct P waves is often helpful for closer analysis; typically, this is one of the inferior leads (2, 3, aVF), V_1, or aVR. The ECG obtained during an arrhythmia episode may be diagnostic by itself and obviate the need for further diagnostic testing. **Fig. 35.1** depicts an algorithm for the diagnosis of specific tachyarrhythmias from the 12-lead ECG (**see Chapters 37 and 39**). A major branch point in the differential diagnosis concerns the QRS duration: wide-QRS (>0.12 second) tachycardias are often VTs, and narrow-QRS (≤0.12 second) tachycardias are almost always SVTs, but there is some overlap (**Table 35.1**). Next, the most important questions to answer, regardless of QRS width, concern the characteristics of P waves. If P waves are not clearly visible on the regular ECG, atrial activity can occasionally be discerned by placing the right and left arm leads in various anterior chest positions (so-called Lewis leads), by recording atrial electrograms using intracardiac right atrial recordings (via permanent or temporary transvenous pacing leads), or by using esophageal electrodes or an echocardiogram; the last methods are not readily available in most clinical situations and consume valuable time when dealing with a sick patient. A long rhythm strip can usually be obtained and can yield important clues by revealing P waves if perturbations occur during the arrhythmia (e.g., changes in rate, premature complexes, sudden termination, and effect of physical maneuvers, as noted earlier).

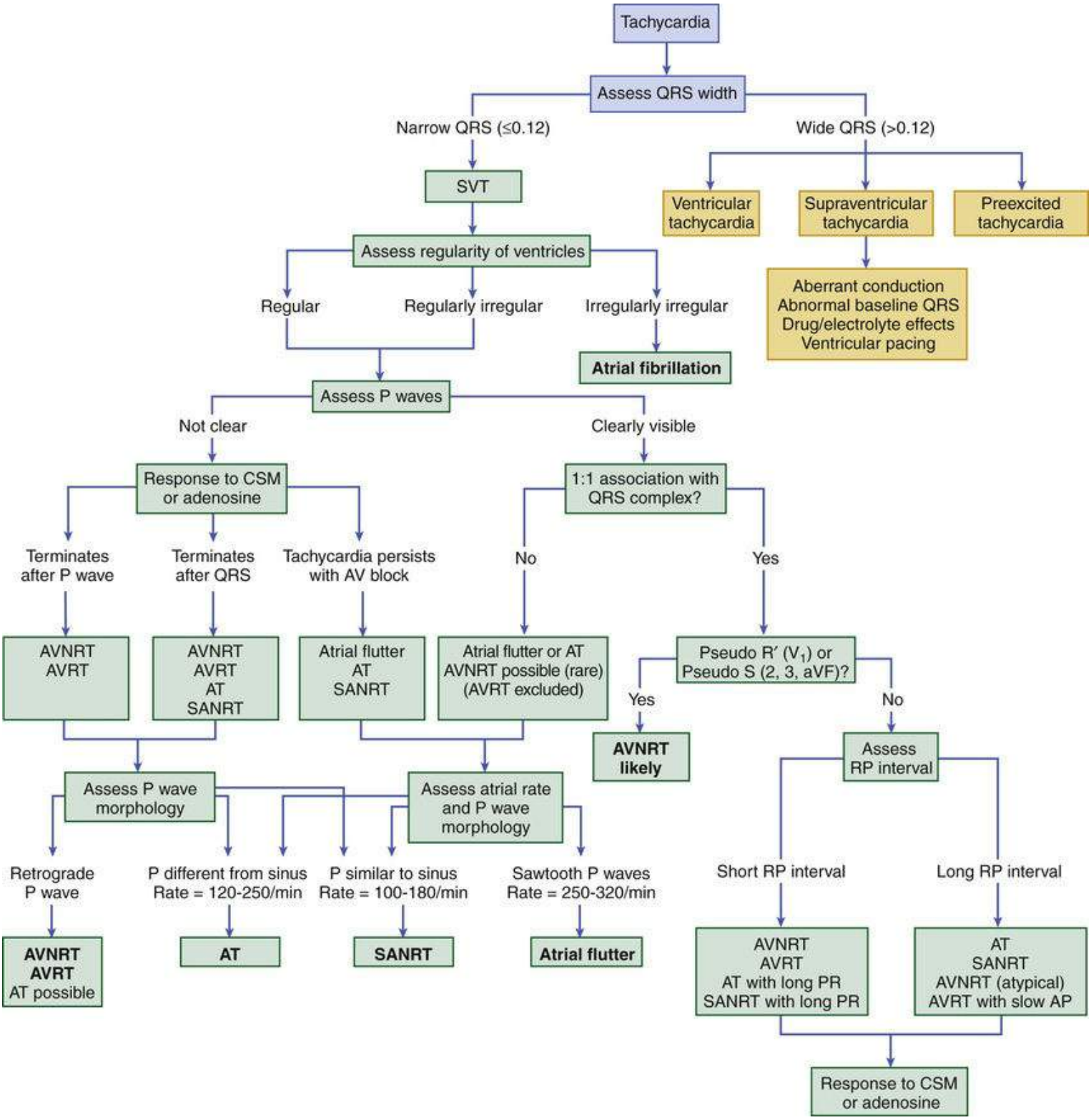


FIGURE 35.1 Stepwise approach to diagnosis of the type of tachycardia based on a 12-lead ECG during the episode. The initial step is to determine whether the tachycardia has a wide or narrow QRS complex. For wide-complex tachycardia, see Table 35.1; the remainder of the algorithm is helpful in diagnosis of the type of narrow-complex tachycardia. *AP,* Accessory pathway; *AT,* atrial tachycardia; *AVNRT,* atrioventricular nodal reentrant tachycardia; *AVRT,* atrioventricular reciprocating tachycardia; *CSM,* carotid sinus massage; *SANRT,* sinoatrial nodal reentry tachycardia.

TABLE 35.1

Electrocardiographic Distinctions for Diagnosis of Wide–QRS Complex Tachycardia

FAVOR SUPRAVENTRICULAR TACHYCARDIA	FAVOR VENTRICULAR TACHYCARDIA
Initiation with a premature P wave	Initiation with a premature QRS complex
Tachycardia complexes identical to those in resting rhythm	Tachycardia beats identical to PVCs during sinus rhythm
"Long-short" sequence preceding initiation	"Short-long" sequence preceding initiation
Changes in the P-P interval preceding changes in the R-R interval	Changes in the R-R interval preceding changes in the P-P interval
QRS contours consistent with aberrant conduction (V_1, V_6)	QRS contours inconsistent with aberrant conduction (V_1, V_6)
Slowing or termination with vagal maneuvers	AV dissociation or other non-1 : 1 AV relationship
Onset of the QRS to its peak (positive or negative) <50 msec	Onset of the QRS to its peak (positive or negative) ≥50 msec
	Fusion beats, capture beats
QRS duration ≤0.14 sec	QRS duration >0.14 sec
Normal QRS axis (0 to +90 degrees)	Left axis deviation (especially −90 to 180 degrees)
	Concordant R wave progression pattern
	Contralateral bundle branch block pattern from the resting rhythm
	Initial R, q, or r >40 msec or notched Q in aVR
	Absence of an "rS" complex in any precordial lead

AV, Atrioventricular; *PVC,* premature ventricular complexes.

Each arrhythmia should be approached in a systematic manner to answer several key questions; as suggested earlier, many of these questions relate to P wave characteristics and underscore the importance of assessing the ECG carefully for them. If P waves are visible, are the atrial and ventricular rates identical? Are the P-P and R-R intervals regular or irregular? If irregular, is it a consistent, repeating irregularity? Is there a P wave related to each QRS complex? Does the P wave seem to precede (long RP interval) or follow (short RP interval) the QRS complex (**Fig. 35.2**)? Are the resultant RP and PR intervals constant? Are all P waves and QRS complexes identical? Is the P wave vector normal or abnormal? Are P, PR, QRS, and QT durations normal? Once these questions have been addressed, the clinician needs to assess the significance of the arrhythmia in view of the clinical setting. Should it be treated, and if so, how? For SVTs with a normal QRS complex, a branching decision tree such as that shown in Fig. 35.1 may be useful.[4]

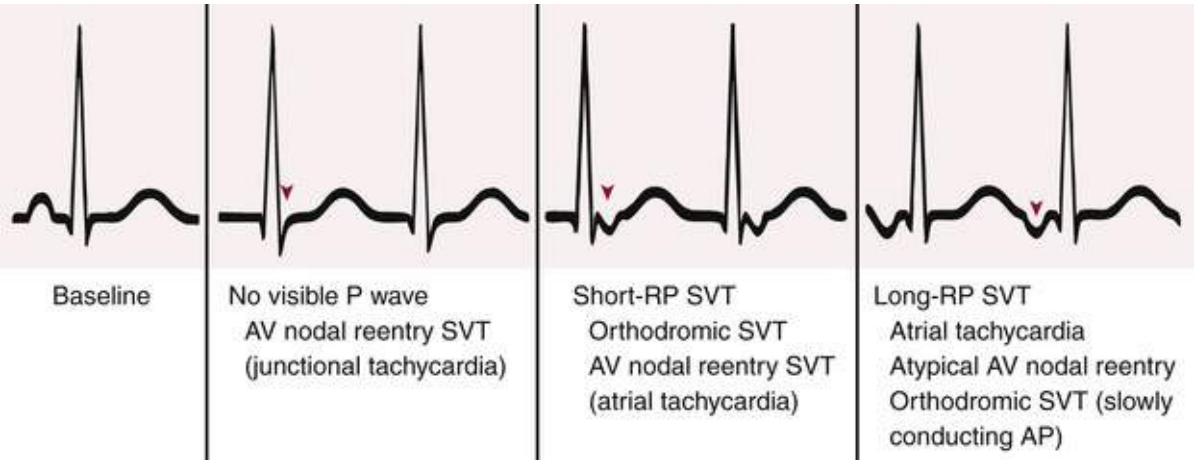


FIGURE 35.2 Differential diagnosis of different types of supraventricular tachycardia (SVT) based on timing of atrial activity (RP and PR intervals). **Left,** Normal beat. Different types of tachycardia are listed below the representative electrocardiographic patterns that they can produce, as categorized by P wave position relative to the QRS complex. An *arrowhead* shows the location of the P wave in each example. Diagnoses in parentheses are rare causes of the noted findings. *AP,* Accessory pathway.

The Ladder Diagram.

A ladder diagram, derived from the ECG, is used to depict depolarization and conduction schematically to aid in understanding the rhythm. Straight or slightly slanting lines drawn on a tiered framework beneath an ECG represent electrical events occurring in the various cardiac structures (**Fig. 35.3**). Because the ECG and therefore the ladder diagram represent electrical activity as a function of time along the *x* axis, conduction is indicated by the lines of the ladder diagram sloping in a left-to-right direction. A steep line represents rapid conduction; more slanting lines depict slower conduction. A short bar drawn perpendicular to a sloping line represents blocked conduction. Activity originating in an ectopic site such as the ventricle is indicated by lines emanating from that tier. Sinus nodal discharge and conduction and, under certain circumstances, AV junctional discharge and conduction can only be inferred; their activity is not directly recorded on the ECG.

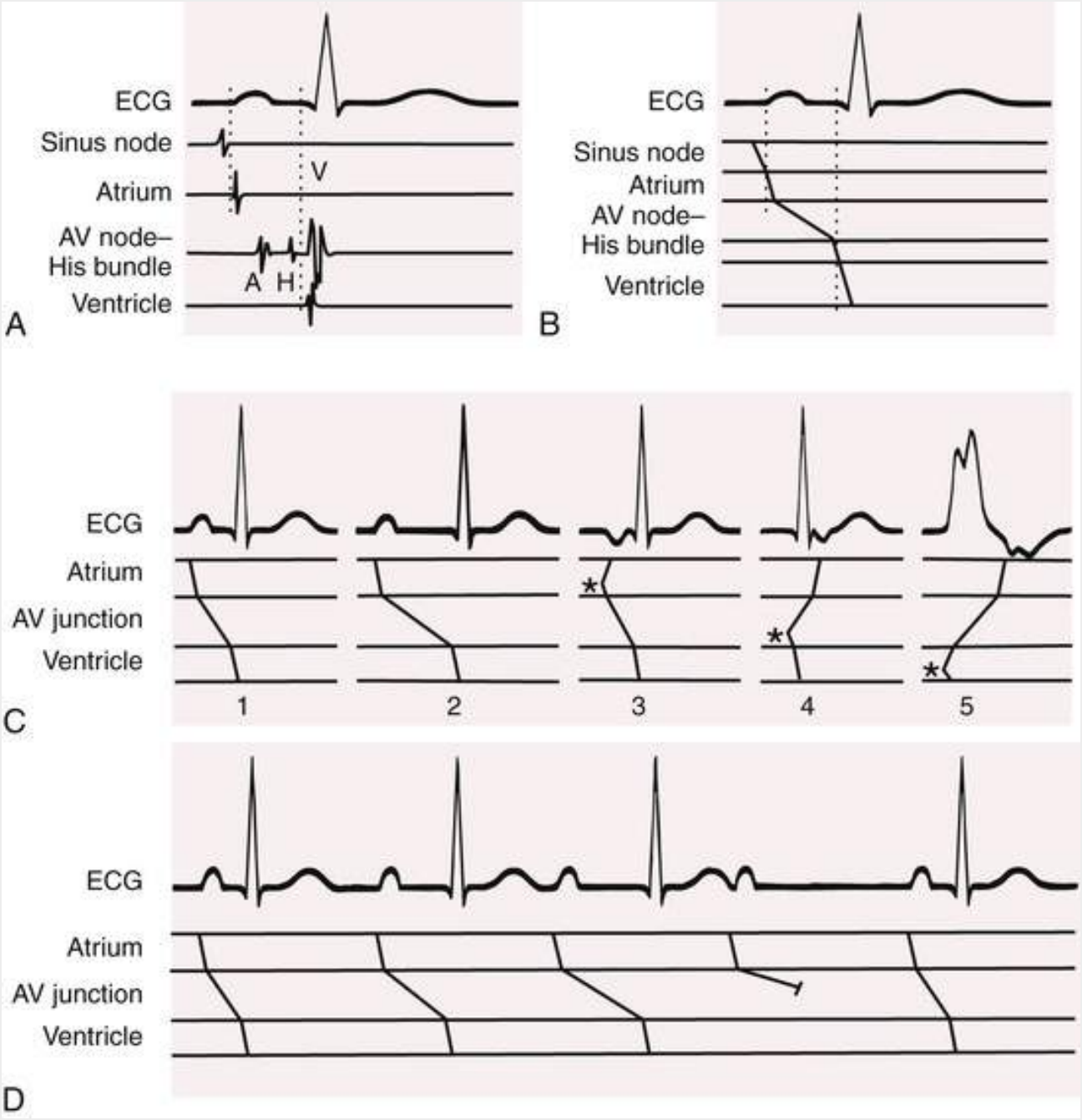


FIGURE 35.3 Intracardiac signals and ladder diagrams. **A,** A single beat is shown with accompanying intracardiac signals from the sinus node, right atrium, atrioventricular (AV) nodal and His bundle regions, and right ventricle. **B,** The same beat is shown with the accompanying ladder diagram below. Cardiac regions have been divided into tiers separated by horizontal lines. Vertical *dotted lines* denote onset of the P wave and QRS complexes. Note the relatively steep lines (rapid conduction through the atrium, His bundle, and ventricular muscle) and more gently sloping lines as the impulse traverses the sinus and AV nodes (signifying slow conduction). **C,** Several different situations are depicted with accompanying explanatory ladder diagrams. Beat 1 is normal, as in **B**; beat 2 shows first-degree AV delay, with the more gradual slope than normal in the AV nodal tier signifying very slow conduction in this region. In beat 3 an atrial premature complex is shown (starting in the atrial tier at the *asterisk*) and is producing an inverted P wave on the ECG. In beat 4 an ectopic impulse arises in the His bundle (*asterisk*) and propagates to the ventricle, as well as retrogradely through the AV node to the atrium. In beat 5 a ventricular ectopic complex (*asterisk*) conducts retrogradely through the His bundle and AV node and eventually to the atrium. **D,** Wenckebach AV cycle (type I second-degree block). As the PR interval progressively increases from left to right in the figure, the slope of the line in the AV nodal region is progressively less steep until it fails to propagate at all after the fourth P wave (small line perpendicular to the sloping AV nodal conduction line), after which the cycle repeats. *A,* Atrial recording; *H,* His recording; *V,* ventricular recording.

Additional Tests

Most patients have only occasional episodes of arrhythmia and spend most of the time in their baseline rhythm (e.g., sinus, AF). The ECG during the patient's resting rhythm can provide clues about the presence of a substrate for arrhythmia (i.e., structural or physiologic abnormalities from which arrhythmias can arise). Several of these abnormalities are shown in **Fig. 35.4**. Recently, the common finding on the ECG of early repolarization (in the lateral precordial and inferior leads) has been observed in some patients with primary ventricular fibrillation (VF) (i.e., without identifiable structural heart disease) (**see Chapter 39**). In most patients with SVT, except those with Wolff-Parkinson-White (WPW) syndrome, findings on the resting ECG are normal. This is also true for many patients with ventricular tachyarrhythmias. Thus, although it is capable of showing an abnormality with possible arrhythmic implications, the resting ECG is not a very sensitive tool. In light of this, the following additional tests can be used to evaluate patients who have cardiac arrhythmias. The physician's choice of which test to use depends on the clinical circumstances. For example, a patient with multiple daily episodes of presyncope is likely to have an event recorded on a 24-hour ambulatory electrocardiographic (Holter) monitor, whereas in a patient who complains of infrequent exercise-induced palpitations, exercise stress testing may be more likely to provide a diagnosis.

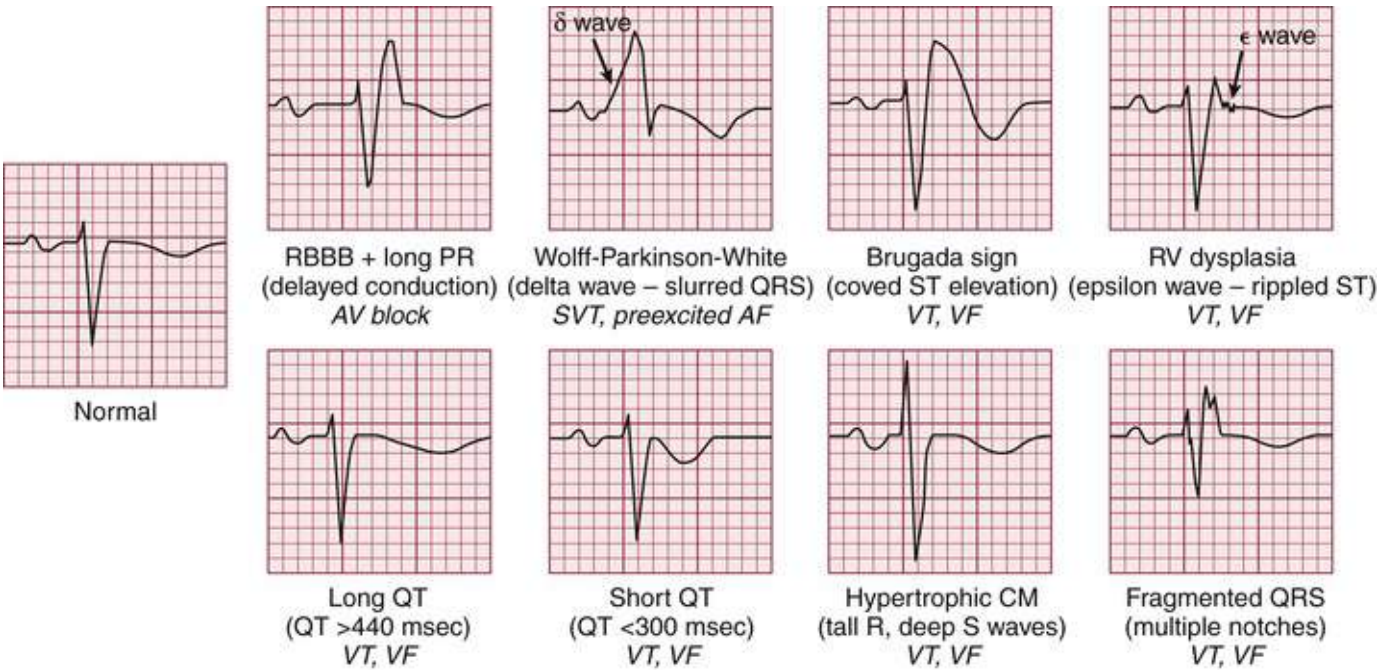


FIGURE 35.4 Electrocardiographic abnormalities in resting rhythm that suggest potential for arrhythmia. Lead V_1 is shown in each example; a normal complex is presented at *left* for reference. *CM,* Cardiomyopathy; *RBBB,* right bundle branch block; *RV,* right ventricular.

Exercise Testing

Exercise can induce various types of supraventricular and ventricular tachyarrhythmias and, infrequently, bradyarrhythmias (**see Chapter 13**). Ventricular ectopy develops in approximately one third of normal individuals in response to exercise testing. Ectopy is more likely to occur at faster heart rates, as occasional PVCs of constant morphology or even pairs of PVCs, and is often not reproducible from one stress test to the next. Three to six beats of nonsustained VT can occur in normal patients, especially elderly persons, and its occurrence neither implicates ischemia or other forms of heart disease nor predicts increased cardiovascular morbidity or mortality. PVCs are often more common during exercise

than at rest and increase in frequency with age. A persistent elevation in heart rate after the end of exercise (delay in return to baseline) is associated with a worse cardiovascular prognosis, as is a rapid resting heart rate.

Premature ventricular complexes develop in approximately 50% of patients with coronary artery disease in response to exercise testing and do so at lower heart rates (<130 beats/min) than in normal individuals, and often in recovery. Frequent (>7 PVCs/min) or complex ectopy is associated with a worse prognosis. Exercise reproduces sustained VT or VF in less than 10% of patients with spontaneous VT or VF late after myocardial infarction (MI), and these patients have a worse prognosis. The relationship of exercise to ventricular arrhythmia in patients with structurally normal hearts and no primary electrical disease has no prognostic implications.

Patients who have symptoms consistent with an arrhythmia induced by exercise (e.g., syncope, sustained palpitations) should be considered for stress testing. Stress testing may be indicated to provoke supraventricular and ventricular arrhythmias, to determine the relationship of the arrhythmia to activity, to aid in choosing antiarrhythmic therapy and uncovering proarrhythmic responses, and possibly to provide some insight into the mechanism of the tachycardia. The test can be performed safely; however, prolonged ambulatory recording is more sensitive than exercise testing in detecting most arrhythmias. Because either technique can uncover serious arrhythmias that the other technique misses, both examinations may be indicated for selected patients. Stress testing is frequently useful in patients with long-QT syndrome and catecholaminergic monomorphic and polymorphic VT[5] (**see Chapters 13 and 33**).

In-Hospital Electrocardiographic Recording

Electrocardiographic monitoring systems are used in increasing proportions of inpatients regardless of history or suspicion of arrhythmias. These systems can provide valuable information about rhythm abnormalities, including mode of onset and termination, and allow prompt acquisition of a full 12-lead ECG for more detail. Telemetry can disclose intermittent heart block in a patient with presyncope that may warrant consideration of pacemaker implantation or reveal nonsustained VT in a patient with previous MI and left ventricular dysfunction and prompt an electrophysiology study for further assessment of risk. Although telemetry is helpful in many cases, it can be misleading: artifact can simulate VT or VF, heart block, or asystole. Careful scrutiny is necessary to avoid unnecessary tests and procedures in patients with these artifactual arrhythmias (**Fig. 35.5**).

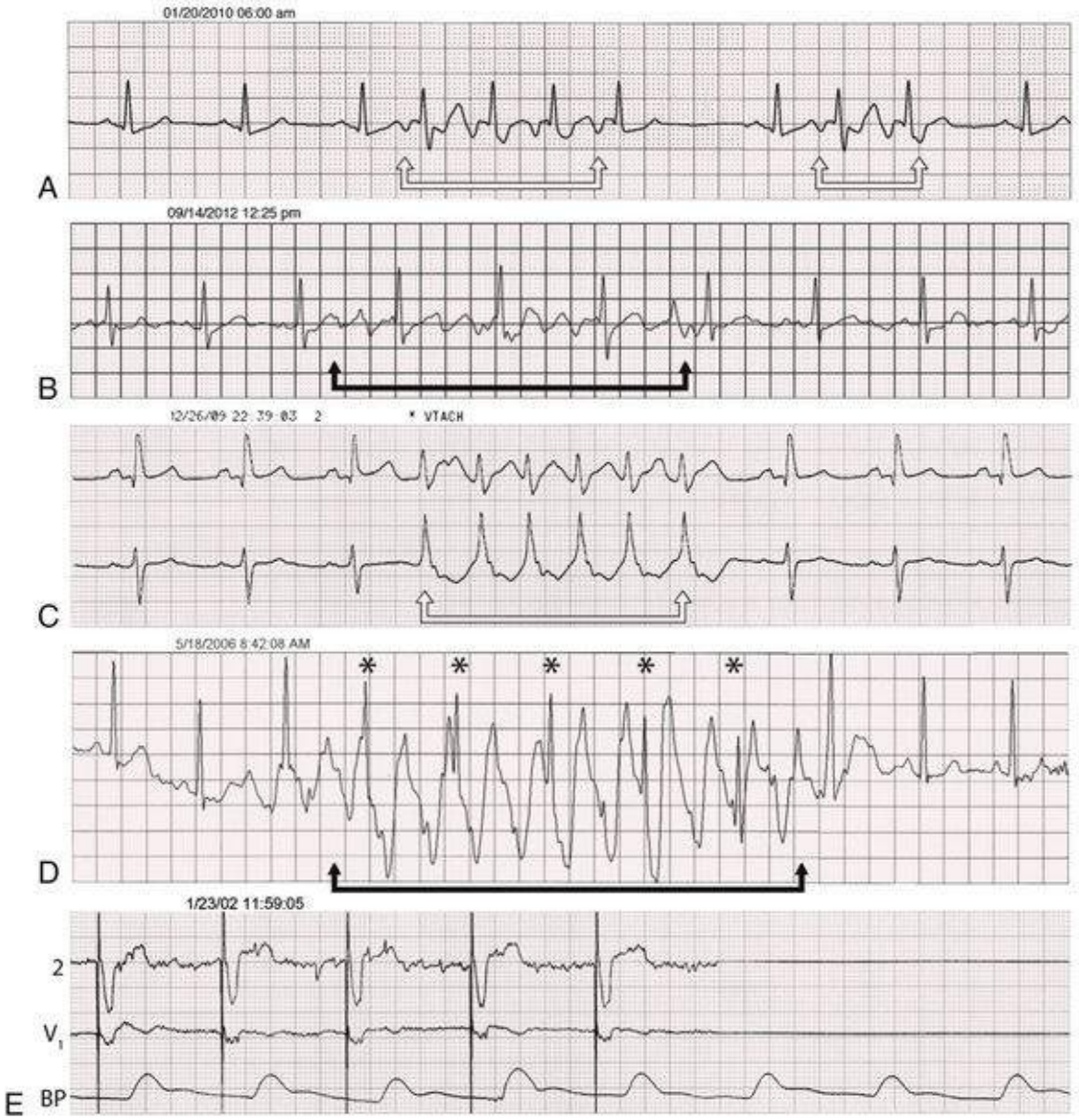


FIGURE 35.5 Electrocardiographic events and artifacts. **A,** Sinus rhythm punctuated by short episodes of atrial tachycardia with a more rapid ventricular rate (between the *white arrows*). **B,** Pseudo–atrial arrhythmia. Sinus rhythm is present throughout (no variation in the R-R interval) despite the appearance of a short episode of atrial flutter or fibrillation (between the *black arrows*). **C,** Nonsustained VT (between the *white arrows*) with wide rapid QRS complexes not preceded by a P wave and seen in two monitor leads. **D,** Pseudo-VT. Despite the appearance of VT (between the *black arrows*), sinus rhythm is present throughout (including complexes indicated by *asterisks*). **E,** Pseudo–pacemaker failure. After the first five paced complexes, the ECG is flat in *both* monitor leads, thus suggesting failure of pacemaker output; however, the pulse contour on the blood pressure (BP) tracing indicates that the heart is still contracting and the pacemaker is still working whereas the ECG monitor is not.

Long-Term Electrocardiographic Recording

Prolonged electrocardiographic recording in patients engaged in normal daily activities is the most useful noninvasive method to document and quantitate the frequency and complexity of an arrhythmia, to correlate the arrhythmia with the patient's symptoms, and to evaluate the effect of antiarrhythmic therapy on spontaneous arrhythmia. For example, recording normal sinus rhythm during the patient's typical symptomatic episode effectively excludes cardiac arrhythmia as a cause.

Ambulatory Electrocardiographic (Holter) Recording

Continuous electrocardiographic recorders represent the traditional Holter monitor and digitally record

three or more electrocardiographic channels for 24 to 48 hours. Computers scan the recording media, with human oversight, to provide a report with snapshot recordings of symptomatic events and other important findings (asymptomatic arrhythmias, ST-segment changes). From 25% to 50% of patients experience a complaint during a 24-hour recording; in 2% to 15% the complaint is caused by an arrhythmia (**Fig. 35.6**). The ability to correlate symptoms temporally with abnormalities on the ECG is one of the strengths of this technique.

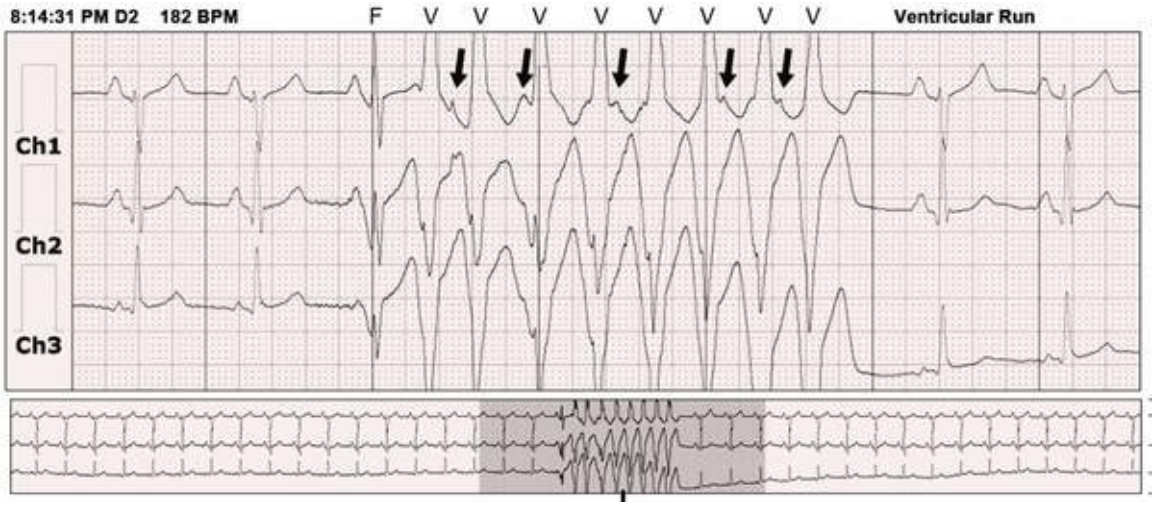


FIGURE 35.6 Long-term electrocardiographic recording in a patient with palpitations. A three-channel monitor shows sinus rhythm followed by nine wide QRS complexes of VT (labeled "V"); the complex that precedes these is a fusion between the normal complex and wide ("F"). *Arrows* indicate retrograde P waves during tachycardia. The presence of fewer P waves than QRS complexes and a fusion complex at the outset confirm the diagnosis of VT (which correlated with the patient's palpitations).

Significant rhythm disturbances are uncommon in healthy young persons. Sinus bradycardia with heart rates of 35 to 40 beats/min, sinus arrhythmia with pauses exceeding 3 seconds, sinoatrial exit block, type I (Wenckebach) second-degree AV block (often during sleep), wandering atrial pacemaker, junctional escape complexes, and premature atrial complexes and PVCs can be observed and are not necessarily abnormal. Frequent and complex atrial and ventricular rhythm disturbances are less frequently observed, however, and type II second-degree AV conduction disturbances (**see Chapter 40**) are not recorded in normal patients. Elderly patients have a higher prevalence of arrhythmias, some of which may be responsible for neurologic symptoms (**Fig. 35.7**; **see Chapters 88 and 97**). It is worth repeating that the long-term prognosis of even frequent and complex PVCs in asymptomatic healthy patients is very good, without an increased risk for death. However, frequent PVCs (>15% of the total) have been shown to produce a cardiomyopathy and heart failure in some people, which can be reversed following elimination of the PVCs.

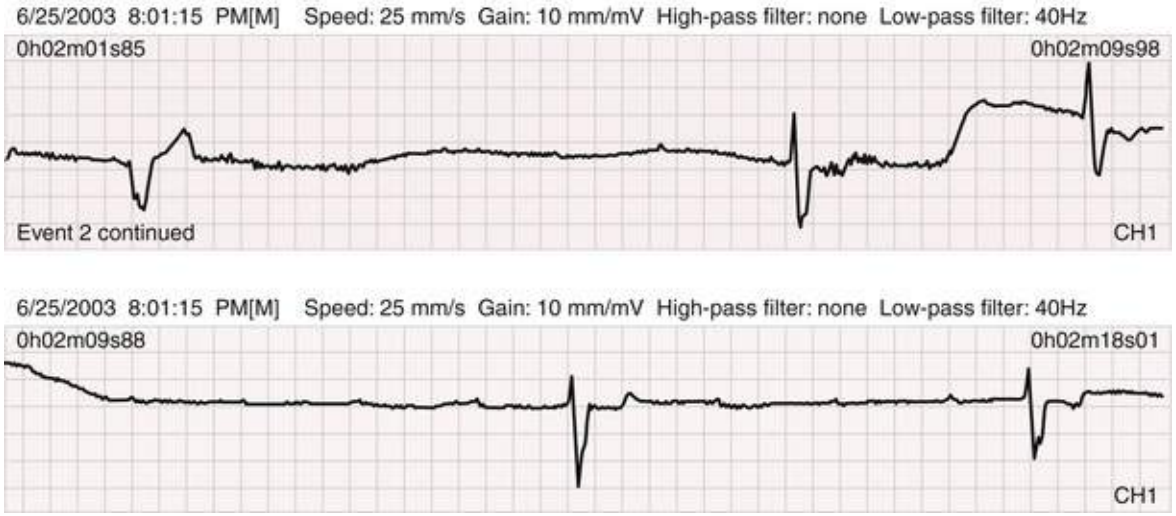


FIGURE 35.7 Continuous electrocardiographic recording from a patient-activated event monitor during an episode of lightheadedness. Sinus rhythm at 75 beats/min with sudden AV block is present with pauses of longer than 4 seconds, and in the *bottom strip* there is an effective heart rate of approximately 8 beats/min.

Most patients with ischemic heart disease, particularly after MI (**see Chapters 58 to 60**), exhibit PVCs when they are monitored for 24 hours. The frequency of PVCs progressively increases during the first several weeks and then decreases at about 6 months after infarction. Frequent and complex PVCs are associated with a twofold to fivefold increased risk for cardiac or sudden death in patients after MI, but treating these PVCs may not improve the prognosis. The Cardiac Arrhythmia Suppression Trial (CAST) showed that PVCs identified patients at increased risk for sudden death, but that successful suppression of PVCs with flecainide, encainide, or moricizine was associated with increased mortality compared with placebo. Recent data indicate that ablation of PVCs after MI may improve previously depressed ventricular function.

Long-term recording of the ECG has also exposed potentially serious arrhythmias and complex ventricular ectopy in patients with left ventricular hypertrophy, as well as in those with hypertrophic, dilated, and ischemic cardiomyopathy; in those with mitral valve prolapse (**see Chapter 69**); in those with otherwise unexplained syncope (**Chapter 43**) or transient vague cerebrovascular symptoms or stroke; and in those with conduction disturbances, sinus node dysfunction, bradycardia-tachycardia syndrome, WPW syndrome (**Chapter 37**), and pacemaker malfunction (**Chapter 41**). It has been shown that asymptomatic AF occurs far more often than symptomatic episodes in patients with AF.

Variations of Holter recording have been used for particular applications. Some monitoring systems are able to reconstruct a full 12-lead ECG from a seven-electrode recording system. This is especially useful in trying to document the electrocardiographic morphology of VT before an ablation procedure or a consistent morphology of PVCs that may arise from an ablatable focus of VT or VF. Most Holter recording and analysis systems can place a clearly recognizable deflection on the recording when a pacemaker stimulus is detected, facilitating diagnosis of potential pacemaker malfunction. On occasion, artifacts on the ECG can mimic bradycardias or tachycardias and lead to erroneous therapy. Finally, most systems can also provide heart rate variability and QT data (see later). Use of these systems for detection of myocardial ischemia (ST-segment analysis) has yielded mixed results (in both specificity and sensitivity).

Event Recording

In many patients, the 24- or 48-hour snapshot provided by the Holter recording is incapable of

documenting the cause of the patient's symptoms. Longer-term monitoring, such as with an event recorder, is necessary in these cases, which occur frequently. These devices come in various forms and are kept by the patient for 30 days. During that time, digital recordings can be made during symptomatic episodes and can be transmitted to a receiving station by telephone at the patient's convenience (**see Fig. 35.7**). Some of these recorders store more than 30 seconds of the ECG before the patient activates the recording. These loop recorders record continuously, but only a small window of time is present in memory at any moment; when the patient presses the event button, the current window is frozen while the device continues recording for another 30 to 60 seconds, depending on how it is configured. Event recorders are highly effective in documenting infrequent events, but the quality of the recordings is more subject to motion artifact than with Holter recorders, and usually only one channel can be recorded. With most systems, the device automatically begins recording the rhythm when the heart rate increases or decreases outside preset parameters. Some systems incorporate cell phone technology that automatically notifies a central monitoring facility when certain conditions are met (e.g., extreme bradycardia or tachycardia). This can significantly shorten the time between occurrence and effective treatment of serious arrhythmias (**see Chapter 32**).

Most currently available pacemakers and implantable defibrillators are capable of providing Holter-like data when premature beats or tachycardia episodes occur and can store electrograms of these events from the implanted leads[6] (**Fig. 35.8**). The device can then be interrogated and the electrograms printed for analysis. Many implanted device systems incorporate remote monitoring so that if symptoms develop, patients can perform device interrogation at home; the information is then transmitted via the Internet to the physician's office and thus enables more prompt diagnosis and treatment than if the patient had to schedule an outpatient visit. For serious rhythm disturbances, such as sustained VT, this information can lead to timely changes in therapy; in other cases, such as incidentally discovered AF, therapeutic implications (e.g., initiation of anticoagulation) are less clear.

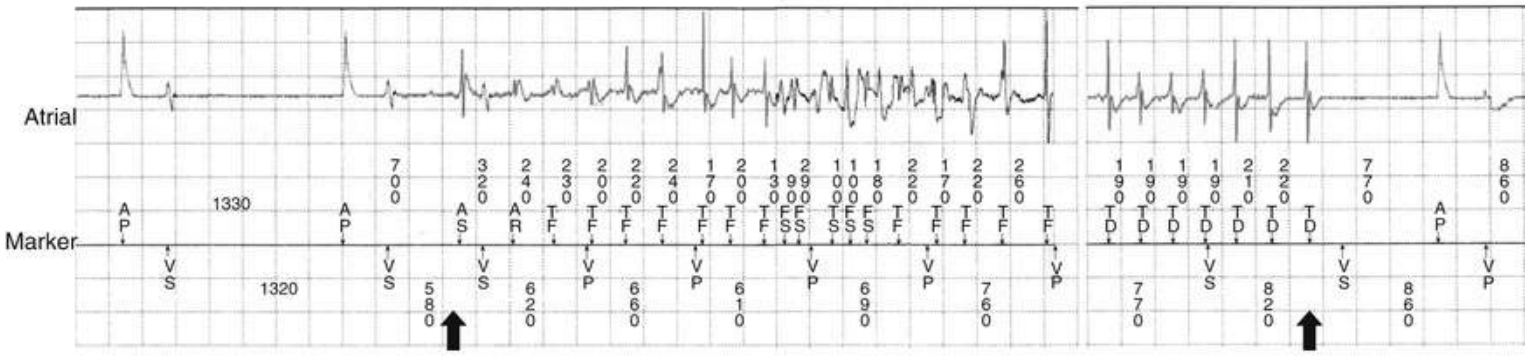


FIGURE 35.8 Recordings from a pacemaker log showing an episode of AF at its onset (*left arrow*) and termination (*right arrow*), more than 4 days later. Two atrial paced complexes ("AP") are followed by an episode of AF characterized by rapid erratic deflections. When the episode ends, atrial pacing resumes. The patient was unaware of the episode, but when discovered at a routine office follow-up visit, this information prompted initiation of anticoagulation in light of an elevated stroke risk and newly discovered AF.

Implantable Loop Recorder

For patients with very infrequent symptoms, neither Holter recorders nor 30-day event recorders may yield diagnostic information. In such patients an implantable loop recorder can be used. These devices (smaller than a pack of chewing gum) are inserted under the skin at about the level of the anterior second

rib on the left chest and are activated by passing a special magnet over the device. It is capable of recording several minutes of a single channel of the ECG before and after a symptomatic event and can have a service life of 2 to 3 years. Both P waves and QRS complexes can usually be identified. The devices can be configured to store patient-activated episodes, automatically activated recordings (heart rate outside preset parameters), or a combination of these. In patients with unexplained syncope, a diagnosis can be made in up to 80% by long-term monitoring, many only after a long period (up to 18 months). Detection of AF as a possible cause of cerebral symptoms has become a common indication for implantable monitors.[7]

Various additional noninvasive tests have been developed primarily to assess the risk for arrhythmic death in different groups of patients; although each has some applicability, none has enjoyed widespread use because of suboptimal sensitivity and specificity. Several of these tests are discussed in the following sections.

Heart Rate Variability

Heart rate variability is used to evaluate vagal and sympathetic influences on the sinus node (inferring that the same activity is also occurring in the ventricles) and to identify patients at risk for a cardiovascular event or death. Frequency domain analysis resolves parasympathetic and sympathetic influences better than time domain analysis does, but both types of analysis are useful. R-R variability predicts all-cause mortality, as well as left ventricular ejection fraction or nonsustained VT in patients after MI, and can be added to other measures of risk to enhance predictive accuracy.[8] Similar results have been obtained in patients with dilated cardiomyopathy (**see Chapters 25 and 77**). High-frequency components of R-R interval variability reflect tonic vagal activity. Reduced R-R interval variability, a marker of increased risk, indicates loss or reduction of the physiologic periodic sinus node fluctuations, which has many potential causes and may not necessarily represent a significant shift in autonomic modulation. New indices of heart rate variability are continually being evaluated. Even the simple measure of resting heart rate has been shown to be an independent cardiovascular risk factor (although a target "safe" heart rate has not been established), as has the heart rate obtained during and after exercise.

Heart Rate Turbulence

Heart rate turbulence is an index of changes in the sinus discharge rate after a PVC that is followed by a compensatory pause.[9] In normal individuals the sinus rate initially accelerates and then slows; this phenomenon is blunted or absent in patients with various heart diseases. Heart rate turbulence is a measure of reflex vagal control of the heart, whereas heart rate variability is more indicative of overall vagal tone. Abnormal heart rate turbulence is a strong independent predictor of mortality in patients with coronary artery disease and dilated cardiomyopathy; abnormal indices in some patients can be improved or normalized after treatment with beta blockers and statin drugs.

QRS and QT Dispersion and T Wave Abnormalities

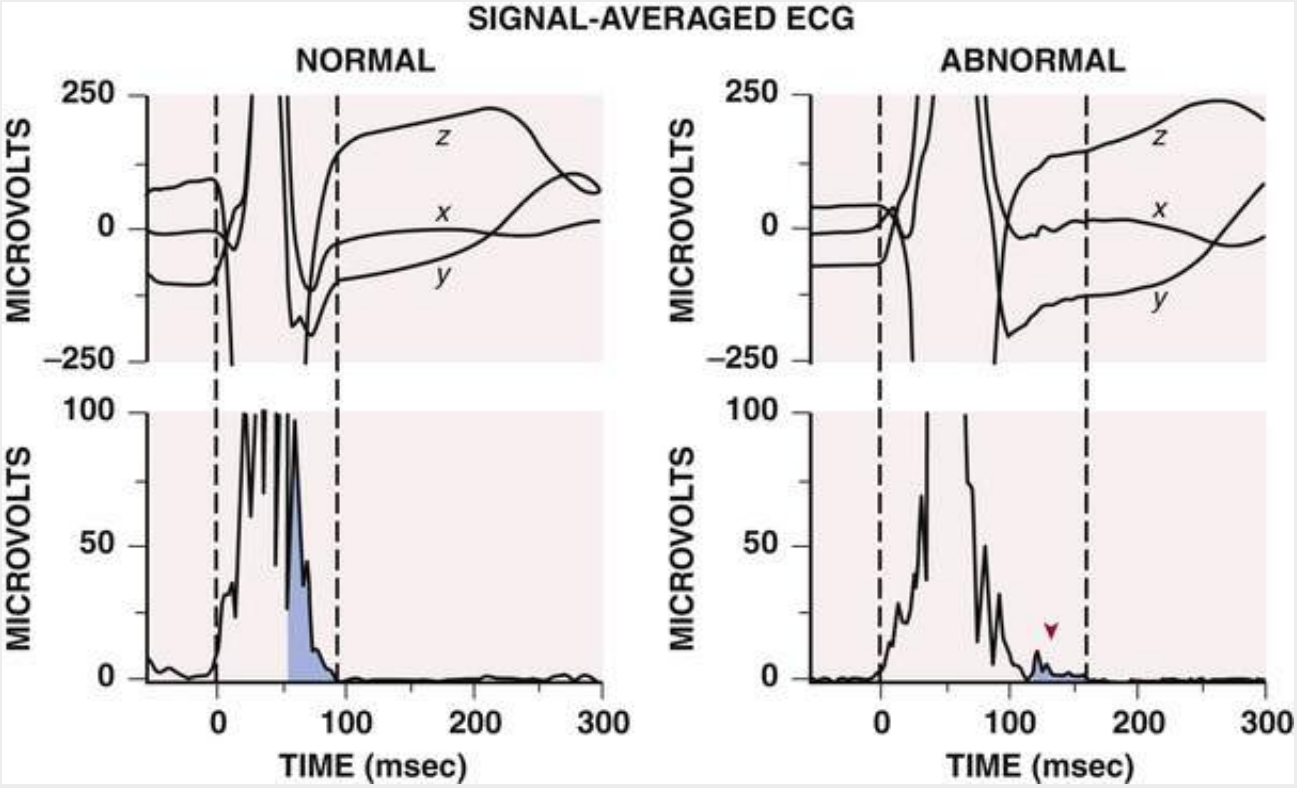
Heterogeneity in refractoriness and conduction velocity is a hallmark of reentrant arrhythmias. One index of the heterogeneity of ventricular conduction is derived from the QRS complex duration on surface ECG leads, while heterogeneity of ventricular refractoriness can be found in differences in the length of the QT interval. Dispersion indices usually measure the maximum difference (shortest to longest) in the intervals of interest, which may be adjusted for heart rate and the number of leads sampled (e.g., when the T wave is flat in some leads for QT dispersion). Abnormally high QRS and QT dispersion have been correlated

with risk for overall mortality and arrhythmic death in patients with various disorders, although the results are not consistent. Different techniques exist for determining dispersion (including automated algorithms), and the results of one study are often difficult to compare with those of another; in addition, the tests are sensitive to a variety of factors, including age, time of day, season of year, and even body position. More recently, T wave morphology and assessment of the interval from T wave peak to end in lead V_5 have been correlated with increased sudden death risk.[10] Overall, assessments of these indices have not gained popularity as useful clinical tools. Other details of the QRS complex, such as fragmentation of the conducted complex[11] (multiple notches in the QRS; **see Fig. 35.4**) and the simple width of PVCs,[12] have been associated with increased cardiovascular risk.

Signal-Averaged Electrocardiography and Late Potentials

Signal averaging is a method that improves the signal-to-noise ratio when the signals are recurrent and the noise is random. In conjunction with appropriate filtering and other methods of noise reduction, signal averaging can detect cardiac signals of a few microvolts in amplitude and reduce noise amplitude, such as muscle potentials, which are typically 5 to 25 mV, to less than 1 mV. With this method, very-low-amplitude electrical potentials generated by the sinus and AV nodes, His bundle, and bundle branches can be detected at the body surface.

One constituent of reentrant ventricular arrhythmias in patients with previous myocardial damage is slow conduction. Direct cardiac mapping techniques can record the myocardial activation from damaged areas that occurs after the end of the surface electrocardiographic QRS complex during sinus rhythm. These delayed signals have a very low amplitude that cannot be discerned by routine electrocardiography and correspond to the delayed and fragmented conduction in the ventricles recorded with direct mapping techniques (**eFig. 35.1**). Signal averaging has been applied clinically most often to detect such late ventricular potentials of 1 to 25 µV. Criteria for late potentials are the following: (1) filtered QRS complex duration longer than 114 to 120 milliseconds, (2) less than 20 µV of the root mean square signal amplitude in the last 40 milliseconds of the filtered QRS complex, and (3) terminal filtered QRS complex remaining below 40 µV for longer than 39 milliseconds. Such late potentials have been recorded in more than 70% of patients with spontaneous sustained and inducible VT after MI, but in only 0% to 6% of normal volunteers. Patients with bundle branch block or paced ventricular rhythms already have wide QRS complexes, thus rendering the technique less useful in these cases.

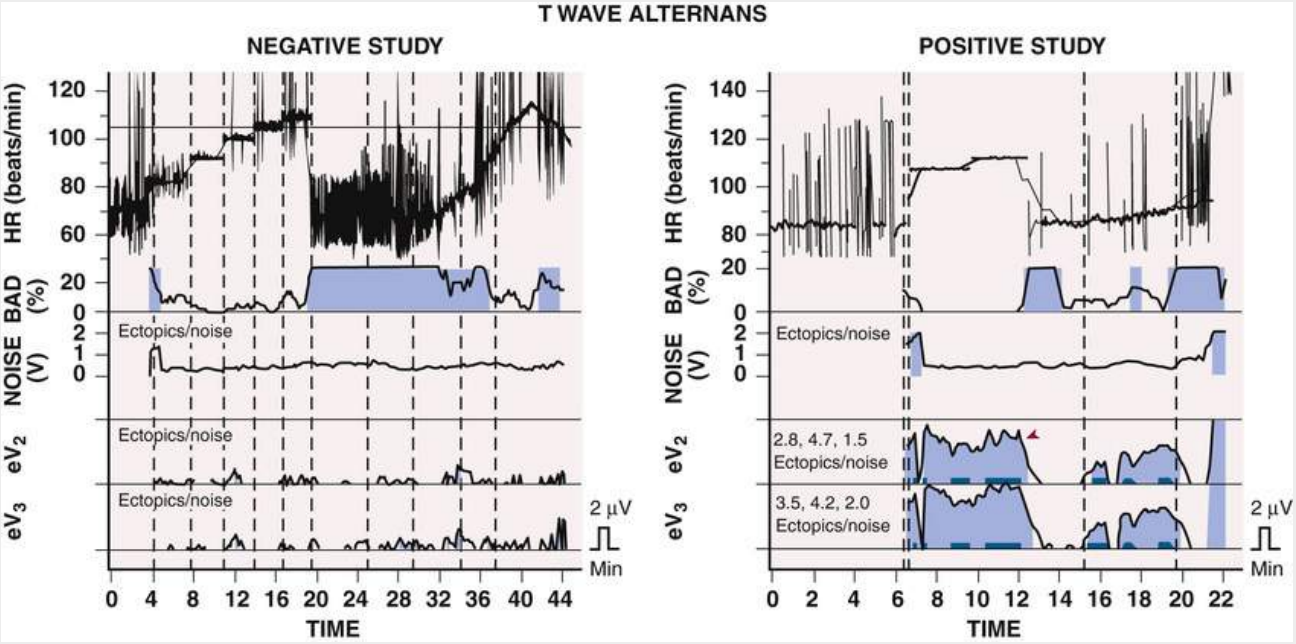


EFIGURE 35.1 Signal-averaged ECG. Normal **(left)** and abnormal **(right)** results are shown from a patient with previous myocardial infarction and VT. **Bottom panels,** *Shaded blue areas* at the end of each tracing represent the voltage content of the last 40 milliseconds of the filtered QRS integral. The small shaded area (*red arrowhead*) in the abnormal study denotes prolonged, slow conduction and suggests the potential for reentrant ventricular arrhythmias.

Late potentials have also been recorded in patients with VT not related to ischemia, such as in those with dilated cardiomyopathy. The presence of a late potential is a sensitive but not specific marker of arrhythmic risk, and therefore its prognostic use is limited. In specific situations it can be helpful, as in a patient suspected of having arrhythmogenic right ventricular cardiomyopathy.

T Wave Alternans

Beat-to-beat alternation in the amplitude or morphology of the electrocardiographic recording of ventricular repolarization, the ST segment and T wave, has been found in conditions favoring the development of ventricular tachyarrhythmias, such as ischemia and long-QT syndrome, and in patients with ventricular arrhythmias. The electrophysiologic basis appears to be the alternation of repolarization of ventricular myocytes. In the presence of a long QT interval, the cellular basis of alternation may be beat-to-beat repolarization changes in midmyocardial cells. Whether this mechanism applies to different disease states is not known. Detection of T wave alternans requires exercise or atrial pacing to achieve a heart rate of 100 to 120 beats/min with relatively little atrial or ventricular ectopic activity. The test is less useful in patients with a wide QRS complex (>120 msec). A positive T wave alternans test result (**eFig. 35.2**) has been associated with a worse arrhythmic prognosis in various disorders, including ischemic heart disease and nonischemic cardiomyopathy. Although the predictive value of a positive test result varies greatly, depending on the population studied, a negative test result strongly predicts freedom from VT and VF in all groups studied thus far, at least during a short follow-up period. T wave alternans may represent a fundamental marker of an electrically unstable myocardium prone to the development of VT or VF, but because of its relatively minor incremental value in defining arrhythmic risk, it is infrequently used at present.



EFIGURE 35.2 T wave alternans. Reports of T wave alternans analysis from two patients are shown and display the heart rate in beats per minute (HR BPM), proportion of beats rejected from analysis (% BAD), ECG noise level (in microvolts), and selected precordial leads (eV_2 and eV_3) as a function of time. **Left panel,** Records from a patient with no structural heart disease; the amplitude of T wave alternans was minimal. **Right panel,** Records from a patient hospitalized for sustained VT after myocardial infarction show T wave alternans (*blue shaded area, arrowhead*).

Baroreceptor Reflex Sensitivity Testing

Acute blood pressure elevation triggers a baroreceptor reflex that augments vagal tone to the heart and slows the sinus rate. The increase in sinus cycle length per millimeter mercury increase in systolic blood pressure is a measure of the sensitivity of the baroreceptor reflex and, when reduced, can identify patients susceptible to the development of VT and VF. The mechanism of the reduction in baroreceptor reflex sensitivity is uncertain. Although this test may be useful to identify patients at risk for developing a serious ventricular arrhythmia after MI, it is rarely used.

Body Surface Mapping

Isopotential body surface maps are used to provide a complete picture of the effects of currents from the heart on the body surface. The potential distributions are represented by contour lines of equal potential, and each distribution is displayed instant by instant throughout activation, recovery, or both.

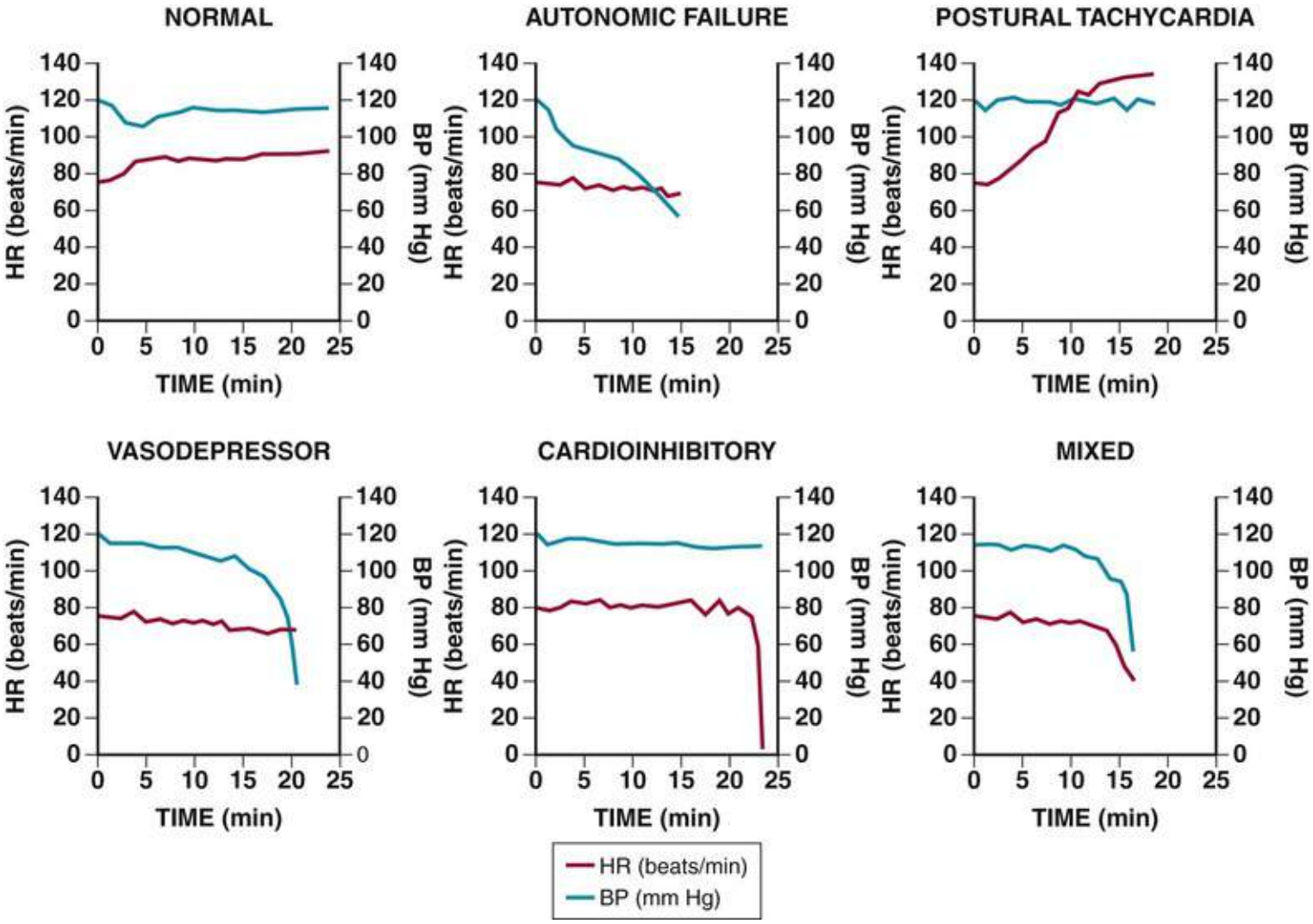
Body surface maps have been used clinically to localize and size areas of myocardial ischemia, to localize ectopic foci or accessory pathways, to differentiate aberrant supraventricular conduction from ventricular origin, to recognize patients at risk for the development of arrhythmias, and possibly to understand the mechanisms involved. Although these procedures are of interest, their clinical usefulness has not yet been established. In addition, the technique is cumbersome and the analysis complex.

Electrocardiographic Imaging

Another promising technology is electrocardiographic imaging, in which cardiac electrical activity recorded at the skin surface is spatially integrated with imaging data (currently, cardiac computed tomography scanning). Using complex mathematical processing of electrical data collected from 224 electrodes on the skin surface, this technique can plot or project atrial and ventricular electrical activity on an epicardial “shell” of the patient's own heart and thereby follow the course of activation or repolarization during sinus rhythm or an arrhythmia. Clinical experience is limited thus far, but both SVTs and VTs (especially focal) have been localized with this method.[13]

Upright Tilt-Table Testing

The tilt-table test is used to identify patients who have a vasodepressor or cardioinhibitory response as a cause of syncope (**see Chapter 43**). Patients are placed on a tilt table in the supine position and tilted upright to a maximum of 60 to 80 degrees for 20 to 45 minutes or longer if necessary (**eFig. 35.3**). Isoproterenol, administered as a bolus or infusion, may provoke syncope in patients whose initial upright tilt-table test result shows no abnormalities or, after a few minutes of tilt, may shorten the time needed to produce a positive response on the test. An initial intravenous isoproterenol dose of 1 µg/min can be increased in 0.5-µg/min steps until symptoms occur or a maximum of 4 µg/min is given. Isoproterenol induces a vasodepressor response in upright susceptible patients (decrease in heart rate and blood pressure along with near-syncope or syncope). Tilt-table test results are positive in two thirds to three fourths of patients susceptible to neurally mediated syncope and are reproducible in approximately 80% but have a 10% to 15% false-positive response rate. A positive test result is more meaningful when it reproduces symptoms that have occurred spontaneously. Positive responses can be divided into cardioinhibitory, vasodepressor, and mixed categories. Therapy with beta blockers, disopyramide, theophylline, selective serotonin reuptake inhibitors, midodrine, fludrocortisone, salt loading, and thigh-high support stockings, alone or in combination, has been reported to be successful but not with reliable reproducibility. Tilt training, in which the patient leans against a wall for prolonged periods to increase tolerance to this body position, may help, as may isometric muscle flexing to abort or lessen an episode. Permanent pacing has been useful in a subset of patients with significant bradycardia provoked on tilt testing.



EFIGURE 35.3 Head-up tilt-table testing. Responses to tilt-table testing are shown; heart rate (HR) and systolic blood pressure (BP) are plotted as time functions. **Top panels**, A normal response is an early, slight drop in BP with a compensatory increase in HR mediated by the autonomic nervous system. With autonomic dysfunction, a progressive fall in BP is not counteracted by an increase in HR. In postural tachycardia syndrome, an exaggerated increase in HR is seen. **Bottom panels,** Findings with neurocardiogenic syncope. A pure vasodepressor response is a relatively sudden drop in BP without a marked change in HR, whereas a pure cardioinhibitory response shows a sudden decrease in HR without a change in BP. A mixed response shows decreases in both HR and BP.

A variant of the neurocardiogenic response, postural orthostatic tachycardia syndrome (POTS), is characterized by dramatic increases in heart rate during the first 10 minutes of tilt-table testing. POTS appears to be distinct from simple orthostatic hypotension, as well as from standard neurocardiogenic responses, and is thought to be caused by various forms of autonomic imbalance. Relief of symptoms has been effected with fludrocortisone, beta blockers, pyridostigmine, or combinations, although randomized controlled trials (RCTs) often show no consistent improvement with these drugs.

Esophageal Electrocardiography

Esophageal electrocardiography is a useful noninvasive technique for diagnosing arrhythmias. The esophagus is located immediately behind the left atrium, between the left and right pulmonary veins. An electrode in the lumen of the esophagus can record atrial potentials. Bipolar recording is superior to unipolar recording because far-field ventricular events can lead to possible diagnostic confusion with unipolar recording. In addition, atrial and occasionally ventricular pacing can be performed by means of

a catheter electrode inserted into the esophagus, and tachycardias can be initiated and terminated. Optimal electrode position for atrial pacing correlates with the patient's height and is within about 1 cm of the site at which the maximum amplitude of the atrial electrogram is recorded. When it is recorded simultaneously with the surface ECG, the esophageal atrial electrogram can be used to differentiate SVT with aberrancy from VT and to define the mechanism of SVTs. Complications of transesophageal recording and pacing are uncommon, but the technique is cumbersome and uncomfortable for most patients, and it is therefore infrequently used.

Invasive Electrophysiologic Studies

An invasive EPS involves introducing multipolar electrode catheters into the venous or arterial system and positioning them at various intracardiac or intrapericardial sites to record or stimulate cardiac electrical activity. Assessment of AV conduction at rest is done by positioning electrodes along the septal leaflet of the tricuspid valve and measuring the atrial-His interval (an estimate of AV nodal conduction time; normally, 60 to 125 milliseconds) and the His-ventricular (H-V) interval (a measure of infranodal conduction; normally, 35 to 55 milliseconds). The heart is stimulated from portions of the atria or ventricles and from the region of the His bundle, bundle branches, accessory pathways, and other structures. EP studies are performed *diagnostically* to provide information about the type of clinical rhythm disturbance and insight into its electrophysiologic mechanism. EPSs are used *therapeutically* to terminate a tachycardia by electrical stimulation or electroshock, to evaluate the effects of therapy by determining whether a particular intervention modifies or prevents electrical induction of a tachycardia or whether an electrical device properly senses and terminates an induced tachyarrhythmia, and to ablate myocardium involved in the tachycardia and prevent further episodes. EPSs have also been used prognostically to identify patients at risk for sudden cardiac death. The study can be helpful in patients with AV block, intraventricular conduction disturbance, sinus node dysfunction, tachycardia, and unexplained syncope or palpitations (**see Chapter 43**).

An EPS is usually effective at initiating VT and SVT when these tachyarrhythmias have occurred spontaneously. This enables the use of similar stimulation techniques after an intervention (e.g., drug therapy or catheter or surgical ablation) to assess the efficacy of treatment. However, false-negative responses (not finding a particular electrical abnormality known to be present) and false-positive responses (induction of a nonclinical arrhythmia) may complicate interpretation of the results because many lack reproducibility. Altered autonomic tone in a supine patient undergoing study, hemodynamic or ischemic influences, changing anatomy (e.g., new infarction) after the study, day-to-day variability, and the use of an artificial trigger (electrical stimulation) to induce the arrhythmia are several of many factors that can explain the occasional disparity between test results and spontaneous occurrence of arrhythmia. Overall, the diagnostic validity and reproducibility of these studies are good, and they are safe when performed by skilled clinical electrophysiologists.

Atrioventricular Block

In patients with AV block, the site of block usually dictates the clinical course of the patient and whether a pacemaker is needed (**see Chapter 40**). In general, the site of AV block can be determined from analysis of the regular ECG. When the site of block cannot be determined from such an analysis and when knowing the site of block is imperative for management of the patient, an invasive EPS is indicated. Candidates include symptomatic patients in whom His-Purkinje block is suspected but not established and patients

with AV block treated with a pacemaker who continue to be symptomatic and in whom a causal ventricular tachyarrhythmia is suspected. Possible candidates are those with second- or third-degree AV block, for whom information about the site of block or its mechanism may help direct therapy or assess prognosis, and patients suspected of having concealed His bundle extrasystoles. Patients with block in the His-Purkinje system become symptomatic because of periods of bradycardia or asystole and require pacemaker implantation more often than do patients who have AV nodal block. Type I (Wenckebach) AV block in older patients can have clinical implications similar to those for type II AV block. However, the results of EPS for evaluating the conduction system must be interpreted with caution. In rare cases the process of recording conduction intervals alters their values. For example, catheter pressure on the AV node or His bundle can cause prolongation of the atrial-His or H-V interval and could lead to erroneous diagnosis and therapy.

Intraventricular Conduction Disturbance

For patients with an intraventricular conduction disturbance, an EPS provides information about the duration of the H-V interval, which can be prolonged with a normal PR interval, or normal with a prolonged PR interval. A prolonged H-V interval (>55 msec) is associated with a greater likelihood for the development of complete AV block (but the rate of progression is slow, 2% to 3% annually) and for having structural disease and with higher mortality.[14] The finding of very long H-V intervals (>80 to 90 msec) identifies patients at increased risk for the development of AV block. The H-V interval has high specificity (approximately 80%) but low sensitivity (66%) for predicting the development of complete AV block. During an EPS, atrial pacing is used to uncover abnormal His-Purkinje conduction. A positive response is provocation of distal His block during 1 : 1 AV nodal conduction at rates of 135 beats/min or less. Again, sensitivity is low but specificity is high. Drug infusion, such as with procainamide or ajmaline, sometimes exposes abnormal His-Purkinje conduction (**Fig. 35.9**). Ajmaline (not available in the United States) can cause arrhythmias and should be used cautiously.

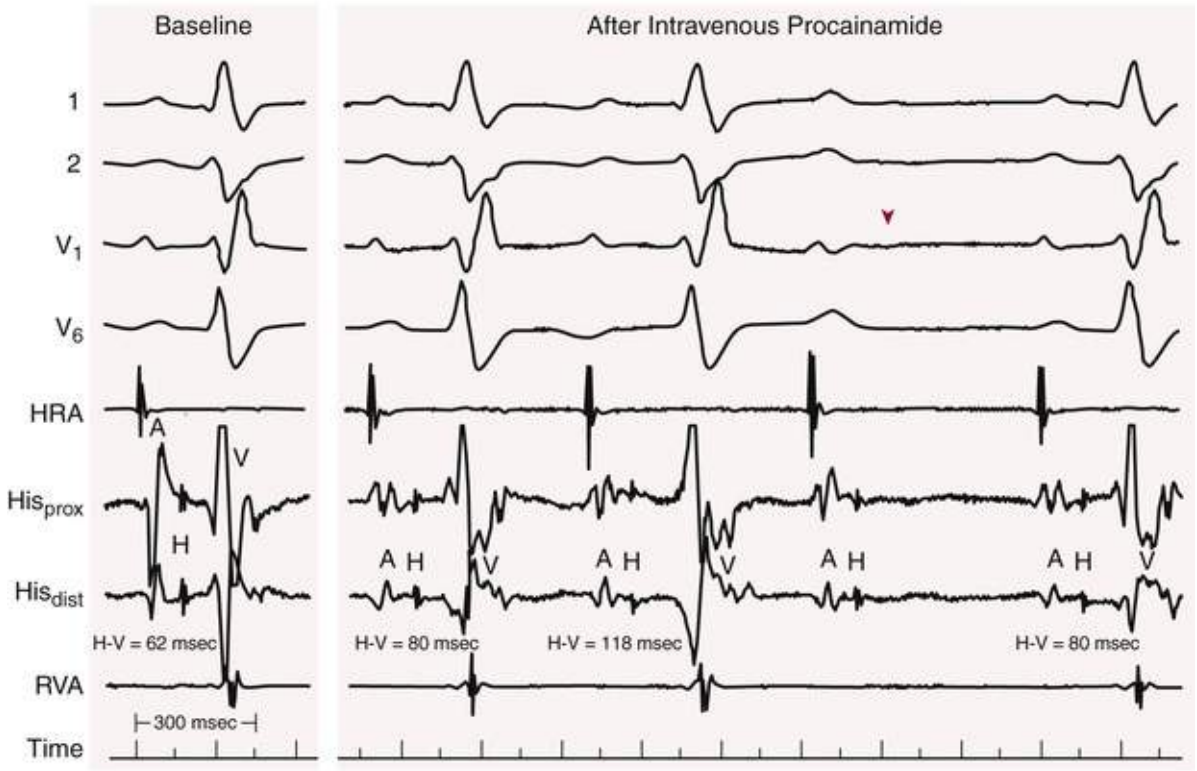


FIGURE 35.9 Testing the His-Purkinje system. A 43-year-old woman with sarcoid underwent EPS after a syncopal episode. Surface leads 1, 2, V_1, and V_6 are shown, with intracardiac recordings from catheters in the high right atrium (*HRA*), the proximal (His_{prox}) and distal (His_{dist}) electrode pairs of a catheter at the AV junction to record the His potential, and right ventricular apex (*RVA*). During baseline recording, the H-V interval is only slightly prolonged (62 milliseconds). After infusion of intravenous procainamide, the H-V interval is longer and an infra-His Wenckebach block is present. The *arrowhead* denotes the missing QRS complex caused by infra-His block. *A,* Atrial electrogram; *H,* His potential; *V,* ventricular electrogram.

An EPS is indicated in patients with symptoms (syncope or presyncope) that appear to be related to a bradyarrhythmia or tachyarrhythmia when no other cause of symptoms is found, including with prolonged ECG monitoring. For many of these patients, ventricular tachyarrhythmias rather than AV block can be the cause of their symptoms, with obvious therapeutic implications.

Sinus Node Dysfunction

Demonstration of slow sinus rates, sinus exit block, or sinus pauses on ECG temporally related to symptoms suggests a causal relationship and usually obviates the need for further diagnostic studies (**see Chapter 37**). Carotid sinus pressure that results in several seconds of complete asystole or AV block and reproduces the patient's usual symptoms exposes the presence of a hypersensitive carotid sinus reflex. Carotid sinus massage must be done cautiously; rarely it can precipitate a stroke. Neurohumoral agents, adenosine, or stress testing can be used to evaluate the effects of autonomic tone on sinus node automaticity and sinoatrial conduction time.

Sinus Node Recovery Time.

Sinus node recovery time (SNRT) is a technique that can be useful for evaluating sinus node function. The interval between the last paced high right atrial response and the first spontaneous (sinus) high right atrial response after termination of pacing is measured to determine SNRT. Because the spontaneous sinus rate influences SNRT, the value is corrected by subtracting the spontaneous sinus node cycle length

(before pacing) from the SNRT (**Fig. 35.10**). This value, the corrected SNRT (CSNRT), is generally shorter than 525 milliseconds. A prolonged CSNRT has been found in patients suspected of having sinus node dysfunction. After cessation of pacing, the first return sinus cycle can be normal but can be followed by secondary pauses (a strong indicator of sinus node dysfunction). It is important to evaluate AV node and His-Purkinje function in patients with sinus node dysfunction because many also exhibit impaired AV conduction.

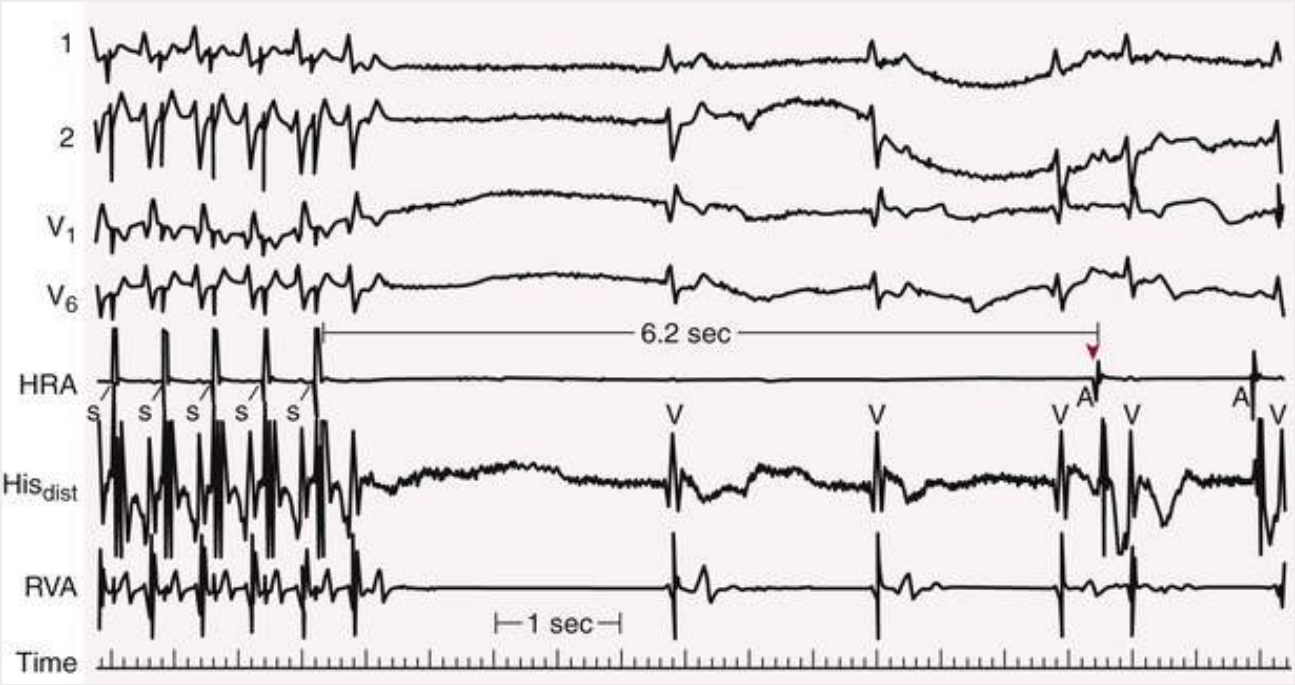


FIGURE 35.10 Abnormal sinus node function. Recordings are similar to those in Fig. 35.9. The last five complexes of a 1-minute burst of atrial pacing (*S*) at a cycle length of 400 milliseconds are shown, after which pacing is stopped. The sinus node does not spontaneously discharge (SNRT) until 6.2 seconds later (*arrowhead*). Three junctional escape beats occurred before this time. His_{dist}, Distal electrode pair; *HRA,* high right atrium; *RVA,* right ventricular apex.

Sinoatrial Conduction Time.

Sinoatrial conduction time (SACT) can be estimated by simple pacing techniques based on the assumptions that (1) conduction times into and out of the sinus node are equal, (2) no depression of sinus node automaticity occurs, and (3) the pacemaker site does not shift after premature stimulation. These assumptions can be erroneous, particularly in patients with sinus node dysfunction. The sensitivity of the SACT and SNRT tests is only approximately 50% for each test alone and 65% when combined. The specificity, combined, is approximately 88%, with a low predictive value. Thus, if these test results are abnormal, the likelihood of the patient having sinus node dysfunction is great. However, normal results do not exclude the possibility of sinus node disease. Candidates for invasive EPS to evaluate sinus node function are symptomatic patients in whom sinus node dysfunction is suspected but has not yet been established as a cause of the symptoms. Potential candidates are patients with clinical sinus node dysfunction in whom other causes of symptoms (e.g., tachyarrhythmias) are to be excluded.

Tachycardia

In patients with tachycardias, an EPS can be used to diagnose the arrhythmia, to determine and deliver therapy, to establish the anatomic sites involved in the tachycardia, to identify patients at high risk for the

development of serious arrhythmias, and to gain insight into the mechanisms responsible for the arrhythmia (**see Chapter 37**). The study can differentiate aberrant supraventricular conduction from ventricular tachyarrhythmias when standard electrocardiographic criteria are equivocal.

An SVT is recognized electrophysiologically by an H-V interval equaling or exceeding that recorded during normal sinus rhythm (**Fig. 35.11**). In contrast, during VT, the H-V interval is shorter than normal, or the His deflection cannot be recorded clearly because of superimposition of the larger ventricular electrogram. Only two situations exist in which a consistently short H-V interval occurs: during retrograde activation of the His bundle from activation originating in the ventricle (i.e., PVC, ventricular pacing, or VT) and during AV conduction over an accessory pathway (preexcitation syndrome). Atrial pacing at rates exceeding the tachycardia rate can demonstrate the ventricular origin of the wide-QRS tachycardia by producing fusion and capture beats and normalization of the H-V interval. The only VT that exhibits an H-V interval equal to or slightly exceeding the normal sinus H-V interval is bundle branch reentry, but His activation will be in the retrograde direction.

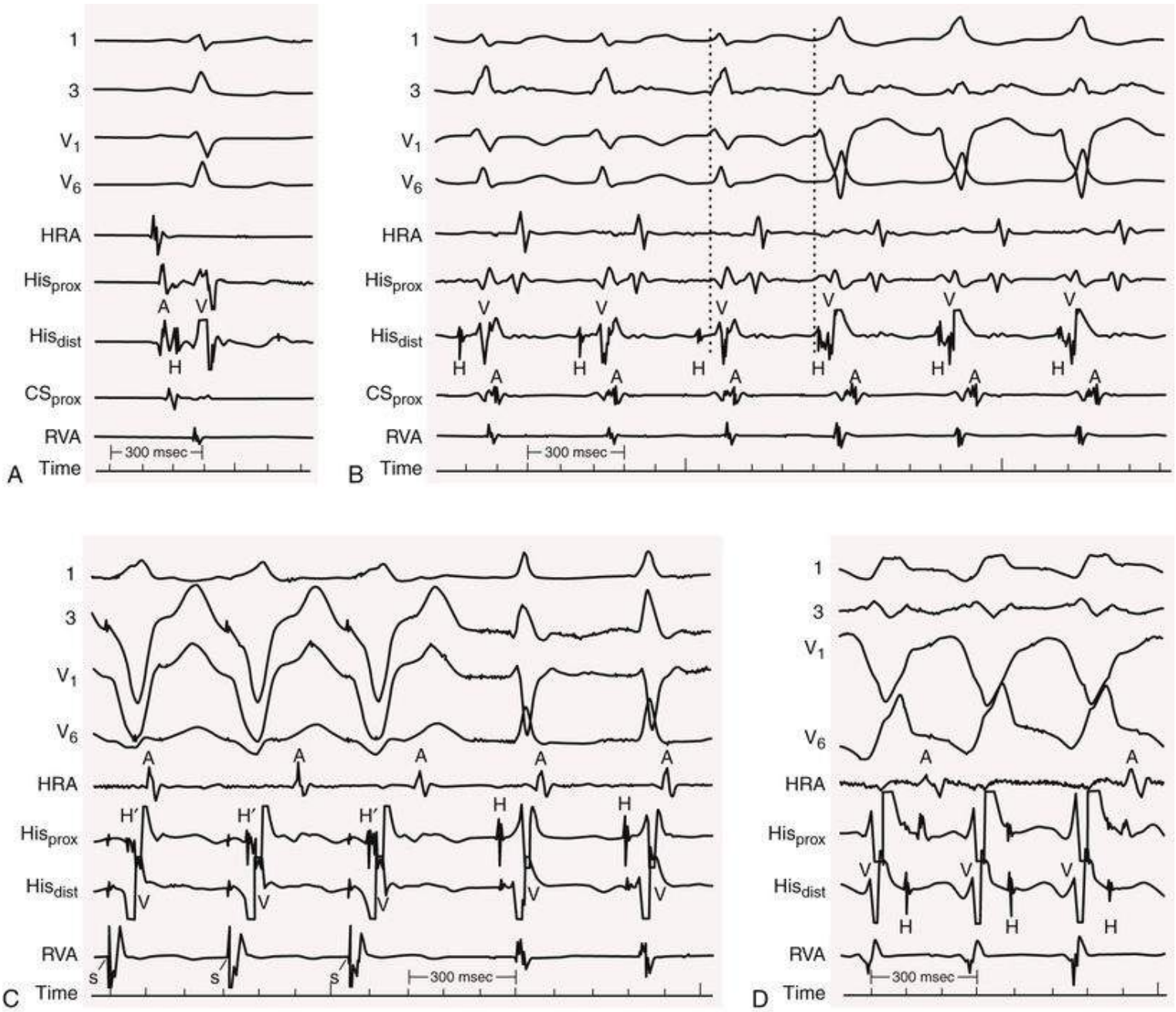


FIGURE 35.11 Bundle of His recordings in different situations similar to those in Figs. 35.9 and 35.10. **A,** Baseline sinus rhythm with normal AV conduction. **B,** Orthodromic SVT with retrograde conduction over a left-sided accessory pathway throughout the tracing. The first three beats have a narrow QRS complex with a normal H-V interval; the last three QRS complexes represent a fusion of conduction over the AV node–His bundle and a slowly conducting right-sided accessory pathway. The His potential occurs after onset of the wide QRS complex (*dashed lines*). **C,** Three paced ventricular beats are shown with a retrograde His potential (H′), followed by initiation of AV node reentrant SVT (atrial depolarization near the end of the QRS complex, as seen in the HRA tracing). **D,** VT with delayed activation of the His potential and complete retrograde AV node block (dissociated atrial complexes). *CS_{prox}*, Proximal coronary sinus; *His_{dist}*, distal electrode pair; *His_{prox}*, proximal electrode pair; *HRA,* high right atrium; *RVA,* right ventricular apex.

An EPS should be considered for the following circumstances: (1) in patients who have symptomatic, recurrent, or drug-resistant supraventricular or ventricular tachyarrhythmias to help select optimal therapy; (2) in patients with tachyarrhythmias occurring too infrequently to permit adequate diagnostic or therapeutic assessment; (3) for differentiation of SVT and aberrant conduction from VT; (4) whenever nonpharmacologic therapy, such as the use of electrical devices, catheter ablation, or surgery, is contemplated; (5) in patients surviving an episode of cardiac arrest occurring more than 48 hours after acute MI or without evidence of an acute Q wave MI; and (6) for assessment of the risk for sustained VT

in patients with a previous MI, ejection fraction of 0.3 to 0.4, and nonsustained VT on an ECG. In general, EPS is not indicated in patients with long-QT syndrome and torsades de pointes.

The process of initiation and termination of SVT or VT with programmed electrical stimulation to establish precise diagnoses and help select sites for catheter ablation is the most common application of EPS in patients with tachycardia. The role of drug therapy in clinically significant arrhythmias continues to diminish; although EPS was once widely used to predict the efficacy of drug therapy in suppressing spontaneous tachycardia recurrences, the technique is now rarely used for this purpose. Noninvasive stimulation from an implanted pacemaker or defibrillator can be used to test the effects of drug therapy given in an attempt to decrease the frequency of arrhythmias, as well as to test the ICD's ability to detect and treat VT that has been slowed or otherwise altered by drug effect.

Unexplained Syncope

The three common arrhythmic causes of syncope are sinus node dysfunction, AV block, and tachyarrhythmias (**see Chapter 43**). Of the three, tachyarrhythmias are most reliably evaluated in the electrophysiology laboratory, followed by sinus node abnormalities and His-Purkinje block.

The cause of syncope remains uncertain in up to 50% of patients, depending in part on the extent of the evaluation. A careful, accurately performed history and physical examination begin the evaluation, followed by noninvasive tests, including a 12-lead ECG, and can lead to a diagnosis in 50% or more of patients. In a small percentage (<5%) of patients, an arrhythmia develops coincident with syncope or presyncope during 24- or 48-hour ECG monitoring, whereas a larger percentage (15%) have symptoms without an arrhythmia, thereby excluding an arrhythmic cause. Prolonged ECG monitoring with patient-activated transtelephonic event recorders that have memory loops may increase the yield. Tilt-table and stress testing can be useful for selected patients.

An EPS helps explain the cause of syncope or palpitations when it induces an arrhythmia that replicates the patient's symptoms or is associated with significant hypotension. Patients with a single episode of syncope and no evidence of structural heart disease, as well as those with a nondiagnostic EPS, have a low incidence of sudden death and an 80% remission rate over the ensuing 10 years. In those with recurrent syncope, the test is falsely negative in 20%, usually because of failure to find AV block or sinus node dysfunction. On the other hand, in many patients with structural heart disease, several abnormalities may be present that could account for syncope and can be diagnosed at EPS. Deciding which among these abnormalities is responsible for syncope and therefore requires therapy, and of what type, can be difficult (**Fig. 35.12**). Mortality and the incidence of sudden cardiac death are determined mainly by the presence of underlying heart disease (**see Chapter 42**).

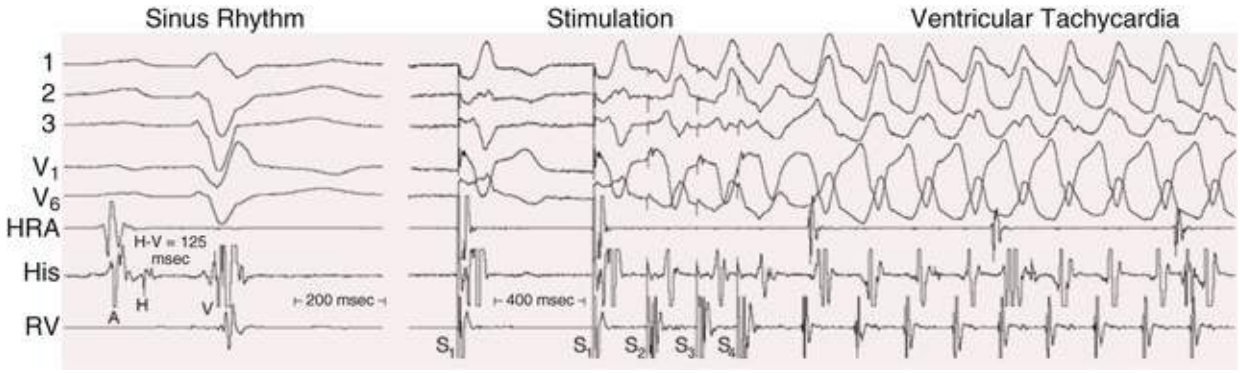


FIGURE 35.12 Multiple abnormalities in a patient with prior myocardial infarction and syncope. Recordings are similar to previous figures. In **left panel,** a sinus rhythm complex shows a right bundle branch block and left axis deviation, with a very prolonged H-V interval of 125 milliseconds (normal, 35 to 55); thus heart block could have caused syncope. However, in **right panel,** ventricular stimulation with three extrastimuli (S_2, S_3, S_4) induces sustained VT, another potential cause of syncope (note the different time scales in the two panels).

Syncopal patients considered for an EPS are those whose spells remain undiagnosed despite general, neurologic, and noninvasive cardiac evaluation, particularly if the patient has structural heart disease.[15] The diagnostic yield is approximately 70% in that group but only 12% in patients without structural heart disease. Therapy for a putative cause found during EPS prevents recurrence of syncope in approximately 80% of patients. Among arrhythmic causes of syncope, intermittent conduction disturbances are the most difficult to diagnose. EPSs are poor in establishing this diagnosis despite an array of provocative tests that can be used. When tachyarrhythmias have been thoroughly sought and excluded and clinical suspicion for intermittent heart block is high (e.g., bundle branch block or long H-V interval), empiric permanent pacing may be justified.

In patients with a nondiagnostic EPS, injection of adenosine triphosphate (different from plain adenosine) distinguishes patients who may benefit from permanent pacing (those with longer than a 10-second sinus pause or AV block) from those who do not. Some have suggested that this test be performed before EPS in some cases or after a negative EPS but before an implantable loop recorder is placed.

Palpitations

An EPS is indicated in patients with palpitations who have had a pulse documented by medical personnel to be inappropriately rapid or slow without an electrocardiographic recording and in those suspected of having clinically significant arrhythmias without electrocardiographic documentation.

In patients with syncope or palpitations, the sensitivity of EPS may be low but can be increased at the expense of specificity. For example, more aggressive pacing techniques (e.g., use of three or four premature stimuli), administration of drugs (e.g., isoproterenol), or left ventricular pacing can increase the likelihood of induction of ventricular arrhythmias by precipitating nonclinical ventricular tachyarrhythmias, such as nonsustained polymorphic VT or VF. Similarly, aggressive techniques during atrial pacing can induce nonspecific episodes of AF or atrial flutter. A diagnostic dilemma arises when the patient's clinical, symptom-producing arrhythmia is one of these nonspecific arrhythmias that can be produced in a normal patient who has no arrhythmia. In most patients, these arrhythmias are regarded as *nonclinical* (i.e., nonspecific responses to intense stimulation). In other patients, such as those with hypertrophic or dilated nonischemic cardiomyopathy, they may be clinically relevant arrhythmias. However, induction of sustained SVT (e.g., AV nodal reentry, AV reciprocating tachycardia) or monomorphic VT is almost never an artifact of stimulation, no matter how intense. Initiation of these arrhythmias in patients who have not had known spontaneous episodes of these tachycardias is uncommon

and provides important information; for example, the induced tachyarrhythmia may be clinically significant and responsible for the patient's symptoms. In addition, inducible SVT episodes can have important implications for patients with implantable cardioverter-defibrillators (ICDs) that may deliver inappropriate therapy for such arrhythmias. In general, other abnormalities, such as prolonged sinus pauses after overdrive atrial pacing or His-Purkinje AV block, are not induced in patients who do not or may not experience these abnormalities spontaneously. Provocation of these abnormalities has a high degree of specificity for clinical relevance.

Complications of Electrophysiologic Studies

The risks associated with undergoing only an EPS are small. Myocardial perforation with cardiac tamponade, pseudoaneurysms at arterial access sites, and provocation of nonclinical arrhythmias can occur, each with less than a 1/500 incidence; the addition of therapeutic maneuvers (e.g., ablation) to the procedure increases the incidence of complications. In many centers, diagnostic EPS and even ablation procedures are performed on an outpatient basis (i.e., same-day discharge). With the increasing use of extensive ablation in the left atrium to treat AF, an increase in systemic thromboembolic complications has been observed, as have pericardial effusion and tamponade, valve damage, and phrenic nerve injury[16] (**see Chapter 37**).

Direct Cardiac Mapping: Recording Potentials Directly From the Heart

Cardiac mapping is a method whereby potentials recorded directly from the heart are spatially depicted as a function of time in an integrated manner (**Fig. 35.13**). The location of recording electrodes (e.g., epicardial, intramural, or endocardial) and the recording mode used (unipolar versus bipolar), as well as the method of display (isopotential, isochronal, unipolar, or bipolar voltage maps), depend on the problem under consideration.

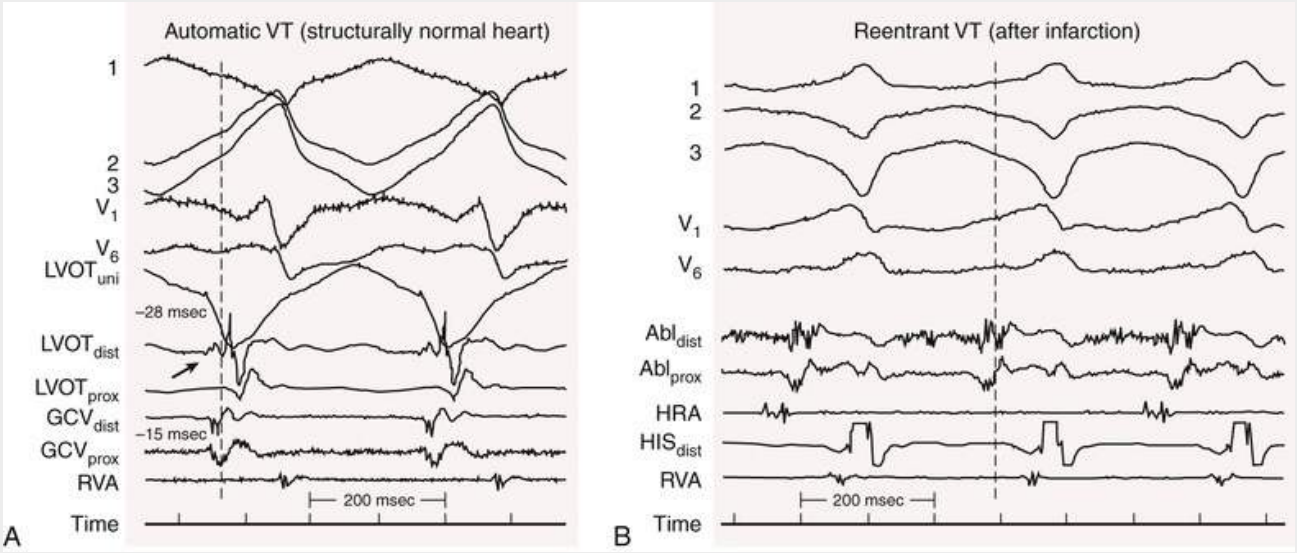


FIGURE 35.13 Endocardial catheter recordings during VT in two patients. *Dashed lines* denote onset of the QRS complexes. **A,** Woman without structural heart disease had a sustained VT arising from the left ventricular outflow tract (*LVOT*). Note the unipolar (uni) electrogram with a sharp "QS" complex and onset (*arrow*) of the distal bipolar recording ($LVOT_{dist}$) preceding the right ventricular recording, as well as recordings from a multielectrode catheter in the great cardiac vein (GCV_{dist} and GCV_{prox}) on the epicardial surface opposite the endocardial recording. Ablation at this site (LVOT) terminated the VT. **B,** Patient with reentrant VT caused by a previous inferior wall infarction. The ablation catheter (Abl_{dist}) on the inferomedial wall shows a prolonged, fragmented electrogram indicative of slow conduction that spans the entire diastolic interval between QRS complexes. Ablation at this site eliminated the VT. Abl_{prox}, Proximal ablation catheter electrodes.

Direct cardiac mapping by catheter electrodes or less frequently at cardiac surgery can be used to identify and localize the areas responsible for rhythm disturbances in patients with supraventricular and ventricular tachyarrhythmias for catheter or surgical ablation, isolation, or resection. Conditions amenable to this approach include accessory pathways associated with WPW syndrome, the pathways in AV node reentry, AV node–His bundle ablation, sites of origin of focal atrial tachycardia (AT) and VTs, isolated pathways essential for the maintenance of reentrant ATs or VTs, and various substrates responsible for episodes of AF (Videos 35.1 and 35.2) (**see Chapter 38**). Mapping can also be used to delineate the anatomic course of the His bundle and phrenic nerve to avoid injury during catheter ablation or open heart surgery for repair of congenital heart disease.

Early efforts at mapping involved moving an electrode from location to location, acquiring data from a single point at a time, and comparing the timing of local activation with some reference recording, as well as other mapped sites. Knowing when enough data points had been obtained to determine where ablation should be performed relied heavily on the memory of the operator. Specialized mapping systems have now been developed that use computers to log not only the activation times and electrogram amplitude (voltage) at various points in the heart, but also the physical locations from which they were obtained. The mapping information acquired in this way can be displayed on a screen to show relative activation times in a color-coded sequence. Using such systems, dozens or even hundreds of sites can be sampled relatively quickly, thereby leading to a clear picture of cardiac activation and potential target sites for ablation (**Figs. 35.14 and 35.15**). These systems can also record the signal amplitude at each site sampled to allow differentiation of normal from scarred myocardium, which can help in planning ablation strategies (**Fig. 35.16**). Other mapping systems can acquire data from several thousand points simultaneously by using a multipolar electrode array. This may be useful for hemodynamically unstable tachycardias or those that terminate spontaneously within seconds, which precludes detailed point-to-point mapping.

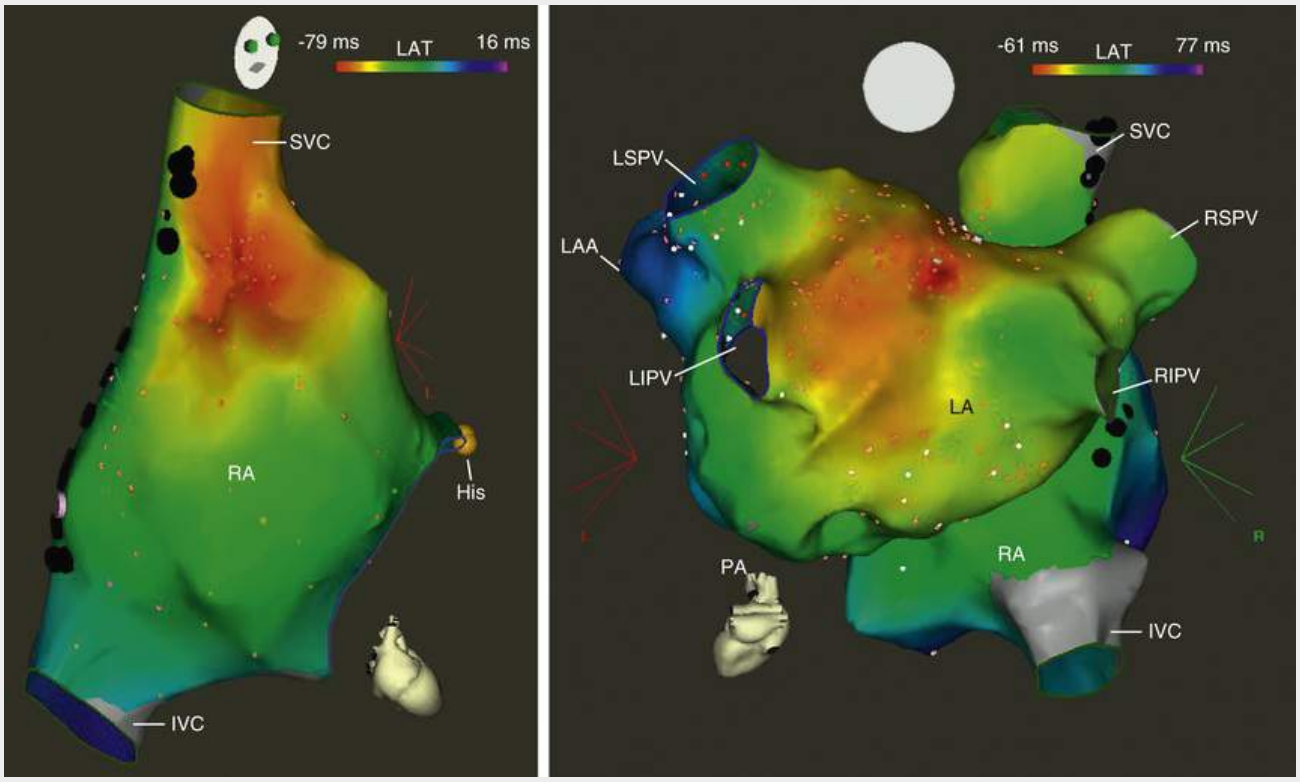


FIGURE 35.14 Electroanatomic maps of focal atrial tachycardias. **Left,** A focal right atrial tachycardia is shown from an almost right lateral view. A color-coded time scale of activation is shown at the right; *red* indicates earliest activation and *purple,* latest. This atrial tachycardia arose in the anterolateral right atrium (*RA*), slightly anterior to where the sinus node resides; ablation here eliminated tachycardia while leaving sinus node function unaffected. **Right,** A left atrial focal tachycardia is shown, with both RA and left atrium (*LA*) viewed from posteriorly. The tachycardia arose from the region of the *small red spot* at top center of the LA, with all other areas activated centrifugally. Ablation at this site eliminated the tachycardia. *SVC,* Superior vena cava; *IVC,* inferior vena cava; *His,* His bundle area (*orange dots*); *LIPV,* left inferior pulmonary vein (PV); *LSPV,* left superior PV; *RSPV,* right superior PV; *RIPV,* right inferior PV.

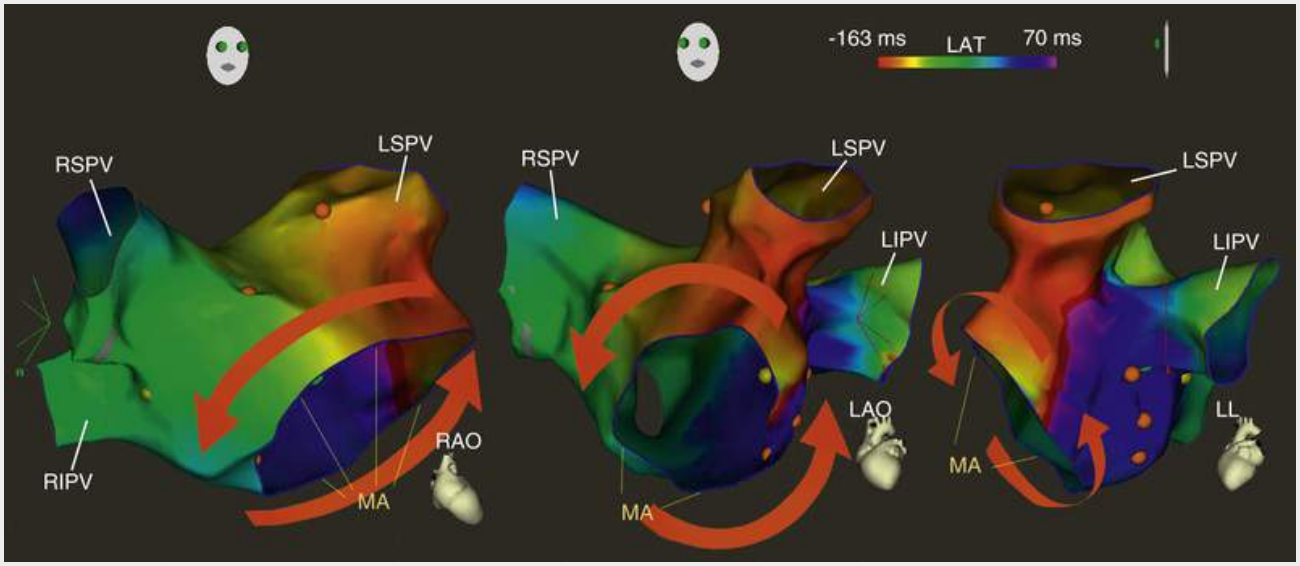


FIGURE 35.15 Electroanatomic activation map of "perimitral" reentrant atrial flutter. Three views of the left atrium are shown: right anterior oblique (*RAO*), left anterior oblique (*LAO*), and left lateral (*LL*). The electrical wave front propagates around the mitral annulus (*MA*) in a "counterclockwise" direction as indicated by *orange arrows*; in this complete circuit, early activation (*red*) abuts late activation (*purple*) at the lateral mitral annulus. The cycle length of the tachycardia was 235 milliseconds, almost completely described by the points shown in the figure (from −163 to +70 milliseconds, a total of 233 milliseconds; time scale at *top*). Abbreviations as in Fig. 35.14.

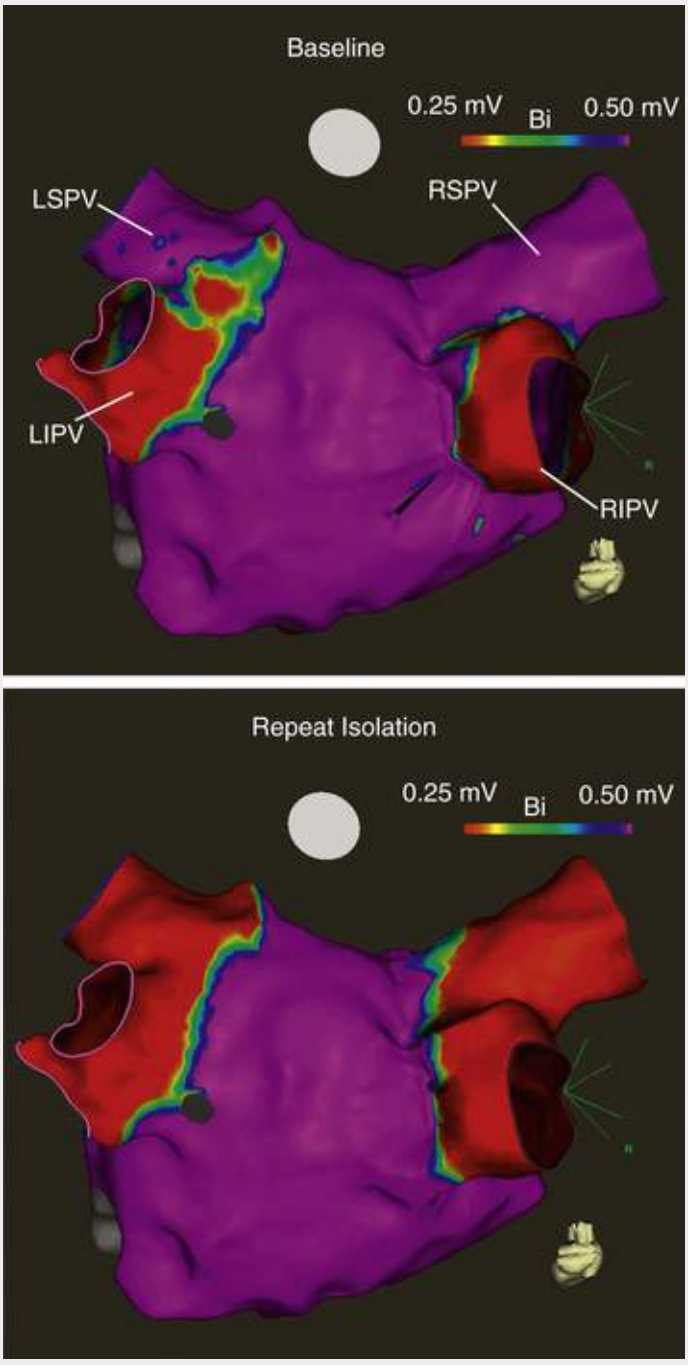


FIGURE 35.16 Electroanatomic left atrial voltage maps during sinus rhythm in a patient with recurrent atrial fibrillation after prior pulmonary vein (PV) isolation. **Top,** Posterior view of the left atrium at baseline, showing low voltage (*red,* tantamount to electrical isolation) in the left (*LIPV*) and right (*RIPV*) inferior PVs, but high residual voltage (*purple*) in the left (*LSPV*) and right (*RSPV*) superior PVs. **Bottom,** After repeat ablation around the PVs, the superior veins now have no residual voltage (*red*); all four PVs are now isolated. The patient has had no recurrence of symptoms. A voltage scale is shown at *upper right* of each panel.

Pace mapping is a technique in which pacing is performed at putative sites from which arrhythmias arise (a focus) or exit (reentrant circuit). The greater the degree of "match" in QRS complexes (for VT) or intracardiac activation sequences (for atrial tachycardias), the more likely that the paced site may be an appropriate site for ablation. Software has been developed to calculate the fidelity of match of the paced complexes to the target arrhythmia; ideally, this should approach 100% (**see Chapter 36**, **Figs. 36.16 and 36.18**). Other algorithms have been developed to analyze propagation patterns during complex arrhythmias such as AF by recording signals from multielectrode "basket" catheters in the atrium (**Fig. 35.17**). This has resolved many cases of an apparently chaotic rhythm to one in which erratic patterns of propagation emanate from a stable rapid source (either rotor or focus). Ablation at these source sites can

eliminate AF in some cases.[17] Work is ongoing in this area. Lastly, although computerized mapping systems acquire activation time and voltage at given sites in the heart, these features have been displayed separately. “Ripple mapping” is a new technique that integrates time and voltage information on the same display. Experience with this technique is limited, but the early results are promising.[18]

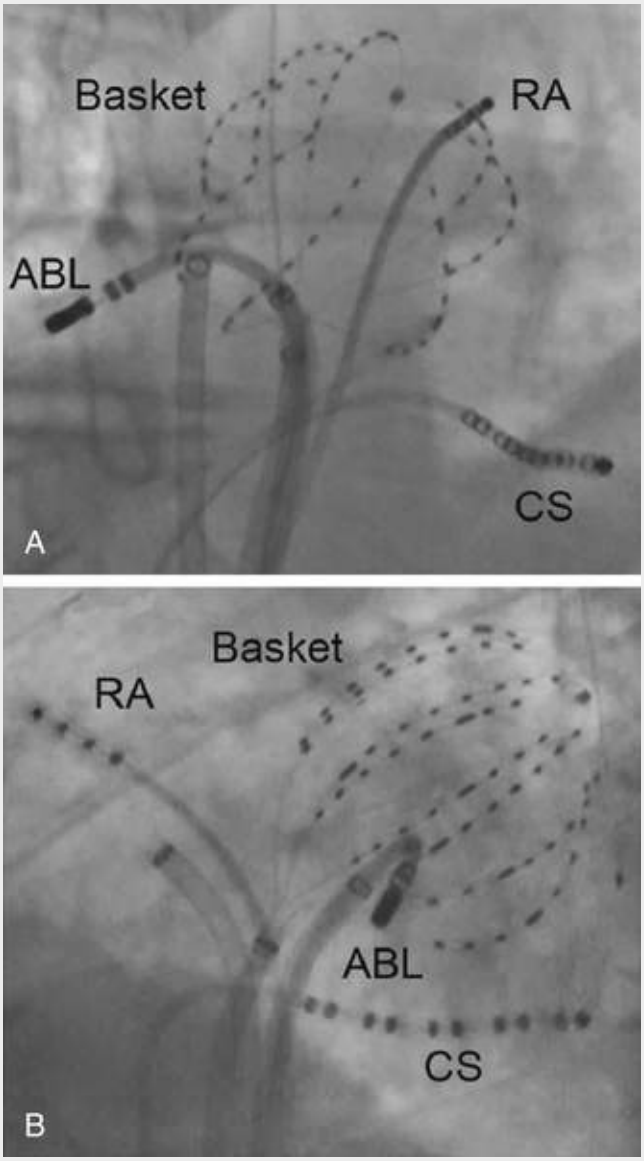


FIGURE 35.17 Basket catheter for mapping AF. Right **(A)** and left **(B)** anterior oblique fluoroscopic views of an eight-spline, eight electrodes per spline (64 total electrodes) “basket” catheter in the left atrium; other catheters are right atrial (*RA*), coronary sinus (*CS*), and an ablation catheter (*ABL*) in the right inferior pulmonary vein.

Current mapping systems have the ability to integrate previous imaging studies (computed tomography, magnetic resonance imaging) into the procedure for additional anatomic reference and to derive anatomic information by moving a catheter throughout a cardiac chamber to develop a contour of its inner surface, on which activation or voltage data can be plotted.

Guidelines

Ambulatory Electrocardiographic and Electrophysiologic Testing

John M. Miller, Gordon F. Tomaselli, and Douglas P. Zipes

Guidelines for the appropriate use of ambulatory electrocardiography (ECG) were first published by the American College of Cardiology and American Heart Association (ACC/AHA) in 1989[1] and updated in 1999.[2] In conjunction with other professional societies, the ACC/AHA issued a statement of requirements for clinical competence in ambulatory ECG in 2001.[3] Guidelines for performance of electrophysiologic testing were first published in 1985[4] and updated in 1989 and 1995.[5] A clinical competence statement was issued by the ACC/AHA for electrophysiologic studies and catheter ablation in 2000[6] and updated in 2006[7]; this was updated by a statement on training in electrophysiology, cardiac pacing, and arrhythmia management in 2006[8] and again in 2008[9] and 2015.[10] The AHA and the Heart Rhythm Society made recommendations on safety-related topics, such as restrictions on driving, for patients with arrhythmia in 1996[11] and updated them in 2007.[12] Since then, efforts to update the guidelines have focused on appropriate indications for the use of pacemakers and implantable cardioverter-defibrillators (ICDs) because of rapid advances in knowledge about the ability of ICDs to improve the survival of patients with arrhythmia with or without electrophysiologic testing. These guidelines were issued in 2002[13] and updated in 2008 and 2013[14] (see Guidelines in **Chapter 41**).

The standard ACC/AHA classification system is used for the following indications:

Class I: conditions for which there is evidence and/or general agreement that the test is useful and effective
Class II: conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness or efficacy of performing the test.
Class IIa: weight of evidence or opinion in favor of usefulness or efficacy.
Class IIb: usefulness or efficacy less well established by evidence or opinion.
Class III: conditions for which there is evidence and/or general agreement that the test is not useful or effective and in some cases may be harmful.

Three levels are used to rate the evidence on which recommendations have been based:

Level A recommendations are derived from data from multiple randomized clinical trials.
Level B recommendations are derived from a single randomized trial or nonrandomized studies.
Level C recommendations are based on the consensus opinion of experts.

Ambulatory Electrocardiography

The evolution of guidelines for the use of ambulatory electrocardiography (ECG) from 1989 to 1999 and updated in 2015 reflected important progress in several areas, including the following:

- Understanding of the limited usefulness of suppression of ventricular ectopy with drug therapy
- Solid-state digital technology, which facilitates transtelephonic

transmission of electrocardiographic data
- Technical advances in long-term event recorders
- Improved signal quality and interpretation
- Improved computer arrhythmia interpretation
- Increasingly sophisticated monitoring capacity of pacemakers and ICDs

As a result of progress in these areas and increased knowledge about arrhythmias, ambulatory ECG monitoring is now considered to be of uncertain appropriateness for many indications for which it was once an accepted strategy.

Diagnosis

In assessing symptoms that may be caused by arrhythmias, ambulatory ECG (Holter) monitoring is clearly established for the evaluation of syncope (**Table 35G.1**; **see Chapter 43**). A 2006 AHA/ACC Foundation scientific statement on the evaluation of syncope stipulates that the type and duration of ambulatory ECG monitoring are dictated by the frequency of symptoms.[15] Holter monitors (24 to 48 hours) are appropriate for episodes that occur at least daily and event recorders (30 to 60 days) for episodes that occur at least monthly. Implantable loop recorders inserted subcutaneously can record bipolar ECG signals for up to 24 months. In patients with unexplained syncope, use of an implantable loop recorder for 1 year is more likely to identify the mechanism of syncope than is a conventional approach that uses Holter or event monitors and electrophysiologic testing and is cost-effective.

TABLE 35G.1

ACC/AHA 1999 Guidelines on Ambulatory Electrocardiography for Assessment of Symptoms and Arrhythmias

INDICATION	CLASS I (INDICATED)	CLASS IIa (GOOD SUPPORTIVE EVIDENCE)	CLASS IIb (WEAK SUPPORTIVE EVIDENCE)	CLASS III (NOT INDICATED)
Assessment of symptoms possibly related to rhythm disturbances	Patients with unexplained syncope, near-syncope, or episodic dizziness in whom the cause is not obvious Patients with unexplained recurrent palpitation		Patients with episodic shortness of breath, chest pain, or fatigue that is not otherwise explained Patients with neurologic events when transient atrial fibrillation or flutter is suspected Patients with symptoms such as syncope, near-syncope, episodic dizziness, or palpitation in whom a probable cause other than an arrhythmia has been identified but in whom symptoms persist despite treatment of this other cause	Patients with symptoms such as syncope, near-syncope, episodic dizziness, or palpitation in whom other causes have been identified by history, physical examination, or laboratory tests Patients with cerebrovascular accidents but without other evidence of arrhythmia
Arrhythmia detection to assess risk for future cardiac events in patients without symptoms from arrhythmia			Post-MI patients with LV dysfunction (ejection fraction <40%) Patients with CHF Patients with idiopathic hypertrophic cardiomyopathy	Patients who have sustained myocardial contusion Systemic hypertensive patients with LV hypertrophy Post-MI patients with normal LV function Preoperative arrhythmia evaluation of patients for noncardiac surgery Patients with sleep apnea Patients with valvular heart disease
Measurement of HRV to assess risk for future cardiac events in patients without symptoms from arrhythmia			Post-MI patients with LV dysfunction Patients with CHF Patients with idiopathic hypertrophic cardiomyopathy	Post-MI patients with normal LV function Diabetic patients to evaluate for diabetic neuropathy Patients with rhythm disturbances that preclude HRV analysis (e.g., atrial fibrillation)
Assessment of antiarrhythmic therapy	To assess antiarrhythmic drug response in individuals in whom the baseline frequency of arrhythmia has been characterized as reproducible and of sufficient frequency to permit analysis	To detect proarrhythmic responses to antiarrhythmic therapy in patients at high risk	To assess rate control during atrial fibrillation To document recurrent or asymptomatic nonsustained arrhythmias during therapy in the outpatient setting	

CHF, Congestive heart failure; *HRV,* heart rhythm variability; *LV,* left ventricular; *MI,* myocardial infarction.

Ambulatory ECG is also supported for the evaluation of recurrent palpitations, particularly if the frequency of these symptoms makes it reasonably likely that they can be correlated with the tracings obtained during a 24-hour monitoring period. The guidelines note that data on the use of ambulatory ECG for near-syncope or dizziness are insufficient to describe the diagnostic performance of this technology for patients with such symptoms.

The ACC/AHA guidelines explicitly discourage ambulatory ECG for patients with syncope or palpitations if other causes have been identified during the clinical evaluation and for patients with cerebrovascular accidents (strokes) and no other evidence of arrhythmia. The guidelines seek to reduce performance of ambulatory ECG “for completeness” in such cases. Little support is provided for use of ambulatory ECG in cases in which the cause of the patient's symptoms is unclear but in which the likelihood of detecting an unsuspected arrhythmia is low (class IIb indications).

Assessment of Risk

The ACC/AHA guidelines discouraged the use of ambulatory ECG for either arrhythmia detection or analysis of heart rhythm variability for the purpose of risk assessment in patients without symptoms of arrhythmia, even if they had cardiovascular conditions such as myocardial contusions, left ventricular hypertrophy, or valvular heart disease (**see Table 35G.1**). Routine use for patients in whom arrhythmia is

a common cause of death (left ventricular dysfunction, hypertrophic cardiomyopathy) was considered a class IIb indication. These recommendations preceded data demonstrating the beneficial impact of ICDs for patients with left ventricular dysfunction after acute myocardial infarction even without symptoms of arrhythmia. These more recent findings are leading to an expanded role for ambulatory ECG in determining which asymptomatic patients most need these expensive devices.

Efficacy of Antiarrhythmic Therapy

In the absence of data demonstrating that oral antiarrhythmic therapy can improve survival through control of ventricular arrhythmias, ambulatory ECG has a diminished role as a test for evaluation of the efficacy of treatment (**see Table 35G.1**). Oral antiarrhythmic agents are important for control of supraventricular arrhythmias, but most patients with such arrhythmias do not have episodes every day. Event recorders can be useful for documenting the relationship between symptoms and recurrent arrhythmia and the interval between episodes, which can help guide therapy.

The guidelines provide some support for the use of ambulatory ECG for detection of proarrhythmia during initiation of drug therapy in patients at high risk (class IIa), but such patients tend to have these medications initiated as inpatients, or have ICDs in place.

Assessment of Pacemaker/ICD Function

Ambulatory ECG was considered to be appropriate for evaluation of the function of pacemakers and ICDs (**see Chapter 41**), but the role of ambulatory ECG is being reduced by increasing the diagnostic and monitoring functions being built into these devices, especially with the use of remote monitoring. Ambulatory ECG can provide useful information by correlating symptoms with device activity and by detecting abnormalities in sensing and capture during chronic follow-up (**Table 35G.2**). However, the ACC/AHA guidelines emphasize that ambulatory ECG should not be used when data available from device interrogation are sufficient to guide clinical management.

TABLE 35G.2

ACC/AHA 1999 Guidelines on Ambulatory Electrocardiography for Assessment of Pacemaker and Implantable Cardioverter-Defibrillator (ICD) Function

CLASS	INDICATION
Class I (indicated)	Evaluation of frequent symptoms of palpitations, syncope, or near-syncope to assess device function, to exclude myopotential inhibition and pacemaker-mediated tachycardia, and to assist in the programming of enhanced features, such as rate responsivity and automatic mode switching Evaluation of suspected component failure or malfunction when device interrogation is not definitive in establishing a diagnosis To assess response to adjunctive pharmacologic therapy in patients receiving frequent ICD therapy
Class IIa (good supportive evidence)	
Class IIb (weak supportive evidence)	Evaluation of immediate postoperative pacemaker function after pacemaker or ICD implantation as an alternative or adjunct to continuous telemetric monitoring Evaluation of the rate of supraventricular arrhythmias in patients with implanted defibrillators
Class III (not indicated)	Assessment of ICD or pacemaker malfunction when device interrogation, electrocardiogram, or other available data (e.g., chest radiograph) are sufficient to establish an underlying cause or diagnosis Routine follow-up in asymptomatic patients

Monitoring for Myocardial Ischemia

The 1999 ACC/AHA guidelines do not provide strong support of any indications for routine clinical use of ambulatory ECG monitoring for myocardial ischemia (**Table 35G.3**). The only indication for which the task force thought that there was good supportive evidence was suspected variant angina. This technology was not considered a first-choice alternative to exercise testing for patients who are unable to exercise.

TABLE 35G.3

ACC/AHA 1999 Guidelines on Monitoring for Ischemia

CLASS	INDICATION
Class I (indicated)	
Class IIa (good supportive evidence)	Patients with suspected variant angina
Class IIb (weak supportive evidence)	Evaluation of patients with chest pain who cannot exercise Preoperative evaluation for vascular surgery in patients who cannot exercise Patients with known coronary artery disease and atypical chest pain syndrome
Class III (not indicated)	Initial evaluation of patients with chest pain who are able to exercise Routine screening of asymptomatic patients

Clinical Competence

The ACC/AHA statement on clinical competence recommended that trainees interpret at least 150 ambulatory electrocardiograms under supervision to acquire minimal competence in this technology.[3] A minimum of 25 test interpretations per year was recommended to maintain competence.

Electrophysiologic procedures for Diagnosis

The ACC/AHA guidelines for the use of intracardiac electrophysiologic procedures from 1985[4] and 1995[5] reflected the emerging role of catheter ablation as a therapeutic strategy but did not fully reflect the reduced importance of antiarrhythmic medications and the growing role of ICDs that had occurred. Nevertheless, most of the basic themes of these guidelines remain valid. An updated clinical competence statement for performing these procedures was issued in 2006.[7]

Evaluation of Sinus Node Function

Clinical evaluation of sinus node dysfunction is often difficult because of the episodic nature of symptomatic abnormalities and the wide variability in sinus node function in asymptomatic individuals. Invasive tests of sinus function can test the ability of the sinus node to recover from overdrive suppression and assess sinoatrial conduction by introducing atrial extrastimuli or by atrial pacing.

The ACC/AHA guidelines consider electrophysiologic studies (EPSs) of sinus node function most appropriate for patients in whom dysfunction is suspected but not proved after a noninvasive evaluation (**Table 35G.4**). In contrast, the guidelines consider such studies inappropriate when a documented bradyarrhythmia has been correlated with the patient's symptoms and if management is unlikely to be influenced by an EPS. Studies are also considered inappropriate in asymptomatic patients and those who have sinus pauses only during sleep. When bradyarrhythmias were recognized as the cause of the patient's symptoms, EPSs were considered to have possible but uncertain appropriateness (class II) if such data might refine treatment choices.

TABLE 35G.4

ACC/AHA Year Guidelines on Clinical Intracardiac Electrophysiologic Studies for Evaluation of Specific Electrocardiographic Abnormalities

INDICATION	CLASS I (APPROPRIATE)	CLASS II (EQUIVOCAL)	CLASS III (INAPPROPRIATE)
Evaluation of sinus node function	Symptomatic patients in whom sinus node dysfunction is suspected as the cause of symptoms, but a causal relationship between an arrhythmia and the symptoms has not been established after appropriate evaluation	Patients with documented sinus node dysfunction in whom evaluation of AV or ventriculoatrial conduction or susceptibility to arrhythmias may aid in selection of the most appropriate pacing modality	Symptomatic patients in whom an association between symptoms and a documented bradyarrhythmia has been established and the choice of therapy would not be affected by EPS results

		Patients with electrocardiographically documented sinus bradyarrhythmias to determine whether abnormalities are caused by intrinsic disease, autonomic nervous system dysfunction, or effects of drugs to help select therapeutic options Symptomatic patients with known sinus bradyarrhythmias to evaluate potential for other arrhythmias as the cause of symptoms	Asymptomatic patients with sinus bradyarrhythmias or sinus pauses observed only during sleep, including sleep apnea
Acquired AV block	Symptomatic patients in whom His-Purkinje block, suspected as a cause of symptoms, has not been established Patients with second- or third-degree AV block treated with a pacemaker who remain symptomatic and in whom another arrhythmia is suspected as a cause of the symptoms	Patients with second- or third-degree AV block in whom knowledge of the site of block or its mechanism or response to pharmacologic or other temporary intervention may help in directing therapy or assessing prognosis Patients with premature, concealed junctional depolarizations suspected as the cause of a second- or third-degree AV block pattern (e.g., pseudo–AV block)	Symptomatic patients in whom the symptoms and presence of AV block are correlated by ECG findings Asymptomatic patients with transient AV block associated with sinus slowing (e.g., nocturnal type I second-degree AV block)
Chronic intraventricular conduction delay	Symptomatic patients in whom the cause of symptoms is not known	Asymptomatic patients with bundle branch block in whom pharmacologic therapy that could increase conduction delay or produce heart block is contemplated	Asymptomatic patients with intraventricular conduction delay Symptomatic patients whose symptoms can be correlated with or excluded by ECG events
Narrow-QRS tachycardia (QRS complex <0.12 sec)	Patients with frequent or poorly tolerated episodes of tachycardia who do not adequately respond to drug therapy and for whom information about the site of origin, mechanism, and electrophysiologic properties of pathways of the tachycardia is essential for choosing appropriate therapy (e.g., drugs, catheter ablation, pacing, or surgery) Patients who prefer ablative therapy to pharmacologic treatment	Patients with frequent episodes of tachycardia requiring drug treatment for whom there is concern about proarrhythmia or effects of the antiarrhythmic drug on the sinus node or AV conduction	Patients with tachycardias easily controlled by vagal maneuvers and/or well-tolerated drug therapy who are not candidates for nonpharmacologic therapy
Wide-complex tachycardias	Patients with wide–QRS complex tachycardia in whom the correct diagnosis is unclear after analysis of available ECG tracings and for whom knowledge of the correct diagnosis is necessary for care	None	Patients with VT or supraventricular tachycardia with aberrant conduction or preexcitation syndromes diagnosed with certainty by ECG criteria and for whom invasive electrophysiologic data would not influence therapy; however, data obtained at baseline EPS in these patients might be appropriate as a guide for subsequent therapy
Prolonged–QT interval syndrome	None	Identification of proarrhythmic effect of a drug in patients experiencing sustained VT or cardiac arrest while receiving the drug Patients who have equivocal abnormalities in QT interval duration or T-U wave configuration, along with syncope or symptomatic arrhythmias, in whom the effects of catecholamine may unmask a distinct QT abnormality	Patients with clinically manifest congenital QT prolongation, with or without symptomatic arrhythmias Patients with acquired prolonged-QT syndrome with symptoms closely related to an identifiable cause or mechanism
Wolff-Parkinson-White syndrome	Patients being evaluated for catheter ablation or surgical ablation of an accessory pathway Patients with ventricular preexcitation who have survived cardiac arrest or who have unexplained syncope Symptomatic patients in whom determination of the mechanism of arrhythmia or knowledge of the electrophysiologic properties of the accessory pathway and normal conduction system would help in determining appropriate therapy	Asymptomatic patients with a family history of sudden cardiac death or with ventricular preexcitation but no spontaneous arrhythmia who engage in high-risk occupations or activities and in whom knowledge of the electrophysiologic properties of the accessory pathway or inducible tachycardia may help determine recommendations for further activities or therapy Patients with ventricular preexcitation who are undergoing cardiac surgery for other reasons	Asymptomatic patients with ventricular preexcitation, except those in class II
Premature ventricular complexes (PVCs), couplets, and nonsustained VT	None	Patients with other risk factors for future arrhythmic events, such as a low ejection fraction, positive signal-averaged electrocardiogram, and nonsustained VT on ambulatory ECG recordings in whom EPS will be used for further risk assessment and for guiding therapy in patients with inducible VT Patients with highly symptomatic, uniform-morphology PVCs, couplets, and nonsustained VT who are considered potential candidates for catheter ablation	Asymptomatic or mildly symptomatic patients with PVCs, couplets, and nonsustained VT without other risk factors for sustained arrhythmias

AV, Atrioventricular; *EPS,* electrophysiologic study; *VT,* ventricular tachycardia.

Acquired Atrioventricular Block

The ACC/AHA guidelines emphasize that EPSs are inappropriate (class III) when ECG findings correlate with symptoms and the EPS findings are unlikely to alter management. For example, documentation of His bundle conduction rarely improves the management of a patient whose other clinical data indicate that placement of a permanent pacemaker is warranted because of symptomatic advanced atrioventricular

(AV) block. Similarly, EPSs are not appropriate for asymptomatic patients with mild degrees of AV block who are not likely to warrant pacemaker implantation. According to these guidelines, EPSs of AV conduction should be performed when a relationship between symptoms and AV block is a reasonable possibility but has not been proved.

Chronic Intraventricular Delay

According to the 1999 ACC/AHA guidelines, the main role of electrophysiologic testing (EPT) in patients with prolonged H-V intervals is not to predict future complications but to determine whether the symptoms of arrhythmia are caused by conduction delay or block versus some other arrhythmia. The only class I (clearly appropriate) indication for EPT is symptomatic patients for whom the cause of symptoms is not known. The guidelines specifically discourage EPT of asymptomatic patients and provide only equivocal support for asymptomatic patients with bundle branch block in whom treatment with drugs that might increase conduction delay is being considered.

Narrow– and Wide–QRS Complex Tachycardia

The ACC/AHA guidelines define different roles for EPT in patients with narrow- and wide-complex tachycardias. In narrow-QRS tachycardia, the site of abnormal impulse formation or the reentry circuit can often be determined from information on the 12-lead electrocardiogram. Thus, EPT was considered more appropriate as a guide to therapy in this setting than as a tool for diagnosis. Class I indications for EPT include patients with recurrent tachycardia for whom data from testing may help clinicians choose among drug therapy, catheter ablation, pacing, and surgery. However, testing is not considered useful for patients whose tachycardias are controlled by vagal maneuvers or medications and who are not candidates for nonpharmacologic therapy.

In wide-complex tachycardias, the correct diagnosis is occasionally not possible from ECG tracings alone. However, EPT permits accurate diagnosis in virtually all patients. Because knowledge of the mechanism of the arrhythmia is essential for selection of optimal therapy, EPT was considered appropriate (class I) for the diagnosis of wide-complex tachycardias in these guidelines. However, when the diagnosis is clear from other data and EPT is not likely to influence therapy, the guidelines consider it inappropriate.

Prolonged QT Intervals

The ACC/AHA guidelines do not consider routine use of EPT appropriate for any indications in patients with prolonged QT intervals. Whether catecholamine infusion during testing is useful for revealing patients who are at high risk for complications or whether EPT can be used to evaluate proarrhythmic effects in this population is considered uncertain.

Wolff-Parkinson-White Syndrome

Electrophysiologic testing is useful for patients with WPW syndrome for both diagnosis and planning of therapy. The ACC/AHA guidelines consider EPT appropriate for patients who are candidates for catheter or surgical ablation, for those who have had cardiac arrests or unexplained syncope, or for patients whose management might be altered by knowledge of the electrophysiologic properties of the accessory pathway and normal conduction system. For asymptomatic patients, however, EPSs are deemed inappropriate except in special situations, such as patients with high-risk occupations or those with a family history of sudden cardiac death. More recently recognized entities, such as Brugada syndrome,

catecholaminergic polymorphic ventricular tachycardia, and right ventricular cardiomyopathy, were not considered.

Nonsustained Ventricular Tachycardia

For patients with ventricular premature complexes, couplets, and nonsustained ventricular tachycardia, the usefulness of EPT is compromised by the lack of therapeutic strategies that have been shown to improve outcomes. There are no clearly appropriate indications for EPSs in these patients, and the guidelines discourage testing in patients without other risk factors for sustained arrhythmias. Research published since these guidelines suggests that exceptions would include patients who fit the MADIT (Multicenter Automatic Defibrillator Implantation Trial) or MUSTT (Multicenter Unsustained Tachycardia Trial) criteria. For certain patients with other features suggesting an adverse prognosis, EPT is thought to have possible but unproven appropriateness (class II).

Unexplained Syncope

In patients with unexplained syncope and structural heart disease (**see Chapter 43**), recent ACC/AHA guidelines on the evaluation of syncope[12] recommend a low threshold for EPT (**Table 35G.5**). In patients without structural heart disease, the yield of electrophysiologic testing is low. Thus the guidelines recommend a higher threshold for use of EPSs in such patients and suggest that head-up tilt testing may be a more useful test. However, given the low risk associated with EPT and the high risk for potentially harmful recurrent syncope, EPT may be beneficial for patients with a malignant episode of syncope.[15]

TABLE 35G.5

ACC/AHA 1995 Guidelines on Clinical Intracardiac Electrophysiologic Studies for Evaluation of Clinical Syndromes

INDICATION	CLASS I (APPROPRIATE)	CLASS II (EQUIVOCAL)	CLASS III (INAPPROPRIATE)
Unexplained syncope	Patients with suspected structural heart disease and syncope that remain unexplained after appropriate evaluation	Patients with recurrent unexplained syncope but without structural heart disease and a negative head-up tilt test result	Patients with a known cause of syncope for whom treatment will not be guided by electrophysiologic testing
Survivors of cardiac arrest	Patients surviving cardiac arrest without evidence of acute Q wave MI Patients surviving cardiac arrest occurring more than 48 hours after acute phase of MI in the absence of recurrent ischemic events	Patients surviving cardiac arrest caused by bradyarrhythmia Patients surviving cardiac arrest thought to be associated with a congenital repolarization abnormality (long-QT syndrome) in whom the results of noninvasive diagnostic testing are equivocal	Patients surviving a cardiac arrest that occurred during acute phase (<48 hr) of MI Patients with cardiac arrest resulting from clearly definable specific causes, such as reversible ischemia, severe valvular aortic stenosis, or noninvasively defined congenital or acquired long-QT syndrome
Unexplained palpitations	Patients with palpitations who have their pulse rate documented by medical personnel as inappropriately rapid and in whom ECG recordings fail to document the cause of the palpitations Patients with palpitations preceding a syncopal episode	Patients with clinically significant palpitations, suspected to be of cardiac origin in whom the symptoms are sporadic and cannot be documented; studies performed to determine mechanisms of arrhythmias, direct or provide therapy, or assess prognosis	Patients with palpitations documented to result from extracardiac causes (e.g., hyperthyroidism)

MI, Myocardial infarction.

Survivors of Cardiac Arrest

The ACC/AHA guidelines consider EPT appropriate for patients who are survivors of cardiac arrest (**see Chapter 42**) other than in the earliest phase of acute myocardial infarction (**see Table 35G.5**). Since publication of these guidelines, acceptance of the usefulness of ICDs has become more widespread, and many of these patients receive such a device without EPT or undergo limited EPT at device implantation. The guidelines consider EPSs inappropriate when cardiac arrest has occurred within the first 48 hours of

myocardial infarction or when the cardiac arrest results from clearly definable and reversible specific causes.

Unexplained Palpitations

The procedure of choice to determine the cause of palpitations is ambulatory ECG according to the ACC/AHA guidelines. The guidelines suggest that EPT should be reserved for patients with palpitations that are associated with syncope or for those in whom electrocardiograms have failed to capture a cause of the palpitations but who have been noted to have a rapid pulse rate by medical personnel (**see Table 35G.5**). EPT is considered to be of equivocal value in patients with symptoms so sporadic that they cannot be documented while ambulatory ECG is performed.

Electrophysiologic Studies for Therapeutic Intervention

The 1995 ACC/AHA guidelines on the appropriateness of EPSs for guidance of drug therapy and implantable electrical devices do not reflect the decline in the role of oral antiarrhythmic therapy and the rise in the use of ICDs for the treatment of patients who have experienced cardiac arrest (**Table 35G.6**). However, the guideline recommendations for the role of catheter ablation remain valid. Characteristics that are common among appropriate indications include supraventricular arrhythmias, including atrial fibrillation, that are symptomatic; that cannot be controlled with medications because of limited effectiveness, side effects, or inconvenience; or that have caused sudden cardiac death.[16] Catheter ablation is also useful for the same reasons in some patients with ventricular tachycardia when it occurs in the absence of structural heart disease, and ablation is often useful as an adjunct to ICD implantation to limit episodes of ventricular tachycardia requiring ICD treatment.[17] Left ventricular dysfunction develops in some patients from frequent premature ventricular complexes, with reversal after ablation of the PVC.

TABLE 35G.6

ACC/AHA 1995 Guidelines on Clinical Intracardiac Electrophysiologic Studies for Therapeutic Intervention

INDICATION	CLASS I (APPROPRIATE)	CLASS II (EQUIVOCAL)	CLASS III (INAPPROPRIATE)
Guidance of drug therapy	Patients with sustained VT or cardiac arrest, especially those with prior MI Patients with AVNRT, AV reentrant tachycardia using an accessory pathway, or AF associated with an accessory pathway for whom chronic drug therapy is planned	Patients with sinus node reentrant tachycardia, atrial tachycardia, AF, or atrial flutter without ventricular preexcitation syndrome for whom chronic drug therapy is planned Patients with arrhythmias not inducible during controlled EPS for whom drug therapy is planned	Patients with isolated atrial or ventricular premature complexes Patients with ventricular fibrillation with a clearly identified reversible cause
Patients who are candidates for or who have implantable electrical devices	Patients with tachyarrhythmias before and during implantation and final (predischarge) programming of an electrical device to confirm its ability to perform as anticipated Patients with an implanted electrical antitachyarrhythmia device in whom changes in status or therapy may have influenced the continued safety and efficacy of the device Patients who have a pacemaker to treat a bradyarrhythmia and receive an ICD to test for device interactions	Patients with previously documented indications for pacemaker implantation to test for the most appropriate long-term pacing mode and sites to optimize symptomatic improvement and hemodynamics	Patients who are not candidates for device therapy
Indications for catheter ablation procedures	Patients with symptomatic atrial tachyarrhythmias who have inadequately controlled ventricular rates unless primary ablation of the atrial tachyarrhythmia is possible Patients with symptomatic atrial tachyarrhythmias such as those above but in whom drugs are not tolerated, or the patient does not wish to take them, even though the ventricular rate can be controlled Patients with symptomatic nonparoxysmal	Patients with a dual-chamber pacemaker and pacemaker-mediated tachycardia that cannot be treated effectively by drugs or by reprogramming the pacemaker	Patients with atrial tachyarrhythmias responsive to drug therapy acceptable to the patient

	junctional tachycardia that is drug resistant, or the patient is drug intolerant or does not wish to take it Patients resuscitated from sudden cardiac death caused by atrial flutter or AF with a rapid ventricular response in the absence of an accessory pathway		
Radiofrequency catheter ablation for AVNRT	Patients with symptomatic sustained AVNRT that is drug resistant, or the patient is drug intolerant or does not desire long-term drug therapy	Patients with sustained AVNRT identified during EPS or catheter ablation of another arrhythmia Finding of dual–AV nodal pathway physiology and atrial echoes but without AVNRT during EPS in patients clinically suspected of having AVNRT	Patients with AVNRT responsive to drug therapy that is well tolerated and preferred by the patient over ablation Finding of dual–AV nodal pathway physiology (with or without echo complexes) during EPS in patients in whom AVNRT is not suspected clinically
Ablation of atrial tachycardia, flutter, and fibrillation: atrium/atrial sites	Patients with atrial tachycardia that is drug resistant, or the patient is drug intolerant or does not desire long-term drug therapy Patients with atrial flutter that is drug resistant, or the patient is drug intolerant or does not desire long-term drug therapy	Atrial flutter or atrial tachycardia associated with paroxysmal AF when the tachycardia is drug resistant, or the patient is drug intolerant or does not desire long-term drug therapy Patients with AF and evidence of a localized site of origin when the tachycardia is drug resistant, or the patient is drug intolerant or does not desire long-term drug therapy	Patients with atrial arrhythmia responsive to drug therapy that is well tolerated and preferred by the patient over ablation Patients with multiform atrial tachycardia
Ablation of atrial tachycardia, flutter, and fibrillation: accessory pathways	Patients with symptomatic AV reentrant tachycardia that is drug resistant, or the patient is drug intolerant or does not desire long-term drug therapy Patients with AF (or other atrial tachyarrhythmia) and a rapid ventricular response through the accessory pathway when the tachycardia is drug resistant, or the patient is drug intolerant or does not desire long-term drug therapy	Patients with AV reentrant tachycardia or AF with rapid ventricular rates identified during EPS for another arrhythmia Asymptomatic patients with ventricular preexcitation whose livelihood or profession, important activities, insurability, or mental well-being or the public safety would be affected by spontaneous tachyarrhythmias or the presence of the ECG abnormality Patients with AF and a controlled ventricular response through the accessory pathway Patients with a family history of sudden cardiac death	Patients who have accessory pathway–related arrhythmias responsive to drug therapy that is well tolerated and preferred by the patient over ablation
Ablation of VT	Patients with symptomatic sustained monomorphic VT when the tachycardia is drug resistant, or the patient is drug intolerant or does not desire long-term drug therapy Patients with bundle branch reentrant VT Patients with sustained monomorphic VT and an ICD who are receiving multiple shocks not manageable by reprogramming or concomitant drug therapy	Nonsustained VT that is symptomatic when the tachycardia is drug resistant, or the patient is drug intolerant or does not desire long-term drug therapy	Patients with VT responsive to drug, ICD, or surgical therapy that is well tolerated and preferred by the patient over ablation Asymptomatic and clinically benign nonsustained VT

AF, Atrial fibrillation; *AVNRT,* atrioventricular nodal reentrant tachycardia; *EPS,* electrophysiologic study; *ICD,* implantable cardioverter-defibrillator; *MI,* myocardial infarction; *VT.* ventricular tachycardia.

Clinical Competence

The ACC/AHA statements on clinical competence[9,10] describes three levels of training: level 1 for every cardiology trainee, level 2 for those wanting to acquire advanced training in the management of arrhythmia, and level 3 for those intending to specialize in invasive diagnostic and therapeutic cardiac electrophysiology. The level 3 guidelines recommend a minimum of 1 year of specialized training in EPSs (as of 2017, 2 years are required), during which the physician should be the primary operator and analyze 100 to 150 initial diagnostic studies, at least 50 of which should involve patients with supraventricular arrhythmias. Because antiarrhythmic devices constitute a major part of current electrophysiology practice, the guidelines suggest that a trainee should be the primary operator during at least 25 electrophysiologic evaluations of implantable antiarrhythmic devices. For maintenance of competence, a minimum of 100 diagnostic EPSs per year is recommended. The statement also recommends that specialists in electrophysiology attend at least 30 hours of formal continuing medical education every 2 years to remain abreast of changes in knowledge and technology.

For physicians who perform catheter ablation, the Heart Rhythm Society Ad Hoc Committee on Catheter Ablation has recommended that training should include at least 75 catheter ablations, at least 10 of which are accessory pathway ablations and 30 to 50 are mentored ablations.[9,10] The ACC/AHA statement recommends that physicians who perform ablations carry out at least 20 to 50 ablations per year.

Individuals receiving training in pacemaker implantation must participate as the primary operator (under direct supervision) in at least 50 primary implantations of transvenous pacemakers and 20 pacemaker system revisions or replacements. At least half the implantations should involve dual-chamber pacemakers. The trainee must also participate in the follow-up of at least 100 pacemaker patient visits and acquire proficiency in advanced pacemaker electrocardiography, interrogation, and programming of complex pacemakers.[9,10]

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36

Therapy for Cardiac Arrhythmias

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According to some evidence, more than 30% of people will have a problematic tachyarrhythmia, most often atrial fibrillation, at some point during a normal life span. Thus, most clinicians will need to manage their patients' rhythm problems, or those treatments may impact or may be impacted by treatment of the patient's other disorders. Treatment of patients with tachyarrhythmias has evolved dramatically over the last 40 years and has become more complex and specialized. A few, relatively ineffective antiarrhythmic drugs (AADs) were the only therapeutic option until the late 1960s, when surgical therapy to cure (not just suppress) tachyarrhythmias was developed. This mode in turn was replaced by catheter ablation for better control or even cure of many types of supraventricular tachycardias and ventricular tachycardias in the absence of structural heart disease starting in the 1980s. The implantable cardioverter-defibrillator (ICD) was introduced in the early 1980s and has become standard therapy for patients with serious ventricular arrhythmias in the presence of structural heart disease. Some patients require a combination of treatments, such as an ICD and AADs or surgery and an ICD; drug therapy can also affect ICD function, positively or negatively. Drug therapy for arrhythmias, at one time the only option, has largely been replaced as the mainstay of therapy by ablation or implanted devices. In most patients, however, tachyarrhythmias are initially treated with AADs, and thus these agents continue to have a significant role in management of patients with a variety of arrhythmias.

Pharmacologic Therapy

The principles of clinical pharmacokinetics and pharmacodynamics are discussed in **Chapter 8**.

General Considerations Regarding Antiarrhythmic Drugs

Most of the AADs available can be classified according to whether they exert blocking actions predominantly on sodium (Na^+), potassium (K^+), or calcium (Ca^{2+}) channels and whether they block receptors (**Table 36.1**). The commonly used classification (Vaughan Williams) is a useful framework for categorizing drug action but is limited because it is based on the electrophysiologic effects exerted by an arbitrary concentration of the drug, generally on a laboratory preparation of normal cardiac tissue. In practice, the actions of these drugs are complex and depend on tissue type, degree of acute or chronic damage, heart rate, membrane potential, ionic composition of the extracellular milieu, autonomic influences (**see Chapter 99**), genetics (**see Chapter 33**), age (**Chapter 88**), and other factors (**Table 36.1**). Many drugs exert more than one type of electrophysiologic effect or operate indirectly, such as by altering hemodynamics, myocardial metabolism, or autonomic neural transmission. Some drugs have active metabolites that exert effects different from those of the parent compound. Not all drugs in the same class have identical effects (e.g., amiodarone, sotalol, and ibutilide). Whereas all class III agents are dramatically different, some drugs in different classes have overlapping actions (e.g., class IA and class IC drugs). Thus, in vitro studies on healthy myocardium usually establish the idealized properties of AADs rather than their actual antiarrhythmic properties in vivo. Since many AADs affect ventricular repolarization and thus have the potential for producing lethal ventricular arrhythmias, development and approval of new agents is uncommon (none in the United States since dronedarone in 2009).[1]

TABLE 36.1

Actions of Drugs Used in Treatment of Arrhythmias

DRUG	CHANNELS						RECEPTORS				PUMPS	PREDOMINANT CLINICAL EFFECTS		
	Na*			Ca	K_r	K_s	α	β	M_2	P	Na-K ATPase	LV Function	Sinus Rate	Extracardiac
	Fast	Med	Slow											
Quinidine		●A					○		○			—	↑	
Procainamide		●I										↓	—	
Disopyramide		●A							○			↓	var	●
Ajmaline		●A										—	— ↓	○
Lidocaine	○											—	— ↓	○
Mexiletine	○											—	—	○
Phenytoin	○											—	—	
Flecainide			●A		○							↓	—	○
Propafenone		●A			○							↓	↓	○
Propranolol	○							●				↓	↓	○
Nadolol								●				↓	↓	○
Amiodarone	○				●							—	↓	●
Dronedarone	○				●							—	↓	○
Sotalol					●			●				↓	↓	○
Ibutilide	activator				○							—	↓	○
Dofetilide					●							—	—	○
Verapamil	○			●								↓	↓	○
Diltiazem												↓	↓	○
Adenosine										□		—	↓	
Digoxin									○		●	↑	↓	
Atropine									●			—	↑	
Ranolazine	○				○							—	—	○

*_Fast, med_ (medium), and _slow_ refer to kinetics of recovery from sodium channel blockade.

Relative potency of blockade or extracardiac side effect: ○ = low; = moderate; ● = high; □ = agonist; A = activated state blocker; I = inactivated state blocker.

— = minimal effect; ↑ = increase; ↓ = decrease; var = variable effects.

K_r, Rapid component of delayed rectifier K^+ current; K_s, slow component of delayed rectifier K^+ current; M_2, muscarinic receptor subtype 2; _P,_ A_1 purinergic receptor; _LV,_ left ventricular.

Modified from Schwartz PJ, Zaza A. Haemodynamic effects of a new multifactorial antihypertensive drug. Eur Heart J 1992;13:26.

Despite its limitations, the Vaughan Williams classification is widely known and provides a useful communication shorthand, but the reader is cautioned that drug actions are more complex than those depicted by the classification. A more realistic but not widely used framework regarding AADs is provided by the “Sicilian Gambit.” This approach to drug classification is an attempt to identify the mechanisms of a particular arrhythmia, to determine the vulnerable parameter of the arrhythmia most susceptible to modification, to define the target most likely to affect the vulnerable parameter, and then to select a drug that will modify the target[2] (**Table 36.2**; **also see Table 36.1**).

TABLE 36.2

Classification of Drug Actions on Arrhythmias Based on Modification of Vulnerable Parameter

MECHANISM	ARRHYTHMIA	VULNERABLE PARAMETER (EFFECT)	DRUGS (EFFECT)
Automaticity			
Enhanced normal	Inappropriate sinus tachycardia Some idiopathic ventricular tachycardias	Phase 4 depolarization (decrease)	β-Adrenergic blocking agents Na^+ channel blocking agents
Abnormal	Atrial tachycardia	Maximum diastolic potential (hyperpolarization)	M_2 agonist
		Phase 4 depolarization (decrease)	Ca^{2+} or Na^+ channel blocking agents M_2 agonist
	Accelerated idioventricular rhythms	Phase 4 depolarization (decrease)	Ca^{2+} or Na^+ channel blocking agents
Triggered Activity			
EAD	Torsades de pointes	Action potential duration (shorten)	β-adrenergic agonists; vagolytic agents (increase rate)
		EAD (suppress)	Ca^{2+} channel blocking agents; Mg^{2+}; β-adrenergic blocking agents; ranolazine
DAD	Digitalis-induced arrhythmias	Calcium overload (unload)	Ca^{2+} channel blocking agents
		DAD (suppress)	Na^+ channel blocking agents
	RV outflow tract ventricular tachycardia	Calcium overload (unload)	β-adrenergic blocking agents
		DAD (suppress)	Ca^{2+} channel blocking agents; adenosine
Reentry—Na^+ Channel Dependent			
Long excitable gap	Typical atrial flutter	Conduction and excitability (depress)	Type IA, IC Na^+ channel blocking agents
	Circus movement tachycardia in WPW	Conduction and excitability (depress)	Type IA, IC Na^+ channel blocking agents
	Sustained uniform ventricular tachycardia	Conduction and excitability (depress)	Na^+ channel blocking agents
Short excitable gap	Atypical atrial flutter	Refractory period (prolong)	K^+ channel blocking agents
	Atrial fibrillation	Refractory period (prolong)	K^+ channel blocking agents
	Circus movement tachycardia in WPW	Refractory period (prolong)	Amiodarone, sotalol
	Polymorphic and uniform ventricular tachycardia	Refractory period (prolong)	Type IA Na^+ channel blocking agents
	Bundle branch reentry	Refractory period (prolong)	Type IA Na^+ channel blocking agents; amiodarone
	Ventricular fibrillation	Refractory period (prolong)	
Reentry—Ca^{2+} Channel Dependent			
	AV nodal reentrant tachycardia	Conduction and excitability (depress)	Ca^{2+} channel blocking agents
	Circus movement tachycardia in WPW	Conduction and excitability (depress)	Ca^{2+} channel blocking agents
	Verapamil-sensitive ventricular tachycardia	Conduction and excitability (depress)	Ca^{2+} channel blocking agents

AV, Atrioventricular; *DAD,* delayed afterdepolarization; *EAD,* early afterdepolarization; *RV,* right ventricular; *WPW,* Wolff-Parkinson-White syndrome.

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Drug Classification

According to the Vaughan Williams classification, class I drugs predominantly block the fast sodium channel (I_{Na}). These in turn are divided into three subgroups, classes IA, IB, and IC (**Table 36.3**). Some also block potassium channels at pharmacologically relevant concentrations.

TABLE 36.3

In vitro Electrophysiologic Characteristics of Antiarrhythmic Drugs

DRUG	APD	dV/dt	MDP	ERP	CV	PF PHASE 4	SN Auto	Contr	SI Curr	AUTONOMIC NERVOUS SYSTEM
Quinidine	↑	↓	0	↑	↓	↓	0	0	0	Antivagal; alpha blocker
Procainamide	↑	↓	0	↑	↓	↓	0	0	0	Slight antivagal
Disopyramide	↑	↓	0	↑	↓	↓	↓ 0 ↑	↓	0	Central: antivagal, antisympathetic
Ajmaline	↑	↓	0	↑	↓	↓	↓ 0	↓	0	Antivagal
Lidocaine	↓	0 ↓	0	↓	0 ↓	↓	0	0	0	0
Mexiletine	↓	0 ↓	0	↓	↓	↓	0	↓	0	0
Phenytoin	↓	↓ 0 ↑	0	↓	0	↓	0		0	0
Flecainide	0 ↑	↓	0	↑	↓↓	↓	0	↓	0	0
Propafenone	0 ↑	↓	0	↑	↓↓	↓	0	↓	0 ↓	Antisympathetic
Propranolol	0 ↓	0 ↓	0	↓	0	↓*	↓	↓	0 ↓	Antisympathetic
Amiodarone	↑	0 ↓	0	↑	↓	↓	↓	0 ↑	0	Antisympathetic
Dronedarone	↑	0 ↓	0	↑	↓	↓	↓	0 ↓	0	Antisympathetic
Sotalol	↑	0 ↓	0	↑	0	0 ↓	↓	↓	0 ↓	Antisympathetic
Ibutilide	↑	0	0	↑	0	0	↓	0	0	0
Dofetilide	↑	0	0	↑	0	0	0	0	0	0
Verapamil	↓	0	0	0	0	↓*	↓	↓	↓↓	? Block alpha receptors; enhance vagal
Adenosine	↑	0 ↓	More (−)	↑	0	0 ↓	↓	0	↓	Vagomimetic
Ranolazine	↑	0	0	↑	0	0	0	0	0	0

*With a background of sympathetic activity.

↑ = increase; ↓ = decrease; 0 = no change; 0 ↑ or 0 ↓ = slight or inconsistent increase or decrease.

APD, Action potential duration; *dV/dt,* rate of rise of action potential; *MDP,* maximum diastolic potential; *ERP,* effective refractory period (longest S_1-S_2 interval at which S_2 fails to produce a response); *CV,* conduction velocity; *PF,* Purkinje fiber; *SN Auto,* sinus nodal automaticity; *Contr,* contractility; *SI Curr,* slow inward current.

Class IA

This class includes drugs that reduce Vmax (rate of rise in action potential upstroke [phase 0]) and prolong the action potential duration (APD; **see Chapter 34**)—quinidine, procainamide, and disopyramide. The kinetics of onset and offset of class IA drugs in blocking the Na^+ channel is of intermediate rapidity (<5 seconds) when compared with class IB and class IC agents.

Class IB

This class of drugs does not reduce Vmax and shortens the APD—mexiletine, phenytoin, and lidocaine. The kinetics of onset and offset of these drugs in blocking the sodium channel is rapid (<500 milliseconds).

Class IC

This class of drugs, including flecainide and propafenone, can reduce Vmax, slow conduction velocity, and prolong refractoriness minimally. These drugs have slow onset and offset kinetics (10 to 20 seconds).

Class II

These drugs block beta-adrenergic receptors and include propranolol, metoprolol, nadolol, carvedilol, nebivolol, and timolol.

Class III

This class of drugs predominantly blocks potassium channels (e.g., I_{Kr}) and prolongs repolarization. Included are sotalol, amiodarone, dronedarone, and ibutilide.

Class IV

This class of drugs predominantly blocks the slow calcium channel ($I_{Ca.L}$)—verapamil, diltiazem, nifedipine, and others (felodipine blocks $I_{Ca.T}$).

Antiarrhythmic agents appear to cross the cell membrane and interact with receptors in the membrane channels when the channels are in the resting, activated, or inactivated state (**see Table 36.1** and **Chapter 34**), and each of these interactions is characterized by different association and dissociation rate constants of a drug on its receptor. Such interactions depend on voltage and time. Transitions among resting, activated, and inactivated states are time and voltage dependent. When the drug is bound (associated) to a receptor site at or close to the channel pore (the drug may not actually "plug" the channel), the channel cannot conduct, even in the activated state.

Use Dependence.

Some drugs exert greater inhibitory effects on the upstroke of the action potential at more rapid rates of stimulation and after longer periods of stimulation, a characteristic called *use dependence*. Drugs with this property depress Vmax to a greater extent after the channel has been "used" (i.e., after action potential depolarization rather than after a rest period). Agents with class IB action exhibit rapid binding and unbinding from their receptor site on the channel protein, or exhibit use-dependent block of the fast channel at fast rates. Class IC drugs have slow kinetics, and class IA drugs are intermediate. With increased time spent in diastole (slower rate), a greater proportion of receptors become drug free, and the drug exerts less effect. Unhealthy cells with reduced (i.e., abnormal) membrane potentials recover more slowly from drug actions than do healthier cells with more negative (i.e., normal) membrane potentials. This is referred to as *voltage dependence of block*.

Reverse Use Dependence.

Some drugs exert greater effects at slow rates than at fast rates, a property known as *reverse use dependence*. This is particularly true for drugs that lengthen repolarization; in the ventricle the QT interval becomes more prolonged at slow rather than at fast rates. This effect is not an ideal antiarrhythmic property, because prolongation of refractoriness should be increased at fast rates to interrupt or prevent a tachycardia and should be minimal at slow rates to avoid precipitation of torsades de pointes (TdP).

Mechanisms of Arrhythmia Suppression.

Given that enhanced automaticity, triggered activity, or reentry can cause cardiac arrhythmias (**see Chapter 34**), mechanisms by which AADs suppress arrhythmias can be postulated (**see Table 36.2**). AADs can slow the spontaneous discharge frequency of an automatic pacemaker by depressing the slope of diastolic depolarization, shifting the threshold voltage toward zero, or hyperpolarizing the resting membrane potential. In general, most AADs in therapeutic doses depress the automatic firing rate of spontaneously discharging ectopic sites while minimally affecting the discharge rate of the normal sinus node. Other agents act directly on the sinus node to slow heart rate, whereas drugs that exert vagolytic effects, such as disopyramide and quinidine, can increase the sinus discharge rate. Drugs can also suppress early or delayed afterdepolarizations and eliminate triggered arrhythmias based on these mechanisms.

Reentry depends critically on the interrelationships between refractoriness and conduction velocity, the presence of unidirectional block in one of the pathways, and other factors that influence refractoriness

and conduction, such as excitability (**see Chapter 34**). An antiarrhythmic agent can stop ongoing reentry that is already present or can prevent it from starting if the drug depresses or, alternately, improves conduction. For example, improving conduction can (1) eliminate unidirectional block so that reentry cannot begin or (2) facilitate conduction in the reentrant loop so that the returning wavefront reenters too quickly, encounters cells that are still refractory, and is extinguished. A drug that depresses conduction can transform unidirectional block into bidirectional block and thus terminate reentry or prevent it from starting by creating an area of complete block in the reentrant pathway. Conversely, a drug that slows conduction without producing block or significantly lengthening refractoriness can actually promote reentry. Lastly, most AADs share the ability to prolong refractoriness relative to their effects on APD; that is, the ratio of the effective refractory period (ERP) to APD exceeds 1.0. If a drug prolongs the refractoriness of fibers in the reentrant pathway, the pathway may not recover excitability in time to be depolarized by the reentering impulse, and reentrant propagation ceases. The different types of reentry influence the effectiveness of a drug.

In considering the properties of a drug, it is important to define carefully the situation or model from which conclusions are drawn. Electrophysiologic, hemodynamic, autonomic, pharmacokinetic, and adverse effects can all differ in normal individuals compared with patients, in normal versus abnormal tissue, in cardiac muscle compared with specialized conduction fibers, and in atrial versus ventricular muscle (**Table 36.4**).

TABLE 36.4

Dosage and Other Information for Clinical Use of Common Antiarrhythmic Agents

DRUG	USUAL DOSAGE RANGES				TIME TO PEAK PLASMA CONCENTRATION (ORAL) (HR)	EFFECTIVE SERUM OR PLASMA CONCENTRATION (µg/mL)	HALF-LIFE (hr)	BIOAVAILABILITY (%)	MA RO ELI
	INTRAVENOUS (mg)		ORAL (mg)						
	Loading	Maintenance	Loading	Maintenance					
Quinidine	6-10 mg/kg at 0.3-0.5 mg/kg/min	—	800-1000	300-600 q6h	1.5-3.0	3-6	5-9	60 to 80	Liver
Procainamide	6-13 mg/kg at 0.2-0.5 mg/kg/min	2-6 mg/min	500-1000	250-1000 q4-6h	1	4-10	3-5	70 to 85	Kidn
Disopyramide	1-2 mg/kg over 15-45 min*	1 mg/kg/hr*	N/A	100-300 q6-8h	1-2	2-5	8-9	80 to 90	Kidn
Lidocaine	1-2 mg/kg at 20-50 mg/min	1-4 mg/min	N/A	N/A	N/A	1-5	1-2	N/A	Liver
Mexiletine	500 mg*	0.5-1.0 g/24 hr*	400-600	150-300 q8-12h	2-4	0.75-2.0	10-17	90	Liver
Phenytoin	100 mg q5min for ≤1000 mg	N/A	1000	100-400 q12-24h	8-12	10-20	18-36	50 to 70	Liver
Flecainide	2 mg/kg*	100-200 q12h*		50-200 q12h	3-4	0.2-1.0	20	95	Kidn
Propafenone	1-2 mg/kg*	N/A	600-900	150-300 q8-12h	1-3	0.2-3.0	5-8	25 to 75	Liver
Propranolol	0.25-0.5 mg q5min to ≤0.20 mg/kg	N/A	N/A	10-200 q6-8h	4	1-2.5	3-6	35 to 65	Liver
Amiodarone	15 mg/min for 10 min 1 mg/min for 6 hr 0.5 mg/min thereafter	0.5 mg/min	800-1600 qd for 7-14 days	200-600 qd	Variable	0.5-1.5	56 days	25	Liver
Dronedarone	N/A	N/A	N/A	400 mg q12h	3-4	0.3-0.6	13-19	70 to 90	Liver
Sotalol	10 mg over 1-2 min*	N/A	N/A	80-160 q12h	2.5-4	2.5	12	90 to 100	Kidn
Ibutilide	1 mg over 10 min	N/A	N/A	N/A	N/A	N/A	6		Kidn
Dofetilide	2-5 µg/kg infusion*	N/A	N/A	0.125-0.5 q12h			7-13	90	Kidn
Verapamil	5-10 mg over 1-2 min	0.005 mg/kg/min	N/A	80-120 q6-8h	1-2	0.10-0.15	3-8	10 to 35	Liver
Adenosine	6-18 mg (rapidly)	N/A	N/A	N/A	N/A	N/A	Seconds	100	Bloo
Digoxin	0.5-1.0 mg	0.125-0.25 qd	0.5-1.0	0.125-0.25 qd	2-6	0.0008-0.002	36-48	60 to 80	Kidn
Ranolazine	N/A	N/A	N/A	500-1000 bid	4-6	N/A	7	60-75	Kidn

*Intravenous use investigational or unavailable in United States.

N/A, Not applicable; *q4-6h,* every 4 to 6 hours; *qd,* every day; *bid,* twice daily.

Results presented may vary according to doses, disease state, and IV or oral administration.

Pregnancy Class: *A,* controlled studies show no fetal risk; *B,* no controlled studies, but no evidence of fetal risk; fetal harm unlikely; *C,* fetal risk cannot be excluded; drug should be used only if potential benefits outweigh potential risk; *D,* definite fetal risk; drug should be avoided unless in a life-threatening situation or safer alternatives do not exist; *X,* contraindicated in pregnancy. Categorization of safety during pregnancy and lactation is currently undergoing revision.

Drug Metabolites.

Drug metabolites can add to or alter the effects of the parent compound by exerting similar actions, competing with the parent compound, or mediating drug toxicity. Quinidine has at least four active metabolites, but none with a potency exceeding that of the parent drug, and none implicated in causing TdP. About 50% of procainamide is metabolized to *N*-acetylprocainamide (NAPA), which prolongs repolarization and is a less effective AAD but competes with procainamide for renal excretion and can increase the parent drug's elimination half-life. A lidocaine metabolite can compete with the parent drug

for sodium channels and partially antagonize its blocking effect.

Pharmacogenetics.

Genetically determined metabolic pathways account for many of the differences in patients' responses to some drugs[3] (**see Chapter 8**). The genetically determined activity of hepatic *N*-acetyltransferase regulates the development of antinuclear antibodies (ANAs) and lupus syndrome in response to procainamide. Slow acetylator phenotypes appear to be more prone than rapid acetylators to the development of lupus. The enzyme cytochrome P-450 (CYP450) is needed to metabolize propafenone, to hydroxylate several beta blockers, and to biotransform flecainide. Lack of this enzyme (in approximately 7% of patients) reduces metabolism of the parent compound and thereby leads to increased plasma concentrations of the parent drug and reduced concentrations of metabolites. Propafenone is metabolized by CYP450 to a compound with slightly less antiarrhythmic and beta-adrenergic blocking effects, as well as fewer central nervous system (CNS) side effects. Thus, poor metabolizers may experience more heart rate slowing and neurotoxicity than extensive metabolizers do.

Drugs such as rifampin, phenobarbital, and phenytoin induce the synthesis of larger amounts of CYP450, which leads to lower concentrations of the parent drugs because of extensive metabolism, whereas erythromycin, clarithromycin, fluoxetine, and grapefruit juice inhibit enzyme activity, which leads to accumulation of the parent compound. Therefore, clinicians caring for patients who take AADs should be sensitive to the effects of noncardiac medications and supplements on AAD metabolism and elimination and to drug-drug interactions. Over-the-counter (OTC) drugs such as proton pump inhibitors can promote hypokalemia and hypomagnesemia and interact with a simple antibiotic such as ceftriaxone to cause TdP.[4] Many astute clinicians use, and refer their patients to, websites such as Crediblemeds.org, where updated information on drug interactions of this type is available.

Clinical Use

In treating cardiac rhythm disorders, most drugs are given on a daily basis (in one to three doses) to prevent episodes from occurring or, in some cases of atrial fibrillation (AF), to control the ventricular rate. Efficacy can be judged in various ways, depending on the clinical circumstances. Symptom reduction (in the case of benign arrhythmias, such as most premature ventricular complexes) and electrocardiographic monitoring (long-term or event; **see Chapter 35**) are useful; electrophysiologic study (EPS) has been used in the past, with suppression of electrical induction of arrhythmia being the goal, but is rarely used currently. Interrogation of implanted device memory can also provide an indicator of the success of drug therapy.

In some patients, tachycardia episodes are infrequent enough (months between occurrences) and symptoms mild enough that reactive drug administration is more reasonable than chronic daily dosing. The patient takes a medication only after an episode has started, in the hope that the tachycardia can be terminated and a visit to a physician's office or emergency department avoided. This “pill in the pocket” strategy has worked well for some patients with AF, who have been given one of various medications orally in a monitored setting to ensure safety as well as efficacy before allowing self-medication at home or elsewhere.

Adverse Effects

Antiarrhythmic drugs produce one group of adverse effects related to excessive dosage and plasma concentrations that result in both noncardiac (e.g., neurologic defects) and cardiac (e.g., heart failure, some arrhythmias) toxicity. Another group of side effects unrelated to plasma concentrations is termed

idiosyncratic; examples include amiodarone-induced pulmonary fibrosis and some arrhythmias, such as quinidine-induced TdP, which can occur in individuals with a forme fruste of long-QT syndrome (i.e., marked prolongation of normal QT interval in the presence of certain medications; **see Chapters 8 and 33**). Genetic variants can underlie susceptibility to idiosyncratic reactions.

The U.S. Food and Drug Administration (FDA) has recently determined that the risk of adverse events during pregnancy and lactation (previously categorized as A, B, C, D, and X; **see Table 36.4**, footnote) should be modified (the Pregnancy and Lactation Labeling rule of 2014). This process is underway but until completed, adverse event risk in this setting is characterized using the previous classification.[5]

Proarrhythmia

Drug-induced or drug-exacerbated cardiac arrhythmias (proarrhythmia) constitute a major clinical problem.[6] Proarrhythmia can manifest as an increase in frequency of a preexisting arrhythmia, sustaining of a previously nonsustained arrhythmia (even making it incessant), or development of arrhythmias that the patient has not previously experienced. Electrophysiologic mechanisms are probably related to prolongation of repolarization or an increase in its transmural dispersion, development of early afterdepolarizations (EADs) with resultant TdP, and alterations in reentry pathways to initiate or to sustain tachyarrhythmias. Proarrhythmic events can occur in as many as 5% to 10% of patients receiving antiarrhythmic agents; heart failure increases this risk. Reduced left ventricular function, treatment with digitalis and diuretics, and a longer pretreatment QT interval characterize patients who experience AAD-induced ventricular fibrillation (VF). The more commonly known proarrhythmic events occur within several days of beginning drug therapy or changing dosage and are represented by such developments as incessant ventricular tachycardia (VT) and long-QT–related TdP. In the Cardiac Arrhythmia Suppression Trial (CAST), however, researchers found that encainide and flecainide reduced spontaneous ventricular arrhythmias but were associated with a total mortality of 7.7%, versus 3.0% in the placebo group. Deaths were equally distributed throughout the treatment period, indicating that another type of proarrhythmic response can occur sometime after the beginning of drug therapy. Such late proarrhythmic effects may be related to drug-induced exacerbation of the regional myocardial conduction delay caused by ischemia and to heterogeneous drug concentrations that can promote reentry. In the future, a candidate antiarrhythmic compound's potential for proarrhythmia may be modeled computationally and tested in stem cells.[7]

The availability of catheter ablation (see later) and implantable devices (pacemakers and ICDs; **see Chapter 41**) to treat a wide variety of arrhythmias has largely relegated drug therapy to a secondary role in the treatment of serious arrhythmias. Drugs are still useful to prevent or to decrease the frequency of recurrences in patients who have relatively infrequent episodes of benign tachycardias, as well as in those who have had incomplete success with catheter ablation procedures and in patients with an ICD, to decrease the frequency of shocks because of supraventricular or ventricular arrhythmias.

Antiarrhythmic Agents

Class IA Agents

Quinidine

Quinidine and quinine are isomeric alkaloids isolated from cinchona bark. Although quinidine shares the antimalarial, antipyretic, and vagolytic actions of quinine, only quinidine has direct cellular electrophysiologic effects. It blocks several channels, including the rapid inward sodium channel, I_{Kr}, I_{to}, and to a lesser extent the slow inward calcium channel, I_{Ks}, and the adenosine triphosphate (ATP)–sensitive potassium current (K_{ATP}). The ultimate biologic effect of the drug in a given patient depends on heart rate, drug concentration, and which channels are more prominently affected. Because of decreased demand for quinidine, manufacturing had ceased for a time, with little remaining supply in many countries; with recent renewed demand for its use in patients with Brugada syndrome, for example, quinidine is more readily available.

Electrophysiologic Actions.

Quinidine exerts little effect on automaticity of the normal sinus node but suppresses automaticity in normal Purkinje fibers (**Table 36.5**; **see also Tables 36.1, 36.2, and 36.3**). In patients with sinus node dysfunction, quinidine can further depress sinus node automaticity. Quinidine lengthens the QT interval in part via formation of EADs in experimental preparations and in humans, which appears to be responsible for TdP. Because of its significant anticholinergic effect and the reflex sympathetic stimulation resulting from alpha-adrenergic blockade, which causes peripheral vasodilation, quinidine can cause a reflex increase the sinus node discharge rate and improve atrioventricular (AV) nodal conduction. Quinidine prolongs repolarization, an effect that is more prominent at slow heart rates (reverse use dependence) because of block of I_{Kr} (as well as enhancing the late inward Na^+ current). Faster rates result in more block of sodium channels and less unblocking because a smaller percentage of time is spent in the rested state (use dependence). Isoproterenol can modulate the effects of quinidine on reentrant circuits in humans. Quinidine at higher doses inhibits the late inward Na^+ current. As noted, quinidine blocks the transient outward current I_{to}, which probably explains its efficacy in suppressing ventricular arrhythmias in Brugada syndrome (**see Chapter 33**).

Table 36.5

In vivo Electrophysiologic Characteristics of Antiarrhythmic Drugs

DRUG	ELECTROCARDIOGRAPHIC MEASUREMENTS					ELECTROPHYSIOLOGIC MEASUREMENTS					
	Sinus Rate	PR	QRS	QT	JT	ERP-AVN	ERP-HPS	ERP-A	ERP-V	AH	HV
Quinidine	0 ↑	↓ 0 ↑	↑	↑	↑	0 ↑	↑	↑	↑	0 ↓	↑
Procainamide	0	0 ↑	↑	↑	↑	0 ↑	↑	↑	↑	0 ↑	↑
Disopyramide	↓ 0 ↑	↓ 0 ↑	↑	↑	↑	↑ 0	↑	↑	↑	↓ 0 ↑	↑
Ajmaline	0	0 ↑	↑	↑	↑	0	↑	↑	↑	↓ 0 ↑	↑
Lidocaine	0	0	0	0 ↓	↓	0 ↓	0 ↑	0	0	0 ↓	0 ↑
Mexiletine	0	0	0	0 ↓	↓	0 ↑	0 ↑	0	0	0 ↑	0 ↑
Phenytoin	0	0	0	0	0	0 ↓	↓	0	0	0 ↑	0
Flecainide	0 ↓	↑	↑	0 ↑	0	↑	↑	↑	↑	↑	↑
Propafenone	0 ↓	↑	↑	0 ↑	0	0 ↑	0 ↑	0 ↑	↑	↑	↑
Propranolol	↓	0 ↑	0	0 ↓	0	↑	0	0	0	0	0
Amiodarone	↓	0 ↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Dronedarone	↓	0 ↑	↑	↑	↑	↑	↑	↑	↑	↑	0
Sotalol	↓	0 ↑	0	↑	↑	↑	↑	↑	↑	↑	0
Ibutilide	↓	0 ↓	0	↑	↑	0	0	↑	↑	0	0
Dofetilide	0	0	0	↑	↑	0	0	↑	↑	0	0
Verapamil	0 ↓	↑	0	0	0	↑	0	0	0	↑	0
Adenosine	↓ then ↑	↑	0	0	0	↑	0	↓	0	↑	0
Digoxin	↓	↑	0	0	↓	↑	0	↓	0	↑	0
Ranolazine	0	0	0	↑	↑	0	0	↑	↑	0	0

Results presented may vary according to tissue type, and drug concentration and autonomic tone.

↑ = increase; ↓ = decrease; 0 = no change; 0 ↑ or 0 ↓ = slight or inconsistent increase or decrease.

A, Atrium; *AVN,* atrioventricular node; *HPS,* His-Purkinje system; *V,* ventricle; *AH,* atrio-His interval (an index of AV nodal conduction); *HV,* His-ventricular interval (an index of His-Purkinje conduction); *ERP,* effective refractory period (longest S_1-S_2 interval at which S_2 fails to produce a response).

Hemodynamic Effects.

Quinidine induces vasodilation by blocking alpha-adrenergic receptors and can cause significant hypotension. It does not result in significant direct myocardial depression.

Pharmacokinetics.

Plasma quinidine concentrations peak at approximately 1.5 to 3 hours after an oral dose of a quinidine gluconate preparation (**see Table 36.4**). Quinidine can be given intravenously if it is infused slowly, but intramuscular dosing should be avoided. Approximately 80% of plasma quinidine is protein bound, especially to $alpha_1$-acid glycoprotein. Both the liver and the kidneys remove quinidine; dose adjustments may be made to achieve appropriate serum concentrations. Its elimination half-life is 8 to 9 hours after oral administration. Quinidine's effect on repolarization and its overall efficacy vary directly with left ventricular function; at the same serum concentration, the QT interval is longer in women than in men.

Dosage and Administration.

The usual oral dose of quinidine sulfate for an adult is 300 to 600 mg four times daily, which results in a steady-state level within about 24 hours (**see Table 36.4**). A loading dose of 600 to 800 mg produces an earlier effective concentration. Oral doses of the gluconate are about 30% higher than those of the sulfate form. Important interactions with other drugs occur.

Indications.

Quinidine is a versatile AAD that was used previously to treat premature supraventricular and ventricular complexes and sustained tachyarrhythmias. However, because of its side effect profile and potential for causing TdP, as well as its limited usefulness in preventing VT and VF in most applications, its use has

decreased greatly. In recent years, however, interest has increased in quinidine for treating primary VF, ventricular arrhythmias in patients with Brugada syndrome[8] (**see Chapter 33**), and short-QT syndrome. Because it crosses the placenta, quinidine can be used to treat arrhythmias in the fetus.

Adverse Effects.

The most common adverse effects of chronic oral quinidine therapy are gastrointestinal (GI) and include nausea, vomiting, diarrhea, abdominal pain, and anorexia (milder with the gluconate form). CNS toxicity includes tinnitus, hearing loss, visual disturbances, confusion, delirium, and psychosis (cinchonism). Allergic reactions include rash, fever, immune-mediated thrombocytopenia, hemolytic anemia, and rarely, anaphylaxis. Side effects may preclude long-term administration of quinidine in 30% to 40% of patients.

Quinidine can slow cardiac conduction, sometimes to the point of block, which is manifested as prolongation of the QRS duration or as sinoatrial (SA) or AV nodal conduction disturbances. Quinidine can produce syncope in 0.5% to 2.0% of patients, most often the result of a self-terminating episode of TdP. Quinidine prolongs the QT interval in most patients, regardless of whether ventricular arrhythmias occur, but significant QT prolongation (QT interval of 500 to 600 milliseconds) is often a characteristic of patients with quinidine-related syncope, who may have a genetic predisposition underlying such a response (**see Chapter 8**). Many of these patients are also receiving digitalis or diuretics or have hypokalemia; women are more susceptible than men. Importantly, syncope is unrelated to plasma concentrations of quinidine or the duration of therapy, although most episodes occur within the first 2 to 4 days of therapy, often after conversion of AF to sinus rhythm. This proarrhythmic effect during initiation of treatment is reproducible and because of this, the drug should not be taken on an intermittent basis. Therapy of proarrhythmia requires immediate discontinuation of use of the drug; magnesium given intravenously (2 g over 1 to 2 minutes, followed by an infusion of 3 to 20 mg/min) is the initial drug treatment of choice. Atrial or ventricular pacing can be used to suppress the ventricular tachyarrhythmia, perhaps by suppressing EADs. When pacing is not available, isoproterenol can be given with caution. The arrhythmia gradually dissipates as quinidine is cleared and the QT interval returns to baseline. Affected patients should not use quinidine thereafter and also should avoid other drugs with similar effects on the QT interval (see Crediblemeds.org).

Drugs that induce hepatic enzyme production, such as phenobarbital and phenytoin, can shorten the duration of action of quinidine by increasing its rate of elimination. Quinidine can increase plasma concentrations of flecainide by inhibiting the CYP450 enzyme system. Quinidine can elevate serum digoxin concentrations by decreasing its clearance and volume of distribution and the affinity of tissue receptors.

Procainamide

Electrophysiologic Actions.

The cardiac actions of procainamide on automaticity, conduction, excitability, and membrane responsiveness resemble those of quinidine (**see Tables 36.1, 36.2, 36.3, and 36.5**). Procainamide predominantly blocks the inactivated state of I_{Na}. It also blocks I_{Kr} and $I_{K.ATP}$. Like quinidine, procainamide usually prolongs the ERP more than it prolongs the APD and thus may prevent reentry. Procainamide exerts the least anticholinergic effects among type IA drugs. It does not affect normal sinus node automaticity. In vitro, procainamide decreases abnormal automaticity, with less effect on triggered

activity or catecholamine-enhanced normal automaticity. Unlike the parent drug, NAPA, its major metabolite, is a K^+ channel blocker (I_{Kr}) and exerts class III action, prolonging the APD of ventricular muscle and Purkinje fibers in a dose-dependent manner. High levels of NAPA, such as in patients with renal disease, can produce EADs, triggered activity, and TdP. Because of decreased demand, availability of intravenous (but not oral) procainamide is limited in some areas.

Hemodynamic Effects.

Procainamide can depress myocardial contractility in high concentrations. It does not produce alpha blockade but can result in peripheral vasodilation, possibly through antisympathetic effects on the brain or spinal cord, which can impair cardiovascular reflexes (e.g., provoking orthostatic symptoms).

Pharmacokinetics.

Oral administration produces a peak plasma concentration in approximately 1 hour. Approximately 80% of oral procainamide is bioavailable; the overall elimination half-life of procainamide is 3 to 5 hours, with 50% to 60% of the drug eliminated by the kidneys and 10% to 30% metabolized by the liver (**see Table 36.4**). The drug is acetylated to NAPA, which is excreted almost exclusively by the kidneys. As renal function decreases and in patients with heart failure, NAPA levels increase and, because of the risk for serious cardiotoxicity, need to be carefully monitored in these situations. NAPA has an elimination half-life of 7 to 8 hours, but the half-life exceeds 10 hours if high doses of procainamide are used. Increased age, congestive heart failure, and reduced creatinine clearance lower the clearance of procainamide and necessitate a reduced dosage.

Dosage and Administration.

Procainamide can be given by the oral, intravenous (IV), or intramuscular (IM) route to achieve plasma concentrations in the range of 4 to 10 mg/mL and produce an antiarrhythmic effect (**see Table 36.4**). Several IV regimens have been used to administer procainamide, but usually doses of 10 to 15 mg/kg are used a rate of up to 50 mg/min until the arrhythmia has been controlled, hypotension results, or the QRS complex is prolonged more than 50%. With this method, the plasma concentration falls rapidly during the first 15 minutes after the loading dose, with parallel effects on refractoriness and conduction. A constant-rate IV infusion of procainamide can be given at a dosage of 2 to 6 mg/min, depending on the patient's response.

Oral administration of procainamide requires a 3- to 4-hour dosing interval at a total daily dose of 2 to 6 g, with a steady-state concentration being reached within 1 day. When a loading dose is used, it should be twice the maintenance dose. Frequent dosing is required because of its short elimination half-life in normal persons. For the extended-release forms of procainamide, dosing is at 6- to 12-hour intervals. Procainamide by IM injection is almost 100% bioavailable.

Indications.

Procainamide is used to treat both supraventricular and ventricular arrhythmias in a manner comparable to that of quinidine. Although both drugs have similar electrophysiologic actions, either drug can effectively suppress a supraventricular or ventricular arrhythmia that is resistant to the other drug. Procainamide can be used to convert recent-onset AF to sinus rhythm. As with quinidine, prior treatment with beta or calcium channel blockers is recommended to prevent acceleration of the ventricular response during atrial flutter or fibrillation after procainamide therapy. Procainamide can block conduction in the accessory pathway of patients with Wolff-Parkinson-White (WPW) syndrome and can be used in patients with AF and a rapid ventricular response related to conduction over the accessory pathway. It can

produce His-Purkinje block and is sometimes administered during an EPS to stress the His-Purkinje system and evaluate the need for a pacemaker (**see Fig. 35.9**). However, it should be used with caution in patients with evidence of His-Purkinje disease (bundle branch block) in whom a ventricular pacemaker is not readily available.

Procainamide is more effective than lidocaine in acutely terminating sustained VT. Most consistently, procainamide slows the VT rate, a change correlated with the increase in QRS duration. The drug also has diagnostic application when given intravenously (10 mg/kg over 5 to 10 minutes). In patients with suspected Brugada syndrome who have a normal resting electrocardiogram (ECG), drug infusion can result in the characteristic "Brugada sign," whereas in patients with WPW syndrome, the drug can cause sudden loss of preexcitation, a finding indicative of an accessory pathway with a long refractory period and suggesting low risk for a dangerously rapid ventricular rate during AF. Evidence for the latter point, however, is mixed.

Adverse Effects.

Noncardiac adverse effects from administration of procainamide include rash, myalgia, digital vasculitis, and Raynaud phenomenon. Fever and agranulocytosis may be the result of hypersensitivity reactions, and the white blood cell and differential counts should be assessed at regular intervals. GI side effects are less frequent than with quinidine, and adverse CNS side effects are less frequent than with lidocaine. Toxic concentrations of procainamide can diminish myocardial performance and promote hypotension. Various conduction disturbances or ventricular tachyarrhythmias can occur, similar to those produced by quinidine. NAPA can cause QT prolongation and TdP. In the absence of sinus node disease, procainamide does not adversely affect sinus node function. In patients with sinus node dysfunction, however, procainamide can prolong sinus node recovery time and worsen symptoms in some patients with bradycardia-tachycardia syndrome.

Arthralgia, fever, pleuropericarditis, hepatomegaly, and hemorrhagic pericardial effusion with tamponade have been described in a systemic lupus erythematosus (SLE)-like syndrome related to procainamide administration. The syndrome occurs more frequently and earlier in patients who are slow acetylators of procainamide and is genetically influenced (**see Chapter 8**). Acetylation of procainamide to form NAPA appears to block the SLE-inducing effect. In 60% to 70% of patients receiving long-term procainamide therapy, ANAs develop, with clinical symptoms occurring in 20% to 30%, but this is reversible when procainamide is stopped. Positive serologic test results are not necessarily a reason to discontinue drug therapy; however, the development of symptoms with a positive anti-DNA antibody generally indicates that drug therapy should be discontinued. Corticosteroid administration in these patients may eliminate the symptoms. In this syndrome, in contrast to naturally occurring SLE, the brain and kidneys are typically spared, and there is no predilection for women.

Disopyramide

Disopyramide has been approved in the United States for oral administration to treat patients with ventricular and supraventricular arrhythmias.

Electrophysiologic Actions.

Disopyramide produces electrophysiologic effects similar to those of quinidine and procainamide, causing use-dependent block of I_{Na} and non–use-dependent block of I_{Kr} (**see Tables 36.1, 36.2, 36.3, and**

36.5). Disopyramide also inhibits $I_{K.ATP}$; it does not affect calcium-dependent action potentials, except possibly at very high concentrations.

Disopyramide is a muscarinic blocker and can increase the sinus node discharge rate and shorten AV nodal conduction time and refractoriness when the nodes are under cholinergic (vagal) influence. However, disopyramide can also slow the sinus node discharge rate by a direct action when given in high concentration and can significantly depress sinus node activity in patients with sinus node dysfunction. It exerts greater anticholinergic effects than quinidine and does not appear to affect alpha or beta adrenoceptors. The drug prolongs atrial and ventricular refractory periods, but its effect on AV nodal conduction and refractoriness is not consistent. Disopyramide prolongs His-Purkinje conduction time, but infra-His block rarely occurs. It can be administered safely to patients who have first-degree AV delay and narrow QRS complexes.

Hemodynamic Effects.

Disopyramide suppresses ventricular systolic performance and is a mild arterial vasodilator. The drug should generally be avoided in patients with reduced left ventricular systolic function because they tolerate its negative inotropic effects poorly.

Pharmacokinetics.

Oral disopyramide is 80% to 90% absorbed, with a mean elimination half-life of 8 to 9 hours in healthy volunteers but almost 10 hours in patients with heart failure (**see Table 36.4**). Renal insufficiency prolongs its elimination time. Thus, in patients with renal, hepatic, or cardiac insufficiency, loading and maintenance doses need to be reduced. Peak blood levels after oral administration occur in 1 to 2 hours. Approximately 50% of an oral dose is excreted unchanged in urine, with 30% occurring as the mono-*N*-dealkylated metabolite. The metabolites appear to exert less effect than the parent compound. Erythromycin inhibits its metabolism.

Dosage and Administration.

Doses are generally 100 to 200 mg orally every 6 hours, with a range of 400 to 1200 mg/day (**see Table 36.4**). A controlled-release preparation can be given as 200 to 300 mg every 12 hours.

Indications.

Disopyramide appears to be comparable to quinidine and procainamide in reducing the frequency of premature ventricular complexes (PVCs) and effectively preventing recurrence of VT in selected patients. Disopyramide has been combined with other drugs, such as mexiletine, to treat patients who do not respond or respond only partially to one drug.

Although rarely used for this, disopyramide helps prevent recurrence of AF after successful cardioversion as effectively as quinidine and may terminate atrial flutter. In treating patients with AF, particularly atrial flutter, the ventricular rate must be controlled before disopyramide is administered, or the combination of a decrease in atrial rate with vagolytic effects on the AV node can result in 1 : 1 AV conduction during atrial flutter (**see Chapter 38**). Disopyramide may be useful in preventing episodes of neurally mediated syncope. It has been used in patients with hypertrophic cardiomyopathy for both AF therapy and its negative inotropic effect.

Adverse Effects.

Three types of adverse effects follow disopyramide administration. The most common effects are related to the drug's potent parasympatholytic properties and include urinary hesitancy or retention, constipation,

blurred vision, closed-angle glaucoma, and dry mouth. Symptoms are less with the sustained-release form. Second, disopyramide can produce ventricular tachyarrhythmias frequently associated with QT prolongation and TdP. Cross-sensitization to both quinidine and disopyramide occurs in some patients, and TdP can develop while receiving either drug. When drug-induced torsades de pointes (DI-TdP) occurs, agents that prolong the QT interval should be used cautiously or not at all. Lastly, disopyramide can reduce contractility of the normal ventricle, but the depression of ventricular function is much more pronounced in patients with preexisting ventricular failure. Rarely, cardiovascular collapse can result.

Ajmaline

Ajmaline, a rauwolfia derivative, has been used extensively to treat patients with ventricular and supraventricular arrhythmias in Europe and Asia but is not available in the United States.

Electrophysiologic Actions.
As with other class IA drugs, ajmaline produces use-dependent block of I_{Na}; it also weakly blocks I_{Kr}. The drug has mild anticholinergic activity (**see Tables 36.1, 36.2, 36.3, and 36.5**).

Hemodynamic Effects.
Ajmaline mildly suppresses ventricular systolic performance but does not affect peripheral resistance. It also inhibits platelet activity more potently than aspirin does.

Pharmacokinetics, Dosage, and Administration.
Ajmaline is well absorbed with a mean elimination half-life of 13 minutes in most patients, thus making it poorly suited to long-term oral use. The dose for termination of acute arrhythmia is generally 50 mg intravenously infused over 1 to 2 minutes (**see Table 36.4**).

Indications.
Although it is useful for terminating supraventricular tachycardias (SVTs) by IV infusion, other medications have largely supplanted ajmaline for this purpose and its use has evolved to that of a diagnostic tool. When administered intravenously at doses of 50 mg over a 3-minute period, or 10 mg/min, to a total dose of 1 mg/kg, ajmaline can have the following effects: (1) delta wave disappearance in patients with WPW syndrome (indicating an accessory pathway anterograde ERP longer than 250 milliseconds); (2) ST-T abnormalities and interventricular conduction blocks in patients with occult Chagasic cardiomyopathy; (3) heart block in patients with bundle branch block and syncope, but in whom no rhythm disturbance had been discovered; and (4) right precordial ST elevation in patients with suspected Brugada syndrome in whom findings on the resting ECG are normal. It is in this last setting that ajmaline is used most frequently.

Adverse Effects.
Ajmaline can produce mild anticholinergic side effects, as well as mild depression of left ventricular systolic function, and can worsen AV conduction in patients with His-Purkinje disease. Rare occurrences of TdP have been reported. Ajmaline can increase the defibrillation threshold.

Class IB Agents

Lidocaine

Electrophysiologic Actions.

Lidocaine blocks I_{Na}, predominantly in the open or inactivated state. It has rapid onset and offset kinetics and does not affect normal sinus node automaticity in usual doses but does depress other normal and abnormal forms of automaticity, as well as early and late afterdepolarizations in Purkinje fibers in vitro (**see Tables 36.1, 36.2, 36.3, and 36.5**). Lidocaine has only a modest depressant effect on Vmax; however, faster rates of stimulation, acidosis, increased extracellular K^+ concentration, and reduced membrane potential (changes that can result from ischemia) increase the ability of lidocaine to block I_{Na}. Lidocaine can convert areas of unidirectional block into bidirectional block during ischemia and inhibit the development of VF by preventing fragmentation of organized large wavefronts into heterogeneous wavelets.

Except in very high concentrations, lidocaine does not affect slow-channel–dependent action potentials despite its moderate suppression of the slow inward current. Lidocaine has minimal effect on atrial fibers and does not affect conduction in accessory pathways. Depressed automaticity or conduction can develop in patients with preexisting sinus node dysfunction, abnormal His-Purkinje conduction, or junctional or ventricular escape rhythms. Part of lidocaine's effects may involve inhibition of cardiac sympathetic nerve activity.

Hemodynamic Effects.

Clinically significant adverse hemodynamic effects are rarely noted with lidocaine at the usual drug concentrations unless left ventricular function is severely impaired.

Pharmacokinetics.

Lidocaine is used only parenterally because oral administration results in extensive first-pass hepatic metabolism and unpredictably low plasma levels, as well as excessive metabolites that can produce toxicity (**see Table 36.4**). Hepatic metabolism of lidocaine depends on hepatic blood flow; severe hepatic disease or reduced hepatic blood flow, as in heart failure or shock, can greatly decrease the rate of lidocaine metabolism. Beta-adrenoceptor blockers can decrease hepatic blood flow and increase the serum concentration of lidocaine. Prolonged infusion can reduce lidocaine clearance. Its elimination half-life averages 1 to 2 hours in normal individuals, longer than 4 hours in patients after uncomplicated myocardial infarction (MI), longer than 10 hours in patients after MI complicated by heart failure, and even longer in the presence of cardiogenic shock. Maintenance doses should be reduced by one third to one half in patients with low cardiac output.

Dosage and Administration.

Although lidocaine can be given intramuscularly, the IV route is most often used, with an initial bolus of 1 to 2 mg/kg body weight at a rate of 20 to 50 mg/min and a second injection of half the initial dose 20 to 40 minutes later to maintain the therapeutic concentration (**see Table 36.4**).

If the initial bolus of lidocaine is ineffective, up to two more boluses of 1 mg/kg may be administered at 5-minute intervals. Patients who require more than one bolus to achieve a therapeutic effect generally need a higher maintenance dose to sustain these higher concentrations, with infusion rates in the range of 1 to 4 mg/min to produce steady-state plasma levels of 1 to 5 mg/mL in patients with uncomplicated MI. These rates must be reduced during heart failure or shock because of the concomitant reduced hepatic blood flow. Higher doses and concentrations are unlikely to provide additional benefit but do increase the risk for toxicity.

Indications.

Lidocaine has moderate efficacy against ventricular arrhythmias of diverse causes; it is generally ineffective against supraventricular arrhythmias and rarely terminates monomorphic VT. Although once used in an attempt to prevent VF in the first 2 days after acute MI, its efficacy was marginal, and because it can produce side effects and a possible increase in the risk for the development of asystole, such use is not recommended. Lidocaine has been effective in patients after coronary revascularization and in those resuscitated from out-of-hospital VF, although amiodarone has been shown to yield higher rates of survival, at least to hospital admission.

Adverse Effects.

The most frequently reported adverse effects of lidocaine are dose-related manifestations of CNS toxicity: dizziness, paresthesias, confusion, delirium, stupor, coma, and seizures. Occasional sinus node depression and His-Purkinje block have been reported. Rarely, lidocaine can cause malignant hyperthermia.

Mexiletine

Mexiletine, a local anesthetic congener of lidocaine with anticonvulsant properties, is used for the oral treatment of patients with symptomatic ventricular arrhythmias.

Electrophysiologic Actions.

Mexiletine is similar to lidocaine in many of its electrophysiologic actions. In vitro, mexiletine shortens the APD and ERP of Purkinje fibers and, to a lesser extent, ventricular muscle. It depresses the Vmax of phase 0 by blocking I_{Na}, especially at faster rates, and depresses the automaticity of Purkinje fibers but not of the normal sinus node. Its onset and offset kinetics are rapid. Hypoxia or ischemia can increase its effects (**see Tables 36.1, 36.2, 36.3, and 36.5**).

Mexiletine can result in severe bradycardia and abnormal sinus node recovery time in patients with sinus node disease, but not in those with a normal sinus node. It does not affect AV nodal conduction and can depress His-Purkinje conduction, but not greatly, unless conduction was abnormal initially. Mexiletine does not appear to affect human atrial muscle. It does not affect the QT interval. It has been used in treating a variety of other disorders, including erythromelalgia (red, painful extremities) in children and myotonia.

Hemodynamic Effects.

Mexiletine exerts no major hemodynamic effects on ventricular contractile performance or peripheral resistance.

Pharmacokinetics.

Mexiletine is rapidly and almost completely absorbed after oral ingestion by volunteers, with peak plasma concentrations being attained in 2 to 4 hours (**see Table 36.4**). Its elimination half-life is approximately 10 hours in healthy individuals but 17 hours in post-MI patients. Therapeutic plasma levels of 0.5 to 2 mg/mL are maintained by oral doses of 200 to 300 mg every 6 to 8 hours. Absorption with less than a 10% first-pass hepatic effect occurs in the upper part of the small intestine and is delayed and incomplete in patients receiving narcotics or antacids. Approximately 70% of the drug is protein bound; the apparent volume of distribution is large because of extensive tissue uptake. Normally,

mexiletine is eliminated metabolically by the liver, with less than 10% being excreted unchanged in urine. Doses should be reduced in patients with cirrhosis or left ventricular failure. Renal clearance of mexiletine decreases as urinary pH increases. Its known metabolites exert no electrophysiologic effects. Metabolism can be increased by phenytoin, phenobarbital, and rifampin and can be reduced by cimetidine.

Dosage and Administration.

The recommended starting dose is 200 mg orally every 8 hours when rapid arrhythmia control is not essential (**see Table 36.4**). Doses may be increased or decreased by 50 to 100 mg every 2 to 3 days and are better tolerated when given with food. The total daily dose should generally not exceed 1200 mg. In some patients, administration every 12 hours can be effective.

Indications.

Mexiletine is a moderately effective antiarrhythmic agent for the treatment of acute and chronic ventricular tachyarrhythmias, but not SVTs. Success rates vary from 6% to 60% and can be increased in some patients if mexiletine is combined with other drugs such as procainamide, beta blockers, quinidine, disopyramide, propafenone, or amiodarone. Most studies show no clear superiority of mexiletine over other class I agents. Mexiletine may be very useful in children with congenital heart disease and serious ventricular arrhythmias. In treating patients with a long QT interval, mexiletine may be safer than drugs that increase the QT interval further, such as quinidine. Limited experience in treating subsets of patients with long-QT syndrome (LQT3, which is related to the *SCN5A* gene for the cardiac sodium channel) suggests a beneficial role (**see Chapter 33**).

Adverse Effects.

Up to 40% of patients may require a change in dose or discontinuation of mexiletine therapy as a result of adverse effects, including tremor, dysarthria, dizziness, paresthesia, diplopia, nystagmus, confusion, nausea, vomiting, and dyspepsia. Cardiovascular side effects are rare but include hypotension, bradycardia, and exacerbation of arrhythmia. The adverse effects of mexiletine appear to be dose related, and toxic effects occur at plasma concentrations only slightly higher than therapeutic levels. Therefore, its effective use requires careful titration of dose and monitoring for adverse effects and possibly plasma concentration. Lidocaine use as an AAD should be avoided or the dose reduced in patients receiving mexiletine.

Phenytoin

Phenytoin was used originally to treat seizure disorders. Its value as an AAD is limited to rare cases of digitalis-toxic atrial and ventricular tachyarrhythmias (for which more rapid and effective control can be achieved with digitalis-specific antibodies) and occasional cases of ventricular arrhythmias when used in combination with other agents (**see Tables 36.1 to 36.5**).

Class IC Agents

Flecainide

Flecainide is approved by the FDA to treat patients with life-threatening ventricular arrhythmias, as well as various supraventricular arrhythmias.

Electrophysiologic Actions.

Flecainide exhibits marked use-dependent depressant effects on the rapid sodium channel by decreasing Vmax and has slow onset and offset kinetics (**see Tables 36.1, 36.2, 36.3, and 36.5**). Drug dissociation from the sodium channel is slow, with time constants of 10 to 30 seconds (versus 4 to 8 seconds for quinidine and <1 second for lidocaine). Thus, marked drug effects can occur at physiologic heart rates. Flecainide shortens the duration of the Purkinje fiber action potential but prolongs it in ventricular muscle, actions that, depending on the circumstances, could enhance or reduce electrical heterogeneity and create or suppress arrhythmias. Flecainide profoundly slows conduction in all cardiac fibers and, in high concentrations, inhibits the slow Ca^{2+} channel (**see Chapter 34**). Conduction time in the atria, ventricles, AV node, and His-Purkinje system is prolonged. Minimal increases in atrial or ventricular refractoriness or in the QT interval result. Anterograde and retrograde refractoriness in accessory pathways can increase significantly in a use-dependent manner. Sinus node function remains unchanged in normal individuals but may be depressed in patients with sinus node dysfunction. Flecainide can facilitate or inhibit reentry and may transform atrial fibrillation to flutter. Pacing and defibrillation thresholds are characteristically slightly to significantly increased.

Hemodynamic Effects.

Flecainide depresses cardiac performance, particularly in patients with compromised ventricular systolic function, and should be used cautiously or not at all in those with moderate or severe ventricular systolic dysfunction.

Pharmacokinetics.

Flecainide is at least 90% absorbed, with peak plasma concentrations achieved in 3 to 4 hours. Its elimination half-life in patients with ventricular arrhythmias is 20 hours, with 85% of the drug excreted unchanged or as an inactive metabolite in urine (**see Table 36.4**). Its two major metabolites have less potency than the parent drug. Elimination is slower in patients with renal disease and heart failure, and doses should be reduced in these situations. Therapeutic plasma concentrations range from 0.2 to 1.0 mg/mL. Approximately 40% of the drug is protein bound. Increases in serum concentrations of digoxin (15% to 25%) and propranolol (30%) result during co-administration with flecainide. Propranolol, quinidine, and amiodarone may increase flecainide serum concentrations. Five to 7 days of dosing may be required to reach a steady-state concentration in some patients.

Dosage and Administration.

The starting dose is 100 mg every 12 hours, increased in increments of 50 mg twice daily, no sooner than every 3 to 4 days, until efficacy is achieved or an adverse effect is noted, or to a maximum of 400 mg/day (**see Table 36.4**). Cardiac rhythm and QRS duration should be monitored after changes in dose.

Indications.

Flecainide is indicated for the treatment of life-threatening ventricular tachyarrhythmias, SVTs, and paroxysmal atrial fibrillation. Encouraging experimental and early clinical data support its use for catecholaminergic polymorphic VT (**see Chapter 33**). Some experts have suggested that therapy should begin in the hospital while the ECG is being monitored because of the possibility of proarrhythmic events (see later). The dosage is adjusted to achieve the desired effect, but the serum concentration should not exceed 1.0 mg/mL. Flecainide is particularly effective in almost totally suppressing PVCs and short runs of nonsustained VT. As with other class I AADs, no data from controlled studies indicate that the drug

favorably affects survival or sudden cardiac death, and data from CAST indicate increased mortality in patients with coronary artery disease. Flecainide produces a use-dependent prolongation of VT cycle length, which can improve hemodynamic tolerance. Flecainide is also useful for various SVTs, such as atrial tachycardia (AT), atrial flutter, and AF (including oral loading to terminate episodes acutely). When it is administered chronically, isoproterenol can reverse some of these effects. It is important to slow the ventricular rate before treatment of AF with flecainide to avoid the 1 : 1 AV conduction of slowed atrial flutter that may result from the effect of flecainide on fibrillation. Flecainide has been used to treat fetal arrhythmias and arrhythmias in children. Flecainide administration can produce ST elevation in lead V_1, characteristic of Brugada syndrome, in susceptible patients (**see Chapter 33**) and has been used as a diagnostic tool in persons suspected of having this disorder.

Adverse Effects.

Proarrhythmic effects are some of the most important adverse effects of flecainide. Its marked slowing of conduction precludes its use in patients with second-degree AV block without a pacemaker and warrants cautious administration in patients with intraventricular conduction disorders. Worsening of existing ventricular arrhythmias or the onset of new ventricular arrhythmias can occur in 5% to 30% of patients, especially in those with preexisting sustained VT, cardiac decompensation, and higher doses of the drug. Failure of the flecainide-related arrhythmia to respond to therapy, including electrical cardioversion-defibrillation, may result in mortality as high as 10% in patients in whom proarrhythmic events develop. Negative inotropic effects can precipitate or worsen heart failure episodes. Patients with sinus node dysfunction may experience sinus arrest, and an increase in the pacing and defibrillation thresholds may develop in those with pacemakers and ICDs, respectively. In CAST, patients treated with flecainide had higher mortality or nonfatal cardiac arrest compared to the placebo group, possibly related to an interaction between the drug and myocardial ischemia. Exercise can amplify the conduction slowing in the ventricle produced by flecainide and in some cases can precipitate a proarrhythmic response. Therefore, exercise testing has been recommended to screen for proarrhythmia (as well as occult ischemia) before and periodically during treatment. CNS complaints, including confusion and irritability, represent the most frequent noncardiac adverse effects. The safety of flecainide during pregnancy has not been determined, although as noted previously, it is occasionally used to treat fetal arrhythmias. It is concentrated in breast milk to a level 2.5- to 4-fold higher than in plasma.

Propafenone

Propafenone has been approved by the FDA for the treatment of patients with life-threatening ventricular tachyarrhythmias, as well as AF.

Electrophysiologic Actions.

Propafenone blocks the fast sodium current in a use-dependent manner in Purkinje fibers and to a lesser degree in ventricular muscle (**see Tables 36.1, 36.2, 36.3, and 36.5**). Its use-dependent effects contribute to its ability to terminate AF. Its dissociation constant from the receptor is slow, similar to that of flecainide. Effects are greater in ischemic than in normal tissue and with reduced membrane potentials. Propafenone decreases excitability and suppresses spontaneous automaticity and triggered activity. The drug is a weak blocker of I_{Kr} and beta-adrenergic receptors. Although ventricular refractoriness increases, slowing of conduction is the major effect. Propafenone has several active metabolites that

exert electrophysiologic effects. It depresses sinus node automaticity, and the A-H, H-V, PR, and QRS intervals increase, as do the refractory periods of all tissues. The QT interval increases only as a function of increased QRS duration.

Hemodynamic Effects.

Propafenone and 5-hydroxypropafenone exhibit negative inotropic properties at high concentrations. In patients with left ventricular ejection fraction (EF) exceeding 40%, the negative inotropic effects are well tolerated, but patients with preexisting left ventricular dysfunction and congestive heart failure may have symptomatic worsening of their hemodynamic status.

Pharmacokinetics.

With more than 95% of the drug absorbed, the maximum plasma concentration of propafenone is achieved in 1 to 3 hours (**see Table 36.4**). Systemic bioavailability is dose dependent and ranges from 3% to 40% because of variable presystemic clearance. Bioavailability increases as the dose increases, and the plasma concentration is therefore not linearly related to dose. A threefold increase in dosage (300 to 900 mg/day) results in a 10-fold increase in plasma concentration, presumably because of saturation of hepatic metabolic mechanisms. Propafenone is 97% bound to $alpha_1$-acid glycoprotein, with an elimination half-life of 5 to 8 hours. Maximum therapeutic effects occur at serum concentrations of 0.2 to 1.5 mg/mL. The marked interpatient variability in pharmacokinetics and pharmacodynamics may be the result of genetically determined differences in metabolism (**see Chapter 8**). Approximately 7% of the population are poor metabolizers and have an elimination half-life of 15 to 20 hours for the parent compound. The (+)-enantiomer provides nonspecific beta-adrenergic receptor blockade with 2.5% to 5% of the potency of propranolol, but because plasma propafenone concentrations may be 50 or more times higher than propranolol levels, these beta-blocking properties may be relevant. Poor metabolizers have a greater beta receptor–blocking effect than extensive metabolizers.

Dosage and Administration.

Most patients respond to oral propafenone doses of 150 to 300 mg every 8 hours, not to exceed 1200 mg/day (**see Table 36.4**). Doses are similar for patients of both metabolizing phenotypes. A sustained-release form is available for the treatment of atrial fibrillation; dosing is 225 to 425 mg twice daily. Concomitant food administration increases its bioavailability, as does hepatic dysfunction. No good correlation between the plasma propafenone concentration and suppression of arrhythmia has been shown. Doses should not be increased more often than every 3 to 4 days. Propafenone increases plasma concentrations of warfarin, digoxin, and metoprolol.

Indications.

Propafenone is indicated for the treatment of paroxysmal SVT, AF, and life-threatening ventricular tachyarrhythmias, and effectively suppresses spontaneous PVCs and nonsustained and sustained VT. Acute termination of AF episodes occurred with a single 600-mg oral dose of propafenone in 76% of patients given the drug (twice the rate of those given placebo). It has been used effectively in the pediatric age group. Propafenone increases the pacing threshold but minimally affects the defibrillation threshold. The sinus rate during exercise is reduced.

Adverse Effects.

Minor noncardiac effects occur in approximately 15% of patients, with dizziness, disturbances in taste, and blurred vision being the most common and GI side effects next. Exacerbation of bronchospastic lung

disease can occur because of mild beta-blocking effects. Cardiovascular side effects develop in 10% to 15% of patients, including AV block, sinus node depression, and worsening of heart failure. Proarrhythmic responses, which occur more often in patients with a history of sustained VT and decreased EF, appear less often than with flecainide (approximately 5%). Applicability of data from CAST about flecainide to propafenone is not clear, but limiting the use of propafenone in a manner similar to that of other class IC drugs seems prudent; however, its beta-blocking actions may make it different. The safety of propafenone administration during pregnancy has not been established (class C).

Class II Agents

Beta Adrenoceptor–Blocking Agents

Although many beta adrenoceptor–blocking drugs have been approved for use in the United States, metoprolol, carvedilol, atenolol, propranolol, and esmolol have been most widely used to treat supraventricular and ventricular arrhythmias. Acebutolol, nadolol, timolol, betaxolol, pindolol, and bisoprolol have been used less extensively for the treatment of arrhythmias. Metoprolol, atenolol, carvedilol, timolol, and propranolol decrease overall mortality and sudden death after MI (**see Chapter 42**). It is generally thought that beta blockers possess class effects, and that when titrated to the proper dose, all can be used effectively to treat cardiac arrhythmias, hypertension, or other disorders. However, differences in pharmacokinetic or pharmacodynamic properties that confer safety, reduce adverse effects, or affect dosing intervals or drug interactions influence the choice of agent. For example, nadolol may be particularly effective in patients with long-QT syndrome (**see Chapter 33**). Also, some beta blockers, such as sotalol, pindolol, and carvedilol, exert unique actions in addition to beta receptor blockade.

Beta receptors can be separated into those that affect predominantly the heart ($beta_1$) and those that affect predominantly blood vessels and the bronchi ($beta_2$). In low doses, selective beta blockers can block $beta_1$ receptors more than they block $beta_2$ receptors and might be preferable for the treatment of patients with pulmonary or peripheral vascular disease. In high doses, the "selective" $beta_1$ blockers also block $beta_2$ receptors. Carvedilol also exerts alpha-blocking effects and is used primarily in patients with heart failure (**see Chapters 24 and 25**). It is a relatively poor agent for rate control in AF because of the alpha-blocking–induced hypotension that accompanies doses large enough to block the AV node adequately.

Some beta blockers exert intrinsic sympathomimetic activity; that is, they slightly activate the beta receptor. These drugs appear to be as efficacious as beta blockers without intrinsic sympathomimetic actions and may cause less slowing of the heart rate at rest and less prolongation of AV nodal conduction time. They have been shown to induce less depression of left ventricular function than do beta blockers without intrinsic sympathomimetic activity. Beta blockers without intrinsic sympathomimetic activity have been shown to reduce mortality in patients after MI, with nonselective agents possibly conferring slightly greater benefit (**see Chapters 58 and 59**).

The following discussion focuses on the use of propranolol as a prototypic antiarrhythmic agent but is generally applicable to other beta blockers.

Electrophysiologic Actions.
Beta blockers exert an electrophysiologic action by competitively inhibiting binding of catecholamines at

beta adrenoceptor sites, or by their quinidine-like or direct membrane-stabilizing action (**see Tables 36.1, 36.2, 36.3, and 36.5**). The latter is a local anesthetic effect that depresses I_{Na} and membrane responsiveness in cardiac Purkinje fibers, occurs at concentrations generally 10 times those necessary to produce beta blockade, and most likely plays an insignificant antiarrhythmic role. Thus, beta blockers exert their major effects in cells most actively stimulated by adrenergic actions. At a beta-blocking concentration, propranolol slows spontaneous automaticity in the sinus node or in Purkinje fibers that are being stimulated by adrenergic tone and produces an I_f block (**see Chapter 34**). Beta blockers also block the $I_{Ca.L}$ stimulated by beta agonists. In the absence of adrenergic stimulation, only high concentrations of propranolol slow normal automaticity in Purkinje fibers, probably by a direct membrane action.

Concentrations that cause beta receptor blockade but no local anesthetic effects do not alter the normal resting membrane potential, maximum diastolic potential amplitude, Vmax, repolarization, or refractoriness of atrial, Purkinje, or ventricular muscle cells in the absence of catecholamine stimulation. However, in the presence of isoproterenol, a relatively pure beta receptor stimulator, beta blockers reverse isoproterenol's accelerating effects on repolarization. Propranolol reduces the amplitude of digitalis-induced delayed afterdepolarizations (DADs) and suppresses triggered activity in Purkinje fibers.

Concentrations exceeding 3 mg/mL are required to depress Vmax, action potential amplitude, membrane responsiveness, and conduction in normal atrial, ventricular, and Purkinje fibers without altering resting membrane potential. These effects probably result from depression of I_{Na}. Long-term administration of propranolol may lengthen the APD. Similar to the effects of lidocaine, acceleration of repolarization of Purkinje fibers is most marked in areas of the ventricular conduction system where the APD is greatest.

Propranolol slows the sinus discharge rate in humans by 10% to 20%, although severe bradycardia occasionally results if the heart is particularly dependent on sympathetic tone or if sinus node dysfunction is present. The PR interval lengthens, as do AV nodal conduction time and AV nodal effective and functional refractory periods (at a constant heart rate), but refractoriness and conduction in the normal His-Purkinje system remain unchanged, even after high doses of propranolol. Beta blockers do not affect conduction or repolarization in normal ventricular muscle, as evidenced by their lack of effect on the QRS complex and QT interval, respectively.

Because administration of beta blockers that do not have direct membrane action prevents many arrhythmias resulting from activation of the autonomic nervous system, it is thought that the beta-blocking action is responsible for their antiarrhythmic effects. Nevertheless, the possible importance of the direct membrane effect of some of these drugs cannot be discounted totally because beta blockers with direct membrane actions can affect the transmembrane potentials of diseased cardiac fibers at much lower concentrations than are needed to affect normal fibers directly. However, indirect actions on the arrhythmogenic effects of ischemia are probably the most important.

Hemodynamic Effects.

Beta blockers exert negative inotropic effects and can precipitate or worsen heart failure. However, beta blockers clearly improve survival in patients with heart failure (**see Chapter 25**). By blocking beta receptors, these drugs may allow unopposed alpha-adrenergic effects to produce peripheral vasoconstriction and exacerbate coronary artery spasm or pain from peripheral vascular disease in some patients.

Pharmacokinetics.

Although various types of beta blockers exert similar pharmacologic effects, their pharmacokinetics

differ substantially. Propranolol is almost 100% absorbed, but the effects of first-pass hepatic metabolism reduce its bioavailability to approximately 30% and produce significant interpatient variability in plasma concentration with a given dose (**see Table 36.4**). Reduced hepatic blood flow, as in patients with heart failure, decreases the hepatic extraction of propranolol; in these patients, propranolol may further decrease its own elimination rate by reducing cardiac output and hepatic blood flow. Beta blockers eliminated by the kidneys tend to have longer half-lives and exhibit less interpatient variability in drug concentration than do beta blockers metabolized by the liver.

Dosage and Administration.

The appropriate dose of propranolol is best determined by a measure of the patient's physiologic response, such as changes in resting heart rate or prevention of exercise-induced sinus tachycardia, because wide individual differences exist between the observed physiologic effect and plasma concentration. For example, IV dosing is best achieved by titration of the dose to clinical effect, beginning with doses of 0.25 to 0.50 mg, increasing to 1.0 mg if necessary, and administering doses every 5 minutes until either a desired effect or toxicity is produced or a total of 0.15 to 0.20 mg/kg has been given. In many cases, the short-acting effects of esmolol are preferred. Orally, propranolol is given in four divided doses, usually ranging from 40 to 160 mg/day to more than 1 g/day (**see Table 36.4**). Some beta blockers, such as carvedilol and pindolol, need to be given twice daily; many are available as once-daily long-acting preparations. In general, if one agent in adequate doses does not produce the desired effect, other beta blockers will also be ineffective. Conversely, if one agent produces the desired physiologic effect but a side effect develops, another beta blocker can often be substituted successfully.

Indications.

Arrhythmias associated with thyrotoxicosis or pheochromocytoma and arrhythmias largely related to excessive cardiac adrenergic stimulation, such as those initiated by exercise or emotion, often respond to beta-blocker therapy. Beta-blocking drugs do not usually convert chronic atrial flutter or AF to normal sinus rhythm but may do so if the arrhythmia is of recent onset and in patients who have recently undergone cardiac surgery. The atrial rate during atrial flutter or fibrillation is not changed, but the ventricular response decreases because beta blockade prolongs AV nodal conduction time and refractoriness. Esmolol can be used intravenously for rapid control of the heart rate. For reentrant SVTs using the AV node as one of the reentrant pathways, such as AV nodal reentrant tachycardia (AVNRT) and orthodromic reciprocating tachycardia in WPW syndrome or inappropriate sinus tachycardia, or for AT, beta blockers can slow or terminate the tachycardia and can be used prophylactically to prevent a recurrence (**see Chapters 37 and 38**). Combining beta blockers with digitalis, quinidine, or various other agents can be effective when the beta blocker as a single agent fails. Metoprolol and esmolol may be useful in patients with multifocal AT. These agents must be used with caution in patients with this arrhythmia, however, because a common setting for AT is advanced lung disease, often with a bronchospastic component.

Beta blockers can be effective for digitalis-induced arrhythmias such as AT, nonparoxysmal AV junctional tachycardia, PVCs, or VT. If a significant degree of AV block is present during digitalis-induced arrhythmia, lidocaine or phenytoin may be preferable to propranolol. Beta blockers can also be useful to treat ventricular arrhythmias associated with prolonged–QT interval syndrome (**see Chapter 33**) and with mitral valve prolapse (**see Chapter 69**). For patients with ischemic heart disease, beta blockers do not generally prevent the episodes of recurrent monomorphic VT that occur in the absence of

acute ischemia. It is well accepted that several beta blockers reduce the incidence of both total and sudden death after MI (**see Chapters 58 and 59**). The mechanism of this reduction in mortality is not entirely clear and may be related to reduction of the extent of ischemic damage, autonomic effects, a direct antiarrhythmic effect, or combinations of these factors. Beta blockers may have been protective against proarrhythmic responses in CAST.

Adverse Effects.

Adverse cardiovascular effects from beta blockers include unacceptable hypotension, bradycardia, and congestive heart failure. The bradycardia can be caused by sinus slowing or AV block. Sudden withdrawal of propranolol in patients with angina pectoris can precipitate or worsen angina and cardiac arrhythmias and cause acute MI, possibly as a result of the heightened sensitivity to beta agonists caused by previous beta blockade (receptor upregulation). Heightened sensitivity may begin several days after cessation of beta-blocker therapy and can last 5 or 6 days. Other adverse effects of beta blockers include worsening of asthma or chronic obstructive pulmonary disease, intermittent claudication, Raynaud phenomenon, mental depression, increased risk for hypoglycemia in insulin-dependent diabetic patients, easy fatigability, disturbingly vivid dreams or insomnia, and impaired sexual function. Many of these side effects were noted less frequently with the use of $beta_1$-selective agents, but even so-called cardioselective beta blockers can exacerbate asthma or diabetic control in individual patients.

Class III Agents

Amiodarone

Amiodarone is an iodinated benzofuran derivative approved by the FDA for the treatment of patients with life-threatening ventricular tachyarrhythmias when other drugs are ineffective or not tolerated.

Electrophysiologic Actions.

With long-term oral administration, amiodarone prolongs the APD and refractoriness of all cardiac fibers without affecting resting membrane potential (**see Tables 36.1, 36.2, 36.3, and 36.5** and **Chapter 34**). When acute effects are evaluated, amiodarone and its metabolite desethylamiodarone prolong the APD of ventricular muscle but shorten the APD of Purkinje fibers. Injected into the sinus and AV node arteries, amiodarone reduces sinus and junctional discharge rates and prolongs AV nodal conduction time. It depresses Vmax in ventricular muscle in a rate- or use-dependent manner by blocking of inactivated sodium channels, an effect that is accentuated by depolarized and reduced by hyperpolarized membrane potentials. Amiodarone depresses conduction at fast rates more than at slow rates (use dependence). It does not prolong repolarization more at slow than at fast rates (i.e., does not demonstrate reverse use dependence) but does exert time-dependent effects on refractoriness, which may in part explain its high antiarrhythmic efficacy and low incidence of TdP.

Desethylamiodarone has relatively greater effects on fast-channel tissue, which probably contributes to its antiarrhythmic efficacy. The delay in building up adequate concentrations of this metabolite may in part explain the delay in amiodarone's antiarrhythmic action.

Amiodarone noncompetitively antagonizes alpha and beta receptors and blocks conversion of thyroxine (T_4) to triiodothyronine (T_3), which may account for some of its electrophysiologic effects. Amiodarone exhibits slow channel–blocking effects; with oral administration, it slows the sinus rate by

20% to 30% and prolongs the QT interval, at times changing the contour of the T wave and producing U waves.

The ERP of all cardiac tissues is prolonged. The H-V interval increases, and the QRS duration lengthens, especially at fast rates. Amiodarone given intravenously modestly prolongs the refractory period of atrial and ventricular muscle. The PR interval and AV nodal conduction time lengthen. The duration of the QRS complex lengthens at increased rates but less than after oral amiodarone. Thus the increase in prolongation of conduction time (except for AV node), duration of repolarization, and refractoriness is much less after IV administration than after the oral route. Considering these actions, it is clear that amiodarone has class I (blocks I_{Na}), class II (antiadrenergic), and class IV (blocks $I_{Ca.L}$) actions in addition to its class III effects (blocks I_K). Amiodarone's actions approximate those of a theoretically ideal drug that exhibits use-dependent Na^+ channel blockade with fast diastolic recovery from block and use-dependent prolongation of the APD. It does not increase and may decrease QT dispersion. Catecholamines can partially reverse some of the effects of amiodarone.

Hemodynamic Effects.

Amiodarone is a peripheral and coronary vasodilator. When administered intravenously (150 mg over 10 minutes, then a 1-mg/min infusion), amiodarone decreases the heart rate, systemic vascular resistance, left ventricular contractile force, and left ventricular dP/dt. Oral doses of amiodarone sufficient to control cardiac arrhythmias do not depress the left ventricular EF, even in patients with reduced EF, and the EF and cardiac output may increase slightly. However, because of the antiadrenergic actions of amiodarone and because it does exert some negative inotropic action, it should be given cautiously, particularly intravenously, to patients with marginal cardiac compensation.

Pharmacokinetics.

Amiodarone is slowly, variably, and incompletely absorbed, with a systemic bioavailability of 25% to 65% (**see Table 36.4**). Plasma concentrations peak 3 to 6 hours after a single oral dose. There is a minimal first-pass effect, indicating minimal hepatic extraction. Elimination is by hepatic excretion into bile with some enterohepatic recirculation. Extensive hepatic metabolism occurs, with desethylamiodarone being a major metabolite. Both accumulate extensively in the liver, lung, fat, “blue” skin, and other tissues. The concentration in myocardium is 10 to 50 times that found in plasma. Plasma clearance of amiodarone is low, and renal excretion is negligible. Doses need not be reduced in patients with renal disease. Amiodarone and desethylamiodarone are not dialyzable. The volume of distribution is large but variable, with an average of 60 L/kg. Amiodarone is highly protein bound (96%), crosses the placenta (10% to 50%), and is found in breast milk.

The onset of action after IV administration generally occurs within 1 to 2 hours. After oral administration, the onset of action may require 2 to 3 days, often 1 to 3 weeks, and on occasion even longer. Loading doses reduce this time interval. Plasma concentrations relate well to oral doses during chronic treatment and average approximately 0.5 mg/mL for each 100 mg/day at doses between 100 and 600 mg/day. Amiodarone's elimination half-life is multiphasic, with an initial 50% reduction in plasma concentration 3 to 10 days after cessation of drug ingestion (probably representing elimination from well-perfused tissues), followed by a terminal half-life of 26 to 107 days (mean, 53 days), with most patients in the 40- to 55-day range. To achieve a steady-state concentration without a loading dose takes about 265 days. Interpatient variability in these pharmacokinetic parameters mandates close monitoring of the patient. Therapeutic serum concentrations range from 0.5 to 1.5 mg/mL. Greater suppression of arrhythmias may occur with up to 3.5 mg/mL, but the risk for side effects increases.

Dosage and Administration.

There is no standard dosing schedule for amiodarone applicable to all patients. One recommended approach is to treat with 800 to 1200 mg/day for 1 to 3 weeks, 400 mg/day for the next several weeks, and finally after 2 to 3 months of treatment, a maintenance dose of 300 mg or less per day (**see Table 36.4**). Maintenance drug can be given once or twice daily and should be titrated to the lowest effective dose to minimize the occurrence of side effects; in general, the earlier during drug loading that arrhythmia control is achieved, the lower the maintenance dose can be. Doses as low as 100 mg every other day can be effective in some patients. Regimens must be individualized for a given patient and clinical situation. To achieve more rapid loading and effect in emergencies, amiodarone can be administered intravenously at initial doses of 15 mg/min for 10 minutes, followed by 1 mg/min for 6 hours and then 0.5 mg/min for the remaining 18 hours and the next several days as necessary. Supplemental infusions of 150 mg over a 10-minute period can be used for breakthrough VT or VF. IV infusions can be continued safely for 2 to 3 weeks. IV amiodarone is generally well tolerated, even in patients with left ventricular dysfunction. Patients with depressed EF should receive IV amiodarone with great caution because of hypotension. High-dose oral loading (800 to 2000 mg/day to maintain trough serum concentrations of 2 to 3 mg/mL) may suppress ventricular arrhythmias in 1 to 2 days.

Indications.

Amiodarone has been used to suppress a wide spectrum of supraventricular and ventricular tachyarrhythmias in utero, in adults, and in children, including AV node and AV reentry, junctional tachycardia, atrial flutter and fibrillation, VT and VF associated with coronary artery disease, and hypertrophic cardiomyopathy. Success rates vary widely, depending on the population of patients, arrhythmia, underlying heart disease, length of follow-up, definition and determination of success, and other factors. In general, however, the efficacy of amiodarone equals or exceeds that of all other AADs and may be in the range of 60% to 80% for most supraventricular tachyarrhythmias and 40% to 60% for ventricular tachyarrhythmias. Amiodarone may be useful in improving survival in patients with hypertrophic cardiomyopathy, asymptomatic ventricular arrhythmias after MI, and ventricular tachyarrhythmia during and after resuscitation from cardiac arrest. Amiodarone given before open heart surgery, as well as postoperatively, has been shown to decrease the incidence of postoperative AF. Amiodarone is superior to class I AADs and sotalol in maintaining sinus rhythm in patients with recurrent AF.

Patients who have an ICD receive fewer shocks if they are treated with amiodarone than if treated with conventional drugs. Amiodarone has little effect on the pacing threshold but typically increases the electrical defibrillation threshold modestly and slows the rate of VT (sometimes below the ICD's detection rate).

Several prospective, randomized controlled trials and meta-analyses have demonstrated improved survival with amiodarone therapy versus placebo. However, amiodarone has been shown to result in inferior survival compared with ICD therapy, and in the SCD-HeFT population (NYHA Class II or III heart failure; EF, 35%), survival of amiodarone-treated patients was no different than for the placebo group. The drug may still be used adjunctively in ICD-treated patients to decrease the frequency of shocks from VT and VF episodes or to control supraventricular tachyarrhythmias that elicit device therapy (**see Chapter 37**). As noted, the drug can slow the ventricular rate during spontaneous VT episodes beneath the detection rate of the device; careful patient assessment and, occasionally, device reprogramming and testing are necessary. It also can be used to slow the ventricular rate during AF and atrial flutter.

Because of the serious nature of the arrhythmias being treated, the unusual pharmacokinetics of the

drug, and its adverse effects, consideration should be given to starting amiodarone therapy with the patient hospitalized and monitored for at least several days. Combining other AADs with amiodarone may improve efficacy in some patients.

Adverse Effects.

Adverse effects are reported by about 75% of patients treated with amiodarone for 5 years, and these effects compel stopping the drug in 18% to 37%. The most frequent side effects requiring drug discontinuation involve pulmonary and GI complaints or abnormal test results. Most adverse effects are reversible with dose reduction or cessation of treatment. Adverse effects are more common when therapy is continued in the long term and at higher doses. Of the noncardiac adverse reactions, pulmonary toxicity is the most serious[9]; in one study, it occurred in 33 of 573 patients between 6 days and 60 months of treatment, with three deaths. The mechanism is unclear but may involve a hypersensitivity reaction, widespread phospholipidosis, or both. Dyspnea, nonproductive cough, and fever are common symptoms, along with crackles on examination, hypoxia, abnormal gallium scan results, reduced carbon monoxide diffusion capacity (D_{LCO}), and radiographic evidence of pulmonary infiltrates. Amiodarone must be discontinued if such pulmonary inflammatory changes occur. Corticosteroids can be tried, but no controlled studies have been done to support their use. Up to 10% mortality results in patients with pulmonary inflammatory changes, often in those with unrecognized pulmonary involvement that is attributed to other causes and is thus allowed to progress. Chest radiography or pulmonary function testing, including D_{LCO}, at 3-month intervals for the first year and then twice a year for several years have been recommended. At maintenance doses lower than 300 mg/day, pulmonary toxicity is uncommon but can occur. Advanced age, high drug maintenance dose, and reduced predrug D_{LCO} are risk factors for the development of pulmonary toxicity. An unchanged D_{LCO} on therapy may be a negative predictor of pulmonary toxicity.

Although asymptomatic elevations in liver enzyme levels are found in most patients, amiodarone is not stopped unless values exceed two or three times normal in a patient with initially normal values. Cirrhosis occurs infrequently but may be fatal.[10] Neurologic dysfunction, photosensitivity (perhaps minimized by sunscreens), bluish skin discoloration, gastroenterologic disturbances, and hyperthyroidism (1% to 2%) or hypothyroidism (2% to 4%) can occur. Because amiodarone appears to inhibit the peripheral conversion of T_4 to T_3, chemical changes result and are characterized by a slight increase in T_4, reverse T_3, and thyroid-stimulating hormone (TSH) and a slight decrease in T_3 levels. The reverse T_3 concentration has been used as an index of drug efficacy. During hypothyroidism the TSH level increases greatly, whereas the level of T_3 increases in hyperthyroidism. Thyroid function tests should be performed approximately every 3 months for the first year while amiodarone is being taken and once or twice yearly thereafter, or sooner if symptoms develop that are consistent with thyroid dysfunction. Corneal microdeposits occur in almost 100% of adults receiving the drug longer than 6 months. More serious ocular reactions, including optic neuritis and atrophy with visual loss, have been reported but are rare, and causation by amiodarone has not been firmly established.[11]

Cardiac side effects include symptomatic bradycardias in approximately 2% of patients; worsening of ventricular tachyarrhythmias with the occasional development of TdP in 1% to 2%, possibly higher in women; and worsening of congestive heart failure in 2%. Possibly because of interactions with anesthetics, complications have been reported after open heart surgery, including pulmonary dysfunction, hypotension, severe bradycardia, hepatic dysfunction, and low cardiac output.

In general, the lowest possible maintenance dose of amiodarone that is still effective should be used to

avoid significant adverse effects. Many supraventricular arrhythmias can be managed successfully with daily dosages of 200 mg or less, whereas ventricular arrhythmias generally require higher doses. Adverse effects are uncommon at dosages of 200 mg/day or less but can still occur. Because of potential toxicity in various organ systems, special multidisciplinary amiodarone clinics have been used by some in an attempt to prevent adverse outcomes when the drug is used.[12]

Important interactions with other drugs occur, and when given concomitantly with amiodarone, the doses of warfarin, digoxin, and other AADs should be reduced by one third to one half and the patient observed closely. Drugs with synergistic actions, such as beta blockers or calcium channel blockers, must be given cautiously. The safety of amiodarone during pregnancy is controversial but categorized currently as class D. It should be used in pregnant patients only if no alternatives exist but should be avoided during breastfeeding.

Dronedarone

Dronedarone is approved by the FDA to facilitate maintenance of sinus rhythm in patients with atrial flutter and AF.

Electrophysiologic Actions.

As with amiodarone, dronedarone alters the activity of multiple cardiac ion channels (**see Tables 36.1, 36.2, 36.3, and 36.5**). It is a more potent blocker of I_{Na} than amiodarone and exhibits similar effects on the L-type calcium current. Blockade of both I_{Kr} and I_{Ks} by dronedarone is also similar to that by amiodarone, whereas its effect on atrial $I_{K.Ach}$ and antiadrenergic effects (via noncompetitive binding) are significantly more potent than for amiodarone. Sinus node function is depressed to a minor degree. Pacing and defibrillation thresholds are slightly increased.

Hemodynamic Effects.

Dronedarone has minimal effect on cardiac performance except in patients with compromised ventricular systolic function and should not be used in those with clinical signs of heart failure.

Pharmacokinetics.

Dronedarone is 70% to 90% absorbed after oral administration, with peak plasma concentrations achieved in 3 to 4 hours; absorption is enhanced by food (**see Table 36.4**). Unlike the very long half-life of amiodarone, the elimination half-life of dronedarone is 13 to 19 hours, with 85% of the drug being excreted unchanged in feces and the remainder in urine. Dronedarone is metabolized by and slightly inhibits the activity of CYP3A4 (as well as CYP2D6) and should not be used in conjunction with other agents that strongly inhibit these enzyme systems. There is minimal warfarin interaction, but dronedarone increases serum levels of dabigatran.

Dosage and Administration.

The standard recommended dose of dronedarone is 400 mg every 12 hours with food (**see Table 36.4**). No parenteral form is currently available.

Indications.

Dronedarone is indicated to facilitate cardioversion of atrial flutter or AF or to maintain sinus rhythm after restoration of sinus rhythm. It is slightly less effective than amiodarone and type IC drugs in this

regard.[13] In the ANDROMEDA (Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease) study, dronedarone-treated patients had a mortality rate more than twice that of the placebo group (8.1% versus 3.8%). Similarly, in the PALLAS (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy) trial, patients with permanent AF who were taking dronedarone had a greater than twofold higher risk for death, stroke, systemic embolism, or MI than did control patients. Thus the medication should not be used in patients with current or recent episodes of clinical heart failure or in those with permanent AF (as a rate control agent). Patients taking dronedarone should be evaluated periodically to ensure that permanent AF or heart failure has not developed.[14]

Adverse Effects.

A transient, predictable increase in serum creatinine, without adversely affecting actual glomerular filtration or other measures of renal function, occurs with standard dosing and is not a reason to alter the dose or to discontinue use of dronedarone. As noted, patients with New York Heart Association (NYHA) Class III or IV heart failure, as well as those with permanent AF, should not be given the drug because these patients have higher mortality. Patients with severe liver dysfunction should not generally receive dronedarone. The QT interval is predictably prolonged, but proarrhythmic effects from this or other mechanisms are rare (although sinus bradycardia is sometimes seen). Rash, photosensitivity, nausea, diarrhea, dyspepsia, headache, and asthenia have occurred in treated patients at higher frequency than in controls. Absence of the iodine molecule appears to account for the lower prevalence of lung and thyroid toxicity in dronedarone-treated patients than in those taking amiodarone. Dronedarone should not be used during pregnancy (category X, evidence or risk of fetal harm) and is possibly unsafe for breastfeeding.

Sotalol

Sotalol is a nonspecific beta adrenoceptor blocker without intrinsic sympathomimetic activity that prolongs repolarization. It is approved by the FDA to treat patients with life-threatening ventricular tachyarrhythmias and those with AF.

Electrophysiologic Actions.

Both the *d*- and *l*-isomers have similar effects on prolonging repolarization, whereas the *l*-isomer is responsible for almost all the beta-blocking activity (**see Tables 36.1, 36.2, 36.3, and 36.5**). Sotalol does not block alpha adrenoceptors and does not block I_{Na} (no membrane-stabilizing effects) but does prolong atrial and ventricular repolarization times by reducing I_{Kr}, thus prolonging the plateau of the action potential. Action potential prolongation is greater at slower rates (reverse use dependence). Resting membrane potential, action potential amplitude, and Vmax are not significantly altered. Sotalol prolongs atrial and ventricular refractoriness, A-H and QT intervals, and sinus cycle length (**see Chapter 37**).

Hemodynamics.

Sotalol exerts a negative inotropic effect only through its beta-blocking action. Although it can slightly increase the strength of contraction by prolonging repolarization, which occurs maximally at slow heart rates, the negative inotropic effects predominate. In patients with reduced cardiac function, sotalol can decrease the cardiac index, increase filling pressure, and precipitate overt heart failure. Therefore, it

must be used cautiously in patients with marginal cardiac compensation but is well tolerated in those with normal cardiac function.

Pharmacokinetics.

Sotalol is completely absorbed and not metabolized, thus making it 90% to 100% bioavailable. It is not bound to plasma proteins, is excreted unchanged primarily by the kidneys, and has an elimination half-life of 10 to 15 hours (**see Table 36.4**). Peak plasma concentrations occur 2.5 to 4 hours after oral ingestion. Over the dose range of 160 to 640 mg, sotalol displays dose proportionality with plasma concentration (usually in the range of 2.5 µg/mL). The dose must be reduced in patients with renal disease. The beta-blocking effect is half-maximal at 80 mg/day and maximal at 320 mg/day.

Dosage.

The typical oral dose is 80 to 160 mg every 12 hours, with 2 to 3 days between dose adjustments to attain a steady-state concentration and to monitor the ECG for arrhythmias and QT prolongation (**see Table 36.4**). Doses exceeding 320 mg/day can be used in patients when the potential benefits outweigh the risk for proarrhythmia. Because of its ability to prolong significantly the QT interval in some patients and cause TdP or provoke severe bradycardia, consideration should be given to inpatient initiation of the drug, especially in those with AF (in whom conversion to sinus bradycardia may cause syncope and/or further QT prolongation at slow rates), as well as in women (with longer baseline QT intervals).

Indications.

Approved by the FDA to treat patients with ventricular tachyarrhythmias and AF, sotalol is also useful to prevent recurrence of a wide variety of SVTs, including atrial flutter, AT, AV node reentry, and AV reentry (**see Chapter 37**). It slows the ventricular response to atrial tachyarrhythmias but rarely causes conversion to sinus rhythm. Sotalol appears to be more effective than conventional AADs and may be comparable to amiodarone in the treatment of patients with ventricular tachyarrhythmias, as well as in prevention of recurrences of AF after cardioversion. Sotalol has been used successfully to decrease the incidence of AF after cardiac surgery. It may be effective in fetal and pediatric patients and young adults with congenital heart disease.[15] Unlike most other antiarrhythmic drugs, sotalol may decrease the frequency of ICD discharges and reduce the defibrillation threshold but typically does not slow VT rates.

Adverse Effects.

Proarrhythmia is the most serious adverse effect. Overall, new or worsened ventricular tachyarrhythmias occur in approximately 4% of patients taking sotalol; this response is the result of TdP in approximately 2.5% but increases to 4% in patients with a history of sustained VT and is dose related (only 1.6% at 320 mg/day but 4.4% at 480 mg/day). This proarrhythmic effect was probably the cause of excess mortality in patients given *d*-sotalol (the enantiomer lacking a beta-blocking effect) after acute MI in the SWORD (Survival With Oral *d*-Sotalol) trial. Other adverse effects typically seen with other beta blockers also apply to sotalol. Sotalol should be used with caution or not at all in combination with other drugs that prolong the QT interval. However, such combinations have occasionally been used successfully.

Ibutilide

Ibutilide is an agent released for acute termination of episodes of atrial flutter and AF (**see Chapter 38**).

Electrophysiologic Actions.

As with other class III agents, ibutilide prolongs repolarization (**see Tables 36.1, 36.2, 36.3, and 36.5**). Although similar to other class III agents that block outward potassium currents, such as I_{Kr}, ibutilide is unique in that it also activates a slow inward sodium current. IV ibutilide causes mild slowing of the sinus rate and has minimal effects on AV conduction or QRS duration, but the QT interval is characteristically prolonged. Ibutilide has no significant effect on hemodynamics.

Pharmacokinetics.

Ibutilide is administered intravenously and has a large volume of distribution (**see Table 36.4**). Clearance is predominantly renal, with a drug half-life averaging 6 hours, but with considerable interpatient variability. Protein binding is approximately 40%. One of the drug's metabolites has weak class III effects.

Dosage and Administration.

Ibutilide is given as an IV infusion of 1 mg over 10 minutes (**see Table 36.4**). It should not be given in the presence of a QTc interval longer than 440 milliseconds or other drugs that prolong the QT interval or in patients with uncorrected hypokalemia, hypomagnesemia, or bradycardia. A second 1-mg dose may be given after the first dose is finished if the arrhythmia persists. Patients must have continuous electrocardiographic monitoring throughout the dosing period and for 6 to 8 hours thereafter because of the risk for ventricular arrhythmias. Pretreatment with IV magnesium may decrease the risk for ventricular arrhythmias and enhance efficacy in treating some atrial arrhythmias.[16] Up to 60% of patients with AF and 70% of those with atrial flutter convert to sinus rhythm after 2 mg of ibutilide has been administered.

Indications.

Ibutilide is indicated for termination of an established episode of atrial flutter or AF. It should not be used in patients with frequent short paroxysms of AF because it merely terminates episodes and is not useful for long-term prevention. Patients whose condition is hemodynamically unstable should proceed to direct-current (DC) cardioversion. Ibutilide has been used safely and effectively in patients who were already taking amiodarone or propafenone but should be used with caution in these cases. Ibutilide has been administered at transthoracic electrical cardioversion to increase the likelihood of termination of AF. In one study, all 50 patients given ibutilide before attempted electrical cardioversion achieved sinus rhythm, whereas only 34 of 50 who did not receive the drug converted to sinus rhythm. Of note, all 16 patients who did not respond to electrical cardioversion without ibutilide were successfully electrically cardioverted to sinus rhythm when a second attempt was made after ibutilide pretreatment.

Ibutilide prolongs accessory pathway refractoriness and can temporarily slow the ventricular rate during preexcited AF. The drug can also occasionally terminate episodes of organized AT, as well as sustained, uniform-morphology VT.

Adverse Effects.

The most significant adverse effect of ibutilide is QT prolongation–related TdP, which occurs in approximately 2% of patients given the drug (twice as often in women as in men). This effect develops within the first 4 to 6 hours of dosing, after which the risk is negligible. Thus, patients must undergo electrocardiographic monitoring for up to 8 hours after dosing. This requirement makes using ibutilide in emergency departments or private offices problematic. The safety of ibutilide during pregnancy has not

been well studied, and its use in pregnant women should be restricted to those in whom no safer alternative exists.

Dofetilide

Dofetilide is approved for the acute conversion of AF to sinus rhythm, as well as for chronic suppression of recurrent AF.

Electrophysiologic Actions.
The sole electrophysiologic effect of dofetilide is block of the rapid component of the delayed rectifier potassium current (I_{Kr}), important in repolarization (**see Tables 36.1, 36.2, 36.3, and 36.5**). This effect is more prominent in the atria than in the ventricles—30% increase in the atrial refractory period versus 20% in the ventricle. The effect of dofetilide on I_{Kr} is prolongation of refractoriness without slowing conduction, which is believed to be largely responsible for its antiarrhythmic effect. It is also responsible for prolongation of the QT interval on the ECG, which averages 11% but can be much greater. This effect on the QT interval is dose dependent and linear. No other important electrocardiographic changes are observed with the drug. It has no significant hemodynamic effects. Dofetilide is more effective than quinidine at converting AF to sinus rhythm. Its long-term efficacy is similar to that of other agents.[17]

Pharmacokinetics.
Oral dofetilide is absorbed well, and more than 90% is bioavailable. Its mean elimination half-life is 7 to 13 hours, with 50% to 60% excreted unchanged in urine (**see Table 36.4**). The remainder of the drug undergoes hepatic metabolism to inert compounds. Significant drug-drug interactions have been reported in patients taking dofetilide; cimetidine, verapamil, ketoconazole, and trimethoprim, alone or in combination with sulfamethoxazole, cause a significant elevation in the dofetilide serum concentration and should not be used with this drug.

Dosage and Administration.

Dofetilide is available only as an oral preparation. Dosing is from 0.125 to 0.5 mg twice daily and must be initiated in a hospital setting with continuous electrocardiographic monitoring to ensure that inordinate QT prolongation and TDP do not develop (**see Table 36.4**). Physicians must be specially certified to prescribe the drug. Its dosage must be decreased in the presence of impaired renal function or an increase in the QT interval of more than 15%, or 500 milliseconds. Dofetilide should not be given to patients with a creatinine clearance lower than 20 mL/min or a baseline QTc interval longer than 440 milliseconds.

Indications.

Oral dofetilide is indicated for prevention of episodes of supraventricular tachyarrhythmias, particularly atrial flutter and fibrillation. The role of dofetilide in the treatment of ventricular arrhythmias is less clear; it has been shown to decrease the defibrillation threshold in patients with an ICD, as well as decrease the frequency of ICD therapies for ventricular arrhythmias.

Adverse Effects.

The most significant adverse effect of dofetilide is QT interval prolongation–related TdP, which occurs in

2% to 4% of patients. Risk is highest in patients with a baseline prolonged QT interval, in those who are hypokalemic, in those taking some other agent that prolongs repolarization, and after conversion from AF to sinus rhythm.[18] Because the risk for TdP is highest at drug initiation, it should be used continuously and not as intermittent outpatient dosing. The drug is otherwise well tolerated, with few side effects. Its use in pregnancy has not been studied extensively, and it should probably be avoided in pregnant women if possible.

Class IV Agents

Calcium Channel Antagonists: Verapamil and Diltiazem

Verapamil, a synthetic papaverine derivative, is the prototype of a class of drugs that block the slow calcium channel and reduce $I_{Ca.L}$ in cardiac muscle (**see Chapter 34**). Diltiazem has electrophysiologic actions similar to those of verapamil. Nifedipine and other dihydropyridine agents exhibit minimal electrophysiologic effects at clinically used doses; these drugs are not discussed here.

Electrophysiologic Actions.

By blocking $I_{Ca.L}$ in all cardiac fibers, verapamil reduces the plateau height of the action potential, slightly shortens muscle action potential at pharmacologic concentrations, and slightly prolongs Purkinje fiber action potential (**see Tables 36.1, 36.2, 36.3, and 36.5**). It does not appreciably affect the action potential amplitude, Vmax of phase 0, or resting membrane voltage in cells that have fast-response characteristics related to I_{Na} (e.g., atrial and ventricular muscle, His-Purkinje system). Verapamil suppresses slow responses elicited by various experimental methods, as well as sustained triggered activity and early and late afterdepolarizations. Verapamil and diltiazem suppress electrical activity in the normal sinus and AV nodes. Verapamil depresses the slope of diastolic depolarization in sinus node cells, Vmax of phase 0, and maximum diastolic potential and prolongs conduction time and refractory periods of the AV node. The AV node–blocking effects of verapamil and diltiazem are more apparent at faster rates of stimulation (use dependence) and in depolarized fibers (voltage dependence). Verapamil slows activation of the slow channel and delays its recovery from inactivation.

Verapamil does exert some local anesthetic activity because the *d*-isomer of the clinically used racemic mixture exerts slight blocking effects on I_{Na}. The *l*-isomer blocks the slow inward current carried by calcium, as well as other ions, traveling through the slow channel. Verapamil does not affect calcium-activated adenosine triphosphatase (ATPase), nor does it block beta receptors, but it may block alpha receptors and potentiate vagal effects on the AV node. Verapamil can also cause other effects that indirectly alter cardiac electrophysiology, such as decreasing platelet adhesiveness or reducing the extent of myocardial ischemia.

In humans, verapamil prolongs conduction time through the AV node (the A-H interval) and lengthens AV nodal anterograde and retrograde refractory periods without affecting the P wave or QRS duration or the H-V interval. The spontaneous sinus rate may decrease slightly, an effect only partially reversed by atropine. More often, the sinus rate does not change significantly because verapamil causes peripheral vasodilation, transient hypotension, and reflex sympathetic stimulation, which mitigates any direct slowing effect that verapamil exerts on the sinus node. If verapamil is given to a patient who is also receiving a beta blocker, the sinus node discharge rate may slow because reflex sympathetic stimulation

is blocked. Verapamil does not exert a significant direct effect on atrial or ventricular refractoriness or on the anterograde or retrograde properties of accessory pathways. However, reflex sympathetic stimulation after IV verapamil administration may increase the ventricular response over the accessory pathway during AF in patients with WPW syndrome, sometimes dangerously so.

Hemodynamic Effects.

Because verapamil interferes with excitation-contraction coupling, it inhibits vascular smooth muscle contraction and causes marked vasodilation in coronary and other peripheral vascular beds. The reflex sympathetic effects of verapamil may reduce its marked negative inotropic action on isolated cardiac muscle, but the direct myocardial depressant effects of verapamil may predominate when the drug is given in high doses. In patients with well-preserved left ventricular function, combined therapy with propranolol and verapamil appears to be well tolerated, but beta blockade can accentuate the hemodynamic depressant effects produced by oral verapamil. Patients with reduced left ventricular function may not tolerate the combined blockade of beta receptors and calcium channels; thus, in these patients, verapamil and a beta blocker should be used in combination either cautiously or not at all. Verapamil reduces myocardial oxygen demand while decreasing coronary vascular resistance. Such changes may be indirectly antiarrhythmic.

Peak alterations in hemodynamic variables occur 3 to 5 minutes after completion of a verapamil injection, with the major effects dissipating within 10 minutes. Systemic resistance and mean arterial pressure decrease, as does left ventricular dP/dt_{max}, and left ventricular end-diastolic pressure increases. Heart rate, cardiac index, and mean pulmonary artery pressure do not change significantly in individuals with normal resting left ventricular systolic function. Thus the afterload reduction produced by verapamil significantly counterbalances its negative inotropic action, so the cardiac index may not be reduced. In addition, when verapamil slows the ventricular rate in a patient with tachycardia, hemodynamics may also improve. Nevertheless, caution should be exercised in giving verapamil to patients with severe myocardial depression or those receiving beta blockers or disopyramide because hemodynamic deterioration may progress in some patients.

Pharmacokinetics.

After single oral doses of verapamil, measurable prolongation of AV nodal conduction time occurs in 30 minutes and lasts 4 to 6 hours (**see Table 36.4**). After IV administration, AV nodal conduction delay occurs within 1 to 2 minutes and A-H interval prolongation is still detectable after 6 hours. After oral administration, absorption is almost complete, but its overall bioavailability of 20% to 35% suggests substantial first-pass metabolism in the liver, particularly of the *l*-isomer. Verapamil's elimination half-life is 3 to 8 hours, with up to 70% of the drug excreted by the kidneys. Norverapamil is a major metabolite that may contribute to the electrophysiologic actions of verapamil. Serum protein binding is approximately 90%. With diltiazem, the percentage of heart rate reduction in AF is related to its plasma concentration.

Dosage and Administration.

For acute termination of SVT or rapid achievement of ventricular rate control during AF, the most common IV dose of verapamil is 10 mg infused over 1 to 2 minutes while cardiac rhythm and blood pressure are monitored (**see Table 36.4**). A second injection of an equal dose may be given 30 minutes later. The initial effect achieved with the first bolus injection, such as slowing of the ventricular response during AF, can be maintained by continuous infusion of the drug at a rate of 0.005 mg/kg/min. The oral dose is 240 to 480 mg/day in divided doses. Diltiazem is given intravenously at a dose of 0.25 mg/kg as a

bolus over 2 minutes, with a second dose in 15 minutes if necessary. Because it is generally better tolerated (less hypotension) with long-term administration, such as for control of the ventricular rate during AF, diltiazem is preferred over verapamil in this setting. Significant hypotension resulting from intravenous diltiazem can be countered by volume expansion or the judicious use of a pure vasoconstrictor agent such as phenylephrine. Orally, doses must be adjusted to the patient's needs, with a 120- to 360-mg range. Various long-acting preparations (once daily) are available for verapamil and diltiazem.

Indications.

After simple vagal maneuvers have been tried and adenosine has been given, IV verapamil or diltiazem is the next treatment of choice for termination of sustained AV node reentry or orthodromic AV reciprocating tachycardia associated with an accessory pathway (**see Chapter 37**). Verapamil is as effective as adenosine for termination of these arrhythmias. Assuming that the patient is stable, verapamil should definitely be tried before termination is attempted by digitalis administration, pacing, electrical DC cardioversion, or acute blood pressure elevation with vasopressors. Verapamil and diltiazem terminate 60% to 90% or more episodes of paroxysmal SVT within several minutes. Verapamil may also be of use in some fetal SVTs. Although IV verapamil has been given along with IV propranolol, this combination should be used only with great caution because of combined adverse hemodynamic effects.

Verapamil and diltiazem decrease the ventricular response over the AV node during AF or atrial flutter, possibly converting a small number of episodes to sinus rhythm, particularly if the atrial flutter or AF is of recent onset. In addition, verapamil may prevent early recurrence of AF after electrical cardioversion. AF can occur in some patients with atrial flutter after verapamil administration. As noted earlier, in patients with preexcited ventricular complexes during AF associated with WPW syndrome, IV verapamil may accelerate the ventricular response; therefore the IV route is contraindicated in this situation. Verapamil can terminate some ATs. Even though verapamil can often terminate an idiopathic left septal VT, hemodynamic collapse can occur if IV verapamil is given to patients with the more common forms of VT because these generally occur in the setting of decreased left ventricular systolic function. A general rule for avoiding complications, however, is not to administer verapamil intravenously to any patient with wide-QRS tachycardia unless one is certain of the nature of the tachycardia and its probable response to verapamil.

Orally, verapamil or diltiazem can prevent the recurrence of AV node reentrant and orthodromic AV reciprocating tachycardias associated with an accessory pathway, as well as help maintain a decreased ventricular response during atrial flutter or AF in patients without an accessory pathway. Verapamil has not generally been effective in treating patients who have recurrent ventricular tachyarrhythmias, although it may suppress some forms of VT, such as left septal VT (noted earlier). It can also be useful in about two thirds of patients with idiopathic VT that has a left bundle branch block morphology (right ventricular outflow tract origin), patients with hypertrophic cardiomyopathy who have experienced cardiac arrest, those with a short-coupled variant of polymorphic VT, and patients with ventricular arrhythmias related to coronary artery spasm. Calcium channel blockers have not been shown to reduce mortality or to prevent sudden cardiac death in patients after acute MI, except for diltiazem in those with non–ST-segment elevation infarctions (**see Chapter 60**).

Adverse Effects.

Verapamil must be used cautiously in patients with significant hemodynamic impairment or in those receiving beta blockers, as noted earlier. Hypotension, bradycardia, AV block, and asystole are more

likely to occur when the drug is given to patients who are already receiving beta-blocking agents. Hemodynamic collapse has been noted in infants, and verapamil should be used cautiously in children younger than 1 year. Verapamil should also be used with caution in patients with sinus node abnormalities because marked depression of sinus node function or asystole can result in some of these patients. IV isoproterenol, calcium, glucagon, dopamine, or atropine, which may be only partially effective, or temporary pacing may be necessary to counteract some of the adverse effects of verapamil. Isoproterenol may be more effective for the treatment of bradyarrhythmias, and calcium may be used for the treatment of hemodynamic dysfunction secondary to verapamil. AV node depression is common in overdoses. Contraindications to the use of verapamil and diltiazem include the presence of advanced heart failure, second- or third-degree AV block without a pacemaker in place, AF and anterograde conduction over an accessory pathway, significant sinus node dysfunction, most VTs, cardiogenic shock, and other hypotensive states. Although these drugs should probably not be used in patients with overt heart failure, if it is caused by one of the supraventricular tachyarrhythmias noted earlier, verapamil or diltiazem may restore sinus rhythm or significantly decrease the ventricular rate and thereby lead to hemodynamic improvement. Also, verapamil can decrease the excretion of digoxin by approximately 30%. Hepatotoxicity may occur on occasion. Verapamil crosses the placental barrier; its use in pregnancy has been associated with impaired uterine contraction, fetal bradycardia, and possibly fetal digital defects. It should therefore be used only if no effective alternatives exist.

Other Antiarrhythmic Agents

Adenosine

Adenosine is an endogenous nucleoside present throughout the body and has been approved by the FDA to treat patients with SVTs.

Electrophysiologic Actions.
Adenosine interacts with A_1 receptors present on the extracellular surface of cardiac cells and activates K^+ channels ($I_{K.Ach}$, $I_{K.Ado}$) in a manner similar to that produced by acetylcholine (**see Tables 36.1, 36.2, 36.3, and 36.5**). The increase in K^+ conductance shortens the atrial APD, hyperpolarizes the membrane potential, and decreases atrial contractility. Similar changes occur in the sinus and AV nodes. In contrast to these direct effects mediated through the guanine nucleotide regulatory proteins G_i and G_o, adenosine antagonizes catecholamine-stimulated adenylate cyclase to decrease accumulation of cyclic adenosine monophosphate (AMP) and to decrease $I_{Ca.L}$ and the pacemaker current I_f in sinus node cells along with a decrease in Vmax. Shifts in the pacemaker site within the sinus node and sinus exit block may occur. Adenosine slows the sinus rate in humans, followed within seconds by a reflex increase in the sinus rate. In the AV node, adenosine produces transient prolongation of the A-H interval, often with transient first-, second-, or third-degree AV node block lasting up to a few seconds. The delay in AV nodal conduction is rate dependent. His-Purkinje conduction is not generally affected directly. Adenosine does not affect conduction in normal accessory pathways. Conduction may be blocked in unusual accessory pathways that have long conduction times or decremental conduction properties. Patients with heart transplants exhibit a supersensitive response to adenosine. Adenosine may mediate the phenomenon of ischemic preconditioning.

Pharmacokinetics.

Adenosine is removed from the extracellular space by washout, enzymatically by degradation to inosine, by phosphorylation to AMP, or by reuptake into cells through a nucleoside transport system (**see Table 36.4**). The vascular endothelium and erythrocytes contain these elimination systems, which result in very rapid clearance of adenosine from the circulation. Its elimination half-life is 1 to 6 seconds. Most of adenosine's effects are produced during its first passage through the circulation. Important drug interactions occur; methylxanthines are competitive antagonists, and therapeutic concentrations of theophylline totally block the exogenous effects of adenosine. Dipyridamole is a nucleoside transport blocker that blocks reuptake of adenosine, thus delaying its clearance from the circulation or interstitial space and potentiating its effect. Smaller adenosine doses should be used in patients receiving dipyridamole.

Dosage and Administration.

To terminate tachycardia, a bolus of adenosine is rapidly injected intravenously at doses of 6 to 12 mg, followed by a flush (**see Table 36.4**). Pediatric (<50 kg) dosing should be 0.05 to 0.3 mg/kg. When it is injected into a central vein and in patients after heart transplantation or those receiving dipyridamole, the initial dose should be reduced to 3 mg. Transient sinus slowing or AV node block results but lasts less than 5 seconds. Doses higher than 18 mg are unlikely to revert a tachycardia and should not be used.

Indications.

Adenosine has become the drug of first choice to terminate an SVT acutely, such as AV node or AV reentry (**see Chapter 37**), and is useful in pediatric patients. Adenosine can produce AV nodal block or terminate ATs and sinus node reentry. It results in only transient AV block during atrial flutter or fibrillation and is thus useful only for diagnosis, not therapy. Adenosine terminates a group of VTs whose maintenance depends on adrenergic drive, which is most often located in the right ventricular outflow tract but can be found at other sites as well; however, idiopathic left septal VT rarely responds. When properly administered, adenosine usually causes transient hypotension, chest discomfort, and dyspnea; if tachycardia persists in the absence of these effects, the drug may not have been given correctly. Adenosine has less potential than verapamil for producing prolonged hypotension, should tachycardia persist after injection.

Doses as low as 2.5 mg terminate some tachycardias; doses of 12 mg or less terminate 92% of SVTs, usually within 30 seconds. Successful termination rates with adenosine are comparable to those achieved with verapamil. Because of its effectiveness and extremely short duration of action, adenosine is preferable to verapamil in most cases, particularly in patients who have previously received IV beta adrenoceptor blockers, in those with poorly compensated heart failure or severe hypotension, and in neonates. Verapamil might be chosen first in patients receiving drugs such as theophylline (which is known to interfere with adenosine's actions or metabolism), in patients with active bronchoconstriction, and in those with inadequate venous access.

Adenosine may be useful to help differentiate among causes of wide-QRS tachycardias because it terminates many SVTs with aberrancy or reveals the underlying atrial mechanism and does not block conduction over an accessory pathway or terminate most VTs. In rare cases, however, adenosine terminates some VTs, characteristically those of right ventricular outflow tract origin as noted earlier, and therefore tachycardia termination is not completely diagnostic of an SVT. This agent may predispose to the development of AF and might transiently increase the ventricular response in patients with AF

conducting over an accessory pathway. Adenosine may also be useful in differentiating conduction over the AV node from that over an accessory pathway during ablative procedures designed to interrupt the accessory pathway. However, this distinction is not absolute because adenosine can block conduction in slowly conducting accessory pathways and does not always produce block in the AV node.

Adverse Effects.

Transient side effects occur in almost 40% of patients with SVT given adenosine and usually consist of flushing, dyspnea, and chest pressure. These symptoms are fleeting, lasting less than 1 minute, and are well tolerated. PVCs, transient sinus bradycardia, sinus arrest, and AV block are common when an SVT is terminated abruptly. AF is occasionally observed (12% in one study) with adenosine administration, perhaps because of the drug's effect in shortening atrial refractoriness. Induction of AF can be problematic in patients with WPW syndrome and rapid AV conduction over the accessory pathway.

Digoxin

Cardiac actions of digitalis glycosides have been recognized for centuries. In adults, digoxin is used mainly for control of the ventricular rate during AF, whereas its use in pediatrics is in a broader range of arrhythmias. Use of digoxin has decreased because of the availability of agents with greater and more reliable efficacy and a wider therapeutic to toxic drug concentration range. Its use is generally discouraged in adults.[19]

Electrophysiologic Actions.

Digoxin acts mainly through the autonomic nervous system, in particular by enhancing both central and peripheral vagal tone. These actions are confined largely to slowing of the sinus node discharge rate, shortening of atrial refractoriness, and prolongation of AV nodal refractoriness (**see Tables 36.1, 36.2, 36.3, and 36.5**). Electrophysiologic effects on the His-Purkinje system and ventricular muscle are minimal, except with toxic concentrations. In studies of denervated hearts, digoxin has relatively little effect on the AV node and causes a mild increase in atrial refractoriness.

The sinus rate and P wave duration are minimally changed in most patients taking digoxin. The sinus rate may decrease in patients with heart failure whose left ventricular performance is improved by the drug; individuals with significant underlying sinus node disease also have slower sinus rates or even sinus arrest. Similarly, the PR interval is generally unchanged, except in patients with underlying AV node disease. The QRS and QT intervals are unaffected. The characteristic ST and T wave abnormalities seen with use of digoxin do not represent toxicity.

Pharmacokinetics.

IV digoxin yields some electrophysiologic effect within minutes, with a peak effect occurring after 1.5 to 3 hours (**see Table 36.4**). After oral dosing, the peak effect occurs in 4 to 6 hours. The extent of digoxin absorption after oral administration varies according to the preparation; tablet forms are 60% to 75% absorbed, whereas encapsulated gel forms are almost completely absorbed. Ingestion of cholestyramine or an antacid preparation at the same time as digoxin ingestion decreases its absorption. The serum half-life of digoxin is 36 to 48 hours, and the drug is excreted unchanged by the kidneys.

Dosage and Administration.

In acute loading doses of 0.5 to 1.0 mg, digoxin can be given orally or intravenously (**see Table 36.4**). Chronic daily oral dosing should be adjusted on the basis of clinical indications and the extent of renal dysfunction. Most patients require 0.125 to 0.25 mg/day as a single dose. However, some patients undergoing renal dialysis need as little as 0.125 mg every other day, whereas young patients may require as much as 0.5 mg/day. Serum digoxin levels may be used to monitor compliance with therapy, as well as to determine whether digitalis toxicity is the cause of new symptoms compatible with the diagnosis. However, routine monitoring of digoxin levels is not warranted in patients whose ventricular rate is controlled during AF and who have no symptoms of toxicity.

Indications.

Digoxin can be used intravenously to slow the ventricular rate during atrial fibrillation (AF) and atrial flutter; it was formerly used in an attempt to convert SVTs to sinus rhythm, but its onset of action is much slower and its success rate less than that of adenosine, verapamil, or beta blockers. Thus it is now rarely used in this fashion. Digoxin is more often used orally to control the ventricular rate in permanent ("chronic") AF. When a patient with AF is at rest and vagal tone predominates, the ventricular rate can be maintained between 60 and 100 beats/min in 40% to 60% of cases. However, when the patient begins to exercise, the decrease in vagal tone and increase in adrenergic tone combine to diminish the beneficial effects of digoxin on AV nodal conduction. Patients can experience a marked increase in ventricular rate with even mild exertion. Digoxin is therefore rarely used as a single agent to control the ventricular rate in AF. The drug has little ability to prevent episodes of paroxysmal AF or to control the ventricular rate during episodes and may even provoke episodes in patients with so-called vagal AF. Furthermore, digoxin is no more effective than placebo in terminating episodes of acute- or recent-onset AF.

Adverse Effects.

One major reason that use of digoxin has decreased is its potential for serious adverse effects and the narrow window between therapeutic and toxic concentrations. Digitalis toxicity produces various symptoms and signs, including headache, nausea and vomiting, altered color perception, halo vision, and generalized malaise. Less common but more serious than these are digitalis-related arrhythmias, which include bradycardias related to a greatly enhanced vagal effect (e.g., sinus bradycardia or arrest, AV node block) and tachyarrhythmias that may be caused by DAD-mediated triggered activity (e.g., atrial, junctional, and fascicular or ventricular tachycardia). Worsening renal function, advanced age, hypokalemia, chronic lung disease, hypothyroidism, and amyloidosis increase a patient's sensitivity to digitalis-related arrhythmias. The diagnosis of toxicity can be confirmed by determination of the serum digoxin level. Therapy for most bradycardias consists of withdrawal of digoxin; atropine or temporary pacing may be needed in symptomatic patients. Phenytoin can be used to control atrial tachyarrhythmias, whereas lidocaine has been successful in treating infranodal tachycardias. Life-threatening arrhythmias can be treated with digoxin-specific antibody fragments. Electrical DC cardioversion should be performed only when absolutely necessary in a digitalis-toxic patient because life-threatening VT or VF can result and can be difficult to control. Some data incriminate digoxin in increasing mortality in patients with AF.[19]

Ranolazine

Ranolazine, approved by the FDA for the treatment of chronic angina, has significant electrophysiologic properties. It has been shown to decrease the incidence of AF, SVT, and ventricular arrhythmias relative to controls in trials of the drug's antianginal effects.

Electrophysiologic Actions.

Ranolazine blocks I_{Kr}, as well as the late Na current; at higher concentrations, the L-type Ca current is mildly affected (**see Tables 36.1, 36.2, 36.3, 36.5**). The drug prolongs atrial and ventricular refractoriness and induces postrepolarization refractoriness; the P wave, PR interval, and QRS are unaffected, but the QT interval is mildly prolonged. Unlike other I_{Kr}-blocking drugs, ranolazine does not induce EADs. Its effects are more pronounced on atrial than on ventricular myocardium, and the drug shows promise for the treatment of AF, particularly when combined with dronedarone.[20]

Hemodynamic Effects.

Ranolazine has no important hemodynamic effects; it does not appear to produce meaningful changes in contractility or vascular resistance.

Pharmacokinetics.

Absorption of oral ranolazine is mediated in part by the P-glycoprotein system, modulators of which may increase or decrease drug exposure. About 75% of a dose is bioavailable, with peak levels reached in 2 to 5 hours (**see Table 36.4**). Absorption is not affected by food. Its half-life is approximately 7 hours; hepatic metabolism to minimally or wholly inactive products occurs via the CYP3A and, to a lesser extent, the CYP2D6 pathways. Approximately 75% of the drug is excreted in urine, the remainder in feces.

Dosage and Administration.

The typical oral dose of ranolazine is 500 mg twice daily, to a maximum of 1000 mg twice daily. The dose should be decreased in the setting of moderate liver disease. It should not be used in conjunction with strong inhibitors of CYP3A, which could increase the drug's serum concentration threefold.

Adverse Effects.

The most widely known potential adverse effect of ranolazine is QTc prolongation, which averages 6 to 15 milliseconds (sometimes more in patients with severe liver failure), because of inhibition of I_{Kr}. Despite this effect on the QT interval, TdP is rare, probably in part because of only modest QT prolongation combined with the drug's inhibition of the late inward Na current, which mitigates the QT effect. As noted, ranolazine does not cause EADs or increases in transmural dispersion of refractoriness, which are believed to be prerequisites for torsades. Ranolazine produces a mild elevation in measured serum creatinine (0.1 mg/dL) without changing the actual glomerular filtration rate. The drug is pregnancy category C; its concentration in breast milk is unknown.

Antiarrhythmic Effects of Nonantiarrhythmic Drugs

Several medications commonly used for other indications also have some degree of antiarrhythmic effect. In some cases, physicians can use these drugs for their standard indications and achieve additional, although often small, amounts of benefit in treating the patient's rhythm disturbance. These drugs include angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor–blocking agents; aldosterone antagonists such as eplerenone, statins, and omega-3 fatty acids (prevention of sudden death); and these same classes of drugs with the addition of nondihydropyridine calcium channel blockers and ranolazine (less AF and perhaps VF). The mechanisms whereby these drugs exert their attenuating effect on arrhythmias is not clear in most cases, and they should not be relied on as the sole form of antiarrhythmic

therapy. In patients who have arrhythmias, as well as another disorder that requires drug therapy (hypertension, heart failure), one of these medications may be preferable to agents that treat the primary disorder but do not possess antiarrhythmic effects.

New Antiarrhythmic Agents

Eleclazine

Eleclazine hydrochloride (dihydrobenzoxazepinone) is selective blocker of late I_{Na} with a half maximal inhibitory concentration (IC50) value of 0.7 μM and minimal effect on other currents in the heart. In experimental models of LQT3, eleclazine shortens the APD and reduces the dispersion of repolarization.[21] The drug (currently not available for clinical use) is being developed for use in LQT3 and hypertrophic cardiomyopathy.

Vernakalant

Vernakalant is a mixed potassium and sodium channel blocker used intravenously for conversion of AF to sinus rhythm. The drug, currently available in Europe, is a use-dependent inhibitor of I_{Na} and blocks the atrial-specific potassium current I_{Kur} as well as $I_{K.ACh}$ and I_{to}. Vernakalant prolongs atrial APD and refractoriness. The safety for IV conversion of AF (initial dose of 3 mg/kg over 10 minutes followed by 2 mg/kg over 15 minutes for persistent arrhythmia) have been demonstrated in the Atrial Arrhythmia Conversion Trials 1 and 3 (ACT1, ACT3).[22] The drug was well tolerated in these studies, with minimal side effects and no TdP episodes. Transient hypotension and bradycardia were observed in 5% to 10% of patients.

Electrotherapy for Cardiac Arrhythmias

Direct-Current Electrical Cardioversion

Cardioversion is a general term used to indicate the termination of an arrhythmia, usually a tachyarrhythmia, by various means, including electrical, pharmacologic, or manual/surgical. *Electrical cardioversion* refers to the delivery of an electrical shock to the heart to terminate a tachycardia, flutter, or fibrillation and includes the technique of both synchronous cardioversion (see below) and defibrillation. It offers obvious advantages over drug therapy because under conditions optimal for close supervision and monitoring, a precisely regulated “dose” of electricity can restore sinus rhythm immediately and safely. The distinction between supraventricular and ventricular tachyarrhythmias, crucial to the proper medical management of arrhythmias, becomes less significant, and the time-consuming titration of drugs with potential side effects is obviated.

Mechanisms.

Electrical cardioversion is most effective in terminating tachycardias related to reentry, such as atrial flutter and many cases of atrial fibrillation (AF), AV node reentry, reciprocating tachycardias associated with WPW syndrome, most forms of VT, ventricular flutter, and VF. The electrical shock, by depolarizing all excitable myocardium and possibly by prolonging refractoriness, interrupts reentrant circuits and

establishes electrical homogeneity, which terminates reentry. The mechanism by which a shock successfully terminates VF has not been completely explained. If the precipitating factors are no longer present, interruption of the tachyarrhythmia for only the brief time produced by the shock may prevent its return for long periods, even though the anatomic and electrophysiologic substrates required for the tachycardia are still present.

Tachycardias thought to be caused by disorders of impulse formation (automaticity) include parasystole, some forms of AT, junctional tachycardia (with or without digitalis toxicity), accelerated idioventricular rhythm, and relatively uncommon forms of VT (**see Chapters 34 and 39**). An attempt to cardiovert these tachycardias electrically is not indicated in most cases because they typically recur within seconds after the shock; release of endogenous catecholamines consequent to the shock can further exacerbate the arrhythmia. It has not been established whether cardioversion can terminate tachycardias caused by enhanced automaticity or triggered activity.

Technique

Synchronous cardioversion refers to a specific technique of delivering an electrical shock, usually of lower energy and timed to the QRS complex ("R wave"), to avoid the vulnerable period of the T wave. Before elective synchronous cardioversion, careful physical examination should be performed, including palpation of limb pulses and inspection of the chest wall and airway. A 12-lead ECG is usually obtained before and after cardioversion, as well as a rhythm strip during the electroshock. The patient, who should be informed completely about what to expect, is in a fasting state and metabolically balanced; that is, respiratory function and electrolyte values should be normal, with no evidence of drug toxicity. Withholding of digitalis for several days before elective cardioversion in patients without clinical evidence of digitalis toxicity is not necessary, although patients in whom digitalis toxicity is suspected should not be electrically cardioverted until this situation has been corrected. Administration of maintenance antiarrhythmic drugs 1 to 2 days before planned electrical cardioversion of patients with AF can revert some patients to sinus rhythm, help prevent recurrence of AF once sinus rhythm is restored, and assist in determining the patient's tolerance of the drug for long-term use.[23] There is also evidence that statin drugs,[24] as well as ACE inhibitors and angiotensin receptor blockers, may help prevent recurrence of fibrillation, especially in patients with ventricular dysfunction.

Self-adhesive patches applied in the standard apicoanterior or anteroposterior paddle positions have transthoracic impedances similar to those of paddles and are useful in elective synchronous cardioversions or other situations in which time is available for their application. Patches 12 to 13 cm in diameter can be used to deliver maximum current to the heart, but the benefits of these patches versus patches 8 to 9 cm in diameter have not been clearly established. Larger patches may distribute the intracardiac current over a wider area and reduce shock-induced myocardial injury.

A synchronized shock (i.e., one delivered during the QRS complex; **Fig. 36.1**) is used for all cardioversions except for very rapid ventricular tachyarrhythmias, such as ventricular flutter or VF. For defibrillation of the latter, energies greater than those for synchronous cardioversion are required, and synchronization is not necessary because there is no vulnerable period of the T wave to avoid. Although generally minimal, shock-related myocardial damage increases directly with increases in applied energy, and thus the minimum effective shock should be used. Therefore, shocks are "titrated" when the clinical situation permits. Except for AF, shocks in the range of 25 to 50 joules (J) successfully terminate most SVTs and should be tried initially. If the shock is unsuccessful, a second shock of higher energy can be delivered. The starting level to terminate AF with older monophasic machines should be no less than 100

J, but with newer biphasic systems, a shock as low as 25 J may succeed. Delivered energy can be increased in stepwise fashion; up to 360 J can be used safely. It is critical to remember to resynchronize the defibrillator to the QRS complex after an unsuccessful shock before delivery of another shock to avoid initiation of VF (machines typically revert to the asynchronous mode after each shock). Anteroposterior patches may have a higher efficacy rate by placing more of the atrial mass in the shock vector than is the case with apicoanterior patches.[25] If a shock of 360 J fails to convert the rhythm, repeated shocks at the same energy may succeed by decreasing chest wall impedance; reversing patch polarity can occasionally help as well. Administration of ibutilide has been shown to facilitate electrical cardioversion of AF to sinus rhythm. Intracardiac or transesophageal defibrillation can be tried if all attempts at external cardioversion fail. For patients with stable VT, starting levels in the range of 25 to 50 J can be used. If there is some urgency to terminate the tachyarrhythmia, the clinician can begin with higher energies. To terminate VF, 100 to 200 J (biphasic; 200 to 360 J with monophasic machines) is generally used, although much lower energies (<50 J) terminate VF when the shock is delivered soon after onset of the arrhythmia, for example, using adhesive patches in the electrophysiology laboratory.

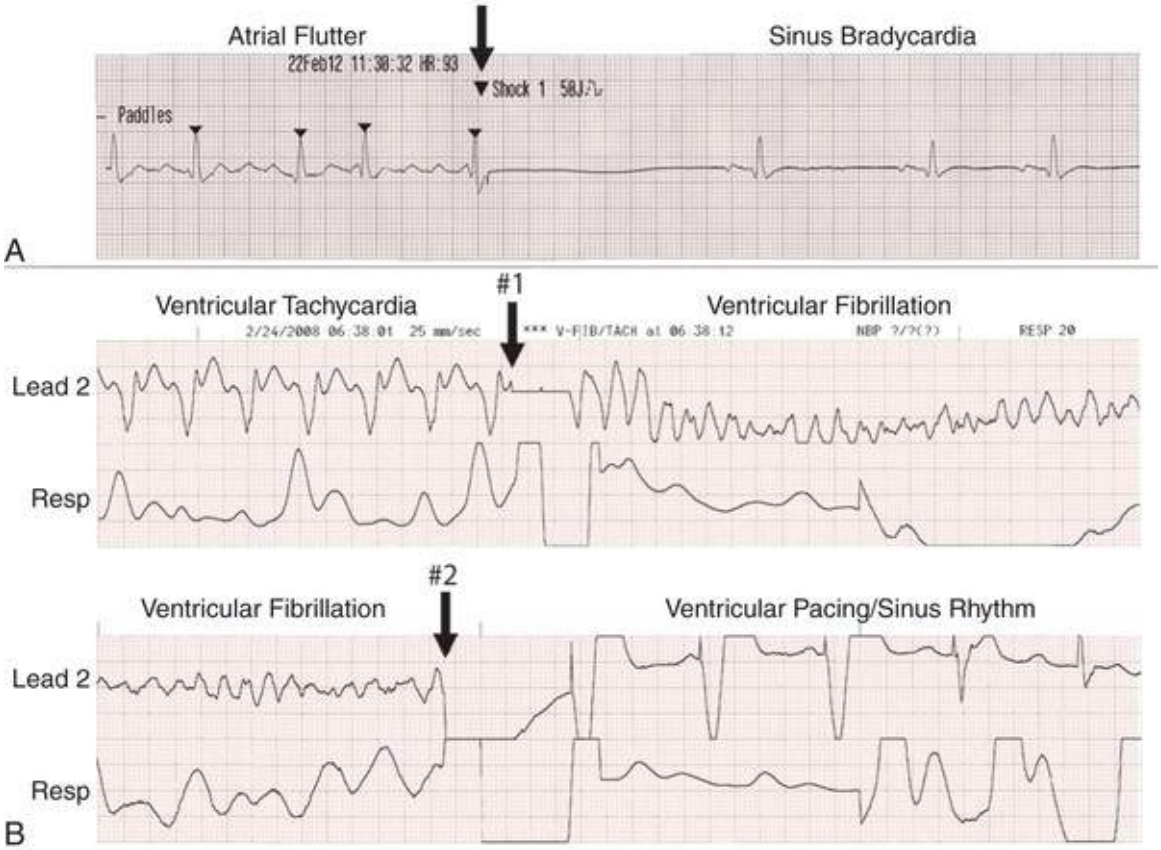


FIGURE 36.1 Cardioversions. In **A,** a synchronized shock (note the synchronization mark in the apex of the QRS complex, *arrowhead*) during atrial flutter is followed by sinus bradycardia. In **B, top panel,** a shock (#1) is delivered during VT but asynchronously (on the T wave); this results in VF, which is then treated with a second, asynchronous shock (#2) that results in sinus rhythm with tracked ventricular pacing. *Resp,* Respirations.

During elective cardioversion, a short-acting barbiturate such as methohexital, a sedative such as propofol, or an amnesic such as diazepam or midazolam can be used. A physician skilled in airway management should be in attendance; an IV route should be established; and pulse oximetry, the ECG, and blood pressure should be monitored. All equipment necessary for emergency resuscitation should be immediately accessible. Before cardioversion, 100% oxygen may be administered for 5 to 15 minutes by

nasal cannula or facemask and is continued throughout the procedure. Manual ventilation of the patient may be necessary to avoid hypoxia during periods of deepest sedation. Adequate sedation of the patient undergoing even urgent cardioversion is essential.

In up to 5% of patients with AF, sinus rhythm cannot be restored by external countershock despite all the preceding measures, including ibutilide pretreatment and biphasic shocks. It is important to distinguish between inability to attain sinus rhythm, indicating failure of the shock to convert the arrhythmia, and inability to maintain sinus rhythm after transient termination of fibrillation; the latter condition (early reinitiation of AF) does not respond to higher-energy shocks because fibrillation has already been terminated but quickly recurs. Pretreatment with an AAD may help maintain sinus rhythm after subsequent shocks. Patients in whom AF simply cannot be terminated with an external shock tend to be very obese or have severe obstructive lung disease. In such patients, internal cardioversion can be performed with the use of specially configured catheters that have multiple large electrodes covering several centimeters of the distal portion of the catheter for distributing the shock energy. By standard percutaneous access, these catheters can be situated in the lateral part of the right atrium and coronary sinus to achieve a shock vector across most of the atrial mass. With such configurations, internal shocks of 2 to 15 J can terminate AF in more than 90% of patients whose arrhythmia was refractory to transthoracic shock. Esophageal cardioversion has also been reported. Rarely, simultaneous shocks from two defibrillators have been reported to terminate refractory VF.

Indications

As a general rule, any nonsinus tachycardia that produces hypotension, congestive heart failure, mental status changes, or angina and does not respond promptly to medical management should be terminated electrically. Very rapid ventricular rates in patients with AF and WPW syndrome are often best treated by electrical cardioversion. In almost all cases, the patient's hemodynamic status improves after cardioversion. Rarely, a patient may experience hypotension, reduced cardiac output, or congestive heart failure after the shock. This problem may be related to complications of the cardioversion, such as embolic events, myocardial depression resulting from the anesthetic agent or the shock itself, hypoxia, lack of restoration of left atrial contraction despite return of electrical atrial systole, or postshock arrhythmias. DC countershock of digitalis-induced tachyarrhythmias is contraindicated (see earlier).

Favorable candidates for electrical cardioversion of AF include patients who (1) have symptomatic AF of less than 12 months' duration, (2) continue to have AF after the precipitating cause has been removed (e.g., after treatment of thyrotoxicosis), (3) have a rapid ventricular rate that is difficult to slow, or (4) have symptoms of decreased cardiac output (e.g., fatigue, lightheadedness, dyspnea) attributable to lack of atrial contraction's contribution to ventricular filling. In patients who have indications for chronic warfarin therapy to prevent stroke, the hope of avoiding anticoagulation by restoring sinus rhythm is not a reason to attempt cardioversion, because these patients are still at increased risk for thromboembolic events. Several large trials have shown that maintenance of sinus rhythm confers no survival advantage over rate control and anticoagulation; thus not all patients with newly discovered AF warrant an attempt at restoration of sinus rhythm. Treatment must be determined individually (**see Chapter 38**).

Unfavorable candidates include patients with (1) digitalis toxicity; (2) no symptoms and a well-controlled ventricular rate without therapy; (3) sinus node dysfunction and various unstable supraventricular tachyarrhythmias or bradyarrhythmias—often bradycardia-tachycardia syndrome—in whom AF finally develops and is maintained, which in essence represents a cure for sick sinus syndrome; (4) little or no symptomatic improvement with normal sinus rhythm who promptly revert to AF after cardioversion despite drug therapy; (5) a large left atrium and longstanding AF; (6) episodes of AF that

revert spontaneously to sinus rhythm; (7) no mechanical atrial systole after the return of electrical atrial systole; (8) AF and advanced heart block; (9) cardiac surgery planned in the near future; and (10) antiarrhythmic drug intolerance. AF is more likely to recur after cardioversion in patients who have significant chronic obstructive lung disease, congestive heart failure, mitral valve disease (particularly mitral regurgitation), AF present longer than 1 year, and an enlarged left atrium (echocardiographic diameter >4.5 cm).

In patients with atrial flutter, slowing the ventricular rate by administration of beta or calcium channel blockers or terminating the flutter with an antiarrhythmic agent may be difficult, and electrical cardioversion is often the initial treatment of choice. For patients with other types of SVT, electrical cardioversion may be used when (1) vagal maneuvers or simple medical management (e.g., IV adenosine and verapamil) has failed to terminate the tachycardia and (2) the clinical setting indicates that fairly prompt restoration of sinus rhythm is desirable because of hemodynamic decompensation or electrophysiologic consequences of the tachycardia. Similarly, in patients with VT, the hemodynamic and electrophysiologic consequences of the arrhythmias determine the need for and urgency of DC cardioversion. Electrical countershock is the initial treatment of choice for ventricular flutter or VF. Speed is essential (**see Chapter 42**).

If reversion of the arrhythmia to sinus rhythm does not occur after the first shock, a higher energy level should be tried. When transient ventricular arrhythmias result after an unsuccessful shock, a bolus of lidocaine can be given before delivery of a shock at the next energy level. If sinus rhythm returns only transiently and is promptly supplanted by the tachycardia, a repeated shock can be tried, depending on the tachyarrhythmia being treated and its consequences. Administration of an AAD intravenously may be useful before delivery of the next cardioversion shock (e.g., ibutilide for resistant AF). After cardioversion, the patient should be monitored, at least until full consciousness has been restored and preferably for 1 hour or more thereafter, depending on the duration of recovery from the particular form of sedation or anesthesia used. If ibutilide has been given, the ECG should be monitored for up to 8 hours because TdP can develop in the first few hours after administration.

Results

Electrical cardioversion restores sinus rhythm in up to 95% of patients, depending on the type of tachyarrhythmia. However, sinus rhythm remains after 12 months in less than one third to one half of patients with longstanding persistent AF. Thus, maintenance of sinus rhythm, once established, is the difficult problem, not immediate termination of the tachyarrhythmia. The likelihood of maintaining sinus rhythm depends on the particular arrhythmia, the presence of underlying heart disease, and the response to AAD therapy. Atrial size often decreases after termination of AF and restoration of sinus rhythm, and functional capacity improves.

Complications

Arrhythmias induced by electrical cardioversion are generally caused by inadequate synchronization, with the shock occurring during the ST segment or T wave (**see Fig. 36.1**). On occasion, even a properly synchronized shock can produce VF. Postshock arrhythmias are usually transient and do not require therapy. Asystole is rare and typically lasts no more than a few seconds before a sinus or junctional rhythm ensues; most defibrillators are also capable of transcutaneous pacing if needed. Embolic episodes are reported to occur in 1% to 3% of patients converted from AF to sinus rhythm. Prior therapeutic anticoagulation with warfarin (international normalized ratio [INR], 2.0 to 3.0) or newer agents such as

dabigatran, rivaroxaban, or apixaban should be used consistently for at least 3 weeks by patients who have no contraindication to such therapy and have had AF for longer than 2 to 3 days or of indeterminate duration. It is important to note that 3 weeks of therapeutic anticoagulation is not the same as simply administering warfarin for 3 weeks, because the warfarin dose may not achieve a therapeutic INR. The newer agents confer almost immediate anticoagulation, such that 3 weeks of treatment equals 3 weeks of anticoagulation. Anticoagulation for at least 4 weeks afterward is recommended because restoration of atrial mechanical function lags behind that of electrical systolic function, and thrombi can still form in largely akinetic atria, although they are electrocardiographically in sinus rhythm. Exclusion of left atrial thrombi by transesophageal echocardiography immediately before cardioversion may not always preclude embolism days or weeks after cardioversion of AF. Atrial thrombi can be present in patients with non–fibrillation-related atrial tachyarrhythmias, such as atrial flutter and AT in patients with congenital heart disease. The same precardioversion and postcardioversion anticoagulation recommendations apply to these patients as to those with AF. Although DC shock has been demonstrated in animals to cause myocardial injury, studies in humans have indicated that elevations in myocardial enzymes after cardioversion are not common. ST-segment elevation, sometimes dramatic, can occur immediately after elective DC cardioversion and can last for 1 to 2 minutes, although cardiac enzymes and myocardial scintigraphy may be unremarkable. ST elevation lasting longer than 2 minutes usually indicates myocardial injury unrelated to the shock. A decrease in serum K^+ and Mg^{2+} levels can occur after cardioversion of VT.

Cardioversion of VT can also be achieved by a chest thump. Its mechanism of termination is probably related to a mechanically induced PVC that interrupts a tachycardia circuit and may be related to commotio cordis (**see Chapter 53**). The thump cannot be timed accurately and is probably effective only when delivered during a nonrefractory part of the cardiac cycle. The thump can alter a VT and possibly induce ventricular flutter or VF if it occurs during the vulnerable period of the T wave. Because there may be a slightly greater likelihood of converting a stable VT to VF than of terminating VT to sinus rhythm, chest thump cardioversion should not be attempted unless a defibrillator is simply unavailable.

Implantable Electrical Devices for Treatment of Cardiac Arrhythmias

Implantable devices that monitor the cardiac rhythm and can deliver competing pacing stimuli and low- and high-energy shocks have been used effectively in selected patients (**see Chapter 41**).

Ablation Therapy for Cardiac Arrhythmias

The purpose of catheter ablation is to destroy myocardial tissue by delivery of energy, generally electrical energy or cryoenergy, through electrodes on a catheter placed next to an area of the myocardium integrally related to onset or maintenance of the arrhythmia. For tachycardias with an apparent focal origin (e.g., automatic, triggered activity, microreentry), the focus itself (<5 mm in diameter) is targeted. In macroreentrant AT and VT, inexcitable scar tissue typically separates strands of surviving myocardium, and wavefronts propagate around these scars. The target for ablation is a narrow portion of myocardium between inexcitable areas (e.g., scar, valve annulus; **Fig. 36.2**). The first catheter ablation procedures were performed with DC shocks, but this energy source has been supplanted by radiofrequency (RF) energy, which is delivered from an external generator and destroys tissue by controlled heat production.

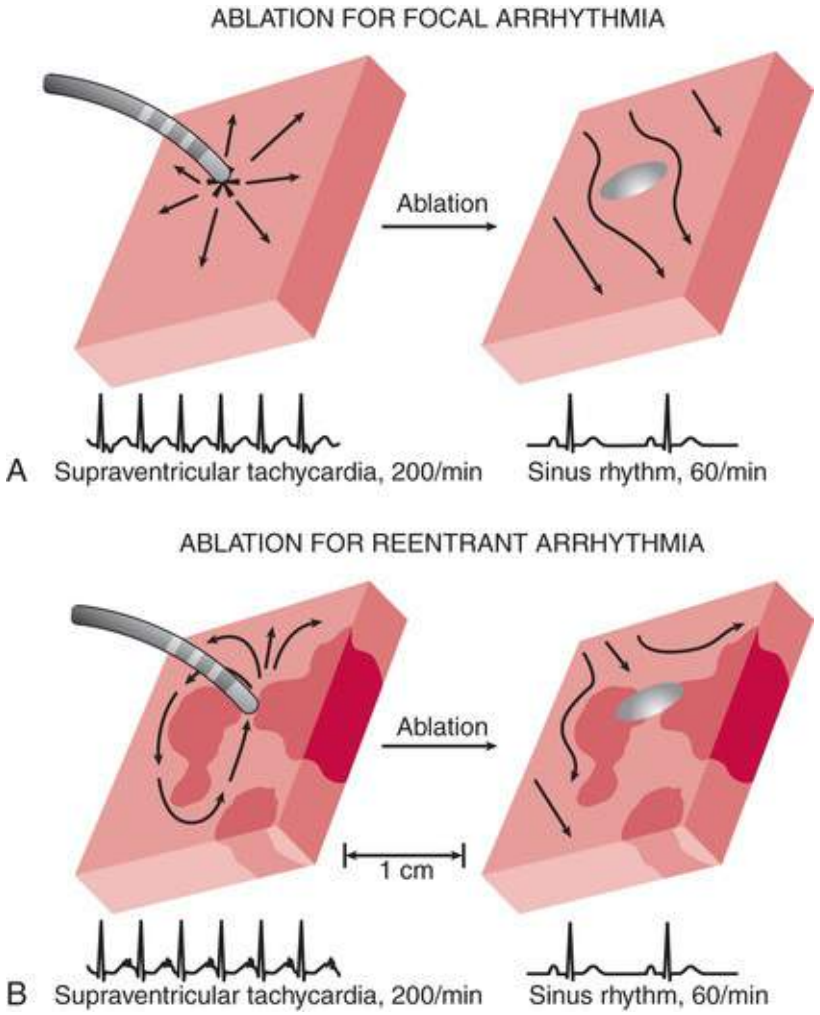


FIGURE 36.2 Strategies for catheter ablation. **A,** Focal tachycardia. **Left,** SVT is caused by an atrial focus, with activation emanating in all directions. **Right,** Ablation of the focus eliminates the arrhythmia with minimal disruption of normal activation. **B,** Macroreentrant SVT in setting of previous atrial damage resulting in scar formation. **Left,** During SVT, a wavefront circulates around a scarred area and through a narrow isthmus between this and another area of scar. **Right,** Ablation at this critical site prevents further reentry.

Lasers and microwave energy sources have been used, but not frequently; cryothermal catheter ablation has been approved for use in humans. When a target tissue has been identified by EPS, the tip of the ablation catheter is maneuvered into apposition with this tissue. After stable catheter position and recordings have been ensured, RF energy is delivered between the catheter tip and an indifferent electrode, usually an electrocautery-type grounding pad on the skin of the patient's thigh. Because energies in the RF portion of the electromagnetic spectrum are poorly conducted by cardiac tissue, RF energy instead causes resistive heating in the cells close to the tip of the catheter (i.e., these cells transduce the electrical energy into thermal energy). When tissue temperature exceeds 50°C, irreversible cellular damage and tissue death occur. An expanding front of conducted heat emanates from the region of resistive heating while RF delivery continues over the next 30 seconds and results in the production of a homogeneous, roughly hemispheric lesion of coagulative necrosis 3 to 5 mm in diameter (**Fig. 36.3A**). RF-induced heating of tissue that has inherent automaticity (e.g., His bundle, foci of automatic tachycardias) results in initial acceleration of a rhythm, whereas RF delivery during a reentrant arrhythmia typically causes slowing and termination of the arrhythmia. In most cases, RF delivery is painless, although ablation of atrial or right ventricular tissue can be uncomfortable for some patients.

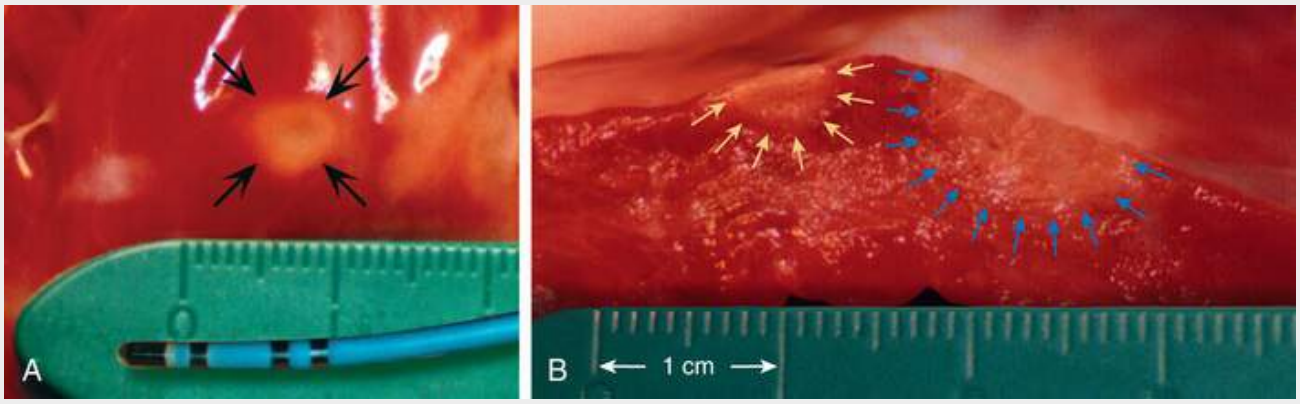


FIGURE 36.3 Radiofrequency lesion in human ventricular myocardium (explanted heart at transplantation). **A,** Energy was applied for 30 seconds at the location denoted by arrows, with the tip of the catheter shown. The lesion is 5 mm in diameter and has a well-demarcated border. A central depression in the lesion results from partial desiccation of tissue. **B,** Extent of radiofrequency lesions (cut surface of specimen in **A**). The lesion outlined by *yellow arrows* was made with a standard electrode (15 W for 30 sec); the lesion outlined by *blue arrows* was made with an irrigated catheter, cooling the tip to allow more power delivery (50 W for 30 sec). The lesion made by the irrigated catheter is more than twice the diameter and 12 times the volume of the standard catheter lesion.

Cooled-Tip Radiofrequency Ablation

In some situations the catheter can be delivered to the correct location, but conventional RF energy delivery cannot eliminate the tachycardia. In some of these cases the amount of damage—depth or breadth—caused by standard RF energy is inadequate. With the use of standard RF energy, power delivery is usually regulated to maintain a preset catheter tip temperature (typically, 55°C to 70°C). Tip temperatures higher than 90°C are associated with coagulation of blood elements on the electrode, which precludes further energy delivery and could also cause this material to become detached and embolize. Cooling of the catheter tip by internal circulation of liquid or continuous fluid infusion through small holes in the tip electrode can prevent excessive heating of the tip and allow delivery of higher power, thus producing a larger lesion (**Fig. 36.3B**) and potentially enhancing efficacy.[26] Cooled-tip ablation has been used to good advantage in cases in which standard (4-mm tip) catheter ablation has failed, as well as for primary therapy for atrial flutter and fibrillation and VT associated with structural heart disease, in which additional damage to already-diseased areas is not harmful and may be required to achieve the desired result.

Catheter-delivered cryoablation causes tissue damage by freezing cellular structures. Nitrous oxide is delivered to the tip of the catheter, where it is allowed to internally boil and cool the tip electrode, after which the gas is circulated back to the delivery console. Catheter tip temperature can be regulated, with cooling to as low as −80°C. Cooling to 0°C causes reversible loss of function and can be used as a diagnostic test (i.e., termination of a tachycardia when the catheter is in contact with a group of cells critical to its perpetuation, or determining its effect on normal conduction when close to the AV node). The catheter tip can then be cooled more deeply to produce permanent damage and thus cure of the arrhythmia. Cryoablation has been used for pulmonary vein isolation to treat paroxysmal AF by situating a collapsed balloon at the end of a catheter near a pulmonary vein ostium and inflating the balloon with nitrous oxide at −80°C. During cryoballoon occlusion of the vein for 3 to 4 minutes at a time, pulmonary vein isolation can usually be effected with one or two applications.[27] Real-time recordings can be done

simultaneously to monitor conduction. Cryoablation appears to cause less endocardial damage than RF energy does and may thus engender less risk for thromboemboli after ablation, as well as less chance of esophageal injury with ablation of AF (although it is not eliminated). However, balloon cryotherapy to isolate right pulmonary veins for the treatment of AF has resulted in phrenic nerve injury, and care must be taken to establish the location of the phrenic nerve. Residual arrhythmias can result (Videos 36.1 and 36.2).

Radiofrequency Catheter Ablation of Accessory Pathways

Location of Pathways

The safety, efficacy, and cost-effectiveness of RF catheter ablation of an accessory AV pathway have made ablation the treatment of choice in most adult and many pediatric patients who have AV reentrant tachycardia (AVRT) or atrial flutter or fibrillation associated with a rapid ventricular response over the accessory pathway (**see Chapter 37**). When RF energy is delivered to an immature heart, the lesion size can increase as the heart grows; however, this has not been shown to cause problems later in life.

An EPS is performed initially to determine that the accessory pathway is part of the tachycardia circuit or capable of rapid AV conduction during AF and to localize the accessory pathway (the optimal site for ablation). Pathways can exist in the right or left free wall or the septum of the heart (**Fig. 36.4**). Septal accessory pathways are further classified as superoparaseptal, midseptal, and posterior paraseptal. Pathways classified as posterior paraseptal are posterior to the central fibrous body within the so-called pyramidal space, which is bounded by the posterosuperior process of the left ventricle and the inferomedial aspects of both atria and is behind (posterior to) the true atrial septum. Superoparaseptal pathways are found near the His bundle, and accessory pathway activation potential as well as His bundle potential can be recorded simultaneously from a catheter placed at the His bundle region. Midseptal pathways are close to the AV node and can usually be ablated from a right-sided approach; rarely, a left atrial approach is needed. Right posterior paraseptal pathways insert along the tricuspid ring in the vicinity of the coronary sinus ostium, whereas left posterior paraseptal pathways are further into the coronary sinus and may be located at a subepicardial site around the proximal coronary sinus, within a middle cardiac vein or coronary sinus diverticulum, or subendocardially along the ventricular aspect of the mitral annulus.

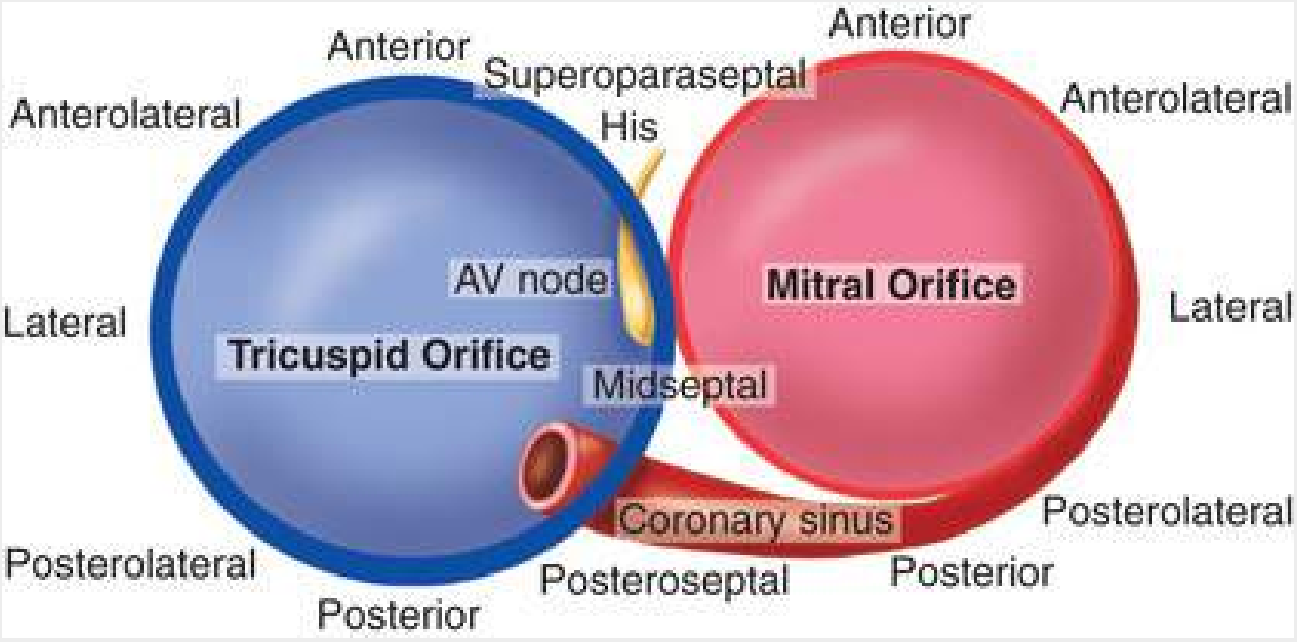
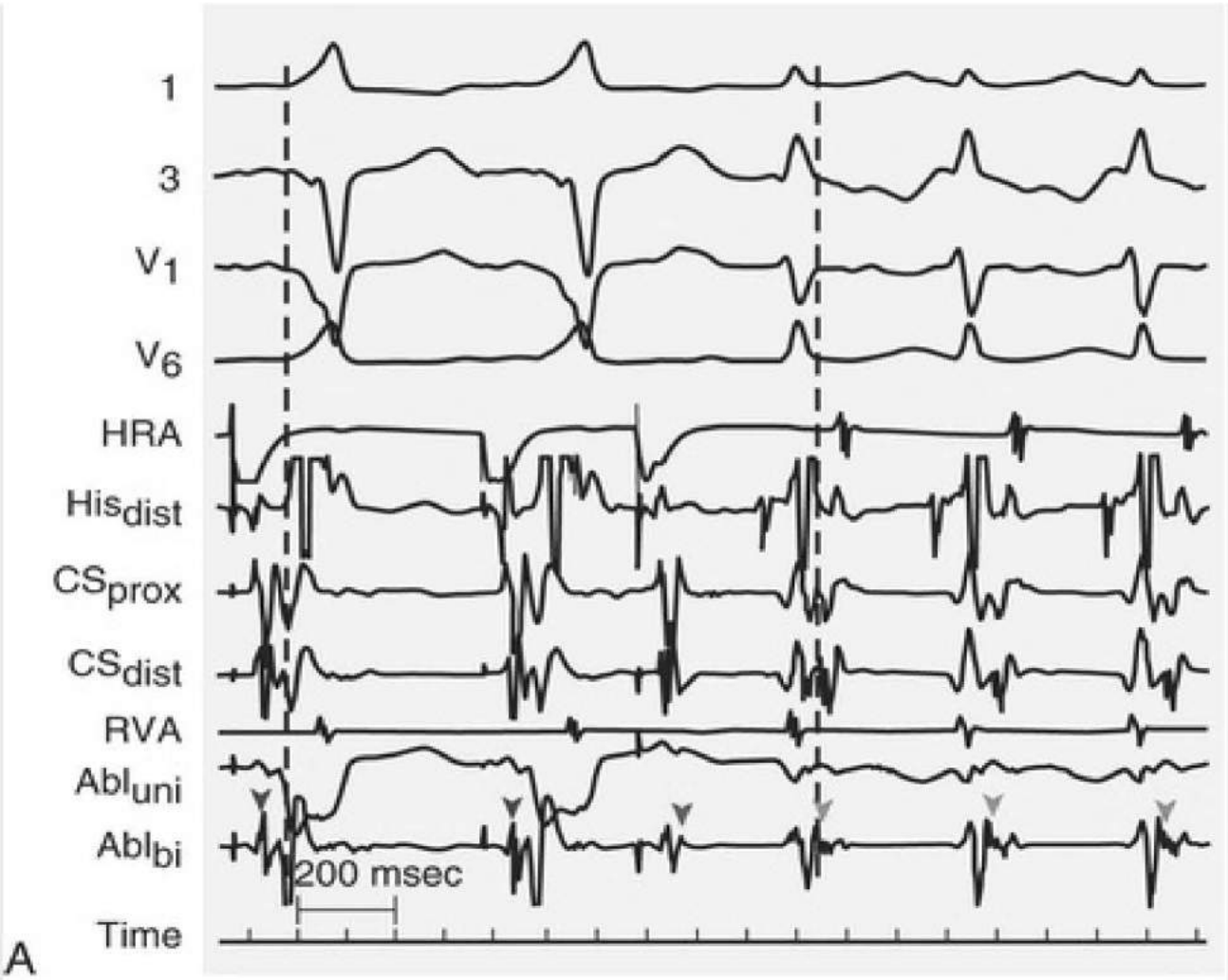


FIGURE 36.4 Locations of accessory pathways by anatomic region. The tricuspid and mitral valve annuli are depicted in a left anterior oblique view. Locations of the coronary sinus, AV node, and bundle of His are shown. Accessory pathways may connect the atrial to the ventricular myocardium in any of the regions shown.

Pathways at all locations and in all age groups can be ablated successfully. Multiple pathways are present in about 5% of patients. Occasional pathways with epicardial locations may be more easily approached from within the coronary sinus. Rarely, pathways can connect an atrial appendage with adjacent ventricular epicardium, 2 cm or more from the AV groove.

Ablation Site.

The optimal ablation site can be found by direct recordings of the accessory pathway (**Fig. 36.5**), although deflections that mimic accessory pathway potentials can be recorded at other sites. The ventricular insertion site can be determined by finding the site of the earliest onset of the ventricular electrogram in relation to the onset of the delta wave. Other helpful guidelines include unfiltered unipolar recordings that register a QS wave and an accessory pathway signal during preexcitation. A major ventricular potential synchronous with onset of the delta wave can be a target site in left-sided preexcitation, whereas earlier ventricular excitation in relation to the delta wave can be found for right-sided preexcitation. The atrial insertion site of manifest or concealed pathways (i.e., delta wave present or absent, respectively) can be found by locating the site showing the earliest atrial activation during retrograde conduction over the pathway. Reproducible mechanical inhibition of accessory pathway conduction during catheter manipulation and subthreshold stimulation has also been used to determine the optimal site. Accidental catheter trauma should be avoided, however, because it can hide the target for prolonged periods. Right free wall and superoparaseptal pathways are particularly susceptible to catheter trauma.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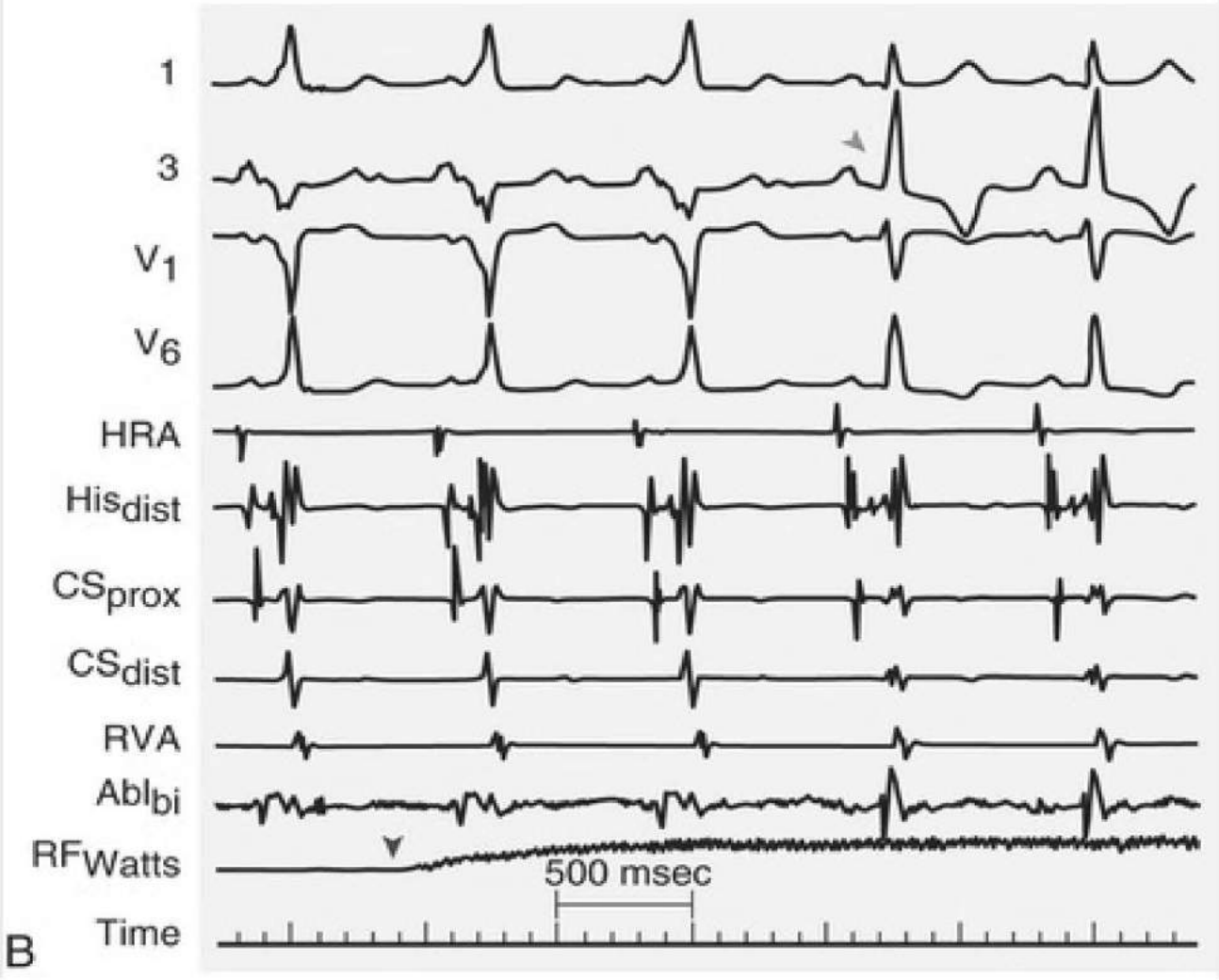
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FIGURE 36.5 Wolff-Parkinson-White syndrome. Surface ECG leads 1, 3, V_1, and V_6 are shown, with intracardiac recordings from high right atrium (HRA), distal His (His_{dist}) bundle region, proximal (CS_{prox}) and distal (CS_{dist}) coronary sinus, right ventricular apex (RVA), and unipolar (Abl_{uni}) and bipolar (Abl_{bi}) tip electrodes of the ablation catheter. RF power in watts (RF_{Watts}) is also shown. **A,** Two beats of atrial pacing are conducted over the accessory pathway (*blue arrowheads* in the Abl_{bi} recording from the site of the accessory pathway) and resulted in a delta wave on the ECG. A premature atrial stimulus (*center*) encounters accessory pathway refractoriness (*red arrowhead*) and instead is conducted over the AV node and bundle of His and resulted in a narrow QRS complex and started an episode of AVRT. After each narrow QRS complex is an atrial deflection, the earliest portion of which is recorded at the ablation site (*green arrowheads*). **B,** Ablation of this pathway by delivery of RF energy from the ablation catheter tip. The *blue arrowhead* denotes the onset of delivery of RF energy; two QRS complexes later, the delta wave is abruptly lost (*green arrowhead* in lead 3) because of elimination of conduction over the accessory pathway.

Left-sided accessory pathways typically cross the mitral annulus obliquely. Consequently, the earliest site of retrograde atrial activation and the earliest site of anterograde ventricular activation are not directly across the AV groove from each other (i.e., ventricular insertion closer to coronary sinus ostium). Identification of the earliest site of atrial activation is usually performed during orthodromic AVRT or relatively rapid ventricular pacing so that retrograde conduction using the AV node does not confuse assessment of the location of the earliest atrial activation.

Successful ablation sites should exhibit anatomic/fluoroscopic stability and consistent electrical characteristics. During sinus rhythm, local ventricular activation at the successful ablation site precedes onset of the delta wave on the ECG by 10 to 35 milliseconds; during orthodromic AVRT, the interval between onset of ventricular activation in any lead and local atrial activation is usually 70 to 90 milliseconds (**see Fig. 36.5**). When temperature-measuring ablation catheters are used, a stable rise in catheter tip temperature is a helpful indicator of catheter stability and adequate contact between the electrode and tissue. In such a case, tip temperature generally exceeds 50°C. The retrograde transaortic and transseptal approaches have been used with equal success to ablate accessory pathways located along the mitral annulus. Routine performance of an EPS weeks after the ablation procedure is not generally indicated but may be considered in patients who have a recurrent delta wave or symptoms of tachycardia. Catheter-delivered cryoablation can be useful in patients with septal accessory pathways (located near AV node or His bundle). With use of this system, the catheter tip and adjacent tissue can be reversibly cooled to test a potential site. If accessory pathway conduction fails while normal AV conduction is preserved, deeper cooling can be performed at the site to complete the ablation. If, however, normal AV conduction is worsened, permanent damage is almost always averted by allowing the catheter quickly to rewarm quickly.

Atriofascicular accessory pathways have connections consisting of a proximal, AV node–like portion, which is responsible for conduction delay and decremental conduction properties, and a long distal segment located along the endocardial surface of the right ventricular free wall, which has electrophysiologic properties similar to those of the right bundle branch. The distal end of the right atriofascicular accessory pathway can insert into the apical region of the right ventricular free wall, close to the distal right bundle branch, or can actually fuse with the latter. Right atriofascicular accessory pathways might represent a duplication of the AV conduction system and can be localized for ablation by recording potentials from the rapidly conducting distal component, which crosses the tricuspid annulus (analogous to the His bundle) and extends to the apical region of the right ventricular free wall. Ablation at such a site on the annulus is usually successful; these pathways are very sensitive to catheter trauma,

and the operator must use great care to avoid such trauma.

Indications

Ablation of accessory pathways is indicated in patients who have symptomatic AVRT that is drug resistant or who are drug intolerant or do not desire long-term drug therapy. It is also indicated in patients who have AF or other atrial tachyarrhythmias and a rapid ventricular response, by means of an accessory pathway when the tachycardia is drug resistant, or in those who are drug intolerant or do not desire long-term drug therapy. Other potential candidates with an accessory pathway include the following: (1) patients with AVRT or AF with rapid ventricular rates identified during an EPS for another arrhythmia; (2) asymptomatic patients with ventricular preexcitation whose livelihood, profession, important activities, insurability, or mental well-being and the public safety would be affected by spontaneous tachyarrhythmias or by the presence of the electrocardiographic abnormality; (3) patients with AF and a controlled ventricular response by means of the accessory pathway; and (4) patients with asymptomatic preexcitation and a family history of sudden cardiac death. Controversy remains whether all patients with accessory pathways (even those without symptoms) need treatment; however, ablation has such a high success rate and low complication rate that in most centers, patients who need any form of therapy are referred for catheter ablation.

Results

Currently, in the hands of an experienced operator, the success rate for accessory pathway ablation is greater than 95% (slightly less for right free wall pathways, in which stable catheter-tissue contact is more problematic), with a 2% recurrence rate after an apparently successful procedure. There is a 1% to 2% complication rate, including bleeding, vascular damage, myocardial perforation with cardiac tamponade, valve damage, stroke, and MI. Heart block occurs in less than 3% of septal pathways. Procedure-related death is very rare.

Radiofrequency Catheter Modification of AV Node for AV Nodal Reentrant Tachycardias

Atrioventricular node reentry is a common cause of SVT episodes (**see Chapters 34 and 37**). Although controversy still exists about the exact nature of the tachycardia circuit, abundant evidence has indicated that two pathways in the region of the AV node participate, one with relatively fast conduction but long refractoriness and the other with shorter refractoriness but slower conduction. Premature atrial complexes can encounter refractoriness in the fast pathway, conduct down the slow pathway, and reenter the fast pathway retrogradely, thereby initiating AV nodal reentrant SVT (**Fig. 36.6**). Although this is the most common manifestation of AV node reentry, some patients have what appears to be propagation in the opposite direction in this circuit (anterograde fast, retrograde slow), as well as a “slow-slow” variant. Other, much less common types have been described. Two or more of these variants can exist in the same patient (**Fig. 36.7**).

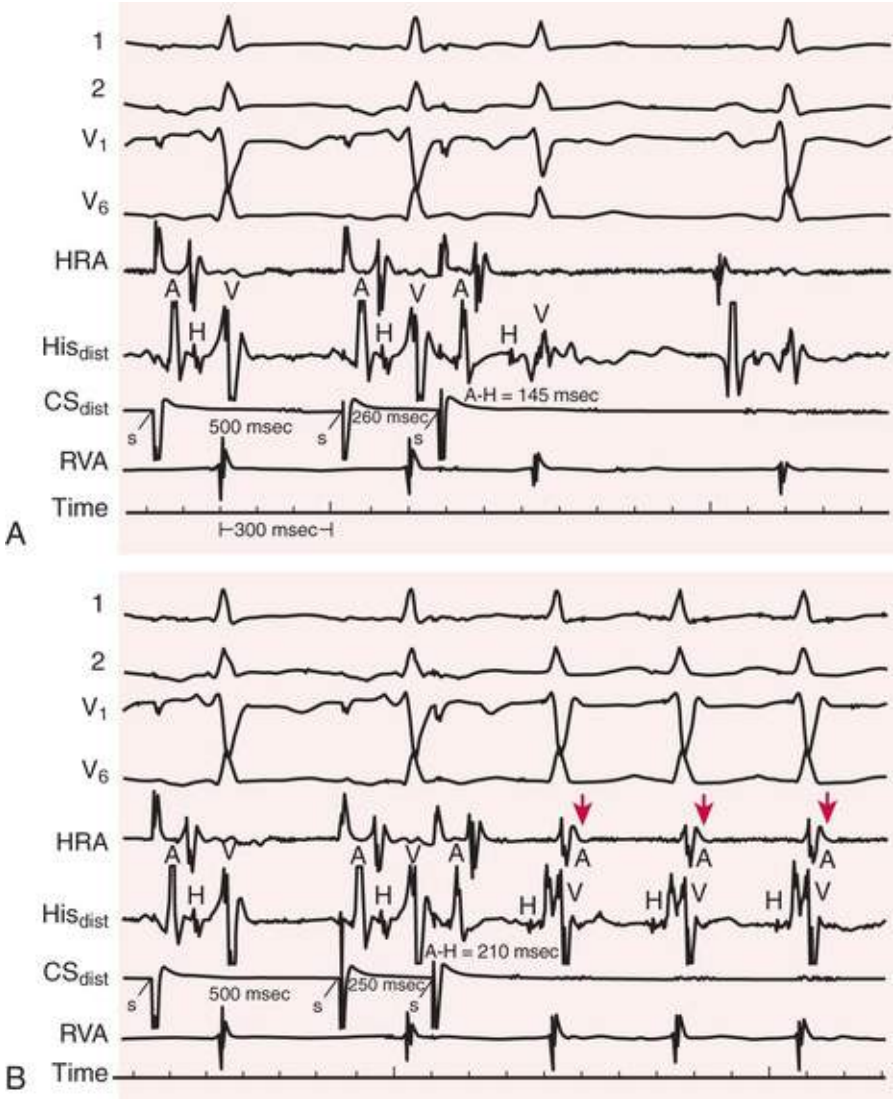


FIGURE 36.6 Atrioventricular node reentry. **A,** Two atrial paced complexes from the coronary sinus (CS) are followed by an atrial premature stimulus at a coupling interval of 260 milliseconds and resulted in an A-H interval of 145 milliseconds. **B,** The same atrial drive train is followed by an atrial extrastimulus 10 milliseconds earlier than before (250 msec). This resulted in a marked increase in the A-H interval to 210 milliseconds, after which AVNRT ensues because the extrastimulus encounters block in a "fast" AV node pathway, conducts down a "slow" pathway, and then conducts back up the fast pathway in a repeating fashion. *Red arrowheads* denote atrial electrograms coincident with QRS complexes, characteristic of the most common type of AV node reentry. Recording was done as in previous figures.

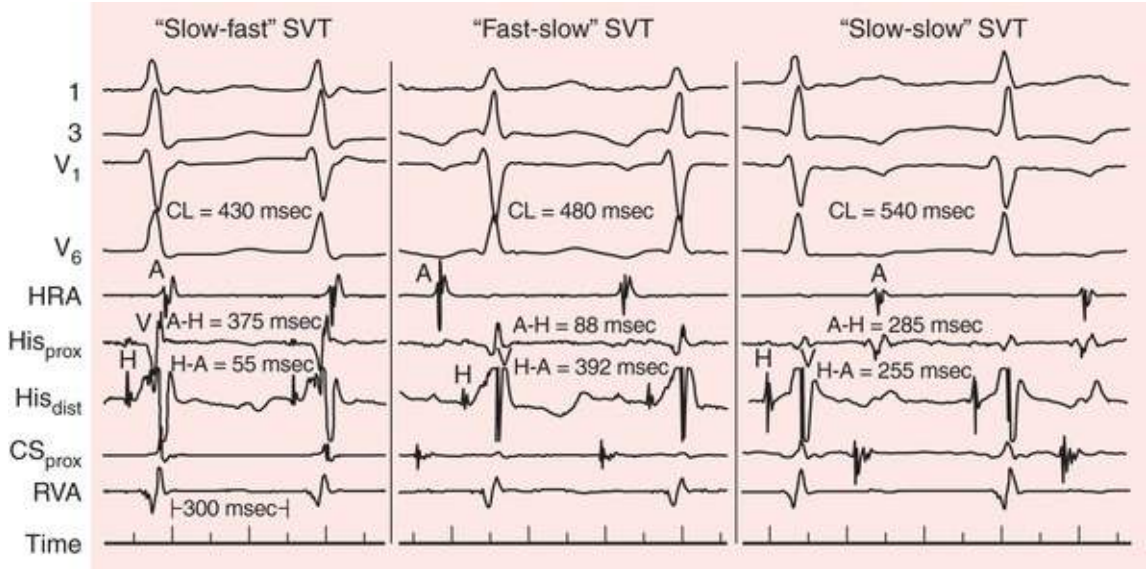


FIGURE 36.7 Three variants of AV node reentrant SVT in the same patient. **Left,** Most common type of AV node SVT (anterograde slow pathway, retrograde fast). Atrial activation is coincident with ventricular activation. **Center,** "Atypical" AV node reentry with anterograde fast pathway conduction and retrograde conduction over a slow pathway. **Right,** A rare variety is shown that consists of anterograde conduction over a slow pathway and retrograde conduction over a second slow pathway. Note the similar atrial activation sequences in the last two (coronary sinus before the right atrium), as distinct from that of slow-fast AV node reentry (coronary sinus and right atrial activation almost simultaneous). Note also the different P-QRS relationships, from simultaneous activation (left, short RP interval) to P in front of the QRS (middle, long RP interval) and P midway in the cardiac cycle (right). Recording was done as in previous figures. *CL,* Cycle length.

Fast Pathway Ablation.

Ablation can be performed to eliminate conduction in the fast pathway or the slow pathway. Currently, fast pathway ablation is rarely performed because it is associated with a prolonged PR interval, a higher recurrence rate (10% to 15%), and a slightly higher risk for complete AV block (2% to 5%) than with slow pathway ablation. One uncommon situation in which fast pathway ablation may be preferred is for patients who have a greatly prolonged PR interval at rest and no evidence of anterograde fast pathway conduction. In such patients, ablation of the anterograde slow pathway may produce complete AV block, whereas retrograde fast pathway ablation can eliminate SVT without altering AV conduction.

Slow Pathway Ablation.

The slow pathway can be located by mapping along the posteromedial tricuspid annulus close to the coronary sinus os. Electrographic recordings are obtained with an atrial-to-ventricular electrogram ratio of less than 0.5 and either a multicomponent atrial electrogram or a recording consistent with a possible slow pathway potential. In the anatomic approach, target sites are selected fluoroscopically. A single RF application eliminates slow pathway conduction in many cases, but in others, serial RF applications may be needed, starting at the most posterior site (near the coronary sinus os) and progressing along the tricuspid annulus more anteriorly. An accelerated junctional rhythm usually occurs when RF energy is applied at a site that will result in successful elimination of SVT (**Fig. 36.8**). The success rate is equivalent with the anatomic and electrographic mapping approaches, and most often, combinations of both are used and yield success rates of greater than 95%, with less than a 1% chance of complete heart block. Catheter-delivered cryoablation has been used for the treatment of AV node reentrant tachycardia (AVNRT) with excellent results and is considered by some to be safer than RF (less chance of permanent

AV block) but in most series has a higher rate of SVT recurrence after apparent successful ablation.

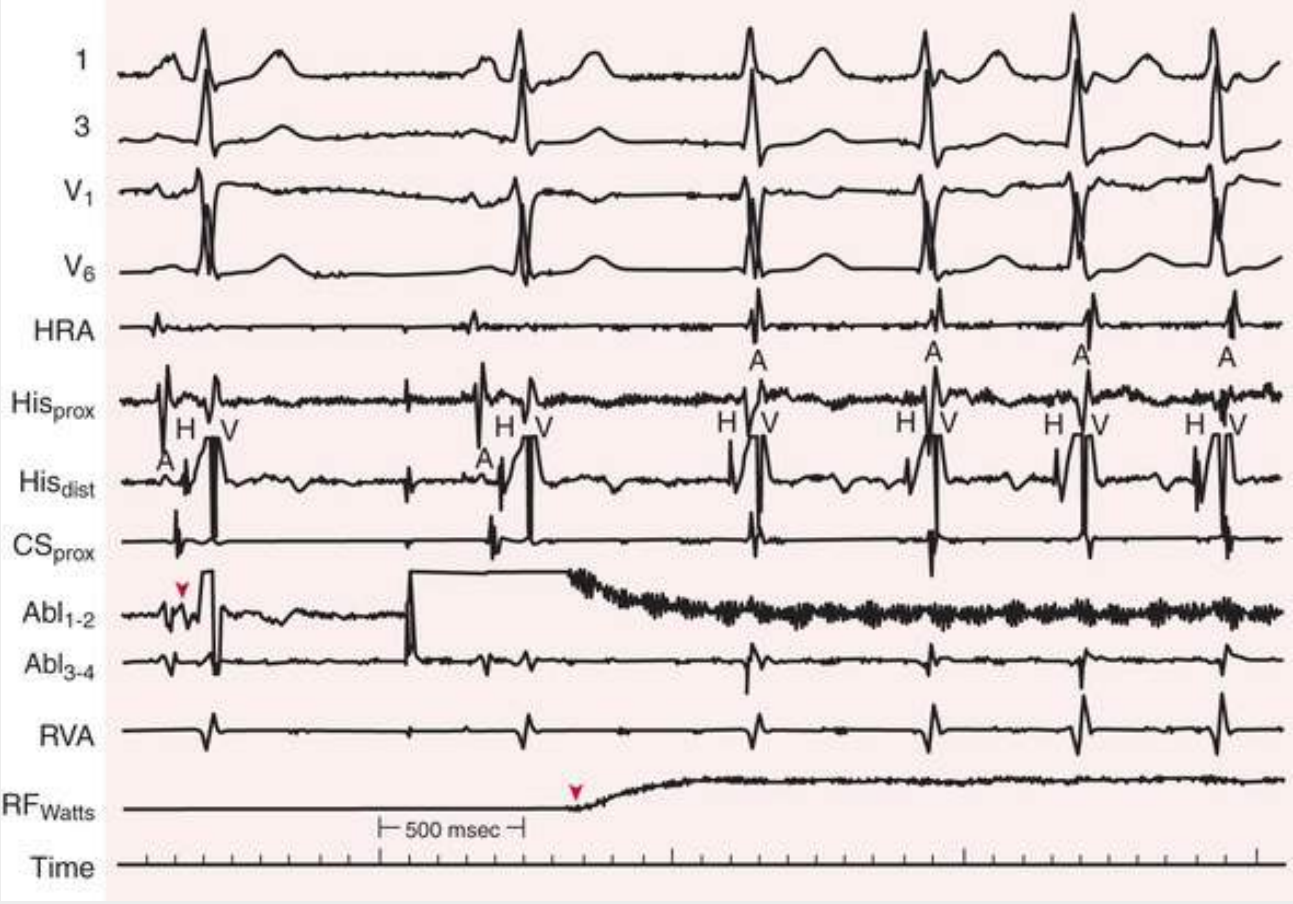


FIGURE 36.8 Atrioventricular node slow pathway modification for cure of AV node reentrant SVT. The ablation recording (*arrowhead* in Abl_{1-2}) shows a slurred deflection between the atrial and ventricular electrogram components; this may represent the AV node slow pathway deflection (but it is not the bundle of His deflection, which is instead recorded from a separate catheter 15 mm away). Shortly after the onset of RF delivery (*arrowhead* in RF_{Watts}), an accelerated junctional rhythm begins and gradually speeds up further. Retrograde conduction is present during the junctional rhythm. *Abl_{3-4}*, Proximal electrode recording from ablation catheter. Recording was done as in previous figures.

Patients in whom slow pathway conduction is completely eliminated almost never have recurrent SVT episodes. Approximately 40% of patients can have evidence of residual slow pathway function after successful elimination of sustained AVNRT, usually manifested as persistent dual–AV node physiology and single–AV node echoes during atrial extrastimulation. The surest endpoint for slow pathway ablation is elimination of sustained AVNRT, with and without an infusion of isoproterenol.

AVNRT recurs in approximately 5% of patients after slow pathway ablation; repeat ablation is almost always successful. In some patients the ERP of the fast pathway decreases after slow pathway ablation, possibly because of electrotonic interaction between the two pathways. Atypical forms of reentry can result after ablation, as can apparent parasympathetic denervation, and result in inappropriate sinus tachycardia. This usually resolves within 3 months after ablation.

At present, the slow pathway approach is the preferred method for ablation of typical AVNRT. Ablation of the slow pathway is also a safe and effective means for the treatment of atypical forms of AVNRT. In patients with AVNRT undergoing slow pathway ablation, junctional ectopy during application of the RF energy is a sensitive but nonspecific marker of successful ablation; it occurs in longer bursts at effective than at ineffective target sites. Ventriculoatrial conduction should be expected during the

junctional ectopy, and poor ventriculoatrial conduction or actual block may herald subsequent anterograde AV block. Junctional ectopic rhythm is caused by heating of the AV node and does not occur with cryoablation.

Indications

RF catheter ablation for AVNRT can be considered in patients with recurrent, symptomatic, sustained AVNRT that is drug resistant or who are drug intolerant or do not desire long-term drug treatment. The procedure can also be considered for patients with sustained AVNRT identified during EPS or catheter ablation of another arrhythmia, or when EPS reveals dual–AV node pathway physiology and atrial echoes but without AVNRT in patients with suspected AVNRT clinically.

Results

Most centers currently use slow pathway ablation, which results in a procedural success rate of 98%, a recurrence rate of less than 5%, and an incidence of heart block requiring permanent pacing of 1% or less. Late development of heart block (months to years later) is rare.

Junctional Tachycardia

Junctional tachycardia, often called ectopic junctional tachycardia (although if the location is junctional, by definition it is ectopic) is a rare form of SVT in which the ECG resembles that in AVNRT but is distinct in that (1) the mechanism is automatic, not reentrant, and (2) the atrium is clearly not involved in the tachycardia. This disorder is most often observed in young healthy individuals, in women more often than in men, and is usually catecholamine dependent. Ablation must be carried out close to the His bundle, and the risk for heart block requiring pacemaker insertion exceeds 5%.

Radiofrequency Catheter Ablation of Arrhythmias Related to the Sinus Node

Inappropriate sinus tachycardia is a syndrome characterized by high sinus rates with exercise and at rest. Patients complain of palpitations at all times of day that correlate with inappropriately high sinus rates. They may not respond well to beta-blocker therapy because of lack of desired effect or occurrence of side effects. Ivabradine, which blocks I_f (principal pacemaker current in sinus node) is indicated for treatment of heart failure but has been used with some success in patients with inappropriate sinus tachycardia.[28] When the sinus node area is to be ablated because of drug-refractory symptoms, it can be identified anatomically and electrophysiologically, and ablative lesions are usually placed between the superior vena cava and crista terminalis at sites of early atrial activation. Intracardiac echocardiography can help in defining the anatomy and in positioning the ablation catheter. Isoproterenol may be helpful in "forcing" the site of impulse formation to cells with the most rapid discharge rate. Care must be taken to apply RF energy at the most cephalad sites first; initial ablation performed farther down the crista terminalis does not alter the atrial rate at the time but can damage any subsidiary pacemaker regions that may be needed after the sinus node has eventually been ablated.

Indications

Patients with *persistent* inappropriate sinus tachycardia should be considered for ablation only after clear failure of medical therapy, because the results of ablation are often less than completely satisfactory.

Whenever ablation is performed in the region of the sinus node, the patient should be apprised of the chance of needing a pacemaker after the procedure. Phrenic nerve damage and superior vena caval stenosis are also possibilities.

Results

Although a good technical result may be obtained at the time of the procedure for inappropriate sinus tachycardia, symptoms often persist because of recurrence of rapid sinus rates (at or near preablation rates) or for nonarrhythmic reasons. In some, after the atrial rate decreases, an inappropriately rapid junctional rhythm (80 to 90/min) is present; this may indicate an overall increased sensitivity of cells with pacemaker capacity to catecholamines in these patients. Multiple ablation sessions are needed in some patients, and approximately 20% eventually undergo pacemaker implantation; however, not all these patients have relief of symptoms, including palpitations, despite a normal heart rate.

Radiofrequency Catheter Ablation of Atrial Tachycardia

Atrial tachycardias are a heterogeneous group of disorders; causative factors include rapid discharge of a focus (focal tachycardia) and reentry. The former can occur in anyone, regardless of the presence of structural abnormalities of the atria, whereas reentrant ATs almost always occur in the setting of structurally damaged atria. Symptoms vary from none, with relatively infrequent or slow ATs in patients without heart disease, to syncope (rapid AT with compromised cardiac function) or heart failure (incessant AT over weeks or months). All forms of AT are amenable to catheter ablation (**see Chapter 37**).

Focal Atrial Tachycardia.

In focal ATs (automatic or triggered foci or microreentry), activation mapping is used to determine the source of the AT by recording the earliest onset of local activation. These tachycardias can behave capriciously and can be practically noninducible during EPS despite the patient complaining of multiple daily episodes before the EPS. Approximately 10% of patients can have multiple atrial foci. Sites tend to cluster near the pulmonary veins in the left atrium and the mouths of the atrial appendages and along the right atrial crista terminalis (**Figs. 36.9A, 36.10, and 36.11**; **also see Fig. 35.15**). Activation times at these sites typically occur only 15 to 40 milliseconds before onset of the P wave on the ECG. Care must be taken to avoid inadvertent damage to the phrenic nerve (**Fig. 36.11**); its location can be determined by pacing at high current at a candidate site of ablation while observing for diaphragmatic contraction. Ablation should not be performed at a site at which this is seen, if at all possible.

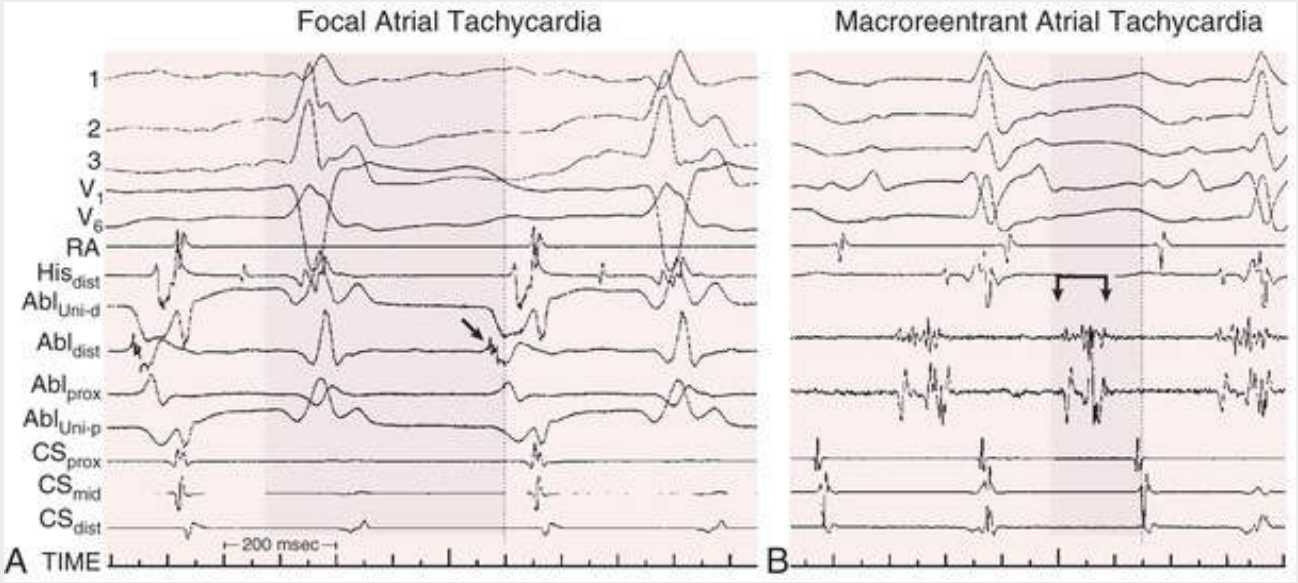


FIGURE 36.9 Atrial tachycardia. In both panels the interval from the end of one P wave to the beginning of the next (atrial diastole) is in *gray*. A *dashed line* denotes onset of the P wave during tachycardia. **A,** Focal AT arising in the right atrium. Two tachycardia complexes are shown; the earliest site found (Abl_{dist}, at which ablation eliminated the tachycardia) is shown as a multicomponent recording that starts only approximately 40 milliseconds before onset of the P wave. The unipolar recording (Abl_{Uni-d}) has a deep negative deflection (indicating propagation away from the electrode). The activation sequence of recordings is very different from that during sinus rhythm, in which the right atrial (RA) recording is at the onset of the P wave. **B,** Macroreentrant AT in a patient who had undergone repair of an atrial septal defect years earlier. The ablation catheter is in the posterior right atrium, where a fragmented signal (between *arrows*) is recorded that almost fills atrial diastole. Ablation at this site terminated the tachycardia. Recording was done as in previous figures.

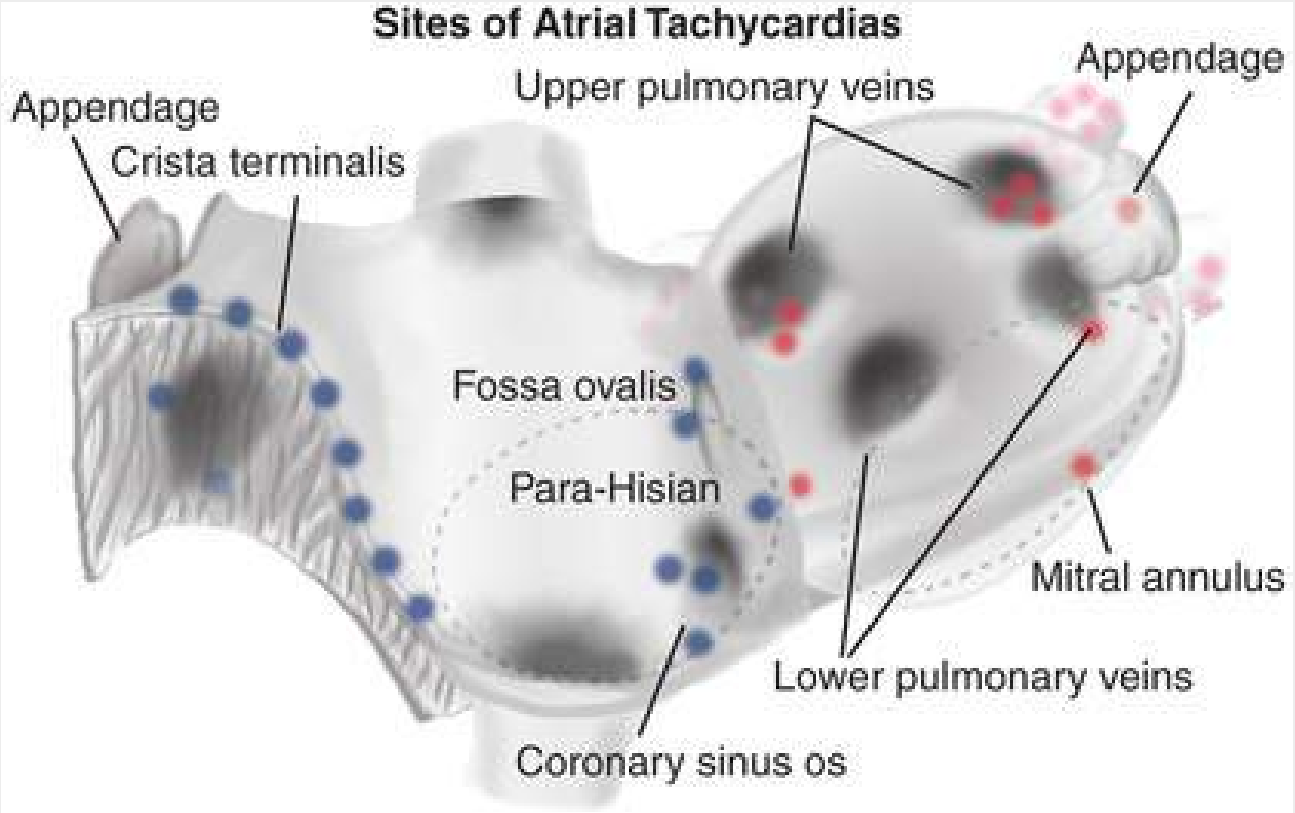


FIGURE 36.10 Locations of origins of focal atrial tachycardias. The atria are viewed from the front with the right atrial free wall retracted to show the interior. Structures are labeled as shown; right atrial foci appear in shades of *blue,* left atrial foci in shades of *red.*

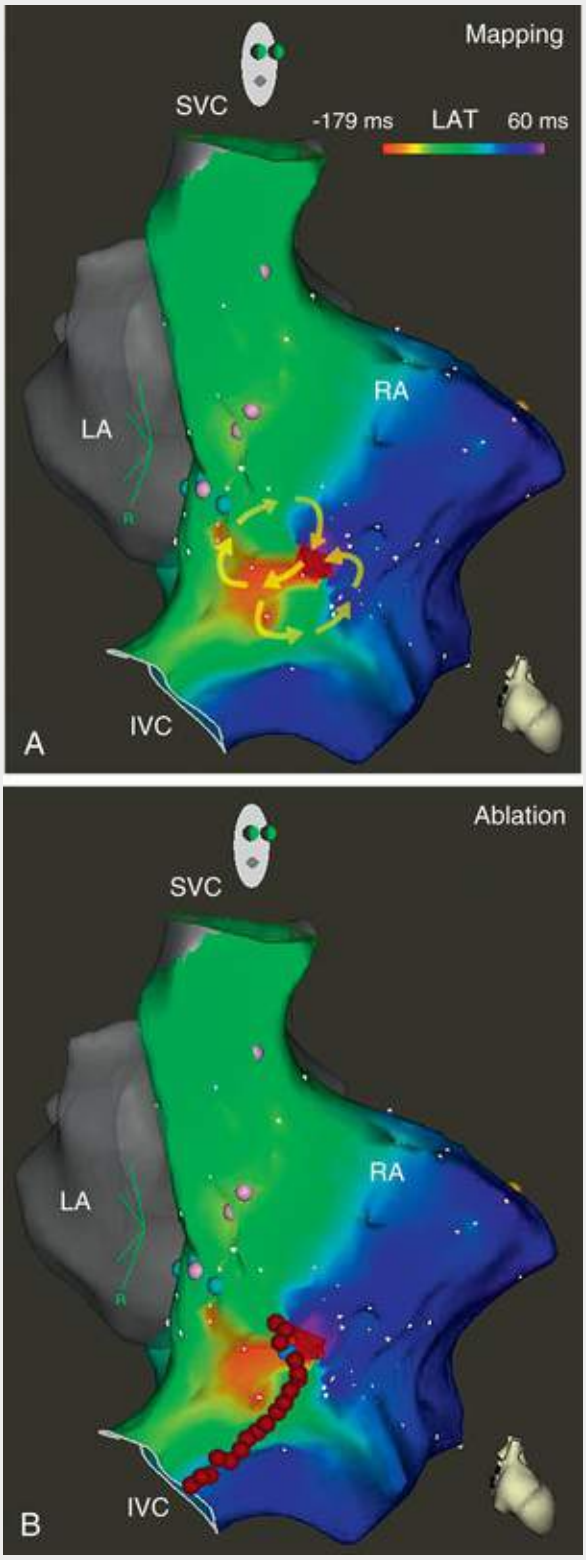


FIGURE 36.11 Reentrant atrial tachycardia. **A,** Electroanatomic activation map of the right atrium (*RA*) is shown in a patient with a previous right atrial incision for closure of an atrial septal defect. *Arrows* depict a double loop of reentry around presumed scars with a common diastolic pathway between scars. The *color bar* shows progression of activation times during AT (from *red* through *green*, *blue*, and *purple*). The tachycardia cycle length (240 msec) is entirely represented in the range of colors. **B,** *Red dots* denote ablation sites connecting scars (transecting diastolic pathway) and connecting one scar to the inferior vena cava (*IVC*) to preclude reentry around all barriers. *LA,* Left atrium; *SVC,* superior vena cava.

Reentrant Atrial Tachycardia.

As noted, these ATs usually occur in the setting of structural heart disease, especially after previous surgery involving an atrial incision (repair of congenital heart disease such as an atrial septal defect, Mustard or Senning repair of transposed great vessels, or one of a variety of Fontan repairs for tricuspid atresia and other disorders), or previous atrial ablation (e.g., for AF). The region of slow conduction is

typically related to an end of an atriotomy or previous ablation scar, the location of which varies from patient to patient. Therefore, preprocedural review of operative and ablation procedure reports and careful electrophysiologic mapping are essential. Because reentry within a complete circuit is occurring, activation can be recorded throughout the entire cardiac cycle. The ablation strategy is to identify regions with mid-diastolic atrial activation during tachycardia (**Fig. 36.11**; **also see Fig. 36.9B**) that can be proved by pacing techniques to be integral to the tachycardia. Such sites are attractive ablation targets because they are composed of relatively few cells—thus electrical silence on the surface ECG in diastole—and so are more easily eliminated by the small amount of damage effected by a typical application of RF energy. Focal ablation of these sites can then be performed, but often tachycardia can still be initiated (usually at a slower rate) or recurs after the procedure. Because these sites are typically located at a relatively narrow zone between the ends of previous scars, surgical incisions, or ablation lines and another nonconducting barrier (e.g., another scar, caval orifice, valve annulus), a line of ablative lesions is generally made from the end of the scar to the nearest electrical barrier; thus reentry can be prevented. This technique is analogous to that used in curing atrial flutter (see later). Because these patients frequently have extensive atrial disease with islands of scar that could serve as barriers for additional ATs, specialized mapping techniques may be needed to locate these regions and preemptively connect them with ablative lesions to prevent future AT episodes.

Indications

Catheter ablation for ATs should be considered in patients who have recurrent episodes of symptomatic sustained ATs that are drug resistant, or who are drug intolerant or do not desire long-term drug treatment.

Results

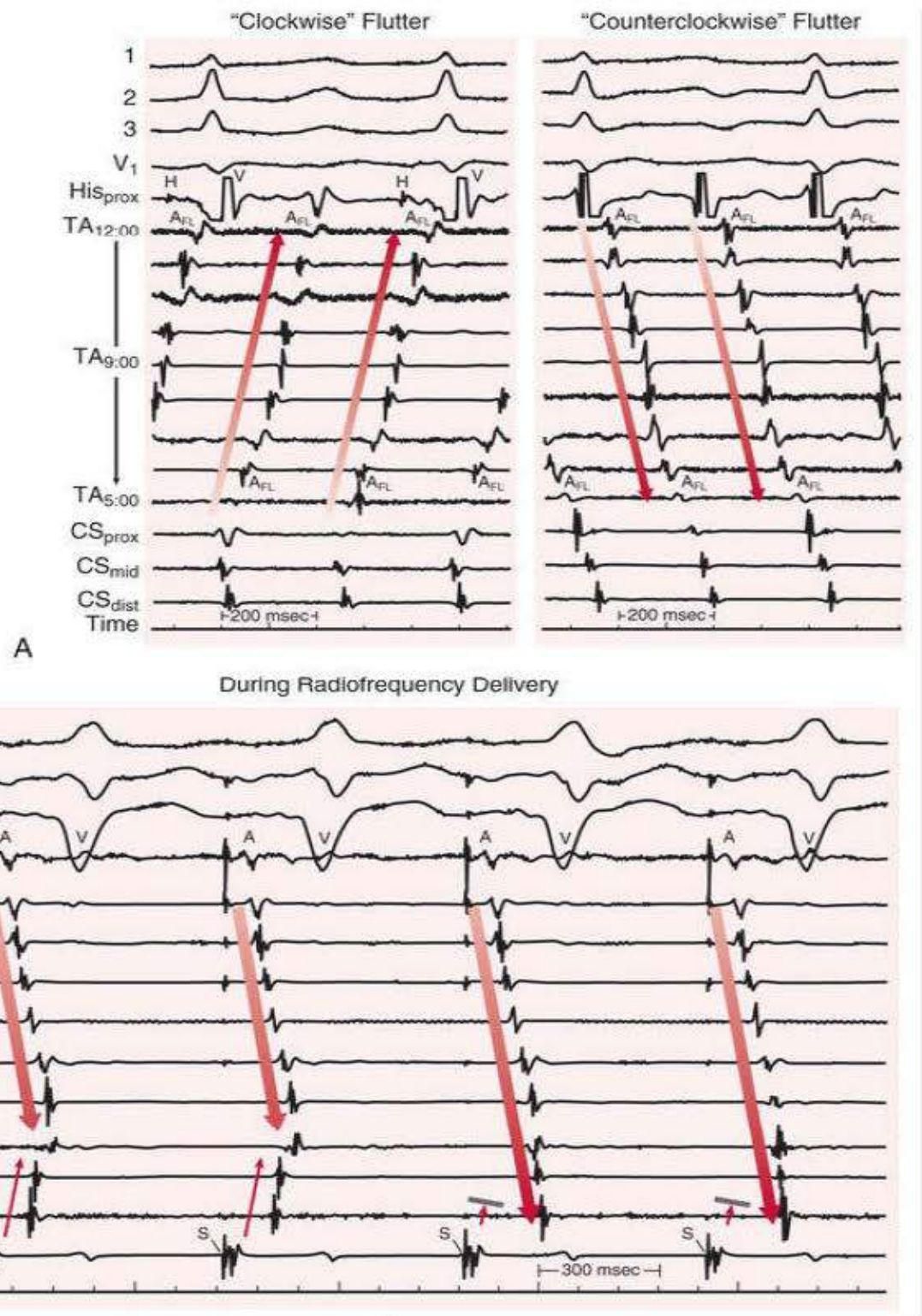
Success rates for ablation of focal AT range from 80% to 95%, largely depending on the ability to induce episodes at EPS. When episodes can be initiated with pacing, isoproterenol, or other means, the AT can usually be ablated. Reentrant ATs, although more readily induced by an EPS, are often more difficult to eliminate completely; initial success rates are high (90%), but recurrences are seen in up to 20% of patients and necessitate drug therapy or another ablation procedure. Complications, which occur in 1% to 2% of patients, include phrenic nerve damage, cardiac tamponade, and heart block (with rare perinodal ATs).

Radiofrequency Catheter Ablation of Atrial Flutter

Atrial flutter can be defined electrocardiographically (most typically, negative sawtooth waves in leads II, III, and aVF at a rate of approximately 300 beats/min) or electrophysiologically (rapid, organized macroreentrant AT, the circuit for which is anatomically determined). Understanding of the reentrant pathway in all forms of atrial flutter is essential for development of an ablation strategy (**see Chapter 37**).

Reentry in the right atrium, with the left atrium passively activated, constitutes the mechanism of the typical electrocardiographic variety of atrial flutter, with caudocranial activation along the right atrial septum and craniocaudal activation of the right atrial free wall (**Fig. 36.12A**). Ablating tissue in a line between any two anatomic barriers that transects a portion of the circuit necessary for perpetuation of

reentry can be curative. Typically, this is across the isthmus of atrial tissue between the inferior vena caval orifice and the tricuspid annulus (the cavotricuspid isthmus), a relatively narrow point in the circuit. Locations for RF delivery can be guided anatomically or electrophysiologically. Less frequently, the direction of wavefront propagation in this large right atrial circuit is reversed ("clockwise" flutter proceeding cephalad up the right atrial free wall and caudad down the septum, with upright flutter waves in the inferior leads; **Fig. 36.12A, left panel**). These two arrhythmias constitute cavotricuspid isthmus–dependent flutter, can be ablated by cavotricuspid isthmus interruption, and are distinct from other rapid atrial arrhythmias that may have a similar appearance on the ECG but use different (and often multiple) circuits in other parts of the right or left atrium. Ablation can be more difficult in these cases, which often occur in the setting of advanced lung disease or previous cardiac surgery or ablation. A common theme in these complex reentrant arrhythmias is the presence of an anatomically determined zone of inexcitability around which an electrical wavefront can circulate. Specialized mapping tools and skills are necessary to achieve successful ablation in these cases.


"Clockwise" Flutter
"Counterclockwise" Flutter
1
2
3
V1
HisProx
TA12:00
TA9:00
TA5:00
CSprox
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CSdist
Time
H
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AFL
200 msec
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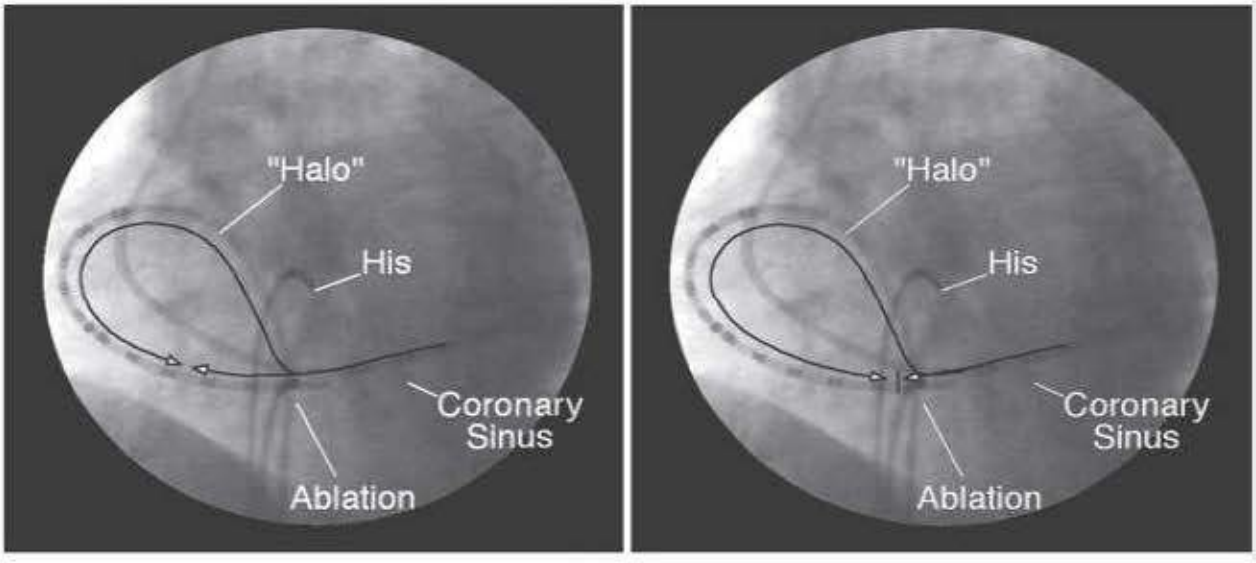
"Halo"
His
Coronary Sinus
Ablation
"Halo"
His
Coronary Sinus
Ablation

B

FIGURE 36.12 **A,** Two forms of atrial flutter in the same patient are shown. A halo catheter with 10 electrode pairs is situated on the atrial side of the tricuspid annulus (*TA*), with recording sites displayed from the top of the annulus (12:00) to the inferomedial aspect (5:00), as shown in the fluoroscopic views in **B.** On the **left,** the wavefront of atrial activation proceeds in a clockwise fashion (*arrows*) along the annulus, whereas on the **right,** the direction of propagation is the reverse. **B,** Ablation of the isthmus of atrial tissue between the tricuspid annulus and the inferior vena caval orifice for cure of atrial flutter. Recordings are displayed from the multipolar catheter around much of the circumference of the tricuspid annulus (see the left anterior oblique fluoroscopic images). Ablation of this isthmus is performed during coronary sinus pacing. In the two beats on the **left,** atrial conduction proceeds in two directions around the tricuspid annulus, as indicated by arrows and recorded along the halo catheter. In the two beats on the **right,** ablation has interrupted conduction in the floor of the right atrium, thereby eliminating one path for transmission along the tricuspid annulus. The halo catheter now records conduction, proceeding all the way around the annulus. This finding demonstrates a unidirectional block in the isthmus; block in the other direction may be demonstrated by pacing from one of the halo electrodes and observing a similar lack of isthmus conduction. (The bundle of His recording in the **right panel** is lost because of catheter movement.)

In patients with AF, an antiarrhythmic drug can slow intra-atrial conduction to such an extent that atrial flutter results and fibrillation is no longer observed. In some of these patients, ablation of atrial flutter and continued AAD therapy can prevent recurrences of these atrial arrhythmias.

The endpoint of atrial flutter ablation procedures was initially termination of atrial flutter, with RF application accompanied by noninducibility of the arrhythmia. However, with use of these criteria, up to 30% of patients had recurrent flutter because of lack of complete and permanent conduction block in the cavotricuspid isthmus. Thus the current endpoint of ablation has changed to ensuring a line of bidirectional block is present in this region, usually by pacing from opposite sides of the isthmus (**Fig. 36.12B**). With use of these criteria, recurrence rates have fallen to less than 5%.

Indications

Candidates for RF catheter ablation include patients with recurrent episodes of atrial flutter that are drug resistant, those who are drug intolerant, and those who do not desire long-term drug therapy. Many patients who undergo AF ablation (**see Chapter 38**) also have episodes of flutter during the procedure that can be treated by ablation of the cavotricuspid isthmus at the same setting.

Results

Regardless of circuit location, atrial flutter can be ablated successfully in more than 90% of cases, although patients with complex right or left atrial flutter require more extensive and complex procedures. Recurrence rates are less than 5% except in patients with extensive atrial disease, in whom new circuits can develop over time as new areas of conduction delay and block form. Complications are rare and include inadvertent heart block and phrenic nerve paralysis.

Ablation and Modification of Atrioventricular Conduction for Atrial Tachyarrhythmias

In some patients who have rapid ventricular rates despite optimal drug therapy during complex atrial tachyarrhythmias that are less amenable to ablation, RF ablation can be used to eliminate or modify AV conduction and control the ventricular rates.

To achieve this, a catheter is placed across the tricuspid valve and positioned to record a small His bundle electrogram associated with a large atrial electrogram. RF energy is applied until complete AV block has been achieved and is continued for an additional 30 to 60 seconds (**Fig. 36.13**). If no change in AV conduction is observed after 15 seconds of RF ablation despite good contact, the catheter is repositioned and the attempt repeated. In occasional patients, attempts at RF ablation via this right-sided approach fail to achieve heart block. These patients can undergo an attempt from the left ventricle with a catheter positioned along the posterior interventricular septum, just beneath the aortic valve, to record a large His bundle electrogram. Success rates currently approach 100%, with AV conduction recurring in less than 5% of cases. Improved left ventricular function can result from control of the ventricular rate during AF and withdrawal of rate-controlling medications with negative inotropic action. Permanent ventricular or AV pacing is required after ablation. With continuing advances in direct ablation of complex atrial arrhythmias, AV nodal ablation is less often used currently. Whereas in some cases the AV junction can be modified to slow the ventricular rate without producing complete AV block by ablation in the region of the slow pathway (as described with AV node modification for AV node reentry), this strategy is almost never used at present.

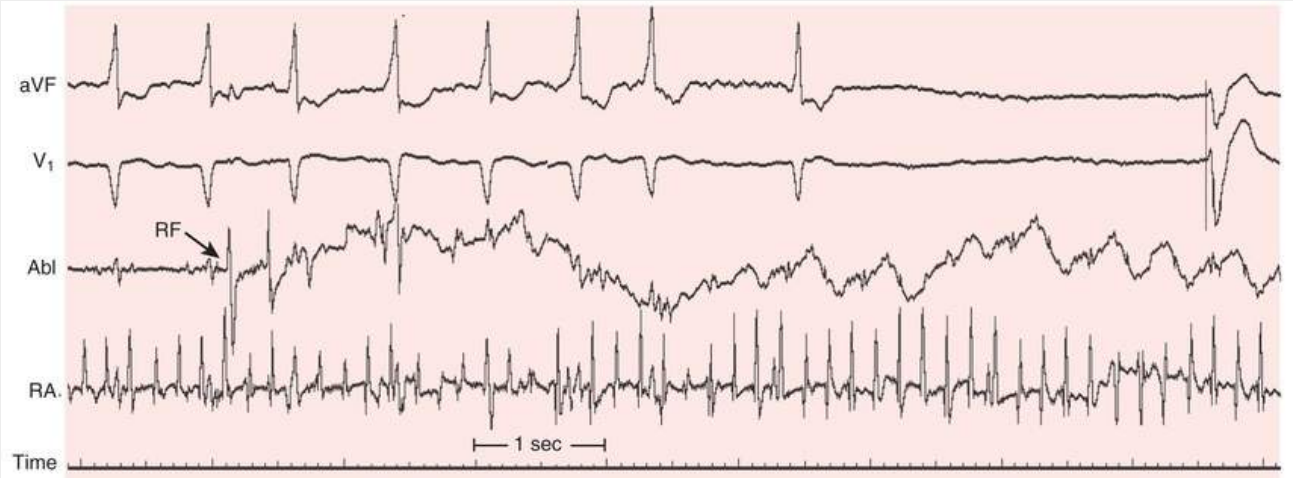

FIGURE 36.13 Atrioventricular nodal ablation for rate control of atrial fibrillation (AF). The ECG shows rapidly conducted AF; application of radiofrequency (*RF*) energy (*arrow*) results in complete AV block within seconds, followed by a ventricular paced complex.

Indications

Ablation and modification of AV conduction can be considered in the following cases: (1) patients with symptomatic atrial tachyarrhythmias who have inadequately controlled ventricular rates, unless primary ablation of the atrial tachyarrhythmia is possible (especially when a permanent pacemaker is already present for treatment of bradycardia-tachycardia syndrome); (2) similar patients when drugs are not tolerated or patients do not choose to take them, even though the ventricular rate can be controlled; (3) patients with symptomatic, nonparoxysmal junctional tachycardia that is drug resistant or in whom drugs are not tolerated or are not desired; (4) patients resuscitated from sudden cardiac death related to atrial flutter or AF with a rapid ventricular response in the absence of an accessory pathway; and (5) patients with a dual-chamber pacemaker and pacemaker-mediated tachycardia that cannot be treated effectively by drugs or reprogramming of the pacemaker. The last three situations are rarely encountered.

Results

As previously noted, successful interruption of AV conduction can be achieved in almost all cases; recurrent conduction is observed in less than 5%. Significant complications occur in 1% to 2%. In early studies, up to 4% of patients had an episode of sudden death after AV junction ablation despite adequate pacemaker function, presumably because of relative bradycardia after long periods of rapid ventricular rates serving as the setting for repolarization-related ventricular arrhythmias. Since then, backup pacing rates are set to 80 to 90/min for the first 1 to 3 months after ablation in most cases, which has almost entirely eliminated this problem. Improvements in quality-of-life indices, as well as in cost-effectiveness, have been demonstrated for this procedure.

Radiofrequency Catheter Ablation of Atrial Fibrillation

See Chapters 37 and 38.

Radiofrequency Catheter Ablation of Ventricular Arrhythmias

In general, the success rate for ablation of VTs is lower than that for AV node reentry or AV reentry because of the heterogeneity of substrates and presentations. In the ideal case, induction of the VT must be reproducible, with uniform QRS morphology from beat to beat, and VT must be sustained and hemodynamically stable so that the patient can tolerate the VT long enough during the procedure to undergo the extensive mapping necessary to localize optimal ablation target sites. These conditions are often not met. Patients with several electrocardiographically distinct, uniform morphologies of VT can still be candidates for ablation, because in many cases a common reentrant pathway is shared by two or more VT morphologies. Also, the target for ablation must be fairly circumscribed and preferably endocardially situated, although catheter mapping and ablation from the epicardial surface after percutaneous pericardial access is performed in many centers. Very rapid VT, polymorphic VT, and infrequent, nonsustained VT can be addressed with catheter ablation using different strategies.

Location and Ablation.

RF catheter ablation of VT can be divided into idiopathic VT, which occurs in patients with essentially structurally normal hearts and includes patients with isolated PVCs; VT that occurs in various disease settings but without coronary artery disease (CAD); and VT in patients with CAD and usually previous MI. In the first group, VTs/PVCs can arise in either ventricle. Right ventricular tachycardias most frequently originate in the outflow tract and have a characteristic left bundle branch block–like, inferior axis morphology (**see Chapter 39**); less often, VTs/PVCs arise in the inflow tract or free wall. Initiation of tachycardia can often be facilitated by catecholamines. Most left VTs in structurally normal hearts are septal in origin and have a characteristic QRS configuration (i.e., right bundle branch block, superior axis). Other VTs/PVCs also occur and arise from different areas of the left ventricle, including the left ventricular outflow region and the aortic sinuses of Valsalva, and are similar in electrocardiographic appearance and clinical behavior to those arising in the right ventricular outflow tract. VTs in abnormal hearts without CAD can be the result of either intramyocardial or bundle branch reentry, most often observed in patients with dilated cardiomyopathy, or as a focal process. Epicardial foci and circuits are more common in this than in other groups. In patients with bundle branch reentry, ablation of the right bundle branch eliminates the tachycardia. VT can occur in patients with right ventricular dysplasia (**see**

Chapter 33), sarcoidosis, Chagas disease, hypertrophic cardiomyopathy (**Chapters 77 and 78**), and a host of other noncoronary disease states.

Activation mapping and pace mapping are effective in patients with idiopathic VTs/PVCs to locate the site of origin of the VT. In *activation mapping* the timing of endocardial electrograms sampled by the mapping catheter is compared with the onset of the surface QRS complex. Sites that are activated 20 to 40 milliseconds before onset of the surface QRS are near the origin of the arrhythmia (**see Fig. 35.13**). In idiopathic VT/PVCs, ablation at a site at which the unipolar electrogram shows a QS complex may yield greater success than if an rS potential is observed (**Fig. 36.14**). *Pace mapping* involves stimulation of various ventricular sites to produce a QRS contour that duplicates the QRS contour of the spontaneous VT or PVC, thus establishing the apparent site of origin of the arrhythmia (**Fig. 36.15**). This technique is limited by several methodologic problems but may be useful when the arrhythmia cannot be initiated and when a 12-lead ECG has been obtained during spontaneous episodes. Presystolic Purkinje potentials, as well as very-low-amplitude mid-diastolic signals, can be recorded during VT from sites at which ablation cures VT in most patients with left ventricular VTs that have a right bundle branch block superior axis; this VT characteristically terminates with IV verapamil and is the only significant reentrant idiopathic VT. Localization of optimal ablation sites for VT in patients with CAD and previous MI can be more challenging than in patients with structurally normal hearts because of the altered anatomy and electrophysiology. Pace mapping has a lower sensitivity and specificity than for idiopathic VT. Furthermore, reentry circuits can sometimes be large and resistant to the relatively small lesions produced by RF catheter ablation in scarred endocardium.

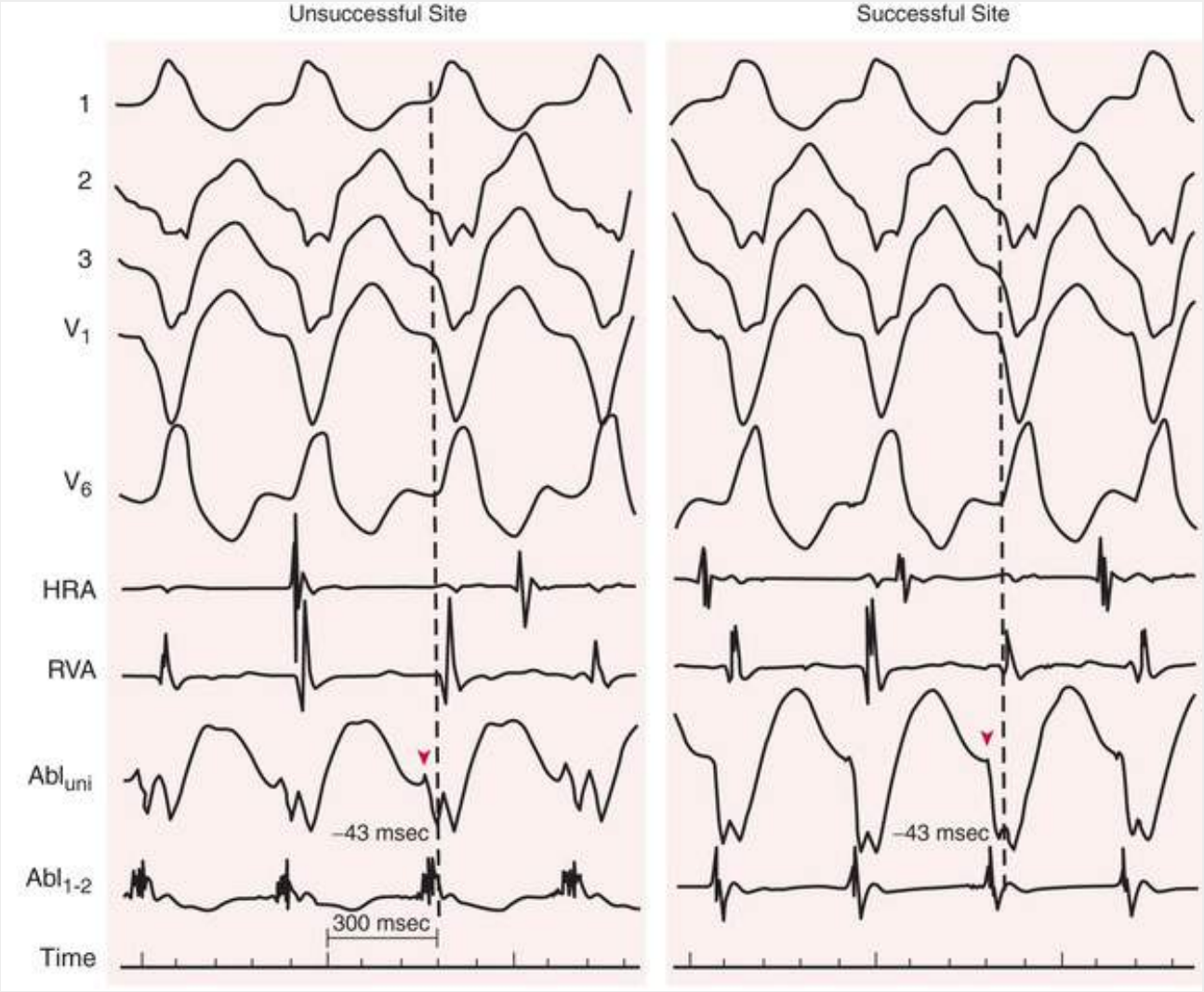

FIGURE 36.14 Recordings from unsuccessful and successful ablation sites in a patient with idiopathic ventricular tachycardia arising in the inferior right ventricular wall. In the recordings from the unsuccessful ablation site, the unipolar signal (*arrowhead*) has a small r wave, which indicates that a portion of the wavefront from the focus of tachycardia is approaching the site from elsewhere. At the successful site, the unipolar recording has a QS configuration, thus indicating that all depolarization is emanating from this site. In each site the bipolar recording (Abl_{1-2}) occurs an identical 43 milliseconds before onset of the QRS (*dashed lines*).

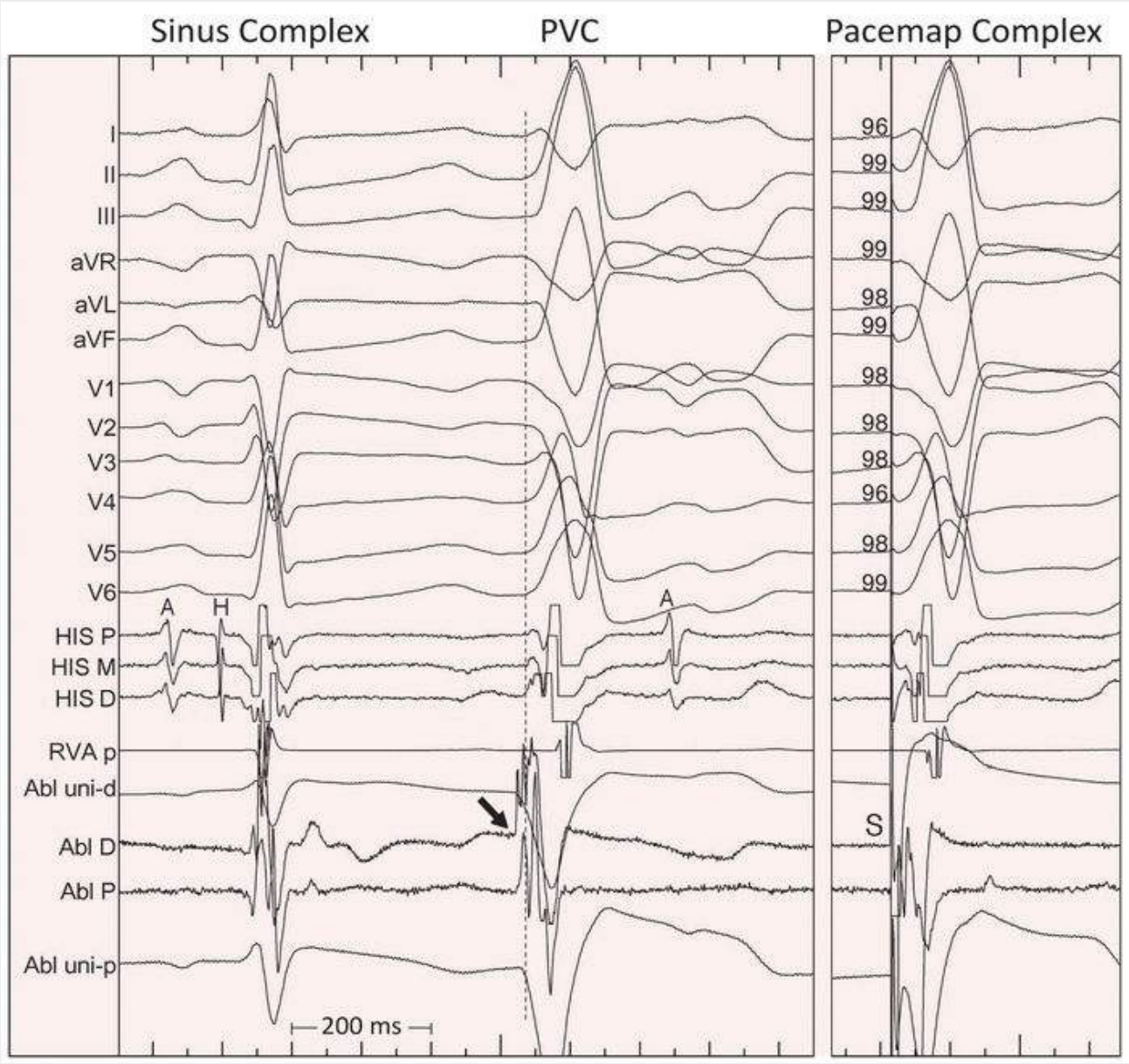

FIGURE 36.15 Premature ventricular complex (PVC) and pace mapping. All 12 surface ECG leads are shown, along with intracardiac recordings in sinus rhythm, a spontaneous PVC, and pacing (*S*) at the site of Abl D (distal recordings of ablation catheter). The Abl D recording shows a sharp deflection (*arrow*) occurring about 25 milliseconds before onset of the QRS (*dashed line*). In the **right panel,** pacing is performed from this site. This produces an identical QRS complex in each lead, with a short stimulus–QRS interval; numbers indicate percentage of "match" between PVC and paced QRS complexes using an algorithm in the recording system. Ablation at this site eliminated VT in 2 seconds. *uni,* Unipolar recording; *A,* atrial electrogram; *H,* His electrogram.

In scar-based VT (e.g., after MI, cardiomyopathies), finding a protected region of diastolic activation used as a critical part of the reentrant circuit is desirable because ablation at this site has a good chance of eliminating the tachycardia (**Fig. 36.16**). As a result of the extensive derangement in electrophysiology caused by the previous damage (e.g., infarct, myopathy), many areas of the ventricle may have diastolic activation but may not be relevant to perpetuation of the VT. These "bystander sites" make activation mapping more difficult. Pacing techniques such as entrainment can be used to test whether a site is actually part of a circuit or is a bystander. *Entrainment* involves pacing for several complexes during a tachycardia at a rate slightly faster than the VT rate; after pacing is stopped and the same tachycardia resumes, the timing of the first complex relative to the last paced beat is an indicator of how close the pacing site is to a part of the VT circuit (**Fig. 36.17**). During entrainment, part of the ventricle is activated by the paced wavefront and part by the VT wavefront being forced to exit earlier than it normally would, thereby resulting in a fusion complex on the ECG. Pacing from within a critical portion of the circuit

itself produces an exact QRS match with the VT; fusion occurs only within the circuit and is “concealed” (not evident on the surface ECG). Sites with a low-amplitude, isolated, mid-diastolic potential that cannot be dissociated from the tachycardia by pacing perturbations, at which entrainment with concealed fusion can be demonstrated, are highly likely to be successful ablation sites.

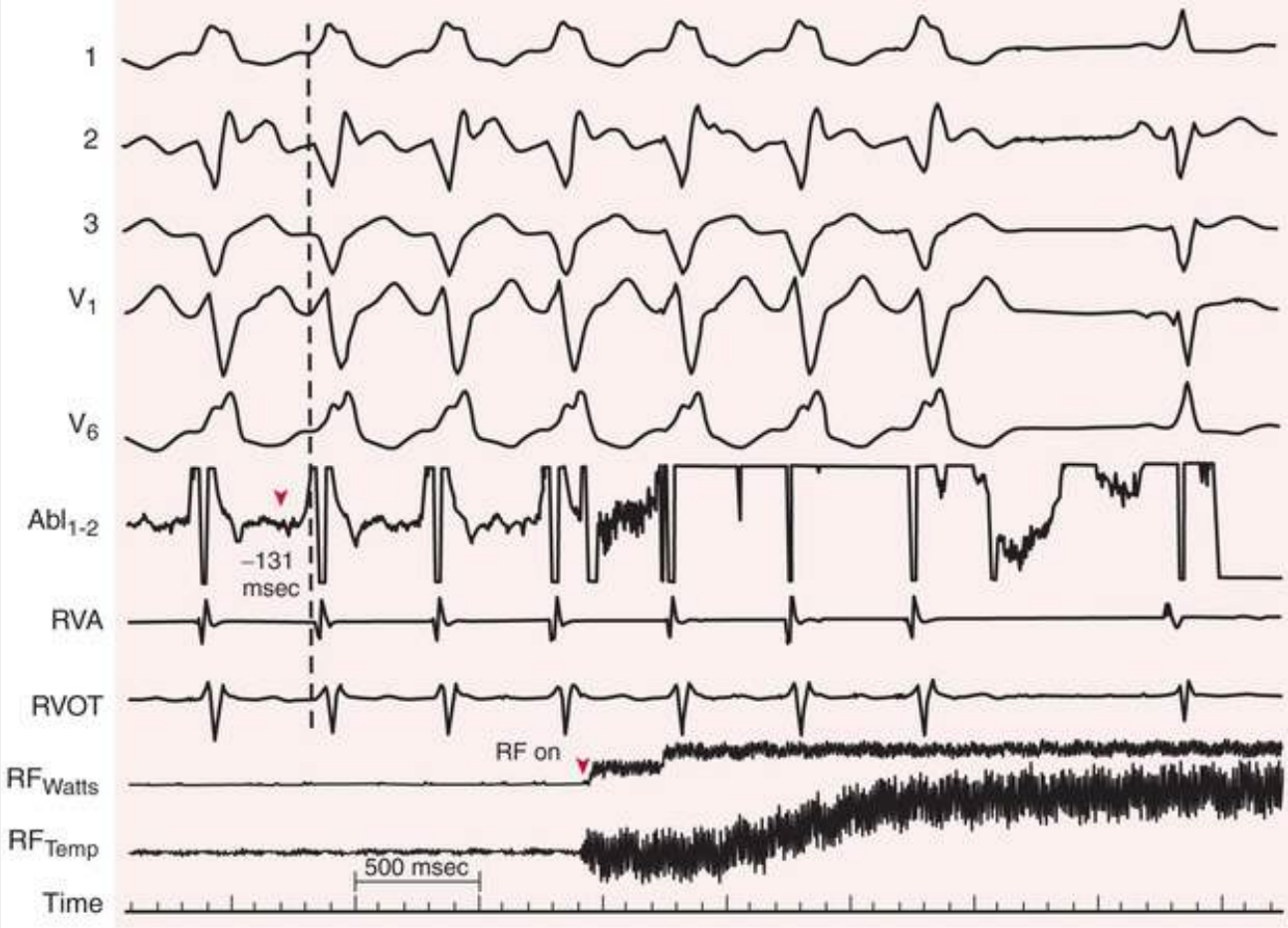

FIGURE 36.16 Radiofrequency ablation of postinfarction ventricular tachycardia. The electrogram in the ablation recording (Abl_{1-2}, *arrowhead*) precedes onset of the QRS (*dashed line*) by 131 milliseconds. Ablation here (RF on) results in slight deceleration of VT before termination in 1.3 seconds. Temperature monitored from the catheter tip had just peaked (approximately 70°C) at the time that VT terminated. Recording was done as in previous figures.

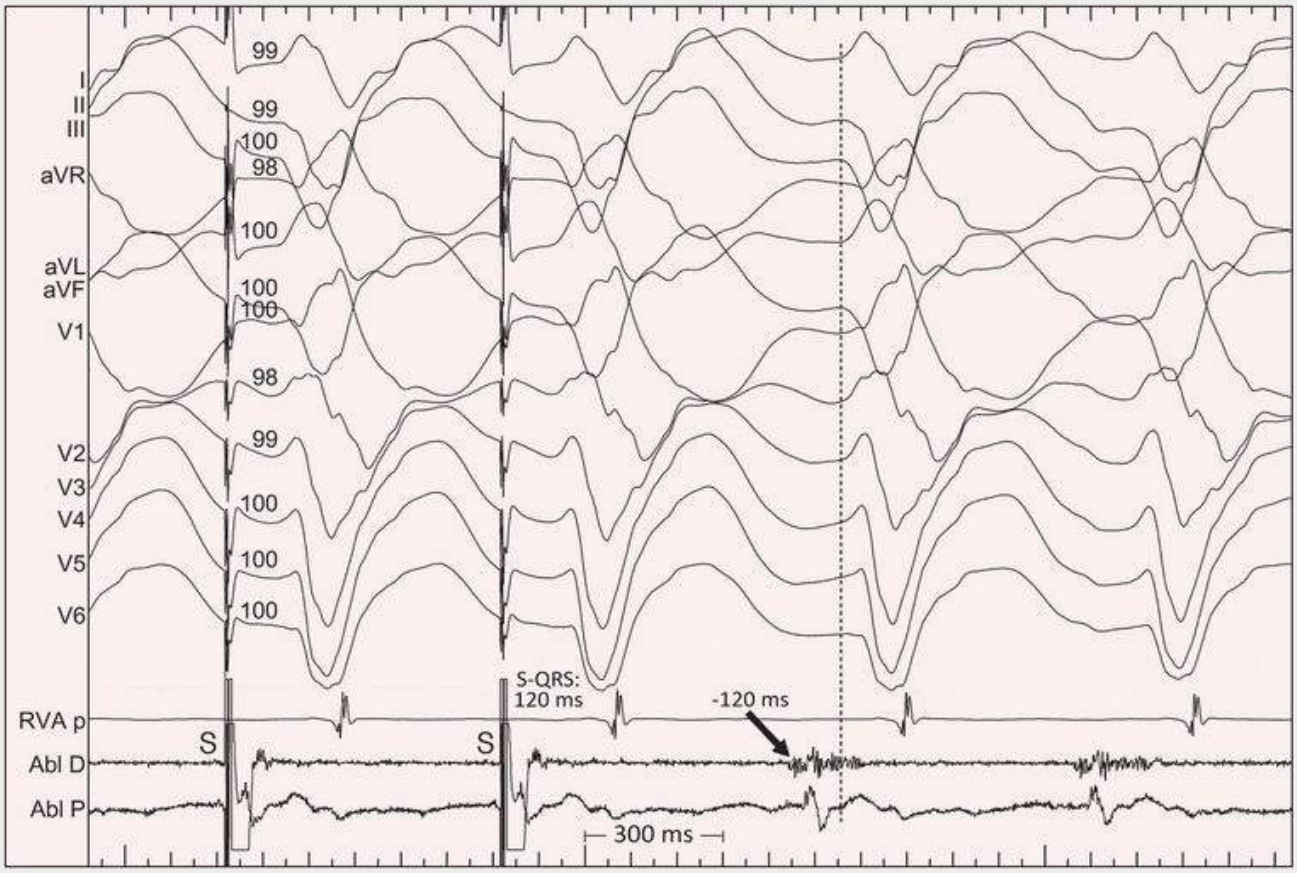

FIGURE 36.17 "Concealed" entrainment of postinfarction ventricular tachycardia. The two complexes on the *left* are pacing during VT, with a stimulus (*S*)-QRS interval 120 milliseconds; after pacing ends, VT resumes. The electrogram (*arrow*) in Abl D (distal electrode pair of the ablation catheter) is 120 milliseconds before QRS onset (*dotted line*). The paced and VT QRS complexes are almost identical (numbers above paced complexes indicate algorithmic "match" assessed by recording system). Ablation at this site quickly terminated VT. *RVA p,* Right ventricular recording; *Abl P,* recording from proximal electrodes on ablation catheter.

In a significant proportion of patients with VT and structural heart disease, activation mapping and entrainment cannot be performed because of poor hemodynamic tolerance of the arrhythmia or inability to initiate sustained tachycardia during an EPS. In these situations, additional methods can be used that are categorized as *substrate mapping*, in which areas of low electrical voltage or from which very delayed potentials are recorded during sinus rhythm, or at which pacing closely replicates a known VT 12-lead ECG morphology (pace mapping) are targeted for ablation without needing any mapping during VT (**Fig. 36.18**). These methods, usually requiring very extensive ablation in diseased areas, have yielded very good results in many cases. In other patients, hemodynamic support in the form of catecholamine infusion, intra-aortic balloon counterpulsation, or a percutaneous temporary ventricular assist device or extracorporeal membrane oxygenation has been used to facilitate mapping during VT.[29]

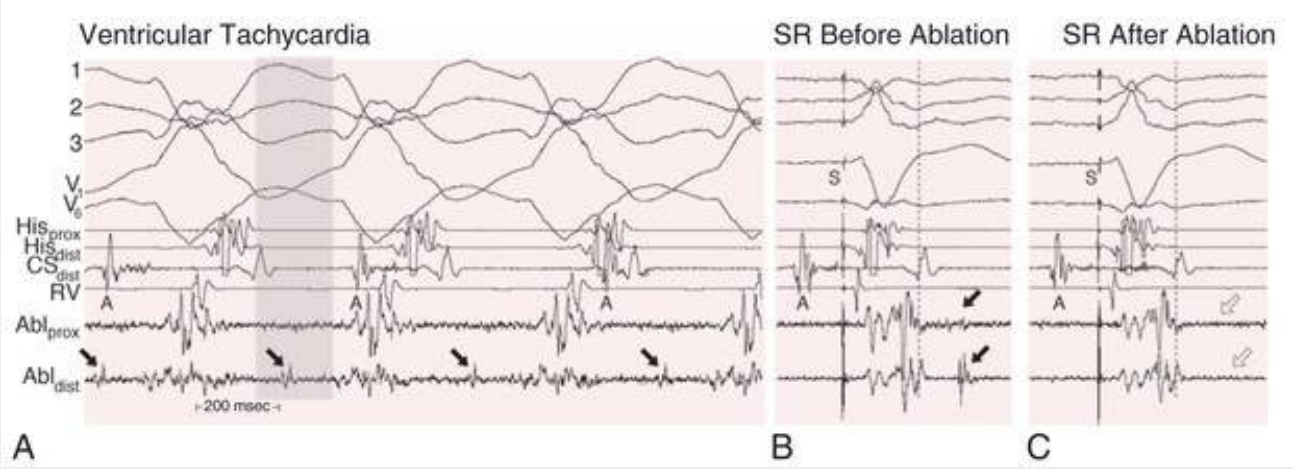

FIGURE 36.18 Mid-diastolic potentials during ventricular tachycardia correlating with late potentials in sinus rhythm (*SR*). In **A,** VT is shown; diastole (from the end of one QRS complex to the beginning of the next) is shaded in *gray*. In the Abl_{dist} recording, a small, sharp signal is seen in mid-diastole that corresponds to a protected corridor of propagation. **B,** After termination of VT with pacing, recording at the same location shows a delayed ("late") potential in SR with tracked ventricular pacing (*black arrows*; the *dashed line* denotes the end of the QRS complex). **C,** Ablation here eliminated the late potential (*white arrows*), as well as inducible VT. *A,* Atrial recording; *S,* stimulus artifact.

In patients without structural heart disease, only a single VT is usually present, and catheter ablation of that VT is most often curative. In patients with extensive structural heart disease, multiple VTs are usually present. Most of these patients already have, or soon will have, an ICD; ablation can be used to decrease the frequency of ICD therapies but is generally not intended to cure the patient of all ventricular arrhythmias. Catheter ablation of a single VT in such patients may be only palliative and may not eliminate the need for further AAD or device therapy, but can improve quality of life by decreasing ICD shocks. The genesis of multiple tachycardia morphologies is not clear, although in some cases they are merely different manifestations of one circuit (e.g., different directions of wavefront propagation or exit to the ventricle as a whole), and ablation of one may prevent recurrence of others. The presence of multiple VT morphologies contributes to the difficulties in mapping and ablation of VT in these patients, because pacing techniques used to validate recordings at potential sites of ablation may result in a change in morphology to another VT that may not arise in the same region.

After ablation of VT, ventricular stimulation is repeated to assess efficacy. In some cases, rapid polymorphic VT or VF is initiated. The clinical significance of these arrhythmias is unclear, but some evidence has suggested that they have a low likelihood of spontaneous occurrence during follow-up.

As noted earlier, most cases of polymorphic VT and VF are not currently amenable to standard ablation methods because of hemodynamic instability and beat-to-beat changes in activation sequence. However, some cases appear to have a focal source (similar to the focal sources of AF), and if the focus can be identified and ablated, further arrhythmia episodes can be prevented. In such cases, repeated episodes of arrhythmia have constant electrocardiographic features of the initiating beat or beats, thus suggesting a consistent source, which may be in either ventricle. The electrogram at sites of successful ablation often has very sharp presystolic potentials reminiscent of Purkinje potentials, with a 50- to 100-millisecond delay until onset of the QRS (**Fig. 36.19**).[30] In some cases of VF, "rotors" (sites of rapid circulation within a small region) have been reported, ablation of which has prevented recurrences (similar to the case with AF). This work is promising but preliminary.

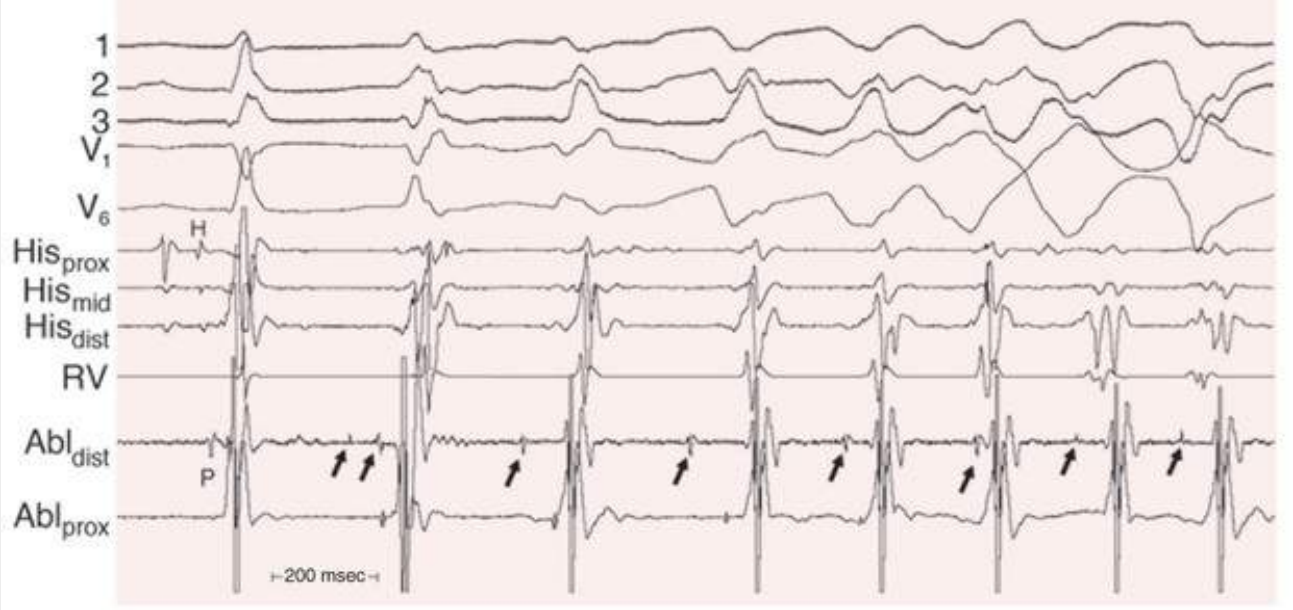

FIGURE 36.19 "Focal ventricular fibrillation." Recordings are shown from a patient with multiple episodes of VF in a day. A sinus rhythm complex, during which a Purkinje potential (*P*) is recorded from the ablation (*Abl*) electrode, is followed by a premature complex from this site that is preceded by sharp Purkinje spikes (*arrows*) that continue to precede subsequent complexes of polymorphic VT that degenerated to VF. Ablation at this site eliminated recurrent episodes of VF.

Indications

Patients considered for RF catheter ablation of VT in the absence of structural heart disease are those with symptomatic, sustained monomorphic VT when the tachycardia is drug resistant, when the patient is drug intolerant, or when the patient does not desire long-term drug therapy. Patients with structural heart disease who are candidates for ablation include those with bundle branch reentrant VT and those with sustained monomorphic VT and an ICD who are receiving multiple shocks not manageable by reprogramming or concomitant drug therapy. In some patients (usually without structural heart disease, but also in patients with diseased ventricles), nonsustained VT or even severely symptomatic PVCs warrant RF catheter ablation. In some of these patients, in whom the ventricular ectopy occurs frequently, significant left ventricular systolic dysfunction has occurred (presumably similar to tachycardia-related cardiomyopathy). After successful ablation, ventricular function may improve significantly or even normalize.

Results

In patients with structurally normal hearts, the success rate of VT or PVC ablation is approximately 85%.[31] In patients with postinfarction VT, more than 70% no longer have recurrences of VT after the ablation procedure despite inducibility of rapid VT or VF; only approximately 30% of patients will have no inducible ventricular arrhythmia of any type and no spontaneous recurrences. As noted earlier, most of these patients already have, or will have, an ICD as backup. Significant complications occur in up to 3%, including vascular damage, heart block, worsening of heart failure, cardiac tamponade, stroke, and valve damage. Death is rare but can occur in patients with severe CAD and/or systolic dysfunction.

New Mapping and Ablation Technologies

Multielectrode Mapping Systems.

Some of the limitations of ablation are related to inadequate mapping. These problems include having only isolated premature complexes during the EPS instead of sustained tachycardias (in idiopathic AT and VT), nonsustained episodes of VT, poor hemodynamic tolerance of VT, and multiple VT morphologies. Standard mapping techniques sample single sites sequentially and are poorly suited to these situations. New mapping systems are available that enable sampling of many sites simultaneously and incorporate sophisticated computer algorithms for analysis and display of global maps. These mapping systems use various technologies ranging from multiple electrodes situated on each of several splines of a basket catheter (**see Fig. 34.16**), to the use of low-intensity electrical or magnetic fields to localize the tip of the catheter in the heart and record and plot activation times on a contour map of the chamber, to the use of complex mathematics to compute "virtual" electrograms recorded from a mesh electrode situated in the middle of a chamber cavity or on the body surface. Some of these systems are capable of generating activation maps of an entire chamber by using only one cardiac complex, an obvious advantage in patients with only rare premature complexes, nonsustained arrhythmias, or poor hemodynamic tolerance of sustained arrhythmias.

Epicardial Catheter Mapping.

Although most VTs can be ablated from the endocardium, occasional cases are resistant to this therapy. In many of these cases, epicardial ablation may be successful. It is often needed in VT attributable to cardiomyopathy but less frequently in postinfarction patients and those without structural heart disease.

For gaining access to the pericardial space for epicardial mapping and ablation, a long spinal anesthesia needle is introduced from a subxiphoid approach under fluoroscopic guidance. As the pericardium is approached, a small amount of radiocontrast agent is injected. If the tip of the needle is still outside the pericardium, the dye stays where it is injected; when the pericardial space has been entered, the dye disperses and outlines the heart. A guidewire is introduced through the needle and a standard vascular introducer sheath exchanged over the wire. The pericardial space is then accessible for a mapping/ablation catheter, and standard mapping techniques can then be applied. When a site is selected for possible ablation, coronary arteriography is usually warranted to avoid delivery of RF energy near a coronary artery. This is less important in cases of postinfarction VT because the VT substrate is typically in a region of previous transmural infarction. For left ventricular sites, high-output pacing should be performed to assess proximity to the left phrenic nerve; if captured, another ablation site may be sought at which phrenic capture is absent, or a balloon catheter can be placed in the pericardial space (or air or fluid instilled) to physically displace and thus protect the nerve from damage during ablation. Epicardial mapping can be used for patients who have previously undergone cardiac surgery, although adhesions may obliterate portions of the pericardial space; on occasion, a small subxiphoid incision is needed for better access and visualization of the space. The most frequent complication of epicardial mapping is pericarditis related to the ablation; cardiac tamponade is rare.

Chemical Ablation.

Chemical ablation of an area of myocardium can be used for treatment of VT refractory to drug and standard catheter ablation. Using this specialized technique, an angioplasty catheter is maneuvered into an arterial (or venous) branch in the region of the VT (determined by mapping). After verifying the correct vessel by injecting iced saline into it and observing transient slowing or termination of VT, the angioplasty balloon is inflated (to prevent spillage of alcohol) and 100% ethanol is injected into the vessel. This generally terminates VT and kills the cells responsible for its continuation. Recurrences of tachycardia several days after apparently successful ablation are possible. Excessive myocardial

necrosis is the major complication, and alcohol ablation should be considered only when other ablative approaches fail or cannot be done.

Several other mapping/imaging techniques have been developed recently, including integration of a previously obtained computed tomography or magnetic resonance study into computerized mapping systems and use of intracardiac ultrasound to construct a facsimile of the intracardiac anatomy in any chamber during ablation procedures, to guide placement of anatomic ablation and reduce fluoroscopic exposure. Other techniques include use of algorithms to select complex fractionated atrial electrograms for ablation in patients with AF and algorithms to assess the fidelity of pace maps with native tachycardia complexes. Cryoablation, high-frequency focused ultrasound, and delivery of RF energy between two catheters on opposite sides of a ventricular wall, or through a needle electrode inserted into myocardium, have had some success in select patients.

Surgical Therapy for Tachyarrhythmias

The objectives of a surgical approach to treatment of a tachycardia are to excise, isolate, or interrupt tissue in the heart critical for initiation, maintenance, or propagation of the tachycardia while preserving or even improving myocardial function. In addition to a direct surgical approach to the arrhythmia, indirect approaches such as aneurysmectomy, coronary artery bypass grafting, and relief of valvular regurgitation or stenosis can be useful in select patients by improving cardiac hemodynamics and myocardial blood supply. *Cardiac sympathectomy* (stellate ganglionectomy) alters adrenergic influences on the heart and has been effective in some patients, particularly those who have recurrent VT with long-QT syndrome despite beta blockade, and catecholaminergic polymorphic VT.

Supraventricular Tachycardias

Surgical procedures exist for patients (adults and children) with AT, atrial flutter and fibrillation, AV node reentry, and AV reentry (**Fig. 36.20**). RF catheter ablation adequately treats most of these patients and thus has replaced direct surgical intervention, except for the occasional patient in whom RF catheter ablation fails or who is undergoing concomitant cardiovascular surgery. In some cases, a prior attempt at RF catheter ablation complicates surgery by obliterating the normal tissue planes that exist in the AV groove of the heart or by rendering tissues friable. On occasion, patients with ATs have multiple foci that require surgical intervention. Several surgical procedures have been developed to treat AF and are reviewed in **Chapter 38**.

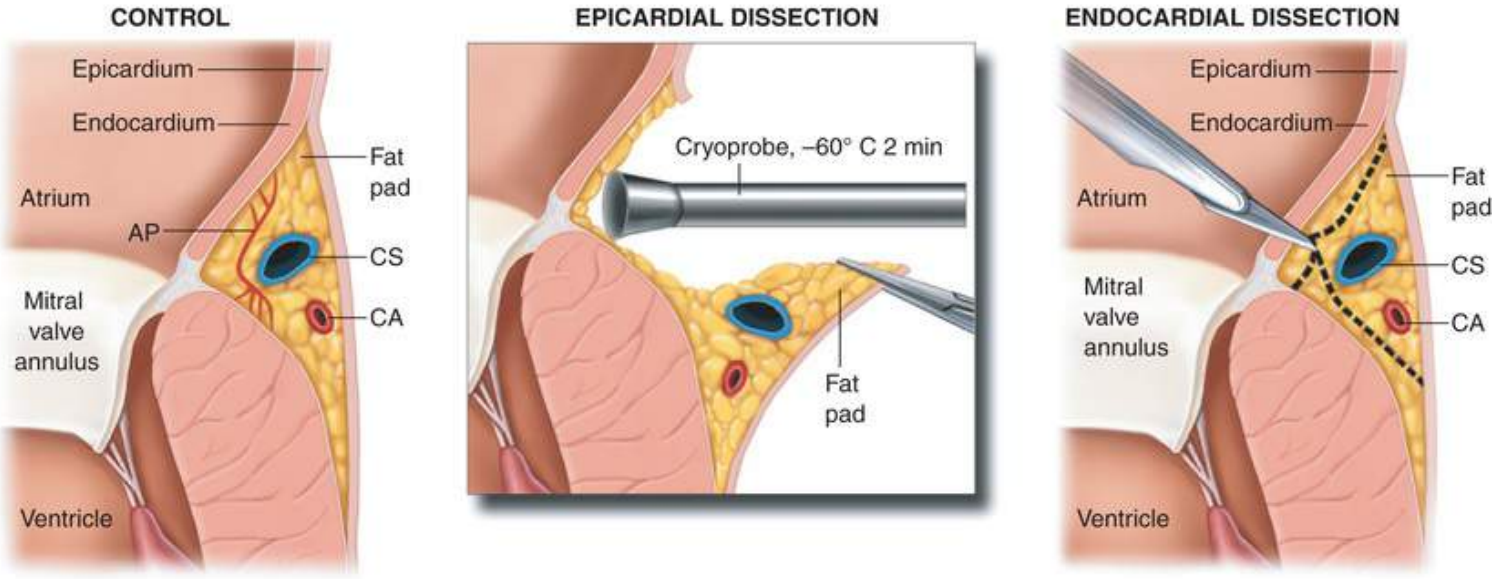

FIGURE 36.20 Schematic diagram showing the two approaches for surgical interruption of an accessory pathway. **Left,** Left AV groove and its vascular contents the coronary sinus (*CS*) and circumflex coronary artery (*CA*). Multiple accessory pathways (*AP*) course through the fat pad. **Middle,** Approach for epicardial dissection. **Right,** Endocardial dissection. Both approaches clear out the fat pad and interrupt any accessory pathways. (From Zipes DP. Cardiac electrophysiology: promises and contributions. J Am Coll Cardiol 1989;13:1329. Reprinted by permission of the American College of Cardiology.)

Ventricular Tachycardia

In contrast to patients with supraventricular arrhythmias, candidates for surgical therapy for ventricular arrhythmias often have severe left ventricular dysfunction, generally the result of CAD. The cause of the underlying heart disease influences the type of surgery performed. Candidates are patients with drug-resistant, symptomatic, recurrent ventricular tachyarrhythmias who ideally have a segmental wall motion abnormality (scar or aneurysm) with preserved residual left ventricular function, have not benefited from previous attempts at catheter ablation, or are not candidates for catheter ablation because of hemodynamic instability during VT or the presence of left ventricular thrombi (precluding endocardial catheter ablation).

Idiopathic VT/PVCs and Nonischemic Cardiomyopathy

Patients with VT or PVCs in the absence of structural heart disease or with nonischemic cardiomyopathy who have undergone unsuccessful drug and catheter ablation therapy for their arrhythmias are candidates for surgical therapy.

The procedure is usually performed through a limited thoracotomy, exposing only the area of the ventricles believed responsible for the arrhythmia. In idiopathic VT/PVC cases, this is often at the basal aspect of the anterior left ventricle, an area where catheter ablation is difficult because of thick epicardial fat and proximity to major coronary arteries. After exposing the area of the ventricular epicardial surface of interest, mapping is done to confirm the source of the arrhythmia, after which cryoablation is usually performed. This typically results in cessation of the arrhythmia. Extensive ablation is often needed in patients with nonischemic cardiomyopathy, in whom epicardial and intramural

scarring in the basal left and right ventricles is a common substrate for ventricular arrhythmias.

Ischemic Heart Disease

In almost all patients who have VT associated with ischemic heart disease, the arrhythmia, regardless of its configuration on the surface ECG, arises in the left ventricle or on the left ventricular side of the interventricular septum. The electrocardiographic contour of the VT can change from a right bundle branch block to a left bundle branch block pattern without a change in the site of earliest diastolic activation, thus suggesting that the location of the circuit within the left ventricle remains the same, often near the septum, but that its exit pathway is altered.

Indirect surgical approaches, including cardiothoracic sympathectomy, coronary artery revascularization, and ventricular aneurysm or infarct resection with or without coronary artery bypass grafting, have been successful in no more than 20% to 30% of VT cases. Coronary artery bypass grafting as a primary therapeutic approach has generally been successful only in patients who experience rapid VT because of severe ischemia, as well as in patients with ischemia-related VF, but it can sometimes be useful in patients with coronary disease resuscitated from sudden death who have no inducible arrhythmias at EPS. These patients generally show a clear relationship between episodes of ventricular arrhythmia and immediately antecedent severe ischemia and have no evidence of infarction or minimal wall motion abnormalities but have preserved overall left ventricular function. Patients with sustained monomorphic VT or only polymorphic VT rarely have their arrhythmias affected by coronary bypass surgery, although it can reduce the frequency of the arrhythmic episodes in some patients and prevent new ischemic events.

Surgical Techniques.

In general, two types of direct surgical procedures are used, resection and ablation (**Fig. 36.21**). The first direct surgical approach to VT was encircling endocardial ventriculotomy, which entails performing a transmural ventriculotomy to isolate areas of endocardial fibrosis that were recognized visually; this procedure is rarely used now. Another procedure, subendocardial resection, is based on data indicating that arrhythmias after MI arise mostly at the subendocardial borders between normal and infarcted tissue. Subendocardial resection involves peeling off a 1- to 3-mm-thick layer of endocardium, often near the rim of an aneurysm, that has been demonstrated by mapping procedures to contain sites of mid-diastolic activation recorded during VT. Tachycardias arising from near the base of the papillary muscles are treated with a cryoprobe cooled to −70°C. Cryoablation can also be used to isolate areas of the ventricle that cannot be resected and is often combined with resection. Lasers have also been used with good success, but the equipment is expensive and cumbersome.

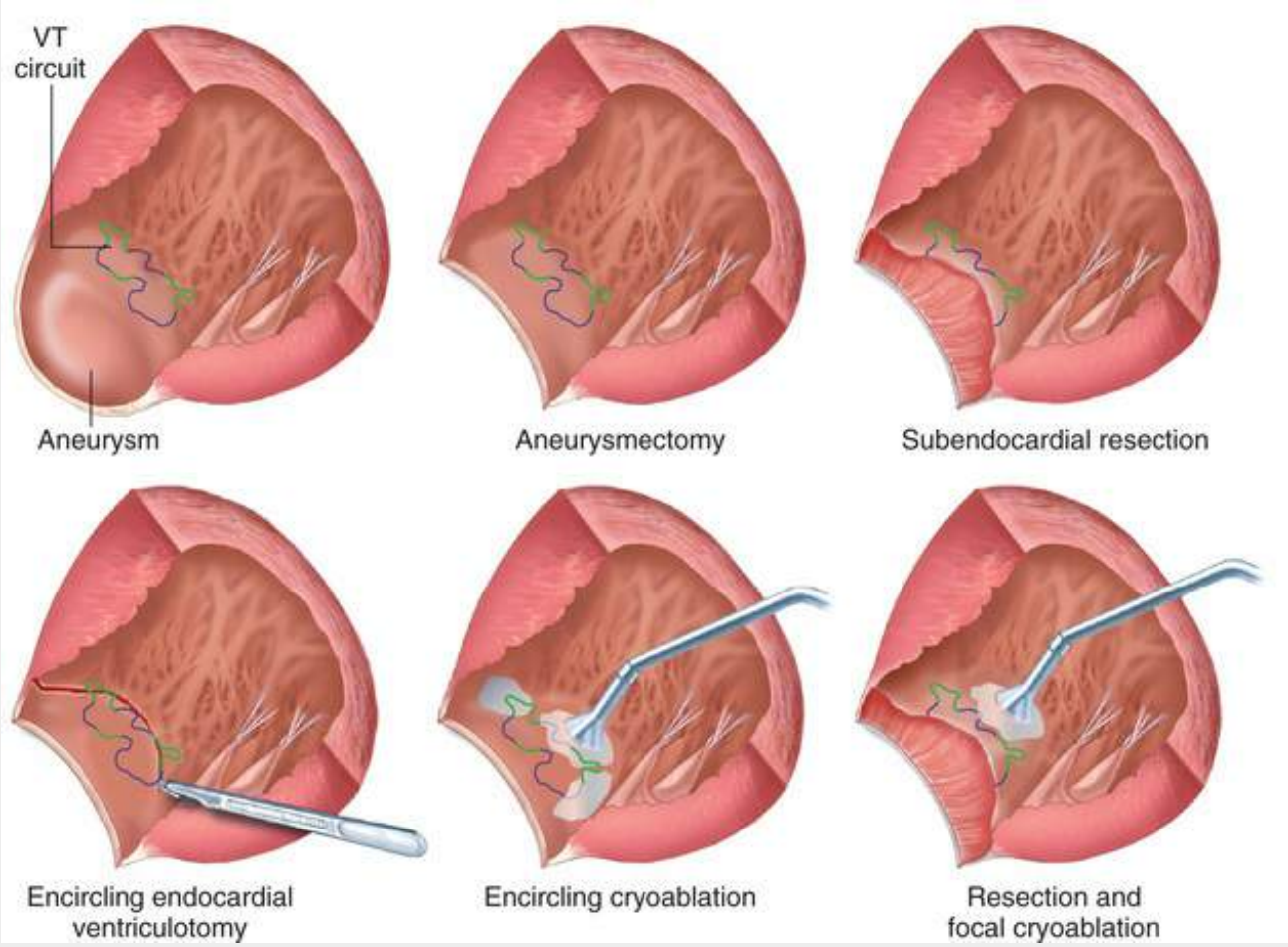

FIGURE 36.21 Schematic diagram showing surgical procedures for the treatment of postinfarction ventricular tachycardia with a left ventricular aneurysm. A damaged left ventricle is depicted as opened along the lateral wall and showing the septum and papillary muscles. The tachycardia circuit **(upper left)** takes a meandering course near the point where the aneurysm meets normal myocardium and at times is superficial (*purple lines*) and at other times is coursing deeper (*green lines*). Simple aneurysmectomy that leaves a portion of the aneurysm for suturing often misses the circuit and thus does not cure the arrhythmia. By subendocardial resection, a layer of endocardium and subjacent tissue is removed, including at least some of the tachycardia circuit. Such resection results in elimination of the tachycardia. Encircling endocardial ventriculotomy attempts to isolate the circuit electrically without removal of tissue, but it probably actually works by incising portions of the circuit. Cryoablation can be used to encircle the infarct zone, alone or in combination with resection of damaged tissue too deep in the wall to be resected safely.

Results

For ventricular tachyarrhythmias, operative mortality ranges from 5% to 10%. Success, defined as the absence of recurrence of spontaneous ventricular arrhythmias, is achieved in 59% to 98% of patients. In experienced centers, operative mortality can be as low as 5% in stable patients undergoing elective procedures, with 85% to 95% of survivors being free of inducible or spontaneous ventricular tachyarrhythmias. Long-term recurrence rates range from 2% to 15% and correlate with results of the patient's postoperative electrophysiologic stimulation study. Operative survival is strongly influenced by the degree of left ventricular dysfunction.

Electrophysiologic Studies

Preoperative Electrophysiologic Study.

In patients for whom direct surgical therapy for VT is planned, a preoperative EPS is usually warranted. This study involves initiation of the VT and electrophysiologic mapping to localize the area to be resected, as is done with catheter ablation. Preoperative catheter mapping is contraindicated in patients with known left ventricular thrombi that might be dislodged by the mapping catheter.

Intraoperative Ventricular Mapping.
Electrophysiologic mapping is also performed at surgery, with the surgeon using a handheld probe or an electrode array coupled with computer techniques that instantaneously provide an overall activation map, cycle by cycle. The sequence of activation during VT can be plotted and the area of earliest activation determined. Resection or cryoablation of tissue from which these recordings are made usually cures the VT, thus indicating that they represent a critical portion of the reentrant circuit. When the earliest recordable endocardial electrical activity occurs less than 30 milliseconds before onset of the QRS complex, the critical portions of the circuit may be in the interventricular septum or near the epicardium of the free wall. In some patients, intramural mapping using a plunge needle electrode can be useful. Most centers have used a strategy of "sequential" subendocardial resection in which VT is initiated, mapped, and ablated (resected or cryoablated) while the heart is warm and beating, and stimulation is repeated immediately. If VT can still be initiated, mapping and resection are also repeated until VT can no longer be initiated. Reentry around an inferior scar, with a critical diastolic pathway confined to an isthmus of ventricular muscle between the scar and mitral valve annulus, can be cured by cryoablation of this isthmus. Cure rates in this situation exceed 93%.

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37

Supraventricular Arrhythmias

Jeffrey E. Olgin, Douglas P. Zipes

Normal Sinus Rhythm

Impulse formation beginning in the sinus node at rates between 60 and 100 beats/min defines normal sinus rhythm. Faster heart rates at rest and during exercise occur in infants and children than in adults. The P wave is upright in electrocardiographic leads I, II, and aVF and negative in lead aVR, with a vector in the frontal plane of between 0 and +90 degrees. The P vector is directed anteriorly and slightly leftward in the horizontal plane and can therefore be negative in leads V_1 and V_2 but positive in V_3 to V_6. The PR interval exceeds 120 milliseconds and can vary slightly with the rate. A change in morphology of the P wave can occur if the pacemaker site (site of impulse origin) shifts. The rate of sinus rhythm varies significantly and depends on many factors, including age, sex, and physical activity.

The sinus rate responds readily to autonomic stimuli. Steady vagal (parasympathetic) stimulation decreases the spontaneous sinus rate and predominates over steady sympathetic stimulation, which increases the spontaneous sinus rate.

Rates less than 60 beats/min are considered to be bradycardia, and rates higher than 100 beats/min, tachycardia. As described in **Chapter 34**, the normal sequence of electrical activation of the heart is from the sinus node through the atria to the atrioventricular (AV) node and His-Purkinje system and to the ventricular myocardium. Specific tachyarrhythmias and bradyarrhythmias presented as disorders of this electrophysiologic hierarchy and their characteristics are summarized in **Table 37.1**.

TABLE 37.1

Characteristics of Arrhythmias*

TYPE OF ARRHYTHMIA	P WAVES			QRS COMPLEXES			VENTRICULAR RESPONSE TO CAROTID SINUS MASSAGE AND ADENOSINE	PHYSICAL EXAMINATION			ACU TREA
	Rate (beats/min)	Rhythm	Contour	Rate (beats/min)	Rhythm	Contour		Intensity of S_1	Splitting of S_2	A Waves	
Sinus rhythm	60-100	Regular†	Normal	60-100	Regular	Normal	Gradual slowing and return to former rate	Constant	Normal	Normal	None
Sinus bradycardia	<60	Regular	Normal	<60	Regular	Normal	Gradual slowing and return to former rate	Constant	Normal	Normal	None, sympto atropin
Sinus tachycardia	100-180	Regular	May be peaked	100-180	Regular	Normal	Gradual slowing‡ and return to former rate	Constant	Normal	Normal	None, sympto treat u disease
AV nodal reentry	150-250	Very regular except at onset and termination	Retrograde; difficult to see; lost in QRS complex	150-250	Very regular except at onset and termination	Normal	Abrupt slowing caused by termination of tachycardia or no effect	Constant	Normal	Constant cannon *a* waves	Vagal st adenosi NDCCI DC sho termina
Atrial flutter	250-350	Regular	Sawtooth	75-175	Generally regular in absence of drugs or disease	Normal	Abrupt slowing and return to former rate; flutter remains	Constant; variable if AV block changing	Normal	Flutter waves	DC sho NDCCI ibutilid amioda
Atrial fibrillation	400-600	Grossly irregular	Baseline undulation, no P waves	100-160	Grossly irregular	Normal	Slowing; gross irregularity remains	Variable	Normal	No *a* waves	NDCCI amioda ibutilid propaf flecaini shock
Atrial tachycardia	100-200	Regular (except at beginning, where there could be "warm up")	Abnormal, but could be similar to sinus P wave if origin near sinus node	100-200	Generally regular in absence of drugs or disease, but at faster rates could have some block (see below)	Normal	Abrupt slowing and return to normal rate; tachycardia remains; some may terminate with CSM or adenosine	Constant; variable if AV block changing	Normal	Normal	BB, ND amioda flecaini propaf
Atrial tachycardia with block	150-250	Regular; may be irregular	Abnormal	75-200	Generally regular in absence of drugs or disease	Normal	Abrupt slowing and return to normal rate; tachycardia remains	Constant; variable if AV block changing	Normal	More *a* waves than *c-v* waves	Stop di toxic; not tox possibl NDCBI (depen rate an of bloc amioda flecaini propaf
AV junctional rhythm	40-100§	Regular	Normal	40-60	Fairly regular	Normal	None; may be slight slowing	Variable‖	Normal	Intermittent cannon waves	None, sympto atropin
AV junctional tachycardia	100-200	Regular	Absent or retrograde	100-200	Regular	Normal	Abrupt termination	Constant	Normal	Constant cannon waves	NDCBI amioda
Reciprocating tachycardias using an accessory (WPW)	150-250	Very regular except at onset and	Retrograde; difficult to see;	150-250	Very regular except at onset and	Normal	Abrupt slowing caused by termination of tachycardia or no	Constant but decreased	Normal	Constant cannon waves	Vagal st adenosi NDCCI

pathway		termination	monitor the QRS complex		termination		effect				DC sho termina procair amioda
Ventricular tachycardia	60-100‖	Regular	Normal if dissociated or retrograde if associated (can be difficult to see)	110-250	Regular	Abnormal, >0.12 sec	None	Variable‖	Abnormal	Intermittent cannon waves‖	Lidocai procair amioda shock
Accelerated idioventricular rhythm	60-100‖	Regular	Normal	50-110	Fairly regular; may be irregular	Abnormal, >0.12 sec	None	Variable‖	Abnormal	Intermittent cannon waves‖	None, sympto lidocai atropin
Ventricular flutter	60-100‖	Regular	Normal; difficult to see	150-300	Regular	Sine wave	None	Soft or absent	Soft or absent	Cannon waves	DC sho
Ventricular fibrillation	60-100‖	Regular	Normal; difficult to see	400-600	Grossly irregular	Baseline undulations; no QRS	None	None	None	Cannon waves	DC sho
First-degree AV block	60-100¶	Regular	Normal	60-100	Regular	Normal	Gradual slowing caused by sinus	Constant, diminished	Normal	Normal	None
Type I second-degree AV block	60-100¶	Regular	Normal	30-100	Irregular**	Normal	Slowing caused by sinus slowing and an increase in AV block	Cyclic decrease, then increase after pause	Normal	Normal; increasing *a-c* interval; *a* waves without *c* waves	None, sympto atropin
Type II second-degree AV block	60-100¶	Regular	Normal	30-100	Irregular¶	Abnormal, >0.12 sec	Gradual slowing caused by sinus slowing	Constant	Abnormal	Normal; constant *a-c* interval; *a* waves	Pacem
Complete AV block	60-100‖	Regular	Normal	<40	Fairly regular	Abnormal, 0.12 sec	None	Variable¶	Abnormal	Intermittent cannon waves¶	Pacem
Right bundle branch block	60-100	Regular	Normal	60-100	Regular	Abnormal, 0.12 sec	Gradual slowing and return to former rate	Constant	Wide	Normal	None
Left bundle branch block	60-100	Regular	Normal	60-100	Regular	Abnormal, >0.12 sec	Gradual slowing and return to former rate	Constant	Paradoxical	Normal	None

*In an effort to summarize these arrhythmias in tabular form, generalizations have to be made. For example, the response to carotid sinus massage may be slightly different from what is listed. Acute therapy to terminate a tachycardia may be different from chronic therapy to prevent recurrence. Some of the exceptions are indicated in the footnotes; the reader is referred to text for a complete discussion.

†P waves initiated by sinus node discharge may not be precisely regular because of sinus arrhythmia.

‡Frequently, carotid sinus massage fails to slow a sinus tachycardia.

§Any independent atrial arrhythmia may exit or the atria may be captured retrogradely.

‖Constant if the atria are captured retrogradely.

¶Atrial rhythm and rate may vary, depending on whether sinus bradycardia, sinus tachycardia, or another abnormality is the atrial mechanism.

**Regular or constant if block is unchanging.

AA, Antiarrhythmic drug (procainamide, quinidine, propafenone, flecainide, sotalol, dofetilide, dronedarone, amiodarone); *BB,* beta blocker (e.g., propranolol, metoprolol); *CSM,* carotid sinus massage; *DC,* direct-current; *ICD,* implantable cardioverter-defibrillator; *NDCCB,* nondihydropyridine calcium channel blocker (e.g., diltiazem, verapamil); *PPM,* permanent pacemaker; *CRT,* cardiac resynchronization therapy.

Tachyarrhythmias

Tachyarrhythmias are broadly characterized as *supraventricular tachycardia* (SVT),[1] defined as a tachycardia in which the driving circuit or focus originates, at least in part, in tissue above the level of the ventricle (i.e., sinus node, atria, AV node, or His bundle). Atrial fibrillation is discussed in **Chapter 38**.

Ventricular tachycardia (VT) is defined as a tachycardia in which the driving circuit or focus originates solely in ventricular tissue (including valves and root of the great arteries) or Purkinje fibers (**see Chapter 39**). Because of differences in prognosis and management, distinction between SVT and VT is critical early in the acute management of a tachyarrhythmia.[2] In general, with the exception of the idiopathic form, VT often carries a much poorer prognosis, usually implies the presence of significant heart disease, results in more profound hemodynamic compromise, and therefore requires immediate attention and measures to revert to sinus rhythm. SVT is not usually lethal and often does not result in hemodynamic collapse; therefore more conservative measures can be applied initially to convert to sinus rhythm.[1,3]

Distinction between SVT and VT can generally be made on the basis of the electrocardiogram (ECG) obtained during tachycardia (**see Chapter 35**). It is important to obtain a 12-lead ECG during tachycardia if possible and to obtain 12-lead (or at least multilead) rhythm strips during any intervention aimed at termination of the tachycardia, because examining the termination (and initiation) can help identify the specific arrhythmia. If the QRS is narrow (duration <120 msec, often referred to as *narrow-complex tachycardias*), the ventricle is usually being activated through the normal His-Purkinje system, and thus the origin of the tachycardia is supraventricular[4] (**Fig. 37.1**). A wide QRS (duration >120 msec) during tachycardia suggests VT, although in some common scenarios, SVT can produce a wide QRS complex. Therefore a more descriptive term, *wide-complex tachycardia* (WCT), is often used when the precise arrhythmia mechanism cannot be determined. For example, SVT with a concurrent bundle branch block (BBB) or intraventricular conduction defect can produce WCTs despite a supraventricular origin, as can preexcited tachycardias (tachycardias in which the ventricle is activated in whole or in part over an accessory pathway). Therefore, although a narrow-complex tachycardia almost always makes the diagnosis of SVT, a WCT can be supraventricular or ventricular. Fusion or capture beats and AV dissociation are diagnostic of VT but are often not present or are difficult to detect. Criteria and algorithms have been developed to determine whether a WCT is more likely to be SVT or VT (**Table 37.2; see Chapter 39**). The general principles behind these algorithms rest on the assumption that the closer the QRS morphology is to a typical BBB pattern, the more likely it is an SVT and assumes that the septum is still rapidly activated in a WCT caused by SVT.

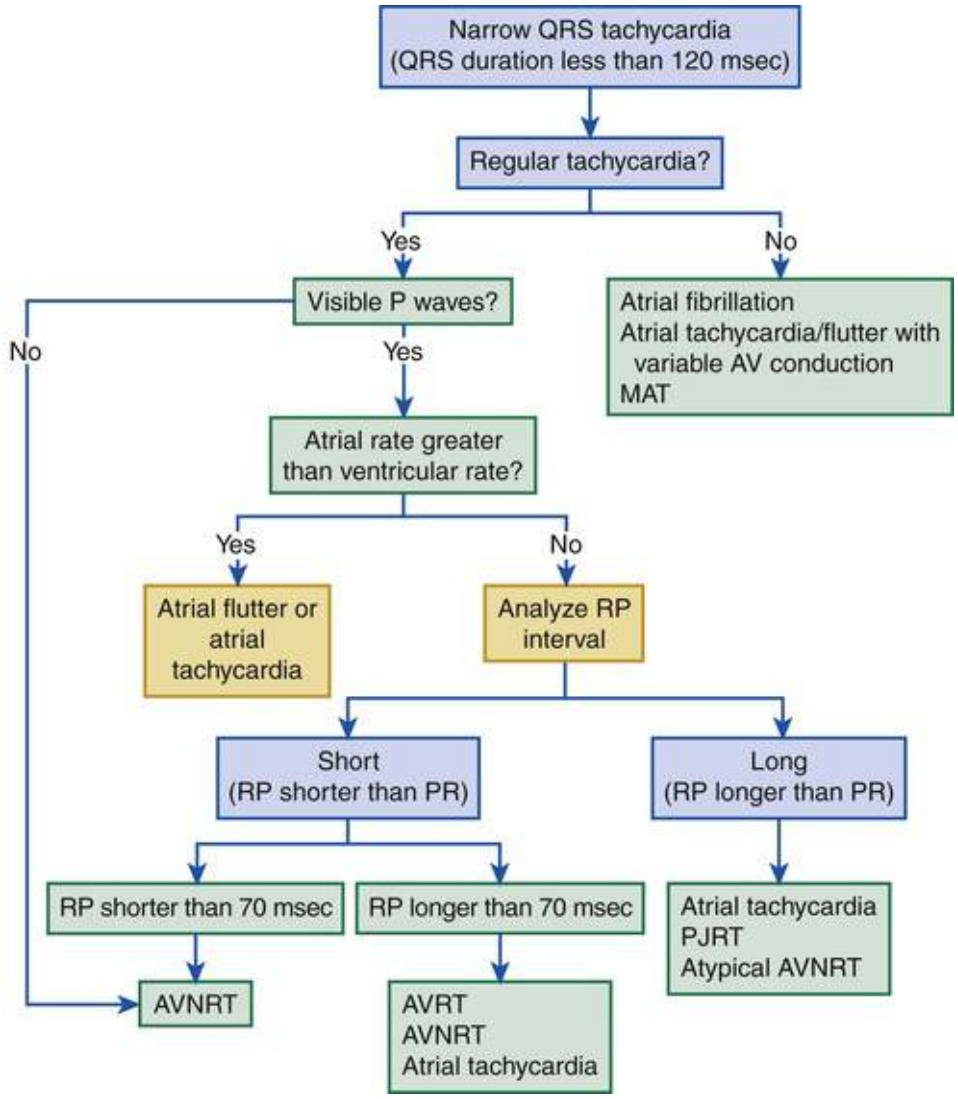


FIGURE 37.1 Algorithm for the diagnosis of a narrow-QRS tachycardia. *AVRT,* Atrioventricular reentrant tachycardia; *AVNRT,* atrioventricular nodal reentrant tachycardia; *MAT,* multifocal atrial tachycardia; *PJRT,* permanent form of AV junctional reciprocating tachycardia. (From Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, et al: ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines [Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias]. Circulation 2003;108:1871.)

TABLE 37.2

Major Features in Differential Diagnosis of Wide-QRS Beats Versus Tachycardia

SUPPORTS SVT	SUPPORTS VT
Slowing or termination by vagal tone Onset with premature P wave RP interval ≤100 msec P and QRS rate and rhythm linked to suggest that ventricular activation depends on atrial discharge, e.g., 2 : 1 AV block rSR′ V_1 Long-short cycle sequence	Fusion beats Capture beats AV dissociation P and QRS rate and rhythm linked to suggest that atrial activation depends on ventricular discharge, e.g., 2 : 1 VA block “Compensatory” pause Left axis deviation; QRS duration >140 msec Specific QRS contours (see text)

Supraventricular Tachycardias

Sinus Tachycardia

Electrocardiographic Recognition

During sinus tachycardia the sinus rate is 100 to 180 beats/min, although it can be higher with extreme exertion and in young individuals (**Fig. 37.2**). The maximum heart rate achieved during strenuous physical activity varies widely but decreases with age. Sinus tachycardia generally has a gradual onset and termination. The P-P interval can vary slightly from cycle to cycle, especially at slower rates, when the normal contour can develop a larger amplitude and become peaked. P waves appear before each QRS complex with a stable PR interval unless concomitant AV block ensues.

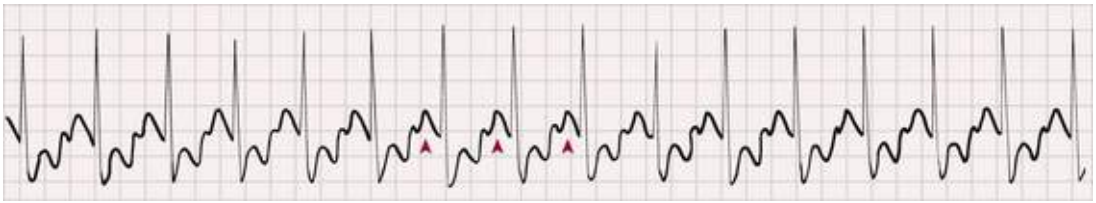


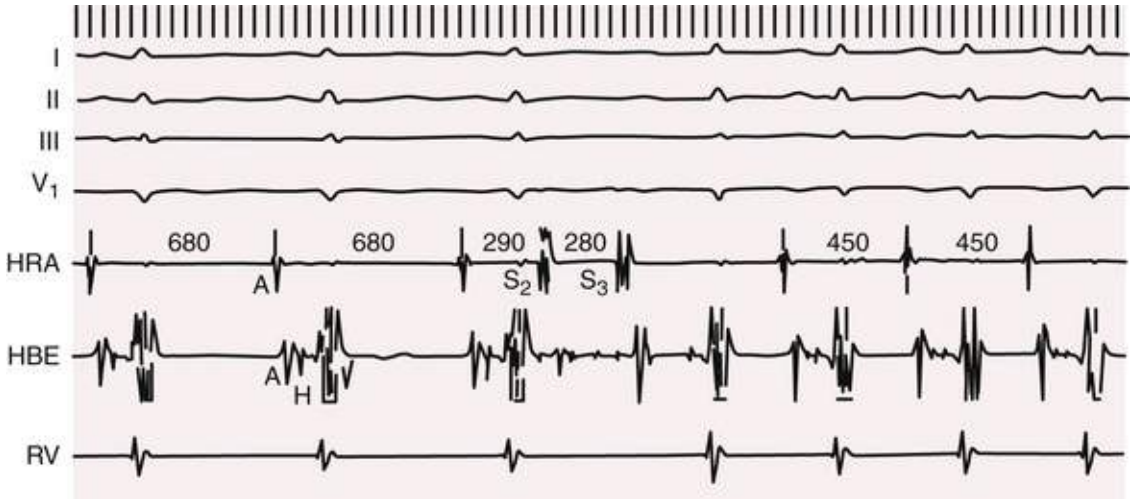
FIGURE 37.2 Sinus tachycardia (150 beats/min) in a patient during acute myocardial ischemia; note the ST-segment depression. P waves are indicated by *arrowheads*.

Accelerated phase 4 diastolic depolarization of sinus nodal cells (**see Chapter 34**) generally causes sinus tachycardia, usually from elevated adrenergic tone or withdrawal of parasympathetic tone. Carotid sinus massage and Valsalva or other vagal maneuvers gradually slow sinus tachycardia, which then accelerates to its previous rate on cessation of the enhanced vagal tone. More rapid sinus rates can fail to slow in response to a vagal maneuver, particularly those driven by high adrenergic tone.

Clinical Features

Sinus tachycardia is common in infancy and early childhood and is the normal reaction to various physiologic or pathophysiologic stresses, such as fever, hypotension, thyrotoxicosis, anemia, anxiety, exertion, hypovolemia, pulmonary emboli, myocardial ischemia, congestive heart failure, and shock. Atropine, catecholamines, and thyroid medications, as well as alcohol, nicotine, caffeine, and amphetamines or other stimulants, can produce sinus tachycardia. Persistent sinus tachycardia can be a manifestation of heart failure.

In patients with structural heart disease, sinus tachycardia can result in reduced cardiac output or angina or can precipitate another arrhythmia, in part related to the abbreviated ventricular filling time and compromised coronary blood flow. Sinus tachycardia can cause inappropriate defibrillator discharge in patients with an implantable cardioverter-defibrillator (ICD; **see Chapter 41**). *Chronic inappropriate sinus tachycardia* (also known as the syndrome of inappropriate sinus tachycardia) has been described in otherwise healthy persons, possibly secondary to increased automaticity of the sinus node or an automatic atrial focus near the sinus node.[5] The abnormality can result from a defect in sympathetic or vagal nerve control of sinoatrial (SA) automaticity or from an abnormality of the intrinsic heart rate. In *postural orthostatic tachycardia syndrome* (POTS), a related syndrome consisting of orthostatic hypotension and sinus tachycardia, the cause of the orthostatic decrease in blood pressure is not hypovolemia or drugs. Both syndromes can result from autonomic neuropathy, either peripheral, as in diabetic patients, or central, from spinal cord injury. Sinus node reentry (**eFig. 37.1**) is an atrial tachycardia originating from tissue near the sinus node and thus has a P wave morphology similar to sinus rhythm (see later, Focal Atrial Tachycardias).



EFIGURE 37.1 Sinus node reentry. After three spontaneous sinus-initiated beats, premature stimulation of the high right atrium (S_2, S_3) initiates a sustained tachycardia at a cycle length of 450 milliseconds that has the identical high-low atrial activation sequence characteristic of sinus node discharge. This is sinus node reentry. Leads I, II, III, and V_1 are scalar leads. *H,* His electrogram; *HBE,* His bundle electrogram; *HRA,* high right atrial electrogram; *RV,* right ventricular electrogram. Numbers are milliseconds.

Management

Management focuses on the cause of the sinus tachycardia. In the hospital setting the cause is usually obvious (e.g., hemorrhage, sepsis, agitation), whereas in the outpatient arena it may be more elusive. The most common reversible causes include hyperthyroidism, anemia, infection or inflammation, and hypovolemia. Diabetic neuropathy is also common but not reversible. Elimination of tobacco, alcohol, caffeine, or other stimulants, such as the sympathomimetic agents in nose drops and cold medications, may be helpful. Beta blockers and nondihydropyridine calcium channel blockers (verapamil and diltiazem), fluid replacement in a hypovolemic patient, or fever reduction in a febrile patient can help slow the sinus nodal discharge rate. Treatment of inappropriate sinus tachycardia requires beta blockers or calcium channel blockers, alone or in combination. In severe cases, sinus node radiofrequency (RF) or surgical ablation may be indicated; however, these approaches are usually only temporarily palliative (**see Chapter 36**). A specific blocker of the pacemaker current (I_f), ivabradine, has been useful in some patients with inappropriate or refractory sinus tachycardia.

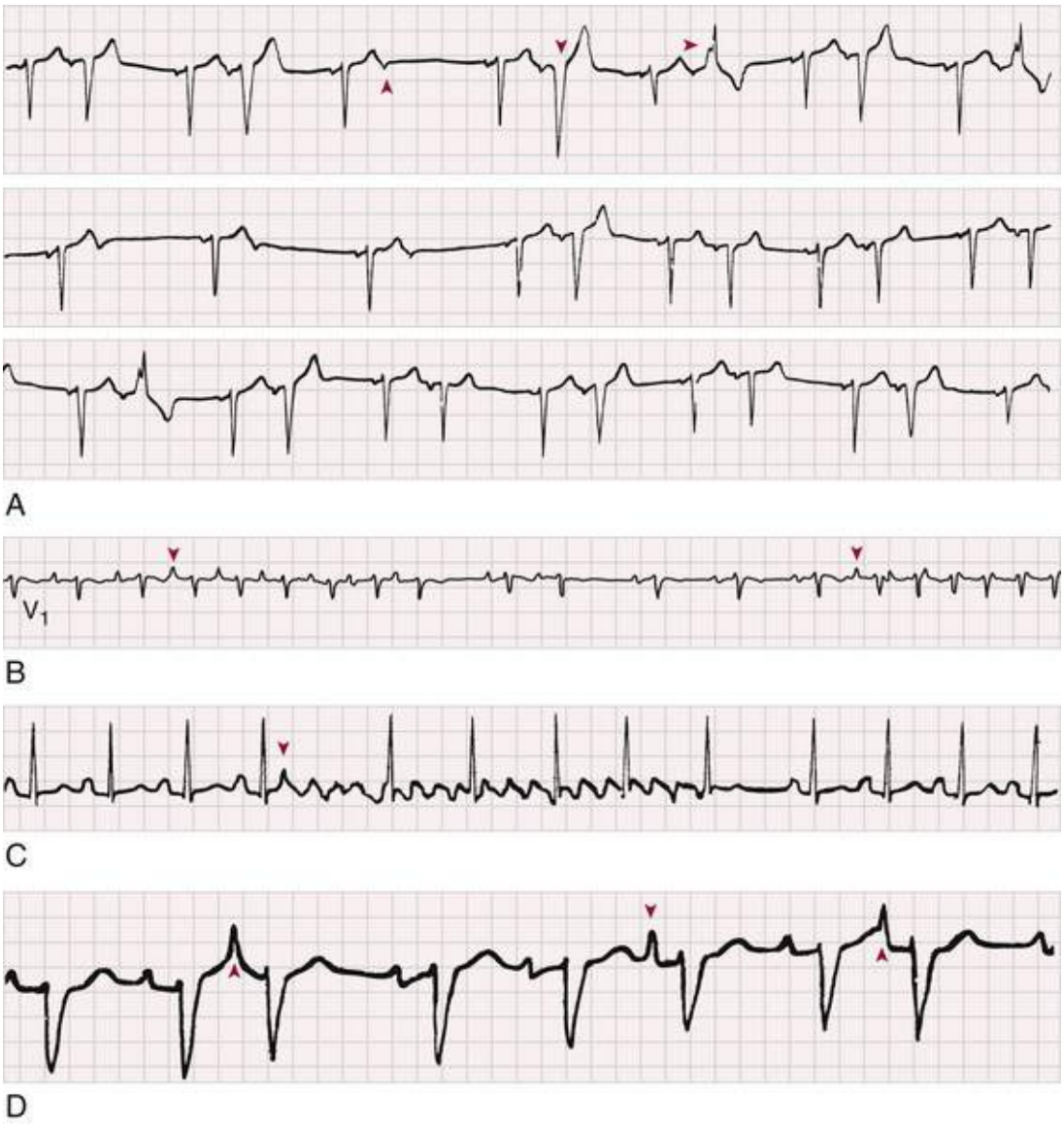
Premature Atrial Complexes

Premature complexes are among the most common causes of an irregular pulse and palpitations. They can originate from any area in the heart—most frequently from the ventricles, less often from the atria and the AV junctional area, and rarely from the sinus node. Premature complexes are common in normal hearts and increase in frequency with age.

Electrocardiographic Recognition

Premature atrial complexes (PACs) are diagnosed electrocardiographically (**Fig. 37.3**) by the presence of a premature P wave with a PR interval exceeding 120 milliseconds (except in Wolff-Parkinson-White [WPW] syndrome, when the PR interval is generally shorter than 120 msec). The contour of a premature P wave can resemble that of a normal sinus P wave, although it generally differs. Variations in the basic sinus rate can make the diagnosis of prematurity difficult, but differences in the contour of the P waves are

usually apparent and indicate a different focus of origin. PACs early in diastole may become blocked (nonconducted PAC; **Fig. 37.3A**) or conduct with a prolonged PR interval. The RP interval is usually inversely related to the PR interval; thus a long PR interval follows a short RP interval produced by an early PAC occurring close to the preceding QRS complex. PACs occurring early in the cardiac cycle can be difficult to discern because of superimposed T waves. Careful examination of tracings from several leads may be necessary before the PAC is recognized as a slight deformity of the T wave. Frequently, such PACs are blocked before reaching the ventricle and can be misinterpreted as a sinus pause or sinus exit block (**see Fig. 37.3A**).



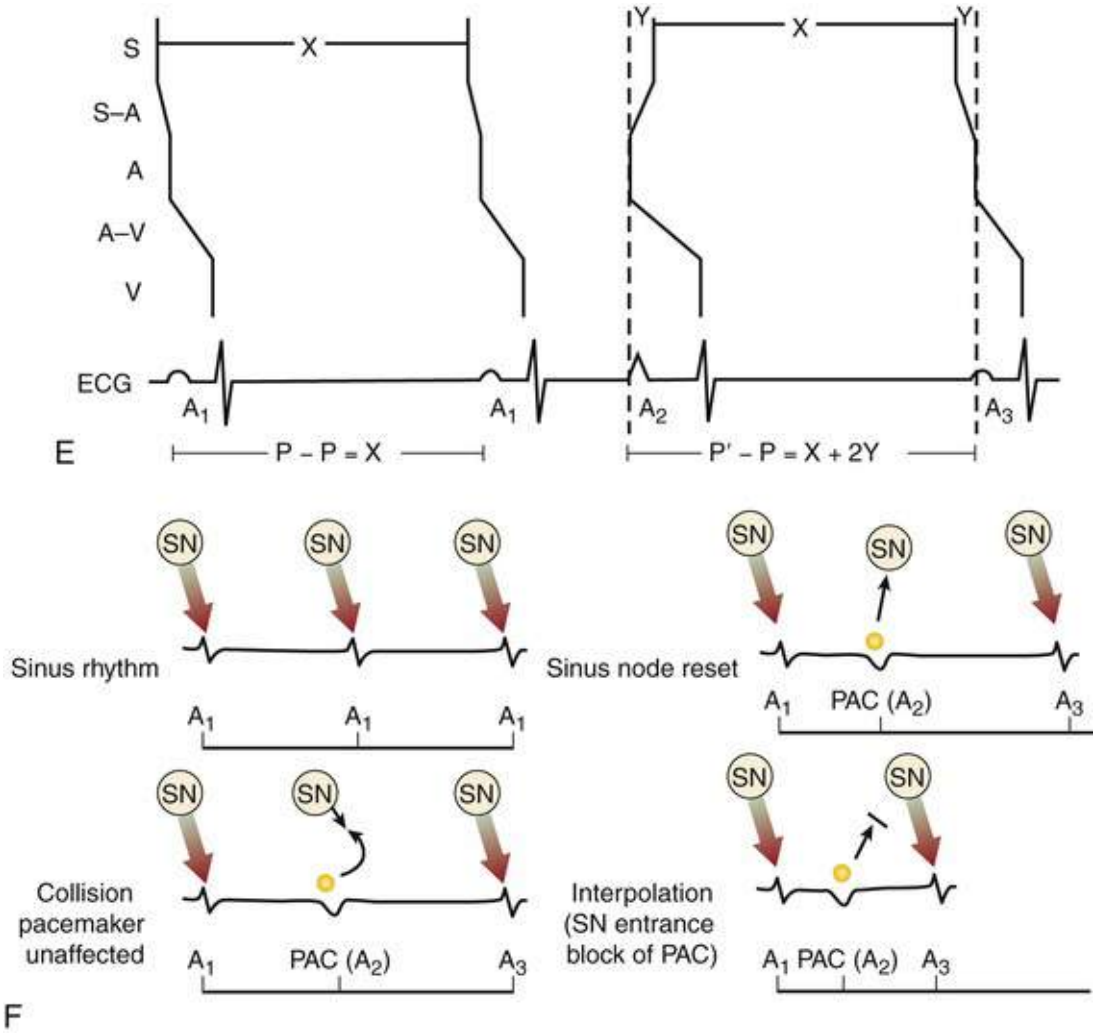


FIGURE 37.3 **A,** Premature atrial complexes (PACs) that block conduction entirely or conduct with a functional right or functional left bundle branch block. Depending on the preceding cycle length and coupling interval of the PAC, the PAC blocks conduction entirely in the AV node (*arrowhead* ↑) or conducts with a functional left bundle branch block (*arrowhead* ↓) or functional right bundle branch block (*arrowhead* →). **B,** A PAC on the left (*arrowhead*) initiates AV nodal reentry that is caused by reentry anterogradely and retrogradely over two slow AV nodal pathways, with a retrograde P wave produced midway in the cardiac cycle. On the right, a PAC (*arrowhead*) initiates AV nodal reentry as a result of anterograde conduction over the slow pathway and retrograde conduction over the fast pathway (**see Fig. 37.8A**), which produces a retrograde P wave in the terminal portion of the QRS complex that simulates an r′ wave. **C, D,** A PAC (*arrowhead* ↓) initiating a short run of atrial flutter **(C)** and a PAC (*arrowhead* ↑) depressing return of the next sinus nodal discharge **(D).** A slightly later PAC (*arrowhead* ↓) in **D** does not depress sinus nodal automaticity. **B-D,** Monitor leads. **E,** Ladder diagram of the effects of a PAC. The sinus interval (A_1-A_1) equals X. The third P wave represents a PAC (A_2) that reaches and discharges the SA node, which causes the next sinus cycle to begin at that time. Therefore the P-P (A_2-A_3) interval equals X + 2Y milliseconds, assuming no depression of SA nodal automaticity. **F,** Diagram of the interactions of a PAC (*yellow circles* indicate origin; QRS complexes omitted) with the sinus node (*SN*) depending on the degree of prematurity. The **top** represents spontaneous sinus rhythm. The **bottom** is a late coupled PAC that collides with the exiting sinus impulse and therefore does not affect (or reset) the sinus pacemaker. The next sinus impulse (S_3) occurs at exactly twice the sinus interval. An early coupled PAC in the next diagram is able to penetrate the SN and resets the pacemaker, thereby resulting in resetting of the SN (as depicted in **E**). An even earlier coupled PAC in the lower part of the figure reaches refractory tissue around the SN and is thus unable to penetrate it (SN entrance block); therefore, it does not affect SN discharge. The next spontaneous sinus beat (S_3) arrives exactly at the sinus interval. (***E,*** Modified from Zipes DP, Fisch C. Premature atrial contraction. Arch Intern Med 1971;128:453.)

Several factors determine the length of the pause that follows any premature complex or series of

premature complexes. If the PAC occurs when the sinus node and perinodal tissue are not refractory, the impulse can be conducted into the sinus node, can discharge it prematurely, and can cause the next sinus cycle to begin from that time. The interval between the two normal P waves flanking a PAC that has reset the timing of the basic sinus rhythm is less than twice the normal P-P interval, and the pause after the PAC is said to be *noncompensatory* (**Fig. 37.3E, F**). Reset (noncompensatory pause) occurs when the A_1-A_2 interval plus the A_2-A_3 interval is less than two times the A_1-A_1 interval and the A_2-A_3 interval is greater than the A_1-A_1 interval. The interval between the PAC (A_2) and the following sinus-initiated P wave (A_3) exceeds one sinus cycle but is less than fully compensatory (see later), because the A_2-A_3 interval is lengthened by the time that it takes the ectopic atrial impulse to be conducted to the sinus node and depolarize it and then for the sinus impulse to return to the atrium. These factors lengthen the return cycle, that is, the interval between the PAC (A_2) and the following sinus-initiated P wave (A_3) (**see Fig. 37.3E, F**). Premature discharge of the sinus node by an early PAC can temporarily depress sinus nodal automatic activity and cause the sinus node to beat more slowly initially (**Fig. 37.3D**). Often when this happens, the interval between the A_3 and the next sinus-initiated P wave exceeds the A_1-A_1 interval.

Less frequently, the PAC encounters a refractory sinus node or perinodal tissue (**see Fig. 37.3F**), in which case the timing of the basic sinus rhythm is not altered because the sinus node is not reset by the PAC and the interval between the two normal sinus-initiated P waves flanking the PAC is twice the normal P-P interval. The interval that follows this PAC is said to be a *full compensatory pause*, that is, of sufficient duration that the P-P interval bounding the PAC is twice the normal P-P interval. However, sinus arrhythmia can lengthen or shorten this pause. Rarely, an interpolated PAC can occur. In this case the pause after the PAC is very short, and the interval bounded by the normal sinus-initiated P waves on each side of the PAC is equal to one normal P-P cycle length or slightly longer. The interpolated PAC fails to affect the sinus nodal pacemaker, and the sinus impulse that follows the PAC is conducted to the ventricles, often with a slightly lengthened PR interval. An interpolated PAC or premature ventricular complex (PVC) of any type represents the only type of premature systole that does not actually replace the normally conducted beat. PACs can originate in the sinus node and are identified by premature P waves that have a contour identical to that of the normal sinus P wave.

On occasion, when the AV node has had sufficient time to repolarize and conduct without delay, the supraventricular QRS complex initiated by the PAC can be aberrant in configuration, because the His-Purkinje system or ventricular muscle has not completely repolarized and conducts with a functional delay or block (**see Fig. 37.3A**). The refractory period of cardiac fibers is directly related to cycle length. (In an adult, the effective AV nodal refractory period is prolonged at shorter cycle lengths.) A slow heart rate (long cycle length) produces a longer His-Purkinje refractory period than does a faster heart rate. As a consequence, a PAC that follows a long R-R interval (long refractory period) can result in a functional BBB (aberrant ventricular conduction). Because the right bundle branch at long cycles has a longer refractory period than the left bundle branch does, aberration with a right bundle branch block (RBBB) pattern at slow rates occurs more commonly than aberration with a left bundle branch block (LBBB) pattern. At shorter cycles, the refractory period of the left bundle branch exceeds that of the right bundle branch, and an LBBB pattern may be more likely to occur.

Clinical Features

PACs can occur in various situations, such as during infection, inflammation, or myocardial ischemia, or can be provoked by various medications, tension states, tobacco, alcohol, or caffeine. PACs can precipitate or presage the occurrence of sustained supraventricular tachyarrhythmias (**Fig. 37.3B, C**) and,

rarely, ventricular tachyarrhythmias. Frequently, PACs occur without any reversible causes and increase in frequency with aging. In general, PACs have a benign prognosis. Most patients do not have significant symptoms with PACs; however, those who do have symptoms most often feel the pauses that occur after the PAC.

Management

PACs generally do not require therapy. In symptomatic patients or when the PACs precipitate tachycardias, treatment with a beta blocker or a calcium antagonist can be attempted. In drug-refractory, highly symptomatic cases, ablation of the PAC focus can be effective when a single focus can be identified.

Atrial Fibrillation

See Chapter 38.

Atrial Tachycardias

Automatic, triggered, and reentrant causes of atrial tachycardia (AT) have been distinguished experimentally. In most cases, clear identification of the mechanism cannot be made clinically because the clinical and electrophysiologic features can overlap, especially when the reentrant circuit is small (i.e., microreentry). For example, adrenergic stimulation can initiate automatic and triggered ATs, and burst pacing can initiate triggered and microreentrant ATs. Therefore, because it determines the approach to mapping and management, ATs are more broadly characterized clinically as being *focal* (originating from a small area of the atrium with atrial excitation emanating centrifugally from this focus) or *macroreentrant* (a relatively large reentrant circuit using conduction barriers to create the circuit).[6] Atrial flutter is the most common type of macroreentrant AT.

Atrial Flutter and Other Macroreentrant Atrial Tachycardias

Atrial flutter is the prototypic macroreentrant atrial rhythm. The typical atrial flutter is a reentrant rhythm in the right atrium that is constrained anteriorly by the tricuspid annulus and posteriorly by the crista terminalis and eustachian ridge. The flutter can circulate in a counterclockwise direction around the tricuspid annulus in the frontal plane (*counterclockwise* flutter) or in a clockwise direction (*clockwise* or *reverse* flutter). Both are typical flutters because they use the cavotricuspid isthmus. Because both these forms use the same circuit and are constrained by the same anatomic structures, their rates and flutter wave morphology on the surface ECG are consistent and predictable (see later). Rarely, intra-isthmus flutter can occur when the reentrant circuit is isolated to the cavotricuspid isthmus rather than rotating around the entire tricuspid annulus; this typically occurs after ablation in this region (usually done as treatment of typical flutter). Other forms of atrial flutter are now recognized as distinct types and include atrial macroreentry caused by incisional scars[7] from previous atrial surgery, previous atrial ablation, mitral annular flutter,[8] idiopathic fibrosis in areas of the atrium, or other anatomic or functional barriers to conduction in the atria. Because the barriers that constrain these flutters are variable, the electrocardiographic pattern of these atrial flutters can vary. Sometimes, flutter wave morphology changes during the same episode of flutter, which indicates multiple circuits or nonfixed conduction barriers.

Electrocardiographic Recognition

The atrial rate during typical atrial flutter is usually 250 to 350 beats/min, although it is occasionally slower, particularly when the patient is treated with antiarrhythmic drugs (AADs), which can reduce the rate to about 200 beats/min. If such slowing occurs, the ventricles can respond in a 1 : 1 fashion to the slower atrial rate.

In typical atrial flutter, the ECG reveals identically recurring, regular, sawtooth flutter waves (**see Fig. 37.3C**), and evidence of continual electrical activity (lack of an isoelectric interval between flutter waves), often best visualized in leads II, III, aVF, or V_1 (**Fig. 37.4**).[9] During 2 : 1 or 1 : 1 conduction, transient slowing of the ventricular response with carotid sinus massage or adenosine is necessary to visualize the flutter waves. The flutter waves for the most common form, counterclockwise typical atrial flutter, are inverted (negative) in these leads because of a counterclockwise reentrant pathway, and sometimes they are upright (positive) when the reentrant loop is clockwise (**see Fig. 37.4**). When the flutter waves are upright from clockwise rotation, they are often notched. If the AV conduction ratio remains constant, the ventricular rhythm will be regular; if the ratio of conducted beats varies (generally the result of a Wenckebach AV block), the ventricular rhythm will be irregular, although this is rare. Various degrees of penetration into the AV junction by flutter impulses can also influence AV conduction. The ratio of flutter waves to conducted ventricular complexes is most often an even number (e.g., 2 : 1, 4 : 1).

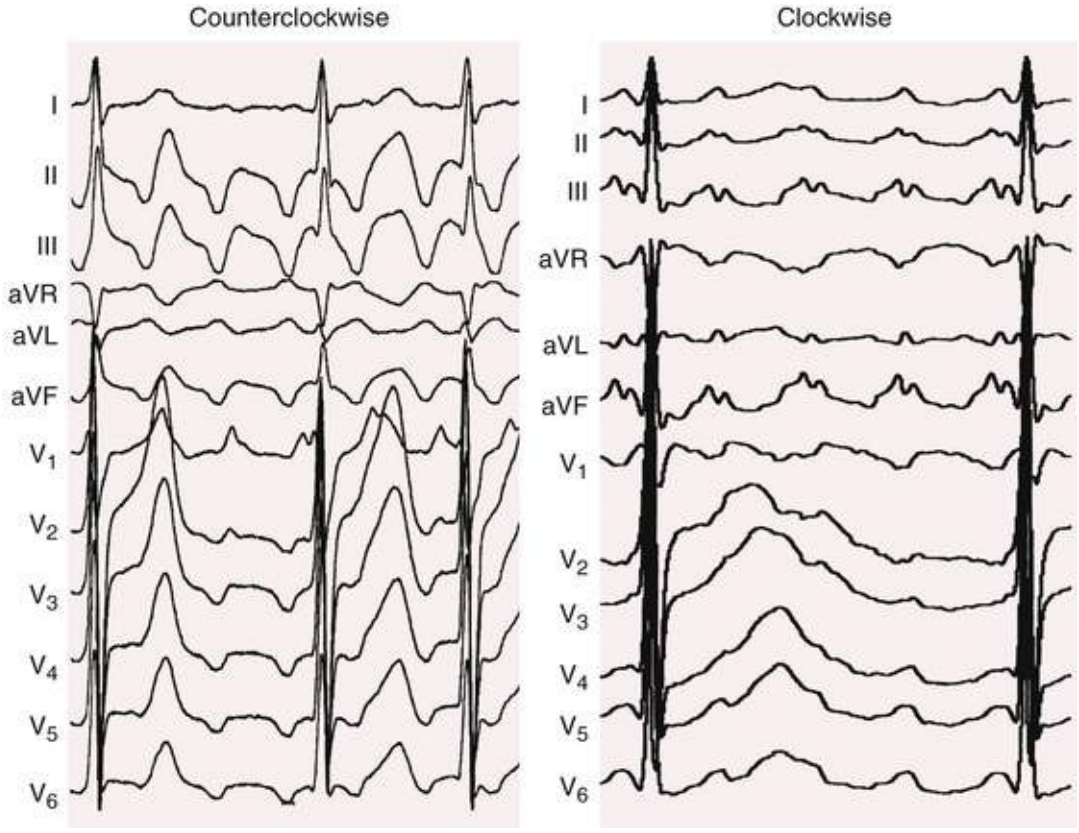


FIGURE 37.4 Twelve-lead ECG showing counterclockwise and clockwise atrial flutter. In counterclockwise atrial flutter, the flutter waves are negative in leads II, III, aVF, and V_6 and upright in V_1. In clockwise atrial flutter, the flutter waves are upright in leads II, III, and aVF and often notched.

As mentioned earlier, because the circuits for atypical flutter (not involving the cavotricuspid isthmus) can be variable, the electrocardiographic features of these macroreentrant ATs are highly variable, without consistent rates or flutter wave contours (**see eFig. 37.2**). However, these tachycardias frequently

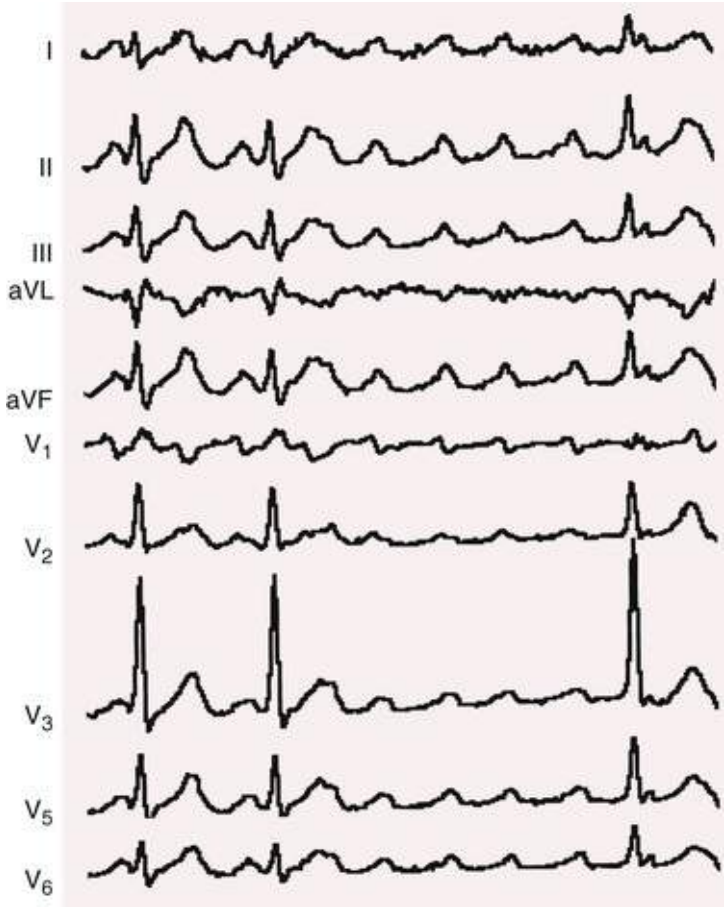
have a flutter rate similar to that of typical flutter (250 to 350 beats/min). **Table 37.3** shows common electrocardiographic findings with the different types of macroreentrant atrial flutter. After extensive left atrial ablation for atrial fibrillation, the electrocardiographic pattern of even typical flutter can change because of the altered left atrial activation caused by altered conduction secondary to ablation. In addition, unusual forms of atrial flutter can occur around ablation lines.

TABLE 37.3

Characteristics of Different Types of Atrial Flutter and Distinguishing Features on Scalar Electrocardiography

TYPE	REENTRANT CIRCUIT	ECG PATTERN	LEAD V_1/V_6
Typical counterclockwise	Tricuspid annulus dependent on the CTI	Sawtooth flutter wave; negative in II, III, and aVF	Positive V_1 Negative V_6
Typical clockwise	Tricuspid annulus dependent on the CTI	"Inverse sawtooth"; positive and often notched in II, III, and aVF	Broad and negative in V_1 (often notched) Positive in V_6
Lower loop reentry	CTI	Usually similar to typical counterclockwise CTI flutter except subtle loss of terminal positive deflection in leads II, III, and aVF	Usually similar to typical counterclockwise
Upper loop reentry	Superior vena cava and upper crista terminalis	Similar to typical clockwise flutter	Similar to typical clockwise flutter
Right atrial free wall	Around areas of scar in lateral or posterior right atrium (caused by previous atrial surgery or spontaneously)	Variable	Typically negative or biphasic with terminal negative deflection in V_1
Septal atrial flutter	Atrial septum, typically after previous surgery	Variable	Usually biphasic or isoelectric in V_1
Mitral annular flutter	Around mitral annulus, often slow zone of block around PV interval; frequently occurs in setting of left atrial surgery or ablation	Variable; I, III, and aVF, often positive but low amplitude	Usually positive in V_1 (or rarely isoelectric) and often broad
Post–atrial fibrillation ablation/maze flutter	Variable; circuit involves previous ablations or scar in left atrium	Variable	Variable

CTI, Cavotricuspid isthmus.



EFIGURE 37.2 Macroreentrant atrial tachycardia in a patient who underwent repair of an atrial septal defect 10 years earlier. This tachycardia uses a reentrant circuit established by the atriotomy on the lateral atrial wall. Ablation to extend the scar to the tricuspid annulus eliminated this tachycardia.

Clinical Features

Atrial flutter is less common than atrial fibrillation. It can result from atrial dilation caused by septal defects, pulmonary emboli, mitral or tricuspid valve stenosis or regurgitation, heart failure, previous extensive atrial ablation, and aging,[10] but it can also occur without underlying heart disease. Toxic and metabolic conditions that affect the heart, such as thyrotoxicosis, alcoholism, and pericarditis, can cause atrial flutter. When it follows surgical repair of congenital heart disease, most patients can have both typical flutter and atypical flutter involving the atriotomy, often occurring years after the surgery.

Carotid sinus massage usually decreases the ventricular rate in stepwise multiples; the ventricular rate returns in reverse manner to the former rate when carotid massage stops. Physical examination can reveal rapid flutter waves in the jugular venous pulse. The first heart sound will have a constant intensity if the relationship of flutter waves to conducted QRS complexes remains constant. Sounds caused by atrial contraction can occasionally be auscultated.

Management

Cardioversion is usually the initial treatment of choice for atrial flutter because it promptly and effectively restores sinus rhythm (**see Chapter 36**). Cardioversion can be accomplished with synchronous direct current (DC), which often requires relatively low energy (approximately 50 J). If the electrical shock results in atrial fibrillation (AF), a second shock at a higher energy level is used to restore sinus rhythm, or depending on clinical circumstances, the AF can be left untreated and can revert to atrial flutter or sinus rhythm. The short-acting AAD ibutilide can also be given intravenously to convert

atrial flutter. Ibutilide appears to successfully cardiovert approximately 60% to 90% of episodes of atrial flutter. However, because this medication prolongs the QT interval, torsades de pointes is a potential complication during and shortly after the infusion. Other medications, such as procainamide or amiodarone, can be given to convert atrial flutter chemically, but they are generally less effective than ibutilide. Rapid atrial pacing with an esophageal or right atrial catheter can effectively terminate typical and some forms of atypical atrial flutter in most patients. Because catheter ablation is highly effective for typical flutter and because of the high relapse rate after cardioversion, catheter ablation is the preferred approach for stable patients who do not require immediate cardioversion. Although the risk for thromboembolism may be lower than for AF, patients with atrial flutter do have a risk for thromboembolism immediately after conversion to sinus rhythm. In general, indications for anticoagulation in patients with atrial flutter are similar to those in patients with AF.

Atrial flutter is usually more difficult to rate-control than AF. To slow the ventricular response, verapamil, given as an initial bolus of 2.5 to 10 mg intravenously (may repeat with an additional 5 to 10 mg after 15 to 30 minutes), or diltiazem, 0.25 mg/kg, can be tried (**see Chapter 36**). Adenosine produces a transient AV block and can be used to reveal flutter waves if diagnosis is in doubt. Adenosine will not generally terminate atrial flutter and can provoke AF. Esmolol, a beta-adrenergic blocker with a 9-minute elimination half-life, or other intravenous (IV) beta blockers can be used to slow the ventricular rate. If calcium channel blockers and beta blockers in combination are insufficient, digoxin can be added. The dose of digitalis necessary to slow the ventricular response varies and at times can result in toxic levels because it is often difficult to slow the ventricular rate during atrial flutter. IV amiodarone can slow the ventricular rate as effectively as digoxin.

If the atrial flutter persists or recurs, class IA, IC, or III drugs can be tried, to restore sinus rhythm and prevent recurrences. Side effects, especially proarrhythmic responses, must be carefully considered (**see Chapter 36**). Treatment of the underlying disorder, such as thyrotoxicosis, is sometimes necessary to effect conversion to sinus rhythm. In many cases, atrial flutter can continue (or even become more persistent) while taking AADs, and the flutter rate will slow. Class IA or IC drugs should not be used unless the ventricular rate during atrial flutter has been slowed with a calcium antagonist or beta blocker. Because class I drugs can slow the flutter rate, AV conduction can be facilitated sufficiently to result in a 1 : 1 ventricular response to the atrial flutter (**Fig. 37.5**).

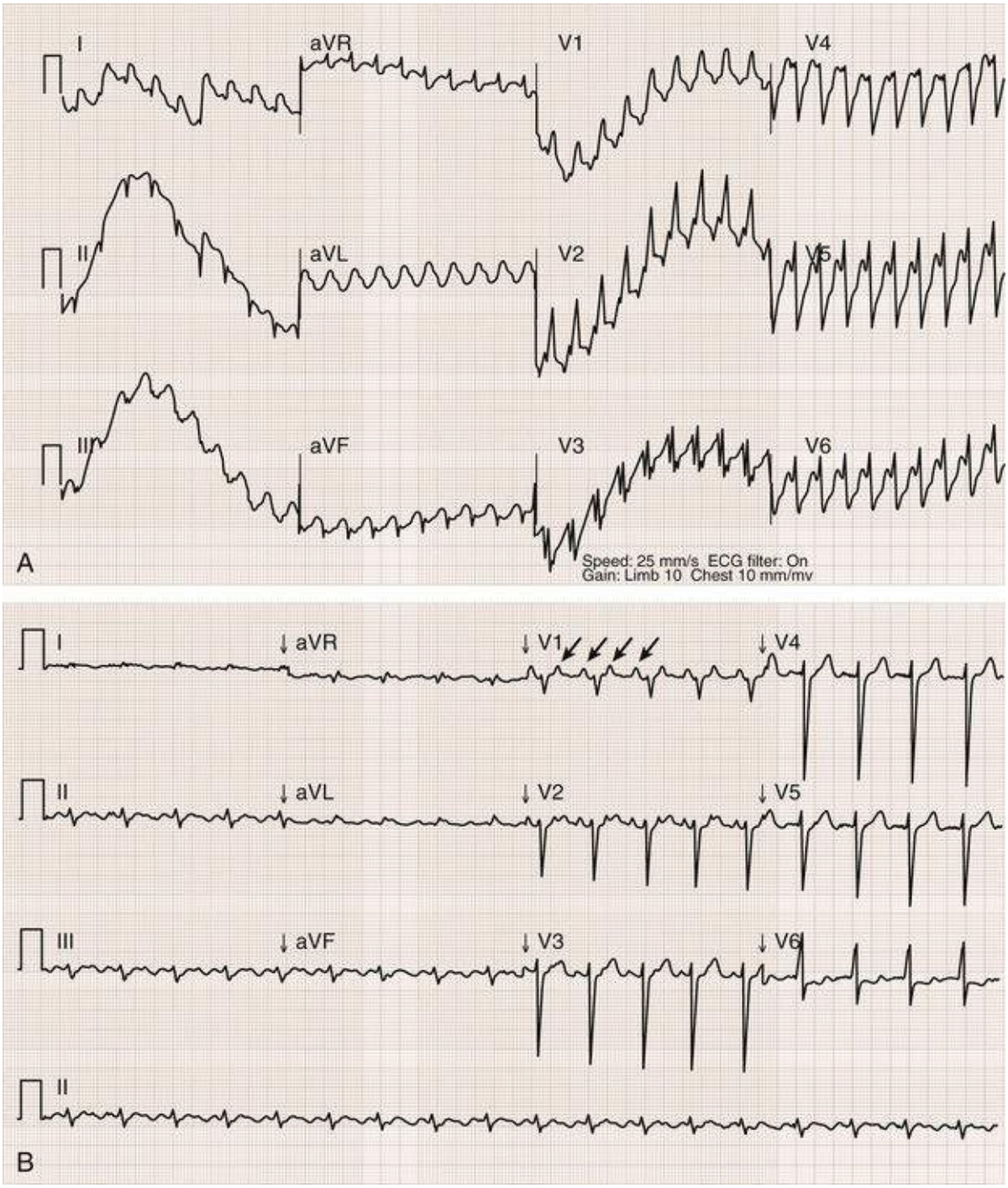


FIGURE 37.5 Atrial flutter with 1 : 1 conduction and QRS widening caused by flecainide. **A,** Atrial flutter occurs with 1 : 1 conduction and a widened QRS because of slowing of the atrial flutter rate as a result of flecainide and acceleration of conduction through the AV node, which leads to a rapid ventricular response. This rapid ventricular response results in a widened QRS complex because of the use dependence of sodium channel blocking by flecainide. **B,** After administration of AV nodal–blocking agents (in this case, metoprolol), 2 : 1 conduction occurs, the ventricular rate is slowed, and the QRS duration shortens. In addition, the flutter waves are now apparent on the ECG (*arrows*).

Prevention of recurrent atrial flutter is frequently difficult to achieve medically but should be approached as outlined for AF (**see Chapters 36 and 38**). Catheter ablation should be considered in patients with symptomatic or recurrent atrial flutter. Catheter ablation of typical flutter (counterclockwise and clockwise) is a highly effective cure and has a long-term success rate of 90% to 100%.[11] Because ablation of atrial flutter is so effective and poses little risk, it can be offered as an alternative to drug therapy. Ablation of other forms of macroreentrant AT is also effective,[7] although success rates are somewhat lower and more variable. Because of the risk for emboli in patients with atrial flutter, and because many patients with atrial flutter also have AF, anticoagulation is usually warranted.

Focal Atrial Tachycardias

Electrocardiographic Recognition

Focal atrial tachycardias generally have atrial rates of 150 to 200 beats/min, with a P wave contour different from that of the sinus P wave (**Fig. 37.6**). However, ATs with foci near the sinus node can have P wave contours very similar to those in sinus rhythm. At onset the rate can increase over the initial several complexes. Frequently, ATs occur in short, recurrent bursts with spontaneous terminations or can become incessant. However, more incessant forms of AT do occur. P waves are generally found in the second half of the tachycardia cycle (long RP–short PR tachycardia). If the atrial rate is not excessive and AV conduction is not depressed, each P wave can conduct to the ventricles. If the atrial rate increases and AV conduction becomes impaired, a Wenckebach (Mobitz type I) second-degree AV block can ensue (**see Chapter 40**), sometimes called *atrial tachycardia with block*. When digitalis causes the AT with block, other manifestations of digitalis excess are present, such as PVCs. In almost half the cases of AT with block, the atrial rate is irregular. Characteristic isoelectric intervals between P waves, in contrast to atrial flutter, are usually present in all leads. However, at rapid atrial rates, distinction between AT with block and atrial flutter can be difficult. Analysis of P wave configuration during tachycardia indicates that a positive or biphasic P wave in V_1 predicts a left atrial focus, whereas a negative P wave in V_1 predicts a right atrial focus.

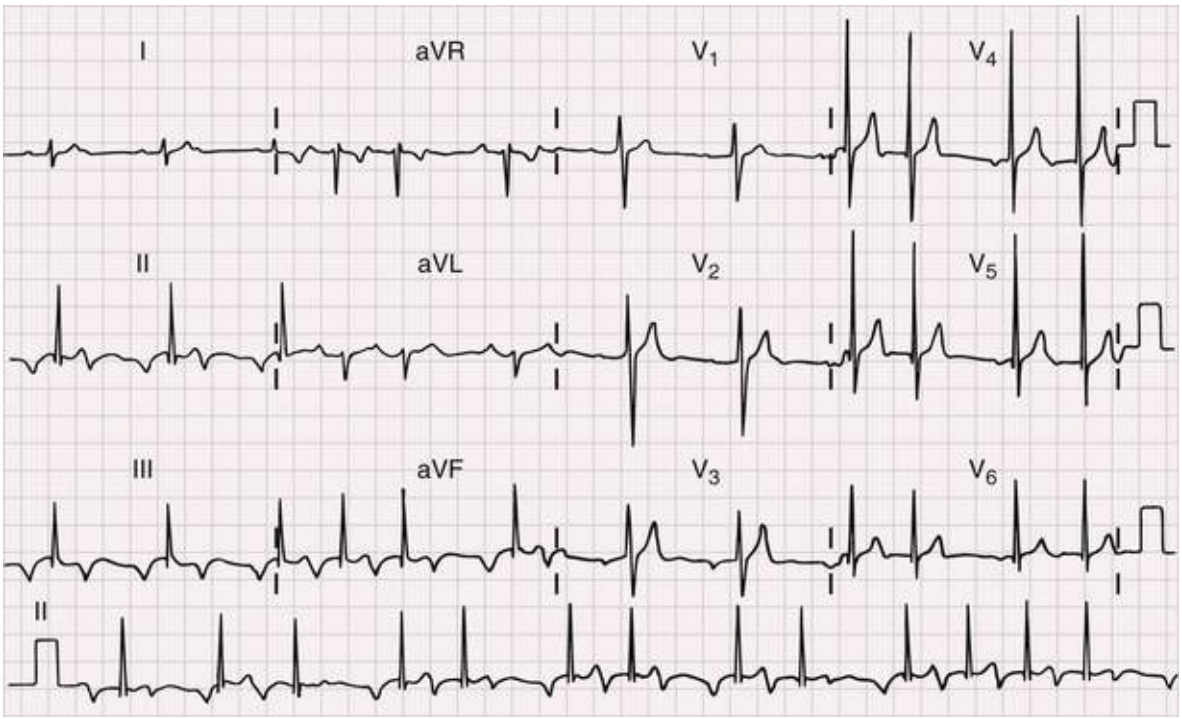


FIGURE 37.6 Atrial tachycardia. This 12-lead ECG and rhythm strip (*bottom*) demonstrate AT at a cycle length of approximately 520 milliseconds. Conduction varies between 3 : 2 and 2 : 1. Note the negative P waves in leads II, III, and aVF and, when consecutive P waves are conducted, that the RP interval exceeds the PR interval. Note also that the tachycardia persists despite the development of an AV block, an important finding that excludes participation of an AV accessory pathway and sharply differentiates this AT from the one shown in **Fig. 37.21**.

Clinical Features

Atrial tachycardia occurs often in patients with significant structural heart disease such as coronary artery

disease, with or without myocardial infarction, heart failure, and cor pulmonale, as well as in patients without structural heart disease. It can also occur with digitalis intoxication, often precipitated by potassium depletion. The signs, symptoms, and prognosis are usually related to the underlying cardiovascular status and the rate of the tachycardia. When symptoms are incessant, tachycardia-induced cardiomyopathy can result, partially or totally reversible with tachycardia elimination.[12] In some patients, exercise or stress can provoke the tachycardia; in others the tachycardia can be positional. Stimulants such as caffeine, chocolate, and ephedrine can also provoke episodes.

Physical findings during a variable rhythm include variable intensity of the first heart sound and systolic blood pressure as a result of the varying AV block and PR interval. An excessive number of *a* waves can be seen in the jugular venous pulse. Carotid sinus massage or administration of adenosine increases the degree of AV block and slows the ventricular rate in stepwise fashion without terminating the tachycardia, as in atrial flutter. Massage should be performed cautiously in patients with digitalis toxicity because serious ventricular arrhythmias can result. On occasion, carotid sinus massage or adenosine can terminate some forms of AT.

Management

Depending on the clinical situation, a beta blocker or a calcium channel blocker can be administered to slow the ventricular rate; if AT is still present, class IA, IC, or III drugs can be added. Catheter ablation procedures are generally effective in eliminating the AT, depending on the mechanism and underlying heart disease.[6] Ablation should be considered in those who fail drug therapy and can be considered as a first-line alternative in patients without underlying heart disease. The most important factor for successful ablation is the ability to induce the tachycardia during the procedure, usually with programmed stimulation and the use of catecholaminergic agents such as isoproterenol. Inducibility can be variable, depending on the mechanism of the AT. ATs can occasionally recur at a different site after successful ablation. If AT develops in a patient taking digitalis, the drug should initially be assumed to be responsible and its use stopped. Administration of digitalis antibodies should be considered in unstable patients.

Chaotic Atrial Tachycardia.

Chaotic (sometimes called *multifocal*) AT is characterized by atrial rates between 100 and 130 beats/min along with marked variation in P wave morphology and totally irregular P-P intervals (**Fig. 37.7**). In general, at least three P wave contours are noted, with most P waves being conducted to the ventricles, although often with variable PR intervals. This tachycardia occurs frequently in older patients with chronic obstructive pulmonary disease and congestive heart failure and may eventually develop into AF. Digitalis appears to be an unusual cause, and theophylline administration has been implicated. Chaotic AT can occur in childhood.

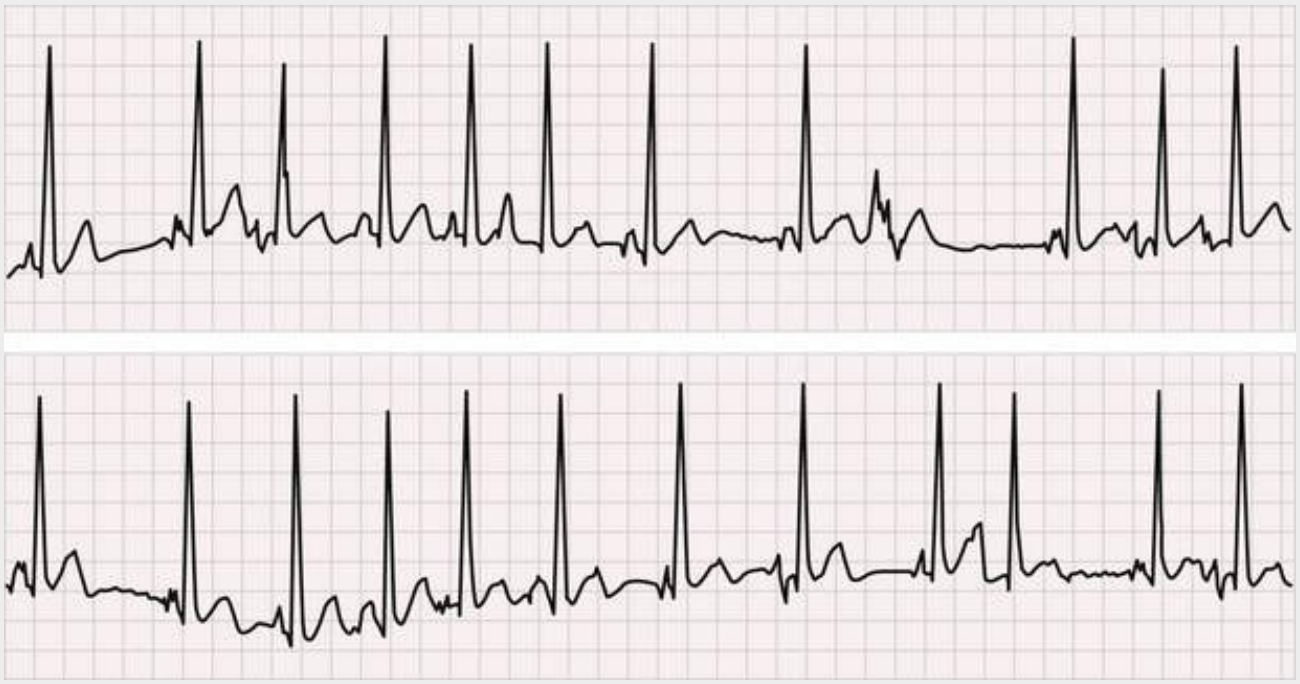


FIGURE 37.7 Chaotic (multifocal) atrial tachycardia. PACs occur at varying cycle lengths and with different contours.

Management.
Management is directed primarily toward the underlying disease. AADs are frequently ineffective in slowing either the rate of the AT or the ventricular response. Beta adrenoceptor blockers should be avoided in patients with bronchospastic pulmonary disease but can be effective if tolerated. Verapamil and amiodarone have been useful. Potassium and magnesium replacement may suppress the tachycardia. Ablation may be effective in some cases.

Tachycardias Involving the Atrioventricular Junction

Confusion exists about the nomenclature of tachycardias characterized by a supraventricular QRS complex, a regular R-R interval, and no evidence of ventricular preexcitation. Because various electrophysiologic mechanisms can account for these tachycardias (**Fig. 37.8**), the nonspecific term *paroxysmal supraventricular tachycardia* has been proposed to encompass the entire group. This term may be inappropriate, however, because some tachycardias in patients with accessory pathways (see later) are no more supraventricular than they are ventricular in origin, since they may require participation of both the atria and the ventricles in the reentrant pathway and may exhibit a QRS complex of normal contour and duration only because anterograde conduction occurs over the normal AV node–His bundle pathways (**Fig. 37.8C**). If conduction over the reentrant pathway reverses direction and travels in an "antidromic" direction (i.e., to the ventricles over the accessory pathway and to the atria over the AV node–His bundle), the QRS complex exhibits a prolonged duration, although the tachycardia is basically the same. The term *reciprocating tachycardia* has been offered as a substitute for paroxysmal SVT, but use of such a term presumes the mechanism of the tachycardia to be "reentrant," which is probably the case for most but not all SVTs. Thus, no universally acceptable nomenclature exists, but rather descriptive labels for specific arrhythmias, as used throughout this chapter.

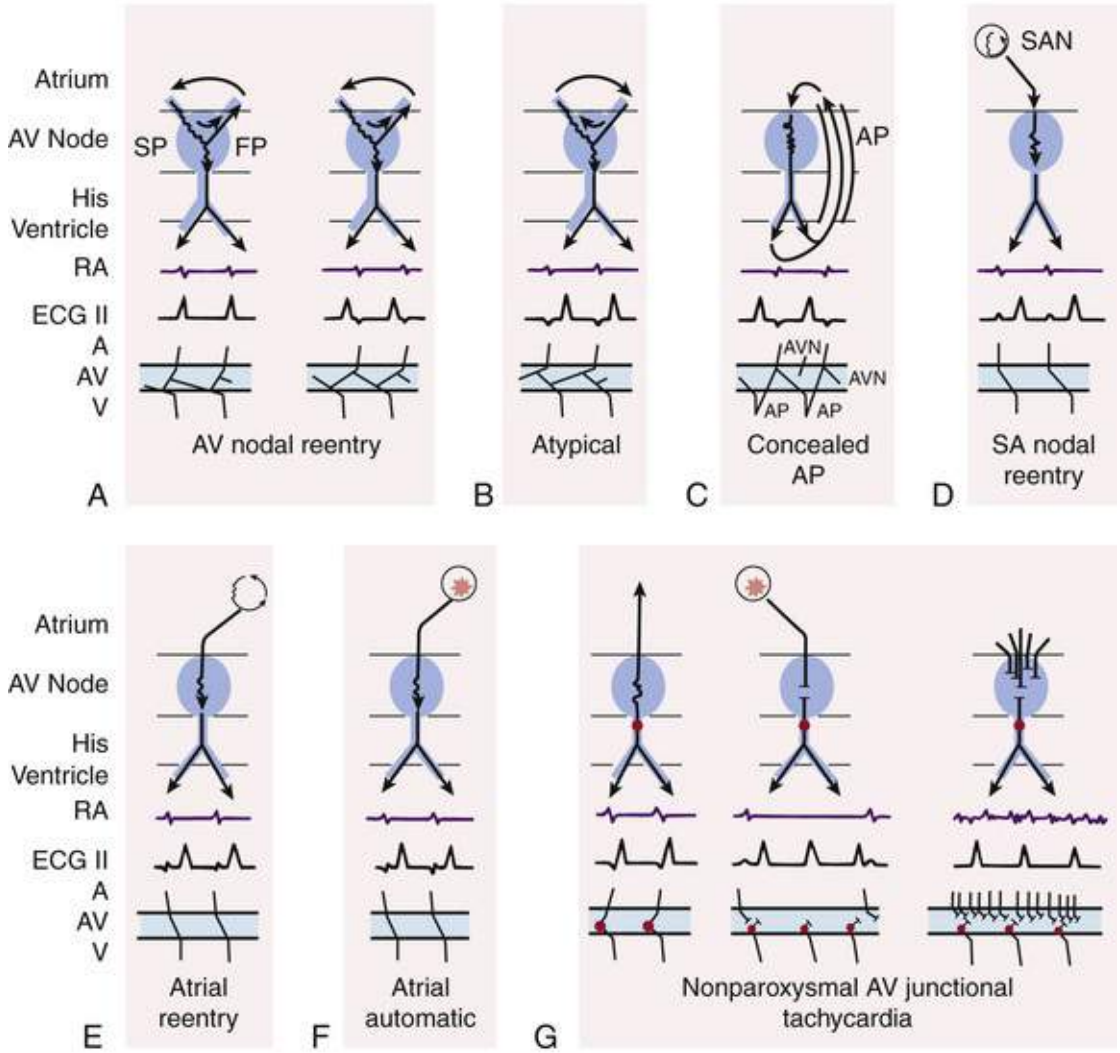


FIGURE 37.8 Diagrammatic representation of various tachycardias. In the *upper* portion of each example, a schematic of the presumed anatomic pathways is shown; in the *lower* half the ECG and explanatory ladder diagram are depicted. **A,** AV nodal reentry. In the **left** example, reentrant excitation is drawn with retrograde atrial activity occurring simultaneously with ventricular activity as a result of anterograde conduction over the slow AV nodal pathway (*SP*) and retrograde conduction over the fast AV nodal pathway (*FP*). In the **right** example, atrial activity occurs slightly later than ventricular activity because of retrograde conduction delay. **B,** Atypical AV nodal reentry caused by anterograde conduction over a fast AV nodal pathway and retrograde conduction over a slow AV nodal pathway. **C,** Concealed accessory pathway (*AP*). Reciprocating tachycardia is caused by anterograde conduction over the AV node (*AVN*) and retrograde conduction over the accessory pathway. Retrograde P waves occur after the QRS complex. **D,** Sinus nodal reentry. The tachycardia is caused by reentry within the sinus node, which then conducts the impulse to the rest of the heart. *SAN,* Sinoatrial node. **E,** Atrial reentry. Tachycardia is caused by reentry within the atrium, which then conducts the impulse to the rest of the heart. **F,** Automatic atrial tachycardia (the *star* indicates the origin). Tachycardia is caused by automatic discharge in the atrium, which then conducts the impulse to the rest of the heart; it is difficult to distinguish from atrial reentry. **G,** Various manifestations of nonparoxysmal AV junctional tachycardia are depicted with retrograde atrial capture, AV dissociation with the sinus node in control of the atria, and AV dissociation with atrial fibrillation. The *star* indicates sinus node discharge. *Red circles* indicate the site of junctional discharge.

Atrioventricular Nodal Reentrant Tachycardia

Electrocardiographic Recognition

Reentrant tachycardia involving the AV node is characterized by a tachycardia with a QRS complex of supraventricular origin, sudden onset and termination generally at rates 150 to 250 beats/min (usually 180 to 200 beats/min in adults), and a regular rhythm. Infrequently, the rate may be as low as 110 beats/min;

occasionally, especially in children, it may exceed 250 beats/min. Unless functional aberrant ventricular conduction or a previous conduction defect exists, the QRS complex is normal in contour and duration. P waves are generally buried in the QRS complex. Frequently, the P wave occurs just before or just after the end of the QRS complex and causes a subtle alteration that results in a pseudo-S or pseudo-r′, which may be recognized only on comparison with the QRS complex in normal sinus rhythm (**Fig. 37.9**). When seen, P waves are generally directed superiorly and are relatively narrow. AV nodal reentry begins abruptly, usually after a PAC that conducts with a prolonged PR interval (**see Figs. 37.3B and 37.8A**). The R-R interval can shorten over the course of the first few beats at the onset or lengthen during the last few beats preceding termination of the AT. Variation in cycle length, particularly at the onset of tachycardia or just before termination, is usually caused by variation in anterograde AV nodal conduction time. Cycle length or QRS alternans can occur, generally when the rate is very fast. Carotid sinus massage can slow the AT slightly before its termination or, if termination does not occur, can produce only slight slowing of the tachycardia.

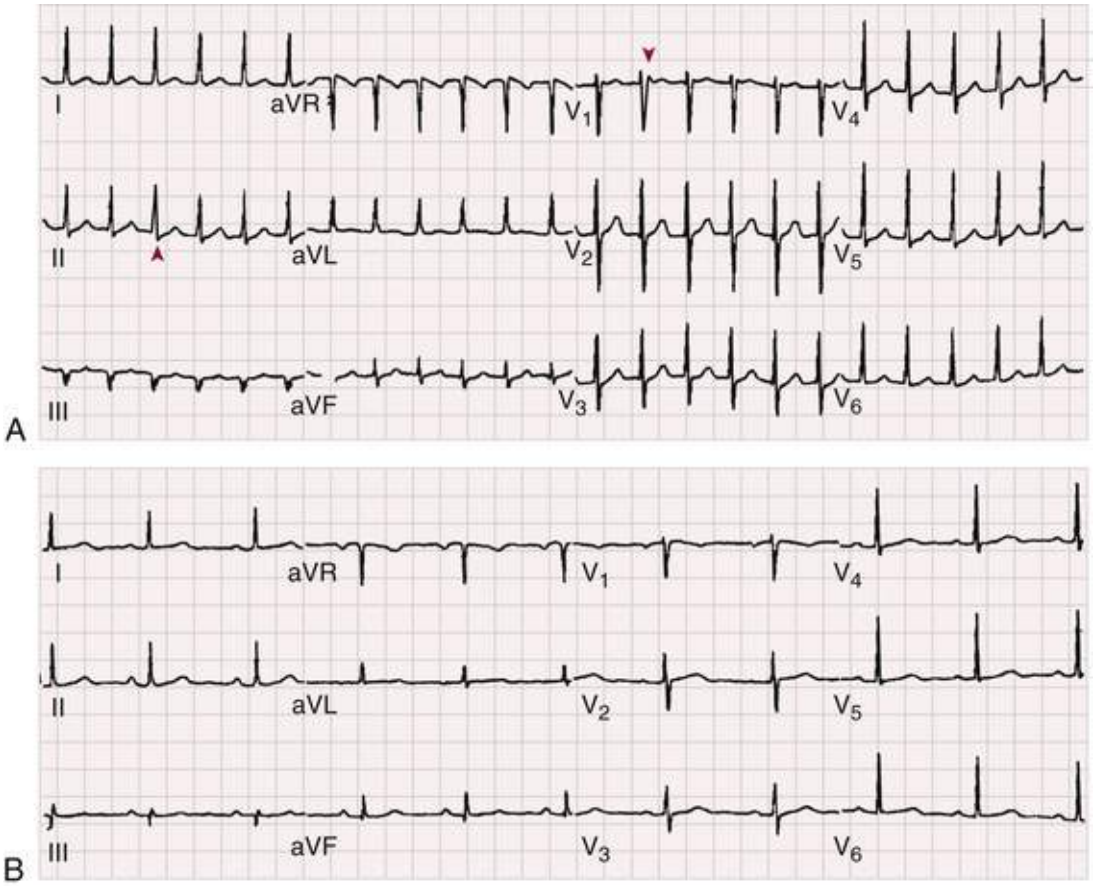


FIGURE 37.9 Twelve-lead ECG of AV nodal reentrant tachycardia (AVNRT). **A,** During tachycardia, a pseudo-r′ is seen in lead V_1 (*arrowhead*), and pseudo-S waves (*arrowhead*) are seen in leads II, III, and aVF. **B,** These waves become more obvious when compared with the QRS complexes during sinus rhythm.

Electrophysiologic Features

An atrial complex that conducts with a critical prolongation of AV nodal conduction time generally precipitates AV nodal reentry (**Figs. 37.10 and 37.11**). Premature ventricular stimulation can also induce AV nodal reentry in about one third of patients. Data from the results of RF catheter ablation and mapping support the presence of differential atrial input into the AV node, the fast and slow pathways, to explain

this tachycardia (**see Chapters 34 and 36**). In **Fig. 37.8A and B**, the atria are shown as a necessary link between the fast and slow pathways. Whether these pathways are discrete pathways (perhaps caused by anisotropy) or are functional in nature is not known. In most examples the retrograde P wave occurs at the onset of the QRS complex, which clearly excludes the possibility of an accessory pathway. If an accessory pathway in the ventricle were part of the tachycardia circuit, the ventricles would have to be activated anterogradely before the accessory pathway could be activated retrogradely and depolarize the atria, thus placing the retrograde P wave no earlier than 30 milliseconds after onset of the QRS and typically during the ST segment.

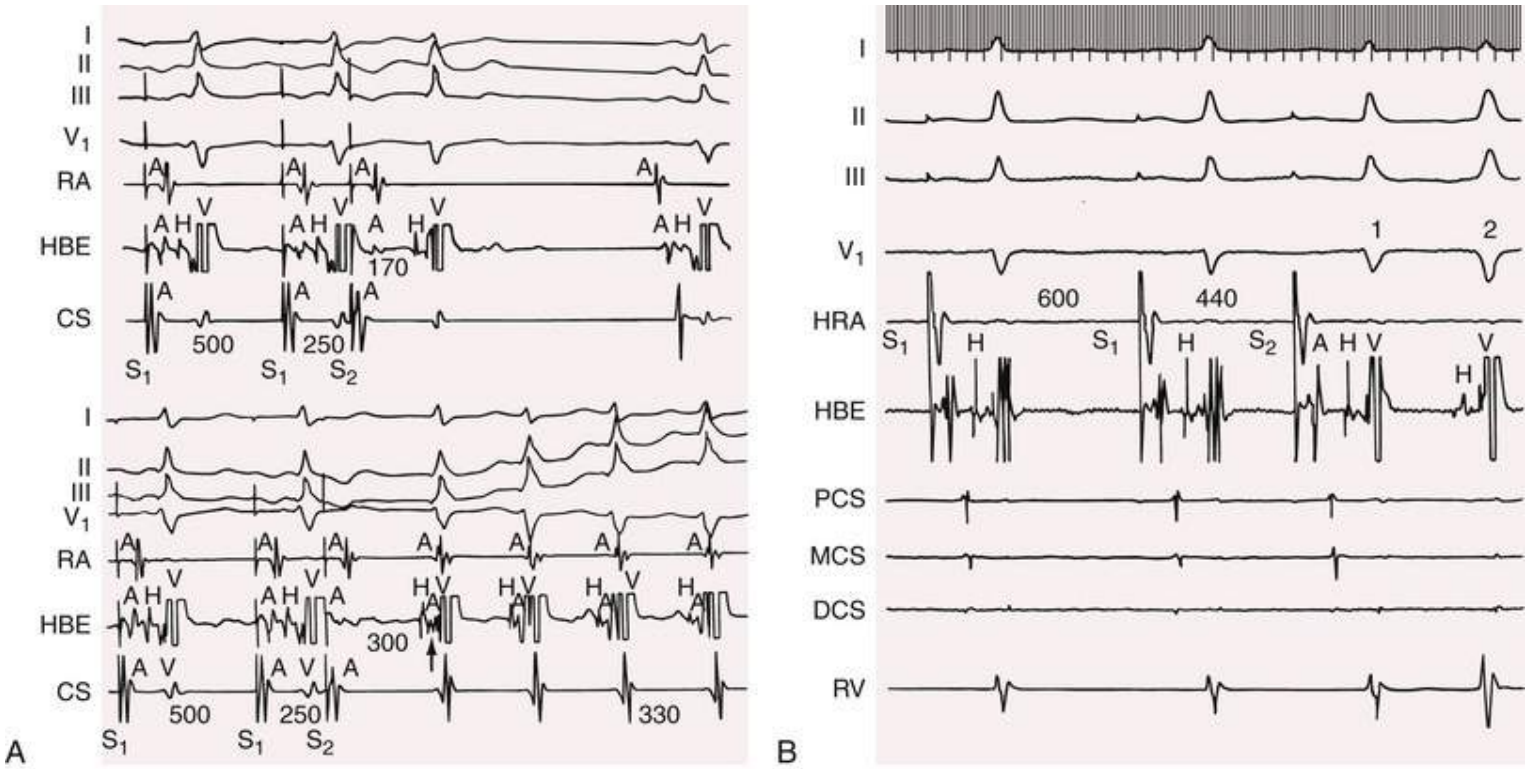


FIGURE 37.10 **A,** Initiation of AVNRT in a patient with dual AV nodal pathways. The upper and lower panels show the last two paced beats of a train of stimuli delivered to the coronary sinus at a pacing cycle length of 500 milliseconds. The results of premature atrial stimulation at an S_1-S_2 interval of 250 milliseconds on two occasions are shown. **Upper panel,** S_2 was conducted to the ventricle with an A-H interval of 170 milliseconds and was then followed by a sinus beat. **Lower panel,** S_2 was conducted with an A-H interval of 300 milliseconds and initiated AV nodal reentry. Note that the retrograde atrial activity occurs (*arrow*) before the onset of ventricular septal depolarization and is superimposed on the QRS complex. Retrograde atrial activity begins first in the low right atrium (HBE lead) and then progresses to the high right atrium (RA) and coronary sinus (CS) recordings. **B,** Two QRS complexes in response to a single atrial premature complex. After a basic train of S_1 stimuli at 600 milliseconds, an S_2 at 440 milliseconds is introduced. The first QRS complex in response to S_2 occurs after a short A-H interval (95 msec) caused by anterograde conduction over the fast AV nodal pathway. The first QRS complex is labeled 1 (in lead V_1). The second QRS complex in response to the S_2 stimulus (labeled 2) follows a long A-H interval (430 msec) caused by anterograde conduction over the slow AV nodal pathway. *DCS,* Distal coronary sinus; *HRA,* high right atrium; *MCS,* mid coronary sinus; *PCS,* proximal coronary sinus; *RV,* right ventricle.

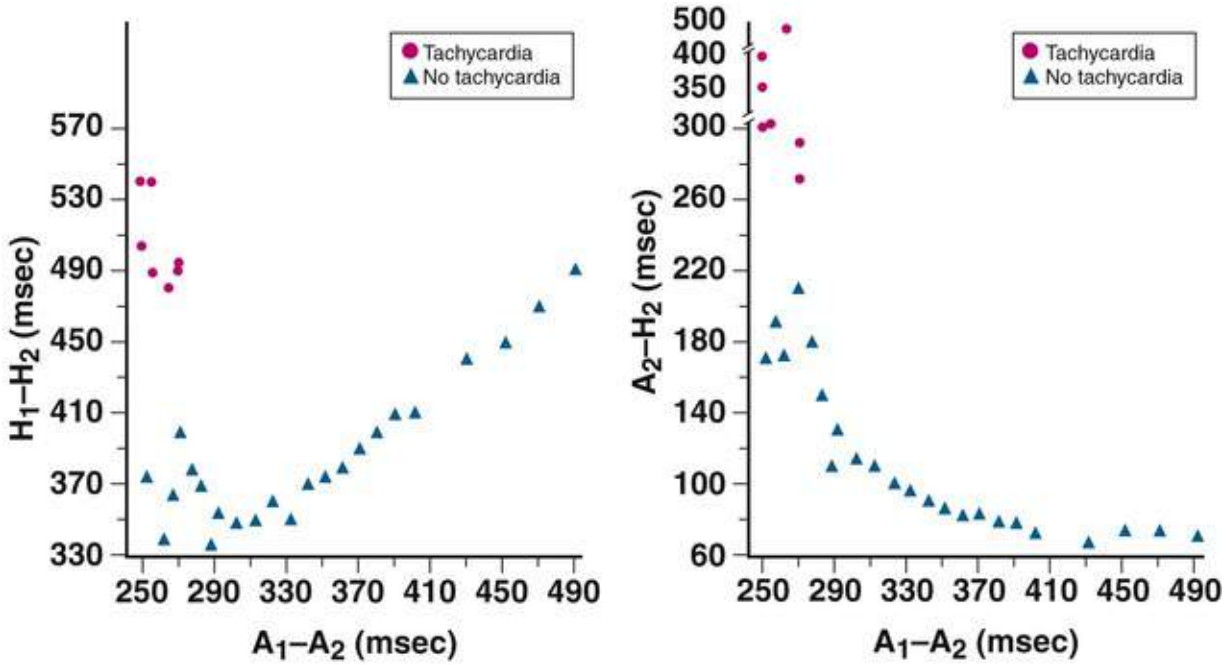


FIGURE 37.11 H_1-H_2 intervals **(left)** and A_2-H_2 intervals **(right)** at various A_1-A_2 intervals with a discontinuous AV nodal curve. At a critical A_1-A_2 interval, the H_1-H_2 and A_2-H_2 intervals increase markedly. At the break in the curves, AVNRT is initiated.

Atrial activation begins at the end of or just after the QRS complex in approximately 30% of cases and gives rise to a discrete P wave on the scalar ECG (often appearing as a nubbin of an R in V_1; **see Fig. 37.8A**). In most patients, P waves are not seen because they are buried within the inscription of the QRS complex. In the most common variety of AV nodal reentrant tachycardia (AVNRT), the ventriculoatrial (VA) interval is less than 50% of the R-R interval (a short-RP tachycardia). These VA intervals are longer in patients with tachycardia related to accessory pathways, as well as in those with atypical forms of AV nodal reentry (**see Fig. 37.8B**).

Slow and Fast Pathways.

In most patients, anterograde conduction to the ventricle occurs over the slow pathway and retrograde conduction occurs over the fast pathway, so-called typical AVNRT (**see Fig. 37.8A, B,** and **Chapter 34**). To initiate tachycardia, an atrial complex blocks anterogradely in the fast pathway (because it typically has a longer refractory period relative to the slow pathway), travels to the ventricle over the slow pathway, and returns to the atrium over the previously blocked fast pathway (slow-fast form). The proximal and distal final pathways for this *circus movement* appear to be located within the AV node, so as currently conceived, the circus movement occurs over the two atrial approaches and the AV node. The reentrant loop for typical AV nodal reentry is the anterograde slow AV nodal pathway to the final distal common pathway (probably the distal AV node), to the retrograde fast AV nodal pathway, and then to the atrial myocardium. In atypical AV nodal reentry, the reentry occurs in the opposite direction. Less often, the reentry pathway can be over two slow pathways or over a slow and intermediate pathway, the so-called slow-slow AV nodal reentry (**see Fig. 37.3B**). Conduction time in the anterograde slow pathway is a major determinant of the cycle length of the tachycardia.

Dual–Atrioventricular Nodal Pathway Concept.

Evidence supporting the dual-pathway concept is derived from several observations, the most compelling of which is that RF catheter ablation of the slow or the fast pathway eliminates AV nodal reentry without

eliminating AV nodal conduction. Additionally, in these patients a plot of the A_1-A_2 pathway versus the A_2-H_2 or the H_1-H_2 interval shows a discontinuous curve (**see Fig. 37.11**), because at a crucial A_1-A_2 interval the impulse is suddenly blocked in the fast pathway and is conducted with delay over the slow pathway, with sudden prolongation of the A_2-H_2 (or H_1-H_2) interval. In general, the A-H interval increases at least 50 milliseconds, with only a 10-millisecond decrease in the coupling interval of the PAC. Less frequently, dual pathways can be manifested by different PR or A-H intervals during sinus rhythm or at identical paced rates or by a sudden jump in the A-H interval during atrial pacing at a constant cycle length. Virtually irrefutable proof of dual AV nodal pathways is the simultaneous propagation in opposite directions of two AV nodal wavefronts without collision (**see Chapter 34**), or the production of two QRS complexes from one P wave (**see Fig. 37.10B**) or two P waves from one QRS complex.

Some patients with AV nodal reentry may not have discontinuous refractory period curves, and some patients who do not have AV nodal reentry can exhibit discontinuous refractory curves. In the latter patients, dual AV nodal pathways can be a benign finding. Many of these patients also exhibit discontinuous curves retrogradely. Triple AV nodal pathways can be demonstrated in occasional patients.

In less than 5% to 10% of patients with AV nodal reentry, anterograde conduction proceeds over the fast pathway and retrograde conduction over the slow pathway (termed the *unusual* or *atypical* form of fast-slow AV nodal reentry), with production of a long VA interval and a relatively short AV interval (generally an AV/VA ratio <0.75; **see Fig. 37.8B**). The least common form (slow-slow) exhibits a retrograde P wave midway in the cardiac cycle. Finally, it is possible to have tachycardias that use the anterograde slow or fast pathways and conduct retrogradely over an accessory pathway (see later).

Because in some instances either the atria or the ventricles are not needed to maintain AV nodal reentry, spontaneous AV block can occur, particularly at the onset of the arrhythmia, in the AV node distal to the reentry circuit, between the AV node and bundle of His, within the bundle of His, or distal to it (**see Chapter 34**). Most often, when a block appears, it is below the bundle of His, rarely in the upper common final pathway between the reentry circuit in the AV node and the atrium, and results in dissociation of the atria from the tachycardia. Termination of the tachycardia generally results from a block in the anterogradely conducting slow pathway (weak link), so a retrograde atrial response is not followed by a His or ventricular response. A functional BBB during AVNRT does not modify the tachycardia significantly.

Retrograde Atrial Activation.

The sequence of retrograde atrial activation is normal (also called *concentric*) during AV nodal reentrant SVT, which means that the earliest site of atrial activation during retrograde conduction over the fast pathway is recorded in the His bundle electrogram, followed by electrograms recorded from the os of the coronary sinus and then spreading to depolarize the rest of the right and left atria. During retrograde conduction over the slow pathway in the atypical type of AV nodal reentry, atrial activation recorded in the proximal coronary sinus precedes atrial activation recorded in the low right atrium, which suggests that the slow and fast pathways can enter the atria at slightly different positions.

Clinical Features

AV nodal reentry frequently occurs in patients without structural heart disease, often in the late teens or 20s; however, there is a second peak in incidence in the 40s and 50s. There is a higher incidence in women, and adult onset tends to be younger in women. Symptoms frequently accompany the AT and range from feelings of palpitations, nervousness, and anxiety to angina, heart failure, syncope, or shock,

depending on the duration and rate of the tachycardia and the presence of structural heart disease. Tachycardia can cause syncope because of the rapid ventricular rate, reduced cardiac output, and cerebral circulation or because of asystole when the tachycardia terminates as a result of tachycardia-induced depression of sinus node automaticity. The prognosis for patients without heart disease is usually good.

Management

Acute Attack.

Management of AVNRT depends on the underlying heart disease, how well the tachycardia is tolerated, and the natural history of previous attacks in the individual patient. For some patients, rest may be all that is required to abort an occasional attack. Vagal maneuvers, including carotid sinus massage, the Valsalva and Müller maneuvers, gagging, and occasionally exposure of the face to ice water, serve as the first line of therapy. These maneuvers can slow the tachycardia rate slightly, which may then speed up to the original rate after cessation of the attempt, or can terminate it. If vagal maneuvers fail, adenosine, 6 to 12 mg administered rapidly intravenously, is the initial drug of choice and successfully terminates (within 1 minute) the tachycardia in about 90% of cases (**see Chapter 36**). Verapamil, 5 to 10 mg intravenously, or diltiazem, 0.25 to 0.35 mg/kg intravenously, terminates AV nodal reentry successfully in about 2 minutes in approximately 90% of cases when simple vagal maneuvers and adenosine fail. Beta receptor blockers can be effective but are not generally used as first-line therapy because adenosine, verapamil, and diltiazem are more effective and faster acting. Calcium antagonists, beta adrenoceptor blockers, and adenosine normally depress conduction in the anterogradely conducting slow AV nodal pathway, whereas class IA and IC drugs (not usually required) depress conduction in the retrogradely conducting fast pathway (**Table 37.4**). DC cardioversion should generally be attempted before use of these latter agents, which are more often administered to prevent recurrence.

TABLE 37.4

Drugs That Slow Conduction in and Prolong Refractoriness of the Accessory Pathway and Atrioventricular Node

AFFECTED TISSUE	DRUGS
Accessory pathway	Class IA
AV node	Class II
	Class IV
	Adenosine
	Digitalis
Both	Class IC
	Class III (amiodarone)

Rarely, if AVNRT results in hemodynamic compromise and is refractory to adenosine, DC cardioversion may be indicated. DC shock in patients who have received excessive amounts of digitalis can be dangerous and can result in serious postshock ventricular arrhythmias (**see Chapter 36**). DC shock, synchronized to the QRS complex to avoid precipitation of ventricular fibrillation (VF), successfully terminates AV nodal reentry with energy in the range of 10 to 50 J; higher energy may be required in some cases. If DC shock is contraindicated or if pacing wires are already in place (postoperatively, or if the patient has a permanent pacemaker), competitive atrial or ventricular pacing can restore sinus rhythm.

Pressor drugs can terminate AV nodal reentry by inducing reflex vagal stimulation mediated by baroreceptors in the carotid sinus and aorta when systolic blood pressure is acutely elevated to levels of

approximately 180 mm Hg. Pressors are rarely needed, however, unless the patient is also hypotensive.

Prevention of Recurrences.

Initially, the clinician must decide whether the frequency and severity of the attacks warrant long-term therapy. If the attacks are infrequent, well tolerated, and short and either terminate spontaneously or are easily terminated by the patient, no prophylactic therapy may be necessary. Longer and more frequent attacks can be treated with drugs, although ablation is an effective first-line alternative. In patients with syncope or near-syncope, ablation should be considered as first-line therapy. A long-acting calcium antagonist or a long-acting beta adrenoceptor blocker is a reasonable initial choice for drug therapy. The clinical situation and potential contraindications, such as beta blockers in an asthmatic patient, usually dictate the selection.

Radiofrequency Ablation.

RF ablation achieves long-term cure in more than 95%, with a low incidence of complications, and should be considered early in the management of patients with symptomatic recurrent episodes of AV nodal reentry, especially for patients who do not want to take drugs, who are drug intolerant, or in whom drugs are ineffective.

Accessory Atrioventricular Pathways

Accessory pathways are fibers that connect the atrium or AV node to the ventricle outside the normal AV nodal–His-Purkinje conduction system. These pathways can conduct impulses in the forward (anterograde from the atrium to the ventricle) or reverse (retrograde from the ventricle to the atrium) direction and are potential substrates for reentrant tachycardias (AV reciprocating tachycardia).[13] When the pathway is capable of anterograde conduction, the ventricle can be depolarized in part by the accessory pathway (outside the normal His-Purkinje system) and produces a QRS complex that is preexcited (i.e., with a delta wave; see later). When ventricular preexcitation is present and the symptoms are compatible with tachycardia, the patient is said to have WPW *syndrome*. In some cases the pathways are able to conduct only in the retrograde direction; thus they do not produce any ventricular preexcitation and are said to be "concealed."

Reentry Over a Concealed (Retrograde-Only) Accessory Pathway

Electrocardiographic Recognition

The presence of an accessory pathway that conducts unidirectionally from the ventricle to the atrium but not in the reverse direction is not apparent by analysis of the ECG during sinus rhythm because the ventricle is not preexcited (**Fig. 37.12**). Therefore, electrocardiographic manifestations of WPW syndrome are absent, and the accessory pathway is "concealed." Because the mechanism responsible for most ATs in patients with WPW syndrome is macroreentry caused by anterograde conduction over the AV node–His bundle pathway and retrograde conduction over an accessory pathway, the accessory pathway, even if it conducts only retrogradely, can still participate in the reentrant circuit and cause an AV reciprocating tachycardia. On electrocardiographic examination, a tachycardia resulting from this mechanism can be suspected when the QRS complex is normal and the retrograde P wave occurs after completion of the QRS complex, in the ST segment, or early in the T wave (**see Fig. 37.8C**). Sometimes the P wave is not clearly visible and can result in depression of the ST segment; when this is seen during

AT, the mechanism of the arrhythmia is most often reentry involving an accessory pathway (AV reentrant tachycardia). In addition, in this setting the ST depression that occurs only during the AT (resolves with termination of the tachycardia) does not indicate ischemia in the absence of other evidence of ischemia (chest pain, enzyme elevation, known coronary disease).

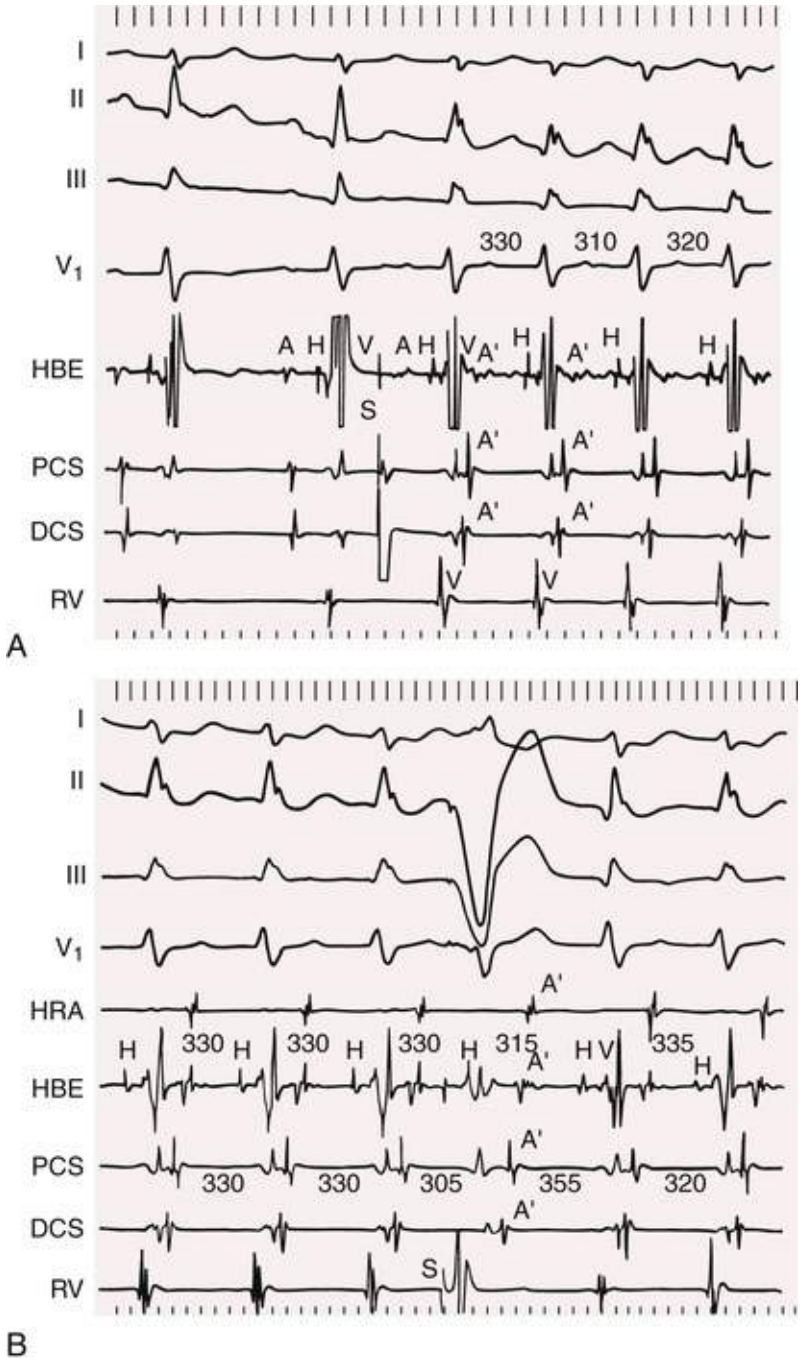


FIGURE 37.12 Atrial preexcitation during AV reciprocating tachycardia in a patient with a concealed accessory pathway. No evidence of accessory pathway conduction is present in the two sinus-initiated beats shown in **A.** A premature stimulus in the coronary sinus (*S*) precipitates SVT at a cycle length of approximately 330 milliseconds. The retrograde atrial activation sequence begins first in the distal coronary sinus (A′, DCS), followed by activation recorded in the proximal coronary sinus (PCS), low right atrium (HBE), and then the high right atrium (not shown). The QRS complex is normal and identical to the sinus-initiated QRS complex. (The terminal portion is slightly deformed by superimposition of the retrograde atrial recording.) Note that the RP interval is short and the PR interval is long. The shortest VA interval exceeds 65 milliseconds, consistent with conduction over a retrogradely conducting AV pathway. **B,** Premature ventricular stimulation at a time when the His bundle is still refractory from anterograde activation during tachycardia shortens the A-A interval from 330 to 305 milliseconds without a change in the retrograde atrial activation sequence. (Note that no change occurs in the H-H interval when the RV stimulus [*S*] is delivered. H-H intervals are in milliseconds in the HBE lead.) Thus the ventricular stimulus, despite His bundle refractoriness, still reaches the atrium and produces an identical retrograde atrial activation sequence. The only way that this finding can be explained is by conduction over a retrogradely conducting accessory pathway. Therefore the patient has a concealed accessory pathway with WPW syndrome. *HRA,* High right atrium; *RV,* right ventricle.

The P wave follows the QRS complex during tachycardia because the ventricle must be activated before the propagating impulse can enter the accessory pathway and excite the atria retrogradely.

Therefore the retrograde P wave must occur after ventricular excitation, in contrast to AV nodal reentry, in which the atria are usually excited during ventricular activation (**see Fig. 37.8A**). Also, the contour of the retrograde P wave can differ from that of the usual retrograde P wave because the atria may be activated eccentrically, that is, in a manner other than the normal retrograde activation sequence, which starts at the low right atrial septum, as in AV nodal reentry. This eccentric activation occurs because the concealed accessory pathway in most cases is left sided (i.e., inserts into the left atrium), which makes the left atrium the first site of retrograde atrial activation and causes the retrograde P wave to be negative in lead I (**see Fig. 37.12**).

Finally, because the tachycardia circuit involves the ventricles, if a functional BBB occurs in the same ventricle in which the accessory pathway is located, the VA interval and cycle length of the tachycardia can become longer (**Fig. 37.13**). This important change ensues because the BBB lengthens the reentrant circuit. For example, the normal activation sequence for a reciprocating tachycardia circuit with a left-sided accessory pathway but without a functional BBB progresses from the atrium to the AV node–His bundle, to the right and left ventricles, to the accessory pathway, and then to the atrium. However, during a functional LBBB, the tachycardia circuit travels from the atrium to the AV node–His bundle, to the right ventricle, to the septum, to the left ventricle, to the accessory pathway, and then back to the atrium. This increase in the VA interval provides definitive proof that the ventricle and accessory pathway are part of the reentry circuit. The additional time required for the impulse to travel across the septum from the right to the left ventricle before reaching the accessory pathway and atrium lengthens the VA interval, which consequently lengthens the cycle of the tachycardia by an equal amount, assuming that no other changes in conduction times occur within the circuit. Thus, lengthening of the tachycardia cycle by more than 30 milliseconds during an ipsilateral functional BBB is diagnostic of a free wall accessory pathway if the lengthening can be shown to be caused by VA prolongation only and not by prolongation of the H-V interval (which can develop with the appearance of a BBB). In an occasional patient, the increase in cycle length because of prolongation of VA conduction can be nullified by a simultaneous decrease in the PR (A-H) interval.

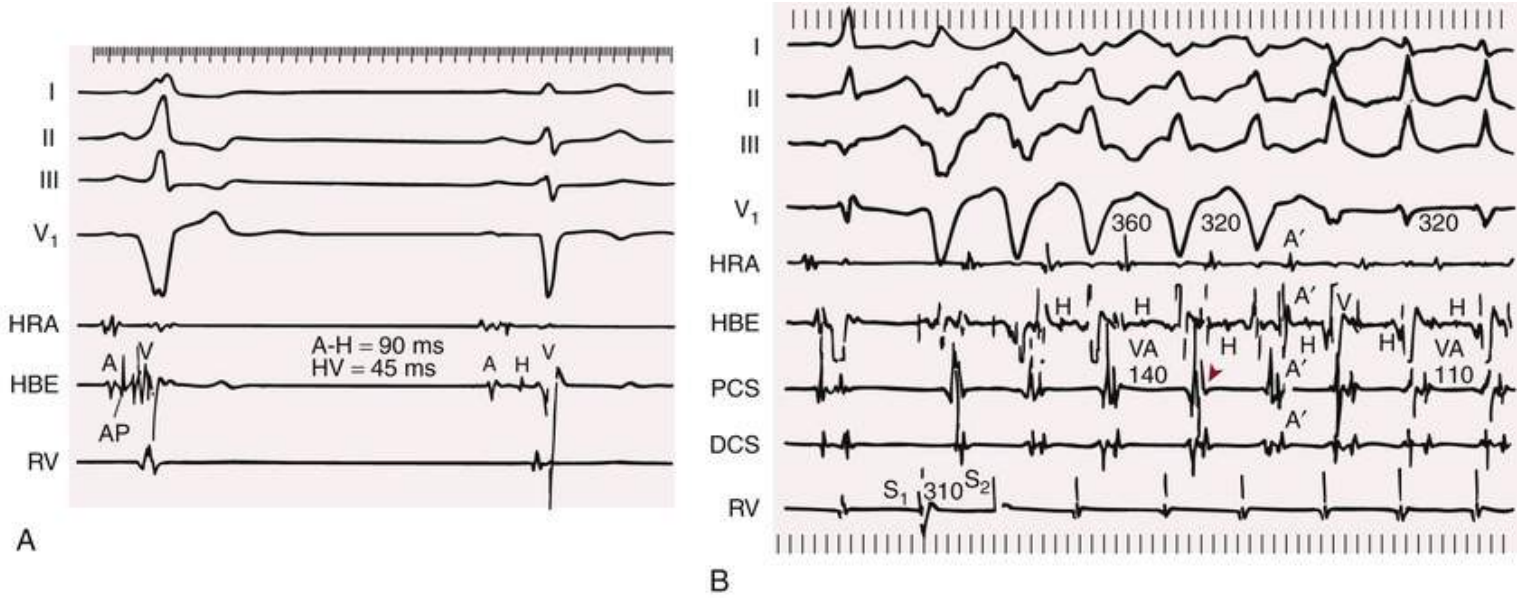


FIGURE 37.13 **A,** Recording of depolarization of an accessory pathway (*AP*) with a catheter electrode. The first QRS complex illustrates conduction over the AP. On the scalar ECG, a short PR interval and delta wave (best seen in leads I and V_1) are apparent. His bundle activation is buried within the ventricular complex. In the following complex, conduction has been blocked over the AP, and a normal QRS complex results. His bundle activation clearly precedes the onset of ventricular depolarization by 45 milliseconds. The A-H interval for this complex is 90 milliseconds. **B,** Influence of a functional ipsilateral bundle branch block on the VA interval during AV reciprocating tachycardia. Partial preexcitation can be noted in the sinus-initiated complex (first complex). Two premature ventricular stimuli (S_1, S_2) initiate a sustained SVT that persists with a left bundle branch block for several complexes before finally reverting to normal. The retrograde atrial activation sequence is recorded first in the proximal coronary sinus lead (*arrowhead,* PCS), then in the distal coronary sinus lead (DCS) and low right atrium (HBE), and then high in the right atrium (HRA). During the functional bundle branch block, the VA interval in the PCS lead is 140 milliseconds, which shortens to 110 milliseconds when the QRS complex reverts to normal. Such behavior is characteristic of a left-sided accessory pathway with prolongation of the reentrant pathway by the functional left bundle branch block. (***A,*** From Prystowsky EN, Browne KF, Zipes DP. Intracardiac recording by catheter electrode of accessory pathway depolarization. J Am Coll Cardiol 1983;1:468.)

The presence of an ipsilateral BBB can facilitate reentry and cause an incessant AV reentrant tachycardia. A functional BBB in the ventricle contralateral to the accessory pathway does not lengthen the tachycardia cycle if the H-V interval does not lengthen.

Septal Accessory Pathway

An exception to these observations occurs in patients with a concealed septal accessory pathway. First, retrograde atrial activation is normal (concentric) because it occurs retrogradely up the septum. Second, the VA interval and cycle length of the tachycardia increase 25 milliseconds or less with the development of an ipsilateral functional BBB.

Vagal maneuvers, by acting predominantly on the AV node, produce a response on AV reentry similar to AV nodal reentry, and the tachycardia can transiently slow and sometimes terminate. In general, termination occurs in the anterograde direction, so the last retrograde P wave fails to conduct to the ventricle.

Electrophysiologic Features

Electrophysiologic criteria supporting the diagnosis of tachycardia involving reentry over a concealed accessory pathway include the fact that initiation of tachycardia depends on a critical degree of AV delay (necessary to allow time for the accessory pathway to recover excitability so that it can conduct

retrogradely), but the delay can be in the AV node or His-Purkinje system; that is, a critical degree of A-H delay is not necessary (as it is in AV nodal reentry). On occasion, a tachycardia can start with little or no measurable lengthening of AV nodal or His-Purkinje conduction time. The AV nodal refractory period curve is smooth, in contrast to the discontinuous curve found in many patients with AV nodal reentry. Dual AV nodal pathways can occasionally be noted as a concomitant but unrelated finding.

Diagnosis of Accessory Pathways

Diagnosis can be made by demonstrating that during ventricular pacing, premature ventricular stimulation activates the atria before retrograde depolarization of the His bundle, thus indicating that the impulse reached the atria before it depolarized the His bundle and therefore must have traveled a different pathway. Also, if the ventricles can be stimulated prematurely during tachycardia at a time when the His bundle is refractory, and the impulse still conducts to the atrium, the retrograde propagation traveled to the atrium over a pathway other than the bundle of His (**see Fig. 37.12B**). If the PVC depolarizes the atria without lengthening the VA interval and with the same retrograde atrial activation sequence, one assumes that the stimulation site (i.e., ventricle) is within the reentrant circuit, without intervening His-Purkinje or AV nodal tissue that might increase the VA interval and therefore the A-A interval. In addition, if a PVC delivered when the His bundle is refractory terminates the tachycardia without activating the atria retrogradely, it must have invaded and blocked conduction in an accessory pathway and is therefore diagnostic of an accessory pathway participating in the reentrant circuit.

The VA interval (a measurement of conduction over the accessory pathway) is generally constant over a wide range of ventricular-paced rates and coupling intervals of PVCs, as well as during the tachycardia in the absence of aberration. Similar short VA intervals can be observed in some patients during AV nodal reentry, but if the VA conduction time or RP interval is the same during tachycardia and ventricular pacing at comparable rates, an accessory pathway is almost certainly present. The VA interval is usually less than 50% of the R-R interval. The tachycardia can easily be initiated after premature ventricular stimulation that conducts retrogradely in the accessory pathway but blocks conduction in the AV node or His bundle. Atria and ventricles are required components of the macroreentrant circuit; therefore, continuation of the tachycardia in the presence of an AV or VA block excludes an accessory AV pathway as part of the reentrant circuit.

Clinical Features

Concealed accessory pathways are estimated to be present in approximately 30% of patients with apparent SVT referred for electrophysiologic evaluation. Most of these accessory pathways are located between the left ventricle and left atrium or in the posteroseptal area, less often between the right ventricle and right atrium. It is important to be aware of a concealed accessory pathway as a possible cause of apparently routine SVT because the therapeutic response may at times not follow the usual guidelines. Tachycardia rates tend to be somewhat faster than those occurring in AV nodal reentry (200 beats/min), but great overlap exists between the two groups.

Syncope can occur because the rapid ventricular rate fails to provide adequate cerebral circulation or because the tachyarrhythmia depresses the sinus pacemaker and causes a period of asystole when the tachyarrhythmia terminates. Physical examination reveals an unvarying, regular ventricular rhythm, with constant intensity of the first heart sound and blood pressure. Jugular venous pressure can be elevated (large A wave), but the waveform generally remains constant.

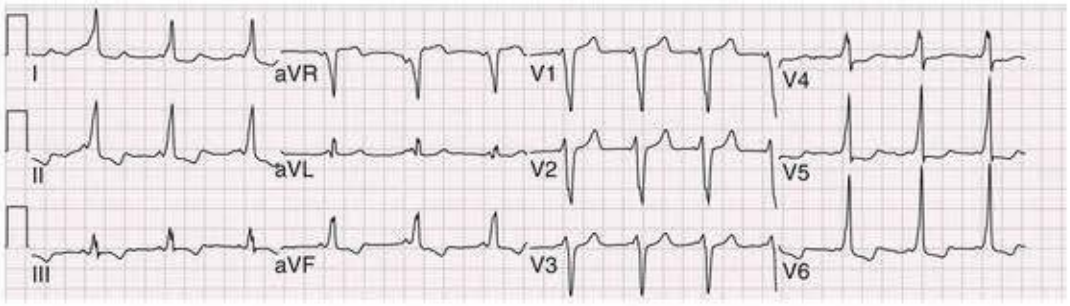
Management

The therapeutic approach to termination of this form of tachycardia acutely is as outlined for AV nodal reentry because the AV node is a critical part of the circuit here as well. It is necessary to achieve block of a single impulse from the atrium to the ventricle or from the ventricle to the atrium. In general, the most successful method is to produce a transient AV nodal block; therefore, vagal maneuvers and IV administration of adenosine, verapamil, or diltiazem and beta blockers are acceptable choices. RF catheter ablation and AADs that prolong the activation time or refractory period in the accessory pathway need to be considered for chronic prophylactic therapy, similar to that discussed for reciprocating tachycardias associated with preexcitation syndrome. RF catheter ablation is curative, has low risk, and should be considered early for symptomatic patients (**see Chapter 36**). The presence of AF in patients with a concealed accessory pathway should not be a greater therapeutic challenge than in patients who do not have such a pathway, because anterograde AV conduction occurs only over the AV node and not over an accessory pathway. IV administration of verapamil is not contraindicated. However, in some circumstances, such as catecholamine stimulation, anterograde conduction can occur in the apparently concealed accessory pathway.

Preexcitation Syndrome

Electrocardiographic Recognition

Preexcitation, or the WPW abnormality on the ECG, occurs when the atrial impulse activates the entire ventricle or some part of it, or the ventricular impulse activates the entire atrium or some part of it, earlier than would be expected if the impulse traveled only by way of the normal specialized conduction system (**Fig. 37.14**). This premature activation is caused by muscle connections of working myocardial fibers that exist outside the specialized conducting tissue and connect the atrium and ventricle while bypassing AV nodal conduction delay. Termed *accessory atrioventricular pathways* or *connections*, they are responsible for the most common variety of preexcitation. The term *syndrome* is attached to this disorder when tachyarrhythmias occur as a result of the accessory pathway. Three basic features typify the electrocardiographic abnormalities in patients with the usual form of WPW conduction caused by an AV connection: (1) PR interval less than 120 milliseconds during sinus rhythm; (2) QRS complex duration exceeding 120 milliseconds with a slurred, slowly rising onset of the QRS in some leads (delta wave) and usually a normal terminal QRS portion; and (3) secondary ST-T wave changes that are generally directed in an opposite direction to the major delta and QRS vectors. Analysis of the scalar ECG can be used to localize the accessory pathway (**see Fig. 37.14D**).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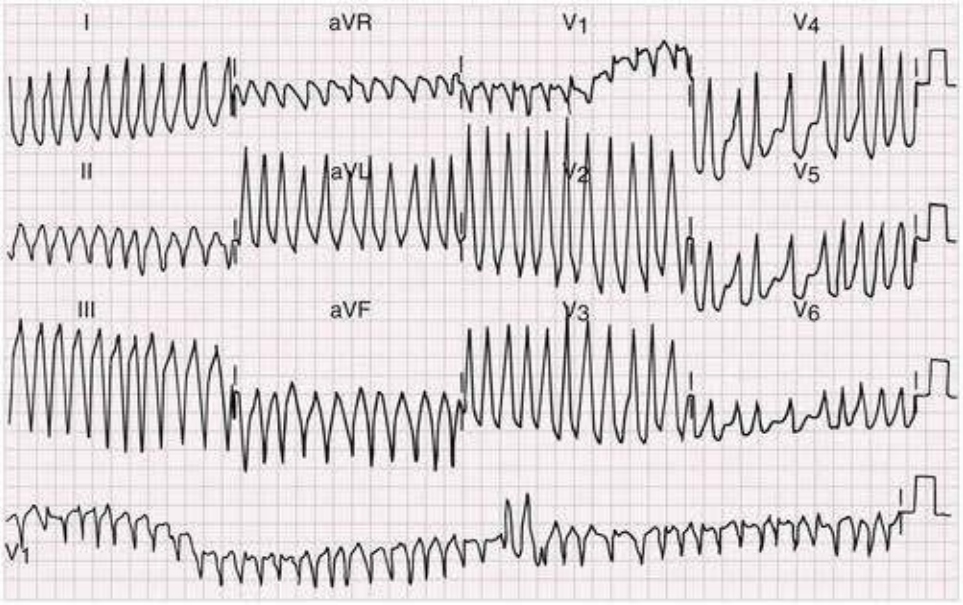
A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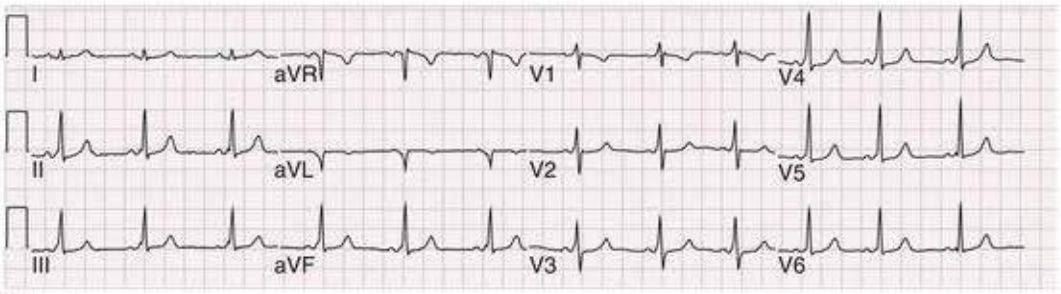
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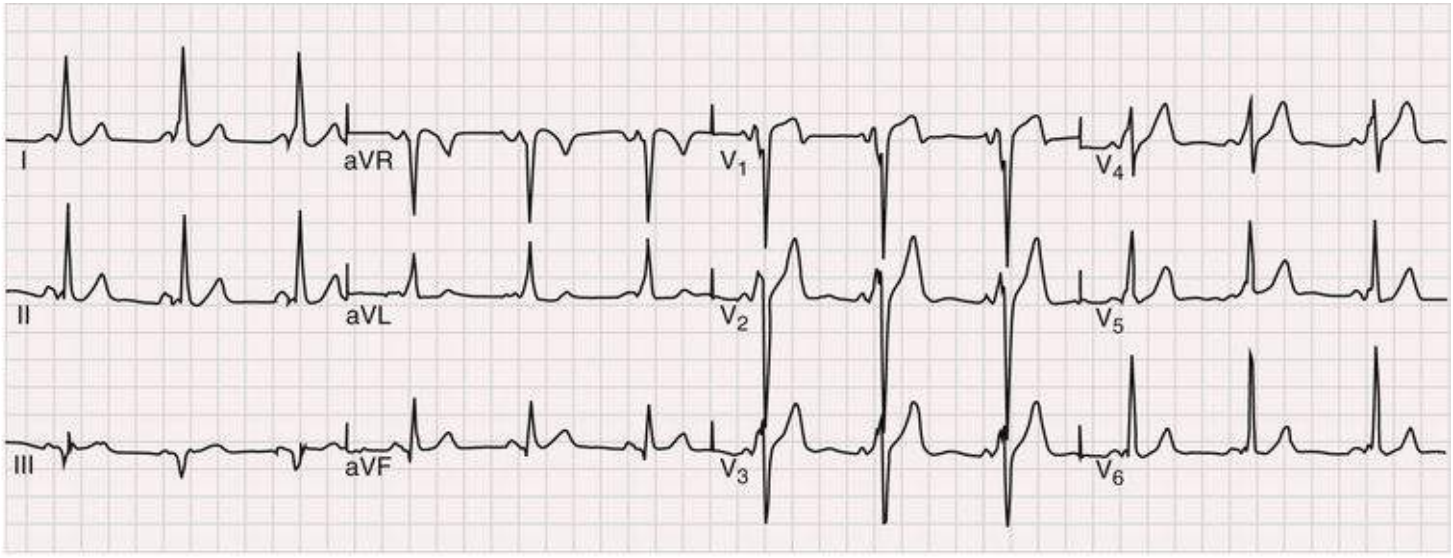

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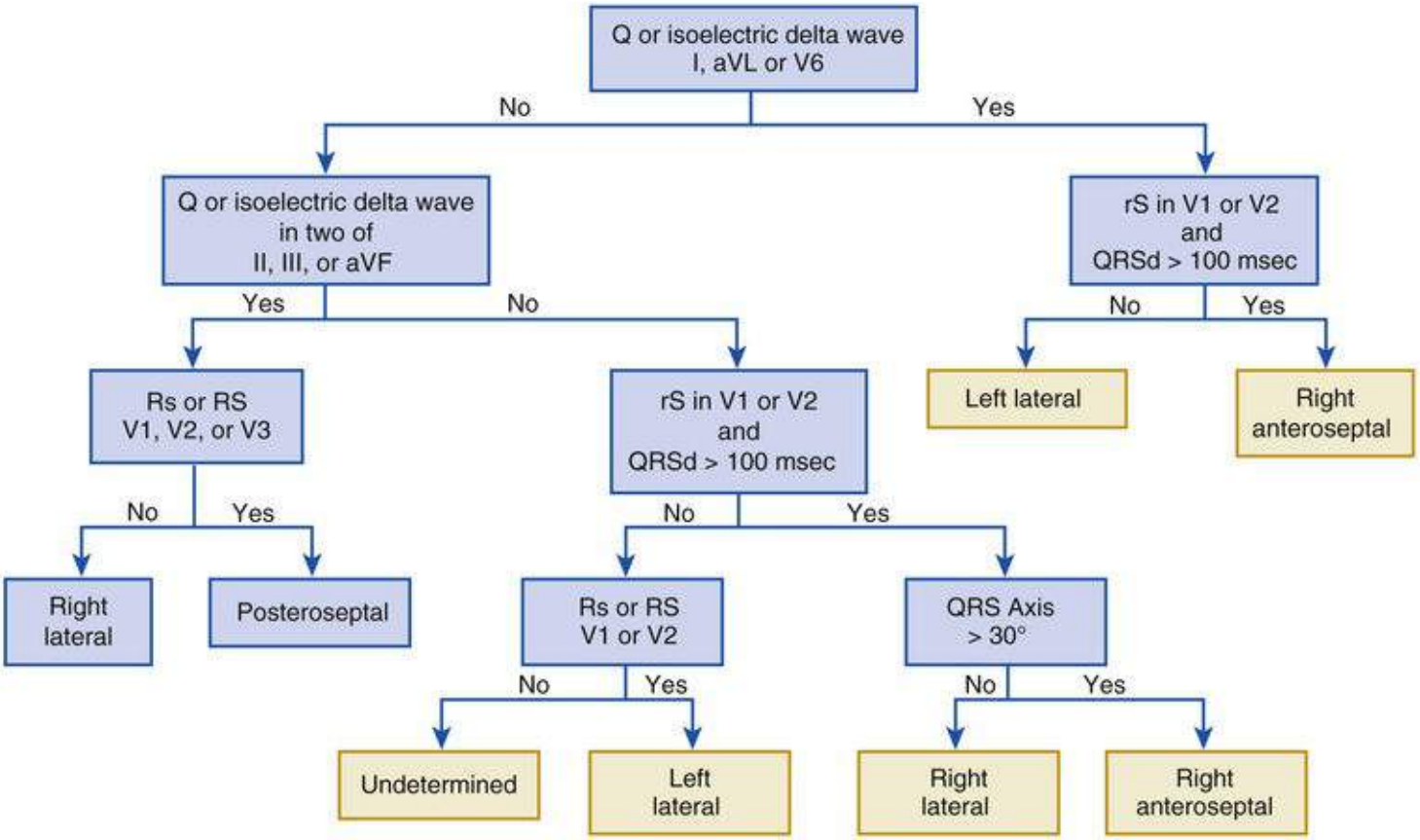


FIGURE 37.14 **A,** Right anteroseptal accessory pathway. The 12-lead ECG characteristically exhibits a normal to inferior axis. The delta wave is upright in leads I, II, and aVF; isoelectric or negative in aVL; and negative in aVR. There is an rS in V_1 and V_2. **B,** Right posteroseptal accessory pathway. Negative delta waves in leads II, III, and aVF, upright in I and aVL, localize this pathway to the posteroseptal region. The negative delta wave in V_1 with sharp transition to an upright delta wave in V_2 pinpoints it to the right posteroseptal area. Atrial fibrillation is present. **C,** Left lateral accessory pathway. A positive delta wave in the anterior precordial leads and in leads II, III, and aVF, positive or isoelectric in leads I and aVL, and isoelectric or negative in leads V_5 and V_6 are typical of a left lateral accessory pathway. Also notice the relatively small amount of preexcitation typical of left lateral accessory pathways during sinus rhythm, which is caused by the sinus impulse taking longer to travel through the entire right and left atria to the accessory pathway than it does from the sinus node to the AV node. **D,** Right free wall accessory pathway. The predominantly negative delta wave in V_1 and the axis more leftward than in **A** indicate the presence of a right free wall accessory pathway. **E,** Stepwise algorithm to determine the general location of accessory pathways on a 12-lead ECG with preexcitation. The algorithm assumes that some preexcitation is present and uses the delta wave polarity (determined as the first 20 msec after the onset of the delta wave on the ECG) and QRS morphology. *QRSd,* QRS duration. (**E,** From Fox DJ, Klein GJ, Skanes AC, et al. How to identify the location of an accessory pathway by the 12-lead ECG. Heart Rhythm 2008;5:1763.)

In WPW syndrome, the most common tachycardia is characterized by a normal QRS, a regular rhythm, ventricular rates of 150 to 250 beats/min (generally faster than AV nodal reentry), and sudden onset and termination, in most respects behaving like the tachycardia described for conduction over a concealed pathway (see earlier). The major difference between the two is the capacity for anterograde conduction over the accessory pathway during atrial flutter or AF (see later).

Variants.

Various other anatomic substrates exist and provide the basis for different electrocardiographic manifestations of several variations of preexcitation syndrome (**Table 37.5 and Fig. 37.15**). Fibers from the atrium to the His bundle bypassing the physiologic delay of the AV node are called *atriohisian tracts* (**Fig. 37.15B**) and are associated with a short PR interval and a normal QRS complex. Although demonstrated anatomically (see later), the electrophysiologic significance of these tracts in the genesis of tachycardias with a short PR interval and a normal QRS complex (so-called Lown-Ganong-Levine [LGL] syndrome) remains to be established. Indeed, evidence does not support the presence of a specific LGL syndrome consisting of a short PR interval, normal QRS complex, and tachycardias related to an atriohisian bypass tract.

TABLE 37.5

Accessory Pathway Variants

PATHWAY TYPE	PR	QRS	TACHYCARDIA	COMMENTS
Atriohisian	Short	Normal	Unlikely	
Atriofascicular	Normal	Preexcitation (LBBB, superior axis)	Antidromic AVRT	Preexcitation with fast atrial rates or atrial extrastimuli
Nodofascicular	Normal	Preexcitation (LBBB, superior axis)	Antidromic AVRT; AVNRT with bystander activation of the AP	Preexcitation with fast atrial rates or atrial extrastimuli
Fasciculoventricular	Normal	Anomalous (short H-V interval)	None	

AP, Accessory pathway; *AVRT,* atrioventricular reentrant (reciprocating) tachycardia; *AVNRT;* AV nodal reentrant (reciprocating) tachycardia; *LBBB,* left bundle branch block.

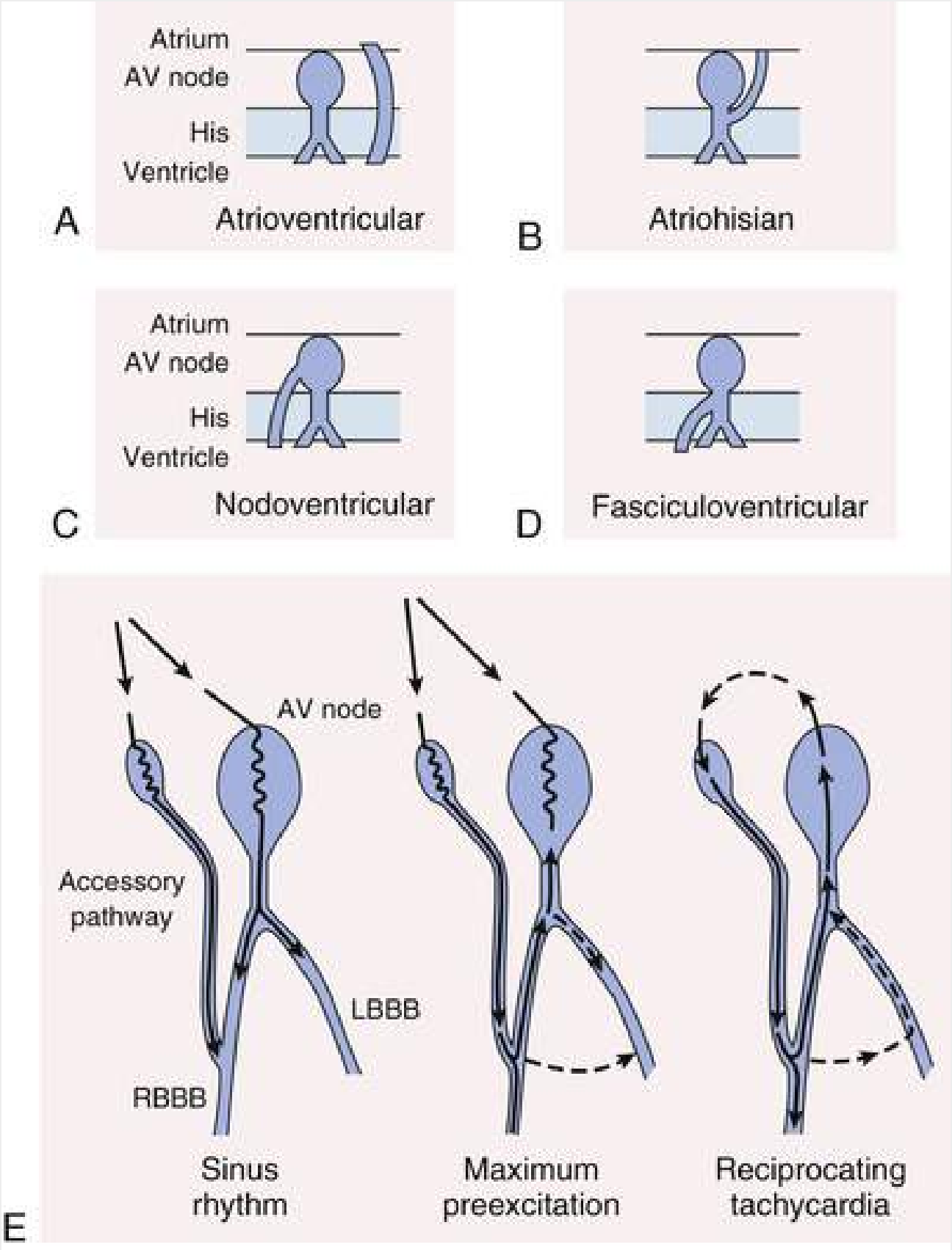


FIGURE 37.15 Schematic representation of accessory pathways. **A,** The "usual" AV accessory pathway giving rise to most clinical manifestations of tachycardia associated with WPW syndrome. **B,** The very uncommon atriohisian accessory pathway. If LGL syndrome is present, it would have this type of anatomy, which has been demonstrated histopathologically on occasion. **C,** Nodoventricular pathways, original concept, in which anterograde conduction travels down the accessory pathway with retrograde conduction in the bundle branch–His bundle–AV node (see later). **D,** Fasciculoventricular connections, which are not thought to play an important role in the genesis of tachycardias. **E,** Current concept of the nodofascicular accessory pathway, in which the accessory pathway is an AV communication with AV node–like properties. Sinus rhythm results in a fusion QRS complex, as in the usual form of WPW syndrome shown in **A.** Maximum preexcitation results in ventricular activation over the accessory pathway, and the His bundle is activated retrogradely. During reciprocating tachycardia, anterograde conduction occurs over the

accessory pathway and retrograde conduction over the normal pathway. *LBBB,* Left bundle branch block; *RBBB,* right bundle branch block. (**E,** From Benditt DG, Milstein S. Nodoventricular accessory connection: a misnomer or a structural/functional spectrum? J Cardiovasc Electrophysiol 1990;1:231.)

Another variant of accessory pathway conduction is that caused by atriofascicular or nodofascicular accessory pathways. These fibers result in a unique AV conduction pattern, sometimes referred to as Mahaim conduction, characterized by the development of ventricular preexcitation (widened QRS and short H-V interval) with a progressive increase in the AV interval in response to atrial overdrive pacing, unlike the behavior of the usual accessory pathway in which preexcitation occurs with short AV intervals (**Fig. 37.16**). Because the accessory pathways responsible for this conduction pattern usually insert into the right bundle branch, preexcitation generally results in an LBBB pattern. This phenomenon can be caused by fibers passing from the AV node to the ventricle, called *nodoventricular fibers* (or *nodofascicular* if the insertion is into the right bundle branch rather than into ventricular muscle; **see Fig. 37.15C**). For nodoventricular connections, the PR interval can be normal or short, and the QRS complex is a fusion beat. This pattern of preexcitation can also result from atriofascicular accessory pathways. These fibers almost always represent a duplication of the AV node and the distal conducting system and are located in the right ventricular free wall. The apical end lies close to the lateral tricuspid annulus and conducts slowly, with AV node–like properties. After a long course, the distal portion of these fibers, which conducts rapidly, inserts into the distal right bundle branch or the apical region of the right ventricle. No preexcitation is generally apparent during sinus rhythm, but it can be exposed by premature or rapid right atrial stimulation. The usual absence of retrograde conduction in these pathways produces only an antidromic AV reentry tachycardia (“preexcited” tachycardia) characterized by anterograde conduction over the accessory pathway and retrograde conduction over the right bundle branch–His bundle–AV node, thus making the atrium a necessary part of the circuit. The preexcited tachycardia has an LBBB pattern, long AV interval (because of the long conduction time over the accessory pathway), and short VA interval. An RBBB can be proarrhythmic by increasing the length of the tachycardia circuit (VA interval is prolonged because of a delay in retrograde activation of His bundle), and the tachycardia can become incessant.

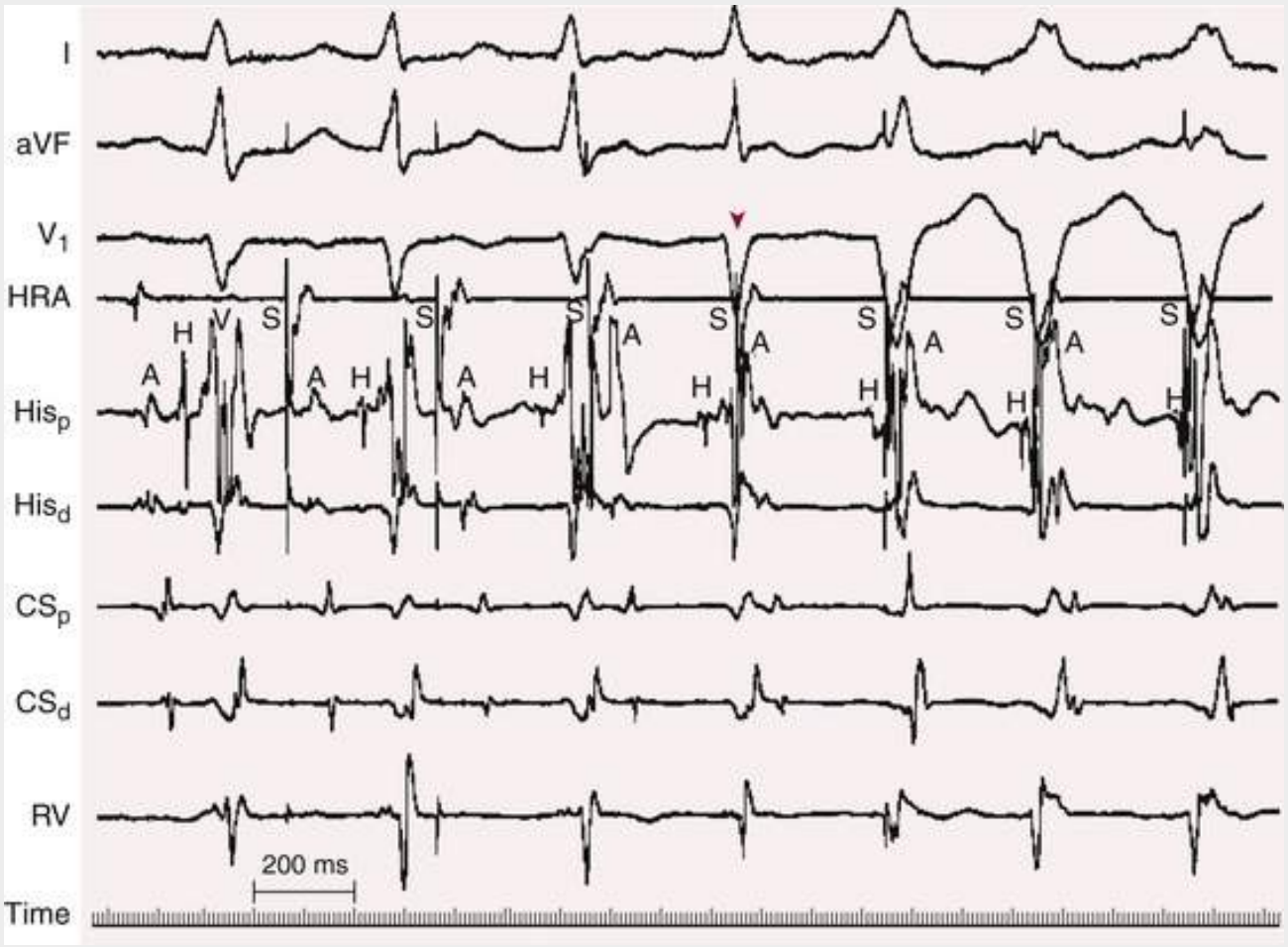


FIGURE 37.16 Development of preexcitation over an atriofascicular accessory pathway. During atrial pacing (*S*) on the left side of the figure, conduction occurs down the AV node, as evidenced by a normal-appearing QRS complex and a normal H-V interval. The stimulus marked by the *arrowhead* conducts the impulse down an atriofascicular fiber, which results in a preexcited QRS, as evidenced by a widened QRS and short H-V interval. *CS,* Coronary sinus; *HRA,* high right atrium; *RV,* right ventricle.

In patients with an atriohisian tract, the QRS complex would theoretically remain normal and the short A-H interval would be fixed or would show negligible increase during atrial pacing at more rapid rates. This response is uncommon. Rapid atrial pacing in patients who have nodoventricular or nodofascicular connections shortens the H-V interval and widens the QRS complex, with production of an LBBB contour, but in contrast to the situation in patients who have an AV connection (**Fig. 37.17**), the AV interval also lengthens. In patients with fasciculoventricular connections, the H-V interval remains short and the QRS complex unchanged and anomalous during rapid atrial pacing.

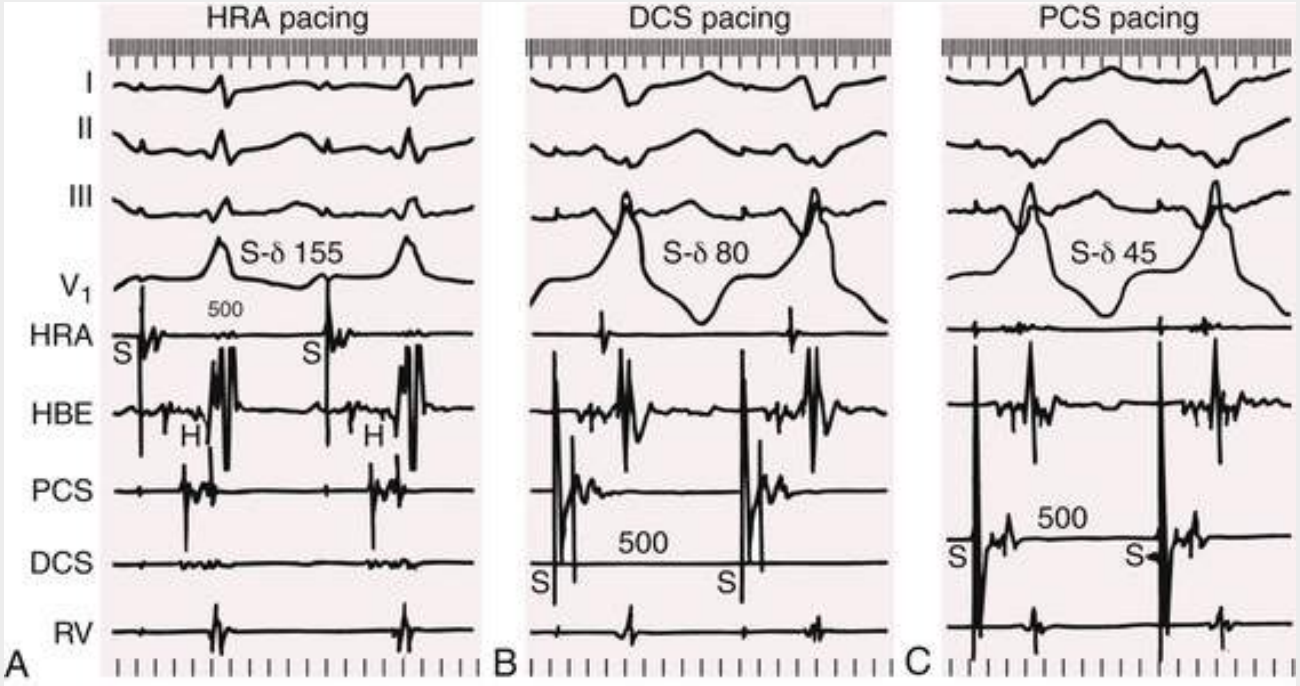
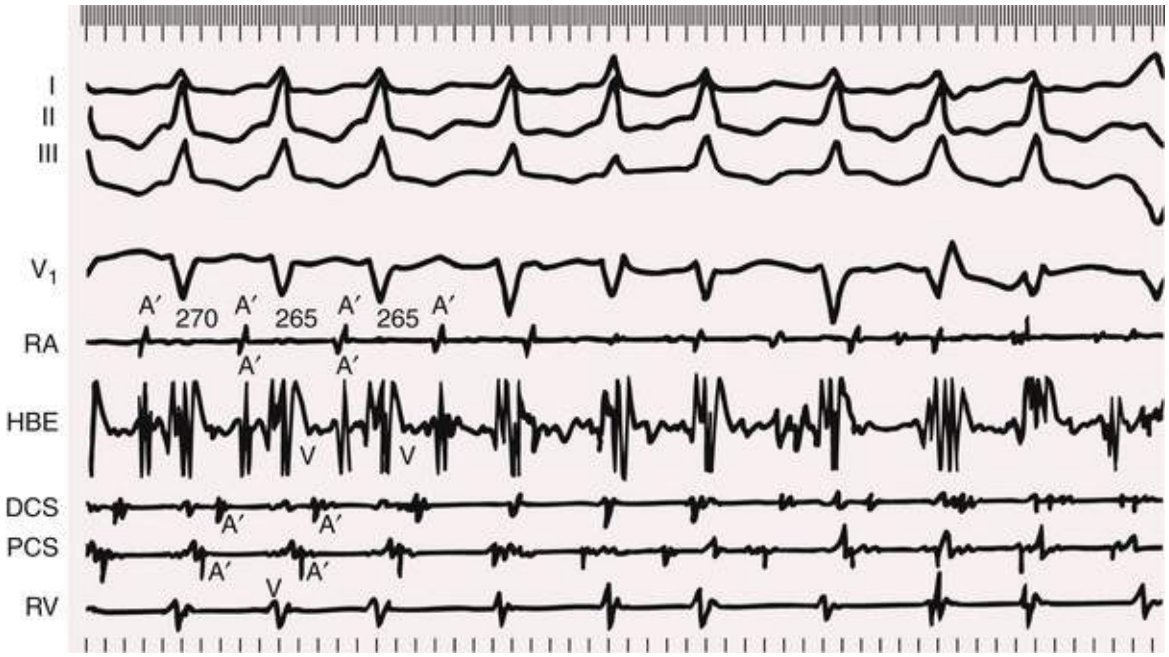


FIGURE 37.17 Atrial pacing at different atrial sites illustrating different conduction over the accessory pathway. **A,** High right atrial (HRA) pacing at a cycle length of 500 milliseconds produces anomalous activation of the ventricle (note the upright QRS complex in V_1) and a stimulus-delta interval of 155 milliseconds (*S-δ 155*). This interval indicates that the time from the onset of the stimulus to the beginning of the QRS complex is relatively long because the stimulus is delivered at a fairly large distance from the accessory pathway. Note that His bundle activation (*H*) occurs at about the onset of the QRS complex. **B,** Atrial pacing occurs through the distal coronary sinus electrode (DCS). At the same pacing cycle length, DCS pacing results in more anomalous ventricular activation and a shorter stimulus-delta interval (80 msec). His bundle activation is now buried within the inscription of the ventricular electrogram in the low right atrium (His bundle electrogram [HBE] lead). **C,** Pacing from the proximal coronary sinus electrode (PCS) results in the shortest stimulus-delta interval (45 msec); such an interval indicates that the pacing stimulus is being delivered very close to the atrial insertion of the accessory pathway, which in this case is located in the left posteroseptal region of the AV groove. *RV,* Right ventricle.

Electrophysiologic Features of Preexcitation

If the accessory pathway is capable of anterograde conduction, two parallel routes of AV conduction are possible, one subject to physiologic delay over the AV node and the other passing directly without delay from the atrium to the ventricle (**see Figs. 37.13 and 37.15 through 37.22; eFig. 37.3**). This direct route of conduction produces the typical QRS complex, which is a fusion beat as a result of depolarization of the ventricle, in part by the wavefront traveling over the accessory pathway and in part by the wavefront traveling over the normal AV node–His bundle route. The delta wave represents ventricular activation from input over the accessory pathway. The extent of the contribution to ventricular depolarization by the wavefronts over each route depends on their relative activation times. If AV nodal conduction delay occurs because of a rapid atrial pacing rate or a PAC, for example, more of the ventricle becomes activated over the accessory pathway and the QRS complex becomes more anomalous in contour. Total activation of the ventricle over the accessory pathway can occur if the AV nodal conduction delay is sufficiently long. In contrast, if the accessory pathway is relatively far from the sinus node (e.g., a left lateral accessory pathway), or if the AV nodal conduction time is relatively short, more of the ventricle can be activated by conduction over the normal pathway (**see Fig. 37.17**). The normal fusion beat during sinus rhythm has a short H-V interval, or His bundle activation actually begins after the onset of ventricular depolarization because part of the atrial impulse bypasses the AV node and activates the ventricle early, at a time when the atrial impulse traveling the normal route just reaches the His bundle.

This finding of a short or negative H-V interval occurs only during conduction over an accessory pathway or from retrograde His activation during a complex originating in the ventricle, such as VT.



EFIGURE 37.3 Atrioventricular reciprocating tachycardia (AVRT) disorganizing into atrial fibrillation (AF). During sustained AVRT at a cycle length of approximately 265 milliseconds, the retrograde atrial activation sequence began first in the right paraseptal region (not shown in this example; location proved at surgery) and was then recorded in the proximal coronary sinus (*PCS*) electrogram, followed by atrial activity in the distal coronary sinus (*DCS*), in the low right atrium recorded in the His bundle lead, and then in the high right atrium. Spontaneously, the atrial activation sequence becomes irregular (after the last A′) and AF begins. Note that the last QRS complex reflects conduction over the accessory pathway. Such a transformation occurred repeatedly in this patient and was associated with quickening of the ventricular rate. AF did not recur after surgical interruption of the accessory pathway. *HBE,* His bundle electrogram; *RA,* right atrium; *RV,* right ventricle.

Pacing the atrium at rapid rates, at premature intervals, or from a site close to the atrial insertion of the accessory pathway accentuates the anomalous activation of the ventricles and shortens the H-V interval even more (His activation may become buried in the ventricular electrogram, as shown in **Fig. 37.17B**). The position of the accessory pathway can be determined by careful analysis of the spatial direction of the delta wave on the 12-lead ECG in maximally preexcited beats (**see Fig. 37.14**). T wave abnormalities can occur after the disappearance of preexcitation, with orientation of the T wave according to the site of preexcitation (T wave memory).

Accessory Pathway Conduction

Even though the accessory pathway conducts more rapidly than the AV node (conduction velocity is faster in the accessory pathway), the accessory pathway usually has a longer refractory period during long cycle lengths (e.g., sinus rhythm); that is, it takes longer for the accessory pathway than the AV node to recover excitability. Consequently, a PAC can occur sufficiently early to block conduction anterogradely in the accessory pathway and conduct to the ventricle only over the normal AV node–His bundle (**Fig. 37.18A, B**). The resultant H-V interval and QRS complex become normal. Such an event can initiate the most common type of reciprocating tachycardia, one characterized by anterograde conduction over the normal pathway and retrograde conduction over the accessory pathway (*orthodromic* AV reciprocating tachycardia). The accessory pathway, which blocks conduction in an anterograde direction, recovers

excitability in time to be activated after the QRS complex in a retrograde direction, thereby completing the reentrant loop.

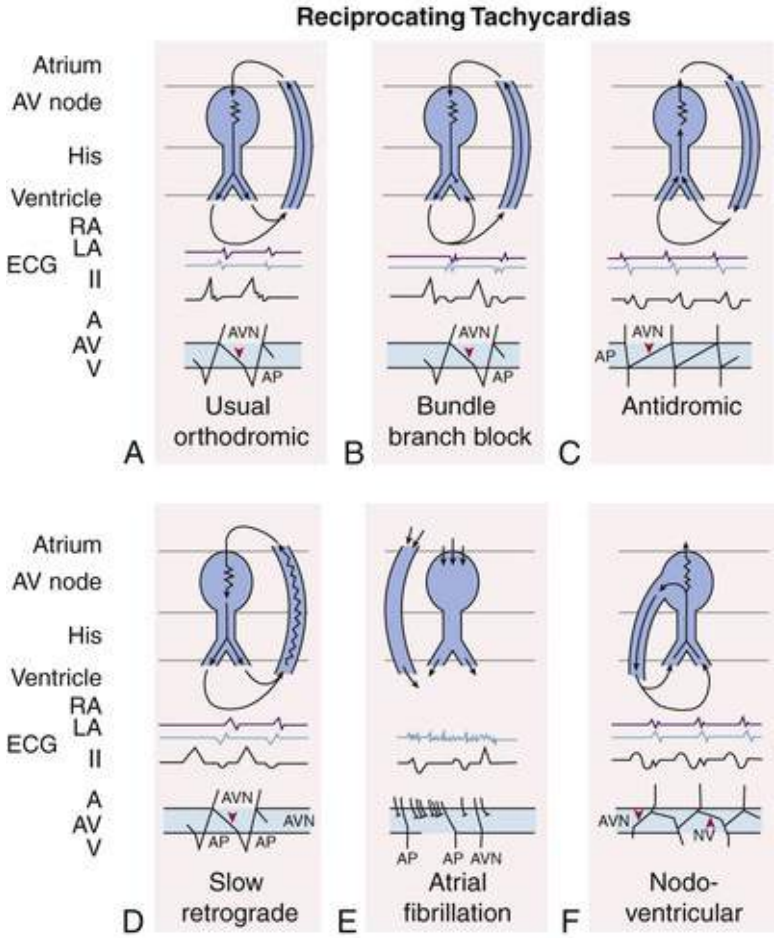


FIGURE 37.18 Schematic diagram of tachycardias associated with accessory pathways. **A,** Orthodromic tachycardia with anterograde conduction (*arrowhead*) over the AV node–His bundle route and retrograde conduction over the accessory pathway (left sided for this example, as depicted by left atrial activation preceding right atrial activation). **B,** Orthodromic tachycardia and ipsilateral functional bundle branch block. **C,** Antidromic tachycardia with anterograde conduction over the accessory pathway and retrograde conduction (*arrowhead*) over the AV node–His bundle. **D,** Orthodromic tachycardia with a slowly conducting accessory pathway (*arrowhead*). **E,** Atrial fibrillation with the accessory pathway as a bystander. **F,** Anterograde conduction over a portion of the AV node and a nodoventricular (*NV*) pathway and retrograde conduction over the AV node (*arrowheads*). *AP,* Accessory pathway; *AVN,* atrioventricular node; *LA,* left atrium; *RA,* right atrium.

Much less often, patients can have tachycardias called *antidromic* tachycardias, during which anterograde conduction occurs over the accessory pathway and retrograde conduction over the AV node. The resultant QRS complex is abnormal because of total ventricular activation over the accessory pathway (**Fig. 37.18C and Fig. 37.19**). In both tachycardias the accessory pathway is an obligatory part of the reentrant circuit.

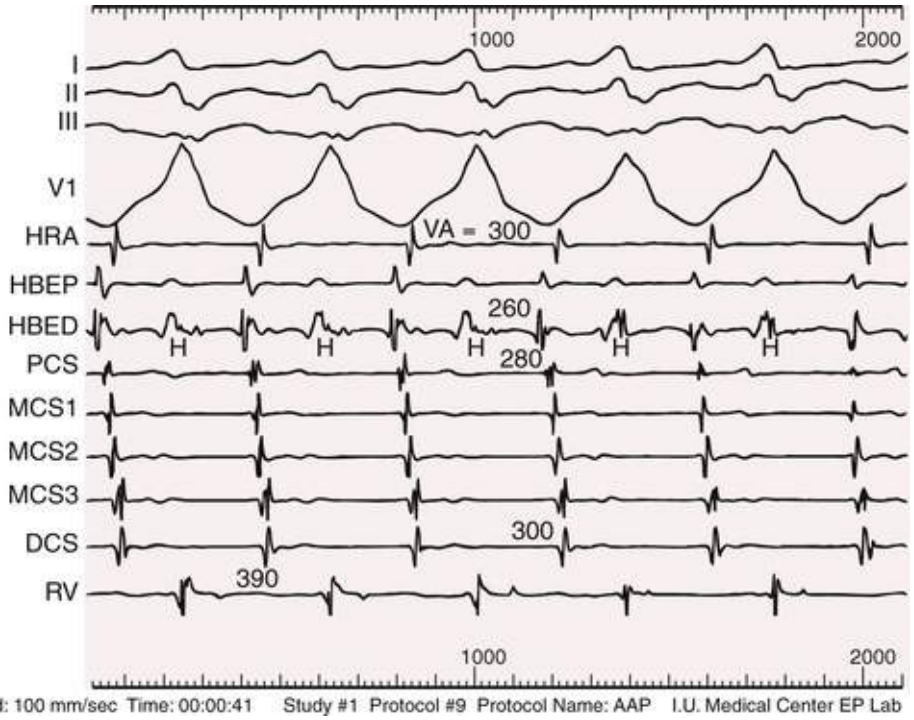


FIGURE 37.19 Antidromic AV reciprocating tachycardia. The tachycardia in this example is caused by anterograde conduction over the accessory pathway (note the abnormal QRS complex of a left posterior accessory pathway) and a normal retrograde atrial activation sequence (beginning first in the HBED lead), which is caused by retrograde conduction over the AV node. The tachycardia cycle length is 390 milliseconds, with a VA interval of 300 milliseconds measured in the high right atrial lead, 260 milliseconds in the distal His lead, and 280 milliseconds in the proximal coronary sinus lead. I, II, III, and V_1 are scalar leads. *DCS,* Distal coronary sinus lead; *HBEP* and *HBED* leads, His bundle electrogram, proximal and distal; *HRA,* high right atrial electrogram; *MCS1* to *MCS3,* midcoronary sinus leads; *PCS,* proximal coronary sinus; *RV,* right ventricular electrogram.

A small percentage of patients have multiple accessory pathways, often suggested by various clues on the ECG, and on occasion, tachycardia can be caused by a reentrant loop conducting anterogradely over one accessory pathway and retrogradely over the other. From 15% to 20% of patients may exhibit AV nodal echoes or AV nodal reentry after interruption of the accessory pathway.

Permanent Form of Atrioventricular Junctional Reciprocating Tachycardia

An incessant form of SVT has been recognized that generally occurs with a long RP interval that exceeds the PR interval (**Figs. 37.20 and 37.21**). Usually, a posteroseptal accessory pathway (most often right ventricle but other locations as well) that conducts very slowly, possibly because of a long and tortuous route, appears to be responsible. Tachycardia is maintained by anterograde AV nodal conduction and retrograde conduction over the accessory pathway (**see Fig. 37.18D**). Although anterograde conduction over this pathway has been demonstrated, the long anterograde conduction time over the accessory pathway usually prevents the electrocardiographic manifestations of accessory pathway conduction during sinus rhythm. Therefore, during sinus rhythm, the QRS duration is prolonged from conduction over this accessory pathway only when conduction times through the AV node–His bundle exceed those in the accessory pathway.

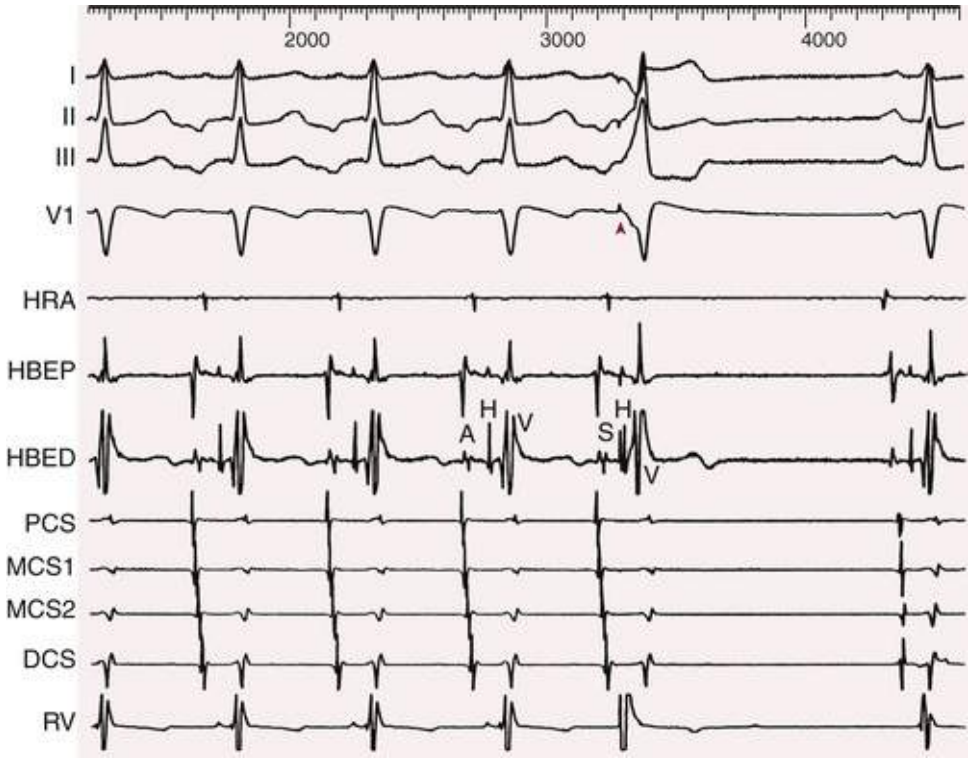


FIGURE 37.20 Termination of the permanent form of AV junctional reciprocating tachycardia (PJRT). In the left portion of this example, PJRT is present. The atrial activation sequence is indistinguishable from atypical AV nodal reentry and atrial tachycardia originating in the low right atrium. The response to premature stimulation identifies the tachycardia as PJRT. Premature ventricular stimulation (*arrowhead*) occurs at a time when the His bundle is refractory from depolarization during the tachycardia (second labeled *H*). Therefore premature ventricular stimulation cannot enter the AV node. Furthermore, premature ventricular stimulation does not reach the atrium. Premature ventricular stimulation, however, terminates the tachycardia. This detail can be explained only by the PVC invading and blocking in a retrogradely conducting accessory pathway. I, II, III, and V_1 are scalar electrocardiographic leads. *DCS,* Distal coronary sinus electrogram; *HBEP, HBED,* His bundle electrogram, proximal and distal; *HRA,* high right atrial electrogram; *MCS1, MCS2,* midcoronary sinus electrograms; *PCS,* proximal coronary sinus electrogram; *RV,* right ventricular electrogram.

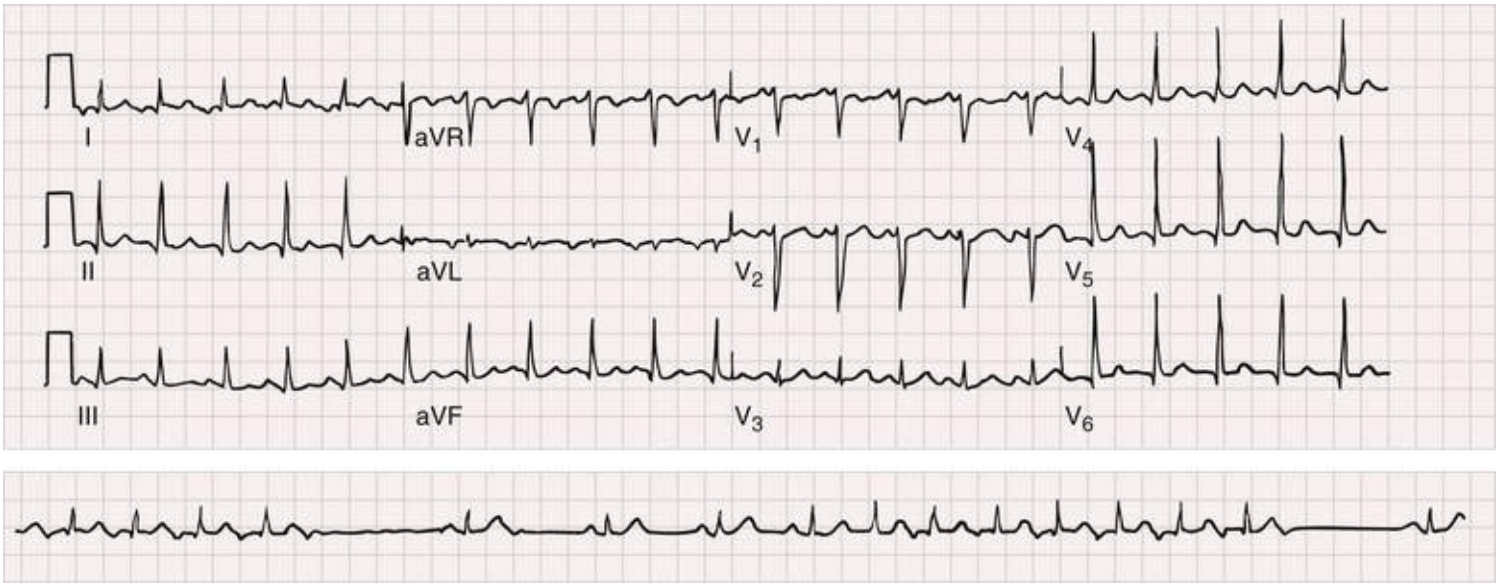


FIGURE 37.21 Permanent form of junctional reciprocating tachycardia (PJRT) in a patient with a left-sided accessory pathway. The 12-lead ECG demonstrates a long RP interval–short PR interval tachycardia, which in contrast to the usual form of PJRT, exhibits negative P waves in leads I and aVL. The rhythm strips below (lead I) indicate that whenever a nonconducted P wave occurs, the tachycardia always terminates, only to begin again after several sinus beats. This pattern is in marked contrast to that in **Fig. 37.6**, in which the tachycardia continues despite nonconducted P waves.

Recognition of Accessory Pathways

When retrograde atrial activation during tachycardia occurs over an accessory pathway that connects the left atrium to the left ventricle, the earliest retrograde activity is recorded from a left atrial electrode usually positioned in the coronary sinus (**see Fig. 37.12**). When retrograde atrial activation during tachycardia occurs over an accessory pathway that connects the right ventricle to the right atrium, the earliest retrograde atrial activity is generally recorded from a lateral right atrial electrode. Participation of a septal accessory pathway creates the earliest retrograde atrial activation in the low right portion of the atrium situated near the septum, anterior or posterior, depending on the insertion site. These mapping techniques provide an accurate assessment of the position of the accessory pathway, which can be anywhere in the AV groove except in the intervalvular trigone between the mitral valve and the aortic valve annuli. Recording electrical activity directly from the accessory pathway obviously provides precise localization.

It may be difficult to distinguish AV nodal reentry from participation of a septal accessory connection by use of the retrograde sequence of atrial activation because activation sequences during both tachycardias are similar. Other approaches to demonstrate retrograde atrial activation over the accessory pathway must be tried and can be accomplished by inducing PVCs during tachycardia to determine whether retrograde atrial excitation can occur from the ventricle at a time when the His bundle is refractory. VA conduction cannot occur over the normal conduction system because the His bundle is refractory, so an accessory pathway must be present for the atria to become excited. No patient with a reciprocating tachycardia from an accessory AV pathway has a VA interval less than 70 milliseconds—this is measured from the onset of ventricular depolarization to the onset of the earliest atrial activity recorded on an esophageal lead—or a VA interval less than 95 milliseconds when it is measured to the high right part of the atrium. In contrast, in most patients with reentry in the AV node, intervals from the onset of ventricular activity to the earliest onset of atrial activity recorded in the esophageal lead are less than 70 milliseconds.

Other Forms of Tachycardia in Patients with Wolff-Parkinson-White Syndrome

Patients can have other types of tachycardia during which the accessory pathway is a bystander, that is, uninvolved in the mechanism responsible for the tachycardia, such as AV nodal reentry or an AT that conducts to the ventricle over the accessory pathway. In patients with atrial flutter or AF, the accessory pathway is not a requisite part of the mechanism responsible for tachycardia, and the flutter or fibrillation occurs in the atrium unrelated to the accessory pathway (**see Fig. 37.18E**). Propagation to the ventricle during atrial flutter or AF can therefore occur over the normal AV node–His bundle or accessory pathway. Patients with WPW syndrome and AF almost always have inducible reciprocating tachycardias as well, which can develop into AF (**eFig. 37.3**). In fact, interruption of the accessory pathway and elimination of AV reciprocating tachycardia usually prevent recurrence of the AF. AF presents a potentially serious risk because of the possibility for very rapid conduction over the accessory pathway. At more rapid rates, the refractory period of the accessory pathway can shorten significantly and permit an extremely rapid ventricular response during atrial flutter or AF (**see Fig. 37.14B**). The rapid ventricular response can exceed the ability of the ventricle to follow in an organized manner; it can result in fragmented, disorganized ventricular activation and hypotension and lead to VF (**Fig. 37.22**). Alternatively, a supraventricular discharge bypassing AV nodal delay can activate the ventricle during the vulnerable period of the antecedent T wave and precipitate VF. Patients who have had VF exhibit ventricular cycle lengths during AF in the range of 240 milliseconds or less.

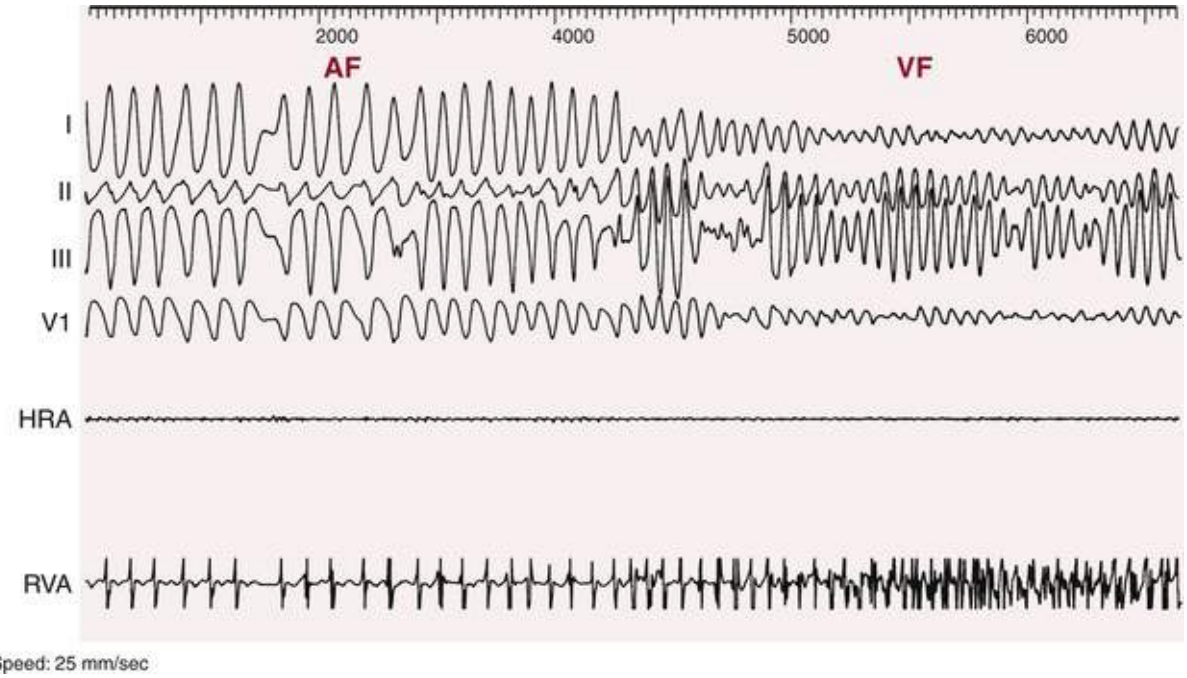


FIGURE 37.22 Atrial fibrillation (AF) becoming ventricular fibrillation (VF). In the left portion of this panel, the ECG demonstrates AF with conduction over an accessory pathway producing a rapid ventricular response, at times in excess of 390 beats/min. In the midportion of the tracing, VF can be seen to develop. I, II, III, and V_1 are scalar electrocardiographic leads. *HRA,* High right atrial electrogram; *RVA,* right ventricular apex electrogram.

Patients with preexcitation syndrome can have other causes of tachycardia, such as AV nodal reentry (sometimes with dual AV nodal curves), sinus nodal reentry, or even VT unrelated to the accessory pathway. Some accessory pathways can conduct anterogradely only; more often, pathways conduct retrogradely only. If the pathway conducts only anterogradely, it cannot participate in the usual form of

reciprocating tachycardia (**see Fig. 37.18A**). It can, however, participate in antidromic tachycardia (**see Fig. 37.18C**), as well as conduct to the ventricle during atrial flutter or AF (**see Fig. 37.18E**). Some data suggest that the accessory pathway demonstrates automatic activity, which could conceivably be responsible for some cases of tachycardia.

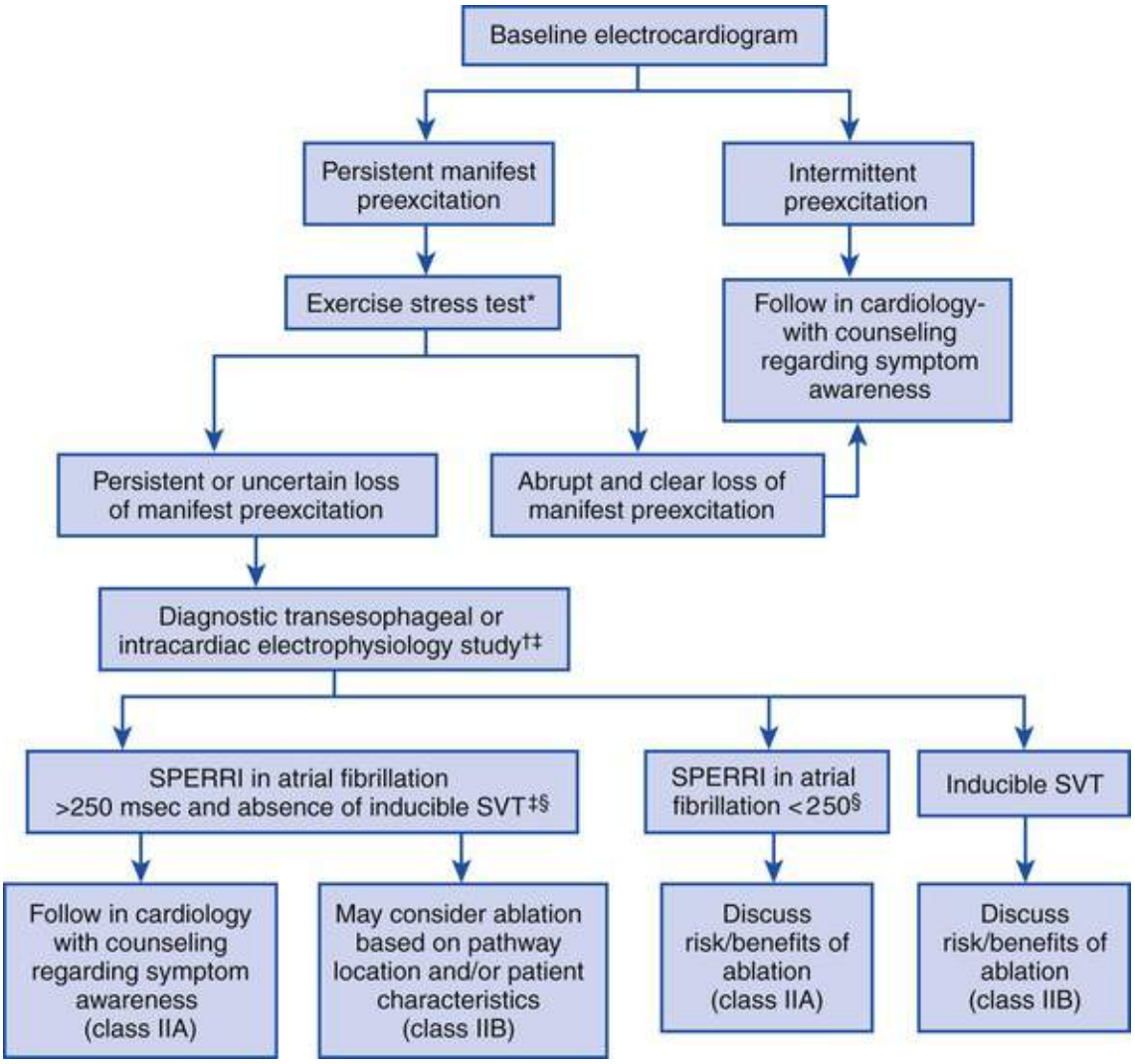
"Wide-QRS" Tachycardias

In patients with preexcitation syndrome, so-called wide-QRS tachycardias can be caused by multiple mechanisms. These include sinus or atrial tachycardias, AV nodal reentry, and atrial flutter or fibrillation with anterograde conduction over the accessory pathway; orthodromic reciprocating tachycardia with functional or preexisting BBB; antidromic reciprocating tachycardia; reciprocating tachycardia with anterograde conduction over one accessory pathway and retrograde conduction over a second pathway; tachycardias using nodofascicular or atriofascicular fibers; and VT.

Clinical Features

The reported incidence of preexcitation syndrome depends in large measure on the population studied and varies from 0.1 to 3 per 1000 in apparently healthy individuals, with an average of about 1.5 per 1000. The incidence of the electrocardiographic pattern of WPW conduction in 22,500 healthy aviation personnel was 0.25%, with a prevalence of documented tachyarrhythmias of 1.8%. Left free wall accessory pathways were most common, followed in frequency by posteroseptal, right free wall, and anteroseptal locations. WPW syndrome is found in all age-groups from the fetal and neonatal periods to the elderly, as well as in identical twins. The prevalence is higher in men and decreases with age, apparently because of loss of preexcitation. Most adults with preexcitation syndrome have normal hearts, although various acquired and congenital cardiac defects have been reported, including Ebstein anomaly, mitral valve prolapse, and cardiomyopathies. Patients with Ebstein anomaly often have multiple right-sided accessory pathways, either in the posterior septum or in the posterolateral wall, with preexcitation localized to the atrialized ventricle (**see Chapter 75**). They frequently have reciprocating tachycardia with a long VA interval and RBBB morphology.

The frequency of paroxysmal tachycardia apparently increases with age, from 10 per 100 patients with WPW syndrome in the 20- to 39-year-old group to 36 per 100 in patients older than 60 years. Approximately 80% of patients with tachycardia have a reciprocating tachycardia, 15% to 30% have AF, and 5% have atrial flutter. VT occurs infrequently. The anomalous complexes can mask or mimic myocardial infarction (**see Chapter 58**), BBB, or ventricular hypertrophy, and the presence of preexcitation syndrome can suggest an associated cardiac defect. For most patients with recurrent tachycardia, the prognosis is good, but sudden death does occur rarely, with an estimated frequency of 0.1%. Risk stratification includes a stress test and electrophysiologic study (EPS) in selected patients[14] (**eFig. 37.4**).



EFIGURE 37.4 Baseline electrocardiogram. *Patients unable to perform an exercise stress test should undergo risk-stratification with an electrophysiologic study. †Before invasive testing, patients and parents/guardians should undergo counseling to discuss the risks and benefits of proceeding with invasive studies, the risks associated with observation only, and risks related to the medication strategy. ‡Patients participating in moderate- to high-level competitive sports should be counseled with regard to the risks and benefits of ablation (class IIA) and follow the 36th Bethesda Conference guidelines. §In the absence of inducible atrial fibrillation, the shortest preexcited RR interval as determined by rapid atrial pacing is a reasonable surrogate. *SPERRI,* Shortest preexcited RR interval. (From Cohen MI, Triedman JK, Cannon BC, et al. PACES/HRS expert consensus statement on the management of the asymptomatic young patient with a Wolff-Parkinson-White [WPW, ventricular preexcitation] electrocardiographic pattern: Developed in partnership between the Pediatric and Congenital Electrophysiology Society [PACES] and the Heart Rhythm Society [HRS]. Endorsed by the governing bodies of PACES, HRS, American College of Cardiology Foundation [ACCF], American Heart Association [AHA], American Academy of Pediatrics [AAP], and Canadian Heart Rhythm Society [CHRS]. Heart Rhythm 2012;9:1006.)

It is highly likely that an accessory pathway is congenital, although its manifestations may be detected in later years and appear to be acquired. Relatives of patients with preexcitation, particularly those with multiple pathways, have an increased prevalence of preexcitation, thus suggesting a hereditary mode of acquisition. Some children and adults can lose their tendency for the development of tachyarrhythmias as they grow older, possibly as a result of fibrotic or other changes at the site of insertion of the accessory pathway. Pathways can lose their ability to conduct anterogradely. Tachycardia beginning in infancy can disappear but frequently recurs. Tachycardia still present after 5 years of age persists in 75% of patients, regardless of the location of the accessory pathway. Intermittent preexcitation during sinus rhythm and abrupt loss of conduction over the accessory pathway after IV administration of procainamide and with exercise suggest that the refractory period of the accessory pathway is long and that the patient is not at risk for a rapid ventricular rate should atrial flutter or fibrillation develop. These approaches are

relatively specific but not very sensitive, with low positive predictive accuracy. Exceptions to these safeguards can occur; the only way to be certain of the accessory pathway's properties and propensity for rapid conduction is by performing an EPS.

Treatment

For patients without symptoms, risk stratification to determine the risk for sudden death as a result of rapid conduction over the accessory pathway inducing VF, although rare, may be necessary in some patients. Patients with asymptomatic intermittent ventricular preexcitation do not require further evaluation or therapy and should simply be observed.[14] Young patients (8 to 21 years of age) who have only persistent electrocardiographic abnormalities, without tachyarrhythmias or a history of palpitations, should undergo stress testing to determine whether abrupt loss of preexcitation occurs. If loss of preexcitation does not occur or is equivocal or not abrupt, an invasive EPS is recommended to risk-stratify patients further[14] (**eFig. 37.4**). For patients with frequent episodes of symptomatic tachyarrhythmia, therapy should be initiated.

Two therapeutic options exist, catheter ablation and pharmacologic therapy. Drugs are chosen to prolong conduction time or refractoriness in the AV node, the accessory pathway, or both to prevent rapid rates from occurring. If successful, such therapy prevents maintenance of an AV reciprocating tachycardia or a rapid ventricular response to atrial flutter or AF. Some drugs can suppress premature complexes that precipitate the arrhythmias.

Adenosine, verapamil, propranolol, and digitalis prolong conduction time and refractoriness in the AV node. Verapamil and propranolol do not directly affect conduction in the accessory pathway, and digitalis has had variable effects. Because digitalis has been reported to shorten refractoriness in the accessory pathway and to speed the ventricular response in some patients with AF, it is advisable to not use digitalis as a single drug in patients with WPW syndrome. Instead, drugs that prolong the refractory period in the accessory pathway should be used, such as class IA and IC drugs (**see Chapter 36**).

The class IC and class III drugs can affect both the AV node and the accessory pathway. Lidocaine does not generally prolong refractoriness of the accessory pathway. Verapamil and IV lidocaine can increase the ventricular rate during AF in patients with WPW syndrome. IV verapamil can precipitate VF when given to a patient with WPW syndrome who has a rapid ventricular rate during AF. This effect does not seem to occur with oral verapamil. Catecholamines can expose WPW syndrome, shorten the refractory period of the accessory pathway, and reverse the effects of some AADs.

Termination of an Acute Episode

Termination of an acute episode of reciprocating tachycardia, suspected electrocardiographically from a normal QRS complex, regular R-R intervals, a rate of approximately 200 beats/min, and a retrograde P wave in the ST segment, should be approached similar to AV nodal reentry. After vagal maneuvers, adenosine followed by IV verapamil or diltiazem is the initial treatment of choice. AF can occur after drug administration, particularly adenosine, along with a rapid ventricular response. An external cardioverter-defibrillator should be immediately available if necessary. For atrial flutter or AF (with AF suspected because of an anomalous QRS complex and grossly irregular R-R intervals; **see Fig. 37.14B and eFig. 37.3**), drugs must be used that prolong refractoriness in the accessory pathway (procainamide, amiodarone), often coupled with drugs that prolong AV nodal refractoriness. In many patients, particularly those with a very rapid ventricular response and any signs of hemodynamic impairment, electrical cardioversion is the initial treatment of choice.

Prevention

For long-term therapy to prevent recurrence, RF catheter ablation of the accessory pathway has become the first-line therapy for most patients. Decisions about ablation depend on (1) risk of AF conducting rapidly over the accessory pathway causing VF, (2) frequency and severity of symptoms from tachycardia, and (3) risk of the procedure (largely determined by location of the accessory pathway). For patients with frequent symptomatic arrhythmias not fully controlled by drugs, those who are drug intolerant, or those who choose not to take drugs, ablation is advisable. This option should be considered early in the course of treatment of a symptomatic patient because of its high success rate, low frequency of complications, and potential cost-effectiveness. Ablation is the treatment of choice in patients with AF and rapid conduction over an accessory pathway. Even though transvenous catheter ablation is generally effective, epicardial ablation through a pericardial approach or surgical interruption of the accessory pathway may be necessary in rare cases. Septal accessory pathways near the AV node (anteroseptal) may require cryoablation instead of RF ablation, to minimize the risk of AV block complicating the procedure.[15]

Drug therapy is an alternative to ablation or is used in rare cases of failed ablation attempts, but it is not always possible to predict which drugs may be most effective for an individual patient. Some drugs can actually increase the frequency of episodes of reciprocating tachycardia by prolonging the duration of anterograde and not retrograde refractory periods of the accessory pathway, thereby making it easier for a PAC to block conduction anterogradely in the accessory pathway and to initiate tachycardia. Oral administration of two drugs, such as flecainide and propranolol, to decrease conduction capability in both limbs of the reentrant circuit can be beneficial. Amiodarone and sotalol, which prolong refractoriness in both the accessory pathway and the AV node, can be effective. Depending on the clinical situation, empiric drug trials or serial electrophysiologic drug testing can be used to determine optimal drug therapy for patients with reciprocating tachycardia. For patients who have AF with a rapid ventricular response, induction of AF while the patient is receiving therapy is essential to be certain that the ventricular rate is controlled. Patients who have accessory pathways with very short refractory periods may be poor candidates for drug therapy because the refractory periods may be insignificantly prolonged in response to the standard agents.

Summary of Electrocardiographic Diagnosis of Supraventricular Tachycardias

Electrocardiographic clues that permit differentiation among the various SVTs are often present. P waves during tachycardia that are identical to sinus P waves and that occur with a long RP interval and a short PR interval are most likely caused by sinus nodal reentry, sinus tachycardia, or an AT arising from the right atrium near the sinus node. Retrograde (inverted in leads II, III, and aVF) P waves usually represent reentry involving the AV junction, either AV nodal reentry or reciprocating tachycardia using a paraseptal accessory pathway. Depression of the ST segment during a narrow-complex tachycardia generally signifies AV reentrant tachycardia using an accessory pathway. Tachycardia without manifest P waves is probably caused by AV nodal reentry (retrograde P waves buried in the QRS complex), whereas a tachycardia with an RP interval exceeding 90 milliseconds can be caused by an accessory pathway. AV dissociation or AV block during tachycardia excludes the participation of an AV accessory pathway and makes AV nodal reentry less likely. Multiple tachycardias can occur at different times in the same patient. QRS alternans, thought to be a feature of AV reciprocating tachycardia, is more likely a rapid rate–related phenomenon independent of the tachycardia mechanism. RP-PR relationships help differentiate SVTs

(**Table 37.6**). QRS voltage can increase during SVT.

TABLE 37.6

Supraventricular Tachycardias

SHORT RP, LONG PR INTERVAL	LONG RP, SHORT PR INTERVAL
AV nodal reentry	Atrial tachycardia
AV reentry	Sinus node reentry
	Atypical AV nodal reentry
	AVRT with a slowly conducting accessory pathway (e.g., PJRT)

AVRT, Atrioventricular reciprocating tachycardia; *PJRT,* paroxysmal junctional reciprocating tachycardia.

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38

Atrial Fibrillation: Clinical Features, Mechanisms, and Management

Fred Morady, Douglas P. Zipes

Electrocardiographic Features

Atrial fibrillation (AF) is a supraventricular arrhythmia characterized electrocardiographically by low-amplitude baseline oscillations (fibrillatory or f waves from the fibrillating atria) and an irregularly irregular ventricular rhythm. The f waves, 300 to 600 beats/min, are variable in amplitude, shape, and timing. Atrial flutter waves have a rate of 250 to 350 beats/min and are constant in timing and morphology (**Fig. 38.1**). In lead V_1, f waves sometimes appear uniform and can mimic flutter waves (**Fig. 38.2**). In some patients, f waves are very small and not perceptible on the electrocardiogram, and the diagnosis of AF is based on the irregularly irregular ventricular rhythm (**Fig. 38.3**).

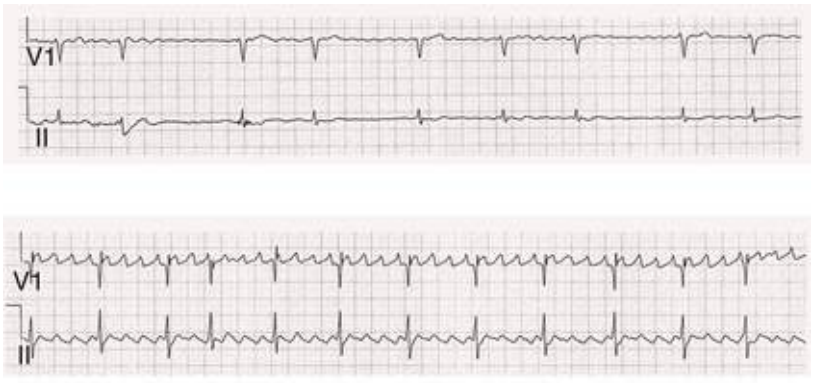

FIGURE 38.1 Comparison between the f waves of AF **(top panel)** and the flutter waves of atrial flutter **(bottom panel).** Note that f waves are variable in rate, shape, and amplitude, whereas flutter waves are constant in rate and all aspects of morphology. Shown are leads V_1 and II.

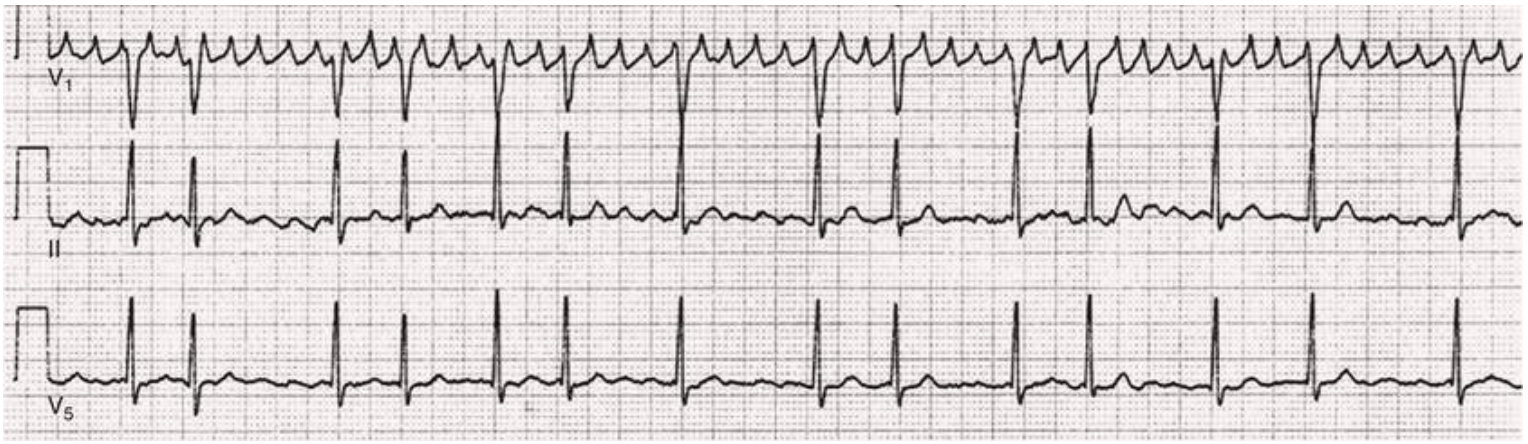

FIGURE 38.2 An example of AF with prominent f waves in V_1 that mimic atrial flutter waves. Note that typical f waves are present in leads II and V_5, establishing the diagnosis of AF.

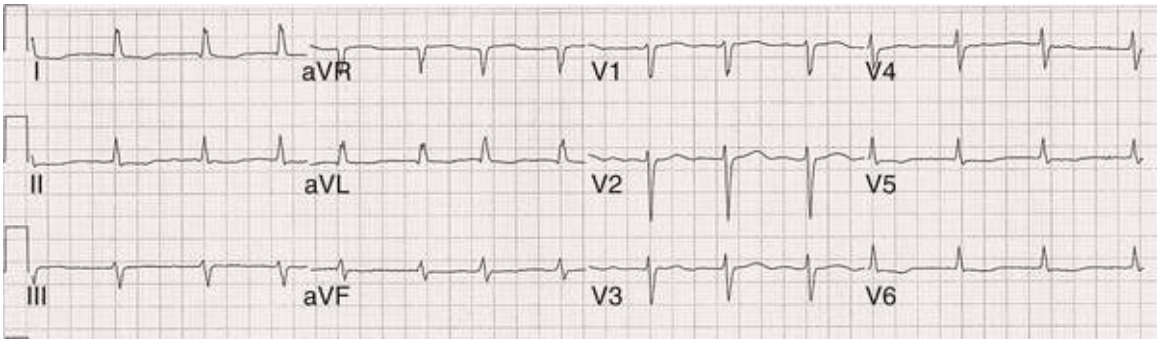

FIGURE 38.3 A 12-lead electrocardiogram of AF in which f waves are not discernible. The irregularly irregular ventricular rate indicates that this is AF.

The ventricular rate during untreated AF typically is 100 to 160 beats/min. Patients with the Wolff-Parkinson-White (WPW) syndrome can experience ventricular rates during AF exceeding 250 beats/min because of conduction over the accessory pathway (**see Chapter 37**). The ventricular rate during AF can appear more regular when the rate is extremely rapid (>170 beats/min) (**Fig. 38.4**), when a junctional tachycardia independently controls the ventricles, when there is high-degree atrioventricular (AV) block with a regular escape rhythm (**Fig. 38.5**), or when the QRS complexes are fully paced. In these cases the diagnosis of AF is based on the presence of f waves. Infrequently, a junctional tachycardia can exhibit a Wenckebach exit block (often during digitalis toxicity) to cause a regularly irregular ventricular rate.

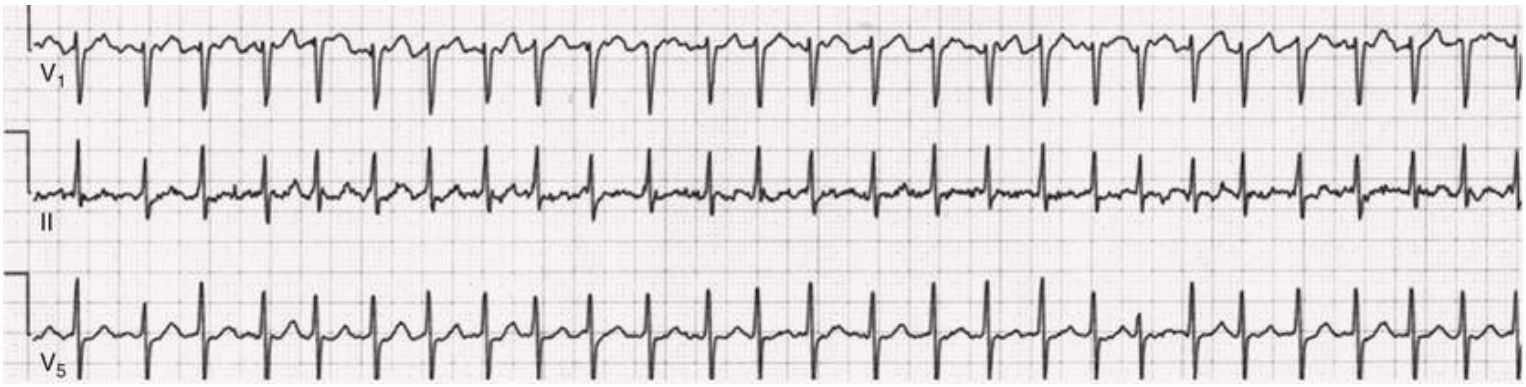

FIGURE 38.4 A recording of AF with a rapid ventricular rate of 160 beats/min. Shown are leads V_1, II, and V_5. On quick review, there may appear to be a regular rate consistent with paroxysmal supraventricular tachycardia. On closer inspection, it is clear that the rate is irregularly irregular.

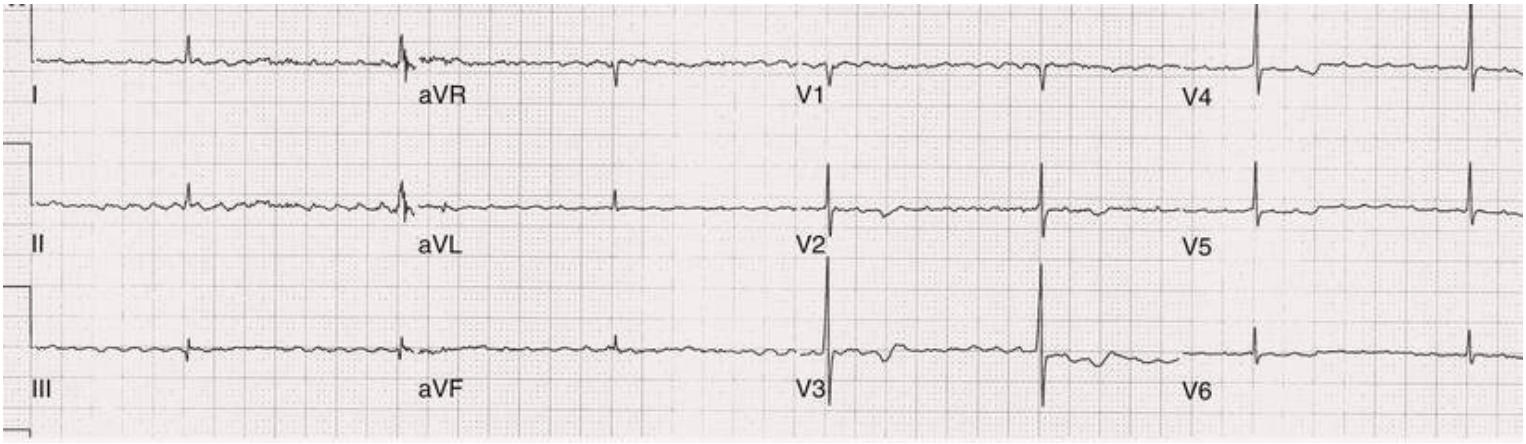

FIGURE 38.5 Atrial fibrillation and a regular junctional rhythm at a rate of 43 beats/min. There is either underlying third-degree AV block or second-degree AV block with extremely slow atrioventricular conduction allowing a junctional escape rhythm to become manifest.

Classification of Atrial Fibrillation

Atrial fibrillation that terminates spontaneously within 7 days is termed *paroxysmal*, and AF present continuously for more than 7 days is called *persistent*. AF that persists for longer than 1 year is termed *longstanding persistent*, whereas longstanding AF refractory to cardioversion is termed *permanent*. However, "permanent AF" is not necessarily permanent in the literal sense because it may be successfully eliminated by surgical or catheter ablation.

Some patients with paroxysmal AF occasionally can have episodes that are persistent, and vice versa. The predominant form of AF determines how it should be categorized.

A confounding factor in the classification of AF is cardioversion and antiarrhythmic drug (AAD) therapy. For example, if a patient undergoes transthoracic cardioversion 24 hours after AF onset, it is unknown whether the AF would have persisted for more than 7 days. Furthermore, AAD therapy can change persistent AF into paroxysmal AF. It is generally thought that the classification of AF should not be altered on the basis of the effects of electrical cardioversion or AAD therapy.

Lone atrial fibrillation refers to AF that occurs in patients younger than 60 years who do not have hypertension or any evidence of structural heart disease. This designation is clinically relevant because

patients with lone AF are at lower risk of thromboembolic complications, eliminating the necessity for anticoagulation. They also may be more likely to have familial or genetic causes. In addition, the absence of structural heart disease allows the safe use of rhythm-control drugs such as flecainide in patients with lone AF.

Paroxysmal AF also can be classified clinically on the basis of the autonomic setting in which it most often occurs. Approximately 25% of patients with paroxysmal AF have *vagotonic* AF, during which AF is initiated in the setting of high vagal tone, typically in the evening when the patient is relaxing or during sleep. Drugs exerting a vagotonic effect (e.g., digitalis) can aggravate vagotonic AF, and drugs with a vagolytic effect (e.g., disopyramide) may be particularly appropriate for prophylactic therapy. Adrenergic AF occurs in approximately 10% to 15% of patients with paroxysmal AF in the setting of high sympathetic tone, as during strenuous exertion. In patients with adrenergic AF, beta blockers not only provide rate control but can prevent the onset of AF. Most patients have a mixed or random form of paroxysmal AF, with no consistent pattern of onset. In some, alcohol can be a precipitant.

Epidemiology of Atrial Fibrillation

Atrial fibrillation is the most common arrhythmia treated in clinical practice and the most common arrhythmia for which patients are hospitalized; approximately 33% of arrhythmia-related hospitalizations are for AF. AF is associated with approximately a fivefold increase in the risk of cerebrovascular accident (stroke) and a twofold increase in the risk of all-cause mortality.[1] AF also is associated with the development of heart failure and has been linked to sudden death.

The incidence of AF is age and gender related, ranging from 0.1% per year before age 40 to more than 1.5% per year in women and more than 2% per year in men older than 80. Congestive heart failure, aortic and mitral valve disease, left atrial enlargement, hypertension, and advanced age are independent risk factors for the development of AF, as are obesity and obstructive sleep apnea[2] (**see Chapter 87**). Another risk factor is psoriasis, which, when severe, triples the risk of AF in patients younger than 50.[3]

A community-based cohort study in Olmstead County, Minnesota, reported that the age-adjusted incidence of AF per 1000 person-years increased significantly between 1980 and 2000 from 4.4 to 5.4 in men and from 2.4 to 2.8 in women.[4] There was a relative increase of 0.6% per year in the age-adjusted AF incidence. An increase in obesity accounted for 60% of the age-adjusted increase in AF incidence. The number of patients with AF in the United States was estimated to be 3.2 million in 1980 and 5.1 million in 2000 and was projected to be 12.1 to 15.9 million in 2050, all of which are higher than previous estimates.

Mechanisms of Atrial Fibrillation

The mechanisms responsible for AF are complex. Triggering events may differ from maintenance mechanisms. In addition, the clinical phenotypes of paroxysmal, persistent, and longstanding persistent have different electrophysiologic characteristics because of remodeling and different clinical modulators that affect the substrate, such as heart failure, atrial stretch and ischemia, sympathovagal influences, inflammation, and fibrosis.

The two likely electrophysiologic mechanisms of AF are one or more automatic, triggered, or microreentrant foci, so-called *drivers*, which fire at rapid rates and cause fibrillation-like activity, and multiple reentrant circuits meandering throughout the atria, annihilating and reforming wavelets that

perpetuate the fibrillation. In many studies the left atrium contains the site of dominant frequency discharge, with a left-to-right gradient. Both mechanisms may be present simultaneously and can change as the atria remodel. In the CONFIRM trial, computational maps were obtained in patients by signal processing of multiple electrograms recorded simultaneously during AF.[5] This technique can reveal rotors and focal sources. A mean of 2.1 sources was found in 97% of 101 patients, with 70% being rotors and 30% being focal sources.

Rapid discharges from the pulmonary veins are the most common triggers of AF and also may play a perpetuating role, more so in paroxysmal AF than in persistent AF. This is why pulmonary vein isolation is particularly effective for elimination of paroxysmal AF. In persistent AF, changes in the atrial substrate, including interstitial fibrosis that contributes to slow, discontinuous, and anisotropic conduction, may give rise to complex fractionated atrial electrograms (CFAEs) and reentry. Therefore, pulmonary vein isolation alone often is insufficient to eliminate persistent AF (**see Chapter 36**).

Genetic Factors

Several mutations that are responsible for familial AF and that predispose to AF have been identified. These mutations cause a gain of function of repolarization potassium currents that results in shortening of atrial refractoriness and facilitation of atrial reentry. Multiple polymorphisms associated with idiopathic AF or structural heart disease or occurring postoperatively also have been identified.[6] These polymorphisms are in genes that affect potassium and sodium channels, sarcolipin, the renin-angiotensin system, connexin-40, endothelial nitric oxide synthase, and interleukin-10. The end results are changes in calcium handling, fibrosis, conduction, and inflammation that predispose to AF.

Causes of Atrial Fibrillation

The majority of patients with AF have hypertension (usually with left ventricular hypertrophy; **Chapters 46 and 47**) or some other form of structural heart disease. In addition to hypertensive heart disease, the most common cardiac abnormalities associated with AF are ischemic heart disease (**Chapter 58**), mitral valve disease (**Chapter 69**), hypertrophic cardiomyopathy (**Chapter 78**), and dilated cardiomyopathy (**Chapter 77**). Less common causes of AF are restrictive cardiomyopathies such as amyloidosis (**Chapter 77**), constrictive pericarditis (**Chapter 83**), and cardiac tumors (**see Chapter 95**). Severe pulmonary hypertension often is associated with AF (**Chapter 85**).

Obstructive sleep apnea and obesity are associated with each other, and both independently increase the risk of AF (**see Chapter 87**). The possible mechanisms of AF in patients with sleep apnea include hypoxia, surges in autonomic tone, and hypertension.[2] Available data suggest that atrial dilation and an increase in systemic inflammatory factors are responsible for the relationship between obesity and AF. Obesity also is associated with increased deposits of epicardial fat (**see Chapter 50**). The most likely mechanisms by which epicardial fat predisposes to AF are slow or anisotropic conduction caused by adipocyte infiltration into atrial muscle, atrial fibrosis caused by adipokines secreted by epicardial fat, and the local secretion of proinflammatory factors (e.g., IL-6, IL-8, TNF-α).[7] The LEGACY study demonstrated that sustained weight loss and exercise can reduce the AF burden.[8]

AF can have causes that are temporary or reversible. The most common temporary causes are excessive alcohol intake (“holiday heart”), open heart or thoracic surgery, myocardial infarction (**see Chapters 58 and 59**), pericarditis (**Chapter 83**), myocarditis (**Chapter 79**), and pulmonary embolism

(**Chapter 84**). The most common correctable cause is hyperthyroidism (**Chapter 92**).

AF is sometimes caused by tachycardia. Patients with tachycardia-induced AF most often have AV nodal reentrant tachycardia or a tachycardia related to WPW syndrome that degenerates into AF. AF in a patient with a history of rapid and regular palpitations before the onset of irregular palpitations or with a WPW electrocardiographic pattern should suggest tachycardia-induced AF. Treatment of the tachycardia that triggers the AF often (but not always) prevents recurrences of AF.

Clinical Features

The symptoms of AF range from none to severe and functionally disabling. The most common symptoms are palpitations, fatigue, dyspnea, effort intolerance, and lightheadedness. Polyuria can occur because of release of atrial natriuretic peptide. Many patients with symptomatic paroxysmal AF also have asymptomatic episodes, and some patients with persistent AF have symptoms only intermittently, making it difficult to assess accurately the frequency and duration of AF on the basis of symptoms.

An estimated 25% of patients with AF are asymptomatic, more often elderly patients and patients with persistent AF. Such patients sometimes are erroneously classified as having “asymptomatic” AF despite having symptoms of fatigue or effort intolerance. Because fatigue is a nonspecific symptom, it may not be clearly caused by persistent AF. A “diagnostic cardioversion” may be helpful by maintaining sinus rhythm for at least a few days to determine whether a patient feels better in sinus rhythm. This can provide a basis to pursue a rhythm-control versus rate-control strategy.

Syncope, an uncommon symptom of AF, can be caused by a long sinus pause on termination of AF in a patient with the sick sinus syndrome. Syncope also can occur during AF with a rapid ventricular rate because of neurocardiogenic (vasodepressor) syncope triggered by the tachycardia or because of a severe drop in blood pressure caused by a reduction in cardiac output.

Asymptomatic or minimally symptomatic AF patients are not prompted to seek medical care and can present with a thromboembolic complication such as stroke or the insidious onset of heart failure symptoms, eventually presenting in florid congestive heart failure.

The hallmark of AF on physical examination is an irregularly irregular pulse. Short R-R intervals during AF do not allow adequate time for left ventricular diastolic filling, resulting in a low stroke volume and the absence of palpable peripheral pulse. This results in a “pulse deficit,” during which the peripheral pulse is not as rapid as the apical rate. Other manifestations of AF on the physical examination are irregular jugular venous pulsations and variable intensity of the first heart sound.

Diagnostic Evaluation

In a patient who describes irregular or rapid palpitations suggestive of paroxysmal AF, ambulatory monitoring is useful to document whether AF is responsible for the symptoms. If the symptoms occur on a daily basis, a 24-hour Holter recording is appropriate. However, extended monitoring for 2 to 4 weeks with an event monitor or by mobile cardiac outpatient telemetry is appropriate for patients whose symptoms are sporadic (**see Chapter 32**).

The history should be directed at determination of the type and severity of symptoms, the first onset of AF, whether the AF is paroxysmal or persistent, the triggers of AF, whether the episodes are random or occur at particular times (e.g., during sleep), and the frequency and duration of episodes. When it is unclear from the history, 2 to 4 weeks of ambulatory monitoring with an autotrigger event monitor or by

mobile cardiac outpatient telemetry is useful to determine whether AF is paroxysmal or persistent and to quantitate the AF burden in patients with paroxysmal AF. The history also should be directed at identification of potentially correctible causes (e.g., hyperthyroidism, excessive alcohol intake), structural heart disease, and comorbidities.

Laboratory testing should include thyroid, liver, and renal function tests. Echocardiography always is appropriate to evaluate atrial size and left ventricular function and to look for left ventricular hypertrophy, congenital heart disease (**see Chapter 75**), and valvular heart disease (**Chapters 68 and 69**). Chest radiography is appropriate if the history or physical examination is suggestive of pulmonary disease (**Chapter 15**). A stress test is appropriate for evaluation of ischemic heart disease in at-risk patients (**Chapter 13**).

Prevention of Thromboembolic Complications

Risk Stratification

A major goal of therapy in patients with AF is to prevent thromboembolic complications such as stroke. Warfarin and other oral anticoagulants are more effective than aspirin for prevention of thromboembolic complications.[9] However, because of the risk of hemorrhage from anticoagulants, their use should be limited to patients whose risk of thromboembolic complications is greater than the risk of hemorrhage. Therefore, it is useful to risk stratify patients with AF to identify appropriate candidates for anticoagulation.

The strongest predictors of ischemic stroke and systemic thromboembolism are a history of stroke or transient ischemic episode and mitral stenosis. When patients with AF and a prior ischemic stroke are treated with aspirin, the risk of another stroke is very high, in the range of 10% to 12% per year. At the other end of the risk spectrum are patients with lone AF, whose cumulative 15-year risk of stroke is in the range of 1% to 2%. Aside from prior stroke, the best-established risk factors for stroke in patients with nonvalvular AF are diabetes (relative risk [RR], 1.7), hypertension (RR, 1.6), heart failure (RR, 1.4), and age 70 or older (RR, 1.4 per decade).[2]

A simple clinical scheme to risk stratify patients on the basis of the major risk factors is the $CHADS_2$ (cardiac failure, hypertension, age, diabetes, stroke) score. Each of the first four risk factors counts as 1 point, and a prior stroke or transient ischemic event is 2 points. There is a direct relationship between the $CHADS_2$ score and the annual risk of stroke in the absence of aspirin or warfarin therapy. The clinical value of the $CHADS_2$ score lies in its simplicity and predictive value. However, the $CHADS_2$ score has been superseded by the CHA_2DS_2-VASc score because it more accurately discriminates low-risk from intermediate-risk patients.[10] In this risk-scoring system, cardiac failure, hypertension, diabetes, vascular disease, age 65 to 74 years, and female gender are 1 point each, and age 75 or older and prior stroke or transient ischemic event are 2 points. The annual risk of stroke is zero or close to zero when the CHA_2DS_2-VASc score is 0, compared to approximately 2% when the $CHADS_2$ score is 0.[11] A score of 1 is associated with an annual stroke risk of approximately 3% with the $CHADS_2$ score, compared to 0.7% with the CHA_2DS_2-VASc score (**Fig. 38.6**).

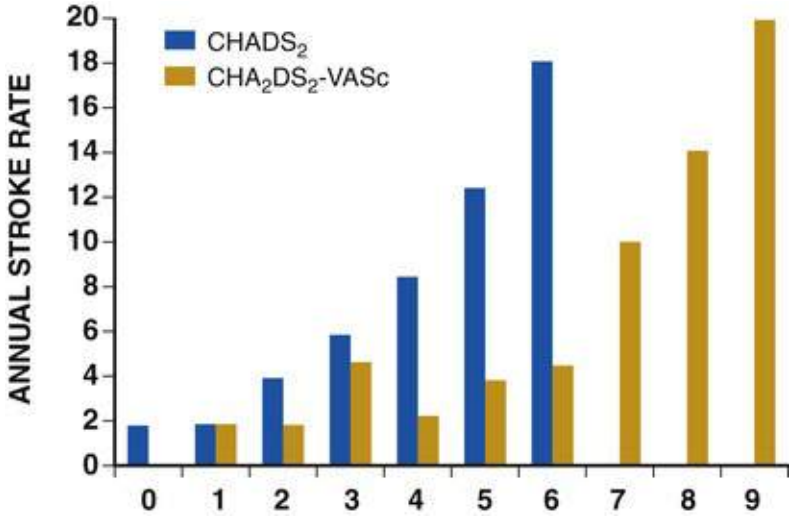

FIGURE 38.6 The annual risk of stroke (percent risk/year) based on the $CHADS_2$ and CHA_2DS_2-VASc scores. (Based on data from Lip GY. Implications of the CHA(2)DS(2)-VASc and HAS-BLED Scores for thromboprophylaxis in atrial fibrillation. Am J Med 2011;124:111-4.)

Renal failure also is an independent risk factor for stroke in patients with AF.[12] The relative risk of a thromboembolic event in the absence of anticoagulation was 1.4 in patients with non–end-stage chronic kidney disease and 1.8 in patients requiring hemodialysis or a renal transplant. The predictive strength of chronic kidney disease for a thromboembolic event appears to be equivalent to that of heart failure and advanced age. Therefore, it may be appropriate to take into account chronic kidney disease in evaluating the risk profile of a patient with AF.

By definition, the burden of AF is greater in patients with persistent AF than in patients with paroxysmal AF. It may seem reasonable to assume that the risk of stroke is lower in patients with occasional episodes of self-limited AF than in patients with AF continuously. However, the available data in fact indicate that the risk of thromboembolic complications is the same in patients with paroxysmal and persistent AF. Accordingly, guideline recommendations for anticoagulation are the same in patients with paroxysmal and persistent AF.[2,13]

Current dual-chamber pacemakers and implantable cardioverter-defibrillators (ICDs) are capable of detecting short episodes of asymptomatic AF that otherwise would not have been detected clinically. In a recent multicenter prospective study, subclinical atrial tachyarrhythmias (atrial rate >190 beats/min for >6 minutes) were detected by device interrogation in 10.1% of patients 65 years or older with hypertension and no history of AF who received a pacemaker or ICD.[14] Subclinical atrial tachyarrhythmias were independently associated with a 2.5-fold increase in the risk of stroke.

An important consideration in patients treated with an oral anticoagulant is the risk of bleeding. Several risk-scoring systems have been developed to assess a patient's susceptibility to hemorrhagic complications. The scoring system with the best balance of simplicity and accuracy is the HAS-BLED score.[15] The components of this score are hypertension, abnormal renal or liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), elderly (>75 years), and concomitant drug (antiplatelet agent or nonsteroidal anti-inflammatory drug) or alcohol use. Each of these components is 1 point. As the score increases from 0 to the maximum of 9, there is a stepwise increase in the risk of bleeding in patients treated with warfarin. For example, in one study the annual rate of major bleeds was 1.1% in patients with a HAS-BLED score of 0, 3.7% with a score of 3, and 12.5% with a score of 5.[16]

In two large-scale cohort studies of 132,372 and 170,292 patients with nonvalvular AF, the CHA_2DS_2-VASc and HAS-BLED scores were calculated for each patient.[17,18] The net clinical benefit of warfarin

was defined as the number of strokes off warfarin minus the number of intracranial bleeds on warfarin. In both studies, warfarin was associated with a net clinical benefit except when the CHA_2DS_2-VASc score was 0. In patients with a CHA_2DS_2-VASc score of 1 or more, the risk of stroke in the absence of warfarin exceeded the number of bleeding complications during treatment with warfarin.

Despite the results of these large cohort studies, the decision to anticoagulate a patient in clinical practice should be individualized. At times it may be appropriate not to anticoagulate a patient with a CHA_2DS_2-VASc score 1 or greater. For example, the annual risk of stroke in a patient with a CHA_2DS_2-VASc score of 2 is approximately 2%, which usually justifies the use of warfarin. However, if that patient has a HAS-BLED score of 5 or more, which is associated with an annual risk of major bleeding of 12% or greater, it would be imprudent to treat that patient with warfarin.

The HAS-BLED score was developed and validated in patients anticoagulated with warfarin. Except for labile INR, the components of the HAS-BLED score likely also apply to patients who are anticoagulated with one of the novel (new) oral anticoagulants (NOACs), either a direct thrombin inhibitor or factor Xa inhibitor. However, clinical trials have indicated that the risk of major bleeding is lower with NOACs than with warfarin (see later). Accordingly, the benefit of anticoagulation with warfarin is estimated to be greater than the risk of bleeding when the annual stroke risk is at least 1.7%, compared to an annual stroke risk of at least 0.9% in patients treated with a NOAC.[19]

Aspirin and Other Antithrombotic Agents

Aspirin does not prevent thromboembolic complications as effectively as warfarin or NOACs in patients with AF. In a meta-analysis of five randomized clinical trials, aspirin did not significantly reduce the risk of stroke compared to placebo in patients with AF.[9] In a large cohort study of patients with non-valvular AF, aspirin had no therapeutic efficacy for preventing strokes.[17] Therefore, if aspirin is used for prophylactic therapy, this should be only in patients at lowest risk of thromboembolic complications (CHA_2DS_2-VASc score of 0). However, the 2014 American College of Cardiology (ACC), American Heart Association (AHA), and /Heart Rhythm Society (HRS) guidelines for management of patients with AF recommend that for patients with nonvalvular AF and a CHA_2DS_2-VASc score of 0, it is reasonable to omit all antithrombotic therapy, including aspirin. When the CHA_2DS_2-VASc score is 1, the guidelines recommend that either no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered.[2] Because of the negligible therapeutic effect of aspirin, a risk of bleeding complications that is close to the risk of oral anticoagulants, and the ability of the CHA_2DS_2-VASc score to accurately identify low-risk patients, the most recent guidelines of the European Society of Cardiology (ESC) recommend no antithrombotic therapy when the CHA_2DS_2-VASc score is 0 and an individualized decision between no antithrombotic therapy versus an oral anticoagulant when the CHA_2DS_2-VASc score is 1.[20]

If aspirin is used for stroke prevention in patients with AF, the appropriate daily dose is 81 to 325 mg/day. No data indicate superiority of a particular dose for prevention of thromboembolism.

In patients with a $CHADS_2$ score greater than 1 who are not able to tolerate anticoagulation with warfarin or a NOAC, combination therapy with aspirin and the platelet inhibitor clopidogrel is more efficacious than aspirin alone for prevention of thromboembolic complications.[21] The potential benefit of combination therapy with aspirin plus clopidogrel may outweigh the increased risk of bleeding complications in high-risk patients who are not suitable candidates for warfarin or a NOAC.

Warfarin and Direct Thrombin Inhibitors

A meta-analysis of the major randomized clinical trials that compared warfarin with placebo for prevention of thromboembolism in patients with AF demonstrated that warfarin reduced the risk of all strokes (ischemic and hemorrhagic) by approximately 60%.[9] The target INR should be 2.0 to 3.0. This range of INRs provides the best balance between stroke prevention and hemorrhagic complications. In clinical practice, maintenance of the INR in therapeutic range has been challenging, and a large proportion of patients often have an INR of less than 2.0. A large prospective study of community-based practices demonstrated that the mean time in therapeutic range in patients treated with warfarin was only 66% and that the time in therapeutic range was less than 60% in 34% of patients.[22] Maintaining the INR at a level of 2.0 or higher is important because even a relatively small decrease in INR from 2.0 to 1.7 more than doubles the risk of stroke.

The annual risk of a major hemorrhagic complication during anticoagulation with warfarin is in the range of 1% to 2%, and a strong predictor of major bleeding events is an INR greater than 3.0. For example, the risk of intracranial bleeding is approximately twice as high at an INR of 4.0 than 3.0. This emphasizes the importance of maintaining the INR in the range of 2.0 to 3.0.

Some studies have indicated that advanced age can be a risk factor for intracranial hemorrhage in patients with AF treated with warfarin. The concern of hemorrhagic complications may lead some clinicians to favor the use of aspirin over warfarin or one of the NOACs in elderly patients. However, the available data indicate that the risk-to-benefit ratio of warfarin and the NOACs is more favorable than that of aspirin even in patients older than 75.[23]

It is well established that genetic factors influence the dose of warfarin required to maintain the INR within therapeutic range. Several single-nucleotide polymorphisms that affect warfarin metabolism have been identified. Algorithms based on pharmacogenetic and clinical factors improve the accuracy of warfarin dose initiation compared with algorithms based only on clinical factors.[24] Additional studies are required to determine whether the clinical benefits of genotyping of warfarin candidates justify the cost of genetic testing (**see Chapter 8**).

Novel Oral Anticoagulants

Direct thrombin inhibitors and factor Xa inhibitors have several advantages over vitamin K antagonists such as warfarin, the most notable being a fixed dosing regimen that eliminates the need for monitoring of a laboratory test such as the INR. Dabigatran, an oral direct thrombin inhibitor, and rivaroxaban and apixaban, factor Xa inhibitors, are approved by the U.S. Food and Drug Administration (FDA) for prevention of stroke/embolism in patients with nonvalvular AF. Randomized clinical trials demonstrated that each of these three NOACs is noninferior or superior to warfarin in efficacy and safety in patients with nonvalvular AF who had risk factors for stroke.[25] One of the most serious risks of anticoagulation is intracranial hemorrhage. Recent studies have indicated that the risk of intracranial hemorrhage is about 50% lower with NOACs compared to warfarin.[26]

The NOACs, in addition to eliminating the need for laboratory monitoring, have other advantages over warfarin: fewer drug interactions, no food interactions, and rapid onset of action that obviates the need for bridging therapy. However, they also have some disadvantages compared to warfarin: higher cost, more gastrointestinal side effects in the case of dabigatran, twice-daily dosing for dabigatran and apixaban, and the absence of a readily available laboratory test to verify compliance. Furthermore, these agents cannot be used safely in patients with severe renal disease. Another limitation is that there are no

specific reversal agents for all the NOACs. The FDA recently approved idarucizumab, an antibody fragment that reverses the anticoagulant effects of dabigatran within minutes.[27] Prothrombin complex concentrate can reverse the anticoagulant effect of the NOACs,[28] but specific and rapid-acting antidotes for rivaroxaban and apixaban are not yet available. Nonetheless, for many patients with AF, the advantages of the newer anticoagulants outweigh the disadvantages.

Older studies showed underutilization of warfarin in patients with AF and risk factors for stroke. The inconvenience and potential risks of warfarin likely contributed to its underutilization. However, underutilization of an oral anticoagulant in patients with AF continues to be the case even with the advent of NOACs and even in patients with a CHA_2DS_2-VASc score 3 or higher.[29]

The major professional societies have incorporated recommendations regarding the use of the factor Xa and direct thrombin inhibitors into their most recent updated guidelines for the management of AF. The ACC/AHA/HRS practice guidelines recommend dabigatran, rivaroxaban, and apixaban as useful alternatives to warfarin for prevention of stroke or systemic embolism in patients with nonvalvular paroxysmal or persistent AF and risk factors for stroke.[2] This recommendation is limited to patients without a prosthetic valve, with creatinine clearance higher than 15 mL/min, and without impaired clotting function from advanced liver disease. The ESC guidelines recommend dabigatran, rivaroxaban, or apixaban for patients with AF in whom maintenance of a therapeutic INR during treatment with warfarin is difficult and state that one of these NOACs should be considered instead of dose-adjusted warfarin for most patients with nonvalvular AF, based on their net clinical benefits.[13] These guidelines recommend that the NOACs not be used in patients with a creatinine clearance of less than 30 mL/min.

The results of a prospective randomized clinical trial and post hoc analysis of three other randomized clinical trials indicate that the NOACs are as effective as warfarin for prevention of thromboembolic complications associated with cardioversion.[30] This is the case regardless of whether a transesophageal echocardiogram is performed before cardioversion to look for left atrial thrombus.

The onset of action of dabigatran, rivaroxaban, and apixaban is approximately 1.5 to 2 hours after a dose. The half-life of dabigatran and apixaban ranges between 10 and 16 hours, and that of rivaroxaban is 5 to 9 hours. These anticoagulants lose most of their effect by 24 hours after discontinuation. The rapid onset of action and washout eliminates the need for bridging therapy with heparin when treatment with one of the NOACs is interrupted for a surgical or invasive procedure. Recent data indicate that the risk of major periprocedural complications does not differ significantly between patients who undergo radiofrequency catheter ablation of AF during uninterrupted therapy with warfarin and patients anticoagulated with a NOAC when the last dose of the NOAC is 1 to 2 days before the procedure and dosing is restarted 6 hours after the procedure, without bridging therapy.[31]

Low-Molecular-Weight Heparin

Low-molecular-weight heparin (LMWH) has a longer half-life than unfractionated heparin and a predictable antithrombotic effect that is attained with a fixed dosage administered subcutaneously twice daily. Because LMWH can be self-injected outside the hospital, it is a practical alternative to unfractionated heparin for initiation of anticoagulation with warfarin in patients with AF. Bridging therapy with LMWH be continued until the INR is 2.0 or higher.

Because of its high cost, LMWH rarely is used in clinical practice as a substitute for long-term conventional anticoagulation. LMWH typically is used as a temporary bridge to therapeutic anticoagulation when therapy with warfarin is initiated or in high-risk patients for a few days before and after a medical or dental procedure when anticoagulation with warfarin has been suspended.

Excision or Closure of the Left Atrial Appendage

Approximately 90% of left atrial thrombi form in the left atrial appendage (LAA), and therefore successful excision or closure of the LAA should greatly reduce the risk of thromboembolic complications in patients with AF. Surgical techniques consist of either excision or closure by suturing or stapling. The efficacy of these techniques is variable and probably dependent on both the technique and the operator.[32] Transesophageal echocardiography (TEE) should be performed after surgical closure of the LAA to confirm successful closure before discontinuation of anticoagulation.

In recent years, several percutaneous LAA occlusion and suturing devices have been developed as alternatives to surgical closure techniques. These devices have their greatest utility in high-risk AF patients who cannot tolerate or who refuse to take an oral anticoagulant.

The only percutaneous occlusion device approved by the FDA specifically for stroke prevention as an alternative to warfarin is the WATCHMAN (Boston Scientific, Marlborough, Massachusetts). This nitinol plug covered with fenestrated fabric became widely available for clinical use after FDA approval in 2015. After implantation of the WATCHMAN using femoral vein access and transseptal catheterization, anticoagulation with warfarin is necessary for at least 45 days, at which time anticoagulation can be discontinued if there is no TEE evidence of peridevice flow. The most recent clinical trial and registry data indicated an implantation success rate of 95% and a procedural complication rate of approximately 2% to 3%, the most common complication being pericardial effusion requiring drainage.[32] Approximately 95% of patients are able to discontinue warfarin at 45 days after implant. Clinical trial data have demonstrated noninferiority of the WATCHMAN compared to warfarin for stroke prevention and a significantly lower risk of hemorrhagic stroke during long-term follow-up.[32]

Another device used in the United States for LAA occlusion is the LARIAT (Sentreheart, Redwood City, California). This device has FDA approval as a method for soft tissue approximation (not stroke prevention) and has been used “off label” in clinical practice in the United States and Europe for LAA occlusion. A guidewire with a magnetic tip is inserted into the left atrium after transseptal catheterization and is positioned at the tip of the LAA and functions as a rail for an epicardial snare. Entry into the pericardial space is attained using a percutaneous approach. A snare with a pretied suture is inserted into the pericardial space and guided toward the LAA. The pretied suture then is tightened to occlude the LAA. In a large multicenter registry, complete LAA closure was achieved in 94% of 712 patients.[33] There was one procedure-related death, and cardiac perforation occurred in 3.4% of patients, with open heart surgery required to repair the perforation in 1.4% of patients.[33] Clinical trial data demonstrating efficacy of the LARIAT for stroke prevention are lacking.

Acute Management of Atrial Fibrillation

Patients who present to the emergency department because of AF often have a rapid ventricular rate, and control of the ventricular rate is most rapidly achieved with intravenous diltiazem or esmolol. If the patient is hemodynamically unstable, immediate transthoracic cardioversion may be appropriate. Cardioversion should be preceded by TEE to rule out a left atrial thrombus if the AF has been present for longer than 48 hours or if the duration is unclear and the patient is not already anticoagulated.

If the patient is hemodynamically stable, the decision to restore sinus rhythm by cardioversion is based on several factors, including symptoms, prior AF episodes, age, left atrial size, and current AAD therapy. For example, in an elderly patient whose symptoms resolve once the ventricular rate is controlled and who already has had early recurrences of AF despite rhythm-control drug therapy, further attempts at

cardioversion usually are not appropriate. On the other hand, cardioversion usually is appropriate for patients with symptomatic AF who present with a first episode of AF or who have had long intervals of sinus rhythm between prior episodes.

If cardioversion is decided for a hemodynamically stable patient who presents with AF that does not appear to be self-limited, two management decisions must be made: early versus delayed cardioversion and pharmacologic versus electrical cardioversion.

The advantages of early cardioversion are rapid relief of symptoms, avoidance of the need for TEE or therapeutic anticoagulation for 3 to 4 weeks before cardioversion if cardioversion is performed within 48 hours of AF onset, and possibly a lower risk of early AF recurrence because of less atrial remodeling (**see Chapter 36**). A reason to defer cardioversion is the unavailability of TEE in an unanticoagulated patient with AF of unclear duration or duration more than 48 hours. Other reasons include a left atrial thrombus by TEE (**see Chapter 14**), a suspicion (based on prior AF episodes) that AF will convert spontaneously within a few days, or a correctable cause of AF (e.g., hyperthyroidism).

When cardioversion is performed early in the course of an episode of AF, there is the option of either pharmacologic or electrical cardioversion. Pharmacologic cardioversion has the advantage of not requiring general anesthesia or deep sedation. In addition, the probability of an immediate recurrence of AF is lower with pharmacologic cardioversion than with electrical cardioversion. However, pharmacologic cardioversion is associated with the risk of adverse drug effects and is not as effective as electrical cardioversion. Pharmacologic cardioversion is unlikely to be effective if the duration of AF is longer than 7 days.

Drugs that can be administered intravenously for cardioversion of AF consist of ibutilide, procainamide, and amiodarone. For AF episodes less than 2 to 3 days in duration, efficacy is approximately 60% to 70% for ibutilide, 40% to 50% for amiodarone, and 30% to 40% for procainamide. To minimize the risk of QT prolongation and polymorphic ventricular tachycardia (torsades de pointes; **see Chapter 39**), the use of ibutilide should be limited to patients with an ejection fraction greater than 35%.

Acute pharmacologic cardioversion of AF also can be attempted with oral drugs in patients without structural heart disease. The most common oral agents for acute conversion of AF are propafenone (300 to 600 mg) and flecainide (100 to 200 mg). It is prudent to administer these drugs under surveillance at first use. If no adverse drug effects are observed, the patient may then be an appropriate candidate for episodic, self-administered AAD therapy on an outpatient basis.

The efficacy of transthoracic cardioversion is approximately 95%. Biphasic waveform shocks convert AF more effectively than monophasic waveform shocks and allow the use of lower energy shocks, resulting in less skin irritation. An appropriate first-shock strength using a biphasic waveform is 150 to 200 J, followed by higher output shocks if needed. If a 360-J biphasic shock is unsuccessful, ibutilide should be infused before another shock is delivered because it lowers the defibrillation energy requirement and improves the success rate of transthoracic cardioversion.

Transthoracic cardioversion can fail to restore sinus rhythm. An increase in shock strength or infusion of ibutilide often results in successful repeat cardioversion. The second type of failure is an immediate recurrence of AF within a few seconds of successful conversion to sinus rhythm. This occurs in approximately 25% for episodes less than 24 hours in duration and 10% for episodes more than 24 hours in duration. For this type of cardioversion failure, an increase in shock strength is of no value. If the patient has not been receiving an oral rhythm-control agent, infusion of ibutilide may be helpful to prevent an immediate recurrence of AF.

Regardless of whether cardioversion is performed pharmacologically or electrically, therapeutic

anticoagulation is necessary for 3 weeks or more before cardioversion to prevent thromboembolic complications if the AF has been ongoing for more than 48 hours. If the time of onset of AF is unclear, for the sake of safety, the AF duration should be assumed to be more than 48 hours. These patients should be therapeutically anticoagulated for 4 weeks after cardioversion to prevent thromboembolic complications that may occur because of atrial stunning. If the duration of AF is known to be less than 48 hours, cardioversion can be performed without anticoagulation. To improve the safety margin, it may be appropriate to use a 24-hour cutoff for the AF duration that allows safe cardioversion without anticoagulation. Postcardioversion atrial stunning and thromboembolic events are possible in patients with comorbidities even when the AF duration is less than 48 hours, and anticoagulation for 4 weeks is appropriate when the CHA_2DS_2-VASc score is more than 2.[34]

When AF duration exceeds 48 hours or is unclear, an alternative to 3 weeks of therapeutic anticoagulation before cardioversion is anticoagulation with heparin and TEE to check for a left atrial thrombus. If no thrombi are seen, the patient can be cardioverted safely but still requires 4 weeks of therapeutic anticoagulation after cardioversion to prevent thromboembolism related to atrial stunning. The major clinical benefit of the TEE-guided approach over the conventional approach is that sinus rhythm is restored several weeks sooner. Compared with the conventional approach, the TEE approach has not been found to reduce the risk of stroke or major bleeding or to affect the proportion of patients still in sinus rhythm at 8 weeks after cardioversion.

Long-Term Management of Atrial Fibrillation

Pharmacologic Rate Control Versus Rhythm Control

Several randomized studies have compared a rate-control strategy with a rhythm-control strategy in patients with AF. Overall, these studies have demonstrated a significantly lower rate of rehospitalization with a rate-control strategy, but no significant differences in other major outcomes, such as all-cause mortality, strokes, bleeding events, worsening heart failure, or quality of life.[35]

The results of these randomized studies should not be applied systematically to all patients with AF. It is important to note that many patients in the rhythm-control arms of these studies continued to have AF, and that the possible beneficial effects of sinus rhythm over AF could have been negated by adverse effects of the AADs. Furthermore, many of the patients included in these studies were elderly and had minimal or no symptoms from the AF.

The decision to pursue a rhythm-control strategy versus a rate-control strategy should be individualized with consideration of several factors. These include the nature, frequency, and severity of symptoms; the length of time that AF has been present continuously in patients with persistent AF; left atrial size; comorbidities; the response to prior cardioversions; age; the side effects and efficacy of the AADs already used to treat the patient; and the patient's preference.

The randomized studies convincingly demonstrated that a rate-control strategy is preferable to a rhythm-control strategy in asymptomatic or minimally symptomatic patients age 65 or older. When the AF is persistent, it is reasonable to restore sinus rhythm with AAD therapy or transthoracic cardioversion at least once in patients younger than 65 and in patients 65 or older who are symptomatic from the AF despite adequate heart rate control. If the AF has been continuous for more than 1 year or if the left atrial diameter is very large (>5.0 cm), there is a high probability of an early recurrence of AF, and this should be taken into account in deciding on the best strategy. After cardioversion, the decision to maintain the patient on AAD therapy to delay the next episode of AF is based on the patient's preference, the perceived

risk of an early recurrence of AF, and the duration of sinus rhythm between prior cardioversions. Treatment by cardioversion without daily AAD therapy is acceptable if episodes of AF are separated by at least 6 months. Treatment with a rhythm-control drug usually is appropriate when AF recurs within a few months of cardioversion.

The most realistic goal of AAD therapy in patients with persistent AF is to delay the onset of the next episode by at least several months, not for several years. It often is appropriate to continue therapy with a particular AAD at a constant dosage if recurrences of AF are limited to approximately one episode per year.

In patients with symptomatic paroxysmal AF, the aggressiveness with which a rhythm-control strategy is pursued should be dictated by the frequency and severity of symptoms and how well AAD therapy is tolerated. Drug therapy is more likely to be judged successful when patients are reminded that the goal of therapy is not complete suppression of AF but a clinically meaningful reduction in frequency, duration, and severity of episodes.

A pharmacologic rhythm-control strategy does not necessarily require daily AAD therapy. Episodic drug therapy (the “pill-in-the-pocket” approach) is useful for patients whose episodes of AF are relatively infrequent. Episodic drug therapy is a reasonable option for patients who are clearly aware of the onset and termination of AF episodes and who have lone AF or only minimal structural heart disease. A typical AAD regimen consists of a class IC drug (flecainide or propafenone) plus a short-acting beta blocker (e.g., propranolol) or calcium channel blocker (e.g., verapamil) for rate control. Many patients with infrequent episodes prefer this approach because it eliminates the inconvenience, cost, and possible side effects of daily prophylactic therapy. However, patients who are disabled by severe symptoms during AF may prefer daily prophylactic therapy even if episodes are infrequent.

Many patients with symptomatic AF also have asymptomatic episodes. Therefore, daily antithrombotic therapy to prevent thromboembolic events is appropriate for all patients being treated for recurrent AF, whether it is persistent or paroxysmal and whether a rhythm-control or rate-control strategy is employed. The choice of no therapy, an oral anticoagulant, aspirin, or aspirin plus clopidogrel should be dictated by an analysis of risk factors.

Pharmacologic Rate Control

An excessively rapid ventricular rate during AF often results in uncomfortable symptoms and decreased effort tolerance and can cause a tachycardia-induced cardiomyopathy if it is sustained for several weeks to months. Optimal heart rates during AF vary with age and should be similar to the heart rates that a patient would have at a particular degree of exertion during sinus rhythm. Heart rate control must be assessed both at rest and during exertion. At rest, the ideal ventricular rate during AF is in the range of 60 to 80 beats/min. During mild to moderate exertion (e.g., rapid walking), the target rate should be 90 to 115 beats/min. During strenuous exercise, the ideal rate is in the range of 120 to 160 beats/min. Optimal assessment of the degree of heart rate control is provided by an ambulatory 24-hour Holter recording or an exercise test.

Oral agents available for long-term heart rate control in patients with AF are digitalis, beta blockers, calcium channel antagonists, and amiodarone. The first-line agents for rate control are beta blockers and the calcium channel antagonists verapamil and diltiazem. A combination is often used to improve efficacy or to limit side effects by allowing the use of smaller dosages of the individual drugs. In patients with sinus node dysfunction and tachycardia-bradycardia syndrome, the use of a beta blocker with intrinsic sympathomimetic activity (pindolol, acebutolol) may provide rate control without aggravating sinus

bradycardia.

Digitalis may adequately control the rate at rest but often does not provide adequate rate control during exertion. However, its use for rate control of AF is controversial because digitalis has been shown to increase the risk of all-cause mortality, particularly among patients with AF.[36]

Amiodarone is much less frequently used for rate control than the other negative dromotropic agents because of the risk of organ toxicity associated with long-term therapy. Amiodarone can be an appropriate choice for rate control if the other agents are not tolerated or are ineffective. For example, amiodarone would be an appropriate choice for a patient with persistent AF, heart failure, and reactive airway disease who cannot tolerate either a calcium channel antagonist or a beta blocker and who has a rapid ventricular rate despite treatment with digitalis.

Strict heart rate control can be difficult to achieve pharmacologically. Based on the results of a single randomized study that demonstrated no significant differences in major outcomes between a lenient rate-control strategy (resting rate <110 beats/min) and a strict rate-control strategy (resting heart rate <80 beats/min, rate during moderate exercise <110 beats/min), a lenient rate-control strategy is reasonable if the patient remains asymptomatic and left ventricular systolic function is not compromised.[2] However, strict rate control often still is an appropriate goal for relief of symptoms, improvement in functional capacity, and avoidance of tachycardia-induced cardiomyopathy during long-term follow-up.

Pharmacologic Rhythm Control

The results of published studies on the efficacy of AADs for AF suggest that all the available drugs except amiodarone have similar efficacy and are associated with a 50% to 60% reduction in the odds of recurrent AF during 1 year of treatment. The one drug that stands out as having higher efficacy than the others is amiodarone. In studies that directly compared amiodarone with sotalol or class I drugs, amiodarone was 60% to 70% more effective in suppressing AF. However, because of the risk of organ toxicity, amiodarone is not appropriate first-line drug therapy for many patients with AF. Because the efficacy of rhythm-control agents other than amiodarone is in the same general range, the selection of an AAD to prevent AF often is dictated by the issues of safety and side effects.

Ventricular proarrhythmia from class IA agents (quinidine, procainamide, disopyramide) and class III agents (sotalol, dofetilide, dronedarone, amiodarone) is manifested as QT prolongation and polymorphic ventricular tachycardia (torsades de pointes). Risk factors for this type of proarrhythmia include female gender, left ventricular dysfunction, and hypokalemia. The risk of torsades de pointes appears to be much lower with dronedarone and amiodarone than with the other class III drugs. The ventricular proarrhythmia from class IC agents (flecainide and propafenone) manifests as monomorphic ventricular tachycardia, sometimes associated with widening of the QRS complex during sinus rhythm but not QT prolongation. Drugs most likely to result in ventricular proarrhythmia are quinidine, flecainide, sotalol, and dofetilide. In controlled studies, these agents increased the risk of ventricular tachycardia by a factor of 2 to 6.

Adverse drug events or side effects resulting in discontinuation of drug therapy are fairly common with rhythm-control drugs, with discontinuation rates reported to be as high as 40%.[37]

The best options for drug therapy to suppress AF depend on the patient's comorbidities. In patients with lone AF or minimal heart disease (e.g., mild left ventricular hypertrophy), flecainide, propafenone, sotalol, and dronedarone are reasonable first-line drugs, and amiodarone and dofetilide can be considered if the first-line agents are ineffective or not tolerated. In patients with substantial left ventricular hypertrophy (left ventricular wall thickness >15 mm), the hypertrophy heightens the risk of ventricular proarrhythmia, and the safest choices for drug therapy are amiodarone and dronedarone.[2] In

patients with coronary artery disease (CAD), several of the class I drugs have been found to increase the risk of death, and the safest first-line options are dofetilide and sotalol, with amiodarone reserved for use as a second-line agent. In patients with heart failure, several AADs have been associated with increased mortality, and the only two drugs known to have a neutral effect on survival are amiodarone and dofetilide (**see Chapter 36**).

At the time of FDA approval, it was known that dronedarone increases mortality in NYHA Class IV heart failure or patients with a recent episode of decompensated heart failure. After approval, the categories of patients in which dronedarone is contraindicated expanded based on the results of a randomized clinical trial that was discontinued prematurely because of major adverse drug effects.[38] Dronedarone should be avoided in patients age 65 or older with permanent AF and CAD, prior stroke, or symptomatic heart failure and in those age 75 or older with hypertension and diabetes.

Rhythm Control with Agents Other Than Antiarrhythmic Drugs

Experimental studies indicate that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have favorable effects on electrical and structural remodeling (**see Chapter 34**). This explains why some studies have shown that ACE inhibitors and ARBs prevent AF. However, other studies have demonstrated that these agents do not prevent AF. A meta-analysis demonstrated that the strongest beneficial effects have been observed with ARBs and in patients with heart failure.[39] However, the quality of the data in the meta-analysis studies was low, and at present, there is insufficient evidence to support the use of ACE inhibitors and ARBs for the sole purpose of preventing AF.

Some evidence indicates that statins prevent AF, perhaps because of their anti-inflammatory effects. A systematic review of 16 observational studies demonstrated a 12% reduction in the relative risk of new-onset AF and a 15% reduction in recurrent AF in patients treated with statins.[40] However, a meta-analysis of 11 randomized clinical trials concluded that statins do not prevent AF in patients who have not undergone open heart surgery.[40] Therefore, the available data do not support the use of statins for the prevention of AF.

Omega-3 polyunsaturated fatty acids (PUFAs) have anti-inflammatory and antioxidant effects and also can have direct ion channel effects. Epidemiologic studies suggested that fish oil could prevent AF, which lead to several randomized clinical trials that assessed the efficacy of PUFAs for AF prevention. These trials reported conflicting results, but the predominance of the data indicate that the daily intake of PUFAs or fish oil does not prevent recurrent AF after cardioversion or episodes of paroxysmal AF.[41]

Nonpharmacologic Management of Atrial Fibrillation

Pacing to Prevent Atrial Fibrillation

Multiple studies have been performed to determine whether various atrial pacing strategies can prevent or terminate AF. Overall, there has been no convincing evidence that any atrial pacing strategy is effective in preventing or terminating episodes of AF, and therefore atrial pacing is not indicated for prevention of AF in patients without bradycardia. In patients with a bradycardia indication for a pacemaker and paroxysmal AF or recurrent episodes of persistent AF, the available data clearly support the use of atrial-based pacing and programming to minimize the amount of ventricular pacing.[42]

Catheter Ablation of Atrial Fibrillation

Catheter ablation reliably and permanently eliminates several types of arrhythmias, such as atrioventricular nodal reentrant tachycardia (AVNRT) and accessory pathway–mediated tachycardias (**see Chapters 36 and 37**). Success rates greater than 95% are attainable when the arrhythmia substrate is well defined, localized, and temporally stable. In contrast, the arrhythmia substrate of AF is not well understood, usually is widespread, is variable between patients, and may be progressive. Furthermore, several factors that promote AF cannot be addressed simply by catheter ablation, including comorbidities (e.g., hypertension, obesity, obstructive sleep apnea), structural remodeling of the atria, inflammatory factors, and genetic factors (**see Chapter 7**). Therefore, whereas late recurrences of AVNRT or accessory pathway conduction are very rare, AF can recur more than 2 or 3 years after an initially successful ablation procedure.

Selection of Patients

Given the limitations of catheter ablation of AF, it usually is appropriate to treat the patient with at least one rhythm-control drug before catheter ablation is considered. This is particularly true if the AF is persistent because the efficacy of catheter ablation is lower for persistent AF than for paroxysmal AF. The most appropriate candidates for catheter ablation have symptomatic AF affecting quality of life and not adequately responding to drug therapy. The ideal candidate has lone AF or only minimal structural heart disease. The recommendation for catheter ablation should depend on the severity of symptoms, AF burden, prior responses to drug therapy or transthoracic cardioversion, and estimated probability of success. Catheter ablation is least likely to be successful when the left atrium is extremely dilated or if the AF has been persistent for more than 3 or 4 years.

Catheter ablation of AF usually is contraindicated in patients who have a left atrial thrombus or who cannot tolerate anticoagulation for at least 6 to 8 weeks after ablation. Catheter ablation usually is also inappropriate in asymptomatic individuals with a CHA_2DS_2-VASc score greater than 1 whose only motivation to undergo the procedure is to eliminate the need for anticoagulation.

Although usually reserved for patients who have not responded adequately to ADD treatment, catheter ablation of AF can also be appropriate first-line therapy in patients younger than 35 with symptomatic AF, patients with sinus node dysfunction in whom ADD therapy is likely to create the need for a permanent pacemaker, and patients who express a strong preference for catheter ablation over drug therapy.

Radiofrequency Catheter Ablation

A commonly used energy for catheter ablation of AF is radiofrequency (RF) energy. RF energy is delivered point by point, typically in association with a three-dimensional electroanatomic mapping system as a navigation guide and to create a visual record of the sites that already have been ablated (**Fig. 38.7**). To improve anatomic accuracy, the electroanatomic map of the left atrium can be merged with a computed tomography scan or magnetic resonance image of the left atrium and pulmonary veins (PVs) or with an ultrasound image generated by intracardiac echocardiography. An important determinant of lesion depth and durability is *contact force,* and the newest generation of RF ablation catheters provides the operator with immediate feedback on contact force.

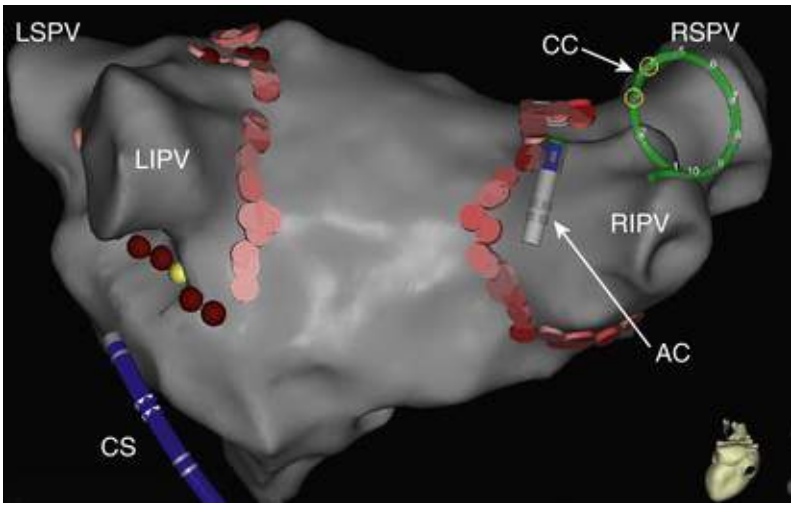

FIGURE 38.7 An electroanatomic map of the left atrium. Icons representing the distal portion of the ablation catheter (*AC*), circular catheter (*CC*) in the right superior pulmonary vein (*RSPV*), and a catheter positioned within the coronary sinus (*CS*) are visualized in real time. Circumferential antral ablation was performed around the left and right pulmonary veins. Each one of the *pink, red,* and *yellow* tags represents a site at which radiofrequency energy was delivered. *LIPV,* Left inferior pulmonary vein; *LSPV,* left superior pulmonary vein; *RIPV,* right inferior pulmonary vein.

Because of their important role in triggering and maintaining episodes of AF, almost all ablation strategies include electrical isolation of the PVs (**Fig. 38.8**). This is often sufficient for patients with paroxysmal AF and sometimes sufficient for patients with persistent AF. Pulmonary vein (PV) isolation can be accomplished by either ostial ablation or wide-area ablation 1 to 2 cm away from the ostia, in the antral regions of the PVs. Most of the available data indicate that wide-area ablation is more effective than ostial ablation, probably because it also targets drivers that are in the antrum, outside the PV itself.[43] Triggers of AF can also arise from other thoracic veins, such as the superior vena cava, coronary sinus, and the vein of Marshall. After the PVs have been isolated, infusion of isoproterenol is helpful to determine whether any non–PV triggers are present.

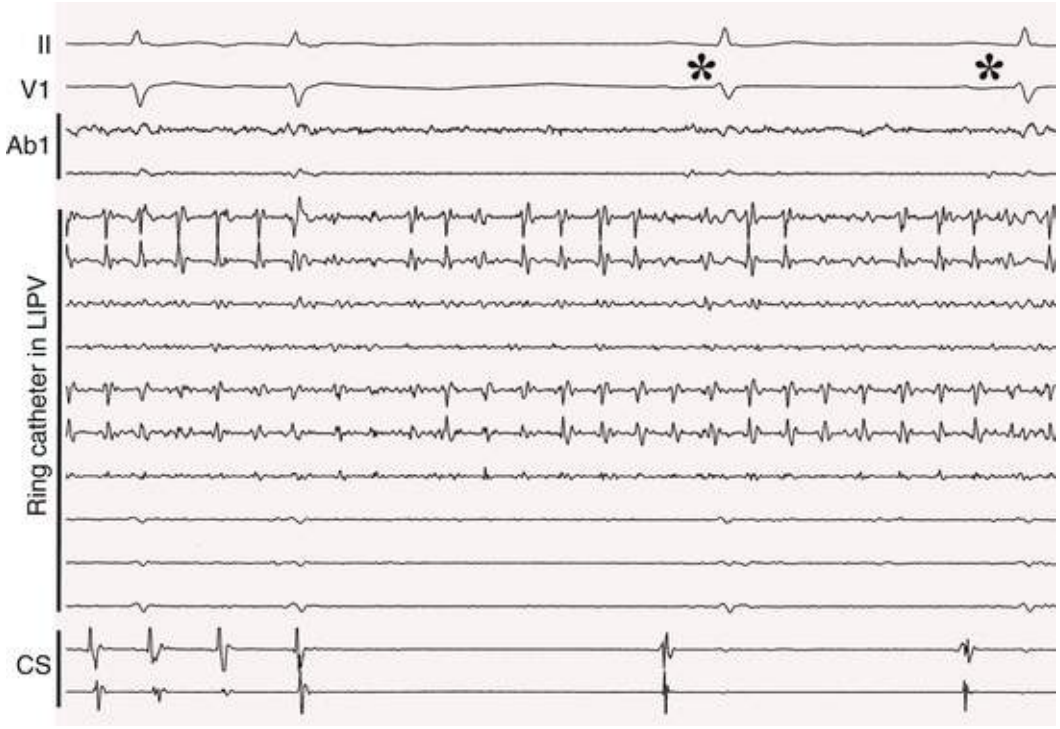

FIGURE 38.8 A tachycardia with a cycle length of 80 milliseconds arising in a left inferior pulmonary vein (*LIPV*) during AF. AF converted to sinus rhythm (*asterisks*) during radiofrequency ablation when the LIPV became electrically isolated. The pulmonary vein tachycardia was still present inside the vein. Conversion to sinus rhythm on electrical isolation of the LIPV is strong evidence that the tachycardia arising in the muscle sleeve of this pulmonary vein was the driver of AF in this patient. Shown are leads II and V_1, the electrograms recorded by the ablation catheter (*Abl*), by a ring catheter in the LIPV, and in the coronary sinus (*CS*).

A variety of ablation strategies have been used for persistent AF after the PVs have been isolated: linear ablation across the left atrial roof, mitral isthmus, or cavotricuspid isthmus; ablation of complex fractionated atrial electrograms (CFAEs) in the left atrium, coronary sinus, or right atrium; various combinations of linear and CFAE ablation; and ablation of ganglionated plexi.[43] The endpoint of catheter ablation of persistent AF is either completion of a prespecified lesion set (in which case sinus rhythm is restored by cardioversion) or stepwise ablation until the AF converts to sinus rhythm. Recent randomized studies have demonstrated that antral PV isolation is as effective as PV isolation plus linear ablation and/or ablation of CFAEs.[44,45]

A novel approach to ablation of AF is based on the hypothesis that AF is sustained by localized sources, either rotors or focal impulses.[5] Signal processing using proprietary software allows identification of focal impulses and rotors that are targeted for RF ablation during ongoing episodes of AF. In one of the first clinical studies using this approach, AF termination or slowing was successfully achieved by ablation of the localized sources in 86% of cases. At a median of 9 months of follow-up, 82% of patients were free of AF, compared to 45% of patients in a control group who underwent conventional ablation.[5] These early results suggested that focal impulse and rotor modulation can improve outcomes of catheter ablation of AF. However, more recent studies in patients with paroxysmal, persistent, and longstanding persistent AF have not confirmed the initial results of ablation of rotors and/or focal impulses. The single-procedure freedom from AF/atrial tachycardia (AT) off AADs at 6 to 18 months of follow-up was only 17% to 21% in these studies.[46,47] Therefore, although focal impulse and rotor modification is potentially an important step forward in understanding the mechanism of AF, its clinical value in patients undergoing catheter ablation of AF is unsettled.

When the efficacy of catheter ablation of AF is evaluated, recurrences of AF in the first 3 months after ablation usually are ignored. A 3-month blanking period excludes early recurrences that are caused by a

transient inflammatory response or incomplete lesion maturation. Even in patients with symptomatic AF, postablation recurrences can be asymptomatic. Therefore, accurate assessment of efficacy requires monitoring for at least 7 days and preferably for 1 month with a device capable of detecting asymptomatic episodes of AF. Ideally, the monitoring should be performed at 6 and 12 months. Continuous monitoring for recurrent AF is possible in patients who have a pacemaker or ICD and an atrial lead. A miniaturized insertable cardiac monitor with wireless telemetry for remote monitoring (Reveal LINQ, Medtronic, Minneapolis, Minnesota) also allows for intense monitoring for postablation AF.[48]

A wide range of success rates has been reported for RF catheter ablation of AF. When the latest-generation ablation catheters are used by experienced operators, 12-month freedom from AF/AT off AADs after a single procedure generally is 70% to 75% for paroxysmal AF[49,50] and 50% to 60% for persistent AF.[44,45]

Recurrent AF after PV isolation in patients with paroxysmal AF most often is attributable to electrical reconnection of one or more PVs but sometimes is caused by triggers or drivers of AF originating in structures such as the superior vena cava or coronary sinus or in the atria themselves. After reisolation of the PVs and ablation of triggers outside the PVs, 12-month efficacy of 85% to 90% can be expected.

Redo ablation procedures in patients with persistent AF usually consist of re-isolation of the PVs if necessary, and additional ablation directed at substrate modification by targeting CFAEs or creating lines of conduction block at sites such as the left atrial roof or mitral isthmus.[43] A 12-month success rate of 75% to 85% typically is achieved after multiple ablation procedures for persistent AF.

Most recurrences of AF after RF catheter ablation occur within the first year of follow-up. However, recurrences continue to occur at a rate of approximately 10% per year at 1 to 3 years, then approximately 4% to 5%/year at 3 to 12 years after ablation.[51] The predictors of late recurrences of AF include a history of persistent AF before the initial ablation procedure, age, left atrial size, diabetes, valvular heart disease, cardiomyopathy, and sleep apnea.[43] In addition, obesity and lack of cardiovascular conditioning have been reported to predispose to recurrences of postablation AF. Treatment of sleep apnea, weight loss, and improvement in cardiovascular fitness have been found independently to reduce the risk of recurrent AF after an ablation procedure.[52,53]

Atrial tachyarrhythmias that occur after catheter ablation of AF can take the form of atrial tachycardia/flutter that can be either focal or reentrant. When the ablation strategy consists only of PV isolation, postablation focal ATs often are attributable to partial recovery of PV conduction. The incidence of reentrant AT/flutter after ablation is related to the extent of ablation at atrial sites other than around the PVs. When extensive ablation is performed in the left atrium or in both atria, AT/flutter can occur during follow-up in up to 50% or more of patients. These arrhythmias do not respond well to AAD therapy and often require another ablation procedure for elimination.

The risk of a major complication from RF catheter ablation of AF is reported to be 5% to 6%.[54,55] The most common major complications are cardiac tamponade, PV stenosis, and cerebral thromboembolism, each with a prevalence of approximately 1%. The risk of a femoral vascular injury is reported to be 1% to 2%. The risk of a major complication is more than twofold higher when the annual operator volume is less than 25 cases compared to more than 25 cases.[54]

The risk of esophageal perforation is reported in the range of 0.01% to 0.02%.[56] Despite its rarity, this complication is of great concern because it often is lethal. Patients typically present 3 to 14 days after ablation with one of more of the following: dysphagia, odynophagia, fever, leukocytosis, bacteremia, and septic, thrombotic, or air emboli. Computed tomography of the chest with intravenous contrast is the diagnostic test of choice. The presence of contrast in the esophagus or air in the mediastinum or cardiac chambers is indicative of esophageal perforation or fistula formation. Instrumentation of the esophagus

should be avoided.

Monitoring of the position of the esophagus and intraluminal esophageal temperature monitoring have been used to prevent esophageal injury during ablation along the posterior wall. Although these maneuvers may reduce the risk, they clearly do not prevent all cases of esophageal injury, since 90% of patients with an esophageal perforation had undergone monitoring of the esophageal position or temperature.[56] There is evidence that limiting the power of RF energy applications to 20 to 25 watts for less than 30 seconds when ablating along the posterior left atrial wall and the use of periprocedural proton pump inhibitors reduce the risk of esophageal injury.[57]

Based on the results of a recent global survey, 72% of patients with an esophageal perforation had evidence of an atrial-esophageal fistula, and mortality among these patients was 79%. In contrast, among the 28% of patients with an esophageal perforation who did not have an atrial-esophageal fistula, mortality was 13%.[56] This highlights the importance of early diagnosis and treatment of esophageal perforations. Early surgical intervention is appropriate regardless of whether an atrial-esophageal fistula is present.

A recently recognized complication of RF ablation is silent cerebral ischemic lesions. Cerebral magnetic resonance imaging has demonstrated silent cerebral ischemic lesions in 2% to 14% of patients in whom an irrigated-tip RF ablation catheter is used.[58] The long-term clinical significance of these lesions is unclear.

Recent randomized clinical trials have demonstrated that RF catheter ablation of AF is superior to AAD therapy for prevention of AF. In previously untreated patients with paroxysmal AF, there was an absolute difference of 18% in the 12-month risk of recurrent AF in favor of RF catheter ablation over AAD therapy.[59] Among patients with persistent AF, there was an absolute difference of 27% in the 12-month risk of recurrent AF in favor of RF catheter ablation over AAD therapy.[60]

Cryoballoon Ablation

In 2010 a cryoballoon catheter designed to isolate PVs became widely available for use in the United States. In contrast to point-by-point RF ablation around the PVs, the cryoballoon was designed to fit into the antrum of a PV and to create a circumferential ablation lesion using cryoenergy. Cryoenergy is delivered through the entire distal half of the second-generation cryoballoon catheter currently in clinical use. Complete occlusion of the PV by the inflated balloon is necessary for reliable PV isolation (**Fig. 38.9**). Two 4-minute applications of cryoenergy initially were recommended for each of the PVs. With the second-generation cryoballoon catheter, a single 3- or 4-minute application of cryoenergy often is sufficient to create durable PV isolation in a majority of PVs **(Fig. 38.10**). Among patients with paroxysmal AF, with a mean of 1.1 to 1.7 applications of cryoenergy per PV, 1-year freedom from recurrent AF was 80% to 82% using a single-freeze protocol.[61,62]

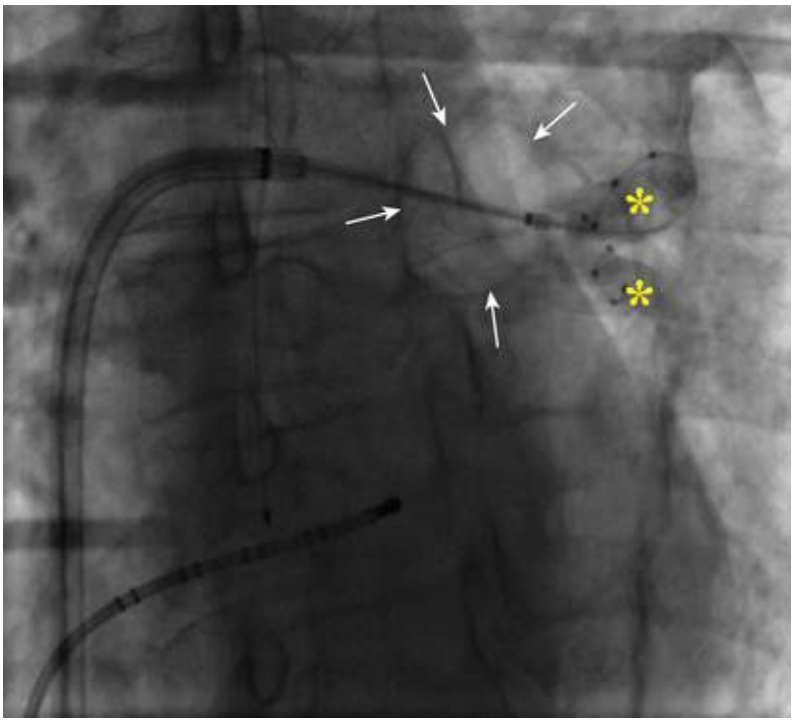

FIGURE 38.9 A left anterior oblique fluoroscopic image of the heart showing a cryoballoon catheter positioned in the antrum of the left inferior pulmonary vein. The 28-mm balloon (*arrows*) is inflated, and there is no leakage of contrast injected through the lumen of the cryoballoon catheter into the vein (*asterisks*). This indicates complete occlusion of the vein, a necessary requirement for durable pulmonary vein isolation. A diagnostic ring catheter is positioned within the vein.

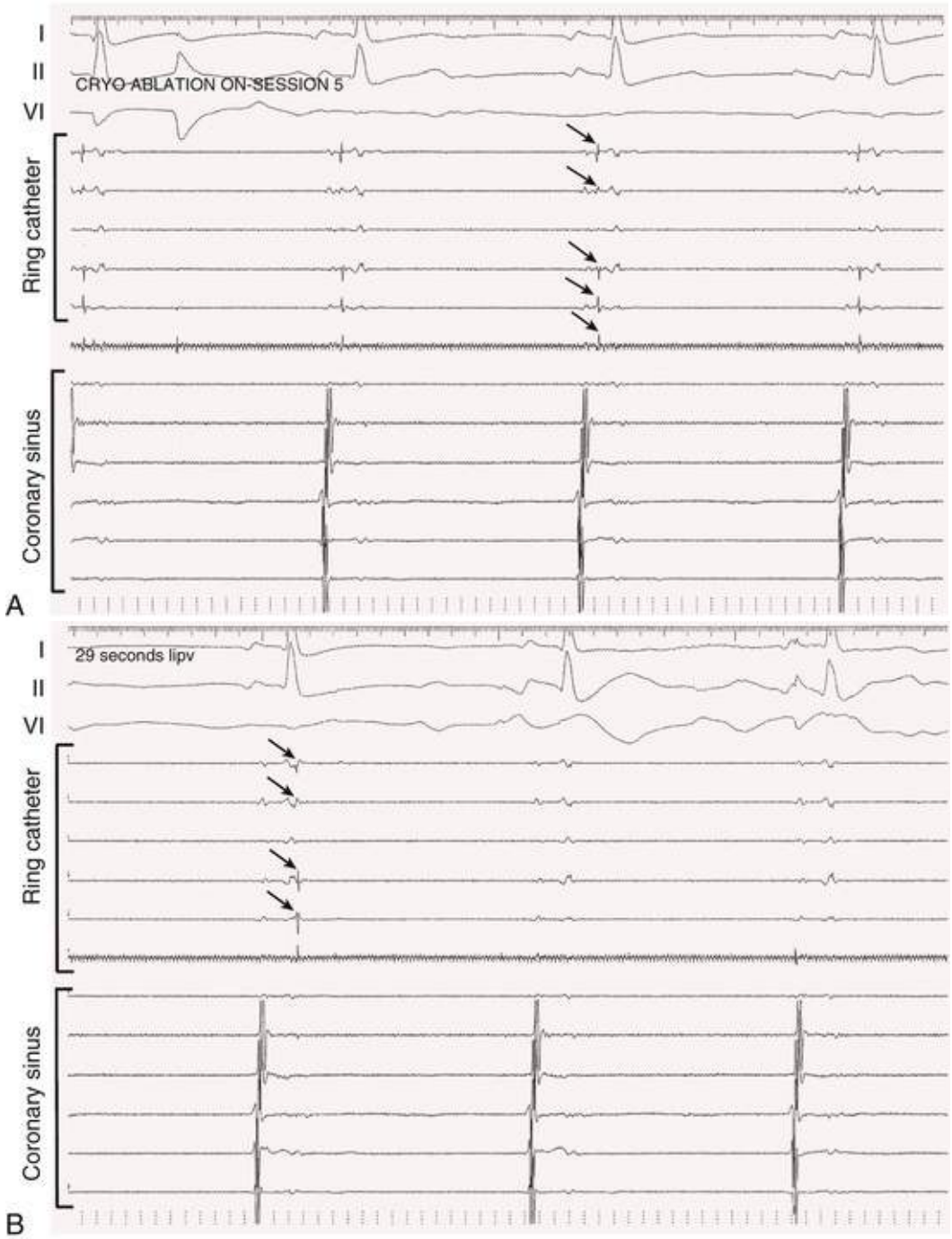

FIGURE 38.10 **A,** Pulmonary vein potentials (*arrows*) recorded from within the left inferior pulmonary vein at the onset of an application of cryoenergy, during sinus rhythm at a rate of 54 beats/min. **B,** At 29 seconds into an application of cryoenergy, there is a conduction delay in the pulmonary vein potentials (*arrows*) followed by their complete disappearance, indicating isolation of the left inferior pulmonary vein (*lipv*). The application of cryoenergy was continued for a total of 4 minutes.

Avoidance of entry of the cryoballoon into the luminal portion of a PV is important to avoid PV stenosis. The most commonly used cryoballoon catheter has a 28-mm diameter when the balloon is fully inflated. The relatively large size of the balloon typically allows occlusion of a PV from the antrum. With use of the 28-mm balloon, up to 40% of the posterior wall between the left and right PVs is rendered electrically silent.[63]

A multielectrode catheter inserted through a central lumen of the cryoballoon catheter often allows recording of PV potentials during an application of cryoenergy. Disappearance or dissociation of PV potentials within the first minute of a cryoenergy application is a strong independent predictor of durable PV isolation[64] (**Fig. 38.10**). Other independent predictors are achieving a balloon temperature of −40°C in less than 60 seconds during an application of cryoenergy and an interval thaw time to 0°C of longer than

10 seconds on completion of a cryoenergy application.[64,65]

There is a lower clinical success rate with use of the cryoballoon catheter in patients with persistent AF than in those with paroxysmal AF. Among patients with persistent AF who undergo PV isolation using the 28-mm cryoballoon catheter, freedom from AF at 12 months of follow-up was 60%.[66] This is similar to the clinical results achieved in similar patients when wide-area circumferential PV isolation is performed by point-by-point RF catheter ablation.[66]

Possible complications associated with the cryoballoon catheter have the same risk as with RF catheter ablation of AF, including cardiac tamponade (approximately 1%) and femoral vascular injury (1% to 2%).

The most common complication of cryoballoon ablation is phrenic nerve injury. During early experience with the cryoballoon catheter, the incidence of right phrenic nerve injury was approximately 10%, with the injury resolving within 12 months in almost all patients.[67] Injury to the left phrenic nerve is possible but rare. It now is standard clinical practice to pace the phrenic nerve with a catheter positioned in the superior vena cava or right subclavian vein during cryoballoon ablation at the right PVs. Various strategies are available to monitor diaphragmatic contraction or phrenic nerve function during phrenic nerve pacing, including direct palpation of diaphragmatic contraction and monitoring the diaphragmatic compound motor action potential.[68] The immediate discontinuation of an application of cryoenergy on the first evidence of phrenic nerve injury greatly reduces the risk of long-lasting or permanent injury. In recent experience with the 28-mm cryoballoon catheter, the risk of right phrenic nerve injury is as low as 1.5% to 2%.[62,69]

A small number of case reports have made it clear that death from an atrial-esophageal fistula is a potential complication of cryoballoon ablation. Measures to minimize the risk of esophageal injury are appropriate, including the periprocedural use of a proton pump inhibitor and monitoring of intraluminal esophageal temperature during cryoablation. It is common practice to discontinue cryoablation if the esophageal temperature drops to 30°C. This provides a large safety margin for avoiding esophageal injury.[70]

Radiofrequency Catheter Ablation Versus Cryoballoon Ablation for Atrial Fibrillation

A small number of randomized studies have compared the efficacy of RF catheter ablation versus cryoballoon ablation to isolate the PVs. These studies have shown no major differences in outcomes. The largest multicenter, randomized clinical trial that compared the safety and efficacy of RF catheter ablation versus cryoballoon ablation was performed in 693 patients with paroxysmal AF who underwent PV isolation using either an irrigated-tip radiofrequency ablation catheter (n = 341) or a cryoballoon catheter (n = 341).[71] Ideally, the most advanced versions of these catheters would have been used in all patients; however in the cryoablation arm, 82% of the cases were performed using the second-generation balloon, but in the RF ablation arm, only 26% of cases were performed using a contact-force-sensing catheter.

Designed to be a noninferiority trial,[71] the primary efficacy endpoint was a combination of recurrence of an atrial tachyarrhythmia longer than 30 seconds, AAD prescription, or a repeat ablation procedure. The primary safety endpoint was a combination of death, stroke, or a treatment-related serious adverse event. A primary efficacy endpoint occurred by 12 months of follow-up in 35.9% of patients in the RF catheter ablation arm and 34.6% of patients in the cryoablation arm. There was also no significant difference in the incidence of primary safety endpoints between the two groups (13.6% in RF catheter ablation arm versus 11.0% in cryoballoon ablation arm). The prevalence of serious adverse events did

not differ significantly between the RF catheter ablation group (9%) and the cryoablation group (7.5%). The mean procedure time was 16 minutes shorter in the cryoballoon ablation arm. This study demonstrated that cryoballoon ablation is not inferior to RF catheter ablation in regard to efficacy or safety.

Given that outcomes are similar with point-by-point RF ablation and cryoballoon ablation, the most important factor in deciding which approach to use is operator preference. The advantages of RF catheter ablation include greater versatility, with the ability to ablate AF triggers or drivers that are outside the pulmonary venous antral regions; greater flexibility in energy delivery (e.g., being able to cut back on power delivery when ablating close to esophagus); a lower risk of phrenic nerve injury; ability to use the same catheter to ablate other arrhythmias (e.g., atrial flutter, AVNRT); and lower cost. The advantages of cryoballoon ablation include a shorter learning process, less demand for technical expertise in catheter manipulation, and a shorter procedure time.

Remote Magnetic Navigation

Two systems currently are available for remote navigation of an RF ablation catheter. One system has large magnets positioned on each side of the patient and small magnets embedded in the tip of the ablation catheter that allow remote navigation by shifting the magnetic field vectors. The other has an ablation catheter navigated remotely by a robotic steerable sheath system. The advantages of these systems are improved catheter stability, marked reduction in radiation exposure to the operator, and avoidance of the technical challenges of manual catheter manipulation. The experience to date with remote magnetic navigation for catheter ablation of AF suggests that safety and efficacy outcomes are similar to the outcomes achieved with manual RF catheter ablation.[72]

Ablation of the Atrioventricular Node

Radiofrequency catheter ablation of the AV node results in complete AV nodal block and substitutes a regular, paced rhythm for an irregular and rapid native rhythm. It is a useful strategy in patients who are symptomatic from AF because of a rapid ventricular rate that cannot be adequately controlled pharmacologically as a result of inefficacy or intolerance to rate-control drugs, and who either are not good candidates for AF ablation or already have undergone unsuccessful attempts at ablation. AV node ablation also can be helpful in patients with heart failure and AF to maximize the benefits of cardiac resynchronization therapy (CRT) if there already is not 100% ventricular pacing.[73]

In patients with AF and an uncontrolled ventricular rate, AV node ablation improves the left ventricular ejection fraction (EF) if there is a tachycardia-induced cardiomyopathy. AV node ablation also has been shown to improve symptoms, quality of life, and functional capacity and to reduce the use of health care resources.[74]

The disadvantages of AV node ablation are that it creates a lifelong need for ventricular pacing and does not restore AV synchrony. Although symptoms and functional capacity typically improve after AV node ablation in patients with AF and an uncontrolled ventricular rate, some patients may not feel as well as during sinus rhythm.

Atrioventricular node ablation is a technically simple procedure with an acute and long-term success rate of 98% or higher and a very low risk of complications. In patients with persistent AF, a ventricular pacemaker is implanted. A dual-chamber pacemaker is appropriate if the AF is paroxysmal. Most patients have a good clinical outcome with right ventricular pacing, but in patients with left ventricular dysfunction, biventricular pacing for CRT is appropriate.[75] In patients with an ischemic or nonischemic

cardiomyopathy and EF of 30% to 35% or lower, an ICD may be appropriate for primary prevention of sudden death. However, a pacemaker without the ICD often is adequate for patients with a borderline EF (30% to 35%) and a rapid ventricular rate because the EF is likely to improve after the ventricular rate has been controlled by AV node ablation.[74] His bundle pacing can be considered in some patients to avoid problems with right ventricular pacing.

Surgical Approaches to Atrial Fibrillation

The most effective surgical procedure for AF is the "cut-and-sew" maze procedure developed by Cox in 1987. This operation involves multiple atrial incisions to isolate the PVs and to create lines of block in the left atrium and right atrium. In addition, the left and right atrial appendages are excised. In a study from a highly experienced surgical center in patients who underwent periodic 24-hour Holter monitoring during follow-up, there was 83% freedom from AF off drugs at a median follow-up of 5.9 years after the most recent version of the cut-and-sew maze procedure (Cox maze III).[76] However, because continuous monitoring for only 24 hours at a time often is insufficient to detect recurrent episodes of AF, the 83% long-term freedom from AF likely was an overestimate.

The cut-and-sew Cox maze procedure has not been widely performed because it requires cardiopulmonary bypass, is technically difficult, and is associated with a mortality rate of 1% to 2%.

A large variety of surgical ablation tools have been developed to simplify the Cox maze III procedure. These tools allow the surgeon to substitute an ablation line for a surgical incision. Some surgeons use a minimally invasive approach in which the ablation tools are inserted through small incisions between the ribs, and thoracoscopic video-assisted epicardial ablation is performed. Several different types of energy have been used for surgical ablation: RF energy, cryoenergy, microwave, laser, and high-intensity focused ultrasound. The tool that most consistently produces transmural ablation lesions is a clamp device developed to isolate the PVs using bipolar RF energy.

Various surgical ablation strategies have been used, including PV isolation, left atrial ablation, and the Cox maze lesion set (Cox maze IV) in which a combination of RF and cryothermal ablation lines replace most of the surgical incisions. In a large series of patients with AF who underwent the Cox maze IV procedure, freedom from AF off AADs at 5 years was 66%, with no difference in efficacy between patients with paroxysmal versus persistent AF or between patients with a stand-alone procedure versus a concomitant procedure.[77]

Surgical therapy for AF is appropriate as a concomitant procedure in patients with symptomatic AF undergoing open heart surgery for CAD or valvular disease. A stand-alone surgical procedure for AF is an option for patients who have not had a successful outcome from catheter ablation, who are not good candidates for catheter ablation, or who prefer a surgical approach over catheter ablation.

Hybrid Approach to Ablation of Atrial Fibrillation

Some AF ablation centers use a hybrid approach that combines surgical and catheter ablation, either on the same day or staged, with the two components separated by days to weeks. The rationale for the hybrid approach is that it capitalizes on the strengths of the two approaches and minimizes their limitations.[78] The surgical component is performed first, allowing exclusion of the left atrial appendage, direct visualization of the antrum of the PVs, access to epicardial structures such as the ligament of Marshall and ganglionated plexi, and avoidance of damage to the esophagus and phrenic nerve. A subsequent catheter ablation procedure consists of additional ablation as needed, for PV isolation, conduction block across epicardial

ablation lines, ablation of complex fractionated electrograms or rotors, and ablation of sites that are not accessible from the epicardium, such as the tricuspid or mitral isthmus.

The 12-month freedom from AF off AADs after the hybrid approach has varied widely, from as low as 37% to as high as approximately 80%.[78] This wide range of success rates likely is attributable to differences in patient selection, operator skill, specific technologies used for ablation, and lesion sets.

In the absence of data from prospective randomized studies, the incremental value of the hybrid approach over surgical or catheter ablation alone has remained unclear.

Specific Clinical Syndromes

Postoperative Atrial Fibrillation

Atrial fibrillation is common after open heart surgery and is reported to occur in 25% to 40% of patients who undergo coronary artery bypass graft (CABG) surgery or valve replacement (**see Chapter 11**). AF is associated with a twofold increase in the risk of postoperative stroke and is the most common reason for prolonged hospitalization. The incidence of AF peaks on the second postoperative day. The pathogenesis of postoperative AF is multifactorial and probably involves adrenergic activation, inflammation, atrial ischemia, electrolyte disturbances, and genetic factors. Several risk factors for AF after open heart surgery have been identified, including age over 70 years, history of prior AF, male gender, left ventricular dysfunction, left atrial enlargement, chronic lung disease, diabetes, and obesity.

The AADs that decrease the risk of postoperative AF are amiodarone and sotalol by 50% to 65%, and beta blockers by approximately 30%.[79] Hypomagnesemia is common after open heart surgery and can heighten the risk of AF. Magnesium administration is reported to decreases the risk of postoperative AF by 20% to 40%.[79]

Right atrial or biatrial pacing using temporary electrodes attached to the right and left atrium is reported to reduce the risk of postoperative AF by approximately 40%.[79]

Colchicine, atorvastatin, and steroids also have been demonstrated in randomized studies to reduce the risk of AF after open heart surgery by approximately 35% to 40%.[79,80] The main mechanism by which these agents prevent AF probably is an anti-inflammatory effect. Omega-3 PUFAs also have an anti-inflammatory effect, but randomized studies on their efficacy for preventing postoperative AF have reported conflicting results.[79]

A novel approach to the prevention of AF after cardiac surgery is injection of botulinum toxin into the four major epicardial fat pads at operation. This causes temporary autonomic blockade and has been shown to reduce the incidence of AF after CABG to less than 10%.[81]

Patients who develop postoperative AF can be managed using a rate- or rhythm-control strategy. In a randomized comparison of rate- and rhythm-control strategies in patients with AF after cardiac surgery, there were no significant differences between the two strategies in the number of days of hospitalization, mortality, or adverse events.[81] The decision on which type of strategy to employ in these patients should be based on the severity of symptoms, hemodynamic effects of the AF, and the patient-specific risk of side effects or adverse reactions to the various rate- and rhythm-control drugs.

AF that occurs after cardiac surgery often resolves within 3 months. In a randomized comparison of rate control versus rhythm control in patients with new-onset AF after cardiac surgery, approximately 95% of patients in both groups were in sinus rhythm at 60 days and had not experienced AF during the prior 30 days.[81] Treatment with an oral anticoagulant should be continued after discharge. Because new-onset AF after cardiac surgery often does not recur after 60 to 90 days, rhythm-control medications can be

discontinued at that time, and if there is no subsequent evidence of symptomatic or asymptomatic AF, as confirmed by monitoring (e.g., 3- to 4-week autotrigger event monitor), anticoagulation can be safely discontinued unless needed for another indication.

New-onset AF occurs postoperatively in less than 5% of patients undergoing major noncardiac surgery. Some of the possible mechanisms of postoperative AF after cardiac surgery (e.g., sympathetic activation, electrolyte abnormalities, hypoxia) most likely also play a role in AF after noncardiac surgery. Beta blockers have been shown to reduce the risk of AF after major noncardiac surgery by approximately 25%.[79]

Wolff-Parkinson-White Syndrome

Patients with the WPW syndrome and an accessory pathway with a short refractory period can experience a very rapid ventricular rate during AF (**see Chapters 36 and 37**). Ventricular rates greater than 250 to 300 beats/min can result in loss of consciousness or precipitate ventricular fibrillation and a cardiac arrest. Patients with WPW syndrome who present in AF with a rapid ventricular rate should undergo transthoracic cardioversion if there is hemodynamic instability. If the patient is hemodynamically stable, intravenous procainamide or ibutilide can be used for pharmacologic cardioversion. Procainamide may be preferable to ibutilide because it blocks accessory pathway conduction and slows the ventricular rate before AF has converted to sinus rhythm. Digitalis and calcium channel antagonists are contraindicated in patients with WPW syndrome and AF. These agents selectively block conduction in the AV node and can result in acceleration of conduction through the accessory pathway.

The preferred therapy for patients with WPW syndrome and AF with a rapid ventricular rate is catheter ablation of the accessory pathway. The efficacy of catheter ablation is 95% or higher for most types of accessory pathways, and the risk of a major complication is very low. AF typically no longer recurs after successful accessory pathway ablation, probably because AF in the WPW syndrome often is induced by tachycardia and a result of atrioventricular reciprocating tachycardia (AVRT).

Congestive Heart Failure

Atrial fibrillation is a common arrhythmia in patients with heart failure, with a prevalence ranging from 10% in patients with New York Heart Association (NYHA) functional Class I up to 50% in Class IV patients (**see Chapters 24 and 25**). AF may be the cause of heart failure in patients who present with a nonischemic cardiomyopathy and AF with a rapid ventricular rate. Occasionally, AF causes left ventricular dysfunction and heart failure even when the ventricular rate is not rapid. In patients with structural heart disease and preexisting left ventricular dysfunction, AF can worsen the heart failure. The deleterious hemodynamic effects of AF are mediated by a rapid and/or irregular ventricular rate and loss of AV synchrony.

The most appropriate rate-control drugs in patients with systolic heart failure are beta blockers and digitalis. If necessary, amiodarone also can be used for rate control. In patients with diastolic heart failure, nondihydropyridine calcium antagonists can be used safely for rate control. Amiodarone and dofetilide are the only two rhythm-control drugs that are not associated with an increased risk of death in patients with heart failure.

As in other patients with AF, the decision to pursue a rate-control or a rhythm-control strategy in patients with heart failure should be individualized. If the heart failure is a result of AF, a rhythm-control strategy should be employed. In patients with heart failure who develop AF, there are no significant

differences in all-cause mortality, cardiovascular mortality, or worsening heart failure between patients treated with a rate-control strategy or a pharmacologic rhythm-control strategy.[2] However, although symptoms improve with both a rate- and rhythm-control strategy, sinus rhythm is associated with greater improvement in NYHA functional class and quality of life.[82]

A limitation of a pharmacologic rhythm-control strategy is that many patients continue to experience episodes of AF. Catheter ablation is more effective than AADs for preventing recurrent AF and therefore could have incremental benefit over drug therapy in patients with heart failure and AF. In patients with heart failure and persistent AF who were randomly assigned to either catheter ablation or treatment with amiodarone, freedom from AF at 24 months was 70% in the catheter ablation group compared to 34% in the amiodarone group, and the relative risks of unplanned hospitalizations and mortality were reduced by 45% to 55% in the catheter ablation group.[83] The EF increases by approximately 13% when AF is successfully eliminated in patients with left ventricular dysfunction.[84]

Four small-scale randomized studies (sample sizes of 41 to 81 patients) compared catheter ablation to either pharmacologic rate control or AV junction ablation in patients with left ventricular dysfunction, and NYHA Class II to IV heart failure.[85] A majority of the patients had persistent AF. Freedom from AF ranged from 50% to 81% at 6 months and was 88% at 12 months after catheter ablation. Compared to rate control, catheter ablation was associated with significantly greater improvements in EF, functional capacity, brain natriuretic peptide levels, and quality of life.

These results suggest that maintenance of sinus rhythm is preferable to rate control in patients with heart failure and that catheter ablation of the AF should be considered if sinus rhythm is not maintained by amiodarone or dofetilide. Large-scale multicenter trials currently are in progress and will be helpful in clarifying the role of catheter ablation in patients with heart failure and AF.

A rate-control strategy is appropriate for patients who do not respond adequately to amiodarone or dofetilide and either are not suitable candidates for catheter ablation of the AF or have had an unsuccessful outcome from ablation. AV node ablation is appropriate for patients when ventricular rate during AF is not adequately controlled by drug therapy. Because left ventricular dysfunction and heart failure can be aggravated by right ventricular pacing, biventricular pacing should be performed after AV node ablation. The decision to implant a biventricular pacemaker versus a biventricular ICD is based on clinical judgment. If it seems likely that the EF will remain less than 30% to 35% after optimal heart rate control, a biventricular ICD is appropriate for primary prevention of sudden cardiac death.

In patients with heart failure who undergo CRT, AF often results in intrinsic and/or fused QRS complexes even when the rate is considered to be adequately controlled. This can limit the extent of biventricular capture. If this is the case in a patient with heart failure and AF, AV node ablation can maximize the benefit of CRT by resulting in 100% biventricular capture.[73]

Hypertrophic Cardiomyopathy

Atrial fibrillation occurs in approximately 25% of patients with hypertrophic cardiomyopathy (HCM) and can cause severe hemodynamic impairment because of an inadequate diastolic filling time and loss of atrial-ventricular synchrony. Because of a high risk of thromboembolic complications, anticoagulation is indicated in AF patients with HCM, independent of the CHA_2DS_2-VASc score.

Severe left ventricular hypertrophy increases the risk of drug-induced torsade de pointes, and the only rhythm-control agents recommended for patients with HCM and a wall thickness greater than 1.5 cm are dronedarone and amiodarone.[2] Catheter ablation of AF also is an option. However, the responses to drug therapy and catheter ablation often are suboptimal because of the extensive atrial remodeling that may be

present in patients with HCM.

Eight observational cohort studies reported on the results of RF catheter ablation of AF in patients with HCM.[86] The median follow-up in these studies was 18 to 19 months, and the rate of redo ablation procedures was 43%. Freedom from AF in these studies was a median of 66% to 86% for patients with paroxysmal AF and 42% to 65% for patients with persistent AF. These results indicate that catheter ablation is a reasonable option in patients with HCM and AF who do not respond well to AAD therapy. However, because of the prominent structural atrial abnormalities that can be associated with HCM, AF is likely to recur during long-term follow-up in many of these patients.

Percutaneous Coronary Intervention for Coronary Artery Disease

In patients with stable ischemic heart disease, treatment with aspirin plus clopidogrel (double-antiplatelet [-antithrombotic] therapy, DAPT) is recommended for a minimum of 1 month after placement of a bare metal stent and for a minimum of 6 months after placement of a drug-eluting stent. In patients with an acute coronary syndrome who undergo percutaneous coronary intervention with either a bare metal stent or a drug-eluting stent, DAPT is recommended for at least 12 months.

In patients who require long-term anticoagulation for AF, the addition of DAPT increases the risk of serious bleeding. The results of a randomized clinical trial indicated that therapy with a vitamin K inhibitor plus clopidogrel after stent placement reduces the risk of major bleeding events compared to therapy with a vitamin K inhibitor plus DAPT, without increasing the risk of adverse outcomes such as myocardial infarction, death, or stent thrombosis.[87]

Pregnancy

The prevalence of AF during pregnancy is very low, approximately 60/100,000 pregnancies. When it occurs, AF often is in the setting of underlying congenital or valvular heart disease, thyrotoxicosis, or electrolyte abnormalities. Pregnancy is associated with a hypercoagulable state, but no data indicate that pregnancy increases the risk of thromboembolic complications related to AF. In women with paroxysmal AF before pregnancy, the frequency of episodes may or may not increase during pregnancy.

The decision to anticoagulate a pregnant woman with AF should be made using the same criteria as in nonpregnant women. If anticoagulation is deemed necessary, warfarin (not an NOAC) is recommended from the second trimester until 1 month before the due date, and subcutaneous low-molecular-weight heparin is recommended during the first trimester and during the final month of pregnancy.

Transthoracic cardioversion is considered safe at all stages of pregnancy. The recommended pharmacologic agents for acute management of AF consist of intravenous metoprolol for rate control and flecainide or sotalol for conversion to sinus rhythm. If ongoing therapy is deemed necessary, the recommended rate-control drug is digoxin. If ineffective, a beta blocker can be used, but only after the first trimester. If there is no structural heart disease, flecainide and sotalol are recommended for long-term rhythm control.[88] In the patient with structural heart disease, amiodarone is recommended for rhythm control.

Future Perspectives

The ideal antiarrhythmic drug to prevent atrial fibrillation would affect only the atrium, thereby eliminating the potential for ventricular proarrhythmia. Such AADs are under development and may improve the safety and efficacy of pharmacologic therapy for AF. It is likely that drugs that modify a single channel will not be as effective as those with multiple actions, and targeting nonchannel functions (e.g., prevention of atrial fibrosis) may prove useful.

In the past few years, significant progress has been made in the field of catheter ablation of AF, but much room remains for improvement in efficacy and procedure duration. The failure to create enduring pulmonary vein isolation often accounts for recurrences of AF after both radiofrequency catheter ablation and cryoballoon ablation. The development of new ablation tools that improve the ability safely to create transmural lesions could reduce the need for redo ablation procedures. The cryoballoon catheter has improved the efficiency of PV isolation compared to point-by-point RF ablation. However, its use is limited to the antral regions of the PVs. The development of ablation catheters that ablate large areas of atrial myocardium with single applications of energy could improve the efficiency of catheter ablation of persistent AF.

In patients with persistent AF, a better understanding of AF mechanisms could result in more efficient and successful ablation strategies. The identification of presumptive localized sources of AF (focal impulses and/or atrial rotors) by computed signal analysis in humans in the past few years possibly represents an important step in this direction.[5] However, the excellent early clinical results have not been consistently reproduced in subsequent studies.[46,47] Better understanding of AF mechanisms in humans is clearly needed. Several studies have shown that a rhythm-control strategy in patients with AF provides no advantages in outcomes over a rate-control strategy. The results of these studies most likely were influenced by the suboptimal safety and efficacy of the drugs used for rhythm control.

To date, no randomized trials have demonstrated that catheter ablation of AF improves outcomes such as stroke or survival. An ongoing trial, Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA), has a primary endpoint of mortality and secondary endpoints of cardiovascular mortality and stroke. If this study shows improved outcomes with AF ablation, it will strengthen the case for rhythm control by ablation.

Guidelines

Atrial Fibrillation

Fred Morady and Douglas P. Zipes

Recent updates have been incorporated into the comprehensive guidelines for the management of atrial fibrillation (AF) published in 2006 by the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines.[1] The following classification system was used for recommendations and for the level of evidence on which the recommendations are based:

Class I: conditions for which there is evidence and/or general agreement that the test is useful and effective
Class IIa: weight of evidence or opinion is in favor of usefulness/efficacy
Class IIb: usefulness or efficacy is less well established by evidence or opinion

Class III: conditions for which there is evidence and/or general agreement that the test is not useful or effective and in some cases may be harmful

Level A recommendations are derived from data from multiple randomized clinical trials.

Level B recommendations are derived from a single randomized trial or nonrandomized studies.

Level C recommendations are based on the consensus opinion of experts.

The guidelines do not necessarily define the standard of care. Management decisions must be individualized on the basis of the particular circumstances of a patient, and there are situations in which a deviation from the guidelines may be appropriate.

Classification of Atrial Fibrillation

The terminology used to classify AF in the guidelines is as follows: *paroxysmal* AF is defined as episodes of AF that last less than 7 days; *persistent* AF is defined as AF that lasts more than 7 days; and *longstanding* AF refers to AF that has been persistent for more than 1 year. These designations are not altered by termination of AF by drug therapy or electrical cardioversion. AF that is resistant to electrical cardioversion is referred to as *permanent* AF. AF is considered recurrent after two or more episodes have occurred.

Some patients with paroxysmal AF occasionally have episodes that are persistent, and vice versa. In this event, the AF should be categorized on the basis of the predominant form. *Lone* AF refers to AF in patients younger than 60 years who do not have structural heart disease or hypertension. AF that is secondary to acute myocardial infarction (MI), cardiac surgery, pericarditis, myocarditis, hyperthyroidism, or an acute pulmonary process is considered separately because the AF often resolves after treatment of the underlying disorder.

Management of Atrial Fibrillation

The guidelines address five aspects of the management of AF: pharmacologic rate control, prevention of thromboembolic complications, cardioversion, maintenance of sinus rhythm, and special considerations, including postoperative AF, MI, Wolff-Parkinson-White (WPW) syndrome, hyperthyroidism, pregnancy, hypertrophic cardiomyopathy (HCM), and pulmonary disease.

An important aspect in the management of patients with AF that is not specifically addressed in the guidelines is how to decide on a rate-control strategy versus a rhythm-control strategy. Several clinical trials have demonstrated that pharmacologic rhythm-control and rate-control strategies result in similar outcomes, even in patients with AF who have left ventricular dysfunction and heart failure. On the other hand, a randomized trial of left atrial radiofrequency catheter ablation versus atrioventricular (AV) node ablation and biventricular pacing demonstrated significantly greater improvement in left ventricular (LV) function, exercise capacity, and quality of life in patients with heart failure who were treated by ablation. It is possible that the side effects from the drugs used for rhythm control offset the benefits of sinus rhythm. Specific recommendations regarding rhythm-control versus rate-control strategies are difficult to provide because the decision must be individualized on the basis of several factors, including age, symptom severity, functional limitations, patient preference, comorbidities, sinus node function, and response to drug therapy.

Pharmacologic Rate Control During Atrial Fibrillation (Table 38G.1)

In addition to specific recommendations on the use of particular drugs for control of the ventricular rate, the guidelines recommend that the effects of drug therapy on ventricular rate be measured at rest and during exercise to ensure adequate heart rate control. The criteria used for rate control are rates of 60 to 80 beats/min at rest and 90 to 115 beats/min during moderate exercise.

TABLE 38G.1

ACC/AHA Recommendations for Pharmacologic Rate Control of Atrial Fibrillation

CLASS	INDICATION	LEVEL OF EVIDENCE
Class I (indicated)	Measurement of the heart rate at rest and control of the rate with pharmacologic agents (either a beta blocker or nondihydropyridine calcium channel antagonist, in most cases) are recommended for patients with persistent or permanent AF.	B
	In the absence of preexcitation, intravenous administration of beta blockers (esmolol, metoprolol, or propranolol) or nondihydropyridine calcium channel antagonists (verapamil, diltiazem) is recommended to slow the ventricular response to AF in the acute setting, exercising caution in patients with hypotension or heart failure.	B
	Intravenous administration of digoxin or amiodarone is recommended to control heart rate in patients with AF and heart failure who do not have an accessory pathway.	B
	In patients who experience symptoms related to AF during activity, the adequacy of heart rate control should be assessed during exercise, adjusting pharmacologic treatment as necessary to keep the rate in the physiologic range.	C
	Digoxin is effective after oral administration to control the heart rate at rest in patients with AF and is indicated for patients with heart failure or left ventricular dysfunction and for sedentary individuals.	C
Class IIa (reasonable)	A combination of digoxin and either a beta blocker or nondihydropyridine calcium channel antagonist is reasonable to control the heart rate both at rest and during exercise in patients with AF. The choice of medication should be individualized and the dose modulated to avoid bradycardia.	B
	It is reasonable to use ablation of the AV node or accessory pathway to control heart rate when pharmacologic therapy is insufficient or associated with side effects.	B
	Intravenous amiodarone can be useful to control heart rate in patients with AF when other measures are unsuccessful or contraindicated.	C
	When electrical cardioversion is not necessary in patients with AF and an accessory pathway, intravenous procainamide or ibutilide is a reasonable alternative.	C
Class IIb (may be considered)	When the ventricular rate cannot be adequately controlled both at rest and during exercise in patients with AF by a beta blocker, nondihydropyridine calcium channel antagonist, or digoxin, alone or in combination, oral amiodarone may be administered to control the heart rate.	C
	Intravenous procainamide, disopyramide, ibutilide, or amiodarone may be considered for hemodynamically stable patients with AF involving conduction over an accessory pathway	B
	When the rate cannot be controlled with pharmacologic agents or tachycardia-mediated cardiomyopathy is suspected, catheter-directed ablation of the AV node may be considered in patients with AF to control the heart rate.	C
Class III (not indicated)	Strict rate control (<80 beats/min at rest or <110 beats/min during 6-minute walk) is not beneficial compared to a resting rate <110 beats/min in asymptomatic patients with persistent AF and an ejection fraction >40%, although uncontrolled tachycardia can lead to reversible left ventricular dysfunction over time.	B
	Digitalis should not be used as the sole agent to control the rate of ventricular response in patients with paroxysmal AF.	B
	Catheter ablation of the AV node should not be attempted without a prior trial of medication to control the ventricular rate in patients with AF.	C
	In patients with decompensated heart failure and AF, intravenous administration of a nondihydropyridine calcium channel antagonist may exacerbate hemodynamic compromise and is not recommended.	C
	Intravenous administration of digitalis glycosides or nondihydropyridine calcium channel antagonists to patients with AF and a preexcitation syndrome may paradoxically accelerate the ventricular response and is not recommended.	C

A 2011 recommendation states that a resting rate of less than 110 beats/min is a reasonable rate-control target in patients with persistent AF and no arrhythmia-related symptoms who have an ejection fraction (EF) greater than 40%. However, the guidelines caution that tachycardia can result in a decline in LV function over time.

Digitalis is much less effective for control of the ventricular rate during exercise than at rest and is indicated for patients with heart failure or LV dysfunction and for sedentary patients. A combination of digitalis and either a beta blocker or nondihydropyridine calcium channel antagonist is appropriate to control the rate at rest and during exercise. The guidelines recommend that digitalis not be used as the sole agent for rate control in patients with paroxysmal AF. Catheter ablation of the AV node should be reserved for patients whose ventricular rate cannot be adequately controlled by drug therapy because of either inefficacy or drug intolerance.

Prevention of Thromboembolism (Table 38G.2)

The 2006 guidelines recommend antithrombotic therapy with either aspirin or a vitamin K antagonist such as warfarin for all patients with AF except those who have lone AF or contraindications. An updated 2011 recommendation is that the direct thrombin inhibitor dabigatran is a useful alternative to warfarin for

stroke/embolism prevention in patients with AF. The choice between aspirin and an anticoagulant is based on the patient's risk profile. The factors associated with the highest risk of thromboembolism are a prior thromboembolic event and rheumatic mitral stenosis, and warfarin or dabigatran is recommended for patients with one of these risk factors. The risk factors associated with a moderate risk of thromboembolism are age 75 years or older, hypertension, heart failure, EF of 35% or less, and diabetes. Aspirin is recommended if none of these risk factors is present, and an anticoagulant is recommended for patients with one or more of these risk factors. In patients with only one of the moderate risk factors, either aspirin or an anticoagulant is reasonable, and the choice should be individualized.

TABLE 38G.2

ACC/AHA Recommendations for Prevention of Thromboembolism in Atrial Fibrillation

CLASS	INDICATION	LEVEL OF EVIDENCE
Class I (indicated)	Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except those with lone AF or contraindications.	A
	The selection of the antithrombotic agent should be based on the absolute risks of stroke and bleeding and the relative risk and benefit for a given patient.	A
	For patients without mechanical heart valves at high risk of stroke, chronic oral anticoagulant therapy with a vitamin K antagonist is recommended in a dose adjusted to achieve the target intensity international normalized ratio (INR) of 2.0 to 3.0 unless contraindicated. Factors associated with highest risk for stroke in patients with AF are prior thromboembolism (stroke, transient ischemic attack, or systemic embolism) and rheumatic mitral stenosis.	A
	Anticoagulation with a vitamin K antagonist is recommended for patients with more than one moderate risk factor. Such factors include age ≥75 years, hypertension, heart failure, impaired left ventricular systolic function (ejection fraction ≤35% or fractional shortening <25%), and diabetes mellitus.	A
	INR should be determined at least weekly during initiation of therapy and monthly when anticoagulation is stable.	A
	Dabigatran is a useful alternative to warfarin in patients with AF and risk factors for stroke who do not have a prosthetic heart valve or significant valve disease, a creatinine clearance <15 mL/min, or advanced liver disease.	B
	Aspirin, 81 to 325 mg daily, is recommended as an alternative to vitamin K antagonists in low-risk patients or in those with contraindications to oral anticoagulation.	A
	For patients with AF who have mechanical heart valves, the target intensity of anticoagulation should be based on the type of prosthesis, maintaining an INR of at least 2.5.	B
	Antithrombotic therapy is recommended for patients with atrial flutter as for those with AF.	C
Class IIa (reasonable)	For primary prevention of thromboembolism in patients with nonvalvular AF who have just one of the following validated risk factors, antithrombotic therapy with either aspirin or a vitamin K antagonist is reasonable, based on an assessment of the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and the patient's preferences: age ≥75 years (especially in female patients), hypertension, heart failure, impaired left ventricular function, or diabetes mellitus	A
	For patients with nonvalvular AF who have one or more of the following less well-validated risk factors, antithrombotic therapy with either aspirin or a vitamin K antagonist is reasonable for prevention of thromboembolism: age 65 to 74 years, female gender, or coronary artery disease. The choice of agent should be based on the risk of bleeding complications, ability to sustain adjusted chronic anticoagulation, and the patient's preferences.	B
	It is reasonable to select antithrombotic therapy by the same criteria irrespective of the pattern (i.e., paroxysmal, persistent, or permanent) of AF.	B
	In patients with AF who do not have mechanical prosthetic heart valves, it is reasonable to interrupt anticoagulation for up to 1 week without substituting heparin for surgical or diagnostic procedures that carry a risk of bleeding.	C
	It is reasonable to reevaluate the need for anticoagulation at regular intervals.	C
Class IIb (may be considered)	In patients ≥75 years at increased risk of bleeding but without frank contraindications to oral anticoagulant therapy, and in other patients with moderate risk factors for thromboembolism who are unable to safely tolerate anticoagulation at the standard intensity of INR 2.0 to 3.0, a lower INR target of 2.0 (range, 1.6 to 2.5) may be considered for prevention of ischemic stroke and systemic embolism.	C
	When surgical procedures require interruption of oral anticoagulant therapy for longer than 1 week in high-risk patients, unfractionated heparin may be administered or low-molecular-weight heparin given by subcutaneous injection, although the efficacy of these alternatives in this situation is uncertain.	C
	After percutaneous coronary intervention or revascularization surgery in patients with AF, low-dose aspirin (<100 mg/day) and/or clopidogrel (75 mg/day) may be given concurrently with anticoagulation to prevent myocardial ischemic events, but these strategies have not been thoroughly evaluated and are associated with an increased risk of bleeding.	C
	In patients undergoing percutaneous coronary intervention, anticoagulation may be interrupted to prevent bleeding at the site of peripheral arterial puncture, but the vitamin K antagonist should be resumed as soon as possible after the procedure and the dose adjusted to achieve an INR in the therapeutic range. Aspirin may be given temporarily during the hiatus, but the maintenance regimen should then consist of the combination of clopidogrel, 75 mg daily, plus warfarin (INR, 2.0 to 3.0). Clopidogrel should be given for a minimum of 1 month after implantation of a bare-metal stent, at least 3 months for a sirolimus-eluting stent, at least 6 months for a paclitaxel-eluting stent, and 12 months or longer in selected patients, following which warfarin may be continued as monotherapy in the absence of a subsequent coronary event. When warfarin is given in combination with clopidogrel or low-dose aspirin, the dose intensity must be carefully regulated.	C
	In patients with AF younger than 60 years without heart disease or risk factors for thromboembolism (lone AF), the risk of thromboembolism is low without treatment, and the effectiveness of aspirin for primary prevention of stroke relative to the risk of bleeding has not been established.	C
	In patients with AF who sustain ischemic stroke or systemic embolism during treatment with low-intensity anticoagulation (INR, 2.0 to 3.0), rather than add an antiplatelet agent, it may be reasonable to raise the intensity of the anticoagulation to a maximum target INR of 3.0 to 3.5.	C
	Clopidogrel plus aspirin may be considered in patients who cannot tolerate or who refuse an oral anticoagulant.	B
Class III (not indicated)	Long-term anticoagulation with a vitamin K antagonist is not recommended for primary prevention of stroke in patients younger than 60 years without heart disease (lone AF) or any risk factors for thromboembolism.	C

Rivaroxaban was approved by the FDA in 2011, after publication of the updated guidelines dealing with dabigatran. It seems appropriate to generalize the recommendations regarding dabigatran to the factor Xa inhibitor rivaroxaban.

Another update to the 2006 guidelines addresses combination therapy with aspirin and clopidogrel. This combination has been demonstrated to be less effective than warfarin for preventing strokes, but more effective than aspirin alone. The guidelines now recommend that aspirin plus clopidogrel be considered for stroke prevention in patients who cannot tolerate or refuse to take an oral anticoagulant.

Cardioversion of Atrial Fibrillation (Table 38G.3)

The first-line drugs recommended for cardioversion are flecainide, dofetilide, propafenone, and ibutilide. Amiodarone is considered a reasonable option. The guidelines state that digoxin and sotalol may be harmful when they are used for cardioversion and recommend against use of these agents for that purpose.

TABLE 38G.3

ACC/AHA Recommendations for Cardioversion of Atrial Fibrillation

CLASS	INDICATION	LEVEL OF EVIDENCE
Pharmacologic Cardioversion		
Class I (indicated)	Administration of flecainide, dofetilide, propafenone, or ibutilide is recommended for pharmacologic cardioversion of AF.	A
Class IIa (reasonable)	Administration of amiodarone is a reasonable option for pharmacologic cardioversion of AF.	A
	A single oral bolus dose of propafenone or flecainide ("pill-in-the-pocket") can be administered to terminate persistent AF outside the hospital once treatment has proved safe in the hospital for selected patients without sinus or AV node dysfunction, bundle branch block, QT interval prolongation, the Brugada syndrome, or structural heart disease. Before antiarrhythmic medication is initiated, a beta blocker or nondihydropyridine calcium channel antagonist should be given to prevent rapid AV conduction in the event atrial flutter occurs.	C
	Administration of amiodarone can be beneficial on an outpatient basis in patients with paroxysmal or persistent AF when rapid restoration of sinus rhythm is not deemed necessary.	C
Class IIb (may be considered)	Administration of quinidine or procainamide might be considered for pharmacologic cardioversion of AF, but the usefulness of these agents is not well established.	C
Class lII (not indicated)	Digoxin and sotalol may be harmful when used for pharmacologic cardioversion of AF and are not recommended.	A
	Quinidine, procainamide, disopyramide, and dofetilide should not be started out of the hospital for conversion of AF to sinus rhythm.	B
Direct-Current Cardioversion		
Class I (indicated)	When a rapid ventricular response does not respond promptly to pharmacologic measures for patients with AF with ongoing myocardial ischemia, symptomatic hypotension, angina, or heart failure, immediate R wave–synchronized direct-current cardioversion is recommended.	C
	Immediate direct-current cardioversion is recommended for patients with AF involving preexcitation when very rapid tachycardia or hemodynamic instability occurs.	B
	Cardioversion is recommended in patients without hemodynamic instability when symptoms of AF are unacceptable to the patient. In case of early relapse of AF after cardioversion, repeated direct-current cardioversion attempts may be made after administration of antiarrhythmic medication.	C
Class IIa (reasonable)	Direct-current cardioversion can be useful to restore sinus rhythm as part of a long-term management strategy for patients with AF.	B
	The patient's preference is a reasonable consideration in the selection of infrequently repeated cardioversions for the management of symptomatic or recurrent AF.	C
Class III (not indicated)	Frequent repetition of direct-current cardioversion is not recommended for patients who have relatively short periods of sinus rhythm between relapses of AF after multiple cardioversion procedures despite prophylactic antiarrhythmic drug therapy.	C
	Electrical cardioversion is contraindicated in patients with digitalis toxicity or hypokalemia.	C
Pharmacologic Enhancement of Direct-Current Cardioversion		
Class IIa (reasonable)	Pretreatment with amiodarone, flecainide, ibutilide, propafenone, or sotalol can be useful to enhance the success of direct-current cardioversion and to prevent recurrent AF.	B
	In patients who relapse to AF after successful cardioversion, it can be useful to repeat the procedure after prophylactic administration of antiarrhythmic medication.	C
Class IIb (may be considered)	For patients with persistent AF, administration of beta blockers, disopyramide, diltiazem, dofetilide, procainamide, or verapamil may be considered, although the efficacy of these agents to enhance the success of direct-current cardioversion or to prevent early recurrence of AF is uncertain.	C
	Out-of-hospital initiation of antiarrhythmic medications may be considered in patients without heart disease to enhance the success of cardioversion of AF.	C
	Out-of-hospital administration of antiarrhythmic medications may be considered to enhance the success of cardioversion of AF in patients with certain forms of heart disease once the safety of the drug has been verified for the patient.	C
Prevention of Thromboembolism in Patients With Atrial Fibrillation Undergoing Cardioversion		
Class I (indicated)	For patients with AF of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation (INR 2.0 to 3.0) is recommended for at least 3 weeks before and 4 weeks after cardioversion, regardless of the method (electrical or pharmacologic) used to restore sinus rhythm.	B
	For patients with AF of more than 48-hour duration requiring immediate cardioversion because of hemodynamic instability, heparin should be administered concurrently (unless contraindicated) by an initial intravenous bolus injection, followed by a continuous infusion in a dose adjusted to prolong the activated partial thromboplastin time to 1.5 to 2 times the reference control value. Thereafter, oral anticoagulation (INR, 2.0 to 3.0) should be provided for at least 4 weeks, as for patients undergoing elective cardioversion. Limited data support subcutaneous administration of low-molecular-weight heparin in this indication.	C
	For patients with AF of less than 48-hour duration associated with hemodynamic instability (angina pectoris, myocardial infarction, shock, or pulmonary edema), cardioversion should be performed immediately, without delay, for prior initiation of anticoagulation.	C
Class IIa (reasonable)	During the 48 hours after onset of AF, the need for anticoagulation before and after cardioversion may be based on the patient's risk of thromboembolism.	C
	As an alternative to anticoagulation before cardioversion of AF, it is reasonable to perform transesophageal echocardiography in search of thrombus in the left atrium or left atrial appendage.	B
	a. For patients with no identifiable thrombus, cardioversion is reasonable immediately after anticoagulation with unfractionated heparin (e.g., initiated by intravenous bolus injection and an infusion continued at a dose adjusted to prolong the activated partial thromboplastin time to 1.5 to 2 times the control value until oral anticoagulation has been established with an oral vitamin K antagonist [e.g., warfarin] as evidenced by an INR ≥2.0).	B
	Thereafter, continuation of oral anticoagulation (INR, 2.0 to 3.0) is reasonable for a total anticoagulation period of at least 4 weeks, as for patients undergoing elective cardioversion.	B
	Limited data are available to support the subcutaneous administration of a low-molecular-weight heparin in this indication.	C
	b. For patients in whom thrombus is identified by transesophageal echocardiography, oral anticoagulation (INR, 2.0 to 3.0) is reasonable for at least 3 weeks before and 4 weeks after restoration of sinus rhythm, and a longer period of anticoagulation may be appropriate even after apparently successful cardioversion because the risk of thromboembolism often remains elevated in such cases.	C
	For patients with atrial flutter undergoing cardioversion, anticoagulation can be beneficial according to the recommendations as for patients with AF.	C

Direct-current (DC) cardioversion is recommended when there is a rapid ventricular rate that does not respond quickly to drug therapy in patients with myocardial ischemia, hypotension, or heart failure and in patients with the WPW syndrome and AF with a very rapid rate or hemodynamic instability. If there is an

early recurrence of AF after DC cardioversion, repeated cardioversion is recommended after treatment with an antiarrhythmic drug (AAD).

If AF has been present for more than 48 hours or if the duration is unknown, anticoagulation with warfarin and an international normalized ratio (INR) of 2 to 3 is recommended for 3 weeks or longer before cardioversion, whether pharmacologic or electrical, and for 4 weeks afterward. It is reasonable to presume that dabigatran or rivaroxaban are suitable alternatives to warfarin.

When cardioversion is performed within 48 hours of the onset of AF, anticoagulation before and after cardioversion may be based on the patient's risk profile.

In patients with AF for more than 48 hours or in whom the duration is unknown, an alternative to anticoagulation for 3 or more weeks before cardioversion is to perform transesophageal echocardiography, to anticoagulate the patient with heparin, to initiate oral anticoagulation, and to proceed with immediate cardioversion if no thrombi are present in the left atrium or left atrial appendage. In patients receiving warfarin, heparin should be continued until the INR is 2, and oral anticoagulation with an INR of 2 to 3 should be continued for 4 weeks or longer. In patients treated with dabigatran or rivaroxaban, heparin can be discontinued 3 to 4 hours after the first oral dose. As with warfarin, anticoagulation therapy should be continued for 4 weeks or longer.

Maintenance of Sinus Rhythm (Table 38G.4)

A reasonable outcome of AAD therapy is infrequent recurrences of well-tolerated AF. Initiation of a rhythm-control medication is reasonable on an outpatient basis in patients without heart disease when the medication is well tolerated. The updated guidelines now recommend dronedarone as being a reasonable option in patients with paroxysmal AF or after conversion of persistent AF. The guidelines recommend catheter ablation of symptomatic paroxysmal AF for patients who have failed treatment with an AAD and have little or no left atrial enlargement and normal or mildly reduced LV function.

TABLE 38G.4

ACC/AHA Recommendations for Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation

CLASS	INDICATION	LEVEL OF EVIDENCE
Class I (indicated)	Before initiation of antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended.	C
	Catheter ablation by an experienced operator is useful in selected patients with symptomatic paroxysmal AF who have failed treatment with an antiarrhythmic drug and have a normal or mildly dilated left atrium and normal or mildly reduced left ventricular function.	A
Class IIa (reasonable)	Pharmacologic therapy can be useful in patients with AF to maintain sinus rhythm and to prevent tachycardia-induced cardiomyopathy.	C
	Infrequent, well-tolerated recurrence of AF is reasonable as a successful outcome of antiarrhythmic drug therapy.	C
	Outpatient initiation of antiarrhythmic drug therapy is reasonable in patients with AF who have no associated heart disease when the agent is well tolerated.	C
	In patients with lone AF without structural heart disease, initiation of propafenone or flecainide can be beneficial on an outpatient basis in patients with paroxysmal AF who are in sinus rhythm at the time of drug initiation.	B
	Sotalol can be beneficial in outpatients in sinus rhythm with little or no heart disease, prone to paroxysmal AF, if the baseline uncorrected QT interval is shorter than 460 milliseconds, serum electrolyte values are normal, and risk factors associated with class III drug–related proarrhythmia are not present.	C
	Catheter ablation is a reasonable for treatment of symptomatic persistent AF.	A
Class IIb (may be considered)	Catheter ablation may be reasonable for patients with symptomatic paroxysmal AF and significant left atrial dilation or significant left ventricular dysfunction.	A
Class III (not indicated)	Antiarrhythmic therapy with a particular drug is not recommended for maintenance of sinus rhythm in patients with AF who have well-defined risk factors for proarrhythmia with that agent.	A
	Pharmacologic therapy is not recommended for maintenance of sinus rhythm in patients with advanced sinus node disease or AV node dysfunction unless they have a functioning electronic cardiac pacemaker.	C

Special Considerations (Table 38G.5)

Postoperative Atrial Fibrillation

The guidelines recommend prophylactic treatment with an oral beta blocker to prevent postoperative AF in patients undergoing cardiac surgery. Preoperative amiodarone also is considered to be appropriate prophylactic therapy to prevent postoperative AF. The use of cardioversion, rhythm-control medications, and antithrombotic medication should be based on the same considerations as in nonsurgical patients.

TABLE 38G.5

ACC/AHA Recommendations for Special Considerations in Atrial Fibrillation

CLASS	INDICATION	LEVEL OF EVIDENCE
Postoperative Atrial Fibrillation		
Class I (indicated)	Unless contraindicated, treatment with an oral beta blocker to prevent postoperative AF is recommended for patients undergoing cardiac surgery.	A
	Administration of AV nodal blocking agents is recommended to achieve rate control in patients who develop postoperative AF.	B
Class IIa (reasonable)	Preoperative administration of amiodarone reduces the incidence of AF in patients undergoing cardiac surgery and represents appropriate prophylactic therapy for patients at high risk for postoperative AF.	A
	It is reasonable to restore sinus rhythm by pharmacologic cardioversion with ibutilide or direct-current cardioversion in patients who develop postoperative AF, as advised for nonsurgical patients.	B
	It is reasonable to administer antiarrhythmic medications in an attempt to maintain sinus rhythm in patients with recurrent or refractory postoperative AF, as recommended for other patients who develop AF.	B
	It is reasonable to administer antithrombotic medication in patients who develop postoperative AF, as recommended for nonsurgical patients.	B
Class IIb (may be considered)	Prophylactic administration of sotalol may be considered for patients at risk for development of AF after cardiac surgery.	B
Acute Myocardial Infarction		
Class I (indicated)	Direct-current cardioversion is recommended for patients with severe hemodynamic compromise or intractable ischemia, or when adequate rate control cannot be achieved with pharmacologic agents in patients with acute myocardial infarction and AF.	C
	Intravenous administration of amiodarone is recommended to slow a rapid ventricular response to AF and to improve left ventricular function in patients with acute myocardial infarction.	C
	Intravenous beta blockers and nondihydropyridine calcium antagonists are recommended to slow a rapid ventricular response to AF in patients with acute myocardial infarction who do not display clinical left ventricular dysfunction, bronchospasm, or AV block.	C
	For patients with AF and acute myocardial infarction, administration of unfractionated heparin by either continuous intravenous infusion or intermittent subcutaneous injection is recommended in a dose sufficient to prolong the activated partial thromboplastin time to 1.5 to 2 times the control value, unless contraindications to anticoagulation exist.	C
Class IIa (reasonable)	Intravenous administration of digitalis is reasonable to slow a rapid ventricular response and to improve left ventricular function in patients with acute myocardial infarction and AF associated with severe left ventricular dysfunction and heart failure.	C
Class III (not indicated)	The administration of class IC antiarrhythmic drugs is not recommended in patients with AF in the setting of acute myocardial infarction.	C
Management of Atrial Fibrillation Associated With Wolff-Parkinson-White (WPW) Preexcitation Syndrome		
Class I (indicated)	Catheter ablation of the accessory pathway is recommended for symptomatic patients with AF who have WPW syndrome, particularly those with syncope due to rapid heart rate or those with a short bypass tract refractory period.	B
	Immediate direct-current cardioversion is recommended to prevent ventricular fibrillation in patients with a short anterograde bypass tract refractory period in whom AF occurs with a rapid ventricular response associated with hemodynamic instability.	B
	Intravenous procainamide or ibutilide is recommended to restore sinus rhythm in patients with WPW in whom AF occurs without hemodynamic instability in association with a wide QRS complex on the electrocardiogram (≥120-msec duration) or with a rapid preexcited ventricular response.	C
Class IIa (reasonable)	Intravenous flecainide or direct-current cardioversion is reasonable when very rapid ventricular rates occur in patients with AF involving conduction over an accessory pathway.	B
Class IIb (may be considered)	It may be reasonable to administer intravenous quinidine, procainamide, disopyramide, ibutilide, or amiodarone to hemodynamically stable patients with AF involving conduction over an accessory pathway.	B
Class III (not indicated)	Intravenous administration of digitalis glycosides or nondihydropyridine calcium channel antagonists is not recommended in patients with WPW syndrome who have preexcited ventricular activation during AF.	B
Hyperthyroidism		
Class I (indicated)	Administration of a beta blocker is recommended to control the rate of ventricular response in patients with AF complicating thyrotoxicosis, unless contraindicated.	B
	In circumstances when a beta blocker cannot be used, administration of a nondihydropyridine calcium channel antagonist (diltiazem or verapamil) is recommended to control the ventricular rate in patients with AF and thyrotoxicosis.	B
	In patients with AF associated with thyrotoxicosis, oral anticoagulation (INR, 2.0 to 3.0) is recommended to prevent thromboembolism, as recommended for AF patients with other risk factors for stroke.	C
	Once a euthyroid state is restored, recommendations for antithrombotic prophylaxis are the same as for patients without hyperthyroidism.	C
Management of Atrial Fibrillation During Pregnancy		
Class I (indicated)	Digoxin, a beta blocker, or a nondihydropyridine calcium channel antagonist is recommended to control the rate of ventricular response in pregnant patients with AF.	C
	Direct-current cardioversion is recommended in pregnant patients who become hemodynamically unstable because of AF.	C
	Protection against thromboembolism is recommended throughout pregnancy for all patients with AF (except those with lone AF and/or low thromboembolic risk). Therapy (anticoagulant or aspirin) should be chosen according to the stage of pregnancy.	C
Class IIb (may be considered)	Administration of heparin may be considered during the first trimester and last month of pregnancy for patients with AF and risk factors for thromboembolism. Unfractionated heparin may be administered either by continuous intravenous infusion in a dose sufficient to prolong the activated partial thromboplastin time to 1.5 to 2 times the control value or by intermittent subcutaneous injection in a dose of 10,000 to 20,000	B

	units every 12 hours, adjusted to prolong the midinterval (6 hours after injection) activated partial thromboplastin time to 1.5 times control.	
	Despite the limited data available, subcutaneous administration of low-molecular-weight heparin may be considered during the first trimester and last month of pregnancy for patients with AF and risk factors for thromboembolism.	C
	Administration of an oral anticoagulant may be considered during the second trimester for pregnant patients with AF at high thromboembolic risk.	C
	Administration of quinidine or procainamide may be considered to achieve pharmacologic cardioversion in hemodynamically stable patients who develop AF during pregnancy.	C
Management of Atrial Fibrillation in Patients With Hypertrophic Cardiomyopathy (HCM)		
Class I (indicated)	Oral anticoagulation (INR, 2.0 to 3.0) is recommended in patients with HCM who develop AF, as for other patients at high risk of thromboembolism.	B
Class IIa (may be considered)	Antiarrhythmic medications can be useful to prevent recurrent AF in patients with HCM. Available data are insufficient to recommend one agent over another in this situation, but (a) disopyramide combined with a beta blocker or nondihydropyridine calcium channel antagonist or (b) amiodarone alone is generally preferred.	C
Management of Atrial Fibrillation in Patients With Pulmonary Disease		
Class I (indicated)	Correction of hypoxemia and acidosis is the recommended primary therapeutic measure for patients who develop AF during an acute pulmonary illness or exacerbation of chronic pulmonary disease.	C
	A nondihydropyridine calcium channel antagonist (diltiazem or verapamil) is recommended to control the ventricular rate in patients with obstructive pulmonary disease who develop AF.	C
	Direct-current cardioversion should be attempted in patients with pulmonary disease who become hemodynamically unstable as a consequence of AF.	C
Class III (not indicated)	Theophylline and beta-adrenergic agonist agents are not recommended for patients with bronchospastic lung disease who develop AF.	C
	Beta blockers, sotalol, propafenone, and adenosine are not recommended in patients with obstructive lung disease who develop AF.	C

Acute Myocardial Infarction

Electrical cardioversion is recommended if there is hemodynamic compromise or ongoing ischemia or when adequate rate control cannot be achieved with drug therapy. The guidelines recommend intravenous (IV) amiodarone or digitalis to slow the ventricular rate in patients and to improve LV function in patients with an acute MI. If there is no LV dysfunction, bronchospasm, or AV block, an IV beta blocker or nondihydropyridine calcium antagonist is recommended for rate control.

Atrial Fibrillation in Wolff-Parkinson-White Syndrome

Catheter ablation of the accessory pathway is recommended in patients with symptomatic AF and the WPW syndrome. Immediate electrical cardioversion is recommended if there is AF with a rapid ventricular rate and hemodynamic instability. If the patient is hemodynamically stable, IV procainamide or ibutilide is recommended for pharmacologic conversion of AF. IV digitalis and nondihydropyridine calcium channel antagonists should be avoided in patients with ventricular preexcitation during AF.

Hyperthyroidism

The guidelines recommend a beta blocker as first-line therapy for rate control in patients with AF and thyrotoxicosis. If a beta blocker cannot be used, verapamil or diltiazem should be used for rate control. Recommendations for therapy to prevent thromboembolic complications are as for patients without hyperthyroidism.

Atrial Fibrillation During Pregnancy

The guidelines recommend digoxin, a beta blocker, or a nondihydropyridine calcium channel antagonist for rate control of AF during pregnancy. DC cardioversion is recommended if there is hemodynamic instability.

Except in patients with a low-risk profile, either aspirin or an anticoagulant is recommended for prevention of thromboembolic complications, depending on the stage of pregnancy (**see Chapter 90**). Unfractionated or low-molecular-weight heparin can be considered during the first trimester and last month of pregnancy in patients with risk factors for thromboembolism, and an oral anticoagulant can be considered during the second trimester in patients at high risk of thromboembolism.

When AF occurs during pregnancy, quinidine or procainamide can be considered for pharmacologic

cardioversion in hemodynamically stable patients.

Hypertrophic Cardiomyopathy

The guidelines point out that there are not adequate data on the best rhythm-control medication to use for AF in the setting of HCM. The preferred therapy is either disopyramide plus a beta blocker, verapamil, or diltiazem for rate control or amiodarone by itself.

Pulmonary Disease

The primary therapy for AF in the setting of an acute pulmonary illness or exacerbation of chronic pulmonary disease should be correction of hypoxemia and acidosis. Verapamil or diltiazem is recommended for rate control in patients with obstructive pulmonary disease. Theophylline and beta-adrenergic agonists are not recommended in patients with bronchospastic disease, and beta blockers, sotalol, propafenone, and adenosine are not recommended in patients with obstructive lung disease.

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39

Ventricular Arrhythmias

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Ventricular rhythm disturbances are those rhythms whose driving circuit or focus originates in ventricular tissue, including myocardium, annuli, valve cusps, aorta, pulmonary artery, bundle branches, or Purkinje fibers (**see Table 37.1**). Ventricular arrhythmias are characterized by a wide QRS (>120 msec). Some supraventricular tachyarrhythmias can exhibit a wide complex (**see Chapter 35**). Because of the differences in prognosis and treatment, proper diagnosis of ventricular tachycardia (VT) is critically important and is largely based on electrocardiographic criteria, although history is important. For example, a patient presenting with a wide-complex tachycardia (WCT) and a past history of a myocardial infarction (MI) most likely has VT.

Premature Ventricular Complexes

Electrocardiographic Recognition

A premature ventricular complex (PVC) is characterized by the premature occurrence of a QRS complex that is abnormal in shape and has a duration usually exceeding the dominant QRS complex, generally longer than 120 milliseconds. The T wave is usually large and opposite in direction to the major deflection of the QRS. The QRS complex is not preceded by a premature P wave but can be preceded by a nonconducted sinus P wave occurring at its expected time. Diagnosis of a PVC can never be made with unequivocal certainty from the scalar electrocardiogram (ECG) because a supraventricular beat or rhythm can mimic the manifestations of ventricular arrhythmia (**Fig. 39.1**). Retrograde transmission to the atria from the PVC occurs fairly frequently but is often obscured by the distorted QRS complex and T wave. If

the retrograde impulse discharges and resets the sinus node prematurely, it produces a pause that is not fully compensatory. More often, the sinus node and atria are not discharged prematurely by the retrograde impulse because interference of impulses frequently occurs at the atrioventricular (AV) junction in the form of a collision between the anterograde impulse conducted from the sinus node and the retrograde impulse conducted from the PVC. Therefore, a fully compensatory pause usually follows a PVC—the R-R interval produced by the two sinus-initiated QRS complexes on either side of the PVC equals twice the normally conducted R-R interval. The PVC may not produce any pause and can therefore be interpolated (**Fig. 39.1E**). In patients with a normal heart, PVCs typically originate from similar sites as described for idiopathic VT (see later), and electrocardiographic morphology of PVCs can be used to determine site of origin similar to that for idiopathic VT (**Table 39.1**).

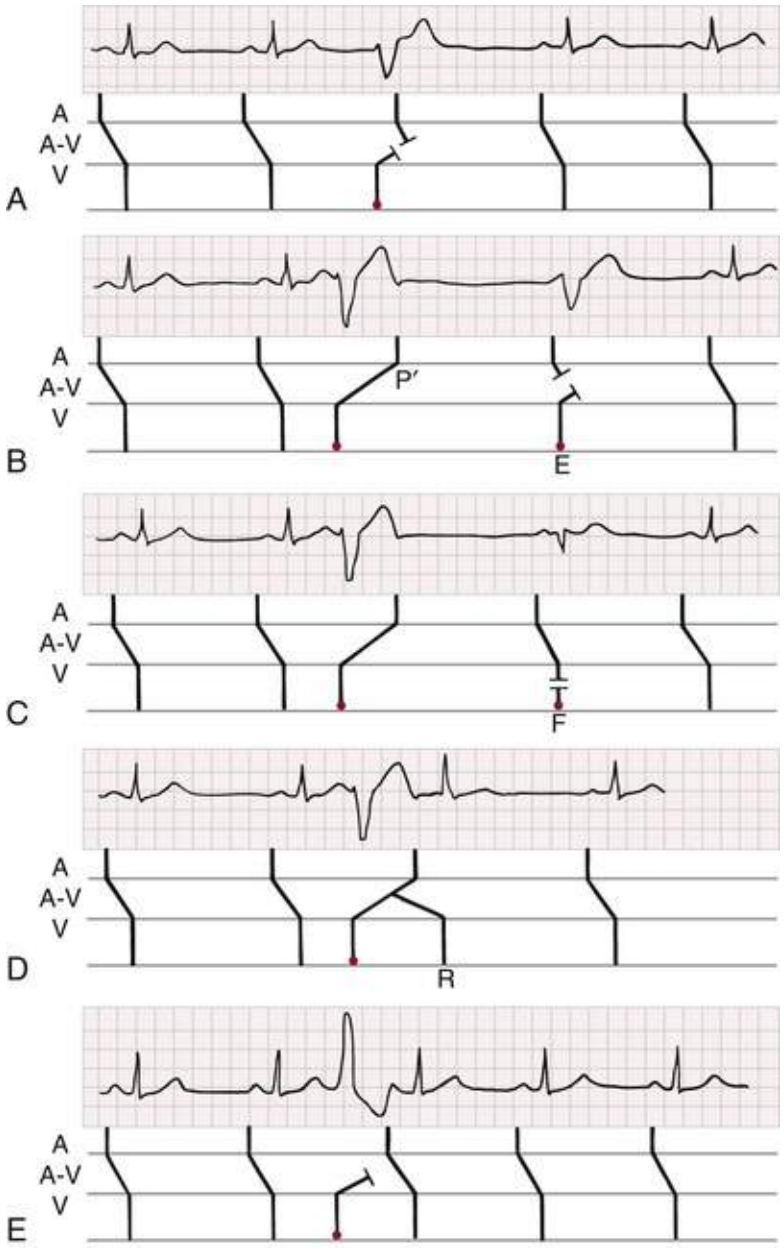

FIGURE 39.1 Premature ventricular complexes (PVCs). **A** to **D** were recorded in the same patient. **A,** Late PVC results in a compensatory pause. **B,** Slower sinus rate and slightly earlier PVC result in retrograde atrial excitation (*P′*). The sinus node is reset, followed by a noncompensatory pause. Before the sinus-initiated P wave that follows the retrograde P wave can conduct the impulse to the ventricle, ventricular escape (*E*) occurs. **C,** Events are similar to those in **B** except that a ventricular fusion beat (*F*) results after the PVC because of a slightly faster sinus rate. **D,** The impulse propagating retrogradely to the atrium reverses its direction after a delay and returns to reexcite the ventricles (*R*) and produce a ventricular echo. **E,** Interpolated PVC is followed by slightly prolonged PR interval of the sinus-initiated beat. The lead II ECG is shown. *Red circles* indicate the origin of the PVCs.

TABLE 39.1

Electrocardiographic Pattern of Idiopathic Ventricular Tachycardia (VT) by Anatomic Location

LOCATION	ECG PATTERN
Outflow Tract VT	LBBB morphology and inferior axis
Right ventricular outflow tract (RVOT)	Later precordial transition (V_3 or later) Narrower R wave duration and lower R/S wave amplitude ratio in V_1 and V_2
Left ventricular outflow tract (LVOT)	Early precordial transition (by V_3) Earlier precordial transition than SR Broader R wave duration and greater R/S wave amplitude ratio in V_1 and V_2 Notch (qrS) in V_1 or V_2
Left aortic cusp	"M" or "W" pattern in V_1 Monophasic R by V_1/V_2 Greater R wave II/III ratio Lead I QS or rS
Right aortic cusp	Monophasic R by V_2/V_3 Positive notched R-wave in lead I
Aortomitral continuity	qR in lead V_1 Positive concordance across precordium Rs/rs complex in lead I R wave ratio <1 in II/III
Epicardial	MDI >55% QS in lead I QS in leads II, III, and aVF (if superiorly directed, near MCV) Q-wave ratio in aVL/aVR >1.4 or S wave amplitude >1.2 mV "Transition break," specifically a loss of R from leads V_1 to V_2 (QS or rS) with prominent R by V_3 (suggests near anterior interventricular vein)
Pulmonary artery	Tall R wave in the inferior leads Larger Q wave ratio in aVL/aVR Larger R/S amplitude in lead V_2 Larger Q wave ratio in aVL/aVR Larger R/S amplitude in lead V_2
Tricuspid annular	LBBB morphology and inferior or superior axis R wave in lead I R or r with overall positive polarity in aVL Later precordial transition (>V_3)
Tricuspid inflow or parahisian	LBBB morphology and inferior axis Large R wave in lead I R wave with flat/positive polarity or "w" pattern in aVL
Mitral annular (MA)	RBBB pattern with concordance in leads V_1 to V_6 Anterior MAVT: positive QRS polarity in leads II, III, and aVF and negative QRS polarity in leads I and aVL Posterior or posteroseptal MAVT: negative QRS polarity in leads II, III, and aVF and positive QRS polarity in leads I and aVL
Fascicular VT	
Left posterior fascicle	RBBB and left axis deviation (LAFB pattern) rsR′ in V_1 q in I and aVL Narrow QRS ≤140 msec
Left anterior fascicle	RBBB and right axis deviation (LPFB pattern) Narrow QRS <140 msec
Left septal	Incomplete RBBB (QRSd ~100-110 msec) and normal axis
Papillary Muscle VT	RBBB; can have varied axes
Posterior papillary muscle	qR or R in V_1 Absent Q in leads I and aVL
Anterior papillary muscle	qR or R in V_1 rS in leads I and aVL
Crux VT	Leftward-superior axis QRS Delayed intrinsicoid deflection Basal crux: LBBB pattern with early precordial transition Apical crux: midprecordial transition with QS in V_5/V_6

LBBB, Left bundle branch block; *RBBB,* right bundle branch block.

Modified from Hoffmayer KS, Gerstenfeld EP. Diagnosis and management of idiopathic ventricular tachycardia. Curr Probl Cardiol 2013;38:131-58.

Interference within the ventricle can result in ventricular fusion beats caused by simultaneous activation of the ventricle by two foci, one from the supraventricular impulse and the other from the PVC. Infrequently, a fusion beat can be narrower than the dominant sinus beat, such as when a right bundle branch block (RBBB) pattern of a PVC arising in the left ventricle fuses with the sinus-initiated left

bundle branch block (LBBB) complex conducting through the AV junction, or when a sinus beat with an RBBB pattern fuses with a right ventricle–paced beat with an LBBB pattern. Narrow PVCs have also been explained as originating at a point equidistant from each ventricle in the ventricular septum and arising high in the fascicular system. Whether a compensatory or noncompensatory pause, retrograde atrial excitation, an interpolated complex, a fusion complex, or an echo beat occurs (**Fig. 39.1D**) is merely a function of how the AV junction conducts and the timing of the events taking place.

The term *bigeminy* refers to pairs of complexes and indicates a normal and premature complex; *trigeminy* indicates a premature complex that follows two normal beats; a premature complex that follows three normal beats is called *quadrigeminy*; and so on. Two successive PVCs are known as a *pair* or a *couplet*, whereas three successive PVCs are called a *triplet*. Arbitrarily, three or more successive PVCs are termed *ventricular tachycardia*. PVCs can have different contours and are often called *multifocal* (**Fig. 39.2**). More properly, these should be called *multiform*, *polymorphic*, or *pleomorphic* because it is not known whether multiple foci are discharging or whether conduction of the impulse originating from the same site is merely changing.

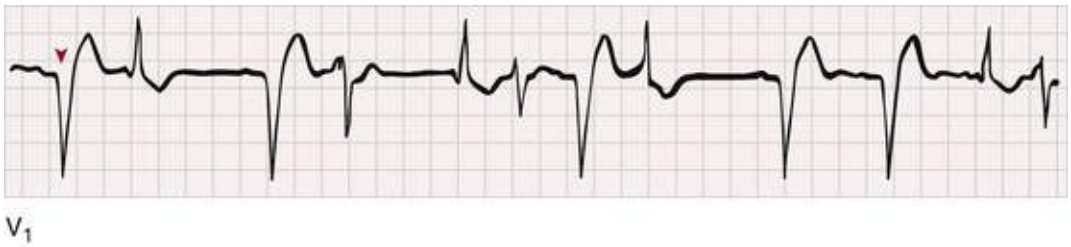

FIGURE 39.2 Multiform PVCs. The normally conducted QRS complexes exhibit a left bundle branch block contour (*arrowhead*) and are followed by PVCs with three different morphologies.

PVCs can exhibit fixed or variable coupling; that is, the interval between the normal QRS complex and the PVC can be relatively stable or variable. *Fixed coupling* can be caused by reentry, triggered activity (**see Chapter 34**), or other mechanisms. *Variable coupling* can be caused by parasystole, changing conduction in a reentrant circuit, or changing discharge rates of triggered activity. Usually, it is difficult to determine the precise mechanism responsible for the PVC on the basis of constant or variable coupling intervals.

Clinical Features

The prevalence of premature complexes increases with age, male sex, and hypokalemia. Symptoms of palpitations or discomfort in the neck or chest can result because of the greater-than-normal contractile force of the postextrasystolic beat or the feeling that the heart has stopped during the long pause after the premature complex. Long runs of frequent PVCs in patients with heart disease can produce angina, hypotension, or heart failure. Frequent interpolated PVCs actually represent a doubling of the heart rate and can compromise the patient's hemodynamic status. In some patients, frequent PVCs can cause heart failure, which can be reversed by ablation. Activity that increases the heart rate can decrease the patient's awareness of the premature systoles or reduce their number. Exercise can increase the number of premature complexes in some patients. Sleep is usually associated with a decrease in the frequency of ventricular arrhythmias, but some patients can experience an increase.

PVCs can be produced by direct mechanical, electrical, and chemical stimulation of the myocardium. Frequently, PVCs are noted during infection, in ischemic or inflamed myocardium, and during hypoxia,

anesthesia, or surgery. PVCs can be provoked by various medications, electrolyte imbalance, tension states, myocardial stretch, and excessive use of tobacco, caffeine, or alcohol. Autonomic stimulation has profound effects on the heart rate and can produce or suppress premature complexes.

Physical examination reveals a premature beat followed by a long pause. A fully compensatory pause can be distinguished from one that is not fully compensatory in that the former does not change the timing of the basic rhythm. The PVC is frequently accompanied by a decrease in intensity of heart sounds, often with auscultation of just the first heart sound, which can be sharp and snapping. A decreased or absent peripheral (e.g., radial) pulse can occur. The relationship of atrial to ventricular systole determines the presence of normal *a* waves or giant *a* waves in the jugular venous pulse, and the length of the PR interval determines the intensity of the first heart sound. The second heart sound can be split abnormally, depending on the origin of the ventricular complex.

The importance of PVCs depends on the clinical setting. In the absence of underlying heart disease, PVCs usually have no impact on longevity or limitation of activity; antiarrhythmic drugs are not indicated. Patients should be reassured if they are symptomatic. Frequent PVCs greater than 24% of all beats during 24-hour Holter monitoring, very wide-QRS PVCs, or PVCs of epicardial origin can cause a cardiomyopathy.[1-3] Ablation generally resolves the cardiomyopathy, although the left ventricular (LV) dysfunction may not resolve completely, depending on the duration and severity of the PVC-induced cardiomyopathy. In patients with acute myocardial infarction (AMI), PVCs are not particularly sensitive or specific predictors in determining who will develop VF.

Management

In most patients, PVCs (occurring as single PVCs, bigeminy, or trigeminy but excluding nonsustained VT; see later) do not need to be treated if the burden is low, particularly if the patient does not have an acute coronary syndrome, and treatment is usually dictated by the presence of symptoms attributable to the PVCs. PVCs accompanying slow ventricular rates can be abolished by increasing the basic rate with atropine or isoproterenol or by pacing, whereas slowing of the heart rate in some patients with sinus tachycardia can eradicate PVCs. In hospitalized patients, intravenous (IV) lidocaine is generally the initial treatment of choice to suppress PVCs but is rarely indicated (**see Chapter 36**). Frequent PVCs, even in the setting of AMI, need not be treated unless they directly contribute to hemodynamic compromise, which is rare. If maximum dosages of lidocaine are unsuccessful, IV procainamide can be tried. Propranolol is suggested if other drugs have been unsuccessful. IV magnesium may be useful.

In most patients, PVCs need not be treated, and reassurance that they are benign in those without structural heart disease is often sufficient for most patients. If treatment is warranted (dictated by symptoms), various class I, II, and III drugs or ablation can be useful. Beta blockers are often the first line of therapy. If they are ineffective, class IC drugs appear to be particularly successful in suppressing PVCs, but flecainide and moricizine have been shown to increase mortality in patients treated after MI and thus should be reserved for those without coronary artery disease (CAD) or LV dysfunction. Amiodarone can be effective, but because of its side effects, it should be reserved for highly symptomatic patients and those with structural heart disease. For patients with significant symptoms, particularly those with reduced cardiac function, radiofrequency (RF) ablation of the PVC focus can be effective and improve cardiac performance. Low levels of serum potassium and magnesium are associated with higher prevalence rates of ventricular arrhythmias. Ablation of PVCs may be warranted on occasion in patients with a high burden, regardless of ejection fraction (EF), or symptoms. Weighing the potential risk of ablation (largely based on PVC location) against the severity of symptoms or likelihood of developing cardiomyopathy is prudent in the absence of clear data.

Accelerated Idioventricular Rhythm

Electrocardiographic Recognition.

The ventricular rate, typically 60 to 110 beats/min, usually hovers within 10 beats of the sinus rate, so control of the cardiac rhythm shifts between these two competing pacemaker sites. Consequently, fusion beats often occur at the onset and termination of the arrhythmia as the pacemakers vie for control of ventricular depolarization (**Fig. 39.3**). Because of the slow rate, capture beats are common. The onset of this arrhythmia is generally gradual (nonparoxysmal) and occurs when the rate of the VT exceeds the sinus rate as a result of sinus slowing or sinoatrial (SA) or AV block. Precipitation of more rapid ventricular arrhythmias is rarely seen. Termination of the rhythm generally occurs gradually as the dominant sinus rhythm accelerates or as the ventricular rhythm decelerates. The ventricular rhythm can be regular or irregular and can occasionally show sudden doubling, which suggests the presence of an exit block. Many characteristics incriminate enhanced automaticity as the responsible mechanism.

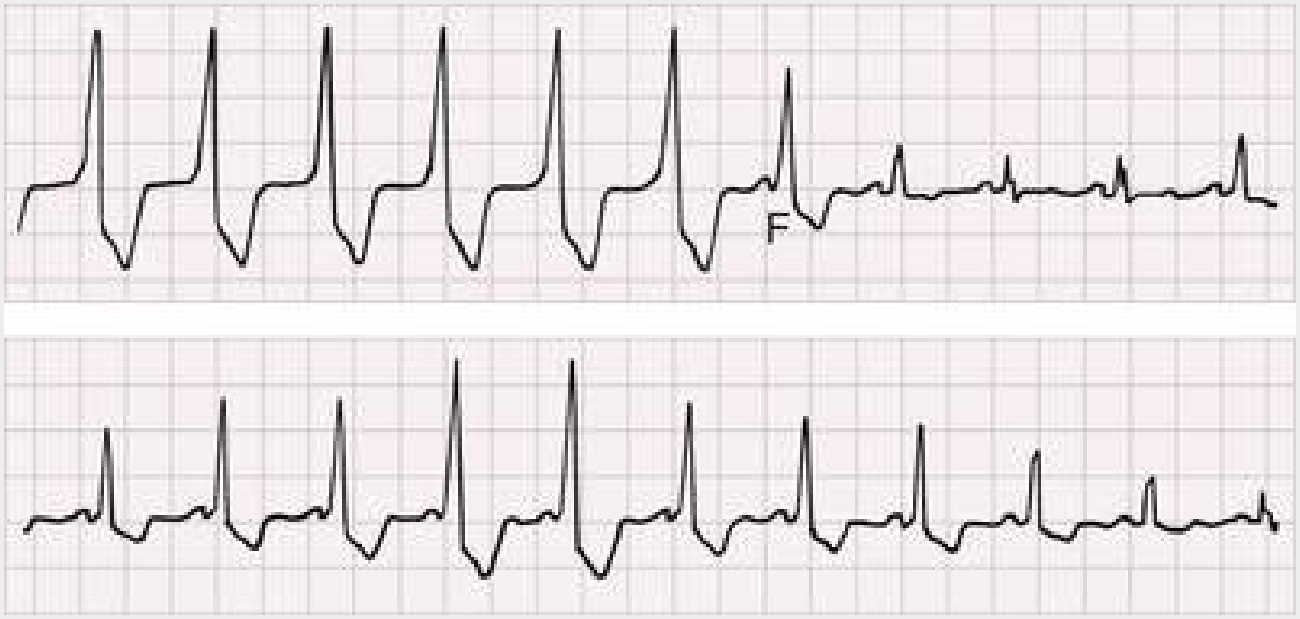

FIGURE 39.3 Accelerated idioventricular rhythm. In this continuous monitor lead recording, an accelerated idioventricular rhythm competes with the sinus rhythm. Wide QRS complexes at a rate of 110 beats/min fuse (*F*) with the sinus rhythm, which takes control briefly, generates the narrow QRS complexes, and then yields once again to the accelerated idioventricular rhythm as the P waves move “in and out” of the QRS complex. This example of isorhythmic AV dissociation may be caused by hemodynamic modulation of the sinus rate via the autonomic nervous system.

The arrhythmia occurs as a rule in patients who have heart disease, such as those with AMI or digitalis toxicity. It is transient and intermittent, with episodes lasting a few seconds to a minute, and does not appear to affect seriously the patient's clinical course or the prognosis. The arrhythmia usually occurs at the moment of reperfusion of a previously occluded coronary artery and can be found during resuscitation.

Management.

Suppressive therapy is rarely necessary because the ventricular rate is generally less than 100 beats/min. Such therapy may be considered, however, when (1) AV dissociation results in loss of sequential AV contraction, (2) an accelerated idioventricular rhythm occurs together with a more rapid VT, (3) an accelerated idioventricular rhythm begins with a PVC discharging in the vulnerable period of the

preceding T wave, (4) the ventricular rate is too rapid and produces symptoms, or (5) ventricular fibrillation (VF) develops as a result of the accelerated idioventricular rhythm. This last event appears to be rare. Therapy, when indicated, should be as noted earlier for VT. Frequently, simply increasing the sinus rate with atropine or atrial pacing suppresses the accelerated idioventricular rhythm.

Ventricular Tachycardia

Ventricular tachycardia can be caused by disorders of impulse formation (enhanced automaticity or triggered activity) and conduction (reentry), considered earlier (**see Chapter 34**). In general, the specific type, prognosis, and management of VT depend on the presence of underlying structural heart disease. With the exception of patients with inherited VT–sudden cardiac death syndromes (**see Chapter 33**), if structural heart disease is absent, the prognosis in patients with VT and PVCs is generally very good,[4] whereas in those with structural heart disease, the subsequent risk for sudden cardiac death (SCD) is increased.

Electrocardiographic Recognition

The electrocardiographic diagnosis of VT is suggested by the occurrence of a series of three or more consecutive, abnormally shaped QRS complexes longer than 120 milliseconds, with the ST-T vector pointing opposite the major QRS deflection. The R-R interval can be regular or varying. Patients can have VTs with multiple morphologies originating at the same or closely adjacent sites with different exits. Others have multiple sites of origin. Atrial activity can be independent of ventricular activity (AV dissociation), or the atria can be depolarized retrogradely (ventriculoatrial [VA] association). Depending on the particular type of VT, rates range from 70 to 250 beats/min, and the onset can be paroxysmal (sudden) or nonparoxysmal. QRS contours during the VT can be unchanging (uniform, monomorphic) or can vary randomly (multiform, polymorphic, or pleomorphic) in a more or less repetitive manner (torsades de pointes), in alternate complexes (bidirectional VT), or in a stable but changing contour (i.e., right bundle branch contour changing to a left bundle branch contour). VT can be *sustained*, defined arbitrarily as lasting longer than 30 seconds or requiring termination because of hemodynamic collapse, or *nonsustained*, when it stops spontaneously in less than 30 seconds. Most often, very premature stimulation is required to initiate VT electrically, whereas late-coupled ventricular complexes usually initiate its spontaneous onset (**Fig. 39.4**).

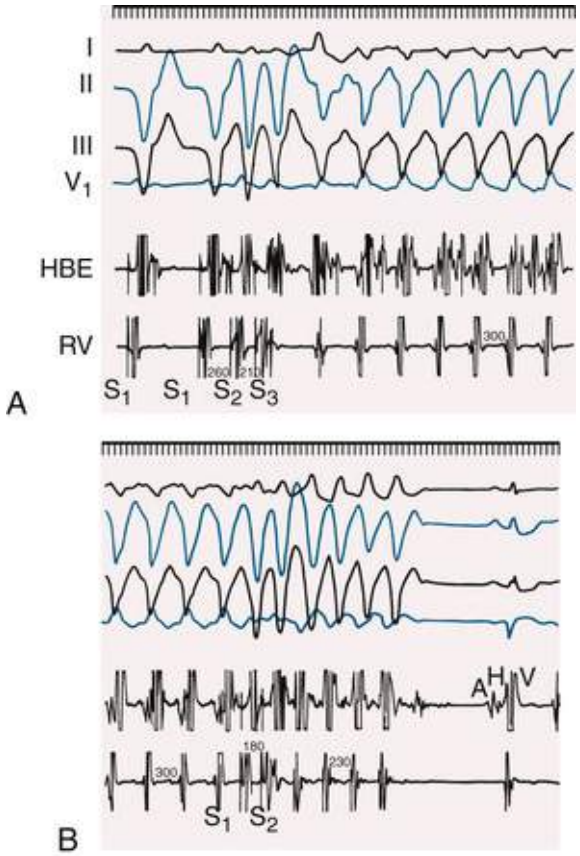

FIGURE 39.4 Initiation and termination of ventricular tachycardia (VT) by means of programmed ventricular stimulation. The last two ventricular-paced beats at a cycle length of 600 milliseconds are shown in **A.** A premature stimulus (S_2) at an S_1-S_2 interval of 260 milliseconds and another premature stimulus (S_3) at a cycle length of 210 milliseconds initiate sustained monomorphic VT at a cycle length of 300 milliseconds. **B,** Two premature ventricular stimuli (S_1-S_2) create an unstable VT that persists for several beats at a shorter cycle length (230 msec) and then terminates, followed by sinus rhythm. *HBE,* His bundle electrogram; *RV,* right ventricle.

It is important to distinguish supraventricular tachycardia (SVT) with aberrancy from VT. When the QRS during tachycardia is narrow (≤120 msec), SVT is easily diagnosed. However, when the QRS during tachycardia is wide (>120 msec), electrocardiographic distinction can be difficult because features of both arrhythmias overlap. Ventricular complexes with an abnormal and prolonged configuration indicate only that conduction through the ventricle is abnormal, and such complexes can occur in supraventricular rhythms as a result of preexisting bundle branch block, aberrant conduction during incomplete recovery of repolarization, conduction over accessory pathways, and several other conditions. These complexes do not necessarily indicate the origin of impulse formation or the reason for the abnormal conduction. Conversely, ectopic beats originating in the ventricle can infrequently have a fairly normal duration and shape. However, VT is the most common cause of tachycardia with a wide QRS complex in patients with a past history of MI or heart failure.

During the course of a tachycardia characterized by wide QRS complexes, the presence of fusion beats and capture beats provides maximum support for the diagnosis of VT but occurs relatively infrequently (**Fig. 39.5**; **see Table 37.2**). Fusion beats indicate activation of the ventricle from two different foci, with the implication that one of the foci had a ventricular origin. Capture of the ventricle by the supraventricular rhythm with a normal configuration of the captured QRS complex at an interval shorter than the tachycardia in question indicates that the impulse has a supraventricular origin and thus excludes a supraventricular origin of the tachycardia. AV dissociation has long been considered a hallmark of VT. However, retrograde VA conduction to the atria from ventricular beats occurs in at least 25% of patients, and therefore VT may not exhibit AV dissociation. AV dissociation can occur infrequently during SVTs.

Even if a P wave appears to be related to each QRS complex, it is at times difficult to determine whether the P wave is conducted anterogradely to the next QRS complex (i.e., SVT with aberrancy and a long PR interval) or retrogradely from the preceding QRS complex (i.e., a VT). As a general rule, however, AV dissociation during tachycardia with a wide QRS complex is strong presumptive evidence that the tachycardia is of ventricular origin.

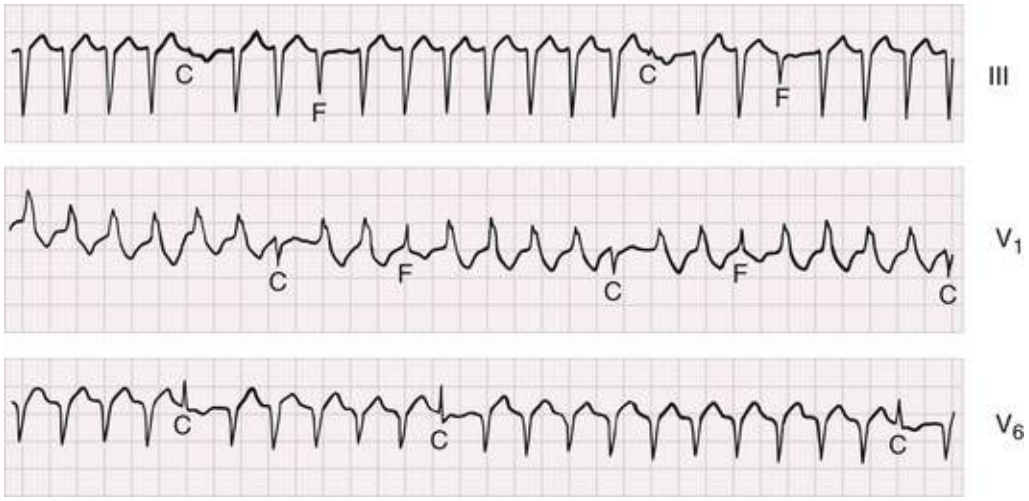

FIGURE 39.5 Fusion and capture beats during VT. The QRS complex is prolonged, and the R-R interval is regular except for occasional capture beats (*C*) that have a normal contour and are slightly premature. Complexes intermediate in contour represent fusion beats (*F*). Thus, even though atrial activity is not clearly apparent, AV dissociation is present during VT and produces intermittent capture and fusion beats.

Differentiation Between Ventricular and Supraventricular Tachycardia

Although fusion and capture beats and AV dissociation provide the strongest electrocardiographic evidence for differentiation of VT from SVT with aberrant conduction, these features are not always present. Other clues characterizing supraventricular arrhythmia with aberrancy include (1) consistent onset of the tachycardia with a premature P wave; (2) very short RP interval (0.1 second), which often requires an esophageal recording or invasive electrophysiologic study (EPS) to visualize the P waves; (3) QRS configuration the same as that occurring from known supraventricular conduction at similar rates; (4) P wave and QRS rate and rhythm linked to suggest that ventricular activation depends on atrial discharge (e.g., P-P interval changes preceding and therefore causing subsequent R-R intervals); and (5) slowing or termination of the tachycardia by vagal maneuvers, although vagal maneuvers can terminate right ventricular outflow tract VTs.

Analysis of specific QRS contours can also be helpful in the diagnosis of VT and localization of its site of origin. For example, QRS contours suggesting VT include left axis deviation in the frontal plane and a QRS duration exceeding 140 milliseconds with normal duration during sinus rhythm. In precordial leads with an RS pattern, the duration of the onset of the R to the nadir of the S exceeding 100 milliseconds suggests VT as the diagnosis. During VT with an RBBB appearance, (1) the QRS complex is monophasic or biphasic in V_1, with an initial deflection different from that of the sinus-initiated QRS complex; (2) the amplitude of the R wave in V_1 exceeds that of R′; and (3) a small R and large S wave or a QS pattern in V_6 may be present. With a VT having an LBBB contour, (1) the axis can be rightward, with negative deflections deeper in V_1 than in V_6; (2) a broad prolonged (>40 msec) R wave can be noted

in V_1; and (3) a small Q–large R wave or QS pattern in V_6 can exist. A QRS complex that is similar in V_1 through V_6, either all negative or all positive, favors a ventricular origin, as does the presence of a 2 : 1 VA block. (An upright QRS complex in V_1 through V_6 can also occur as a result of conduction over a left-sided accessory pathway.) Supraventricular beats with aberration often have a triphasic RSR′ pattern in V_1, an initial vector of the abnormal complex similar to that of the normally conducted beats, and a wide QRS complex that terminates a short cycle length after a long cycle (long-short cycle sequence).

During atrial fibrillation (AF), fixed coupling, short coupling intervals, a long pause after the abnormal beat, and runs of bigeminy rather than a consecutive series of abnormal complexes all favor a ventricular origin of the premature complex rather than a supraventricular origin with aberration. A grossly irregular, wide-QRS tachycardia with ventricular rates exceeding 200 beats/min should suggest AF with conduction over an accessory pathway (**see Fig. 37.22**).

In the presence of a preexisting bundle branch block, a wide-QRS tachycardia with a contour different from the contour during sinus rhythm is most likely a VT. On the basis of these criteria, several algorithms to distinguish VT from SVT with aberrancy have been suggested (**Table 39.2 and Fig. 39.6**). Exceptions exist to all the aforementioned criteria, especially in patients with preexisting conduction disturbances or preexcitation syndrome; when in doubt, one must rely on sound clinical judgment and consider the ECG as only one of several helpful ancillary tests.

TABLE 39.2

Stepwise Criteria Favoring Ventricular Tachycardia in Patients with Wide-Complex Tachycardias Using Different Algorithms*

KINDWALL CRITERIA†	WELLENS CRITERIA‡	BRUGADA CRITERIA§	MILLER CRITERIA‖
R >30 msec in V_1 or V_2 → VT	AV dissociation → VT	Absence of RS complex in all precordial leads → VT	Initial R wave in aVR → VT
Any Q in V_6 → VT	QRS width >140 msec → VT	Longest R/S interval >100 msec in any precordial lead → VT	aVR with initial r or q >40 msec in duration → VT
>60 msec to S wave nadir in V_1 or V_2 → VT	Left axis deviation >−30 degrees → VT	AV dissociation → VT	aVR with a notch on the descending limb of a negative-onset and predominantly negative QRS in aVR → VT
Notched downstroke S wave in V_1 or V_2 → VT	If RBBB morphology, monophasic or biphasic QRS in V_1 → SVT or R-to-S ratio of <1 in V_6 → VT	If RBBB morphology, monophasic R or qR in V_1 → VT R taller than R′ → VT rS in V_6 → VT	In aVR, mV of initial 40 msec divided by terminal 40 msec ($v_i/v_t \leq 1$) → VT
	If LBBB morphology, S in V_1-V_2 → VT	If LBBB morphology, initial R >40 msec in duration → VT Slurred or notched S in V_1 or V_2 → VT Beginning Q or QS in V_6 → VT	

*ACC/AHA/ESC algorithm: see **Fig. 39.6**.

†Kindwall KE, Brown J, Josephson ME. Electrocardiographic criteria for ventricular tachycardia in wide complex left bundle branch block morphology tachycardias. Am J Cardiol 1988;61:1279.

‡Wellens HJ, Bär FW, Lie KI. The value of the electrocardiogram in the differential diagnosis of a tachycardia with a widened QRS complex. Am J Med 1978;64:27.

§Brugada P, Brugada J, Mont L, et al. A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. Circulation 1991;83:1649.

‖Vereckei A, Duray G, Szénási G, et al. New algorithm using only lead aVR for differential diagnosis of wide QRS complex tachycardia. Heart Rhythm 2008;5:89.

LBBB, Left bundle branch block; *RBBB,* right bundle branch block.

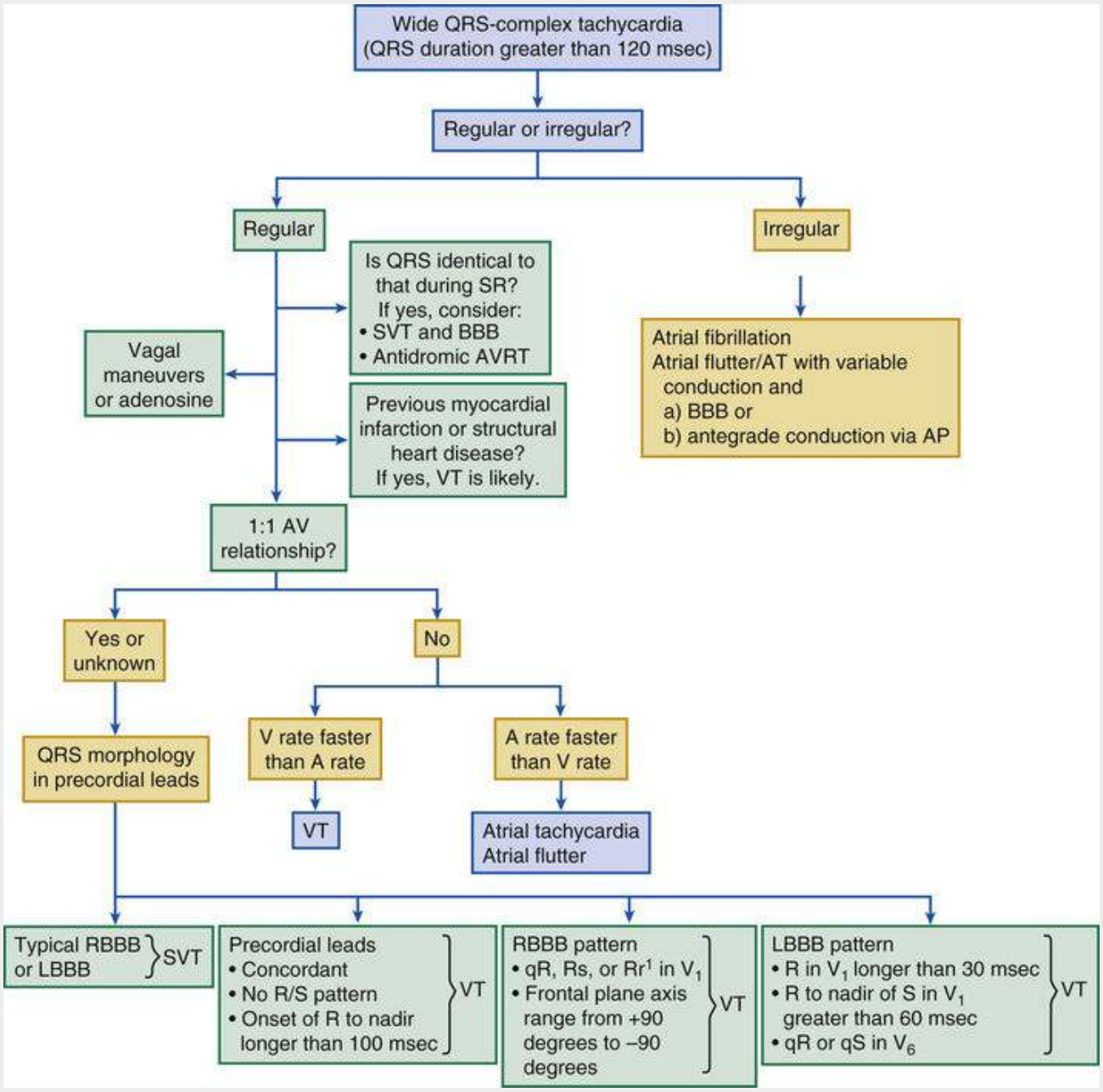

FIGURE 39.6 Algorithm for diagnosis of wide-QRS tachycardia. *AP,* Accessory pathway; *AT,* atrial tachycardia; *AVRT,* atrioventricular reentrant tachycardia; *LBBB,* left bundle branch block; *RBBB,* right bundle branch block. (From Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, et al. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary. Areport of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines [Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias]. Circulation 2003;108:1871.)

The VT origin or exit site can often be determined on the surface ECG. VTs from the left ventricular free wall typically exhibit an RBBB contour, whereas those from the right ventricle or septum have an LBBB contour (**Fig. 39.7A**). Septal VTs typically have narrower QRS complexes than free wall VTs. Apical VTs exhibit negative precordial lead concordance, whereas more basal sites typically have positive concordance. VTs from the posterior (inferior) left or right ventricle often have predominantly negative QRS complexes in leads II, III, and aVF (**Fig. 39.7B**), whereas outflow tract VTs frequently exhibit predominantly positive QRS complexes in these leads. Epicardial VTs have a delayed *intrinsicoid* (initial) deflection that slurs the early portion of the QRS complex; an intrinsicoid deflection exceeding 55% of the QRS duration is likely to be epicardial (**Fig. 39.7B**).

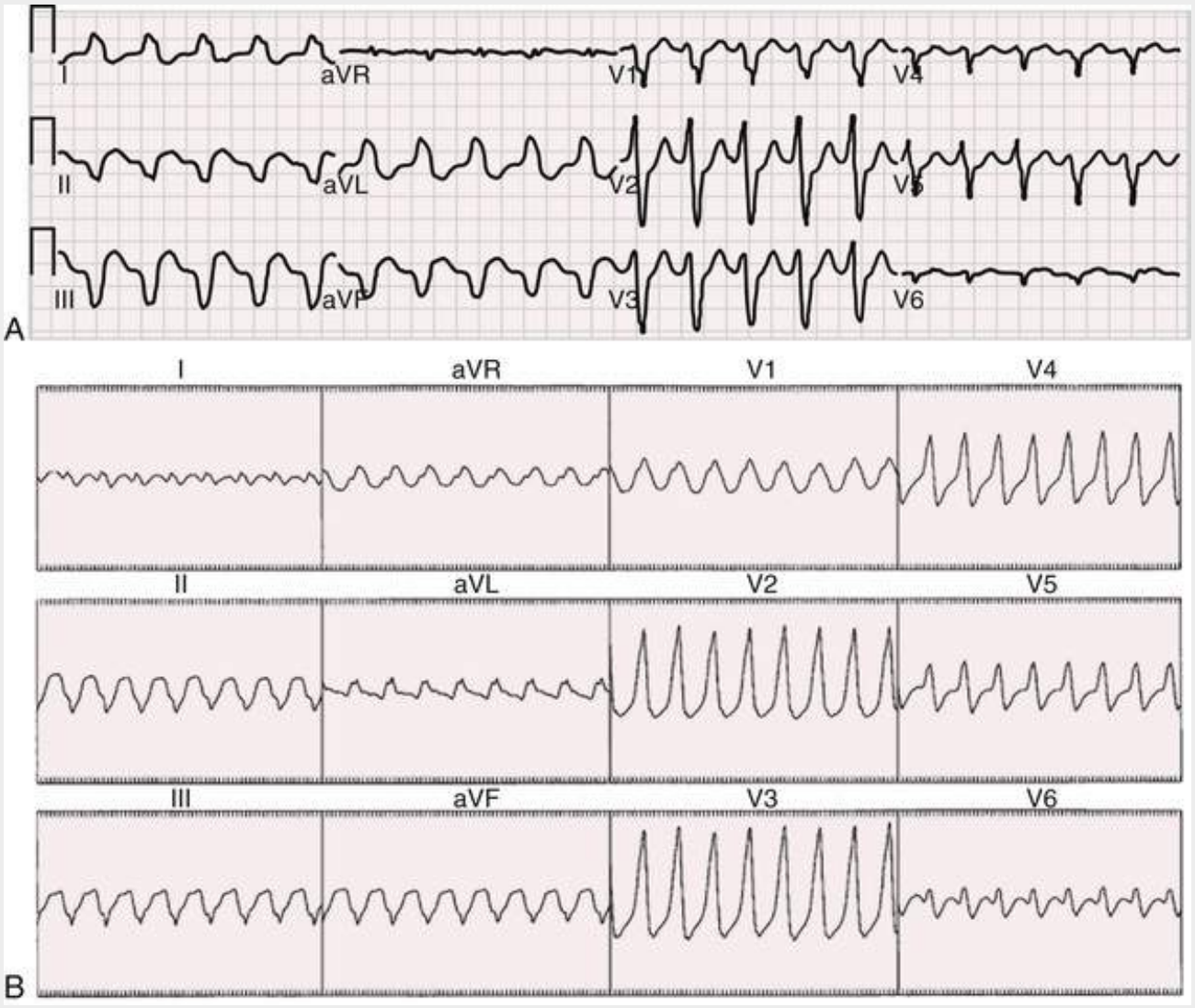

FIGURE 39.7 **A,** Ventricular tachycardia in a patient with a previous myocardial infarction. The VT exit is in the left ventricular septum (left bundle branch block morphology), inferiorly (QS in II, III, and aVF) close to the apex (QS in V_6). **B,** Epicardial ventricular tachycardia in a patient with Chagas disease. The VT has shortest intrinsicoid deflection, greater than 55% of the QRS in the precordium, and is therefore of epicardial origin. Because it has right bundle branch block morphology in V_1 and QS in leads II, III, and aVF, the origin is in the inferior left ventricle.

Electrophysiologic Features.

VT can be distinguished electrophysiologically by a short or negative H-V interval (i.e., H begins after the onset of ventricular depolarization) because of retrograde activation from the ventricles (**see Chapters 34 and 35**). His bundle deflections are usually obscured by simultaneous ventricular septal depolarization or inadequate catheter position. The latter must be determined during supraventricular rhythm before the onset or after the termination of VT (**see Fig. 39.4**). His bundle deflections dissociated from more rapid ventricular activation are diagnostic of VT, with rare exceptions.

Successful electrical induction of VT by premature ventricular stimulation depends on the characteristics of the VT and the anatomic substrate (**see Fig. 39.4**). Patients with sustained, hemodynamically stable VT and VT secondary to prior myocardial infarction (MI) have monomorphic VT induced more frequently (90%) than patients with nonsustained VT, VT from non–coronary-related causes or acute ischemia, and cardiac arrest (40% to 75%). In general, it is more difficult to induce VT with late premature ventricular stimuli than with early premature stimuli, during sinus rhythm than during ventricular pacing, with one premature stimulus than with two or three, and in normal hearts without drugs on board. The specificity of VT induction using more than two premature ventricular stimuli begins

to decrease, whereas the sensitivity increases; nonsustained polymorphic VT or VF can be induced in patients with no history of VT. On occasion, VT can be initiated only from the left ventricle or from specific sites in the right ventricle when they are closer to the reentrant circuit. Multiple premature stimuli can reduce the need for LV stimulation. Drugs such as isoproterenol can facilitate the induction of VT, as can alcohol.

Termination by pacing depends on the mechanism (reentrant VT can be pace-terminated), rate of the VT, and the site of pacing. Slower VTs are terminated more easily and with fewer stimuli. An increasing number of stimuli are required to terminate more rapid VTs, which increases the risks associated with pacing-induced VT acceleration.

Clinical Features

Symptoms during VT depend on the ventricular rate, duration of the tachycardia, and the presence and extent of the underlying heart disease and peripheral vascular disease. VT can occur in several forms: short, asymptomatic, nonsustained episodes; sustained, hemodynamically stable events (generally occurring at slower rates or in otherwise normal hearts); or unstable runs, often resulting in hemodynamic collapse and degenerating into VF. VTs initially nonsustained can later become sustained. Physical findings depend in part on the P-to-QRS relationship. If atrial activity is dissociated from the ventricular contractions, the findings of AV dissociation are present. If the atria are captured retrogradely, regularly occurring cannon *a* waves appear when atrial and ventricular contractions occur simultaneously, and signs of AV dissociation are absent.

Most patients treated for symptomatic recurrent VT have ischemic heart disease. The next largest group has cardiomyopathy (both congestive and hypertrophic; **see Chapters 77 and 78**), with lesser percentages divided among those with primary electrical disease such as inherited ion channel abnormalities (**Chapter 33**), idiopathic VT, congenital heart disease (**Chapter 75**), and miscellaneous causes. LV hypertrophy can lead to ventricular arrhythmias, as can areas of fibrosis detected by gadolinium magnetic resonance imaging (MRI; **Chapter 17**). Coronary artery spasm can cause transient myocardial ischemia with ventricular arrhythmias in some patients, during ischemia as well as during the apparent reperfusion period (**Chapter 59**). Many patients resuscitated from SCD (**Chapter 42**) have CAD or cardiomyopathy. When VT occurs in an ambulatory patient, it is infrequently induced by R-on-T PVCs. Patients with sustained VT are more likely to have a reduced EF, slowed intraventricular conduction and electrographic abnormalities (e.g., wide QRS), LV aneurysm, and previous MI. In patients with CAD, sustained VT displays a circadian variation, with the peak frequency occurring in the morning.

Many approaches have been used to assess prognosis in patients with ventricular arrhythmias, although none has sufficient positive or negative predictive value (**see Chapter 35**). Inducibility of VT during an EPS, reduced LV function, spontaneous ventricular arrhythmias, late potentials on a signal-averaged ECG, QT-interval dispersion, T wave alternans, prolonged QRS duration, heart rate turbulence, decreased heart rate variability, and reduced baroreceptor sensitivity all carry increased risk for total mortality and sudden death. Currently, however, no technique reliably predicts outcome better than assessment of LV function. LV function and inducibility of VT during EPS are the two strongest predictors of a poor outcome. In general, the prognosis for patients with idiopathic VT (see later) in the absence of structural heart disease is good, and less aggressive treatment is warranted than for patients with structural heart disease. Patients with inherited arrhythmia syndromes are an exception to this statement (**see Chapter 33**).

Management

Multiple large clinical trials have led to alterations of the management of VT and aborted sudden death (**Table 39.3**). Management decisions can be stratified into those involved in acute management (or termination) and those involved in long-term therapy (or prevention of recurrence or sudden death; **see Chapters 36 and 42**).

TABLE 39.3

Clinical Trials on the Treatment of Ventricular Tachycardia and Prevention of Cardiac Arrest

STUDY	PATIENT INCLUSION	ENDPOINTS	TREATMENT ARMS	KEY RESULTS
Primary Prevention Studies				
BHAT[a]	Post-MI	Total mortality SCD	Propranolol Placebo	Total mortality, sudden cardiac death reduced in the treatment arm
CAST[b,c]	Post-MI ≥6 PVCs/hr LVEF ≤40%	Arrhythmic death	Flecainide Encainide Moricizine Placebo	Arrhythmic death increased in all treatment arms
SWORD[d]	Post-MI LVEF <40% *or* Remote MI NYHA Class II-III	Total mortality	*d*-Sotalol Placebo	Increased mortality in the treatment arm
EMIAT[e]	Post-MI LVEF <40%	Total mortality Arrhythmic death	Amiodarone Placebo	Amiodarone reduced arrhythmic death but not total mortality
CAMIAT[f]	Post-MI ≥10 PVCs/hr or NSVT	Arrhythmic death Total mortality	Amiodarone Placebo	Amiodarone reduced arrhythmic death but not total mortality
GESICA[g]	CHF LVEF ≤35%	Total mortality	Amiodarone Best therapy	Amiodarone reduced mortality; patients with NSVT had higher mortality
CHF-STAT[h]	CHF LVEF ≤40% ≥10 PVCs/hr (asymptomatic)	Total mortality	Amiodarone Placebo	No effect on ischemic cardiomyopathy but trend toward reduced mortality in nonischemic cardiomyopathy
CABG-PATCH[i]	CAD undergoing CABG LVEF <36% Positive SAECG	Total mortality	CABG CABG + ICD	No difference in total mortality
MADIT[j]	Post-MI NSVT LVEF ≤35% NYHA Class I-III Inducible VT not suppressed by procainamide	Total mortality	ICD AAD (80% amiodarone)	ICD reduced mortality
MUSTT[k]	Post-MI LVEF <40% NSVT	Arrhythmic death or cardiac arrest	ICD in nonsuppressible group AAD in suppressible group No therapy	Improved survival in ICD group; no difference between no therapy and AAD group
MADIT II[l]	Post-MI EF ≤30% >10 PVCs/hr or couplets	Total mortality	ICD No ICD	Improved survival in ICD arm
DINAMIT[m]	Immediately post-MI EF ≤35%	Total mortality Arrhythmic mortality	ICD No ICD	No improvement in survival with ICD
IRIS[n]	Immediately post-MI EF ≤40%	Total mortality	ICD No ICD	No improvement in survival with ICD
COMPANION[o]	Ischemic or nonischemic CM NYHA Class III-IV QRS ≥120 msec	Total mortality	Medical therapy PM-CRT ICD-CRT	Improved survival in ICD-CRT group > PM-CRT > medical therapy
DEFINITE[p]	Nonischemic CM EF ≤36% PVCs or NSVT	Total mortality Arrhythmic	ICD No ICD	Improved survival in the ICD arm

		mortality		
SCD-HeFT[q]	CHF LVEF ≤35% NYHA Class II-III	Total mortality Arrhythmic mortality Cost Quality of life	ICD Amiodarone Placebo	Improved survival with ICD; no effect of amiodarone on survival
Secondary Prevention Studies				
ESVEM[r,s]	Cardiac arrest, sustained VT, or syncope ≥10 PVCs/hr Inducible VT	Recurrence of arrhythmia	EPS-guided AADs (imipramine, mexiletine, procainamide, quinidine, sotalol, pirmenol, propafenone) Holter-guided AADs	No difference between Holter- and EPS-guided groups; sotalol group had the lowest recurrence rate of VT, arrhythmic death, and total death
CASCADE[t]	Cardiac arrest Not associated with acute MI	Cardiac mortality Aborted cardiac arrest	EPS- or Holter-guided conventional drug therapy Empiric amiodarone	Survival with amiodarone better than with conventional guided drug therapy
CASH[u]	Cardiac arrest Not associated with acute MI	Total mortality	Empiric amiodarone Metoprolol Propafenone ICD	SCD mortality lowest in ICD arm; increased mortality in propafenone arm
AVID[v]	Cardiac arrest or sustained VT	Total mortality Cost Quality of life	ICD Drug therapy (empiric amiodarone or EPS- or Holter-guided sotalol)	Survival better in ICD group, with most benefit occurring in first 9 mo; benefit most pronounced in patients with EF <35%
CIDS[w,x]	Cardiac arrest or sustained VT	Total mortality	ICD Amiodarone	Survival trended better in ICD group

[a]β-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA 1982;247:1707.

[b]Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991;324:781.

[c]The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. N Engl J Med 1992;327:227.

[d]Waldo AL, Camm AJ, deRuyter H, et al. Effect of *d*-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. Lancet 1996;348:7.

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AAD, Antiarrhythmic drug; *CABG,* Coronary artery bypass graft; *CAD,* coronary artery disease; *CHF,* congestive heart failure; *CM,* cardiomyopathy; *CRT,* cardiac resynchronization therapy; *EF,* ejection fraction; *EPS,* electrophysiologic study; *ICD,* implantable cardioverter-defibrillator; *LVEF,* left ventricular ejection fraction; *MI,* myocardial infarction; *NSVT,* nonsustained ventricular tachycardia; *NYHA,* New York Heart Association; *PM,* pacemaker; *SAECG,* signal-averaged electrocardiogram; *SCD,* sudden cardiac death.

Acute Management of Sustained Ventricular Tachycardia

VT that does not cause hemodynamic decompensation can be treated medically to achieve acute termination by IV administration of amiodarone, lidocaine, or procainamide, followed by an infusion of the successful drug. Lidocaine is often ineffective; amiodarone and procainamide appear to be superior. However, in a randomized trial of out-of-hospital cardiac arrest, neither amiodarone nor lidocaine improved survival to hospital discharge.[5] In patients in whom procainamide is ineffective or may be problematic (severe heart failure, renal failure), IV amiodarone is frequently effective. In general, an initial amiodarone loading dose of 15 mg/min is given during a 10-minute period. This dose is followed by an infusion of 1 mg/min for 6 hours and then a maintenance dose of 0.5 mg/min for the remaining 18 hours and for the next several days, as necessary. If the VT does not terminate or if it recurs, a repeated loading dose can be given. Rarely, sinus bradycardia or AV block can be seen with IV amiodarone. The hypotension associated with IV amiodarone does not seem to be a frequent problem and is usually related to the rate of infusion.

If the arrhythmia does not respond to medical therapy, electrical direct-current (DC) cardioversion can be used. VT that precipitates hypotension, shock, angina, congestive heart failure, or symptoms of cerebral hypoperfusion should be treated promptly with DC cardioversion (**see Chapters 36 and 42**). Very low energies can terminate monomorphic VT, beginning with a synchronized shock of 10 to 50 J. After conversion of the arrhythmia to a normal rhythm, it is essential to institute measures to prevent recurrence.

When a defibrillator is not readily available, striking the patient's chest can infrequently terminate the VT. However, chest stimulation at the vulnerable period during the arrhythmia can accelerate the VT or possibly provoke VF, so backup defibrillation may be necessary.

In some cases, such as VT associated with a remote MI (which is caused by reentry), ventricular pacing via a pacing catheter inserted into the right ventricle or transcutaneously at rates faster than the tachycardia can terminate the tachycardia. This procedure incurs the risk of accelerating the VT to ventricular flutter or VF. In patients with recurrent VT, overdrive ventricular pacing can be used to prevent recurrences. Intermittent VT, interrupted by several supraventricular beats, generally is best treated pharmacologically.

A search for reversible conditions contributing to the initiation and maintenance of VT should corrected, if present. For example, VT related to ischemia, hypotension, or hypokalemia can at times be terminated by antianginal treatment, vasopressors, or potassium, respectively. Correction of heart failure can reduce the frequency of ventricular arrhythmias. Slow ventricular rates caused by sinus bradycardia or AV block can permit the occurrence of PVCs and ventricular tachyarrhythmias, which is corrected by transvenous pacing. Rarely, SVT can initiate ventricular tachyarrhythmias and should be prevented if this is the observed mechanism of VT initiation.

Long-Term Therapy for Prevention of Recurrences

Because the goal of long-term therapy is to prevent SCD and recurrence of symptomatic VT, asymptomatic nonsustained ventricular arrhythmias in low-risk populations (i.e., preserved LV function) often need not be treated. In patients with symptomatic nonsustained tachycardia, beta blockers may prevent recurrences. In patients refractory to beta blockers, class IC agents, sotalol, or amiodarone can be effective. However, class IC agents should be avoided in patients with structural heart disease, especially those with CAD, because of the increased mortality associated with these drugs secondary to their proarrhythmic effects. Sotalol should be used cautiously because of its potential for prolonging the QT interval and producing torsades de pointes. Patients with nonsustained VT after MI and poor LV function are at significant risk for sudden death. The major multicenter, randomized implantable cardioverter-defibrillator (ICD) trials are summarized in **Table 39.3**.

For secondary prevention of sustained VT or cardiac arrest in patients with structural heart disease, class I antiarrhythmic drugs (AADs) produce a worse outcome than do class III AADs, empiric amiodarone results in better survival than does EPS-guided AADs, and ICDs provide better survival than amiodarone, particularly in patients with an LVEF less than 0.35 (**see Table 39.3 and Chapters 36 and 42**). Therefore, in patients who have survived cardiac arrest or who have sustained VT resulting in hemodynamic compromise and poor LV function, an ICD is the treatment of choice.[6] In patients who refuse an ICD, empiric amiodarone may be the next best therapy, although no reduction in mortality was found in SCD-HeFT. The optimal therapy for patients with CAD who have preserved LV function with *sustained* VT is not currently known. Empiric amiodarone appears to be the safest therapy, although Holter-guided sotalol has been advocated, and ablation of monomorphic VT may be effective and preferable long-term.[7] Some patients who receive ICDs experience frequent shocks because of recurrent VT. In these patients, concomitant therapy with amiodarone or VT ablation may be required to reduce the frequency of VT or to slow the rate of the VT so that it can be pace-terminated. Other drugs, such as sotalol, procainamide, mexiletine, and flecainide, may be required if amiodarone is not effective. On occasion, a combination of drugs can be effective when a single drug is not. Ablation can also be considered in this situation. Although RF ablation of certain types of idiopathic VT (see later) is very effective (**see Chapter 36**), ablation for postinfarction VT or that associated with dilated cardiomyopathy is somewhat less effective. In addition, because of the significant mortality associated with these arrhythmias in patients with structural heart disease and depressed LV function, ablation is generally used as an adjunct to ICD placement to reduce the frequency of VT and ICD shocks.[8] However, in patients with

well-tolerated postinfarction VT and well-preserved LV function, or in patients refractory to drugs, ablation can be used as first-line therapy. In patients with VT or VF, prophylactic ablation of the VT substrate can reduce future shocks.[7]

Specific Types of Ventricular Tachycardia

A number of fairly specific types of VT have been identified, and distinction is based on a constellation of electrocardiographic and electrophysiologic features, a specific set of clinical events, and genetics (**see Chapter 33**). These different types of VT often have different prognoses and responses to different therapy.

Ventricular Arrhythmias in Patients with Cardiomyopathies

See **Chapters 61, 77, and 78**.

Ischemic Cardiomyopathy

Patients with previous MI are at risk for developing VT.[9] In the setting of a remote MI, the mechanism of VT is reentry and involves the infarct scar, in particular the border zone or other areas of the scar with deranged conduction (**see Chapter 34**). As a result, the VT in this setting is typically monomorphic, sometimes with more than one morphology because of different exit sites, reversal of the direction of reentry using the same circuit, or other circuits in the infarct scar. Polymorphic VT or VF in the setting of ischemic heart disease usually occurs during active ischemia or infarction.

Treatment of VT in the patient with ischemic heart disease follows the recommendations described earlier. In general, ICDs are indicated to prevent SCD from VT, especially in those with depressed LV function. Monomorphic VT in this setting is often amenable to pace termination from the ICD. In patients with preserved LV function and no hemodynamic compromise, optimal long-term treatment is still controversial. Primary suppression with AADs (e.g., amiodarone), implantation with an ICD, antitachycardia pacing, and ablation are options. Newer approaches to ablation of VT caused by a previous infarct scar have increased the efficacy,[10] but the recurrence rate is high because of multiple circuits, and ablation is in general reserved for refractory VT or well-tolerated VT (**see Chapter 36**). Surgical endocardial resection of the scarred area is also an effective treatment of refractory VT caused by previous MI. For recurrent VT or VT storm refractory to medications or ablation, cardiac sympathetic denervation has been effective in limited studies.

Nonischemic Cardiomyopathy

Both dilated and hypertrophic cardiomyopathy can be associated with VTs and an increased risk for SCD (**see Chapter 77**). Induction of VT by programmed stimulation does not reliably identify high-risk patients. Because it is difficult to predict patients at risk for SCD or those who might respond favorably to an AAD, ICDs have been advocated for patients with life-threatening ventricular arrhythmias and dilated cardiomyopathy (**see Table 39.3**). Bundle branch reentry can be the basis of some VTs in this population and can be treated by ablation of the right bundle branch. In patients with refractory or recurrent VT, ablation is an effective adjunct to an ICD, but ablation from the epicardial surface is often required.[10]

Hypertrophic Cardiomyopathy

The risk for SCD in patients with hypertrophic cardiomyopathy is increased by the presence of syncope, a

family history of SCD in first-degree relatives, septal thickness greater than 3 cm, or the presence of nonsustained VT on 24-hour electrocardiographic recordings (**see Chapter 78**). Asymptomatic or mildly symptomatic patients with brief and infrequent episodes of nonsustained VT have low mortality. Electrophysiologic testing to risk-stratify for ventricular arrhythmias and SCD is controversial and has not been shown to reliably identify patients at increased risk. Amiodarone has been useful in some patients with mildly symptomatic, nonsustained VT, but not in improving survival. Septal alcohol ablation and myotomy/myectomy have been useful in reducing the outflow gradient, but their role in reducing ventricular arrhythmias has not been established. Currently, no totally acceptable way to risk-stratify patients with hypertrophic cardiomyopathy in terms of VT has been identified. In patients believed to be at high risk for SCD or those with sustained VT or frequent nonsustained VT, an ICD may be indicated.[11]

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC), also called arrhythmogenic right ventricular dysplasia (ARVD), is a heterogeneous inherited disease that results in fibrofatty infiltration of predominantly the right ventricle, although the disease can also affect the left ventricle, typically the posterior portion (**see Chapters 33 and 77**). Mutations in genes that encode various proteins of the desmosome (plakoglobin, desmoplakin, plakophilin, desmoglein, and desmocollin) have been found to cause the disease but are present in only approximately 50% of patients.[12] Right-sided heart failure or asymptomatic right ventricular (RV) enlargement can be present. Male patients predominate, and most are usually found to have an abnormal right ventricle on echocardiography, RV angiography, or MRI, although this abnormality may not be apparent on initial evaluation. Patients with ARVC have VT that generally has an LBBB contour (because the tachycardia arises in right ventricle) and can have several morphologies (including those consistent with outflow tract VT). The ECG during sinus rhythm can exhibit complete or incomplete RBBB and T wave inversions in V_1 to V_3. A terminal notch in the QRS, called an *epsilon wave,* can be present as a result of slowed intraventricular conduction. Findings on the signal-averaged ECG can be abnormal because of delayed conduction in the right ventricle (**Fig. 39.8A**).

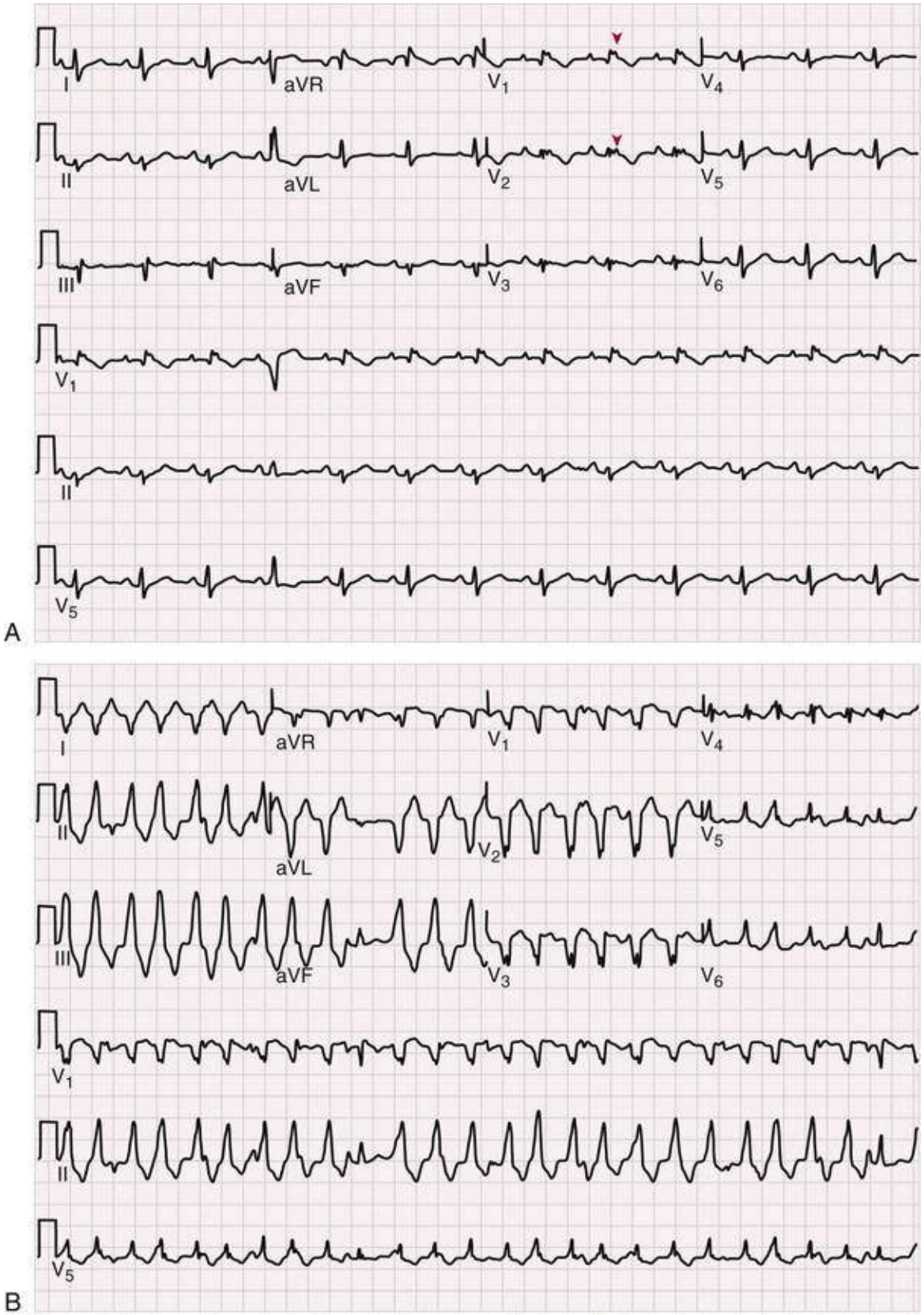


FIGURE 39.8 **A,** Normal sinus rhythm in a patient with arrhythmogenic right ventricular (RV) cardiomyopathy (dysplasia). The *arrowheads* in V_1 and V_2 point to late RV activation called an epsilon wave. **B,** VT in the same patient with RV dysplasia.

ARVC can be an important cause of ventricular arrhythmia in children and young adults with apparently normal hearts, as well as in older patients. The initial findings can be subtle and often mimic those of outflow tract VT, manifested only by tachycardia and no symptoms of right-sided heart failure. Diagnosis of ARVD can be elusive because of nonspecific findings on several tests depending on the stage and severity of the disease, desmosomal mutations present in only approximately 50% of cases, and low

penetrance of the inherited trait. Therefore the diagnosis of ARVD is based on fulfilling the diagnostic criteria established by the ARVD Task Force to provide guidance on the role of diagnostic tests and specificity[13] (**Table 39.4**). ICDs are generally preferable to pharmacologic approaches because of the progressive nature of the disease and poor prognosis, particularly if the patient has poorly tolerated VT resulting in syncope or SCD. RF catheter ablation can be tried but often requires ablation of multiple morphologies, as well as extensive substrate ablation to eliminate all potential reentrant circuits.[7,13] Because most of the circuits and scarring are located on the epicardial surface, epicardial ablation is often required.

TABLE 39.4

Diagnostic Criteria for Arrhythmogenic Right Ventricular (RV) Cardiomyopathy

Definite diagnosis	2 major criteria *or*
	1 major and 2 minor criteria *or*
	4 minor criteria from different categories
Borderline	1 major and 1 minor criteria *or*
	3 minor criteria from different categories
Possible	1 major *or*
	2 minor criteria from different categories
	CRITERIA
I. Global or Regional Dysfunction and Structural Alterations	
Major criteria	*By two-dimensional echocardiography*: Regional RV akinesia, dyskinesia,* or aneurysm *and* 1 of the following (end diastole): PLAX RVOT ≥32 mm (corrected for body size—PLAX/BSA ≥19 mm^2) PSAX RVOT ≥36 mm (corrected for body size—PSAX/BSA ≥21 mm^2) Fractional area change ≤33%
	By MRI: Regional RV akinesia or dyskinesia or dyssynchronous RV contraction *and* 1 of the following: Ratio of RV end-diastolic volume to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female) RV ejection fraction ≤40%
	By RV angiography: Regional RV akinesia, dyskinesia, or aneurysm
Minor criteria	*By two-dimensional echocardiography*: Regional RV akinesia or dyskinesia *and* 1 of the following (end diastole): PLAX RVOT ≥29 to <32 mm (corrected for body size—PLAX/BSA ≥16 to ≤19 mm/m^2) PSAX RVOT ≥32 to <36 mm (corrected for body size—PSAX/BSA ≥18 to <21 mm/m^2) Fractional area change >33% to ≤40%
	By MRI: Regional RV akinesia or dyskinesia or dyssynchronous RV contraction *and* 1 of the following: Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (female) RV ejection fraction >40% to ≤45%
II. Tissue Characterization of Wall	
Major criteria	Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Minor criteria	Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
III. Repolarization Abnormalities	
Major criteria	Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals >14 yr (in the absence of complete RBBB QRS ≥120 msec)
Minor criteria	Inverted T waves in leads V_1 and V_2 in individuals >14 yr (in the absence of complete RBBB) or in V_4, V_5, or V_6
	Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 yr in the presence of complete RBBB
IV. Depolarization/Conduction Abnormalities	
Major criteria	Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of T wave) in right precordial leads (V_1 to V_3)
Minor criteria	Filtered QRS duration (fQRS) ≥114 msec
	Duration of terminal QRS ≤40 μV (low-amplitude signal duration) ≥38 msec
	Root-mean-square voltage of terminal 40 msec ≤20 μV
	Terminal activation duration of QRS ≥55 msec measured from nadir of S wave to end of QRS, including R′, in V_1, V_2, or V_3, in the absence of complete RBBB
V. Arrhythmias	
Major criteria	Nonsustained or sustained VT of LBBB morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)
Minor criteria	Nonsustained or sustained ventricular tachycardia of RV outflow configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis
	>500 ventricular extrasystoles per 24 hr (Holter)
VI. Family History/Genetics	
Major criteria	ARVC/D confirmed in a first-degree relative who meets the current task force criteria
	ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative
	Identification of a pathogenic mutation† categorized as associated or probably associated with ARVC/D in the patient under evaluation
Minor	History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets the current task force criteria

criteria	Premature sudden death (<35 yr) because of suspected ARVC/D in a first-degree relative
	ARVC/D confirmed pathologically or by current task force criteria in a second-degree relative

*Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.

†A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree.

ARVC/D, Arrhythmogenic right ventricular cardiomyopathy/dysplasia; *aVF,* augmented voltage unipolar left foot lead; *aVL,* augmented voltage unipolar left arm lead; BSA, body surface area; *LBBB,* left bundle branch block; *PLAX,* parasternal long-axis view; *PSAX,* parasternal short-axis view; *RBBB,* right bundle branch block; *RVOT,* right ventricular outflow tract; *VT,* ventricular tachycardia.

From Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation 2010;121:1533.

Tetralogy of Fallot

Chronic serious ventricular arrhythmias can occur in patients years after repair of tetralogy of Fallot (**see Chapter 75**). Sustained VT after repair can be caused by reentry at the site of previous surgery in the RV outflow tract and can be cured by resection or catheter ablation of this area. Findings on the signal-averaged ECG can be abnormal. Decreased cardiac output can occur during VT and residual RV outflow obstruction and lead to VF. In some patients, worsening of pulmonary insufficiency and RV dilation can trigger the VT. Replacement of the pulmonic valve and concomitant cryoablation of the outflow tract may be required to eliminate the tachycardia.

Inherited Arrhythmia Syndromes (see Chapter 33)

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic VT (CPVT) is an uncommon form of inherited VT that occurs in the absence of overt structural heart disease.[14-17] Mutations in genes encoding proteins responsible for intracellular calcium handling have been identified as causes of the disease.[18] Patients typically have syncope or aborted sudden death with highly reproducible, stress-induced VT that is often bidirectional. These patients have no structural heart disease and normal QT intervals. A family history of sudden death or stress-induced syncope is present in approximately 30% of cases. During exercise, typical responses include initial sinus tachycardia and ventricular extrasystoles, followed by salvoes of monomorphic or bidirectional VT, which eventually lead to polymorphic VT as exercise continues (**Fig. 39.9**). The treatment of choice is beta blockers[17] and an ICD, although breakthrough can occur despite beta blockade. Left-sided or bilateral sympathectomy has been reported to be effective in a few cases (**see Chapter 99**). In addition, flecainide inhibits ryanodine receptor–mediated calcium release and has had some clinical success.[17] Patients with CPVT should be instructed to avoid vigorous exercise.

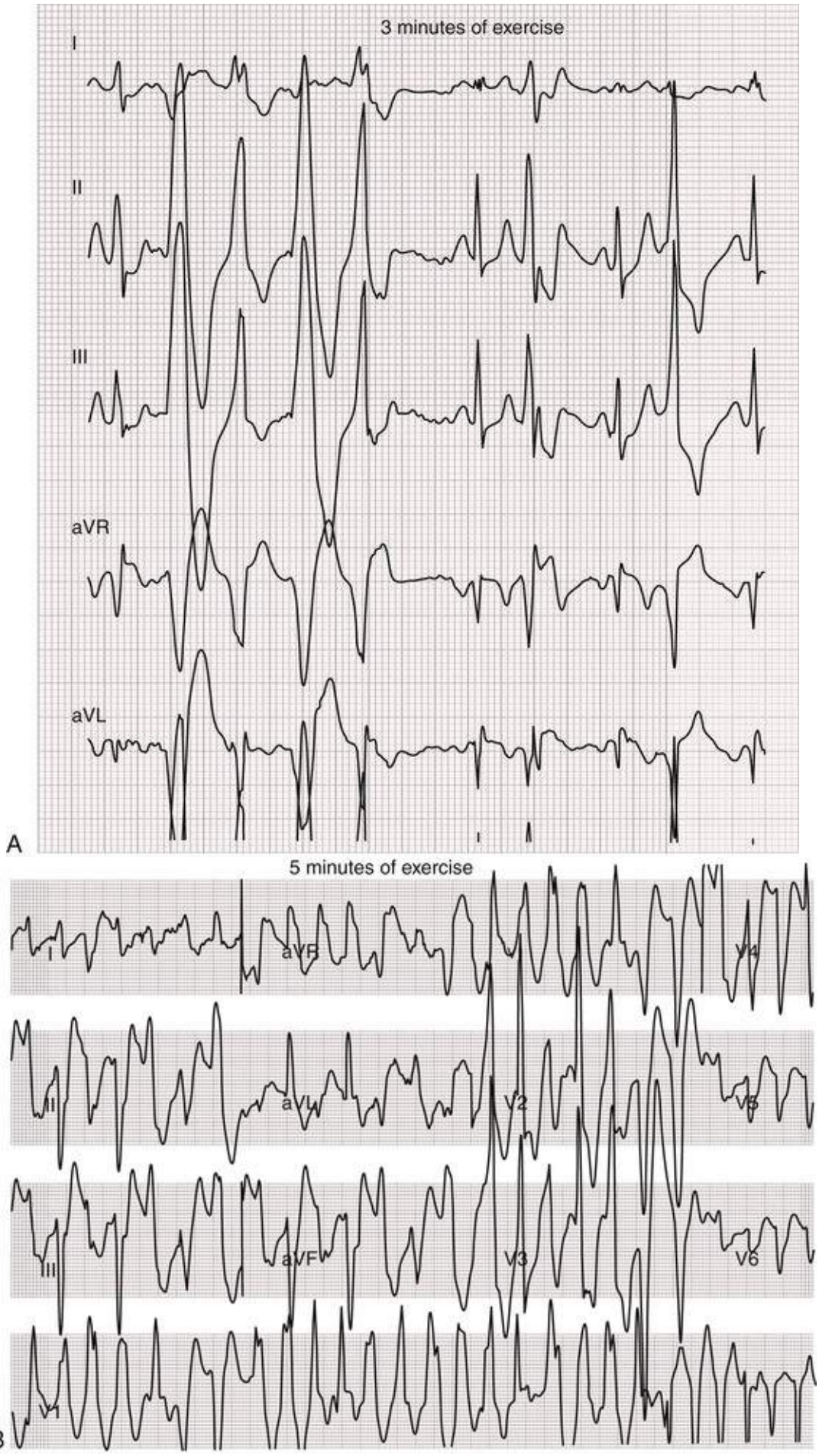


FIGURE 39.9 ECG obtained during an exercise treadmill test in a patient with catecholaminergic polymorphic VT. **A,** During the early phase of exercise, short runs of polymorphic VT and PVCs occur. **B,** With further exercise, bidirectional VT ensues.

Torsades de Pointes

Electrocardiographic Recognition

The term *torsades de pointes* (TdP) refers to a VT characterized by QRS complexes of changing amplitude that appear to twist around the isoelectric line and occur at rates of 200 to 250 per minute (**Fig. 39.10A**). Originally described in the setting of bradycardia caused by complete heart block, TdP usually connotes a syndrome, not simply an electrocardiographic description of the QRS complex of the tachycardia, characterized by prolonged ventricular repolarization with QT intervals generally exceeding 500 milliseconds. The U wave can also become prominent and merge with the T wave, but its role is not clear. The abnormal repolarization need not be present or at least prominent in all beats, but it may be apparent only on the beat before the onset of TdP (i.e., after a PVC). Long-short R-R cycle sequences usually precede the onset of TdP from acquired causes. Relatively late PVCs can discharge during termination of the long T wave and precipitate successive bursts of VT, during which the peaks of QRS complexes appear successively on one side and then on the other side of the isoelectric baseline; these peaks give the typical twisting appearance with continuous and progressive changes in QRS contour and amplitude. TdP can terminate with progressive prolongation of cycle length and larger and more distinctly formed QRS complexes and culminate in a return to the basal rhythm, a period of ventricular standstill, and a new attack of TdP or VF.

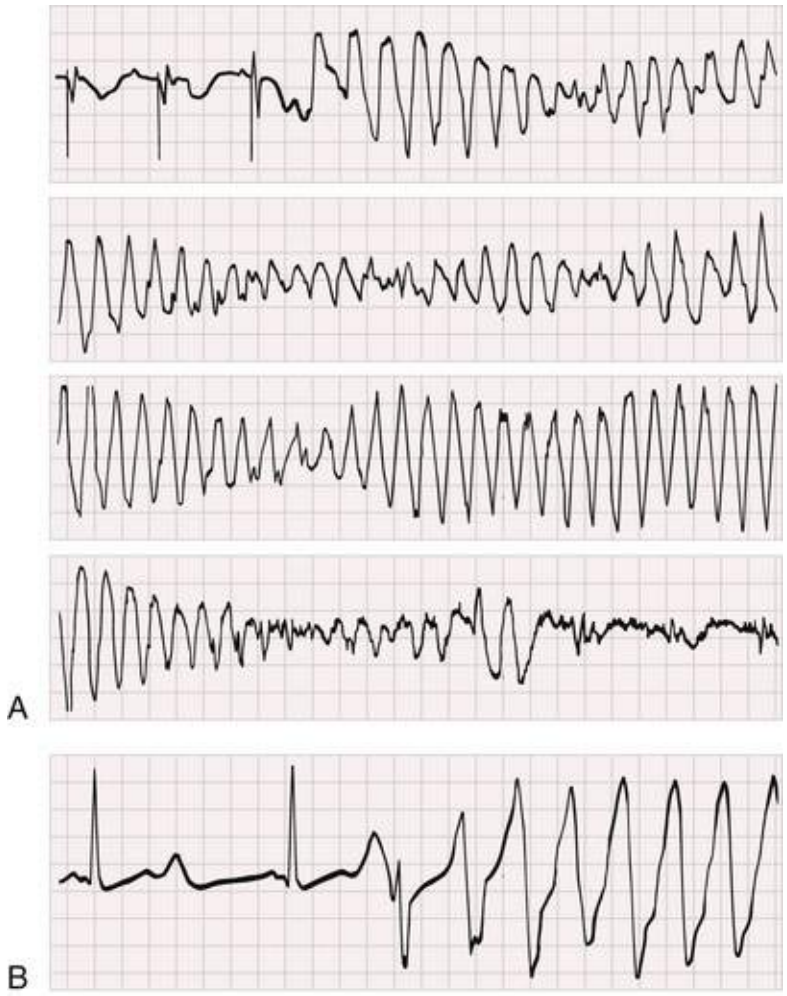


FIGURE 39.10 Torsades de pointes. **A,** Continuous monitor lead recording. A demand ventricular pacemaker (VVI) had been implanted because of a type II second-degree AV block. After treatment with amiodarone for recurrent VT, the QT interval became prolonged (approximately 640 msec during paced beats), and episodes of TdP developed. In this recording the tachycardia spontaneously terminates, and a paced ventricular rhythm is restored. Motion artifact is noted at the end of the recording as the patient lost consciousness. **B,** Tracing from a young boy with congenital long-QT syndrome. The QTU interval in the sinus beats is at least 600 milliseconds. Note the TU wave alternans in the first and second complexes. A late premature complex occurring in the downslope of the TU wave initiates an episode of VT.

A less common form, the short-coupled variant of TdP, is a malignant disease with a high mortality rate that shares several characteristics with idiopathic VF. The ventricular arrhythmia in this setting is initiated with a close-coupled PVC and does not usually involve preceding pauses or bradycardia.

VT that is similar morphologically to TdP and occurs in patients without QT prolongation, whether spontaneous or electrically induced, should generally be classified as polymorphic VT, not as TdP. The distinction has important therapeutic implications (see later).

Electrophysiologic Features

The electrophysiologic mechanisms responsible for TdP are not completely understood. Most data suggest that early afterdepolarizations (EADs) are responsible for both long-QT syndrome and TdP, or at least its initiation (**see Chapter 34**). Perpetuation can be caused by triggered activity, reentry resulting from dispersion of repolarization produced by the EADs, or abnormal automaticity. However, most data currently point to transmural reentry as the most likely mechanism of perpetuation.

Clinical Features

Although many predisposing factors have been cited for TdP, the most common causes are congenital

severe bradycardia, potassium depletion, and use of QT-prolonging medications, such as class IA or III AADs. More than 50 drugs have been noted to prolong the QT interval. Clinical features depend on whether the TdP is caused by acquired or congenital (idiopathic) long-QT syndrome (see later). Symptoms from the tachycardia depend on its rate and duration, as with other VTs, and range from palpitations to syncope and death. Women, perhaps because of a longer QT interval, are at greater risk than men for TdP.

Management

The approach to management of VT with a polymorphic pattern depends on whether it occurs in the setting of a prolonged QT interval. For this practical reason, and because the mechanism of the tachycardia can differ according to whether a long QT interval is present, it is important to restrict the definition of torsades de pointes to the typical polymorphic VT in the setting of a long QT or U wave in the basal complexes. In all patients with TdP, administration of class IA, possibly some class IC, and class III AADs (e.g., amiodarone, dofetilide, sotalol) can increase the abnormal QT interval and worsen the arrhythmia. IV magnesium is the initial treatment of choice for TdP from an acquired cause, followed by temporary ventricular or atrial pacing. Isoproterenol, given cautiously because it may exacerbate the arrhythmia, can be used to increase the rate until pacing is instituted. Lidocaine, mexiletine, or phenytoin can be tried. The cause of the long QT should be determined and corrected, if possible. When the QT interval is normal, polymorphic VT resembling TdP is diagnosed, and standard AADs can be prescribed. In borderline cases the clinical context may help determine whether treatment should be initiated with AADs. Torsades de pointes resulting from congenital long-QT syndrome is treated with beta blockade, pacing, and ICDs (see later). ECGs obtained from close relatives can help secure the diagnosis of long-QT syndrome in borderline cases.

Long-QT Syndrome

Electrocardiographic Recognition

The upper limit for duration of the normal QT interval corrected for heart rate (QTc) is often given as 0.44 second (**see Fig. 39.10B**). However, the normal QTc interval may actually be longer (0.46 second in men and 0.47 second in women), with a normal range of ±15% of the mean value. The nature of the U wave abnormality and its relationship to long-QT syndrome (LQTS) are not clear. The probable risk for development of life-threatening ventricular arrhythmias in patients with idiopathic LQTS is related to the length of the QTc interval, with risk increasing at values of 500 milliseconds or longer. T wave “humps” on the ECG can suggest the presence of LQTS and can be caused by EADs. Unique T wave contours have been ascribed to specific genotypes causing LQTS.

Clinical Features

Long-QT syndrome can be divided into congenital and acquired forms. The congenital form is a familial disorder that can be associated with sensorineural deafness (Jervell and Lange-Nielsen syndrome, autosomal recessive) or normal hearing (Romano-Ward syndrome, autosomal dominant). Congenital LQTS is caused by inherited channelopathies created by mutations in one or more genes[19,20] (**see Chapter 33**).

Patients with the acquired form may also have an underlying genetic predisposition, with a long QT interval developing from various drugs, such as quinidine, procainamide, *N*-acetylprocainamide, sotalol,

amiodarone, disopyramide, phenothiazines, tricyclic antidepressants, erythromycin, pentamidine, some antimalarials, cisapride, and probucol. Other causes are electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia), effects of a liquid protein diet and starvation, central nervous system lesions, significant bradyarrhythmias, cardiac ganglionitis, and mitral valve prolapse. A more comprehensive list that is regularly updated can be found at https://www.crediblemeds.org.

Patients with congenital LQTS can initially have syncope, at times misdiagnosed as epilepsy, as a result of TdP. Sudden death can occur in this group of patients; it develops in approximately 10% of pediatric patients without preceding symptoms. In some patients the ventricular arrhythmia becomes sustained and probably transitions to VF to cause SCD. Patients with LQTS at increased risk for SCD include those with family members who died suddenly at an early age and those who have experienced syncope. Exercise, particularly swimming, and emotional stress appear to be triggers in LQT1, with lethal cardiac events occurring more frequently at rest or during sleep in LQT3. Patients with LQT2 have many events occurring during emotional stress or a sudden loud noise (e.g., telephone or alarm clock) (**see Chapter 33**).

Stress testing can prolong the QT interval and produce T wave alternans, the latter indicative of electrical instability. ECGs should be obtained for all family members when the proband has symptoms. Premature ventricular stimulation electrically does not generally induce arrhythmias in this syndrome, and EPSs are not usually helpful in making the diagnosis.

Management

For patients who have LQTS but not syncope, complex ventricular arrhythmias, a family history of SCD, or a QTc interval of 500 milliseconds or more, no therapy or treatment with a beta blocker is generally recommended. In asymptomatic patients with complex ventricular arrhythmias, a family history of early SCD, or a QTc interval of 500 milliseconds or more, beta adrenoceptor blockers such as nadolol at maximally tolerated doses are recommended. Implantation of a permanent pacemaker to prevent the bradycardia or pauses that may predispose to the development of TdP may be indicated. In patients with syncope or aborted sudden death, an ICD is warranted. These patients should also be treated with concomitant beta blockers. An ICD is beneficial in these patients not simply because of its shocking capabilities, but also because of the ability to pace continually for prevention of bradycardia-induced TdP and algorithms to prevent post-PVC pauses. Use of an ICD in patients without syncope but with a long QT interval and a strong family history of SCD is still controversial but may be warranted in select high-risk patients (**see Chapter 36**).

Left-sided cervicothoracic sympathetic ganglionectomy that interrupts the stellate ganglion and the first three or four thoracic ganglia may be helpful and can be done thorascopically. Participation in competitive sports, previously contraindicated for patients with congenital LQTS, has been liberalized.[21,22] For patients with the acquired form and TdP, IV magnesium and atrial or ventricular pacing are initial choices. Avoidance of precipitating drugs is mandatory.

Short-QT Syndrome

An inherited syndrome resulting in a short QT interval carries an increased risk for sudden death because of VF[23] and may be one of the syndromes responsible for “idiopathic VF.” Patients with short-QT syndrome (SQTS) are also prone to the development of AF. Several genetic abnormalities have been identified, many of which are gain-of-function mutations in the same genes that cause LQTS (**see Chapter 33**). Diagnostic criteria proposed by an expert consensus recommendation[14] includes QTc of 330

milliseconds or less or QTc of 360 milliseconds or less *and* at least one clinical criterion: pathogenic mutation, family history of SQTS or SCD before or at age 40, or survival of VT/VF arrest without heart disease. In many patients with SQTS, the QT does not change with the heart rate, and thus the conventional formulas for QT correction may not apply to these patients. A short QT interval on an ECG without a family history of SCD or a history of syncope, palpitations, or AF may not necessarily indicate an increased risk for SCD, and similarly, some patients with known SQTS mutations have QT intervals in the lower range of normal. Patients often have persistently short QT intervals, short or absent ST segments, and tall and narrow T waves in the precordial leads. Other causes of SQTS, such as hyperkalemia, hypercalcemia, hyperthermia, acidosis, and digitalis, should be excluded.

ICDs are considered the treatment of choice in symptomatic patients with SQTS to prevent SCD. AADs that prolong refractoriness have reportedly been effective in some patients. In particular, quinidine was effective in patients with a gain-of-function mutation in the *HERG* (*KCNH2*) gene.

J Wave Syndromes

The J wave, also referred to as the Osborn wave, is the junction of the QRS complex and the ST segment on a surface ECG. The J wave can be accentuated in hypothermia and hypercalcemia. It is now recognized that spontaneous accentuation of the J wave (previously thought to be benign), may predispose to ventricular arrhythmias (polymorphic VT and VF).[24] The J wave syndromes—a spectrum of pathologic early repolarization predisposing to ventricular arrhythmias—includes Brugada syndrome (BrS) and early repolarization syndrome (ERS). BrS and ERS share several features: male predominance (70% to 80%); average age of first event in fourth to sixth decade; ECG abnormalities are often dynamic and can be augmented by sodium channel blockers and fever; VF often occurs in sleep and can be triggered by short-coupled PVCs; and association with $I_{K.ATP}$ gain-of-function or I_{Na} or I_{Ca} loss-of-function mutations (**see Chapter 33**). The main differences between the syndromes lie in the region of the myocardium most affected and thus the ECG leads in which the J wave abnormalities are seen. BrS predominantly affects the RV outflow tract and thus ECG leads V_1 to V_3. ERS affects the inferior LV wall and thus ECG leads I, II, III, aVF, aVL, and V_4 to V_6. In addition, there is a higher prevalence of AF, structural abnormalities (primarily RV) and late potentials on signal-averaged ECG in BrS (sometimes making the differential between BrS and ARVC difficult).

The precise mechanisms of the J wave syndromes are not entirely clear. The majority of evidence points to abnormalities in the transmural gradient of the action potential notch (caused by I_{to}) present in the epicardium but not endocardium because of an abnormal transmural distribution of I_{to} (**see Chapter 35**). The mechanism of VT/VF in these patients likely results from phase 2 reentry because of this repolarization gradient. However, at least in BrS, conduction slowing may also play a role.

Brugada Syndrome

Brugada syndrome is characterized by an RBBB and ST-segment elevation in the anterior precordial leads, often without evidence of structural heart disease[24,25] (**Fig. 39.11**) (**see Chapter 33**). BrS is more common in apparently healthy young Southeast Asians but also exists in other areas of the world and ethnicities. Findings on the ECG are characterized as type 1, type 2, or type 3 patterns (**Table 39.5** and **eFig. 39.1**), seen in leads V_1 to V_3. Placing the right precordial leads in the second or third intercostal space (“high leads”) can increase the sensitivity of detecting a type 1 pattern. Only type 1 is diagnostic of BrS. Signature findings on the ECG can be transient, and subtle similar ECG changes can be found in

patients without BrS, making the diagnosis difficult in patient without spontaneous type 1 patterns captured at presentation. The 2013 consensus statement on inherited arrhythmias[14] and the 2015 European Society of Cardiology (ESC) guidelines for management of ventricular arrhythmias[7] proposed diagnostic criteria for BrS as 2 mm or more of ST-segment elevation in one or more right precordial leads placed in the second, third, or fourth intercostal space, occurring spontaneously or provoked by a class I drug. According to these guidelines, a type 2 or 3 pattern is only diagnostic when it converts to a type 1 pattern with drug provocation. However, since the population with the drug-provoked type 1 pattern is at relatively low risk, the 2016 consensus report on J wave syndromes[24] proposes a modification to the diagnostic criteria: when type 1 ST-segment elevation is only provoked by a class I drug, diagnosis of BrS is made only with one additional clinical feature: documented VF or VT, syncope of probable arrhythmic cause, family history of SCD before age 45, family history of Brugada type 1 pattern, or nocturnal agonal respirations.

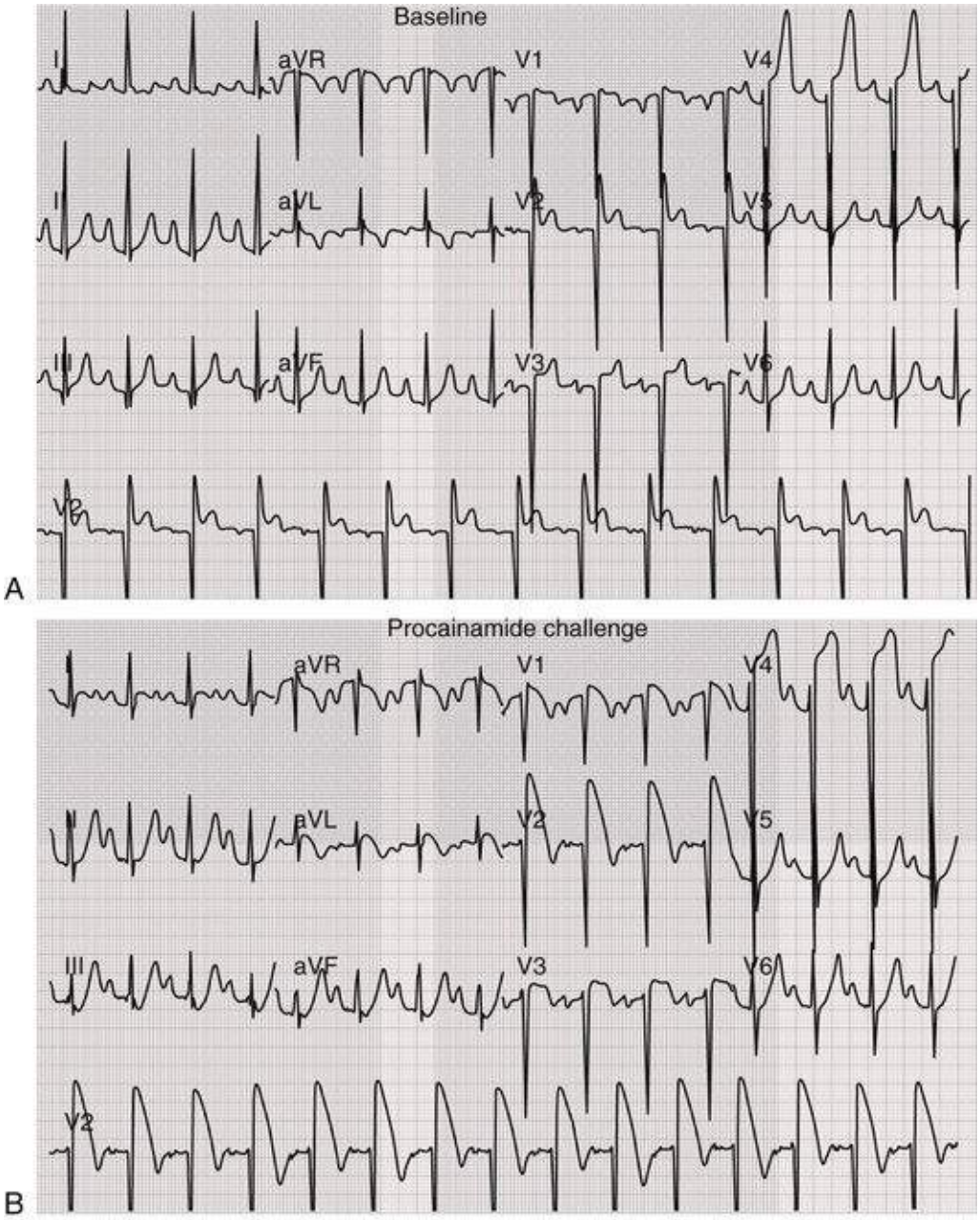


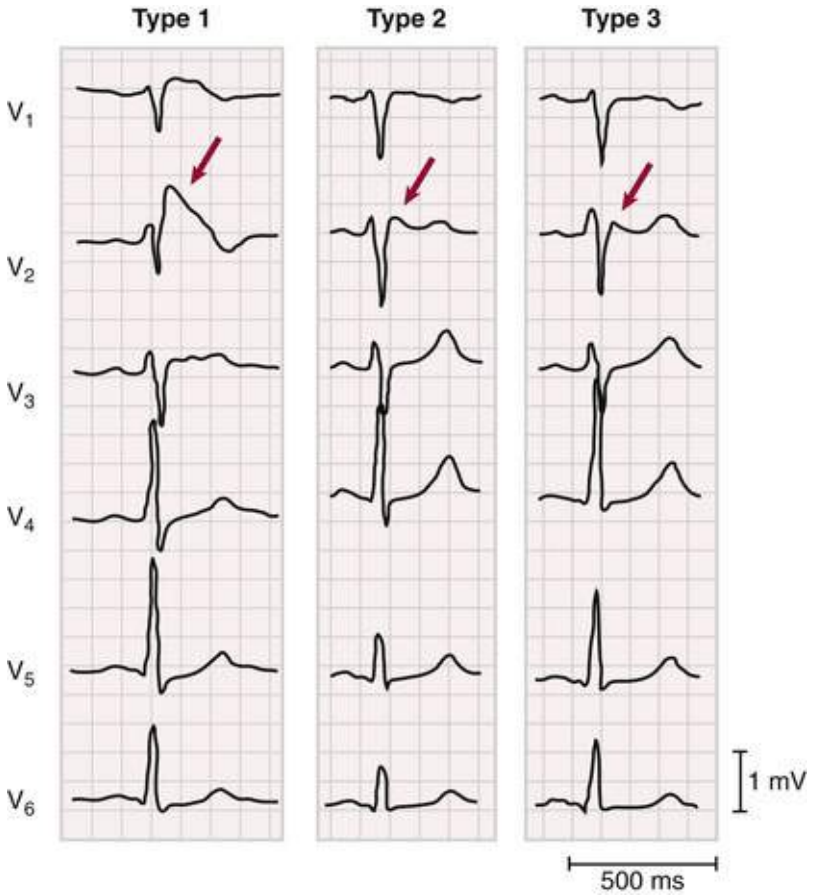
FIGURE 39.11 **A,** Twelve-lead ECG of a patient with Brugada syndrome. The ECG is characterized by a right bundle branch block pattern and persistent ST elevation in leads V_1 through V_3. This ECG shows a type 2 Brugada pattern with a "saddleback" ST-segment elevation greater than 1 mm and a biphasic T wave in V_1 (positive in V_2-V_3). **B,** After procainamide challenge, the prototypic changes on the ECG are exaggerated, with an increase in ST elevation, and the ECG shows a type 1 pattern with a downward-sloping coved ST elevation and negative T waves in V_1 to V_3.

TABLE 39.5

Characteristics of Brugada-Pattern Electrocardiograms

	TYPE 1	TYPE 2	TYPE 3
J wave amplitude	≥2 mm	≥2 mm	≥2 mm
T wave	Negative	Positive or biphasic	Positive
ST-T configuration	Coved	Saddleback	Saddleback
ST segment (terminal portion)	Gradually descending	Elevated ≥1 mm	Elevated <1 mm

From Wilde AAM, Antzelevitch C, Borggrefe M, et al. Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation 2002;106:2514.



EFIGURE 39.1 Precordial leads of a patient with Brugada syndrome showing dynamic changes on the ECG over several days. The second two ECGs (types 2 and 3) were obtained from the same patient as the first ECG (type 1), just 13 days later. *Arrows* denote the J wave. (From Wilde AAM, Antzelevitch C, Borggrefs M, et al. Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation 2002;106:2514.)

Controversy remains as to whether additional risk stratification is useful in BrS.[26] Drug challenge with a class I AAD (procainamide, flecainide, ajmaline, or pilsicainide) to provoke ECG changes should be considered when there is a clinical suspicion of BrS in the absence of a diagnostic type 1 ECG pattern. Drug challenge is not indicated in patients with spontaneous type 1 Brugada pattern (whether the patient is symptomatic or not) since there is no additional diagnostic value. Other causes of ST elevation mimicking Brugada type 1 pattern (RBBB, pectus excavatum, occlusion of left anterior descending or conus branch, ARVC) should be excluded. EPSs to risk-stratify patients remain controversial, with some suggesting that VT/VF inducibility is unable to identify high-risk patients with BrS and others demonstrating an increased risk (especially with fewer extrastimuli).[27,28] However, a negative EPS does not predict low risk in patients with clinical risk factors (aborted SCD, spontaneous VT/VF or syncope), and the most recent consensus statement proposes that EPS may be considered in asymptomatic patients with type 1 Brugada pattern.[24] An ICD should be considered if such a patient has inducible VT/VF with two or less extrastimuli. A spontaneous ECG pattern of BrS (type 1), a history of syncope, ventricular refractoriness less than 200 milliseconds, and QRS fragmentation were the best predictors of a high-risk group.[28] Mutations in *SCN5A* account for 18% to 28% of BrS cases, with mutations in the voltage-gated calcium channel (*CACNA1C, CACNB2b, CACNA2D1*) accounting for about another 13%. A variety of mutations in other genes involved in regulation of I_{Na} (loss of function), I_{Ca} (loss of function), I_{to} (gain of function), or $I_{K.ATP}$ (gain of function) have been rarely reported. Genetic testing may not be helpful in risk stratification, although it can be helpful in family screening if there is an identifiable causative mutation (**see Chapter 33**).

ICD implantation is warranted in patients with BrS with aborted SCD or spontaneous VT/VF (class I

indication) or with a history of syncope (class IIa).[7] ICD implantation may be considered in patients with a type 1 ECG pattern and inducible VT/VF with two or less extrastimuli.[24] Ablation in the epicardium of the anterior RV outflow tract can normalize the ECG and suppress VT, perhaps by eliminating the I_{to}-rich area of the RV outflow tract.[29] Ablation may be considered in patients with frequent ICD shocks (class IIb).[7,24] Quinidine can normalize the ECG and suppress the VT, presumably by blocking the calcium-independent transient outward potassium current (I_{to}), or perhaps a late sodium current. Quinidine has been effective in patients with frequent or storms of VT/VF on ICD (Class IIb).[7,24,30] and may also be useful in patients who qualify for an ICD but either refuse or are otherwise contraindicated (class IIa).[7,24] In patients with VT storm secondary to Brugada syndrome, low-dose isoproterenol can also be effective in suppressing the arrhythmia. In patients with diagnosed or suspected Brugada syndrome, fevers should be aggressively treated and drugs that can provoke Brugada syndrome should be avoided (see http://www.brugadadrugs.org/avoid/).

Early Repolarization Syndrome

Most patients with early repolarization are not at risk for ventricular arrhythmias. However, ERS is diagnosed in patients presenting with aborted sudden cardiac death or documented VT/VF and early repolarization pattern in the inferior and/or lateral ECG leads. This early repolarization pattern is identified as the presence of a J wave (terminal QRS notch) or J point elevation (slurred downslope of a prominent R wave) of 0.1 mV or more in two or more contiguous leads (excluding V_1 to V_3) in the setting of a narrow QRS (QRSd <120 msec), with or without ST-segment elevation.[24,31] The differential diagnosis of this pattern overlaps with BrS and includes juvenile ST patterns, stress (takotsubo) cardiomyopathy, hypothermia, hypocalcemia, pericardial disease, hypertrophy, and myocardial ischemia. ERS shares many of the same features as BrS, and although fewer mutations have been identified for ERS, these appear to be in similar genes as BrS (**see Chapter 33**).

There is currently no risk stratification strategy of patients with early repolarization ECG pattern. Electrophysiologic testing does not appear to be helpful in risk stratification. Symptoms (aborted SCD, spontaneous VT/VF, syncope), family history of SCD, and coexistence of Brugada pattern or short QT appear to be the strongest predictors of risk. Treatment is similar to that of BrS. Symptomatic patients (aborted SCD, spontaneous VT/VF, or syncope of presumed arrhythmic origin) should undergo ICD implantation. Quinidine and isoproterenol can be used to treat recurrent, frequent VT/VF. Treatment of the asymptomatic patient with an ECG pattern suggestive of ERS and a family history of SCD at an early age could be considered for ICD implantation.[24]

Idiopathic Ventricular Tachycardias

Idiopathic VT is defined as monomorphic VT in patients without structural heart disease or coronary disease. When more than one morphology of VT is present, one should suspect other disease entities, such as ARVD. Idiopathic VTs have any one of several characteristic electrocardiographic morphologies representing three distinct entities based on the location of the VT—outflow tract tachycardias, annular tachycardias, and fascicular tachycardias. The prognosis for all forms of idiopathic monomorphic VT without structural heart disease is good. They are amenable to ablation and frequently respond well to drug therapy. Idiopathic VTs with monomorphic contours can be divided into several types, based largely on anatomic location of origin.[32] Location of idiopathic VT can often be deduced from the QRS pattern on 12-lead ECG (**see Table 39.1**).

Outflow Tract Tachycardias

Right ventricular outflow tract (RVOT) VT accounts for about 70% of idiopathic VTs, while 10% to 15% originate from the LVOT. Two types, paroxysmal VT and repetitive monomorphic VT, appear to originate from the region of the RVOT (**Figs. 39.12 and 39.13**) or the LVOT; occasionally, however, outflow tract VT can also be sustained, although infrequently. Rarely the VT can originate from the proximal pulmonary artery (just beyond the pulmonic valve) or from the cusps of the aortic valve. Outflow tract VTs have a characteristic electrocardiographic appearance of an LBBB contour in V_1 and an inferior axis in the frontal plane. Distinguishing ECG features indicating RVOT origin of the VT include later precordial transition (V_3 or later) and narrower R wave duration in V_1 and V_2. Distinguishing ECG features indicating LVOT origin include the presence of an S wave in lead I, an early precordial R wave transition (V_1 to V_2), notched qrS in V_1 or V_2, and broader R wave duration in V_1 and V_2.

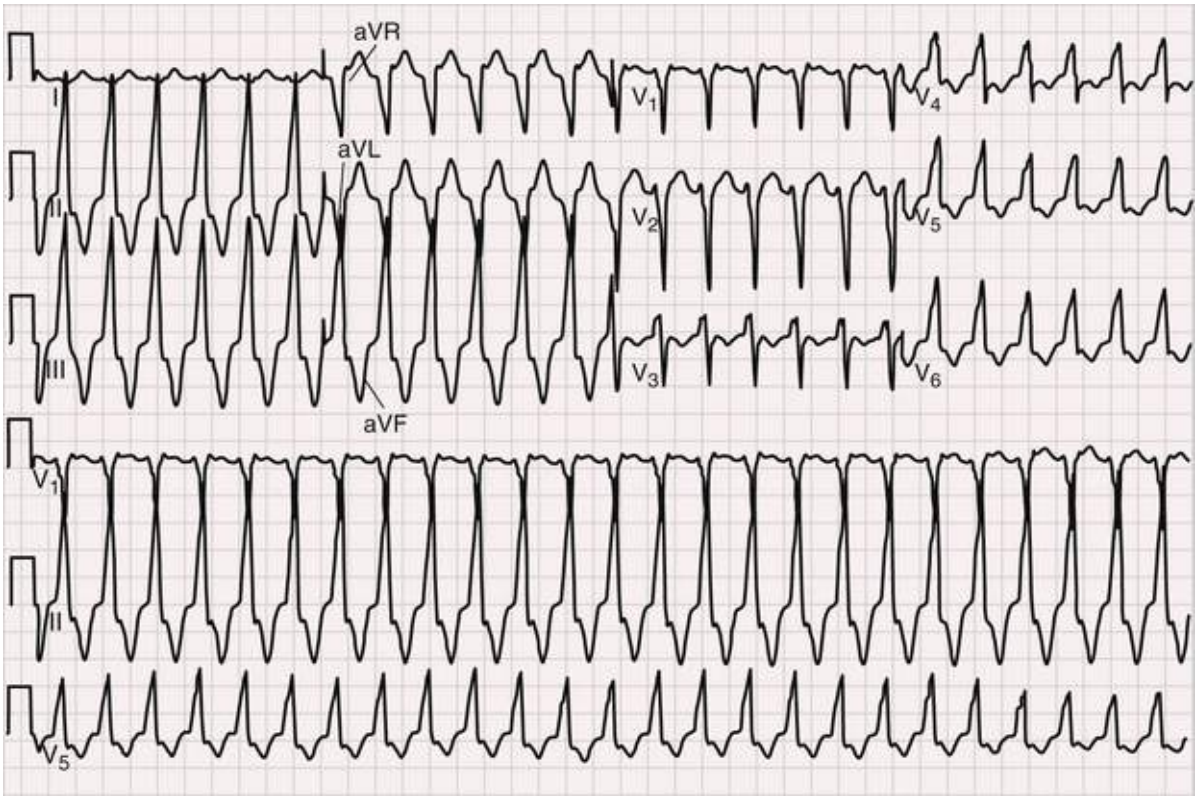


FIGURE 39.12 VT originating from the RV outflow tract. This tachycardia is characterized by a left bundle branch block contour in lead V_1 and an inferior axis.

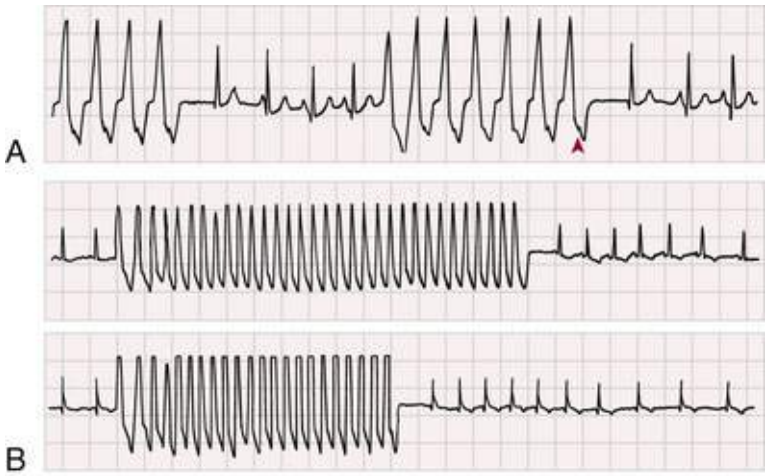


FIGURE 39.13 **A,** Repetitive monomorphic VT. Short episodes of a monomorphic VT at a rate of 160 beats/min repeatedly interrupt the normal sinus rhythm. Retrograde atrial capture probably occurs (*arrowhead* points to deflection in ST segment), and the retrograde P wave of the last complex of the repetitive monomorphic VT conducts over the normal pathway to produce a QRS complex with a normal contour. **B,** Short runs of a very rapid (260 beats/min) VT of uniform contour. They probably provoke a compensatory sympathetic response because each is followed by a brief period of sinus tachycardia. The sinus pacemaker appears to be unstable because of the resultant changes in P wave morphology.

Vagal maneuvers, including adenosine, can terminate outflow tract VT, whereas exercise, stress, isoproterenol infusion, and rapid or premature stimulation often initiate or perpetuate the tachycardia. Beta blockers and verapamil can suppress this tachycardia as well. The paroxysmal form is induced by exercise or stress, whereas the repetitive monomorphic type occurs at rest, with sinus beats interposed between runs of nonsustained VT that may be precipitated by transient increases in sympathetic activity unrelated to exertion. In a small number of patients, the tachycardia seems to arise in the inflow tract or apex of the right ventricle. The prognosis for most patients with outflow tract (RV or LV) VT is good. RF catheter ablation effectively eliminates this focal tachycardia in symptomatic patients. In others, AADs can be effective.

Annular Ventricular Tachycardias.

VTs arising from the mitral or tricuspid annulus account for 5% to 8% of idiopathic VTs, with a relative similar distribution between mitral and tricuspid. Most often these are of the repetitive monomorphic type. For mitral annular VT, the ECG morphology is typically an RBBB pattern (transition in V_1 or V_2), S wave in V_6, and monophasic R or Rs in leads V_2 through V_6. For tricuspid annular VT, the foci generally originate in the septal region, and thus the typical finding on the ECG is an LBBB pattern (Qs in lead V_1), an early transition in precordial leads (V_3), and narrower QRS complexes. These VTs behave similar to outflow tract VT, both in prognosis and in drug response. Annular VTs are amenable to ablation.

Fascicular Ventricular Tachycardia (Left Septal Ventricular Tachycardia).

A left septal VT has been described as most often arising in the left posterior septum, frequently preceded by a fascicular potential, and is sometimes called a *fascicular tachycardia* (**Fig. 39.14**). The tachycardias most often arise from the left posterior fascicle but can also arise (or exit) from the anterior fascicle. Because they arise from the fascicle, the VT appearance on an ECG typically has a rapid initial component and resembles either a typical left anterior fascicular block (for those arising from the posterior fascicle) or less frequently a typical left posterior fascicular block (for those arising from the anterior fascicle). Entrainment has been demonstrated, which suggests reentry as a cause of some of the

tachycardias. Verapamil or diltiazem often suppresses left septal VT, whereas adenosine does so only rarely, thus suggesting that I_{Ca} current may be important. Several mechanisms may be operative, and the group may not be homogeneous. Once initiated, the tachycardia is paroxysmal and sustained. Left septal VT can be started by rapid atrial or ventricular pacing and sometimes by exercise or isoproterenol. The prognosis is generally good. RF catheter ablation is effective in symptomatic patients.

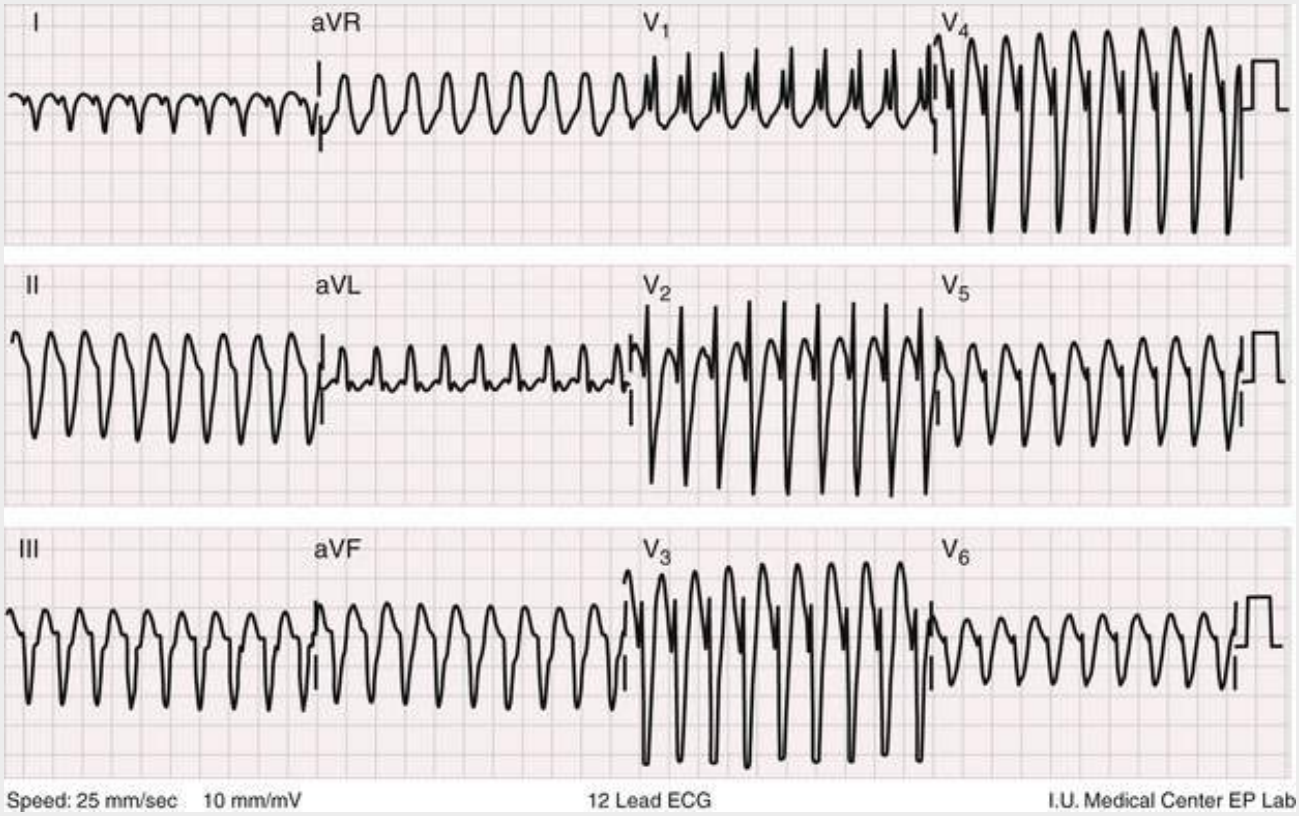


FIGURE 39.14 Left septal VT. This tachycardia is characterized by a right bundle branch block contour. In this instance the axis was rightward. The site of the VT was established to be in the left posterior septum by electrophysiologic mapping and ablation.

Other Forms of Idiopathic VT.

Several other, less common forms of idiopathic VT have also been reported. VT originating from the papillary muscle (origin from posterior papillary muscle is more common than from anterior muscle) is typically focal in origin, can have multiple morphologies, and is often exercise induced (catecholamine sensitive) and can mimic fascicular VT on ECG. In general, however, papillary muscle VT has wider a wider QRS. Papillary muscle VT is amenable to ablation.

Idiopathic VT can also arise from the crux of the heart. Anatomically, this area is an epicardial location near the junction of the middle cardiac vein and the coronary sinus. For this VT, ablation usually requires percutaneous epicardial access and can be attempted from within the coronary sinus or middle cardiac vein; however, the origin can be near the posterior descending artery.

Idiopathic Ventricular Fibrillation.

Idiopathic VF can occur in approximately 1% to 8% of individuals with out-of-hospital VF. Findings on cardiovascular evaluation are normal, except for the arrhythmia. Monomorphic VT is rarely induced at EPS. Its natural history is incompletely known, but recurrences are reported. It is important to remember that in this entity, as well as in idiopathic VT, the arrhythmia may be an early manifestation of a developing cardiomyopathy, at least in some patients. There is overlap of idiopathic VF with SQTS and J

wave syndromes (see earlier). In some cases, short-coupled PVCs can trigger VF (**Fig. 39.15**). In patients with idiopathic VF, ICDs are a useful therapeutic choice. Ablation of short-coupled PVCs that trigger VF, often from Purkinje fibers, has also been effective in reducing recurrence.

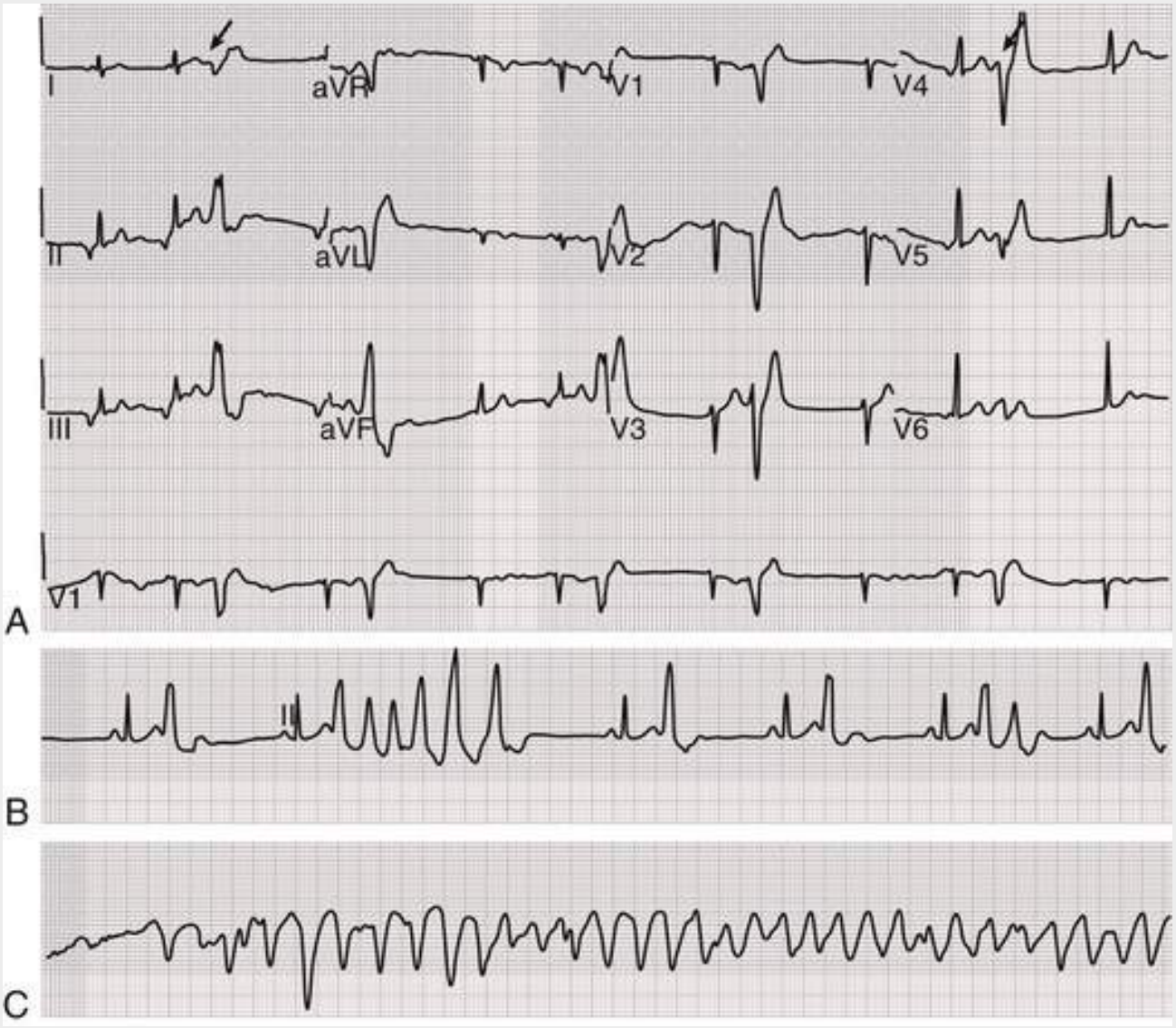


FIGURE 39.15 Tracings from a patient with idiopathic VF as a result of short-coupled premature ventricular complexes. **A,** ECG showing frequent, spontaneous short-coupled PVCs occurring on the late phase of the T wave. **B,** When occurring during bradycardia, the PVCs occur in the early phase of the T wave and produce a short run of VF. **C,** Spontaneous VF in the same patient after another short-coupled spontaneous PVC.

Bidirectional Ventricular Tachycardia.

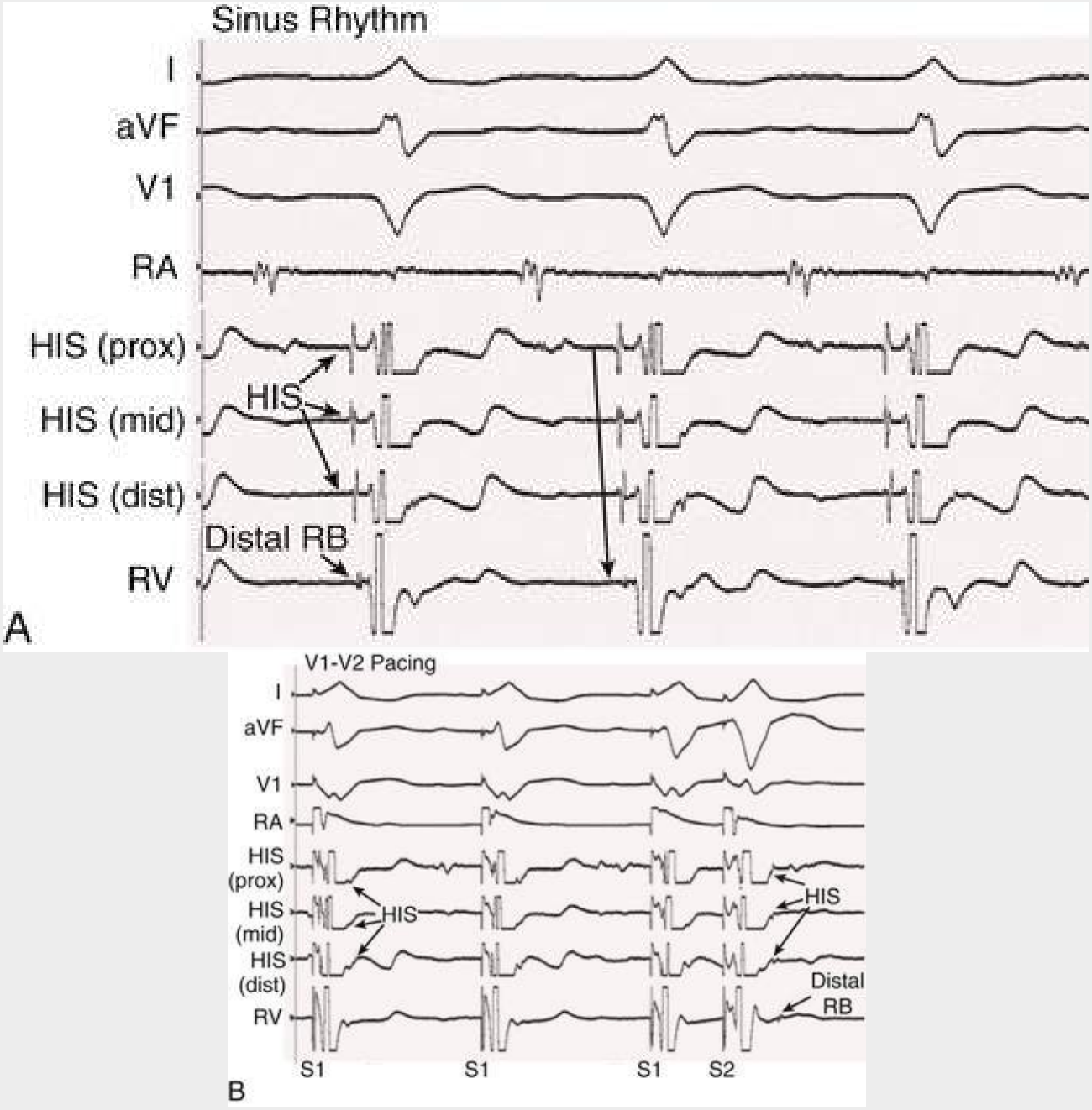
Bidirectional VT is an uncommon type of VT characterized by QRS complexes with RBBB pattern, polarity in the frontal plane alternating from −60 to −90 degrees to +120 to +130 degrees, and a regular rhythm. The ventricular rate is between 140 and 200 beats/min. Although the mechanism and site of origin of this tachycardia have remained somewhat controversial, most evidence supports a ventricular origin.

Bidirectional VT can be a manifestation of digitalis excess, typically in older patients and those with severe myocardial disease. When the tachycardia is caused by digitalis, the extent of toxicity is frequently advanced, and the prognosis is poor. As the use of digitalis has decreased, this form of VT has become very uncommon. When seen in the absence of digitalis, a diagnosis of CPVT should be

considered (**see Fig. 39.9**).

Bundle Branch Reentrant Ventricular Tachycardia.

VT secondary to bundle branch reentry is characterized by a QRS morphology determined by the circuit established over the bundle branches or fascicles. Retrograde conduction over the left bundle branch system and anterograde conduction over the right bundle branch create a QRS complex with LBBB contour and constitute the most common form. The frontal plane axis may be approximately +30 degrees. Conduction in the opposite direction produces RBBB contour. Reentry can also occur over the anterior and posterior fascicles. Electrophysiologically, bundle branch reentrant complexes are started after a critical S_2-H_2 or S_3-H_3 delay. The H-V interval of the bundle branch reentrant complex equals or exceeds the H-V interval of the spontaneous, normally conducted QRS complex (**Fig. 39.16**).



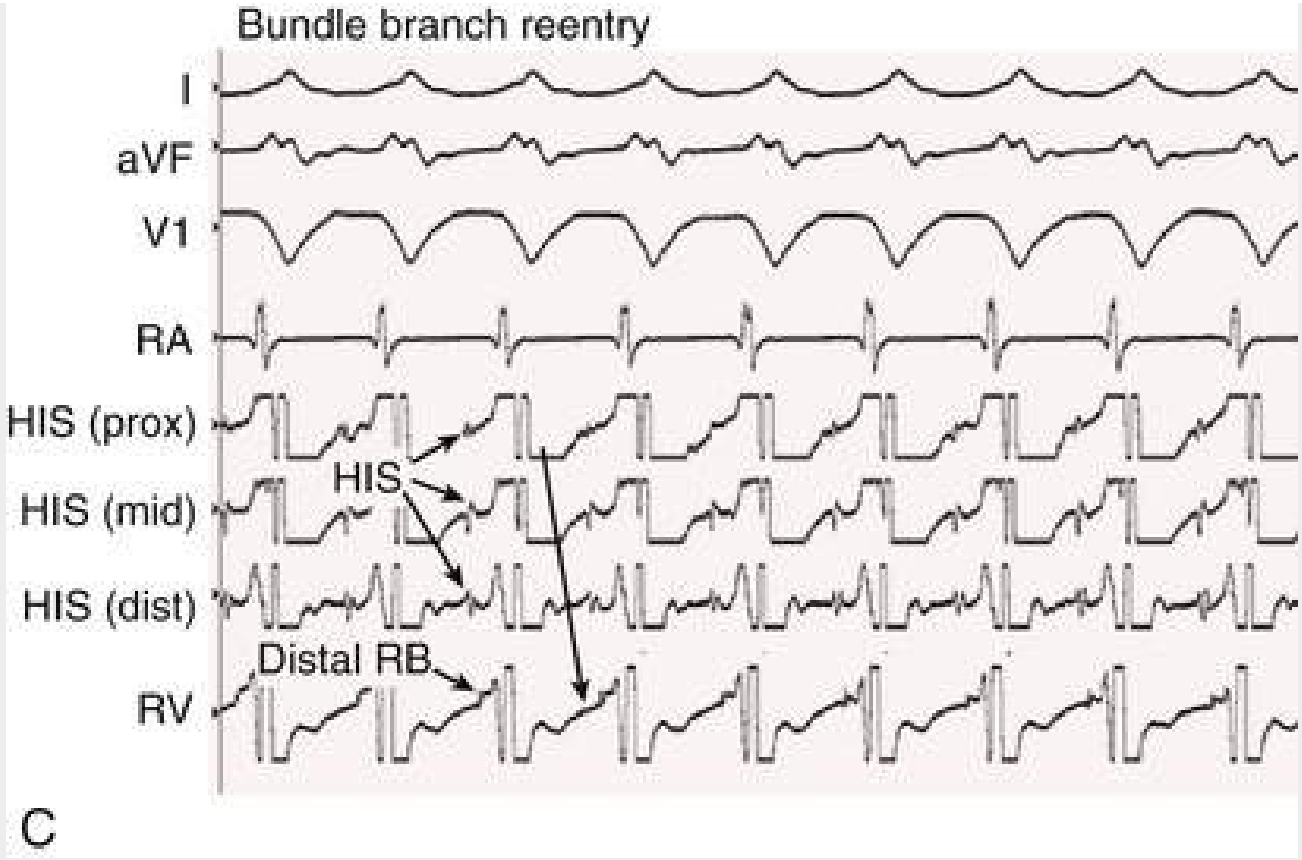


FIGURE 39.16 Surface and intracardiac recordings in a patient with inducible bundle branch reentry. Catheter position is labeled on the left. The His catheter is somewhat distal in its recording position, and the RV catheter is positioned in the right ventricle to record a distal right bundle potential. **A,** His bundle recordings and distal right bundle branch recording (on the RV catheter) during sinus rhythm. Notice that the right bundle potential (*RB*) is normally activated after the His bundle. **B,** Delay in S_2-H_2 and reversal of activation between His and right bundle during premature stimulation. During S_1 pacing, the RB is not visible because it is buried in the complex immediately after the pacing artifact (simultaneous with local ventricular activation). Following the premature beat (S_2), the His moves out (is prolonged), and the right bundle is activated after the His potential, demonstrating that with the S_2, there was unidirectional block in the retrograde right bundle, transmural conduction, retrograde up the left bundle (not recorded), and then anterograde down the distal His to the right bundle. **C,** Bundle branch reentry induced with the S_1-S_2. The distal His bundle and right bundle are activated anterogradely, and the H-V interval during bundle branch reentry is slightly longer that in sinus rhythm **(A).** *prox,* Proximal; *dist,* distal; *RA,* right atrium; *RV,* right ventricle.

Bundle branch reentry is a form of monomorphic sustained VT that is usually seen in patients with structural heart disease, such as dilated cardiomyopathy, and generally in the setting of a wide QRS during sinus rhythm because of an intraventricular conduction delay. Infrequently, bundle branch reentry can occur in the absence of myocardial disease.

The therapeutic approach is as for other types of VT; however, ablation is very effective. In the acute setting, pace termination is frequently effective.

Ventricular Flutter and Fibrillation

Electrocardiographic Recognition

Ventricular flutter and ventricular fibrillation (VF) are arrhythmias that represent severe derangements of the heartbeat that can terminate fatally or produce significant brain damage within 3 to 5 minutes unless corrective measures are undertaken promptly (**see Chapter 42**). Ventricular flutter is manifested as a sine

wave in appearance—regular large oscillations occurring at a rate of 150 to 300 beats/min (usually about 200) (**Fig. 39.17A**). Distinction between rapid VT and ventricular flutter can be difficult and is usually of academic interest only. Hemodynamic collapse is present with both. VF is recognized by the presence of irregular undulations of varying contour and amplitude (**Fig. 39.17B**). Distinct QRS complexes, ST segments, and T waves are absent. Fine-amplitude fibrillatory waves (0.2 mV) are present with prolonged VF. These fine waves identify patients with worse survival rates and are sometimes confused with asystole.

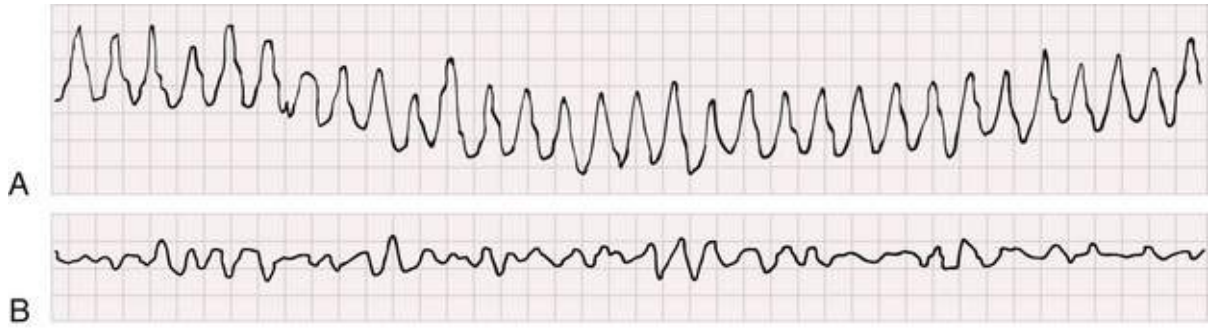


FIGURE 39.17 Ventricular flutter and VF. **A,** The sine wave appearance of the complexes occurring at a rate of 300 beats/min is characteristic of ventricular flutter. **B,** The irregular undulating baseline typifies VF.

Mechanisms

Ventricular fibrillation occurs in various clinical situations but most often in association with CAD and as a terminal event (**see Chapters 42, 58, and 59**). Cardiovascular events, including SCD from VF, occur most frequently in the morning. VF can occur during AAD administration, hypoxia, ischemia, or AF that results in very rapid ventricular rates in patients with preexcitation syndrome; after electrical shock administered during cardioversion (**see Chapters 36 and 41**) or accidentally by improperly grounded equipment; and during competitive ventricular pacing to terminate VT.

Clinical Features

Ventricular flutter or VF results in faintness, followed by loss of consciousness, seizures, apnea, and eventually, if the rhythm continues untreated, death. Blood pressure is unobtainable, and heart sounds are usually absent. The atria can continue to beat at an independent rhythm for a time or in response to impulses from the fibrillating ventricles. Eventually, electrical activity of the heart ceases (**see Chapter 42**).

Management

Management should follow basic life support and advanced cardiac life support guidelines (**see Chapter 42**). Immediate nonsynchronized DC electrical shock using 200 to 400 J is mandatory therapy for VF, ventricular flutter, and pulseless VT. Cardiopulmonary resuscitation is performed only until the defibrillation equipment is ready or if the “downtime” has been long. Defibrillation requires fewer joules if it is done early. If the circulation is markedly inadequate despite return to sinus rhythm, closed-chest massage should be instituted. The use of anesthesia during electrical shock is dictated by the patient's condition but is not generally required. After conversion of the arrhythmia to a normal rhythm, it is essential to monitor the rhythm continuously and to institute measures to prevent recurrence. Metabolic

acidosis quickly follows cardiovascular collapse. If the arrhythmia is terminated within 30 to 60 seconds, significant acidosis does not occur.

References

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40

Bradyarrhythmias and Atrioventricular Block

Jeffrey E. Olgin, Douglas P. Zipes

Bradyarrhythmias

Bradyarrhythmia is arbitrarily defined as a heart rate less than 60 beats/min. Frequently, bradyarrhythmias are physiologic, as in well-conditioned athletes with low resting heart rates or in type I atrioventricular (AV) block during sleep. In other cases, bradyarrhythmias can be pathologic. Similar to tachyarrhythmias, bradyarrhythmias can be categorized on the basis of the level of disturbance in the hierarchy of the normal impulse generation and conduction system (from sinus node to AV node to His-Purkinje system) (**see Chapter 37 and Table 37.1**).

Sinus Bradycardia

Electrocardiographic Recognition

Sinus bradycardia is diagnosed in an adult when the sinus node discharges at a rate less than 60 beats/min (**Fig. 40.1A**). P waves have a normal contour and occur before each QRS complex, usually with a constant PR interval longer than 120 milliseconds. Sinus arrhythmia often coexists.

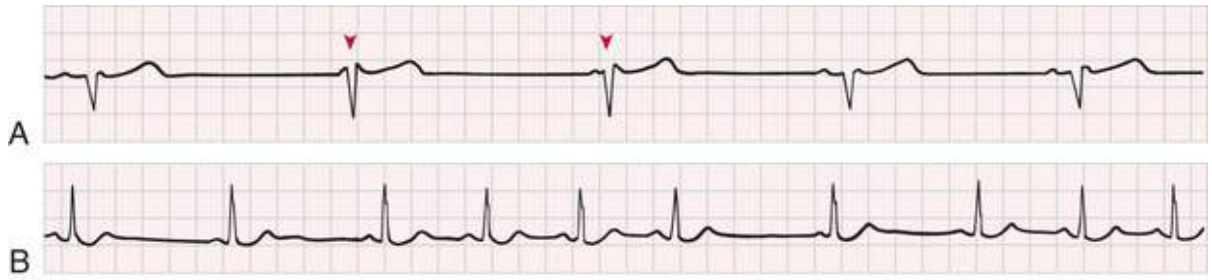


FIGURE 40.1 **A,** Sinus bradycardia at a rate of 40 to 48 beats/min. The second and third QRS complexes (*arrowheads*) represent junctional escape beats. Note the P waves at the onset of the QRS complex. **B,** Nonrespiratory sinus arrhythmia occurring as a consequence of digitalis toxicity. Monitor leads were used.

Clinical Features

Sinus bradycardia can result from excessive vagal or decreased sympathetic tone, as an effect of medications, or from anatomic changes in the sinus node. In most cases, symptomatic sinus bradycardia is caused by the effects of medication. Asymptomatic sinus bradycardia frequently occurs in healthy young adults, particularly well-trained athletes, and decreases in prevalence with advancing age. During sleep, the normal heart rate can fall to 35 to 40 beats/min, especially in adolescents and young adults, with marked sinus arrhythmia sometimes producing pauses of 2 seconds or longer. Eye surgery, coronary arteriography, meningitis, intracranial tumors, increased intracranial pressure, cervical and mediastinal tumors, and certain disease states (e.g., severe hypoxia, myxedema, hypothermia, fibrodegenerative changes, convalescence from some infections, gram-negative sepsis, mental depression) can produce sinus bradycardia. Sinus bradycardia also occurs during vomiting or vasovagal syncope (**see Chapter 43**) and can be produced by carotid sinus stimulation or by the administration of parasympathomimetic drugs, lithium, amiodarone, beta adrenoceptor–blocking drugs, clonidine, propafenone, ivabradine (a specific I_f pacemaker current blocker; **see Chapters 34 and 37**), or calcium antagonists. Conjunctival instillation of beta blockers for glaucoma can produce sinus or AV nodal abnormalities, especially in elderly patients.

In most cases, sinus bradycardia is a benign arrhythmia and can actually be beneficial by producing a longer period of diastole and increasing ventricular filling time, especially for heart failure patients. It can be associated with syncope caused by an abnormal autonomic reflex (cardioinhibitory; **see Chapter 43**). Sinus bradycardia occurs in 10% to 15% of patients with acute myocardial infarction (MI) and may be even more prevalent when patients are seen in the early hours of infarction. Unless it is accompanied by hemodynamic decompensation or arrhythmias, sinus bradycardia is generally associated with a more favorable outcome after MI than sinus tachycardia. It is usually transient and occurs more commonly during inferior than during anterior MI; it has also been noted during reperfusion with thrombolytic agents (**see Chapter 62**). Bradycardia that follows resuscitation from cardiac arrest is associated with a poor prognosis.

Management

Treatment of sinus bradycardia is not usually necessary unless cardiac output is inadequate or arrhythmias result from the slow rate. Atropine (0.5 mg intravenously as an initial dose, repeated if necessary) is generally effective acutely; lower doses, particularly given subcutaneously or intramuscularly, can exert an initial parasympathomimetic effect, possibly by a central action. For recurrent symptomatic episodes, temporary or permanent pacing may be needed (**see Chapters 36 and 41**). As a general rule, no drugs are

available that increase the heart rate reliably and safely during long periods without important side effects.

Sinus Arrhythmia

Sinus arrhythmia is characterized by a phasic variation in sinus cycle length during which the maximum sinus cycle length minus the minimum sinus cycle length exceeds 120 milliseconds or the maximum sinus cycle length minus the minimum sinus cycle length divided by the minimum sinus cycle length exceeds 10% (**Fig. 40.1B**). It is the most frequent form of arrhythmia and is considered a normal event. P wave morphology does not usually vary, and the PR interval exceeds 120 milliseconds and remains unchanged because the focus of discharge remains relatively fixed within the sinus node. On occasion, the pacemaker focus can wander within the sinus node, or its exit to the atrium may change and produce P waves of a slightly different contour (but not retrograde) and a slightly changing PR interval that exceeds 120 milliseconds.

Sinus arrhythmia usually occurs in the young, especially those with slower heart rates or after enhanced vagal tone, such as following the administration of digitalis or morphine or athletic training, and decreases with age or with autonomic dysfunction, such as in diabetic neuropathy. Sinus arrhythmia appears in two basic forms. In the respiratory form the P-P interval cyclically shortens during inspiration, primarily as a result of reflex inhibition of vagal tone, and slows during expiration; breath-holding eliminates the variation in cycle length (**see Chapter 35**). Nonrespiratory sinus arrhythmia is characterized by a phasic variation in the P-P interval unrelated to the respiratory cycle and can be the result of digitalis intoxication. Loss of sinus rhythm variability is a risk factor for sudden cardiac death (**see Chapter 42**).

Symptoms produced by sinus arrhythmia are uncommon, but on occasion, if the pauses are excessively long, palpitations or dizziness can result. Marked sinus arrhythmia can produce a sinus pause sufficiently long to cause syncope if it is not accompanied by an escape rhythm.

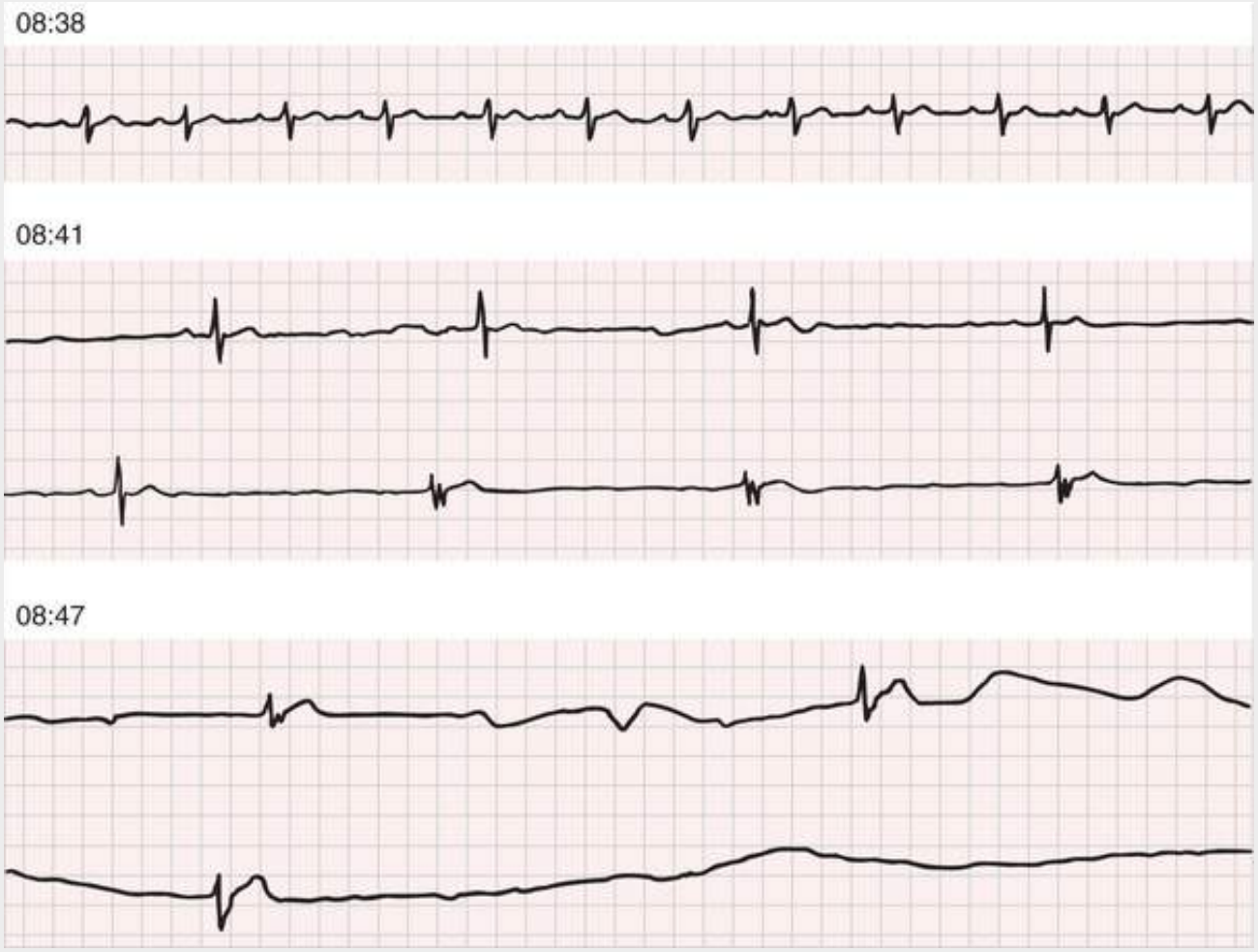
Treatment is usually unnecessary. Increasing the heart rate by exercise or drugs generally abolishes sinus arrhythmia. Symptomatic individuals may experience relief from palpitations with sedatives, tranquilizers, atropine, ephedrine, or isoproterenol administration, as for the treatment of sinus bradycardia.

Ventriculophasic Sinus Arrhythmia.

The most common example of ventriculophasic sinus arrhythmia occurs during complete AV block and a slow ventricular rate, when P-P cycles that contain a QRS complex are shorter than P-P cycles without a QRS complex. Similar lengthening can be present in the P-P cycle that follows a PVC with a compensatory pause. Alterations in the P-P interval are probably caused by the influence of the autonomic nervous system responding to changes in ventricular stroke volume.

Sinus Pause or Sinus Arrest.

Sinus pause or sinus arrest is recognized by a pause in the sinus rhythm (**eFig. 40.1**). The P-P interval delimiting the pause does not equal a multiple of the basic P-P interval. Differentiation of sinus arrest, which is thought to be caused by slowing or cessation of spontaneous sinus node automaticity and therefore a disorder of impulse formation, from sinoatrial (SA) exit block in patients with sinus arrhythmia can be difficult without direct recordings of sinus node discharge.



EFIGURE 40.1 Sinus arrest. The patient had a long-term electrocardiographic recorder connected when he died suddenly of cardiac standstill. The rhythms demonstrate progressive sinus bradycardia and sinus arrest at 8:41 AM. The rhythm then becomes a ventricular escape rhythm, which progressively slows and finally ceases at 8:47 AM. The paired electrocardiographic strips are continuous recordings.

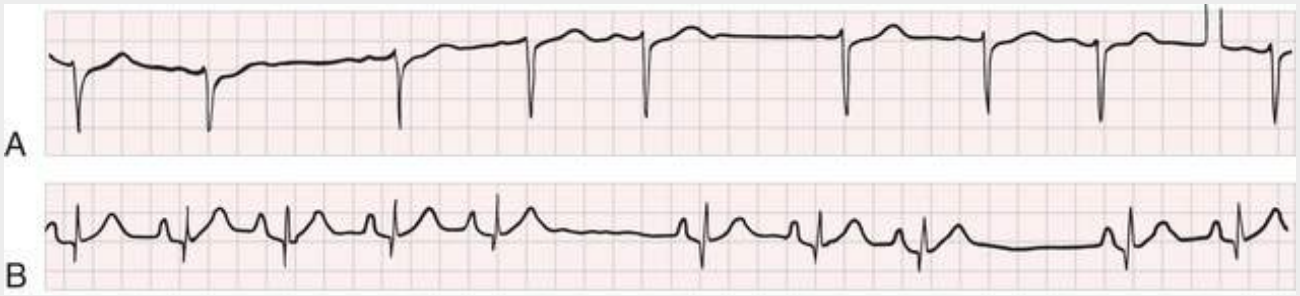
Failure of sinus nodal discharge results in the absence of atrial depolarization and in periods of ventricular asystole if escape beats initiated by latent pacemakers do not occur (**eFig. 40.1**). Involvement of the sinus node by acute MI, degenerative fibrotic changes, effects of digitalis toxicity, stroke, or excessive vagal tone can produce sinus arrest. Transient sinus arrest (especially while sleeping) may have no clinical significance by itself if latent pacemakers promptly escape to prevent ventricular asystole or the genesis of other arrhythmias precipitated by the slow rates. Sinus arrest and AV block have been demonstrated in many patients with sleep apnea (**see Chapter 87**).

Treatment is as outlined earlier for sinus bradycardia. In patients who have a chronic form of sinus node disease characterized by marked sinus bradycardia or sinus arrest, permanent pacing is often necessary. However, as a general rule, chronic pacing for sinus bradycardia is indicated only in symptomatic patients or those with a sinus pause exceeding 3 seconds while awake.

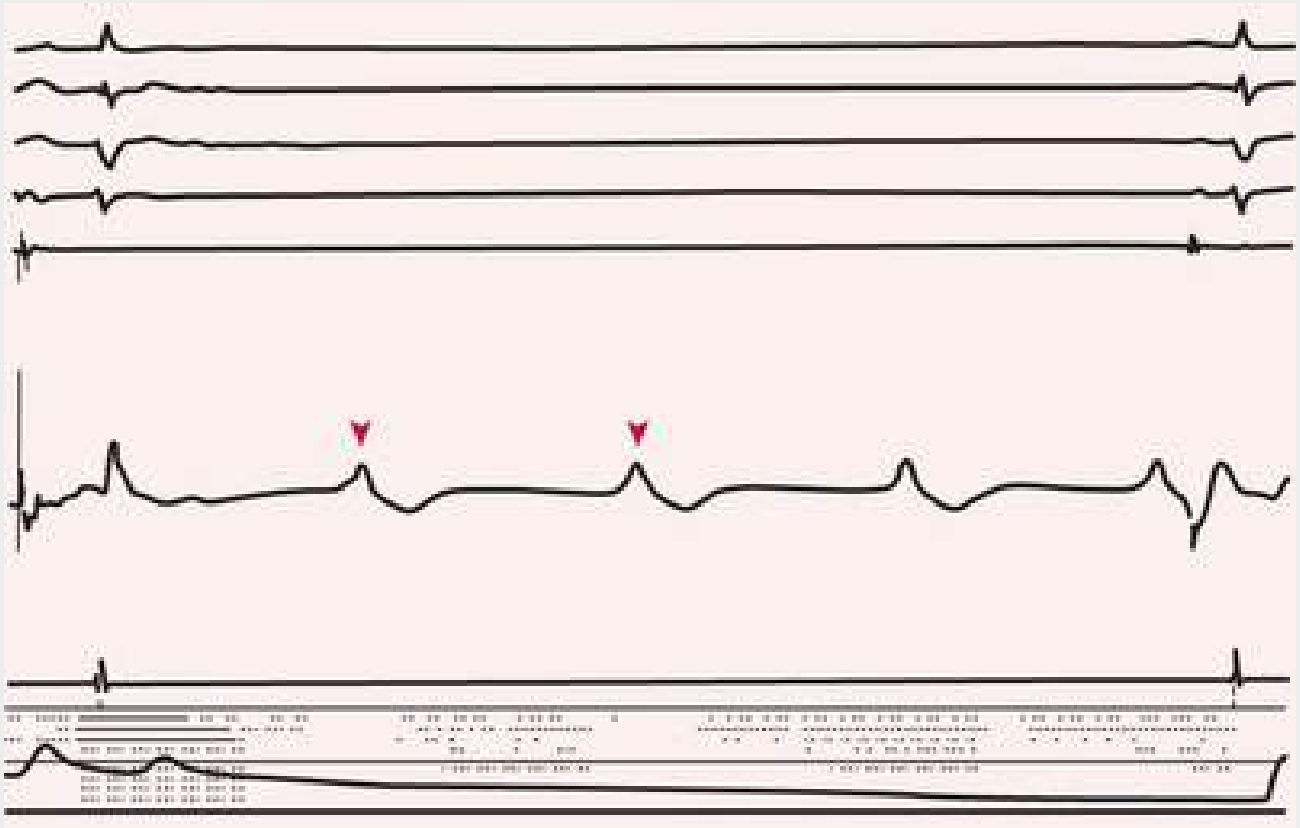
Sinoatrial Exit Block.

SA exit block is an arrhythmia that is recognized electrocardiographically by a pause resulting from absence of the normally expected P wave (**eFig. 40.2**). The duration of the pause is a multiple of the basic P-P interval. SA exit block is caused by a conduction disturbance during which an impulse formed within the sinus node fails to depolarize the atria or does so with delay (**eFig. 40.3**). An interval without P waves that equals approximately two, three, or four times the normal P-P cycle characterizes type II second-degree SA exit block. During type I (Wenckebach) second-degree SA exit block, the P-P interval progressively shortens before the pause, and the duration of the pause is less than two P-P cycles. (**See**

Chapter 35 for further discussion of Wenckebach intervals.) First-degree SA exit block cannot be recognized on the electrocardiogram (ECG) because SA nodal discharge is not recorded. Third-degree SA exit block can be manifested as a complete absence of P waves and is difficult to diagnose with certainty without sinus node electrograms.



EFIGURE 40.2 Sinus nodal exit block. **A,** Type I SA nodal exit block has the following features. The P-P interval shortens from the first to the second cycle in each grouping, followed by a pause. The duration of the pause is less than twice the shortest cycle length, and the cycle after the pause exceeds the cycle before the pause. The PR interval is normal and constant. Lead V_1 is shown. **B,** The P-P interval varies slightly because of sinus arrhythmia. The two pauses in sinus nodal activity equal twice the basic P-P interval and are consistent with a type II 2 : 1 SA nodal exit block. The PR interval is normal and constant. Lead III recording is shown.



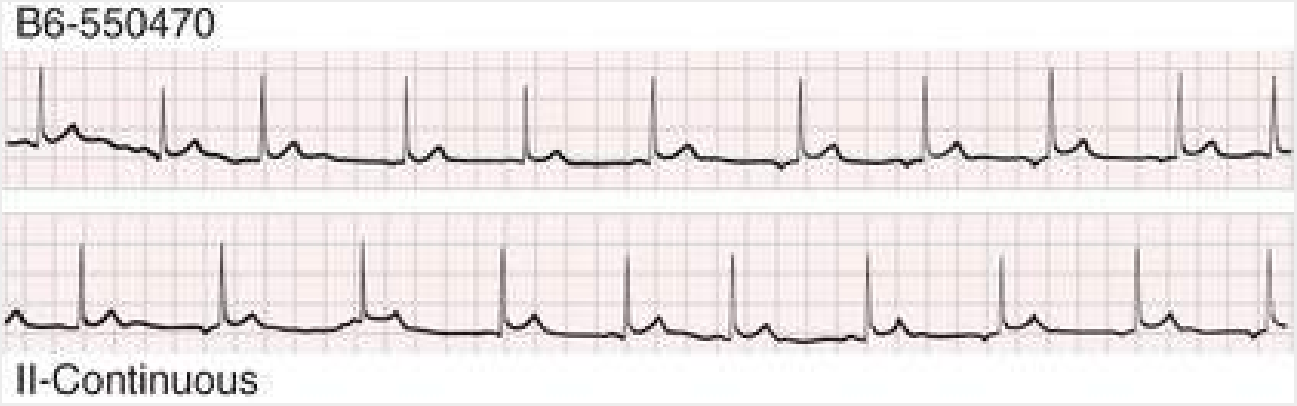
EFIGURE 40.3 Sinus node exit block. After a period of atrial pacing (only the last paced cycle is shown), a sinus node exit block developed. The tracing demonstrates sinus node potentials (*arrowheads*), recorded with a catheter electrode, not conducting to the atrium until the last complex. Recordings are leads I, II, III, and V_1, right atrial recording, sinus node recording, and RV apical recording. The bottom tracing is femoral artery blood pressure.

Excessive vagal stimulation, acute myocarditis, MI, or fibrosis involving the atrium, as well as drugs such as quinidine, procainamide, flecainide and digitalis, can produce SA exit block. SA exit block is usually transient. It may be of no clinical importance except to prompt a search for the underlying cause. On occasion, syncope can result if the SA block is prolonged and unaccompanied by an escape rhythm. SA exit block can occur in well-trained athletes.

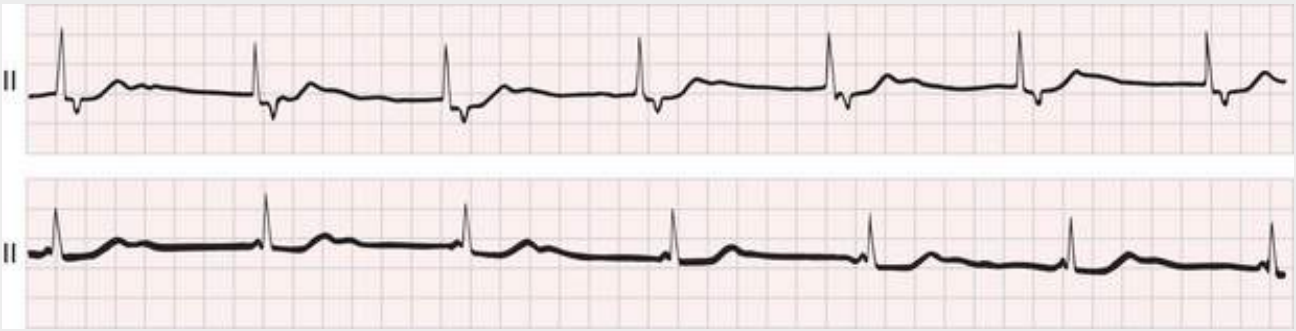
Therapy for patients who have symptomatic SA exit block is as outlined earlier for sinus bradycardia.

Wandering Pacemaker.

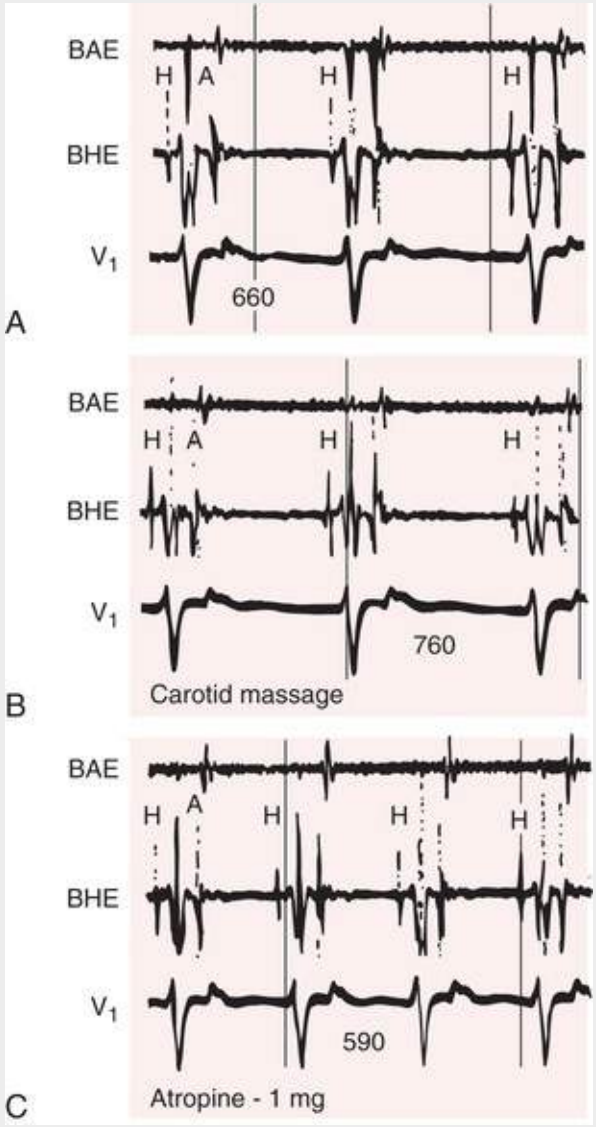
This variant of sinus arrhythmia involves passive transfer of the dominant pacemaker focus from the sinus node to latent pacemakers that have the next highest degree of automaticity located in other atrial sites (usually lower in the crista terminalis) or in AV junctional tissue. The change occurs in a gradual fashion over the duration of several beats; thus only one pacemaker at a time controls the rhythm, in sharp contrast to AV dissociation. The ECG displays a cyclic increase in the R-R interval: a PR interval that gradually shortens and can become less than 120 milliseconds, and a change in the P wave contour that becomes negative in lead I or II (depending on the site of discharge) or is lost within the QRS complex (**eFig. 40.4**). In general, these changes occur in reverse as the pacemaker shifts back to the sinus node. Wandering pacemaker is a normal phenomenon that often occurs in very young persons and particularly in athletes, presumably because of augmented vagal tone. Persistence of an AV junctional rhythm for long periods, however, may indicate underlying heart disease (**eFigs. 40.5 and 40.6**). Treatment is not usually indicated but, if necessary, is the same as that for sinus bradycardia (see earlier).



EFIGURE 40.4 Wandering atrial pacemaker. As the heart rate slows, the P waves become inverted and then gradually revert toward normal when the heart rate speeds up again. The PR interval shortens to 0.14 second with the inverted P wave and is 0.16 second with the upright P wave. This phasic variation in cycle length with varying P wave contour suggests a shift in pacemaker site and is characteristic of a wandering atrial pacemaker.



EFIGURE 40.5 AV junctional rhythm. **Top,** AV junctional discharge occurs fairly regularly at a rate of approximately 50 beats/min. Retrograde atrial activity follows each junctional discharge. **Bottom,** Recording made on a different day in the same patient. The AV junctional rate is slightly more variable, and retrograde P waves precede onset of the QRS complex. The positive terminal portion of the P wave gives the appearance of AV dissociation, which was not present.



EFIGURE 40.6 Nonparoxysmal AV junctional tachycardia. **A,** Control. **B,** Response to carotid sinus massage. **C,** Response to atropine, 1 mg intravenously. Note that His bundle depolarization is the earliest recordable electrical activity in each cycle. The atria are depolarized retrogradely; low right atrial activity recorded in the bipolar His electrogram (*BHE*) precedes high right atrial activity recorded in the bipolar atrial electrogram (*BAE*). Note also that carotid sinus massage slows the junctional discharge rate, whereas atropine speeds it up. From these tracings alone, one could not distinguish the rhythm from some other types of supraventricular tachycardia. However, the onset and termination of this tachycardia were typical of nonparoxysmal AV junctional tachycardia.

Hypersensitive Carotid Sinus Syndrome

Electrocardiographic Recognition

Hypersensitive carotid sinus syndrome is characterized most frequently by ventricular asystole caused by cessation of atrial activity as a result of sinus arrest or SA exit block (**Fig. 40.2**). AV block is observed less frequently, probably in part because the absence of atrial activity from sinus arrest precludes the manifestations of AV block. However, if an atrial pacemaker maintained an atrial rhythm during the episodes, a higher prevalence of AV block would probably be noted. In symptomatic patients, AV junctional or ventricular escapes generally do not occur or are present at very slow rates, suggesting that heightened vagal tone and sympathetic withdrawal can suppress subsidiary pacemakers located in the ventricles, as well as in supraventricular structures.

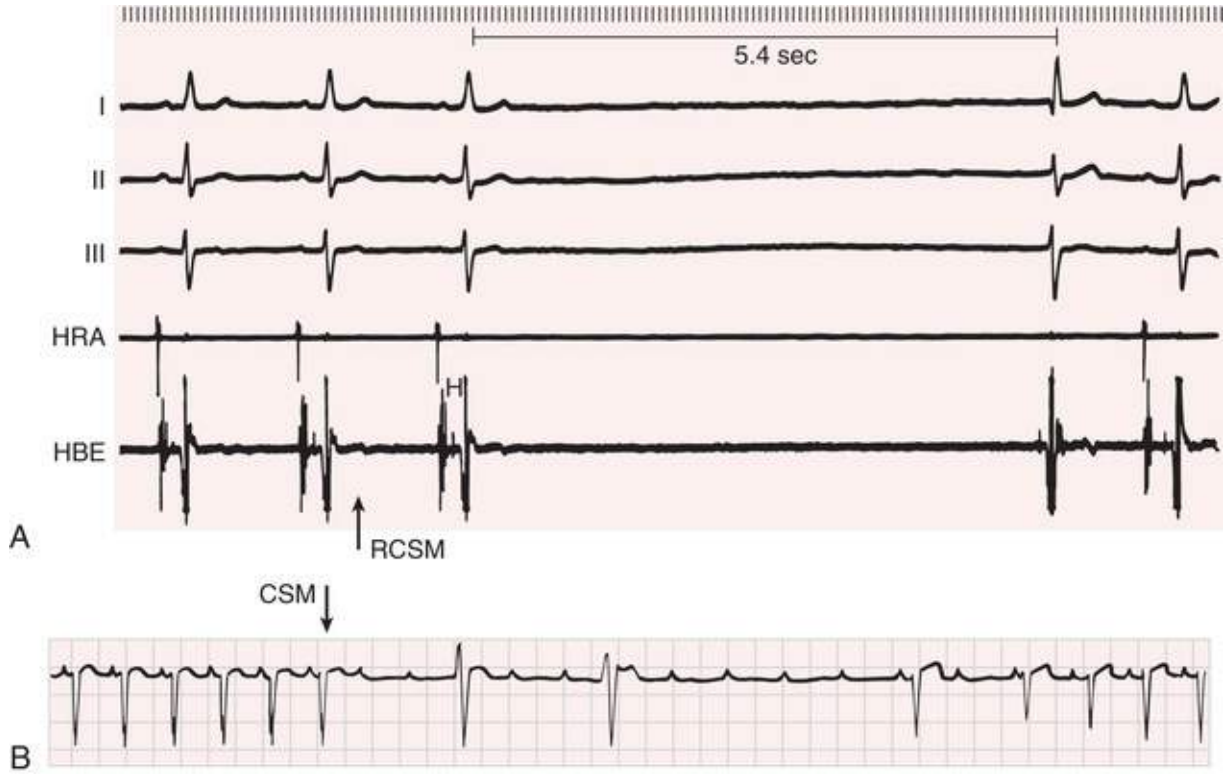


FIGURE 40.2 **A,** Right carotid sinus massage (RCSM, *arrow*) results in sinus arrest and a ventricular escape beat (probably fascicular) 5.4 seconds later. Sinus discharge then resumes. **B,** Carotid sinus massage (CSM, *arrow;* monitor lead) results in slight sinus slowing but, more important, advanced AV block. Obviously, an atrial pacemaker without ventricular pacing would be inappropriate for this patient. *HBE,* His bundle electrogram; *HRA,* high right atrial electrogram.

Clinical Features

Hypersensitive carotid sinus syndrome is a reflex or neutrally mediated cause of bradycardia and syncope.[1] Two types of hypersensitive carotid sinus responses are noted. *Cardioinhibitory* carotid sinus hypersensitivity is generally defined as ventricular asystole exceeding 3 seconds during carotid sinus stimulation, although normal limits have not been definitively established. In fact, asystole exceeding 3 seconds during carotid sinus massage is not common but can occur in asymptomatic subjects (**Fig. 40.2**). *Vasodepressor* carotid sinus hypersensitivity is usually defined as a decrease in systolic blood pressure (SBP) of 50 mm Hg or more without associated cardiac slowing or a decrease in SBP exceeding 30 mm Hg when the patient's symptoms are reproduced.

Even if a hyperactive carotid sinus reflex is elicited in patients, particularly in older patients who complain of syncope or presyncope, the hyperactive reflex elicited with carotid sinus massage may not necessarily be responsible for these symptoms. Direct pressure or extension of the carotid sinus as a result of head turning, neck tension, and tight collars can also be a source of syncope by reducing blood flow through the cerebral arteries. Hypersensitive carotid sinus reflex is most often associated with coronary artery disease. The mechanism responsible for hypersensitive carotid sinus reflex is not known.

Management

Atropine acutely abolishes cardioinhibitory carotid sinus hypersensitivity. However, most symptomatic patients require pacemaker implantation. Because AV block can occur during periods of hypersensitive carotid reflex, some form of ventricular pacing, with or without atrial pacing, is generally required. Atropine and pacing do not prevent the SBP decrease in the vasodepressor form of carotid sinus hypersensitivity, which may result from inhibition of sympathetic vasoconstrictor nerves and possibly

from activation of cholinergic sympathetic vasodilator fibers. Combinations of vasodepressor and cardioinhibitory types can occur, and vasodepression can account for continued syncope after pacemaker implantation in some patients. Patients who have a hyperactive carotid sinus reflex that does not cause symptoms require no treatment. Drugs such as digitalis, methyldopa, clonidine, and propranolol can enhance the response to carotid sinus massage and be responsible for symptoms in some patients. Elastic support hose and sodium-retaining drugs may be helpful in patients with vasodepressor responses.

Sick Sinus Syndrome

Electrocardiographic Recognition

Sick sinus syndrome is a term applied to a syndrome encompassing several sinus nodal abnormalities, including (1) persistent spontaneous sinus bradycardia not caused by drugs and inappropriate for the physiologic circumstance, (2) sinus arrest or exit block (**Fig. 40.3**), (3) combinations of SA and AV conduction disturbances, and (4) alternation of paroxysms of rapid regular or irregular atrial tachyarrhythmias and periods of slow atrial and ventricular rates (bradycardia-tachycardia syndrome; **Fig. 40.4**). More than one of these conditions can be recorded in the same patient on different occasions, and their mechanisms can often be shown to be causally interrelated and combined with an abnormal state of AV conduction or automaticity.

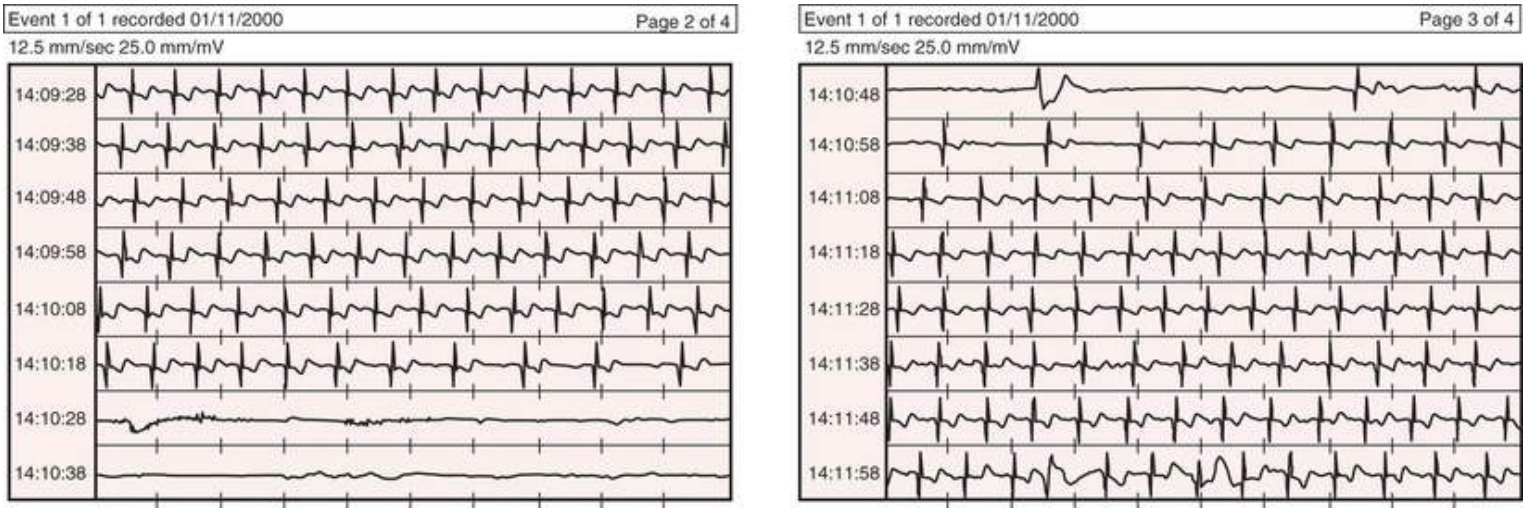


FIGURE 40.3 Continuous recording from an implanted loop recorder in a patient with syncope. The tracing shows paroxysmal sinus node arrest and a sinus pause of nearly 30 seconds. The preceding sinus cycle length appears to lengthen just before the pause, which suggests an autonomic component of the pause. There is also a single ventricular escape complex at 14 : 10 : 48.

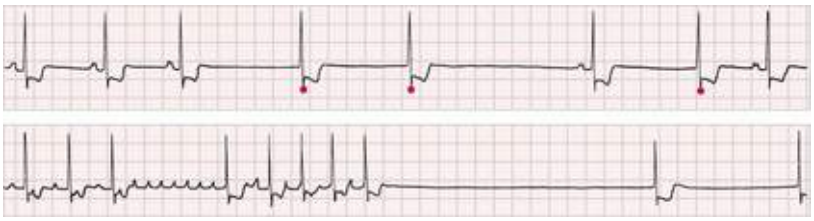


FIGURE 40.4 Sick sinus syndrome with bradycardia-tachycardia. **Top,** Intermittent sinus arrest is apparent with junctional escape beats at irregular intervals (*red circles*). **Bottom,** In this continuous monitor lead recording, a short episode of atrial flutter is followed by almost 5 seconds of asystole before a junctional escape rhythm resumes. The patient became presyncopal at this point.

Patients with sinus node disease can be categorized as having intrinsic disease unrelated to autonomic abnormalities or combinations of intrinsic and autonomic abnormalities. Symptomatic patients with sinus pauses or SA exit block frequently show abnormal responses on electrophysiologic testing and can have a relatively high incidence of atrial fibrillation. In children, sinus node dysfunction most frequently occurs in those with congenital or acquired heart disease, particularly after corrective cardiac surgery. Sick sinus syndrome can occur in the absence of other cardiac abnormalities. The course of the disease is frequently intermittent and unpredictable because it is influenced by the severity of the underlying heart disease. Excessive physical training can heighten vagal tone and produce syncope related to sinus bradycardia or AV conduction abnormalities in otherwise normal individuals.

The anatomic basis of sick sinus syndrome can involve total or subtotal destruction of the sinus node, areas of nodal-atrial discontinuity, inflammatory or degenerative changes in the nerves and ganglia surrounding the node, and pathologic changes in the atrial wall. Fibrosis and fatty infiltration occur, and the sclerodegenerative processes generally involve the sinus node and the AV node or the bundle of His and its branches or distal subdivisions. Occlusion of the sinus node artery may be important.

Management

For patients with sick sinus syndrome, treatment depends on the basic rhythm problem but usually involves permanent pacemaker implantation when symptoms are manifested (**see Chapter 41**). Pacing for the bradycardia, combined with drug therapy to treat the tachycardia, is required in those with bradycardia-tachycardia syndrome.

Atrioventricular Block (Heart Block)

Heart block is a disturbance of impulse conduction that can be permanent or transient, depending on the anatomic or functional impairment. It must be distinguished from *interference,* a normal phenomenon that is a disturbance of impulse conduction caused by physiologic refractoriness resulting from inexcitability secondary to a preceding impulse. Interference or block can occur at any site where impulses are conducted, but they are recognized most often between the sinus node and atrium (SA block), between the atria and ventricles (AV block), within the atria (intra-atrial block), or within the ventricles (intraventricular block). SA exit block was discussed earlier (see Sinus Bradycardia). An AV block exists if the atrial impulse is conducted with delay or is not conducted at all to the ventricle when the AV junction is not physiologically refractory. During AV block, the block can occur in the AV node, His bundle, or bundle branches. In some cases of bundle branch block (BBB), the impulse may only be delayed and not completely blocked in the bundle branch, yet the resulting QRS complex may be indistinguishable from a QRS complex generated by a complete BBB.

The conduction disturbance is classified by severity into three categories. During first-degree heart

block, conduction time is prolonged but all impulses are conducted. Second-degree heart block occurs in two forms, Mobitz type I (Wenckebach) and type II. Type I heart block is characterized by progressive lengthening of the conduction time until an impulse is not conducted. Type II heart block denotes an occasional or repetitive sudden block of conduction of an impulse, without prior measurable lengthening of conduction time. When no impulses are conducted, complete or third-degree block is present. The degree of block may depend in part on the direction of impulse propagation. For unknown reasons, normal retrograde conduction can occur in the presence of advanced anterograde AV block. The reverse can also occur. Some electrocardiographers use the term *advanced* or *high-grade heart block* to indicate blockage of two or more consecutive impulses.

First-Degree Atrioventricular Block

During first-degree AV block, every atrial impulse is conducted to the ventricles and a regular ventricular rate is produced, but the PR interval exceeds 0.20 second in adults. PR intervals as long as 1.0 second have been noted and can at times exceed the P-P interval, a phenomenon known as *skipped P waves*. Clinically important PR interval prolongation can result from a conduction delay in the AV node (A-H interval), in the His-Purkinje system (H-V interval), or at both sites. Equally delayed conduction over both bundle branches can infrequently produce PR prolongation without significant QRS complex aberration. On occasion, an intra-atrial conduction delay can result in PR prolongation. If the QRS complex on the scalar ECG is normal in contour and duration, the AV delay almost always resides in the AV node and rarely within the His bundle itself. If the QRS complex shows a BBB pattern, the conduction delay may be within the AV node or the His-Purkinje system (**Fig. 40.5**). In the latter case, a His bundle ECG is necessary to localize the site of conduction delay. Acceleration of the atrial rate or enhancement of vagal tone by carotid massage can cause first-degree AV nodal block to progress to type I second-degree AV block. Conversely, type I second-degree AV nodal block can revert to a first-degree block with deceleration of the sinus rate.

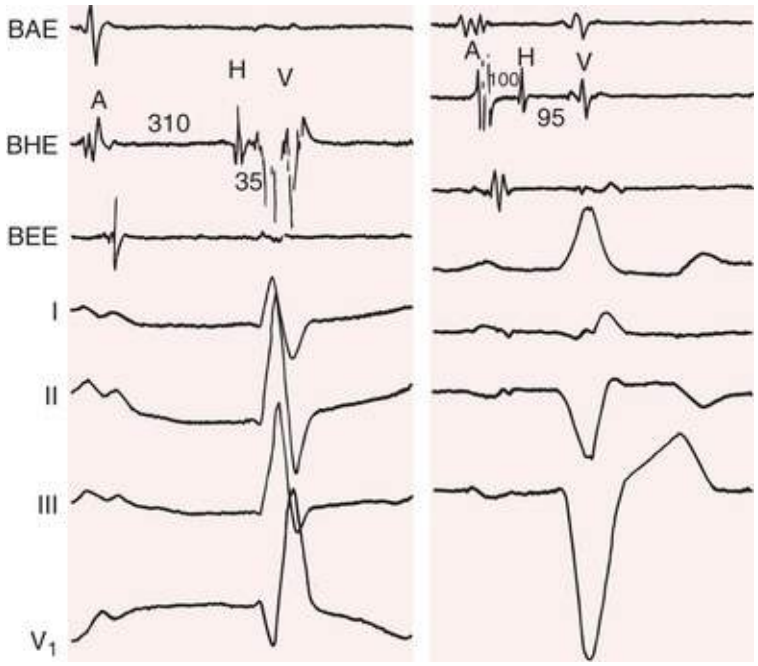


FIGURE 40.5 First-degree AV block. One complex during sinus rhythm is shown. **Left panel,** The PR interval measured 370 milliseconds (PA = 25 msec; A-H = 310 msec; H-V = 39 msec) during a right bundle branch block. Conduction delay in the AV node causes the first-degree AV block. **Right panel,** The PR interval is 230 milliseconds (PA = 39 msec; A-H = 100 msec; H-V = 95 msec) during a left bundle branch block. The conduction delay in the His-Purkinje system is causing the first-degree AV block. *BAE,* Bipolar atrial electrogram; *BEE,* bipolar esophageal electrogram; *BHE,* bipolar His electrogram.

Second-Degree Atrioventricular Block

Blocking of some atrial impulses conducted to the ventricle at a time when physiologic interference is not involved constitutes second-degree AV block (**Figs. 40.6, 40.7, and 40.8; eFig. 40.7**). The nonconducted P wave can be intermittent or frequent, can occur at regular or irregular intervals, and may be preceded by fixed or lengthening PR intervals. A distinguishing feature is that conducted P waves relate to the QRS complex with recurring PR intervals; that is, the association of P with QRS is not random. Electrocardiographically, typical type I second-degree AV block is characterized by progressive PR prolongation culminating in a nonconducted P wave (**Figs. 40.7 and 40.8B; eFig. 40.7**), whereas in type II second-degree AV block, the PR interval remains constant before the blocked P wave (**Fig. 40.8A**). In both cases the AV block is intermittent and generally repetitive and can block several P waves in a row. Frequently, the eponyms Mobitz type I and Mobitz type II are applied to the two types of block, whereas Wenckebach block refers to type I block only. A Wenckebach block in the His-Purkinje system in a patient with a BBB can closely resemble an AV nodal Wenckebach block (**Fig. 40.8B**).

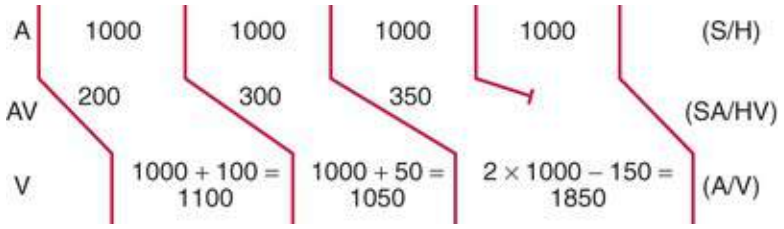


FIGURE 40.6 Typical 4 : 3 Wenckebach cycle. P waves (A tier) occur at a cycle length of 1000 milliseconds. The PR interval (AV tier) is 200 milliseconds for the first beat and generates a ventricular response (V tier). The PR interval increases by 100 milliseconds in the next complex, which results in an R-R interval of 1100 milliseconds (1000 + 100). The increment in the PR interval is only 50 milliseconds for the third cycle, and the PR interval becomes 350 milliseconds. The R-R interval shortens to 1050 milliseconds (1000 + 50). The next P wave is blocked, and an R-R interval is created that is less than twice the P-P interval by an amount equal to the increments in the PR interval. Thus the Wenckebach features explained in the text can be found in this diagram. If the increment in the PR interval of the last conducted complex increased rather than decreased (e.g., 150 msec rather than 50 msec), the last R-R interval before the block would increase (1150 msec) rather than decrease and thus become an example of an atypical Wenckebach cycle (**see Fig. 40.1**). If this were a Wenckebach exit block from the sinus node to the atrium, the sinus node cycle length (*S*) would be 1000 milliseconds, and the SA interval would increase from 200 to 300 to 350 milliseconds and culminate in a block. These events would be inapparent on a scalar ECG. However, the P-P interval on the ECG would shorten from 1100 to 1050 milliseconds, and finally, there would be a pause of 1850 milliseconds (*A*). If this rhythm were a junctional rhythm arising from the His bundle and conducting to the ventricle, the junctional rhythm cycle length would be 1000 milliseconds (*H*) and the H-V interval would progressively lengthen from 200 to 300 to 350 milliseconds, whereas the R-R interval would decrease from 1100 to 1050 milliseconds and then increase to 1850 milliseconds (*V*). The only clue to the Wenckebach exit block would be the changes in cycle length in the ventricular rhythm.

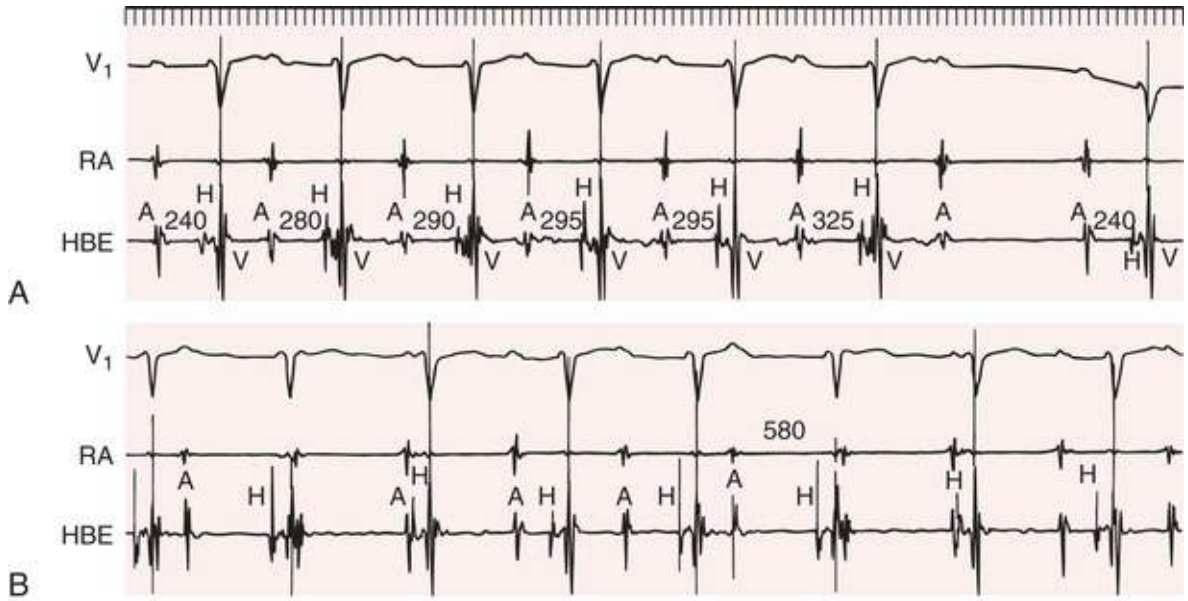


FIGURE 40.7 **A,** Type I (Wenckebach) AV nodal block. During spontaneous sinus rhythm, progressive PR prolongation occurs and culminates in a nonconducted P wave. From the His bundle recording (HBE), it is apparent that the conduction delay and subsequent block occur within the AV node. Because the increment in conduction delay does not consistently decrease, the R-R intervals do not reflect the classic Wenckebach structure. **B,** Recorded 5 minutes after the intravenous administration of atropine, 0.5 mg. Atropine has had its predominant effect on sinus and junctional automaticity by this time, with little improvement in AV conduction. Consequently, more P waves are blocked and AV dissociation is present, caused by a combination of AV block and an enhanced junctional discharge rate. At 8 minutes (not shown), when atropine finally improved AV conduction, 1 : 1 AV conduction occurred. *RA,* Right atrium.

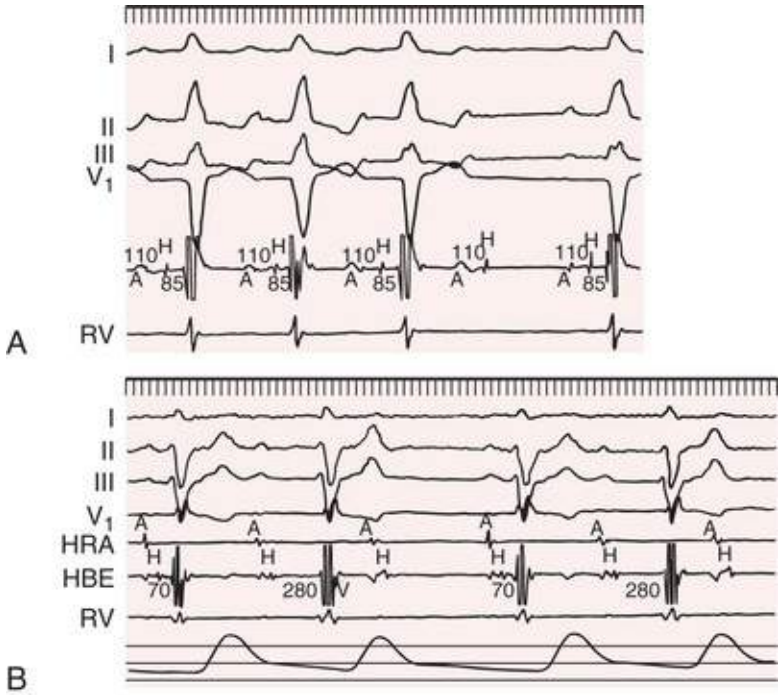
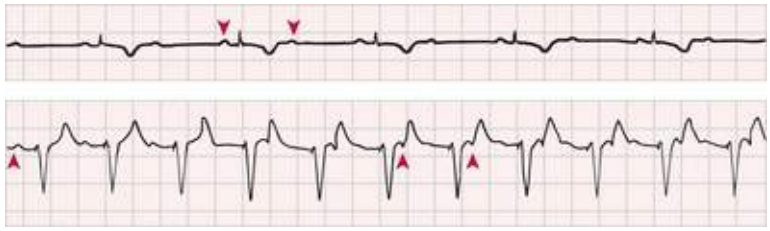


FIGURE 40.8 Type II AV block. **A,** The sudden development of a His-Purkinje block is apparent. The A-H and H-V intervals remain constant, as does the PR interval. A left bundle branch block is present. **B,** Wenckebach AV block in the His-Purkinje system. The QRS complex exhibits a right bundle branch block morphology. However, note that the second QRS complex in the 3 : 2 conduction exhibits a slightly different contour from the first QRS complex, particularly in V_1. This finding is the clue that the Wenckebach AV block might be in the His-Purkinje system. The H-V interval increases from 70 to 280 milliseconds, and then a block distal to the His bundle results. *HBE,* His bundle electrogram; *HRA,* high right atrium; *RV,* right ventricle.



EFIGURE 40.7 Unidirectional block. **Top,** During spontaneous sinus rhythm at a rate of 68 beats/min, 2 : 1 anterograde AV conduction occurs. **Bottom,** 1 : 1 retrograde conduction is seen during ventricular pacing at a rate of 70 beats/min. P waves are indicated by *arrowheads*.

Certain features of type I second-degree block deserve special emphasis because when actual conduction times are not apparent on the ECG—for example, during SA, junctional, or ventricular exit block (**see Fig. 40.6**)—a type I conduction disturbance can be difficult to recognize. During a typical type I block, the increment in conduction time is greatest in the second beat of the Wenckebach group, and the absolute increase in conduction time decreases progressively over subsequent beats. These two features serve to establish the characteristics of classic Wenckebach group beats: (1) the interval between successive beats progressively decreases, although the conduction time increases (but by a decreasing function); (2) the duration of the pause produced by the nonconducted impulse is less than twice the interval preceding the blocked impulse (which is usually the shortest interval); and (3) the cycle that follows the nonconducted beat (beginning the Wenckebach group) is longer than the cycle preceding the blocked

impulse. Although much emphasis has been placed on this characteristic grouping of cycles, primarily to be able to diagnose a Wenckebach exit block, this typical grouping occurs in fewer than 50% of patients with a type I Wenckebach AV nodal block.

Differences in these cycle-length patterns can result from changes in pacemaker rate (e.g., sinus arrhythmia), in neurogenic control of conduction, and in the increment of conduction delay. For example, if the PR increment in the last cycle increases, the R-R cycle of the last conducted beat can lengthen rather than shorten. In addition, because the last conducted beat is often at a critical state of conduction, it can become blocked and produce a 5 : 3 or 3 : 1 conduction ratio instead of a 5 : 4 or 3 : 2 ratio. During a 3 : 2 Wenckebach structure, the duration of the cycle that follows the nonconducted beat will be the same as the duration of the cycle that precedes the nonconducted beat.

Although it has been suggested that type I and type II AV block are different manifestations of the same electrophysiologic mechanism that differ only quantitatively in the size of the increments, clinical separation of second-degree AV block into types I and II serves a useful function, and in most cases the differentiation can be made easily and reliably from the surface ECG. Type II AV block often antedates the development of Adams-Stokes syncope and complete AV block, whereas type I AV block with a normal QRS complex is generally more benign and does not progress to more advanced forms of AV conduction disturbance. In older people, type I AV block with or without BBB has been associated with a clinical picture similar to that seen in type II AV block.

In a patient with an acute MI, type I AV block usually accompanies inferior infarction (perhaps more often if an right ventricular infarction also occurs), is transient, and does not require temporary pacing, whereas type II AV block occurs in the setting of acute anterior MI, can require temporary or permanent pacing, and is associated with high mortality, generally as a result of pump failure. A high degree of AV block can occur in patients with acute inferior MI and is associated with more myocardial damage and a higher mortality rate than in those without AV block.

Although type I conduction disturbance is ubiquitous and can occur in any cardiac tissue in vivo as well as in vitro, the site of block for the usual forms of second-degree AV block can generally be determined from the surface ECG with sufficient reliability to permit clinical decisions without an invasive electrophysiologic study (EPS). Type I AV block with a normal QRS complex almost always takes place at the level of the AV node, proximal to the His bundle. An exception is the uncommon patient with type I intrahisian block. Type II AV block, particularly in association with a BBB, is localized to the His-Purkinje system. Type I AV block in a patient with a BBB can be caused by a block in the AV node or in the His-Purkinje system. Type II AV block in a patient with a normal QRS complex can be caused by an intrahisian AV block, but the block is likely to be a type I AV nodal block, which exhibits small increments in AV conduction time.

Differentiation of Type I from Type II Atrioventricular Block.

The preceding generalizations encompass most patients with second-degree AV block. However, certain caveats must be heeded to avoid misdiagnosis because of subtle electrocardiographic changes or exceptions.

1. A 2 : 1 AV block can be a form of type I or type II AV block (**Fig. 40.9**). If the QRS complex is normal, the block is more likely to be type I and located in the AV node, and one should search for

transition of the 2 : 1 block to a 3 : 2 block, during which the PR interval lengthens in the second cardiac cycle. If a BBB is present, the block can be located in the AV node or His-Purkinje system.

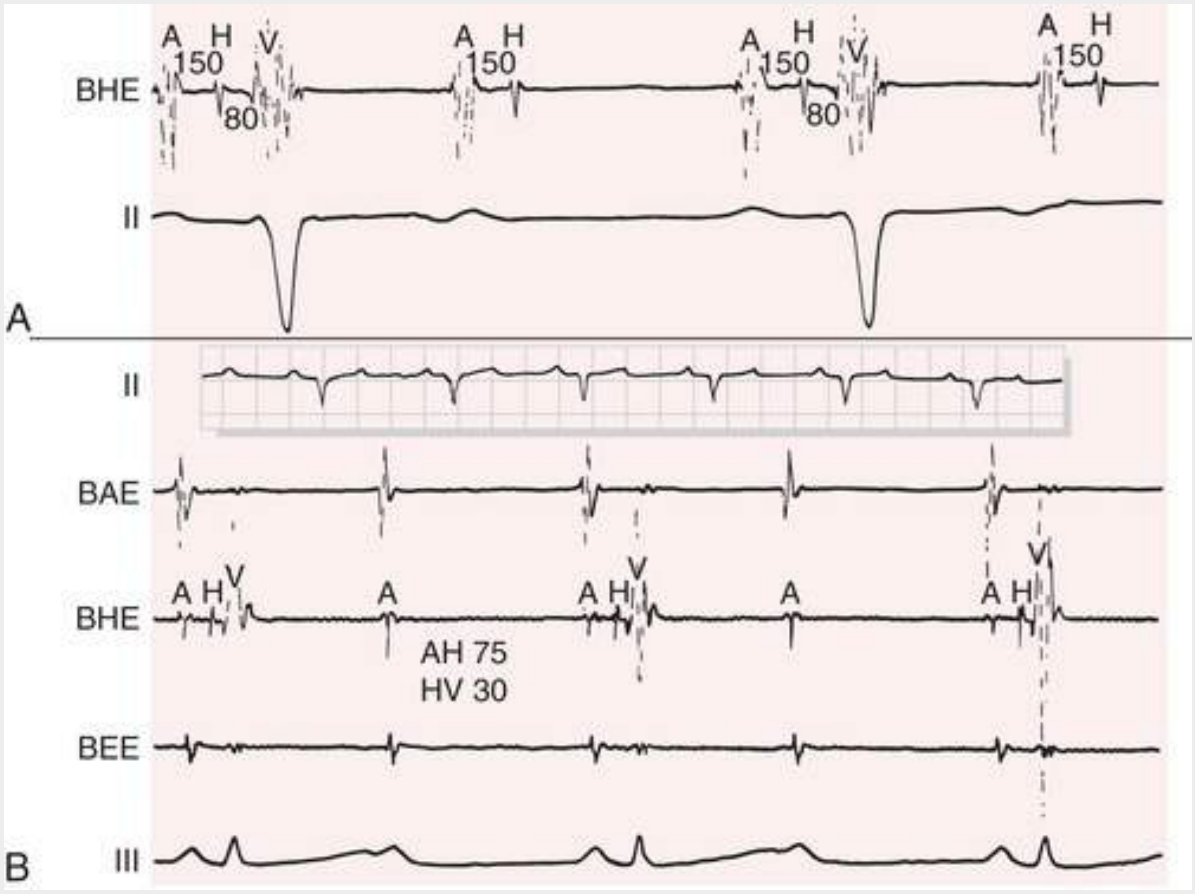


FIGURE 40.9 A 2 : 1 AV block proximal and distal to the His bundle deflection in two different patients. **A,** 2 : 1 AV block seen on the scalar ECG occurs distal to the His bundle recording site in a patient with a right bundle branch block and anterior hemiblock. The A-H interval (150 msec) and H-V interval (80 msec) are both prolonged. **B,** 2 : 1 AV block proximal to the bundle of His in a patient with a normal QRS complex. The A-H interval (75 msec) and the H-V interval (30 msec) remain constant and normal. *BAE,* Bipolar atrial electrogram; *BEE,* bipolar esophageal electrogram; *BHE,* bipolar His electrogram.

2. AV block can occur simultaneously at two or more levels and cause difficulty in distinguishing between types I and II.
3. If the atrial rate varies, it can alter conduction times and cause a type I AV block to stimulate a type II block or change a type II AV block into type I. For example, if the shortest atrial cycle length that has just achieved 1 : 1 AV nodal conduction at a constant PR interval is decreased by only 10 or 20 milliseconds, the P wave of the shortened cycle can block conduction at the level of the AV node without an apparent increase in the antecedent PR interval. An apparent type II AV block in the His-Purkinje system can be converted to type I in the His-Purkinje system in some patients by increasing the atrial rate.
4. Concealed premature His depolarizations can create electrocardiographic patterns that simulate those of type I or II AV block.
5. Abrupt transient alterations in autonomic tone can cause sudden block of one or more P waves without altering the PR interval of the conducted P wave before or after the block. Thus, an apparent type II AV block would be produced at the AV node. Clinically, a burst of vagal tone usually lengthens the P-P interval, as well as produces an AV block.

6. The response of the AV block to autonomic changes, either spontaneous or induced, to distinguish type I from type II AV block can be misleading. Although vagal stimulation generally increases and vagolytic agents decrease the extent of type I AV block, such conclusions are based on the assumption that the intervention acts primarily on the AV node and fail to consider rate changes. For example, atropine can minimally improve conduction in the AV node and greatly increase the sinus rate, which results in an increase in AV nodal conduction time and the degree of AV block as a result of the faster atrial rate (**see Fig. 40.7B**). Conversely, if an increase in vagal tone minimally prolongs AV conduction time but greatly slows the heart rate, the net effect on type I AV block may be to improve conduction. In general, however, carotid sinus massage improves and atropine worsens AV conduction in patients with His-Purkinje block, whereas the opposite results are to be expected in patients with AV nodal block. Similarly, exercise or isoproterenol is likely to increase the sinus rate and improve AV nodal block but worsen His-Purkinje block. These interventions can help differentiate the site of block without invasive study, although damaged His-Purkinje tissue may be influenced by changes in autonomic tone.
7. During type I AV block with high ratios of conducted beats, the increment in PR interval can be quite small and can suggest a type II AV block if only the last few PR intervals before the blocked P wave are measured. Comparing the PR interval of the first beat in the long Wenckebach cycle with that of the beats immediately preceding the blocked P wave readily reveals the increment in AV conduction.
8. The classic AV Wenckebach structure depends on a stable atrial rate and a maximal increment in AV conduction time for the second PR interval of the Wenckebach cycle along with a progressive decrease in subsequent beats. Unstable or unusual alterations in the increment of AV conduction time or in the atrial rate, often seen with long Wenckebach cycles, result in atypical forms of type I AV block in which the last R-R interval can lengthen because the PR increment increases; such alterations are common.
9. Finally, the PR interval on the scalar ECG consists of conduction through the atrium, AV node, and His-Purkinje system. An increment in H-V conduction, for example, can be masked on the scalar ECG by a reduction in the A-H interval, and the resulting PR interval will not reflect the entire increment in His-Purkinje conduction time. Very long PR intervals (200 msec) are more likely to result from AV nodal conduction delay (and block), with or without concomitant His-Purkinje conduction delay, although an H-V interval of 390 milliseconds is possible.

First-degree and type I second-degree AV block can occur in normal healthy children, and a Wenckebach AV block can be a normal phenomenon in well-trained athletes, as noted earlier, probably related to an increase in resting vagal tone. On occasion, progressive worsening of the Wenckebach AV conduction disorder can result, and the athlete becomes symptomatic and needs to decondition. In patients who have chronic second-degree AV nodal block (proximal to the His bundle) without structural heart disease, the course is relatively benign (except in older age-groups), whereas in those with structural heart disease, the prognosis is poor and related to the underlying heart disease.

Third-Degree (Complete) Atrioventricular Block

Third-degree or complete AV block occurs when no atrial activity is conducted to the ventricles and therefore the atria and ventricles are controlled by independent pacemakers. Thus, complete AV block is one type of complete AV dissociation. The atrial pacemaker can be sinus or ectopic (tachycardia, flutter,

or fibrillation) or can result from an AV junctional focus occurring above the block with retrograde atrial conduction. The ventricular focus is usually located just below the region of the block, which can be above or below the His bundle bifurcation. Sites of ventricular pacemaker activity that are in or closer to the His bundle appear to be more stable and can produce a faster escape rate than those located more distally in the ventricular conduction system. The ventricular rate in acquired complete heart block is less than 40 beats/min but can be faster with congenital complete AV block. The ventricular rhythm, usually regular, can vary in response to premature ventricular complexes (PVCs), a shift in the pacemaker site, an irregularly discharging pacemaker focus, or autonomic influences.

Complete AV block can result from a block at the level of the AV node (usually congenital; **Fig. 40.10**), within the bundle of His, or distal to it in the Purkinje system (usually acquired; **eFig. 40.8**).[2] Block proximal to the His bundle generally exhibits normal QRS complexes and rates of 40 to 60 beats/min because the escape focus that controls the ventricle arises in or near the His bundle. In complete AV nodal block, the P wave is not followed by a His deflection, but each ventricular complex is preceded by a His deflection (**Fig. 40.10**). His bundle recording can be useful to differentiate AV nodal from intrahisian block because the intrahisian may carry a more serious prognosis than the AV nodal block. Intrahisian block is recognized infrequently without invasive studies. In patients with AV nodal block, atropine generally speeds both the atrial and the ventricular rate. Exercise can reduce the extent of AV nodal block. Acquired complete AV block occurs most often distal to the bundle of His because of trifascicular conduction disturbance. Each P wave is followed by a His deflection, and the ventricular escape complexes are not preceded by a His deflection (**see eFig. 40.8**). The QRS complex is abnormal, and the ventricular rate is generally less than 40 beats/min. A hereditary form caused by degeneration of the His bundle and bundle branches has been linked to the *SCN5A* gene, which is also responsible for LQT3 (**see Chapter 33**).

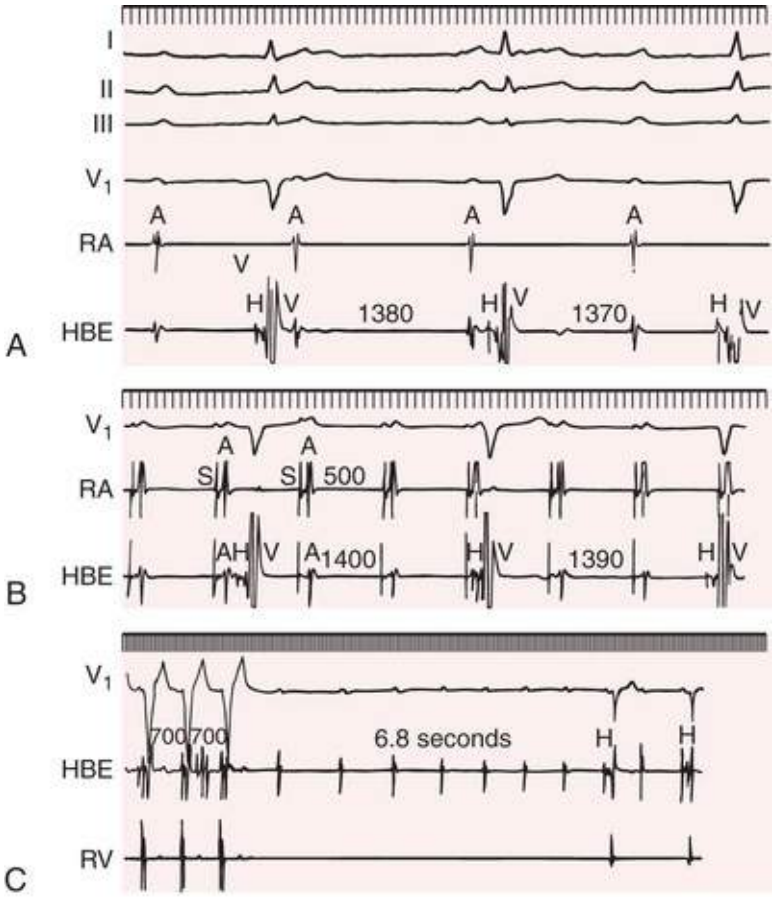
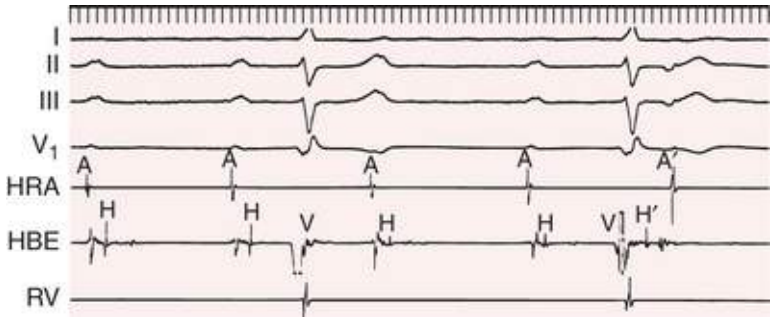


FIGURE 40.10 Congenital third-degree AV block. **A,** Complete AV nodal block is apparent. No P wave is followed by a His bundle potential, whereas each ventricular depolarization is preceded by a His bundle potential. **B,** Atrial pacing (cycle length of 500 msec) fails to alter the cycle length of the functional rhythm. Still, no P wave is followed by a His bundle potential. **C,** After 30 seconds of ventricular pacing (cycle length of 700 msec), suppression of the junctional focus results for almost 7 seconds (overdrive suppression of automaticity). *HBE,* His bundle electrogram; *RA,* right atrium; *RV,* right ventricle.



EFIGURE 40.8 Complete anterograde AV block with retrograde VA conduction. All the sinus P waves are blocked distal to the His bundle, consistent with acquired complete AV block. The ventricles escape at a cycle length of approximately 1800 milliseconds (33 beats/min) and are not preceded by His bundle activation. The ventricular escape rhythm produces a QRS contour with left axis deviation and a right bundle branch block, possibly caused by impulse origin in the posterior fascicle of the left bundle branch. Of interest is the fact that the second ventricular escape beat conducts retrogradely through His (*H*) and to the atrium (note the low-high atrial activation sequence and the negative P wave in leads II and III). The first ventricular complex does not conduct retrogradely, probably because the His bundle is still refractory from the immediately preceding atrial impulse. *HBE,* His bundle electrogram; *HRA,* high right atrium; *RV,* right ventricle.

Paroxysmal AV block in some cases can be caused by hyperresponsiveness of the AV node to vagotonic reflexes.[3] Surgery, electrolyte disturbances, myoendocarditis, tumors, Chagas disease, rheumatoid nodules, calcific aortic stenosis, myxedema, polymyositis, infiltrative processes (e.g., amyloidosis,

sarcoidosis, scleroderma), and an almost endless assortment of common and unusual conditions can produce AV block. In adults, rapid rates may be followed by block (called *tachycardia-dependent* AV block), which is thought to result from a phase 3 block (block caused by incomplete action potential recovery), postrepolarization refractoriness, and concealed conduction in the AV node. Less common than tachycardia-dependent AV block, *pause-dependent paroxysmal* AV block can also occur; it results in AV block after a pause or during relative bradycardia and thus can be difficult to distinguish from vagal AV block. This form of AV block is often referred to as a *phase 4 block* because it is thought that spontaneous depolarizations during the resting phase of the action potential result in an inability to depolarize, although other mechanisms may also play a role.

In children the most common cause of AV block is congenital (**see Chapter 75**). In such circumstances the AV block can be an isolated finding or associated with other lesions. Neonatal autoimmune disease, from maternal antibodies crossing the placenta, accounts for most cases of heart block in utero or in the immediate neonatal period but only for rare cases of congenital heart block occurring after this period. Anatomic disruption between the atrial musculature and peripheral parts of the conduction system and nodoventricular discontinuity are two common histologic findings. Children are most often asymptomatic; however, in some children, symptoms requiring pacemaker implantation develop. Mortality from congenital AV block is highest in the neonatal period, is much lower during childhood and adolescence, and increases slowly later in life. Adams-Stokes attacks can occur in patients with congenital heart block at any age. It is difficult to predict the prognosis in an individual patient. A persistent heart rate at rest of 50 beats/min or less correlates with the incidence of syncope, and extreme bradycardia can contribute to the frequency of Adams-Stokes attacks in children with congenital complete AV block. The site of block may not distinguish symptomatic children who have congenital or surgically induced complete heart block from those without symptoms. Prolonged recovery times of escape foci after rapid pacing (**see Fig. 40.10C**), slow heart rates on 24-hour electrocardiographic recordings, and the occurrence of paroxysmal tachycardias may be factors predisposing to the development of symptoms.

Clinical Features

Many of the signs of AV block are evident at the bedside. First-degree AV block can be recognized by a long *a* to *c* wave interval in the jugular venous pulse and by diminished intensity of the first heart sound (S_1) as the PR interval lengthens. In type I second-degree AV block, the heart rate may increase imperceptibly with gradually diminishing intensity of S_1; widening of the *a* to *c* interval, terminated by a pause; and an *a* wave not followed by a *v* wave. Intermittent ventricular pauses and *a* waves in the neck not followed by *v* waves characterize type II AV block. S_1 maintains a constant intensity. In complete AV block, the findings are the same as those in AV dissociation (see later).

Significant clinical manifestations of first- and second-degree AV block usually consist of palpitations or subjective feelings of the heart “missing a beat.” Persistent 2 : 1 AV block can produce symptoms of chronic bradycardia. Complete AV block can be accompanied by signs and symptoms of reduced cardiac output, syncope or presyncope, angina, or palpitations from ventricular tachyarrhythmias. It can occur in twins.

Management

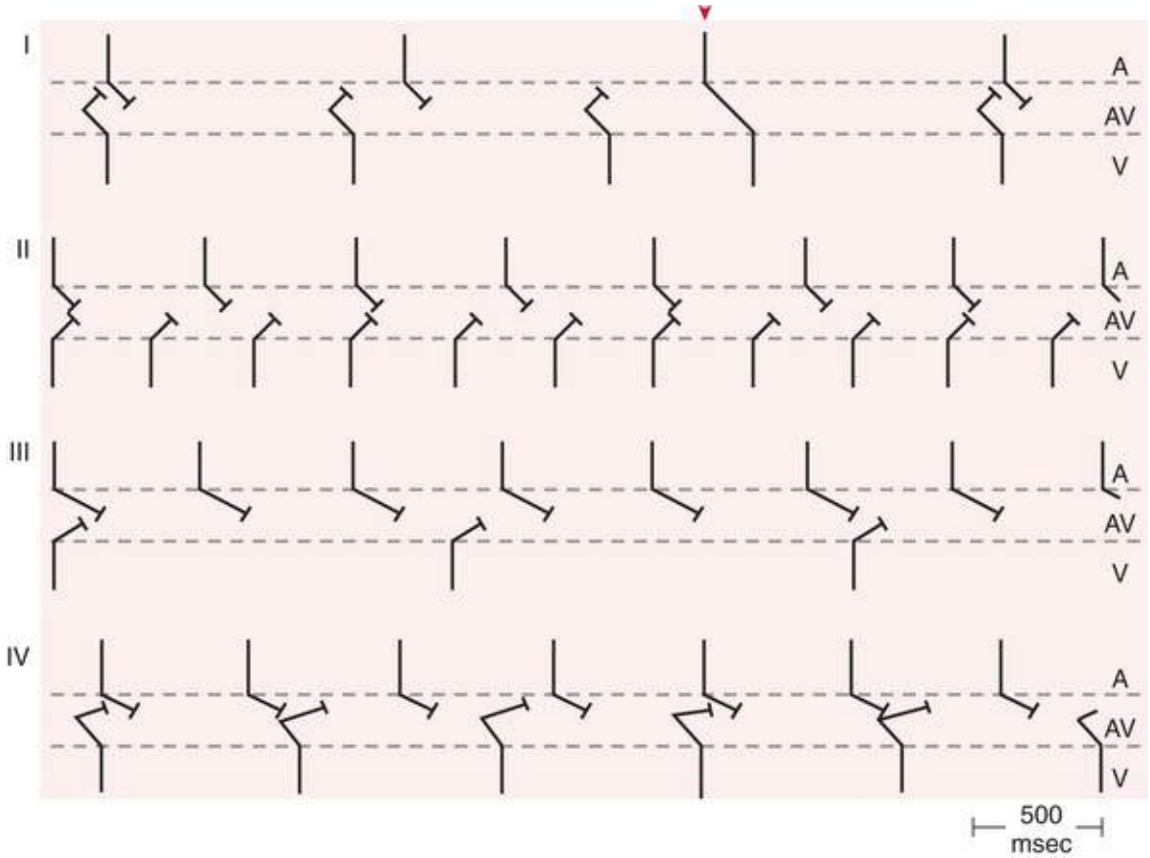
For patients with transient or paroxysmal AV block and presyncope or syncope, the diagnosis can be elusive. Ambulatory monitoring (Holter or external loop recorders) can be useful, but monitoring for longer periods may be necessary, with extended (>3 weeks) Holter or external loop recorders being

required. Longer periods of recording require an implantable loop recorder to establish the diagnosis. In patients with presyncope or syncope, one should suspect intermittent infrahisian block in those with BBB or an intraventricular conduction defect. An EPS to evaluate AV conduction thoroughly (including infusion of isoproterenol and/or procainamide) may be warranted to make the diagnosis, particularly in those with severe symptoms (**see Chapter 35**).

Drugs cannot be relied on to increase the heart rate for more than several hours to several days in patients with symptomatic heart block without producing significant side effects. Therefore, temporary or permanent pacemaker insertion is indicated for patients with symptomatic bradyarrhythmias. For short-term therapy, when the block is likely to be evanescent but still requires treatment or until adequate pacing therapy can be established, vagolytic agents such as atropine are useful for patients who have AV nodal disturbances, whereas catecholamines such as isoproterenol can be used transiently to treat patients who have heart block at any site (see earlier, Sinus Bradycardia). Isoproterenol should be used with extreme caution or not at all in patients with acute MI. The use of transcutaneous or temporary transvenous pacing is preferable. For symptomatic AV block or high-grade AV block (e.g., infrahisian, type II AV block, third-degree heart block not caused by congenital AV block), permanent pacemaker placement is the treatment of choice.[4,5] There is growing evidence that some patients with AV block, especially those with preexisting left ventricle dysfunction, may benefit from biventricular pacing rather than right ventricle–only pacing to prevent the development or progression of symptoms caused by heart failure.[6]

Atrioventricular Dissociation

As the term indicates, *dissociated* or *independent* beating of the atria and ventricles defines AV dissociation. AV dissociation is never a primary disturbance of rhythm but rather is a “symptom” of an underlying rhythm disturbance produced by one of three causes or a combination of causes that prevents the normal transmission of impulses from atrium to ventricle. See the online supplement for content on atrioventricular dissociation (**eFig. 40.9**).



EFIGURE 40.9 Diagrammatic illustration of the four causes of AV dissociation. A sinus bradycardia allowing escape of an AV junctional rhythm that does not capture the atria retrogradely illustrates cause I; intermittent sinus capture occur (arrow) and produce incomplete AV dissociation. For cause II, VT without retrograde atrial capture produces complete AV dissociation (**see Fig. 39.5 and eFig. 40.7**). As the third cause, complete AV block with a ventricular escape rhythm is diagrammed (**see Fig. 40.10 and eFig. 40.8**). In the **bottom panel,** the combination of causes II and III is shown, which represents a nonparoxysmal AV junctional tachycardia and some degree of AV block.

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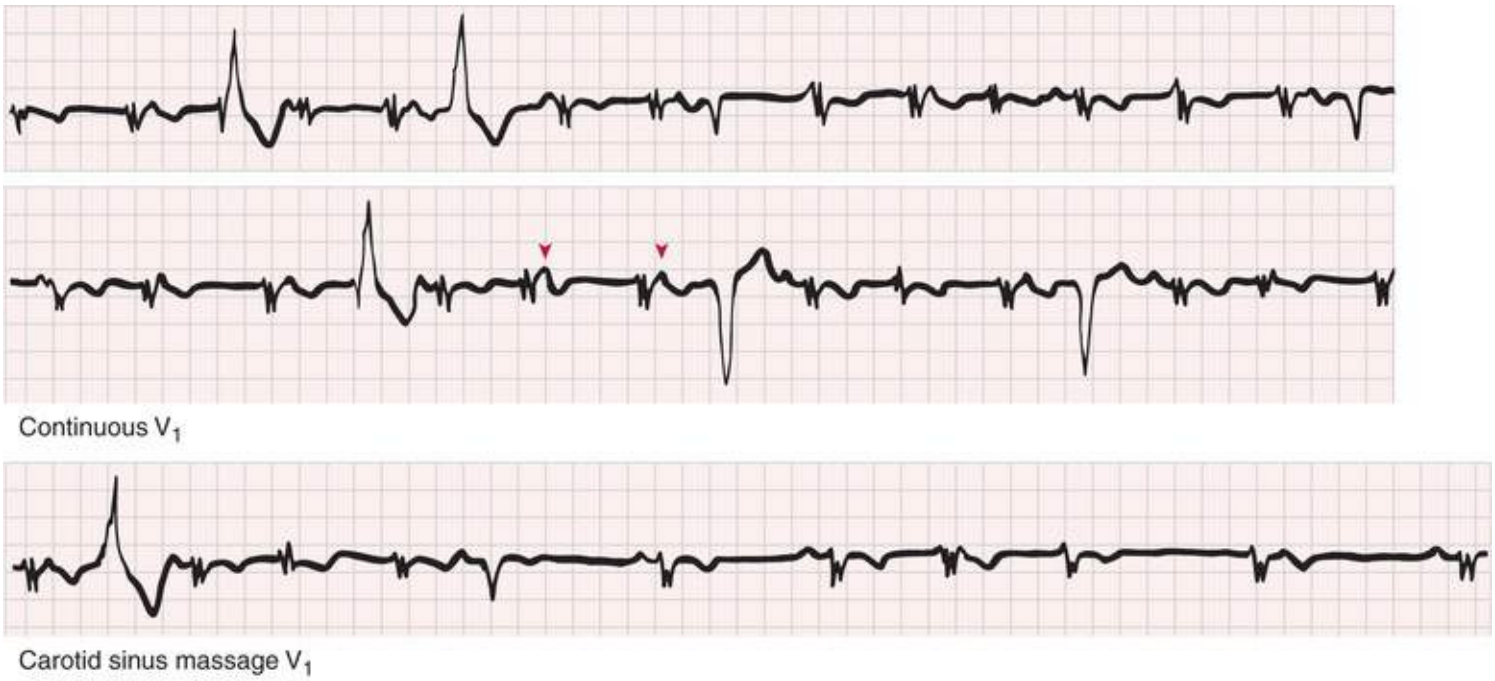
Atrioventricular Dissociation

Classification

1. Slowing of the dominant pacemaker of the heart (usually the sinus node), which allows escape of a subsidiary or latent pacemaker. Atrioventricular (AV) dissociation by default of the primary pacemaker to a subsidiary one in this manner is often a normal phenomenon. It may occur during sinus arrhythmia or sinus bradycardia and permit an independent AV junction rhythm to arise (**see Fig. 40.1A**).
2. Acceleration of a latent pacemaker, for example, a tachycardia in which the atria are not required and that usurps control of the ventricles. An abnormally enhanced discharge rate of a usually slower subsidiary pacemaker is pathologic and typically occurs during nonparoxysmal AV junctional tachycardia or VT without retrograde atrial capture (**eFig. 40.10**).
3. A block, generally at the AV junction, that prevents impulses formed at a normal rate in a dominant pacemaker from reaching the ventricles and allows the ventricles to beat under the control of a subsidiary pacemaker. Junctional or ventricular escape rhythm during AV block, without retrograde atrial capture, is a common example in which block gives rise to AV dissociation. Complete AV block is not synonymous with complete AV dissociation. Patients who have complete AV block have complete AV dissociation, but patients who have complete AV dissociation may or may not have complete AV block (**see Fig. 40.10 and eFig. 40.8**).
4. A combination of causes, as when excess digitalis results in the production of nonparoxysmal AV junctional tachycardia associated with sinoatrial (SA) or AV block.



EFIGURE 40.10 Nonparoxysmal AV junctional tachycardia in a healthy young adult. **Top,** This tachycardia occurs at a fairly regular interval (W-shaped complexes) and is interrupted intermittently with sinus captures that produce functional right and left bundle branch blocks. **Middle,** Two P waves are indicated by *arrowheads*. The junctional discharge rate is approximately 120 beats/min (cycle length = 500 msec), and the rhythm is irregular, sometimes shortened by sinus captures or delayed by concealed conduction that resets and displaces the junctional focus. **Bottom,** Carotid sinus massage slows both the junctional and the sinus discharge rates.

Mechanisms

With this classification in mind, it is important to emphasize that AV dissociation is not a diagnosis and is used in a manner similar to jaundice or fever. One must state that "AV dissociation is present and is caused by…" and then give the cause. An accelerated rate of a slower, normally subsidiary pacemaker and a slower rate of a faster, normally dominant pacemaker that prevents conduction because of physiologic collision and mutual extinction of opposing wavefronts (interference) or the manifestations of AV block are the basic disturbances producing AV dissociation. The atria in all these cases beat independently from the ventricles, under control of the sinus node or ectopic atrial or AV junctional pacemakers, and can exhibit any type of supraventricular rhythm. If a single pacemaker establishes control of both the atria and the ventricles for one beat (capture) or a series of beats (e.g., sinus rhythm, AV junctional rhythm with retrograde atrial capture [**see eFigs. 40.7 and 40.8**], ventricular tachycardia [VT] with retrograde atrial capture), AV dissociation is abolished for that period. Conversely, whenever the atria and ventricles fail to respond to a single impulse for one beat (premature ventricular complex without retrograde capture of the atrium) or a series of beats (VT without retrograde atrial capture), AV dissociation exists for that period. Interruption of AV dissociation by one or a series of beats under the control of one pacemaker, anterogradely or retrogradely, indicates that the AV dissociation is incomplete. Complete or incomplete dissociation can also occur in association with all forms of AV block. Usually, when AV dissociation results from AV block, the atrial rate exceeds the ventricular rate. For example, a subsidiary pacemaker with a rate of 40 beats/min can escape in the presence of a 2 : 1 AV block when the atrial rate is 78 beats/min. If the AV block is bidirectional, AV dissociation results.

Electrocardiographic and Clinical Features

The ECG demonstrates the independence of P waves and QRS complexes. P wave morphology depends on the rhythm controlling the atria—sinus, atrial tachycardia, junctional, flutter, or fibrillation. During complete AV dissociation, both the QRS complex and the P waves appear to be regularly spaced without a fixed temporal relationship to each other. When the dissociation is incomplete, a QRS complex with a supraventricular contour occurs early and is preceded by a P wave at a PR interval exceeding 0.12 second and within a conductible range. This combination indicates ventricular capture by the supraventricular focus. Similarly, a premature P wave with retrograde morphology and a conductible RP interval may indicate retrograde atrial capture by the subsidiary focus.

Physical findings include a variable intensity of the first heart sound as the PR interval changes, atrial sounds, and *a* waves in the jugular venous pulse lacking a consistent relationship to ventricular contraction. Intermittent large (cannon) *a* waves may be seen in the jugular venous pulse when atrial and ventricular contractions occur simultaneously. The second heart sound can split normally or paradoxically, depending on the manner of ventricular activation. A premature beat representing ventricular capture can interrupt a regular heart rhythm. When the ventricular rate exceeds the atrial rate, a cyclic increase in intensity of the first heart sound is produced as the PR interval shortens, climaxed by a very loud sound (bruit de canon). This intense sound is followed by a sudden reduction in intensity of the first heart sound and the appearance of giant *a* waves as the PR interval shortens and P waves “march through ” the cardiac cycle.

Management

Management is directed toward the underlying heart disease and precipitating cause. The individual components producing the AV dissociation, not the AV dissociation per se, determine the specific type of antiarrhythmic approach.

41

Pacemakers and Implantable Cardioverter-Defibrillators

Charles D. Swerdlow, Paul J. Wang, Douglas P. Zipes

Cardiac implantable electrical devices (CIEDs) deliver therapeutic electrical stimuli. An applied stimulus produces an electrical field that is proportional to the spatial derivative of the applied voltage (local change in voltage with respect to distance). This resultant field interacts with intrinsic cardiac

electrical activity. The response of the heart is mediated by the passive and active (ion channel) properties of cell membranes, by the properties of electrical connections between cardiac cells, and possibly by direct intracellular electrical effects (**see Chapter 34**).

Electrical therapy for cardiac arrhythmias includes low-voltage (1 to 5 V) pacing stimuli (pulses) and high-voltage (500 to 1400 V) stimuli (shocks). Pacemakers deliver pacing pulses to treat bradycardia. Implantable cardioverter defibrillators (ICDs) deliver shocks to defibrillate ventricular fibrillation (VF) or to cardiovert ventricular tachycardia (VT). They also deliver pacing pulses to treat bradycardia or sequences of rapid pacing pulses (antitachycardia pacing) to treat VT. Cardiac resynchronization therapy (CRT) pacemakers (CRT-P) or ICDs (CRT-D) also provide electrical therapy for heart failure in the form of pacing pulses that resynchronize the ventricular contraction sequence. This chapter covers antiarrhythmic electrical therapy delivered by CIEDs. See **Chapter 27** for CRT in the treatment of heart failure.

Pacemakers

Indications for Pacemakers

The Guidelines section at the end of this chapter provides guidelines for pacemakers and ICDs.[1] Pacemakers are indicated to relieve or prevent symptomatic bradycardia not resulting from a reversible cause. Although supported by strong expert consensus, these indications were developed before the era of randomized controlled trials (RCTs). The strongest indications relate to relief of symptoms confirmed to be caused by bradycardia. Pacing is also indicated in patients who have documented asymptomatic bradycardia and serious symptoms consistent with bradycardia, but no documentation of symptomatic bradycardia, provided that alternative causes for the symptoms have been excluded. Pacing is also indicated to prevent future symptomatic bradycardia in patients who are presently asymptomatic if the risk of rapid progression to serious symptoms is high. This indication is applied most frequently to patients with advanced disease of the His-Purkinje system who are at risk for abrupt, high-grade, atrioventricular (AV) block without an adequate escape rhythm (**see Chapter 40**).

Pacemaker Leads and Generators

Leads.
Transvenous pacemaker leads comprise a small, distal tip electrode for pacing and sensing with a fixation mechanism that anchors the lead to the heart, a proximal terminal that connects to the generator, and a lead body connecting the two (**Fig. 41.1A**). Unipolar leads have only a single-tip electrode. Bipolar leads have a second ring electrode located about 10 mm proximal to the tip. Pacemakers use a separate lead for each chamber paced.

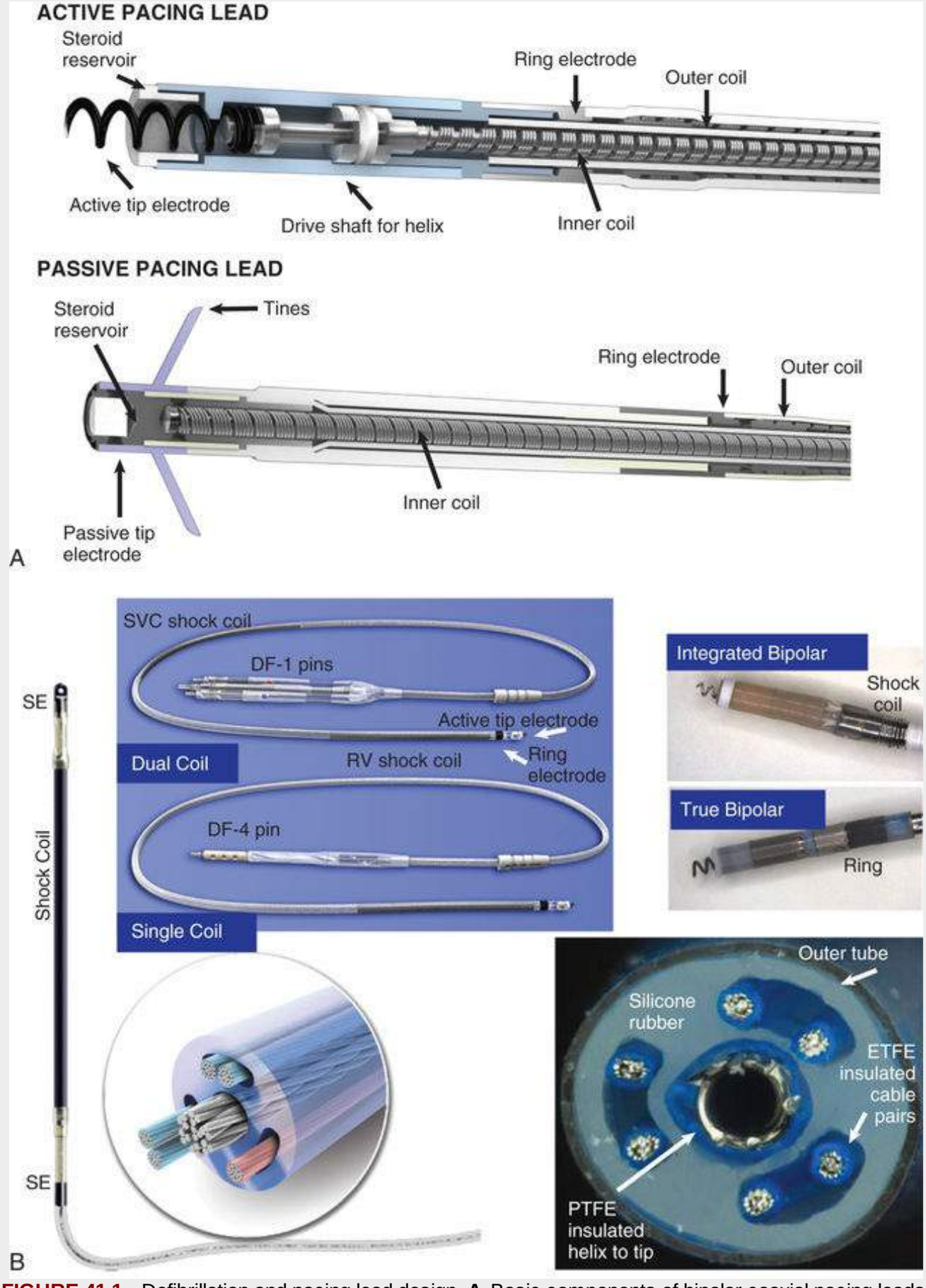


FIGURE 41.1 Defibrillation and pacing lead design. **A,** Basic components of bipolar coaxial pacing leads. **Top panel,** Active fixation design with helical screw serving as distal electrode. **Bottom panel,** Passive (tined design). **B,** Defibrillation leads. **Top left,** Dual-coil lead with DF-1 connector above single-coil lead with DF-4 connector. **Top right,** True bipolar *(top)* and integrated bipolar *(bottom)* defibrillation leads. The true bipolar lead senses between the distal tip and the proximal ring, which are dedicated for pacing and sensing. True bipolar leads have a single coil. In contrast, integrated bipolar leads pace and sense between the tip and the distal coil. The distal coil is used for sensing, pacing, and defibrillation. Integrated bipolar leads also contain a second, proximal coil, which increases the lead surface area for defibrillation.

Lower left, Subcutaneous ICD lead. **Lower right,** Cross section of transvenous ICD lead. *ETFE,* Ethyltetrafluoroethylene; *PTFE,* polytetrafluoroethylene; *RV,* right ventricular; *SE,* sensing electrode; *SVC,* superior vena cava.

Right atrial leads are frequently placed in or near the right atrial appendage. Most right ventricular (RV) leads are placed near the RV apex or septum; however, there is increasing interest in positioning RV leads to pace from or near the His bundle to improve the hemodynamics of RV pacing[2] (see later).

Generators.

Conventional pacemaker generators include a plastic header to which the leads are attached and a 10- to 15-cm^3 titanium casing or "can" that houses the battery, tiny capacitors that generate pacing pulses, and electronic circuitry for control and telemetry (**eFig. 41.1**). Battery performance must be predictable over time to provide an elective replacement indicator. Usually, generators are implanted subcutaneously over the pectoral muscle in the chest.

Recent advances in microelectronics permitted development of leadless capsule pacemakers[3,4] that comprise both the generator and the lead system. These pacemakers are placed in the RV endocardium through a catheter delivery system (**Fig. 41.2**) and thus are not susceptible to complications caused by transvenous leads. Leadless capsule pacemakers have two major limitations: first-generation devices permit only single-chamber ventricular pacing, and the feasibility of extracting chronically implanted devices is unknown.

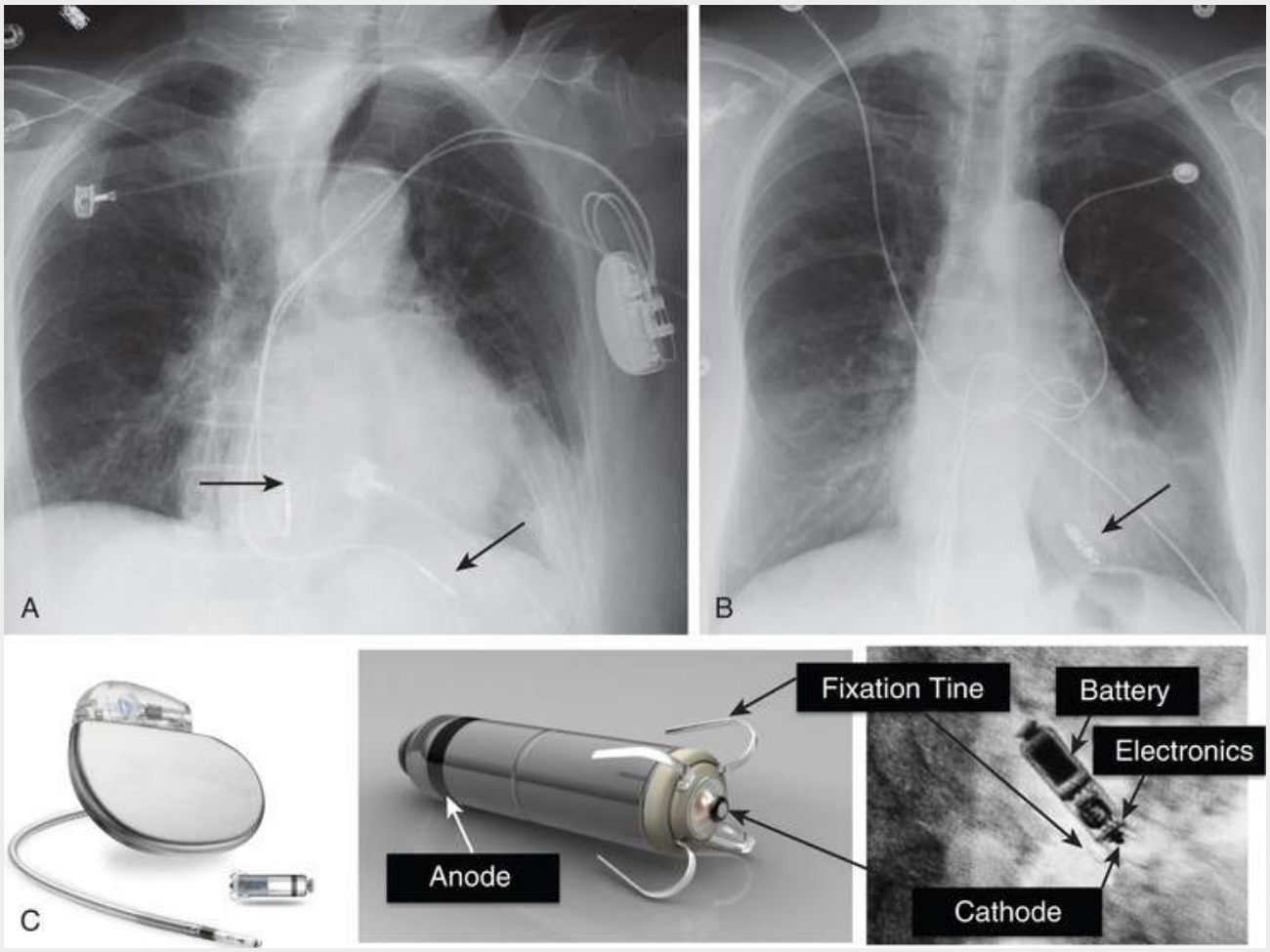
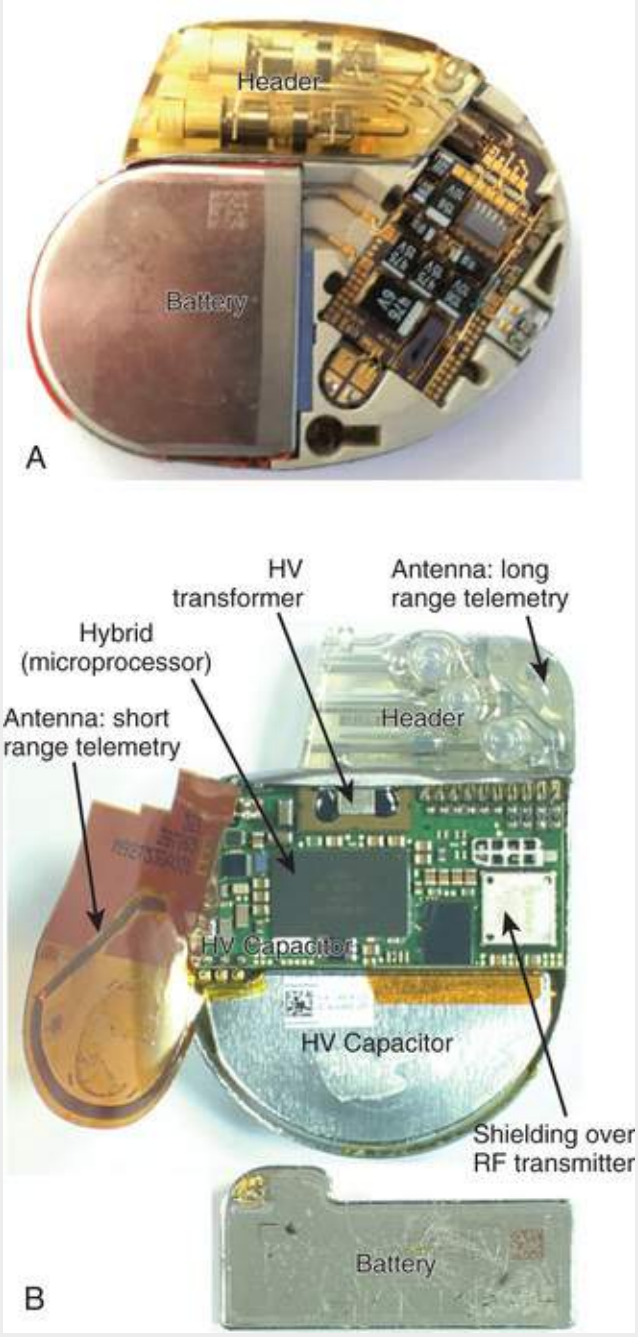


FIGURE 41.2 Transvenous versus leadless pacemakers. **A,** Radiograph of transvenous pacemaker with generator in left pectoral pocket. *Left arrow* denotes tip of atrial lead. *Right arrow* denotes tip of ventricular leads. Leads have active fixation screws. **B,** Radiograph of leadless capsule pacemaker implanted in right ventricular apical septum (*arrow*). **C, Left panel,** Transvenous pacemaker and lead to scale with one model of leadless capsule pacemaker. The lead's active fixation mechanism is shown in Fig. 41.1. **Middle panel,** Enlarged image of leadless capsule pacemaker. **Right panel,** Right anterior oblique cinefluoroscopy frame shows components of leadless capsule pacemaker.



EFIGURE 41.1 **A,** Pacemaker generator. **B,** Implantable cardioverter-defibrillator (ICD) pulse generator. The battery, which has been removed, fits under electronic components. See text for details. *HV,* High-voltage; *RF,* radiofrequency.

Principles: Capture, Sensing, and Hemodynamics of Pacing

Pacemakers sense intracardiac electrical signals (electrograms) and deliver low-voltage electrical stimuli (pulses) when the intrinsic cardiac rate is too slow.

Cardiac Electrical Stimulation.

Cardiac pacing requires a local stimulus that creates a field sufficient to depolarize (reduce the membrane potential of) local myocardium during diastole to threshold voltage and thus initiate a self-propagating wavefront of depolarization. A stimulus that brings local myocardium to threshold is said to "capture" it. Pacemaker electrodes with small surface area (1 to 5 mm^2) provide sufficient current

density to achieve a sufficient field strength (approximately 1 V/cm) with minimum battery energy.

Waveform.

The waveform of an electrical pulse is the temporal pattern of its amplitude, measured by voltage (or current). Voltage is a critical parameter for pacing because it determines the electrical field that interacts with the heart. In general, current is linearly related to voltage by Ohm's law (V = IR, where V is voltage, I is current, and R is resistance). Waveform duration is critical for characterization of either a pacing or a defibrillation waveform because the stimulus interacts with the heart for the duration of the waveform. Furthermore, the time course of the heart's response to the stimulus depends on time-dependent passive and active ion channel processes, collectively referred to as the *membrane time constant* (τ_m) (**see Chapter 34**). Either pacing or defibrillation pulses are most efficient when their durations approximate τ_m. Thus the most easily measured electrical parameter relevant to pacing is voltage (or current) as a function of time (**eFig. 41.2**).

Strength-Duration Relationship.

The strength-duration curve plots stimulus strength required for pacing as a function of pulse duration (**Fig. 41.3**). It can be represented by an inverse exponential or hyperbolic function. Two parameters, the rheobase and the chronaxie, characterize this curve. The *rheobase* is the minimum current for a pulse of infinite duration that results in depolarization. The *chronaxie* is the pulse duration on the curve that corresponds to twice the rheobase current; it approximates τ_m. The chronaxie is important for design of efficient pacing pulses because a pulse with duration equal to the chronaxie paces with the lowest energy. This is important for generator size and longevity.

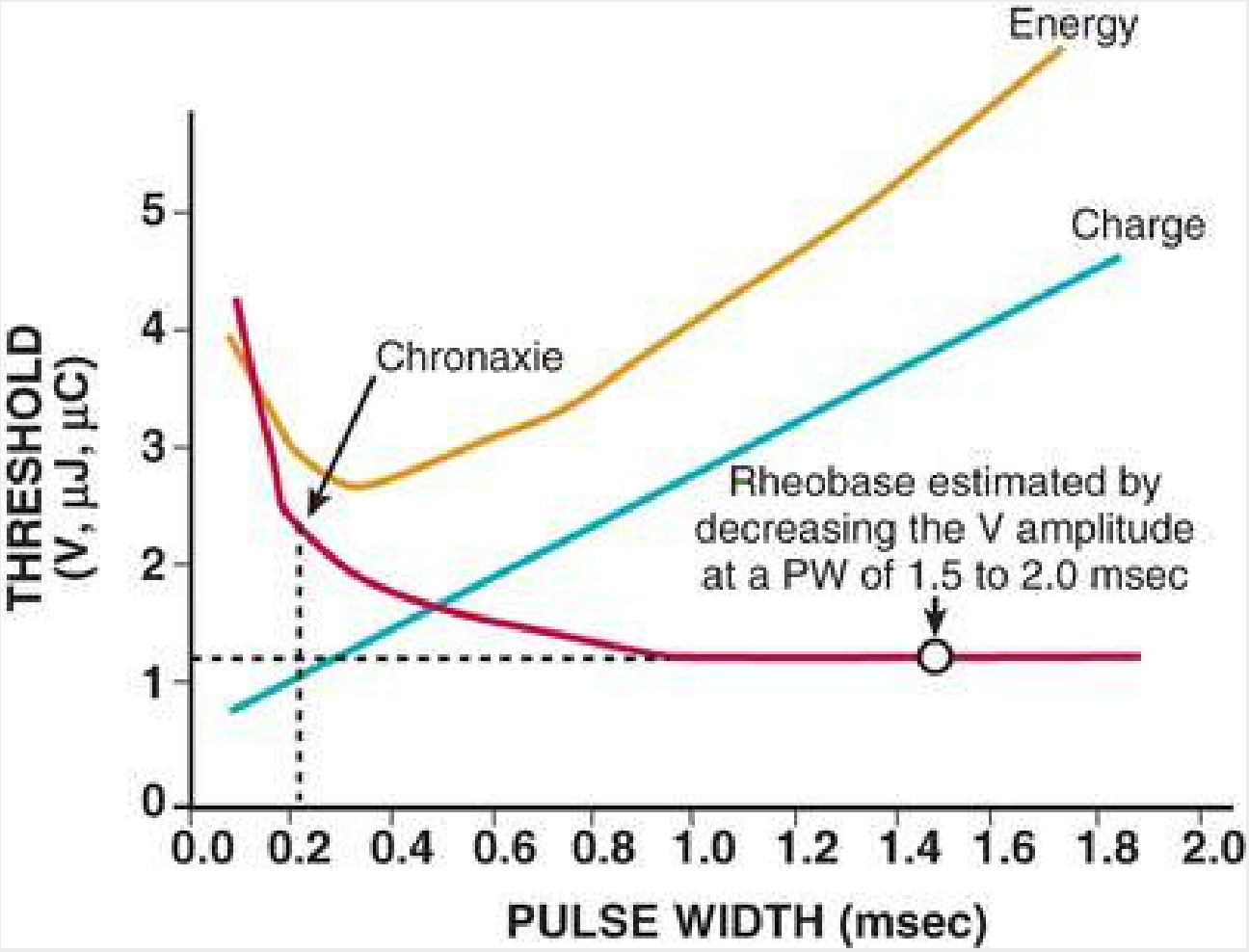


FIGURE 41.3 Relationships among chronic ventricular strength-duration curves from a canine, expressed as potential (V), charge (μC), and energy (μJ). Rheobase is the threshold at an infinitely long pulse width (PW) duration. Chronaxie is the pulse duration at twice the rheobase. (From Stokes K, Bornzin G. The electrode-biointerface stimulation. In Barold SS, editor. Modern Cardiac Pacing. Mount Kisco, NY: Futura; 1985, pp 33-77.)

Pacing Pulses: Polarity, Strength, and Duration.

Because pacing requires a voltage applied between two points, two electrodes are always required. However, in common use, the terms “unipolar” and “bipolar” refer to the number of intracardiac electrodes. Thus, *bipolar pacing* is performed between intracardiac cathodal tip and anodal ring electrodes. *Unipolar pacing* is performed between a cathodal tip electrode and the pacemaker generator housing that serves as the anode. Unipolar pacing at high outputs can result in pectoral muscle stimulation from voltage applied to the pacemaker can.

The durations of pacing pulses are optimized to capture with minimum energy consumption. Typically, voltage is set to a safety margin of 1.5 to 2 times the voltage threshold at durations near the chronaxie (0.4 to 0.5 msec for transvenous leads, 0.2 to 0.3 msec for leadless capsule pacemakers). Automatic assessment of pacing capture threshold is performed by closed-loop feedback algorithms that periodically measure the pacing threshold and adjust the output. When performed on a beat-to-beat basis, it can conserve battery by delivering safe pacing with an output minimally above the pacing threshold.

Metabolic and Drug Effects on Pacing Threshold.

The most clinically important metabolic abnormality is *hyperkalemia,* which raises pacing thresholds and alters sensing by causing conduction delays and local conduction block. Marked acidosis or alkalosis and profound hypothyroidism also raise the pacing threshold. **eTable 41.1** summarizes drug effects. Sodium channel–blocking drugs increase pacing thresholds. This is particularly true for class IC

drugs (e.g., flecainide) during pacing near the upper rate limit or antitachycardia pacing (ATP) because of use dependence, the enhancement of drug-induced sodium channel blockade at faster rates.

Electrograms and Pacemaker Sensing

Intracardiac Electrograms.

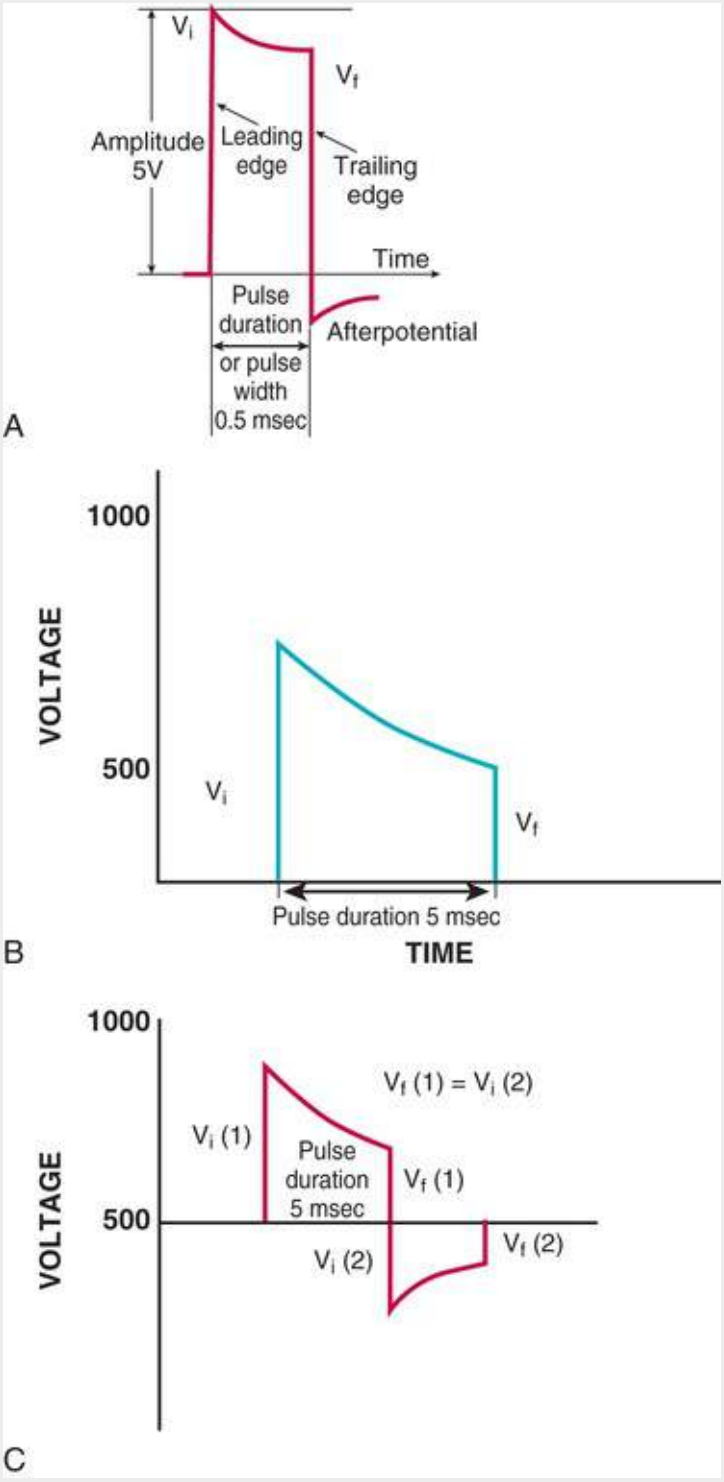
An electrogram (EGM) displays the electrical potential difference between two points in space as a function of time. The electrocardiogram (ECG), recorded from the body's surface, records electrical activity from much of the heart. In contrast, EGMs recorded from small intracardiac electrodes record only local activity. Because EGMs record a potential difference between two points, two electrodes are always required. However, as in pacing, the terms “unipolar” and “bipolar” refer to the number of intracardiac electrodes in the recording pair. *Unipolar* EGMs are recorded between a small electrode on the lead tip and a large remote (indifferent) electrode, the generator can. The location of the remote electrode has little effect on the EGM, but it may record noncardiac potentials, such as pectoral myopotentials. EGM signals that do not originate in local myocardium adjacent to the intracardiac electrode(s) are called *far-field signals*. These include both noncardiac signals and cardiac signals originating at a distance. In the context of CIEDs, far-field signals originate in a different cardiac chamber.

The typical amplitude of transvenous atrial and ventricular EGMs is in the range of 1.0 to 5 mV and 5 to 20 mV, respectively. The frequency content of ventricular and atrial EGMs is similar (5 to 50 Hz). T waves have lower frequency content (1 to 10 Hz), whereas most noncardiac myopotentials and electromagnetic interference (EMI) have higher frequencies (**eFig. 41.3**). This permits use of electronic bandpass filters to reduce sensing of signals that do not represent myocardial depolarization (oversensing).

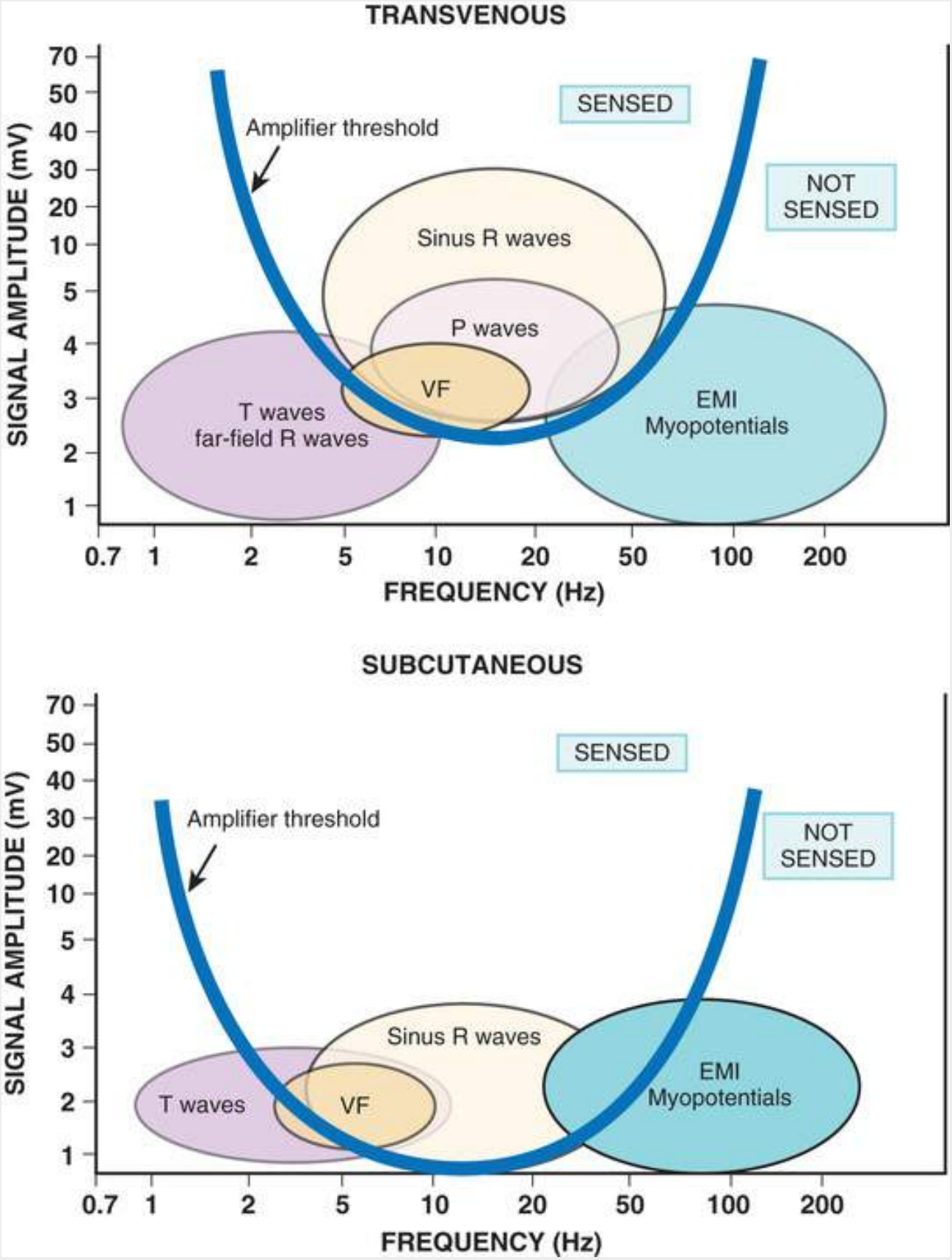
Sensing.

When a depolarization wavefront passes the tip electrode, a deflection in the EGM signal travels instantaneously through the electrode to the generator. There, the signal is amplified, filtered, processed by the sensing electronics, and compared to a threshold voltage (*sensing threshold*; **eFig. 41.4**). A sensed event occurs when the processed signal exceeds this sensing threshold, and the device determines that an atrial or ventricular depolarization has occurred.

Most pacemaker sensing thresholds are programmed to fixed values, typically about 2.0 mV for ventricular channels and 0.3 to 0.6 mV for atrial channels, with bipolar sensing to allow sensing of lower-amplitude P waves and atrial EGMs during atrial fibrillation (AF). Highly sensitive programmed values can result in *oversensing*, sensing of unintended signals not originating in the cardiac chamber of interest. EGMs sensed from a different cardiac chamber (usually ventricular signals sensed on the atrial channel) are referred to as *far-field* EGMs. Because the sensing dipole is smaller in bipolar sensing circuits than unipolar circuits, oversensing of noncardiac signals (e.g., pectoral myopotentials, EMI) is less likely to occur with bipolar sensing, especially with closely spaced electrodes.

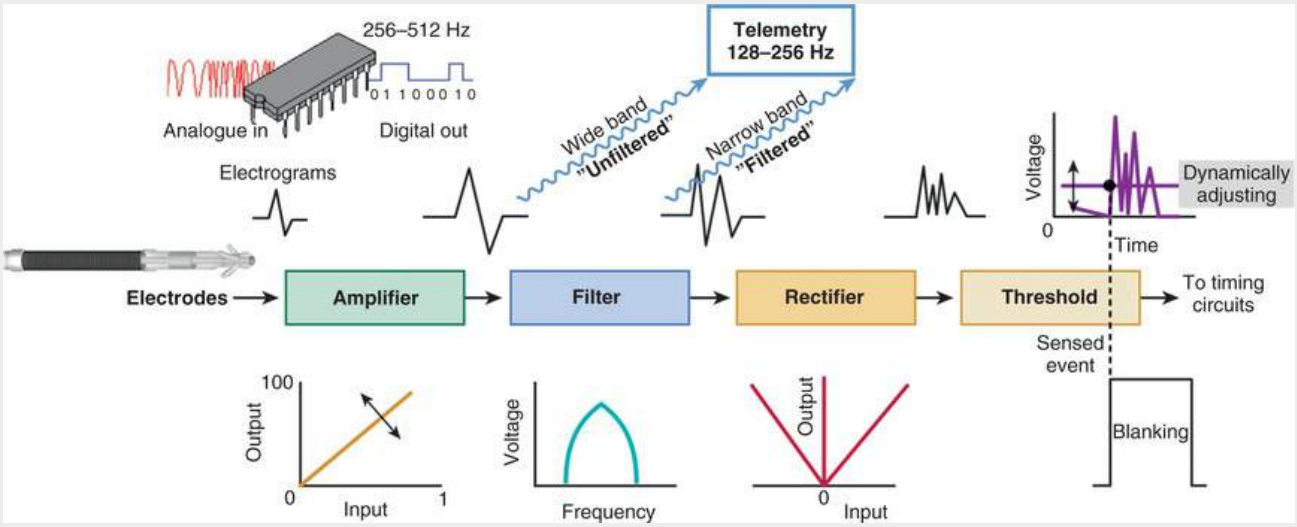


EFIGURE 41.2 Pacing and defibrillation waveforms. All pacing and defibrillation pulses in implantable devices have capacitive-discharge waveforms with a fixed leading-edge voltage and a trailing-edge voltage determined by the waveform duration and time constant. **A,** Pacing waveform. **B,** Monophasic truncated exponential waveform with initial voltage V_i and final voltage V_f. In comparison to the pacing waveform, the voltage is approximately 100 times greater, and the duration is approximately 10 times greater. **C,** Biphasic truncated exponential waveform with initial voltage of the second phase, V_i (2), equal to the final voltage of the first phase, V_f (1). This "single-capacitor" waveform is generated by reversing polarity during capacitor discharge and is the waveform used in all ICDs.



EFIGURE 41.3 Signal amplitude versus frequency. **Top,** Approximate characteristics of the premature ventricular beats (PVCs) and R waves that pacemakers and transvenous ICDs are intended to sense and characteristics of T waves that they are intended not to sense. The sense amplifier's filters are designed to sense signals that are above the U-shaped amplifier threshold curve and to reject signals that are below the curve. PVCs and R waves have higher dominant frequency than T waves. Myopotentials usually have higher-frequency components than intracardiac signals. T waves and far-field R waves have lower frequencies. As shown, there are overlaps in these amplitude-frequency characteristics that cause oversensing or undersensing in particular situations. The *ellipses* representing the amplitude-frequency characteristics in this figure are conceptual and are not based on quantitative measurements. **Bottom,** Corresponding diagram for electrograms (EGMs) recorded by subcutaneous ICDs. R wave amplitude and frequency content are lower. Thus there is more overlap with T waves, especially ventricular fibrillation

(*VF*). For subcutaneous ICDs, it is not possible to rely on filtering alone to reject T wave limits reliably while retaining accurate sensing in VF. *EMI,* Electromagnetic interference. (From: Swerdlow C, Brown M, Bordachar P. Sensing and detection with cardiac implantable electronic devices. In Ellenbogen KA, Kay GN, Lau CP, Wilkoff BL, editors. Clinical Cardiac Pacing, Defibrillation, and Resynchronization Therapy. 4th ed. Philadelphia: Saunders; 2016.)



EFIGURE 41.4 Functional block diagram of ICD sense amplifier. The analog differential EGM signal recorded between two implanted electrodes is first digitized at a sampling rate of 256 to 512 Hz and then amplified for subsequent processing. Bandpass filtering reduces the amplitude of lower-frequency signals such as T waves and far-field R waves and higher-frequency signals such as myopotentials and electromagnetic interference. Both the wide-band (unfiltered) and narrow-band (filtered) signals are down-sampled to 128 to 256 Hz for telemetry. After filtering, the signal usually is rectified to nullify effects of polarity. The threshold operation compares the amplitude of the amplified, filtered, and rectified signals with the sensing threshold voltage. The ICD's timing circuits record a sensed event at the instant the amplitude of the processed signal exceeds the threshold voltage. After sensing, the amplifier is blanked (turned off) for a short period, so that each depolarization is sensed only once. In older ICDs, the blanking period displayed on the programmer represented true hardware blanking. In modern ICDs, hardware blanking lasts only 20 to 30 milliseconds, followed by software blanking in which the ICD does not display or count signals that exceed the sensing threshold. Programmable values control the high and lower limits on the sensing threshold, which automatically adjusts on a beat-by-beat basis (see text discussion). Circuit designs may integrate some functions, such as amplification and filtering. (From Swerdlow CD, Asirvatham SJ, Ellenbogen KA, Friedman PA. Troubleshooting implanted cardioverter-defibrillator sensing problems. I. Circ Arrhythm Electrophysiol 2014;7(6):1237-61.)

ETABLE 41.1

Common Interactions Between Drugs and Pacemakers/Implantable Cardioverter-Defibrillators (ICDs)

Pacemakers
Effects on Pacing Threshold
Higher threshold
Class 1C drugs (e.g., flecainide)
Amiodarone (chronic effect, especially atrial thresholds)
Lower pacing threshold
Glucocorticoids
Isoproterenol and epinephrine
Effect on Pacing Burden
Increased atrial pacing burden: drugs that cause sinus bradycardia (e.g., beta blockers, amiodarone, lithium)
Increased ventricular pacing burden: drugs that slow AV conduction (e.g., beta blockers, amiodarone)
ICDs
Frequency of VT or VF
Increased
Antiarrhythmic drugs
Drugs with proarrhythmic side effects
Drugs that interact with proarrhythmic drugs
Decreased
Beta blockers
Antiarrhythmic drugs (e.g., sotalol, amiodarone)
Consideration for Detection of VT or VF
VT rate
Decrease (most oral antiarrhythmic drugs, especially class 1C, amiodarone)
SVT/AF ventricular rate
Decrease (beta blockers, amiodarone, sotalol)
Increase (class 1C drugs, 1 : 1 conduction of atrial flutter)
Device SVT-VT discrimination algorithms
VT interval stability (class IC drugs, amiodarone: more irregular)
Altered EGM morphology
Therapy for VT or VF
Defibrillation energy requirement
Increase (class IB, class IC, chronic amiodarone, verapamil)
Decrease (sotalol, dofetilide)

AF, Atrial fibrillation; *AV,* atrioventricular; *EGM,* electrogram; *SVT,* supraventricular tachycardia; *VF,* ventricular fibrillation; VT, ventricular tachycardia.

Hemodynamics Related to Pacing

Chronotropic Response and Rate-Adaptive Pacing

Heart rate and stroke volume determine cardiac output, which increases fivefold to sixfold from rest to meet metabolic demands of peak exercise. The ability to increase heart rate with exertion (chronotropic competence) provides most of this increase as exertion approaches its peak.

Rate-adaptive pacing adjusts the pacing rate to the metabolic demands of the body. A sensor located in the pacemaker generator or lead monitors a signal that indicates the need for a faster rate. Common sensors monitor body motion (accelerometer), respiration (minute ventilation), or cardiac motion (endocardial acceleration); each has specific advantages and limitations. Some pacemakers combine two sensors (blended sensor) in designs intended to maximize the benefits and minimize the limitations of each sensor. Algorithms translate the sensor values to pacing rate. Most algorithms have programmable parameters to achieve the optimal heart rate for the body's metabolic needs.

Atrioventricular Synchrony

Atrial filling of the left ventricle begins in early diastole and continues as long as the mitral valve remains open. Immediately before ventricular systole, the atria contract, resulting in a bolus of blood (atrial transport) that contributes appreciably to ventricular stroke volume. Maximizing this atrial contribution to

cardiac output requires optimal timing of atrial systole immediately before ventricular systole, atrioventricular synchrony. Loss of physiologic AV synchrony may reduce cardiac output by 20% to 25%. Patients with impaired diastolic function or impaired systolic function are most dependent on atrial transport. Patients with long PR intervals exhibit several causes of mechanical AV dyssynchrony (despite electrical synchrony), depending on the degree of PR prolongation.[5] Thus, in dual-chamber pacemakers, the AV delay is programmed to achieve efficient AV mechanical synchrony.

Any condition that alters the timing of atrial or ventricular electrical activation can impair mechanical AV synchrony. *Pacemaker syndrome* refers to the constellation of symptoms caused by loss of AV synchrony, including fatigue, shortness of breath, chest pain, headache, and neck pulsations. It may occur with AV dissociation or 1 : 1 AV association that results in an adverse sequence of ventricular and atrial contraction. The most hemodynamically disadvantageous AV timing relationship occurs during ventricular pacing with retrograde (V-A) conduction, resulting in reverse (VA) synchrony and atrial contraction while the mitral and tricuspid valves are closed.

Effect of Ventricular Pacing on Synchrony of Ventricular Contraction

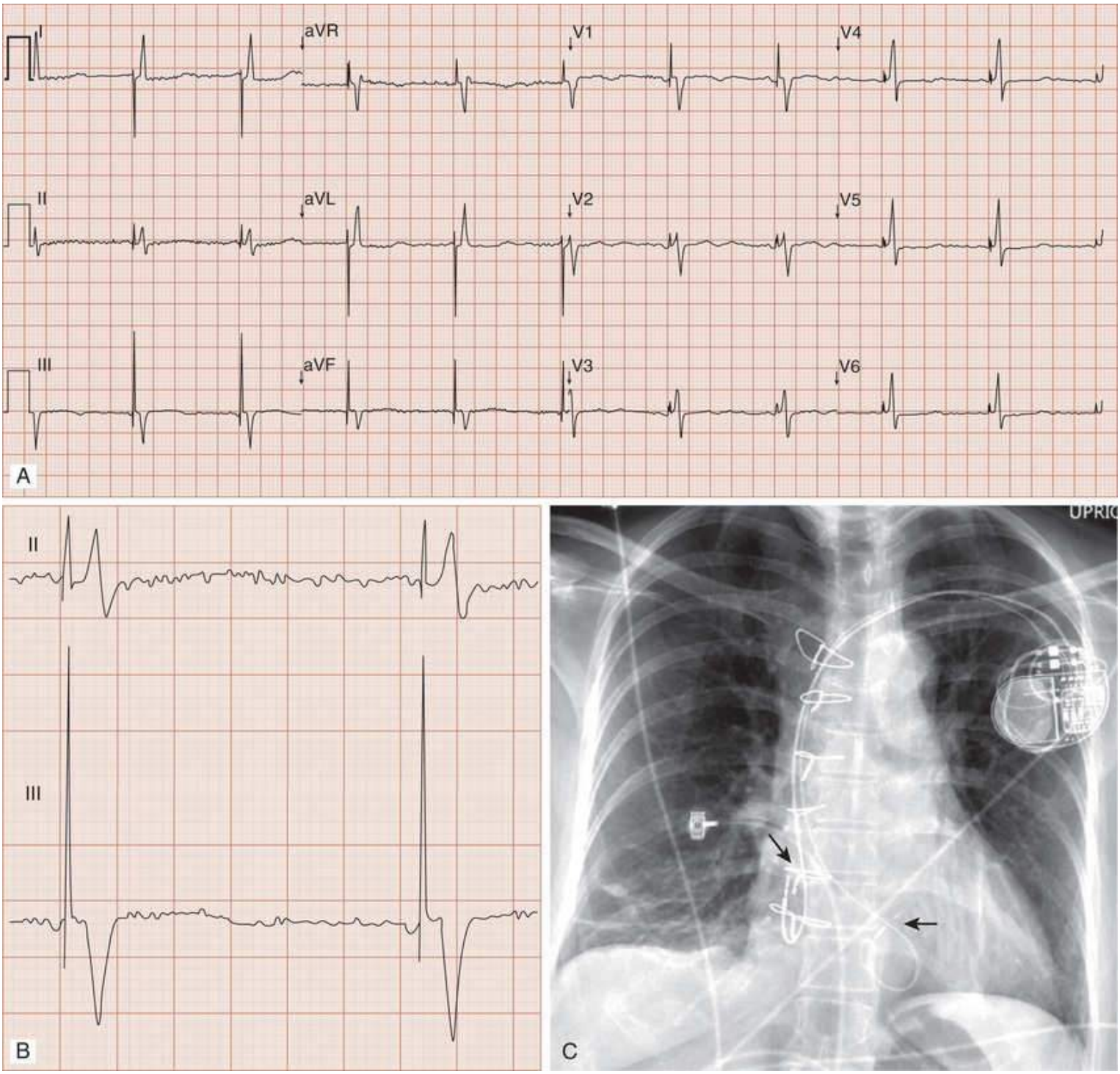
Adverse Consequences of Right Ventricular Pacing.

In patients with impaired AV conduction, DDD pacing ensures that the AV interval is in the physiologic range. However, right ventricular (RV) apical pacing produces both intraventricular and intraventricular dyssynchrony,[2] even if the pacing pulse is synchronized to the atrial impulse. Pacing alternative RV sites such as the septum and outflow tract have not reduced dyssynchrony consistently. Pacing-induced dyssynchrony is hemodynamically-significant in patients with left ventricular (LV) dysfunction, in whom it increases the incidence of heart failure (HF) and persistent AF[2] (**see Chapter 27**).

Dual-chamber programming strategies that promote intrinsic AV conduction can minimize RV pacing in patients with AV conduction (see later). In patients with normal PR intervals, these strategies retain hemodynamic AV synchrony; but in patients with long PR intervals, they sacrifice some or all of the hemodynamic benefits of AV synchrony to avoid RV pacing–induced dyssynchrony. Further, these strategies cannot be used in patients with persistent AV block.

Permanent His Bundle Pacing.

An alternative approach is to pace the His bundle using an active-fixation RV lead.[2,6] The paced QRS complex activates the ventricle over the physiologic His-Purkinje system, restoring ventricular electrical synchrony in patients with normal ventricular conduction and in some with bundle branch block (**eFig. 41.5**). Compared with RV apical pacing, small randomized studies indicate that His Bundle pacing improves exercise capacity, ventricular synchrony, and LV ejection fraction (LVEF); observational data indicate that it reduces HF hospitalizations. However, His bundle pacing using present technology has limitations. Experienced operators achieve procedural success in only about 80% of cases, and pacing thresholds are more than twice as high as RV thresholds, reducing generator longevity.



EFIGURE 41.5 Permanent His bundle pacing. **A,** 12-Lead ECG shows atrial synchronous ventricular pacing with narrow QRS complex. **B,** Enlarged image of leads II and III. There is a 35-millisecond isoelectric interval between pacing stimulus and QRS corresponding to the His-ventricular (HV) conduction interval between His bundle and ventricular myocardium. **C,** *Left arrow* in radiograph denotes atrial lead tip in lateral right atrium. *Right arrow* denotes ventricular lead in His Bundle.

Pacemaker Mode and Timing Cycles

Definitions

Pacing modes describe which chambers are sensed and paced and are characterized by a four-letter code (**Table 41.1**). The first letter indicates the chamber paced: A for atrium, V for ventricle, and D for dual—both atrium and ventricle. The second letter denotes the chamber sensed. The third letter describes pacemaker function: I for inhibition, T for triggered, and D for dual—tracking of atrial activity but

inhibited by ventricular activity. “O” indicates absence of any of these functions. The fourth letter is R, for rate-adaptive pacing.

TABLE 41.1

NASPE/BPEG Generic Code for Bradycardia Pacing

	POSITION			
	I	II	III	IV
Category	Chamber(s) paced	Chamber(s) sensed	Response to sensing	Rate modulation
	O = None	O = None	O = None	O = None
	A = Atrium	A = Atrium	T = Triggered	R = Rate modulation
	V = Ventricle	V = Ventricle	I = Inhibited	
	D = Dual (A + V)	D = Dual (A + V)	D = Dual (T + I)	
Manufacturers' designation only	S = Single (A or V)	S = Single (A or V)		

See text for explanation of use of the code.

BPEG, British Pacing and Electrophysiology Group; *NASPE,* North American Society of Pacing and Electrophysiology.

Modified from Bernstein AD, Daubert JC, Fletcher RD, et al. The revised NASPE/BPEG generic code for antibradycardia, adaptive-rate, and multisite pacing. Pacing Clin Electrophysiol 2002;25:260.

Timing cycles are the rules that define a pacemaker's beat-by-beat response to sensed and paced beats. Often it is easier to analyze timing cycles in terms of their associated time intervals measured in milliseconds (msec) rather than in rate measured in beats per minute (bpm). Since 1 minute is equivalent to 60,000 milliseconds, the interval in milliseconds corresponding to a rate in beats per minute can be determined by dividing the 60,000 by the rate (**eTable 41.2**).

ETABLE 41.2

Interval (milliseconds) vs. Rate (beats per minute)

Bradycardia						
Interval (msec)	1500	1200	1000	800	700	600
Rate (bpm)	40	50	60	75	86	100
Tachycardia						
Interval (msec)	450	400	360	350	320	300
Rate (bpm)	133	150	167	171	188	200

Specific Pacing Modes

The *VVI* mode is the basic single-chamber ventricular mode. Pacing occurs when the ventricular rate slows below the programmed *lower rate limit* (**Fig. 41.4**). The interval corresponding to the lower rate limit is the ventricular pacing interval. Usually, this is equal to the interval between a sensed ventricular event and the next paced ventricular event, referred to as the “ventricular escape interval.” There is no atrial sensing, so AV synchrony is not preserved. This mode is indicated in patients with permanent AF and in those in whom AV synchrony is less important than simplicity of the pacing system.

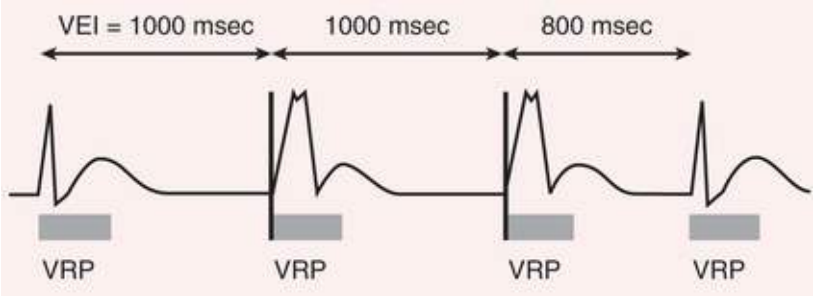


FIGURE 41.4 The VVI timing cycle consists of a defined lower rate limit and a ventricular refractory period (VRP, represented by *rectangles*). When the ventricular escape interval (VEI) from the ventricular sensed event of 1000 milliseconds is completed, a paced event occurs. Because no ventricular sensed event occurs within 1000 milliseconds after the paced event, a second ventricular paced event occurs. Because a ventricular sensed event occurs 800 milliseconds later, a ventricular paced event does not occur. A VRP begins with any sensed or paced ventricular activity.

The *AAI* mode is the corresponding single-chamber atrial pacing mode (**Fig. 41.5**). It is appropriate for patients with sinus node dysfunction and intact AV conduction. Because it does not provide ventricular pacing, AAI mode should not be used in patients who are at risk for AV block.

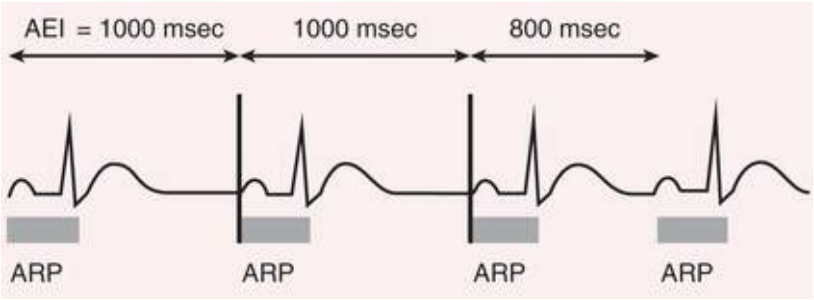


FIGURE 41.5 The AAI timing cycle consists of a defined lower rate limit and an atrial refractory period (ARP, represented by *rectangles*). When the atrial escape interval (AEI) from the atrial sensed event of 1000 milliseconds is completed, a paced event occurs. Because no atrial sensed event occurs within 1000 milliseconds after the paced event, a second atrial paced event occurs. Because an atrial sensed event occurs 800 milliseconds later, an atrial paced event does not occur. An ARP begins with any sensed or paced atrial activity.

The *DDD* pacing mode preserves AV synchrony whenever possible (**Fig. 41.6**). In DDD mode the atrial rate cannot go lower than the programmed lower rate. The AV delay is the maximum permitted time from an atrial event to a ventricular event. If a spontaneous ventricular event does not occur by the time the AV delay elapses, a ventricular paced event occurs. In the setting of AV block, all ventricular events are paced. The special characteristic of the DDD pacing mode is the ability to “track” intrinsic atrial activity so that a ventricular beat follows each P wave in order to maintain AV synchrony. The *upper rate limit* is the maximum rate at which intrinsic atrial activity will be tracked, and it is selected to exceed the patient's maximum sinus rate. The upper rate limit prevents rapid ventricular tracking of atrial activity in AF and other atrial tachyarrhythmias.

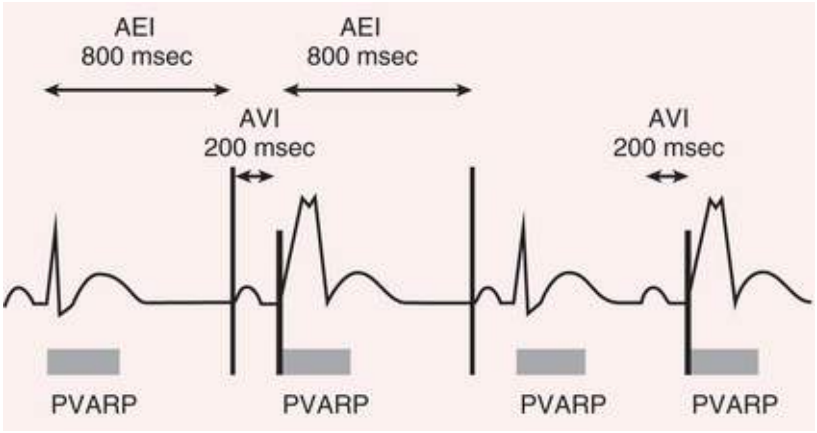
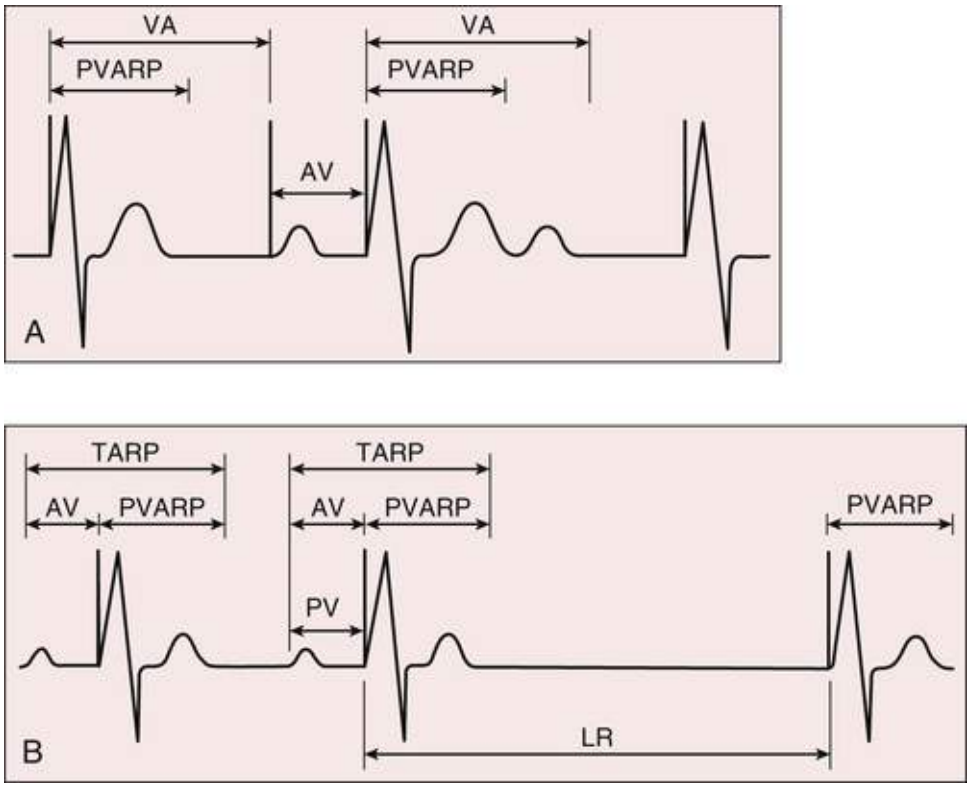


FIGURE 41.6 The timing cycle in DDD consists of a lower rate limit, an AV interval, a ventricular refractory period (not shown), a postventricular atrial refractory period (PVARP), and an upper rate limit. Because an intrinsic atrial event occurs and is followed by an intrinsic ventricular event within the AV interval, no ventricular pacing occurs in the first beat. In ventricular-based timing, the time from a ventricular paced or sensed event to the next atrial paced event is called the atrial escape interval (AEI), which is the lower rate limit interval minus the AV interval. Because no intrinsic atrial event occurs before the AEI times out, a paced atrial event occurs in the second beat. Since no intrinsic ventricular event occurs within the AV interval after this atrial paced event, a ventricular paced event occurs. Following this ventricular paced event an atrial paced event is delivered when the AEI times out 800 milliseconds later to initiate the third beat. Since AV conduction follows this atrial paced event, ventricular pacing is inhibited. The fourth beat begins with an intrinsic atrial event that is not followed by an intrinsic ventricular event within the AV interval. Hence the intrinsic atrial event is "tracked" and followed by a paced ventricular event.

The DDI and VDD pacing modes comprise complementary subsets of DDD functionality (**eFig. 41.6**). The *DDI* mode lacks atrial tracking and is suitable for patients with sinus bradycardia, with or without intact AV conduction. Because AV synchrony is lost when the sinus rate exceeds the lower rate limit, the DDI mode is rarely programmed unless atrial sensing problems prevent reliable mode switching in DDD mode. The *VDD* mode lacks atrial pacing and is suitable for patients with normal sinus node function and AV block. It can be achieved using a single lead with additional atrial sensing electrodes, permitting ventricular tracking of atrial activity to achieve AV synchrony. The VDD mode should not be used in patients with sinus bradycardia, since ventricular pacing without AV synchrony will occur at the lower rate limit, equivalent to the VVI mode.



EFIGURE 41.6 **A,** DDI pacing mode. **B,** VDD pacing mode. See text for details and abbreviations.

Optimizing Dual-Chamber Pacing

Automatic Mode Switching

The DDD and VDD pacing modes need a method to prevent rapid ventricular pacing as a result of ventricular tracking of atrial EGMs during paroxysmal AF, other atrial tachyarrhythmias, or EMI. Automatic mode switching initiates a temporary mode change to a nontracking mode (usually DDI or DDIR) in response to an atrial sensed rate above a specified value. When the atrial rhythm slows sufficiently, the mode switches back to an atrial tracking mode (**Fig. 41.7**).

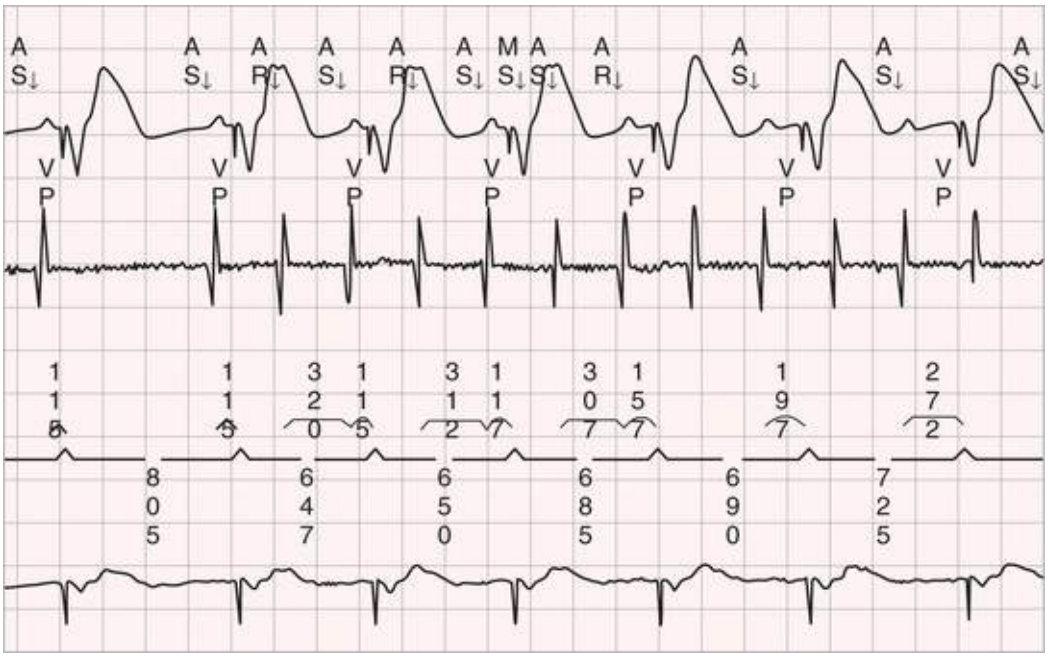


FIGURE 41.7 Mode switch from the DDDR to the DDIR mode during transient atrial tachycardia (AT). The top channel is the surface electrocardiogram (ECG) with markers. The second channel is the atrial electrogram (EGM). The third channel displays atrial intervals above the line and ventricular intervals below the line. The bottom channel is the ventricular EGM. The first two atrial events (AS) are sinus beats tracked with the programmed interval for atrial synchronous pacing. The AT begins with the third atrial event. Mode switch (MS) occurs after the fourth rapid atrial event interval. In the DDI mode, P waves are not tracked, so the AV interval varies. AS, Atrial sense; AR, event in atrial refractory period; VP, ventricular pace.

"Noise" reversion algorithms are intended to prevent pacemaker inhibition during continuous ventricular oversensing, such as that occurring during EMI. They initiate a fixed-rate, asynchronous pacing modes (DOO, VOO) for the duration of oversensing.

Programming to Avoid Unnecessary Right Ventricular Pacing

Facilitating AV conduction is important to minimize RV pacing in patients without permanent AV block. The first approach was to prolong the AV interval or extend it periodically ("positive search AV hysteresis"). The primary limitation is that it may result in extremely long AV delays that cause pacemaker syndrome.[5] There is no consensus about the maximal acceptable PR interval, but 350 to 400 milliseconds is typically used.

A second strategy is a variation on AAIR pacing with backup ventricular pacing. Some algorithms use the AAIR pacing mode when AV block is not present but switch automatically to a DDDR mode when AV block is detected. This strategy can be tolerant of occasional single beats of AV block without resorting to consistent RV pacing, and thus delivers less RV pacing than strategies that prolong the AV interval. However, it may mimic intermittent failure of ventricular pacing for a single beat (**Fig. 41.8**). Another variation is AAIR pacing with backup VVIR pacing.

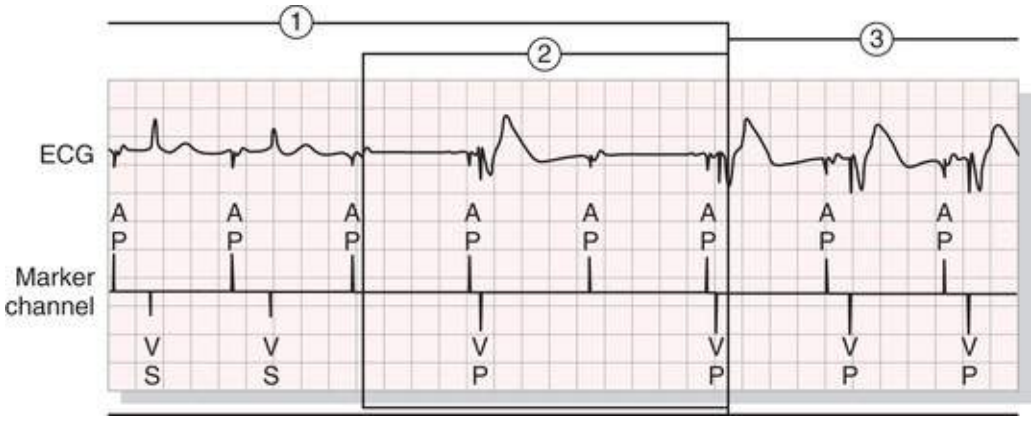


FIGURE 41.8 One algorithm to minimize right ventricular pacing. Initially, AAIR pacing is seen *(1)*; if an atrial pace event occurs without a ventricular sensed event, a ventricular backup output occurs *(2)*, and the pacemaker then switches to the DDDR mode *(3)*. The paced AV interval after a nonconducted beat has a short AV delay (80 msec).

Single- versus Dual-Chamber Pacing Mode and Pacemaker Selection

An expert consensus document provides recommendations for selection of single- versus dual-chamber pacemakers.[7] **Fig. 41.9** provides a simplified overview.

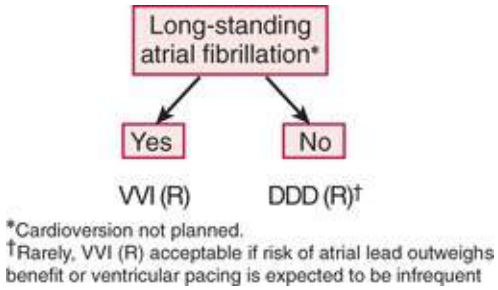


FIGURE 41.9 Selection of pacemaker modes and generators. See text for details.

Sinus Node Disease.

In patients with sinus node disease, RCTs demonstrate that DDD pacing reduces AF and pacemaker syndrome in comparison with VVI pacing.[8] These studies report inconsistent results regarding mortality, reduction in HF, stroke, and quality of life.[7] Rate-adaptive pacing is recommended for patients with significant, symptomatic *chronotropic incompetence*, the inability to increase heart rate for metabolic needs of exertion. When programming AAIR, it is important that the sensor-driven atrial rate is not fast enough to cause AV block.

AV Block and Bifascicular/Trifascicular Block.

Expert consensus recommends dual-chamber pacing over single-chamber ventricular pacing provided sinus rhythm is present.

Blanking and Refractory Periods

Definitions.

After each paced or sensed event, the sense amplifier is turned off for a short hardware *blanking period* (20 to 250 msec) to prevent multiple sensed events during a single cardiac depolarization. The blanking period's role is particularly important following a paced event because of the large amplitude signal and polarization effect. Following each blanking period, there is usually a software *refractory period* during which sensed events are not used to reset the timing cycle but may be used to calculate rate for features such as mode switching (**Fig. 41.10**). Some newer pacemakers include additional software blanking. Events "sensed" during software blanking periods are not used to control timing cycles, but may be used for specialized functions, such as detecting oversensing or atrial arrhythmias.

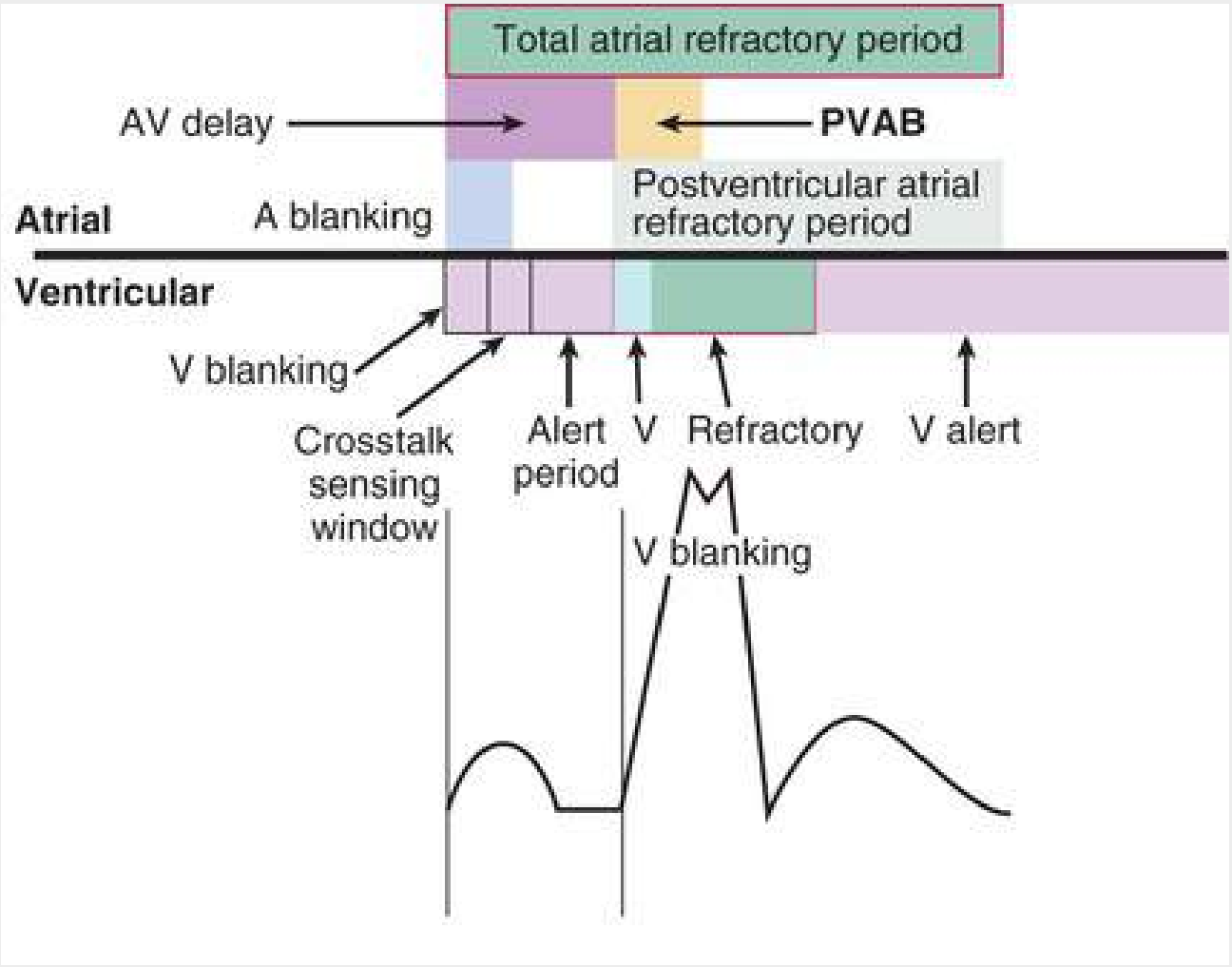
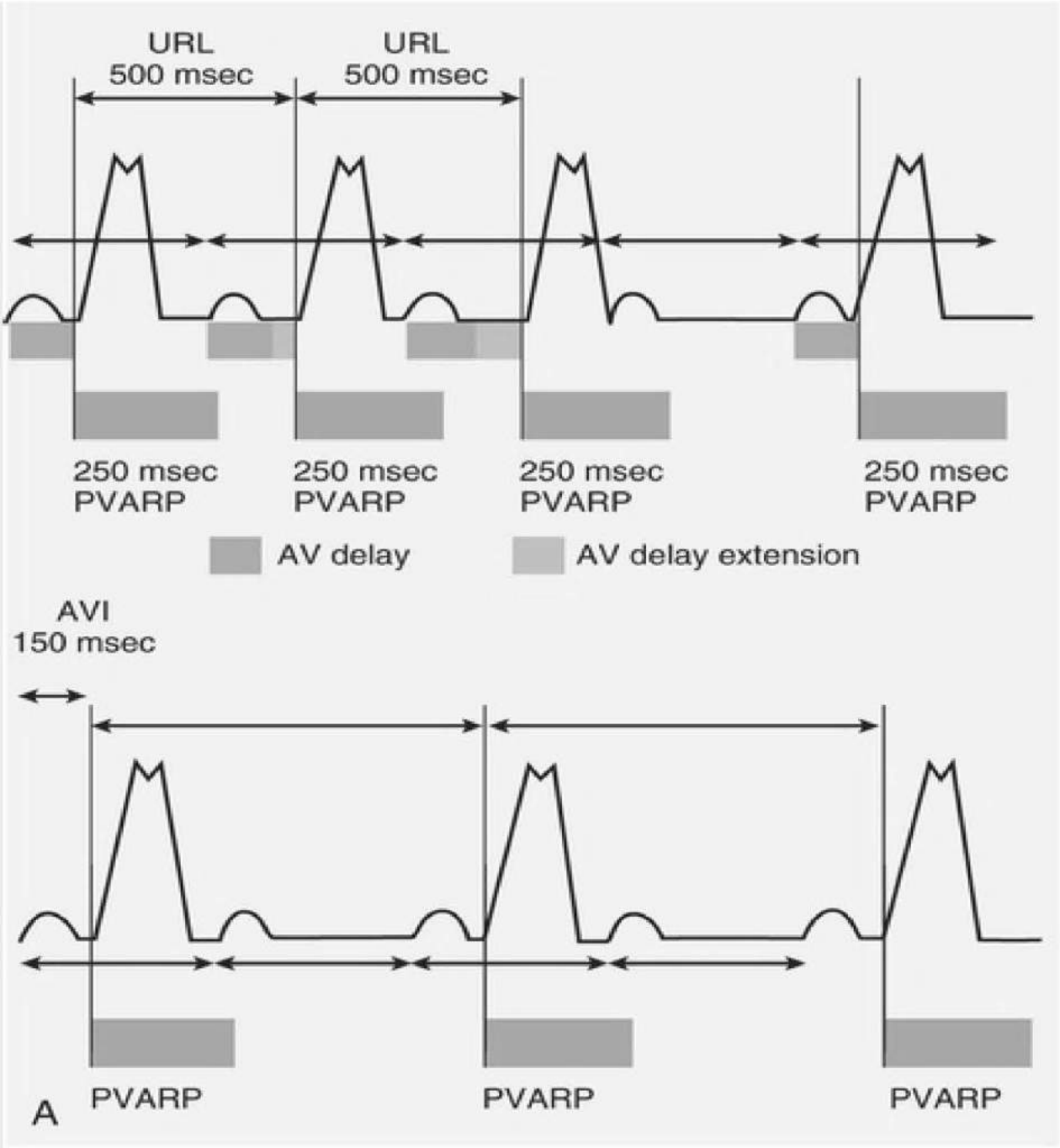


FIGURE 41.10 Schematic representation of the timing cycle interactions of most refractory and blanking periods in contemporary dual-chamber pacemakers. **Top,** Atrial channel; **bottom,** ventricular channel. Total atrial refractory period (TARP) is the sum of the AV delay and the postventricular atrial refractory period (PVARP). Postventricular atrial blanking (PVAB) is the time that the atrial channel is blanked after a ventricular event. "A blanking" is the atrial blanking period, representing the blanking period after an atrial event. There are two ventricular blanking periods, one after the atrial paced event, which prevents atrial paced events from being sensed on the ventricular channel, and one after the ventricular event. A ventricular sensed event in the crosstalk sensing window will result in safety pacing. There are two ventricular alert periods, one at the end of the AV delay and one after the ventricular refractory period.

Postventricular Atrial Refractory Period and Upper Rate Limit Behavior.

In the DDD mode, the *postventricular atrial refractory period* (PVARP) starts with a sensed or paced ventricular event and defines a period on the atrial channel during which a spontaneous atrial event is not tracked (**Fig. 41.10**). It serves multiple important roles critical to DDD pacing, including avoiding pacemaker-mediated tachycardia (PMT) and setting a boundary on upper rate behavior. Since the paced

ventricular rate cannot exceed the programmed upper rate limit (URL), an algorithm is needed to determine how the ventricular pacing rate should be adjusted in patients with AV block when the sinus rate exceeds URL. All pacemakers extend the AV delay when the sinus rate exceeds URL so that the ventricular pacing rate remains at the programmed upper rate. Since the sinus rate is faster than the ventricular pacing rate, the P waves will occur progressively earlier after each successive ventricular paced beat until the P wave times within PVARP and is not tracked. This progressive prolongation of the AV delay until a sinus beat is not tracked is often called “pseudo–AV Wenckebach” (**Fig. 41.11**). If the sinus rate increases further, every other P wave falls in the PVARP, resulting in 2 : 1 atrial tracking (2 : 1 block) and an abrupt decrease of ventricular rate that usually results in exertional intolerance. Because of this, it is important to keep the programmed upper rate and the 2 : 1 AV block rate higher than the maximum sinus rate during exercise. The 2 : 1 AV block rate corresponds to the interval represented by the sum of the programmed AV delay and the PVARP, called the *total atrial refractory period* (TARP).


URL
500 msec
URL
500 msec
250 msec
PVARP
250 msec
PVARP
250 msec
PVARP
250 msec
PVARP
AV delay
AV delay extension
AVI
150 msec
PVARP
PVARP
PVARP
A

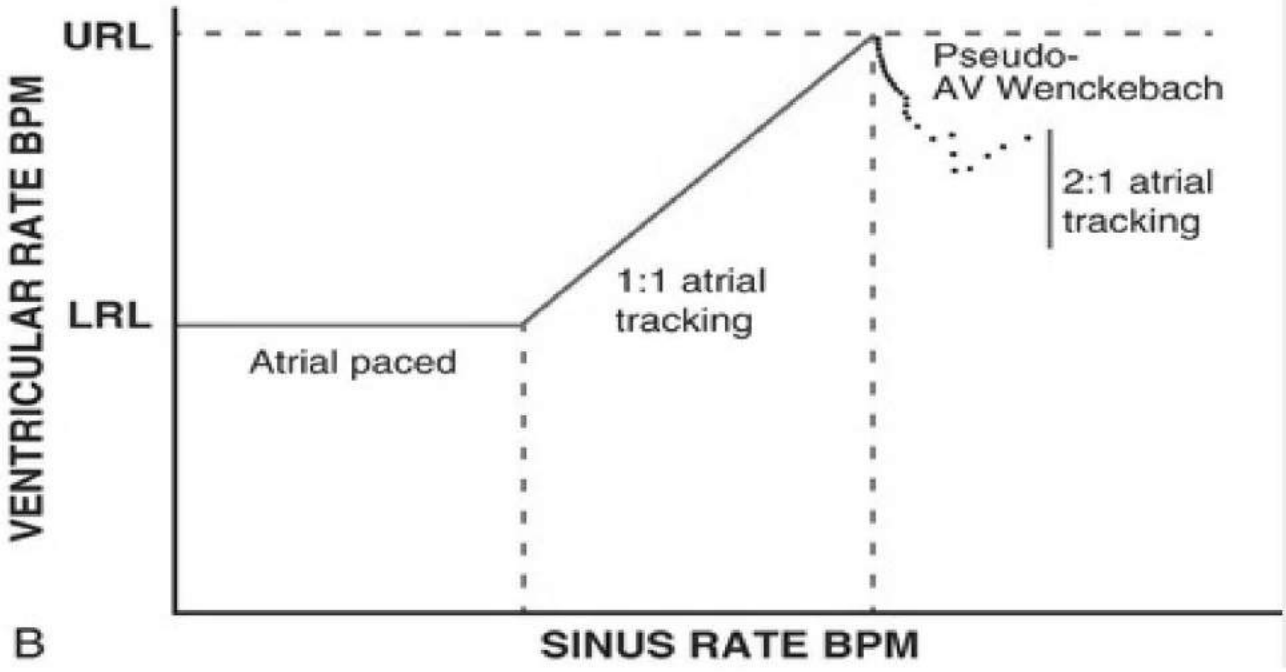

URL
LRL
VENTRICULAR RATE BPM
Pseudo-
AV Wenckebach
2:1 atrial
tracking
1:1 atrial
tracking
Atrial paced
SINUS RATE BPM
B

FIGURE 41.11 Upper rate limit behavior of dual-chamber pacemaker. **A, Upper panel,** Pseudo-Wenckebach behavior occurs when the sinus rate exceeds the programmed maximum tracking rate but the P-P interval is longer than the total atrial refractory period (TARP, sum of atrioventricular interval [AVI] and postventricular atrial refractory period [PVARP]). **Lower panel,** When the P-P interval is less than the TARP, every other P falls within the PVARP and therefore cannot be tracked. Thus the ventricular rate falls to half the atrial rate (2 : 1 atrial tracking). **B,** Response of DDD pacemaker (*ordinate*) as sinus rate (*abscissa*) increases. URL, Programmed upper rate limit; LRL programmed lower rate limit; BPM, beats per minute.

Pacemaker Troubleshooting

Noninvasive troubleshooting tools include history, chest radiography, surface ECG, stored device data (programming, lead impedance values and trends, stored EGMs, marker channels), and real-time device data (pacing-sensing thresholds, real-time EGMs during pocket manipulation or arm motion). The most common pacing problems can be classified as failure to capture, failure to pace, pacing at a rate inconsistent with the programmed rate, and unanticipated rapid pacing (**Table 41.2**).

TABLE 41.2

Common Causes of Pacemaker Problems

Failure to Capture
Pacing output below threshold
Changes at electrode-myocardial interface
Output programmed below threshold
Lead dislodgement
Lead insulation failure or conductor fracture
Connection problem between header and lead
Functional failure to capture (undersensing or asynchronous pacing)
Failure to Pace
Corrected by magnet or programming to asynchronous mode
Oversensing of physiological or nonphysiological signals
Not corrected by magnet or programming to asynchronous mode
Failure in the pulse generator
Lead conductor fracture
Connection problem between header and lead
Pacing at a Rate Not Consistent with Programmed Rate
Shorter-than-expected escape interval: undersensing
Longer-than-expected escape interval: oversensing
Battery depletion
Unanticipated Rapid Pacing
Pacemaker-mediated tachycardia
Inappropriate ventricular tracking of rapid sensed atrial rates, electromagnetic interference, or myopotentials
Sensor-driven pacing unrelated to patient activity

Failure to Capture

Failure to capture is defined as a pacing stimulus without subsequent cardiac depolarization (**Fig. 41.12**). It can be related to the pacing system, the patient, or patient-system interactions. The most common cause is an elevated pacing threshold caused by changes at the electrode-myocardial interface. System-related causes are common in the perioperative period, especially lead dislodgment. An otherwise sufficient stimulus will fail to capture if it occurs in the physiologic refractory period of a spontaneous depolarization. This “functional failure to capture” can result from undersensing.

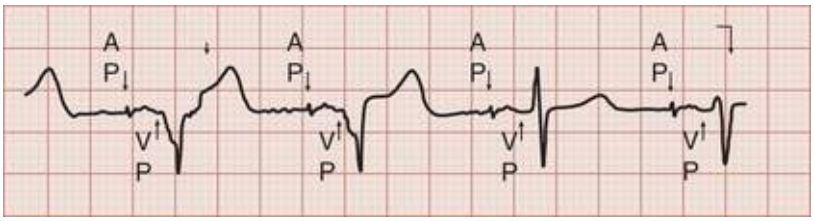


FIGURE 41.12 Failure to capture. Surface ECG lead with atrial and ventricular markers. AP, Atrial paced; VP, ventricular paced. The third and fourth beats show failure of ventricular capture with conducted QRS complexes. The conducted QRS complexes are timed in the postpacing ventricular blanking period and are thus not sensed.

Failure to Pace

Failure to output an indicated pacing stimulus is most frequently caused by oversensing of physiologic or nonphysiologic signals, resulting in inhibition of the pacing output (**Fig. 41.13**), causing failure to pace. Lead or header-connector problems can cause both oversensing of noncardiac signals and impedance abnormalities (see later, ICD Troubleshooting and ICD Lead Failure). Rarely, failure to pace can be caused by failure of the output circuit in the pulse generator or an open circuit (e.g., lead fracture, loose set screw). The combination of failure to capture and failure to pace usually indicates a pacing-system problem rather than a physiologic problem.

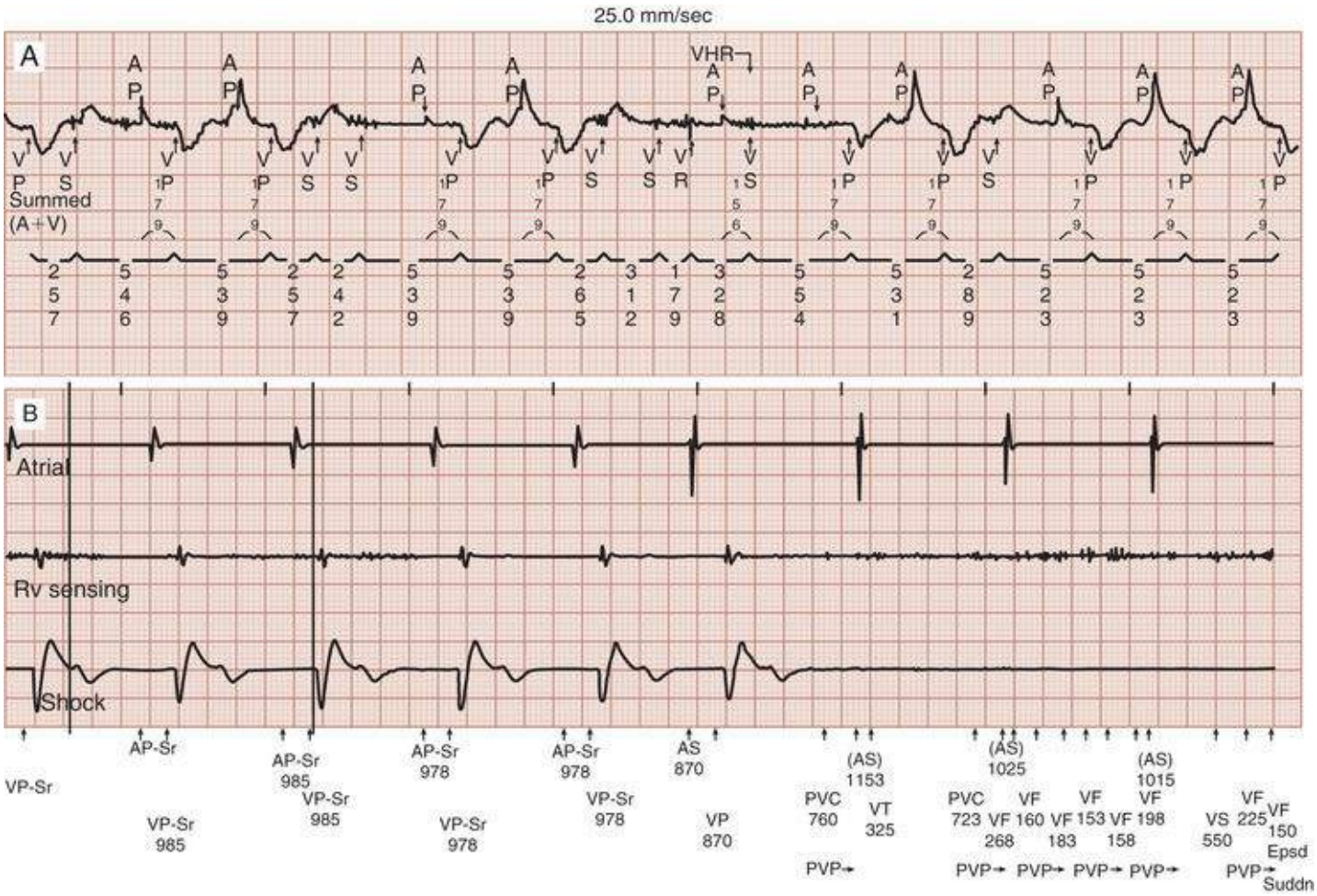
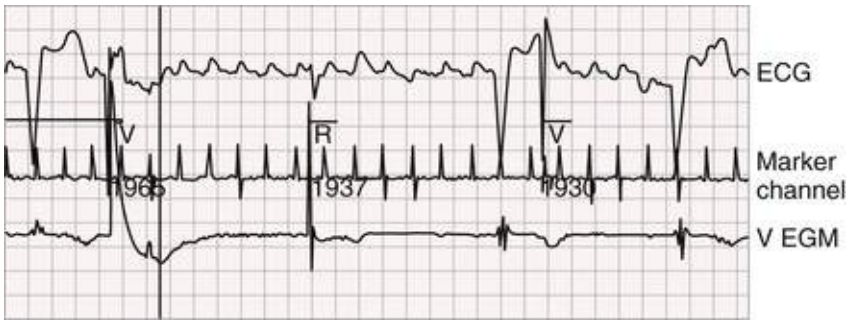


FIGURE 41.13 Ventricular oversensing. **A,** Dual-chamber electrogram (EGM) showing ventricular oversensing caused by lead fracture. The summed EGM (a composite of atrial and ventricular EGMs) with markers and interval channel are shown. VS events denote oversensing caused by lead fracture and correspond to the artifact seen on the summed EGM. The VS events reset the timing cycle and delay the onset of the atrial paced events, which are followed by ventricular paced events. "VHR" indicates that the ventricular oversensed events have resulted in detection of a ventricular high rate (VHR). The number values on the *top* of the interval channel indicate the AV interval, whereas the number values on the *bottom* of the interval channel indicate the VV interval. AP, Atrial pacing; VP, ventricular pacing; VS, ventricular sensing. **B,** Oversensing of diaphragmatic myopotentials in a patient with complete heart block and a dual-chamber ICD with integrated bipolar, right ventricular (RV) sensing. Atrial bipolar, RV integrated bipolar, and RV coil-can shock EGMs and dual-chamber marker channels are shown. Myopotentials are relatively uniform, low-amplitude signals with a dominant frequency in the range 80 to 200 Hz. Oversensing inhibits pacing, resulting in ventricular asystole best identified on the shock channel. Simultaneously, the ICD classifies most rapidly sensed intervals in the VF zone ("VF" markers). VF is detected at right of tracing when enough intervals are classified in the VF zone, initiating a VF episode ("Epsd"). Diaphragmatic myopotentials have greater amplitude on the RV sensing channel than atrial channel because of its larger sensing dipole and proximity of the RV lead tip to the diaphragm.

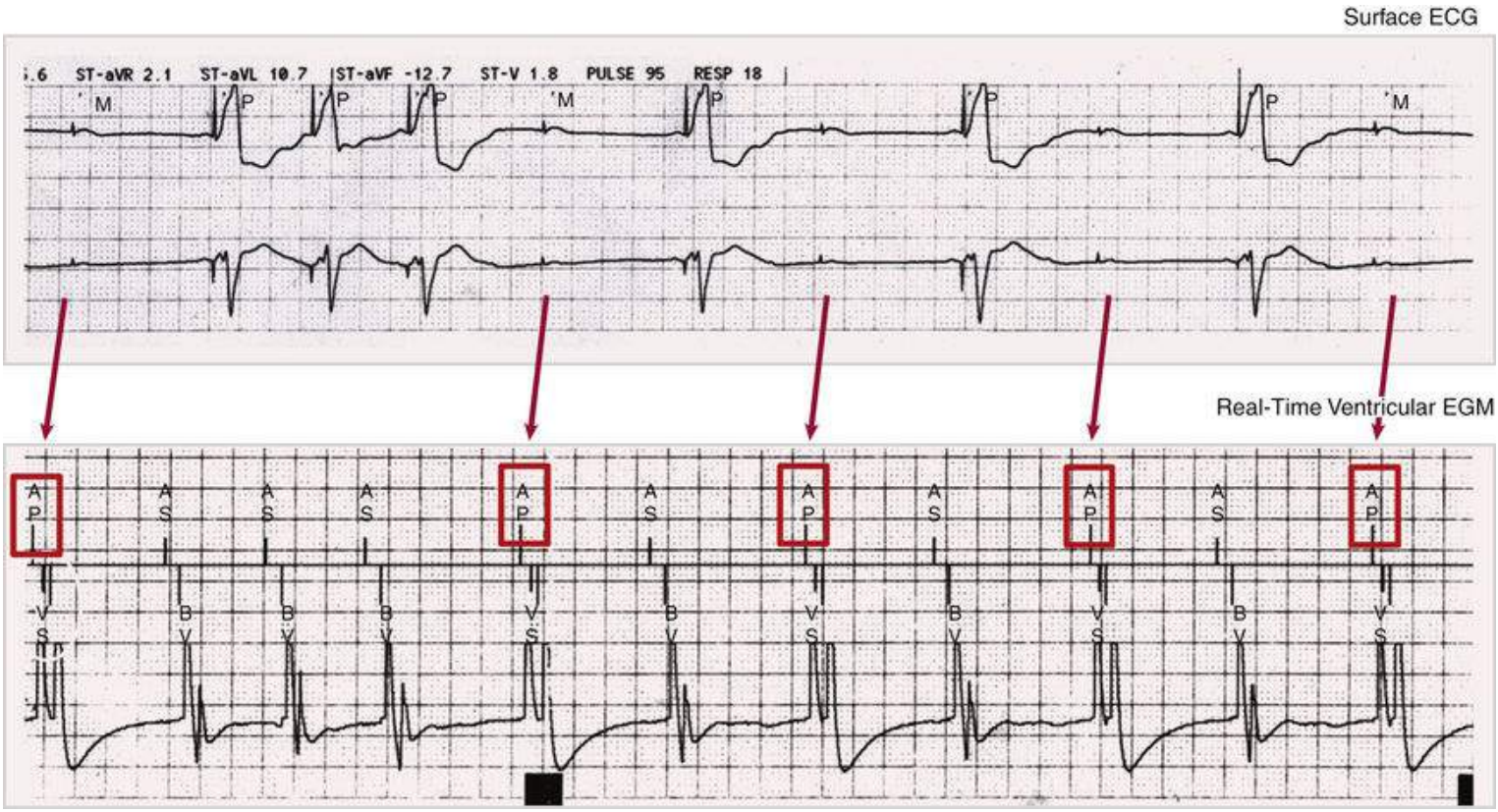
Crosstalk is a specific form of oversensing in which the pacing stimulus is sensed in the opposite chamber. Clinically, the most important crosstalk is oversensing of the atrial pacing stimulus on the ventricular channel, resulting in inhibition of ventricular pacing in a patient with AV block (**eFig. 41.7**). It is minimized by ventricular blanking after atrial pacing. Settings that promote crosstalk include high atrial output, ventricular sensing parameter programmed to a very sensitive value, and short duration of ventricular blanking after atrial pacing. Pacemakers have features to prevent crosstalk, including ventricular blanking after atrial pacing and ventricular safety pacing in response to a sensed event in the AV interval. Safety pacing may be identified electrocardiographically by a shorter-than-programmed AV delay, usually 80 to 130 milliseconds.



EFIGURE 41.7 Ventricular undersensing: telemetry with a surface ECG **(top),** atrial (A) EGM **(middle),** and ventricular (V) EGM **(bottom).** Markers correspond to the ventricular channel. There are six ventricular events but only three with marker annotation. The first ventricular event is neither sensed nor annotated. The second ventricular event is paced (V). The third is intrinsic (R). The fourth is not sensed and is followed approximately 360 milliseconds later by a paced event (V) that corresponds to an escape interval timed from the event marked "R." Undersensing results in escape intervals shorter than the programmed escape interval. The final intrinsic event is not sensed.

Pacing at a Rate Inconsistent With Programming

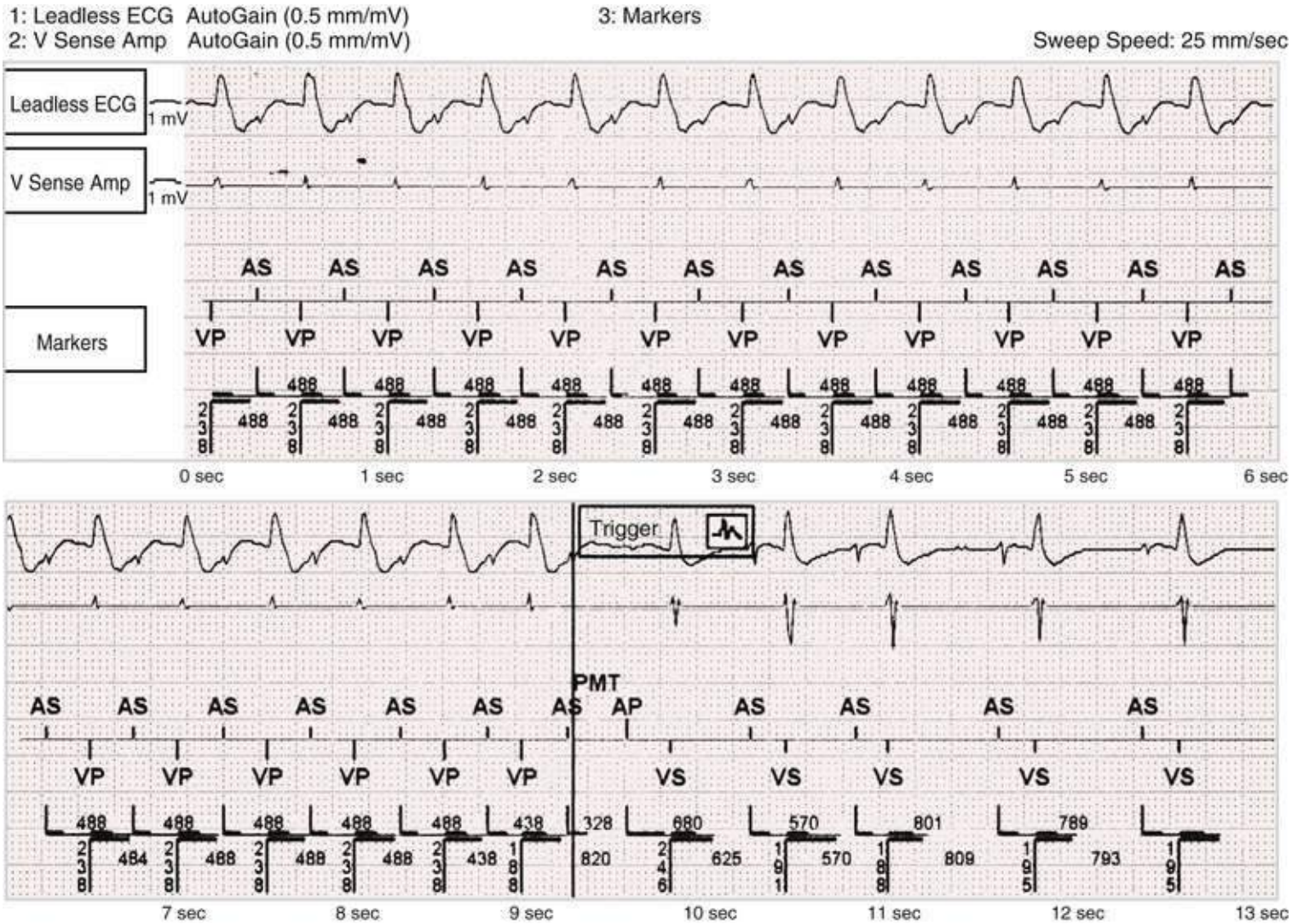
Pacing with a shorter-than-expected escape interval usually indicates undersensing (**eFig. 41.8**). Pacing with a longer-than-expected escape interval usually indicates oversensing (**Fig. 41.13**). As with oversensing, undersensing can be related to the pacing system, the patient, or patient-system interactions. EGMs of premature beats may not be sensed even if sensing of normal beats is reliable. Consistent pacing at a rate slower than the programmed lower rate limit usually indicates oversensing of a constant signal during each cardiac cycle (usually T wave oversensing). It may also indicate battery depletion.



EFIGURE 41.8 Crosstalk inhibition. *Upper panel,* Surface ECG showing intermittent failure of ventricular output when the surface ECG is assessed. *Lower panel,* Dual-chamber marker channel and real-time ventricular EGM showing oversensing during the AV interval of a high-amplitude potential that saturates the sensing amplifier. A, Atrial; B, biventricular pacing; S, sensed event; V, ventricular.

Unanticipated Rapid Pacing

In dual-chamber pacemakers, rapid pacing, usually at or near URL, is most often caused by a PMT or ventricular tracking of rapid signals on the atrial channel (**eTable 41.3**). In patients with retrograde conduction, if the PVARP is too short, a premature ventricular beat that is conducted retrogradely and sensed on the atrial channel may be tracked, initiating a repetitive sequence of ventricular pacing, retrograde conduction, and atrial tracking of the retrogradely conducted EGM. In this “endless loop” type of PMT, the pacemaker functions as the anterograde limb of AV reentrant tachycardia (AVRT), and the conduction system functions as the retrograde limb (**eFig. 41.9**). In contrast, ventricular tracking of rapid, sensed atrial signals can be caused by failure to mode switch during atrial tachyarrhythmias or sensing of extracardiac signals (e.g., pectoral myopotentials, EMI). Both can be terminated by programming to a nontracking mode. Less frequently, rapid sensor-driven rates may occur if the sensor responds to signals that are unrelated to patient activity, such as an accelerometer responding to vibrations in a helicopter or a minute ventilation sensor responding to respiratory rate in an asthma attack.



EFIGURE 41.9 Pacemaker-mediated tachycardia (PMT). The **top panel** shows a far-field EGM similar to a surface ECG. The second channel gives the ventricular EGM. Below are the atrial and ventricular markers. Each ventricular paced event is followed by an intrinsic atrial event. In the **bottom panel** this pattern is identified as PMT. The final atrial sensed event following the last ventricular paced beat is not tracked and is followed by an atrial paced beat that is conducted to the ventricle. This stops the PMT.

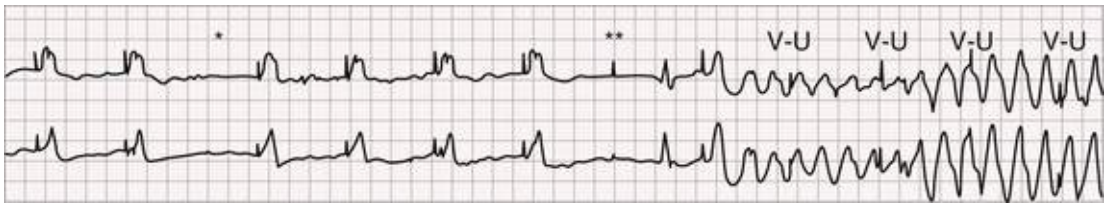
ETABLE 41.3

Common Causes of Rapid Ventricular Pacing

Ventricular Pacing at Upper Rate Limit in DDD Mode
Pacemaker-mediated tachycardia
Ventricular tracking of rapid atrial signals
Atrial tachyarrhythmias
Rapid oversensed signals (e.g., electromagnetic interference, lead- or connection-related oversensing)
Other Causes
Sensor-driven pacing
Magnet application
Algorithms for rate regularization in atrial fibrillation
Rate-smoothing algorithms that prevent abrupt change in ventricular rate

Proarrhythmia

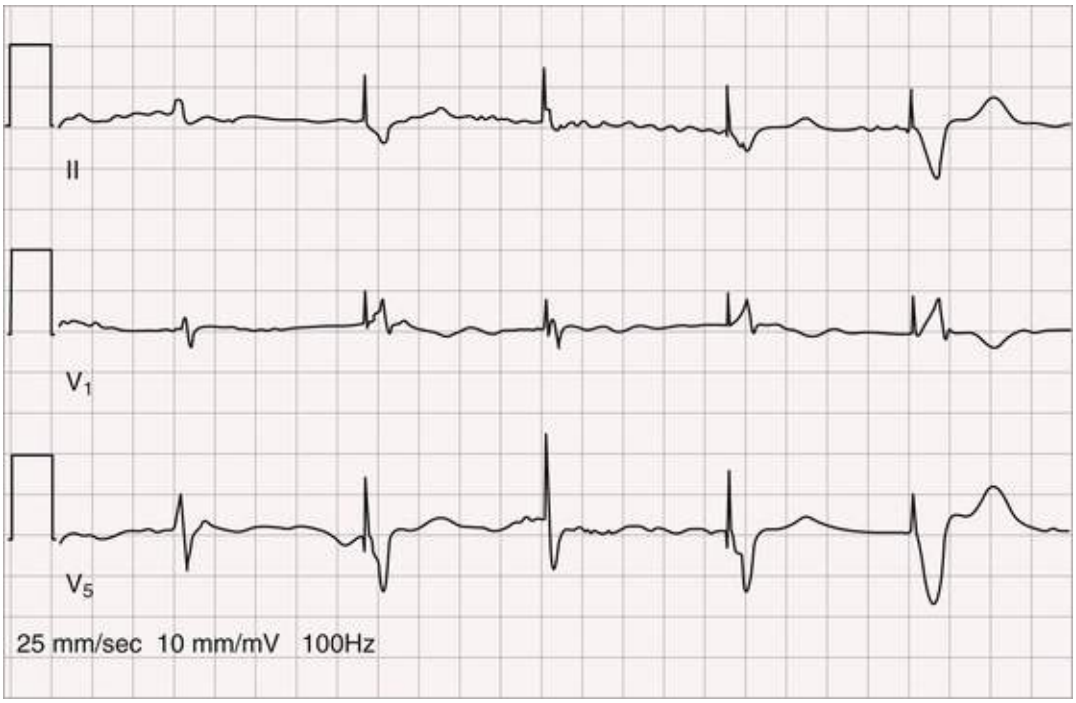
Rarely, pacing can be proarrhythmic in either the atrium or the ventricle. Pacing-induced short-long-short sequences may initiate initiating pause-dependent VT/VF (**eFig. 41.10**). These typically result from algorithms that promote AV conduction or loss of ventricular capture, which occurs routinely during threshold testing. Thus, an external defibrillator should be available during pacemaker programming.



EFIGURE 41.10 Pacing-induced proarrhythmia seen on electrocardiographic tracing from patient with pacemaker programmed to VVI at approximately 70 pulses/min. There is a longer V-V interval representing oversensing (*); a subsequent pacing spike occurs with failure to capture (**); and in the terminal portion of the tracing, VT develops and the pacemaker does not sense the tachyarrhythmia. Pacing artifacts can be seen during VT, labeled "V-U" (ventricular undersensing).

Misinterpretation of Normal Pacemaker Function

Historically, fusion and pseudofusion beats on the ECG have been a source of confusion (**eFig. 41.11**). At times, the surface ECG may not permit determination of the chamber paced. For example, atrial undersensing during AF results in functional failure of atrial capture but can be misinterpreted as failure of ventricular capture. Algorithms that minimize RV pacing to promote intrinsic AV conduction may also cause confusion (**see Fig. 41.8**).



EFIGURE 41.11 Fusion and pseudofusion on a three-channel ECG tracing from an ambulatory monitor. *Fusion* indicates that depolarization occurs in part because of intrinsic activation and in part because of capture from the pacemaker stimulus. *Pseudofusion* indicates that the pacemaker stimulus does not alter intrinsic QRS morphology on the surface ECG. This occurs when the stimulus is delivered after intrinsic activation depolarizes the ventricles. The first QRS is intrinsic. The second and fourth beats represent fusion. The third beat is pseudofusion; that is, the underlying morphology is almost identical to the intrinsic QRS. The final QRS represents paced depolarization.

Implantable Cardioverter Defibrillators

Indications for ICDs

ICDs are indicated for prevention of sudden death from VT/VF, either as *secondary prevention* in patients who have been resuscitated from VT/VF or *primary prevention* in patients who have not had VT/VF but are at sufficiently-high risk (see later, Guidelines).

Secondary Prevention

ICDs are the treatment of choice for secondary prevention of VT/VF, providing patients remain at risk for recurrence of VT/VF and have sufficient life expectancy and quality of life to justify implantation. The strong consensus for secondary prevention ICDs is based on the AVID trial and other RCTs that compared antiarrhythmic drugs to ICDs.[9]

Primary Prevention

Presently, more than 80% of ICDs are implanted for primary prevention based primarily on two RCTs.[9] The MADIT II trial of patients with ischemic cardiomyopathy and LVEF of 30% or less demonstrated significant survival benefit continuing through 8 years of follow-up. The SCD-HeFT trial of patients with LVEF of 35% or less found that ICDs reduced total mortality in patients with both ischemic and nonischemic cardiomyopathy. However, retrospective analyses indicate that ICDs do not prolong life in identifiable subgroups with extensive comorbidities, including advanced HF and renal failure. Further, these trials were performed before present pharmacologic therapy and CRT of HF. A subsequent RCT of patients with nonischemic cardiomyopathy and LVEF of 35% or less found that ICDs did not reduce total mortality in patients who received guideline-directed medical therapy (GDMT) and indicated CRT pacemakers.[10]

Clinical trials do not support ICD implantation in low-LVEF patients within 40 days of myocardial infarction (MI) or 90 days of surgical revascularization; low-LVEF patients with recent percutaneous revascularization are not well represented in clinical trials.[11] With few exceptions,[12] ICD implantation in these patients is not indicated (see Guidelines).

Expert consensus statements provide recommendations for ICD implantation in patients under specific circumstances not covered in clinical trials[12] and clinical scenarios not addressed by guidelines.[13] These include high-risk patients with less common diseases, including specific cardiomyopathies (e.g., hypertrophic cardiomyopathy; **Chapter 78**), ion channelopathies[14] (**Chapters 33 and 35**), and certain forms of congenital heart disease[15] (**Chapter 75**).

ICD Leads and Generators

An ICD system comprises the generator and at least one defibrillation lead. Usually, the generator is implanted pectorally, and a single, transvenous defibrillation lead is implanted in the right ventricle (analogous to a ventricular pacemaker lead) (**Fig. 41.14A**). Dual-chamber ICDs incorporate a bipolar atrial pace-sense lead to provide dual-chamber bradycardia pacing and dual-chamber algorithms that discriminate supraventricular tachycardia (SVT) from VT. CRT-Ds incorporate an LV pacing lead (**see Chapter 27**). The totally subcutaneous[16] ICD system consists of a defibrillation lead implanted parallel to the sternum and tunneled to the ICD generator located near the left anterior axillary line (**Fig. 41.14B**).

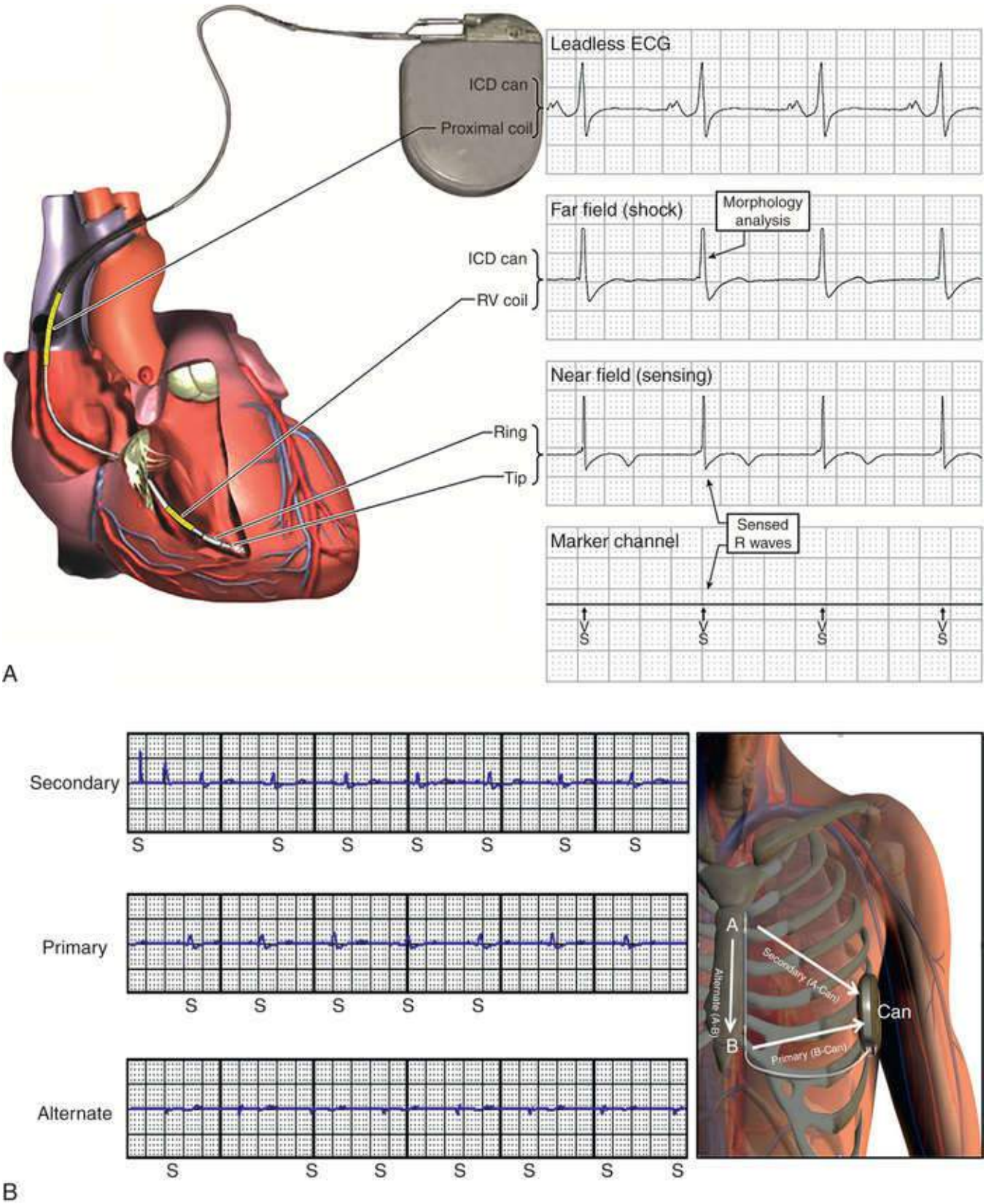


FIGURE 41.14 Implantable cardioverter-defibrillators and electrograms (EGMs). **A, Left**, Single-chamber ICD system, including left pectoral active can and right ventricle (RV) lead; **right,** telemetered EGM recorded between proximal coil and can ("leadless ECG"), high-voltage (shock) far-field EGM, and sensing near-field EGM, with annotated markers. The dual-coil lead uses true bipolar sensing between tip and ring electrodes. Marker channel denotes timing of sensed R waves from the near-field EGM (*arrows*) and ICD's classification of each ventricular event by letter symbols. Numbers indicate R-R intervals in milliseconds. "VS" denotes sensed ventricular events in the sinus rate zone. Sensing is accurate because there is a 1 : 1 correspondence between ventricular EGMs and markers. Morphology of shock EGMs stored during detected tachycardias is useful for distinguishing ventricular tachycardia from supraventricular tachycardia. Leadless electrocardiograms (ECGs) provide a signal with identifiable atrial EGM with a single-chamber ICD if a dual-coil lead is used. **B,** Subcutaneous ICD records subcutaneous EGMs from one of three vectors. The amplitude of the alternate vector is smallest (as in this tracing) because it often overlies atrial tissue and the sternum. The secondary vector is prone to myopotential artifact because it

usually overlies the pectoralis muscles. “S” denotes sensed ventricular events in the sinus rate zone.
(From Swerdlow CD, Friedman P. Implantable cardioverter-defibrillator: clinical aspects. In Zipes D, Jalife J, editors. Cardiac Electrophysiology: From Cell to Bedside. 7th ed. Philadelphia: Saunders Elsevier; 2018.)

Defibrillation Leads.

Right-ventricular defibrillation leads comprise a small, distal tip electrode for pacing and sensing with a fixation mechanism that anchors the lead to the heart, proximal terminals that connect to the generator, and a lead body connecting the two. The lead body consists of a flexible, plastic, insulating cylinder with longitudinal lumens through which conductors run from the proximal terminals to small pace-sense electrodes and larger shock coil electrodes. This “multilumen” design permits more conductors in a smaller diameter than coaxial designs typically used in pacemaker leads.

All defibrillation leads have a distal (RV) defibrillation coil and a tip pace-sense electrode. Optionally, they may have a second ring sensing electrode, which is dedicated to the pace-sense circuit, to permit *dedicated bipolar* sensing and pacing between the tip and ring. If the lead has only a tip electrode, *integrated bipolar* sensing and pacing occur between the tip electrode and the distal defibrillator coil, which is integrated into the defibrillation circuit. *Dual-coil* leads have a second proximal defibrillation coil in the superior vena cava. For single-coil leads, shocks are delivered between the RV defibrillation coil and the housing (“can”) of the generator. In dual-coil leads, the proximal pole has the same polarity as the can. Left pectoral implants are preferred over right pectoral implants because the defibrillation vector to the can includes more of the left ventricle. The new standard DF-4 connector permits conductors to all the lead's electrodes to connect to the generator with a single pin, minimizing connection problems compared with the older DF-1 connector.[17]

The subcutaneous ICD lead utilizes a multilumen design with the shock coil straddled by two small sensing electrodes (**Fig. 41.14B**).

ICD Generators.

ICD generators include a clear-plastic header that connects to the lead(s) and a titanium can that houses high-voltage electronics, in addition to the battery and other low-voltage components found in pacemakers (**eFig. 41.1B**).

Unlike pacemakers, ICDs must deliver high-voltage shocks in addition to low-voltage pacing pulses. However, low-voltage batteries have approximately 1000 times the energy density of high-voltage capacitors. Thus, ICDs require a high-voltage transformer and charging circuit to convert electrochemical energy stored in an electrochemical cell (about 3 V) to the high voltage needed for defibrillation shocks (750 to 900 V for transvenous ICDs; 1400 V for subcutaneous ICDs). Unlike pacemaker batteries, ICD batteries must be able to deliver high current (up to 3 A) and high power (up to 10 W) to provide high-voltage electricity for shocks. The charging circuit requires 6 to 15 seconds for transvenous ICDs and 15 to 25 seconds for subcutaneous ICDs. During charging, high-voltage electricity is stored in a high-voltage capacitor. To deliver the shock, the high-voltage capacitor is disconnected from the charging circuit and connected to the shock electrodes.

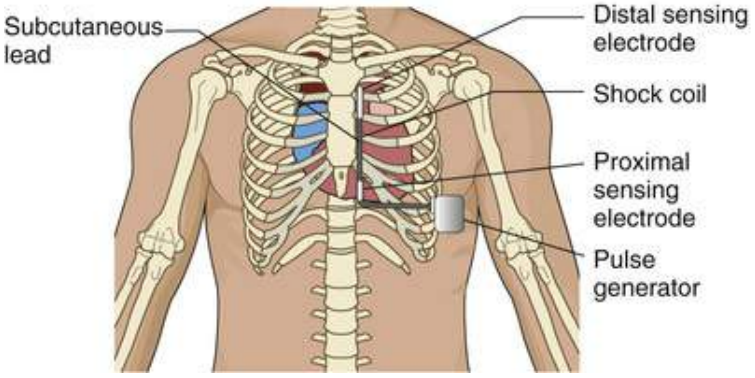
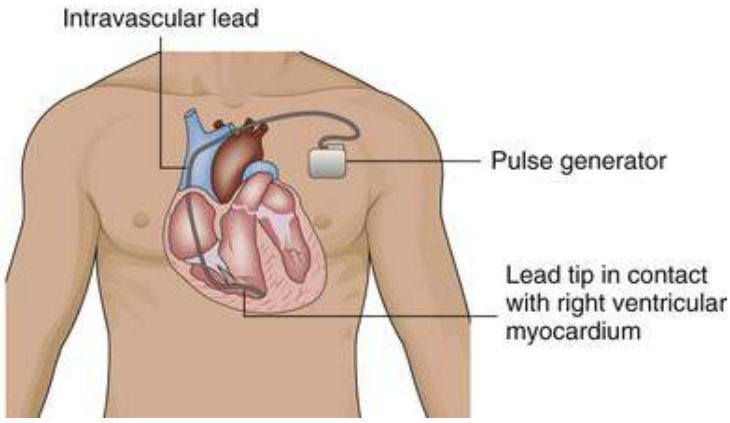
ICD System Selection

Transvenous versus Subcutaneous ICD Systems

The subcutaneous ICD[16] eliminates morbidity associated with transvenous lead insertion, lead-related complications during MRI scans, and the hazards of transvenous extraction when lead removal is required. Candidates for a subcutaneous ICD undergo screening using surface ECG electrodes to assess the risk of T wave oversensing or R wave double-counting; 7% to 10% of candidates fail screening. Despite this, inappropriate shocks caused by oversensing are more common in subcutaneous ICDs than in modern transvenous ICDs (5% to 10% versus <2% in the first year).[16,18] Subcutaneous ICDs cannot perform ATP, resynchronization, or long-term bradycardia pacing. However, future models are expected to communicate with leadless capsule pacemakers. **eTable 41.4** compares transvenous and subcutaneous ICDs.

ETABLE 41.4

ICD System Selection: Subcutaneous (S) vs. Transvenous ICD

SUBCUTANEOUS-ICD	TRANSVENOUS ICD
	
Advantages	
Eliminates need for vascular, intravascular lead, and related complications (e.g., pneumothorax) No intravascular system infection Implant possible without fluoroscopy Lead failure may be less likely Relative simplicity and safety of lead extraction	Bradycardia, antitachycardia, and cardiac resynchronization pacing No preimplant ECG screening necessary Fewer inappropriate and avoidable shocks Greater battery longevity Shorter charge time; faster shock delivery Smaller pulse generator Long-term follow-up data
Patient Selection	
Limited vascular access (e.g., dialysis) History or high risk of intravascular infection (e.g., prosthetic valve) Intracardiac shunt Young patient (ease of lead extraction and possible greater lead longevity)	Need bradycardia, antitachycardia, or cardiac resynchronization pac Fail subcutaneous ICD ECG screening

Images from Lewis GF, Gold MR. Safety and efficacy of the subcutaneous implantable defibrillator. J Am Coll Cardiol 2016;67(4):445-54.

Dual- versus Single-Chamber Transvenous ICDs

In addition to providing dual-chamber bradycardia pacing, dual-chamber ICDs provide atrial EGMs that enhance physician interpretation of stored EGMs and permit both diagnostics for AF and dual-chamber algorithms to discriminate SVT from VT. The present consensus recommends reserving dual-chamber ICDs for patients who need dual-chamber pacing or have SVT and monomorphic VT at overlapping ventricular rates.[12]

Transvenous Defibrillation Leads

Dual versus Single Coil.

Dual-coil leads improved defibrillation efficacy of early ICDs but do not provide a clinically significant advantage for left pectoral implants of present ICDs.[19] They provide better defibrillation for some right-sided implants as well as reliable atrial cardioversion and alternate EGMs for diagnostic interpretation. However, the proximal coil often adheres to the superior vena cava. If lead extraction is required, this increases procedural difficulty and may increase risk. Thus, single-coil leads usually are preferred for left pectoral implants.

Integrated versus Dedicated Sensing Bipoles.

Compared with dedicated bipolar leads, the integrated bipolar design simplifies the lead by reducing the number of conductors. However, reliable leads have been developed with both designs. Integrated bipolar EGMs have a wider field of view than dedicated bipolar EGMs and are thus more likely to oversense nonphysiologic signals or physiologic signals that do not reflect local myocardial depolarization[20] (**see Fig. 41.13**).

ICD Therapy

Transvenous ICDs deliver two types of therapy for tachyarrhythmias: low-voltage trains of ATP stimuli (pulses), and high-voltage cardioversion or defibrillation stimuli (shocks). ICDs deliver shocks to treat VF and *tiered therapy* to treat VT–first ATP and then shocks if ATP is unsuccessful. Because ICDs synchronize almost all defibrillation shocks to the intracardiac EGM, cardioversion and defibrillation are essentially equivalent when delivered by ICDs.

Antitachycardia Pacing

ATP refers to the use of pacing stimuli to terminate reentrant tachycardias. In patients with structural heart disease, most monomorphic VT is reentrant (**see Chapter 39**) and thus can be terminated by ATP. Current subcutaneous ICDs cannot deliver ATP.

Principles

Bradycardia pacing requires only that the stimulus capture fully excitable, local myocardium during diastole. In contrast, ATP stimuli must interact with the specific reentrant circuit driving the VT, which usually is remote from the site of pacing, and it must do so while most of the myocardium is refractory or relatively refractory. Thus the required stimulus strength is higher than that for bradycardia pacing in fully excitable myocardium. The ATP stimulus must then propagate to the reentry circuit through relatively refractory myocardium and capture myocardium in the VT circuit during an excitable gap in refractoriness. To facilitate propagation in relatively refractory myocardium and ensure that at least one stimulus enters the excitable gap, ATP is delivered as a sequence or “train” of 3 to 10 stimuli at a rate faster than the VT (**Fig. 41.15**). ATP terminates VT by causing bidirectional block, which occurs when the stimulus propagates antidromically to collide with the head of the circulating wavefront and blocks orthodromically in tissue rendered inexcitable by the preceding wavefront (**see Chapters 34 and 36**). Clinically, the cycle length of ATP is programmed as a percentage of the VT cycle length (adaptive ATP). More than one ATP sequence may be required because of the uncertainties introduced by the multiple variables involved. However, the number of programmed ATP trains must be limited to prevent hemodynamic collapse during prolonged VT and repeated sequences of even faster ATP.

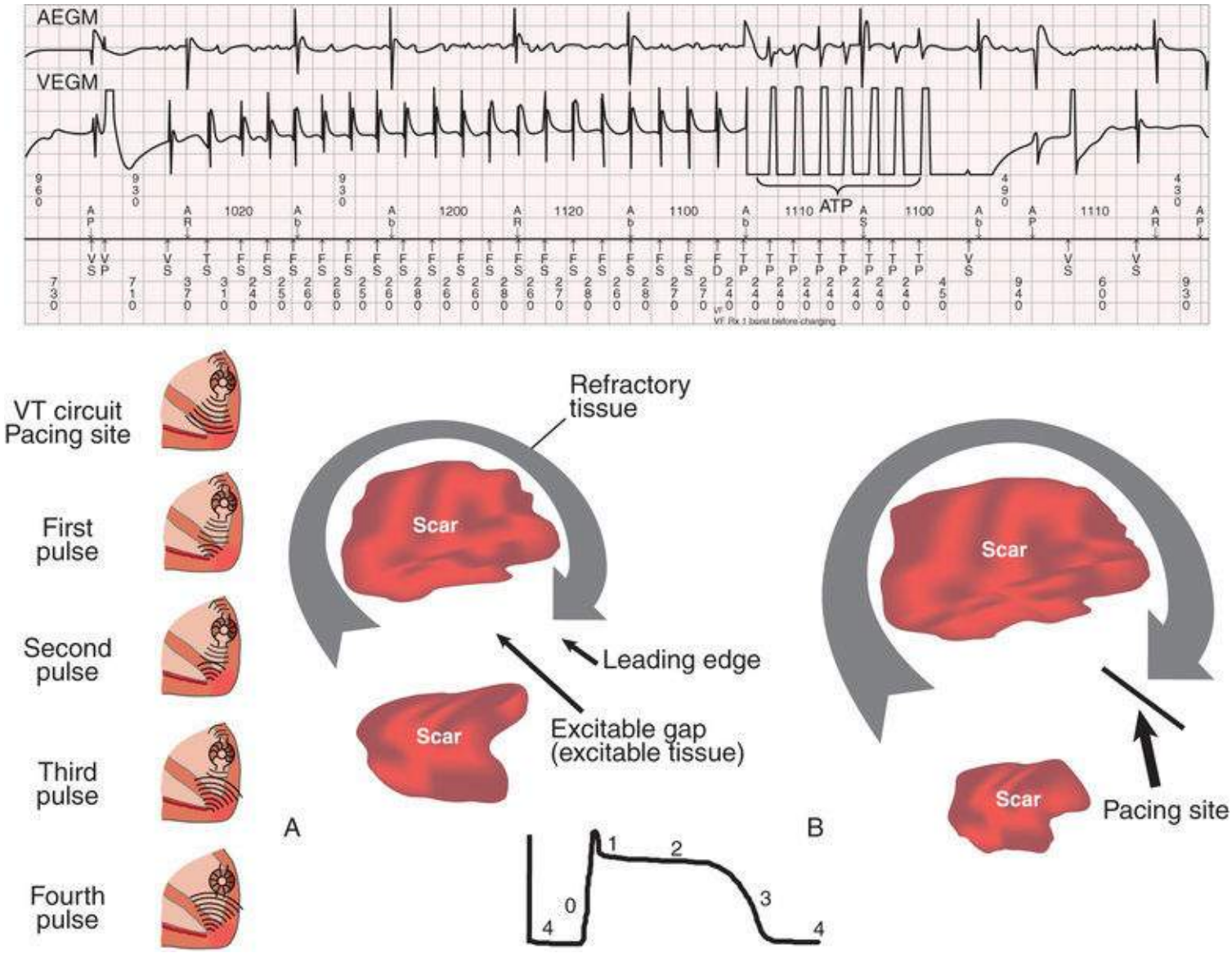


FIGURE 41.15 Antitachycardia pacing (ATP) for monomorphic ventricular tachycardia (VT): stored atrial (AEGM) and ventricular (VEGM) electrograms and atrial and ventricular marker channels from an episode of rapid monomorphic VT (cycle length, 240 to 270 milliseconds; rate, 220 to 250 beats/min). VT with AV dissociation begins with the second VEGM. After 18 intervals shorter than the programmed ventricular fibrillation (VF) detection interval of 320 milliseconds, an adaptive train of eight ATP pulses is delivered at a cycle length of 240 milliseconds, 88% of the VT cycle length, to terminate the VT. On the marker channel, VS, TS, and FS indicate intervals classified in the sinus, VT, and VF rate zones, respectively. FD, Detection of VF; TP, ATP. Note that a burst of ATP is delivered even though the intervals are in the VF zone. AP, Atrial paced events. "Ab" and "AR" indicate atrial intervals in the postventricular atrial blanking and refractory periods, respectively. At the **lower left,** vertical panels show a conceptual model of why multiple ATP pulses are required in a train. The **top panel** shows that during VT the region between the pacing lead in the right ventricular apex and the VT reentry circuit in the left ventricle is activated by the circuit. Subsequent panels represent conditions after the first, second, third, and fourth ATP pulses. After each successive pulse, ATP propagates to more of the region before colliding with the VT wavefront. The **lower panel** shows a conceptual model of the interaction between ATP pulses and the VT circuit. In **A,** the circuit around a fixed scar is depicted by the *large curved arrow.* The head of the arrow depicts the leading edge of the wavefront, and the body of the arrow back to the tail (*gray*) represents depolarized tissue that is refractory because the wavefront has just propagated through it. The repolarized tissue between the tip and the tail of the arrow is excitable ("excitable gap"). For the head of the arrow to continue around the scar, an excitable gap must be present; if the wavefront encounters refractory tissue, it cannot proceed. In **B,** a wavefront generated by an ATP pulse enters the excitable gap and terminates the VT. Tachycardias with a small excitable gap (i.e., the head of the arrow follows the tail very closely so that only a small "moving rim" of excitable tissue is in the circuit) are less likely to be terminated with ATP. (**Lower panel,** From Hayes DL, Friedman PA, editors. Cardiac Pacing and Defibrillation: A Clinical Approach. 2nd ed. West Sussex, UK: Wiley-Blackwell; 2008.)

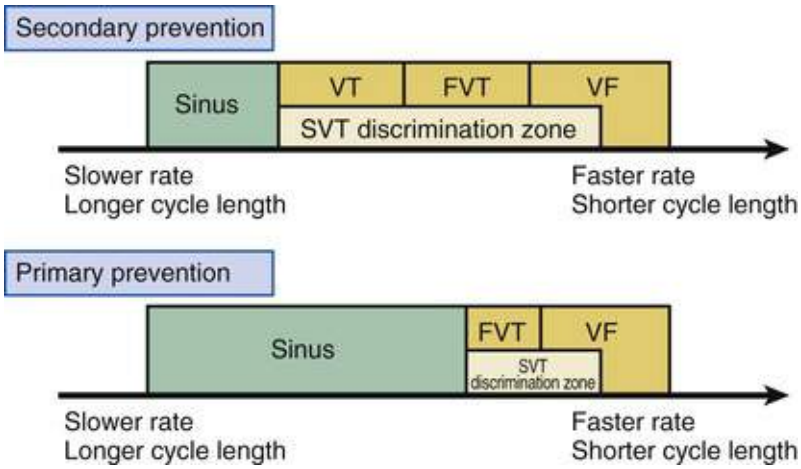
Clinical Application

Despite these uncertainties, ATP has become the primary transvenous-ICD therapy for monomorphic VT because ATP is painless, whereas shocks are painful. In comparison with shocks, ATP improves quality of life, reduces hospitalizations for VT, requires much less power, and does not depress myocardial contractility acutely.[21] However, ATP can fail for reasons that do not affect shocks, such as conduction block between the pacing site and the reentry circuit. Rarely, ATP may be proarrhythmic or may accelerate hemodynamically stable VT to unstable VT/VF.

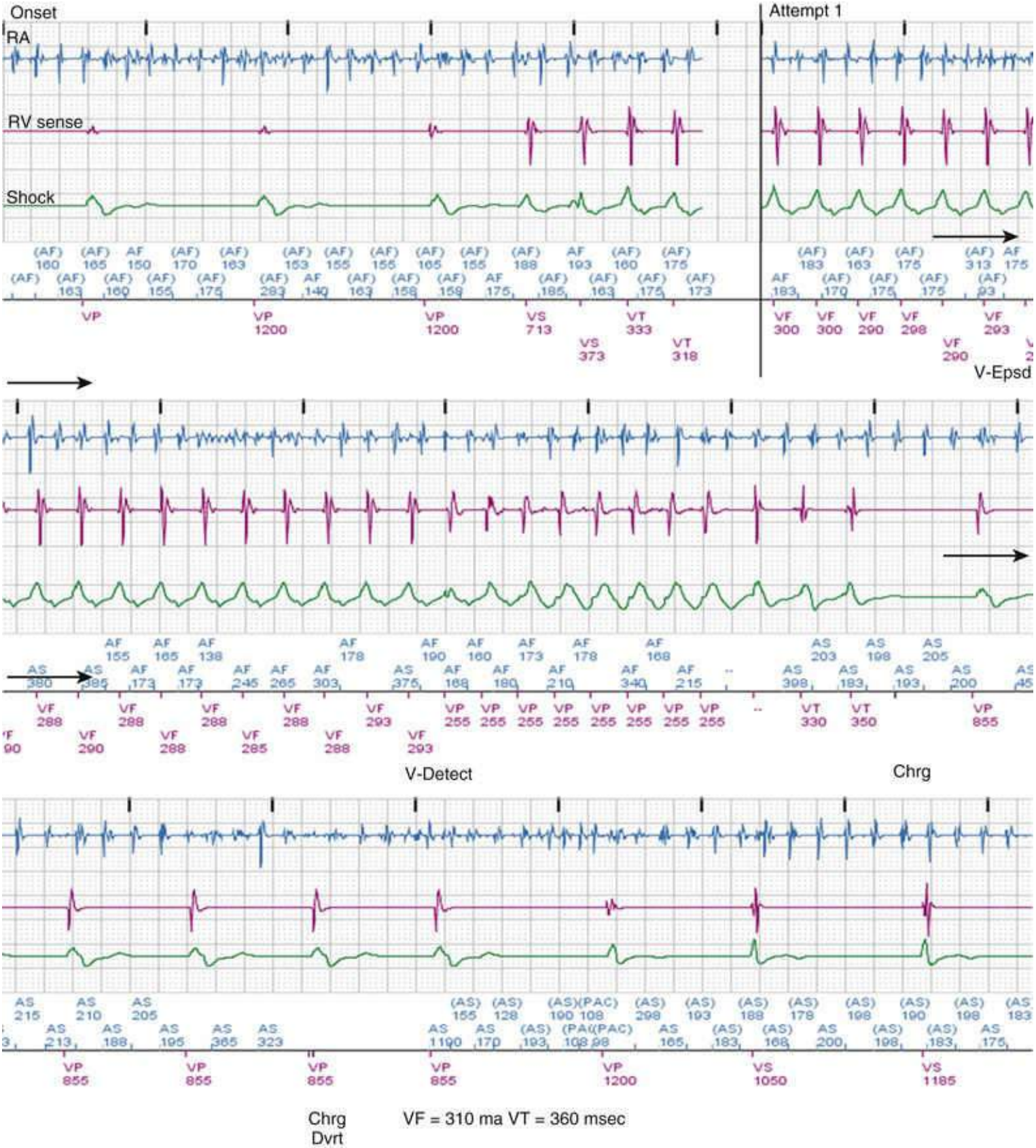
Early studies reported that ATP terminated 80% to 95% of slow VT (<180 beats/min) and 70% or more of fast VT (>180 beats/min). However, these studies were performed with short detection durations, and many of these VTs probably would have terminated spontaneously with presently recommended longer detection durations. This is an example of the concept of "avoidable therapy" discussed later. With longer detection durations, ATP terminates about 80% of slower VTs and 40% to 50% of faster VTs, with a low risk of acceleration (1% to 5%).[21]

Tiered Therapy and Therapy Zones

ICDs have up to three rate-based therapy zones to permit zone-specific therapy for VT/VF (**eFig. 41.12**). Many ICDs permit programming of an additional monitor-only zone between the sinus tachycardia and slowest VT zones. Usually, two to four sequences of ATP are programmed for slower VTs, one or two sequences faster VTs, and at most one sequence for rhythms detected in the fastest "VF" zone. ATP may be effective in an ICD-defined "VF" zone because most arrhythmias detected in this rate-defined zone (usually >185 to 220 beats/min) are fast, monomorphic VT (**eFig. 41.13**). Two sequences terminate approximately 90% of VTs that can be terminated by ATP. If ATP is unsuccessful, the ICD delivers shocks.



EFIGURE 41.12 ICD rate detection zones. Some ICDs permit programming of an additional monitor-only zone. **Upper panel** shows programming for secondary prevention patients; **lower panel** shows programming for primary prevention patients. Generally, the sinus-ventricular tachycardia (VT) rate boundary should be slow enough to ensure detection of all hemodynamically compromising VTs. The optional boundary between the two VT zones should be based on the cycle length at which different durations for detection or different antitachycardia pacing (ATP) is preferred. The VT-ventricular fibrillation (VF) rate boundary is based on the cycle length below which shocks should not be delayed for more than one trial of ATP. Additionally, programming a nontherapy, monitor-only detection zone permits storing EGMs for tachycardias slower than the slowest zone in which VT therapy is programmed. FVT, Fast ventricular tachycardia.



EFIGURE 41.13 ICD EGM illustrates tiered therapy. The continuous stored EGM shows atrial (RA), near-field integrated bipolar (RV Sense), and far-field (Shock) EGMs. The dual-chamber marker channel displays atrial intervals above and ventricular intervals below the line. The atrial rhythm throughout is AF (marker channel). The first three ventricular intervals are paced at 1200 milliseconds (50 beats/min). The fourth beat shows the onset of regular tachycardia, which accelerates to a cycle length of 300 to 290 milliseconds. The *vertical line* denotes interruption of recording after the onset of tachycardia until just before VF is detected initially (V-Epsd at end of **top panel**). Persistence of device-detected "VF" is confirmed in the middle of the **middle panel** (V-Detect), followed by ATP in the VF zone, which terminates the tachycardia. ATP is followed by post-therapy pacing for 5 beats at 855 milliseconds (70 beats/min). Because ATP was delivered in the VF zone, the ICD begins to charge as soon as ATP is completed. In the **lower panel,** "Chrg Dvrt" indicates that the ICD classifies the tachycardia episode as completed, so the charge on the high-voltage capacitors is dissipated. Thus the patient is spared a shock, but the battery

loses the corresponding energy. The last two ventricular EGMs in the **lower panel** represent slowly conducted AF and differ markedly in morphology from tachycardia EGMs. The ICD's classification of this rhythm based on rate alone is “VF.” The ICD does not apply SVT-VT discriminators in the VF zone. The physician's classification is monomorphic VT during AF based on an abrupt onset of rapid, regular tachycardia with morphology different from conducted beats during AF. The ICD should be reprogrammed so that this tachycardia is classified in a VT zone and ATP can be delivered without charging.

Defibrillation

Principles

Bioelectrical Stimulation for Defibrillation.

Pacing pulses are required only to generate a local electric field sufficient to bring excitable myocardial cells to threshold voltage, but defibrillation pulses (shocks) must generate a global electric field throughout all or almost all of the ventricles that is strong enough to alter refractoriness and conduction in partially refractory myocardium. Defibrillation electrodes are much larger than pacing electrodes because of the requirement for global stimulation. Although the required field strength is only a few multiples of that required for pacing (1 V/cm versus 3 to 5 V/cm), shocks need approximately 1 million times more energy than pacing pulses because of the spatial difference in field requirements and the differences in required pulse duration (0.3 to 0.6 msec versus 6 to 12 msec).

Waveforms.

As discussed in relation to pacing, stimulating waveforms are best specified by voltage and duration. However, by custom ICD shocks are specified as delivered energy, even though energy is not a direct determinant of defibrillation. Biphasic waveforms defibrillate more efficiently (lower voltage) than monophasic waveforms (**eFig. 41.2B**). For transvenous ICDs, defibrillation is more efficient if the RV electrode is the anode (versus cathode) for phase 1 of a biphasic waveform.

Shock Strength for Defibrillation.

The relationship between shock strength and defibrillation success is described by a probability of success curve (**Fig. 41.16**). Thus the same clinically relevant strength may either succeed or fail on successive attempts. Nevertheless, the term *defibrillation threshold* (DFT) is often used as a shorthand to describe the results of testing defibrillation shocks with different strengths. The DFT is lower if the shock electrodes are positioned to provide a uniform electric field throughout the ventricles. It is increased by metabolic effects such as hyperkalemia, acidemia, and ischemia. **eTable 41.1** summarizes common drug effects on the DFT. Chronic amiodarone therapy increases DFT, whereas potassium channel–blocking drugs such as sotalol or dofetilide decrease DFT.

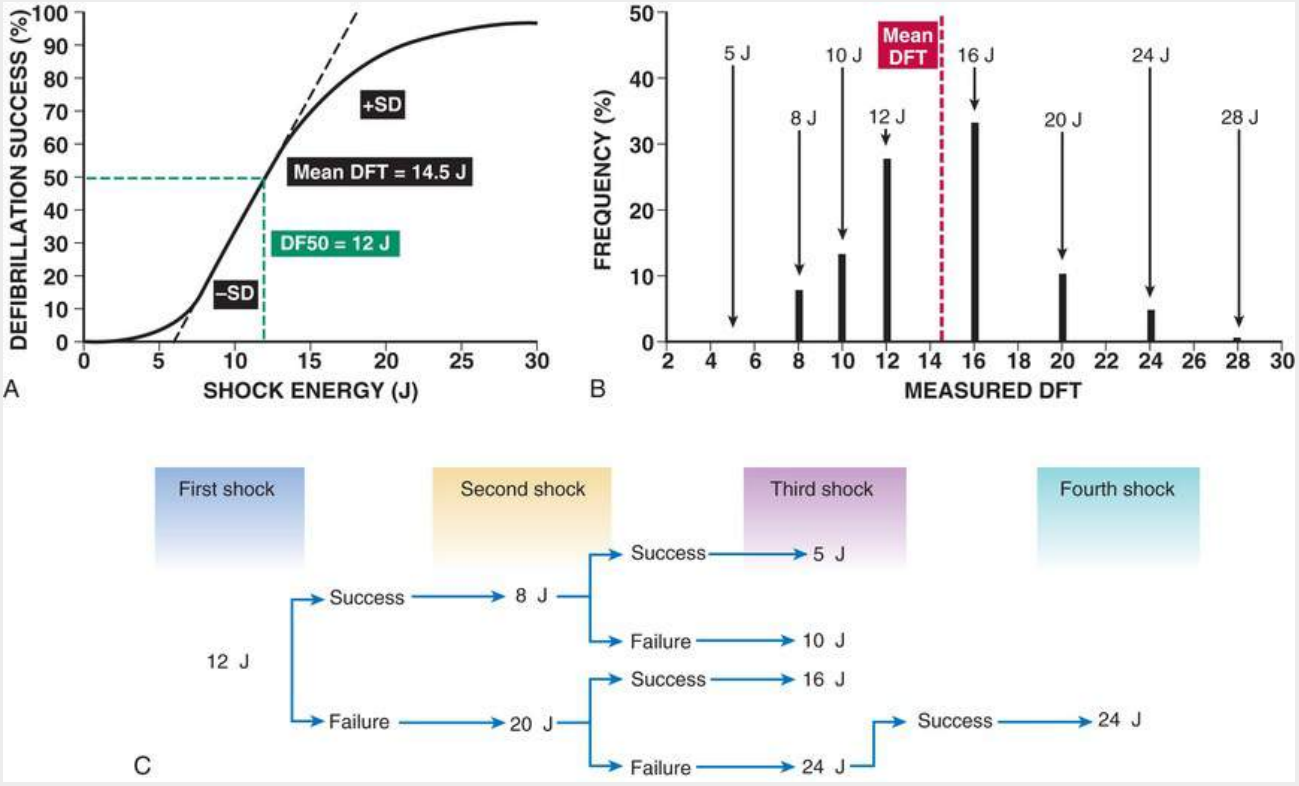


FIGURE 41.16 Relationship in an individual, simulated patient between the defibrillation probability-of-success curve and the measured defibrillation threshold (DFT) using a binary search protocol. **A,** Patient's defibrillation probability-of-success curve. **B,** Plot showing frequency of individual measured DFT values during repeated testing. **C,** Binary search sequence of three or four test shocks used to measure each DFT, starting at 12 J, the shock strength with a 50% probability of success (DF50). The process defined by the binary search protocol results in a single value, which the clinician records as the patient's "DFT." **B** shows the statistical distribution of 50,000 simulated repetitions of this binary search DFT process applied to the defibrillation probability-of-success curve. Even for the most frequently measured DFT value (16 J), there is only about a one-third chance that repeating the process will yield the same result. The mean measured DFT (14.5 J) corresponds to DF68 on the probability of success curve. However, 1 standard deviation of measured DFTs extends from DF30 to DF87. (Modified from Smits K, Virag N. Impact of defibrillation test protocol and test repetition on the probability of meeting implant criteria. Pacing Clin Electrophysiol 2011;34:1515.)

Clinical Application

Implant Testing.

For early ICDs, induction of VF at implant was required to ensure adequate sensing of VF and reliable defibrillation. Subsequently, improved ICD performance and risks of defibrillation testing led to evidence-based omission of defibrillation testing in many patients. Defibrillation safety margin usually is assessed by defibrillation testing, electrically inducing VF and defibrillating at one or more shock strengths (**Fig. 41.16**). With experienced personnel and proper equipment, serious complications are rare.[22] Defibrillation safety margin can also be assessed by vulnerability testing based on the upper limit of vulnerability (ULV; **Fig. 41.17**), which does not require induction of VF with its rare but serious risks.[23] Identifying modern ICD systems with insufficient defibrillation safety margins is challenging because defibrillation is probabilistic, and these devices constitute only about 5% of left pectoral implants.[24]

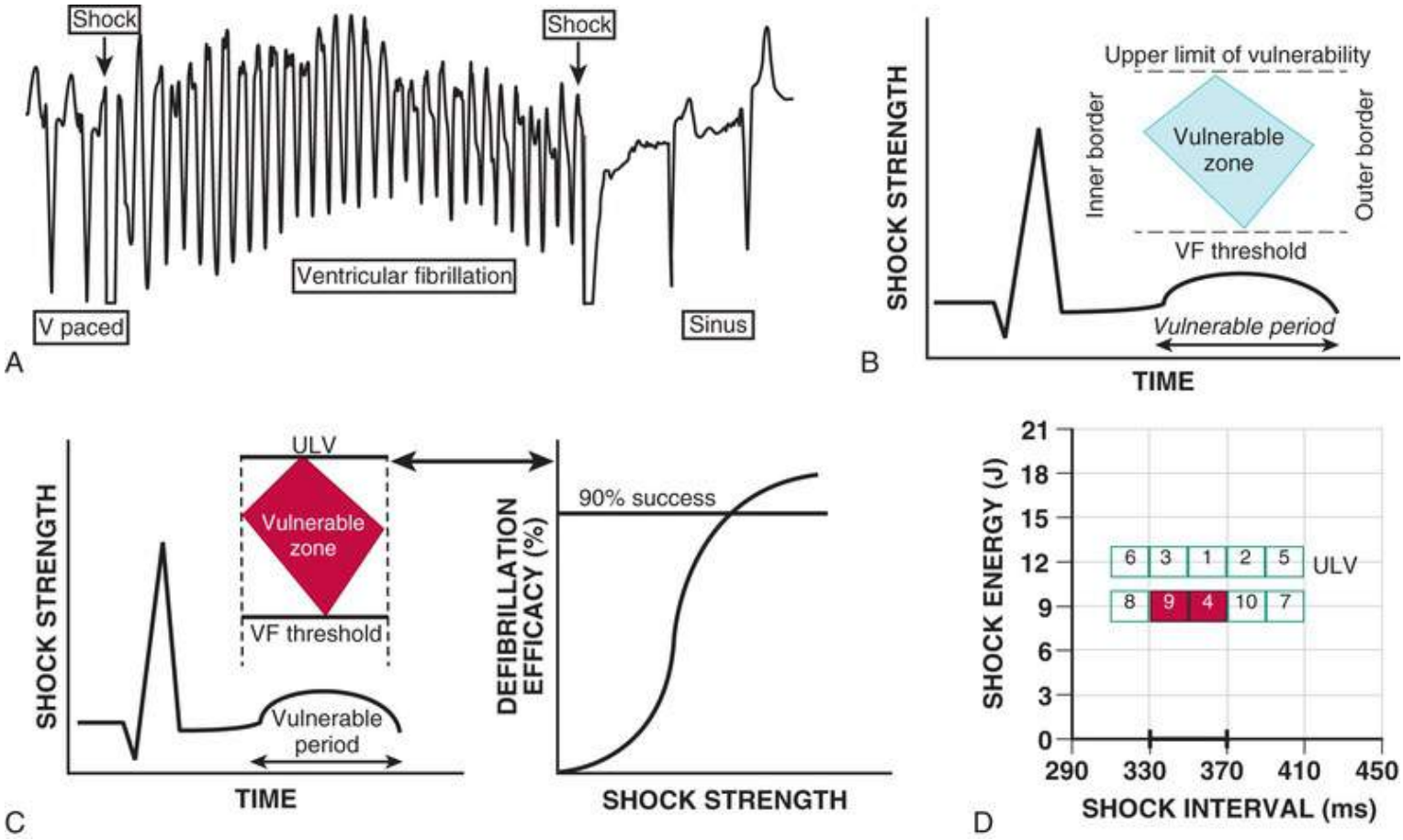


FIGURE 41.17 The vulnerable zone, upper limit of vulnerability (ULV), and the relationship between the ULV and efficacy of defibrillation shocks with the same strength. **A,** Effects of shocks in paced rhythm and VF. Recording during ICD implantation shows surface ECG lead II. At *left arrow,* 2-J monophasic shock delivered on T wave (T shock) of ventricular paced rhythm induces VF. At *right arrow,* 10-J biphasic shock terminates VF. **B,** The vulnerable zone to induction of VF is displayed as a bounded, homogeneous region in a two-dimensional space defined by time (coupling interval) on the abscissa and shock strength on the ordinate. *The ULV is the weakest shock strength at or above which VF is not induced at any time during the vulnerable period*. The upper border (ULV) and the lower borders (VF threshold) are defined by shock strength. The inner (*left*) and outer (*right*) borders are defined by time (coupling interval). **C,** Relationship between ULV and defibrillation probability of success curve. **Left panel** is a smaller version of **B. Right panel** shows defibrillation probability of success curve. The ULV corresponds to the shock strength with a 90% probability of success (DF90), and the ULV + 3 J approximates the DF100. **D,** Methodology. The peak of the vulnerable zone times near the peak of the latest peaking T wave on the surface ECG during ventricular pacing, but the precise relationship may vary from patient to patient. This panel shows procedure for using T shocks to determine a sufficient safety margin for ICD shocks (vulnerability safety margin) without inducing VF in 80% to 90% of patients, as well as the procedure for determining the shock strength at the ULV and the timing of the peak of the vulnerable zone, corresponding to the most vulnerable intervals. For each T shock, the coupling interval after the last pacing stimulus in the S1 train is plotted on the *abscissa,* and the shock strength is plotted on the *ordinate* in units of energy. Each *box* represents a shock in this two-dimensional space. Boxes are 20 milliseconds wide and centered on the measured shock coupling interval. *Open* (*green*) *boxes* represent shocks that did not induce VF. The lowest row of shocks that does not include a *red box* corresponds to the ULV. The height of each box denotes the resolution of tested shock strength, 3 J in this example. The *black bar* on the abscissa denotes the range of most vulnerable intervals. The left end of the bar denotes the inner border, and the right end denotes the outer border. The number in each box indicates its order in the shock sequence. *Filled* (*red*) *boxes* represent shocks that induced VF. *For clinical testing, only noninducing shocks 1, 2, 3, and 5 are sufficient to determine a safety margin for programming ICD shocks*. The remaining shocks are needed to determine the ULV for research purposes. (**D,** From Shehata M et al. Automatic determination of timing intervals for upper limit of vulnerability using ICD electrograms. Pacing Clin Electrophysiol 2008;31[6]:691-700.)

Clinical trials have established that clinical defibrillation testing does not improve outcomes for patients with new, left-sided ICDs and well-positioned defibrillation leads that have satisfactory sensing and pacing thresholds.[22,25] There are at least two plausible reasons: (1) clinical defibrillation failures can

be caused by factors that cannot be measured at implant, such as ischemia; and (2) the low incidence of VT/VF requiring shocks in primary prevention patients limits the impact of differences in defibrillation efficacy on total mortality. Accordingly, current recommendations do not require routine testing in all new, left-sided pectoral implants. However, assessment of defibrillation efficacy or shock testing is recommended for other implants, including subcutaneous ICDs.[25]

Shocks in Clinical Practice.

Shocks are the most reliable therapy for patients with life-threatening VT/VF (**Fig. 41.18**). Most shocks are programmed near maximum output because shock pain is independent of shock strength over the clinically useful range. Clinically, the first-shock success rate for spontaneous VF or rapid, hemodynamically unstable VT is 80% to 95%. ICDs can deliver four to eight shocks per VT/VF episode. Approximately 98% of all spontaneous VT/VF is terminated by the first two shocks, and the overall success rate approximates 99.9% for a VT/VF event.

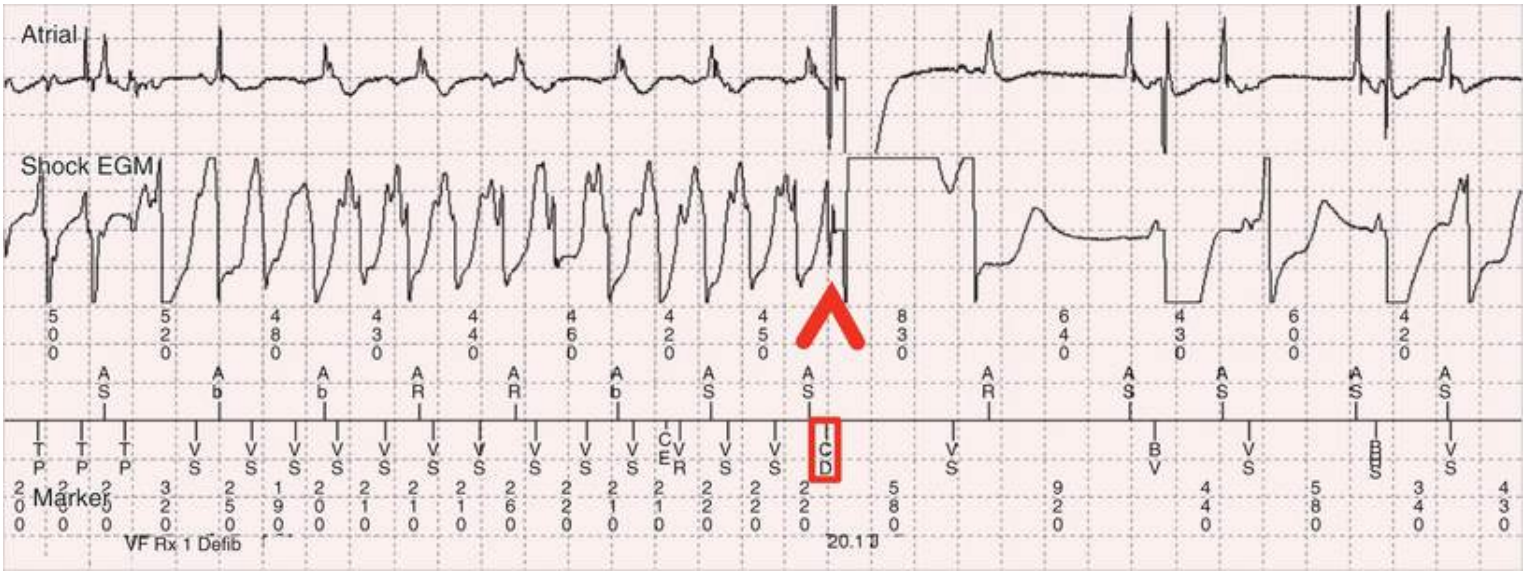


FIGURE 41.18 Dual-chamber EGM showing polymorphic VT with AV dissociation treated with shock. The atrial EGM, high-voltage ("shock") EGM, and dual-chamber marker channel are shown. The *arrowhead* denotes shock, designated by *CD* (charge delivered) on the marker channel. After the shock, the atrial rhythm is sinus with premature atrial complexes; the ventricular rhythm is biventricular paced (BV) with premature ventricular complexes (PVCs) in the sinus rate zone (VS). The second BV beat (BV/VS) has a slightly shorter paced AV delay (110 versus 130 milliseconds) than first BV beat because a PVC occurs during the AV delay and triggers "safety pacing," a feature that reduces crosstalk inhibition.

Although ICD shocks for VT/VF can be lifesaving, minimizing shocks is important because they have adverse psychosocial consequences and increase utilization of medical care (**see Chapter 96**). Additionally, there is a strong correlation between patient mortality and ICD shocks for either VT/VF or AF.[26] This correlation primarily results from more advanced heart disease in patients who experience these shocks. Shocks may also play an incremental, independent causal role in increasing mortality.[25]

ICD Sensing and Detection

Delivery of appropriate ICD therapy depends on both accurate *sensing* of the EGMs that correspond to individual cardiac depolarizations and *detection* of arrhythmias by analyzing a sequence of sensed signals to determine the cardiac rhythm.

ICD Sensing

Dynamic Sensing Threshold.

ICDs need reliable sensing of low-amplitude EGMs during VF, whereas pacemakers do not. Because continuous high sensitivity results in undesirable oversensing, ICDs use feedback mechanisms based on R wave amplitude that adjust sensing threshold dynamically (**Fig. 41.19**) in relation to the amplitude of each sensed intrinsic depolarization or pacing pulse. Compared with a fixed sensing threshold, a dynamic threshold increases the likelihood of sensing low-amplitude and varying EGMs during VF, while reducing the likelihood of T wave oversensing. ICDs do not use unipolar sensing because of the high risk of oversensing when operating at a high sensitivity.

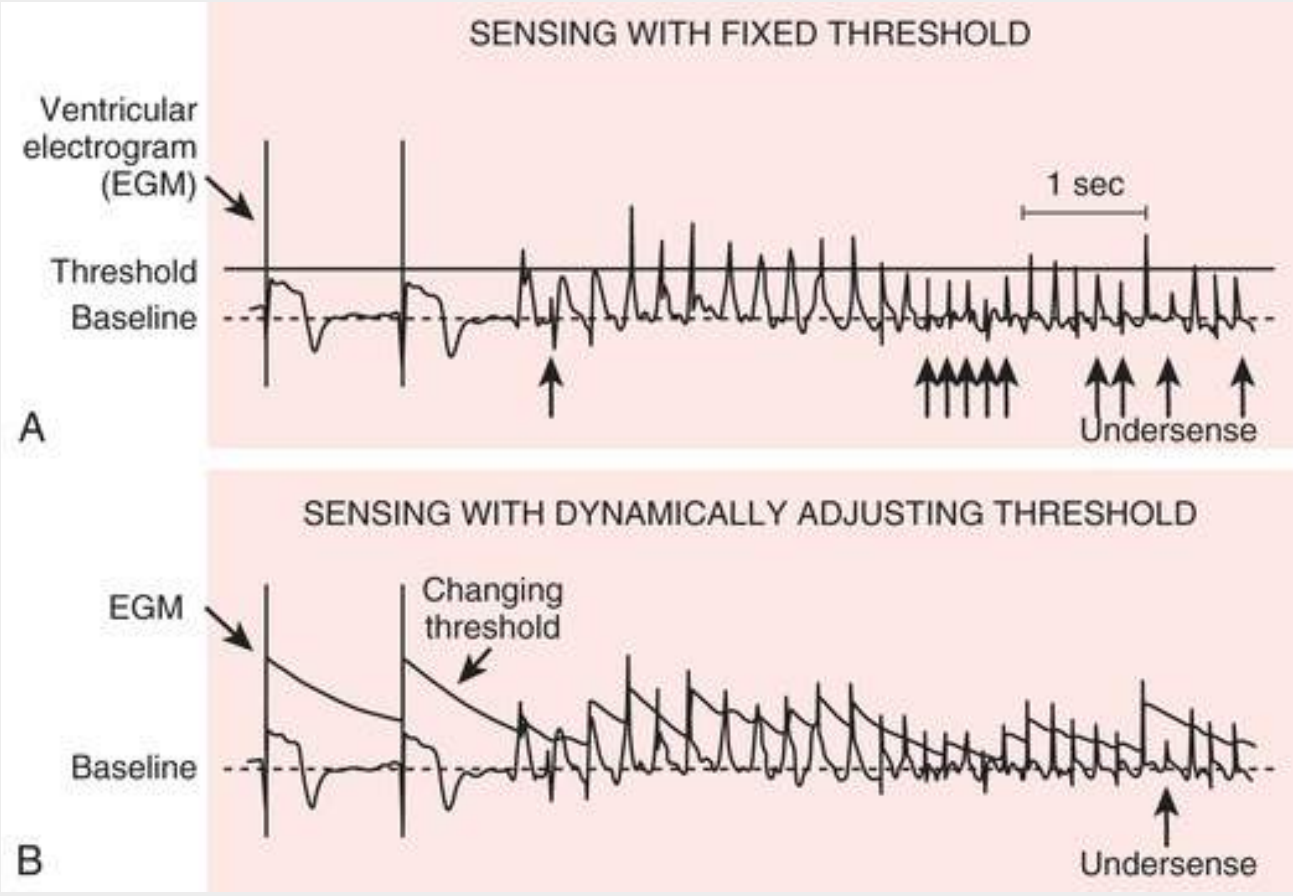


FIGURE 41.19 Dynamic versus fixed sensing threshold in VF. **A,** Fixed sensitivity requires that the sensed potential exceed a fixed threshold. Because of the highly variable amplitude during VF, undersensing occurs (*arrows*). If the threshold is lowered, T wave oversensing may occur. Note that the threshold is just above the T wave amplitude during sinus rhythm, first two complexes. **B,** Dynamic adjustment of sensitivity. At the end of the blanking period after each sensed (or paced) event, the sensing threshold is set to a high value. It then decreases with time until a minimum value is reached. Undersensing is diminished while still retaining a safety margin to prevent T wave oversensing. (Modified from Olson WH. Tachyarrhythmia sensing and detection. In Singer I, editor. Implantable Cardioverter-Defibrillator. Armonk, NY: Futura; 1994, pp 71-107.)

Enhanced Features to Prevent or Mitigate Oversensing.

Dynamic sensing alone cannot both ensure reliable sensing of VF and prevent all oversensing. Thus, ICDs include enhanced features to recognize and prevent oversensing, including “noise” rejection algorithms that reject high-frequency, noncyclic signals; algorithms that reject T waves based on frequency content or morphology (**Fig. 41.20**); and algorithms designed to withhold therapy from

oversensing caused by failure of pace-sense components in ICD leads.[20]

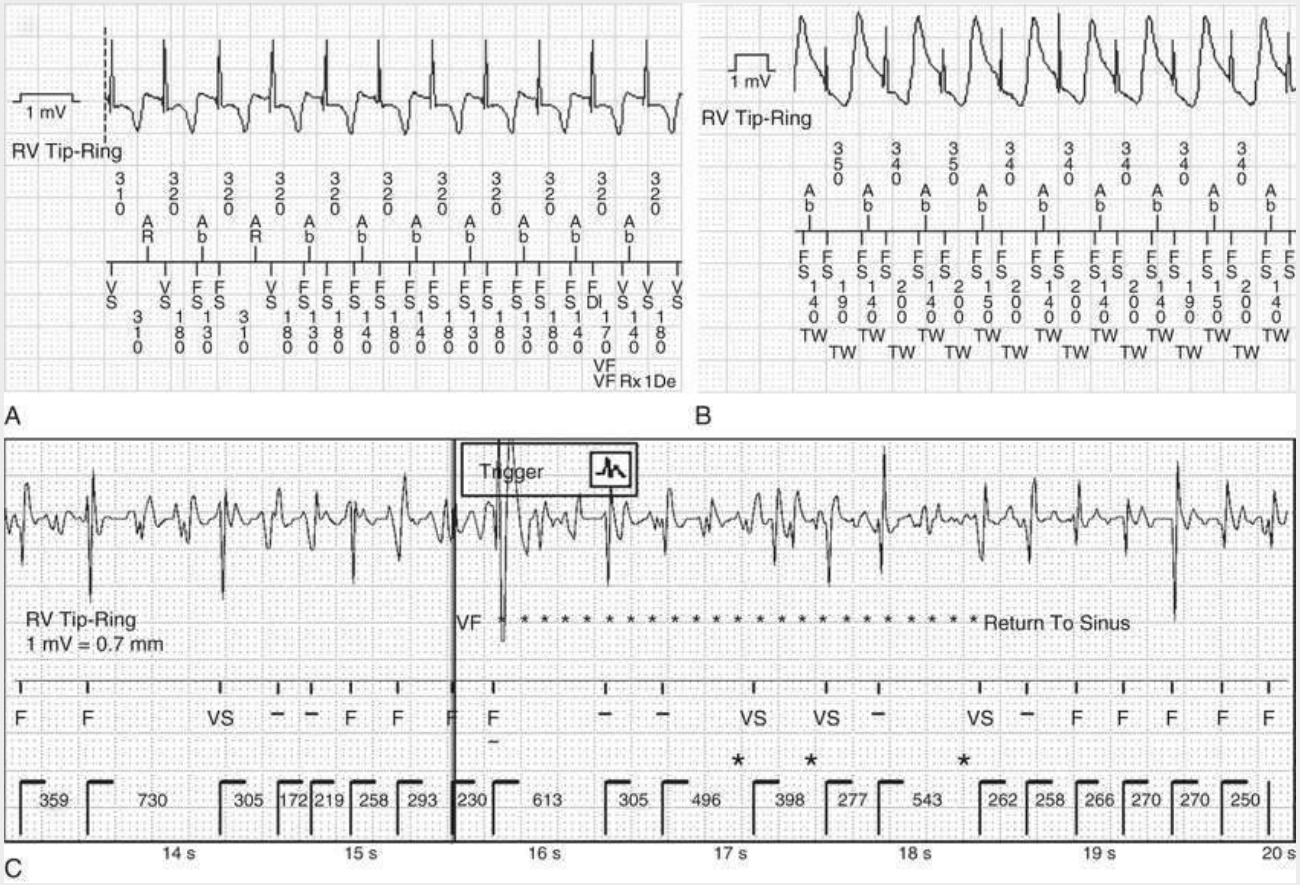


FIGURE 41.20 **A, B,** Oversensing of T waves. Wide-band dedicated bipolar RV EGMs during sinus tachycardia with dual-chamber markers. Each EGM shows the characteristic pattern of alternating high-frequency and low-frequency sensed events, with two ventricular events for each atrial event. One millivolt (mV) calibration markers are shown at *left.* **A,** Oversensing causes inappropriate detection of ventricular fibrillation (VF). High-amplitude T waves cause intermittent oversensing despite adequate (10 mV base to peak) R waves. "VF Rx [Therapy] 1 De" at *lower right* denotes inappropriate detection of VF. **B,** Enhanced sensing algorithm identifies the pattern of T wave oversensing therapy (TW markers) and prevents inappropriate detection of VF despite consistent T wave oversensing. Low-amplitude (1.5 to 4.0 mV) R waves are the root cause of this T wave oversensing. **C,** Undersensing. Dedicated bipolar, filtered EGM is shown during ongoing VF. Between 15 and 18 seconds (s), there are fewer markers than true EGMs indicating undersensing. The single-zone VF detection interval is 360 msec and programmed minimum sensitivity 0.3 mV. Undersensing occurs primarily from amplitude of EGMs changing faster than dynamic sensitivity can adjust despite EGM amplitudes that exceed the minimum sensitivity. Shortly after detection of VF at vertical line (Trigger, VF), three consecutive classified intervals (separated by one unclassified interval) are classified in the sinus zone (VS, *asterisks*). This results in clinically incorrect termination of the device-defined VF episode (Return to Sinus) despite ongoing VF. The ICD subsequently performed a second initial detection of VF and delivered a successful shock. (From Swerdlow CD, Friedman P. Implantable cardioverter-defibrillator: clinical aspects. In Zipes D, Jalife J, editors. Cardiac Electrophysiology: From Cell to Bedside. 7th ed. Philadelphia: Saunders Elsevier; 2018.)

Detection of Ventricular Tachycardia and Fibrillation

Rate and Duration for Detection

Fig. 41.21 provides an overview of the process ICDs use to detect VT/VF. A device-defined episode begins when *ventricular rate* and preliminary *duration* criteria are fulfilled. Essentially, the ICD determines whether the ventricular rate is fast enough for a long enough period to warrant further analysis.

Initial detection requires that enhanced sensing features confirm that sensed events are valid ventricular EGMs, that rate and duration requirements are fulfilled, and if applicable, that the ICD explicitly classifies the rhythm as VT rather than supraventricular tachycardia (SVT).

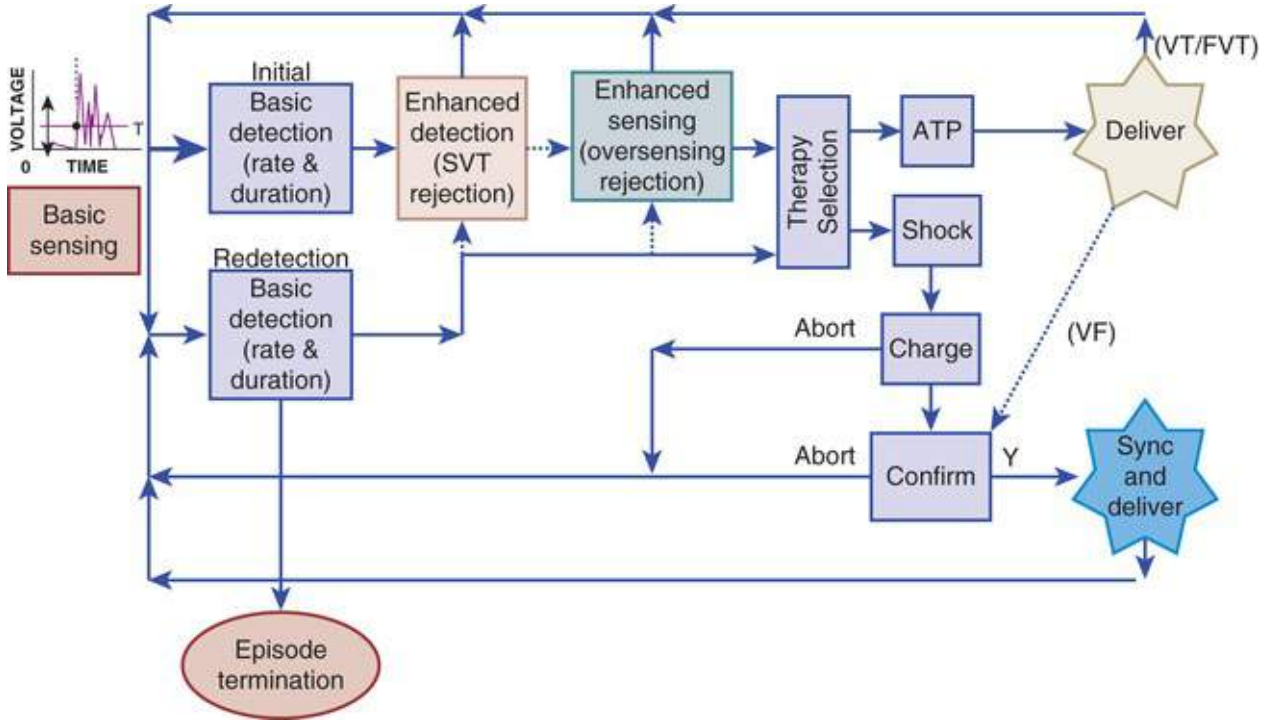
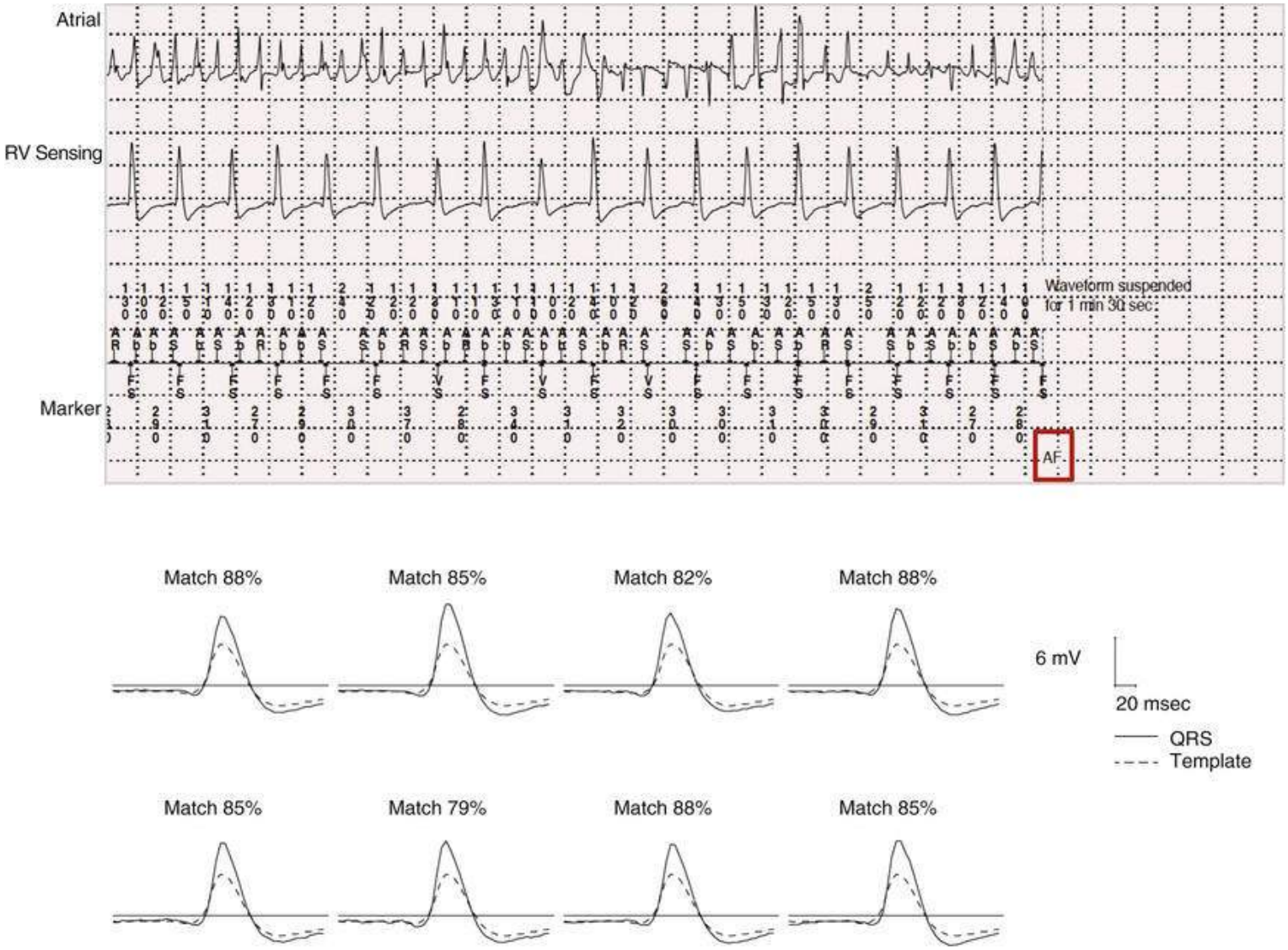


FIGURE 41.21 Overview of ICD detection algorithm. After initial basic (rate and duration) criteria are fulfilled, algorithms apply enhanced detection comprising supraventricular tachycardia–ventricular tachycardia (SVT-VT) discrimination, enhanced sensing features, to detect and redetect VT, fast ventricular tachycardia (FVT), and ventricular fibrillation (VF). Enhanced sensing features may be applied either before intervals are counted or (as shown) after rate and duration are fulfilled. In the first case, oversensed signals are rejected, and only validated intervals contribute to the count. In the second case, episodes are classified specifically as oversensing events. Next, SVT-VT discriminators may classify the tachycardia as SVT; otherwise it is classified as VT/VF. When VT/VF is detected, antitachycardia pacing (ATP) is delivered immediately, but shocks require capacitor charging, which takes 6 to 15 seconds for maximum-energy. After charging is completed, ICDs perform a brief *confirmation* or *reconfirmation* process to determine if VT/VF is still present. The shock is delivered if VT/VF is reconfirmed; otherwise it is aborted. After therapy, ICDs monitor the rhythm for persistence of VT/VF or return to baseline. *Redetection* is the process by which ICDs determine whether VT/VF persists; typically it is less strict than initial detection. If VT/VF is redetected, the next programmed therapy is delivered. Simultaneously, ICDs monitor for a sufficient duration of slow intervals to fulfill the *episode termination* criterion, returning to the initial detection criteria. The VT/VF episode continues until either the ICD redetects VT or declares *episode termination*. Y, Yes. (Modified from Swerdlow C, Brown M, Bordachar P. Sensing and Detection With Cardiac Implantable Electronic Devices. In Ellenbogen KA, Kay GN, Lau CP, et al, editors. Clinical Cardiac Pacing, Defibrillation and Resynchronization Therapy. 5th ed. Philadelphia: Saunders; 2017.)

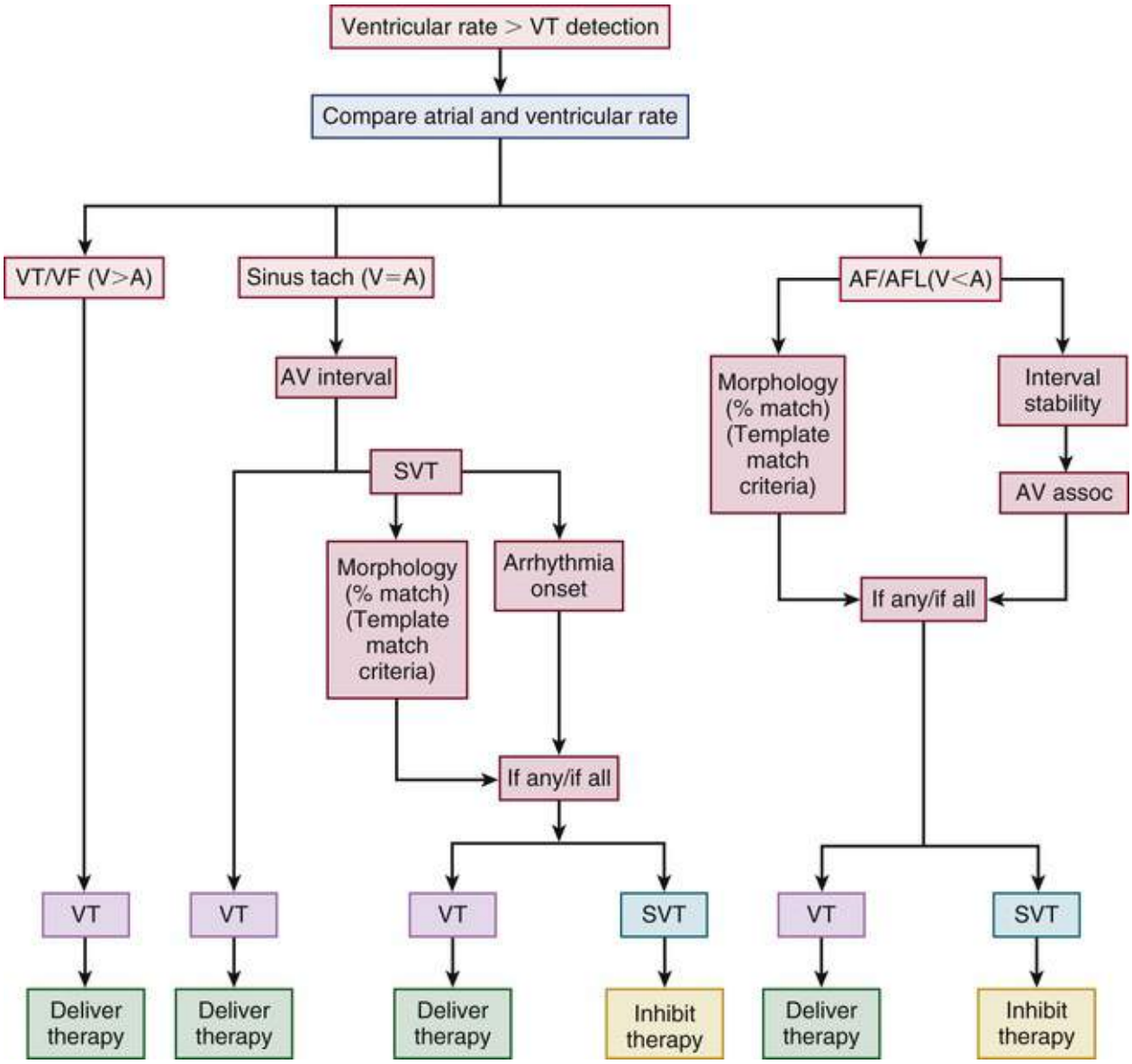
SVT-VT Discrimination

The combination of ventricular rate and duration serves as an implicit SVT-VT discriminator and suffices in many patients,[25,27] but patients in whom SVTs and VTs overlap in rate require an explicit discrimination process in which a sequence of sensed EGMs that satisfies rate and duration criteria for VT/VF are classified as either SVT or VT/VF. *Discriminators* are individual algorithm components or “building blocks” that provide a partial or complete rhythm classification for a subset of rhythms. Individual discriminators may be considered in relation to the EGMs analyzed (ventricular only or both atrial and ventricular), the rhythm that they identify (e.g., AF, sinus tachycardia, VT), or the type of EGM

information analyzed (intervals versus morphology).[25,27] **eTable 41.5** summarizes the most commonly used individual discriminators. *Discrimination algorithms* integrate complementary component discriminators to classify tachycardias as VT/VF or SVT (**eFigs. 41.13 to 41.15**).



EFIGURE 41.14 Correct classification of rapidly conducted atrial fibrillation (AF) by ventricular EGM morphology. The atrial EGM, right ventricular sensing EGM, and dual-chamber marker channel are shown. Most intervals are classified in the ventricular fibrillation (VF) zone (FS), which is programmed to less than 320 milliseconds. The "AF" designation at right of the marker channel (*red box*) indicates that the rhythm is classified as AF. The basis for this classification is shown in the **lower panel,** which compares the morphology of shock (high-voltage) EGMs during tachycardia (*solid lines*) with those of a template stored during baseline sinus rhythm (*dotted line*). Match percentages of 70% or greater between the two EGMs are considered sufficiently close that the rhythm is classified as "supraventricular." It is designated as AF based on the atrial rhythm.



EFIGURE 41.15 Supraventricular tachycardia (SVT)–ventricular tachycardia (VT) discrimination algorithm. This figure shows the hierarchic sequence of individual discriminators in one manufacturer's dual-chamber algorithm (St. Jude Medical). Most manufacturers use conceptually similar algorithms. The first step is comparison of atrial (A) versus ventricular (V) rate. Rhythms are classified into three Rate Branches: ventricular rate greater than atrial rate (V > A), ventricular rate equal to atrial rate (V = A), and ventricular rate less than atrial rate (V < A). All rhythms in the V > A rate branch are treated as VT. The V < A rate branch discriminates rapidly conducted atrial fibrillation (AF)/atrial flutter (AFL) from VT during AF/AFL. The V = A rate branch discriminates sinus tachycardia and other 1 : 1 SVTs from VT with 1 : 1 VA conduction. The primary single-chamber discriminator in both these rate zones is ventricular EGM morphology. If V < A, the algorithm may also apply regularity of the ventricular rhythm (interval stability to reject AF) and N:1 AV association (to reject atrial flutter). If V = A, the algorithm may also incorporate analysis of arrhythmia onset, which may be either chamber of onset or ventricular sudden onset to differentiate pathologic tachycardias form sinus tachycardia. When multiple single-chamber discriminators are used, they may be combined to detect VT only if all discriminators classify the rhythm as VT ("If All") or if any one of the discriminators ("If Any") classifies the rhythm as VT. "Morphology" indicates morphology of the ventricular EGM; Sinus Tach, sinus tachycardia; VF, ventricular fibrillation.

ETABLE 41.5

SVT-VT Discriminators Used in ICDs

DISCRIMINATOR	PURPOSE/INFORMATION	POTENTIAL WEAKNESSES
Single-Chamber Ventricular Discriminators		
R-R regularity	Discrimination of monomorphic VT (regular cycle lengths) from rapid AF (irregular cycle lengths)	May lose effectiveness as ventricular rates during AF increase; 2 : 1 atrial flutter has regular R-R intervals; may cause underdetection of VT with irregular R-R intervals
R-R onset	Identifies sudden ventricular rate changes	Not specific for atrial or ventricular tachyarrhythmias; may miss VT arising during sinus tachycardia
VEGM morphology	Abnormal VEGM morphology may indicate VT/VF	Confounded by conduction aberrancy or changes in "normal" VEGM morphology
Commonly Used Dual-Chamber Discriminators		
Comparison of atrial vs. ventricular rate	VT diagnosed if atrial rate is less than ventricular rate	Confounded by atrial undersensing or far-field R wave oversensing
P-R dissociation	P-R dissociation usually indicates VT	AV reentrant tachycardia; VT with 1 : 1 retrograde conduction; AF that conducts rapidly with apparent P-R dissociation
P-R patterns/relationships	Consistent P-R patterns/relationships usually indicate SVT	AV reentrant tachycardia and VT with 1 : 1 retrograde conduction
Chamber of onset (acceleration)	Identifies whether tachycardia initiates in atrium or ventricle	A single oversensed/undersensed event may result in misclassification.

AEGM, atrial electrogram; *AF,* atrial fibrillation; *AV,* atrioventricular; *SVT,* supraventricular tachycardia; *VEGM,* ventricular electrogram; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia.

Strategic Programming to Reduce Shocks and ATP

Appropriate ICD shocks save lives but are painful to the conscious patient and have other adverse effects. Further, both shocks and ATP can be proarrhythmic. An expert consensus statement addresses strategies to program sensing, detection, and therapy to reduce adverse effects of ATP and shocks.[25] This statement classifies therapies as *appropriate* if delivered for sustained VT/VF and *inappropriate* if delivered for a rhythm other that VT/VF. In addition, it classifies appropriate therapy as *avoidable* if it could have been withheld without adverse clinical consequences. Examples of avoidable therapy include shocks for self-terminating VT or VT that could be terminated by ATP. Avoidable therapies are also referred to as *unnecessary*.

Strategic programming of sensing, detection, and therapy reduces inappropriate and avoidable therapies and may reduce overall mortality.[25] Such programming has reduced the rate of inappropriate or avoidable shocks to 2% to 5% for the first year after transvenous ICD implant[18,25] (**Table 41.3** and **eTable 41.6**).

TABLE 41.3

Strategic Programming Principles for Shock Reduction*

PRINCIPLE	RATIONALE
Sufficiently long detection time	Do not treat self-terminating VT. AF with rapid ventricular rate is less likely to exceed the rate threshold for a longer detection time.
Fast VT detection rate in primary prevention patients and secondary-prevention survivors of VF	Do not treat slower tachycardias, which are more likely to be SVT.
SVT-VT discrimination	Do not treat SVT.
ATP in all VT/VF detection zones	ATP is painless. Even in the "VF" zone, most rhythms are monomorphic VT; many can be terminated by ATP.
Maximum shock strength†	Minimize unsuccessful shocks for VT, VF, or AF with rapid ventricular rate.
Enhanced sensing features	Minimize shocks for oversensing.

*Providing AV conduction is normal and discriminator is reliable.

†Adult patients.

AF, Atrial fibrillation; *ATP,* antitachycardia pacing; *SVT,* supraventricular tachycardia; *VT,* ventricular tachycardia.

ETABLE 41.6

Selected Consensus Recommendations for Strategic ICD Programming*

TACHYCARDIA DETECTION PROGRAMMING RECOMMENDATIONS	CLASS	LEVEL OF EVIDENCE	COMMENT
Detection duration should be programmed to at least 6 to 12 seconds or 30 intervals.	I	A/B-R*	Reduce total therapies
For primary prevention adult patients, the slowest detection rate should be programmed to 185 to 200 beats/min.	I	A	Reduce total therapies
For secondary prevention patients, it is reasonable to program the slowest detection rate at least 10 beats/min less than documented VT rate but not greater than 200 beats/min.	IIa	C-EO	Reduce total therapies
Supraventricular tachycardia (SVT)–ventricular tachycardia (VT) discrimination algorithms should be programmed "on" up to 200 to 230 beats/min.	I	B-R	Reduce inappropriate therapies
Antitachycardia pacing (ATP) should be programmed for all VT/ventricular fibrillation (VF) zones up to 230 beats/min in all patients with structural heart disease.	I	A	Reduce shocks

**A,* Primary prevention; *B-R,* secondary prevention.

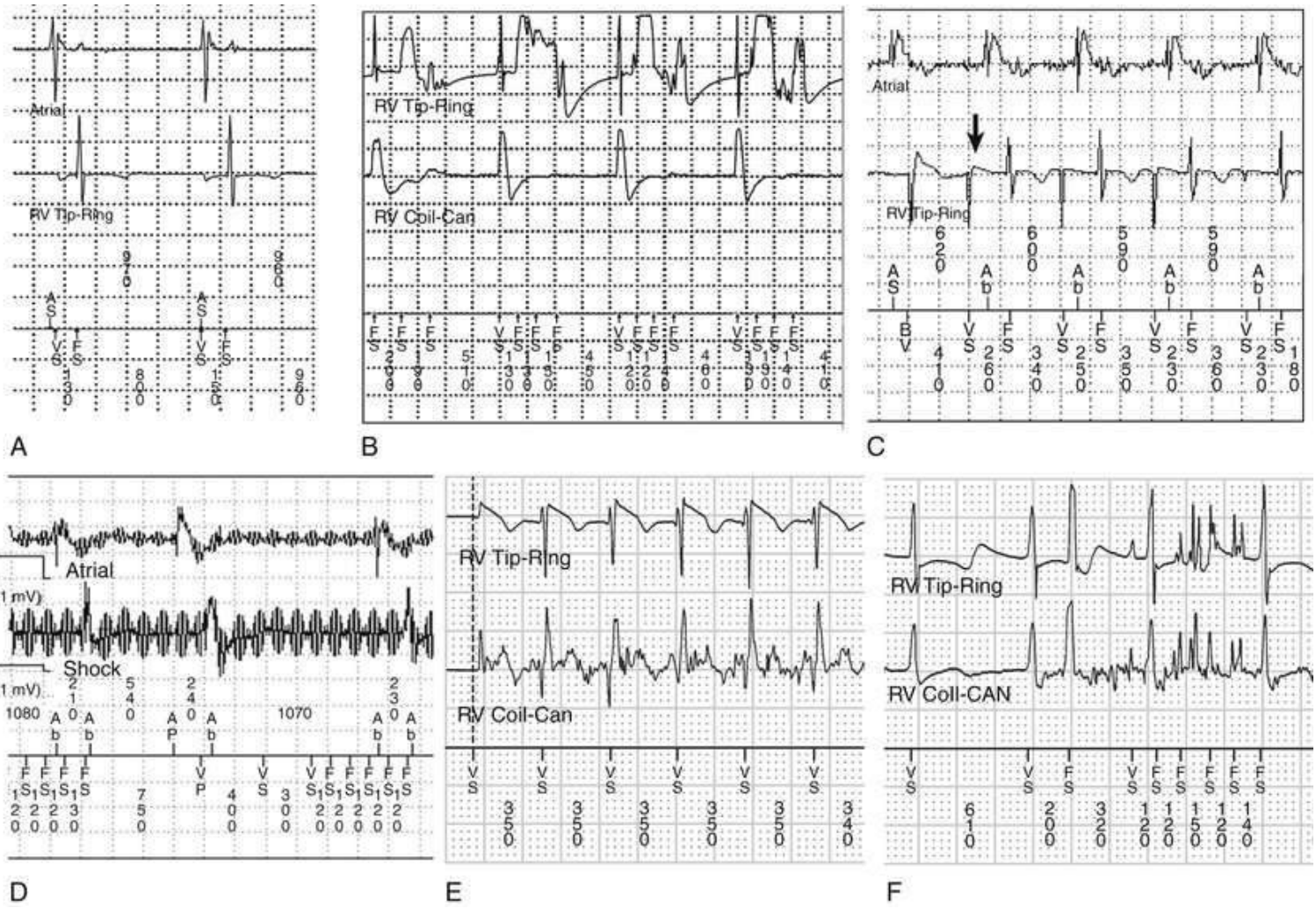
From Wilkoff BL, Fauchier L, Stiles MK, et al. 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. Heart Rhythm 2016;13(2):e50-86.

ICD Troubleshooting

Ventricular Oversensing

In early ICDs, ventricular oversensing of rapid signals usually presented as inappropriate detection of VT/VF with delivered therapy or aborted shocks. In modern ICDs with enhanced sensing features, oversensing typically presents as oversensing alerts.

Oversensing can be classified by EGM morphology, temporal pattern (cyclic versus noncyclic), source type (physiologic versus nonphysiologic), and source location (intracardiac versus extracardiac) (**eFig. 41.16**). Signals that vary with the cardiac cycle (cyclic signals) indicate an intracardiac sources. Nonphysiologic sources usually are extracardiac (e.g., EMI), except for those generated by intracardiac lead failures. Physiologic signals can be intracardiac (P, R, or T waves that cause one oversensed signal per cardiac cycle) or extracardiac (myopotentials). Specific sources can generate oversensed signals with characteristic features that differ from true cardiac EGMs in frequency content and amplitude.[20]



EFIGURE 41.16 EGM patterns of ventricular oversensing. Each panel shows labeled EGMs and marker channel. **Upper panels,** Cyclic oversensing patterns of intracardiac signals. **A,** Atrial and ventricular sensing EGMs in P wave oversensing. Cyclic oversensing of physiologic T waves and P waves or R-wave double-counting results in a pattern of 1 oversensed signal per true cardiac cycle that corresponds consistently to P waves, T waves, or a second component of R waves. In contrast, oversensing of cyclic, nonphysiologic signals from intracardiac lead failure is diagnosed by the superimposition of nonphysiologic signals on true ventricular EGMs at a fixed time in the ventricular cycle. **B,** Multiphasic signal superimposed on ST segment and T wave in Fidelis lead (Medtronic) ring-cable fracture results in multiple oversensed events per cardiac cycle. **C,** Cyclic spikes caused by inside-out insulation breach of Riata lead (St. Jude Medical). **Lower panels,** Noncyclic oversensing patterns of extracardiac signals. **D,** External electromagnetic interference (EMI) typically appears on multiple channels. The 60-Hz signal from line current appears with an 8-Hz modulation due to telemetry sampling at 128 Hz, just above the Nyquist limit. **E,** High-frequency pectoral myopotentials are a *normal* finding on EGMs that include the Can as one electrode. No oversensing occurs on marker channel. **F,** In-pocket lead, insulation breach results in oversensing of pectoral myopotentials on dedicated bipole in RV apex (upper EGM). Myopotential on lower (shock) EGM are a normal finding (see **E**) and do not indicate a breach of the conductor to the RV coil.
(From Swerdlow CD, Friedman P. Implantable cardioverter-defibrillator: clinical aspects. In Zipes D, Jalife J, editors. Cardiac Electrophysiology: From Cell to Bedside. 7th ed. Philadelphia: Saunders Elsevier; 2018.)

Shocks: Diagnosis and Management

Minimizing shocks requires strategic programming, use of patient alerts, and remote monitoring. Once shocks occur, diagnosis and management tools include clinical data (history, chest radiograph), ICD diagnostics (e.g., lead impedance trends), and stored EGMs.

Approach to the Patient with Shocks

Fig. 41.22 summarizes a three-step approach to the patient who presents with a shock. First, analyze

stored EGMs to determine if it was delivered in response to a tachycardia or oversensing. Second, if the shock responded to a tachycardia, determine if the rhythm is VT or SVT using established principles of ECG and EGM analysis. Third, determine if an appropriate shock for VT/VF could have been be avoided by either strategic programming (**see Table 41.3 and eTable 41.6**) or nondevice interventions (**eTable 41.7**)

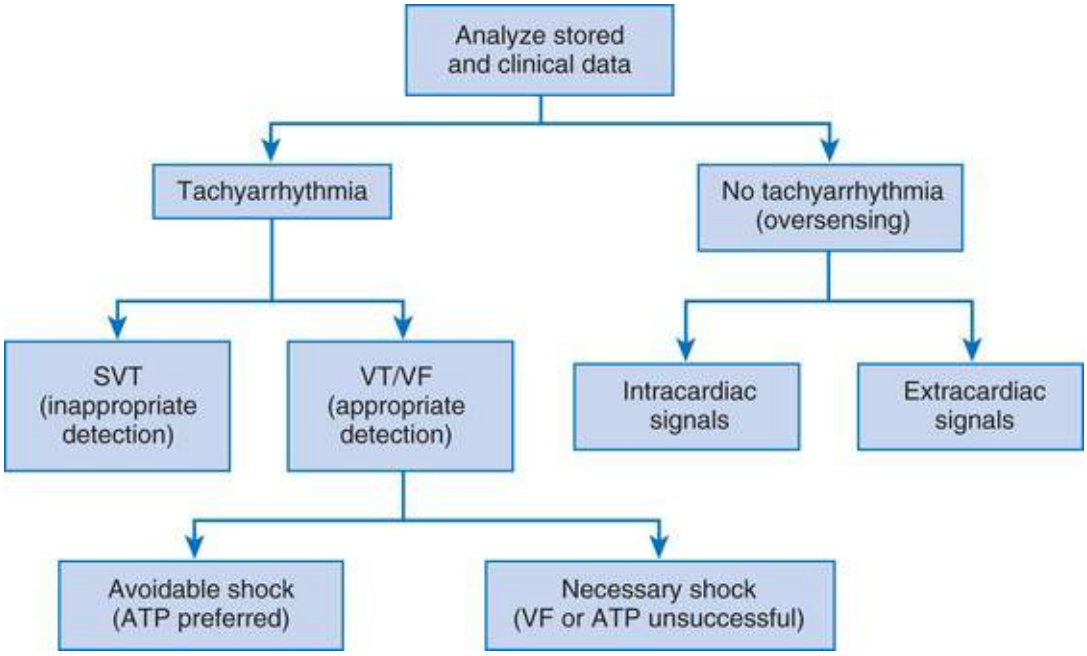


FIGURE 41.22 Differential diagnosis of ICD shocks. See text for details.

ETABLE 41.7

Non–Device-Related Interventions to Reduce Shocks in ICD Patients

	SHOCKS FOR VT/VF	SHOCKS FOR AF/SVT
General Cardiac Care		
Prevent metabolic abnormalities (e.g. K^+)	X	
Prevent ischemia	X	
Optimize heart failure therapy	X	X
Maximize beta blocker dose	X	X
Nondevice Therapy for Arrhythmias		
Antiarrhythmic drugs (sotalol, amiodarone)	X	X
Catheter ablation	X	X
Neuraxial modulation	X	
Minimize Proarrhythmia		
From drugs	X	
From pacing	X	X
Lifestyle		
Minimize triggers in susceptible patients	X	X

AF, Atrial fibrillation; *SVT,* supraventricular tachycardia; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia.

Because shocks for VT/VF or rapidly conducted AF are associated with increased mortality over weeks to months,[26] the clinician should not only diagnose and treat the immediate precipitant of shocks but also consider treatments to reduce delayed mortality. Thus, patients who present with a change in shock pattern should be reassessed for HF and ischemia.

The approach to shocks delivered for oversensing is guided by the cause of oversensing. T wave oversensing was once a common cause of inappropriate shocks in transvenous ICDs (**see Fig. 41.21**), but its frequency has been reduced by multiple sensing enhancements and programming options.[20] Despite

prescreening, it remains the most common cause of oversensing in subcutaneous ICDs. Shocks for SVT may be corrected by reprogramming (rate zones or SVT-VT discriminators) and treatment with beta blockers, antiarrhythmic drugs, or ablation. Most avoidable shocks for self-terminating VT may be prevented by strategic programming.

A patient with a *single shock* should be evaluated in person or by remote monitoring within 24 to 48 hours. In contrast, *repetitive shocks* constitute an emergency (**Fig. 41.23**). The cause must be determined, and VT/VF detection may be disabled using a programmer or magnet. Repetitive shocks for VT/VF may be caused by multiple unsuccessful shocks for a single episode or recurrent VT/VF after successful shock termination ("VT storm").

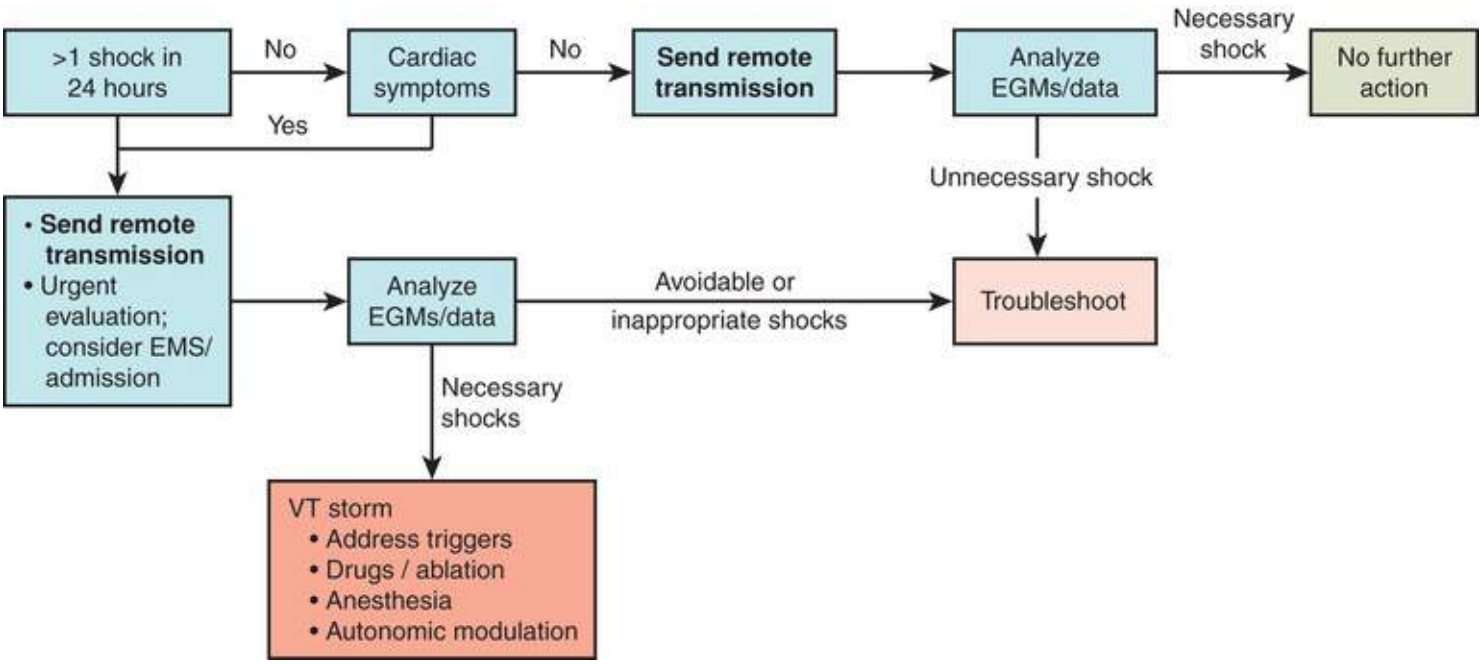


FIGURE 41.23 Approach to the patient with ICD shocks at home. Remote monitoring facilitates care of patients who receive shocks. In the absence of ongoing cardiac symptoms, a single appropriate shock (reviewed remotely) does not require further intervention. Multiple shocks or ongoing symptoms require urgent action to treat VT storm, treat SVT, or troubleshoot to prevent oversensing. (From Swerdlow CD, Friedman P. Implantable cardioverter-defibrillator: clinical aspects. In Zipes D, Jalife J, editors. Cardiac Electrophysiology: From Cell to Bedside. 7th ed. Philadelphia: Saunders Elsevier; 2018.)

Treatment of VT storm includes reversal of precipitating events, beta blockers, and antiarrhythmic therapy. Neuraxial interventions may also be useful.[28] Causes include acute ischemia, exacerbation of HF, metabolic abnormalities (e.g., hypokalemia, amiodarone-induced hyperthyroidism), and drug proarrhythmia or noncompliance.

Unsuccessful Shocks

Table 41.4 summarizes causes of unsuccessful shocks. If an ICD classifies a shock for VT/VF as unsuccessful, stored EGMs should be reviewed to determine if the shock truly failed to terminate VT/VF, or if the ICD misclassified effective therapy as ineffective (e.g., due to immediate arrhythmia recurrence). Because defibrillation success is probabilistic, occasionally shocks fail, but failure of two maximum-output shocks is rare if the safety margin is adequate. Shocks from chronic ICD systems fail to terminate true VT/VF because of both patient-related and ICD system–related causes. Many patient-related causes can be reversed, but system-related causes usually require operative intervention. ICD data should be

reviewed for clues to system-related causes, including excessive detection or charge times, evidence of lead or connection failure, mismatch between programmed and delivered shock strength, and out-of-range high-voltage impedance, suggesting a failure in lead components of the shock circuit. In the absence of a diagnosis, defibrillation testing should be performed.

TABLE 41.4

Causes of Unsuccessful ICD Shocks

Successful Termination of VT/VF Misclassified by the ICD
VT/VF recurs before the device determines the VT/VF episode has terminated.
Failure to terminate SVT (e.g., sinus tachycardia)
Postshock rhythm is SVT in the VT rate zone.
Patient-Related Factors
Metabolic (hyperkalemia)
Ischemia
Progression of heart failure
Some antiarrhythmic drugs (e.g., amiodarone, type IC)
Pleural or pericardial effusions
Device System–Related Reasons
Insufficient programmed shock strength
Battery depletion
Failure of generator component or lead
Device-lead connection problem
Lead dislodgment
Delayed detection resulting in a prolonged VT/VF that increases required shock strength

Failure to Deliver Therapy or Delayed Therapy

Delayed therapy or failure to deliver therapy can be caused by sensing problems, programmed detection parameters, or ICD system malfunction. In modern ICDs, clinically significant undersensing of VF is rare but may be caused by low-amplitude EGMs, rapidly varying EGM amplitudes (**see Fig. 41.20C**), drug effects, postshock tissue changes, and device-device or intradevice interactions.[20] Rarely, enhanced sensing features may classify VF as oversensing and withhold therapy. VF may be underdetected despite adequate sensing due to device inactivation or programming (sensitivity, rate, duration, SVT-VT discriminators). Lead, connector, or generator malfunction can also prevent shock delivery.

ICD Lead Failure: Presentation and Management

The serious consequences of ICD lead failure combined with reliability concerns for specific lead models and have focused efforts on early diagnosis.[17,29] Excluding leads with known high failure rates, the overall incidence of clinical failure is about 1.3 per 100 lead-years.[30]

Clinical Presentations

Pace-sense malfunctions account for most failures. Oversensing is the most common initial electrical abnormality with either conductor fracture or insulation breach.[17,29] Conductor fractures usually cause a characteristics pattern of oversensing[17] (**Fig. 41.24**). Unlike conductor fractures, insulation breaches themselves do not generate abnormal signals. Instead, oversensing occurs because external signals enter the conductor at the breach; EGM patterns vary, reflecting the source signal (**eFig. 41.16C, F**). Several enhanced sensing features incorporate specific features of lead-related oversensing to alert patients and physicians and, in some cases, withhold inappropriate shocks[20,29] (**see Fig. 41.20B**).

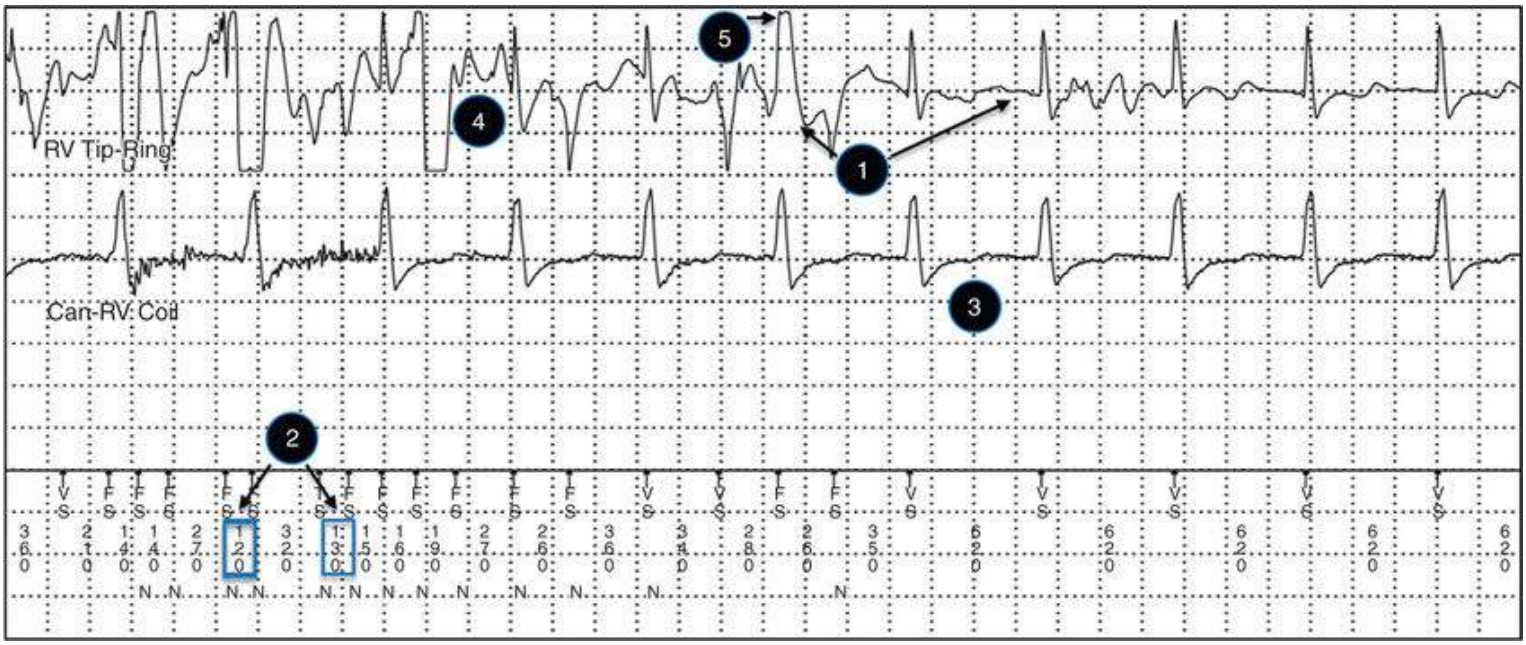


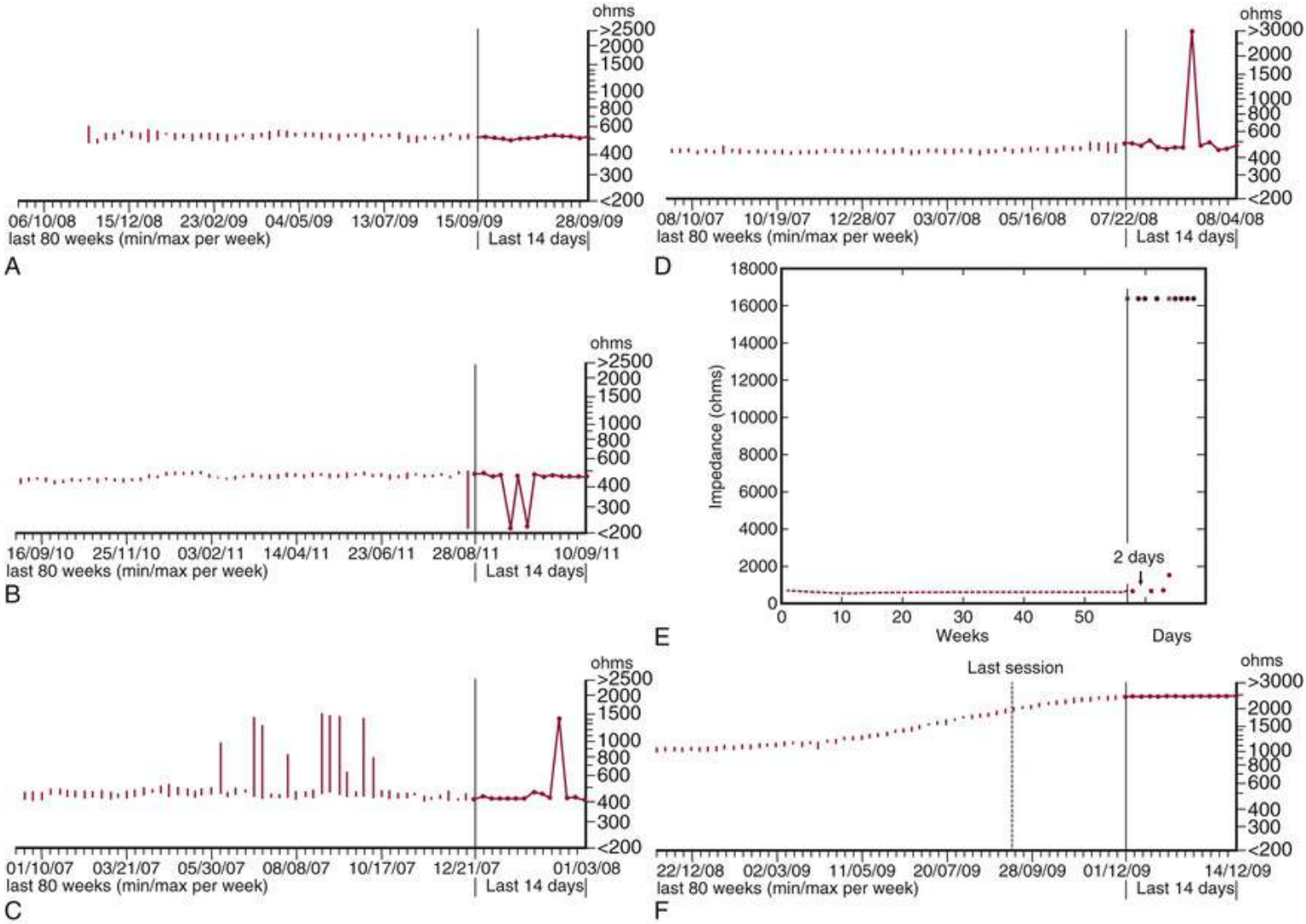
FIGURE 41.24 Characteristic features of EGM in conductor fracture or connection problem between DF1 lead and header: (1) intermittent nonphysiologic signals; (2) "nonphysiologic" intervals too short to correspond to successive ventricular depolarizations; (3) no abnormal signals on shock channel of dedicated sensing bipole; (4) variable amplitude, morphology, and frequency; (5) may saturate sensing amplifier. Enhanced sensing feature (Lead Noise Algorithm) prevents inappropriate detection of VF, classifying intervals as "N" (noise) on marker channel. High-frequency signal superimposed on shock channel probably is caused by pectoral myopotentials, which are a normal finding on EGMs, including the can (see eFig. 41.16E, F). (From Swerdlow CD, Friedman P. Implantable cardioverter-defibrillator: clinical aspects. In Zipes D, Jalife J, editors. Cardiac Electrophysiology: From Cell to Bedside. 7th ed. Philadelphia: Saunders Elsevier; 2018.)

Pacemakers and ICDs periodically measure direct-current electrical resistance ("impedance") of the pacing circuit. Usually, pacing impedance is in the normal range when oversensing occurs. Pace-sense malfunctions can also present with pacing impedance changes, loss of capture, or abrupt decrease in R wave amplitude. Pacemaker lead failures present identically to failures of ICD pace-sense components, except that oversensing causes only inhibition of pacing, not inappropriate therapy for VF.

Shock-component malfunction presents with shock-impedance changes, abnormal signals on shock EGMs, or failed defibrillation shocks. Insulation breaches that cause high-voltage short circuits may also cause ICD generator failure.

Impedance and Impedance Trends in Diagnosis of Lead Failure

Conductor fractures may cause abrupt increases in impedance; conversely, insulation breaches may cause abrupt decreases in impedance. **eFig. 41.17** shows examples of pace-sense impedance trends in various conditions. Oversensing usually precedes impedance changes in pace-sense component failures, but impedance changes occur before or concurrently with oversensing in a minority of cases. When the cause of oversensing is in doubt, impedance abnormalities confirm the diagnosis of lead failure.

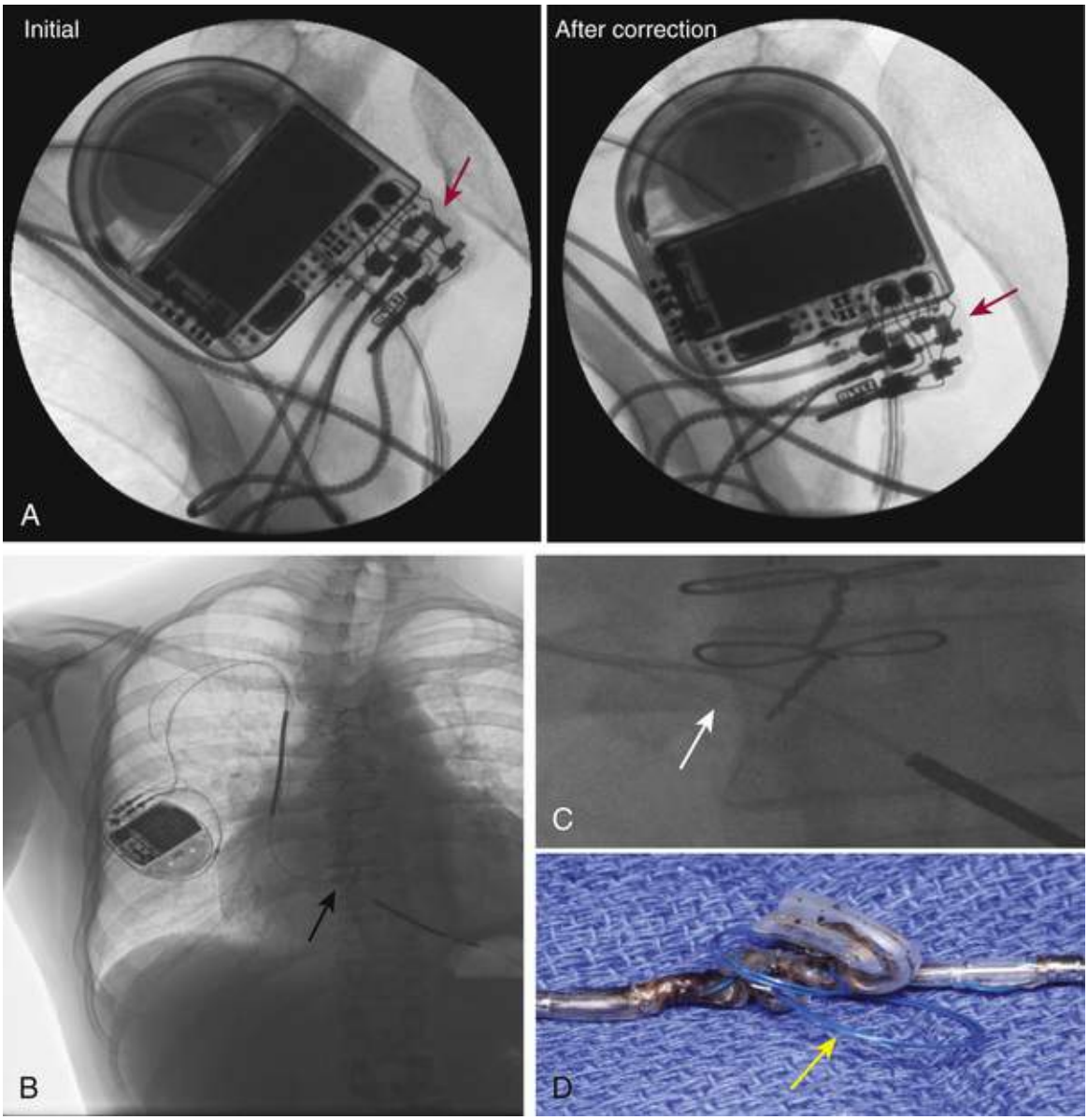


EFIGURE 41.17 Impedance trends for pace-sensing electrodes. To the *left* of the longest vertical line, data are displayed as *vertical bars* connecting weekly maximum and minimum impedance values. To the *right, black points* indicate daily values. An abrupt 50% to 75% relative increase in impedance is a highly specific indicator of an ICD system problem, either conductor fracture or connection problem between lead and header. Conversely, a gradual impedance increase without oversensing usually occurs at the electrode-myocardial interface, caused at least in some cases by calcium deposition in the form of hydroxyapatite; lead replacement is not indicated unless pacing or sensing is compromised. Occasionally, silicone insulation breaches present with low or decreasing pacing impedance. **A,** Normal impedance trend. Although this trend occurred in a normal lead, normal trends may occur with conductor fractures and insulation failures. **B,** Lead insulation failure showing a late, abrupt fall in impedance. **C,** Connection problem between the header and lead because of incomplete insertion of the pin. Highly variable impedances are seen beginning approximately 4 months after implantation, followed by approximately a 2-month return to baseline between early October and December 2007. **D,** Lead conductor fracture with a late, abrupt increase in impedance to highest reported value (>3000 Ω). **E,** Engineering-level display of stored data for another lead conductor fracture. Although the programmer displays impedance only up to a maximum value of 3000 Ω, impedance is measured up to 16,000 Ω. A late, abrupt increase in impedance to an open-circuit value is diagnostic of a conductor fracture. **F,** Gradual increase in impedance in a normally functioning lead, thought to be caused by changes at the electrode-myocardial interface.

Fractures of high-voltage conductors can present as abrupt increases in shock impedance. Low shock impedance occurs in some high-voltage insulation breaches. However, diagnosing high-voltage insulation breaches by painless measurements of shock impedance is challenging because high-voltage shocks above the insulating material's dielectric breakdown voltage can cause catastrophic short circuits even if low-voltage test pulses encounter intact insulation.

Imaging

The chest x-ray film is unrevealing in most cases of lead failure, but it should be inspected for lead conductor discontinuity, kinks or acute angles that identify stress points, and twisting suggesting “twiddler's syndrome.” It is important for excluding alternative causes of oversensing, such as lead dislodgment, abandoned leads or lead fragments that cause a lead-lead interaction, and incomplete insertion of DF-1 pins into the header (**eFig. 41.18A**). Cinefluoroscopy in multiple views is more sensitive than chest radiography for identifying “inside-out” insulation breaches that cause cable conductors to protrude outside the outer insulation (externalized cables; **eFig. 41.18B-D**).



EFIGURE 41.18 Radiography in evaluation of suspected lead failure. **A,** Intraoperative fluoroscopic images of a cardiac resynchronization ICD show incomplete insertion of the RV pace-sensing lead pin into the header. The ICD has been removed from the pocket to enhance image quality. Before revision, the lead connector pin was not advanced completely into the header (*red arrow*). The proximal connection between the ring electrode and the header was intermittent, which resulted in high impedance and oversensing causing pauses in the paced rhythm. After revision, the RV electrode is advanced completely into the header. **B to D,** Outer insulation breach of ICD lead resulting in "externalized" cables protruding out of the breach near the tricuspid valve. **B,** *Arrow* in chest radiograph indicates site of breach. These breaches typically are better seen on cine fluoroscopy. **C,** Magnified view. **D,** Photograph of extracted lead shows insulation breach with *blue* inner insulation (ethylene tetrafluoroethylene, ETFE, see Fig. 41.1) protruding from lead body. (**A,** From Swerdlow CD, Gillberg JM, Khairy P. Sensing and detection. In Ellenbogen KA, Kay GN, Lau CP, Wilkoff BL, editors. Clinical Cardiac Pacing, Defibrillation, and Resynchronization Therapy. 4th ed. Philadelphia: Saunders; 2011; **B-D,** From Swerdlow CD, Friedman PA, Asirvatham SJ, Hayes DL. Troubleshooting: interpreting diagnostic information. In Hayes DL, Friedman PA, editors. Cardiac Pacing and Defibrillation: A Clinical Approach. 3rd ed. West Sussex, UK: Wiley-Blackwell; 2014.)

Approach to the Patient

Fig. 41.25 summarizes the approach to patients with findings suggestive of lead failure. All lead-failure diagnostics have false positives, and the diagnosis of lead failure must be confirmed before surgical intervention to remove a failed lead.[29] Connection problems between the lead and header must be excluded (**eFig. 41.18**). System revision involves either abandoning or extracting the failed lead and inserting a replacement lead. Usually, lead abandonment is associated with lower procedural risk and

lead extraction with fewer long-term problems. The trade-offs depend on multiple factors related to the patient, operator/institution, specific lead model, and patient preference.[17,29,31]

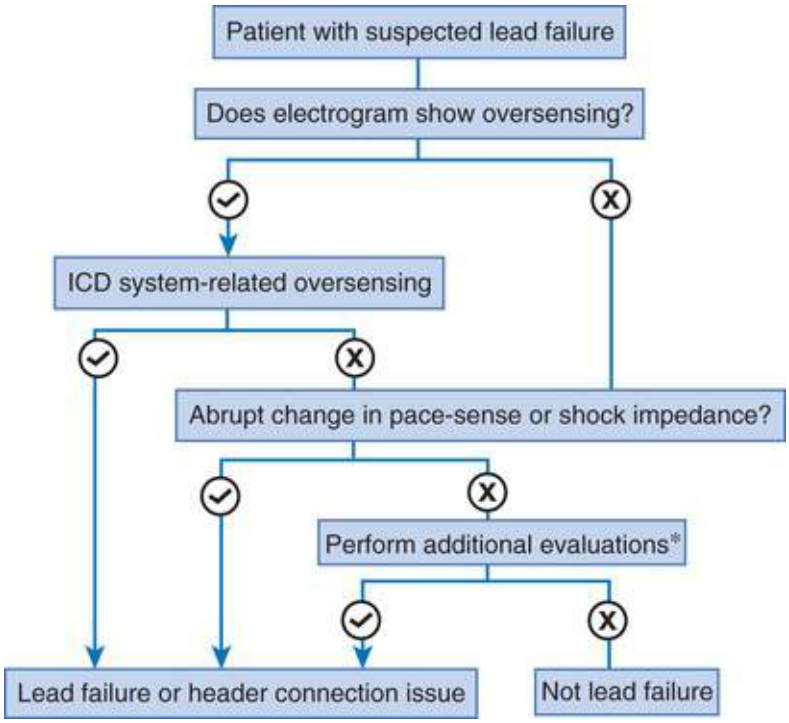


FIGURE 41.25 Deductive approach to suspected ICD lead failure. See text for details. *Additional evaluations include real-time, pace-sense electrograms with muscle exercise and pocket manipulation; shock EGMs; differential EGMs; and pacing and sensing thresholds. (From Swerdlow CD, Kalahasty G, Ellenbogen KA. Implantable cardiac defibrillator lead failure and management. J Am Coll Cardiol 2016;67(11):1358-68.)

Complications

Complications can be divided into early surgical complications and late complications related to the patient or pacemaker/ICD system (**eTable 41.8**).

ETABLE 41.8

Major Complications of Pacemakers and ICDs

Vascular Access
Pneumothorax
Hemopneumothorax
Vascular perforation
Placement of lead into left atrium or left ventricle via patent foramen ovale
Placement of lead into subclavian artery and retrograde across aortic valve
Lead Placement
Lead dislodgment
Lead microdislodgment
Cardiac perforation with hemopericardium (possible cardiac tamponade)
Extracardiac stimulation*: phrenic nerve, intercostal muscle, left hemidiaphragm
Tricuspid regurgitation
Subclavian or axillary vein thrombosis
Loose set screw
Device-Related Infection
Erosions
Pocket infection
Endocarditis
Bacteremia

*May indicate perforation of lead tip or screw.

Implant-Related Complications

Transvenous lead insertion may result in complications related to vascular access, lead placement, pocket integrity, and infection. Overall, major complications occur in about 4% to 5% of new implants[32] and 2% to 3% of generator changes.[33]

Vascular Access

Vascular access for transvenous leads can be complicated by pneumothorax and less often by hemothorax or injury to neurovascular structures. Rarely, failure to recognize inadvertent entry into the arterial system results in placement of a lead retrograde through the aorta into the left ventricle. There is also a risk of entry into the left atrium from the right atrium via a patent foramen ovale. An unexplained stroke should prompt echocardiographic examination to confirm that the atrial and ventricular leads are not in left-sided chambers. Upper extremity swelling on the side of the implant indicates thrombosis of the accessed vein. It usually resolves with elevation of the extremity and time, with or without anticoagulation.

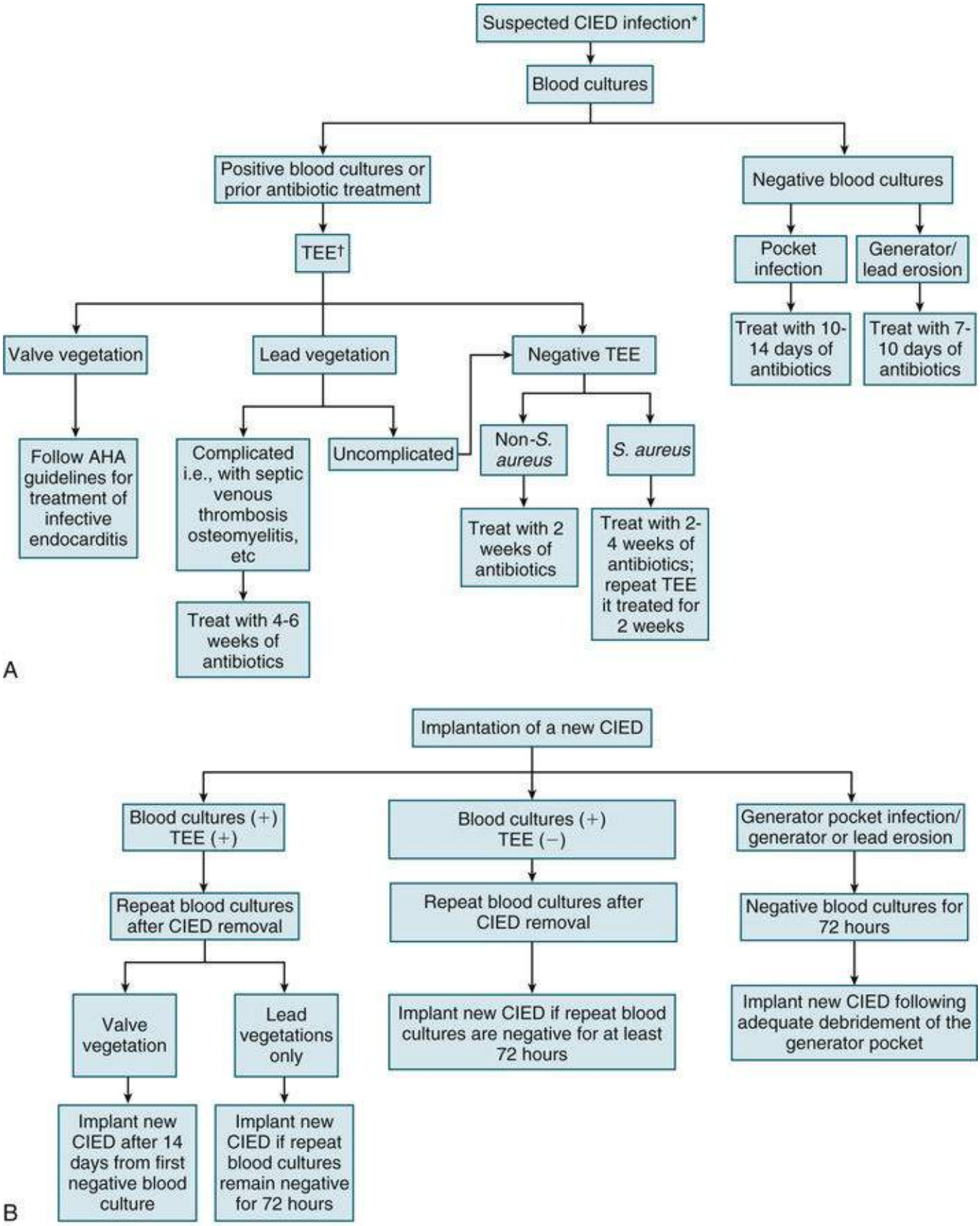
Lead Placement

The most common complication is dislodgment of the lead, and this usually requires prompt revision. Cardiac perforation may result in pericarditis, pericardial effusion, or cardiac tamponade but may also occur without clinical findings. A loose set screw or inadequate connection with the header may result in oversensing or failure to capture (**eFig. 41.18**).

Pacing may stimulate extracardiac nerves or muscles, including atrial stimulation of the right phrenic nerve or ventricular stimulation of the left hemidiaphragm. Intercostal muscle stimulation may indicate RV lead perforation. Lead placement can cause ventricular premature complexes due to mechanical effects, but these usually resolve within 24 hours. Rarely, RV leads may cause clinically significant tricuspid regurgitation.

CIED Infections

Infections may occur early after implant or may be delayed. Early infections usually are caused by skin organisms, such as staphylococci or streptococci. Antibiotic prophylaxis given immediately before device implant reduces the risk of perioperative infection.[34,35] Late infections may be caused by intraoperative contamination with indolent organisms or hematogenous spread. Pocket infections can present with pain, erythema, or purulent drainage; erosion may be caused by indolent infection (**eFig. 41.19**). Septic pulmonary emboli may be the first indication of systemic CIED infection. Treatment requires intravenous antibiotics and removal of both the generator and the leads. Recent scientific statements provide guidance based on factors that include clinical presentation, blood cultures, and presence or absence of lead or valve vegetations, as determined by echocardiography.[34,35]

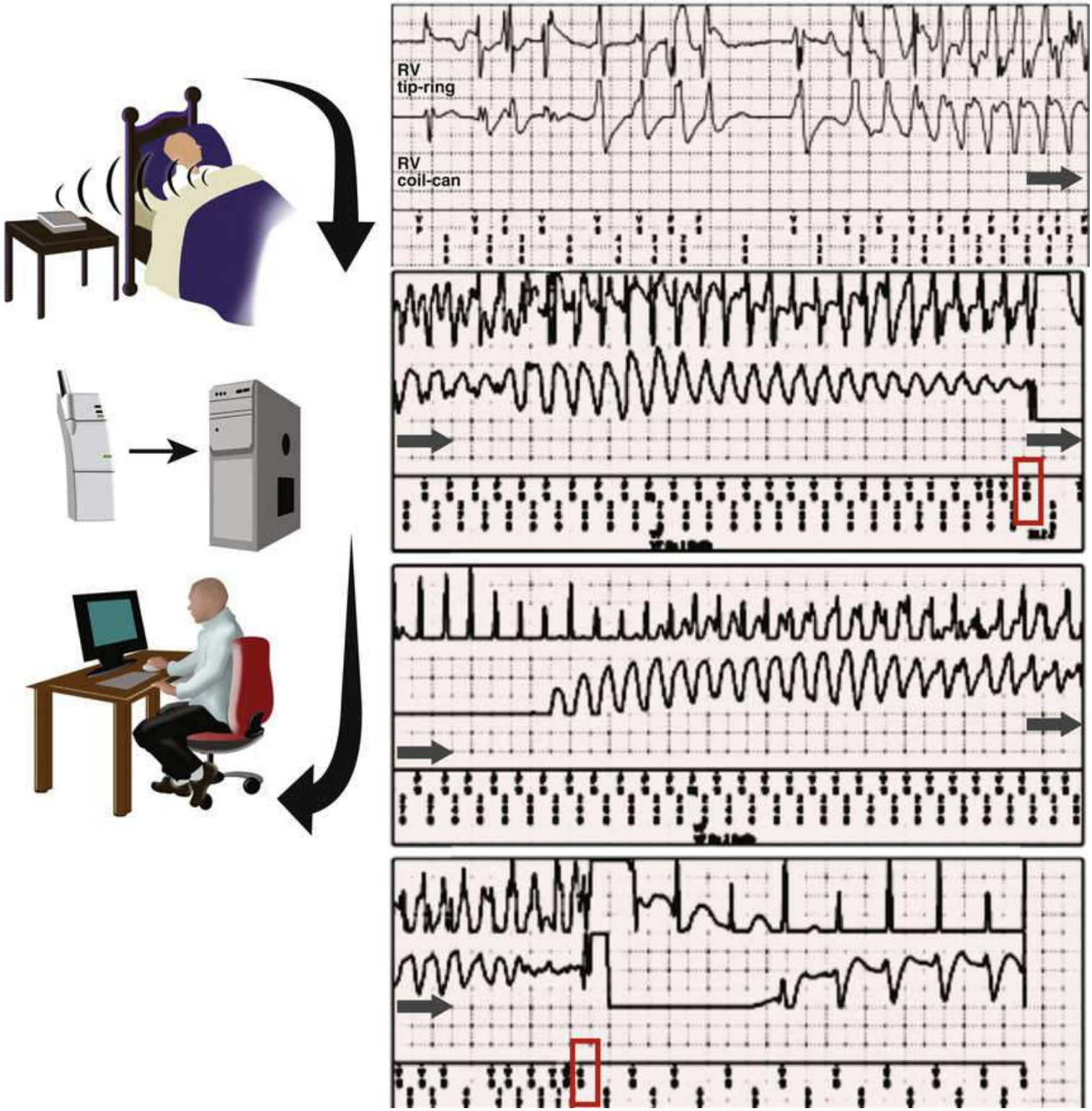


EFIGURE 41.19 Cardiac implantable electrical device (CIED) infection: approach to diagnosis, antibiotic therapy, and reimplantation. **A,** Diagnosis and management of adults with CIED infection. A history, physical examination, chest radiograph, ECG, and device interrogation are standard baseline procedures before CIED removal. *Duration of antibiotics should be counted from the day of device explantation. †Transesophageal electrocardiography. Treatment can be extended to 4 or more weeks if there are metastatic septic complications or sustained bloodstream infection despite CIED removal. **B,** Approach to implantation of a new device in patients after removal of an infected CIED. (From: Baddour LM, Epstein AE, Erickson CC, et al. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. Circulation 2010;121(3):458-77.)

Follow-Up

Remote Monitoring

The convergence of Internet technology, improved telemetry, and enhanced CIED diagnostics permits remote monitoring of multiple device functions and improves patient management[36] (**eFig. 41.20**). Currently, most ICDs and many pacemakers use “wireless telemetry” to transmit stored data stored automatically to a home monitor, which then relays the data to a server via an Internet connection. By convention, *remote interrogation* refers to scheduled, routine device interrogation at a distance, corresponding to in-clinic interrogation; *remote monitoring* refers to automatic data transmission based on device-generated alerts.[36] Colloquially, “remote monitoring” includes both. Routine, scheduled transmissions include battery status, pacing and sensing thresholds, lead impedances, and detected arrhythmias. Patients can also initiate transmissions in response to symptoms. Health care providers log into a Web server to review alerts and transmitted data. ICDs and some pacemakers provide programmable alerts for system malfunction (e.g., suspected lead failure), potential programming errors (e.g., VF detection or therapy “off”), or high-risk arrhythmias. Alerts may be transmitted daily or even immediately. Alerts may also notify the patient through audible tones or generator vibration. A “lead integrity alert” reduces inappropriate shocks caused by lead failure.[29]



EFIGURE 41.20 Remote monitoring of pacemakers and ICDs. The drawings at the **left** illustrate the function of a remote monitoring network. Device diagnostics and EGMs are transmitted to a bedside monitor or wearable cellular unit that retransmits the data to a central server. The server prioritizes the data and sends the formatted report to the patient's health care provider. Continuous EGMs at the **right** show an example of a patient-initiated transmission that was reviewed from home within minutes of being sent by one of the authors (CDS). It shows a pause-dependent polymorphic VT that required two shocks for termination (*red boxes* on the marker channel). The patient's internist had recently increased the dose of diuretics, and the serum potassium concentration was 2.7 mEq/L. RV tip-ring, EGM recording between tip of lead and ring electrode on the lead; RV coil-can, EGM recording between coil in lead and can of ICD.

CIED Diagnostics for Atrial Fibrillation

Remote monitoring can be used to monitor comorbidities if relevant data are stored in the device or input into the local hub from another source. AF is an important comorbidity that can be monitored reliably by

CIEDs with an atrial lead. ICD patients with rapidly conducted AF have an increased risk of inappropriate shocks, and early diagnosis may permit treatment or reprogramming to prevent inappropriate therapy. Early treatment of new-onset, persistent AF may reduce exacerbations of HF. Alerts for AF facilitate early anticoagulation and adjustment of rate and rhythm control medications.[36] In CIED patients, asymptomatic AF episodes as short as 5 minutes are associated with an increased rate of stroke, although it is not clear if AF is causal. Present data are insufficient to determine if continuous device monitoring of patients with infrequent paroxysmal AF might permit safe withdrawal of anticoagulation or intermittent use of short-acting anticoagulants.

Common Clinical Issues in CIED Patients

Psychosocial Issues

ICD patients may experience anxiety about shocks, but they may also feel protected from the risk of sudden death. They may benefit from interventions such as counseling, education, and support groups.[37] It is important to provide patients with a plan for what to do when a shock occurs. **eTable 41.9** summarizes an approach consistent with the clinical approach in **Fig. 41.23**, which emphasizes that patient-initiated remote transmission is the most rapid and efficient approach to transfer information required for medical decision making to the clinician. ICD patients benefit from counseling after shocks occur.[37] This includes reviewing what triggered the shock and what intervention has been taken to mitigate the trigger, estimating the likelihood of future shocks after this intervention, explaining that shocks are one of multiple challenges of living with heart disease, and usually emphasizing the value of returning to normal activity.

ETABLE 41.9

Patient Plan for ICD Shocks

SHOCKS IN 24 HOURS	RESPONSE
First shock	Send remote transmission. Call immediately if cardiac symptoms,* otherwise within 24 hours.
Second shock	Send remote transmission. Call immediately.
Third shock	Send remote transmission. Receive medical care immediately.

*Chest pain, dyspnea, syncope.

A consensus statement addresses legal and ethical issues related to withdrawal of CIED therapy to reduce suffering at the end of a patient's life.[38] This is important because 20% of ICD patients receive painful shocks in their last weeks of life. A patient (or legally defined surrogate decision maker) has the right to request withdrawal of any medical therapy, including CIED therapy, even if such withdrawal allows the patient to die naturally from an underlying disease.

Lifestyle Issues

Driving

Pacemaker patients are not restricted from driving after the perioperative period. Guidelines for ICD patients recommend that patients refrain from driving for 6 months after each shock for VT/VF and for 6 months after ICD implant for secondary prevention.[39] Primary prevention patients are not restricted from driving personal cars (versus commercial vehicles).

Participation in Sports

Exercise improves health and quality of life but may induce VT/VF in patients with specific diseases.[40] Decisions regarding sports participation should be based on the patient's underlying disease, indication for ICD therapy (e.g., primary versus secondary prevention, risk of exercise-induced VT/VF), and risks of specific sports (e.g., ICD system damage in contact sports, risk of trauma with transient loss of consciousness).[40] Athletes with ICDs experience shocks for both VT/VF and SVT more frequently during sports than at rest, but the risk of injury or failure to terminate VT/VF is low.[41] Swimming presents the risk of drowning even if VT/VF is treated promptly.

Drug Interactions

Antiarrhythmic drugs are used in pacemaker patients to prevent AF and in ICD patients to prevent both AF and VT/VF. RCTs report reduction in VT/VF using either sotalol or the combination of amiodarone and beta blockers. However, antiarrhythmic and other drugs have important interactions with devices (**see eTable 41.1**). Beta blockers and other drugs that prolong AV conduction may increase RV pacing burden and thereby exacerbate HF. Antiarrhythmic drugs prescribed for VT/VF or AF (e.g., amiodarone) may slow the rate of VT and thus require decreasing the rate threshold to ensure that VT is detected.

Electromagnetic Interference

Ubiquitous electromagnetic waves can interfere with CIEDs, potentially causing temporary or permanent inactivation, inappropriate pacing or inhibition of pacing or shocks, and inappropriate detection of VT/VF.[42] EMI is less common with smaller, dedicated, bipolar sensing dipoles than with unipolar sensing (pacemakers) or integrated bipolar sensing (ICDs).

Nonmedical Sources

Clinically significant EMI is extremely rare for household appliances. Although the risk is extremely low, patients should hold activated digital cellular phones to the contralateral ear and should avoid carrying phones in the ipsilateral breast pocket. CIED patients may walk through airport metal detectors and electronic article surveillance devices at a normal pace. Prolonged exposure can inhibit pacing and detection of VT/VF, cause inappropriate detection of VT/VF, or (rarely) program VT/VF detection “off.”

Medical Sources

Medical sources of EMI are most frequently associated with electrosurgery (electrocautery) or magnetic resonance imaging (MRI).

Perioperative Management of CIED Patients.

A consensus statement requires preoperative determination of pacemaker dependency, device model, type of lead, and plans to use electrocautery to inform management[43] (**eTable 41.10**). The arterial pulse must be monitored intraoperatively. Intraoperative management strategies may include magnet application or perioperative reprogramming. When a magnet is placed over a pacemaker, it paces asynchronously. In contrast, a magnet placed over an ICD disables detection of VT/VF but does not alter pacing mode.

ETABLE 41.10

Perioperative Management of Pacemakers and ICDs

Preoperative Evaluation
Determine if electrosurgery will be used; if so, determine operative site in relation to pulse generator. Determine type and model of cardiac implantable electrical device (CIED) and leads (history, identification card, chest radiograph). Assess whether patient is pacemaker dependent. Assess device function if full check not performed within 6 months.
Preoperative Preparation
Apply magnet or reprogram if surgical site above umbilicus. Pacemaker and ICD reprogramming: disable rate-responsive pacing; consider increasing pacing output if high-risk surgery, metabolic shifts likely. ICD reprogramming: disable VT/VF therapies; reprogram to asynchronous or triggered mode. (In ICDs, magnet application does not result in asynchronous pacing.) Position dispersive grounding pad to minimize current near generator (e.g., apply to shoulder contralateral to device for head and neck surgery).
Intraoperative Management
Monitor the ECG and the peripheral pulse (arterial line, plethysmography, pulse oximetry). Use transcutaneous pacing and defibrillation pads (anterior-posterior position) for pacemaker-dependent patients if surgical site permits. Use bipolar cautery, ultrasonic (harmonic) scalpel, or short bursts of monopolar electrosurgery.
Interrogate Before Discharge from Telemetry *if*:
Device was reprogrammed preoperatively. Intraoperative power-on-reset likely (e.g., cardiothoracic surgery). Patient experienced clinically significant intraoperative arrhythmia. Pacing/sensing thresholds may have changed because of intraoperative hypotension or metabolic abnormalities. CIED cannot be evaluated within 1 month after procedure (including remote monitoring).

The risk of oversensing is greatest for monopolar electrocautery delivered between a pen and a remote dispersive ground electrode, or when the surgical site is in proximity to the device or sensing electrodes.[43] If the surgical incision and dispersive ground pad are both below the umbilicus, the risk of EMI is low. Rate-adaptive sensors should be disabled.

Magnetic Resonance Imaging.

MRI exposes CIED patients to risks resulting from mechanical forces generated by the static magnetic field, heat and current flow in the leads induced by the radiofrequency fields, and current induced by gradient magnetic fields.[44] MRI-conditional pacemaker and ICD systems employ pulse generators and leads designed to permit safe imaging under specific MRI conditions when programmed to fixed rate (VOO, DOO) or nonpacing (ODO) modes.[44] MRI of patients with standard CIEDs may be performed safely by implementing rigorous risk mitigation strategies.[42]

Other Medical Procedures and Devices.

When external cardioversion is required, defibrillation pads should be placed at least 8 inches (20 cm) from the pulse generator. In ICD patients, cardioversion of AF should be performed through the device whenever possible. Ionizing radiation therapy can damage CIED circuitry, and CIEDs should be shielded or moved to the contralateral side. Left-ventricular assist devices (LVADs) cause specific forms of EMI.[42]

Guidelines

Cardiac Pacemakers and Cardioverter-Defibrillators

Charles D. Swerdlow, Paul J. Wang, and Douglas P. Zipes

The American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines for the use of cardiac pacemakers, implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT) were most recently updated in 2008.[1] ACC, AHA, and the European Society of Cardiology (ESC), along with HRS, collaborated on guidelines for the

management of patients with ventricular arrhythmias and the prevention of sudden cardiac death (SCD) in 2006.[2] Similar guidelines for cardiac pacing and CRT were published by ESC in 2007.[3]

As with other ACC/AHA guidelines, these use the standard ACC/AHA classification system for indications:

Class I: Conditions for which there is evidence and/or general agreement that the test is useful and effective
Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness or efficacy of performing the test
Class IIa: Weight of evidence/opinion in favor of usefulness or efficacy
Class IIb: Usefulness or efficacy less well established by evidence/opinion
Class III: Conditions for which there is evidence and/or general agreement that the test is not useful or effective and in some cases may be harmful

Three levels are used to rate the evidence on which recommendations have been based:

Level A recommendations are derived from data from multiple randomized clinical trials.
Level B recommendations are derived from a single randomized trial or nonrandomized studies.
Level C recommendations are based on the consensus opinion of experts.

Indications for Permanent Pacing

Acquired Atrioventricular Block

For patients with complete or second-degree atrioventricular (AV) block, the ACC/AHA guidelines consider permanent pacing to be appropriate when the abnormality causes symptoms and is not precipitated by a drug whose use can be discontinued (**Table 41G.1**) or a condition that is likely to be reversible, such as acute inferior myocardial infarction (MI) with a narrow QRS complex. Examples of symptoms include fatigue, syncope or presyncope, seizures, congestive heart failure, and confusional states. In asymptomatic patients, pacing is indicated for those at high risk for the development of complications, such as patients with periods of asystole of 3 seconds or longer or an escape rate of less than 40 beats/min or those who have specific high-risk conditions.

TABLE 41G.1

Indications for Pacing in Patients with Atrioventricular (AV) Block

Class I
1. Third-degree or advanced second-degree AV block at any anatomic level associated with any one of the following conditions: a. Symptoms (including heart failure) or ventricular arrhythmias attributable to AV block. *(Level of evidence: C.)* b. Arrhythmias and other medical conditions requiring drugs that result in symptomatic bradycardia. *(Level of evidence: C.)* c. Documented periods of asystole >3.0 second, any escape rate <40 beats/min, or any escape rhythm below the AV junction in awake, asymptomatic patients in sinus rhythm. *(Level of evidence: C.)* d. A documented period of asystole >5 second in awake, asymptomatic patients in atrial fibrillation. *(Level of evidence: C.)* e. After catheter ablation of the AV junction. *(Level of evidence: C.)* f. Postoperative AV block that is not expected to resolve after cardiac surgery. *(Level of evidence: C.)* g. Neuromuscular diseases, such as myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb (limb-girdle) muscular dystrophy, and peroneal muscular atrophy, with or without symptoms of bradycardia. *(Level of evidence: B.)*
2. Symptomatic second-degree AV block regardless of type or site of block. *(Level of evidence: B.)*
3. Asymptomatic third-degree AV block at any anatomic site with an average awake ventricular rate >40 beats/min in patients with cardiomegaly or left ventricular dysfunction or if the site of block is below the AV node. *(Level of evidence: B.)*
4. Second- or third-degree AV block during exercise in the absence of myocardial ischemia. *(Level of evidence: C.)*
Class IIa
1. Persistent third-degree AV block at any anatomic site with an average ventricular rate >40 beats/min in asymptomatic adult patients in the absence of cardiomegaly. *(Level of evidence: C.)*
2. Asymptomatic second-degree AV block at the intra- or infra-His levels found at electrophysiologic study. *(Level of evidence: B.)*
3. First- or second-degree AV block with symptoms similar to those of pacemaker syndrome or hemodynamic compromise. *(Level of evidence: B.)*
4. Asymptomatic type II second-degree AV block with a narrow QRS complex. When type II second-degree AV block occurs with a wide QRS complex, including isolated right bundle branch block, pacing becomes a class I recommendation. *(Level of evidence: B.)*
Class IIb
1. Neuromuscular diseases such as myotonic muscular dystrophy, Erb (limb-girdle) dystrophy, and peroneal muscular atrophy with any degree of AV block (including first-degree AV block), with or without symptoms of bradycardia. *(Level of evidence: B.)*
2. AV block as a result of drug use or toxicity when the block is expected to recur even after cessation of use of the drug. *(Level of evidence: B.)*
Class III
1. Asymptomatic first-degree AV block. *(Level of evidence B.)*
2. Asymptomatic type I second-degree AV block at the supra-His (AV node) level or another site or not known to be intra- or infra-Hisian by electrophysiologic study. *(Level of evidence: C.)*
3. AV block expected to resolve and unlikely to recur (e.g., drug toxicity, Lyme disease, or transient increases in vagal tone or during hypoxia in sleep apnea in the absence of symptoms). *(Level of evidence: B.)*

The guidelines do not support pacing for patients with asymptomatic first-degree or type I second-degree AV block, and do not support the use of pacing for patients with hypoxia and sleep apnea syndrome in the absence of symptoms.

Chronic Bifascicular and Trifascicular Block

Syncope is common in patients with chronic bifascicular or trifascicular block, but the risk for SCD or progression to complete heart block varies in patient subsets. Guidelines for pacing in these settings (**Table 41G.2**) include alternating bundle branch block as a class I indication because it indicates abnormal and unstable conduction in all three fascicles. The guidelines also support pacing in patients with markedly abnormal infranodal conduction at electrophysiologic study (EPS), even if they are asymptomatic (class IIa). Pacing is not supported for patients without symptoms, even if first-degree AV block is also present.

TABLE 41G.2

Indications for Pacing in Patients with Chronic Bifascicular and Trifascicular Block

Class I
1. Advanced second-degree AV block or intermittent third-degree AV block. *(Level of evidence: B.)*
2. Type II second-degree AV block. *(Level of evidence: B.)*
3. Alternating bundle branch block. *(Level of evidence: C.)*
Class IIa
1. Syncope not demonstrated to be caused by AV block when other probable causes, specifically ventricular tachycardia, have been excluded. *(Level of evidence: B.)*
2. Incidental finding at electrophysiologic study of a markedly prolonged H-V interval (≥100 msec) in asymptomatic patients. *(Level of evidence: B.)*
3. Incidental finding at electrophysiologic study of pacing-induced infra-His block that is not physiologic. *(Level of evidence: B.)*
Class IIb
1. Neuromuscular diseases such as myotonic muscular dystrophy, Erb (limb-girdle) dystrophy, and peroneal muscular atrophy with bifascicular block or any degree of fascicular block, with or without symptoms of bradycardia. *(Level of evidence: C.)*
Class III
1. Fascicular block without AV block or symptoms. *(Level of evidence: B.)*
2. Fascicular block with first-degree AV block without symptoms. *(Level of evidence: B.)*

Acute Myocardial Infarction

Symptoms do not play a role in appropriateness for pacing in patients with acute MI because of the high risk for SCD in some post-MI patients with conduction system disturbances (**Table 41G.3**). The guidelines emphasize that the requirement for temporary pacing after acute MI does not automatically indicate a need for permanent pacing. However, permanent pacemakers are supported in patients with transient (presumed) infranodal AV block and associated bundle branch block, one of the rare times that transient AV block is judged to be an indication for permanent pacing. The usefulness of permanent pacemakers for patients with advanced AV block at the AV node level is less clear (class IIb).

TABLE 41G.3

Indications for Permanent Pacing After Acute Myocardial Infarction

Class I
1. Permanent ventricular pacing is indicated for
a. Persistent second-degree AV block in the His-Purkinje system with alternating bundle branch block or third-degree AV block within or below the His-Purkinje system after ST-segment elevation myocardial infarction. *(Level of evidence: B.)*
b. Transient second- or third-degree infranodal AV block and associated bundle branch block. If the site of block is uncertain, an electrophysiologic study may be necessary. *(Level of evidence: B.)*
c. Persistent and symptomatic second- or third-degree AV block. *(Level of evidence: C.)*
Class IIb
1. Permanent ventricular pacing may be considered for persistent second- or third-degree transient AV block at the AV node level, with or without symptoms. *(Level of evidence: B.)*
Class III
1. Transient AV block without intraventricular conduction defects. *(Level of evidence: B.)*
2. Transient AV block with isolated left anterior fascicular block. *(Level of evidence: B.)*
3. Acquired new bundle branch block or fascicular block without AV block. *(Level of evidence: B.)*
4. Asymptomatic first-degree AV block with bundle branch or fascicular block. *(Level of evidence: B.)*

Sinus Node Dysfunction

As for patients with acquired AV block, pacing is indicated for those with symptoms caused by bradycardia that is not the result of a drug whose use can be discontinued (**Table 41G.4**). Pacing is discouraged in asymptomatic patients, even when resting heart rates are lower than 40 beats/min, and in symptomatic patients when symptoms cannot be proved to be caused by bradycardia. A class IIa recommendation supports pacing in patients with syncope of unexplained origin when major abnormalities in sinus node function are demonstrated at electrophysiologic testing.

TABLE 41G.4

Indications for Pacing in Patients with Sinus Node Dysfunction

Class I
1. Symptomatic bradycardia or frequent symptomatic sinus pauses. *(Level of evidence: C.)* 2. Symptomatic chronotropic incompetence. *(Level of evidence: C.)* 3. Symptomatic bradycardia that results from required drug therapy. *(Level of evidence: C.)*
Class IIa
1. Sinus node dysfunction occurring with a heart rate <40 beats/min when a clear association between significant symptoms consistent with bradycardia and the actual presence of bradycardia has not been documented. *(Level of evidence: C.)* 2. Syncope of unexplained origin when clinically significant sinus node dysfunction is discovered or provoked during electrophysiologic testing. *(Level of evidence: C.)*
Class IIb
1. Minimally symptomatic patients with a chronic heart rate <40 beats/min while awake. *(Level of evidence: C.)*
Class III
1. Sinus node dysfunction in asymptomatic patients. *(Level of evidence: C.)* 2. Sinus node dysfunction in patients with symptoms that are clearly documented in the absence of bradycardia. *(Level of evidence: C.)* 3. Sinus node dysfunction with symptomatic bradycardia caused by nonessential drug therapy. *(Level of evidence: C.)*

Prevention and Termination of Tachyarrhythmias

In some patients with long-QT syndrome, continuous pacing can prevent recurrent tachyarrhythmias. In addition, paroxysmal reentrant tachyarrhythmias can be terminated in some patients through programmed stimulation and short bursts of rapid pacing. However, the guidelines do not provide support for the routine use of antitachycardia pacemakers without extensive testing before implantation (**Table 41G.5**), but continue to consider bradycardia pacing appropriate (class I indication) for patients with sustained pause-dependent ventricular tachycardia (VT, unrelated to a drug whose use can be discontinued), with or without a prolonged QT interval, if the efficacy of temporary pacing has been demonstrated (**Table 41G.6**). However, some patients have or are at risk for other types of VT. In these patients an ICD may be more appropriate.

TABLE 41G.5

Indications for Pacemakers to Terminate Tachycardia

Class IIa
1. Symptomatic recurrent supraventricular tachycardia that is reproducibly terminated by pacing in the unlikely event that catheter ablation and/or drugs fail to control the arrhythmia or produce intolerable side effects. *(Level of evidence: C.)*
Class III
1. The presence of accessory pathways with the capacity for rapid anterograde conduction. *(Level of evidence: C.)*

TABLE 41G.6

Indications for Pacemakers to Prevent Tachycardia

Class I
1. Pause-dependent sustained ventricular tachycardia with or without a prolonged QT interval. *(Level of evidence: C.)*
Class IIa
1. Pacing is reasonable for patients with congenital long-QT syndrome considered to be at high risk. *(Level of evidence: C.)*
Class IIb
1. Prevention of symptomatic, drug-refractory recurrent atrial fibrillation in patients with coexisting sinus node dysfunction. *(Level of evidence: B.)*
Class III
1. Frequent or complex ventricular ectopic activity without sustained ventricular tachycardia in patients without long-QT syndrome. *(Level of evidence: C.)* 2. Torsades de pointes ventricular tachycardia secondary to reversible causes. *(Level of evidence: A.)*

Carotid Sinus Syndrome and Neurocardiogenic Syncope

The only class I indication for permanent pacing is recurrent syncope caused by carotid sinus stimulation

in the absence of any drug that depresses the sinus node or AV conduction (**Table 41G.7**). Pacing is discouraged in patients without symptoms or in those who have syncope without bradycardia.

TABLE 41G.7

Indications for Pacing in Patients with Neurally Mediated Reflex Syncope

Class I
1. Recurrent syncope caused by carotid sinus hypersensitivity, defined as minimal carotid sinus pressure inducing ventricular asystole of >3 seconds in patients not receiving medications that depress the sinus node or AV conduction. *(Level of evidence: C.)*
Class IIa
1. Syncope in the absence of a definite provocative event with a pause of ≥3 seconds with carotid massage. *(Level of evidence: C.)*
Class IIb
1. Recurrent symptomatic neurocardiogenic syncope with a cardioinhibitory response during tilt-table testing. *(Level of evidence: B.)*
Class III
1. A cardioinhibitory response during carotid sinus stimulation without symptoms or with vague symptoms. *(Level of evidence: C.)* 2. Situational vasovagal syncope in which avoidance behavior is effective. *(Level of evidence: C.)*

Hypertrophic Cardiomyopathy

The guidelines minimize indications for pacing in patients with hypertrophic cardiomyopathy (HCM) unless they have associated sinus node dysfunction or AV block that would fulfill related indications for pacing (**Table 41G.8**). A class IIb indication permits pacing in medically refractory symptomatic patients with HCM and a significant resting or provoked left ventricular (LV) outflow tract gradient. Pacing should really be considered only if the patient is truly refractory to pharmacologic therapy.

TABLE 41G.8

Pacing in Patients with Hypertrophic Cardiomyopathy

Class IIb
1. Medically refractory symptomatic patients with significant resting or provoked LV outflow tract obstruction. *(Level of evidence: A.)*
Class III
1. Asymptomatic patients or those whose symptoms are medically controlled. *(Level of evidence: C.)* 2. Symptomatic patients without LV outflow tract obstruction. *(Level of evidence: C.)*

Cardiac Transplantation

Table 41G.9 details these indications.

TABLE 41G.9

Indications for Pacing After Cardiac Transplantation

Class I
1. Persistent symptomatic or inappropriate bradycardia that is not expected to resolve. *(Level of evidence: C.)*
Class IIb
1. Relative bradycardia is recurrent or prolonged and is limiting rehabilitation or hospital discharge. *(Level of evidence: C.)* 2. Syncope after transplantation without a documented bradyarrhythmia. *(Level of evidence: C.)*

Cardiac Resynchronization Therapy

For guidelines on CRT, **see Chapter 27**.

Selection of Pacemakers

The guidelines provide recommendations and decision trees to help physicians match patients' needs to

the technology implanted and to anticipate future needs of the patient. In keeping with the guidelines, elderly patients should receive devices according to the same indications as for younger patients (**Table 41G.10**).

TABLE 41G.10

Indications for Permanent Pacemaker in Children, Adolescents, and Patients with Congenital Heart Disease

Class I
1. Advanced second- or third-degree AV block associated with symptomatic bradycardia, ventricular dysfunction, or low cardiac output. *(Level of evidence: C.)*
2. Sinus node dysfunction with correlation of symptoms during age-inappropriate bradycardia. The definition of bradycardia varies with the patient's age and expected heart rate. *(Level of evidence: B.)*
3. Postoperative advanced second- or third-degree AV block that is not expected to resolve or that persists at least 7 days after cardiac surgery. *(Level of evidence: B.)*
4. Congenital third-degree AV block with a wide QRS escape rhythm, complex ventricular ectopy, or ventricular dysfunction. *(Level of evidence: B.)*
5. Congenital third-degree AV block in an infant with a ventricular rate <55 beats/min or with congenital heart disease and a ventricular rate <70 beats/min. *(Level of evidence: C.)*
Class IIa
1. Congenital heart disease and sinus bradycardia for prevention of recurrent episodes of intra-atrial reentrant tachycardia; sinus node dysfunction may be intrinsic or secondary to antiarrhythmic treatment. *(Level of evidence: C.)*
2. Congenital third-degree AV block beyond the first year of life with an average heart rate <50 beats/min and abrupt pauses in ventricular rate that are 2 or 3 times the basic cycle length or associated with symptoms as a result of chronotropic incompetence. *(Level of evidence: B.)*
3. Sinus bradycardia with complex congenital heart disease and a resting heart rate <40 beats/min or pauses in ventricular rate >3 seconds. *(Level of evidence: C.)*
4. Congenital heart disease and impaired hemodynamics as a result of sinus bradycardia or loss of AV synchrony. *(Level of evidence: C.)*
5. Unexplained syncope in a patient with previous congenital heart surgery complicated by transient complete heart block and a residual fascicular block after a careful evaluation to exclude other causes of syncope. *(Level of evidence: B.)*
Class IIb
1. Transient postoperative third-degree AV block that reverts to sinus rhythm with a residual bifascicular block. *(Level of evidence: C.)*
2. Congenital third-degree AV block in asymptomatic children or adolescents with an acceptable rate, a narrow QRS complex, and normal ventricular function. *(Level of evidence: B.)*
3. Asymptomatic sinus bradycardia after biventricular repair of congenital heart disease with a resting heart rate <40 beats/min or pauses in ventricular rate >3 seconds. *(Level of evidence: C.)*
Class III
1. Transient postoperative AV block with return of normal AV conduction in an otherwise asymptomatic patient. *(Level of evidence: B.)*
2. Asymptomatic bifascicular block with or without first-degree AV block after surgery for congenital heart disease in the absence of previous transient complete AV block. *(Level of evidence: C.)*
3. Asymptomatic type I second-degree AV block. *(Level of evidence: C.)*
4. Asymptomatic sinus bradycardia with the longest relative risk interval <3 seconds and a minimum heart rate >40 beats/min. *(Level of evidence: C.)*

Implantable Cardioverter-Defibrillator Therapy

The 2008 guidelines group all indications together; that is, they no longer separate primary and secondary indications (**Table 41G.11**). The strongest evidence for use of ICDs for “secondary prevention” is in patients with LV dysfunction who have been resuscitated from ventricular fibrillation (VF), hemodynamically unstable VT, or VT with syncope and who remain at risk for future cardiac arrests. There is also strong evidence supporting the use of ICDs for “primary prevention” in patients at least 40 days after MI who have depressed LV function with ejection fraction (EF) of less than 30% to 40% and in patients with nonischemic dilated cardiomyopathy who have LVEF of less than 30% to 35%.

TABLE 41G.11

Indications for Implantable Cardioverter-Defibrillator Therapy

Class I
1. Survivors of cardiac arrest secondary to ventricular fibrillation (VF) or hemodynamically unstable sustained ventricular tachycardia (VT) after evaluation to define the cause of the event and to exclude any completely reversible causes. *(Level of evidence: A.)*
2. Structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable. *(Level of evidence: B.)*
3. Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiologic study. *(Level of evidence: B.)*
4. Left ventricular ejection fraction (LVEF) <35% because of previous myocardial infarction (MI) in patients at least 40 days after MI and in New York Heart Association (NYHA) Functional Class II or III. *(Level of evidence: A.)*
5. Nonischemic dilated cardiomyopathy in patients who have an LVEF ≤35% and are in NYHA Functional Class II or III. *(Level of evidence: B.)*
6. LV dysfunction because of previous MI in patients who are at least 40 days after MI, have an LVEF <30%, and are in NYHA Functional Class I. *(Level of evidence: A.)*
7. Nonsustained VT because of previous MI, LVEF <40%, and inducible VF or sustained VT at electrophysiologic study. *(Level of evidence: B.)*
Class IIa
1. Unexplained syncope, significant LV dysfunction, and nonischemic dilated cardiomyopathy. *(Level of evidence: C.)*
2. Sustained VT and normal or near-normal ventricular function. *(Level of evidence: C.)*
3. Patients with hypertrophic cardiomyopathy and (a) a family history of sudden death presumably caused by hypertrophic cardiomyopathy in one or more first-degree relatives, (b) LV wall thickness ≥30 mm, or (c) one or more unexplained syncopal episodes in the last 6 months. *(Level of evidence: C.)*
4. Selected patients with hypertrophic cardiomyopathy and either nonsustained VT (particularly those <30 years of age) or an abnormal blood pressure response with exercise* in the presence of other established risk markers† or potential risk modifiers.‡ *(Level of evidence: C.)*
5. Arrhythmogenic right ventricular dysplasia/cardiomyopathy in patients who have 1 or more risk factors for sudden cardiac death. *(Level of evidence: C.)*
6. Long-QT syndrome in patients who are experiencing syncope and/or VT while receiving beta blockers. *(Level of evidence: B.)*
7. Nonhospitalized patients awaiting transplantation. *(Level of evidence: C.)*
8. Brugada syndrome in patients who have had syncope or documented VT that has not resulted in cardiac arrest. *(Level of evidence: C.)*
9. Catecholaminergic polymorphic VT in patients who have syncope and/or documented sustained VT while receiving beta blockers. *(Level of evidence: C.)*
10. Cardiac sarcoidosis, giant cell myocarditis, or Chagas disease. *(Level of evidence: C.)*
Class IIb
1. Nonischemic heart disease in patients with an LVEF ≤35% and in NYHA Functional Class I. *(Level of evidence: C.)*
2. Long-QT syndrome and risk factors for sudden cardiac death. *(Level of evidence: B.)*
3. Syncope and advanced structural heart disease in patients in whom thorough invasive and noninvasive investigations have failed to define a cause. *(Level of evidence: C.)*
4. Familial cardiomyopathy associated with sudden death. *(Level of evidence: C.)*
5. LV noncompaction. *(Level of evidence: C.)*
6. Patients with hypertrophic cardiomyopathy and either an abnormal blood pressure response to exercise* or isolated bursts of nonsustained VT in the absence of any other risk factors† or risk modifiers‡ for sudden cardiac death. *(Level of evidence: C.)*
Class III
1. Patients who do not have a reasonable expectation of survival with acceptable functional status for at least 1 year, even if they meet the ICD implantation criteria specified in the class I, IIa, and IIb recommendations. *(Level of evidence: C.)*
2. Incessant VT or VF. *(Level of evidence: C.)*
3. Significant psychiatric illnesses that may be aggravated by device implantation or may preclude systematic follow-up. *(Level of evidence: C.)*
4. Drug-refractory congestive heart failure in patients who are not candidates for cardiac transplantation or CRT-D. *(Level of evidence: C.)*
5. Syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease. *(Level of evidence: C.)*
6. When VF or VT is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with Wolff-Parkinson-White syndrome, right ventricular or LV outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease). *(Level of evidence: C.)*
7. Ventricular tachyarrhythmias caused by a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, trauma). *(Level of evidence: B.)*

*Defined either as failure to increase by 20 mm Hg or greater or as a drop of 20 mm Hg or greater.

†*Established risk markers:* Sudden death presumably caused by hypertrophic cardiomyopathy in one or more first-degree relatives, LV wall thickness of 30 mm or greater, one or more unexplained syncopal episodes in the last 6 months, nonsustained VT, abnormal blood pressure response to exercise.

‡*Potential risk modifiers:* Resting LV outflow tract gradient of 30 mm Hg or greater, late gadolinium enhancement on cardiac magnetic resonance imaging, LV apical aneurysm.

CRT-D, Cardiac resynchronization therapy defibrillator.

However, it is important to recognize the conceptual difference between class I indications for pacing ICDs and those for ICDs for primary prevention. Many class I indications for pacing relieve serious symptoms that occur frequently in day-to-day life. In contrast, class I ICD indications for primary prevention address the risk for infrequent but catastrophic events, and the decision to implant an ICD should include consideration of the presence of severe comorbid conditions, which could limit benefit from the ICD. In contrast, pacing is almost never withheld from patients with persistent symptomatic bradycardia because of comorbidities.

Expert Consensus Statement on Use of ICD Therapy

Accompanying the previous guidelines, an expert consensus statement on the use of ICD therapy was published and approved by HRS/ACC/AHA to expand the guidelines to include “Patients Who Are Not

Included or Not Well Represented in Clinical Trials." The following is extracted from that statement.[4]

Patient Population #1: Patients with an abnormal troponin level (or other biomarker) for myocardial infarction who do not fulfill criteria for MI, and who previously satisfied primary prevention or secondary prevention criteria for ICD implantation.

In patients with abnormal cardiac biomarkers not thought to be caused by an MI and who otherwise would be candidates for implantation on the basis of primary prevention or secondary prevention criteria, implantation of an ICD is recommended. *This statement clarifies the guidelines for primary prevention ICD implantation in the absence of criteria for MI.*

Patient Population #2: Patients within 40 days of acute MI who have known left ventricular dysfunction and who have previously satisfied criteria for implantation of a primary prevention ICD.

Implantation of an ICD with in the first 40 days following acute MI in patients with preexisting systolic ventricular dysfunction (who would have qualified for a primary prevention ICD) is not recommended. *Although the patient meets criteria for ICD otherwise, multiple randomized controlled trials (RCTs) have found no benefit in the 40 days after MI.*

Patient Population #3: Patients within 40 days of an acute MI who also have an indication for permanent pacemaker implantation.

In patients who, within 40 days of an MI, require nonelective permanent pacing, who also would meet primary prevention criteria for implantation of an ICD, and in whom recovery of LV function is uncertain or not expected, implantation of an ICD with appropriately selected pacing capabilities is recommended. *If a pacemaker were implanted, it is likely that an ICD would need to be implanted at a later date, exposing the patient to the risk of a second operation.*

Patient Population #4: Patients within 40 days of an MI who subsequently present sustained or hemodynamically significant ventricular tachyarrhythmias.

In patients who, within 40 days of an MI, develop sustained (or hemodynamically significant) ventricular tachyarrhythmias more than 48 hours after an MI and in the absence of ongoing ischemia, implantation of an ICD is recommended. *The waiting period of 40 days after MI applies only to primary prevention indications for an ICD, not to the secondary prevention indication of sustained or hemodynamically significant ventricular arrhythmias.*

In patients who, within 40 days of an MI, develop sustained (or hemodynamically significant) VT more than 48 hours after an MI that can be treated by ablation, implantation of an ICD can be useful.

In patients who, within 40 days of an MI, develop sustained (or hemodynamically significant) ventricular tachyarrhythmias where there is clear evidence of an ischemic etiology with coronary anatomy amenable to revascularization (and appropriately treated), implantation of an ICD is not recommended. *Ischemic VT/VF should be treated with revascularization, not an ICD.*

Patient Population #5: Patients who, within 40 days of an MI (but >48 hours), present with syncope likely due to ventricular tachyarrhythmia, and in whom there is no evidence of ongoing ischemia.

In patients who, within 40 days of an MI, present with syncope thought to be caused by ventricular tachyarrhythmia (by clinical history, documented NSVT, or EPS), implantation of an ICD can be useful. *This is another example that the waiting period of 40 days after MI applies only to primary prevention indications for an ICD, not to secondary prevention indications.*

Patient Population #6: Patients within 40 days of an MI who have a previously implanted ICD that requires elective replacement for battery depletion.

In patients within 40 days of an MI and who have an ICD that requires elective replacement due to battery depletion, after careful assessment of comorbidities and the current clinical situation, replacement of the ICD generator is recommended. *Elective replacement MI is indicated even when, within 40 days of MI, the battery status jeopardizes device performance. This circumstance should occur rarely if patients are followed by remote monitoring.*

Patient Population #7: Patients with significant left ventricular dysfunction within 40 days following an acute MI who are also listed for heart transplantation or who undergo implantation of a left ventricular assist device.

ICD implantation in patients within 40 days of an MI who have been listed for heart transplant or implanted with an LVAD is not recommended. *Listing for transplant or LVAD implantation within 40 days of MI is not an ICD indication.*

Patient Population #8A: Patients within 90 days of revascularization who have known left ventricular dysfunction and who have previously satisfied criteria for implantation of a primary prevention ICD.

In patients who are within 90 days of revascularization and who previously qualified for the implantation of an ICD for primary prevention of SCD, and who have undergone revascularization that is unlikely to result in an improvement in LVEF greater than 0.35, and who are not within 40 days after an acute MI, implantation of an ICD can be useful. *An RCT showed no benefit of ICD implantation with epicardial leads after surgical revascularization. ICD implantation has not been studied within 90 days of percutaneous revascularization.*[5]

Patient Population #8B: Patients within 90 days of revascularization who have previously satisfied criteria for implantation of a secondary prevention ICD (resuscitated from cardiac arrest due to VT/VF).

In patients within 90 days of revascularization who have previously qualified for the implantation of an ICD for secondary prevention of SCD (resuscitated from cardiac arrest due to ventricular tachyarrhythmia

not caused by acute ischemia or other reversible cause) and have abnormal LV function, implantation of an ICD is recommended. *Similar to the post-MI waiting period, the postrevascularization waiting period applies only to primary prevention indications for an ICD.*

In patients within 90 days of revascularization who have previously qualified for the implantation of an ICD for secondary prevention of SCD (resuscitated from cardiac arrest due to ventricular tachyarrhythmia) that is unlikely related to myocardial ischemia/injury and have normal LV function, implantation of an ICD is recommended.

In patients within 90 days of revascularization who have previously qualified for the implantation of an ICD for secondary prevention of SCD (resuscitated from cardiac arrest due to ventricular tachyarrhythmia) that was not related to acute myocardial ischemia/injury and who were subsequently found to have coronary artery disease that is revascularized with normal LV function, implantation of an ICD can be useful. *Again, the postrevascularization waiting period applies only to primary prevention indications for an ICD.*

In patients within 90 days of revascularization who were resuscitated from cardiac arrest due to ventricular tachyarrhythmia that was related to acute myocardial infarction/injury, with normal LV function, and who undergo complete coronary revascularization, an ICD is not recommended. *Acute ischemic VF in the setting of acute MI is never an indication for an ICD.*

Patient Population #9: Patients within 90 days of revascularization who also have an indication for permanent pacemaker (PPM) implantation.

In patients within 90 days of revascularization who require nonelective permanent pacing, who would also meet primary prevention criteria for implantation of an ICD, and in whom recovery of LV function is uncertain or not expected, implantation of an ICD with appropriately selected pacing capabilities is recommended. *Similar to the post-MI recommendation, if a pacemaker were implanted, it is likely that an ICD would need to be implanted at a later date, exposing the patient to the risk of a second operation.*

Patient Population #10: Patients within 90 days of revascularization who subsequently present sustained or hemodynamically significant ventricular tachyarrhythmia.

In patients within 90 days of revascularization with structural heart disease and sustained (or hemodynamically significant) ventricular tachyarrhythmia that was not clearly related to acute myocardial infarction/ischemia, implantation of an ICD is recommended.

In patients who, within 90 days of revascularization, develop sustained (or hemodynamically significant) VT that can be treated by ablation therapy, implantation of an ICD can be useful. *This is consistent with the principle that postrevascularization criteria apply only to primary prevention indications.*

Patient Population #11: Patients within 90 days of revascularization who present with syncope likely caused by ventricular tachyarrhythmia.

In patients within 90 days of revascularization who present with syncope thought to be caused by ventricular tachyarrhythmia (by clinical history or documented NSVT, or EPS),implantation of an ICD can

be useful. *This consensus also applies the principle that postrevascularization criteria apply only to primary prevention indications.*

Patient Population #12: Patients within 90 days of revascularization who have a previously implanted ICD that requires elective replacement because of battery depletion.

In patients within 90 days of revascularization with an ICD that requires replacement because of battery depletion, after careful assessment of comorbidities and the current clinical situation, replacement of the ICD generator is recommended.

Patient Population #13: Patients within 90 days of revascularization who are also listed for heart transplantation or who undergo implantation of a ventricular assist device.

In patients within 90 days of revascularization who have been listed for heart transplant or implanted with a ventricular assist device, and who are not within 40 days of an acute MI, implantation of an ICD can be useful. *Unlike other parallels between post-MI and postrevascularization restrictions on primary prevention ICDs, this restriction does not apply solely because of revascularization.*

Patient Population #14: Patients less than 9 months from the initial diagnosis of nonischemic cardiomyopathy (NICM) who have significant left ventricular dysfunction and heart failure symptoms.

Implantation of an ICD for primary prevention is not recommended within the first 3 months after initial diagnosis of NICM. If recovery of LV function is unlikely, implantation of an ICD for primary prevention can be useful between 3 and 9 months after initial diagnosis of NICM. *This consensus supports a 3-month waiting period after diagnosis for primary prevention implants if recovery is unlikely (e.g., extensive scar and no improvement with medical therapy at 3 months).*

Patient Population #15: Patients less than 9 months from the initial diagnosis of NICM who meet criteria for primary prevention ICD who also have an indication for PPM implantation.

In patients less than 9 months from the initial diagnosis of NICM who require nonelective permanent pacing, who would meet primary prevention criteria for implantation of an ICD, and in whom recovery of LV function is uncertain or not expected, implantation of an ICD with the appropriately selected pacing abilities is recommended. *ICD implant for primary prevention is recommended even within the first 9 months of diagnosis of NICM when there is a permanent pacing indication.*

Patient Population #16: Patients less than 9 months from the initial diagnosis of NICM who also have sustained or hemodynamically significant ventricular tachyarrhythmia.

In patients less than 9 months from the initial diagnosis of NICM with sustained (or hemodynamically significant) ventricular tachyarrhythmia, implantation of an ICD is recommended. *Again, waiting periods do not apply to implantation of secondary prevention ICDs.*

Patient Population #17: Patient less than 9 months from the initial diagnosis of NICM who present with syncope likely caused by ventricular tachyarrhythmia.

In patients less than 9 months from the initial diagnosis of NICM with syncope thought to be caused by a ventricular tachyarrhythmia (by clinical history or documented NSVT), implantation of an ICD can be useful. *This is another example of a secondary prevention indication.*

Patient Population #18: Patients less than 9 months from the initial diagnosis of NICM who are also listed for heart transplantation or who undergo implantation of a ventricular assist device.

In patients <9 months from the initial diagnosis of NICM who have been listed for heart transplant or implanted with an LVAD, implantation of an ICD can be useful.

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42

Cardiac Arrest and Sudden Cardiac Death

Robert J. Myerburg, Jeffrey J. Goldberger

Perspective

Sudden cardiac arrest (SCA), and its common consequence sudden cardiac death (SCD), is a major public health problem because of its frequency and demographics. With current estimates for out-of-hospital SCDs still in the range of 390,000 per year in the United States alone,[1,2] plus an additional 200,000 in-hospital cardiac arrests,[3] its impact is defined by the “rule of the 50s”[2]: SCD accounts for 50% of all cardiovascular deaths[4]; approximately 50% of all SCDs are unexpected first expressions of a cardiac disorder[5]; and SCD often strikes during the victim's productive years, accounting for up to 50% of years of potential life lost from heart disease.[6] Despite recognition of an association between forewarning symptoms of chest pain or syncope and SCD dating to Hippocrates around 400 BC, the description of a “shrunken and withered” artery to the heart in a victim of SCD in the late 1490s by Da Vinci, and an epidemiologic survey in Rome by Lancisi at the request of Pope Clement XI in 1706, advances in prediction, prevention, and management of unexpected SCA and SCD did not begin to emerge until approximately 50 years ago. It is anticipated that the major insights into causes, pathophysiology, and preventive and management strategies developed during the past few decades will continue to evolve.

Definitions

Sudden cardiac death is natural death from cardiac causes heralded by abrupt loss of consciousness within 1 hour of the onset of an acute change in cardiovascular status (**Table 42.1**). Preexisting heart disease may or may not have been known to be present, but the time and mode of death are unexpected. This definition incorporates the key elements of natural, rapid, and most importantly, unexpected death by a cardiac cause or mechanism. It consolidates previous definitions that have conflicted, mainly because

the most useful operational definition of SCD in the past differed for clinicians, cardiovascular epidemiologists, pathologists, and scientists attempting to define pathophysiologic mechanisms. As the epidemiology, clinical expression, causes, and mechanisms began to be understood, these differences merged.

TABLE 42.1

Terms Related to Sudden Cardiac Death

TERM	DEFINITION	QUALIFIERS	MECHANISMS
Sudden cardiac death	Sudden, irreversible cessation of all biologic functions as a consequence of cardiac arrest	None	—
Cardiac arrest	Abrupt cessation of cardiac mechanical function, leading to death in the absence of reversal by a prompt intervention	Rare spontaneous reversions; the likelihood of successful intervention is related to the mechanism of arrest, clinical setting, and prompt return of spontaneous circulation	VF, pulseless VT, PEA, asystole, extreme bradycardia, mechanical factors
Cardiovascular collapse	Sudden loss of effective blood flow because of cardiac and/or peripheral vascular factors that may reverse spontaneously (e.g., neurocardiogenic syncope, vasovagal syncope) or require interventions (e.g., cardiac arrest)	Nonspecific term; includes SCA and its consequences and transient non–life-threatening conditions that usually revert spontaneously	Same as cardiac arrest, plus vasodepressor-induced syncope or other causes of transient loss of blood flow

PEA, Pulseless electrical activity; *SCA,* sudden cardiac arrest; *VF,* ventricular fibrillation, *VT,* ventricular tachycardia.

To satisfy clinical, scientific, legal, and social considerations, four temporal elements must be considered: (1) prodromes, (2) onset, (3) cardiac arrest, and (4) biologic death (**Fig. 42.1**). Because the proximate cause of SCA is an abrupt disturbance in cardiovascular function resulting in loss of consciousness due to cessation of cerebral blood flow, any definition must recognize the brief interval between onset of the mechanism *directly* responsible for cardiac arrest and the consequent loss of blood flow. The 1-hour definition primarily refers to the duration of the “terminal event,” which defines the interval between the onset of symptoms signaling the pathophysiologic disturbance leading to cardiac arrest and the onset of the cardiac arrest itself. Based on human centrifuge studies carried out during the early years of the U.S. space program, the time between abrupt cessation of cerebral blood flow and loss of consciousness can be 10 seconds or less.

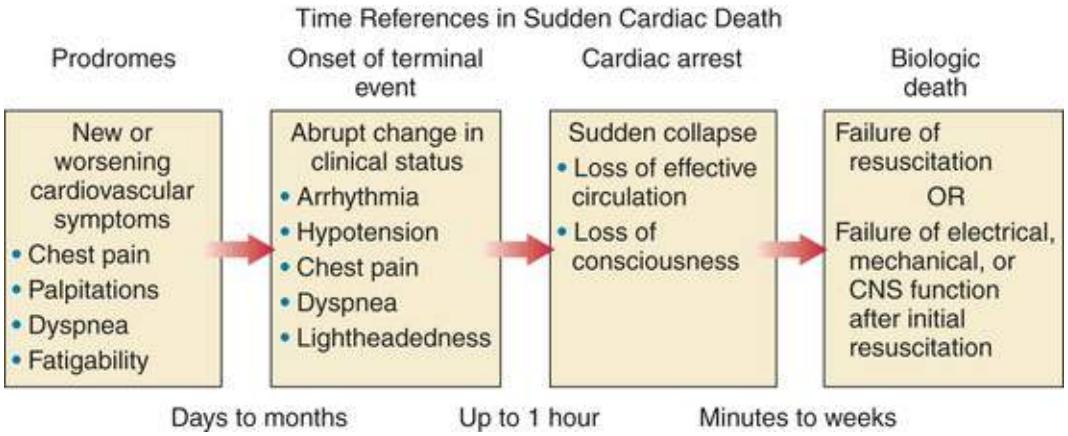


FIGURE 42.1 Sudden cardiac death (SCD) viewed from four temporal perspectives: (1) prodromes, (2) onset of the terminal event, (3) cardiac arrest, and (4) progression to biologic death. Individual variability of the components influences clinical expression. Some victims experience no prodromes, with onset leading almost instantaneously to cardiac arrest; others may have an onset that lasts up to 1 hour before clinical arrest. Other patients may live days to weeks after the cardiac arrest before biologic death, often because of irreversible brain damage and dependence on life support. These factors influence interpretation of the 1-hour definition. The two most relevant clinical factors are onset of the terminal event and the clinical cardiac arrest itself; legal and social considerations focus on the time of biologic death. *CNS,* Central nervous system.

Prodromes, occurring weeks or months before an event, are generally predictors of an impending cardiac event, but not specific for SCA itself. The same premonitory signs and symptoms may be more specific for imminent cardiac arrest when they begin abruptly. Sudden *onset* of chest pain, dyspnea, or palpitations and other symptoms of arrhythmias often precede the onset of cardiac arrest and define the 1-hour onset of the terminal event that brackets the *cardiac arrest*. The fourth element, *biologic death,* was an immediate consequence of cardiac arrest in the past and usually occurred within minutes. However, the generally accepted clinical-pathophysiologic definition of up to 1 hour between onset of the terminal event and biologic death requires qualifications for specific circumstances. For example, since the development of community-based interventions and life support systems, patients may now remain biologically alive for a long period after the onset of a pathophysiologic process that has caused irreversible damage and will ultimately lead to death. In this circumstance, the causative pathophysiologic and clinical event is the cardiac arrest itself rather than the factors responsible for the delayed biologic death. Thus, death remains defined biologically, legally, and literally as an absolute and irreversible event timed to cessation of all biologic functions, but most studies link the definition of SCD to the cardiac arrest rather than to a biologic death that occurs during hospitalization after cardiac arrest or within 30 days. Finally, forensic pathologists studying unwitnessed deaths continue to use the definition of sudden death for a person known to be alive and functioning normally 24 hours before, and this remains appropriate within obvious limits. Among the precautions is the recognition that not all sudden deaths are cardiac in origin.[7]

Epidemiology

Epidemiologic Overview

Epidemiologic studies of SCD are difficult to interpret for both theoretical and practical reasons. There are persisting inconsistencies about the definition and challenges in accessing data and adjudicating individual cases in datasets, in determining pathophysiologic mechanisms, and in making distinctions between population risk and individual risk.[8] In addition, SCA leading to SCD has short-term dynamics

superimposed on a long-term static or dynamic substrate, which introduces unusual epidemiologic complexities, including long-term risk prediction based on the evolution of atherogenesis, myocardial hypertrophy, and ventricular muscle dysfunction over time and modulation by transient (short-term) variables such as ischemia, hemodynamic shifts, atherosclerotic plaque disruption and thrombosis, and autonomic variations. The differences between chronic disease evolution and transient events call for different forms of epidemiologic modeling (**Table 42.2A**). Furthermore, the emerging field of genetic epidemiology adds another dimension for consideration, and there is a need to focus on *interventional epidemiology*, a term coined to define the population dynamics of therapeutic outcomes.

TABLE 42.2

Pathophysiologic Epidemiology and Power Cascade for Indicators of Risk for Sudden Cardiac Death

STRATEGY	EXAMPLES	MEASURES	POWER
A. Power Cascade for Risk Prediction			
Conventional risk factors	Framingham risk index	Prediction of evolution of disease	High for the population Low for the individual
Anatomic disease screening	Coronary calcium score and CT angiography	Identification of abnormal coronary arteries	High for anatomic identification Low for individual event prediction
Clinical risk profiling	Ejection fraction, stress testing, imaging techniques	Extent of disease	High for small, high-risk subgroups Low for large, low-risk subgroups
Transient risk predictors	Inflammatory markers; thrombotic cascade	Prediction of unstable plaques; acute changes in vascular status	Uncertain feasibility
Personalized risk predictors	Familial/genetic profiles	Individual SCD expression	Uncertain clinical precision; in evolution
B. Pathophysiologic Epidemiology			
Substrate-based risk	Coronary heart disease State of epicardial and intramyocardial vessels Myocardial infarction Myopathy, infiltration, inflammation, valvulopathy Hypertrophy; myocardial fibrosis		
Expression-based risk	Left ventricular dysfunction and heart failure Metabolic abnormalities Autonomic fluctuations		
Mechanism-based causes	VF/pulseless VT PEA Asystole		

In reference to risk for SCD from coronary heart disease, clinical categories ranging from general population risk to personalized risk profiling are paralleled by the partition of risk predictors into the pathophysiologic categories of substrate-based risk and expression-based risk[2,9] (**Table 42.2B**). *Substrate-based risk* refers to prediction of the evolution or identification of vascular or myocardial substrates that establish risk for SCD (i.e., atherogenesis, scar patterns, remodeling) and to quantification of these risks. It should not be perceived as limited to anatomic features because risk substrates may exist at a molecular level. In contrast, *expression-based risk* refers to the identification of mechanisms and pathways that contribute to the clinical manifestation of the risk established by the substrate. This category includes plaque transition and acute coronary syndromes (plaque disruption and thrombogenesis) and their potential for specific expression as an arrhythmic event in susceptible individuals. The arrhythmogenic category of risk can also be viewed to include modifiers of molecular-based risk that drive individual expression.

Incidence and the Population Burden of Sudden Cardiac Death

The worldwide incidence of out-of-hospital cardiac arrest (OHCA) leading to SCD is difficult to

estimate because numbers vary as a function of the prevalence of coronary heart disease in different countries[10] (**see Chapter 1**). The annual number of out-of-hospital SCDs in the United States is derived from multiple sources, such as retrospective death certificate data, American Heart Association (AHA) statistical updates based on data from the National Center for Health Statistics,[1] and national extrapolations from a large emergency rescue experience in one community[11] and a community-wide multisource data set from another.[12] Recently, data from large surveillance studies, such as the Resuscitation Outcomes Consortium (ROC), are contributing additional insight into the subtleties of data collection and interpretation.[13]

Statistical analyses from the same death certificate data sources have ranged from fewer than 250,000 SCDs annually when the etiologic definition is limited to coronary heart disease (*International Classification of Diseases,* ninth edition [ICD-9], classifications 410 to 414) to more than 460,000 SCDs per year when all causes are included.[9,10,14] Extrapolations from the two community-based sources set nationwide figures at fewer than 200,000 SCDs annually.[11,12] Because these broad ranges and the reported regional differences in incidence and outcomes of cardiac arrest[15] suggest that an accurate number can be found only by performing carefully designed prospective epidemiologic surveillance studies, the most widely cited estimates remain in the range of 390,000 SCDs annually, as suggested in the 2016 AHA statistical update.[1] These figures suggest an overall incidence of between one and two deaths per 1000 persons in the general population. The annual number of emergency medical services (EMS)–assessed OHCAs in the United States is 356,000, among whom 347,500 are adults over age 18 years.[1]

The temporal definition of sudden death strongly influences epidemiologic data. Retrospective death certificate studies have demonstrated that a temporal definition of sudden death of less than 2 hours after the onset of symptoms results in 12% to 15% of all natural deaths being defined as “sudden” and almost 90% of all natural sudden deaths having cardiac causes. In contrast, application of a 24-hour definition of sudden death increases the fraction of all natural deaths falling into the sudden category to more than 30% but reduces the proportion of all sudden natural deaths resulting from cardiac causes to 75%.

Prospective studies have demonstrated that approximately 50% of all deaths caused by coronary heart disease are sudden and unexpected and occur shortly (instantaneous to 1 hour) after the onset of symptoms. Because coronary heart disease is the dominant cause of both sudden and nonsudden cardiac deaths in the United States, the fraction of total cardiac deaths that are sudden is similar to the fraction of deaths from coronary heart disease that are sudden, although there does appear to be geographic variation in the fraction of coronary deaths that are sudden.[14,15] It is also of interest that the age-adjusted decline in mortality from coronary heart disease in the United States during the past half-century has not changed the fraction of coronary deaths that are sudden and unexpected,[16,17] even though there may be a decline in out-of-hospital deaths relative to emergency department deaths. Furthermore, the decreasing age-adjusted mortality does not imply a decrease in absolute numbers of cardiac or sudden deaths, because of the growth and aging of the U.S. population and the increasing prevalence of chronic heart disease,[14] including heart failure. It appears that the cumulative SCD burden in absolute numbers is not tracking the age-adjusted decrease in cardiac deaths that has been evolving during the past 40 to 50 years.[18] The figures previously cited suggest that SCD numbers have not decreased, although the landscape of SCD over time is further complicated by the suggested shift of mechanisms of out-of-hospital SCA from ventricular tachyarrhythmias to pulseless electrical activity or asystole, in part because of implantable

cardioverter-defibrillator (ICD) efficacy.[19]

Population Pools, Risk Gradients, and Time Dependence of Risk

Four factors are of primary importance for identification of populations at risk and consideration of strategies for prevention of SCD: (1) the absolute numbers and event rates (incidence) among population subgroups (**Fig. 42.2A**), (2) the clinical subgroups in which SCDs occur (**Fig. 42.2B**), (3) competing risks, and (4) the time dependence of risk.

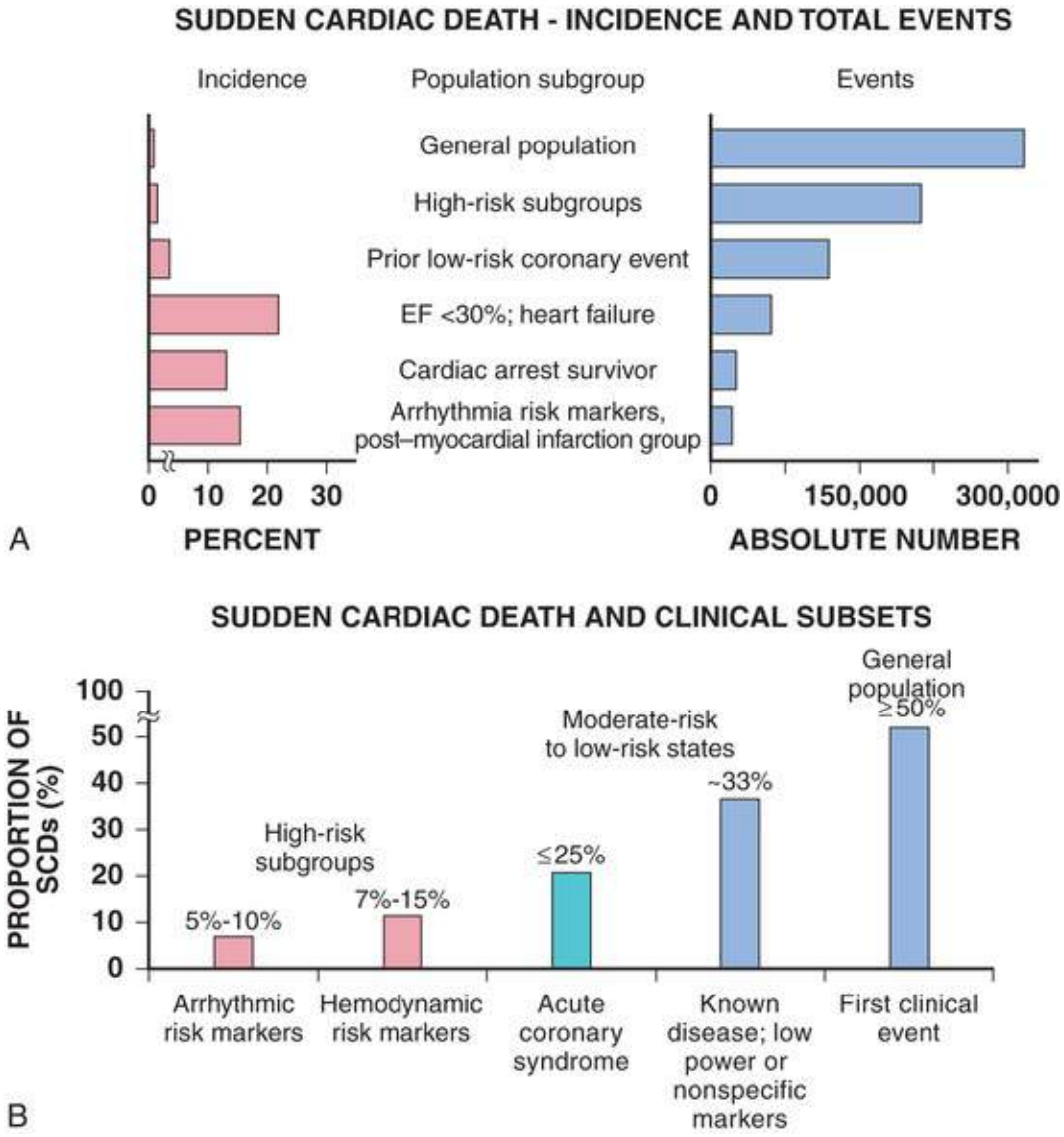


FIGURE 42.2 Impact of population subgroups and time from events on the clinical epidemiology of sudden cardiac death (SCD). **A,** Estimates of incidence (percent per year) and the total number of events per year for the general adult population in the United States and for increasingly high-risk subgroups. The overall adult population has an estimated incidence of sudden death of 0.1% to 0.2% per year, which accounts for a total of more than 300,000 events per year. With the identification of increasingly powerful risk factors, the incidence increases progressively, but this is accompanied by a progressive decrease in the total number of events represented by each group. The inverse relationship between incidence and the total number of events results from the progressively smaller denominator pool in the highest subgroup categories. In contrast to earlier iterations of this incidence profile, the magnitude of risk in the heart failure category exceeds that in the high-risk post–myocardial infarction and post–primary cardiac arrest groups. Successful interventions in larger population subgroups require identification of specific markers to increase the ability to identify specific patients who are at particularly high risk for a future event. (*Note:* The horizontal axis for the incidence figures is not linear and should be interpreted accordingly.) **B,** Distribution of the clinical status of victims at the time of SCD. Approximately 50% of all cardiac arrests caused by coronary heart disease occur as the first clinically manifested event, and up to an additional 30% occur in the clinical setting of known disease in the absence of strong risk predictors. Less than 25% of victims have high-risk markers based on arrhythmic or hemodynamic parameters. *EF,* Ejection fraction. (**A,** Modified from Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: structure, function, and time-dependence of risk. Circulation 1992;85[Suppl I]:I2; **B,** modified from Myerburg RJ. Sudden cardiac death: exploring the limits of our knowledge. J Cardiovasc Electrophysiol 2001;12:369.)

Population and Subgroup Risk Versus Individual Risk Assessment

When the estimated 390,000 SCDs that occur annually in the United States are viewed as a global figure for an unselected adult population 35 years and older, the overall incidence is calculated to be in the range of 0.1% to 0.2% per year (1 to 2 per 1000 population; **Fig. 42.2A**). This general population

includes the large proportion of SCDs that occur as a first clinical manifestation of previously unrecognized heart disease, as well as SCDs that can be predicted with somewhat greater accuracy in higher-risk subgroups (**Fig. 42.2B**). Because it is impractical to plan an intervention designed for the general population that would be applied to the 999 per 1000 who do not have an event to reach and possibly influence the 1 per 1000 who will experience an event, better risk profiling is needed to identify smaller high-risk subsets in whom interventions are practical. **Fig. 42.2A** highlights this problem by expressing the incidence (percent per year) of SCD among various subgroups and comparing the incidence figures with the total number of events that occur annually in each subgroup. Thus, despite the large absolute number at risk in the general population and the impact of preventive interventions on populations risk for coronary artery disease (CAD), the precise ability to identify these individuals for targeted therapy for SCD prevention is an unmet challenge.[2] The cost and risk-to-benefit uncertainties limit the nature of such broad-based interventions and demand a higher resolution of risk identification.[20] Two fundamental approaches to this challenge can be followed: (1) a general population strategy targeting prevention of acquired risk factors, such as obesity (primordial prevention), and primary prevention by control of manifest risk factors,[21] and (2) a more focused individual risk strategy based on identification and intervention in small subsets of the general population with a high density of risk (**Fig. 42.3**).

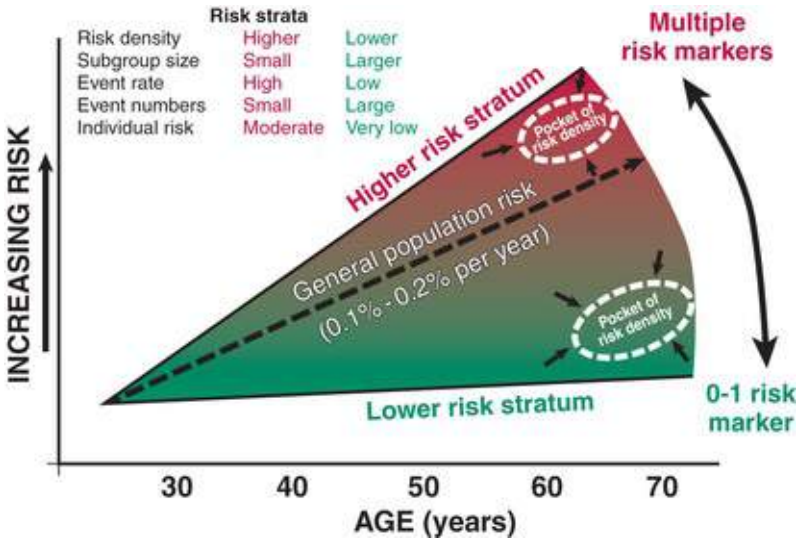


FIGURE 42.3 Stratification of risk as a continuum across the population. The mean risk in the general population is demonstrated as a continuum across four decades. The mean risk of approximately 0.1% to 0.2% per year is bracketed by extremes of higher and lower risk strata, with the larger absolute numbers accumulated in the lower risk strata. Potentially identifiable subgroups with varying risk densities populate each range of risk. The ability to identify high–risk density subgroups within the general population would contribute to better individual risk prediction. (Modified from Myerburg RJ, Junttila MJ. Sudden cardiac death caused by coronary heart disease. Circulation 2012;125:1043.)

On moving from the total adult population to a subgroup at higher risk because of the presence of selected coronary risk factors, there may be a 10-fold or greater increase in the annual incidence of events, with the magnitude dependent on the number and types of risk factors operating in specific subgroups. The size of the denominator pool, however, remains very large, and implementation of interventions remains problematic, even at this heightened level of risk. Higher resolution is desirable and can be achieved by identification of more specific subgroups. However, the corresponding absolute number of deaths becomes progressively smaller as the subgroups become more focused (see **Fig. 42.2A**), thus limiting the potential benefit of interventions to a much smaller fraction of the total number of

patients at risk. Up to half of all SCDs attributable to coronary heart disease are first clinical events,[8] and another 20% to 30% occur in subgroups of patients with known coronary heart disease who are profiled to be at relatively low risk for SCD on the basis of current clinically available markers (**see Fig. 42.2B**). The principle of a high proportion of SCDs occurring as first events or in previously asymptomatic individuals applies to the less common causes as well.[22]

Biologic and Clinical Time-Dependent Risk

Temporal elements in risk for SCD have been analyzed in the context of both biologic and clinical chronology. In the former, epidemiologic analyses of risk for SCD in populations have identified three patterns: diurnal, day of the week, and seasonal. General patterns of heightened risk during the morning hours, on Mondays, and during the winter months have been described.[18] An exception to the diurnal risk pattern is SCD in sleep apnea, in which the risk tends to be nocturnal.[23]

Ambient temperature is an environmental factor associated with risk for SCD. Both excessive cold[18] and excessive heat[24] have been linked to risk for cardiac arrest, although the studies did not determine whether temperature extremes are associated with ventricular tachyarrhythmias versus other mechanisms of cardiac arrest. However, significant cooling of the core temperature can lengthen the time course of repolarization of ventricular myocardium and prolong the QT interval, whereas sweating associated with increases in core temperature can alter electrolyte balance. Elevated temperature is a risk for SCA in patients with Brugada syndrome (**see Chapters 33 and 39**). Another environmental variable, transient ambient air pollution conditions, has been correlated with an increased incidence of ventricular arrhythmias stored in ICD memories,[18] but the question of whether these are cardiac arrest equivalents is uncertain.

In the longer-term clinical paradigm, risk for SCD is not linear as a function of time after changes in cardiovascular status.[16,17,25] Survival curves after major cardiovascular events, which identify risk for both SCD and total cardiac death, usually demonstrate that the most rapid rate of attrition occurs during the first 6 to 18 months after an index event. Thus, there is a time dependence of risk that focuses the potential opportunity for maximum efficacy of an intervention during the early period after a cardiovascular event. Curves that have these characteristics have been generated from among survivors of OHCA, new onset of heart failure, and unstable angina and from patients with recent myocardial infarction (MI) and low ejection fraction or heart failure. For the latter, however, early nonarrhythmic deaths also contribute a large proportion of the fatal events. Even though the rate of attrition decreases after the early spike in mortality, a secondary delayed increase in risk occurs in post-MI patients 2 to 5 years after an index event, probably related to ventricular remodeling and heart failure.

Age, Race, Sex, and Heredity

Age

The incidence of sudden death has two peak ages: within the first year of life (including sudden infant death syndrome [SIDS]; **see Chapter 75**) and between 45 and 75 years of age. Among the general populations of infants younger than 1 year and middle-aged or older adults, the incidence is surprisingly similar.[26] In adults older than 35 years, the incidence of SCD is in the range of 1 per 1000 persons per year (**Fig. 42.4A**), with an age-related increase in risk over time as the prevalence of coronary heart disease increases in parallel with advancing age.[16]

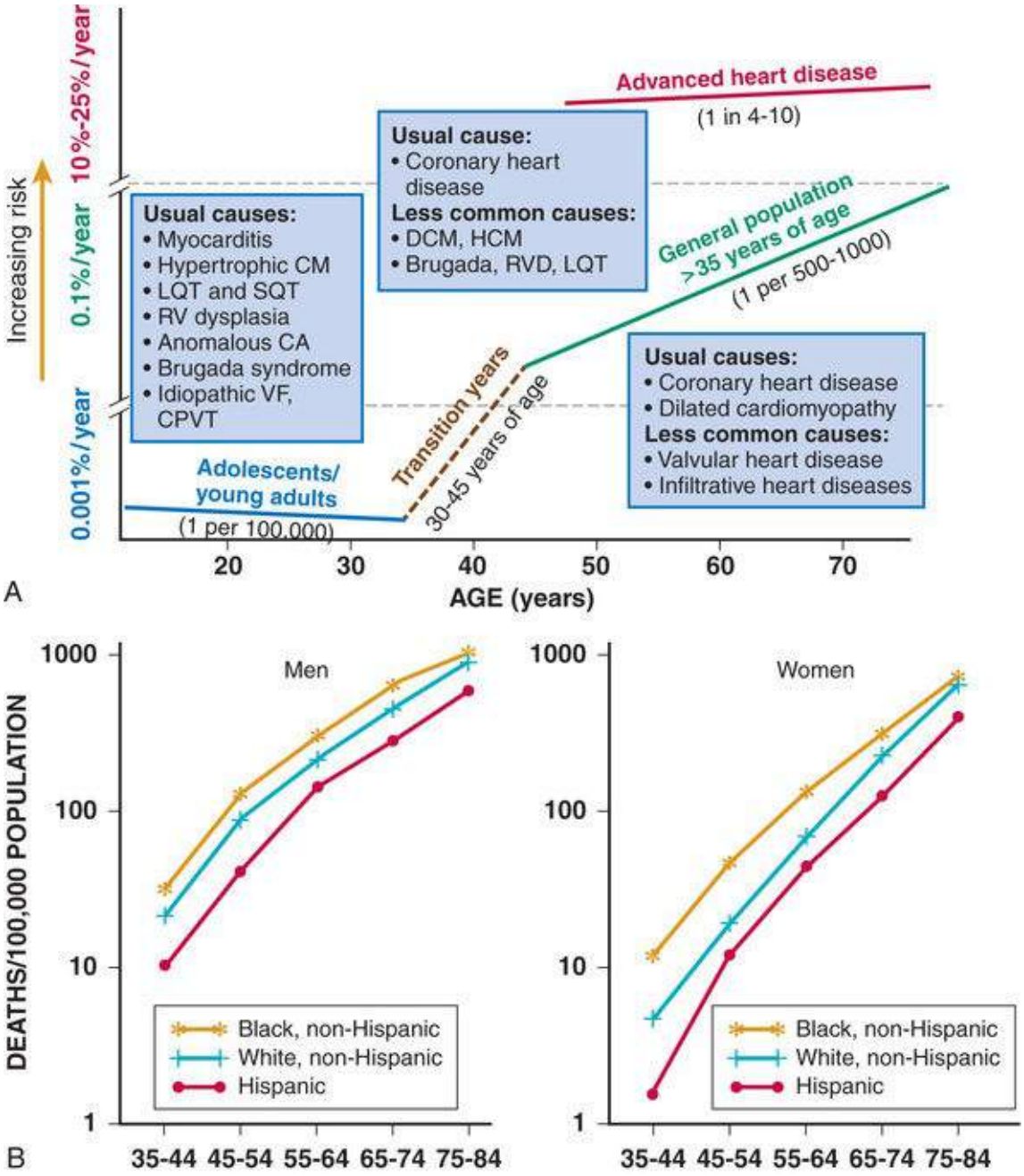


FIGURE 42.4 Age-, sex-, and race-specific risks for sudden cardiac death (SCD). **A,** Age-related and disease-specific risk for SCD. For the general population 35 years and older, the risk for SCD is 0.1% to 0.2% per year (1/500 to 1000 population), with a wide spread in subgroup risk based on the number and power of individual risk factors. Causes are dominated by coronary heart disease and, to a lesser extent, nonischemic cardiomyopathy in this age range. The risk for SCD increases dramatically beyond age 35 years and continues to increase past age 70. In patients older than 30 with advanced structural heart disease and markers of high risk for cardiac arrest, the event rate may exceed 25% per year, and the age-related risk is attenuated. In adolescents and adults younger than 30, the overall risk for SCD is 1/100,00 population or 0.001% per year, with a variety of causes such as inherited structural and electrical disorders, developmental defects, and myocarditis dominating. In adolescents and young adults at risk for SCD from specific identified causes, it is difficult to ascertain the risk in individual patients because of variable expression of the disease state (see text for details). In the transition range from 30 to 45 years of age, the relative frequency of the uncommon disease yields to the dominance of coronary heart disease and nonischemic cardiomyopathy, but both groups of potential causes must be entertained because many of the rare disorders are expressed in that age range. **B,** SCD risk as a function of age, sex, and race or culture (white, black, and Hispanic). *CA,* Cardiac arrest; *CM,* cardiomyopathy; *CPVT,* catecholaminergic polymorphic ventricular tachycardia; *DCM,* dilated CM; *HCM,* hypertrophic CM; *LQT,* long QT syndrome; *RV,* right ventricular; *RVD,* RV dysplasia; *SQT,* short QT syndrome; *VF,* ventricular fibrillation. (**B,** Data modified from Gillum RF. Sudden cardiac death in Hispanic Americans and African Americans. Am J Public Health 1997;87:1461.)

An evaluation of the lifetime risk of SCD resulting from CAD in the Framingham population

demonstrated a significant decrease in the lifetime risk for the population at age 75 and older, compared to populations at 45 and 55 years, with the difference most prominent in men.[27]

The incidence in infants is 73 per 100,000 person-years and is most often associated with complex congenital heart disease. The incidence in children, adolescents, and adults younger than 30 is approximately 6 per 100,000 person-years,[18,26] or 1% of the risk in middle-aged and older adults (**Fig. 42.4A**). One study demonstrated that approximately 40% of SCDs in this age category were unexplained, based on the absence of an autopsy or premortem clinical diagnosis, but postmortem genetic studies identified a likely cause in 27% of such cases that underwent studies.[28] Defined causes of SCD and CAD etiologies were more common in the 30- to 35-year-old subgroup.

In contrast to incidence, however, the proportion of deaths caused by coronary heart diseases that are sudden and unexpected decreases with advancing age. In the 20- to 39-year age-group, approximately 75% of the deaths attributable to coronary heart disease in men are sudden and unexpected, with the proportion falling to approximately 60% in the 45- to 54-year age-group and hovering close to 50% thereafter. Age also influences the proportion of any cardiovascular cause among all causes of natural sudden death in that the proportion of coronary deaths and of all cardiac causes of death that are sudden is highest in the younger age-groups, whereas the fraction of total sudden natural deaths that result from any cardiovascular cause is higher in the older age-groups. At the other end of the age range, only 19% of sudden natural deaths in children between 1 and 13 years have cardiac causes; the proportion increases to 30% in the 14- to 21-year age-group.

In the transition age range between adolescence and young adulthood (to 25 years) and in the middle and older ages (beginning at 35 years), coronary heart disease emerges to its position as the dominant cause of SCD. However, rare disorders, such as hypertrophic cardiomyopathy, Brugada syndrome, long-QT syndrome, and right ventricular dysplasia, are significant contributors to the distribution of causes of SCD in this age-group. In one study, myocardial fibrosis of unknown etiology was a significant cause in this group.[29]

Race

A number of studies comparing racial differences in the relative risk for SCD in whites and blacks with coronary heart disease in the United States had yielded conflicting and inconclusive data. However, the most recent studies demonstrate a higher risk for cardiac arrest and SCD in blacks than in whites[30] (**see Fig. 42.4B**). SCD rates in Hispanic populations were lower. These differences were observed across all age-groups.

Sex

SCD syndrome has a large preponderance in men relative to women during the young adult and early middle-age years because of the protection that women enjoy from coronary atherosclerosis before menopause (**see Fig. 42.4B**). Various population studies have demonstrated a fourfold to sevenfold greater incidence of SCD in men than in women before 65 years of age, at which point the difference decreases to 2 : 1 or less, and continues to decrease with advancing age. As risk for coronary events increases in postmenopausal women, risk for SCD increases proportionately, but men remain at higher risk than women across the entire age spectrum.[27,31] Even though the overall risk for SCD is much lower in younger women, CAD is the most common cause of SCD in women older than 40 years, and the classic coronary risk factors, including cigarette smoking, diabetes, use of oral contraceptives, and hyperlipidemia, all influence risk in women[32] (**see Chapter 89**). Data from the Nurses' Health Study

suggest that a healthy lifestyle, defined as no cigarette smoking, a low body mass index, regular exercise, and a healthy diet, reduces the risk for SCD in women by as much as 46% to more than 90%, depending on the number of low-risk markers present.[18] Women are 50% less likely to have severe left ventricular dysfunction and 66% less likely to have known coronary heart disease before SCD[33] and are therefore less likely to be profiled as high risk and more likely to have SCD as a first cardiac event.

Heredity

Familial patterns of risk for SCD, which result from known or suspected genetic variations, are emerging as important factors for risk profiling. This concept is generally applicable in regard to both disease development and SCD expression in the common acquired disorders and in a specific sense to inherited arrhythmogenic conditions associated with SCD. The various genetic associations can be separated into four categories (**Table 42.3**): uncommon inherited primary arrhythmic syndromes (e.g., long-QT syndromes, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia or fibrillation; **see Chapter 33**), uncommon inherited structural diseases associated with risk for SCD (e.g., hypertrophic cardiomyopathy, right ventricular dysplasia; **Chapters 77 and 78**), "acquired" or induced risk for arrhythmias (e.g., drug-induced long QT interval or proarrhythmia, electrolyte disturbances), and common acquired diseases associated with risk for SCD (e.g., coronary heart disease, nonischemic cardiomyopathies; **Chapters 59 and 60**). Genetic variants mapped to loci on many chromosomes are being defined as the molecular bases for these entities and associations.

TABLE 42.3
Genetic Contributors to Risk for Sudden Cardiac Death

Genetically Based Primary Arrhythmia Disorders
Congenital long–QT interval syndrome, short-QT syndrome Brugada syndrome Catecholaminergic polymorphic VT/VF Nonsyndromic VT/VF
Inherited Structural Disorders With Risk for Arrhythmic SCD
Hypertrophic cardiomyopathy Right ventricular dysplasia/cardiomyopathy
Genetic Predisposition to Induced Arrhythmias and SCD
Drug-induced "acquired" long–QT interval syndrome (drugs, electrolytes) Electrolyte and metabolic arrhythmogenic effects
Genetic Modulation of Complex Acquired Diseases
Coronary artery disease, acute coronary syndromes Congestive heart failure, dilated cardiomyopathies

The multiple specific mutations at gene loci–encoding ion channel proteins associated with the various inherited arrhythmia syndromes (**see Chapter 33**) represent a major advance in the understanding of a genetic and pathophysiologic basis for these causes of sudden death. In addition, the role of modifier genes and mutation specificity in the severity of clinical phenotypes in long–QT interval syndromes[34-36] and structural diseases such as hypertrophic cardiomyopathy[37] is of increasing interest. These observations may provide screening tools for individuals at risk, as well as the potential to devise specific therapeutic strategies. A study of screening electrocardiograms (ECGs) for long-QT syndrome (LQTS) in children entering first grade and repeated in the seventh grade, with subsequent genetic testing in children who were positive, suggested that the incidence of inherited LQTS was considerably higher (approximately 1 in 1000) by age 12 years (seventh grade) than earlier estimates from studies based on diagnoses from general clinical expressions.[38] Moreover, the cumulative risk of SCA among those with unrecognized or untreated LQTS was reported to be 13% before age 40 years.[39,40] In addition, gene loci identified by genome-wide association studies may also serve as candidates for investigation of the role

of low-penetrance mutations or polymorphisms in SCD caused by more common conditions, such as coronary heart disease.[41] At this time, the hope for common variants linked to common syndromes such as SCD apparently will be superseded by multiple rare-variant associations.

To the extent that SCD is an expression of underlying coronary heart disease, hereditary factors that contribute to risk for coronary heart disease operate nonspecifically for the SCD syndrome. Various studies have identified mutations and relevant polymorphisms along multiple steps of the cascade, from atherogenesis to plaque destabilization, thrombosis, and arrhythmogenesis, each of which is associated with increased risk for a coronary event[18,42] (**Fig. 42.5**). Integration of these individual markers may provide more powerful individual risk prediction in the future. In addition, several studies have suggested that SCD as the initial expression of coronary heart disease demonstrates familial clustering,[9] including general population surveillance studies, family histories of cardiac arrest survivors in the community, studies of ventricular fibrillation (VF) during acute MI, and postmortem evaluation of SCD cases (**Table 42.4**).

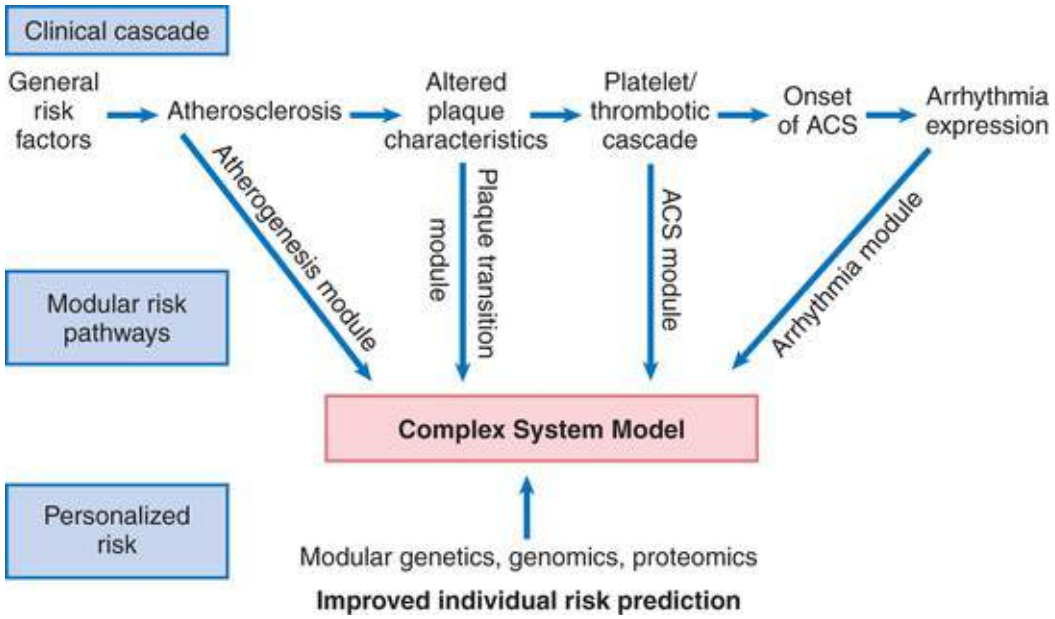


FIGURE 42.5 Coronary atherosclerosis heart disease cascade and genetic imprints on the progression to SCD. The cascade from conventional risk factors for coronary atherosclerosis to arrhythmogenesis in SCD related to coronary heart disease includes initiation and development, progression to an active state, initiation of acute coronary syndromes (*ACS*), and finally, progression to the specific expression of life-threatening arrhythmias. Multiple factors enter at each level, including specific risk based on the genetic profiles of individual patients. Individual risk based on genetic profiles has been identified for atherogenesis, plaque evolution, the thrombotic cascade, and arrhythmia expression. Stepwise integration of these characteristics for individuals through genetics, genomics, proteomics, and biologic system analyses offers the hope of a field of molecular epidemiology that may lead to higher single-patient probabilities for individual SCD risk prediction. (Modified from Myerburg RJ, Junttila MJ. Sudden cardiac death caused by coronary heart disease. Circulation 2012;125:1043.)

TABLE 42.4

Family History of and Risk for Primary Sudden Cardiac Death

STUDY SITE	COHORT	CONTROLS	FAMILY HISTORY MEASURE	OUTCOME
Seattle* 1988–1994	EMS SCA patients	Population matched	Hx of MI or PCA in 1° relatives	2.85 vs. 1.96/1000/yr RR = 1.57 (95% CI, 1.27-1.95)
Paris† 1967–1994	Population surveillance	Retrospective analysis	Hx of PCA in 1° relatives	18.6% vs. 9.9% OR = 1.80 (95% CI, 1.11-2.88)
Netherlands‡ 2001–2005	STEMI with VF	STEMI without VF	Hx of SCD in 1° relatives	43.1% vs 25.1% OR = 2.72 (95% CI, 1.84-4.03)
Finland§ 2000–2003	SCD with AMI AMI survivors	Population controls	SCD or AMI in 1° relatives without ASHD	SCD = 5.2%; AMI = 3.3% OR for SCD/AMI = 1.6 (95% CI, 1.2-2.2; *P* = 0.01)
				SCD = 5.2%; Controls = 2.3% OR for SCD/controls = 2.2 (95% CI, 1.6-3.0; *P* = 0.001)

*Friedlander Y, Siscovick DS, Weinmann S, et al. Family history as a risk factor for primary cardiac arrest. Circulation 1998;97:155.

†Jouven X, Desnos M, Guerot C, Ducimetiere P. Predicting sudden death in the population: the Paris Prospective Study I. Circulation 1999;99:1978.

‡Dekker LR, Bezzina CR, Henriques JP, et al. Familial sudden death is an important risk factor for primary ventricular fibrillation: a case-control study in acute myocardial infarction patients. Circulation 2006;114:1140.

§Kaikkonen KS, Kortelainen MI, Linna E, Huikuri HV. Family history and the risk of sudden cardiac death as a manifestation of an acute coronary event. Circulation 2006;114:1462.

1°, First-degree; *AMI,* acute myocardial infarction; *ASHD,* arteriosclerotic heart disease; *CI,* confidence interval; *EMS,* emergency medical services; *Hx,* history; *MI,* myocardial infarction; *OR,* odds ratio; *PCA,* primary cardiac arrest; *RR,* relative risk; *STEMI,* ST-segment elevation myocardial infarction.

Risk Factors for Sudden Cardiac Death

General Risk Profile

Risk prediction for SCD is far more challenging than simply profiling risk for CAD by means of the conventional risk factors for coronary atherogenesis (**see Chapters 33 and 34**). Although the latter is useful for identifying levels of population risk and some aspects of individual risk, it is not sufficient for distinguishing individual patients at risk for SCD from those at risk for other manifestations of coronary heart disease (**see Chapters 56 to 61**), and there have been careful analyses of the complexities and considerations of new approaches to clinically applicable, individual risk assessment.[4,43]

Multivariate analyses of selected risk factors (e.g., age, diabetes mellitus, systolic blood pressure, heart rate, electrocardiographic abnormalities, vital capacity, relative weight, cigarette consumption, serum cholesterol level) have determined that approximately 50% of all SCDs occur in the 10% of the population in the highest-risk decile on the basis of multiple risk factors (**Fig. 42.6**). Thus the interactions of multiple risk factors potentiate the sum of the individual risks. Comparison of risk factors in victims of SCD with those in people who develop any manifestation of CAD does not provide useful patterns, by either univariate or multivariate analysis, to distinguish SCD victims from the overall pool. However, a history of diabetes mellitus and a tendency to longer QTc intervals on random ECGs are suggested as potential markers of interest for prediction of SCD.[44] Although angiographic and hemodynamic patterns discriminate SCD risk from non-SCD risk only under limited conditions, familial clustering of SCD as a specific manifestation of the disease may lead to the identification of specific genetic abnormalities that predispose to SCD.[9]

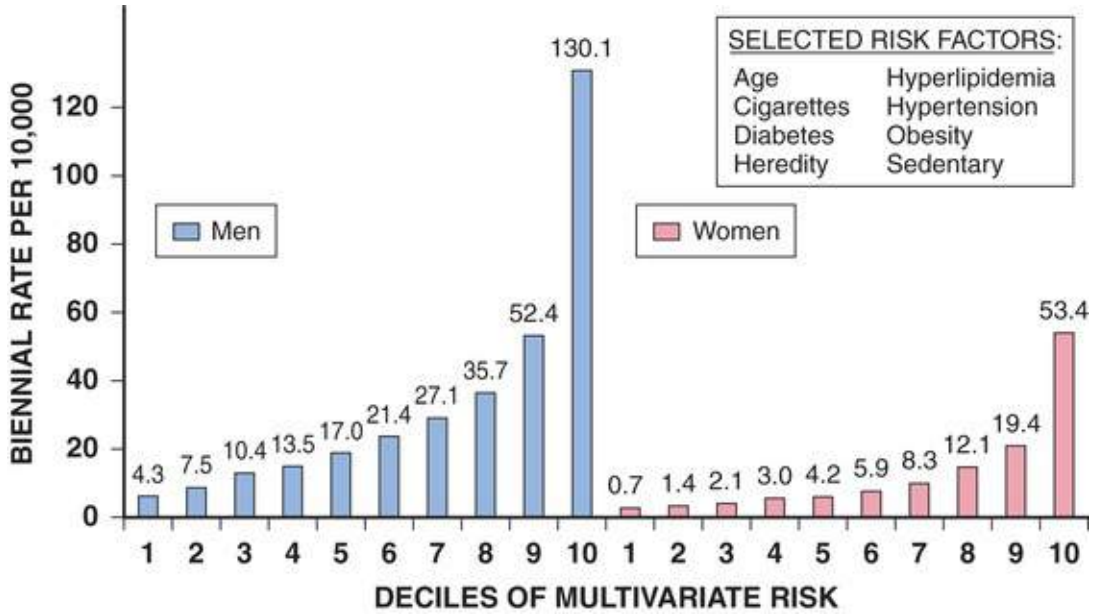


FIGURE 42.6 Risk for sudden death by decile of multivariate risk—the Framingham Study. Selected risk variables are shown. (Modified from Kannel WB, Shatzkin A. Sudden death: lessons from subsets in population studies. J Am Coll Cardiol 1985;5[Suppl 6]:141B. Reprinted by permission of the American College of Cardiology.)

Hypertension is a clearly established risk factor for coronary heart disease and also emerges as a highly significant risk factor in the incidence of SCD (**see Chapters 46 and 47**). However, increasing systolic blood pressure levels have no influence on the ratio of sudden deaths to total coronary heart disease deaths. No relationship has been observed between cholesterol concentration and the proportion of coronary deaths that were sudden. Neither the electrocardiographic pattern of left ventricular hypertrophy nor nonspecific ST-T wave abnormalities influence the proportion of total coronary deaths that are sudden and unexpected. Only intraventricular conduction abnormalities are suggestive of a disproportionate number of SCDs, an old observation reinforced by data from some device trials that suggest the importance of QRS duration as a risk marker. Low vital capacity also suggests a disproportionate risk for sudden versus total coronary deaths. This is of interest because such a relationship was particularly striking in the Framingham Study in analysis of data from women who had died suddenly.

The conventional risk factors used in early studies of SCD are risk factors for the evolution of CAD. The rationale is based on two facts: (1) CAD has been considered the structural basis for 80% of SCDs in the United States, and (2) coronary risk factors are easy to identify because they tend to be present continuously over time (**see Fig. 42.5**). Two recent observations modify this rationale. First, evolving evidence indicates that the anatomic consequences of CAD may not account for as large a proportion of SCDs in adults as previously estimated, with hypertension, left ventricular hypertrophy, and myocardial fibrosis identified as dominant anatomic and pathophysiologic factors.[29] Second, a 10-year longitudinal study of clinical associations identified in hospitalized OHCA victims demonstrated a trend toward decreasing structural heart disease associations, paralleled by an increasing dominance of risk factor markers.[45] However, many of the risk factors specific for triggering fatal arrhythmias are dynamic pathophysiologic events and occur transiently.[9,18] Transient pathophysiologic events are being modeled epidemiologically in an attempt to express and use them as clinical risk factors for both profiling and intervention.[2] Nonetheless, data suggest that longitudinal and transient risk predictors may have their power blunted by clinical interventions, such as percutaneous coronary intervention during acute coronary syndromes and post-MI beta-blocker therapy.[46,47]

Identification of specific clinical markers of risk for SCD as a specific expression of both coronary

heart disease and other cardiovascular disorders has been a goal for many years.[16,17] Left ventricular ejection fraction has been the most popular of such markers for clinical trials and patient profiling. However, its sensitivity limitations and inability to identify the large subgroup in which SCD is the first expression of heart disease have encouraged investigators to seek additional markers. For example, exercise data from a large cohort of men observed for years after a stress test demonstrated that a profile of higher resting heart rates, smaller increments in rate during exercise, and lower decrement in heart rate during the first minute after exercise predicted higher risk for SCD during follow-up.[48] In addition, a number of electrocardiographic indicators (e.g., microvolt T wave alternans, indices of QT duration/dispersion), genetic profiles, and other indices of the extent of disease are also predictive.

Functional Capacity and Sudden Death

The Framingham Study demonstrated a striking relationship between functional classification and death during a 2-year follow-up. However, the proportion of deaths that were sudden did not vary with the functional classification, with a range of 50% to 57% in all groups, including those free of clinical heart disease and those in functional class IV. Other studies have also suggested that patients with heart failure and better functional capacity are at lower risk for dying, as expected, but that a higher proportion of such deaths are sudden.[18]

Lifestyle and Psychosocial Factors (see Chapter 96)

A strong association has been found between cigarette smoking and all manifestations of coronary heart disease. The Framingham Study demonstrated that cigarette smokers have a twofold to threefold increase in risk for sudden death in each decade of life at entry between 30 and 59 years, and that this is one of the few risk factors in which the proportion of deaths attributable to coronary heart disease that are sudden increases in association with the risk factor. The excess risk for SCD in current smokers with coronary heart disease was not observed in former smokers, whose risk was similar to that of those who never smoked.[49] In addition, in a study of 310 OHCA survivors, the recurrent cardiac arrest rate was 27% at 3 years of follow-up in those who continued to smoke versus 19% in those who stopped.

Conversely, light to moderate alcohol consumption was associated with a reduced risk for SCD in male physicians.[18] Obesity is a second factor that appears to influence the proportion of coronary deaths that occur suddenly. With increasing relative weight, the percentage of coronary heart disease deaths that were sudden in the Framingham Study increased linearly from a low of 39% to a high of 70%. Total coronary heart disease deaths increased with increasing relative weight as well.

Associations between levels of physical activity and SCD have been studied with variable results. Epidemiologic observations have suggested a relationship between low levels of physical activity and increased risk for death from coronary heart disease. The Framingham Study, however, showed an insignificant relationship between low levels of physical activity and the incidence of sudden death, but a high proportion of sudden to total cardiac deaths with higher levels of physical activity. An association between acute physical exertion and the onset of MI has been suggested, particularly in individuals who are habitually physically inactive. A subsequent case-crossover cohort study confirmed this observation for SCD by demonstrating a 17-fold relative increase in SCD associated with vigorous exercise versus lower-level activity or inactive states.[50] However, the absolute risk for events was very low (one event per 1.5 million exercise sessions). Habitual vigorous exercise greatly attenuated risk. In contrast, SCD has a higher incidence in young athletes than in young nonathletic individuals in the same age range (**see Chapter 53**). A clue that intensity of exercise may play a role in SCA risk comes from an observation in

college athletes, suggesting that Division 1 basketball players are at higher risk than Division 2 or 3 athletes.[51] Information about physical activity relationships in various clinical settings, such as overt and silent disease states, is still lacking.

The magnitude of recent life changes (health, work, home, family) and personal and social factors has been related to MI and SCD. There is an association with significant elevations in life change scores during the 6 months before a coronary event, and the association is particularly striking in victims of SCD. Women who died suddenly less often were married, had fewer children, and had greater educational discrepancies with their spouses than did age-related controls living in the same neighborhood. A history of psychiatric treatment, including phobic anxieties,[18] cigarette smoking, and greater quantities of alcohol consumption than in controls also characterized the sudden death group. After controlling for other major prognostic factors, the risk for sudden and total deaths and other coronary events is affected by social and economic stress. Alteration of modifiable lifestyle factors has been proposed as a strategy to reduce the risk for SCD in patients with coronary heart disease, although studies of pharmacologic and psychotherapeutic treatment of depression after MI failed to demonstrate an effect on event rates, even though the symptoms of depressive states improved.[18] Behavioral changes (e.g., inactivity) secondary to depression appeared to relate more closely to event rates than did depression itself. Acute psychosocial stressors have been associated with a higher risk for cardiovascular events, including SCD.[52] The risk appears to cluster around the time of the stress and seems to occur in victims with preexisting risk, with the stressor simply advancing the time of an impending event. The possibility of physical stress–induced coronary plaque disruption has also been suggested.

Left Ventricular Ejection Fraction in Chronic Ischemic Heart Disease

A marked reduction in the left ventricular ejection fraction (EF) is the most powerful of the known predictors of total mortality and SCD in patients with chronic ischemic heart disease, as well as in those at risk for SCD from other causes (see later). Increased mortality, independent of other risk factors, is measurable with EF higher than 40%, but the greatest rate of change in mortality occurs at levels between 30% and 40%. An EF of 30% or lower is the single most powerful independent predictor of SCD but has low sensitivity and specificity.[53] Nonetheless, relying on a low EF as the sole major predictor limits the predictive power because of the large number of SCDs that occur at low incidence rates among the very large subset of patients with normal or moderately reduced EF and unrecognized disease.[54] There are emerging implications that left ventricular volume and other structural evaluations of the left ventricle (e.g., infarct size, degree of fibrosis) may be a better predictor of cardiac events than EF alone.[55,56]

Ventricular Arrhythmias in Chronic Ischemic Heart Disease

Most forms of ambient ventricular ectopic activity—premature ventricular complexes (PVCs) and short runs of nonsustained ventricular tachycardia (VT)—have a benign prognosis in the absence of structural heart disease (**see Chapters 37 and 61**). An exception is the polymorphic forms of nonsustained VT that occur in patients without structural heart disease but who can have a molecular, functional, drug-related, or electrolyte-related basis for high-risk arrhythmias. When present in the coronary-prone age-groups, however, PVCs select a subgroup with a higher probability of CAD and SCD. Exercise-induced PVCs and short runs of nonsustained VT indicate some level of risk for SCD, even in the absence of recognizable structural heart disease. However, the data available to support this hypothesis are conflicting, with the possible exception of polymorphic runs of nonsustained VT. Additional data suggest that PVCs and nonsustained VT during both the exercise and the recovery phases of a stress test are

predictive of increased risk. Arrhythmias in the recovery phase, previously thought to be benign, appear to predict higher risk than do arrhythmias in the exercise phase, and there is a gradient of risk with increasing severity of arrhythmias.

The occurrence of PVCs in MI survivors, particularly if frequent and having complex forms such as repetitive PVCs, predicts an increased risk for SCD and total mortality during long-term follow-up. Data are conflicting on the role of measures of frequency and forms of ventricular ectopic activity as discriminators of risk, but most studies have cited a frequency cutoff of 10 PVCs per hour as a threshold level for increased risk. Several investigators have emphasized that the most powerful predictors among the various forms of PVCs are runs of nonsustained VT, although this relationship is now questioned. Many of the reported studies have been based on a single ambulatory monitor sample recorded 1 week to several months after the onset of acute MI, and the duration of the samples has ranged from 1 to 48 hours. Other studies have suggested that ambulatory ventricular arrhythmias in patients with heart failure do not specifically predict an increased risk for death.

The results of the Cardiac Arrhythmia Suppression Trial (CAST; **see Chapter 36**), which was designed to test the hypothesis that suppression of PVCs by antiarrhythmic drugs alters the risk for SCD after MI, were surprising for two reasons: mortality in the randomized placebo group was lower than expected, and mortality among patients in the encainide and flecainide arms exceeded control rates by more than threefold. Subgroup analysis has demonstrated increased risk for patients with nonsustained VT and EF of 30% or less in the placebo group, but excess risk in the treated group was still observed. The excess mortality rates may be accounted for by the occurrence of ischemic events in the presence of drug. No adverse effect (other than short-term proarrhythmic risk at initiation of therapy) was observed with the other drug in the study (moricizine), and no long-term benefit emerged with further study. The SWORD (Survival with Oral *d*-Sotalol) study, a comparison of *d*-sotalol with placebo in a post-MI population with a low mortality rate, also demonstrated excess risk in the drug-treated group. Whether the conclusions from CAST, CAST II, and SWORD extend beyond the drug studies or to other diseases remains to be learned.

Left ventricular (LV) dysfunction is the major modulator of risk implied by chronic PVCs after MI. The risk for death predicted by post–MI PVCs is enhanced by the presence of LV dysfunction, which appears to exert its influence most strongly in the first 6 months after infarction. Delayed deterioration of LV function, probably because of remodeling after MI, may increase the risk further.

Emerging Markers of Risk for Sudden Cardiac Death

Additional risk markers with independent or added predictive power are being studied for risk profiling. These include techniques such as microvolt T wave alternans,[57] contrast-enhanced magnetic resonance imaging (MRI) of the infarction as well as noninfarct patterns of fibrosis seen on MRI delayed hyperenchancement,[58] measures of QT variability,[59] derivatives of heart rate variability methods,[60] sympathetic imaging with 11C-hydroxyephedrine or I-*m*-iodobenzylguanidine (MIBG),[61] and studies of familial clustering of SCD as an expression of coronary heart disease[4] and for potential genetic risk profiling.[9] These techniques are all in early clinical application.

Causes of Sudden Cardiac Death

Coronary Artery Abnormalities

Diseases of the coronary arteries and their consequences have been estimated to account for at least 80%

of SCDs in Western countries, but recent observations are beginning to suggest that the magnitude of this excess burden may be decreasing.[62] Coronary artery disease is also the most common cause in many areas of the world where the prevalence of atherosclerosis is lower. In this regard, it is anticipated that as third-world countries improve access to health care for communicable disease in the earlier years of life, coronary atherosclerosis and its consequences will emerge as a larger problem.[63]

Despite the established dominant relationship between coronary atherosclerosis and SCD, complete understanding of SCD requires recognition that less common and often rare coronary vascular disorders may be identifiable before death and may have therapeutic implications (**Table 42.5**). Many of these entities are relatively more common causes of SCD in adolescents and young adults, in whom the prevalence of coronary heart disease–related SCDs is much lower before age 30 years[28] (**see Fig. 42.4A**).

TABLE 42.5

Causes of and Contributing Factors in Sudden Cardiac Death

I. Coronary artery abnormalities
- A. Coronary atherosclerosis
  1. Chronic coronary atherosclerosis with acute or transient myocardial ischemia—thrombosis, spasm, physical stress
  2. Acute myocardial infarction, onset and early phase
  3. Chronic atherosclerosis with a change in myocardial substrate, including previous myocardial infarction
- B. Congenital abnormalities of coronary arteries
  1. Anomalous origin from the pulmonary artery
  2. Other coronary arteriovenous fistula
  3. Origin of a left coronary artery from the right or noncoronary sinus of Valsalva (lower incidence; higher risk)
  4. Origin of the right coronary artery from the left sinus of Valsalva (higher incidence; lower risk)
  5. Hypoplastic or aplastic coronary arteries
  6. Coronary-intracardiac shunt
- C. Coronary artery embolism
  1. Aortic or mitral endocarditis
  2. Prosthetic aortic or mitral valves
  3. Abnormal native valves or left ventricular mural thrombus
  4. Platelet embolism
- D. Coronary arteritis
  1. Polyarteritis nodosa, progressive systemic sclerosis, giant cell arteritis
  2. Mucocutaneous lymph node syndrome (Kawasaki disease)
  3. Syphilitic coronary ostial stenosis
- E. Miscellaneous mechanical obstruction of the coronary arteries
  1. Coronary artery dissection in Marfan syndrome
  2. Coronary artery dissection in pregnancy (primarily labor/delivery)
  3. Prolapse of aortic valve myxomatous polyps into the coronary ostia
  4. Dissection or rupture of the sinus of Valsalva
- F. Functional obstruction of the coronary arteries
  1. Coronary artery spasm with or without atherosclerosis
  2. Myocardial bridges

II. Hypertrophy of the ventricular myocardium
- A. Left ventricular hypertrophy associated with coronary heart disease
- B. Hypertensive heart disease without significant coronary atherosclerosis
- C. Hypertrophic myocardium secondary to valvular heart disease
- D. Hypertrophic cardiomyopathy
  1. Obstructive
  2. Nonobstructive
- E. Primary or secondary pulmonary hypertension
  1. Advanced chronic right ventricular overload
  2. Pulmonary hypertension in pregnancy (highest-risk peripartum)

III. Myocardial diseases and dysfunction, with or without heart failure
- A. Chronic congestive heart failure
  1. Ischemic cardiomyopathy
  2. Idiopathic dilated cardiomyopathy, acquired
  3. Hereditary dilated cardiomyopathy
  4. Alcoholic cardiomyopathy
  5. Hypertensive cardiomyopathy
  6. Postmyocarditis cardiomyopathy
  7. Peripartum cardiomyopathy
  8. Idiopathic fibrosis
- B. Acute and subacute cardiac failure
  1. Large acute myocardial infarction

VI. Congenital heart disease
- A. Congenital aortic (potentially high risk) or pulmonic (low risk) valve stenosis
- B. Congenital septal defects with Eisenmenger physiology
  1. Advanced disease
  2. During labor and delivery
- C. Late after surgical repair of congenital lesions (e.g., tetralogy of Fallot)

VII. Electrophysiologic abnormalities
- A. Abnormalities of the conducting system
  1. Fibrosis of the His-Purkinje system
     a. Primary degeneration (Lenègre disease)
     b. Secondary to fibrosis and calcification of the "cardiac skeleton" (Lev disease)
     c. Postviral conducting system fibrosis
     d. Hereditary conducting system disease
  2. Anomalous pathways of conduction (Wolff-Parkinson-White syndrome, short refractory period bypass)
- B. Abnormalities of repolarization
  1. Congenital abnormalities in duration of the QT interval
     a. Congenital long–QT interval syndrome
     (1) Romano-Ward syndrome (without deafness)
     (2) Jervell and Lange-Nielsen syndrome (with deafness)
     b. Congenital short–QT interval syndrome
  2. Acquired (or provoked) long–QT interval syndromes
     a. Drug effect (with genetic predisposition?)
     (1) Cardiac, antiarrhythmic
     (2) Noncardiac
     (3) Drug interactions
     b. Electrolyte abnormality (response modified by genetic predisposition?)
     c. Toxic substances
     d. Hypothermia
     e. Central nervous system injury, subarachnoid hemorrhage
  3. Brugada syndrome—right bundle branch block and ST-segment elevations in the absence of ischemia
  4. Early repolarization syndrome
- C. Ventricular fibrillation of unknown or uncertain cause
  1. Absence of identifiable structural or functional causes
     a. "Idiopathic" ventricular fibrillation
     b. Short-coupled torsades de pointes, polymorphic ventricular tachycardia
     c. Nonspecific fibrofatty infiltration in a previously healthy victim (variation of right ventricular dysplasia?)
  2. Sleep-death in Southeast Asians (see VIIB3, Brugada syndrome)
     a. Bangungut
     b. Pokkuri
     c. Lai-tai

VIII. Electrical instability related to neurohumoral and central nervous system influences
- A. Catecholaminergic polymorphic ventricular tachycardia
- B. Other catecholamine-dependent arrhythmias
- C. Central nervous system related
  1. Psychic stress, emotional extremes (takotsubo syndrome)
  2. Auditory related
  3. "Voodoo death" in primitive cultures
  4. Diseases of the cardiac nerves
  5. Arrhythmia expression in congenital long–QT interval syndrome

IX. Sudden cardiac death in the young

2. Myocarditis, acute or fulminant
3. Acute alcoholic cardiac dysfunction
4. Takotsubo syndrome (uncertain risk for sudden death)
5. Ball valve embolism in aortic stenosis or prosthesis
6. Mechanical disruptions of cardiac structures
    a. Rupture of the ventricular free wall
    b. Disruption of the mitral apparatus
    (1) Papillary muscle
    (2) Chordae tendineae
    (3) Leaflet
    c. Rupture of the interventricular septum
7. Acute pulmonary edema in noncompliant ventricles

IV. Inflammatory, infiltrative, neoplastic, and degenerative processes
A. Viral myocarditis, with or without ventricular dysfunction
1. Acute phase
2. Postmyocarditis interstitial fibrosis
B. Myocarditis associated with the vasculitides
C. Sarcoidosis
D. Progressive systemic sclerosis
E. Amyloidosis
F. Hemochromatosis
G. Idiopathic giant cell myocarditis
H. Chagas disease
I. Cardiac ganglionitis
J. Arrhythmogenic right ventricular dysplasia, right ventricular cardiomyopathy
K. Neuromuscular diseases (e.g., muscular dystrophy, Friedreich ataxia, myotonic dystrophy)
L. Intramural tumors
1. Primary
2. Metastatic
M. Obstructive intracavitary tumors
1. Neoplastic
2. Thrombotic

V. Diseases of the cardiac valves
A. Valvular aortic stenosis/insufficiency
B. Mitral valve disruption
C. Mitral valve prolapse
D. Endocarditis
E. Prosthetic valve dysfunction

A. Sudden cardiac death in newborns
1. Complex congenital heart disease
2. Neonatal myocarditis
B. Sudden infant death syndrome
1. Immature respiratory control function
2. Long–QT interval syndrome
3. Congenital heart disease
4. Myocarditis
C. Sudden death in children
1. Eisenmenger syndrome, aortic stenosis, hypertrophic cardiomyopathy, pulmonary atresia
2. After corrective surgery for congenital heart disease
3. Myocarditis
4. Genetic disorders of electrical function (e.g., long–QT interval syndrome)
5. No identified structural or functional cause

X. Miscellaneous
A. Sudden death during extreme physical activity (seek predisposing causes)
B. Commotio cordis—blunt chest trauma
C. Mechanical interference with venous return
1. Acute cardiac tamponade
2. Massive pulmonary embolism
3. Acute intracardiac thrombosis
D. Cardiorespiratory arrest secondary to mechanical asphyxia
E. Dissecting aneurysm of the aorta
F. Toxic and metabolic disturbances (other than the QT interval effects listed above)
1. Electrolyte disturbances
2. Metabolic disturbances
3. Proarrhythmic effects of antiarrhythmic drugs
4. Proarrhythmic effects of noncardiac drugs
G. Mimics sudden cardiac death
1. “Café coronary”
2. Acute alcoholic states (“holiday heart”)
3. Acute asthmatic attacks
4. Air or amniotic fluid embolism

Atherosclerotic Coronary Artery Disease

The structural and functional abnormalities of the coronary vasculature as a result of coronary atherosclerosis interact with the electrophysiologic alterations that result from the myocardial impact of an ischemic burden (**see Chapters 58 to 62**). The relationship between the vascular and myocardial components of this pathophysiologic model, as well as its modulation by hemodynamic, autonomic, genetic, and other influences, establishes multiple patterns of risk derived from the fundamental disease state[2] (**Fig. 42.7**). Risk is modulated by multiple factors that can be either transient or persistent, and transient modulations may interact with persistent changes. The myocardial component of this pathophysiologic model is not static over time, and the term *persistent* must be viewed with caution because of the gradual effects of remodeling after an initial ischemic event and the effects of recurrent ischemic episodes. SCA and SCD resulting from transient ischemia or acute MI differ in physiology and prognosis from the risk for SCA implied by a previous MI with or without subsequent ischemic cardiomyopathy. In general, the short-term risk for life-threatening events is associated more closely with acute ischemia or the acute phase of MI, and longer-term risk is associated more with transient ischemia, myocardial scarring, remodeling, ischemic cardiomyopathy, and heart failure.

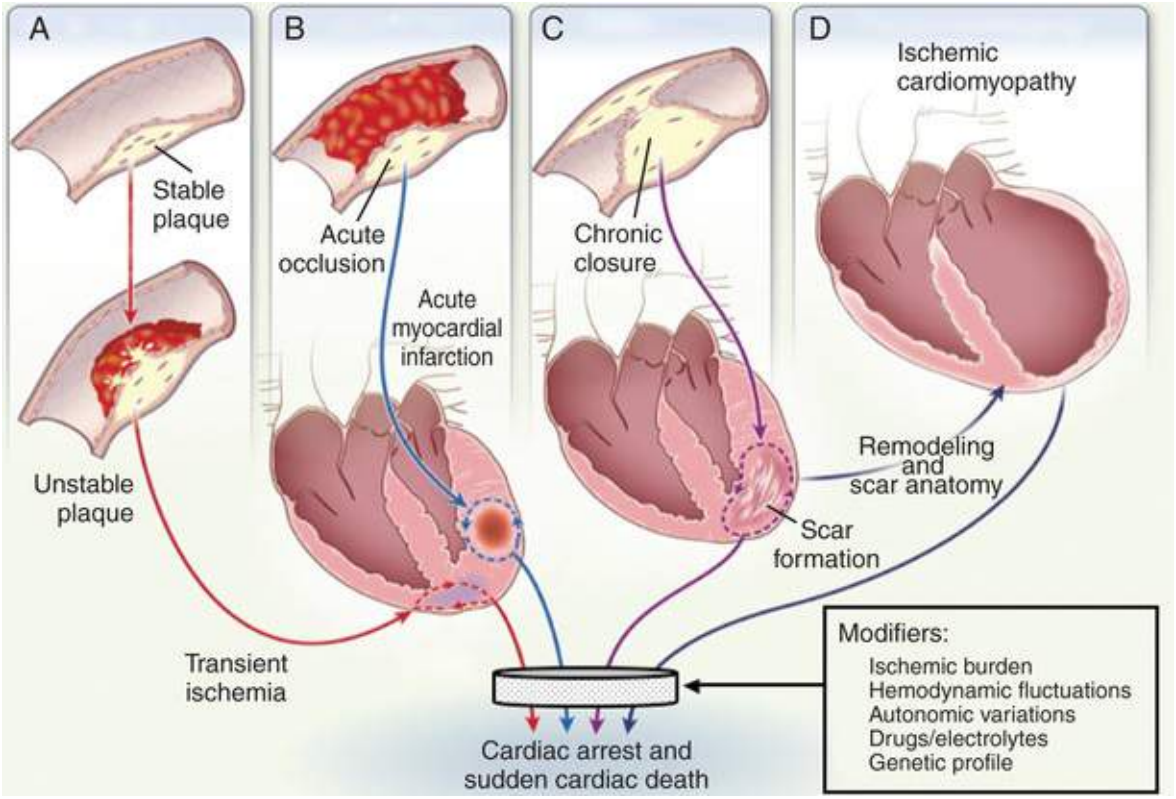


FIGURE 42.7 Pathophysiology of ventricular tachyarrhythmias in coronary heart disease. The short- and long-term risks for the development of VT or VF and recurrent events are related to the presence of transient or persistent physiologic factors. VT/VF caused by transient ischemia **(A)** and the acute phase (24 to 48 hours) of MI **(B)** are not predictive of recurrent events if the recurrent ischemia is preventable. In contrast, VT/VF associated with healed MI, with or without acute transient ischemia **(C),** is associated with risk for recurrence. Longstanding ischemic cardiomyopathy **(D),** especially when accompanied by heart failure, establishes a substrate associated with risk for VT/VF and recurrences over time. A series of modifying influences contribute to individual expression. (Modified from Myerburg RJ. Implantable cardioverter-defibrillators after myocardial infarction. N Engl J Med 2008;359:2245.)

Nonatherosclerotic Coronary Artery Abnormalities

Nonatherosclerotic coronary artery abnormalities include congenital lesions, coronary artery embolism, coronary arteritis, and mechanical abnormalities of the coronary arteries. Among the congenital lesions, anomalous origin of a left coronary artery (LCA) from the pulmonary artery is relatively common and associated with increased mortality in infancy and early childhood without surgical treatment (**see Chapters 53 and 75**). The early risk for SCD is not excessively high, but patients who survive to adolescence and young adulthood without surgical intervention are at risk for SCD. Other forms of coronary arteriovenous fistulas are much less common and associated with a low incidence of SCD.

Anomalous Origin of Coronary Arteries from the Wrong Sinus of Valsalva

These anatomic variants are associated with an increased risk for SCD, particularly during exercise. When the anomalous artery passes between the aortic and the pulmonary artery root, the takeoff angle of the anomalous ostium creates a slitlike opening of the vessel that reduces the effective cross-sectional area for blood flow. The less common origin of the LCA from the right sinus of Valsalva is a higher-risk variant, but the LCA origin from the left sinus of Valsalva, while lower risk, accounts for a proportion of SCDs that should not be ignored, based on the incidence of this anomaly.[64] Congenitally hypoplastic, stenotic, or atretic LCAs are uncommon abnormalities associated with a risk for MI in young persons, but not for SCD.

Embolism to the Coronary Arteries.

Coronary artery emboli occur most frequently in aortic valve endocarditis and from thrombotic material on diseased or prosthetic aortic or mitral valves. Emboli can also originate from left ventricular mural thrombi or as a consequence of surgery or cardiac catheterization. Symptoms and signs of myocardial ischemia or MI are the most common manifestations. In each of these categories, SCD results from the electrophysiologic consequences of embolic ischemia.

Coronary Arteritis.

Mucocutaneous lymph node syndrome (Kawasaki disease; **see Chapter 94**) carries a risk for SCD in association with coronary arteritis. Polyarteritis nodosa and related vasculitis syndromes can cause SCD, presumably because of coronary arteritis, as can coronary ostial stenosis in syphilitic aortitis. The latter has become a rare manifestation of syphilis.

Mechanical Obstruction of Coronary Arteries.

Several types of mechanical abnormalities are listed among the causes of SCD. Coronary artery dissection, with or without dissection of the aorta, occurs in Marfan syndrome (**see Chapter 75**) and has also been reported after trauma and in the peripartum period of pregnancy. Among the rare mechanical causes of SCD is prolapse of myxomatous polyps from the aortic valve into the coronary ostia, as well as dissection or rupture of a sinus of Valsalva aneurysm with involvement of the coronary ostia and proximal coronary arteries. Deep myocardial bridges over coronary arteries have been reported in association with SCD occurring during strenuous exercise, possibly caused by dynamic mechanical obstruction (**see Chapter 53**). Scattered fibrosis in the distribution of the affected vessel is typically seen at postmortem examination and suggests a chronic or intermittent ischemic burden over time. Deep bridging seems to be more common in association with hypertrophic cardiomyopathy. However, the more common superficial bridges in the absence of other disorders are of less concern, and SCD associated with this anatomy is uncommon.

Coronary Artery Spasm.

This may cause serious arrhythmias and SCD (**see Chapter 58**). Coronary artery spasm is usually associated with some degree of concomitant coronary atherosclerotic disease. Painless myocardial ischemia, associated with either spasm or fixed lesions, is recognized as a mechanism of previously unexplained sudden death. Based on absence of markers of risk for a high rate of recurrence, patients with documented life-threatening arrhythmias associated with vasospastic angina should receive either medical therapy or ICD, or both.[65] Different patterns of silent ischemia (e.g., totally asymptomatic, post-MI, mixed silent/anginal patterns) may have different prognostic implications. In post-MI patients, silent ischemia has been correlated with an increased risk for SCD.[66]

Ventricular Hypertrophy and Hypertrophic Cardiomyopathy

Left ventricular hypertrophy is an independent risk factor for SCD, is associated with many causes of SCD, and may be a physiologic contributor to mechanisms of potentially lethal arrhythmias. Underlying states resulting in LV hypertrophy include hypertensive heart disease with or without atherosclerosis, valvular heart disease, obstructive and nonobstructive hypertrophic cardiomyopathy (HCM; **see Chapters 53 and 78**), primary pulmonary hypertension with right ventricular hypertrophy, and advanced right ventricular overload secondary to congenital heart disease. Each of these conditions is associated with risk for SCD, and patients with severely hypertrophic ventricles may be particularly susceptible to

arrhythmic death.

Risk for SCD in patients with obstructive and nonobstructive HCM was identified in the early clinical and hemodynamic descriptions of this entity. In patients who have obstructive HCM, up to 70% of all deaths are sudden. However, survivors of cardiac arrest in this group may have a better long-term outcome than survivors with other causes, and reports have suggested that the risk for primary cardiac arrest and SCD in those with HCM is lower than previously thought.

A substantial proportion of patients with obstructive and nonobstructive HCM have a family history of affected relatives or premature SCDs of unknown cause. Genetic studies have confirmed autosomal dominant inheritance patterns, but with much allele and phenotypic heterogeneity. Most of the mutations are at loci that encode elements in the contractile protein complex, the most common being beta-myosin heavy chain and cardiac troponin T, which together account for more than half of identified abnormalities. The genetics of HCM is characterized by a large number of private mutations with variable expression. Possible interaction with modifier genes may account for variable expression among carriers of a specific variant, although a number of HCM variants thought to cause disease in the black population may actually be benign variants unique to the black population that are missed because of underrepresentation of blacks in control populations.[67]

Specific clinical markers have not been especially predictive of SCD in individual patients, although young age at onset, a strong family history of SCD, magnitude of the left ventricular mass, septal thickness greater than 3 cm, ventricular arrhythmias, a fall in blood pressure during exercise, and worsening symptoms (especially syncope) appear to indicate higher risk. Both a substantial provocable gradient, regardless of the resting gradient, and a high resting gradient alone identify high risk for SCD.[68] The mechanism of SCD in patients with HCM was initially thought to involve outflow tract obstruction, possibly a result of catecholamine stimulation, but later data have focused on lethal arrhythmias as the common mechanism of sudden death in HCM. Risk may also be suggested by nonsustained VT on ambulatory recording, inducibility of potentially lethal arrhythmias during programmed electrical stimulation, or a fall in blood pressure during exercise. Rapid or polymorphic symptomatic nonsustained VTs, or both, have better predictive power.

The pathogenesis of the arrhythmias in HCM is discussed in **Chapters 34 and 78**. Patients with nonobstructive HCM, such as the diffuse, the midcavitary, and to a lesser extent the apical variety, are also at risk for SCD, which suggests that an electrophysiologic mechanism secondary to the hypertrophied muscle itself plays a major role. In athletes younger than 35 years, HCM is the most common cause of SCD, in contrast to athletes older than 35, in whom coronary heart disease is the most common cause.

Nonischemic Cardiomyopathy and Systolic and Diastolic Heart Failure

The advent of therapeutic interventions that provide better long-term control of congestive heart failure has improved the long-term survival of these patients (**see Chapters 21, 25, and 77**). However, the proportion of patients with heart failure who die suddenly is substantial, especially among those who appear clinically stable (i.e., functional class I or II).[18] The mechanism of SCD may be tachyarrhythmic (VT or VF) or nonshockable bradyarrhythmias or asystole. The absolute risk for SCD increases with

deteriorating LV function, but the ratio of sudden to nonsudden deaths is inversely related to the extent of functional impairment.[18] In patients with cardiomyopathy who have good functional capacity (classes I and II), total mortality risk is considerably lower than in those with functional classes III and IV, but a higher probability exists that a death will be sudden (**Fig. 42.8**). Unexplained syncope has been observed to be a powerful predictor of SCD in patients who have functional class III or IV symptoms, regardless of the cause of cardiomyopathy. Ambulatory ventricular arrhythmias do not appear to identify specific risk for SCD in such patients.

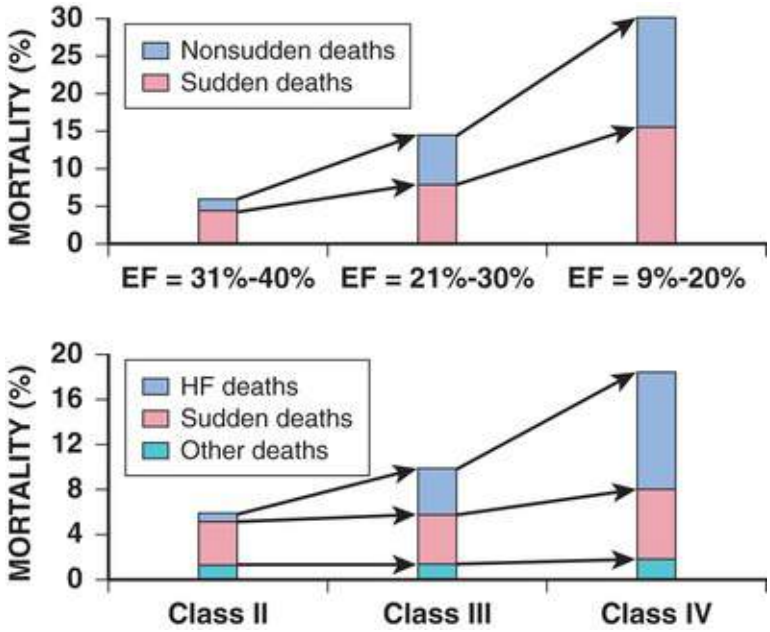


FIGURE 42.8 Risk for SCD related to left ventricular ejection fraction (*EF*) and functional classification in heart failure (*HF*). The relative probability of death being sudden is higher and absolute mortality risk is lower in patients with higher EF and better functional capacity. (Modified from Cleland JG, Chattopadhyay S, Khand A, et al. Prevalence and incidence of arrhythmias and sudden death in heart failure. Heart Fail Rev 2002;7:229, with permission from Springer Science and Business Media.)

Heart failure with a preserved EF carries a risk for mortality over time similar to that of heart failure with a reduced EF (**see Chapter 26**). Although risk for SCD in heart failure patients with a preserved EF may parallel that associated with systolic heart failure, possibly modulated by other risk factors,[69] additional studies are needed to clarify this relationship and its implication for medical practice.

An interaction between post-MI ventricular arrhythmia and depressed EF in determining risk for SCD has been described, but the strongest association between chronic heart failure and SCD is ischemic cardiomyopathy. The prevalence of ischemic cardiomyopathy had been increasing because of better acute MI survival statistics coupled with late remodeling. Other causes include “idiopathic” fibrosis,[29] alcoholic, and postmyocarditis cardiomyopathies; peripartum cardiomyopathy (**see Chapter 90**); and the familial pattern of dilated cardiomyopathy, often associated with lamin A/C mutations.[70] Other gene loci have also been implicated. A residual group of undefined causes have been classified as “idiopathic myocarditis.”

Acute Heart Failure

All causes of acute cardiac failure, in the absence of prompt interventions, can result in SCD as a result of the circulatory failure itself or secondary arrhythmias (**see Chapters 23 and 24**). The electrophysiologic

mechanisms involved may be caused by acute stretching of ventricular myocardial fibers or the His-Purkinje system, based on experimentally demonstrated arrhythmogenic effects. However, the roles of neurohumoral mechanisms and acute electrolyte shifts have not been fully evaluated. Causes of acute cardiac failure associated with SCD include massive acute MI, acute myocarditis, acute alcoholic cardiac dysfunction, acute pulmonary edema in any form of advanced heart disease, and a number of mechanical causes of heart failure, such as massive pulmonary embolism, mechanical disruption of intracardiac structures secondary to infarction or infection, and ball valve embolism in aortic or mitral stenosis (**see Table 42.5**).

Inflammatory, Infiltrative, Neoplastic, and Degenerative Diseases of the Heart.

Almost all diseases in this category have been associated with SCD, with or without concomitant cardiac failure. Acute viral myocarditis with LV dysfunction is frequently associated with cardiac arrhythmias, including potentially lethal arrhythmias[71] (**see Chapters 77 and 81**). Serious ventricular arrhythmias or SCD can occur in patients with myocarditis in the absence of clinical evidence of LV dysfunction.[72] In a report of 19 SCDs in 1,606,167 previously screened U.S. Air Force recruits, 8 of 19 victims (42%) had evidence of myocarditis (5 nonrheumatic, 3 rheumatic) at postmortem examination, and 15 of 19 (79%) had their cardiac arrests during strenuous exertion. Of myocarditis-related SCDs in a study from Sweden, 68% of victims had no premortem symptoms[22] (**Fig. 42.9**), and most data available suggest a bias toward victims younger than 35, both for absolute numbers and for percentages of SCD caused by myocarditis. Focal myocarditis can be associated with SCD and may be missed on autopsy depending on the extent of the cardiac evaluation. Giant cell myocarditis and acute necrotizing eosinophilic myocarditis are particularly virulent for both myocardial damage and arrhythmias.[71] Viral myocarditis can also cause damage isolated to the specialized conducting system and result in a propensity to arrhythmias; the rare association of this process with SCD has been reported. Varicella in adults is a rare cause of striking conduction system disorders, largely involving the intraventricular specialized conducting tissue with very prolonged QRS complexes and nonspecific patterns. LV function is usually preserved, and its relationship to SCD is unclear.

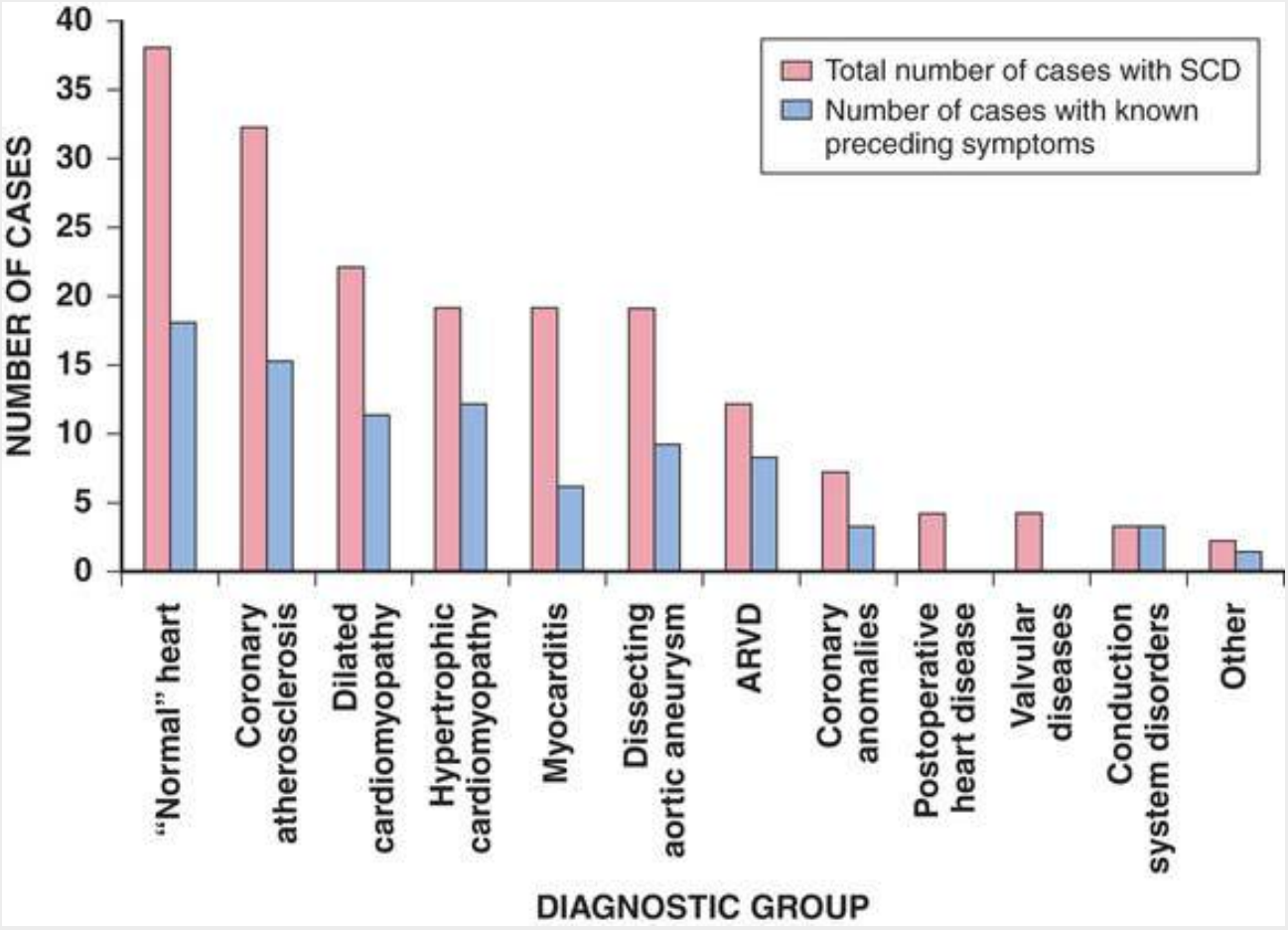


FIGURE 42.9 SCD in adolescents and young adults in Sweden. The frequency of preceding symptoms in 181 cases of SCD in persons 15 to 35 years old is shown by diagnostic group. *ARVD,* Arrhythmogenic right ventricular dysplasia. (Modified from Wisten A, Forsberg H, Krantz P, Messner T. Sudden cardiac death in 15-35-year olds in Sweden during 1992-99. J Intern Med 2002;252:529.)

Myocardial involvement in collagen-vascular disorders, tumors, chronic granulomatous diseases, infiltrative disorders, and protozoan infestations varies widely, but SCD can be the initial or terminal manifestation of the disease process in all cases. Among the granulomatous diseases, sarcoidosis stands out because of the frequency of associated SCD. SCD was the terminal event in 67% of deaths attributable to sarcoid heart disease. The risk for SCD has been related to the extent of cardiac involvement, but ambient arrhythmias, such as nonsustained VT, may indicate risk in such patients with lesser degrees of cardiac involvement. In a report of the pathologic findings in nine patients who died of progressive systemic sclerosis, eight who died suddenly had evidence of transient ischemia and reperfusion histologically, thus suggesting that this might represent spasm caused by Raynaud-like involvement of the coronary vessels. Amyloidosis of the heart can also cause sudden death (**see Chapter 77**). An incidence of 30% has been reported, and diffuse involvement of ventricular muscle or the specialized conducting system may be associated with SCD. Cardiac involvement can occur in both acquired and inherited forms. In the latter, variants in the transthyretin gene (TTR) are often identified.[73] TTR-associated cardiac amyloid tends to express later in life, almost always after age 50, and observed in up to 4% of the black population, with or without the disease.

Arrhythmogenic Right Ventricular Dysplasia or Cardiomyopathy.

ARVD/C is associated with a high incidence of ventricular arrhythmias, including polymorphic nonsustained VT and VF and recurrent sustained monomorphic VT (**see Chapters 33 and 39**). Although symptomatic monomorphic VT has been well recognized in this syndrome for many years, the risk for SCD had been unclear and thought to be relatively low until the risks associated with the disease were

clarified by a number of subsequent studies. In a high proportion of victims, perhaps as many as 80%, the first manifestation of ARVD/C is “unexplained” syncope or SCD. SCD is often exercise related, and in some areas of the world where HCM screening has excluded affected athletes from competition, ARVD/C has emerged as the most common cause of sports-related SCD. Moderate- to high-level competitive sports participation is not recommended for those with a confirmed diagnosis, although exceptions can be considered for specific sports among those with an ICD and proper preparticipation counseling.[74] Although it is generally considered a right ventricular (RV) abnormality, with possible late involvement of the left ventricle in advanced cases, a left ventricle–dominant pattern has also been described.

ARVD/C is predominantly an inherited disorder in which the variants cause or predispose to the disease, interacting with high RV strain during exercise. In addition, there is some basis for considering that RV arrhythmogenic responses may be caused by very-high-intensity athletic activity as a result of repeated RV strain exposures.[75] The inheritance pattern is autosomal dominant, except in one geographically isolated cluster in which it is autosomal recessive (Naxos disease, plakoglobin locus on chromosome 17). Four loci encoding desmosome structure (plakoglobin, desmoplakin, plakophilin 2, and desmoglein 2) are collectively the most common known mutations associated with RV dysplasia.[76] Autosomal dominant mutations have also been identified in the ryanodine receptor locus on chromosome 1 (1q42) (**see Chapter 33**).

Valvular Heart Disease

Before the advent of surgery for valvular heart disease, severe aortic stenosis was associated with high risk for mortality. Approximately 70% of deaths were sudden and accounted for an absolute SCD mortality rate of 15% to 20% among all affected patients. A retrospective observational study of 133 asymptomatic patients with normal LV function and severe aortic stenosis, defined as a peak aortic gradient of greater than 60 mm Hg, observed without surgery, identified seven patients with SCDs (5%) during a mean follow-up of 3.3 years. Three of the deaths were preceded by a change in status: onset of dyspnea, decreasing LV function, and a coronary event.[77] The advent of aortic valve replacement has reduced the incidence, but patients with prosthetic or heterograft aortic valve replacements remain at some risk for SCD caused by arrhythmias, prosthetic valve dysfunction, or coexistent coronary heart disease. The incidence peaks 3 weeks after surgery and then levels off after 8 months. A high incidence of ventricular arrhythmia has been observed during the follow-up of patients with valve replacement, especially those who had aortic stenosis, multiple valve surgery, or cardiomegaly. Sudden death during follow-up was associated with ventricular arrhythmias and thromboembolism. An association between stenotic lesions of other valves and SCD has not been demonstrated. Regurgitant lesions, particularly chronic aortic regurgitation and acute mitral regurgitation, may cause SCD, but the risk is lower than with aortic stenosis. However, one study did detect greater ease of induction of VT/VF in patients with regurgitant lesions and clinical tachyarrhythmias.[78]

Mitral Valve Prolapse

Mitral valve prolapse is prevalent, but probably less so than previously thought, and is associated with a high incidence of annoying low-risk cardiac arrhythmias (**see Chapter 69**). However, the risk for SCD is apparent, although low. It correlates best with marked redundancy of mitral leaflets, in conjunction with nonspecific ST-T wave changes in inferior leads.

Endocarditis of the Aortic and Mitral Valves

Endocarditis of the aortic and mitral valves may be associated with rapid death resulting from acute disruption of the valvular apparatus (**see Chapter 73**), coronary embolism, or abscesses of valvular rings or the septum. However, such deaths are rarely true sudden deaths because conventionally defined tachyarrhythmic mechanisms are uncommon. Coronary embolism from valvular vegetations can trigger fatal ischemic arrhythmia on rare occasion.

Congenital Heart Disease

The congenital lesions most often associated with SCD are aortic stenosis (**see Chapter 75**) and communications between the left and right sides of the heart with the Eisenmenger physiology. In the latter, risk for SCD is a function of the severity of pulmonary vascular disease; also, pregnant patients with Eisenmenger syndrome have an extraordinarily high risk for maternal mortality during labor and delivery[79] (**see Chapter 90**). Potentially lethal arrhythmias and SCD have been described as late complications after surgical repair of complex congenital lesions, particularly tetralogy of Fallot, transposition of the great arteries, and atrioventricular canal defects. These patients should be observed closely and treated aggressively when cardiac arrhythmias are identified, although the late risk for SCD may not be as high as previously thought.

Electrophysiologic Abnormalities

Acquired disease of the atrioventricular (AV) node and His-Purkinje system and the presence of accessory pathways may be associated with SCD (**see Chapter 37**). Clinical surveillance and follow-up studies have suggested that intraventricular conduction disturbances in coronary heart disease are one of the few factors that can increase the proportion of SCD in these patients. Early studies demonstrated a very high risk for total mortality and SCD during the late in-hospital course and the first few months after hospital discharge in patients with anterior MIs and right bundle branch or bifascicular block. In a later study evaluating the impact of thrombolytic therapy versus the prethrombolytic era experience, the incidence of pure right bundle branch block was higher, but that of bifascicular block was lower, as were late complications and mortality.

Primary fibrosis (Lenègre disease) or injury secondary to other disorders (Lev disease) of the His-Purkinje system is frequently associated with intraventricular conduction abnormalities and symptomatic AV block and less often with SCD. Identification of those at risk and the efficacy of pacemakers for prevention of SCD, rather than only amelioration of symptoms, have been subjects of debate. However, survival appears to depend more on the nature and extent of the underlying disease than on the conduction disturbance itself.

Patients with congenital AV block (**see Chapter 40**) or nonprogressive congenital intraventricular block, in the absence of structural cardiac abnormalities and with a stable heart rate and rhythm, have been characterized as being at low risk for SCD in the past. Later data suggested that patients with the patterns of congenital AV block previously thought to be benign are at risk for dilated cardiomyopathy,[80] and routine pacemaker implantation in patients older than 15 years, if not indicated sooner based on symptoms, has been suggested by at least one group. Confirmation from clinical trial data is not available. Hereditary forms of AV block have also been reported in association with a familial propensity to SCD. Sodium channel gene mutations have been associated with progressive conduction system disturbances, along with aging, and some are variants of Brugada gene expression.[81] External ophthalmoplegia and

retinal pigmentation with progressive conduction system disease (Kearns-Sayre syndrome), which is associated with mitochondrial DNA variants, may lead to high-grade heart block and pacemaker dependence.

The anomalous pathways of conduction in Wolff-Parkinson-White (WPW) syndrome are frequently associated with nonlethal arrhythmias. However, when the anomalous pathways of conduction have short anterograde refractory periods, the occurrence of atrial fibrillation may allow the initiation of VF during very rapid conduction across the accessory pathway (**see Chapter 37**). Patients who have multiple pathways appear to be at higher risk for SCD, as do patients with a familial pattern of anomalous pathways and premature SCD. An infrequent genetic predisposition to WPW syndrome has been suggested.[82]

Long-QT Syndromes

Congenital long-QT syndrome is a functional abnormality usually caused by inherited mutations affecting the molecular structure of ion channel proteins and is associated with environmental or neurogenic triggers that can initiate symptomatic or lethal arrhythmias[83] (**see Chapters 33 to 39**). Less often, but not rarely, such mutations may occur de novo or may be transmitted from an apparently normal mosaic parent.[84] Syncope is the most common manifestation in symptomatic patients. SCD is less common, although data are limited by the absence of information on undiagnosed carriers in whom fatal cardiac arrest is the first clinical event. For example, the prevalence of LQT variants in the population is generally cited in the range of 1 per 2000 to 2500, but a study from Japan on routine ECG screening among first- and seventh-grade schoolchildren estimated a prevalence of 1 per 988, more than double the generally accepted figure from referral populations.[38] Some patients have prolonged QT intervals throughout life without any manifest arrhythmias, whereas others are highly susceptible to symptomatic and potentially fatal ventricular arrhythmias.[39,85] The concept of modifier genes interacting with the primary defect or physiologic contributors to expression is being explored.[86,87]

Higher levels of risk for LQTS are associated with female sex, greater degrees of QT prolongation or QT alternans, unexplained syncope, family history of premature SCD, and documented torsades de pointes (TdP) or previous VF. Patients with LQTS require avoidance of drugs that are associated with QT lengthening and careful medical management, which may include implantable defibrillators. Moreover, it is important to identify and to manage medically relatives who carry the mutation and may be at risk. Variants in *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, and *SCN4B* have been implicated in various patterns of the Romano-Ward and Jervell and Lange-Nielsen syndromes. LQT4 is associated with a mutation at a locus on chromosome 4 encoding the cytoskeletal element ankyrin-B.[88] A number of other loci have been linked with less common genetic variants associated with long QT (**see Chapters 33 and 39**).

There is epidemiologic interest in whether QT interval abnormalities or the propensity to these, interacting with acquired diseases, predisposes to SCD as a specific clinical expression.[2,44] In a prospective cohort study, a prolonged QTc emerged as a powerful risk factor for SCD in the presence of acquired cardiovascular disorders.[89] The hypothesis that common genetic variants may modulate QTc in unselected populations has stimulated interest in the relationship to selective risk for SCD in individuals with acquired diseases. However, a number of rare variants may be even more important.

The acquired form of prolonged–QT interval syndrome refers to excessive lengthening of the QT interval and the potential for the development of TdP in response to environmental influences. As with congenital LQTS, it is more common in women. The syndrome may be caused by drug effects or an individual patient's idiosyncrasies (particularly related to class IA or III antiarrhythmic drugs and

psychotropic drugs; **see Chapter 96**), electrolyte abnormalities, hypothermia, toxic substances, bradyarrhythmia-induced QT adjustments, and central nervous system injury (most often subarachnoid hemorrhage). It had also been reported in intensive weight reduction programs that involved the use of certain liquid-protein diets and in patients with anorexia nervosa. Lithium carbonate can prolong the QT interval and has been reported to be associated with an increased incidence of SCD in cancer patients with preexisting heart disease. Drug interactions have been recognized as a mechanism of prolongation of the QT interval and TdP. Inherited polymorphisms or mutations with low penetrance involving the same gene loci associated with phenotypically expressed LQTS may underlie the acquired form, in many cases.[18] In acquired prolonged-QT syndrome, as in the congenital form, TdP is frequently the specific arrhythmia that triggers or degenerates into VF.

Short-QT Syndrome

A familial pattern of risk for SCD has been associated with abnormally short QT intervals, defined as a QTc shorter than 300 milliseconds (QT <280 msec) (**see Chapter 33**).[18] Short-QT syndrome (SQTS) is much less common than LQTS, and there is little to guide risk profiling other than documented life-threatening arrhythmias and familial clustering of SCD.[72] Several ion channel gene loci variants have been suggested.[90]

Brugada Syndrome

Brugada syndrome (BrS), now considered part of the J wave syndromes (**see Chapter 39**), is characterized by an atypical right bundle branch block (RBBB) pattern and unusual forms of nonischemic ST-T wave elevations in the anterior precordial leads (**Fig. 42.10**). It is a familial disorder associated with risk for SCD and occurs most commonly in young and middle-aged men (**see Chapter 33**). Mutations involving the cardiac Na^+ channel gene (*SCN5A*) are the most commonly observed variants but are identified in only a minority of cases, and a number of other ion channel defects have been associated with BrS.[90,91] A variant in *SCN10A* has been observed in more than 16% of affected individuals.[92] The RBBB and ST-T wave changes may be intermittent and evoked or exaggerated by Na^+ channel blockers (e.g., flecainide, procainamide). Individual risk for SCD is difficult to predict. Persistent type I electrocardiographic patterns, syncope, gender, and life-threatening arrhythmias, in various combinations, are thought to be the best predictors.[93] The reliability and added value of inducibility of VTs during programmed electrical stimulation studies are controversial; it appears to be of no value in patients with type III electrocardiographic patterns, of limited if any value in those with type II patterns, but may be of some value in select patients with type I patterns or those who vary between type I and II, with or without provocation studies.[94]

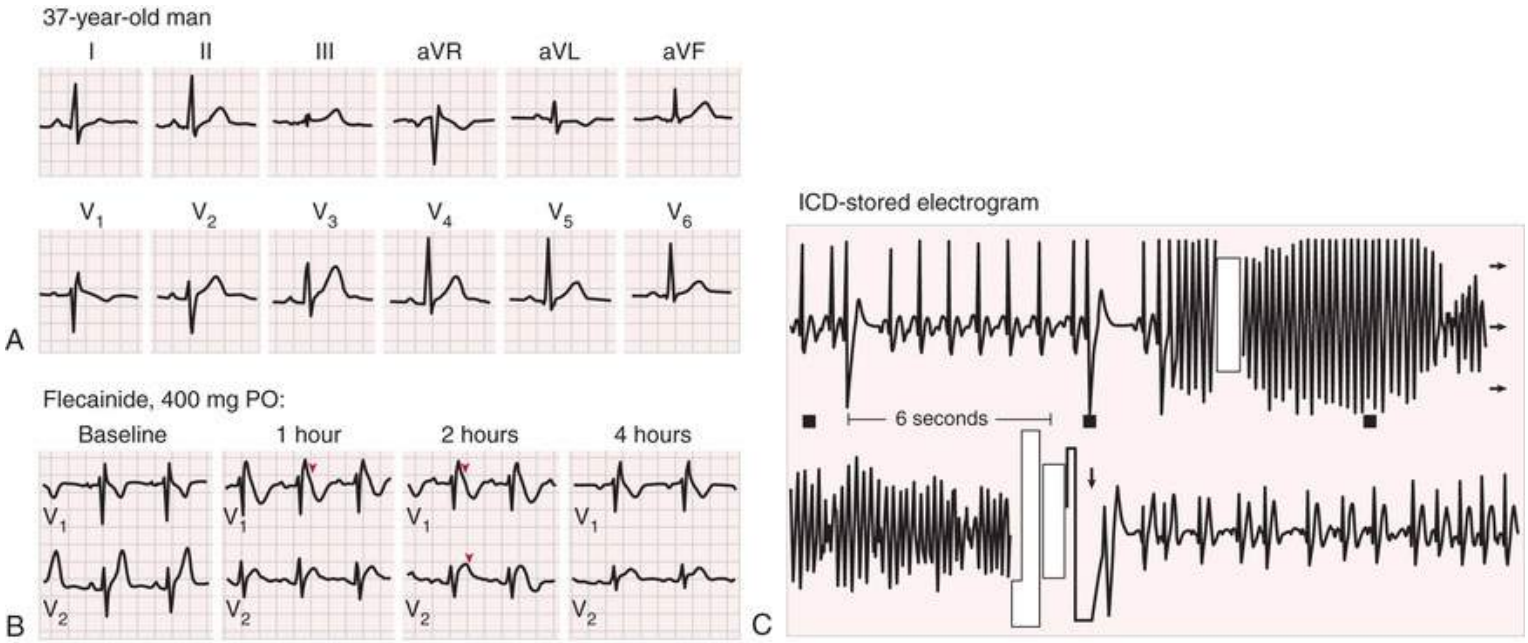


FIGURE 42.10 Electrocardiographic and clinical findings in a 37-year-old man with Brugada syndrome. The patient was resuscitated after out-of-hospital VF. No structural disease was identified. **A,** The 12-lead ECG shows an incomplete right bundle branch block pattern, which is not typical of Brugada syndrome. **B,** The typical repolarization changes associated with Brugada syndrome (*arrowheads*) were elicited by a single oral dose of flecainide, 400 mg. The patient received an ICD and 6 months later had an appropriate shock (*arrow*, **C**), as shown on the accompanying electrogram stored in the device.

In a prospective registry in Italy, Priori and colleagues[95] evaluated the predictive accuracy of sustained VT/VF inducibility to identify patients considered to be at high risk for sudden death and who might be candidates for a prophylactic ICD. A total of 308 individuals with a spontaneous or drug-induced type I ECG pattern but without a history of SCA underwent programmed electrical stimulation at enrollment, and patients were evaluated every 6 months. An induced arrhythmia was not a significant predictor of events at follow-up. A spontaneous type I ECG pattern plus a history of syncope was an independent predictor of arrhythmic outcomes, as was an effective ventricular refractory period of less than 200 milliseconds and QRS fragmentation.

Early Repolarization and Sudden Cardiac Death

An association between the ECG pattern of early repolarization (ER) and risk for idiopathic VF has been described[96] (J wave syndromes; **see Chapter 39**). ER was limited to the inferior and lateral leads, in contrast to the anterior leads, which were associated with the conventional definition of benign ER. The magnitude of J point elevation was significantly greater in cardiac arrest survivors than in controls with ER. Interestingly, a number of the clinical features were similar to the responses seen in patients with BrS, thus leading to speculation whether the reported cases of VF associated with ER might be another expression of the Brugada pathophysiologic process.[97]

An association between ER and risk for SCD was observed in a long-term surveillance study in Finland.[98] The observation that excess risk is expressed later in life suggests a possible interaction between the physiology of ER and acquired diseases, such as coronary heart disease. A subsequent study did demonstrate an association between ER and a higher incidence of SCA during acute coronary syndrome.[99] Risk was primarily associated with the presence of horizontal or downsloping ST segments with ER in the inferior leads.[100]

Catecholaminergic Polymorphic Ventricular Tachycardia.

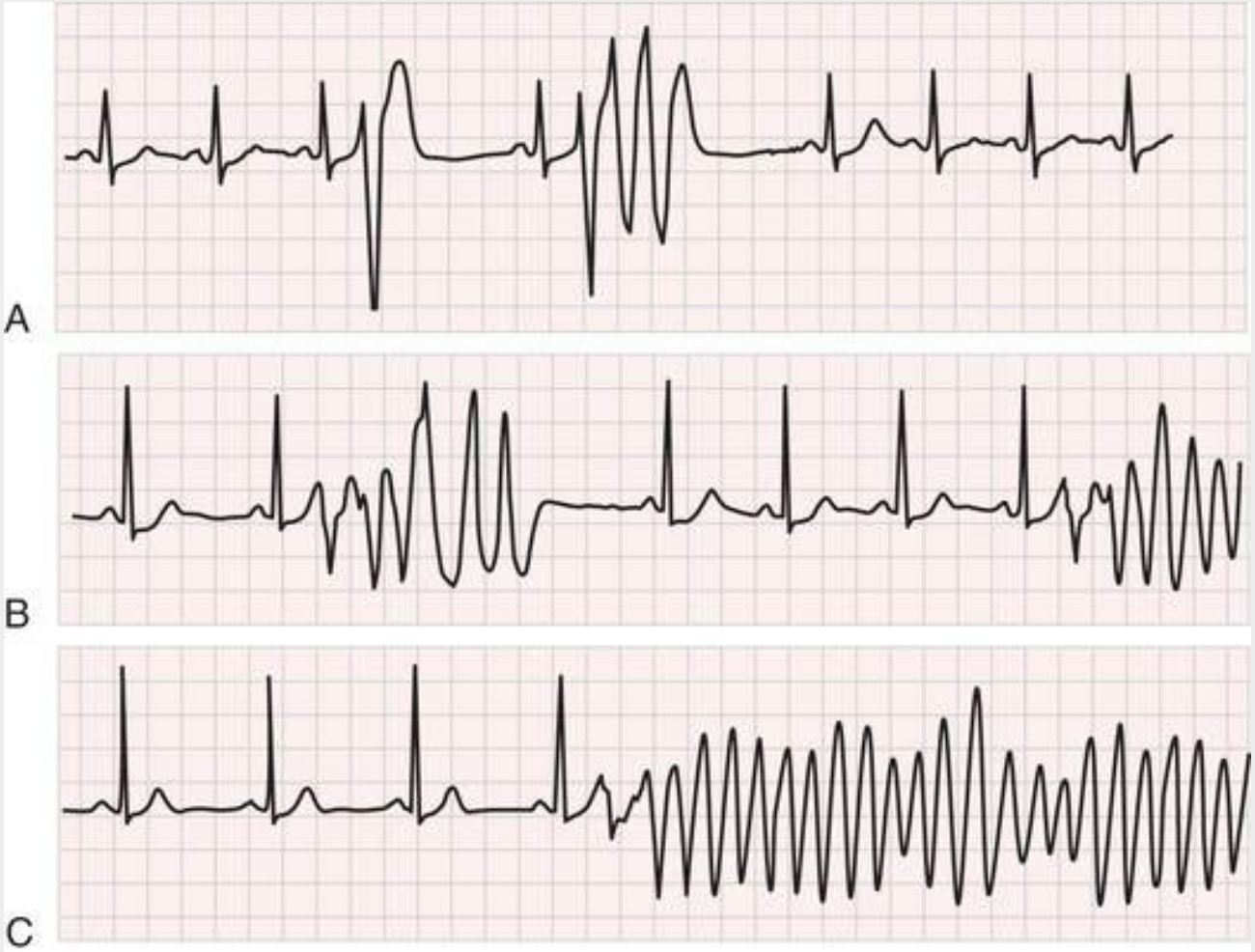
CPVT is an inherited syndrome associated with catecholamine-dependent lethal arrhythmias in the absence of forewarning ECG abnormalities and with at least partial control by beta adrenoceptor–blocking agents (**see Chapters 33 and 39**). An autosomal dominant pattern involving the ryanodine receptor locus (RyR2) was initially described predominantly in younger patients, usually men, with bidirectional or polymorphic VT associated with risk for SCD. A pattern not associated with that genotype appeared to be more likely in older patients (young adults), usually women. More recent data suggest less dominance by male sex for RyR2 variants and another variant involving autosomal recessive inheritance of calsequestrin loci (*CASQ2*) in approximately 10% of genotyped cases and relatives.[101]

Electrical Instability Resulting from Neurohumoral and Central Nervous System Influences.

Several CNS-related interactions with cardiac electrical instability have been suggested (**see Chapters 34 and 99**). Epidemiologic data also suggest an association between behavioral abnormalities and risk for SCD. Psychological stress and emotional extremes have long been suggested as triggering mechanisms for advanced arrhythmias and SCD, but only limited, largely observational data support such associations (**see Chapter 96**). Takotsubo cardiomyopathy[102] is a catecholamine-mediated condition with a generally good long-term prognosis, but the short-term risk for SCD during the acute phase remains uncertain and can be associated with QT prolongation. The possibility that it contributed to unexplained SCD in the young and middle-aged population should be explored.[103]

Stress-induced arrhythmias are better supported than stress-induced risk for mortality, which requires further study. Data from the 1994 Los Angeles earthquake identified an increased rate of fatal cardiac events on that day, but the event rate was reduced during the ensuing 2 weeks, thus suggesting triggering of events about to happen rather than independent causation. Associations between auditory stimulation and auditory auras and SCD have been reported. Auditory abnormalities in some forms of congenital QT prolongation have also been observed.

A variant of torsades de pointes characterized by short coupling intervals between a normal impulse and the initiating impulse has been described (**eFig. 42.1**). It appears to have familial trends and to be related to alterations in autonomic nervous system activity. The 12-lead ECG demonstrates normal QT intervals, but VF and sudden death are common (**see Chapters 33 and 39**).



EFIGURE 42.1 Short-coupled runs of nonsustained polymorphic ventricular tachycardia. This variant has been observed in people without structural heart disease and with normal QT intervals. They are subject to spontaneous episodes of polymorphic ventricular tachycardia (torsades de pointes), which may degenerate into ventricular fibrillation. This uncommon syndrome is associated with a high risk for sudden death. Panels A, B, and C are not continuous but are three separate episodes of nonsustained polymporphic ventricular tachycardia.

The phenomenon of "voodoo death" has been studied in pockets of isolation in underdeveloped countries. Isolation from the tribe, a sense of hopelessness, severe bradyarrhythmias, and sudden death appear to be associated. Limited clinical observations and experimental data modeling voodoo death have suggested a mechanism related to parasympathetic overactivity, as opposed to the evidence of an adrenergic basis for syndromes related to acute emotional stress.

Sudden Infant Death Syndrome and Sudden Cardiac Death in Children

SIDS occurs between birth and 6 months of age, is more common in male infants, and had an incidence of 1.2 deaths per 1000 live births before widespread publication of appropriate sleep positions in at-risk infants.[104] Between 1992 and 2002, the incidence fell to 0.57 death per 1000 live births as attention to sleep position grew, thus supporting a major role for obstructive sleep apnea as a mechanism. Vulnerability as a result of various mechanisms of dysfunctional central respiratory control, both inherent and related to prematurity, is likely to interact with sleep position as a multicomponent mechanism.[105]

Because of its abrupt nature, a primary cardiac mechanism had been suspected in some cases, and a large study of ECGs of infants suggested prolonged QT intervals associated with risk for SIDS. A near-miss survivor with a de novo mutation of the cardiac Na^+ channel gene (*SCN5A*) provided proof of

concept that a long QT may be a mechanism of SIDS. Subsequent data have supported that as many as 15% of cases of SIDS may occur by this mechanism. Other, very rare potential cardiac associations, such as accessory pathways and dispersed or immature AV nodal or bundle branch cells in the annulus, have also been described.

Sudden death in children beyond the SIDS age-group and in adolescents and young adults is associated with identifiable heart disease in most cases. Approximately 25% of SCDs in children occur in those who have undergone previous surgery for congenital cardiac disease. Of the remaining 75%, more than half occur in children who have one of four lesions: congenital aortic stenosis, Eisenmenger syndrome, pulmonary stenosis or atresia, or obstructive HCM (**see Chapter 75**). Other common causes included myocarditis, hypertrophic and dilated cardiomyopathy, congenital heart disease, and aortic dissection.

Sudden Cardiac Death in Competitive and Recreational Athletes and During Intense Exercise

SCD can occur during or after extreme physical activity in competing athletes or under special circumstances in the general population (**see Chapter 53**). Examples of the latter include intense conditioning exercise and basic military training. Among adolescent and young adult competitive athletes, the estimated incidence was 1 per 75,000 annually in Italy, versus less than 1 per 125,000 for the general nonathlete population in the same age-group. In a survey of high school athletes in Minnesota, the frequency of sudden unexpected death related to cardiovascular disease during competitive sports was approximately 1 per 100,000 individual student athlete participants, a figure similar to that in the general population in that age-group.[106]

Exercise-related incidence figures are more difficult to ascertain in other populations, but one study reported an incidence of one SCD per 1.5 million exercise sessions in health clubs.[50] The incidence of exercise-related cardiac arrest appears to be lower in women. In a large study of both competitive and recreational athletes in France, the incidence of SCD was 0.5 per 1 million population in women, compared to 10.1 per million in men.[107] Most athletes and nonathletes have a previously known or unrecognized cardiac abnormality. In middle-aged and older adults, in whom coronary disease dominates as the cause of SCD, exercise-related deaths appear to be associated with acute plaque disruption. Whether exercise contributed to the initiation of plaque disruption or preexisting disruption simply set the stage for the fatal response during exercise remains unclear. Among adolescent and young adult athletes, HCM with or without obstruction (**see Chapter 78**) and occult congenital or acquired CAD (**Chapter 57**) are the most common causes identified after death,[108] with myocarditis contributing a significant minority (**Chapter 79**). In a report of a large cohort of U.S. Air Force recruits, a surprisingly large fraction of those who died suddenly during exertion had unsuspected myocarditis. Diseases attributed to molecular structural abnormalities, such as LQTS and RV dysplasia, are increasingly being recognized as causes of SCD in athletes and exercising nonathletes. Blunt chest wall trauma by sports objects, such as baseballs and hockey pucks, can initiate lethal arrhythmias, a syndrome known as *commotio cordis*.[109]

Attention to recreational athletics and high-level conditioning activities is emerging. A 5-year survey of sports-related SCD and resuscitated SCA among the general population in France was based on a prospective, comprehensive survey of individuals 10 to 75 years old.[110] The investigators detected an incidence of 4.6 cases per million population per year, with only 6% of cases occurring in young competitive athletes. The remainder occurred during recreational athletic activities, usually cycling, jogging, or soccer. Analysis of suspected underreporting suggested that the incidence of sports-related sudden death throughout France might be as high as 5 to 17 new cases per million population per year.

Case participants were predominantly male (95%) and had no previous history of heart disease. The mean age was 46 years. Just more than half (51.9%) of the sports-related SCDs occurred in public sports venues, and 99.8% of these were witnessed. However, bystander cardiopulmonary resuscitation (CPR) was performed in only 35.5%.

A study of SCA risk in marathon and half-marathon runners suggested that the overall incidence did not appear to be higher than that for the general population in the age-group of participants.[111] The most common identified causes were HCM, with or without other disorders, and CAD.

Sudden death from true cardiac causes in athletes should not be confused with precipitous death related to noncardiac causes, such as acute cerebrovascular accident (CVA, stroke),[7] heat stroke, or malignant hyperthermia. In the latter, the victim has usually exercised excessively in hot weather, often with athletic gear that impairs heat dissipation and sometimes with the use of substances such as ephedrine that may cause vasoconstriction, impairing heat exchange. This leads to collapse with greatly elevated core body temperatures and, ultimately, irreversible organ system damage. As a result, the U.S. Food and Drug Administration (FDA) has banned marketing of these substances for enhancement of athletic performance or weight loss.[112]

Other Causes and Circumstances Associated with Sudden Death

A small group of victims has neither previously determined functional abnormality nor identifiable structural abnormalities at postmortem examination. Such events or deaths, when associated with documented VF, are classified as “idiopathic.” Although long-term survival after an idiopathic, potentially fatal event is still unclear, some degree of risk appears to remain. The idiopathic category is decreasing as the subtle molecular causes become better defined, including recognition by postmortem genetic studies. Limited data suggest that higher risk persists primarily in patients with subtle cardiac structural abnormalities, in contrast to patients who are truly normal. In addition, these events tend to occur in young, otherwise healthy people.

A number of non–cardiac-related conditions can also cause or mimic SCD. Sleep apnea is associated with a risk for nocturnal death, including deaths attributable to cardiac causes (**see Chapter 87**). The risk for death peaks during the night rather than in the early-morning hours.[23] Another respiratory system–based cause of sudden death is the “café coronary,” in which food lodges in the oropharynx and causes an abrupt obstruction at the glottis. The “holiday heart” syndrome is characterized by cardiac arrhythmias, most often atrial, as well as other cardiac abnormalities associated with acute alcoholic states. It has not been determined whether potentially lethal arrhythmias occurring in such settings account for the reported sudden deaths associated with acute alcoholic states. Massive pulmonary embolism can cause acute cardiovascular collapse and sudden death (**see Chapter 84**); sudden death in severe acute asthmatic attacks, without prolonged deterioration of the patient's condition, is well recognized (**Chapter 86**). Air or amniotic fluid embolism at the time of labor and delivery may cause sudden death on rare occasion, with the clinical picture mimicking that of SCD. Peripartum air embolism caused by unusual sexual practices has been reported as a cause of such sudden deaths.

A number of abnormalities that do not directly involve the heart may cause sudden deaths that mimic SCD. Such abnormalities include aortic dissection (**see Chapter 63**), acute cardiac tamponade (**Chapter 83**), and rapid exsanguination. The electrical mechanism associated with these deaths is usually severe bradyarrhythmias, pulseless electrical activity, or asystole rather than VT/VF.

Pathology and Pathophysiology

Protocols and observations from postmortem studies of SCD victims have changed in recent years. It is now recommended that in SCD cases that do not have obvious causes identified on routine postmortem studies or available clinical information, specialized cardiac pathology centers should perform postmortem examination. This is particularly important for younger populations with unexplained SCA. A series of 200 cases in which information was available from both routine autopsies and referral evaluations yielded a 41% discrepancy in final diagnoses.[113] Notably, there was a tendency for the routine autopsy to overdiagnose cardiomyopathy as a cause of death, and CAD was less common than in other studies. However, the study was limited to some extent by an age discrepancy (median, 32 years), limiting extrapolation to the overall population. Additional data from unselected sources also suggest that the proportion of CAD-associated SCDs has decreased,[77] and that hypertensive heart disease, idiopathic "fibrosis," and other, less common causes are significant contributors. In addition, a number of studies now support the notion that postmortem genetic studies are useful for increasing the probability identifying a probable cause that is unexplained based on anatomic changes.[28,114,115] Earlier pathologic studies in SCD victims across a broader age spectrum reflected the epidemiologic and clinical observations that coronary atherosclerosis is the major predisposing cause. In one report, 81% of 220 victims of SCD had significant coronary heart disease at autopsy. At least one vessel with more than 75% stenosis was found in 94% of the victims, acute coronary occlusion in 58%, healed MI in 44%, and acute MI in 27%. These observations were consistent with studies of the frequency of CAD in SCD victims, but the focus has evolved from the simple anatomic presence of coronary lesions to specific associations with unstable plaque. All other causes of SCD collectively account for no more than 20% of cases, but they have provided a large base of enlightening pathologic data (**see Table 42.5**).

Pathology of Sudden Death Caused by Coronary Artery Abnormalities

Coronary Arteries.

Extensive atherosclerosis has long been recognized as the most common pathologic finding in the coronary arteries of victims of SCD. Combined study results have suggested a general pattern of at least two coronary arteries with 75% or greater narrowing in more than 75% of the victims. Several studies have demonstrated no specific pattern of distribution of coronary artery lesions that preselect for SCD, but the extent of coronary artery narrowing at postmortem examination was greater in SCD victims than in controls.

The role of active coronary artery lesions, characterized by plaque fissuring, plaque erosion or rupture, platelet aggregation, and thrombosis, as a major pathophysiologic mechanism of the onset of cardiac arrest has been further clarified (**see Chapter 58**). In an early study of 100 consecutive victims of sudden coronary death, 44% had major (>50% luminal occlusion) recent coronary thrombi, 30% had minor occlusive thrombi, and 21% had plaque fissuring. Only 5% had no acute coronary artery changes; 65% of the thrombi occurred at sites of preexisting high-grade stenoses, and an additional 19% were found at sites with greater than 50% stenosis. In a subsequent study, 50 (30%) of 168 victims had occlusive intraluminal coronary thrombi, and 73 (44%) had mural intraluminal thrombi. Disruption, platelet aggregation, and thrombosis are associated with markers of inflammation and various conventional risk factors for coronary atherosclerosis, such as cigarette smoking and hyperlipidemia.

Some of the less common, nonatherosclerotic coronary artery abnormalities have specific pathologic features as well. Coronary artery spasm, an established cause of acute ischemia and SCD, is commonly associated with nonobstructive plaque (**Fig. 42.11**), and the consequences of spasm/reperfusion have been recognized at postmortem examination. When deep myocardial bridges are identified in association with SCD, patchy fibrosis in areas subserved by the affected vessel is often seen at postmortem

examination. Coronary vasculitis in association with various autoimmune disorders may cause diffuse myocardial abnormalities, but asymptomatic cardiac involvement or global myocardial dysfunction is more common than SCD.

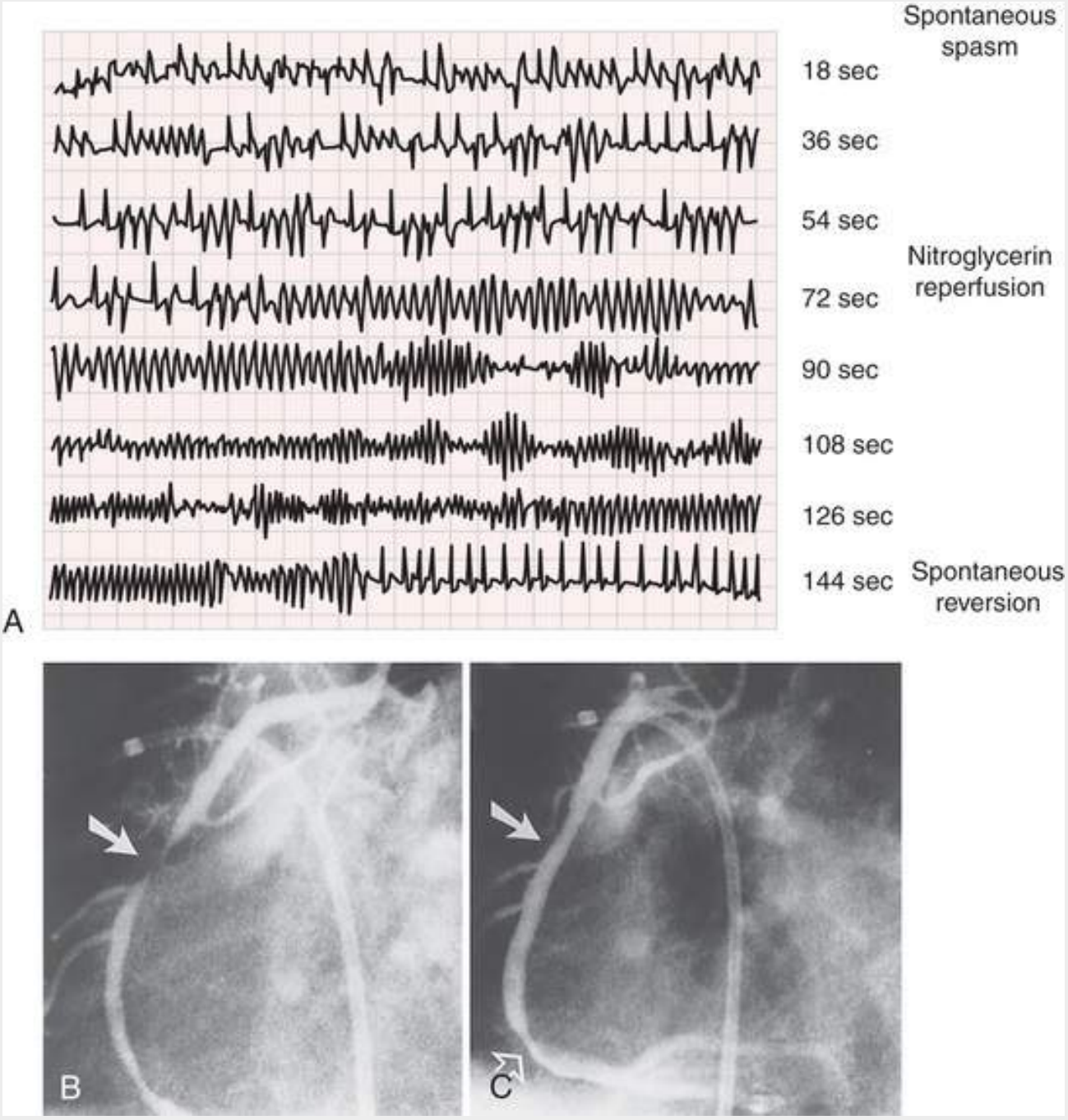


FIGURE 42.11 Life-threatening ventricular arrhythmias associated with acute myocardial ischemia related to coronary artery spasm and with reperfusion. **A,** Continuous lead II electrocardiographic monitor recording during ischemia (time, 0 to 55 seconds) caused by spasm of the right coronary artery **(B).** Following the administration of nitroglycerin at approximately 55 seconds, an abrupt transition from repetitive ventricular ectopy to a rapid polymorphic, prefibrillatory tachyarrhythmia occurs (time, 80 to 130 seconds) in association with reversal of the spasm **(C).** *Closed arrows* indicate the site of spasm before and after nitroglycerin; the *open arrow* indicates a lower-grade distal lesion. (Modified from Myerburg RJ, Kessler KM, Mallon SM, et al. Life-threatening ventricular arrhythmias in patients with silent myocardial ischemia due to coronary artery spasm. N Engl J Med 1992;326:1451.)

Myocardium.

Myocardial injury in SCD caused by coronary heart disease reflects the extensive atherosclerosis usually

present. Studies of victims of out-of-hospital SCD and from epidemiologic sources have indicated that healed MI is a common finding in SCD victims, with most investigators reporting frequencies ranging from 40% to more than 70%. In one study, 72% of men in the 25- to 44-year age-group who died suddenly (≤24 hours) with no previous clinical history of coronary heart disease had scars from large (63%) or small (<1-cm cross-sectional area, 9%) areas of healed myocardial necrosis. The incidence of acute MI is considerably lower, with cytopathologic evidence of recent MI found in approximately 20% of individuals. This estimate corresponds well with the results of studies of OHCA survivors, who were found to have an incidence of new MI of 20% to 30%, but with a wide range of numbers reported in various studies, especially among survivors. These pathologic observations do not provide insight into the likely possibility that many SCDs result from acute coronary syndrome mechanisms and progress from ischemia to fatal arrhythmias without time for structural markers to become visible. Since elevations in troponin levels occur during chest pain syndromes and also in a substantial proportion of cardiac arrest survivors, the determination whether myocardial injury preceded or resulted from the cardiac arrest is difficult to resolve in individual cases. In the absence of ST-segment elevation MI, it is difficult to distinguish primary from secondary troponin elevations. How troponin levels are handled (e.g., repeated measures over the first 48 hours after arrest) can impact on conclusions whether troponin release is primary or secondary.

Ventricular Hypertrophy.

Myocardial hypertrophy can coexist and interact with acute or chronic ischemia but appears to confer an independent risk for mortality. No close correlation has been found between increased heart weight and the severity of coronary heart disease in SCD victims; however, heart weight is higher in SCD victims than in those whose death is not sudden despite a similar prevalence of a history of hypertension before death. Risk for hypertrophy-associated mortality is also independent of LV function and the extent of CAD, and LV hypertrophy itself may predispose to SCD. Experimental data have also suggested increased susceptibility to potentially lethal ventricular arrhythmias in patients with LV hypertrophy and ischemia and reperfusion.

Specialized Conducting System.

Fibrosis of the specialized conducting system may be observed in SCD victims. Although this process is associated with AV block or intraventricular conduction abnormalities, its role in SCD is uncertain. Lev disease, Lenègre disease, ischemic injury caused by small-vessel disease, and numerous infiltrative or inflammatory processes can result in such changes. In addition, active inflammatory processes (e.g., myocarditis) and infiltrative processes (e.g., amyloidosis, scleroderma, hemochromatosis, morbid obesity) may damage or destroy the AV node, bundle of His, or both and result in AV block.[116]

Focal diseases, such as sarcoidosis, rheumatoid arthritis, fibrotic or fatty infiltration of the AV node or His-Purkinje system with apparent discontinuities, and very rarely Whipple disease, can also involve the conducting system (**see Chapter 40**). These various categories of conducting system disease have been considered possible pathologic substrates for SCD that might be overlooked because of the difficulty of performing careful postmortem examinations of the conducting system routinely, and careful studies of the conducting system has been suggested to identify up to 22% of otherwise unexplained SCDs in persons younger than 40.[117] Focal involvement of conducting tissue by tumors (especially mesothelioma of the AV node, but also lymphoma, carcinoma, rhabdomyoma, and fibroma) has also been reported, and rare cases of SCD have been associated with these lesions. Abnormal postnatal morphogenesis of the specialized conducting system may be a significant factor in some cases of SCD in infants and children.

Cardiac Nerves.

Diseases of cardiac nerves have been postulated to have a role in SCD (**see Chapter 99**). Neural involvement may result from random damage to neural elements within the myocardium (i.e., secondary cardioneuropathy) or may be primary, as in diabetic cardiac autonomic neuropathy, which is associated with a 3.5-fold increased risk of SCD, or rarely a selective cardiac viral neuropathy. Secondary involvement can be a consequence of ischemic neural injury in coronary heart disease and has been proposed to result in autonomic destabilization, thereby enhancing the propensity to arrhythmias, possibly by a mechanism of denervation supersensitivity to catecholamines causing increased dispersion of refractoriness. Nerve sprouting may be important.[118] Some experimental data have supported this hypothesis, and a clinical technique for imaging of cardiac neural fibers suggests a changing pattern over time after MI. Viral, neurotoxic, and hereditary causes (e.g., progressive muscular dystrophy, Friedreich ataxia) have been emphasized.

Mechanisms and Pathophysiology

Electrical mechanisms of cardiac arrest are divided into tachyarrhythmic and bradyarrhythmic-asystolic events, or conversely, shockable versus nonshockable. The tachyarrhythmias include VF and pulseless sustained VT, in which a perceptible pulse may not be present (<60 mm Hg), and adequate blood flow is not maintained. Bradyarrhythmic-asystolic events include severe bradyarrhythmias, pulseless electrical activity (PEA; formerly electromechanical dissociation, or EMD), and inability to generate a mechanical event because of complete absence of electrical activity (asystole). To qualify as a mechanism of cardiac arrest, severe bradyarrhythmias must be slow enough to result in an inability to perfuse adequately and maintain consciousness, which usually requires a heart rate of less than 20 beats/min. In PEA the electrical rate can be considerably faster, but in general much slower than true pulseless ventricular tachycardia (pVT). The important distinction between PEA and pVT is that pVT is a shockable rhythm. The classification of this group of rhythms includes the very slow agonal rhythm heralding death (random irregular depolarizations that do not generate a pulse), PEA at rates from 40 to more than 100 beats/min without a pulse, and pVT, which is a true VT, very rapid and equivalent to VF (**see Fig. 42.11**). In PEA, there is no perfusion because of absent mechanical activity or mechanical obstruction to blood flow, as in massive pulmonary embolism. However, echocardiographic imaging during PEA has suggested that residual LV wall motion may persist but is not adequate for generating a pulse, as in pVT. This phenomenon has implications for exploring new therapeutic approaches for PEA.[119] Many victims found to be asystolic at contact likely were initially in VF or VT. After a variable time, fibrillation may cease and asystole or less often PEA emerges. In contrast to earlier data, the most common initial recording documented in recent years is asystole or PEA, which can continue as such or very rarely transform into VF.

The occurrence of potentially lethal tachyarrhythmias or severe bradyarrhythmia or asystole is the end of a cascade of pathophysiologic abnormalities that result from complex interactions between coronary vascular events, myocardial injury, variations in autonomic tone, and the metabolic and electrolyte state of the myocardium[17] (**see Fig. 42.5**). There is no uniform hypothesis of mechanisms by which these elements interact to lead to the final pathway of lethal arrhythmias. However, **Fig. 42.7** shows models of the pathophysiologic process of SCD that include vascular, myocardial, and functional components. The risk for cardiac arrest is conditioned by the presence of structural abnormalities and modulated by functional variations.

Pathophysiologic Mechanisms of Lethal Tachyarrhythmias

Coronary Artery Structure and Function

Among the large fraction of SCDs associated with coronary atherosclerosis, an extensive distribution of chronic arterial narrowing has been well defined by pathologic studies. However, the specific mechanisms by which these lesions lead to potentially lethal disturbances in electrical stability are not simply the consequence of steady-state reductions in regional myocardial blood flow in association with variable demands[16,17] (**see Chapter 44**). A simple increase in myocardial oxygen demand, in the presence of a fixed supply, may be a mechanism of exercise-induced arrhythmias and sudden death during intense physical activity or in others whose heart disease had not previously become clinically manifested. However, the dynamic nature of the pathophysiologic mechanism of coronary events has led to the recognition that superimposed acute lesions create a setting where alterations in the metabolic or electrolyte state of the myocardium are the common circumstance leading to disturbed electrical stability. Active vascular events resulting in an acute or transient reduction in regional myocardial blood flow in the presence of a normal or previously compromised circulation constitute a common mechanism of ischemia, angina pectoris, arrhythmias, and SCD. Coronary artery spasm or modulation of coronary collateral flow, predisposed to by local endothelial dysfunction, exposes the myocardium to the double hazard of transient ischemia and reperfusion (**see Fig. 42.11**). Neurogenic influences may play a role but do not appear to be a sine qua non for the production of spasm. Vessel susceptibility and humoral factors, particularly those related to platelet activation and aggregation, also appear to be important mechanisms.

Transition of stable atherosclerotic plaque to an “active” state because of endocardial damage, with plaque fissuring leading to platelet activation and aggregation followed by thrombosis, is a mechanism that appears to be present in many SCDs related to coronary heart disease (**see Chapter 61**). Inflammatory responses in atherosclerotic plaque are now viewed as the condition leading to lesion progression, including erosion, disruption, platelet activation, and thrombosis. In addition to causing a subacute or acute critical reduction in regional blood flow, these mechanisms produce a series of biochemical alterations that may enhance or retard susceptibility to VF by means of vasomotor modulation.

The step in the cascade of coronary artery pathophysiology leading to ischemia-induced arrhythmias that follows conversion to an active plaque involves the thrombotic module of platelet aggregation and thrombosis (**see Figs. 42.5 and 42.7** and **Chapter 44**). However, there is a discrepancy between the relatively high incidence of platelet aggregation or acute thrombi in postmortem studies and the low incidence of evolution of new MI in survivors of out-of-hospital VF. The rapid initiation of lethal arrhythmias, the spontaneous thrombolysis, a dominant role of spasm induced by platelet products, or a combination of these factors may explain this observation.

Acute Ischemia and Initiation of Lethal Arrhythmias

The onset of acute ischemia produces immediate electrical, mechanical, and biochemical dysfunction of cardiac muscle. The specialized conducting tissue is more resistant to acute ischemia than working myocardium, and therefore the electrophysiologic consequences are less intense and are delayed in onset in specialized conduction tissue. In addition to the direct effect of ischemia on normal or previously abnormal tissue, reperfusion after transient ischemia can cause lethal arrhythmias (**see Fig. 42.11**). Reperfusion of ischemic areas can occur by three mechanisms: (1) spontaneous thrombolysis, (2) recruitment of collateral vessels from other vascular beds in response to local ischemia, and (3) reversal of vasospasm. Some mechanisms of reperfusion-induced arrhythmogenesis appear to be related to the

duration of ischemia before reperfusion. Experimentally, there is a window of vulnerability beginning 5 to 10 minutes after the onset of ischemia and lasting up to 20 to 30 minutes.

Electrophysiologic Effects of Acute Ischemia.

Within the first minutes after experimental coronary ligation, there is a propensity to ventricular arrhythmias that abates after 30 minutes and reappears after several hours (**see Chapter 34**). The initial 30 minutes of arrhythmias is divided into two periods, the first of which lasts for approximately 10 minutes and is presumably directly related to the initial ischemic injury. The second period (20 to 30 minutes) may be related either to reperfusion of ischemic areas or to the evolution of different injury patterns in epicardial and endocardial muscle. Multiple mechanisms of reperfusion arrhythmias have been observed experimentally, including slow conduction and reentry and afterdepolarizations and triggered activity.

At the level of the myocyte, the immediate consequences of ischemia, which include alterations in cell membrane physiology, with efflux of ionized potassium (K^+), influx of ionized calcium (Ca^{2+}), acidosis, reduction of transmembrane resting potentials, and enhanced automaticity in some tissues, are followed by a separate series of changes during reperfusion. Those of particular interest are the possible continued influx of Ca^{2+}, which may produce electrical instability; responses to alpha or beta adrenoceptor stimulation, or both; and afterdepolarizations as triggering responses for Ca^{2+}-dependent arrhythmias. Other possible mechanisms studied experimentally include the formation of superoxide radicals in reperfusion arrhythmias and differential responses of endocardial and epicardial muscle activation times and refractory periods during ischemia or reperfusion. The adenosine triphosphate–dependent K^+ current ($I_{K.ATP}$), which is inactive during normal conditions, is activated during ischemia. Its activation results in a strong efflux of K^+ from myocytes and marked shortening of the time course of repolarization, which leads to slow conduction and ultimately to inexcitability. This response is more marked in epicardium than in endocardium, which leads to a prominent dispersion of repolarization across the myocardium during transmural ischemia. At an intercellular level, ischemia alters the distribution of connexin 43, the primary gap junction protein between myocytes. This alteration results in uncoupling of myocytes, a factor that is arrhythmogenic because of altered patterns of excitation and regional changes in conduction velocity.[18]

The state of the myocardium at the onset of ischemia is important. Tissue healed after previous injury appears to be more susceptible to the electrical destabilizing effects of acute ischemia, as is chronically hypertrophied muscle. Remodeling-induced local stretch, regional hypertrophy, or intrinsic cellular alteration may contribute to this vulnerability. Of more direct clinical relevance is the suggestion that potassium depletion by diuretics and clinical hypokalemia may make ventricular myocardium more susceptible to potentially lethal arrhythmias, in part by its effect on repolarization (QT) duration.

The association of metabolic and electrolyte abnormalities and neurophysiologic and neurohumoral changes with lethal arrhythmias emphasizes the importance of integrating changes in the myocardial substrate with systemic influences. Most direct among myocardial metabolic changes in response to ischemia are local acute increase in interstitial K^+ levels to values exceeding 15 mM, decrease in tissue pH to below 6.0, changes in adrenoceptor activity, and alterations in autonomic nerve traffic, all of which tend to create and maintain electrical instability, especially if it is regional in distribution. Other metabolic changes, such as elevation of cyclic adenosine monophosphate levels, accumulation of free fatty acids and their metabolites, formation of lysophosphoglycerides, and impaired myocardial

glycolysis, have also been suggested as myocardial-destabilizing influences.[18] These local myocardial changes integrate with systemic patterns of autonomic fluctuation that can be observed as patterns of altered heart rate variability and fractal dynamics,[120] thus potentially identifying subsets of patients predetermined to be at higher risk for SCD during an ischemic event.

Transition from Myocardial Instability to Lethal Arrhythmias

The combination of a triggering event and a susceptible myocardium is a fundamental electrophysiologic concept for the mechanism of initiation of potentially lethal arrhythmias (**see Figs. 42.5 and 42.7**). The triggering event for VT or VF can be electrophysiologic, ischemic, metabolic, or hemodynamic. For VF, the endpoint of their interaction is disorganization of patterns of myocardial activation into multiple uncoordinated reentrant pathways. Clinical, experimental, and pharmacologic data have suggested that triggering events in the absence of myocardial instability are unlikely to initiate lethal arrhythmias.

Bradyarrhythmias and Asystolic Arrest

The basic electrophysiologic mechanism in asystolic arrest is failure of normal subordinate automatic activity to assume the pacing function of the heart in the absence of normal function of the sinus node, AV junction, or both. Asystolic arrest is more common in severely diseased hearts and in patients with a number of end-stage disorders, both cardiac and noncardiac. These mechanisms may result in part from diffuse involvement of subendocardial Purkinje fibers in advanced heart disease.

Pulseless Electrical Activity

PEA is separated into primary and secondary forms. No one unifying definition for PEA, mechanistically or clinically, is recognized. The common denominator in both forms is the presence of organized cardiac electrical activity in the absence of effective mechanical function.[119] The absence of rapid return of spontaneous circulation (ROSC) is important in that it excludes transient losses of cerebral blood flow, such as the various patterns of vasovagal reflex syncope, which have different clinical implications than the meaning attributed to true PEA. The secondary form of PEA results from an abrupt cessation of cardiac venous return, such as massive pulmonary embolism, acute malfunction of prosthetic valves, exsanguination, and cardiac tamponade from hemopericardium. Primary PEA is the more familiar form, in which none of these obvious mechanical factors is present, but ventricular muscle fails to produce an effective contraction despite continued electrical activity. It usually occurs as an end-stage event in advanced heart disease, but can occur in patients with acute ischemic events or, more often, after electrical resuscitation from prolonged cardiac arrest. Although primary PEA is not thoroughly understood, it appears that diffuse disease, metabolic abnormality, or global ischemia provides the pathophysiologic substrate. The proximate mechanism for failure of electromechanical coupling may be abnormal intracellular Ca^{2+} metabolism, intracellular acidosis, or perhaps depletion of ATP.

Clinical Features of Patients With Cardiac Arrest

Although the pathologic anatomy associated with SCD caused by CAD often reflects the changes associated with acute myocardial injury, less than 20% of survivors of OHCA have clinical evidence of a new transmural MI. Nonetheless, many have elevated enzyme levels along with nonspecific electrocardiographic changes suggesting myocardial damage, which may be caused by transient ischemia as a triggering event or by the loss of myocardial perfusion during the cardiac arrest. The recurrence rate is low in survivors of OHCA caused by transmural MI. In contrast, early studies demonstrated a 30% recurrence rate at 1 year and 45% at 2 years in the survivors who did not have a new transmural MI. Recurrence rates decreased subsequently, probably in part the result of long-term interventions.

Prodromal Symptoms

Patients at risk for SCD can have prodromes such as chest pain, dyspnea, weakness or fatigue, palpitations, syncope, and a number of nonspecific complaints. Several epidemiologic and clinical studies have demonstrated that such symptoms can presage coronary events, particularly MI and SCD, and result in contact with the medical system weeks to months before SCD.

Attempts to identify early prodromal symptoms specific for SCD risk have not been successful. Although several studies have reported that 12% to 46% of fatalities occur in patients who had seen a physician 1 to 6 months before death, such visits are more likely to presage MI or nonsudden death, and most complaints responsible for these visits are not heart related. However, patients who have chest pain as a prodrome to SCD appear to have a higher probability of intraluminal coronary thrombosis at postmortem examination. Fatigue has been a particularly common symptom in the days or weeks before SCD in a number of studies, but this symptom is nonspecific. The symptoms that occur within the last hours or minutes before cardiac arrest are more specific for heart disease and may include symptoms of arrhythmias, ischemia, and heart failure.

Onset of the Terminal Event

Ambulatory recordings fortuitously obtained during the onset of an unexpected cardiac arrest have indicated dynamic changes in cardiac electrical activity during the minutes or hours before the event. Increasing heart rate and advancing grades of ventricular ectopy are common antecedents of VF. Alterations in autonomic nervous system activity may also contribute to onset of the event. Studies of short-term variations in heart rate variability or related measures have identified changes that correlate with the occurrence of ventricular arrhythmias. Although these physiologic properties may be associated with transient electrophysiologic destabilization of the myocardium, the extent to which they are paralleled by clinical symptoms or events has been less well documented.[120] SCDs caused by arrhythmias or acute circulatory failure mechanisms correlate with a high incidence of acute myocardial disorders at the onset of the terminal event. Such disorders are more likely to be ischemic when the death is caused by arrhythmias and to be associated with low-output states or myocardial anoxia when the deaths are caused by circulatory failure.

Cardiac Arrest

Cardiac arrest is characterized by abrupt loss of consciousness caused by lack of adequate cerebral blood flow as a result of failure of cardiac pump function. In contrast to previous data, the most common electrical mechanism of OHCA currently identified by EMS is asystole (50%), with VF/pVT and PEA each estimated in the range of 25%. The extent to which these proportions of first-recorded rhythms reflect the rhythms that trigger the onset of SCA remains unknown because of the lag between onset, 911 contact, and EMS arrival. Mechanical mechanisms include rupture of the ventricle, cardiac tamponade, acute mechanical obstruction to flow, and acute disruption of a major blood vessel, each of which is more likely to present with PEA or asystole.

The potential for successful resuscitation is a function of the setting in which the cardiac arrest occurs, the mechanism of the arrest, and the underlying clinical status of the victim. The decision whether to attempt to resuscitate is closely related to the potential for success.[121]

At present, fewer low-risk patients with otherwise uncomplicated MI are weighting in-hospital cardiac arrest (IHCA) statistics than in the past. In one report, only 14% of patients receiving in-hospital cardiopulmonary resuscitation (CPR) were discharged from the hospital alive, and 20% of these patients died within the ensuing 6 months. Although 41% of the patients had an acute MI, 73% had a history of congestive heart failure, and 20% had experienced previous cardiac arrests. The mean age of 70 years may have influenced the outcome statistics, but patients with high-risk complicated MI and those with other high-risk markers heavily influenced the population of patients at risk for IHCA. Non–cardiac-related clinical diagnoses were dominated by renal failure, pneumonia, sepsis, diabetes, and a history of cancer. The strong male preponderance consistently reported in OHCA studies is not present with in-hospital patients, but the better prognosis of VT or VF mechanisms than PEA or asystolic mechanisms persists (27% versus 8% survival rate). However, the proportion of arrests caused by in-hospital VT or VF is considerably less (33%), with the combination of respiratory arrest, asystole, and PEA dominating the statistics (61%). In another report, a 22% survival rate to hospital discharge was observed. Adverse risks were age older than 70 years, previous stroke or renal failure, and heart failure on admission. Better outcomes were predicted by previous angina pectoris or admission because of ventricular arrhythmias. Strategic factors affecting survival after IHCA include the location in the hospital, the type of hospital, daytime and evening events versus night and weekend events, and a rapid time to performance of defibrillation.[122]

A multihospital study of outcomes after IHCA in pediatric patients demonstrated a major improvement in survival to hospital discharge between 2000 and 2009, with a risk-adjusted improvement from 14.3% in 2000 to 43.4% in 2009.[123] There was neither improvement nor worsening of the proportion with residual neurologic deficits. The proportion with VF or pVT decreased from 22% in 2000 to 2003 to 9.7% in 2007 to 2009, and those with asystole decreased from 51.4% to 20%. In contrast, PEA increased from 26.6% to 70.3%. The reason for the dramatic increase in the proportion of PEA events is not clear because respiratory insufficiency as an initial condition increased only from 68.8% to 75.5%. However, the proportion maintained on mechanical ventilators at the time of arrest did increase from 67.4% (2000 to 2003) to 81.6% (2007 to 2009).

Important risk factors for death after in-hospital CPR are listed in **eTable 42.1**. Survival after IHCA is lower for events that occur during weeknights and weekends than during the daytime and evening hours during the week,[121] and more rapid times to defibrillation are advantageous.[124] Such data suggest the need for additional strategies for uniformly rapid in-hospital responses, as well as for the limitations reported for in-hospital early-warning systems.[125]

ETABLE 42.1

Predictors of Mortality after in-Hospital Cardiopulmonary Resuscitation

Before Arrest
Hypotension (systolic BP <100 mm Hg)
Pneumonia
Renal failure (BUN >50 mg/dL)
Cancer
Homebound lifestyle
During Arrest
Arrest duration >15 min
Intubation
Hypotension (systolic BP <100 mm Hg)
Pneumonia
Homebound lifestyle
After Resuscitation
Coma
Need for pressors
Arrest duration >15 min

BP, Blood pressure; *BUN,* blood urea nitrogen.

Modified from Bedell SE, Delbanco TL, Cook EF, Epstein FH. Survival after cardiopulmonary resuscitation in the hospital. N Engl J Med 1983;309:569.

Among elderly persons, outcomes after community-based responses to OHCA are not as good as for younger victims. In one study comparing persons younger than 80 (mean age, 64) with those in their 80s and 90s, the survival rate to hospital discharge in the younger group was 19.4%, compared to 9.4% for octogenarians and 4.4% for nonagenarians. However, when the groups were analyzed according to markers favoring survival (e.g., VF, pVT), the incremental benefit was even better for the elderly than for the younger patients (36%, 24%, and 17%, respectively), but the frequency of ventricular tachyarrhythmias versus nonshockable rhythms was lower in elderly persons. Overall, advanced age is only a weak predictor of an adverse outcome and should not be used in isolation as a reason not to resuscitate. Long-term neurologic status and length of hospitalization were similar in older and younger surviving patients.

Progression to Biologic Death

The time course for progression from cardiac arrest to biologic death is related to the mechanism of the cardiac arrest, the nature of the underlying disease process, and the delay between onset and resuscitative efforts. The onset of irreversible brain damage usually begins within 4 to 6 minutes after loss of cerebral circulation, and biologic death follows quickly in unattended cardiac arrest. In large series, however, it has been demonstrated that a limited number of victims can remain biologically alive for longer periods and may be resuscitated after delays in excess of 8 minutes before beginning basic life support and in excess of 16 minutes before advanced life support. Despite these exceptions, it is clear that the probability of a favorable outcome—survival neurologically intact—deteriorates rapidly as a function of time after cardiac arrest. Younger patients with less severe cardiac disease and the absence of coexistent multisystem disease have a higher probability of a favorable outcome after such delays.

Irreversible injury to the central nervous system usually occurs before biologic death, and the interval may extend days to weeks and occasionally result in very prolonged persistent vegetative states in patients who are resuscitated during the temporal gap between brain damage and biologic death. IHCA caused by VF is less likely to have a protracted course between the arrest and biologic death, with patients surviving after a prompt intervention or succumbing rapidly because of inability to stabilize their cardiac rhythm or hemodynamics. Overall, patients who have ROSC with persistent neurologic status of

CPC 3 or 4 have a very low survival rate, both in-hospital and at 6 months after arrest.

Patients whose cardiac arrest is caused by sustained VT with cardiac output inadequate to maintain consciousness can remain in VT for considerably longer periods with blood flow that is marginally sufficient to maintain viability. Thus there is a longer interval between the onset of cardiac arrest and the end of the period that allows successful resuscitation. The lives of such patients usually end in VF or an asystolic event (PEA or asystole) if the VT is not reverted.

The progression in patients with asystole or PEA as the initiating event is more rapid. Such patients, whether in or out of hospital, have a poor prognosis because of advanced heart disease or coexistent multisystem disease. They tend to respond poorly to interventions, even if the heart is successfully paced. Although survival from PEA has increased in recent years, it is generally limited to the small subgroup of patients with reversible conditions (e.g., respiratory, electrolyte imbalances) that respond well to interventions, and most progress rapidly to biologic death. Cardiac arrests caused by mechanical factors such as tamponade, structural disruption, and impedance to flow by major thromboembolic obstructions to right or left ventricular outflow are reversible only in patients in whom the mechanism is recognized and an intervention is feasible.

Survivors of Cardiac Arrest

Hospital Course

Cardiac arrests during the acute phase of MI may be primarily related to an electrical event, or secondarily to LV dysfunction or cardiogenic shock. Patients who are resuscitated immediately from primary VF associated with ST-segment elevation myocardial infarction (STEMI) usually stabilize promptly, and they require no long-term arrhythmia management based on the early arrhythmia (**see Chapter 62**). Management after secondary cardiac arrest in MI patients is dominated by the patient's hemodynamic status.

Survivors of OHCA may have repetitive ventricular arrhythmias during the initial 24 to 48 hours of hospitalization. These arrhythmias have variable responses to antiarrhythmic therapy, depending on hemodynamic status. The overall rate of recurrent cardiac arrest is low, 10% to 20%, but the mortality rate in patients who have recurrent cardiac arrests is approximately 50%. Only 5% to 10% of in-hospital deaths after out-of-hospital resuscitation are caused by recurrent cardiac arrhythmias. Patients with recurrent cardiac arrest have a high incidence of new or preexisting AV or intraventricular conduction abnormalities.

The most common causes of death in hospitalized OHCA survivors are noncardiac events related to CNS injury, including anoxic encephalopathy and sepsis related to prolonged intubation and hemodynamic monitoring lines. During the index hospitalization after out-of-hospital resuscitation, 59% of deaths have been reported from these causes. Approximately 40% of those who arrive at the hospital in coma never awaken after admission to the hospital and die after a median survival of 3.5 days. Two thirds of those who regain consciousness have no gross deficits, and an additional 20% have persisting cognitive deficits only. Of the patients who do awaken, 25% do so by admission, 71% by the first hospital day, and 92% by the third day. A small number of patients have awakened after prolonged hospitalization. Among those who die in the hospital, 80% do not awaken before death. Therapeutic hypothermia in patients with post–cardiac arrest coma is beneficial[126,127] (see next section).

Cardiac causes of delayed death during hospitalization after OHCA are most often related to hemodynamic deterioration, which accounts for about one third of deaths in hospitals. Among all deaths, those that occurred within the first 48 hours of hospitalization were usually caused by hemodynamic

deterioration or arrhythmias regardless of neurologic status; later deaths were dominated by neurologic complications. Admission characteristics most predictive of subsequent awakening included motor response, pupillary light response, spontaneous eye movement, and blood glucose level below 300 mg/dL.

Clinical Profile of Survivors of Out-of-Hospital Cardiac Arrest

The clinical features of OHCA survivors are heavily influenced by the type and extent of the underlying disease associated with the event. Causation is dominated by coronary heart disease and cardiomyopathies. All other structural heart diseases plus functional abnormalities and toxic or environmental causes are responsible for the remainder.

In a study of 63 survivors of OHCA with normal EF and no obvious heart disease, no cause was identified after intensive studies in 44% of the patients.[128] The remainder were found to have LQTS (23%), catecholaminergic polymorphic VT (23%), RV dysplasia (17%), ER (14%), coronary spasm (11%), BrS (9%), and myocarditis (3%). The mean age of this group was 43 years, and 46% had had no previous history of presyncope or syncope.

Postresuscitation Electrocardiographic Changes

Among survivors of OHCA, the 12-lead ECG has proved to be of value only for discriminating risk for recurrence in those whose cardiac arrest was associated with new transmural MI (**see Chapter 12**). Patients in whom documented new Q waves develop in association with a clinical picture that supports acute STEMI as the mechanism of cardiac arrest itself are at lower risk for recurrence, unless they develop criteria for post-MI primary prevention, such as EF less than 30%. In contrast, nonspecific electrocardiographic markers of ischemia, associated with elevation of troponin or creatine kinase MB levels, indicate higher risk for recurrence. Nonspecific repolarization abnormalities (e.g., ST-segment depression, flat T waves) are frequently present, often transiently, after a cardiac arrest. Transient prolongation of the QT interval, often associated with postresuscitation hypokalemia, can follow CPR and is associated with risk of recurrent arrhythmias. A prolonged QRS duration in association with a greatly reduced EF portends increased risk for mortality.

Left Ventricular Function

LV function is abnormal in most survivors of OHCA, often severely abnormal, but ranging from severe dysfunction to normal or near-normal measurements.[129] The severity of MI estimated shortly after cardiac arrest results from a combination of myocardial stunning caused by the cardiac arrest itself and the extent of preexisting dysfunction. Stunning usually improves within the first 24 to 48 hours,[130] and the residual is assumed to be a result of preexisting disease or the acute injury leading to the cardiac arrest. Reliance on postarrest troponin elevations alone to determine whether MI caused a cardiac arrest can be treacherous, because cardiac arrest and even non–life-threatening sustained arrhythmias, as well as ICD shocks, can be associated with transient elevations.[131] If the EF is severely reduced initially, failure to begin improvement within the first 48 hours is an adverse short-term prognostic sign. In a study of resuscitated OHCA victims admitted to the hospital and subsequently discharged neurologically intact, 47% had acute coronary syndromes identified during evaluation and had a mean EF of 42%, compared to 32% in nonsurvivors.[132] Among survivors to hospital discharge, a reduced EF is an adverse long-term prognostic sign.

Exercise Testing

Exercise testing is no longer commonly used to evaluate the need for and response to anti-ischemic therapy in OHCA survivors, except when transient ischemia is in question as a mechanism for onset (**see Chapter 13**). The probability of a positive test result related to ischemia is relatively low, although termination of testing because of fatigue is common. Mortality during follow-up is higher in patients who fail to achieve a normal rise in systolic blood pressure during exercise.

Coronary Angiography

Coronary angiography is performed with increasing frequency during initial hospitalization after OHCA. In a recent report based on data from the National Inpatient Sample, 143,607 of 407,974 OHCA survivors (35.2%) underwent coronary angiography, increasing from 27.2% in 2000 to 43.9% 2012, and percutaneous coronary intervention (PCI) increased from 9.5% in 2000 to 24.1% in 2012.[133] OHCA survivors tend to have extensive coronary disease but no specific pattern of abnormalities. Acute coronary lesions, often multifocal, are present in many survivors. Significant lesions in two or more vessels are present in at least 70% of patients who have any coronary lesion. Patients with recurrent cardiac arrests have a higher incidence of triple-vessel disease than those without recurring arrest.. However, the frequency of moderate to severe stenosis of the left main coronary artery does not differ between cardiac arrest survivors and the overall population of patients with symptomatic coronary heart disease.

Blood Chemistry

Serum potassium levels are lower in survivors of cardiac arrest than in patients with acute MI or stable coronary heart disease. This finding is often a consequence of resuscitation interventions rather than a preexisting hypokalemic state because of chronic diuretic use or other causes. Among survivors who are hypokalemic during the first 12 to 24 hours after SCA, serum K^+ levels following stabilization should be checked to exclude a chronic potassium-wasting state. Low Ca^{2+} levels with normal total calcium levels were also observed during OHCA resuscitation. Higher resting lactate levels have been reported in OHCA survivors than in normal individuals. Lactate levels are correlated inversely with EF and directly with PVC frequency and complexity.

Long-Term Prognosis

Studies from Miami, Florida, and Seattle, Washington, in the early 1970s had indicated that the risk for recurrent cardiac arrest in the first year after survival of an initial VT/VF event was approximately 30% and at 2 years was 45%. Total mortality at 2 years was approximately 60% in both studies. More recent mortality data, including those from the control groups of secondary prevention ICD trials,[72] have demonstrated 2-year mortality rates between 15% and 25%. The apparent improved outcomes, independent of the benefit provided by ICD therapy, are probably attributable to the current interventions used in survivors, such as beta adrenoceptor blockers, statins and angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), anti-ischemic procedures, and heart failure therapies that were not previously available or in general use. The risk for recurrent cardiac arrest and all-cause mortality is higher during the first 12 to 24 months after the index event and relates best to the EF during the first 6 months.

Management of Cardiac Arrest

The response to cardiac arrest is driven by two principles: (1) maintaining continuous cardiopulmonary support until ROSC has been achieved and (2) achieving ROSC as quickly as possible. To meet these goals, the management strategy is divided into five elements: (1) initial assessment by a witness/bystander and summoning of an emergency response team, (2) basic life support (BLS), (3) early defibrillation by a first responder (if available), (4) advanced life support, and (5) post–cardiac arrest care. If successful, the algorithm is followed by a sixth element, long-term management. The initial elements can be applied by physicians and nurses, emergency medical technicians (EMTs) or paramedics, laypeople trained in bystander interventions, and untrained bystanders prompted in CPR by 911 telecommunicators trained to prompt callers in BLS technique. Emerging data suggest that telephone prompts by 911 operators can improve survival with preserved neurologic status.[134] Requirements for specialized knowledge and skills increase progressively as the patient is moved through post–cardiac arrest management into long-term follow-up care. These emergency response principles are intended for both in-hospital and community-based responses.

In-Hospital Interventions

Development of the coronary care unit (CCU) resulted in an immediate reduction of in-hospital mortality risk during acute MI from 30% to 15% based almost entirely on the reduction of cardiac arrests. Other specialized monitoring and intensive care units demonstrated various levels of benefit as well, but the impact has been less in general care hospital units and for cardiac arrests associated with complex comorbid states.[135] A registry study from 2000 to 2009 provided trends for risk-adjusted rates of survival to discharge after cardiac arrest in monitored units and general hospital units.[136] Among 84,625 patients, 20.7% had VF or pulseless VT (pVT) as the initial rhythm, and 79.3% had asystole or PEA, with the proportion of cardiac arrests attributable to asystole/PEA increasing over time ($P < 0.001$). The overall survival rate to discharge increased from 13.7% in 2000 to 22.3% in 2009 ($P < 0.001$), with improvement in both the VT/VF and the PEA/asystole subsets (**Fig. 42.12A**). Absolute rates of survival to discharge remained higher for the VT/VF group, whereas improvement in survival occurred in the two rhythm groups. The improvement in survival appeared to be a result of both improved acute resuscitation actions and postresuscitation care. A small decrease in rates of clinically significant neurologic disability in survivors occurred over time (32.9% in 2000 and 28.1% in 2009 ([$P = 0.02$]).

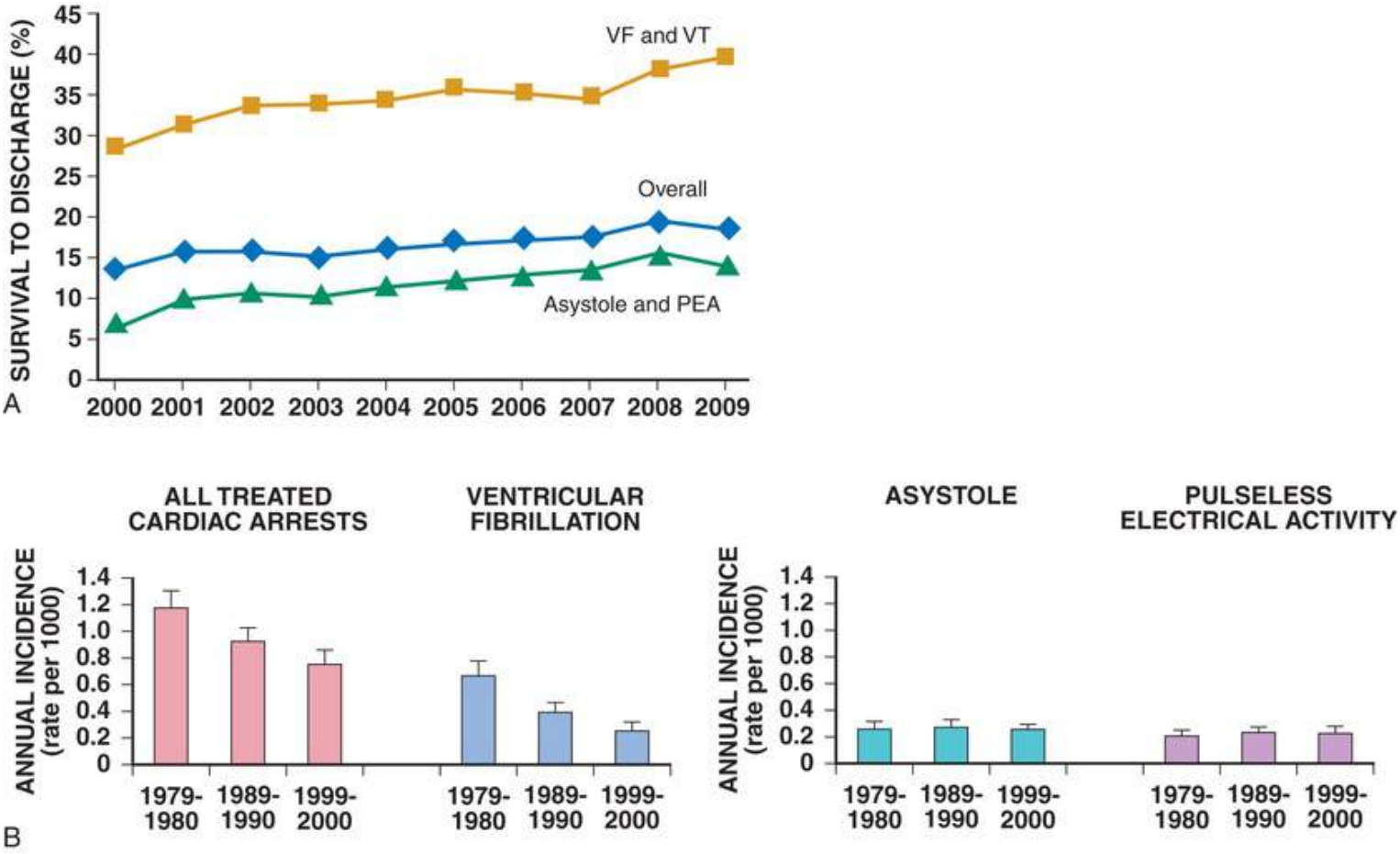


FIGURE 42.12 Changing incidence of shockable and nonshockable rhythms. **A,** Survival to discharge for VF and pulseless VT versus asystole and PEA between 2000 and 2009 ($P < 0.001$ for trend in each survival curve). **B,** Between 1980 and 2000 a progressive decrease in the VF event rate occurred in the Seattle, Washington, community for unexplained reasons. Of note, no concomitant increase in nonshockable rhythms took place. The proportion of events with VF at initial contact is decreasing, as observed in several other studies. (**A,** From Girotra S, Nallamothu BK, Spertus JA, et al. Trends in survival after in-hospital cardiac arrest. N Engl J Med 2012;367:1912; **B,** modified from Cobb LA, Fahrenbruch CE, Olsufka M, Copass MK. Changing incidence of out-of-hospital ventricular fibrillation, 1980-2000. JAMA2002;288:3008.)

Community-Based Interventions

The initial out-of-hospital intervention experience in Miami and Seattle yielded only 14% and 11% rates of survival to discharge, respectively (**eFig. 42.2**). Subsequent improvements correlated with the addition of EMTs as another tier of responders to provide CPR and earlier defibrillation. In general, rural areas have lower success rates, and the U.S. national success rate is probably 5% or less. Regional variability is highlighted by a 10-community analysis in the United States and Canada demonstrating a range of VF survival rates from 0% to 39.5%.[15]

HISTORY OF COMMUNITY-BASED EMERGENCY RESPONSE SYSTEMS

1971-1974	Initial Miami/Seattle outcomes	14%, 11%
1978-1985	Peak Miami/Seattle outcomes	25%-35%
1984	Rural outcomes:	
	• Standard basic life support	3%
	• Ambulance-based expanded access	19%
1991	Estimated cumulative U.S. survival	1%-3%
1992-1994	Major metropolitan population centers	2%
1996	Dade County, Florida, current outcomes	9%
1996-1998	Updated U.S. EMS outcomes, cumulative	<5%
1999	"Optimized" EMS systems [OPALS]	5%
2000-2004	Nonconventional responders:	17% to >50%
	Public access sites [police, security guards, airline personnel, laypersons; airports and airliners, malls, casinos, stadiums]	

EFIGURE 42.2 The history of out-of-hospital cardiac arrest survival statistics demonstrates that standard emergency rescue systems are not sufficient to have a meaningful impact on sudden cardiac death in the community. *EMS,* Emergency medical services. (From Myerburg RJ. Sudden cardiac death: exploring the limits of our knowledge. J Cardiovasc Electrophysiol 2001;12:369.)

Reports from different areas in the United States show marked variations in outcomes.[137] Some very densely populated areas (i.e., Chicago and New York City) have provided disturbing outcome data. A study from Chicago reported that only 9% of OHCA victims survive to be hospitalized, and only 2% are discharged alive. Moreover, outcomes in blacks are much worse than in whites (0.8% versus 2.6%). A large majority had bradyarrhythmias, asystole, or PEA on initial contact with EMS, which suggests prolonged times between collapse and EMS arrival, absent or ineffective bystander interventions, or both. The New York City report indicated a survival to hospital discharge rate of only 1.4%. Among those who undergo bystander CPR, the rate increases to 2.9%, and bystander CPR plus VF as the initial rhythm yields a further increase to 5.3%. For those whose arrest occurred after EMS arrival, the success rate increases further to 8.5%. These trends support the concept that delays and breaks in the "chain of survival"[121] have a major negative impact on EMS results in densely populated areas.[137]

In some circumstances, resuscitative effort in the out-of-hospital setting is deemed futile. A victim found unconscious after an unwitnessed collapse, reasonably assumed to be found after a prolonged interval (e.g., cool skin, rigor mortis), obviously fulfills this classification. However, studies have provided markers of futility under less stark circumstances. In a study involving trained responders with automated external defibrillators (AEDs), only 0.5% of victims survived if (1) the arrest was not witnessed by EMS personnel, (2) there was no ROSC, and (3) no shocks were delivered per protocol. Adding a response time longer than 8 minutes reduced the survival rate to 0.3%, and events unwitnessed by a bystander yielded no survivors.

Impact of Tiered Response Systems

Improvements in both out-of-hospital care and in-hospital technology and practices can contribute to better outcomes, as described in the chain-of-survival concept.[121] Of these two general factors, the influence of out-of-hospital care has been studied in more detail.[138] Many studies support the importance of early defibrillation for improving outcome (**eFig. 42.3**). These observations have motivated a search for strategies that shorten response times, largely by the development of two-tiered systems, in which nonconventional first responders, such as police, firemen, security guards, and lay bystanders, deploy AEDs now commonly available in public places (**Fig. 42.13**). Available data suggest that this strategy may improve outcome, primarily in public locations.[13,139]

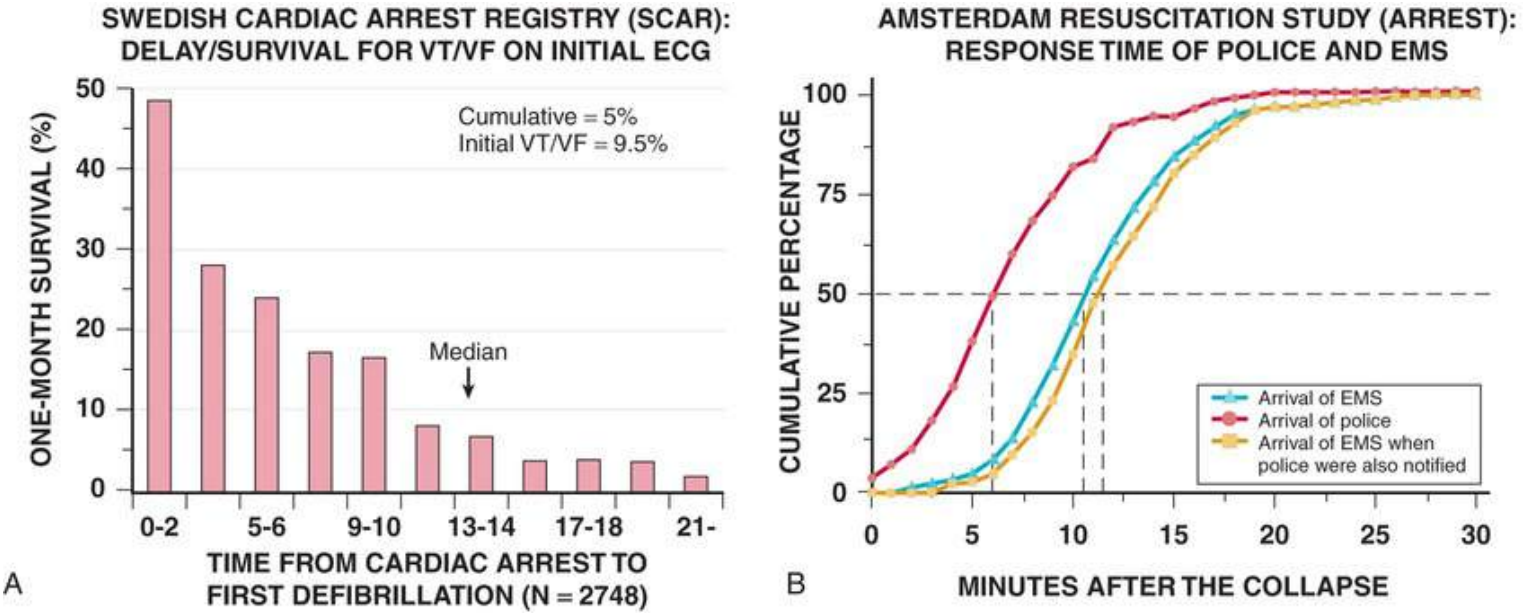
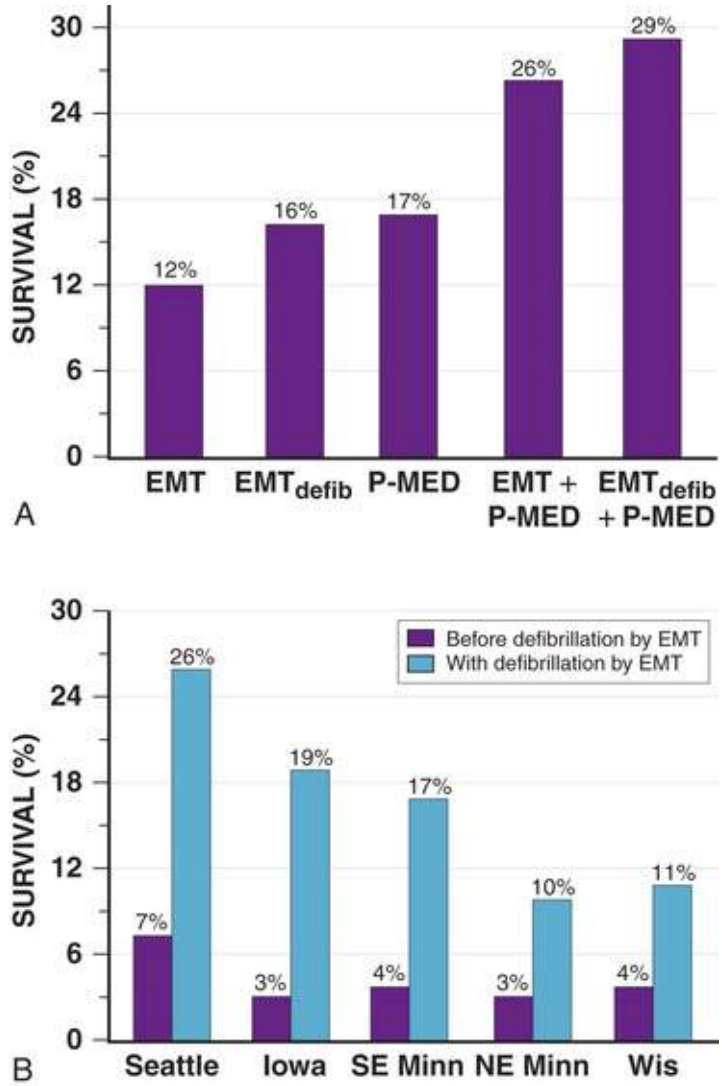


FIGURE 42.13 Influence of response time on survival from out-of-hospital cardiac arrest. **A,** The time from the onset of cardiac arrest to the initial defibrillation attempt is related to 1-month survival on the basis of data from the Swedish Cardiac Arrest Registry. The cumulative survival rate was 5%, and the survival rate for victims whose initial rhythm was VT or VF was 9.5%. The median response time was almost 13 minutes. Thirty-day survival rates ranged from a maximum of 48% with responses shorter than 2 minutes to less than 5% with response time longer than 15 minutes. **B,** Potential for faster response systems based on the Amsterdam Resuscitation Study. The response times of police vehicles are compared with those of conventional emergency medical services (EMS). At the 50th percentile of response times, police vehicles provided an almost 5-minute improvement in arrival time (approximately 6 minutes). (**A,** Modified from Holmberg M, Holmberg S, Herlitz J. The problem of out-of-hospital cardiac arrest: prevalence of sudden death in Europe today. Am J Cardiol 1999;83:88D; **B,** modified from Waalewijn RA, de Vos R, Koster RW. Out-of-hospital cardiac arrests in Amsterdam and its surrounding areas: results from the Amsterdam Resuscitation Study [ARREST] in "Utstein" style. Resuscitation 1998;28:157.)



EFIGURE 42.3 Impact of emergency rescue system design and immediate defibrillation on out-of-hospital cardiac arrest survival. **A,** Percent survival to hospital discharge with rescue activities by standard emergency medical technicians (EMTs) trained in cardiopulmonary resuscitation (CPR), EMTs allowed to defibrillate immediately (EMT_{defib}), initial response by paramedics (P-MED), two-tiered system with EMT and P-MED, and two-tiered system with EMTs allowed to defibrillate if they are the first responders plus P-MED. Training of first-responders (EMT_{defib}) and a two-tiered system have the best outcome. **B,** Comparison of outcomes observed in five geographic areas, with EMTs providing only CPR (*purple*) versus EMTs trained to defibrillate as first responders (*blue*). Each group had a marked improvement in outcome when EMTs were trained and permitted to defibrillate. (Modified from Ornato JP, Om A. Community experience in treating out-of-hospital cardiac arrest. In Akhtar M, Myerburg RJ, Ruskin JN, editors: Sudden Cardiac Death: Prevalence, Mechanisms and Approach to Diagnosis and Management. Baltimore: Williams & Wilkins; 1994, p 450.)

In rural communities, earlier defibrillation by ambulance technicians yielded a 19% survival rate, versus only 3% for standard CPR. In another report, analysis of the relationship between response delay and survival to hospital discharge revealed a 48% survival rate for response times of 2 minutes or less and less than 10% survival when response was longer than 10 minutes (**Fig. 42.13**). The mean response time was approximately 13 minutes, and the overall survival rate was 5%. Survival was 9.5% for those in VT or VF on first contact. A second element in out-of-hospital care that contributes to outcome is the role of bystander CPR by laypeople awaiting EMS arrival.[140] Although there was no significant difference in the percentage of patients successfully resuscitated and admitted to the hospital alive with (67%) or without (61%) bystander intervention, almost twice as many OHCA victims were ultimately discharged alive when they had undergone bystander CPR (43%) than when such support was not provided (22%). CNS protection, expressed as early regaining of consciousness, is the major protective element of bystander CPR. The rationale for bystander intervention is further highlighted by the relationship between

time to defibrillation and survival when analyzed as a function of time to initiation of basic CPR. It has been reported that more than 40% of victims whose defibrillation and other advanced life support activities were instituted more than 8 minutes after collapse survived if basic CPR had been initiated less than 2 minutes after onset of the arrest. A period of CPR before defibrillation may also be helpful, particularly if the time to defibrillation exceeds 4 minutes from the onset of arrest.[141]

Importance of Electrical Mechanisms

Several sources have identified a changing distribution of initial rhythms recorded by EMS personnel. Compared with data from the 1970s and 1980s, there has been a decrease in the number of events in which ventricular tachyarrhythmias are the initial rhythm recorded, with a consequent reduction in the proportion of victims who have rhythms amenable to cardioversion-defibrillation (**see Fig. 42.12B**). Similar observations have been reported for in-hospital settings.[136,142] Some studies now suggest that less than 50% of victims have shockable rhythms at initial contact. This fact is paralleled by a reduction in cumulative survival probability with community-based interventions,[11,119] even with a smaller percentage of shockable rhythms.[143] It is likely that pre-911 delays in recognition of and reaction to an event may be playing a role, in conjunction with longer response times based on geographic considerations. This suggests a need for more extensive public education programs. Thus response times may not accurately reflect true downtimes, and consequently the potential for success is impaired. The 4- to 6-minute time for a desirable response is not optimal. By 4 minutes, significant circulatory and ischemic changes have taken place, and conditions worsen rapidly beyond that time.

The electrical mechanism of OHCA, as defined by the initial rhythm recorded by EMS personnel, has a powerful impact on outcome. They are generally categorized as shockable (VF, pVT) and nonshockable (PEA, asystole) rhythms[119] (**Table 42.6**). The distinction between pVT and PEA is sometimes confused and has relevance because it impacts response strategies. The subgroup of patients who are in pVT at the time of first contact, although small, has the best outcome. Of patients in cardiac arrest related to VT, 88% were successfully resuscitated and admitted to the hospital alive, and 67% were ultimately discharged alive. However, this relatively low-risk group represents only 7% to 10% of all cardiac arrests. Because of the inherent time lag between collapse and initial recordings, it is likely that many more cardiac arrests begin as rapid, sustained VT and degenerate into VF before the arrival of rescue personnel.

TABLE 42.6

Tachyarrhythmic and Nontachyarrhythmic Cardiac Arrest

PRIMARY ARRHYTHMIAS	ELECTRICAL MECHANISMS	MECHANICAL MECHANISMS
Tachyarrhythmic Cardiac Arrest		
Ventricular fibrillation (VF)	Absence of organized ventricular depolarization	Absence of LVWM
Pulseless ventricular tachycardia	Organized ventricular pattern; rapid rate	Absent LVWM or LVWM insufficient for organ perfusion
Secondary Arrhythmias		
Sinus tachycardia; other	Sinus or other supraventricular rhythm; narrow QRS complex	Obstruction to cardiac blood flow; hypovolemia
Nontachyarrhythmic Cardiac Arrest		
PEA, Primary (Initial Rhythm)		
With residual LV contraction	Organized QRS complexes, usually wide	LVWM insufficient for organ perfusion
Without LV contraction	Organized QRS complexes, usually wide	Absence of LVWM
PEA, Secondary		
Postshock	Regular or irregular QRS complexes, usually wide	Absent LVWM or LVWM insufficient for organ perfusion
Primary noncardiac	Regular or irregular QRS complexes, usually wide	Usually LVWM insufficient for organ perfusion; LVWM may be absent
Agonal PEA	Slow, usually irregular, wide QRS	Absence of LVWM
Ventricular asystole	Absent ventricular electrical activity; exclude fine VF	Absence of LVWM

LV, Left ventricular; *LVWM,* left ventricular wall motion; *PEA,* pulseless electrical activity.

Modified from Myerburg RJ, Halperin H, Egan D, et al. Pulseless electrical activity: definition, causes, mechanisms, management, and research priorities for the next decade. Report from a National Heart, Lung, and Blood Institute Workshop. Circulation 2013;128:2532.

Patients with a bradyarrhythmia or with asystole or PEA at initial contact have the worst prognosis; only 9% of such patients in the Miami study were admitted to the hospital alive, with none discharged. In a later experience, some improvement in outcome was noted, although this was limited to patients in whom the initial bradyarrhythmia recorded was an idioventricular rhythm that responded promptly to chronotropic agents in the field. In a large, prospective, observational in-hospital study of cardiac arrests in children and adults, children had a higher probability of asystole or PEA as the initial documented rhythm, but had a better overall survival rate because they had better outcomes of interventions for these rhythms than adults.[142] Overall survival after PEA appears to be better in recent years,[143] but it is not clear whether this applies to asystole.

Bradyarrhythmias also have adverse prognostic implications after defibrillation from VF in the field. Patients with a heart rate lower than 60 beats/min after defibrillation, regardless of the specific bradyarrhythmic mechanism, had a poor prognosis, with 95% of such patients dying before hospitalization or in the hospital. The outcome in the group of patients in whom VF is the initial rhythm recorded is intermediate between the outcomes associated with sustained VT and with bradyarrhythmia and asystole. Of such patients, 40% were resuscitated successfully and admitted to the hospital alive, and 23% were ultimately discharged alive. Later data indicate improvement in outcome. The proportion of each of the electrophysiologic mechanisms responsible for cardiac arrest varied among the earlier reports, with VF ranging from 65% to more than 90% of the study populations, and bradyarrhythmia and asystole ranging from 10% to 30%. In reports from densely populated metropolitan areas, however, the ratios of tachyarrhythmic to bradyarrhythmic or pulseless activity events were reversed, and outcomes were much worse.[137]

Initial Assessment and Basic Life Support

Activities at initial contact with the unconscious victim include diagnostic maneuvers and basic cardiopulmonary support interventions. The first action must be confirmation that collapse is or is suspected of being a cardiac arrest. A few seconds of evaluation for response to voice, observation for respiratory movements and skin color, and simultaneous palpation of major arteries for the presence or

absence of a pulse yields sufficient information to determine whether a life-threatening incident is in progress. Once a life-threatening event has been suspected or confirmed, contact with an available emergency medical rescue system (911) for out-of-hospital settings or a “code” team in the hospital should be an immediate priority.

The absence of a carotid or femoral pulse detected by a medical professional, particularly if it is confirmed by the absence of an audible heartbeat, is a primary diagnostic criterion. For lay responders, the pulse check is no longer recommended.[121] Skin color may be pale or intensely cyanotic. Absence of respiratory effort or the presence of only agonal respiratory effort in conjunction with an absent pulse is diagnostic of cardiac arrest; however, respiratory effort can persist for 1 minute or longer after onset of the arrest. In contrast, absence of respiratory effort or the presence of severe stridor with persistence of a pulse suggests a primary respiratory arrest that will lead to cardiac arrest in a short time. In the latter circumstance, initial efforts should include exploration of the oropharynx in search for a foreign body and performance of the Heimlich maneuver, particularly if the incident occurs in a setting in which aspiration is likely (e.g., restaurant death or café coronary).

Chest Thump

A blow to the chest (precordial thump, “thumpversion”) may be attempted by a properly trained rescuer. It has been recommended that it be reserved as an advanced life support activity.[139] Its use has been supported on the basis of a prospective study involving 5000 patients. Precordial thumps successfully reverted apparent VF in 5 events, VT in 11, asystole in 2, and undefined cardiovascular collapse in 2 others in which the electrical mechanism was unknown. In no case was conversion of VT to VF observed. Because the latter is the only major concern and electrical activity can be initiated by mechanical stimulation in an asystolic heart, the technique is considered optional for responding to a pulseless cardiac arrest in the absence of monitoring when a defibrillator is not immediately available. It should not be used unmonitored in a patient with a rapid tachycardia without complete loss of consciousness. The thumpversion technique involves one or two blows delivered firmly to the junction of the middle and lower thirds of the sternum from a height of 8 to 10 inches (20 to 25 cm). The effort should be abandoned if a spontaneous pulse does not develop immediately. Another mechanical method, which requires that the patient still be conscious, is so-called cough-induced cardiac compression. It is a conscious act of forceful coughing by the patient that may support forward flow by cyclic increases in intrathoracic pressure during VF or may cause conversion of sustained VT. Available data supporting its successful use are limited; it is not an alternative to conventional techniques.

Basic Life Support—Initial Steps in Cardiopulmonary Resuscitation

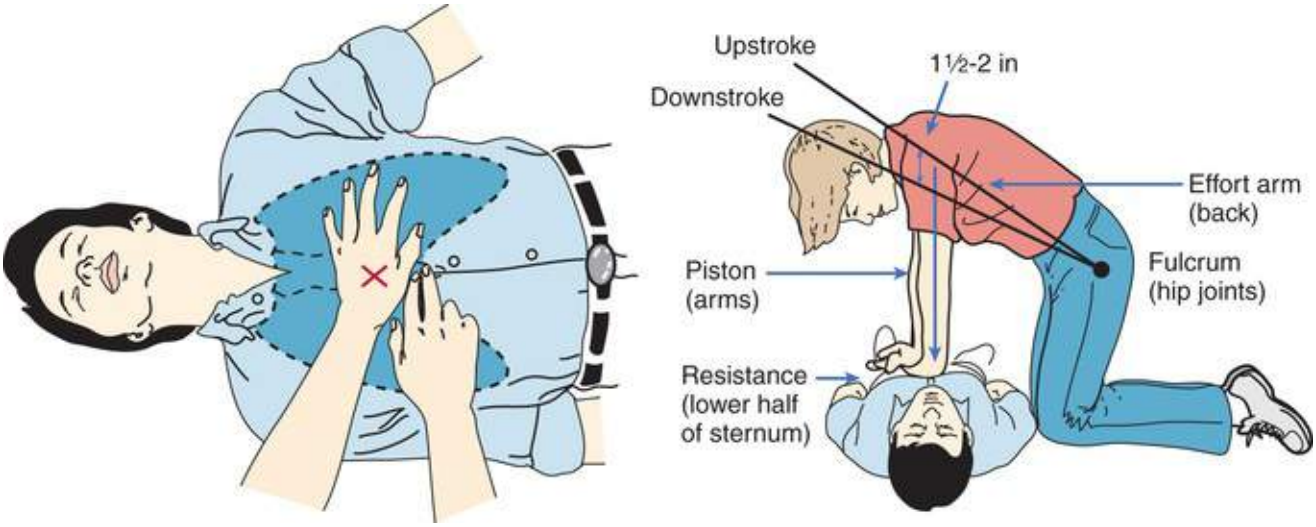
The goal of BLS is to maintain viability of the central nervous system, heart, and other vital organs until definitive return of spontaneous circulation can be achieved. BLS encompasses both the initial responses outlined earlier and their natural flow into establishing perfusion and ventilation. This range of activities can be carried out not only by professional and paraprofessional personnel but also by trained EMTs and laypeople. There should be minimal delay between diagnosis and preparatory effort in the initial response and institution of BLS. The first steps are to verify the environmental safety of the site and confirm that the victim is unresponsive.[144] The responder should call for nearby help, activate an emergency response system (via mobile device, if appropriate), and send for an AED.

These principles have measurable impact for both OHCA and IHCA. The survival rate to discharge for IHCA, considering all causes and mechanisms, was reported to be 33% when CPR was initiated within

the first minute, versus 14% when the time was longer than 1 minute (odds ratio [OR], 3.06).[124] When VF was the initial rhythm, the corresponding figures were 50% and 32%, respectively. In OHCA, if only one witness is present, notification of emergency personnel (calling 911) is the only activity that should precede BLS. The previous sequence of the "ABC" of basic life support—airway, breathing, compression—has been changed to "CAB"—compression, airway, breathing—based on the recognition that compression alone is the better strategy[145] because it minimizes interruptions in perfusion and avoids excessive ventilation.[121]

Circulation

This element of BLS is intended to maintain blood flow (i.e., circulation) until definitive steps can be taken. The rationale is based on the hypothesis that chest compression allows the heart to maintain an externally driven pump function by sequential emptying and filling of its chambers, with competent valves favoring forward direction of flow. In fact, application of this technique has proved successful when it is used as recommended.[121] The palm of one hand is placed over the lower half of the sternum and the heel of the other rests on the dorsum of the lower part of the hand. The sternum is then depressed, with the resuscitator's arms straight at the elbows to provide a less tiring and more forceful fulcrum at the junction of the shoulders and back (**eFig. 42.4**). By use of this technique, sufficient force is applied to depress the sternum at least 2 inches (5 cm). Compressions should be followed by abrupt relaxation, and the cycle is carried out at a rate of about 100 compressions/min.[121]



EFIGURE 42.4 External chest compression. **Left,** Locating the correct hand position on the lower half of the sternum. **Right,** Proper position of the rescuer, with the shoulders directly over the victim's sternum and the elbows locked. (From National Academy of Sciences, National Research Council. Standards and guidelines for cardiopulmonary resuscitation [CPR] and emergency cardiac care [ECC]. JAMA 1986;255:2906.)

Techniques of CPR based on the hypothesis that increased intrathoracic pressure is the prime mover of blood, rather than cardiac compression itself, have been evaluated, and the guidelines for conventional CPR ventilatory techniques were modified in 2005. For single responders to victims from infants (excluding newborns) to adults, and for two-rescuer response to adults, a compression/ventilation ratio of 30 : 2 is now recommended.[121] For two-rescuer CPR in infants and children, the former compression/ventilation ratio of 15 : 2 is retained. A more recent modification intended to encourage more bystander participation in CPR and to allay concerns about mouth-to-mouth ventilation of unknown victims is the "hands-only" (compression-only) technique.[146] This technique is particularly important for

untrained or remotely trained bystanders who are not confident in their ability to perform compression-ventilation sequences. The 2005 changes in CPR recommendations, in which the number of successive shocks and pulse checks during initial responses is reduced (see later, Defibrillation-Cardioversion, and **Chapter 36**), are retained in the 2010 recommendations. This is intended in part to increase the cumulative time of circulatory support during CPR before restoration of a spontaneous pulse.

Concept of Cardiocerebral Resuscitation

Cardiocerebral resuscitation, also referred to as "minimally interrupted cardiac resuscitation," is based on the hypothesis that the primary benefit of CPR is its pumping action rather than the combination of compression and ventilation. It challenges the general guidelines, which assume a benefit of interrupting compression to provide ventilation, and that an initial phase of ventilation before initial defibrillation improves outcomes when response times are longer than 4 or 5 minutes. Cardiocerebral resuscitation emphasizes continuous chest compressions, interrupted primarily for single shocks and evaluation of responses to shocks, and deferring and limiting ventilatory and certain pharmacologic actions. Data from studies in Japan[147] and the United States[148] suggest a neurologically intact survival advantage of the cardiocerebral protocol over conventional CPR based on the 2000 guidelines and 2005 update. For witnessed arrests with documented VF, the study from Japan demonstrated a neurologically intact survival rate advantage of 22% versus 10%. The two recent reports from the United States demonstrated comparable advantages of 39% versus 15% for neurologically intact survival and 28.4% versus 11.9% for survival, respectively. Despite these interesting data, it remains generally agreed that a randomized trial is needed before the minimal interruption concept can replace the current guidelines.

Even though conventional techniques produce measurable carotid artery flow with a record of successful resuscitations, the absence of a pressure gradient across the heart in the presence of an extrathoracic arteriovenous pressure gradient has led to the concept that it is not cardiac compression per se but rather a *pumping action* produced by changes in pressure in the entire thoracic cavity that optimizes systemic blood flow during resuscitation. Experimental work in which the chest is compressed during ventilations rather than between them (simultaneous compression-ventilation) has demonstrated better extrathoracic arterial flow. However, increased carotid artery flow does not necessarily equate with improved cerebral perfusion, and the reduction in coronary blood flow caused by elevated intrathoracic pressure with the use of certain techniques may be too high a price for the improved peripheral flow. In addition, a high thoracoabdominal gradient has been demonstrated during experimental simultaneous compression-ventilation, which could divert flow from the brain in the absence of concomitant abdominal binding. On the basis of these observations, new mechanically assisted techniques, including an active decompression phase (i.e., active compression-decompression), have been evaluated for improved circulation during CPR.[149] More clinical studies are needed before their general clinical application can be established.

Airway

Clearing of the airway is a critical step in preparing for successful resuscitation. This process includes tilting the head backward and lifting the chin, in addition to exploring the airway for foreign bodies, including dentures, and removing them. The Heimlich maneuver should be performed if there is reason to suspect that a foreign body is lodged in the oropharynx. This maneuver entails wrapping the arms around the victim from the back and delivering a sharp thrust to the upper part of the abdomen with a closed fist. If it is not possible for the person in attendance to carry out the maneuver because of insufficient physical

strength, mechanical dislodgment of the foreign body can sometimes be achieved by abdominal thrusts with the unconscious patient in a supine position. The Heimlich maneuver is not entirely benign; ruptured abdominal viscera in the victim have been reported, as has a case in which the rescuer disrupted his own aortic root and died. If there is strong suspicion that respiratory arrest precipitated cardiac arrest, particularly in the presence of a mechanical airway obstruction, a second precordial thump should be delivered after the airway has been cleared.

Breathing

With the head placed properly and the oropharynx clear, mouth-to-mouth resuscitation can be initiated if no specific rescue equipment is available. To a large extent the procedure used to establish ventilation depends on the site at which the cardiac arrest occurs. Various devices are available, including plastic oropharyngeal airways, esophageal obturators, masked Ambu bags, and endotracheal tubes. Intubation is the preferred procedure, but time should not be sacrificed, even in the in-hospital setting, while awaiting an endotracheal tube or a person trained to insert it quickly and properly. Thus, in the in-hospital setting, temporary support with Ambu bag ventilation is the usual method until endotracheal intubation can be carried out, and in the out-of-hospital setting, mouth-to-mouth resuscitation is used while awaiting EMS. The effect of acquired immunodeficiency syndrome and hepatitis B transmission on attitudes about mouth-to-mouth resuscitation by bystanders and even professional personnel in hospitals is an area of concern, but currently available data assessing risk for infection suggest that it is minimal.[121] The impact of this concern on attitudes toward and outcomes of resuscitative efforts has not been evaluated.

Early Defibrillation by First Responders

The time from the onset of cardiac arrest to advanced cardiac life support (ACLS) influences outcome statistics. Both early neurologic status and survival are better in patients defibrillated by first responders than if one awaits the assistance of more highly trained paramedics. The term *first responder* refers to the person on scene providing initial CPR and has emerged from minimally trained EMTs allowed to carry out defibrillation in conjunction with BLS to nonconventional responders, such as trained security guards and police, and subsequently to lay bystanders knowledgeable in CPR with access to AEDs. Because the time to defibrillation plays a central role in determining outcome in cardiac arrest caused by VF, the development and deployment of AEDs in public locations has had impact on outcomes (**see Chapter 41**). This technology is potentially applicable to a number of different strategic models, each with its own benefits and limitations (**Fig. 42.14**; **see eFig. 42.2**). A study from France demonstrated a considerable increase in sports-related deaths when recreational athletes of a wider age range are considered.[110] Because CPR (OR, 3.73; $P < 0.0001$) and cardiac defibrillation (OR, 3.71; $P < 0.0001$) were the strongest independent predictors of survival to hospital discharge (15.7%), survival from SCA in recreational sports settings could be improved significantly by increased public education in CPR responses and availability of public AEDs.

AED DEPLOYMENT STRATEGIES

Deployment	Examples	Rescuers	Advantages	Limitations
Emergency vehicles	• Police cars • Fire engines • Ambulances	• Trained emergency personnel	• Experienced users • Broad deployment • Objectivity	• Deployment time • Arrival delays • Community variations
Public access sites	• Public buildings • Stadiums, malls • Airports • Airliners	• Security personnel • Designated rescuers • Random laypersons	• Population density • Shorter delays • Lay and emergency personnel access	• Low event rates • Inexperienced users • Panic and confusion
Multifamily dwellings	• Apartments • Condominiums • Hotels	• Security personnel • Designated rescuers • Family members	• Familiar locations • Defined personnel • Shorter delays	• Infrequent use • Low event rates • Geographic factors
Single-family dwellings	• Private homes • Apartments • Neighborhood "Heart watch"	• Family members	• Immediate access • Familiar setting	• Acceptance • Victim may be alone • One-time user; panic

FIGURE 42.14 Various deployment strategies for nonconventional responders with access to automated external defibrillators (AEDs). For each example, the type of rescuer and the advantages and limitations of each strategy are provided. It is unlikely that any single strategy will dominate; rather, there will be a cumulative benefit from the additive effect of multiple approaches. (From Myerburg RJ. Sudden cardiac death: exploring the limits of our knowledge. J Cardiovasc Electrophysiol 2001;12:369.)

Among the strategies that have yielded various levels of identifiable survival benefit to date are deployment in police vehicles, airliners and airports, casinos, and more general community-based sites.[150,151] Police AED deployment data have been inconsistent in various studies, possibly because of appropriateness for various types of communities and the specific deployment strategies used, but data suggest that it is beneficial in large metropolitan areas (**eFig. 42.5**). Initial airline data were similarly uncertain, but a more recent report on data from a large airline with a well-organized system has suggested benefit (**eFig. 42.6**). Similar encouraging results have been reported with the deployment of AEDs in the Chicago airport system. The special circumstance of casinos, in which continuous television monitoring alerts security officers to medical problems immediately, has yielded impressive survival rates (**Fig. 42.15**). For more general community sites, defined as true public access, a large study has suggested a twofold benefit.[150] However, there appears to be great variability in efficiency on the basis of expected event rates at different types of community sites, and deployment strategies have been suggested on the basis of projected event rates at various locations.[150,151] Deployment in schools, accompanied by comprehensive response planning, is associated with good outcomes, even with relatively low event rates.[152] A study of the deployment of AEDs in the homes of patients with recent MI who were not candidates for implantable defibrillators did not demonstrate benefit.[153] Because the home is the most common site of cardiac arrest, and survival rates are lower than in public sites, additional strategies for both AEDs and other technologies should be tested. Additional data have also demonstrated limited efficacy of home-based AEDs[13]; further research on effective strategies is needed because most community-based cardiac arrests occur in the home.

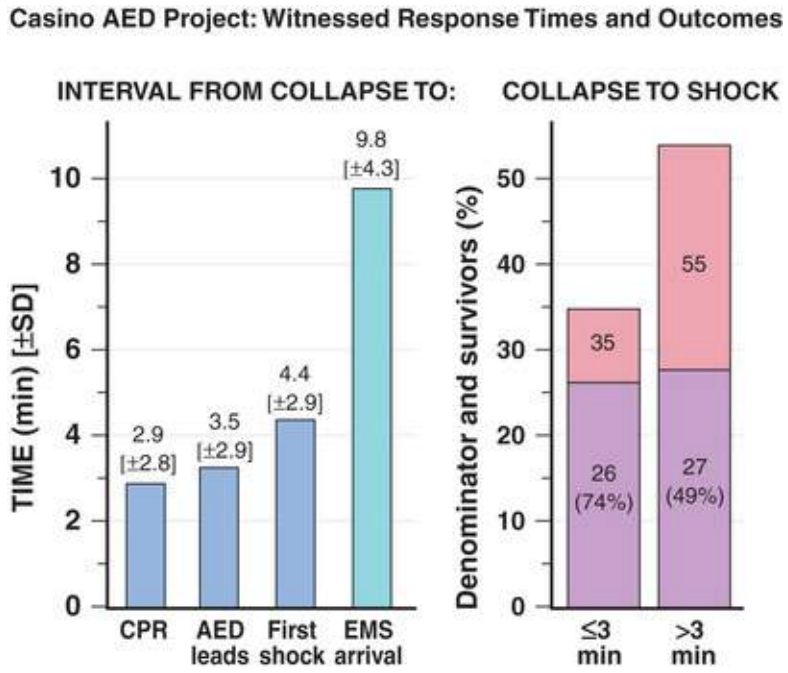
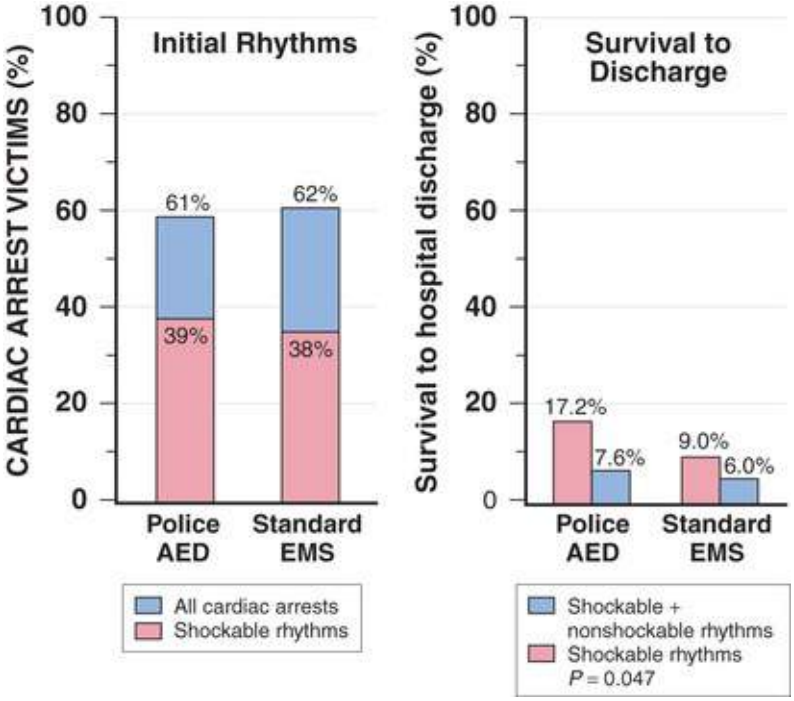
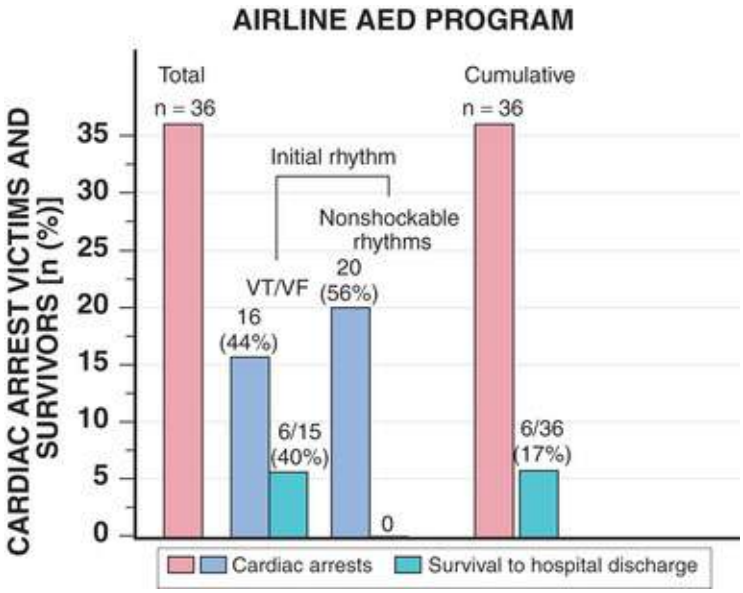


FIGURE 42.15 Results of AED deployment in the controlled environment of casinos. Because the onset of cardiac arrest can frequently be witnessed, short intervals from the onset of collapse to CPR and AED shocks were achieved. Response times were reduced by more than 50% in comparison to the standard EMS. For those found in VT/VF, the survival rate was better than expected from other community-based systems and approached 60% for VT/VF with a witnessed onset. When response time was less than 3 minutes, the survival rate after VT/VF was higher than 70%. (Modified from Valenzuela TD, Roe DJ, Nichol G, et al. Outcomes of rapid defibrillation by security officers after cardiac arrest in casinos. N Engl J Med 2000;343:1206.)



EFIGURE 42.5 Rhythms at initial contact and survival statistics from the Miami–Dade County, Florida, police automated external defibrillator (AED) project. Shockable rhythms were observed in just less than 40% of cardiac arrest victims in both the police AED program and the standard emergency medical services (EMS) historical control data. Those with shockable rhythms had improved survival to hospital discharge, but the improvement was small when both shockable and nonshockable rhythms were included in the data analyzed. (Modified from Myerburg RJ, Fenster J, Velez M, et al. Impact of community-wide police car deployment of automated external defibrillators on out-of-hospital cardiac arrest. Circulation 2002;106:1058.)



EFIGURE 42.6 Data on outcomes after deployment of AEDs by a major airline demonstrated that approximately 44% of the cardiac arrests were associated with a documented ventricular tachycardia/fibrillation (VT/VF) mechanism, and 40% of these victims survived. There were no survivors among the 56% of victims who had nonshockable rhythms. The cumulative survival rate for the program was 17%. (**A,** Modified from Page RL, Joglar JA, Kowal RC, et al. Use of automated external defibrillators by a U.S. airline. N Engl J Med 2000;343:1210.)

As with any medical device,[154] malfunctions of AEDs may occur infrequently because of design or manufacturing defects[155] or failure to adhere to manufacturers' recommendations for replacement of batteries and leads. It is an obligation of those responsible for maintaining AEDs to remain cognizant of FDA safety alerts and recalls and the shelf-life of batteries and leads.

Advanced Cardiac Life Support

This next step in the resuscitative sequence is designed to achieve stable ROSC and hemodynamic stabilization.[121] Implementation of ACLS is not intended to suggest an abrupt cessation of BLS activities, but rather a transition from one level of activity to the next. In the past, ACLS required judgments and technical skills that removed it from the realm of activity of lay bystanders and even EMTs, instead limiting these activities to specifically trained paramedical personnel, nurses, and physicians. With further education of EMTs, most community-based CPR programs now permit them to carry out ACLS activities. However, some studies suggest that the addition of ACLS to an otherwise optimized out-of-hospital response system (i.e., bystander CPR and early defibrillation) does not improve statistics for neurologically intact survival.[156] In this regard, the development and testing of AEDs that have the ability to sense and analyze cardiac electrical activity and to prompt the user to deliver definitive electrical intervention provide a role for rapid defibrillation by less highly trained rescue personnel (i.e., police, ambulance drivers) and even minimally trained lay bystanders.

The general goals of ACLS are to restore cardiac rhythm to hemodynamic effectiveness, to optimize ventilation, and to maintain and support the restored circulation. Thus, during ACLS, the patient's cardiac rhythm is promptly cardioverted or defibrillated as the first priority if appropriate equipment is immediately available. A short period of closed-chest cardiac compression immediately before defibrillation enhances the probability of survival, especially if circulation has been absent for 4 to 5 or more minutes.[137,141] After the initial attempt to restore a hemodynamically effective rhythm, the patient is intubated and oxygenated, if needed, and the heart is paced if bradyarrhythmia or asystole occurs. An intravenous (IV) line is established to deliver medications. After intubation, the goal of ventilation is to

reverse the hypoxemia and not merely to achieve high alveolar oxygen pressure (P_{O_2}). Thus, oxygen rather than room air should be used to ventilate the patient; if possible, arterial P_{O_2} should be monitored. Respiratory support in the hospital by means of an endotracheal tube and Ambu bag—or facemasks in the out-of-hospital setting—is generally used.

Successful ROSC after IHCA is associated with a shorter median duration of resuscitation than in nonsurvivors (12 minutes, interquartile range [IQR] of 6 to 21, versus 20 minutes, IQR of 14 to 30). Nonetheless, hospitals that habitually ran the longest maximum code runs (the median value in the longest quartile was 25 versus 16 minutes) generated a higher likelihood of ROSC and survival to discharge.[157] This observation supports longer attempts at resuscitation in patients without "do-not-resuscitate" instructions and/or futile medical status.

Defibrillation-Cardioversion

Rapid conversion to an effective cardiac electrical mechanism is a key step in successful resuscitation (**Fig. 42.16**). Delay should be minimal, even when conditions for CPR are optimal. When VF or VT that is pulseless and/or accompanied by loss of consciousness is recognized on a monitor or by telemetry, defibrillation should be carried out immediately. An initial shock of 360 J should be delivered by monophasic devices and 120 to 200 J by biphasic devices, with the energy depending on the recommendations for the individual biphasic devices. Energies delivered through AEDs are generally preprogrammed and vary among the devices available. Failure of the initial shock to provide an effective rhythm is a poor prognostic sign. The 2010 updated guidelines[121] recommend that failure of a single adequate shock to restore a pulse should be followed by continued CPR and a second shock delivered after five cycles of CPR. This supersedes the previous strategy of three successive shocks before resuming CPR. The intent is to maximize circulatory time by chest compressions until a pulse has been restored. If cardiac arrest persists, the patient is intubated and IV access achieved. Epinephrine is administered and followed by repeated defibrillation attempts at 360 J (monophasic) or 200 J or higher (biphasic). Epinephrine may be repeated at 3- to 5-minute intervals with a defibrillator shock in between,[121] but studies of the value of high-dose versus standard-dose epinephrine have been inconsistent with regard to short-term added benefit (i.e., ROSC); there is no apparent long-term benefit (i.e., survival to hospital discharge) with higher doses.[158] Vasopressin is an effective alternative to epinephrine.

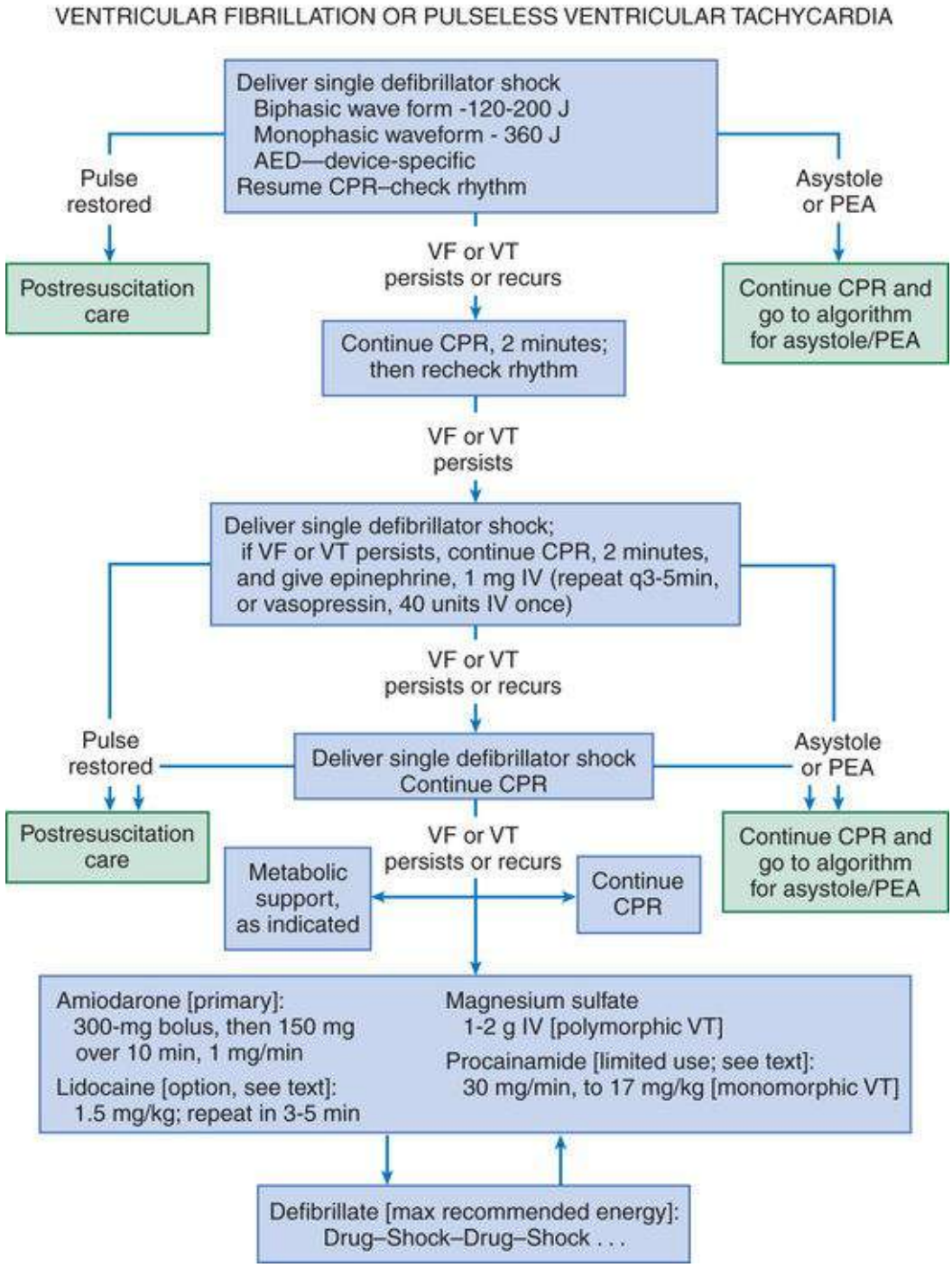


FIGURE 42.16 Advanced cardiac life support for VF and pulseless VT. If initial defibrillation fails, the patient should be intubated and IV access established immediately while CPR is continued. Epinephrine, 1 mg intravenously, should be administered and may be repeated several times with additional defibrillation attempts at 360 J. If conversion is still unsuccessful, epinephrine may be administered again, although it is unlikely that higher doses will provide any further benefit. Sodium bicarbonate should be administered at this time only if the patient is known to be hyperkalemic, and IV antiarrhythmic drugs should be tried (see text). Additional attempts to defibrillate should follow the administration of each drug attempted. Concomitant with all steps, continuation of CPR is paramount. (Modified from 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science. Circulation 2010;122[Suppl 3]:S640.)

Simultaneously, the rescuer should focus on ventilation to correct the chemistry of the blood and render the heart more likely to reestablish a stable rhythm, such as improved oxygenation, reversal of acidosis, and improvement of the underlying electrophysiologic condition. Although adequate oxygenation of the blood is crucial in immediate management of the metabolic acidosis of cardiac arrest, additional correction can be achieved, if necessary, by the IV administration of sodium bicarbonate. Sodium bicarbonate is recommended for circumstances of known or suspected preexisting bicarbonate-responsive

causes of acidosis, certain drug overdoses, and prolonged resuscitation runs.[121] A more general role for bicarbonate during cardiac arrest has been questioned, but in any circumstance, much less sodium bicarbonate than previously recommended is adequate for treatment of acidosis in this setting. Excessive quantities can be deleterious. Although some investigators have questioned the use of sodium bicarbonate because the risk for alkalosis, hypernatremia, and hyperosmolality may outweigh its benefits, patients in the circumstances cited may benefit from the administration of sodium bicarbonate while CPR is performed. Up to 50% of the dose may be repeated every 10 to 15 minutes during the course of CPR. When possible, arterial pH, P_{O_2}, and P_{CO_2} should be monitored during the resuscitation.

Pharmacotherapy

For patients who continue to have persistent or recurrent VT or VF despite direct-current cardioversion after epinephrine, IV administration of antiarrhythmic agents has been recommended to achieve electrical stability of the heart during continued resuscitative efforts (**see Fig. 42.16 and Chapter 36**). Based on a single controlled trial with a survival to hospital admission endpoint, IV amiodarone emerged as the initial treatment of choice.[121] Bolus therapy (150 mg), followed by a maintenance dose during the next 18 hours and for several days if necessary, was recommended, depending on response. A bolus of lidocaine (60 to 100 mg) may be given intravenously and the dose repeated in 2 minutes for patients in whom amiodarone is unsuccessful and possibly for those who have an acute transmural MI as the triggering mechanism for the cardiac arrest. IV procainamide is rarely used in this setting now, but it may be tried for persisting, hemodynamically stable arrhythmias. A recent study, randomizing IV amiodarone (150 mg, followed by a second bolus if necessary) or lidocaine (60 mg) against placebo, showed no difference between either drug or placebo for survival to discharge outcomes or survival with favorable neurologic status.[159] However, survival to hospital admission was significantly better with both active drugs compared to placebo. In addition, survival to discharge was improved with both drugs among the subgroup with bystander-witnessed arrest, although neither active drug was superior to the other.

For patients in whom acute hyperkalemia is the triggering event for resistant VF or for those who have hypocalcemia or are toxic from Ca^{2+} entry–blocking drugs, 10% calcium gluconate may be helpful.[121] Calcium should not be used routinely during resuscitation, even though ionized calcium levels may be low during resuscitation from cardiac arrest. Some resistant forms of polymorphic VT or torsades de pointes, rapid monomorphic VT or ventricular flutter (rate ≥260/min), or resistant VF may respond to IV beta-blocker therapy or IV magnesium sulfate. For patients with acute ventricular arrhythmias or VT storm associated with LQTS, IV magnesium sulfate is often an effective antiarrhythmic, even if it has no effect on QT duration.

Bradyarrhythmic and Asystolic Arrest; Pulseless Electrical Activity

The approach to patients with bradyarrhythmic or asystolic arrest or with PEA differs from the approach to those with a tachyarrhythmic event[121] (**Fig. 42.17**). When this form of cardiac arrest is recognized, effort should focus first on establishing control of cardiorespiratory status (i.e., continue CPR, intubate, and establish IV access), reconfirming the rhythm (in two leads if possible), and then taking action that favors the emergence of a stable spontaneous rhythm or an attempt to pace the heart. Possible reversible causes, particularly for bradyarrhythmia and asystole, should be considered and excluded (or treated) promptly. Such causes include hypovolemia, hypoxia, cardiac tamponade, tension pneumothorax, preexisting acidosis, drug overdose, hypothermia, and hyperkalemia. Epinephrine is commonly used in an attempt to elicit spontaneous electrical activity or to increase the rate of a bradycardia. It has had only

limited success, as has IV isoproterenol infusions in doses of up to 15 to 20 µg/min. In the absence of an IV line, epinephrine, 1 mg (10 mL of a 1 : 10,000 solution) may be given by the intracardiac or intraosseous (IO) route, but there is danger of coronary or myocardial laceration with the former. Endotracheal delivery can be used if neither IV nor IO administration can be achieved. The added value of high-dose epinephrine is unclear,[158] as in the case of resistant VF. Atropine is no longer considered of value for PEA or asystole,[121] although it may be of benefit for other bradyarrhythmic mechanisms. Sodium bicarbonate, 1 mEq/kg, may be tried for known or strongly suspected preexisting hyperkalemia or bicarbonate-responsive acidosis.

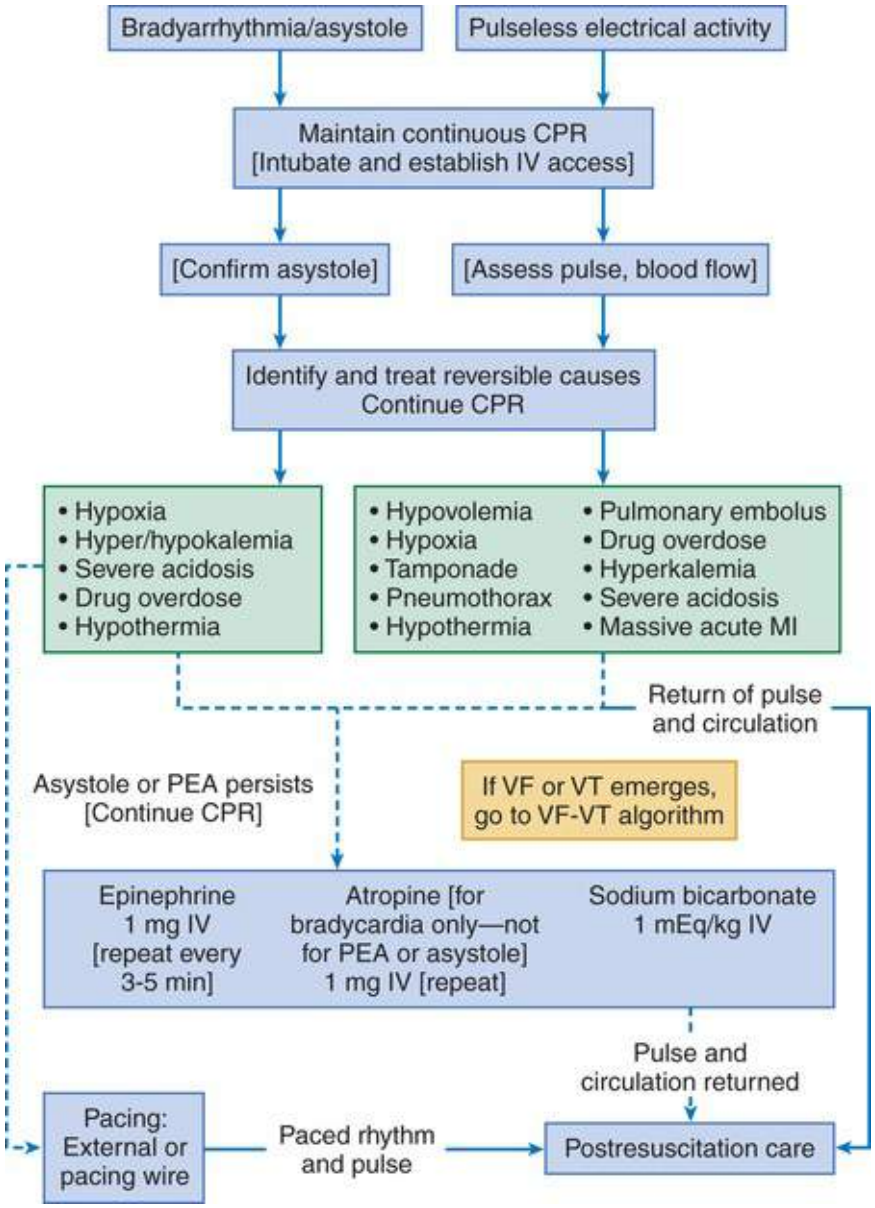


FIGURE 42.17 Advanced cardiac life support for patients with bradyarrhythmic-asystolic arrest and PEA. A patient in any of these states should have CPR continued and be intubated, with IV access established, before pharmacologic treatment. The initial activity is to confirm persisting asystole or attempt to assess blood flow in patients thought to have PEA. An immediate attempt should be made to identify and treat reversible or treatable causes of these forms of cardiac arrest. Epinephrine is generally administered first, and atropine or bicarbonate, or both, may be administered subsequently. An attempt to pace the heart with an external device or an intracardiac pacing catheter is advisable although not usually successful, except for certain reversible bradyarrhythmias. (From 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science. Circulation 2010;122[Suppl 3]:S640.)

Pacing of a bradyarrhythmic or asystolic heart has been limited in the past by the unavailability of

personnel capable of carrying out such procedures at the scene of cardiac arrest. With the development of more effective external pacing systems, the role of pacing and its influence on outcome must now be reevaluated. Unfortunately, all data to date have suggested that asystolic patients continue to have a very poor prognosis despite new techniques.

The published standards for CPR and emergency cardiac care[121] include a series of teaching algorithms to be used as guides to appropriate care. **Figs. 42.16 and 42.17** provide the algorithms for VF and pulseless VT, asystole (or cardiac standstill), and PEA. These general guides are not to be interpreted as inclusive of all possible approaches or contingencies. CPR in pregnant women requires attention to the influence of the gravid uterus on the mechanics of CPR. The pregnant patient should be placed in a left lateral decubitus position with left uterine displacement during CPR to relieve aortocaval compression,[160] and standard defibrillation has no risk for the fetus. Acute antiarrhythmic drug (AAD) therapy during ACLS is generally safe, although long-term amiodarone therapy raises concern for potential fetal organ toxicity.

Stabilization of Cardiac Rhythm after Initial Return of Spontaneous Circulation

If frequent PVCs and runs of nonsustained VT persist after restoration of a sinus mechanism, continuous infusion of an effective AAD is used. IV amiodarone is the preferred agent, but lidocaine is an option for arrhythmias caused by acute ischemic events, and IV procainamide may be considered if the others fail. On occasion, continuous infusion of propranolol or esmolol is used, sometimes in conjunction with magnesium sulfate, especially for recurrent episodes of polymorphic VT or VT storm unresponsive to amiodarone.

Catecholamines are used for cardiac arrest not only in an attempt to achieve better electrical stability (e.g., conversion from fine to coarse VF or increasing the rate of spontaneous contraction during bradyarrhythmias) but also for their inotropic and peripheral vascular effects. Epinephrine is the first choice among the catecholamines for use in cardiac arrest because it increases myocardial contractility, elevates perfusion pressure, may convert electromechanical dissociation to electromechanical coupling, and improves the chances for successful defibrillation. Because of its adverse effects on renal and mesenteric flow, norepinephrine is a less desirable agent despite its inotropic effects. When the chronotropic effect of epinephrine is undesirable, dopamine or dobutamine is preferable to norepinephrine for inotropic effect. Isoproterenol may be used for the treatment of primary or postdefibrillation bradycardia when heart rate control is the primary goal of therapy intended to improve cardiac output. Calcium chloride is sometimes used in patients with PEA that persists after the administration of catecholamines. The efficacy of this intervention is uncertain. Stimulation of alpha adrenoceptors may be important during definitive resuscitative efforts. For example, the alpha adrenoceptor–stimulating effects of epinephrine and higher dosages of dopamine, which elevate aortic diastolic pressure by peripheral vasoconstriction with increased cerebral and myocardial flow, have been reemphasized.

Post–Cardiac Arrest Care and Post–Cardiac Arrest Syndrome

After return of spontaneous or stable assisted circulation, focus shifts to the diagnostic and therapeutic elements of post–cardiac arrest syndrome,[161] a field of pathophysiology and clinical intervention that emerged from the recognition that the various elements of injury following cardiac arrest should be organized into a multidisciplinary continuum. The four elements of post–cardiac arrest syndrome include

brain injury, myocardial dysfunction, systemic ischemia and reperfusion responses, and control of persistent precipitating factors. The therapeutic goal is to achieve and maintain stable electrical, hemodynamic, and CNS status, based on complex algorithms.[161] The specialized and multidisciplinary nature of post–cardiac arrest care have led to the proposal and preliminary data supporting the concept of specialized cardiac centers for post–cardiac arrest patients,[162] analogous to trauma or stroke centers. When transporting the hemodynamically unstable or comatose patient, EMS responders would selectively bypass the nearest hospital in favor of the closest facility having facilities and staff sufficient to manage post–cardiac arrest complexities, assuming an added transport time of no more than 15 minutes. The profile of the patient ready for transport is matched to the capabilities of the institution to which the victim is transported (**Fig. 42.18**).

Level	Patient Status	Hospital Resource Minimums
Level 1 	Failure to restore circulation; ROSC without regaining consciousness ± hemodynamic instability ± acute coronary syndrome; ± recurrent arrhythmias	Local or regional facility capable of providing highest level of neurological, cardiovascular, and intensive care support 24/7 (ICU/CCU/NICU)
Level 2 	ROSC with restoration of consciousness; Persistent hemodynamic instability ± acute coronary syndrome; ± recurrent arrhythmias	Nearest facility capable of providing high level cardiovascular and intensive care support 24/7; cardiac catheterization laboratory capable of providing PCI within 90 minutes
Level 3 	ROSC with restoration of consciousness; hemodynamically stable Evidence of acute coronary syndrome; ± recurrent arrhythmias	Nearest facility with cardiac catheterization laboratory capable of providing PCI within 90 minutes - 24/7
Level 4 	ROSC with restoration of consciousness; hemodynamically stable; no evidence of acute coronary syndrome ± recurrent arrhythmias	Nearest facility capable of providing standard ED, ICU/CCU; cardiac catheterization desirable with PCI capability within 24 hours

FIGURE 42.18 A four-tiered EMS bypass model aligning immediate post–cardiac arrest status and level of required care is illustrated to reflect a priority-based hospital bypass system. The Copenhagen model provides a foundation for this additional level of coordination. Patients can be transported to the closest facility appropriate to the optimal or minimal care requirements. Color-coded symbols link level of patient urgency to recommended hospital resources on community grid maps. *CCU,* Coronary care unit; *ED,* emergency department; *ICU,* intensive care unit; *NICU,* neurologic ICU; *PCI,* percutaneous coronary intervention; *ROSC,* return of spontaneous circulation. (From Myerburg RJ: Initiatives for improving out-of-hospital cardiac arrest outcomes. Circulation 2014; 30:1840. Reproduced with permission of the publisher.)

For successfully resuscitated cardiac arrest victims, whether the event occurred in or out of the hospital, post–cardiac arrest care includes admission to an intensive care unit (ICU) and continuous monitoring for a minimum of 48 to 72 hours. Some elements of post–cardiac arrest syndrome are common to all resuscitated patients, but the prognosis and certain details of management are specific for the clinical setting in which the cardiac arrest occurred. The major management categories include (1) primary cardiac arrest in patients with acute myocardial infarction (AMI); (2) secondary cardiac arrest in patients with AMI; (3) cardiac arrest associated with non–cardiac-related diseases, drug effects, or

electrolyte disorders; and (4) survival after out-of-hospital cardiac arrest.

Cardiac Arrest in Patients with Hemodynamically Stable Acute Myocardial Infarction

Ventricular fibrillation in patients with AMI free of concomitant hemodynamic complications (i.e., primary VF; **see Chapter 59**) is now less common in hospitalized patients compared to the 15% to 20% incidence noted before the availability of cardiac care units (CCUs). The events that do occur are almost always reverted successfully by prompt interventions in properly equipped emergency departments or CCUs. If ventricular arrhythmias persist after successful resuscitation, a lidocaine infusion is used. AAD support is generally discontinued after 24 hours if sustained arrhythmias do not recur (**see Chapter 36**). The occurrence of VF during the early phase of AMI (i.e., first 24 to 48 hours) does not identify long-term risk and is not an indication for long-term AAD or device therapy. Pulseless VT producing the clinical picture of cardiac arrest in AMI is treated similarly; its intermediate- and long-term implications are the same as those of VF, as with polymorphic VT. The implications for sustained hemodynamically stable monomorphic VT in this situation are less clear in the early setting and warrant reevaluation of the patient during the convalescent phase. Cardiac arrest caused by bradyarrhythmias or asystole in acute *inferior* wall MI, in the absence of primary hemodynamic deterioration, is uncommon, and the patient may respond to atropine or pacing. The prognosis is good, with no special long-term care required in most cases. Persistent symptomatic bradyarrhythmias requiring permanent pacemakers rarely occur in such patients. In contrast, bradyarrhythmic cardiac arrest associated with large *anterior* wall MI (and AV or intraventricular block) has a poor prognosis.

Cardiac Arrest in Patients with Hemodynamically Unstable Acute Myocardial Infarction

Cardiac arrest occurring in association with, or as a result of hemodynamic or mechanical dysfunction, during the acute phase of MI has an immediate mortality rate ranging from 59% to 89%, depending on the severity of the hemodynamic abnormalities and size of the MI. Resuscitative efforts usually fail in such patients, and when successful, post–cardiac arrest management is often difficult. When secondary cardiac arrest occurs by the mechanisms of VT or VF in this setting, aggressive postresuscitation hemodynamic or anti-ischemic measures may help achieve rhythm stability. IV amiodarone has emerged as the antiarrhythmic therapy of choice. Lidocaine may also be tried if the mechanism appears to be ischemic but is less likely to be successful in this setting than in primary VF. The success of interventions and prevention of recurrent cardiac arrest are closely related to the success in managing the patient's hemodynamic status. The proportion of cardiac arrests caused by bradyarrhythmias or asystole or by PEA is higher in hemodynamically-unstable patients with AMI. Such patients usually have large MI and major hemodynamic abnormalities and may be acidotic and hypoxemic. Even with aggressive therapy, the prognosis after asystolic arrest in such patients is poor, and they are resuscitated only rarely from PEA. All patients in circulatory failure at the onset of arrest are in a high-risk category, with only a 2% survival rate in hypotensive patients noted in one study.

Cardiac Arrest among in-Hospital Patients with Noncardiac Abnormalities.
These patients fall into two major categories: (1) those with life-limiting diseases, such as malignant

neoplasms, sepsis, organ failure, end-stage pulmonary disease, and advanced CNS disease, and (2) those with acute toxic or proarrhythmic states that are potentially reversible. In the former category, the ratio of tachyarrhythmic to bradyarrhythmic cardiac arrest is low, and the prognosis for survival of cardiac arrest is poor. Although the data may be somewhat skewed by the practice of assigning “do-not-resuscitate” orders to patients with end-stage disease, the data available for attempted resuscitations show a poor outcome. Only 7% of cancer patients, 3% of renal failure patients, and no patients with sepsis or acute CNS disease were successfully resuscitated and discharged from the hospital. For the few successfully resuscitated patients in these categories, postarrest management is dictated by the underlying precipitating factors.

Most antiarrhythmic drugs (**see Chapter 36**), a number of drugs used for noncardiac purposes, and electrolyte disturbances can precipitate potentially lethal arrhythmias and cardiac arrest. Class IA and class III AADs can cause proarrhythmic responses by lengthening the QT interval and generating torsades de pointes (TdP). Class IC drugs rarely cause TdP but result in excess risk for SCD in patients with recent MI, possibly by interacting with transient ischemia. Among other categories of drugs, the phenothiazines, tricyclic antidepressants, lithium, terfenadine interacting with ketoconazole (or other blockers of enzymes in the hepatic cytochrome P-450 system), pentamidine, cocaine, erythromycin, and cardiovascular drugs that are not AADs (e.g., lidoflazine) are recognized causes (see https://www.crediblemeds.org). Beyond these, a broad array of pharmacologic and pathophysiologic-metabolic causes have been reported. Hypokalemia, hypomagnesemia, and perhaps hypocalcemia are the electrolyte disturbances most closely associated with cardiac arrest. Acidosis and hypoxia can potentiate the vulnerability associated with electrolyte disturbances. Proarrhythmic effects are often forewarned by prolongation of the QT interval, although this electrocardiographic change is not always present.

Impending or manifest cardiac arrest caused by TdP is managed by IV magnesium, pacing, or treatment with isoproterenol and removal of the offending agent. When QT prolongation is the basis, magnesium may effectively control the arrhythmia without shortening the QT interval. Class IC drugs may cause a rapid, sinusoidal VT pattern, especially in patients with poor LV function. This VT tends to recur repetitively after cardioversion until the drug has begun to clear, and it has been controlled by propranolol in some patients. When the patient's condition can be stabilized until the offending factor is removed (e.g., proarrhythmic drugs) or corrected (e.g., electrolyte imbalances, hypothermia), the prognosis is excellent. Recognition of TdP and identification of its risk by prolongation of the QT interval in association with the offending agent are helpful in managing these patients (**see Chapter 39**).

Risk Identification by QT Interval Prolongation after Cardiac Arrest

The initial management of survivors of OHCA centers on stabilizing cardiac electrical status, supporting hemodynamics, and providing supportive care for reversal of any organ damage resulting from the cardiac arrest. The in-hospital risk for recurrent cardiac arrest is relatively low, and arrhythmias account for only 10% of in-hospital deaths after successful out-of-hospital resuscitation. However, the mortality rate during the index hospitalization is 50%, indicating that nonarrhythmic mortality dominates the mechanisms of early postresuscitation deaths (30% hemodynamic, 60% CNS related). Antiarrhythmic therapy, usually IV amiodarone, is used in an attempt to prevent recurrent cardiac arrest in patients who demonstrate recurrent arrhythmia during the first 48 hours of postarrest hospitalization. Patients who have preexisting or new AV or intraventricular conduction disturbances are at particularly high risk for recurrent cardiac arrest. The routine use of temporary pacemakers has been evaluated in such patients but has not been found to be helpful for prevention of early recurrent cardiac arrest. Invasive techniques for hemodynamic

monitoring are used in patients whose condition is unstable but are not used routinely in those whose condition is stable on admission.

Anoxic encephalopathy is a strong predictor of in-hospital death or death within 6 months after discharge. The induction of therapeutic hypothermia to reduce metabolic demands and cerebral edema[126,127] should be applied promptly to a postarrest survivor who remains unconscious on hospital admission, providing a measurable survival benefit. A randomized study of prehospital infusion (IV cold saline) hypothermia demonstrated a small reduction in ROSC and no benefit for survival to hospital discharge.[163] The initial temperature target was 32°C to 34°C (89.6°F to 93.2°F), but subsequent data suggest that a target of 36°C (96.8°F) is equally effective and easier to achieve.[164] The benefit may derive from prevention of hyperthermia.

During the later convalescent period, continued attention to CNS status, including physical rehabilitation, is of primary importance for an optimal outcome. Respiratory support by conventional methods is used as necessary. Management of other organ system injury (e.g., renal, hepatic), as well as early recognition and treatment of infectious complications, also contributes to ultimate survival.

Long-Term Management of Survivors of Out-of-Hospital Cardiac Arrest

When a survivor of OHCA has awakened and achieved electrical and hemodynamic stability, usually within a few days if it is to occur at all, decisions must be made about the nature and extent of the workup required to establish a long-term management strategy. The goals of the workup are to identify the specific causative and triggering factors of the cardiac arrest, to clarify the functional status of the patient's cardiovascular system, and to establish long-term therapeutic strategies. Patients who have limited return of CNS function usually do not undergo extensive workups, and patients whose cardiac arrest was triggered by an transmural AMI have workups similar to those for other AMI patients (**see Chapter 59**).

Survivors of OHCA not associated with AMI who have good return of neurologic function appear to have a long-term survival probability commensurate with their age, sex, and extent of disease when they are treated according to existing guidelines.[165-167] These patients should undergo diagnostic workups to define the cause of the cardiac arrest and to tailor long-term therapy, the latter targeted to the underlying disease and strategies for prevention of recurrent cardiac arrest or SCD. The workup includes cardiac catheterization with coronary angiography if coronary atherosclerosis is known or considered to be the possible cause of the event, evaluation of the functional significance of coronary lesions by stress imaging techniques if indicated, determination of functional and hemodynamic status, and assessment of whether the life-threatening arrhythmic event was caused by a transient risk associated with AMI or there is persisting risk based on clinical characteristics.

General Care

The general management of survivors of cardiac arrest is determined by the specific cause and the underlying pathophysiologic process. For patients with ischemic heart disease (**see Chapters 60 and 61**), interventions to prevent myocardial ischemia, optimization of therapy for LV function, and attention to general medical status are all addressed. Although limited data suggest that revascularization procedures may improve the recurrence rate and total mortality rates after survival from OHCA, no properly controlled prospective studies have validated this impression for bypass surgery or percutaneous interventions. The indications for revascularization after cardiac arrest are limited to those who have a

generally accepted indication for angioplasty or surgery, including a documented ischemic mechanism of the cardiac arrest.

Although no data from placebo-controlled trials are available to define a benefit of various anti-ischemic strategies (including beta blockers or other medical therapy) for long-term management after OHCA, medical, catheter interventional, or surgical anti-ischemic therapy, rather than AAD therapy, is generally considered the primary approach to long-term management of the subgroup of prehospital cardiac arrest survivors in whom transient myocardial ischemia was the inciting factor. Moreover, in an uncontrolled observation comparing cardiac arrest survivors who had ever received beta blockers after the index event with those who had not, a significant improvement in long-term outcome with beta-blocker therapy was noted. Further evaluation of the specific role of revascularization procedures and anti-ischemic medical therapy after OHCA is needed.

Whether the various pharmacologic strategies (e.g., ACE inhibitors, carvedilol and other beta-adrenergic blocking agents, spironolactone) that have been shown to provide a clinical and mortality benefit in patients with LV dysfunction provide a specific SCD benefit separate from a total mortality benefit remains uncertain.

Prevention of Cardiac Arrest and Sudden Cardiac Death

Prevention of SCA can be classified into five clinical subgroup categories: (1) prevention of recurrent events in survivors of cardiac arrest (secondary prevention) (**Table 42.7**); (2) prevention of an initial event in patients at high risk because of advanced heart disease with low ejection fraction and other markers of risk (primary prevention) (**Table 42.8**); (3) primary prevention in patients with less advanced common or uncommon structural heart diseases; (4) primary prevention in patients with structurally normal hearts, subtle or minor structural abnormalities, or genetically based molecular disorders (**Table 42.9**); and (5) primary prevention in the general population. The last category includes the substantial proportion of SCDs that occur as a first cardiac event in victims previously free of known disease (see earlier).

TABLE 42.7

Secondary Prevention Implantable Cardioverter-Defibrillator Trials

TRIAL (FOLLOW-UP ANALYSIS), YEAR PUBLISHED	STUDY GROUP, DEFINED ENTRY CRITERIA	TIME FROM DIAGNOSIS OF QUALIFYING CONDITION TO RANDOMIZATION	EJECTION FRACTION, ENROLLED PATIENTS	ALL-CAUSE MORTALITY		BENEFIT	
				Control	ICD	Rel RR	Abs RR
AVID (2-yr analysis), 1997	VF, VT with syncope, VT with EF ≤40%	Entry criterion: undefined Actual: not reported EF: 3 days after qualifying event (median)	32% (SD, ±13%)	25%	18%	−27%	−7%
CIDS (2-yr analysis), 2000	VF, out-of-hospital cardiac arrest because of VF or VT, VT with syncope, VT with symptoms and EF ≤35%, unmonitored syncope with subsequent spontaneous or induced VT	Entry criterion: undefined Actual: time from qualifying event to randomization not reported; median time from randomization to ICD of 7 days (>90% in ≤21 days) EF: not reported	34% (SD, ±14%)	21%	15%	−30%	−6%
CASH (9-year analysis) 2000	VF, VT	Entry criteria: not defined Actual: not reported EF: not reported	46% (SD, ±18%)	44%	36%	−23%	−8%

Abs RR, Absolute risk reduction; *EF,* ejection fraction; *Rel RR,* relative risk reduction; *SD,* standard deviation; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia.

From Myerburg RJ, Reddy V, Castellanos A. Indications for implantable cardioverter-defibrillators based on evidence and judgment. J Am Coll Cardiol 2009;54:747.

TABLE 42.8

Primary Prevention Implantable Cardioverter-Defibrillator Trials

TRIAL (FOLLOW-UP ANALYSIS), YEAR PUBLISHED	STUDY GROUP, DEFINED ENTRY CRITERIA	TIME FROM DIAGNOSIS OF QUALIFYING CONDITION TO RANDOMIZATION	EJECTION FRACTION, ENROLLED PATIENTS	ALL-CAUSE MORTALITY		BENEFIT	
				Control	ICD	Rel RR	Abs RR
MADIT (2-yr analysis), 1996	Prior MI, EF ≤35%, inducible VT, failed IV PA	Entry criterion: ≥3 wk Actual: 75% ≥6 mo Qualifying EF: interval not reported	26% (SD, ±7%)	32%	13%	−59%	19%
CABG Patch (2-yr analysis), 1997	Coronary bypass surgery, EF <36%, SAECG (+)	Diagnosis of CAD: interval not reported Qualifying EF: interval not reported SAECG: day of randomization	27% (SD, ±6%)	18%	18%	N/A	N/A
MUSTT (5-yr analysis), 1999	CAD (prior MI ≈95%), EF ≤40%, N-S VT, inducible VT	Qualifying N-S VT: ≥4 days from MI Time from MI: 17% ≤1 mo 50% ≥3 yr Qualifying EF: interval not reported	30% (21%, 35%) [median (25th, 75th percentile)]	55%	24%	−58%	−31%
				[EP guided arm: AAD vs. ICD at 60 mo]			
MADIT II (2-yr analysis), 2002	Prior MI (>1 mo), EF ≤30%	Entry criteria: ≥1 mo Actual: 88% ≥6 mo Qualifying EF: interval not reported	23% (SD, ±5%)	22%	16%	−28%	−6%
DEFINITE (2½-yr analysis), 2004	Nonischemic CM, Hx HF, EF ≤35%, ≥10 PVCs/hr or N-S VT	Heart failure onset (mean): Controls = 3.27 yr ICD group = 2.39 yr	21% (range, 7%-35%)	14%	8%	−44%	−6%
DINAMIT (2½-yr analysis), 2004	Recent MI (6-40 days), EF ≤35%, abnormal HRV or mean 24-hr heart rate >80/min	Entry criteria: 6-40 days Actual: mean = 18 days	28% (SD, ±5%)	17%	19%	N/A	N/A
SCD-HeFT (5-yr analysis), 2005	Class II-III CHF, EF ≤35%	Entry criteria: interval not reported Qualifying EF: interval not reported	25% (20%, 30%) [median (25th, 75th percentile)]	36%	29%	−23%	−7%

AAD, Antiarrhythmic drug; *Abs RR,* absolute risk reduction; *CAD,* coronary artery disease; *CHF,* congestive heart failure; *CM,* cardiomyopathy; *EF,* ejection fraction; *EP,* electrophysiologically; *HRV,* heart rate variability; *Hx HF,* history of heart failure; *IV PA,* intravenous procainamide; *MI,* myocardial infarction; *N-S,* nonsustained; *Rel RR,* relative risk reduction; *PVCs,* premature ventricular complexes; *SAECG* (+), positive signal-averaged electrocardiography.

From Myerburg RJ, Reddy V, Castellanos A: Indications for implantable cardioverter-defibrillators based on evidence and judgment. J Am Coll Cardiol 54:747, 2009.

TABLE 42.9

Indications for Implantable Cardioverter-Defibrillators in Genetic Disorders Associated with Risk for Sudden Cardiac Death

DIAGNOSIS	ICD INDICATION	PRIMARY SOURCE OF DATA	RISK INDICATORS	GUIDELINES	
				Classification	Evidence
HCM	Secondary SCA protection	Registries, cohorts	Previous SCA, pulseless VT	Class I	Level B
			Sustained VT, unexplained syncope	Class IIa	Level C
	Primary SCA protection	Registries, cohorts	LV thickness >30 mm, high LV outflow gradient, family history of SCD, N-S VT, blunted blood pressure response to exercise	Class IIa	Level C
ARVD/RVCM	Secondary SCA protection	Registry, case series	Previous SCA, sustained VT	Class I	Level B, C
			Unexplained syncope	Class IIa	Level C
	Primary SCA protection	Registry, case series	Induced VT, ambient N-S VT, extensive disease	Class IIa	Level C
Congenital LQT	Secondary SCA protection	Registry, cohorts	Previous SCA, symptomatic VT	Class I	Level B
	Primary SCA protection	Registry, cohorts	VT or syncope while taking a beta blocker, QTc >500 msec, family history of premature SCA (?)	Class IIa, IIb	Level B
Familial SQT	Secondary SCA protection	Small case series	Previous SCA, "idiopathic" VF	Class I	Level C
	Primary SCA protection	Small case series	Unknown; family history of SCD (?)	Class IIb, III	Level C
Brugada syndrome	Secondary SCA protection	Case cohorts	Previous SCA, pulseless VT	Class I	Level B
	Primary SCA protection	Case cohorts	Symptomatic VT, unexplained syncope, family history of premature SCA with type I electrocardiographic pattern	Class IIa	Level C
CPVT/F	Secondary SCA protection	Small case series	Previous SCA, pulseless VT	Class I	Level C
	Primary SCA protection	Small case series	Syncope or VT while taking beta blockers, family history of premature SCA (?)	Class IIa	Level C

ARVD/RVCM, Arrhythmogenic right ventricular dysplasia/cardiomyopathy; *CPVT/F,* catecholaminergic polymorphic ventricular tachycardia/"idiopathic" ventricular fibrillation; *HCM,* hypertrophic cardiomyopathy; *LQT,* long-QT syndrome; *LV,* left ventricular; *N-S,* nonsustained; *PVT,* polymorphic ventricular tachycardia; *SCA,* sudden cardiac arrest; *SQT,* short-QT syndrome; *VA,* ventricular arrhythmia; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia; (?), uncertain.

Guideline classifications and levels of evidence are derived from an amalgamation of narrative and tabular statements in two recent guidelines documents,[165,166] with variations in the documents adjudicated by the authors. Definitions are the standard usages provided in guideline documents.

From Myerburg RJ, Reddy V, Castellanos A. Indications for implantable cardioverter-defibrillators based on evidence and judgment. J Am Coll Cardiol 2009;54:747-63.

Four antiarrhythmic strategies, which are not mutually exclusive, can be considered for patients at high risk for cardiac arrest: implantable defibrillators, antiarrhythmic drugs, catheter ablation, and antiarrhythmic surgery. The mainstay of therapy for the highest-risk patients is the implantable defibrillator. The role of the other options for secondary prevention of subsequent SCD, as opposed to adjunctive therapy, has not been established. In addition to these specific antiarrhythmic strategies, therapies for other medical and cardiovascular conditions are integral to managing patients at risk for SCD.

The choice of a therapy, or combinations of therapies, is based on estimation of risk determined by evaluation of the individual patient by various risk-profiling techniques, coupled with available efficacy and safety data.

Methods to Estimate Risk for Sudden Cardiac Death

General Medical and Cardiovascular Risk Markers

The presence and severity of acquired medical disorders (e.g., coronary atherosclerosis and associated myocardial ischemia or MRI-defined scar patterns, LV dysfunction and ventricular volume, heart failure) and general medical conditions (e.g., hypertension, diabetes, dyslipidemias, chronic renal failure,

cigarette smoking) are integral to estimation of risk for SCD. Although lacking the specificity of individual SCD risk prediction, they provide general indicators of risk and data supporting the benefit of therapies (e.g., beta blockers, ACE inhibitors and ARBs, statins) in appropriate subgroups of patients. In a recent report a series of easily identified markers was used to generate a risk score for SCD among participants in two long-term population studies without a history of cardiovascular disease.[168] The model demonstrated large, nonlinear gradients of risk, with the major impact in the highest one or two deciles. This type of model moves in the right direction for individual risk prediction but is limited by its effect sizes: a 5% SCD risk over 10 years in the highest decile in a population with a mean age of 54 years and 11% risk in those with a mean age of 72 years. This magnitude of risk is not sufficient to justify certain interventions, and further risk stratification is needed to identify even higher-risk subgroups at sufficient risk to merit advanced therapies.

In patients with known or suspected coronary heart disease or nonischemic cardiomyopathy, other noninvasive markers of risk are being explored, including measures reflecting autonomic function, QT interval stability, and genetic influences on risk for SCD (see earlier, Risk Factors for Sudden Cardiac Death). The potential importance of proper timing and combining of risk markers has been explored.[2] One study suggested greater risk predictive power for post-MI adverse events when markers were evaluated after 8 weeks, versus closer to the index event.[169] Another study of a cohort of 231 patients with acute MI and an initial EF less than 35% reported that the distribution of EFs on echocardiograms at 90 days of follow-up remained at 35% or less in 43%, increased to 36% to 49% in 31%, and increased to 50% or more in 26% of patients.[170] How this impacts future SCD risk remains to be determined. In another study, optimized medical therapy at the time of an AMI was associated with a dramatically reduced risk for SCD during a 2.9-year mean follow-up (optimized treatment, 1.2%, and annual incidence, 0.4%; compared with nonoptimized treatment, 3.6%, and annual incidence, 1.4%; $P < 0.01$), with the largest impact provided by PCI during the acute event.[171]

Ambulatory Monitoring

Ambulatory monitoring remains useful for profiling the risk for development of life-threatening sustained arrhythmias in individuals with certain forms of structural or electrophysiologic disease who are considered to be at high risk (**see Chapter 35**). Technological advances facilitate very-long-term monitoring and allow identification of episodic arrhythmias as causes of relevant symptoms, such as near-syncope and syncope. In addition to the common disorders associated with SCA, loop recorders are useful in disorders such as HCM, LQTS, and RV dysplasia and in patients with dilated cardiomyopathy or heart failure.

Programmed Electrical Stimulation for Risk Profiling

Despite a large but somewhat conflicting database on the role of electrophysiologic testing (EPT) for risk profiling, particularly in patients with advanced heart disease, its use is currently more limited than in the past. In primary prevention trials such as MADIT and MUSTT, programmed electrical stimulation studies were used to profile risk and suggested large benefits.[72] MADIT II, which enrolled patients with lower EF than in MADIT or MUSTT and did not use programmed stimulation or other arrhythmia markers, demonstrated a survival benefit of ICD therapy without the need for incorporating EPT results in the treatment decision. The question of whether EPT is generally useful has yet to be fully resolved, although it appears to have a role in select patients and clinical circumstances. Of interest, a follow-up study of patients in MADIT II suggested inducibility was associated with a higher incidence of VT and

noninducibility with a higher incidence of VF.[172]

The secondary prevention trials of cardiac arrest survivors did not seek to determine whether routine EPT offered predictive value.[72] EPT is not a necessary component of the evaluation unless there is no structural heart disease or unless a supraventricular tachycardia is suspected as the initiating rhythm for cardiac arrest. In the latter patients, treatment targeting the supraventricular tachycardia should be pursued rather than ICD therapy. For the evaluation of precipitating ventricular arrhythmias, most previous studies had demonstrated limitations because an average of less than 50% of cardiac arrest survivors had inducible ventricular arrhythmias. Under conditions in which a potentially reversible trigger for cardiac arrest can be identified, and perhaps in some cardiac arrest survivors in whom transient ischemia was the initiating mechanism and EF is normal or near-normal, there might be a continuing limited role for EPT as a guide to therapy.

For patients without prior cardiac arrest who have symptomatic arrhythmias or who are considered to be at potentially high risk, programmed stimulation is still used, although to a more limited extent. Inducibility of sustained or hemodynamically unstable monomorphic VT, initiated with an appropriate protocol, is considered positive and predictive. However, the implications of induced nonsustained or polymorphic forms of VT or VF are more controversial. Although it has been suggested that induction of nonsustained ventricular rhythms may indicate risk, it is generally considered nonspecific in the absence of structural heart disease or when an aggressive protocol is used. The reliability of noninducibility to predict absence of risk is also questioned.[172] A recent meta-analysis demonstrated that the inducibility of even polymorphic VT and VF indicates risk in patients with nonischemic dilated cardiomyopathies.[173]

Strategies to Reduce Risk for Sudden Cardiac Death

Antiarrhythmic Drugs

Historically, the earliest approach to management of risk for out-of-hospital cardiac arrest and VT with hemodynamic compromise was the use of membrane-active AADs. This approach was based initially on the assumption that a high frequency of ambient ventricular arrhythmias constituted a triggering mechanism for potentially lethal arrhythmias, and that their suppression by AADs was protective. It was also assumed that electrophysiologic instability of the myocardium, likely associated with regional disease changes in refractory periods and conduction velocities, predisposed to potentially lethal arrhythmias and could be modified by AADs. Suppression of inducibility of VT or VF during programmed electrical stimulation studies likely reflected this effect as well. Suppression of ambient arrhythmias was demonstrated by the empiric use of amiodarone, beta-adrenergic blocking agents, or membrane-active AADs, but scientifically valid demonstration of a survival benefit was lacking. The discrepancy between ambient arrhythmia suppression and survival benefit was clarified by the results of CAST, which showed that certain class I AADs increased mortality despite suppression of ambient ventricular ectopy. In contrast, beta-blocker therapy might have some benefit in such patients, and amiodarone might also be effective for some,[72] although it did not perform better than the control group in the heart failure patients studied in SCD-HeFT (Sudden Cardiac Death–Heart Failure Trial). A subgroup analysis of patients in AVID suggested that cardiac arrest survivors with EF greater than 35% had identical outcomes with ICD and amiodarone, but there was no untreated control group to determine if both were beneficial versus ineffective. In summary, ambient arrhythmia suppression and empiric AAD therapy enjoyed a short period of popularity as a strategy for reduction of risk in VT/VF survivors and in high-risk primary prevention candidates, but in time yielded to the benefit of AADs for arrhythmia symptom control, in the presence or absence of ICD.

Therapy Guided by Programmed Electrical Stimulation

The use of programmed electrical stimulation to identify benefit on the basis of suppression of inducibility by an AAD gained popularity for evaluation of long-term therapy in OHCA survivors. It had evolved as the preferred method of management despite concerns about the sensitivity and specificity of the various pacing protocols and the extent to which myocardial status at the time of the programmed electrical stimulation study reflects that present at the clinical cardiac arrest. Nonetheless, as mentioned, most studies have demonstrated limitations based on observations that a relatively small fraction of cardiac arrest survivors (an average of <50% on the basis of multiple studies) had inducible arrhythmias.

Drug suppression of inducibility of sustained ventricular arrhythmias during EPT as an endpoint for secondary prevention of SCD or primary prevention in high-risk post-MI patients has yielded to the benefits of ICD therapy in most subgroups, with a few exceptions in the primary prevention categories.[174]

Surgical Intervention Strategies

The previously popular antiarrhythmic surgical techniques now have limited applications. Intraoperative map-guided cryoablation may be used for patients who have inducible, hemodynamically stable, sustained monomorphic VT during EPT and ventricular and coronary artery anatomy amenable to catheter ablation. However, it has minimal applicability to OHCA survivors because the type of arrhythmia favoring this surgical approach is infrequently observed in cardiac arrest survivors. It can be used as adjunctive therapy for ICD recipients whose arrhythmia burden requires frequent shocks.

Catheter Ablation Therapy

The use of catheter ablation techniques to prevent ventricular tachyarrhythmias has been most successful for benign focal tachycardias that originate in the right ventricle or left side of the interventricular septum (**see Chapter 36**) and for some reentrant VTs. With rare exceptions, catheter ablation techniques are not used for the treatment of higher-risk ventricular tachyarrhythmias or for definitive therapy in patients at risk for progression of the arrhythmic substrate. For VT caused by bundle branch reentrant mechanisms, which occur in cardiomyopathies as well as in other structural cardiac disorders, ablation of the right bundle branch to interrupt the reentrant cycle has been successful. However, this has limited applicability to many patients with structural heart disease who are at risk for SCD or those who have survived a cardiac arrest. Nonetheless, catheter ablation is an appropriate adjunctive treatment strategy for patients with ICD who are having multiple tachyarrhythmic events. Catheter-based substrate modification or ablation has been demonstrated to be useful in ICD recipients receiving multiple therapies,[175] and it performed somewhat better than escalation of antiarrhythmic therapy in another study.[176] Presently, this benefit is limited to reducing the number of patients receiving ICD therapies; further studies are needed to determine whether it has an expanded role for survival.

Implantable Defibrillators

Development of the ICD added a new dimension to the management of patients at high risk for cardiac arrest (**see Chapter 41**). After the initial reports of small case series of very-high-risk patients in the early 1980s, a number of observational studies confirmed that ICDs can achieve rates of sudden death consistently less than 5% at 1 year and total death rates in the 10% to 20% range in populations at high risk for mortality, as predicted by mortality surrogates such as historical controls or time to the first delivered appropriate therapy.[72] However, determination of the mortality benefit of ICDs remained uncertain and was debated (**Fig. 42.18**). More than 16 years elapsed between the first clinical use of an

implanted defibrillator and publication of the first major randomized clinical trial comparing implantable defibrillator therapy with AAD therapy.[72] During that period, reports had documented the ability of ICDs to revert potentially fatal arrhythmias but could not identify a valid relative or absolute mortality benefit because of confounding factors, such as competing risks for sudden and nonsudden death and determination of whether appropriate shocks represented the interruption of an event that would have been fatal.

MADIT (Multicenter Automatic Defibrillator Implantation Trial) provided the first randomized trial data on the relative benefit of defibrillators over AAD therapy (largely amiodarone) for primary prevention of SCD in a high-risk population. The outcome demonstrated a 59% reduction in the relative risk for total mortality (54% cumulative) and a 19% reduction in the absolute risk of dying at 2 years of follow-up. It was followed over less than 10 years by a series of randomized trial reports evaluating ICD therapy for primary and secondary prevention of SCD in patients with previous MI, previous cardiac arrest, and heart failure.

Although these studies documented the ability of ICDs to revert potentially fatal arrhythmias and showed a relative benefit over amiodarone in some groups of patients, the absence of placebo-controlled trials still prevents quantitation of the true magnitude of any mortality benefit because of the inability of positive-controlled trials to identify the absolute benefit of an intervention. Despite these limitations, an ICD is now the preferred therapy for survivors of cardiac arrest at risk for recurrences and for primary prevention in patients in a number of high-risk categories. Major questions remain and include the relative benefit of amiodarone versus ICDs in lower-risk subgroups of survivors of OHCA and the role of beta blockers, catheter-based and surgical anti-ischemic therapy, and medical therapy as definitive approaches.

Application of Therapeutic Strategies to Specific Groups of Patients

Secondary Prevention of SCD after Survival from Cardiac Arrest

As populations of OHCA survivors began to accumulate from community-based emergency rescue activities, the development of therapeutic strategies intended to improve long-term survival emerged as a mandate for clinical investigators. The problem that affects all long-term strategies for cardiac arrest survivors, however, is the lack of a reliable concurrent natural history denominator against which to compare the effects of interventions, because of ethical concerns about withholding therapy in a placebo-controlled study model for patients at high risk of dying, in conjunction with the confounding influence of specific cardiovascular therapies that may also improve survival. Early approaches to long-term therapy centered on the use of AADs, largely guided by EPT results or the empiric use of AADs, particularly amiodarone. Various observational and positive-controlled studies had suggested that suppression of inducible ventricular arrhythmias yielded a better outcome than did failure of suppression, and that amiodarone was better than class I AADs. This approach is no longer widely used.

The first adequately powered secondary prevention trial of ICDs versus AADs was published in 1997. This study, the AVID Trial, demonstrated a 27% reduction in the relative risk for total mortality at 2 years of follow-up, with an absolute risk reduction of 7% (**Fig. 42.19**).[72] It was followed shortly thereafter by reports of two other studies, CIDS (Canadian Implantable Defibrillator Study) and CASH (Cardiac Arrest Study Hamburg), both limited by their enrollment numbers but suggesting trends toward similar benefits (**see Table 42.7**). A meta-analysis of these data confirmed the benefit of ICDs for secondary

prevention,[177] although only AVID demonstrated a statistically significant survival benefit of an ICD over AAD therapy, usually amiodarone. A subgroup analysis of AVID has also suggested that ICDs had no advantage over AADs for VT/VF survivors with EF greater than 35%. Because it is a retrospective analysis and underpowered, the observation calls for confirmation. Since a placebo-controlled trial cannot be done on ethical grounds, this would require a rigidly designed and executed postimplant surveillance study. Currently, despite these limitations, ICDs have emerged as the preferred therapy for survivors of OHCA or hemodynamically significant VT, regardless of EF, in the absence of identifiable and correctable transient causes of cardiac arrest.

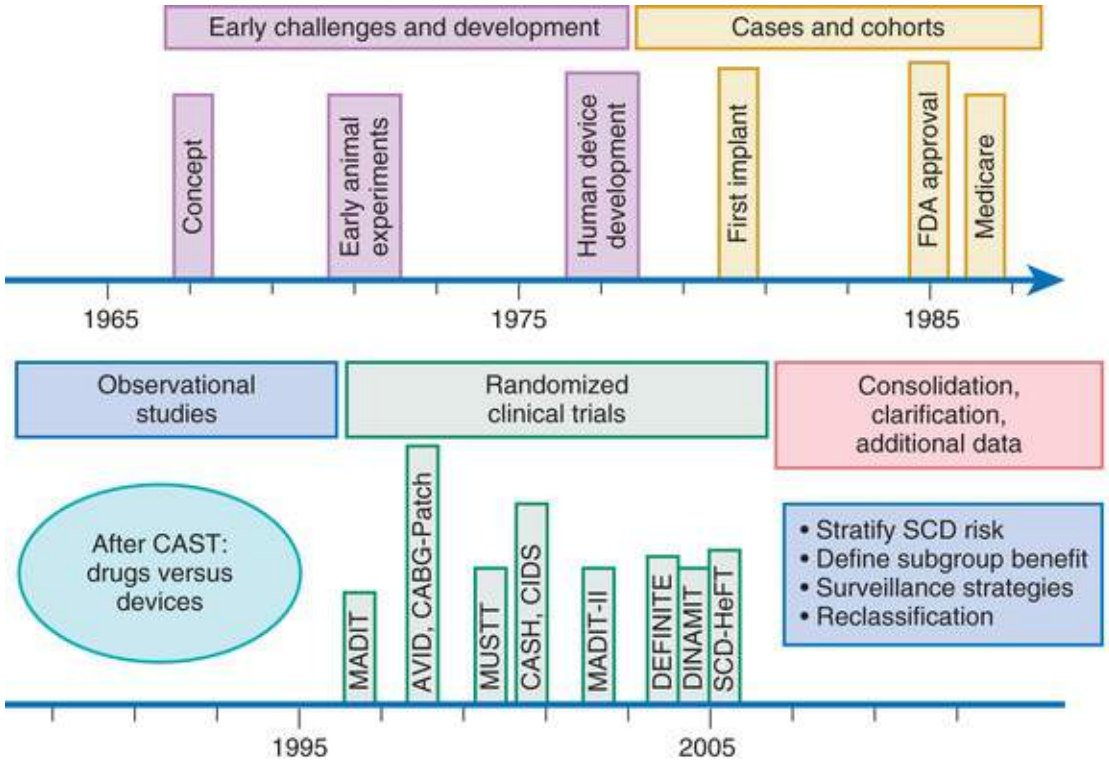


FIGURE 42.19 The concept of an implantable cardioverter-defibrillator (ICD) originated in the late 1960s, and development of the technology and proof of concept leading to the first clinical implant extended to 1980. From 1980 until late 1996, data supporting the benefit of ICDs were largely observational or based on small high-risk cohorts or case-control studies. All the major trials for both primary and secondary indications were published during an interval of 10 years between late 1996 and early 2005. Additional studies since then have aided in interpretation of the outcomes from the clinical trials, but there remains a need for consolidation and clarification and for additional data to better define the efficiency of therapy and targeted selection of individual candidates who have a high likelihood of benefit. (Modified from Myerburg RJ, Reddy V, Castellanos A. Indications for implantable cardioverter-defibrillators based on evidence and judgment. J Am Clin Cardiol 2009;54:747.).

Primary Prevention of SCD in Patients with Advanced Heart Disease

After the disturbing outcome of CAST and suggestions of a lack of efficacy or adverse effects of the class I AADs in general when used for primary or secondary prevention of SCD, interest shifted to the use of amiodarone and implantable defibrillators. Two major trials of amiodarone in post-MI patients, EMIAT and CAMIAT, one of which required EF lower than 40%, demonstrated no total mortality benefit, even though both trials demonstrated AAD benefit, expressed as a reduction in arrhythmic deaths or resuscitated VF. Subgroup analyses have suggested that the concomitant use of beta blockers does confer a mortality benefit.

In parallel with the amiodarone trials, the first randomized controlled trial comparing AAD therapy (primarily amiodarone) with ICD therapy (MADIT) was carried out (**see Table 42.8**). The randomly assigned patients had EF lower than 35%, nonsustained VT during ambulatory recording, and inducible VT that was not suppressible by procainamide. This very-high-risk group demonstrated a 54% reduction in total mortality with ICD therapy versus drug therapy, primarily amiodarone. At the same time, a trial comparing ICD implantation with no specific therapies for arrhythmias in patients with EF less than 36% who were undergoing coronary bypass surgery (CABG Patch Trial) demonstrated no benefit of defibrillators on total mortality. The only markers for arrhythmic risk required for entry into the study were a low EF and a positive signal-averaged ECG. A third trial, MUSTT,[72] was a complex study designed to determine whether electrophysiologically guided therapy would lead to an improved outcome in patients with ambient nonsustained VT, inducible VT, history of previous MI, and EF less than 40%. The results demonstrated that although a statistically significant beneficial effect on total mortality was achieved by EPT-guided therapy, compared to patients with inducible tachycardia who did not receive therapy, the subgroup of patients who received ICDs because they failed to respond to drug therapy accounted for all the benefit. Mortality was 24% in ICD-treated patients at 5 years of follow-up versus 55% in those receiving EPT-guided drug therapy and 48% in those randomly assigned to no therapy. MADIT II, the next post-MI primary prevention trial, demonstrated that ICD therapy provided a mortality benefit over conventional therapy in patients with previous MI and EF less than 30%, with a relative risk reduction of 28% and an absolute risk reduction of 6% (22% versus 16%) at 2 years (**see Fig. 42.19**). During long-term follow-up, a constant annualized risk of approximately 8.5% was estimated in survivors, with the most powerful risk predictors being age over 65 years, class III or IV heart failure, diabetes, non–sinus rhythm, and elevated blood urea nitrogen levels.[178]

MADIT and MADIT II had set entry requirements of more than 3 weeks and more than 1 month after the qualifying infarction, but the actual enrollment in these studies and MUSTT was considerably longer on average. Because both old and recent[25] data suggested higher risk for SCD early after MIs, DINAMIT (Defibrillator in Acute Myocardial Infarction Trial) was designed to evaluate any possible benefit of ICD implantation early after MI in patients with EF of 35% or lower[179] and other markers of risk. DINAMIT demonstrated no survival benefit attributable to early implantation of ICDs in patients randomly assigned at 6 to 40 days after MI (mean, 18 days) despite reduced arrhythmic mortality. There was also an unexplained increase in nonarrhythmic mortality over conventional therapy that needs to be explored in future studies. The IRIS (Immediate Risk Stratification Improves Survival) trial also evaluated ICD implantation early after MI (entry criteria for days from infarct to randomization, 5 to 31; mean to randomization, 13 ±7 days) in patients with either EF of 40% or lower and other markers of risk or nonsustained VT.[180] No survival benefit was noted with ICD therapy. These data suggest that either some SCDs in the early post-MI period are caused by a nonarrhythmic mechanism, or that different risk predictors are required in this setting. Indeed, limited data support both these possibilities. The VALIANT investigators evaluated autopsy findings in 105 patients considered to be SCD and identified that approximately half the SCDs in the early post-MI period were caused by mechanical complications, with a large proportion being recurrent MI and ruptured ventricular aneurysms.[181] Another ICD trial in the early post-MI period (BEST-ICD) was terminated prematurely because of low enrollment. In this trial, ICD implantation early after MI (days 5 to 30) in patients with EF less than 35% and other markers of risk was considered only in patients randomized to an electrophysiology study (EPS)–guided treatment approach in whom sustained ventricular arrhythmias were inducible.[182] The point estimates for mortality in the conventional versus EPS-guided treatment groups were 18% versus 14% at 1 year and 29.5% versus 20% at 2 years. This trend was not statistically significant, but the study was also underpowered

because of premature termination. Observational data from Australia support the potential for this approach to identify risk for SCD in the early post-MI period.[183] Further efforts to address SCD risk prediction properly in this critical period are necessary.

The promise of early ICD benefit came from intervention studies reported between 1996 and 2005 and designed and executed beginning in the early 1990s and extending to 2004. More recent data suggest that optimized therapy during and after MI, with "optimized" being defined as revascularization and the use of beta blockers, acetylsalicylic acid, statins, and ACE inhibitors, may beneficially influence risk for SCD during long-term follow-up after the event.[171] In this study, the greatest impact was achieved by revascularization. Even though EF was improved in association with these interventions, it was not determined whether risk is reduced with EFs equivalent to those in the early ICD trials. However, the population burden of SCD in post-MI patients was reduced by these MI-related interventions. Another study also suggested that both thrombolytic therapy and PCI during acute MI and other changes in therapy that have occurred between 1995 and 2010 have improved 30-day mortality.[47] A 2009 to 2011 randomized trial was designed to evaluate ICD therapy programming strategies on delivered shocks and mortality.[184] Higher detection rates and longer detection times were associated with fewer shocks and improved survival compared to conventional programming. Interestingly, cumulative mortality at 24 months in the conventional programming group was 10% versus 16% in the original MADIT II cohort (1997 to 2001), thus suggesting beneficial influences other than ICDs on outcomes.

The DEFINITE study, designed to determine whether patients with nonischemic cardiomyopathy and a history of heart failure, EF of 35% or lower, and PVCs or nonsustained VT could benefit from prophylactic ICD therapy, was underpowered to achieve statistical significance ($P = 0.08$). However, the reported results demonstrated a strong trend toward benefit, with a 35% reduction in relative risk and a 6% reduction in absolute risk during 2 years of follow-up.[185] Subgroups with prolonged QRS durations, EF higher than 20%, and class III heart failure performed better than did the overall cohort data. SCD-HeFT was designed to test the potential benefit of ICDs versus amiodarone and placebo in patients with functional class II or III congestive heart failure and EF lower than 35%. Nonischemic cardiomyopathy and ischemic cardiomyopathy were almost equally represented, with 85% of patients with ischemic cardiomyopathy having a history of MI. Results demonstrated a 23% reduction in relative risk and 7% reduction in absolute risk during 5 years[186] (**Fig. 42.20**). Amiodarone provided no added benefit over conventional therapy. In contrast to DEFINITE, the class II patients in SCD-HeFT had better outcomes than did the class III patients.

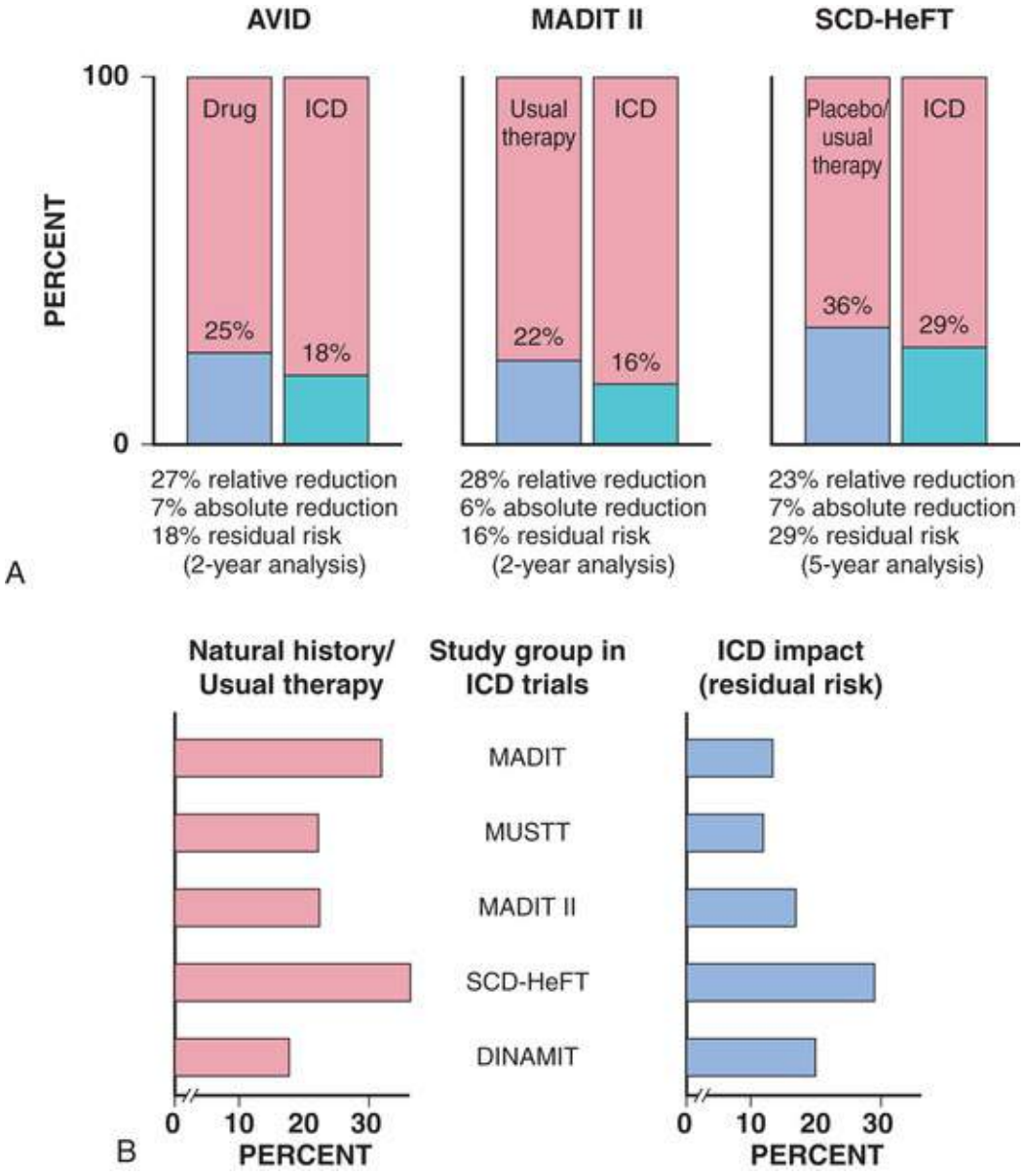


FIGURE 42.20 **A,** Relative and absolute benefits of ICDs in three ICD trials: a secondary prevention study (AVID) trial, a primary prevention trial (MADIT II), and a heart failure sudden death trial (SCD-HeFT); see text for definitions and trial descriptions. Relative risk reductions indicate proportional differences in outcomes between test and control populations, absolute reductions indicate proportional benefits for individuals, and residual risks indicate mortality remaining after accounting for ICD benefits. **B,** Residual risk after accounting for ICD-associated survival benefit in five major primary prevention ICD clinical trials. (**A,** Modified from Myerburg RJ, Mitrani R, Interian AJr, Castellanos A. Interpretation of outcomes of antiarrhythmic clinical trials: design features and population impact. Circulation 1998;97:1514.)

The mortality benefit of ICDs combined with cardiac resynchronization therapy is unclear. Although one study suggested a small mortality benefit in patients with class III and IV heart failure,[187] another study that enrolled class I and II heart failure patients (most of the enrollees being class II) with prolonged QRS duration demonstrated a heart failure hospitalization benefit without a mortality benefit.[188] Several meta-analyses have been inconclusive about the mortality benefit of combined therapy, although reduction of hospitalizations appears consistent. However, a randomized study of patients with nonischemic systolic heart failure suggested no added survival benefit of prophylactic ICDs when appropriate medical therapy is employed.[189]

Primary Prevention in Patients with Less Advanced Common Heart Diseases or Uncommon

Diseases.

Primary prevention trials have been designed to enroll populations of patients with advanced heart disease who were estimated to be at very high risk for SCD and total mortality as a consequence of the severity of the underlying disease. Most clinical trials testing the question of the relative efficacy of antiarrhythmic versus ICD therapy have used the EF as the marker for advanced disease, with the upper limits of qualifying ejection fractions being between 30% and 40% and the majority set at 35%. The mean or median values of those actually enrolled ranged from 21% to 30%,[53,72] and subgroups with EF higher than 30%, particularly those in the range of 35% to 40%, had lower if any benefit (**Fig. 42.21**).

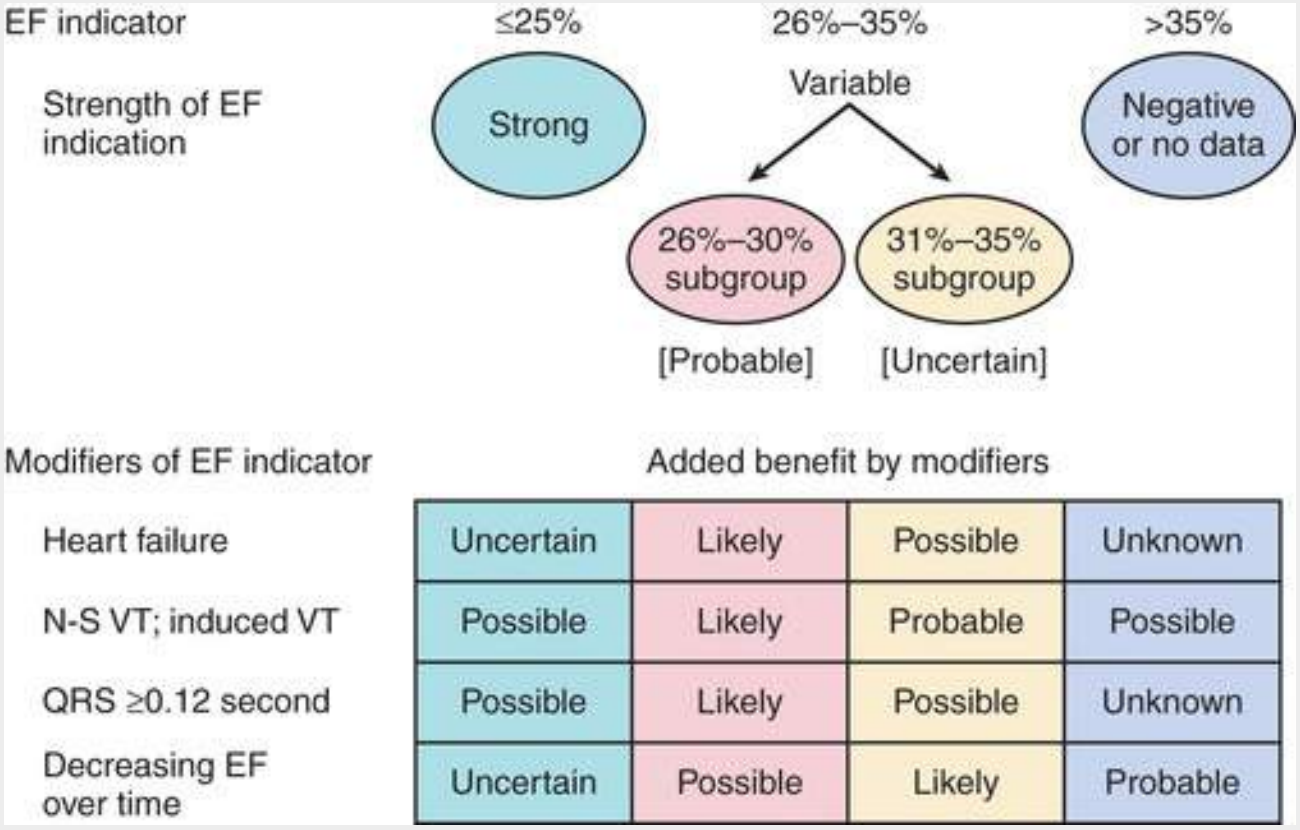


FIGURE 42.21 Modifiers of post-MI ejection fraction (EF) indicators for ICDs. The strength of EF as a primary determinant of indications for an ICD after MI varies and is apparently modulated by a number of clinical factors. Although stratified trial data are not available, indications from subgroup analyses suggest general patterns of modification of EF indicators by other influences. In circumstance in which EF alone appears to be a strong indicator (e.g., 20% to 25%), modifiers that have an effect at other levels of EF (e.g., heart failure) may not add further strength of prediction for total mortality. *N-S VT,* Nonsustained ventricular tachycardia. (Modified from Myerburg RJ. Implantable cardioverter-defibrillators after myocardial infarction. N Engl J Med 2008;359:2245.)

Although the risk for SCD and total mortality is highest in patients with advanced structural heart disease, characterized by low EF, impaired functional capacity, or both, a substantial proportion of the total SCD burden occurs in patients with coronary heart disease or the various nonischemic cardiomyopathies with EF between 35% and 40% and higher. In addition, in patients with heart failure related to various forms of cardiomyopathy, even though the total mortality risk is considerably lower in those with functional class I or early class II than in those with late class III or class IV status, the probability of a death being sudden is higher in the former group[18] (**see Fig. 42.8**). Despite this observation, no data are available to guide therapy for primary prevention of cardiac arrest in such patients.[17] This limitation is confounded by patients in these categories generally having low event rates but cumulatively accounting for large numbers of SCD (**see Fig. 42.2**). In addition, certain other

structural entities associated with some elevation in risk for SCD in the absence of a severely reduced EF, such as some patterns of viral myocarditis, HCM, RV dysplasia, and sarcoidosis, are managed without the benefit of clinical trials to guide therapeutic decisions (**see Table 42.8**). Patients with symptomatic ventricular arrhythmias related to structural disorders such as RV dysplasia, in which most of the mortality risk is arrhythmic, are often advised to have an ICD, even in the absence of a previous cardiac arrest or hemodynamically significant VT. Whether AAD therapy would be just as effective remains unknown, but the judgment of using defibrillators in patients with a disorder whose fatal expression is primarily arrhythmic carries the strength of logic, often supported by risk profiling based on observational data of clinical markers. Among the entities in which the family history is helpful in defining risk, clinical judgment is facilitated in patients with a strong family history of SCD. Specific support for this approach is derived from genetic studies of individuals with HCM. In addition, clinical observational data have supported the use of ICDs in high-risk subsets of patients with HCM.[68]

Primary Prevention in Patients with Structurally Normal Hearts or Molecular Disorders of Cardiac Electrical Activity

Clinically subtle or inapparent structural disorders and entities with pure electrophysiologic expression, such as the congenital long-QT syndromes, Brugada syndrome, and idiopathic VF, are receiving increasing attention with regard to preventive activities (**see Chapter 33**). The decision-making process for cardiac arrest or symptomatic VT survivors with LQTS is similar to that for other entities in that survivors of a potentially fatal arrhythmia generally receive ICD therapy (**see Table 42.9**). In contrast, individuals who express the electrocardiographic phenotype of LQTS in the absence of symptomatic arrhythmias generally receive beta-blocker therapy. Beta blockers are also considered useful for affected family members who have not had an event and for subgroups of LQTS patients with syncope of undocumented mechanism.[72] Between these extremes are asymptomatic affected family members of patients with symptomatic LQTS. The threshold for consideration of ICD therapy is decreasing,[39] primarily among carriers who break through with symptoms while receiving beta-blocker therapy. Currently, many such clinical therapeutic decisions are still based on judgment rather than driven by data.[72] In this context, a family history of premature SCD in affected relatives is often considered in the decision-making process for preventive therapy in this general category of patients, although it is uncertain whether family history is applicable to LQTS syndrome.

Among the other molecular arrhythmia syndromes, management strategies for Brugada syndrome remain problematic and debated.[93-95] An ICD is accepted as the secondary prevention strategy in SCA survivors and as the primary prevention therapy in symptomatic patients with type I Brugada patterns, even though based largely on observational data. Studies have suggested that syncope associated with ECG changes suggestive of this disorder at baseline is a marker of risk sufficient to warrant ICD therapy, and that baseline ECG changes associated with inducibility of ventricular tachyarrhythmias during EPT may also be a marker of risk in some subgroups.[94] Conversely, the absence of right bundle branch block and ST-T wave changes without provocation suggests low risk. The appropriate role of EPT is still debated, complicated in part by the absence of uniform protocols and selection biases based on subgroups studied at various centers. However, a family history of SCD is often considered in judgment-based decisions. Similar arguments, but supported by even fewer data, apply to affected family members of patients with RV dysplasia.

Prediction and Primary Prevention in the General Population

Because SCD is frequently the first clinical expression of underlying structural heart disease or occurs in identified patients profiled to be at low risk (**see Fig. 42.2B**), there has been longstanding interest in risk profiling and therapeutic strategies targeted to primary prevention. To have a major impact on the problem of SCD in the general population, including adolescents and young adults, physicians need to move beyond the identification of high-risk patients who have specific clinical entities, advanced or subtle, that predict high risk for SCD. Rather, it is necessary to find small subgroups of patients in the general population at specific risk for SCD as a manifestation of underlying heart disease, if and when that disease manifests. For example, studies that demonstrate familial clustering of SCD as the first expression of underlying coronary artery disease and thus suggest a genetic or behavioral predisposition may provide some help for the future.[9] If highly specific markers related to electrophysiologic properties or along multiple points in the cascade of coronary events can be found (**see Fig. 42.4**), preventive therapy before the first expression of an underlying disease may have a major effect on the population burden of SCD. Otherwise, success will be limited to community-based intervention and to subgroups who are easier to identify and in whom it is more justifiable to use prophylactic interventional therapy on the basis of population size and magnitude of risk.[2,72]

Adolescents and young adults, including athletes (**see Chapter 53**), constitute a group for special consideration. Risk for SCD in these groups is approximately 1% of the risk in the general adult population older than 35 years[10,72] (**see Fig. 42.3**). However, most causes of SCD in these populations are not characterized by advanced, life-limiting structural heart disease, and therefore, with appropriate long-term therapy, cardiac arrest survivors can be expected to have significantly extended life. Because most deaths are arrhythmic, the ability to identify individuals at risk before a life-threatening arrhythmic event offers more long-term impact than in older populations. For both the general young population and athletes, identification of individuals at risk may lead to prevention of events triggered by physical activity. One study demonstrated a reduction in SCDs in athletes with the use of widespread ECG screening.[190] In the United States, strategies for screening of adolescents, young adults, and athletes to identify entities that create risk have largely been limited to medical and family histories and physical examination,[191] although a consensus statement spearheaded by the National Collegiate Athletic Association (NCAA) has taken a more permissive position on ECG screening.[192] The European and the International Olympic Committee recommendations add ECG screening for athletes, which continues to be debated in the United States[193] despite data indicating both feasibility and suggestions of cost-effectiveness.[194] ECG screening of the general adolescent population, including athletes, can identify many of those at potential risk because of congenital LQTS, HCM, RV dysplasia, and Brugada syndrome. In Japan, where ECG screening of first- and seventh-grade schoolchildren is routine, the apparent incidence of LQTS is considerably higher than recognized in the United States and Europe: 1 in 3298 first graders and 1 in 988 by the seventh grade, versus 1 in 2000 to 2500 in the general population elsewhere.[38] Although ECG screening in the adolescent and athletic subgroups is imperfect and usually accompanied by depolarization and repolarization patterns that may be difficult to interpret, this strategy can lead to further testing in appropriate individuals. Echocardiography has also been suggested as a screening method, but it is more expensive and less cost-efficient and does not recognize conditions such as LQTS and Brugada syndrome.

Risk for SCD must be evaluated in competitive athletes with previously known cardiovascular disorders or those discovered during preparticipation screening, as well as in those with known disorders who want to participate in recreational sports. Recommendations for competitive athletes are available based on the intensity of exercise,[195] the nature of the diseases,[74,196] response stragegies,[197] and legal considerations.[198] Issues for recreational athletes are more complex because of the absence of

organizational infrastructure in most cases.

Sudden Death and Public Safety

The unexpectedness of SCD has raised questions concerning secondary risk to the public created by people in the throes of cardiac arrest. No data from controlled studies are available to guide public policy regarding people at high risk for potentially lethal arrhythmias and for abrupt incapacitation. In a report of observations on 1348 sudden deaths caused by coronary heart disease in people 65 years or younger during a 7-year period in Dade County, Florida, 101 (7.5%) of the deaths occurred in people who were engaged in activities at the time of death that were potentially hazardous to the public (e.g., driving a motor vehicle, working at altitude, piloting aircraft), and 122 (9.1%) of the victims had occupations that could create potential hazards to others if an abrupt loss of consciousness had occurred while they were at work. No catastrophic events occurred as a result of these cardiac arrests, only minor property damage in 19 and minor injuries in five.

In specific reference to private automobiles, a study from Seattle, Washington, identified 33 SCDs per year while driving the estimated 1.32 million vehicles in the community. An analysis of recurrent events in cardiac arrest survivors has suggested limitation of driving privileges for the first 8 months after the index event on the basis of the clustering of recurrent event rates early after the index event.[199] Therefore, although there are likely to be isolated cases in which cardiac arrest causes public hazards, the risk appears to be small, and because it is difficult to identify specific individuals at risk, sweeping restrictions to avoid such risks appear to be unwarranted. The exceptions are people with multisystem disease, particularly senility, and individual circumstances that require specific consideration, such as patients with documented or substantial risk for loss of consciousness associated with the onset of arrhythmias and high-risk patients who have special responsibilities—school bus drivers, aircraft pilots, train operators, and truck drivers.

Among patients with primary prevention ICDs, it was originally suggested that driving be avoided for 6 months after implant, but revised recommendations reduced that to 1 week or more, depending on individual circumstances.[199] Once a therapy has been delivered, the post-therapy guideline of up to 6 months still prevails, again with modification based on individual circumstances and preshock symptoms. A study of temporal patterns of recurrent ICD shock therapies identified an acceleration of time to recurrent events after a first event has occurred, an observation that may have implications for driving depending on associated symptoms in individual patients.[200]

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43

Hypotension and Syncope

Hugh Calkins, Douglas P. Zipes

Definition

Syncope, or transient loss of consciousness (LOC), is a symptom that presents with abrupt, transient, complete LOC associated with the inability to maintain postural tone, with rapid and spontaneous recovery. The presumed mechanism of syncope is cerebral hypoperfusion.[1,2] The metabolism of the brain, in contrast to that of many other organs, is exquisitely dependent on perfusion. Consequently, cessation of cerebral blood flow leads to LOC within approximately 10 seconds. Restoration of appropriate behavior and orientation after a syncopal episode is usually immediate. Retrograde amnesia, although uncommon, can be present in older adults. It is important to recognize that syncope, as previously defined, represents a subset of a much wider spectrum of conditions that can result in transient LOC, including conditions such as cerebrovascular accident (stroke) and epileptic seizures. Nonsyncopal causes of transient LOC differ in their mechanism and duration.[1,2]

Syncope is an important clinical problem because it is common, costly, and often disabling; can cause injury; and can be the only warning sign before sudden cardiac death (SCD)[1-3] (**see Chapter 42**). Patients with syncope account for 1% of hospital admissions and 3% of emergency department (ED) visits. Up to 50% of young adults report a previous episode of LOC, mostly isolated events that never come to medical attention. The prevalence of a first episode of syncope is particularly high between the ages 10 and 20, with additional peaks at approximately 60 and 80 years.[4] Patients who experience syncope also report greatly reduced quality of life; syncope can result in traumatic injury.

The prognosis of patients with syncope varies greatly with the diagnosis. Patients with syncope in the setting of structural heart disease or primary electrical disease have an increased incidence of SCD and overall mortality. Syncope caused by orthostatic hypotension is associated with a twofold increase in mortality, which reflects the presence of multiple comorbid conditions in this patient group. In contrast, young patients with neurally mediated syncope have an excellent prognosis.

Classification

Tables 43.1 and **43.2** present the diagnostic considerations in patients with real or apparent transient LOC and in those with syncope, respectively. Syncope can be distinguished from most other causes of transient LOC by asking whether the LOC was transient, of rapid onset, of short duration, and followed by spontaneous recovery. If the answer to each of these questions is yes and the transient LOC did not result from head trauma, the diagnostic considerations include true syncope in which the mechanism of transient LOC is global cerebral hypoperfusion, epileptic seizures, psychogenic syncope, and other rare causes. It is important to consider nonsyncopal conditions when evaluating a patient with transient LOC, such as metabolic disorders, epilepsy, or alcohol, as well as conditions in which consciousness is only apparently lost (i.e., conversion reaction). These psychogenic causes of syncope, being recognized with increased frequency, are typically diagnosed in patients 40 years or younger and especially in those with a history of psychiatric disease.[1,5]

TABLE 43.1

Causes of Real or Apparent Transient Loss of Consciousness

Syncope (**see Table 43.2**)
Neurologic or cerebrovascular disease
Epilepsy
Vertebrobasilar transient ischemic attack
Metabolic syndromes and coma
Hyperventilation with hypocapnia
Hypoglycemia
Hypoxemia
Intoxication with drugs or alcohol
Coma
Psychogenic syncope
Anxiety, panic disorder
Somatization disorders

TABLE 43.2

Causes of Syncope

Vascular Causes
Anatomic
Vascular steal syndromes (subclavian steal syndrome)
Orthostatic
Autonomic insufficiency
Idiopathic
Volume depletion
Drug and alcohol induced
Reflex Mediated
Carotid sinus hypersensitivity
Neurally mediated syncope (common faint, vasodepressor, neurocardiogenic, vasovagal)
Glossopharyngeal syncope
Situational (acute hemorrhage, cough, defecation, laugh, micturition, sneeze, swallow, postprandial)
Cardiac Causes
Anatomic
Obstructive cardiac valve disease
Aortic dissection
Atrial myxoma
Pericardial disease, tamponade
Hypertrophic obstructive cardiomyopathy
Myocardial ischemia, infarction
Pulmonary embolism
Pulmonary hypertension
Arrhythmias
Bradyarrhythmias
Atrioventricular block
Sinus node dysfunction, bradycardia
Tachyarrhythmias
Supraventricular tachycardia
Atrial fibrillation
Paroxysmal supraventricular tachycardia (AVNRT, WPW)
Other
Ventricular tachycardia
Structural heart disease
Inherited syndromes (ARVD, HCM, Brugada syndrome, long-QT syndrome)
Drug-induced proarrhythmia
Implanted pacemaker or ICD malfunction
Syncope of Unknown Origin

AVNRT, Atrioventricular nodal reentrant tachycardia; *ARVD,* arrhythmogenic right ventricular dysplasia; *HCM,* hypertrophic cardiomyopathy; *ICD,* implantable cardioverter-defibrillator; *WPW,* Wolff-Parkinson-White syndrome.

The differential diagnosis of syncope (**Table 43.2**) most often involves vascular causes, followed by cardiac causes, most frequently arrhythmias. Although knowledge of the common conditions that can cause syncope is essential and allows the clinician to arrive at a probable cause of the syncope in most patients, it is equally important to be aware of several less common but potentially lethal causes of syncope, such as long-QT syndrome, arrhythmogenic right ventricular dysplasia, Brugada syndrome, hypertrophic cardiomyopathy, idiopathic ventricular fibrillation, catecholaminergic polymorphic

ventricular tachycardia, short-QT syndrome, and pulmonary emboli[1,6-11] (**see Chapter 84**).

It is important to recognize that the distribution of causes of syncope varies both with patient age and with the clinical setting in which the patient is evaluated. Neurally mediated syncope and other causes of reflex-mediated syncope are the most frequent causes of syncope at any age and in any setting. Cardiac causes of syncope, especially cardiac tachyarrhythmias and bradyarrhythmias, are the second most common causes of syncope. The incidence of cardiac causes of syncope is higher in older adults and in patients evaluated in the ED. Orthostatic hypotension is extremely uncommon in patients younger than 40 years but is common in very elderly adults (**see Chapter 88**).

Vascular Causes of Syncope

Vascular causes of syncope, particularly reflex-mediated syncope and orthostatic hypotension, are by far the most common causes and account for at least one third of all syncopal episodes.[12,13] In contrast, vascular steal syndromes are exceedingly uncommon causes of syncope.

Orthostatic Hypotension

Standing upright displaces 500 to 800 mL of blood to the abdomen and lower extremities, thereby resulting in an abrupt drop in venous return to the heart. This drop leads to a decrease in cardiac output and stimulation of aortic, carotid, and cardiopulmonary baroreceptors, which triggers a reflex increase in sympathetic outflow. As a result, heart rate, cardiac contractility, and vascular resistance increase to maintain stable systemic blood pressure (BP) on standing. *Orthostatic intolerance* is a term used to refer to the signs and symptoms of an abnormality in any portion of this BP control system. Orthostatic hypotension is defined as a 20–mm Hg drop in systolic BP or a 10–mm Hg drop in diastolic BP within 3 minutes of standing. Orthostatic hypotension can be asymptomatic or associated with syncope, lightheadedness/presyncope, tremulousness, weakness, fatigue, palpitations, diaphoresis, and blurred or tunnel vision. These symptoms are often worse immediately on arising in the morning or after meals or exercise. Initial orthostatic hypotension is defined as less than a 40–mm Hg decrease in BP immediately on standing with rapid (<30 seconds) return to normal.[1,2,11] In contrast, *delayed progressive* orthostatic hypotension is characterized by a slow progressive decrease in systolic BP on standing. Syncope that occurs after meals, particularly in elderly people, can result from a redistribution of blood to the gut. A decline in systolic BP of approximately 20 mm Hg approximately 1 hour after eating has been reported in up to one third of elderly nursing home residents. Although usually asymptomatic, it can result in lightheadedness or syncope.

Drugs that either cause volume depletion or result in vasodilation are the most common causes of orthostatic hypotension (**Table 43.3**). Elderly patients are particularly susceptible to the hypotensive effects of drugs because of reduced baroreceptor sensitivity, decreased cerebral blood flow, renal sodium wasting, and an impaired thirst mechanism that develops with aging (**see Chapter 88**). Orthostatic hypotension can also result from neurogenic causes, which can be subclassified into primary and secondary *autonomic failure* (**see Chapter 99**). Primary causes are generally idiopathic, whereas secondary causes are associated with a known biochemical or structural anomaly or are seen as part of a particular disease or syndrome.

TABLE 43.3
Causes of Orthostatic Hypotension

Drugs
Diuretics
Alpha-adrenergic blocking drugs
Terazosin (Hytrin), labetalol
Adrenergic neuron-blocking drugs
Guanethidine
Angiotensin-converting enzyme inhibitors
Antidepressants
Monoamine oxidase inhibitors
Alcohol
Diuretics
Ganglion-blocking drugs
Hexamethonium, mecamylamine
Tranquilizers
Phenothiazines, barbiturates
Vasodilators
Prazosin, hydralazine, calcium channel blockers
Centrally acting hypotensive drugs
Methyldopa, clonidine
Primary Disorders of Autonomic Failure
Pure autonomic failure (Bradbury-Eggleston syndrome)
Multisystem atrophy (Shy-Drager syndrome)
Parkinson disease with autonomic failure
Secondary Neurogenic Causes
Aging
Autoimmune disease
Guillain-Barré syndrome, mixed connective tissue disease, rheumatoid arthritis
Eaton-Lambert syndrome, systemic lupus erythematosus
Carcinomatosis autonomic neuropathy
Central brain lesions
Multiple sclerosis, Wernicke encephalopathy
Vascular lesions or tumors involving hypothalamus and midbrain
Dopamine beta-hydroxylase deficiency
Familial hyperbradykininism
General medical disorders
Diabetes, amyloid, alcoholism, renal failure
Hereditary sensory neuropathies, dominant or recessive
Infections of the nervous system
Human immunodeficiency virus infection, Chagas disease, botulism, syphilis
Metabolic disease
Vitamin B_{12} deficiency, porphyria, Fabry disease, Tangier disease
Spinal cord lesions

Modified from Bannister SR, editor. Autonomic Failure. 2nd ed. Oxford: Oxford University Press, 1988, p 8.

There are three types of primary autonomic failure. *Pure autonomic failure* (Bradbury-Eggleston syndrome) is an idiopathic sporadic disorder characterized by orthostatic hypotension, usually in conjunction with evidence of more widespread autonomic failure, such as disturbances in bowel, bladder, thermoregulatory, and sexual function. Patients with pure autonomic failure have reduced supine plasma norepinephrine levels. *Multisystem atrophy* (Shy-Drager syndrome) is a sporadic, progressive, adult-onset disorder characterized by autonomic dysfunction, parkinsonism, and ataxia in any combination. The third type of primary autonomic failure is *Parkinson disease* with autonomic failure. A small subset of patients with Parkinson disease may also experience autonomic failure, including orthostatic hypotension. In addition to these forms of chronic autonomic failure is a rare, acute *panautonomic neuropathy.* This neuropathy generally occurs in young people and results in severe, widespread sympathetic and parasympathetic failure with orthostatic hypotension, loss of sweating, disruption of bladder and bowel function, fixed heart rate, and fixed dilated pupils.

Postural orthostatic tachycardia syndrome (POTS) is clinical syndrome characterized by frequent symptoms that occur with standing (e.g., lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, fatigue), an increase in heart rate of 30 beats/min or more on standing (or ≥40 beats/min in those 12 to 19 years of age), and absence of a more than 20–mm Hg reduction in systolic BP.[1,2,12] The precise pathophysiologic basis for POTS has not been well defined.

Some patients have both POTS and neurally mediated syncope.

Reflex-Mediated Syncope

Reflex-mediated, or *situational,* causes of syncope are listed in **Table 43.2**. In this group of conditions, the cardiovascular reflexes that control the circulation become inappropriate in response to a trigger, which results in vasodilation with or without bradycardia and a drop in BP and global cerebral hypoperfusion. In each case the reflex is composed of a trigger (the afferent limb) and a response (the efferent limb). This group of reflex-mediated syncopal syndromes has in common the response limb of the reflex, which consists of increased vagal tone and withdrawal of peripheral sympathetic tone and leads to bradycardia, vasodilation, and ultimately, hypotension, presyncope, or syncope. If hypotension secondary to peripheral vasodilation predominates, it is classified as a *vasodepressor-type* reflex response; if bradycardia or asystole predominates, it is classified as a *cardioinhibitory* response; and when both vasodilation and bradycardia play a role, it is classified as a *mixed* response. Specific triggers distinguish these causes of syncope. For example, micturition-induced syncope results from activation of mechanoreceptors in the bladder, defecation-induced syncope results from neural input from gut wall tension receptors, and swallowing-induced syncope results from afferent neural impulses arising from the upper gastrointestinal tract. The two most common types of reflex-mediated syncope, carotid sinus hypersensitivity and neurally mediated hypotension, are discussed later. Identification of the trigger is of importance because of its therapeutic implications, with avoidance of the trigger, where possible, preventing further syncopal episodes.

Neurally Mediated Hypotension or Syncope (Vasovagal Syncope)

The term *neurally mediated hypotension* or *syncope* (also known as neurocardiogenic, vasodepressor, and vasovagal syncope and “fainting”) has been used to describe a common abnormality in regulation of BP characterized by an abrupt onset of hypotension with or without bradycardia. Triggers associated with the development of neurally mediated syncope include orthostatic stress, such as can occur with prolonged standing or a hot shower, and emotional stress, such as can result from the sight of blood.[1,2,12] A large proportion of patients with neurally mediated syncope may have minor psychiatric disorders. Patients with syncope caused by neutrally mediated hypotension may also have psychogenic pseudosyncope.[5] It has been proposed that neurally mediated syncope results from a paradoxical reflex that is initiated when ventricular preload is reduced by venous pooling. This reduction leads to a decrease in cardiac output and BP, which is sensed by arterial baroreceptors. The resultant increased catecholamine levels, combined with reduced venous filling, leads to a vigorously contracting, volume-depleted ventricle. The heart itself is involved in this reflex by virtue of the presence of mechanoreceptors, or C fibers, consisting of nonmyelinated fibers found in the atria, ventricles, and pulmonary artery. It has been proposed that vigorous contraction of a volume-depleted ventricle leads to activation of these receptors in susceptible individuals. These afferent C fibers project centrally to the dorsal vagal nucleus of the medulla and can result in “paradoxical” withdrawal of peripheral sympathetic tone and an increase in vagal tone, which in turn causes vasodilation and bradycardia. The ultimate clinical consequence is syncope or presyncope. Not all neurally mediated syncope, however, results from activation of mechanoreceptors. In humans the sight of blood or extreme emotion can trigger syncope, thus suggesting that higher neural centers can also participate in the pathophysiology of vasovagal syncope. In

addition, central mechanisms can contribute to the production of neurally mediated syncope.

Carotid Sinus Hypersensitivity

Syncope caused by carotid sinus hypersensitivity results from stimulation of carotid sinus baroreceptors located in the internal carotid artery above the bifurcation of the common carotid artery. It is diagnosed by the reproduction of clinical syncope during carotid sinus massage, with a cardioinhibitory response if asystole is longer than 3 seconds or AV block occurs; or a significant vasodepressor response if there is a more than 50–mm Hg drop in systolic BP; or a mixed cardioinhibitory and vasodepressor response.[1] Carotid sinus hypersensitivity is detected in approximately one third of elderly patients evaluated for syncope or falls.[2] It is important, however, to recognize that carotid sinus hypersensitivity is also frequently observed in asymptomatic elderly patients. Thus the diagnosis of carotid sinus hypersensitivity should be approached cautiously after excluding alternative causes of the syncope. Once diagnosed, dual-chamber pacemaker implantation is recommended for patients with recurrent syncope or falls resulting from carotid sinus hypersensitivity that is cardioinhibitory or mixed (class 2A/IIa, level of evidence [LOE] B-R).[1,2,14]

Cardiac Causes of Syncope

Cardiac causes of syncope, particularly tachyarrhythmias and bradyarrhythmias, are the second most common cause of syncope and account for 10% to 20% of syncopal episodes (**see Table 43.2 and Chapters 37 and 39**). Ventricular tachycardia (VT) is the most common tachyarrhythmia that can cause syncope. Supraventricular tachycardia (SVT) can also cause syncope, although the great majority of patients with supraventricular arrhythmias have less severe symptoms, such as palpitations, dyspnea, and lightheadedness. Bradyarrhythmias that can result in syncope include sick sinus syndrome and atrioventricular (AV) block. Anatomic causes of syncope include obstruction to blood flow, such as massive pulmonary embolism (**see Chapter 84**), atrial myxoma (**Chapter 81**), or aortic stenosis (**Chapter 68**).

Neurologic Causes of Transient Loss of Consciousness

Neurologic causes of transient LOC, including migraines, seizures, Arnold-Chiari malformations, and transient ischemic attacks, are surprisingly uncommon and account for less than 10% of all cases of syncope (**see Chapters 65 and 97**). Most patients in whom a “neurologic” cause of transient LOC is established are in fact found to have had a seizure rather than true syncope.

Metabolic Causes of Transient Loss of Consciousness

Metabolic causes of transient LOC are rare and account for less than 5% of syncopal episodes. The most common metabolic causes of syncope are hypoglycemia (**see Chapter 51**), hypoxia, and hyperventilation (**Chapter 86**). Establishing hypoglycemia as the cause of apparent LOC requires demonstration of

hypoglycemia during the syncopal episode. Although hyperventilation-induced syncope has generally been considered to result from a reduction in cerebral blood flow, one study demonstrated that hyperventilation alone was not sufficient to cause syncope. This observation suggests that hyperventilation-induced syncope may also have a psychological component. Psychiatric disorders can also cause syncope. Up to one fourth of patients with syncope of unknown origin may have psychiatric disorders for which apparent syncope is one of the initial symptoms[1] (**see Chapter 96**).

Diagnostic Tests

Identification of the precise cause of the syncope is often challenging. Because syncope usually occurs sporadically and infrequently, it is extremely difficult to examine a patient or obtain an electrocardiogram (ECG) during an episode of syncope. For this reason, the primary goal in the evaluation of a patient with syncope is to arrive at a presumptive determination of the cause of the syncope.

History, Physical Examination, and Carotid Sinus Massage

The history and physical examination are by far the most important components of the evaluation of a patient with transient LOC and syncope and can be used to identify the cause in more than 25% of patients.[1,2,13,15-17] The 2017 ACC/AHA/HRS syncope guidelines provide a class I (LOE B-NR) recommendation for performing a detailed history and physical examination in patients with syncope.[1] Maximal information can be obtained from the clinical history when it is approached in a systematic and detailed manner. Initial evaluation should begin by determining whether the patient did in fact experience a syncopal episode by asking the following: (1) Did the patient experience complete LOC? (2) Was the LOC transient with a rapid onset and short duration? (3) Did the patient recover spontaneously, completely, and without sequelae? and (4) Did the patient lose postural tone? If the answer to one or more of these questions is negative, other nonsyncopal causes of transient LOC should be suspected. Although falls can be differentiated from syncope by the absence of LOC, an overlap between symptoms of falls and syncope has been reported,[2,18] because elderly individuals may experience amnesia for the LOC episode. When evaluating a patient with syncope, particular attention should then be focused on (1) determining whether the patient has a history of cardiac disease or metabolic disease (i.e., diabetes) or a family history of cardiac disease, syncope, or sudden death; (2) identifying medications that may have played a role in syncope, especially those that may cause hypotension, bradycardia/heart block, or a proarrhythmic response (antiarrhythmics); (3) quantifying the number and chronicity of previous syncopal and presyncopal episodes; (4) identifying precipitating factors, including body position and activity immediately before syncope; and (5) quantifying the type and duration of prodromal and recovery symptoms. It is also useful to obtain careful accounts from witnesses to provide a detailed description of the episode, including how the patient collapsed and the patient's skin color and breathing pattern, duration of unconsciousness, and movements during the episode of unconsciousness. **Table 43.4** summarizes features of the clinical history most helpful in differentiating neurally mediated hypotension, arrhythmia, seizures, and psychogenic syncope.

TABLE 43.4

Differentiation of Syncope Caused by Neurally Mediated Hypotension, Arrhythmias, Seizures, and Psychogenic Causes

	NEURALLY MEDIATED HYPOTENSION	ARRHYTHMIAS	SEIZURES	PSYCHOGENIC
Demographics and clinical setting	Female > male sex Younger age (<55 yr) More episodes (>2) Standing, warm room, emotional upset	Male > female sex Older age (>54 yr) Fewer episodes (<3) During exertion or supine Family history of sudden death	Younger age (<45 yr) Any setting	Female > male sex Occurs in presence of others Younger age (<40 yr) Many episodes (often many episodes in a day) No identifiable trigger
Premonitory symptoms	Longer duration (>5 sec) Palpitations Blurred vision Nausea Warmth Diaphoresis Lightheadedness	Shorter duration (<6 sec) Palpitations less common	Sudden onset or brief aura (déjà vu, olfactory, gustatory, visual)	Usually absent
Observations during the event	Pallor Diaphoresis Dilated pupils Slow pulse, low BP Incontinence may occur. Brief clonic movements may occur.	Blue, not pale Incontinence may occur. Brief clonic movements may occur.	Blue face, no pallor Frothing at the mouth Prolonged syncope (duration >5 min) Tongue biting Horizontal eye deviation Elevated pulse and BP Incontinence more likely* Tonic-clonic movements if grand mal	Normal color Not diaphoretic Eyes closed Normal pulse and BP No incontinence Prolonged duration (minutes) common
Residual symptoms	Residual symptoms common Prolonged fatigue common (>90%) Oriented	Residual symptoms uncommon (unless prolonged unconsciousness) Oriented	Residual symptoms common Aching muscles Disoriented Fatigue Headache Slow recovery	Residual symptoms uncommon Oriented

*May be observed with any of these causes of syncope but more common with seizures; *BP,* blood pressure.

The clinical histories obtained from patients with syncope related to AV block and VT are similar. In each case, syncope typically occurs with less than 5 seconds of warning and few if any prodromal and recovery symptoms. Demographic features suggesting that the syncope results from an arrhythmia such as VT or AV block include male sex, fewer than three previous episodes of syncope, and increased age. Features of the clinical history that point toward a diagnosis of neurally mediated syncope include palpitations, blurred vision, nausea, warmth, diaphoresis, or lightheadedness before syncope and the presence of nausea, warmth, diaphoresis, or fatigue after syncope.

Features of the clinical history useful in distinguishing seizures from syncope include orientation following an event, a blue face or not becoming pale during the event, frothing at the mouth, aching muscles, feeling sleepy after the event, time of seizure relative to onset of syncope—early points to neurologic while late suggests arrhythmic cause—and a duration of unconsciousness of longer than 5 minutes.[16] Tongue biting strongly points toward a seizure rather than syncope as the cause of LOC. One recent study reported that a history of tongue biting during an episode of LOC had 33% sensitivity and 96% specificity in predicting a seizure as the cause of the LOC.[17] Other findings suggestive of a seizure as a cause of the syncopal episode include (1) an aura before the episode, (2) horizontal eye deviation during the episode, (3) elevated BP and pulse during the episode, and (4) a headache following the event. Urinary or fecal incontinence can be observed with either a seizure or a syncopal episode but occurs more often with a seizure. Grand mal seizures are usually associated with tonic-clonic movements. It is important to note that syncope caused by cerebral ischemia can result in decorticate rigidity with clonic movements of the arms. Akinetic or petit mal seizures can be recognized by the patient's lack of responsiveness in the absence of loss of postural tone. Temporal lobe seizures last several minutes and

are characterized by confusion, changes in LOC, and autonomic signs such as flushing. Vertebral basilar insufficiency should be considered as the cause of the syncope if it occurs in association with other symptoms of brainstem ischemia (i.e., diplopia, tinnitus, focal weakness or sensory loss, vertigo, or dysarthria). Migraine-mediated syncope is often associated with a throbbing unilateral headache, scintillating scotomata, and nausea.

Physical Examination

In addition to a complete cardiac examination, particular attention should be focused on whether structural heart disease is present, defining the patient's level of hydration, and detecting the presence of significant neurologic abnormalities suggestive of dysautonomia or a cerebrovascular accident. Orthostatic vital signs are a critical component of the evaluation. The patient's BP and heart rate should be determined while supine and then repeated each minute for approximately 3 minutes while standing. The two abnormalities that should be sought are (1) early orthostatic hypotension, defined as a 20–mm Hg drop in systolic BP or a 10–mm Hg drop in diastolic BP within 3 minutes of standing, and (2) POTS (see earlier, Orthostatic Hypotension). The significance of POTS lies in its close overlap with neurally mediated syncope.

Carotid Sinus Massage

Carotid sinus massage should be performed after checking for bruits by applying *gentle* pressure over the carotid pulsation, first one side and then the other, just below the angle of the jaw where the carotid bifurcation is located. Pressure should be applied for 5 to 10 seconds in both the supine and the upright position because an abnormal response to carotid sinus massage is present only in the upright position in up to one third of patients. Since the main complications associated with performing carotid sinus massage are neurologic, it should be avoided in patients with previous transient ischemic attacks, strokes within the past 3 months, and carotid bruits, except if significant stenosis has been excluded by carotid Doppler studies. A normal response to carotid sinus massage is a transient decrease in the sinus rate, prolongation of AV conduction, or both. Carotid sinus hypersensitivity is diagnosed by the reproduction of clinical syncope during carotid sinus massage and the responses previously noted.[1] Diagnosis of carotid sinus hypersensitivity as the cause of the syncope requires reproduction of the patient's symptoms during carotid sinus massage.

Laboratory Testing: Blood Tests

Routine use of blood tests, such as serum electrolytes, cardiac enzymes, glucose, and hematocrit levels, is of low diagnostic value in syncopal patients and therefore not recommended routinely. The 2017 ACC/AHA/HRS syncope guidelines state that targeted blood tests are reasonable in the evaluation of selected patients with syncope identified based on clinical assessment from history, physical examination, and ECG (class IIa, LOE B-NR).[1]

Tilt-Table Test

The tilt-table test is a valuable diagnostic test for evaluating patients with syncope,[1,2,13] with a positive response indicating susceptibility to neurally mediated syncope. The 2017 ACC/AHA/HRS syncope guidelines state that tilt-table testing can be useful for patients with suspected vasovagal syncope if the diagnosis is unclear after initial evaluation (class IIa, LOE B-NR).[1] Upright tilt testing is generally

performed for 30 to 45 minutes following a 20-minute horizontal pretilt stabilization phase at an angle between 60 and 80 degrees (with 70 degrees being most common). The sensitivity of the test can be increased, along with an associated fall in specificity, by the use of longer tilt durations, steeper tilt angles, and provocative agents such as isoproterenol or nitroglycerin. When isoproterenol is used, it is recommended that the infusion rate be increased incrementally from 1 to 3 μg/min to increase the heart rate 25% greater than baseline. When nitroglycerin is used, a fixed dose of 300 to 400 μg of nitroglycerin spray should be administered sublingually after a 20-minute unmedicated phase with the patient in the upright position. These two provocative approaches are equivalent in diagnostic accuracy. In the absence of pharmacologic provocation, the specificity of the test has been estimated to be 90%; when provocative agents are used, specificity decreases significantly.

The main indication for upright tilt testing is to confirm a diagnosis of neurally mediated syncope when the initial evaluation was insufficient to establish this diagnosis. Tilt-table testing is also of value in diagnosing psychogenic pseudosyncope.[5] Upright tilt testing is not generally recommended in patients in whom the diagnosis can be established from the initial history and physical examination. However, for some patients, confirmation of the diagnosis with a positive response to upright tilt testing is very reassuring. Induction of reflex hypotension/bradycardia without reproduction of the syncope points toward a diagnosis of neurally mediated syncope but is a less specific response. If a patient has structural heart disease, other cardiovascular causes of syncope should be excluded before considering a positive response to upright tilt testing to be diagnostic of neurally mediated syncope. Upright tilt testing is also indicated in the evaluation of patients for whom the cause of the syncope has been determined (i.e., asystole), but the presence of neurally mediated syncope on upright tilt would influence treatment. Upright tilt testing has also been shown to be of value in patients with psychogenic causes of syncope in that it may trigger LOC in association with a normal BP and heart rate. Induction of LOC with no change in vital signs points strongly toward a diagnosis of psychogenic pseudosyncope. Upright tilt testing has no value in assessing the efficacy of treatment of neurally mediated syncope.

Cardiac Imaging

Echocardiograms are frequently used to evaluate patients with syncope (**see Chapter 14**), but current guidelines suggest that an echocardiogram should be performed only in patients suspected of having structural heart disease.[1,2] The 2017 ACC/AHA/HRS syncope guidelines state that echocardiography can be useful in selected patients presenting with syncope if structural heart disease is suspected (class IIa, LOE B-NR).[1] The guidelines also state that routine cardiac imaging is not useful in the evaluation of patients with syncope unless cardiac etiology is suspected on the basis of an initial evaluation including history, physical examination, or ECG (class 3/III, LOE B-NR).[1] These guidelines also recommend that computed tomography (CT) or magnetic resonance imaging (MRI) may be useful in selected patients presenting with syncope of suspected cardiac etiology (class IIb, LOE B-NR).[1] Studies have shown that the diagnostic yield of an echocardiogram in a syncope patient with a normal ECG and physical examination is extremely low. Therefore, routine echocardiograms are not advised in this setting. For example, an echocardiogram should be obtained in patients who have clinical features suggestive of a cardiac cause of the syncope, such as syncope with exertion or while supine, a family history of sudden death, or syncope of abrupt onset. Echocardiographic findings considered diagnostic of the cause of syncope include severe aortic stenosis, pericardial tamponade, aortic dissection, congenital abnormalities of the coronary arteries, and obstructive atrial myxomas or thrombi. Findings of impaired right or left ventricular function, evidence of right ventricular overload or pulmonary hypertension (pulmonary

emboli), or the presence of hypertrophic cardiomyopathy (**see Chapter 78**) are of prognostic importance and justify additional diagnostic testing.

Stress Tests and Cardiac Catheterization

Myocardial ischemia is an unlikely cause of syncope and, when present, is usually accompanied by angina (**see Chapter 56**). The use of stress tests (**see Chapter 13**) is best reserved for patients in whom syncope or presyncope occurred during or immediately after exertion in association with chest pain or in a patient at high risk for coronary artery disease.[1,2] The 2017 ACC/AHA/HRS syncope guidelines state exercise stress testing can be useful to establish the cause of syncope in selected patients who experience syncope or presyncope during exertion (class IIa, LOE C-LD).[1] Syncope occurring during exercise is suggestive of a cardiac cause. In contrast, syncope following exercise is usually caused by neurally mediated syncope. Even in patients with syncope during exertion, exercise stress testing is highly unlikely to trigger another event. Coronary angiography is recommended in patients with syncope suspected to result, directly or indirectly, from myocardial ischemia.

Electrocardiography

The 12-lead ECG is another important component in the workup of a patient with syncope (**see Chapter 12**). The 2017 ACC/AHA/HRS syncope guidelines provide a class I (LOE B-NR) recommendation for performing an ECG in patients with syncope.[1] The initial ECG results in establishment of a diagnosis in approximately 5% of patients and suggests a diagnosis in another 5% of patients. Specific findings that can identify the probable cause of the syncope include QT prolongation (long-QT syndrome), the presence of a short PR interval and a delta wave (Wolff-Parkinson-White syndrome), the presence of a right bundle branch block pattern with ST-segment elevation (Brugada syndrome), or evidence of acute myocardial infarction, high-grade AV block, or T wave inversion in the right precordial leads (arrhythmogenic right ventricular dysplasia) (**see Chapters 33, 37, and 39**). Any abnormal finding on the baseline ECG is an independent predictor of cardiac syncope or increased mortality and suggests the need to pursue evaluation of cardiac causes of syncope.[1] Most patients with syncope have normal findings on ECGs, which is useful because it suggests a low likelihood of a cardiac cause of the syncope and is associated with an excellent prognosis, particularly when observed in a young patient with syncope. Despite the low diagnostic yield of electrocardiography, the test is inexpensive and risk free and is considered a standard part of the evaluation of virtually all patients with syncope.[1]

Signal-Averaged Electrocardiography

Signal-averaged electrocardiography (SAECG) is a noninvasive technique used to detect low-amplitude signals in the terminal portion of the QRS complex (late potentials), which are a substrate for ventricular arrhythmias (**see Chapter 35**). In contrast to a standard ECG, the role of SAECG in the evaluation of patients with syncope is not well established, and it is not recommended as a standard part of the evaluation of patients with syncope.[2] The 2017 ACC/AHA/HRS syncope guidelines make no mention of SAECG in the evaluation of patients with syncope.[1] The only situation in which SAECG may be of diagnostic value is when arrhythmogenic right ventricular dysplasia is being considered.[8]

Cardiac Monitoring

Continuous ECG monitoring via telemetry or Holter monitoring is frequently performed in patients with

syncope but is unlikely to identify the cause of the syncope (**see Chapter 35**). The information provided by ECG monitoring at the time of syncope is extremely valuable in that it allows an arrhythmic cause of syncope to be established or excluded. However, because of the infrequent and sporadic nature of syncope, the diagnostic yield of Holter monitoring in the evaluation of patients with syncope and presyncope is extremely low. Another clinically useful finding is detection of symptoms in the absence of an arrhythmia, which is observed in up to 15% of patients undergoing continuous ECG monitoring. It is important to emphasize that the absence of an arrhythmia and symptoms during continuous ECG monitoring may not exclude an arrhythmia as the cause of the syncope. In patients suspected of having an arrhythmia as the cause of the syncope, additional evaluation, such as electrophysiologic (EP) testing or event monitoring, should be considered. Inpatient telemetry monitoring or Holter monitoring is recommended for patients who have clinical or ECG features suggesting an arrhythmic syncope or a history of recurrent syncope with injury. Holter monitoring and inpatient telemetry monitoring are most likely to be diagnostic when used for the occasional patient with frequent (i.e., daily) episodes of syncope or presyncope.

Some transtelephonic event monitors are worn continuously to capture both retrospective and prospective ECG recordings, whereas other types record only when they are activated by the patient. Continuous-loop event monitors, often programmed with 5 to 15 minutes of preactivation memory stored by the device, are preferred because the data can be retrieved for analysis. Prospective event monitors not worn continuously by the patient are of value to investigate palpitations but play no role in the evaluation of patients with syncope. Event monitors are indicated in the early phase of the evaluation of patients with syncope of uncertain origin who do not have high-risk criteria that require immediate hospitalization or intensive evaluation. They are also indicated in high-risk patients in whom a comprehensive evaluation did not demonstrate a cause of the syncope or lead to specific treatment.[1,2] Over the past 5 years, external devices for real-time outpatient telemetry monitoring have been developed with wireless technology to transmit real-time ECG recordings to a service center. These devices result in higher diagnostic yield in patients with syncope or presyncope than do the conventional event monitors just described.

In patients with extremely infrequent episodes of syncope (e.g., once or twice a year), a traditional event monitor is unlikely to record an event. Implantable event recorders address this problem by triggering automatically on the basis of programmed detection criteria, as well as with a handheld activator, and storing the ECG signal in a circular buffer (**see Chapter 35**). Some of these devices can transmit the signals transtelephonically. These devices allow a longer monitoring period (12 to 36 months) and have higher diagnostic yield, but they have the disadvantages of requiring surgical implantation and increased cost. A recent advancement in this technology is that these implantable event monitors can be accessed by remote monitoring, which further increases their diagnostic effectiveness.[29] Implantable loop recorders with a battery life of 2 to 3 years have also been shown to improve the diagnostic yield in patients with syncope.[19] However, a recent Cochrane meta-analysis showed no impact of implantable loop recorders on mortality.[19]

The 2017 ACC/AHA/HRS syncope guidelines state that the choice of a specific cardiac monitor should be determined on the basis of the frequency and nature of the syncope events (class I, LOE C-EO). The guidelines also state that each of the monitors previously discussed can be useful to evaluate selected ambulatory patients with syncope of suspected arrhythmic etiology (class IIa, LOE B-NR).[1]

Electrophysiologic Testing

EP testing can provide important diagnostic information in patients with syncope by establishing a diagnosis of sick sinus syndrome, carotid sinus hypersensitivity, heart block, SVT, and VT (**see Chapter 35**). **Table 43.5** presents indications for EP testing and diagnostic findings in the evaluation of patients with syncope.[2] The 2017 ACC/AHA/HRS syncope guidelines state that an electrophysiologic study (EPS) can be useful for evaluation of select patients with syncope of suspected arrhythmic etiology (class IIa, LOE B-NR). These guidelines further note that EPS is not recommended for syncope evaluation in patients with a normal ECG and normal cardiac structure and function, unless an arrhythmic etiology is suspected (class III, LOE B-NR).[1] It is generally agreed that EP testing should be performed in patients when the initial evaluation suggests an arrhythmic cause of the syncope,[2] such as those with abnormal findings on an ECG or structural heart disease, those whose clinical history suggests an arrhythmic cause of the syncope, and those with a family history of sudden death. EP testing should not be performed in patients with normal findings on an ECG and no heart disease and in whom the clinical history does not suggest an arrhythmic cause of the syncope. The class II indications for performing EPS are shown in **Table 43.5**, which indicates that EP testing is appropriate when the results may have an impact on treatment and also in patients with "high-risk" occupations, in whom every effort should be expended to determine the probable cause of the syncope. EP testing is no longer indicated for patients with a severely depressed ejection fraction, because in this setting an implantable cardioverter-defibrillator (ICD) is indicated regardless of the presence or mechanism of the syncope.[1,2]

TABLE 43.5

Indications for and Diagnostic Findings of Electrophysiologic (EP) Testing in Evaluation of Patients with Syncope

INDICATIONS/DIAGNOSTIC CRITERIA	CLASS	LEVEL OF EVIDENCE
Indications		
In patients with ischemic heart disease when the initial evaluation suggests an arrhythmic cause and there is no established indication for an ICD.	I	B
In patients with BBB, EPS should be considered when noninvasive tests do not establish a diagnosis.	IIa	B
In patients with syncope preceded by sudden and brief palpitations when noninvasive tests do not establish a diagnosis.	IIb	B
In patients with syncope and Brugada syndrome, ARVD, or hypertrophic cardiomyopathy, EPS is appropriate in selected cases.	IIb	C
In patients with high-risk occupations, in whom every effort to exclude a cardiovascular cause of syncope is warranted.	IIb	C
EPS is not recommended in syncopal patients with normal findings on an ECG, no structural heart disease, and no palpitations.	III	B
Diagnostic Criteria		
EPS is diagnostic and no additional tests are required in the following situations:		
Sinus bradycardia and a prolonged CSNRT (>525 msec)	I	B
BBB and either a baseline H-V interval ≥100 msec or second- or third-degree His-Purkinje block during incremental atrial pacing or with pharmacologic challenge	I	B
Induction of sustained monomorphic VT in patients with a previous myocardial infarction	I	B
Induction of SVT with reproduction of the hypotensive or spontaneous symptoms	I	B
H-V interval between 70 and 100 msec should be considered diagnostic.	IIa	B
Induction of polymorphic VT or VF in patients with Brugada syndrome, patients with ARVD, or patients resuscitated from cardiac arrest.	IIb	B
Induction of polymorphic VT or VF in patients with ischemic disease or DCM should not be considered a diagnostic finding.	III	B

ARVD, Arrhythmogenic right ventricular dysplasia; *BBB,* bundle branch block; *CSNRT,* corrected sinus node recovery time; *DCM,* dilated cardiomyopathy; *EPS,* electrophysiologic study; *H-V,* His-ventricular; *ICD,* implantable cardioverter-defibrillator; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia.

Modified from Moya A, Sutton R, Ammirati F, et al. Guidelines for the diagnosis and management of syncope 2009. Eur Heart J 2009;30:2631.

Electrophysiologic Testing Protocol

A comprehensive EP evaluation should be performed in patients with syncope, including evaluation of sinus node function by measuring the sinus node recovery time (SNRT) and evaluation of AV conduction

by measuring the His-ventricular (H-V) interval at baseline, with atrial pacing, and following pharmacologic challenge with intravenous procainamide. In addition, programmed electrical stimulation using standard techniques should be performed to evaluate the inducibility of ventricular and supraventricular arrhythmias. Although the minimal suggested EP protocol includes only double extra stimuli and two basic drive train cycle lengths, it is common practice in the United States to include triple extra stimuli and three basic drive train cycle lengths. It is also common practice to limit the shortest coupling interval to 200 milliseconds. In select patients in whom suspicion for ventricular arrhythmia is high, EP testing with atrial and ventricular programmed stimulation may be repeated following an infusion of isoproterenol, which is of particular importance for patients suspected of having a supraventricular arrhythmia, such as AV nodal reentrant tachycardia or orthodromic AV reciprocating tachycardia, as the cause of the syncope.

Sinus node function is evaluated during EP testing primarily by determining the SNRT. Identification of sinus node dysfunction as the cause of syncope is uncommon during EP tests (<5%). The sensitivity of an abnormal SNRT or corrected SNRT (CSNRT) is approximately 50% to 80%. The specificity of an abnormal SNRT or CSNRT is less than 95%. It is important to note that the absence of evidence of sinus node dysfunction during EP testing does not exclude a bradyarrhythmia as the cause of the syncope (**see Chapter 35**).

During EP testing, AV conduction is assessed by measuring the AV nodal–to–His bundle conduction time (A-H interval) and the His bundle–to–ventricular conduction time (H-V interval) and also by determining the response of AV conduction to incremental atrial pacing and atrial premature stimuli. If the results of an initial assessment of AV conduction in the baseline state are inconclusive, procainamide (10 mg/kg) can be administered intravenously and atrial pacing and programmed stimulation repeated. Findings on EPS that allow heart block to be established as the probable cause of the syncope are bundle branch block and a baseline H-V interval of 100 milliseconds or longer, or demonstration of second- or third-degree His-Purkinje block during incremental atrial pacing or provoked by an infusion of procainamide (**see Table 43.5**). An H-V interval of 70 to 100 milliseconds is of less certain diagnostic value. In studies of EP testing to evaluate patients with syncope, AV block was identified as the probable cause of syncope in approximately 10% to 15% of patients.

Although it is uncommon for SVT to result in syncope, this is an important diagnosis to establish because most types of supraventricular arrhythmias can be cured with catheter ablation (**see Chapters 36 and 37**). The usual setting in which SVT causes syncope is in a patient with underlying heart disease and/or limited cardiovascular reserve, a patient with SVT of abrupt onset and with an extremely rapid rate, or a patient who has a propensity for the development of neurally mediated syncope. The typical pattern is the development of syncope or near-syncope at the onset of the SVT because of an initial drop in BP. The patient often regains consciousness despite continuation of the arrhythmia as a result of activation of a compensatory mechanism. Completion of a standard EP test allows accurate identification of most types of supraventricular arrhythmias that may have caused the syncope, and it should be repeated during an isoproterenol infusion to increase the sensitivity of the study, particularly for detecting AV nodal reentrant tachycardia in a patient with dual–AV node physiology or catecholamine-sensitive atrial fibrillation. According to the 2009 European guidelines on management of syncope, an EPS is considered diagnostic of SVT as the cause of syncope when induction of a rapid supraventricular arrhythmia reproduces the hypotensive or spontaneous symptoms[2] (**see Table 43.5**). A supraventricular arrhythmia is diagnosed as the probable cause of syncope in fewer than 5% of patients who undergo EP testing for evaluation of syncope of unknown origin, but the probability is increased in patients who report a history of palpitations (“heart racing”) before syncope.

Ventricular tachycardia is the most common abnormality uncovered during EP testing in patients with syncope and was identified as the probable cause in approximately 20% of patients (**see Chapter 39**). In general, an EP test is interpreted as positive for VT when sustained monomorphic VT is induced. Induction of polymorphic VT and ventricular fibrillation (VF) may represent a nonspecific response to EP testing. The diagnostic and prognostic importance of induction of polymorphic VT or VF remains uncertain. According to the 2009 European guidelines on management of syncope, an EPS is considered diagnostic of VT as the cause of the syncope when sustained monomorphic VT is induced[2] (**see Table 43.5**), with less certain diagnostic value with induction of polymorphic VT or VF in patients with Brugada syndrome or arrhythmogenic right ventricular dysplasia and in patients resuscitated from cardiac arrest. The role of EP testing and pharmacologic challenge with procainamide in syncope patients with suspected Brugada syndrome is controversial.[19]

Overall, approximately one third of patients with syncope referred for diagnostic EP testing have a presumptive diagnosis established.

Test to Screen for Neurologic Causes of Syncope

Syncope as an isolated symptom rarely has a neurologic cause. As a result, widespread use of tests to screen for neurologic conditions is rarely diagnostic.[1,2] In many institutions, CT scans, electroencephalograms (EEGs), and carotid duplex scans are overused; these are obtained in more than 50% of patients with syncope. A diagnosis is almost never uncovered that was not first suspected on the basis of a careful history and neurologic examination. Transient ischemic attacks that result from carotid disease are not accompanied by LOC. No studies have suggested that carotid Doppler ultrasonography is beneficial in patients with syncope. EEGs should be obtained only in patients with a relatively high likelihood of epilepsy. CT and MRI should be avoided in patients with uncomplicated syncope (**see Chapters 17 and 18**). Although the low diagnostic yield of screening "neurologic tests" has been recognized for more than a decade, they continue to be overused and result in a dramatic increase in costs.

The 2017 ACC/AHA/HRS syncope guidelines state that MRI and CT of the head are not recommended in the routine evaluation of patients with syncope in the absence of focal neurologic findings or head injury that support further evaluation (class III, LOE B-NR). The guidelines also provide a class III recommendation for the routine use of carotid artery imaging and EEG in the evaluation of patients with syncope.[1]

Approach to the Evaluation of Patients With Syncope

Fig. 43.1 outlines the approach to the diagnostic evaluation of a patient with transient LOC proposed by the European Society of Cardiology Task Force on Syncope.[2] This is consistent with the approach also recommended in the 2017 ACC/AHA/HRS syncope guidelines.[1] The initial evaluation begins with a careful history, physical examination, supine and upright BP, and a 12-lead ECG, followed by additional testing in select patient subgroups, including carotid sinus massage, echocardiography, ECG monitoring, and tilt-table testing, as discussed earlier. The various types of neurologic testing are generally of little or no value except in the case of head trauma and when nonsyncopal causes of transient LOC such as epilepsy are suspected.

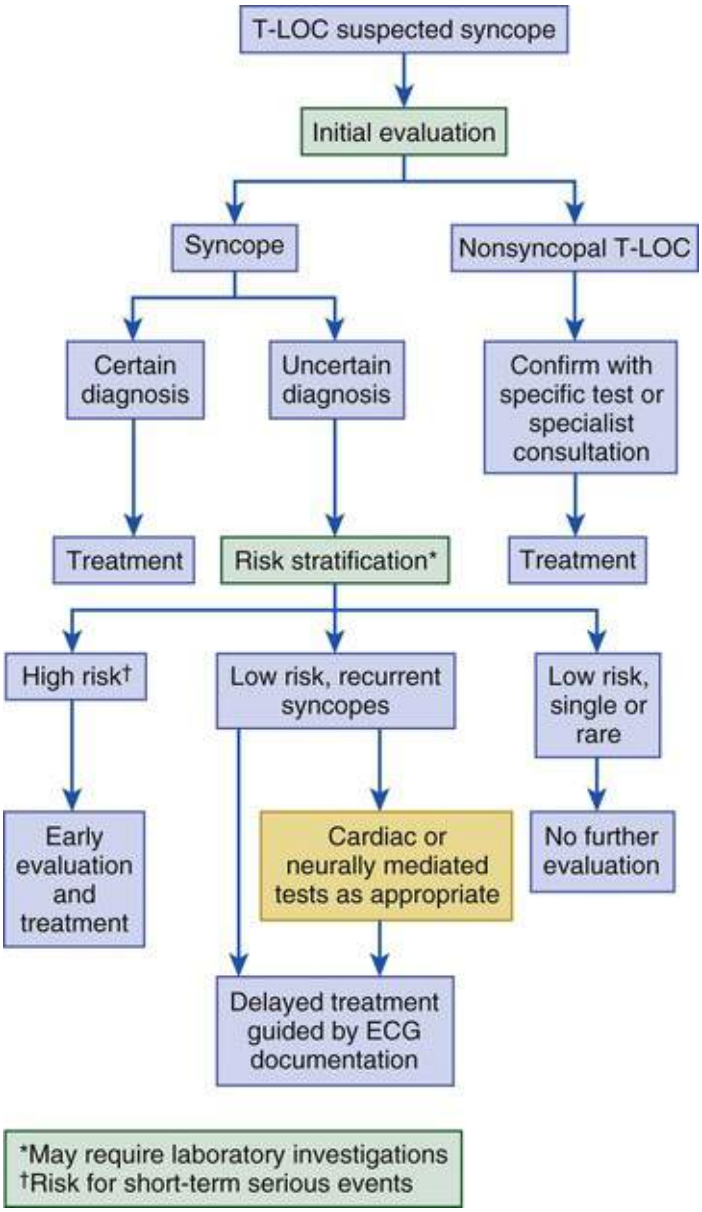

FIGURE 43.1 Diagnostic approach to the evaluation of patients with transient loss of consciousness (T-LOC) and syncope.

Based on this initial evaluation, patients can be classified into those with true syncope and those with nonsyncopal transient LOC. Patients with syncope can be further divided into two groups: those in whom a certain diagnosis has been established and in whom treatment can be initiated and those with an uncertain diagnosis. For the latter, attention should focus on determining whether the patient is at increased risk for a cardiovascular event or death. These patients should be hospitalized and/or should undergo an intensive timely outpatient cardiovascular evaluation that may include exercise stress testing, cardiac catheterization, and EP testing (**Table 43.6**). Conversely, patients who have experienced only a single episode of syncope and are determined to be at low risk for a cardiovascular event or death may require no further evaluation. Patients who fall between these two extremes can undergo further testing based on results of the initial evaluation (**see Fig. 43.1**). When this diagnostic approach has been completed, a probable cause of syncope can be determined in more than three fourths of patients.

TABLE 43.6

Clinical Variables for Identification of High-Risk Syncope Patients Who May Benefit from Hospitalization or an Accelerated Outpatient Evaluation

Severe structural heart disease (low ejection fraction, previous myocardial infarction, heart failure)
Clinical or ECG features suggesting arrhythmic syncope
Syncope during exertion or while supine
Palpitations at the time of syncope
Family history of sudden death
Nonsustained ventricular tachycardia
Bifascicular block or QRS >120 msec
Severe sinus bradycardia (<50 beats/min) in the absence of medications or physical training
Preexcitation
Prolonged or very short QT interval
Brugada ECG pattern (right bundle branch block with ST elevation in leads V_1-V_3)
Arrhythmogenic right ventricular dysplasia ECG pattern (T wave inversion in leads V_1-V_3 with or without epsilon waves)
ECG suggestive of hypertrophic dilated cardiomyopathy
Clinical evidence or suspicion of a pulmonary embolus (clinical setting, sinus tachycardia, shortness of breath)
Severe anemia
Important comorbid conditions
Significant electrolyte abnormalities
Severe anemia

The European and ACC/AHA/HRS guidelines on management of syncope have called attention to the importance of a structured care pathway in the evaluation of patients with syncope.[1,2,20,21] Other studies have reported favorable outcomes when a syncope evaluation unit or standardized approach to the evaluation of syncope is used.[22,23]

Management of Patients With Syncope

Treatment of a patient with syncope has three goals: (1) prolong survival, (2) prevent traumatic injuries, and (3) prevent recurrences of syncope. The approach to treatment of a patient with syncope depends largely on the cause and mechanism of the syncope. For example, the appropriate treatment of a patient with syncope related to AV block would be a pacemaker in most situations. However, a patient with syncope secondary to heart block in the setting of an inferior wall myocardial infarction will not usually require a permanent pacemaker because the heart block usually resolves spontaneously. Similarly, heart block resulting from neurally mediated syncope does not generally require pacemaker implantation. Treatment of a patient with syncope related to Wolff-Parkinson-White syndrome typically involves catheter ablation, and treatment of a patient with syncope related to VT or in the setting of ischemic or nonischemic cardiomyopathy would probably involve placement of an implantable defibrillator (**see Chapter 41**). However, ICD implantation may not be required for patients with VT/VF occurring within 48 hours of an acute myocardial infarction. For other types of syncope, optimal management may involve discontinuation of an offending pharmacologic agent, an increase in salt intake, or education of the patient.[24]

Other issues that need to be considered include the indication for hospitalization of a patient with syncope and the duration of driving restrictions. Current guidelines recommend that patients with syncope be hospitalized when there is known or suspected heart disease, ECG abnormalities suggestive of arrhythmic syncope, syncope with severe injury or during exercise, and syncope in patients with a family history of sudden death (**see Table 43.6**).[1]

Physicians who care for patients with syncope are often asked to address the issue of driving risk. Patients who experience syncope while driving pose a risk both to themselves and to others. A recent study has reported that a prior hospitalization for syncope was associated with a small increase in the risk

of a motor vehicle accident during follow-up.[25] Although some would argue that all patients with syncope should never drive again because of the theoretical possibility of recurrence, this is an impractical solution that would be ignored by many patients. Factors that should be considered when making a recommendation for a particular patient include (1) the potential for recurrent syncope, (2) the presence and duration of warning symptoms, (3) whether syncope occurs while seated or only when standing, (4) how often and in what capacity the patient drives, and (5) whether any state laws may be applicable.

When considering these issues, physicians should note that acute illnesses, including syncope, are unlikely to cause a motor vehicle accident. The American Heart Association and the Canadian Cardiovascular Society have published guidelines concerning this issue. For noncommercial drivers, it is generally recommended that driving be restricted for several months. If the patient remains asymptomatic for several months, driving can then be resumed.

Neurally Mediated Syncope

Because neurally mediated syncope and reflex syncope are so common, treatment options are reviewed[1,13] (**Table 43.7**). Treatment of syncope resulting from neurally mediated hypotension begins with a careful history with particular attention on identifying precipitating factors, quantifying the degree of salt intake and current medication use, and determining whether the patient has a previous history of peripheral edema, hypertension, asthma, or other conditions that may alter the approach used for treatment. For most patients with neurally mediated syncope, particularly those with infrequent episodes associated with an identifiable precipitant, education plus reassurance is sufficient. Patients should be educated about common precipitating factors, such as dehydration, prolonged standing, alcohol, and medications (e.g., diuretics, vasodilators). Patients should also be taught to sit or lie down at the onset of symptoms and to initiate physical counterpressure maneuvers. One recent study reported that a standardized education protocol significantly reduced traumatic injuries and recurrence of syncope.[24] In this trial the syncope burden was reduced from 0.35 ±0.3 at initial evaluation to 0.08 ±0.02 during follow-up. Volume expansion by salt supplementation is also frequently recommended. Ingestion of approximately 500 mL of water acutely improves orthostatic tolerance to tilt in healthy persons and may be of value as prophylaxis for syncope in blood donors. The effectiveness of water ingestion alone in the management of patients with recurrent neurally mediated syncope has not been well studied.

TABLE 43.7

Treatment of Neurally Mediated and Reflex-Mediated Syncope

TREATMENT	CLASS	LEVEL OF EVIDENCE
Patient education on diagnosis and prognosis.	I	C-EO
Physical counterpressure maneuvers can be useful in patients with vasovagal syncope (VVS) who have a sufficiently long prodromal period.	IIa	B-R
Midodrine is reasonable in patients with recurrent VVS with no history of hypertension, heart failure, or urinary retention. Cardiac pacing should be considered with frequent recurrent reflex syncope, age >40 years, and documented spontaneous cardioinhibitory response during monitoring of recurrent syncope.	IIa	B-R
The use of orthostatic training is uncertain in patients with frequent VVS. Midodrine may be indicated in patients with neurally mediated syncope refractory to conservative treatment approaches.	IIb	B-R
Dual-chamber pacing might be reasonable in a select population of patients age 40 or older with recurrent VVS and prolonged spontaneous pauses.	IIb	B-R
Fludrocortisone might be reasonable for patients with recurrent VVS and inadequate response to salt and fluid intake, unless contraindicated.	IIb	B-R
Beta blockers might be reasonable in patients age 42 or older with recurrent VVS.	IIb	B-NR
Encouraging increased salt and fluid intake may be reasonable in select patients with VVS, unless contraindicated.	IIb	C-LD
In select patients with VVS, it may be reasonable to reduce or withdraw medications that can cause hypotension when appropriate.	IIb	C-LD
In select patients with VVS, a selective serotonin reuptake inhibitor might be considered.	IIb	C-LD
Beta blockers are not indicated.	IIb	C-LD

Modified from Shen W, Sheldon RS, Benditt D, et al. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope. J Am Coll Cardiol 2017 [in press].

A recent important shift in the approach used for the treatment of neurally mediated syncope has resulted from the effectiveness of “physical” measures and maneuvers in the treatment of patients with this condition.[1] Isometric physical counterpressure maneuvers such as leg crossing or handgrip with arm tensing can prevent syncope in many patients with neurally mediated hypotension. The 2017 ACC/AHA/HRS guidelines on management of syncope identify the following physical measures as class IIA treatments of neurally mediated syncope.[1] It has been reported that 2 minutes of an isometric handgrip maneuver initiated at the onset of symptoms during tilt testing rendered two thirds of patients asymptomatic. Other studies have demonstrated that tilt (standing) training is effective in the treatment of neurally mediated syncope. Standing training involves leaning against a wall with the heel 10 inches (25 cm) from the wall for progressively longer periods for 2 to 3 months. Standing time should initially be 5 minutes two times per day with a progressive increase to 40 minutes twice daily. Although the results of nonrandomized studies of standing training have been positive, the results of randomized trials suggest that standing training may have only limited effectiveness.

In contrast to these effective physical maneuvers, the value of pharmacologic agents is less certain. Medications that are generally relied on to treat neurally mediated syncope include beta blockers, fludrocortisone, serotonin reuptake inhibitors, and midodrine. Despite the widespread use of these agents, the quality and quantity supporting these medications in the treatment of neutrally mediated syncope are limited. **Table 43.7** shows the recommendation class for each of these medications based on the 2017 ACC/AHA/HRS syncope guidelines.[1] Even though beta blockers were previously considered by many to be first-line therapy, recent studies have reported that the beta blockers metoprolol, propranolol, and nadolol are no more effective than placebo.[13] A recent subanalysis of data from a randomized prospective study evaluating the effectiveness of fludrocortisone (Florinef) reported weak evidence that fludrocortisone may be of therapeutic value despite missing its primary endpoint.[26]

Even though pacemakers have also been found to be valuable in the treatment of some patients with neurally mediated syncope in nonrandomized and nonblinded clinical trials, blinded randomized clinical trials have shown that pacemakers have no benefit.[27] In contrast, one recent randomized trial demonstrated the benefit of implanted pacemakers in a select population of patients with neurally mediated syncope.[28] This double-blind placebo-controlled clinical trial randomly assigned 77 patients 40 years or older with recurrent neurally mediated syncope, documented by implantable loop monitor as associated with 3 seconds or longer of asystole or a 6-second or greater pause without syncope, to dual-chamber pacing

with rate-drop hysteresis or to sensing only. The 2-year estimated syncope recurrence rate was 57% with pacing off and 25% with pacing on. Overall, the risk for recurrent syncope was reduced by 57% with pacing. Although the 2008 guidelines for device-based therapy state that pacemaker implantation has a class IIb indication for the treatment of patients with highly symptomatic, neurally mediated syncope associated with bradycardia documented spontaneously or at tilt-table testing, this recent prospective randomized clinical trial provides stronger evidence for pacemaker therapy in patients with neurally mediated syncope who meet the clinical profile of the patient population enrolled in this trial. The 2017 ACC/AHA/HRS syncope guidelines provide a class IIb indication for pacing in a specific subgroup of patients with neutrally mediated syncope over 40 years of age[1] (**see Table 43.7**).

When considering pacemaker implantation for patients with neurally mediated syncope, pacemakers that provide specialized pacing algorithms are often selected. These include rate-drop hysteresis or closed-loop stimulation. Closed-loop stimulation is a form of rate-adaptive pacing that responds to myocardial contraction dynamics by measuring variations in right ventricular intracardiac impedance. When an incipient, neurally mediated syncopal episode is detected, the pacing rate is increased. Although no prospective randomized clinical trials exist to determine which pacing feature is superior, several recent nonrandomized or retrospective trials suggest that closed-loop stimulation may be preferable.[28,29] Further research on this evolving approach to the management of neurally mediated syncope is needed.

Future Perspectives

As the U.S. population ages and the prevalence of cardiac disease increases, it is inevitable that syncope will become an increasingly common and important problem that physicians of all types will need to address. The 2017 ACC/AHA/HRS syncope guidelines provide a timely, comprehensive update on syncope and also emphasize that further research is needed. A new generation of experts in syncope must help develop further knowledge regarding the diagnosis and management of patients with syncope. A particularly challenging problem is the management of patients with various types of orthostatic hypotension. Similarly, despite that neurally mediated syncope is the most common cause of syncope, remarkably little progress has been made in understanding the mechanisms of this condition or identifying effective therapies. It is hoped that the next generation of researchers in the field will make important discoveries that will be critical to the development of new treatment approaches for the millions of patients who suffer from this condition.

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PART VI
Preventive Cardiology

OUTLINE

44

The Vascular Biology of Atherosclerosis

Peter Libby

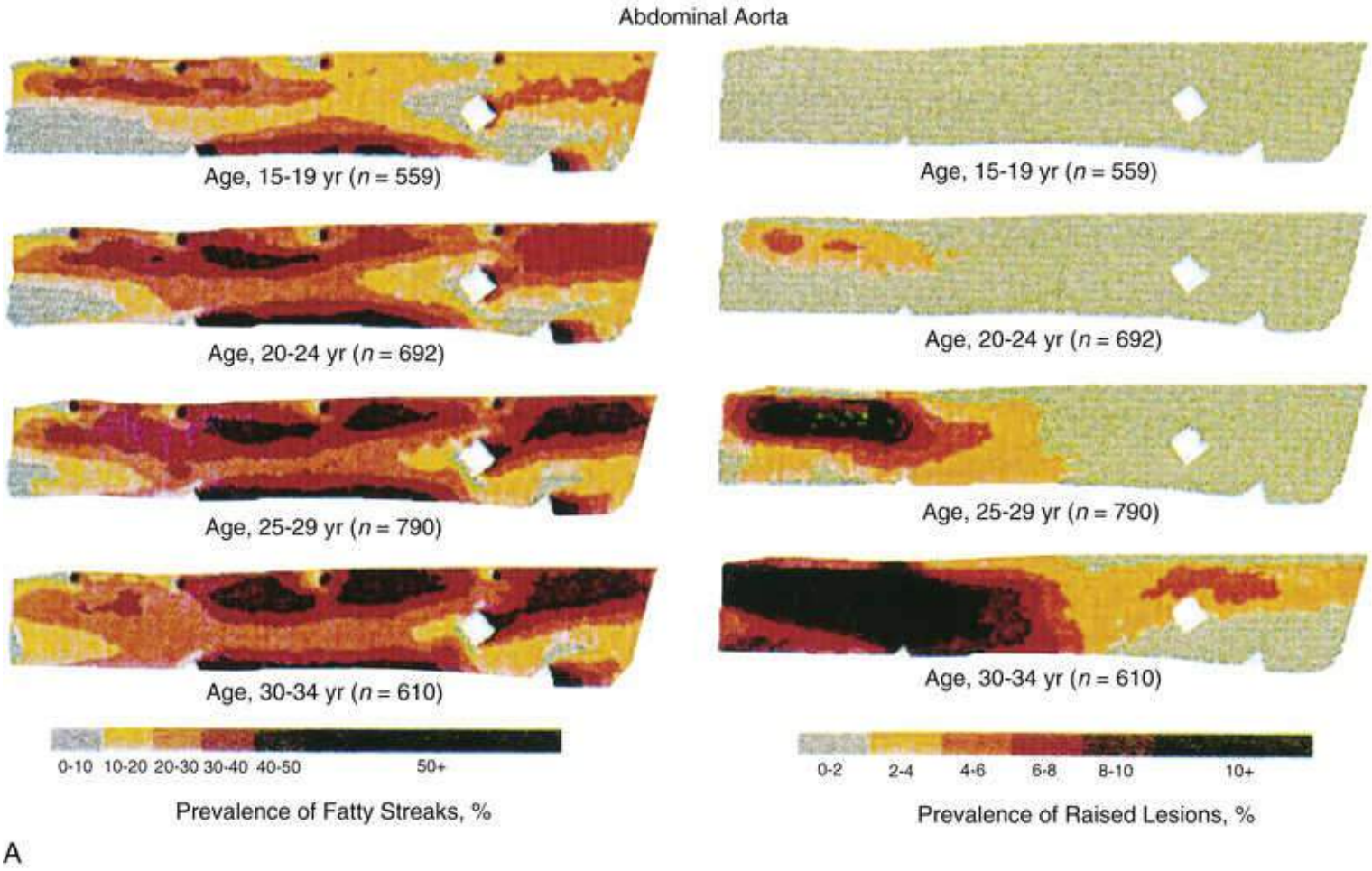
Overview and Background

The 20th century witnessed a remarkable evolution in concepts concerning the pathogenesis of atherosclerosis. This disease has a venerable history, having left traces in the arteries of Egyptian mummies.[1] Atherosclerosis became epidemic as populations increasingly survived early mortality associated with communicable diseases and malnutrition. Economic development and urbanization promoted habits of poor diet (e.g., a surfeit of saturated fats) and diminished physical activity, which can favor atherogenesis (**see Chapters 1, 45, 49, and 50**). These environmental factors have spread steadily, such that we face an epidemic of atherosclerosis that reaches far beyond Western societies.[2]

Currently, arteries are no longer viewed as inanimate tubes. In the mid-19th century, Rudolf Virchow recognized the participation of cells in atherogenesis. A controversy raged between Virchow, who viewed atherosclerosis as a proliferative disease, and Carl von Rokitansky, who believed that atheroma derived from healing and resorption of thrombi. Experiments performed in the early part of the 20th century used dietary modulation to produce fatty lesions in the arteries of rabbits and ultimately identified cholesterol as the culprit. These observations, followed by the characterization of human lipoprotein particles in the mid-20th century, promoted the insudation of lipids as a cause for atherosclerosis. Elements of all these mechanisms indeed contribute to atherogenesis. This chapter summarizes evidence from human studies, animal experimentation, and in vitro work and presents a synoptic view of atherogenesis from the biologic perspective.[3]

Acquaintance with the vascular biology of atherosclerosis should prove useful to the practitioner. Our daily contact with this common disease lulls us into a complacent belief that we understand it better than we actually do. For example, we have begun to understand why atherosclerosis affects certain regions of the arterial tree preferentially and why its clinical manifestations occur only at certain times. Atherosclerosis can involve both large and midsize arteries diffusely.[4] Postmortem and intravascular ultrasound clinical studies have revealed widespread intimal thickening in patients with atherosclerosis. Many asymptomatic persons have intimal lesions in their coronary or carotid arteries even in the early decades of life. At the same time, atherosclerosis produces focal stenoses in certain areas of affected vessels much more often than in others.

Atherosclerosis also displays heterogeneity in time; this disease has both chronic and acute manifestations. Few human diseases have a longer “incubation” period than atherosclerosis, which begins to affect the arteries of many Americans in the second and third decades of life (**Fig. 44.1**). Indeed, many young Americans have abnormal thickening of the coronary arterial intima; yet typically, symptoms of atherosclerosis emerge only after several decades of delay, characteristically appearing even later in women. Despite this indolent time course and prolonged period of clinical inactivity, the dreaded complications of atheroma—myocardial infarction, unstable angina, and stroke—typically occur suddenly and often without warning.



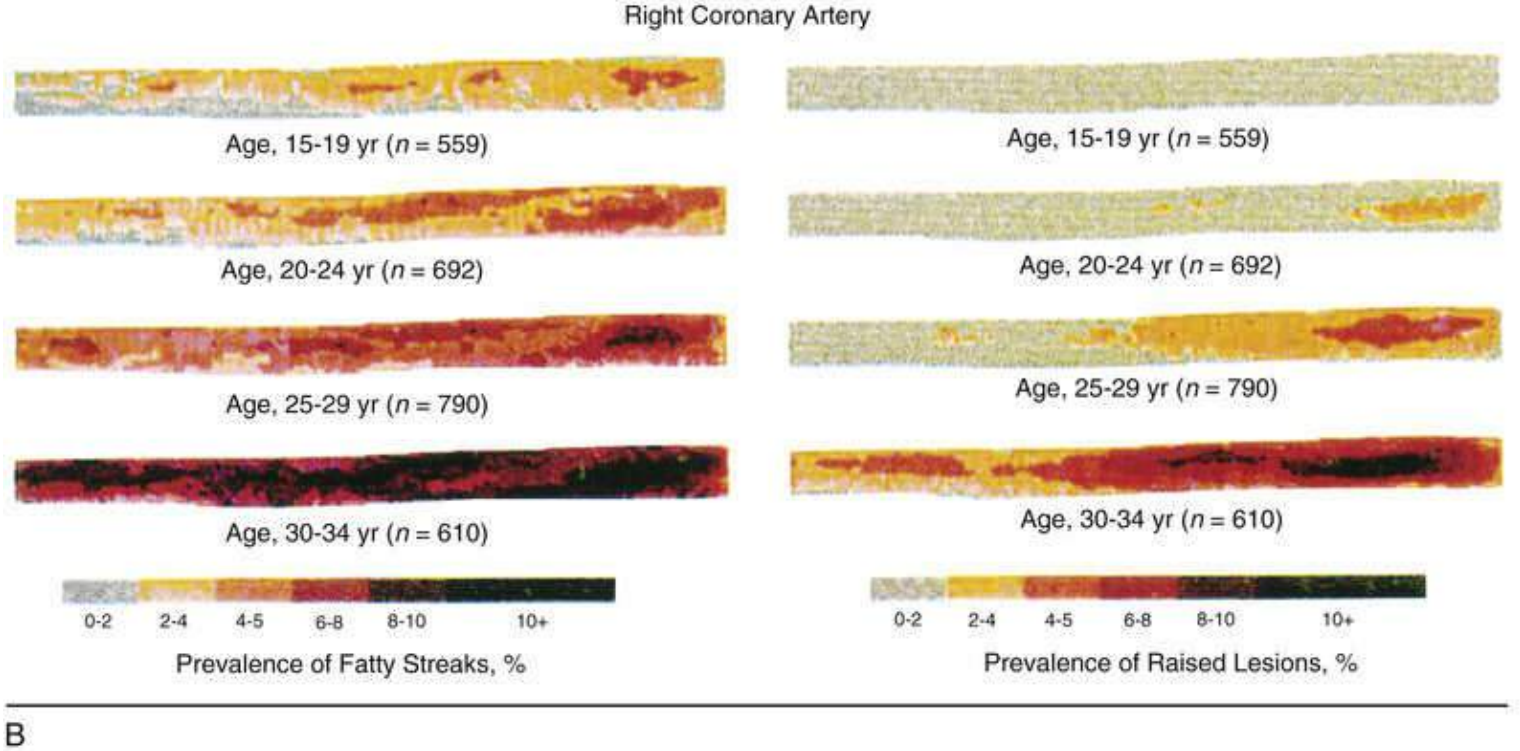


FIGURE 44.1 Prevalence maps of fatty streaks and raised lesions in the abdominal aorta: Pseudocolored representations of morphometric analysis of composite data, from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, on more than 2800 aortas from Americans younger than age 35 who succumbed for noncardiac reasons. **A,** Note the early involvement of the dorsal surface of the infrarenal abdominal aorta by fatty streaks, followed by raised lesions. **B,** A similar but slightly slower progression of lesions affects the right coronary artery. The *bar scales* at bottom in both **A** and **B** show the coding for the pseudocoloring. (From Strong JP, Malcolm GJ, McMahan CA, et al. Prevalence and extent of atherosclerosis in adolescents and young adults. JAMA1999;281:727.)

Another poorly understood issue regarding atherogenesis is its role in the narrowing, or stenosis, of some vessels and in the dilation, or ectasia, of others. Traditionally, cardiologists have focused on stenoses in coronary arteries, but atherosclerosis commonly manifests as aneurysms, as in the aorta. Even in the life history of a single atherosclerotic lesion, a phase of ectasia known as *positive remodeling*, or *compensatory enlargement*, precedes the formation of stenotic lesions. Contemporary vascular biology has begun to shed light on some of these puzzling aspects of atherosclerosis.

Structure of the Normal Artery

Cell Types Composing the Normal Artery

Endothelial Cells

The endothelial cell (EC) of the arterial intima constitutes the crucial contact surface with blood. Arterial ECs possess many highly regulated mechanisms of capital importance in vascular homeostasis that often go awry during the pathogenesis of arterial diseases. For example, the EC provides one of the only surfaces, either natural or synthetic, that can maintain blood in a liquid state during protracted contact (**Fig. 44.2**). This remarkable blood compatibility derives in part from the expression of heparan sulfate proteoglycan molecules on the surface of the EC. These molecules, as with heparin, can serve as a cofactor for antithrombin III, causing a conformational change that allows this inhibitor to bind to and inactivate thrombin. The surface of the EC also contains *thrombomodulin*, which binds thrombin molecules and can exert antithrombotic properties by activating proteins S and C. Should a thrombus begin to form, the normal EC possesses potent fibrinolytic mechanisms associated with its surface. The EC can produce both tissue- and urokinase-type plasminogen activators. These enzymes—t-PA and u-PA, respectively—catalyze the activation of plasminogen to form *plasmin*, a fibrinolytic enzyme. (For a complete discussion of the role of endothelium in hemostasis and fibrinolysis, **see Chapter 93**.)

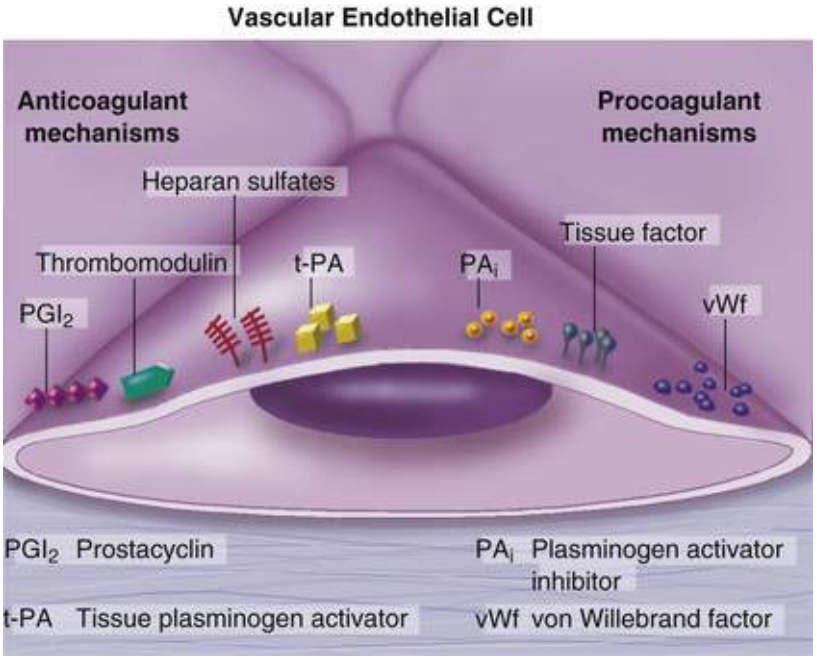


FIGURE 44.2 The endothelial thrombotic balance. This diagram depicts the anticoagulant profibrinolytic functions of the endothelial cell (*left*) and certain procoagulant and antifibrinolytic functions (*right*).

Endothelial cells have a common origin but acquire “bed-specific” characteristics during development. The ECs that form the inner lining of all blood vessels arise during embryogenesis from regions known as the “blood islands,” located on the embryo's periphery. *Angioblasts,* the predecessors of ECs, share this site with the precursors of blood cells. Despite arising from the same site, cells display considerable heterogeneity even during embryologic and early postnatal development. Although ECs presumably derive from a common precursor, the signals they encounter during vessel development differ. As rudimentary blood vessels begin to form, endothelial precursors interact with surrounding cells. The interchange permits spatial and temporal gradients of various stimuli and their receptors on the ECs, leading to this cell type's heterogeneity in the adult. EC heterogeneity depends on both environmental stimuli and epigenetic features acquired during development.[5] Noncoding RNAs also appear pivotal in the regulation of endothelial functions related to atherogenesis[6] (**see Chapter 7**).

Cells that make up various compartments of the arterial wall may originate from bone marrow during postnatal life, as well as from their traditional embryologic sources. In particular, peripheral blood may contain endothelial precursor cells that may help repair areas of endothelial desquamation, a concept that has generated considerable controversy.

Arterial Smooth Muscle Cells

The second major cell type of the normal artery wall, the smooth muscle cell (SMC), has many important functions in normal vascular homeostasis, as a target of therapies in cardiovascular medicine, and in the pathogenesis of arterial diseases.[7] These cells contract and relax and thus control blood flow through the various arterial beds, generally at the level of the muscular arterioles. In the larger types of arteries involved in atherosclerosis, however, abnormal smooth muscle contraction may cause *vasospasm,* a complication of atherosclerosis that may aggravate the embarrassment of blood flow. SMCs synthesize the bulk of the complex arterial extracellular matrix (ECM) that plays a key role in normal vascular homeostasis and in the formation and complication of atherosclerotic lesions. These cells also can migrate and proliferate, contributing to the formation of intimal hyperplastic lesions, including atherosclerosis and restenosis; stent stenosis after percutaneous intervention; or anastomotic hyperplasia, complicating vein grafts. Death of SMCs may promote destabilization of atheromatous plaques or may favor ectatic remodeling and ultimately aneurysm formation.

In contrast with ECs, thought to derive from a common precursor, SMCs can arise from many sources (**Fig. 44.3**). After ECs form tubes, the rudimentary precursor of blood vessels, they recruit the cells that will become SMCs or *pericytes* (smooth muscle–like cells associated with microvessels). In the descending aorta and arteries of the lower body, the regional mesoderm serves as the source of smooth muscle precursors. The mesodermal cells in somites give rise to the SMCs that invest much of the distal aorta and its branches. In arteries of the upper body, however, SMCs actually can derive from a completely different germ layer—neuroectoderm, rather than mesoderm. Before the neural tube closes, neuroectodermal cells migrate and become the precursors of SMCs in the ascending aorta and some of its branches, including the carotid arteries. SMCs in the coronary arteries derive from mesoderm, but in a special way: The precursors of coronary artery SMCs arise from yet another embryologic source, a structure known as the *proepicardial* organ.

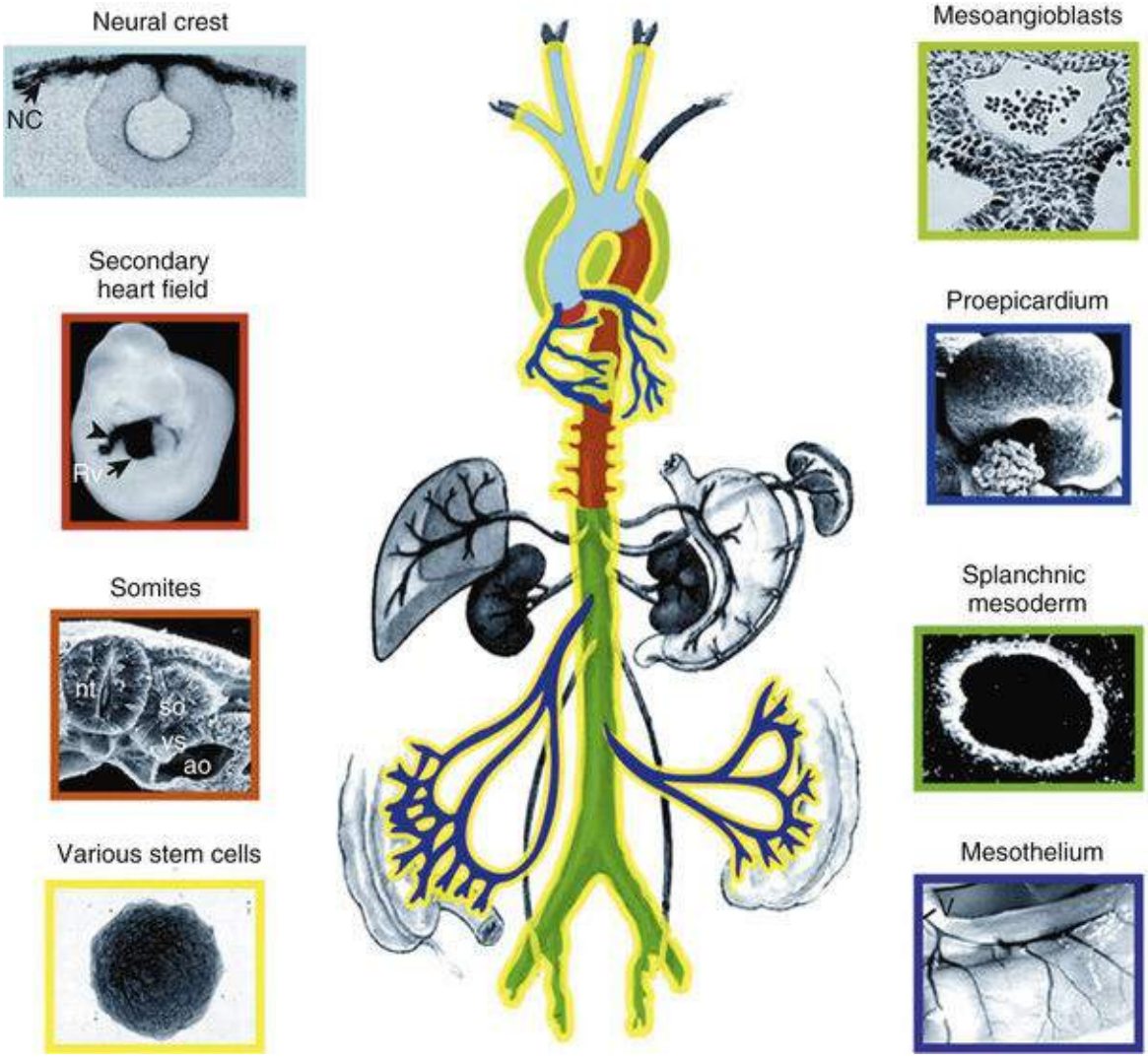


FIGURE 44.3 Diversity of the embryologic origin of vascular smooth muscle cells (SMCs). Different colors represent different embryonic sources for SMCs, as indicated in the outlines on the *boxed images* along the sides of the main drawing. The *yellow outline* indicates local and systemic contributions by various sources of vascular stem cells. The "fate map" (*center*) shows a diverse distribution of SMCs derived from different sources in the aorta and its major branch arteries. With few exceptions, the exact boundaries of SMCs from various sources within the arteries shown are uncertain; accordingly, the boundaries depicted are approximate. In the boxed image at *left* labeled Somites, note the close proximity of the developing dorsal aorta (*ao*) to the ventral sclerotome (*vs*) of the somite (*so*); *NC,* Neural crest; *nt,* neural tube. The lineage-specific boundaries shown may shift during growth and with aging of vessels. *Rv,* Right ventricle. (From Majesky MW. Developmental basis of vascular smooth muscle diversity. Arterioscler Thromb Vasc Biol 2007;27:1248.)

Lineage analyses indicate that large patches of SMCs in arteries arise as expansions of small clones established early in development. A small population of precursor cells may reside in the tunica media of normal arteries that give rise to the SMCs accumulating in injured or atherosclerotic arteries. The transcription factors Krüppel-like factor 4 and myocardin regulate the phenotype of vascular SMCs (**Fig. 44.4**). The heterogeneity of SMCs may have direct clinical implications for understanding several common observations, such as the propensity of certain arteries or regions of arteries to develop atherosclerosis or heightened responses to injury (e.g., proximal left anterior descending coronary artery), and medial degeneration (e.g., proximal aorta in Marfan syndrome). Differential responses of SMCs to regulators of ECM production help explain why the clinical manifestations of systemic defects in fibrillin and elastin characteristically occur locally in the ascending aorta (**see Chapter 63**). The plasticity of SMCs may even extend to giving rise to cells with characteristics and functions of mononuclear phagocytes in murine atherosclerotic plaques.[7]

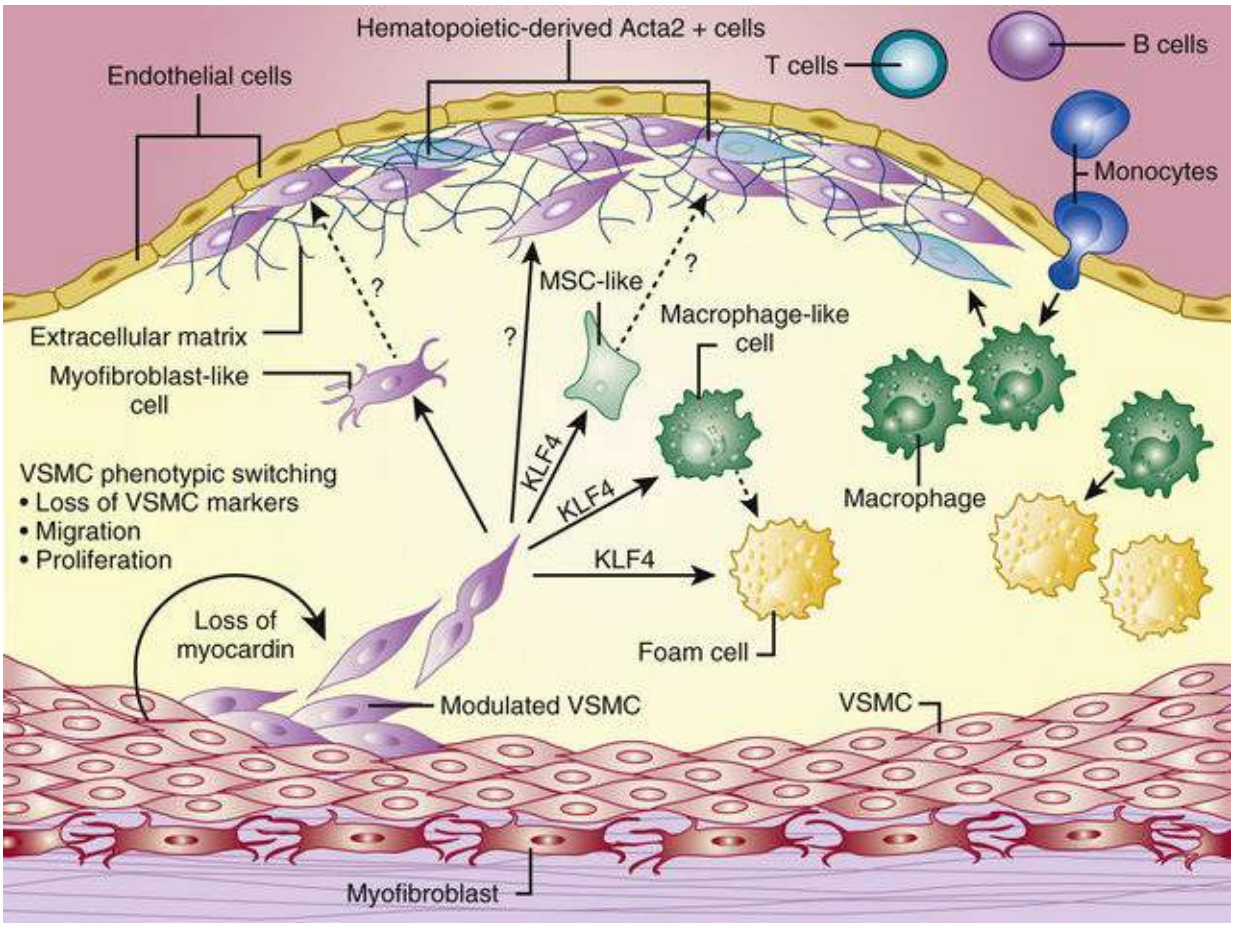


FIGURE 44.4 This diagram summarizes the current knowledge of the identity and origins of vascular smooth muscle cells (VSMCs), mononuclear phagocytes, and their putative derivatives in atheromata. The *solid lines* show pathways known to furnish lesion cells; the *dotted lines* with a "?" indicate possible pathways not yet directly ascertained in animals or in humans. *Acta2,* α-smooth muscle actin; *KLF4,* Krüppel-like factor 4. (Illustration by Ben Smith.) (From Bennett MR et al. Vascular smooth muscle cells in atherosclerosis. Circ Res 2016;118:692-702.)

Layers of the Normal Artery

Intima

An understanding of the pathogenesis of atherosclerosis first requires knowledge of the structure and biology of the normal artery as well as its indigenous cell types. Normal arteries have a well-developed trilaminar structure (**Fig. 44.5**). The innermost layer, the tunica intima, is thin at birth in humans and in many nonhuman species. Although it often is depicted as a monolayer of ECs abutting directly on a basal lamina, the adult human intima actually has a much more complex and heterogeneous structure. The endothelial monolayer resides on a basement membrane containing nonfibrillar collagen types, such as type IV collagen, laminin, fibronectin, and other ECM molecules. With aging, human arteries develop a more complex intima containing arterial SMCs and fibrillar forms of interstitial collagen (types I and III). SMCs produce these ECM constituents of the arterial intima. The presence of a more complex intima, known by pathologists as "diffuse intimal thickening," characterizes most adult human arteries. Some locales in the arterial tree tend to develop a thicker intima than other regions, even in the absence of atherosclerosis (**Fig. 44.6**). For example, the proximal left anterior descending coronary artery often contains a more fully developed intimal cushion of SMCs than that in typical arteries. The diffuse intimal thickening process does not necessarily go hand in hand with lipid accumulation and may occur in persons without substantial burden of atheroma. The internal elastic membrane bounds the tunica intima

abluminally and serves as the border between the intimal layer and the underlying tunica media.

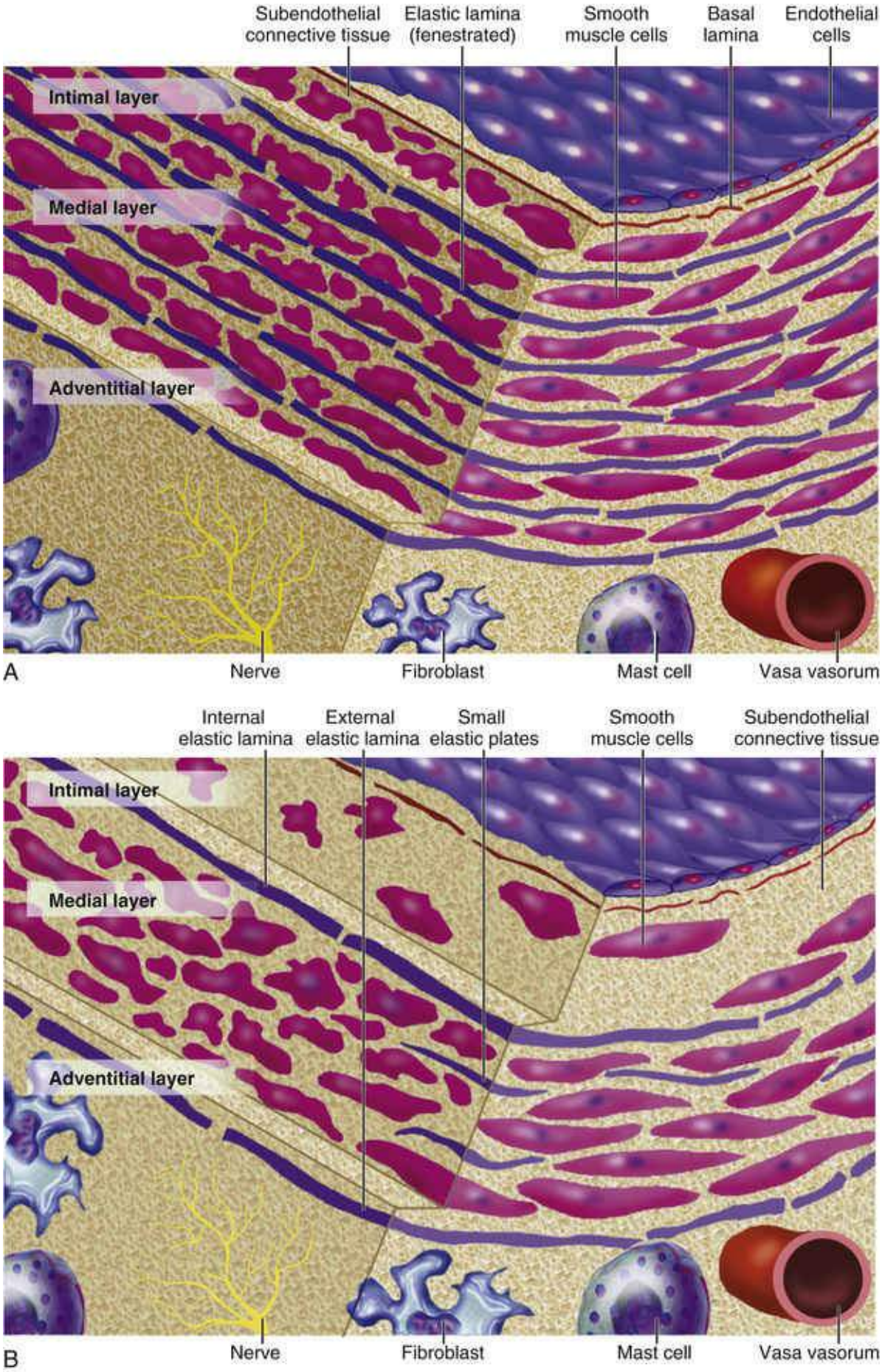


FIGURE 44.5 The structures of normal arteries. **A,** Elastic artery. Note the concentric laminae of elastic tissue that form sandwiches with successive layers of smooth muscle cells (SMCs). Each level of the elastic arterial tree has a characteristic number of elastic laminae. **B,** Muscular artery. In the muscular artery, a collagenous matrix surrounds the SMCs, but the architecture lacks the concentric rings of the well-organized elastic tissue characteristic of larger arteries.

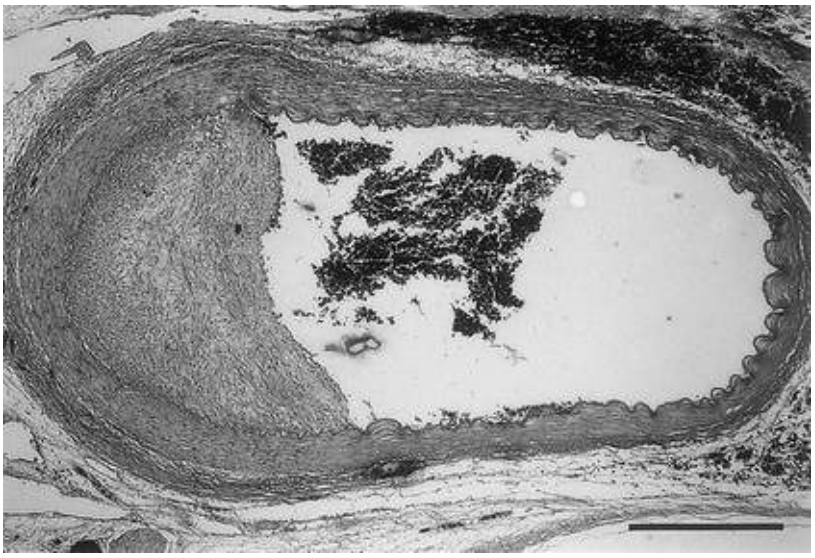


FIGURE 44.6 An intimal cushion shown in cross section through the internal carotid artery of a 10-week-old male infant. Areas in which intimal cushions form in early life tend to develop atheromas more often in later years. *Bar* = 0.5 mm. (From Weniger WJ, Muller GB, Reiter C, et al. Intimal hyperplasia of the infant parasellar carotid artery: Apotential developmental factor in atherosclerosis and SIDS. Circ Res 1999;85:970.)

Tunica Media

The tunica media lies under the intima and internal elastic lamina. The media of elastic arteries such as the aorta has well-developed concentric layers of SMCs, interleaved with layers of elastin-rich ECM (**see Fig. 44.5**). This structure appears well adapted to the storage of the kinetic energy of left ventricular systole by the walls of great arteries. The lamellar structure also certainly contributes to the structural integrity of the arterial trunks. The media of smaller muscular arteries usually has a less stereotypic organization. SMCs in these smaller arteries generally embed in the surrounding matrix in a more continuous than lamellar array. The SMCs in normal arteries seldom proliferate. Indeed, rates of both cell division and cell death are low under usual circumstances. In the normal artery, a state of ECM homeostasis also typically prevails. Because ECM neither accumulates nor atrophies, rates of arterial matrix synthesis and dissolution usually balance each other. The external elastic lamina bounds the tunica media abluminally, forming the border with the adventitial layer.

Adventitia

The adventitia of arteries typically has received little attention, although appreciation of its potential roles in arterial homeostasis and pathology has increased. The adventitia contains collagen fibrils in a looser array than that usually encountered in the intima. Vasa vasorum and nerve endings localize in this outermost layer of the arterial wall. The cellular population in the adventitia is sparser than in other arterial layers. Cells encountered in this layer include fibroblasts and mast cells (**see Fig. 44.5**). Emerging evidence suggests a role for mast cells in atheroma and aneurysm formation in animal models, but their importance in humans remains speculative.[8]

Atherosclerosis Initiation

Extracellular Lipid Accumulation

The first steps in human atherogenesis remain largely conjectural, but the integration of observations of

tissues obtained from young humans with the results of experimental studies of atherogenesis in animals provides hints in this regard. On initiation of an atherogenic diet, typically rich in cholesterol and saturated fat, small lipoprotein particles accumulate in the intima (**Fig. 44.7**, steps 1 and 2). These lipoprotein particles appear to decorate the proteoglycan of the arterial intima and tend to coalesce into aggregates (**Fig. 44.8**). Detailed kinetic studies of labeled lipoprotein particles indicate that a prolonged residence time characterizes sites of early lesion formation in rabbits. The binding of lipoproteins to proteoglycan in the intima leads to their capture and retention, accounting for their prolonged residence time. Lipoprotein particles bound to proteoglycan have increased susceptibility to oxidative or other chemical modifications, considered by many to contribute to the pathogenesis of early atherosclerosis (step 2 in **Fig. 44.7**). Other studies suggest that permeability of the endothelial monolayer increases at sites of lesion predilection to low-density lipoprotein (LDL). Contributors to oxidative stress in the nascent atheroma could include reduced nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate (NADH/NADPH) oxidases expressed by vascular cells, lipoxygenases expressed by infiltrating leukocytes, or the enzyme myeloperoxidase.

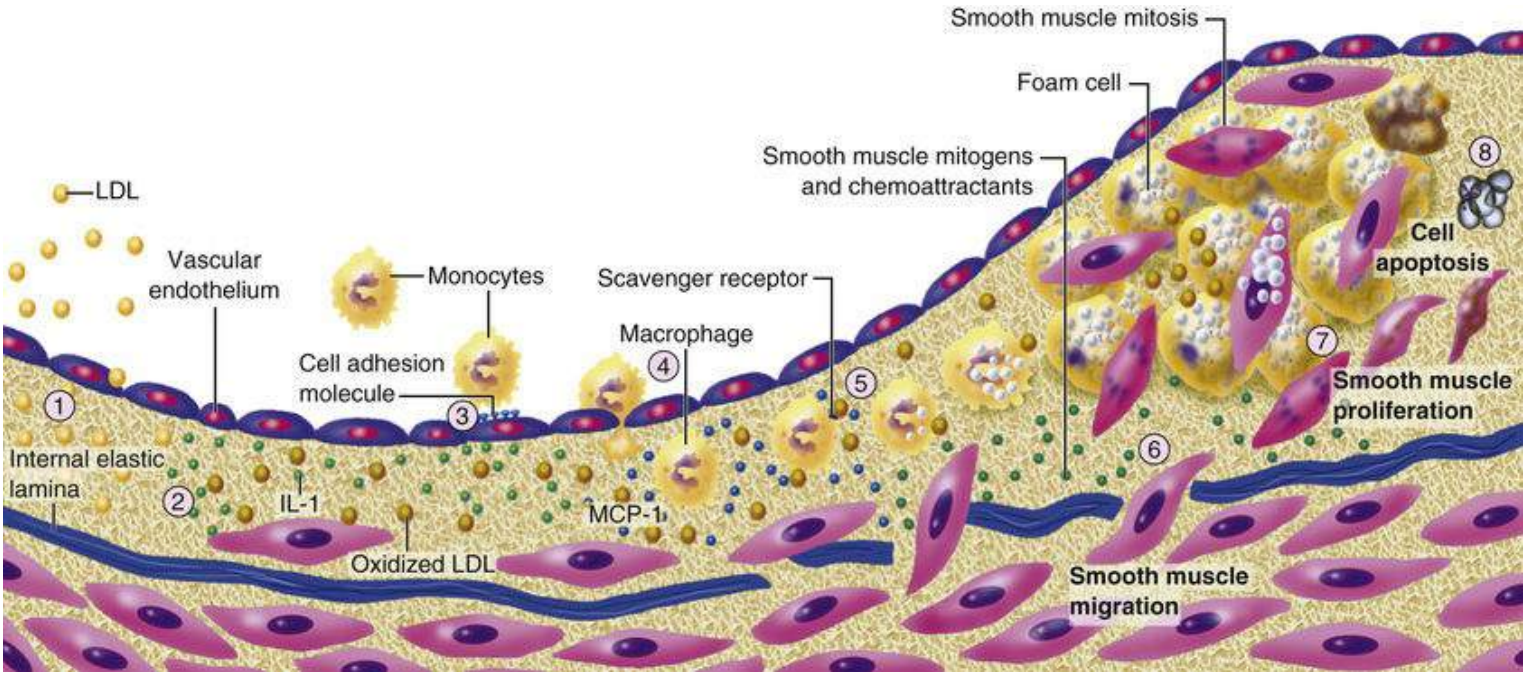


FIGURE 44.7 Schematic of the evolution of the atherosclerotic plaque. *1,* Accumulation of lipoprotein particles in the intima (*yellow spheres*). The modification of these lipoproteins is depicted by the *darker color*. Modifications include oxidation and glycation. *2,* Oxidative stress, including products found in modified lipoproteins, can induce local cytokine elaboration (*green spheres*). *3,* The cytokines thus induced increase expression of adhesion molecules (*blue stalks on endothelial surface*) for leukocytes that cause their attachment and chemoattractant molecules that direct their migration into the intima. *4,* Blood monocytes, on entering the artery wall in response to chemoattractant cytokines such as monocyte chemoattractant protein 1 (*MCP-1*), encounter stimuli such as macrophage colony-stimulating factor that can augment their expression of scavenger receptors. *5,* Scavenger receptors mediate the uptake of modified lipoprotein particles and promote the development of foam cells. Macrophage foam cells are a source of mediators, such as additional cytokines and effector molecules such as hypochlorous acid, superoxide anion (O_2^-), and matrix metalloproteinases. *6,* Smooth muscle cells (SMCs) migrate into the intima from the media. *7,* SMCs can then divide and elaborate extracellular matrix, promoting ECM accumulation in the growing atherosclerotic plaque. In this manner, the fatty streak can evolve into a fibrofatty lesion. *8,* In later stages, calcification can occur (*not depicted*) and fibrosis continues, sometimes accompanied by SMC death (including programmed cell death or apoptosis), yielding a relatively acellular fibrous capsule surrounding a lipid-rich core that also may contain dying or dead cells and their detritus. *IL,* Interleukin; *LDL,* low-density lipoprotein.

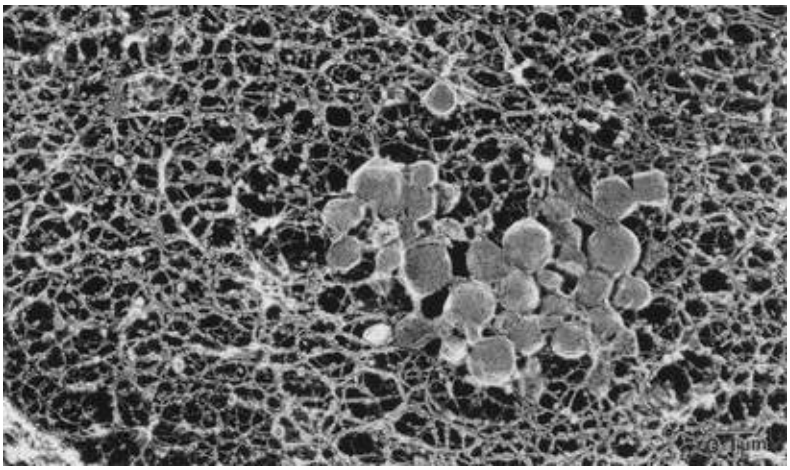


FIGURE 44.8 Scanning electron micrograph of a freeze-etch preparation of rabbit aorta that received an intravenous injection of human low-density lipoprotein (LDL). Round LDL particles decorate the strands of proteoglycan found in the subendothelial region of the intima. By binding LDL particles, proteoglycan molecules can retard their traversal of the intima and promote their accumulation. Proteoglycan-associated LDL appears particularly susceptible to oxidative modification. Accumulation of extracellular lipoprotein particles is one of the first morphologic changes noted after initiation of an atherogenic diet in experimental animals. (From Nievelstein PF, Fogelman AM, Mottino G, Frank JS. Lipid accumulation in rabbit aortic intima 2 hours after bolus infusion of low density lipoprotein: a deep-etch and immunolocalization study of ultrarapidly frozen tissue. Arterioscler Thromb 1991;11:1795.)

Leukocyte Recruitment and Retention

Another hallmark of atherogenesis, leukocyte recruitment and accumulation (step 4 in **Fig. 44.7**), also occurs early in lesion generation (**Fig. 44.9**). The normal EC generally resists adhesive interactions with leukocytes. Even in inflamed tissues, most recruitment and trafficking of leukocytes occurs in postcapillary venules and not in arteries. Very soon after initiation of hypercholesterolemia, however, leukocytes adhere to the endothelium and move between EC junctions, or even penetrate through ECs (transcytosis) to enter the intima, where they begin to accumulate lipids and become foam cells[9-11] (step 5 in **Fig. 44.7**). In addition to the monocyte, T lymphocytes also tend to accumulate in early human and animal atherosclerotic lesions.[12] The expression of certain leukocyte adhesion molecules on the surface of the EC regulates the adherence of monocytes and T cells to the endothelium.[5] Several categories of leukocyte adhesion molecules exist. Members of the *immunoglobulin* (Ig) superfamily include structures such as vascular cell adhesion molecule 1 (VCAM-1), or CD106. This adhesion molecule is of particular interest in the context of early atherogenesis because it interacts with an integrin, very late antigen 4 (VLA-4), characteristically expressed by only those classes of leukocytes that accumulate in nascent atheroma—monocytes and T cells. Moreover, experimental studies have shown expression of VCAM-1 on ECs overlying very early atheromatous lesions. Other members of the Ig superfamily of leukocyte adhesion molecules include intercellular adhesion molecule 1 (ICAM-1). This molecule is more promiscuous, both in the types of leukocytes it binds and in its wide and constitutive expression at low levels by ECs in many parts of the circulation.

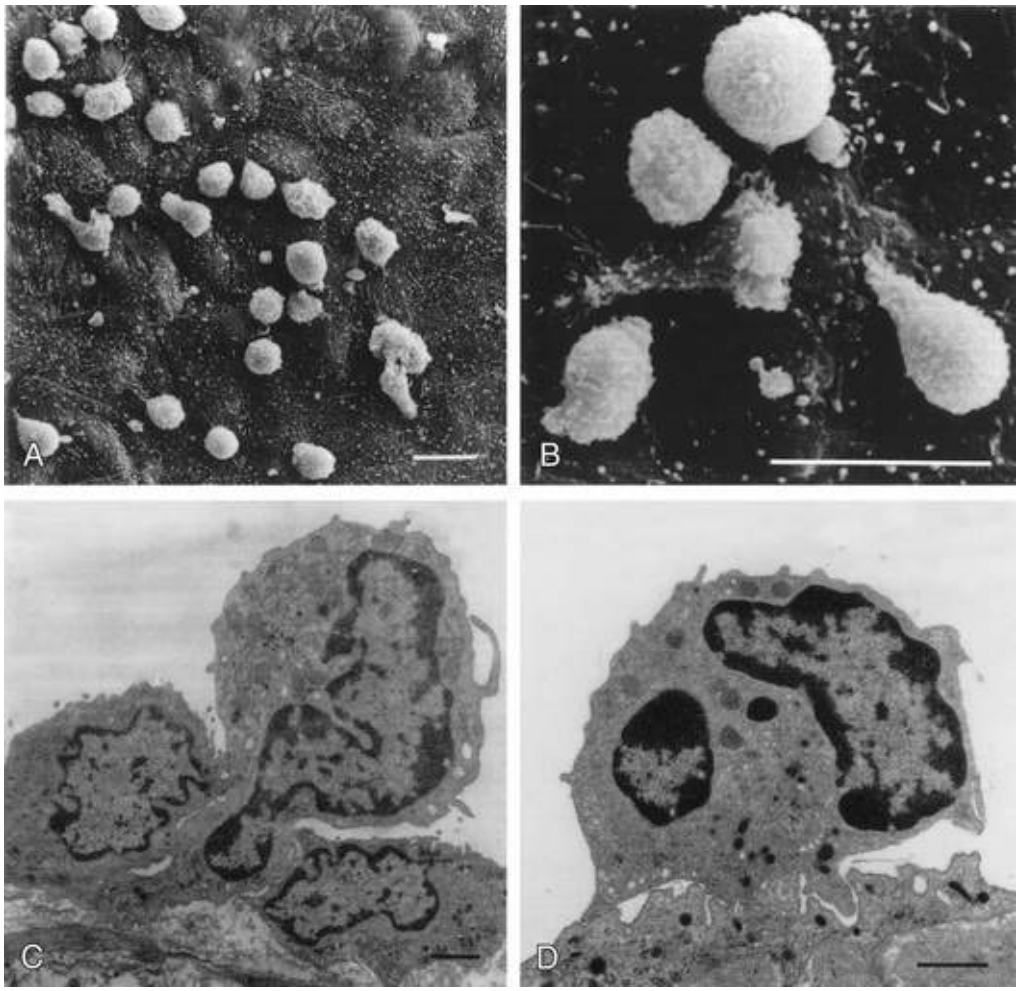


FIGURE 44.9 Electron microscopy of leukocyte interactions with the artery wall in hypercholesterolemic nonhuman primates. **A, B,** Scanning electron micrographs demonstrate the adhesion of mononuclear phagocytes to the intact endothelium 12 days after initiation of a hypercholesterolemic diet in monkeys. **C, D,** Transmission electron micrographs. Note the abundant interdigitations and intimate association of the monocyte with the endothelium in **C.** In **D,** a monocyte appears to come between two endothelial cells to enter the intima. (From Faggiotto A, Ross R, Harker L. Studies of hypercholesterolemia in the nonhuman primate. I. Changes that lead to fatty streak formation. Arteriosclerosis 1984;4:323.)

Selectins constitute the other broad category of leukocyte adhesion molecules. The prototypic selectin, E-selectin or CD62E (E stands for "endothelial," the cell type that selectively expresses this particular family member), probably has little to do with early atherogenesis. E-selectin preferentially recruits polymorphonuclear leukocytes, a cell type seldom found in early atheromata (but an essential protagonist in acute inflammation and host defenses against bacterial pathogens). Moreover, ECs overlying atheroma do not express high levels of this adhesion molecule. Other members of this family, including P-selectin, or CD62P (P stands for "platelet," the original source of this adhesion molecule), may play a greater role in leukocyte recruitment in atheroma, because ECs overlying human atheroma express this adhesion molecule. Selectins tend to promote saltatory or rolling locomotion of leukocytes over the endothelium. Adhesion molecules belonging to the immunoglobulin superfamily tend to promote tighter adhesive interactions and immobilization of leukocytes. Studies in genetically altered mice have proven roles for VCAM-1 and P-selectin (including both platelet-derived and endothelium-derived P-selectin) in experimental atherosclerosis. Increasing evidence supports the accumulation in atheromas of distinct subtypes of mononuclear phagocytes.[13,14] The functional consequences of this heterogeneity of macrophage populations in plaques require further study, especially in humans. In mice, a particularly proinflammatory subset of monocytes accumulates in the spleen and peripheral blood in response to hypercholesterolemia and preferentially populates nascent atheroma.[13]

Once adherent to the endothelium, leukocytes must receive a signal to penetrate the endothelial monolayer and enter the arterial wall (step 4 in **Fig. 44.7**). The current concept of directed migration of leukocytes involves the action of protein molecules known as chemoattractant cytokines, or *chemokines*. Observations on human atheroma and functional studies in vitro and in genetically altered mice point to causal roles of various chemokines in atherogensis.[5,15] In addition to recruitment, the accumulation of leukocytes in the arterial wall depends on factors that cause their retention in the intimal lesions. Retention factors include netrin-1 interacting with its receptor UNC5b (both induced by hypoxia), a protein that impairs macrophages from exiting plaques.[16]

Focality of Lesion Formation

The spatial heterogeneity of atherosclerosis is challenging to explain in mechanistic terms. Equal concentrations of blood-borne risk factors such as lipoproteins bathe the endothelium throughout the vasculature. It is difficult to envisage how injury resulting from inhalation of cigarette smoke could produce any local rather than global effect on arteries, yet stenoses caused by atheromas typically form focally. Some researchers have invoked a multicentric origin hypothesis of atherogenesis, positing that atheromas arise as benign leiomyomas of the artery wall. The monotypia of various molecular markers in individual atheromas supports this monoclonal hypothesis of atherogenesis. The location of sites of lesion predilection at proximal portions of arteries after branch points or bifurcations at flow dividers, however, suggests a hydrodynamic basis for early lesion development. Arteries without many branches (e.g., the internal mammary and radial arteries) tend not to develop atherosclerosis.

Two concepts can aid in understanding how local flow disturbances might render certain foci sites of lesion predilection. Locally disturbed flow could induce alterations that promote the steps of early atherogenesis. Alternatively, the laminar flow that usually prevails at sites that do not tend to develop early lesions may elicit antiatherogenic homeostatic mechanisms (atheroprotective functions).[5] The EC experiences the laminar shear stress of normal flow and the disturbed flow (usually yielding decreased shear stress) at sites of predilection. Multiple transduction mechanisms operate to signal the local shear stress environment to ECs.[17] For example, these cells have cilia on their luminal surface and adhesion receptors in their lateral cell membrane that can sense tension, transmit forces to the cortical cytoskeleton, and potentially regulate ion channels or G protein–coupled receptors that signal changes in gene expression (**Fig. 44.10**). In vitro data suggest that laminar shear stress can augment the expression of genes that may protect against atherosclerosis, including forms of the enzymes superoxide dismutase (SOD) and nitric oxide synthase (NOS). SOD can reduce oxidative stress by catabolizing the reactive and injurious superoxide anion. Endothelial NOS produces the well-known endogenous vasodilator nitric oxide. Beyond its vasodilating actions, however, nitric oxide (NO) can resist inflammatory activation of endothelial functions, such as expression of VCAM-1. NO appears to exert this anti-inflammatory action at the level of gene expression by interfering with the transcriptional regulator nuclear factor kappa B (NF-κB). NO increases the production of IκBα, an intracellular inhibitor of this important transcription factor. NF-κB regulates numerous genes involved in inflammatory responses in general and in atherogenesis in particular.

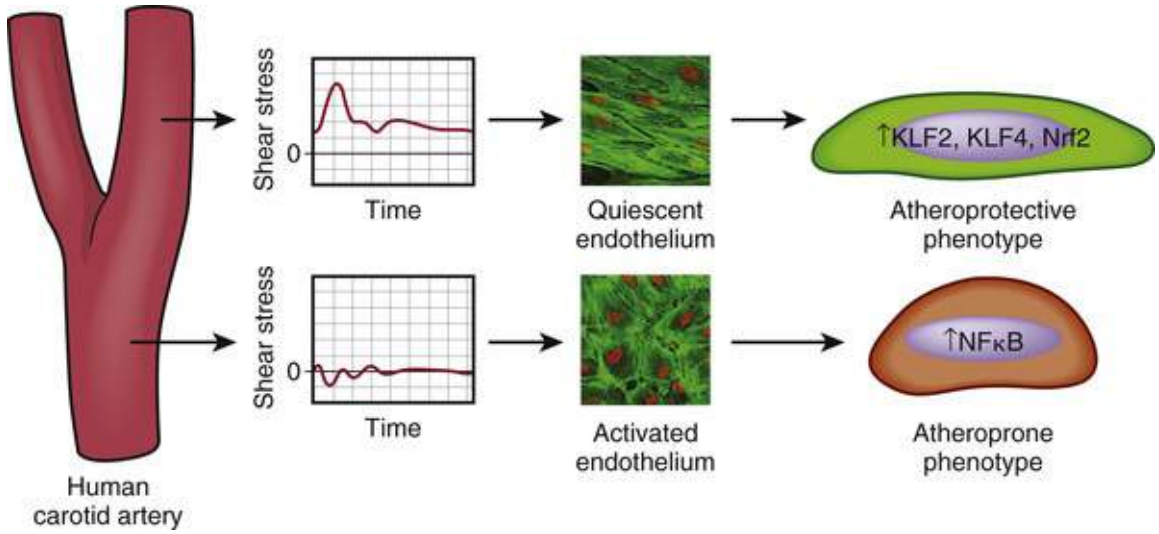


FIGURE 44.10 Hemodynamics determine endothelial functions. Computational analyses of blood flow patterns in vivo in the normal human carotid artery bifurcation provided representative near-wall shear stress waveforms from two hydrodynamically distinct locations known to have distinct predilection to atherogenesis: the distal internal carotid (a region that generally resists lesion formation) and the carotid sinus (a common location for plaque formation). Exposure of monolayers of human endothelial cell in culture to these different biomechanical environments yielded substantially different cell morphologies (depicted by cytoskeletal actin staining) and functions. Pulsatile (unidirectional) laminar flow induced the pivotal transcription factors (Krüppel-like factor [KLF]-2, KLF4, and nuclear factor erythroid 2–related factor [Nrf]-2), which coordinately elicit a palette of atheroprotective functions. In contrast, disturbed (oscillatory) flow enhanced expression of NF-κB, a central transcription factor that governs a number of proinflammatory and proatherogenic functions.

Studies also implicate transcription factors, notably Krüppel-like factor 2 (KLF2), as important regulators of endothelial anti-inflammatory properties. KLF2 can induce endothelial NOS expression and also inhibits NF-κB function by sequestering cofactors needed to boost NF-κB transcriptional activity, resulting in inhibition of the expression of the cassette of NF-κB–dependent genes involved in the inflammatory pathways that operate during atherogenesis.[5] Thus, several atheroprotective mechanisms operate such that under usual conditions of laminar shear stress in normal arteries, the endothelium tonically expresses locally acting anti-inflammatory function. Studies in intact pigs and humans show that sites of low shear stress in coronary arteries are associated with the development of plaque characteristics associated with rupture and thrombosis.[18,19]

Intracellular Lipid Accumulation: Foam Cell Formation

The monocyte, once recruited to the arterial intima, can imbibe lipid and become a foam cell or lipid-laden macrophage (step 5 in **Fig. 44.7**). Although most cells can express the classic cell surface receptor for LDL, that receptor does not mediate foam cell accumulation (**see Chapter 48**). This assertion agrees with the clinical finding of tendinous xanthomas filled with foamy macrophages that develop in patients that lack functional LDL receptors (familial hypercholesterolemia homozygotes). The LDL receptor does not mediate foam cell formation, because of its exquisite regulation by cholesterol. As soon as a cell collects enough cholesterol for its metabolic needs from LDL capture, an elegant transcriptional control mechanism quenches expression of the receptor.[20]

Instead of the classic LDL receptor, various molecules known as *scavenger* receptors appear to mediate the excessive lipid uptake characteristic of foam cell formation. These surface molecules, belonging to several families, bind modified rather than native lipoproteins and participate in their internalization.[21] Because scavenger receptors have functions such as recognition of apoptotic cells and modified lipoproteins, they likely have complex roles during different stages of atherosclerosis. (See

Table 48.3 for a table of that lists scavenger receptors.)

Once macrophages have taken up residence in the intima and become foam cells, they can replicate. In experimental atherosclerosis in mice, monocyte recruitment from blood initially populates the nascent lesion with mononuclear phagocytes, but local proliferation predominates in the established lesion.[11,22] The factors that trigger macrophage cell division in the atherosclerotic plaque probably include hematopoietic growth factors such as macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and interleukin-3 (IL-3). These co-mitogens and survival factors for mononuclear phagocytes exist in human and experimental atheromatous lesions.

Up to this point in the development of the nascent atheroma, the lesion consists primarily of lipid-engorged macrophages. Complex features such as fibrosis, thrombosis, and calcification do not characterize the *fatty streak*, the precursor lesion of the complex atheroma. Several lines of evidence suggest that such fatty streaks can regress, at least to some extent. The relative contributions of reduced recruitment, death of cells within lesions, and egress of cells to reduced accumulation on mononuclear phagocytes in atheromata under conditions of lipid lowering remain controversial.

Evolution of Atheroma

Innate and Adaptive Immunity: Mechanisms of Inflammation in Atherogenesis

During the past decade, the convergence of basic and clinical evidence has demonstrated a fundamental role for inflammation and immunity in atherogenesis[23-27] (**see Chapter 45**). The macrophage foam cells recruited to the artery wall early in this process serve not only as a reservoir for excess lipid, but in the established atherosclerotic lesion also furnish many proinflammatory mediators, including proteins (e.g., cytokines, chemokines),various eicosanoids, and other lipid mediators. These phagocytic cells also can elaborate large quantities of oxidant species, such as superoxide anion or hypochlorous acid, in the milieu of the atherosclerotic plaque. This ensemble of inflammatory mediators can promote inflammation in the plaque and thereby contribute to the progression of lesions. The term *innate immunity* describes this type of amplification of the inflammatory response that does not depend on antigenic stimulation (**Fig. 44.11**).

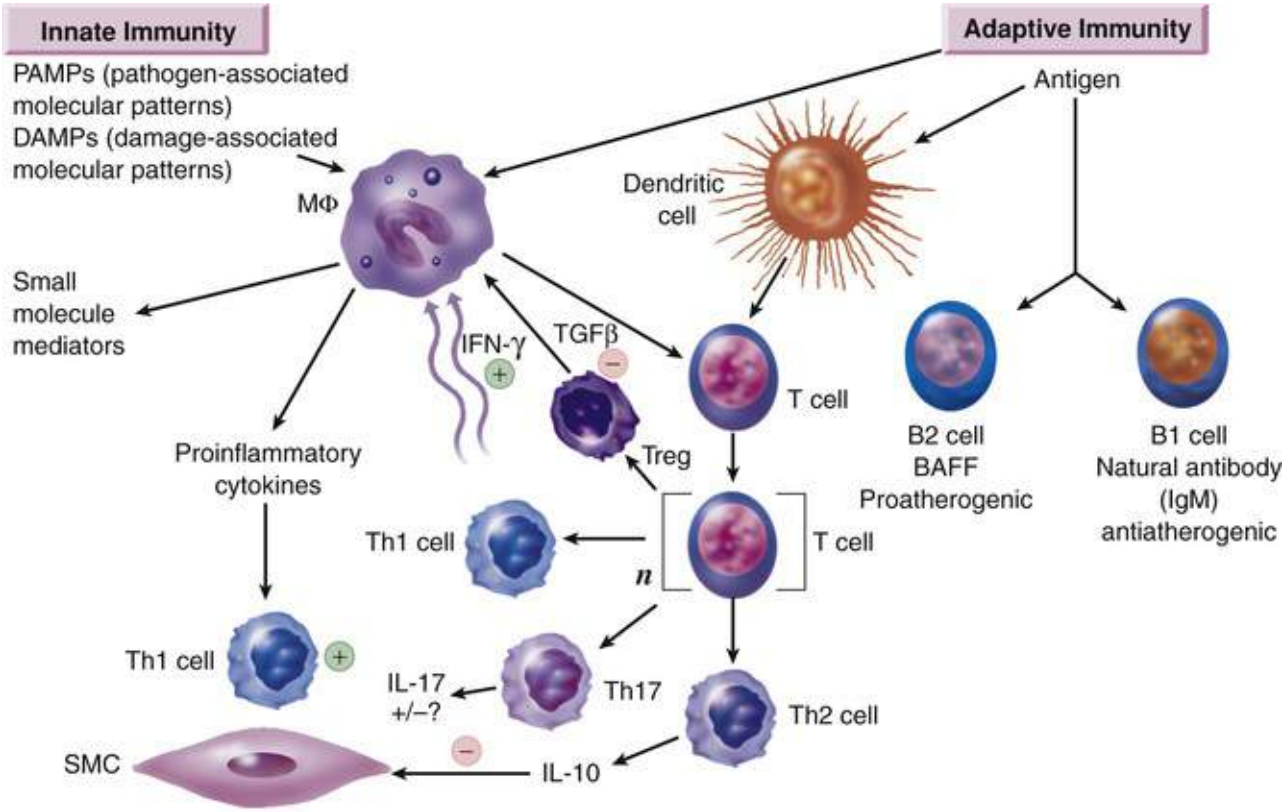


FIGURE 44.11 Innate and adaptive immunity in atherosclerosis. A diagram of the pathways of innate (*left*) and adaptive (*right*) immunity operating during atherogenesis. *BAFF,* B cell–activating factor; *IFN,* interferon; *IL,* interleukin; *MΦ,* macrophage; *SMC,* smooth muscle cell; *Th,* T helper; *TGF,* transforming growth factor. (After Hansson G, Libby P, Schoenbeck U, Yan ZQ: Innate and adaptive immunity in the pathogenesis of atherosclerosis. Circ Res 91:281, 2002.)

In addition to innate immunity, mounting evidence supports a prominent role for antigen-specific or *adaptive immunity* in plaque progression.[25,28] In addition to the mononuclear phagocytes, dendritic cells in atherosclerotic lesions can present antigens to the T cells that constitute an important minority of the leukocytes in atherosclerotic lesions.[11] Candidate antigens for stimulation of this adaptive immune response include modified or native lipoproteins, heat shock proteins, beta$_2$-glycoprotein Ib, and infectious agents.[25] The antigen-presenting cells (macrophages, dendritic cells, or ECs) allow the antigen to interact with T cells in a manner that triggers their activation. The activated T cells can then secrete copious quantities of cytokines that modulate atherogenesis.

The helper T cells (bearing CD4) fall into two general categories. Cells of the T helper 1 (Th1) subtype elaborate proinflammatory cytokines such as interferon (IFN)-γ, lymphotoxin, CD40 ligand, and tumor necrosis factor (TNF)-α. This panel of Th1 cytokines can in turn activate vascular wall cells and orchestrate alterations in plaque biology that can lead to plaque destabilization and heightened thrombogenicity. On the other hand, helper T cells slanted toward the production of Th2 cytokines, such as interleukin-10, can inhibit inflammation in the context of atherogenesis. Cytolytic T cells (bearing CD8) can express Fas ligand and other cytotoxic factors that can promote cytolysis and apoptosis of target cells, including SMCs, ECs, and macrophages. The death of all three of these cell types can occur in the atherosclerotic lesion and may contribute to plaque progression and complication. Regulatory T cells (Tregs) can elaborate transforming growth factor (TGF)-β and interleukin-10. Treg lymphocytes bear the markers CD4 and CD25. Both TGF-β and IL-10 can exert anti-inflammatory effects. Several experimental preparations suggest an antiatherosclerotic function of Tregs in vivo.[25,29] Distinct from such anti-inflammatory mechanisms, the operation mediators of resolution may provide another avenue to dampening the inflammatory response during atherogenesis.[30,31]

The role of B cells and antibody in atherosclerosis remains incompletely explored. Humoral immunity may have either atheroprotective or atherogenic properties, depending on the circumstances.[26] B1 cells that produce natural antibodies, many of which recognize oxidatively modified LDL, can protect against experimental atherosclerosis. B2 cells aggravate atherosclerosis in mice by promoting proinflammatory cytokine production, which created interest in immunotherapy to mitigate atherosclerosis.[32,33]

Smooth Muscle Cell Migration and Proliferation

Whereas the early events in atheroma initiation involve primarily altered endothelial function and recruitment and accumulation of leukocytes, the subsequent evolution of atheroma into more complex plaques also involves SMCs (steps 6 and 7 in **Fig. 44.7**). SMCs in the normal arterial tunica media differ considerably from those in the intima of an evolving atheroma.[7] Some SMCs probably arrive in the arterial intima early in life; others accumulate in advancing atheroma after recruitment from the underlying media into the intima or arise from blood-borne precursors. Some cells bearing macrophage markers in mouse atheromata appear to derive from mononuclear phagocytic leukocytes.[7,34]

SMCs in the atherosclerotic intima appear to exhibit a less mature phenotype than that for the quiescent SMCs in the normal arterial medial layer. Instead of expressing primarily isoforms of smooth muscle myosin characteristic of adult SMCs, those in the intima have higher levels of the embryonic isoform of smooth muscle myosin. Thus, SMCs in the intima seem to recapitulate an embryonic phenotype. These intimal SMCs in atheroma appear to be morphologically distinct as well. They contain more rough endoplasmic reticulum and fewer contractile fibers than do normal medial SMCs.

Although replication of SMCs in the steady state appears uncommon in mature human atheroma, bursts of SMC replication may occur during the life history of a given atheromatous lesion. For example, as discussed later, episodes of plaque disruption with thrombosis may expose SMCs to potent mitogens, including the coagulation factor thrombin itself. Thus, accumulation of SMCs during atherosclerosis and growth of the intima may not occur in a continuous and linear manner. Rather, “crises” may punctuate the history of an atheroma, during which bursts of smooth muscle activity may occur (**Fig. 44.12**).

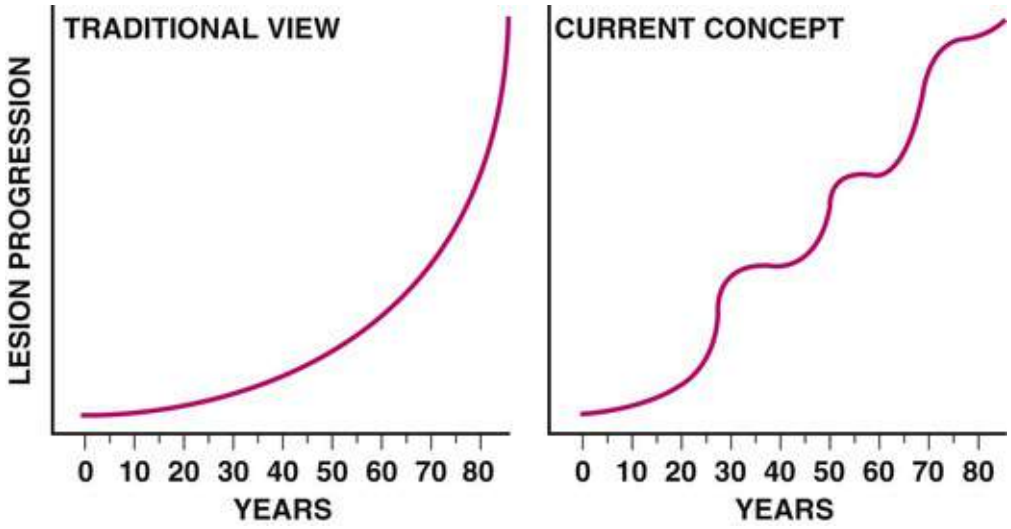


FIGURE 44.12 The time course of atherosclerosis. **Left,** Traditional teaching held that atheroma formation followed an inexorably progressive course with age, as depicted by the smooth upward curve. **Right,** Current thinking suggests an alternative model, a step function rather than a monotonically upward course of lesion evolution in time, as depicted by the serpentine curve. According to this latter model, "crises" can punctuate periods of relative quiescence during the life history of a lesion. Such crises might follow an episode of plaque disruption, with mural thrombosis and healing, yielding a spurt in smooth muscle proliferation and matrix deposition. Intraplaque hemorrhage from rupture of a friable microvessel might produce a similar scenario. Such episodes usually are clinically inapparent. Extravascular events, such as an intercurrent infection with systemic cytokinemia or endotoxemia, could elicit an "echo" at the level of the artery wall, evoking a round of local cytokine gene expression by "professional" inflammatory leukocytes resident in the lesion. The episodic model of plaque progression fits better with human angiographic data than does the traditional model of continuous function.

Smooth Muscle Cell Death During Atherogenesis

In addition to SMC replication, death of these cells also may participate in complication of the atherosclerotic plaque (step 8 in **Fig. 44.7**).[7] Some SMCs in advanced human atheroma exhibit fragmentation of their nuclear DNA that is characteristic of programmed cell death or apoptosis. Apoptosis may occur in response to inflammatory cytokines present in the evolving atheroma. In addition to soluble cytokines that may trigger programmed cell death, T cells in atheroma may participate in eliminating some SMCs. In particular, certain T cell populations known to accumulate in plaques can express Fas ligand on their surface. Fas ligand can engage Fas on the surface of SMCs and, in conjunction with soluble proinflammatory cytokines, lead to SMC death.

Thus, SMC accumulation in the growing atherosclerotic plaque probably results from a tug-of-war between cell replication and cell death. Contemporary cell and molecular biologic research has identified candidates for mediation of both the replication and the attrition of SMCs, a concept that originated from Virchow's careful morphologic observations made in the mid-19th century. Referring to the SMCs in the intima, Virchow noted that early atherogenesis involves a "multiplication of their nuclei" but also noted that cells in lesions can "hurry on to their own destruction."

Arterial Extracellular Matrix

Rather than cells themselves, ECM makes up much of the volume of an advanced atherosclerotic plaque. Accordingly, extracellular constituents of plaque also require consideration. The major ECM macromolecules that accumulate in atheroma include interstitial collagens (types I and III) and proteoglycans such as versican, biglycan, aggrecan, and decorin. Elastin fibers also may accumulate in

atherosclerotic plaques. Arterial SMCs produce these ECM molecules in disease, just as they do during development and maintenance of the normal artery (step 7 in **Fig. 44.7**). Stimuli for excessive collagen production by SMCs include platelet-derived growth factor (PDGF) and TGF-β, a constituent of platelet granules, and a product of many cell types found in lesions, including Treg lymphocytes.

As with accumulation of SMCs, ECM secretion also depends on a balance, as noted earlier. In this case, the counterpoise to biosynthesis of the ECM molecules is breakdown catalyzed in part by catabolic enzymes, notably the matrix metalloproteinases (MMPs). Dissolution of ECM macromolecules undoubtedly contributes to the migration of SMCs as they penetrate into the intima from the media through a dense ECM, traversing the elastin-rich internal elastic lamina.

Extracellular matrix breakdown also likely plays a role in arterial remodeling that accompanies lesion growth. During the early life of an atheromatous lesion, plaques grow outwardly, in an abluminal direction, rather than inwardly, in a way that would lead to luminal stenosis. This outward growth of the intima leads to an increase in the caliber of the entire artery. This so-called positive remodeling or compensatory enlargement must involve turnover of ECM molecules to accommodate the circumferential growth of the artery. Luminal stenosis tends to occur only after the plaque burden exceeds approximately 40% of the cross-sectional area of the artery.

Angiogenesis in Plaques

Atherosclerotic plaques develop their own microcirculation as they grow, because of endothelial migration and replication. Histologic examination with appropriate markers for ECs reveals a rich neovascularization in evolving plaques. These microvessels probably form in response to angiogenic peptides overexpressed in atheroma. These angiogenesis factors include vascular endothelial growth factor (VEGF) forms of fibroblast growth factors, placental growth factor (PlGF), and oncostatin M.

These microvessels within plaques probably have considerable functional significance. For example, the abundant microvessels in plaques provide a relatively large surface area for the trafficking of leukocytes, which could include both entry and exit of leukocytes. Indeed, in the advanced human atherosclerotic plaque, microvascular endothelium displays mononuclear cell–selective adhesion molecules such as VCAM-1 much more prominently than does the macrovascular endothelium overlying the plaque. The microvascularization of plaques also may allow growth of the plaque, overcoming diffusion limitations on oxygen and nutrient supply, analogous to the concept of tumor angiogenic factors and growth of malignant lesions. Consistent with this view, administration of inhibitors of angiogenesis to mice with experimentally induced atherosclerosis limits lesion expansion. Further, the plaque microvessels may be friable and prone to rupture, as with the neovessels in the diabetic retina. Hemorrhage and thrombosis in situ could promote a local round of SMC proliferation and matrix accumulation in the area immediately adjacent to the microvascular disruption (**Fig. 44.13**). This scenario illustrates a special case of the crises described earlier in the evolution of the atheromatous plaque (**see Fig. 44.12**). Attempts to augment myocardial perfusion by enhancing new vessel growth through the transfer of angiogenic proteins or their genes may have adverse effects on lesion growth or may induce clinical complications of atheroma by these mechanisms.

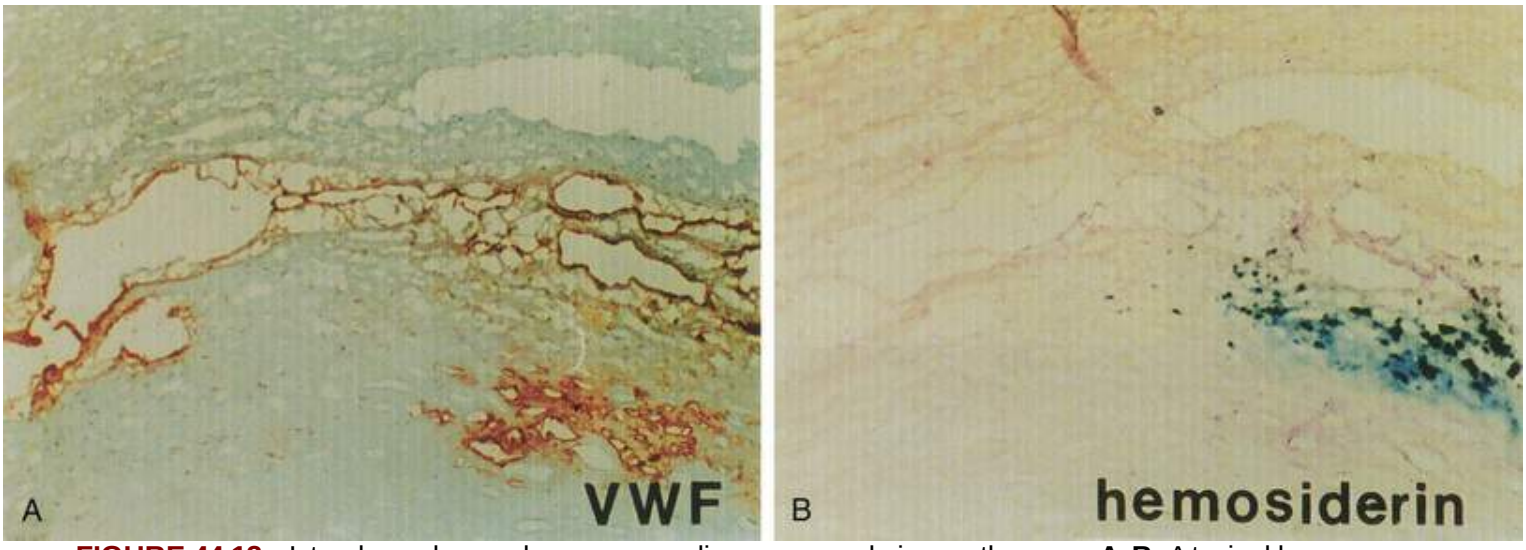


FIGURE 44.13 Intraplaque hemorrhage surrounding neovessels in an atheroma. **A, B,** A typical human atherosclerotic plaque, stained for von Willebrand factor (VWF) **(A)** and for iron by Prussian blue **(B).** The VWF stains the endothelial cells that line the microvascular channels and lakes. Note the extravasated VWF, which colocalizes with iron deposition, indicating hemosiderin deposition consistent with an intraplaque hemorrhage. (After Brogi E, Winkles JA, Underwood R, et al. Distinct patterns of expression of fibroblast growth factors and their receptors in human atheroma and non-atherosclerotic arteries: association of acidic FGF with plaque microvessels and macrophages. J Clin Invest 1993;92:2408.)

Plaque Mineralization

Plaques often develop areas of calcification as they evolve. Indeed, Virchow recognized morphologic features of bone formation in atherosclerotic plaques in early microscopic descriptions of atherosclerosis. Understanding of the mechanism of mineralization during the evolution of atherosclerotic plaques has advanced considerably.[35] Some subpopulations of SMCs may foster calcification by enhanced secretion of cytokines such as bone morphogenetic proteins, homologues of TGF-β. Atheroma calcification shares many mechanisms with bone formation. Receptor activator of NF-κB ligand (RANKL), a member of the TNF family, appears to promote SMC mineral formation through a bone morphogenetic protein 4–dependent pathway. *Osteoprotegerin* can antagonize plaque mineralization by inhibiting RANKL signaling. Genetic absence of osteoprotegerin augments calcification of mouse atheromas, and administration of exogenous osteoprotegerin limits it. The transcription factor Runx-2, activated by inflammatory mediators and oxidative stress among other stimuli, can promote SMC mineral formation by activating AKT (i.e., protein kinase B). Markers of inflammation colocalize with foci of mineralization in nascent mouse atheromata.[35] Microparticles elaborated by macrophages may provide nidi for plaque calcification, yielding another link between inflammatory cells and cardiovascular calcification.[36,37] Sortilin (Sort-1), a genome-wide association study (GWAS) “hit” in atherosclerosis, regulates the loading of alkaline phosphatase into extracellular vesicles, thereby promoting calcification.[38]

Complication of Atherosclerosis

Arterial Stenoses and Clinical Implications

The phases of the atherosclerotic process generally last many years, during which the affected person often has no symptoms. After the plaque burden exceeds the capacity of the artery to remodel outward,

encroachment on the arterial lumen begins. During the chronic asymptomatic or stable phase of lesion evolution, growth probably occurs discontinuously, with periods of relative quiescence punctuated by episodes of rapid progression (**see Fig. 44.12**). Human angiographic studies support this discontinuous growth of coronary artery stenoses. Eventually, the stenoses may progress to a degree that impedes blood flow through the artery. Lesions that produce stenoses of greater than 60% can cause flow limitations under conditions of increased demand. This type of athero-occlusive disease commonly produces chronic stable angina pectoris or intermittent claudication on increased demand. Thus the symptomatic phase of atherosclerosis usually begins many decades after lesion initiation.

In many cases of myocardial infarction (MI), however, no history of previous stable angina heralds the acute event. Acute coronary syndromes may result from thrombi that form as a consequence of disruption of plaques that do not produce a critical stenosis.[39] These findings do not imply that small atheromas cause most MIs. Indeed, culprit lesions of acute MI may be sizable but may not produce a critical luminal narrowing because of compensatory enlargement. Critical stenoses do cause MIs, however, and high-grade stenoses more likely cause acute MI than do nonocclusive lesions. Because the noncritical stenoses by far outnumber the tight focal lesions in a given coronary tree, however, the lesser stenoses cause more MIs, even though high-grade stenoses have a greater individual likelihood of causing infarction.

Thrombosis and Atheroma Complication

Several major modes of plaque disruption provoke most coronary thrombi.[39,40] The first mechanism, accounting for about two thirds of acute MIs, involves a fracture of the plaque's fibrous cap (**Fig. 44.14**, left). Another mode involves a superficial erosion of the intima (**Fig. 44.14, right, and Fig. 44.15**), accounting for a quarter to a third of acute MIs.

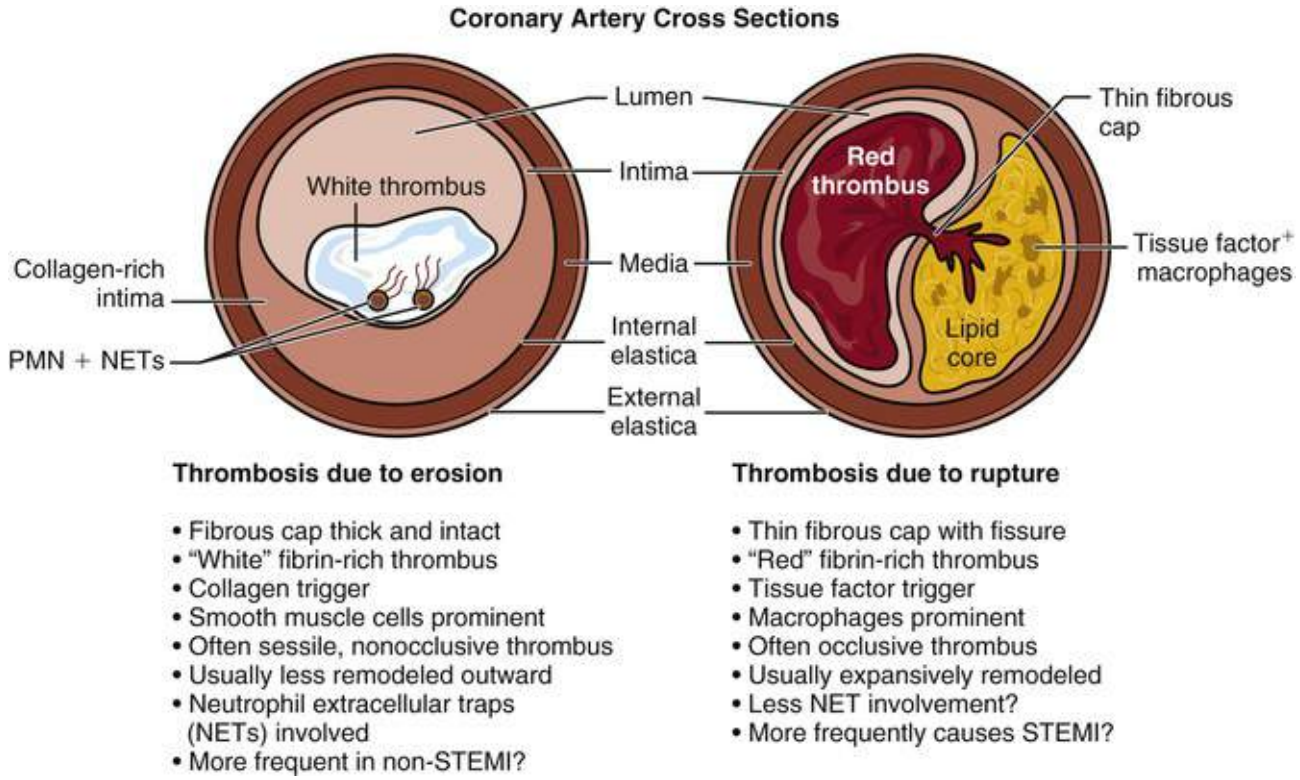


FIGURE 44.14 Distinct mechanisms may cause coronary thrombosis resulting from superficial erosion versus fibrous cap rupture. **Left,** Thrombosis caused by erosion, associated with a sessile, "white" thrombus superimposed on a lesion with abundant extracellular matrix and limited expansive remodeling. Endothelial cell desquamation or death can uncover collagen within the plaque that can trigger such platelet-rich thrombi. Polymorphonuclear leukocytes (PMN) that arrive on the scene can then contribute to a second wave of amplification and propagation of thrombosis resulting from their elaboration of neutrophil extracellular traps (NETs). Erosion may also more frequently cause non–ST-segment elevation myocardial infarction (non-STEMI) than STEMI. **Right,** Thrombosis resulting from rupture, usually associated with lesions with a thin fibrous cap. Such thrombi have more of the character of a "red" fibrin-rich clot. Tissue factor produced by the numerous macrophages in ruptured plaques promote thrombosis. The lesions that rupture and cause thrombi may more often have undergone outward remodeling and are more likely to cause STEMI than non-STEMI.

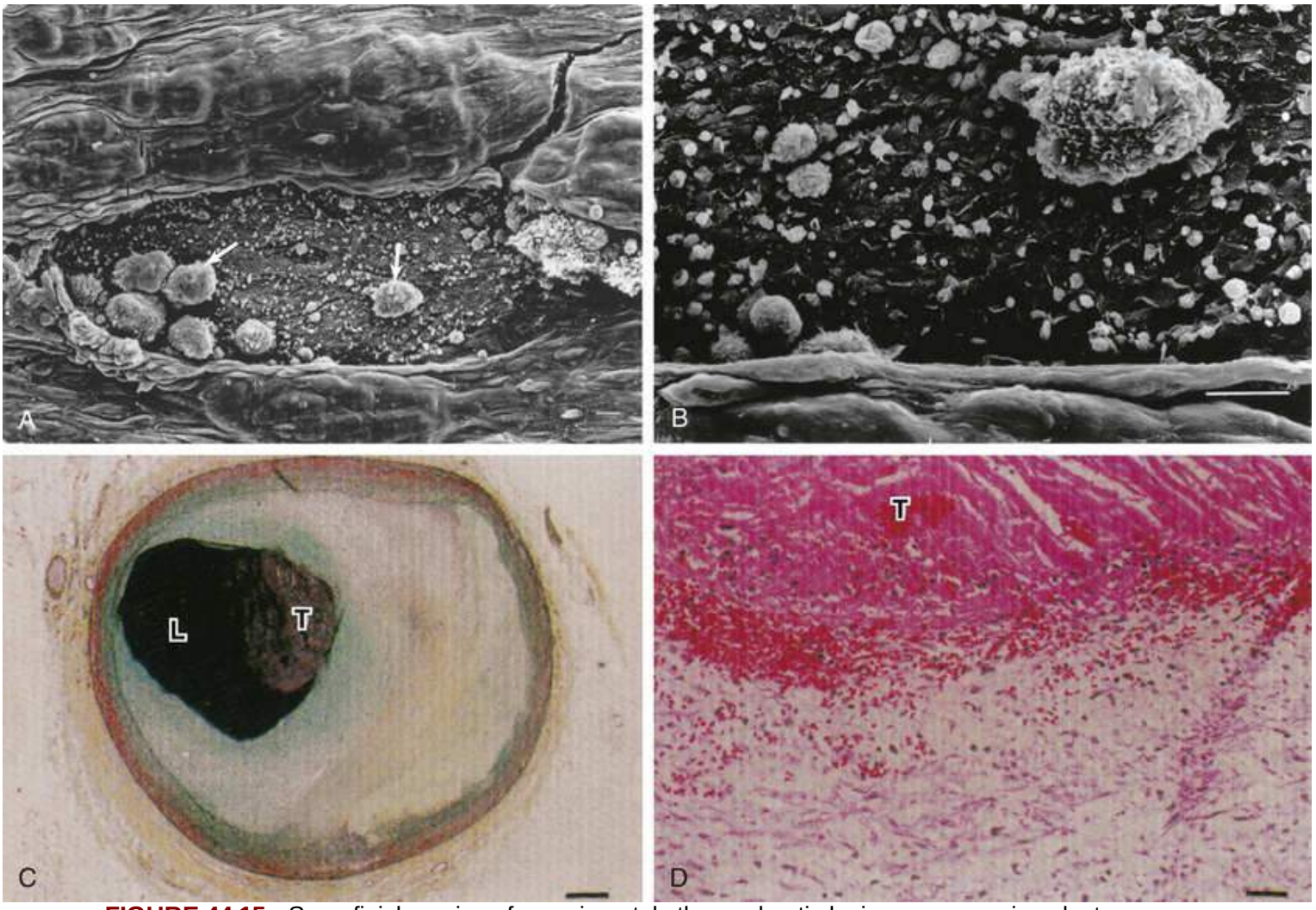


FIGURE 44.15 Superficial erosion of experimental atherosclerotic lesions on scanning electron microscopy. Advanced atherosclerotic plaques can promote thrombosis by superficial erosion of the endothelial layer, exposing the blood and platelets to the subendothelial basement membrane containing collagen platelet activation and thrombosis. **A,** Low-power view shows a rent in endothelium. Leukocytes (*arrows*) have adhered to the subendothelium, which is beginning to be covered with a carpet of platelets. **B,** High-power view is a field selected from the center of **A** that shows the leukocytes and platelets adherent to the subendothelium. **C,** Low-power histologic section through a coronary artery, thrombosed as a result of superficial erosion. **D,** High-power histologic section through a coronary artery, also thrombosed as a result of superficial erosion. *L,* Lumen; *T,* thrombus. (**A, B,** From Faggiotto A, Ross R. Studies of hypercholesterolemia in the nonhuman primate. II. Fatty streak conversion to fibrous plaque. Arteriosclerosis 1984;4:341; **C, D,** from Farb A, Burke AP, Tang AL, et al. Coronary plaque erosion without rupture into a lipid core: a frequent cause of coronary thrombosis in sudden coronary death. Circulation 1996;93:1354.)

Plaque Rupture and Thrombosis

The rupture of the plaque's fibrous cap probably reflects an imbalance between the forces that impinge on the cap and the mechanical strength of the cap. Interstitial forms of collagen provide most of the biomechanical resistance to disruption of the fibrous cap. Thus the metabolism of collagen probably participates in regulating the propensity of a plaque to rupture (**Fig. 44.16**). Factors that decrease collagen synthesis by SMCs can impair their ability to repair and to maintain the plaque's fibrous cap. For example, the T cell–derived cytokine IFN-γ potently inhibits SMC collagen synthesis. On the other hand, as already noted, certain mediators released from platelet granules during activation (e.g., TGF-β, PDGF) can increase SMC collagen synthesis, tending to reinforce the plaque's fibrous structure.

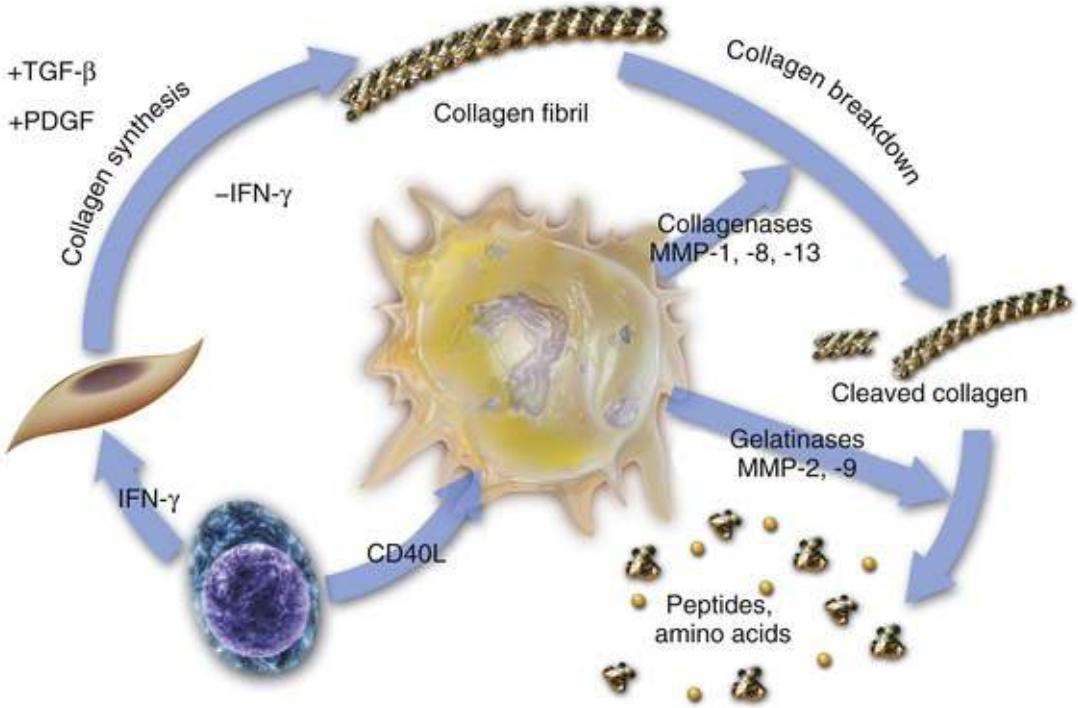


FIGURE 44.16 Inflammation regulates metabolism of fibrillar collagen, which may influence atherosclerotic plaque disruption. The T lymphocyte releases proinflammatory cytokines such as interferon (IFN)-γ (*lower left*) that inhibit smooth muscle cells from producing the new collagen required to lay down the collagenous matrix of the plaque's fibrous cap, which protects the plaque from rupture. The T cell–derived cytokine CD40L stimulates mononuclear phagocytes (*center*) to elaborate interstitial collagenases including matrix metalloproteinase (MMP)-1, MMP-8, and MMP-13, which catalyze the initial proteolytic cleavage of the intact collagen fibril. The cleaved collagen can then undergo additional degradation by gelatinases such as MMP-9. In this way, inflammation can threaten the stability of atherosclerotic plaques and increase their tendency to rupture, thereby causing thromboses, which trigger most acute coronary syndromes. *PDGF,* Platelet-derived growth factor; *TGF,* transforming growth factor. (From Libby P. The molecular mechanisms of the thrombotic complications of atherosclerosis. J Intern Med 2008;263:517.)

In addition to reduced de novo collagen synthesis by SMCs, increased catabolism of the ECM macromolecules that compose the fibrous cap also can contribute to weakening of this structure, rendering it susceptible to rupture and thus thrombosis. The same matrix-degrading enzymes thought to contribute to smooth muscle migration and arterial remodeling also may contribute to weakening of the fibrous cap[39] (**see Fig. 44.16**). Macrophages in advanced human atheroma overexpress MMPs and elastolytic cathepsins, which can break down the collagen and elastin of the arterial ECM. Therefore the strength of the plaque's fibrous cap undergoes dynamic regulation, linking the inflammatory response in the intima with the molecular determinants of plaque stability and thus thrombotic complications of atheroma. Thin fibrous caps are associated with plaque rupture, probably from reduced collagen synthesis and increased degradation.

A relative lack of SMCs also characterizes plaques that have caused fatal MIs. As explained earlier, inflammatory mediators, both soluble and associated with the surface of T lymphocytes, can provoke programmed death of SMCs. Dropout of SMCs from regions of local inflammation within plaques probably contributes to the relative lack of SMCs at points of plaque rupture. Because these cells produce new collagen needed to repair and to maintain the matrix of the fibrous cap, the lack of SMCs may contribute to weakening of the fibrous cap and the propensity of that plaque to rupture.[39]

Plaques that have fatally ruptured exhibit another microanatomic feature: prominent accumulation of macrophages with a large lipid pool. From a strictly biomechanical viewpoint, a large lipid pool can serve to concentrate biomechanical forces on the shoulder regions of plaques, where they frequently fracture. From a metabolic standpoint, the activated macrophage characteristic of the plaque's core region

produces the cytokines and the matrix-degrading enzymes thought to regulate aspects of matrix catabolism and SMC apoptosis in turn. Apoptotic macrophages and SMCs can generate particulate tissue factor, a potential instigator of microvascular thrombosis after spontaneous or iatrogenic plaque disruption. The success of lipid-lowering therapy in reducing the incidence of acute MI or unstable angina in patients at risk may result from a reduced accumulation of lipid and a decrease in inflammation and plaque thrombogenicity. Animal studies and accumulated data from monitoring peripheral markers of inflammation in humans support this concept.[39,41,42]

Thrombosis Caused by Superficial Erosion of Plaques

The underlying molecular and cellular mechanisms of superficial erosion have received much less attention than those involved in plaque rupture[43] (**Fig. 44.14, left**). In experimental atherosclerosis in the nonhuman primate, areas of endothelial loss and platelet deposition occur in more advanced plaques (**see Fig. 44.15**). Apoptosis of ECs could contribute to desquamation of ECs in areas of superficial erosion. Likewise, MMPs, such as certain gelatinases specialized in degrading the nonfibrillar collagen found in the basement membrane (e.g., collagen type IV), also may sever the tetherings of the EC to the subjacent basal lamina and promote their desquamation. Vasospasm of atherosclerotic coronary arteries in rabbits can promote endothelial damage, thrombosis, and MI.[44]

The lesions that provoke superficial erosion appear quite distinct from those that cause plaque rupture (**see Fig. 44.14**). Lesions associated with superficial erosion contain abundant proteoglycan and glycosaminoglycan, as opposed to the collagen-depleted fibrous cap characteristic of ruptured plaques. Eroded lesions have few macrophages, whereas these chronic inflammatory cells abound in ruptured plaques. In contrast, plaques complicated by superficial erosion have thrombi that contain many granulocytes, acute inflammatory cells. Activated granulocytes release many pro-oxidant and proinflammatory mediators, and when they die, they extrude their nuclear DNA to form neutrophil extracellular traps (NETs.) These strands of DNA bind many of the released neutrophil products and provide a “solid-state reactor” that can aggravate the local pro-oxidant, proinflammatory, and prothrombotic environment.[45-47]

Recent work has implicated the innate immune receptor Toll-like receptor 2 (TLR2) in signaling endothelial alterations that may predispose to superficial erosion.[46,48] ECs subjected to disturbed flow in vitro or those overlying atheroma-prone regions of arteries in hyperlipidemic mice overexpress TLR2. Hyaluronic acid in eroded-type plaques may serve as one endogenous ligand for TLR2, causing chronic smoldering endothelial activation that predisposes to sloughing of these cells.[46] Experimentally, neutrophil depletion preserves endothelial barrier function and limits desquamation of intimal ECs in regions of disturbed flow in arteries with fibrous intimal hyperplasia, reminiscent of plaques that undergo erosion in humans.[48]

Thrombosis and Healing in Progression of Atheroma

Most plaque disruptions do not give rise to clinically apparent coronary events. Careful pathoanatomic examination of hearts obtained from patients who have succumbed to noncardiac death has shown a surprisingly high incidence of focal plaque disruptions with limited mural thrombi. Moreover, hearts fixed immediately after explantation from persons with severe but chronic stable coronary atherosclerosis who had undergone transplantation for ischemic cardiomyopathy show similar evidence for ongoing but asymptomatic plaque disruption. Experimentally, in atherosclerotic nonhuman primates, mural platelet

thrombi can complicate plaque erosions without causing arterial occlusion. Therefore, repetitive cycles of plaque disruption, thrombosis in situ, and healing probably contribute to lesion evolution and plaque growth. Such episodes of thrombosis and healing constitute one type of crisis in the history of a plaque that may cause a burst of SMC proliferation, migration, and matrix synthesis (**see Fig. 44.12**).

Plaque disruptions with healing underlie many thrombi that cause sudden death, indicating that nonocclusive thrombosis may precede the fatal event more frequently than previously recognized.[49] TGF-β and PDGF released from platelet granules may promote healing at the site of thrombosis by stimulating migration and collagen synthesis by SMCs, as noted earlier. Thrombin, generated at sites of mural thrombosis, potently stimulates SMC proliferation. The "burned-out" fibrous and calcific atheroma may represent a late stage of a plaque that previously was lipid rich with characteristics associated with rupture, but that has become fibrous and hypocellular because of a wound-healing response mediated by the products of thrombosis and calcification seeded by cell death.

Diffuse and Systemic Nature of Plaque Susceptibility to Rupture and Inflammation in Atherogenesis

Studies at autopsy of atherosclerotic plaques that caused fatal thrombosis brought the notion of the "vulnerable" or "high-risk" plaque to the fore. This observation stimulated many investigators to seek ways of identifying and treating such high-risk atherosclerotic lesions. Current evidence, however, suggests that more than one such high-risk plaque often resides in a given coronary tree. Moreover, the inflammation thought to characterize the so-called vulnerable plaque appears widespread.[50] Studies using various imaging modalities have underscored the multiplicity of such high-risk plaques.[39,50] Angiography, intravascular ultrasound, optical coherence tomography, magnetic resonance imaging, and computed tomographic angiography (among other technologies) all have shed light on the morphology of plaques that cause acute coronary syndromes.[51,52] These various modalities generally have found an association of lesions that cause acute manifestations ("culprit lesions") with positive remodeling or compensatory enlargement of arteries, radiolucency, and spotty calcification.

Several concordant lines of evidence support the systemic and diffuse nature of inflammation associated with acute coronary syndrome (ACS).[50] Moreover, multiple studies have shown that various systemic markers of inflammation, such as C-reactive protein, increase in patients at risk for ACS (**see Chapter 45**). Inflammation precedes ACS, as revealed by profiling of the platelet transcriptome, providing a window on gene transcription many days before the acute event.[53] Thus a combination of imaging studies and investigations using inflammatory markers supports the diffuse and systemic nature of instability of atheromas in individuals with or at risk for ACS. This recognition has important therapeutic implications. In addition to appropriately deployed local revascularization strategies, affected patients also should receive systemic therapy aimed at stabilizing the usually multiple high-risk lesions that may cause recurrent events.

Thrombosis depends not only on the "solid state" of the plaque that may rupture or erode to trigger thrombosis, but also on the "fluid phase" of blood that determines the consequences of a given plaque disruption[54] (**Fig. 44.17**). The amount of tissue factor in the lipid core of a plaque (the solid state) can control the degree of clot formation that will ensue after disruption. The level of fibrinogen in the fluid phase of blood can influence whether a plaque disruption will cause an occlusive thrombus that can precipitate an acute ST-segment elevation myocardial infarction (STEMI) or yield merely a small mural thrombus. Likewise, elevated levels of inhibitors of fibrinolysis, such as plasminogen activator inhibitor 1 (PAI-1), will impede the ability of endogenous thrombolytic enzymes to limit thrombus growth or

persistence. Inflammation regulates both the fluid-phase and the solid-state factors delineated earlier, including tissue factor, fibrinogen, and PAI-1. This helps explain the links between inflammation and thrombotic complications of atherosclerosis that have emerged from laboratory and clinical investigations.

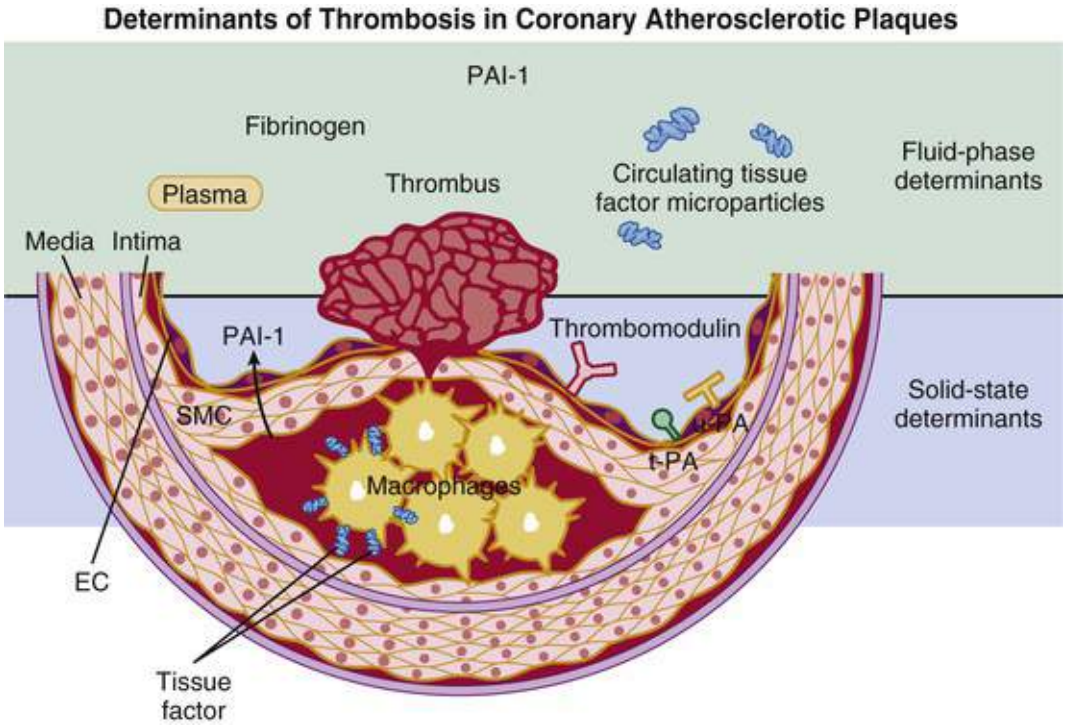


FIGURE 44.17 A two-state concept of atherothrombosis. The high-risk atheroma has a thin fibrous cap overlying a large lipid core that contains tissue factor–bearing macrophages. When the fibrous cap fractures, coagulation proteins in the fluid phase of blood gain access to tissue factor–associated macrophages and tissue factor–bearing microparticles derived from apoptotic cells in the solid state of the plaque. These events trigger thrombus formation on the ruptured plaque. The clinical consequences depend on the amount of tissue factor and apoptosis in the plaque's core and on the levels of fibrinogen and plasminogen activator inhibitor (PAI)-1 in the fluid phase of blood. The interaction of the fluid phase with the solid state will determine whether a given plaque disruption provokes a partial or transient coronary artery occlusion (that can be clinically silent or less often cause an episode of unstable angina) or a devastating persistent and occlusive thrombus that can precipitate an acute myocardial infarction. Inflammation regulates the thrombotic/fibrinolytic balance in both the solid state and the fluid phase, because PAI-1 and fibrinogen both are acute-phase reactants and because the inflammatory mediator CD40 ligand (CD154) induces tissue factor expression. *EC,* Endothelial cell; *SMC,* smooth muscle cell; *t-PA,* tissue plasminogen activator; *u-PA,* urokinase-type plasminogen activator. (From Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation 2005;111:3481.)

Special Cases of Arteriosclerosis

Restenosis After Arterial Intervention

The problems of restenosis and in-stent stenosis after percutaneous arterial intervention represent special cases of arterial hyperplastic disease (**see Chapter 62**). After balloon angioplasty, luminal narrowing recurs in approximately one third of cases within 6 months. Work on the pathophysiology of restenosis after angioplasty initially focused on smooth muscle proliferation. Much of the thinking regarding the pathobiology of restenosis or in-stent stenosis depended on extension to the human situation of the results of withdrawal of an overinflated balloon or overexpanded stents in previously normal animal arteries.

Study of balloon-injured rat carotid arteries permitted precise understanding of the kinetics of intimal thickening after this type of injury, but the attempts to transfer this information to human restenosis met with considerable frustration. This disparity between experimental injury of animal arteries and human restenosis should not be surprising. The substrate of the animal studies was usually a normal artery rather than an atherosclerotic one, with all the attendant cellular and molecular differences.[55] These animal studies, however, did reveal evidence for sustained inflammation in injured arteries.

The widespread use of stents refocused the restenosis problem. The process of in-stent stenosis, in contrast with restenosis after balloon angioplasty, depends primarily on intimal thickening as opposed to negative remodeling. The stent provides a firm scaffold that prevents constriction from the adventitia. The use of drug-eluting stents (DESs) that release agents with anti-inflammatory and antiproliferative properties has greatly reduced in-stent stenosis, and newer-generation DESs appear to limit the potential for augmenting late stent thrombosis associated with earlier DESs. The risk of late thrombosis after radiation brachytherapy or with stents that contain antiproliferative agents may relate to impaired endothelial healing, with attendant loss of the anticoagulant and profibrinolytic properties of the normal intimal lining (**see Fig. 44.2**).

Accelerated Arteriosclerosis After Transplantation

Since the advent of effective immunosuppressive therapy such as cyclosporine, the major limitation to long-term survival of cardiac allografts is the development of an accelerated form of arterial hyperplastic disease (**see Chapter 28**). I favor the term *arteriosclerosis* (hardening of the arteries) rather than atherosclerosis (gruel-hardening) to describe this process because of the inconstant association with lipids (the “gruel” in atherosclerosis). This form of arterial disease often presents a diagnostic challenge. The patient may not experience typical anginal symptoms because of post-transplantation cardiac denervation. In addition, graft coronary disease is concentric and diffuse, not only affecting the proximal epicardial coronary vessels but also penetrating smaller intramyocardial branches (**Fig. 44.18**). For this reason, the angiogram, well suited to visualize focal and eccentric stenoses, consistently underestimates the degree of transplantation arteriosclerosis. Computed tomographic angiography provides a newer avenue to diagnose this condition but still has limitations, although it avoids invasive contrast arteriography.[56,57]

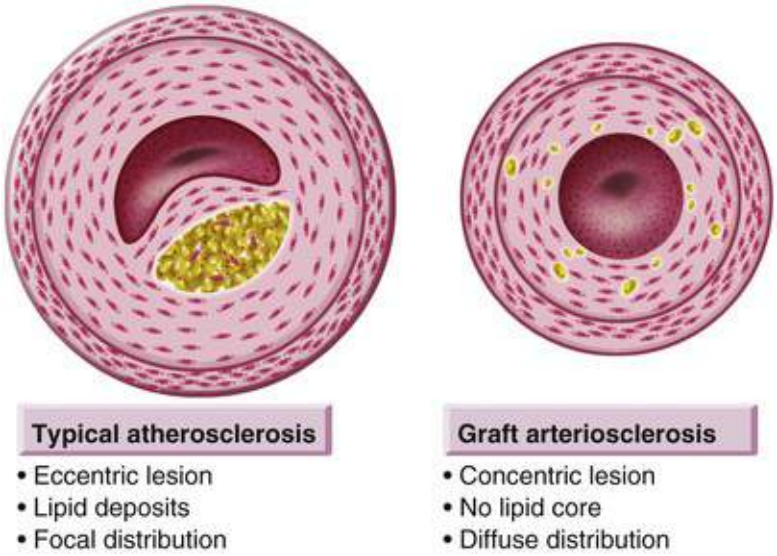


FIGURE 44.18 Comparison of typical and transplantation arteriosclerosis. **Left,** Typical atherosclerosis characteristically forms an eccentric lesion with a lipid core and fibrous cap. **Right,** By contrast, the lesion of transplantation-associated accelerated arteriosclerosis characteristically exhibits a concentric intimal expansion without a clear, central lipid core.

In most centers, most patients undergoing transplantation have atherosclerotic disease and ischemic cardiomyopathy, but a sizable minority undergo heart transplantation for idiopathic dilated cardiomyopathy and may have few (if any) risk factors for atherosclerosis. Even in the absence of traditional risk factors, this latter patient group shares the risk for development of accelerated arteriosclerosis, suggesting that the pathophysiology of this form of accelerated arteriosclerosis differs from that of typical atherosclerosis.

The selective involvement of the engrafted vessels, with sparing of the host's native arteries, suggests that accelerated arteriopathy does not merely result from immunosuppressive therapy or other systemic factors in the transplantation recipient. Rather, these observations suggest that the immunologic differences between the host and recipient vessels might contribute to the pathogenesis of this disease.[23] Considerable evidence from both human and experimental studies currently supports this viewpoint.[58,59] ECs in the transplanted coronary arteries express histocompatibility antigens that can engender an allogeneic immune response from host T cells. The activated T cells can secrete cytokines (e.g., IFN-γ) that can augment histocompatibility gene expression, recruit leukocytes by induction of adhesion molecules, and activate macrophages to produce SMC chemoattractants and growth factors. Interruption of IFN-γ signaling can prevent experimental graft coronary disease in mice.[23]

Therefore, graft arteriosclerosis represents an extreme case of immunologically driven arterial hyperplasia (**Fig. 44.19**) that can occur in the absence of other risk factors. At the other extreme, patients with homozygous familial hypercholesterolemia can develop fatal atherosclerosis in the first decade of life solely as a result of an elevation in LDL. Atherosclerosis in most patients falls somewhere between these two extremes. Analysis of usual atherosclerotic lesions shows evidence for a chronic immune response and lipid accumulation. Thus the study of the extreme cases, such as transplantation arteriopathy and familial hypercholesterolemia, provided insight into elements of the pathophysiology that contribute to the multifactorial form of atherosclerosis that affects the majority of patients.

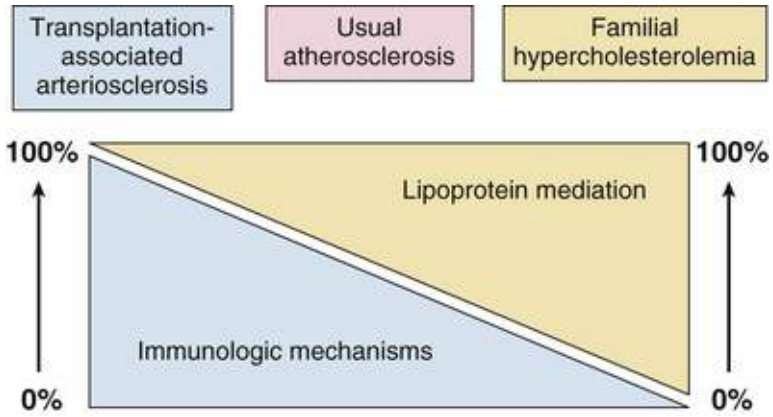


FIGURE 44.19 Multifactorial view of pathogenesis of atherosclerosis, depicting relative contributions of main pathogenic mechanisms in two extreme cases of atherosclerosis. In transplantation-associated disease (*left*), accelerated arteriosclerosis can occur in the transplanted heart in the absence of traditional coronary risk factors. This disease probably represents primarily immune-mediated arterial intimal disease. At the other extreme (*right*), familial hypercholesterolemia, the patient may succumb to rampant atherosclerosis in the first decade of life solely because of an elevated low-density lipoprotein (LDL) level caused by a mutation in the LDL receptor (homozygous familial hypercholesterolemia). Between these two extremes lie most cases of atherosclerosis, probably involving various mixtures of immune and inflammatory or lipoprotein-mediated disease. One can further consider that this diagram extends to a third dimension that would involve other candidate risk factors, such as homocysteine, lipoprotein(a), infection, and tobacco abuse.

Aneurysmal Disease

Atherosclerosis also produces aneurysmal disease (**see Chapter 63**). Why is a single disease process manifested in directionally opposite ways, for example, most often producing stenoses in the coronary arteries but also causing ectasia of the abdominal aorta? In particular, aneurysmal disease characteristically affects the infrarenal abdominal aorta. This region is highly prone to the development of atherosclerosis. Data from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study show that the dorsal surface of the infrarenal abdominal aorta has a particular predilection for the development of fatty streaks and raised lesions in Americans younger than 35 years of age who succumbed for noncardiac reasons (**see Fig. 44.1**). Because of the absence of vasa vasorum, the relative lack of blood supply to the tunica media in this portion of the abdominal aorta might explain the regional susceptibility of this part of the arterial tree to aneurysm formation. In addition, the lumbar lordosis of the biped human may alter the hydrodynamics of blood flow in the distal aorta, yielding flow disturbances that may promote lesion formation.

Histologic examination shows considerable distinction between occlusive atherosclerotic disease and aneurysmal disease. In typical coronary artery atherosclerosis, expansion of the intimal lesion produces stenotic lesions. The tunica media underlying the expanded intima often is thinned, but its general structure remains relatively well preserved. By contrast, transmural destruction of the arterial architecture occurs in aneurysmal disease. In particular, the usually well-defined laminar structure of the normal tunica media disappears with obliteration of the elastic laminae. The tunica media of advanced aortic aneurysms have few SMCs, cells often prominent in typical stenotic lesions.

Study of the pathophysiology that underlies these anatomic-pathologic findings has proved frustrating. Experimental aneurysm formation in animals has uncertain relevance to the clinical disease.[55] The human specimens obtainable for analysis generally represent the late stages of this disease. Nonetheless, recent work has identified several mechanisms that may underlie the peculiar pathology of aneurysmal disease. Widespread destruction of the elastic laminae suggests a role for degradation of elastin, collagen, and

other constituents of the arterial ECM. Many studies have documented overexpression of matrix-degrading proteinases, including MMPs, in human aortic aneurysm specimens. Clinical trials have tested the hypothesis that MMP inhibitors can reduce the expansion of aneurysms. In atherosclerotic mice, angiotensin II potentiates aneurysm formation. Alterations in TGF-β signaling can predispose to aneurysm formation. Mutations in TGF-β receptors can cause arterial ectasia.[60,61]

Thus, heightened elastolysis may explain the breakdown of the usually ordered structure of the tunica media in this disease.[62] A slant toward Th2 cell populations in aneurysmal versus occlusive disease may contribute to the overexpression of certain elastolytic enzymes. In addition, aortic aneurysms show evidence for considerable inflammation, particularly in the adventitia. The lymphocytes that characteristically abound on the adventitial side of aneurysmal tissue suggest that apoptosis of SMCs triggered by inflammatory mediators (e.g., soluble cytokines, Fas ligand) elaborated by these inflammatory cells may contribute to SMC destruction and promote aneurysm formation. Although ECM degradation and SMC death also occur in sites where atherosclerosis causes stenosis, these processes appear to predominate in regions of aneurysm formation and to affect the tunica media much more extensively, for reasons that remain obscure.

Infection, the Microbiome, and Atherosclerosis

Interest persists in the possibility that infections may cause atherosclerosis. A considerable body of seroepidemiologic evidence supported a role for certain bacteria, notably *Chlamydia pneumoniae*, and certain viruses, notably cytomegalovirus (CMV), in the etiology of atherosclerosis. These studies spurred a number of in vivo and in vitro experiments that have lent various degrees of support to this concept. Indeed, multiple clinical trials have not shown benefit of antibiotic therapy in secondary prevention of atherosclerotic events.[63]

Several caveats apply in the evaluation of the seroepidemiologic evidence. First, confounding factors should be carefully considered. For example, smokers may have a higher incidence of bronchitis caused by *C. pneumoniae*. Therefore, evidence for infection with *C. pneumoniae* may merely serve as a marker for tobacco use, a known risk factor for atherosclerotic events. In addition, a strong bias favors the publication of positive rather than negative studies. Thus, meta-analyses of seroepidemiologic studies may be slanted toward the positive merely because of underreporting of negative studies. Also, atherosclerosis is a common and virtually ubiquitous disease in developed countries. Many adults have serologic evidence of previous infections with members of Herpesviridae (e.g., CMV) and respiratory pathogens (e.g., *C. pneumoniae*). Sorting out coincidence from causality is difficult when a majority of the population studied exhibit evidence of both infection and atherosclerosis.

Although proof that bacteria or viruses can cause atherosclerosis remains elusive, infections may potentiate the action of traditional risk factors, such as hypercholesterolemia. Based on the vascular biology of atherosclerosis discussed in this chapter, several scenarios might apply. First, cells within the plaque itself may harbor infection. For example, macrophages existing in an established atherosclerotic lesion might become infected with *C. pneumoniae,* which could spur their activation and accelerate the inflammatory pathways currently believed to operate within the atherosclerotic intima. Specific microbial products, such as lipopolysaccharides, heat shock proteins, or other virulence factors, may act locally at the level of the artery wall to potentiate atherosclerosis in infected lesions.

Increased focus on the intestinal microbiome supports the view that exposure of vascular cells to bacterial products such as endotoxin applies in vivo. A slight breach in the integrity of the intestinal epithelium, with release of microbial danger signals, could have a direct effect on vascular cells or could

alter systemic risk factors by activating inflammation in visceral adipose tissue, contributing to insulin resistance and other features of the “metabolic syndrome” cluster.[64] Moreover, metabolites produced by gut microflora from dietary constituents may augment atherogenesis.[65,66]

Extravascular infection also may potentially influence the development of atheromatous lesions and provoke their complication. For example, circulating endotoxin or cytokines produced in response to a remote infection can act locally at the level of the artery wall to promote the activation of vascular cells and of leukocytes in preexisting lesions, producing an “echo” at the level of the artery wall of a remote infection.[67] The acute-phase response to an infection in a nonvascular site also may affect the incidence of thrombotic complications of atherosclerosis by increasing fibrinogen or PAI or by otherwise altering the balance between coagulation and fibrinolysis. Such disturbance in the prevailing prothrombotic, fibrinolytic balance may critically influence whether a given plaque disruption will produce a clinically inapparent, transient or nonocclusive thrombus or sustained and occlusive thrombi that could cause an acute coronary event (**see Fig. 44.16**).

Acute infections also can produce hemodynamic alterations that could trigger coronary events. For example, the tachycardia and increased metabolic demands of fever can augment the oxygen requirements of the heart, precipitating ischemia in an otherwise compensated individual. These various scenarios illustrate how infectious processes, either local in the atheroma or extravascular, may aggravate atherogenesis, particularly in preexisting lesions or in concert with traditional risk factors.

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Risk Markers and the Primary Prevention of Cardiovascular Disease

Paul M. Ridker, Peter Libby, Julie E. Buring

Rethinking Core Approaches to Primary Prevention

For almost half a century, interventions to reduce the risk of heart attack and stroke among persons without known heart disease have largely used a two-step process based on absolute risk. First, using a global risk–estimating algorithm such as the Framingham risk score, the Reynolds risk score, or the European Systematic Coronary Risk Evaluation (SCORE), physicians have stratified candidates for primary prevention into lower-, intermediate-, and higher-risk subgroups, typically calculated over a 10-year time frame. Then, guidelines based on such stratification have traditionally targeted lifestyle interventions to those persons at "lower" and "intermediate" risk while limiting more aggressive pharmacologic interventions (e.g., statin therapy) to those with "higher" risk profiles.

Until recently, it was assumed that such a risk-based triage system would distribute primary prevention services efficiently. If the relative benefit of a preventive intervention is similar across all levels of risk, the greatest absolute benefit should occur among persons with the highest absolute risk. Furthermore, treatment allocation on the basis of high global risk should maximize the benefits of intervention (by targeting those at greatest need) while reducing potential adverse actions and cost (by avoiding exposure to treatment among those with the least need).

Currently, however, some in the preventive cardiology community have challenged these long-held beliefs and proposed instead that preventive services should be allocated on the basis of proven randomized trial data—that is, "what works?" and "in whom?"—rather than on the basis of an arbitrary scaling of global risk.[1] This reconsideration has implications for how we think about preventive cardiovascular care as well as for guidelines, for the design of future clinical trials, and for drug treatment.

Consider the situation for statin therapy. Twenty years ago, the volume of trial data on the efficacy of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors as an adjunct to diet, exercise, and smoking cessation in specific patient groups was limited, safety data were incomplete, and the cost of treatment was relatively high, particularly for higher-potency statin agents. Thus, facing uncertainty, those writing older guidelines chose to model the potential benefits of lipid-lowering treatment on the basis of epidemiologic risk scales, even though those scores had never themselves undergone randomized evaluation for improvement of outcomes, nor were they used as trial enrollment criteria.

Unfortunately, this system of drug allocation based on epidemiologic modeling rather than completed trials has substantive limitations. First, smoking and hypertension are the major drivers of high global risk, yet the interventions of choice for such individuals should be smoking cessation and blood pressure reduction rather than lipid-lowering therapy. Second, risk prediction models often have proved inadequate in terms of discrimination and calibration (**see Chapter 9**). Third, on a population basis, the vast majority of future vascular events occur in persons with intermediate or low 10-year risk estimates, so limiting intervention only to those with highest absolute risk misses large opportunities for prevention. Concepts of lifetime risk suggest that those patients with low 10-year risks often are among those with the highest long-term event rates, for whom early interventions could prove most effective.[2] Finally, genetic modeling shows that earlier interventions (e.g., low-density lipoprotein [LDL]–lowering therapy) confers

much greater benefit than their delayed use.[3,4]

Indeed, the results of multiple randomized trials completed since 2005 do not support the notion that statin therapy has constant relative benefits across all risk groups, yet this assumption remains the fundamental justification for arguments to base therapy on absolute risk. Consider the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure), AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: an Assessment of Survival and Cardiovascular Events), 4D (German Diabetes and Dialysis Study), and GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca–Heart Failure) trials, which in total included 13,613 patients and were reported between 2005 and 2009. All four of these well-conducted trials enrolled high–absolute-risk patients who achieved large LDL cholesterol reductions with statin therapy, yet none showed significant clinical benefit.[5]

Consider further the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study), MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese), and HOPE-3 (Heart Outcomes Protection Evaluation) trials, which included more than 44,000 primary prevention patients and were published between 1998 and 2016.[6] These four trials enrolled low–absolute risk patients, yet each showed marked benefit of statin therapy.

Taken together, these trials challenge the concept that absolute risk alone is the only clinically effective method for allocation of statin therapy. Why then continue to recommend that statins be prescribed on the basis of an epidemiologic calculation of absolute risk? Why not allocate statins instead to patient subgroups proven in clinical trials to benefit from them?

What Works and in Whom? A Simple Evidence-Based Alternative to the Prevention of Cardiovascular Disease

At least with regard to statin therapy, few if any of the basic justifications for a “risk-based” approach to prevention remain relevant. Data on safety now abound, and the evidence base has established that benefits of statin therapy on myocardial infarction (MI), cerebrovascular accident (stroke), revascularization procedures, and cardiovascular death outweigh the risks even for those at the lower end of the absolute vascular risk spectrum. Second, generic formulations of almost all statin agents have become available, and the cost of treatment has declined dramatically. Third, the cardiovascular community currently has abundant data from large-scale, randomized, placebo-controlled trials (RCTs) that cover a wide range of patient groups, enabling the direct application of trial data to clinical care without need for epidemiologic extrapolation.

In view of the current abundance of data, a simple evidence-based guideline for statin therapy using the concepts of “what works?” and “in whom?” from completed RCTs needs no complex modeling. As an example of this emerging approach, preventive cardiologists in the United States, Canada, and Europe have suggested the following list of five recommendations as a simple, easily understood guideline for the use of statin therapy in the prevention of cardiovascular disease (CVD):

1. On this basis of high-quality randomized clinical trial data, statin therapy should be used as an adjunct to diet, exercise, and smoking cessation for secondary prevention patients with a previous

history of MI, stroke, or clinically apparent atherosclerosis (4S [Scandinavian Simvastatin Survival Study], HPS [Heart Protection Study], CARE [Cholesterol And Recurrent Events], LIPID [Long-Term Intervention with Pravastatin in Ischaemic Disease]).

2. High-quality randomized trial data support the use of statin therapy as an adjunct to diet, exercise, and smoking cessation in the setting of primary prevention for those age 50 and over with either diabetes (CARDS [Collaborative Atorvastatin Diabetes Study]), elevated LDL cholesterol (WOSCOPS [West of Scotland Coronary Prevention Study], MEGA), low HDL cholesterol (AFCAPS), elevated high-sensitivity C-reactive protein (hsCRP) (JUPITER), or multiple risk factors (HOPE-3). For patients who do not meet these criteria, physicians may consider issues such as genetic predisposition or a strong family history of premature coronary disease when making decisions for individual patients at different ages in primary prevention. For some of these patients, such as those suspected of having familial hyperlipidemia, referral to lipid or atherosclerosis specialists may be useful for considerations of secondary testing and potential use of alternative or additional lipid-lowering therapies.[7]
3. On the basis of high-quality randomized trial data, when prescribing statin therapy, physicians should seek to maximize the intensity of treatment and then focus efforts on compliance and long-term adherence (PROVE-IT [Pravastatin or Atorvastatin Evaluation and Infection Therapy], TNT [Treating to New Targets], IDEAL [Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering]). The target dose for an individual patient should be a dose close to or at the highest level the individual patient tolerates without side effects.
4. On the basis of high-quality randomized trial data, the use of nonstatin lipid-lowering agents for monotherapy or in combination with a statin should be limited awaiting evidence that such an approach further reduces cardiovascular event rates in specific patient groups. A number of trials with nonstatin agents have failed to show benefits (**see Chapter 48**) (AIM-HIGH [Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes], HPS2-THRIVE [Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events], ACCORD [Action to Control Cardiovascular Risk in Diabetes], FIELD [Fenofibrate Intervention and Event Lowering in Diabetes]). By contrast, trial data have demonstrated that the addition of ezetimibe to statin therapy modestly improves outcomes (IMPROVE-IT [Improved Reduction of Outcomes: Vytorin Efficacy International Trial]).[8] Patients who demonstrate statin intolerance or have familial hyperlipidemia and exceptionally high LDL cholesterol, or who have a risk of pancreatitis may benefit from secondary evaluation by lipid specialists.
5. A guideline based on trial evidence (to determine what works) and on trial entry criteria (to ascertain in whom) is simple, practical, and consistent with evidence-based principles and should therefore result in broad clinical acceptance. New advances in prevention should be incorporated into guidelines as quickly as possible. Thus, if data on new agents demonstrate evidence of event reduction superior to that achieved with statin therapy alone, evidence of event reduction among those who are statin intolerant, or evidence of incremental event reduction as an adjunct to statin therapy, rapid updates to guidelines should address such important advances.

Several recent investigations have evaluated how the incorporation of trial data can best be introduced into guidelines for practice.[9,10] Clinicians should be aware that not all individuals with a calculated risk above the American College of Cardiology (ACC) and American Heart Association (AHA) threshold of 10% would have qualified for a major statin trial (**Fig. 45.1**).

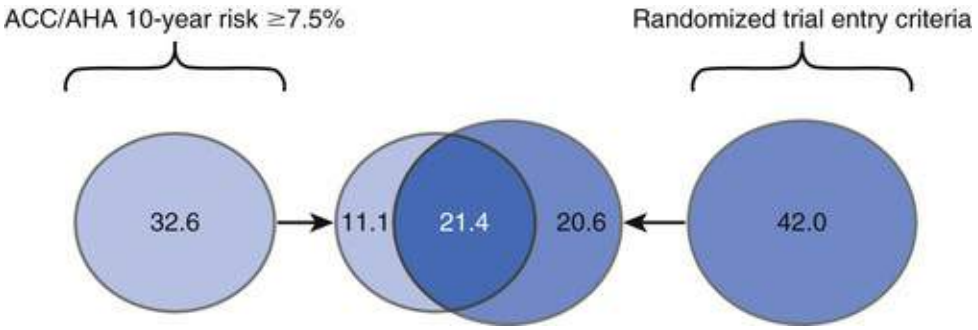


FIGURE 45.1 These Venn diagrams illustrate an approach to statin allocation in primary prevention: Base Case Venn diagram comparing the 10-year absolute risk approach with the trial entry criteria approach for allocation of statin therapy in primary prevention. The ACC/AHA 10-year risk criteria of ≥7.5% would recommend that 32.6 million Americans take statins (*light-blue circle, left*), while 42.0 million Americans would receive statin therapy according to a base case randomized trial entry criteria (*medium-blue circle, right*). The area of intersection of these two approaches indicates that 21.4 million individuals have both a calculated 10-year risk ≥7.5% and would meet eligibility requirements for at least one of the major statin trials that established efficacy (*dark blue, middle*). (From Ridker PM, Rose L, Cook N. A proposal to incorporate trial data into a hybrid ACC/AHA algorithm for the allocation of statin therapy in primary prevention. J Am Coll Cardiol 2015;65:942-8.)

Merging Epidemiology and Randomized Trial Evidence: Why Measure Risk Factors?

This chapter reviews the epidemiologic and clinical trial evidence underlying risk markers and interventions to reduce atherothrombotic risk in three parts. The next section describes the conventional risk factors of smoking, hypertension, hyperlipidemia, and insulin resistance and diabetes, as well as general strategies for reducing risk related to these disorders. This section explores some of the issues and controversy surrounding the concept of the "metabolic syndrome." It also reviews evidence describing the use of low-dose aspirin in primary prevention and briefly discusses the conceptual basis for the "polypill."

Not all coronary events occur in people with multiple traditional risk factors, however, and in some patients, abnormalities of inflammation, hemostasis, and thrombosis appear to contribute decisively. In particular, almost half of all MIs and strokes occur among persons without hyperlipidemia. Thus, after conventional risk factors, another section review atherothrombotic risk markers, including hsCRP and other markers of inflammation, such as interleukin (IL)-1, IL-6, fibrinogen, and lipoprotein-associated phospholipase A_2 (Lp-PLA_2), as well as lipoprotein(a) (Lp[a]). Each case reviews the evidence that these novel risk indicators add to risk prediction beyond conventional factors. This section also addresses the use of direct plaque imaging as a method of risk detection and emerging concepts in the use of genetic biomarkers to help elucidate vascular risk and target novel therapies.

The final section of the chapter addresses a series of environmental exposures and behavioral issues that have a major impact on vascular health. This section reviews mental stress and depression and cardiovascular risk; diet, dietary supplements, obesity, exercise, and weight loss; current evidence supporting moderate alcohol use; controversies surrounding postmenopausal estrogen; and community-based and multiple–risk factor intervention programs.

Each of the following sections begins by focusing on the epidemiologic evidence linking the specific biomarker, exposure, or behavior to subsequent vascular risk. In the setting of primary prevention, it is important to recognize that physicians do not measure biomarkers simply to predict risk (**see Chapter 9**).

Rather, they do so to target therapy better and to improve the lives of their patients. Thus, when considering the use of any biomarker for cardiovascular risk prediction in primary prevention, thoughtful clinicians should insist that two fundamental questions be answered affirmatively: First, does evidence establish that the biomarker of interest predicts future cardiovascular events independent of other risk markers? Second, does evidence show that persons identified by the biomarker of interest benefit from a therapy they otherwise would not have received?

As described later, on the basis of current data, no imaging biomarker can yet answer these questions affirmatively, nor can measurement of a variety of plasma biomarkers, such as Lp(a), homocysteine, and triglycerides. For cholesterol and for hsCRP, however, the answer to both of these questions is "yes," because RCTs have shown that patients identified by either of these biomarkers benefit greatly from statin therapy. These findings are of particular pathophysiologic interest in the modern view of atherothrombosis as resulting from hyperlipidemia interacting with inflammation to initiate and accelerate all phases of the disease process[11] (**see Chapter 44**). Supporting this view, cholesterol crystals trigger IL-1β–activating inflammasome, thus providing a key link between lipids, inflammation, and vascular disease.[12,13]

Finally, we should strive for more "personalized" approaches to treatment in both primary and secondary prevention. Consider for example the three individuals in **Fig. 45.2**, all of whom have known atherosclerosis and are being treated with a higher-intensity statin and other standard-of-care measures. The individual on the left has "residual cholesterol risk" because the on-treatment LDL cholesterol levels remain high; this individual might benefit from the use of ezetimibe or a PCSK9 inhibitor. The middle individual presents a very different profile, with a well-controlled LDL but above-median hsCRP, a situation denoted "residual inflammatory risk." The individual on the right has LDL and hsCRP in an acceptable range, but triglycerides higher than desired; this patient could have "residual triglyceride-remnant risk." Optimum treatment regimens for individuals in these three distinct categories could differ greatly.

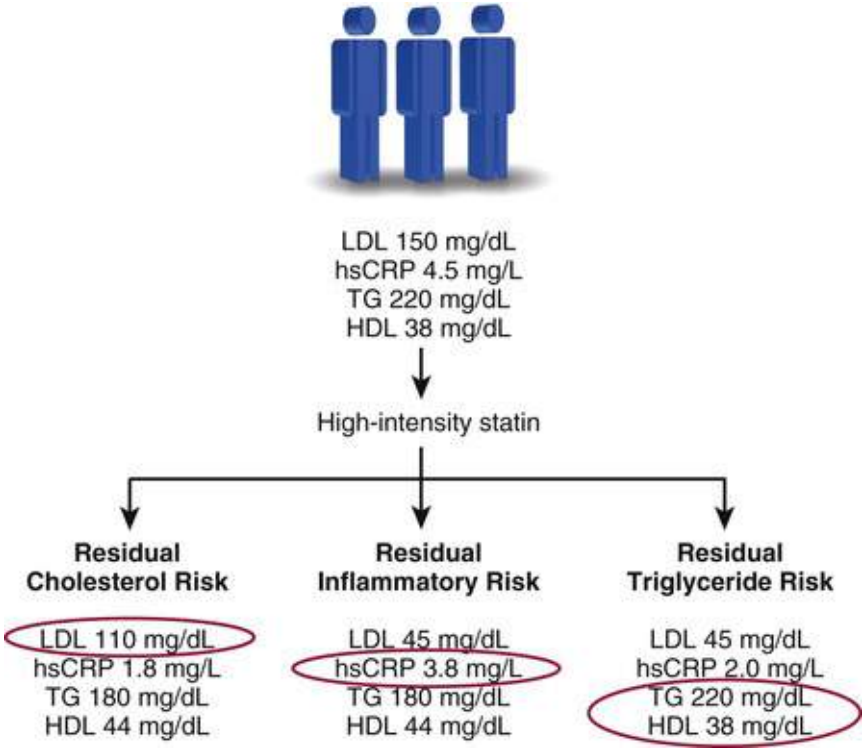


FIGURE 45.2 "Personalized" secondary prevention treatment strategies for patients treated with statins. The figure compares residual inflammatory risk to residual cholesterol risk. LDL, Low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; TG, triglycerides; HDL, high-density lipoprotein. (From Ridker PM. Residual inflammatory risk: addressing the obverse side of the atherosclerosis prevention coin. Eur Heart J 2016;37:1720.)

Conventional Risk Markers and Associated Interventions

Smoking

Smoking remains the leading preventable cause of death and disease in the United States and the single most important risk factor for coronary artery disease. As described in the 2014 Surgeon General's Report, The Health Consequences of Smoking—50 Years of Progress,[14] more than 20 million premature deaths attributable to smoking and exposure to secondhand smoke have occurred since the first Surgeon General's Report on smoking and health in 1964. Most of these deaths have been among those with a history of smoking, but 2.5 million are among nonsmokers who died from diseases caused by exposure to secondhand smoke. Despite the declines in the prevalence of current smoking, cigarette consumption still accounts for approximately 480,000 deaths from smoking-related illnesses each year. Smoking causes 32% of coronary heart disease deaths. Moreover, the annual smoking-attributable economic costs for the years 2009 to 2012 totaled $300 billion, including direct health care expenditures and loss in productivity.

The prevalence of adults smoking cigarettes declined to 16.8% in 2014 from 42% in 1965;[14,15] for adults 18 to 24 years of age, current smoking prevalence declined from 24.4% to 18.9%. However, the decline in smoking prevalence has slowed recently (**Fig. 45.3**). Males have higher prevalence of smoking than females (18.8% versus 14.8%). Smoking is greater among those 25 to 44 years of age (20.0%) than those 65 years of age and older (8.5%). Large disparities persist in tobacco use across racial/ethnic groups and between groups defined by education level, socioeconomic status, and region. Prevalence is lowest among non-Hispanic Asians (9.5%) and highest among non-Hispanic American Indians and

Alaska Natives (29.2%). Prevalence is also higher among adults living below the federal poverty level (26.3%), those reporting a General Education Development certificate (43.0%), and those receiving Medicaid or who are uninsured (28%) (**eFigs. 45.1 and 45.2**).

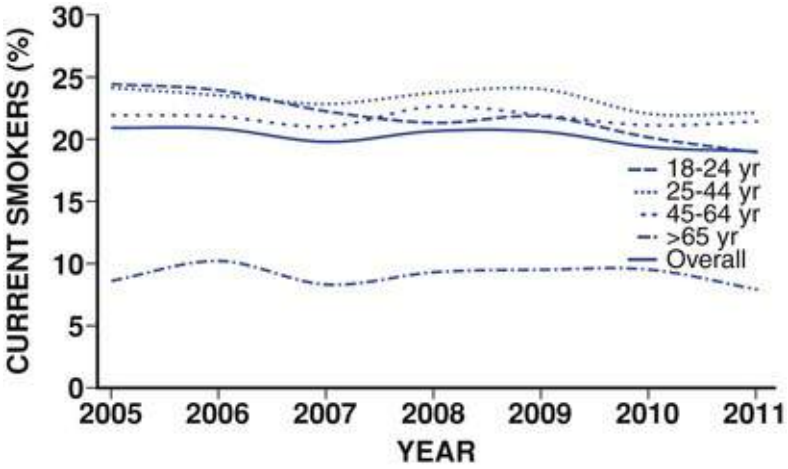
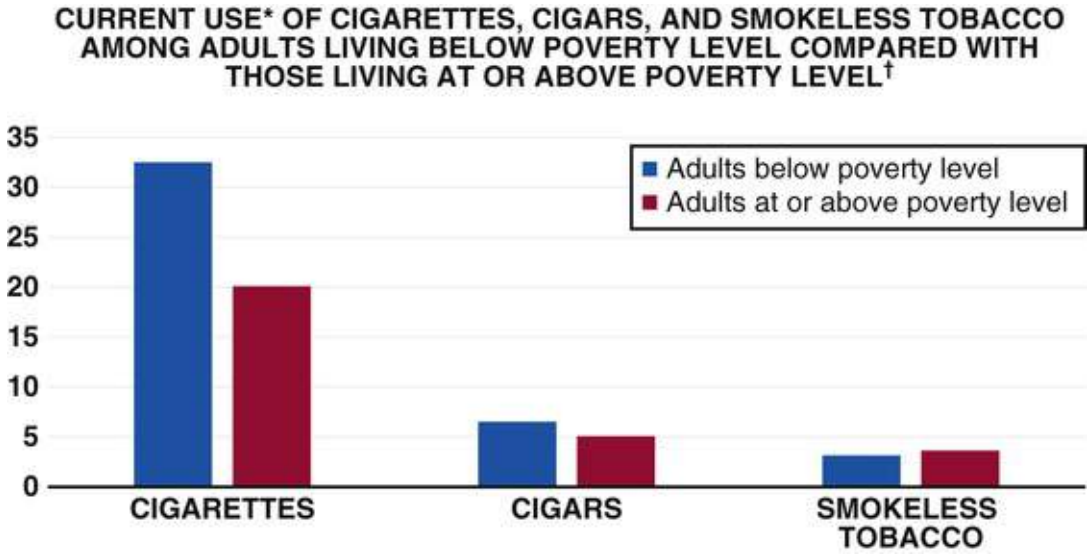
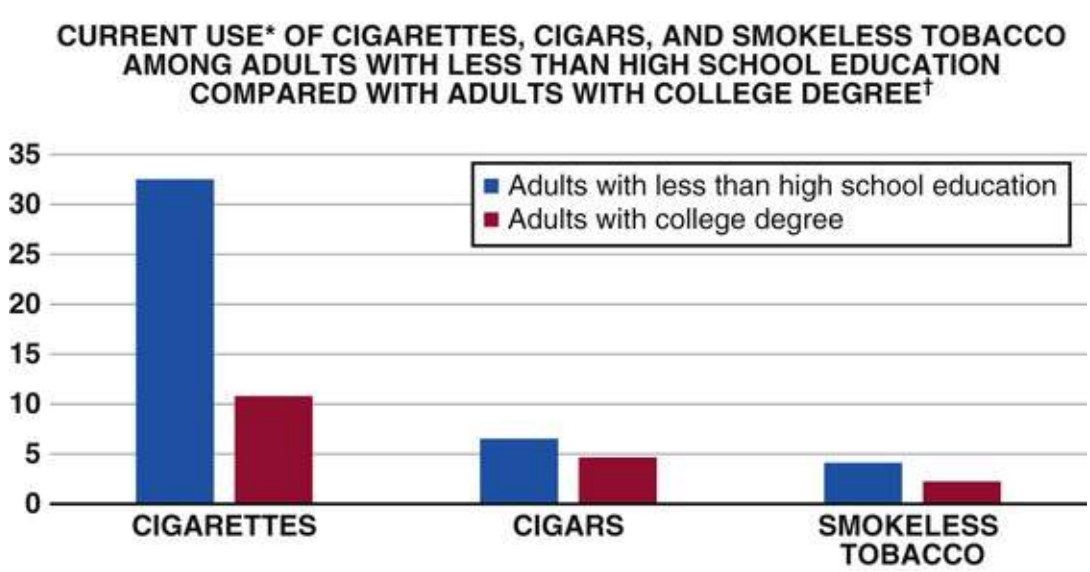


FIGURE 45.3 The percentage of adults aged 18 years and older who self-report as current smokers, by age group. National Health Interview Survey, United States, 2005 to 2011. (From US Centers for Disease Control and Prevention. Current cigarette smoking among adults—United States, 2011. MMWR 2012;61:889.)



EFIGURE 45.1 *Self-reported use of cigarettes, cigars, or smokeless tobacco in month before the time of survey constituted "Current Use." †These data from the National Survey on Drug Use and Health, 2012, refer to adults ≥18 years old.



EFIGURE 45.2 *Self-reported use of cigarettes, cigars, or smokeless tobacco in month before the time of survey constituted "Current Use." †These data from the National Survey on Drug Use and Health, 2012, refer to adults ≥18 years old.

The U.S. *Healthy People 2020* initiative aims to reduce the national prevalence of cigarette smoking among adults to a target of 12%. The most recent period of 2005 to 2014 saw only a slight overall decline in current smoking prevalence, but the mean number of cigarettes smoked per day among daily smokers declined (16.7 in 2005 to 13.8).[14] However, a significant decline from 2005 to 2011 did not result from smoking cessation; although the proportion who smoked 30 cigarettes or more per day dropped, those smoking 1 to 9 cigarettes per day increased correspondingly.

Consumption of tobacco products is increasing globally, with almost 80% of the world's 1 billion smokers living in low- and middle-income countries[16] (**see Chapter 1**). The use of tobacco products among children is also an increasing global issue; according to the Global Youth Tobacco Survey among students 13 to 15 years of age, the prevalence of use of any tobacco products has a wide range throughout the world, from 1.7% in Kazakhstan to 28.9% in Timor-Leste.[17]

Recent reports indicate the patterns of tobacco use are changing, with increasing use of other products, such as electronic cigarettes and hookahs. Among U.S. working adults, an estimated 3.45 million (4.5%) males and 2.05 million (3.0%) females used e-cigarettes in 2014, with the highest prevalence among 18- to 24-year-olds (5.1%) and whites (4.5%).[18] With regard to high school and middle school students,[19] in 2015 an estimated 3.82 million high school students (25.3%) used any tobacco product, with 16.0% using e-cigarettes, 9.3% cigarettes, and 7.2% hookah pipes. More males than females used any tobacco product, and Hispanics used more than other racial/ethnic groups. An estimated 7.4% (880,000) middle school students used any tobacco product: with 5.3% using e-cigarettes, 2.3% cigarettes, and 2.0% hookah pipes. As with the high school students, more males than females used any tobacco product, and more Hispanics than other racial/ethnic groups.

We currently lack adequate data to assess long-term the patterns of e-cigarette use, the harmful effects, or the beneficial effects on smoking cessation. Recent reviews[20,21] and the U.S. Preventive Services Task Force (PSTF)[22] have concluded that the current evidence is insufficient at this time to recommend electronic nicotine delivery systems for tobacco cessation in adults, including pregnant women. As of August 8, 2016, the U.S. Food and Drug Administration (FDA) has extended the agency's regulatory authority to all tobacco products, including e-cigarettes and hookahs (waterpipes), and required manufacturers to report product ingredients and undergo the agency's premarket review to receive marketing authorization.[23]

Landmark studies in the early 1950s first reported strong positive associations between cigarette smoke

exposure and coronary heart disease (CHD). Over the next 50 years, an exceptionally consistent series of prospective studies have documented the effects of smoking on coronary risk. The 1964 Surgeon General's report reaffirmed the epidemiologic correlation, and by 1983 the Surgeon General had firmly established cigarette smoking as the leading avoidable cause of CVD. Based largely on studies among men, the 1989 Surgeon General's report showed that smoking doubles the incidence of CHD and increases CHD-related mortality by 50%, and that these risks increase with age and the number of cigarettes smoked. “Light” levels of smoking have a major impact on MI and all-cause mortality, even among smokers who do not report inhalation. In addition to MI, cigarette consumption directly relates to increased rates of sudden death, aortic aneurysm formation, symptomatic peripheral vascular disease, and ischemic stroke. Prospective evidence has linked cigarette consumption to an elevated risk of hemorrhagic stroke, including intracranial hemorrhage and subarachnoid hemorrhage, again in a dose-response manner. Continued smoking is also a major risk factor for recurrent MI, as well as adverse clinical outcomes in patients undergoing revascularization with coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).[24] Even among nonsmokers, inhaled smoke, whether from passive exposure or from cigar or pipe consumption, increases CHD risk. Passive smoking exposure can cause endothelial vasodilator dysfunction in the coronary circulation, as well as increased bronchial responsiveness and concomitant pulmonary dysfunction. There is no safe level of exposure to secondhand tobacco smoke.

Beyond acute unfavorable effects on blood pressure and sympathetic tone and a reduction in myocardial oxygen supply, smoking contributes to the pathogenesis of atherothrombosis by several other mechanisms. In addition to impaired endothelium-dependent vasodilation, smoking has adverse hemostatic and inflammatory effects, including increases in levels of C-reactive protein (CRP), soluble intercellular adhesion molecule-1 (ICAM-1), fibrinogen, and homocysteine. Additionally, smoking is associated with spontaneous platelet aggregation, increased monocyte adhesion to endothelial cells, and adverse alterations in endothelium-derived fibrinolytic and antithrombotic factors, including tissue-type plasminogen activator (t-PA) and tissue pathway factor inhibitor. Compared with nonsmokers, smokers have an increased prevalence of coronary spasm and a reduced threshold for ventricular arrhythmias. Accruing evidence has suggested that insulin resistance represents an additional mechanistic link between smoking and premature atherosclerosis.

Smokers lose at least one decade of life expectancy compared with never-smokers.[25] Women's risks for CVD from smoking have risen sharply over the last 50 years and now equal that of men.[14,26] Women incur similar increases in the relative risk for CHD. Moreover, smoking acts synergistically with oral contraceptives (OCs), placing young female smokers who take OCs at particularly elevated risks for premature CHD, stroke, and venous thromboembolism.[27] Smoking is especially hazardous for women with diabetes.

Interventions for Smoking Cessation

The prevalence of smoking is declining, although slowly. If current rates continue, the annual burden of smoking-attributable mortality will remain at high levels for decades, with 5.6 million Americans younger than 18 years of age projected to die prematurely from smoking-related disease.[14] Cessation of cigarette consumption overwhelmingly remains the single most important intervention in preventive cardiology. Although data from large-scale, randomized trials concerning the risk reduction associated with smoking cessation are limited, observational studies consistently demonstrate the benefits of smoking cessation. Smokers who quit reduce their excess risk of a coronary event by 50% within the first 2 years after cessation, with much of this benefit seen even within the first few months (**Fig. 45.4**). CHD risk falls

substantially within 1 to 2 years of cessation, with the risk in former smokers approaching that in never-smokers after 3 to 5 years. Similarly, the risk of stroke decreases steadily after smoking cessation, with former smokers having the same stroke risk as in nonsmokers after 5 to 15 years. Moreover, the beneficial effects on CHD and mortality rates are seen even among elderly persons, supporting the idea that it is never too late to quit smoking for decreasing CHD-associated risks. These risk reductions equal or exceed those for other secondary prevention interventions that have received more attention from physicians and the pharmaceutical industry, including the use of aspirin, statins, beta-adrenergic blocking agents, and angiotensin-converting enzyme (ACE) inhibitors.

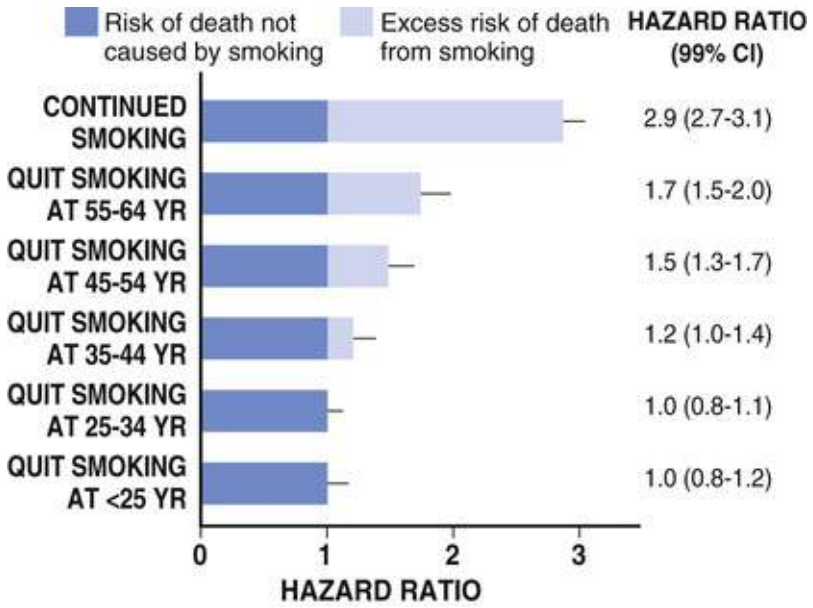


FIGURE 45.4 Risks of death for continuing smokers and those who quit, according to age at time of cessation; CI, confidence interval. (From Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med 2013;368:341.)

In 2012, more than 4 of 10 (42.7%) adult daily cigarette smokers in the United States stopped smoking for more than 1 day because they were trying to quit,[14,28,29] including 48.5% of smokers age 18 to 24. Poor patient understanding of the importance of smoking cessation continues. Substantial misunderstanding surrounds, for example, the observation that smoking predicts better outcome after various reperfusion strategies (the so-called smoker's paradox). Some researchers have regarded this effect as a “benefit” of smoking, but it probably reflects that smokers tend to undergo such procedures at a much younger age and thus have on average lower rates of comorbid illness.[30]

Clinical practice guidelines recognize tobacco dependence as a chronic condition that often requires repeated interventions. Nevertheless, effective evidence-based treatments do exist.[29] Multiple attempts may be necessary, but smokers can and do quit smoking. In fact, since 2002, the number of former smokers has exceeded number of current smokers.[14]

Multifaceted smoking cessation interventions have proved effective. A number of individual-level treatments have shown less efficacy for smokers who want help to quit.[31,32] These approaches include brief clinical interventions (e.g., a physician taking 10 minutes or less to deliver advice and assistance about quitting); counseling (e.g., individual, group, or telephone); behavioral cessation therapies (e.g., training in problem solving); treatments with more person-to-person contact and intensity; and programs to deliver treatments using mobile phones. Cessation medications effective for treating tobacco dependence include nicotine replacement products, either over-the-counter (e.g., nicotine patch, gum,

lozenge) or prescription (e.g., nicotine patch, inhaler, nasal spray), and prescription non-nicotine medications such as bupropion or varenicline. A 2012 Cochrane review[33] of 150 trials of nicotine replacement therapy (NRT) with more than 50,000 people found no overall difference in effectiveness between different forms of NRT; found that NRT was effective with or without counseling; that a combination of NRT and bupropion was more effective than bupropion alone; and found no evidence that NRT increased the risk of heart attacks.

Reductions in smoking from any mechanism improve health outcomes, particularly when linked to lifestyle changes, including exercise and dietary control. Pharmacologic programs, as well as physician-guided counseling, are cost-effective and should be provided as standard prevention services. Smoking low-tar or low-nicotine cigarettes rather than regular cigarettes does not appear to reduce the risk of CHD. Although the elevated cardiovascular risks associated with smoking decrease significantly after cessation, the risk for development of cancer of the lungs, pancreas, or stomach persists for more than a decade, as it does that for chronic obstructive pulmonary disease (COPD). Smoking cessation has clear benefit, but smoking reduction alone appears to have only a marginal effect.

A number of global evidence-based methods for population-based smoking cessation also exist.[29,16] The World Health Organization (WHO) Framework Convention on Tobacco Control, which began in 2005, has been one of the most widely accepted treaties in the history of the United Nations, with more than 180 parties covering 90% of the world's population. In 2008, WHO introduced a package of evidence-based tobacco control measures to help countries implement the WHO Framework Convention. Entitled MPOWER, the interventions include increasing prices of tobacco products; antitobacco media campaigns featuring graphic personal stories on the adverse health impacts of smoking; implementing smoke-free laws for workplaces and public places; barrier-free access to help quitting; and enforcing restrictions on tobacco advertising, promotion, and sponsorship. Studies carried out after the implementation of pictorial package warnings in a number of countries consistently have shown that they significantly increase people's awareness of the harms of tobacco use. Increasing tobacco taxes have also reduced tobacco use.

Accomplishing the goal of *Healthy People 2020* to reduce the U.S. national prevalence of cigarette smoking among adults to a target of 12% will require more extensive implementation of the evidence-based tobacco control interventions just listed. These measures are critical to reduce cigarette smoking among U.S. adults.[31,32] Sustained comprehensive state tobacco control programs funded at the U.S. Centers for Disease Control and Prevention (CDC)–recommended levels could accelerate progress towards reducing the health and economic burdens of tobacco-related diseases. Only two states have funded tobacco control programs at CDC-recommended levels, whereas 27 states are funded at less than a quarter of these levels. State funding in tobacco control programs has in fact decreased during the last 5 years. Good monitoring is important to track the extent and character of the tobacco epidemic and indicates how best to tailor policies.

Several advances in tobacco control have occurred recently in the United States. Four new laws have reinvigorated the national effort, including expansion of the 2009 Family Smoking Prevention and Tobacco Control Act, which grants the FDA the authority to regulate the manufacture, distribution, and marketing of all tobacco products; the Children's Health Insurance Reauthorization Act; the Prevent All Cigarette Trafficking Act; and the Patient Protection and Affordable Care Act (ACA). These laws have granted federal agencies more authority and funding to regulate tobacco products, decrease youth access to tobacco, and increase access to treatment programs. In 2010, the U.S. Department of Health and Human Services (DHHS) presented its first national strategic plan for tobacco control, with 21 action steps involving coverage of cessation treatment, reduction of youth access to tobacco, investments in state and local tobacco control initiatives, and communication efforts to engage the public. A federal mass media

campaign began in early 2012, using graphic personal stories on the adverse health impact of smoking.

In the context of these renewed efforts, however, the low success rates in smoking cessation continue to challenge clinicians. Preventing smoking in the first place should receive greater emphasis. Community education and physician-based primary prevention remain the most important components of any smoking reduction strategy.

Hypertension

Elevated blood pressure (BP) is a major risk factor for CHD, heart failure, cerebrovascular disease, peripheral arterial disease, renal failure, atrial fibrillation, and total mortality, as well as loss of cognitive function and increased incidence of dementia (**see Chapters 46 and 47**). Observational data indicate that death from both CHD and stroke increases progressively from BP levels as low as 115 mm Hg systolic and 75 mm Hg diastolic. For patients 40 to 70 years of age, each increment of 20 mm Hg in systolic or 10 mm Hg in diastolic BP doubles the risk of CVD across a BP range of 115/75 to 185/115 mm Hg. *Prehypertension,* defined as systolic BP of 120 to 139 mm Hg or diastolic BP of 80 to 89 mm Hg, is associated with almost twice the risk of MI and stroke in women compared with normal BP.

More than 75 million adults in the United States and over 1 billion worldwide have *hypertension,* defined as systolic BP of 140 mm Hg or greater or diastolic blood pressure of 90 mm Hg or greater, or taking antihypertensive medicine.[34] Men have a higher percentage of hypertension than women until age 45 years; between 45 and 64, men and women have similar percentages of hypertension; and after 64, a higher percentage of women have diagnosed hypertension than men (**Fig. 45.5**). The prevalence of hypertension increases greatly with age in all races and ethnicities. The age-adjusted prevalence of hypertension in the United States (both diagnosed and undiagnosed) approaches 75% for older women and 65% for older men, and varies geographically, ranging from 23% in Utah to 40% in Alabama.

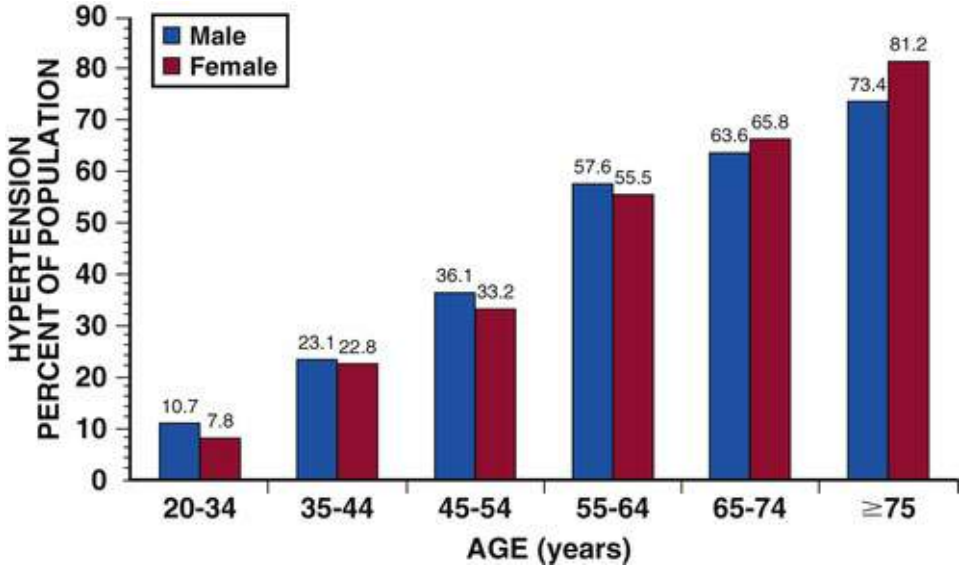


FIGURE 45.5 The prevalence of hypertension in individuals ≥20 years of age according to sex and age (NHANES 2011–2014). Hypertension was defined by systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, a "yes" answer to taking medication for hypertension, or if individual was told twice that she or he had elevated blood pressure. NHANES, National Health and Nutrition Examination Survey. Source: US National Center for Health Statistics and National Heart, Lung, and Blood Institute. (From Benjamin EJ et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation 2017;135:e146.)

Disparities in hypertension by racial and ethnic groups persist (**Fig. 45.6**) (**see Chapter 91**). Blacks develop high BP more often, and at an earlier age, than do whites and Mexican Americans and have higher average BP levels. Among blacks, more women than men have hypertension. As a result, compared with whites, blacks have a 1.3 times greater rate of nonfatal stroke, a 1.8 times greater rate of fatal stroke, a 1.5 times greater rate of death attributable to heart disease, and a 4.2 times greater rate of end-stage kidney disease. Within the black community, rates of hypertension vary substantially, with persons with the highest rates more likely to be middle-aged or older, less educated, overweight or obese, and physically inactive and more likely to have diabetes mellitus, but those with uncontrolled high BP who do not take antihypertensive medication tending to be male and younger and to have infrequent contact with physicians.

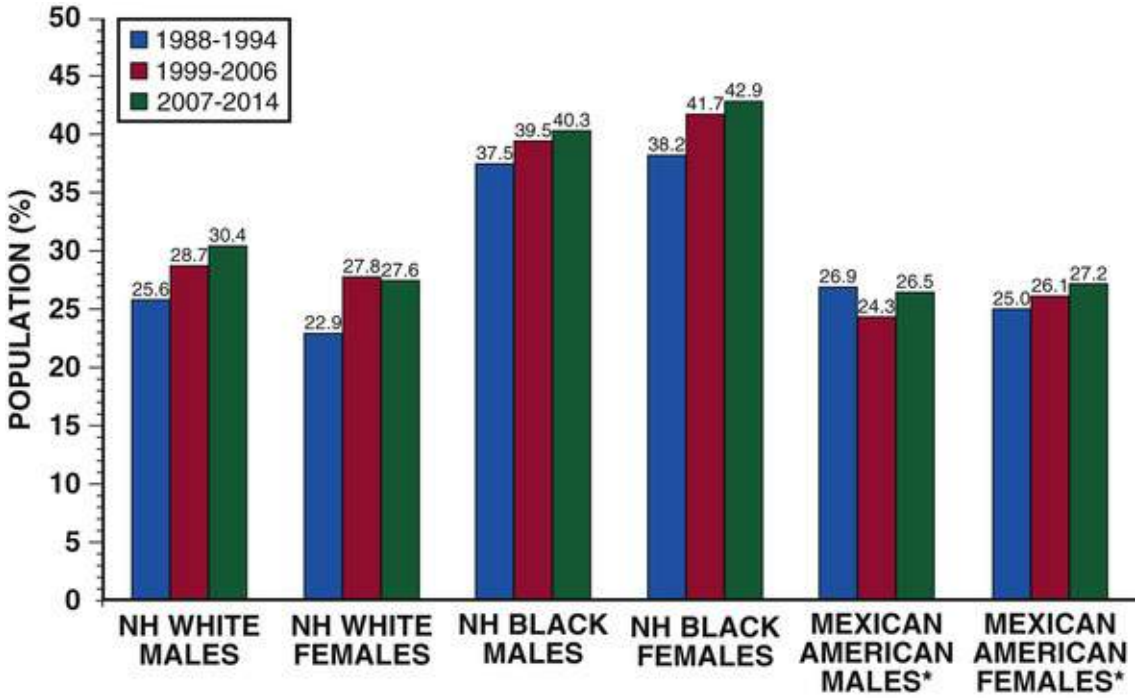


FIGURE 45.6 Age-adjusted prevalence trends for high blood pressure in individuals ≥20 years old according to race/ethnicity, sex, and survey year (NHANES 1988–1994, 1999–2006, and 2007–2014). Hypertension was defined as in **Fig. 45.5**. NH, Non-Hispanic; NHANES, National Health and Nutrition Examination Survey. *All NHANESs collected the category "Mexican Americans," but the use of the combined category of Hispanics only started in 2007. The long-term trend data therefore use the category Mexican American. Source: US National Center for Health Statistics and National Heart, Lung, and Blood Institute. (From Benjamin EJ et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation 2017;135:e146.)

Data from the National Health and Nutrition Examination Survey (NHANES) 2007 to 2010 indicate that 6% of U.S. adults have undiagnosed high BP. Of those with hypertension age 20 or older, 81.5% were aware of hypertension; 74.9% were under current treatment, 52.5% had their BP under control, and 47.5% did not achieve control.[35] Rates of control differ substantially by ethnic and racial groups.

Current evidence indicates that most U.S. patients know their hypertension status, but nearly half do not have their hypertension controlled[36] (**Fig. 45.7**). Data from the Framingham Heart Study show that among those age 80 or older, only 38% of men and 23% of women had BP that met targets set forth in the National High Blood Pressure Education Program's clinical guidelines. Similarly, data from the Women's Health Initiative (WHI) observational study of almost 100,000 postmenopausal women across the country indicate that despite similar treatment rates, older women maintain especially poor hypertensive control.[37]

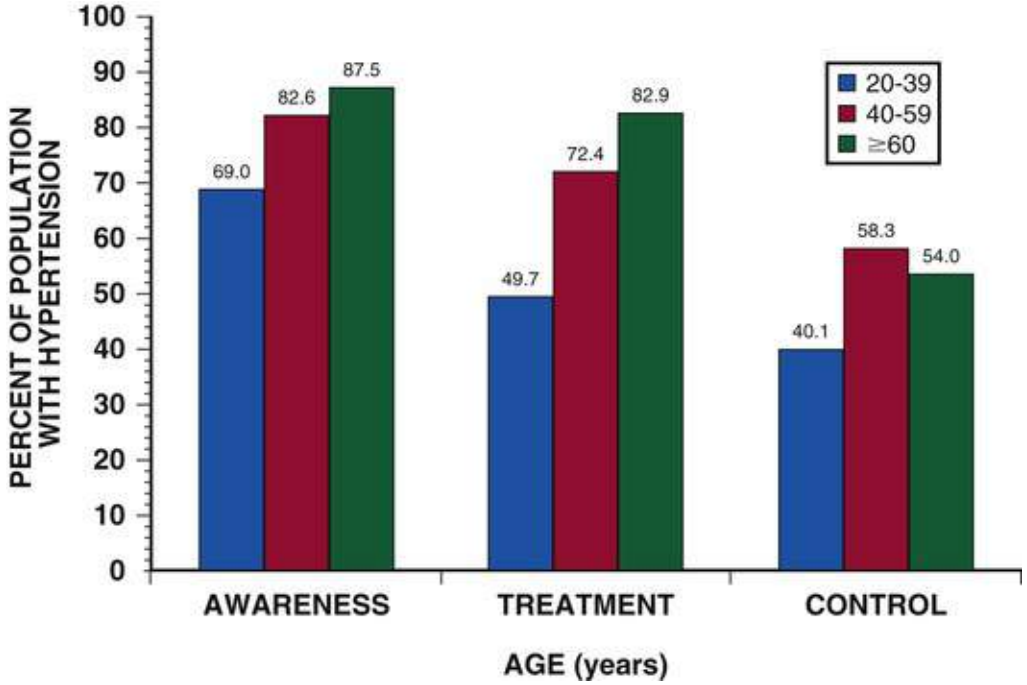


FIGURE 45.7 Extent of awareness, treatment, and control of high blood pressure according to age (NHANES 2007–2012). Hypertension is defined as in **Fig. 45.5**. NHANES, National Health and Nutrition Examination Survey. Source: US National Center for Health Statistics and National Heart, Lung, and Blood Institute. (From Benjamin EJ et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation 2017;135:e146.)

Among U.S. adults with hypertension, 8.9% meet the criteria for resistant hypertension (BP ≥140/90 mm Hg, despite reported use of antihypertensive medications from three different drug classes or drugs from four or more antihypertensive drug classes regardless of BP). This segment represents 12.8% of the population taking antihypertensive medications.[38] On the other end of the spectrum, data from NHANES 1999 to 2006 indicate that 29.7% of U.S. adults age 20 or older have prehypertension, defined as untreated systolic BP of 120 to 139 mm Hg or untreated diastolic BP of 80 to 89 mm Hg and not having been told on two occasions by a physician or other health professional that they have hypertension. Prehypertension is associated with elevated relative and absolute risks for cardiovascular outcomes across the age spectrum, including incident stroke, particularly in nonelderly persons and for those with BP values in the higher prehypertension range.

Costs directly attributable to high BP for the United States total almost $131 billion annually in direct medical expenses and $25 billion in lost productivity, and projections show that by 2030, the total cost of high BP will increase to an estimated $343 billion. By 2025, the total number of adults with hypertension is anticipated to top 1.5 billion. Hypertension causes 7.6 million premature deaths worldwide annually, with 80% of this burden occurring in low-income and middle-income countries[39] (**see Chapter 1**). Approximately three quarters of persons with hypertension (639 million) live in developing countries with limited health resources, and where people have a very low awareness of hypertension and poor BP control. Several hypertension risk factors appear more common in developing countries, including urbanization, aging of the population, changes to dietary habits, and social stress. High illiteracy rates, limited access to health facilities, poor dietary habits, poverty, and high costs of drugs all contribute to poor BP control.

Numerous risk factors and markers for development of hypertension have been identified, including increasing age, ethnicity, family history of hypertension, genetic factors, lower education and socioeconomic status, greater weight, lower physical activity, tobacco use, psychosocial stressors, sleep apnea, and dietary factors (including increased dietary fats, higher sodium intake, lower potassium intake,

and excessive alcohol intake). Patients with concomitant chronic kidney disease (estimated glomerular filtration rate [eGFR] <60 mL/m^2) constitute a high-risk group for focused BP treatment, both to prevent CVD and to slow progression to end-stage renal disease (ESRD). Patients with obesity, the metabolic syndrome, and diabetes also represent high-risk groups for treatment. High BP occurs in more than two thirds of patients with type 2 diabetes, and its development coincides with the development of hyperglycemia.[40] In patients with diabetes, hypertension confers an enhanced risk of CVD. People with controlled diabetes have a similar CVD risk to patients without diabetes but with hypertension. The 10-year risk of a cardiovascular event among women 30 to 74 years of age with uncontrolled hypertension is 6%; however, 56% of these events could be prevented if BP were controlled to normal levels.

Recent (within the last 10 years) and remote antecedent BP levels may contribute importantly to risk beyond the current BP level. Data from the Harvard Alumni Health Study found that higher BP in early adulthood was associated several decades later with higher risk for all-cause, cardiovascular, and coronary heart disease mortality, but not stroke mortality;[41] total life expectancy was 5.1 years longer for normotensive men and 4.9 years longer for normotensive women than for hypertensive people of the same sex at age 50. Similar data have been reported in the CARDIA study, in which cumulative exposure to high BP over 25 years, from young adulthood to middle age, was associated with both systolic and diastolic dysfunction.[42]

Part of the complexity of hypertension as a risk factor relates to changing definitions of risk and the recognition that systolic BP and pulse pressure can contribute as much to risk as does diastolic BP, contrary to decades of clinical teaching. Isolated systolic hypertension, in particular, carries at least as much risk as diastolic BP for the outcomes of total cardiovascular mortality and stroke. Isolated systolic hypertension thus appears to represent a distinct pathophysiologic state in which elevated BP reflects reduced arterial elasticity not necessarily associated with increased peripheral resistance or an elevation in mean arterial pressure.[43]

Pulse pressure, generally reflecting vascular wall stiffness, also predicts first and recurrent MI. Defined as the difference between systolic and diastolic blood pressures, pulse pressure appears to predict cardiovascular events independently and provides prognostic utility beyond that of mean arterial pressure.[44] These data stress the importance of arterial compliance and stiffness in atherogenesis as well as in the development of left ventricular hypertrophy. Arterial stiffness in the carotid distribution is also a major risk marker for incident stroke.[45]

Ambulatory monitoring of BP over 24 hours may provide a stronger predictor of cardiovascular morbidity and mortality than office-based measures. However, studies of home BP evaluation have yielded mixed results. In one cohort of elderly persons, self-measurement of BP had better prognostic accuracy for vascular events than office-based evaluation; another study has determined that nocturnal hypertension diagnosed by continuous monitoring is associated with increased risk of congestive heart failure. By contrast, in a randomized trial comparing office with home BP measurement, self-measurement allowed identification of those persons with “white coat” hypertension, but did not greatly improve overall management or alter objective measures of compliance, such as left ventricular mass. In a recent study from the Dallas Heart Study, both white-coat hypertension (elevated office BP with normal ambulatory BP) and masked hypertension (elevated ambulatory BP with normal office BP) associated independently with increased aortic stiffness, renal damage, and incident vascular events.[46]

Interventions to Reduce Blood Pressure

Past overviews and randomized trials demonstrate that BP reductions as small as 3 to 5 mm Hg result in large and clinically significant reductions in risk for stroke, vascular mortality, congestive heart failure,

and total CHD in middle-aged individuals, elderly persons, and specified high-risk patients such as those with diabetes and peripheral arterial disease. Diet and lifestyle management remain the cornerstone of prevention of hypertension, and clinical trial evidence continues to accrue showing that adopting low-risk dietary measures along with weight reduction, particularly at the societal level, could substantially reduce the burden of BP (**see Chapter 47**).

Experts disagree, however, about the target for pharmacologic BP reduction, an issue of considerable controversy. After many years of a BP goal of less than 140/90 mm Hg, the 7th Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7)[47] suggested lowering the treatment goal to less than 130/80 mm Hg for those with diabetes or renal insufficiency. However, in 2014, another group reversed this trend and, based on available randomized trials, increased the systolic BP goal to less than 150 mm Hg for the majority of individuals age 60 or older.[34] In 2017, another set of guidelines issued jointly by AHA recommended initiation of treatment with lifestyles measures and, in some individuals, medication at a BP as low as 130/80.[48]

Two major clinical trials published in 2015 and 2016 add to the complexity of these seemingly inconsistent guidelines. In the first of these trials, the Systolic Blood Pressure Intervention Trial (SPRINT) investigators randomly assigned 9361 persons without diabetes but with vascular risk and systolic BP greater than 130 mm Hg to a target of less than 120 mm Hg or to a target of less than 140 mm Hg.[49] At 1 year, the mean systolic BPs in the two groups were 121 and 136 mm Hg, respectively. The trial halted early because of a 25% reduction in the incidence of major cardiovascular death in the <120 mm Hg group (hazard ration [HR], 0.75; 95% confidence interval [CI] 0.64 to 0.89), a concomitant 27% reduction in all-cause mortality (HR, 0.73; 95%CI 0.60 to 0.90), and the finding of consistent effects in all major subgroups evaluated (**see Chapter 47 and Fig. 47.5**). Because almost 17 million U.S. adults meet the SPRINT enrollment criteria, these more aggressive BP goals need careful consideration.[50] The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial evaluated the potential benefits of targeting a systolic BP below 120 mm Hg versus below 140 mm Hg in 4733 patients with type 2 diabetes (individuals excluded from SPRINT.) After a mean of 4.7 years, the annual rate of the primary outcome, a composite of rates of nonfatal MI, nonfatal stroke, and death from cardiovascular causes did not differ significantly between groups (**see Fig. 47.4**). The intensive therapy group experienced fewer strokes but more frequent serious adverse events attributable to BP problems.[51] The investigators thus concluded that the evidence did not justify a systolic BP target below 120 mm Hg in patients with type 2 diabetes.

The Heart Outcomes Prevention Evaluation (HOPE-3) enrolled 12,705 participants at intermediate risk without known CVD allocated to a combination of candesartan (16 mg/day) and hydrochlorothiazide (12.5 mg/day) or to placebo.[52] HOPE-3 was designed as a 2 × 2 factorial trial that also included a statin versus placebo arm described later. HOPE-3 did not require elevated baseline BP for entry. Overall, BP reduction as compared to placebo had no significant effect in HOPE-3 on the trial primary outcomes. However, among those in the top third of the trial's BP range at baseline (>143.5 mm Hg), had a significant benefit on vascular events, whereas effects were neutral among those in the lower two BP categories (**Fig. 45.8**).

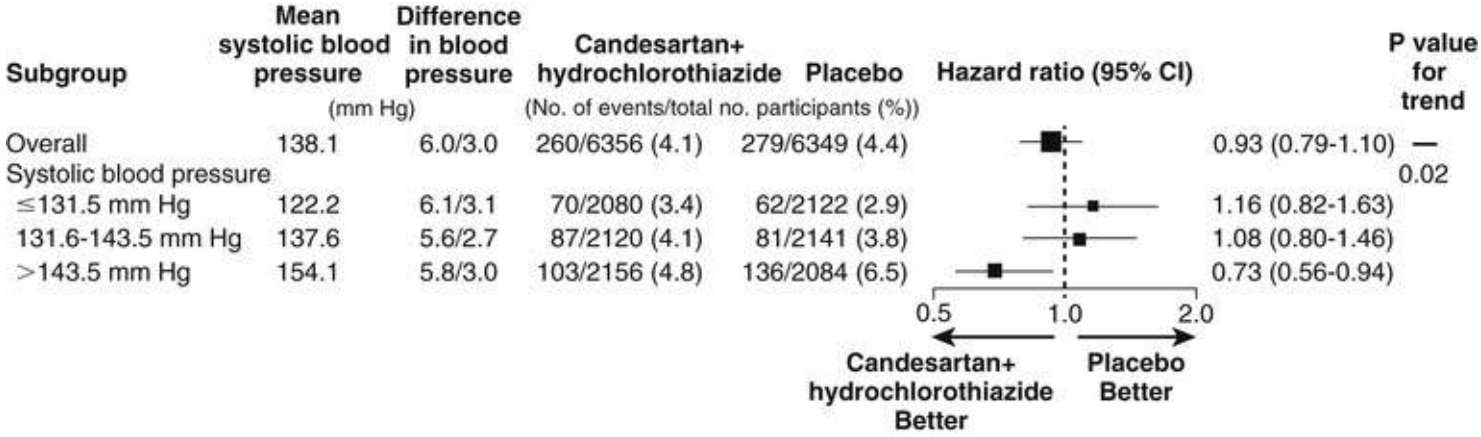


FIGURE 45.8 Forest plot of the co-primary results of the Heart Outcomes Prevention Evaluation (HOPE) 3 trial stratified by systolic blood pressure strata. The difference in BP refers to the average difference of the systolic and diastolic BPs between groups in trial, with the active-treatment group having lower mean values. The composite co-primary outcome included death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke; the size of each square reflects the number of events. (From Lonn EM. et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016;26;374[21]:2009-20.)

Taken together, the ACCORD, SPRINT, and HOPE-3 trials provide a contemporary new database from which clinicians can decide how aggressive to be with pharmacologic BP reduction. Specific treatment plans for various forms of hypertension are reviewed in detail in **Chapter 47** and the 2017 AHA/ACC guideline. Regardless of pharmacologic treatment plan, for all patients with elevated BP, lifestyle modifications remain important and should include smoking cessation, weight reduction if needed, increased physical activity, limited alcohol intake, limited sodium intake, adequate potassium and calcium intake, and adoption of the Dietary Approaches to Stop Hypertension (DASH) eating plan, a diet with a reduced content of saturated and total fat that also includes abundant fruits, vegetables, and low-fat dairy products.

Initiation of drug therapy depends on BP and the absolute level of risk. Most patients require more than one agent to achieve their BP goals. Meta-analyses have shown that the magnitude of BP reduction determines reduction in cardiovascular risk more than drug choice, and that long-term control usually requires combination therapy, thereby making the choice of drug class less important. Evidence supports the use of ACE inhibitors (or angiotensin receptor blockers [ARBs] in patients who cannot tolerate ACE inhibitors), calcium channel blockers, or thiazide-type diuretics as first-line agents. Available evidence no longer supports the use of beta-adrenergic blocking agents (beta blockers) as first-line therapy for primary prevention, because of less benefit than with other drugs, particularly in elderly persons, and increasing evidence that the most frequently used beta blockers at usual doses carry an unacceptable risk of inducing type 2 diabetes.

Successful treatment of hypertension is difficult despite the availability of several classes of antihypertensive drug and the value of strategies to combat the effect of adverse lifestyle on BP. From 5% to 30% of the overall hypertensive population have resistant hypertension, and approximately 10% of patients have true resistant hypertension without a modifiable cause. Unfortunately, novel interventions such as renal denervation have not demonstrated clinical benefit when tested in rigorous clinical trials.[53]

Low-Density Lipoprotein (LDL) Cholesterol

Of plasma-based atherothrombotic risk factors, LDL cholesterol is the best-established risk factor causally linked to incident MI and cardiovascular death[6] (**see Chapter 48**). High LDL cholesterol levels

consistently predict risk of future cardiovascular events in human populations. Animal studies in multiple species have shown a causal relationship between hypercholesterolemia and atherosclerosis. Abundant evidence provides biologic plausibility for the involvement of LDL in atherogenesis. Furthermore, human mutations that produce hypercholesterolemia on a monogenic basis lead to accelerated atherosclerosis as early as the first decade of life in patients with homozygous familial hypercholesterolemia, while those with heterozygous hypercholesterolemia develop disease approximately 10 to 15 years later. This and other observations have led to the useful office-based concept of a threshold "cumulative lifetime exposure" to LDL cholesterol that, when crossed, results in clinically evident atherosclerosis[54,55] (**Fig. 45.9**). Other recently described mutations that affect LDL metabolism, such as those in the enzyme proprotein convertase subtilisin/kexin type 9 (PCSK9), result in life-long reductions in LDL cholesterol and reduced lifetime risks of events.[56] By contrast, lifetime exposure to moderately elevated levels of LDL cholesterol typically leads to clinical events in the seventh and eighth decades (i.e., 60s and 70s). Finally, interventions in large clinical trials to lower LDL cholesterol levels by various approaches have shown a reduction in cardiovascular events. Thus, LDL cholesterol fulfills the criteria of modified Koch postulates as one causative agent in atherosclerosis.

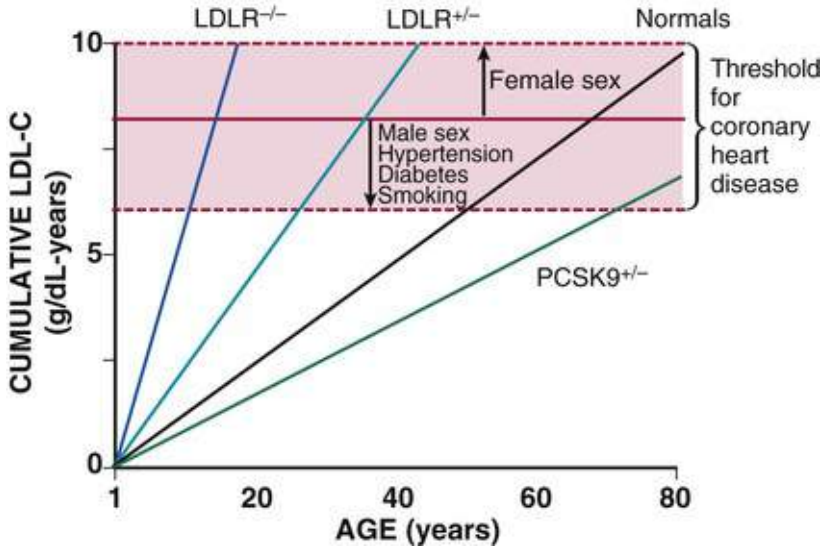


FIGURE 45.9 Graph of the concept of a threshold for cumulative lifetime exposure to LDL cholesterol and the development of clinically manifest atherosclerotic disease. The lines shown are theoretical. (From Horton JD, Cohen JC, Hobbs HH. PCSK9: a convertase that coordinates LDL catabolism. J Lipid Res 2009;50[Suppl]:S172.)

Several independent lines of evidence suggest that what is regarded as "normal" cholesterol levels in Western society exceeds levels that good health requires. In particular, certain rural agrarian societies with very low rates of atherothrombosis exhibit total and LDL cholesterol levels well below those accepted as normal in Western societies. Another line of evidence derives from *phylogeny*. Contemporary humans have much higher total and LDL cholesterol levels than those of many other species of higher organisms that thrive nonetheless. Thus, observational, ecologic, and genetic studies suggest that ever-lower LDLC levels are likely to confer cardiovascular benefits regardless of starting cholesterol levels for an individual patient.[55]

Cholesterol levels measured early in life influence long-term cardiovascular risk and the burden of risk factors for atherosclerosis, including hypercholesterolemia, and correlate with autopsy-proven fatty streak and raised lesion formation in the arterial tree. Studies with long-term follow-up have suggested that cholesterol levels in youth correlate with long-term risk of MI. Substantial evidence suggests that the

burden of risk for CVD begins in young adulthood. Autopsy studies from the Korea and Vietnam conflicts and recent explorations of coronary anatomy by intravascular ultrasonography all indicate that atherosclerosis affects adolescents in Western society, and that this early exposure to elevated levels of LDL cholesterol leads to premature disease in midlife. Visit-to-visit variability in LDL cholesterol is surprisingly wide, and such fluctuations indeed predict subsequent vascular risk.[57]

Interventions to Lower LDL Cholesterol

All patients with elevated LDL cholesterol should undergo aggressive diet and exercise programs before the initiation of pharmacologic therapy. Lowering LDL cholesterol with statins in both primary and secondary prevention, however, is a cornerstone for cardiovascular therapeutics and an elegant demonstration of the power that RCTs can have on the practice of medicine.

In the 2010 Cholesterol Treatment Trialists (CTT) meta-analysis, which included 21 separate statin trials and more than 129,000 participants,[5] every 1.0 mmol/liter reduction in LDL cholesterol was associated with a 22% reduction in vascular events and a 10% reduction in all-cause mortality. Trials that compared statin therapy with placebo and trials that compared higher-intensity regimens with lower-intensity regimens showed similar effects (**see Fig. 48.7**). All subgroups evaluated showed risk reductions of similar magnitude, with no evidence of effect modification according to baseline LDL cholesterol level. With regard to side effects, no evidence was found for any increase in cancer or deaths from nonvascular causes.

In an even more comprehensive CTT 2012 meta-analysis, the benefits associated with statin use are, if anything, at least as impressive in primary prevention as in secondary prevention.[58] Indeed, in the primary prevention trials (WOSCOPS, AFCAPS/TexCAPS, MEGA, JUPITER, and HOPE-3), relative risk reductions exceeded those observed in the remaining trials of secondary prevention trials. Thus, for the endpoints of major coronary events, stroke, coronary revascularization, and major vascular events, the greatest relative risk reductions occur among patients at lowest absolute risk, suggesting that ever-earlier therapy over a lifetime of risk may be the best biologic way to handle elevated cholesterol levels (**Fig. 45.9**). The JUPITER trial (see later, High-Sensitivity C-Reactive Protein) demonstrated almost 50% reductions in MI and stroke with rosuvastatin in a primary prevention population with LDL cholesterol levels below 130 mg/dL at study entry.[6] In this trial, even those with baseline LDL cholesterol level of less than 70 mg/dL showed clinical benefits. On the other hand, as described previously, those with higher absolute risk attain greater absolute risk reductions with statin use. Thus, those with the highest baseline risk and who achieve the greatest LDL cholesterol reductions avoid the most vascular events and vascular deaths.[59] Of particular biologic interest, there appear to be “legacy effects” associated with statin therapy. For example, 20-year follow-up of participants in the West of Scotland Coronary Prevention Study showed that allocation to statin treatment for the first 5 years conferred continued improvement in survival and substantial reductions in vascular events.[60]

Statins can have adverse effects. Some patients suffer myopathy while on statin therapy, an effect that may be genetically determined at least for simvastatin at higher doses. Statin therapy is associated with small increases in the risk of diabetes, an effect that may be greater with more intensive regimens.[61] Development of diabetes occurs mostly in those who already have impaired fasting glucose, a group in whom the net benefits on preventing MI, stroke, and cardiovascular death outweigh these risks, even in primary prevention. As discussed earlier with regard to trials of congestive heart failure and renal failure, high absolute risk does not automatically indicate that statin therapy will be effective. For most patients, however, after initiation of diet, exercise, and smoking cessation, the best evidence supports addition of statin therapy among available pharmacologic interventions, an option that has become increasingly cost-

effective as potent generic statin agents become available.

Not all agents that lower LDL cholesterol (LDLC) lower vascular event rates, so physicians should exercise caution when using nonstatin agents in both primary and secondary prevention. However, the concept that “lower is better” was affirmed in the large-scale Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT), where the addition of ezetimibe to statin therapy alone further modestly reduced LDLC, hsCRP, and vascular event rates.[8] These effects were larger in analyses considering all vascular events rather than first events only.[62]

Two recent studies demonstrate that the variability in percent LDLC reduction following high-intensity statin therapy is wide and that this response relates directly to efficacy[63,64] (**Fig. 45.10**). These data have clinical importance because they again affirm that “lower is better,” and that on-treatment measurement of LDLC (or apo B) levels is needed for practice.

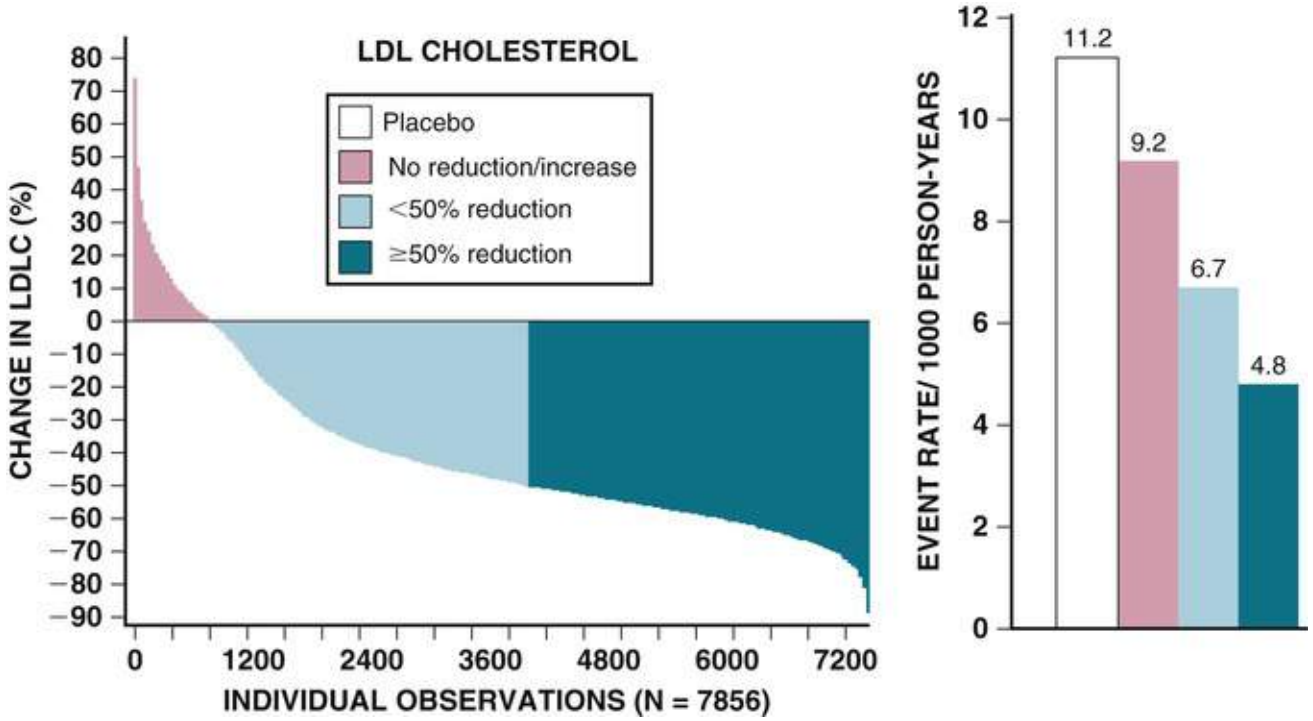


FIGURE 45.10 Waterfall plot for individual Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin Primary Endpoint (JUPITER) trial participants receiving rosuvastatin (20 mg daily) showing the percent change in cholesterol grouped into the three categories shown (*left*) and the incident event rates (per 1000 person-years) for each group (*right*): placebo group (*white bars*), those allocated to rosuvastatin who had no reduction or an increase in low-density lipoprotein cholesterol (LDL-C) (*pink*), a >0 but <50% fall in LDL-C (*light green*), and a ≥50% reduction in LDL-C (*dark green*). (From Ridker PM et al. Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents. Eur Heart J 2016;37:1373-9.)

Although rare in the general population, statin intolerance can be a more common compliant in specialized referral-based lipid clinics. Some patients have true statin intolerance (often on a genetic basis), but not all statin intolerance is reproducible, and thus clinicians should clearly explain benefits to patients and try different statins at low doses and on potentially alternate-day dosing schedules before abandoning this drug class.[65] Starting an exercise program and statin therapy simultaneously may lead patients who experience muscle aches to ascribe these symptoms incorrectly to the pharmacologic intervention.

Statin therapy is the cornerstone for pharmacologic LDLC reduction, but there is considerable interest in monoclonal antibodies that inhibit PCSK9 binding and consequently prolong the effective half-life of

hepatic surface LDL receptors (LDLRs). These agents reduce LDLC substantially when given as monotherapy, as adjuncts to statin therapy with or without ezetimibe, and among those with statin intolerance. Monoclonal antibodies to PCSK9 are also effective in reducing LDLC in patients with heterozygous familial hypercholesterolemia (in whom LDLR activity is reduced) and those with homozygous familial hypercholesterolemia who are LDLR defective, a rare clinical setting where statin efficacy is limited.[66] Evolocumab and bococizumab reduce cardiovascular events[67,68] (**see Fig. 48.9**), although bococizumab, a non–fully humanized antibody, stimulated the development of neutralizing antidrug antibodies that yielded reduced LDL lowering with time, halting the development of that agent.[69] Evolocumab demonstrated an acceptable safety profile in FOURIER in 2.2 years of mean follow-up.[67] A large-scale outcome trial with alirocumab continues.[70,71] A small interfering RNA that targets PCSK9 (inclisiran) also lowers LDL very effectively, with a much longer duration of action than the anti-PCSK9 antibodies.[72]

High-Density Lipoprotein (HDL) Cholesterol

Abundant prospective epidemiologic data demonstrate a strong inverse relationship between HDL cholesterol and vascular risk. In general, observational data suggest that each incremental increase in HDL cholesterol of 1 mg/dL is associated with a 2% to 3% decrease in risk of total CVD. Patients with angiographically proven CAD more often have low levels of HDL than high levels of LDL, as defined by current criteria. Indeed, a large body of observational and experimental data supports a protective role for HDL in atherosclerosis. Thus, measurement of HDL figures in all global risk prediction algorithms, and the ratio of total to HDL cholesterol remains among the most potent lipid-based predictors of cardiovascular risk. However, recent human genetic data do not support such a protective effect of HDL.[73] A recently described rare variant in scavenger receptor BI raises HDL cholesterol but increases CHD risk.[74] Moreover, multiple pharmacologic attempts to rise HDL have failed to improved cardiovascular outcomes in clinical trials, as described next (**see Chapter 48**). This disparity illustrates the importance of distinguishing between risk markers documented by observational epidemiology and causal risk factors.

Interventions to Raise HDL Cholesterol

The large-scale endpoint trials of HDL-raising interventions completed to date have found no reductions in clinical events and in some cases have suggested harm. For example, in the recent AIM-HIGH and HPS-THRIVE trials, random allocation of high-risk patients to niacin supplementation significantly increased HDL cholesterol (as well as reductions in triglycerides and LDL cholesterol), yet showed no beneficial effects at all on clinical event rates.[75,76] Similarly, in the ACCORD trial, fenofibrate reduced triglycerides and increased HDL cholesterol yet produced no significant reduction in hard vascular events.[77] Of concern, in the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial, in which patients at high vascular risk who received the cholesteryl ester transfer protein (CETP) inhibitor torcetrapib, showed an unanticipated increase in all-cause mortality.[78,79] Although some of this hazard probably resulted from off-target effects, two further major trials using the CETP inhibitor dalcetrapib and evacetrapib also failed to reduce cardiovascular event rates despite substantial increases in HDL cholesterol and reductions in LDL cholesterol.[78-81] Thus, at least to date, pharmacologic therapy that increases HDL cholesterol shows no benefit, and if anything may cause harm. The recognition that a biomarker such as HDL can have clinical usefulness for risk prediction without being in the causal pathway for disease postulates has importance for clinical practice

and has implications for several other emerging risk factors, such as those that measure vascular inflammation (**see Chapter 9**).

Alternative Lipid and Lipoprotein Measures

LDL particles exhibit considerable heterogeneity. Small, dense LDL particles associated with high levels of triglycerides, low levels of HDL cholesterol, increased inflammation, and considerably increased cardiovascular risk, a common scenario in diabetic patients. By contrast, larger and less dense LDL particles appear less tightly associated with acute vascular events. In univariate analyses, several studies suggest that the measurement of LDL's major apolipoprotein, apo B, predicts cardiovascular risk better than LDL cholesterol in clinical practice. Most of these studies find, however, that non–HDL cholesterol (defined as total cholesterol minus HDL cholesterol) provides clinical risk information as least as strong as that for apo B—an unsurprising observation because non–HDL cholesterol correlates very closely with apo B levels. Furthermore, most studies report that the total cholesterol/HDL cholesterol ratio remains a very strong predictor of risk, superior even to the ratio of apo B to apo A-I, the dominant apolipoprotein carried by HDL cholesterol. Thus, despite evidence favoring apo A-I and apo B100 in univariate analyses as replacements for HDL and LDL cholesterol, only marginal clinical data seem to indicate that these measures improve overall risk prediction over standard lipid testing. In a recent comprehensive meta-analysis of 37 prospective cohort studies of patients without known CVD, the addition of information on apo B and apo A-I led to only slight improvements in risk prediction.[82] Among patients treated with statin therapy, similar overviews have found that on-treatment levels of LDL cholesterol, non–HDL cholesterol, and apo B each was associated with a risk of recurrent vascular events, but non–HDL cholesterol showed the greatest strength of association. This relative advantage has uncertain clinical importance in current practice; in patients treated with more potent statin agents, recent analyses suggest that on-treatment LDL cholesterol predicts residual risk, as does non–HDL cholesterol, apo B, or lipid ratio.[83]

Beyond standard chemical measures of total, LDL, and HDL cholesterol (which appropriately form the basis of current lipid screening and reduction guidelines), the amount of cholesterol carried by different classes of lipoprotein particles may influence specific functions and vary widely among individuals. Therefore, measures of core lipid composition and lipoprotein particle size might provide better measures for risk prediction. Several lines of evidence have indicated that small LDL particles may be more atherogenic than large particles and contribute particularly to the dyslipidemia of diabetes. Currently, a number of technologies can evaluate LDL subclasses and particle size. Studies using density gradient ultracentrifugation and gradient gel electrophoresis generally have found that lipoprotein subclass identifies patients at higher risk for CHD and have shown a preferential benefit of lipid-lowering therapy for those with small, dense LDL particles compared with large LDL particles. LDL particle concentration, as measured by nuclear magnetic resonance (NMR) imaging studies, correlates well with coronary arterial lumen diameter after statin therapy to predict future vascular events. In the Women's Health Study, NMR-measured LDL particle concentration predicted incident vascular events better than standard chemical measurement of LDL cholesterol.[84] In this study, however, lipoprotein profiles evaluated by NMR did not show superiority to standard measures such as the total/HDL cholesterol ratio or non–HDL cholesterol. HDL particle concentration, as measured by NMR, also may predict residual risk after statin therapy to a greater extent than HDL size or HDL cholesterol.

Thus, although data for advanced lipid testing continue to accrue, it remains unclear whether novel

methods of lipid evaluation add importantly to standard lipid screening in routine practices or should remain specialized tools for research and lipid clinics. In this regard, the most recent recommendations from the National Lipid Association recommend caution when using any novel lipid measure among those at low risk, although LDL particle concentration and apo B level were considered “reasonable” for use among patients at intermediate risk. However, discordance between apo B and LDL cholesterol levels is a strong predictor of incident vascular events that correlates with extent of underlying atherosclerosis.[85,86] For all these reasons, measurement of apo B (or non–HDL cholesterol) may enter future clinical guidelines.[87]

Triglycerides

Triglycerides tend to vary inversely with HDL. The compelling association between HDL and cardiovascular protection led to adjustment of risk from triglycerides for HDL that attenuated the relationship. This approach suggested that triglycerides did not contribute causally to CVD. Recent human genetic and clinical trial data have strongly challenged this traditional stance. As noted earlier, genetic variants that confer lifelong increases in HDL are *not* associated with reduction in cardiovascular risk. Multiple pharmacologic interventions that raise HDL cholesterol have failed to show clinical benefit.

In contrast to HDL, recent human genetic studies consistently implicate triglycerides as a causal risk factor for CVD. Lipoprotein lipase (LPL) has emerged as a key regulator of triglyceride (TG) concentrations in blood. This enzyme, associated with the endothelial cell surface, trims triglycerides from triglyceride-rich lipoproteins (TGRL.) Reduced LPL function causes increased TG concentrations caused by slowed clearance of TGRL. Genetic variants that impair LPL function raise TG concentrations and are associated strongly and consistently with increased cardiovascular risk. Conversely, variants that augment LPL activity are associated with lower cardiovascular risk. These variants reside in the genes that encode apolipoprotein CIII, ANGPTL3, ANGPTL4, Apo A5, and LPL itself.[88-92]

Guidelines continue to recommend measurement of triglycerides in the fasting state, yet much of the prognostic value of plasma TG levels may derive from postprandial levels. On this basis, some investigators suggest adoption of nonfasting TG levels to predict vascular risk. TG measurements serve as a biomarker of classes of TGRL that appear to confer cardiovascular risk. Indeed, the cholesterol in the TGRL may mediate this aggravated risk, not the triglycerides themselves.[93] Studies are evaluating their clinical utility of various assays for remnant lipoprotein particles that may resolve some of the issues surrounding assessment of triglyceride-related risk. (**See also Chapter 48**.)

Interventions to Reduce Triglyceride Levels

Dietary discretion, exercise, and weight reduction as recommended for LDL cholesterol control also have relevance for triglyceride management. Agents approved by the FDA for the reduction of TG levels include omega-3 fatty acid supplements. Two ongoing large-scale studies, STRENGTH and REDUCE-IT, are evaluating the effects of different omega-3 fatty acid preparations on cardiovascular events.[94,95] In the large-scale Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial of high-risk patients with impaired fasting glucose or diabetes, the use of omega-3 fatty acid supplementation reduced triglycerides but did not lower rates of major vascular events.[96] Although fibrate trials did not show significant reductions in vascular events with triglyceride lowering, subgroup analyses raise the hypothesis that further trials focused on patients with elevated triglycerides and low levels of HDL cholesterol merit consideration.

For these reasons, current guidelines do not establish a target value for triglycerides, and

pharmacologic TG reduction is not broadly recommended other than for patients at high risk for pancreatitis. In view of the tight link of TG levels with known risk factors for atherosclerosis (e.g., low HDL cholesterol level, uncontrolled diabetes, hypothyroidism), however, the finding of marked and persistently elevated TG levels should enter into overall risk assessment for an individual and stimulate consideration of the reason for TG level elevation, including careful exclusion of secondary causes such as excessive alcohol consumption, renal disease, Cushing syndrome, and hypothyroidism or the use of concomitant medications such as estrogen, corticosteroids, cyclosporine, and protease inhibitors. Genetic studies also support a causal role for triglycerides in atherogenesis, thus encouraging continued research into triglyceride-lowering approaches.

Metabolic Syndrome, Insulin Resistance, and Diabetes

Insulin resistance and diabetes rank among the major cardiovascular risk factors (**see Chapters 50 and 51**). These effects loom even larger in ethnic minority populations and in patients with other concomitant risk factors. Insulin resistance promotes atherosclerosis even before it produces frank diabetes, and insulin resistance independently increases risk for atherothrombosis. In the Emerging Risk Factors Collaboration, even small increases in fasting glucose were associated with increased rates of vascular deaths, cancer deaths, and nonvascular, noncancer deaths[97] (**Fig. 45.11**). Such findings have prompted interest in the "metabolic syndrome," a cluster of glucose intolerance and hyperinsulinemia accompanied by hypertriglyceridemia, low HDL levels, hypofibrinolysis, hypertension, microalbuminuria, predominance of small dense LDL particles, and central obesity. A harmonized definition proposes cut points for this constellation.[98]

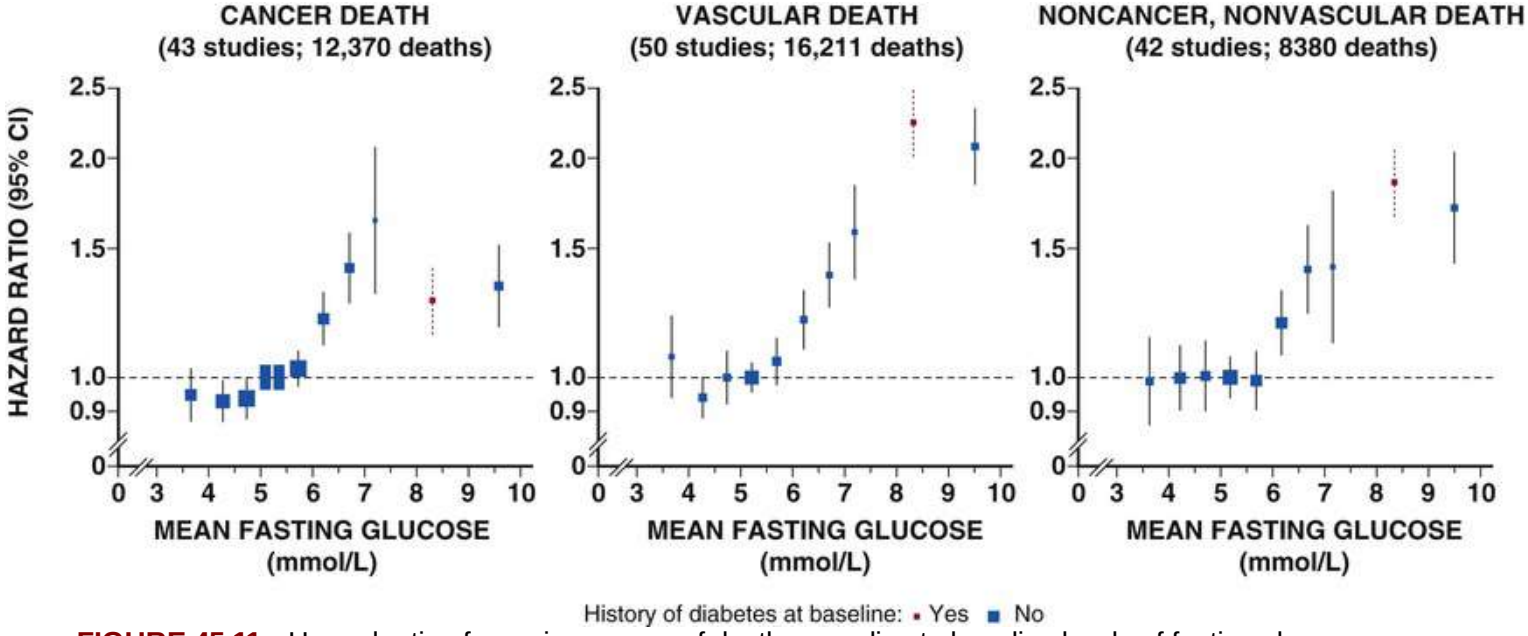


FIGURE 45.11 Hazard ratios for major causes of death according to baseline levels of fasting glucose; CI, confidence interval. (From Seshasai SR et al; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829.)

Some have raised concerns regarding the concept of metabolic syndrome. Controversy continues regarding insulin resistance as a unifying pathophysiologic pathway that accounts for all the features of the so-called metabolic syndrome, rendering it a true "syndrome." In addition, the question of whether coalescence of risk factors incorporated in the concept of metabolic syndrome augment risk beyond the

sum of risk attributable to the individual components remains unsettled. Nonetheless, several studies have documented that persons with the metabolic syndrome have elevated vascular event rates. Most definitions of the metabolic syndrome include a measurement of "central obesity," and much evidence supports the visceral adipose depot as a driver of dysmetabolism, including many components of the metabolic syndrome (**see Chapter 50**). Inflammation also provides a unifying concept that links the elements of the metabolic syndrome. Inflammatory biomarkers such as hsCRP may help further stratify clinical risk and improve the prognostic value of metabolic syndrome, and hsCRP concentrations also predict incident type 2 diabetes.[99] Despite the controversies, many clinicians find the concept of metabolic syndrome useful because it fits the profile of many patients presenting in primary care in contemporary practice.

In addition to systemic metabolic abnormalities, hyperglycemia causes accumulation of advanced glycation end products associated with vascular damage. Diabetic patients have impaired endothelial vasodilator function and appear to have increased leukocyte adhesion to vascular endothelium, a critical early step in atherogenesis. Diabetic nephropathy, detected by microalbuminuria, accelerates these adverse processes. Among persons with non–insulin-dependent diabetes, microalbuminuria predicts cardiovascular and all-cause mortality. Diabetic and prediabetic patients also typically have abnormalities of endogenous fibrinolysis. These effects, in concert with the impaired endothelium-dependent (nitric oxide–mediated) vasodilation common in diabetic patients, contribute to endothelial cell dysfunction and accelerated atherogenesis.

Interventions to Reduce Cardiovascular Risk Among Diabetic Patients

We are fortunate to now have evidence that glucose-lowering therapies can reduce cardiovascular risk (**see Chapter 51**). Lifestyle, as implemented in the Look-AHEAD trial, did not reduce cardiovascular events during a median follow-up of almost 10 years in patients with well-established diabetes, despite providing multiple other benefits.[100] The intensive lifestyle intervention focusing on weight loss did not reduce the rate of cardiovascular events in this group, despite beneficial effects on levels of several biomarkers.[100] This study may have implemented interventions too late to alter the course of cardiovascular events in this population. Social effects may also influence diabetes prevention. The opportunity to move from neighborhoods with high poverty levels to those with low poverty levels associated with reductions in both obesity and incident diabetes. In contrast with the case for lipid lowering, surgical approaches to diabetes and diabetes prevention have on several occasions proved superior to medical approaches (**see Chapter 50**).

Aspirin for Primary Prevention

Low-dose aspirin therapy clearly and consistently provides substantial net benefit for persons at high risk for subsequent events secondary to existing CVD. Earlier meta-analyses by the Antithrombotic Trialists' (ATT) Collaboration showed significant reductions in mortality and nonfatal cardiovascular events among those with a previous MI, stroke, bypass surgery, angioplasty, peripheral vascular surgery, or angina.[101] Doses greater than 75 mg/day demonstrated consistent benefit on vascular events, with no trend toward increasing benefit for higher doses. Below 75 mg, a nonsignificant attenuated risk reduction of only 15% was noted, although there were only three trials that used that dose. The most recently updated ATT review in 2009 included 16 secondary prevention trials comparing long-term aspirin versus control among 17,000 high-risk individuals with a total of 3306 serious vascular events (MI, stroke, or vascular death). It underscored the previous conclusions in secondary prevention and indicated that aspirin is

associated with statistically significant reductions of 19% in any serious vascular event, 31% in nonfatal MI, 20% in major CHD events, and 19% in total stroke. In absolute terms, these represented benefits of aspirin versus control in rates of serious vascular events of 6.7% versus 8.2% per year; in total stroke, 2.08% versus 2.54%; and in coronary events, 4.3% versus 5.3%. There was a nonsignificant increase in hemorrhagic stroke. The reductions in serious vascular events were similar for men and women. Thus, for secondary prevention, antiplatelet therapy with aspirin yields substantial net benefit, and use of low-dose aspirin is advised unless there are major contraindications. If the bleeding risk is high, gastrointestinal (GI) prophylaxis such as proton pump inhibitors may be considered. Use of other antiplatelet agents with demonstrated efficacy such as clopidogrel, would be limited to patients with aspirin allergy or intolerance, those with acute coronary syndromes, implanted stents, or those on anticoagulant therapy.

In primary prevention of CVD, however, the role of aspirin is not straightforward.[101] There is a less clear balance of beneficial effects and bleeding hazards, because patients without evidence of CVD have a lower absolute risk for a cardiovascular event, and thus less consequent absolute benefit, whereas the risk of major adverse effects (e.g., bleeding) remains the same. The 2009 updated ATT Collaboration meta-analysis also included six primary trials of long-term aspirin versus control among 95,000 individuals at low average risk, experiencing 3554 serious vascular events.[102] Aspirin use associated with a statistically significant 12% reduction in any serious vascular event (0.51% aspirin versus 0.57% control per year), mainly because of a significant reduction of 23% in nonfatal MI (0.18% versus 0.23% per year). The net effects on vascular mortality and total stroke were not statistically significant. There was a 14% reduction in risk of ischemic stroke and a 32% increased risk of hemorrhagic stroke (0.04% versus 0.03% per year), both of which were of borderline significance. As in secondary prevention, aspirin significantly increased risk of major GI and extracranial bleeds compared to control by 54% (0.10% versus 0.07% per year).

In 2016 the USPSTF published an updated summary of their systematic evidence review of aspirin for the primary prevention of CVD[103] (**Fig. 45.12**). This review supported the previous results, showing a statistically significant 22% reduction in nonfatal MI, a borderline statistically significant 6% benefit for total mortality, and a nonsignificant 5% benefit for nonfatal stroke and 6% benefit on cardiovascular mortality. The observed benefits on nonfatal MI and total stroke persisted for daily doses of 100 mg or less, and the benefit was seen within 5 years of treatment initiation and continued with active use.

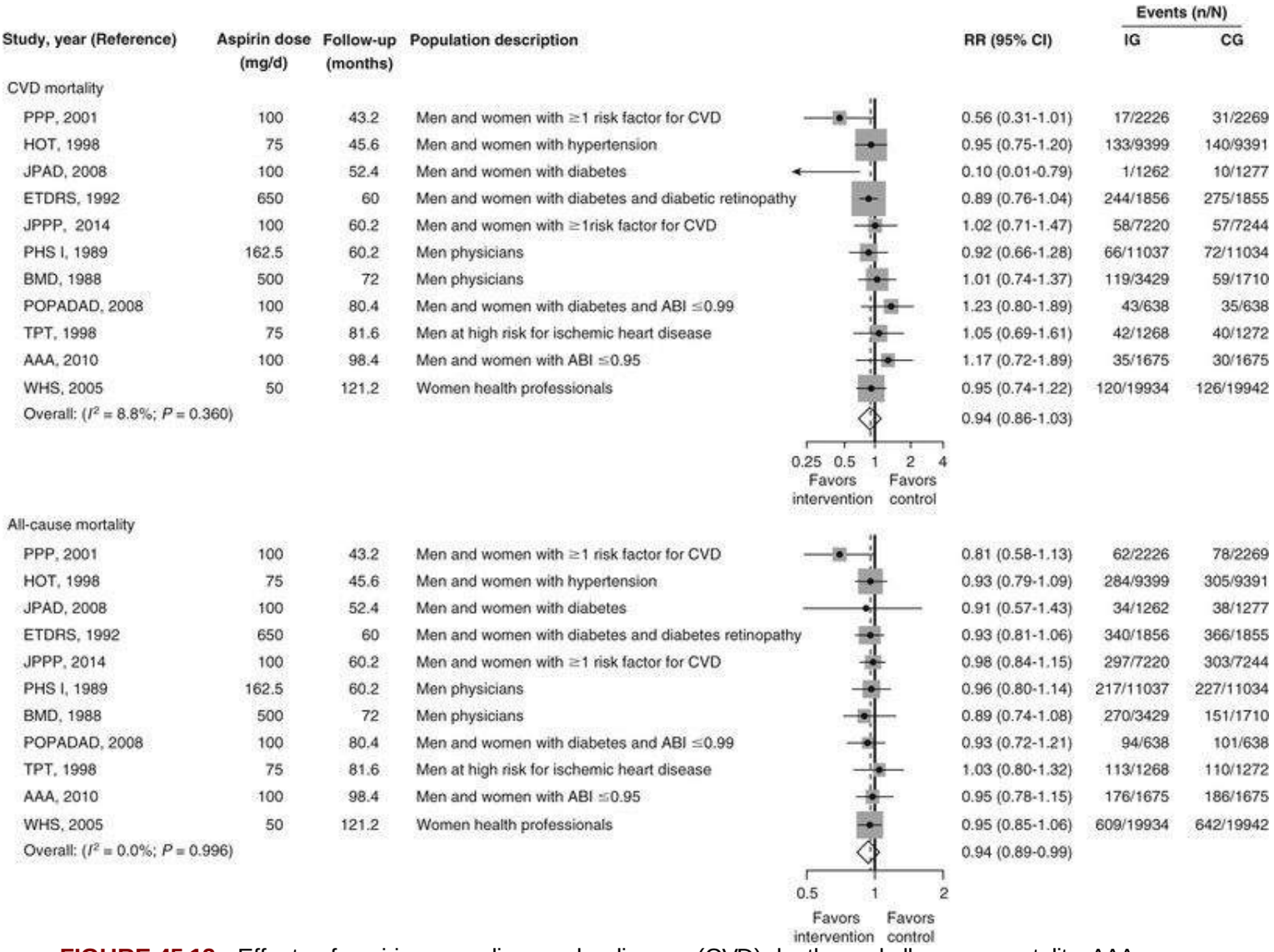


FIGURE 45.12 Effects of aspirin on cardiovascular disease (CVD) deaths and all-cause mortality. AAA, Aspirin for Asymptomatic Atherosclerosis; ABI, ankle-brachial index; BMD, British Male Doctors Trial; CG, control group; ETDRS, Early Treatment Diabetic Retinopathy; HOT, Hypertension Optimal Treatment; IG, intervention group; JPAD, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP, Japanese Primary Prevention Project; PHS, Physicians' Health Study; POPADAD, Prevention of Progression of Arterial Disease and Diabetes; PPP, Primary Prevention Project; RR, relative risk; TPT, Thrombosis Prevention Trial; WHS, Women's Health Study. (From Guirguis-Blake JM et al. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 2016;164(12): 804-13.)

Bleeding is the major known liability of aspirin use, an important consideration in assessing the likely risk to benefit ratio of aspirin in primary prevention.[104] A systematic review of bleeding risks with aspirin use indicated that in CVD prevention trials, even very-low-dose aspirin (≤100 mg daily) is associated with a statistically significant increase in major GI bleeding of 58% and a nonsignificant 27% increase in the rarer event of hemorrhagic stroke. The risk of bleeding remained constant throughout the use of aspirin. Absolute baseline bleeding rates differed by age, sex, and cardiovascular risk factors such as diabetes, smoking, and high BP, as well as by history of upper GI or peptic ulcer disease. A useful smartphone application "Aspirin-Guide" to calculate the number needed to treat and number needed to harm with aspirin use in primary prevention provides the clinician with an aid in shared decision making with patients in this regard.[105]

Three variables merit particular consideration regarding the efficacy of aspirin in primary prevention of cardiovascular disease: diabetes, sex, and age. The 2009 updated ATT meta-analysis[102] included six primary prevention trials in which patients with diabetes constituted subgroups within the study

population, and an additional three primary prevention trials enrolled exclusively patients with diabetes. The pooled subgroup analyses showed no effect modification in cardiovascular effects of aspirin by diabetes, either in primary or secondary prevention. In the three primary prevention trials among diabetic patients—Early Treatment Diabetic Retinopathy Study (ETDRS), Prevention of Progression of Arterial Disease and Diabetes (POPADAD), and Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD)—showed no significant effects of aspirin. A recent meta-analysis[106] among patients with diabetes found no significant differences between aspirin and placebo with respect to prevention of total mortality, individual atherosclerotic events, bleeding, GI bleeding, or hemorrhagic stroke. Two ongoing studies of the use of aspirin in patients with diabetes—ACCEPT-D (Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes) and ASCEND (A Study of Cardiovascular Events in Diabetes)—should provide additional information concerning the safety and benefit profile of aspirin in patients with diabetes. The ACCEPT-D trial will also assess whether aspirin has any additional benefit among patients who are also receiving statin therapy.[107,108]

With regard to potential effect modification by sex and age, aspirin has proved effective for both men and women in secondary prevention of CVD. Aspirin's efficacy in primary prevention, however, remains less certain.[109] The large-scale Women's Health Study found that aspirin significantly lowered the risk of total stroke and ischemic stroke. Although aspirin did not lower the risk of MI overall, there was a significant reduction with aspirin on MI among women over age 65.[101] This finding contrasted with the significant reduction in MI for men in the Physicians' Health Study but no benefit on stroke.[101] Still, analyses from the 2016 U.S. Preventive Service Task Force[103] concluded that no strong evidence supported effect modification for aspirin in primary prevention by sex. This report also concluded that based on analyses of limited subgroup data, the most consistent evidence of subgroup differences was an increased effect on MI in older age-groups.[103] However, a recent trial of low-dose aspirin for primary prevention of CVD in Japanese patients age 60 or older with atherosclerotic risk factors found no benefit in the reduction of risk of their composite endpoint, but a reduction in risk of nonfatal MI.[110] A large ongoing trial (ASPREE: Aspirin in Reducing Events in the Elderly) will provide further information on this question. An additional ongoing trial (ARRIVE: A Study to Assess the Efficacy and Safety of Enteric-Coated Acetylsalicylic Acid in Patients at Moderate Risk of Cardiovascular Disease) will provide information on primary prevention for those at moderate or higher risk of CVD.[111,112]

Of additional note, long-term follow-up analyses of randomized trials of daily aspirin in primary and secondary prevention of vascular events showed a beneficial effect on cancer.[104] Taken together, a recent review of the systematic evidence[113] indicated no significant benefits of long-term low-dose aspirin use on total cancer mortality and total cancer incidence. However, evidence supports a significant reduction in post-trial incidence of colorectal cancer beginning 5 or even 10 or more years after initiation, and a significant reduction in 20 year colorectal cancer mortality. Given the known hazards of aspirin use, wide adoption of aspirin for the chemoprevention of cancer would require an individual weighing of risks and benefits.[114]

Taken together, the data currently available show no clear net benefit of low-dose aspirin in primary prevention of CVD,[115] in contrast to the established benefit-risk ratio in secondary prevention. The FDA has not approved aspirin for use in primary prevention, in contrast to the use of aspirin in secondary prevention. The 2016 USPSTF recommendation statement for use of aspirin includes both the primary prevention of CVD and colorectal cancer.[115] It represents an update of the 2009 Task Force recommendations on aspirin in primary prevention of CVD, and the 2007 recommendation on aspirin and nonsteroidal anti-inflammatory drug (NSAID) use to prevent colorectal cancer. Unlike the previous report, which had separate guidelines for men and women, this updated statement recommends, without

sex-specific differentiation, initiating low-dose aspirin use for the primary prevention of CVD and colorectal cancer in adults age 50 to 59 who have a 10% or greater 10-year cardiovascular risk, do not have increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. The decision to initiate aspirin for the prevention of CVD and colorectal cancer for adults age 60 to 69 who have a 10% or greater 10-year risk should be individualized. The current evidence does not permit assessment of the balance of risks and benefits of initiating aspirin for primary prevention of CVD and cancer for those under age 50 or in adults 70 or older. Other guidelines have varying recommendations (**Table 45.1**).[101]

TABLE 45.1

Summary of Guideline Recommendations on the Use of Low-Dose Aspirin for Primary Prevention of Atherosclerotic Cardiovascular Disease (ASCVD)

U.S. Preventive Services Task Force, 2016
Use aspirin for adults aged 50-59 years with 10-year ASCVD risk ≥10%, not at increased risk of bleeding, life expectancy of ≥10 years, and willing to take aspirin for ≥10 years. Individualize the decision for adults aged 60-69 years with 10-year ASCVD risk 10%, not at increased risk of bleeding, life expectancy of ≥10 years, and willing to take aspirin for ≥10 years. No recommendation for adults aged <50 years or ≥70 years.
U.S. Preventive Services Task Force, 2009
Use aspirin when potential benefit outweighs the risk of GI bleeding. *Men* Age 45-59 years with 10-year CHD risk ≥4% Age 60-69 years with 10-year CHD risk ≥9% Age 70-79 years with 10-year CHD risk ≥12% *Women* Age 55-59 years with 10-year stroke risk ≥3% Age 60-69 years with 10-year stroke risk ≥8% Age 70-79 years with 10-year stroke risk ≥11%
American Diabetes Association, 2016
Use aspirin 75 to 162 mg/day for individuals with diabetes who are not at increased bleeding risk and who have 10-year ASCVD risk >10% (includes most men and women ≥50 years with diabetes and with ≥1 other ASCVD risk factors). Individualize for adults with diabetes <50 years, and multiple ASCVD risk factors (10-year ASCVD risk, 5%-10%). Not recommended for adults with diabetes who are at low ASCVD risk (10-year risk <5%).
American College of Chest Physicians, 2012
Suggest aspirin use for adults ≥50 years.
European Society of Cardiology, 2012
Not recommended.
American Heart Association, 2011
Can be useful in women ≥65 years if blood pressure is controlled and benefit outweighs risk. May be reasonable in women <65 years for prevention of ischemic stroke. Not recommended for women <65 years for prevention of myocardial infarction.
Canadian Cardiovascular Society, 2011
Consider only in special circumstances (CHD risk is high and bleeding risk is low). Not recommended for routine use.

CHD, Coronary heart disease; *GI,* gastrointestinal.

Data from Mora S, Manson JE. Aspirin for primary prevention of atherosclerotic cardiovascular disease: advances in diagnosis and treatment. JAMA Intern Med. 2016;176:1195–1204.

Diabetes in itself does not qualify individuals for aspirin therapy. The 2016 statement of the American Diabetes Association[116] supports the last consensus statement of the AHA, ACC Foundation, and American Diabetes Association[117] and recommends consideration of low-dose aspirin for the primary prevention of CVD for type 1 or type 2 diabetic patients who have a 10-year CVD risk of at least 10% and who do not have an increased risk of bleeding. This group consists of men and women with diabetes who are at least 50 years of age and who have at least one additional major CVD risk factor. Aspirin should not be recommended for adults with diabetes mellitus who are at low risk (<50 years of age with no additional atherosclerotic CVD risk factor).

Interventions to Increase Appropriate Use of Aspirin

An analysis of the 2011–2012 NHANES examined the use of aspirin for secondary and primary prevention of CVD.[118] Individuals who reported that a doctor had previously told them that they had been diagnosed with a stroke or heart attack were considered candidates for secondary prevention. Of the secondary prevention population, 75.9% reported being told to take aspirin by their physician, and of these, 89.9% were taking aspirin. Individuals without previously diagnosed CVD were considered candidates for primary prevention and classified into high and low risk based on whether their Framingham Risk Score of 10-year CHD risk was greater than 10% or 10% or less. For those without previously diagnosed CVD, 22.5% were classified as high risk: of these, 40.9% reported being told by their physician to take aspirin, with 79.0% complying. Among those at low risk, 26.0% were told by their physician to take aspirin, with 76.5% complying. Among high-risk individuals, significant predictors of patient-reported physician recommendations for aspirin use for primary prevention included age, race, and insurance status; among those who were low risk, the identified factors were age and insurance status, as well as obesity and education. These results suggest that objective risk level and subsequent risk of future CVD did not lead to recommendations for aspirin.

Clinical decision support tools that could assist physicians in identifying patients at risk might be beneficial. Consideration of the safety of primary prevention with aspirin requires an individualized assessment of both aspirin's expected benefits on CVD as well as expected bleeding risk. The 2016 USPSTF used a calculator derived from the ACC/AHA pooled cohort equations to predict 10-year risk for first hard atherosclerotic cardiovascular event. This is currently the only internally validated calculator that reports risks as a combination of cerebrovascular and coronary events (online version of calculator: http://tools.acc.org/ASCVD-Risk-Estimator/). No validated tool for predicting bleeding risk is available. Other new and novel approaches are being considered to aid physicians in assessing the risk-benefit ratio for aspirin in primary prevention for CVD. For example, the aforementioned Aspirin-Guide[105] is a personalized approach for shared decision making that incorporates information about the patient's risk factors to calculate both a 10-year atherosclerotic cardiovascular event risk score (the ACC/AHA ASCVD score) as well as a bleeding risk score (www.aspiringuide.com; free mobile app: https://appsto.re/us/emRMcb.i). At this time, however, assessing the balance of baseline risk for bleeding against cardiovascular benefits, and the recommendation for low-dose aspirin in the primary prevention of CVD, is a qualitative assessment.

Conceptual Basis for the “Polypill”

In contrast with interventions that separately alter platelet function and reduce BP and cholesterol, a trend has emerged in preventive intervention to consider use of “polypills.” Such preparations might, for example, contain aspirin, folic acid, a statin, and a various BP-lowering agents. In secondary prevention, use of polypill approaches has theoretical advantages particularly in the developing world, where a single inexpensive intervention might provide improved delivery of care at reduced cost, and perhaps through the use of trained nonphysician health care workers. The Indian Polycap Study demonstrated such benefit: a single combined agent significantly reduced BP, lipids, and overall medication compliance.[119]

In primary prevention, however, few of the assumptions underlying the polypill concept have withstood hypothesis testing. With regard to drug selection, randomized trials have found that folic acid does not lower event rates and that aspirin may prove of net benefit only to those at highest risk. Adherence to polypill regimens has also been less than anticipated, and “age-only” screening has largely been replaced by “absolute risk screening.”[120] Most importantly, effects of different therapies have not proved to be additive as assumed. In the HOPE-3 polypill trial of 12,075 intermediate-risk participants, the benefit

observed compared to placebo when two antihypertensive agents were added to rosuvastatin 10 mg (HR, 0.71; 95% CI 0.56 to 0.90) was not significantly greater than that of rosuvastatin 10 mg alone (HR, 0.74; 95% CI 0.60 to 0.93).[121] Given that this magnitude of relative risk reduction was substantially smaller than that observed in the comparable JUPITER trial (which used rosuvastatin 20 mg daily instead of 10 mg daily), moderate- to high-intensity statin therapy (without additional agents) may well serve as an optimum "polypill"[122] (**Fig. 45.13**).

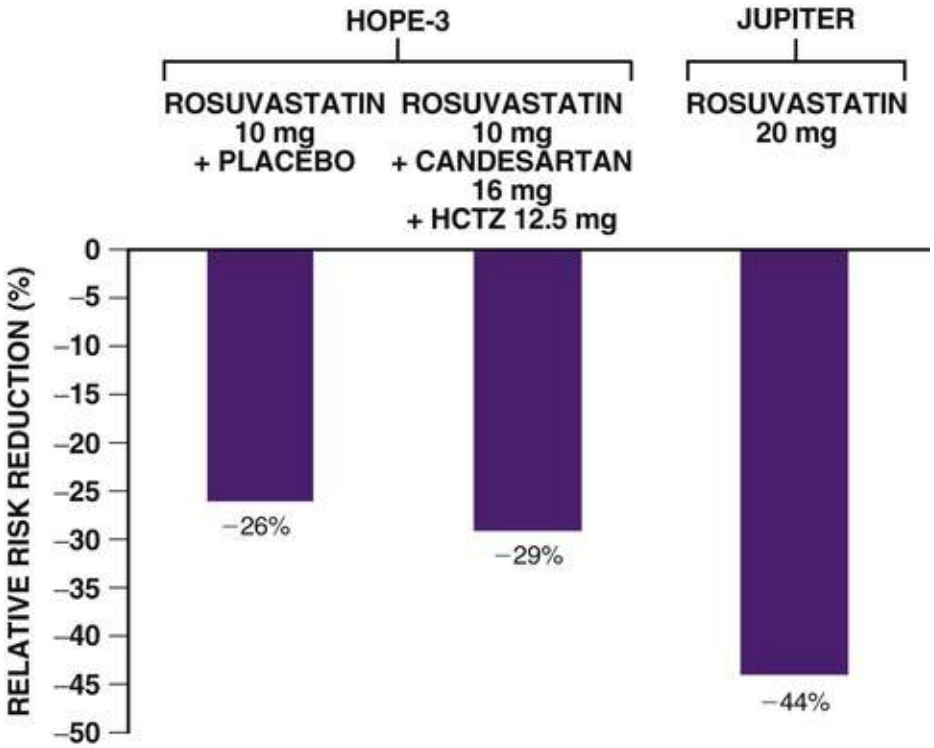


FIGURE 45.13 Statin monotherapy versus the "polypill" concept. This figure plots the relative risk reductions shown by rosuvastatin 10 mg alone (*left*), the combination of rosuvastatin 10 mg plus candesartan 16 mg plus hydrochlorothiazide (HCTZ) 12.5 mg (*center*) (data from Heart Outcomes Prevention Evaluation [HOPE] 3 trial), and rosuvastatin 20 mg alone from Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER, *right*). (From Ridker PM. Is statin monotherapy the perfect polypill? Circulation 2016;134[2]:91-3.)

Nonconventional Risk Markers and Associated Interventions

Despite the importance of blood lipids, half of all heart attacks occur in persons without overt hyperlipidemia, and almost one quarter occur in the absence of any of the major classic vascular risk factors. This fact challenges several basic issues related to current screening programs for risk detection and disease prevention. It is thus not surprising that much recent research has focused on the identification and evaluation of novel atherosclerotic risk markers.

When valuating any novel risk marker as a potential new screening tool, clinicians need to consider (1) whether there is a standardized and reproducible assay for the biomarker of interest; (2) whether there is a consistent series of prospective studies demonstrating that a given parameter predicts future risk; (3) whether the novel marker adds to the predictive value of lipid screening; (4) whether there is evidence that the novel marker adds to global risk prediction scores, such as that in the Framingham Heart Study;

and (5) whether knowledge of the biomarker would lead to a proven intervention to reduce risk that the patient otherwise would not have received. (**See Chapter 9** for a detailed discussion of quantitative approaches to answering these questions.) A discussion of some examples of these basic epidemiologic requirements follows: hsCRP and other markers of inflammation, Lp(a), and homocysteine. Physicians also should consider the relative magnitude of novel markers in terms of risk prediction, particularly compared with lipid screening.

High-Sensitivity C-Reactive Protein

Inflammation characterizes all phases of atherothrombosis and provides a critical pathophysiologic link between plaque formation and acute rupture, leading to occlusion and infarction (**see Chapter 44**.) Inflammatory cytokines such as IL-1 or tumor necrosis factor (TNF) implicated in atherogenesis elicit the expression of the messenger cytokine IL-6, which can travel from local sites of inflammation to the liver, and change in the program of protein synthesis to produce the acute-phase response.

In clinical practice, the best-studied and most easily applied biomarker of this inflammatory process is the downstream acute-phase reactant CRP. Composed of five 23-kDa subunits, CRP, a circulating member of the pentraxin family, functions in the human innate immune response. More than 50 large-scale prospective cohorts conducted worldwide indicate that CRP, when measured with high-sensitivity assays (hsCRP), independently predicts risk of MI, stroke, peripheral arterial disease, and sudden cardiac death (SCD) among apparently healthy persons, even when LDL cholesterol levels are low.[123] In comprehensive meta-analyses, the multivariable hazard associated with hsCRP, if anything, exceeded that associated with either BP or cholesterol, and hsCRP yielded an increment in the C-statistic in terms of predicting future CHD events virtually identical in magnitude to that of total and HDL cholesterol[124,125] (**Fig. 45.14**). hsCRP adds prognostic information at all levels of LDL cholesterol and at all levels of risk, as determined by the Framingham Risk Score.

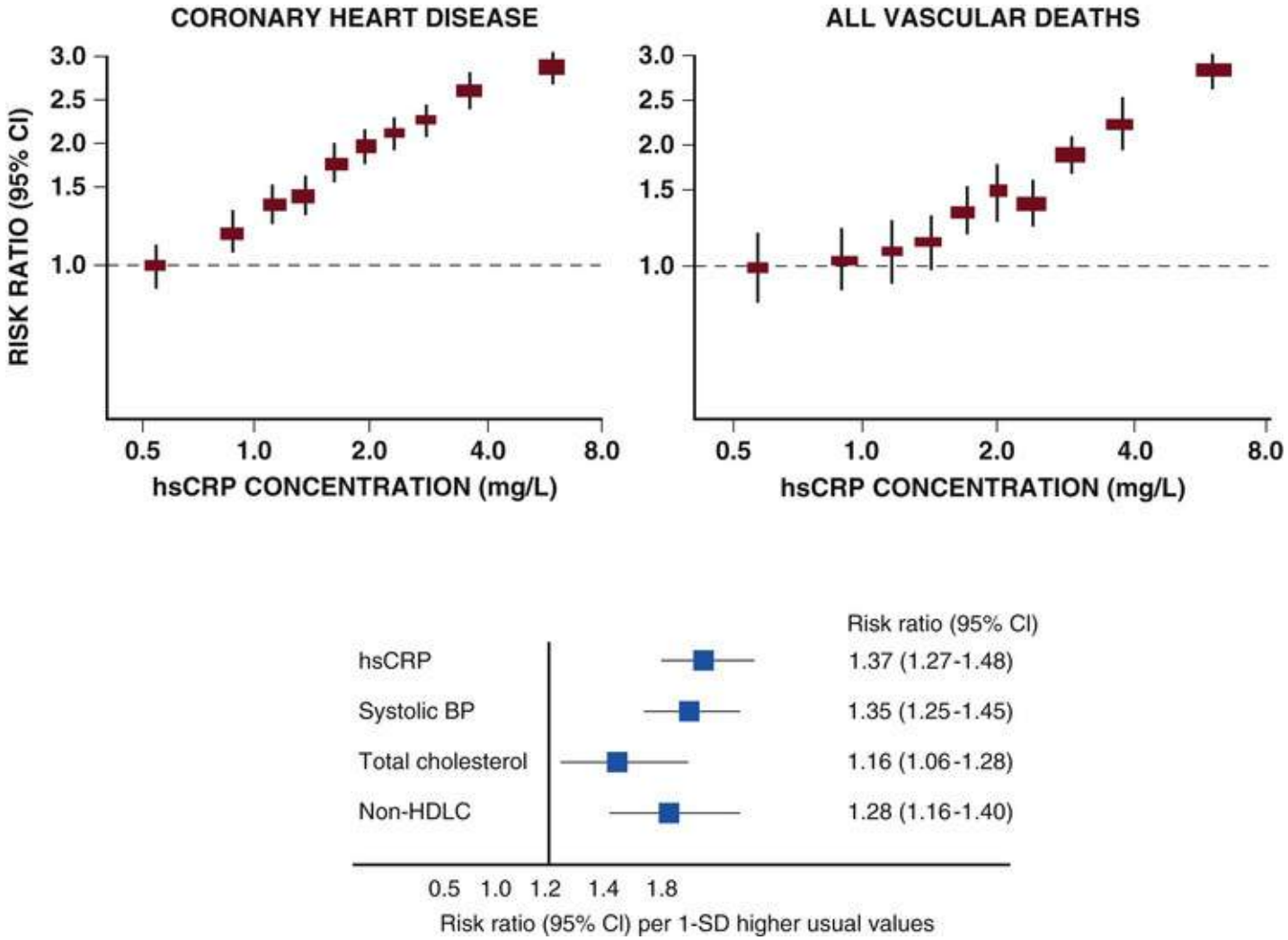


FIGURE 45.14 Predictive ability of high-sensitivity C-reactive protein (hsCRP) in primary prevention. This meta-analysis shows the relationship of hsCRP concentrations in healthy individuals with incident coronary heart disease and vascular death (*top*), and the risk associated with a 1–standard deviation (SD) increase in hsCRP compared to comparable changes in blood pressure or total cholesterol (*bottom*).
(From Ridker PM. Atest in context: high-sensitivity C-reactive protein. J Am Coll Cardiol 2016;67[6]:712-23.)

The AHA and CDC issued the first guidance for the use of hsCRP levels in clinical practice in 2003. Briefly stated, hsCRP levels of less than 1, 1 to 3, and higher than 3 mg/liter should be interpreted as lower, moderate, and higher relative vascular risk, respectively, when considered along with traditional markers of risk (**Fig. 45.15**). Application within the Framingham Heart Study has corroborated this critical finding.[126] Screening for hsCRP should be done at the discretion of the physician as part of global risk evaluation. Although hsCRP predicts risk across the entire population spectrum, it is likely to be of greatest usefulness in patients at intermediate risk—that is, those with anticipated 10-year event rates between 7.5% and 20%. Current AHA/ACC guidelines suggest the use of hsCRP when decision making regarding statin therapy is uncertain. Values of hsCRP in excess of 8 mg/liter may represent an acute-phase response caused by an underlying inflammatory disease or intercurrent infection and should lead to repeat testing in approximately 2 to 3 weeks. Because hsCRP levels have equivalent stability over long periods to that of traditional risk factors, exhibit minimal circadian variation, and do not depend on prandial state, outpatients can undergo screening at the cholesterol evaluation.

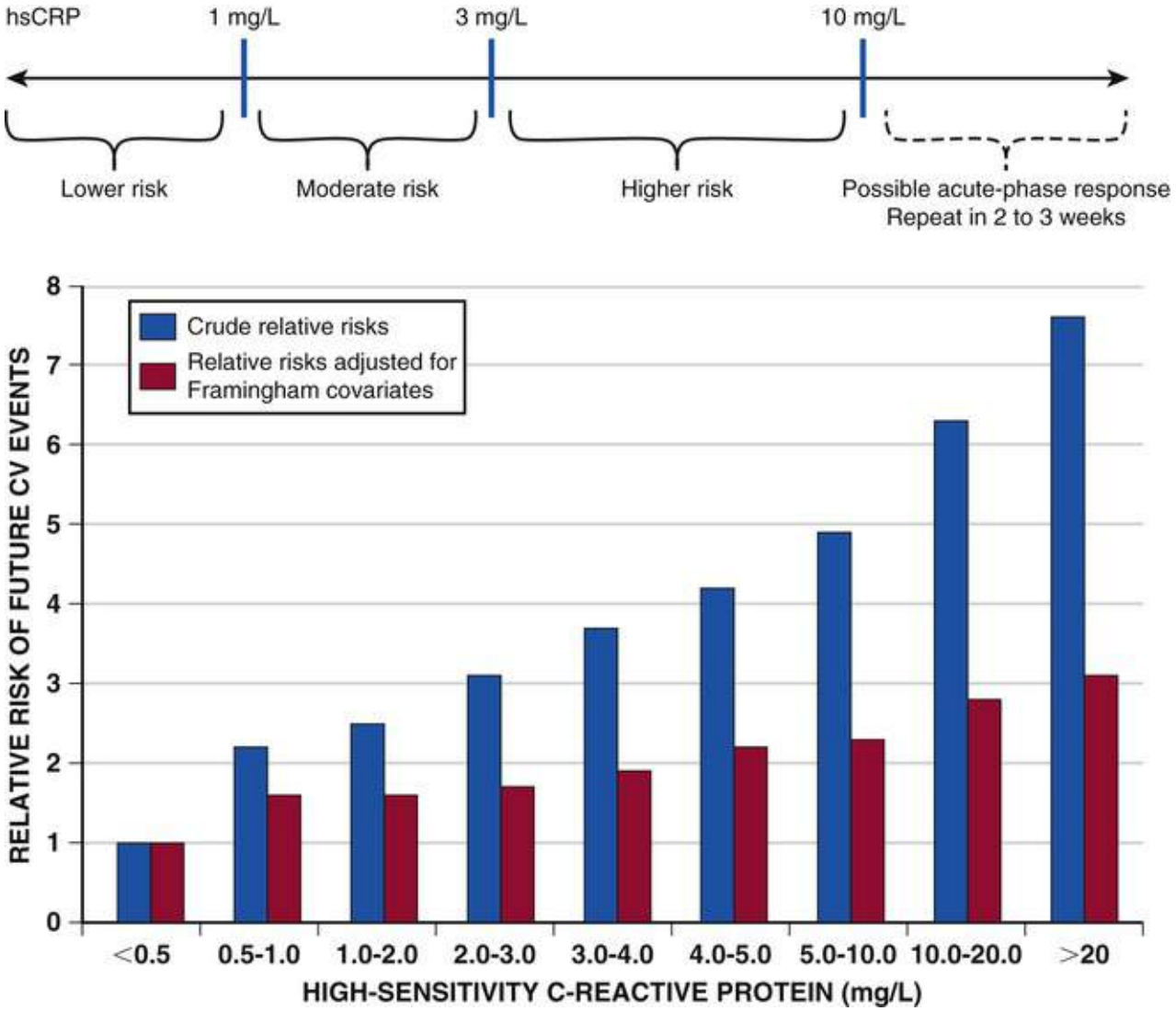


FIGURE 45.15 Clinical interpretation of hsCRP values for cardiovascular (CV) risk prediction. High-sensitivity C-reactive protein (hsCRP) relates linearly to cardiovascular risk across a wide range. The *blue bars* show crude relative risks and the *red bars* show relative risks adjusted for the Framingham risk factors. (From Ridker PM. A test in context: high-sensitivity C-reactive protein. J Am Coll Cardiol 2016;67[6]:712-23.)

In clinical practice, many physicians now use both hsCRP and family history as part of global risk prediction. The freely available Reynolds Risk Score for men and women facilitate this process (www.reynoldsriskscore.com). In several independent cohorts, the Reynolds Risk Score has proved to have superior discrimination and calibration than the Framingham Risk Score or the current AHA/ACC pooled cohort equations.[126,127] Levels of hsCRP greater than 3 mg/liter also predict recurrent coronary events, thrombotic complications after angioplasty, poor outcome in the setting of unstable angina, and vascular complications after bypass surgery.

All these data support the concept that inflammation plays a critical role throughout the atherothrombotic process. Additionally, hsCRP has prognostic usefulness in cases of acute ischemia, even without elevated troponin level, suggesting that enhanced inflammation at hospital admission can determine subsequent plaque rupture. These findings help explain why persons with elevated hsCRP levels may accrue greater benefit from aggressive interventions compared with those with low hsCRP levels. This marker also is associated with vascular events and ischemic episodes in patients with ischemia with angiographically normal-appearing coronary arteries (INOCA), suggesting a role for inflammation in coronary microvascular function.[128]

Levels of hsCRP correlate only modestly with underlying atherosclerotic disease as measured by carotid intimal medial thickness or by coronary calcification. This observation suggests that hsCRP does

not simply reflect the presence of subclinical disease but indicates an increased propensity for plaque disruption and/or thrombosis. Autopsy data support this hypothesis: elevated hsCRP levels are more common in patients with frankly ruptured plaques than in those with erosive disease or those who died of nonvascular causes. Elevated levels of hsCRP predict not only cardiovascular events but also the onset of type 2 diabetes, perhaps because hsCRP levels correlate with several components of the metabolic syndrome, including those not easily measured in clinical practice, such as insulin sensitivity, endothelial dysfunction, and impaired fibrinolysis.

Interventions for Primary Prevention in Patients With Elevated hsCRP Levels

As for those with elevated LDL cholesterol, diet, exercise, and smoking cessation are the first-line interventions for those with elevated hsCRP. At a minimum, an elevated hsCRP level should provide considerable motivation to improve lifestyle, particularly for those previously told that they were not at risk because of an absence of hyperlipidemia. In this regard, the two interventions proven to lower vascular risk in the Mediterranean PREDIMED trial, mixed nuts and olive oil, both reduce hsCRP levels.[129]

Beyond lifestyle change, the use of statin therapy to reduce vascular risk among individuals with elevated hsCRP, even with low LDL cholesterol levels, represents a fundamental change in treatment strategies for CVD prevention. Most importantly, in the JUPITER trial in apparently healthy men and women with LDL cholesterol levels less than 130 mg/dL who were at increased risk because of hsCRP levels of 2 mg/liter or greater, the use of rosuvastatin resulted in a 44% reduction in the trial primary endpoint of all vascular events ($P < 0.000001$), a 54% reduction in MI ($P = 0.0002$), a 48% reduction in stroke ($P = 0.002$), a 46% reduction in need for arterial revascularization ($P < 0.001$), and a 20% reduction in all-cause mortality ($P = 0.02$). All prespecified subgroups within JUPITER significantly benefited from statin therapy, including those previously considered at “low risk,” such as women, nonsmokers, those without metabolic syndrome, and those with Framingham scores less than 10%. From a public policy perspective, the 5-year number needed to treat (NNT) within JUPITER was only 25, a value smaller than the comparable 5-year NNT associated with the treatment of hyperlipidemia or hypertension in primary prevention. In an additional prespecified analysis, rosuvastatin reduced incident venous thromboembolism by 43%, a result with clinical relevance and an important observation regarding pleiotropic effects of statin therapy.[130,131] As described earlier, these vascular benefits outweigh the small hazard of diabetes associated with statin use.

The JUPITER trial also demonstrates that achieving low levels of *both* LDL cholesterol and hsCRP after the initiation of statin therapy might maximize preventive efforts, at least with statin therapy. Within the JUPITER cohort, those who not only reduced LDL cholesterol to less than 70 mg/dL but also reduced hsCRP to below 1 mg/liter had an 80% reduction in risk.[131] This observation made in a primary prevention setting extends prior work in high-risk secondary prevention demonstrating the benefit of lowering both LDL cholesterol and hsCRP.[132] For example, in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial, conducted in patients with acute coronary syndromes treated with statin therapy, achieving levels of hsCRP less than 2 mg/liter conferred equivalent long-term event-free survival as achieving levels of LDL cholesterol less than 70 mg/dL; indeed, those who met both these levels had the best long-term outcomes.[132] An analysis of the IMPROVE-IT trial of ezetimibe added to simvastatin supports the concept of lowering both LDL and hsCRP[133] (**Fig. 45.16**).

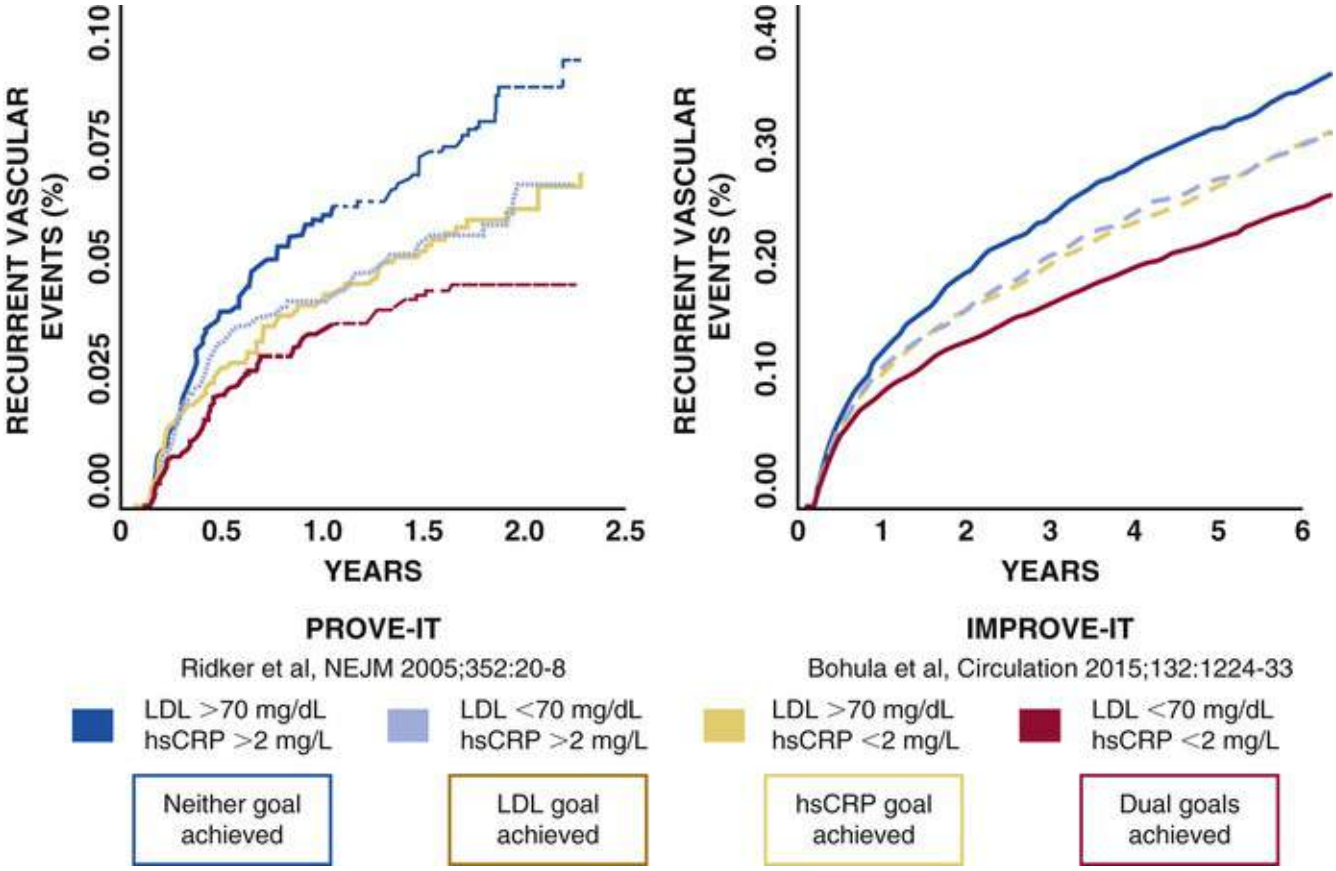


FIGURE 45.16 Recurrent cardiovascular event rates according to whether or not patients achieved below-median low-density lipoprotein (LDL) reduction (<1.8 mmol/L [<70 mg/dL]), high-sensitivity C-reactive protein (hsCRP) reduction below median (<2 mg/L), neither, or both following initiation of statin therapy (PROVE-IT, *left*) or the combination of statin therapy and ezetimibe (IMPROVE-IT, *right*). (From Ridker PM. Residual inflammatory risk: addressing the obverse side of the atherosclerosis prevention coin. Eur Heart J 2016;37:1720.)

Although inflammation participates in vascular injury and hsCRP provides an inexpensive and clinically useful measure of this process, the stimulus that initiates the underlying inflammation remains uncertain. Patients with chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, and psoriasis tend to have elevated hsCRP levels and, on average, somewhat elevated vascular risk.[134] Patients with low-grade infections such as gingivitis or those who are chronic carriers of *Chlamydia pneumoniae*, *Helicobacter pylori*, herpes simplex virus, and cytomegalovirus also may have a higher risk for vascular problems on the basis of a chronic systemic inflammation. However, careful prospective studies of antibody titers directed against these organisms have not consistently found evidence of association, and large-scale antibiotic trials have not shown reduced event rates.

It remains uncertain whether lowering inflammation can reduce vascular event rates. Early "mendelian randomization" analyses have not supported a direct causal role for CRP in atherothrombosis, but more recent studies of this type endorse a causal role for related upstream IL-6 pathways.[135,136] These data strongly support ongoing "cardiovascular inflammation reduction trials" such as those evaluating low-dose methotrexate, colchicine, and the anti–IL-1β antibody canakinumab. Further, the concept of "residual inflammatory risk" as being a separate and distinct clinical entity from "residual cholesterol risk" has emerged.[137]

Other Biomarkers of Inflammation

Although hsCRP currently is the best-characterized inflammatory biomarker for clinical use, several

other markers of inflammation have shown promise in predicting vascular risk and provide further insights into the role played by inflammation in atherothrombosis. These include cytokines such as IL-1 and IL-6, soluble forms of certain cell adhesion molecules such as intercellular adhesion molecule (sICAM-1), P-selectin, and the mediator CD40 ligand, as well as markers of leukocyte activation such as myeloperoxidase, pregnancy-associated plasma protein A, and the IL-1 receptor family member ST2. Unfortunately, many of these alternative inflammatory biomarkers have analytic limitations that to date have reduced clinical usefulness. For example, some have too short a half-life for clinical diagnostic testing, and the ability of others to predict risk in settings of broad populations has proved to be marginal thus far. Nonetheless, measurement of several of these inflammatory biomarkers can shed critical pathophysiologic light on the atherothrombotic process, particularly at the time of plaque rupture. For example, soluble CD40 ligand (probably released from activated platelets) may provide insight into the efficacy of specific antithrombotic agents independently of CRP. Similarly, myeloperoxidase may provide prognostic information in cases of acute ischemia beyond that associated with troponin or CRP, whereas clinical studies with ST2 indicate novel associations in heart failure and ischemia.[138]

Although also an acute-phase reactant and thus often considered an inflammatory biomarker, plasma *fibrinogen* additionally influences platelet aggregation and blood viscosity, interacts with plasminogen binding and, in combination with thrombin, mediates the final step in clot formation and the response to vascular injury. Fibrinogen levels associate positively with age, obesity, smoking, diabetes, and LDL cholesterol level and negatively with HDL cholesterol level, alcohol use, physical activity, and exercise level. Given these relationships, fibrinogen was among the first "novel" risk factors evaluated. Early reports from the Gothenburg, Northwick Park, and Framingham heart studies all found significant positive associations between fibrinogen levels and future risk of cardiovascular events. Since then, a number of other prospective studies have confirmed these findings, and in meta-analyses, an approximately linear logarithmic association was seen between usual fibrinogen level and the risk of CHD and stroke.[139] In recent studies, hsCRP and fibrinogen levels showed additive ability to predict risk, although hsCRP appeared to have a larger absolute effect. This observation holds interest because CRP and fibrinogen have distinct genetic determinants. Despite the consistency of these data, measurement of fibrinogen has found limited use in clinical practice because of suboptimal assay standardization and inconsistency across reference laboratories.

Other than hsCRP, the only inflammatory biomarker commercially available is lipoprotein-associated phospholipase A_2 (Lp-PLA_2). As with hsCRP, most but not all published studies indicate a positive relationship between Lp-PLA_2 and vascular risk. In contrast with hsCRP, however, Lp-PLA_2 circulates bound to lipoproteins such as apo B, so its levels strongly correlate with LDL cholesterol. Because of this effect, adjustment for lipid levels largely attenuates the strength of association between Lp-PLA_2 and vascular events, making contributions to risk detection modest. Clinically, the availability of both mass and activity assays, each with suboptimal reproducibility, has further complicated the evaluation of Lp-PLA_2. In two recent large-scale trials, Lp-PLA_2 no longer predicted residual risk after aggressive LDL cholesterol reduction with statin therapy. Accordingly, expert reviews suggest limited clinical applicability of Lp-PLA_2 measurement.[140]

Interventions to Reduce Alternative Markers of Inflammation

To date, four clinical trials have evaluated the potential benefits of fibrinogen reduction, and all have found disappointing results. Specifically, two trials of bezafibrate have shown no reduction in event rates with active therapy despite significant reductions in fibrinogen levels. Similarly, in the Heart and

Estrogen/Progestin Replacement Study (HERS) and in the WHI, hormone replacement therapy lowered fibrinogen but did not improve clinical outcomes. Equally disappointing, two major trials of darapladib, an inhibitor of Lp-PLA$_2$, showed no clinical benefit,[141,142] as has an exploratory trial of losmapimod, a MAP-kinase inhibitor.[143] Nonetheless, at this time, several multinational trials are evaluating whether specific agents that directly or indirectly target inflammation can reduce vascular event rates. Therapies under evaluation include canakinumab (a monoclonal antibody that neutralizes IL-1β), the generic anti-inflammatory agent low-dose methotrexate (LDM) that already sees wide use for the treatment of rheumatoid arthritis, and colchicine, a microtubule inhibitor with anti-inflammatory effects used to treat gout and pericarditis. Trials with these latter agents should provide unconfounded direct tests of the inflammation hypothesis of atherothrombosis. Indeed the recently reported Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) affirmed the inflammatory hypothesis of atherosclerosis and demonstrated the utility of hsCRP as a tool to target anti-interleukin-1-beta therapy.[144]

Lipoprotein(a)

Lp(a) consists of an LDL particle with its apo B100 component linked by a disulfide bridge to apolipoprotein(a) [apo(a)], a variable-length protein that shares sequence similarity with plasminogen (**see Chapter 48**). The apo(a) component of Lp(a) contains a variable number of cysteine-rich kringle IV repeats that result in great heterogeneity. Accordingly, plasma Lp(a) concentrations vary inversely with apo(a) isoform size but also may vary even in isoform size, based on differential levels of production. Underlying its molecular complexity, more than 25 heritable forms of Lp(a) exist, demonstrating the importance of the genome in determining plasma levels, an important issue for risk prediction across different population groups. The close homology between Lp(a) and plasminogen has raised the possibility that this lipoprotein may inhibit endogenous fibrinolysis by competing with plasminogen binding on the endothelium. More recent studies have suggested that Lp(a) binds and inactivates tissue factor pathway inhibitor and may augment the expression of plasminogen activator inhibitor, further linking lipoproteins and thrombosis. Lp(a) also colocalizes within atherosclerotic lesions and may have local actions through oxidized phospholipid pathways. Thus, several mechanisms may contribute to a role for Lp(a) in atherothrombosis.[145]

In an updated meta-analysis of 36 prospective studies that included more than 12,000 cardiovascular endpoints, the adjusted risk ratios for each standard deviation (SD) increase in plasma Lp(a) level were 1.13 for CHD and 1.10 for ischemic stroke.[146] Adjustment for classic cardiovascular risk factors only modestly attenuated these effects, in part because Lp(a) and other markers of risk correlate minimally. Whether the assessment of Lp(a) truly adds prognostic information to overall risk in primary prevention remains uncertain, however, because in most studies, Lp(a) typically has proved to be predictive for persons already known to be at high risk because of the presence of other risk factors, in particular elevated levels of LDL cholesterol. By contrast, recent data from the Bruneck study suggest that discrimination and new reclassification of cardiovascular risk can be improved modestly with Lp(a) assessment, particularly for those with markedly elevated levels.[147] Some investigators have advocated Lp(a) assessment in certain patient groups, such as those with established coronary disease or renal failure. Evidence that children with recurrent ischemic stroke have elevated Lp(a) levels also supports the potential use of this biomarker in unusual high-risk settings.

Standardization of commercial Lp(a) assays has improved considerably, with most reference laboratories using commercial assays that measure Lp(a) in a manner independent of apo(a) isoform size. In several recent investigations using these assays, the risk increase with Lp(a) was nonlinear and limited

to patients with concomitant elevations of LDL cholesterol levels, confirming earlier work. Thus the presence of threshold effects and interactions with LDL cholesterol may limit the routine measurement of Lp(a) for cardiovascular risk stratification in the general population. However, there remains considerable interest in those with greatly elevated Lp(a) levels resulting from genetic effects.[148,146]

Interventions to Reduce Lipoprotein(a)

With the exception of high-dose niacin, few approved interventions lower Lp(a) level, and no study to date has shown that Lp(a) reduction lowers vascular risk. However, the genetic investigations previously noted have provided important insights into Lp(a) regulation and suggest the potential for a causal relationship between Lp(a) and vascular events. For these reasons, there is considerable interest in exploring agents with Lp(a)-lowering effects.[145] Several novel agents, including PCSK9 inhibitors and a modified antisense oligonucleotide drug, have shown substantial ability to reduce Lp(a) levels and are now undergoing outcome evaluations.[145] Enthusiasm is somewhat tempered by the failure of CETP inhibitors such as evacetrapib to lower event rates despite substantial Lp(a) reduction. Mechanisms of Lp(a) reduction may prove important, and definitive trials may need to focus on those with marked elevations, a difficult group to screen.

Homocysteine

Homocysteine is a sulfhydryl-containing amino acid derived from the demethylation of dietary methionine. In patients with rare inherited defects of methionine metabolism, severe hyperhomocysteinemia (plasma levels >100 mmol/liter) can develop; such patients have a greatly elevated risk for premature atherothrombosis as well as venous thromboembolism. Mechanisms that may account for these effects include endothelial dysfunction, accelerated oxidation of LDL cholesterol, impairment of flow-mediated endothelium-derived relaxing factor with subsequent reduction in arterial vasodilation, platelet activation, and oxidative stress. In contrast with severe hyperhomocysteinemia, mild to moderate elevations of homocysteine (plasma levels >15 mmol/liter) are more common in the general population, primarily because of insufficient dietary intake of folic acid. Other patient groups who may have elevated levels of homocysteine include those receiving folate antagonists such as methotrexate and carbamazepine and those with impaired homocysteine metabolism caused by hypothyroidism or renal insufficiency.

A common polymorphism in the methylene tetrahydrofolate reductase gene (*MTHFR*) that encodes a thermolabile protein is also linked to elevated homocysteine levels and to increased vascular risk, at least among persons homozygous for the variant. Familial association studies have reported higher homocysteine levels in offspring of parents with premature CAD. The *MTHFR* polymorphism appears to have modest clinical importance, however, and heterozygous persons display little evidence of elevated homocysteine levels, even in those with low folate intake. In a meta-analysis of 40 observational studies, patients homozygous for the *MTHFR* 677 TT variant had a 16% increase in relative risk (odds ratio [OR], 1.16; 95% CI 1.05 to 1.28), and this observation was evident only in studies originating in Europe.[149] In populations in which folate fortification exists, such as in North America, little compelling evidence supports genetic evaluation of *MTHFR* to predict vascular risk.

Reliable immunoassays for total plasma homocysteine (the combination of free homocysteine, bound homocysteine, and mixed disulfides), now widely available, have largely replaced the use of high-performance liquid chromatography. Despite the availability of newer assays, measurement of

homocysteine remains controversial, and recent guidelines have not advocated their use. This lack of enthusiasm reflects modest overall effects reported in prospective cohort studies and the publication of several large trials of homocysteine reduction. In the United States, fortification of the food supply has greatly reduced the frequency of low folate and elevated homocysteine levels, particularly for persons with values initially in the moderately elevated range. Thus the number of patients potentially identifiable by screening for homocysteine has decreased considerably.

Interventions to Reduce Homocysteine.

With regard to clinical trials of homocysteine reduction, several major studies have been completed, and none has shown substantive benefit. These null trials include the Vitamin Intervention for Stroke Prevention (VISP) trial, the Norwegian Vitamin Trial (NORVIT), the Heart Outcomes Prevention Evaluation (HOPE-2) trial, and a Department of Veterans Affairs trial, all of which demonstrated reduced homocysteine levels but no reduction in vascular event rates.[150-153] These consistently negative trial results conflict with the supposition made from studies of mendelian randomization that had previously argued for a clear causal role between homocysteine concentration and vascular events.[149]

Despite reduced enthusiasm and lack of evidence that homocysteine reduction lowers vascular risk, continuing folate supplementation in the general population is crucial to reduce the risk of neural tube defects—an inexpensive practice that has been in place in the United States for more than a decade, yet remains a public health challenge for much of Europe and the developing world.

Direct Plaque Imaging

In contrast with biologic factors that predispose to disease, direct imaging of preclinical atherosclerosis provides an alternative method to detect high-risk individuals who might benefit from early preventive interventions.[154,155] Although several novel imaging tests are in development, the best studied to data are ultrasound measures of the *common carotid intima-media thickness* (CIMT) and computed tomography (CT) to detect coronary artery calcification. Both these imaging modalities can detect high-risk individuals, but both have engendered controversy in preventive practice. With regard to CIMT, a meta-analysis of 14 population-based cohorts reported a consistent and statistically significant 9% increase in future vascular risk for each 0.1-mm increase in CIMT thickness; however, that same analysis found CIMT unlikely of clinical importance once risk estimates and reclassification underwent adjustment for usual risk factors.[155] The Framingham investigators also have recently reported limited usefulness for CIMT in risk prediction,[156] and current ACC/AHA guidelines do not endorse this approach to risk detection.

To date, multiple studies have shown increased levels of *coronary artery calcification* (CAC) to predict strongly vascular risk, and advocates of this approach correctly note that unlike CIMT, CAC can provide substantial reclassification in primary prevention. Both the Heinz Nixdorf Recall Study and the Multi-Ethnic Study of Atherosclerosis (MESA) have shown that CAC, ankle-brachial index (ABI), hsCRP levels, and family history (but not CIMT) independently predict incident vascular events among persons at “intermediate risk”; in MESA, CAC also modestly improved discrimination when added to the ACC/AHA pooled cohort equations.[157,158] Similar data have been presented from the BioImage study for carotid and coronary vessels using a combination of CAC and three-dimensional ultrasound.[159] CAC scanning, however, causes radiation exposure and results in increased downstream testing from unanticipated false-positive findings. Thus, whether CAC can cost-effectively improve prevention remains controversial. To date, trials have shown CAC to have quite limited impact on changing patient or physician behavior with regard to preventive interventions.[160]

Part of the difficulty with coronary calcification as a clinical biomarker is that CT imaging probably detects the plaques least likely to rupture and does not detect the noncalcified, thin-capped lesions that appear to cause most clinical events. Thus, although coronary calcium provides a noninvasive measure of atherosclerotic burden, patients with low calcium scores cannot be dismissed as being at low risk. In a major study of currently asymptomatic individuals, 41% of all future vascular events occurred in those with a coronary artery calcium score (CACS) less than 100, and 17% occurred in those with a CACS of 0.[161] In this study, those with high Framingham risk scores but low coronary calcium scores remained at high risk. Thus the absence of CAC does not preclude occurrence of coronary events over longer-term follow-up. Moreover, statin use increases CAC, despite consistently reducing cardiovascular events.[162,163]

Imaging of atherosclerosis has already extended well beyond anatomic evaluation to focus instead on functional properties that define vascular inflammation and unstable plaque.[164] Such studies exploit the ability of different imaging modalities and selective imaging probes to detect molecular and microanatomic targets that have specificity for plaque rupture. In part, the impetus for this new research stems from recognition that “stable” plaques with a fibrotic morphology have relatively low rupture rates, whereas plaques with inflammatory activity have a higher likelihood of causing vascular events, even though both look similar on current macroanatomic imaging. Potential new targets for this functional imaging approach include measures of glucose uptake, specific adhesion molecules, and biomarkers of apoptosis and protein degradation (**Fig. 45.17**). Magnetic resonance imaging (MRI), positron emission tomography (PET), and contrast-enhanced ultrasonography (CEUS)—each linked to specific molecular targets—all are now under investigation, as are functional measures of vascular reactivity such as coronary flow reserve.

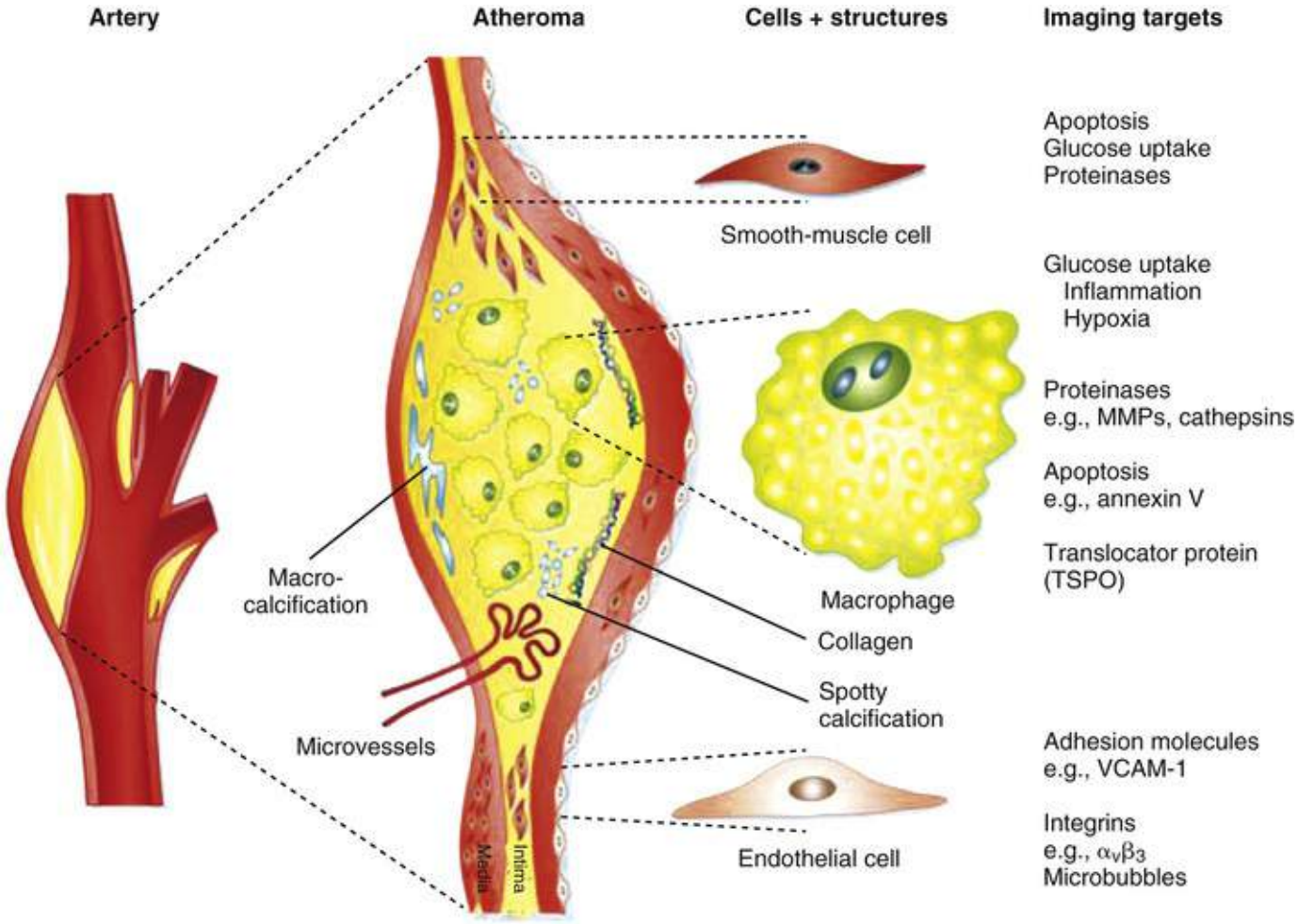


FIGURE 45.17 Targets for noninvasive vascular imaging of the atherosclerotic plaque. MMPs, Matrix metalloproteinases. (From Camici PG, Rimoldi OE, Gaemperli O, Libby P. Non-invasive anatomic and functional imaging of vascular inflammation and unstable plaque. Eur Heart J 2012;33:1309.)

Interventions Based on Vascular Imaging

A major limitation of all imaging modalities is that, unlike the situation for plasma biomarkers such as LDL cholesterol or hsCRP, scant trial data indicate that patients identified by any imaging biomarker benefit from a therapy they otherwise would not have received. The Detection of Ischemia in Asymptomatic Diabetics (DIAD) trial underscores the importance of performing such trials. In DIAD, random allocation to ischemia screening with myocardial perfusion imaging failed to reduce incident MI, vascular death, or episodes of ischemia during follow-up.[165] Furthermore, little evidence exists that imaging improves general preventive measures; as noted in the randomized Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) trial, knowledge of CAC failed to improve rates of smoking cessation or exercise and had no impact on total cholesterol, HDL cholesterol, triglycerides, glucose, body weight, or adherence to preventive medicines including statins or aspirin. In symptomatic patients, a major 10,000-participant clinical trial failed to show improved outcomes when anatomic imaging with coronary computed tomographic angiography (CTA) was employed as an alternative to common functional stress testing methods.[166] Observational nonrandomized data suggest that CAC testing could serve to allocate statin therapy;[167] however, since statins increase CAC, the biologic mechanisms of lipid lowering and arterial calcification may diverge. Thus, in view of issues of cost (and, in some cases, radiation exposure), the expanded use of imaging as a screening tool for vascular risk detection in the setting of primary prevention should await substantive work, including hard-outcome trials.

Genetic Markers for Cardiovascular Risk

Heritability accounts for up to one half of the susceptibility to coronary heart disease (**see Chapter 7**). Until recently, however, genetic risk factors predisposing to CHD were difficult to quantify. This situation has markedly changed with the advent of very-large-scale genome-wide association studies (GWASs) capable of defining small but highly significant risks for individual single-nucleotide polymorphisms (SNPs) common in the general population[168] (**Fig. 45.18**). In an up-to-date meta-analysis, 58 common polymorphisms are associated with CHD while an additional 100 loci are associated with various lipid phenotypes, which together explain 28% of the estimated heritability of CHD.[169] Other informative genetic studies have focused on inflammation phenotypes such as CRP and the IL-6 receptor pathway, the latter suggesting a causal role of inflammation in the atherothrombotic process.[135,136]

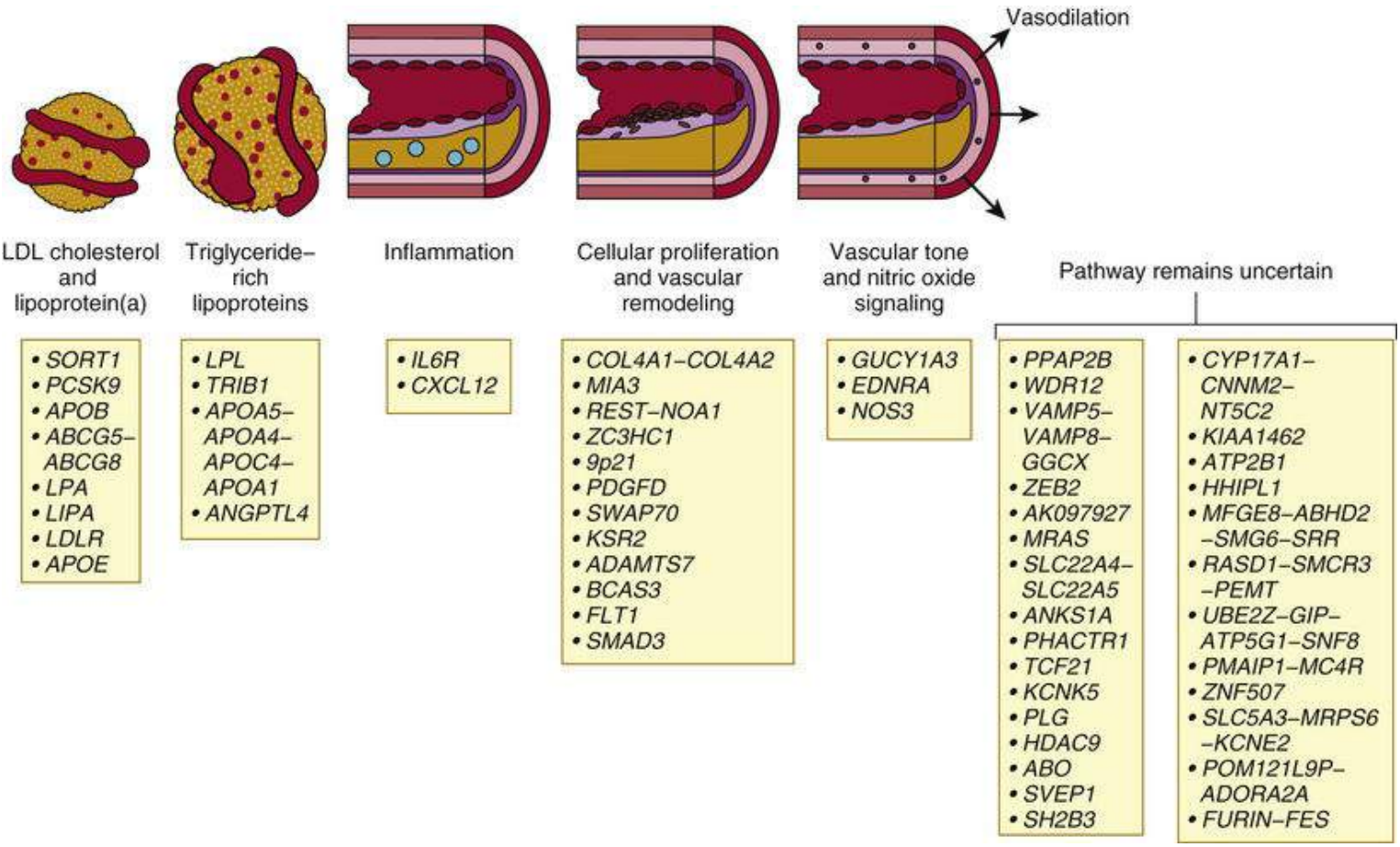


FIGURE 45.18 Pathophysiologic pathways related to regions in the genome that are associated with coronary artery disease. The presumed causal pathways on *top* relate to the positions of genetic variants listed below. We lack definitive identification of the causal genes and variants in many cases, so this compilation lists the nearest neighboring genes; this approach may require revision in some cases. (From Khera AV, Kathiresan S. Genetics of coronary artery disease: discovery, biology and clinical translation. Nat Rev Genet 2017;18:331.)

Several important observations result from these accumulating data. First, although some genetic variants mediate risk through lipids and hypertension, many loci identified by GWASs appear to act on the process of atherothrombosis independent of known or traditional risk factors.[92,170] This observation has considerable importance because it suggests that novel pathways not yet exploited for vascular prevention can play substantial roles in susceptibility to vascular events. Other genetic data provide strong suggestions that pathways related to Lp(a) and triglyceride-rich lipoproteins may be causal for

atherothrombosis and thus support further intervention trials that target these particles.

Second, the magnitude of risk associated with any one genetic variant tends to be small, yet specific patients such as those with early-onset disease often carry as many as 30 known variants, which together may contribute substantively to individual risk. The observation that most of the genetic variants associated with CHD localize in DNA sequences that do not code for a protein product has considerable relevance for future work. The need for functional genomics and translation of these data from loci to clinically relevant biology is paramount.[171]

Third, although early studies were disappointing, more recent evaluations inclusive of 50 or more genetic loci have found that risk prediction can improve at least modestly with genetic screening and that this effect is largely independent of family history[172,173] (**Fig. 45.19**). However, the magnitude of these effects is small, and thus genetic screening for the general population is unlikely to have clinical utility.[174] In specific situations, however, genetic screening should be considered, most importantly when LDL cholesterol levels exceed 190 mg/dL and concern exists about heterozygous or homozygous familial hypercholesterolemia (FH). Family cascade screening is particularly important in children, in whom decades of life may be gained by early detection and treatment, a perspective that has led some to call for universal FH screening in childhood.[175,176]

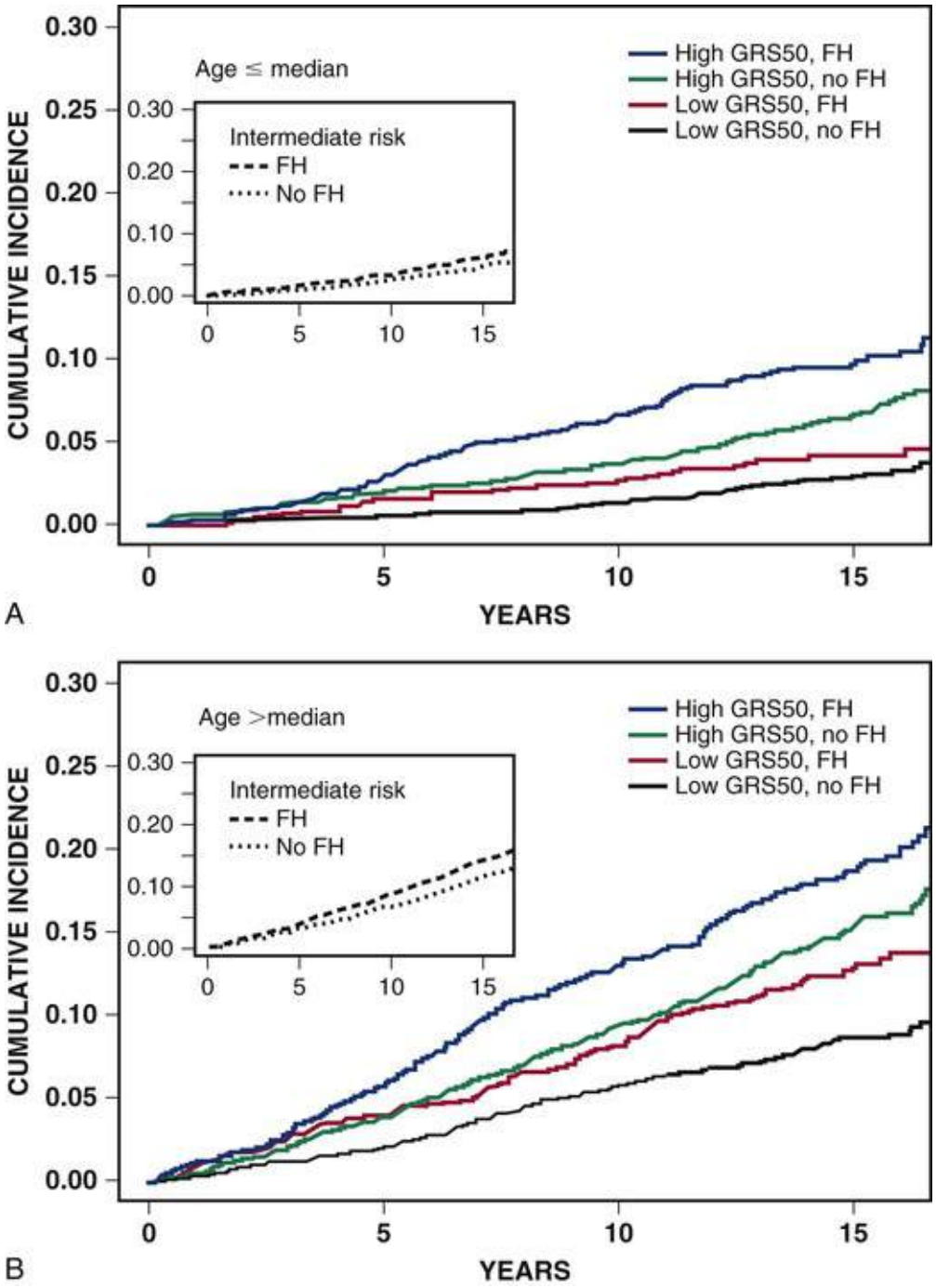


FIGURE 45.19 Cumulative incidence of coronary heart disease events according to self-reported family history (FH) of coronary heart disease and 50-variant genetic risk score (GRS50). *Blue* and *green*: Those with high GRS50 with (*blue*) or without (*green*) a self-reported FH. *Red* and *black*: Those with low GRS50 with (*red*) or without (*black*) a self-reported FH. *Inset*: Those with intermediate GRS50 with (*dashed*) or without (*dotted*) a self-reported FH. Cumulative incidence was estimated while considering non–coronary heart disease death as competing risk. **A,** Participants younger than median age (≤57.6). Median age for this younger group is 51.4 (interquartile range, 48.8-54.2). **B,** Participants older than median age (>57.6). Median age for this older group is 64.7 (interquartile range, 61.1-67.7). (From Tada H, Melander O, Louie JZ, et al. Risk prediction by genetic risk scores for coronary heart disease is independent of self-reported family history. Eur Heart J 2016;37:561-7.)

Interventions for Prevention Based on Genotype

Advancing knowledge of cardiovascular genetics not only is producing novel targets for therapy but also is introducing to clinical practice the potential for improved drug safety and efficacy. Broadly stated, *pharmacogenetics* is the study of inherited and acquired genetic variation in drug response that can affect both individuals and selected populations[177] (**see Chapter 8**). Prominent examples of clinical

applications in which knowledge of genotype has potential impact for cardiovascular medicine are in the prediction of statin-induced efficacy and myopathy, in clopidogrel efficacy, and in warfarin dosing.

With regard to statins and adverse effects, in a pharmacogenetic study conducted within the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) identified a common variant in *SLCO1B1* associated strongly with an increased risk of simvastatin-induced myopathy.[178] *SLCO1B1* encodes an organic anion-transporting protein known to regulate the hepatic uptake of statins. For the relevant SNP in this region, the hazard ratio for myopathy was 4.5 per copy of the C allele (and almost 17 in the CC compared with TT homozygotes). With regard to efficacy, a recently described genetic risk score has shown the ability to detect both high risk and those with the largest relative and absolute risk reductions attributable to statin therapy.[179] While this risk score is not needed to prescribe statins because their efficacy is well known in broad patient groups, these data reinforce emerging concepts of drug-genome interactions that may impact other vascular interventions (**Fig. 45.20**).

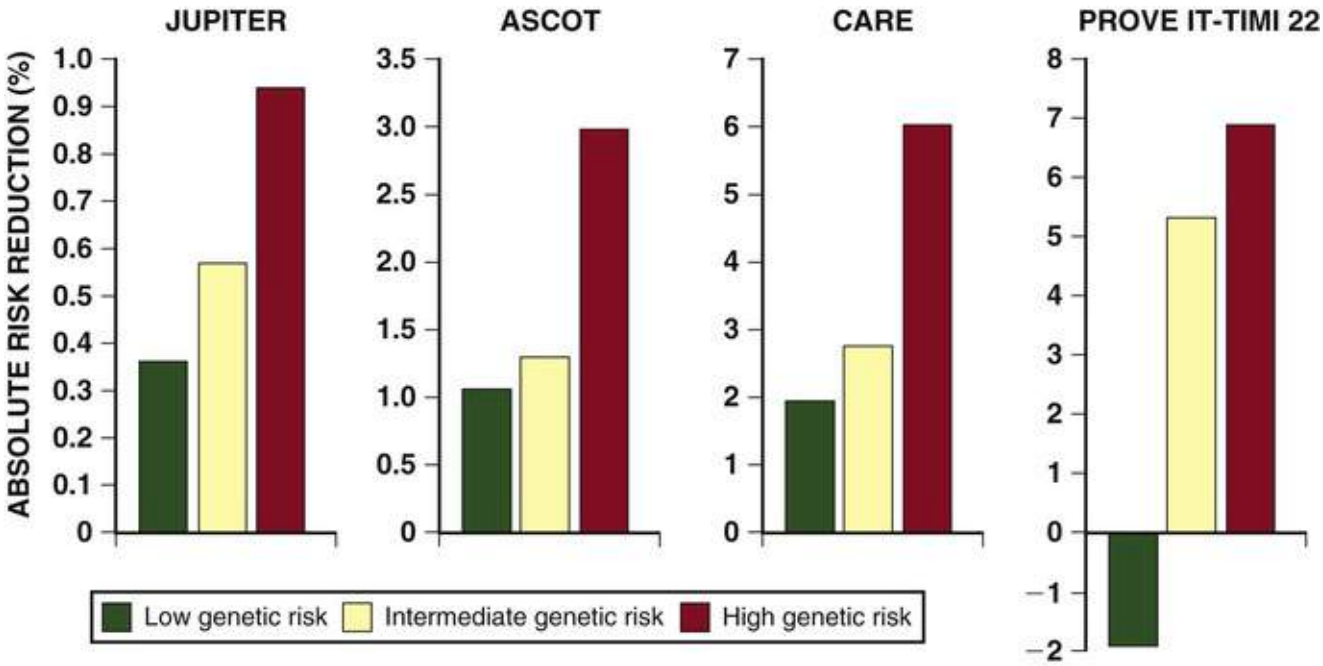


FIGURE 45.20 Genetic risk and efficacy of statin therapy. Those with higher strata of genetic risk show the greatest absolute risk reductions of coronary heart disease events in statin-treated participants in the trials shown. JUPITER, Justification for the Use of Statins in Prevention trial: an Intervention Trial Evaluating Rosuvastatin; ASCOT, Anglo Scandinavian Cardiac Outcomes Trial; CARE, Cholesterol and Recurrent Events trial; PROVE IT-TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 trial. (From Mega J, Stitziel NO, Smith JG, et al. Genetic risk, coronary heart disease, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials. Lancet 2015;385:2264-71.)

Regarding antiplatelet therapy with agents such as clopidogrel or prasugrel, several investigators have found that polymorphisms in *CYP2C19* (where clopidogrel undergoes prodrug metabolism) and in *ABCB1* (which encodes an efflux transporter for clopidogrel) are associated with antiplatelet response and clinical outcomes. These data initially led the FDA to impose warnings about clopidogrel pharmacogenetics, but the ACC and AHA have suggested selective genetic testing because of a lack of clear outcome data. Ongoing clinical trials are comparing genetic screening to standard clinical approaches in this evolving arena.[180]

With regard to warfarin dosing, several genetic polymorphisms that interfere with hepatic metabolism and vitamin K epoxide reductase affect the dose of warfarin required to achieve a specific therapeutic

target and the speed with which an individual patient achieves that goal. However, controversy persists regarding whether any of these pharmacogenetic effects should lead to clinical testing, since only marginal effects have been seen in clinical trials to date[181,182] (**see Chapter 93**).

Finally, pharmacogenetics in theory can substantially improve patient outcomes, even for drugs that have failed in the general population. For example, polymorphism in the *ADCY9* gene may modify the effects of the CETP inhibitor dalcetrapib.[183] Incorporating genetic risk scores into clinical practice may increase compliance with lipid-lowering therapy.[184] Although each of these latter studies may reflect overoptimism about the clinical potential for genetic screening, certainly routine preventive practice should include evaluation of family history. In the Framingham Offspring Study, when compared with those with no parental history of CVD, men with at least one parent with premature atherothrombosis (onset before age 55 for fathers and before 65 for mothers) had an age-adjusted OR of 2.6 (95% CI 1.7 to 4.1), whereas the similar OR for women was 2.3 (95% CI 1.2 to 3.1).[19] These effects compare in magnitude with those of smoking, hypertension, and hyperlipidemia in the Framingham cohort itself.

Environmental Exposures and Associated Interventions

Physical Activity

A large body of epidemiologic evidence has accumulated since the 1950s demonstrating that physical activity is associated with reduced rates of cardiovascular morbidity and mortality, as well as all-cause mortality (**see Chapters 53 and 54**). This correlation pertains across a wide age range, in both sexes, as well as among different racial/ethnic groups.[109,185] Notable advances in recent years include elucidation of the dose-response relation (i.e., what percent risk reduction is associated with different levels of physical activity), as well as suggestive, but not yet definitive, research showing that sedentary behavior may constitute an independent risk factor, even among persons who engage in sufficient physical activity to meet the current guidelines. Unfortunately, in 2015, only 49.0% of U.S. adults age 18 and older met the 2008 federal physical activity guidelines for aerobic activity based on leisure-time activity. However, the percentage meeting the guidelines has increased from 41.1% in 2006. As age increased, the percentage meeting the guidelines decreased, and women were less likely than men to meet the guidelines. Non-Hispanic white adults were more likely to meet the guidelines than Hispanic adults and non-Hispanic black adults. This lack of activity is worldwide, such that inactivity may cause as many deaths globally each year as those from smoking, because inactive persons outnumber smokers.[186]

The U.S. Federal Government issued its physical activity guidelines in 2008 and received reinforcement from the most recent AHA/ACC lifestyle guidelines.[187] The heart-healthy guidelines recommend that adults should engage in 150 minutes per week of moderate-intensity physical activity (e.g. walking), or 75 minutes per week of vigorous-intensity aerobic activity (e.g. jogging), or a combination of moderate- and vigorous-intensity aerobic physical activity. Aerobic activity should be performed in episodes of at least 10 minutes, preferably spread throughout the week, which may also minimize the risk of musculoskeletal injuries. Additionally, muscle-strengthening exercises should be performed on 2 days of the week.

For those persons who do not meet the recommended minimum, the guidelines encouragingly state that "some physical activity is better than none." Data have quantified the inverse dose-response relationship, showing that persons meeting the recommended minimum have a 14% lower risk of CHD compared with those engaging in no leisure-time activity.[188] Twice the minimum guideline level yielded a 20% risk reduction. Risks continued to decline at higher levels of energy expenditure, although with more modest magnitudes of additional risk reduction. Even achievement of half the guideline-recommended amount of physical activity yielded a significant risk reduction.

In secondary prevention, a Cochrane systematic review and meta-analysis of RCTs of exercise-based cardiac rehabilitation has shown, compared with usual care, reductions in cardiovascular mortality as well as reductions in hospital admissions and improvements in quality of life that applied consistently across patients and intervention types[189] (**see Chapter 54**). The findings related to the primary prevention of cardiovascular disease have come from observational epidemiologic studies. Although such study designs cannot prove causality, the totality of evidence strongly indicates a causal relationship. Randomized trials that support this inverse relationship have demonstrated many plausible biologic mechanisms.[187]

Regular physical activity reduces myocardial oxygen demand and increases exercise capacity (i.e.,

improving cardiorespiratory fitness). Physical activity also lowers systolic and diastolic BP; improves insulin sensitivity and glycemic control, with major benefits for diabetic patients, including reductions in glycated hemoglobin along with reduced requirements for therapy; and improves dyslipidemia, as well as vascular inflammation. Regular physical activity is associated with lower CRP levels (particularly when adiposity decreases) and improvement in hemostatic variables, including tissue-type plasminogen activator, fibrinogen, von Willebrand factor, fibrin D-dimer, and plasma viscosity. It also enhances endogenous fibrinolysis and coronary endothelial function. Physical activity helps control body weight, and lower levels of adiposity improve many of the physiologic variables that contribute to cardiovascular risk. The AHA/ACC lifestyle management guidelines explicitly advise adults to engage in aerobic physical activity to reduce LDL and non-HDL cholesterol, as well as BP, with three or four sessions per week of moderate- to vigorous-intensity physical activity, lasting on average 40 minutes per session, and resulting in a total amount consistent with the 2008 federal guidelines.[187]

For people who consume a usual American diet, the level of physical activity recommended by the federal guidelines may not be sufficient to prevent weight gain with age. Nonetheless, the available data clearly indicate that physical activity lowers cardiovascular risk among not only individuals with normal body mass index but also those who are overweight or obese (see later). Because of the difficulty in maintaining sustained weight loss among overweight and obese persons, the importance of physical activity—even without weight loss—for cardioprotection should be emphasized to patients. An analysis pooling data from several studies[190] demonstrated that persons of normal weight who met physical activity guidelines lived 4.7 years longer than normal-weight persons with no leisure-time physical activity. Among overweight persons, the corresponding years of life gained were 3.9; even class I and class II or more obese persons gained 3.4 and 2.7 years, respectively.

A current area of great interest relates to understanding the role of sedentary behavior on health[191] distinct from physical activity level, since one can be both sedentary and physically active (e.g., an office worker who sits during most of the workday but who also jogs regularly). It is estimated that adults spend 6 to 8 hours per day in sedentary behavior (e.g., sitting, watching TV, using electronic devices/computers). It is not yet clear whether the prevalence of sedentary behavior differs by sex or race/ethnicity. This relationship between sedentary behavior and CVD has biologic plausibility, since animal and human studies show that sedentary behavior is associated with elevated levels of cardiometabolic biomarkers and a poor cardiovascular risk factor profile. A meta-analysis of prospective cohort studies[192] estimated that if every adult in the United States decreased sitting time to less than 3 hours per day, life expectancy of the population would increase by 2.0 years, and if every adult reduced television viewing time to less than 2 hours per day, life expectancy would increase by 1.4 years. Further evidence is required to better inform interventions and guidelines on sedentary behavior and primary prevention of CVD.

Finally, physical activity can be associated with adverse events[187] (**see Chapter 53**). The most common adverse events are musculoskeletal injuries and risks related directly to the amount and intensity of physical activity undertaken. At the level recommended by the federal guidelines, risk is low. One of the most severe adverse events related to physical activity is the risk of a sudden cardiac event (e.g., sudden death) during or shortly after exercise, but these events are extremely rare. Vigorous-intensity activities can precipitate such events, particularly when unaccustomed. Adding a small amount of light- to moderate-intensity activity (e.g., walking, 5 to 15 minutes per session, two or three times a week) carries no known risk for sudden severe cardiac events, compared with periods of less intense activity or at rest. Compared with inactive people, active people are at lower overall risk for CVD, because when averaged over the whole day, the risk during activity and during all other periods in active people yields a lower

average risk than in inactive people. The benefits of regular physical activity clearly outweigh the inherent risk of adverse events.

Interventions to Increase Physical Activity

How can clinicians help patients increase their physical activity levels? A meta-analysis examined the effectiveness of physical activity promotion in the primary care setting, based on RCTs with at least 12 months of follow-up.[193] Studies have employed a wide range of interventions, with most including the use of written materials and two or more sessions of physical activity counseling, delivered in person or by telephone. A range of professionals—including primary care physicians, nurses, physiotherapists, exercise or physical activity specialists, health educators, health promotion specialists, and trained facilitators from a range of health professions—delivered the interventions. The interventions resulted in significant, small to medium-sized effects, with an estimated NNT of 12 for one additional sedentary adult to achieve recommended levels of physical activity at 12 months, which compares favorably with the 50 to 120 estimated NNT for smoking cessation. Provision of pedometers to participants in physical activity promotion programs can improve cardiovascular risk biomarkers.[194]

Workplace wellness programs are increasing in the United States and include exploration of approaches such as providing financial incentives for health promotion.[195] However, individual approaches toward increasing physical activity levels, although important, have limited impact because they focus only on a single patient. A comprehensive public health approach would involve health agencies; schools; businesses; policy, advocacy, nutrition, recreation, planning, and transport agencies; and health care organizations. A recent review identified several evidence-based interventions that increase physical activity levels in populations.[196] These included community-wide campaigns, mass media campaigns, and decision prompts encouraging the use of stairs versus lifts and escalators; initiatives to increase social support for physical activity within communities, specific neighborhoods, and worksites; school-based strategies for children and adolescents, which include physical education, classroom activities, afterschool sports, and active transport; and environmental and policy approaches (e.g., active transport policies) to create or enhance access to places for physical activity.

Obesity and Weight Loss

Obesity is a major and growing public health problem worldwide,[197,198] both in adults and children,[199] with effects on increased morbidity and mortality, decreased quality of life, increased medical costs, and losses to productivity (**see Chapter 50**). Obesity is a major risk factor for comorbidities, such as type 2 diabetes, CVD, musculoskeletal disorders, and certain forms of cancer. Governments and health agencies have launched a multitude of campaigns, but with limited effects on reducing obesity for anything but the short term. Obesity is very difficult to treat after it has developed,[200] and preventing unhealthy weight gain is easier and more effective than reversing it afterward. Obesity is indeed a chronic disease.[201] There is an immense need for the development of effective treatments, but the focus of antiobesity campaigns must have prevention as a priority for both individuals and populations to provide long-term health gains. To improve prevention and treatment strategies is challenging, and a better understanding of factors contributing to obesity is essential.[202-207]

For population-level comparisons, overweight and obesity are defined using the measure of body mass index (BMI), calculated as weight in kilograms divided by height in meters squared. A BMI of 25 or greater defines *overweight*, and *obesity* is a BMI of 30 or greater. Obesity class I (moderately obese) is a BMI range from 30 to 35; class II (severely obese) is from 35 to 40; and class III (very severely obese) is

a BMI greater than 40.

Based on analyses of data from the most recent NHANES, for the years 2013 to 2014, the overall age-adjusted prevalence of obesity in the United States was 37.7%, with 35.0% in men and 40.4% in women.[197] The prevalence of class III obesity overall was 7.7%, with 5.5% in men and 9.9% in women. Analyses of changes over the decade from 2005 to 2014, adjusted for age, race/Hispanic origin, smoking status, and education, showed significant increasing linear trends among women for overall obesity and class III obesity, but not among men. Early release data from NHANES 2015 indicate that the level of obesity continues to be a risk overall, although at a slower rate,[208] and that the prevalence of obesity differs substantially by race and ethnic group. Non-Hispanic black women were most likely to be obese (45.0%), followed by Hispanic women (32.6%) and non-Hispanic white women (27.2%). Non-Hispanic black men (35.1%) were more likely to be obese compared with non-Hispanic white men (30.2%). Higher-income women were less likely have obesity than low-income women. Prevalence of obesity also increases with lower levels of education. There is no relationship between obesity and education among men, but women with college degrees are less likely to be obese than less educated women.

Overweight and obesity are the fifth leading risk for global deaths.[209] Approximately 44% of the diabetes burden and 23% of the ischemic heart disease burden are attributable to overweight and obesity. Worldwide, obesity has more than doubled since 1980. In 2014, more than 1.9 billion adults over age 18 were overweight, 600 million of whom were obese, representing 39% of adults being overweight and 13% obese. About 41 million children under age 5 were overweight or obese, and most of the world's population now lives in countries where overweight and obesity kill more people than overweight. The Non-Communicable Disease (NCD) Risk Factor Collaboration[198] estimated that if the post-2000 trends in obesity continue, the probability of meeting the global obesity target of halting the rise in obesity at its 2010 levels will be “virtually zero.”

Childhood obesity has caused increasing concern in the United States and worldwide. With obesity defined as a BMI at or above the sex-specific 95th percentile on the CDC growth chart, and extreme obesity as a BMI of 120% or greater, the most recent data from NHANES indicated that the prevalence of obesity in 2011–2014 was 17.0% and extreme obesity 5.8%.[199] Trends in child and adolescent obesity vary by age, race/Hispanic origin, and education level of the household head. During 1988 to 2014, for children age 2 to 5 years, the prevalence increased until 2003–2004, but then decreased; for children age 6 to 11, the prevalence increased until 2007–2008, and then leveled off; and among those 12 to 19 years, the prevalence of obesity has consistently increased during this time. Extreme obesity showed no change for children age 2 to 5 years, but increased among children 6 to 11 and adolescents 12 to 19. The odds of obesity among children and adolescents were higher among non-Hispanic blacks (19.5%) and Hispanics (21.9%) than non-Hispanic whites (14.7%) and lower for non-Hispanic Asians (8.6%).

Overweight and obesity are consistently associated with increased all-cause mortality, as shown in a U.S.-wide evaluation between 2001 and 2014,[207] a systematic review,[210] and a pooled analysis of 1.46 million white adults.[211] Obesity strongly predicts incident CVD and CHD, as well as hypertension, dyslipidemia, type 2 diabetes mellitus, gallbladder disease, osteoarthritis, sleep apnea, some cancers, low quality of life, mental disorders (e.g., depression, anxiety), and physical function limitations, with risk increasing as BMI levels rise. Obese children have a risk for short-term health consequences, including the dramatic increases in type 2 diabetes among children and adolescents, breathing difficulties, increased risk of fracture, hypertension, early markers of CVD, insulin resistance, and psychological effects. However, childhood obesity is also a long-term condition with associated comorbidities. Obese children are at risk for long-term tracking of obesity to adulthood. Overweight or obese children who are obese as adults have increased risks of cardiovascular outcomes, but nonobese adults who were

overweight or obese during childhood have risks of these outcomes similar to those who were never obese.[212] An elevated BMI in adolescence constitutes a substantial risk factor for obesity-related disorders in midlife.[213] Although the risk of diabetes is associated with increased BMI close to the time of diagnosis, the risk of CHD is related to elevated BMI both in adolescence and in adulthood.

Some have raised doubt whether obesity itself is a true risk factor for CVD beyond its impact on vascular risk mediated solely through interrelations with glucose intolerance, insulin resistance, hypertension, physical inactivity, and dyslipidemia. Midlife obesity, however, strongly correlates with risk factors for hospitalization and future complications of CHD, even among those with few or no other major risk factors. In terms of the relative importance of obesity and physical activity as predictors of CHD risk, both fitness and fatness have implications for vascular risk. Obesity alone is associated with all-cause mortality regardless of level of physical activity.[214] The distribution of body fat also is a factor in the development of CHD, with abdominal obesity posing a substantially greater risk in both men and women. The waist-to-hip ratio, a surrogate for centripetal or abdominal obesity, independently predicts vascular risk in women and in older men. The prevalence of abdominal obesity increases with age and varies by race and ethnicity. **Chapter 50** discusses the mechanisms that link these anthropometric measures and CHD risk, which require further research, particularly among disproportionally affected racial and ethnic minority groups,

Obesity is a complex issue to address. An increased intake of energy-dense foods, a decrease in physical activity, and an increase in being sedentary because of changes in work, transportation, and urbanization have contributed to this epidemic.[209] Effective treatment strategies generally involve a multifaceted approach, including dietary counseling, behavioral modification, increased physical activity, and psychosocial support, and potentially pharmacologic intervention. Even modest behavioral and environmental improvements for individuals can attenuate or reverse weight gain and adiposity. Key diet-related priorities to reduce adiposity are reductions in refined grains, starches, sugars, and meats and increasing intake of fruits, vegetables, nuts, yogurt, fish, vegetable oils, and whole grains, in the context of regular physical activity and adequate sleep.[215] Data from the PREDIMED trial of the Mediterranean diet indicated that an increase in vegetable fat intake from natural sources in this setting had little effect on body weight or central adiposity in older individuals who were mostly overweight or obese at baseline.[216] This finding addresses the concern of weight gain from high-fat foods as an obstacle to adherence to a dietary pattern such as the Mediterranean diet that provides clinical and metabolic benefits.

Observational studies and clinical trials suggest that surgical intervention (bariatric surgery) holds promise in promoting weight loss. Joint statements by the American Society for Metabolic and Bariatric Surgery, National Lipid Association, and Obesity Medicine Association,[217,218] as well as AHA,[219] endorse the ability of surgical intervention to improve and maintain over time excess weight and comorbidities, including type 2 diabetes mellitus, dyslipidemia, liver disease, hypertension, obstructive sleep apnea, cardiovascular dysfunction, and prolonged survival. Bariatric procedures may also favorably affect bile acid metabolism and the intestinal microbiome, which may also improve dyslipidemia.[206] Bariatric procedures improve multiple cardiovascular risk factors, including glucose metabolism, BP, thrombosis, kidney function, adipocyte and adipose tissue function, inflammatory markers, and vascular markers. The greater the fat mass loss, the greater is the improvement in lipid variables such as triglycerides and especially LDL cholesterol. Bariatric procedures can decrease the use of drug treatment for dyslipidemia. After bariatric procedures, HDL cholesterol may transiently decrease for the first 3 to 6 months, often followed by an increase in HDL cholesterol to above the baseline value before the bariatric procedure.

Bariatric surgery can yield long-term benefits.[220,221] The Veterans Administration patients receiving

bariatric surgery lost substantially more weight than nonsurgical matches, and only 19 of 564 patients receiving gastric bypass regained weight back to within an estimated 5% of their baseline weight by 10 years.[220] A multicenter, prospective study of bariatric surgery in adolescents documented the durability of clinically meaningful weight loss and improvements in key health conditions (prediabetes, diabetes, abnormal kidney function, elevated BP) and weight-related quality of life among adolescents who underwent gastric bypass surgery or sleeve gastrectomy.[221] Significant improvements were seen in weight, cardiometabolic health, and weight-related quality of life at 3 years after the procedure. Risks associated with the procedure included specific micronutrient deficiencies and the need for additional abdominal procedures (**see Chapter 50**).

Recent technological advances in *epigenome profiling* have led to an increasing number of studies investigating the role of the epigenome in obesity, as well as the role that environmental exposures during early life plays in inducing persistent alterations in the genome, which may lead to an increased risk in later life (**see Chapter 7**). Multiple studies have investigated the association between obesity and global, site-specific or genome-wide methylation of DNA.[222] These investigations provided no consistent evidence for a relationship between global methylation and obesity but did identify multiple obesity-associated differentially methylated sites, mainly in blood cells. Extensive but small alterations in methylation were seen at specific sites in weight loss intervention studies, with several associations between methylation marks at birth and later-life obesity. This research may help in predicting an individual's obesity risk at a young age and may offer possibilities for introducing targeted prevention strategies.

Intervention Studies of Weight Loss

Data from numerous observational studies and small or short-term randomized clinical trials have supported the substantial health benefits of weight loss. Modest weight loss of 5% to 10% is associated with a significant improvement in BP among persons with and without hypertension; improves the lipoprotein profile, yielding lower levels of serum triglycerides, higher levels of HDL cholesterol, and small reductions in total cholesterol and LDL cholesterol; and results in improvements in glucose tolerance and insulin resistance. However, longer-term behavioral-nutrition weight loss trials have not been able definitively to evaluate a reduction in total mortality, CVD, or CHD, primarily because of the participants' inability to maintain long-term weight loss in these trials.

Despite promising data from cohort studies, randomized trials of weight loss interventions have provided mixed results. In a comparison of four popular diet regimens, as well as in a study of carbohydrate substitution, all interventions yielded modest weight reductions and beneficial effects, but with limited long-term adherence levels. In one of the few trials to attempt follow-up evaluation beyond 1 year, reduced caloric intake resulted in clinically meaningful weight loss regardless of which macronutrients were emphasized, suggesting that caloric intake is more important than any specific dietary plan (**see Chapters 49 and 50**).

A review of published trials evaluating the effectiveness of treatments for obesity in adults relevant to primary care indicates that a behaviorally based approach resulted in a 6.6-pound greater weight loss in the intervention group than in control participants after 12 to 18 months, with more treatment sessions associated with greater loss, and with limited data suggesting weight loss maintenance for 1 year or longer.[223] A number of individual trials have examined the importance of counseling, behavioral factors, and motivation in conjunction with lifestyle modification, including diet and exercise.[214,224,225] A trial for a new weight loss program that emphasized reducing unhealthy relationships with food, body image dissatisfaction, and internalized weight bias, versus a program that emphasized environmental

modification and habit formation and disruption, found equivalent weight loss outcomes during treatment but significant differences in outcomes at 6 months. In a trial of weight loss during a 2-year period in response to three lifestyle interventions, all delivered by primary care providers in collaboration with auxiliary health professionals (lifestyle coaches) in their practices,[226] enhanced weight loss counseling helped approximately one third of obese patients achieve long-term, clinically meaningful weight loss. Nonetheless, even trials limited to motivated participants have shown only modest weight reduction and maintenance in the long term.

The rising prevalence of obesity requires a larger focus beyond a biologic approach alone, with examination of how the built environment in which choices are made can influence physical activity, diet, and weight change. Similarly, because a substantial burden of obesity and poor dietary intake exists among poor and less educated groups, community-based efforts to make healthy choices an easier part of people's lives is essential. This challenge merits a sustained worldwide effort to monitor, prevent, and control obesity, with many parties, including governments, international organizations, the private sector, and civil society, needed to contribute complementary actions in a coordinated approach.[206] Such policies require outcomes assessment.[227] Approaches can move beyond traditional environmental-focused policy measures, such as collaboration with the food and restaurant industry,[203,204] to achieve responsible marketing especially to children, expand available health food choices, and reduce the fat, sugar, and salt content of processed foods. In addition, there is a need for better prediction of who will become obese, including the development of “precision prevention” to tailor appropriate policies and courses of action for the individual.[202,227] In the meantime, all preventive cardiology practices should encourage individual weight control, given obesity's strong association with CVD and its ability to be measured by easily obtainable BMI or waist circumference.

Diet, Dietary Supplements, and Moderate Alcohol Consumption

Diet

A large body of evidence, both from epidemiologic and intervention studies, has demonstrated that dietary factors have an important impact on CHD risk (**see Chapters 49 and 50**). Dietary habits also influence multiple cardiovascular risk factors, including both established risk factors (BP, lipoprotein profiles, glucose levels, and obesity), as well as cardiometabolic risk factors including inflammation. A global analysis of behavioral, environmental, occupational, and metabolic risk factors derived from 188 countries revealed that 87.9% of CVD disability-adjusted life-years were largely caused by 25 factors, 9 of which were related to diet and included low intakes of fruit, vegetables, nuts and seeds, omega-3 fatty acids, and fiber.[228]

A solid body of evidence has demonstrated that in addition to the identification of individual foods and nutrients that can improve health and prevent CVD, several heart healthy dietary patterns have been identified to assess more global dietary quality.[215] Patterns such as the Healthy Eating Index, Alternative Healthy Eating Index, western versus prudent dietary patterns, Mediterranean dietary pattern, and the DASH-type diet are consistent in emphasizing fruits, vegetables, other plant foods (e.g., beans, nuts), and in many patterns, whole grains and fish, and limiting processed red meats and sugar-sweetened beverages. These dietary patterns conform with the food-based priorities for cardiovascular health that include foods that are higher in dietary fiber, mono- and polyunsaturated fatty acids, vitamins, potassium and other minerals, and phytochemicals, and lower in poor-quality carbohydrates, salt, saturated fatty

acids, and *trans* fat.

Meta-analyses of randomized clinical trials and prospective cohorts reveal statistically significant reductions (relative risk; 95% CI) in the risk of CHD with increased number of daily or weekly servings of fruits (0.94; 0.91, 0.98) and vegetables (0.95; 0.92, 0.98),[229] whole grains (0.78; 0.71, 0.86),[230] nuts and seeds (0.76; 0.69, 0.84),[231] and fish (0.79; 0.67, 0.92).[232] In contrast, an increased risk was associated with processed red meats (1.24; 1.09, 1.40),[233] while no significant correlations were found with total dairy (0.94; 0.82, 1.07)[234] or eggs (0.99; 0.85, 1.15).[235] The magnitude of these overall changes in individual foods and food groups would predict modest to substantial reductions in risk of CVD. The choice of protein sources influences other components of diet and may be a critical determinant of CVD risk. For example, a 26- to 32-year follow-up of two large prospective cohorts found high–animal protein diets were positively associated (1.08; 1.01, 1.16) and high–plant protein diets inversely associated (0.88; 0.80, 0.97) with cardiovascular mortality.[236] Indeed, examining overall high-quality food patterns, rather than focusing on single nutrients and foods, may better address the inherent complexity of dietary exposures and their association with CVD risk.[237]

AHA/ACC guidelines on lifestyle management to reduce cardiovascular risk stress modifying diet and increasing physical activity.[187] Dietary recommendations for lowering LDL cholesterol and BP emphasize a dietary pattern that includes greater intake of vegetables, fruits, and whole grains, including low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts. The recommendations limit consumption of sweets, sugar-sweetened beverages, and red meats. They suggest dietary planning and nutritional counseling to help patients adapt this dietary pattern to appropriate calorie requirements, personal and cultural food preferences, as well as nutrition therapy for other medical conditions, such as diabetes. These recommendations broadly agree with those proffered by the 2013 AHA/ACC/Obesity Society Guideline for the Management of Overweight and Obesity in Adults[238] and the Dietary Guidelines for Americans 2015–2010.[239]

Despite the general consensus on healthy dietary patterns in the United States by government agencies and professional biomedical societies, the typical eating pattern by Americans is in marked contrast to these recommendations.[239] About three fourths of the population has an eating pattern that is low in vegetables, fruits, dairy, and unsaturated oils. More than half the population meets or exceeds total grain and total protein food guidelines but fall outside the recommended intakes within the subgroups of these two food categories. Most Americans substantially exceed the recommendations for added sugars, saturated fats, sodium, and total calories. Beyond motivating and facilitating behavioral change at the individual level, implementing dietary guidelines and related policy recommendations will require changes in the food environment at household, community, and national levels.[239] For example, reducing the frequency of eating at fast-food restaurants, limiting screen time, and increasing the frequency of family-shared meals can enhance the effectiveness of interventions. Efforts within communities can include providing food and nutrition assistance programs, promoting food and calorie label education through schools and retail programs, and facilitating access to healthy and affordable food choices that respect cultural preferences.

Optimizing an individual's compliance with choosing and consuming foods consistent with healthy dietary patterns requires consideration of the social, economic, and cultural context in which people live in their homes and communities. Thus, current efforts try to place dietary guidance within a socioecologic framework across the life span. This type of framework incorporates individual factors, social environment or networks, physical or built environment, and macrolevel environments and can help inform potential strategies to improve diet and develop partnerships to translate into action the recommendations for choosing healthy foods and dietary patterns.

Dietary Supplements

Dietary patterns in the United States result in micronutrient intakes that fall below the Estimated Average Requirement (EAR), the average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group. For several vitamins and minerals, a substantial percent of the population consumes less than the EAR, including potassium (97.0%), vitamin D (94.3%), choline (91.7%), vitamin E (88.5%), vitamin K (66.9%), magnesium (52.2%), vitamin A (43.0%), calcium (43.0%), and folate (15.0%), several of which may support heart health. In addition, overall consumption of dietary fiber also falls below recommended Adequate Intakes (95.0%). Dietary supplement use is common among Americans, with slightly more than half of adults using these products, most commonly multivitamins and minerals.[240-242] Results from the 2007–2010 NHANES indicates the most commonly reported reasons adults used supplements were to “improve” or “maintain” overall health.[242] Observational studies have often reported lower rates of CHD events among those who take dietary supplements, particularly multivitamins.[243,244] However, large-scale randomized trials of most dietary supplements have generally shown no significant benefits for cardiovascular risk, and even have raised potential for harm.

Currently available evidence suggests provides greater justification for a focus on evidence-based foods and overall dietary patterns than on individual nutrients or supplements for primary prevention of CVD. While some cohort studies suggest that low intakes or serum status of beta-carotene are associated with increased CVD risk, these results contrast with those from randomized clinical trials of beta-carotene supplementation.[245] Meta-analyses of calcium supplementation are conflicting, with some showing a null association and others an increased risk of MI.[246,247] Several prospective cohort studies have linked vitamin E intake from supplements with a lower risk of CHD, but meta-analyses of observational studies and clinical trials indicate either no such benefit or an increased risk of mortality.[245] Observational studies of people with poor intakes of folate, vitamin B_6, and vitamin B_{12} and corresponding high levels of total plasma homocysteine are at increased risk of CVD, but clinical trials of supplementation with folic acid with or without vitamins B_6 and B_{12} have generally not shown a benefit.[149] In 2013 the USPSTF systematically reviewed the evidence for the benefit and harms of vitamin and mineral supplements in community-dwelling adults without known nutrient deficiencies for the primary prevention of CVD and cancer.[248] Although most of the studies considered were conducted in older adults, had durations of less than 10 years, and employed various doses with individual or combinations of nutrients, they concluded that limited evidence from randomized clinical trials supported any benefit from vitamin or mineral supplementation for the prevention of CVD or cancer.

Data from laboratory studies, ecologic studies, prospective cohort studies, and secondary analyses of small randomized trials have suggested a protective effect for vitamin D against a number of chronic diseases, including CVD. Many clinicians now include vitamin D blood tests as part of routine laboratory work and recommend vitamin D supplements to patients without definitive randomized trial data supporting efficacy. Possible mechanisms of protection against CVD include inhibition of inflammation, inhibition of vascular smooth muscle proliferation and vascular calcification, regulation of BP and volume homeostasis, and regulation of glucose metabolism.[249] However, the Institute of Medicine critically reviewed the dietary requirements for calcium and vitamin D in relation to a wide variety of health outcomes and concluded that unlike the available scientific evidence supporting a key role of calcium and vitamin D in skeletal health, the evidence that vitamin D or calcium affects CVD risk is inconsistent and inconclusive, and does not meet criteria for establishing a cause-and-effect relationship.[249]

The marine omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), components of fish and fish oil supplements, have shown considerable promise for the prevention of CVD in laboratory and observational studies, as well as large randomized trials in secondary prevention or high-risk settings. These polyunsaturated fatty acids may have a number of mechanisms for cardioprotection, including lowering triglycerides and BP, decreasing platelet aggregation, reducing susceptibility of the heart to ventricular arrhythmias, and providing anti-inflammatory actions.[250,251] However, meta-analyses of placebo-controlled trials show either modest or null effects for CVD and mortality.[252,253] The recent AHA guidelines for CVD prevention in women recommend consideration of omega-3 fatty acids in the form of fish or in capsule form (e.g., EPA 1800 mg/day) in women with hypercholesterolemia or hypertriglyceridemia for primary and secondary prevention (with pregnant women being counseled to avoid eating fish with the potential for the highest level of mercury contamination).[254] However, no trials have studied marine omega-3 fatty acid supplements for the primary prevention of CVD in a general population. Two ongoing large-scale cardiovascular trials are evaluating EPA or EPA plus DHA in patients with or at high risk for atherosclerotic CVD.[94,95] Whether alpha-linolenic acid, the short-chain omega-3 fatty acid found in walnuts and other plant sources, provides the same potential cardiovascular benefit attributed to the EPA and DHA found in fish requires more research.

At this time, the available trial data do not support the recommendation of vitamin D or fish oil supplementation for the primary prevention of CVD. Trials to evaluate definitively the roles of vitamin D and fish oil in CVD prevention are addressing this gap. These trials include the VITamin D and OmegA-3 TriaL (VITAL), an NIH-funded, large-scale randomized trial of vitamin D (cholecalciferol, 2000 IU/day) and a marine omega-3 fatty acid supplement (in the form of a fish oil supplement, EPA plus DHA, 1 g/day) for the primary prevention of CVD and cancer. This currently ongoing trial enrolled more than 25,000 participants (women older than 55 years and men older than 50, with an oversampling of African Americans) with no known CVD at baseline.[255,256]

Moderate Alcohol Consumption

Alcohol consumption has complex effects on CVD; the difference between daily intake of small to moderate quantities and large quantities may tip the balance between preventing and causing disease. The 2015–2020 Dietary Guidelines for Americans[239] recommends that if alcohol is to be consumed, it should be consumed in moderation—up to one drink per day for women and two drinks per day for men—and only by adults of legal drinking age. A drink-equivalent is described using the reference beverages of 12 fl oz of regular beer (5% alcohol), 5 fl oz of wine (12% alcohol), or 1.5 fl oz of 80-proof distilled spirits (40% alcohol). Each drink-equivalent delivers about 12 to 14 grams of alcohol.

Habitual heavy alcohol consumption, defined as 8 or more drinks per week for women and 15 or more drinks a week for men,[239] is a major cause of preventable death in most countries. It increases risk of total mortality, CVD mortality, CHD, and stroke; fatal traffic accidents; liver damage; harm in pregnancy; risk of developing breast and other cancers in both men and women; and depression and violence. By contrast, a consistent body of observational epidemiologic evidence has shown that light to moderate alcohol consumption, compared with either nondrinkers or heavy drinkers, is associated with lower risk of heart attack, ischemic stroke, death from all cardiovascular causes, peripheral vascular disease, sudden cardiac death, diabetes mellitus, gallstones, and increased health and well-being. This relationship represents a U-shaped curve, s moderate alcohol consumption confers lower risk of CVD compared to both heavy drinkers and nondrinkers.[215,257-260]

More than 100 prospective studies have shown an inverse association between moderate drinking and

risk of heart attack, ischemic stroke, peripheral vascular disease, sudden cardiac death, and death from all cardiovascular causes. The effect is fairly consistent, corresponding to a 25% to 40% reduction in risk. It applies to men and women, older individuals, and to primary prevention as well as secondary prevention among those with at high risk for a cardiovascular event, including those with existing CVD, type 2 diabetes, and hypertension. However, even moderate alcohol is associated with risk. An immediately higher cardiovascular risk appears to follow any alcohol consumption, although by 24 hours, only heavy alcohol intake conferred continued risk.[261] Demonstrated physiologic effects from basic research and randomized trials underlying the observed benefits of moderate alcohol consumption on risk of CVD include raising of HDL cholesterol, improvements in fibrinolytic capacity and insulin resistance, and reductions in platelet aggregation and systemic inflammation.[257,262] Although some investigators have suggested that red wine may have particular cardioprotective properties because of its nonalcohol component of resveratrol and other components, evidence from trials of risk factors as well as prospective cohort studies of clinical endpoints have found equal benefits for all forms of alcohol when consumed in moderation, supporting that alcohol per se accounts for most of the observed protective association with alcoholic beverage consumption.[263] The pattern of drinking affects the observed benefit of moderate alcohol on CVD, with no benefit seen with binge drinking (4 or more drinks for women on one or more occasions and 5 or more drinks for men within about 2 hours); drinking 7 drinks a week but on one night does not confer the observed benefit on CVD seen in those having one drink a day.[264]

Researchers have questioned whether it is the alcohol itself that causes the observed benefits on CVD, because people who drink in moderation are different from nondrinkers or heavy drinkers in ways that could influence health and disease.[265,266] Previous studies have shown that moderate drinkers are more likely to be at a healthy weight, get adequate sleep, and exercise regularly. Benefits among moderate drinkers remain after control for such differences, suggesting that alcohol itself, in moderation, is responsible for the reduced risk of CVD.

Any individual or public health recommendation must consider the complexity of alcohol's metabolic, physiologic, and psychological effects.[215] Because of the health hazards of alcohol associated with higher intake, moderate alcohol use does not offer a population-based strategy to reduce cardiovascular risk. Discussions of alcohol consumption require individual considerations and should take into account other medical problems, coronary risk factors, comorbid conditions, concurrent medications, pregnancy, and family history of medical conditions or alcoholism. Patients who are heavy drinkers should be counseled to limit intake. The initiation of moderate alcohol drinking to reduce risk of heart disease is not recommended, especially in view of other known preventive measures, such as physical activity.

Postmenopausal Hormone Therapy

Age-specific coronary heart disease (CHD) death rates in women lag approximately 10 years behind those of men. Rates of CHD mortality among women rise exponentially with age and vary substantially by race and ethnicity. Cardiovascular disease (CVD) afflicts relatively few women younger than 45 years in developed countries, but by age 60, it is the leading cause of death among women, both in the United States and worldwide. More than 80% of CVD deaths in women now occur in low-income and middle-income countries as a result of increasing longevity and large population sizes. Although men exhibit a higher incidence of CHD at every age as well as higher CHD mortality rates, the gap narrows substantially because women's rates increase after either natural menopause or bilateral oophorectomy.[35,267]

A wide range of factors may explain the increased risk of CHD after menopause. These include

adverse changes in lipid and glucose metabolism that result in an increase in LDL cholesterol and a decrease in HDL cholesterol, an increase in glucose intolerance, and changes in hemostatic factors and vascular function. These changes appear to result not only from the decline in endogenous estrogen that accompanies menopause, but also from the hormonal shift toward androgen dominance as estradiol levels fall[268] (**see Chapter 89**).

In regard to the observed increase in CHD in women after menopause, numerous observational studies consistently demonstrated that ever and current use of postmenopausal hormone therapy was associated with a reduced risk of CHD. Recommendations from professional societies all led to the widespread use in the 1990s of hormone therapy in postmenopausal women to prevent CVD as well as other diseases, such as osteoporosis and cognitive decline and dementia.[109]

The physiologic effects of exogenous estrogen are compatible with a cardioprotective effect. Estrogen reduces LDL and increases HDL cholesterol levels; reduces lipoprotein(a), plasminogen activator inhibitor type 1, and insulin levels; inhibits oxidation of LDL; and improves endothelial vascular function. Estrogen has complex effects on inflammation: levels of fibrinogen decrease, whereas levels of hsCRP increase. Estrogen also may improve glucose tolerance.

Although the observational study data among women who began hormone therapy around menopause consistently suggested CHD benefits of hormone replacement therapy (HRT), the randomized trial data have not demonstrated that replacement with estrogen and progestin, or estrogen alone, confers cardioprotection.[269,270] The Heart and Estrogen/Progestin Replacement Study (HERS), while finding benefits on the lipid profile, did not find significant differences in cardiovascular endpoints. The National Institutes of Health (NIH)–funded Women's Health Initiative (WHI) evaluated the role of hormone therapy in the prevention of CVD and assessed the balance of benefits and risks of HRT when used for chronic disease prevention. For many outcomes, the WHI is the only large, long-term randomized trial of postmenopausal women using hormone therapy.

One WHI arm evaluated the relative benefits and risks of combined hormone therapy of conjugated estrogen plus medroxyprogesterone acetate versus placebo among 16,608 postmenopausal women, 50 to 79 years of age, with an intact uterus at baseline during a planned 8-year period. After a mean follow-up period of 5.2 years, the trial's Data and Safety Monitoring Board recommended stopping the trial 3 years early because the overall risk-benefit ratio of estrogen-progesterone therapy was unfavorable. Risks in the hormone therapy group in terms of increases in CHD, stroke, venous thromboembolism, and breast cancer exceeded the benefits on reductions of fracture and colon cancer.

The increased risk of CVD and the adverse risk-benefit ratio was unexpected, and seemed apparently inexplicable in the face of the existing body of literature supporting the concept that HRT was cardioprotective. After the release of these results, HRT prescriptions abruptly and dramatically declined. Two years later, the unopposed estrogen versus placebo arm of the WHI, which included 10,739 generally healthy postmenopausal women age 50 to 79 without a uterus, also was halted early because of an increased risk of stroke, particularly in women age 60 or older, in the absence of net health benefits.

The discrepancies between the observational study results and the randomized trial findings led to a careful examination of how the clinical trials may have differed from the observational studies in ways that may have affected the results. Detailed scrutiny of subgroups of the trial data suggested that age and time since menopause modulate the effect of estrogen on cardiovascular risk.[271] The WHI demonstrated a number of demographic and biologic differences from the observational studies that limited generalizing the findings to all postmenopausal women. Perhaps most importantly, the WHI and the observational studies were conducted in different populations. The WHI enrolled generally healthy, largely

asymptomatic postmenopausal women age 50 to 79 in a prevention trial, whereas the observational studies generally included primarily relatively young and symptomatic women who began HRT early in menopause. WHI participants were on average 63 years of age and more than 10 years beyond menopause, whereas the observational study participants were younger than 55 at the time HRT was initiated and within 2 to 3 years of menopause. Analysis of the relevant data by age and time since menopause showed that the estrogen-only arm of the WHI appeared to agree generally with the observational studies suggesting that estrogen therapy reduces CHD risk when initiated in younger and more recently postmenopausal women without a uterus. Further analyses indicated that women who start HRT more than 10 years beyond menopause had increased risk for CHD, but the women in whom heart disease was diagnosed within 10 years of menopause tended to have a lower CHD risk. A meta-analysis of more than 39,000 women concluded that menopausal hormone therapy reduces coronary risk in women under 60 but not in older women.[271]

The WHI showed that postmenopausal hormone therapy did not prevent coronary disease in women who started treatment distant from menopause onset. Yet the question remained of whether estrogen therapy initiated close to menopause onset may reduce CHD risk. Two subsequent trials addressed the issue of timing of initiation of HRT and atherosclerosis progression using noninvasive imaging, but the results have not been consistent. The Kronos Early Estrogen Prevention Study (KEEPS) was a 4-year randomized trial of low-dose oral conjugated equine estrogens (CEE) or transdermal estradiol and cyclic monthly progesterone in 727 healthy women (mean age, 52 years) within 3 years after menopause at randomization.[272] Hormone therapy decreased menopausal symptoms, depression, and anxiety; increased in HDL (with oral CEE); and improved of insulin sensitivity (with transdermal E2).[109] There were no significant differences in frequency of adverse events, including diagnosis of breast cancer, endometrial cancer, MI, stroke, transient ischemic attack, and venous thromboembolic disease, although the absolute numbers of such events were extremely small. Although the data reassured that no increases in cardiac risk occurred during this short-term use of HRT, neither hormone regimen significantly reduced or accelerated progression of atherosclerosis, as measured by carotid intimal medial thickness (CIMT) and coronary artery calcium.[273] In the Early Versus Late Intervention Trial with Estradiol (ELITE), 643 healthy women stratified by time since menopause (<6 years or ≥10 years) were randomized to oral estradiol plus progesterone vaginal gel versus placebo. After 5 years, oral estradiol therapy was associated with less progression of subclinical atherosclerosis, measured as CIMT, than was placebo when therapy was initiated within 6 years after menopause, but not when initiated 10 or more years after menopause.[274]

Interventions of Hormone Therapy for Cardioprotection

Over the last decade, a consensus has developed regarding the overall central recommendations related to the safety and benefits of hormone therapy in menopausal management.[275] Menopausal hormone therapy remains an appropriate treatment for menopausal symptoms, used in early menopause (<60 years of age, or within 10 years of menopause) at the lowest effective dose and period of time, and in the absence of contraindications. The evidence does not, however, support its prescription for the focused purpose of preventing CVD.[276,277]

Statements from a number of different societies support this general recommendation. The joint Global Consensus Statement on menopausal hormone therapy,[278] the 2015 Endocrine Society Clinical Practice Guidelines,[279] and the 2016 Recommendations of the International Menopause Society on women's midlife health and menopause hormone therapy[280] all agree with these principles. The 2012 Hormone Therapy Position Statement[281] of the North American Menopause Society added that the more favorable benefit-

risk ratio for estrogen-only therapy allows more flexibility in extending the duration of use compared with estrogen-progestogen therapy, where the earlier appearance of increased breast cancer risk precludes a recommendation for use beyond 3 to 5 years. In 2015 the North American Menopause Society issued an additional statement supporting continuing use of systemic hormone therapy after age 65, as needed to address continuing duration of vasomotor symptoms into the late 60s and 70s.[282]

All the recommendations explicitly note that the necessity of individualizing the decision to use menopausal hormone therapy, including a personal benefit-risk profile with clinical and biologic variables as well as quality-of-life priorities. Methods to assist in this personalized decision-making process are becoming available.[283,284]

Community-Based and Multiple–Risk Factor Intervention Programs

Many primary prevention measures have focused on targeting a single risk factor in individuals, and while great progress has been made, few Americans have ideal cardiovascular health. Moreover, the prevalence of many risk factors is still high, the prevalence of obesity is still increasing,[35] and the favorable trends in total cholesterol and LDL cholesterol have leveled off and may be reversing.[285] Thus the need exists for complementary population approaches such as community-based interventions, as well as interventions that target multiple risk factors.

In 2011, to reduce the cardiovascular burden in the United States and to help meet the goals of *Healthy People 2020*, the DHHS launched the Million Hearts initiative to prevent 1 million heart attacks and strokes in 5 years.[286,287,288] With leadership from the CDC as well as the Centers for Medicare and Medicaid Services (CMS), the Million Hearts initiative (www.millionhearts.hhs.gov) emphasizes the formation of public-private partnerships at the federal, national, state, and local levels. This initiative takes two complementary approaches to cardiovascular prevention, clinical and community based. Clinically, Million Hearts focuses on improving the management of the "ABCS"—aspirin for high-risk patients, blood pressure control, cholesterol reduction, and smoking cessation. This effort increased the focus on improving ABCS care; health information technology and standardization of core ABCS metrics that will allow better tracking of the goals across all types of health systems; and clinical innovations such as use of patient-centered medical homes. At the same time, Million Hearts aims to expand population initiatives through policies and programs to reduce smoking, improve nutrition, and reduce BP. This undertaking includes endorsing at the community level policies for sodium restriction and the elimination of artificial *trans* fats from the diet; implementing policies and programs designed to dramatically lower cigarette consumption and exposure to secondhand smoke; and emphasizing programs designed to increase community access to exercise facilities and to programs that target weight reduction and nutrition. Million Hearts is designed to "leverage, focus and align" existing investments, not require extensive new monetary expenditures.[287]

The Affordable Care Act (ACA) has provided great opportunities for accomplishing prevention on a community level. Tax-exempt status hospitals must perform a community health needs assessment on a regular basis and develop plans to address identified needs. To facilitate collaborative efforts to improve both health care and non–health care determinants of health outcomes, in 2015 the CDC released its online Community Health Improvement Navigator.[289] This resource allows the user to search for multisector, collaborative, evidence-based interventions to address tobacco use and exposure, physical inactivity, unhealthy diet, high cholesterol, high BP, and diabetes. The 2016 Annual Report to Congress of the Community Preventive Services Task Force ranked CVD prevention and control as the first of their 11

priority areas for new Community Guide reviews in the coming years.[290] The AHA guide for improving cardiovascular health at the community level, updated in 2013, provides a comprehensive inventory of evidence-based goals, strategies, and recommendations for CVD prevention appropriate for implementation at a community level.[291]

Past success in federally sponsored programs that use evidence-based policy approaches to improve population dietary habits supports the efficacy of such community-based approaches.[215] An initiative in a rural county of Maine demonstrated that collaboration among health systems, public health, and community organizations can substantially improve risk factors and clinical health outcomes.[292] This study documented health outcomes associated with an integrated, multicomponent, sustained community-wide program for cardiovascular risk reduction program in Franklin County, Maine, a low-income rural community. Over a 40-year follow-up period, community-wide programs targeted hypertension, cholesterol, and smoking, as well as diet and physical activity. Over these 40 years, rates of control of hypertension, control of elevated cholesterol, and quitting smoking showed clinically significant improvements. In addition, total hospitalizations and hospitalizations per capita (with lower mortality) fell compared to other counties in the state over the same periods. This program demonstrated that a coordinated, evidence-based, sustained community-wide effort can measurably improve cardiovascular health in a community. This successful experience from a socioeconomically disadvantaged community could serve as a model for implementation and study in other rural communities, as well as urban and communities outside the United States.[293]

Recent studies have evaluated the effect of simultaneous control of multiple risk factors. Analyses in the BARI 2D trial (Bypass Angioplasty Investigation Revascularization 2 Diabetes) demonstrated the feasibility of simultaneous control of six risk factors (smoking, non-HDL cholesterol, triglycerides, systolic and diastolic blood pressure, and glycosylated hemoglobin) through protocol-guided intensive medical therapy, and that the number of risk factors under control was related strongly to total mortality and cardiovascular morbidity and mortality.[294] These observations support previous studies. The Stepathlon Cardiovascular Health Study[295] evaluated an international, low-cost, mass-participation mHealth (mobile health) intervention on physical activity, sitting, and weight and demonstrated its association with short-term, large scale, across-the-board improvements in these risk factors. The Fifty-Fifty study[296] evaluated a year-long peer group–based intervention versus self-management in improving healthy behavior in individuals with cardiovascular risk factors. The peer group intervention had beneficial effect on cardiovascular risk factors, with significant improvement in the composite score of BP, exercise, weight, diet, and tobacco, with specific benefit on tobacco cessation.

Community-based interventions have particular relevance to prevention in addressing lifetime risk rather than 10-year risk. As shown in a meta-analysis of 18 cohort studies involving 257,000 persons across the United States, those with “optimal” risk factor profiles had substantially lower risks of death from CVD up to 80 years of age, compared with those with two or more major risk factors. Those with controlled risk factors also had markedly lower lifetime risks of fatal CHD or nonfatal MI as well as of fatal and nonfatal stroke[297] (**Fig. 45.21**). These effects maintained consistency across birth cohorts and ethnic groups and between men and women. Lifetime risk estimates thus suggest that efforts to lower the burden of CVD will require prevention of the development of risk factors (primordial prevention) in concert with treatment of established risk factors (primary prevention).

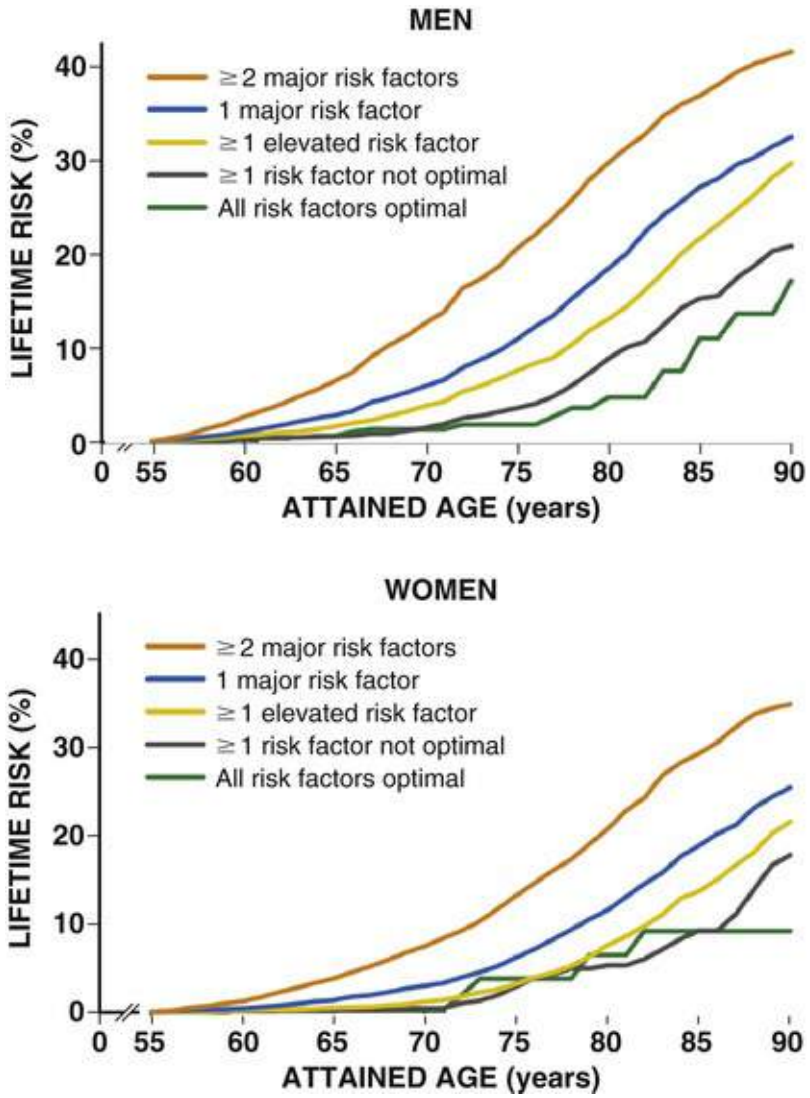


FIGURE 45.21 Lifetime risk of death from cardiovascular disease in men **(top)** or in women **(bottom)** at 55 years of age, with varying burden of risk factors, adjusted for competing mortality risks. (From Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. N Engl J Med 2012;366:321.)

The AHA has recommended a prescription for health called Life's Simple 7,[298] encouraging the population to meet seven cardiovascular metrics for ideal cardiovascular health. These include four modifiable risk factors (not smoking, healthy weight, eating healthy, and being physically active) and three biometric measures (blood pressure, cholesterol, and blood sugar). These simplified metrics, easily introduced in the primary care office as well as in community wellness centers, correlate closely with all-cause mortality, cardiovascular mortality, and ischemic heart disease mortality.[299] Thus the reduction to practice of the precepts and evidence base reviewed in this chapter and related chapters could produce prodigious public health benefits worldwide.

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Systemic Hypertension

Mechanisms and Diagnosis

Ronald G. Victor

Overview of Hypertension

Affecting 80 million people in the United States and over 1 billion worldwide, hypertension remains the most common, readily identifiable, and reversible risk factor for myocardial infarction (MI), stroke, heart failure, atrial fibrillation, aortic dissection, peripheral arterial disease, and cognitive decline.[1] The global burden of hypertension is rising due to escalating obesity and population aging, and is projected to affect 1.5 billion persons—one third of the world's population—by 2025.[2] The prevalence of hypertension is increasing most rapidly in developing countries (80% of the world), where poor hypertension treatment and control contribute to the growing epidemic of cardiovascular disease (CVD). High blood pressure (BP) continues to be the largest single contributor to the global burden of disease, causing two thirds of all cerebrovascular accidents (strokes) and half of all ischemic heart disease worldwide, and thus 9.4 million deaths each year.[2] Half of this disease burden occurs in people with hypertension (i.e., BP ≥140/90 mm Hg); the other half occurs in people with lesser degrees of high BP (*prehypertension*). During the past four decades, the highest worldwide BP levels have shifted from high-income countries to low-income countries in south Asia and sub-Saharan Africa, while BP remained persistently high in central and eastern Europe.[3] Thus, high BP remains the leading cause of death worldwide and one of the world's great public health problems (**see Chapters 1 and 45**).

The asymptomatic nature of systemic hypertension delays diagnosis. Effective treatment requires continuity of care by a knowledgeable clinician and frequent medical checkups, which are less accessed by men and members of low-income minority groups. Most patients diagnosed with hypertension do not manifest a single disease-causing mechanism. Treatment thus remains empiric, often requiring three (or more) BP-lowering drugs with synergistic mechanisms of action along with lipid-lowering drugs (and drugs for concomitant medical conditions such as diabetes).[4,5] Pill burden, prescription drug costs, medication side effects, and insufficient time for patient education contribute to medication noncompliance. Physicians often undertreat hypertension[6] (**see Chapter 47**). For all these reasons, BP remains elevated—140/90 mm Hg or higher—in half of affected individuals in the United States, Canada, and other developed countries.[2] Even among patients whose hypertension appears controlled by conventional standards, fewer than one in three may yet develop subsequent stroke, MI, or heart failure. The resultant annual cost to the U.S. health care system exceeds $48 billion, a value that is projected to increase to $274 billion by the year 2030.[7] This chapter and **Chapter 47** review the scientific basis for rapidly evolving recommendations for the diagnosis, evaluation, and management of hypertension, and present emerging concepts from clinical and basic research that affect clinical decision making.

Definition

Hypertension is defined as a usual office BP of 140/90 mm Hg or higher.[8] Yet, epidemiologic data show continuous positive relationships between the risk of coronary artery disease (CAD) and stroke deaths with systolic or diastolic BP down to values as low as 115 or 75 mm Hg, respectively[9] (**Fig. 46.1**). The artificial dichotomy between *hypertension* and *normotension* may delay medication management until irreversible compromise of vascular health by elevated BP values previously considered normal.

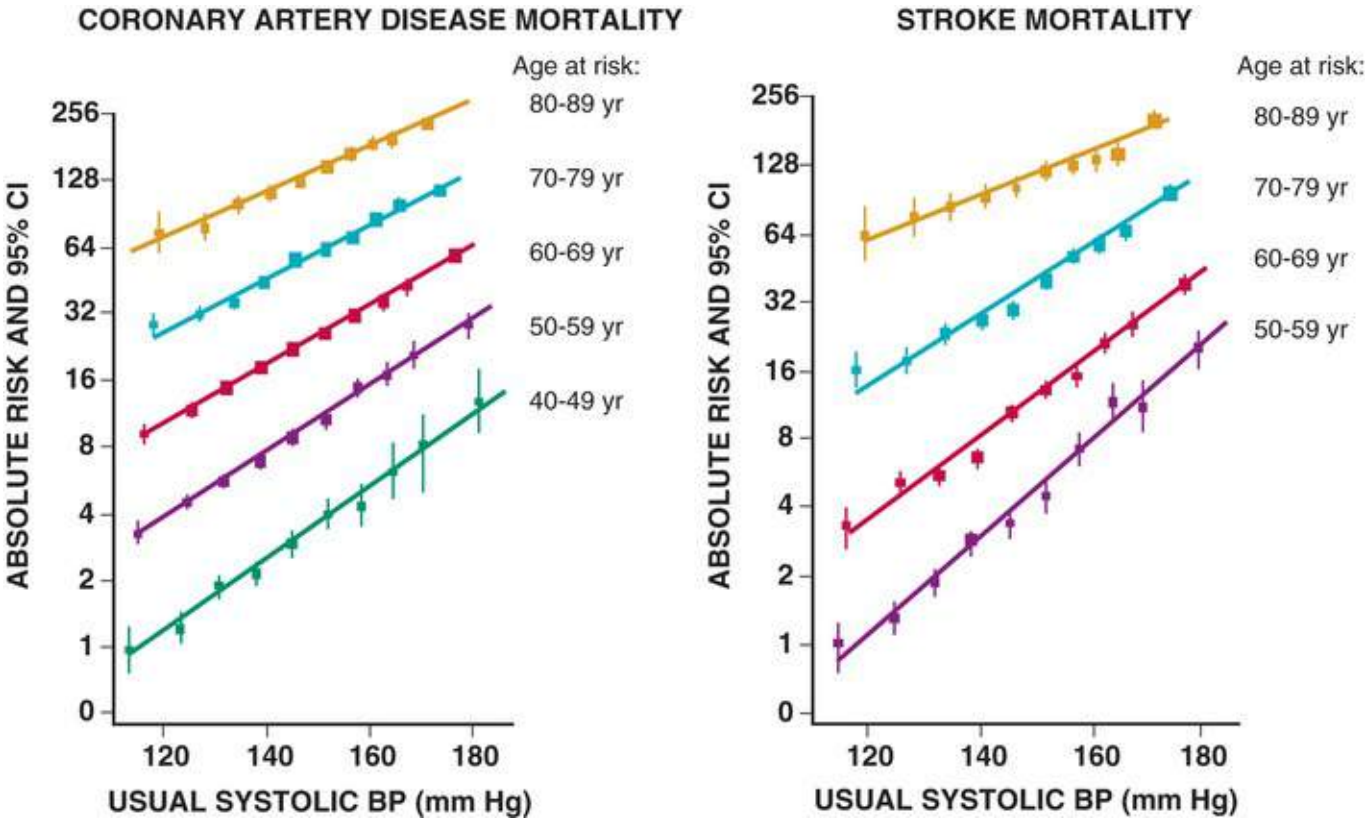


FIGURE 46.1 Absolute risks of coronary artery disease mortality **(left)** and stroke mortality **(right)** for each decade of life (plotted on a logarithmic scale) by usual systolic blood pressure (BP) level (plotted on a linear scale); CI, confidence interval. (From Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903.)

Prevalence

In the United States and other developed countries, the prevalence of hypertension increases with age, rising exponentially after 30 (**see Chapter 1**). Before 50 years of age, women have a somewhat lower prevalence of hypertension than men. After menopause, the prevalence of hypertension increases rapidly in women and surpasses that in men. Eventually, by age 78—below the average life span of U.S. men and women—almost 90% will have hypertension.

Currently, 41% of non-Hispanic black adults in the United States have hypertension, compared with 28% of non-Hispanic white adults, 25% of Asian adults, and 26% of Hispanic adults.[10] Black Americans also have earlier onset, more severe hypertension, and greater target organ damage, leading to excess premature disability and death. Hypertension and its complications are even more prevalent in many predominantly white European countries than among black Americans, but are much less prevalent among black Africans[11,12] (**Fig. 46.2**). Hypertension prevalence does not vary between black and non-black Hispanic adults in Cuba. Genetic factors may contribute to the disproportionate burden of hypertension in black Americans, but these international data underscore the importance of environment. From 90% to 95% of hypertensive patients have no apparent single reversible cause of elevated BP, thus the term *primary hypertension*. The remaining 5% to 10%—cases denoted *secondary* (identifiable) *hypertension*—demonstrate a more discrete mechanism.

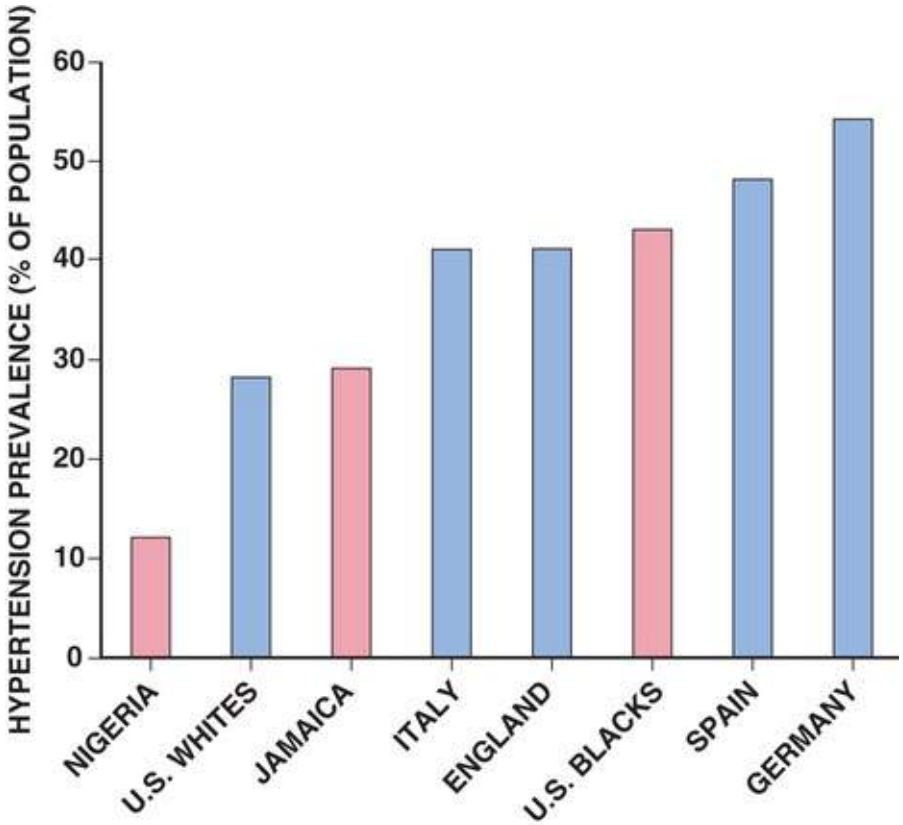


FIGURE 46.2 Geographic variation in hypertension prevalence in populations of African descent (*pink bars*) and European descent (*blue bars*). (Modified from Cooper RS, Wolf-Maier K, Luke A, et al. An international comparative study of blood pressure in populations of European vs. African descent. BMC Med 2005;3:2.)

Blood Pressure Variability and Its Determinants

Behavioral Determinants

In most patients with primary hypertension, readily identifiable behaviors contribute to the elevated BP. The nicotine in cigarette smoke transiently raises BP by 10 to 20 mm Hg, thereby elevating the average daytime BP in habitual smokers. Moderate alcohol drinkers (one or two drinks per day) generally have less hypertension than teetotalers, but the risk for development of hypertension increases in heavy drinkers (three or more drinks per day). Hypertension is rare in Asian men who abstain from alcohol to avoid the nausea and flushing reaction associated with their loss-of-function mutation in the alcohol dehydrogenase gene (*ALDH2*).[13] Caffeine consumption typically causes only a small transient rise in BP, which in some individuals habituates after the first cup of coffee. The risk for development of hypertension does not vary with coffee consumption, but increases steeply when caffeine is consumed in diet sodas; thus coffee may contain protective antioxidant polyphenols not present in sodas. Physical inactivity also increases the risk for developing hypertension.

Lifetime dietary habits clearly influence the risk for developing hypertension (**see Chapter 49**). Across populations, hypertension prevalence increases linearly with average body mass index (BMI). However, the impact of weight gain or weight loss on BP is less clear than the major impact on glucose metabolism and diabetes. On the other hand, there is abundant evidence that the risk for developing hypertension increases with dietary sodium intake and decreases with dietary potassium intake. In adolescent girls, a high-potassium diet appears to negate the adverse effect of a high-salt diet on BP.[14] Potassium ingestion acts like a thiazide-type diuretic: it acutely decreases the activity of the thiazide-sensitive Na^+/K^+ cotransporter, thus lowering renal Na^+ reabsorption.[15] Epidemiologic studies have not settled the debate

as to whether or not very-low-sodium diets can cause reflex activation of neural and hormonal mechanisms that can increase CVD despite preventing hypertension.[16,17] In practical terms, it is very difficult to achieve and maintain very low levels of sodium intake in Western countries. Individual variability in BP responses to dietary sodium loading and sodium restriction indicates an important genetic underpinning.

Genetic Determinants

Concordance of BP is higher in families than in unrelated individuals, higher between monozygotic than dizygotic twins, and higher between biologic than adoptive siblings living in the same household. Although approximately 50% of BP variability is heritable, the associated genetic variations identified to date explain at most 2% to 3% of this variability.[18] The large gap between estimated and observed variance, termed “missing heritability,” may be caused in part by epigenetic mechanisms such as DNA methylation.[19]

The complex regulation of BP has thwarted the genetic dissection of primary human hypertension. Whereas mutations in 20 salt-handling genes cause ultrarare monogenic forms of severe early-onset hypotension (salt-wasting syndromes) and hypertension (all inherited as mendelian traits), applicability to common primary hypertension has proved elusive. Data from the Framingham Heart Study indicate that 1% to 2% of the general adult population has gene mutations underlying the pediatric salt-wasting syndromes (Bartter, Gitelman) that may confer resistance against primary hypertension[20] (**Fig. 46.3**). Although the rare monogenic forms of severe hypertension all emphasize renal mechanisms—defects in the kidneys' ability to excrete sodium—as the primary driver of hypertension, the largest study thus far to investigate the genomics of BP variation in the general population found a new set of 66 variants that commonly affect vascular endothelial cell regulation and a separate set associated with hypertensive target-organ damage in heart, cerebral vessels, carotid artery, and eye, but not the kidney.[18] These new data confirm the importance of vascular mechanisms in the pathogenesis and progression of hypertension, with the hope of uncovering new drug targets.

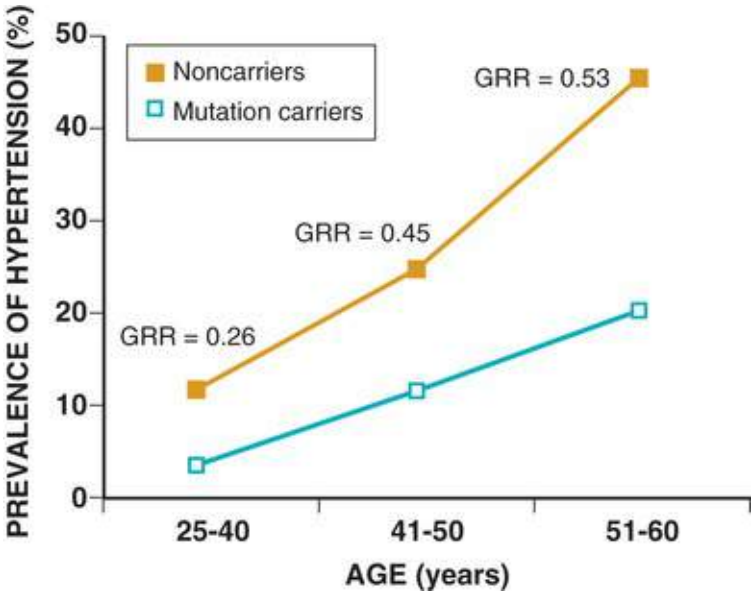


FIGURE 46.3 Reduced prevalence of hypertension among mutation carriers. Prevalence of hypertension at the last examination within ages 25-40, 41-50, and 51-60 years, for mutation carriers and noncarriers of genes causing Bartter and Gitelman syndromes. The genotype relative risk (GRR) for mutation carriers is shown. (From Ji W, Foo JN, O'Roak BJ, et al. Rare independent mutations in renal salt handling genes contribute to blood pressure variation. Nat Genet 2008;40:592.)

Mechanisms of Primary (Essential) Hypertension

Hemodynamic Subtypes

Primary hypertension falls into three distinctly different hemodynamic subtypes that vary sharply by age.

Systolic Hypertension in Teenagers and Young Adults

Typically associated with hypertension in elderly patients (see later), *isolated systolic hypertension* (ISH) also is the main type in young adults (typically 17 to 25 years of age). The key hemodynamic abnormalities are increased cardiac output and a stiff aorta, both presumably reflecting an overactive sympathetic nervous system. The prevalence may reach as high as 25% in young men, but only 2% of young women. Several recent studies show that young persons with ISH have elevated central as well as brachial systolic BP, indicating significantly increased hemodynamic burden.[21] Thus, ISH in youth may predispose to diastolic hypertension in middle age.

Diastolic Hypertension in Middle Age

Hypertension diagnosed in middle age (typically 30 to 50 years) usually has the elevated diastolic pressure pattern, with normal systolic pressure (isolated diastolic hypertension) or elevated systolic pressure (combined systolic-diastolic hypertension). This pattern constitutes classic “essential hypertension.” Isolated diastolic hypertension is more common in men and often is associated with middle-age weight gain. Without treatment, isolated diastolic hypertension often progresses to combined systolic-diastolic hypertension. The fundamental hemodynamic fault is an elevated systemic vascular resistance (SVR) coupled with an inappropriately normal cardiac output. Vasoconstriction at the level of the resistance arterioles results from increased neurohormonal drive and an autoregulatory reaction of vascular smooth muscle to an expanded plasma volume, the latter because of impairment in the kidneys' ability to excrete sodium.

Isolated Systolic Hypertension in Older Adults

After 55 years of age, ISH (systolic BP >140 mm Hg and diastolic BP <90 mm Hg) predominates. In developed countries, systolic pressure rises steadily with age; in contrast, diastolic pressure rises until about 55 years of age, then falls progressively thereafter (**Fig. 46.4**). The resultant widening of pulse pressure indicates stiffening of the central aorta and a more rapid return of reflected pulse waves from the periphery, augmenting systolic aortic pressure[22] (**eFigs. 46.1 to 46.3**). Accumulation of collagen (which is poorly distensible) adversely affects its ratio to elastin in the aortic wall.

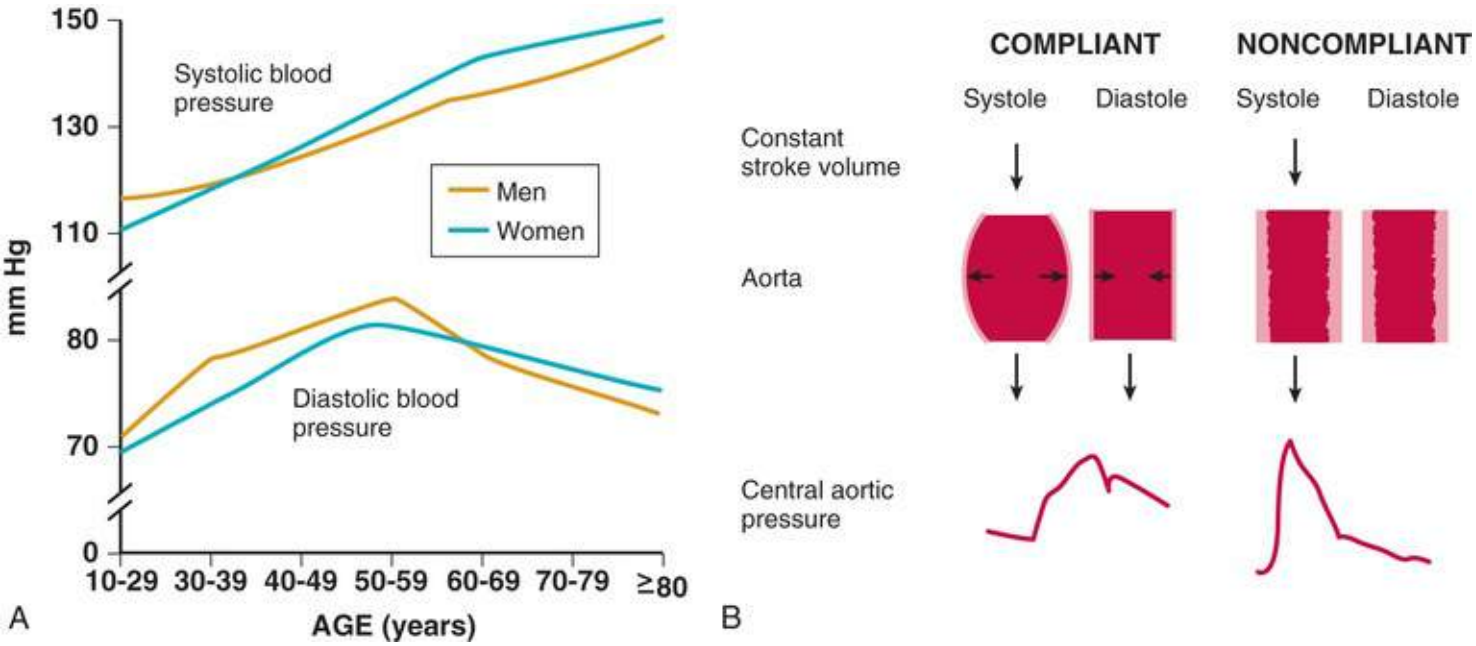
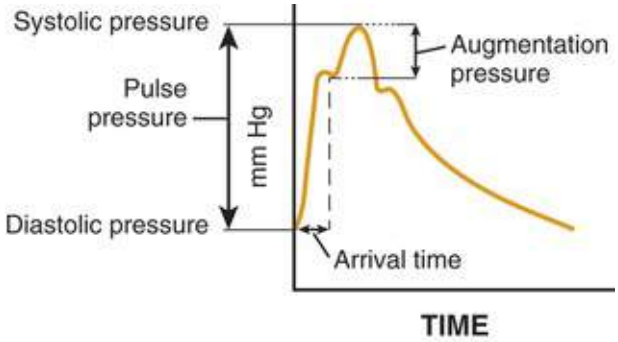
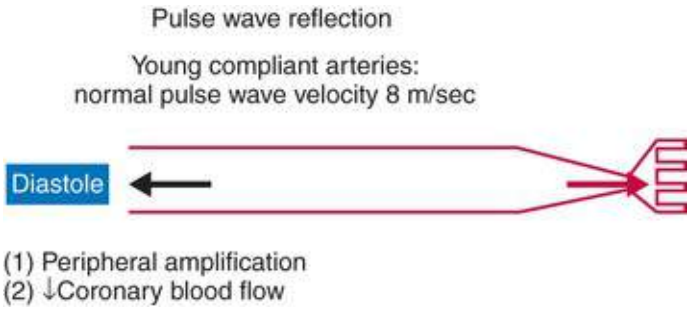


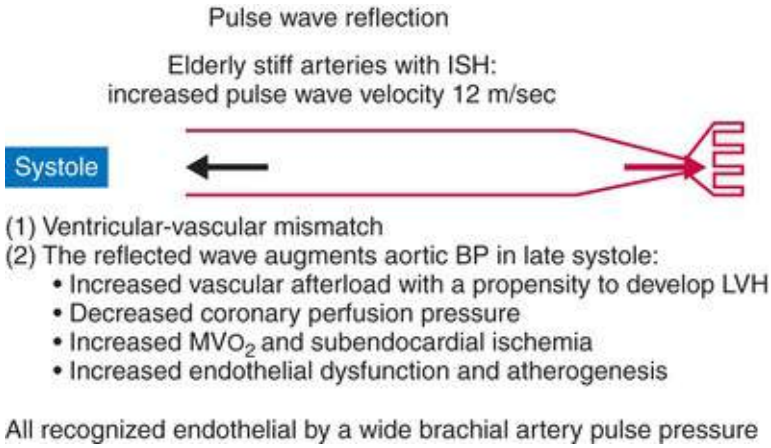
FIGURE 46.4 **A,** Age-dependent changes in systolic and diastolic blood pressure in the United States. **B,** Schematic representation of the relationship between aortic compliance and pulse pressure. (**A,** From Burt V, Whelton P, Rocella EJ, et al. Prevalence of hypertension in the U.S. adult population: results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension 1995;25:305; **B,** from Dr. Stanley Franklin, University of California at Irvine.)



EFIGURE 46.1 Central aortic pressure waveform. The height of the late systolic peak above the inflection defines the augmented pressure, and the ratio of augmented pressure to pulse pressure defines the augmentation index (in percentage). (Modified from Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006;27:2588–2605.)



EFIGURE 46.2 Artist's rendering of normal pulse wave velocity and the timing of the reflected wave. In a young person with compliant arteries, pulse wave velocity is 8 m/sec. The reflected pulse wave reaches the central aorta in diastole, thereby amplifying central diastolic pressure and thus coronary perfusion pressure. (Courtesy Dr. Stanley Franklin, Cedars-Sinai Heart Institute/Hypertension Center, Los Angeles.)



EFIGURE 46.3 Artist's rendering of increased pulse wave velocity in isolated systolic hypertension (ISH) and resultant changes in central aortic pressure and hemodynamic load. In an elderly patient with ISH and stiff arteries, pulse wave velocity is 12 m/sec, abnormally fast. The reflected pulse wave reaches the central aorta in systole, thereby amplifying central systolic pressure and widening the central pulse pressure. The augmented aortic systolic pressure accelerates the development of left ventricular hypertrophy (LVH), increases myocardial oxygen demands (MVO_2), and accelerates endothelial dysfunction and atherosclerosis. The rapid diastolic runoff can compromise coronary perfusion pressure, thereby predisposing to subendocardial ischemia. (Courtesy Dr. Stanley Franklin, Cedars-Sinai Heart Institute/Hypertension Center, Los Angeles.)

ISH may represent an exaggeration of this age-dependent stiffening process, although systolic BP and pulse pressure do not rise with age in the absence of urbanization (e.g., cloistered nuns). ISH is more common in women and is associated prominently with heart failure with preserved systolic function, a syndrome also more prevalent in women (**see Chapters 26 and 89**). Compared with young or middle-aged adults with optimal BP, those with BP in the high-normal range (prehypertension) will more likely develop ISH after 55 years of age. Many neurohormonal, renal, and vascular mechanisms interact to varying degrees to the pathogenesis and progression of the different hemodynamic forms of hypertension.

Neural Mechanisms

Two device-based interventional approaches to treat hypertension—baroreflex activation therapy (BAT) and renal denervation (RDN)—have rekindled interest in neural mechanisms of clinical hypertension.[23,24] **Fig. 46.5** shows the major central and reflex mechanisms that drive sympathetic overactivity in human hypertension, including resetting of the baroreceptors and activation of renal sensory nerves termed *renal afferents*.

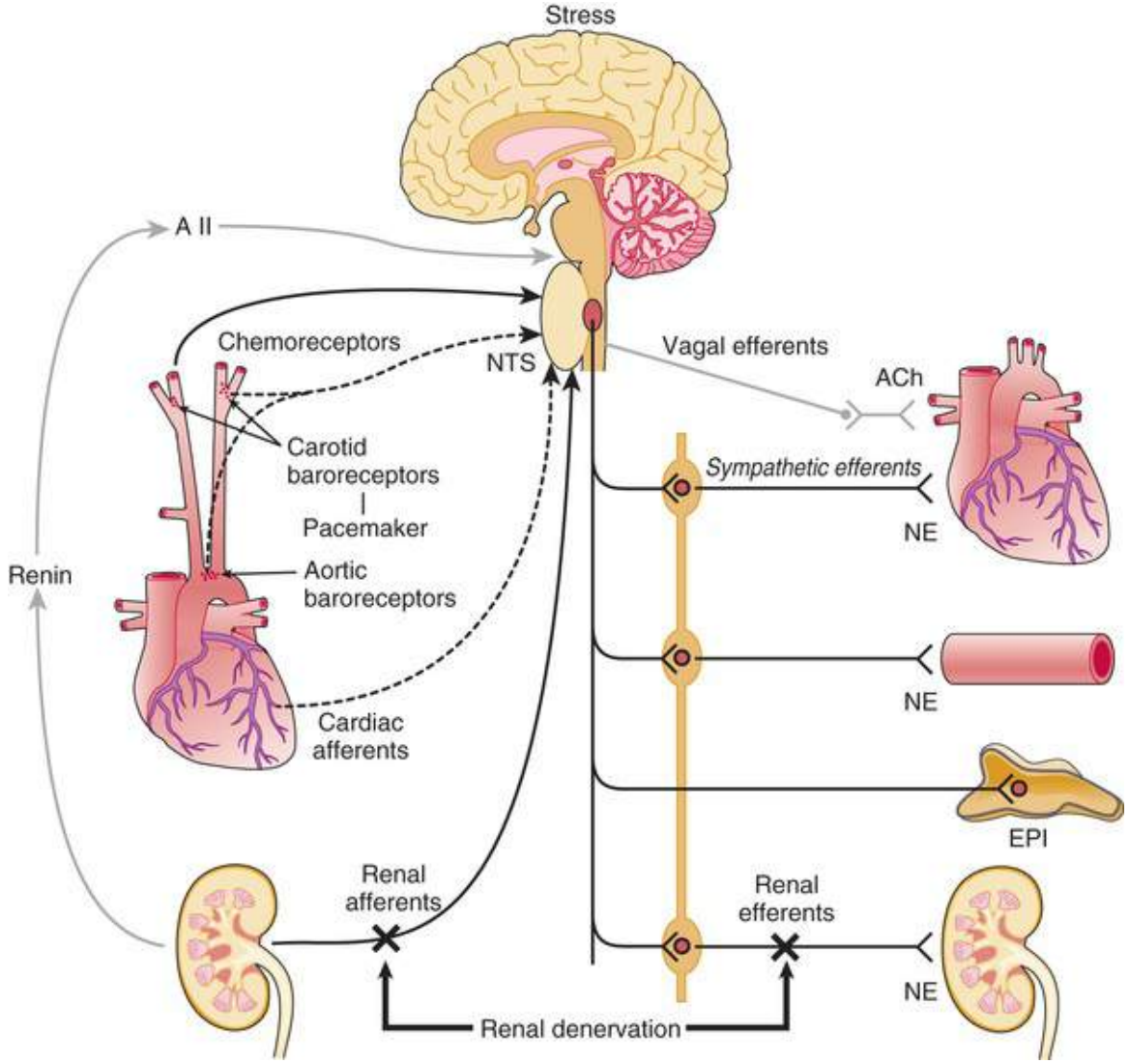


FIGURE 46.5 Sympathetic neural mechanisms of blood pressure regulation and treatment targets of carotid baroreceptor pacing and renal denervation. Note that aortic baroreceptors, which also influence blood pressure, are not paced. Also note that renal denervation affects afferent and efferent renal nerves. *Dotted arrows* represent inhibitory neural influences, and *solid arrows* represent excitatory neural influences on sympathetic outflow to the heart, peripheral vasculature, and kidneys. *A II,* Angiotensin II; *Ach,* acetylcholine; *EPI,* epinephrine; *NE,* norepinephrine; *NTS,* nucleus tractus solitarius. (Modified from Martin EA, Victor RG. Premise, promise, and potential limitations of invasive devices to treat hypertension. Curr Cardiol Rep 2011; 13:86-92).

Fig. 46.5 also shows the specific mechanisms that are targeted by the device-based therapies. With carotid BAT, electrical field stimulation of the carotid sinus nerve sends afferent neural signals that the brainstem interprets as a rise in BP, evoking a reflex reduction in BP. The efferent arm of this reflex arc involves decreased efferent sympathetic nerve activity to the heart, which slows heart rate; to the peripheral circulation, which lowers SVR; and to the kidney, which reduces renin release and increases renal sodium excretion. With RDN, a catheter is inserted into the renal arteries and radiofrequency or ultrasound is used to ablate the renal nerves, which are located on the adventitial surface of the renal arteries. The RDN aims to destroy both efferent and afferent renal nerves. The efferent renal (sympathetic) nerves contribute to hypertension by causing renal vasoconstriction and vascular hypertrophy via $alpha_1$-adrenergic receptors, stimulate renin release via $beta_1$-adrenergic receptors, and enhance renal sodium and water reabsorption via $alpha_1$ receptors (**Fig. 46.6**). Renal afferent nerves contribute to hypertension by evoking reflex activation of central sympathetic outflow triggered to multiple tissues and vascular beds. However, with both BAT and RDN, U.S. sham-controlled phase 3 randomized controlled trials (RCTs) yielded disappointing results (**see Chapter 47**). Neither device

gained U.S. Food and Drug Administration (FDA) approval, but research continues.

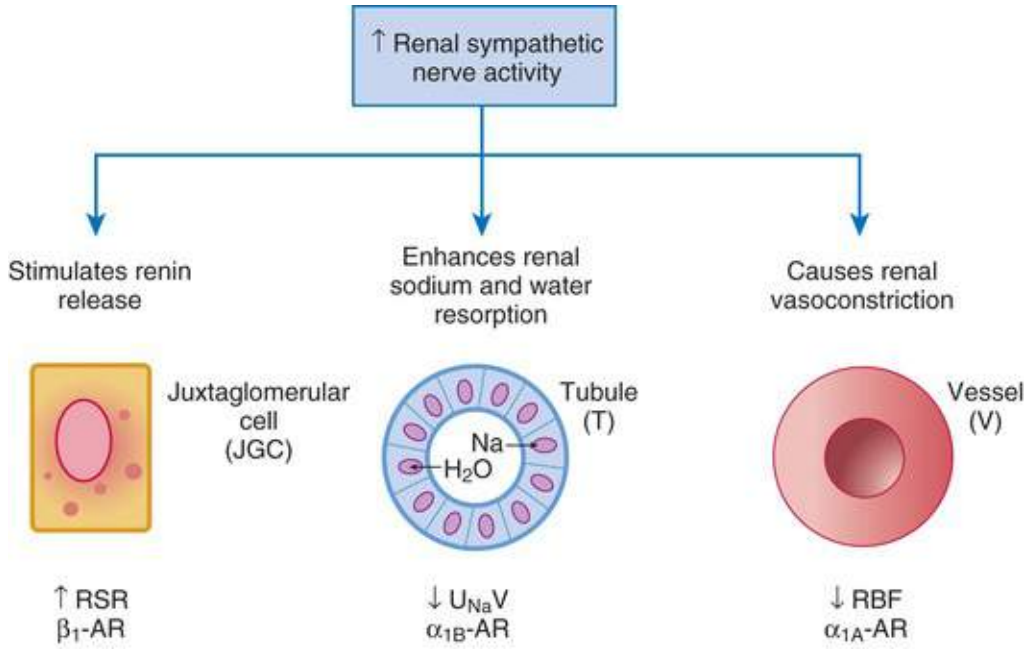


FIGURE 46.6 Effects of increased renal sympathetic nerve activity on the three renal neuroeffectors: juxtaglomerular granular cells (JGC) with increased renin secretion rate (RSR) via stimulation of the β_1-adrenoceptors (AR); renal tubular epithelial cells (T) with increased renal tubular sodium reabsorption and decreased urinary sodium excretion (UNaV) via stimulation of α_{1B} AR; and the renal vasculature (V) with decreased renal blood flow (RBF) via stimulation of α_{1A} AR. (From DiBona GF. Physiology in perspective: the wisdom of the body. Neural control of the kidney. Am J Physiol Regul Integr Comp Physiol 2005;289:R633.)

Overactivity of the sympathetic nervous system may play a greater role in the initiation of primary hypertension than in its progression.[25] A sympathetic component may contribute to the pathogenesis of hypertension associated with obesity, sleep apnea, metabolic syndrome, chronic kidney disease (CKD), heart failure, and immunosuppressive therapy with calcineurin inhibitors such as cyclosporine. Increased sympathetic activity may also drive some drug-resistant hypertension.[26] In these conditions, central sympathetic activation can result from deactivation of inhibitory neural inputs (e.g., baroreceptors), activation of excitatory neural inputs (e.g., carotid body chemoreceptors, renal afferents), or from circulating angiotensin II (A II), which activates pools of excitatory brainstem neurons without a blood-brain barrier (**see Fig. 46.5**).

In hypertension the baroreceptors reset to defend a higher level of BP. Baroreflex control of sinus node function is abnormal even in mild hypertension, but baroreflex control of SVR and BP is well preserved until diastolic function is impaired.[25] Complete baroreflex failure causes labile hypertension, most often seen in throat cancer survivors as a late complication of radiation therapy, which causes a gradual destruction of the baroreceptor nerves (**see Chapter 99**). Partial baroreceptor dysfunction is common in elderly hypertensive patients and typically manifests with a triad of orthostatic hypotension, supine hypertension, and symptomatic postprandial hypotension—the last initiated by splanchnic pooling after carbohydrate-rich meals.

Obesity-Related Hypertension

With weight gain, reflex sympathetic activation is an important compensation to burn fat, but at the expense of sympathetic overactivity in target tissues such as vascular smooth muscle and kidney that

produces hypertension. Hypertensive patients with the metabolic syndrome have near-maximal rates of sympathetic firing. Although the sympathetic activation is associated with insulin resistance, the precise stimulus to sympathetic outflow is unknown; candidates include leptin, other adipokines, and angiotensin II (A II). Why weight loss improves hypertension much less than diabetes remains unknown.[25]

Obstructive Sleep Apnea as a Cause of Neurogenic Hypertension

Patients with obstructive sleep apnea (OSA) can have greatly elevated plasma and urine catecholamine levels, mimicking those seen in patients with pheochromocytoma (**see Chapters 87 and 92**). With repeated arterial desaturation during apneas, activation of carotid body chemoreceptors triggers BP surges throughout the night and resets the chemoreceptor reflex; daytime normoxia is misinterpreted as hypoxia, producing sustained reflex sympathetic activation and hypertension even during waking hours. Frequent nocturnal arousal with fragmented sleep also triggers daytime sympathetic excitation regardless of OSA severity.[27] The OSA accelerates the emergence of hypertensive complications such as atrial fibrillation and stroke.[28]

Renal Mechanisms

A fundamental abnormality in hypertension is an acquired or inherited defect in the kidneys' ability to excrete the excessive sodium load imposed by a modern diet high in salt. Humans evolved in a low-sodium/high-potassium environment, and the human kidney handles poorly exposure to high sodium and low potassium. Renal sodium retention expands the plasma volume, increasing cardiac output and triggering autoregulatory responses that increase SVR. Salt retention also augments the smooth muscle contraction produced by endogenous vasoconstrictors. Beyond raising BP, a high-salt diet also accelerates hypertensive target-organ damage.

The typical U.S. diet is high in NaCl, with most dietary salt coming from processed food (**see Chapter 49**). Whereas men consume an estimated 10.7 g of NaCl daily, and women 7.3 g, the U.S. Department of Agriculture and Department of Health and Human Services recommend a daily intake of less than 5.8 g of NaCl (2300 mg of sodium) for the general population, and 3.7 g for persons with hypertension or prehypertension. If the food industry agreed to a palatable reduction in the salt content of processed food, reducing dietary salt by 3 g per day likely would reduce the annual number of new cases of coronary heart disease by 60,000 to 120,000, new cases of stroke by 32,000 to 66,000, and new cases of MI by 54,000 to 99,000, and would reduce the annual number of deaths from any cause by 44,000 to 92,000. All segments of the population would benefit, with blacks benefiting proportionately more, women benefiting particularly from stroke reduction, older adults from reductions in coronary heart disease events, and younger adults from lower mortality rates.[29]

Resetting of Pressure-Natriuresis

In normotensive individuals, BP elevation invokes an immediate increase in renal sodium excretion to shrink plasma volume and to return BP to normal. In hypertension, this pressure-natriuresis curve is shifted to the right, and in salt-sensitive hypertension, the slope is reduced. Resetting of pressure-natriuresis prevents the return of BP to normal so that fluid balance is maintained, but at the expense of high BP. Pressure-natriuresis causes profound nocturia in rare patients with pure autonomic failure who have supine nocturnal hypertension. Nocturia also may be an unrecognized symptom of uncontrolled primary hypertension.[30]

Low Birth Weight

Because of fetal undernutrition, low birth weight with reduced nephrogenesis increases the risk for development of adult salt-dependent hypertension. Hypertensive adults have fewer glomeruli per kidney but very few obsolescent glomeruli, suggesting that nephron dropout with decreased total filtration surface area is the cause and not the consequence of the hypertension. When low-birth-weight children consume a fast-food diet, they are susceptible to rapid postnatal weight gain, leading to adolescent obesity and hypertension.

Genetic Contributions

Animal and human studies have implicated an important genetic contribution to salt-sensitive hypertension. Rats with inbred defects in the kidneys' ability to excrete sodium remain relatively normotensive on a sodium-restricted diet, but become severely hypertensive when fed a high-sodium diet—a model of salt-sensitive hypertension that can be cured by interstrain renal transplantation. A similar gene-environment interaction may explain why persons of sub-Saharan African ancestry remain normotensive on a sodium-restricted diet, but are predisposed to hypertension when they encounter a high-sodium diet. Ancestral gene analysis has not defined the molecular basis for salt-dependent human hypertension, but has identified a common genetic predisposition of African-origin populations to all nondiabetic forms of CKD, including focal glomerulosclerosis, acquired immunodeficiency syndrome (AIDS), and hypertensive nephropathy. Sequence variations in the *APOL1* gene associate strongly with African ancestry and confer a twofold to fourfold increased risk of end-stage renal disease (ESRD). In such patients, strict control of hypertension may slow progression to ESRD.[31] As the kidneys fail, BP becomes increasingly salt dependent.

Vascular Mechanisms

Alterations in the structure and function of small and large arteries are pivotal in the pathogenesis and progression of hypertension.

Endothelial Cell Dysfunction

The endothelial lining of blood vessels is critical to vascular health and constitutes a major defense against hypertension (**see Chapter 57**). Dysfunctional endothelium displays impaired release of endothelium-derived relaxing factors (e.g., nitric oxide, endothelium-derived hyperpolarizing factor) and enhanced release of endothelium-derived constricting, proinflammatory, prothrombotic, and growth factors[32] (**Fig. 46.7**).

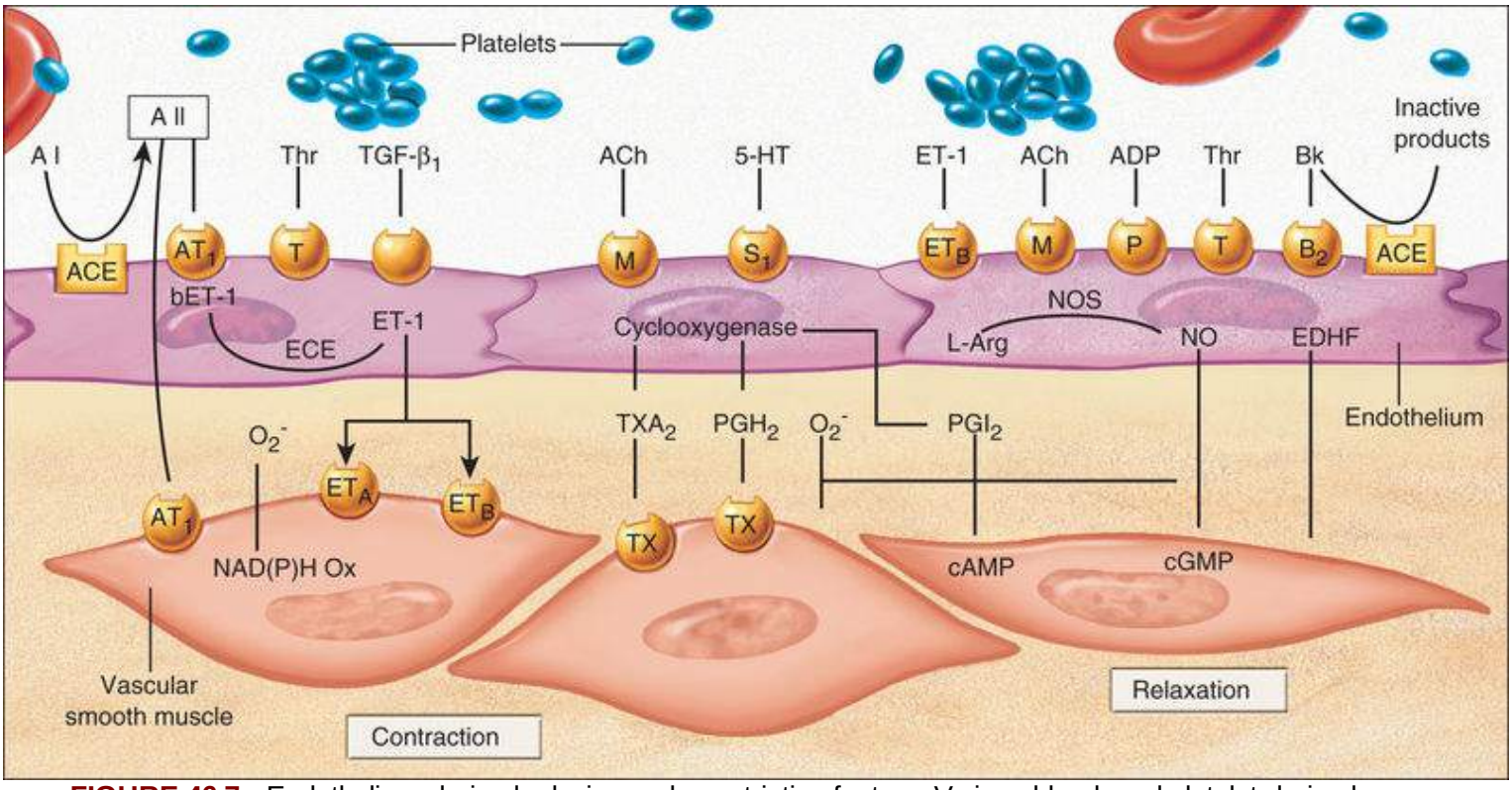


FIGURE 46.7 Endothelium-derived relaxing and constricting factors. Various blood- and platelet-derived substances can activate specific receptors (*orange circles*) on the endothelial membrane to release relaxing factors such as nitric oxide (NO), prostacyclin (PGI_2), and an endothelium-derived hyperpolarizing factor (EDHF). Contracting factors also are released, such as endothelin (ET-1), angiotensin (A II), and thromboxane A_2 (TXA_2), as well as prostaglandin H_2 (PGH_2). ACE, Angiotensin-converting enzyme; 5-HT, serotonin; Bk, bradykinin; ECE, endothelin-converting enzyme; L-Arg, L-arginine; NOS, nitric oxide synthase; O_2^-, superoxide; TGF-β_1, transforming growth factor β_1; Thr, thrombin. (From Ruschitzka F, Corti R, Noll G, et al. Arationale for treatment of endothelial dysfunction in hypertension. J Hypertens 1999;17[Suppl 1]:25.)

The endothelium of all blood vessels expresses the enzyme nitric oxide synthase (NOS), which can be activated by bradykinin, acetylcholine (ACh), or cyclic laminar shear stress. NOS generates nitric oxide (NO), a volatile gas that diffuses to the adjacent vascular smooth muscle and activates a series of G protein kinases that culminate in vasodilation (**Fig. 46.7**). In humans, endothelium-dependent vasodilation can be assessed by measuring increases in the large artery (forearm or coronary) diameter after intra-arterial infusion of ACh or release of ischemia (e.g., arrested forearm circulation) or a sudden elevation in BP (cold pressor test).

Mounting evidence indicates that smoldering vascular inflammation contributes to the genesis and complications of high BP. C-reactive protein (CRP), an easily measured serum biomarker, reports on inflammation.[33] Cross-sectional studies show strong correlations between elevated CRP and arterial stiffness and elevated pulse pressure. Longitudinal studies implicate elevated CRP levels as a risk marker for new-onset hypertension and accelerated progression of hypertensive target-organ disease, possibly beyond that explained by BP elevation alone (**see Chapters 9 and 45**).

Oxidative stress also contributes to endothelial cell vasodilator dysfunction in hypertension. Superoxide anion and other reactive oxygen species (ROS) quench NO, thereby reducing its bioavailability.[32] Several pathways produce superoxide in arteries: nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, which are expressed in all vascular cell types and activated by circulating A II; NOS, which produces superoxide only when an important cofactor (tetrahydrobiopterin)

is deficient, a process known as NOS uncoupling; xanthine oxidase, which produces uric acid; and mitochondria. Generation of ROS by xanthine oxidase accounts for the association of hyperuricemia with endothelial dysfunction and hypertension. The xanthine oxidase inhibitor allopurinol can normalize BP in two thirds of adolescents with hyperuricemia and recently diagnosed hypertension and can rectify prehypertension in obese adolescents,[34] but cannot be recommended as a routine antioxidant because of its side effect profile. The weak oral antioxidants vitamins C and E have little effect on BP.

Vascular Remodeling.

Over time, endothelial cell dysfunction, neurohormonal activation, and elevated BP cause remodeling of blood vessels, which further perpetuates hypertension[35,36] (**Fig. 46.8**). An increase in the medial thickness relative to the lumen diameter (increased media-to-lumen ratio) is the hallmark of hypertensive remodeling in small and large arteries. Vasoconstriction initiates small-artery remodeling, which normalizes wall stress. Normal smooth muscle cells (SMCs) rearrange themselves around a smaller lumen diameter, a process termed *inward eutrophic remodeling*. The media/lumen ratio increases, but the medial cross-sectional area remains unchanged. By decreasing lumen diameter in the peripheral circulation, inward eutrophic remodeling increases SVR, the hemodynamic hallmark of diastolic hypertension.

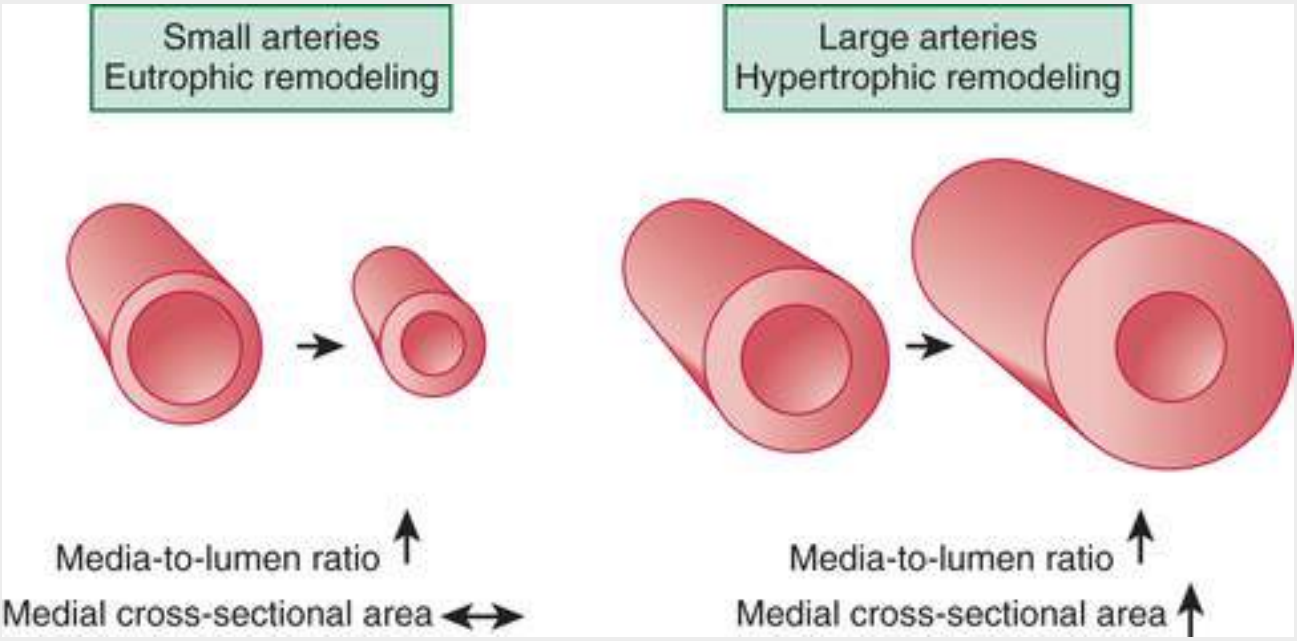


FIGURE 46.8 Vascular remodeling of small and large arteries in hypertension. Diagrams represent arteries in cross section showing the tunica adventitia, tunica media, and tunica intima. (Modified from Duprez DA: Role of renin-angiotensin-aldosterone system in vascular remodeling and inflammation: Aclinical review. J Hypertens 24:983, 2006.)

In contrast, large-artery remodeling is characterized by the expression of hypertrophic genes, triggering increases in medial thickness and media/lumen ratio. Such hypertrophic remodeling involves an increase in the size of vascular SMCs and an accumulation of extracellular matrix proteins, such as collagen, due to activation of transforming growth factor (TGF)-β. The resultant large-artery stiffness is the hemodynamic hallmark of ISH. Antihypertensive therapy may not provide optimal cardiovascular protection unless it prevents or reverses vascular remodeling by normalizing hemodynamic load, restoring normal endothelial cell function, and eliminating the underlying neurohormonal activation.[35]

Hormonal Mechanisms: Renin-Angiotensin-Aldosterone System

Activation of the renin-angiotensin-aldosterone system (RAAS) is one of the most important mechanisms contributing to endothelial cell dysfunction, vascular remodeling, and hypertension (**Fig. 46.9**; **see also Fig. 23.3**). Renin, a protease produced solely by the renal juxtaglomerular cells, cleaves angiotensinogen (renin substrate produced by the liver) to A I, which is converted to A II by angiotensin-converting enzyme (ACE). ACE is most abundant in the lungs but is also present in the heart and systemic vasculature (tissue ACE). Chymase, a serine protease in the heart and systemic arteries, provides an alternative pathway for conversion of A I to A II. The interaction of A II with G protein–coupled AT1 receptors activates numerous cellular processes that contribute to hypertension and accelerate hypertensive end-organ damage (**Fig. 46.9**), including vasoconstriction, ROS generation, vascular inflammation, vascular/cardiac remodeling, and production of aldosterone, the principal mineralocorticoid. Aldosterone, A II, and prorenin activate multiple signaling pathways that can damage vascular health and cause hypertension.

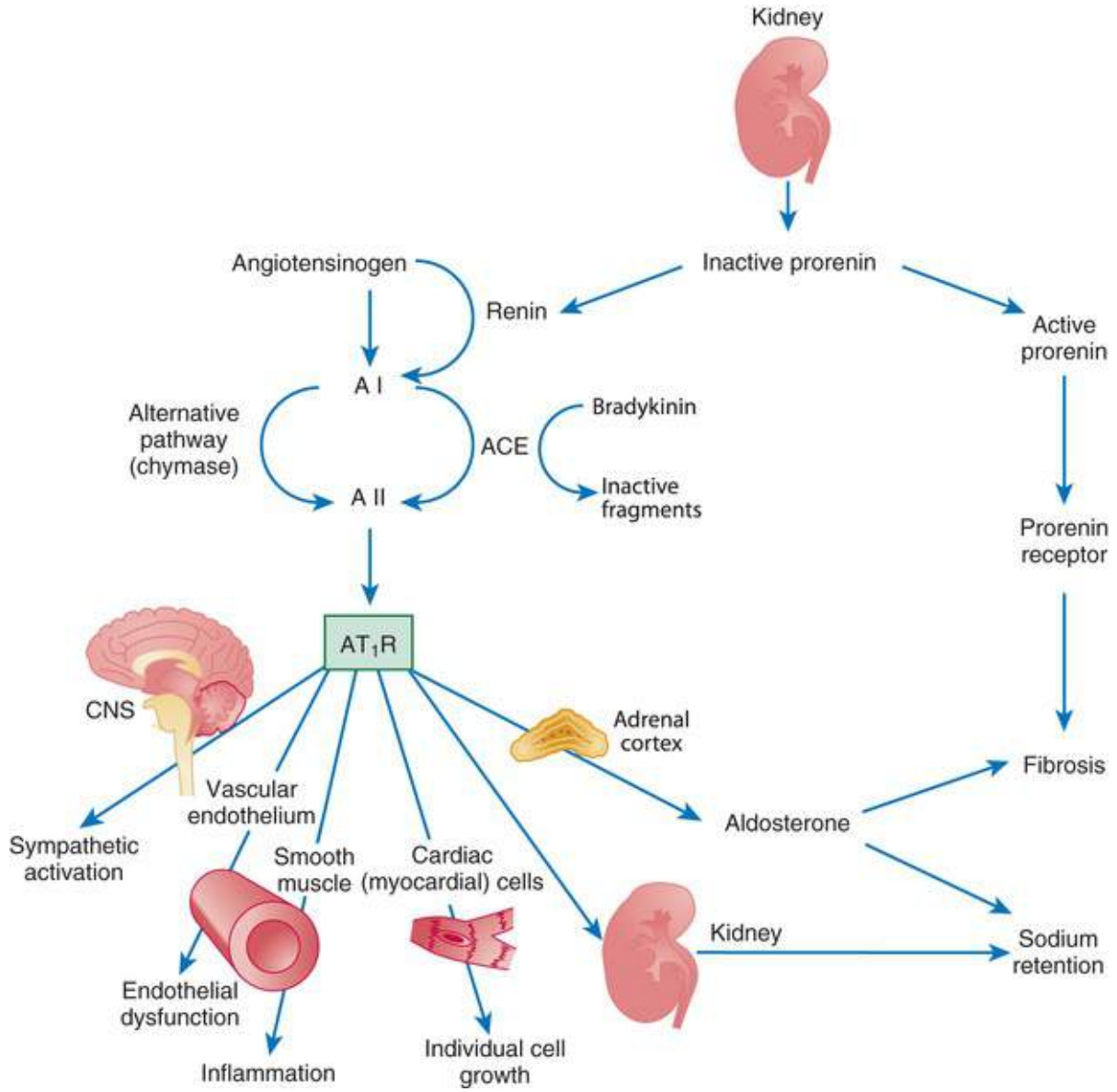


FIGURE 46.9 The renin-angiotensin-aldosterone system. A I, Angiotensin I; A II, angiotensin II; ACE, angiotensin-converting enzyme; AT_1R, angiotensin type 1 receptor; CNS, central nervous system.

RAAS activation is a major homeostatic mechanism to counter hypovolemic hypotension (as with hemorrhage or salt and water deprivation). Interaction of aldosterone with cytosolic mineralocorticoid receptors in the renal collecting duct cells recruits sodium channels from the cytosol to the surface of the renal epithelium. The recruited epithelial sodium channels (ENaCs) increase Na^+ reabsorption, thereby reexpanding plasma volume. Conversely, modern high-salt diets should engender continual feedback inhibition of the RAAS. Suppression of serum aldosterone triggers sequestration of ENaCs by endocytosis and increased renal Na^+ excretion, thereby shrinking plasma volume to protect against salt-sensitive hypertension.

Thus, in the setting of high dietary sodium and elevated BP, the RAAS should be completely suppressed, and any degree of RAAS activity is inappropriate. In normotensive individuals the risk for development of hypertension increases with increasing levels of serum aldosterone that are well within the normal range. By stimulating mineralocorticoid receptors in the heart and kidney, circulating aldosterone may contribute to the development of cardiac and renal fibrosis in hypertension.[37] Also, aldosterone contributes to sympathetic overactivity by stimulating mineralocorticoid receptors in the brainstem.

Two main angiotensin receptor types (AT) are known. AT1 receptors are widely expressed in the vasculature, kidneys, adrenals, heart, liver, and brain. A I receptor activation explains most of the hypertensive actions of A II. Furthermore, enhanced AT1-mediated signaling provides a central mechanistic explanation for the frequent coexistence of elevated BP with insulin resistance and atherosclerosis and constitutes a major therapeutic target for interruption of every step in CVD progression, from vascular remodeling and formation of atherosclerotic plaque to stroke, MI, and death (**Fig. 46.10**).

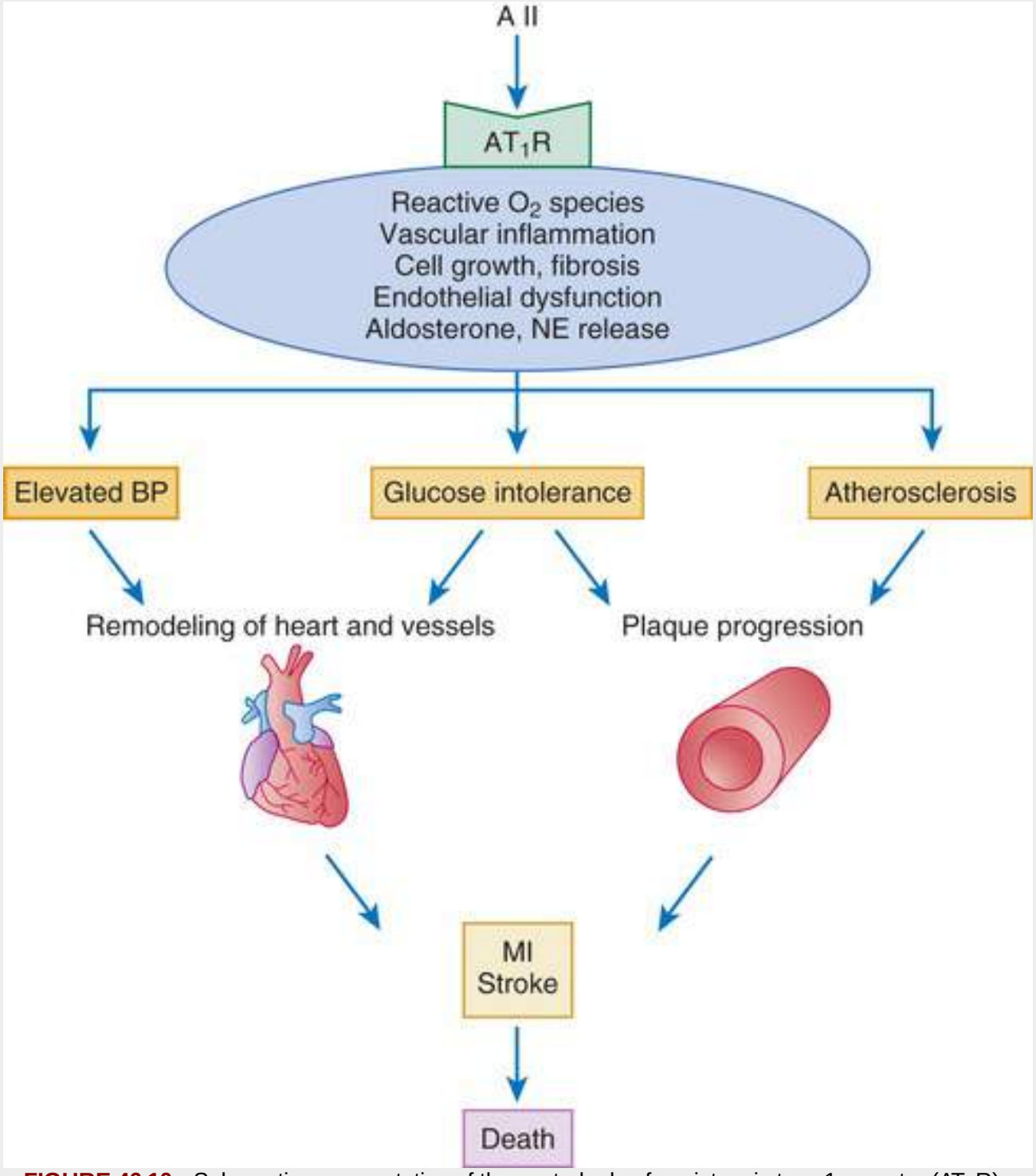
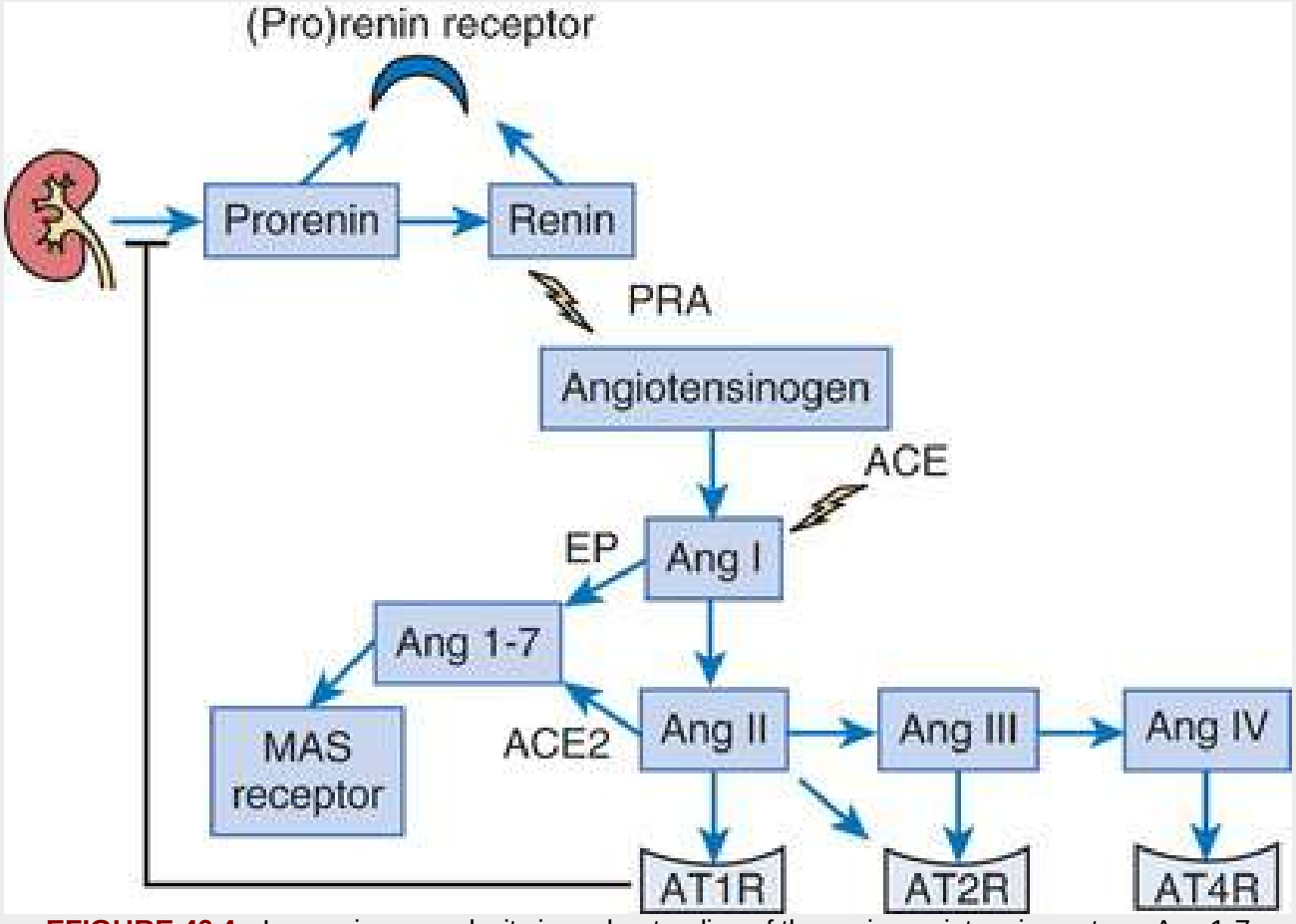


FIGURE 46.10 Schematic representation of the central role of angiotensin type 1 receptor (AT_1R)–mediated signaling in cardiovascular disease progression. A II, Angiotensin II; MI, myocardial infarction; NE, norepinephrine.

In contrast, AT2 receptors distribute widely in the fetus, but in adults localize only in the adrenal medulla, uterus, ovaries, vascular endothelium, and distinct brain regions. In rodents, AT2 receptor activation opposes some of the deleterious effects of AT1 receptors by promoting endothelium-dependent vasodilation by bradykinin and NO pathways. Animal studies have suggested that AT2 receptors can be profibrotic, but their role in human hypertension remains speculative (**eFig. 46.4**).



EFIGURE 46.4 Increasing complexity in understanding of the renin-angiotensin system. Ang 1-7 interacts with a specific G protein–coupled MAS receptor and generally opposes the vasoconstrictor and proliferative actions of Ang II. ACE, Angiotensin-converting enzyme; ACE2, type 2 angiotensin converting enzyme; Ang I, angiotensin I; Ang II, angiotensin II; Ang III, angiotensin III; Ang IV, angiotensin IV; Ang 1-7, angiotensin one through seven; AT1R, type 1 angiotensin receptor; AT2R, type 2 angiotensin receptor; AT4R, type 4 angiotensin receptor; EP, endopeptidase; PRA, plasma renin activity.

Prorenin is both the inactive precursor of renin and also binds to a prorenin receptor that increases TGF-β production, leading to collagen deposition and fibrosis. All RAAS blockers trigger large, reactive increases in prorenin production that may counter some of the cardiovascular protection afforded by reduced AT1 receptor activation.

Hypertension as an Immunologic Disorder.

Macrophages and T cells accumulate and promote inflammation in the central nervous system (CNS), perivascular fat, heart, and kidneys of mice with experimental hypertension, particularly that caused by infusion of A II. Renal sympathetic activation initiates A II–induced hypertension, whereas systemic T cell activation in perinephric and perivascular fat is key in progression of experimental hypertension[38] (**Fig. 46.11**). Translation of this preclinical work to human hypertension is beginning.[39]

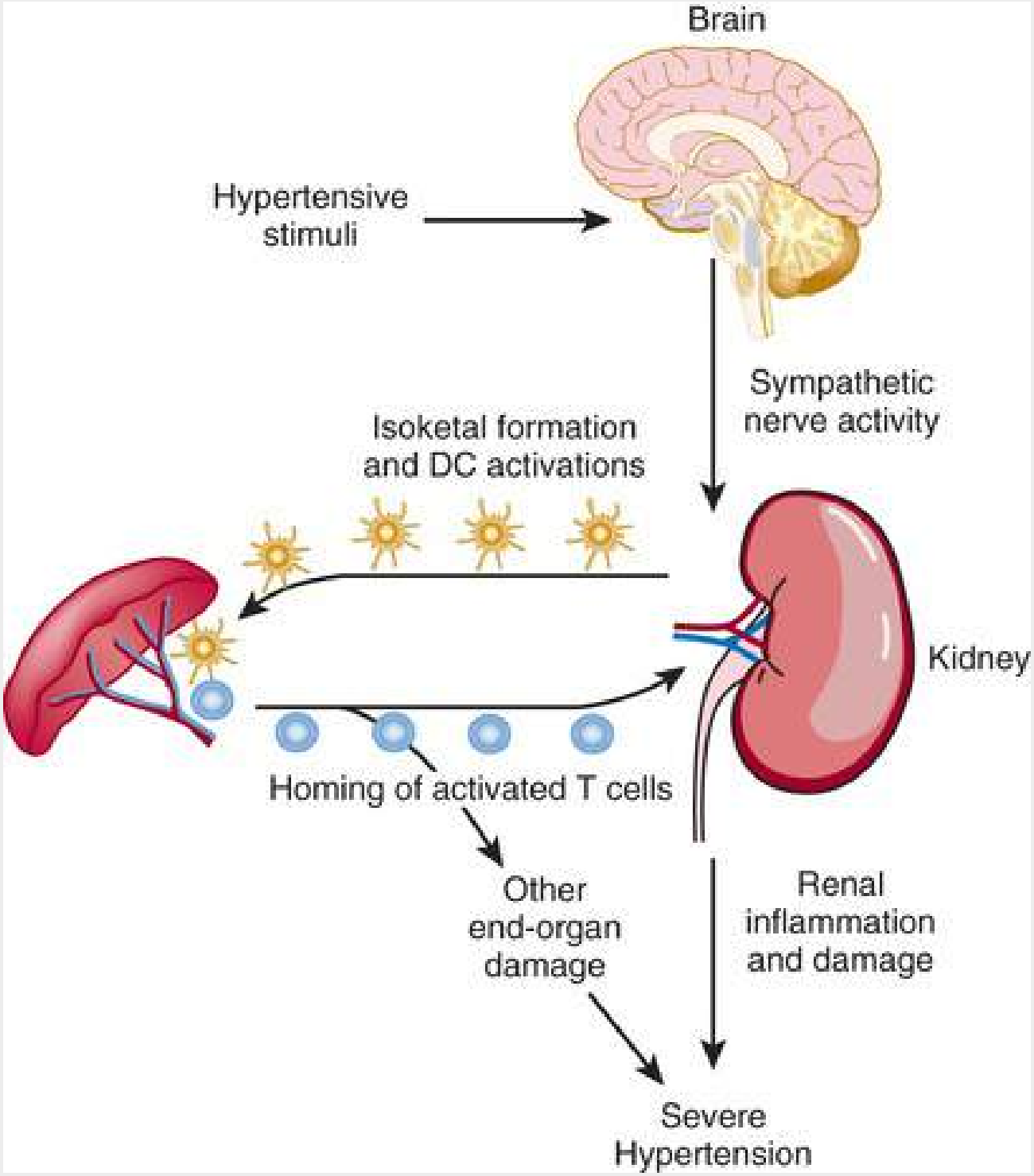


FIGURE 46.11 Proposed scheme for the contribution of renal sympathetic nerves in the activation of adaptive immunity in hypertension. Hypertensive stimuli such as angiotensin II and sodium act in the central nervous system to increase renal sympathetic nerve activity. The sympathetic activation promotes inflammation and damage in the kidney and other organs (especially the systemic vasculature) leading to severe hypertension. The mechanism involves accumulation of proteins oxidized by high reactive gamma-ketoaldehydes termed *isoketals* in antigen-presenting *dendritic cells* (DC), which in turn promote T cell activation. The activated T cells are homed by local expression of adhesion molecules (e.g., VCAM-1) to perinephric fat (and perivascular fat), where they produce proinflammatory cytokines (e.g., IL-17, TNF-α) causing renal (and vascular) inflammation and damage. (From American Heart Association; Xiao L, Kirabo A, Wu J, et al. Renal denervation prevents immune cell activation and renal inflammation in angiotensin II-induced hypertension. Circ Res 2015;117:547.)

Initial Evaluation of the Hypertensive Patient

Hypertension is the “silent killer,” an asymptomatic chronic disorder that, undetected and untreated, silently damages the blood vessels, heart, brain, and kidneys. However, it may not be entirely asymptomatic. In double-blind placebo-controlled trials, patients' quality of life rating often improves with successful drug treatment of hypertension. Hypertension control can improve exertional dyspnea caused by diastolic dysfunction, nocturia caused by resetting of pressure-natriuresis, and possibly even erectile dysfunction caused by endothelial dysfunction.

The initial evaluation for hypertension should accomplish three goals: (1) the accurate measurement of BP; (2) the assessment of the patient's global cardiovascular disease (CVD) risk; and (3) the detection of secondary (i.e., identifiable and potentially curable) forms of hypertension.

Measurement of Blood Pressure

There are now four approaches to BP measurement: (1) conventional office BP, (2) automated office BP, (3) home monitoring, and (4) ambulatory BP monitoring.[40] In all cases, BP should be measured with appropriate technique using validated devices with “AA” ratings from the British Hypertension Society protocol on the Educational Trust website: http://dableducational.org/. **Table 46.1** provides the cutoff values for the diagnosis of hypertension.

TABLE 46.1

Criteria for Diagnosis of Hypertension Using Different Methods of Blood Pressure (BP) Measurement (Systolic and/or Diastolic)

METHOD	SYSTOLIC (mm Hg)	DIASTOLIC (mm Hg)
Office		
Conventional office BP	≥140	≥90
Unattended automated office BP (AOBP)	≥135	≥85
Home		
Home BP	≥135	≥85
Ambulatory BP Monitoring (ABPM)		
Daytime (awake)	≥135	≥85
Nighttime (asleep)	≥120	≥70
24 or 48 hour (average)	≥130	≥80

Modified from Gabb GM, Mangoni A, Anderson CS, et al. Guideline for the diagnosis and management of hypertension in adults—2016. Med J Aust 2016;205:85.

Conventional Auscultatory Office Blood Pressure.

Auscultatory measurement of BP by medical personnel is the conventional approach to the diagnosis of hypertension in the United States and the method used, until recently, in most RCTs. The latest 2016 hypertension guidelines from the National Heart Foundation of Australia stages office BP by the average of two or more readings taken at two or more office visits[41] (**Table 46.2**). The BP should be measured at least twice after 5 minutes of rest, with the patient seated in a chair, the back supported, and the arm bare and at heart level. A large adult-sized cuff should be used to measure BP in overweight adults, because the standard-sized cuff can spuriously elevate readings. Tobacco and caffeine should be avoided for at least 30 minutes. BP should be measured in both arms and after 5 minutes of standing, the latter to exclude a significant postural fall in BP, particularly in older persons and in those with diabetes or other conditions (e.g., Parkinson disease) that predispose to autonomic insufficiency. In practice, conventional office-based readings often are inaccurate because of too common measurement errors, the small number

of readings, the “white coat” (alerting) reaction, and the large number of factors that influence BP outside the medical office.

TABLE 46.2

Staging of Office Blood Pressure*

BP STAGE	SYSTOLIC (mm Hg)	DIASTOLIC (mm Hg)
Normal	<120	<80
Prehypertension (high-normal)	120-139	80-89
Stage 1 (mild) hypertension	140-159	90-99
Stage 2 (moderate) hypertension	160-179	
Stage 3 (severe) hypertension	≥180	≥110
Isolated systolic hypertension	≥140	<90

*Calculation of seated BP is based on the mean of two or more readings on two separate office visits.

Modified from Gabb GM, Mangoni A, Anderson CS, et al. Guideline for the diagnosis and management of hypertension in adults—2016. Med J Aust 2016;205:85.

Automated Office Blood Pressure (AOBP).

The Systolic Blood Pressure Intervention Trial (SPRINT) was the first to utilize unattended AOBP.[4] An oscillometric monitor was set to take three readings at 1-minute intervals after the patient was unattended by medical staff and unaccompanied by family members in the examination room for 5 minutes.[42] Other protocols take five readings at 1-minute intervals (or on STAT mode) and average all five readings or the last three readings.[6] The 2016 hypertension guidelines from both Australia and Canada (where AOBP was pioneered by Dr. Martin Myers) endorse AOBP as the preferred method over conventional office BP because it (1) minimizes the white coat reaction, (2) correlates better with home or awake ambulatory BP, and (3) eliminates digit preference.[41,43] On average, AOBP is 15/10 mm Hg lower than conventional office BP, but there are large interindividual differences.[44] Hypertension is diagnosed when the AOBP is 135/85 mm Hg or higher.

Home Blood Pressure Monitoring (HBPM).

Office BP can both overestimate and underestimate a person's BP measured at home. HBPM improves medication adherence by actively involving patients in their own medical care. The latest guidelines[45] recommend that patients be carefully instructed to perform HBPM as follows: rest quietly for 5 minutes in the seated position with the back supported and the arm supported on a table at heart level; take two readings in the morning and two readings in the evening for at least 3 consecutive days (preferably 7 days). The first day's readings should be discarded as being falsely elevated, and all other readings be averaged to make clinical decisions. Hypertension is diagnosed when the average home BP is 135/85 mm Hg or higher. Each patient's monitor needs to be checked in the office for accuracy and cuff size. Monitors with sizable memory storage eliminate reporting bias. Wrist monitors are inaccurate and not recommended. The oscillometric method may not work well in patients with atrial fibrillation or frequent extrasystoles. Some patients become obsessive about taking their BP and must be advised to stop self-measurement altogether.

Ambulatory Blood Pressure Monitoring

Ambulatory BP monitoring (ABPM) is the “gold standard”: it provides automated measurements of BP during a 24-hour or (better) a 48-hour period while patients are engaged in their usual activities, including sleep. Prospective studies show that ABPM predicts fatal and nonfatal MI and stroke better than standard office measurement does[46] (**Fig. 46.12**). Current consensus guidelines[47] define *out-of-office*

hypertension as average daytime BP of 135/85 mm Hg or higher, nighttime BP 120/70 mm Hg or higher, or 24-hour BP 130/80 mm Hg or higher (**see Table 46.1**). Moreover, optimal values are daytime BP less than 130/80, nighttime BP less than 110/65, and 24-hour BP less than 125/75. At least two measurements per hour should be taken during the patient's waking hours, and the average value of at least 14 measurements during that time confirms the diagnosis of hypertension.[45]

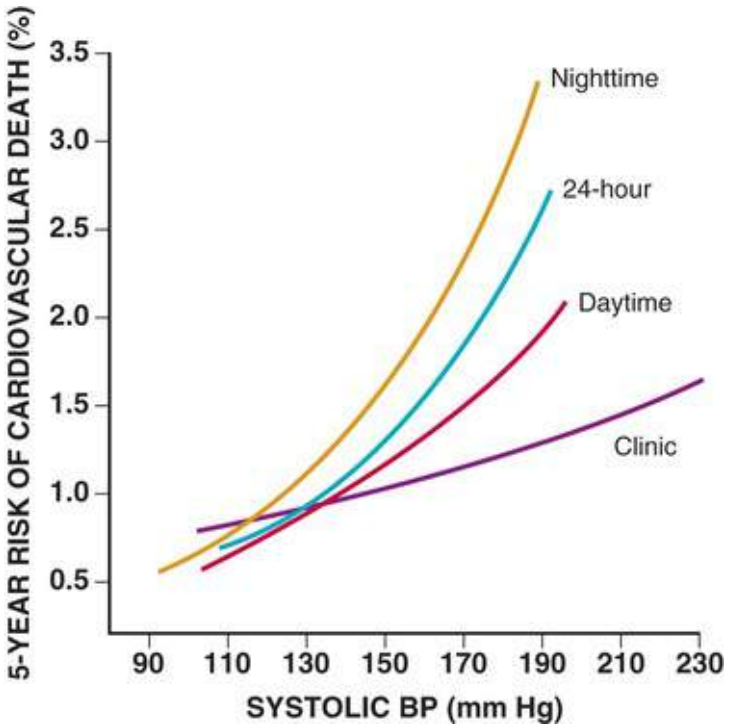


FIGURE 46.12 Superiority of ambulatory over office BP measurement as a measure of cardiovascular risk. Shown is the adjusted 5-year risk of cardiovascular death (number of deaths per 100 individuals) in the study cohort of 5292 patients for office BP and ambulatory BP. (From Dolan E, Santon A, Thijs L, et al. Superiority of ambulatory over clinic BP measurement in predicting mortality: The Dublin Outcome Study. Hypertension 2005;46:156.)

White Coat Hypertension

Patients with elevated office BP can have normal home and ambulatory BPs. If the daytime BP is less than 135/85 mm Hg and there is no target-organ damage despite consistently elevated office readings, the patient has “office-only” or “white coat” hypertension, caused by a transient adrenergic response to the measurement of BP only in the physician's office. Patients with white coat hypertension typically do not show exaggerated pressor reactions to stressful stimuli in their daily lives. Debate continues as to whether white coat hypertension is completely benign or confers an intermediate level of CVD risk.[48] White coat hypertension is benign if global CVD risk is low[49] (**Fig. 46.13A**), especially if the mean awake and sleep BP are optimal (<130/80 and <110/65 mm Hg, respectively). Both the prevalence and the severity of white coat hypertension increase sharply with age (**Fig. 46.13B**). In elderly persons, most of the CVD risk associated with white coat hypertension is caused by aging or isolated systolic hypertension incorrectly diagnosed as white coat hypertension.[49] Many patients do not have pure white coat hypertension but rather “white coat aggravation,” a white coat reaction superimposed on a milder level of out-of-office hypertension that nevertheless requires treatment (**eFig. 46.5**).

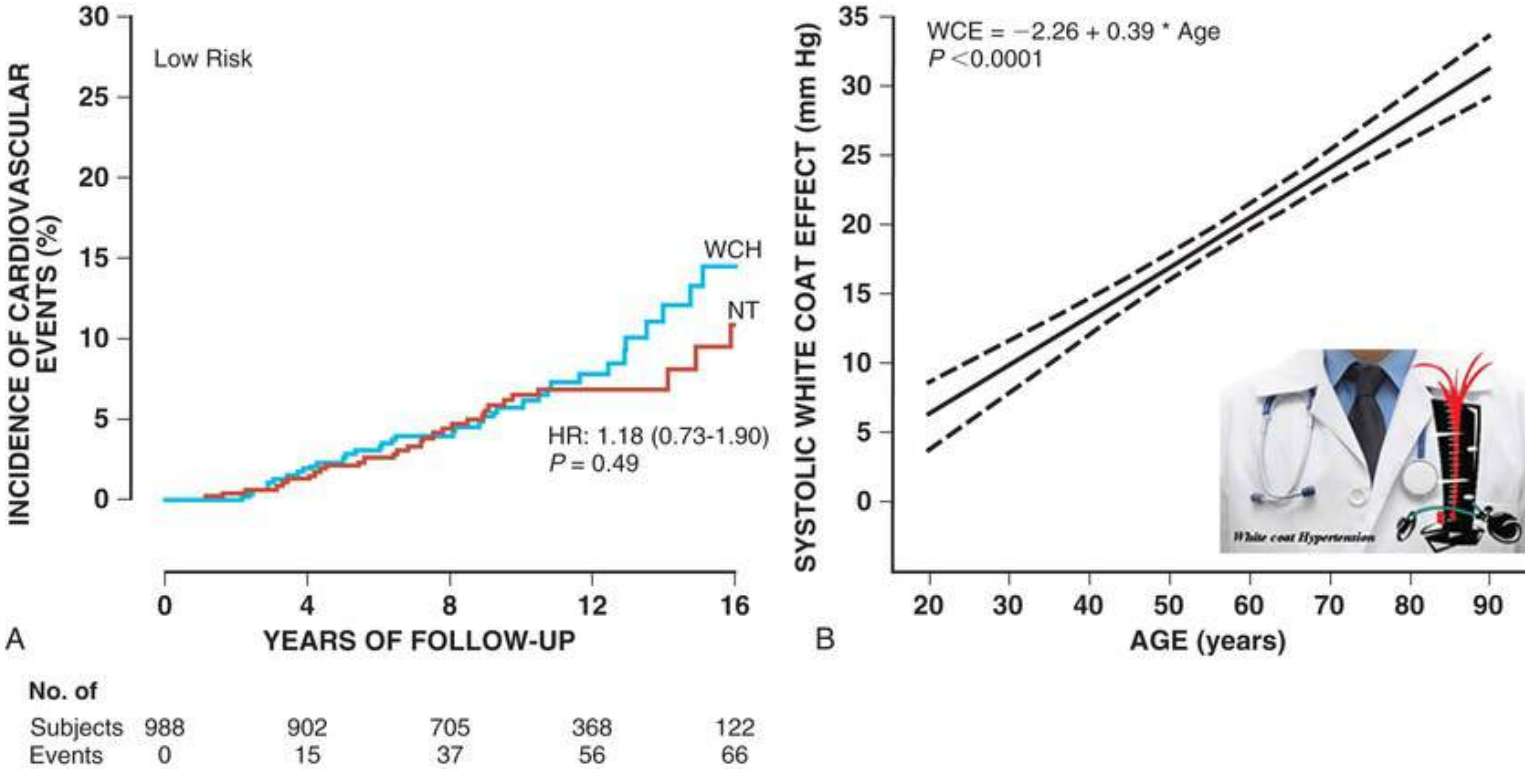
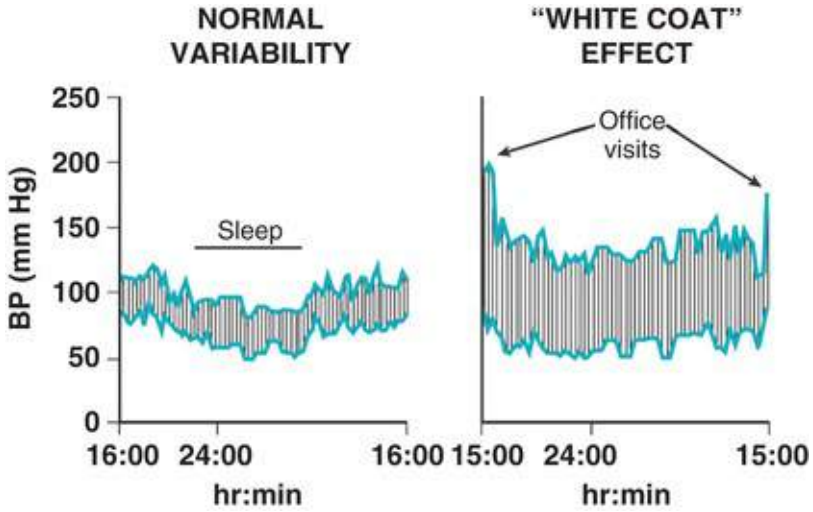


FIGURE 46.13 "White coat" hypertension from the 11-country International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes (IDACO). **A,** Kaplan-Meier cumulative incidence of cardiovascular disease (CVD) events in a cohort of patients with white coat hypertension (WCH) and low CVD risk compared with a cohort of approximately age-matched normotensive (NT) controls. **B,** Prevalence of WCH increases linearly with age. (From Franklin SS, Thijs L, Asayama K, et al. The cardiovascular risk of white-coat hypertension. J Am Coll Cardiol 2016;68:2033.)



EFIGURE 46.5 Twenty-four-hour ambulatory blood pressure (BP) monitor tracings in two different patients. **Left,** Optimal BP in healthy 37-year-old woman. Note the normal variability in BP, nocturnal dip in BP during sleep, and sharp increase in BP on awakening. **Right,** Pronounced "white coat" effect in an 80-year-old woman referred for evaluation of medically refractory hypertension. Documentation of the white coat effect prevented overtreatment of the patient's isolated systolic hypertension. (**Left,** Courtesy Dr. Ronald G. Victor, Heart Institute/Hypertension Center, Cedars-Sinai Medical Center, Los Angeles; **Right,** Provided by Dr. Wanpen Vongpatanasin, Hypertension Division, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas.)

Masked Hypertension

Also, ABPM is key to detect patients in whom office readings underestimate out-of-office BP, presumably because of sympathetic overactivity in daily life caused by job or home stress, tobacco abuse, or other adrenergic stimulation (OSA) that dissipates when they come to the office (**Fig. 46.14**). Such documentation prevents undertreatment of this *masked hypertension*, which unequivocally increases CVD risk, despite normal office BP readings.[47] Masked hypertension is defined as daytime BP of 135/85 mm Hg or higher or nighttime BP of 120/70 mm Hg or higher despite conventional office BP lower than 140/90 mm Hg. It is particularly common in African American patients and in patients with diabetes or those with CKD.[47] Masked hypertension is more common in patients being treated with BP medication than in untreated patients.[47] One reason is that some patients are more likely to take their BP medication the morning of their doctor visit. Another reason is that short-acting medication such as hydrochlorothiazide (HCTZ), when dosed in the morning, causes a sizable decrease in BP for the clinic visit but wears off before bedtime, providing no protection against nocturnal hypertension.[50]

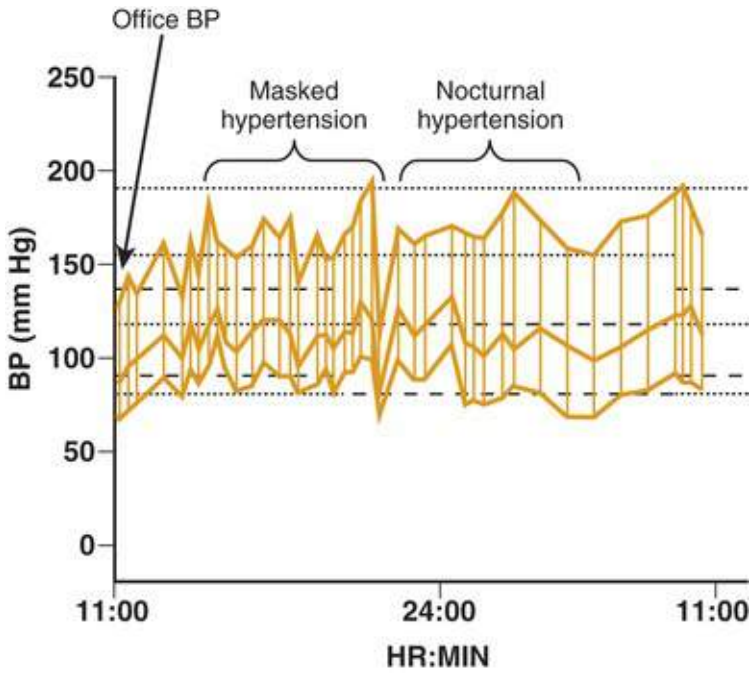


FIGURE 46.14 A 24-hour ambulatory BP recording in a patient with normal office BP but with masked daytime (awake) and masked nocturnal (asleep) hypertension. (From Dr. R. G. Victor, Cedars-Sinai Heart Institute/Hypertension Center, Los Angeles.)

ABPM is the only way to detect high BP during sleep (**Fig. 46.14**). BP normally dips during sleep and increases sharply when a person awakens and becomes active (**eFig. 46.5**). Nocturnal hypertension increases the aggregate hemodynamic load on the cardiovascular system and predicts CVD outcomes better than either daytime ambulatory BP or conventional office measurement[46] (**see Fig. 46.13**). Thus, high nocturnal BP, which accounts for most masked uncontrolled hypertension, is an especially ominous CVD risk factor.[51]

Indications for Ambulatory BP Monitoring

Currently, the U.S. Centers for Medicare and Medicaid Services (CMS) reimburses ABPM (CPT code 93784) only for one indication: elevated BP without a diagnosis of hypertension (ICD 796.2), that is, suspected white coat hypertension. The following strict criteria must be met: office BP of 140/90 mm Hg or higher on at least three separate office visits, with two measurements made at each visit; at least two

out-of-office BP readings lower than 140/90 mm Hg; and no evidence of target-organ damage. Based on a wealth of compelling evidence, expansion of the CMS-approved indications for ABPM is long overdue.

The 2015 U.S. Preventive Services Task Force concluded that "ABPM is the best method for diagnosing hypertension."[52] ABPM prevents unnecessary treatment of large numbers of patients with white coat hypertension and is a powerful CVD risk factor independent of the office BP. This task force document and the 2016 Canadian and 2016 Australian hypertension guidelines all recommend ABPM to confirm or reject the diagnosis of hypertension in the patients with an initially high office BP, except those with extremely high office BP of 180/110 mm Hg or higher. Also, a cogent argument can be made for ABPM in routine screening of high-risk populations to prevent undertreatment of masked hypertension: African American patients and those with diabetes or CKD. ABPM also is invaluable in the management of patients with apparent drug-resistant hypertension and in those with orthostatic hypotension or supine hypertension resulting from autonomic failure.

Cardiovascular Disease Risk Stratification

In hypertensive individuals, cardiovascular risk increases sharply with BP stage, but this is not the only factor to consider. The gradient between increasing levels of BP and CVD risk becomes progressively steeper as additional risk factors accumulate. Cardiovascular risk also increases dramatically with hypertensive target-organ damage and with additional CVD risk factors often present in patients with hypertension or prehypertension[53] (**Table 46.3**). The vast majority of hypertensive patients meet current criteria for initiation of lipid-lowering therapy (**see Chapter 48**). Thus the minimal laboratory testing required for the initial evaluation of hypertension includes determination of a fasting lipid panel, blood electrolyte values, fasting glucose concentration, and serum creatinine level with estimated glomerular filtration rate (GFR); hematocrit; spot urinalysis, including urine albumin/creatinine ratio; and resting 12-lead electrocardiogram (ECG). The patient's global cardiovascular risk can be estimated from the 2013 American Heart Association and American College of Cardiology (AHA/ACC) Pooled Cohort Calculator (http://tools.acc.org/ASCVD-Risk-Estimator/). **Chapter 45** addresses the process of tailoring goals of therapy to CVD risk.

TABLE 46.3

Risks Influencing Prognosis in Patients with Hypertension

Risk Factors for Cardiovascular Disease
Systolic and diastolic BP levels
Levels of pulse pressure (in elderly patients)
Age: men >55 years; women >65 years
Smoking
Dyslipidemia (LDL-C >115 mg/dL)
Impaired fasting glucose (102-125 mg/dL) or abnormal glucose tolerance test result
Family history of premature cardiovascular disease
Abdominal obesity
Diabetes mellitus
Subclinical Target Organ Damage
Left ventricular hypertrophy
Carotid wall thickening or plaque
Low estimated glomerular filtration rate ≤60 mL/min/1.73 m^2
Microalbuminuria
Ankle-brachial BP index <0.9
Established Target Organ Damage
Cerebrovascular disease: ischemic stroke, cerebral hemorrhage, transient ischemic attack
Heart disease: myocardial infarction, angina, coronary revascularization, heart failure
Renal disease: diabetic nephropathy, renal impairment
Peripheral arterial disease
Advanced retinopathy: hemorrhages or exudates, papilledema

BP, Blood pressure; *LDL-C,* low-density lipoprotein cholesterol.

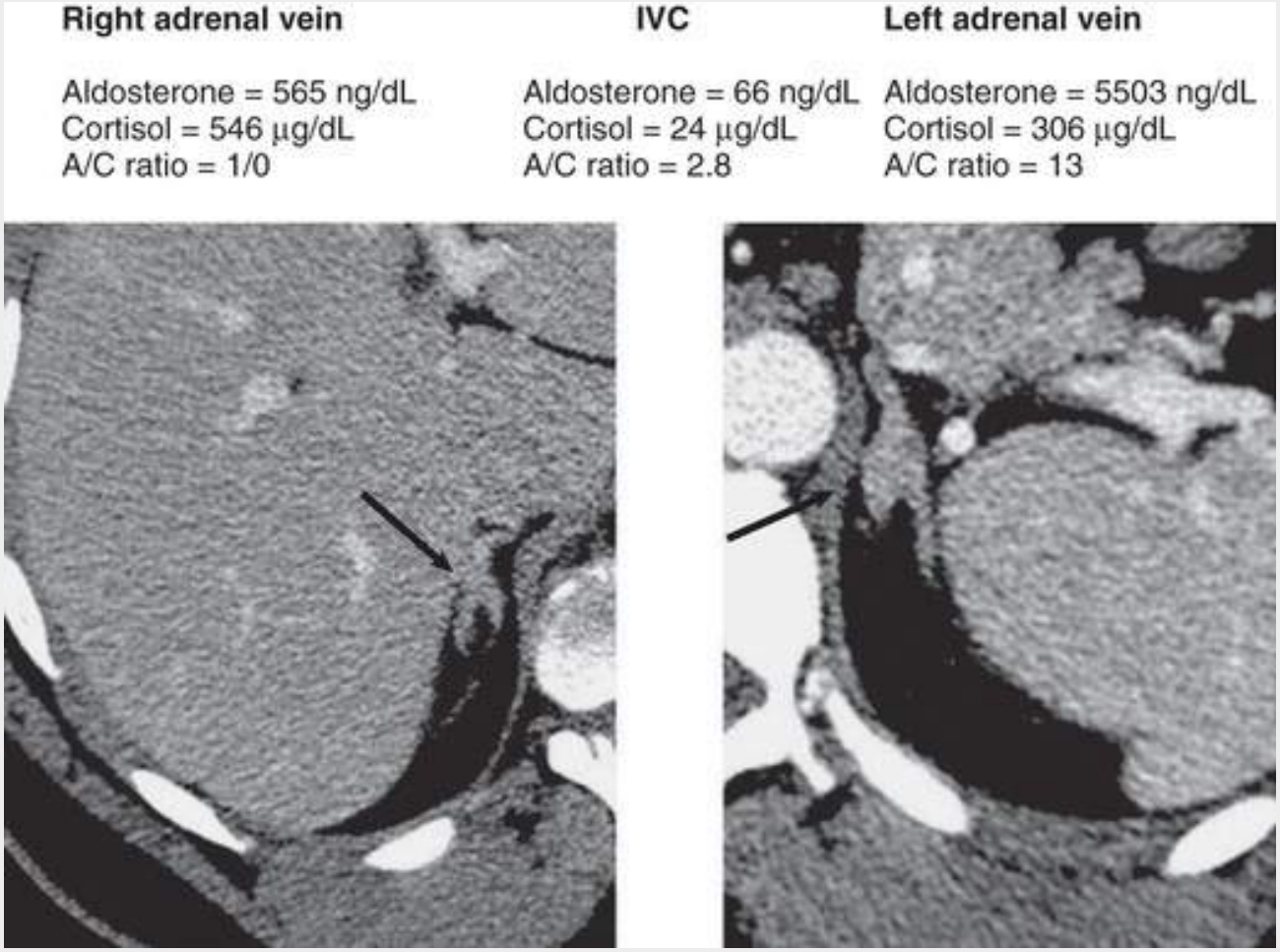
Modified from Mancia G, Fagard R, Narkkiewicz K, et al. 2013 ESH/ESC practice guidelines for the management of arterial hypertension: Blood Pressure 2014;23:3.

Methods to Improve CVD Risk Stratification in Hypertension

Visit-to-Visit Blood Pressure Variability

In addition to high average BP, mounting evidence indicates that high visit-to-visit variability in systolic BP independently predicts risk of CVD and CKD.[54] This fluctuation is most common in elderly patients and may represent a stiff aorta with impaired arterial baroreflexes and/or generalized anxiety disorder.[55]

Noninvasive Measurement of Aortic Stiffness and Central Aortic Pressure by Pulse Tonometry. Aortic stiffness is both the cause and the consequence of isolated systolic hypertension.[56] The central aortic pressure waveform is the sum of the pressure wave generated by the left ventricle and reflected waves from the peripheral circulation. When the large conduit arteries are healthy and compliant, the reflected wave merges with the incident wave during diastole, which enhances coronary blood flow. When the conduit arteries become stiff (as in ISH), however, pulse wave velocity increases such that the reflected and incident waves merge in systole, thereby augmenting systolic rather than diastolic pressure, which increases left ventricular afterload and reduces diastolic coronary flow. Sphymocor (AtCor Medical, Houston, Texas) is a commercial device that uses brachial artery BP and a generalized transfer function (proprietary software) to convert the radial waveform, measured by applanation tonography, to a derived central aortic BP waveform (**see eFig. 46.1**). This device has received FDA approval for clinical use (CPT code 93784). Pulse tonometry provides two principal measures of aortic stiffness that are typically increased in hypertension: pulse wave velocity and augmentation index.[40] Recently, a 24-hour ambulatory central BP monitor has received approval for clinical use.



EFIGURE 46.6 Computed tomography showing a left adrenal mass (*arrow*) and nodularity to the right adrenal gland. Adrenal vein sampling confirmed the diagnosis of a left aldosterone-producing adenoma. IVC, Inferior vena cava. (Case provided by Dr. Richard Auchus, Internal Medicine Department/Endocrinology Division, University of Michigan, Ann Arbor.)

Erectile Dysfunction.

Self-reported erectile dysfunction occurs in more than half of men with hypertension and independently predicts fatal and nonfatal cardiovascular events.[57]

Evaluation of Target-Organ Disease.

Traditionally, the complications of hypertension are viewed as *hypertensive* (caused by the increased level of BP per se) or *atherosclerotic* (caused by concomitant atherosclerosis), with BP elevation playing a variable role. This view is oversimplified, however, because both types of complications frequently coexist, as exemplified by hypertensive retinopathy[58] or hypertensive heart disease.

Pathogenesis of Hypertensive Heart Disease

Hypertension is a major risk factor not only for CAD, but also for left ventricular hypertrophy and heart failure.

Pressure Overload Hypertrophy

Left ventricular hypertrophy (LVH) is the anatomic hallmark of hypertensive heart disease. In hypertensive patients, LVH constitutes a powerful independent risk factor for heart failure (HF), ventricular arrhythmias and sudden cardiac death (SCD), ischemic stroke, atrial fibrillation, and embolic stroke.[59] It represents a failure to diagnosis and to treat hypertension effectively. Major advances have increased our understanding of the molecular signal transduction pathways underlying the hypertensive

myocardium.[60] These include myocyte hypertrophy *plus* medial hypertrophy of the intramyocardial coronary arterioles, collagen deposition leading to perivascular and interstitial fibrosis, capillary rarefaction, and cardiomyocyte apoptosis and autophagy; these processes culminate in altered contraction, relaxation (lusitropy), perfusion, and electrical activity[59] (**Fig. 46.15**). These alterations result from both pressure overload *plus* accompanying neurohormonal activation, fetal reprogramming of cardiomyocyte genes, and inflammation. In animal experiments, A II, aldosterone, norepinephrine, and prorenin accelerate pressure-overload cardiomyocyte hypertrophy and promote cardiac fibrosis, the hallmark of pathologic LVH (in contrast to physiologic hypertrophy of exercise training, which involves less fibrosis). Non–contrast-enhanced cardiac magnetic resonance imaging (MRI) can now quantify the extent of the fibrosis by using T1 mapping.[61]

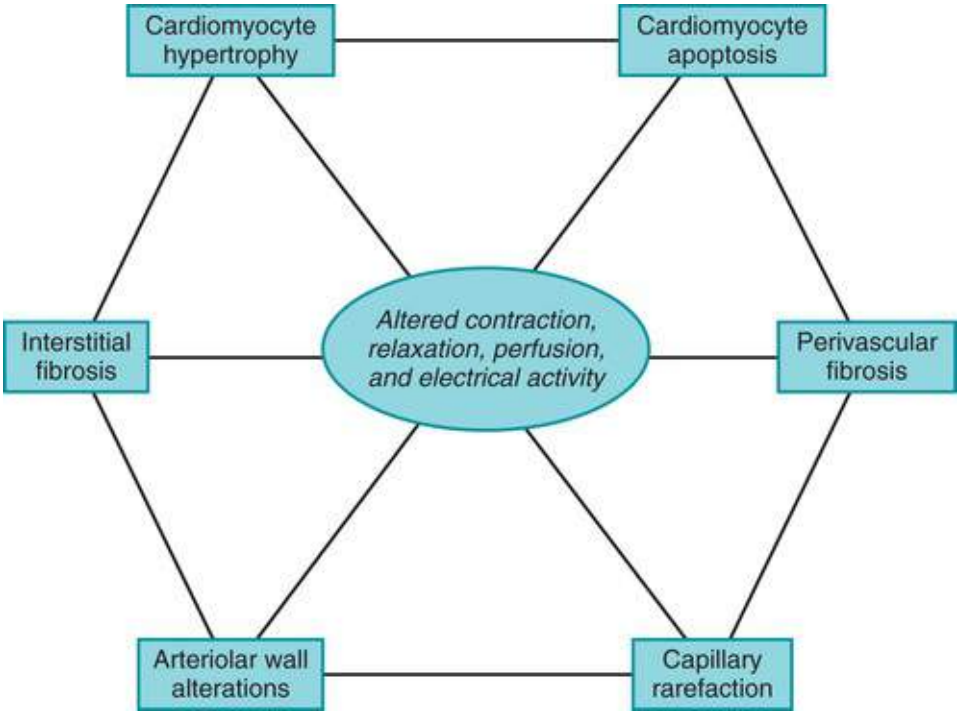


FIGURE 46.15 Mosaic of interactions among the microscopic lesions found in the hypertensive myocardium, which result in alterations in left ventricular function, demand ischemia, and arrhythmia.
(From Morena, MU, Eiros R, Gavira JJ, et al. The hypertensive myocardium. Med Clin North Am 2017;101:43, 2017.)

Classification and Complications

Hypertensive heart disease is classified by the severity of the complications[59] (**Table 46.4**). These range from mild asymptomatic diastolic dysfunction to heart failure with preserved (HFpEF) or reduced (HFrEF) ejection fraction. Hypertension is most likely to cause LVH and HF in black patients and patients with CKD.

TABLE 46.4

Classification of Hypertensive Heart Disease

Class I: Subclinical diastolic dysfunction by echocardiography without left ventricular hypertrophy
Asymptomatic patients with abnormal left ventricular relaxation/stiffness by Doppler echocardiography, a common finding in hypertensive individuals >65 years
Class II: Left ventricular hypertrophy
IIA: with normal functional capacity (NYHA Class I)
IIB: with abnormal functional capacity (NYHA Class >II)
Class III: Heart failure with preserved ejection fraction (HFpEF)
Class IV: Heart failure with reduced ejection fraction (HFrEF)

NYHA, New York Heart Association.

Impaired Coronary Vasodilator Reserve and Heart Failure

The hypertrophied hypertensive heart has normal resting coronary blood flow, but vasodilator reserve becomes impaired because a proportionate increase in the myocardial microvasculature does not accompany the increased myocyte mass, but rather by capillary rarefaction. Microvascular ischemia is a hallmark of hypertensive heart disease and is more common in women. Even in the absence of atherosclerosis, the hypertensive heart has blunted or absent coronary vasodilator reserve, producing subendocardial ischemia under conditions of increased myocardial oxygen demand. The combination of subendocardial demand ischemia and cardiac fibrosis impairs diastolic relaxation, leading to exertional dyspnea and HFpEF (**see Chapter 26**).

Large-Vessel Disease

Hypertension also constitutes a major risk factor for, and is present in, an overwhelming majority of patients with aortic dissection,[62] as well as abdominal aortic aneurysm (AAA), and peripheral arterial disease (**see Chapters 63 and 64**). One-time abdominal ultrasound screening for AAA is recommended after age 65 in smokers and in those with severe systolic hypertension, and it should be performed if aortic pulsations are detected below the umbilicus, because most AAAs occur below the origin of the renal arteries. Hypertension occurs in 50% of patients with Takayasu arteritis (**see Chapter 94**).

Cerebrovascular Disease

Hypertension is a major risk factor for stroke and dementia, often the two most dreaded complications of aging (**see Chapter 65**). Hypertension accounts for 50% of strokes. In hypertensive individuals, 80% of strokes are ischemic (thrombotic or embolic) and 20% are hemorrhagic. The onset of ischemic stroke greatly increases on awakening, corresponding to the morning surge in BP. Hypertensive patients with asymptomatic carotid bruits should undergo Doppler ultrasonography. Older patients with ISH have a particular risk of stroke. In middle-aged and elderly hypertensive patients, remarkably common asymptomatic cerebral white matter lesions on MRI likely accelerate the brain atrophy and vascular dementia that occur with aging.

Chronic Kidney Disease

Hypertension is second only to diabetes as a major risk factor for CKD. Traditionally, the typical pathologic change of small, scarred kidneys (termed *hypertensive nephrosclerosis*), likely the result of chronic exposure of the renal parenchyma to excessive pressure and flow, is the most common cause of end-stage renal disease among blacks. The greater susceptibility of non-Hispanic black hypertensive patients to nephrosclerosis is in part genetically determined by an African ancestral risk allele on

chromosome 22 (*APOL1* variants).[31]

Quantitative estimates of urinary albumin excretion and GFR (the latter from www.kdoqi.org) should be obtained from a spot urine collection. Microalbuminuria (defined as a urine albumin/creatinine ratio of 30 to 300 mg/day) is a sensitive early marker of CKD and independently predicts CVD complications from hypertension, because it reflects systemic vascular disease. In patients with hypertension, renal damage dramatically increases CVD risk. Most patients with hypertension-associated CKD die of MI, stroke, or SCD before developing ESRD.

Identifiable (Secondary) Forms of Hypertension

The third goal of the initial evaluation of the hypertensive patient is to detect identifiable causes of hypertension, thereby offering the possibility of cure to some patients, particularly those with severe or refractory hypertension (**Table 46.5**).

TABLE 46.5

Overall Guide to Workup for Identifiable Causes of Hypertension

DIAGNOSIS	DIAGNOSTIC PROCEDURE	
	Initial	**Additional**
Primary aldosteronism	Plasma renin, serum aldosterone	Salt loading, adrenal vein sampling
Chronic kidney disease	Urinalysis, serum creatinine, renal sonography	Isotopic renography, renal biopsy
Renovascular disease	Duplex Doppler sonography	Magnetic resonance or computed tomography (CT) angiography, digital subtraction renal angiography
Coarctation of the aorta	Blood pressure in legs	Echocardiography, magnetic resonance imaging (MRI), aortography
Cushing syndrome	1-mg dexamethasone suppression test	24-hour urinary cortisol, salivary cortisol, adrenal CT
Pheochromocytoma	Plasma-free metanephrines	24-hour urinary metanephrines and catecholamines; adrenal CT or MRI

Renal Parenchymal Disease

Renal parenchymal disease is the most common cause of secondary hypertension, responsible for 2% to 5% of cases. As chronic glomerulonephritis has become less common, diabetes and hypertension are the most common risk factors for CKD. Chronic kidney disease, defined by a reduction in the GFR to less than 60 mL/min/1.73 m^2 or persistent albuminuria of more than 300 mg/day, affects about 11% (19.2 million) of the adult U.S. population (**see Chapter 98**).

As previously noted, microalbuminuria of 30 to 300 mg/day relates closely to target-organ damage and should be determined in every new hypertensive patient by testing of a single-voided urine specimen. Measurement of the serum creatinine level by itself is an inadequate screening test for significant renal damage, particularly in elderly patients. Creatinine clearance should be calculated with the Cockcroft-Gault equation or the Modification of Diet in Renal Disease (MDRD) equation, although the latter does not account for other factors that affect creatinine generation by muscle, such as diet and physical conditioning. Serum cystatin C, an endogenous 13-kDa protein filtered by the glomeruli and reabsorbed and metabolized by the proximal tubular epithelium, with very little being excreted in the urine, has promise as a replacement for serum creatinine because it is less affected by muscle mass.[63] Once renal disease begins, it usually progresses, following the concept that a loss of filtration surface leads to both glomerular and systemic hypertension, which engenders more glomerular sclerosis, setting up a cycle of progressive disease. Identifying renal damage early therefore is critical, because removal of causal or aggravating factors can prevent the otherwise inexorable progress of renal damage. These factors include obstructive uropathy, hypovolemia, nephrotoxic agents, and most important, uncontrolled hypertension.

Acute Renal Diseases

Hypertension may appear with any sudden, severe insult to the kidneys that markedly impairs excretion of salt and water, which leads to volume expansion, or that reduces renal blood flow (e.g., sudden bilateral renal ischemia because of cholesterol emboli), or that activates the RAAS (e.g., bilateral ureteral obstruction). Reversal of hypertension has been particularly striking in men with high-pressure chronic retention of urine, who may manifest renal failure and severe hypertension, both of which may improve after relief of the obstruction. Hypertension can be the presenting sign of systemic vasculitis involving the kidney.

Two common classes of drugs—nonsteroidal anti-inflammatory drugs (NSAIDs) and RAAS inhibitors—can precipitate acute kidney injury (AKI) in patients with preexisting CKD. NSAIDs block the synthesis of prostaglandins, which act as vasodilators within the kidney. Renin-angiotensin inhibitors, including ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), may precipitate acute renal failure in patients with bilateral renovascular disease whose renal perfusion depends on high levels of A II.

Chronic Renal Diseases

The kidney is both the culprit and the victim in hypertension. In patients with CKD, an overly aggressive antihypertensive regimen, especially based on a potent RAAS inhibitor and potent diuretic, can precipitate AKI. However, a modest increase in the serum creatinine level, averaging 30% above baseline, predicts better preservation of renal function, presumably reflecting a successful reduction in intraglomerular pressure. About two thirds of patients with CKD have nocturnal masked hypertension detectable only by ABPM (**see Fig. 46.14**).[47]

Patients with diabetic nephropathy show particular protection against progressive renal damage by reduction of elevated BP with an ARB-based or ACEI-based regimen (**see Chapters 51 and 98**). The results of the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) show that addition of the direct renin inhibitor aliskiren to standard RAAS blockade with either an ACEI or an ARB in high-risk patients with type 2 diabetes did not improve cardiovascular or renal outcomes compared with standard RAAS blockade alone, but produced higher rates of adverse events, especially hyperkalemia and hypotension.[64] Thus the FDA issued a “black box” warning that aliskiren is contraindicated in patients with type 2 diabetes being treated with an ACEI or ARB and should be avoided in nondiabetic patients taking an ACEI or ARB for nondiabetic CKD. Most CKD patients require at least two more drugs in addition to an ACEI or ARB—typically, a loop diuretic or potent thiazide-type diuretic and a calcium channel blocker—to control their hypertension.

Hemodialysis Patients

In patients on dialysis, hypertension is a risk factor for mortality. Beyond the primary influence of excess fluid volume, the accumulation of endogenous inhibitors of NOS and sympathetic overactivity can accentuate hypertension. The BP may be particularly labile and sensitive to changes in fluid volume. In patients receiving maintenance hemodialysis every 48 hours, elevated BPs tend to fall progressively after dialysis, remain low during the first 24 hours, and rise again during the second day due to fluid retention. Gradually achieving and maintaining dry weight, as with 8-hour nocturnal hemodialysis, can greatly improve BP control.

Renal Transplantation

Although successful renal transplantation may cure primary hypertension, various problems can result, with about 50% of recipients becoming hypertensive within 1 year. These problems include stenosis of the renal artery at the site of anastomosis, rejection episodes, high doses of glucocorticoids and cyclosporine or tacrolimus, and excess renin derived from the retained diseased kidneys. ACEI or ARB therapy may obviate the need to remove the native diseased kidneys to relieve hypertension caused by their persistent secretion of renin. The source of the donor kidney may also play a role in the subsequent development of hypertension in the recipient. Hypertension occurs more frequently when donors have a family history of hypertension or when donors have died of subarachnoid hemorrhage and probably had high BP.

Renovascular Hypertension

Renovascular hypertension is a conundrum. Although the pathophysiology clearly involves A II–dependent hypertension, this involves a wide spectrum of disorders, beginning with (1) *incidental, hemodynamically insignificant renal artery stenosis* and progressing to (2) *renovascular hypertension* with reduced perfusion and activation of RAAS; (3) *accelerated cerebrovascular disease* with diastolic dysfunction, heart failure, and stroke; and (4) *ischemic nephropathy* with renal tissue hypoxia, extensive microvascular disease, and progressive renal atrophy.[65]

Classification

In the United States, *atherosclerotic renal artery stenosis* (ARAS) causes more than 85% of cases of renovascular disease (**Fig. 46.16**). Affecting the origin of the main renal artery, ARAS occurs mostly in older patients with CVD risk factors. In contrast, *fibromuscular disease* (FMD) involving mainly the distal two thirds and branches of the renal arteries appears most frequently in women between 20 and 60 years of age[66] (**see also Chapter 64 and Fig. 64.15**). FMD typically affects the media but can also affect the intima and adventitia. Carotid FMD and less often coronary artery FMD may accompany renal artery FMD, frequently presenting with dissection before the diagnosis of FMD.[67]

FIGURE 46.16 Computed tomography angiogram with three-dimensional reconstruction, showing a severe proximal atherosclerotic stenosis of the right renal artery and mild stenosis of the left renal artery **(A)** and the classic "string of beads" lesion of fibromuscular dysplasia (bilateral in this patient) **(B)**. (**See also Fig. 64.15**.) (Courtesy of Bart Dolmatch, MD.)

Other intrinsic and extrinsic causes of renovascular hypertension include arterial emboli in the renal artery or extrinsic compression of this vessel by nearby tumors. Renovascular stenosis is often bilateral, although usually one side predominates. Bilateral disease should be suspected in those with renal insufficiency, particularly if rapidly progressive oliguric renal failure develops without evidence of obstructive uropathy, and even more so if it develops after the start of ACEI or ARB therapy.

Mechanisms

Renovascular hypertension is triggered initially by renal ischemia causing secondary activation of the RAAS. At first, the normal contralateral kidney responds to the A II–dependent hypertension with pressure natriuresis, thus maintaining normal blood volume. With time the contralateral kidney becomes damaged, and as a result the increased BP no longer is offset by increased sodium excretion, leading to volume expansion and a secondary reduction in renin secretion from the stenotic kidney. The renal parenchyma can tolerate partial renal ischemia for a remarkably long time but eventually develops irreversible microvascular disease with inflammation, renal atrophy, and fibrosis.

Diagnosis

Table 46.6 lists the clinical features of patients with renovascular hypertension.[65] Most patients with ARAS are older persons with hypertension, hyperlipidemia, and evident CAD and/or peripheral artery disease and cerebrovascular disease. The three most specific presentations of severe ARAS are drug-refractory hypertension, flash pulmonary edema, and ischemic nephropathy. Such patients (<5% of all hypertensive persons) should be screened for renovascular hypertension. Young to middle-age women who have moderate to severe hypertension with little or no family history of hypertension should be screened for FMD. A whooshing or swishing sound with each heartbeat is a pathognomonic symptom of carotid FMD.[66] The initial screening test is noninvasive Duplex ultrasonography, which has a sensitivity of 75% and specificity of 90% when performed in an experienced vascular laboratory. If stenosis is detected and the resistive index is less than 80, indicating insignificant microvascular disease, high-grade stenosis should be confirmed by spiral CT or MR angiography (**Fig. 46.16**) unless there is advanced CKD, which increases the risk of contrast-induced AKI or gadolinium-induced fatal nephrogenic systemic fibrosis. Digital subtraction angiography (DSA) is the reference standard for making the diagnosis of a severe lesion with a gradient amenable to intervention.

TABLE 46.6

Clinical Clues for Renovascular Hypertension

1. Onset of hypertension before age 30 or after 50
2. Acceleration of treated primary hypertension
3. Deterioration in renal function in treated primary hypertension
4. Acute kidney injury (AKI) during treatment of hypertension
5. Flash pulmonary edema
6. Progressive renal failure
7. Refractory heart failure
8. Unilateral small (atrophic) kidney size by ultrasound examination

Modified from Textor SC. Renal arterial disease and hypertension. Med Clin North Am 2017;101:65.

Management

Balloon angioplasty without stenting is the treatment of choice for renal artery FMD (**see Chapters 64**

and 66). Outcomes are excellent when technically excellent results are achieved in experienced centers. With three negative major RCTs of stenting versus medical management, however, a conservative approach based on medical management of cardiovascular risk factors—with ACEI- or ARB-based antihypertensive regimen, statins, antiplatelet therapy, and smoking cessation—is the cornerstone for the treatment for ARAS. Notably, all three RCTs failed to enroll patients with the most severe ARAS who stand to benefit the most from stenting, namely, those with (1) intractable hypertension, (2) AKI induced by ACEI or ARB treatment of hypertension, or (3) recurrent, episodic (flash) pulmonary edema. Registry data strongly indicate that such patients are the best candidates for renal artery stenting.[65]

Renin-Secreting Tumors

Composed of juxtaglomerular cells or hemangiopericytomas, renin-secreting tumors occur mostly in young patients with severe hypertension, with very high renin levels in both peripheral blood and the kidney harboring the tumor, and with secondary aldosteronism manifested by hypokalemia. The tumor can generally be recognized by selective renal angiography, usually performed for suspected renovascular hypertension, although a few are extrarenal. More often, children with Wilms tumors (nephroblastoma) may have hypertension and high plasma renin and prorenin levels that revert to normal after nephrectomy.

Adrenal and Other Causes of Hypertension

Adrenal causes of hypertension include primary excesses of aldosterone, cortisol, and catecholamines; more rarely, excess deoxycorticosterone is present with congenital adrenal hyperplasia. Together, these conditions cause less than 1% of all cases of hypertension in general practice, yet primary aldosteronism accounts for 10% to 20% of patients referred to hypertension specialists. Despite their relative ease of recognition and the availability of simple efficient screening tests, these adrenal disorders are easily overlooked (**see Chapter 92**).

An increasingly common clinical problem is an incidentally discovered solitary adrenal mass—the *incidental adrenaloma*—which is found on 5% of abdominal CT scans obtained for nonadrenal indications.[8] Although most are benign and nonfunctional, an adrenal incidentaloma must never be ignored, because 10% to 15% will be either functional or malignant. The probability of adrenal cancer varies by the imaging characteristics. The risk of cancer is low if a non–contrast-enhanced CT scan shows a tumor density of less than 10 HU, consistent with low-density lipid; if an MRI scan confirms a high lipid content by loss of signal on out-of-phase images; or if the tumor is smaller than 4 cm. Tumors 4 cm or larger should be resected because many are malignant.

Table 46.5 lists the screening and confirmatory tests for adrenal hyperfunction: increased cortisol production (of subtle elevations with subclinical Cushing syndrome) in up to 33%, pheochromocytoma in 6%, and primary aldosteronism (Conn syndrome) in 1%.

Primary Aldosteronism and Other Forms of Mineralocorticoid-Induced Hypertension

Several syndromes of mineralocorticoid excess exist (**Table 46.7**). Of these, primary aldosteronism is by far the most common; it also is the most common reversible form of hypertension. Systemic hyperaldosteronism causes cardiac fibrosis (producing severe LVH, atrial fibrillation, CAD, ventricular tachycardia, and SCD), renal fibrosis with CKD, hypokalemia, endothelial dysfunction,

hyperparathyroidism, sleep apnea, and anxiety/depression. Spontaneous and inherited potassium channel mutations are the disease-causing mechanism in at least 50% of aldosterone-producing adenomas. The mutations make the potassium channel abnormally permeant to sodium, which depolarizes the adrenal glomerulosa cells to produce excessive calcium entry, the signal for both aldosterone secretion and cell proliferation.[68]

TABLE 46.7
Syndromes of Mineralocorticoid Excess

Adrenal Origin
Aldosterone Excess (Primary)
Aldosterone-producing adenoma Bilateral hyperplasia Primary unilateral adrenal hyperplasia Glucocorticoid-remediable aldosteronism (familial hyperaldosteronism, type I) Adrenal carcinoma Extra-adrenal tumors
Deoxycorticosterone Excess
Deoxycorticosterone-secreting tumors Congenital adrenal hyperplasia 11β-Hydroxylase deficiency 17α-Hydroxylase deficiency
Cortisol Excess
Cushing syndrome from ACTH-producing tumor Glucocorticoid receptor resistance
Renal Origin
Activating mutation of mineralocorticoid receptor Pseudohypoaldosteronism, type II (Gordon) 11β-Hydroxysteroid dehydrogenase deficiency *Congenital*: Apparent mineralocorticoid excess *Acquired*: Licorice, carbenoxolone

Pathophysiology of Mineralocorticoid Excess

Hyperaldosteronism results in excessive stimulation of the mineralocorticoid receptor in the distal nephron, causing excessive sodium retention through the ENaCs. This both expands the blood volume, causing severe hypertension, and drives the renal Na^+,K^+-ATPase, causing renal potassium wastage. Whereas the classic picture of primary aldosteronism is a young adult with severe systolic/diastolic hypertension and hypokalemia, in some patients the degree of renal potassium loss may be insufficient to decrease serum K^+ into the frankly hypokalemic range.

Diagnosis.

As detailed in the 2016 Endocrine Society guidelines,[69] the three steps to the systematic evaluation of suspected primary aldosteronism are screening, salt loading for biochemical confirmation, and adrenal vein sampling for localization. Screening is recommended only for hypertensive patients who have a higher likelihood of aldosterone-producing adenoma, including those with unprovoked hypokalemia or excessive hypokalemia on diuretic therapy, a family history of aldosteronism, resistant hypertension, or an adrenal incidentaloma. Hyperaldosteronism occurs in as many as 20% of patients with resistant hypertension, with two thirds of these having unilateral disease and thus surgical candidates.

Screening involves measurement of both plasma renin activity (PRA) and serum aldosterone. Although the test ordered is the aldosterone/renin ratio, a positive result should be based not on the ratio but rather on the finding of both an elevated plasma aldosterone level (>15 ng/dL) and a suppressed PRA (<1 ng/mL • h; with <0.6 being severely suppressed). Hypokalemia causes underestimation of the serum

aldosterone level; if the aldosterone level is borderline, the screening test should be repeated after giving enough KCl supplementation to bring the serum K^+ to greater than 4.0.

If the screening test is positive, the next step is 3-day oral salt-loading suppression of 24-hour urine aldosterone to document the autonomy of hyperaldosteronism; rapid intravenous saline suppression testing is less accurate and not recommended.[70] If the suppression test result is abnormal, adrenal vein sampling by an experienced tertiary center is strongly recommended to differentiate unilateral adenoma from bilateral hyperplasia and to confirm exactly which gland should be removed by laparoscopic surgery (**eFig. 46.6**). Because detection of microscopic adenomas may be below the resolution of CT scanning, and because minor adrenal nodularity and nonfunctioning adrenal incidentalomas are common, CT findings alone lead to the wrong conclusion in almost half the cases.[69] Adrenal vein sampling is reserved for patients who are surgical candidates and prefer surgery over medical management with an aldosterone antagonist–based regimen.

Differential Diagnosis: Mendelian Forms of Hypertension

In patients presenting with severe hypertension and hypokalemia, primary aldosteronism requires distinguishing from rare forms of mineralocorticoid-induced hypertension that are inherited as mendelian traits. Clinical clues of syndromic hypertension are premature onset (often before age 30), severity of the hypertension (frequently dramatic), and a compelling family history indicative of mendelian inheritance. All these familial syndromes involve excessive activation of ENaC as a final common mechanism, caused either by gain-of-function mutations of ENaC or the mineralocorticoid receptor or by increased production or decreased clearance of the mineralocorticoid receptor ligands, aldosterone, as well as deoxycorticosterone and cortisol (**Fig. 46.17**).

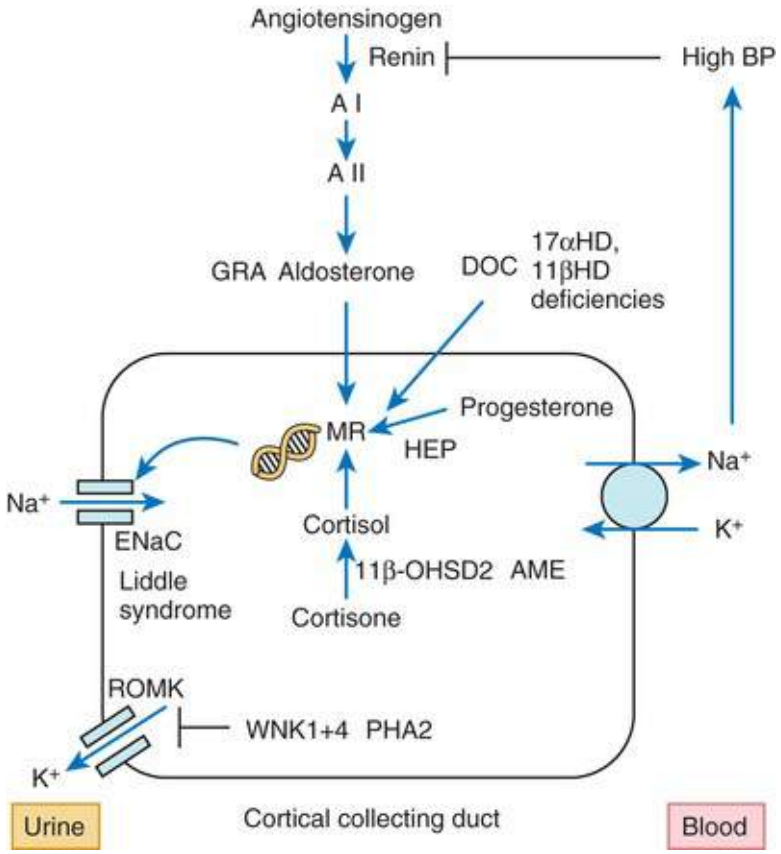


FIGURE 46.17 Mendelian forms of hypertension that cause mineralocorticoid-induced hypertension. AME, Apparent mineralocorticoid excess; A I, angiotensin I; A II, angiotensin II; BP, blood pressure; GRA, glucocorticoid-remediable aldosteronism; 11β-OHSD2, 11β-hydroxysteroid dehydrogenase type 2; DOC, deoxycorticosterone; ENaC, epithelial sodium channel; MR, mineralocorticoid receptor; PHA2, pseudohypoaldosteronism type II; ROMK, rectifying outer medullary potassium channel; WNK, with no lysine kinases; HEP, hypertension exacerbated by pregnancy; 11βHD, 11β-hydroxylase; 17αHD, 17α-hydroxylase. The effect of PHA2 on the activity of the thiazide-sensitive Na-Cl cotransporter in the distal collecting duct is not shown. See text for explanation. (Modified from Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. Cell 2001;104:545.)

One type, *familial glucocorticoid-remediable aldosteronism,* results from recombination of genes encoding the aldosterone synthase enzyme (CYP11B2), normally found only in the outer zona glomerulosa, and the 11β-hydroxylase enzyme (CYP11B1) in the zona fasciculata. The chimeric gene induces an enzyme that catalyzes the synthesis of 18-hydroxylated cortisol in the zona fasciculata. The glucocorticoid suppressibility of the syndrome occurs because this zone is under the control of adrenocorticotropic hormone (ACTH). Genetic testing for the chimeric gene should diagnose the syndrome, treatable by glucocorticoid suppression.

Another rare form is apparent mineralocorticoid excess caused by deficiency of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-OHSD2) in the renal tubule, where it normally converts cortisol, which can act on the mineralocorticoid receptor, to cortisone, which cannot. Persistence of high levels of cortisol induces all the features of mineralocorticoid excess. The 11β-OHSD2 enzyme may be congenitally absent (the syndrome of apparent mineralocorticoid excess) or inhibited by the glycyrrhizic acid contained in licorice. Another unusual syndrome with hypertension and hypokalemia but suppressed mineralocorticoid secretion is *Liddle syndrome,* in which the kidney reabsorbs excess sodium and wastes potassium because of a mutation in the beta or gamma subunits of the ENaC.

In most of these cases, volume expansion and severe hypertension cause feedback suppression of

plasma renin, and mineralocorticoid receptor activation leads to renal potassium wasting and hypokalemia. One exception is *pseudohypoaldosteronism type II*, in which the disease-causing mutation produces both low-renin and salt-sensitive hypertension caused by overactivity of the thiazide-sensitive Na^+/Cl^- cotransporter in the distal collecting duct and hyperkalemia caused by underactivity of the renal outer medullary potassium channel.

Therapy.

Laparoscopic adrenalectomy is recommended for patients with a unilateral aldosterone producing adenoma (*Conn syndrome*).[69] Those with bilateral hyperplasia are treated medically with an aldosterone antagonist (eplerenone or spironolactone) and other antihypertensive drugs as needed. Aldosterone antagonists also are an option for patients with unilateral adenoma who do not want surgery or do not have access to a tertiary hospital with both an interventional radiologist and endocrinologist with considerable experience in the performance and interpretation of adrenal vein sampling, a technically demanding procedure.[71] Laparoscopic adrenalectomy eliminates the need for antihypertensive medication in up to 50% of patients and reduces medication requirements in patients who may have coexisting primary hypertension or renal damage from prolonged exposure to elevated BP and undiagnosed hyperaldosteronism.

Cushing Syndrome

Hypertension occurs in about 80% of patients with Cushing syndrome. If left untreated, it can cause marked LVH and congestive heart failure. As with hypertension of other endocrine causes, the longer it is present, the less likely it will improve when the underlying cause is relieved (**see Chapter 92**).

Mechanism of Hypertension.

BP can increase for a variety of reasons. The secretion of mineralocorticoids can increase along with cortisol, which itself is a potent activator of the mineralocorticoid receptor. The excess cortisol can overwhelm the ability of renal 11β-OHSD2 to convert it to cortisone, which is not a mineralocorticoid receptor ligand; the excess cortisol overstimulates renal mineralocorticoid receptors to retain sodium and expand plasma volume. Cortisol stimulates the synthesis of renin substrate and the expression of A I receptors, which may cause enhanced pressor effects.

Diagnosis.

Cushing syndrome should be suspected in patients with truncal obesity, wide purple striae, thin skin, muscle weakness, and osteoporosis. If clinical features are suggestive, the diagnosis often can be either ruled out or virtually ensured by the measurement of free cortisol in a 24-hour urine sample, the simple overnight dexamethasone suppression test, or the determination of late-night salivary cortisol. Some cases of metabolic syndrome may be caused by subclinical Cushing syndrome.

Therapy.

In about two thirds of patients with Cushing syndrome, the process begins with overproduction of ACTH by the pituitary, which leads to bilateral adrenal hyperplasia (BAH). Although pituitary hyperfunction may reflect a hypothalamic disorder, most patients have discrete pituitary adenomas that can usually be resected by selective transsphenoidal microsurgery. An adrenal tumor, if present, should be removed surgically, with appropriate steroid coverage to avoid acute adrenal insufficiency. With earlier diagnosis and more selective surgical therapy, more patients with Cushing syndrome might be cured without the need for lifelong glucocorticoid replacement therapy and with permanent relief of their hypertension. Therapy may require a drug temporarily, but rarely permanently.

Congenital Adrenal Hyperplasia.

Enzymatic defects may induce hypertension by interfering with cortisol biosynthesis. Low levels of cortisol lead to increased ACTH levels; this increases the accumulation of precursors proximal to the enzymatic block, specifically deoxycorticosterone, which induces mineralocorticoid hypertension. The more common of these is *11-hydroxylase deficiency,* which has been attributed to various mutations in the gene and leads to virilization (from excessive androgens) and hypertension with hypokalemia (from excessive deoxycorticosterone). The other is *17-hydroxylase deficiency,* which also causes hypertension from excess deoxycorticosterone, in addition to failure of secondary sexual development because sex hormones are also deficient. Affected children are hypertensive, but the defect in sex hormone synthesis may not become obvious until pubertal failure is recognized in adolescence.

Pheochromocytoma and Paraganglioma

Pheochromocytomas are rare catecholamine-secreting tumors of the adrenal chromaffin cells. Paragangliomas are even rarer, extra-adrenal tumors of the sympathetic or vagal ganglion cells. For clinical purposes, the term *pheo* generally refers to any catecholamine-secreting tumor, whether a true adrenal pheochromocytoma or a functional extra-adrenal paraganglioma. The wild fluctuations in BP and dramatic symptoms of pheo usually alert both patient and physician to the possibility of this diagnosis (**Table 46.8**). However, such fluctuations may be missed, or as occurs in 50% of patients, the hypertension may be persistent. On one hand, the spells typical of a pheochromocytoma (with headache, sweating, palpitations, and pallor) may be incorrectly attributed to migraine, menopause, or panic attacks. On the other hand, most patients with severe paroxysmal hypertension do not have a pheochromocytoma but rather marked anxiety. When correctly diagnosed and treated, most pheos are curable. When undiagnosed or improperly treated, pheos can be fatal.[72,73] (**See Chapter 92** for details regarding the pathophysiology, diagnosis, and treatment of pheochromocytoma.)

TABLE 46.8

Features Suggestive of Pheochromocytoma

Hypertension, Persistent or Paroxysmal
Markedly variable blood pressures (± orthostatic hypotension)
Sudden paroxysms (± subsequent hypertension) in relation to:
Stress: anesthesia, angiography, parturition
Pharmacologic provocation: histamine, nicotine, caffeine, beta blockers, glucocorticoids, tricyclic antidepressants
Manipulation of tumors: abdominal palpation, urination
Rare patients persistently normotensive
Unusual settings
Childhood, pregnancy, familial
Multiple endocrine adenomas: medullary carcinoma of the thyroid (MEN-2), mucosal neuromas (MEN-2B)
Von Hippel–Lindau syndrome
Neurocutaneous lesions: neurofibromatosis
Associated Symptoms
Sudden spells with headache, sweating, palpitations, nervousness, nausea, vomiting
Pain in chest or abdomen
Associated Signs
Sweating, tachycardia, arrhythmia, pallor, weight loss

Other Causes of Hypertension

Hypertension has a host of other causes. One that is probably becoming more common is the ingestion of various drugs: prescribed (e.g., cyclosporine, tacrolimus, erythropoietin), over the counter (e.g., NSAIDs, ephedra), and illicit (e.g., cocaine, methamphetamine). As previously noted, obstructive sleep apnea

commonly coexists with hypertension, but causal attribution is unclear.

Coarctation of the Aorta

Congenital narrowing of the aorta can occur at any level of the thoracic or abdominal aorta, but typically localizes just beyond the origin of the left subclavian artery or distal to the insertion of the ligamentum arteriosum (**see Chapter 75**). With less severe postductal lesions, symptoms may not appear until the teenage years or later, particularly during pregnancy. Hypertension in the right arm with weak femoral pulses and a loud murmur heard over the back in a young adult strongly suggest coarctation. Up to 12% of young women with Turner syndrome have coarctation. The pathogenesis of the hypertension can involve more than simple mechanical obstruction and seems to involve systemic endothelial dysfunction. The diagnosis is usually made by suprasternal notch echocardiography and confirmed by cardiac MRI. Preoperative management with an ACEI followed by early repair in childhood is recommended to reduce recurrence of the coarctation and persistent or recurrent hypertension in adulthood.[8] Once repaired, patients may continue to have hypertension, which requires careful monitoring and treatment.

Hormonal Disturbances

As many as half of patients with various hormonal disturbances, including acromegaly, hypothyroidism, and hyperparathyroidism, have hypertension. Diagnosis of the last two conditions has been facilitated by readily available blood tests, and affected hypertensive patients can have high BP relieved by correction of the hormonal disturbance. Such relief occurs more frequently in patients with hypothyroidism than in those with hyperparathyroidism (**see Chapter 92**).

Future Perspectives

There now exists abundant evidence that masked hypertension—especially masked nocturnal hypertension, which can be diagnosed only by ambulatory blood pressure monitoring (ABPM)—constitutes a potent independent risk factor for myocardial infarction, stroke, end-stage renal disease, and death. There is an urgent need for properly powered, multicenter RCTs to prove unequivocally that treating masked nocturnal hypertension improves cardiovascular disease outcomes and renal outcomes and saves lives. Such findings would provide the rigorous evidence needed to expand the indications for ABPM, causing a sea change in the approach to the diagnosis and management of hypertension.

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47

Systemic Hypertension

Management

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Hypertension remains the most common diagnosis in adult outpatient medicine and the most frequent indication for prescription drugs. Lifestyle modification, particularly at the societal level, can prevent or delay the development of hypertension. However, hypertension is becoming more prevalent in both developed and developing countries and remains poorly identified and poorly controlled in the United States and abroad.[1,2]

High blood pressure (BP) treatment yields large reductions in the risk for stroke, heart failure, renal failure, aortic dissection, coronary events, and death. Patients with the highest global cardiovascular (CV) risk benefit the most (**Fig. 47.1**).[1] With important exception of some forms of secondary hypertension, most cases of hypertension cannot be cured. Although interventions such as renal denervation or baroreflex activation therapy remain in development, effective tools—lifestyle modifications and antihypertensive drugs—permit management of hypertension. In this chapter, we discuss deployment of these tools based on the available evidence. Then, with hypertension guidelines in flux[3-15] because of different conclusions—from major new trials, meta-analyses, observational studies, and expert opinions—we provide a practical clinical approach to the management of hypertensive patients.

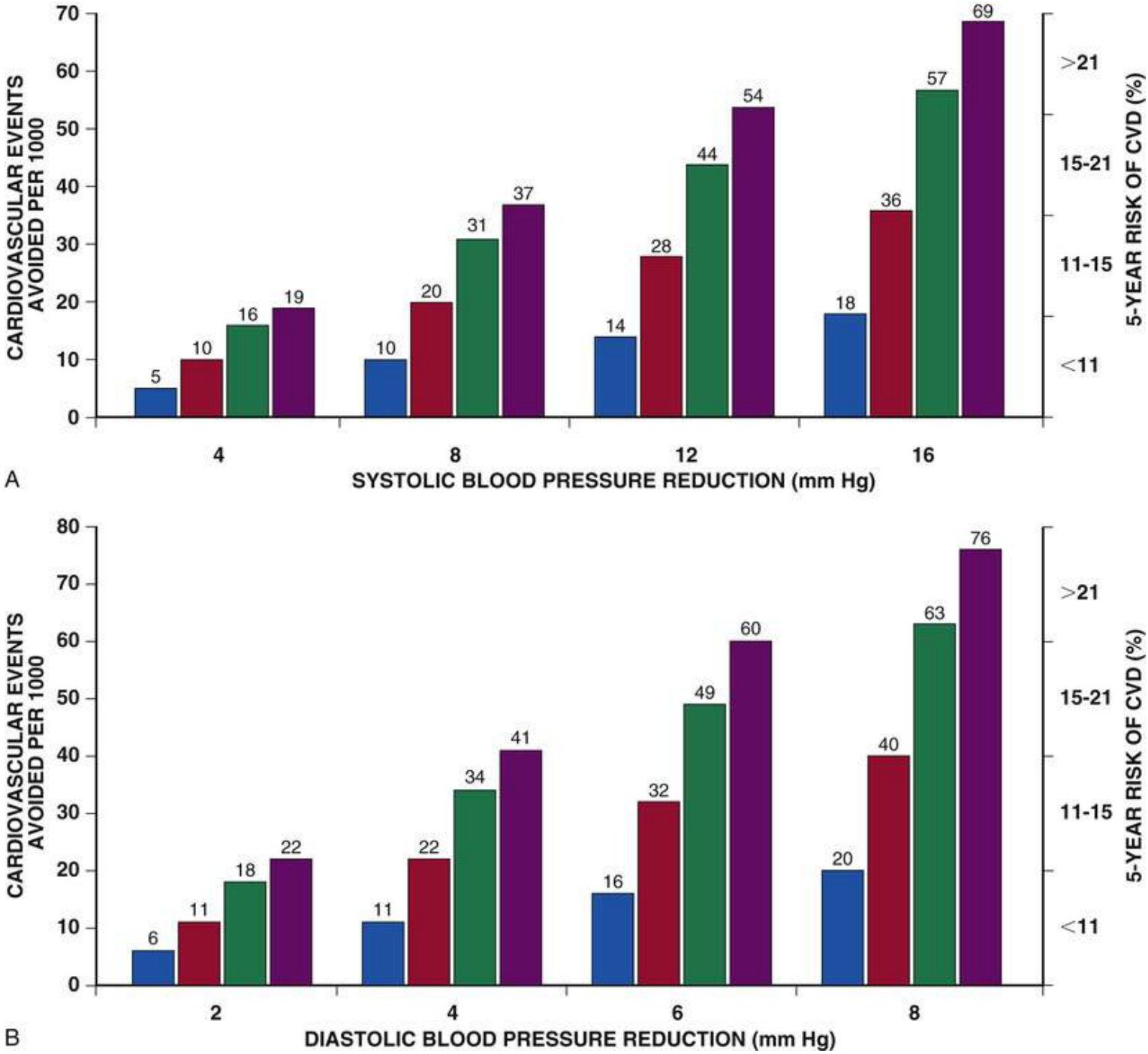


FIGURE 47.1 Avoidable cardiovascular disease (CVD) events by baseline risk and extent of lowering of systolic blood pressure **(A)** or diastolic blood pressure **(B).** (From Sundstrom J; The Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet 2014;384:595.)

Lifestyle Modification

Lifestyle choices and interventions can influence BP and furnish a foundation for prevention and treatment of hypertension. The current evidence base regarding dietary patterns and specific dietary components has sufficient strength to merit recommendations both on a population, public health level and for the management of individual patients. Evidence regarding physical activity interventions has lagged behind the evidence base on dietary approaches to the treatment of hypertension. Limitations in the evidence base regarding lifestyle and BP management require consideration. First, few studies have examined the effects of lifestyle interventions on CV outcomes; most rely on BP as a surrogate endpoint. Second, the effect of

lifestyle modification on BP and CV outcomes may vary depending on sex, age, and ethnicity.[16-19] Few studies of lifestyle intervention have incorporated sufficient numbers of older adults or minority populations to provide strong evidence for specific recommendations for these important groups.

Dietary Interventions for Blood Pressure Control

Traditional approaches to the study of diet and BP have focused on individual nutrients. A more recent concept recognizes that consumption of specific nutrients occurs in the context of food in a diet (**see Chapter 49**). Thus the contemporary approach to studies of nutrition and health focuses more on dietary patterns than on specific nutrients. This section first considers dietary patterns that have undergone evaluation with respect to BP control, followed by individual macronutrients and micronutrients of particular interest in this regard.

Two dietary patterns in particular have undergone contemporary and rigorous study in relation to BP control: the Mediterranean diet pattern and the Dietary Approaches to Stop Hypertension (DASH) diet pattern. **Table 47.1** provides brief definitions of the Mediterranean and DASH diet patterns derived from the 2013 American Heart Association (AHA) and American College of Cardiology (ACC) guideline on lifestyle management to reduce CV risk[20-23] (**see Chapters 45, 46, and 49**).

TABLE 47.1

Descriptions of Dietary Patterns

Mediterranean Pattern
There is no uniform definition of the Mediterranean diet in the randomized controlled trials and cohort studies examined. The most common features in these studies were diets that were higher in fruits (particularly fresh fruits), vegetables (emphasizing root and green varieties), whole grains (cereals, breads, rice, pasta), and fatty fish (rich in omega-3 fatty acids); were lower in red meat (and emphasizing lean meats); had lower-fat or fat-free dairy products substituted for higher-fat dairy foods; and had oils (olive or canola), nuts (walnuts, almonds, or hazelnuts), or margarines blended with rapeseed or flaxseed oil instead of butter and other fats. The Mediterranean patterns examined tended to be moderate in total fat (32% to 35% of total calories), relatively low in saturated fat (9% to 10% of total calories), high in fiber (27 to 37 g/day), and high in polyunsaturated fatty acids (particularly omega-3 fatty acids).
Dietary Approaches to Stop Hypertension Pattern
The DASH dietary pattern is high in vegetables, fruits, low-fat dairy products, whole grains, poultry, fish, and nuts; low in sweets, sugar-sweetened beverages, and red meats; low in saturated fat, total fat, and cholesterol; and rich in potassium, magnesium, and calcium, as well as in protein and fiber.

Modified from the Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Clin Cardiol 2014;63(25 Pt B):2960-84.

Mediterranean Diet Pattern

The PREDIMED (Prevención con Dieta Mediterránea) study stimulated interest among CV specialists in the potential benefits of a Mediterranean diet.[24] This trial showed an overall reduction in CV outcomes in the dietary intervention groups driven by a decrease in stroke, an endpoint closely associated with BP.[25] Meta-analysis shows small overall reductions in BP associated with a Mediterranean diet. Consumption of a Mediterranean diet pattern correlated with improvement in numerous biomarkers associated with CV benefit, including anti-inflammatory effects, as assessed by reduced C-reactive protein levels.[26] However, the most recent AHA/ACC guidelines on lifestyle management assessed the strength of evidence as “low” regarding consumption of a Mediterranean diet pattern versus a low-fat dietary pattern.

DASH Diet Pattern

The DASH diet (**Table 47.1**) evolved from studies supported by the U.S. National Heart, Lung and Blood

Institute (NHLBI).[27,28] These randomized, controlled DASH feeding studies showed that this dietary pattern could lower systolic blood pressure (SBP) by more than 5 mm Hg in adults with hypertension compared with the control diet, findings buttressed by meta-analyses. Members of minority groups may have larger drops in BP than white participants. The 2013 AHA/ACC guidelines consider the strength of evidence "high" for adherence to the DASH diet in individuals with hypertension.[20]

Sodium Consumption and Blood Pressure

The relationship between sodium and BP provides a particularly important example of the necessity of considering public health interventions, as well as lifestyle change, in individual patients to control CV risk. The effects of sodium intake on BP and the CV benefits of limiting sodium consumption continue to generate controversy. In May 2013 the U.S. Institute of Medicine (IOM) released a report on sodium intake in populations that assessed the evidence in this regard.[29] The IOM committee identified many methodologic concerns about studies of sodium intake and health, yet the report concluded that the weight of the evidence supported a link between higher levels of sodium consumption and CV risk but judged the evidence insufficient to support a restriction in sodium intake to below 2.3 g daily. A compilation of results from four studies affirmed the relationship between high sodium excretion and increased SBP and CV events, but with a "J curve" showing worsened outcomes at very low levels.[30] An analysis of TOHP (Trials of Hypertension Prevention) showed during long-term follow-up a lower but nonsignificant reduction in mortality in the active sodium reduction group, but a significant continuous relationship between sodium intake and mortality by spline analysis, without evidence of nonlinearity.[31] The different conclusions may be related to the method used to estimate dietary sodium consumption: four to seven 24-hour urine sodium collections per patient in TOHP compared with either a single 24-hour urine sodium or a single spot urine sodium in the studies indicating a J curve. Some question the justification for a population-wide policy to encourage very low sodium intake.[32] For hypertensive individuals or those with or at high risk for CV events, at least moderate sodium restriction does appear appropriate. An estimated 1.65 million deaths worldwide could result from sodium intake above 2 g daily.[33]

The 2013 AHA/ACC lifestyle management guidelines concluded that in adults age 25 to 80 with SBP of 120 to 159 mm Hg, reducing sodium intake lowers BP.[20] The guidelines further found the evidence "strong" that for adults age 30 to 80 with or without hypertension, reduction of sodium intake by approximately 1 g daily lowers SBP by 3 to 4 mm Hg. The guidelines judged the strength of evidence insufficient to support an association between sodium intake and the development of heart failure (HF) or worsened CV outcomes in patients with established HF.

Potassium Intake and Blood Pressure

Considerable observational data suggest an association between high potassium intake and lower BP. Increased consumption of potassium may lower BP, particularly in blacks compared with whites. Even though the American Society of Hypertension (ASH) recommends an increase in potassium intake to 4.7 g daily (the level provided in the DASH diet), the 2013 AHA/ACC lifestyle guidelines find the strength of evidence insufficient to establish a relationship between increased dietary potassium and lower BP or altered risk for coronary heart disease (CHD), HF, or CV mortality.[20]

Carbohydrate Consumption and Blood Pressure

The observational data base yields disparate data regarding the effect of the amount and composition of dietary carbohydrates on BP. The 2013 AHA/ACC lifestyle guidelines considered the strength of

evidence insufficient to make recommendations regarding the potential benefits of low-glycemic diets versus high-glycemic diets for individuals without diabetes.[20]

Ethanol Intake and Blood Pressure

A large body of observational evidence supports higher levels of BP in association with excessive alcohol intake.[34] Based on observational data and this meta-analysis, the ASH recommends limiting consumption to one alcoholic drink per day in women and no more than two alcoholic drinks per day in men.

Sugar-Sweetened Beverages

The increased consumption of sugar-sweetened beverages (SSBs) worldwide has been linked to the epidemic of obesity, particularly in young persons.[35] Evidence also supports an association between increased consumption of SSBs and higher levels of BP. A prospective analysis of the PREMIER study showed that after adjustment for confounders, a reduction in SSBs by one serving daily resulted in an almost 2–mm Hg decrease in SBP.[36] An international study of the effect of macronutrients and micronutrients on BP reported cross-sectional associations of SSBs with BP and found that one serving of an SSB daily was associated with a difference in SBP of greater than 1.5 mm Hg. This and other analyses showed a direct relationship between fructose and glucose intake with BP.[36,37] These observational and trial data suggest that curbing SSB consumption could lower BP in the population, and that restriction of SSB intake should be considered in individuals with established hypertension.

Other Macronutrients and Micronutrients and Blood Pressure Control

Many studies have linked other macronutrients and micronutrients with BP control. The previous discussion considered those supported by the strongest evidence base. **Table 47.2** provides a more ample list of the dietary factors and dietary patterns implicated in BP control, with estimates of the strength of the evidence adapted from the ASH position paper on dietary approaches to lower BP.[16]

TABLE 47.2

Effects of Dietary Factors and Dietary Patterns on Blood Pressure: Summary of the Evidence

	HYPOTHESIZED EFFECT	EVIDENCE*
Weight	Direct	+/+
Sodium chloride (salt)	Direct	+/+
Potassium	Inverse	+/+
Magnesium	Inverse	+/−
Calcium	Inverse	+/−
Alcohol	Direct	+/+
Fat		
Saturated	Direct	+/−
Omega-3 polyunsaturated	Inverse	+/+
Omega-6 polyunsaturated	Inverse	+/−
Monounsaturated	Inverse	+
Protein		
Total	Uncertain	+
Vegetable	Inverse	+
Animal	Uncertain	+/−
Carbohydrate	Direct	+
Fiber	Inverse	+
Cholesterol	Direct	+/−
Dietary Patterns		
Vegetarian diets	Inverse	+/+
DASH-type patterns	Inverse	+/+

*+/−, Limited or equivocal evidence; +/+, persuasive evidence, typically from clinical trials.

DASH, Dietary Approaches to Stop Hypertension.

Modified from Appel LJ. ASH position paper: Dietary approaches to lower BP. J Am Soc Hypertens 2009;3:321.

Obesity and Body Weight

Considerable observational data support a relationship between body mass index (BMI) and the development of hypertension across broad populations and outcomes, including mortality in those with morbid obesity.[38] Visceral adiposity and other ectopic fat deposits may also be associated with hypertension.[39] As with other components of "metabolic syndrome," hypertension may develop in Asians at a lower waist circumference than in whites or blacks. Weight reduction might eliminate considerable morbidity associated with hypertension and lessen the number and dosage of BP drugs and thus unwanted medication side effects (**Table 47.3**)[40] (**see Chapter 50**).

TABLE 47.3

Risk for Hypertension According to Individual Factors Evaluated on the Basis of Estimated Population Attributed Risk

FACTOR	RISK (95% CI)
BMI ≥25 kg/m^2	50% (49-52%)
Non-narcotic analgesic use	17% (15-19%)
No DASH diet	14% (10-17%)
No vigorous exercise	14% (10-19%)
No or excessive alcohol	10% (8-12%)
Folic acid use ≤400 μg/day	4% (1-7%)

BMI, Body mass index; *CI,* confidence interval; *DASH,* Dietary Approaches to Stop Hypertension.

Modified from Liebson PR. Diet, lifestyle, and hypertension and Mediterranean diet and risk of dementia. Prev Cardiol 2010;13:94.

Physical Activity

Epidemiologic and observational studies have linked insufficient physical activity to increased CV risk. Because physical activity influences both CV fitness and body weight and visceral adiposity, the mechanisms through which exercise interacts with CV risk factors—and potentially with outcomes—remain difficult to define. Moreover, the effects of physical activity depend on whether the activity involves aerobic exercise, strength training, or a combination of both. In the case of BP control, the response to physical activity may be heterogeneous. Some individuals may have increases in BP when they undergo exercise training, whereas others may have reductions. The effects of physical activity on BP also depend on whether acute effects during or immediately following exercise are measured versus chronic changes in this risk factor.[41] An occasional hypertensive patient may even experience symptomatic hypotension immediately after exercise, thereby requiring a reduction in the dose of BP medication. As in other aspects of lifestyle intervention, few studies have examined actual CV outcomes rather than biomarkers or surrogate endpoints.[37] Meta-analyses support benefits of exercise interventions.[42] Some evidence supports a genetic basis in determining the BP response to exercise, but no clinically applicable findings have emerged from such genomic analyses thus far.[43] Some evidence supports a decrease in biomarkers of inflammation with interval exercise training in patients with hypertension.[44]

The 2013 AHA/ACC guideline summarizes an extensive evidentiary review that includes the 2008 report of the Physical Activity Guidelines Advisory Committee of the U.S. Department of Health and Human Services.[45] The 2013 guideline database included 15 recent meta-analyses. The guideline states that in adults with or without hypertension, aerobic physical activity reduces SBP up to 5 mm Hg, with high strength of evidence. The committee concluded that the evidence was insufficient to provide an assessment of the effect of resistance exercise training on BP. They similarly pointed to a paucity of data regarding combined aerobic and resistance exercise intervention on regulation of BP. The committee provided a grade B recommendation that all adults engage in regular physical activity (**Table 47.4**). An AHA Scientific Statement on Alternative Approaches to Lowering Blood Pressure found the evidence strongest for resistance and aerobic exercise as an adjunct to treatment of hypertension.[46]

TABLE 47.4

Diet and Physical Activity Recommendations for Lowering Blood Pressure (BP)

Dietary Recommendations
1. Advise adults who would benefit from BP lowering to consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts; and limits intake of sweets, SSBs, and red meat: a. Adapt this dietary pattern to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions (including diabetes mellitus). b. Achieve this pattern by following plans such as the DASH dietary pattern, the U.S. Department of Agriculture (USDA) Food Pattern, or the AHA Diet.
NHLBI grade: A (strong); ACC/AHA COR: I; LOE: A.
2. Advise adults who would benefit from BP lowering to lower sodium intake.
NHLBI grade: A (strong); ACC/AHA COR: I; LOE: A.
3. Advise adults who would benefit from BP lowering to a. Consume no more than 2400 mg/day of sodium. b. Further reduce sodium intake to 1500 mg/day because it is associated with an even greater reduction in BP. c. Reduce sodium intake by at least 1000 mg/day because this will lower BP even if the desired daily sodium intake is not yet achieved.
NHLBI grade: B (moderate); ACC/AHA COR: IIa; LOE: B.
4. Advise adults who would benefit from BP lowering to combine the DASH dietary pattern with lower sodium intake.
NHLBI grade: A (strong); ACC/AHA COR: I; LOE: A.
Physical Activity Recommendations
In general, advise adults to engage in aerobic physical activity to lower BP: 3-4 sessions a week lasting on average 40 minutes per session and involving physical activity of moderate to vigorous intensity.
NHLBI grade: B (moderate); ACC/AHA COR: IIa; LOE: A.

COR, Class of recommendation; *LOE,* level of evidence; *DASH,* Dietary Approaches to Stop Hypertension; *SSBs,* sugar-sweetened beverages.

Modified from the Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Clin Cardiol 2014;63(25 Pt B):2960-84.

Cigarette Smoking

The effect of cigarette smoking on hypertension and outcomes in hypertensive patients remains difficult to define because of confounding by increases in waist girth with smoking cessation.[47] Each cigarette evokes a transient pressor response that dissipates over the next hour. Despite the lack of precise mechanistic information regarding smoking and BP control, the overwhelming deleterious effect of smoking on CV risk, as well as the public health benefits of preventing the start of smoking and promoting cessation of smoking, renders this issue moot for public health and individual patient management.

Barriers to Adoption and Maintenance of Lifestyle Change and Possible Solutions

In practice, encouraging sustainable lifestyle change has proved extremely difficult. Substantial recent efforts have explored strategies and tools for encouraging the adoption of healthier lifestyles, including weight control, diet, and physical activity. Some challenges to lifestyle change identified in the literature will resonate with practitioners. Individuals often express a low desire for, interest in, or awareness of dietary change, including weight loss, decreased sodium intake, smoking cessation, or reduced alcohol consumption. Barriers to adoption of physical activity recommendations include comorbid conditions that limit physical activity, as well as limited time.[48] Contemporary adjuncts to the usual medical model for lifestyle intervention include Internet-based interventions, which are currently under intense evaluation.[40,49-51] Given its critical importance for CV and metabolic health, effective measures for implementing and sustaining lifestyle change should remain an important goal for research and process improvement.

Antihypertensive Drugs

Although all hypertensive individuals should heed the lifestyle measures previously outlined, most also will require drug therapy to optimize outcomes. Metaregression analyses of hundreds of thousands of hypertensive patients in randomized controlled trials (RCTs) have indicated that reduction in BP (hemodynamic load) explains most of the CV benefits of treating hypertension, with minor differences noted across major drug classes.[52] The U.S. Food and Drug Administration (FDA) has approved numerous oral antihypertensive drugs (**Table 47.5**). Some drug classes have contraindications (**Table 47.6**). Certain patient subsets have preferred antihypertensive drug classes (**Table 47.7**).

TABLE 47.5

Oral Antihypertensive Drugs

DRUG	DOSE RANGE, TOTAL mg/day (DOSES PER DAY)
Diuretics	
Thiazide-Type Diuretics	
Indapamide	0.625-2.5 (1)
Chlorthalidone	6.25-50 (1)
HCTZ	6.25-100 (1)
Metolazone	2.5-5 (1)
Loop Diuretics	
Furosemide	20-160 (2)
Torsemide	2.5-0 (1-2)
Bumetanide	0.5-2 (2)
Ethacrynic acid	25-100 (2)
Potassium-Sparing Diuretics: Mineralocorticoid Receptor Antagonists	
Eplerenone	25-100 (1-2)
Spironolactone	12.5-100 (1-2)
Other Potassium-Sparing Diuretics	
Amiloride	5-20 (1)
Triamterene	25-100 (1)
Beta Blockers	
Standard Beta Blockers	
Acebutolol	200-800 (2)
Atenolol	25-100 (1)
Betaxolol	5-20 (1)
Bisoprolol	2.5-20 (1)
Carteolol	2.5-10 (1)
Metoprolol	50-450 (2)
Metoprolol XL	50-200 (1-2)
Nadolol	20-320 (1)
Penbutolol	10-80 (1)
Pindolol	10-60 (2)
Propranolol	40-180 (2)
Propranolol LA	60-180 (1-2)
Timolol	20-60 (2)
Vasodilating Beta Blockers	
Carvedilol	6.25-50 (2)
Carvedilol CR	10-40 (1)
Nebivolol	5-40 (1)
Labetalol	200-2400 (4)
Calcium Channel Blockers	
Dihydropyridines	
Amlodipine	2.5-10 (1)
Felodipine	2.5-20 (1-2)
Isradipine CR	2.5-20 (2)
Nicardipine SR	30-120 (2)
Nifedipine XL	30-120 (1)
Nisoldipine	10-40 (1-2)
Nondihydropyridines	
Diltiazem CD	120-540 (1-2)
Verapamil HS	120-480 (1-2)
Angiotensin-Converting Enzyme Inhibitors	
Benazepril	10-80 (1-2)
Captopril	25-150 (2)
Enalapril	2.5-40 (2)
Fosinopril	10-80 (1-2)

Lisinopril	5-80 (1-2)
Moexipril	7.5-30 (1)
Perindopril	4-16 (1)
Quinapril	5-80 (1-2)
Ramipril	2.5-20 (1)
Trandolapril	1-8 (1)
Angiotensin Receptor Blockers	
Azilsartan	40-80 (1)
Candesartan	8-32 (1-2)
Eprosartan	400-800 (1-2)
Irbesartan	75-300 (1)
Losartan	25-100 (2)
Olmesartan	5-40 (1)
Telmisartan	10-80 (1)
Valsartan	80-320 (2)
Direct Renin Inhibitor	
Aliskiren	75-300 (1)
Alpha Blockers	
Doxazosin	1-16 (1)
Prazosin	1-40 (2-3)
Terazosin	1-20 (1)
Phenoxybenzamine	20-120 (2) for pheochromocytoma
Central Sympatholytics	
Clonidine	0.3-1.2 (3)
Clonidine patch	0.1-0.6 (weekly)
Guanabenz	2-32 (2)
Guanfacine	1-3 (1) (at bedtime)
Methyldopa	250-1000 (2)
Reserpine	0.05-0.25 (1)
Direct Vasodilators	
Hydralazine	25-300 (3)
Minoxidil	2.5-100 (1-2)
Fixed-Dose Combinations	
Aliskiren/HCTZ	75-300/12.5-25 (1)
Amiloride/HCTZ	5/50 (1)
Amlodipine/benazepril	2.5-5/10-20 (1)
Amlodipine/valsartan	5-10/160-320 (1)
Amlodipine/olmesartan	5-10/20-40 (1)
Amlodipine/telmisartan	5-10/40-80 (1)
Atenolol/chlorthalidone	50-100/25 (1)
Azilsartan/chlorthalidone	40/12.5-25 (1)
Benazepril/HCTZ	5-20/6.25-25 (1)
Bisoprolol/HCTZ	2.5-10/6.25 (1)
Candesartan/HCTZ	16-32/12.5-25 (1)
Enalapril/HCTZ	5-10/25 (1-2)
Eprosartan/HCTZ	600/12.5-25 (1)
Fosinopril/HCTZ	10-20/12.5 (1)
Irbesartan/HCTZ	15-30/12.5-25 (1)
Losartan/HCTZ	50-100/12.5-25 (1)
Olmesartan/amlodipine	20-40/5-10 (1)
Olmesartan/HCTZ	20-40/12.5-25 (1)
Olmesartan/amlodipine/HCTZ	20-40/5-10/12.5-25 (1)
Spironolactone/HCTZ	25/25 (1/2-1)
Telmisartan/HCTZ	40-80/12.5-25 (1)
Telmisartan/amlodipine/HCTZ	40-80/2.5-10/12.5-25 (1)
Trandolapril/verapamil	2-4/180-240 (1)
Triamterene/HCTZ	37.5/25 (½ -1)
Valsartan/HCTZ	80-160/12.5-25 (1)
Valsartan/amlodipine/HCTZ	80-160/5-10/12.5-25 (1)

HCTZ, Hydrochlorothiazide.

TABLE 47.6

Contraindications to Use of Specific Antihypertensive Drugs

DRUG	COMPELLING	POSSIBLE
Diuretics (thiazides)	Gout	Metabolic syndrome Glucose intolerance Pregnancy Hypercalcemia Hypokalemia
Beta blockers	Asthma Atrioventricular block (grade 2 or 3)	Metabolic syndrome Glucose intolerance (except for vasodilating beta blockers) Athletes and physically active patients Chronic obstructive pulmonary disease
Dihydropyridine calcium channel blockers		Tachyarrhythmia Heart failure
Nondihydropyridine calcium channel blockers	Atrioventricular block (grade 2 or 3, trifascicular block) Severe left ventricular heart dysfunction Heart failure	
Angiotensin-converting enzyme inhibitors	Pregnancy Angioedema Hyperkalemia Bilateral renal artery stenosis	Women with childbearing potential
Angiotensin receptor blockers	Pregnancy Hyperkalemia Bilateral renal artery stenosis	Women with childbearing potential
Aldosterone antagonists	Acute or severe renal failure (estimated glomerular filtration rate <30 mL/min) Hyperkalemia	

TABLE 47.7

Preferred Antihypertensive Drugs for Specific Conditions

CONDITION	DRUG OR DRUGS
Patients with prehypertension	ARB?
Hypertensive patients in general	CCB, ARB or ACEI, D
Hypertension in older patients	CCB, ARB or ACEI, D
Hypertension with LVH	ARB, D, CCB
Hypertension in patients with diabetes mellitus	CCB, ACEI or ARB, D
Hypertension in patients with diabetic neuropathy	ARB, D
Hypertension in patients with nondiabetic chronic kidney disease	ACEI, BB, D
BP reduction for secondary prevention of coronary events	ACEI, CCB, BB, D
BP reduction for secondary prevention of stroke	ACEI + D, CCB
BP for patients with heart failure	D, BB, ACEI, ARB, MR antagonists
Pregnancy	BB (labetalol), CCB (nifedipine)
Aortic aneurysm	BB
Atrial fibrillation, ventricular rate control	BB, non-DHP CCB

ACEI, Angiotensin-converting enzyme inhibitor; *ARB,* angiotension receptor blocker; *CCB,* calcium channel blocker; *BB,* beta blocker; *D,* diuretic; *LVH,* left ventricular hypertrophy; *MR,* mineralocorticoid receptor; *DHP,* dihydropyridine.

Modified from Mancia G, Fagard R, Narkiewicz K, et al: 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 31:1281, 2013.

First-Line Drug Classes

The current practice guidelines[3-15] (see end of chapter) all recommend initiating treatment of hypertension with one or more of three classes of first-line BP-lowering agents: (1) calcium channel blockers (CCBs); (2) renin-angiotensin system (RAS) inhibitors, either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs); and (3) thiazide-type diuretics. These drugs reduce the risk for nonfatal and fatal CV events. They have additive effects when used in combination. Although beta-adrenergic blockers (beta blockers) are first-line drugs for angina and HF, experts disagree whether they

should be included among the first-line drugs for uncomplicated hypertension because of their inferior stroke protection and increased risk for incident diabetes. Experts also differ in the emphasis placed on diuretics.

Calcium Channel Blockers for Hypertension

As popular antihypertensive drugs, CCBs are generally well tolerated, do not require monitoring with blood tests, and have proved safe and effective in many large RCTs. CCBs also have antianginal and some antiarrhythmic effects and seem to provide more protection against cerebrovascular accident (stroke) than other antihypertensive agents. ALLHAT (Antihypertensive Lowering to Prevent Heart Attack Trial) and subsequent RCTs showed that CCBs (represented by amlodipine) prevent coronary events as effectively as diuretics and RAS blockers.[53] These data allayed earlier concerns that long-acting CCBs might cause excess coronary events.

Mechanism of Action

All CCBs block the opening of voltage-gated (L-type) calcium (Ca^{2+}) channels in cardiac myocytes and vascular smooth muscle cells. They lower BP by causing peripheral arterial dilation, with the rank order of potency being dihydropyridines > diltiazem > verapamil.

Clinical Use

Amlodipine, by far the best studied of the dihydropyridine CCBs, has undergone evaluation in multiple RCTs. In ALLHAT, amlodipine was equivalent to chlorthalidone (a potent thiazide-like diuretic) and lisinopril (an ACEI) in protecting against nonfatal coronary events, stroke, and death but provided less protection against HF.[53] Advantages of amlodipine include predictable dose-dependent potency, once-daily dosing because of its long half-life, tolerability, and cost (≤$10 per month for generic amlodipine). Unlike diuretics and RAS inhibitors, a high-salt diet or concurrent nonsteroidal anti-inflammatory drug (NSAID) therapy does not compromise the effectiveness of dihydropyridine CCBs. These drugs have some diuretic action (due to dilation of the afferent renal arteriole), which may reduce requirements for additional diuretic therapy for mild hypertension. Unlike ACEIs, they lower BP and prevent hypertensive complications equally in black and nonblack patients.[53] ASCOT (Anglo-Scandinavian Cardiovascular Outcomes Trial)[54] and the ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension)[55] trial indicated that amlodipine plus an ACEI is one of the most effective drug combinations for preventing CV complications of hypertension. For comparable reductions in office (and ambulatory) BP, amlodipine/ACEI combination therapy improved CV outcomes better than did beta-blocker/thiazide combination therapy in ASCOT or than did ACEI/thiazide combination therapy in ACCOMPLISH.[55] Multiple fixed-dose single-pill combinations of amlodipine with an ACEI or an ARB are available; some have added a thiazide for triple therapy (**see Table 47.5**).

Dihydropyridine CCBs such as amlodipine are less renoprotective than ACEIs or ARBs in patients with proteinuric chronic kidney disease (CKD); such patients should not receive amlodipine as first-line therapy, but a CCB may be useful as adjunctive therapy after initiation of appropriate first-line therapy with an ACEI or ARB and a diuretic. Verapamil is weakly antihypertensive and has limited usefulness because of dose-dependent constipation. Diltiazem is intermediate in potency between verapamil and the dihydropyridines and is usually well tolerated.

Side Effects

The principal side effect of the dihydropyridines is dose-dependent ankle edema. With amlodipine, ankle edema is much more common with a 10-mg dose than with 2.5- or 5-mg doses. The edema is mainly vasogenic because of selective arterial dilation and can be improved by concomitant therapy with an ACEI or ARB that causes balanced arterial and venous dilation. Long-acting dihydropyridine CCBs are rarely associated with flushing and headache. All CCBs can cause gingival hyperplasia, a rare but serious side effect that is reversible if detected early. Verapamil and diltiazem can impair cardiac conduction, especially in older patients also receiving digoxin, beta blockers, or central sympatholytic agents.

Renin-Angiotensin Inhibitors for Hypertension: Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Blockers, and Direct Renin Inhibitors

RAS inhibitors are among the best tolerated of the antihypertensive drugs. The large study ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) showed comparable effects of the ACEI ramipril and the ARB telmisartan with regard to reducing CV events and preventing deterioration of renal function in high-risk hypertensive patients.[56] Other data suggest that ARBs may provide slightly more protection against stroke. The outcomes of many RCTs have not substantiated the hypothesis that RAS inhibitors produce BP-independent benefits in hypertensive patients. There is no compelling indication to prescribe the direct renin inhibitor aliskiren. “Dual RAS blockade”—either with an ACEI plus an ARB or with aliskiren plus an ACEI or ARB—is now contraindicated. These combinations must be avoided because they can precipitate hypotension, acute kidney injury (AKI), and hyperkalemia (see Side Effects).

Mechanisms of Action

ACEIs block conversion of the inactive precursor angiotensin I (A I) to A II. ARBs block the action of A II on the type 1 angiotensin receptor. Aliskiren blocks the conversion of prorenin to renin, thereby blocking RAS activation at its origin. High levels of circulating prorenin may stimulate A I receptor–independent signaling pathways, which are both potentially beneficial and potentially harmful (**see Fig. 46.9**).

Clinical Use

ACEIs offer ease of use and have rather flat dose-response curves. In ALLHAT, ACEI monotherapy with lisinopril was equivalent to amlodipine or chlorthalidone monotherapy in all aspects except for producing a smaller reduction in BP and thus less stroke protection in black hypertensive individuals.[53] As monotherapy, ACEIs are generally less effective in lowering BP in black patients and in older patients with low-renin hypertension, but they are quite effective in these groups when combined with a CCB or low-dose diuretic. Meta-analyses show ACEIs equivalent to CCBs in protecting against coronary events, slightly less effective in protecting against stroke, but better in protecting against HF.[57]

ARBs confer the same benefits as ACEIs in treating hypertension while avoiding the ACEI-related cough (see Side Effects). Potent, once-daily, long-acting ARBs are olmesartan, irbesartan, telmisartan, and azilsartan (the last being most potent). By contrast, losartan is a weak antihypertensive agent. The shorter half-life of valsartan requires twice-daily dosing.

ACEIs and ARBs have become standard first-line antihypertensive therapy for patients with diabetic

and nondiabetic CKD, but evidence indicates that RAS inhibitors provide superior renal protection than do other antihypertensive agents, mainly for nondiabetic proteinuric CKD,[12] as in AASK (African American Study of Kidney Disease). Head-to-head comparison in ONTARGET has indicated that ACEIs and ARBs have comparable effects on renal outcomes.[58] A recent meta-analysis indicates that diabetes mellitus should no longer be a compelling indication for RAS inhibitors: for hypertensive patients with diabetes, ACEIs and ARBs are not superior to other antihypertensive agents at reducing the risk of CV outcomes or end-stage renal disease.[59] RCTs have not substantiated the attractive hypothesis that RAS blockers slow progression from glucose intolerance to type 2 diabetes. In meta-analyses, ARBs produce somewhat more regression of left ventricular hypertrophy (LVH) than do other antihypertensive drugs.[60]

Side Effects

All RAS inhibitors are contraindicated in pregnancy because they cause fetal renal agenesis and other birth defects. The most common side effect of ACEIs is a dry cough, which is more common in black patients and more common still in Asian patients. ACEIs block the degradation of bradykinin, which activates nociceptive sensory fibers in the lungs that trigger cough. Bradykinin may also underlie ACEI-induced angioedema, a much less common but more serious adverse effect. If a cough develops in a patient taking an ACEI who needs RAS inhibition, an ARB should be substituted. Only isolated reports link cough or angioedema with ARBs. ACEIs and ARBs can provoke hyperkalemia in the setting of CKD or diabetes with type 4 renal tubular acidosis. In patients with stage 3 CKD with proteinuria, initiation of ACEI or ARB therapy is often associated with a small transient increase in serum creatinine; therapy can be continued unless the elevation in creatinine is greater than 30%, an indication to decrease the dose or temporarily withhold therapy.

ACEIs and ARBs have been used together for extrarenal protection in proteinuric patients. However, ONTARGET showed that such dual RAS blockade increases serious renal outcomes, hypotensive events, and hyperkalemia compared with monotherapy using either agent alone.[58] The combination of an ACEI or ARB with aliskiren entails similar risks,[61,62] which caused the FDA to issue a “black box” warning and to halt marketing of the fixed-dose combination. Moreover, the COOPERATE (Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting-Enzyme Inhibitor in Non-diabetic Renal Disease) trial, which had provided the earlier evidence supporting the practice of “dual RAS blockade,” was retracted from publication in *Lancet* on the basis of scientific misconduct.[63]

Diuretics for Hypertension

Diuretics are among the oldest and most effective antihypertensive medications. They have furnished the cornerstone of antihypertensive therapy since the first Joint National Committee (JNC) report in 1977 through the 2003 JNC 7 report. The 2013 scientific advisory statement from the AHA/ACC/Centers for Disease Control and Prevention (CDC) and the 2016 Canadian Hypertension Guidelines[7,11] still recommend thiazide-type diuretics as the best choice to initiate antihypertensive therapy, whereas most other recent guidelines list them as one of three first-line choices (see **Table 47G.2** in the Guidelines section). Multiple RCTs have shown that thiazide-type diuretics reduce the risk of coronary events, strokes, and HF in elderly patients. In ALLHAT the diuretic was equally effective as the ACEI and CCB in preventing coronary events and strokes, more effective than the CCB in preventing HF, and in black patients, more effective than the ACEI in preventing strokes. When combined with most other classes of antihypertensive drugs, diuretics exert a synergistic effect on BP reduction, but in the ACCOMPLISH trial, the combination of an ACEI with a CCB yielded better outcomes than did combination with

hydrochlorothiazide (HCTZ).[55]

Despite the widespread popularity of HCTZ in the United States, the bulk of clinical trials supporting the benefits of diuretic therapy for hypertension did not use HCTZ but rather indapamide or chlorthalidone, thiazide-type diuretics that are more potent and longer lasting than HCTZ (see later). Thiazide-type diuretics (especially in higher doses) cause more metabolic mischief and possibly more erectile dysfunction (the latter being controversial) than do ACEIs or CCBs and have higher discontinuation rates.[64]

Mechanisms of Action

With initiation of diuretic therapy, contraction of blood volume causes the initial fall in BP. With continued therapy, blood volume is partially restored, and vasodilator mechanisms (e.g., opening of adenosine triphosphate [ATP]–sensitive potassium [K^+] channels) sustain the antihypertensive action. Loop diuretics block Na^+-K^+-$2Cl^-$ transport in the thick ascending loop of Henle. Thiazide and thiazide-like diuretics (chlorthalidone, indapamide) block the Na^+-Cl^- cotransporter in the distal convoluted tubule. Spironolactone and eplerenone prevent aldosterone from activating the mineralocorticoid receptor, thereby inhibiting activation of the epithelial sodium channel (ENaC), whereas triamterene and amiloride block ENaC directly; because less sodium is presented to the Na^+,K^+-ATPase on the vascular side of the collecting duct cells, less potassium is excreted in urine.

Clinical Use: Indapamide or Chlorthalidone Is Superior to Hydrochlorothiazide

HCTZ is the most commonly prescribed drug for hypertension, yet the most commonly prescribed daily dose of 12.5 mg is insufficient to control hypertension and has never been shown to improve CV outcomes, even when combined with other drugs. Greater effectiveness of chlorthalidone (CTD) than HCTZ is shown by post hoc analysis of the MRFIT (Multiple Risk Factor Intervention Trial) data, which showed better outcomes with CTD,[65] by a network meta-analysis,[66] and by two separate monotherapy studies in which ambulatory blood pressure monitoring (ABPM) showed a much longer duration of action.[67,68]

The ABPM data show that, with 12.5 mg of HCTZ every morning (qAM), the antihypertensive effect disappears by late afternoon, providing no protection against nocturnal hypertension during sleep (**Fig. 47.2**),[67] which is the strongest risk factor for stroke. By comparison, 6.25 mg of CTD qAM reduces BP for the full 24 hours; at 4 AM, systolic BP was 35 mm Hg lower on average with 6.25 mg of CTD than with 12.5 mg of HCTZ (**Fig. 47.2**).[67] The drop in daytime clinic SBP of approximately 15 mm Hg with 12.5 mg of HCTZ qAM (or with 6.25 mg of CTD qAM), lulls physicians into believing in the efficacy of low-dose HCTZ (while minimizing dose-dependent metabolic side-effects), but this regimen actually just converts untreated/uncontrolled hypertension to partially treated/masked uncontrolled hypertension (**see Chapter 46**).

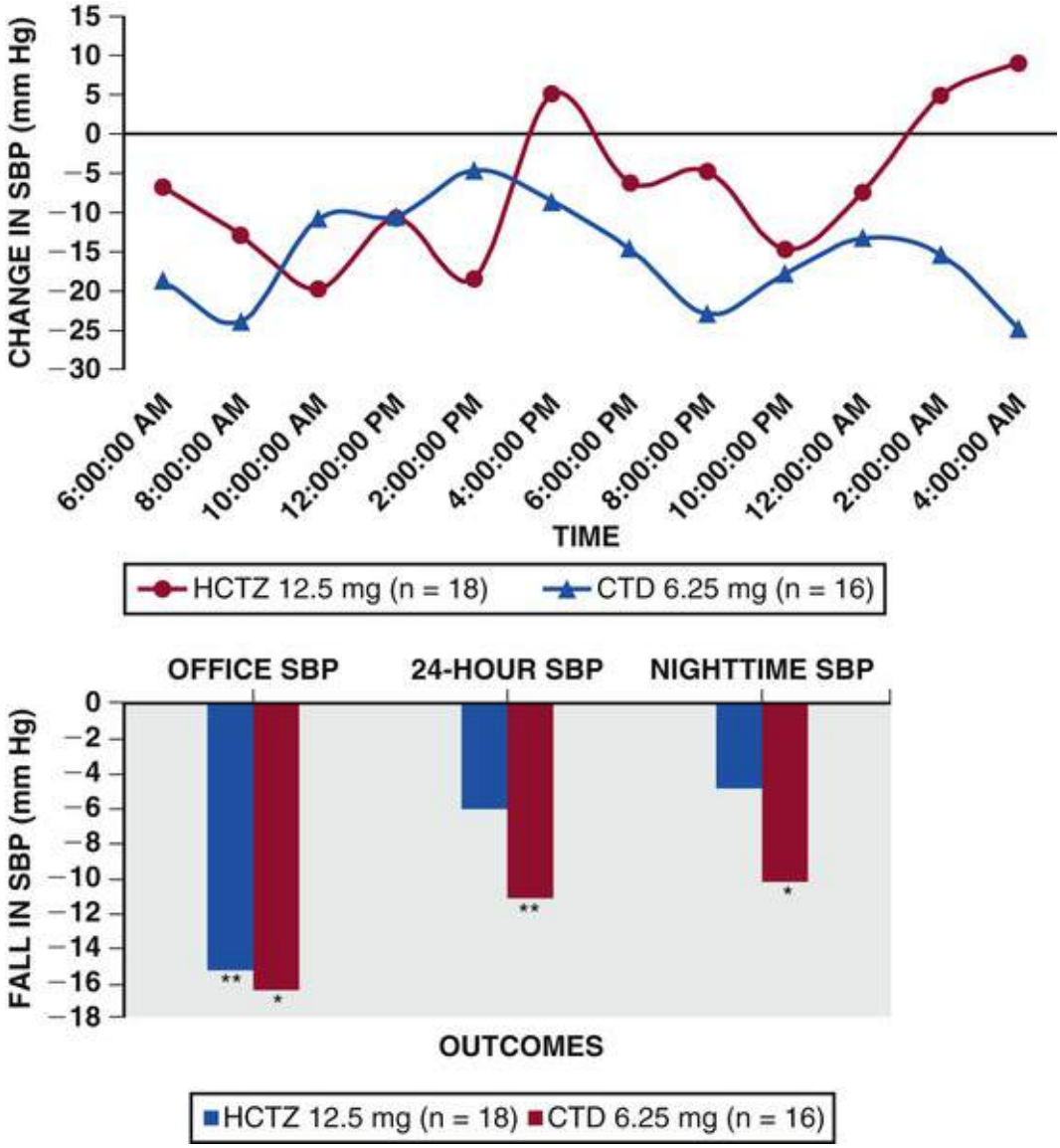


FIGURE 47.2 Comparative effects on systolic blood pressure (SBP) in patients with stage 1 hypertension randomized to monotherapy with either hydrochlorothiazide (HCTZ), 12.5 mg every morning, or chlorthalidone (CTD), 6.25 mg every morning. **Top,** Mean changes from baseline to week 12 in ambulatory blood pressure. **Bottom,** Bar graphs showing group mean reductions in office SBP, 24 hour SBP, and nighttime SBP. (From Pareek AK, Messerli FH, Chandurkar NB, et al. Efficacy of low-dose chlorthalidone and hydrochlorothiazide as assessed by 24-h ambulatory blood pressure monitoring. J Am Coll Cardiol 2016;67:383.)

Similar ABPM data are not yet available for indapamide, but a recent meta-analysis found that indapamide is more potent than HCTZ at commonly prescribed doses without causing any more adverse metabolic side-effects.[68] Indapamide, mainly in combination with perindopril, has performed well in several major phase III RCTs, including HYVET (Hypertension in the Very Elderly Trial)[69] and the PROGRESS (Preventing Strokes by Lowering Blood Pressure in Patients with Cerebral Ischemia) Trial.[70] Indapamide is available in the United States in 1.25- and 2.5-mg tablets, but the starting dose is 0.625 mg daily (one-half the low-dose tablet). For comparable reduction in office BP: 1.25 mg indapamide = 25 mg CTD = 50 to 60 mg HCTZ.[68] For uninsured patients, indapamide is more affordable than CTD.[71] Loop diuretics are less effective BP-lowering agents and should be reserved for treating hypertension in the setting of advanced CKD (stage 3 or higher). Indapamide or CTD also may be effective in patients with stage 3 CKD.

Diuretics enhance the potency of all other classes of antihypertensive agents. Thiazide-type diuretics combine particularly well with ACEIs and ARBs, which blunt the reactive RAS activation and thus increase antihypertensive efficacy. Such low-dose combinations should also reduce dose-dependent

diuretic side effects, a conjecture as yet not substantiated in formal dose-finding studies.

Side Effects

Thiazide-type diuretics can aggravate glucose intolerance (particularly in higher doses and when used in combination with a standard beta blocker), cause hypokalemia and hypomagnesemia and hyponatremia (see later), precipitate gout, and elevate serum lipids with increased hepatic triglyceride content;[72] they can also cause photosensitive dermatitis. They may be more likely than other antihypertensive drugs to cause erectile dysfunction but evidence is limited.[73] Thiazide-type diuretics are the most common cause of severe hyponatremia, especially in older women[74,75] (**Fig. 47.3**). Although less well recognized than thiazide-induced hypokalemia, thiazide-induced hyponatremia is a common reason why some elderly hypertensive individuals simply cannot tolerate even low-dose thiazides. In hypertensive patients with CKD, high doses of loop diuretics may precipitate acute renal failure, especially if combined with high-dose ACEI or ARB therapy.

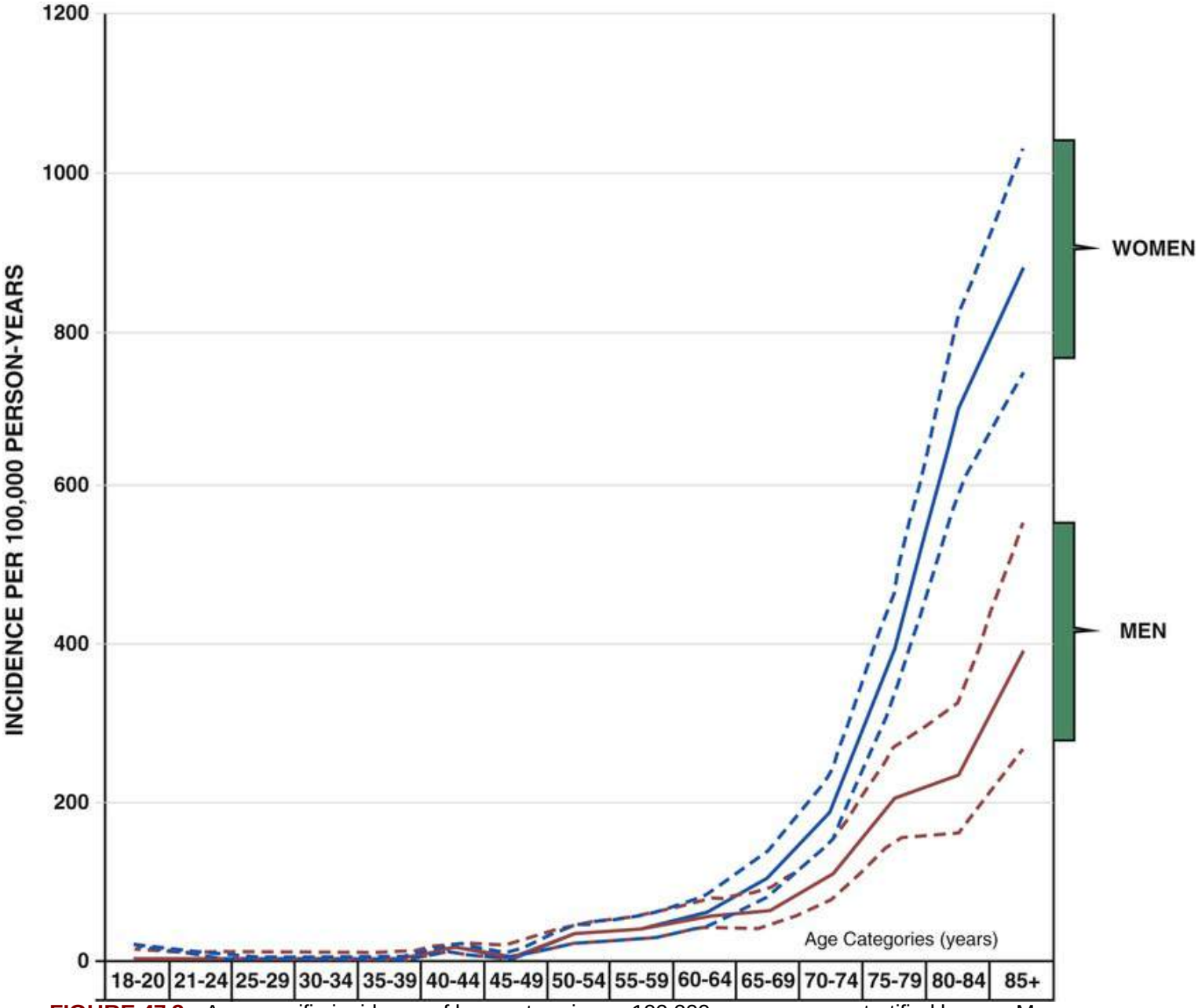


FIGURE 47.3 Age-specific incidence of hyponatremia per 100,000 person-years stratified by sex. Means (*solid lines*) and 95% confidence intervals (*dashed lines*) are shown. A total of 1033 cases of hyponatremia (serum sodium <130 mmol/L) from the Dutch Integrated Primary Care Information database between 1996 and 2011. (Modified from van Blijderveen JC, Straus SM, Rodenburg EM, et al. Risk of hyponatremia with diuretics: chlorthalidone versus hydrochlorothiazide. Am J Med 2014;127:765.)

Add-On Drug Classes for Difficult Hypertension

Aldosterone Antagonists

Low-dose spironolactone (12.5 to 50 mg daily) or eplerenone (25 to 100 mg daily) are highly effective add-on drugs for difficult cases of hypertension.[76,77] The PATHWAY-2 trial, the first RCT to compare spironolactone with other BP-lowering drugs for patients with resistant hypertension, showed that spironolactone was far superior to doxazosin ($alpha_1$-adrenergic blocker) or bisoprolol ($beta_1$-adrenergic blocker).[77] After 3 months, spironolactone was twice as effective as either of the other two active drugs in lowering home SBP, the study's primary outcome. The efficacy of spironolactone related inversely to the patients' plasma renin activity, implicating a pivotal role for excessive renal sodium retention in the pathogenesis of difficult primary hypertension. This study provides new evidence for an old idea: “The

Miracle of Low-Dose Spironolactone" [for resistant hypertension]—the title of a 1972 "clinical pearls" article penned by the late Dr. John Laragh, a concept bolstered by recent work of Dr. David Calhoun and coworkers.[78] Eplerenone is a much more specific antagonist that avoids the infrequent but disconcerting sexual side effects of low-dose spironolactone (painful gynecomastia, erectile dysfunction, nonmenstrual uterine bleeding). Hyperkalemia must be avoided when using these agents in patients with CKD.

Beta-Adrenergic Blockers

The vasodilating beta blockers carvedilol and nebivolol also are highly effective add-on drugs for difficult hypertension; standard beta blockers such as metoprolol are not.[79]

Mechanism of Action

With the initiation of standard beta-blocking drug therapy, BP changes little at first because a compensatory increase in peripheral resistance offsets the fall in cardiac output. Over time, BP falls progressively as the peripheral vasculature relaxes. Thus the antihypertensive effect of beta blockade involves decreases in cardiac output ($beta_1$ receptors), renin release ($beta_1$ receptors), and norepinephrine release (prejunctional $beta_2$ receptors). The prototype beta blocker propranolol nonselectively blocks both $beta_1$ and $beta_2$ receptors. Other standard beta blockers (metoprolol, atenolol, acebutolol, and bisoprolol) are relatively cardioselective. In low doses, they exert a greater inhibitory effect on $beta_1$ receptors than on $beta_2$ receptors, but loose selectivity at high doses. Vasodilating beta blockers such as labetalol or carvedilol also block alpha-adrenergic receptors, whereas nebivolol stimulates endogenous production of nitric oxide.

Clinical Use and Side Effects

Standard beta blockers have rather weak BP-lowering action. Atenolol and metoprolol provide little if any stroke protection compared with that afforded by ACEIs, ARBs, CCBs, or diuretics. Standard beta blockers provide modest protection against CV events but do not reduce all-cause mortality. They also increase the risk for diabetes, particularly when combined with a diuretic. Common side effects such as fatigability cause high discontinuation rates.[64] Beta blockers can impair cardiac conduction and precipitate acute bronchospasm in adults who had asthma in childhood. All beta-blocking drugs promote weight gain. Vasodilating beta blockers are much more potent antihypertensive agents and do not adversely affect glucose tolerance, but they have not undergone evaluation in large RCTs in hypertension. Data are also lacking on whether branded nebivolol is more cardioprotective than generic carvedilol, which is now included in $4/month formularies. The main limitations with generic carvedilol are the short half-life requiring twice-daily dosing and inconsistent gastrointestinal (GI) absorption, which is improved by dosing after breakfast and after dinner. Nebivolol can be dosed once daily with more consistent absorption independent of food intake. Labetalol is effective treatment of hypertensive urgency but is too short-acting to be recommended for chronic hypertension management.

Alpha-Adrenergic Blockers

Mechanism of Action

By blocking the interaction of norepinephrine on vascular alpha-adrenergic receptors, these drugs cause peripheral vasodilation, thereby lowering BP. By increasing blood flow in skeletal muscle, alpha

blockers increase insulin sensitivity. By dilating urethral smooth muscle, they improve symptoms of prostatism. Prazosin, doxazosin, terazosin, and intravenous phentolamine selectively block $alpha_1$ adrenoceptors; phenoxybenzamine blocks both $alpha_1$ and $alpha_2$ receptors.

Clinical Use and Side Effects

Phenoxybenzamine remains the drug of choice for preoperative management of pheochromocytoma (**see Chapter 92**); after alpha blockade is achieved, a beta blocker should be added to block an otherwise excessive reflex tachycardia. Selective $alpha_1$-blocking drugs are not first-line agents and should not be used as monotherapy because their propensity to cause fluid retention can lead to tachyphylaxis and unmask or exacerbate HF. When used in a combination regimen that includes a diuretic, however, they are effective add-on therapy for difficult hypertension and are particularly useful in older men with prostatism. Although marketed specifically for prostatism and not as an antihypertensive agent, the selective $alpha_{1A}$ blocker tamsulosin lowers BP and can precipitate symptomatic orthostatic hypotension in some older men.

Central Sympatholytics

Mechanism of Action

Stimulation of postsynaptic $alpha_2$-adrenergic receptors and imidazoline receptors in the central nervous system (CNS) lowers central sympathetic outflow, whereas stimulation of presynaptic $alpha_2$ receptors causes feedback inhibition of norepinephrine release from peripheral sympathetic nerve terminals. These combined actions reduce adrenergic drive to the heart and peripheral circulation.

Clinical Use and Side Effects

The central sympatholytics are best reserved for short-term oral treatment of hypertensive urgency when beta blockers (i.e., labetalol) are contraindicated. The central sympatholytics are potent antihypertensive agents that may be needed as add-on therapy for very difficult hypertension, but their troublesome CNS side effects reduce quality of life. To avoid rebound hypertension between doses, short-acting clonidine must be given every 6 to 8 hours or, whenever possible, discontinued through gradual tapering.[80] Rebound hypertension is less of a problem with guanfacine, a longer-acting oral central sympatholytic that is dosed at bedtime. The transdermal clonidine has erratic absorption and causes frequent dermatitis. Alpha-methyldopa is poorly tolerated and no longer a first-line therapy for hypertension in pregnancy.

Direct Vasodilators

Mechanism of Action

The potent hyperpolarizing arterial vasodilators minoxidil and hydralazine act by opening vascular ATP-sensitive K^+ channels.

Clinical Use

By causing selective and rapid arterial dilation, both drugs induce profound reflex sympathetic activation and tachycardia. Hydralazine is useful for the treatment of preeclampsia and as rescue therapy for very

difficult hypertension. A combination of hydralazine plus nitrates is useful for the treatment of HF, specifically in non-Hispanic black patients, in whom hypertensive heart disease causes HF most frequently (**see Chapters 25 and 26**). Severe hypertension accompanying advanced CKD is the main indication for minoxidil, which must be combined with a beta blocker to prevent excessive reflex tachycardia and with a loop diuretic to prevent excessive fluid retention. Initiation of chronic hemodialysis usually is a more effective means of controlling hypertension in this setting.

Percutaneous Interventions for Management of Blood Pressure

Renal Denervation

Percutaneous catheter-based radiofrequency ablation of the renal nerves, referred to as renal denervation (RDN), entered clinical practice in Europe and Asia as a novel treatment of drug-resistant hypertension, with clinical guidelines published by 2013. Based on unblinded data from phase I and phase II trials and office BP measurements, these guidelines are being reevaluated because of the disappointing results of the blinded sham-controlled phase III Symplicity HTN-3 Trial, which did not reach its primary efficacy endpoint.[81] Ongoing research hopes to define the extent of renal nerve destruction at the point of care, relative merits of RDN versus optimal medication management, patient subsets who would be most likely and least likely to benefit, sustainability of the therapeutic benefit in view of possible reinnervation, and long-term safety (**see Chapter 46**).

Carotid Baroreflex Activation Therapy

Electrical field stimulation of the carotid sinus, known as carotid baroreflex activation therapy, holds promise as a device-based intervention to supplement, but not replace, drug therapy for patients with resistant hypertension.[82] Acute electrical field stimulation of even one carotid sinus can cause a sufficiently large reflex decrease in BP to overcome offsetting reflexes from the contralateral carotid baroreceptors and aortic baroreceptors that are not paced. However, the initial phase III Rheos Pivotal Trial on continuous carotid baroreceptor pacing for resistant hypertension with the first-generation baroreceptor pacemaker yielded equivocal data on efficacy and adverse effects due to facial nerve injury during surgical implantation.[83] A miniaturized second-generation pacing electrode has seemingly overcome the safety issue, and early results with the new device suggest efficacy of unilateral carotid sinus stimulation in HF.

Evidence-Based Approach to Hypertension Management

A large body of RCTs has produced unequivocal evidence that drug treatment of hypertension reduces the risk of major cardiovascular events, end-stage renal disease, and death. In most hypertension trials, the follow-up is 3 to 5 years. The reported short-term risk reductions underestimate the lifetime benefit accrued over decades of effectively managed high BP.

Important questions remain, however. This section reviews the evidence, keyed to **Tables 47.8 to 47.11**, to address two issues: how far to lower BP and which drugs for which patients.

TABLE 47.8

Recent Hypertension Trials Randomizing Patients to More Intensive vs. Less Intensive Drug Therapy

	ACCORD (2010)	SPRINT (2015)	SPRINT (age ≥75) (2016)	HOPE-3 (2016)	SPS3 (2014)
Sample size	4733	9361	2636	12,705	3020
Patient population	Type 2 diabetes	Nondiabetics, high CV risk, no prior stroke	Nondiabetics, high CV risk, no prior stroke	Intermediate risk, no prior CV disease	Prior lacunar stroke
Mean age (yr)	62	68	80	66	63
Annual CV event rate of control group (%)	2.09	2.19	3.85	0.94	2.77
Method of BP measurement	Office oscillometric monitor (medical staff present)	Unattended AOBP	Unattended AOBP	Conventional office BP	Conventional office BP
Group difference in achieved SBP (mm Hg)	−15 (119 vs. 134)	−15 (121 vs. 136)	−11 (124 vs. 135)	−6 (128 vs. 134)	−11 (127 vs. 138)
Group difference in achieved DBP (mm Hg)	−7 (64 vs. 71)	−7 (69 vs. 76)	−5 (62 vs. 67)	−3 (76 vs. 79)	−11 (127 vs. 138)
BP medications	3 vs. 2 classes	3 vs. 2 classes (CTD + amlodipine + azilsartan)	3 vs. 2 classes (CTD + amlodipine + azilsartan)	Candesartan 16 mg QD + HCTZ 12.5 mg QD vs. placebo	2.4 vs. 1.8 drug classes (no specific protocol)
Outcomes	NS difference in CV events or renal events −41% stroke ($P = 0.03$)	−25% CV events ($P < 0.001$) −27% all-cause mortality ($P < 0.001$)	−34% CV events ($P < 0.001$) −33% all-cause mortality ($P < 0.001$)	NS reduction in CV events	−19% all strokes ($P = 0.08$) −63% intracerebral hemorrhage ($P = 0.03$)

AOBP, Automatic office blood pressure; *CTD,* chlorthalidone; *CV,* cardiovascular; *DBP,* diastolic blood pressure; *HCTZ,* hydrochlorothiazide; *NS,* no significant; *SBP,* systolic blood pressure.

ACCORD, Action to Control Cardiovascular Risk in Diabetes; HOPE-3, third Heart Outcomes Protection Evaluation; SPRINT, Systolic Blood Pressure Intervention Trial; SPS3, Secondary Prevention of Small Subcortical Strokes.

TABLE 47.9

Recent Meta-Analyses Comparing Outcomes with More Intensive vs. Less Intensive Antihypertensive Drug Therapy

BOTH DIABETIC AND NONDIABETIC PATIENTS					DIABETIC PATIENTS ONLY	
	Sundstrom et al (2015)	**Ettehad et al (2015)**	**Xie et al (2016)**	**Verdecchia et al (2016)**	**Emdin et al (2015)**	**Brunstrom, Carlberg (2016)**
Sample size	15,266 participants of 13 trials	613,815 participants of 123 trials	44,989 participants of 19 trials	53,405 participants of 18 trials	100,350 participants of 40 trials	73,738 participants of 49 trials
Patient population	Diabetics with mild (stage 1) hypertension and no prior CV events; mean age 63 ("old" by JNC 8)	Includes comorbidities excluded from SPRINT: diabetes, stroke, advanced CKD	Includes comorbidities excluded from SPRINT: diabetes, stroke, advanced CKD	Includes SPRINT and comorbidities excluded from SPRINT: diabetes, prior stroke, advanced CKD	Type 2 diabetes with or without hypertension	Diabetics with baseline SBP >150, 140-150, or <140 mm Hg
Blood pressure	From baseline of 146/84 mm Hg, achieved BP reduction: 3.6/2.4 mm Hg lower with active therapy	From baseline SBP <130, further 10 mm Hg reduction in SBP	Achieved BP: 133/76 vs. 140/81 mm Hg	Achieved BP reduction: 8/5 mm Hg lower with intensive therapy	Achieved SBP:≥130 vs. <130 mm Hg	Achieved SBP: 130-140 vs. <130 mm Hg
Outcomes	−25% CV deaths ($P < 0.05$) −15% stroke ($P = 0.06$) −9% coronary events (P = NS)	−36% CV events ($P < 0.001$) −45% CHD ($P < 0.001$) −47% all mortality ($P < 0.001$) +2% ESRD (P = NS)	−14% CV events ($P < 0.01$) −13% MI ($P < 0.05$) −22% stroke ($P < 0.01$) −19% retinopathy ($P < 0.01$) −10% ESRD (P = NS)	−19% CV death ($P = 0.04$) −20% stroke ($P = 0.01$) −15% MI ($P = 0.02$) −24% HF ($P = 0.04$)	Achieved SBP ≥130 vs. <130: −26% vs. −4% CV death (P=0.002) −30% vs. −3% CHD ($P = 0.004$) −24% vs. −28% stroke (P = NS) −25% vs. 0% HF ($P = 0.07$) −26% vs. +1% ESRD (P = NS)	Achieved SBP ≥130 vs. <130: −14% vs. +26% CV death (P<.05) −12% vs. −6% MI ($P < 0.05$) −9% vs. 35% stroke ($P = 0.05$) −19% vs. −7% HF ($P < 0.05$) −16% vs. +1% ESRD (P = NS)

CHD, Coronary heart disease; *CKD,* chronic kidney disease; *CV,* cardiovascular; *ESRD,* end-stage renal disease; *HF,* heart failure; *MI,* myocardial infarction; *NS,* not significant; *SBP,* systolic blood pressure SPRINT, Systolic Blood Pressure Intervention Trial.

TABLE 47.10

Recent Observational Studies of the J-Curve Hypothesis

	VERDECCHIA ET AL (2015)	KJELDSEN ET AL (2016)	VIDAL-PETIOT ET AL (2016)	ADAMSSON ERYD ET AL (2016)	MYERS ET AL (2016)	MCEVOY ET AL (2016)
Study design	Post hoc analysis of ONTARGET (both treatment arms combined)	Post hoc analysis of VALUE (both treatment arms combined)	CAD Registry (CLARIFY: 45 countries)	Primary Care Registry (Sweden)	Hypertension Registry (Ontario, Canada)	Natural History Study (ARIC)
Sample size	19,102 participants	15,244 participants	22,672 patients	187,106 patients	6183 patients	11,565 participants
Study population	Patients with hypertension and CAD; 31% diabetics	Patients with hypertension and high CVD risk;46% had CAD	Patients with hypertension and stable CAD; 33% diabetics	Outpatients all with type 2 diabetes and no prior CV events	Outpatients all taking BP medication; 27% diabetics	28% taking BP medication; 8% diabetics
Mean age (yr)	66	67	65	60	76	57
BP method	Oscillometric office BP (2 readings)	Manual office BP	Manual office BP	Manual office BP	AOBP (mean of 5 readings)	Manual office BP (random zero)
Average baseline BP (mm Hg)	141/82	155/87	134/78	145 SBP	134/72	121 SBP
Achieved DBP <60 mm Hg (%)	0	<5	9	Not reported	10	9
Cardiac diastolic J curve?	No flat MI risk from DBP 85 to <70 mm Hg	No flat MI risk with DBP <76 mm Hg	Yes, at DBP 60-69 mm Hg: +40% CV events +43% MI At DBP <60 mm Hg: +200% CV events +238% MI	Not studied	Unclear at DBP <60 mm Hg: +31% CV events (CHD/MI not reported)	Yes (but different thresholds for hs-cTNT and CHD events) At DBP 70-79 mm Hg: −15% hs-cTNT (P = 0.004) +20 CHD (P = 0.01) At DBP 60-69 mm Hg: −5% hs-cTNT (P = 0.005) +23% CHD (P = 0.01) At DBP <60 mm Hg: +46% hs-cTNT +49% CHD
Cardiac systolic J curve?	No flat MI risk from SBP 139 to <120 mm Hg	No flat MI risk with SBP <131 mm Hg	Yes, at SBP <120 mm Hg: +156% CV events +48% MI	No, at SBP 110-119 mm Hg: −24% nonfatal MI (P = 0.003) −18% nonfatal CVD (P = 0.002)	Yes, at SBP <110 mm Hg: +38% CV events	No
Stroke diastolic J curve?	No Progressive reduction in stroke risk from DBP 81 to <70 mm Hg	No Progressive reduction in stroke risk to DBP 60 mm Hg	No	Not studied	Not studied	No
Stroke systolic J curve?	No Progressive reduction in stroke risk from SBP 139 to <120 mm Hg	No Progressive reduction in stroke risk to SBP 122 mm Hg	No	No At SBP 110-119 mm Hg: −16% nonfatal stroke (P = 0.07) −15% total stroke (P = 0.09)	Not studied	No

CAD, Coronary artery disease; *CHD,* coronary heart disease; *CKD,* chronic kidney disease; *CV,* cardiovascular; *DBP,* diastolic blood pressure; *hs-cTNT,* high-sensitivity cardiac troponin T; *MI,* myocardial infarction; *NS,* not significant; *SBP,* systolic blood pressure.

ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; VALUE, Valsartan Antihypertensive Long-term Use Evaluation.

TABLE 47.11

Hypertension Randomized Trials Organized by Risk Gradient

BASELINE SBP IN	ACHIEVED SBP IN	GROUP

TRIAL	TREATMENT GROUP	COMPARATOR GROUP	TREATMENT GROUP (mm Hg)	TREATMENT GROUP (mm Hg)	SBP DIFF (mm Hg)	OUTCOMES
Patients with Prehypertension						
TROPHY	ARB	Placebo	134	134	−2	−12% incident hypertension ($P < 0.001$)
Intermediate Risk Persons Without CVD						
HOPE 3	ARB + D	Placebo	138	128	−6	NS difference in CV events
Hypertensive Patients in General						
FEVER	CCB + D	D + placebo	159	137	−4	−27% CV events ($P < 0.001$)
ELSA	CCB + D	BB + D	162	142	0	NS difference in CV events
NORDIL	CCB (DLTZ) + ACEI	BB + D	174	154	−3	NS difference in CV events ($P = 0.04$)
CAPPP	ACEI (captopril)	BB + D	162	152	+3	+5% CV events (P = NS)
CONVINCE	CCB (verapamil) + D	BB + D	150	136	0	NS difference in CV events
VALUE	CCB + D	ARB + D	156	139	−2	−3% CV events (P = NS)
ASCOT	ACEI + CCB	BB + D	164	137	−3	−16% CV events ($P < 0.001$)
ACCOMPLISH	ACEI + CCB	ACEI + D	145	132	−1	−21% CV events ($P < 0.001$)
ALLHAT	D + BB	ACEI + BB	145	134	−1	NS difference in CV events
ALLHAT	D + BB	CCB + BB	145	134	−1	NS difference in CV events
ONTARGET	ACEI + ARB	ACEI or ARB	142	132	−2	NS difference in CV events, +175% hypotension ($P < 0.001$), +58% renal impairment ($P < 0.001$)
Hypertension in Elderly Patients						
HYVET	ACEI + D	Placebo	173	145	−15	−34% CV events ($P < 0.001$)
SCOPE	ARB + D	D + placebo	166	144	−3.2	−28% nonfatal strokes ($P = 0.04$)
SHEP	BB + D	Placebo	171	145	−13	−36% strokes ($P < 0.001$)
SPRINT (age ≥75 yr)	More intensive Rx (drugs)	Less intensive Rx (drugs)	142	123	—	—
SystEur	ACEI + CCB	Placebo	174	151	−10	−31% CV events ($P < 0.001$)
SystChina	ACEI + CCB	Placebo	170	159	−9	−37% CV events ($P < 0.004$)
Coope and Warrender	BB + D	Placebo	196	178	−18	−42% strokes ($P < 0.03$)
STOP	BB + D	Placebo	195	167	−20	−40% CV events ($P < 0.003$)
STOP 2	ACEI or CCB	BB + D	194	159	0	NS difference in CV events
Hypertension with Left Ventricular Hypertrophy						
LIFE	ARB + D	BB + D	176	146	−2	−37% CV mortality ($P = 0.03$)
Hypertension in Patients with Diabetes Mellitus						
ADVANCE	ACEI + D	Placebo	145	139	−6	−18% CV events ($P < 0.03$)
ALTITUDE	DRI + ACEI or ARB	Placebo + ACEI or ARB	137	139	−1	NS difference in CV + renal events; +34% hyperkalemia ($P < 0.001$); +46% hypotension ($P < 0.001$)
ACCORD	More intensive Rx (3.4 drugs)	Less intensive Rx (2.1 drugs)	139	119	−14	NS difference in CV + renal events; −41% stroke ($P = 0.03$)
Hypertension in Patients at High CV Risk Without Diabetes						
SPRINT	More intense (3.0 drugs)	Less intense (1.9 drugs)	140	121	−15	Stopped early due to −25% CV events ($P < 0.0001$); −27% all-cause mortality ($P = 0.003$); −43% CV death ($P = 0.005$)
Hypertension in Patients with Diabetic Nephropathy						
IDNT	ARB	Placebo	160	140	−3	−20% renal impairment ($P < 0.001$)
IDNT	ARB	CCB	160	140	0	−23% renal impairment ($P = 0.006$)
RENAAL	ARB	Placebo	152	140	−3	−16% renal impairment ($P = 0.02$)
Hypertension in Patients with Nondiabetic Chronic Kidney Disease						
AASK	ACEI + D + AB	BB + D + AB	151	135	−1	−22% renal impairment ($P = 0.04$)
AASK	ACEI + D + AB	CCB + D + AB	151	135	+1	−38% renal impairment ($P = 0.004$)
REIN	ACEI	Placebo	150	145	+1	−56% renal decline ($P = 0.03$)
Blood Pressure Reduction for Secondary Prevention of Coronary Events						
INVEST	CCB (verapamil) + ACEI	BB + D	150	132	0	NS difference in CV events
Blood Pressure Reduction for Secondary Prevention of Stroke						
SPS3	2.4 drugs	1.8 drugs				
PROGRESS	ACEI + D	Placebo	149	133	−12	−43% strokes ($P < 0.001$)
PROGRESS	ACEI	Placebo	147	140	−5	NS difference in stroke
PROFESS	ARB	Placebo	144	136	−4	NS difference in stroke

AB, Alpha blocker; *BB,* beta blocker; *DIFF,* difference in SBP reduction between the experimental treatment group and the comparison group; *DLTZ,* diltiazem; *NS,* not significant.

TROPHY, Trial of Preventing Hypertension; FEVER, Felodipine Event Reduction; ELSA, European Lacidipine Study on Atherosclerosis; NORDIL, Nordic Diltiazem; CAPPP, Captopril Prevention Project; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular Endpoints; VALUE, Valsartan Antihypertensive Long-term Use Evaluation; ASCOT, AngloScandinavian Outcomes Trial; ACCOMPLISH, Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension; ALLHAT, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; HYVET, Hypertension in the Very Elderly Trial; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; SystEur, Systolic Hypertension in Europe; SystChina, Systolic Hypertension in China; STOP, Swedish Trial in Old Patients with

Hypertension; STOP-2, Second Swedish Trial in Old Patients with Hypertension; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension; ADVANCE, Action in Diabetes in Vascular Disease Preterax and Diamicron MR Controlled Evaluation; ALTITUDE, Aliskiren Trial in Type 2 Diabetes using Cardiorenal Endpoints; ACCORD, Action to Control Cardiovascular Risk in Diabetes; SPRINT, Systolic Blood Pressure Intervention Trial; IDNT, Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; AASK, African American Study of Kidney Disease; REIN, Ramipril Efficacy in Nephropathy; INVEST, International Verapamil Trandolapril Study; SPS3, Secondary Prevention of Small Subcortical Strokes; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; PROFESS, Prevention Regimen for Effectively Avoiding Second Strokes.

How Far to Lower Blood Pressure

Considerable current controversy surrounds the optimal threshold level of SBP to initiate medication therapy and the optimal target level of BP to be achieved.[84,85] Epidemiologic data establish that CV risk begins to increase with BP above 110/70 mm Hg (**Chapter 46**), a level much below any currently recommended threshold for initiation of BP-lowering medication. However, in most hypertension RCTs published before 2014, the active treatment group never achieved a mean SBP below 140 mm Hg and in older patients rarely achieved a mean systolic BP below 150. Most of these RCTs were designed to compare a new drug with an old drug or to compare different drug classes, not to compare more intensive with less intensive treatment goals. Based on the available evidence and with concern that overtreatment of high BP in older patients could cause symptomatic orthostatic hypotension with injurious falls, the 2014 JNC 8 report[8] relaxed the recommended treatment thresholds for hypertensive patients age 60 or older from 140/90 to 150/90 mm Hg. Based largely on the results of the 2010 ACCORD (Action to Control Risk in Diabetes) trial,[86] this report also relaxed the recommended treatment threshold for patients with diabetes from 130/80 to 140/90 mm Hg. Subsequently, new trials have addressed this issue (**see Table 47.8**), as have recent meta-analyses (**Table 47.9**), and observational studies (**Table 47.10**). With the new data reviewed next, some but not all expert panels have begun to endorse more intensive therapy for hypertension for selected high-risk groups of patients (**see Tables 47G.2 and 47G.3** in the Guidelines section).

Recent Trials

Table 47.8 compares ACCORD with subsequent major trials regarding the outcomes of more intensive versus less intensive antihypertensive drug therapy. ACCORD was underpowered with fewer-than-expected CV events for patients with type 2 diabetes;[86] nonetheless, there was a significant reduction in relative stroke risk (**Fig. 47.4**).[86] Then, in 2015–2016, publication of SPRINT (Systolic Blood Pressure Intervention Trial)[87,88] directly challenged the 2014 recommendation to relax the BP treatment target for older patients—at least for nondiabetic patients with high CV risk scores but without prior stroke, prior HF, or advanced CKD. With twice the sample size as ACCORD, SPRINT was well powered for the primary composite CV outcome and was stopped early because of a 27% reduction in mortality for the overall group (**Fig. 47.5**)[87] and a 33% reduction in those age 75 or older.[88] In subgroup analysis, all the point estimates show approximately a 25% reduction in CV events with intensive therapy, but the 95% confidence intervals cross the line of identity for several important subgroups, including women, blacks, or those with prior CV disease or prior CKD (**Fig. 47.5**).[87] Because each of these subgroups comprised approximately 30% of the total cohort, the lack of a statistically significant intervention effect may be caused by subgroup sample size. The lack of a statistically significant intervention effect on stroke or on myocardial infarction (MI), another limitation of SPRINT,[84] also may result from statistical power. In direct challenge to the 2014 guidance, the greatest risk reduction was in patients age 75 and older (**Table**

47.8) and in those with baseline SBP of 132 mm Hg or higher (Fig. 47.5). Intensive therapy did not increase rates of symptomatic orthostatic hypotension, injurious falls, or acute coronary syndrome, even in those 75 or older.

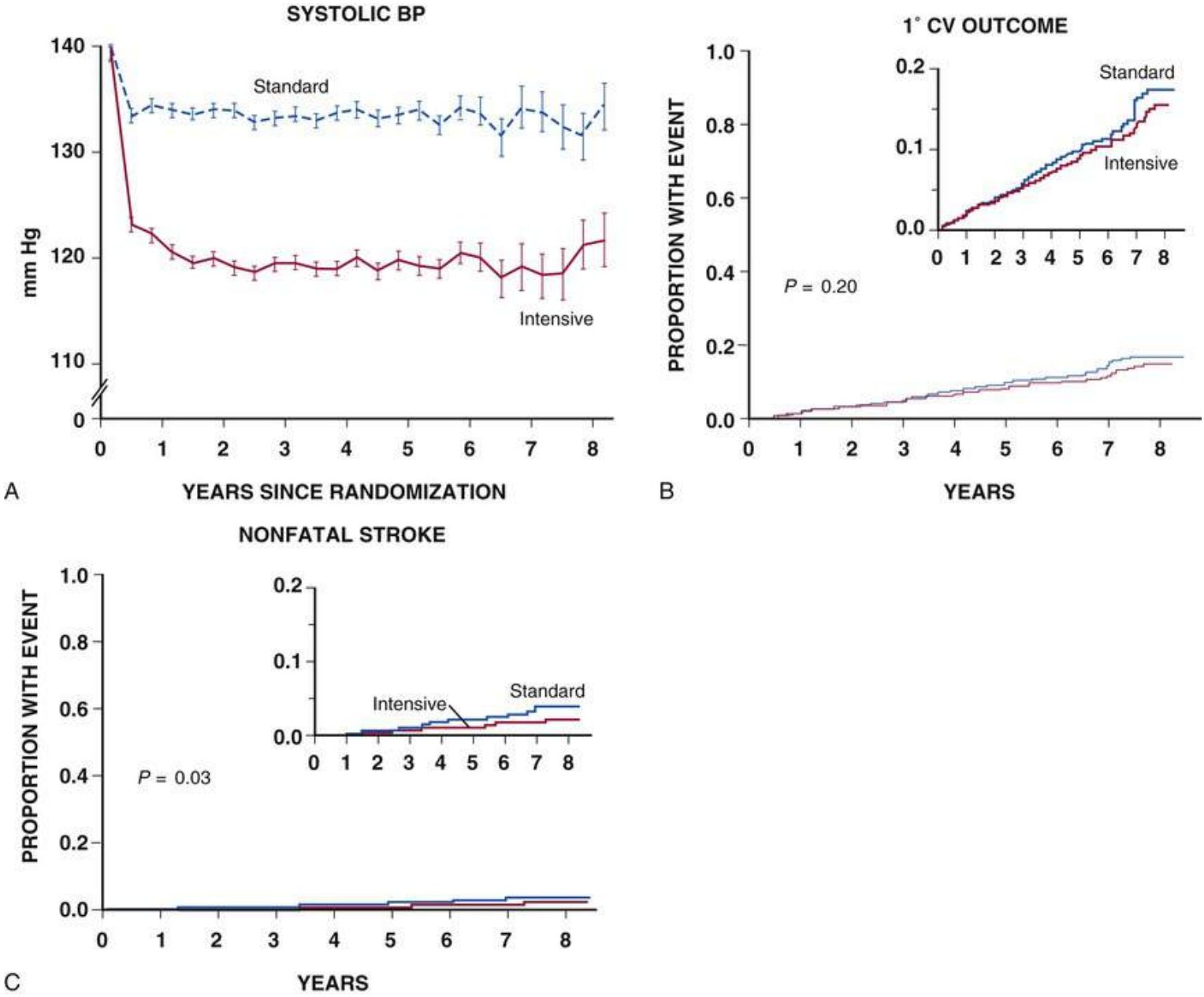
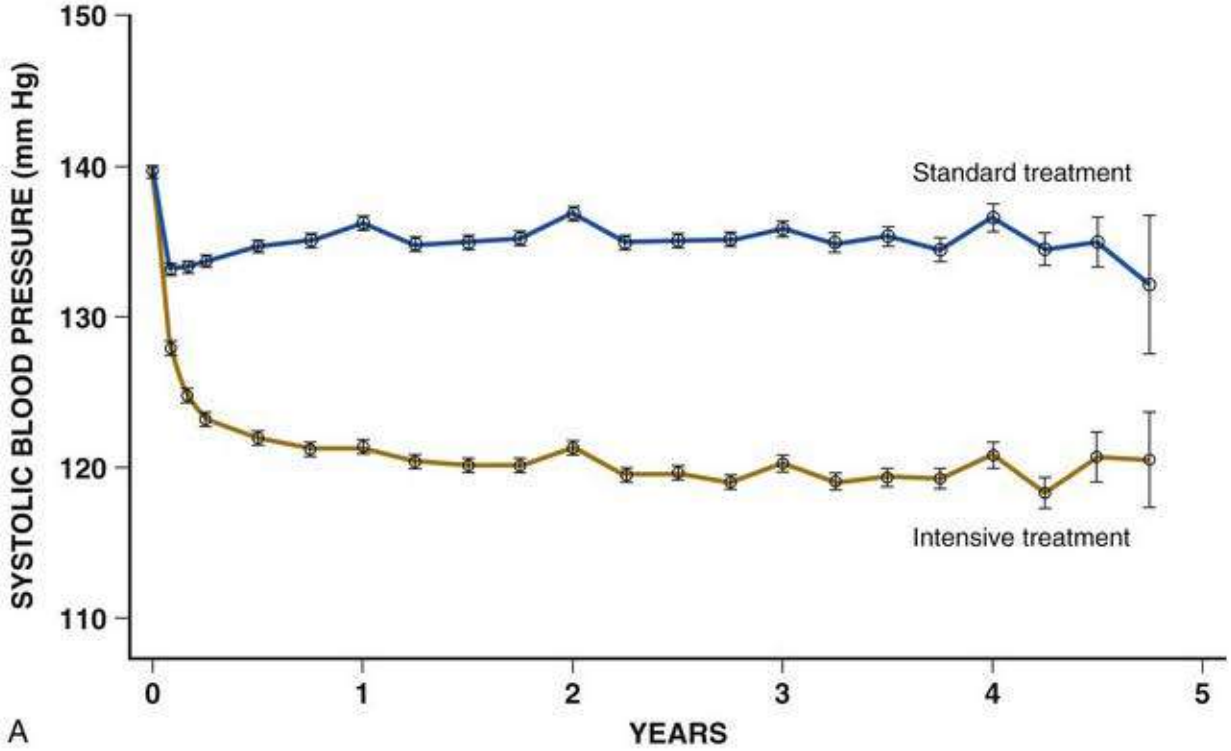
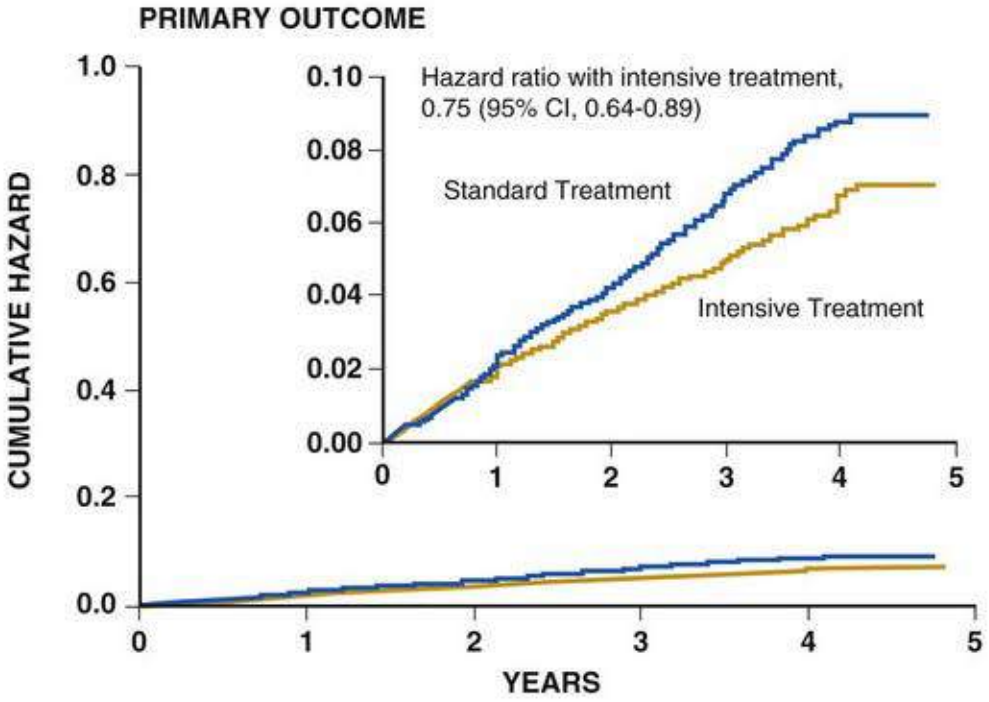


FIGURE 47.4 Major outcomes of the ACCORD study. **A,** Systolic blood pressure (BP) levels achieved with standard and intensive treatment are shown, along with corresponding Kaplan-Meier analyses for **B,** the primary cardiovascular (CV) outcome (nonfatal myocardial infarction, nonfatal stroke, or death from CV causes), and **C,** nonfatal stroke. The *insets* show close-up versions of the graphs in each panel. (From Cushman WC, Evans GW, Byington RP, et al; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575.)

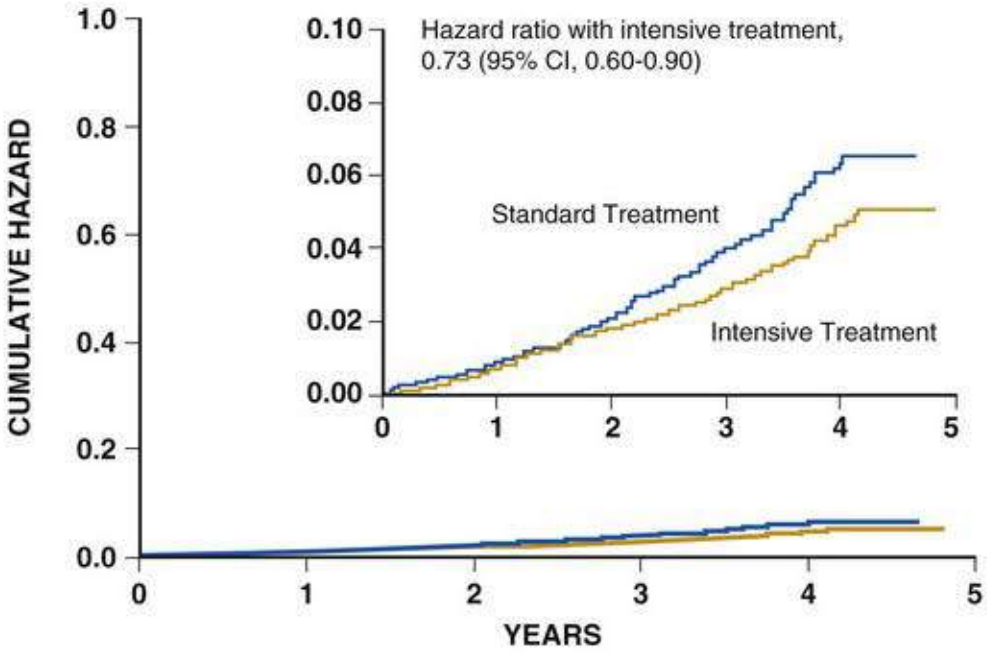

150
140
130
120
110
SYSTOLIC BLOOD PRESSURE (mm Hg)
Standard treatment
Intensive treatment
0
1
2
3
4
5
YEARS

A



No. at Risk

Standard Treatment	4683	4437	4228	2829	721
Intensive Treatment	4678	4436	4256	2900	779



No. at Risk

Standard Treatment	4683	4528	4383	2998	789
Intensive Treatment	4678	4516	4390	3016	807

B

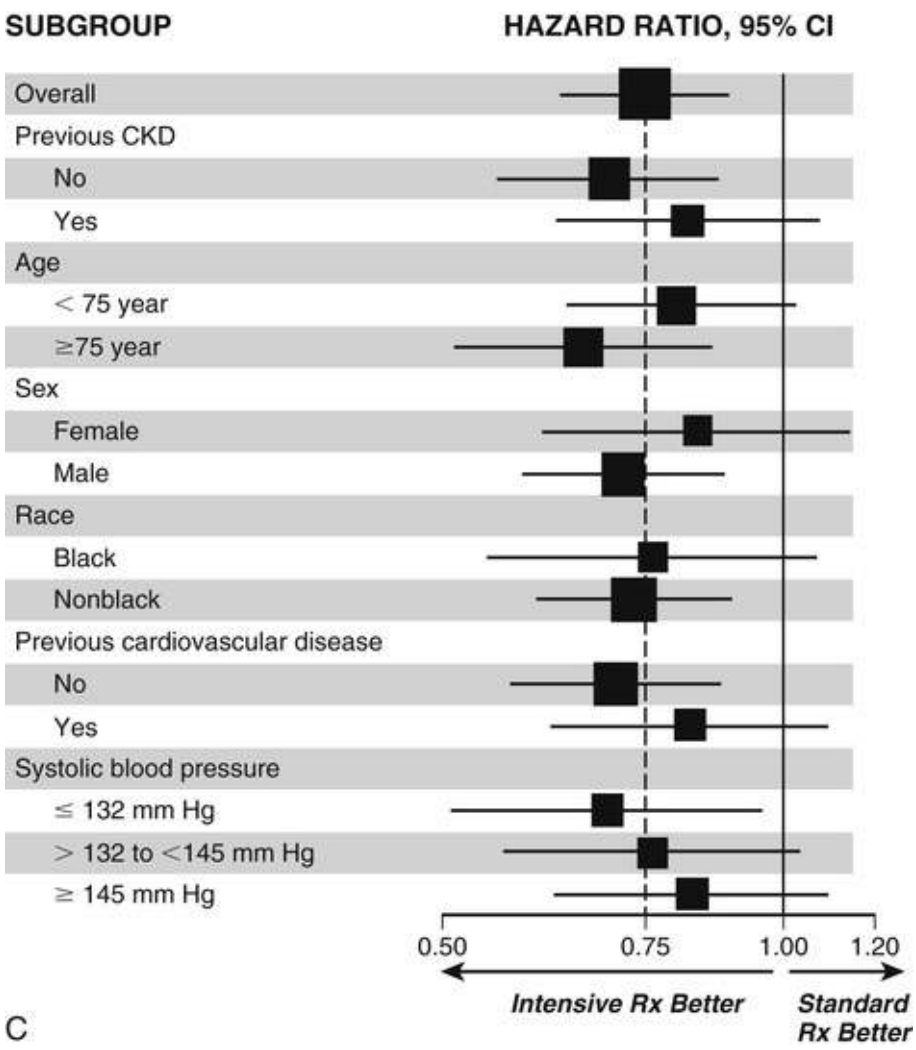


FIGURE 47.5 Major outcomes of SPRINT. **A,** Systolic blood pressure levels achieved with standard and intensive treatment are shown, along with corresponding Kaplan-Meier analyses for **B,** the primary outcome (nonfatal myocardial infarction, nonfatal stroke, or death from CV causes) and death from any cause (*insets* showing close-up versions of the graphs), and **C,** forest plot of the primary outcome according to subgroup; CI, confidence interval; CKD, chronic kidney disease. (From The SPRINT Research Group, Wright JT, Williamson JD, Whelton PK et al.: A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373(22):2103-16.)

However, the benefits of intensive therapy came at a price: increased rates of adverse events, including hyponatremia, hypokalemia, hypotension, and acute kidney injury (AKI), all of which may related to combination therapy with the most potent ARB (azilsartan) and the most potent thiazide-type diuretic (CTD). Also, the results of SPRINT do not apply directly to patients excluded from the trial: patients with diabetes, those with low or intermediate CV risk scores, elderly patients who are institutionalized, or those with advanced CKD or prior HF or stroke. In this regard, the SPS3 (Secondary Prevention of Small Subcortical Strokes) trial compared more to less intensive therapy for secondary stroke prevention in patients with lacunar infarcts.[89] This likely underpowered study yielded equivocal results except for a positive effect on hemorrhagic stroke (**Table 47.8**).

SPRINT also has been compared with the HOPE (Heart Outcomes Prevention Evaluation) 3 BP trial (**Table 47.8**), which used a mild fixed-dose BP regimen of candesartan (16 mg daily) plus HCTZ (12.5 mg daily) versus placebo. HOPE-3 was not a hypertension trial per se: the patients had intermediate CV risk scores, no prior CV disease, and only one third had hypertension.[90] The candesartan dose was half-maximum and the 6–mm Hg greater reduction in SBP in the active treatment group represents an overestimate of the BP reduction actually afforded because, as shown earlier in **Fig. 47.2**, the BP-lowering effect of 12.5 mg HCTZ qAM dissipates in the afternoon with no effect on nocturnal

hypertension.[67]

When comparative efficacy of more intensive versus less intensive BP treatment targets is a trial's primary objective, the accuracy of BP measurement is a key consideration. Although HOPE-3 and SPS3 relied on casual office BP measurements and ACCORD measured office BP with an oscillometric monitor, only SPRINT utilized automated office blood pressure (AOBP, **Chapter 46**), in an effort to minimize the "white coat" (alerting) reaction that plagues conventional office-based measurement of BP.[87] With the patient unattended in the examination room for 5 minutes, an automatic monitor took three readings (one per minute), which were averaged. The AOBP is at least 5/5 mm Hg lower than conventional office readings, but this approach does not fully eliminate the white coat reaction.[11] Moreover, a medication regimen that corrects the patient's AOBP may leave ambulatory and nocturnal hypertension uncorrected. As such, lack of ABPM is a key limitation of SPRINT (and most other hypertension trials). Antihypertensive medication converts uncontrolled hypertension to masked ambulatory/nocturnal hypertension in as many as 40% to 70% of hypertensive patients with type 2 diabetes, those with CKD, and those of non-Hispanic black race/ethnicity (**see Chapter 46**).[91] Because unknown numbers of patients in these trials were overtreated or undertreated, the optimal benefit of therapy was underestimated.

Recent Meta-Analyses

Several recent meta-analyses compared the benefits of more intensive versus less intensive antihypertensive drug therapy by including RCTs that enrolled hypertensive patients with comorbidities that were exclusion criteria for SPRINT: diabetes, prior stroke, and advanced CKD (**Table 47.9**). Meta-analyses have potential inherent biases related to the RCTs the authors chose to include and exclude. Yet, the results of these separate analyses support and extend the SPRINT outcomes in important ways. Analyses that included RCTs of both diabetic and nondiabetic patients generally indicate that the benefits of more intensive BP-lowering therapy apply not only to the composite endpoint of CV events but also to the separate components of stroke and MI.[92,93] However, the benefit of more intensive therapy does not seem to apply to end-stage renal disease (ESRD), raising the possibility that in some patients the optimum level of SBP to preserve renal function is higher than to prevent MI and stroke.[93] Analyses that included RCTs of diabetic patients exclusively[94,95] indicate that for patients with type 2 diabetes, the 2014 recommendation treatment target of office SBP of 130 to 140 mm Hg provides optimal protection against CV death, MI, and ESRD, whereas the more intensive treatment target of office SBP below 130 mm Hg provides less protection against those outcomes and even may be detrimental, while providing better protection against stroke and retinopathy.[95] In contrast, a new large-scale Swedish registry study indicates that an achieved SBP of 110 to119 mm Hg provides optimal CV protection in patients with type 2 diabetes (see later).[96]

Recent Observational Studies on Cardiac J-Curve Hypothesis

Several new observational studies have rekindled the debate over the J-curve hypothesis (**Table 47.10**). This hypothesis holds that intensive reduction of diastolic blood pressure (DBP)—coronary perfusion pressure—can cause coronary underperfusion and provoke myocardial ischemia, MI, and death, especially in patients with obstructive coronary disease and LVH.[97] Although a DBP of 0 obviously is lethal, the question is, "Does reduction in DBP to the levels routinely achieved in outpatient practice provoke myocardial ischemia?" The 2015 ACC/AHA/ASH scientific statement on the treatment of hypertension in patients with CAD relaxed the recommended treatment target from office BP less than

130/80 mm Hg to less than 140/90 mm Hg.[14] The authors compromised by saying that the previously recommended lower office BP target of less than 130/80 may be appropriate in some patients with coronary artery disease (CAD) or CAD risk equivalents. They also cautioned that overzealous reduction of DBP to less than 60 mm Hg may precipitate myocardial ischemia in patients with stable CAD over 60 years of age or those with diabetes.

Subsequent observational studies both support and contradict the J-curve hypothesis and raise concerns about reverse causality: comorbidity (e.g., advanced cancer) or isolated systolic hypertension (which itself carries a high CV risk) may have caused the low DBP. Because forward blood flow in the epicardial coronary arteries occurs only during diastole (a unique feature of the coronary circulation due to systolic compression), the hypothesis also holds that there is no cardiac "J curve" for SBP reduction and no selective diastolic J-curve for stroke risk. Indeed, none of the recent studies in **Table 47.10** showed any J curve for stroke.

Of the two studies restricted to patients with established CAD, post hoc analysis of the large ONTARGET study found no cardiac J curve,[98] whereas the equally large CLARIFY Registry study found a cardiac J curve for both DBP (<70 mm Hg) and SBP (<120 mm Hg) (**Fig. 47.6**).[99] In the Swedish registry study previously mentioned, of over 186,000 patients with type 2 diabetes and no prior CV events, both MI and stroke risk fell progressively with reduced SBP as low as 110 to 119 mm Hg; DBP was not reported, yet patients with a mean age of 60 years have low DBP because of isolated systolic hypertension (**Fig. 47.7**).[96] Post hoc analysis of the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial found no diastolic J curve in patients with or without preexisting CAD.[100] In contrast, post hoc analysis of the ARIC cohort, which also included patients with or without CAD, found a cardiac-specific diastolic J curve for both high-sensitivity cardiac troponin T (hs-cTNT) (**Fig. 47.8**) and for incident coronary heart disease (CHD) events and death.[101] However, DBP of 70 to 79 mm Hg associated with an increased risk of CHD but a reduced level of the myocardial injury biomarker, which increased only with DBP less than 60 mm Hg. Because only 28% of the cohort was being treated for hypertension, treatment-induced myocardial injury cannot be distinguished from other causes. In a Canadian community-based AOBP registry study, composite CV event risk was lowest with on-treatment DBP of 60 to 69 mm Hg or SBP of 110 to 119 mm Hg, then increased with DBP less than 60 or SBP less than 110, indicating a diastolic and a systolic J curve.[102] The mixed results of these and earlier observational studies may result in part from dwindling sample size at the critically important levels of DBP below 60 to 70 mm Hg (**Fig. 47.8**).

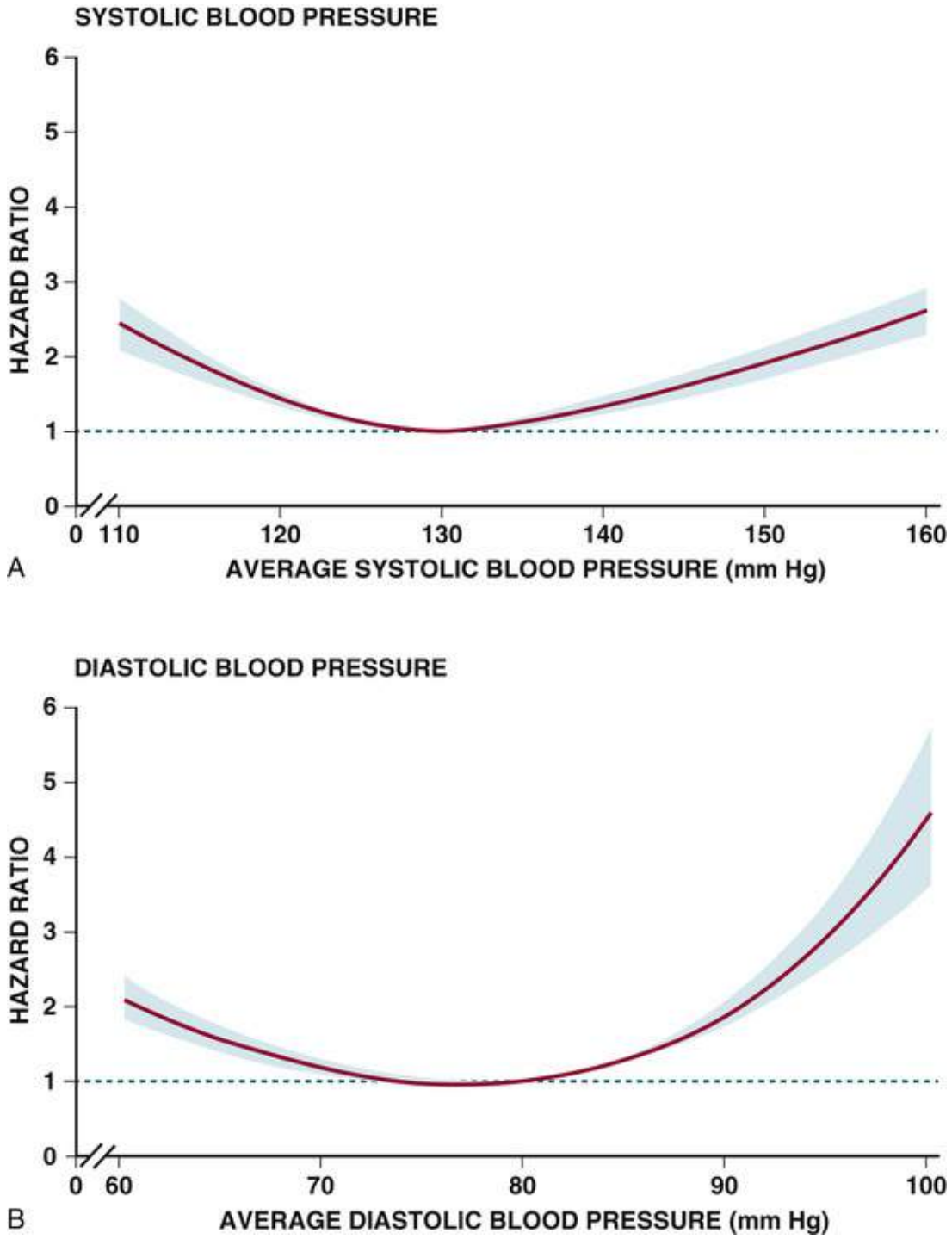


FIGURE 47.6 Data derived from analysis of 22,672 patients with stable coronary artery disease (CAD) in the CLARIFY Registry; patients from 45 countries were treated for hypertension. Graphs plot the primary outcome (cardiovascular death, myocardial infarction, or stroke) against average systolic **(A)** or diastolic **(B)** blood pressure as splines. These analyses were adjusted using a Cox proportional hazards model that accounted for numerous risk factors and drug treatments. (From Vidal-Petiot E, Ford I, Greenlaw N et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. Lancet 2016;S0140-6736(16)31326-5.)

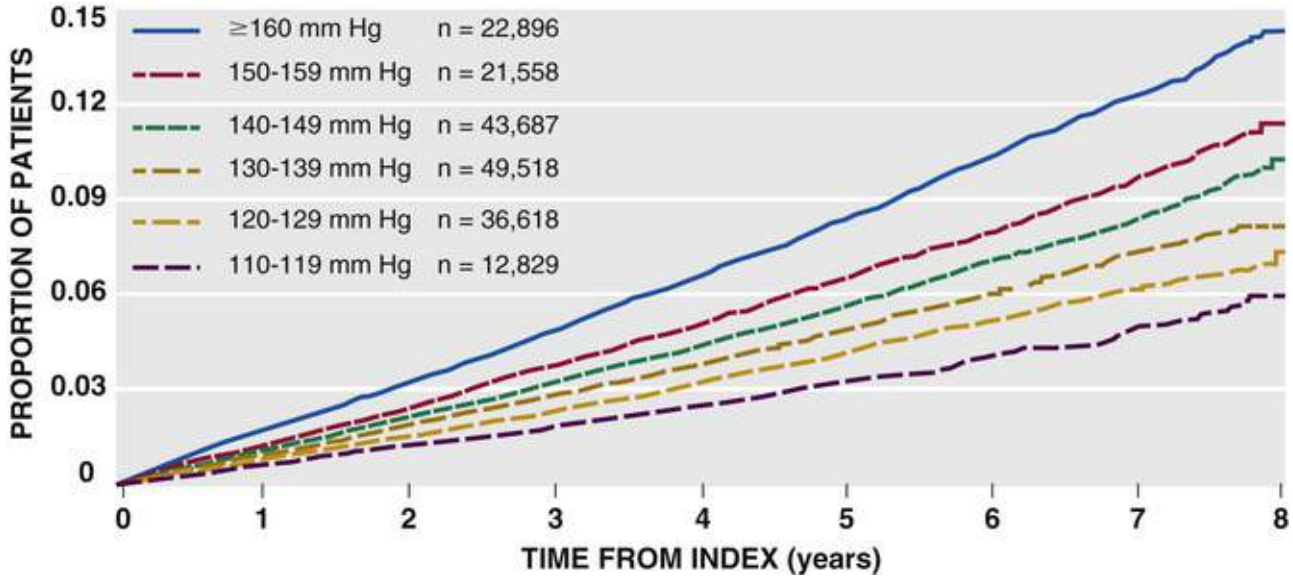


FIGURE 47.7 Kaplan-Meier analysis of nonfatal cardiovascular events, showing proportion of patients with events (composite of nonfatal myocardial infarction or stroke) stratified by different levels of achieved systolic blood pressure. (From Adamsson Eryd S, Gudbjornsdottir S, Manhem K, et al. Blood pressure and complications in individuals with type 2 diabetes and no previous cardiovascular disease: national population based cohort study. BMJ 2016;254:i4070.)

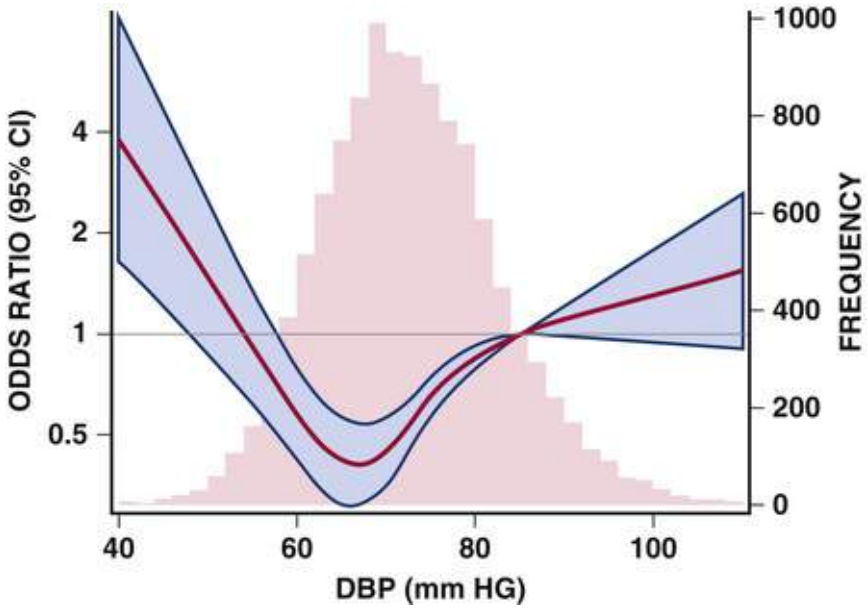


FIGURE 47.8 When diastolic blood pressure (DBP) was less than 65 mm Hg, a linear inverse relationship between DBP and high-sensitivity cardiac troponin-T (hs-cTnT) emerged when DBP was modeled continuously using linear splines. The odds ratio was adjusted for age (years), race-center, sex, body mass index, smoking, alcohol intake, systolic BP, hypertension medication use, diagnosed diabetes, low- and high-density lipoprotein cholesterol, triglycerides, current use of cholesterol-lowering medication, and estimated glomerular filtration rate. Restricted cubic spline provided odds of elevated hs-cTnT (14 ng/L) with background distributional histogram of baseline DBP. Frequency ¼ number of participants at each point on background histogram. The *shaded area* around the regression line represents the 95% confidence interval (CI). (From McEvoy JW, Chen Y, Rawlings A, et al.: Diastolic blood pressure, subclinical myocardial damage, and cardiac events: implications for blood pressure control. J Am Coll Cardiol 2016;68:1717.)

The most direct evidence against the cardiac J-curve hypothesis is that the two major RCTs that compared more intensive versus less intensive antihypertensive therapy (SPRINT and ACCORD) showed no evidence for a cardiac J curve, at least when intensive treatment achieved a mean SBP of 120 mm Hg.[86,87] The associated reductions in DBP were not reported in the major outcomes publications.

Parenthetically, the concept of the strictly diastolic cardiac J curve is partially flawed: while flow in the epicardial coronary arteries occurs mainly in diastole, blood flow within the myocardium (in intramyocardial nutrient microvessels) occurs throughout the cardiac cycle.[103]

Therefore, although cautious BP reduction is advised for patients with critical coronary stenosis or those with CKD (especially in the setting of longstanding diabetes), undertreatment of hypertension rather than overtreatment is much more common in outpatient medical practice, with missed opportunities to prevent needless MIs, strokes, and other hypertensive complications.

Which Drugs for Which Patients

Patients with Prehypertension

Prehypertension may precede stage 1 hypertension and predicts augmented CV risk. The outcomes of TROPHY (Trial of Preventing Hypertension) suggest that pharmacologic treatment of prehypertension with an ARB—together with lifestyle coaching—can postpone stage 1 hypertension.[104]

Hypertensive Patients in General

In RCTs, group differences in CV event rates are largely explained by small group differences in reduction of SBP (hemodynamic load) rather than drug class, with three caveats. First, beta blockers provide less stroke protection and CCBs more stroke protection than do other drugs. Second, the combination of an ACEI (or ARB) and a CCB is an excellent option to initiate medication management for hypertension, because it prevented more CV events than did the beta blocker/thiazide diuretic combination in ASCOT[54] and the ACEI/HCTZ combination in the ACCOMPLISH trial,[55] with the caveat that indapamide or chlorthalidone (CTD) likely would have provided better CV protection than the HCTZ used in ACCOMPLISH. CCBs are better tolerated and avoid the metabolic cost of the thiazides, including hyponatremia, hypokalemia, aggravation of glucose intolerance, increased hepatic triglyceride content, and gout. Yet, the 2013 scientific advisory from the AHA/ACC/CDC[7] and the 2016 Canadian hypertension guidelines[11] still emphasize thiazide-based therapy, believing the totality of the evidence is greater than with any other drug class. Third, ONTARGET showed that “dual RAS blockade” is dangerous as combined treatment with both an ACEI and an ARB (ramipril plus telmisartan) has no advantage on CV outcomes over monotherapy with either drug alone,[56] but results in more symptomatic hypotension and more renal impairment.[58]

Systolic Hypertension in Elderly Patients

Most hypertensive patients are older than 65 years, and most have isolated systolic hypertension (**see Chapter 46**). Six placebo-controlled trials have provided unequivocal proof that any BP-lowering regimen reduces CV events in elderly hypertensive patients (**Table 47.11**). The mean age of the patients at baseline ranged from 70 to 76 years except for HYVET (Hypertension in the Very Elderly Trial), in which all patients were 80 years or older.[69] The benefits of treatment include fewer coronary events, strokes, HF events, and deaths.[57] However, the intensity of the BP reduction in elderly patients must be weighed against increased risk for hypotension, which can precipitate falls and ischemic events. In SPRINT, patients age 75 or older had a large reduction in CV events and death and no increase in injurious falls with intensive reduction in systolic AOBP to a mean value of 124 mm Hg, regardless of frailty, as measured by walking speed.[88] Those results do not apply to nursing home residents. Perindopril and indapamide were the drugs used in HYVET; amlodipine, azilsartan, and CTD were used most often in

SPRINT.

The 2013 European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines and the 2016 Canadian and 2016 Australian hypertension guidelines place far greater emphasis than any U.S. guidelines do on home and ambulatory BP monitoring for clinical decision making (see Guidelines section).[6,11,12] Based on registry data from the 11-country International Database on Ambulatory BP in Relation to Cardiovascular Outcomes (IDACO), ambulatory and home BP monitoring should be routine in hypertensive elderly individuals; white coat (office only) hypertension and masked (out-of-office only) hypertension are so common in older adults that conventional office BP readings alone will promote either overtreatment or undertreatment of hypertension in three of four patients.[91] Likewise, the recent Masked Hypertension Study indicates that 1 in 8 U.S. adults—17 million people—and 1 in 3 people age 75 or older have masked hypertension.[105] Moreover, ambulatory monitoring is key to detecting *postprandial hypotension* and *orthostatic hypotension*, which are common in hypertensive elderly patients (**Fig. 47.9**). Management of postprandial hypotension is challenging. Useful strategies include frequent small low-carbohydrate meals, caffeine with meals, and liberalized salt intake. If these non–drug-related strategies prove insufficient, fludrocortisone (Florinef) can be added but often causes or worsens supine hypertension, which can be managed by elevation of the head of the bed (with 6-inch cinder blocks to produce a 30-degree head-up tilt) and a low-dose short-acting ARB (losartan, 25 to 50 mg) at bedtime.[106] The evidence is insufficient to recommend the use of midodrine, an alpha-adrenergic agonist, for orthostatic hypotension, whereas recent evidence indicates that abdominal compression garments and droxidopa are the most effective and safest approaches to manage severe orthostatic hypotension.[107-109]

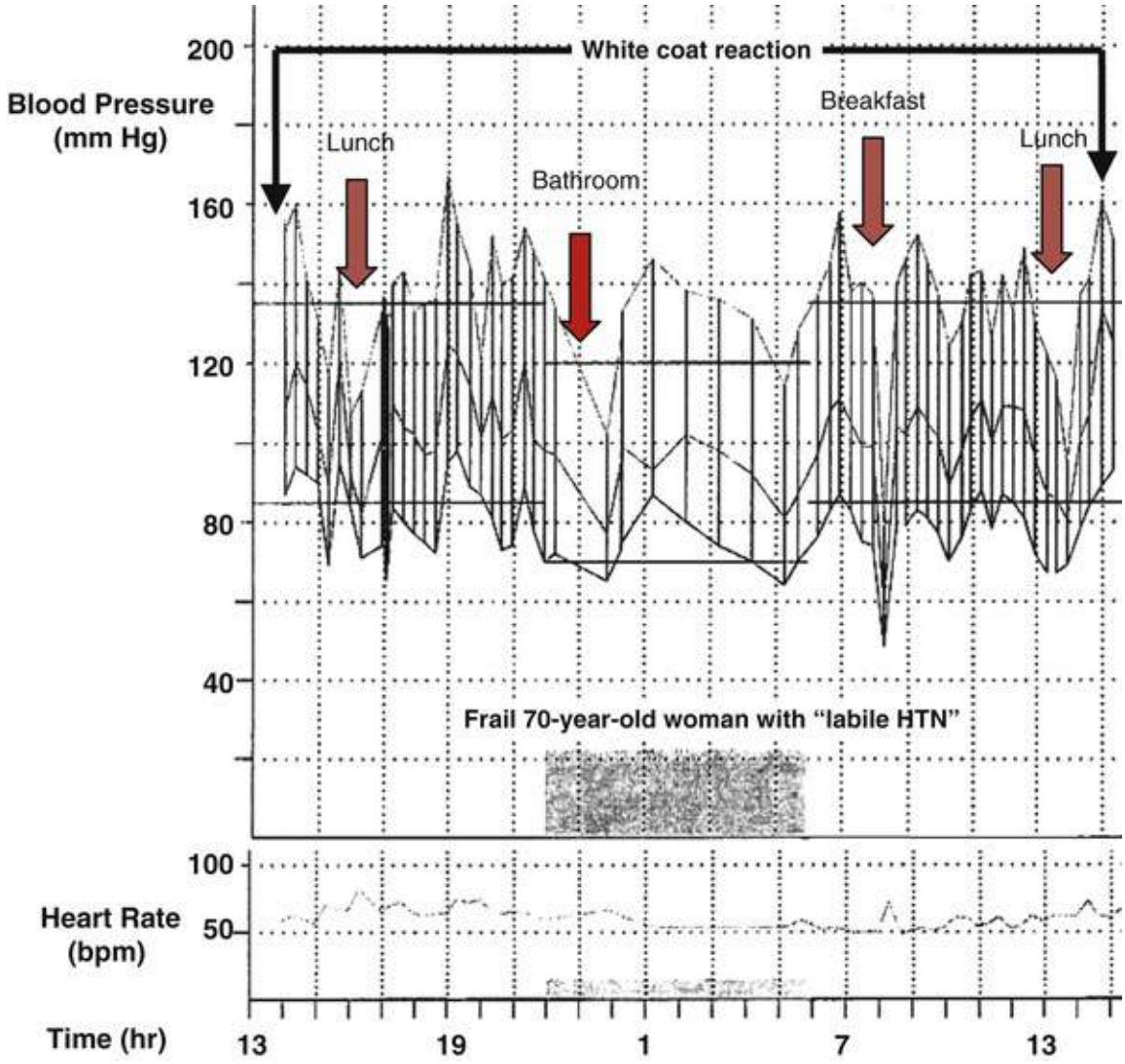


FIGURE 47.9 Postprandial and orthostatic hypotension demonstrated by ambulatory blood pressure (BP) monitoring. The 24-hour ambulatory BP recording is from a frail 70-year-old woman referred for evaluation of labile hypertension and dizziness. *Red arrows* show repeated episodes of postprandial hypertension and one episode of orthostatic hypotension when the patient walked to the bathroom 90 minutes after going to sleep. "White coat" reactions also seen when the patient came to the clinic to have the monitor placed and then to have it removed. HTN, Hypertension; bpm, beats per minute.

Several expert consensus documents including the 2016 Canadian guidelines recommend initiating antihypertensive therapy for isolated systolic hypertension with any one of the three first-line drugs CCB, ACEI or ARB, or thiazide, while placing the most emphasis on thiazide-type diuretics.[11] Most patients will require combination therapy with two or three drugs, so it is important to titrate more slowly in elderly patients and to check frequently for orthostatic hypotension and adverse drug reactions, especially thiazide-induced hyponatremia,[74,75] which are more common. On average, elderly patients take more than six prescription drugs, heightening concern regarding polypharmacy, noncompliance, and potential drug interactions. Regimens with combination drugs and agents or formulations that permit less frequent dosing can simplify the treatment program and promote persistence. Therapy should be individualized and be based more on the person's overall health than on chronologic age (see later, Practical Clinical Approach to Evaluation and Management of Ambulatory Hypertensive Patients).

Hypertension with Left Ventricular Hypertrophy

More than one third of hypertensive patients have electrocardiographically apparent LVH by the time of diagnosis, a finding that places them at increased risk for hypertensive complications, including HF, stroke, sudden death, and atrial fibrillation. The LIFE (Losartan Intervention for Endpoint Reduction in

Hypertension) trial exclusively enrolled patients with electrocardiographically confirmed LVH and showed superiority of an ARB/HCTZ-based regimen over a beta blocker/HCTZ–based regimen for regression of LVH and prevention of CV events, especially stroke. Subsequent meta-analyses have confirmed the superiority of ARBs for regression of LVH.[6] Beta blockers are the least effective; alpha- rather than beta-adrenergic receptors mediate the trophic effect of catecholamines on cardiac myocytes.

Hypertension in Patients with Diabetes Mellitus and Normal Renal Function

Patients with diabetes mellitus frequently have hypertension. No compelling evidence supports an indication for RAS blockers in type 2 diabetes.[59] Antihypertensive therapy should be instituted with one or more of the standard first-line drugs for hypertension. If additional drugs are needed to control hypertension, vasodilating beta blockers do not aggravate glucose tolerance in patients with type 2 diabetes. ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints) showed that addition of aliskiren to background therapy with an ACEI or ARB increases the incidence of hyperkalemia and hypotension while producing no added CV benefit; these results led to the “black box” FDA warning against this form of dual RAS blockade.[62]

Hypertension in Patients with Diabetic Nephropathy

Diabetic nephropathy is characterized by proteinuria, loss of renal autoregulation, hypertension, progression to ESRD, and a high incidence of CV events. In RCTs, addition of an ARB to background antihypertensive therapy slowed progression of nephropathy in patients with type 2 diabetes, whereas amlodipine did not.[110,111] Thus, type 2 diabetes with nephropathy is an indication for an ARB, even though the trials were not powered to determine whether this regimen also afforded CV protection. Evidence supports a recommend office BP goal of 140/90 mm Hg or lower for patients with type 2 diabetic nephropathy (**Table 47.11**). The 2013 Kidney Disease Improving Global Outcomes (KDIGO) guideline[9] recommends a goal of less than 130/80 mm Hg and a RAS blocker in those with significant proteinuria (urine-to–plasma albumin–to-creatinine ratio ≥30 mg/g, corresponding to ≥30 mg of urinary albumin excretion in 24 hours), as applies to most patients.

Hypertension in Patients with Nondiabetic Chronic Kidney Disease

Almost all patients with nondiabetic CKD have hypertension. Control of hypertension in patients with CKD has two goals: (1) slowing further deterioration in renal function and (2) preventing CV events, which are the main cause of death. In AASK, the ACEI ramipril was more renoprotective than either amlodipine or metoprolol in black patients with baseline proteinuria.[112] Long-term follow-up of the AASK participants and a recent meta-analysis indicate that intensive reduction of SBP to below 130 mm Hg rather than a less intense goal of 140 mm Hg slows progression of renal disease only in patients with baseline proteinuria.[113,114] These trials lacked power to assess CV outcomes. Thus the 2012 KDIGO guideline recommends a goal office BP of lower than 140/90 mm Hg for patients with nondiabetic nonproteinuric CKD and a stretch goal of less than 130/80 mm Hg with an ACEI- or ARB-based regimen for those with proteinuria. These guidelines are in flux with the SPRINT data showing that reducing SBP to 120 mm Hg—by triple therapy with the most potent ARB, thiazide-type diuretic, and CCB—increased the risk of AKI but, at least in the short duration of the trial, did not increase the risk of ESRD in the subgroup of patients with baseline CKD.[87]

Reduction of Blood Pressure for Secondary Prevention of Coronary Events

The 2015 AHA/ACC/ASH Scientific Statement on Treatment of Hypertension in Patients with Coronary Artery Disease,[14] which predated SPRINT, emphasized that most of the cardioprotective effects of antihypertensive agents result from reduction in BP independent of drug class. For secondary prevention of coronary events in patients with stable CAD, first-line agents include the combination of beta blockers and dihydropyridine CCBs, both of which are antianginal. Other first-line agents are ACEIs or ARBS, and thiazide-type diuretics. Nondihydropyridine CCBs are recommended for beta blocker–intolerant patients. Aldosterone antagonists are reserved for patients with HF or difficult hypertension. In INVEST, combination therapy with CCB/ACEI was equally effective as beta blocker/thiazide for secondary prevention.[14] As previously reviewed, prospective data from RCTs have not defined the critical lower limit of on-treatment BP that increases the risk for ischemic events in patients with stable CAD. Current data support caution in decreasing DBP to lower than 60 mm Hg in patients with coronary stenoses.

Reduction of Blood Pressure for Secondary Prevention of Stroke

Stroke survivors are at high risk for recurrent stroke and thus further disability and death. Reduction in SBP by more than 10 mm Hg can reduce these risks.[115] In PROGRESS (Perindopril Protection Against Recurrent Stroke Study), patients who had survived ischemic or hemorrhagic stroke, a reduction of SBP by 12 mm Hg to a value of 135 mm Hg with an ACEI/diuretic (perindopril/indapamide) combination reduced the relative risk for recurrent ischemic stroke by 36% and that for recurrent hemorrhagic stroke by 76% in comparison to placebo, but a smaller reduction in BP of just 5 mm Hg with perindopril monotherapy showed no stroke protection.[70] Similarly, the PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial of patients with ischemic stroke showed no statistical benefit when SBP was reduced by only 4 mm Hg with ARB (telmisartan) monotherapy versus placebo.[116] In the SPS3 trial of hypertensive patients with lacunar infarcts, reduction in SBP to less than 130 mm Hg rather than less than 140 mm Hg reduced the risk of subsequent hemorrhagic stroke.[89] Emergency management of BP during acute stroke is discussed later (see Management of Hypertensive Crises).

Special Considerations in Management

Special Populations

Hypertension in Non-Hispanic Black Patients

Hypertension proves particularly devastating in non-Hispanic black adults, who have a higher prevalence of hypertension than other groups and higher rates of hypertensive complications and death (**see Chapter 46**). Black hypertensive patients were exclusively recruited in AASK (discussed earlier) and, by design, accounted for 25% of ALLHAT participants and 30% of SPRINT participants, but otherwise have been underrepresented in most RCTs of hypertension. Among the subset of black participants in ALLHAT, the ACEI provided less BP reduction and thus less stroke protection than either the diuretic or the CCB. In clinical practice, achieving BP targets and thus CV protection requires combining an ACEI with either a CCB or a diuretic, or both. A higher prevalence of masked and nocturnal hypertension in black persons argues for greater use of home and ambulatory BP monitoring in clinical practice.[91,117,118] An RCT showed that a barber-based BP monitoring and physician referral program can improve control of hypertension in black men.[119]

Hypertensive Disorders of Women (See Chapter 89)

Oral Contraceptives and Hormonal Replacement Therapy

Estrogen-containing oral contraceptives (OCs) occasionally cause hypertension, which is often mild. BP normalizes within 6 months of stopping OC therapy in 50% of patients. The hypertensive mechanism involves both RAS activation and volume expansion. Use of OCs should be limited in women older than 35 years or those who are obese or have preexisting hypertension. BP should be monitored closely with initiation of OCs; if BP rises into the prehypertensive range, an alternative contraceptive method should be offered. If OCs remains the only acceptable contraceptive method, drug therapy can reduce the elevated BP. Unlike OCs, hormonal replacement therapy (HRT) does not appear to elevate BP.

Hypertension in Pregnancy

Hypertensive disorders in pregnancy are a major cause of maternal-fetal morbidity and mortality, including a 25% incidence of preterm births (**see Chapter 90**). Current guidelines are provided by the 2013 executive summary of the American College of Obstetricians and Gynecologists (ACOG).[120] Four categories of hypertension in pregnancy are recognized: (1) preeclampsia, (2) chronic hypertension, (3) chronic hypertension with superimposed preeclampsia, and (4) gestational hypertension. *Preeclampsia* is a severe progressive multisystem disorder diagnosed by hypertension accompanied by any one of the following: proteinuria, BP of 160/110 mm Hg or higher despite bed rest, thrombocytopenia, impaired liver function, progressive renal insufficiency, pulmonary edema, or new-onset cerebral or visual disturbance (**Table 47.12**). Preeclampsia causes 15% of maternal deaths. *Gestational hypertension* is BP elevation after 20 weeks of gestation in the absence of the additional systemic features listed in **Table 47.12**. Chronic hypertension predates pregnancy. In all cases, ambulatory BP monitoring is very useful and was reported to be superior to conventional office measurement of BP for prediction of outcomes. Although the pathogenesis of gestational hypertension/preeclampsia remains enigmatic, risk factors include maternal age younger than 20 or older than 35, positive personal or family history of gestational hypertension, preexisting hypertension, obesity, diabetes, and antiphospholipid antibodies. Preeclampsia is a risk factor for peripartum cardiomyopathy, conditions that may share common causative factors.[121,122]

TABLE 47.12
Diagnostic Criteria for Preeclampsia

Blood pressure	≥140/90 mm Hg on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal pregnancy
	≥160/110 mm Hg; hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy
and	
Proteinuria	≥300 mg per 24-hour urine collection
	or
	Protein/creatinine ratio ≥0.3
or in the absence of proteinuria, new-onset hypertension with new onset of any of the following:	
Thrombocytopenia	Platelet count <100,000/mL
Renal insufficiency	Serum creatinine >1.1 mg/dL or doubling of serum creatinine in the absence of other renal disease
Impaired liver function	Serum liver transaminases elevated twice normal
Pulmonary edema	
Cerebral or visual symptoms	

Modified from Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122.

Low-dose aspirin (60 to 80 mg daily beginning in the first trimester) is recommended as being slightly effective in reducing the risk for recurrent preeclampsia. Women with gestational hypertension or chronic

hypertension should be monitored closely for the development of preeclampsia with serial measurements of BP twice weekly and weekly assessment of platelet counts, liver enzymes, and proteinuria. Weight loss and salt restriction are not recommended. Currently, antihypertensive medication is not recommended for uncomplicated stage 1 gestational hypertension and is reserved only for stage 2 hypertension (BP >160/110 mm Hg). Drug treatment of stage 1 maternal hypertension does not improve perinatal outcome and may be associated with fetal growth restriction. However, these guideline recommendations do not consider the long-term risk to the mother of untreated stage 1 hypertension during pregnancy.

Definitive cure of preeclampsia is termination of pregnancy. The decision regarding premature termination of pregnancy depends on findings of fetal growth restriction, evidence of impaired placental blood flow by umbilical artery Doppler assessment, and condition of the mother. Intravenous (IV) magnesium sulfate is not a reliable antihypertensive agent but is effective in treating or preventing seizures in the setting of eclampsia or severe preeclampsia. IV labetalol has replaced hydralazine as the drug of choice for treating severe preeclampsia/eclampsia. Compared with hydralazine, labetalol carries a lower risk for *overshoot hypotension*, which can impair fetal blood flow, and does not cause reflex tachycardia. Beyond delay of pregnancy until after the teenage years and better prenatal care, the only other effective strategy to prevent preeclampsia is the use of low-dose aspirin. The only cure for preeclampsia is delivery, which removes the diseased placenta. To achieve this apparently simple end, the clinician must detect the often-symptomless prodromal condition by screening all pregnant women, admitting those with advanced preeclampsia to the hospital to keep track of an unpredictable situation, and timing preemptive delivery to maximize safety of the mother and baby.

Pregnant women with stage 2 hypertension but without severe preeclampsia/eclampsia who are prescribed oral drug therapy should initially receive any one of three preferred drugs: labetalol, nifedipine, or methyldopa. Despite being the conventional drug of choice, methyldopa is poorly tolerated and, if used after delivery, may cause postpartum depression. All RAS inhibitors must be discontinued. Delivery soon after maternal stabilization is recommended regardless of gestational age for women with superimposed preeclampsia and any of the following: uncontrollable severe hypertension, eclampsia, pulmonary edema, abruptio placentae, disseminated intravascular coagulation, or fetal distress. IV nitroglycerin is the treatment of choice when pulmonary edema accompanies preeclampsia, a main cause of maternal death. Preeclampsia can start in the early postpartum period. Preeclampsia constitutes an important major CV risk factor for later life. Women with preeclampsia causing preterm delivery have an almost 10-fold increased risk for CV disease in later life and thus require exquisite global risk factor modification. Women with preeclampsia or even gestational hypertension should have close BP monitoring in the hospital for 72 hours postpartum and again on outpatient basis 7 to 10 days after delivery. All BP drugs enter into human breast milk.

Pediatric and Adolescent Hypertension

Historically, childhood hypertension was a rare occurrence caused mainly by parenchymal renal disease. The worldwide childhood obesity epidemic, however, has increased the prevalence of primary juvenile hypertension, which has now become one of the most common health conditions in young people. The 2016 European Society of Hypertension (ESH) Guidelines for Management of Hypertension in Children and Adolescents continues to define pediatric hypertension as SBP or DBP higher than the 95th percentile for age, sex, and height according to normative data.[123] The prevalence of hypertension is now 5% and that of prehypertension is 10% in U.S. children. The frequency of primary (largely obesity-related) hypertension in pediatric referral series has risen steadily and now exceeds 90%.[124] College football players have a disproportionate prevalence of hypertension compared with collegiate athletes in other

sports; in one cross-sectional series, 19% of college football players had hypertension and 62% had prehypertension, which is partially explained by a high BMI.[125] In a longitudinal series, a single season of freshman collegiate football consistently caused increases in SBP and DBP associated with increased concentric left ventricular mass; these increases were greatest in linemen, who are heavier and gain more weight than those who are not linemen.[126]

Ambulatory BP monitoring is the method of choice for confirming the diagnosis of pediatric or adolescent hypertension, but it is underused.[127] The initial evaluation should include an echocardiogram for detection of LVH, as well as urine microalbumin, serum creatinine, and urinalysis to test for renal parenchymal injury. Glomerulonephritis and reflux nephropathy can also be associated with pediatric hypertension. A history of recurrent urinary tract infections in girls may indicate reflux nephropathy, a condition that can lead to renal scarring (suggested by renal asymmetry). This situation should prompt consultation with a pediatric nephrologist to consider reimplantation of the ureters. Renovascular hypertension occurs in almost 10% of hypertensive pediatric patients. Coarctation of the aorta, the most common cause of hypertension in infants, responds well to stenting.[128] Rare causes of secondary pediatric hypertension are syndromic pheochromocytoma/paraganglioma, monogenic disorders (**see Chapters 46 and 92**), and congenital adrenal hyperplasia caused by deficiency of either 11β-hydroxylase or 17α-hydroxylase. No data from RCTs inform the decision on when to initiate antihypertensive drug therapy in children or adolescents or on which drug classes are preferred. ACEIs are typically used to treat primary pediatric hypertension and secondary hypertension caused by renal parenchymal disease; CCBs may be added as a second drug if needed.[123]

Hypertension and Erectile Dysfunction

Two thirds of men with hypertension have erectile dysfunction (ED).[129] TOMHS (Treatment of Mild Hypertension Study) is the only RCT on hypertension to include ED as a prespecified patient-reported outcome.[130] Among men with a mean age of 50 years and previously untreated hypertension, most ED preceded initiation of antihypertensive medication and was related both to age and to baseline SBP. After men were randomly assigned to monotherapy with one of five main classes of BP medication or placebo, CTD was the only drug that increased incident ED more than placebo did. However, this result has not received systematic confirmation.[73] Overall, phosphodiesterase-5 inhibitors have had a very good safety record in treating ED, even in men with high CV risk, but they should be avoided in those taking nitrates or alpha blockers to prevent hypotension.

Hypertension and Hypertrophic Cardiomyopathy

Hypertension is at least as prevalent in patients with hypertrophic cardiomyopathy (HCM) as in the general population. Management of hypertension in HCM patients presents challenges because all the first-line antihypertensive drugs—dihydropyridine CCBs, RAS blockers, and thiazides—can exacerbate outflow tract obstruction and thus may prove harmful. Hypertension is best treated with a beta blocker and/or verapamil or diltiazem, with central sympatholytics and very-low-dose thiazide reserved as add-on drugs.[131]

Hypertension and Atrial Fibrillation

Hypertension is the most common comorbid condition in atrial fibrillation (AF), found in almost 90% of patients. In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events) trial of more than 18,000 patients (mean age 70 years) with nonvalvular AF, any elevated office reading of

SBP ≥140 or DBP ≥90 mm Hg at any point during the 2-year trial was associated with a 53% increased risk of ischemic stroke and an 85% increased risk of hemorrhagic stroke.[132] These new data underscore the importance of intensive antihypertensive drug therapy to achieve strict BP control to reduce the risk of stroke in older patients with nonvalvular AF.

Resistant Hypertension

Resistant hypertension, defined as high BP uncontrolled with three or controlled with at least four antihypertensive drugs (including a diuretic), is associated with a higher prevalence of secondary hypertension and worse CV and renal outcomes. With aging of the population, the prevalence of resistant hypertension is increasing and may affect 13% to 20% of the adult U.S. population.[76] More than half these patients will have pseudo–resistant hypertension from improper BP measurement technique, white coat reactions, medication noncompliance, pressor substances (e.g., NSAIDs, excessive alcohol, psychiatric drugs), or an inadequate BP regimen (**Table 47.13**). Common correctable issues include clonidine rebound (especially with as-needed dosing) and inadequate diuretic therapy: inappropriate use of a loop diuretic in a patient with normal renal function, infrequent dosing with a short-acting loop diuretic (e.g., once-daily furosemide), or low-dose HCTZ in a patient with impaired renal function.

TABLE 47.13
Causes of Resistant Hypertension

Pseudoresistant Hypertension
Inadequate blood pressure regimen
Pressor substances
White coat reaction
Medication nonadherence
Improper blood pressure measurement
True Resistant Hypertension
Chronic kidney disease
Primary aldosteronism
Other secondary hypertension
Difficult primary hypertension

Truly drug-resistant patients are a special high-risk population because of their severe hypertension along with target-organ damage and concomitant CV risk factors. Patients should be screened for secondary hypertension, especially primary aldosteronism and CKD, as well as pheochromocytoma. In the absence of an identifiable cause of the hypertension, a mineralocorticoid receptor antagonist or a vasodilating beta blocker can serve as highly effective add-on therapies. Low-dose spironolactone (or eplerenone) can be remarkably effective for resistant hypertension, even when serum aldosterone is within the normal range.[77,78]

Perioperative Management of High Blood Pressure

Preexisting hypertension should be well controlled before elective surgery (**see Chapter 11**). Preoperative correction of diuretic-induced potassium depletion requires particular attention. Antihypertensive agents should be taken the morning of surgery, particularly to avoid withdrawal from beta blockers or clonidine. Some surgeons prefer to withhold ACEIs and ARBs before cardiac surgery to prevent postoperative vasodilation and hypotension, but little evidence supports this practice. Beta blockers have not proved to reduce perioperative risk in patients with uncomplicated hypertension undergoing noncardiac surgery and might even increase risk of major CV events.[133] Fortunately, IV

formulations of most agents are available if oral intake is not possible; labetalol is particularly useful in this regard. Hypertension may appear or worsen in the perioperative period, perhaps more frequently with cardiac than noncardiac surgery. Hypertension is of particular concern after heart transplantation and develops for a variety of reasons, including immunosuppression with calcineurin inhibitors (cyclosporine and tacrolimus) and possibly cardiac denervation; treatment includes dihydropyridine CCBs, diuretics, and central sympatholytics.

Management of Hypertensive Crises

Definitions

Hypertensive crises are a heterogeneous group of hypertensive disorders characterized by severe hypertension and acute target-organ damage to the brain, heart, kidney, retina, or blood vessels. Typically, BP is 220/130 mm Hg or higher but may be much lower in women with preeclampsia who do not have preexisting hypertension, such that cerebral autoregulation has not been reset. Hypertensive crises require immediate reduction of BP with IV medication and intra-arterial monitoring in an intensive care unit. In contrast, *hypertensive urgency* denotes severe uncontrolled hypertension without evidence of acute target-organ damage. In the absence of symptoms and acute target-organ damage, a patient with a BP of 220/130 mm Hg should be treated with a short-acting oral medication. *Severe hypertension*, defined as a BP of 180/110 to 220/130 mm Hg without symptoms or acute target-organ damage, almost always occurs in patients with chronic hypertension who depleted or discontinued their BP medication. Long-acting oral medication can simply be restarted. Patients with either hypertensive urgency or severe hypertension require outpatient follow-up within 24 to 72 hours by either a primary care physician or hypertension specialist.

Specific Hypertensive Crises

Adapted from the updated Dutch guidelines,[134] **Table 47.14** summarizes treatment recommendations for hypertensive crises by affected organ system. **Table 47.15** summarizes the recommended parenteral drugs for treatment of hypertensive crises.

TABLE 47.14

Intravenous Drugs for Treatment of Hypertensive Emergencies

DRUG	ONSET OF ACTION	HALF-LIFE	DOSE	CONTRAINDICATIONS AND SIDE EFFECTS
Labetalol	5-10 min	3-6 hr	0.25-0.5 mg/kg; 2-4 mg/min until goal BP is reached, thereafter 5-20 mg/hr	Second- or third-degree AV block; systolic heart failure, COPD (relative); bradycardia
Nicardipine	5-15 min	30-40 min	5-15 mg/hr as continuous infusion, starting dose of 5 mg/hr, increase q15-30 min with 2.5 mg until goal BP achieved, thereafter decrease to 3 mg/hr	Liver failure
Nitroprusside	Immediate	1-2 min	0.3-10 μg/kg/min, increase by 0.5 μg/kg/min q5min until goal BP achieved	Liver/kidney failure (relative), cyanide toxicity
Nitroglycerin	1-5 min	3-5 min	5-200 μg/min, 5-μg/min increase q5min	
Urapidil	3-5 min	4-6 hr	12.5-25 mg as bolus injections; 5-40 mg/hr as continuous infusion	
Esmolol	1-2 min	10-30 min	0.5-1.0 mg/kg as bolus; 50-300 μg/kg/min as continuous infusion	Second- or third-degree AV block, systolic heart failure, COPD (relative); bradycardia
Phentolamine	1-2 min	3-5 min	1-5 mg, repeat after 5-15 min until goal BP is reached; 0.5-1 mg/hr as continuous infusion	Tachyarrhythmia, angina pectoris

AV, Atrioventricular; *COPD,* chronic obstructive pulmonary disease.

Modified from van den Born BJ, Beutler JJ, Gaillard CA, et al. Dutch guideline for the management of hypertensive crisis—2010 revision. Neth J Med 2011;69:248.

TABLE 47.15

Recommended Treatment of Hypertensive Emergencies by End-Organ Involved

TYPE OF EMERGENCY	TIMELINE, TARGET BLOOD PRESSURE	FIRST-LINE THERAPY	ALTERNATIVE THERAPY
Hypertensive crisis with retinopathy, microangiopathy, or acute renal insufficiency	Several hours, MAP −20% to −25%	Labetalol	Nitroprusside Nicardipine Urapidil
Hypertensive encephalopathy	Immediate, MAP −20% to −25%	Labetalol	Nicardipine Nitroprusside
Acute aortic dissection	Immediate, SBP <110 mm Hg	Nitroprusside + metoprolol	Labetalol
Acute pulmonary edema	Immediate, MAP 60-100 mm Hg	Nitroprusside with loop diuretic	Nitroglycerin Urapidil with loop diuretic
Acute coronary syndrome	Immediate, MAP 60-100 mm Hg	Nitroglycerin	Labetalol
Acute ischemic stroke and BP >220/120 mm Hg	1 hour, MAP −15%	Labetalol	Nicardipine Nitroprusside
Cerebral hemorrhage and SBP >180 mm Hg or MAP >130 mm Hg	1 hour, SBP <180 mm Hg and MAP <130 mm Hg	Labetalol	Nicardipine Nitroprusside
Acute ischemic stroke with indication for thrombolytic therapy and BP >185/110 mm Hg	1 hour, MAP less than −15%	Labetalol	Nicardipine Nitroprusside
Cocaine/XTC intoxication	Several hours, SBP <140 mm Hg	Phentolamine (after benzodiazepines)	Nitroprusside
Pheochromocytoma crisis	Immediate	Phentolamine	Nitroprusside Urapidil
Perioperative hypertension during or after CABG	Immediate	Nicardipine	Urapidil Nitroglycerin
During or after craniotomy	Immediate	Nicardipine	Labetalol
Severe preeclampsia/eclampsia	Immediate, BP <160/105 mm Hg	Labetalol (plus $MgSO_4$ and oral antihypertensives)	Ketanserin Nicardipine

CABG, Coronary artery bypass graft; *MAP,* mean arterial pressure; *$MgSO_4$,* magnesium sulfate; *XTC,* "Ecstasy" (3,4-methylenedioxymethamphetamine).

Modified from van den Born BJ, Beutler JJ, Gaillard CA, et al: Dutch guideline for the management of hypertensive crisis—2010 revision. Neth J Med 69:248, 2011.

Hypertensive Crisis with Advanced Retinopathy

Patients with full-blown hypertensive crisis are critically ill with BP of 220/130 mm Hg or higher and grade 3 or grade 4 hypertensive retinopathy (**Fig. 47.10**), accompanied by headache, visual disturbances, nausea/vomiting, HF, neurologic sequelae (encephalopathy), electrocardiographically confirmed LVH, renal impairment, and microangiopathic hemolytic anemia. African American patients are more likely to

have hypertensive HF. First-line drug options are IV labetalol (a combined alpha/beta blocker), nitroprusside, nicardipine (a dihydropyridine CCB), or urapidil (a new central sympatholytic that acts on central serotonergic pathways and also selectively blocks peripheral $alpha_1$-adrenergic receptors). In patients with impaired cerebral autoregulation (see later), labetalol causes a smaller adverse fall in cerebral blood flow than nitroprusside but has a longer half-life, which leads to more adverse episodes of systemic hypotension. IV nicardipine appears to produce a more predictable and consistent reduction in BP than labetalol, but with a similar safety profile; however, physicians and hospital pharmacies are less familiar with nicardipine.[135]

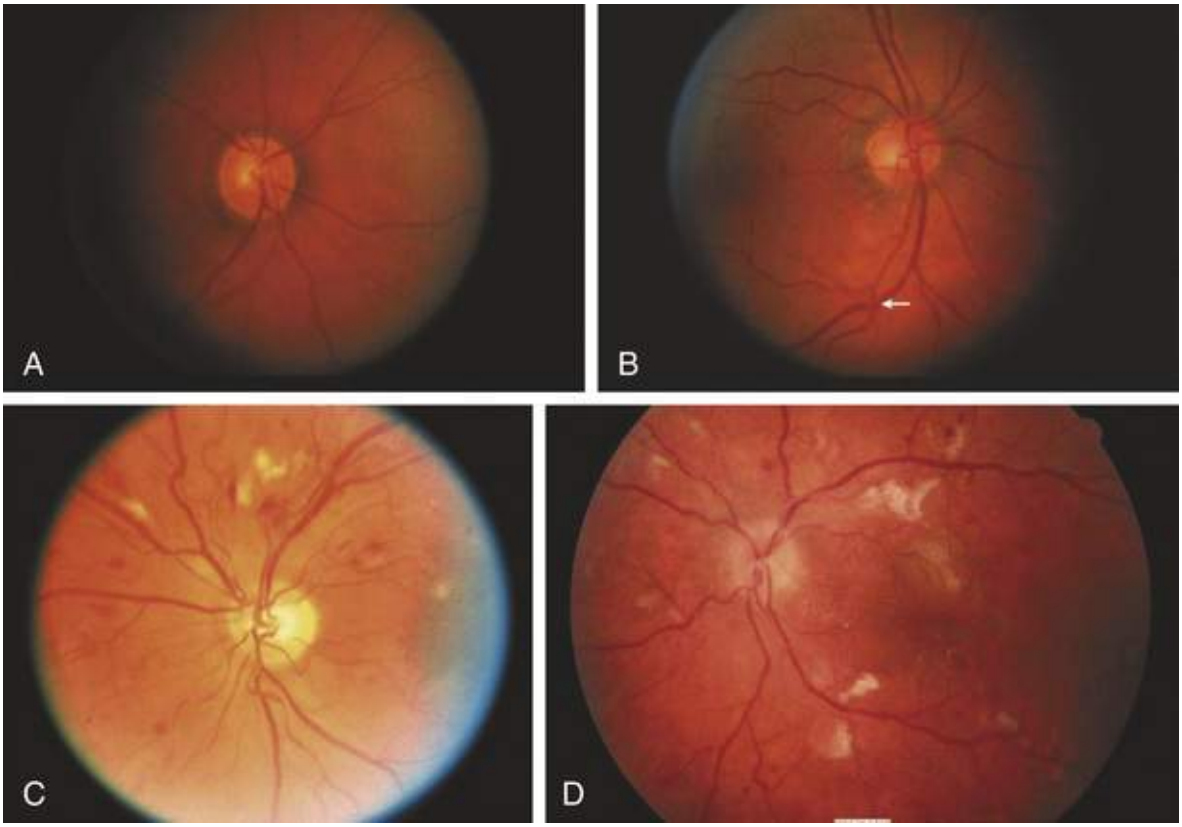


FIGURE 47.10 Retinal photographs showing the stages of hypertensive retinopathy. **A,** Mild diffuse arteriolar narrowing. **B,** Arteriovenous nicking *(arrow).* **C,** Hemorrhages and exudates. **D,** Papilledema. (From Grosso A, Veglio F, Porta M, et al. Hypertensive retinopathy revisited: some answers, more questions. Br J Ophthalmol 2005;89:1646.)

Hypertensive Crisis with Encephalopathy

Findings in hypertensive encephalopathy include a reduced level of consciousness, delirium, agitation, stupor, seizures, or cortical blindness in the setting of acute severe high BP. Focal neurologic signs are rare and suggest ischemic or hemorrhagic stroke rather than encephalopathy. Hypertensive encephalopathy is a cause of reversible *posterior leukoencephalopathy syndrome,* which is often seen in the setting of cyclosporine- or tacrolimus-induced hypertension (particularly in heart transplant recipients) or that caused by bevacizumab or bortezomib. Brain computed tomography (CT) or magnetic resonance imaging (MRI) showing areas of cerebral edema confirms the diagnosis of encephalopathy. The edema typically localizes in posterior brain regions perfused by the vertebral arteries, which have less sympathetic innervation and thus less dampening of BP oscillations than the carotid arteries. The areas of brain edema will resolve with timely treatment of the hypertensive crisis.

Encephalopathy occurs when BP exceeds the upper limit of cerebral autoregulation, which normally maintains cerebral blood flow constant over a range of mean arterial pressure from 60 to 150 mm Hg. In patients without preexisting hypertension, such as those with preeclampsia, encephalopathy will develop when mean arterial pressure exceeds 150 mm Hg. In those with chronic hypertension, the autoregulatory curve shifts to the right to defend against a higher level of BP, but this adjustment makes patients vulnerable to cerebral underperfusion if BP is lowered too quickly into the normotensive range. Thus, patients with hypertensive encephalopathy should receive IV antihypertensive therapy, preferably with labetalol, immediately to lower BP in a controlled manner that avoids cerebral hypoperfusion and thus irreversible brain damage. A good rule of thumb is to lower the initially elevated arterial pressure by 10% in the first hour and by an additional 15% during the next 12 hours to a BP of no less than 160/110 mm Hg. BP can be reduced further during the next 48 hours. IV saline is often needed to prevent hypovolemic hypotension from pressure natriuresis and nausea/vomiting.

Acute Ischemic or Hemorrhagic Stroke

In acute ischemic stroke, BP should be lowered cautiously to avoid ischemic insult to potentially salvageable tissue (termed the *ischemic penumbra*), which would extend the infarct (**see Chapter 65**). Acknowledging a limited evidence base, the 2013 guidelines from the AHA/American Stroke Association[136] recommend the following: (1) if the stroke cannot be treated with thrombolytic therapy, BP should be treated if it remains higher than 220/120 mm Hg and initially lowered by no more than 15%, and (2) if the stroke can be treated with thrombolytic therapy, BP needs to be lowered to less than 185/110 mm Hg. Results of INTERACT2 (Intensive BP Reduction in Acute Hemorrhage Trial 2) showed improved functional outcomes without more adverse events in patients with acute hemorrhagic stroke randomly assigned to intensive treatment to lower SBP to less than 140 mm Hg than to the conservative guideline-recommended goal of less than 180 mm Hg.[137] Optimal protection against death or major disability after acute hemorrhagic stroke was observed in patients without severe hemorrhage and early planned surgery who achieved the greatest SBP reductions of 30 mm Hg in the first hour after randomization and maintained it consistently for 7 days.[138] For either ischemic or hemorrhagic stroke, agents of choice to lower BP include urapidil, nicardipine, or labetalol; nitroprusside and hydralazine should be avoided because they may increase intracranial pressure.

Acute Coronary Syndrome

In hypertensive patients with acute coronary syndrome (ACS), BP should be lowered with IV nitroglycerin after the administration of a beta blocker such as IV metoprolol to prevent reflex tachycardia. IV esmolol lowers BP more than metoprolol, is rapidly reversible, and produces a more predictable dose-dependent reduction in BP than IV nitroglycerin (which alleviates angina more reliably than lowering BP). Nitroprusside can cause coronary steal and should be avoided. Hypotension must be avoided in ACS patients to prevent infarct extension (**see Chapters 59 and 60**).

Acute Heart Failure

Nitroprusside is the drug of choice to treat hypertensive crisis and acute HF. Concomitant loop diuretics both decrease acute pulmonary edema and further lower BP (**see Chapter 24**).

Adrenergic Crisis

Pheochromocytoma crisis should be treated acutely with phentolamine followed by administration of a

beta blocker. Nitroprusside and urapidil are effective alternatives. Clonidine withdrawal can be aborted by reintroduction of this agent. Based on limited evidence, cocaine- or methamphetamine-induced acute hypertension should be treated with IV benzodiazepines and labetalol[139] (**see Chapter 24**).

Practical Clinical Approach to Evaluation and Management of Ambulatory Hypertensive Patients

Unlike the preceding seven reports of the Joint National Committee, the 2014 majority report of members invited to serve on the JNC 8 panel was not sanctioned by the NHLBI or any professional organization and thus does not constitute an official U.S. hypertension guideline.[8] Following the IOM guidelines for strict interpretation of the evidence from RCTs, this panel recommended (1) less intensive drug treatment of high BP for patients age 60 or older, (2) conventional office BP—the metric for clinical decision making in most prior hypertension RCTs, and (3) dose escalation to match the high drug doses proven effective in RCTs. New evidence obtained from 2015 to 2017 calls each of these recommendations into question. The SPRINT results favor more intensive—not less intensive—therapy for older patients, but with important caveats related to the trial's strict eligibility criteria. Application of the SPRINT eligibility criteria to the entire U.S. population would classify an additional 16.8 million adults as eligible for either initiation or intensification of antihypertensive drug therapy.[140] Achieving the stricter BP goals would require more careful titration of medication, greater use of fixed-dose drug combinations, more frequent monitoring for adverse effects, and thus more frequent patient visits than ever before.[141] The seemingly contradictory outcomes of other RCTs, meta-analyses, and observational studies have generated confusion among internists and cardiologists, who are left in a quandary regarding an ideal BP.[141,142] Replacing manual with automated office BP measurement would represent a sea change in clinical medicine and mental recalibration of what clinicians consider normal versus high BP values. Despite ever-increasing evidence that ambulatory BP monitoring is far superior to office-based BP measurement for prediction of CV risk, the guidelines are less clear about how to use this information to gauge drug therapy. Although combination drug therapy with two or three drugs of different classes is needed to achieve the BP goals in SPRINT (and ACCORD), experts differ as to whether a thiazide-type diuretic is the best drug to initiate therapy for most patients, and whether their dose-dependent side-effects are common or uncommon, serious or trivial.

We therefore offer the following approach for practical office-based evaluation and management of hypertension.[143]

Initial Evaluation (See Chapter 46)

Staging of Blood Pressure

We have started using automated office BP (AOBP) measurement to make the diagnosis of hypertension. With the patient seated quietly alone in the examination room for 5 minutes, a highly rated oscillometric monitor takes five readings on STAT mode. Hypertension is diagnosed if the average of the last three readings is 135/85 mm Hg or higher *and* the patient has electrocardiographically confirmed LVH or other evidence of hypertension-induced target-organ damage.

In the absence of target-organ damage or very severe AOBP (≥180/110 mm Hg), we routinely use ambulatory BP monitoring (ABPM) or home BP monitoring to confirm the diagnosis of hypertension and stage the BP, because AOBP can overestimate and often underestimates out-of-office BP. We generally

initiate antihypertensive drug therapy if the average awake BP is 135/85 mm Hg or higher, or the average sleeping BP is 120/70 mm Hg or higher. Most private insurance plans will reimburse ABPM, but Medicare currently will not, except for suspected white coat hypertension without target-organ damage. For home BP monitoring, the key is to calibrate the patient's monitor in the office against the validated AOBP monitor. Most BP monitors are graded by the British Hypertension Society (http://www.dableducatioonal.org/). Patients should take a set of three readings every morning before taking their pills and again every evening for 4 days consecutively and record all the readings. The first day's readings and the first reading of each set are discarded as being artificially high, and the rest are averaged; if the mean is 135/85 mm Hg or higher, we diagnose and treat hypertension.

Global Cardiovascular Risk Assessment

We use the 2013 ACC/AHA pooled cohort calculator to estimate 10-year CV risk both to help set each patient's personal BP goal and to decide about starting concomitant high-potency statin therapy, which is indicated in 75% or more of hypertensive individuals. This practice is based on compelling data from both the recent HOPE-3 trial[144] and the earlier ASCOT trial[145] showing that addition of 10 mg of rosuvastatin or 10 mg of atorvastatin (the only two high-potency statins) provides additional CV risk reduction in hypertensive patients (or prehypertensive patients with intermediate CV risk in the case of HOPE-3) and an average baseline low-density lipoprotein (LDL) cholesterol of 130 mg/dL. Thus, we initiate statin therapy with 10 mg of rosuvastatin or atorvastatin if the calculated 10-year CV risk is 7.5% or more or LDL cholesterol is 130 mg/dL or greater.

Secondary Hypertension

Secondary hypertension should be suspected whenever the BP elevation is unusually severe (160/100 or especially if 180/110 mm Hg). The two most common forms of secondary hypertension are CKD and primary aldosteronism. A spot urine microalbumin/creatinine ratio is part of our initial evaluation for hypertension. A spot 8 AM plasma renin activity (PRA) and serum aldosterone is ordered if the serum potassium (K^+) level is less than 3.5 mmol/L or the patient has stage 2 hypertension (BP >160/100 mm Hg) even with normal serum K^+, or if abdominal imaging studies show an incidental adrenal mass. A positive screening test for primary aldosteronism requires both a suppressed PRA below 1.0 ng/mL/hr (<0.6 is severely suppressed) and an elevated serum aldosterone above 12 ng/dL.[146] We ignore the reported aldosterone/renin ratio, which will be falsely high if the PRA is less than 1.0 ng/mL/hr, even if serum aldosterone is low. Although obese hypertensive patients often have obstructive sleep apnea, we have not routinely ordered formal polysonography, because the only large RCT of continuous positive airway pressure (CPAP) found that it is not effective in lowering BP or preventing CV events (e.g., AF).[147] We screen for fibromuscular dysplasia (FMD) with a CT angiogram mainly in women of any age with a unilateral small kidney or with stage 2 systolic/diastolic hypertension, or who complain of a pulsatile swishing sound, which suggests carotid FMD; in experienced centers, percutaneous angioplasty (without stenting) has a high cure rate.[148]

We screen for atherosclerotic renal artery stenosis only in selected patients, because percutaneous intervention with stenting is reserved for patients with medically refractory hypertension, rapidly progressive CKD, or recurrent flash pulmonary edema; absence of microalbuminuria may identify patients without microvascular renal disease and a more favorable outcome with stenting.[149] We screen for pheochromocytoma with plasma metanephrines in any patient with an incidental adrenal mass; otherwise, we only screen if symptoms are compelling (e.g., paroxysmal hypertension with pallor rather than

flushing) or family history of syndromic pheochromocytoma.

Management

Blood Pressure Thresholds and Goals of Therapy

Given the recent SPRINT outcomes and the totality of the evidence, we believe the relaxed drug treatment threshold (SBP ≥150 mm Hg) for patients age 60 years or older, recommended by both the 2014 JNC 8 panelists' report[8] and the 2017 American College of Physicians/American Academy of Family Physicians guidelines,[13] is too conservative to be broadly applied. It is based solely on conventional office BP and trials that were not designed to address this key issue. The recommendation does not account for large interindividual differences in CV risk or frailty.

We take a more personalized approach. For most patients, we initiate antihypertensive drug therapy if the average awake BP (by ABPM, home monitoring, or AOBP) is ≥135/85 mm Hg or the average sleep BP (by ABPM) is ≥120/70 mm Hg, even if the AOBP is <135/85 mm Hg. This is masked hypertension. It is associated with a high CV risk, and we treat it. If the AOBP is ≥135/85 mm Hg, we will withhold drug therapy only if the awake BP and the sleeping BP are unequivocally normal (<130/80 and <110/60 mm Hg, respectively), the global 10-year CV risk score is low (<7.5%), and there is no evidence of target-organ damage. This is white coat hypertension, and, when so strictly defined, it should not be treated. However, many patients with suspected white coat hypertension have a white coat reaction superimposed on mild hypertension that requires treatment.

For high-risk patients, we consider initiating or intensifying drug therapy if the average awake BP is ≥130/80 mm Hg or the sleeping BP is ≥115/65 mm Hg. *High-risk patients* are those meeting one or more of the following SPRINT inclusion criteria:

- Documented CAD, MI, or angina
- Estimated glomerular filtration rate (eGFR) of 20 to 59 mL/min/1.73 m^2
- 10-year CV risk of 15% or greater
- Age 75 years or older

High-risk patients are also those with:

- African ancestry
- LVH by electrocardiography (without critical coronary stenosis)
- Diabetes mellitus without orthostatic hypotension
- Prior stroke or transient ischemic attack (TIA)
- Prior heart failure admissions

For intensive therapy in robust patients age 75 or older, we start with low-dose medication and intensify the regimen slowly. We involve the patient in the clinical decision making. We schedule more

frequent follow-up office visits to avoid causing orthostatic hypotension, symptomatic postexercise hypotension, acute kidney injury (renal J curve), or worsening angina (cardiac J curve), which would require less intensive therapy.

For frail elderly patients (orthostatic or postprandial hypotension or unsteady gait), we relax the goal of therapy such that standing systolic BP is 135 mm Hg or greater without orthostatic symptoms. This often means that a rather high supine BP must be accepted to permit safe ambulation. We discuss this trade-off with the patient and family member or caretaker. Ambulatory monitoring is extremely helpful if available. A seated home BP of 155 mm Hg may be an appropriate treatment target for a frail 70-year-old patient with marked orthostatic and postprandial hypotension (**as in Fig. 47.9**), whereas a home seated BP of 130 mm Hg may be an appropriate treatment target for a vigorous healthy 85-year-old patient whose chief concern is to avoid a disabling stroke. Symptomatic orthostatic hypotension must be avoided, particularly when treating older adults and patients with longstanding diabetes who have developed autonomic neuropathy.

ABPM is particularly informative in patients with stage 3 CKD or higher because most will have masked (otherwise undertreated) nocturnal hypertension and because overtreatment of hypertension can precipitate AKI. As a rule of thumb, average awake BP should be 135/85 mm Hg or lower and nighttime BP 120/70 mm Hg or lower, but these goals will require relaxation if renal function deteriorates (due to loss of renal autoregulation) during intensification of the BP regimen in patients with CKD.

Lifestyle Modification

The DASH diet and other lifestyle modifications are indicated for all patients with hypertension or prehypertension, as detailed in the 2013 AHA/ACC guideline on lifestyle management to reduce CV risk.[20] Because recidivism is common, patients need continual encouragement from their physicians and support from family and peers. We recommend lifestyle modification as an essential adjunct—but not as a substitute—for antihypertensive drug therapy. We start both simultaneously.

First-Line Drugs

The three first-line drug classes for hypertension are (1) a CCB, (2) an ACEI or ARB, and (3) a thiazide-type diuretic. We use amlodipine as the preferred CCB for most patients because it is long acting (once-daily dosing), is the best studied of the CCBs and performed well in multiple RCTs, and is now available in generic form. The choice of an ACEI or ARB involves consideration of cost and tolerability. We use a long-acting ARB for once-daily dosing. For diuretic therapy, the evidence overwhelmingly favors indapamide or chlorthalidone over HCTZ; low doses minimize metabolic side effects.

Low-Dose Combination Therapy

We typically initiate medication management with low-dose combination therapy, both for synergistic efficacy and to minimize dose-dependent side effects. Our go-to combination is amlodipine plus either telmisartan or irbesartan (long-acting, once-daily, potent generic ARBs that performed well in RCTs). Most adults require 5 to 10 mg of amlodipine and either 40 to 80 mg telmisartan or 150 to 300 mg irbesartan daily to effectively manage their hypertension. The starting doses rarely cause side-effects in patients with uncomplicated hypertension.

The higher (10-mg) dose of amlodipine will cause some degree of ankle edema in approximately 20% of patients. The higher dose of irbesartan or telmisartan increases the risk of AKI and hyperkalemia if there is underlying CKD or hypovolemia. We inspect the patient's gums because any CCB can rarely

cause gingival hyperplasia, which resolves (slowly) if diagnosed and the medication is stopped; if not diagnosed and the CCB is continued, it can cause serious dental problems. Most ambulatory patients can achieve BP goals safely and without any side effects in 6 to 12 weeks. This rather rapid intensification of therapy requires home monitoring, frequent clinic follow-up initially, and lifestyle modification.

For patients with uncomplicated hypertension, we generally reserve diuretic therapy for triple therapy, not initial therapy, because of the drugs' metabolic side effects and high-discontinuation rates. Whereas the JNC 8 panelists 2014 report recommended prescribing the high target doses of thiazides used in RCTs, in practice we use the lowest dose of a thiazide-type diuretic needed to achieve the desired BP. The evidence clearly supports the use of long-acting indapamide or CTD over short-acting HCTZ. For patients with hypertension that is not controlled with amlodipine plus telmisartan or irbesartan, we will add half of a 1.25-mg tablet of indapamide, which is less costly than CTD and is a superoxide scavenger.

We prescribe a vasodilating beta blocker, such as carvedilol or nebivolol, as first-line therapy for hypertension in patients with CAD or HF. These vasodilating beta blockers are much better antihypertensive agents than metoprolol. However, they are less effective than metoprolol in treating supraventricular tachycardia, if SVT is an important comorbidity. We also will use one of these drugs as first-line therapy if hypertension accompanies significant chronic anxiety, particularly if the patient's resting heart rate is 80 beats/min or more. Generic carvedilol is on most formularies at $4 per month, whereas nebivolol and Coreg CR are branded and expensive. Carvedilol should be taken after breakfast and after dinner on a full stomach to optimize absorption and to prevent GI upset. Nebivolol is more convenient with once-daily dosing and absorption unaffected by food.

Resistant Hypertension

Many cases of apparent drug-resistant hypertension are pseudoresistant. A common issue is an inadequate medication regimen. If white coat hypertension and medication compliance have been excluded, if screening tests for secondary hypertension are negative, if NSAIDs have been eliminated, and if the goal BP still cannot be achieved with appropriate *first-line triple therapy* (amlodipine *plus* a long-acting ARB *plus* indapamide or CTD), the best add-on drugs are mineralocorticoid receptor antagonists (spironolactone, eplerenone) and vasodilating beta blockers (carvedilol, nebivolol). Low-dose spironolactone (12.5 to 25 mg/day) may take 8 weeks or more to achieve peak BP reduction, which can be impressive. Eplerenone avoids the sexual side effects of spironolactone but is more expensive, and higher daily doses (50 to 100 mg) and twice-daily dosing may be required. Clonidine should be avoided whenever possible and should not be prescribed for patients to self-medicate on an as-needed basis, because this practice will create labile rebound hypertension.

Table 47.16 furnishes tips on optimal BP management. Undertreatment of hypertension and underuse of combination drug therapy—even for resistant hypertension—is common in outpatient office-based practice.[150-152] Impressive data from Kaiser-Permanente show that a large managed care organization can improve hypertension control rates in their population from 45% to over 80% by (1) continually reviewing their registry data to identify patients with elevated BP and contacting the patients proactively, (2) using a simple system-wide medication intensification protocol with fixed-dose/once-daily combination pills, and (3) increasing access with walk-in BP checks performed by medical assistants as part of a pharmacist-based hypertension management team.[153] Pharmacists can work with patients to develop shared goals and reconcile medications, and in most states they may implement a preset medication intensification protocol under collaborative practice agreement with physician oversight. Pharmacist-based team interventions for the management of hypertension have proved effective in more than 50 RCTs[154] and allow the physician time to focus on health care team leadership, diagnostic

evaluations, and other complex issues.[155] With all these measures, hypertension control rates of up to 80% can be achieved in office-based practice. Patients with drug-resistant hypertension should be referred to a hypertension specialist.

TABLE 47.16

Strategies to Optimize Management of Hypertension

Health System Level
Clinical pharmacist team–based approach
Standardized medication intensification protocol
Pay providers for performance approaches
Drug Treatment Level
Low-dose combination therapy
Best tolerated drug classes
Fixed-dose single-pill combinations
Long-acting once-daily drugs
Low-cost generics
Patient Level
Patient activation
Shared goals
Self-monitoring of blood pressure
Social support

Future Perspectives

Large randomized controlled trials are needed to test the appealing but unproven hypothesis that effective treatment of masked hypertension—especially nocturnal hypertension—reduces the attendant risk of major cardiovascular events and death.

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Guidelines

Treatment of Hypertension

Ronald G. Victor and Peter Libby

The Systolic Blood Pressure Intervention Trial (SPRINT) is the most important hypertension trial to be published since the last edition of this textbook.[1,2] SPRINT used a novel, unattended automated office blood pressure (AOBP) protocol to minimize the “white coat” reaction. The trial's positive outcomes favor more intensive rather than less intensive treatment of hypertension for select patients with high cardiovascular (CV) risk. Thus, SPRINT has potentially profound implications for changing both the routine diagnosis and the outpatient management of hypertension for tens of millions of patients in the United States[3] and hundreds of millions of patients worldwide. The question is to what extent SPRINT will impact the different practice guidelines from the United States and other countries,[4-16] given the exclusion of patients with diabetes and some other important comorbidities from SPRINT; the seemingly contradictory null outcome of the third Heart Outcomes Protection Evaluation (HOPE-3) blood pressure (BP) trial, which treated lower-risk patients with a much milder BP drug regimen than SPRINT;[17] and the

real concern that overzealous reduction in high BP can cause hypotension with falls in frail elderly patients, myocardial ischemia in patients with significant coronary disease, and acute kidney injury (AKI) in patients with chronic kidney disease (CKD).

In fact, SPRINT already has impacted the new 2016 guidelines from Canada[5] and from Australia[6] (both written by leading hypertension specialists in their respective countries) but not the 2017 guideline from the American College of Physicians/American Academy of Family Physicians (authored entirely by generalists).[4] It is not surprising that practicing physicians are confused. The 2015 AHA/ACC/ASH Scientific Statement on Treatment of Hypertension in Patients with Coronary Artery Disease[7] predated SPRINT, as did the 2014 Report of JNC 8 panelists (referred to as JNC 8 for convenience).[8]

Diagnosis of Hypertension

Table 47G.1 summarizes the different methods and cutoff BP values used to diagnose hypertension. The new 2016 Canadian hypertension guidelines[5] strongly endorsed AOBP as the preferred method of measuring office BP: with the patient alone without medical personnel in a quiet exam room for 5 minutes, the automated monitor takes a set of five readings at a rate of one reading per minute; the monitor displays the mean of the five readings, which is the AOBP.[5] An initially elevated office BP ≥135/85 mm Hg by AOBP or ≥140/90 mm Hg by conventional manual cuff measurement, must always be confirmed either by ambulatory or home blood pressure monitoring—as emphasized by the current guidelines from Canada, Australia, Europe, and the United Kingdom[5,6,11,14]—or laboriously remeasured during three to five more clinic visits over 4 to 6 weeks to ensure that hypertension is present.[5] All guidelines, except those from the United States, emphasize the importance of ambulatory blood pressure monitoring (ABPM) as the gold standard. Only if the office level is very high (>180/110 mm Hg) or if symptomatic target-organ damage is present should therapy be begun before the diagnosis is carefully established.

TABLE 47G.1

Definition of Hypertension by Conventional Office, Automated Office, and Out-of-Office Blood Pressure (BP) Levels

CATEGORY	SYSTOLIC BP (mm Hg)		DIASTOLIC BP (mm Hg)
Conventional Office BP	≥140	*and/or*	≥90
Automated Office BP (AOBP)	≥135		≥85
Home BP	≥135	*and/or*	≥85
Ambulatory BP Monitor (ABPM)			
Daytime (awake)	≥135	*and/or*	≥85
Nighttime (sleep)	≥120	*and/or*	≥70
24 hour	≥130	*and/or*	≥80

Modified from Parati G et al. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens 2014;32:1359; and Gabb GM et al. Guideline for the diagnosis and management of hypertension in adults—2016. Med J Aust 2016;205:64.

Management of Hypertension

Lifestyle Modification

All patients with hypertension or prehypertension should receive counseling on lifestyle modification using the 2013 ACC/AHA Guideline on Lifestyle Management to Reduce Cardiovascular Risk.[18]

Drug Therapy

Table 47G.2 compares 13 sets of hypertension guidelines last updated between 2010 to 2017. With gaps in the evidence base, expert panels (and individual panelists) disagree on some key aspects but agree on others, as when to start or intensify drug therapy and which drugs are best for which patients.

TABLE 47G.2

Comparison of Recent Guidelines for Adults with Hypertension

GUIDELINE	POPULATION	THRESHOLD OFFICE BP LEVEL (mm Hg) FOR INITIATION OR INTENSIFICATION OF THERAPY	INITIAL DRUG THERAPY OPTIONS
2017 ACP/AAFP[4]	≥60 yr:		Thiazide, ACEI or ARB, CCB
	General Stroke or TIA High CV risk	≥150 ≥140 ≥140	
2016 Hypertension Canada's CHEP[5]	Low risk Macrovascular TOD or other risk factors Selected high risk (including ≥75 yr)	≥160/100 ≥140/90 Consider goal SBP <120 by SPRINT criteria)	Thiazide,* or BB (<60 yr), or ACEI or ARB (nonblack), or long-acting CCB Thiazide-type diuretic + ARB + CCB for intensive therapy
	Diabetes	≥130/80	ACEI or ARB, CCB, thiazide-type
	CKD	≥140/90	ACEI or ARB, CCB, thiazide-type
2016 Australia[6]	Low risk Moderate risk Selected high risk (including ≥75 yr)	≥160/100 ≥140/90 Consider goal SBP <120 by SPRINT criteria	Thiazide, or BB (<60 yr), or ACEI or ARB (nonblack), or long-acting CCB Thiazide-type diuretic + ARB + CCB for intensive therapy
	Diabetes	≥140	ACEI or ARB, CCB, thiazide-type
	CKD	≥140/90	ACEI or ARB, CCB, thiazide-type
2015 AHA/ACC/ASH Patients with CAD[7]	Stable CAD	≥140/90 ≥130/80 for some patients with CAD, prior MI, prior stroke or TIA, or CAD risk equivalents (carotid disease, PAD, AAA) Avoid reducing DBP <60 in patients with diabetes or ≥60 yr	BB, ACEI or ARB; thiazide or thiazide-type diuretic; non-DHP CCB for BB-intolerant patients; DHP CBB for add-on therapy
2014 JNC 8 Committee[8]	General ≥60 yr General <60 yr	≥150/90 ≥140/90	Nonblack: thiazide,* ACEI or ARB, CCB Black: thiazide, CCB
	Diabetes	≥140/90	Thiazide, ACEI or ARB, CCB
	CKD	≥140/90	ACEI or ARB
2014 ASH/ISH[9]	General ≥80 yr General <80 yr Diabetes CKD	≥150/90 ≥140/90 ≥140/90 ≥140/90	Nonblack/stage 1: thiazide, ACEI or ARB, CCB Black/stage 1: thiazide, CCB Stage 2: CCB or thiazide + ACEI or ARB ACEI or ARB ACEI or ARB
2013 AHA/ACC/CDC[10]	General	≥40/90	Stage 1: thiazide for most or ACEI or ARB, CCB Stage 2: thiazide + ACE-I or ARB *or* thiazide + CCB *or* ACEI or ARB + CCB
2013 ESH/ESC[11]	General ≥80 yr General 60-79 yr General ≤60 yr Diabetes CKD, no proteinuria CKD + proteinuria	≥160/90 ≥150/90 *or* ≥140/90 ≥140/90 ≥140/85 ≥140/90 ≥130/90	BB, thiazide, CCB, ACE-I or ARB ACEI or ARB ACEI or ARB ACEI or ARB
2013 ADA[12]	Diabetes	≥140/80	ACEI or ARB
2012 KDIGO[13]	CKD, no proteinuria CKD + proteinuria	≥140/90 ≥130/80	ACEI or ARB
2011 UK NICE[14]	General ≥80 yr General <80 yr	≥150/90 ≥140/90	≥55 yr or black: CCB, thiazide <55 yr: ACEI or ARB
2011 ACCF/AHA: elderly hypertensive patients[15]	General ≥80 yr General <80 yr	≥150/90 ≥40/90	ACEI or ARB, CCB, thiazide
2010 ISHIB[16]	Black Black + target-organ disease or CVD risk	≥135/85 ≥130/80	Thiazide, CCB

*Evidence from randomized controlled trials supports the use of indapamide or chlorthalidone, thiazide-like diuretics, rather than hydrochlorothiazide.

ACEI, Angiotensin-converting enzyme inhibitor; *ARB,* angiotension receptor blocker; *CCB,* calcium channel blocker; *BB,* beta blocker; *DHP,* dihydropyridine.

AAA, Abdominal aortic aneurysm; *CKD,* chronic kidney disease; *CVD,* cardiovascular disease; *DBP,* diastolic blood pressure; *MI,* myocardial infarction; *PDA,* peripheral artery disease; *SBP,* systolic blood pressure; *TIA,* transient ischemic attack; SPRINT, Systolic Blood Pressure Intervention Trial.

ACP, American College of Physicians; AAFP; American Academy of Family Physicians; CHEP, Canadian Hypertension Education Program; ASH, American Society of Hypertension; ISH, International Society of Hypertension; AHA, American Heart Association; ACC, American College of Cardiology; CDC, Centers for Disease Control and Prevention; ADA, American Diabetes Association; KDIGO, Kidney Disease: Improving Global Outcome; UK, United Kingdom; NICE, National Institute for Health and Clinical Excellence.

Modified from James PA et al. 2014 Evidence-based guideline for the management of high BP in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507.

When to Start or Intensify Drug Therapy

Table 47G.3 emphasizes the differences between the recommendation of the panelists concerned for JNC 8 and the newer guidelines from Canada and Australia, which incorporated SPRINT into their updated recommendations. Unlike past JNCs, JNC 8 was endorsed by neither the U.S. National Institutes of Health nor any professional medical society, and thus the 2014 report does not constitute the official U.S. hypertension guidelines. The most controversial recommendation by JNC 8 was to relax the threshold for initiating or intensifying drug therapy for patients age ≥60 years from a systolic BP of 140 to 150 mm Hg. It also recommended relaxing the threshold for patients with diabetes or CKD from a BP of 130/80 to 140/90 mm Hg, the latter being the same for general patients with hypertension. These recommendations were based strictly on conventional office BP. They did not account for the patient's overall CV risk. Statin therapy for additional risk reduction was not addressed.

TABLE 47G.3

Comparison of 2014 JNC 8 Panelists Report with New Recommendations Common to the 2016 Canadian and 2016 Australian Hypertension Guidelines

	2014 JNC 8 REPORT*	2016 GUIDELINES†
Blood pressure (BP) threshold for initiation of drug therapy	≥150/90 mm Hg for patients ≥60 yr ≥140/90 mm Hg for general patients <60 yr and patients with diabetes or chronic kidney disease	Risk-based thresholds: ≥160/100 mm Hg for low risk ≥140/90 mm Hg for moderate risk Consider intensified therapy (goal SBP ≤120 mm Hg by AOBP for selected high-risk patients meeting SPRINT inclusion criteria.
Office BP measurement	Conventional manual sphygmomanometer	Automated office blood pressure (AOBP) or conventional sphygmomanometer
Combination drug therapy	An option to initiate therapy for stage 1 or 2 hypertension	For high-risk patients meeting SPRINT inclusion criteria for intensified therapy
	Combine any two of the first-line drugs	Triple therapy with potent/long-acting drugs: CCB + ACEI or ARB + thiazide-type diuretic
Statin therapy	Not addressed	Recommended for hypertensive patients with high cardiovascular risk

*Modified from James PA et al. 2014 Evidence-based guideline for the management of high BP in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507.

†Modified from Leung AA, et al. Hypertension Canada's 2016 Canadian Hypertension Education Program guidelines for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol 2016;32:569, 2016; and Gabb GM et al. Guideline for the diagnosis and management of hypertension in adults—2016. Med J Aust 2016;205:64.

ACEI, Angiotensin-converting enzyme inhibitor; *ARB,* angiotension receptor blocker; *CCB,* calcium channel blocker; *SBP,* systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial.

In contrast, the new Canadian and Australian guidelines[5,6] are risk based. They recommend an even higher treatment threshold of office BP ≥160/100 mm Hg for low-risk patients, office BP ≥140/90 mm Hg for moderate-risk patients, and to consider intensified therapy with a goal of achieving systolic BP <120 mm Hg by AOBP for select high-risk patients who meet one or more of the SPRINT inclusion criteria

(**Table 47G.4**). These were age ≥50 years, systolic BP 130 to 180 mm Hg, and high CV risk: clinical coronary disease, or estimated glomerular filtration rate (eGFR) of 20 to 59 mL/min/1.73 m^2, 10-year CVD risk ≥15%, or age ≥75 years.[1,3] Exclusion criteria were diabetes, history of stroke, >1 g/24 hr of proteinuria daily, heart failure, history of stroke or transient ischemic attack (TIA), eGFR <20 mL/min/1.73 m^2, or receiving dialysis.[1,3]

TABLE 47G.4

SPRINT Inclusion and Exclusion Criteria

Inclusion Criteria
1. Age ≥50 years, *and* 2. Systolic BP 130-180 mm Hg, *and* 3. High CVD risk (one or more) • Clinical coronary disease (MI, CHD, angina) • eGFR 20-59 mL/min/1.73 m2 • Framingham risk score for 10-year CVD risk ≥15% • Age ≥75 years
Exclusion Criteria
1. Diabetes, *or* 2. History of stroke, *or* 3. Proteinuria >1 g in 24 hr, *or* 4. Heart failure, *or* 5. eGFR <20 mL/min/1.73 m^2 *or* dialysis

CHD, Coronary heart disease; *CVD,* cardiovascular disease; *MI,* myocardial infarction; *eGFR,* estimated glomerular filtration rate.

Modified from Bress AP et al. Generalizability of SPRINT results to the U.S. adult population. J Am Coll Cardiol 2016;67:465.

Several other points merit consideration regarding the different sets of guidelines in **Table 47G.2**:

- Most of the guidelines that predated SPRINT recommended relaxed BP treatment thresholds for elderly patients. The SPRINT outcomes challenge this recommendation.[1,2]
- Only the 2014 statement from the JNC 8 panelists defined “elderly” as 60 years or older. The other guidelines defined elderly as 80 years or older.
- Most guidelines relaxed the treatment threshold in CKD to ≥140/90 mm Hg, except for the 2013 KDIGO guidelines,[13] which recommended ≥130/80 mm Hg for proteinuric CKD.
- There is no consensus about the recommended BP treatment threshold for patients with diabetes. This reflects the large gap in the evidence base (left by the underpowered ACCORD trial).[19] Less intensive therapy may be indicated for patients with longstanding diabetes who already are prone to orthostatic hypotension from diabetic autonomic neuropathy, AKI and hyperkalemia from loss of renal autoregulation and type 4 renal tubular acidosis, and myocardial ischemia from

coronary disease and microvascular rarefication.
• All except the recent U.S. guidelines use global CV risk in considering when to initiate therapy. The European guidelines remain the most conservative, reserving drug therapy in stage 1 hypertension only for those with clinical CV disease, target-organ damage, diabetes, CKD, or an estimated 10-year CV disease risk of ≥20%.[11]
• The 2010 ISHIB guidelines[16] were risk-based, recommending initiation of drug therapy for office BP ≥135/85 mm Hg in black patients with uncomplicated hypertension (who are at higher risk of developing complications than other groups) and for BP ≥130/80 mm Hg in the presence of target-organ disease, comorbidity, or an estimated 10-year CV disease risk of ≥10%.

With all these guidelines, the goal of therapy is to achieve average systolic and diastolic BP levels just below the thresholds for initiating or intensifying therapy.

Which Drugs for Which Patients

• There is consensus that most hypertensive patients—regardless of their age, race/ethnicity, and absence or presence of target-organ damage or comorbidities—will require double-, or more often, triple-drug combination therapy with a calcium channel blocker (CCB), an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), and a diuretic. The only issue is which drug(s) to prescribe first.
• Most guidelines prefer both a thiazide and a CCB over an ACEI or ARB to initiate therapy in black patients.
• There is consensus that alpha blockers are not first-line therapy for hypertension.
• There is consensus that beta blockers are not first-line therapy for uncomplicated hypertension in patients ≥60 years of age. The expert panels disagree whether beta blockers should be considered a first-line option for nonblack patients younger than 60.
• The newer guidelines no longer list diabetes as a compelling

indication for an ACEI or ARB. Any of the first-line drugs is recommended.

• There is overwhelming consensus that an ACEI or ARB is first-line antihypertensive therapy for patients with CKD.

• There is overwhelming consensus to avoid dual renin-angiotensin system (RAS) blockade (ACEI *plus* ARB), which increases the risk of AKI.

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Lipoprotein Disorders and Cardiovascular Disease

Jacques Genest, Peter Libby

The burden of cardiovascular disease (CVD), especially atherosclerotic cardiovascular disease (ASCVD), on national health care systems remains a formidable challenge, although public health measures and targeted pharmacologic therapies can modify cardiovascular risk.[1-3] Lipoprotein disorders, especially those that increase exposure of the arterial wall to cholesterol, constitute a major modifiable cardiovascular risk factor. Modulation of plasma cholesterol levels by lifestyle or, when required, pharmacologic therapy (statins), have proved to be one of the most efficacious intervention for the prevention and treatment of ASCVD.

Lipids constitute approximately 70% (by mass) of the dry weight of plasma. Amino acids (proteins), nucleic acids, and carbohydrate make up the remainder. Approximately half of circulating lipids are sterols, and the other major components include glycerophospholipids (phospholipids) and glycerolipids (triglycerides), which circulate in lipoproteins.[4] Thus, circulating lipoproteins continuously bathe vascular endothelial cells, and the interaction between lipoproteins and cells of the arterial wall contribute causally to the pathogenesis of human atherosclerosis (**see Chapter 44**).

Convincing data affirm the "lipid hypothesis." Observational data described in **Chapter 45** show a strong and consistent association across populations between elevated blood cholesterol and low-density lipoprotein cholesterol (LDL-C) and CVD, especially coronary artery disease (CAD). Experimental data in animals show that the development of atherosclerosis requires cholesterol. Human genetic studies provide strong support of causality for genes related to LDL-C levels.[5-7] Reduction of LDL-C levels reduces the risk for CAD, and the effect size is associated with the magnitude of the reduction in LDL-C. Thus, LDL meets the modified Koch postulates as a causal risk factor for ASCVD.[8-10]

The terms *dyslipidemia* or *dyslipoproteinemia* reflect disorders of the lipid and lipoprotein transport pathways associated with arterial disease more appropriately than "hyperlipidemia." Dyslipidemia encompasses patterns often encountered in clinical practice, such as low high-density lipoprotein cholesterol (HDL-C) and elevated triglyceride concentrations but average total plasma cholesterol level. Dyslipidemia also includes elevated lipoprotein(a) and uncommon genetic or acquired disorders of lipoprotein metabolism. Certain rare lipoprotein disorders can cause overt clinical manifestations, but most common dyslipoproteinemias seldom cause symptoms or clinical signs. Rather, these disorders require laboratory tests for detection. Proper recognition and management of dyslipoproteinemias can reduce cardiovascular and total mortality rates. The fundamentals of lipidology presented here have importance for the daily practice of cardiovascular medicine.

Lipoprotein Transport System

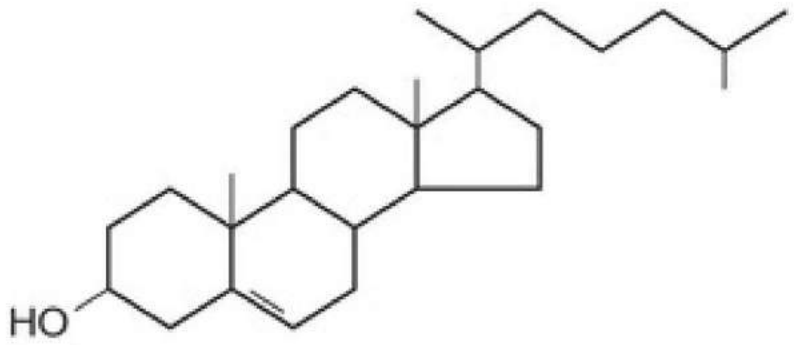
Biochemistry of Lipids

Biologic lipids usually refer to a broad grouping of naturally occurring molecules that include fatty acids, waxes, eicosanoids, monoglycerides, diglycerides, triglycerides, phospholipids, sphingolipids, sterols, terpenes, prenols, and fat-soluble vitamins (A, D, E, and K), in contrast to the other major groupings of biologic molecules, such as nucleic acids, proteins, amino acids, and carbohydrates. The major biologic functions of lipids include critical contributions to biologic membranes, energy storage, and the

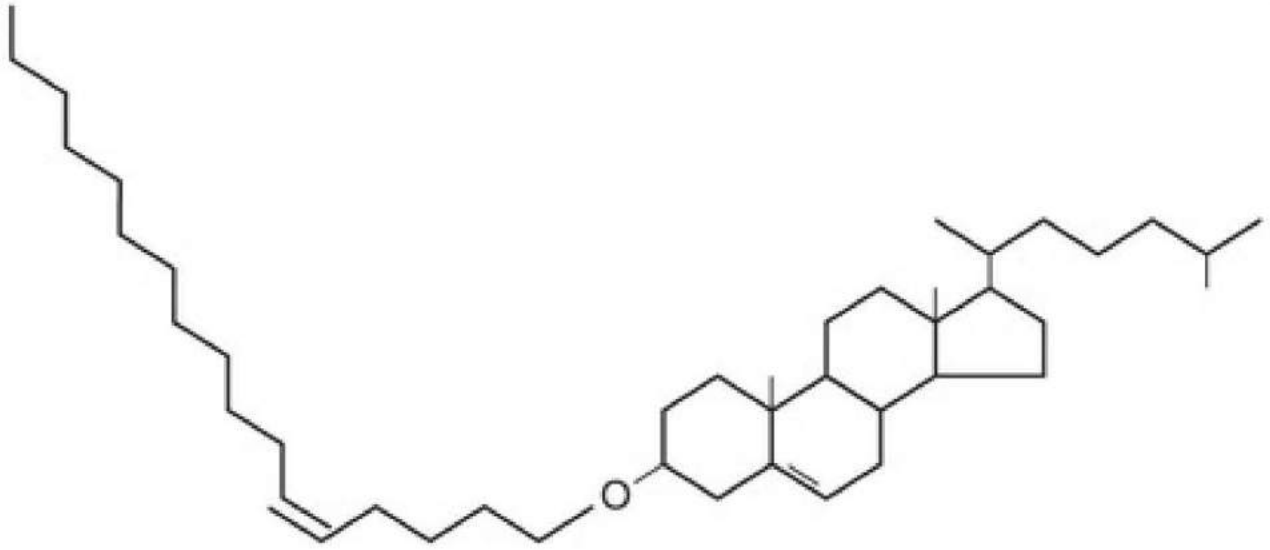
backbones or modifiers of many signaling molecules. Certain lipids, especially fatty acids, readily undergo oxidation and can generate substances highly toxic to cells. Fatty acids can be degraded in the mitochondrion by beta-oxidation, whereas the sterol nucleus resists enzymatic degradation. Elimination of cholesterol therefore requires excretion as bile acids or shedding with skin cells.

Lipids generally do not dissolve in water. The lipid transport system has evolved in animals over eons of evolution to carry hydrophobic molecules (fat) from sites of origin (the intestinal system) to sites of utilization (muscles and rapidly dividing tissues) through the aqueous (water) environment of plasma. Proteins highly conserved through evolution, termed *apolipoproteins* (apo), mediate this process. Most apolipoproteins derive from an ancestral gene and contain both hydrophilic and hydrophobic domains. This amphipathic structure enables these proteins to bridge the interface between the aqueous environment of plasma and the phospholipid constituents of lipoprotein. The major types of lipids that circulate in plasma include cholesterol and cholesteryl esters, glycerophospholipids, sphingolipids, and glycerolipids (triglycerides) (**Fig. 48.1**). The LIPIDmaps (Lipid Metabolites and Pathways Strategy) Consortium has provided standardized nomenclature for lipids.[11]

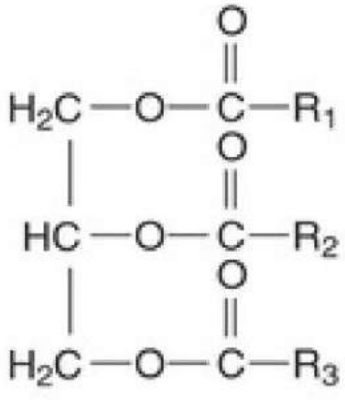
Cholesterol



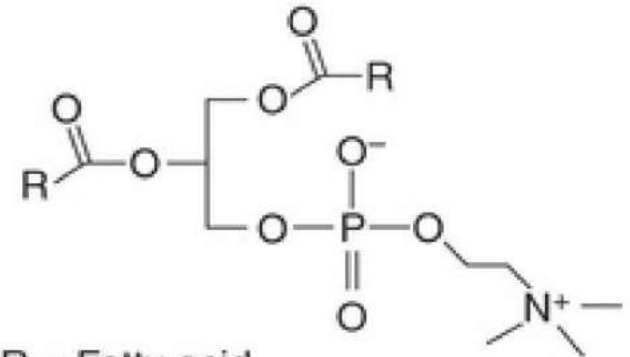
Cholesteryl ester



Triglyceride



Phosphatidylcholine



R = Fatty acid

Sphingomyelin

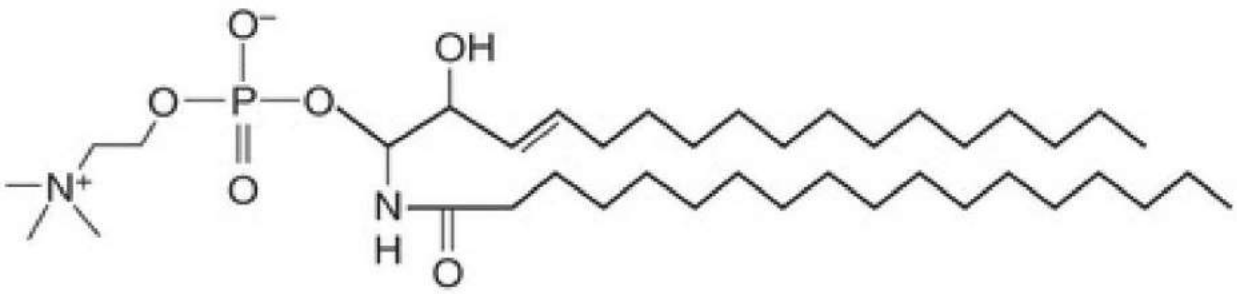


FIGURE 48.1 Biochemical structure of the major lipid molecules: cholesterol, cholesteryl esters, glycerolipids (triglycerides), and glycerophospholipids (e.g., phosphatidylcholine) and sphingomyelin. R indicates a fatty acyl chain.

The membranes of mammalian cells and their subcellular organelles require *cholesterol*. This lipid gives rise to steroid hormones and bile acids and contributes to the integrity of the epidermis. Many cell functions depend critically on membrane cholesterol, and cells regulate tightly their cholesterol content. Most of the cholesterol in plasma circulates as *cholesteryl esters* in the core of lipoprotein particles. The enzyme lecithin-cholesterol acyltransferase (LCAT) forms cholesteryl esters in the blood compartment by transferring a fatty acyl chain from phosphatidylcholine to cholesterol.

Glycerolipids (*triglycerides*) consist of a three-carbon glycerol backbone covalently linked to three fatty acid chains ($R_{1\text{-}3}$). The fatty acid composition varies in terms of chain length and the presence of double bonds (degree of saturation). The highly hydrophobic triglyceride (TG) molecules circulate in the core of the lipoprotein. Hydrolysis of triglycerides by lipases generates the free fatty acids (FFAs) used for energy.

Glycerophospholipids are constituents of all cellular membranes and consist of a glycerol molecule linked to two fatty acids (designated R_1 and R_2; **see Fig. 48.1**). Fatty acids differ in length and in the number of double bonds. The third carbon of the glycerol backbone carries a phosphate group linked to one of four molecules: *choline* (phosphatidylcholine, also called lecithin), *ethanolamine* (phosphatidylethanolamine), *serine* (phosphatidylserine), or *inositol* (phosphatidylinositol). More complex phospholipids include *phosphatidylglycerol* (e.g., cardiolipin is formed by fusion of two phosphatidylglycerol molecules; antibodies against cardiolipin often occur in systemic lupus) and *plasmalogens,* an important constituent of eukaryotic membranes. Another phospholipid, *sphingomyelin*, has special functions in the plasma membrane in the formation of membrane microdomains such as rafts and caveolae. The structure of sphingomyelin resembles that of phosphatidylcholine. The backbone of sphingolipids uses the amino acid serine rather than glycerol. Phospholipids are polar molecules, more water soluble than triglycerides or cholesterol or its esters. Phospholipids participate in signal transduction pathways: hydrolysis by membrane-associated phospholipases generates second messengers, including diacylglycerols, lysophospholipids, phosphatidic acids, and FFAs such as arachidonate, that regulate many cell functions. The phosphorylation of phosphatidylinositol contributes critically to membrane and cell organelle signaling and transport.

Lipoproteins, Apolipoproteins, Receptors, and Processing Enzymes

Lipoproteins are complex macromolecular structures coated by a water-compatible envelope of phospholipids, free cholesterol, and apolipoproteins covering a hydrophobic core of cholesteryl esters and triglycerides. Lipoproteins vary in size, density in the aqueous environment of plasma, and lipid and apolipoprotein content (**Fig. 48.2 and Table 48.1**). The classification of lipoproteins reflects their density in plasma (the density of plasma is 1.006 g/mL) as gauged by flotation in an ultracentrifuge. The triglyceride-rich lipoproteins (TRLs) consist of chylomicrons, chylomicron remnants, and very-low-density lipoprotein (VLDL) and have a density of less than 1.006 g/mL. The rest (bottom fraction) of the ultracentrifuged plasma consists of low-density lipoprotein (LDL), high-density lipoprotein (HDL), and lipoprotein(a) (Lp[a]).

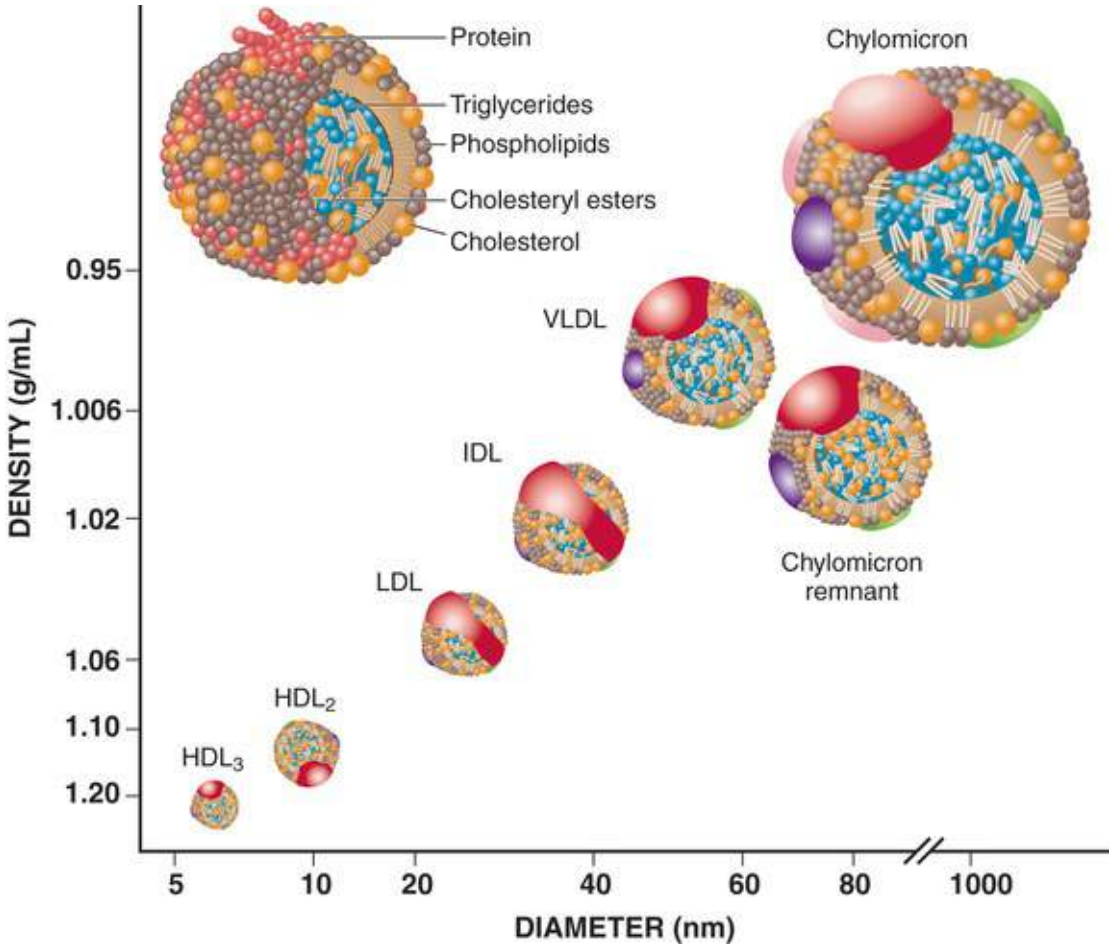


FIGURE 48.2 Relative size of plasma lipoproteins according to their hydrated density. The density of plasma is 1006 g/mL. *Inset,* Structure of lipoproteins. Phospholipids are oriented with their polar group toward the aqueous environment of plasma. Free cholesterol is inserted within the phospholipid layer. The core of the lipoprotein is composed of cholesteryl esters and triglycerides. Apolipoproteins are involved in the secretion of lipoprotein, provide structural integrity, and act as cofactors for enzymes or as ligands for various receptors.

TABLE 48.1

Plasma Lipoprotein Composition

	ORIGIN	DENSITY (g/mL)	SIZE (nm)	PROTEIN (%)	[CHOLESTEROL] IN PLASMA (mmol/L)*	[TRIGLYCERIDE] IN FASTING PLASMA (mmol/L)†	MAJOR APO	OTHER APO
Chylomicrons‡	Intestine	<0.95	100-1000	1-2	0.0	0	B48	A-I, Cs
Chylomicron remnants‡	Chylomicron metabolism	0.95-1.006	30-80	3-5	0.0	0.0	B48, E	A-I, A-IV, Cs
VLDL	Liver	<1.006	40-50	10	0.1-0.4	0.2-1.2	B100	A-I, Cs
IDL	VLDL	1.006-1.019	25-30	18	0.1-0.3	0.1-0.3	B100, E	
LDL	IDL	1.019-1.063	20-25	25	1.5-3.5	0.2-0.4	B100	
HDL	Liver, intestine	1.063-1.210	6-10	40-55	0.9-1.6	0.1-0.2	A-I, A-II	A-IV
Lp(a)	Liver	1.051-1.082	25	30-50			B100, (a)	

*In mmol/L; for mg/dL, multiply by 38.67.

†In mmol/L; for mg/dL, multiply by 88.5.

‡In the fasted state, serum (or plasma) should not contain chylomicrons or their remnants.

Apo, Apolipoprotein; *LDL,* Low-density lipoprotein; *IDL,* intermediate-density lipoprotein; *HDL,* high-density lipoprotein; *VLDL,* very-low-density lipoprotein; *Lp(a),* lipoprotein(a).

Apolipoproteins have four major roles: (1) assembly and secretion of the lipoprotein (apo A-I, B100, and B48), (2) structural integrity of the lipoprotein (apo B, E, A-I, and A-II), (3) coactivators or

inhibitors of enzymes (apo A-I, A-V, C-I, C-II, and C-III), and (4) binding or docking to specific receptors and proteins for cellular uptake of the entire particle or selective uptake of a lipid component (apo A-I, B100, and E) (**Table 48.2**). The role of several apolipoproteins (A-IV, A-V, D, H, J, L, and M) remains incompletely understood.

TABLE 48.2
Apolipoproteins

NAME	PREDOMINANT LIPOPROTEIN	MOLECULAR WEIGHT (kDa)	PLASMA CONCENTRATION (mg/dL)	ROLE	HUMAN DISEASE
Apo (a)	Lp(a)	250-800	0.2-200	Unknown	Lp(a) excess
Apo A-I	HDL	28.3	90-160	ACAT activation, structural	HDL deficiency
Apo A-II	HDL	17	25-45	Structural	
Apo A-IV	HDL	45	10-20	Structural, absorption	
Apo A-V	VLDL, HDL			TRL metabolism	Hypertriglyceridemia
Apo B100	LDL, VLDL	512	50-150	Structural, LDL-R binding	Hypobetalipoproteinemia
Apo B48	Chylomicrons	241	0-100	Structural	
Apo C-I	Chylomicrons	6.63	5-6	TRL metabolism	
Apo C-II	Chylomicrons, VLDL	8.84	3-5	LPL activation	Hyperchylomicronemia
Apo C-III	Chylomicrons, VLDL	8.76	10-14	LPL inhibition	Hypertriglyceridemia
Apo D	HDL	33	4-7	LCAT	
Apo E	Chylomicrons remnant, IDL	34	2-8	LDL-R, apo E receptor binding	Type III hyperlipoproteinemia
Apo H	Chylomicrons, VLDL, LDL, HDL	38-50	1.4-1.6	$Beta_2$-glycoprotein Platelet aggregation	Cardiolipin-binding defect
Apo J	HDL	70	10	Complement system	
Apo L1-6	HDL	43.9	—	Unknown	
Apo M	HDL	25	1 μM	Unknown	

See Tables 48.1 and 48.3 for abbreviations. *TRL,* Triglyceride-rich lipoprotein.

Many proteins regulate the synthesis, secretion, and metabolic fate of lipoproteins; their characterization has provided insight into molecular cellular physiology and targets for drug development (**Table 48.3**). Discovery of the LDL receptor (LDL-R) represented a landmark in understanding cholesterol metabolism and receptor-mediated endocytosis.[12] The LDL-R regulates the entry of cholesterol into cells, and tight control mechanisms alter its expression on the cell surface, depending on intracellular cholesterol. The LDL-R belongs to a superfamily of membrane receptors that include LDL-R, VLDL-R, LDL-R–mediated peptide type 1 (LRP1; apo E receptor), LRP1B, LRP4 (MGEF7), LRP5 and LRP6 (involved in the process of bone formation), LRP8 (apo E receptor-2), and LRP9.[13] LRP1, which mediates the uptake of chylomicron remnants and VLDL, preferentially recognizes apo E. LRP1 also interacts with hepatic lipase. The complex interaction between hepatocytes and the various lipoproteins containing apo E involves cell surface proteoglycans that provide scaffolding for lipolytic enzymes (lipoprotein lipase [LPL] and hepatic lipase) involved in recognition of remnant lipoproteins. Macrophages express receptors that bind modified (especially oxidized) lipoproteins. These scavenger lipoprotein receptors mediate the uptake of oxidatively modified LDL into macrophages. In contrast to the exquisitely regulated LDL-R, high cellular cholesterol content does not suppress scavenger receptors, thereby enabling intimal macrophages to accumulate abundant cholesterol, become foam cells, and form fatty streaks. Sterol accumulation in the endoplasmic reticulum (ER) may lead to cell apoptosis via the unfolded protein response.[14] Endothelial cells can also take up modified lipoproteins through specific receptors such as the oxidized LDL-R LOX-1.

TABLE 48.3

Lipoprotein Processing Enzymes, Receptors, Modulating Proteins

ABBREV	NAME	ROLE	Gene	HUMAN DISEASE
ABCA1	ATP-binding cassette A1	Cellular phospholipid efflux	*ABCA1*	Tangier disease
ABCG5/G8	ATP-binding cassette G5 and G8	Intestinal sitosterol transporter	*ABCG5 ABCG8*	Sitosterolemia
ACAT1	Acetyl-CoA acetyltransferase 1	Cellular cholesterol esterification	*ACAT1*	
ACAT2	Acetyl-CoA acetyltransferase 2	Cellular cholesterol esterification	*ACAT2*	
ANGPTL3	Angiopoietin-like protein 3	Inhibit LDl and EL	*ANGPTL3*	Familial hypolipoproteinemia 2
Apo E-R	Apo E–containing lipoprotein receptor	TRL uptake	*APOER2*	
CD36	Fatty acid translocase	Fatty acid transport	*CD36*	
CETP	Cholesteryl ester transfer protein	Lipid exchange in plasma	*CETP*	Elevated HDL-C
Cyp27A1	Cytochrome	Sterols hydroxylation	*CYP27A1*	Cerebrotendinous xanthomatosis
DGAT1	Acyl-CoA:diacylglycerol acyltransferase 1	Triglyceride synthesis	*DGAT1*	Elevated triglycerides
EL	Endothelial lipase	Phospholipid hydrolysis	*LIPG*	
HL	Hepatic lipase	Triglyceride hydrolysis	*LIPC*	Remnant accumulation
HSL (LIPE)	Hormone-sensitive lipase	Fatty acid release from adipocytes	*LIPE*	
LCAT	Lecithin-cholesterol acyltransferase	Cholesterol esterification (plasma)	*LCAT*	LCAT deficiency, low HDL
LDL-R	Low-density lipoprotein receptor	LDL uptake	*LDLR*	Familial hypercholesterolemia
LDL-R AP1	LDL-R adapter protein	LDL uptake	*LDLRAP1*	Recessive FH
LAL	Lysosomal acid lipase	Cholesteryl ester (CE) storage	*LIPA*	Wollman disease, CE storage disease
LOX-1	Scavenger receptor	OxLDL uptake, endothelium	*OLR1*	Oxidized lipoprotein uptake
LPL	Lipoprotein lipase	Triglyceride hydrolysis	*LPL*	Hyperchylomicronemia
LRP1	LDL-R–related protein	Protease uptake, many ligands	*LRP1*	
LRP2	LDL-R–related protein 2 (megalin)	Protease uptake, apo J	*LRP2*	
MTTP	Microsomal triglyceride transfer protein	Apo B assembly	*MTTP*	Abetalipoproteinemia
NPC1	Niemann-Pick C gene product	Cellular cholesterol transport	*NPC1*	Niemann-Pick type C
NPC1L1	Niemann-Pick C1-like 1 protein	Intestinal cholesterol absorption	*NPC1L1*	
PLTP	Phospholipid transfer protein	Lipid exchange in plasma	*PLTP*	
PCSK9	Proprotein convertase subtilisin/kexin type 9	Protein cleavage	*PCSK9*	Hypercholesterolemia
SMPD1	Sphingomyelinase phosphodiesterase 1	Sphingomyelin hydrolysis	*SMPD1*	Niemann-Pick types A and B
SRA	Macrophage scavenger receptor A	OxLDL uptake, macrophages	*MSR1*	
SR-B1	Scavenger receptor B1	HDL cholesteryl ester uptake	*SCARB1*	
VLDL-R	Very-low-density lipoprotein receptor	VLDL uptake	*VLDLR*	

At least three physiologically relevant receptors interact with HDL particles: the scavenger receptor class B (SR-B1) and the adenosine triphosphate (ATP)–binding cassette transporters A1 (ABCA1) and G1 (ABCG1). SR-B1 is a receptor for HDL (also for LDL and VLDL, but with less affinity). SR-B1 mediates the selective uptake of HDL cholesteryl esters in steroidogenic tissues, hepatocytes, and endothelium. ABCA1 mediates cellular phospholipid (and possibly cholesterol) efflux and HDL formation. The ABCG1 transporter transfers cellular cholesterol to already-formed HDL particles.

Lipoprotein Metabolism and Transport

The lipoprotein transport system has two major roles: (1) efficient transport of triglycerides from the intestine and liver to sites of utilization (fat tissue or muscle) and (2) transport of cholesterol to peripheral tissues for membrane synthesis and steroid hormone production or to the liver for bile acid synthesis (**Fig. 48.3**).

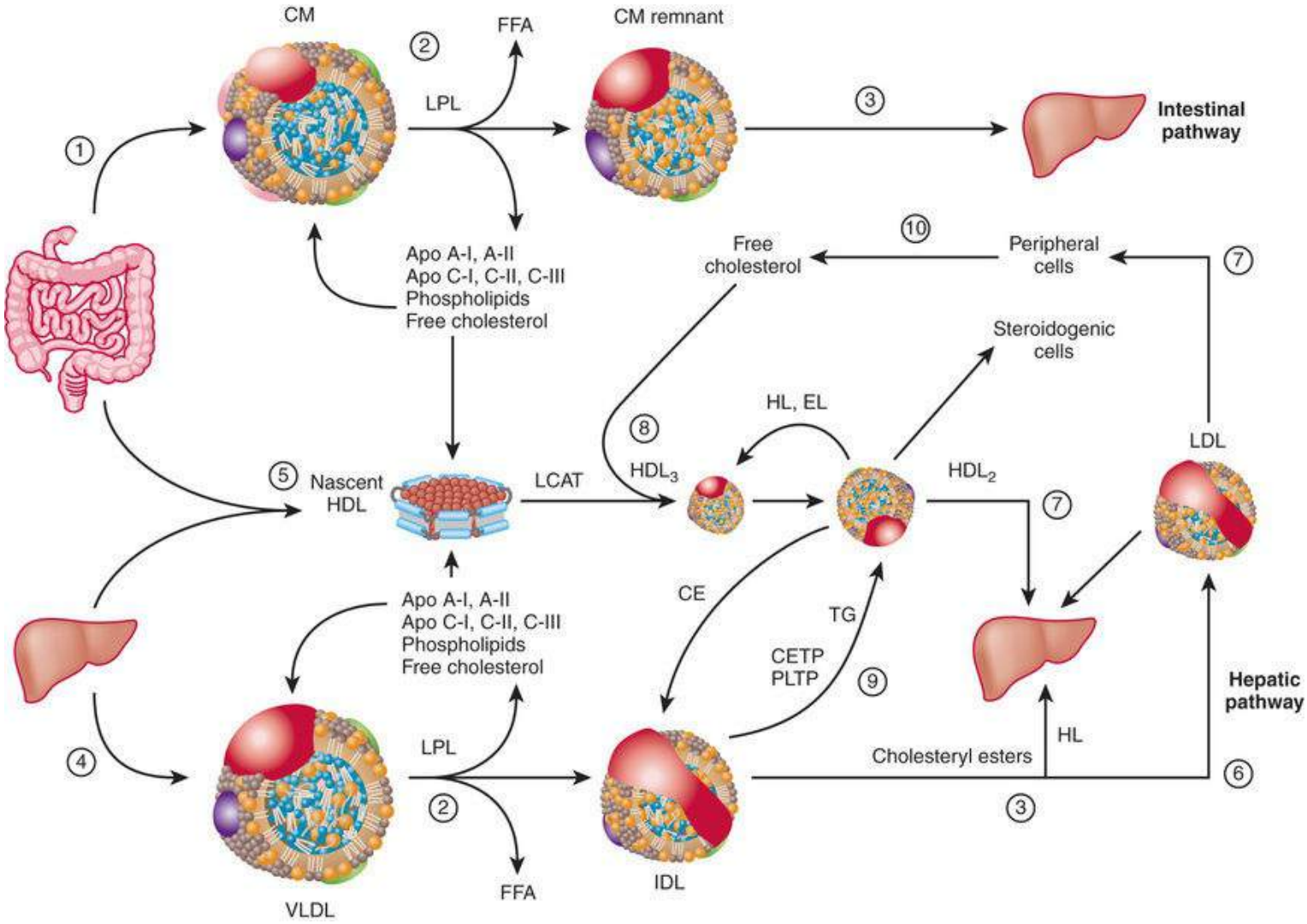


FIGURE 48.3 Schematic diagram of the lipid transport system. Numbers in circles refer to explanations in text. Refer to **Tables 48.1 and 48.3** for abbreviations. *CM,* Chylomicron; *FFA,* free fatty acid.

Intestinal Pathway (Chylomicrons to Chylomicron Remnants).

Life requires fats. The human body derives from the diet essential fatty acids that it cannot make (*linoleic acid*, from which arachidonic acid is derived, and *linolenic acid*, which leads to the formation of eicosapentaenoic acid). Fat typically furnishes 20% to 40% of the daily calories. Triglycerides account for the major portion of ingested fats. For an individual consuming 2000 kcal/day, with 30% in the form of fat, this represents approximately 66 g of triglycerides and 250 mg (0.250 g) of cholesterol per day. The intestine has very efficient fat absorption mechanisms, probably evolved to maximize provision of the organism with nutrients under circumstances of limited or irregular availability of food.

On ingestion, lingual and pancreatic lipases hydrolyze triglycerides into FFAs and monoglycerides or diglycerides. Emulsification by bile salts leads to the formation of intestinal micelles. Micelles resemble lipoproteins in that they consist of phospholipids, free cholesterol, bile acids, diglycerides and monoglycerides, FFAs, and glycerol. The mechanism of micelle uptake by intestinal brush border cells still engenders debate. The Niemann-Pick C1-like 1 (NPC1L1) protein is part of an intestinal cholesterol transporter complex and the target for the selective cholesterol absorption inhibitor ezetimibe. After uptake into intestinal cells, fatty acids undergo re-esterification to form triglycerides and packaging into chylomicrons inside the intestinal cell and enter the portal circulation (**Fig. 48.3, part 1**). Chylomicrons

contain apo B48, the amino-terminal component of apo B100. In the intestine, the apo B gene is modified during transcription into messenger RNA (mRNA) by substitution of a uracil for a cytosine via an apo B48–editing enzyme complex (ApoBec). This mechanism involves a cytosine deaminase and leads to a termination codon at residue 2153 and a truncated form of apo B. Only intestinal cells express ApoBec. Apo B48 does not bind to LDL-R. Intestinal cells absorb plant sterols (sitosterol, campesterol), sort these compounds into a separate cellular compartment, and resecrete them into the intestinal lumen via the ABCG5/8 heterodimeric transporter. Mutations of the *ABCG5/8* genes cause the rare disorder sitosterolemia.

Chylomicrons rapidly enter the plasma compartment after meals. In capillaries of adipose tissue or muscle cells in the peripheral circulation, chylomicrons encounter the enzyme LPL attached to heparan sulfate proteoglycans on the luminal surface of endothelial cells (**Fig. 48.3, part 2**). Apo C-II or apo A-V activate and apo C-III inhibits LPL activity. LPL has broad specificity for triglycerides; it cleaves all fatty acyl residues attached to glycerol and in the process generates three molecules of FFA for each molecule of glycerol. Muscle cells rapidly take up fatty acids. Fatty acids provide the energy substrate for muscle contraction by the generation of ATP during beta-oxidation of fatty acyl residues in mitochondria. Adipose cells can store triglycerides made from fatty acids for energy utilization, a process that requires insulin. The triglyceride lipase hormone–sensitive lipase, which is activated by cyclic adenosine monophosphate (cAMP) in response to stress, releases stored fatty acids from adipose tissues. Fatty acids can also travel to the liver bound to fatty acid–binding proteins or albumin and undergo repackaging into VLDLs. Peripheral resistance to insulin can thus increase the delivery of FFAs to the liver, with a consequent increase in VLDL secretion and increased apo B particles in plasma, a characteristic of the “metabolic syndrome” and type 2 diabetes. The remnant particles, derived from chylomicrons following LPL action, contain apo E and enter the liver for degradation and reutilization of their core constituents (**Fig. 48.3, part 3**).

Hepatic Pathway (Very-Low-Density Lipoprotein to Intermediate-Density Lipoprotein). Food is not always available, and dietary fat content varies. The body requires readily available triglycerides to meet energy demands. Hepatic secretion of VLDL particles serves this function (**Fig. 48.3, part 4**). VLDLs are TRLs smaller than chylomicrons (**see Table 48.1 and Fig. 48.2**). They contain apo B100 as their main lipoprotein. Unlike apo B48, apo B100 contains a domain recognized by LDL-R (the apo B/E receptor). VLDL particles follow the same catabolic pathway as chylomicrons through LPL (**Fig. 48.3, part 2**). During hydrolysis of TRLs by LPL, an exchange of proteins and lipids takes place: VLDL particles (and chylomicrons) acquire apo Cs and apo E, in part from HDL particles. VLDLs also exchange triglycerides for cholesteryl esters from HDL (mediated by cholesteryl ester transfer protein [CETP]) (**Fig. 48.3, part 9**). Such bidirectional transfer of constituents between lipoproteins serves several purposes: acquisition of specific apolipoproteins by lipoproteins that will dictate their metabolic fate, transfer of phospholipids onto nascent HDL particles mediated by phospholipid transfer protein (PLTP) (during loss of the core triglycerides, the phospholipid envelope becomes redundant and sheds apo A-I to form new HDL particles), and transfer of cholesterol from HDL to VLDL remnants so that it can be metabolized in the liver. This exchange constitutes a major part of the “reverse cholesterol transport pathway.”

Apo CIII, a small but important 79–amino acid peptide, has a high affinity for TRLs and attenuates the activity of LPL and the clearance of TRLs, thus contributing to elevated triglycerides. Apo CIII also resides within HDL, which seems to act as a “reservoir” for this apolipoprotein. Recent work identified an intracellular role for apo CIII for the assembly and secretion of VLDL.[15] Mendelian randomization experiments and epidemiologic studies have established that apo CIII can contribute causally to

ASCVD.[16,17] This recognition has spurred therapeutic efforts to decrease apo CIII (see later).

After hydrolysis of triglycerides removes some triglycerides from VLDL, these particles have relatively more cholesterol, shed several apolipoproteins (especially the C apolipoproteins), and acquire apo E. The VLDL remnant lipoprotein, called *intermediate-density lipoprotein* (IDL), undergoes liver uptake via its apo E moiety (**Fig. 48.3, part 3**) or further delipidation by hepatic lipase to form LDL particles (**Fig. 48.3, part 6**). At least four receptors take up TRLs, TRL remnants, and apo B–containing lipoproteins: VLDL-R, the remnant receptor (apo ER2), LDL-R (also called the apo B/E receptor), and LRP1. Most hepatic receptors share the ability to recognize apo E, an engagement that mediates the uptake of several classes of lipoproteins, including VLDL and IDL.[5] The complex interaction between apo E and its ligand involves the "docking" of TRLs on heparan sulfate proteoglycans to present the ligand to its receptor.

Low-Density Lipoproteins

LDL particles contain predominantly cholesteryl esters packaged with apo B100. Normally, triglycerides constitute only 4% to 8% of the LDL mass (**see Table 48.1**). Elevated plasma TG levels can become enrich LDL particles in triglycerides and deplete their core cholesteryl esters. Such changes in core constituents influence LDL particle size: an increase in triglycerides and a relative decrease in cholesteryl esters yields smaller, denser LDL particles.

Humans are unusual among mammals because they use LDL as a major cholesterol transporter. Nonhuman primates fed a cholesterol-enriched diet also carry cholesterol in LDL. In other mammals, such as rodents or rabbits, VLDL carries triglycerides, and HDL particles transport most of the cholesterol. Cells can either make cholesterol from acyl coenzyme A (CoA) through enzymatic reactions requiring at least 33 steps or obtain it as cholesteryl esters from HDL or LDL particles. Cells internalize LDL via LDL-R[12] (**Fig. 48.4**). LDL particles contain one molecule of apo B. Although several highly lipophilic domains of apo B are associated with phospholipids, a region surrounding residue 3500 binds with high affinity to LDL-R. LDL-R localizes in a region of the plasma membrane rich in the protein *clathrin* (**Fig. 48.4**; **also see Fig. 48.3, part 7**). Once bound to the receptor, clathrin polymerizes and forms an endosome that contains LDL bound to its receptor, a portion of the plasma membrane, and clathrin. This internalized particle then fuses with lysosomes whose hydrolytic enzymes (cholesteryl ester hydrolase, cathepsins) release free cholesterol and degrade apo B. LDL-R releases its ligand and can recycle to the plasma membrane. The chaperone *proprotein convertase subtilisin/kexin type 9* (PCSK9), secreted by hepatocytes, undergoes autocatalytic cleavage and binds to the LDL-R. Association with PCSK9 diverts the complex to the "lysosomal degradative pathway," thus preventing the normal recycling of the LDL-C[18] (**Fig. 48.5**). Gain-of-function mutations in the *PCSK9* gene cause autosomal dominant hypercholesterolemia, whereas loss-of-function mutations increase LDL-R and lower LDL-C substantially.[19]

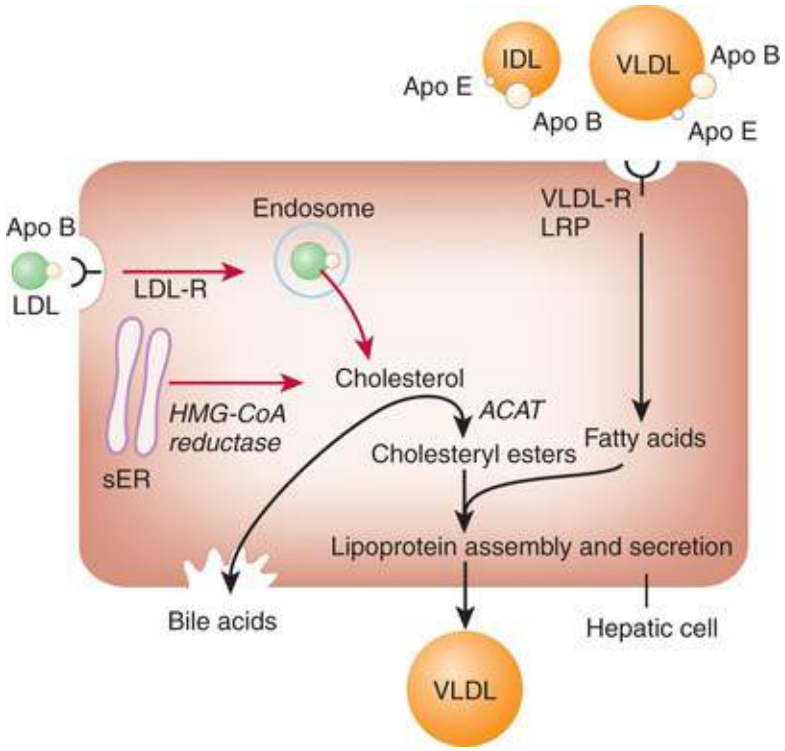


FIGURE 48.4 Cellular cholesterol homeostasis in hepatocytes. Refer to **Tables 48.1 and 48.3** for abbreviations. *sER,* Smooth endoplasmic reticulum.

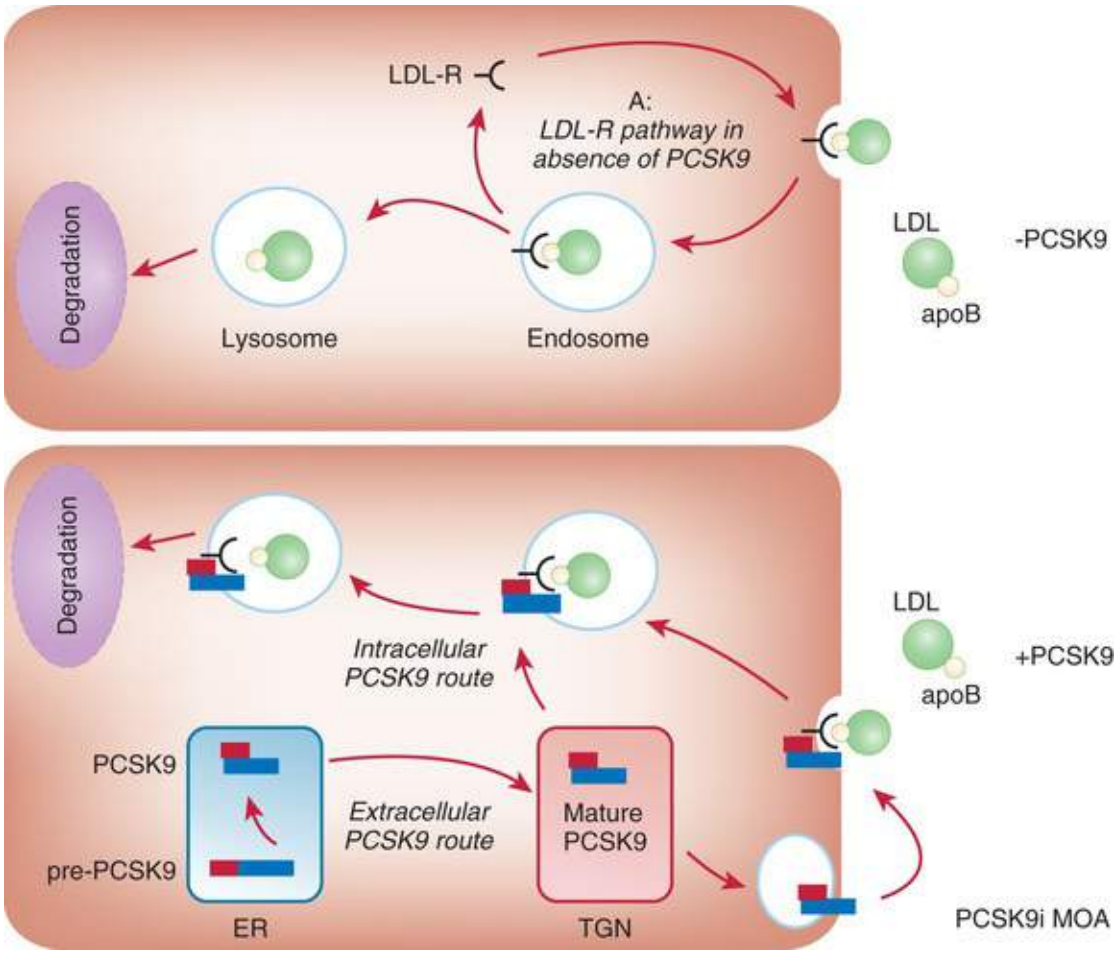


FIGURE 48.5 Diagram of a hepatocyte expressing the low-density lipoprotein receptor (LDL-R). **Top panel,** In the absence (or mAb blockade) of PCSK9, the LDL-R recycles rapidly to the cell surface. LDL particles are cleared by LDL by receptor-mediated endocytosis, thereby lowering LDL-C concentration in the blood. **Bottom panel,** PCSK9 chaperones the internalized LDL-R/LDL particle complex to the endosome-lysosomal compartment, where it undergoes degradation. The consequent decrease in LDL-R impairs LDL clearance, yielding accumulation of cholesterol-rich LDL particles in the blood. *ER,* Endoplasmic reticulum; *TGN*, Trans Golgi network.

Cells regulate their cholesterol content tightly by (1) synthesis of cholesterol in the smooth ER (via the rate-limiting step hydroxymethylglutaryl-CoA [HMG-CoA] reductase), (2) receptor-mediated endocytosis of LDL (two mechanisms under control of steroid-responsive element binding protein-2 [SREBP-2]), (3) efflux of cholesterol from the plasma membrane to cholesterol acceptor particles (predominantly apo A-I and HDL) via the ABCA1 and ABCG1 transporters, and (4) intracellular cholesterol esterification via the enzyme acetyl-CoA acetyltransferase (ACAT) (**see Fig. 48.4**). SREBP-2 coordinately regulates the first two pathways at the level of gene transcription. Cellular cholesterol binds to SCAP (SREPB cholesterol-activated protein), which localizes on the ER. Cholesterol inhibits the interaction of SCAP with SREPB. In the absence of cholesterol, SCAP mediates the cleavage of SREBP at two sites by specific proteases with the release of an amino-terminal fragment of SREBP. This SREBP fragment migrates to the nucleus and increases the transcriptional activity of genes involved in cellular cholesterol and fatty acid homeostasis.[12] The ACAT pathway regulates the cholesterol content in membranes. Humans express two separate forms of ACAT. ACAT1 and ACAT2 derive from different genes and mediate cholesterol esterification in cytoplasm and in the ER lumen for lipoprotein assembly and secretion.

High-Density Lipoprotein and Reverse Cholesterol Transport

Regulation of cholesterol efflux from cells depends in part on the ABCA1 pathway, controlled in turn by hydroxysterols (especially 24- and 27-OH cholesterol, which act as ligands for the liver-specific

receptor [LXR] family of nuclear transcription factors). In conditions of cholesterol sufficiency, the cell can decrease cholesterol synthesis. The cell can also limit the amount of cholesterol that enters the cell via the LDL-R, thereby augmenting the amount stored as cholesteryl esters, and can promote cholesterol removal by increasing its movement to the plasma membrane for efflux.

Epidemiologic studies have consistently shown an inverse relationship between plasma levels of HDL-C and the presence of CAD (**see Chapter 45**). HDL promotes reverse cholesterol transport and can prevent lipoprotein oxidation and exert anti-inflammatory actions in vitro, among many other seemingly salutary functions.[20,21] Yet, mendelian randomization analyses have cast doubt on the causal role of HDL as a protective cardiovascular (CV) risk factor. Mutations of the genes for ABCA1 that cause lifelong HDL deficiency do not impart additional CV risk, and conversely, genetic polymorphisms of genes that increase HDL-C are not associated with protection from CV events.[22]

HDL has a complex and incompletely understood metabolism. The complexity arises because HDL particles acquire their components from several sources, and these components undergo metabolism at different sites. In addition, steady-state levels of HDL in plasma may not reflect the dynamic nature of HDL-mediated cholesterol trafficking, in contrast to the situation with LDL. The intestine and liver synthesize apo A-I, the main protein of HDL. Approximately 80% of HDL originates from the liver and 20% from the intestine (**see Fig. 48.3, part 5**). Lipid-free apo A-I acquires phospholipids from cell membranes and from redundant phospholipids shed during the hydrolysis of TRLs. Lipid-free apo A-I binds to ABCA1 and promotes the transporter's phosphorylation via cAMP, which increases the net efflux of phospholipids and cholesterol onto apo A-I to form a nascent HDL particle (**see Fig. 48.3, part 10**). This particle contains apo A-I, phospholipids, and some free cholesterol (**Fig. 48.6**). These nascent HDL particles will mediate further cellular efflux of cholesterol. Currently, standard laboratory tests do not measure these HDL precursors because they contain little or no cholesterol. On reaching a cell membrane, the nascent HDL particles capture membrane-associated cholesterol and promote the efflux of free cholesterol onto other HDL particles (**see Fig. 48.3, part 10**). Conceptually, the formation of HDL particles appears to involve two steps. The first step involves binding of HDL apo A-I to ABCA1 and generation of a specific membrane microdomain that allows the subsequent lipidation of apo A-I. Efflux of cellular cholesterol from peripheral cells, such as macrophages, does not contribute importantly to overall HDL-C mass but could export cholesterol from atheromas. Macrophages can transfer cholesterol to apo A-I and apo E, to nascent discoid or ellipsoid HDL particles, via the ABCA1 transporter (**Fig. 48.6**). The ABCG1 transporter does not promote cellular cholesterol efflux to lipid-free or lipid-poor apo A-I but to mature HDL particles. In vitro assays can measure HDL-mediated cellular cholesterol efflux by plasma samples, a process that appears altered in many disease states, including diabetes and CAD. LCAT, an enzyme activated by apo A-I, then esterifies the free cholesterol (**see Figs. 48.1, 48.3 part 8, and 48.6**). HDL also furnishes cholesterol to steroid hormone–producing tissues and the liver through *selective uptake of cholesterol* mediated by the scavenger receptor SR-B1.

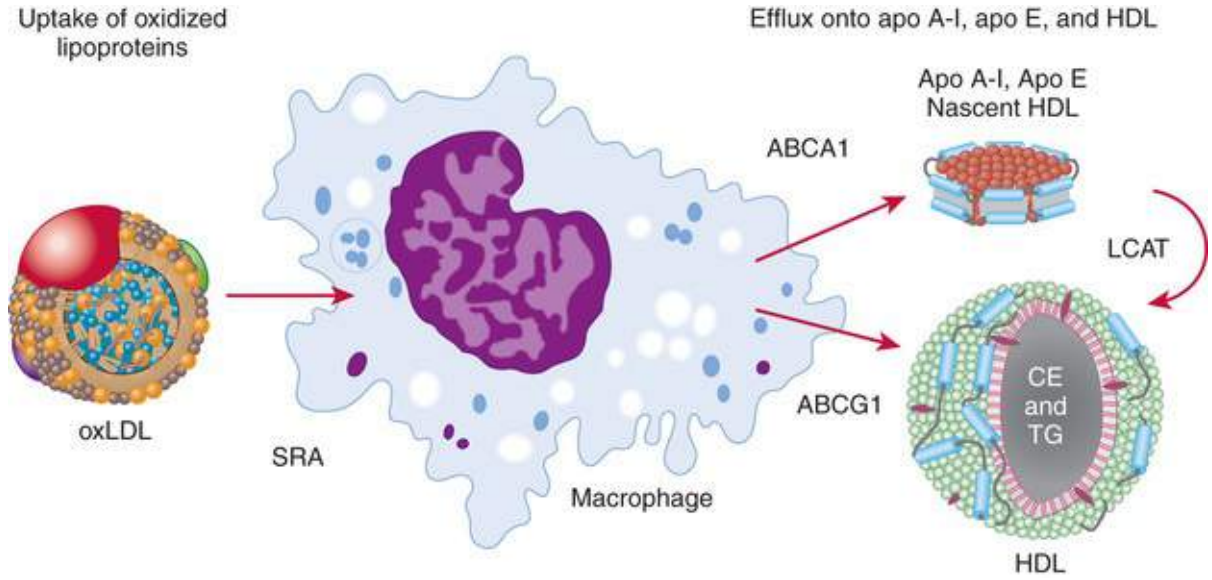


FIGURE 48.6 Initial step in cellular cholesterol efflux from macrophages and HDL formation. *CE,* Cholesterol esters; *LCAT,* lecithin-cholesterol acyltransferase; *SRA,* macrophage scavenger receptor A; *TG,* triglyceride.

Because of their hydrophobicity, cholesteryl esters move to the core of the lipoprotein, and the HDL particle now assumes a spherical configuration (a particle denoted HDL_3). With further cholesterol esterification, the HDL particle increases in size to become the more buoyant HDL_2. The cholesterol within HDL particles can transfer to TRLs via CETP, which mediates an equimolar exchange of cholesterol from HDL to TRL and movement of triglyceride from TRL onto HDL (**see Fig. 48.3, part 9**). Inhibition of CETP increases HDL-C in blood and has undergone exploration as a therapeutic target for prevention of CVD. PLTP mediates the transfer of phospholipids between TRL and HDL particles. Triglyceride-enriched HDLs are denoted HDL_{2b}. Hepatic lipase can hydrolyze triglycerides and endothelial lipase can hydrolyze phospholipids within these particles and thereby convert them back to HDL_3 particles.

Reverse cholesterol transport involves the uptake of cellular cholesterol from extrahepatic sources, such as lipid-laden macrophages, and its esterification by LCAT, transport by large HDL particles, and exchange for one TG molecule by CETP. Hepatic receptors can now take up the cholesterol molecule originally on an HDL particle and residing in a TRL or LDL particle after this exchange. HDL particles therefore act as shuttles among tissue cholesterol, TRL, and the liver.

Reverse cholesterol transport by HDL constitutes a small but potentially important portion of the plasma HDL mass. Indeed, selective inactivation of macrophage ABCA1 does not change HDL-C levels in mice but increases atherosclerosis. The protein component of HDL particles is exchangeable with lipoproteins of other classes. The kidneys appear to be a route of elimination of apo A-I and other HDL apolipoproteins.

Lipoprotein Disorders

Definitions

Time and new knowledge have stimulated changes in the classification of lipoprotein disorders. The original classification of lipoprotein disorders by Fredrickson, Lees, and Levy (1967) depended on analysis of lipoprotein patterns by ultracentrifugation or electrophoresis and has fallen into disuse (see prior editions of this textbook for details). Most clinicians now classify lipoprotein disorders by which

specific lipoprotein lipid is elevated and, when carefully characterized, by the genetic defect (e.g., familial hypercholesterolemia). For example, a young patient with eruptive xanthomas and a plasma TG level of 22 mmol/L (2000 mg/dL) probably has familial hyperchylomicronemia as a result of LPL deficiency or other monogenic defects. An obese, hypertensive middle-aged man with a cholesterol level of 6.4 mmol/L (245 mg/dL), TG level of 3.1 mmol/L (274 mg/dL), HDL-C level of 0.8 mmol/L (31 mg/dL), and calculated LDL-C level of 4.2 mmol/L (162 mg/dL) probably has metabolic syndrome, and this should trigger the clinician to seek other components of this cluster, including hypertension and hyperglycemia. Conversely, an obese middle-aged man with a plasma TG level of 7 mmol/L (620 mg/dL) probably has mutations in several genes associated with plasma TG levels.

The clinical usefulness of apolipoprotein levels has stirred debate (**see Chapter 45**). Taken as a single measurement, the apo B level provides information on the number of potentially atherogenic particles and can be used as a goal of lipid-lowering therapy. Similarly, LDL particle size correlates highly with plasma HDL-C and TG levels, and most studies do not show it to be an independent CV risk factor. Small, dense LDL particles tend to track with features of metabolic syndrome, which usually involves dyslipoproteinemia with elevated plasma TG and reduced HDL-C levels. The Emerging Risk Factors Collaboration studies have shown that measurement of non–HDL-C is equivalent to measurement of apo B in determination of CV risk. Indeed, measurement of non–HDL-C captures the cholesterol content in apo B–containing lipoproteins. Similarly, HDL-C tracks as well with CVD risk as apo A-I does.[23]

Genetic Lipoprotein Disorders

Understanding of the genetics of lipoprotein metabolism has expanded rapidly. Classification of genetic lipoprotein disorders usually requires a biochemical phenotype in addition to a clinical phenotype. With the exception of familial hypercholesterolemia, monogenic disorders tend to be infrequent or very rare. Disorders considered heritable on careful family study may be difficult to characterize unambiguously because of age, sex, penetrance, and gene-gene and environmental interactions. Most common lipoprotein disorders encountered clinically result from the interaction of increasing age, lack of physical exercise, weight gain, and a suboptimal diet with individual genetic makeup. Genetic lipoprotein disorders can either raise or lower levels of LDL, Lp(a), remnant lipoproteins, TRLs (chylomicrons and VLDL), or HDL (**Table 48.4**).

TABLE 48.4
Genetic Lipoprotein Disorders

DISORDER	GENE	FIGURE 48.3
Low-Density Lipoprotein (LDL) Particles		
Autosomal dominant hypercholesterolemia (ADH)		
Heterozygous familial hypercholesterolemia (HeFH)	*LDLR*	7
Homozygous familial hypercholesterolemia (HoFH)	*LDLR*	7
Familial defective apo B100	*Apo B*	7
Gain-of-function PCSK9 mutations	*PCSK9*	7
Autosomal recessive hypercholesterolemia	*LDLRAP1*	7
Abetalipoproteinemia	*MTTP*	
Hypobetalipoproteinemia	*APOB*	
Familial sitosterolemia	*ABCG5/ABCG8*	
Familial Lp(a) hyperlipoproteinemia	*APOA*	
Remnant Lipoproteins		
Dysbetalipoproteinemia type III	*APOE*	3
Hepatic lipase deficiency	*LIPC*	6
Triglyceride-Rich Lipoproteins (TRLs)		
Lipoprotein lipase deficiency (familial chylomicronemia syndrome, FCS)	*LPL*	2
Apo C-II deficiency	*APOCII*	2
Apo A-V deficiency	*APOAV*	
Familial hypertriglyceridemia	Polygenic	
Familial combined hyperlipidemia	Polygenic	
High-Density Lipoproteins (HDLs)		
Apo A-I deficiency	*APOAI*	5
Tangier disease/familial HDL deficiency	*ABCA1*	10
Familial LCAT deficiency syndromes	*LCAT*	8
CETP deficiency	*CETP*	9
Niemann-Pick disease types A and B	*SMPD1*	
Niemann-Pick disease type C	*NPC1*	
Other		
Cerebrotendinous xanthomatosis	*CYP27A1*	

CETP, Cholesteryl ester transfer protein; *LCAT,* lecithin-cholesterol acyltransferase.

Low-Density Lipoproteins (Type II Hyperlipidemia)

Familial Hypercholesterolemia

Elucidation of the pathway by which complex molecules enter the cell by receptor-mediated endocytosis and discovery of LDL-R represent landmarks in cell biology and clinical investigation.[12] Affected persons have an elevated LDL-C level greater than the 95th percentile for age and sex, approximately 190 mg/dL (5.0 mmol/L) in adults. In adulthood, clinical manifestations include corneal arcus, tendinous xanthomas over the extensor tendons (metacarpophalangeal joints, patellar, triceps, and Achilles tendons), and xanthelasmas. Transmission is autosomal codominant. The diagnosis of familial hypercholesterolemia (FH) is usually made according to the Dutch Lipid Clinics Network (**Table 48.5**) or the Simon-Broome criteria (**Table 48.6**).[24] Both are highly concordant and rely on the absolute levels of LDL-C, family history of premature ASCVD, family history of elevated LDL-C, cutaneous manifestations, and if available, DNA analysis. FH affects approximately 1 in 250 persons,[25,26] and this prevalence is higher in populations with a founder effect. Patients with FH have high risk for the development of CAD by the third to fourth decade in men and approximately 8 to 10 years later in women. Diagnosis is based on an elevated plasma LDL-C level, family history of premature CAD, and the presence of xanthomas. The presence of a mutation in a gene known to cause FH increases CV risk by more than 20-fold.[27] Remarkably, prompt recognition in childhood or early adulthood and treatment (statins) can normalize life expectancy.[24]

TABLE 48.5

Diagnosis of Familial Hypercholesterolemia (FH) According to Dutch Lipid Clinic Network Criteria

CRITERIA	DIAGNOSTIC POINTS*
Family History	
First-degree relative known with premature (men <55 yr, women <60 yr) coronary and vascular disease *or* First-degree relative known with low-density lipoprotein cholesterol (LDL-C) >95th percentile *or* First-degree relative with tendon xanthomata and/or arcus cornealis	1 point
Or	
Children <18 yr with LDL-C >95th percentile	2 points
Clinical History	
Patient has premature (men <55 yr, women <60 yr) coronary artery disease	2 points
Patient has premature (men <55 yr, women <60 yr) cerebral or peripheral vascular disease	1 point
Physical Examination	
Tendon xanthomata	6 points
Arcus cornealis <45 yr	4 points
Laboratory Analysis	
LDL-C >8.5 mmol/L	8 points
LDL-C 6.5-8.4 mmol/L	5 points
LDL-C 5.0-6.4 mmol/L	3 points
LDL-C 4.0-4.9 mmol/L	1 point
Dna Analysis	
Functional mutation *LDLR* gene present	8 points

*Diagnosis of FH is:

Certain when >8 points.
Probable when 6-8 points.
Possible when 3-5 points.

TABLE 48.6

Simon-Broome Criteria for Familial Hypercholesterolemia (FH)

Diagnose a person with **DEFINITE FH** if she/he has:
- Total cholesterol >7.5 mmol/L in adults or total cholesterol >6.7 mmol/L in children <16 yr **OR** LDL-C >4.9 mmol/L in adults or LDL-C >4.0 mmol/L in children **AND** tendon xanthomas or evidence of these signs in first- or second-degree relative

OR

- DNA-based evidence of an *LDLR* mutation, familial defective of apo B-100, or a *PCSK9* mutation

Diagnose a person with **PROBABLE FH** if she/he has:
- Total cholesterol >7.5 mmol/L in adults or total cholesterol >6.7 mmol/L in children <16 yr **OR** LDL-C >4.9 mmol/L in adults or LDL-C >4.0 mmol/L in children

PLUS

- Family history of myocardial infarction <50 yr in a second-degree relative or <60 yr in a first-degree relative

OR

- Family history of elevated total cholesterol concentration >7.5 mmol/L in a first- or second-degree relative

Low-Density Lipoprotein Receptor Gene.

Defects in the *LDLR* gene cause an accumulation of LDL particles in plasma and thus alter the function of the LDL-R protein and cause FH (**see Fig. 48.3, part 7**). Well in excess of 1700 mutations of the *LDLR* gene can cause FH.

Familial Defective Apolipoprotein B.

Mutations within the *APOB* gene that lead to an abnormal ligand-receptor interaction can cause a form of autosomal dominant hypercholesterolemia clinically indistinguishable from FH. Several mutations at the postulated binding site to LDL-R cause familial defective apo B100 (**see Fig. 48.3, part 7**). The defective apo B has reduced affinity (20% to 30% of control) for LDL-R. LDL particles with defective apo B have

a plasma half-life threefold to fourfold greater than the half-life of normal LDL. Because of their increased persistence, these LDL particles can more readily undergo oxidative modifications that can enhance their atherogenicity. Affected persons usually have LDL-C levels elevated up to 400 mg/dL (10.4 mmol/L) but may also have normal levels. Familial defective apo B100 has a lower prevalence than *LDLR* mutations (1 in 500).

Proprotein Convertase, Subtilisin/Kexin Type 9.

Gain-of-function mutations in the *PCSK9* gene decrease surface availability of the LDL-R protein and cause accumulation of LDL-C in plasma. A loss-of-function mutation in *PCSK9* confers lower LDL-C than in individuals without the mutation. Black Americans had a higher prevalence of this protective mutation than did whites in the ARIC (Atherosclerosis Risk in Communities) study, and participants with lifelong low LDL-C because of a mutation at the *PCSK9* gene locus had a marked reduction in coronary events,[19] thus confirming that genetically low LDL-C states lower CV risk. Although PCSK9 is a therapeutic target, small-molecule inhibition has not succeeded in blocking PCSK9 function. Parenteral administration of injectable, humanized or fully human monoclonal antibodies (mAbs) directed against PCSK9 greatly reduces LDL-C in humans.[28,29] Large-scale clinical trials examining the effect of further LDL-C lowering with PCSK9 inhibitors will determine the clinical usefulness of these agents for ASCVD prevention and treatment.

Polygenic Hypercholesterolemia.

In most cohorts of "definite FH" patients, as many as 20% do not have a mutation in the *LDLR*, *APOB*, or *PCSK9* genes. Exome-wide sequencing has identified several other genes causing a phenocopy of FH, but some patients have an accumulation of single-nucleotide polymorphisms (SNPs) of genes known to elevate LDL-C in large-scale genome-wide association studies (GWASs).[30]

Autosomal Recessive Hypercholesterolemia.

An autosomal recessive form of FH identified in a kindred from Sardinia results from a mutation in the gene encoding the LDL-R adaptor protein (*LDL-RAP-1* gene), which encodes a protein involved in recycling of LDL-R.[31] Other genes, including *APOE* del166LEU,[32,33] *STAP1*,[34] and lysosomal acid lipase (LIPA),[35] cause a phenocopy of FH.

Hypobetalipoproteinemia and Abetalipoproteinemia.

Mutations within the *APOB* gene can lead to truncations of the mature apo B100 peptide. Many such mutations cause a syndrome characterized by reduced LDL-C and VLDL-C but little or no clinical manifestations and no known risk for CVD, a condition referred to as *hypobetalipoproteinemia*. Apo B truncated close to its amino terminus loses the ability to bind lipids and produces a syndrome similar to *abetalipoproteinemia*, a rare recessive lipoprotein disorder of infancy that causes mental retardation and growth abnormalities. Abetalipoproteinemia results from a mutation in the gene coding for the microsomal triglyceride transfer protein (*MTTP*), which is required for assembly of apo B–containing lipoproteins in the liver and the intestine. The resulting lack of apo B–containing lipoproteins in plasma causes a lack of fat-soluble vitamins (A, D, E, and K) that circulate in lipoproteins. In turn, this deficiency result in mental and developmental impairment in affected children.

Sitosterolemia.

A rare condition of increased intestinal absorption and decreased excretion of plant sterols (sitosterol

and campesterol) can mimic severe FH with extensive xanthoma formation.[36] Premature atherosclerosis, often apparent clinically well before adulthood, occurs in patients with sitosterolemia. Diagnosis requires specialized analysis of plasma sterols documenting an elevation in sitosterol, campesterol, cholestanol, sitostanol, and campestanol. Patients with sitosterolemia have normal or reduced plasma cholesterol levels and normal TG concentrations. Patients with sitosterolemia have rare homozygous (or compound heterozygous) mutations in the *ABCG5* and *ABCG8* genes. The gene products of ABCG5 and ABCG8 are half ABC transporters and form a heterodimer localized in the villous border of intestinal cells that actively pumps plant sterols back into the intestinal lumen. A defect in either of the genes inactivates this transport mechanism, and net accumulation of plant sterols (because of impaired elimination) ensues.

Lipoprotein(a)

Lp(a) (pronounced "lipoprotein little a") consists of an LDL particle linked covalently with one molecule of apo (a). The apo (a) moiety consists of a protein with a high degree of homology with plasminogen. The gene for apo (a) appears to have arisen from the plasminogen gene. The apo (a) gene has multiple repeats of one of the kringle motifs (kringle IV), which vary in number from 12 to more than 40 in each individual. Plasma Lp(a) levels depend almost entirely on genetics and correlate inversely with the number of kringle repeats and therefore with the molecular weight of apo (a). Human genetic data implicate Lp(a) as a causal CV risk factor. Lp(a) concentrations follow a skewed distribution in the population, and black Americans tend to have higher Lp(a) levels than do other ethnic groups in the United States. Few environmental factors or medications modulate plasma Lp(a) levels. The pathogenesis of Lp(a) may result from an antifibrinolytic potential and ability to bind oxidized lipoproteins.[37] Genetic polymorphisms at the *LPA* gene have shown a strong association with aortic calcification and may have a causal role in aortic stenosis.[38]

Triglyceride-Rich Lipoproteins

In persons with metabolic syndrome and in diabetic patients, elevation of plasma TG levels occurs most often in the presence of visceral (abdominal) obesity and a diet rich in calories, carbohydrates, and saturated fats (**see Chapters 45 and 50**). Severe elevation of plasma triglycerides can result from genetic disorders of the processing enzymes or apolipoproteins and poorly controlled diabetes. Controversy regarding a causal role of triglycerides in the pathogenesis of ASCVD continues. It is likely that the cholesterol content of TRLs, their remnants, and associated apo CIII, rather than triglycerides themselves, constitute the causal moiety in this lipoprotein class.[39]

Familial Hypertriglyceridemia (Type IV Hyperlipoproteinemia)

Familial hypertriglyceridemia is not associated with clinical signs such as corneal arcus, xanthoma, and xanthelasmas. Plasma triglycerides, VLDL-C, and VLDL triglycerides are moderately to markedly elevated; the LDL-C level is usually low, as is HDL-C. Total cholesterol is normal or elevated, depending on VLDL-C levels. Fasting plasma TG concentrations range from 2.3 to 5.7 mmol/L (200 to 500 mg/dL). After a meal, plasma triglycerides may exceed 11.3 mmol/L (1000 mg/dL). The disorder clusters in first-degree relatives but varies phenotypically depending on sex, age, hormone use (especially estrogens), and diet. Alcohol intake potently stimulates hypertriglyceridemia in these patients, as does caloric or carbohydrate intake. Familial hypertriglyceridemia has a weaker relationship with CAD than familial combined hyperlipidemia, and not all studies support this association. Depending on the criteria

used, the prevalence of familial hypertriglyceridemia ranges from 1 in 100 to 1 in 50. This highly heterogeneous disorder probably results from several genes, as well as a strong environmental influence.[40]

An unrelated X-linked genetic disorder, *familial glycerolemia,* may mimic familial hypertriglyceridemia because most measurement techniques for triglycerides use the measurement of glycerol after enzymatic hydrolysis of triglycerides. Diagnosis of familial hyperglycerolemia requires ultracentrifugation of plasma and analysis of glycerol.

Hepatic overproduction of VLDL causes familial hypertriglyceridemia (**see Fig. 48.3, part 4**); the catabolism (uptake) of VLDL particles can be normal or reduced. Lipolysis by LPL appears adequate under basal conditions, but not with excess TG load, especially following fatty meals. Human genetic studies have shown that many cases of severe hypertriglyceridemia result from mutations in one or more of the genes associated with TG metabolism.[40] Treatment is based first on lifestyle modifications, including weight reduction in overweight individuals, limiting alcohol intake, reducing caloric intake, increasing exercise, and withdrawal of hormones (estrogens and progesterone or anabolic steroids).

An uncommon disorder characterized by a severe elevation in plasma TG levels (both VLDL and chylomicrons) is associated with a fat-rich diet, obesity, and poorly controlled diabetes. Recognized as *type V hyperlipidemia,* the pathogenesis is multifactorial and results from overproduction of both VLDL and chylomicrons and decreased catabolism of these particles.

Familial Hyperchylomicronemia Syndrome (Type I Hyperlipidemia).
This rare disorder of severe hypertriglyceridemia elevates fasting plasma triglycerides to greater than 11.3 mmol/L (>1000 mg/dL). These patients have recurrent bouts of pancreatitis and eruptive xanthomas. Severe hypertriglyceridemia can also be associated with lipemia retinalis, xerostomia, xerophthalmia, and behavioral abnormalities. The hypertriglyceridemia results from markedly reduced or absent LPL activity or, more rarely, absence of its activator apo C-II (**see Fig. 48.3, part 2**). These defects lead to a lack of hydrolysis of chylomicrons and VLDL and their accumulation in plasma, especially after meals. Extreme elevations of plasma triglycerides (>113 mmol/L; >10,000 mg/dL) can result. Mutations at several genes associated with TG metabolism can result in elevated chylomicron levels.

Plasma from a patient with very high TG levels is milky white, and a clear band of chylomicrons can be seen on top of the plasma after it stands overnight in a refrigerator. Populations with a founder effect can a have high prevalence of LPL mutations. At least 60 LPL mutations can cause LPL deficiency. LPL_{188}, $LPL_{asn291ser}$, and LPL_{207} are frequently associated with hyperchylomicronemia. Heterozygotes for the disorder tend to have an increase in fasting plasma triglycerides and smaller, denser LDL particles. Many patients with complete LPL deficiency exhibit failure to thrive in childhood and have recurrent bouts of pancreatitis. To underscore the importance of the role of LPL, *lpl* deficiency in the mouse leads to a perinatal lethal phenotype. Treatment of acute pancreatitis includes intravenous hydration and avoidance of fat in the diet (including fat in parenteral nutrition), and only rarely requires plasma filtration. Chronic treatment includes avoidance of alcohol and dietary fat. Addition of short-chain fatty acids (which are not incorporated in chylomicrons) can increase palatability of the diet. An antisense RNA (volanesorsen, IONIS-APOCIIIRx) directed against apo CIII shows promise in the treatment of severe hypertriglyceridemia[41] but requires long-term safety assessment. Inhibition of diacylglycerol acyltransferase 1 (DGAT1), which mediates chylomicron TG synthesis, with the compound pradigastat, represents a potential therapeutic avenue for these patients.[42]

Type III Hyperlipoproteinemia.
Also referred to as *dysbetalipoproteinemia* or *broad beta disease*, type III hyperlipoproteinemia is a rare genetic lipoprotein disorder characterized by accumulation of remnant lipoprotein particles in plasma. Lipoprotein agarose gel electrophoresis shows a typical pattern of a broad band between the prebeta (VLDL) and beta (LDL) lipoproteins, thus the name "broad beta disease." Patients with this disease have increased CV risk. Clinical findings include of pathognomonic tuberous xanthomas and palmar striated xanthomas. The lipoprotein profile shows increased cholesterol and TG levels and reduced HDL-C. Remnant lipoproteins (partly catabolized chylomicrons and VLDL) accumulate in plasma and become enriched with cholesterol esters. The defect results from abnormal apo E, which does not bind to hepatic receptors that recognize apo E as a ligand (**see Fig. 48.3, part 3**). Patients with type III hyperlipoproteinemia have an elevated ratio of VLDL cholesterol to triglycerides, normally less than 0.7 (when measured in mmol/L; <0.30 in mg/dL), because of cholesteryl ester enrichment of remnant particles. Thus, calculation of LDL-C in such patients is unreliable, requiring direct LDL-C measurement. Diagnosis includes plasma ultracentrifugation for lipoprotein separation, lipoprotein electrophoresis, and apo E phenotyping or genotyping. Patients with type III hyperlipoproteinemia have the apo $E_{2/2}$ phenotype or genotype. Apo E has three common alleles: E_2, E_3, and E_4. The apo E_2 allele has greatly decreased binding to the apo B/E receptor.

The apo $E_{2/2}$ genotype has a prevalence of approximately 0.7% to 1.0%. Type III hyperlipoproteinemia occurs in approximately 1% of persons bearing the apo $E_{2/2}$ genotype. Reasons for the relative rarity of type III dyslipoproteinemia are not fully understood. Mutations in other genes associated with TG metabolism contribute to phenotypic expression of the apo $E_{2/2}$ genotype.[40] Other rare mutations of the gene for apo E can cause type III hyperlipoproteinemia. In general, type III dyslipoproteinemia responds well to dietary therapy, correction of other metabolic abnormalities (diabetes, obesity, hypothyroidism), and in patients requiring drug therapy, use of fibric acid derivatives or statins. The importance of the apo E gene and protein is underscored by the widespread use of the apo E–deficient mouse, which develops atherosclerosis.

Familial Combined Hyperlipidemia

Familial combined hyperlipoproteinemia is one of the most common familial lipoprotein disorders. Described initially in survivors of myocardial infarction (MI), the definition of familial combined hyperlipoproteinemia has undergone several refinements. It is characterized by the presence of elevated total cholesterol and/or TG levels based on arbitrary cut points in several members of the same family. Advances in analytic techniques have added measurement of LDL-C and, in some cases, apo B levels. Because of the lack of a clear-cut clinical or biochemical marker, considerable overlap exists between familial combined hyperlipoproteinemia, familial dyslipidemic hypertension, metabolic syndrome, and hyperapobetalipoproteinemia. Genetic heterogeneity probably underlies familial combined hyperlipoproteinemia, which has a prevalence of approximately 1 in 50 and accounts for 10% to 20% of patients with premature CAD. The condition has few clinical signs; corneal arcus, xanthomas, and xanthelasmas occur infrequently. Biochemical abnormalities include elevation of plasma total cholesterol and LDL-C levels (>90th to 95th percentile) and/or elevation of plasma triglycerides (>90th to 95th percentile)—a type IIb lipoprotein phenotype, often in correlation with low HDL-C and elevated apo B levels; small, dense LDL particles occur frequently. Diagnosis of familial combined hyperlipoproteinemia requires identification of the disorder in at least one first-degree relative. Underlying metabolic disorders appear to include hepatic overproduction of apo B–containing lipoproteins, delayed postprandial

clearance of TRLs, and increased flux of FFAs to the liver.

Experimental data have shown that substrate levels drive hepatic apo B secretion, the most important substrates being FFAs and cholesteryl esters. Increased delivery of FFAs to the liver, as occurs in states of insulin resistance and visceral obesity, leads to increased hepatic apo B secretion. Familial combined hyperlipoproteinemia has complex genetics. It was initially considered an autosomal codominant trait; modifying factors include gender, age at onset, and comorbid states such as obesity, lack of exercise, and diet. Novel loci in the upstream transcription factor 1 (*USF1*) and stearoyl-CoA desaturase 1 genes are promising candidate genes related to familial combined hyperlipoproteinemia. The description of loss of function in the angiopoietin-like protein-3 gene (*ANGPTL3*) in a kindred with familial hypolipidemia renewed interest in the angiopoietin-like proteins 3, 4 and 5, which modulate the activities of LPL and endothelial lipase[43,44] (**Fig. 48.3, part 2**).

The genetic basis for type III dyslipidemia and familial combined hyperlipidemia likely lies in the combination of multiple genetic defects, the cumulative sum of which produces a clinical phenotype, especially in the context of a poor lifestyle.[40]

High-Density Lipoproteins

Reduced plasma levels of HDL-C consistently correlate with the development or presence of CAD. Most cases of reduced HDL-C result from elevated plasma triglycerides or apo B levels and often keep company with other features of metabolic syndrome. Genetic disorders of HDL can result from decreased production or abnormal maturation and increased catabolism. Genetic lipoprotein disorders leading to moderate to severe elevations in plasma triglycerides cause a reduction in HDL-C levels. Familial hyperchylomicronemia, familial hypertriglyceridemia, and familial combined hyperlipoproteinemia all are associated with reduced HDL-C levels. In complex disorders of lipoprotein metabolism such as familial combined hyperlipidemia, metabolic syndrome, and common forms of hypertriglyceridemia, several factors most likely correlate with low HDL-C level. Plasma TG and HDL-C levels vary inversely. Several reasons exist for this association: (1) decreased lipolysis of TRLs decreases the availability of substrate (phospholipids) for HDL maturation, (2) HDL enriched with triglyceride has an increased catabolic rate and thus reduced plasma concentration, and (3) the augmented pool of TRLs saps cholesterol from the HDL compartment by CETP-mediated exchange.

Disorders of High-Density Lipoprotein Biogenesis[44]

Apolipoprotein A-I Gene Defects.

Primary defects affecting the production of HDL particles may be caused by mutations in the apo A-I–C-III–A-IV-AV gene complex. More than 50 mutations affect the structure of apo A-I and lead to a marked reduction in HDL-C levels. Not all these defects are associated with premature CVD. Clinical findings can vary from extensive atypical xanthomatosis and corneal infiltration of lipids to no manifestations at all. Treatment of these apo A-I gene defects generally fails to raise HDL-C. Other mutations of apo A-I lead to an increased catabolic rate of apo A-I and may not be associated with CVD. One such mutation, apo $A\text{-}I_{Milano}$ (apo $A\text{-}I_{Arg173Cys}$), appears not to increase risk for CVD despite very low HDL levels.

Tangier Disease and Familial High-Density Lipoprotein Deficiency.

A rare disorder of HDL deficiency, identified in a proband from Tangier Island, Tangier disease and

familial HDL deficiency result from mutations in the *ABCA1* gene, which encodes the ABCA1 transporter (**see Fig. 48.6**). More than 200 mutations in *ABCA1* can cause Tangier disease (homozygous or compound heterozygous mutations) or familial HDL deficiency (heterozygous mutations). Patients with Tangier disease or familial HDL deficiency may be at increased risk for CAD, counterbalanced by their very low levels of LDL-C. Mendelian randomization analysis has not supported a causal relationship between mutations in the *ABCA1* gene and ASCVD.

Niemann-Pick type C disease is a disorder of lysosomal cholesterol transport. In these patients, mental retardation and neurologic manifestations occur frequently. The cellular phenotype involves greatly decreased cholesterol esterification and a defect in the cellular transport of cholesterol to the Golgi apparatus. The gene for Niemann-Pick type C disease (*NPC1*) shuttles cholesterol between the "late endosomal pathway" and the plasma membrane. Niemann-Pick type C cells lack NPC1 protein; intracellular cholesterol sequestration suppresses ABCA1, impairing cellular cholesterol efflux and HDL assembly.

Disorders of High-Density Lipoprotein–Processing Enzymes.

Lecithin-Cholesterol Acyltransferase Deficiency.

Genetic defects in the HDL-processing enzymes give rise to interesting phenotypes. Deficiencies of LCAT, the enzyme that catalyzes the formation of cholesteryl esters in plasma, cause corneal infiltration of neutral lipids and hematologic abnormalities as a result of the abnormal constitution of red blood cell membranes. LCAT deficiency can lead to an entity called "fish eye disease" because of the characteristic pattern of corneal infiltration observed in affected individuals. Despite the profound HDL-C deficiency, LCAT deficiency does not appear to increase risk for CAD.

Cholesteryl Ester Transfer Protein Deficiency.

Patients without CETP have very elevated levels of HDL-C, which is enriched in cholesteryl esters. Because CETP facilitates the transfer of HDL cholesteryl esters into TRLs, a deficiency of this enzyme causes accumulation of cholesteryl esters within HDL particles. CETP deficiency is not associated with premature CAD but may not afford protection against CAD. Because of its effects on HDL-C, CETP inhibition has undergone testing as a therapy, which thus far has proved disappointing.

Niemann-Pick type I disease (subtypes A and B), which is caused by mutations in the sphingomyelin phosphodiesterase 1 (*SMPD1*) gene, is associated with a low HDL-C level. The *SMPD1* gene encodes a lysosomal (acidic) and secretory sphingomyelinase. The low HDL-C level in patients with Niemann-Pick A and B disease appears to result from a decrease in LCAT reaction because of abnormal HDL constituents.

Recent GWASs have identified multiple gene loci associated with plasma lipid levels, thus raising the possibility of identifying novel pathways in lipoprotein metabolism and potential novel therapeutic targets.

Secondary Causes of Hyperlipidemia and Metabolic Syndrome (Table 48.7)

Hormonal Causes

Hypothyroidism often manifests as elevated LDL-C, triglycerides, or both (**see Chapter 92**). An elevated level of thyroid-stimulating hormone (TSH) provides the key to the diagnosis, and the lipoprotein abnormalities often revert to normal after correction of thyroid status. Rarely, hypothyroidism may uncover a genetic lipoprotein disorder such as type III hyperlipidemia. Estrogens can elevate plasma TG

and HDL-C levels because of increases in both hepatic VLDL and apo A-I production. In postmenopausal women, estrogens may reduce LDL-C by up to 15%. Use of estrogens for the treatment of lipoprotein disorders is no longer recommended because of the slight increase in CV risk with prolonged use of estrogens in the postmenopausal period (**see Chapter 89**). Rarely, pregnancy causes severe increases in plasma triglycerides on a background of LPL deficiency or yet-to-be-identified genetic defects. Such cases present a serious threat to mother and child and require referral to specialized centers. Male sex hormones and anabolic steroids can increase hepatic lipase activity and have been used for the treatment of hypertriglyceridemia in men. However, these agents can also contribute to an elevated TG level, reduced HDL-C, increased blood pressure, and other features of metabolic syndrome. Growth hormone can reduce LDL-C and increase HDL-C but is not recommended for the treatment of lipoprotein disorders.

TABLE 48.7

Secondary Causes of Dyslipoproteinemias

CAUSE	DISORDER
Metabolic	Diabetes Lipodystrophy Glycogen storage disorders
Renal	Chronic renal failure Glomerulonephritis with nephritic syndrome
Hepatic	Cirrhosis Biliary obstruction Porphyria Primary biliary cirrhosis (with secondary LCAT deficiency)
Hormonal	Estrogens Progesterones Growth hormone Thyroid disorders (hypothyroidism) Corticosteroids
Lifestyle	Physical inactivity Obesity Diet rich in fats, saturated fats Alcohol intake Smoking
Medications	Retinoic acid derivatives Glucocorticoids Exogenous estrogens Thiazide diuretics Beta-adrenergic blockers (selective) Testosterone and other anabolizing steroids Immunosuppressive medications (cyclosporine) Antiviral medications (HIV protease inhibitors) Antischizophrenic medications

HIV, Human immunodeficiency virus; *LCAT,* lecithin-cholesterol acyltransferase.

Metabolic Causes

The most frequent secondary cause of dyslipoproteinemia is probably the constellation of metabolic abnormalities seen in patients with metabolic syndrome (**see Chapters 45 and 50**). The finding of increased visceral fat (abdominal obesity), elevated blood pressure, and impaired glucose tolerance often clusters with increased plasma triglycerides and a reduced HDL-C level and represents the major components of metabolic syndrome. Overt diabetes, especially type 2 diabetes, frequently elevates plasma triglycerides and reduces HDL-C. These abnormalities have prognostic implications in patients with type 2 diabetes (**see Chapter 51**) Poor control of diabetes, obesity, and moderate to severe hyperglycemia can yield severe hypertriglyceridemia with chylomicronemia and increased VLDL-C levels. Patients with poorly controlled type 1 diabetes can also have severe hypertriglyceridemia.

Familial lipodystrophy (complete or partial) may be associated with increased VLDL secretion. *Dunnigan lipodystrophy*, a genetic disorder with features of metabolic syndrome, results from mutations within the lamin A/C gene and is associated with limb-girdle fat atrophy. Excess plasma triglycerides often accompany glycogen storage disorders.

Renal Disorders

In patients with glomerulonephritis and protein-losing nephropathies (**see Chapter 98**), a marked increase in secretion of hepatic lipoproteins can raise LDL-C, which may approach the levels seen in patients with FH. By contrast, patients with chronic renal failure have a pattern of hypertriglyceridemia with reduced HDL-C. Patients with end-stage renal disease (ESRD), including those undergoing hemodialysis or chronic ambulatory peritoneal dialysis, have a poor prognosis and accelerated atherosclerosis. Statin treatment has not improved outcomes in ESRD patients. After organ transplantation, the immunosuppressive regimen (glucocorticoids and cyclosporine) typically elevates triglycerides and reduces HDL-C levels. Because transplant recipients generally have an increase in CV risk, this secondary hyperlipidemia may warrant treatment. Patients receiving the combination of a statin plus cyclosporine merit careful dose titrations and monitoring for myopathy. The Kidney Disease: Improving Global Outcomes (KDIGO) group recommends statin treatment for patients with chronic kidney disease but does not recommend lipid-lowering treatment initiation in patients undergoing dialysis.[45]

Liver Disease

Obstructive liver disease, especially primary biliary cirrhosis, may lead to the formation of an abnormal lipoprotein termed *lipoprotein-x*. This type of lipoprotein, also associated with LCAT deficiency, consists of an LDL-like particle with a marked reduction in cholesteryl esters. Extensive xanthoma formation on the face and palmar areas can result from accumulation of lipoprotein-x.

Lifestyle

Factors contributing to obesity, such as an imbalance between caloric intake and energy expenditure, lack of physical activity, and a diet rich in saturated fats and refined sugars, contribute in large part to the lipid and lipoprotein lipid levels within a population (**see Chapters 45 and 50**).

Medication

Several medications can alter lipoproteins (**see Table 48.8**). Thiazide diuretics can increase plasma TG levels. Beta-adrenergic blocking agents (beta blockers), especially non–$beta_1$-selective agents, increase triglycerides and lower HDL-C levels. Retinoic acid and estrogens can increase TG levels, sometimes dramatically. Corticosteroids and immunosuppressive agents can elevate plasma triglycerides and lower HDL-C. Estrogens can increase plasma HDL-C and often raise TG concentrations. Anabolic steroids, frequently used by endurance or body-building athletes, can cause hypertriglyceridemia and very low HDL-C. The exact composition, dosage, and frequency of use of anabolic steroids are often impossible to determine from the patient history. The use of antipsychotic medications may lead to metabolic disorders, weight gain, and lipoprotein abnormalities. Highly active antiretroviral therapy (HAART) agents may cause severe lipoprotein disorders and an increase in CAD in patients with chronic human immunodeficiency virus (HIV) infection (**see Chapter 82**).

TABLE 48.8

Current Lipid-Lowering Medications

GENERIC NAME	TRADE NAME	RECOMMENDED DOSE RANGE
Statins		
Atorvastatin	Lipitor	10-80 mg
Fluvastatin	Lescol	20-80 mg
Lovastatin	Mevacor	20-80 mg
Pravastatin	Pravachol	10-40 mg
Rosuvastatin	Crestor	10-40 mg
Simvastatin	Zocor	10-80 mg
Pitavastatin	Questran	2-4 mg
Bile Acid Absorption Inhibitors		
Cholestyramine	Questran	2-24 g
Colestipol	Colestid	5-30 g
Colesevelam	Welchol	3.8-4.5 g
Cholesterol Absorption Inhibitors		
Ezetimibe	Zetia (Ezetrol)	10 mg
Fibrates*		
Bezafibrate	Bezalip	400 mg
Fenofibrate	Tricor, Trilipix Lipidil (Micro, EZ)	40-200 mg
Gemfibrozil	Lopid	600-1200 mg
Niacin†	Niacin	1-3 g
Nicotinic acid	Niaspan	1-2 g

*Avoid in patients with renal insufficiency.

†Use with caution in patients with diabetes or glucose intolerance.

In clinical practice, many dyslipoproteinemias, other than the genetic forms mentioned earlier, share an important environmental cause. Lifestyle changes (diet, exercise, reduction of abdominal obesity) should form the foundation for the treatment of most dyslipidemias. The effects of marked alterations in lifestyle, reduction in dietary fats (especially saturated fats), and exercise can improve CV risk factors. Rigorous clinical data showing that these measures improve outcomes, as well as implementing them in a sustained manner in practice, however, have proved more difficult (**see Chapters 45 and 50**).

Pharmacologic Management of Lipid Risk (Tables 48.8 and 48.9)[46,47]

Hydroxymethylglutaryl–Coenzyme A Reductase Inhibitors (Statins)

Mechanisms of Action

Statins inhibit the enzyme HMG-CoA reductase and prevent the formation of mevalonate, the rate-limiting step of sterol synthesis. To maintain cellular cholesterol homeostasis, expression of LDL-R increases and rate of cholesteryl ester formation declines. These homeostatic adjustments to HMG-CoA reductase inhibition increase clearance of LDL-C from plasma and decrease hepatic production of VLDL and LDL. In addition to blocking the synthesis of cholesterol, statins also interfere with the synthesis of lipid intermediates with important biologic effects. Two of these intermediates, geranylgeranyl and farnesyl, participate in protein *prenylation,* the covalent attachment of a lipid moiety to a protein, thereby allowing anchoring into cell membranes and enhancing its biologic activity. Prenylated proteins important in CV signaling include the guanosine triphosphate (GTP)–binding proteins Rho A, Rac, and Ras. Statins may increase HDL-C in part by preventing the geranylgeranylation of Rho A and phosphorylation of peroxisome proliferator–activated receptor-alpha (PPAR-α), a factor that regulates apo A-I transcription.

Altered protein prenylation may also mediate some of the effects attributed to statins not related to a reduction in LDL-C levels.

TABLE 48.9

Expected Decrease in Low-Density Lipoprotein Cholesterol (LDL-C) with Lipid-Lowering Medications

Drug	MEAN REDUCTION BY DOSE: PERCENT CHANGE FROM BASELINE				
	5 mg	10 mg	20 mg	40 mg	80 mg
Rosuvastatin	−40%	−46%	−52%	−55%	—
Atorvastatin	—	−37%	−43%	−48%	−51%
Simvastatin	−26%	−30%	−38%	−41%	−47%
Lovastatin	—	−21%	−27%	−31%	−40%
Pravastatin	—	−20%	−24%	−30%	−36%
Fluvastatin	—	—	−22%	−25%	−35%
Ezetimibe alone	—	−20%	—	—	—
Bile acid sequestrants (cholestyramine, colestipol, colesevelam): add a mean 15% decrease					

Modified from Hou R, Goldberg AC. Lowering low-density lipoprotein cholesterol: statins, ezetimibe, bile acid sequestrants, and combinations: comparative efficacy and safety. Endocrinol Metab Clin North Am 2009;38(1):79-97, and Stroes ES et al. Statin-associated muscle symptoms: impact on statin therapy. European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J 2015;36(17):1012-22.

Atherosclerosis involves inflammation (**see Chapter 44**). Statins decrease C-reactive protein (CRP), augment the collagen content of atherosclerotic plaque, alter endothelial function, and decrease the inflammatory component of plaque.

Statin Pharmacology

The currently available drugs are fluvastatin (Lescol), 20 to 80 mg/day; lovastatin (Mevacor), 20 to 80 mg/day; pravastatin (Pravachol), 20 to 40 mg/day; simvastatin (Zocor), 10 to 40 mg/day (the 80-mg dose may increase risk for rhabdomyolysis, especially within the first year of treatment); atorvastatin (Lipitor), 10 to 80 mg/day; and rosuvastatin (Crestor), 5 to 40 mg/day. Pitavastatin (Livalo), 2 to 4 mg/day, is available in some countries. Statins do not reduce LDL in a linear manner; for every doubling of the statin dose, LDL-C drops by about an additional 6% (**Tables 48.8 and 48.9**).

Concomitant drugs that interfere with the metabolism of statins by inhibiting the cytochrome P-450 (CYP) 3A4 and 2C9 systems can increase plasma concentrations of statins. Such agents include antibiotics, antifungal medications, certain antiviral drugs, grapefruit juice, cyclosporine, amiodarone, and several others. The major side effects of statins have been attributed to muscle symptoms ranging from diffuse myalgias (normal creatinine kinase [CK] levels), seen in up to 10% to 15% of statin users, to myositis, defined as diffuse muscle pain with evidence of muscle inflammation and elevated CK levels. A minority of statin users have increased CK levels, and a causal link with muscle symptoms must be established by rechallenge.[48,49] In many cases of statin-associated myositis, a neuromuscular disease is identified (inclusion body myositis and myopathies of genetic origin and spinal cord compression). Rarely, statin use is associated with rhabdomyolysis. This life-threatening situation is often related to predisposing factors: advanced age, frailty, renal failure, shock, concomitant use of antifungal agents, antibiotics, the fibric acid derivative gemfibrozil, and hypothyroidism.[48,49] Statin intolerance has been shown to affect CV outcomes adversely.[49]

Statins are generally well tolerated; side effects include reversible elevation of transaminases and myositis, which necessitates discontinuation of the drug in less than 1% of patients. After initiation of statin therapy, the response should be checked within the first 3 to 6 months, along with transaminase and

CK levels. Thereafter, clinical judgment should dictate the interval between follow-up visits. Although frequent visits are probably not useful for the detection of serious side effects, they serve to encourage compliance and adherence to diet and lifestyle changes.

Clinical Trials with Statins

Twenty-seven trials with more than 1000 participants randomized to a statin versus a placebo (or a statin comparator) have reported effects of statins on CV outcomes, as reviewed in previous versions of this chapter and elsewhere[8,9] (**Fig. 48.7**) (**see Chapter 45**). Imaging studies have shown that treatment with more potent statins can actually produce limited regression of atheromata. With the advent of PCSK9 inhibitors, the GLAGOV study tested the hypothesis that lowering LDL-C with evolocumab, 420 mg monthly by subcutaneous (SC) injection, resulted in a greater change in coronary atheroma volume from baseline than placebo in 968 participants treated for 78 weeks (all participants received maximally tolerated statin therapy)[50] (**Fig. 48.8**).

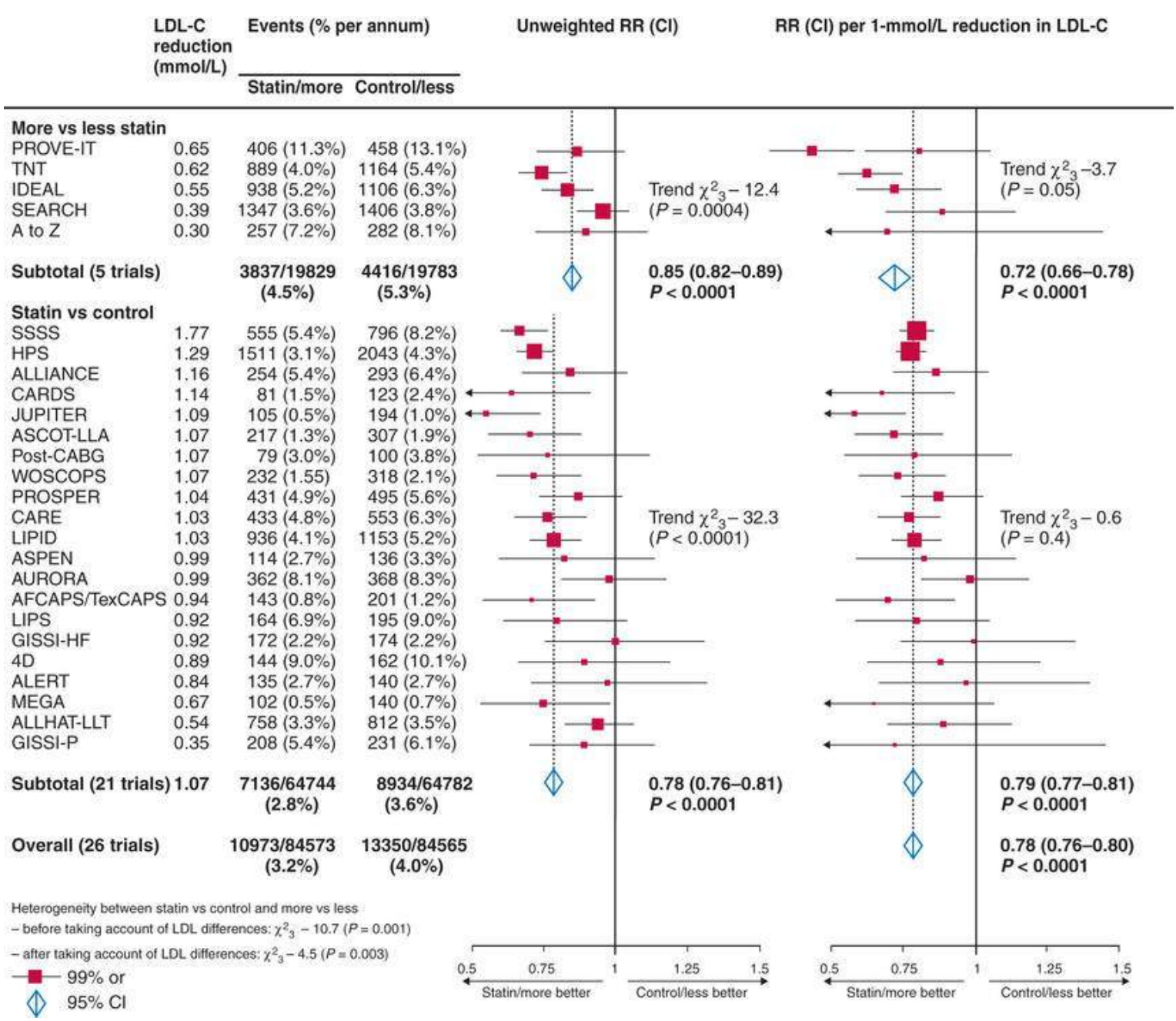


FIGURE 48.7 Meta-analysis of clinical trials of statin therapy: proportional reduction in nonfatal myocardial infarction or coronary heart disease (CHD) death versus absolute LDL-C reduction. The effects on major vascular events are shown for each of the 26 studies included in the meta-analysis. **Left panel,** Unweighted rate ratios (RR) for each trial are plotted along with 99% CI. **Right panel,** RRs are weighted per 1.0 mmol/L LDL-C difference at 1 year. Subtotals and totals with 95% confidence intervals (CIs) are shown by *open diamonds*. (From Baigent C et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-81.)

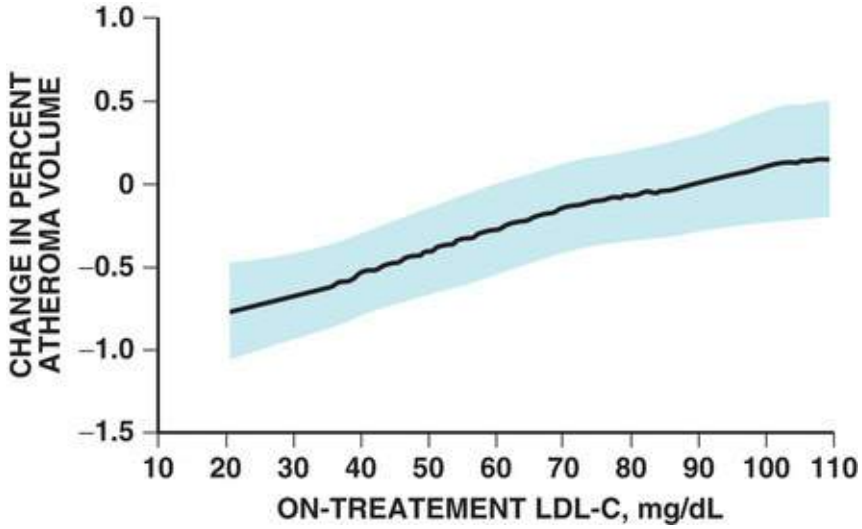


FIGURE 48.8 Meta-analysis of angiographic regression studies, including the Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) study. Compared with placebo, the evolocumab group achieved lower mean, time-weighted LDL-C levels. (From Nicholls SJ et al. Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. JAMA 2016;316(22):2373-84.)

Use of Statins in Special Populations

Diabetic Patients

Patients with diabetes should receive a statin. Multiple observational studies have documented a greatly increased risk for ASCVD in adult diabetic patients over the long term. Preventive strategies with aspirin, angiotensin-converting enzyme inhibitors, tight glycemic control, and statins have all shown benefit. Data from the CTT (Cholesterol Treatment Trialists) meta-analysis of statin trials in patients with diabetes showed a 21% reduction in CVD events and a 9% all-cause mortality benefit in favor of statins.[51]

Statins and Risk for Diabetes

The use of statins is associated with a small but significant increase in diabetes.[52,53] Further analysis of the clinical study data shows that statins hasten the diagnosis almost exclusively in patients with preexisting risk factors for the development of diabetes, such as baseline elevation of plasma glucose levels. Based on the available data, the benefits of statin use in persons at high CV risk or in the secondary prevention of CVD far exceed the small risk for development of diabetes. Nevertheless, statin therapy should accompany a diet and exercise program aimed at achieving a healthy diet and ideal body weight.

Older Patients

Elderly patients represent a special challenge; age accounts for most of the attributable CV risk in patients older than 75 or 80 years, and the predictive value of elevated cholesterol decreases with increasing age. A recent meta-analysis of statin trials using data on patients older than 75 showed a 22% relative reduction in all-cause mortality. This analysis supports continued use of statins in older patients if clinically indicated. Physicians must nevertheless exercise caution in implementing preventive strategies in older patients already taking multiple medications. However, age is a major determinant of CV risk. Starting statins in an otherwise healthy elderly patient requires clinical judgment and shared decision making.

Women

Most clinical trials are not statistically powered to show an effect in women as a subgroup. A meta-analysis of statin studies involving women showed a statistically significant reduction in the primary endpoint of acute MI, stroke, CVD-related death, arterial revascularization, and hospitalization for unstable angina in favor of statins. The available outcomes data support the contention that statins confer CV protection in women.

Non-Caucasian Populations

The INTERHEART study has shown the universality of CV risk factors in a study of almost 15,000 patients with acute MI versus healthy controls.[3] Even though most studies underrepresent the number of nonwhite and various ethnic groups, current data provide no indication that lipid-lowering therapy will not reduce CV risk in various ethnic groups. The MEGA study included Japanese men and women. JUPITER included more than 4400 black or Hispanic individuals and showed no heterogeneity in response to statin therapy compared with whites. The third Health Outcomes and Population Evaluation (HOPE-3) study randomized 12,705 participants in 21 countries at intermediate risk of ASCVD to rosuvastatin (10 mg/day) or placebo. After a mean follow-up of 5.6 years, the primary outcome (death from CV causes, nonfatal MI, or nonfatal stroke) occurred in 235 participants (3.7%) in the rosuvastatin group and in 304 participants (4.8%) in the placebo group (hazard ratio [HR], 0.76; 95% confidence interval [CI] 0.64 to 0.91; $P = 0.002$). The results were consistent in race and ethnic groups.[54]

Advanced Heart Failure

Recent studies have addressed the issue of statin treatment of patients with advanced heart failure (left ventricular ejection fraction <30%). The CORONA (Controlled Rosuvastatin in Multinational Trial in Heart Failure) and GISSI heart failure trials examined the effect of rosuvastatin on CV outcomes in patients with reduced systolic function. These studies suggest that statin therapy does not reduce CVD-related morbidity or mortality in patients with advanced heart failure of ischemic or nonischemic cause.

Renal Failure

Several trials have examined the use of statins in patients with renal failure and in patients undergoing hemodialysis for ESRD. Patients with chronic kidney disease have CV risk at least equivalent to that in patients with diabetes, thus emphasizing the need for prompt recognition and aggressive therapy. Patients with end-stage renal failure do not appear to benefit from statin therapy.[45]

Taken together, the heart failure trials and the renal failure trials suggest that lipid management strategies in patients with end-stage disease produce limited improvement in outcomes. Clinical judgment must carefully weigh the benefits of such preventive measures in these patients.

Risks Associated with Low Levels of Low-Density Lipoprotein Cholesterol

The cumulative evidence from large-scale clinical outcomes data supports the concept that reaching a low level of total cholesterol and LDL-C state decreases CV risk. Some have expressed concern that low LDL-C could impair health. Several lines of evidence argue against this concern. First, most animals have little or no LDL-C and produce LDL particles only when dietary consumption of cholesterol and saturated fats increases. Second, because of its importance in cellular functions, most (if not all) cell types have the cellular machinery to make cholesterol endogenously. Third, the HDL transport system, via the SR-B1

receptor, appears to be able to deliver cholesterol from hepatic sources to organs. Fourth, LDL deficiency states in humans, hypobetalipoproteinemia caused by *APOB* mutations, and loss-of function *PCSK9* mutations are associated with normal health and a marked reduction in life-long CV events.[55] The CTT meta-analysis of more than 170,000 patients treated with statins has not shown an increase in cancers,[9] and the JUPITER trial showed no increase in cancers, renal or hepatic diseases, or hemorrhagic strokes despite one fourth of the patients having reached an LDL-C concentration lower than 44 mg/dL (1.2 mmol/L) for up to 5 years. CTT did not identify any signal of harm in patients treated with statins.[9] The EBBINGHAUS trial examined the effect of evolocumab on cognitive function in 1204 patients enrolled in the large outcomes trial FOURIER. After a mean follow-up of 20 months, there was no evidence of cognitive events in patients treated with evolocumab compared with placebo. Importantly, these conclusions apply to patients who reached a very low LDL-C (<25 mg/dL; 0.7 mmol/L).[56]

Cholesterol Absorption Inhibitors

The development of selective inhibitors of intestinal sterol absorption has added to the treatment of lipoprotein disorders. Ezetimibe is the first such compound. Ezetimibe limits selective uptake of cholesterol and other sterols by intestinal epithelial cells by interfering with NPC1L1. This agent has seen use in patients with LDL-C levels above target while receiving the maximally tolerated statin dose. Ezetimibe lowers LDL-C by about 18% and adds to the effect of statins. Because ezetimibe also prevents the intestinal absorption of sitosterol, it might be the drug of choice in patients with sitosterolemia.

The IMPROVE-IT trial tested the hypothesis that adding ezetimibe to simvastatin results in a greater reduction in LDL-C and a further decrease in CV events. This randomized trial involved 18,144 patients who had a recent acute coronary syndrome (within 10 days) with LDL-C levels of 50 to 100 mg/dL (1.3 to 2.6 mmol/L) in those receiving lipid-lowering therapy or 50 to 125 mg/dL (1.3 to 3.2 mmol/L) in those not receiving therapy. The difference in LDL-C was 69.5 mg/dL (1.8 mmol/L) in the simvastatin-only group and 53.7 mg/dL (1.4 mmol/L) in the simvastatin-ezetimibe group ($P < 0.001$). The rate for the primary endpoint at 7 years was 34.7% in the simvastatin-only group and 32.7% in the simvastatin-ezetimibe group, (absolute risk difference, 2.0 %; HR, 0.936; 95% CI 0.89 to 0.99; $P = 0.016$).[58] The effect on ASCVD reduction was modest and correlated with the relatively small decrease in LDL-C obtained in the trial. With a meta-analysis of statin trials and IMPROVE-IT, taken together, these data support prompt initiation of highly effective statin therapy in patients with acute coronary syndromes, treatment of ASCVD patients with statins, and use of statins in high-risk individuals. Starting statins in the hospital may also improve compliance on discharge.

Fibric Acid Derivatives (Fibrates)

Two derivatives of fibric acid are currently available in the United States. Gemfibrozil (Lopid), 300 to 600 mg twice daily, is indicated for hypertriglyceridemia and in the secondary prevention of CVD in patients with low HDL-C levels, the latter based on VA-HIT (Veterans Administration HDL Intervention Trial). The dose of fenofibrate (TriCor, Trilipix, Lipidil Micro, Lipidil EZ) is 200 mg/day, and a new formulation is available to vary the dose from 40 mg/day (especially in patients with renal failure) to 267 mg/day. In other countries, ciprofibrate (Lypanthyl, Lipanor), clofibrate (Atromid), and bezafibrate (Bezalip) are available. The U.S. Food and Drug Administration (FDA) took the unusual step of withdrawing approval for fenofibric acid with statins to treat high cholesterol, citing a lack of CV benefit.

The mechanism of action of fibrates involves interaction with the nuclear transcription factor PPAR-α,

which regulates transcription of the LPL, apo C-II, and apo A-I genes. Side effects of fibrates include cutaneous manifestations, gastrointestinal (GI) effects (abdominal discomfort, increased bile lithogenicity), erectile dysfunction, elevated transaminase levels, interaction with oral anticoagulants, and elevated plasma homocysteine, especially with fenofibrate and, to a lesser extent, with bezafibrate. Because fibrates increase LPL activity, LDL-C levels may rise in patients with hypertriglyceridemia treated with this class of medications. Fibrates, especially gemfibrozil, can inhibit the glucuronidation of statins and thus impair their elimination. For this reason, gemfibrozil combined with statins may increase the risk for myotoxicity, and therefore such a combination is contraindicated. The clinical usefulness of fibrates is not well established, particularly in view of failure of the FIELD and ACCORD trials to achieve their primary endpoints. Subgroup analyses suggest a benefit of some fibrates in individuals with baseline high triglyceride levels, but no large endpoint study has tested this conjecture rigorously. Some advocate their use in very-high-risk groups such as diabetic patients with CVD and patients with renal failure.

Older fibrate trials such as the Helsinki Heart Study, BIP, and VA-HIT have little relevance to current practice because they did not use statins, which now are considered the standard of care for most patients eligible for fibrate therapy. Gemfibrozil was used in these older studies but has little relevance to current therapy because of a drug-drug interaction that renders concomitant administration with statins contraindicated. Even though the overall effect of fibrates is neutral on CV mortality, subgroup analysis suggests that fibrates might be indicated in high-risk patients with residual CV risk characterized by elevated TG levels, reduced HDL-C, and elevated non–HDL-C who are receiving statin therapy.

Another consideration with the use of fibrates is the theoretical prevention of pancreatitis in patients with severe hypertriglyceridemia (>11 mmol/L; 1000 mg/dL). However, fibrates have little usefulness in LPL-deficient patients with hyperchylomicronemia. Lifestyle changes, including a marked reduction in fats (especially saturated fats), tight control of glycemia in diabetic patients, avoidance of alcohol, frequent small meals during the acute phase of a severe episode of hypertriglyceridemia, fish oil consumption, and avoidance of estrogens in women, remain the fundamentals of prevention of pancreatitis in hypertriglyceridemic individuals.

Nicotinic Acid (Niacin)

Niacin increases HDL-C and lowers TG levels but has more modest effects on LDL levels. Niacin requires doses in the range of 2000 to 3000 mg/day in three separate doses to maximize effects on lipid levels. An escalating dose schedule to reach the full dose in 2 to 3 weeks rather than starting with the full dose can help manage the adverse effects of this agent. Slow-release forms of niacin, including Niaspan (1 to 2 g/day), decrease the side effect profile of the drug. Daily aspirin intake can attenuate skin flushing, as does the prostaglandin D_2 receptor (DP1) antagonist laropiprant. Niacin decreases the hepatic secretion of VLDL and reduces FFA mobilization in the periphery. In the long-term follow-up of the Coronary Drug Project, which was conducted before the availability of statins, niacin decreased mortality at 15 years. Significant and common minor side effects, less frequent serious adverse actions, and statin development hamper niacin use. Side effects of niacin include flushing, hyperuricemia, hyperglycemia, hepatotoxicity, dysglycemia, bleeding, acanthosis nigricans, and gastritis. Recent clinical trials do not support the ability of niacin therapy to improve CV outcomes in patients receiving statins. AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) tested the hypothesis that patients with CAD optimally treated with a

statin but with residual atherogenic dyslipidemia (low HDL-C and high triglycerides) would benefit from niacin, 2 g/day. The trial was abruptly stopped after 3 years because of a lack of beneficial effect on the primary outcome. The large HPS2-THRIVE (Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events) study randomized 25,673 people with CVD to a strategy of LDL-C reduction with simvastatin (with ezetimibe, if required, to reach target goals) alone or in combination with niacin, 2 g/day, or laropiprant to limit the cutaneous flushing.[59] The THRIVE investigators found that this intervention did not produce clinically meaningful reductions in CV events. The results of AIM-HIGH and THRIVE cast doubt on niacin's ability to lower CV risk, reinforced its undesired effects, and present yet another challenge to the hypothesis that elevation of HDL can improve outcomes of individuals treated with statins. As for fibrates, the FDA withdrew approval for the combination of niacin with statins to treat high cholesterol, citing a lack of CV benefit.

Bile Acid–Binding Resins

Bile acid–binding resins interrupt the enterohepatic circulation of bile acids by inhibiting their reabsorption in the intestine, the site of reabsorption of more than 90% of bile acids. Currently, their main use is adjunctive therapy in patients with severe hypercholesterolemia secondary to increased LDL-C. Because bile acid–binding resins are not absorbed systemically (they remain in the intestine and are eliminated in stool), they are considered safe in children and in pregnant women. Cholestyramine (Questran) is used in 4-g unit doses as a powder, and colestipol (Colestid) is used in 5-g unit doses. Effective doses range from 2 to 6 unit doses/day, always taken with meals. The most important side effects are predominantly gastrointestinal: constipation, a sensation of fullness, and GI discomfort. These drugs can cause hypertriglyceridemia. Decreased absorption of concomitantly administered drugs dictates careful scheduling of other medications 1 hour before or 4 hours after the patient takes bile acid–binding resins. Bile acid–binding resins can be used in combination with statins and/or cholesterol absorption inhibitors in patients with severe hypercholesterolemia. *Colesevelam* is a bioengineered bile acid–binding resin that has approximately twice the capacity to bind cholesterol as cholestyramine does. In doses of 3.8 to 4.5 g/day, it can be a useful third-line therapy for patients not meeting their LDL-C targets or in whom the side effects of statins preclude their optimal use. Colesevelam can also decrease hemoglobin (Hb) A_{1c}, thus making this drug a potentially useful adjunct in the treatment of complicated diabetic patients. Even though relatively few drug-drug interactions have been reported with colesevelam, prudence still warrants a careful dosage schedule (4 hours), which makes the use of all bile acid–binding resins cumbersome in patients taking multiple medications.

Cholesteryl Ester Transfer Protein Inhibitors

Inhibition of CETP by pharmacologic agents mimics the genetic heterozygous CETP deficiency state (**see Fig. 48.3, part 9**). Of several agents tested in humans, torcetrapib proved toxic and increased mortality, an effect attributed to off-target effects. Dalcetrapib, another CETP inhibitor, had more modest effects on HDL-C and LDL-C, and investigations on its use were stopped because of lack of effect in clinical trials. Similarly, the ACCELERATE trial tested the hypothesis that evacetrapib would prevent CV disease in optimally treated patients. Those who received evacetrapib demonstrated a 130% increase in HDL-C (46 to 104 mg/dL) and a 37% drop in LDL-C (84 to 55 mg/dL). The trial was stopped prematurely for clinical futility on the recommendation of the data monitoring committee.[60] Two CETP inhibitors, anacetrapib and TA-8995, remain. Anacetrapib is undergoing a large, outcome-driven clinical trial, Randomized Evaluation of the Effects of Anacetrapib Through Lipid-Modification (REVEAL). CETP inhibitors greatly increase larger, more buoyant HDL particles; these particles appear to promote cellular cholesterol efflux efficiently. Results of these ongoing trials are expected by 2018. Because of the

significant LDL-C–lowering effects of the CETP inhibitor anacetrapib, it may prove difficult to determine whether any benefit is derived from raising HDL-C levels.

Fish Oils

Fish oils are rich in polyunsaturated fatty acids (PUFAs) such as eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA), with the first double bond on the omega-3 position. These fatty acids lower plasma TG levels and have antithrombotic properties. Although used to treat hypertriglyceridemia, fish oils are reserved for patients with severe hypertriglyceridemia refractory to conventional therapy. Fish oils decrease VLDL synthesis and decrease VLDL apo B. The response to fish oils depends on the dose, with a daily intake of up 10 g of EPA or DHA required for maximal reduction of plasma TG levels. Fish oils may raise LDL levels. A prescription form of omega-3 fatty acids is available in the United States for patients with extreme hypertriglyceridemia (>500 mg/L, or 5.6 mmol/L). A diet containing polyunsaturated fats may be beneficial in terms of CV health. We lack robust and rigorous clinical trials to examine the effects of fish oil on MI and stroke events. Two large-scale trials are currently investigating this issue.

Phytosterols

Phytosterols are derivatives of cholesterol from plants and trees. They interfere with the formation of micelles in the intestine and prevent intestinal absorption of cholesterol. Phytosterols are available as "nutraceuticals" and are incorporated in soft margarines. Sterols may prove useful for the adjunctive management of lipoprotein disorders. The safety of plant sterols has not been established.

PCSK9 Inhibitors

Inhibiting proprotein convertase subtilisin/kexin type 9 (PCSK9) currently requires the use of monoclonal antibodies (mAbs) administered subcutaneously every 2 weeks or monthly. Evolocumab and alirocumab are fully human mAbs, and both recently approved in the United States, Canada, and Europe. The development of bococizumab, a humanized mAb, was stopped because of the development of neutralizing antibodies in a large percentage of participants.[61] LY3015014 is a second humanized mAb undergoing phase 3 clinical trials.[62]

In the large phase 2/3 clinical program, both evolocumab[28] and alirocumab[29] have demonstrated excellent LDL-C–lowering capacity (50% to 70%), regardless of background therapy, in many different patients, including those taking statins. The observation of a large and concordant relative reduction (approximately 50%) in clinical outcomes in LDL-C efficacy studies (OSLER and ODYSSEY LONG TERM) is consistent with the LDL hypothesis and with the metaregression results from the CTTC. The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial examined the effect of evolocumab (140 mg every 2 weeks or 420 mg monthly SC) added to the standard of care in 27,564 high-risk patients. Compared with placebo, LDL-C was reduced by 59% from 92 mg/dL (2.4 mmol/L) to 30 mg/dL (78 mmol/L). Evolocumab treatment significantly reduced the risk of the primary composite endpoint (9.8% versus 11.3%; HR, 0.85; 95% CI 0.79 to 0.92; $P < 0.001$) and the secondary endpoint of CV death, nonfatal MI, and stroke (5.9% versus 7.4%; HR, 0.80; 95% CI 0.73 to 0.88; $P < 0.001$)[63] (**Fig. 48.9**). The ODYSSEY outcomes trial will examine CV outcomes in 18,000 patients post–acute coronary syndrome treated with alirocumab.[64] The SPIRE-1 and SPIRE-2 studies compare bococizumab (a humanized PCSK9 mAb, 150 mg SC every 2 weeks) to matching placebo in 28,000 patients at high CV risk. The trial was stopped, but a slight clinical benefit was found in participants with LDL-C higher than 100 mg/dL (2.6 mmol/L) with a median follow-up of 10

months.[65]

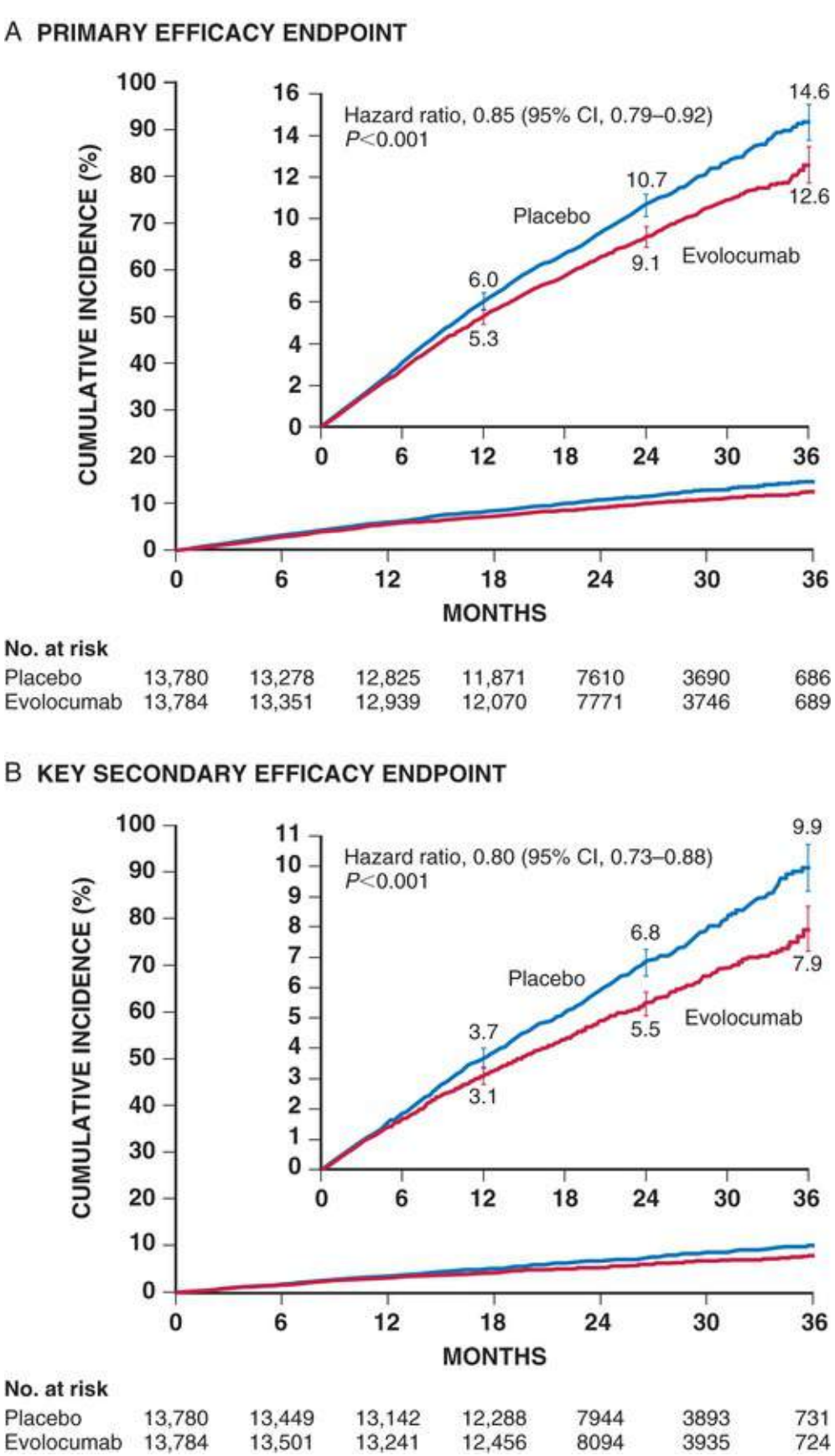


FIGURE 48.9 Results of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial. Evolocumab reduced the risk of the primary composite endpoint of cardiovascular (CV) death, myocardial infarction (MI), stroke, hospitalization for unstable angina, and coronary revascularization in 1344 patients (9.8%) in the evolocumab group and in 1563 patients (11.3%) in the placebo group (hazard ratio, 0.85; 95% CI 0.79 to 0.92; $P < 0.001$). Evolocumab significantly reduced the risk of the key secondary composite endpoint of CV death, MI, and stroke in 816 patients (5.9%) in the evolocumab group and in 1013 patients (7.4%) in the placebo group (hazard ratio, 0.80; 95% CI 0.73 to 0.88; $P < 0.001$). (From Sabatine MS et al; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376(18):1713-22.)

Overall, more than 46,000 individuals at high or very high risk of ASCVD will be exposed to PCSK9 inhibitors to determine the effect of this new class of drugs on CV outcomes.

Approval to date for evolocumab (Repatha), 140 mg SC every 2 weeks or 420 mg monthly, and alirocumab (Praluent), 75 mg or uptitrated to 150 mg SC every 2 weeks, has been given for patients with established clinical atherosclerotic vascular disease or familial hypercholesterolemia and whose LDL-C remains above target despite maximally tolerated statin dosing with or without ezetimibe. In statin-intolerant patients, evolocumab proved superior to ezetimibe in the carefully designed GAUSS-3 study; only patients with statin intolerance who did not tolerate atorvastatin, 20 mg, were randomized to ezetimibe or evolocumab. The mean percent LDL-C change was −16.7% (95% CI −20.5% to −12.9%) in those taking ezetimibe and was −54.5% (95% CI, −57.2% to −51.8) in those taking evolocumab (P = 0.001).[66] Similar findings were reported in the ODYSSEY ALTERNATIVE randomized trial with alirocumab.[67]

The use of liver-targeted antisense RNA against PCSK9 was shown to lower PCSK9 and LDL-C markedly in a phase 2 study, with a dosing interval of 3 to 6 months, making this approach clinically appealing.[68] It is not yet clear if there are safety concerns for blocking the intracellular PCSK9 pathway.

Novel Agents

In severe hypercholesterolemia, especially autosomal dominant hypercholesterolemia, several approaches have been approved to reduce LDL-C. Inhibition of MTTP with the small-molecule *lomitapide* reduces LDL-C by approximately 30% to 50%.[69] Another approach is to inhibit apo B mRNA with phosphorothioate-linked antisense oligonucleotides. *Mipomersen* is the first such compound approved for limited use in patients with homozygous FH.[70] Mipomersen reduces LDL-C by 20% to 30%. Although safety concerns were raised with these compounds, the severity of homozygous FH was deemed to warrant novel therapeutic avenues.[71] Inhibition of apo B synthesis and secretion is associated with accumulation of fat in the liver. Because of the small number of patients included in these trials, no outcome data are likely to become available.

Patients with elevated Lp(a) represent a therapeutic challenge. Statins have little effect on Lp(a) levels; niacin can lower Lp(a) by 20% to 30%, but its use is accompanied by adverse events.[62] PCSK9 inhibitors evolocumab[72] and alirocumab[73] lower Lp(a) significantly by 20% to 25%. Antisense RNA directed against apo(a) markedly decreased Lp(a) levels in humans in a proof-of-concept study, paving the way for clinical trials.[74]

A novel compound, bempedoic acid, inhibits ATP-citrate lyase (ACL), a key enzyme in the "cholesterol biosynthesis pathway." Phase 1 and 2 studies show a 20% to 39% reduction in LDL-C in a variety of individuals.[75]

Clinical Approach to Treatment of Lipoprotein Disorders

Patients with lipoprotein disorders should undergo comprehensive evaluation and management in the context of a global risk reduction program. Most patients with dyslipoproteinemias lack symptoms, except for those with severe hypertriglyceridemia, who can have acute pancreatitis, and those with familial lipoprotein disorders, who have cutaneous manifestations (xanthomas, xanthelasmas). Evaluation of patients with dyslipidemia should include seeking and treating secondary causes. Clinical evaluation

should include a thorough history, including a complete family history, which may reveal clues to a genetic cause, as well as clues to a genetic susceptibility to CVD. The physician should seek and address other risk factors (cigarette smoking, obesity, diabetes, hypertension, lack of exercise) and institute a management plan to improve lifestyle, such as diet, physical activity, and alcohol intake. Such interventions should make use of nonphysician health professionals (e.g., those with training in diet and nutrition, physical therapy, and smoking cessation).

The physical examination should include a search for xanthomas (in extensor tendons, including the hand, elbow, knee, and Achilles tendons, as well as palmar xanthomas) and the presence of xanthelasmas, corneal arcus, and corneal opacifications. Blood pressure, waist circumference, weight, and height should be recorded and signs of arterial compromise sought, and a complete cardiovascular examination must be performed. Evaluation of peripheral pulses and determination of the ankle-brachial index may reveal important clues to the presence of peripheral vascular disease.

The diagnosis of lipoprotein disorders depends on laboratory measurements. A nonfasting lipid profile generally suffices for most lipoprotein disorders, and specialized laboratories can refine the diagnosis and provide expertise for extreme cases. A fasting lipid profile is indicated in patients with moderately severe hypertriglyceridemia (>400 mg/dL, or >4.5 mmol/L) because the calculated LDL-C is not reliable. Additional tests often involve considerable expense and may not increase the predictive value beyond that of the lipid profile, although these can help in refining the diagnosis. To assess baseline risk in individuals receiving lipid-lowering therapy, the medication should be stopped for 1 month before measuring a lipid profile, unless clinical circumstances contraindicate such a treatment gap. Advanced lipid tests seldom add to the clinical assessment just specified.

After diagnosis of a lipid disorder (based on at least two lipid profiles), measurement of TSH and glucose help in evaluating secondary causes. Measurement of HbA_{1c} and the urinary albumin/creatinine ratio may provide additional information in diabetic and hypertensive patients. Patients who will receive medications should undergo measurement of baseline liver function (alanine transaminase) and CK. Drug treatment of high-risk patients (e.g., with an acute coronary syndrome or after MI or coronary revascularization) should start immediately, with concomitant lifestyle changes.

Lifestyle Changes: Diet

Individuals with dyslipoproteinemias should always adopt dietary therapy. High-risk patients should have medications started concomitantly with a diet because in many cases, diet may not suffice to reach target levels. The diet should have three objectives: (1) allow the patient to reach and maintain ideal body weight, (2) provide a well-balanced diet with fruits, vegetables, and whole grains, and (3) have restrictions on sodium, saturated fats, and refined carbohydrates. Dietary counseling should involve a professional dietitian. Frequently, the help of dietitians, weight loss programs, or diabetic outpatient centers can aid in achieving sustained weight loss. (**See also Chapters 45 and 49**.)

Treatment of Combined Lipoprotein Disorders

Combined lipoprotein disorders, characterized by an increase in plasma total cholesterol and triglycerides, frequently occur in clinical practice and present difficult challenges. Patients with combined lipoprotein disorders have an increase in LDL-C and LDL particle number (as reflected by an increase in total or LDL apo B or non–HDL-C), small dense LDL particles, increased VLDL-C and VLDL triglycerides, and a reduced HDL-C level. Patients with this pattern of combined dyslipidemia often have

obesity and metabolic syndrome. Treatment should begin with lifestyle modifications consisting of a diet reduced in total calories and saturated fats, weight reduction, and increased physical activity. Drug treatment, when warranted, aims to correct the predominant lipoprotein abnormality. Statins can reduce plasma TG levels, particularly in individuals with high baseline levels. Fibrates reduce triglycerides and may change the composition of LDL to larger and less dense particles. The combination of a statin with a fibrate or with niacin, however, has proved effective in correcting the laboratory abnormalities that characterize the combined dyslipoproteinemias, but as noted earlier, currently available clinical trials have not established that this approach prevents CV events. Because of the effects of gemfibrozil on glucuronidation of statins, we advise against use of gemfibrozil in combination with statins. Patients taking a fibrate plus a statin merit close medical follow-up for evidence of hepatotoxicity or myositis within the first 6 weeks of therapy and every 6 months thereafter. The results of IMPROVE-IT support the combined use of a statin and ezetimibe.[57]

The use of other combinations, including fibric acid derivatives with bile acid–binding resins and niacin with these resins, lacks support from outcome trials and regulatory agencies and requires caution because of the risk of adverse effects such as hepatotoxicity and myositis. The search for correctable causes (e.g., uncontrolled diabetes, obesity, hypothyroidism, alcohol use) of combined dyslipidemia and the benefit of lifestyle modifications require reemphasis. Again, the help of dietitians, weight loss programs, or diabetic outpatient centers often adds considerably to management. (**See also Chapters 45 and 50**.)

Extracorporeal Filtration of Low-Density Lipoprotein

Patients with severe hypercholesterolemia, especially those with homozygous FH or severe heterozygous FH, may warrant treatment by extracorporeal elimination of LDL. These techniques use selective filtration, adsorption, or precipitation of LDL (or apo B–containing particles) after plasma separation. Specialized centers have LDL apheresis available. This approach can dramatically reduce the risk for development of CVD and improve survival.

Future Perspectives

The development of novel pharmaceutical agents for the treatment of lipoprotein disorders will probably continue because CVD secondary to atherosclerosis represents the largest burden of disease worldwide for the foreseeable future. Newer therapies, especially PCKS9 inhibitors, show considerable promise for the treatment of severe hypercholesterolemia. These new agents will offer personalized medicine based on genotype and phenotype. Better targeting of high-risk individuals will allow optimization of expensive therapies.

Therapies aimed at raising HDL-C have proved disappointing. Other therapeutics under evaluation seek to increase HDL biogenesis, especially from lipid-laden macrophages.

Gene Therapy

Severe, homozygous, monogenic disorders may eventually be treated by gene therapy. The initial trials of gene therapy in patients with homozygous FH proved disappointing. Refinement in viral delivery vectors has rekindled interest in disease-specific gene therapy. Especially for homozygous familial hypercholesterolemia, this approach could prove lifesaving for a disease associated with considerable

morbidity and premature mortality. Other diseases, such as abetalipoproteinemia, LPL deficiency, Niemann-Pick type C disease, sitosterolemia, and Tangier disease, may become targets for gene therapy. If the approach to correcting these disorders is successful, the more widespread application of gene-based therapies to reduce potential CV risk will become a challenging medical, social, and ethical problem.

Societal Changes

It is extremely unlikely that drugs alone will prevent and cure atherosclerosis. Societal changes encouraging healthy lifestyles as well as public health measures and infrastructure can provide overall, not just cardiovascular, health benefits. Public health measures to reduce cigarette smoking have already reduced rates of MI. As humanity continues to accommodate more than half the population in cities, organization of neighborhoods into local networks allowing energy expenditure (rather than conservation via easy access to motorized transportation) will become necessary, especially in affluent countries. Personal changes with respect to food consumption and caloric intake will remain a major challenge. Indeed, the changes in diet and physical activity that have occurred in the past 50 years (now spreading globally) probably contributed to the epidemic of obesity and the increased prevalence of lipoprotein disorders, hypertension, and diabetes, with consequent ASCVD. (**See also Chapters 45, 49, and 50.**)

Guidelines

Lipid Management

Jacques Genest and Peter Libby

Since 1985, originally under the auspices of the National Heart, Lung and Blood Institute (NHLBI) of the U.S. National Institutes of Health (NIH), various organizations have offered guidelines for the detection and treatment of dyslipidemias.[1] Certain common broad principles informed these various recommendations: (1) assessing the global risk of atherosclerotic cardiovascular disease (ASCVD) by including known risk factors, (2) treating patients with established or at high risk of ASCVD; and (3) treating patients according to specific targets. As scientific knowledge accrued and clinical trials became increasingly focused on outcomes rather than specific lipoprotein levels or surrogate endpoints, guidelines adapted. Increasingly, the process of rating the evidence, using specific tools such as the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) standards; PICO (population, intervention, comparator, outcomes) questions; and outlining areas of uncertainty have continuously changed recommendations.

In the past few years, some confusion has risen among clinicians regarding cardiovascular risk stratification and the use of biomarkers and imaging techniques for CV risk stratification and target levels. The 2013 the American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines proposed a new tool for assessing absolute risk assessment: a pooled cohort equation for ASCVD, including thromboembolic strokes.[2,3] (See the previous edition of this text for a summary of this guideline.) This risk calculator includes a broader distribution of gender and ethnic background. The guideline lowered the threshold for defining “high risk” for ASCVD to a 7.5% 10-year risk. Second, statins became the only class of medications with a strong recommendation, based on the large outcome studies then available. Third, this guideline abandoned targets in favor of recommending the intensity of

statin therapy (moderate or high), depending on risk category. Finally, this guideline aimed to reflect the trial evidence base rather than mere expert opinion. In 2016, based on data that became available after the release of the 2013 AHA/ACC lipid guideline,[4] participants in that process issued a consensus statement on the use of nonstatin therapies (including ezetimibe) for LDL lowering in the management of ASCVD risk[5] (**Fig. 48.G1**).

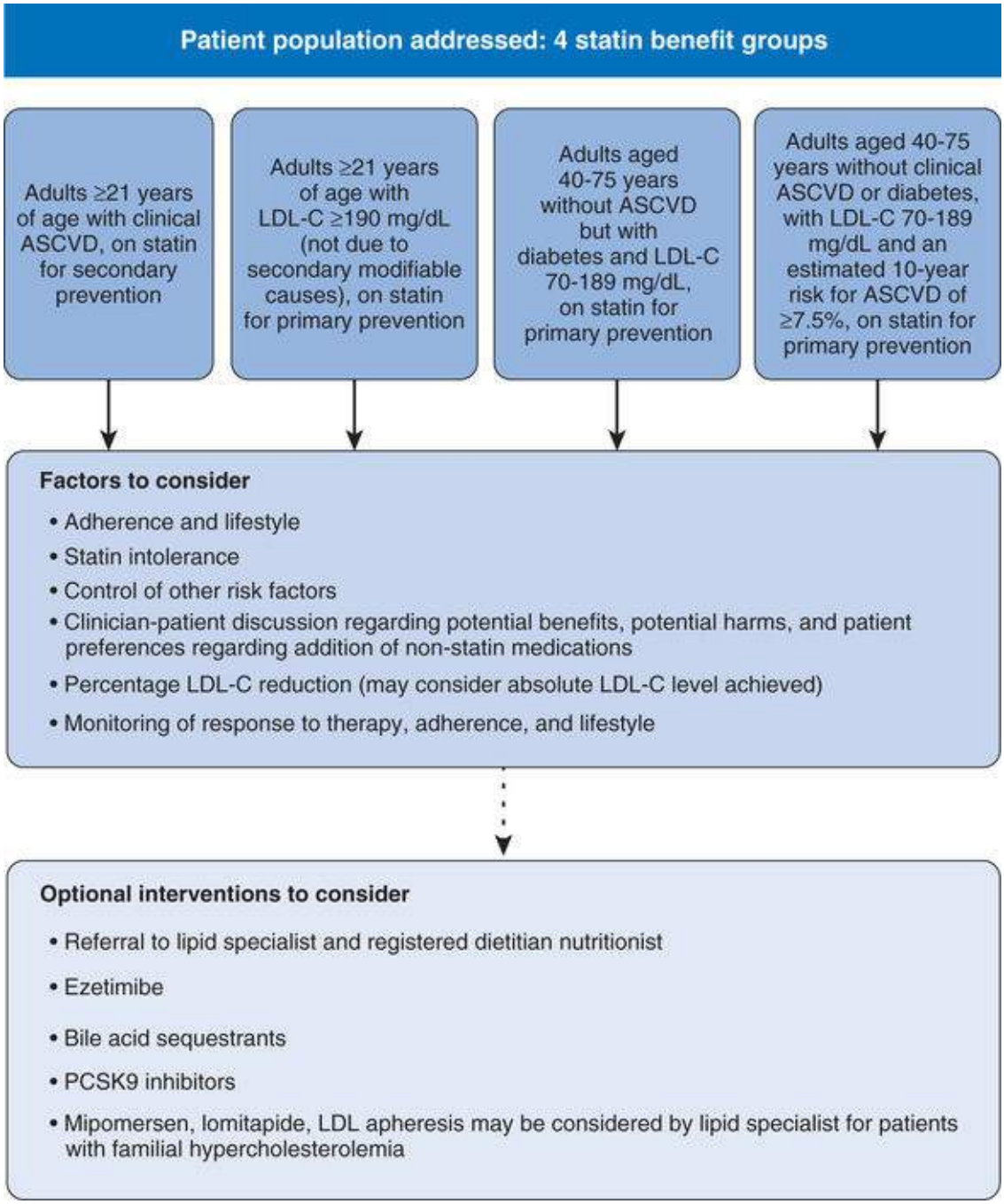


FIGURE 48.G1 Patient populations addressed and factors and interventions to consider for statin therapy. ASCVD, Atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol. (From Lloyd-Jones DM et al. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2016;68(1):92-125.)

The release of this guideline led to enthusiastic and robust discussions, but also to some confusion among societies, experts, and clinicians who apply these new recommendations. Indeed, all have free access to the body of evidence that serves as the basis for guidelines and recommendations. The major

discussions surround the interpretation of the data and applicability in the clinical setting. Despite the controversies, the broad principles of assessing CV risk and statin treatment aimed at lowering LDL-C to prevent ASCVD outcomes remain the foundation of all guidelines. Although guidelines may differ, they share much more commonality. **Tables 48.G1 and 48.G2** summarize the major guidelines since 2013.

TABLE 48.G1

Comparison of Atherosclerotic Cardiovascular Disease (ASCVD) Risk Assessment Tools

YEAR	SOURCE	RECOMMENDED RISK ASSESSMENT TOOL	FORECAST CAPABILITY OF TOOL	RISK FACTORS INCLUDED FOR RISK ESTIMATION	ASCVD OUTCOME PREDICTED	POPULATION USED FOR DERIVATION/VALIDATION OF RISK ALGORITHM
2013	2013 ACC/AHA guidelines* United States	Pooled cohort risk equations	10 yr Lifetime or 30 yr (for ages 20-59 yr)	Age, sex, ethnicity (Caucasian or African American), TC, HDL-C, systolic BP, treatment for hypertension, DM	Nonfatal MI, CHD death, fatal or nonfatal stroke	ARIC, CHS, CARDIA, FHS African American, white men and women Ages 40-74 yr
2014	IAS United States	Updated Framingham Risk Score with recalibration coefficients for different patient populations	Lifetime	Risk factor status age 50 yr: TC, systolic BP, diastolic blood pressure, smoking status, diabetes	MI, coronary insufficiency, angina, stroke, claudication, CVD death based on measured risk factors at age 50 yr	Framingham original and offspring cohorts
2014	NICE United Kingdom	QRISK2	10-yr risk of CHD death, MI or angina, stroke or TIA	Age, sex, cholesterol/HDL-C, HP, BP treatment, DM, smoking, family history of CHD, high BMI, CKD, RS, and atrial fibrillation	CHD death, MI or angina, stroke or TIA	British population from medical practices, annual update
2014	NLA United States	Risk factor counting	10 or 30 yr, depending of risk calculator used	Age, family history, smoking, high BP, low HDL-C	ASCVD	Not specified. FRS, PCE, Framingham 30-yr risk
2016	ESC/EAS European Union	SCORE (with risk adjustment algorithm/tables provided based on population, country)	10-yr risk of CV death	TC or TC/HDL-C ratio, sex, smoking status, systolic BP	Fatal atherosclerotic event (MI, stroke, occlusive arterial disease, sudden cardiac death)	104,961 participants from 7 pooled European (Belgium, Britain, Denmark, Finland, Germany, Italy, Spain) prospective studies Men, 55% (20-89 yr) Women, 45% (20-99 yr)
2016	CCS Canada	FRS: global CVD risk	10 yr	Age, sex, TC, HDL-C, systolic BP, BP treatment, smoking status, DM, vascular age	Absolute ASCVD event (CHD, cerebrovascular, peripheral vascular, and heart failure)	Framingham original and offspring cohorts

*On treatment of blood cholesterol to reduce ASCVD risk in adults.

See Table 48.G2 footnote for abbreviations.

TABLE 48.G2

Lipoprotein Lipid Assessment, Statin Indication, and Target Levels

YEAR	SOURCE	LIPOPROTEIN MEASUREMENT FOR RISK ASSESSMENT	SPECIFIC TARGETS	STATIN INDICATION	TARGETS
2013	2013 ACC/AHA guidelines* United States	Fasting lipid profile	None	ASCVD; most diabetes, LDL-C >190 mg/dL (4.9 mmol/L, pooled cohort equation risk ≥7.5%, LDL-C ≥70 mg/dL (1.8 mmol/L)	No specific target Expected 50% reduction in LDL-C with high-dose statins
2014	IAS United States	Fasting or nonfasting lipid profile	Yes	According to risk level to age 80 yr	LDL-C <70 mg/dL and non–HDL-C <100 mg/dL in secondary prevention
2014	NICE United Kingdom	Nonfasting lipid profile	None	10-yr risk >10%	No specific target Expect 40% reduction in non–HDL-C
2014	NLA United States	Fasting or nonfasting lipid profile	Yes	Non–HDL-C.>100 mg/dL in high-risk subjects	Non–HDL-C <100 mg/dL (LDL-C<70 mg/dL)
2016	ESC/EAS European Union	Nonfasting lipid profile	Yes	LDL-C >190 mg/dL; LDL-C mg/dL and 10-yr risk >10%; LDL-C >1.8 mmol/L	LDL-C (non–HDL-C, apo B)
2016	CCS Canada	Nonfasting lipid profile	Yes	ASCVD, most DM, LDL-C >190 mg/dL (5.0 mmol/L); FRS >20% 10-yr risk	LDL-C <80 mg/dL (2.0 mmol/L) or LDL-C reduction 50% in high-risk patients Alternate: non–HDL-C <3.2 mmol/L

*On treatment of blood cholesterol to reduce ASCVD risk in adults.

ASCVD, Atherosclerotic cardiovascular disease; *apo B,* apolipoprotein B; *BMI,* body mass index; *BP,* blood pressure; *CHD,* coronary heart disease; *CKD,* chronic kidney disease; *CV,* cardiovascular; *DM,* diabetes mellitus; *HDL-C,* high-density lipoprotein cholesterol; Hb_{A1c}, hemoglobin A_{1c}; *hsCRP,* high-sensitivity C-reactive protein; *LDL-C,* low-density lipoprotein cholesterol; *MI,* myocardial infarction; FRS, Framingham Risk Score; *TC,* total cholesterol after LDL-C; *TIA,* transient ischemic attack.

ACC, American College of Cardiology; AHA, American Heart Association; ARIC, Atherosclerosis Risk in Communities; CARDIA, the Coronary Risk Development in Young People; CCS, Canadian Cardiovascular Society; CHS, Cardiovascular Health Study; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; FHS, the Framingham Heart Study; FRS, Framingham Risk Score; IAS, International Atherosclerosis Society; NICE, National Institutes for Clinical Excellence; NLA, National Lipid Association; SCORE, Systematic Coronary Risk Evaluation.

The 2013 ACC/AHA cholesterol guidelines considered the evidence derived from randomized, controlled clinical trials (RCTs), [2] whereas the 2014 International Atherosclerosis Society (IAS),[6] 2014 National Institute of Clinical Excellence (NICE, UK),[7] 2014 National Lipid Association (NLA, U.S.),[8,9] 2016 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS, European Union),[10] and 2016 Canadian Cardiovascular Society (CCS)[11] lipid guidelines used comprehensive literature reviews to make their recommendations.[12] The critical questions posed by the 2013 ACC/AHA cholesterol guidelines were as follows: (1) What is the evidence for LDL-C and non–HDL-C goals in the secondary prevention of ASCVD? (2) What is the evidence in the primary prevention of ASCVD? and (3) What are the efficacy and safety of lipid-lowering drugs in the primary and secondary prevention of ASCVD?[2] The goal was to ensure an unbiased assessment of the evidence and eliminate lower-quality studies.

The risk assessment tool differs differ greatly between guidelines, especially in the United States. The new pooled cohort equation is derived from four cohort studies sponsored by the NHLBI: Atherosclerosis Risk in Communities (ARIC), Cardiovascular Health Study (CHS); Coronary Risk Development in Young People (CARDIA), and Framingham Heart Study (FHS).[3] This new model allows more gender and ethnic diversity than the FHS. The IAS recommends the Framingham Risk Score (FRS), and NLA guidelines recommend the FRS, pooled cohort equation, or the Framingham 30-year risk assessment tool. NICE updates annually the QRISK2 calculator, depending on data obtained from medical clinics across the

UK.[13] The EU uses the Systematic Coronary Risk Evaluation (SCORE), adjusted for region-specific risk of CVD, to determine risk.[14] CCS guidelines continue to recommend the FRS[11] (**Table 48.G1**).

Most guidelines advocate target levels of LDL-C (or non-HDL-C) since the inception of the National Cholesterol Education Program.[15] Clinicians have become familiar with the use of targets for lipid values and blood pressure over the past three decades. A generation of clinicians therefore has embedded lipid targets in their clinical practices, and change often proves difficult. Both the AHA/ACC and the NICE guidelines have proposed statin therapy (high or moderate intensity) according to the absolute risk of ASCVD. Nevertheless, both recommend follow-up lipid testing, with an expected 50% decrease in LDL-C[2] and 40% decrease in non–HDL-C.[7] In contrast, other guidelines recommend LDL-C or non–HDL-C targets depending on absolute risk.

The use of (biochemical) biomarkers of CV risk or imaging techniques, especially coronary calcium score and carotid ultrasound, has received limited endorsement for clinical decision making, but the language used allows clinicians to use their judgment. The initial assessment of global CV risk generally does not use these biomarkers or imaging techniques, but some guidelines sanction their use to reclassify a patient's risk in the primary prevention setting.

Equally important, all guidelines recommend involving the patient in clinical decision making and take into account values and preferences of individual patients. The QRISK2 score uses intuitive computer designs to frame the risk of developing ASCVD compared to age- and gender-matched controls.[16] In the end, physicians may elect to adopt guidelines that are recognized nationally and internationally and that undergo regular updates.

These considerations indicate that lipid management in primary prevention should not rely solely on any simple algorithm or complicated set of flowcharts unlikely to be used routinely by busy practitioners. Rather, primary prevention should involve consideration of the benefits and risks from trials that actually provide evidence, along with respectful interpretation of patient preferences in shared decision making. Physicians should recognize that the guidelines emanating from various organizations in different locales do not constitute hard and fast rules, but rather provide informed and thoughtful suggestions to guide approaches to management and conversations with patients.

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49

Nutrition and Cardiovascular and Metabolic Diseases

Dariush Mozaffarian

Together with smoking and physical activity, dietary habits constitute the foundation for causation, prevention, and treatment of most cardiometabolic diseases, including coronary heart disease (CHD), stroke, type 2 diabetes mellitus (DM), and related conditions. In 2010, eight of the top 25 modifiable causes of global disease were dietary, largely because of their contributions to these diseases (**see also Chapter 1**). The top burdens resulted from insufficient intake of fruits, nuts, whole grains, vegetables, seafood omega-3 fats, and dietary fiber and excess intake of salt and processed meats.[1] In the United States, suboptimal diet is now the leading cause of poor health, estimated to cause 1 in 4 deaths and 14% of lost disability-adjusted life-years (DALYs).[2]

These burdens have increased in recent decades as a result of rapid social, cultural, and environmental transitions, transmitted primarily through changes in diet and other lifestyle habits.[1] Familiarity with the evidence for effects of different dietary factors is essential to prioritize interventions for individual patients and for populations and reduce the considerable disease caused by suboptimal diets.

The science of nutrition and chronic diseases has progressed rapidly in the 21st century. Whereas prior dietary guidance derived largely from ecologic (cross-population) studies, short-term experiments, and animal studies, nutritional science has undergone transformation by more robust evidence from prospective cohorts and randomized trials with cardiovascular disease (CVD) endpoints and well-conducted metabolic trials of multiple risk markers and pathways. Several key lessons have emerged.[3] First, dietary habits influence a wide range of established and emerging risk factors, including blood pressure (BP), glucose-insulin homeostasis, lipoprotein concentration and composition, weight gain, inflammation, endothelial function, and cardiac function and arrhythmia (**Fig. 49.1**). Consequently, the full effects of any dietary factor should not be inferred only from its effects on any single biomarker, such as blood cholesterol concentration. Rather, valid conclusions should be derived from concordant evidence across different research avenues. A second key lesson is the importance of foods and overall dietary patterns, rather than single isolated nutrients, for preventing and managing cardiometabolic diseases. A third lesson is the consistent observed benefits for “foods that give rise to life,” including fruits, seeds, nuts, beans, and whole grains. Such foods are naturally rich in phytochemicals and nutrients that function to preserve and nurture new life, which appears increasingly relevant for promotion of healthy aging.

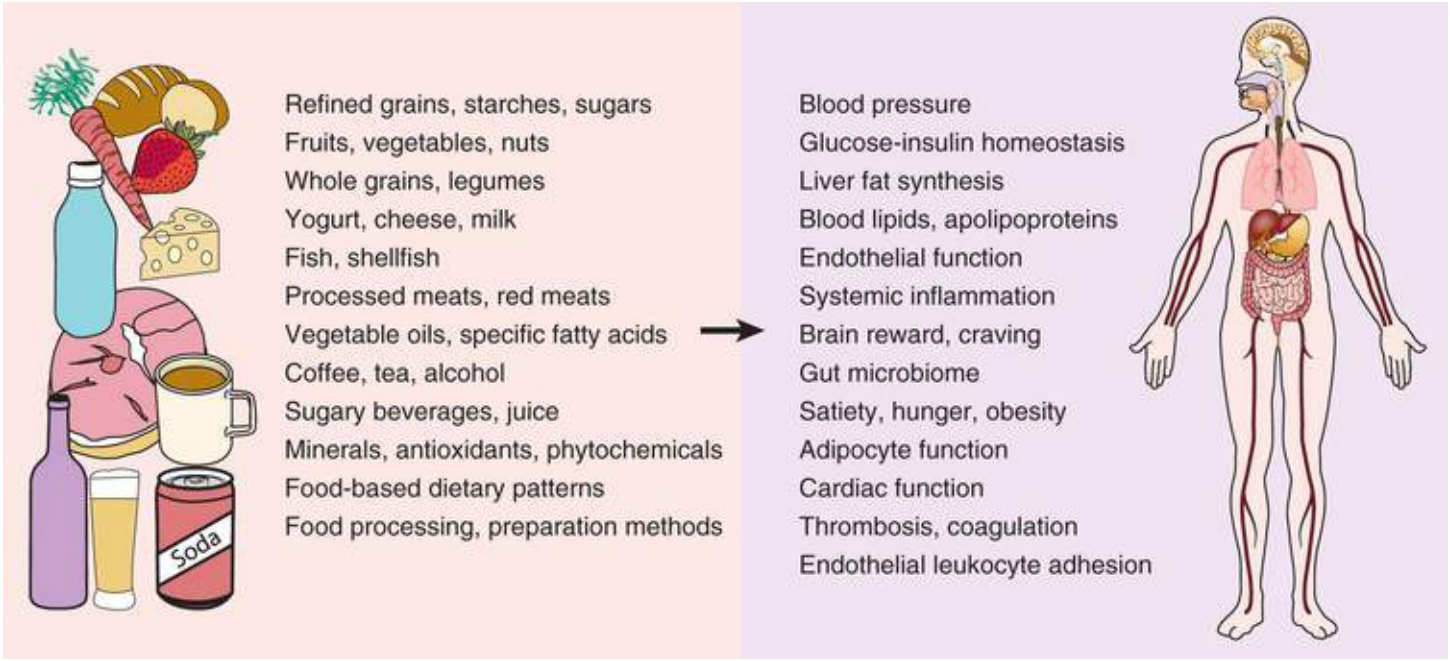

FIGURE 49.1 Diet and cardiovascular and metabolic risk: pathways and mechanisms. Multiple dietary factors influence diverse pathways of risk, and these effects are in some cases further modified by underlying individual characteristics. Selected major effects are detailed in the text sections on each dietary factor. (From Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review. Circulation 2016;133:187-225.)

This chapter reviews the dietary factors with the strongest evidence for cardiometabolic effects and highlights key knowledge gaps. Because translation of knowledge into action is essential, this chapter also reviews effective individual- and population-based strategies for behavior change.

Foods

In the early and mid-20th century, nutritional science and dietary guidelines focused on nutrient deficiency diseases (e.g., scurvy, rickets), leading to reductionist approaches that emphasized isolated single nutrients.[4] As chronic diseases emerged as a major public health problem in the late 20th century, this scientific emphasis on single nutrients lingered. For example, dietary fat was considered the major cause of obesity, and saturated fat and cholesterol the major causes of heart disease. With the exception of additives such as sodium or *trans* fat, however, a single nutrient in isolation has minimal effects on cardiometabolic diseases. Modern nutrition science recognizes the relevance of foods and dietary *patterns*, comprising a complex matrix of fatty acids, proteins, carbohydrate quality, micronutrients, and phytochemicals that together modify cardiometabolic risk. Such a focus on foods, rather than single nutrients, also facilitates dietary guidance and behavior change.

Fruits and Vegetables

Higher fruit and vegetable intake is associated with lower incidence of CHD and cerebrovascular accident (stroke); and fruit, with a nonsignificant trend toward less diabetes[5,6] (**Fig. 49.2**). Total vegetable intake is not associated with DM, perhaps because of the greater importance of certain subtypes, such as green leafy vegetables.[7] In controlled trials lasting up to 2 years, diets with an emphasis on consuming fruits and vegetables improved several cardiometabolic risk factors, including BP, lipid levels, insulin resistance, inflammation, adiposity, and endothelial function.[3] Such benefits likely derive from the sets of micronutrients, phytochemicals, and fiber in fruits and vegetables, as well as from their replacing less

healthful foods. Together, these studies provide strong evidence that fruit and vegetable consumption lowers CVD risk. Although individual studies suggest that phytochemical-rich fruits, such as berries, may have particular benefit,[8-11] the effects of specific subtypes, as well as of 100% juice,[12-14] require further study.

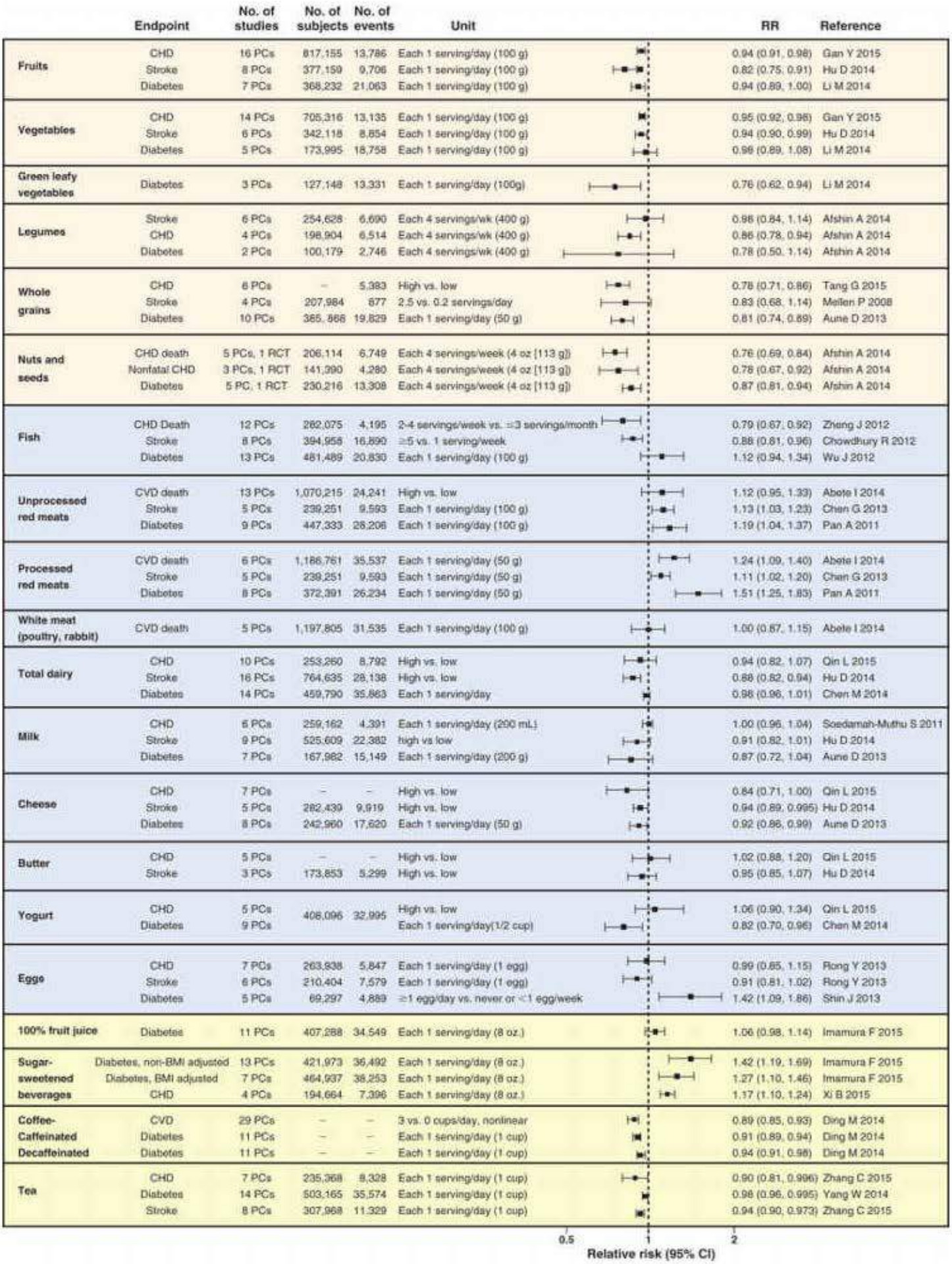

FIGURE 49.2 Meta-analyses of foods and incidence of coronary heart disease, stroke, and diabetes. BMI, Body mass index; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; PCs, prospective cohorts; RCT, randomized clinical trial; RR, relative risk. (From Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review. Circulation 2016;133:187-225.)

Nuts and Legumes

Nuts are rich in unsaturated fats, vegetable protein, fiber, folate, minerals, tocopherols, and phenolic compounds. Consumption of nuts lowers low-density lipoprotein cholesterol (LDL-C) and apolipoprotein (apo) B in randomized trials;[15] was associated with lower incidence of CHD and DM in prospective studies (**Fig. 49.2**);[16] and in the large, randomized PREDIMED trial, was a key component of the Mediterranean dietary intervention that reduced risk of hard CVD endpoints by 30%.[17] Although the energy density of nuts has raised theoretical concerns for weight gain, both long-term observational studies and controlled trials demonstrate that nuts and seeds do not promote, and actually may reduce, weight gain and visceral adiposity.[18-20]

Cardiovascular effects of legumes (beans) are less well established. Like nuts, legumes contain bioactive compounds, including phenolics, minerals, and fiber, although also more starch, compared with unsaturated fat-rich nuts. In a limited number of cohorts, legume intake was inversely associated with CHD, but not diabetes or stroke[16] (**Fig. 49.2**). Meta-analyses of small trials of soy foods suggest modest improvements in blood cholesterol levels, especially in diabetic patients, and small to no effects on other risk factors, such as glycemic control, BP, inflammation, and body weight, although with occasional positive findings in post hoc patient subgroups.[21-25] Based on available evidence, increased intake of nuts is a clear priority for cardiovascular health; legumes require further research.

Whole Grains, Refined Grains, Starches, and Sweets

Similar to dietary fat, the total carbohydrate content of the diet is less relevant than overall carbohydrate *quality* and specific food choices (**Fig. 49.2**). Because both simple sugars and refined carbohydrates can be rapidly digested after ingestion, the conventional separation into simple (e.g., sugars) versus complex (e.g. starches in grains and potatoes) carbohydrates has little relevance. Rather, carbohydrate quality is better characterized by dietary fiber content, glycemic load (GL), and whole-grain content,[3] each of which is related to cardiometabolic risk (**Fig. 49.3**; see later, Carbohydrates).

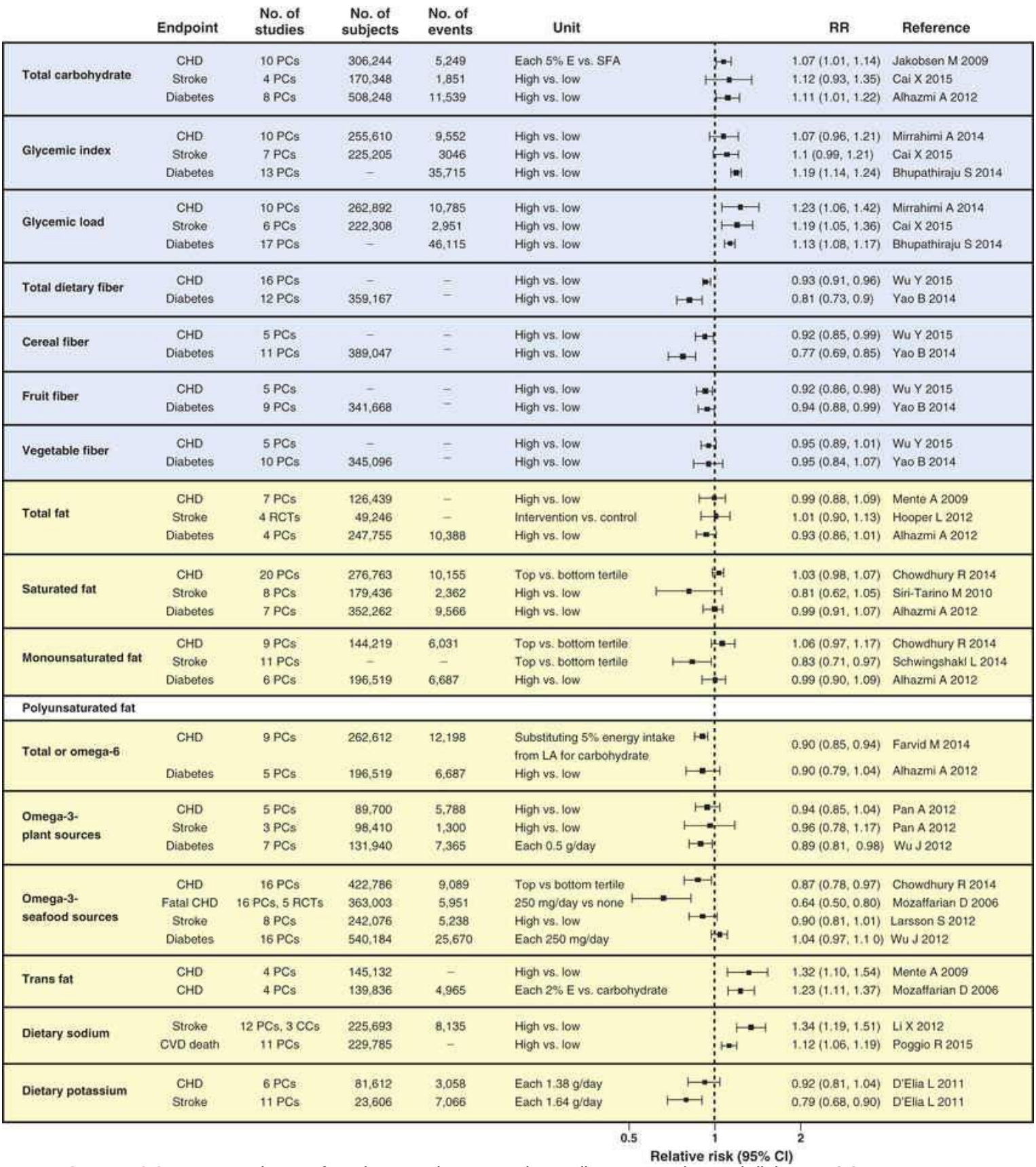

FIGURE 49.3 Meta-analyses of nutrients and coronary heart disease, stroke, and diabetes. CCs, case-control studies; CHD, coronary heart disease; CI, confidence interval; E, energy; LA, linoleic acid; PCs, prospective cohorts; RCTs, randomized clinical trials; RR, relative risk; SFA, saturated fatty acid. (From Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review. Circulation 2016;133:187-225.)

Whole grains are seeds made up of bran (exterior skin), endosperm (starchy interior), and germ (plant embryo). The bran provides fiber, B vitamins, minerals, flavonoids, and tocopherols, while the germ provides fatty acids, antioxidants, and phytochemicals. Refined grains (e.g., white flour, white rice) have

been stripped of their bran and germ, leaving the starchy endosperm (chains of glucose). Whole-grain intake is associated with lower risk of CHD and DM[26,27] (**Fig. 49.2**), as well as less weight gain.[18] In trials, whole grains improve glucose-insulin homeostasis, LDL-C, and possibly endothelial vasodilator function and inflammation.[28] As with fruits and vegetables, no single nutrient appears to accounts for these benefits, which may arise from multiple synergistic effects.

Many commercially available whole-grain products (e.g., breads, cereals, crackers) contain the bran and germ, but have been finely milled during their preparation. Thus, while beneficial fiber and nutrients are retained, the loss of intact food structure exposes the endosperm to rapid digestion by salivary and pancreatic enzymes, increasing the glycemic index (GI) compared with less finely milled whole grains (e.g., steel-cut oats, stone-ground bread). The relevance of this distinction to health has not been adequately studied, but it seems reasonable to select less finely milled whole-grain products, when available. Carbohydrates in liquid form, such as sugar sweetened beverages, seem especially harmful (see later), perhaps related to high doses and lower satiation compared with solid foods.

Refined grains (e.g., white bread, rice, most breakfast cereals), starches (e.g., white potatoes), and sweets are associated with greater weight gain[29] and drive dietary GL, a risk factor for CHD, stroke, and DM (see later, Carbohydrates). These effects may result from both direct metabolic harms (e.g., on postprandial glucose-insulin, endothelial, and inflammatory responses) and displacement of healthier choices (e.g., whole grains, fruits, vegetables). Effects may be greatest in people who are sensitive to insulin resistance and atherogenic dyslipidemia, such as women and persons with DM, lower physical activity, and greater adiposity. Based on their prevalence in most diets, reducing refined grains, starches, and sugars, with replacement by whole grains, fruits, vegetables, nuts, and other healthier foods, is a major dietary priority.

Dietary fiber content, whole-grain content, GI/GL, and extent of processing can be separately altered in carbohydrate-rich products, creating a complex hierarchy of choices (**Fig. 49.4**). As a simple rule of thumb, choosing grain-rich foods with at least 1 g of fiber for every 10 g of carbohydrate (carb/fiber ratio <10 : 1) appears to identify the most healthful grain choices, compared with other recommended approaches.[30]

Type	Processing and Structure	Examples
Intact whole grains	Whole grain with the bran, germ, and endosperm from the natural cereal intact	Brown rice, bulgur wheat, amaranth, wheat berries
Minimally processed whole grains	Some processing is performed to improve palatability or digestibility, yet the bran and germ remain partially intact	Stone-ground whole wheat bread, cracked wheat, steel-cut oats
Milled whole grains	The whole grain, including bran, germ, and endosperm, is milled to fine flour	Most commercially available whole grain breads, whole grain breakfast cereals, whole grain pasta
Refined grains*	The bran and germ are removed during processing, leaving the endosperm comprised largely of refined starch	White bread, white rice, most ready-to-eat breakfast cereals, instant oatmeal, regular pasta
Starchy vegetables*	Plants that have been bred or engineered to contain high levels of starch with relatively low dietary fiber and micronutrients	Potatoes, corn†
Refined sugars*	Natural and industrially produced monosaccharides, disaccharides, and oligosaccharides, including sucrose, glucose, fructose, high-fructose corn syrup, maltose, dextrose, and maltodextrin	Candies, other sugars added to foods
Sweetened refined grains*	Refined grains with added refined sugars	Sweetened breakfast cereals, grain-based desserts (cakes, cookies, pies, doughnuts, sweet rolls, muffins)
Refined sugars in liquid form	Natural and industrially produced monosaccharides and disaccharides in liquid form	Sugar-sweetened beverages, including sodas, iced teas, sports drinks, and fruit drinks

FIGURE 49.4 A hierarchy of carbohydrate quality. Partly overlapping characteristics that influence cardiometabolic effects of carbohydrate-rich foods include dietary fiber content, whole grain (bran, germ) content, glycemic response to ingestion, and food structure (e.g., solid, liquid). Such effects may be especially relevant postprandially and among individuals predisposed to insulin resistance. Based on these characteristics, carbohydrate-rich foods can be classified from healthiest (*dark green*) to most harmful (*dark red*). For instance, minimally processed whole grains may have greater benefits than milled whole grains due to intact food structure and lower glycemic index; while refined sugars in liquid form may have greater adverse effects than other refined carbohydrates due to additional unfavorable effects on satiety and weight gain. *Simple and complex refined carbohydrates induce similarly high glycemic responses following ingestion and, in amounts typically consumed in Western diets, induce hepatic de novo lipogenesis, i.e., conversion of carbohydrates to fat. †Corn provides reasonable fiber and modestly lowers glycemic responses than many types of potatoes. Yams and sweet potatoes are not included here due to higher nutrient contents and lower glycemic responses.

Fish

Fish consumption is associated with less fatal CHD (**Fig. 49.2**), but not total CHD or nonfatal myocardial infarction (MI), suggesting potential specificity to pathways of fatal ventricular arrhythmia.[31,32] Because fish are a rich source of omega-3 fats (see later, Macronutrients), several clinical trials of fish oil supplements have been performed. Although pooled meta-analyses are consistent with lower risk of fatal CHD and not total CHD,[33] individual trial results have been conflicting, with largely null findings in multiple recent studies. Reasons for these discrepancies remain unclear; one possibility is a nonlinear benefit, with modest fish intake (2 servings/wk) providing significant benefit compared with no consumption, but higher consumption (as achieved with supplements) not producing appreciable further effects.[31]

In observational studies, fish consumption is associated with less ischemic stroke, but fish oil

supplements have not influenced stroke in post hoc analyses of CHD trials.[33,34] Some observational studies have evaluated other CVD outcomes, such as atrial fibrillation and heart failure, but with mixed findings.[31] Meta-analyses suggest no significant associations with incident DM, although inverse associations are seen in Asian populations.[35,36]

Types of fish consumed and preparation methods may influence CVD effects. Greatest benefits may accrue from nonfried oily (dark-meat) fish, which contain up to 10-fold more omega-3 fats than other types.[31] Fish also contain other unsaturated fats, selenium, and vitamin D, which could provide benefit. Methylmercury in fish has no detectable influence on CVD events or incident hypertension.[37,38] Presence of persistent organic pollutants (e.g., dioxins, polychlorinated biphenyls) may partly reduce but do not appear to fully offset cardiometabolic benefits of fish intake.[39,40]

Red Meats

Although prevalent guidelines recommend lean meats to lower dietary cholesterol and saturated fat, effects of meat intake on cardiometabolic risk appear more complex, with other factors (e.g., preservatives, heme iron) being potentially more relevant.[41] The available evidence suggests that processed meats (preserved with sodium or other additives; e.g., delicatessen meats, sausage, hot dogs) increase risk of CHD, stroke, and DM, whereas unprocessed red meats have generally smaller effects[42-44] (**Fig. 49.2**). Because unprocessed and processed meats contain similar amounts of average total fat, saturated fat, and cholesterol,[45] the stronger associations for processed meats suggest the importance of other ingredients. For example, *sodium content* is approximately 400% higher in processed meats, a difference that can explain about two thirds of the observed higher CHD risk.[41] Similarly, *heme iron,* rather than fat content, may explain associations of both unprocessed and processed meats with incident DM.[41]

These findings, together with evidence for relatively neutral effects of total saturated fat on CHD and diabetes (see Macronutrients), suggest that lean meats are not necessarily healthier choices than higher-fat options; and that extent of processing may be most relevant. In this light, low-fat, processed deli meats are not better, and may be worse choices, than unprocessed red meats. Based on available evidence, unprocessed meats can be occasionally consumed (e.g., 1 or 2 servings/wk), whereas processed meats should be avoided.

Poultry and Eggs

In long-term observational studies, poultry intake appears generally neutral for CVD risk[44] and has mixed associations with incident diabetes and hypertension.[46,47] When combined with its relatively low levels of bioactive nutrients, these findings suggest that poultry consumption has minimal cardiometabolic effects. Findings appear similar for eggs and CVD, at least in general populations[48,49] (**Fig. 49.2**). Eggs may influence and interact with diabetes. In some studies,[49] frequent consumers (7+ eggs/wk) have a higher rate of new-onset diabetes; however, these findings may not be generalized outside the United States,[50] suggesting potential bias from other dietary or other lifestyle factors associated with frequent egg intake in some countries. Among patients with prevalent diabetes, frequent consumers experience more clinical CVD events.[49] Yet, higher egg consumption is also associated with lower risk of hemorrhagic stroke,[48] perhaps related to protective effects of dietary cholesterol on vascular fragility.[51,52] Relevance of these conflicting findings remains uncertain. Overall evidence suggests little cardiometabolic effect of occasional egg intake (e.g., up to 2 or 3/wk); consistent with recent similar conclusions on dietary

cholesterol[53] (see later, Dietary Cholesterol). Based on current knowledge, it appears prudent to consider poultry and eggs as healthful alternatives to certain foods (e.g., processed meats, starch, sugars) but less beneficial than others (e.g., fruits, nuts, beans, fish).

Dairy Foods

Conventional guidelines for dairy foods are based on predicted effects of isolated nutrients (e.g., eat 3 servings/day to provide calcium and vitamin D), while choosing reduced-fat options to minimize fat, saturated fat, and calories. Growing evidence suggests that effects are much more complex, depending on other factors, such as fermentation, branch-chain and medium-chain fatty acids, probiotics, and milk fat globule membrane content, which may alter lipoprotein and genetic effects.[54,55] In long-term cohorts, total dairy intake was associated with lower risk of stroke, whereas yogurt, cheese, and possibly butter, but not milk, was associated with lower risk of diabetes[56-61] (**Fig. 49.2**). In contrast, fat content (regular versus reduced-fat) is not consistently associated with cardiometabolic risk. Indeed, emerging evidence suggests that dairy fat may have metabolic benefits: in seven cohorts, individuals with higher blood biomarkers of dairy fat intake experienced about a 50% lower incidence of diabetes.[62]

Dairy intake may also benefit adiposity. In randomized trials, milk or dairy consumption reduced body fat and increased lean mass in the setting of energy-restricted diets, with little effect in ad libitum diets.[63,64] In long-term observational studies, yogurt is associated with relative weight loss,[29] potentially related to probiotic-microbiome interactions.[65] In summary, current evidence supports recommendations for modest dairy intake (2 or 3 servings/day), especially of yogurt and cheese, with insufficient data to define the most relevant active ingredients or health differences between whole-fat and reduced-fat dairy foods.

Beverages

Sugar-Sweetened Beverages

Ecologic data, prospective cohorts, and trials together provide convincing evidence that sugar-sweetened beverage (SSB) intake increases adiposity. In the United States, calories from beverages nearly doubled, from 11.8% to 21.0% of all calories consumed, between 1965 and 2002, an increase of 222 kcal per person per day, largely from SSBs (sodas, energy drinks, sweetened ice teas, fruit drinks)[66] (**Fig. 46.2**). The average American teenager consumes 18 (boys) and 14 (girls) 8-oz servings of SSBs weekly,[67] mostly at home.[68] Per serving, SSBs are more strongly associated with long-term weight gain than almost any other dietary factor.[29] Randomized trials confirm that reducing SSBs decreases weight gain and fat accumulation.[69,70] Calories in liquid form, compared with solid foods, appear to be less satiating and increase total calories consumed.[71] SSB intake is also associated with significantly higher incidence of DM and metabolic syndrome,[72] likely related to both weight gain and independent harms of the high-sugar and glycemic load. Given clear evidence for harms and multiple alternatives (e.g., water, seltzer, unsweetened tea, diet soda, milk), SSBs should be largely eliminated from the diet.

Alternative sweeteners can be artificial (e.g., saccharin, sucralose, aspartame) or naturally low calorie (e.g., stevia).[73] Based on observational studies and clinical trials,[18,74] beverages with alternative sweeteners are better options than SSBs. Yet, alternative sweeteners may not be completely benign: animal experiments and limited human data suggest influences on brain reward, taste perception, oral-gastrointestinal taste receptors, glucose-insulin and energy homeostasis, metabolic hormones, and the gut

microbiome.[75-78] For example, if a child's taste becomes accustomed to intense sweetness, will that reduce attractiveness of naturally sweet foods such as apples or carrots? In sum, alternative sweeteners can be a useful bridge to eliminate SSBs, but should not be considered innocuous; and subsequent shifts to nonsweetened drinks (e.g., seltzer, tea) should be encouraged.

Milk

See earlier, Dairy Foods.

Coffee and Tea

Although coffee and tea elicit thoughts of caffeine, these plant extracts derived from beans and leaves contain other bioactive compounds. Unrelated to caffeine content, frequent coffee intake (e.g., 3 to 4 cups/day) is associated with less insulin resistance, DM, CVD, and in a few studies, heart failure[79,80] (**Fig. 49.2**). However, physiologic benefits have not been documented in trials to support these observations. Acutely, caffeinated coffee worsens BP, insulin resistance, and glucose intolerance[81,82] longer term, but habitual coffee intake does not affect BP or insulin resistance, suggesting tachyphylaxis or other partly offsetting factors.[83-85] In a mendelian randomization analysis, genetic variants linked to coffee intake were not associated with any cardiovascular or metabolic risk factors.[86]

As with coffee, frequent tea drinking (e.g., 3+ cups/day) is associated with lower CVD and DM, although with borderline statistical significance[87,88] (**Fig. 49.2**). In trials, certain types of tea modestly lower BP (green, black, herbal roselle)[89-91] and LDL-C (green, black),[92-94] but clear effects on glucose-insulin homeostasis have not been identified.[95,96] Overall, observational evidence supports possible cardiometabolic benefits of frequent coffee or tea drinking, but strong conclusions require better demonstration of these associations as well as biologic plausibility in long-term physiologic trials.

Alcohol

Habitual heavy alcohol intake can cause severe, often irreversible nonischemic dilated cardiomyopathy.[97] Alcohol use is also associated with higher risk of atrial fibrillation in a dose-response manner[98] and with greater long-term weight gain.[29] Compared to nondrinkers, moderate drinkers (≤2 drinks/day in men, 1 to 1.5 drinks/day in women) experience lower incidence of CVD and DM; higher intakes are often linked to harm.[97,99,100] Although analyses of some cohorts suggest red wine may be superior, others show similar associations for white wine, beer, or spirits. Drinking patterns appear more relevant than type: lower risk is observed for regular moderate drinking, not irregular or binge drinking.[101]

In short- and medium-term trials, alcohol use does not significant alter glycemic measures in patients with DM.[102] but favorably affects high-density lipoprotein cholesterol (HDL-C) and inflammation.[103] The consistency of observed lower CVD risk with moderate drinking across many populations, together with these latter physiologic benefits, support a potential casual effect. However, mendelian randomization studies have not confirmed the lower risk seen in observational cohorts,[97,104] raising concern for bias caused by unmeasured poor health in subsets of people who elect not to drink, even lifelong nondrinkers.[105] In addition, across the population, alcohol-related cancers, liver disease, cardiomyopathy, accidents, homicides, and suicides cause greater harms than potential CVD benefits.[1,106] Thus, alcohol use should not be advised as a means to reduce CVD risk; for adults who already drink, counseling should emphasize no more than moderate use. (**See also Chapter 80**.)

Macronutrients

Carbohydrates

For decades, carbohydrates were considered the foundation of a healthful diet, e.g., grain products formed much of the base of the 1992 Food Guide Pyramid. It is now evident that the types, rather than total amount, of carbohydrate-rich foods is most relevant for cardiometabolic health.[3] Certain carbohydrate-containing foods are protective (e.g., fruits, beans, vegetables, minimally processed whole grains), while others are harmful (e.g., white bread, white rice, crackers, cereals, bakery desserts, sweets) (see earlier, Whole Grains, Refined Grains, Starches, and Sweets). Because most carbohydrates in modern diets derives from the latter group, a "low-carb" diet will often produce metabolic benefit. Yet, healthful carbohydrate-containing foods should not be avoided. For most patients, the focus should be to reduce refined grains, starch, and added sugars (glycemic load) and increase dietary fiber, not reduce "carbohydrate" consumption per se[107-113] (**Fig. 49.3**).

Refined grains and starches (essentially long chains of glucose) are rapidly digested, producing similar glycemic responses as table sugar. While marketing claims are often made about different forms of sugar, all types (cane or beet sugar, honey, high-fructose corn syrup) are molecularly similar: about half glucose and half fructose. Thus, few health differences are expected or observed between them.[114-116] In contrast, glucose and fructose, each present in both natural sugars and high-fructose corn syrup, have some differing physiologic effects. When consumed at high, rapidly digested doses, both cause metabolic harms. Glucose induces postprandial hyperglycemia, hyperinsulinemia, and related disturbances, as well as hepatic de novo lipogenesis; whereas fructose has minimal influence on blood glucose or insulin, but more directly stimulates hepatic de novo lipogenesis, hepatic and visceral adiposity, and uric acid production.[115-117] In comparison, such harms are avoided by modest, slowly digested doses of either glucose or fructose (e.g., as found in fruit or beans). Thus the dose, rapidity of digestion, and accompanying nutrients in the sugar-containing foods modify the health effects of sugars.

Fats

Total Fat

Whereas early ecologic (cross-national) studies suggested that fat intake increased cardiometabolic risk, robust evidence from prospective cohorts and randomized trials shows that the percent of total fat in foods or diets has negligible effects on CVD, DM (**see Fig. 49.3**), or weight loss, weight gain, or overweight/obesity[108,118-120] (see later, Energy Balance). In contrast, the types of fats and fatty acids consumed are quite relevant. Conventionally, dietary fats are categorized based on chemistry—the number and position of double bonds—rather than their physiologic effects. This classification obscures differences in dietary sources and biologic effects of individual fatty acids, which influence gene transcription, cell membrane fluidity, receptor function, and lipid metabolites. This chapter follows the conventional categories, but discusses effects of individual fatty acids where sufficient data exist.

Saturated Fatty Acids

Major sources include meats, dairy products, and tropical oils (e.g., palm, coconut). Based on ecologic comparisons, effects on LDL-C, and animal experiments, saturated fatty acid (SFA) intake would be expected to increase CHD risk. However, actual health effects appear more complex. Compared with total carbohydrate, SFA increases LDL-C but has small effects on apo B (i.e., increased LDL-C

concentrations partly reflect larger particles), while also lowering triglyceride-rich particles and lipoprotein(a) and raising HDL-C and apo A1.[121,122] In comparison to total carbohydrate, SFA does not significantly effect fasting glucose, hemoglobin (Hb) A_{1c}, or insulin resistance.[123] Together, these physiologic effects suggest relatively neutral net effects on clinical CVD risk, compared with carbohydrate or the average background diet. Prospective cohort studies confirm this prediction[108,124,125] (**Fig. 49.3**). Similarly, in a large randomized trial targeting total fat reduction, SFA intake was reduced by approximately 27%, largely replaced with carbohydrates, without effects on incident CHD (relative risk [RR] = 0.98), stroke (RR = 1.02), or diabetes (RR = 0.96).[119,120]

The relatively neutral effect of total SFA results at least part from the divergent cardiometabolic effects of its different major food sources (see Foods, above). Individual SFA may also have heterogeneous effects, e.g., comparing medium-chain SFA; lauric (12:0), myristic (14:0), palmitic (16:0), and stearic (18:0) acid; and very long-chain SFA. These fatty acids have known different effects on blood lipids; yet beyond such individual surrogate outcomes, long-term health effects of different SFA remain unclear.121 Replacement of SFA with polyunsaturated fatty acids (PUFA) reduces CHD risk (see PUFA, below), but this appears largely attributable to benefits of PUFA, rather than harms of SFA.

Monounsaturated Fatty Acids

Monounsaturated fatty acids (MUFAs) favorably affect BP and cholesterol levels,[121,126] but are not consistently associated with incident CHD, stroke, or DM[108,125,127] (**Fig. 49.3**). In nonhuman primates, oleic acid (18:1 n-9), by far the most common MUFA, reduces LDL-C levels yet increases atherosclerosis, possibly by enriching LDL-C particles with potentially proatherogenic cholesteryl oleate.[128] In contrast, in controlled feeding trials, replacing carbohydrate with MUFA lowers HbA_{1c}, postchallenge insulin, and insulin resistance, indicating metabolic benefits.

Because both animal fats and vegetable oils (e.g., olive, canola) provide MUFAs, the food source may modify overall health effects. For example, olive oil, but not mixed animal and plant sources of MUFA, is associated with lower CHD;[127] whereas vegetable oil sources of MUFA reduce LDL proteoglycan binding, suggesting antiatherogenic effects.[129] Thus, focusing on specific foods and oils, rather than MUFA content per se, may be most prudent. Extra-virgin olive oil and mixed nuts, and perhaps high-oleic canola oil, are good dietary choices to improve cardiometabolic health.[16,17,130-133]

Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (PUFAs) are classified as n-6 or n-3, based on the carbon location of the first double bond. The predominant PUFA is n-6 linoleic acid (LA, 18 : 2 n-6), derived principally from vegetable oils. Flaxseed, canola, walnuts, and soybeans provide alpha-linoleic acid (ALA, 18 : 3 n-3); and seafood, eicosapentaenoic acid (EPA, 20 : 5 n-3) and docosahexaenoic acid (DHA, 22 : 6 n-3).

n-6 PUFAs

Although speculative harms of n-6 PUFAs have been popularized, metabolic interventions, cohort studies, and clinical trials demonstrate clear benefits. LA lowers LDL-C and triglyceride-rich lipoproteins and raises HDL-C.[134] LA also lowers HbA_{1c}, lowers fasting insulin, and improves insulin secretion capacity.[123] Proinflammatory effects have been theorized,[135] but such effects are not seen in practice.[136] Indeed, LA appears to reduce hepatic steatosis and systemic inflammation.[137,138] Arachidonic acid (AA), the prototypic metabolite of LA, is also generally considered proinflammatory, but also gives rise to *specialized proresolving mediators* (SPMs) of inflammation,[139] and in prospective studies, is associated

with lower CHD.[125] LA also is associated with lower CHD (**see Fig. 49.3**), whether replacing carbohydrate or saturated fat.[140] In meta-analysis of clinical trials, intake of n-6–rich vegetable oils, in place of animal fats, reduces CHD events.[134]

n-3 PUFAs

CVD effects of ALA, the plant-derived n-3 PUFA, remain inconclusive[141-143] (**Fig. 49.3**). In a Dutch trial, an ALA-rich margarine did not significantly reduce CVD events (RR, 0.91; 95% CI 0.78 to 1.05).[144] Seafood-derived EPA and DHA produce multiple physiologic benefits, including on heart rate, BP, triglyceride-rich lipoproteins (TRLs), endothelial function, adiponectin, cardiac function, and inflammatory responses.[31,145] In observational studies of different clinical endpoints, dietary EPA plus DHA was most consistently associated with fatal CHD,[125,143,146,147] consistent with dog and primate experiments showing benefits for ischemia-induced ventricular fibrillation.[31]

Multiple clinical trials have evaluated n-3 PUFA supplements in the form of fish oil, with mixed findings.[31] Meta-analyses suggest reductions in cardiac death, but not total CVD, CHD, or stroke.[33] Such pooled results obscure temporal differences; four of five older trials, but no newer trials, demonstrate benefits.[148] These discrepant findings could be related to more aggressive lipid- and BP-lowering drug treatment or higher background intake of fish, in recent trials, which may diminish the ability to detect additional benefits of fish oil.[148] Other clinical trials of fish oil supplements, including in patients with hypertriglyceridemia, are ongoing.

Effects of fish consumption on other vascular conditions, such as stroke, heart failure, atrial fibrillation, and cognitive decline, remain unclear, with conflicting findings.[31,34,147,149] Fish and omega-3 intake have little association with diabetes, although protective associations are seen in Asian populations,[143,150] and fish oil supplementation modestly raises adiponectin.[145] Types of fish consumed and preparation methods may be relevant, with potential larger benefits from nonfried, dark (oily) fish that contain up to 10-fold higher n-3 levels than white fish.[31]

Overall, strong evidence supports cardiovascular benefits of LA-rich foods, including vegetable oils (e.g., soybean, canola) and nuts. Although recent trials of fish oil are conflicting, the clear physiologic effects, consistent protective associations in cohorts, and an excellent safety profile support recommendations to eat fish once or twice weekly, with fish oil a safe adjunct that may provide further benefits.

Trans Fatty Acids

Trans fatty acids (TFAs) are unsaturated fats that cannot be synthesized by mammals, with one or more double bonds in a *trans*, rather than *cis*, position. The small amounts naturally present in ruminant meats and milk (e.g., from cows, sheep, goats; formed by gut microorganisms) contribute minimally to diet (<0.5% energy [E]) and are not associated with CVD risk.[151] Indeed, higher blood levels of *trans*-16 : 1 n-7, a natural TFA present in dairy fat, is strongly associated with lower risk of diabetes.[62]

Conversely, industrial TFAs, formed by partial hydrogenation of vegetable oils, can be consumed at high levels and are consistently associated with higher CHD (**see Fig. 49.3**), as well as sudden death.[118,152] Industrial TFAs have advantages for commercial deep frying, baking, and shelf stability for packaged snacks and shortening. However, TFA also have uniquely adverse effects on blood lipid and lipoproteins, raising LDL-C, apo B, triglycerides, and lipoprotein(a) and lowering HDL-C and apo A1.[153] TFAs also have nonlipid adverse effects, promoting inflammation, endothelial dysfunction, insulin resistance, visceral adiposity, and arrhythmia, although strength of evidence for these nonlipid effects

varies.[154] In summary, the implicated pathways suggest effects on adipocyte dysfunction and insulin resistance. Emerging evidence suggests that 18 : 2 TFA isomers may be most adverse, which can be formed not only by partial hydrogenation but also by other industrial processes, such as oil deodorization and high-temperature cooking.[155,156] Because partially hydrogenated oils are food additives with clear adverse effects, their elimination is a public health priority.

Dietary Cholesterol

Dietary cholesterol raises both LDL-C and HDL-C, resulting in small net change in the total cholesterol/HDL-C ratio. In certain animals, dietary cholesterol is proatherogenic. In long-term prospective studies, however, neither dietary cholesterol nor its major sources (e.g., eggs, shellfish) were associated with incident CHD or total stroke, and may be protective against hemorrhagic stroke.[48,118,157] Among patients with prevalent DM, however, dietary cholesterol was associated with higher CHD risk;[48] associations with incident DM appear mixed.[49,50] In summary, dietary cholesterol appears to have minor CVD effects in the general population, but may increase CVD among diabetic patients; reasons for this potential difference require further investigation.

Protein

Cardiometabolic effects of dietary protein are not well established. In randomized trials, protein intake has little effect on adiposity, lipids, BP, inflammation, or glucose.[158] Few longitudinal studies have evaluated total protein and CHD events, with generally null results.[159,160] These observations agree with findings for total fat and total carbohydrate: total protein intake derives from diverse foods (e.g., red meats, processed meats, milk, cheese, yogurt, fish, nuts, legumes) with widely varying health effects. Overall, a focus on dietary protein per se appears less relevant for CVD than considering specific types of foods consumed.

Micronutrients

Sodium

In Western countries, most sodium (approximately 75%) comes from packaged foods and restaurants, and little from home cooking or table salt, whereas in Asian countries, most sodium comes from soy sauce and salt added during cooking or at the table.[161] Almost every country in the world exceeds the recommended mean sodium intake of 2000 mg/day.[162] (**See also Chapters 46 and 47**.)

Sodium raises BP in a dose-dependent manner, with stronger effects among older individuals, hypertensive persons, and blacks.[163] In meta-analyses, high sodium intakes was associated with incident total stroke, stroke mortality, and CHD mortality[164-166] (**see Fig. 49.3**). The strength of BP as a surrogate endpoint, as well as ecologic and experimental studies of sodium and CVD, supports such harms.[163,167] Indeed, animal studies suggest that habitually high sodium induces additional, BP-independent damage to renal, myocardial, and vascular tissues.[168]

Most observational studies demonstrate a positive association between very high sodium intakes (e.g., 4000+ mg/day) and CVD, in particular stroke.[164-166] Some studies have also observed a potential J-shaped relationship, with higher CVD risk at low intakes (e.g., <3000 g/day).[169-171] These findings have generated recent controversy about optimal lowest levels of sodium intake.[172]

It remains unclear what physiologic effects could offset, let alone reverse, BP-lowering benefits of

sodium reduction to explain a true J-shaped effect on CVD. For example, although large, rapid sodium reductions can increase renin-aldosterone and serum triglyceride levels,[173] more moderate, gradual reductions may have small effects. For example, a meta-analysis of 74 sodium reduction trials found that renin elevations significantly decline over time.[174]

Furthermore, assessment of sodium in observational studies, whether by urine spot, 24-hour urine, or dietary questionnaire, has unique potential biases that could produce a spurious J shape.[175] These include potentially incomplete 24-hour collections (leading to underestimation of sodium intake in less compliant, sicker individuals), reverse causation (at-risk individuals, as with higher BP or diabetes, actively lowering sodium intakes), confounding by physical activity (which increases total energy intake, which is highly correlated with total sodium intake[176]), and confounding by frailty (which reduces total energy intake, again correlated with total sodium). These limitations together could explain the J shapes seen in certain observational studies.

In comparison, during extended surveillance in a large sodium study that excluded sick individuals at baseline and used serial 24-hour urine collections, participants with lowest intakes (<2300 mg/day) experienced a 32% lower CVD risk than those consuming high intake, with evidence for linearly decreasing risk.[177,178] In ecologic studies, the lowest mean intake level associated with both lower systolic BP and lower age-BP slope is 614 mg/day.[179] In randomized trials, BP reductions have been documented down to intakes of 1500 mg/day.[180] In meta-analyses of prospective observational studies, the mean intakes associated with lower risk of CVD events range from 1787 to 2391 mg/day.[163,165] Taken together, these findings support target intakes in current official guidelines, which range from 1200 to 2400 mg/day.[163]

Potassium, Calcium, and Magnesium

Vegetables, fruits, whole grains, beans, nuts, and dairy are major sources of minerals. In trials, potassium lowers BP, with stronger effects among hypertensive individuals and when dietary sodium intake is high.[181] Consistent with this, potassium-rich diets are associated with lower risk of stroke[182] (**see Fig. 49.3**). Potassium also attenuates, whereas insufficient dietary potassium exacerbates, the BP-raising effects of sodium.[180,182] Overall, the evidence strongly supports the importance of potassium-rich foods for reducing BP and CVD.

In short-term trials, calcium and magnesium supplements also modestly lower BP, although with substantial heterogeneity between studies. However, calcium supplements with or without vitamin D may increase risk of MI in long-term trials.[183,184] In observational analyses, dietary and blood magnesium levels were inversely associated with CVD, especially fatal CHD;[185] long-term trials have not been performed. Calcium and magnesium supplements cannot yet be recommended for general CVD prevention.

Antioxidant Vitamins

Several dietary vitamins and nutrients are associated with lower CVD in observational studies, but fail to lower risk in trials of supplements, including folate, B vitamins, beta-carotene, vitamin C, vitamin E, and selenium.[118,186,187] Most of these trials, for reasons of power, evaluated up to a few years of treatment in high-risk patients or those with established CVD. In contrast, most observational studies evaluated long-term or habitual intake among generally healthy people. Thus, discrepancies in findings could partly relate to different time periods of biologic sensitivity (e.g., some vitamins and nutrients could be important only early in the disease course). Such explanations require confirmation in prospective

studies and trials. Discrepancies between observational studies and supplement trials may also be related to residual bias in observational studies from other lifestyle behaviors (i.e., observed benefits are not caused by diet) or from other nutritional factors in vitamin-rich foods (i.e., observed benefits are caused by diet, but not by the specific identified vitamins or nutrients). For example, diets higher in antioxidant vitamins tend to be rich in fruits, vegetables, nuts, and whole grains, foods that contain multiple other beneficial factors, including other vitamins, minerals, phytochemicals, and fiber, as well as being foods that can provide benefit by replacing unhealthful foods. Thus, isolating one or even several components of these foods may not produce similar effects as would occur from consuming the whole food.[4,188]

Vitamin D

Higher plasma vitamin D is associated with lower CVD, yet levels are largely driven by sun exposure, not diet; and large supplement trials have not found benefits.[189] If higher plasma vitamin D does prove to lower CVD risk, brief sun exposure can efficiently provide such levels. Ongoing trials are testing whether higher doses of vitamin D influence CVD; for now, such supplementation is not indicated to improve cardiometabolic health.

Phenolic Compounds

Bioactive polyphenols include flavanols (in onions, broccoli, tea, various fruits), flavones (in parsley, celery, chamomile tea), flavanones (in citrus fruits), flavanols (flavan-3-ols) such as catechins and procyanidins (in cocoa, apples, grapes, red wine, tea), anthocyanidins (in colored berries), and isoflavones (in soy). In laboratory studies and randomized trials, flavonoid-rich cocoa has small but measurable benefits on BP, endothelial function, insulin resistance, and blood lipids.[190-192] BP-lowering occurs with as little as 6.3 g/day (30 kcal/day) of dark chocolate and is related to increased endothelial nitric oxide production.[193] The latter mechanism suggests potential benefits beyond BP lowering. A few short-term trials of other dietary sources (e.g., tea, red wine, grapes) or specific flavonoid extracts have not consistently improved BP, lipid levels, or endothelial function.[190-192] Some observational studies evaluating total or selected dietary flavonoids observe lower risk of cardiometabolic events;[194,195] a first large clinical trial is ongoing. The heterogeneity of different flavonoids and their dietary sources limits inference for class effects, and clinical benefits and dose-response effects remain unclear. However, many foods with evidence for cardiometabolic benefits, including berries, nuts, and extra-virgin olive oil, are rich in phenolics, and their physiologic and molecular effects are highly promising for further study.

Energy Balance

In most countries, the current obesity epidemic is a striking change from decades of relative stability; in the United States, obesity began steeply rising only about 35 years ago.[196] Abdominal adiposity, which produces the greatest metabolic harms, has also increased more than overall weight in many nations, especially in younger women.[197] The breadth, depth, and pace of this epidemic, including in young children,[198] suggest strong environmental drivers rather than population-wide changes in genetics or willpower. (**See also Chapter 50**.)

Current concepts of obesity treatment prioritize energy balance: count calories, reduce portion sizes, eat less, and move more. As seen for cardiometabolic health, however, the complex effects of different foods and diet patterns may be more relevant for long-term weight homeostasis than reductionist

approaches focused on total calories. For short-term weight loss, total calories are most relevant, which is why almost any type of diet may initially work. For long-term weight maintenance, however, and more importantly for cardiometabolic health, healthful food-based patterns appear especially important.[53]

Humans have multiple, redundant biologic mechanisms to maintain weight homeostasis. Current concepts postulate that different foods may, over years, help or hinder these intrinsic mechanisms.[3] For example, foods rich in refined grains, starches, and sugar appear especially harmful,[18,199] driving obesogenic pathways.[200-204] Other foods, such as milk, appear relatively neutral, neither helping nor perturbing homeostatic mechanisms for long-term weight control.[199,205] Effects of meats, cheese, and eggs may vary as to whether they are eaten with refined carbohydrates (in which case they seem to worsen weight gain) or in place of refined carbohydrates (which are associated with less weight gain or even relative weight loss).[199] Also, fruits, nonstarchy vegetables, beans, nuts, yogurt, fish, and whole grains appear to protect against chronic weight gain.[9,18,199,205] Mechanisms underlying these observations are being elucidated but may involve satiety, brain craving and reward,[203] glucose-insulin responses,[200] hepatic fat synthesis,[201] adipocyte function,[206] visceral adiposity,[202] metabolic expenditure,[204] and the gut microbiome.[18,199,205,207-209] Because habitual excess energy intakes as small as 50 to 100 kcal/day may explain much of the obesity epidemic,[67] very subtle effects on these pathways may be sufficient, when sustained, to account for population shifts in weight.

Other factors appear to interact with diet to influence adiposity, including TV watching, sleep duration, circadian alignment, and possibly maternal-fetal (e.g., placental) influences.[18,196,210-213] For example, lower sleep duration and altered circadian rhythms predict weight gain and obesity, altered hunger and food preferences, and changes in leptin, ghrelin, insulin, and gut-peptide concentrations.[18,210] TV watching increases obesity and weight gain,[18,211] at least partly mediated by changes in diet, rather than physical activity, because of increased eating while watching TV and altered choices from TV marketing.[214,215] Increasing physical activity has complementary benefits on weight maintenance and metabolic health. More liquid calories, larger portion sizes, and more meals away from home are also linked to risk of adiposity. Changes in social norms and networks, industry marketing, and local food availability also appear important.[216-218]

In summary, these complex and often insidious influences can make unintended weight gain very easy. Conversely, these drivers can also serve as positive levers to attenuate or reverse chronic energy gaps, weight gain, and adiposity. Regardless of body weight, overall dietary quality strongly influences cardiometabolic health,[3,53] analogous to weight-independent health benefits of physical activity. In contrast, other conventional dietary metrics, such as calorie content, total fat, and energy density, may not reliably identify how specific foods influence long-term weight gain.[18,199,205] Based on current evidence, key diet-related priorities to reduce adiposity include fewer refined grains, starches, sugars, and red meats; more fruits, vegetables, beans, nuts, yogurt, fish, vegetable oils, and whole grains; less TV watching; sleeping at least 7 to 8 hours nightly; and further elucidating maternal-fetal, microbiome, and sleep/circadian influences.

Dietary Patterns

Dietary patterns represent overall combinations of foods consumed, which together can produce synergistic health effects. Evidence-based beneficial diet patterns share several key characteristics: more minimally processed, bioactive-rich foods, such as fruits, nuts/seeds, nonstarchy vegetables, beans, whole grains, seafood, yogurt, and vegetable oils, and fewer red meats, processed (sodium-preserved) meats,

and processed and packaged foods rich in refined grains, starches, added sugars, salt, and *trans* fat (**Table 49.1**). Two of the best studied, each consistent with this description, are the traditional Mediterranean and Dietary Approaches to Stop Hypertension (DASH) dietary patterns.[53,186]

TABLE 49.1

Food-Based Components of Dietary Patterns That Improve Cardiometabolic Health*

	GOAL†	SERVING SIZES
Consume More:		
Fruits	3 servings per day	Approximately 100 g, e.g., 1 medium-sized fruit; ½ cup of fresh, frozen, or canned fruit; ¼ cup of dried fruit; ½ cup of 100% juice. Goals should not be met with juice alone.
Vegetables and beans	3-4 servings per day	Approximately 100 g, e.g., 1 cup of raw leafy vegetable; ½ cup of cut-up raw vegetables, cooked vegetables, or 100% juice. Limit potatoes to ½ cup or less per day.
Whole grains‡	3 servings per day, in place of refined grains	Approximately 50 g, e.g., 1 slice of whole-grain bread; 1 cup of high-fiber whole-grain cereal; ½ cup cooked whole-grain rice, pasta, or cereal
Nuts	4 to 5 servings per week	Approximately 28 g (1 oz)
Fish and shellfish	2+ servings per week, preferably oily	Approximately 100 g (3.5 oz). Goals should not be met with commercially prepared deep-fried or breaded fish.
Dairy products§	2 to 3 servings per day	1 cup of milk or yogurt; 1.5 oz of cheese
Vegetable oils	2 to 6 servings per day	Approximately 1 teaspoon of oil, e.g., in cooking or salad dressing; or 1 tablespoon of vegetable spread
Consume Less:		
Foods containing partially hydrogenated vegetable oils (*trans* fat)	Avoid intake.	
Refined grains and starches		
Processed meats (e.g., bacon, sausage, hot dogs, processed deli meats)	Avoid intake or at most modest intake, e.g., up to 2 servings per week	Approximately 100 g (3.5 oz)
Sugar-sweetened beverages, sweets, and bakery foods	Avoid intake or at most modest intake, e.g., up to 5 servings per week	8 oz of soda; 1 small cookie, doughnut, or muffin; 1 slice of cake or pie
Alcohol	Up to 2 daily drinks for men, 1 daily drink for women	5 oz of wine; 12 oz of beer; 1.5 oz of spirits
Energy Balance:	Eat healthy foods as above, reduce portion sizes, eat fewer fast-food and prepared meals, increase physical activity, limit TV watching, and ensure adequate (7-8 hours) sleep.	

*Adapted from the evidence described in this chapter.

†Based on a 2000-kcal/day diet. Servings should be adjusted accordingly for higher or lower energy consumption.

‡A practical rule of thumb for selecting healthier grain or carbohydrate-rich products is to choose foods containing at least 1 g of dietary fiber for every 10 g of total carbohydrates per serving (carb:fiber ratio <10:1), based on the Nutrition Facts Panel.[30]

§Based on available evidence, the types of dairy (yogurt, cheese, milk, butter) appears more relevant than fat content (whole or reduced fat); see text for details.

Randomized trials in both primary and secondary prevention populations confirm cardiometabolic benefits of such healthful, food-based diet patterns.[17,132,219,220] In comparison, observational cohorts and randomized trials confirm little clinical effect of diets focused on isolated nutrient targets, such as low-fat, low-saturated fat diets.[119-121,125] Because sodium and *trans* fats can be added to or removed from otherwise similar foods and dietary patterns, a specific nutrient focus on these industrial additives is warranted.[53] Focusing on overall diet patterns can lead to health benefits from modest changes across multiple foods, rather than large changes in a few factors, potentially increasing effectiveness and compliance. This flexibility can also facilitate behavioral counseling, permitting a more personalized focus[53] (**Table 49.2**).

TABLE 49.2

Effects of Food and Nutrients on Specific Cardiometabolic Risk Factors and Disease Endpoints

	STRENGTH OF EVIDENCE FOR BENEFITS*			INSUFFICIENT EVIDENCE FOR EFFECTS
	Convincing	**Probable**	**Possible**	
Hypertension	Higher intakes of: Mediterranean- or DASH-type dietary pattern Dietary fiber Fruits and vegetables Fish or fish oil Cocoa or dark chocolate Potassium Lower intakes of: Sodium Alcohol	Higher intakes of: Tea Lower intakes of: Caffeine	Higher intakes of: Whole grains Magnesium Calcium Vitamin D Soy foods MUFAs in place of SFAs	Isoflavones Coffee or tea PUFAs or carbohydrate in place of SFAs
High LDL-C	Higher intakes of: MUFAs or PUFAs Dietary fiber Fruits and vegetables Green tea Soy protein Lower intakes of: *Trans* fat SFAs (12:0-16:0) Dietary cholesterol	Higher intakes of: Butter Whole grains Soy foods Tea Lower intakes of: Unfiltered coffee	Higher intakes of: Cheese Yogurt Cream	
Atherogenic dyslipidemia (low HDL-C, high triglycerides)	Higher intakes of: Mediterranean- or DASH-type dietary pattern MUFAs or PUFAs Fish or fish oil Lower intakes of: Simple or complex refined carbs (high GI or GL) *Trans* fat	Lower intakes of: SSBs	Higher intakes of: Fruits and vegetables Dairy foods	
Insulin resistance, type 2 diabetes	Higher intakes of: Whole grains Dietary fiber PUFAs or vegetable oils Lower intakes of: Processed meats SSBs Simple or complex refined carbs (high GL)	Higher intakes of: MUFAs Lower intakes of: Unprocessed meats	Higher intakes of: Fruits Beans Coffee Cheese Yogurt Dairy fat Lower intake of: Eggs Dietary cholesterol *Trans* fat	Carbohydrate in place of SFAs Vegetables Beans Poultry Fish or fish oil Milk Butter Tea
Obesity	Higher intakes of: Whole unprocessed foods (e.g., whole grains, nuts, fruits, vegetables, beans) Lower intakes of: SSBs Simple or complex refined carbs (high GL)	Higher intakes of: Dietary fiber Yogurt Lower intakes of: Large portion sizes Red meats Processed meats Less TV watching Greater sleep duration	Higher intakes of: Green tea Protein Lower intakes of: Deep-fried foods Meals from quick service restaurants *Trans* fat	Total fat (% E) SFAs, MUFAs, or PUFAs
Systemic inflammation	Higher intakes of: Fruits and vegetables	Higher intakes of: Mediterranean- or DASH-type diet pattern Whole grains Fish oil (supplements). Lower intakes of: TFAs	Higher intakes of: Fish, fish oil (diet), ALA PUFAs Nuts Lower intakes of: Simple or complex refined carbs (high GI/GL)	SFAs or MUFAs
Coronary heart disease	Higher intakes of: Mediterranean- or DASH-type dietary pattern Fruits and vegetables Whole grains Nuts Dietary fiber PUFAs in place of SFAs Fish (CHD mortality) Lower intakes of: Trans fat Processed meats	Higher intakes of: Beans Lower intakes of: Simple or complex refined carbs (high GI or GL) Sodium Moderate alcohol use	Higher intakes of: Fish or fish oil (nonfatal CHD) Cheese ALA MUFAs in place of SFAs Vitamin D Lower intakes of: Unprocessed meats Dietary cholesterol in patients with diabetes	Total fat (% E) Carbohydrate in place of SFAs Antioxidant or vitamin supplements Poultry Eggs Yogurt Milk Coffee or tea Dietary cholesterol in patients without diabetes
Ischemic stroke	Higher intakes of: Mediterranean- or DASH-type dietary pattern Fruits Lower intakes of: Sodium		Higher intakes of: Whole grains Vegetables SFAs Fish or fish oil Tea Cheese Lower intakes of: Processed meats Red meats	Poultry Eggs Milk ALA Antioxidant or vitamin supplements

Hemorrhagic stroke		Higher intakes of: Whole grains Mediterranean- or DASH-type dietary pattern Lower intakes of: Sodium	Higher intakes of: Total fat SFAs Animal protein Tea	Fish or fish oil
Heart failure[†]	Lower intakes of: Heavy alcohol use		Higher intakes of: Mediterranean- or DASH-type dietary pattern Whole grains Fish Moderate alcohol use	
Atrial fibrillation		Lower intakes of: Heavy alcohol use	Higher intakes of: Fish or fish oil	

[*]Strength of evidence based on Bradford-Hill and World Health Organization criteria: Micha R, Kalantarian S, Wirojratana P, et al. Estimating the global and regional burden of suboptimal nutrition on chronic disease: methods and inputs to the analysis. Eur J Clin Nutr 2012;66:119-29. For most dietary factors, evidence is derived from controlled trials of risk factors plus long-term prospective cohorts of disease endpoints. For fish/EPA plus DHA, n-6 PUFAs, total fat, and Mediterranean-type dietary patterns, evidence is also derived from randomized clinical trials of clinical endpoints.

[†]Incidence. Limited data on dietary treatment for secondary prevention, except for one large randomized trial of EPA plus DHA supplementation that reduced total mortality, and clinical experience with sodium restriction to prevent fluid overload.

ALA, Alpha-linoleic acid; *CHD,* coronary heart disease; *DASH,* Dietary Approaches to Stop Hypertension; *E,* energy; *GI,* glycemic index; *GL,* glycemic load; *MUFAs,* monounsaturated fatty acids; SFAs, saturated fatty acids; *PUFAs,* polyunsaturated fatty acids; *SSBs,* sugar-sweetened beverages; TFAs, *trans* fatty acids.

Other popular dietary patterns include vegetarian or vegan, low-carbohydrate, and “paleo” diets. People who follow these patterns may be health conscious and tend to make better choices. Yet, these dietary patterns can vary dramatically in their healthfulness; each can range from excellent to poor, depending on the specific foods selected. A cardioprotective diet pattern is best characterized by being rich in specific healthful foods (**see Table 49.1**).

Changing Behavior

Because dietary changes can be low risk, low cost, and broadly available, strategies for effective behavior change are essential at individual, health system, and population levels.[216,217,221]

Clinical (Individual-Based) Strategies

Numerous controlled trials have identified effective approaches for individual behavior change: setting proximal, targeted goals; self-monitoring; regular feedback; peer support; increasing self-efficacy; and motivational interviewing.[221,222] These strategies should be incorporated into practice to improve specific dietary priorities. Providers should remember that patient compliance with both lifestyle counseling and medication prescriptions is similarly incomplete, yet such strategies, even imperfectly implemented, improve clinical outcomes.[223]

Novel Technologies

Novel personal technologies such as mobile applications (mHealth), Internet programs, and personal devices (e.g., FitBits) hold promise due to scalability, lower cost, and opportunities for continuous, personalized modifications and improvements. Optimally, deployment of these approaches should incorporate established individual-based behavior change strategies. A systematic review of randomized trials and quasi-experimental studies demonstrated general effectiveness of these approaches for dietary change and/or weight loss.[224] While promising, most of these studies had a duration of 6 weeks to 6

months and thus require evaluation of long-term effectiveness and sustainability.

Health Systems

For many clinicians, certain barriers may limit their ability to implement effective behavior change strategies: limited patient visit time, insufficient financial or other provider incentives, suboptimal knowledge or experience, and inadequate electronic tools for assessing diets and monitoring changes over time. Specific health system changes, now being introduced for tobacco and obesity control, can support and facilitate behavior change.[217,222,225,226] Expansion of these approaches to target diet quality is crucial. Integrated systems can provide coordinated care by multidisciplinary teams; with alignment of payments, practice goals, and quality benchmarks to reward dietary change efforts.

Policy Strategies

Given the key roles of social and environmental forces in shaping dietary habits, policy (population-based) approaches are crucial to achieve broad success. When widespread, even modest behavioral changes meaningfully alter population risk. Effective strategies can be implemented at local (e.g., schools, worksites, communities) as well as city, state, national, and international levels. These include focused media/education, product labeling/point-of-purchase information, comprehensive school and workplace wellness programs, built-environmental changes in types and locations of food outlets, economic incentives such as taxes and subsidies, and quality standards (e.g., on marketing to children, levels of *trans* fat or sodium).[216] Available evidence suggests that education or information alone, without additional economic or environmental changes, has lower efficacy.[216,227,228] Integrated, multicomponent approaches that include upstream policy measures, midstream educational efforts, and downstream community and environmental approaches appear especially effective, as seen with reducing tobacco use and deaths from motor vehicle accidents. Policy strategies can complement individual and health system efforts while also reducing social and racial disparities caused by clustering of suboptimal diet habits, local environments, and disease risk factors in disadvantaged groups.

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Obesity and Cardiometabolic Disease

Jean-Pierre Després, Eric Larose, Paul Poirier

A medical perspective defines obesity as excess body fat associated with comorbid conditions and increasing mortality risk. This chapter discusses basic concepts on the etiology of obesity as it relates to cardiovascular outcomes, including (1) fat accumulation in selective adipose depots and nonadipose tissues as related to various health outcomes, (2) the tools to assess the risk associated with the different forms of overweight and obesity, and (3) the options available in clinical practice to prevent or reduce the risk of cardiovascular disease (CVD) in overweight and obese patients. (**See also Chapter 49**.)

Epidemiology

Traditional Definition of Obesity

Obesity increases risk of developing numerous health outcomes, including cardiovascular events[1-4] (**Fig. 50.1**). In clinical practice the most common index used to estimate adiposity has been the body mass index (BMI, expressed in kg/m^2), initially introduced by Quetelet more than a century ago and largely popularized by the American physiologist Ancel Keys.[3,4] Since then, many population-based studies, including a recent international study pooling data of about 4 million individuals from 189 studies who were followed for an average of 13 years, have shown that a BMI value above approximately 25 kg/m^2 is associated with a progressive increase in mortality rate and risk of chronic conditions.[1] A BMI of 25 kg/m^2 or higher defines *overweight*, BMI of 30 kg/m^2 or higher defines *obesity*, and BMI of 40 kg/m^2 or higher, or 35 kg/m^2 or higher with comorbidities, defines *severe obesity*.[2-4] The prevalence of obesity has increased worldwide, particularly since the early 1980s, with little evidence of plateauing[5,6] (**eFig. 50.1**). The prevalence of severe obesity has reached epidemic proportions in the United States and elsewhere[5-8] (**see Chapter 1**).

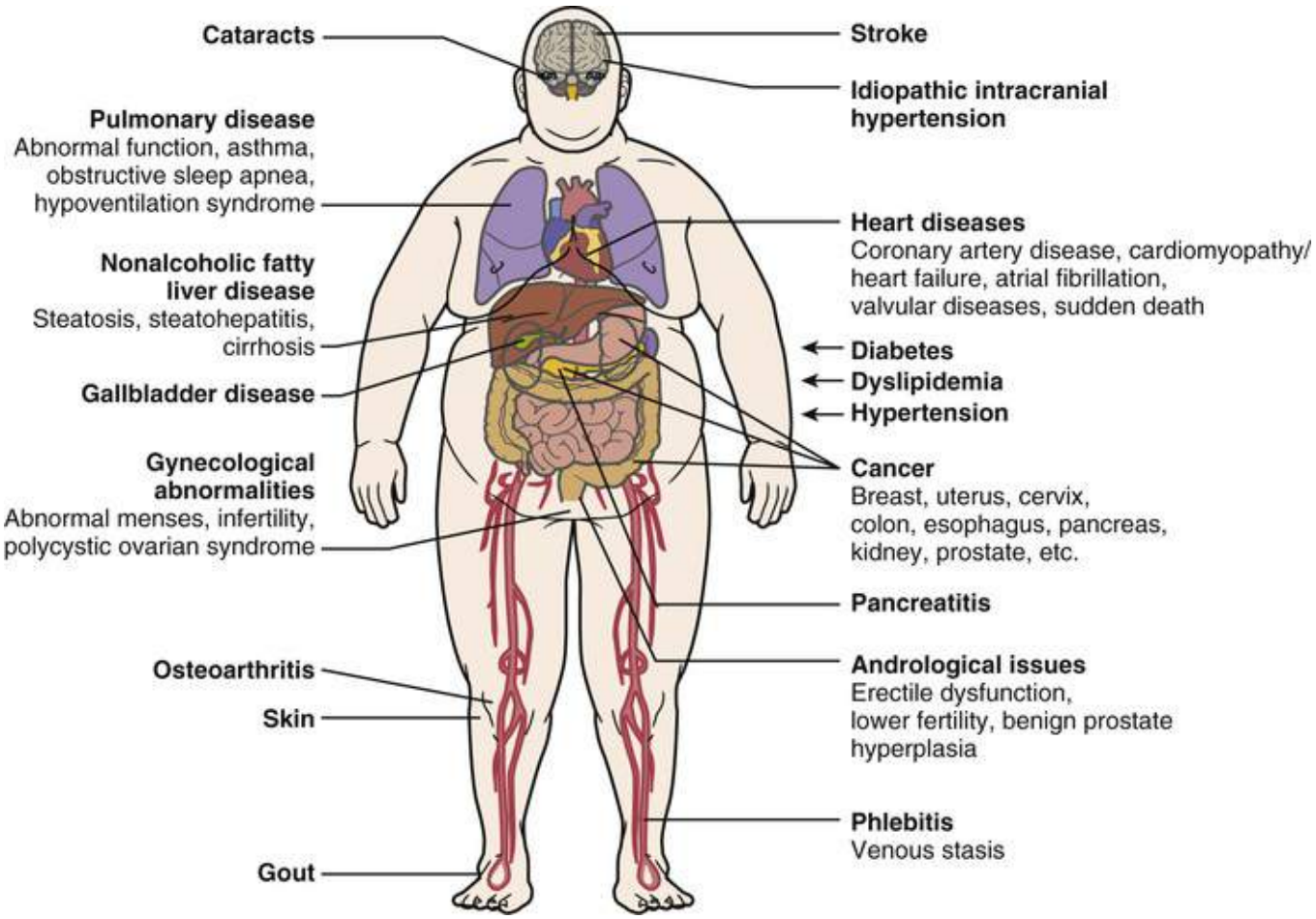
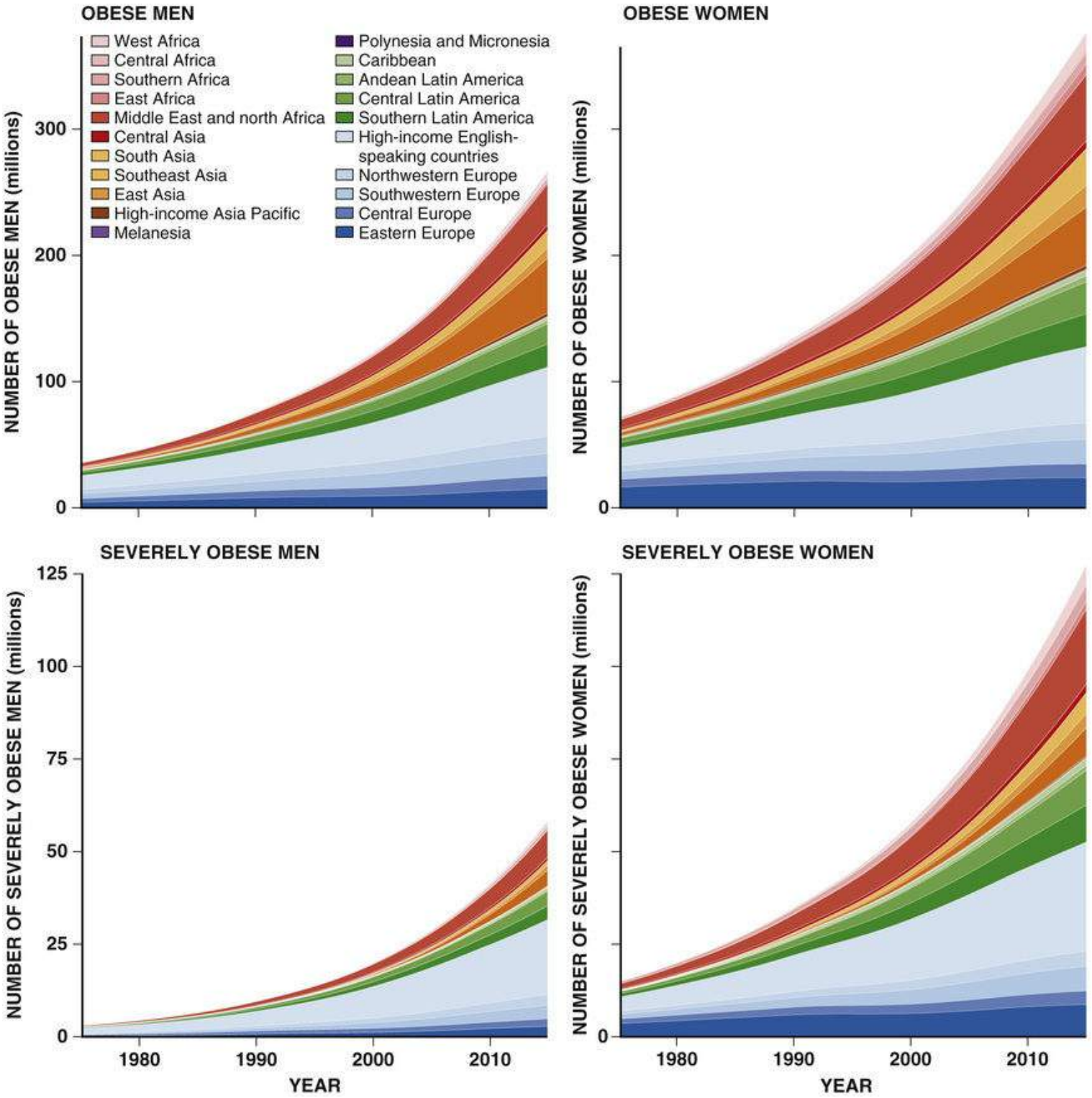


FIGURE 50.1 Some of the key medical complications associated with obesity.



EFIGURE 50.1 Trends in the number of obese and severely obese people by region. A person is obese if they have a body mass index (BMI) of 30 kg/m^2 or higher, or is severely obese if they have a BMI of 35 kg/m^2 or higher. (From NCD Risk Factor Collaboration. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 387:1377-1396, 2016. http://creativecommons.org/licenses/by/4.0/.)

Puzzling Relationship of Excess Body Weight and Fat with Cardiovascular Disease

Although excess body weight or obesity is associated with an increased risk of many health complications (**Fig. 50.1**), equally overweight or obese patients display a remarkable heterogeneity in CVD risk[9,10] (**Fig. 50.2**). Thus, although an elevated BMI increases the risk of finding CVD risk factors or health

complications, not every overweight/obese patient develops risk factors or health issues. Some investigators use the term “metabolically healthy” or “fit fat” obesity to refer to such individuals.[9-12] The existence of such metabolically healthy obese individuals has engendered debate. Indeed, there is no healthy pattern of increased weight.[13] Nevertheless, reasons for such major individual differences in the cardiometabolic risk profile of equally obese patients had remained unclear until imaging studies (computed tomography [CT] and then magnetic resonance imaging [MRI]) revealed marked individual differences in the way people store adipose tissue in the visceral depot. For any given level of total body fat, individuals characterized by a low accumulation of abdominal visceral adipose tissue generally have a lower CVD risk profile than individuals closely matched for BMI or for total body fat but with high levels of visceral adipose tissue. Those with excessive visceral fat display a constellation of metabolic abnormalities, including insulin resistance, glucose intolerance leading to type 2 diabetes, atherogenic dyslipidemia (including increased triglyceride levels, increased concentrations of non-high-density lipoprotein [HDL] cholesterol and apolipoprotein B, low HDL cholesterol levels, small dense low-density lipoprotein [LDL] and HDL particles), elevated blood pressure (BP), subtle chronic inflammation, and a prothrombotic profile[9,10,14] (**Fig. 50.2**). This risk cluster characterizes the so-called metabolic syndrome.[10,14]

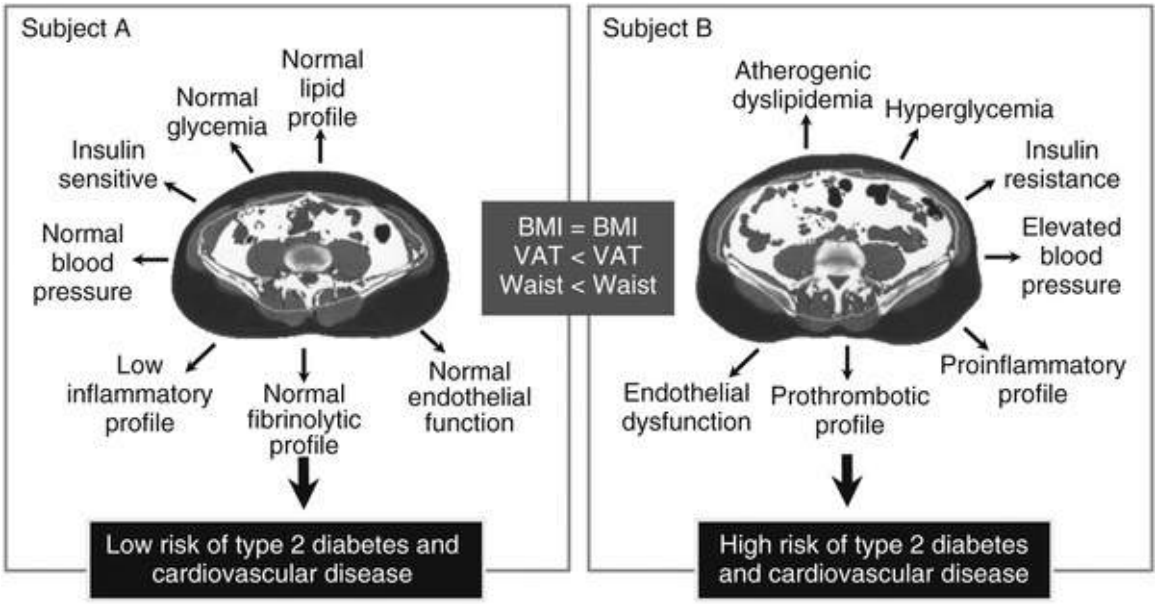
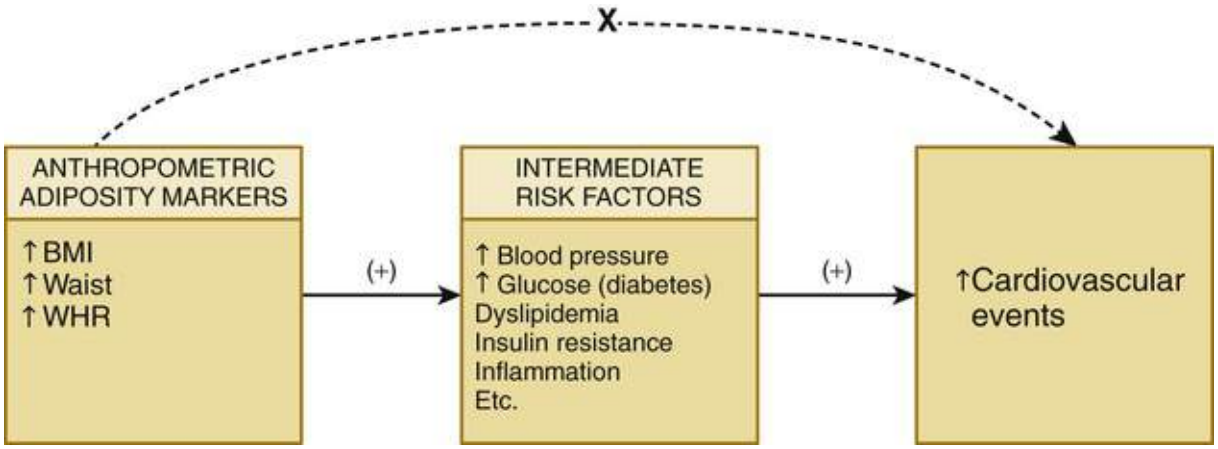


FIGURE 50.2 Marked differences in visceral adipose tissue (VAT) accumulation measured by computed tomography in two individuals having the same body mass index (BMI). However, subject B has a greater cross-sectional accumulation of VAT than subject A. This higher accumulation of VAT in subject B is associated with an altered cardiometabolic risk profile increasing the risk of type 2 diabetes and cardiovascular disease compared to subject A.

In clinical practice, assessing CVD risk specifically related to obesity or excess adiposity has remained a challenge. One large study concluded that, after control for intermediate CVD risk factors (BP, lipids, diabetes), anthropometric adiposity indices such as BMI or waist circumference are not independently related to CVD mortality.[15] The study reported very strong associations between adiposity indices and intermediate CVD risk factors, however, suggesting that increased adiposity changed CVD risk[16] (**eFig. 50.2**). Thus the clinician must decide whether to reduce CVD risk by lowering BP, lipids (LDL cholesterol), and blood glucose with pharmacologic agents or to target weight loss. Whereas randomized trials have shown the clinical benefits of targeting BP, lipids, and glucose control (within certain limits), no weight loss drug targeting obesity has unequivocally been proven to reduce

cardiovascular events and mortality, with the exception of new diabetes drugs, which are not neutral in terms of body weight.[17,18] A large well-conducted diet and weight loss trial in obese patients with type 2 diabetes (Look AHEAD) showed no reduction in CVD events as a result of an intensive lifestyle intervention that yielded weight loss, despite beneficial effects on some CVD risk factors and quality of life.[19] Various explanations may account for this result.[20]



EFIGURE 50.2 Relationships among adiposity indices, intermediate risk factors, and cardiovascular events in the general population. Under this model, most of the association between adiposity indices and cardiovascular disease is explained by altered levels of intermediate risk factors. BMI, Body mass index; WHR, waist-to-hip ratio. (From Bastien M et al. Overview of epidemiology and contribution of obesity to cardiovascular disease. Prog Cardiovasc Dis 2014;56:369-81.)

Risk Assessment in Overweight/Obese Patients: Waistline as Key Indicator

Because excess visceral adiposity exacerbates CVD risk in overweight and obese patients, it remains essential to measure the patient's waist circumference in addition to BMI.[21] This variable should be assessed while the patient is standing, placing the tape just above the iliac crest. If a given patient has a large waistline for a given BMI, with altered risk factors, the CVD risk factor profile likely reflects excess abdominal visceral fat.[9,10,22] Simple clinical alterations (e.g., high-triglyceride low–HDL cholesterol dyslipidemia, elevated BP, increased fasting blood glucose levels) confirm a dysmetabolic state. Additional tests to confirm insulin resistance include fasting insulin, 2-hour glucose tolerance, hemoglobin (Hb) A_{1c} level and C-reactive protein (CRP) concentrations. In overweight or obese patients, the presence of these abnormalities along with an elevated waist circumference suggests an excess of abdominal visceral fat.[9,10,14]

Because the waistline and BMI are strongly correlated, waist circumference alone largely reflects total adiposity. For any given BMI value, however, waist circumference can vary considerably and reflects CVD risk[23] (**Fig. 50.3 and eFig. 50.3**). Thus, although clinical guidelines have proposed waist cutoff values to define abdominal obesity, interpretation of these cutoffs requires caution. For example, a waist circumference of 105 cm reflects *abdominal* obesity in a man with a BMI of 26 kg/m^2. However, the same waistline value would simply reflect *overall* obesity in another individual with a BMI of 31 kg/m^2. Further work is required to refine clinically relevant BMI-specific waist cutoff values beyond those specified in current guidelines[2,24] (**Table 50.1**).

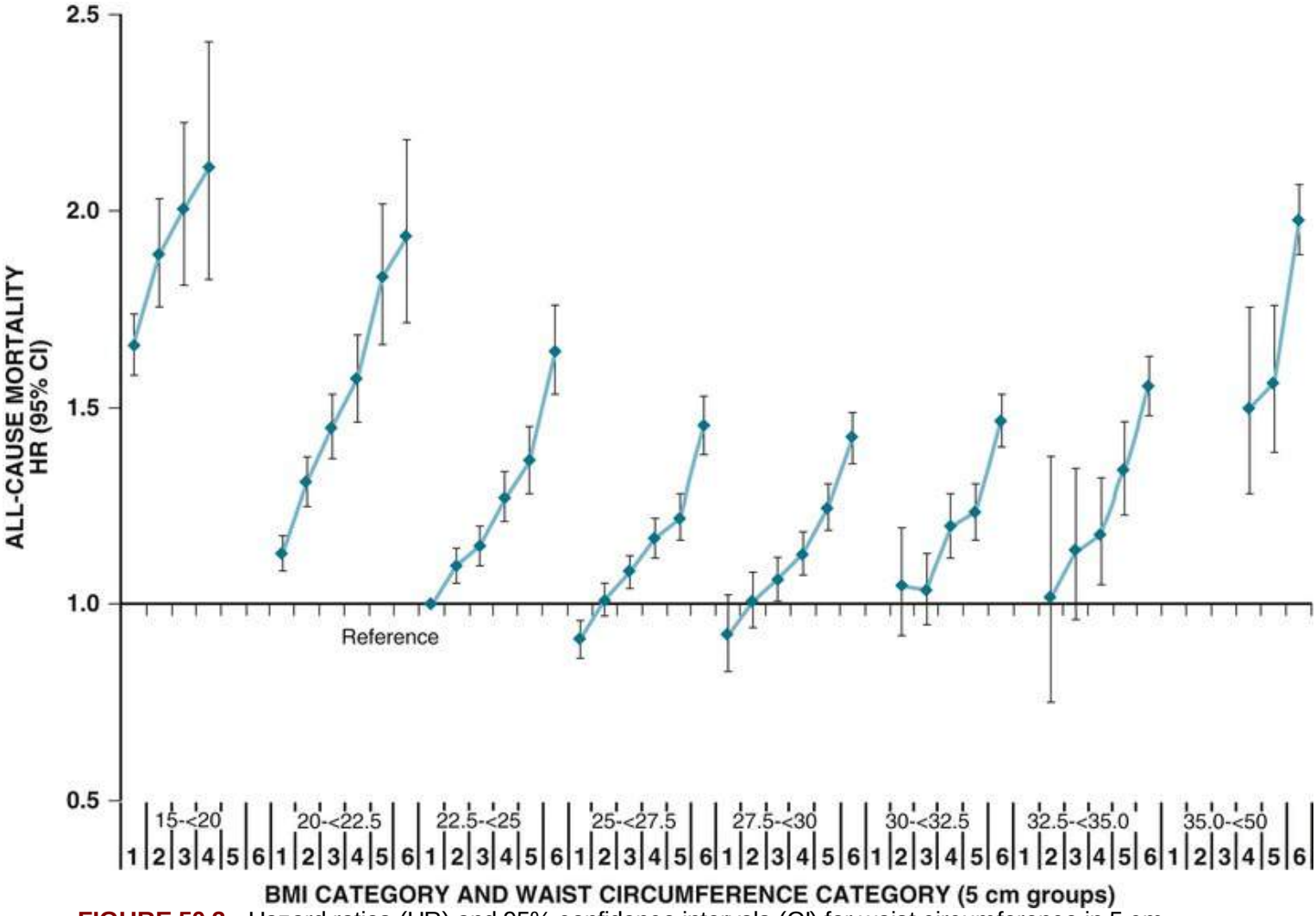


FIGURE 50.3 Hazard ratios (HR) and 95% confidence intervals (CI) for waist circumference in 5 cm increments* and all-cause mortality by body mass index (BMI) category (men and women combined), adjusted for education, marital status, smoking status, alcohol consumption, physical activity, and BMI. *Waist circumference cut points (cm) for men, <90.0, 90.0-94.9, 95.0-99.9, 100.0-104.9, 105.0-109.9, and 110.0+; and for women, <70.0, 70.0-74.9, 75.0-79.9, 80.0-84.9, 85.0-89.9, and 90.0+. (From Cerhan JR et al. A pooled analysis of waist circumference and mortality in 650,000 adults. Mayo Clin Proc 2014;89:335-45.)

TABLE 50.1

Health Risk Classification According to Body Mass Index (BMI) and Waist Circumference

OBESITY CLASS		BMI (KG/M^2)	DISEASE RISK* RELATIVE TO NORMAL WEIGHT AND WAIST CIRCUMFERENCE	
			Waist Circumference (cm)	
			Men ≤102 Women ≤88	Men >102 Women >88
Underweight		<18.5	Increased	Increased
Normal		18.5-24.9	Least	Increased
Overweight		25.0-29.9	Increased	High
Obesity	I	30.0-34.9	High	Very high
	II	35.0-39.9	Very high	Very high
Severe obesity	III	≥40	Extremely high	Extremely high

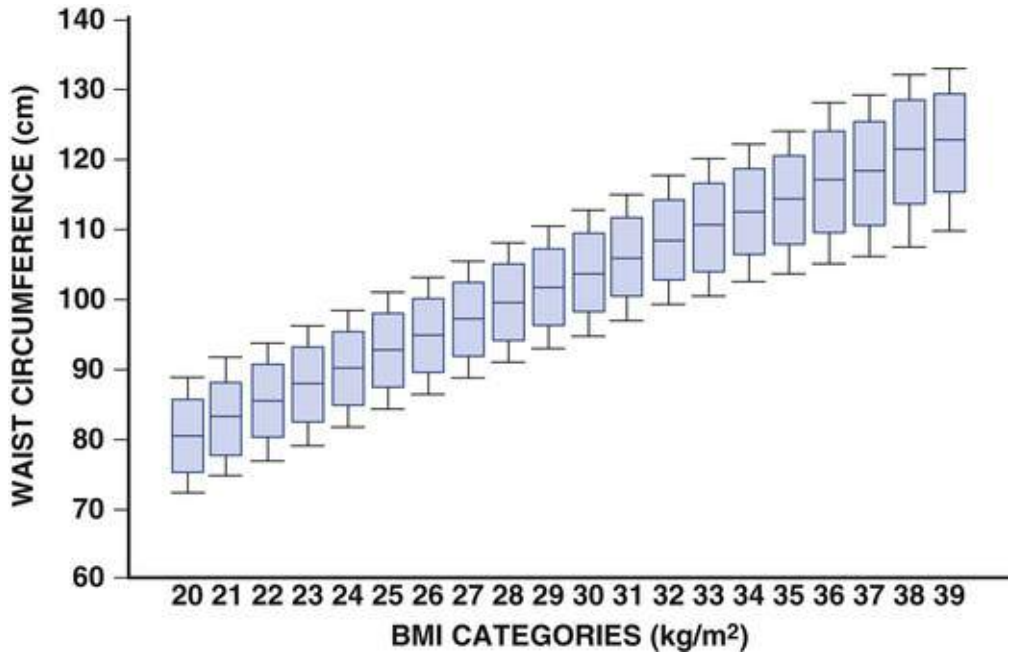
*Risk of type 2 diabetes, hypertension, cardiovascular disease, sleep apnea, and certain forms of cancer relative to normal BMI and a normal waist circumference.

Waist circumference and BMI cutoff values presented in the table are to be used in Europids/Caucasians only.

Individuals with BMI <18.5 kg/m^2 and ≥40 kg/m^2 are considered at, respectively, increased risk and extremely high risk, independent of their waist circumference value.

The International Chair on Cardiometabolic Risk has proposed that desirable waist circumference values should be <90 cm in men and <85 cm in women.

Modified from US National Institutes of Health, National Heart, Lung, and Blood Institute, in cooperation with National Institute of Diabetes and Digestive and Kidney Diseases. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. 1998. NIH Pub No 98-4083.



EFIGURE 50.3 Box-and-whisker plots showing the distribution of waist circumference values (age-adjusted) per unit of body mass index (BMI) in the subsample of 64,624 men of the IDEA study who had BMI values of 20 kg/m^2 or higher and less than 40 kg/m^2. Data shown are medians, quartiles, and 10th and 90th percentiles. (From Després JP. Excess visceral adipose tissue/ectopic fat: the missing link in the obesity paradox? J Am Coll Cardiol 2011;57:1887-9.)

Evolving Focus from Adipose Tissue Mass to Quality and Functionality

As mentioned, the regional distribution of body fat is much more important than adipose tissue mass.[9,10,14,25] For instance, excess accumulation of body fat in the lower part of the body (hips and thigh) is not associated with an increased risk of CVD or type 2 diabetes. Indeed, a large accumulation of lower body fat rather is associated with a reduced risk of developing these outcomes,[26] consistent with previous findings that hip and thigh fat is associated with a favorable CVD risk profile.[10] In contrast, excess abdominal fat, particularly *visceral adipose tissue*, confers risk as previously detailed.[9,10,14] Imaging also showed substantial individual differences in the size of these inner fat depots, particularly the amount of fat in the abdominal cavity, which includes omental fat, mesenteric fat, and retroperitoneal adipose tissue.[9,10,14,27]

Visceral Obesity

Marker of Ectopic Fat Deposition

The mechanisms underlying the independent association between excess visceral fat and cardiometabolic alterations remain an unsettled issue. Three non–mutually exclusive scenarios may pertain: (1) the portal free fatty acid (FFA) hypothesis, (2) the endocrine functions of visceral adipose tissue, and (3) excess visceral adipose tissue as a marker of dysfunctional subcutaneous adipose tissue.[9,10,14]

Portal Free Fatty Acid Hypothesis

In vitro studies of the metabolic properties of visceral adipose tissue—mainly the omental fat depot drained by the portal vein—have shown that these omental adipocytes exhibit a hyperlipolytic state poorly inhibited by insulin compared to subcutaneous adipose tissue.[10] Therefore the hypertrophied omental adipocytes in visceral adipose tissue deliver FFAs directly through the portal vein, leading to overproduction of triglyceride-rich lipoproteins, reduction of insulin extraction, and increased hepatic glucose production, hallmarks of obesity and type 2 diabetes. Despite its appeal, the finding that most circulatory FFAs originate from subcutaneous adipose tissue has challenged this hypothesis. Dog experiments indicated that excess visceral adiposity does elevate nocturnal FFA levels.[28]

Visceral Adipose Tissue as an Endocrine Organ

The visceral adipose depot preferentially expands through adipose cell hypertrophy, generating very large fat cells that are prone to rupture and have a different FFA composition than subcutaneous adipose tissue.[10] Macrophages accumulate especially in visceral adipose tissue, contributing to local inflammation and an expanding list of “adipokines” that could exacerbate the metabolic risk profile of the patient with excess visceral adiposity.[29,30] Also, activation of the sympathetic nervous system may particularly occur in visceral adipose tissue.[31]

Visceral Adipose Tissue: Marker of Dysfunctional Subcutaneous Adipose Tissue?

Excess visceral adipose tissue may also accumulate when subcutaneous adipose tissue fails to expand in an energy surplus[32] (**Fig. 50.4**). Subcutaneous adipose tissue normally expands first by adipocyte hypertrophy, followed by proliferation of surrounding preadipocytes (hyperplasia).[10,32] If the hyperplastic response is adequate, subcutaneous adipose tissue will expand and act as a “sink” for excess calories[10] and will maintain autonomic balance.[33]

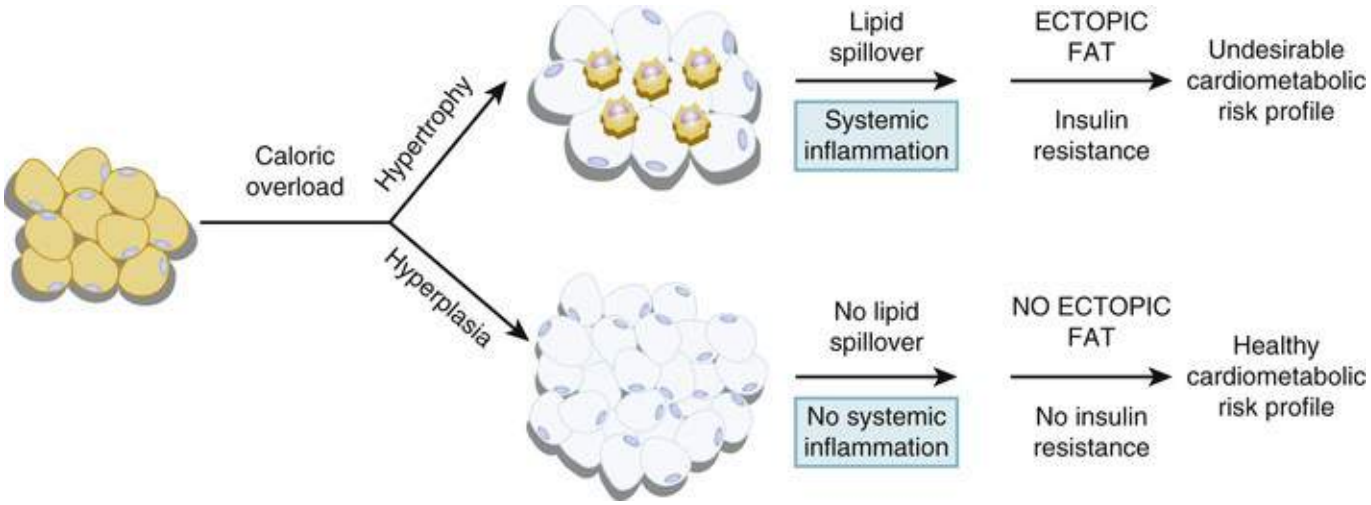


FIGURE 50.4 Simplified model to illustrate the concept that when facing a chronic energy surplus, inability of subcutaneous adipose tissue to expand through hyperplasia may lead to hypertrophic and "inflamed" adipose tissue. Resulting systemic inflammation and lipid spillover would lead to ectopic fat deposition, insulin resistance, and a deteriorated cardiometabolic risk profile. (From Després JP. Abdominal obesity and cardiovascular disease: is inflammation the missing link? Can J Cardiol 2012;28:642-52.)

Genetic forms of lipodystrophy illustrate the importance of properly functioning and expanding (when required) adipose tissue.[10] Individuals lacking subcutaneous fat develop an excess of visceral adipose tissue as well as fat accumulation in normally lean tissues. Large cohort imaging studies have revealed that viscerally obese individuals have an increased accumulation of fat in lean tissues such as the liver, heart, skeletal muscle, and kidney, a phenomenon described as "ectopic fat deposition."[9,10,14,34,35] Thus, excess visceral adipose tissue may be a marker or consequence of the relative inability of subcutaneous adipose tissue to act as a protective "metabolic sink" and thus reflects ectopic fat deposition (**Fig. 50.5**).

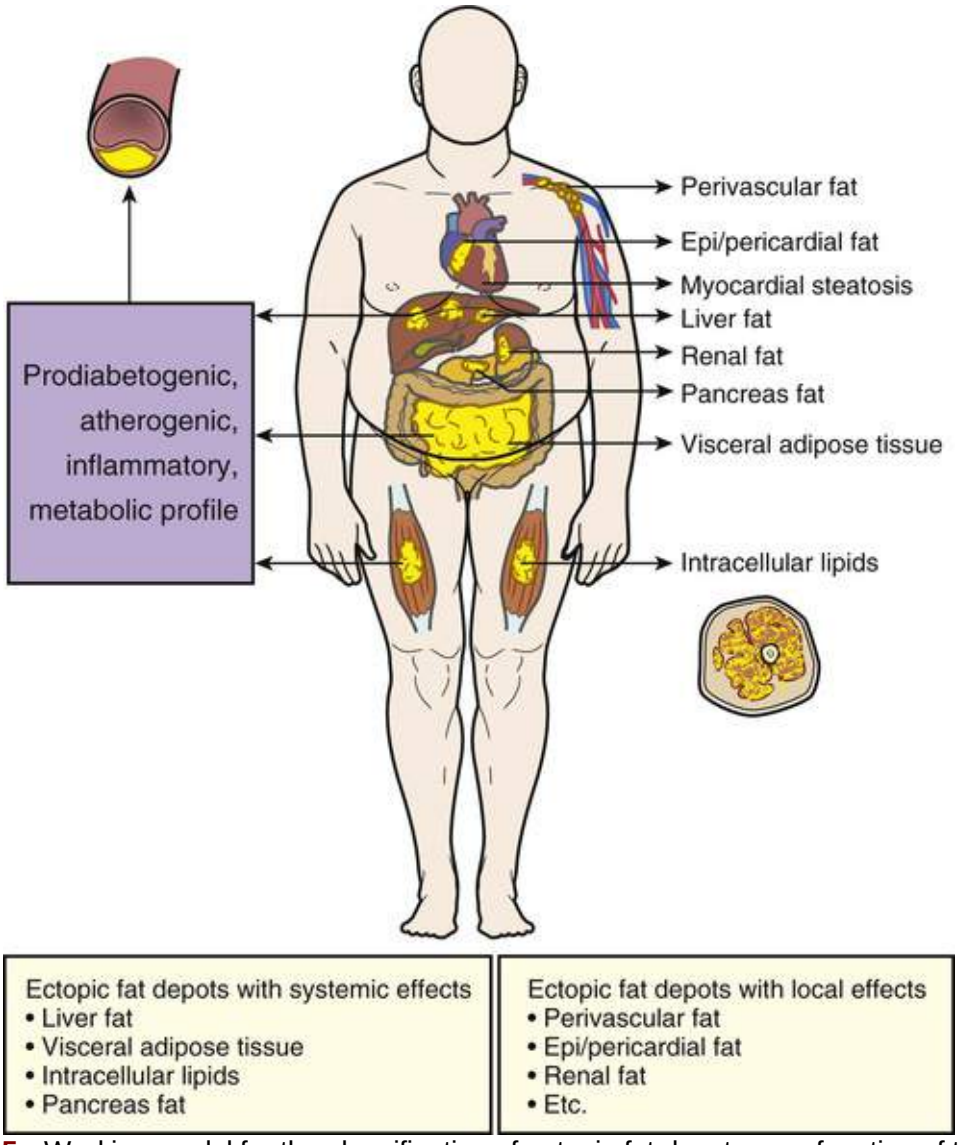


FIGURE 50.5 Working model for the classification of ectopic fat depots as a function of their putative systemic and local effects. (From Després JP. Body fat distribution and risk of cardiovascular disease: an update. Circulation 2012;126:1301-13.)

The extent to which each of these ectopic fat depots contributes to various cardiovascular outcomes is currently under investigation in several laboratories.[22,36-39] Considerable evidence suggest that excess liver fat is a key abnormality responsible for the several cardiometabolic complications found in viscerally obese individuals.[40,41] Similar data linking excess epi/pericardial fat with various clinical outcomes have also been reported.[36-38,42] On the other hand, the healthy cardiometabolic risk profile and low levels of visceral/ectopic fat observed in healthy premenopausal obese women with large hips and selective accumulation of lower body fat remain consistent with the protective role of healthy lower body subcutaneous adipose tissue.

Key Factors Associated with Visceral Obesity

The study of factors associated with the selective deposition of visceral/ectopic fat has generated considerable interest.[10]

Age and Sex

Age and sex show marked association with visceral adiposity. With age, visceral adipose tissue can accumulate and contribute to progressive cardiometabolic risk. Before menopause, women have on

average 50% less visceral adipose tissue than men.[10] At menopause, the relative decline in some key sex steroids contributes to a progressive and selective deposition of visceral adipose tissue.[10] Such sex difference in visceral adipose tissue contributes to sex-dependent cardiometabolic risk. After menopause, because of the acceleration in visceral adipose tissue deposition, women progressively catch up to men (over 10 to 15 years), as can their cardiometabolic risk profile.

Sex Hormones

The major sex difference in visceral adiposity and cardiometabolic risk profile has stimulated exploration of the link between regional body fat distribution and sex hormones. The most informative intervention study supporting a major role of sex steroids involved transsexual patients. Male-to-female transsexuals receiving sex hormone therapy show substantial changes in regional body fat accumulation, with loss of visceral/ectopic fat and increase in the size of lower body fat.[10] Female-to-male transsexuals show the reverse pattern, with related deterioration in their cardiometabolic risk profile.[10,43]

Genetics

Genes can regulate susceptibility to visceral obesity.[10] Offspring of viscerally obese parents often develop the same pattern when they reach their 30s and 40s, a finding that may reflect both heritability and shared environmental factors. When exposed to the same standardized energy excess for 100 days, monozygotic twin pairs tend to show the same pattern of accumulation of visceral and subcutaneous adipose tissue.[44] No major gene associated with this process has yet been identified, although numerous investigations worldwide continue to explore this topic.

Ethnicity

Ethnicity is also associated with variations in visceral adiposity and ectopic fat.[45] Large imaging cardiometabolic studies have shown susceptibility to visceral adiposity/ectopic fat greatest in Asians, then Caucasians, and then African Americans.[10,46,47] Indeed, Asians develop diabetes because of excess visceral/ectopic fat at lower BMI values than whites or blacks.[48,49]

Hypothalamic-Pituitary-Adrenal Axis and Endocannabinoid System

The hypothalamic-pituitary-adrenal (HPA) axis and the endocannabinoid (EC) system can also modulate visceral adiposity/ectopic fat. Maladaptive responses to stress are associated with chronic exposure of various tissues, including adipose tissue, to glucocorticoids, which can contribute to visceral and liver fat accumulation.[10] Adipose tissue contains EC receptors, and overactivation of the EC system may occur in visceral obesity, leading to altered metabolism of visceral adipocytes.[50] Lifestyle changes inducing weight loss can mitigate such overactivity of the EC system.[51] Drugs developed to reduce the activity of the EC system had shown promising results in inducing selective losses of visceral adipose tissue and liver fat, but their unwanted effects compromised their clinical use.[52]

Drugs

Clinicians should consider whether medications might contribute to a patient's excess weight and body fat.[53] **Table 50.2** lists some key drugs that induce weight gain.[54]

TABLE 50.2

Drugs That May Lead to Weight Gain

CATEGORY	DRUGS
Antidiabetics	Insulin, sulfonylureas (many), meglitinides (nateglinide, repaglinide), glitazones (pioglitazone, rosiglitazone)
Antidepressants or mood stabilizers	Monoamine oxidase inhibitors (many), tricyclics (some; e.g., doxepin), serotonin reuptake inhibitors (some; e.g., paroxetine), mirtazapine, lithium
Antipsychotics	Clozapine, risperidone, olanzapine, quetiapine, haloperidol, perphenazine
Anticonvulsants	Carbamazepine, gabapentin, valproate
Antihistamines	Cycloheptadine, diphenhydramine, doxepin
Adrenergic blockers	Propranolol, doxazosin
Adrenal steroids	Corticosteroids

From Bray GA et al. Management of obesity. Lancet 2016;387:1947-56.

Lifestyle: Key Contributor to Visceral Obesity

Once identified, the overweight or obese patient with excess visceral/ectopic fat and increased CVD risk may benefit from pharmacotherapy, including antihypertensive and lipid-lowering agents, to improve risk factors, in accord with guidelines and the results of clinical trials.[55-58] Because excess body weight and obesity result largely from lifestyle, however, even for those with a genetic susceptibility, the clinician should also evaluate factors such as nutritional quality and level of physical activity.[59] Tools available for use in clinical practice have helped identify sedentary individuals and those with poor nutritional habits who could benefit substantially from improving lifestyle habits.[59,60] Our own lifestyle intervention studies have shown the value of targeting nutritional quality and sedentary behaviors to reduce waist circumference and improve cardiorespiratory fitness as well as CVD risk factors, irrespective of concomitant pharmacotherapy targeting intermediate CVD risk factors.[59,61] Patients in the waiting room may complete simple standardized questionnaires regarding diet and physical inactivity/activity. Food-based recommendations (less of some specific food categories and more of other, less-processed foods of high nutritional value and low energy density) combined with a written “lifestyle prescription” to reduce sedentary/sitting time and to introduce regular physical activity could contribute to substantially improve a patient's health profile.[59,62]

Clinical Tools to Identify Patients

Simple anthropometric tools can help to identify overweight and obese individuals with an excess of visceral adipose tissue/ectopic fat in clinical practice. As previously discussed, the simultaneous presence of an increased waistline for a given BMI and altered CVD risk factors should alert the clinician to the presence of excess visceral adiposity/ectopic fat. However, a large waistline alone cannot distinguish excess subcutaneous from visceral adiposity. Another simple clinical marker, plasma triglyceride levels, suggests the presence of excess visceral adipose tissue, a phenotype that we defined as “hypertriglyceridemic waist.”[63] For instance, the simultaneous presence of an increased waistline (≥90 cm in men, ≥85 cm in women) and high triglyceride levels (≥2.0 mmol/L in men, ≥1.5 mmol/L in women) predicted a 75% to 80% probability that a given individual had an excess of visceral adipose tissue and an altered cardiometabolic risk profile, a finding showing the importance of paying attention to these two markers..[63-65]

Clinical Management

Key Nutritional Factors (Toward a Food-Based Approach)

Although excess visceral adiposity and ectopic fat has a genetic basis, diet clearly plays a pivotal role. A diet rich in added sugar, refined carbohydrates, and saturated fat may favor the selective accumulation of visceral adipose tissue through as-yet poorly understood mechanisms.[66-69] Some simple precepts can guide clinician conversations with patients about dietary choices (**Table 50.3**). Recent guidelines and authoritative reviews have highlighted the potential of such an approach that is clearly more "user friendly" to patients than technical recommendations about diet macronutrient and fatty acid composition.[62,70,71] For example, the public health recommendation to decrease *saturated fat* in our diet, while still relevant, has unfortunately drifted to a reduction in *diet fat* content, which boosted the intake of refined carbohydrates and of refined products with a considerable amount of added sugar. Thus the low dietary fat message likely contributed to the current epidemic of obesity and type 2 diabetes.[62,72] Accordingly, lifestyle intervention trials focusing on reducing the fat content of the diet[73] and on caloric restriction and weight loss[19] have not improved cardiovascular outcomes. On the other hand, a trial that used a simple approach in overweight and obese patients (50% with diabetes), giving participants olive oil and mixed, nuts (PREDIMED), reported a significant reduction in cardiovascular outcomes, particularly the incidence of stroke.[74] The dietary intervention did not cause weight loss.[75] These results illustrate how overall nutritional quality, rather than caloric restriction and fat content of the diet, can improve cardiovascular outcomes.[75] (**See also Chapter 49**.)

TABLE 50.3

International Chair on Cardiometabolic Risk "Eat Well, Drink Well, Move" Recommendations for Adults

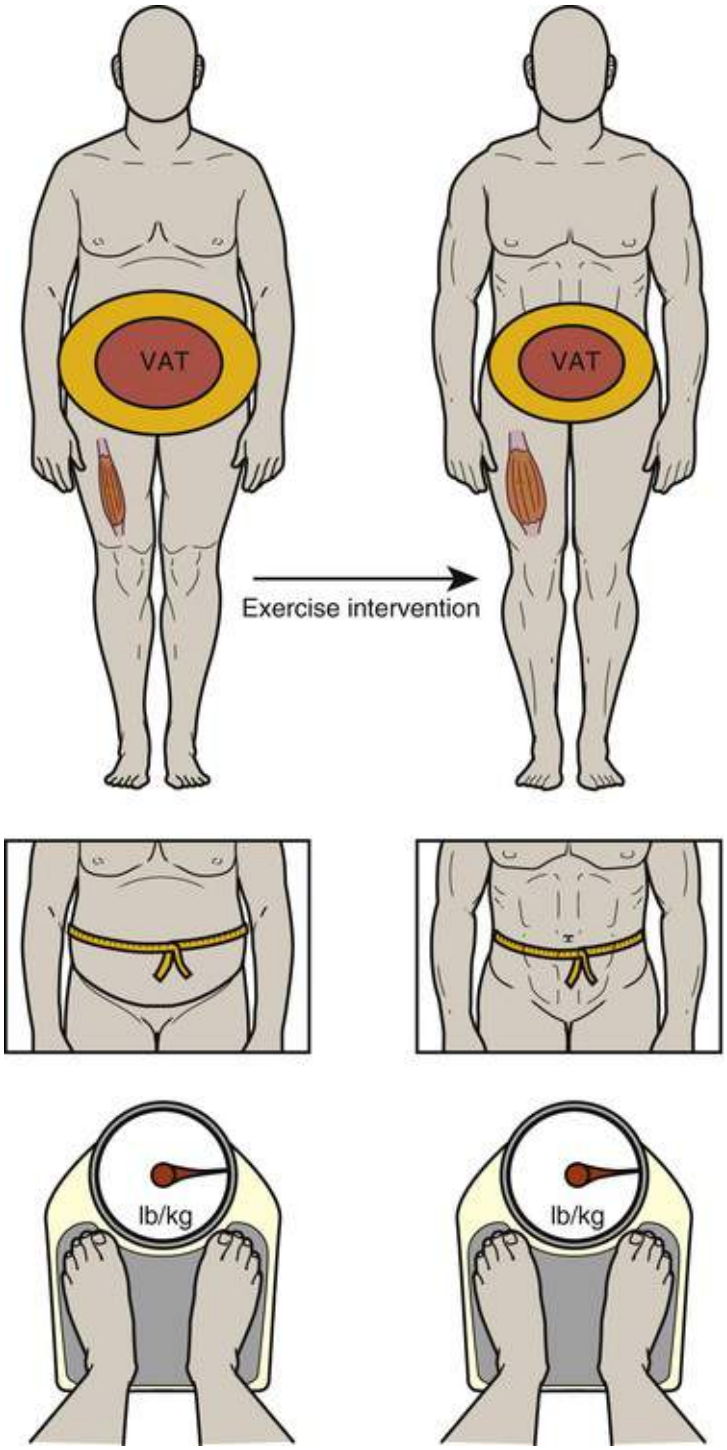
Eat Well*
• Olive and vegetable oils, nuts, seeds, legumes, grains (mostly whole), fruits, vegetables *Base every meals on these foods* • Eggs, poultry, cheese, yogurt, other dairy *Daily to weekly* • Fish, seafood *Often, at least two times per week* • Processed meat, red meat, sweets *Less often*
Drink Well†
• Water *On several occasions daily* • Tea or coffee *Daily* • Low-fat milk and soya-based beverages *Daily to weekly* • Diet drinks and 100% fruit juices *Occasionally* • Sugar-sweetened beverages *Sparingly*
Move
• Move as much as you can. • Do at least 150 minutes of moderate-intensity aerobic physical activity weekly or 75 minutes of vigorous-intensity aerobic physical activity weekly or a mix of both. • Do muscle-strengthening activities 2 or more days a week. • Limit screen time and sitting time.

*Drink water to hydrate yourself. Drink wine in moderation. This healthy diet pattern is good for humans and for the planet.

†Sugar-sweetened beverages (SSBs) refer to any beverages with added sugar and include, but are not limited to, regular soda, sugar-sweetened fruit drinks such as fruit punch and lemonade, and sports or energy drinks. The 100% fruit juices contain natural fruit sugars. Tea and coffee should be consumed preferably unsweetened.

Physical Activity and Exercise

Physical inactivity and sedentary behaviors (for which sitting and screen time are good markers) predict increased risk of developing chronic diseases, including cardiovascular conditions.[59,76] This association does not depend solely on adiposity. Moderate- to vigorous-intensity physical activity or exercise increases cardiorespiratory fitness, one of the key predictors of the risk of developing CVD, independent of adiposity.[77] Therefore, practitioners should include assessment of physical inactivity/activity level in their patient evaluations. Advice regarding physical activity along with nutritional counseling can reduce visceral adiposity while improving all features of the cardiometabolic risk profile.[59,78-80] Furthermore, because physical activity and exercise can increase lean body mass, body weight may not always reflect beneficial changes in body composition, and thus an increase in lean body mass can balance the loss of harmful visceral/ectopic fat, an outcome particularly beneficial for the elderly frail patient (**eFig. 50.4**). Weight loss should not be the sole target for CVD risk reduction in the management of overweight and obese patients.[60,81]



EFIGURE 50.4 Effects of exercise intervention on body weight, waist circumference, and visceral adipose tissue (VAT) in a sedentary, viscerally obese individual. Even in the absence of weight loss resulting from an increase in muscle mass, exercise is associated with a reduction in waist circumference and VAT in a sedentary individual.

Sleep and Stress Management

Sleep duration and quality can also influence energy balance and metabolism.[82] The most obvious group of patients with disturbed sleeping habits are those with *sleep apnea,* a condition frequently observed among sedentary overweight and obese patients, particularly those with an excess of visceral/ectopic fat.[83] The viscerally obese patient with sleep apnea or with episodes of apnea/hypopnea may enter a vicious cycle in which the fatigue associated with the poor quality of sleep may lead to additional inactivity, exacerbating their already disturbed cardiometabolic risk profile. Several mechanisms may link visceral adiposity/ectopic fat to sleep apnea, including physical obstruction of the upper airways by

soft tissues infiltrated with fat.[84] Treatment of sleep apnea by positive-pressure devices may help progressively improve sleep quality of the viscerally obese patient and help break this cycle. Lifestyle intervention studies have also shown that weight loss in sleep apnea patients substantially improves their cardiometabolic risk profile.[82] In addition, because stress contributes to the selective accumulation of visceral/ectopic fat,[10] stress management strategies may constitute another measure to improve the lifestyle of these high-risk patients. (**See also Chapter 87**.)

Pharmacotherapy

Pharmacologic tools to treat high-risk overweight and obese patients are limited by a lack of evidence for efficacy or long-term benefit.[54] Drugs currently approved for the chronic management of obesity have not yet demonstrated improved cardiovascular outcomes or efficacy in reducing visceral adipose tissue or ectopic fat[54] (**Table 50.4**).

TABLE 50.4

Weight Loss Drugs Available in the United States* and European Union†

DRUGS	MECHANISM OF ACTION
Phentermine* (15-30 mg orally)	Sympathomimetic
Orlistat*† (120 mg orally three times a day before meals)	Pancreatic lipase inhibitor
Lorcaserin* (10 mg orally twice a day)	5-HT_{2C} serotonin agonist with little affinity for other serotonergic receptors
Phentermine/Topiramate ER* (7.5 mg/46 mg or 15 mg/92 mg orally indicated as rescue; requires titration)	Sympathomimetic anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)
Naltrexone SR/bupropion SR*† (32 mg/360 mg orally; requires titration)	Opioid receptor antagonist; dopamine and noradrenaline reuptake inhibitor
Liraglutide*† (3.0 mg injection; requires titration)	GLP-1 receptor agonist

ER, Extended release; *SR,* sustained release; *GLP,* glucagon-like peptide.

From Bray GA et al. Management of obesity. Lancet 2016;387:1947-56.

Recently, trials of diabetes drugs with mechanisms that also impact energy balance and induce weight loss have shown, for the first time, a significant influence on reducing adverse cardiovascular outcomes[17,18] (**see Chapter 51**). Imaging studies could test to what extent the loss of visceral/ectopic fat that may be associated with these drugs could contribute to the observed reduction in CVD risk.

Severe Obesity and Bariatric Surgery

Between 1986 and 2000, individuals with a BMI ≥30, ≥40, and ≥50 kg/m^2 have doubled, quadrupled, and quintupled, respectively, in the United States.[85] In Canada the prevalence of severe obesity, defined as a BMI of ≥40 or ≥35 kg/m^2 with comorbidities, rose by 533% between 1985 and 2011.[86] Severe obesity is associated with increased morbidity and all-cause mortality and represents a major health care problem.[87] Caucasian women 20 to 30 years old with BMI ≥45 kg/m^2 will lose 8 years of life, and their male counterparts will lose 13 years.[8] The three principal treatments for severe obesity are changes in lifestyle habits, pharmacotherapy, and bariatric surgery. Bariatric surgery can be either *restrictive* or *hybrid*, a combination of restriction and malabsorption[88] (**Fig. 50.6**). From an evidence-based perspective, of these three options, only bariatric surgery yields substantial long-term weight loss and durably improves cardiometabolic risk in the severely obese patient (**Table 50.5**).

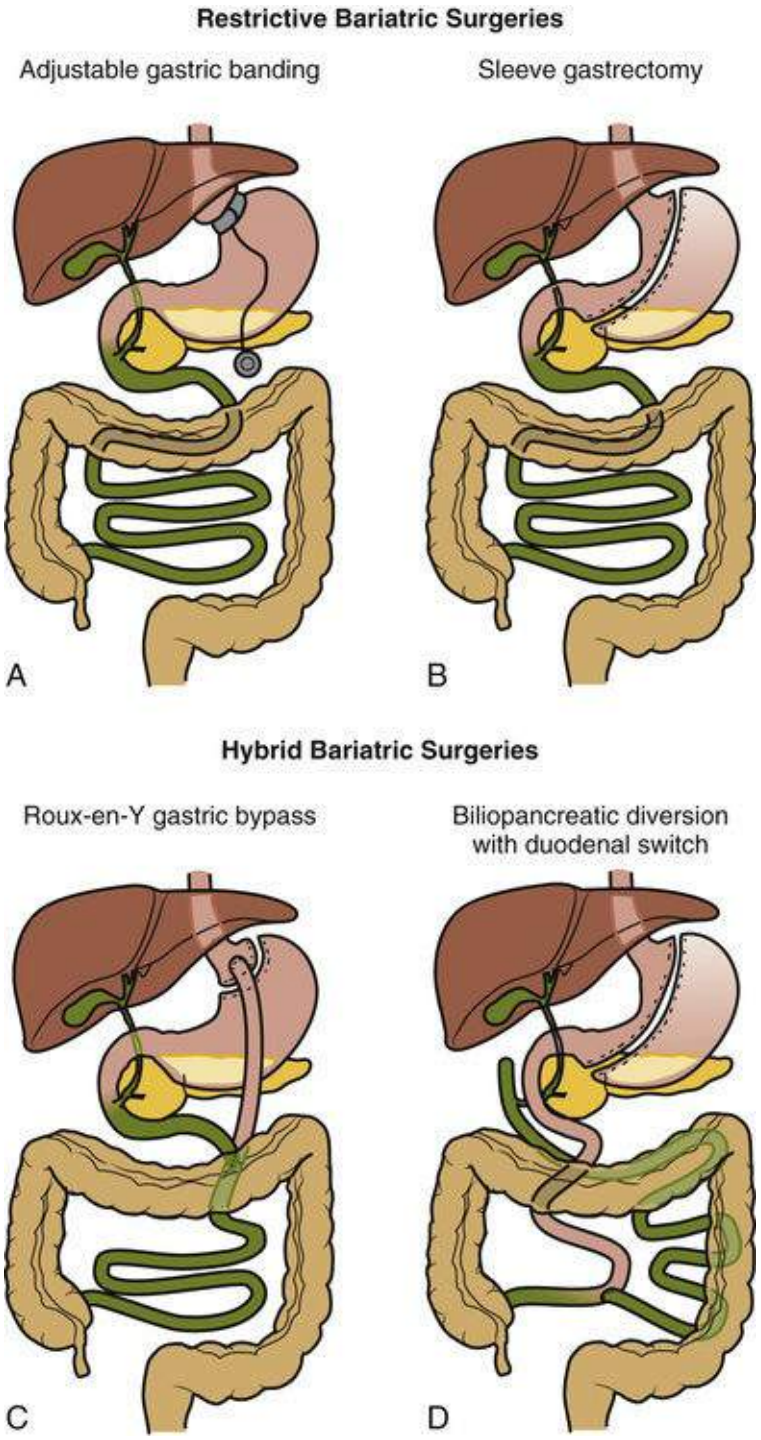


FIGURE 50.6 Restrictive (**A** and **B**) and hybrid (**C** and **D**) bariatric surgeries. *Dark pink,* Alimentary limb, food passage. *Light green,* Biliopancreatic limb, digestive juices from the stomach, bile, and pancreas. *Dark green,* Common limb, food mixed with digestive juices from the stomach, bile, and pancreas.

TABLE 50.5

Outcomes of Bariatric Surgery

	RESTRICTIVE PROCEDURES		HYBRID PROCEDURES	
	Adjustable Gastric Banding	**Sleeve Gastrectomy**	**Roux-en-Y Gastric Bypass**	**Biliopancreatic Diversion With Duodenal Switch**
Mortality Rates				
<30-day	0-0.10%	0.13-0.50%	0.15-1.15%	0.30-1.20%
Complications	0.2% to 20.0% (all procedures)			
Weight Loss				
1 year	14-30%	20-28%	23-43%	38-52%
2-5 years	17-35%	21%	30-42%	34-53%
≥6 years	13-14%	22%	25-28%	36-55%
Comorbidities Resolution				
Type 2 Diabetes				
1 year	23-61%	37-81%	17-93%	59-95%
2-5 years	20-74%	14-86%	50-84%	90-100%
Dyslipidemia				
1 year	17%	16-83%	33-47%	33-65%
2-5 years	23-61%	5-48%	52-97%	70-100%
Hypertension				
1 year	19-55%	15-82%	20-45%	24-53%
2-5 years	17-64%	25-75%	29-80%	57-85%
Sleep Apnea				
1 year	78%	52-100%	33-100%	100%
2-5 years	33-96%	39-91%	67-80%	74-92%

From Piché MA et al. How to choose and use bariatric surgery in 2015. Can J Cardiol 2015;31:153-66.

Bariatric surgery improves CVD risk factors and reduces the incidence of type 2 diabetes, cancer, and overall mortality.[89,90] The Swedish Obese Subjects study showed that bariatric surgery reduced cardiovascular events by 30% and cardiovascular deaths by 50% in almost 15 years of follow-up in severely obese patients, compared with those who received usual care.[90]

In obese patients with type 2 diabetes, bariatric surgery provides clinical benefits such as improved glycemic control and cardiometabolic risk profile.[91,92] Debate surrounds whether less severely obese patients should undergo surgical intervention.[93]

Surgical techniques differ in terms of morbidity and mortality, magnitude of weight loss, weight loss maintenance, and rate of resolution of comorbidities over time.[7,88] Hybrid procedures appear most effective in terms of the amount of weight loss and the improvement in comorbidities.[8,91,92] Early complications (<30 days) after bariatric surgery are less than 10% and tend to be lower in restrictive surgeries than hybrid surgeries, and 30-day operative mortality rates range from 0.1 to 1.2%.[88] Severe obesity disturbs cardiac structure and function as a result of left ventricular (LV) remodeling and LV systolic and diastolic dysfunction.[88] Increased pulmonary vascular resistance and pulmonary artery pressure resulting in an increase in right ventricular (RV) afterload may also occur in patients with severe obesity, causing RV hypertrophy, enlargement, and dysfunction.[94,95] Bariatric surgery can improve cardiac geometry as well as diastolic and systolic function of both ventricles.[89,96]

In the 1991 consensus the U.S. National Institutes of Health reported that bariatric surgical therapy should be proposed to those patients with a BMI >40 or >35 kg/m^2 with serious obesity-related comorbidities such as systemic hypertension, type 2 diabetes, and obstructive sleep apnea (OSA).[97] Currently, several guidelines provide eligibility criteria for bariatric surgery. The American Diabetes Association,[98] International Diabetes Federation,[99] and other organizations[2,93] have issued consensus statements identifying bariatric surgery as the only proven effective option for sustainable weight loss and weight control inducing beneficial clinical outcomes in patients with severe obesity. They have proposed bariatric surgery therapy for adult patients with BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 with obesity-related comorbidities (e.g., hypertension, diabetes, OSA) that are difficult to control with lifestyle and

pharmacotherapy. No guideline suggests that one procedure is more appropriate than the others for cardiac patients.

Summary and Perspectives

It is important to assess and manage high-risk overweight and obese patients in cardiovascular practice. Because of the increasing worldwide prevalence of overweight/obesity, cardiovascular specialists manage many overweight and obese patients, a number of whom also have excessive visceral adipose tissue/ectopic fat. Several simple metrics can alert practitioners to this metabolically dangerous condition, notably an elevated waistline (for a given BMI) and increased triglycerides. In addition, the clinician's evaluation should include simple lifestyle markers such as duration and quality of sleep, overall food-based nutritional quality, sedentary/sitting time, level of moderate/vigorous physical activity, and cardiorespiratory fitness, as well as medications that promote weight gain.

Many current curricula provide only limited exposure of physicians and trainees to the importance of and tools for assessing and targeting lifestyle in overweight and obese patients. Physicians should never underestimate the potential impact on their patients' lifestyle as role models. A patient could be greatly influenced by a physician who would pay equal attention to his/her waistline, nutritional quality, physical activity level, and quality of sleep as to his/her cholesterol, BP and blood glucose.[100] Finally, we must recognize that the epidemic proportions reached by obesity and type 2 diabetes reflect societal conditions that extend beyond the traditional medical model. As key stakeholders, physicians can advocate for environments that promote human health rather than disease.[101]

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51

Diabetes and the Cardiovascular System

Darren K. Mcguire, Silvio E. Inzucchi, Nikolaus Marx

Scope of the Problem

Diabetes Mellitus

Diabetes mellitus involves insufficient production of insulin, failure to respond appropriately to insulin, or both, resulting in hyperglycemia. **Table 51.1** summarizes the current diagnostic criteria.[1] Insulin resistance and relative insulin deficiency characterizes type 2 diabetes (>90% of all diabetes cases),

whereas absolute insulin deficiency characterizes type 1 diabetes. In view of the excess and increasing prevalence of type 2 diabetes and its incremental cardiovascular (CV) risk compared with type 1 diabetes, this chapter focuses on type 2 diabetes, except when specifically indicated otherwise.

TABLE 51.1

American Diabetes Association Diagnostic Criteria for Diabetes Mellitus*

1. Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours. *or*
2. Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. *or*
3. Glycated hemoglobin (A_{1c}) ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay. *or*
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*Criteria 1 to 3 require confirmatory testing; criterion 4 does not.

Modified from American Diabetes Association: Diagnosis and classification of diabetes mellitus. Diabetes Care 2016;39(Suppl 1):S13-22.

Diabetes, one of the most common chronic diseases in the world, affects an estimated 285 million adults in 2010.[2] The mounting incidence and prevalence of type 2 diabetes, driven by increasing population age, obesity, and physical inactivity, compound this high global burden (**see Chapters 1, 45, and 50**), as does the increasing longevity of patients with the disease. It is estimated that diabetes will affect more than 430 million persons, 7.7% of the global adult population, by 2030[2] (**Fig. 51.1**).

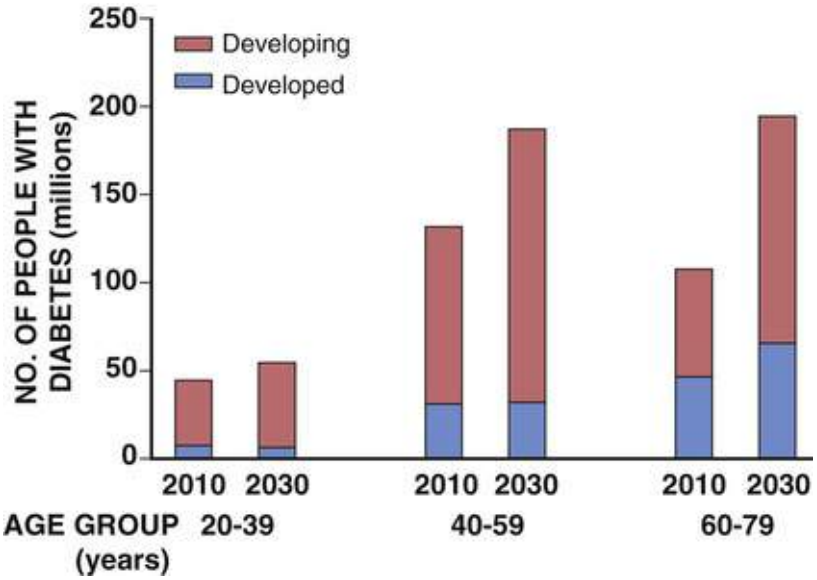

FIGURE 51.1 Estimated number of adults with diabetes in 2010 and projected for 2030 stratified by age group, with projections for the overall global population, and by developed and developing country categories. (From Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010;87:4, 2010.)

Cardiovascular disease (CVD) remains the principal comorbid condition and primary contributor to mortality in the patient with diabetes, usually in the form of coronary heart disease (CHD), but also in the incremental risk associated with diabetes for cerebrovascular disease, peripheral vascular disease, heart failure (HF), and atrial fibrillation (AF). For these reasons, continuing effort toward mitigating the risk of CVD in diabetes remains a global public health imperative.

Atherosclerotic Vascular Disease

Patients with diabetes have a twofold to fourfold increased risk for CHD, CV mortality, and all-cause mortality compared to those without diabetes[3] (**Fig. 51.2**). Although older studies suggested a diabetes-associated CVD risk similar to that for nondiabetic patients with a prior myocardial infarction (MI), more recent observations from trials of patients with diabetes demonstrate substantially lower risk, most likely reflecting effectiveness of contemporary therapeutic interventions.[4] Still, CV risk and mortality in patients with diabetes remain significantly increased over those without diabetes, underscoring the substantial remaining residual CVD risk of diabetes and its unmet clinical need[5] (**Fig. 51.3**).

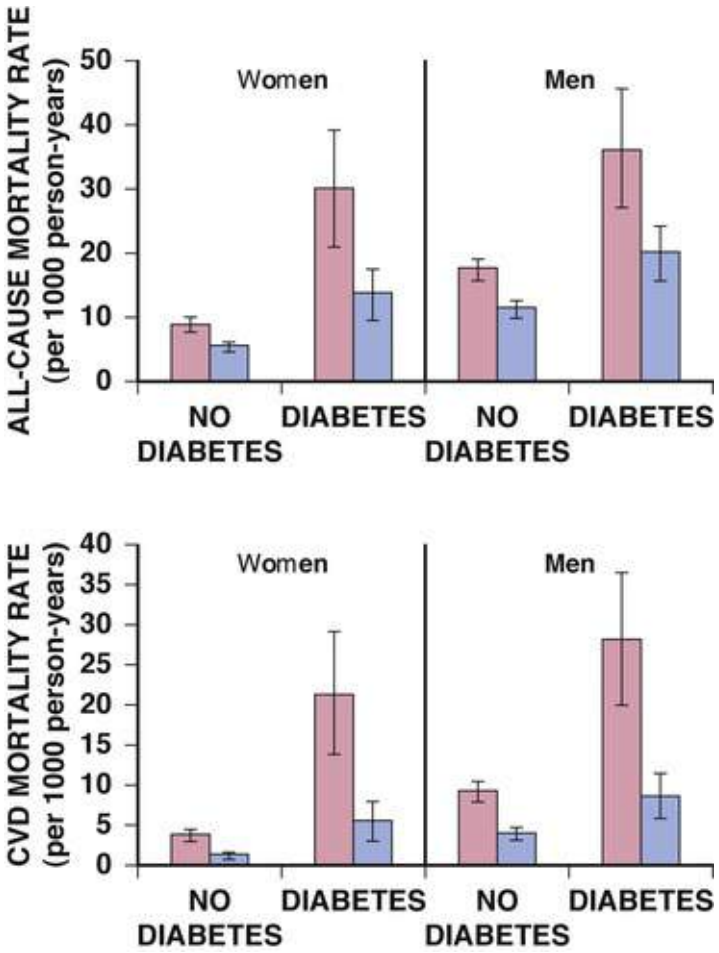

FIGURE 51.2 Age-adjusted all-cause **(top)** and cardiovascular disease (CVD) **(bottom)** mortality rates among Framingham Heart Study participants with and without diabetes mellitus by sex and time period. *Pink bars* represent earlier time period (1950 to 1975); *blue bars* represent later time period (1976 to 2001). Bars indicate 95% confidence intervals. Rates are adjusted for age in 10-year intervals. (From Preis SR, Hwang SJ, Coady S, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. Circulation 2009;119:1728.)

Disease status at baseline	No. of participants	No. of deaths	Person-years	Mortality rate (95% CI)[a]	Hazard ratio (95% CI)	I^2 (95% CI)
Diabetes, stroke, and MI	541	379	3584	59.5 (47.0–71.9)	6.9 (5.7–8.3)	51 (38–62)
Stroke and MI	1836	1174	14,210	32.8 (28.1–37.6)	3.5 (3.1–4.0)	61 (52–69)
Diabetes and stroke	1321	778	10,234	32.5 (27.0–37.9)	3.8 (3.5–4.2)	18 (0–38)
Diabetes and MI	3233	1794	25,321	32.0 (28.1–35.9)	3.7 (3.3–4.1)	69 (62–75)
MI	21,591	9636	216,081	16.8 (15.2–18.3)	2.0 (1.9–2.2)	84 (80–86)
Stroke	8583	3814	82,208	16.1 (14.4–17.8)	2.1 (2.0–2.2)	50 (36–61)
Diabetes	24,677	8087	254,608	15.6 (14.1–17.0)	1.9 (1.8–2.0)	76 (70–80)
None	627,518	103,181	8,772,977	6.8 (6.2–7.4)	1 [Reference]	

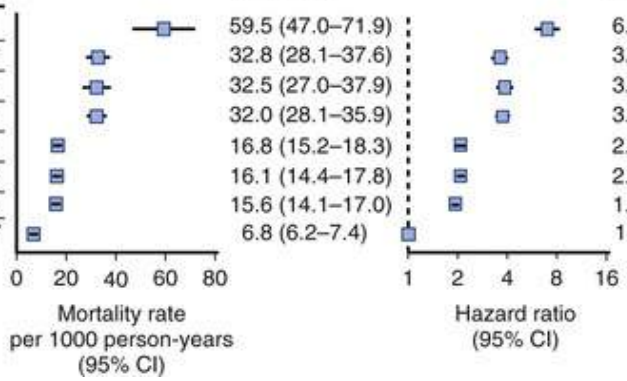

FIGURE 51.3 All-cause mortality by disease status of participants at baseline for the Emerging Risk Factors Collaboration. The mortality rates were calculated using a Poisson regression model and are sex-adjusted rates to age 60 years. The hazard ratios were calculated using a Cox proportional hazards regression model and are stratified by sex and adjusted by age at baseline. Analyses were based on participants from 91 studies. MI, Myocardial infarction. [a]Mortality rate is per 1000 person-years. (From Di Angelantonio E, Kaptoge S, Wormser D, et al; Emerging Risk Factors Collaboration. Association of cardiometabolic multimorbidity with mortality. JAMA 2015;314:52-60.)

Diabetes is associated with an increased risk for MI. Across the spectrum of acute coronary syndrome (ACS) events, in which diabetes may affect more than one in three patients, those with diabetes have worse CVD outcomes after ACS events[6] (**see Chapters 58 to 60**). Despite overall improvements in outcomes during the past several decades for ACS patients with and without diabetes, the gradient of risk associated with diabetes persists (**Fig. 51.4**), although incremental in-hospital mortality risk associated with diabetes after an ACS event has declined (**Fig. 51.5**).[6] Furthermore, the graded association of increased risk observed with diabetes in the setting of ACS extends to glucose values in the range well below the diabetes threshold (**Fig. 51.6**).

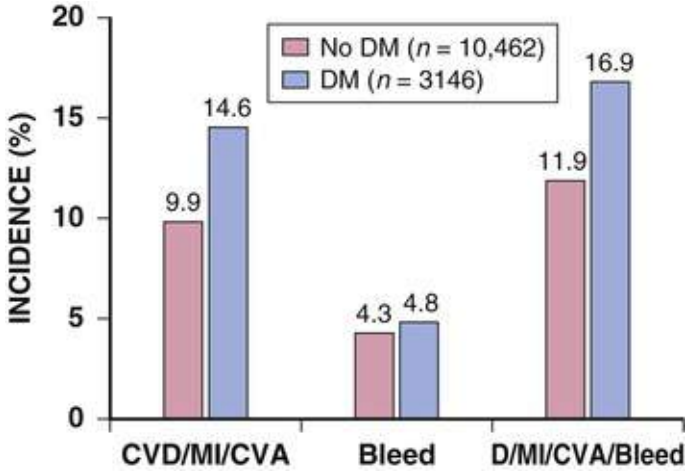

FIGURE 51.4 Adverse clinical outcomes after acute coronary syndromes during more than 1 year of follow-up, according to diabetes status, among patients participating in the TRITON–TIMI 38 randomized trial. CVA, Cerebrovascular accident (stroke); CVD, cardiovascular death; D, death; DM, diabetes mellitus; *MI,* myocardial infarction. (Modified from Wiviott SD, Braunwald E, Angiolillo DJ, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38. Circulation 2008;118:1626.)

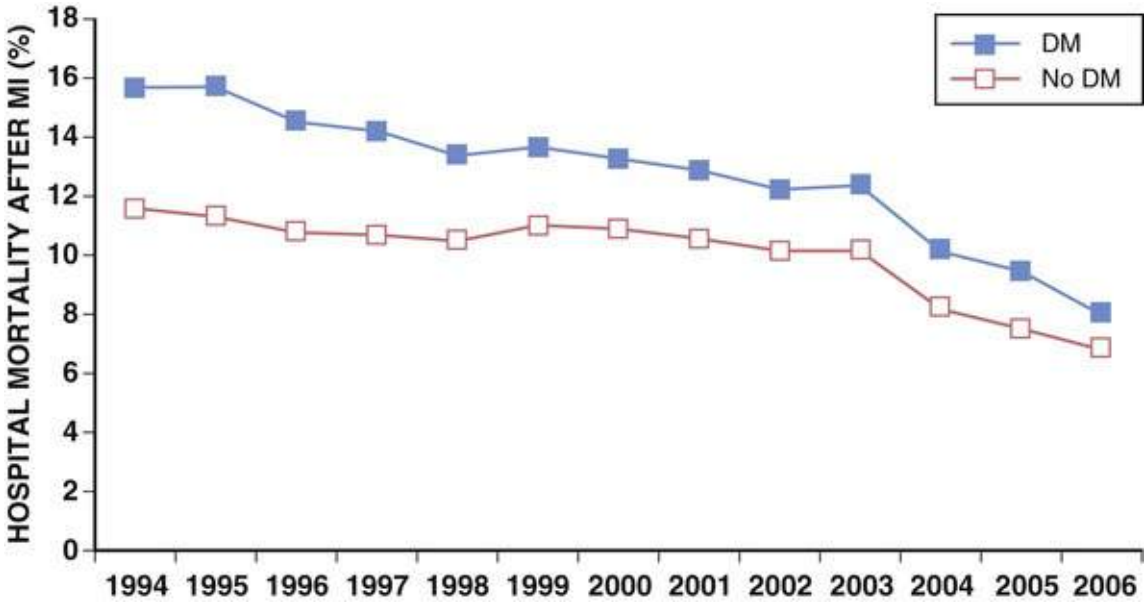

FIGURE 51.5 Unadjusted hospital mortality after myocardial infarction (MI) by year of study enrollment according to diabetes mellitus (DM) status (in-hospital deaths as percentage of total number of patients enrolled during each year of the study) among 1,734,431 patients with acute MI registered in the National Registry of Myocardial Infarction (NRMI), 1994 to 2006. (From Gore MO, Patel MJ, Kosiborod M, et al. Diabetes mellitus and trends in hospital survival after myocardial infarction, 1994 to 2006: data from the National Registry of Myocardial Infarction. Circ Cardiovasc Qual Outcomes 2012;5:791.)

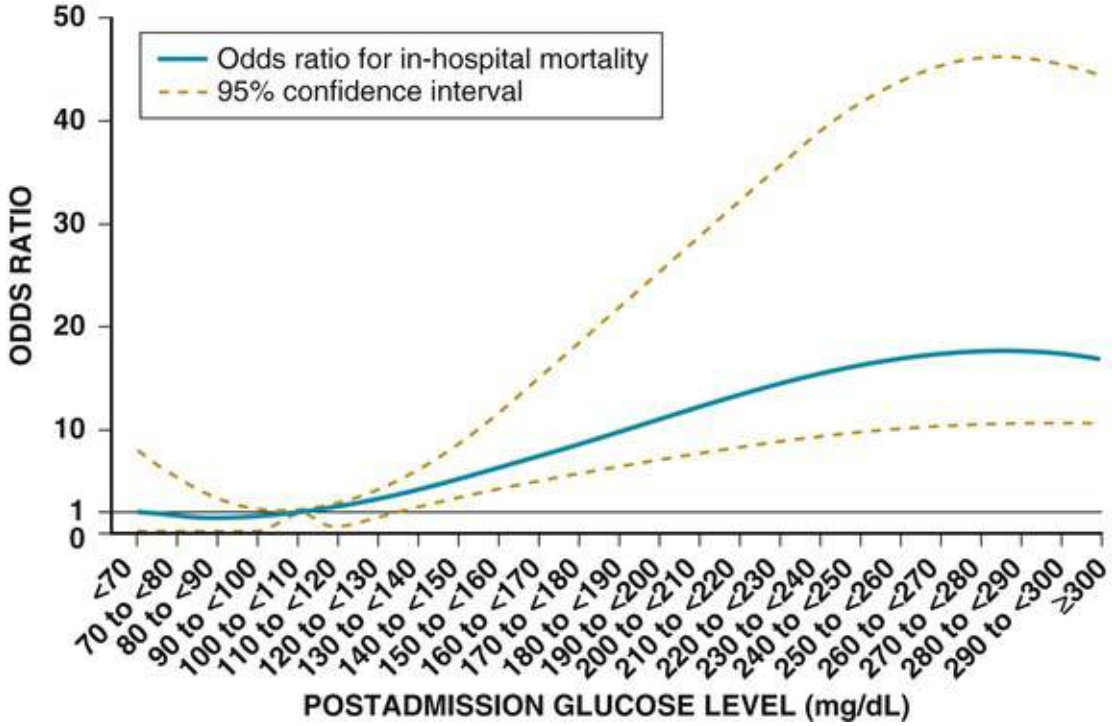

FIGURE 51.6 Postadmission glucose levels and mortality in cohort of patients admitted for acute MI with hyperglycemia on arrival, after multivariable adjustment (to convert glucose values to millimol/liter, multiply by 0.0555). (From Kosiborod M, Inzucchi SE, Krumholz HM, et al. Glucose normalization and outcomes in patients with acute myocardial infarction. Arch Intern Med 2009;169:438.)

In addition to CHD, diabetes increases the risks of stroke, cerebrovascular disease, and peripheral arterial disease. Diabetic patients have a twofold increased stroke risk compared with nondiabetic persons[5] (**see Chapter 65**). Multiple diabetes-related factors contribute to the incremental stroke risk, including multiple common comorbidities of type 2 diabetes mellitus (DM), each independently

associated with stroke risk, such as AF, hypertension, ischemic heart disease, obesity, and dyslipidemia. Hyperglycemia affects approximately one in three patients with acute stroke and is associated with a twofold to sixfold increased risk for subsequent adverse clinical outcomes.

Heart Failure

In the ambulatory setting, diabetes is associated independently with a twofold to fivefold increased risk for HF over that in persons without diabetes, and patients with diabetes have worse outcomes once HF has developed.[7] For decades, basic science research, as well as the development of novel therapeutic options for CV risk reduction in patients with diabetes, focused primarily on atherosclerosis-related events. Only recently, HF in diabetes has gained recognition as a key driver of CV morbidity and mortality, leading to the inclusion of HF as a major endpoint in contemporary clinical trials.[7]

Atrial Fibrillation

Diabetes increases risk for AF, and in the patient with AF, diabetes increases absolute stroke rate/year by 2% to 3.5% (**see Chapter 65**).[8] However, it remains uncertain as to what degree diabetes independently augments risk for AF, largely because of the difficulty in adjusting for risk factors common to both diseases. The inclusion of diabetes as one of seven categorical classifications used in the CHA_2DS_2–VASc score[9] and guideline recommendations for anticoagulation for all diabetes patients who have AF affirm the stroke risk associated with diabetes in the setting of AF.[10]

Coronary Heart Disease in the Patient With Diabetes

Mechanistic Considerations Linking Diabetes and Atherosclerosis

Traditional CHD risk factors such as hypertension, dyslipidemia, and adiposity cluster in patients with diabetes (**see Chapters 45 to 50**). However, this clustering does not completely account for the increased CHD risk observed among patients with diabetes, with numerous other implicated mechanisms (**Table 51.2**).

TABLE 51.2

Examples of Mechanisms Implicated in Diabetic Vascular Disease

Endothelium	↑ NF-κB activation ↓ Nitric oxide production ↓ Prostacyclin bioavailability ↑ Endothelin 1 activity ↑ Angiotensin II activity ↑ Cyclooxygenase type 2 (COX-2) activity ↑ Thromboxane A_2 activity ↑ Reactive oxygen species ↑ Lipid peroxidation products ↓ Endothelium-dependent relaxation ↑ RAGE expression
Vascular smooth muscle cells and vascular matrix	↑ Proliferation and migration into intima ↑ Increased matrix degradation Altered matrix components
Inflammation	↑ IL-1β, IL-6, CD36, MCP-1 ↑ ICAMs, VCAMs, and selectins ↑ Activity of protein kinase C ↑ AGEs and AGE-RAGE interactions

AGEs, Advanced glycation end products; *ICAMs,* intracellular adhesion molecules; *IL,* interleukin; *MCP,* monocyte chemoattractant protein; *NF,* nuclear factor; *RAGE,* receptor for advanced glycation end products; *VCAMs,* vascular cell adhesion molecules.

Modified from Orasanu G, Plutzky J. The pathologic continuum of diabetic vascular disease. J Am Coll Cardiol 2009;53:S35.

The mechanisms by which hyperglycemia may increase atherosclerotic risk remain poorly understood, but given the associations between severity of hyperglycemia and risk for atherosclerosis in both type 1 and type 2 DM, it probably directly influences atherosclerosis development, progression, and instability. The principal vascular perturbations linked to hyperglycemia include endothelial vasomotor dysfunction, vascular effects of advanced glycation end products, adverse effects of circulating free fatty acids, increased systemic inflammation, and a prothrombotic state. *Endothelial vasomotor dysfunction,* a hallmark of diabetic vascular disease, is associated with increased hypertension and adverse CVD outcomes. The myriad mechanisms contributing to endothelial dysfunction include abnormal nitric oxide biology, increased circulating endothelin and angiotensin II, and reduced prostacyclin (i.e., prostaglandin I_2) activity, all of which contribute to perturbations in the regulation of blood flow. Abnormalities in lipid metabolism also contribute to the increased atherosclerotic risk associated with diabetes (**see Chapters 45 and 48**). High triglyceride (TG) levels, low levels of high-density lipoprotein cholesterol (HDL-C), and increased small, dense low-density lipoprotein (LDL) particles characterize diabetic dyslipidemia, and each may contribute to the accelerated development and progression of atherosclerosis.

Perturbations in the coagulation and fibrinolytic pathways and in platelet biology add to the vascular risk of diabetes, yielding a constitutive prothrombotic milieu.[11] These abnormalities include increased circulating tissue factor, factor VII, von Willebrand factor, and plasminogen activating inhibitor 1, with decreased levels of antithrombin III and protein C. In addition, disturbances of platelet activation, aggregation, morphology, and life span further contribute to increased thrombotic potential, as well as to the acceleration of atherosclerosis.

Increased systemic inflammation portends an increased risk for diabetes and associated CVD, associated with increased oxidative stress and the accumulation of advanced glycation end products.[11] For example, diabetes is associated with lipid-rich atherosclerotic plaque with increased inflammatory cell content, expression of tissue factor, and expression of the receptor for advanced glycation end products.

Prevention of Coronary Heart Disease and Its Complications

in the Diabetic Patient

Therapeutic lifestyle interventions remain the cornerstone of prevention of the atherosclerotic complications associated with diabetes. As recommended by the American Diabetes Association (ADA), American Heart Association (AHA), European Society of Cardiology (ESC), and European Association for the Study of Diabetes (EASD), therapeutic lifestyle targets include smoking abstinence, 150 minutes or more of aerobic activity weekly, weight control, and healthy diet habits.[10,12-14]

Beyond lifestyle, pharmacologic strategies effectively reduce CVD risk in diabetes.[10,13,15] Such interventions include assiduous blood pressure (BP) and LDL cholesterol (LDL-C) management for all patients, and for patients at highest risk, angiotensin-converting enzyme (ACE) inhibitors independent of BP, and consideration for daily aspirin.[10,13,15] In the context of these evidence-based CVD interventions, the accumulated data regarding the effects of glucose control on CVD risk mitigation remain far less robust.[14,15]

Lipid Management

Type 2 DM is associated with a characteristic pattern of dyslipidemia, reviewed in detail in **Chapter 48**. Each component of the diabetic dyslipidemia profile is independently associated with CVD risk, including increased small dense LDL particles, increased apolipoprotein B concentration, increased TG levels, and decreased HDL-C. Despite extensive research in modifying TG and HDL-C levels with a variety of pharmacologic agents, however, the net influence on CVD risk of these strategies remains uncertain, and statin treatment remains the cornerstone of therapeutic lipid intervention in patients with diabetes (**see Chapter 45**).

Statins

Contemporary guidelines for the management of diabetic dyslipidemia focus on the use of statin medications,[10,13,15,16] with estimates of numbers needed to treat to prevent one major adverse CVD complication over 5 years in the setting of diabetes: 39 for primary prevention and 19 among patients with prevalent CVD (**see Chapters 45 and 48**). These guidelines do not require elevation of LDL-C as a requisite for statin therapy for patients with diabetes and are recommended for all diabetic patients age 40 or older with one or more CVD factors, as well as younger patients with prevalent CVD, with most endorsing a target of at least LDL-C less than 100 mg/dL, or 35% to 50% reduction from baseline.[10,13,15] A recent update has endorsed an optional more intensive target for patients with diabetes of LDL-C less than 70 mg/dL and non–HDL-C less than 100 mg/dL.[13] The AHA/American College of Cardiology Foundation (ACCF) lipid management guideline recommends statin prescription at an intensity predicated on estimated 10-year risk for atherosclerotic vascular disease (ASCVD),[16] independent of LDL-C level or specified LDL-C or non-HDL-C targets. Patients with diabetes exceeding 7.5% estimated 10-year ASCVD risk should receive at least moderate-intensity statin therapy. These guidelines also discourage add-on lipid-modifying therapies, such as ezetimibe, bile acid binders, fibric acid derivatives, fish oil, or niacin, reserving their use for patients intolerant of statins.

Intensive-dose versus moderate-dose statin therapy further reduces CVD risk. Intensive-dose statin is associated with hastened onset of diabetes due to unknown mechanisms.[17] Whether intensive-dose statin therapy adversely affects glucose control among patients with diabetes remains uncertain. In view of the potent favorable influence of statin therapy at reducing CVD risk, however, the observed adverse effects on glucose indices should not discourage aggressive use of intensive-dose statin therapy in eligible patients with diabetes.

The ESC guidelines endorse a treat-to-target approach.[18,19] According to their individual risk estimation, patients with diabetes have high or very high CVD risk, with "very high risk" defined by the presence of target-organ damage, such as proteinuria, or with at least one additional major CV risk factor, such as smoking, marked hypercholesterolemia, or marked hypertension. These patients should achieve an LDL-C target of less than 70 mg/dL, or achieve a decrease in LDL-C of at least 50%. Most other patients with diabetes are categorized as "high risk," with an LDL-C target of less than 100 mg/dL.

Ezetimibe.

Ezetimibe inhibits the intestinal cholesterol transporter Niemann-Pick C1-like 1 (NPC1L1). The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) assessed the effect of more intensive LDL-C targets with simvastatin/ezetimibe versus standard target control using simvastatin in 18,144 patients following ACS events, with LDL-C levels above contemporary targets.[20] After a mean follow-up of 5.7 years, ezetimibe/simvastatin reduced LDL-C to 53.7 mg/dL versus 69.5 mg/dL in the simvastatin group and yielded a significant 6.7% relative risk reduction (RRR) for the primary composite endpoint of CV death, MI, stroke, hospitalization for unstable angina, or revascularization. Subgroup analyses of IMPROVE-IT showed that the benefit in the overall trial was mainly driven by a robust benefit in the diabetes subset. The results demonstrate that lowering LDL-C to levels below contemporary targets translates into a further reduction of CV events.

PCSK9 Inhibitors.

Another novel LDL-C–lowering strategy is inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) with antibodies such as alirocumab or evolocumab (both approved in Europe and the United States), which has shown promising results in various patient populations, including those with diabetes (**see Chapter 48**). These antibodies potently reduce LDL-C by 40% to 60%, with similar effects in patients with or without diabetes.[21,22] The recently published FOURIER trial (NCT01764633) showed a significant 15% relative risk reduction for the primary composite endpoint of CV death, myocardial infacrtion, stroke, hospitalization for unstable angina, or coronary revascularization with evolocumab versus placebo in 27,564 patients with clinically evident CVD.[22a] At study baseline, 11,031 patients (40%) had diabetes. Evolocumab significantly reduced cardiovascular outcomes consistently in patients with and without diabetes at baseline. Evolocumab did not increase the risk of new-onset diabetes in patients without diabetes at baseline (HR 1.05, 0.94-1.17), including patients with prediabetes (HR 1.00, 0.89-1.13).[22b] The ongoing ODYSSEY outcome trial (NCT01663402) will examine the effect of alirocumab versus placebo on CV risk in 18,313 post-ACS patients who have been enrolled in the trial. The study includes a large number of patients with diabetes and should report in 2018.

Fibric Acid Derivatives (Fibrates).

Fibrates are agonists of the nuclear transcriptional regulator peroxisome proliferator–activated receptor alpha (PPAR-α) that lower triglycerides and modestly increase HDL-C, in addition to modest lowering of LDL-C. Although fibrates favorably affect two of the fundamental abnormalities of diabetic dyslipidemia beyond LDL-C lowering, the net CVD effects of this drug class remain uncertain, with no significant benefit observed in two CV outcomes trials of patients with type 2 DM, many of whom were treated with statins.[16] Subanalyses of these trials suggest that the subset of patients with baseline high triglycerides concomitant with low HDL-C may derive incremental CVD risk reduction with fibrates added to background therapy—a hypothesis pending confirmation in a dedicated randomized trial. Fibrates remain an option for patients with statin intolerance, for isolated hypertriglyceridemia in

patients with diabetes at otherwise low CVD risk, and as add-on therapy to maximally tolerated statin when patients do not achieve therapeutic targets, with the recognition of some increased myopathy risk when combined with a statin, in particular with gemfibrozil, which should *never* be combined with statin treatment.[23]

Omega-3 Fatty Acids.

Omega-3 fatty acids (fish oil) can reduce circulating triglycerides up to 40% (**see Chapters 45 and 48**), and hold promise in the treatment of diabetic dyslipidemia. With no interactions with statins, fish oil is attractive as an add-on therapy to statins for incremental TG reduction. A series of randomized trials demonstrated beneficial effects on CVD outcomes with fish oil, but subsequent results from the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) randomized trial have challenged these findings. In ORIGIN, 12,536 patients with impaired fasting glucose, impaired glucose tolerance, or diabetes randomly received either a 1-g capsule containing at least 900 mg (≥90%) of ethyl esters of n-3 fatty acids or a capsule containing 1 g of olive oil daily.[24] The primary outcome was CV mortality. Over a median follow-up of 6.2 years with 1155 CV deaths to analyze, there was no effect on the primary outcome with fish oil versus control (9.1% versus 9.3%, respectively; $P = 0.72$). Fish oil remains a reasonable adjunct to statin therapy in patients with extremely high triglycerides (>500 mg/dL) to mitigate hyperviscosity or pancreatitis complications, with no clear evidence that it reduces CV risk.

Niacin.

The net CVD effects and safety of niacin, which potently raises HDL-C and lowers triglycerides, appears unfavorable. Two large-scale randomized outcome trials comprising evaluation of almost 30,000 patients demonstrated no CV benefit of niacin.[25,26] Thus, current data do not support the use of niacin.

Hypertension Management

Hypertension affects approximately 70% of patients with diabetes, with a steep-graded association between increasing BP and adverse CV outcomes[27] (**Fig. 51.7**) (**see Chapters 46 and 47**). Numerous classes of antihypertensive medications have proved especially effective at reducing CVD risk in patients with diabetes.[27] BP targets for diabetic patients have historically been more aggressive than for the overall population, with a goal of less than 130/80 mm Hg for diabetic patients who can tolerate such aggressive management without undue clinical burden, and a target of less than 140/80 mm Hg for all others.[10,12,15,27,28]

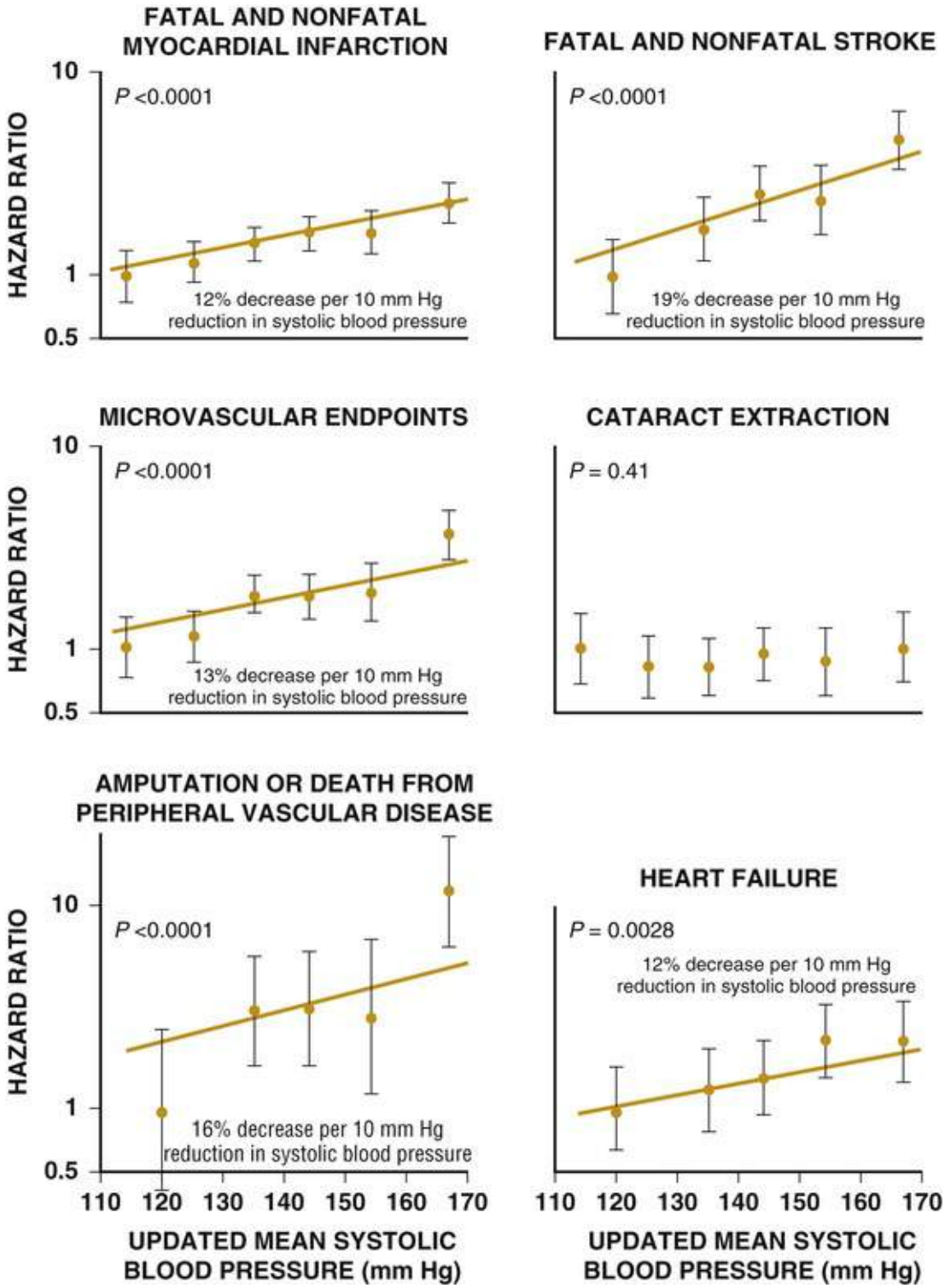

FIGURE 51.7 Hazard ratios (HR; 95% confidence intervals as floating absolute risks) as estimate of association between category of updated mean systolic blood pressure (BP) and myocardial infarction (MI), stroke, and heart failure (HF), with log linear scales. Reference category (HR of 1.0) is systolic BP less than 120 mm Hg for MI and less than 130 mm Hg for stroke and HF; *P* values reflect contribution of systolic BP to multivariable model. Data adjusted for age at diagnosis of diabetes, ethnic group, smoking status, presence of albuminuria, HbA_{1c}, HDL and LDL cholesterol, and triglyceride. (Modified from Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes [UKPDS 36]: a prospective observational study. BMJ 2000;321:412.)

Renin-Angiotensin-Aldosterone System Antagonists

ACE inhibitors and angiotensin II receptor blockers (ARBs) are cornerstones of therapy for hypertension in diabetes because of their favorable effects on diabetic nephropathy and CVD outcomes.[13,15,27]

Angiotensin-Converting Enzyme Inhibitors.

Data from randomized trials of patients with and without hypertension underpin the recommendation for ACE inhibitors as first-line agents for treatment of hypertension in the patient with diabetes. For example, the Heart Outcomes Prevention Evaluation (HOPE) trial compared ramipril (10 mg daily) with placebo in patients at increased risk for CVD and found that ramipril was superior to placebo in the diabetes subset of 3577 patients for the primary outcome of CV death, MI, and stroke (RRR, 25%; $P = 0.004$) and for overt nephropathy (RRR, 24%; $P = 0.027$).[27] Similar observations were reported from the diabetes subanalysis of the EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease) trial,[27] which tested perindopril versus placebo; with RRR of 19% among the 1502 participants with diabetes. On the basis of these results and support from meta-analyses of data from reported trials,[27] ACE inhibitors should be considered for all patients with diabetes who have prevalent CVD, a clustering of CVD risk factors, or nephropathy with or without albuminuria.[10,13,15]

Angiotensin II Receptor Blockers.

CV outcomes data for ARBs are much less robust than for ACE inhibitors, particularly in patients with diabetes. The Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trial enrolled 5926 patients with intolerance to ACE inhibitors, randomly assigned to receive telmisartan (80 mg daily) or placebo, including 2118 patients with diabetes.[27] The overall trial failed to achieve statistical superiority for telmisartan versus placebo on the primary composite of CVD death, MI, stroke, and HF hospitalization (hazard ratio [HR], 0.92; 95% confidence interval [CI] 0.81 to 1.05), with the point estimate of effect completely neutral in the subset with diabetes. Guidelines from the ADA and AHA have endorsed ARBs and ACE inhibitors with similar levels of recommendation,[10,13,15] acknowledging the much weaker evidence for ARBs. ACE inhibitors should remain first-line agents, with ARBs reserved for patients intolerant of ACE inhibitors, and the two classes of medications should not be combined.[10]

Calcium Channel Blockers

Dihydropyridine calcium channel blockers (e.g., amlodipine, felodipine, nitrendipine, nisoldipine) are generally well tolerated and effectively lower BP. Analyses of data for diabetes subsets in randomized clinical trials suggest a magnitude of CVD clinical benefit similar to or greater than that observed in nondiabetic cohorts.[27]

Thiazide Diuretics

Concern about the adverse glycemic and triglyceridemic effects of the thiazide diuretic class of medications, including hydrochlorothiazide, chlorthalidone, indapamide, and bendroflumethiazide, has resulted in some degree of hesitancy regarding use of these medications in patients with diabetes. However, randomized trials of chlorthalidone and indapamide that included substantial numbers of patients with diabetes have consistently demonstrated CVD benefits. In a subanalysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the CVD effects of chlorthalidone compared with both lisinopril and amlodipine were similar in patients with diabetes or impaired fasting glucose, despite modest but statistically significant increases in incident diabetes associated with chlorthalidone use.[29] Also, the use of indapamide combined with perindopril in the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial of 11,140 patients with diabetes was associated with superior CV outcomes.[30] A meta-

analysis of randomized trials further supports the benefits of chlorthalidone and indapamide in the treatment of patients with diabetes.[27] Given the absence of outcomes data with hydrochlorothiazide and bendroflumethiazide, their use is not recommended for patients with or without diabetes.[29]

Beta Blockers

Beta blockers have largely fallen out of favor for routine use as antihypertensive therapies[31] and in patients with diabetes. Beta blockers offer no benefit over other evidence-based classes of medications, with some concern for increased risk for a composite of CV disease, stroke, and HF based on recent meta-analysis.[27] Therefore, use of beta blockers should be primarily limited to patients with systolic HF (carvedilol, metoprolol succinate, or bisoprolol) and after MI. Beta blockers can also be used for antianginal therapy and for rate control of AF.

Antihypertensive Therapy Summary

Four classes of antihypertensive medications reduce CVD risk in patients with diabetes: ACE inhibitors, ARBs, calcium channel blockers, and thiazide diuretics (specifically, chlorthalidone, indapamide). Beta blockers have some evidence of efficacy but have no advantage for hypertension treatment over the other drugs, and their use for BP control should be reserved for patients not achieving target or unable to tolerate combinations of the other four medication classes. In addition, evidence supports a BP target of at least less than 140/80 mm Hg for all patients with diabetes, with a more intensive systolic BP target of less than 130 mm Hg for those patients who can achieve that target without excessive adverse effects.

Antiplatelet Therapy

Daily Aspirin

The ADA and AHA recommend daily aspirin (75 to 162 mg/day) for all patients with diabetes who have established CVD and for primary prevention in diabetic men older than 50 and diabetic women older than 60 who have additional CVD risk factors (or younger in those with prevalent CVD risk).[13,15] The 2013 ESC/EASD guidelines for primary prevention use of aspirin are more restrictive, recommending consideration for daily aspirin for only those patients with diabetes at the highest estimated CV risk.[10] A substantial evidence base in the setting of secondary CVD risk modification supports these recommendations, but a meta-analysis of primary prevention with aspirin in patients with diabetes failed to show statistically significant benefit.[32] Two randomized clinical trials are under way to explore further the role of aspirin for primary CVD risk prevention in patients with diabetes, ASCEND (NCT00135226) and ACCEPT-D (ISRCTN48110081). For patients with aspirin indication but with aspirin allergy or intolerance, $P2Y_{12}$ receptor antagonists may be considered, such as clopidogrel, prasugrel, or ticagrelor.[13,15]

Glucose Management

A total of 12 drug classes of antihyperglycemic medications are presently available for type 2 DM (**Table 51.3**), with complementary mechanisms of action, such as increasing endogenous or exogenous insulin supply, improving insulin action, enhancing the incretin system, delaying intestinal carbohydrate absorption, or increasing urinary glucose excretion. These agents are often used in combination, typically two or three drugs, to reduce hyperglycemia.

TABLE 51.3

Glucose-Lowering Medications for Type 2 Diabetes Mellitus

CLASS	COMPOUND(S)	CELLULAR MECHANISM	MAIN PHYSIOLOGIC ACTION(S)	ADVANTAGES	DISADVANTAGES	COST
Biguanides	Metformin	Activates AMP-kinase ? Other	↓ Hepatic glucose production ? Other	Extensive experience No weight gain No hypoglycemia Likely ↓ CVD events (UKPDS)	GI side effects (diarrhea, abdominal cramping) Lactic acidosis risk (rare) Vitamin B_{12} deficiency Multiple contraindications: advanced CKD, acidosis, hypoxia, dehydration, ethanol abuse, other	Low
Sulfonylureas	*Second generation*: Glyburide (glibenclamide) Glipizide Gliclazide* Glimepiride	Closes K_{ATP} channels on beta cell plasma membranes	↑ Insulin secretion	Extensive experience ↓ Microvascular risk (UKPDS)	Hypoglycemia Weight gain ? Blunts myocardial ischemic preconditioning Low durability	Low
Meglitinides (glinides)	Repaglinide Nateglinide	Closes K_{ATP} channels on beta cell plasma membranes	↑ Insulin secretion	↓ Postprandial glucose excursions Dosing flexibility	Hypoglycemia Weight gain ? Blunts myocardial ischemic preconditioning Frequent dosing schedule	High
Thiazolidinediones	Pioglitazone Rosiglitazone†	Activates the nuclear transcription factor PPAR-γ	↑ Insulin sensitivity	No hypoglycemia Durability ↑ HDL-C ↓ Triglycerides (pioglitazone) ↓ Albuminuria ? ↓ CVD events (pioglitazone)	Weight gain Edema/heart failure Bone fractures ↑ LDL-C (rosiglitazone) ? ↑ MI (meta-analyses, rosiglitazone)	Moderate
α-Glucosidase inhibitors‡	Acarbose Miglitol Voglibose*§	Inhibits intestinal α-Glucosidase	Slows intestinal carbohydrate digestion/absorption	No hypoglycemia ↓ Postprandial glucose excursions Nonsystemic	Generally modest HbA_{1c} efficacy GI side effects (flatulence, diarrhea) Frequent dosing schedule	Moderate
DPP4 inhibitors	Vildagliptin* Sitagliptin Saxagliptin Alogliptin Linagliptin	Inhibits DDP4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations	↑ Insulin secretion (glucose dependent) ↓ Glucagon secretion (glucose-dependent)	No hypoglycemia Well tolerated	Generally modest HbA_{1c} efficacy Urticaria/angioedema ? Pancreatitis Possible ↑ heart failure (saxagliptin; alogliptin)	High
Bile acid sequestrants‡	Colesevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production ? Activation of farnesoid receptor (FXR) in liver	Unknown ? ↓ Hepatic glucose production ? ↑ Incretin levels	No hypoglycemia ↓ LDL-C	Generally modest HbA_{1c} efficacy Constipation ↑ Triglycerides May alter absorption of other medications	High
Dopamine-2 agonists‡	Bromocriptine (quick release)§	Activates dopaminergic receptors	Modulates hypothalamic regulation of metabolism ↑ Insulin sensitivity	No hypoglycemia ? ↓ CVD events (Cycloset Safety Trial)	Generally modest HbA_{1c} efficacy Dizziness/syncope Nausea Fatigue Rhinitis	High
SGLT2 inhibitors	Dapagliflozin Canagliflozin Empagliflozin	Inhibits SGLT2 in the proximal renal tubule	Decreases glucose reabsorption, leading to glucosuria	Effective at all disease stages No hypoglycemia Weight loss Blood pressure reduction ↓ Albuminuria Reduced risk for CV death and hospitalization for heart failure (empagliflozin, canagliflozin) Reduced risk for progression of diabetic kidney disease (empagliflozin, canagliflozin)	Diabetic ketoacidosis Genitourinary infections Polyuria Volume depletion ↑ LDL-C Reversible ↓ eGFR ? Fracture risk (canagliflozin) ? Acute kidney injury ? Toe amputations (canagliflozin)	High
GLP-1 receptor agonists	Exenatide Exenatide (once weekly) Liraglutide Albiglutide Dulaglutide Lixisenatide	Activates GLP-1 receptors	↑ Insulin secretion (glucose-dependent) ↓ Glucagon secretion (glucose-dependent) Slows gastric emptying ↑ Satiety	No hypoglycemia Weight reduction ↓ CV risk factors Reduced risk for CV death and MACE (liraglutide) Reduced risk for progression to macroalbuminuria (liraglutide)	GI side effects (nausea/vomiting) ↑ Pulse rate ? Acute pancreatitis ? Mitogenicity/cancer risk Injectable Training requirements	High
Amylin mimetics‡	Pramlintide§	Activates amylin receptors	↓ Glucagon secretion Slows gastric emptying ↑ Satiety	↓ Postprandial glucose excursions Weight reduction	Generally modest HbA_{1c} efficacy GI side effects (nausea/vomiting) Hypoglycemia unless insulin dose is simultaneously reduced Injectable Training requirements Frequent dosing schedule	High

Insulins	Human NPH Human regular Lispro Aspart Glulisine Glargine Detemir Degludec Premixed (several types)	Activates insulin receptors	↑ Glucose disposal ↓ Hepatic glucose production	Universally effective Theoretically unlimited efficacy ↓ Microvascular risk (UKPDS)	Hypoglycemia Weight gain ? Mitogenicity/cancer risk Injectable Training requirements "Stigma" (for patients)	Variable[¶]

[*]Not licensed in the United States.

[†]Prescribing highly restricted in the United States; withdrawn in Europe.

[‡]Limited use in the United States/Europe.

[§]Not licensed in Europe.

[¶]Depends on type (analogues > human insulins) and dosage.

AMP, Adenosine monophosphate; *CKD,* chronic kidney disease; *CVD,* cardiovascular disease; *DPP4,* dipeptidyl peptidase 4; *eGFR,* estimated glomerular filtration rate; *GI,* gastrointestinal; *GIP,* glucose-dependent insulinotropic peptide; *GLP-1,* glucagon-like protein 1; *HDL-C,* high-density lipoprotein cholesterol; *LDL-C,* low-density lipoprotein cholesterol; *MACE,* major adverse cardiovascular event; *MI,* myocardial infarction; *SGLT2,* sodium-glucose cotransporter 2.

PROactive, Prospective Pioglitazone Clinical Trial in Microvascular Events; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; UKPDS, United Kingdom Prospective Diabetes Study.

Modified and updated from Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach—update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:141.

Cardiovascular Effects of Selected Medications for Diabetes

Until 2008, the approval of drugs for diabetes depended almost exclusively on proof of glucose lowering, without required demonstration of efficacy on clinical outcomes.[33] The regulatory landscape for diabetes drugs more recently underwent major changes, such that all glucose-lowering agents must now demonstrate designated margins of CV safety to achieve regulatory approval. This has led to a rapid proliferation of CV outcome trials of antihyperglycemic therapies, some recently concluded but many still underway (**Table 51.4 and Fig. 51.8**). In this context, the available data on the net CVD safety and efficacy of such medications has been quite limited, and current management strategies and most guidelines remain grounded on the proven microvascular disease benefits demonstrated through glucose control alone.[14,15]

TABLE 51.4

Summary of Completed and Ongoing Cardiovascular Outcomes Trials of Medications for Type 2 Diabetes

TRIAL	DRUG*	PATIENTS (*n*)	STAGE	NCT
Completed Trials				
SAVOR-TIMI 53[45]	Saxagliptin	16,492	Completed	NCT01107886
EXAMINE[46]	Alogliptin	5380	Completed	NCT00968708
TECOS[48]	Sitagliptin	14,671	Completed	NCT00790205
ELIXA[51]	Lixisenatide	6068	Completed	NCT01147250
EMPA-REG-OUTCOME[54]	Empagliflozin	12,500	Completed	NCT01131676
LEADER[52]	Liraglutide	9340	Completed	NCT01179048
SUSTAIN 6[53]	Semaglutide	3299	Completed	NCT01720446
CANVAS[58a]	Canagliflozin	4330	Completed	NCT01032629
EXSCEL[52a]	Exenatide LAR	14,752	Started 6/2010	NCT01144338
CV Outcomes-ITCA 650	Exenatide ITCA 650	4156	Started 1/2012	NCT01455896
DEVOTE[44a]	Insulin degludec	7637	Started 10/2013	NCT01959529
CANVAS-R[58a]	Canagliflozin	5812	Started 1/2014	NCT01989754
Ongoing Trials				
CAROLINA	Linagliptin versus glimepiride	6000	Started 10/2010	NCT01243424
REWIND	Dulaglutide	9600	Started 7/2011	NCT01394952
DECLARE-TIMI 58	Dapagliflozin	17,160	Started 4/2013	NCT01730534
CARMELINA	Linagliptin	6980	Started 7/2013	NCT01897532
VERTIS	Ertugliflozin	3900	Started 11/2013	NCT01986881
CREDENCE	Canagliflozin	3627	Started 2/2014	NCT02065791

*All versus placebo except where noted.

NCT, National Clinical Trial [registration number].

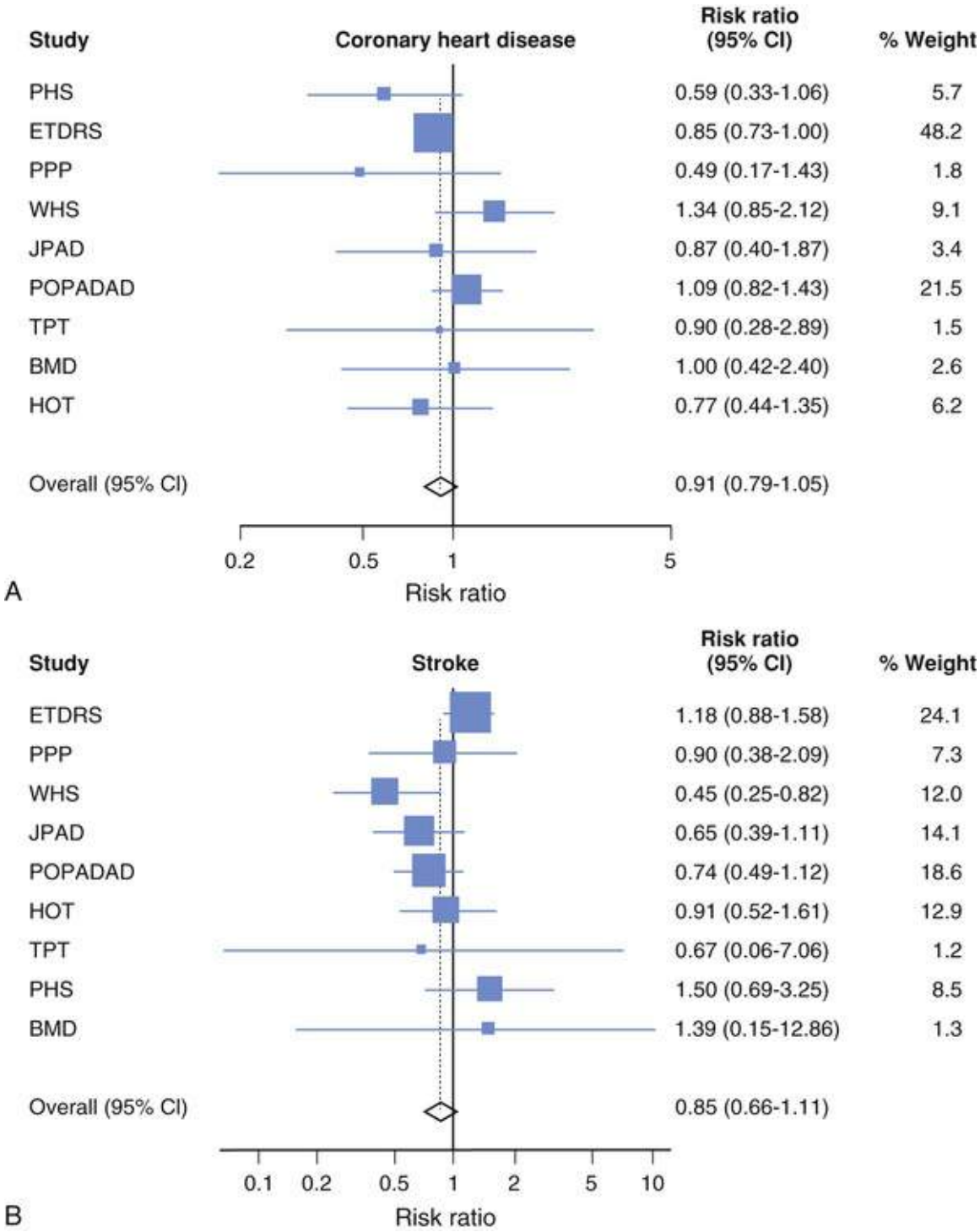

FIGURE 51.8 Meta-analysis of trials examining the effects of aspirin on risk of cardiovascular disease events in patients with diabetes. **A,** Effect of aspirin on coronary heart disease events. Tests for heterogeneity: $\chi^2 = 8.71$, $P = 0.367$, $I^2 = 8.2\%$. **B,** Effect of aspirin on risk of stroke in patients with diabetes. Tests for heterogeneity: $\chi^2 = 12.48$, $P = 0.131$, $I^2 = 35.9\%$. BMD, British Medical Doctors; ETDRS, Early Treatment of Diabetic Retinopathy Study; HOT, Hypertension Optimal Treatment; JPAD, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; PHS, Physicians' Health Study; POPADAD, Prevention of Progression of Arterial Disease and Diabetes; PPP, Primary Prevention Project; TPT, Thrombosis Prevention Trial; WHS, Women's Health Study. (From Pignone M, Alberts MJ, Colwell JA, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: A position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. Circulation 2010;121:2694.)

Metformin.

Metformin, in the biguanide class, likely reduces blood glucose primarily by decreasing hepatic glucose output and with some improvement in peripheral insulin sensitivity.[30] Recent data suggest that metformin

stimulates incretin hormone release (e.g., glucagon-like protein [GLP]-1, glucose-dependent insulinotropic polypeptide [GIP]) from the lower intestines, which augment endogenous insulin secretion. In addition, metformin use is associated with modest weight reduction, favorable effects on lipid levels, decrease in inflammatory markers, improvement in coagulation profiles, and low risk for hypoglycemia. In the United Kingdom Prospective Diabetes Study (UKPDS) of various glucose-lowering strategies in a population of patients with newly diagnosed type 2 DM, patients who were overweight at study entry were eligible for randomization to a policy of more intensive glucose control with metformin versus usual care. Those treated with metformin had statistically superior outcomes for all diabetes-related endpoints (RRR, 32%; 95% CI 13% to 47%), diabetes-related death (RRR, 42%; 95% CI 9% to 63%), and all-cause mortality (RRR, 36%; 95% CI 9% to 55%).[30] A second trial, the HOME study, randomized 390 patients with insulin-treated type 2 DM to metformin versus placebo.[30] The effect on the primary composite outcome, including micro- and macrovascular complications, proved neutral. However, the secondary outcome of major adverse CV events fell in the metformin group (RRR, 39%; 95% CI 6% to 60%), similar in magnitude to the macrovascular risk reductions seen in the UKPDS. Given the relatively small size and few CV events to analyze in both these trials, the CV efficacy of metformin remains uncertain.

Concerns about the potential of metformin to cause lactic acidosis delayed its regulatory approval in the United States and hindered its clinical uptake, stemming from earlier observations with another biguanide, phenformin, that clearly caused lactic acidemia and was removed from the market on that basis. In response to this concern, metformin has been contraindicated for use in patients with impaired kidney function, for 48 to 72 hours after the administration of iodinated contrast, and in unstable HF. Despite widespread global use of metformin for more than five decades, however, and a substantial aggregated database of comparative clinical trials, no convincing signal for increased lactic acidemia with metformin treatment has emerged.[34,35] Given this absence of data supporting the concern for lactic acidosis with metformin, in 2006 the U.S. Food and Drug Administration (FDA) removed the product label warning for its use in patients with HF. More recently, the FDA also adjusted the prescribing guidelines for metformin products with regard to kidney contraindications.[36] Previously contraindicated with serum creatinine in men of 1.5 mg/dL or higher and in women of 1.4 mg/dL or higher, the updated recommendations allow for use in those with stable, mild-moderate chronic kidney disease (CKD). The new cut points are based on estimated glomerular filtration rate (eGFR) instead of serum creatinine. Metformin is now allowed with eGFR less than 60 mL/min/1.73 m^2, with safety reassessed for those taking metformin with eGFR less than 45 mL/min/1.73 m^2, and with metformin contraindicated or to be stopped for eGFR less than 30 mL/min/1.73 m^2. These changes should allow use of this effective, safe, and inexpensive medication to hundreds of thousands of patients in the United States alone. As for recommendations after iodinated contrast administration, metformin need not be interrupted if the eGFR is greater than 60 mL/min/1.73 m^2, but should still be held in patients whose kidney function is below this level until no decrement in kidney function can be documented.

On the basis of safety, tolerability, low hypoglycemia risk, CV clinical outcomes data, and relatively low cost of the generic formulation, metformin is widely considered the first-line drug for type 2 DM in the absence of contraindications or intolerance.[14,15] Metformin is the only oral antihyperglycemic medication routinely recommended to be continued in combination with insulin therapy.

Sulfonylureas.

Sulfonylureas, in clinical use since 1950, are the oldest oral antihyperglycemic medications. They lower glucose by augmenting insulin release through inhibition of adenosine triphosphate (ATP)–dependent

potassium (K_{ATP}) channels in pancreatic beta cells. Although sulfonylureas typically are well tolerated and are relatively potent, their use results in the highest rate of hypoglycemia of any available oral antihyperglycemic drug. They are also associated with weight gain. Although tolbutamide, a first-generation sulfonylurea, increased CV and all-cause mortality in an early randomized trial, no such adverse CV safety signals have emerged from subsequent randomized trials with assignment to second- and third-generation sulfonylureas.[30] On the basis of the extensive clinical experience, the availability of low-cost generics, and the efficacy of glucose control demonstrated in several clinical trials, sulfonylureas constitute a category of second-line drugs (after metformin) for the treatment of type 2 DM.[14]

Concerns persist, however, about the use of sulfonylureas in CVD cohorts, driven by their associated weight gain, increased risk for hypoglycemia and consequent stimulation of the adrenergic stress-response system with potential adverse CVD effects, and the potential of these drugs to inhibit so-called ischemic preconditioning through blockade of myocardial K_{ATP} channels. In animal models of MI, activation of myocardial K_{ATP} channels reduces infarct size, an effect termed *ischemic preconditioning* that is blocked by sulfonylureas. The relevance of these observations in humans remains poorly understood, but this blocking effect is one potential explanation for the increased MI case-fatality rate observed in the more intensively treated patients in the ACCORD trial—a conjecture that remains unproved because of limited ability to analyze outcomes according to drug allocation in that trial.[30] Observations from the UKPDS trial counter the likelihood of such an effect, because an intensive glucose control policy with two different sulfonylureas, chlorpropamide and glibenclamide (glyburide in U.S.), yielded MI and CV death outcomes similar to those with insulin, metformin, and usual (diet) therapy.[30]

On the basis of these concerns, sulfonylureas that are relatively specific for pancreatic K_{ATP} channels have been developed (e.g., glimepiride), although no CV clinical outcomes trials have yet evaluated the CV safety and efficacy of these newer members of the class. More recent observational data from a Danish national registry, however, support ongoing concerns with regard to the all-cause and CV mortality effects of sulfonylureas. Statistically significant increased odds after multivariable and propensity adjustment were associated with all sulfonylureas analyzed compared with metformin, including the pancreatic-specific glimepiride, except for gliclazide, which had no associated mortality signal but is not FDA approved.[37] Data from other observational studies have been inconsistent,[38-40] with some finding an association with adverse CV outcomes.

This potential discrepancy between the apparent safety of sulfonylureas when studied in randomized trials versus their purported risk that emerges in observational studies has two leading explanations. First, the observational studies could be wrong, their findings influenced by confounders not assessable in the datasets, most importantly indication. Alternatively, under the careful observation of clinical trials the drugs could be safe, but their potential dangers may only emerge when used in the general practice setting. The ongoing CV outcomes trial CAROLINA (NCT01243424) comparing the DPP4 inhibitor linagliptin versus glimepiride may shed additional light on this issue.[41]

Thiazolidinediones.

Thiazolidinediones (e.g., rosiglitazone, pioglitazone) decrease glucose levels in type 2 DM by increasing insulin sensitivity of target tissues and induce a wide variety of nonglycemic effects mediated through activation of the nuclear receptor PPAR-γ, including some favorable effects on intermediate markers of CVD and CVD risk. This led to much early interest in their effects on CVD morbidity and mortality.[14] The Prospective Pioglitazone Clinical Trial in Macrovascular Events (the PROactive study) was the first

randomized trial designed to assess the effect of a glucose-lowering medication on CV clinical outcomes. Treatment with pioglitazone yielded a significant 16% RRR for the prioritized secondary composite major adverse cardiovascular event (MACE) endpoint of all-cause mortality, nonfatal MI, and stroke compared with placebo in patients with type 2 DM and prevalent CVD at study entry, treated during a 34.5-month follow-up period, although the effect on the primary endpoint did not achieve statistical significance.[30] These data were considered hypothesis generating because of failure to meet the primary outcome. More recently, in a 4.5-year study involving patients with insulin resistance but without diabetes who had a recent stroke or transient ischemic attack (TIA), pioglitazone versus placebo was associated with a 24% RRR in recurrent stroke or MI (HR, 0.76; 95% CI 0.62 to 0.93).[42] These data, admittedly in patients without diabetes, support the original PROactive MACE findings. In IRIS, pioglitazone was associated with a 52% reduction in risk of developing diabetes (HR, 0.48; 95% CI 0.33 to 0.69).[43] Pioglitazone is the only drug to show both CV risk reduction and diabetes prevention in the same trial, although it is unknown if these effects are necessarily linked.

By contrast, rosiglitazone was at one point suspected of increasing CVD risk—specifically, MI risk.[14] These data from a controversial meta-analysis of phase 2 and 3 data initially led to severe product label restrictions for use in the United States and to withdrawal of rosiglitazone from the market elsewhere. However, a randomized open-label CV outcome trial, RECORD, showed a neutral effect of rosiglitazone on CV outcomes in high-risk patients taking metformin or sulfonylureas. The rosiglitazone product label has since undergone updating to reflect this finding, but the drug remains infrequently used.

Either rosiglitazone or pioglitazone increase the risk for peripheral edema, with a small but consistent increase in risk for new or worsening HF. On that basis, the labels for both agents warn against their use in patients with HF, with a contraindication for initiation in patients with New York Heart Association (NYHA) Class III or IV HF and a caution against their use in any patient with HF. Although the mechanism of the observed increase in edema and HF remains unclear, it appears to result primarily from increased renal sodium reclamation and plasma volume expansion, with no evidence to date of pernicious cardiac effects of these drugs. In IRIS, HF outcomes did not differ between the two randomized groups, likely a reflection of HF being an exclusion in the trial and on-trial protocols for study drug dose reduction if significant edema or excessive weight gain occurred.[42]

Insulin.

Suggested CVD benefits with insulin derive from trials including both type 1 and type 2 DM, but these studies all had limited statistical power to assess such effects. Most recently, results emerged from the ORIGIN trial.[44] This study randomly assigned 12,537 patients with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or prevalent type 2 diabetes to treatment with insulin glargine or standard care management, with dual primary trial outcomes of (1) nonfatal MI, nonfatal stroke, or death from CV causes and (2) these events plus revascularization or hospitalization for HF. After a median follow-up of 6.2 years, no differences were found between the insulin glargine and placebo groups in the rate of the first co-primary outcome (2.94 versus 2.85 events per 100 patient-years; $P = 0.63$) or the second co-primary outcome (5.52 versus 5.28 per 100 person-years; $P = 0.27$). Although ORIGIN did not demonstrate superiority of insulin glargine, the co-primary outcomes had point estimates of effect of 1.02 and 1.04, respectively, both with an upper confidence limit of 1.11—well within the current regulatory standard of upper confidence limit for CV effects of less than 1.3 to demonstrate CV safety of glucose-lowering drugs. As expected, insulin use is associated with more hypoglycemia and weight gain. Only one trial has assessed CV outcomes between two different types of basal insulins. DEVOTE randomized 7637 patients with T2DM to either insulin degludec or glargine or insulin.[44a] The incidence of the primary

MACE outcome proved similar at 8.5% vs. 9.3% (HR, 0.91; 95%, CI 0.78-1.06). Fewer patients using degludec, however, experience severe hypoglycemia (4.9 vs. 6.6%; rate ratio, 0.60; $p < 0.001$).

Dipeptidyl Peptidase 4 (DPP4) Inhibitors.

The DPP4 inhibitors selectively inhibit the action of dipeptidyl peptidase 4, a circulating enzyme that degrades the endogenous incretin hormones' glucagon-like protein (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP), which stimulate glucose-appropriate insulin secretion and/or inhibit glucagon release. Inhibiting DDP4 therefore potentiates GLP-1 and GIP action, reducing glucose levels. Four DPP inhibitors—saxagliptin, alogliptin, sitagliptin, and linagliptin—have been approved for clinical use in the United States, with a fifth drug (vildagliptin) approved elsewhere. Each of these is administered as a once-daily tablet, with modest glucose-lowering potency and with the clinical benefits of neutral effects on weight and low risk for hypoglycemia.

Randomized CV outcomes trials of three DPP4 inhibitors have been completed, with two other trials ongoing (**Table 51.4 and Fig. 51.9**). In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 trial, 16,492 patients with type 2 diabetes with or at increased risk for atherosclerotic CV disease randomly received blinded treatment with saxagliptin, 5 mg daily (or 2.5 mg daily in patients with eGFR ≤50 mL/min/1.73 m^2) versus placebo.[45] Saxagliptin had no effect on the primary composite outcome of CV death, MI, and ischemic stroke (HR, 1.00; 95% CI 0.89 to 1.12), but unexpectedly increased hospitalization for HF (HR, 1.27; 95% CI 1.07 to 1.51), an observation that remains poorly understood and requires further exploration and assessment in the other outcomes trials evaluating the DPP4 inhibitors.

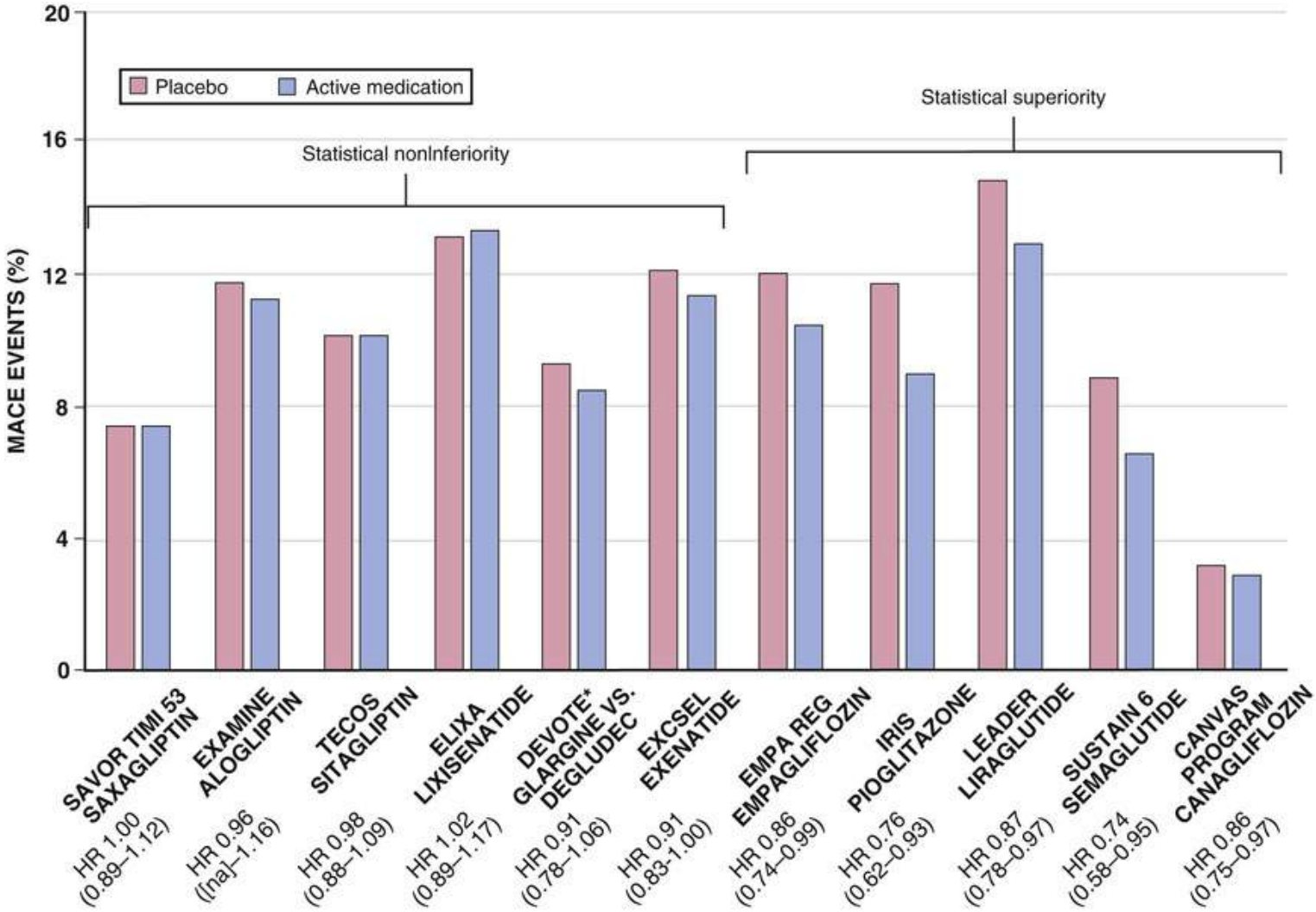

FIGURE 51.9 Summary results of the primary composite cardiovascular outcome results from completed trials of antihyperglycemic therapies reported to date. *Active-controlled trial. SAVOR TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction);[45] EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin Versus Standard of Care);[46,47] TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin);[48] ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome);[51] EMPA REG (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients);[54] IRIS (Insulin Resistance Intervention after Stroke);[42] LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results);[52] EXSCEL (Exenatide Study of Cardiovascular Event Lowering);[52a] DEVOTE (Degludec Cardiovascular Outcomes Trial);[44a] SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes-6);[53] CANVAS (Canagliflozin Cardiovascular Assessment Study).[58a] *MACE,* Major adverse cardiovascular events, comprising the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke for all trials; also including hospitalization for unstable angina for TECOS and ELIXA.

In the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial, 5380 patients with type 2 diabetes and a recent ACS event were randomly assigned to blinded treatment with alogliptin versus placebo.[46] Alogliptin had no effect on the primary composite outcome of CV death, MI, and stroke (HR, 0.96; upper 97.5% confidence limit = 1.16). In a subsequent report, HF hospitalization as the first event of an expanded MACE composite that included HF occurred similarly between patients assigned to alogliptin versus placebo (HR, 1.07; 95% CI 0.79 to 1.46), yet hospitalization for HF was statistically higher in alogliptin-treated patients without prevalent HF at trial entry (HR, 1.76; 95% CI 1.07 to 2.90).[47]

In the Trial Examining Cardiovascular Outcomes with Sitagliptin (TECOS), the CV effects of sitagliptin versus placebo was assessed in 14,671 patients with type 2 DM and prevalent ASCVD.[48]

Sitagliptin had no effect on the primary composite outcome of CV death, MI, stroke, and hospitalization for unstable angina (HR, 0.98; 95% CI 0.88 to 1.09). In contrast to SAVOR and EXAMINE, the sitagliptin group did not experience increased HF hospitalization rates (HR, 1.0; 95% CI 83 to 1.20) in subgroups with or without HF at baseline.[49]

When data from these 3 CV outcome trials were pooled, the HR for HF hospitalization with active therapy was 1.15 (0.98, 1.34), mainly driven by the outcomes in SAVOR-TIMI 53.[49] In a meta-analysis involving 84 DPP4 inhibition trials, the overall risk of HF hospitalization was greater in patients randomized to a DPP4 inhibitor compared with placebo or active comparator (odds ratio [OR], 1.19; 95% CI 1.03 to 1.37). In an observational study involving almost 60,000 patients with type 2 DM with average follow-up of 2.4 years, use of DPP4 inhibitors was not associated with increased HF ($OR_{adjusted}$, 0.88; 95% CI 0.63 to 1.22.).[50] Based on the randomized trial data, in February 2016, the FDA added an HF warning to the prescribing labels for both saxagliptin and alogliptin, but not sitagliptin, nor the DPP4 inhibitor yet to report its CV outcome trials, linagliptin. The warning states that prescribers should consider stopping the medications if patients develop HF on therapy. In summary, the DDP4 inhibitors in relatively short-term clinical trials appear neutral regarding effects on CV outcomes (**Fig. 51.9**), with some concern about a modest increase in in HF hospitalization rates with at least two DPP4 inhibitors, saxagliptin and alogliptin.

Glucagon Like Peptide (GLP)-1 Receptor Agonists.

The GLP-1 receptor agonists (RAs) are injectable agents that enhance the incretin system.[30] The incretin hormones GLP-1 and GIP are neuroendocrine hormones secreted by the intestine in response to meal ingestion. They have variable effects on glucose metabolism that include the stimulation of glucose-dependent insulin secretion, suppression of glucagon (also in a glucose-dependent fashion), a slowing of gastric emptying, and satiety enhancement. Therapeutic benefits with GLP-1 RAs in addition to glucose lowering include associated weight loss (typically 3 to 4 kg), and modest improvement in BP and lipid profiles. They do not increase the risk of hypoglycemia unless used with other drugs that themselves increase the risk (e.g., sulfonylureas, insulin).

In the first GLP-1 RA CV outcomes trial, the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial, lixisenatide was tested 6068 patients with recent ACS and found to be neutral with regard to the primary composite MACE outcome (HR, 1.02; 95% CI 0.89 to 1.17).[51] However, in the second CV outcome trial of this class to report, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER),[52] liraglutide reduced CV death, MI, and stroke by 13% (HR, 0.87; 95% CI 0.78 to 0.97), with directionally concordant results with CV death (HR, 0.78; 95% CI 0.66 to 0.93), nonfatal MI (HR, 0.88; 95% CI 0.75 to 1.03), and stroke (HR, 0.89; 95% CI 0.72 to 1.11) (**Fig. 51.9**). There was no difference in HF hospitalization. In EXSCEL, exenatide once weekly proved neutral for MACE (HR, 0.91; 95% CI, 0.83-1.00; p = 0.061 for superiority), although adherence to study drug was lower than in most trials and likely reduced the trial's power to detect a benefit.[52a] It should be noted that all-cause mortality was reduced in the active therapy arm in this trial (HR, 0.86; 0.77-0.91; p = 0.016).

Other GLP-1 RAs are under CV outcome investigation, including albiglutide and dulaglutide. Semaglutide is an investigational once-weekly GLP-1 RA whose CV outcome trial, SUSTAIN 6, showed a significant decrease in CV death, nonfatal MI, or nonfatal stroke in patients receiving semaglutide compared to placebo.[53]

Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors.

SGLT2 inhibitors, the newest class of antihyperglycemic drugs, block the SGLT2-receptor in the proximal tubule of the kidney, increasing urinary excretion of glucose as well as sodium. This effect results not only in glucose lowering but also in modest reductions in body weight (approximately 2 kg) and BP (approximately 4/2 mm Hg). The first completed CV outcome trial to assess the effect of an SGLT2 inhibitor, EMPA-REG OUTCOME, tested whether empagliflozin compared with placebo influences the incidence of CV events.[54] The study enrolled a high-risk population of patients with type 2 DM and prevalent ASCVD. It enrolled 7020 patients with longstanding diabetes (57% for >10 years) with mean follow-up of 3.1 years; 75% of the patients had coronary artery disease (CAD), 46% had prior MI, and about 10% had a history of HF. The patient population in EMPA-REG OUTCOME was very well treated at baseline, with more than 75% taking a statin, more than 95% receiving antihypertensive therapy, and about 90% taking anticoagulant/antiplatelet drugs. Such evidence-based therapies resulted in good risk factor management, with mean BP of 135/77 mm Hg and mean LDL-C of 85 mg/dL. The trial demonstrated a significant 14% reduction of the primary composite outcome of CV death, nonfatal MI, and nonfatal stroke (HR, 0.86; 95% CI 0.74 to 0.99) (**Fig. 51.9**). A 38% reduction in CV death (5.9% versus 3.7%; HR, 0.62; 95% CI 0.49 to 0.77) drove this result, translating into a number needed to treat (NNT) of 39 over 3.1 years to prevent a CV death. In addition, empagliflozin significantly reduced hospitalization for HF by 35% (HR, 0.65; 95% CI 0.50 to 0.85). All-cause mortality was reduced by 32% (HR, 0.68; 95% CI 0.57 to 0.80). The HF benefit appeared to extend to both those with and those without a prior HF, suggesting that empagliflozin could prevent not only the clinical deterioration of HF but also its occurrence.[55] In this light, ESC has endorsed the consideration of empagliflozin as a preventive therapy for HF in patients with type 2 DM in its latest set of guidelines.[56]

The event curves for both CV death and HF hospitalization outcomes diverged early during the first few weeks of EMPA-REG OUTCOME. Along with the nonsignificant effect of empagliflozin on MI, stroke, or unstable angina, this suggests that the benefits of empagliflozin did not depend on the effects on atherosclerosis, but instead may occur through hemodynamic effects related to its diuretic mechanism of action and other effects on glomerular hemodynamics.[7,57,58] This issue is under intense investigation to understand the surprising effects of this SGLT2 inhibitor, the first drug to actually demonstrate a clear CV benefit in high-risk CV patients with diabetes.

The second SGLT2 inhibitor CV outcome trial to report, the CANVAS program, involved 10,142 patients with type 2 diabetes at high CV risk who were randomized to either canagliflozin or placebo.[58a] About two-thirds had established CVD while approximately one-third had risk factors only. The canagliflozin group experienced nearly identical risk reductions to those seen in EMPA-REG OUTCOME for MACE (HR, 0.86; 95% CI, 0.75-0.97), heart failure hospitalization (HR, 0.67; 95% CI, 0.52-0.87), and progression of CKD (HR, 0.60; 95% CI, 0.47-0.77). As for the components of MACE, each HR was <1.00, but none achieve statistical significance. Specifically, the point estimate for CV mortality (HR, 0.87; 95% CI, 072-1.06) did not approach the major reduction observed in EMPA-REG OUTCOME. In addition, two adverse effects of canagliflozin were found in CANVAS: a doubling in the risk of lower limb amputations (HR, 1.97; 95% CI, 1.41-2.75) and a smaller increase in the risk of fracture (HR, 1.23; 95% CI, 1.04-1.52). The mechanisms behind these complications of therapy are unknown. Similar effects with empagliflozin and dapagliflozin have not been reported.

So far, only data for the effects of empagliflozin and canagliflozin on CV events are available within the SGLT2 inhibitor class, while awaiting the results of the ongoing CV outcome trials with dapagliflozin (NCT01730534), and ertugliflozin (NCT01986881) to discern whether the beneficial CV outcome effects reported from the EMPA-REG-OUTCOME and CANVAS trials are a class effect.

Other Glucose-Lowering Medications.

Data on CVD outcomes are limited for other glucose-lowering medications, with numerous new classes of medications recently becoming available or in late stages of phase III investigation, summarized in **Tables 51.3 and 51.4**.[30] These newer agents share the advantage of a very low risk for hypoglycemia, and many are weight-neutral or cause weight loss. *Colesevelam,* a bile acid sequestrant initially approved for the treatment of hypercholesterolemia, is also approved for use as a glucose-lowering drug to treat type 2 DM, and *alpha-glucosidase inhibitors* impair intestinal carbohydrate absorption. The effects of these drugs on CV outcomes remain unknown, with the exception of a reduced incidence of MIs reported with *acarbose* in a diabetes prevention trial, STOP NIDDM.[30] However, in the larger ACE trial, involving 6522 Chinese patients with coronary heart disease and impaired glucose tolerance, acarbose had no effect to reduce a CV composite outcome (HR, 0.98; 95% CI, 0.86-1.11).[58b] Gastrointestinal intolerance has limited their clinical use.[14]

Cardiovascular Effects of More Intensive Versus Less Intensive Glucose Control Strategies

The UKPDS trial randomly assigned 5102 patients with newly diagnosed type 2 DM to intensive glucose control with sulfonylurea or insulin or to management with diet alone; those overweight at study entry (n = 795) also could be randomized in the intensive arm to receive metformin.[30] In the insulin and sulfonylurea analyses, resulting in hemoglobin (Hb) A_{1c} levels of 7.0% versus 7.9%, respectively, during an average follow-up of 10 years, intensive control decreased risk for a composite endpoint of all diabetes-related complications (RRR, 12%; P = 0.029) and significantly improved microvascular disease risk (RRR, 25%; P = 0.01). Although intensive control showed a trend toward decreased risk of MI (14.8% versus 16.8%; P = 0.052), the number of strokes was increased, although the difference did not achieve statistical significance (5.6% versus 5.2%; P = 0.52). In overweight patients, metformin yielded better glucose control (HbA_{1c} 7.4% versus 8.0%) and significantly decreased risk for MI (RRR, 39%; P = 0.01) and all-cause mortality (RRR, 36%; P = 0.011). The long-term follow-up of the UKPDS trial cohort has extended these observations to an average duration of 10 years,[30] during which glucose control converged rapidly after discontinuation of the study treatment. These analyses reveal a significantly reduced risk for MI in those originally randomly assigned to intensive control, both in the insulin and sulfonylurea group (RRR, 15%; P = 0.01) and in the metformin group (RRR, 33%; P = 0.005). The continued divergence of the CV event curves throughout the entire follow-up after randomized study treatment was discontinued, and despite rapid convergence of average glycemic control at study end, suggests a “legacy” of CV benefit of early assiduous glycemic control, a finding similarly observed in the long-term follow-up of the Diabetes Control and Complications Trial (DCCT) in patients with type 1 DM.[30] The biologic underpinnings of such an effect are not well understood.

Results from three trials assessed the CVD effects of more intensive versus standard glucose control among patients with type 2 diabetes at high CV risk.[30] Comprising more than 23,000 patients treated on study protocol from 3 to 5 years, all three trials showed no significant CVD benefit of intensified glucose control compared with contemporary glucose management.

The ACCORD trial compared intensive versus standard glucose control in 10,251 patients with type 2 DM who had high CVD risk, achieving a HbA_{1c} of 6.4% versus 7.5%.[30] This trial halted early due to an excess of all-cause mortality in the intensively treated group (257 versus 203 events; P = 0.04), with no significant difference observed in the primary composite CVD endpoint of CV death, MI, and stroke (HR, 0.90; 95% CI 0.78 to 1.04). The initial trial observations persisted up to 17 months of follow-up in this

cohort,[30] during which the primary composite outcome risks remained similar between groups. The risk of death from any cause was 19% higher in patients randomly assigned to the more intensive glucose control strategy in the trial ($P < 0.05$), and the HR for nonfatal MI was 0.83 ($P < 0.05$). The basis for the increased mortality remains unresolved; possible explanations include increased hypoglycemia precipitating CV death, pernicious effects of specific drugs or drug combinations, and a chance finding in the context of the other reported trials. The absence of randomization to specific therapies renders post hoc analysis of cause especially difficult.

The ADVANCE trial enrolled 11,140 patients with type 2 diabetes who had CVD, microvascular disease, or another vascular risk factor at study entry.[30] Patients randomly received either intensive glucose control with gliclazide plus other drugs in the intensive arm, compared with standard control with other drugs. Similar to the ACCORD trial, the ADVANCE trial did not show statistically significant improvement in the composite CVD outcome of CV death, MI, and stroke with intensive control (achieved HbA^{1c} of 6.4% versus 7.0%), despite the ascertainment of 1147 events (RRR, 6%; 95% CI −6% to 16%). In contrast to the effects seen in UKPDS, 5-year follow-up data from ADVANCE did not show a reduction in macrovascular events in the group treated initially with intensive control.[59]

In the Veterans Affairs Diabetes Trial (VADT), 1791 U.S. veterans with type 2 DM and inadequate glucose control were randomly assigned to either intensive or standard glucose control.[30] Despite a wide separation in glucose control values (HbA_{1c} of 6.9% versus 8.4%) and ascertainment of 499 primary MACEs, this trial also found no significant improvement in CV outcomes with intensive control (29.5% versus 33.5%; $P = 0.14$). However, follow-up data obtained 3.3 years later in 78% of the initial study population suggest that intensive glucose control compared with standard therapy leads to a significant 17% reduction ($P = 0.04$) of the primary endpoint.[60]

From post hoc analyses of data for each of these trials and supported by the long-term observations from UKPDS in patients with newly diagnosed diabetes at study entry, the concept has emerged that more intensive glycemic control may be safer and may have more favorable CV effects when used in patients earlier in the course of diabetes, particularly among those without prevalent CVD. The corollary to this strategy is that more liberal glycemic targets may be acceptable for selected patients at increased risk, such as very elderly patients and those with a high burden of underlying comorbidities, especially those with prevalent CVD. Although these hypotheses require confirmation in additional clinical trials, the most recent ADA/EASD guidelines for chronic glucose management for patients with type 2 DM endorse such a strategy of targeting intensity of glucose control in the context of global CVD risk, advocating HbA_{1c} target of 8% (or possibly higher) for selected patients, including those with moderate to severe CVD.[14,15] An overriding consideration of such an approach is the limited evidence of short-term benefits from any reduction in microvascular disease in those with limited life expectancy.

In summary, whereas these recent randomized trials did not demonstrate significant incremental CV benefits with more intensive glucose control compared with contemporary targets, the analyses of the primary composite endpoints for each trial revealed point estimates of RRR ranging from 6% to 12%, each with upper 95% confidence limits of 1.04 to 1.06. Such results provide significant assurance of a margin of CV safety with more intensive glucose control, supported by recently published meta-analyses of the available data, demonstrating statistically significant reductions in MI (HR, 0.83; 95% CI 0.75 to 0.93), with no significant effects on stroke (HR, 0.93; 95% CI 0.81 to 1.06) or all-cause mortality (HR, 1.02; 95% CI 0.87 to 1.19). These observed upper confidence limits are well within the noninferiority margins recently adopted by U.S. and European regulatory agencies for diabetes drug registration, to exclude the upper noninferiority 95% confidence limit of 1.3 (or 95% certainty of no greater than 30% worse than comparator) for CV safety.

Summary of Glucose Management

Intensive glucose control favorably affects microvascular disease risk, but its importance in CVD risk modification remains uncertain. Reflecting the accumulated data, the most recent guidelines from the ADA and EASD endorse a more individualized approach than previously recommended, with more liberal HbA_{1c} targets for patients with shorter expected life span and with significant comorbidity, including prevalent CVD (**Fig. 51.10**), suggesting a HbA_{1c} target of 8% (or higher).[14,15] Until recently, in the context of the paucity of clinical outcomes data for most antihyperglycemic therapies used for type 2 DM, the ordered addition of subsequent glucose-lowering medications after metformin was left to the discretion of the provider, taking individual patient and drug characteristics into such treatment determinations. Given the landmark findings from EMPA-REG OUTCOME, LEADER, IRIS, and SUSTAIN-6 trials, the *method* that lowers glucose levels matters, particularly those with established CVD. Whether empagliflozin, liraglutide, semaglutide, or pioglitazone would prove effective in primary prevention remains unknown.

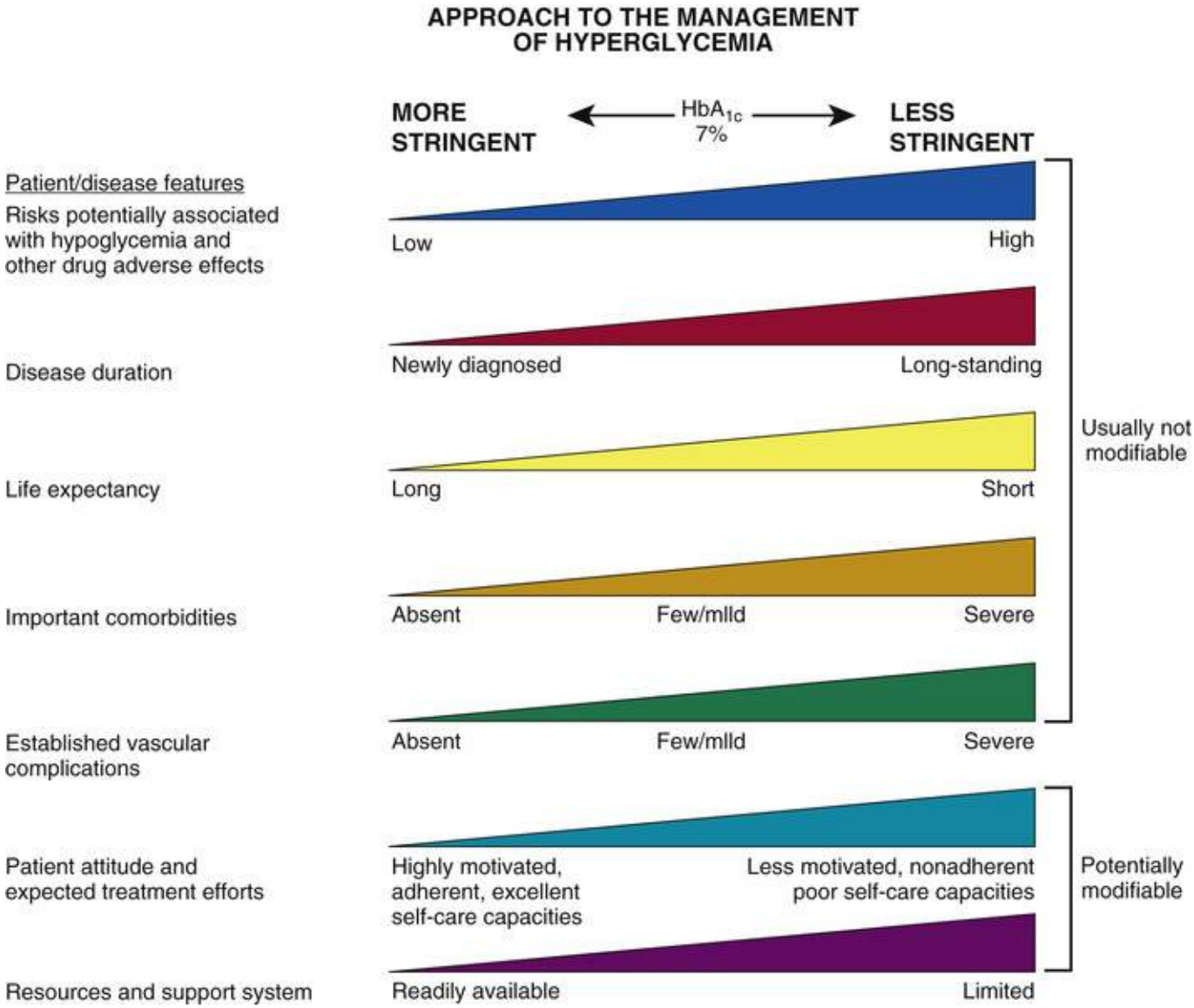

FIGURE 51.10 Modulation of the intensiveness of glucose lowering in type 2 diabetes mellitus (DM). Depiction of patient and disease factors that may be used by the practitioner to determine optimal HbA_{1c} targets in patients with type 2 DM. Greater concerns regarding a particular domain are represented by increasing height of the corresponding ramp. Thus, characteristics/predicaments toward the *left* justify more stringent efforts to lower HbA_{1c}, whereas those toward the *right* suggest (indeed, sometimes mandate) less stringent efforts. Where possible, such decisions should be made with the patient, reflecting his or her preferences, needs, and values. This "scale" is not designed to be applied rigidly but to be used as a broad construct to guide clinical decision making. (From Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:141.)

Acute Coronary Syndromes

In view of the high risk associated with diabetes in the setting of ACS, much investigation has focused on this population. In general, as endorsed by the most recent ACS guidelines,[61,62] the treatment of patients with diabetes should mimic that of the overall population (**see Chapters 58 to 60**). Some specific therapies also are recommended for diabetic patients.

Screening for Diabetes in ACS Patients

Patients with ACS events frequently have diabetes, with approximately one third of ACS patients having diabetes previously diagnosed.[6,63] In addition, many patients present with an ACS event as the first

complication of diabetes, and in this context, previously undetected diabetes is also common, affecting up to an additional 20% to 25% of ACS patients.[63] Therefore, all patients with non–ST-segment elevation (NSTE) ACS should be screened for diabetes.[63,64] Given the stress hyperglycemia associated with ACS events that may confound blood glucose testing, screening should extend beyond assessment of fasting blood glucose and include HbA_{1C} testing and/or predischarge oral glucose tolerance testing.[10,63,65] The diagnosis of diabetes early in the hospital course is important because it influences later therapeutic decisions.

Insulin Administration and Glucose Control

Research over decades has evaluated the role of myocardial metabolic modulation during ACS events, with insulin delivery as the primary focus of investigation. Almost all trials completed to date evaluating the role of intravenous (IV) insulin in ACS used very high insulin dosing supported by exogenous glucose administration to avoid hypoglycemia, with or without adjunctive delivery of potassium, so-called glucose-insulin-potassium (GIK) therapy. These protocols typically targeted permissive hyperglycemia of 126 to 200 mg/dL during the infusion. This strategy ultimately proved futile in contemporary ACS management in the CREATE ECLA GIK trial of 20,201 patients with ST-segment elevation MI (STEMI), randomized to GIK therapy versus usual care and accumulating 1980 mortality events—demonstrating no benefit of GIK therapy compared with usual care.[66] These results have led to the abandonment of GIK treatment for ACS patients.

No adequately powered clinical outcomes trial has been completed to date in the ACS setting evaluating targeted glucose control with IV insulin or any other therapy. The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial enrolled 620 patients with hyperglycemia at presentation with MI, randomly assigned to insulin infusion acutely, followed by multidose subcutaneous insulin injection or usual care, with significant mortality reduction demonstrated in the insulin-treated group during long-term follow-up.[66] DIGAMI used an acute infusion of high-dose insulin (5 units/hr), coupled with IV glucose administration with protocol-targeted permissive hyperglycemia of 126 to 198 mg/dL, an insulin-dosing protocol used in subsequent GIK trials, including the negative CREATE ECLA GIK trial previously summarized. Often misinterpreted as a trial of intensive glucose control, this study provided the basis of ACCF/AHA guideline recommendations for intensive glucose control in the management of ACS events since 2004. However, in the absence of evidence of beneficial effects of intensive glucose control in ACS populations, and a series of trials in other intensive care unit (ICU) settings demonstrating no significant benefit for the most part,[66] and increased mortality with intensive glucose control with IV insulin in the medical and surgical intensive care units in the largest trial to date, guidelines for the management of hyperglycemia in the ACS setting have changed considerably.[66] Both ACCF/AHA and ESC guidelines currently advocate IV insulin to target glucose levels less than 180 mg/dL in the patient with ACS, with a key focus of avoiding hypoglycemia.[10,62,64]

The risk of hypoglycemia associated with intensive glucose control in acutely ill patients remains an important concern, with an incidence of severe hypoglycemia as high as 19% in the reported randomized trials from various ICU settings. This concern may be especially important in the treatment of ACS, in which the counterregulatory response associated with hypoglycemia may prove particularly deleterious to ischemic myocardium. Data from observational studies have shown increased risk associated with hypoglycemia among ACS cohorts, but whether hypoglycemia simply marks disease severity or contributes to adverse outcomes remains unclear.[66] In the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial,[66] the incidence of hypoglycemia

associated with the insulin infusion was the lowest (6.8%) among of all reported trials, yet this is the only trial to demonstrate statistically significant increased mortality with intensive glycemic control in the ICU setting, suggesting that alternative mechanisms may mediate the adverse effects of the insulin infusion. This observation implies that the ability to avoid excess hypoglycemia does not justify the continued use of insulin infusions targeting tight glycemic control for ICU patients, including those with ACS.[66]

Antiplatelet Medications

Aspirin therapy is effective in an ACS setting, with or without diabetes. Because of the aberrations of platelet function associated with diabetes, however, significant interest and investigation have centered on the potential for more intensive antiplatelet therapies to provide particular benefit to diabetic patients experiencing ACS events.

$P2Y_{12}$ Receptor Antagonists

The incremental efficacy of adding thienopyridine and nonthienopyridine antagonists of the platelet receptor $P2Y_{12}$ (clopidogrel, prasugrel, and ticagrelor) to aspirin therapy in the treatment of ACS (**see Chapters 59 and 60**) has been demonstrated in randomized clinical trials that included substantial numbers of patients with diabetes.[67,68] In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial,[67] which included 2840 patients with diabetes, the estimate of treatment benefit of clopidogrel in this subpopulation of 15% RRR was numerically similar to the overall trial results (14.2% versus 16.7%; $P > 0.05$). Prasugrel (a third-generation thienopyridine) added to aspirin therapy, compared with clopidogrel plus aspirin, significantly reduced CVD risk in the diabetes subset of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON–TIMI 38) trial, including patients with ACS undergoing a primary invasive management strategy (12.2% versus 17.0%; $P < 0.001$).[69] Of note, the incremental reduction in CVD risk with prasugrel within the diabetes subset did not entail a significant increase in major bleeding complications (2.6% versus 2.5%). The subsequent Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial, however, which enrolled patients with MI treated medically without revascularization, randomly assigned to treatment with clopidogrel or prasugrel,[70] found no significant differences between the groups in the primary composite outcome of CV death, MI, and stroke in the overall trial population, or in the diabetes subset, in which the interaction of treatment efficacy of prasugrel by diabetes status observed in the TRITON trial was not evident. Finally, in the Platelet Inhibition and Patient Outcomes (PLATO) trial, which enrolled 18,624 patients with an ACS, with or without ST-segment elevation, randomly assigned to receive ticagrelor or clopidogrel, ticagrelor (a nonthienopyridine $P2Y_{12}$ antagonist) significantly reduced the primary composite outcome of death from vascular causes, MI, and stroke (9.8% versus 11.7%; $P < 0.001$).[69] Similar findings pertained to the subset of 4662 patients with diabetes at study entry.[68]

In aggregate, these observations support the incremental benefits of more potent antiplatelet treatment added to aspirin therapy in diabetic patients with ACS events, with superiority of both prasugrel and ticagrelor over clopidogrel. The $P2Y_{12}$ receptor antagonists should be considered as part of routine clinical management for patients with diabetes and ACS.

Renin-Angiotensin-Aldosterone System Antagonists

The ACE inhibitors have several favorable effects in the setting of ACS events that may be especially beneficial in the patient with diabetes, including improvements in ventricular structure and function, endothelial function, fibrinolytic system, and metabolic and neurohormonal effects. On the basis of observational data and subanalyses of diabetic patients in randomized trials, beneficial effects on HF incidence and mortality appear greater in the setting of diabetes. Thus the routine use of ACE inhibitors for patients with diabetes is a level I (A) recommendation across the spectrum of ACS events.[10,62,71]

Although ARBs have similar effects on intermediate markers of myocardial structure and function to those of ACE inhibitors, the evidence base for their overall effects on clinical outcomes remains less robust, especially for the subset of patients with diabetes. For example, in the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL), a randomized trial comprising patients with MI events complicated by HF, losartan versus captopril was associated with a trend toward increased mortality (RR, 1.13; 95% CI 0.99 to 1.28), although the observed differences were not statistically significant.[27] In contrast, the Valsartan in Acute Myocardial Infarction Trial (VALIANT), which enrolled patients within 10 days of an acute MI complicated by HF, including 3400 patients with diabetes, showed no significant difference in mortality between patients randomly assigned to treatment with captopril and those treated with valsartan, and effects in the diabetes subset mirroring those observed in the overall study cohort.[27,28] Thus, ARBs should be considered an alternative only for patients intolerant of ACE inhibitors.

In addition to its effects on sodium retention and potassium excretion, *aldosterone* also may directly stimulate the production of inflammatory mediators, cause myocardial fibrosis, and promote endothelial dysfunction and vascular stiffening, prompting investigation into the role of aldosterone blockade in the setting of ACS. The Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) compared the mineralocorticoid-selective aldosterone antagonist eplerenone to placebo, added to optimal therapy, in a population of 6632 patients with MI and decreased ejection fraction (EF) who had either clinical HF or, in the absence of manifest HF, diabetes.[72] In the overall study cohort, treatment with eplerenone compared with placebo reduced the risk of CV death by 17% (RR, 0.83; 95% CI 0.72 to 0.94), with numerically similar observations in the subset of 2232 patients with diabetes. On the basis of this trial, the use of an aldosterone antagonist for patients with diabetes and reduced EF (with or without clinical HF) after MI is recommended across the spectrum of ACS events,[62,71] with the important caveat that such therapy should not be used in patients with impaired kidney function (creatinine >2.0 mg/dL) or hyperkalemia (potassium concentration [K^+] >5.0 mEq/liter). In addition, patients with diabetes should have serial monitoring of [K^+], given the high prevalence of type 4 renal tubular acidosis in the diabetic population.

Beta-Adrenergic Blocking Agents

Despite evidence of their incremental effectiveness in the treatment of patients with diabetes after ACS events, beta blockers continue to be underprescribed in this group.[6] Biologic effects that support the incremental efficacy of beta blockers in the setting of diabetes include the restoration of sympathovagal balance in diabetic patients with autonomic neuropathy and decreasing fatty acid metabolism within the myocardium, reducing myocardial oxygen demand. Therefore, beta blockers should be prescribed for all patients after ACS events, independent of diabetes status, unless other contraindications exist.[10,62,64,71] In the selection, one may consider the variable effects of available beta blockers on glycometabolic parameters, with favorable effects of some (e.g., carvedilol, labetalol) and unfavorable for others (e.g., metoprolol, atenolol), although the clinical relevance of these considerations remains less clear.[73]

Primary Invasive Strategy for Non–ST-Segment Elevation ACS

In randomized trials comparing primary invasive versus noninvasive strategies for the treatment of ACS events, the subsets of patients with diabetes derived similar or greater benefits than those without diabetes associated with a primary invasive management strategy, although mortality and reinfarction rates were still higher in the groups with diabetes in both treatment arms[64,71] (**see Chapter 62**). Despite these benefits, a primary invasive strategy for patients with diabetes continues to be underused in patients with ACS events.[6]

Primary Reperfusion Therapy for ST-Segment Elevation MI

Analyses from trials of primary percutaneous coronary intervention (PCI) suggest greater benefit in patients with diabetes than in those without diabetes, with primary angioplasty proving superior to thrombolysis in these patients.[74] Similarly, in analyses of diabetic subsets from randomized trials of thrombolytics, patients with diabetes derive greater absolute benefit from thrombolytic therapy than nondiabetic patients.[62] Therefore, diabetic patients with STEMI should undergo reperfusion therapy in the absence of contraindications, preferentially with a strategy of primary PCI when available[10] (**see Chapter 60**).

Coronary Revascularization Considerations

The main goals of coronary revascularization in diabetic patients with stable CAD are the improvements in symptoms and prognosis.[75] Current guidelines recommend medical treatment, including anti-ischemic drugs as first-line treatment of this patient population. For patients requiring revascularization, the optimal revascularization strategy remains controversial. Thus, careful evaluation of the general treatment indication and consideration of the optimal therapeutic strategy has particular importance in this high-risk population.

Optimal Medical Therapy Versus Revascularization in Diabetes

Studies examining optimal medical therapy (OMT) versus a revascularization strategy in patients with diabetes with stable CAD are scarce. The largest such trial, the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) trial, randomized 2368 diabetic patients with obstructive CAD either to immediate revascularization (coronary artery bypass grafting [CABG] $n = 347$; PCI, $n = 765$) in addition to OMT or to OMT alone. Regarding the entire study cohort, the BARI-2D trial did not show a significant difference in terms of freedom from major adverse cardiac and cerebrovascular events (MACCE) or death between the revascularization and the OMT-alone group (88.3% versus 87.8%; $P = 0.97$) after 5 years. Still, the CABG stratum subgroup, despite having more advanced CAD, showed a significantly higher rate of freedom from MACCE and death compared with OMT alone (77.5% versus 69.6%; $P = 0.01$). In contrast, in the PCI stratum compared with OMT alone, there was no difference in freedom from MACCE (77% versus 78.9%; $P = 0.15$).[74] Thus, BARI-2D demonstrated that OMT is a reasonable therapeutic option in patients with diabetes and less advanced CAD. independent of the presence of ischemia. Moreover, regarding the indirect comparison between CABG and PCI in this trial, overall mortality was significantly lower with CABG compared with PCI at 5-year follow-up (19.4% versus 34.5%; $P = 0.003$).[74] This suggests that in patients with more extensive CAD and proven ischemia, CABG may be the preferred treatment modality, whereas in low-risk patients with diabetes (less advanced CAD on angiogram, stable clinical situation, normal left ventricular function) with reliable

compliance to medical therapy, a conservative pharmacologic approach may be a preferable option.[74]

A pooled analysis of completed trials with a total of 5034 patients with diabetes,[76] including the diabetic subgroup of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, BARI-2D, as well as the FREEDOM trial that compared PCI directly with CABG in patients with diabetes (see later), investigated the achievement of the four main targets of OMT (BP, LDL-C, smoking abstinence, HbA_{1c}) with disillusioning results: only 18% of patients in COURAGE, 23% of patients in BARI-2D, and 8% of patients in FREEDOM reached all four prespecified treatment targets at 1-year follow-up. These data strongly suggest that treatment targets of OMT are often not achieved, calling for more intensive efforts to ensure appropriate risk factor management and medical adherence.

Percutaneous Coronary Intervention Versus CABG

Patients with diabetes have worse clinical outcomes after revascularization by either PCI or CABG than those without diabetes. Patients with diabetes have a significantly higher risk of recurrent CV events after PCI, particularly in-stent restenosis, target-vessel revascularization, MI, and stent thrombosis.[77] After CABG, patients with diabetes are especially prone to sternal wound infections, acute kidney injury, HF, and death.[74] The optimal strategy of coronary revascularization for patients with diabetes remains controversial.

Several large trials have compared PCI versus CABG,[78-81] but given technical advances in both interventional cardiology as well as coronary surgery over recent decades, some of the results of these trials apply only partially today.[82] The Coronary Artery Revascularization in Diabetes (CARDia) trial comparing PCI versus CABG in 510 patients with diabetes and multivessel CAD found no difference between groups for the primary composite endpoint of death or MI (PCI 13.0% versus CABG 10.5%; $P = 0.39$).[79] However, the addition of repeat revascularization to the composite outcome showed a benefit favoring CABG (11.3% versus 19.3%; $P = 0.016$) at 1-year follow-up. Important limitations of the CARDia trial were the mixed use of bare-metal stents (BMS, 31%) and first-generation (sirolimus) drug-eluting stents (DES) in the PCI arm and the relatively small sample size.[79]

A subanalysis of the 452 patients with diabetes with left main or three-vessel CAD enrolled in the Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial of PCI versus CABG demonstrated higher rates of MACCE with PCI using paclitaxel-eluting stents (PES) compared with CABG at 1 year (26% versus 14.2%; $P = 0.003$), as well as after 5 years of follow-up (46.5% versus 29.6%; $P < 0.001$),[78] differences driven by more repeat revascularization in the PCI group at 1 year (PCI 20.3% versus CABG 6.4%; $P < 0.001$) and at 5 years (PCI 35.3% versus CABG 14.6%; $P < 0.001$). With respect to lesion complexity according to SYNTAX score, only patients with diabetes with more complex disease (SYNTAX score ≥33) had a treatment benefit of CABG.[78]

In contrast to these studies, the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multi-Vessel Disease (FREEDOM) trial was designed and conducted in a cohort limited to patients with type 2 DM and multivessel disease.[81] Among 1900 enrolled patients, the primary composite endpoint (death, MI, or stroke) was lower in patients treated with CABG versus PCI at 1 year (CABG 18.7% versus PCI 26.6%; $P = 0.005$), as well at 5 years of follow-up (CABG 11.8% versus PCI 16.8%; $P = 0.004$).[81] Of note, this result was driven largely by significant differences favoring CABG in death (CABG 10.9% versus PCI 16.3%; $P = 0.049$) and MI (CABG 6.0% versus PCI 13.9%; $P < 0.001$) at 5 years. Moreover, the incidence of repeat revascularization at 1 year after initial revascularization was significantly higher with PCI versus CABG (12.6% versus 4.8%; $P < 0.01$). However, stroke risk was conversely higher in the CABG group (5.2% versus 2.4%; $P = 0.03$), and no differences in CV

mortality were observed. Challenging contemporary generalizability, first-generation DES (sirolimus-eluting stent [SES] 51% and paclitaxel-eluting stent [PES] 43%) were used, and relatively low proportions of women (28.6%), patients with EF less than 40% (2.5%), and patients with less advanced CAD (SYNTAX score <22; 35.5%) were enrolled.[81]

Based on these trials, for patients with diabetes with stable CAD, the 2014 ACC/AHA guideline upgraded its previous recommendation in favor of CABG over PCI from class II (A) to class I (A),[83] in particular if a left inferior mammary artery (LIMA) graft can be anastomosed to the left anterior ascending (LAD) artery, provided the patient is otherwise a good candidate for surgery. Similarly, the 2014 ESC/EACTS Guideline on Myocardial Revascularization updated its previous recommendation of CABG over PCI in patients with diabetes and multi-vessel disease with an acceptable surgical risk to a class 1 (A) recommendation.[84] It bears consideration that the recommendations of these guidelines are based on trials that did not employ stents of the latest generation, with meta-analysis suggesting superiority of the newer stents compared with first-generation DES in patients with diabetes.[85]

Heart Failure in the Patient With Diabetes

Scope of the Problem

Although MI and hypertension are the most common risk factors associated with HF, diabetes also independently predicts HF risk, with an associated twofold to fivefold increased risk[7,86,87] (see Part IV, Heart Failure), Once HF is present, diabetes portends an especially adverse prognosis for subsequent morbidity and mortality.[7] In patients with diabetes and prevalent ASCVD observed in a registry over 4 years, HF at baseline was independently associated with increased CV death ($HR_{adjusted}$, 2.5; 95% CI 2.2 to 2.8).[87] In view of these observations, improved understanding of the pathobiologic underpinnings linking diabetes with HF and optimization of strategies for the prevention and treatment of HF in this population remain key public health considerations.

Mechanistic Considerations

Patients with and without diabetes share common causes of HF, such as ischemic heart disease, hypertension, left ventricular hypertrophy, and AF. Yet, these common risk factors do not completely account for the incremental HF risk with diabetes, suggesting increased myocardial vulnerability in the setting of diabetes and probable synergistic effects between such factors and diabetes that increase HF risk,[7] yielding the concept of “the ominous octet” of common conditions in diabetes that may underpin HF risk[7] (**Fig. 51.11**).

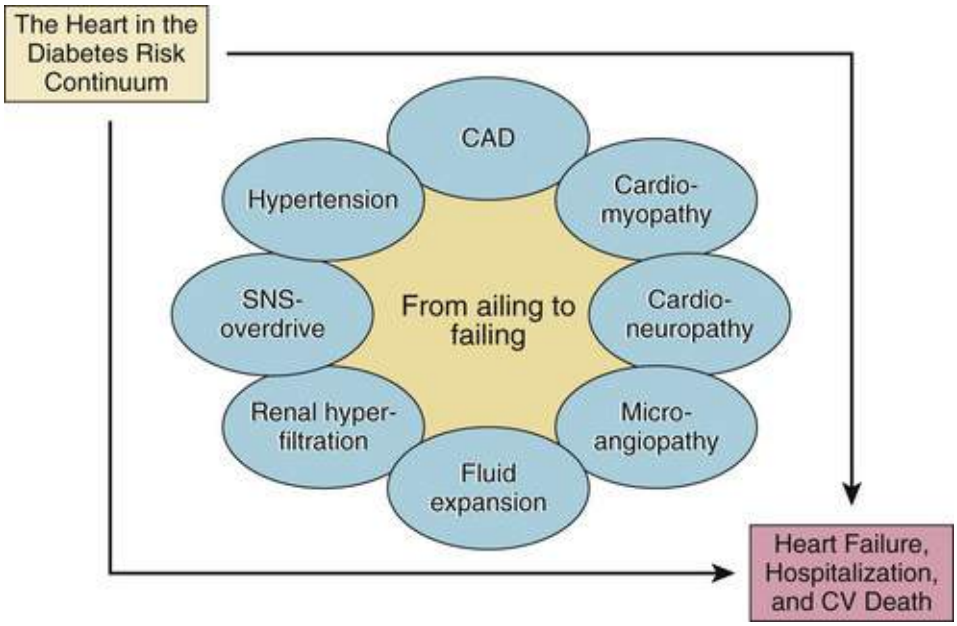

FIGURE 51.11 Heart failure in type 2 DM: the "ominous octet"—multiple comorbidities typically associated with type 2 DM that individually and in aggregate contribute to the increased risk for heart failure in such patients. CAD, Coronary artery disease; CV, cardiovascular; SNS, sympathetic nervous system. (From Standl E, Schnell O, McGuire DK. Heart failure considerations of antihyperglycemic medications for type 2 diabetes. Circ Res 2016;118:1831.)

Ischemic Heart Disease and Hypertension

In view of its high prevalence among patients with diabetes, ischemic heart disease remains the principal risk factor for HF in these patients, both in the chronic ambulatory setting and after ACS events. In addition to the burden of coronary atherosclerosis, other contributors to this increased risk may include increased prevalence of silent or atypical symptoms of ischemia delaying diagnosis and intervention, suboptimal use of therapeutic interventions, perturbed sympathovagal balance, a prothrombotic milieu, impaired coronary endothelial function, and disordered ischemic myocardial metabolism.[7] In aggregate, these effects and others probably increase ischemic burden, increase infarct size, and adversely affect remodeling in the setting of ischemic heart disease and ACS events. Affecting both ischemic heart disease and HF risk, hypertension prevalence exceeds 70% in populations with diabetes. Among patients with type 2 DM, risk of HF increases 12% to 14% for every increment of 10 mm Hg in systolic BP[27] (**see Fig. 51.7**).

Myocardial Metabolism and Structure

The direct effects of hyperglycemia and insulin resistance on myocardial cellular metabolism may contribute to cardiac dysfunction in diabetes,[7] with altered energy substrate supply and impairment of metabolic substrate switching under conditions of stress (**see Chapter 23**). The myocardium uses predominantly free fatty acids (FFAs) under aerobic conditions, but increasingly shifts to glycolysis and pyruvate oxidation during ischemia (**Fig. 51.12**).[7] In the diabetic heart, insulin resistance impairs such substrate switching and glucose transport into cells, resulting in anaerobic fatty acid oxidation and compromising the efficiency of myocardial energetics, as well as generating pernicious oxidative byproducts. Systemic FFA excess, combined with cellular dysregulation of lipid metabolism in type 2 DM, contributes to the accumulation of myocellular triglyceride (myocardial steatosis), resulting in further perturbations of myocyte metabolism and inducing apoptosis due to lipotoxicity, in addition to the adverse influence of cardiac mechanical function attributable to the increased myocardial mass.[7]

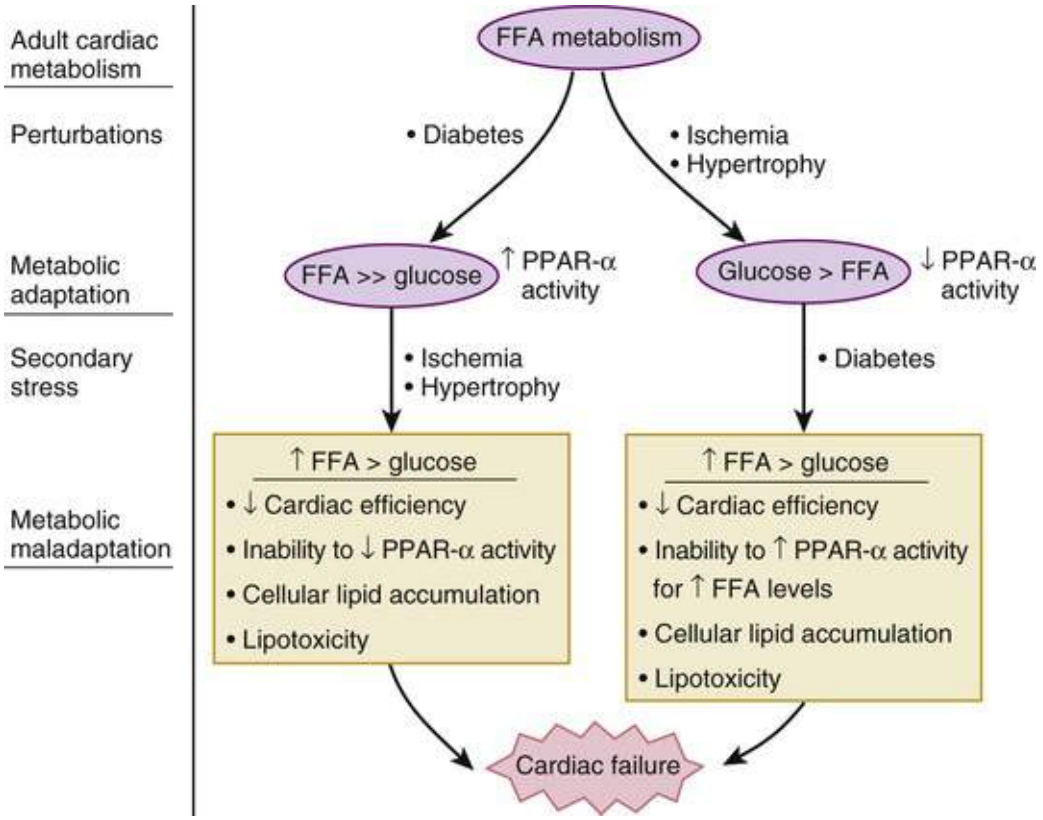

FIGURE 51.12 Schematic summary of cardiac adaptive and maladaptive metabolic modifications occurring in response to diabetes with or without superimposed ischemia or hypertrophy, culminating in overt cardiomyopathy. *FFA,* Free fatty acid; *PPAR*-α, peroxisome proliferator–activated receptor alpha.
(From Saunders J, Mathewkutty S, Drazner MH, McGuire DK. Cardiomyopathy in type 2 diabetes: Update on pathophysiological mechanisms. Herz 2008;33:184.)

Diabetes causes a variety of morphologic changes in the myocardium, with abnormalities in myocytes, extracellular matrix (ECM), and microvasculature.[7] Whereas such abnormalities are usually present across causes of cardiomyopathy, they tend to be more common and severe in the setting of diabetes. In addition, more specific to diabetes, the myocardial accumulation of advanced glycation end products (AGEs), including macromolecules nonenzymatically modified by glucose, the formation and accumulation of which depend on the severity of hyperglycemia, may contribute to HF risk. Deposition of AGEs within the myocardial ECM adversely affects both systolic and diastolic cardiac function, largely attributable to AGE cross-linking of matrix collagen.

Prevention and Management of Heart Failure in Diabetes

In general, drug therapies for HF evaluated in the overall population of patients with risk and disease generally have similar if not better efficacy in patients with diabetes compared with those without diabetes (**see Chapter 25**).

Modulation of the Renin-Angiotensin-Aldosterone System

In patients with diabetes, meta-analysis of the effects of ACE inhibitors demonstrates a trend to reduce incident HF (RR, 0.87; 95% CI 0.72 to 1.06),[27,28] and in patients with moderate to severe systolic dysfunction, significantly reduce mortality (RR, 0.84; 95% CI 0.7 to 1.0)[56,88]—numerically similar observations to those observed in patients without diabetes. Likewise, meta-analysis of placebo-controlled trials demonstrates significant reduction for incident HF with ARBs (HR, 0.70; 95% CI 0.59 to 0.83).[27] In the treatment of patients with prevalent HF, the data for ARBs are less consistent. Therefore,

ACE inhibitors should be first-line agents for the prevention and treatment of HF in patients with diabetes, and ARBs may be considered alternatives for patients intolerant of ACE inhibitors.[10,72]

The effect of aldosterone antagonists (e.g., spironolactone, eplerenone) in patients with diabetes and systolic HF has not been extensively studied. In the EPHESUS randomized trial in post-MI patients, superior efficacy of eplerenone was observed in the diabetes subset of 2122 patients, similar to that in the overall trial. On the basis of these results, eplerenone is recommended for all patients with diabetes and acute MI with decreased EF, except in the presence of contraindications such as kidney dysfunction or hyperkalemia, as described earlier.[10,62,64]

Angiotensin-Neprilysin Inhibition

Neprilysin is a circulating endopeptidase that degrades several vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. Neprilysin inhibition increases the levels of these substances and augments their favorable effects on vasomotor tone and renal sodium handling. The clinical efficacy and safety of the neprilysin inhibitor *sacubitril* in fixed-dose combinations with valsartan (LCZ696) was compared with enalapril in patients with systolic HF in the PARADIGM HF trial.[89] The trial enrolled 8442 patients with class II to IV HF and with EF of 40% or less to receive either LCZ696 (200 mg) or enalapril (10 mg), each twice daily. Overall, LCZ696 significantly reduced the risk for composite outcome of HF hospitalization and CV death (HR, 0.80; 95% CI 0.73 to 0.87), death from any cause (HR, 0.84; 95% CI 0.76 to 0.93), and CV death (HR, 0.80; 95% CI 0.71 to 0.89). In the subset of 2907 patients with diabetes at baseline (39.4%), LCZ696 versus enalapril had comparable efficacy on the composite of HF hospitalization and CV death as observed in the overall trial, but there was heterogeneity of the effect on CV death, with the effect numerically smaller in the group with versus without diabetes ($P_{interaction}$ = 0.05), with a difference that was no longer significant. Therefore, in patients with diabetes, morbidity seems to be improved by LCZ696 over enalapril in patients with or without diabetes, but there is no clear mortality benefit of LCZ696 over enalapril in patients with diabetes.

Beta Blockers

Beta blockers and diuretic medications significantly reduce incident HF among patients with diabetes.[27] In addition, some beta blockers, including metoprolol succinate, carvedilol, and bisoprolol, have demonstrated benefit in the setting of HF with systolic dysfunction (**see Chapter 25**), and these effects appear to be similar independent of diabetes status.[10,72,88] Carvedilol may offer advantages in diabetic patients because of its favorable effects on insulin sensitivity and plasma lipid profiles, but the clinical relevance of these observations remains uncertain.[73] All beta blockers proven effective in the treatment of HF appear to yield similar effects in patients with diabetes.[10,72]

Heart Failure Considerations for Glucose Management Strategies and Antihyperglycemic Medications

Poor glycemic control is associated with risk of HF in patients with diabetes, with a stronger association in women than men. Whether dysglycemia is causal or simply an associated marker of underlying CVD risk remains uncertain. No trials to date have rigorously assessed the effect of targeting glucose control to any specific therapeutic levels, or the comparative effect of existing therapies alone or in combination with regard to their influence on major adverse HF events.[7] Meta-analyses of available data demonstrate no significant effect of more versus less aggressive glucose control on the risk for HF. Therefore the role of glucose control in the prevention and treatment of HF remains poorly understood, and pending further

data, patients with diabetes and HF should be treated to achieve the recently liberalized HbA_{1c} target of less than 8% with the avoidance of hypoglycemia, as endorsed for patients with recognized moderate to severe CVD.[14,15]

Some specific considerations warrant attention with regard to drugs and strategies used to treat hyperglycemia in the setting of HF.[7] Drugs with a propensity to precipitate hypoglycemia, especially sulfonylureas and exogenous insulin administration, should be used with some caution, because the stress response to hypoglycemia stimulates the neurohormonal axis implicated in the clinical complications of HF.

Thiazolidinedione medications have a propensity to increase plasma volume and to precipitate incident or worsening HF; their use requires caution in patients with any degree of HF, and they are contraindicated in patients with NYHA Class III or IV HF.[90] Although the modulators of the incretin axis, the GLP-1 RAs and DPP4 inhibitors, appear to have some favorable effects on a variety of intermediate markers associated with myocardial dysfunction and HF, thus far, large CV outcome trials involving several members of these two classes have shown no benefit on HF outcomes, with saxagliptin and alogliptin potentially increasing HF risk,[49] as now reflected in their U.S. product labeling.

Although metformin historically was thought to be contraindicated in the setting of HF, those product cautions were removed in 2006 on the basis of no incremental risk for lactic academia in a meta-analysis of all comparative data,[34] as well as observational studies in populations with HF yielding no sign of lactic acidosis risk and suggesting net clinical benefit. The product label did retain a caution for use specifically in the setting of acute or decompensated HF. The best available evidence supports consideration of metformin in patients with stable and compensated HF, especially in the context of the available CVD outcomes data, low risk of hypoglycemia, low cost, and favorable tolerability profile.

Insulin therapy remains an option in patients who fail to achieve benefit with conventional oral glucose-lowering therapies, although some concern persists based on the plausibility that insulin may exacerbate signs and symptoms of HF by increasing renal sodium reclamation, contributing to increased intravascular volume.[7] In the ORIGIN trial, patients randomly assigned to receive insulin glargine versus usual care tended to have fewer hospitalizations for HF, although this difference was not statistically significant (4.9% versus 5.5%; $P = 0.16$).[44] These observations from a large randomized trial analyzing 653 adjudicated HF hospitalization events support the probability that epidemiologic associations of worse outcomes in patients with HF treated with insulin result from confounding by indication, rather than from a pernicious effect of insulin, and challenge the concept that insulin may be detrimental because of its effects on sodium handling. Therefore, in patients with HF who fail to achieve acceptable HbA_{1c} targets with oral agents, insulin remains an acceptable option.[7]

As noted previously, the SGLT2 inhibitor empagliflozin reduced HF hospitalization by 38% in the EMPA-REG-OUTCOME trial that involved more than 7000 patients with type 2 DM and established CVD.[54,55] This benefit appeared to extend from those with and without HF at baseline, the latter comprising about 10% of the study cohort. A similar effect was seen with canagliflozin in CANVAS. Studies are currently underway with other SGLT2 inhibitors to assess whether this effect extends to the entire class, potentially related to their diuretic properties.

In summary, HF is common among patients with diabetes, and in addition to usual pathologic contributors to HF in common with the overall population, numerous metabolic and pathologic abnormalities associated with diabetes may explain the increased HF risk and inform drug development efforts toward new therapeutic targets.[7] Although the safety and efficacy of drugs and strategies of glucose control in patients with HF remain uncertain, the bulk of the evidence accumulated for the broader therapeutic arsenal for HF treatment in the overall population suggests that patients with diabetes derive

at least as much benefit (and often more) from such evidence-based therapies. Accordingly, in addition to ongoing research in this area, clinical efforts should focus on the optimal application of existing risk-mitigating therapies in patients with diabetes and HF. As for specific glucose-lowering agents, metformin may provide an advantage, as is also likely with SGLT2 inhibitors. Thiazolidinediones should be avoided. The GLP-1 RAs appear safe. Data regarding the DPP4 inhibitors varies from drug to drug. Saxagliptin and alogliptin should probably be avoided for patients with HF until more safety data have accumulated.

Atrial Fibrillation

Type 2 DM is independently associated with AF[8] and aggravates risk for stroke and systemic thromboembolism,[9] resulting in guideline recommendations for systemic anticoagulation for all patients with diabetes who have AF.[10] Although warfarin has historically been the mainstay of systemic anticoagulation for AF, the direct oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban now offer alternatives. For each therapy, the subanalyses of efficacy and safety for patients with diabetes participating in the pivotal registration trials of these medications suggest similar or even favorably amplified benefit/risk balance.[91] In fact, with similar relative risk reductions with the novel agents versus warfarin and the greater absolute risk for stroke observed in each trial, patients with versus without diabetes have more favorable number needed to treat (NNT) for benefit.[91]

Summary and Future Perspectives

Overall, diabetes increases risk for virtually all CVD complications and, most notably, atherosclerotic vascular disease, heart failure, and atrial fibrillation. Virtually all the advances in the care of patients at risk for CVD complications during the past few decades apply to patients with diabetes, with similar or even greater benefit in this high-risk population. Nonetheless, the gradient of risk associated with diabetes persists. Further progress requires continued efforts in two areas: First, increased and optimal application of the existing evidence for CVD risk reduction is of paramount importance, with studies consistently demonstrating a substantial gap between the accumulated evidence and its application in patients with diabetes. Second, continued investigation into specific therapies and strategies targeting the unique risks for CVD associated with diabetes remains a critical global public health imperative. In that light, driven largely by the regulatory evolution toward requiring CVD safety and efficacy evaluations for all antihyperglycemic medications developed for diabetes management, a proliferation of randomized CVD clinical outcomes trials currently are underway or in development, providing great promise for the future management of diabetic CVD. Currently, three such medications have proven CVD benefit: empagliflozin, liraglutide, and semaglutide, as well as pioglitazone in patients with insulin resistance.

Guidelines

Diabetes and Heart Disease

Darren K. McGuire, Silvio E. Inzucchi, and Nikolaus Marx

Recommendations for the management of patients with diabetes appear in various guidelines and

scientific statements from the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA), European Society of Cardiology (ESC), and other cardiovascular societies; from the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and other endocrinologic societies; and from the National Cholesterol Education Program—Adult Treatment Panel and Joint National Committee, among others. Principal among these publications are dedicated scientific statements, developed by the ACCF and/or the AHA in collaboration with the ADA, and the ESC in collaboration with the EASD, focused on the care of patients with diabetes for the primary prevention of cardiovascular disease (CVD),[1-3] the management of hyperglycemia for hospitalized patients,[4] and the use of aspirin for primary prevention of CVD complications.[3,5] In addition, diabetes-specific guidance appears in ACCF/AHA guidelines for the management of non–ST-segment elevation acute coronary syndromes[6,7] and ST-segment elevation myocardial infarction (STEMI),[8] as well as the management of patients with heart failure (HF).[9-11] For the most part, guidelines are harmonious between the American and European societies regarding specific recommendations for patients with diabetes, with additional comments or clarifications included when such recommendations differ. Finally, the ADA provides recommendations for the global management of patients with diabetes, including but extending well beyond cardiovascular issues in the Standards of Medical Care in Diabetes,[12,13] updated annually—a breadth of guidance well beyond the scope of this chapter—and specific guidance in collaboration with the EASD on chronic glucose management targets and strategies.[14]

Primary and Secondary Prevention of Cardiovascular Disease

Therapeutic Lifestyle Counseling

Therapeutic lifestyle counseling (TLC) interventions are the cornerstone for the treatment of all patients with diabetes, including counseling for regular physical activity, nutritional counseling for weight management and healthy food choices, and counseling for smoking abstinence.[2,3,12,15] Medical nutrition therapy should be targeted at caloric restriction for weight management, increased dietary fiber intake, and limited fat intake (<30% of daily energy; <7% from saturated fats per ADA;[12] <35% of daily energy, saturated fat <10%, and monounsaturated fatty acids >10% per ESC/EASD.[3] Leisure time physical activity targets are at least 150 minutes weekly of modest-intensity exercise, or at least 90 minutes weekly of vigorous exercise. Beyond these, specific recommendations are available for the treatment of other cardiovascular (CV) risk factors, with the ACCF/AHA recommendations (**Table 51G.1**).

TABLE 51G.1

ACCF/AHA Recommendations for Primary Prevention of Cardiovascular Disease (CVD) in People with Diabetes

Lifestyle Management
Weight
Structured programs that emphasize lifestyle changes such as reduced fat (<30% to 35% of daily energy) and total energy intake and increased regular physical activity, along with regular participant contact, can produce long-term weight loss on the order of 5% to 7% of starting weight, with improvement in blood pressure.
For persons with elevated plasma triglycerides and reduced high-density lipoprotein (HDL) cholesterol, improved glycemic control, moderate weight loss (5% to 7% of starting weight), dietary saturated fat restriction, increased physical activity, and modest replacement of dietary carbohydrate (5% to 7%) by either monounsaturated or polyunsaturated fats may be beneficial.
Medical Nutrition Therapy
To achieve reductions in low-density lipoprotein (LDL) cholesterol: Saturated fats should be less than 7% of energy intake. Dietary cholesterol intake should be less than 200 mg/day. Intake of *trans*-unsaturated fatty acids should be less than 1% of energy intake. Total energy intake should be adjusted to achieve body weight goals.
Total dietary fat intake should be moderated (<30% to 35% of total calories) and should consist mainly of monounsaturated or polyunsaturated fat.
Ample intake of dietary fiber (≥14 g/1000 calories consumed) may be of benefit.
If individuals choose to drink alcohol, daily intake should be limited to one drink for adult women and two drinks for adult men. One drink is defined as 12 ounces (oz) of beer, 4 oz

of wine, or 1.5 oz of distilled spirits. Alcohol ingestion increases caloric intake and should be minimized when weight loss is the goal.
Individuals with elevated plasma triglyceride levels should limit intake of alcohol, because it may exacerbate hypertriglyceridemia.
In both normotensive and hypertensive persons, a reduction in sodium intake may lower blood pressure. The goal should be to reduce sodium intake to 1200 to 2300 mg/day (50 to 100 mmol/day), equivalent to 3000 to 6000 mg/day of sodium chloride.

Physical Activity

To improve glycemic control, assist with weight loss or maintenance, and reduce risk of CVD, at least 150 minutes of moderate-intensity aerobic physical activity or at least 90 minutes of vigorous aerobic exercise per week is recommended. The physical activity should be distributed over at least 3 days per week, with no more than 2 consecutive days without physical activity.
For long-term maintenance of major weight loss, a larger amount of exercise (7 hours of moderate or vigorous aerobic physical activity per week) may be helpful.

Blood Pressure

Blood pressure (BP) should be measured at every routine diabetes visit. Patients found to have systolic blood pressure (SBP ≥130 mm Hg or diastolic blood pressure (DBP) ≥80 mm Hg should have BP confirmed on a separate day.
Patients with diabetes should be treated to achieve SBP at least <140 mm Hg and DBP <90 mm Hg, and for patients who can tolerate without adverse symptoms, can target as low as SBP <130 mm Hg and DBP <80 to 85 mm Hg. Patients with SBP of 130 to 139 mm Hg or DBP of 80 to 89 mm Hg should initiate lifestyle modification alone (weight control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products) for a maximum of 3 months. If, after these efforts, targets are not achieved, treatment with pharmacologic agents should be initiated.
Patients with hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg) should receive drug therapy in addition to lifestyle and behavioral therapy.
All patients with diabetes and hypertension should be treated with a regimen that includes either an ACE inhibitor, or if intolerant to an ACE inhibitor, an ARB. If one class is not tolerated, the other should be substituted. Other drug classes demonstrated to reduce CVD events in patients with diabetes—dihydropyridine calcium channel blockers, thiazide diuretics (chlorthalidone and indapamide), and beta blockers—should be added, in listed order of preference, as needed to achieve BP targets.
If ACE inhibitors, ARBs, or diuretics are used, kidney function and serum potassium levels should be monitored within the first 3 months. If BP is stable, follow-up could occur every 6 months thereafter.
Multiple-drug therapy generally is required to achieve BP targets.
In elderly hypertensive patients, BP should be lowered gradually to avoid complications.
Orthostatic measurement of BP should be performed in people with diabetes and hypertension when clinically indicated.
Patients not achieving target BP despite multidrug therapy should be referred to a physician specializing in the care of patients with hypertension.

Lipids

In adult patients with diabetes, lipid levels should be measured at least annually and more often if needed to achieve goals. In adults with diabetes younger than 40 with low-risk lipid values (LDL-C <100 mg/dL, HDL-C >50 mg/dL, triglycerides <150 mg/dL), lipid assessments may be repeated every 2 years.
Lifestyle modification deserves primary emphasis in all individuals with diabetes. Patients should focus on the reduction of saturated fat and cholesterol intake, weight loss (if indicated), and increases in dietary fiber and physical activity. These lifestyle changes have been shown to improve the lipid profile in patients with diabetes. In persons with diabetes who are older than 40, without overt CVD, statin therapy should be considered for primary prevention with recommendation to use at least moderate-dose and ideally intense-dose statins, independent of baseline LDL-C levels. On maximally tolerated statin, the goal is a LDL-C level <100 mg/dL (2.6 mmol/L), and ideally <70 mg/dL (1.8 mmol/L) for those as highest CVD risk. If LDL-lowering drugs are used, a reduction of at least 50% in LDL-C levels should be obtained.
If baseline LDL-C is <100 mg/dL, statin therapy should be initiated based on risk factor assessment and clinical judgment. Major risk factors in this category include age, sex, race/ethnicity, cigarette smoking, hypertension (BP >140/90 mm Hg or use of antihypertensive medication), high total cholesterol and low HDL-C (<40 mg/dL), and family history of premature coronary heart disease (CHD in male first-degree relative ≤55 years of age; CHD in female first-degree relatives ≤65 years of age).
In people with diabetes who are younger than 40, without overt CVD, but who are estimated to be at increased risk for CVD either by clinical judgment or by risk calculator, at least moderate-intensity statin therapy is recommended, with LDL-C goal of <100 mg/dL.
Combination therapy with LDL-lowering drugs (e.g., statins, ezetimibe, PCSK9 inhibitors) and fibrates or niacin may be necessary to achieve lipid targets, but to date, only the addition of ezetimibe to statin therapy has proven incremental CV outcomes benefit.
Beyond the consensus of therapeutic lifestyle intervention, the ADA and AHA guidelines have evolved significantly over recent years, no longer recommending pharmacologic treatment of low HDL-C or high triglyceride levels, except for those with extremely high fasting triglyceride levels, to consider fish oil or a fibrate to mitigate pancreatitis risk.

Tobacco

All patients with diabetes should be asked about tobacco use status at every visit.
Every tobacco user should be advised to quit.
The tobacco user's willingness to quit should be assessed.
The patient can be assisted by counseling and by developing a plan to quit.
Follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement and bupropion) should be incorporated as needed.

Antiplatelet Agents

The ADA and AHA recommend aspirin therapy (75 to 162 mg/day) for primary prevention in patients with diabetes at increased CV risk (e.g., estimated 10-year risk >10%), including most age 50 and older who have additional risk factors (e.g., family history of CVD, hypertension, smoking, dyslipidemia, albuminuria). In contrast, the ESC/EASD guidelines discourage aspirin for primary prevention in patients with diabetes, except for those estimated to be at the very highest CV risk, in whom such use may be considered.
People with aspirin allergy, bleeding tendency, existing anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease are poor candidates for aspirin, especially for primary prevention. Other antiplatelet agents may be a reasonable alternative for patients with high risk.

Glycemic Control

The HbA_{1c} goal for most patients with diabetes in general is less than 7% in the absence of CVD, with higher targets such as 8% (or higher) endorsed for patients with moderate to severe CVD or other serious comorbidities.

Type 1 Diabetes Mellitus

At present, all the recommendations listed above for patients with type 2 DM appear to be appropriate for those with type 1 DM as well.

Data from Fox CS et al. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation 2015; 132:691-718; Ryden L et al. ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. The Task Force on Diabetes, Pre-diabetes, and Cardiovascular Diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J. 2013; 34: 3035-87; ADA Standards of Medical Care in Diabetes—2016: abridged for primary care providers. Diabetes Care 2016;34:3-21; Inzucchi SE et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach—update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2013;38:140-149; and Stone NJ et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129(Suppl 2):S1-45.

Lipids (see also Guidelines Section, Chapter 48)

Lipid profiles should be obtained in all adults with diabetes.[2,3,12,15] As an adjunct to TLC interventions, the primary treatment for dyslipidemia is statin therapy,[2,3,12,15] with combination therapy reserved for those patients not tolerating statin therapy, acknowledging the limited outcomes data available to support the efficacy of any of the presently available add-on therapies. Statin medications should be prescribed for all patients with diabetes between ages 40 and 75 with low-density lipoprotein cholesterol (LDL-C) levels greater than70 mg/dL.[2,3,12,15,16] The U.S. guidelines endorse prescribing at least a moderate-intensity statin for patients with diabetes meeting indications, without specifying a therapeutic target.[12,16] The ESC/EASD guidelines have a slightly different approach, recommending statin therapy in patients with type 1 and type 2 diabetes mellitus (DM) at very high-risk (i.e., if combined with documented CVD, severe chronic kidney disease [CKD], or with one or more CV risk factors, and/or target-organ damage) with an LDL-C target of less than 1.8 mmol/L (<70 mg/dL) or at least a 50% or more LDL-C reduction if this target goal cannot be reached. Patients with type 2 DM at high risk (without any other CV risk factor and free of target-organ damage) should receive statins with an LDL-C target of less than 2.5 mmol/L (<100 mg/dL).[3] At present, no medical therapies are recommended specifically to target treatment of low levels of high-density cholesterol (HDL-C) or high levels of triglycerides. Also, no consensus has been reached, and no compelling data are available, to endorse any one additional therapy over another for this purpose, with options including ezetimibe, PCSK9 inhibitors, bile acid binders, fish oil, fibrates, and niacin.[12,15]

Blood Pressure

Blood pressure (BP) should be measured at every clinical encounter in patients with diabetes.[1-3,12] All patients with diabetes should be treated to a BP target of no higher than 140/80-85 mm Hg,[2,3,17] with a more intensive target of below 130/80 mm Hg for those who can achieve it without side effects or undue clinical burden of therapy.[12] TLC interventions, including physical activity, weight management, and dietary sodium restriction, form the cornerstone for the management of hypertension. Angiotensin-converting enzyme (ACE) inhibitors should be used as the primary antihypertensive therapy in the absence of contraindications or intolerance, or alternatively, angiotensin receptor blockers (ARBs) can be used in persons who experience cough, rash, or angioedema while taking ACE inhibitors. Other drug classes should be added as needed to achieve therapeutic targets, with dihydropyridine calcium channel blockers, thiazide diuretics (chlorthalidone or indapamide), and beta blockers, in order of preference based on evidence of CVD risk reduction in populations with diabetes.[2,3,12,17]

Aspirin

For primary prevention, the American guidelines endorse daily aspirin for patients with diabetes, age 50 years or older with one or more additional CVD risk factors.[2,13] The dose of aspirin recommended is 75 to 162 mg daily. The European guidelines discourage the use of aspirin for primary prevention for most patients, including those with diabetes, advising only that daily low-dose aspirin may be considered in highest-risk patients with DM on an individual basis (class IIb, level of evidence C).[3] The international guidelines are consistent in recommending daily low-dose aspirin (75 to 160 mg) for secondary prevention in patients with DM.

Glucose Management

In general, a hemoglobin (Hb) A_{1c} target of below 7% is recommended for most patients with diabetes.[2,3,12,14] The most recent guidance from ADA/EASD endorses a more personalized approach to

determination of the most appropriate HbA_{1c} targets based on patient and drug characteristics, with the consideration of more intensive control for younger patients, shorter duration of diabetes, and/or fewer comorbid conditions, and more liberal HbA_{1c} targets for higher-risk patients.[14] In addition to TLC, metformin is recommended for all patients with type 2 DM in the absence of contraindication or intolerance, with the addition of other therapies left to the discretion of the care provider, taking into account anticipated adverse effects and patient tolerance, contraindications, potential additional benefits, HbA_{1c} lowering potency, and cost.[14] In addition, in the wake of recent data demonstrating superiority of effects with regard to CV outcomes, recommendations have emerged supporting the use of selected antihiyperglycemic medications for patients with T2DM, independent of indication for glucose control, to reduce cardiovascular risk. The European Society of Cardiology guidelines for the diagnosis and treatment of heart failure recommend the use of empagliflozin specifically for the prevention of HF in patients with type 2 DM,[11] and the ESC Guidelines for the prevention of CVD recommend the use of an SGLT2 inhibitor for patients with T2DM and ASCVD early in the course of disease to reduce CV and all-cause mortality.[18] Similarly, the American Diabetes Association Standards of medical care for type 2 diabetes recommends empagliflozin, as well as liraglutide, for patients with T2DM and prevalent ASCVD.[19]

Secondary Prevention

In general, guidelines for the management of secondary CVD prevention are similar for patients with and without diabetes. **Table 51G.2** summarizes diabetes-specific recommendations for secondary prevention.[2,3,20]

TABLE 51G.2

ACCF/AHA Recommendations for Secondary Prevention of Cardiovascular Disease (CVD) Specific to Patients with Diabetes

CLASS	INDICATION	LEVEL OF EVIDENCE
I	Care for diabetes should be coordinated with the patient's primary care physician and/or endocrinologist.	C
	Lifestyle modifications including daily physical activity, weight management, blood pressure control, and LDL cholesterol management are recommended for all patients with diabetes.	B
	ACE inhibitors (or ARBs for those with ACE inhibitor intolerance) should be started and continued indefinitely in patients with diabetes, unless contraindicated.	A
	Use of aldosterone blockade in post-MI patients without significant kidney dysfunction or hyperkalemia is recommended in patients who are already receiving therapeutic doses of an ACE inhibitor and beta blocker, who have a left ventricular ejection fraction ≤40% and diabetes.	A
IIa	Metformin is an effective first-line pharmacotherapy and can be useful if not contraindicated.	A
	Individualizing the intensity of blood glucose–lowering interventions based on the individual patient's risk of hypoglycemia during treatment is reasonable.	C
IIb	Initiation of pharmacotherapy interventions to achieve target HbA_{1c} may be reasonable.	A
	A target HbA_{1c} of 7% or lower may be considered, whereas the ADA/EASD endorse a target of 8% or higher for those with moderate to severe CVD.	C
	Less stringent HbA_{1c} goals may be considered for other patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular complications, or extensive comorbidity, or those in whom the goal is difficult to attain despite intensive therapeutic interventions.	C

Data from Fox CS et al. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation 2015;132:691-718; Ryden L et al. ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. The Task Force on Diabetes, Pre-diabetes, and Cardiovascular Diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J 2013;34:3035-87; ADA Standards of Medical Care in Diabetes—2016: abridged for primary care providers. Diabetes Care 2016;34:3-21; Inzucchi SE et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach—update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140-149; and Stone NJ et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129(Suppl 2):S1-45.

Acute Coronary Syndromes

With few exceptions, the management of patients with diabetes and unstable angina/non–ST-segment elevation myocardial infarction (UA/NSTEMI) or STEMI should be similar to that of patients without diabetes.[2,3,7,8,21] **Table 51G.3** summarizes diabetes-specific recommendations. In general, the recommendations unique to the diabetes population focus on an increased level of evidence for ACE inhibitors for all patients and aldosterone antagonists for those with left ventricular ejection fraction less than 40%, with or without clinical HF, following acute coronary syndrome (ACS) or myocardial infarction (MI) events; a higher level of recommendation for the adjunctive use of GP IIb/IIIa antagonists for patients with UA/NSTEMI; and preferential use of coronary artery bypass grafting (CABG) over percutaneous coronary intervention (PCI) for patients with more extensive coronary artery disease (CAD), independent of left ventricular systolic function. In addition, recommendations provide guidance for the use of insulin for targeted glucose control, noting a substantial evolution from the original guidelines in 2004 and 2007 that advocated normal or near-normal glucose target levels,[6,22] to the present targets of permissive hyperglycemia, reserving insulin only to maintain blood glucose below 180 mg/dL.[8,21]

TABLE 51G.3

ACCF/AHA Recommendations for Management of Unstable Angina/Non–ST-Segment Elevation Myocardial Infarction (UA/NSTEMI) and ST-Segment Elevation Myocardial Infarction (STEMI) in Patients with Diabetes

CLASS	INDICATION	LEVEL OF EVIDENCE
I	ACE inhibitors should be given and continued indefinitely for patients recovering from MI with diabetes unless contraindicated.	A
	Long-term aldosterone receptor blockade should be prescribed for patients with MI without significant renal dysfunction (estimated creatinine clearance should be >30 mL/min) or hyperkalemia (potassium should be <5 mEq/liters) who are already receiving therapeutic doses of an ACE inhibitor, have an ejection fraction less than 40%, and have diabetes, with or without clinical heart failure.	A
IIa	Use of an insulin-based regimen to achieve and maintain glucose levels less than 180 mg/dL while avoiding hypoglycemia for hospitalized patients with acute coronary syndromes, with either a complicated or uncomplicated course, is reasonable.	B
	For patients with UA/NSTEMI and multivessel disease, CABG using the internal mammary arteries can be beneficial over PCI in patients with medically treated diabetes.	B
	PCI is reasonable for UA/NSTEMI patients with diabetes with single-vessel disease and inducible ischemia.	B
IIb	The use of upstream GP IIb/IIIa inhibitors may be considered in UA/NSTEMI patients with diabetes already receiving aspirin and a $P2Y_{12}$ receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) who are selected for an invasive strategy and are not otherwise at high risk for bleeding.	B

Data from Jneid H et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2012;126:875-910; Roffi M et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267-315; O'Gara PT et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127:e362-425; and ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569-619.

Coronary Revascularization

For patients requiring coronary revascularization, patients with diabetes have been among the most controversial population with regard to the merits of PCI versus CABG. The most recent ACCF/AHA/SCAI (Society for Cardiac Angiography and Interventions) guidelines for PCI have only one diabetes-specific graded recommendation—class IIb (B): CABG is probably recommended over PCI to improve survival in patients with multivessel CAD and DM, particularly if a left internal mammary artery graft can be anastomosed to the left anterior descending artery, a position echoed by the European guidelines.[3,23]

Patients with diabetes represent approximately one third of all patients undergoing PCI. For patients undergoing PCI, DM is among the characteristics favoring preferential use of drug-eluting stents (DES) over bare-metal stents (BMS), with no clear evidence favoring any one DES type over others.[23] Even with the use of DES, however, diabetes remains associated with significantly increased risk for in-stent restenosis. In addition, diabetes is identified as a specific risk factor for post-PCI complications, including periprocedural death and development of contrast-induced acute kidney injury, with recommendations for adequate preparatory hydration and minimization of the volume of contrast media used in such patients. In the setting of UA/NSTEMI, diabetes is among the patient characteristics favoring an early invasive management strategy.

Heart Failure

The diagnosis and management of HF generally are the same for patients with and without diabetes. **Table 51G.4** summarizes diabetes-specific recommendations from the most recent updates of the ACCF/AHA and ESC guidelines for the diagnosis and management of HF in adults.[10,11] The staging system for HF

identifies diabetes alone as HF stage A,[9] reflecting the high risk associated with diabetes for the development of HF, with modest incremental risk in men but threefold increased risk in women for developing HF in the setting of diabetes.

TABLE 51G.4

ACCF/AHA Recommendations for the Diagnosis and Management of Heart Failure (HF) in Patients with Diabetes

CLASS	INDICATION	LEVEL OF EVIDENCE
I	For patients with DM (all of whom are at high risk for developing HF), blood sugar should be controlled in accordance with contemporary guidelines.	C
I	Physicians should control systolic and diastolic hypertension and diabetes mellitus in patients with HF in accordance with recommended guidelines.	C
IIa	Empagliflozin should be considered in patients with type 2 DM to prevent or delay the onset of HF and to prolong life.	B
IIa	Treating dysglycemia should be considered to prevent or delay the onset of HF.	C
IIb	ACE inhibitors can be useful to prevent HF in patients with diabetes.	A
IIb	ARBs can be useful to prevent HF in patients with diabetes.	C

Approximately one third of patients with HF have diabetes. The importance of BP control, preferentially with ACE inhibitors or ARBs, is underscored for the prevention of HF in patients with diabetes. Metformin may be used in patients with stable HF with preserved renal function but should be avoided in patients with unstable HF or that necessitating hospitalization.[12] Pioglitazone should not be initiated in patients with NYHA Class III or IV HF, with caution for use in patients with any degree of HF.[12] Based on CV outcomes trial results with empagliflozin, the European Society of Cardiology HF Guidelines specifically endorse consideration for the use of empagliflozin for patients with type 2 DM for the prevention of HF.[11]

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Air Pollution and Cardiovascular Disease

Aruni Bhatnagar

Although chemical contamination of the natural environment has been an inevitable consequence of human habitat development and civilization since prehistoric times, the levels of environmental pollutants in the air have increased most significantly since the Industrial Revolution. The accumulation of air pollutants emitted by industrial, traffic, household, and agricultural sources results in adverse effects on the health of exposed populations. The 2010 estimate of the Global Burden of Disease Study indicates that exposure to ambient and household air pollution is a leading cause of death worldwide.[1] Globally, 7 million premature deaths can be attributed to air pollution each year, including 200,000 premature deaths in the United States, 1.6 million death in China, and 1.3 million deaths in India per year. Almost 80% of these deaths are a result of cardiovascular disease (CVD), and more than 60% of these result from indoor air pollution. In its health impact, exposure to air pollution rivals the effects of hypertension, smoking, or physical inactivity.[2] Exposure of polluted air is pervasive, and in some geographic locations, ubiquitous. More than 95% of the urban population currently lives in cities where the levels of air pollution exceed the air quality guidelines of the World Health Organization (WHO).[2] Therefore, even though exposure to

air pollution increases the individual risk of CVD and death only slightly, the overall population health impact of air pollution is substantial.

Composition of Air Pollution

Particulate Matter

Humans living in urban areas are exposed to air pollutants generated by both outdoor and indoor sources. The outdoor sources that generate these pollutants and the type of the pollutants produced vary with geographic location, weather, and local urbanization. Most air pollution consists of aerosols containing a mixture of both particles and gases. Of these, *particulate matter* (PM) suspended in air has received the most attention because it is easily measured and readily relatable to the adverse health effects of polluted air. When analyzed for mass, urban air particle distribution reveals two peaks corresponding to *coarse particles*, approximately 10 to 20 µm, and *fine particles*, varying from 0.1 to 2.5 µm. The fine-particle mode contains one third to two thirds of total PM mass. Within this category, a small fraction consists of *ultrafine particles* (UFP). This fraction, despite its modest contribution to the overall volume of PM, contains the largest number of particles and thus presents the most surface area (**Table 52.1**).

TABLE 52.1

Ambient Air Aerosols and Cardiovascular (CV) Effects

POLLUTANT	U.S. EPA STANDARD	SOURCES	ACUTE CV EFFECTS	CHRONIC CV EFFECTS
PM_{10} (aerodynamic diameter >2.5 microm)	150 µg/m^3 (24 hr)	Windblown soil, agriculture, surface mining, plants	Increased all-cause mortality, CVD mortality, increased BP, exacerbation of asthma, stroke, hospital admissions, suppression of heart rate variability	Exacerbation of ischemic heart disease, congestive heart failure
$PM_{2.5}$ (aerodynamic diameter 0.1 to 2.5 microm)	35 µg/m^3 (24 hr)	Combustion particles, smog, diesel, gasoline	All-cause mortality, CVD mortality, MI, atrial fibrillation, sudden cardiac death, peripheral artery disease exacerbation of heart failure, increased BP, stroke, hospital admission, suppression of heart rate variability	Atherosclerotic lesion formation, increased intima-media thickness, coronary artery calcification
SO_4	75 ppb (1 hr)	Combustion of sulfur-containing fuels: coal and petroleum	All-cause mortality, CVD mortality	—
NO_2	100 ppb (1 hr)	Combustion of fossil fuels, power plants, automobiles	Acute MI	—
Ozone	70 ppb (8 hr)	UV photolysis of NOx and VOCs	All-cause mortality	—

BP, Blood pressure; *CVD,* cardiovascular disease; *EPA,* Environmental Protection Agency; *MI,* myocardial infarction; *NOx,* nitrogen oxides; *PM,* particulate matter; *ppb,* parts per billion; *UV,* ultraviolet: *VOCs,* volatile organic compounds.

Both primary and secondary particles are present in the atmosphere. *Primary particles* are directly emitted into the atmosphere. *Secondary particles* arise from gas-to-particle conversion in the air. *Primary aerosols* are mineral dust, metals, soot, salt particles, pollen, and spores, whereas *secondary aerosols* are generated by sulfates, nitrates, and organic compounds. The formation of secondary aerosols proceeds through the processes of *nucleation,* in which gases transition to liquid or solid phase by condensation or chemical reaction. This leads to the formation of nuclei or particles and is followed by condensation of hot gases and coagulation or agglomeration of particles by turbulence, gravitational sedimentation, and brownian motion to generate secondary particles. The nature, composition, and size distribution of secondary particles is determined by several atmospheric factors, such as humidity, temperature, and sunlight as well as specific gases and primary particles. As a result, PM composition

varies between different locations depending on local emission sources. In most U.S. cities, the current average daily concentration of fine particles ($PM_{2.5}$) varies between 5 and 15 μg/m^3, although episodes of $PM_{2.5}$ levels exceeding 100 μg/m^3 are not uncommon. The $PM_{2.5}$ concentration in cities in the developing countries is much higher; the 24-hour average $PM_{2.5}$ levels in China range from 18 to 116 μg/m^3; with a mean of approximately 60 μg/m^3 (**Table 52.1**).[3,4]

Gaseous Pollutants

In addition to PM, the indoor and the outdoor air also contains a variety of other pollutants. These include gases or vapor-phase compounds such as carbon monoxide (CO), nonmethane hydrocarbons, nitrogen oxides (NOx), sulfur oxides (SOx), ozone (O_3), and volatile organic carbons (VOCs). Most of these gases are present naturally in the atmosphere, but their abundance in the atmosphere increases when they are generated by combustion processes such as burning of fossil fuels or high-temperature industrial processes. These gaseous pollutants could also arise from "fugitive release" by a variety of human activities (e.g., agriculture) or natural phenomena (e.g., erosion, volcanic eruptions). In addition, secondary pollutant gases are generated by atmospheric chemistry-mediated by sunlight, water, and vapor. Such chemistry gives rise to many gases, such as sulfates, nitrates, and ammonia, which are associated with and constitute the organic component of PM. Pollutants such as hydroxyl radical, peroxyacetyl nitrate, nitric acid, formic acid, and acetic acid, as well as formaldehyde and acrolein, arise from such atmospheric reactions. VOCs (e.g., formaldehyde, acrolein, benzene, xylene, 1,4-butadiene) and polycyclic aromatic hydrocarbons (PAHs) partition between particle and gaseous phases and contribute to the formation of O_3. Many VOCs are oxidized in the atmosphere to form semivolatile organic compounds that subsequently partition within particles and contribute to both PM mass and PM composition.

Because of the complex chemistry of gaseous pollutants, their variable condensation reactions, and multiple interactions with airborne particles, the nature of air pollution varies with time, weather, season, and temperature. In urban environments, NOx, CO, and VOCs are coemitted with black carbon and therefore peak during "rush hour" motor vehicle traffic, whereas O_3 and other photochemical oxidants peak in the afternoon, particularly on sunny days. This variability in gaseous co-pollutants contributes to a diversity of exposures across different geographic locations and natural conditions and thus are difficult to characterize and quantify.

Outdoor and Indoor Air Pollution

Outdoor or ambient atmospheres contain PM generated by both natural and anthropomorphic sources. Processes such as volcanic eruptions, spontaneous forest fires, sea sprays, and soil erosion are natural sources that generate atmospheric PM, which can arise also from unpaved roads, traffic, mining, welding, building and other human activities. Most *coarse* PM (PM_{10}) arises from dust and ground materials, endotoxin, pollen grains, fungal spores, vegetation, and debris, whereas *fine* PM ($PM_{2.5}$) is derived mostly from smog, traffic, and combustion. In most urban environments, traffic is the major source of PM; in London, 83% of atmospheric PM_{10} can be attributed to traffic. Generally, combustion of any fossil fuel —wood, gas, diesel, and gasoline—generates PM, particularly fine and ultrafine PM.

In developing countries, most of indoor air pollution arises from biomass fuels, coal, and kerosene burned in open fires for cooking and heating.[5] Cooking, particularly frying, is an important source of

indoor pollution. Most of the particles generated by frying are *ultrafine* particles, and cooking indoors can lead to a 10-fold increase in the number of ultrafine particles. Ultrafine particles are also generated by gas flame and wood smoke. Burning of candles or incense can generate high levels of particulate air pollution. Air fresheners generate xylene, aldehydes, and esters, which can react with O_3 to produce secondary pollutants such as formaldehyde, secondary organic aerosols, and ultrafine particles. In many residential buildings the indoor air contains pollen, dander, toxic molds, and dust, which frequently consists of fungi, endotoxin and bacteria, as well as tobacco smoke. Depending on the construction and use pattern, indoor air may also be polluted by ambient or outdoor pollutants. In developed countries the indoor level of most air pollutants is often lower than, but highly correlated with, their outdoor concentration. There are few indoor sources of $PM_{2.5}$, which comes mostly from outdoor sources and traffic. Therefore, living next to a major street increases the levels of indoor $PM_{2.5}$ and increases exposure to traffic-generated pollutants such as NOx and VOCs.

Air Pollution and Cardiovascular Mortality

Data from the first longitudinal cohort studies showed that the adjusted mortality rate ratio of the most polluted to the least polluted cities was 1.26 (1.08 to 1.47). Air pollution was positively associated with deaths from lung cancer and cardiopulmonary disease. Subsequent work showed that 80% of the excessive deaths attributable to chronic air pollution exposure are caused by CVD, particularly ischemic heart disease, arrhythmias, heart failure, and cardiac arrest. It has been estimated that each $10\mu g/m^3$ increase in $PM_{2.5}$ levels is associated with an 8% to 18% excessive risk of cardiovascular (CV) mortality, with comparable or greater risks for smokers than nonsmokers.[3] The risk persists even at concentrations well below the current regulatory standards, and no threshold has been detected below which air pollution does not affect CV health or mortality. The exposure-response relationship between long-term exposure to $PM_{2.5}$ and the risk of CVD mortality is not linear, but rather steep at low levels of exposure and flattening at high exposure levels, such that most of the risk is imparted at low levels of exposure, with declining marginal effects at higher concentrations. Thus the risk of CVD mortality caused by long-term $PM_{2.5}$ exposure may be comparable in different cities, even with widely different levels of air pollution.

Short-term increases in PM are associated with increased risk of total mortality. For each $10\mu g/m^3$ increase in $PM_{2.5}$, there is a 0.7% to 1.7% increase in all-cause mortality on subsequent days. In Europe, outdoor pollution was found to be responsible for 6% of total mortality, half of which could be attributed to automobile emission. Interestingly, the number of deaths attributable to air pollution exceeded that from motor vehicle crashes. Similar risk estimates have been observed for CV mortality. Short-term elevations in daily PM levels lead to a greater absolute risk for CVD-related mortality than for all other causes. CVD mortality accounts for 69% of the increase in absolute mortality attributable to short-term PM exposure. Consistent associations between CVD mortality and short-term increases in PM levels have been reported from more than 100 cities worldwide. In most studies the relationship between PM exposure and excessive mortality appears to be independent of gaseous co-pollutants; however, CVD mortality has also been associated with episodic increases in ambient levels of NO_2, CO, and O_3 levels. Although PM exposure leads to a population-wide increase the risk of CVD mortality, smokers, elderly persons, and patients with diabetes or heart failure appear to be particularly sensitive to PM exposure.

Like outdoor exposure, indoor exposure to air pollution is also linked to excessive CV mortality. It has

been estimated that indoor air pollution is associated with 1.6 to 3.5 million deaths globally each year. Cumulative health impacts from inhalation in U.S. residences of indoor air pollution ($PM_{2.5}$, acrolein, and formaldehyde, which account for a vast majority of disability-adjusted life-year [DALY] losses) are 400 to 1100 DALYs lost annually per 100,000 persons. This impact is comparable or greater than estimates for secondhand smoke exposure. In Europe, exposure to biomass smoke has been linked to 40,000 premature deaths per year. In developing countries, indoor air pollution caused by biomass burning is associated with 2 million deaths per year; many of these are women who die from CVD. Current epidemiologic evidence indicates that the use of biomass fuels for cooking and heating increases the risk of coronary heart disease (CHD) twofold to fourfold.[5]

Cardiovascular Effects of Air Pollution

Exposure to air pollution has a wide range of acute and chronic CV effects[6] (**Fig. 52.1**). Most such effects have been linked to particulate air pollution, which is a readily measured constituent of air pollution. However, the levels of PM co-vary with other pollutants, and therefore, it is often difficult to rule out the effects of other co-pollutants or the effects of co-pollutants that might act additively or synergistically with PM. Moreover, PM by itself is a heterogeneous collection of particles of varying size and chemical composition, and as a result the biologic effects of PM vary substantially with its composition. It is still unclear which PM constituents are linked with which specific health effects. No specific exposure biomarkers of PM exposure have been identified to date, and therefore, in most epidemiologic studies, exposure misclassification cannot be ruled out. Also, no characteristic pathologic states can be specifically attributed to PM. Exposure to PM affects the final common pathways of CVD. Systemically, PM exposure affects blood pressure, lipids, insulin resistance, coagulation, and organ-specific effects such as neuronal activation, myocardial excitability, oxidative stress, and inflammation. As a result, no specific pathologic feature or clinical state can be directly linked to PM exposure. Nevertheless, the major effects of PM on cardiovascular tissue and function are related to the disease states discussed next.

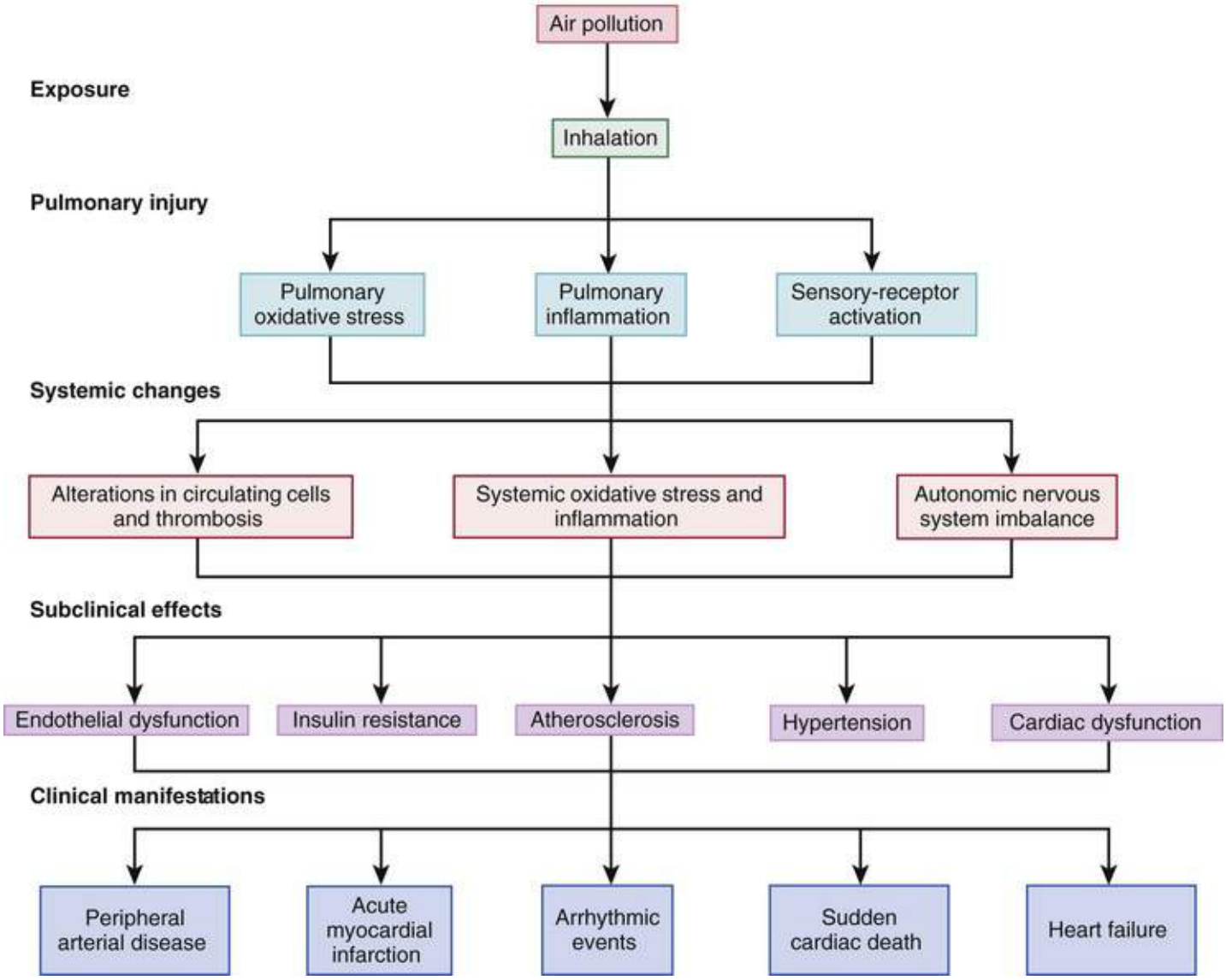

FIGURE 52.1 Cardiovascular effects of exposure to particulate matter (PM). Airborne particles inhaled from the ambient air are deposited in the lung or transported in the circulation, where they induce oxidative stress and establish a state of mild inflammation. Exposure to PM also activates sensory receptors, leading to an imbalance in the autonomic nervous system activity. Systemic oxidative stress and inflammation caused by PM exposures are associated with alterations in the circulating leukocytes and stem cells and subclinical injury to cardiovascular tissues, leading to endothelial dysfunction and exaggeration of insulin resistance, atherogenesis, hypertension, and cardiac dysfunction in susceptible individuals. These alterations manifest as worsening of peripheral artery disease, heart failure, and arrhythmic events and can precipitate acute myocardial infarction or sudden cardiac death.

Myocardial Infarction

Exposure to air pollution significantly increases the risk of acute myocardial infarction (MI) (**see Chapters 58 to 60**). Increased MI risk is associated with exposure to ambient particulate air pollution, gaseous pollutants, household air pollution, and traffic-generated pollutants. Both acute and chronic exposures increase risk. Elevated risk for MI is associated with exposure to elevated PM or traffic exposure over a period as brief as 1, 2, or 6 hours or a few days. The acute risk may remain elevated and may increase even 2 days after exposure. The increase in risk is variable and may range from 10% to 20% increase in risk per 10μg/m^3 increase in $PM_{2.5}$ levels, depending on geographic location, season, and individual vulnerability. The risk is more strongly associated with $PM_{2.5}$ than UFP, PM_{10}, or gaseous co-pollutants. At levels present in most U.S. cities, $PM_{2.5}$ represents an acute threat mostly to elderly

individuals or those who have recognized or unrecognized coronary artery disease (CAD) or structural heart disease. Obese women may be particularly at risk. However, daily $PM_{2.5}$ levels seem to be associated with the risk of ST-segment elevation MI (STEMI) but not non–ST-segment elevation MI (NSTEMI).

Acute exposure to traffic-generated pollution within the hour prior to MI is strongly associated with the onset of MI (odds ratio [OR], 2.9), suggesting that pollutants generated by motor vehicles could trigger acute events. An estimated 7.4% of acute MIs would be prevented if exposure to traffic air pollution did not occur. Long-term exposure to traffic-related air pollution is also associated with a significant increase in acute MI as well as MI recurrence. Similarly, long-term exposure to elevated ambient $PM_{2.5}$ levels also increases the risk of ischemic heart disease death, and each 10μg/m^3 increase in $PM_{2.5}$ levels is associated with a 10% to 30% increase in ischemic cardiac events in those living in areas of high pollution. Significantly higher levels of mortality risk have been seen in those living within 50 m of major roadway with high levels of traffic, and relocation from a less polluted to a more polluted neighborhood increases MI risk in susceptible individuals. Conversely, a decrease in area $PM_{2.5}$ levels reduces ischemic heart disease admissions. In the United States, stronger association of $PM_{2.5}$ levels with CV events has been observed in the Northeast than in other regions, possibly because of differences in the source of air pollution (e.g., greater sulfate-containing pollutants generated by power plants in the East and higher nitrate content of pollutants in the West, generated mainly by transportation sources).

Arrhythmogenesis

Exposure to both ambient air pollution and traffic-related pollutants is associated with cardiac electrical instability, alterations in heart rate, and heart rate variability (**see Chapters 37 to 39**). Similarly, chronic exposure to indoor air pollution can lead to electrical perturbations that may increase arrhythmia risk. Although healthy individuals may be somewhat impervious to the arrhythmogenic effects of air pollution exposure, individuals with preexisting disease are likely to be more sensitive. Exposure to particulate air pollution can affect the autonomic nervous system, often leading to a decrease in parasympathetic tone (**see Chapter 99**). Some studies have reported that even in healthy individuals, long-term exposure to air pollution is associated with QT prolongation (OR, 1.6), intraventricular conduction delay, and dispersion of ventricular repolarization, in part by increasing sympathetic modulation of the heart rate. Ventricular repolarization may also be affected on exposure to household wood smoke. The incremental risk of air pollution in triggering arrhythmias may be higher in elderly persons or individuals who have underlying cardiac disease. The associations with arrhythmias appear to be strongest for PM_{10}, $PM_{2.5}$, and O_3, as well as traffic-generated pollutants. In patients with implantable cardioverter-defibrillators (ICDs; **see Chapter 41**), even moderate increases in air pollution appear to be associated with ventricular arrhythmias within 2 hours of exposure, although the effects may persist over longer durations. Ambient levels of $PM_{2.5}$ within the past 1 to 2 days show a positive dose-dependent relationship with increased risk of out-of-hospital cardiac arrest, particularly in individuals with high CVD risk burden (**see Chapter 42**).

Acute exposure to ambient or traffic-related pollution can increase the risk of atrial fibrillation (AF) as well[7] (**see Chapter 38**). Exposure to $PM_{2.5}$ pollution is associated with prolongation of the PR duration and an increase in the P wave complexity, which are predictors of AF and atrial flutter. In patients with known CVD, for each 6.0μg/m^3 increase in $PM_{2.5}$, the risk of AF increases by 26% within 2 hours of exposure. Exposure to air pollution also leads to a slight increase in the daily maximum heart rate, heart

block frequency, and percentage of time in AF. Episodes of paroxysmal AF detected by ICDs are increased in a few hours after exposure to ambient O_3 levels, although significant associations between AF have also been observed with $PM_{2.5}$, gaseous pollutants, and atmospheric CO. Long-term exposure to traffic-related air pollution in particular is associated with a higher risk of AF and ventricular tachycardia. Independent of other CVD risk factors, living next to major roadways may also increase the risk of sudden cardiac death (SCD) and fatal CHD.[8] A linear 6% increase in the hazard ratio for SCD has been reported for each 100-m increase in residential proximity to a major roadway.

Heart Failure

Although not as strong as that for ischemic heart disease, there is a significant relationship between deaths from heart failure (HF) and exposure to air pollution (**see Chapters 23 and 24**). Short-term changes in PM levels are associated with an increase in daily hospitalization for HF, and a 10μg/m^3 increase in same-day $PM_{2.5}$ is associated with a 1% to 1.5% increase in HF admissions, whereas a reduction in $PM_{2.5}$ reduces HF admissions. In most locations, HF deaths account for 10% of all CVD deaths, but for 30% of CVD deaths related to PM exposure, suggesting that the failing heart may be particularly vulnerable to air pollution. During HF, the heart undergoes adverse remodeling that can compromise cardiac function and electrical conduction. Direct effects of chronic exposure to air pollution on cardiac function and remodeling have been reported in both human and animal studies. Residential proximity to major roadways and higher residential levels of air pollution are associated with increased right and left ventricular mass, even in a cohort free of clinical CVD. Also, exposure to the traffic-generated pollutant NO_2 has been associated with a 5% increase in right ventricular mass, comparable to the increase associated with diabetes or smoking. That HF may be a particularly vulnerable state is supported by a significant association between traffic-related air pollution and increased mortality risk after HF.[2]

Hypertension

Changes in blood pressure (BP) are associated with exposure to both indoor and outdoor air pollution[3] (**see Chapters 46 and 47**). Even modest increases in air pollution are associated acutely with changes in systemic arterial BP (approximately 1 to 4 mm Hg per 10μg/m^3 increase in PM), although the effects may be larger in elderly individuals or those with preexisting CVD. Larger (8 to 9 mm Hg) effects have also been reported 2 to 5 days after exposure to higher levels of $PM_{2.5}$. Chronic exposure to elevated levels of air pollution may lead to the onset of hypertension. Individuals who live near major roadways and are therefore exposed recurrently to traffic-generated pollutants have a higher prevalence of hypertension. Comparing those who live less than 100 m of a major roadway with those who live more than 1000 m, a 9% higher prevalence has been reported. That exposure to air pollution affects BP regulation is supported by data from studies in which healthy young adults were exposed to particulate air pollution. These studies have shown that acute exposure to PM or diesel exhaust could lead to a modest (3 to 4 mm Hg), but rapid increase in systolic BP and a smaller increase in diastolic BP. It is likely that the effect of air pollution on BP may be greater in individuals with CVD, or that the magnitude of the effect may be sufficient to trigger acute events or to induce chronic CV dysfunction. Significantly, antihypertensive drugs appear to mitigate against the effects of air pollution on BP, and therefore appropriate medical management of hypertension could attenuate the impact of air pollution exposure.[2]

In addition to ambient and traffic pollution, indoor air pollution from household biomass burning could

also affect BP and hypertension.[5] In healthy individuals, exposure to $PM_{2.5}$ generated by biomass combustion increases systolic, and to a lesser extent, diastolic BP. The increase is rather small, 2- to 4-mm Hg in systolic and 0.5 to 2 mm Hg for diastolic blood pressure, but may be significant in individuals with preexisting disease. Indoor air pollution due to the use of solid fuels is also associated with increased prevalence of hypertension and an increase in the markers of oxidative stress, inflammation, and cell adhesion; changes that collectively can contribute to the impact of household pollutants on CV health.

Pathophysiology

Inhalation of ambient air particles (<10 μm) results in the deposition of airborne particles in the lung, particularly on bifurcations or angle ramifications of the bronchial tree due to air flow and turbulence, which increases the interaction of PM with the mucous membrane.[9] In humans the median ratio of carinal/tubular deposition of PM is 9 : 1. Within the lung, the coarse (PM_{10}) and fine ($PM_{2.5}$) particles follow different deposition routes, and because they contain different constituents, they elicit different responses. Larger particles are deposited solely in the extrathoracic airways. PM_{10} is preferentially deposited in the bronchial airways, through impaction and sedimentation, and its deposition activates the innate immune response, in part by endotoxin and other bacterial components often associated with aerosolized PM_{10} in ambient atmospheres. However, independent of this biologic material, interactions of PM_{10} with the lung epithelial cells results in the production of interleukin (IL)-8, and the resultant recruitment of neutrophils to the lung leads to airway inflammation. Fine particles are deposited in lung, especially in the alveoli, through sedimentation and brownian diffusion and can also pass into the systemic circulation. These particles carry little or no biologic material and are deposited in the lung in greater quantities than larger particles. In the alveolar spaces, fine particles initially impact the surfactant-rich alveolar lining layer. Interactions between PM and surfactant lipids can lead to physical impairment of lung surface and may be involved in their clearance by macrophages. In addition, impaired surfactant function could lead to chronic lower airway inflammation. The ultrafine particles are mainly deposited in the lung by brownian motion and can pass from the lung to other peripheral organs, including the heart and the brain.

Deposition of PM in the lung leads to the production of reactive oxygen species (ROS) such as the oxygen-centered free radicals superoxide and hydroxyl. The ability of the PM to generate ROS is correlated with its overall metal content. Airborne particles contain a variety of metals (e.g., Fe, V, Cr, Mn, Co, Ni, Cu, Zn, Ti), and these metals catalyze Fenton-type reactions that generate ROS. In addition, PM collected from U.S. cities also contains persistent free radicals derived from redox-active semiquinones. The semiquinone-like radicals are chemisorbed on the particles and provide persistent redox-active surfaces of the particles that, in the presence of oxygen, undergo autocatalysis to generate free radicals such as superoxide. In addition, PAHs present in the particles, which can be metabolically converted to redox-active quinones, may be another source of ROS production. Some investigators suggest that even without ROS on the surface, the carbonaceous core of ultrafine PM can cause oxidative stress merely by presenting a large surface area. PM could also increase ROS production by stimulating an oxidative burst in resting human peripheral blood polymorphonuclear leukocytes (PMNs). Thus, deposition of fine and ultrafine particles could lead to extensive ROS generation in the lung. Data from animal models showing that increased removal of ROS in the lung prevents the vascular effects of PM support the concept that local, pulmonary ROS generation triggers the systemic effects of PM.[10]

Increased ROS production by PM in the lung results in the development of oxidative stress, characterized by depleted antioxidant capacity and accumulation of lipid peroxidation products. This is usually accompanied by a decrease in lung capacity and pulmonary inflammation characterized by the production of several cytokines such IL-8, IL-6, TNF-α, and IL1β. Increased production of cytokines in the lung promotes the accumulation of neutrophils, protein and fibrinogen in the bronchoalveolar fluid. These changes often impair host defense by inducing apoptosis in alveolar macrophages and inhibiting PMN phagocytosis and respiratory bursts. As a result, inhalation of PM induces a state of mild pulmonary inflammation, the systemic consequences of which exacerbate CVD risk. In addition, PM inhalation directly activates sensory receptors.[11] Stimulation of these receptors can cause an imbalance in the autonomic nervous system, which may affect both cardiac rhythm and cardiac conduction, leading to an increase in the risk of arrhythmias and SCD, particularly in vulnerable individuals.

The plausibility of a direct link between PM exposure and adverse CV events is supported by data from studies on humans and animals exposed to PM under well-controlled conditions. For instance, even in normal adult humans, exposure to air pollutants such as diesel exhaust elicits an inflammatory response in the lungs. Similarly, healthy humans respond to concentrated ambient PM with small changes in acute brachial artery vasoconstriction and increased diastolic BP, suggesting that PM exposure acutely affects conduit artery flow. Animal studies have allowed a more detailed evaluation of the CV effects of PM exposure. Exposure to concentrated PM increases vascular inflammation and accelerates atherosclerotic lesion formation in atherosclerosis-prone mice and rabbits, and exposure to diesel exhaust particles results in rapid activation of circulating blood platelets, suggesting that PM exposure increases peripheral thrombosis.[3] The atherogenic effects of air pollution have also been seen in humans. It was recently reported that exposure to increased concentration of $PM_{2.5}$ or traffic-related air pollution is associated with progression of coronary calcification,[12] consistent with acceleration of atherosclerosis, suggesting that exposure to air pollution increases subclinical CVD progression or CVD risk (**see Chapter 44**). Indeed, exposure to high PM levels has been associated with increased platelet activation[13] and increased fibrinogen levels even in healthy adult humans. More recent work has shown that prolonged exposure to concentrated PM exaggerates adipose tissue inflammation and systemic insulin resistance in mouse models of diet-induced obesity. [14] Exposure to PM has also been linked to an increase in insulin resistance, as well as prevalent and incident diabetes in humans.[2] Together, these results provide strong support for the view that PM exposure elicits a range of adverse CV effects, which could explain, at least in part, the positive associations between PM levels and the incidence of CV events and mortality, reported in epidemiologic studies.

Occupational Exposures

In addition to exposures at home, outside, and in traffic, many individuals are exposed to air pollution at work.[6] This may involve exposure to molds, endotoxin, particulates, and gases such as formaldehyde (generated from compressed wood) that might impair CV health and increase CVD risk. Many office buildings contain high levels of indoor particulates and gases, and office equipment such as photocopiers that generate high levels of PM, but mostly these exposures are similar to those at residential locations.

However, workers at plants that generate high levels of PM or gaseous pollutants (e.g., formaldehyde, acrolein, butadiene, benzene) may be particularly at risk, because occupational exposure to these gases has been linked to increased CVD risk. Plant workers involved in the synthesis of aldehydes such as formaldehyde, undertakers, embalmers, and perfumery workers reportedly have a higher risk of

atherosclerotic heart disease, presumably from recurrent exposure to volatile aldehydes. Exposure to 1,3-butadiene, a gas used for the synthesis of rubber, has been associated with an increased incidence of CVD, particularly in African American workers in styrene-butadiene polymer manufacturing plants. Experimental studies with animals have substantiated that exposure to 1,3-butadiene can have atherogenic effects. Chronic occupational exposure to vinyl chloride has also been linked to increased risk of CVD, including hypertension, MI, and other circulatory disorders. Similarly, the use of solvents such as phenol and ethanol is associated with an increase in CVD risk, and carbon disulfide exposure is associated with increased atherosclerosis. Benzene exposure leads to arrhythmogenesis in animals, and workers exposed to benzene show increased prevalence of arterial hypertension, conduction defects, and repolarization disturbances.

Air pollution can also affect workers in occupations that involve frequent exposure to fire and smoke, such as firefighters and military personnel. Firefighters may be particularly at risk.[15] Heart disease accounts for 45% of deaths among U.S. firefighters, and the chances of dying from CHD are 12 to 136 times higher during fire suppression than nonemergency duties. The risk of CV mortality is increased during alarm response (2.8 to 14 times) but is much lower than fighting active fires, suggesting a component of smoke inhalation in triggering CV events. Some studies have suggested that incinerator workers, communities around incinerators, and veterans from the Gulf War have a higher risk of developing CVD because of recurrent exposure to smoke and smoke constituents; however, the evidence is weak and requires additional study.

Management and Intervention

Because it is a community-wide problem, air pollution exposure is difficult to control at an individual level. Clearly, the well-established link between air pollution and heart disease should spur and support regulations limiting industrial emissions and traffic. Indeed, a decrease in air pollution levels in major U.S. cities has resulted in a decrease in CV events and admissions and an increase in life span. Nevertheless, given that 95% of the urban population in major cities is exposed to pollution levels exceeding WHO air quality guidelines, exposure can be reduced by individual choices to diminish the impact of air pollution on CV health. These choices may include avoidance of areas of high pollution, especially traffic pollution, particularly by individuals with high CVD risk. Because residential proximity to major roadways increases exposure to traffic pollutants, avoidance of such exposure may be particularly beneficial for post-MI patients or those with HF.

Individual initiative may be particularly important in minimizing exposure to indoor air pollution. Most indoor pollutants (e.g., molds, endotoxin, bacteria, dust) can be eliminated by maintaining clean living environments, and exposure to large numbers of ultrafine particles can be minimized by avoiding the use of candles, incense, or air fresheners indoors. In developing countries, indoor air pollution can be drastically reduced by discontinuing the use of solid biomass for fuel or by using chimney woodstoves that prevent the accumulation of indoor air particulates. In developed countries, exposure to particles generated by cooking and frying can be minimized by proper ventilation or filtration. Proper indoor air filtration improves endothelial and microvascular function and may decrease systemic inflammation, even in asymptomatic individuals. Gaseous pollutants are difficult to remove, but most airborne particles can be removed by an electrostatic precipitator in a single-pass efficiency of 90% or greater, even for smaller particles. Similarly, in-vehicle air conditioning can reduce exposure to traffic-generated air pollutants. Given the extensive evidence supporting a link between exposure to secondhand tobacco smoke and CVD

risk, eliminating tobacco smoke might have the most robust effect on improving indoor air quality. Lastly, although some dietary interventions have been shown to be marginally effective in decreasing the effects of air pollution, more extensive research is required before such recommendations can be widely advocated or adopted.

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53

Exercise and Sports Cardiology

Paul D. Thompson, Aaron L. Baggish

This chapter presents basic exercise physiology, describes cardiovascular (CV) adaptations to exercise training, and addresses common clinical issues among physically active individuals. The goal is to help clinicians evaluate symptoms produced by exercise, manage questions and clinical problems in athletes and physically active people, and assess the risks and benefits of exercise for individual patients.

Historical Perspective

Debate has long surrounded the cardiovascular risks and benefits of exercise. In 1867 the London surgeon F.C. Sky equated the Oxford-Cambridge crew race to cruelty to animals and opined that such extreme exertion would cause heart disease.[1] Concern about rowers', runners', and bicyclists' hearts emerged in the late 19th century, when these activities migrated from being occupational competitions among only the working classes to being sporting activities for the social elite.[1] The normal CV adaptations to exercise training include resting bradycardia, global cardiac enlargement, and functional pulmonic and aortic valve flow murmurs. Evaluation of these normal adaptations by auscultation and cardiac percussion, the diagnostic tests of the day, led to their interpretation as signs of pathologic conduction disease, dilated cardiomyopathy, and valvular obstruction, respectively.[1] Concerns about the risks associated with prolonged and vigorous exercise were commonplace in the 19th and early 20th centuries. Clarence DeMar, seven-time winner of the Boston Marathon, took a 5-year hiatus from competition during the peak of his competitive years, in part because, according to DeMar, “The frequent warnings of the doctors and fans of the danger to one's heart … had left their impression.”[1] Current concerns about the risks and benefits of exercise include the risk of exercise-related acute cardiac events, the effects of exercise training on cardiac structure, and whether or not long-term endurance exercise training has deleterious CV effects.[2]

Cardiovascular Response to Exercise and Exercise Training

The basic principles of the acute response to exercise[3] and the CV adaptations to exercise training have been summarized elsewhere[4] (**see Chapter 54**). This chapter reiterates relevant essential principles. Physical activity acutely increases systemic oxygen (O_2) demand, which prompts the CV system to increase cardiac output (Q) and the arterial-venous (A-V) O_2 difference. The increase in Q is coupled to the energy required such that there is a 5- to 6-liter increase in Q for each 1-liter increase in oxygen consumption (V_{O_2}). Q is increased by augmentation of both the heart rate (HR) and stroke volume (SV). Several mechanisms increase the A-V O_2 difference. Myocardial oxygen (M_{O_2}) demand depends in part on HR and systolic blood pressure (SBP) and increases with exertion because both HR and SBP increase. This increase in M_{O_2} can produce ischemia in individuals with flow-limiting coronary artery lesions. In addition, the coronary arteries should dilate in response to the myocardial metabolic demands of exertion, but inadequate vasodilation or frank vasoconstriction develops with exercise in some individuals with coronary atherosclerosis because of endothelial dysfunction.[5] Cardiac ischemia, induced by exercise, can contribute to cardiac events during exercise, as discussed later.

The CV response to exercise has both an external and internal work rate.[3] The *external work rate* is the V_{O_2} required by the exercise task and, as mentioned, is a direct determinant of Q. V_{O_2} can also be crudely estimated from treadmill speed and grade or from a stationary bicycle watt requirement. The *internal work rate* refers to the M_{O_2} required for the exercise task and relates directly to increases in HR. In contrast to Q, the HR response to exercise, and therefore the M_{O_2}, is not determined by the external work rate or V_{O_2} but instead by the V_{O_2} required relative to the individual's *maximal exercise capacity*, or V_{O_2}max. Individuals with higher exercise capacity and a greater V_{O_2}max have a larger SV at any given external work rate, such that any exercise task, and V_{O_2} demand, requires a slower HR to generate the

same externally determined Q.

Repetitive aerobic exercise sessions and aerobic exercise training increase maximal exercise capacity, measured physiologically by an increase in V_{O_2}max. This increase in healthy individuals results from increases in both maximal Q and the maximal A-V O_2 difference.[3] Because maximal HR is largely immutable, determined by age, and minimally affected by exercise training, the increase in maximal Q results from an increase in maximal SV. The increase in SV means that performing the same exercise task, which requires the same V_{O_2}, can be performed at a slower HR and a lower MO_2 or internal work rate. The reduction in HR and thereby MO_2 contributes to the increase in exercise capacity in patients with angina pectoris after exercise training (**see Chapter 54**). In addition to the increase in maximal exercise capacity, exercise training also increases *endurance capacity*, the ability to perform submaximal effort for a prolonged period. This effect contributes critically to the exercise training response, because few work and recreational tasks require maximal CV effort.

Intense and prolonged aerobic exercise training produces an array of CV adaptations, commonly referred to as "athlete's heart"[10] (**Fig. 53.1**). Such changes include an increase in resting SV and a decrease in resting HR. The physiologic mediators of training-induced reductions in resting HR are related in part to increased resting vagal tone and reduced resting sympathetic tone. However, the bradycardia persists in trained mice after autonomic blockade or sinus node denervation, suggesting that autonomic changes alone cannot explain the training effect on HR.[6] Indeed, trained mice show widespread remodeling of pacemaker ion channels, including downregulation of the I_f, or funny channel, and blockade of I_f abolished the reduced HR. Highly trained endurance athletes often develop resting bradycardia, which may be associated with marked sinus arrhythmia, first-degree heart block, Mobitz I second-degree atrioventricular (AV) block, or even third-degree AV block during sleep. The reduced AV conduction velocity may make accessory conduction pathways, such as those of Wolff-Parkinson-White syndrome, more apparent. Athletes also have an increased prevalence of an early-repolarization ST-segment pattern and ST-T wave abnormalities, findings also historically attributed to increased vagal tone[7] (**Fig. 53.2**).

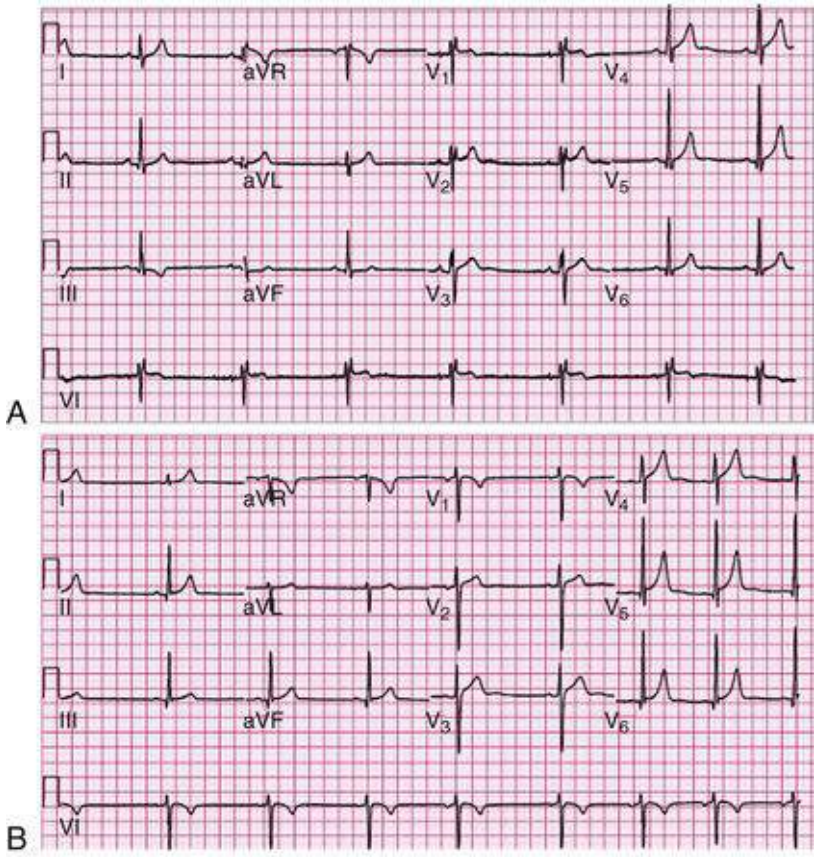

FIGURE 53.1 Twelve-lead ECG tracings from asymptomatic athletes without structural or electrical diseases of the heart demonstrating common findings associated with exercise training. **A,** Sinus bradycardia and an incomplete right bundle branch block resulting from physiologic right ventricular dilation in a 23-year-old male professional hockey player. **B,** Sinus bradycardia with respirophasic sinus arrhythmia, precordial ST-segment elevation characteristic of benign normal early repolarization, and prominent precordial lead QRS voltage, often associated with underlying physiologic left ventricular hypertrophy, in a 19-year-old male distance runner.

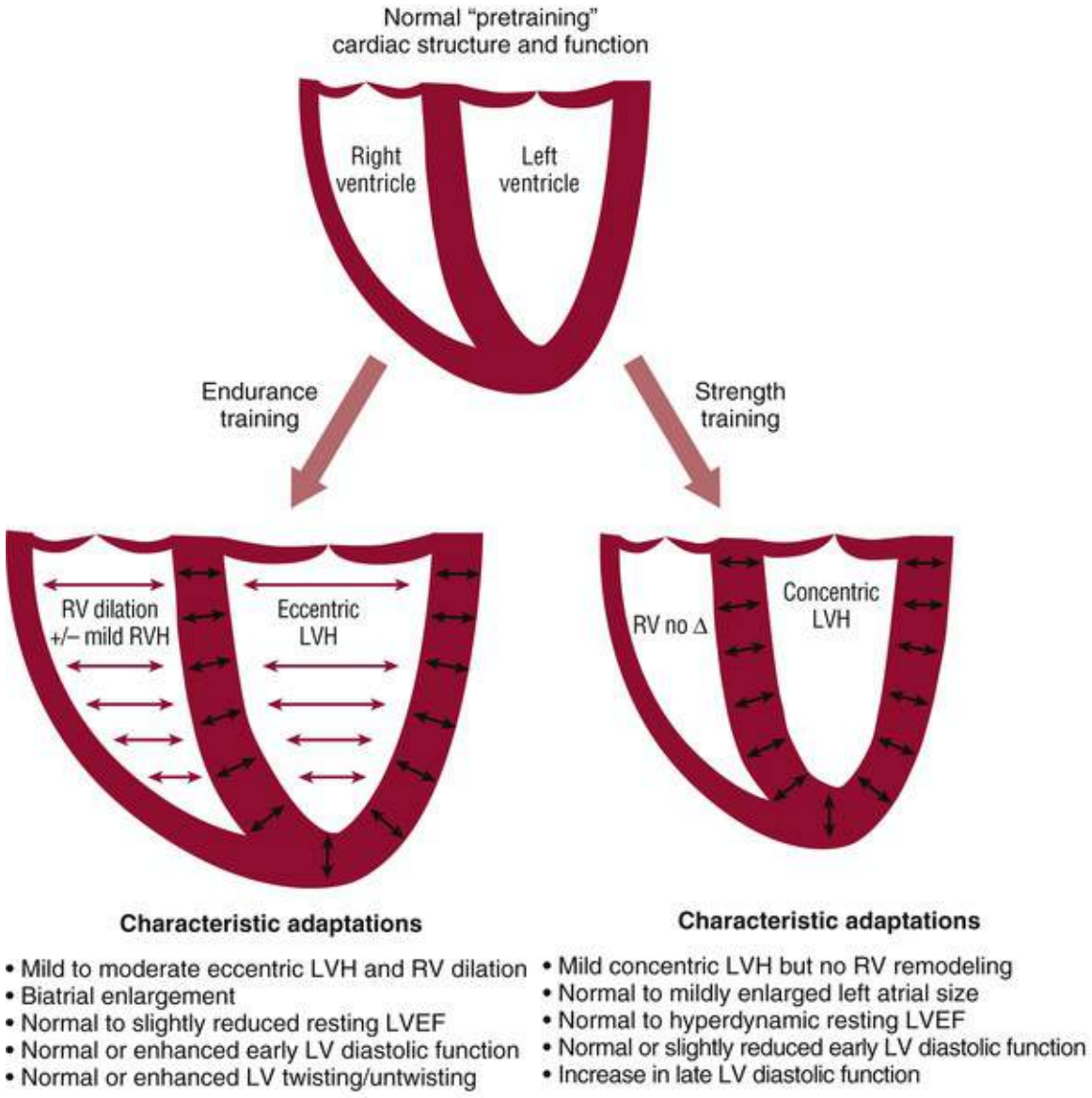

FIGURE 53.2 Summary of the ventricular remodeling that occurs with endurance and resistance exercise training. *LVEF,* Left ventricular ejection fraction; *LVH,* left ventricular hypertrophy; *RV no* Δ, no change in right ventricle; *RVH,* right ventricular hypertrophy. (From Weiner RB, Baggish AL. Exercise-induced cardiac remodeling. Prog Cardiovasc Dis 2012;54:380.)

Four-chamber cardiac enlargement accompanies the increase in SV with training, but left ventricular (LV) wall thickness usually increases only mildly,[4] although chamber dimensions can exceed the standard upper limits of normal (ULN). Small increases in aortic root dimensions also occur, but increases in aortic size greater than expected for body size seldom occur in athletes,[8] even among those playing in the National Basketball Association.[9] In contrast to the extensive cardiac changes reported in endurance-trained athletes, strength exercise training produces modest increases in LV wall thickness with little change in chamber dimensions.[4] Among 1300 elite Italian athletes, 45% exceeded the ULN of 55 mm, with the most marked increases in LV size occurring in the largest athletes and those with the slowest HR.[12] In contrast, LV wall thickness rarely exceeds ULN among trained athletes. For example, among 947 national-caliber and international-caliber Italian athletes, only 16 had LV wall thickness greater than 12 mm.[11] Trained athletes usually have normal resting LV systolic function, most frequently measured as LV ejection fraction (LVEF), but may be near the lower limit of the normal range because large ventricles can meet resting metabolic demands with a lower LVEF.

Cessation of exercise training, or "detraining," may help in clinically differentiating adaptations to

exercise training from hypertrophic cardiomyopathy. Several studies have examined the effect of detraining in endurance athletes with eccentric LV hypertrophy (LVH), a geometric pattern characterized by concomitant LV wall thickening and chamber dilation. Regression of eccentric LVH can occur in highly trained athletes after 6 to 34 weeks (mean, 13 weeks) of abstinence from exercise.[13] A detraining study of 40 Italian male athletes with eccentric LVH and peak fitness LV dimensions (mean ±SD) of 61.2 ±2.9 mm and LV wall thickness of 12.0 ±1.3 mm reported complete normalization of wall thickness and a significant but incomplete reduction in cavity dilation after 5.8 ±3.6 years of detraining[14] (**Figs. 53.3 and 53.4**). Because the LV wall thickening and concentric LVH common in strength-trained athletes can regress partially after 3 months and completely after 6 months of detraining, such diagnostic trials should last 6 months.[15]

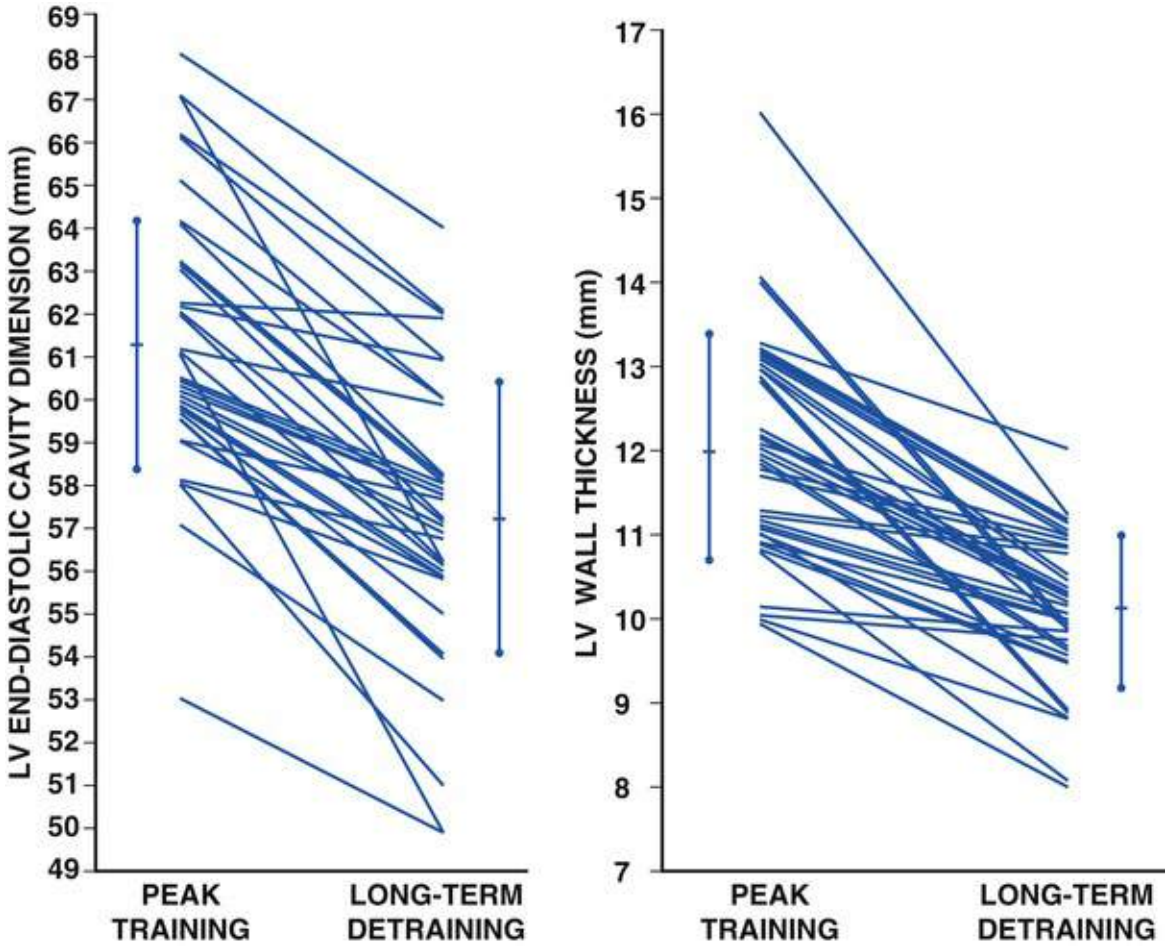

FIGURE 53.3 Echocardiographic measurements of left ventricular (LV) chamber dimensions and LV wall thickness (LVWT) in 40 male Italian athletes measured at their peak of athletic performance (age 24 ±4 years) and after detraining of 1 to 13 years (mean ± SD, 5.6 ± 3.8 years). All had either increased LV chamber enlargement (LVE) of 60 mm or greater or LVWT of 13 mm or greater, or both, at their peak. Nine of the athletes (22%) had persistent LVE greater than 60 mm, but LVWT normalized in all participants. (From Pelliccia A, Maron BJ, Di Paolo FM, et al. Prevalence and clinical significance of left atrial remodeling in competitive athletes. J Am Coll Cardiol 2005;46:690.)

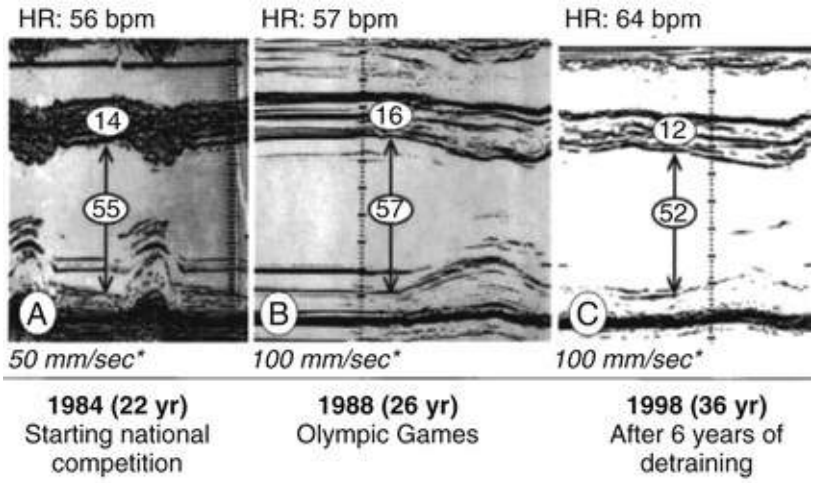

FIGURE 53.4 Serial echocardiograms from an elite canoeist at 22 years of age, when he joined the Italian national team; at 26 years of age, when he competed in the Olympics; and at 36 years of age, after 6 years of detraining; *bpm,* beats per minute; *ovals* show measurements in millimeters. *Paper speed.
(From Pelliccia A, Maron BJ, Di Paolo FM, et al. Prevalence and clinical significance of left atrial remodeling in competitive athletes. J Am Coll Cardiol 2005;46:690.)

Effects of Habitual Physical Activity on Cardiovascular Risk

Multiple epidemiologic, cross-sectional studies examining the frequency of CV events in healthy individuals demonstrate that the more active participants have lower CV risk than their more sedentary counterparts.[16] The reduction in risk in the most active versus the least active individuals is approximately 40%.[16] Even small amounts of physical activity, such as standing, reduce CV risk. CV risk falls progressively with increasing physical activity until approximately 9.1 hours per week of moderate-intensity activity, such as brisk walking.[16] After this level of exertion, there appears to be little additional benefit and, possibly diminution, of the beneficial effects[16] (**Fig. 53.5**) (**see Chapter 45**).

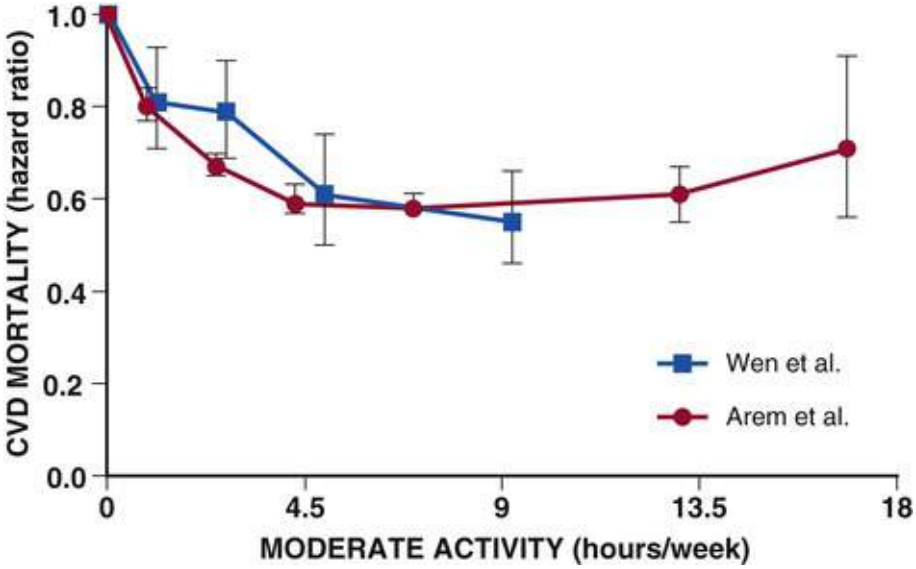

FIGURE 53.5 Relationship between hours of moderate-intensity physical activity and cardiovascular disease (CVD) mortality. (Data from Wen CP et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. Lancet 2011;378:1244–53; and Arem H et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. JAMA Intern Med 2015;175:959-67. Modified from Eijsvogels TM et al. Exercise at the extremes: the amount of exercise to reduce cardiovascular events. J Am Coll Cardiol 2016;67:316-29.)

Also, as discussed in **Chapter 54**, patients participating in cardiac rehabilitation programs have a reduced risk for recurrent cardiac events. The specific mechanisms that mediate this effect have remain undefined, but habitual physical activity has multiple, potentially beneficial effects on atherosclerotic risk factors. Specifically, habitual physical activity reduces SBP, body weight, blood glucose, and triglycerides and increases high-density lipoprotein cholesterol.[17]

Cross-sectional studies, however, cannot prove that the reductions in CV risk result from physical activity alone. Individuals who engage in physical activity may inherit greater exercise capacity, thereby leading them to select active lifestyles and have lower CV risk. Supporting this possibility, rats selected and bred over multiple generations for superior exercise performance have lower CV "risk" profiles, even though these factors did not enter into the selection process.[18] The same physiologic factors associated with increased exercise capacity may also be associated with reduced CV risk, and individuals choosing an active lifestyle may have lower CV risk independent of their exercise habits. This possibility appears unlikely, however, given the plethora of epidemiologic and experimental evidence linking increased physical activity with lower CV risk, but it remains a possibility that requires consideration.

Cardiovascular Risks of Exercise

Despite the putative benefits of habitual physical activity, convincing evidence has shown that vigorous physical activity, generally defined as 6 or more METS, or metabolic equivalents, of resting energy expenditure (1 MET = 3.5 mL of O_2 per kilogram of body weight per minute), transiently increases the risk for sudden cardiac death (SCD) and acute myocardial infarction (AMI).[19] Most of this evidence derives from studies comparing the hourly cardiac event rate during vigorous exertion with rates during more sedentary activities. The pathologic substrate associated with these acute cardiac events varies by age, primarily because the prevalence of the pathologic cardiac conditions responsible for SCD also varies by age. Exercise-related SCD in young individuals, defined as younger than 30 or 40, has historically been attributed to inherited and congenital conditions, including hypertrophic cardiomyopathy

(HCM) (**see Chapters 42 and 78**) and anomalous origin of the coronary arteries (ACA), although acquired conditions such as myocarditis and cardiomyopathy can also cause exercise-related SCD in young individuals.[20]

Recent studies, however, have noted that up to 40% of SCDs in young athletes remained unexplained even after careful autopsy suggesting that other conditions, such as inherited channelopathies, may be the cause.[21] HCM was responsible for only 6% of deaths.[21] The reasons for this apparent shift in the causes of SCD are not clear but could be related to selected case ascertainment in both the present and the earlier studies or more effective diagnosis and care of athletes with HCM. Atherosclerotic cardiovascular disease (ASCVD) causes most exercise-related AMI and SCD in adults.[19] AMI in previously asymptomatic adults during exercise is usually associated with acute coronary arterial plaque disruption.[22] Several triggering mechanisms for plaque disruption may pertain, including increased flexing and bending of atherosclerotic coronary arteries.[19] Approximately 33% of SCDs in adults caused by ASCVD are associated with clinicopathologic findings of an acute coronary syndrome (ACS), whereas the remainder show evidence of nonacute ASCVD.[23]

The frequency of exercise-related CV events appears to be low, but several factors prevent calculation of a definitive incidence in children or adults. Because of the rarity of exercise-related events, the studies available often include only a small number of participants, so slight changes in the number of cases can greatly affect the incidence. A large population registry could address the paucity of events, but few such registries are available. The lack of systematically collected registries has forced many studies to depend on media reports of CV events, an approach that cannot guarantee total case ascertainment. Furthermore, even if all cases were collected, estimation of the denominator—or the population at risk for an exercise event—is difficult because the number of individuals engaged in vigorous exercise in the study cohort is often unknown. These caveats require consideration when evaluating current estimates. The most consistent estimate is one death per year for every 200,000 high school and college athletes,[24] but the rate may be as high as one death per year for every 5100 Division 1 male National Collegiate Athletic Association (NCAA) basketball players.[25] Estimates for adults suggest that one exercise-related death occurs per year for every 15,000 to 18,000 previously healthy adult men.[19] These estimates are derived largely from studies from the early 1980s and represent overestimates, because overall ASCVD events have now decreased in American adults. The risk for exercise-related AMI may be sevenfold higher than for SCD, so the risk for exercise-related AMI in the exercising population may be as high as 1 per 2000 men per year.[19] All studies suggest that women have a much lower risk for exercise-related events.

Approach to Common Clinical Problems in Sports Cardiology

Athletes and active individuals may seek CV evaluation for a multitude of reasons, but the following section discusses several common clinical complaints in athletic patients and the clinical approach to their management.

Decreased Exercise Capacity

Athletes with decreased exercise capacity are frequently referred to CV specialists for evaluation. SV contributes critically to Q and therefore to exercise capacity, but V_{O_2}max also requires maximal performance from its other CV components, HR and A-V O_2 difference, as well as from the central

nervous system, lungs, and skeletal muscle. Decrements in any of these components can compromise exercise performance. An inappropriately fast HR at low levels of exertion as a result of hyperthyroidism can decrease exercise performance, as can exercise-induced asthma, diseases of skeletal muscle, and reduced O_2-carrying capacity from anemia (often resulting from iron deficiency in female endurance athletes who eat a vegetarian diet). Atrial fibrillation or frequent premature contractions during exercise can reduce exercise capacity. Other conditions not directly related to the CV system, including viral illnesses (e.g., mononucleosis, hepatitis) and autoimmune conditions, can initially be manifest in athletes as decreased exercise capacity or exercise intolerance.

These same issues can reduce exercise performance in older athletes, but occult coronary disease with atypical symptoms always requires consideration first in older patients. Many adult athletes with reduced exercise capacity referred for expert evaluation have LV diastolic dysfunction because prior encounters have eliminated the more obvious diagnoses. This scenario often presents as a lifelong endurance athlete with “borderline hypertension” who somehow avoided antihypertensive treatment. These patients frequently have mild resting hypertension but exhibit an exaggerated blood pressure response to exercise.

Psychological factors and overtraining also can cause decreased exercise capacity in athletes. Psychological issues generally occur in young athletes who have lost their desire to compete before their parents have lost interest in the child's sport. This diagnosis often becomes clear if parents or other key adults are included in the patient's assessment. Some athletes appear to find it easier to use a medical excuse for stopping sports participation than to admit that they have lost interest, want to pursue other interests, or “just aren't good enough” to continue.

Evaluation of athletes complaining of decreased exercise performance requires listening to the athlete's history carefully. Practitioners may dismiss many complaints in athletes because their exercise performance remains superior to that of nonathletes, but important cardiac conditions may present sooner in athletes because of the physical demands of their sport. Evaluating performance times and training diaries in endurance athletes often helps plot the time course of the complaint. The conditions mentioned earlier must be excluded, as must obvious cardiac disease. Exercise testing using protocols designed to mimic the athlete's sport frequently helps document the complaint and its cause. Exercise echocardiography and cardiopulmonary exercise testing with specific attention to the oxygen pulse curve are useful when the history suggests diastolic dysfunction. The oxygen pulse can be calculated by dividing V_{O_2} by HR, and assuming no important change in the A-V O_2 difference, it reflects SV. It can help determine when cardiac performance becomes a limiting factor during exercise. Long-term electrocardiographic monitoring, occasionally performed with implanted monitoring devices, can detect cardiac rhythm disorders in athletes with infrequent symptoms. Psychological and emotional issues should be diagnosed only after the exclusion of other, more medical conditions and require frank discussions with the athlete and family. Depression can frequently cause otherwise unexplained fatigue.

Overtraining is a complex interaction of psychological and physiologic fatigue in athletes that can occur after prolonged high-intensity training. The diagnosis of overtraining is made by careful history since there is no diagnostic test for this condition. Diminished exercise tolerance (sometimes with an elevated resting HR), the sensation of nocturnal fevers, and insomnia all characterize overtraining. The insomnia appears paradoxical because the athletes often experience extreme fatigue but find it difficult to sleep as a result of restlessness and sometimes involuntary muscle contractions. Overtraining should be diagnosed only when other conditions are excluded and frequently requires a therapeutic trial of markedly reduced training to see whether the symptoms resolve and performance improves.

Abnormalities Found on Screening

Many athletes are referred to cardiologists because of CV abnormalities found on preparticipation screening. Both the American Heart Association (AHA) and the American College of Cardiology (ACC),[26] as well as the European Society of Cardiology (ESC),[27] recommend preparticipation screening for athletes. The ESC but not the AHA recommends including a resting electrocardiogram (ECG) in the screening evaluation. The debates on CV screening in general, on screening athletes versus screening all children, and on the role of the ECG exceed the scope of this chapter.[28] One widely cited Italian study suggests that screening greatly reduces cardiac events in athletes,[29] but studies from Minnesota[30] and Israel[31] suggest that screening has no benefit. A U.S. National Institutes of Health consensus conference concluded that the data were insufficient to recommend routine screening of the general population or athletes with an ECG.[32] Regardless of the scientific merit, many young athletes do undergo screening with an ECG, and abnormalities emerge.

Screening athletes with or without an ECG can detect a multitude of CV "problems." Well-trained endurance athletes have a slow HR and large SV, which can produce nonpathologic pulmonic flow murmurs in young athletes, especially if the athlete is examined in the supine position, which expands central blood volume. Pulmonic flow murmurs are soft systolic ejection murmurs heard best in the left second and third intercostal spaces in the supine position. Such murmurs typically diminish or disappear when the athlete assumes a sitting position. Older athletes with hemodynamically insignificant aortic sclerosis may have aortic flow murmurs. Athletes can also have ECG evidence of biatrial hypertrophy, LVH, incomplete or complete right bundle branch block, ST-T wave abnormalities, and conduction abnormalities. Most of these abnormalities occur in endurance athletes undergoing intense training. Such changes in strength-trained athletes or in endurance athletes with low training volumes should raise suspicion of a cardiac problem.

Most CV abnormalities found on screening are variants of normal, and most can be dismissed by a simple clinical examination and review of the ECG, with cardiac imaging procedures used to remove any residual doubt. Some families and athletes have ongoing concern once a screening abnormality is identified, so having the athlete and family return in 3 to 6 months is sometimes useful, even when no abnormalities are found, to provide additional reassurance.

A common problem in athletes with a screening abnormality is "diagnostic creep"—the finding of a minor abnormality on screening such as early ECG repolarization, which prompts a second diagnostic test such as echocardiography, which reveals another borderline finding such as mild LVH, which may prompt another diagnostic test such as cardiac magnetic resonance imaging (MRI). Sometimes, because of the CV adaptations that accompany exercise training, each diagnostic study reveals an additional borderline abnormality, thus making it difficult for a clinician to declare the athlete "normal." Screening abnormalities, especially if borderline abnormal, should be judged with less concern than definite abnormalities found in symptomatic athletes, because the screening abnormalities will most frequently represent normal variants.

Cardiovascular Complaints in Athletes

Athletes are sensitive to changes in their physical being and exercise performance and are more likely to note early CV abnormalities because of the CV demands of exercise training and competition. On the other hand, some athletes are excessively concerned about anything that may affect their performance and may seek evaluation for normal body sensations such as muscular aches produced by new training

regimens. Nevertheless, possible CV complaints in athletes should cause greater concern than borderline abnormalities found on screening, and such complaints require careful evaluation with techniques appropriate for the differential diagnosis.

Chest pain is a common complaint in young and old athletes, possibly because the importance of chest pain in public perception, and because athletes have increasing concerns about the possible risks associated with exercise. Chest discomfort in athletes should never be dismissed summarily. Exertional chest pain may be the first sign of important cardiac diseases, including HCM, ACA, or coronary artery atherosclerosis, but several issues pertain particularly to athletes. Determining the duration of chest pain is important, since many athletes without underlying disease experience momentary chest pain. The sensation of momentary chest pain may accompany premature atrial or ventricular contractions, possibly because contraction against closed AV valves produces a momentary sensation of chest fullness. Fleeting chest pain with movement in athletes may also be related to muscle and joint issues. The relationship between chest pain and recent resistance exercise involving the chest muscles, such as push-ups and bench presses, is also important because such training is a frequent cause of chest discomfort in athletes. Some athletes who have died with ACA had normal exercise stress test results,[33] indicating the importance of pursuing workups that include coronary imaging in athletes if the symptoms are worrisome, even when exercise testing yields normal results. Such an approach differs distinctly from what we advise in asymptomatic athletes with borderline test results.

Well-trained athletes often have *vasovagal syncope*, also known as "neurally mediated syncope," probably because of their resting bradycardia and large venous capacity, which permits sequestration of large amounts of blood when the athlete is upright and motionless.[34] Athletes also often have positive tilt-table tests as a result of the same physiologic changes. Neurally mediated syncope most often occurs in athletes immediately following exercise, particularly with abrupt termination of exercise. This common entity, "postexertional syncope," is benign and can frequently be managed by teaching the athlete avoidance techniques. The most important avoidance technique is for the athlete to keep moving after effort so that the muscle pump in the calf continues to return blood to the systemic circulation. Dietary sodium augmentation, aggressive pre-exercise hydration, and the use of commercially available compression socks may also prove useful. The key issue in evaluating syncope in athletes is to determine whether the syncope occurred during exertion. Syncope at rest or immediately after exercise under conditions consistent with vasovagal syncope or postural syncope is usually caused by these conditions. In contrast, syncope during exercise should prompt a careful search for more serious problems, including HCM, aortic stenosis, cardiac arrhythmia, or ACA.[34]

Determining Athletic Eligibility

The AHA and ACC have developed eligibility and disqualification recommendations for cardiac conditions according to the advice of 15 task forces who created the guidelines based on literature review and expert opinion.[35] Guidelines are necessarily restrictive because they are used by a wide variety of clinicians, many of whom will have no special qualifications or expertise in evaluating athletes. As clinicians gain more experience in evaluating athletes with minor variants of CV disease, many of these guidelines may appear overly restrictive, but they are periodically updated and currently provide the best available consensus opinion on how to advise athletes regarding their risk related to sports participation.

We use these guidelines as the basis for most of our recommendations but alter the final decision depending on multiple factors, including our perception of the athlete's risk given the severity of the lesion

and symptoms, the importance of participation for the athlete's mental health, the danger to others, and the willingness of the athlete and family to share risk in making the decision. The diagnosis, its attendant risk, and the basis for any recommendations also require discussion (if the athlete agrees) with other key individuals, such as parents, school or team administrators, coaches, athletic trainers, and business agents. We use a similar decision-making approach with older athletes, although they usually have a greater ability to understand and assume personal risk.

Advising Adult Athletes with Atherosclerotic Cardiovascular Disease

Vigorous exercise increases the risk for SCD and AMI in adults with occult ASCVD, and individuals with diagnosed disease have greater increased risk with exercise. Many adults with ASCVD want to return to active athletic competition, often in demanding endurance events such as marathon running or long-distance cycling. Imaging techniques such as scanning for coronary artery calcification have expanded the detection of asymptomatic and presymptomatic disease. All athletes with ASCVD require an explanation that vigorous exercise acutely increases their CV risk and that moderate amounts of exercise probably confer as much ASCVD reduction benefit as more intense activity.[16] Despite such discussion, many such athletes want to return to competition or intense exercise training. Plaque stability may increase with decreasing lipid content of the plaque;[36] most plaque regression occurs within 2 years of aggressive lipid lowering.[37,38] Consequently, in athletes strongly wanting to return to competition, we advise a minimum of 2 years of aggressive lipid treatment with the goal of achieving the lowest possible serum lipid levels before returning to competition. We also emphasize the importance of blood pressure (BP) control and tobacco avoidance, as well as the need to report symptoms that may indicate progression of disease. This approach allows the athlete to have the hope of further competition, but it also helps motivate them to adhere to risk reduction strategies.

Adult athletes receiving lipid-lowering or antihypertensive treatment occasionally inquire whether their medications should be stopped before endurance athletic competition. We encourage athletes to continue aspirin and other antiplatelet medications under the assumption that they may help avoid an acute cardiac event if plaque disruption occurs. We continue therapy with a beta blocker to avoid the increase in adrenergic activity that occurs when use of these drugs is stopped abruptly. We generally discontinue other antihypertensive medications on the day of the athletic event because exercise acutely reduces BP, and we want to avoid postexertional hypotension. We routinely discontinue statins for 5 to 7 days before endurance athletic competition because statins magnify the increase in creatine kinase (CK) that occurs with exercise,[39] and the combined effects of statins and exercise could lead to rhabdomyolysis.

Valve Disease

Valvular disease in athletes should be managed according to principles for the nonathletic population and AHA/ACC recommendations,[40] although several issues merit note.[41] Athletes with echocardiographic evidence of critical aortic stenosis (AS) should undergo careful evaluation for symptoms and maximal exercise stress testing that simulates as closely as possible the athlete's typical exercise training and competition.[41] Many adult athletes with critical AS ignore important dyspnea at the start of exercise because it dissipates within 5 to 10 minutes, but this “warm-up dyspnea” frequently indicates clinically important AS.

Athletes generally tolerate aortic regurgitation (AR) well, probably because the increased HR during

exercise decreases diastole and regurgitant flow.[41] Consequently, we rarely restrict athletic competition despite severe AR in the absence of evidence of ventricular deterioration or unexplained symptoms with exertion. We also rarely restrict resistance exercise in this group despite concern that this type of exercise increases AR, because we know of no data that indicate any benefit of such restriction.

Great concern exists regarding exercise and aortic dissection in athletes with a bicuspid aortic valve (BAV), and some clinicians have restricted participation in this group because of concern that athletics will contribute to aortic dilation.[41] Given the prevalence of BAV in approximately 1% of the population and the rarity of aortic dissection in young athletes, we do not restrict activity unless the aortic diameter exceeds 45 mm. The AHA/ACC Aortic Diseases Task Force recommends aortic root measurements biannually for individuals with aortic diameter greater than 40 mm in men and 36 mm in women.[42] Athletes found to have BAV should undergo imaging to determine proximal ascending aortic dimensions at diagnosis and then should be monitored by serial imaging during their years of competitive sport participation.

Elevated "Cardiac Enzymes"

Cardiac troponin T and I (cTnT and cTnI) are used as markers of myocardial necrosis, but athletes have increased cTnT and CTnI levels[43] after prolonged exertion, such as a marathon run,[43] or even after a brief intense treadmill run lasting only 30 minutes[44] (**Fig. 53.6**). Clinicians need to be aware that endurance athletes may have elevated cTn levels after exertion, and that the diagnosis of an acute cardiac event in an athlete requires confirmatory evidence in the form of either symptoms, the ECG, or echocardiographic evidence of myocardial injury.[43]

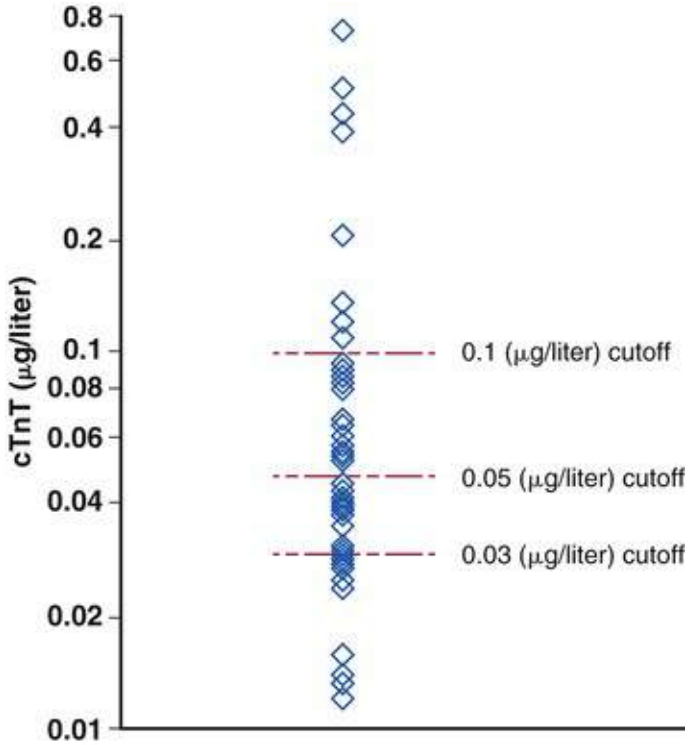

FIGURE 53.6 Cardiac troponin T (cTnT) values obtained 30 minutes after these 72 runners completed the 2002 or 2003 London Marathon (a 42-km footrace). The acute myocardial infarction (AMI) level for this assay was set at greater than 0.05 μg/liter; 36% of the runners exceeded this value. (From Shave RE, Whyte GP, George K, et al. Prolonged exercise should be considered alongside typical symptoms of acute myocardial infarction when evaluating increases in cardiac troponin T. Heart 2005;91:1219.)

Emerging Issues in the Cardiac Care of Athletes

Several emerging concerns suggest that lifelong endurance exercise may have deleterious effect on cardiac function.[2] Although not well documented, clinicians treating athletes should be aware of these concerns.

Atrial Fibrillation

Atrial fibrillation (AF) is epidemic and affects 1% of the U.S. population.[45] Low levels of physical activity and low exercise capacity are both risk factors for AF, and improved physical fitness with exercise training reduces the recurrence of AF independent of weight loss.

In contrast to this reduction in AF with moderate physical activity, the incidence of AF in the Cardiovascular Health Study in those exercising at the highest level was not different from that in inactive subjects.[45] Other studies have demonstrated higher rates of AF among participants in endurance events who ran the most races or had the most years of exercise training. The compendium of results suggests a U-shaped relationship between exercise training and AF, with reductions in AF with moderate amounts of physical activity and an increase with more intense and prolonged activity. Possible mechanisms for this relationship include increased atrial size, changes in autonomic tone, or increased inflammation.[45]

Accelerated Atherosclerosis

Several reports suggest that long-term endurance athletes have increased coronary artery calcification (CAC) scores compared to their sedentary counterparts.[2] We have seen many asymptomatic athletes with remarkably high CAC values despite low ASCVD risk factors. Such increased CAC scores have unclear significance. Increasing CAC scores in the general public are associated with increased ASCVD risk, but the degree to which this relationship applies to athletes is unknown. It is noteworthy that dense CAC portends lower risk,[46] perhaps because densely calcified plaques are less likely to rupture. Our approach is to evaluate the athlete for exercise-induced ischemia, treat ASCVD risk factors aggressively, especially with lipid-lowering agents, and provide reassurance that the significance of this finding is unknown and may be protective rather than deleterious.

Myocardial Fibrosis

At least three studies have detected the presence of late gadolinium enhancement (LGE) with cardiac MRI in 12% to 50% of veteran endurance athletes.[2] Athletes with LGE had exercise-trained for much of their lives and had cardiac dimensions larger than comparison athletes. The LGE volume was small and often located near right ventricular insertion sites, suggesting mechanical stress as the cause. The presence of LGE suggests that prolonged exercise training produces myocardial fibrosis, but this possibility requires more extensive study for confirmation and determination of its significance.

Noncompaction Cardiomyopathy

The left ventricle is highly trabeculated during embryonic cardiac development to increase myocardial surface area and thus facilitate the delivery of oxygen and nutrients from intracavitary blood to the myocardium. These trabeculae regress and the myocardium becomes compacted during normal embryonic

development. The degree of embryonic trabecular regression varies, and many healthy people have some trabecular tissue within the left ventricular (LV) cavity. Noncompaction cardiomyopathy (NCCM) results from an arrest of this process characterized by a hypertrabeculated left ventricle with a thin, subepicardial, compacted layer. First described in 1984 and named in 1990, NCCM is a relatively new entity.[47] NCCM presenting in adults is inherited in an autosomal dominant pattern, but an X-linked pattern is seen in pediatric patents.[47] NCCM can produce myocardial dysfunction, systemic emboli from the deep ventricular pits, and SCD. There are various diagnostic criteria, but a ratio of noncompacted (NC) to compacted (C) myocardium greater than 2 is frequently used.[47] This cut point can be problematic for clinicians treating athletes, especially African American athletes, because 20% of 1146 athletes had increased trabeculations and 8% fulfilled criteria for NCCM,[48] and because African Americans have increased LV trabeculae even in the absence of exercise training. Referrals for possible NCCM in athletes are increasing because of clinicians' growing awareness of the condition, and because the expanded ECG screening of athletes has increased the number of athletes referred for echocardiography. Most of the individuals referred do not have NCCM but rather the benign, mildly trabeculated, normal LV variant previously described. We advise obtaining a careful family history and reviewing the myocardial images, with special attention to LV systolic function and thickness of the compacted layer. Patients with true NCCM should have decreased ventricular function and a thin, compacted layer. The compacted layer is normal and can even be slightly thickened in athletes. (**See also Chapter 75**.)

Exercise in Arrhythmogenic Right Ventricular Cardiomyopathy

Multiple studies since the 1990s have demonstrated that the right ventricle can dilate after prolonged endurance exercise, possibly because the relative increase in right ventricular strain during exercise exceeds that of the left ventricle.[2] Arrhythmogenic right ventricular cardiomyopathy/dysplasia results from defects in the desmosomal proteins that help connect myocytes. Athletes with defects in desmosomal protein genes are more likely to satisfy the diagnostic criteria and to have a worse prognosis than similarly endowed nonathletes.[49] Exercise also accelerates the disease process in animals with genetic desmosomal defects.[50] These results demonstrated that exercise training accelerates the clinical course of right ventricular cardiomyopathy in individuals genetically predisposed to the disease, suggesting that prolonged exercise or exercise training may exacerbate the clinical course of other genetic cardiac diseases.

Conclusion

Cardiovascular clinicians require a working knowledge of exercise physiology, the CV adaptations to exercise training, and the risks and benefits of exercise to advise and evaluate active patients appropriately. Clinicians should avoid overreacting to borderline findings detected on CV screening of asymptomatic athletes, but should also avoid ignoring possible cardiac symptoms in active individuals. Sports cardiology has emerged as a subspecialty of cardiology, but general cardiologists can deal with many of the management issues and queries adequately if they understand the CV adaptations to exercise and the most common pathologic conditions that affect athletic patients.

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Exercise-Based, Comprehensive Cardiac Rehabilitation

Paul D. Thompson, Philip A. Ades

Historical Perspective

Until the early 1950s, the standard treatment of myocardial infarction (MI) was several weeks of hospitalization followed by months of restricted physical activity. Exercise-based cardiac rehabilitation (CR) originated to reverse the physical deconditioning produced by this restriction of physical activity. Exercise training was central to this process and was one of the few interventions that reduced exertional angina pectoris in the era before beta-adrenergic blocking agents and coronary artery revascularization procedures.[1]

Shorter hospitalizations, along with effective medications and procedures to treat myocardial ischemia, have changed CR programs. Exercise training is still important, but the rehabilitation effort now includes education and counseling to increase secondary prevention behaviors, improve psychological well-being, and increase adherence to medications and diet as key components.[2] U.S. Centers for Medicare and Medicaid Services (CMS) guidelines reflect these changes and require that CR programs not only provide exercise training but include education and counseling to modify cardiac risk factors. Consequently, CR programs are now often referred to as "cardiac rehabilitation/secondary prevention programs."[2] The American Heart Association (AHA) and American College of Cardiology Foundation (ACCF) strongly recommend comprehensive CR programs (class I indication) for patients who have undergone percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG), who have suffered an acute cardiac syndrome, or who have stable angina pectoris or peripheral vascular disease.[3] This recommendation received the highest level of evidence (A) for all conditions except angina (level B).[3] Exercise training is a class I recommendation for patients with stable chronic systolic heart failure and a left ventricular ejection fraction (LVEF) of 35% or less, whereas CR is a class IIa recommendation.[4] CMS also considers comprehensive CR to be "reasonable and necessary" for patients after valve surgery and heart or heart-lung transplantation.[5] Participation rates in CR have been low, ranging from 19% to 34% nationally,[6] although increased use of electronic medical records may increase referral rates.[7]

Exercise training is central to CR and risk reduction programs because it increases exercise capacity and reduces exercise-induced cardiac ischemia and angina. Meta-analyses of randomized controlled trials (RCTs) of CR have shown benefits of exercise training alone or exercise training combined with comprehensive secondary prevention practices.[8,9] Because risk factor reduction is discussed elsewhere in detail (**see Chapters 45, 47, and 48**), this chapter specifically addresses exercise training in the CR process.

Basic Principles of Exercise Physiology and Training

Maximal Oxygen Uptake

Skeletal muscle contains only small amounts of energy for immediate use. Exercise increases the body's oxygen (O_2) requirements to supply energy to the exercising muscle. The amount of O_2 consumed, referred to as ventilatory oxygen consumption (V_{O_2}), assesses the amount of energy used during effort. Rearranging the Fick equation—cardiac output (Q) = V_{O_2}/arterial-venous O_2 difference (A-V O_2 Δ)—demonstrates that V_{O_2} is the product of Q and A-V O_2 Δ. Thus, the metabolic demands of exercise are met by increasing O_2 delivery through increases in Q, which in turn is the product of heart rate (HR) and

cardiac stroke volume (SV), as well as through increases in A-V O_2 Δ. A-V O_2 Δ increases during exercise by redistribution of blood flow from nonexercising tissue (e.g., kidneys, splanchnic bed) to exercising muscle, by increased O_2 extraction in the exercising muscle, and by hemoconcentration as a result of plasma fluid losses into the interstitial space of exercising muscle. The increase in Q during exercise is tightly linked to the increase in VO_2, such that a 1-liter increase in VO_2 elicits approximately a 6-liter increase in Q. VO_2max—the maximal amount of oxygen that an individual can transport during exercise before being limited by fatigue or dyspnea—measures maximal exercise capacity. VO_2max expressed as either an absolute value (liters per minute) or relative to body weight (milliliters per kilogram per minute) provides a highly stable and reproducible measure of exercise capacity. The maximal increase in A-V O_2 Δ is fixed at approximately 15 to 17 vol-%. Because the exercise work rate determines VO_2, which is the product of Q and A-V O_2 Δ, and because the maximal A-V O_2 Δ is relatively fixed, VO_2max provides an indirect measure of maximal cardiac pump capacity, or maximal Q and SV.

Myocardial Oxygen Uptake

Myocardial oxygen demand (MO_2) can be estimated as the product of HR and systolic blood pressure (SBP)—the so-called double product. Although the absolute exercise work rate determines VO_2 and Q, increases in HR and SBP are determined by the exercise VO_2 requirement as a percentage of VO_2max. Consequently, for any absolute exercise level, an individual with a larger VO_2max uses less maximal capacity and has a lower HR and SBP response to exercise. The key point is that MO_2 is not determined solely by the external exercise work rate, but by the exercise work rate *relative* to maximal exercise capacity.

Ventilatory Threshold

Expired carbon dioxide (VCO_2) also increases as the exercise work rate increases. Increases in VO_2 and VCO_2 are parallel early during exercise, but the rate of CO_2 expiration increases more rapidly, and the coupling of VO_2 and VCO_2 diverge at what is termed the *ventilatory threshold* (VT). This divergence results from the increase in blood lactic acid, buffering of the lactic acid H^+ ions by bicarbonate, and the subsequent exhalation of additional CO_2. VT has also been called the “anaerobic threshold” and OBLA (for “onset of blood lactate accumulation”). Because CO_2 stimulates the respiratory drive, VT is also associated with a nonlinear increase in the respiratory rate and mild dyspnea. VT occurs at approximately 50% of VO_2max in non–exercise-trained individuals but at higher levels of the percentage of VO_2max in exercise-trained subjects. VT is an important measurement of exercise tolerance because it represents the maximal steady work rate that can be maintained during submaximal exercise.

Effect of Cardiac Disease on Exercise Performance

Exercise performance may be normal for age and sex in individuals with cardiac disease. Alternatively, diseases that limit maximal SV, impair the HR response, or cause myocardial ischemia that produces limiting symptoms or a diminished increase in SV may impair exercise capacity. Medications that limit the HR response to exercise (e.g., beta blockers) or restrictions in physical activity that produce a detraining effect may also contribute to reduced exercise tolerance in cardiac patients.

Effect of Exercise Training on Exercise Performance

Either aerobic or strength training increases exercise capacity. Strength training produces an increase muscular size, strength, and endurance of the exercise-trained muscle. Aerobic exercise training principally increases exercise capacity, reflected as an increased V_{O_2}max. This increase in maximal exercise capacity means that any submaximal work rate requires a lower percentage of V_{O_2}max, thereby reducing the HR and SBP response and MO_2 requirements. Endurance exercise training also increases the absolute VT and VT as a percentage of V_{O_2}max. Multiple adaptations contribute to improvement in aerobic exercise tolerance after training, including increases in SV and widening of the A-V O_2 Δ.

The magnitude of the increase in exercise V_{O_2}max with endurance exercise training depends on multiple factors, including the individual's age, baseline fitness level, the intensity and duration of the training regimen, genetic factors, underlying disease states, and whether testing and training use similar exercises, referred to as the “specificity” of training. In general, young persons trained intensively have greater improvement in exercise tolerance. Increases in V_{O_2}max average 11% to 36% in CR patients,[10] although the response varies with the severity of the underlying disease. Individuals with markedly reduced ventricular function, for example, may achieve much of their increase in exercise capacity by widening the A-V O_2 Δ, whereas increases in Q have been documented with 12 months of exercise training in some cardiac patients.[1] In addition to increasing maximal exercise capacity, endurance exercise training—by virtue of its effects on VT—increases endurance capacity. This effect is extremely important because increased submaximal exercise endurance capacity reduces dyspnea at submaximal work rates and facilitates the performance of most daily tasks.

Effects of Cardiac Rehabilitation and Exercise Training on Morbidity and Mortality

Patients with Angina Pectoris

Most patients with angina pectoris currently control their symptoms with medication or eliminate them by undergoing PTCA or CABG. Consequently, with rare exceptions,[11] much of the evidence that exercise training improves effort tolerance in patients with angina pectoris antedates 1990. Exercise training increases exercise time until the onset of angina—or eliminates angina entirely—by at least two mechanisms. First, as discussed earlier, exercise training increases V_{O_2}max, thereby reducing the HR and SBP response to submaximal exercise. This reduction in the double product reduces the MO_2 requirements and delays the onset of angina. Second, exercise training improves endothelial function.[11] With exercise, normal coronary arteries dilate, but atherosclerotic coronary arteries often fail to dilate or vasoconstrict. Exercise training improves endothelial vasodilator function, as measured by quantitative coronary angiography during infusion of acetylcholine.[12] Some patients also demonstrate increases in the rate-pressure product at the onset of angina after only a short period of exercise training,[1] further suggesting improved endothelial function (**Fig. 54.1**).

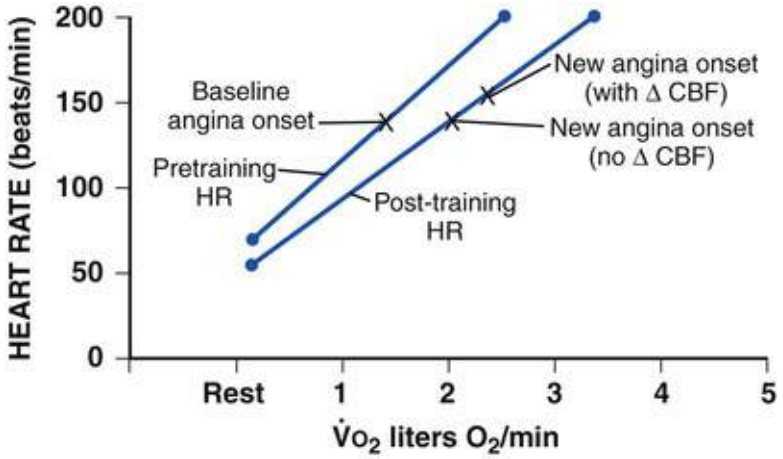

FIGURE 54.1 Changes in exercise tolerance and the onset of angina with exercise training. The heart rate (HR) versus oxygen consumption (VO_2) slope shifts so that any work rate (VO_2) elicits a slower HR response. Angina is delayed but occurs at the same HR if there is no change in coronary blood flow (CBF) (new angina onset [no Δ CBF]). Angina is delayed but occurs at a higher HR if CBF is increased by improved endothelial function. (Reproduced from Thompson PD: Exercise prescription and proscription for patients with coronary artery disease. Circulation 112:2354, 2005.)

Exercise training has particular utility in patients with angina who are not amenable to coronary interventions, but a clinical trial of 101 men age 70 or younger suggested that exercise training is useful in other patients with stable angina.[11] Participants were randomly assigned to 1 year of exercise training or to PTCA. The exercise training consisted primarily of daily 20-minute home bicycle ergometer exercise sessions plus a weekly 60-minute supervised session. Forty-seven participants in each group completed the trial. The exercise level at the onset of ischemia increased 30% in the exercise-trained group and 20% in the PTCA group (P = NS), a nonsignificant difference, but maximal exercise capacity (20% versus 0%) and VO_2max (16% versus 2%) increased significantly more in the exercise-trained group. At 1 year, 88% of the PTCA participants versus only 70% of the exercise-trained participants experienced a major cardiovascular event (P = 0.023) (**Fig. 54.2**). This study predated the widespread use of drug-eluting stents, but only 15% of the PTCA group demonstrated greater than 50% narrowing at the PTCA site, and even assuming no in-stent restenosis, the exercise group would still have had a greater event-free survival rate (88% versus 72%, P = 0.039). The authors noted that angioplasty treats one culprit lesion, whereas exercise training addresses endothelial dysfunction throughout the vascular system. These results may not apply to all individuals with stable angina, but do document the suitability of exercise training for managing select patients with angina.

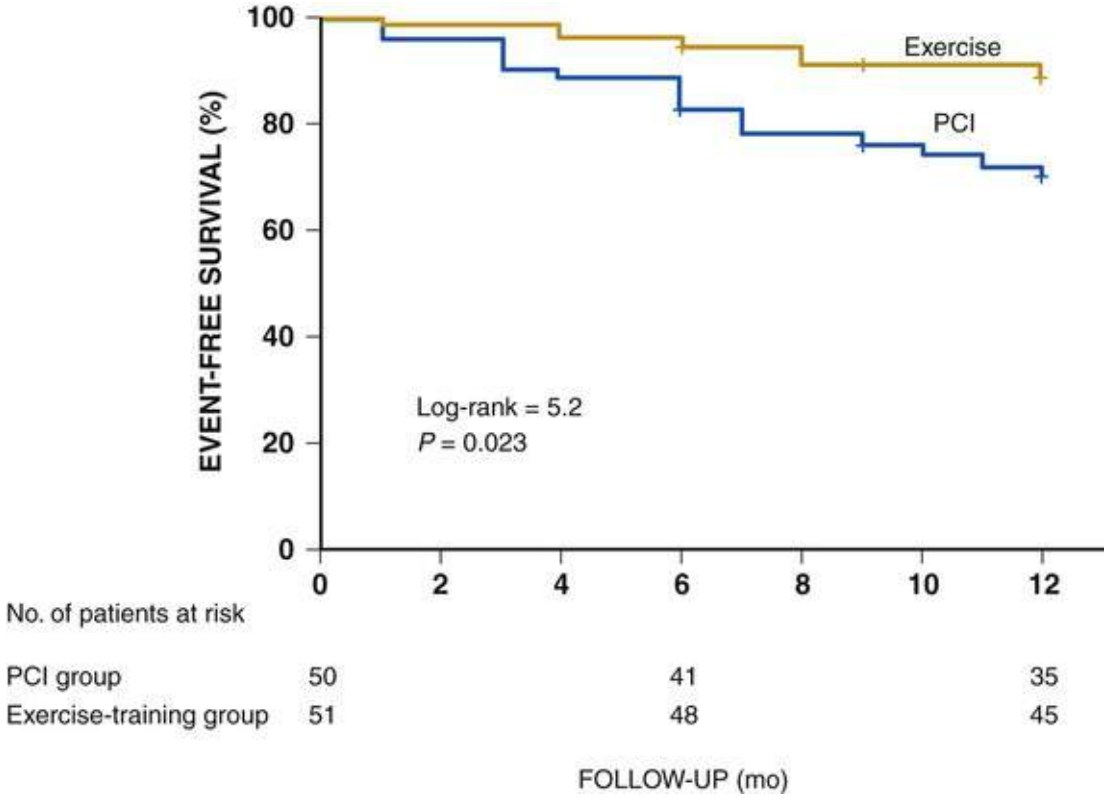

FIGURE 54.2 Event-free survival in 101 carefully selected patients with stable angina randomly assigned to percutaneous coronary intervention (PCI/stent) or to 1 year of exercise training. Numbers at bottom indicate patients free of events. Event-free survival was significantly better in the exercise-training group (88% versus 70%; $P = 0.02$ by log-rank test). (Reproduced from Hambrecht R, Walther C, Mobius-Winkler S, et al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. Circulation 2004;109:1371.)

Patients with Coronary Artery Disease

A systematic review identified 47 studies in which 10,794 patients with MI, CABG, PTCA, or angina were randomly assigned to exercise-based CR or to usual care.[8] Total mortality and cardiovascular (CV) mortality were 13% and 26% lower, respectively, at 12 months or more of follow-up, and hospital admissions were 31% lower in the first year of the study ($P < 0.05$ for all). Subsequent MI, CABG, or PTCA did not decrease. The most recent meta-analysis included 63 studies of 14,486 patients with MI, PTCA, CABG, angina, or angiographically defined coronary disease.[9] CV mortality and hospital admissions decreased 26% and 18%, respectively, with CR. Total mortality was 11% lower with CR ($P > 0.05$), but these mortality data were affected by a large study in which the CR intervention was generally only once weekly for 6 to 8 weeks and in which the 1-year data suggested that the controls were doing more exercise than those randomized to CR.[13] CR showed similar benefits regardless of the nature of the program (exercise only versus other).[8,9]

Patients After Percutaneous Transluminal Coronary Angioplasty

Few large trials have examined the effects of exercise-based CR in patients following PTCA. A retrospective analysis of 2395 patients after PTCA noted an approximately 45% reduction in mortality ($P < 0.001$) in the 40% of patients who participated in CR.[14] Rehabilitation did not affect recurrent MI or subsequent revascularization, but the reduction in mortality did not differ by sex, age, or PTCA urgency,

suggesting that CR benefits almost all patients after PTCA. Unfortunately, self-selection bias might contribute to these results, but they agree with the overwhelming theme that CR improves clinical outcomes.

Patients with Heart Failure

Until 2009, meta-analytic data supported a benefit of exercise in patients with heart failure (HF) (**see also Chapter 25**).[15] HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) was the first large-scale, adequately powered trial to examine the effect of exercise training on CV outcomes in patients with stable HF.[16] HF-ACTION randomly assigned 2331 patients with LVEF of 35% or less to exercise training or a control group. Exercise-training patients were encouraged to participate in 36 supervised exercise sessions over 3 months and were transitioned to home exercise, with the goal of exercising five times weekly for 40 minutes.

The mean duration of follow-up was 3.1 years, with a range of 1 to 4 years. Total mortality (−4%, P = 0.7), CV mortality or CV hospitalization (−8%, P = 0.14), and CV mortality or hospitalization for HF (−13%, P = 0.06) decreased insignificantly more in the exercise-trained group than in the control group. These results were reexamined after adjusting for prespecified confounders, including baseline exercise duration, LVEF, a psychological depression index, and a history of atrial fibrillation or flutter. After this adjustment, total mortality or hospitalization (−11%, P = 0.03), CV mortality or hospitalization (−9%, P = 0.09), and CV mortality or CV hospitalization (−15%, P = 0.03) decreased, suggesting that exercise training had beneficial effects in patients with HF (**Fig. 54.3**).

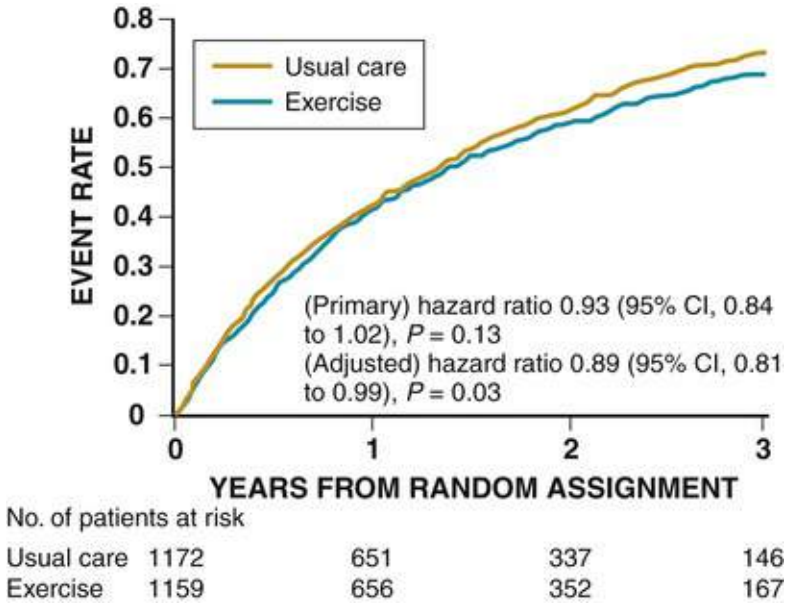

FIGURE 54.3 All-cause mortality or all-cause hospitalization in HF-ACTION. The hazard ratio was not reduced in the unadjusted data but was statistically significant when adjusted for baseline exercise duration, left ventricular ejection fraction, Beck Depression Inventory II score, history of atrial fibrillation or flutter, and cause of heart failure. (Reproduced from O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439.)

The HF-ACTION results were less robust than expected, given a prior meta-analysis suggesting that exercising training reduces overall mortality by 35%,[17] but HF-ACTION may have underestimated the benefits of exercise training in patients with HF. The analysis used an intention-to-treat approach, but the exercise group had poor adherence to exercise training. Only 736 patients (60%) completed the 36

supervised exercise sessions. The poor adherence to exercise is important because exercise volume was a highly significant predictor of CV mortality and HF hospitalization,[18] and even moderate exercise was associated with greater than 30% reductions in subsequent risk.[18] The investigators attempted to enhance long-term exercise adherence by providing home treadmills or exercise cycles, HR monitors, and other adherence optimization strategies.[16] Despite such efforts, peak V_{O_2} increased only 4% in the exercise-training group. This effect was short of the 10% increase projected by the study investigators and well below the 17% increase reported in HF patients exercising in supervised sessions.[15] HF-ACTION employed an exercise-only intervention and did not include the counseling considered a component of comprehensive CR for HF.

In contrast, an Italian study with an 88% adherence to exercise over 10 years suggests that prolonged exercise training can profoundly affect clinical outcomes in patients with HF.[19] This study randomly assigned 123 patients with LVEF lower than 40% to formal exercise-training or to control. Exercise sessions occurred twice weekly, with participants encouraged to exercise a third time on their own. Most of the training was done in a "cardiac club," which also promoted healthy lifestyles. Peak V_{O_2} increased 14.7% in the exercise-training group and decreased 2.5% in the control group after 1 year. At 10 years, peak V_{O_2} was 21.8% higher in the exercise-training group. Remarkably, LVEF increased only in the exercise-training group, and this difference appeared only after 5 years into the study (**Fig. 54.4**). Twelve cardiac events occurred in the exercise-trained group and 35 in the control group, a 45% reduction (95% confidence interval [CI] −28% to −74% reduction; $P < 0.001$) (**Fig. 54.5**). Similarly, four deaths occurred in the exercise-training group and 10 deaths in the control group—a 32% reduction (95% CI −28% to −70% reduction).

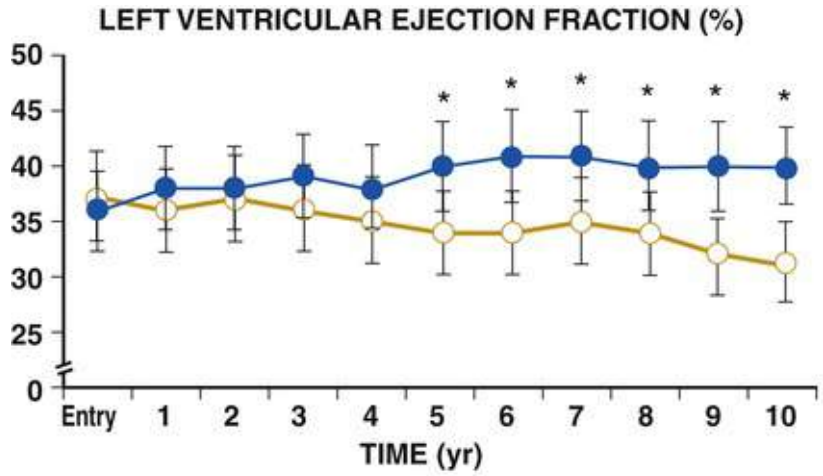

FIGURE 54.4 Left ventricular ejection fraction (LVEF) in exercise-trained (*solid circles*) and non–exercise-trained (*open circles*) patients with heart failure over time. Changes in LVEF were different between the groups over time, but not until 5 years after the start of exercise training. (Reproduced from Belardinelli R, Georgiou D, Cianci G, Purcaro A. 10-Year exercise training in chronic heart failure: a randomized controlled trial. J Am Coll Cardiol 2012;60:1521.)

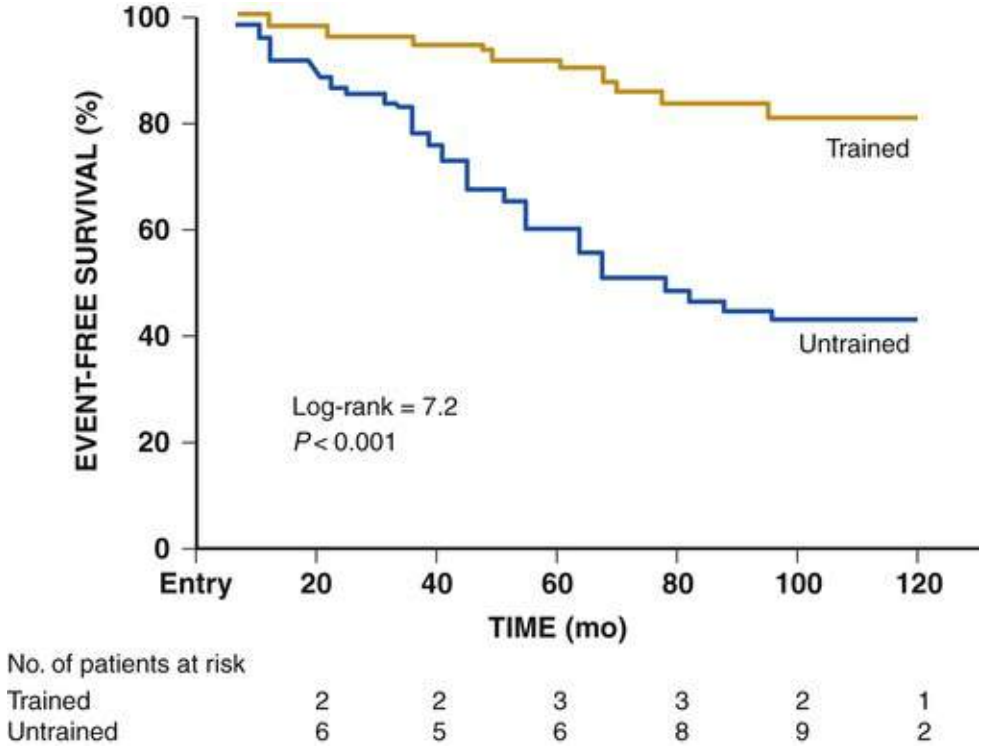

FIGURE 54.5 Event-free survival in exercise-trained and non–exercise-trained patients with heart failure over time. (Reproduced from Belardinelli R, Georgiou D, Cianci G, Purcaro A: 10-year exercise training in chronic heart failure: A randomized controlled trial. J Am Coll Cardiol 60:1521, 2012.)

Practical Aspects of Cardiac Rehabilitation Programs

Program Structure

Cardiac rehabilitation programs involve three phases based on the patient's clinical status. Phase 1 CR refers to inpatient programs started soon after the acute cardiac event or intervention. These programs are uncommon presently because of the brevity of most hospital stays, although some European countries have inpatient rehabilitation programs lasting up to several weeks. Phase 1 programs remain useful in mobilizing elderly patients after complicated cardiac events, as well as for many types of patients after cardiac surgery. In the United States, physical therapy departments or dedicated CR staff often direct these programs. Phase 1 is also an excellent way to introduce patients to the concept of cardiac rehabilitation and to solicit appropriate referrals to phase 2. Separate reimbursement for phase 1 programs in the United States is not available because charges for the acute event include this service, if provided.

Phase 2 CR refers to physician-supervised outpatient programs in the postdischarge period. Patients in these programs usually exercise three times weekly, for a total of 36 sessions over 3 to 4 months. Medical insurance usually covers these programs, although co-pays and deductibles can hinder participation. Other approaches to CR, including simple home-based, self-supervised programs; home-based, visiting nurse–supervised programs; and home-based programs with telephone electrocardiographic (ECG) monitoring, have been examined in research settings and compare favorably with standard facility-based programs.[20] Although most insurance carriers do not cover such alternative programs, these CR programs should be developed because many patients cannot attend the standard, facility-based programs for many reasons, including lack of a local program.[20]

Phase 3 CR refers to non–ECG-monitored long-term maintenance programs. These programs are usually provided by the same facilities providing phase 2 programs, but because phase 3 programs do not

include direct medical supervision, health clubs and fitness facilities may also provide them. In the United States, medical insurance generally does not cover phase 3 programs.

Staff Coverage

The standard CR program has a physician medical director, a staff nurse, and other individuals with training in exercise physiology to design the exercise and educational programs and to supervise the exercise sessions. To qualify for Medicare reimbursement in the United States, phase 2 CR programs must have a physician medical director. This individual must review and approve a treatment plan for each patient every 30 days[21] and must be immediately available during the rehabilitation sessions. Definition of the term “immediately available” is open to interpretation but generally means being in the facility and available within moments for any emergency. All CR staff must be trained in advanced cardiac life support. A nurse must be available during the exercise rehabilitation sessions to handle emergencies and administer medications. Staffing-level recommendations are one staff member per five participants during phase 2 programs and one staff member per 10 to 15 participants during phase 3 sessions.

Design and Implementation of Exercise Training Program

Patients referred to CR should undergo a symptom-limited exercise test before entering the program to identify and evaluate any important symptoms, ischemia, or arrhythmias that might require other interventions before exercise training. The exercise test also establishes baseline exercise capacity and determines the maximum HR to prepare an exercise-training prescription. Tests are usually performed with patients taking their usual medications to mimic the HR response likely to occur during exercise training.

A typical exercise-training session for CR patients consists of 5 minutes of warm-up, followed by 20 to 45 minutes of aerobic exercise training and 5 to 15 minutes of cool-down. The warm-up session consists of stretching and light calisthenics. Some resistance exercise training using light weights or exercise machines should also be performed, often after the aerobic session and as part of an extended cool-down period. The resistance exercises should address most of the major muscle groups to increase patients' ability to perform daily living and work tasks, such as lifting and carrying.

The aerobic exercise–training component is generally performed at 60% to 70% of V_{O_2}max, which corresponds to approximately 70% to 80% of the maximum HR. Some patients require lower training intensities. Although 20 to 45 minutes of exercise training is standard, shorter periods have benefit, and longer sessions almost certainly provide additional benefit. Most CR programs recommend other activities, such as walking or gardening, on days when patients do not attend supervised sessions.

Recent studies have examined the use of high-intensity interval training (HIIT) in CR to accelerate the exercise-training effect.[22,23] A typical protocol starts with a 10-minute walking warm-up followed by four 4-minute intervals of walking at 90% to 95% of maximal HR, followed by 3-minute recovery periods at 50% to 70% of maximal HR. HITT provides enhanced improvements in peak V_{O_2} in patients with systolic HF, after CABG, and after MI compared with continuous moderate-intensity training.[22,23] HITT does not appear to increase cardiac risk, but studies to date are relatively small. Many patients find it less “boring” than standard training.

Exercise testing before starting CR is useful, but not all patients—especially those after recent MI—undergo such testing. Patients who do not undergo exercise testing before starting a CR program can

exercise at a HR 20 beats faster than their resting value. Another approach consists of exercising patients at their resting HR, plus a specified additional percentage of their rest HR. For example, during month 1, a patient might exercise at rest HR plus 20% to 30% of rest HR; month 2, rest HR plus 20% to 40% of rest HR; and month 3, rest HR plus 20% to 50% of rest HR. Alternatively, such patients can exercise to the point of mild dyspnea and maintain that level during the training session. As discussed earlier, the onset of dyspnea approximates VT and indicates adequate intensity for a training stimulus. Finally, patients can exercise to a "somewhat hard" level by using number scales designed to estimate the intensity of exertion, such as the modified Borg Scale of Perceived Exertion.

Unsupervised Exercise Training

Many patients cannot attend supervised exercise training sessions but should be advised to exercise for its CV benefits. Patients without lower limb orthopedic problems should be encouraged to use brisk walking as their exercise-training modality. Patients in unsupervised programs should generally be encouraged to exercise to the onset of mild dyspnea for the reasons mentioned earlier. Such an approach obviates the need for pulse monitoring. Many patients either cannot accurately monitor their HR or become unduly concerned about pulse irregularities caused by premature atrial or ventricular contractions. Patients exercising on their own can also be encouraged to judge their exercise intensity by using the "talk test"—exercising at the fastest rate that still permits comfortable conversation. This work rate corresponds to the exercise-training range recommended for cardiac patients.[1]

Other Components of Comprehensive Cardiac Rehabilitation

Nutritional, psychological, and vocational counseling, as well as serum lipid, blood pressure (BP), and smoking risk factor management, are core components of CR and required by Medicare. Addressing issues such as BP and lipid management and smoking cessation often requires balancing the roles of the CR staff and the primary care physician. CR personnel generally focus on the counseling aspects of risk factor management. They can also interpret laboratory results and physician instructions and act as patient advocates with the primary health care providers. (**See also Chapter 45**.)

Programs differ in how they deliver the counseling and education components. Many programs use the time when the patient is on the exercise apparatus to visit and educate. Some programs simply make printed material available to the participants. Other programs use television monitors and either commercially available or locally prepared video programs to deliver the counseling and risk reduction messages. Some programs have replaced exercise sessions with educational programs. Creatively scheduled classroom activities in addition to the exercise sessions permit participants to craft education programs that best meet their needs.

Approximately 80% of CR patients are overweight or obese.[24] Significant weight loss does not occur with CR exercise alone.[24] CR provides the opportunity for behavioral weight loss counseling combined with an exercise prescription that recommends almost daily, longer-distance walking. Such "high caloric expenditure exercise" programs can achieve a body weight loss of 5% to 10%. This weight loss is associated with improvements in insulin sensitivity, BP, lipids, clotting factors, and endothelial function.[24]

Insurance Coverage

Insurance coverage of CR activities is important for patients to be able to receive these services.[25] Medicare generally provides reimbursement for patients who have stable angina pectoris, have suffered acute MI, or have undergone CABG, cardiac valve repair or replacement, PTCA, or heart or heart-lung transplantation within the previous 12 months. Since 2014, CMS also covers CR for stable systolic HF with LVEF lower than 35% on optimal medical therapy.[26] Many private insurers follow the Medicare reimbursement procedures. Routine coverage includes 36 exercise sessions.

Current Challenges

Exercise-based CR is an AHA guideline class Ia recommendation but is underutilized. Only 14% to 35% of MI survivors and approximately 31% of patients following coronary revascularization participate in CR programs.[20] Women, older patients, minority groups, and low–socioeconomic status patients—the very groups at greatest risk for recurrent events—have especially low referral rates.[20] Simple, available techniques can increase referral. For example, automatic electronic medical-based referral systems can almost triple referral rates,[7] but such approaches see little use. Physician endorsement of CR is one of the most important predictors of participation.[20] Why physicians do not routinely refer patients to rehabilitation is unclear, although physicians' underestimation of the benefits of exercise, lack of knowledge about exercise training, and the absence of exercise advocates similar to pharmaceutical representatives may contribute. Physician referral to cardiac rehabilitation will probably increase when and if referral to such programs becomes a core measure of hospital performance.

Future Perspectives

Use of CR should increase greatly if CMS adopts referral to CR as a core performance measure for the management of patients with coronary disease and after cardiac surgery, as proposed.[26] Furthermore, the ability of CR to reduce cardiac mortality and possibly recurrent cardiac events will probably be a component of any efforts to control medical care costs by accountable care organizations.[20] Cost containment efforts could also result in the wider use of exercise-based CR/secondary prevention as a method to reduce rehospitalization. Furthermore, the role of cardiac rehabilitation with optimal medical therapy to manage stable angina pectoris before proceeding to more costly interventions such as PTCA and CABG requires consideration and more study. Such a change seems unlikely in the present fee-for-service environment but will be more important in a capitated system.

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55

Integrative Approaches to the Management of Patients with Heart Disease

Stephen Devries

Integrative Cardiology

Integrative cardiology is more a philosophy of care than a description of a particular set of practices. Integrative cardiology is focused on the prevention of disease, with an emphasis on maximizing the benefits of nutrition and lifestyle interventions. Completely inclusive of guideline-based medical therapy, integrative cardiology seeks to empower patients to the greatest degree possible with health goals and therapeutic plans developed collaboratively (**Fig. 55.1**).

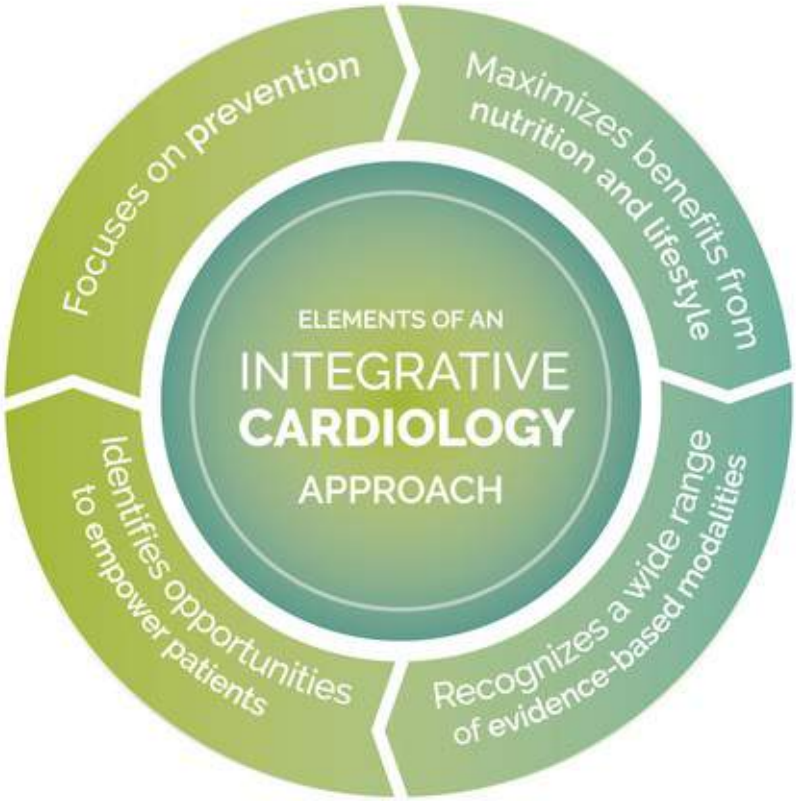

FIGURE 55.1 Key elements of an integrative cardiology approach.

Integrative cardiology is important because it addresses unmet needs in conventional care. Despite the technological advances, a report from the U.S. Centers for Disease Control and Prevention (CDC) describes a recent plateau in the decline of cardiovascular disease (CVD), largely a manifestation of the lifestyle-related problems of obesity and diabetes.[1]

Nutrition and lifestyle are not typically emphasized in the training or practice of cardiology. For example, in the current 38-page document from the Accreditation Council for Graduate Medical Education that details specific requirements for fellowship training in CVD, there is no mention of a requirement for including nutrition in the curriculum.[2] An integrative approach seeks to address this deficiency by highlighting nutrition and lifestyle as integral components of the therapeutic plan.

One of the tenets of integrative cardiology is an emphasis on patient empowerment. The need for greater attention to shared decision making is exemplified by a recent analysis of conversations between cardiologists and patients regarding percutaneous coronary intervention (PCI). In this study, cardiologists inquired about the patient's preferences for treatment in only 54% of discussions and mentioned alternatives to PCI in only 25%.[3]

Most importantly, adoption of an integrative cardiology approach can lead to improved outcomes. An excellent example, as discussed later, is the improved outcome when lifestyle modifications are implemented after an ablation procedure for atrial fibrillation.

Associated Treatment Modalities

Nutrition

Although it can be argued that nutrition is (or should be) part of all medical care, dietary considerations take on an especially prominent role in an integrative model. Nutritional interventions are the foundation of cardiac care for both the prevention and the treatment of CVD.

Mind/Body Therapy

In recognition of the strong influence of thoughts and emotional state on cardiovascular (CV) health, an integrative approach emphasizes the connection between mind and body. In addition to the more traditional approaches with cognitive behavioral therapy and medication, modalities that might be recommended in an integrative model include meditation, breathing exercises, yoga, biofeedback, healing touch, and Reiki.

Acupuncture

Although acupuncture is most often associated with treatment of musculoskeletal pain, emerging data shows promise for acupuncture to be used as adjunctive treatment for a range of CV conditions, including hypertension.

Supplements and Botanicals

It is incumbent on the cardiologist at least to be knowledgeable about the supplements most frequently used by cardiac patients. Also, for some clinicians, review of the evidence may lead them to consider selective use of some over-the-counter (OTC) products (e.g., patient intolerant of prescription statins). Although it is considered good medical practice to document all OTC products taken by patients, this information has limited value if the clinician is unaware of the product and does not know how to obtain credible scientific information about it. Fortunately, several excellent resources are available to help clinicians learn about the science of supplements (**Table 55.1**).

TABLE 55.1

Resources for Evidence-Based Assessment of Supplements

RESOURCE	DESCRIPTION
U.S. National Library of Medicine MedlinePlus https://medlineplus.gov/druginfo/herb_All.html	Clinical summary of supplements with key references (free)
Natural Medicines Database http://www.naturaldatabase.com/	Extensive supplement reviews with links to the original literature; includes patient handouts (paid)
ConsumerLabs.com http://www.ConsumerLabs.com	Independent laboratory analysis of over-the-counter (OTC) products for dosage and purity (paid)
U.S. National Institutes of Health Office of Dietary Supplements http://ods.od.nih.gov	Supplement fact sheets; Spanish version available (free)
CredibleMeds https://www.crediblemeds.org	OTC and prescription drugs that can prolong the QT interval and lead to arrhythmias (free)

Need for Interprofessional Collaboration

The need for close collaboration between all members of the cardiovascular team is clear, but communication between cardiologists and allied health professionals involved with integrative care has historically been challenging. Regardless of differences in language and perspectives, mutual respect and open communication between all health professionals, conventional and alternative, is essential for optimal patient care.

Integrative Strategies for Specific Cardiac Conditions

The foundation of integrative cardiology begins with guideline-based therapy. This sections describes a select group of evidence-based approaches not often utilized in conventional management. These tools,

added to guideline-based therapy, may extend its benefits and provide additional opportunities to engage and empower patients.

Ischemic Heart Disease

See also Chapter 58.

Nutrition

Perhaps no therapy in clinical medicine is as impactful as nutritional interventions for prevention and treatment of ischemic heart disease. The final report of the Lyon Diet Heart Study, a study of a Mediterranean-style diet in patients with prior myocardial infarction (MI), showed a 72% reduction in cardiac death and recurrent infarction.[4] A Mediterranean-style diet encourages intake of vegetables and fruit, whole grains instead of refined grains, nuts, fish in place of red meat, and olive oil as the predominant cooking oil.

A more recent study of a Mediterranean-style diet in a high-risk primary prevention group, PREDIMED, was terminated prematurely because of early positive results: a 30% reduced risk of major CV events.[5] Interestingly, the primary component that distinguished the intervention and control dietary groups was the source of dietary fats. Both arms of the Mediterranean-style intervention, high consumption of either extra-virgin olive oil or nuts, showed benefit compared to the control diet.

Among the components of a cardioprotective diet, green leafy vegetables, including spinach and kale, appear to be especially beneficial. Combined data from the Nurses' Health Study and Health Professionals Follow-Up Study showed that each daily serving of green leafy vegetables (0.5 cups cooked) reduced the adjusted risk of coronary disease by 23% in women ($P = 0.0004$) and 11% in men ($P = 0.02$).[6]

Anthocyanins are dietary flavonoids that enhance endothelial function and have antioxidant and antihypertensive properties. Anthocyanin-rich foods, especially blueberries and strawberries, are strongly linked to cardiac health. During an 18-year follow-up of the Nurses' Health Study, including 93,600 women, intake of four or more servings of blueberries and strawberries was associated with a 34% decreased risk of MI.[7]

Nut consumption is also strongly associated with reduced risk of heart disease and improved longevity. The health-promoting properties of nuts are likely related to their rich content of magnesium, sterols, vitamin E, alpha-linolenic acid, and monounsaturated fats. In a meta-analysis of 18 prospective studies, the relative risk for ischemic heart disease was reduced by 28% with each daily serving of nuts.[8] In another study, nut intake was associated with a 21% reduced risk of death over a 5-year period in those with the highest versus lowest consumption of nuts ($P < 0.05$).[9]

Mind/Heart Connection

There is no better example of the connection between the mind and heart than takotsubo syndrome, a condition of acute and severe left ventricular failure precipitated by psychological stress.[10] Takotsubo syndrome, quite dramatic in its presentation, is only one of the many manifestations of stress and emotional state on cardiac health.

Meditation

The link between mind and heart can be harnessed for prevention of ischemic heart disease. In a

randomized controlled study of meditation added to conventional cardiac care in 201 individuals with coronary disease, the meditation group experienced a 48% reduced risk of a composite endpoint including all-cause mortality, MI, and stroke ($P = 0.025$).[11] The underlying mechanism of benefit is unclear but likely includes a favorable effect on blood pressure. Mindfulness-based stress reduction has also been linked to an attenuated inflammatory response, another potentially cardioprotective mechanism.[12]

Tai Chi

Tai chi can be described as "meditation in motion" and is practiced as a series of flowing, smoothly executed movements. A regular tai chi practice may favorably alter risk factors associated with atherosclerosis. A study of women with multiple coronary risk factors found that an 8-week program of tai chi was associated with a marked downregulation of proinflammatory cytokines associated with CVD.[13]

Healing Touch

Although unfamiliar to many health professionals, healing touch and Reiki are increasingly popular modalities used for stress management and pain reduction. In both, a practitioner uses light touch and hand motions around the body to redirect "energy." Regardless of the mechanism, many patients report significant relief. In a study of 237 inpatients recovering from coronary bypass surgery, those randomized to receive healing touch had lower anxiety scores, as well as shorter length of stay (6.9 versus 7.2 days; $P = 0.04$).[14]

Environment

The physical environment may influence risk factors that contribute to CVD. Ambulatory heart rate (HR) was monitored in urban settings, with and without greenery. Those who walked in urban green spaces had significantly lower HR then those moving within urban spaces without greenery.[15] A tendency to lower HR while viewing parks and green space may be a reflection of "biophilia," the innate affinity that most people experience to contact with nature.

Supplements

Omega-3 Fatty Acids

Early studies suggested cardiac benefit with omega-3 fatty acids, but more recent publications have not consistently confirmed the preliminary findings. Nevertheless, remaining questions regarding the optimal dose of omega-3 acids, as well as patient selection, make the ultimate role of omega-3 supplements uncertain. Underscoring the possibility that high doses are required, a recent study of post-MI patients showed a favorable effect on left ventricular remodeling with 3.4 g combined docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), a dose much higher than used in many previous studies.[16]

Currently, a widely supported recommendation is to obtain omega-3 fatty acids from fish, at least 2 servings of omega-3–rich fish per week. Nevertheless, for those who cannot or choose not to eat fish, omega-3 supplements may be particularly beneficial. Several brands of prescription omega-3 fatty acids are now available.

OTC fish oil supplements may also be considered, but dosing requires special attention. Many OTC omega-3 supplements include a front label with total omega-3 content. The amount can be misleading,

however, because accurate dosing depends on DHA and EPA content, which may be only a fraction of the total omega-3 content listed. If, for example, 1000 mg of combined DHA and EPA are prescribed, patients should be advised to review the back label of an OTC omega-3 product and take as many pills as needed to total 1000 mg of combined DHA and EPA. Despite a front label indicating 1000 mg of fish oil per pill, some omega-3 preparations require 2 or 3 pills daily to total 1000 mg of combined DHA and EPA.

Vegans can also enhance their intake of omega-3 fatty acids with algal oil supplements that contain both DHA and EPA. Studies show significant elevation of plasma and erythrocyte DHA levels with consumption of algae-derived DHA supplements.[17]

Multivitamins

Most large trials of multivitamin use for prevention of heart disease have not shown beneficial effects, including a trial limited to men (Physicians' Health Study II)[18] and a large study of women (Women's Health Initiative).[19] However, a more recent analysis of data from the Physicians' Health Study I, involving 18,530 men, found that a duration of multivitamin use of 20 or more years was associated with a 44% lower risk of a major CV event ($P = 0.05$).[20]

Antioxidants

Smaller, early trials of antioxidants showed promising results for prevention of ischemic disease. Nevertheless, more recent, larger studies of vitamins E and C have failed to demonstrate benefit.[21,22] However, most studies of vitamin E evaluated only a single isoform of vitamin E (mostly α-tocopherol), from among the full complement of eight vitamin E isoforms (four tocopherols, four tocotrienols), some of which have opposing effects. Additional studies including varying formulations of vitamin E are needed. In the meantime, it is definitely known that whole-food sources rich in antioxidants, especially vegetables and fruit, are strongly cardioprotective.[23]

Hypertension (see Chapter 47)

Nutrition

DASH Diet and Potassium

Dietary approaches are extremely potent interventions for treatment of hypertension. The best-studied diet for hypertension is DASH (Dietary Approaches to Stop Hypertension). The DASH diet, similar to a Mediterranean-style diet, includes 8 to 10 servings of combined vegetable and fruit in addition to low-fat dairy. Among patients with baseline hypertension, systolic and diastolic blood pressure (BP) were reduced by 11.4 and 5.5 mm Hg, respectively ($P < 0.001$).[24] There is a common misconception that dietary changes require an extended period to realize benefits. To the contrary, the maximal BP-lowering effect of the DASH diet was evident within the first 2 weeks of the trial and was maintained throughout the study period.

The DASH diet was designed to boost potassium intake to approximately the 75th percentile of U.S. consumption. An inverse relationship between potassium and BP reduction is well established.[25] The high-potassium intake in the DASH diet, from increased consumption of potassium-rich fruit and vegetables, was likely responsible for a significant portion of the BP-lowering effect.

The sodium content of both the intervention and the control arm of the original DASH diet were similar, approximately 3 g/day. In a follow-up DASH study, a stepwise reduction of sodium consumption was

superimposed on the original DASH diet. The subset of DASH participants who consumed the lowest versus highest amount of sodium had an additional BP reduction of 3.0 mm Hg systolic and 1.6 mm Hg diastolic.[26]

Dietary Nitrates

Dietary nitrates play a key role in BP reduction through production of the vasodilator nitric oxide. The mechanism by which this occurs is novel. Dietary nitrates are rapidly absorbed into the circulation, where a significant amount is actively taken up and concentrated in the salivary glands, resulting in a salivary nitrate concentration approximately 10-fold that of plasma. Concentrated nitrates in saliva interact with facultative bacteria in the mouth that reduce nitrates to nitrites, the substrate for nitric oxide production.

Beverages made from concentrated preparations of foods rich in dietary nitrates, including arugula, spinach, and beetroot, were associated with BP reductions of 5 to 7 mm Hg within 2.5 hours of consumption.[27] In another study, beetroot juice, consumed daily for 4 weeks, led to a reduction in ambulatory BP of 7.7 mm Hg systolic and 5.2 mm Hg diastolic ($P < 0.001$ for both).[28]

Of note, antiseptic mouthwash can disrupt the bacteria-assisted reduction of nitrates to nitrites in the mouth. Use of an antiseptic mouthwash for 1 week reduced oral nitrite production by 90%, associated with an increase in both systolic and diastolic BP of 2 to 3 mm Hg ($P < 0.001$).[29]

Physical Activity

Aerobic exercise, involving high repetition movement of large muscle groups, is the form of physical activity best studied for BP reduction, with sufficient data to warrant a rating of class I, level of evidence (LOE) A, in an American Heart Association (AHA) scientific statement.[30]

Less well appreciated is the potential for dynamic resistance (class IIa, LOE B) and isometric handgrip exercise (class IIa, LOE C) to aid in BP reduction.[30] Gender appears to be a factor in the response to exercise, with women showing a greater reduction in BP after resistance compared to aerobic exercise. Men have comparable BP-lowering effects with either form of exercise.

Of special note are studies of isometric handgrip exercise. Although the data are limited, available studies demonstrate a particularly strong BP-lowering effect from handgrip exercise. Findings include the observation that handgrip exercise appears to require a relatively short duration for BP lowering, an average of 33 minutes per week.[30]

Mind/Heart Connection

Breathing Exercises

Breathing exercises that include periods of slow, deep breaths are integral to meditation and yoga and help facilitate reflection and relaxation. More recently, device-guided slow-breathing protocols have also been shown to have BP-lowering effects (class IIa, LOE B). A daily device-guided exercise of 7 minutes of slow breathing for 15 minutes has been shown to reduce BP by an average of 4 mm Hg systolic and 3 mm Hg diastolic within 1 to 2 weeks.[30] Although not as well studied, a wide range of instructions for self-directed breathing exercises are widely available, with the advantages of promoting patient empowerment and being free and accessible to all patients.

Biofeedback

Biofeedback (class IIb, LOE B), a technology that permits individuals to visualize their physiologic

responses to breathing and relaxation exercises, has also been shown to be effective for BP management.[30] Biofeedback can be an especially attractive modality for individuals who thrive on quantitative self-monitoring.

Meditation

Transcendental meditation (class IIb, LOE B) has been particularly well studied for treatment of patients with established hypertension, with BP reduction up to 15 mm Hg systolic.[30] The mechanisms are not well defined but likely involve a favorable impact on the autonomic nervous system, resulting in decreased HR and vascular tone. Individuals who are drawn to self-reflection may be especially interested in considering meditation as an adjunctive tool for BP control.

Acupuncture

A randomized controlled study recently evaluated acupuncture performed twice weekly over 8 weeks, with an additional 4-week follow-up. At the end of follow-up, systolic BP was lowered by 9 mm Hg and diastolic by 8 mm Hg.[31] Significant differences were noted in measurements of HR variability between the acupuncture and control groups, consistent with a favorable influence on autonomic function.

Supplements

Magnesium

Several studies have demonstrated an inverse relationship between serum magnesium and BP. In one trial, hypertensive patients treated with magnesium pidolate, 600 mg/day for 12 weeks, had a reduction in BP of 4.3 mm Hg systolic and 1.8 mm Hg diastolic ($P = 0.002$ for both).[32] Magnesium supplements can cause diarrhea and should be avoided in patients with significant renal insufficiency.

Probiotics

Probiotics are supplements containing live microorganisms intended to confer health benefits. A meta-analysis of nine trials of probiotics, with a total of 543 participants, demonstrated a mean reduction in BP of 3.6 mm Hg systolic and 2.4 mm Hg diastolic.[33] Subgroup analysis showed greatest benefit when the dose of probiotics included multiple species with daily consumption of 10^{11} or more colonies for 8 or more weeks.

Environment

Contact with Nature

Physical environment appears to play a role in BP regulation. In an experiment of healthy volunteers with BP measurements during walks in forest and city areas, walks in the forest were associated with lower systolic and diastolic BP, as well as indices of HR variability reflective of lower sympathetic and increased parasympathetic tone.[34]

Environmental Toxin

Bisphenol A (BPA) is a chemical used to coat the inner linings of many canned and plastic products, but not glass. A recent study identified a greater than 1600% increase in urinary BPA level after consuming

two cans of a beverage, with BP increasing 5 mm Hg higher than after drinking the same beverage stored in glass ($P < 0.02$).[35]

Dyslipidemia (see Chapter 48)

Nutrition

Dietary approaches are the foundation of treatment for dyslipidemia. Consistent with the recent AHA/American College of Cardiology (ACC) Guideline on Lifestyle Management to Reduce Cardiovascular Risk, the recommended diet emphasizes vegetables, fruit, nuts, whole grains, and fish and minimizes or avoids intake of sugar-sweetened beverages and red meat.[36] Avoidance of *trans* fats found in some fried foods and bakery items and replacement of saturated fats with polyunsaturated and monounsaturated fats are also key components of a cholesterol-lowering diet.

Physical Activity

Approximately 20% of the reduction in CVD from exercise can be attributed to its beneficial effect on lipids. In adults, aerobic exercise has been shown to reduce low-density lipoprotein cholesterol (LDL-C) by 3 to 6 mg/dL. Resistance training is similarly effective, with an average reduction in LDL-C of 6 to 9 mg/dL when performed 3 or more days a week with three sets of nine exercises.[36]

Statin Intolerance

For those who require cholesterol reduction beyond that achievable with lifestyle measures alone, statins are typically prescribed. Although the majority of statin users experience no significant side effects, a significant number do experience at least mild adverse reactions, most often myalgias. From a survey of 10,138 current or former statin users, 17% recalled experiencing muscular side effects while taking a statin. Among those who discontinued their statin use, 60% reported having experienced muscular side effects.[37]

Many strategies exist to address statin intolerance, including a reduction in daily dose, increasing the interval between doses, and switching brands of statins. For patients in whom these strategies are not successful, and for those who are philosophically opposed to taking prescription statins, OTC supplements may be considered.

Supplements

Dietary Fiber

Water-soluble dietary fiber has long been recognized as helpful in reducing plasma cholesterol levels. Although the mechanisms are not well defined, soluble fiber likely acts as a bile acid sequestrant, in addition to upregulating LDL hepatic receptors. The ideal source of dietary soluble fiber is from whole foods, with fiber from whole-grain sources most closely linked to reduction of CVD risk.[38]

Psyllium is the best studied fiber supplement. In a meta-analysis of eight trials, consumption of 10 g of psyllium (2 tsp)/day, in conjunction with a low-fat diet, reduced LDL-C by 7% ($P < 0.0001$).[39]

Stanols and Sterols

Stanols and sterols are compounds naturally present in all plant-derived foods and are especially

concentrated in seeds, nuts, and grain products. These compounds lower serum cholesterol by competing for cholesterol absorption in the gastrointestinal tract. The average daily intake from food is 200 to 400 mg/day. A meta-analysis of eight studies showed that daily doses of stanols and sterols of up to 3 g reduced LDL-C by 12%.[40] Stanols/sterols can be used as monotherapy for treatment of hypercholesterolemia or in conjunction with statins.

Red Yeast Rice

Red yeast rice is derived from the fermentation of rice with the yeast *Monascus purpureus*, yielding a series of cholesterol-lowering monacolins. The monacolin in highest concentration in red yeast rice is monacolin K, also known as *lovastatin,* the first FDA-approved HMG-CoA reductase inhibitor. Typical dosages of red yeast rice (1200 to 2400 mg/day) result in an average reduction in LDL-C of 27%.[41] This degree of LDL lowering is greater than expected based on the concentration of monacolin K alone, likely because of multiple cholesterol-lowering constituents contained in red yeast rice.

Red yeast rice has been studied as an alternative for patients intolerant of prescription statins. In a randomized study of 62 patients previously statin intolerant, 87% were able to take red yeast rice without adverse reaction. Red yeast rice reduced LDL-C by 26%.[42] In a 5-year study of 4870 patients with prior MI, red yeast rice (compared to placebo) resulted in a 4.7% absolute and 45% relative risk reduction in the primary endpoint of nonfatal MI and cardiac death, as well as a 33% decrease in total mortality.[43]

Brands of red yeast rice differ in both potency and purity. The concentration of total monacolins and monacolin K can vary several-fold between manufacturers. A few brands have been found to contain small amounts of citrinin, a nephrotoxin. Chemical analysis of various red yeast rice formulations, including analysis of monacolin and citrinin concentrations, is available through the independent group ConsumerLabs.com (**see Table 55.1**). Red yeast rice could be considered a therapeutic option for individuals with dyslipidemia who refuse or are intolerant of prescription statins. Because red yeast rice is a form of a statin, patients should be advised of precautions common to all statins and should be monitored by a health care professional.

Coenzyme Q10

Coenzyme Q10 (CoQ10, ubiquinone) is a fat-soluble compound needed for the production of cellular adenosine triphosphate (ATP). Statin therapy has been shown to reduce circulating levels of CoQ10, a finding hypothesized as a possible factor in statin-related adverse reactions, including myalgias. In 120 patients with previous symptoms of statin intolerance studied in an 8-week, randomized, double-blind crossover trial,[44] those receiving 600 mg/day of CoQ10 (ubiquinol) showed no improvement in muscle pain. A meta-analysis of six studies of CoQ10 in 302 patients receiving statin therapy showed a nonsignificant trend toward decreased muscle pain.[45]

Despite the logic implicit in CoQ10 as a therapy for statin-related adverse reactions, the data supporting this use is not strong. However, because the safety profile for CoQ10 is excellent and anecdotal cases have reported benefit, CoQ10 remains a therapeutic option to consider in patients with mild statin-related myalgias.

Probiotics

The effect of probiotics on serum cholesterol was evaluated in a meta-analysis of 11 studies that included fermented milk products and probiotic supplements.[46] On average, the reduction in serum LDL-C associated with probiotic use was 8 mg/dL. The *Lactobacillus acidophilus* strain was especially

effective for LDL-C reduction. No significant impact on HDL-C or triglycerides was noted.

Congestive Heart Failure (see Chapter 23)

Nutrition and Lifestyle

Nutrition and lifestyle are key factors in the development of congestive heart failure (CHF). In a study of 84,537 women from the Women's Health Initiative (WHI), a lifestyle score was developed that included a healthy eating index, physical activity, body mass index, and smoking status.[47] The multivariable-adjusted risk of developing CHF over 11 years had a graded relationship to the ranking of lifestyle measures. Those with the most versus the least favorable lifestyle measures in all four categories, noted in 8% of all patients studied, had a 77% reduced risk of developing CHF.

Once CHF develops, healthy dietary interventions are associated with prolonged survival. In a study of CHF patients in the WHI study, multivariable-adjusted survival improved in a graded manner with level of adherence to a DASH diet.[48] Those with the closest adherence to the DASH diet, compared to the reference group, had a 16% improvement in survival over a follow-up of 4.6 years. Food groups most strongly linked to improved survival included vegetables, whole grains, and nuts.

Mind/Heart Connection

Optimism

The degree to which patients exhibit optimism has been linked to the development of heart failure (HF). In a study of 6808 seniors, adjusted for a wide range of behavioral, biologic, and psychological variables, each standard deviation increase in a measure of optimism was associated with a 26% reduced risk of developing HF.[49] The link between optimism and HF may warrant attempts to help patients cultivate a positive outlook. It is estimated that only 25% of optimism is heritable, with the remainder being shaped by a combination of social factors and learned behavior. Even a short-term intervention of guided imagery, in which patients imagine “a best possible self” for 5 minutes daily, was successful in boosting optimism.[50]

Tai Chi

In a study of patients with HF and preserved ejection fraction (EF), 16 patients were randomized to a 12-week program of tai chi or aerobic exercise, both performed in a group for 1 hour twice a week. At the completion of the study, peak oxygen uptake was similar, but distance on the 6-minute walk test increased more with tai chi, as did a measurement of depression.[51] A similar study of tai chi in patients with HF and EF of 40% or lower also showed no improvement in exercise indices, but did confirm significant improvement in quality-of-life scores and mood.[52]

Acupuncture

Dysregulation of the autonomic nervous system is a hallmark of CHF and a potential target for therapeutic acupuncture. Seventeen stable patients with New York Heart Association (NYHA) Class II or III symptoms and EF less than 40% were randomized to true acupuncture or control acupuncture (blunted, telescopic needle), with sessions twice a week for 10 weeks. No improvement in peak oxygen uptake was observed, but those who received true acupuncture increased their 6-minute walk time by 32 m (P = 0.002).[53]

Supplements

Coenzyme Q10

In patients with CHF, reduced levels of Q10 in the myocardium are linked in a graded manner to both HF symptoms and degree of systolic dysfunction. Accordingly, supplementation with CoQ10 has been studied as an adjunct to treatment of patients with systolic HF. A meta-analysis of CoQ10 supplementation in 13 studies with a total of 395 patients found a mean net change in EF of 3.7% and a decrease in NYHA class of 0.3.[54]

More recently, 420 patients with moderate to severe HF receiving conventional medical therapy were randomized to CoQ10 (300 mg/day) or placebo.[55] No short-term benefits (16 weeks) were observed, but after 2 years, significant improvement was noted in the group receiving CoQ10. NYHA functional class increased by at least 1 grade in 58% receiving CoQ10, compared to 45% in the placebo group (P = 0.028). CV mortality was also lower in the CoQ10 group than in the placebo group (9% versus 16%; P = 0.039).

Although additional research is needed, these preliminary findings hold promise for the use of CoQ10 as adjunctive treatment to improve both symptoms and outcomes of patients with CHF caused by systolic dysfunction. CoQ10 doses of approximately 300 mg have been used most often for this purpose.

Arrhythmias (see Chapter 35)

Comprehensive Lifestyle Approach

There is no better example of the benefits of an integrative approach in cardiology than the data in patients following ablation for atrial fibrillation (AF). Catheter ablation for AF is a highly effective modality, but recurrences are not uncommon. Because many of the risk factors for AF, including hypertension, obesity, and diabetes, are highly modifiable through lifestyle, it was speculated that an aggressive risk factor modification program after ablation might be helpful to reduce recurrent AF. A total of 281 consecutive patients receiving ablation for AF with a body mass index of 27 kg/m^2 or higher and at least one cardiac risk factor were entered into either a risk factor management group or a control group.[56] The risk factor management group received counseling for weight reduction and dietary salt restriction, started an exercise program, and were advised to take home BP measurements. Smokers received behavioral support with the goal of cessation. At the 42-month follow-up, arrhythmia-free survival was 4.8 times as likely ($P < 0.001$) in the risk factor management group than in controls. This finding exemplifies the benefits of a truly integrative approach: the combination of low- and high-tech strategies to achieve optimal results.

Yoga

Yoga combines aspects of both physical activity and meditation, making it a promising candidate for reducing the burden of AF. A group of 52 patients with paroxysmal AF were enrolled in the Yoga My Heart Study.[57] Participants were observed for 3 months, followed by 3 months of an intervention that consisted of twice-weekly yoga sessions. Following 3 months of yoga, symptomatic episodes of AF were reduced by 45% and asymptomatic episodes by 67% ($P < 0.001$ for both).

Conclusion

An integrative approach to heart health seeks to enlarge both the scope of available treatments and the level of patient engagement. An integrative approach opens the door to many low-risk, high-impact interventions that, when added to guideline-based therapy, can make a powerful difference to improve satisfaction, for both patients and physicians, and improve outcomes.

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Volume 2

OUTLINE

PART VII
Atherosclerotic Cardiovascular Disease

OUTLINE

56

Approach to the Patient with Chest Pain

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Acute chest pain is one of the most common reasons for seeking care in the emergency department (ED), accounting for approximately 10% of all visits or 6 million presentations annually in the United States. Although chest pain raises the possibility of an acute coronary syndrome (ACS), after diagnostic evaluation only 10% to 15% of patients with acute chest pain actually have ACS.[1] The difficulty lies in discriminating patients with ACS or other life-threatening conditions from those with noncardiovascular, non–life-threatening chest pain. The diagnosis of ACS is missed in approximately 2% of patients, which can lead to substantial consequences—for example, the short-term mortality in patients with acute myocardial infarction (AMI) who are mistakenly discharged from the ED increases twofold over that expected for patients who are admitted to the hospital. For patients with a lower risk for complications, however, these concerns must be balanced against the cost and inconvenience of admission and against the risk for complications from tests and procedures with a low probability of improving patient outcomes.

Several recent advances have enhanced the accuracy and efficiency of evaluation of patients with acute chest pain, including better blood markers for myocardial injury,[2] decision aids to stratify patients according to their risk for complications, early exercise testing,[3] radionuclide scanning for lower-risk patient subsets[3] (**see Chapter 16**), multislice computed tomography (CT) for anatomic evaluation of coronary artery disease (CAD), pulmonary embolism (PE), and aortic dissection[4] (**see Chapter 18**), and the use of chest pain units[3] and critical pathways for efficient and rapid evaluation of lower-risk patients.[5]

Causes of Acute Chest Pain

In a typical population of patients undergoing evaluation for acute chest pain in EDs, about 10% to 15% have AMI or unstable angina.[1] A small percentage has other life-threatening problems, such as PE or acute aortic dissection, but most leave the ED without a diagnosis or with a diagnosis of a non–cardiac-related condition.[6] Such noncardiac conditions include musculoskeletal syndromes, disorders of the abdominal viscera (including gastroesophageal reflux disease), and psychological conditions (**Table 56.1**).

TABLE 56.1

Common Causes of Acute Chest Pain

SYSTEM	SYNDROME	CLINICAL DESCRIPTION	KEY DISTINGUISHING FEATURES
Cardiac	Angina	Retrosternal chest pressure, burning, or heaviness; radiating occasionally to the neck, jaw, epigastrium, shoulders, left arm	Precipitated by exercise, cold weather, or emotional stress; duration of 2-10 min
	Rest or unstable angina	Same as angina, but may be more severe	Typically <20 min; lower tolerance for exertion; crescendo pattern
	Acute myocardial infarction	Same as angina, but may be more severe	Sudden onset, usually lasting ≥30 min; often associated with shortness of breath, weakness, nausea, vomiting
	Pericarditis	Sharp, pleuritic pain aggravated by changes in position; highly variable duration	Pericardial friction rub
Vascular	Aortic dissection	Excruciating, ripping pain of sudden onset in either the anterior chest or the back	Marked severity of unrelenting pain; usually occurs in the setting of hypertension or underlying connective tissue disorder such as Marfan syndrome
	Pulmonary embolism	Sudden onset of dyspnea and pain, usually pleuritic with pulmonary infarction	Dyspnea, tachypnea, tachycardia, signs of right-sided heart failure
	Pulmonary hypertension	Substernal chest pressure, exacerbated by exertion	Pain associated with dyspnea and signs of pulmonary hypertension
Pulmonary	Pleuritis and/or pneumonia	Pleuritic pain, usually brief, over the involved area	Pain pleuritic and lateral to the midline, associated with dyspnea
	Tracheobronchitis	Burning discomfort in the midline	Midline location, associated with coughing
	Spontaneous pneumothorax	Sudden onset of unilateral pleuritic pain, with dyspnea	Abrupt onset of dyspnea and pain
Gastrointestinal	Esophageal reflux	Burning substernal and epigastric discomfort, 10-60 min in duration	Aggravated by a large meal and postprandial recumbency; relieved by antacid
	Peptic ulcer	Prolonged epigastric or substernal burning	Relieved by antacid or food
	Gallbladder disease	Prolonged epigastric or right upper quadrant pain	Unprovoked or following a meal
	Pancreatitis	Prolonged, intense epigastric and substernal pain	Risk factors, including alcohol, hypertriglyceridemia, medications
Musculoskeletal	Costochondritis	Sudden onset of intense fleeting pain	May be reproduced by pressure over the affected joint; occasionally, swelling and inflammation over the costochondral joint
	Cervical disc disease	Sudden onset of fleeting pain	May be reproduced with movement of the neck
	Trauma or strain	Constant pain	Reproduced by palpation or movement of the chest wall or arms
Infectious	Herpes zoster	Prolonged burning pain in a dermatomal distribution	Vesicular rash, dermatomal distribution
Psychological	Panic disorder	Chest tightness or aching, often accompanied by dyspnea and lasting ≥30 min, unrelated to exertion or movement	Patient may have other evidence of an emotional disorder

Myocardial Ischemia or Infarction

The most common serious cause of acute chest discomfort is myocardial ischemia or myocardial infarction (MI) (**see Chapter 59**), which occurs when the supply of myocardial oxygen is inadequate for

the demand. Myocardial ischemia usually occurs in the setting of coronary atherosclerosis, but it may also reflect dynamic components of coronary vascular resistance. Coronary spasm can occur in normal coronary arteries or, in patients with CAD, near atherosclerotic plaque and in smaller coronary arteries (**see Chapter 57**). Other, less common causes of impaired coronary blood flow include syndromes that compromise the orifices or lumina of the coronary arteries, such as coronary arteritis, proximal aortitis, spontaneous coronary artery dissection, proximal aortic dissection, coronary emboli from infectious or noninfectious endocarditis or thrombus in the left atrium or left ventricle, myocardial bridge, or a congenital abnormality of the coronary arteries (**see Chapter 20**).

The classic manifestation of ischemia is *angina,* which is usually described as a heavy chest pressure or squeezing, a burning feeling, or difficulty breathing (**see Chapter 10**). The discomfort often radiates to the left shoulder, neck, or arm. It typically builds in intensity over a few minutes. The pain may begin with exercise or psychological stress, but ACS most frequently occurs without obvious precipitating factors.

Atypical descriptions of chest pain reduce the likelihood that the symptoms represent myocardial ischemia or injury. The American College of Cardiology (ACC) and American Heart Association (AHA) guidelines list the following as pain descriptions *uncharacteristic* of myocardial ischemia[5]:

- Pleuritic pain (i.e., sharp or knifelike pain brought on by respiratory movements or coughing)
- Primary or sole location of the discomfort in the middle or lower abdominal region
- Pain that may be localized by the tip of one finger, particularly over the left ventricular apex
- Pain reproduced with movement or palpation of the chest wall or arms
- Constant pain that persists for many hours
- Very brief episodes of pain that last a few seconds or less
- Pain that radiates into the lower extremities

Nevertheless, data from large populations of patients with acute chest pain indicate that ACS occurs in those with atypical symptoms at sufficient frequency that no single factor suffices to exclude the diagnosis of acute ischemic heart disease. Clinicians should be mindful of “angina equivalents” such as jaw or shoulder pain in the absence of chest pain; nausea or vomiting; and diaphoresis. In particular, women, older persons, and individuals with diabetes may be more likely to report atypical symptoms of myocardial ischemia or MI (**see Chapter 89**). Data from the National Registry of Myocardial Infarction demonstrate that among patients hospitalized with MI, women—particularly young women—are significantly less likely than men to manifest chest pain. Not surprisingly, patients without chest pain had higher in-hospital mortality.[7]

Pericardial Disease

The visceral surface of the pericardium is insensitive to pain, as is most of the parietal surface. Therefore, noninfectious causes of pericarditis (e.g., uremia; **see Chapter 83**) usually cause little or no

pain. In contrast, infectious pericarditis almost always involves the surrounding pleura, so patients typically experience pleuritic pain with breathing, coughing, and changes in position. Swallowing may induce the pain because of the proximity of the esophagus to the posterior portion of the heart. Because the central diaphragm receives its sensory supply from the phrenic nerve and the phrenic nerve arises from the third to fifth cervical segments of the spinal cord, pain from infectious pericarditis is frequently felt in the shoulders and neck. Involvement of the diaphragm more laterally can lead to symptoms in the upper part of the abdomen and back, and thus create confusion with pancreatitis or cholecystitis. Pericarditis occasionally causes a steady, crushing substernal pain resembling that of AMI.[8]

Vascular Disease

Acute aortic dissection usually causes a sudden onset of excruciating ripping pain, the location of which reflects the site and progression of the dissection (**see Chapter 63**). *Ascending* aortic dissection tends to manifest as pain in the midline of the anterior aspect of the chest, and *posterior descending* aortic dissection tends to cause pain in the back of the chest. Aortic dissections are rare, with an estimated annual incidence of 3 per 100,000, and usually occur in the presence of risk factors, including Marfan and Ehlers-Danlos syndromes, bicuspid aortic valve, pregnancy (for proximal dissections), and hypertension (for distal dissections).

Pulmonary emboli often cause a sudden onset of dyspnea and pleuritic chest pain, although they may be asymptomatic (**see Chapter 84**). The annual incidence is at least 1 per 1000. Massive pulmonary emboli tend to cause severe and persistent substernal pain, which is attributed to distention of the pulmonary artery. Smaller emboli that lead to pulmonary infarction can cause lateral pleuritic chest pain. Hemodynamically significant pulmonary emboli may cause hypotension, syncope, and signs of right-sided heart failure. Pulmonary hypertension can result in chest pain similar to that of angina pectoris, presumably because of right heart hypertrophy and ischemia (**see Chapter 85**).

Pulmonary Conditions

Pulmonary conditions that cause chest pain generally produce dyspnea and pleuritic symptoms, the location of which reflects the site of pulmonary disease. Tracheobronchitis tends to be associated with a burning midline pain, whereas pneumonia can produce pain over the involved lung. The pain of pneumothorax begins suddenly and is usually associated with dyspnea. Primary pneumothorax typically occurs in tall, thin young men; secondary pneumothorax occurs in the setting of pulmonary disease such as chronic obstructive pulmonary disease (COPD), asthma, or cystic fibrosis. A tension pneumothorax can be life-threatening. Asthma exacerbations can cause chest discomfort, typically characterized as tightness.

Gastrointestinal Conditions

Irritation of the esophagus by acid reflux can produce a burning discomfort that may be exacerbated by alcohol, aspirin, and some foods. Assuming a recumbent position often worsens symptoms, and sitting upright and acid-reducing therapies alleviate them. Esophageal spasm can produce a squeezing chest discomfort similar to that of angina. Mallory-Weiss tears of the esophagus can occur in patients who have had prolonged vomiting episodes. Severe vomiting can also result in esophageal rupture (Boerhaave syndrome) with mediastinitis. Chest pain caused by peptic ulcer disease usually occurs 60 to 90 minutes after meals and typically responds rapidly to acid-reducing therapies. This pain generally localizes in the

epigastrium but can radiate to the chest and shoulders. Cholecystitis produces a wide range of pain syndromes and generally causes right upper quadrant abdominal pain, but chest and back pain caused by this disorder is not unusual. The pain is frequently described as being aching or colicky. Pancreatitis typically causes an intense, aching epigastric pain that may radiate to the back. Relief through acid-reducing therapies is limited.

Musculoskeletal and Other Causes

Chest pain can arise from musculoskeletal disorders involving the chest wall (e.g., costochondritis), by conditions affecting the nerves of the chest wall (e.g., cervical disc disease), by herpes zoster, or following heavy exercise. Chest pain due to musculoskeletal causes is often elicited by direct pressure over the affected area or by movement of the patient's neck. The pain itself can be fleeting, or it can be a dull ache that lasts for hours. Panic syndrome is a major cause of chest discomfort in ED patients. The symptoms typically include chest tightness, often accompanied by shortness of breath and a sense of anxiety, and generally last 30 minutes or longer.

Diagnostic Considerations

See also Chapters 10, 59, and 60 and Fig. 60G.1

Clinical Evaluation

When evaluating patients with acute chest pain, clinicians must address a series of issues related to prognosis and immediate management.[9] Even before trying to arrive at a definite diagnosis, high-priority questions include the following:

- *Clinical stability:* Does the patient need immediate treatment for actual or impending circulatory collapse or respiratory insufficiency?
- *Immediate prognosis:* If the patient is currently clinically stable, what is the risk of a life-threatening condition such as ACS, PE, or aortic dissection?
- *Safety of triage options:* If the risk for a life-threatening condition is low, is it safe to discharge the patient for outpatient management, or should further testing or observation to guide management be undertaken?

Initial Assessment

Evaluation of a patient with acute chest pain can begin before the physician sees the patient, and thus effectiveness may depend on the actions of the office staff and other nonphysician personnel. Guidelines from the ACC and AHA[5] (**see Chapters 59 and 60**, Guidelines sections) emphasize that patients with

symptoms consistent with ACS should not be evaluated solely over the telephone but should be referred to facilities that allow evaluation by a physician and recording of a 12-lead electrocardiogram (ECG).[5,10,11] These guidelines also recommend strong consideration of immediate referral to an ED or a specialized chest pain unit for patients with suspected ACS who experience chest discomfort at rest for longer than 20 minutes, hemodynamic instability, or recent syncope or near-syncope. Transport as a passenger in a private vehicle is considered an acceptable alternative to an emergency vehicle only if the wait would lead to a delay longer than 20 to 30 minutes.

Guidelines[5,10] recommend that patients with the following chief complaints undergo immediate assessment by triage nurses and be referred for further evaluation:

- Chest pain, pressure, tightness, or heaviness; pain that radiates to the neck, jaw, shoulders, back, or one or both arms
- Indigestion or heartburn; nausea and/or vomiting associated with chest discomfort
- Persistent shortness of breath
- Weakness, dizziness, lightheadedness, loss of consciousness

For such patients, initial assessment involves taking a history, performing a physical examination, obtaining an ECG and chest radiograph, and measuring biomarkers of myocardial injury.

History

If the patient does not need immediate intervention because of impending or actual circulatory collapse or respiratory insufficiency, the physician's assessment should begin with a clinical history that captures the characteristics of the patient's pain, including its quality, location, and radiation; the time and tempo (abrupt or gradual) of onset; the duration of symptoms; provoking or palliating activities; and any associated symptoms, particularly those that are pulmonary or gastrointestinal. Patients typically describe ACS discomfort as a diffuse substernal chest pressure that starts gradually, radiates to the jaw or arms, worsens with exertion, and is relieved by rest or nitroglycerin. Because angina tends to be manifested in the same way in a given patient (at least if it is caused by ischemia in the same territory), it is useful to compare the current episode with any previous documented episodes of angina. The response to nitroglycerin may not reliably discriminate cardiac chest pain from non–cardiac-related chest pain.[5] In contrast to the tempo of the chest discomfort in ACS, that of PE, aortic dissection, and pneumothorax is usually sudden and severe in onset. Moreover, pain that is pleuritic or positional in nature suggests PE, pericarditis, pneumonia, or a musculoskeletal condition. A review of the literature yielded eight factors from the chest pain history with a likelihood ratio for ACS significantly greater than 1 and six factors with a likelihood ratio significantly lower than 1 (**Table 56.2**).[5,6]

TABLE 56.2

Value of Elements of the Chest Pain History for the Diagnosis of Acute Coronary Syndrome

PAIN DESCRIPTOR	POSITIVE LIKELIHOOD RATIO (95% CI)
Increased Likelihood of AMI	
Radiation to the right arm or shoulder	4.7 (1.9-12.0)
Radiation to both arms or shoulders	4.1 (2.5-6.5)
Associated with exertion	2.4 (1.5-3.8)
Radiation to the left arm	2.3 (1.7-3.1)
Associated with diaphoresis	2.0 (1.9-2.2)
Associated with nausea or vomiting	1.9 (1.7-2.3)
Worse than previous angina or similar to previous MI	1.8 (1.6-2.0)
Described as pressure	1.3 (1.2-1.5)
Decreased Likelihood of AMI	
Described as pleuritic	0.2 (0.1-0.3)
Described as positional	0.3 (0.2-0.5)
Described as sharp	0.3 (0.2-0.5)
Reproducible with palpation	0.3 (0.2-0.4)
Inframammary location	0.8 (0.7-0.9)
Not associated with exertion	0.8 (0.6-0.9)

AMI, Acute myocardial infarction; *CI,* confidence interval.

Modified from Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. JAMA 2005;294:2623.

In addition to the characteristics of the acute episode, the presence of risk factors for atherosclerosis (e.g., advanced age, male sex, diabetes) increases the likelihood that the chest pain results from myocardial ischemia. A history of MI is associated not only with a high risk for obstructive CAD, but also with an increased likelihood of multivessel disease. Younger patients have a lower risk for ACS but should be screened with greater care for a history of recent cocaine use[5,6] (**see Chapter 80**). Although a thorough history is critical, clinician assessment alone does not suffice to rule in or rule out ACS. Combining clinician assessment with physical exam and, more importantly, ECG and biomarkers greatly improves diagnostic assessment.[12]

Physical Examination

The initial examination of patients with acute chest pain should endeavor to identify potential precipitating causes of myocardial ischemia (e.g., uncontrolled hypertension), important comorbid conditions (e.g., COPD), and evidence of hemodynamic complications (e.g., congestive heart failure, new mitral regurgitation, hypotension).[5,6,12] In addition to vital signs, examination of peripheral vessels should include assessment for the presence of bruits or absent pulses, which suggest extracardiac vascular disease (**see Chapter 64**).

For patients whose clinical findings do not suggest myocardial ischemia, the search for noncoronary causes of chest pain should focus first on potentially life-threatening issues (e.g., aortic dissection, PE) and then turn to the possibility of other cardiac diagnoses (e.g., pericarditis) and noncardiac diagnoses (e.g., esophageal discomfort). Aortic dissection may produce blood pressure or pulse disparities or a new murmur of aortic regurgitation accompanied by back or midline anterior chest pain. A friction rub may accompany pericarditis. Differences in breath sounds in the presence of acute dyspnea and pleuritic chest pain suggest pneumothorax. Tachycardia, tachypnea, and an accentuated pulmonic component of the second heart sound (P_2) may be the major manifestations of PE on physical examination.

Electrocardiography

An ECG, a source of decisive data, should be obtained within 10 minutes after arrival for individuals with ongoing chest discomfort and as rapidly as possible in those who have a history of chest discomfort consistent with ACS, but whose discomfort has resolved by the time of evaluation, to identify patients who might benefit from immediate reperfusion therapy (mechanical or pharmacologic)[5,10] (**see Chapter 12**). Obtaining a prehospital ECG decreases the door-to-diagnosis time and, for ST-segment elevation MI (STEMI), the door-to-balloon time. The pre-hospital ECG reduces both scene and transport times for patients with STEMI.[11,13]

The ECG helps to define both diagnosis and prognosis. New persistent or transient ST-segment abnormalities (≥0.05 mV) that develop during a symptomatic episode at rest and resolve when the symptoms resolve strongly suggest acute ischemia and severe CAD. Nonspecific, ST-segment changes or T wave abnormalities of 0.2 mV or less are not as helpful for risk stratification. The likelihood ratios for ACS with various findings on the ECG are shown in **Table 56.3**.[5] A completely normal ECG does not exclude ACS: the risk for AMI is approximately 4% in patients with a history of CAD and 2% in those with no such history.[5,13,14] Patients with normal or near-normal findings on an ECG, however, have a better prognosis than those with abnormal ECG at initial evaluation. Moreover, a normal ECG has a negative predictive value of 80% to 90%, regardless of whether the patient was experiencing chest pain at the time that the ECG was obtained.[5,10,14] Diffuse ST-segment elevation and PR-segment depression suggest pericarditis. Tachycardia with right axis deviation, right bundle branch block, T wave inversions in leads V_1 to V_4, and an S wave in lead I and Q wave and T wave inversions in lead III suggest PE.

TABLE 56.3

Value of Electrocardiographic (ECG) Findings for Diagnosis of Acute Coronary Syndrome (ACS)

ECG FINDING	POSITIVE LIKELIHOOD RATIO (95% CI WHERE AVAILABLE)
New ST-segment elevation ≥1 mm	5.7-53.9
New Q wave	5.3-24.8
Any ST-segment elevation	11.2 (7.1-17.8)
New conduction defect	6.3 (2.5-15.7)
New ST-segment depression	3.0-5.2
Any Q wave	3.9 (2.7-5.7)
Any ST-segment depression	3.2 (2.5-4.1)
T wave peaking and/or inversion ≥1 mm	3.1
New T wave inversion	2.4-2.8
Any conduction defect	2.7 (1.4-5.4)

CI, Confidence interval.

Modified from Panju AA, Hemmelgarn BR, Guyatt GH, Simel DL: Is this patient having a myocardial infarction? JAMA 280:1256, 1998.

The availability of a previous ECG improves diagnostic accuracy and reduces admission rates for patients with abnormal baseline tracings. Serial electrocardiographic tracings improve the clinician's ability to diagnose AMI, especially in the patient remains symptomatic and particularly if combined with serial measurement of cardiac biomarkers. Continuous electrocardiographic monitoring to detect ST-segment shifts makes an uncertain contribution to patient management. Posterior leads can help identify ischemia in the territory supplied by the circumflex coronary artery, an otherwise relatively silent zone on ECGs.

Chest Radiography

All patients with chest pain typically have a chest radiograph. It is usually nondiagnostic in patients with ACS but can show pulmonary edema secondary to ischemia-induced diastolic or systolic dysfunction. It is

more useful for diagnosing or suggesting other disorders; for example, it may show a widened mediastinum or aortic knob in patients with aortic dissection. The chest radiograph generally has normal findings in PE but can show atelectasis, an elevated hemidiaphragm, a pleural effusion, or more rarely a Hampton hump or Westermark sign. The chest radiograph can reveal pneumonia or pneumothorax.

Biomarkers

Patients with chest discomfort possibly consistent with ACS should undergo measurement of biomarkers of myocardial injury (**see Chapters 57 to 59**). The preferred biomarker is cardiac troponin T (cTnT) or I (cTnI); creatine kinase MB isoenzyme (CK-MB) is less sensitive.[5,15]

Diagnostic Performance

Studies of the diagnostic performance of cTnI, cTnT, and CK-MB indicate that when any of these test findings is abnormal, the patient is highly likely to have ACS. These assays aid indispensably the diagnosis of MI and have excellent sensitivity and specificity when viewed as part of all the clinical evidence.

Troponins.

Different genes encode troponins in cardiac muscle, slow skeletal muscle, and fast skeletal muscle; therefore, assays for cardiac troponins are more specific for myocardial injury than assays for CK-MB, and cardiac troponin is the preferred diagnostic biomarker.[15] The high specificity of cardiac troponins for myocardium makes false-positive elevations (i.e., elevation in the absence of myocardial injury) exceedingly rare. Rather, elevations in the absence of other clinical data consistent with ACS usually represent true myocardial damage from causes other than coronary artery thrombosis. Type 2 MIs occur in the setting of stable CAD, from either reduced myocardial oxygen supply (e.g., hypotension, vasospasm, severe anemia) or increased myocardial oxygen demand (e.g., hypertensive crisis, tachycardia, critical aortic stenosis, severe hypertrophic cardiomyopathy, extreme exercise). Myocardial damage may occur with direct forms of myocardial injury, such as in the setting of myocarditis, myocardial contusion, or cardioversion or defibrillation. Conditions that affect the pulmonary circulation, such as in PE or other causes of acute pulmonary hypertension, can also lead to biochemically detectable right ventricular injury. Patients with renal disease may have elevated levels of cardiac troponins.[15] The exact mechanism remains unclear, but in patients with a clinical history suggestive of ACS, an elevated cardiac troponin level conveys a similarly increased risk for ischemic complications in patients across a broad range of renal function.[15] Elevated cTn levels can also occur in patients with severe sepsis. Sex-specific cut points for troponin assays do not appear to offer any practical advantage.[16]

The greater sensitivity of contemporary sensitive cTn assays has allowed the traditional serial biomarker sampling over 24 hours to be shortened considerably. Current U.S. guidelines recommend measurement at presentation and then 3 to 6 hours after symptom onset (with additional measurements if there are electrocardiographic changes or other high-risk features).[5] Such a strategy yields a negative predictive value (NPV) approaching 99%.[17-19]

More recently, high-sensitivity troponin (hsTn) assays now enable even lower limits of detection (e.g., <0.001 ng/mL or <1 pg/mL) and allow at least 50% (some ≥95%) of healthy individuals below the 99th percentile to have a measurable level of troponin.[15,20] These assays can shorten the time interval to the next measurement to 1 to 2 hours and still achieve NPVs ≥99.5%.[21,22] Moreover, such assays may also permit the safe discharge of patients based on a single troponin value at presentation. Using a cutoff well

below the 99th percentile and often the limit of detection, approximately 20% to 25% of patients will have such a low or undetectable level with a corresponding >99% NPV.[23-26] The generalizability of these findings may also depend on the timing and nature of the presenting syndrome, with patients with a very short time from symptom onset to presentation needing serial sampling.[27] Serial sampling with hsTn assays also offers the ability to examine the change in troponin concentration between the two time points, with relative and particularly absolute increases above certain thresholds offering the potential for greater specificity for MI.[2,28-30]

Overall studies evaluating hsTn support the concept of accelerated diagnostic protocols that demonstrate a high NPV of very low concentrations in patients presenting with suspected ACS. However, time from symptom onset and the risk of the population require consideration. In addition, in centers without availability of high-sensitivity assays, serial testing at presentation and after 3 to 6 hours remains the standard of care.[20]

Creatine Kinase MB Isoenzyme.

CK-MB has less specificity than cardiac troponins because of its production by skeletal muscle, tongue, diaphragm, small intestine, uterus, and prostate. Use of the CK-MB relative index (ratio of CK-MB to total CK) partially addresses this limitation for skeletal muscle as a source. The amount of CK-MB in skeletal muscle, however, increases in patients with conditions that cause chronic muscle destruction and regeneration (e.g., muscular dystrophy), those who participate in high-performance athletics (e.g., marathon running), and those with rhabdomyolysis.[31] CK-MB elevations are particularly common in ED patients because they have higher rates of alcohol abuse or trauma history. One advantage of CK-MB is a shorter half-life in the circulation, which makes it useful for gauging the timing of an MI (a normal CK-MB with an elevated troponin level could represent a small MI or an MI that occurred several days ago) and for diagnosing reinfarction in a patient who had an MI in the past week. However, hsTn assays offer similar value.

Other Markers.

(see also **eTable 60.1**). Copeptin is secreted from the pituitary gland early in the course of MI. It has been investigated in combination with troponin in patients presenting with suspected ACS. In the CHOPIN study, both a negative copeptin and a sensitive troponin assay in patients presenting within 6 hours of symptom onset had NPV of 99.2%.[32] However, a study that evaluated the incremental diagnostic contribution of a 1-hour copeptin test when added to hsTn showed no benefit in NPV for MI.[33-35] Myoglobin, heart-type fatty acid–binding protein, and ischemia-modified albumin (IMA) have been studied as diagnostic biomarkers, but none is specific to myocardial tissue. The advent of sensitive and now high-sensitivity troponin assays leaves little room for added value for these assays.[36]

Many patients with ACS, including those without evidence of myocyte necrosis, have elevated concentrations of inflammatory biomarkers such as C-reactive protein, serum amyloid A, myeloperoxidase, or interleukin-6.[37-39] To date, no study has identified exact decision cut points or shown an incremental benefit with an admission or treatment strategy based on these new markers, thus limiting the clinical usefulness of these observations.

D-dimer testing is useful for patients with chest pain to help rule out PE, because a negative enzyme-linked immunosorbent assay (ELISA) has NPV >99% in patients with a low clinical probability (patients with a higher clinical probability should undergo an imaging study).[40] Similarly, a negative D-dimer has NPV of 96% for aortic dissection.[41]

B-type natriuretic peptides (BNP and N-terminal pro-BNP) reflects increased ventricular wall stress. Natriuretic peptides often aid in the diagnosis of heart failure. BNP levels can rise in the setting of transient myocardial ischemia,[42] and the magnitude of elevation in patients with ACS is related to prognosis.[43] Although not specific for ACS, adding natriuretic peptide measurements to the diagnostic algorithm does improve discrimination and results in improved reclassification.[44] Circulating microRNAs have been evaluated in small studies but have not yet been shown to provide incremental diagnostic or prognostic value in patients presenting with suspected AMI.[45]

Testing Strategy

Current practice guidelines recommend measurement of biomarkers of cardiac injury in patients with symptoms that suggest ACS.[5,29] Furthermore, patients with a very low probability of ACS should not undergo measurement of biomarkers because false-positive results could lead to unnecessary hospitalizations, tests, procedures, and complications. The ACC/AHA and European Society of Cardiology (ESC) guidelines recommend cTnI or cTnT as the preferred first-line marker, although CK-MB (by mass assay) is an acceptable alternative. The preference for cardiac troponins reflects the greater specificity of these markers than CK-MB and the prognostic value of troponin elevations in the presence of normal CK-MB levels. If the initial set of markers is negative, another sample should be drawn 3 to 6 hours later; if a high-sensitivity assay is used, a 1-hour algorithm can be considered.[3,5]

Decision Aids

Fig. 56.1 presents an algorithm for the diagnostic evaluation of chest pain. Integration of the history, physical examination, ECG, and biomarkers of myocardial injury allow the clinician to assess the likelihood of ACS and the risk for complications (**Tables 56.4 and 56.5**). Furthermore, prospectively validated multivariable algorithms improve risk stratification in patients with acute chest pain. These algorithms can estimate the probability of AMI, acute ischemic heart disease, or the risk for major cardiac complications in individual patients. They serve mainly to identify patients who are at low risk for complications and who therefore do not require admission to the hospital or coronary care unit.[46] Decision aids also exist for acute PE (**Chapter 84**) and aortic dissection (**Chapter 63**).

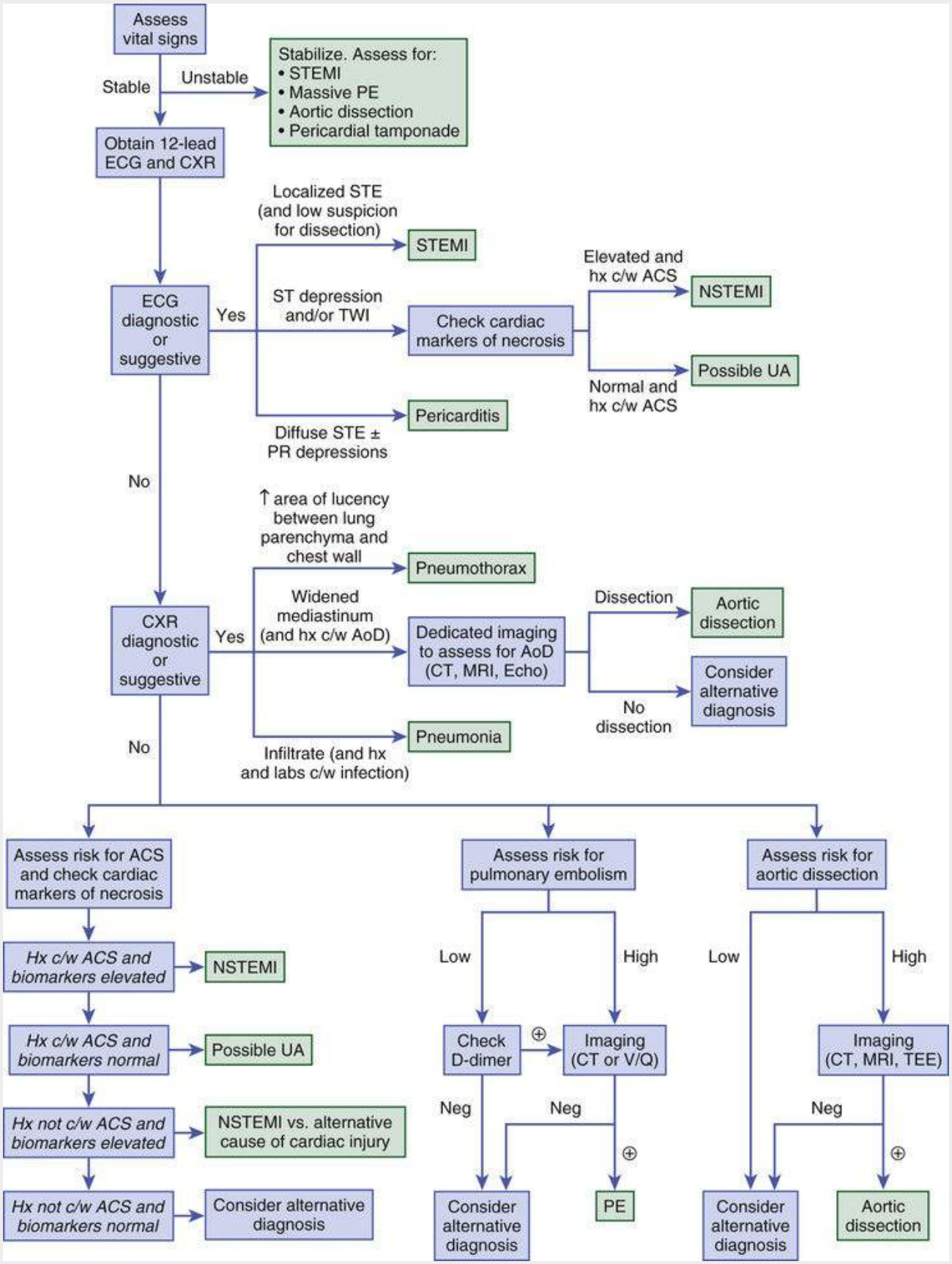

FIGURE 56.1 Algorithm for the initial diagnostic approach to a patient with chest pain. ACS, Acute coronary syndrome; AoD, aortic dissection; c/w, consistent with; CT, computed tomography; CXR, chest x-ray film; Echo, echocardiography; hx, history; MRI, magnetic resonance imaging; NSTEMI, non–ST-segment elevation myocardial infarction; STE, ST-segment elevation; STEMI, ST-segment elevation myocardial infarction; TEE, transesophageal echocardiography; UA, unstable angina; TWI, T wave inversion; V/Q, ventilation-perfusion scan.

TABLE 56.4

Likelihood That Signs and Symptoms Represent an Acute Coronary Syndrome (ACS)

FEATURE	HIGH LIKELIHOOD Any of the Following	INTERMEDIATE LIKELIHOOD Absence of High-Likelihood Features and Presence of Any of the Following	LOW LIKELIHOOD Absence of High- or Intermediate-Likelihood Features but May Have Any of the Following
History	• Chest or left arm pain or discomfort as the chief symptom reproducing documented previous angina • Known history of coronary artery disease, including myocardial infarction	• Chest or left arm pain or discomfort as the chief symptom • Age >70 yr • Male sex • Diabetes mellitus	• Probable ischemic symptoms in the absence of any of the intermediate-likelihood characteristics • Recent cocaine use
Examination	• Transient mitral regurgitation murmur, hypotension, diaphoresis, pulmonary edema, or rales	• Extracardiac vascular disease	• Chest discomfort reproduced by palpation
Electrocardiogram	• New or presumably new transient ST-segment deviation (≥0.1 mV) or T wave inversion (≥0.2 mV) in multiple precordial leads	• Fixed Q waves • ST-segment depression of 0.05-0.1 mV or T wave inversion >0.1 mV	• T wave flattening or inversion <0.1 mV in leads with dominant R waves • Normal ECG
Cardiac markers	• Elevated cTnI, cTnT, or CK-MB	• Normal levels	• Normal levels

From Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): Developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation 2007;116:e148.

TABLE 56.5

Short-Term Risk for Death or Nonfatal Myocardial Ischemia in Patients with Unstable Angina

FEATURE	HIGH RISK At Least One of the Following Features Must Be Present	INTERMEDIATE RISK No High-Risk Features but Must Have One of the Following	LOW RISK No High- or Intermediate-Risk Features but May Have Any of the Following
History	• Accelerating tempo of ischemic symptoms in preceding 48 hr	• Previous MI, peripheral or cerebrovascular disease, or CABG; previous ASA use	
Character of pain	• Prolonged ongoing (>20 min) pain at rest	• Prolonged (>20 min) rest angina, now resolved, with intermediate or high likelihood of CAD • Rest angina (>20 min) or relieved with rest or sublingual nitroglycerin • Nocturnal angina • New-onset or progressive CCS Class III or IV angina in the past 2 wk without prolonged (20 min) rest pain but with intermediate or high likelihood of CAD	• Increased angina frequency, severity, or duration • Angina provoked at a lower threshold • New-onset angina with onset 2 wk to 2 mo before initial evaluation
Clinical findings	• Pulmonary edema, most likely caused by ischemia • New or worsening MR murmur • S_3 or new or worsening rales • Hypotension, bradycardia, tachycardia • Age >75 yr	• Age >70 yr	
Electrocardiogram	• Angina at rest with transient ST-segment changes >0.05 mV • Bundle branch block, new or presumed new • Sustained ventricular tachycardia	• T wave changes • Pathologic Q waves or resting ST-segment depression <0.1 mV in multiple lead groups (anterior, inferior, lateral)	• Normal or unchanged ECG
Cardiac markers	• Elevated cTnI, cTnT, or CK-MB	• Slightly elevated cTnI, cTnT, or CK-MB	• Normal levels

ASA, Acetylsalicylic acid (aspirin); *CABG,* coronary artery bypass grafting; *CAD,* coronary artery disease; *CCS,* Canadian Cardiovascular Society; *ECG,* electrocardiogram; *MR,* mitral regurgitation.

From Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): Developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation 2007;116:e148.

The Thrombolysis in Myocardial Ischemia (TIMI) risk score was derived and validated in patients enrolled in clinical trials with ACS.[5] A care pathway (ADAPT) that allows for the safe disposition of patients integrates this score. A prospective observational study of 2000 patients with suspected ACS evaluated an accelerated protocol including the TIMI risk score and 0- and 2-hour troponin measurements. The NPV for adverse cardiovascular events at 20 days was 99.7%.[47] Using this protocol, the proportion of patients safely discharged within 6 hours increased from 11% to 19%.[48] Limitations of these analyses include their performance at a single center and that they included close follow-up with stress testing within 72 hours for patients discharged early.[19]

The HEART score uses similar components as the TIMI risk score. When combined with serial troponin measurements, it demonstrated the potential to reduce cardiac testing by 82%.[49] A subsequent evaluation of the HEART score and serial hsTn measurements at 0 and 3 hours in patients presenting with suspected ACS (HEART pathway) decreased testing at 30 days by 12.1%, decreased length of stay by 12 hours, and increased early discharge by 21%. At 30 days, no patients identified for early discharge had cardiac events.[50]

Immediate Management

The ACC and AHA guidelines suggest an approach to the immediate management of patients with possible ACS that integrates information from the history, physical examination, 12-lead ECG, and initial cardiac marker tests to assign patients to four categories: non–cardiac-related diagnosis, chronic stable angina, possible ACS, and definite ACS[5] (**Fig. 56.2**). This algorithm triages patients with ST-segment elevations to immediate reperfusion therapy, in accordance with the ACC and AHA guidelines for acute MI. Patients with ACS who have ST-segment or T wave changes, ongoing pain, positive cardiac markers, or hemodynamic abnormalities require hospital admission for the management of acute ischemia. Patients with possible or definite ACS who do not have diagnostic ECGs and with normal initial serum cardiac markers can be observed in a chest pain unit or other non–intensive care facility, with subsequent additional testing (see later).

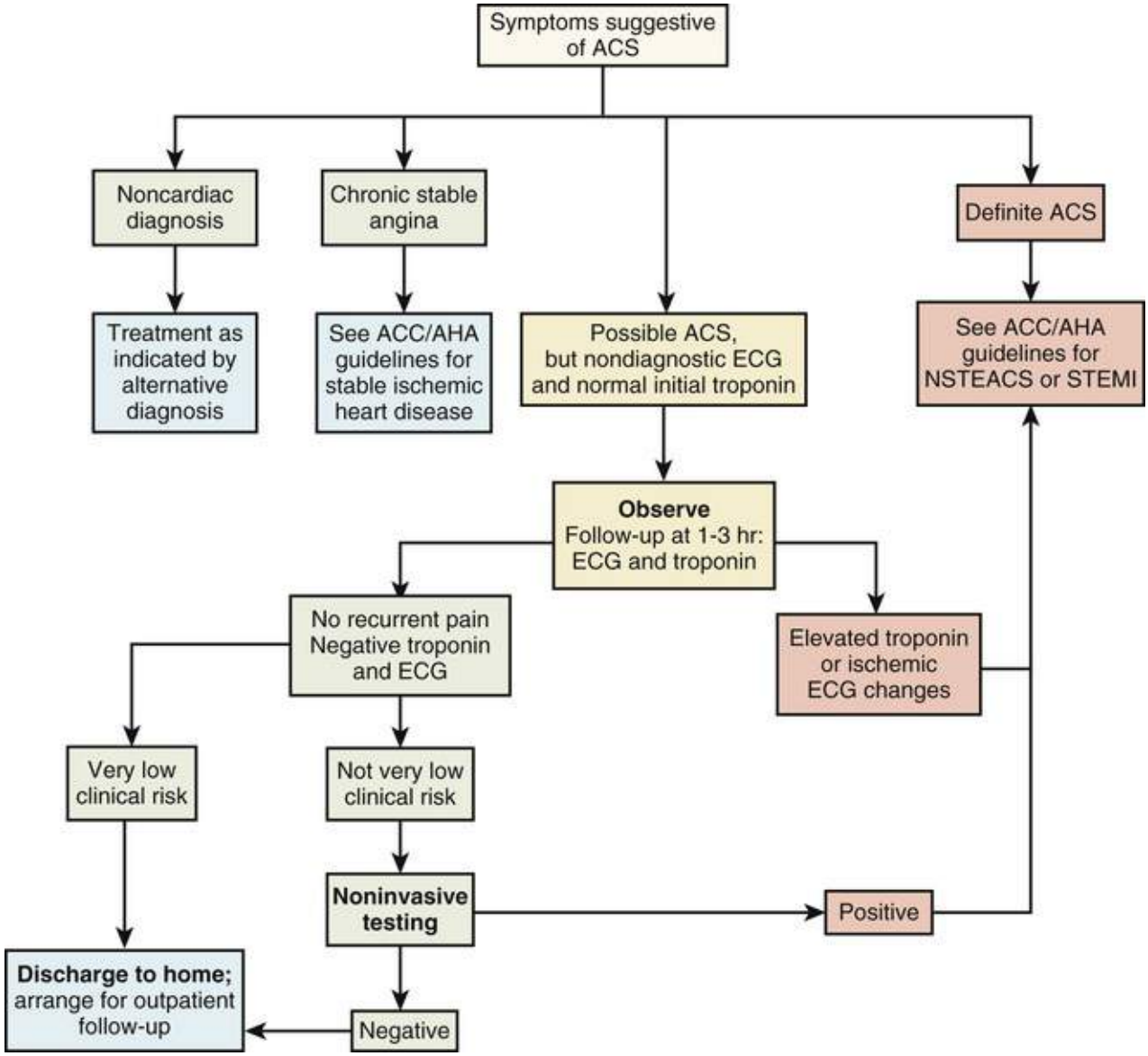

FIGURE 56.2 Algorithm for the evaluation and management of patients suspected of having acute coronary syndrome (ACS). The necessary duration of the observation period (1-3 hours) will depend on the sensitivity of the troponin assay. Key decisions in **bold.** ACC/AHA, American College of Cardiology/American Heart Association; ECG, electrocardiogram; STEMI, ST-segment elevation myocardial infarction; NSTEACS, non–ST-segment elevation acute coronary syndrome. (Adapted from Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment–elevation myocardial infarction: executive summary and recommendations: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina) [published correction appears in Circulation. 2000;102:1739]. Circulation. 2000;102:1193–1209.)

Chest Pain Protocols and Units

A typical chest pain critical pathway includes several main elements (**Fig. 56.2**). According to the ACC and AHA recommendations,[5] patients with a low risk for ACS or associated complications can be observed for several hours while undergoing electrocardiographic monitoring and serial measurement of cardiac markers. Patients in whom evidence of ischemia or other indicators of increased risk develop should be admitted to a cardiology service (step-down or coronary care unit) for further management. Patients in whom recurrent pain or other predictors of increased risk do not develop can either be discharged home if they are very low risk or be scheduled for early noninvasive testing (see later) before or after discharge. Specifically, as previously noted, patients with normal troponin levels, no ECG abnormalities concerning for ischemia, and a TIMI risk score of 0 or a HEART score of ≤3 have extremely low risk of adverse cardiovascular events and can be considered for discharge to home. Patients without biochemical or ECG evidence of ischemia and very low risk can undergo noninvasive testing. Outpatient stress testing is a reasonable option if the patient is at low risk for ACS and if the testing can be accomplished within 72 hours; such a strategy can be safe. Such patients can receive aspirin and possibly beta-adrenergic blocking agents (beta blockers) and sublingual nitroglycerin.

To enhance the efficiency and reliability of implementation of such chest pain protocols, many hospitals triage low-risk patients with chest pain to special chest pain units.[3] These units often localize adjacent to or within EDs. The rate of MI approximates 1% to 2% in most such units, and they have proved safe and cost-saving for care of low-risk patients. Chest pain units are also sometimes used for intermediate-risk patients, such as those with a previous history of CAD but no other high-risk predictors. In one community-based randomized trial, patients with unstable angina and an overall intermediate risk for complications had similar outcomes and lower cost if they received care in a chest pain unit versus conventional hospital management.

Early Noninvasive Testing

Treadmill Electrocardiography

Treadmill exercise electrocardiography is inexpensive and available at many hospitals every day, beyond traditional laboratory hours, and prospective data indicate that early exercise test results provide reliable prognostic information for low-risk patient populations (**see Chapter 13**). Most studies have used the Bruce or modified Bruce treadmill protocol. Multiple studies have demonstrated the safety of exercise testing in low-risk patients, and a negative predictive value of typically greater than 99%, although the positive predictive value is frequently less than 50% (depending on the prevalence of ACS in the tested population).[3]

Patients with low clinical risk for complications can safely undergo exercise testing after their second negative troponin test (typically 3 to 6 hours later) and no other evidence of myocardial ischemia.[3] In general, protocols for early or immediate exercise testing exclude patients with electrocardiographic findings consistent with ischemia not recorded on previous tracings, ongoing chest pain, or evidence of congestive heart failure. Analyses of pooled data have suggested that the prevalence of CAD in populations undergoing early exercise testing averages approximately 5% to 10%, the rate of adverse events is negligible, and fewer than 1% ultimately proceed to angiography and revascularization.[51] The AHA has issued a scientific statement regarding the indications for and contraindications to exercise on electrocardiographic stress testing in the ED (**Table 56.6**).[3] For low-risk patients with no evidence of myocardial ischemia after serial ECGs and biomarkers, outpatient stress testing ideally within 24 hours,

and no later than 72 hours, has proved safe.[3]

TABLE 56.6

Indications and Contraindications for Exercise Electrocardiographic Testing in the Emergency Department (ED)

Requirements before exercise electrocardiographic testing that should be considered in the ED setting:
• Two sets of cardiac enzymes at 4-hour intervals should be normal.
• ECG at arrival and preexercise 12-lead ECG show no significant abnormality.
• Absence of rest electrocardiographic abnormalities that would preclude accurate assessment of the exercise ECG.
• From admission to availability of results from the second set of cardiac enzymes: patient asymptomatic, lessening chest pain symptoms, or persistent atypical symptoms.
• Absence of ischemic chest pain at exercise testing.
Contraindications to exercise electrocardiographic testing in the ED setting:
• New or evolving electrocardiographic abnormalities on the rest tracing.
• Abnormal cardiac biomarker levels.
• Inability to perform exercise.
• Worsening or persistent ischemic chest pain symptoms from admission to exercise testing.
• Clinical risk profiling indicating that imminent coronary angiography is likely.

Imaging Tests

Stress echocardiography and radionuclide scans are the preferred noninvasive testing modalities for patients who cannot undergo treadmill electrocardiographic testing because of physical disability or who have resting ECGs that confound interpretation. Imaging studies are less readily available and more expensive than exercise electrocardiography but have increased sensitivity for the detection of CAD and the ability to quantify the extent of and localize jeopardized myocardium. High-risk rest perfusion scans indicate an increased risk for major cardiac complications, whereas patients with low-risk scans have low 30-day cardiac event rates (<2%).[52-54]

In addition to stress imaging studies to detect provocable ischemia, rest radionuclide scans can also help determine whether a patient's symptoms represent myocardial ischemia.[53] In a multicenter prospective randomized trial of 2475 adult ED patients with ongoing or recently resolved (<3 hours) chest pain or other symptoms suggestive of acute cardiac ischemia and with normal or nondiagnostic initial electrocardiographic results, patients underwent random assignment to a usual evaluation strategy or the usual strategy supplemented with results from acute resting myocardial perfusion imaging. The availability of scan results did not influence the management of patients with acute MI or unstable angina, but it reduced rates of hospitalization for patients without acute cardiac ischemia from 52% to 42%. Rest myocardial perfusion imaging is most sensitive if performed when a patient is experiencing ischemic symptoms, with its sensitivity progressively diminishing thereafter. Imaging should be performed within 2 hours of the resolution of symptoms, although data support its use for up to 4 hours.[53] It should be noted that perfusion defects seen at rest could represent either acute ischemia or previous MI, which can be differentiated on subsequent pain-free rest imaging.

Echocardiography, with and without stress, can detect wall motion abnormalities consistent with myocardial ischemia or MI. The presence of induced or baseline regional wall motion abnormalities is associated with a worse prognosis. The sensitivity of stress echocardiography appears comparable to that of myocardial perfusion imaging (85% to 90%), and its specificity is somewhat better (80% to 95% versus 75% to 90%).[53] As for myocardial perfusion imaging, the results are less interpretable in patients with previous MI, in whom it is difficult to exclude whether the abnormalities are preexisting in the absence of a prior study. Myocardial contrast-enhanced echocardiography using microbubble imaging agents offers reasonable (77%) concordance with radionuclide scanning, and the combination of regional wall motion abnormalities and reduced myocardial perfusion has a sensitivity of 80% to 90% and a

specificity of 60% to 90% for ACS.[53]

Cardiac magnetic resonance imaging (MRI) may also aid the assessment of patients with suspected ACS.[55-57] A study that used cardiac MRI to quantify myocardial perfusion, ventricular function, and hyperenhancement in patients with chest pain showed sensitivity for ACS of 84% and specificity of 85%. The addition of T2-weighted imaging, which can detect myocardial edema and thus help differentiate acute from chronic perfusion defects, improves the specificity to 96% without sacrificing sensitivity.[57] Integration of coronary magnetic resonance angiography is under study.[56] Stress MRI using adenosine, although more labor intensive, also shows excellent sensitivity and specificity.[55] A randomized study of 1202 patients with suspected ACS found that cardiac MRI resulted in a lower probability of unnecessary angiography within 12 months compared to guideline-directed care, with no difference in adverse cardiac outcomes.[58] Resource availability and time requirements may limit common utilization of cardiac MRI in this setting.

In contrast to the functional imaging data from stress testing, coronary computed tomographic angiography (CTA) offers noninvasive anatomic data.[59] Using multidetector CT, coronary CTA has sensitivity of approximately 90% and specificity of 65% to 90% for coronary stenosis greater than 50%. Coronary CTA has been evaluated in patients presenting with suspected ACS. In a randomized trial of 1370 patients presenting with suspected ACS with a TIMI risk score of 0 to 2 (low risk), those receiving coronary CTA had higher rates of ED discharge (49.6% versus 22.7%), shorter length of stay (18.0 hours versus 24.8 hours), and higher rates of CAD detection (9.0% versus 3.5%), with only one adverse event in each group.[60] In a second randomized study, 1000 patients with symptoms suggestive of ACS, a nonischemic ECG, and negative initial troponin were randomized to early coronary CTA or standard care. Overall, the rate of ACS was 8%, and early coronary CTA reduced the mean length of stay by 7.6 hours and resulted in more patients discharged directly from the ED (47% versus 12%). There were no undetected ACS events and no difference in adverse cardiovascular events at 28 days. The coronary CTA group had more downstream testing, higher radiation exposure, and similar cost to standard evaluation.[4] An observational cohort study evaluated the combination of hsTn at presentation and coronary CTA, looking at advanced features of CAD (≥50% stenosis, high-risk plaque features: positive remodeling, low <30-Hounsfield units plaque, napkin-ring sign, spotty calcium), relative to conventional troponin and coronary CTA, looking at traditional features of CAD (no CAD, nonobstructive CAD, ≥50% stenosis), and found greater diagnostic accuracy for ACS using hsTn and advanced CTA assessment.[61] In addition to diagnosis, coronary CTA can provide calcium scores, giving prognostic information and potentially informing the need for additional cardiac testing.[62] The most recent ACC/AHA guidelines acknowledge coronary CTA as a reasonable alternative to stress testing in patients with low to intermediate probability of CAD.[5]

Another advantage of CTA is that it is often the test of choice for PE and for aortic dissection (**see Chapters 63 and 83**), and thus "triple-rule-out CTA" can evaluate for CAD, PE, and aortic dissection.[63-65] Although this approach accurately detects CAD, the low prevalence of PE and aortic dissection and the increased radiation and contrast exposure relative to traditional coronary CTA suggest restricting triple-rule-out scans to patients with a reasonable suspicion for PE or aortic dissection.[66,67] Ultimately, the traditional trifecta of a clinician's careful assessment of the prior probability of a cardiovascular origin for the chest discomfort, the nature of the acute episode, and the physical examination should be coupled with ever more precise objective data, including serial ECGs, rapid biochemical testing, and imaging to help optimize patient triage.

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57

Coronary Blood Flow and Myocardial Ischemia

Dirk J. Duncker, John M. Canty Jr

The coronary circulation is unique in that the heart is responsible for generating the arterial pressure that is required to perfuse the systemic circulation and yet, at the same time, has its own perfusion impeded during the systolic portion of the cardiac cycle. Because myocardial contraction is closely connected to coronary flow and oxygen delivery, the balance between oxygen supply and demand is a critical

determinant of the normal beat-to-beat function of the heart (see Classic References, Feigl). When this relation is acutely disrupted by diseases affecting coronary blood flow, the resulting imbalance can immediately precipitate a vicious cycle whereby ischemia-induced contractile dysfunction precipitates hypotension and further myocardial ischemia. Thus, knowledge of the regulation of coronary blood flow, determinants of myocardial oxygen consumption, and the relation between ischemia and contraction is essential for understanding the pathophysiologic basis and management of many cardiovascular disorders (see Classic References, Hoffman and Spaan).

Control of Coronary Blood Flow

There are pronounced systolic and diastolic coronary flow variations throughout the cardiac cycle, with coronary arterial inflow out of phase with venous outflow (**Fig. 57.1**). Systolic contraction increases tissue pressure, redistributes perfusion from the subendocardial to the subepicardial layers of the heart, and impedes coronary arterial inflow, which reaches a nadir. At the same time, systolic compression reduces the diameter of intramyocardial microcirculatory vessels (arterioles, capillaries, and venules) and increases coronary venous outflow, which peaks during systole. During diastole, coronary arterial inflow increases with a transmural gradient that favors perfusion to the subendocardial vessels. At this time, coronary venous outflow falls.

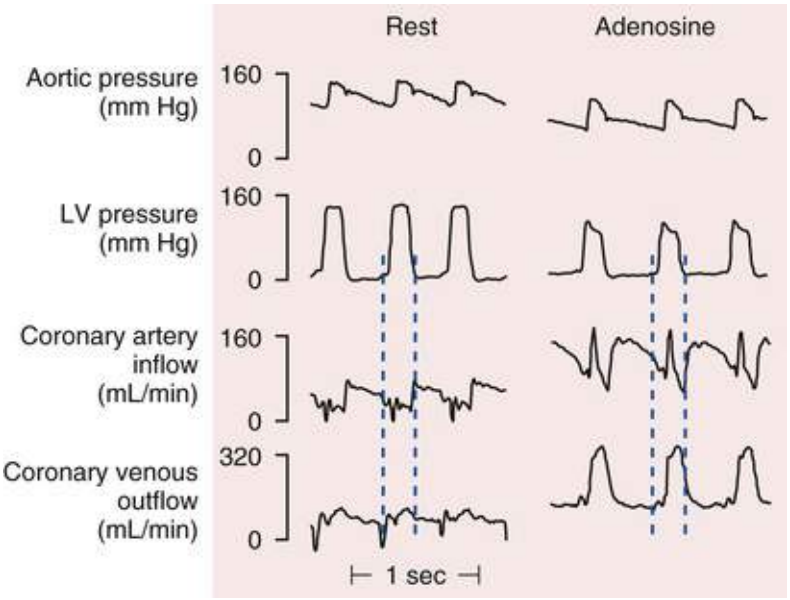


FIGURE 57.1 Phasic coronary arterial inflow and venous outflow at rest and during adenosine vasodilation. Arterial inflow primarily occurs during diastole. During systole (*dotted vertical lines*), arterial inflow declines as venous outflow peaks, reflecting the compression of microcirculatory vessels during systole. After adenosine administration, the phasic variations in venous outflow are more pronounced. LV, Left ventricular. (Modified from Canty JM Jr, Brooks A. Phasic volumetric coronary venous outflow patterns in conscious dogs. Am J Physiol 1990;258:H1457.)

Determinants of Myocardial Oxygen Consumption

In contrast to most other vascular beds, myocardial oxygen extraction is near-maximal at rest, averaging 70% to 80% of arterial oxygen content.[1,2] The ability to increase oxygen extraction as a means to increase oxygen delivery is limited to circumstances associated with sympathetic activation and acute

subendocardial ischemia. Nevertheless, coronary venous oxygen tension (Pv_{O_2}) can only decrease from 25 mm Hg to approximately 15 mm Hg. Because of the high resting oxygen extraction, increases in myocardial oxygen consumption are primarily met by proportional increases in coronary flow and oxygen delivery (**Fig. 57.2**). In addition to coronary flow, oxygen delivery is directly determined by arterial oxygen content (Ca_{O_2}). This is equal to the product of hemoglobin concentration and arterial oxygen saturation plus a small amount of oxygen dissolved in plasma that is directly related to arterial oxygen tension (Pa_{O_2}). Thus, for any given flow level, anemia results in proportional reductions in oxygen delivery, whereas hypoxia, due to the nonlinear oxygen dissociation curve, results in relatively small reductions in oxygen content until Pa_{O_2} falls to the steep portion of the oxygen dissociation curve (below 50 mm Hg).

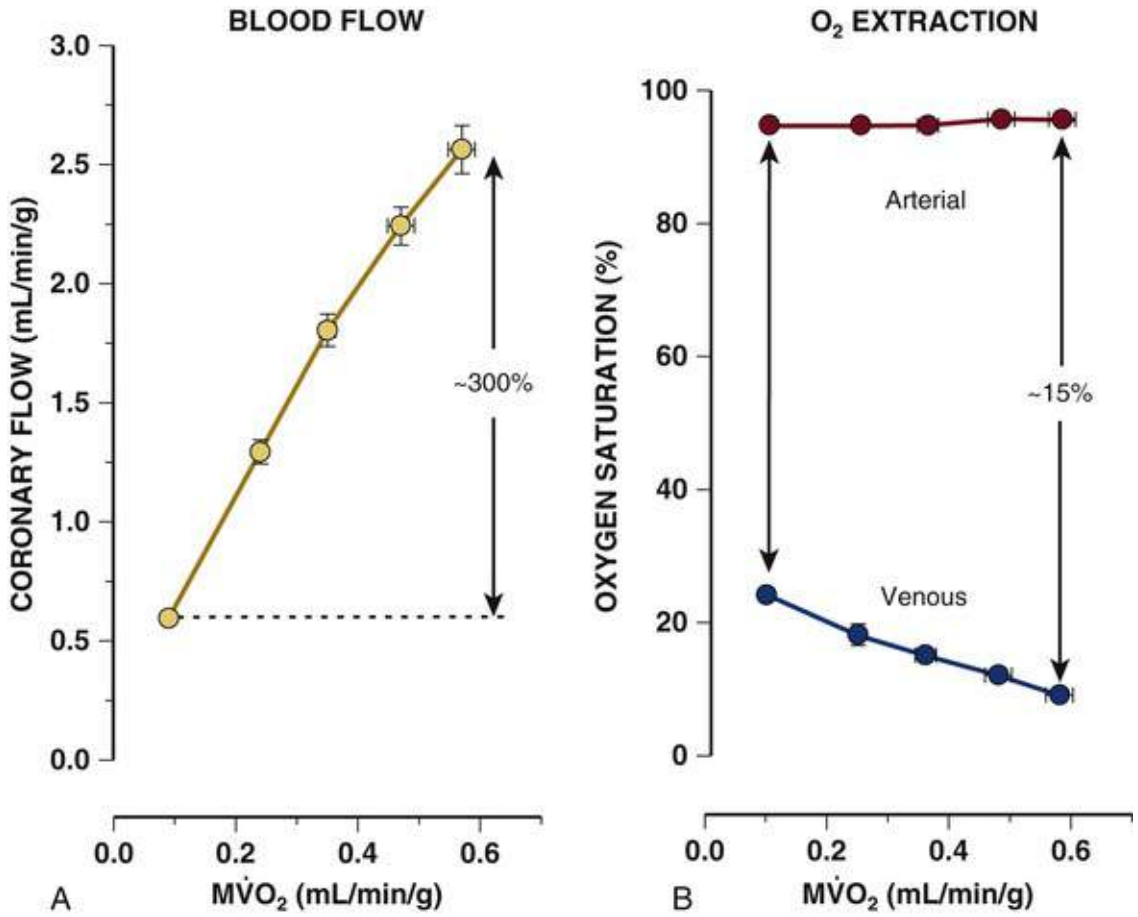


FIGURE 57.2 Tight matching of myocardial oxygen consumption (MVO_2) and coronary blood flow during exercise-induced increases in myocardial oxygen demand. **A,** Increases in MVO_2 are primarily met by increases in coronary flow. **B,** High basal levels of myocardial oxygen extraction allow only modest (approximately 15%) further increases in oxygen extraction during exercise.

The major determinants of myocardial oxygen consumption are heart rate, systolic pressure (or myocardial wall stress), and left ventricular (LV) contractility (**see Chapter 22**). A twofold increase in any of these individual determinants of oxygen consumption requires an approximately 50% increase in coronary flow. Experimentally, the systolic pressure volume area is proportional to myocardial work and linearly related to myocardial oxygen consumption. The basal myocardial oxygen requirements needed to maintain critical membrane function are low (approximately 15% of resting oxygen consumption), and the cost of electrical activation is trivial when mechanical contraction ceases during diastolic arrest (as with cardioplegia) and diminishes during ischemia.

Coronary Autoregulation

Regional coronary blood flow remains constant as coronary artery pressure is reduced below aortic pressure over a wide range when the determinants of myocardial oxygen consumption are kept constant. This phenomenon is termed *autoregulation* (**Fig. 57.3**). When pressure falls to the lower limit of autoregulation, coronary resistance arteries are maximally vasodilated to intrinsic stimuli, and flow becomes pressure-dependent, resulting in the onset of subendocardial ischemia. Resting coronary blood flow under normal hemodynamic conditions averages 0.7 to 1.0 mL/min/g and can increase between four- and fivefold during vasodilation. The ability to increase flow above resting values in response to pharmacologic vasodilation is termed *coronary flow reserve*. Flow in the maximally vasodilated heart is dependent on coronary arterial pressure. Maximum perfusion and coronary flow reserve are reduced when the diastolic time available for subendocardial perfusion is decreased (tachycardia) or the compressive determinants of diastolic perfusion (preload) are increased. Coronary reserve also is diminished by anything that increases resting flow, including increases in the hemodynamic determinants of oxygen consumption (systolic pressure, heart rate, and contractility) and reductions in arterial oxygen supply (anemia and hypoxia). Thus, circumstances can develop that precipitate subendocardial ischemia in the presence of normal coronary arteries (see Classic References, Hoffman and Spaan). Although initial studies suggested that the lower pressure limit of autoregulation is 70 mm Hg, it was later shown that coronary flow can be autoregulated to mean coronary pressures as low as 40 mm Hg (diastolic pressures of 30 mm Hg) in conscious dogs in the basal state (**Fig. 57.4**). These coronary pressure levels are similar to those recorded in humans without symptoms of ischemia, distal to chronic coronary occlusions, using pressure wire micromanometers. The lower autoregulatory pressure limit increases during tachycardia because of an increase in flow requirements, as well as a reduction in the time available for perfusion.

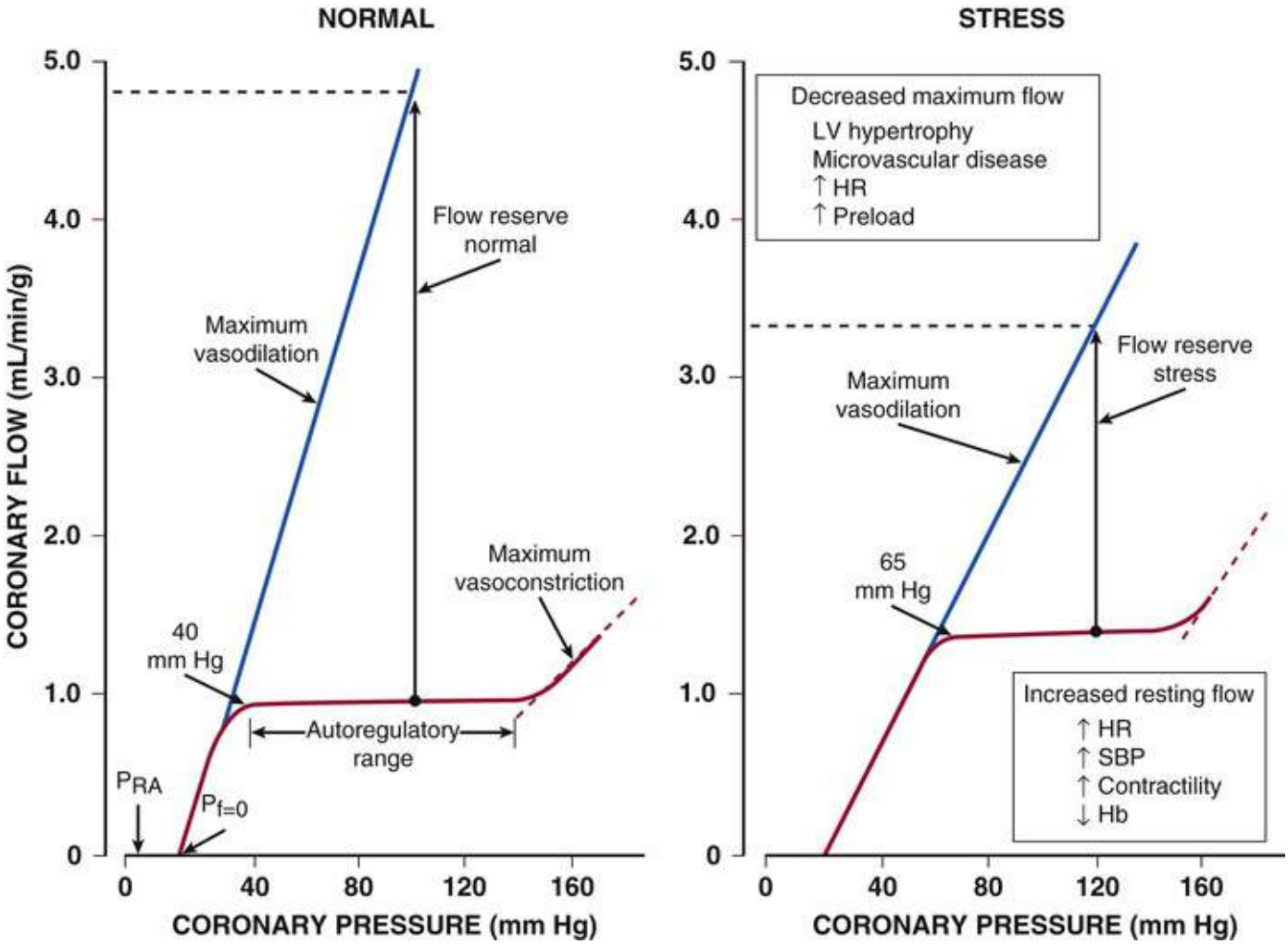


FIGURE 57.3 Autoregulatory relation under basal conditions and after metabolic stress (e.g., tachycardia). **Left**, The normal heart maintains coronary blood flow constant as regional coronary pressure is varied over a wide range when the global determinants of oxygen consumption are kept constant (*red lines*). Below the lower autoregulatory pressure limit (approximately 40 mm Hg), subendocardial vessels are maximally vasodilated and myocardial ischemia develops. During vasodilation (*blue lines*), flow increases four to five times above resting values at a normal arterial pressure. Coronary flow ceases at a pressure higher than right atrial pressure (P_{RA}), called *zero flow pressure* ($P_{f=0}$), which is the effective backpressure to flow in the absence of coronary collaterals. **Right,** After stress, tachycardia increases the compressive determinants of coronary resistance by decreasing the time available for diastolic perfusion and thus reduces maximum vasodilated flow. Left ventricular (LV) hypertrophy and microvascular disease also limit maximal blood flow per gram of myocardium. In addition, increases in myocardial oxygen demand or reductions in arterial oxygen content (e.g., from anemia or hypoxemia) increase resting flow. These changes reduce coronary flow reserve, the ratio between dilated and resting coronary flow, and cause ischemia to develop at higher coronary pressures. Hb, Hemoglobin; HR, heart rate; SBP, systolic blood pressure.

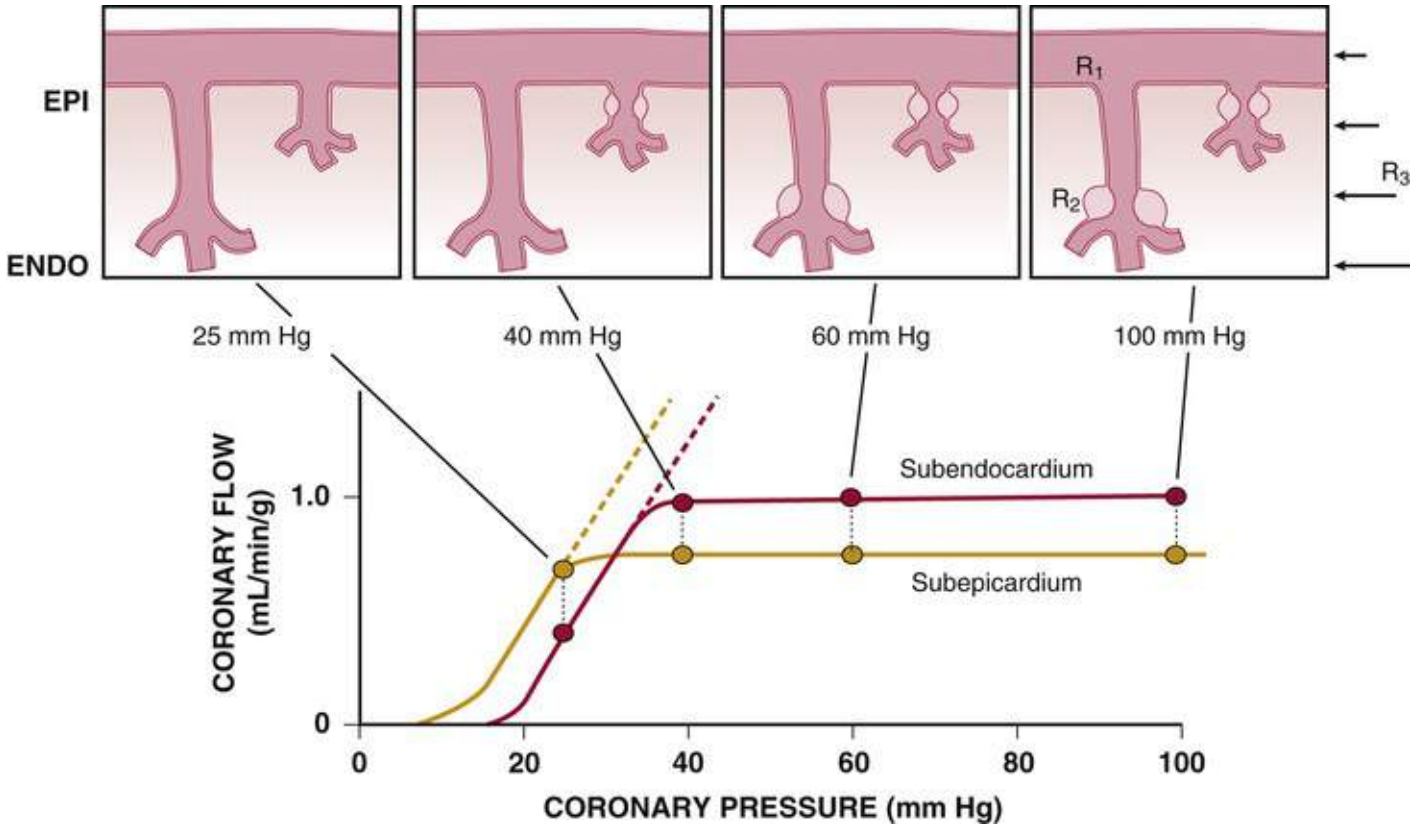


FIGURE 57.4 Transmural variations in coronary autoregulation and myocardial metabolism. Increased vulnerability of the subendocardium (ENDO, *red*) versus subepicardium (EPI, *gold*) to ischemia reflects the fact that autoregulation is exhausted at a higher coronary pressure (40 versus 25 mm Hg). This is the result of increased resting flow and oxygen consumption in the subendocardium and an increased sensitivity to systolic compressive effects, because subendocardial flow only occurs during diastole. Subendocardial vessels become maximally vasodilated before those in the subepicardium as coronary artery pressure is reduced. These transmural differences can be increased further during tachycardia or during conditions with elevated preload, which reduce maximum subendocardial perfusion. (Modified from Canty JM Jr. Coronary pressure-function and steady-state pressure-flow relations during autoregulation in the unanesthetized dog. Circ Res 1988;63:821.)

Fig. 57.4 also illustrates important transmural variations in the lower autoregulatory pressure limit, which result in increased vulnerability of the subendocardium to ischemia. Subendocardial flow occurs primarily in diastole and begins to decrease below a mean coronary pressure of 40 mm Hg. In contrast, subepicardial flow occurs throughout the cardiac cycle and is maintained until coronary pressure falls below 25 mm Hg. This difference arises from increased oxygen consumption in the subendocardium, requiring a higher resting flow level, as well as the more pronounced effects of systolic contraction on subendocardial vasodilator reserve. The transmural difference in the lower autoregulatory pressure limit results in vulnerability of the subendocardium to ischemia in the presence of a coronary stenosis. Although there is no pharmacologically recruitable flow reserve during ischemia in the normal coronary circulation, reductions in coronary flow below the lower limit of autoregulation can occur in the presence of pharmacologically recruitable coronary flow reserve under certain circumstances, e.g. exercise (see Classic References, Duncker and Bache).

Determinants of Coronary Vascular Resistance

The resistance to coronary blood flow can be divided into three major components (**Fig. 57.5**) (see Classic References, Klocke, 1976). Under normal circumstances, there is no measurable pressure drop in the epicardial arteries, indicating negligible conduit resistance (R_1). With the development of hemodynamically significant epicardial artery narrowing (>50% diameter reduction), the fixed conduit

artery resistance begins to contribute an increasing component to total coronary resistance and, when severely narrowed (>90%), may reduce resting flow.

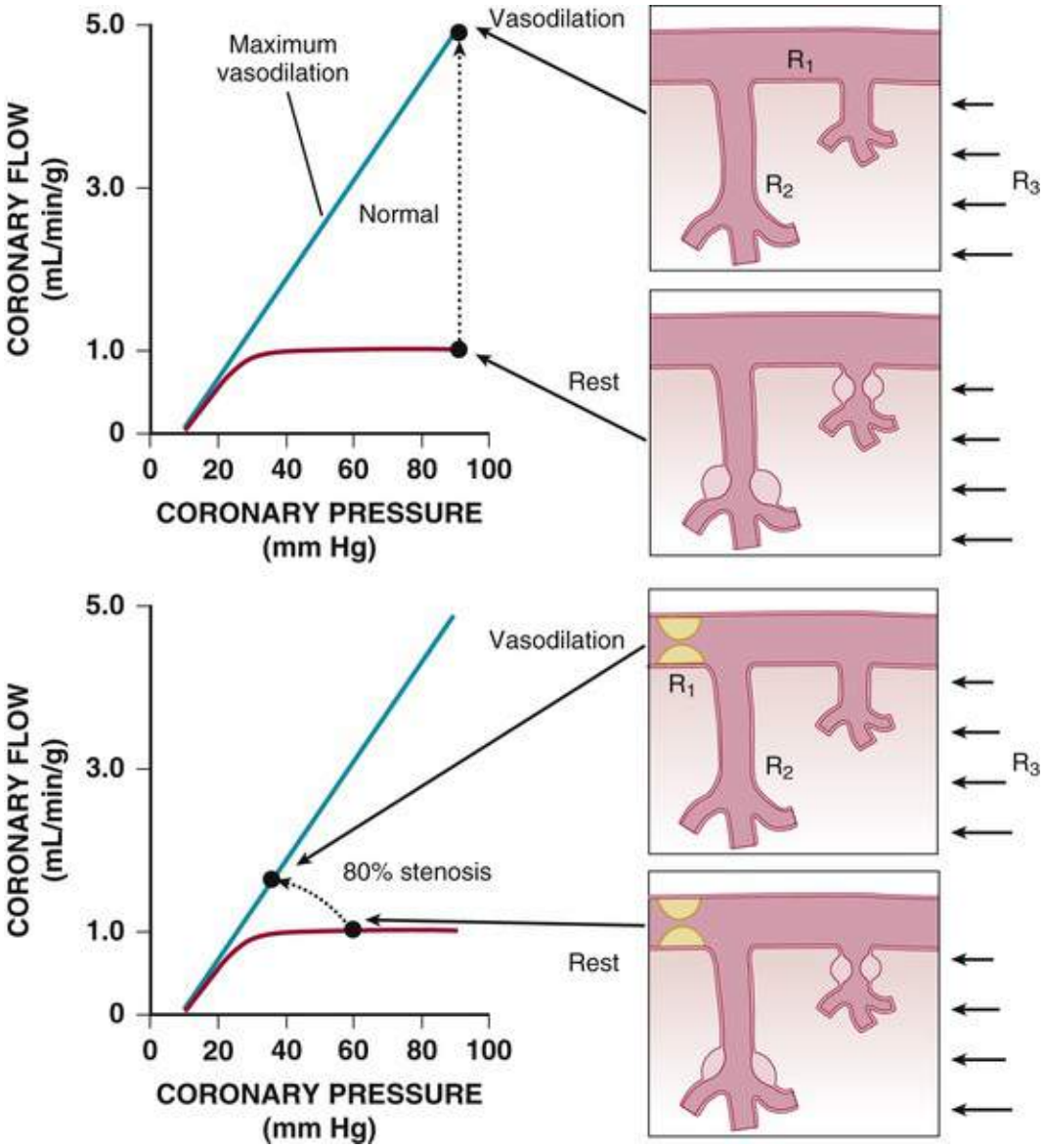


FIGURE 57.5 Schematic of components of coronary vascular resistance with and without a coronary stenosis. R_1 is epicardial conduit artery resistance, which normally is insignificant; R_2 is resistance secondary to metabolic and autoregulatory adjustments in flow and occurs in arterioles and small arteries; and R_3 is the time-varying compressive resistance that is higher in subendocardial than subepicardial layers. In the normal heart **(upper panel),** $R_2 > R_3$ R $_1$. The development of a proximal stenosis or pharmacologic vasodilation reduces arteriolar resistance (R_2). In the presence of a severe epicardial stenosis **(lower panel),** $R_1 > R_3 > R_2$.

The second component of coronary resistance (R_2) is dynamic and arises primarily from microcirculatory resistance arteries and arterioles. This is distributed throughout the myocardium across a broad range of microcirculatory resistance vessel sizes (20 to 400 µm in diameter) and changes in response to physical forces (intraluminal pressure and shear stress), as well as the metabolic needs of the tissue. Normally, little resistance is contributed by coronary venules and capillaries, and their resistance remains fairly constant during changes in vasomotor tone. Even in the maximally vasodilated heart, capillary resistance accounts for no more than 20% of the microvascular resistance.[3] Thus a twofold increase in capillary density would increase maximal myocardial perfusion by only approximately 10%.

Minimal coronary vascular resistance of the microcirculation is primarily determined by the size and density of arterial resistance vessels and results in substantial coronary flow reserve in the normal heart.

Extravascular Compressive Resistance.

The third component, extravascular compressive resistance (R_3), varies with time throughout the cardiac cycle and is related to cardiac contraction and systolic pressure development within the left ventricle. In heart failure, compressive effects from elevated ventricular diastolic pressure also impede perfusion by passive compression of microcirculatory vessels from elevated extravascular tissue pressure during diastole. Increases in preload effectively raise the normal backpressure to coronary flow above coronary venous pressure levels. Compressive effects are most prominent in the subendocardium (see later).

During systole, cardiac contraction raises extravascular tissue pressure to values equal to LV pressure at the subendocardium. This declines to values near pleural pressure at the subepicardium. The increased effective backpressure during systole produces a time-varying reduction in the driving pressure for coronary flow that impedes perfusion to the subendocardium. Although this paradigm can explain variations in systolic coronary inflow, it is not able to account for the increase in coronary venous systolic outflow. To explain both impaired inflow and accelerated venous outflow, some investigators have proposed the concept of the intramyocardial pump (see Classic References, Hoffman and Spaan). In this model, microcirculatory vessels are compressed during systole and produce a capacitive discharge of blood that accelerates flow from the microcirculation to the coronary venous system (**Fig. 57.6**). At the same time, the upstream capacitive discharge impedes systolic coronary arterial inflow. Although this explains the phasic variations in coronary arterial inflow and venous outflow, as well as its transmural distribution in systole, vascular capacitance cannot explain compressive effects related to elevated tissue pressure during diastole. Thus, intramyocardial capacitance, compressive changes in effective coronary backpressure, increases in systolic coronary resistance, and a time-varying driving pressure all contribute to the compressive determinants of phasic systolic coronary blood flow.

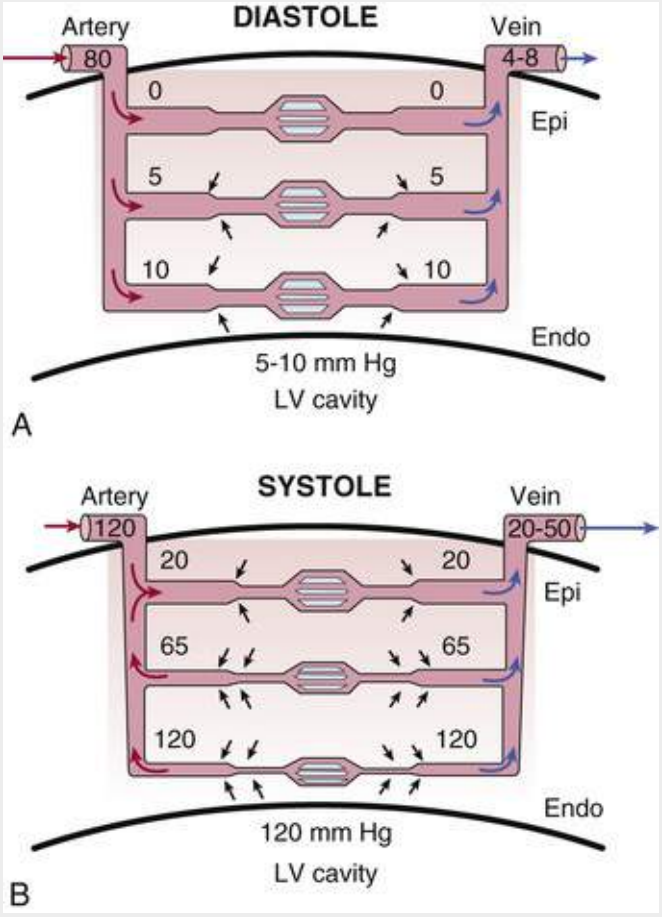


FIGURE 57.6 Effects of extravascular tissue pressure on transmural perfusion. **A,** Compressive effects during diastole are related to tissue pressures that decrease from the subendocardium (*Endo*) to subepicardium (*Epi*). At diastolic left ventricular (LV) pressures greater than 20 mm Hg, preload determines the effective backpressure to coronary diastolic perfusion. **B,** During systole, cardiac contraction increases intramyocardial tissue pressure surrounding compliant arterioles and venules. This produces a concealed arterial "backflow" that reduces systolic epicardial artery inflow, as depicted in **Fig. 57.1**. Compression of venules accelerates venous outflow. (Modified from Hoffman JI, Spaan JA. Pressure-flow relations in the coronary circulation. Physiol Rev 1990;70:331.)

Transmural Variations in Minimum Coronary Resistance (R_2) and Diastolic Driving Pressure.

The subendocardial vulnerability to compressive determinants of vascular resistance is partially compensated by a reduced minimal resistance resulting from an increased arteriolar and capillary density. Because of this vascular gradient, subendocardial flow during maximal pharmacologic vasodilation of the nonbeating heart is greater than subepicardial perfusion. Coronary vascular resistance in the maximally vasodilated heart also is pressure dependent, reflecting passive distention of arterial resistance vessels. Thus the instantaneous vasodilated value of coronary resistance obtained at a normal coronary distending pressure will be lower than that at a reduced pressure.

The precise determinants of the effective driving pressure for diastolic perfusion continue to be controversial. Most experimental studies demonstrate that the effective backpressure to flow in the heart is higher than right atrial pressure. This has been termed *zero flow pressure* ($P_{f=0}$) and its minimum value is approximately 10 mm Hg in the maximally vasodilated heart. This increases to values close to LV diastolic filling pressure when preload is elevated above 20 mm Hg. Elevated preload reduces coronary driving pressure and diminishes subendocardial perfusion. It is particularly important in determining flow when coronary pressure is reduced by a stenosis, as well as in the failing heart.

Endothelium-Dependent Modulation of Coronary Tone

Epicardial conduit arteries do not contribute significantly to coronary vascular resistance, yet arterial diameter is modulated by a wide variety of paracrine factors that can be released from platelets, as well as by circulating neurohormonal agonists, neural tone, and local control through vascular shear stress.[1] **Fig. 57.7 and eTable 57.1** summarize the most common factors related to cardiovascular disease. The net effect of many of these agonists is critically dependent on whether a functional endothelium is present. Furchgott and Zawadzki (see Classic References) originally demonstrated that acetylcholine normally dilates arteries through an endothelium-dependent relaxing factor that was later identified to be nitric oxide (NO). This binds to guanylyl cyclase and increases cyclic guanosine monophosphate (cGMP), resulting in vascular smooth muscle relaxation. When the endothelium is removed, the dilation to acetylcholine is converted to vasoconstriction, reflecting the effect of muscarinic vascular smooth muscle contraction. Subsequent studies have demonstrated that coronary resistance arteries also exhibit endothelial modulation of diameter, and that the response to physical forces such as shear stress, as well as paracrine mediators, vary with resistance vessel size.[3,4] The major endothelium-dependent biochemical pathways involved in regulating coronary epicardial and resistance artery diameter are discussed next.

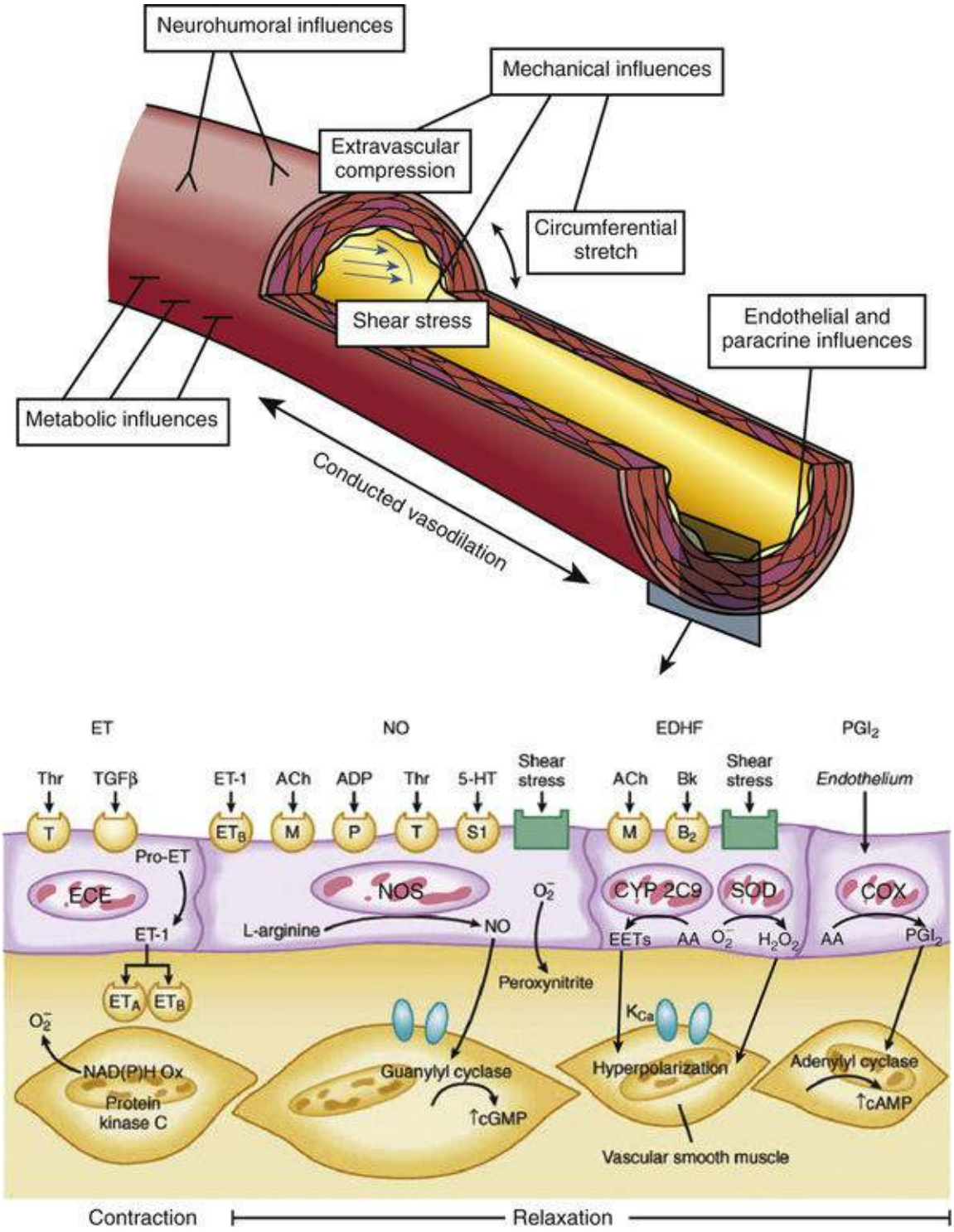


FIGURE 57.7 Endothelium-dependent control of vascular tone. In the normal coronary circulation, endothelium-dependent vasodilation occurs after increases in luminal flow or shear stress, as well as in response to agonists (e.g., released from platelets or cardiac nerves) that bind to receptors on the endothelial surface. These stimulate the production of nitric oxide (*NO*) and endothelium-dependent hyperpolarizing factor (*EDHF*), including epoxyeicosatrienoic acid products (*EETs*) and hydrogen peroxide (H_2O_2) released from mitochondria, which diffuse into vascular smooth muscle and cause relaxation. Prostacyclin, or prostaglandin I_2 (PGI_2), is produced in the coronary endothelium of collateral vessels and causes tonic vasodilation. The endothelium also produces endothelin (*ET*), which activates protein kinase C in vascular smooth muscle to produce coronary constriction and competes with endothelium-derived relaxing factors. Impaired endothelium-dependent vasodilation can result from the lack of production of relaxing factors (e.g., disrupted endothelium) or by inactivation of NO in disease states associated with oxidative stress and superoxide anion production (e.g., NO and O_2^- combining to produce peroxynitrite). In these circumstances, the effect of autacoids on vascular tone can be converted to vasoconstriction because of their direct effects on vascular smooth muscle (*not shown*). *AA,* Arachidonic acid; Ach, acetylcholine; *Bk,* bradykinin; *5-HT,* 5-hydroxytryptamine [serotonin]; K_{Ca}, calcium-activated potassium channel; *TGFβ,* transforming growth factor beta$_1$; *Thr,* thrombin. (Modified from Laughlin MH, Davis M, Secher NH,

ETABLE 57.1

Endothelium-Dependent and Net Direct Effects of Neural Stimulation, Autacoids, and Vasodilators on Coronary Tone in Isolated Conduit and Coronary Resistance Arteries

SUBSTANCE	ENDOTHELIUM DEPENDENT	NORMAL RESPONSE	ATHEROSCLEROSIS
Acetylcholine			
Conduit	Nitric oxide	Net dilation	Constriction
Resistance	Nitric oxide, EDHF	Dilation	Attenuated dilation
Norepinephrine			
Conduit			
$Alpha_1$	—	Constriction	Constriction
$Beta_1$ and $Beta_2$	Nitric oxide	Dilation	Attenuated dilation
Resistance			
$Alpha_1$	—	Constriction	Constriction
$Alpha_2$	Nitric oxide	No effect	Constriction
$Beta_2$		Dilation	Dilation
Platelets			
Thrombin	Nitric oxide	Dilation	Constriction
Serotonin			
Conduit	Nitric oxide	Constriction	Constriction
Resistance	Nitric oxide	Dilation	Constriction
Adenosine Diphosphate (ADP)			
	Nitric oxide	Dilation	Attenuated dilation
Thromboxane			
	Endothelin	Constriction	Constriction
Paracrine Agonists			
Bradykinin	Nitric oxide, EDHF	Dilation	Attenuated dilation
Histamine	Nitric oxide	Dilation	Attenuated dilation
Substance P	Nitric oxide	Dilation	Attenuated dilation
Endothelin (ET)			
ET-1	Nitric oxide	Net constriction	Increased constriction

EDHF, Endothelium-dependent hyperpolarizing factor.

Nitric Oxide (Endothelium-Derived Relaxing Factor)

Nitric oxide is produced in endothelial cells by the enzymatic conversion of L-arginine to citrulline via type III nitric oxide synthase (NOS). Endothelial NO diffuses abluminally into vascular smooth muscle, where it binds to guanylyl cyclase, increasing cGMP production and causing relaxation through a reduction in intracellular calcium. NO-mediated vasodilation is enhanced by cyclic or pulsatile changes in coronary shear stress. Chronic upregulation of NOS occurs in response to episodic increases in coronary flow, such as during exercise training, which also potentiates the relaxation to various endothelium-dependent vasodilators. NO-mediated vasodilation is impaired in many disease states and in patients with one or more risk factors for coronary artery disease (CAD). This occurs via inactivation of NO by superoxide anion generated in response to oxidative stress. Such inactivation is the hallmark of impaired NO-mediated vasodilation in atherosclerosis, hypertension, and diabetes.

Endothelium-Dependent Hyperpolarizing Factor

Endothelium-dependent hyperpolarization is an additional endothelium-dependent mechanism for selected agonists (e.g., bradykinin), as well as shear stress–induced vasodilation, in the human coronary microcirculation. Endothelium-dependent hyperpolarizing factor (EDHF), produced by the endothelium, hyperpolarizes vascular smooth muscle and dilates arteries by opening calcium-activated potassium channels (K_{Ca}). The exact biochemical species of EDHF is still unclear, but prominent candidates are

endothelium-derived hydrogen peroxide[4] and epoxyeicosatrienoic acid, a metabolite of arachidonic acid metabolism produced by the cytochrome P-450 epoxygenase pathway.[4,5]

Prostacyclin

Metabolism of arachidonic acid via cyclooxygenase (COX) also can produce prostacyclin, which is a coronary vasodilator when administered exogenously. Although some evidence indicates that prostacyclin contributes to tonic coronary vasodilation, COX inhibitors fail to alter flow during ischemia distal to an acute stenosis or limit oxygen consumption in response to increases in metabolism. This suggests that it is overcome by other compensatory vasodilator pathways.[1,2] In contrast with the coronary resistance vasculature, vasodilator prostaglandins are very important determinants of coronary collateral vessel resistance, and inhibiting COX reduces collateral perfusion in dogs.[6]

Endothelin

The endothelins—ET-1, ET-2, and ET-3—are peptide endothelium-dependent constricting factors. ET-1 is a potent constrictor derived from the enzymatic cleavage of a larger precursor molecule (pre-pro–endothelin) via endothelin-converting enzyme. In contrast with the rapid vascular smooth muscle relaxation and recovery characteristic of endothelium-derived vasodilators (NO, EDHF, and prostacyclin), the constriction to endothelin is prolonged. Changes in endothelin levels are largely mediated through transcriptional control and produce longer-term changes in coronary vasomotor tone. The effects of endothelin are mediated by binding to both ET_A and ET_B receptors. ET_A-mediated constriction is caused by the activation of protein kinase C in vascular smooth muscle. ET_B-mediated constriction is less pronounced and counterbalanced by ET_B-mediated endothelium-dependent NO production and vasodilation. Endothelin is only marginally involved in regulating coronary blood flow in the normal heart but can modulate vascular tone when interstitial and circulating concentrations increase in pathophysiologic states such as heart failure.

Neural Control of Coronary Conduit and Resistance Arteries.

Sympathetic and vagal nerves innervate coronary conduit arteries and segments of the resistance vasculature. Neural stimulation affects tone through mechanisms that alter vascular smooth muscle as well as by stimulating the release of NO from the endothelium. Diametrically opposite effects can occur in the presence of risk factors that impair endothelium-dependent vasodilation. Their actions in normal and pathophysiologic states are summarized in **eTable 57.1**.

Cholinergic Innervation.

Resistance arteries dilate to acetylcholine, resulting in increases in coronary flow. In conduit arteries, acetylcholine normally causes mild coronary vasodilation. This reflects the net action of a direct muscarinic constriction of vascular smooth muscle counterbalanced by an endothelium-dependent vasodilation caused by direct stimulation of NOS and an increased flow-mediated dilation from concomitant resistance vessel vasodilation. The response in humans with atherosclerosis or risk factors for CAD is distinctly different. The resistance vessel dilation to acetylcholine is attenuated and the reduction in flow-mediated NO production leads to net epicardial conduit artery vasoconstriction, which is particularly prominent in stenotic segments (**Fig. 57.8A**).

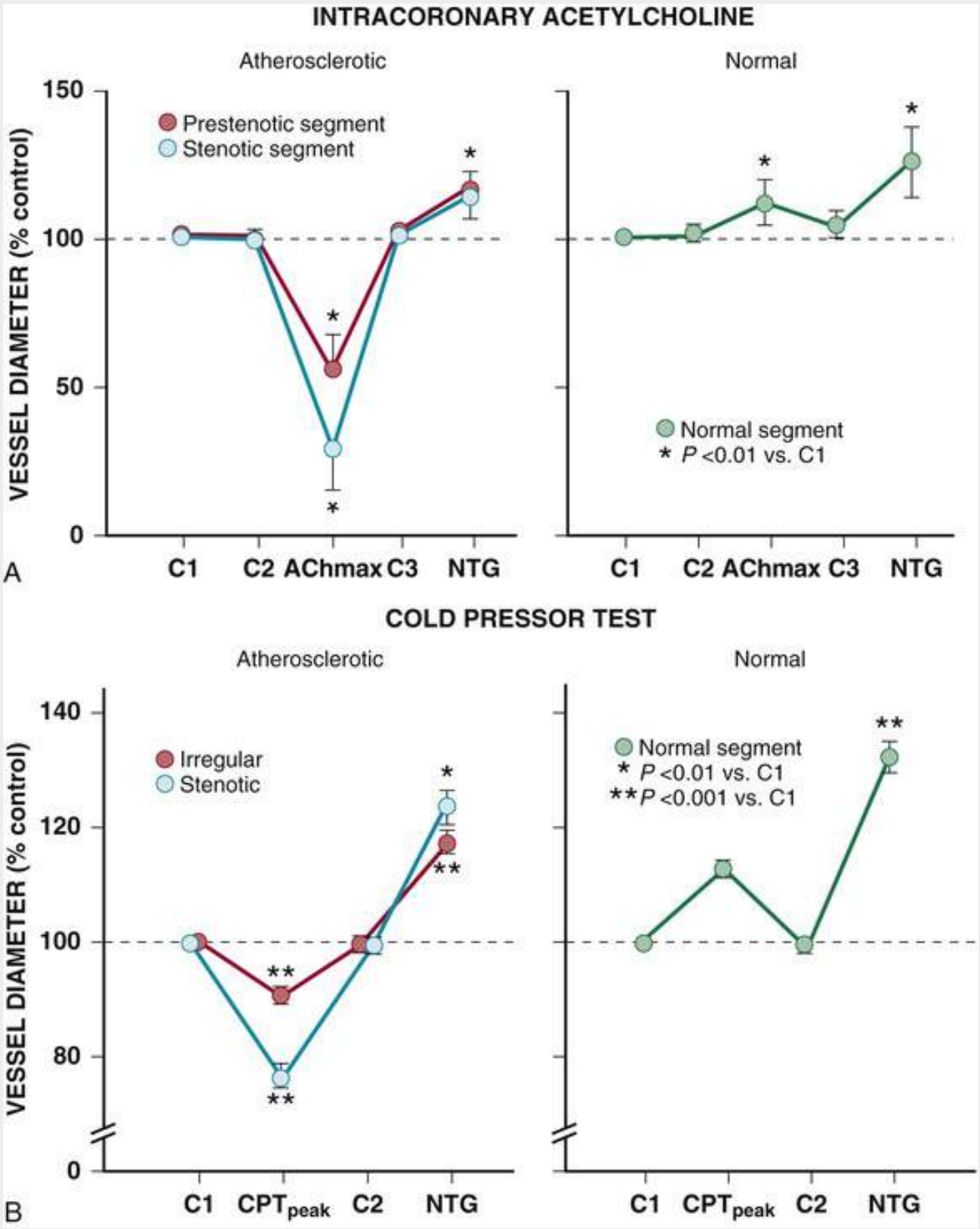


FIGURE 57.8 Differential conduit artery diameter responses in normal and atherosclerotic epicardial arteries. **A,** Acetylcholine. In normal arteries, acetylcholine elicits vasodilation, but there is vasoconstriction in the atherosclerotic artery, which is particularly pronounced in the stenosis. **B,** Cold pressor testing. Activation of sympathetic tone normally leads to net epicardial dilation, but vasoconstriction in irregular and stenotic coronary segments occurs in patients with atherosclerosis. Ach, Acetylcholine; C, control; CPT, cold pressor test [response]; NTG, nitroglycerin. (**A,** Modified from Ludmer PL et al. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. N Engl J Med 1986;315:1046; **B,** modified from Nabel EG et al. Dilation of normal and constriction of atherosclerotic coronary arteries caused by the cold pressor test. Circulation 1988;77:43.)

Sympathetic Innervation.

Under basal conditions, there is no resting sympathetic tone in the heart and thus no effect of denervation

on resting perfusion. During sympathetic activation, coronary tone is modulated by norepinephrine released from myocardial sympathetic nerves, as well as by circulating norepinephrine and epinephrine.[1,2] In conduit arteries, sympathetic stimulation leads to $alpha_1$ constriction as well as beta-mediated vasodilation. The net effect is to dilate epicardial coronary arteries. This dilation is potentiated by concomitant flow-mediated vasodilation from metabolic vasodilation of coronary resistance vessels. When NO-mediated vasodilation is impaired, $alpha_1$ constriction predominates and can dynamically increase stenosis severity in asymmetric lesions where the stenosis is compliant. This is one of the mechanisms by which ischemia can be provoked during cold pressor testing (**Fig. 57.8B**).

The effects of sympathetic activation on myocardial perfusion and coronary resistance vessel tone are complex and depend on the net actions of $beta_1$-mediated increases in myocardial oxygen consumption (resulting from increases in the determinants of myocardial oxygen consumption), direct $beta_2$-mediated coronary vasodilation, and $alpha_1$-mediated coronary constriction. Under normal conditions, exercise-induced $beta_2$-adrenergic "feed-forward" dilation predominates, resulting in a higher flow relative to the level of myocardial oxygen consumption.[6] This neural control mechanism produces transient vasodilation before the buildup of local metabolites during exercise and prevents the development of subendocardial ischemia during abrupt changes in demand. After nonselective beta blockade, sympathetic activation unmasks $alpha_1$-mediated coronary artery constriction. Although flow is mildly decreased, oxygen delivery is maintained by increased oxygen extraction and a reduction in coronary venous P_{O_2} at similar levels of cardiac workload. Intense $alpha_1$-adrenergic constriction can overcome intrinsic stimuli for metabolic vasodilation to result in ischemia in the presence of pharmacologic vasodilator reserve.[6] The role of pre- and postsynaptic $alpha_2$ responses is controversial. They appear to have a less significant role in controlling flow. This partly reflects the competing effects of presynaptic $alpha_2$ receptor stimulation, leading to reduced vasoconstriction by inhibiting norepinephrine release.

Paracrine Vasoactive Mediators and Coronary Vasospasm

Many paracrine factors can affect coronary tone in normal and pathophysiologic states that are unrelated to normal coronary circulatory control. The most important of these are summarized in **Fig. 57.7 and eTable 57.1**. Paracrine factors are released from epicardial artery thrombi after activation of the thrombotic cascade initiated by plaque rupture. They can modulate epicardial tone in regions near eccentric ulcerated plaques still responsive to stimuli that alter smooth muscle relaxation and constriction, leading to dynamic changes in the physiologic significance of a stenosis. Paracrine mediators also can have differential effects on downstream vessel vasomotion that depend on vessel size (conduit arteries versus resistance arteries) as well as on the presence of a functionally normal endothelium, because many also stimulate the release of NO and EDHF.

Serotonin released from activated platelets causes vasoconstriction in normal and atherosclerotic conduit arteries and can increase the functional severity of a dynamic coronary stenosis through superimposed vasospasm. By contrast, it dilates coronary arterioles and increases coronary flow through the endothelium-dependent release of NO. In atherosclerosis or circumstances in which NO production is impaired, the direct effects on smooth muscle predominate, and the response of the microcirculation is converted to vasoconstriction. As a result, serotonin release generally exacerbates ischemia in CAD.

Thromboxane A_2 is a potent vasoconstrictor that is a product of endoperoxide metabolism and is released during platelet aggregation. It produces vasoconstriction of conduit arteries as well as isolated

coronary resistance vessels and can accentuate acute myocardial ischemia.

Adenosine diphosphate (ADP) is another platelet-derived vasodilator that relaxes coronary microvessels as well as conduit arteries. It is mediated by NO and abolished by removing the endothelium.

Thrombin normally leads to vasodilation in vitro that is endothelium dependent and mediated by the release of prostacyclin as well as NO. In vivo, thrombin also releases thromboxane A_2, leading to vasoconstriction in epicardial stenoses in which endothelium-dependent vasodilation is impaired. In the coronary resistance vasculature, thrombin acts as an endothelium-dependent vasodilator and increases coronary flow.

Coronary Vasospasm

Coronary spasm results in transient functional occlusion of a coronary artery that is reversible with nitrate vasodilation. It most frequently occurs in the setting of a coronary stenosis, leading to dynamic stenosis behavior that can dissociate the effects on perfusion from anatomic stenosis severity (**see Chapter 20**). In CAD, endothelial disruption probably plays a role in focal vasospasm; the normal vasodilation from autacoids and sympathetic stimulation is converted into a vasoconstrictor response because of the lack of competing endothelium-dependent vasodilation. Nevertheless, although impaired endothelium-dependent vasodilation is a permissive factor for vasospasm, it is not causal, and a trigger is required (e.g., thrombus formation, sympathetic activation).

The mechanisms responsible for variant angina with normal coronary arteries, or Prinzmetal angina, are less clear. Data from animal models have pointed to sensitization of intrinsic vasoconstrictor mechanisms (see Classic References, Konidala and Gutterman). Coronary arteries demonstrate supersensitivity to vasoconstrictor agonists in vivo and in vitro as well as reduced vasodilator responses. Some studies have demonstrated that Rho, a guanosine triphosphate (GTP)–binding protein, can sensitize vascular smooth muscle to calcium by inhibiting myosin phosphatase activity through the effector protein Rho kinase.

Pharmacologic Vasodilation.

The effects of pharmacologic vasodilators on coronary flow reflect direct actions on vascular smooth muscle as well as secondary adjustments in resistance artery tone. Flow-mediated dilation can amplify the vasodilator response, whereas autoregulatory adjustments can overcome vasodilation in a segment of the microcirculation and restore flow to normal. The potent resistance vessel vasodilators are specifically used in assessing coronary stenosis severity.[7]

Nitroglycerin.

Nitroglycerin dilates epicardial conduit arteries and small coronary resistance arteries but does not increase coronary blood flow in the normal heart (see Classic References, Duncker and Bache). The latter observation reflects the fact that transient arteriolar vasodilation is overcome by autoregulatory escape, which returns coronary resistance to control levels.[3,4] Although nitroglycerin does not increase coronary blood flow in the normal heart, it can produce vasodilation of larger coronary resistance arteries that improves the distribution of perfusion to the subendocardium when flow-mediated NO-dependent vasodilation is impaired.[6] It also can improve subendocardial perfusion by reducing LV end-diastolic pressure through systemic venodilation in heart failure. Similarly, coronary collateral vessels dilate in response to nitroglycerin, and the reduction in collateral resistance can improve regional

perfusion in some settings.[6]

Calcium Channel Blockers.

All calcium channel blockers induce vascular smooth muscle relaxation and are, to various degrees, pharmacologic coronary vasodilators. In epicardial arteries the vasodilator response is similar to nitroglycerin and is effective in preventing coronary vasospasm superimposed on a coronary stenosis, as well as in normal arteries of patients with variant angina. Calcium channel blockers also submaximally vasodilate coronary resistance vessels. In this regard, dihydropyridine derivatives such as nifedipine are particularly potent and can sometimes precipitate subendocardial ischemia in the presence of a critical stenosis. This arises from a transmural redistribution of blood flow (coronary steal) as well as the tachycardia and hypotension that transiently occur with short half-life formulations of nifedipine.

Adenosine and A_2 Receptor Agonists.

Adenosine dilates coronary arteries through activation of A_2 receptors on vascular smooth muscle and is independent of the endothelium in coronary arterioles isolated from humans with heart disease.[8] Experimentally, a differential sensitivity of the microcirculation to adenosine is observed, with the direct effects related to resistance vessel size and restricted primarily to vessels smaller than 100 μm.[3,4] Larger upstream resistance arteries dilate through a NO-dependent mechanism from the increase in shear stress. Thus, in states where endothelium-dependent vasodilation is impaired, maximal coronary flow responses to intravenous or intracoronary adenosine may be reduced in the absence of a stenosis[4] and can be increased by interventions that improve NO-mediated vasodilation, such as lowering low-density lipoprotein (LDL) levels. Single-dose adenosine A_2 receptor agonists (e.g., regadenoson) are now more often employed in pharmacologic stress testing and are as effective as adenosine. These agents circumvent the need for continuous infusions during myocardial perfusion imaging[7] (**see Chapter 16**).

Dipyridamole.

Dipyridamole produces vasodilation by inhibiting the myocyte reuptake of adenosine released from cardiac myocytes. It therefore has actions and mechanisms similar to those of adenosine, with the exception that the vasodilation is more prolonged. It can be reversed with the administration of the nonspecific adenosine receptor blocker aminophylline.

Papaverine.

Papaverine is a short-acting coronary vasodilator that was the first agent used for intracoronary vasodilation. It causes vascular smooth muscle relaxation by inhibiting phosphodiesterase and increasing cyclic adenosine monophosphate (cAMP). After bolus injection, it has a rapid onset of action, but the vasodilation is more prolonged than after adenosine (approximately 2 minutes). Its actions are independent of the endothelium.

Structure and Function of the Coronary Microcirculation

The schematics in **Figs. 57.4 and 57.5** suggest a fairly localized site for the control of coronary vascular resistance that is useful for conceptualizing the major determinants of coronary vascular resistance. In fact, individual coronary resistance arteries are a longitudinally distributed network, and in vivo studies of the coronary microcirculation have demonstrated considerable spatial heterogeneity of specific resistance vessel control mechanisms[3,4,6] (**Fig. 57.9**). Each resistance vessel needs to dilate in an orchestrated fashion to meet the needs of the downstream vascular bed, which is frequently removed from the site of metabolic control of coronary resistance. This can be accomplished independently of metabolic signals by sensing physical forces such as intraluminal flow (shear stress–mediated control) or

intraluminal pressure changes (myogenic control). Epicardial arteries (>400 µm in diameter) serve a conduit artery function, with diameter primarily regulated by shear stress, and contribute minimal pressure drop (<5%) over a wide range of coronary flow. Coronary arterial resistance vessels can be divided into small arteries (100 to 400 µm), which regulate their tone in response to local shear stress and luminal pressure changes (myogenic response), and arterioles (<100 µm), which are sensitive to changes in local tissue metabolism and directly control perfusion of the low-resistance coronary capillary bed[3,4] (**Fig. 57.10 and eFig. 57.1**). Capillary density of the myocardium averages 3500/mm^2 (resulting in average intercapillary distance of 17 µm), which is greater in the subendocardium than in the subepicardium.

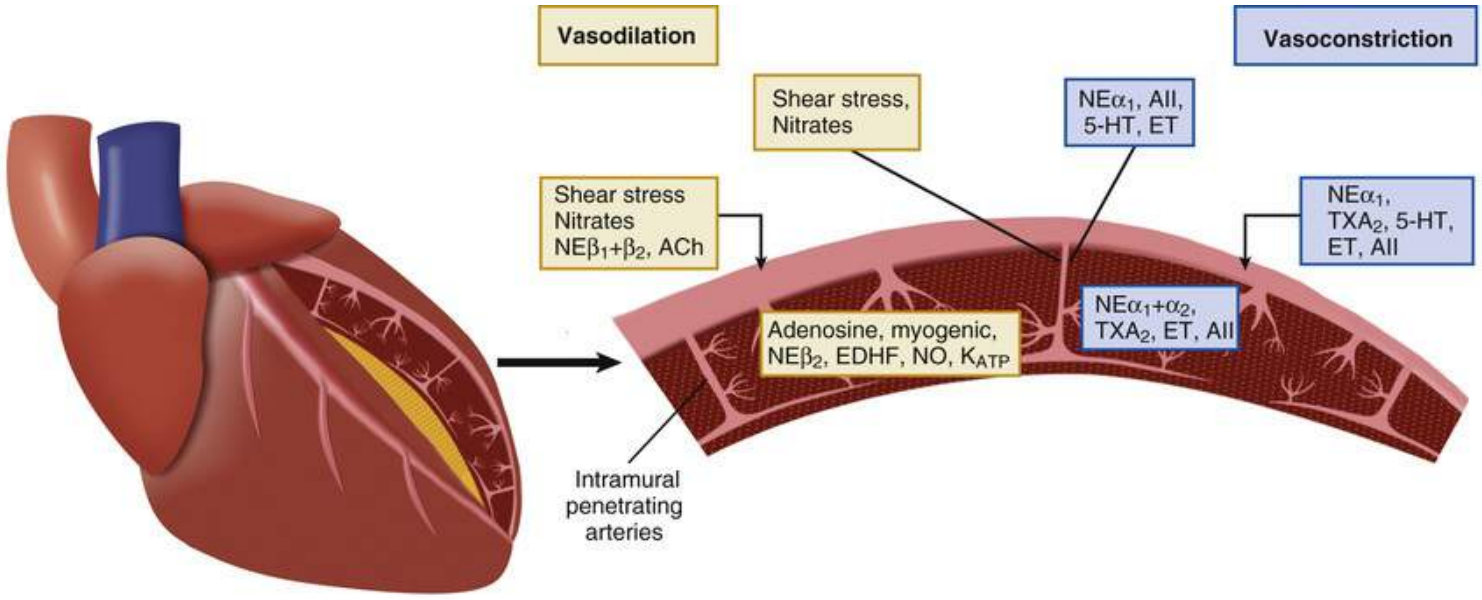


FIGURE 57.9 Transmural distribution of coronary resistance vessels—major vasodilator and vasoconstrictor mechanisms in epicardial conduit arteries and different sites of the microcirculation. The epicardial conduit arteries arborize into subepicardial and subendocardial resistance arteries. Intramural penetrating resistance arteries are unique in that they are removed from subendocardial metabolic stimuli and theoretically are more dependent on regulating their tone in response to shear stress and luminal pressure as mechanisms to produce dilation in response to changes in metabolism of the distal subendocardial arteriolar plexus. See text for further discussion. AII, Angiotensin II; Ach, acetylcholine; EDHF, endothelium-dependent hyperpolarizing factor; ET, endothelin; 5-HT, 5-hydroxytryptamine [serotonin]; K_{ATP}, ATP-dependent potassium channel; $NE\beta_1$, norepinephrine beta$_1$-adrenergic; $NE\alpha_1$, norepinephrine alpha$_1$-adrenergic; TXA_2, thromboxane A_2. (Modified from Duncker DJ, Bache RJ. Regulation of coronary vasomotor tone under normal conditions and during acute myocardial hypoperfusion. Pharmacol Ther 2000;86:87.)

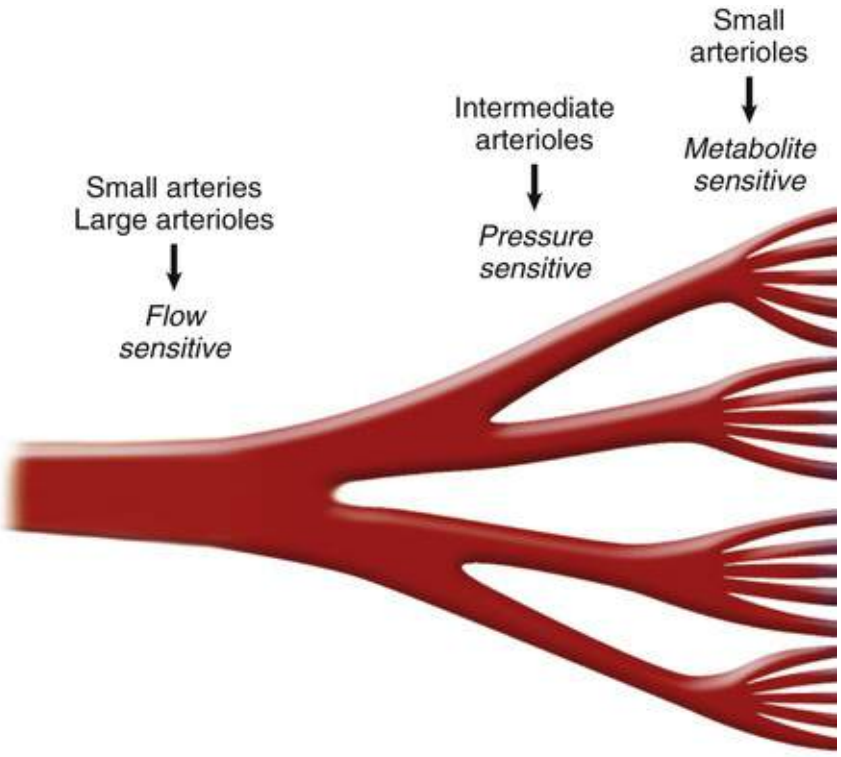
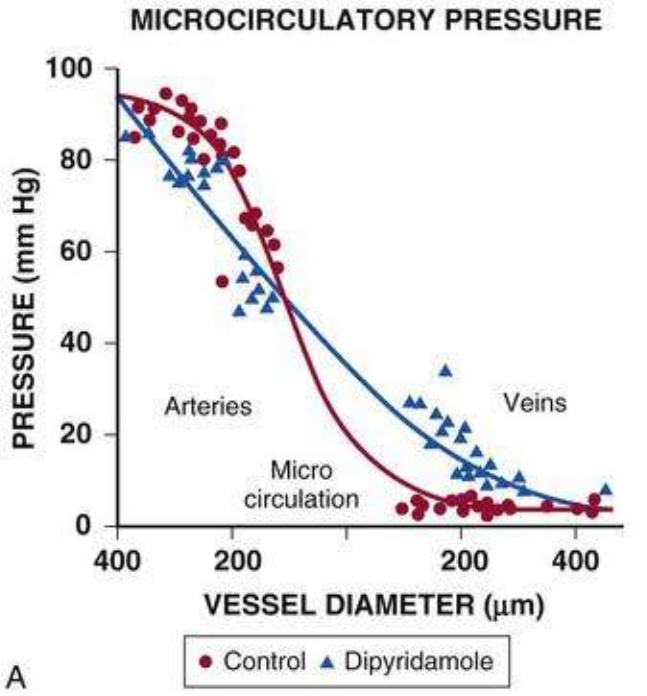
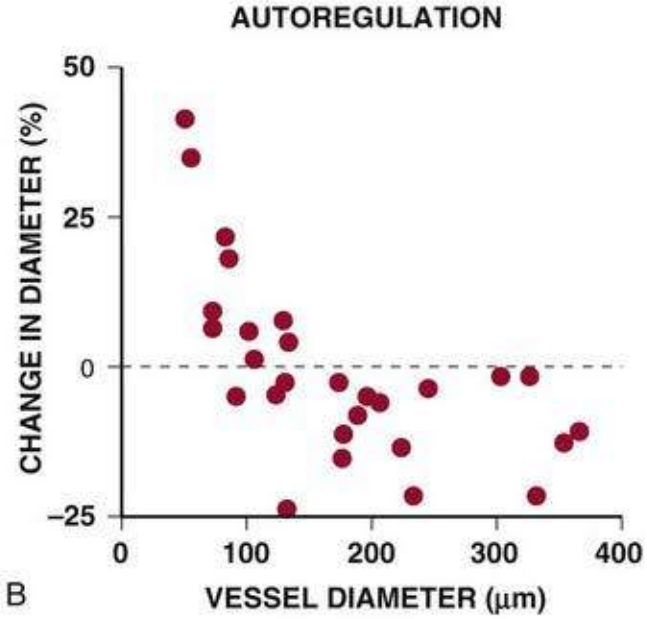
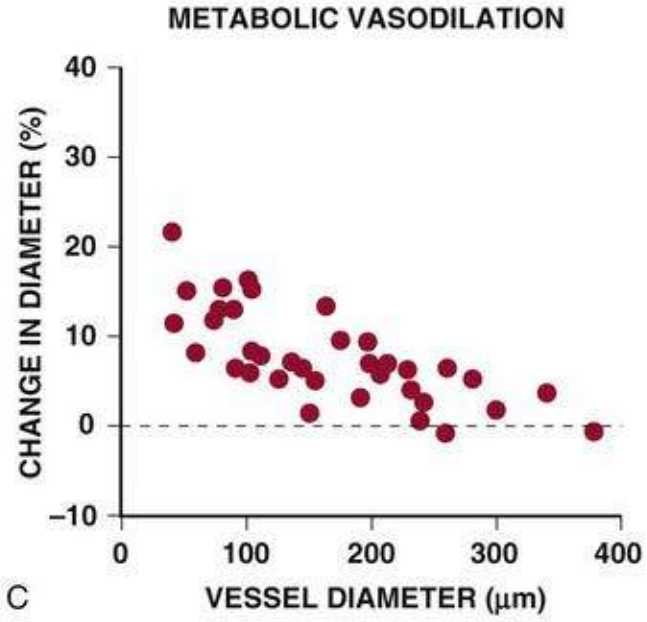


FIGURE 57.10 Integrative regulation of coronary flow by ascending, metabolic, myogenic, and shear stress–induced mechanisms in response to metabolic activation. Small distal arterioles immediately before the capillaries are sensitive to tissue metabolites. Upstream intermediate arterioles are pressure sensitive, with myogenic mechanisms predominating. Small resistance arteries are removed from the metabolic milieu and primarily adjust local tone in response to shear stress and flow. Capillary and venular resistances are small and primarily considered to be fixed. (Modified from Davis MJ, Hill MA, Kuo L. Local regulation of microvascular perfusion. In Tuma RF, Duran WN, Ley K, editors. Handbook of Physiology: Microcirculation. San Diego: Academic Press; 2008, p 161.)







EFIGURE 57.1 Microcirculatory pressure profile and local resistance changes to physiologic stimuli in subepicardial microvessels. **A,** Under resting conditions, most of the pressure drop to flow arises from small arteries and arterioles. After dipyridamole vasodilation, a redistribution of microcirculatory resistance

is seen, with a greater pressure drop occurring across small arteries and postcapillary venules that do not alter their resistance. **B,** Heterogeneous arterial microvessel response during autoregulation. A reduction in pressure to 38 mm Hg elicited dilation in arterioles smaller than 100 µm, whereas larger arteries tended to constrict passively from the reduction in distending pressure. **C,** Homogeneous vasodilation of resistance arteries during increases in myocardial oxygen consumption. Dilation occurs in all microvascular resistance arteries, being greatest in vessels smaller than 100 µm. (**A,** Modified from Chilian WM et al. Redistribution of coronary microvascular resistance produced by dipyridamole. Am J Physiol 1989;256:H383; **B,** modified from Kanatsuka H et al. Heterogeneous changes in epimyocardial microvascular size during graded coronary stenosis: evidence of the microvascular site for autoregulation. Circ Res 1990;66:389; **C,** modified from Kanatsuka H et al. Comparison of the effects of increased myocardial oxygen consumption and adenosine on the coronary microvascular resistance. Circ Res 1989;65:1296.)

Under resting conditions, most of the pressure drop in the microcirculation arises in resistance arteries between 50 and 200 µm, with minimal pressure drop occurring across capillaries and venules at normal flow levels[4] (**eFig. 57.1A**). After pharmacologic vasodilation with dipyridamole, resistance artery vasodilation attenuates the precapillary pressure drop in arterial resistance vessels. At the same time, there is an increased pressure drop and redistribution of resistance to venular vessels, in which smooth muscle relaxation is limited and the already low resistance is fairly fixed.

Considerable heterogeneity in microcirculatory vasodilation is evident during physiologic adjustments in flow. For example, as pressure is reduced during autoregulation, dilation is accomplished primarily by arterioles smaller than 100 µm, whereas larger resistance arteries tend to constrict because of the reduction in perfusion pressure[3] (**eFig. 57.1B**). By contrast, metabolic vasodilation results from a more uniform vasodilation of resistance vessels of all sizes[4] (**eFig. 57.1C**). Similar inhomogeneity in resistance vessel dilation occurs in response to endothelium-dependent agonists as well as pharmacologic vasodilators.

A unique component of subendocardial coronary resistance vessels is the transmural penetrating arteries that course from the epicardium to the subendocardial plexus (see Classic References, Duncker and Bache). These vessels not only are less sensitive to metabolic signals but are also removed from the metabolic stimuli that develop when ischemia is confined to the subendocardium. As a result, local control by altered shear stress and myogenic relaxation to local pressure become critical determinants of diameter in this “upstream” resistance segment. Even during maximal vasodilation, this segment creates an additional longitudinal component of coronary vascular resistance that must be traversed before the arteriolar microcirculation is reached. Because of this greater longitudinal pressure drop, the microcirculatory pressures in subendocardial coronary arterioles are lower than in the subepicardial arterioles.[4]

Intraluminal Physical Forces Regulating Coronary Resistance

Because much of the coronary resistance vasculature can be upstream from the effects of metabolic mediators of control, local vascular control mechanisms are critically important in orchestrating adequate regional tissue perfusion to the distal microcirculation. The differential expression of mechanisms that is evident among different sizes and classes of coronary resistance vessels coincides with their function.

Myogenic Regulation

The *myogenic response* refers to the ability of vascular smooth muscle to oppose changes in coronary arterial diameter.[3] Thus, vessels relax when distending pressure is decreased and constrict when distending pressure is elevated (**Fig. 57.11A**). Myogenic tone is a property of vascular smooth muscle and occurs across a large size range of coronary resistance arteries in animals as well as in humans. Although

the cellular mechanism is uncertain, it depends on vascular smooth muscle calcium entry, perhaps through stretch-activated L-type Ca^{2+} channels, eliciting cross-bridge activation. The resistance changes arising from the myogenic response tend to bring local coronary flow back to the original level. Myogenic regulation has been postulated as an important mechanism of the coronary autoregulatory response and in vivo appears to occur primarily in arterioles smaller than 100 µm (e.g., during autoregulation) (**eFig. 57.1B**).

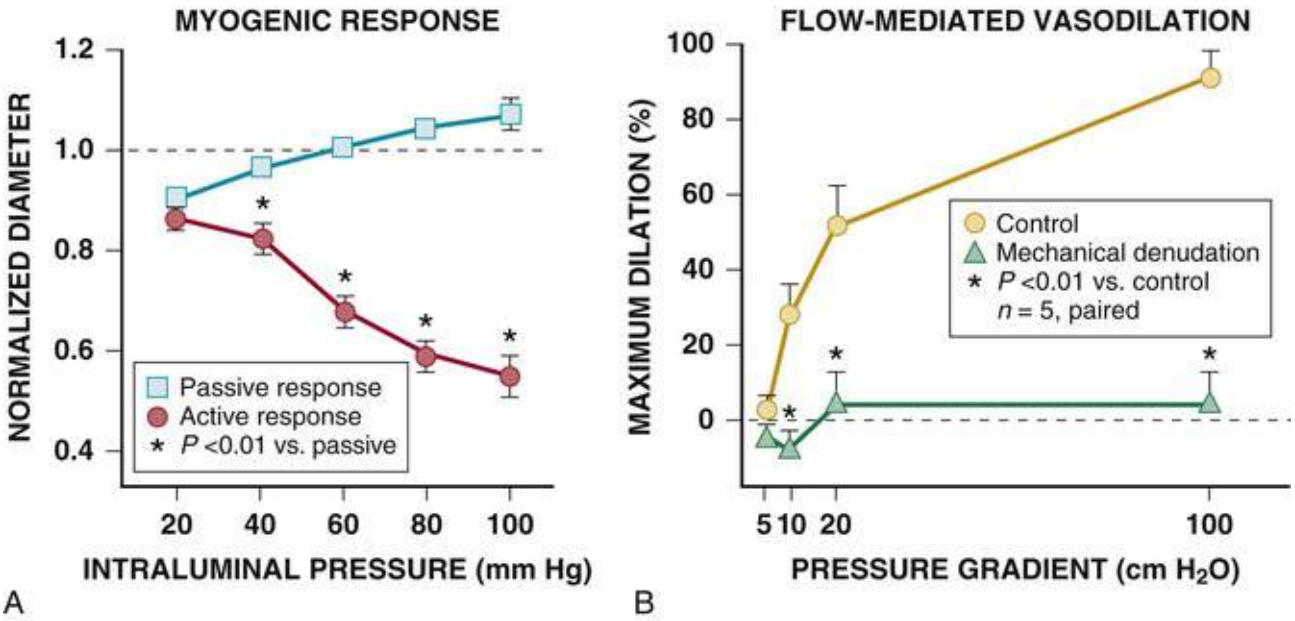


FIGURE 57.11 Effects of physical forces on coronary diameter in isolated human coronary resistance arteries (nominal diameter, 100 µm). **A,** As distending pressure is reduced from 100 mm Hg, progressive vasodilation occurs, consistent with myogenic regulation. Myogenic dilation reaches the maximum passive diameter of the vessel at 20 mm Hg. **B,** Flow-mediated vasodilation in cannulated human resistance arteries. As the pressure gradient across the isolated vessel is increased, intraluminal flow rises, causing progressive dilation that is abolished by removing the endothelium. Similar flow-mediated dilation occurs in most arterial vessels, including the coronary conduit arteries. (**A,** Modified from Miller FJ, Dellsperger KC, Gutterman DD. Myogenic constriction of human coronary arterioles. Am J Physiol 1997;273:H257; **B,** modified from Miura H et al. Flow-induced dilation of human coronary arterioles: important role of Ca^{2+}-activated K^+ channels. Circulation 2001;103:1992.)

Flow-Mediated Resistance Artery Control

Coronary small arteries and arterioles also regulate their diameter in response to changes in local shear stress (**Fig. 57.11B**). Flow-induced dilation in isolated coronary arterioles is endothelium dependent and mediated by NO, because it could be abolished with an L-arginine analogue. By contrast, isolated atrial vessels from patients undergoing cardiac surgery exhibit flow-mediated vasodilation by EDHF. The disparity with animal studies may reflect age or species variability in the relative importance of EDHF versus NO in the coronary circulation. The mechanisms also appear to vary as a function of vessel size, with studies in pigs demonstrating that hyperpolarization regulates epicardial conduit arteries,[8] and NO predominates in the resistance vasculature. Also, EDHF may represent a compensatory pathway that normally is inhibited by NO and becomes upregulated in acquired disease states in which NO-mediated vasodilation is impaired.[8] More recent studies have demonstrated that this factor appears to be hydrogen peroxide.[5,8] Despite the variability in isolated vessels, blocking NOS with an L-arginine analogue in the coronary circulation of humans reduces vasodilation to pharmacologic endothelium-dependent agonists

and attenuates flow increases during metabolic vasodilation. This demonstrates that NO-mediated vasodilation plays a role in determining physiologic vascular tone in some segments of the coronary resistance vasculature.

Metabolic Mediators of Coronary Resistance Vessel Control.

Although increasing knowledge has emerged regarding the distribution of coronary microvascular resistance, there is still no consensus regarding specific mediators of metabolic vasodilation.[1,9] Coronary resistance in any segment of the microcirculation represents the integration of local physical factors (e.g., pressure, flow), vasodilator metabolites (e.g., adenosine, P_{O_2}, pH), autacoids, and neural modulation. Each of these mechanisms contributes to net coronary vascular smooth muscle tone, which may ultimately be controlled by opening and closing vascular smooth muscle adenosine triphosphate (ATP)–sensitive K^+ (K_{ATP}) channels. There is considerable redundancy in the available local control mechanisms.[1,2] Because of this, blocking single mechanisms fails to alter coronary autoregulation or metabolic flow regulation at normal coronary pressures. This redundancy can, however, be unmasked by stressing the heart and evaluating flow regulation at reduced pressures distal to a coronary stenosis at rest or during exercise. Some of the candidates proposed and their role in metabolic resistance control and ischemia-induced vasodilation are summarized here (see Classic References, Feigl and Duncker and Bache).

Adenosine.

There has been a longstanding interest in the role of adenosine as a metabolic mediator of resistance artery control. It is released from cardiac myocytes when the rate of ATP hydrolysis exceeds its synthesis during ischemia. Its production and release also increase with myocardial metabolism. Adenosine has an extremely short half-life (<10 seconds) as a result of its rapid inactivation by adenosine deaminase. It binds to A_2 receptors on vascular smooth muscle, increases cAMP, and opens K_{ATP} and intermediate calcium-activated potassium channels.[6,8] Adenosine has a differential effect on coronary resistance arteries, primarily dilating vessels smaller than 100 μm.[4] Although adenosine has no direct effect on larger resistance arteries and conduit arteries, these dilate through endothelium-dependent vasodilation from the concomitant increases in local shear stress as arteriolar resistance falls.[3] Despite the attractiveness of adenosine as a local metabolic control mechanism, substantial in vivo experimental data now demonstrate convincingly that it is not required for adjusting coronary flow to increases in metabolism or autoregulation.[6] However, adenosine may contribute to vasodilation during hypoxia as well as during acute exercise-induced myocardial ischemia distal to a stenosis.[2]

ATP-Sensitive K^+ Channels.

Coronary vascular smooth muscle K_{ATP} channels are tonically active, contributing to coronary vascular tone under resting conditions. Preventing K_{ATP} channel opening with glibenclamide causes constriction of arterioles smaller than 100 μm, reduces coronary flow, and accentuates myocardial ischemia distal to a coronary stenosis by overcoming intrinsic vasodilator mechanisms.[2] The K_{ATP} channels can modulate both coronary metabolic and autoregulatory responses. It is a potentially attractive mechanism, because many of the other candidates for metabolic flow regulation (e.g., adenosine, NO, $beta_2$-adrenoreceptors, prostacyclin) are ultimately affected by blocking this pathway. K_{ATP} channel opening is likely a common effector rather than sensor of metabolic activity or autoregulatory adjustments in flow. Also, reductions in coronary flow observed after blocking K_{ATP} channel vasodilation may be pharmacologic, caused by vasoconstriction of the microcirculation that overcomes intrinsic vasodilator stimuli, as seen when other

potent vasoconstrictors (e.g., endothelin, vasopressin) are administered at pharmacologic doses.

Oxygen Sensing.

Although a potent coronary vasodilator stimulus, the role of local P_{O_2} in the regulation of arteriolar tone remains unresolved. Coronary flow increases in proportion to reductions in arterial oxygen content (reduced P_{O_2} or anemia), and there is a twofold increase in perfused capillary density in response to hypoxia. The underlying mechanism may involve the release of NO and ATP (which stimulates vascular endothelial P2 receptors to produce NO) from red blood cells, when intravascular P_{O_2} levels drop.[1,2] Studies demonstrating a direct effect of oxygen on metabolic or autoregulatory adjustments are lacking, however, and the vasodilator response to reduced arterial oxygen delivery may simply reflect the close relation between myocardial metabolism and flow.

Acidosis.

Arterial hypercapnia and acidosis are potent stimuli shown to produce coronary vasodilation independent of hypoxia. Whereas their precise role in the local regulation of myocardial perfusion remains unclear,[1] it seems reasonable that some of the vasodilation occurring with increased myocardial metabolism could arise from increased myocardial carbon dioxide (CO_2) production and tissue acidosis in the setting of acute ischemia.

Right Coronary Artery Flow

Although the general concepts of coronary flow regulation developed for the left ventricle apply to the right ventricle, there are differences related to the extent of the right coronary artery supply to the right ventricular (RV) free wall. This has been studied in dogs, in which the right coronary artery (RCA) is a nondominant vessel.[6] In terms of coronary flow reserve, arterial pressure supplying the RCA substantially exceeds RV pressure, minimizing the compressive determinants of coronary reserve. RV oxygen consumption is lower than LV consumption, and coronary venous oxygen saturations are higher than in the left coronary circulation. Because there is considerable oxygen extraction reserve, coronary flow decreases as pressure is reduced and oxygen delivery is maintained by increased extraction. These differences appear specific to the RV free wall. In humans, in whom the RCA is dominant and supplies much of the inferior left ventricle, factors affecting flow regulation to the LV myocardium are likely to predominate.

Physiologic Assessment of Coronary Artery Stenoses

The physiologic assessment of stenosis severity is a critical component of the management of patients with obstructive epicardial CAD[10] (**see Chapter 61**). Epicardial artery stenoses arising from atherosclerosis increase coronary resistance and reduce maximal myocardial perfusion. Abnormalities in coronary microcirculatory control also can contribute to causing myocardial ischemia in many patients. Separating the role of a stenosis from coronary resistance vessels can be accomplished by simultaneously assessing coronary flow and distal coronary pressure using intracoronary transducers currently available for clinical care[11,12] (**see Chapter 62**).

Stenosis Pressure-Flow Relation

The angiographically visible epicardial coronary arteries are normally able to accommodate large increases in coronary flow without producing any significant pressure drop and thus serve a conduit function to the coronary resistance vasculature. This changes dramatically in CAD, in which the epicardial artery resistance becomes dominant. This fixed component of resistance increases with stenosis severity and limits maximal myocardial perfusion.

As a starting point, it is helpful to consider the idealized relation among stenosis severity, pressure drop, and flow, as validated in animals as well as in humans studied under circumstances where diffuse atherosclerosis and risk factors that can impair microcirculatory resistance vessel control are minimized. **Fig. 57.12** summarizes the major determinants of stenosis energy losses. The relation between pressure drop across a stenosis and coronary flow for stenoses between 30% and 90% diameter reduction can be described using the Bernoulli principle. The total pressure drop across a stenosis is governed by three hydrodynamic factors—viscous losses, separation losses, and turbulence—although the last usually is a relatively minor component of pressure loss. The most important determinant of stenosis resistance for any given level of flow is the minimum lesional cross-sectional area within the stenosis (see Classic References, Klocke, 1983). Because resistance is inversely proportional to the square of the cross-sectional area, small dynamic changes in luminal area caused by thrombi or vasomotion in asymmetric lesions (where vascular smooth muscle can relax or constrict in a portion of the stenosis) lead to major changes in the stenosis pressure-flow relation and reduce maximal perfusion during vasodilation. Separation losses determine the curvilinearity or "steepness" of the stenosis pressure-flow relation and become increasingly important as stenosis severity or flow rate increases. Stenosis length and changes in cross-sectional area distal to the stenosis are relatively minor determinants of resistance for most coronary lesions.

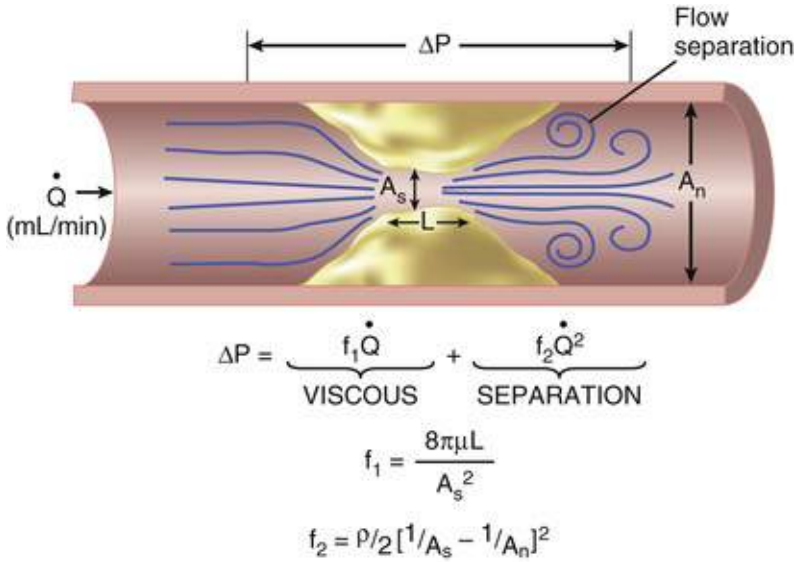


FIGURE 57.12 Fluid mechanics of a stenosis. The pressure drop across a stenosis can be predicted by the Bernoulli equation. It is inversely related to the minimum stenosis cross-sectional area and varies with the square of the flow rate as stenosis severity increases. A_n, Area of the normal segment; A_s, area of the stenosis; f_1, viscous coefficient; f_2, separation coefficient; L, stenosis length; μ, viscosity of blood; ρ, density of blood; ΔP, pressure drop; Q̇, flow.

Diffuse abluminal outward remodeling with thickening of the arterial wall is common in coronary atherosclerosis but does not alter the pressure-flow characteristics of the stenosis for a given intraluminal geometry. By contrast, diffuse inward remodeling effectively reduces minimal lesion area along the length

of the vessel and can lead to underestimation of stenosis severity using relative diameter or area measurements (**see Chapter 20**) and at the same time can contribute to a significant longitudinal pressure drop that also reduces maximum perfusion.[10]

Stenosis pressure drop and resistance increase exponentially as minimum lesional cross-sectional area decreases (**Fig. 57.13A, B**). This reflects that the pressure drop becomes flow dependent and varies with the square of the flow or flow velocity. As a result, the instantaneous stenosis resistance progressively increases during vasodilation. This becomes particularly important in determining the stenosis pressure-flow behavior for severely narrowed arteries, leading to a situation in which small reductions in luminal area result in large reductions in poststenotic coronary pressure that limit maximum coronary perfusion of the distal microcirculation.

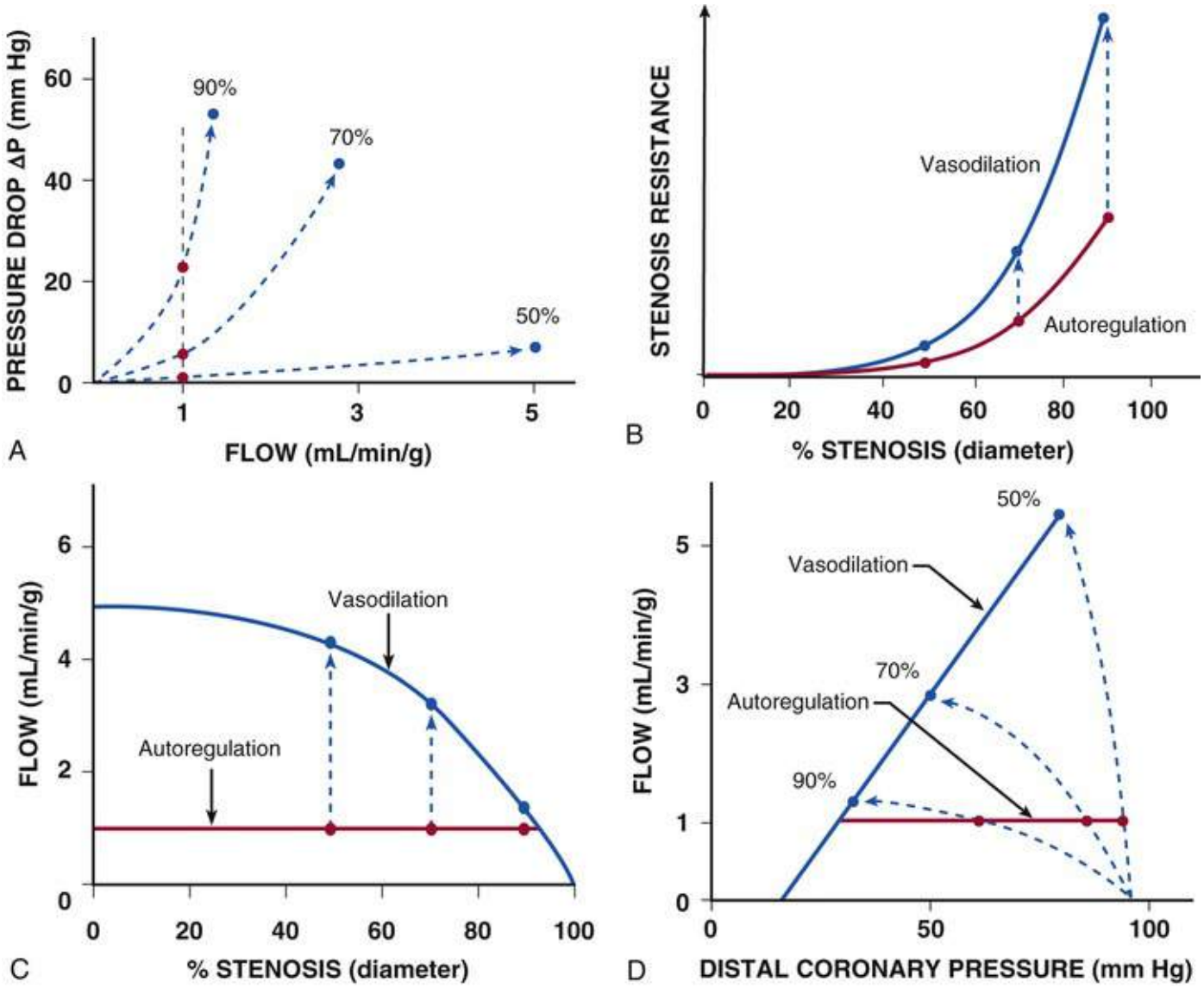


FIGURE 57.13 Interrelation of the epicardial artery stenosis pressure-flow relation **(A)**, stenosis resistance at the autoregulated resting and maximally vasodilated flow **(B)**, absolute coronary flow reserve **(C)**, and the distal coronary pressure-flow relation **(D)**. *Red circles and lines* depict resting flow, and *blue circles and lines* show maximal vasodilation for stenoses of 50%, 70%, and 90% diameter reduction. As shown in **A**, the stenosis pressure-flow relation becomes extremely nonlinear as stenosis severity increases. Thus the instantaneous resistance of the stenosis increases during vasodilation **(B)**. As a result of the nonlinear stenosis pressure-flow behavior, very little pressure drop across a 50% stenosis is seen, and distal coronary pressure and vasodilated flow remain near normal. By contrast, a 90% stenosis critically impairs flow and, because of the steepness of the stenosis pressure-flow relation, causes a marked reduction in distal coronary pressure.

Interrelation of Distal Coronary Pressure, Flow, and Stenosis Severity

Because maximum myocardial perfusion is ultimately determined by the coronary pressure distal to a stenosis, it is helpful to place the epicardial stenosis pressure-flow relation into the context of the coronary autoregulatory and vasodilated coronary pressure-flow relations. **Fig. 57.13C** summarizes the effects of a stenosis on resting and vasodilated flow as a function of percentage diameter reduction, when diffuse intraluminal narrowing is absent and coronary microcirculatory resistance is normal. Because of coronary autoregulation, flow remains constant as stenosis severity increases. Thus imaging resting perfusion cannot identify hemodynamically significant stenoses (**see Chapter 16**). By contrast, the maximally vasodilated pressure-flow relation is much more sensitive to detect increases in stenosis

severity. There is normally substantial coronary flow reserve, and flow can increase approximately five times the resting flow values. As illustrated in **Fig. 57.13D**, there is no significant pressure drop across a stenosis (ΔP) or stenosis-related alteration in maximal myocardial perfusion until stenosis severity exceeds a 50% diameter reduction (cross sectional area reduction of 75%). As stenosis severity exceeds 50%, the curvilinear coronary stenosis pressure-flow relation steepens, and increases in stenosis resistance are accompanied by concomitant increases in ΔP across the stenosis (**Fig. 57.13A**). This reduces distal coronary pressure, the major determinant of perfusion to the microcirculation, and maximum vasodilated flow (and coronary flow reserve) decreases. A critical stenosis, one in which subendocardial flow reserve is completely exhausted at rest, usually develops when stenosis severity exceeds 90%. Under these circumstances, pharmacologic vasodilation of subepicardial resistance vessels results in a reduction in distal coronary pressure that actually redistributes flow away from the subendocardium, leading to a "transmural steal" phenomenon.[6]

Concept of Maximal Perfusion and Coronary Reserve

Gould[10] originally proposed the concept of coronary reserve. With technological advances, it has become possible to characterize this in humans using invasive catheter-based measurements of intracoronary pressure and flow (**Fig. 57.14**) (**see Chapter 62**), as well as with noninvasive imaging of myocardial perfusion with positron emission tomography (PET), single-photon emission tomography (SPECT), and more recently, cardiac magnetic resonance (CMR) (**Chapters 16 and 17**). With physiologically based approaches to quantify perfusion and coronary pressure, it also has become increasingly apparent that abnormalities in coronary microcirculatory control contribute to the functional significance of isolated epicardial artery stenoses in many patients with CAD, as well as leading to impaired coronary flow responses in the presence of normal coronary arteries. Because of these complexities, multiple complementary approaches frequently are required to define limitations in myocardial perfusion that arise from stenosis severity versus abnormalities of the coronary microcirculation. The three major indices currently used to quantify coronary flow reserve are absolute, relative, and fractional flow reserve (**Fig. 57.15**).

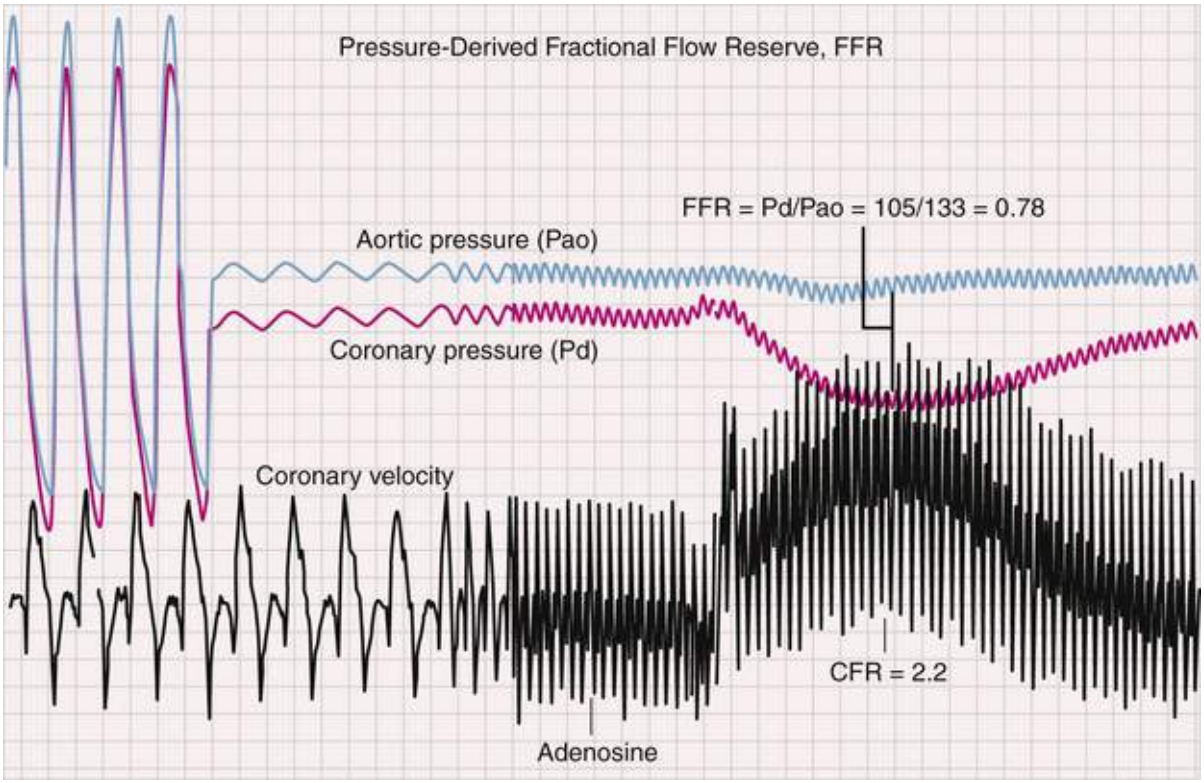


FIGURE 57.14 Coronary pressure and flow velocity tracings in a patient with an intermediate stenosis. After intracoronary adenosine administration, flow velocity transiently increases and mean distal coronary pressure (Pd) falls. Absolute coronary flow reserve (CFR) is the ratio of peak flow to resting flow. FFR is the ratio of Pd/Pao (distal coronary pressure divided by mean aortic pressure).

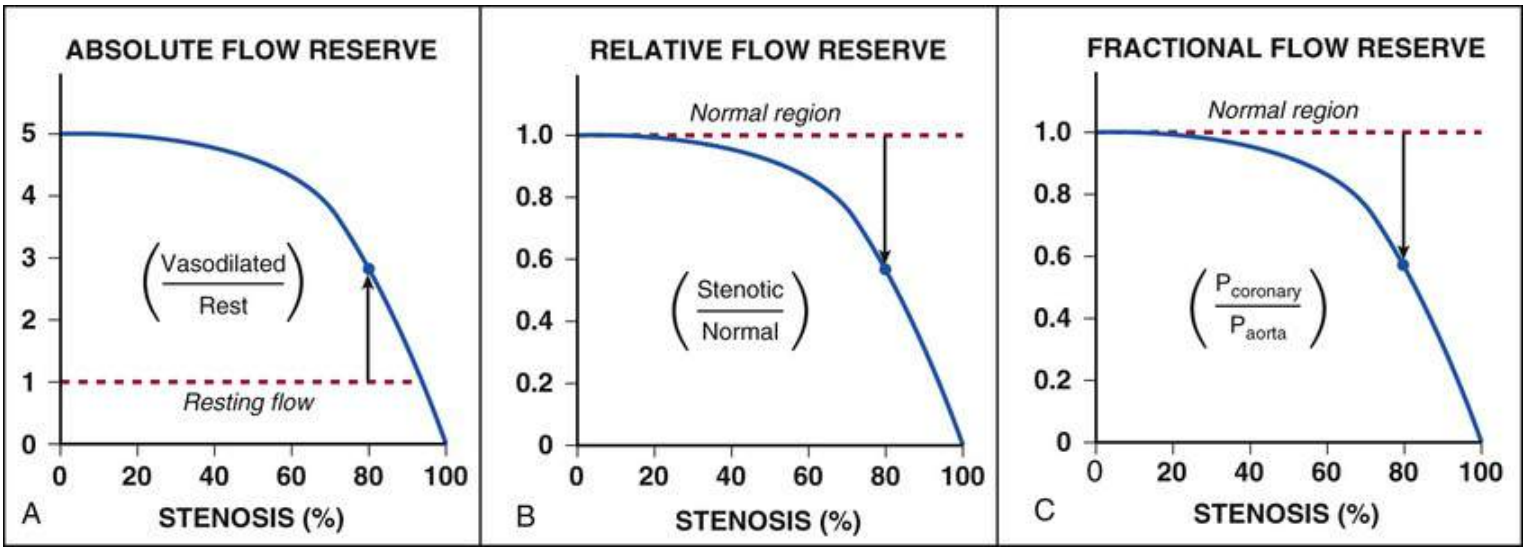
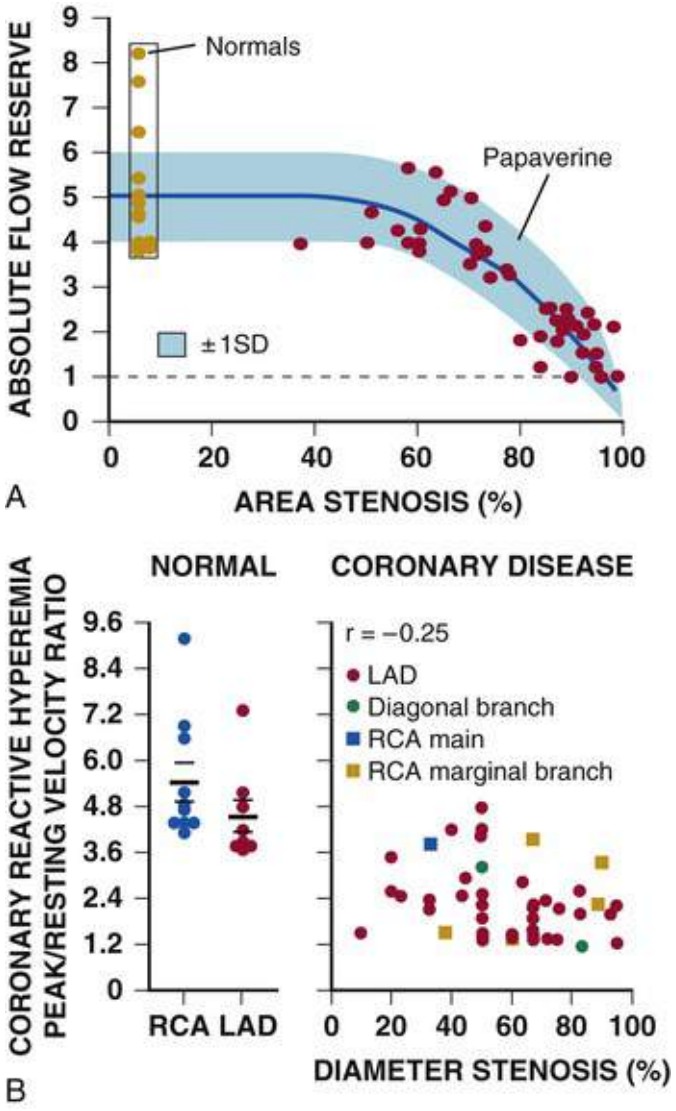


FIGURE 57.15 Interrelation of absolute flow reserve, relative flow reserve, and fractional flow reserve (FFR). **A,** Absolute flow reserve is the ratio of coronary flow during vasodilation to the resting value. It can be obtained with invasive measurements of intracoronary flow velocity or quantitative kinetic perfusion measurements with PET. **B,** Relative flow reserve compares maximal vasodilated flow in a stenotic region with an assumed normal region in the same heart and is most commonly measured with perfusion imaging during stress. **C,** FFR is conceptually similar to relative flow reserve and assesses maximal flow indirectly from coronary pressure measurements distal to a stenosis during vasodilation. Absolute flow reserve reflects the summed effects of a stenosis as well as abnormalities in the coronary microcirculation. By contrast, relative flow reserve and FFR identify the relative effects of a stenosis compared with a normal vessel. They assume maximal vasodilatory responses of coronary resistance vessels and cannot identify the potential contribution of abnormalities in microcirculatory resistance control to the development of myocardial ischemia.

Absolute Flow Reserve

Initial approaches to assess functional stenosis severity focused on assessing the relative increase in flow after ischemic vasodilation (reactive hyperemic response after transient occlusion of the coronary artery) or pharmacologic vasodilation of the microcirculation with intracoronary papaverine, adenosine, or intravenous dipyridamole. Absolute flow reserve can be quantified using intracoronary Doppler velocity or thermodilution flow measurements, as well as by quantitative approaches to image absolute tissue perfusion based on PET and magnetic resonance imaging (MRI). It is expressed as the ratio of maximally vasodilated flow to the corresponding resting flow value in a specific region of the heart and quantifies the ability of flow to increase above the resting value (**Fig. 57.15A**). Clinically important reductions in maximum flow correlating with stress-induced ischemia on SPECT generally are associated with absolute flow reserve values below 2 (**see Chapter 16**). Absolute flow reserve is not only altered by factors that affect maximal coronary flow (e.g., stenosis severity, impaired microcirculatory control, arterial pressure, heart rate) but also by the corresponding resting flow value. As noted previously, resting flow can vary with hemoglobin content, baseline hemodynamics, and the resting oxygen extraction. Reductions in absolute flow reserve, therefore, can arise from inappropriate elevations in resting coronary flow as well as from reductions in maximal perfusion.

In the absence of diffuse atherosclerosis or LV hypertrophy, absolute flow reserve in conscious humans is similar to that measured in animals, with vasodilated flow reaching four to five times the value at rest. Thus, fairly good reduplication of the idealized relation between stenosis severity and absolute flow reserve occurs in patients with isolated one- or two-vessel CAD (**eFig. 57.2A**) with intracoronary papaverine–induced vasodilation. By contrast, abnormalities in the coronary microcirculation as well as uncertainty in stenosis geometry or diffuse atherosclerosis leads to considerably more variability of the observed relation between stenosis severity and absolute flow reserve in patients with more extensive disease (**eFig. 57.2B**). Part of this reflects that patients with risk factors for CAD such as hypercholesterolemia and no significant coronary luminal narrowing have microcirculatory impairment in flow or attenuated vasodilator responsiveness, with absolute flow reserve using PET being lower than in normal individuals. Thus a significant limitation of absolute flow reserve measurements is that the importance of an epicardial stenosis cannot be dissociated from changes caused by functional abnormalities in the microcirculation that are common in patients (e.g., hypertrophy, impaired endothelium-dependent vasodilation). Likewise, recent studies have also identified abnormalities in coronary flow regulation in metabolic syndrome.[13]



EFIGURE 57.2 Absolute coronary flow reserve as a function of stenosis severity in patients. **A,** Measured absolute flow reserve after intracoronary papaverine vasodilation in single-vessel disease without hypertrophy demonstrates a good correlation with values predicted theoretically. **B,** Absolute flow reserve assessed using intraoperative epicardial Doppler flow measurements after onset of reactive hyperemia to a 20-second occlusion in patients with diffuse multivessel coronary artery disease. For all vessels, there is a poor relation with stenosis severity. This reflects variability in stenosis severity with visual interpretation, as well as abnormal microcirculatory responses to ischemia and multiple risk factors for impaired endothelial function. LAD, Left anterior descending artery; RCA, right coronary artery. (**A,** Modified from Wilson RF, Marcus ML, White CW. Prediction of the physiologic significance of coronary arterial lesions by quantitative lesion geometry in patients with limited coronary artery disease. Circulation 1987;75:723; **B,** modified from White CW et al. Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? N Engl J Med 1984;310:819.)

Relative Flow Reserve

Relative coronary flow reserve measurements are the cornerstone of noninvasive identification of hemodynamically important coronary stenoses using nuclear perfusion imaging (**see Chapter 16**). In this approach, relative differences in regional perfusion (per gram of tissue) are assessed during maximal pharmacologic vasodilation or exercise stress and expressed as a fraction of flow to normal regions of the heart (**see Fig. 57.15B**). This approach compares relative perfusion states under the same hemodynamic conditions and is fairly insensitive to variations in mean arterial pressure, heart rate, and preload. An alternative approach uses invasive absolute flow reserve measurements and derives relative flow reserve by dividing absolute flow reserve in a stenotic vessel by absolute flow reserve in a remote normally perfused territory.[11]

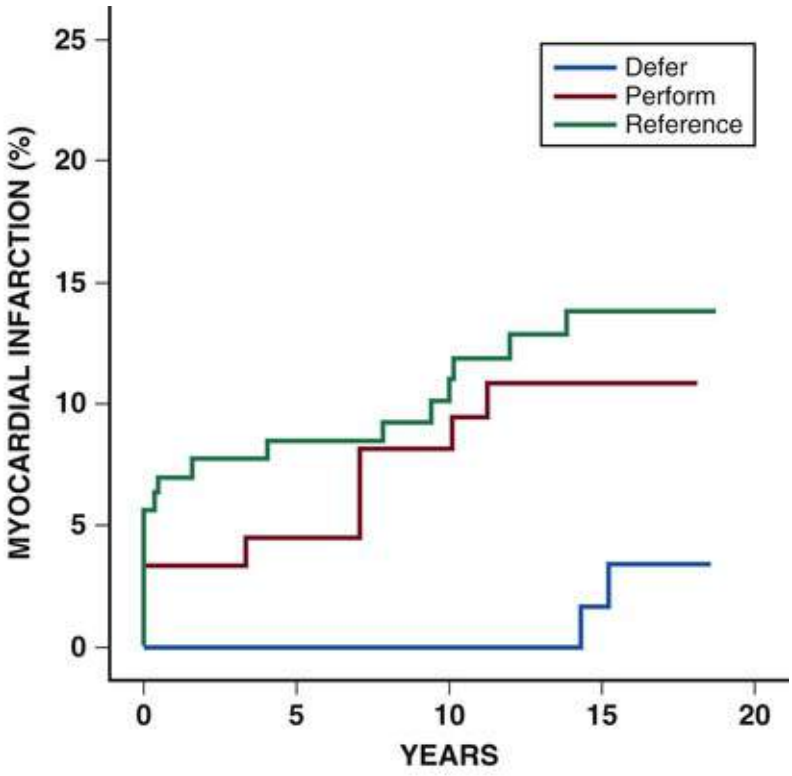
Although widely used to identify hemodynamically significant stenoses, significant limitations arise in using imaging to quantify relative flow reserve. First, conventional SPECT imaging requires a normal reference segment within the left ventricle for comparison. Because of this, relative flow reserve measurements cannot accurately quantify stenosis severity when diffuse abnormalities in flow reserve related to either balanced multivessel CAD or impaired microcirculatory vasodilation are present. Large differences in relative vasodilated flow are required to detect SPECT perfusion differences because nuclear tracers become diffusion limited, and their myocardial uptake fails to increase proportionally with increases in vasodilated flow. As a result, differences in tracer deposition will variably underestimate the actual relative difference in perfusion. This problem can be overcome with use of PET tracers of perfusion and appropriate kinetic modeling to quantify flow. Lastly, although prognostic data related to the perfusion deficit size are available, no imaging studies have been conducted to evaluate the quantitative severity of the stress or vasodilated flow reduction as a continuous outcome measure; conceptually, however, this should be similar to fractional flow reserve.

Fractional Flow Reserve

Considerable focus has turned toward invasive point-of-care approaches that use pressure measurements made distal to a coronary stenosis as an indirect index of stenosis severity[11] (**see Fig. 57.14**). This technique, pioneered by Pijls and Sels,[14] is based on the principle that the distal coronary pressure measured during vasodilation is directly proportional to maximum vasodilated perfusion (**see Fig. 57.15C**). *Fractional flow reserve* (FFR) is an indirect index determined by measuring the driving pressure for microcirculatory flow distal to the stenosis (distal coronary pressure minus coronary venous pressure) relative to the coronary driving pressure available in the absence of a stenosis (mean aortic pressure minus coronary venous pressure). The approach assumes linearity of the vasodilated pressure-flow relation (which is known to be curvilinear at reduced coronary pressure[15]) and usually assumes that coronary venous pressure is zero. This results in the simplified clinical FFR index of mean distal coronary pressure/mean aortic pressure (Pd/Pao). Although derived, the measurements are conceptually similar to those of relative coronary flow reserve because they only rely on minimum mean coronary pressure measurements during intracoronary vasodilation and compare stenotic with normal regions under similar hemodynamic conditions. They are attractive for clinical use in that they can immediately assess the physiologic significance of an intermediate stenosis to help guide decisions regarding the need for percutaneous coronary intervention and are unaffected by alterations in resting flow (**see Chapter 62**). Similarly, because they require only vasodilated coronary pressure determinations, FFR can be used to assess the functional effects of a residual lesion immediately after percutaneous coronary intervention (PCI).

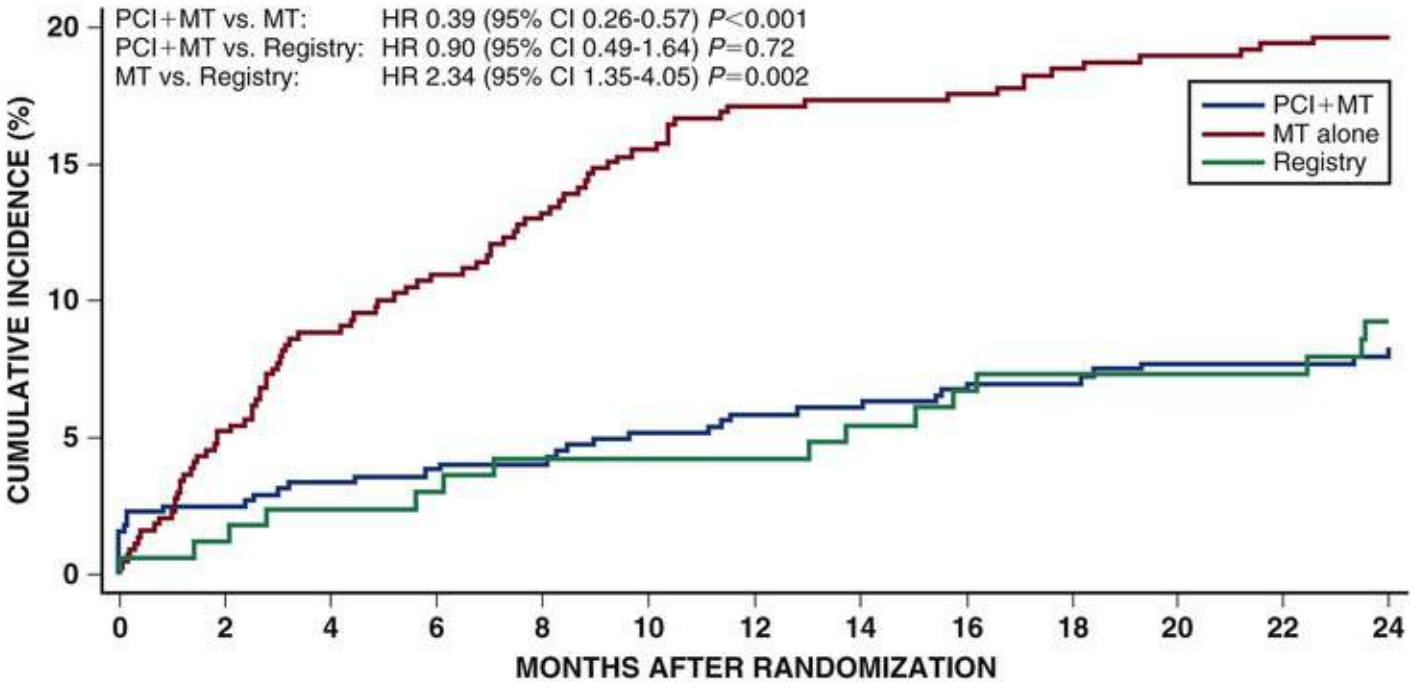
A significant advantage of FFR is the availability of now-considerable prognostic information. The 15-year follow-up of a large prospective randomized study demonstrates that coronary lesions having FFR measurements greater than 0.75 are associated with excellent outcomes with deferred rather than prophylactic intervention in patients with stable ischemic heart disease[16] (**Fig. 57.16**). Physiologically guided PCI using FFR versus angiographic criteria was safe and cost-effective and reduced the number of stents required to treat patients with multivessel CAD. Furthermore, a strategy based on assessing the physiologic severity of stenoses was accompanied by a significant reduction in major adverse cardiac events at 1 year (13.2% using FFR versus 18.3% in angiography-guided treatment)[17] (**eFig. 57.3**). In subsequent trials, the same investigators showed that FFR-guided coronary intervention provided additional benefit over optimal medical therapy alone.[18] Thus, patients with a FFR below 0.80 who underwent a coronary intervention in addition to optimal medical therapy displayed a reduction in major

adverse cardiac events (**Fig. 57.17**), which was principally driven by a lesser need for urgent revascularization triggered by a myocardial infarction (MI) or evidence of ischemia on an electrocardiogram (ECG).[18] Collectively, these studies support the importance of functional stenosis severity in determining prognosis and the use of a physiologic-guided approach to determining the need for PCI in the patient stable ischemic heart disease.



No. at risk				
Defer	91	83	70	56
Perform	90	81	68	59
Reference	144	118	102	80

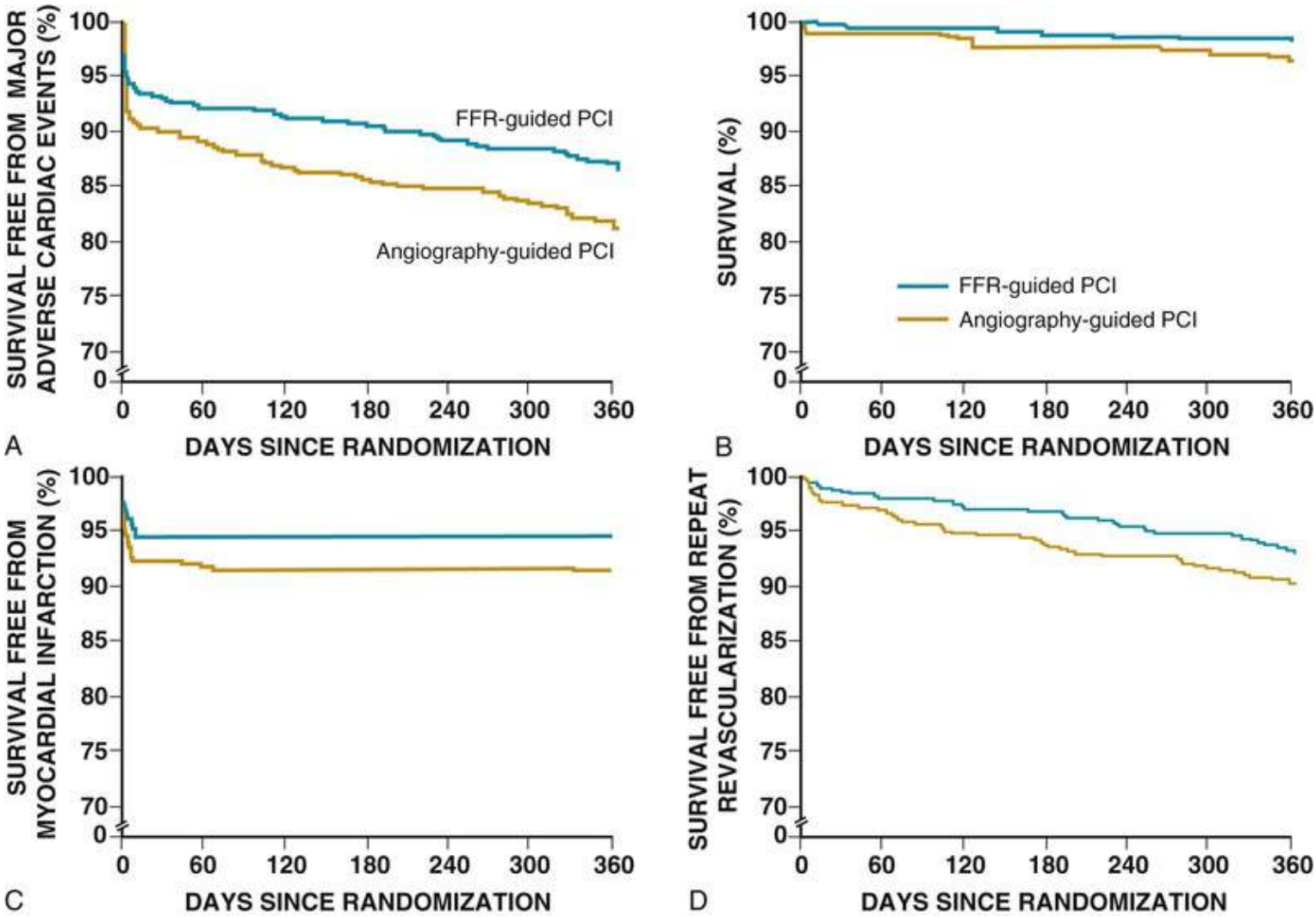
FIGURE 57.16 Deferral versus performance of percutaneous coronary intervention (PCI) of functionally nonsignificant coronary stenosis. Patients with angiographically significant coronary stenosis but fractional flow reserve (FFR) of 0.75 or greater who underwent optimal medical treatment alone (*Defer*) displayed a significantly lower incidence of myocardial infarction compared to patients undergoing PCI plus optimal medical treatment (*Perform*). The *Reference* group consisted of patients with FFR less than 0.75 undergoing PCI plus optimal medical treatment. (From Zimmermann FM, Ferrara A, Johnson NP, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. Eur Heart J 2015;36;3182.)



No. at risk

MT	441	417	398	389	379	369	362	360	359	355	353	351	297
PCI+MT	447	434	429	426	425	420	416	414	410	408	405	403	344
Registry	166	164	162	160	157	157	156	153	151	150	150	150	122

FIGURE 57.17 Patients with stable coronary artery disease with a fractional flow reserve (FFR) value of less than 0.80 randomized to percutaneous coronary intervention (PCI) plus optimal medical therapy (MT) displayed lower rates of the combined endpoint of death, myocardial infarction, and urgent revascularization than patients randomized to optimal medical therapy only. Patients receiving FFR-guided PCI had an event rate similar to those in a registry who had no lesion with FFR less than 0.80 at enrollment. HR, Hazard ratio; CI, confidence interval. (From De Bruyne B, Fearon WF, Pijls NH, et al. Fractional flow reserve–guided PCI for stable coronary artery disease. N Engl J Med 2014;371:1208.)



EFIGURE 57.3 Percutaneous coronary intervention (PCI) guided by assessing the physiologic significance of a coronary stenosis is associated with significant reductions in coronary events. Patients randomly assigned to an angiography-guided strategy based on stenosis severity using fractional flow reserve (FFR) had higher rates of the combined endpoint of death, myocardial infarction, and repeat revascularization than did patients in whom management was guided by a FFR **(A).** Individual endpoint trends showed no difference in mortality **(B)** but higher rates of survival free from myocardial infarction **(C)** and survival free from repeat revascularization **(D)** in patients with the FFR-guided strategy. (From Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213.)

Unfortunately, FFR can assess only the functional significance of epicardial artery stenoses and cannot assess limitations in myocardial perfusion that arise from abnormalities in microcirculatory flow reserve in coronary resistance vessels. While simple, FFR measurements are also critically dependent on achieving maximal pharmacologic vasodilation (underestimating stenosis severity if vasodilation is submaximal at the time of measurement). In addition, ignoring the backpressure to coronary flow by assuming that it is equal to zero and ignoring curvilinearity of the pressure-flow relation will cause the FFR to underestimate the physiologic significance of a stenosis.[15] This is particularly problematic at low coronary pressures and in assessing the functional significance of coronary collaterals, where venous pressure needs to be considered. Lastly, inserting the pressure wire across a stenosis can lead to artifactual overestimation of stenosis severity. This error can be caused by the reduction in effective intralesional area in the presence of diffuse disease or a severe stenosis, as well as placement that results in partial occlusion of small branch vessels. Despite these concerns and its invasive nature, determination of FFR is currently the most direct way to assess the physiologic significance of individual coronary lesions.

Advantages and Limitations of Coronary Flow Reserve Measurements.

Assessing qualitative perfusion differences with noninvasive imaging is useful because relative perfusion deficit size is an important determinant of prognosis. Although the clinical role of invasive measurements that quantify functional stenosis severity continues to evolve, measurement of FFR, available at the point of interventional care, has been demonstrated to affect postprocedural outcomes favorably at reduced cost. The need to use these measurements routinely in decision making for PCI in patients with stable ischemic heart disease may change in future clinical care guidelines.[11,12]

The major assumption common to all flow reserve measurements is that the administered pharmacologic vasodilator consistently achieves maximal vasodilation of the resistance vasculature in normal individuals as well as in patients with atherosclerotic disease and impaired endothelial function. The reductions in absolute flow reserve in humans with microvascular disease and angiographically insignificant stenoses (**eFig. 57.2B**), as well as variability in quantitative perfusion measurements with normal epicardial arteries and coronary risk factors, indicate that this may not always be the case. The extent to which this variability is related to structural (e.g., caused by regional hypertrophy or vascular remodeling) versus functional (e.g., altered microcirculatory vasodilator response versus impaired endothelium-dependent vasodilation) abnormalities in the microcirculation remains unclear (see later). A second limitation is that currently available approaches can measure only coronary flow reserve averaged across the entire wall of the heart. This is because they are based on invasive epicardial coronary measurements (**see Chapter 62**) or, in the case of imaging (e.g., SPECT), have insufficient spatial resolution to assess transmural variations in flow (**Chapter 16**). An imaging technique that could assess the physiologic significance of a stenosis in the subendocardial layers would be a major advance, because this region is most severely affected by an epicardial stenosis. This is now feasible with CMR (**see Chapter 17**).

Pathophysiologic States Affecting Microcirculatory Coronary Flow Reserve

Various pathophysiologic states can accentuate the effects of a fixed-diameter coronary stenosis and may precipitate subendocardial ischemia during stress in the presence of normal coronary arteries.[19] Thus it is important to consider measurements of stenosis severity in the context of coexisting abnormalities of coronary arterial resistance vessel control. In the former case, treatment will be directed at the epicardial stenosis, whereas in the latter, medical therapies designed to improve abnormalities in resistance vessel control will be required. The prognostic importance of abnormalities in coronary resistance vessel control is underscored by emerging data in women evaluated for chest pain thought to be of ischemic origin.[20] Abnormalities in coronary flow reserve and endothelium-dependent vasodilation are common in women with insignificant epicardial coronary disease, produce metabolic evidence of myocardial ischemia as assessed by magnetic resonance spectroscopy (**see Chapter 17**), and negatively affect prognosis.[21] Common factors affecting microcirculatory resistance control independent of coronary stenosis severity in patients are LV hypertrophy, coronary microvascular disease, and impaired NO-mediated resistance vessel vasodilation, which is the result of many of the risk factors for CAD.

Left Ventricular Hypertrophy.

The effects of hypertrophy on coronary flow reserve are complex and must be seen in terms of the absolute flow level (e.g., measured with intracoronary Doppler probe) as well as the flow per gram of myocardial tissue[22] (**Fig. 57.18**). With acquired hypertrophy, resting flow per gram of myocardium remains constant, but the increase in LV mass necessitates an increase in the absolute level of resting flow (mL/min) through the coronary artery (see Classic References, Bache). In terms of maximal perfusion, pathologic hypertrophy does not result in appreciable vascular proliferation (as opposed to physiologic hypertrophy produced by exercise training), and coronary resistance vessels remain essentially unchanged. Since maximum absolute flow (mL/min) during vasodilation remains unchanged, the increase in LV mass in the absence of vascular proliferation reduces the maximum perfusion per gram of myocardium. The net effect of LV hypertrophy is that coronary flow reserve at any given coronary arterial pressure is reduced in a manner that is inversely related to the change in LV mass. For example, in the absence of a change in mean aortic pressure, a twofold increase in LV mass, as with severe LV hypertrophy, can reduce absolute coronary flow reserve in a nonstenotic artery from 4 to 2. This will increase the functional severity of any anatomic degree of coronary artery narrowing and can even precipitate subendocardial ischemia with normal coronary arteries.

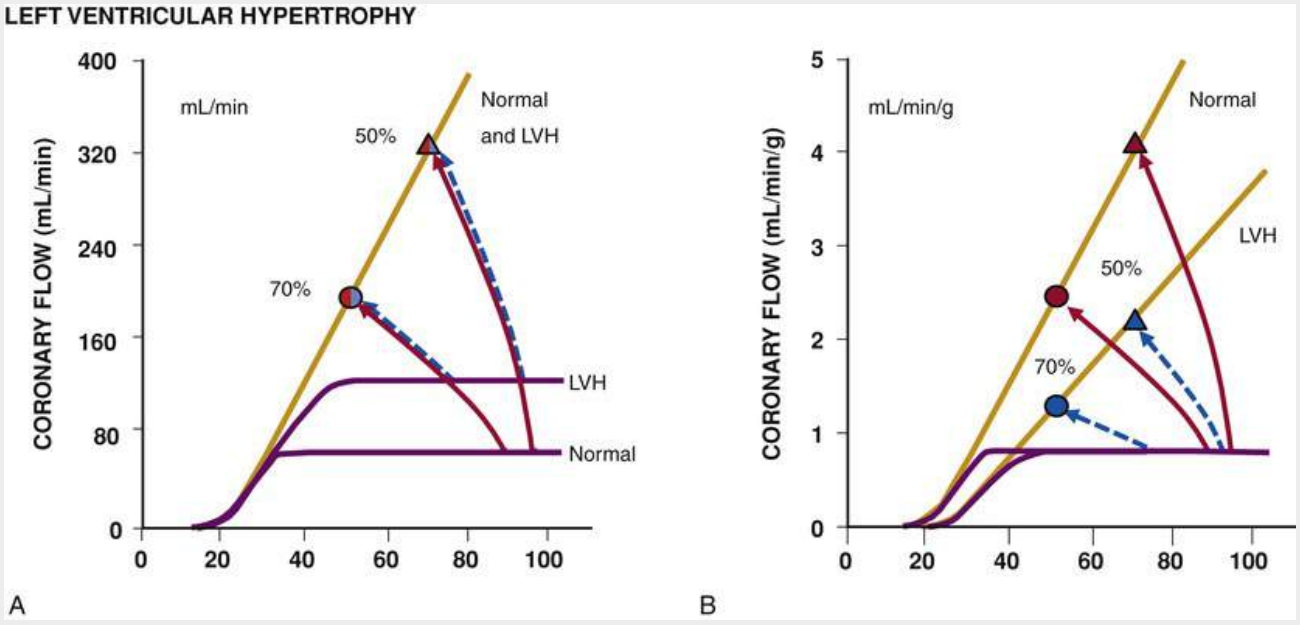


FIGURE 57.18 Effects of hypertrophy on absolute flow (mL/min) and flow per gram of tissue (mL/min/g). With acquired hypertrophy, myocardial mass increases without proliferation of the microcirculatory resistance arteries. **A**, The increase in left ventricular (LV) mass causes a proportional increase in absolute flow at rest (*purple lines*), while the maximum absolute flow per minute during vasodilation (*gold lines*) remains unchanged. **B,** When tissue perfusion is assessed using flow per gram of myocardium (e.g., as obtained using PET), the maximum flow per gram of tissue (*gold lines*) falls inversely with the increase in LV mass. By contrast, the resting flow per gram of myocardium (*purple lines*) remains constant, because the increase in absolute resting flow is proportional to the increase in LV mass. Regardless of whether absolute flow or flow per gram is measured, the net effect of these opposing actions is to decrease coronary flow reserve at any coronary pressure in LV hypertrophy (LVH). As a result of the reduction in microcirculatory reserve in the absence of a coronary stenosis, the functional significance of a 50% stenosis (*triangles*) in the hypertrophied heart could approach a more severe stenosis (in the example, 70%, *circles*) in normal myocardium. This can even lead to ischemia with normal coronary arteries during stress.

Some degree of LV hypertrophy is common in patients with CAD, and it probably contributes to reductions in coronary flow reserve that are independent of stenosis severity. The actual coronary flow reserve in hypertrophy will be critically dependent on the underlying cause of hypertrophy and its effects

on coronary driving pressure. A similar degree of hypertrophy caused by untreated systemic hypertension will be associated with a higher coronary flow reserve than in aortic stenosis, in which mean arterial pressure remains normal. Similarly, when hypertrophy results from systolic hypertension and increased pulse pressure is caused by reduced aortic compliance, the accompanying reduction in diastolic pressure can lower coronary reserve because myocardial perfusion occurs primarily in diastole.

Coronary Microvascular Disease and Dysfunction.

The effects of primary coronary microvascular dysfunction (**Fig. 57.19**) on reducing coronary flow reserve are somewhat similar to those of LV hypertrophy but differ in terms of the effect on maximum coronary flow. As with hypertrophy, flow per gram of myocardium will be normal at rest and reduced during pharmacologic vasodilation. In contrast to hypertrophy, absolute flow remains normal at rest in microvascular disease, and the absolute vasodilated flow is reduced. Because absolute flow across the stenosis during vasodilation is the major determinant of the pressure drop and thus of distal coronary pressure, a similar stenosis will have a smaller pressure gradient and higher distal pressure in a patient with microvascular disease than in a patient with LV hypertrophy. Abnormalities in microvascular vasodilation may be functional rather than structural and, as discussed later, can arise from cumulative coronary risk factors that lead to endothelial dysfunction.

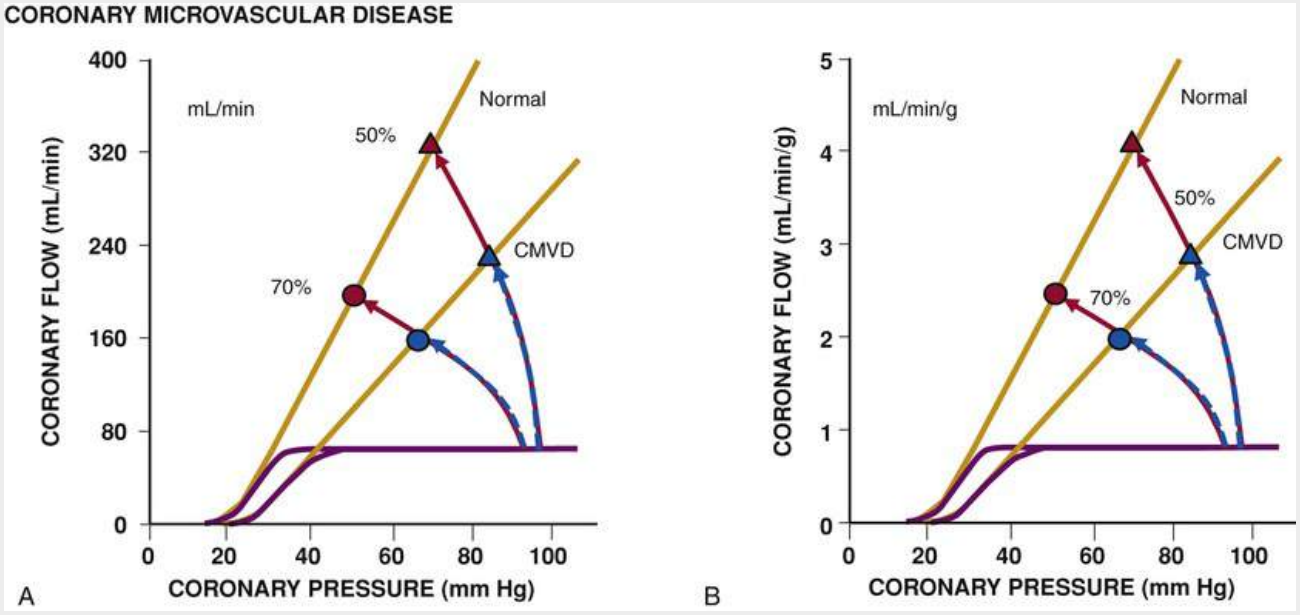


FIGURE 57.19 Effects of microvascular dysfunction on absolute flow (mL/min) and flow per gram of tissue (mL/min/g). In microvascular disease, resting flow and LV mass remain normal. Thus, under resting conditions (*purple lines*), absolute flow and flow per gram of tissue are similar in patients with microvascular disease compared with normal subjects. By contrast, during maximum vasodilation (*gold lines*) absolute flow **(A)** and flow per gram of tissue **(B)** both are reduced in microvascular disease, reflecting a functional or structural abnormality of coronary resistance vessels. CMVD, Coronary microvascular dysfunction.

Impaired Endothelium-Dependent Vasodilation in the Microcirculation.

Measurements of coronary flow reserve in humans with risk factors for atherosclerosis (**see Chapter 45**) are systematically lower than in normal individuals without coronary risk factors, underscoring the importance of functional abnormalities in microvascular control in determining coronary flow reserve.[23,24] Perturbations in microvascular control may arise from abnormal local resistance vessel control through impaired endothelium-dependent vasodilation arising from NO inactivation associated with risk factors for CAD. Experimental hypercholesterolemia markedly attenuates the dilation of

coronary arterioles in response to shear stress as well as pharmacologic agonists that stimulate NOS in the absence of epicardial stenoses (**Fig. 57.20**). This was reversed with L-arginine, suggesting that it reflects impaired NO synthesis or availability. CAD is associated with a shift from NO to the EDHF hydrogen peroxide (H_2O_2), which acts to compensate in part for the loss of NO.[5] This shift appears to be mediated by the sphingolipid ceramide (produced by neutral sphingomyelinase in patients with CAD), resulting in the endothelial production of reactive oxygen species, thereby reducing NO and increasing H_2O_2 levels[8] (**Fig. 57.21**).

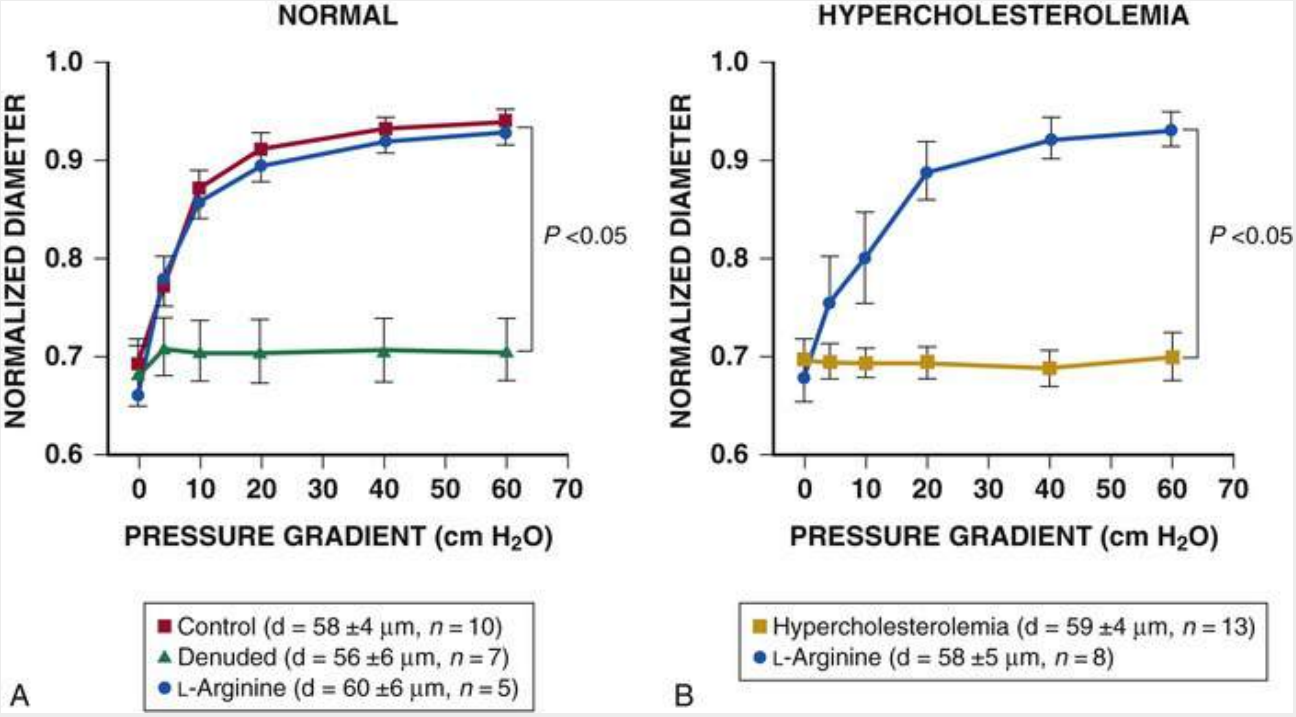


FIGURE 57.20 Flow-mediated vasodilation in coronary resistance arteries is abolished by dietary hypercholesterolemia in swine. **A,** In normal arterioles, increased flow (pressure gradient) elicits vasodilation that, similar to human vessels, is abolished by removing the endothelium (denuded). **B,** In animals with dietary hypercholesterolemia but no significant epicardial stenosis, flow-mediated vasodilation of arterioles is abolished. It was restored by administering L-arginine to increase NO production. Luminal diameters were normalized to the diameter at a luminal pressure of 60 cm H_2O in the presence of nitroprusside (10^{-4} M). Numbers of vessels (*n*) and average luminal diameter (d) with spontaneous tone in physiologic salt solution-albumin at 60 cm H_2O are shown. *Vertical bars* denote mean ±SEM. (Modified from Kuo L, Davis MJ, Cannon MS, et al. Pathophysiological consequences of atherosclerosis extend into the coronary microcirculation: restoration of endothelium-dependent responses by L-arginine. Circ Res 1992;70:465.)

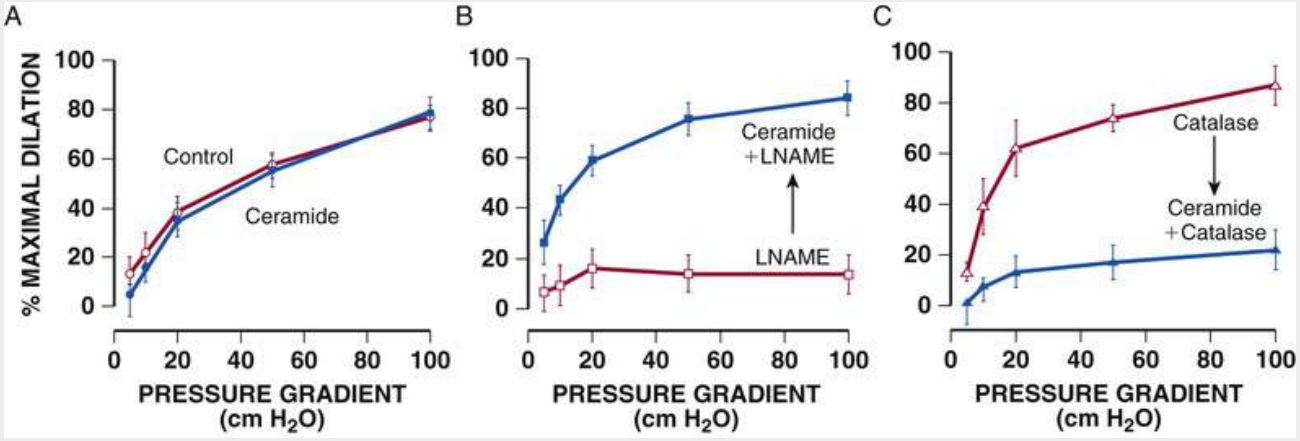


FIGURE 57.21 Effect of ceramide on flow-induced dilation (FID). Ceramide, a risk factor for coronary artery disease (CAD), inhibits neutral sphingomyelinase and increases mitochondrial hydrogen peroxide (H_2O_2) production. **A,** Magnitude of FID is not affected with overnight incubation of ceramide alone compared with vehicle-treated control. **B,** FID in healthy arterioles is reduced in the presence of nitric oxide (NO) synthase inhibition with N^{ω}-nitro-L-arginine methyl ester (LNAME) but is maintained if first preincubated with ceramide. **C,** Breakdown of H_2O_2 with catalase has minimal effect on FID in healthy arterioles but impairs FID in ceramide-treated arterioles. These data suggest that ceramide (which is increased in patients with CAD) may cause the shift in the FID mediator from NO to H_2O_2 in human coronary microvessels. *Vertical bars* denote mean ±SEM. (Modified from American Heart Association; Freed JK, Beyer AM, LoGiudice JA, et al. Ceramide changes the mediator of flow-induced vasodilation from nitric oxide to hydrogen peroxide in the human microcirculation. Circ Res 2014;115:525.)

These in vitro abnormalities in NO-mediated vasodilation can be functionally significant and can impair the ability of the heart to autoregulate coronary blood flow. **Fig. 57.22A** shows the effects of inhibiting NO on the coronary autoregulatory relation in normal dogs. Although resting blood flow is not altered, there is a marked increase in the coronary pressure at which intrinsic autoregulatory adjustments become exhausted, with flow beginning to decrease at a distal coronary pressure of 60 versus 45 mm Hg, approximately similar to the shift occurring in response to a twofold increase in heart rate. In vivo microcirculatory studies have demonstrated that inhibiting NO production prevents resistance arteries from dilating maximally in response to shear stress.[2,4] This limiting effect probably reflects excess resistance in the transmural penetrating arteries, which are upstream of metabolic stimuli for vasodilation and extremely dependent on shear stress as a stimulus for local vasodilation. These functional abnormalities amplify the physiologic effects of a coronary stenosis, resulting in the development of subendocardial ischemia at a lower workload (**Fig. 57.22B**).

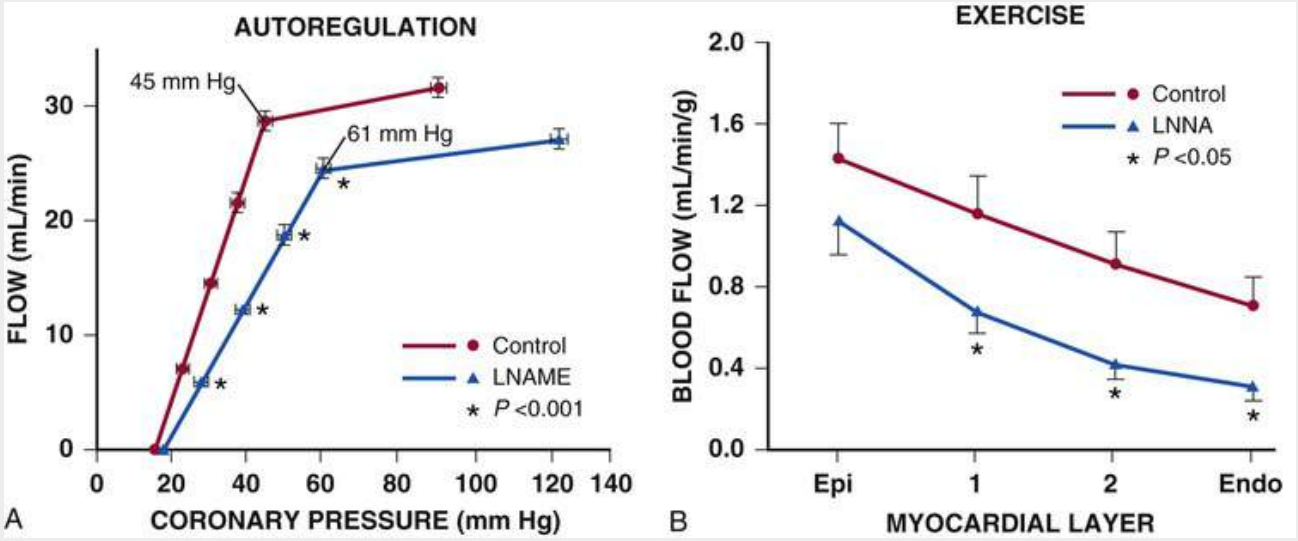


FIGURE 57.22 Impaired microcirculatory control with abnormal NO-mediated endothelium-dependent resistance artery dilation. **A,** Effects of blocking nitric oxide synthase (NOS) with the L-arginine analogue LNAME in chronically instrumented dogs. There is an increase in the lower autoregulatory pressure limit, resulting in the onset of ischemia at a coronary pressure of 61 mm Hg versus 45 mm Hg under normal conditions that occurred without a change in heart rate. **B,** Transmural perfusion before and after blocking NO-mediated dilation with LNNA in exercising dogs subjected to a coronary stenosis. Although coronary pressure and hemodynamics were similar, blood flow was less in each layer of the heart after blocking NOS and was not overcome by metabolic dilator mechanisms during ischemia. Collectively, these experimental data support the notion that abnormalities in endothelium-dependent microvascular vasodilation can amplify the functional effects of a proximal coronary stenosis. Endo, Endocardium; Epi, epicardium; LNAME, N^{ω}-nitro-L-arginine methyl ester; LNNA, N^{ω}-nitro-L-arginine. (**A,** Modified from Smith TP Jr, Canty JM Jr. Modulation of coronary autoregulatory responses by nitric oxide: evidence for flow-dependent resistance adjustments in conscious dogs. Circ Res 1993;73:232; **B,** modified from Duncker DJ, Bache RJ. Inhibition of nitric oxide production aggravates myocardial hypoperfusion during exercise in the presence of a coronary artery stenosis. Circ Res 1994;74:629.)

These observations in normal animals with impaired NO production appear to be relevant to pathophysiologic states associated with impaired endothelium-dependent vasodilation in humans. For example, coronary flow reserve is markedly reduced in the absence of a coronary stenosis in familial hypercholesterolemia, and improving endothelial function by lowering elevated LDL levels with statins produces a delayed improvement in coronary flow reserve in normal and stenotic arteries and also ameliorates clinical signs of myocardial ischemia.[25] Impaired NO-mediated vasodilation probably affects the regulation of myocardial perfusion in other disease states in which endothelium-dependent vasodilation is impaired.

Impact of Microcirculatory Abnormalities on Physiologic Measures of Stenosis Severity

If microcirculatory dysfunction is absent, quantitative measures of stenosis severity during vasodilation that are derived using absolute flow reserve, relative flow reserve, and FFR should all be closely related. Unfortunately, this is the exception rather than the rule, and microvascular dysfunction or variability in the microcirculatory response to pharmacologic vasodilation dissociates the idealized relation between various indices of coronary flow reserve for a given stenosis severity. **Fig. 57.23A** shows the relation between paired invasive measurements of absolute flow reserve versus distal coronary pressure–derived FFR. Hemodynamically insignificant stenoses (FFR >0.8) can have an absolute flow reserve that varies from 1 to more than 5. Although this variability decreases when FFR is less than 0.8, it is still considerable until FFR falls below 0.5.

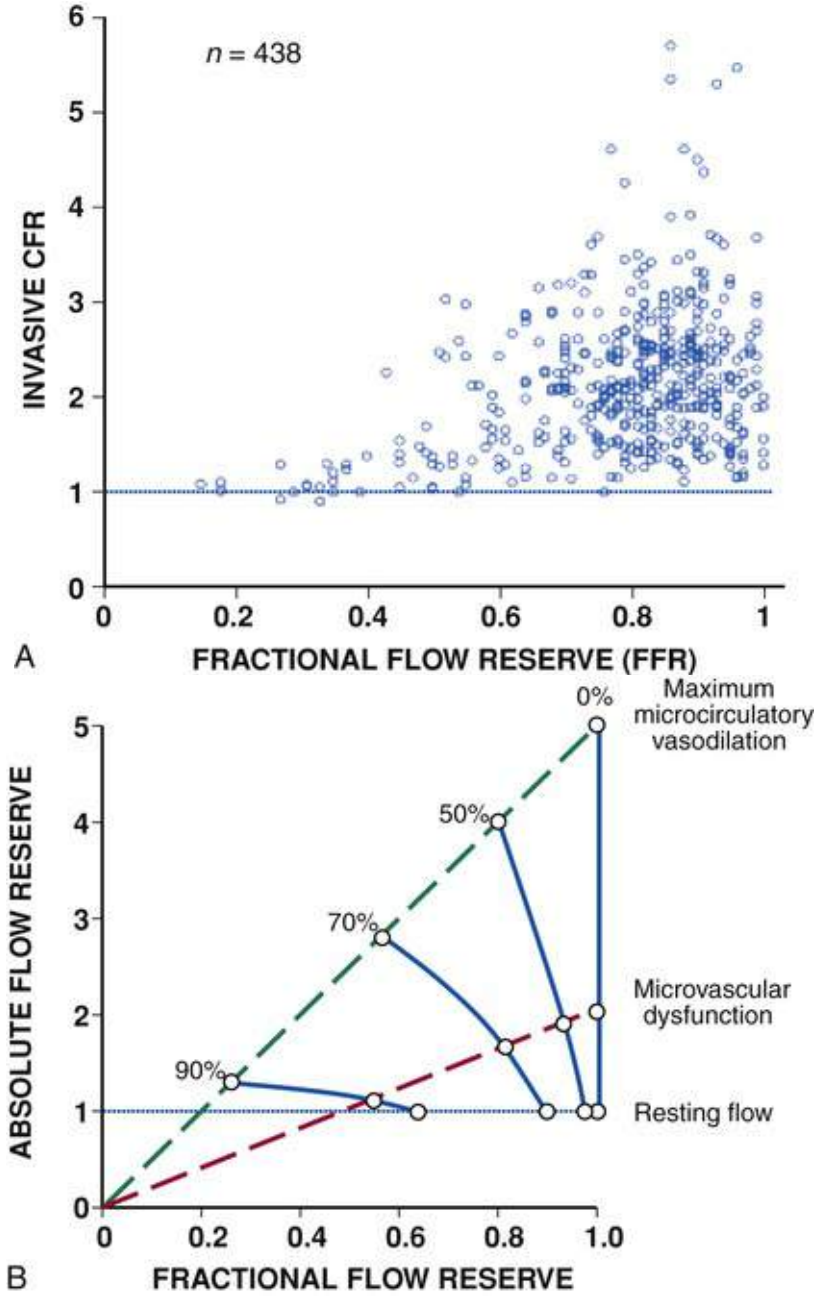


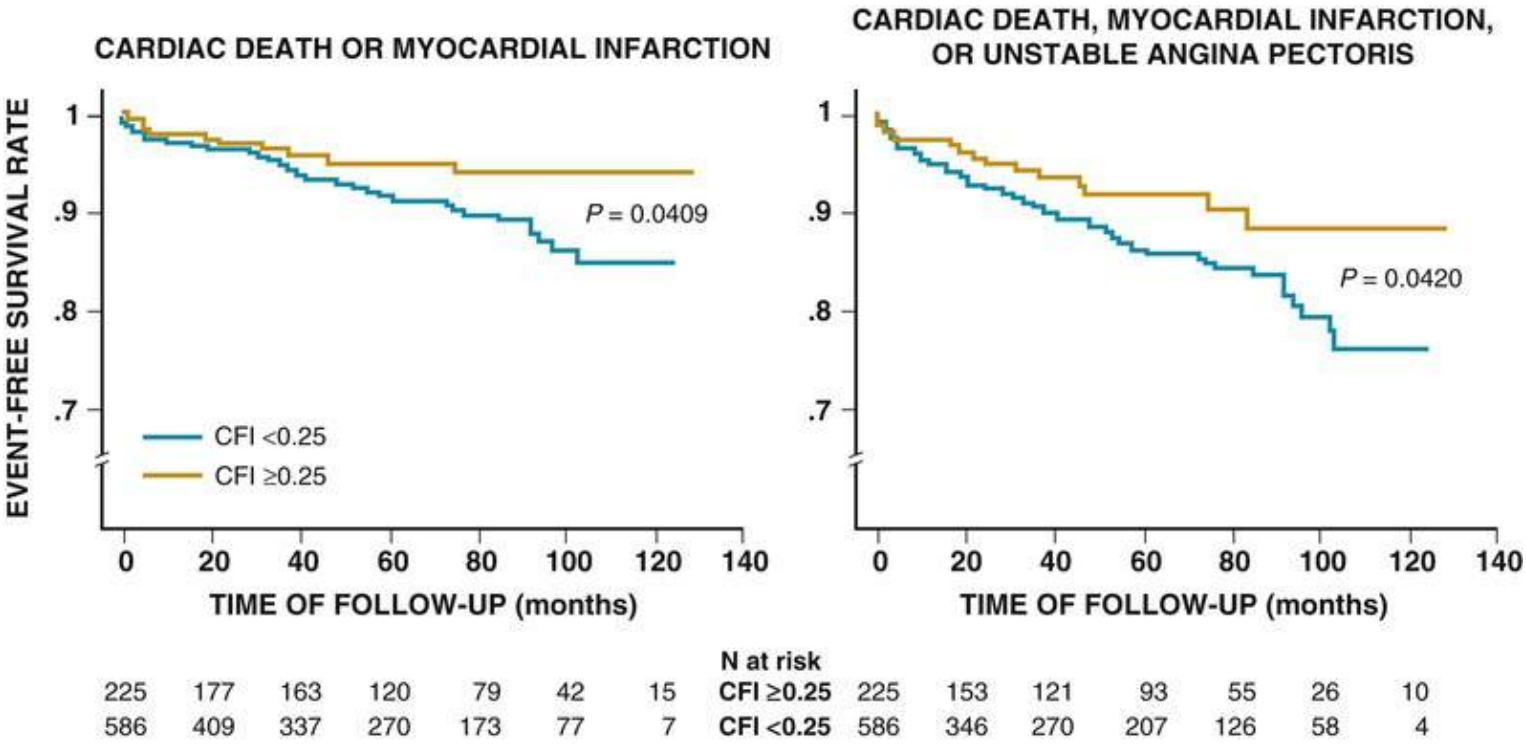
FIGURE 57.23 Wide variation in paired measurements of functional stenosis severity is observed with use of different indices of flow reserve in the same patient, suggesting the presence of coronary microvascular dysfunction. **A,** Simultaneous intracoronary catheter–based measurements of absolute coronary flow reserve (CFR) are compared with FFR. This variability reflects differences in the contribution of the microcirculation and stenosis in individual patients. **B**, Effects of microvascular dysfunction on the stenosis pressure-flow relation and measurements of flow reserve. The *upper green dashed line* shows the idealized linear relation between absolute flow reserve and FFR when the coronary microcirculation is normal and maximally vasodilated. The *lower red dashed line* indicates the relation between absolute flow reserve and FFR when there is microvascular dysfunction. Individual stenoses are illustrated by the *solid blue lines*. The horizontal blue line indicates the resting flow situation (panel **A**) or absolute flow reserve of 1.0 (panel **B**). The presence of microvascular dysfunction will limit vasodilation. Thus, absolute flow reserve will be reduced and will overestimate stenosis severity. By contrast, because distal coronary pressure is higher with submaximal vasodilation, FFR (and relative flow reserve) will underestimate stenosis severity. It is likely that these interactions contribute to the variability demonstrated in panel **A.** (**A,** Modified from Johnson NP, Kirkeeide RL, Gould KL. Is discordance of coronary flow reserve and fractional flow reserve due to methodology or clinically relevant coronary pathophysiology? J Am Coll Cardiol Imaging 2012;5:193.)

The variability in microvascular dysfunction and submaximal pharmacologic vasodilator responses can have a significant impact on assessing the physiologic significance of a coronary stenosis using FFR (or relative perfusion with imaging). In **Fig. 57.23B**, the two dashed lines show idealized relations between absolute flow reserve and FFR (or relative flow reserve from perfusion imaging). Microvascular

dysfunction in the presence of normal coronary arteries (0% stenosis) *attenuates* coronary flow reserve. Conversely, for any given stenosis, the FFR measured in the presence of microvascular disease will be *higher* than when vasodilator responses are normal. Thus, when maximum vasodilation is not achieved, FFR will underestimate the physiologic severity of the stenosis. This probably contributes to at least some of the discordance between FFR and coronary flow reserve observed in clinical studies, underscoring the importance of combining both pressure- and flow-derived indices to assess vasodilator reserve of the total coronary vascular bed. Indeed, the availability of high-fidelity pressure and flow measurements on a single wire has now facilitated the development of approaches to assess the stenosis pressure-flow relation as well as abnormalities in microcirculatory reserve by determining FFR and absolute coronary flow reserve simultaneously. When assessed together, these measurements have the potential to identify circumstances in which mixed abnormalities from a stenosis and abnormal microcirculation contribute to the functional impact of a coronary stenosis.

Coronary Collateral Circulation

After a total coronary occlusion, residual perfusion to the myocardium persists through native coronary collateral channels that open with development of an intercoronary pressure gradient between the source and recipient vessel. In most animal species, the native collateral flow during occlusion is less than 10% of the resting flow levels and is insufficient to maintain tissue viability for longer than 20 minutes. Tremendous individual variability in the function of coronary collaterals is recognized among patients with chronic stenoses. In humans without coronary collaterals, coronary pressure during balloon angioplasty occlusion falls to approximately 10 mm Hg. In other patients, collaterals proliferate to the point where they are sufficient not only to maintain resting perfusion normal, but also to prevent stress-induced ischemia at submaximal cardiac workloads. Ischemia does not develop during PCI balloon occlusion when FFR (based on coronary wedge pressure during occlusion minus venous pressure) is greater than 0.25.[26] A large observational cross-sectional study has demonstrated that patients with elevated distal coronary pressure arising from recruitable collaterals during transient total balloon occlusion (FFR >0.25) have a lower cardiovascular event rate and improved survival[26] (**eFig. 57.4**).



EFIGURE 57.4 Favorable effect of coronary collaterals on prognosis. Patients with collateral flow index (CFI) of 0.25 or less measured during total occlusion of a coronary artery had a worse prognosis as reflected by the combined endpoint of death or myocardial infarction. These data support the concept that preventing ischemia with physiologically functional collaterals protects the heart from irreversible injury and other coronary events. (From Meier P, Gloeker S, Rainer Z, et al. Beneficial effect of recruitable collaterals: a 10-year follow-up study in patients with stable coronary artery disease undergoing quantitative collateral measurements. Circulation 2007;116:975.)

Arteriogenesis and Angiogenesis

Proliferation of coronary collaterals (**see Chapter 20**) occurs in response to repetitive stress-induced ischemia as well as the development of transient interarterial pressure gradients between the source and recipient vessel through a process termed *arteriogenesis*.[27] Resting distal coronary pressure consistently falls as stenosis severity exceeds 70%, and the resultant interarterial pressure gradient increases endothelial shear stress in preexisting collaterals smaller than 200 μm in diameter. This causes progressive enlargement of collaterals through a process dependent on physical forces and growth factors, particularly vascular endothelial growth factor (VEGF), that is mediated by NOS. Thus, patients with impaired NO-mediated vasodilation caused by coronary risk factors may have a limited ability to develop coronary collaterals in response to a chronic coronary stenosis.

Most functional collateral flow arises from arteriogenesis in existing epicardial anastomoses that enlarge into mature vessels, which can reach 1 to 2 mm in diameter.[27] Collateral perfusion also can originate from de novo vessel growth, or *angiogenesis*, which refers to the sprouting of smaller, capillary-like structures from preexisting blood vessels. These vessels may provide nutritive collateral flow when they develop in the border between ischemic and nonischemic regions. Capillary angiogenesis may also occur within the ischemic region and can reduce the intercapillary distance for oxygen exchange. Nevertheless, because capillary resistance is already a small component of microcirculatory resistance, increases in capillary density in the absence of changes in arteriolar resistance will not significantly increase myocardial perfusion.

Great interest is currently directed toward experimental interventions to improve collateral flow (e.g., recombinant growth factors, in vivo gene transfer, adult progenitor cells) (**see Chapter 30**). Although

many interventions have been demonstrated to cause favorable angiogenesis of capillaries and improve myocardial function, few interventions have increased arteriogenesis in mature collaterals, and randomized human clinical trials have been disappointing.[28,29] Part of this limitation may arise from the fact that no intervention has resulted in measurable increases in maximum vasodilated myocardial perfusion or coronary flow reserve indices, the sine qua non of functional collateral formation. Improvements in myocardial function have been used as an endpoint, but such improvement may occur independent of increased perfusion and may arise from mechanisms that alter cardiac myocyte growth and repair rather than angiogenesis.[30]

Regulation of Collateral Resistance

The control of blood flow to collateral-dependent myocardium is governed by a series resistance arising from interarterial collateral anastomoses, largely epicardial, as well as the native downstream microcirculation. Collateral resistance is therefore the major determinant of perfusion, and coronary pressure distal to a chronic occlusion is already near the lower autoregulatory pressure limit. Consequently, subendocardial perfusion is critically dependent on mean aortic pressure and LV preload, with ischemia easily provoked by systemic hypotension, increases in LV end-diastolic pressure, and tachycardia. As with the distal resistance vessels, collaterals constrict when NO synthesis is blocked, which aggravates myocardial ischemia and can be overcome by nitroglycerin.[6] In contrast with the native coronary circulation, experimental studies have demonstrated that coronary collaterals are under tonic dilation from vasodilator prostaglandins, and blocking COX with aspirin exacerbates myocardial ischemia in dogs.[6] The role of prostanoids in human coronary collateral resistance regulation is unknown.

The distal microcirculatory resistance vasculature in collateral-dependent myocardium appears to be regulated by mechanisms similar to those present in the normal circulation, but it is characterized by impaired endothelium-dependent vasodilation compared with normal vessels.[6] Of interest, the remote normally perfused zone in collateralized hearts also shows alterations in coronary resistance vessel control, suggesting that abnormalities are not restricted to the collateral-dependent region. The extent to which these microcirculatory abnormalities alter the normal metabolic and coronary autoregulatory responses in collateral-dependent and remote myocardial regions is unknown.[6]

Metabolic and Functional Consequences of Ischemia

Because oxygen delivery to the heart is closely related to coronary blood flow, a sudden cessation of regional perfusion after a thrombotic coronary occlusion quickly leads to the cessation of aerobic metabolism, depletion of creatine phosphate, and onset of anaerobic glycolysis. This is followed by the accumulation of tissue lactate, a progressive reduction in tissue ATP levels, and an accumulation of catabolites, including those of the adenine nucleotide pool. As ischemia continues, tissue acidosis develops and there is an efflux of potassium into the extracellular space. Subsequently, ATP levels fall below those required to maintain critical membrane function, resulting in the onset of myocyte death.

Irreversible Injury and Myocyte Death

The temporal evolution and extent of irreversible tissue injury after coronary occlusion are variable and depend on transmural location, residual coronary flow, and the hemodynamic determinants of oxygen

consumption. Irreversible myocardial injury begins after 20 minutes of coronary occlusion in the absence of significant collaterals (see Classic References, Kloner and Jennings, 2001a). Irreversible injury starts in the subendocardium and progresses as a wavefront over time, from the subendocardial layers to the subepicardial layers (**Fig. 57.24**). This reflects the higher oxygen consumption in the subendocardium and the redistribution of collateral flow to the outer layers of the heart by the compressive determinants of flow at reduced coronary pressure. In experimental infarction, the entire subendocardium is irreversibly injured within 1 hour of occlusion, and the transmural progression of infarction is largely completed within 4 to 6 hours after coronary occlusion. Factors that increase myocardial oxygen consumption (e.g., tachycardia) or reduce oxygen delivery (e.g., anemia, arterial hypotension) accelerate the progression of irreversible injury. By contrast, repetitive reversible ischemia or angina occurring before an occlusion can reduce irreversible injury through preconditioning.[31]

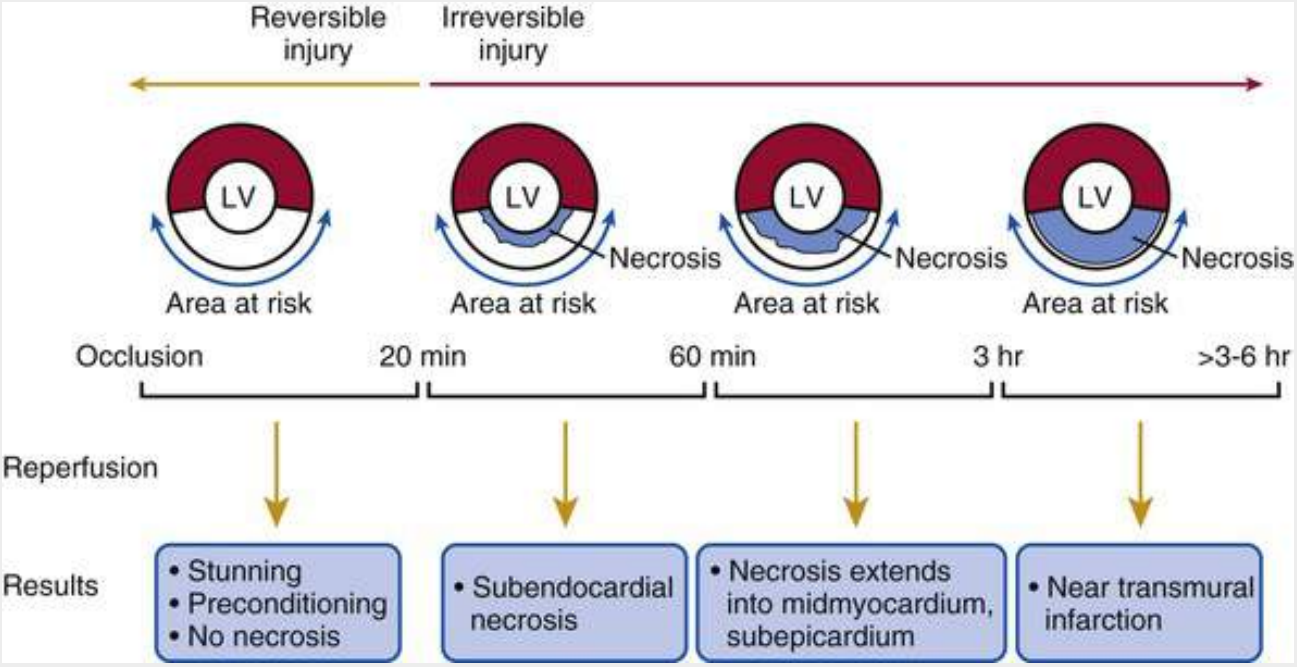


FIGURE 57.24 Wavefront of necrosis in infarction. Total coronary artery occlusions shorter than 20 minutes do not cause irreversible injury but can cause myocardial stunning and also precondition the heart and protect it against recurrent ischemic injury. Irreversible injury begins after 20 minutes and progresses as a wavefront from endocardium to epicardium. After 60 minutes, the inner third of the left ventricle (LV) wall is irreversibly injured. After 3 hours, only a subepicardial rim of tissue remains, with the transmural extent of infarction completed between 3 and 6 hours after occlusion. The most important factor delaying the progression of irreversible injury is the magnitude of collateral flow, which is directed primarily to the outer layers of the heart. (Modified from Kloner RA, Jennings RB. Consequences of brief ischemia: Stunning, preconditioning, and their clinical implications: Part 1. Circulation 2001;104:2981.)

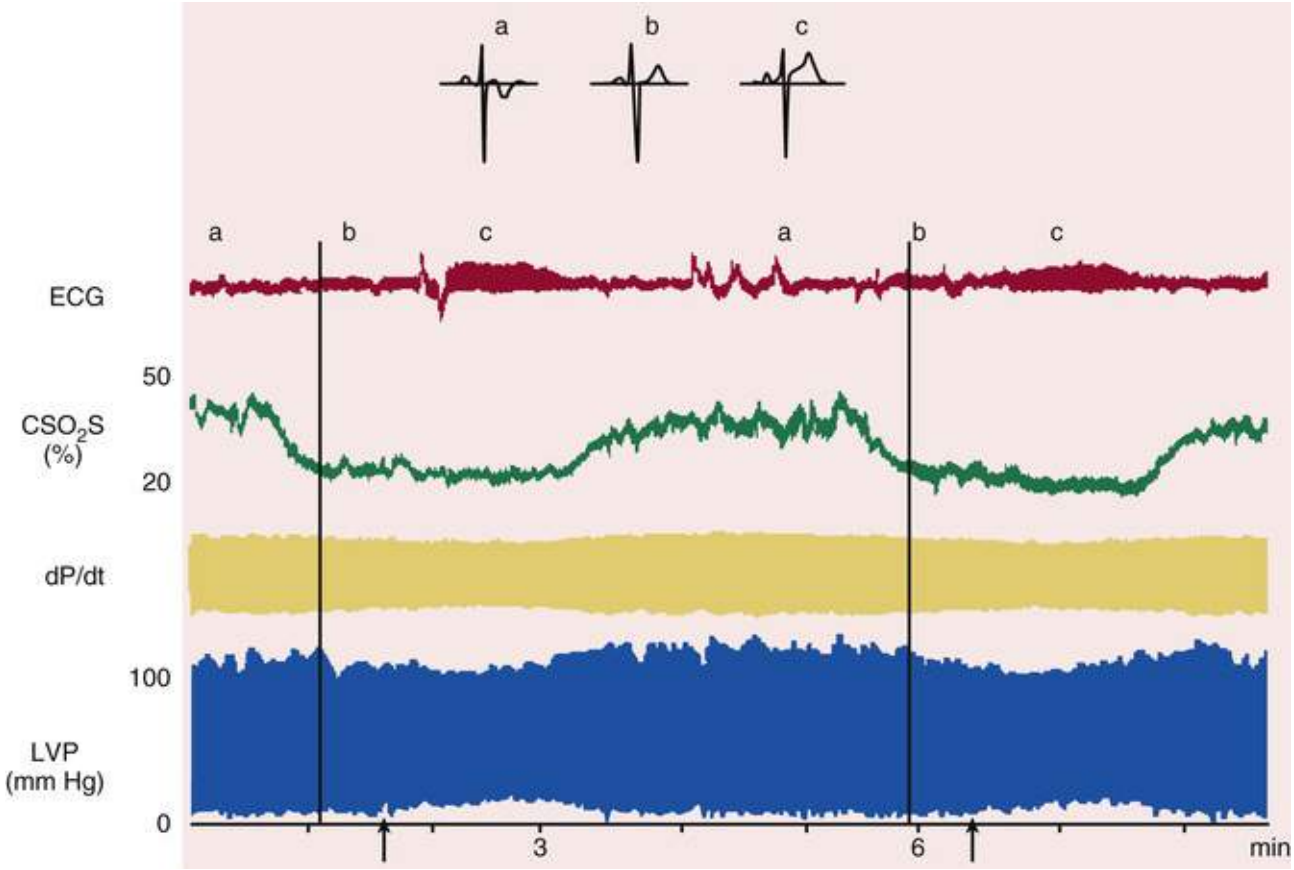
The magnitude of residual coronary flow through collaterals or through a subtotal coronary occlusion is the most important determinant of the actual time course of irreversible injury in patients with chronic CAD. The relation between infarct size and the area at risk of ischemia during a total occlusion is inversely related to collateral flow and likely explains the important role of collateral vessel function in determining prognosis.[26] When subendocardial collateral flow is more than approximately 30% of resting flow values, it prevents infarction after periods of ischemia lasting longer than 1 hour. More moderate subendocardial ischemia from a subtotal occlusion (e.g., flow reduced by no more than 50%) can persist for at least 5 hours without producing significant irreversible injury.[32] This explains why signs and symptoms of ischemia can be present for long periods without producing significant myocardial necrosis.

It also explains the clinical observation that late coronary reperfusion with ongoing ischemia can salvage myocardium beyond the 6-hour time limit predicted from experimental models of MI.[33]

Cell death arises from multiple mechanisms in MI[34] (**see Chapter 58**). Reperfusion immediately causes myocyte necrosis and sarcolemmal disruption, with the leakage of cell contents into the extracellular space. The injury may be further amplified by the reentry of leukocytes into the area of injury. At later time points, myocytes initially salvaged can undergo programmed cell death or apoptosis, which can contribute to further delayed myocardial injury. *Apoptosis* is a coordinated involution of myocytes that circumvents the inflammation associated with necrotic cell death. Because apoptosis is an energy-dependent process, cells can be forced to switch to a necrotic pathway if energy levels are depleted below critical levels. In the setting of more chronic injury, autophagy can contribute to the mechanisms of myocyte death. Because of the temporal complexity of irreversible injury, the relative importance of each mechanism in MI continues to be controversial. Nevertheless, modulating mechanisms contributing to late cell death could prevent deleterious LV remodeling.

Reversible Ischemia and Perfusion-Contraction Matching

Reversible ischemia is considerably more common than irreversible injury. *Supply-induced ischemia* can arise from transient coronary occlusion resulting from coronary vasospasm or transient thrombosis in a critically stenosed coronary artery, producing transmural ischemia similar to that present at the onset of MI. *Demand-induced ischemia* arises from an inability to increase flow in response to increases in myocardial oxygen consumption in which ischemia predominantly affects the subendocardium (**see Chapter 61**). These have fundamentally different effects on myocardial diastolic relaxation, with supply-induced ischemia increasing LV compliance and demand-induced ischemia reducing it. There is a fairly stereotypic sequence of physiologic changes that develop during an episode of spontaneous transmural ischemia (**eFig. 57.5**). Coronary occlusion results in an immediate fall in coronary venous oxygen saturation, with a reduction in ATP production. This causes a decline in regional contraction within several beats, reaching dyskinesis within 1 minute. As regional contraction ceases, concomitant changes include a reduction in global LV contractility (dP/dt), a progressive rise in LV end-diastolic pressure, and a fall in systolic pressure. The magnitude of the systemic hemodynamic changes varies with the severity of ischemia as well as the amount of the left ventricle subjected to ischemia. Significant electrocardiographic ST-segment changes develop within 2 minutes as efflux of potassium into the extracellular space reaches a critical level. Symptoms of chest pain are variable and usually are the last event in the evolution of ischemia. On restoring perfusion, the sequence is reversed, with resolution of chest pain occurring before hemodynamic changes resolve, but regional contraction can remain depressed, reflecting the development of stunned myocardium. A similar temporal sequence of events occurs during exercise-induced ischemia, although the time frame of evolution can be more protracted because ischemia occurs primarily in the subendocardium. Because of the temporal delay in the development of angina and other factors, many episodes of ST-segment depression are symptomatically silent. It is also likely that very brief episodes of ischemia, as reflected by more sensitive indices, such as reduced regional contraction or elevations in end-diastolic pressure, can be electrocardiographically silent.



EFIGURE 57.5 Physiologic changes during two episodes of spontaneous asymptomatic ischemia in a patient with an acute coronary syndrome. High-speed electrocardiographic tracings depict the baseline ECG (a), pseudonormalization of T waves in early ischemia (b), and ST elevation with late ischemia (c). A primary reduction in coronary flow is depicted by the sudden fall in coronary venous oxygen saturation (CSO_2S). Shortly thereafter, left ventricular (LV) dP/dt falls, reflecting regional contractile dysfunction (*solid vertical lines*). Within 1 minute, LV end-diastolic pressure begins to rise (*arrows*) and is associated with a reduction in systolic pressure. Significant ST elevation begins after the rise in LV end-diastolic pressure (c). On spontaneous resolution of ischemia (rise in CSO_2S), the changes resolve. Each episode lasted 2 minutes and was not associated with chest pain. LVP, Left ventricular pressure. (Modified from Chierchia S, Brunelli C, Simonetti I, et al. Sequence of events in angina at rest: primary reduction in coronary flow. Circulation 1980;61:759.)

Acute Perfusion-Contraction Matching During Subendocardial Ischemia

When coronary pressure distal to a stenosis falls below the lower limit of autoregulation, flow reserve is exhausted, resulting in the onset of subendocardial ischemia. In this case, reductions in subendocardial flow are closely related to reductions in regional contractile function of the heart, as measured by sensitive approaches such as regional wall thickening.[32] An approximately linear relation has been shown between relative reductions in subendocardial blood flow and relative reductions in regional wall thickening at rest, during tachycardia, and during exercise-induced dysfunction distal to a critical stenosis[32] (**Fig. 57.25**). This forms the basis for using regional myocardial function as an index of the severity of subendocardial ischemia during stress imaging (**see Chapter 14**).

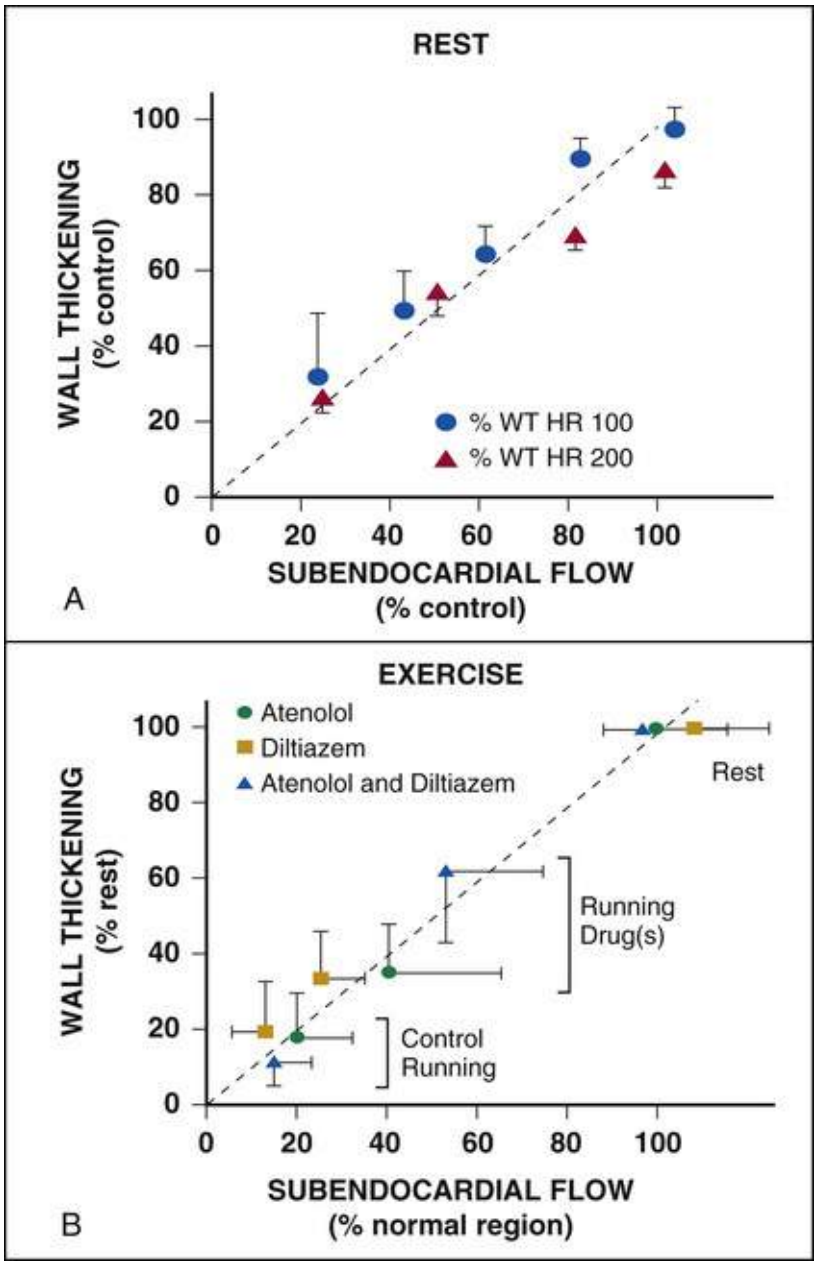


FIGURE 57.25 Perfusion-contraction matching during acute ischemia. Relative reductions in function (regional wall thickening) are proportional to the relative reduction in subendocardial flow measured with microspheres in conscious dogs. This relation is maintained over a wide range of heart rates during autoregulation **(A)** as well as during exercise with a fixed coronary stenosis **(B)**. In the latter case, medical interventions that ameliorate ischemia improve both subendocardial flow and wall thickening (WT) during exercise. HR, Heart rate. (**A,** Modified from Canty JM Jr. Coronary pressure-function and steady-state pressure-flow relations during autoregulation in the unanesthetized dog. Circ Res 1988;63:821; and Canty JM Jr, Giglia J, Kandath D. Effect of tachycardia on regional function and transmural myocardial perfusion during graded coronary pressure reduction in conscious dogs. Circulation 1990;82:1815; **B,** modified from Matsuzaki M et al. Effect of the combination of diltiazem and atenolol on exercise-induced regional myocardial ischemia in conscious dogs. Circulation 1985;72:233.)

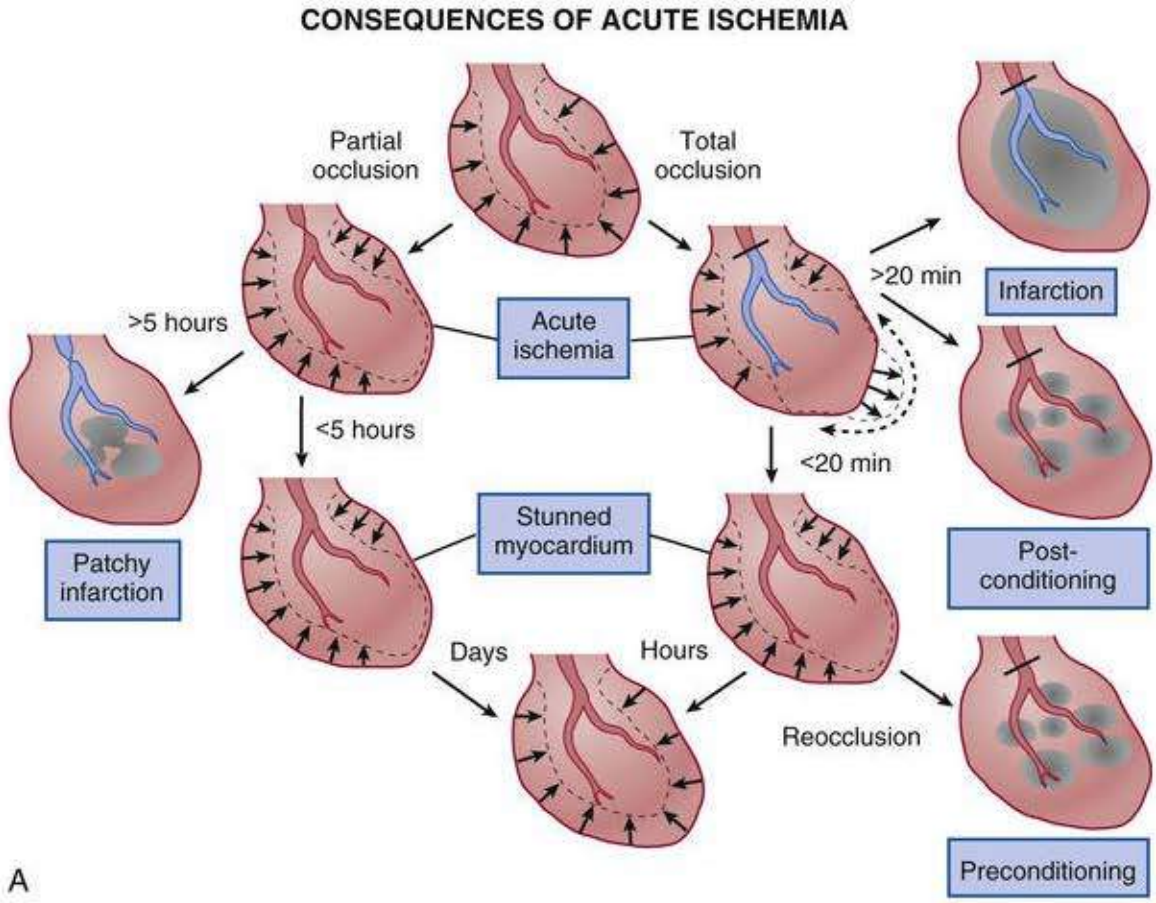
Short-Term Hibernation

In steady-state ischemia, the close matching between perfusion and contraction leads to a reduced regional oxygen consumption and energy utilization, a phenomenon termed *short-term hibernation*.[32] This reestablishes a balance between supply and demand, as reflected by regeneration of creatine phosphate and ATP with the resolution of lactate production, despite persistent hypoperfusion. Short-term hibernation is an extremely tenuous state, and small increases in the determinants of myocardial oxygen demand precipitate further ischemia and a rapid deterioration in function and metabolism (see Classic Reference, Heusch). Thus the ability of short-term hibernation to prevent necrosis is limited by the

severity and duration of ischemia, with irreversible injury developing frequently after periods longer than 12 to 24 hours.[35]

Functional Consequences of Reversible Ischemia

Various late consequences of ischemia have been documented after normal myocardial perfusion is reestablished. These reflect both acute and delayed effects on regional function, as well as protection of the heart from subsequent ischemic episodes. In the most chronic state, they result in hibernating myocardium, characterized by chronic contractile dysfunction and regional cellular mechanisms that downregulate contractile and metabolic function of the heart so as to protect it from irreversible injury. **Fig. 57.26** summarizes the complex interplay among these entities. In clinical practice, it is difficult to separate all the various mechanisms involved in contributing to ischemia-induced viable dysfunctional myocardium, because they all may coexist to some extent in the same heart. They can be separated experimentally, however, and the important features and mechanisms from basic studies are summarized next.



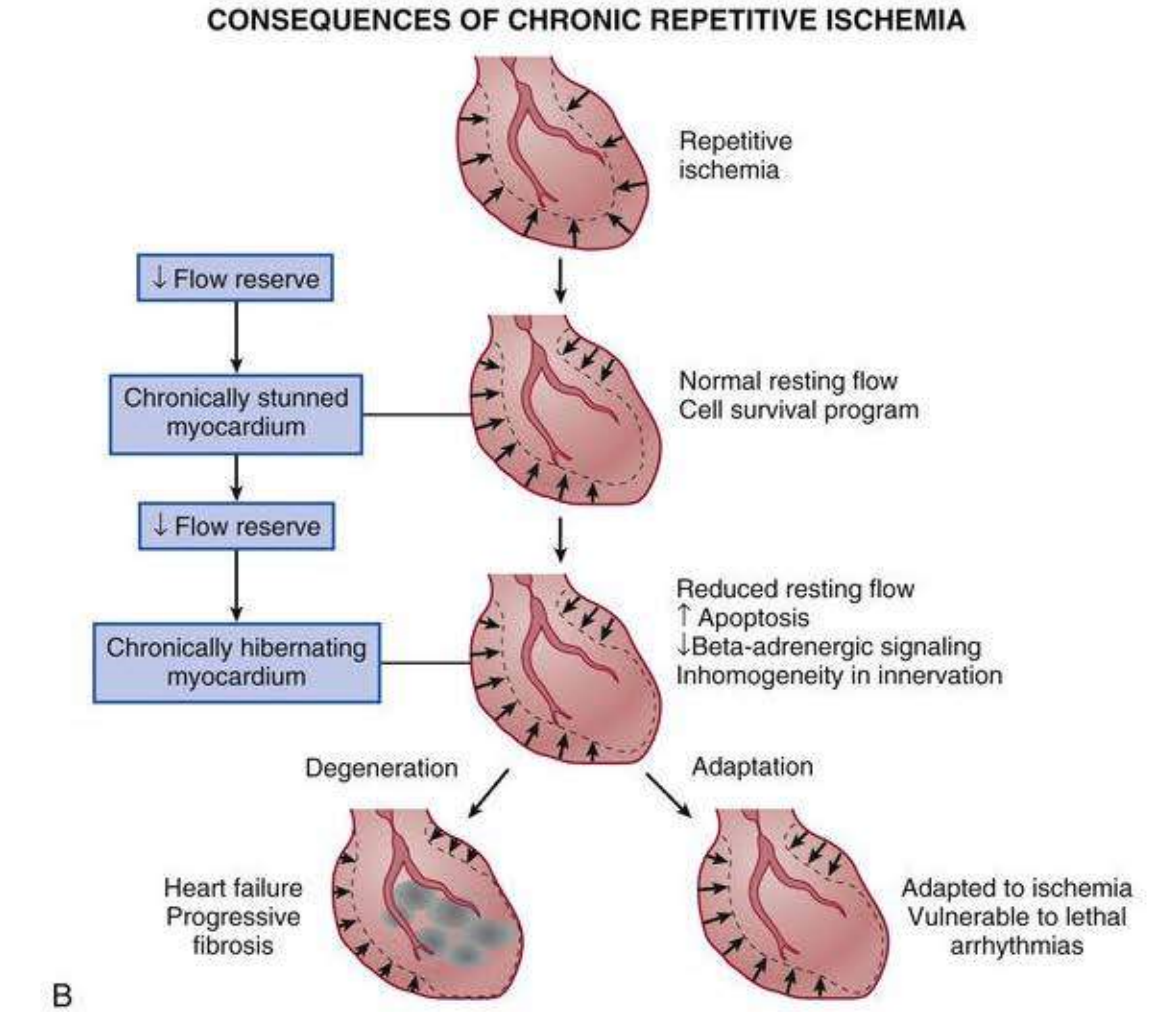
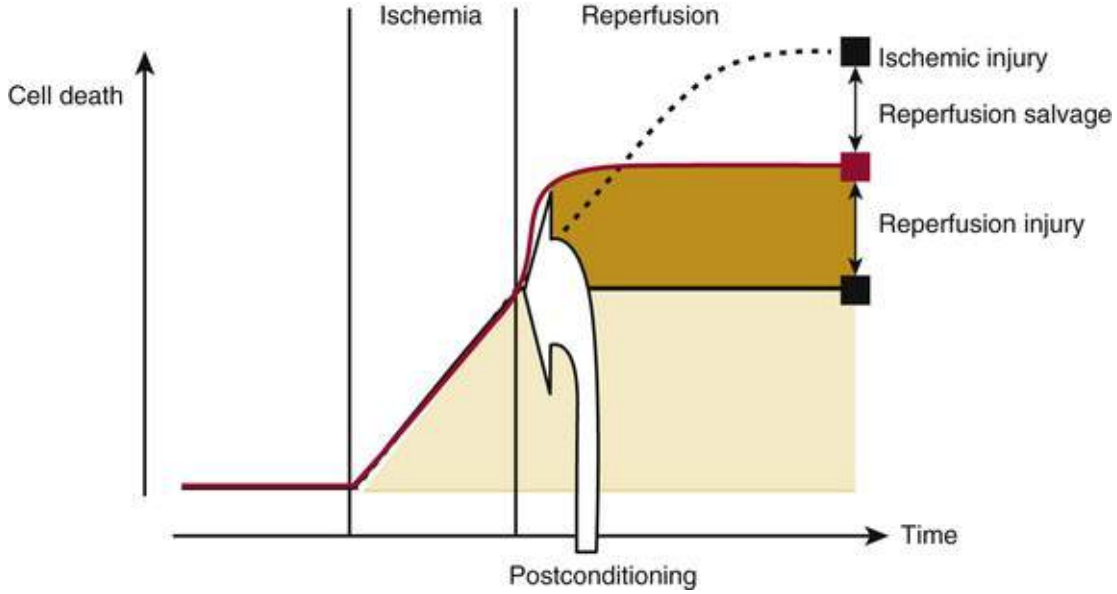


FIGURE 57.26 Effects of ischemia on left ventricular function and irreversible injury. The ventriculograms illustrate contractile dysfunction (*dashed lines* and *arrows*). **A,** Consequences of acute ischemia. A brief total occlusion (*right*) or a prolonged partial occlusion (caused by an acute high-grade stenosis, *left*) leads to acute contractile dysfunction proportional to the reduction in blood flow. Irreversible injury begins after 20

minutes after a total occlusion but is delayed for up to 5 hours after a partial occlusion (or with significant collaterals) caused by short-term hibernation. When reperfusion is established before the onset of irreversible injury, stunned myocardium develops, and the time required for recovery of function is proportional to the duration and severity of ischemia. With prolonged ischemia, stunning in viable myocardium coexists with subendocardial infarction and accounts for a variable amount of irreversible dysfunction. Experimental infarct size can be reduced by cardioprotective mechanisms. Intermittent occlusion at the time of reperfusion (postconditioning) can limit infarct size. Likewise, brief episodes of ischemia preceding prolonged ischemia elicit protection against infarction from prolonged ischemia (preconditioning). **B,** Effects of chronic repetitive ischemia on function distal to a stenosis. As stenosis severity increases, coronary flow reserve decreases and the frequency of reversible ischemia increases. Reversible repetitive ischemia initially leads to chronic preconditioning against infarction and stunning (*not shown*). Subsequently, there is a gradual progression from contractile dysfunction with normal resting flow (chronically stunned myocardium) to contractile dysfunction with depressed resting flow (hibernating myocardium). This transition is related to the physiologic significance of a coronary stenosis and can occur in a time period as short as 1 week or develop chronically in the absence of severe angina. The cellular response during the progression to chronic hibernating myocardium is variable, with some patients exhibiting successful adaptation with little cell death and fibrosis and others developing degenerative changes difficult to distinguish from subendocardial infarction.

Myocardial Preconditioning and Postconditioning

Brief reversible ischemia preceding a prolonged coronary occlusion reduces myocyte necrosis, a phenomenon termed *acute preconditioning*.[31] Because acute MI frequently is preceded by angina, preconditioning is an endogenous mechanism that can delay the evolution of irreversible myocardial injury. Acute preconditioning can be induced pharmacologically using adenosine A_1 receptor stimulation as well as various pharmacologic agonists that stimulate protein kinase C or open mitochondrial K_{ATP} channels. It has been demonstrated in humans during angioplasty with reduced subjective and objective ischemia during successive coronary occlusions as an endpoint. Preconditioning also develops on a chronic basis (*delayed preconditioning*) and, once induced, persists for up to 4 days (see Classic References, Kloner and Jennings, 2001b). It reduces MI size and protects the heart from ischemia-induced stunning. The mechanisms of chronic preconditioning involve protein synthesis, with upregulation of the inducible form of NOS (iNOS), COX-2, and opening of the mitochondrial K_{ATP} channel. A final protective mechanism, *myocardial postconditioning*,[36] refers to the ability to engage cardiac protection by producing intermittent ischemia or administering pharmacologic agonists at reperfusion. It has the great potential to affect irreversible injury because it can be induced after myocardial ischemia is established rather than requiring pretreatment[37] (**eFig. 57.6**). Protection occurs principally through activation of reperfusion injury salvage kinase pathways, thereby limiting opening of the mitochondrial permeability transition pore.[38] A number of small clinical trials, using mechanical or pharmacologic postconditioning, have shown promise.[38-40] However, the first large randomized controlled clinical trial failed to demonstrate a significant reduction by postconditioning in combined all-cause mortality and hospitalization for heart failure.[41] Therefore, the role for these novel approaches as an adjunctive therapy in the setting of reperfusion treatment of acute MI remains to be proven.[40]



EFIGURE 57.6 The concept of lethal reperfusion injury. During ischemia, irreversible cell injury leading to cell death occurs within the ischemic risk zone in a time-dependent manner. In the absence of reperfusion, ischemic injury will progressively kill more and more cells (*dashed line*). Reperfusion stops the process of ischemic cell death but in its early stages imposes injury that results in further cell death. This is beyond the damage that would be produced by ischemia alone and is termed *lethal reperfusion injury*. The net result is that the reperfused tissue still sustains less cell death than would occur in ischemic tissue without reperfusion. Targeting cell death due to reperfusion injury has the potential to maximize cell salvage. Postconditioning applied at the onset of reperfusion limits the extent of reperfusion injury and can potentially maximize myocardial salvage. (Modified from Ovize M, Baxter GF, Di Lisa F, et al. Postconditioning and protection from reperfusion injury: where do we stand? Position paper from the Working Group of Cellular Biology of the Heart of the European Society of Cardiology. Cardiovasc Res 2010;87:406.)

Stunned Myocardium.

Myocardial function normalizes rapidly after single episodes of ischemia lasting less than 2 minutes. As ischemia increases in duration and severity, a temporal delay in the recovery of function occurs despite that blood flow has been restored. Regional myocardial function remains depressed for up to 6 hours after resolution of ischemia following a 15-minute occlusion in the absence of tissue necrosis, a phenomenon called *myocardial stunning* (**Fig. 57.27**). A defining feature of isolated myocardial stunning is that function remains depressed while resting myocardial perfusion is normal.[32] Thus there is a dissociation of the usual close relation between subendocardial flow and function. Stunned myocardium also develops after demand-induced ischemia. For example, exercise-induced ischemia can result in depressed regional function distal to a coronary stenosis for hours after perfusion is restored, and repetitive ischemia can lead to cumulative stunning. Prolonged sublethal ischemia, as seen in short-term hibernation, leads to stunning on restoration of perfusion that may take up to 1 week to resolve in the absence of necrosis. This may be an important cause of reversibly dysfunctional myocardium in the setting of an acute reduction in flow, as in an acute coronary syndrome. Stunned myocardium is also responsible for postoperative pump dysfunction after cardiopulmonary bypass. Further, areas of stunned myocardium can coexist with irreversibly injured myocardium, contributing to time-dependent improvements in function after MI.

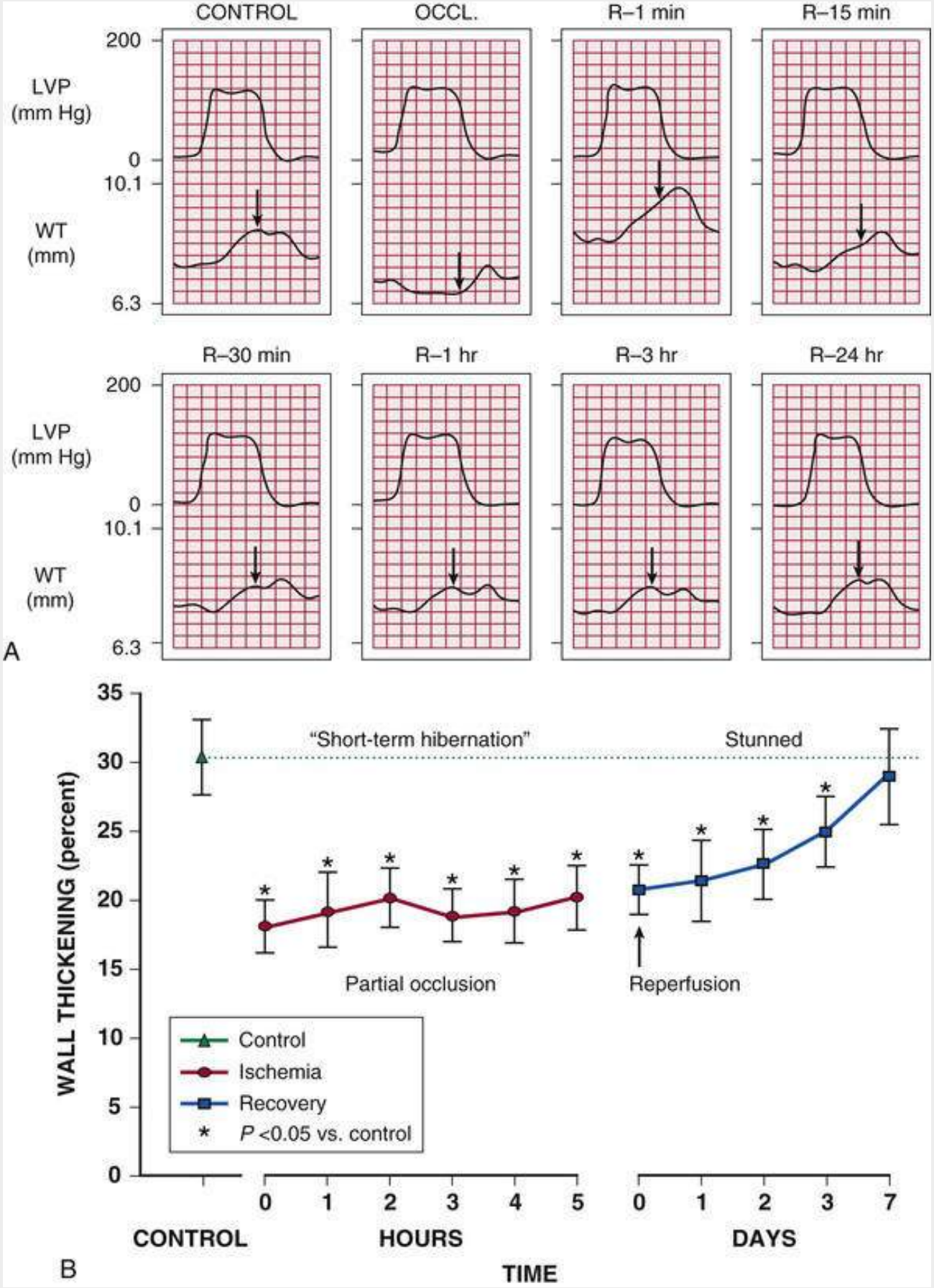


FIGURE 57.27 Stunned myocardium. **A,** Myocardial stunning after a brief total occlusion (OCCL.). Wall thickening (WT) measured by ultrasonic crystals is dyskinetic, with systolic thinning during occlusion. After reperfusion (R), function is completely normal after 24 hours. **B,** Myocardial stunning after a prolonged partial occlusion. During acute ischemia (*red circles*), there is short-term hibernation, reflecting an acute match between reduced flow, wall thickening, and metabolism. With reperfusion (*blue squares*), WT remains depressed and gradually returns to normal after 1 week. LVP, Left ventricular pressure. (**A,** Modified from Heyndrickx GR et al. Depression of regional blood flow and wall thickening after brief coronary occlusions. Am J Physiol 1978;234:H653; **B,** modified from Matsuzaki M et al. Sustained regional dysfunction produced by prolonged coronary stenosis:

gradual recovery after reperfusion. Circulation 1983;68:170.)

Acutely stunned myocardium is clinically important to recognize because contractile function normalizes during stimulation with various inotropic agents, including beta-adrenergic agonists. In contrast with other dysfunctional states, function will spontaneously normalize within 1 week, provided that there is no recurrent ischemia. If repetitive episodes of reversible ischemia develop before function normalizes, they can cause a state of persistent dysfunction or chronic stunning. The cellular mechanism of stunning probably involves free radical–mediated myocardial injury and reduced myofilament calcium sensitivity (see Classic References, Bolli and Marban).

Chronic Hibernating Myocardium

Viable dysfunctional myocardium is defined as any myocardial region in which contractile function improves after coronary revascularization.[37] This broad definition of reversible dyssynergy includes three distinct categories with fairly diverse pathophysiologic mechanisms (**Table 57.1**). Complete normalization of function is the rule after acute ischemia but the exception in chronically dysfunctional myocardium. Brief occlusions or prolonged moderate ischemia (short-term hibernation) will result in postischemic stunning in the absence of infarction, with complete functional recovery occurring rapidly (within 1 week after reperfusion). The time course of improvement is somewhat dependent on the duration and severity of the ischemic episode. Reversible dyssynergy with delayed functional improvement can also arise from structural remodeling of the heart that is independent of ischemia or a coronary stenosis (e.g., remote myocardial remodeling in heart failure, reduced infarct volume over initial weeks after coronary reperfusion). The latter conditions can be readily identified when the clinical setting, coronary anatomy, and assessment of myocardial perfusion are taken into account. Many clinical studies have evaluated the presence of contractile reserve during dobutamine administration as a predictor of functional recovery. Although this identifies the likelihood of functional recovery (**see Chapter 14**), it cannot distinguish the diverse pathophysiologic states underlying reversible dyssynergy. Understanding the cause may be important to the extent that it affects the time course and magnitude of functional recovery after revascularization in patients undergoing revascularization to treat ischemic heart failure.[33]

TABLE 57.1

Viable Dysfunctional Myocardium: Patterns of Contractile Reserve, Resting Perfusion, and Temporal Recovery of Function after Revascularization

PARAMETER	CONTRACTILE RESERVE	RESTING FLOW	EXTENT OF FUNCTIONAL RECOVERY	TIME COURSE OF RECOVERY
Transient Reversible Ischemia				
Postischemic stunning	Present	Normal	Normalizes	<24 hr
Short-term hibernation	Present	Normal	Normalizes	<7 days
Chronic Repetitive Ischemia				
Chronic stunning	Present	Normal	Improves	Days to weeks
Chronic hibernating myocardium	Variable	Reduced	Improves	Up to 12 mo
Structural Remodeling				
Subendocardial infarction	Variable	Reduced	Variable	Weeks
Remodeled, tethered myocardium	Present	Normal	Improves	Months

Chronic segmental dysfunction arising from repetitive episodes of ischemia (frequently clinically silent) is common and present in at least one coronary distribution area in more than 60% of patients with

ischemic cardiomyopathy (**Fig. 57.28**). When resting flow relative to a remote region is normal in dysfunctional myocardium distal to a stenosis, the region is *chronically stunned*. In contrast, when relative resting flow is reduced in the absence of symptoms or signs of ischemia, *hibernating myocardium* is present. It is now clear that both entities can exist in patients and represent extremes in the spectrum of adaptive and maladaptive responses to chronic reversible ischemia. Viability studies are primarily required to distinguish infarction from hibernating myocardium because the myocardium is always viable when the resting flow is normal.[32,35]

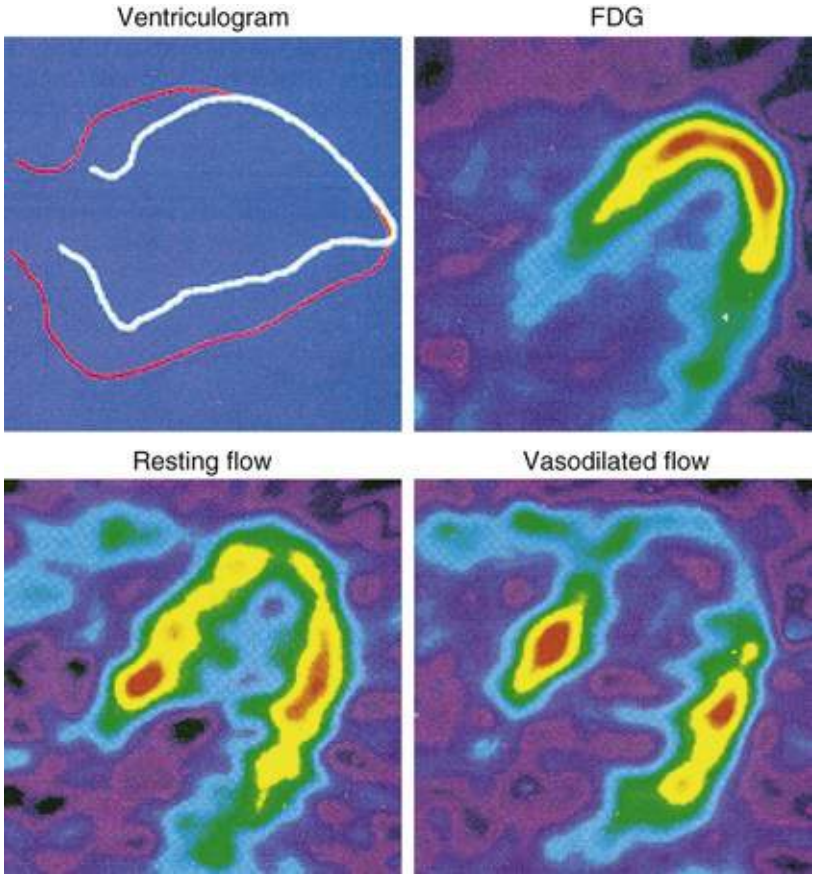
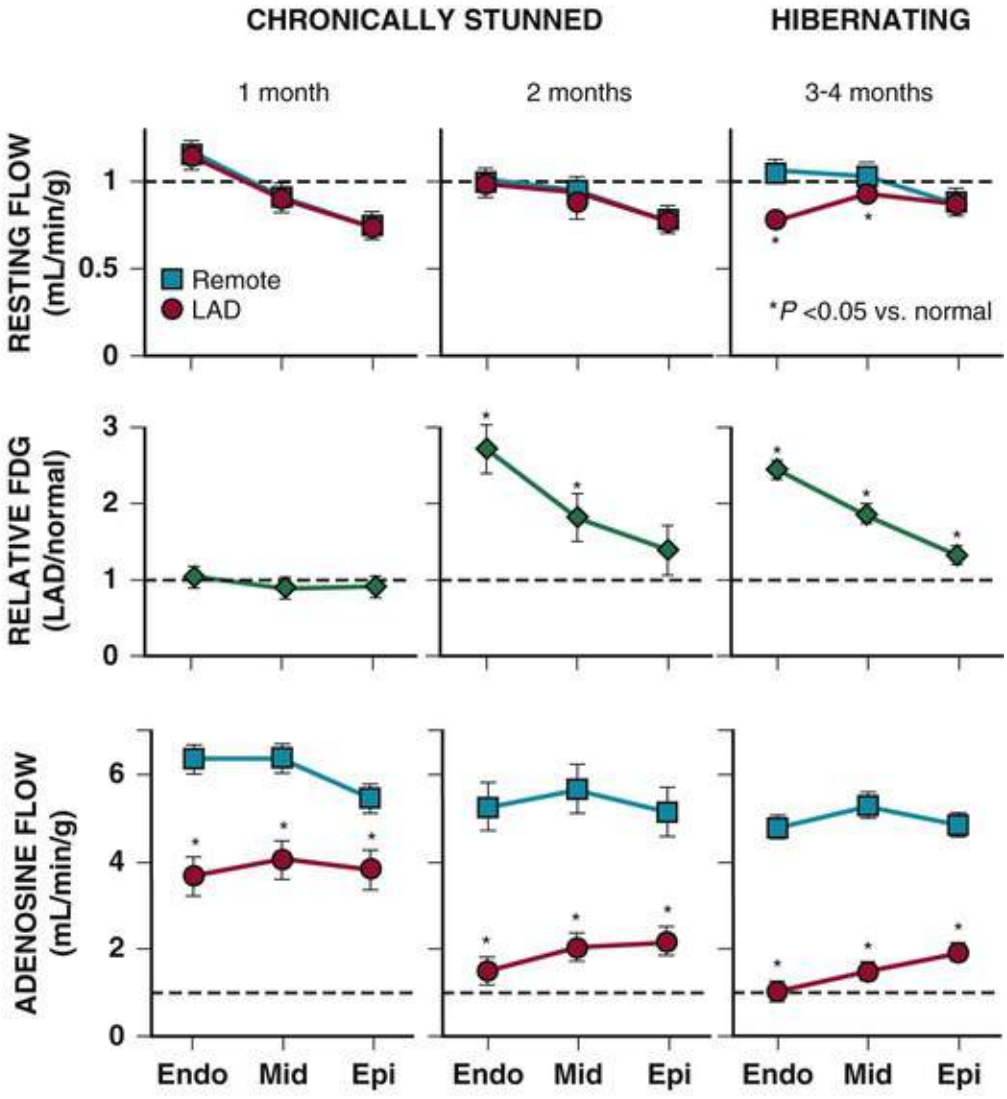


FIGURE 57.28 Hibernating myocardium in humans with a chronic left anterior descending artery (LAD) occlusion and collateral-dependent myocardium. The right anterior oblique (RAO) tracing of the left ventriculogram shows anterior akinesis (*upper left*). Transaxial PET scans illustrate $^{13}NH_3$ flow measurements at rest (*lower left*) and after pharmacologic vasodilation with dipyridamole (*lower right*). Quantitative perfusion measurements showed LAD flow to be critically impaired. Viability (after an oral glucose load) is identified by increased ^{18}F-2-fluoro-2-deoxyglucose (FDG) uptake in the anterior wall (*upper right*). (Modified from Vanoverschelde JL, Wijns W, Depre C, et al. Mechanisms of chronic regional postischemic dysfunction in humans: new insights from the study of noninfarcted collateral-dependent myocardium. Circulation 1993;87:1513.)

It was originally thought that hibernating myocardium arose from a primary reduction in flow similar to experimental models of prolonged moderate ischemia and short-term hibernation. Whereas this is a plausible mechanism for the development of hibernating myocardium in association with an acute coronary syndrome, experimental studies have subsequently demonstrated that delayed subendocardial infarction is the rule rather than the exception when moderate flow reductions are maintained for more than 24 hours.[32] Many patients with hibernating myocardium present with LV dysfunction rather than symptomatic ischemia. Serial studies in animals (see Classic References, Fallavollita) have now demonstrated that the reductions in relative resting flow are a consequence rather than a cause of the contractile dysfunction.[32] This paradigm, relevant to chronic CAD, was proposed after experimental

studies with a slowly progressive left anterior descending artery (LAD) stenosis demonstrated that dysfunction with normal resting flow, consistent with chronic stunning, precedes the development of hibernating myocardium after 3 months[32,35] (**Fig. 57.29**). The progression from chronically stunned myocardium (with normal resting flow) to hibernating myocardium (with reduced flow) is related to the functional significance of the chronic stenosis supplying the LAD region and is probably a reflection of its propensity to produce repetitive supply- or demand-induced ischemia. This progression can be seen as soon as 1 week after placement of a critical stenosis that exhausts coronary flow reserve.[35] As regional dysfunction progresses from chronically stunned to hibernating myocardium, the myocyte takes on regional characteristics similar to those from an explanted heart with advanced failure. Normally perfused remote-zone cardiac myocytes can be normal or can take on structural alterations similar to the dysfunctional region. Some of the major cellular responses are summarized here.



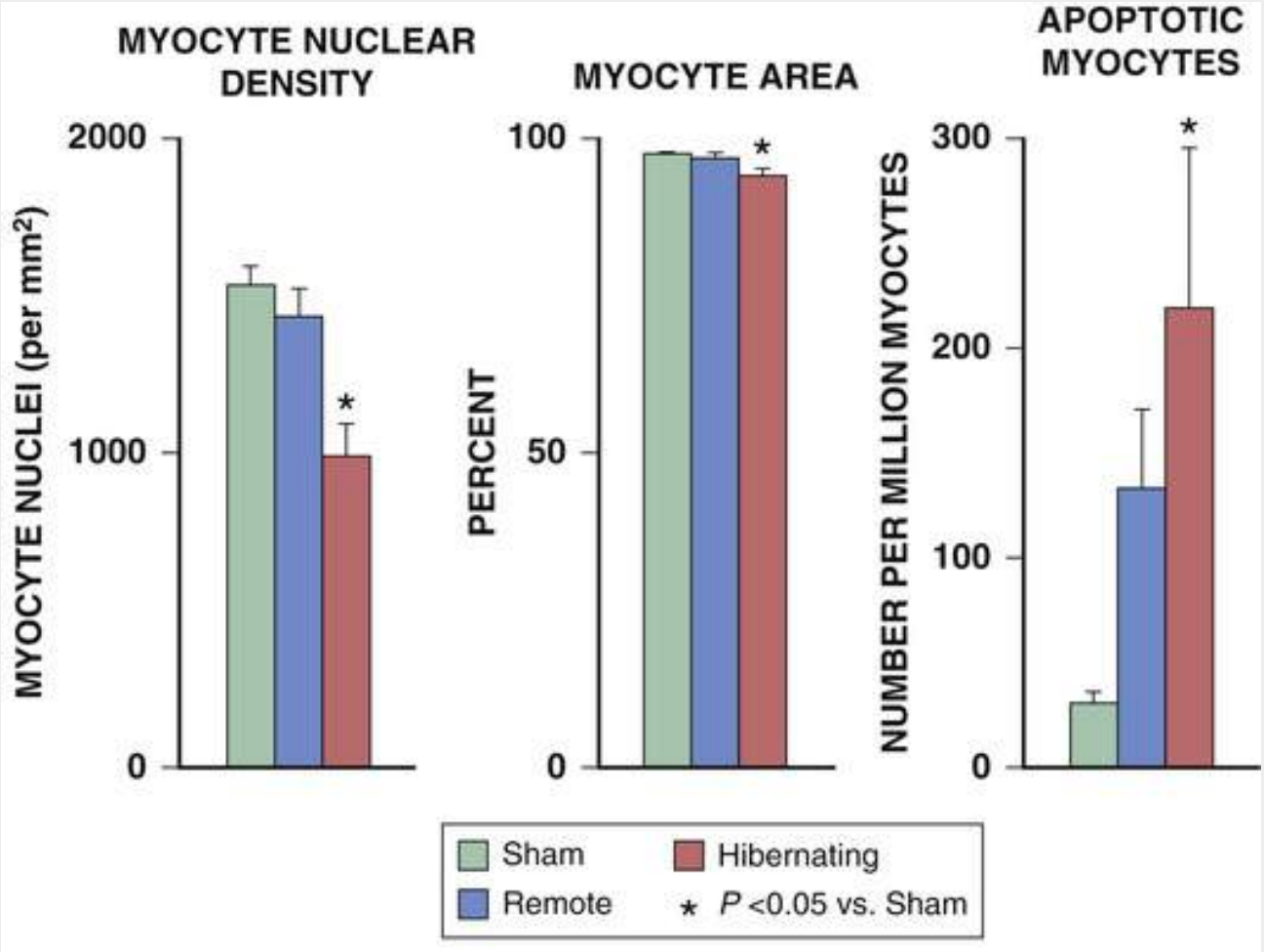
STENOSIS (%)	74 ± 5%	83 ± 6%	97 ± 2% †
ANTERIOR WALL MOTION	2.1 ± 0.1	1.5 ± 0.3	0.7 ± 0.2 †

† *P* <0.05 vs. 1 month

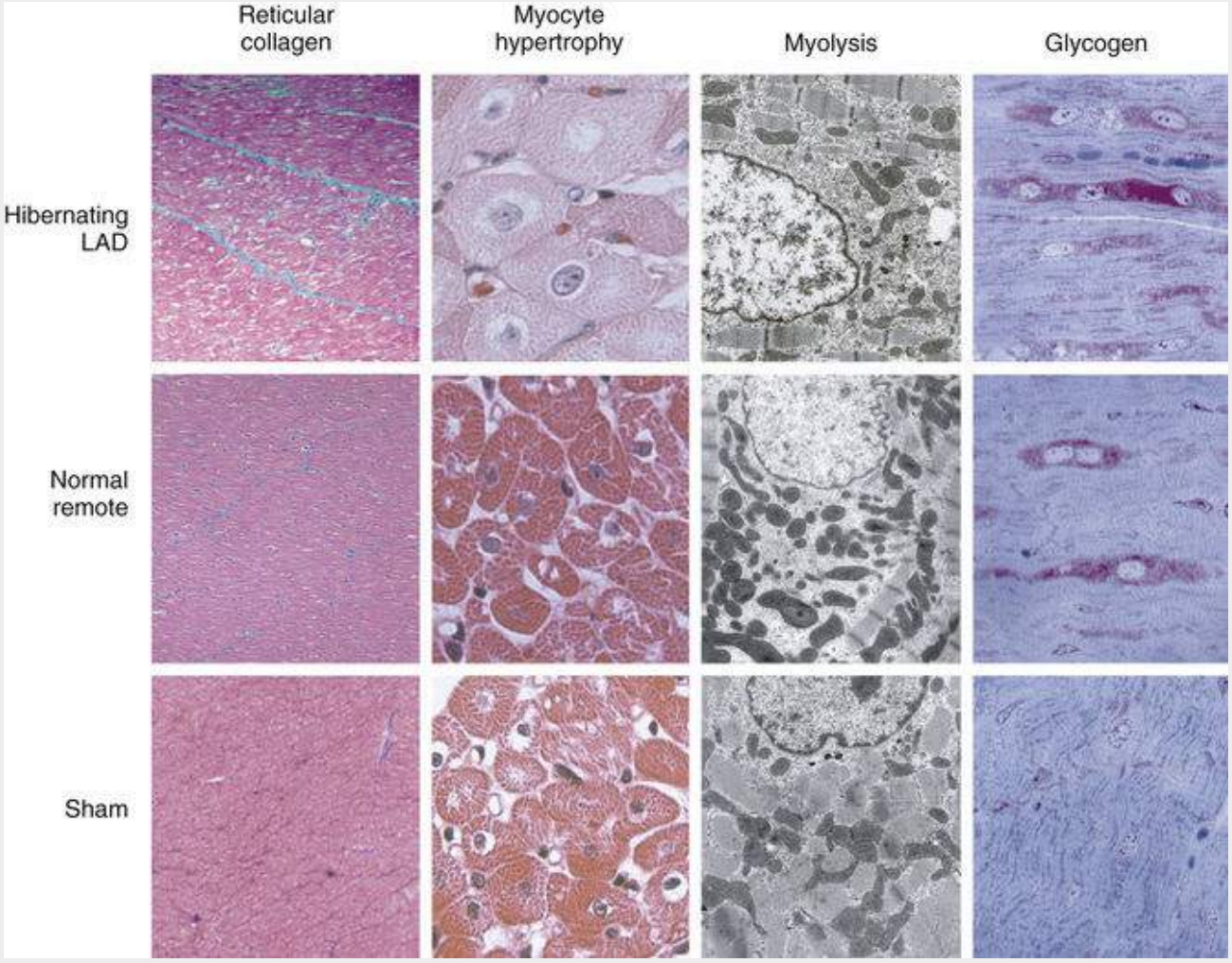
FIGURE 57.29 Progression from chronically stunned to hibernating myocardium as stenosis severity increases in swine with viable dysfunctional myocardium from a chronic left anterior descending artery (LAD) stenosis. Transmural flow measurements (microspheres) at rest and adenosine vasodilation are shown, along with regional ^{18}F-2-fluoro-2-deoxyglucose (FDG) uptake (under fasting conditions). Shown below are the angiographic stenosis severity and anterior wall motion score—3, normal; 2, mild hypokinesis; 1, severe hypokinesis; 0, akinesis. As stenosis severity increases over time, there is a reduction in vasodilated flow (adenosine) to the LAD region. Initially, there is anterior hypokinesis, with normal resting flow consistent with chronically stunned myocardium. After 3 months, the stenosis progresses to occlusion with collateral-dependent myocardium. Subendocardial flow is critically reduced and there is a reduction in resting flow to the inner two thirds of the LAD myocardium. At this time, hibernating myocardium is present, and there is no evidence of infarction. The temporal progression of abnormalities demonstrates that chronic stunning precedes the development of hibernating myocardium. In contrast with short-term hibernation resulting from acute ischemia, the reduction in resting flow is a consequence, rather than a cause, of the contractile dysfunction. Endo, Endocardium; Epi, epicardium. (Modified from Fallavollita JA, Canty JM Jr: Differential ^{18}F-2-deoxyglucose uptake in viable dysfunctional myocardium with normal resting perfusion: Evidence for chronic stunning in pigs. Circulation 99:2798, 1999.)

Apoptosis, Myocyte Loss, and Myofibrillar Loss.

The frequency of focal myocyte death from apoptosis varies during the development of viable dysfunctional myocardium and thus is probably responsible for the variability in the frequency of apoptosis when analyzing biopsies from patients.[35] Experimentally, apoptosis is particularly prominent during the transition from chronically stunned to hibernating myocardium, at which time there is a loss of approximately 30% of the regional myocytes (**eFigs. 57.7 and 57.8**). The myocyte loss results in compensatory regional myocyte hypertrophy to maintain approximately normal wall thickness. Light microscopic and ultrastructural characteristics of hibernating myocardium from transmural biopsy samples are characterized by small increases in interstitial connective tissue, myofibrillar loss (myolysis), increased glycogen deposition, and mini-mitochondria. Experimental animal models of hibernating myocardium also develop these structural changes as quickly as 2 weeks, but they also are present in remote, normally perfused regions of the heart.[32,35] Global cellular changes also have been reported in patients in the absence of a stenosis, suggesting that the structural changes probably are the result of chronically elevated preload. Thus, although cellular dedifferentiation had been emphasized as a mechanism of adaptation, the global ultrastructural changes probably are not causally related to the regional responses to ischemia in hibernating myocardium.[32,35]



EFIGURE 57.7 Progressive myocyte loss and compensatory cellular hypertrophy in hibernating myocardium. Data for hibernating left anterior descending artery (LAD) regions are compared with those for remote regions as well as with those for LAD regions from normal animals. The progression from chronically stunned to hibernating myocardium is accompanied by regional myocyte apoptosis. Although this occurs in only 1 in 5000 myocytes at any instant in time, it is a continuous process that over several months leads to substantial myocyte loss. The result is an approximately 30% reduction in myocyte nuclear number without significant fibrosis, because the myocyte area remains essentially normal. The latter is the result of compensatory myocyte cellular hypertrophy (**see eFig. 57.8**). (From Lim H, Fallavollita JA, Hard R, et al. Profound apoptosis-mediated regional myocyte loss and compensatory hypertrophy in pigs with hibernating myocardium. Circulation 1999;100:2380.)



EFIGURE 57.8 Myocyte cellular changes in hibernating myocardium. The increased myocyte apoptosis results in compensatory myocyte cellular hypertrophy in hibernating myocardium (**see eFig. 57.7**). Although reticular collagen is regionally increased (approximately 2%), there is no evidence of infarction. The electron microscopic characteristics of hibernating myocardium (myolysis, glycogen) demonstrate myofibrillar loss, an increased number of small mitochondria, and increased glycogen content. Although these are markedly different from normal myocardium (sham), biopsy samples from normal remote, nonischemic segments show similar electron microscopic changes, indicating that these ultrastructural abnormalities are not directly related to ischemia, nor are they the cause of regional contractile dysfunction. LAD, Left anterior descending coronary artery region. (From Canty JM, Fallavollita JA. Hibernating myocardium. J Nucl Cardiol 2005;12:104.)

Cell Survival and Antiapoptotic Program in Response to Repetitive Ischemia.

Variability in the regulation of cell survival pathways in response to repetitive ischemia has been well documented. Some studies have demonstrated upregulation of cardioprotective mechanisms in response to repetitive reversible ischemia, which may be operative in minimizing myocyte cell death and fibrosis in the chronic setting. In experimental studies in animals without heart failure, antiapoptotic and stress proteins such as heat shock protein (HSP)-70 have been found to be upregulated,[42] whereas increased proapoptotic proteins and a profile of progressive cell death and fibrosis have been reported in biopsies of patients with hibernating myocardium and heart failure.[35] This variability among reported studies probably reflects the frequency and severity of ischemia, modulation by neurohormonal activation in heart failure, and the complexity of the temporal expression of adaptive and maladaptive responses in myocardium subjected to chronic repetitive ischemia. In this regard, the physiologic significance of a stenosis (i.e., coronary flow reserve) has been shown to be a major determinant of the intrinsic myocardial adaptations to ischemia.[43]

Metabolism and Energetics in Hibernating Myocardium.

Once adapted, the metabolic and contractile response of hibernating myocardium appears to be dissociated from external determinants of workload. As a result, submaximal increases in oxygen consumption can occur without immediately leading to subendocardial ischemia.[35] Experimentally, the hibernating myocardial region appears to operate over a lower range of the normal myocardial supply-demand relation in a manner similar to that for the nonischemic failing heart. Although glycogen content is increased, maximum rates of glucose uptake during insulin stimulation are not altered. Studies of isolated mitochondria from swine with hibernating myocardium have demonstrated alterations in mitochondrial respiration, with downregulation of energy utilization and oxygen consumption.[44] This slows ATP utilization and presumably maintains cell viability during superimposed acute ischemia. Proteomic analysis has demonstrated a reduction in multiple proteins involved in oxidative metabolism and electron transport.[42] Some but not all of the molecular and cellular changes associated with hibernating reverse after revascularization, which can contribute to the failure of contractile function to normalize completely in the absence of MI.[45]

Inhomogeneity in Sympathetic Innervation, Beta-Adrenergic Responses, and Sudden Death.

The contractile response of hibernating myocardium is blunted and partly related to a regional downregulation in beta-adrenergic adenylyl cyclase coupling, similar to that found globally in advanced heart failure.[46] This effect may be related to local norepinephrine overflow and reduced presynaptic uptake of norepinephrine.[46] The resultant inhomogeneity in myocardial sympathetic nerve function may be one of the reasons responsible for the vulnerability of experimental hibernating myocardium to develop lethal ventricular arrhythmias and ventricular fibrillation.[47] Thus, reversing electrical instability as well as improving contractile dysfunction may account for the positive impact of coronary revascularization on survival.[35] Despite this effect, the extent of viable, denervated myocardium remains a strong predictor of arrhythmic death in patients with ischemic cardiomyopathy.[48]

Successful Adaptation versus Degeneration in Hibernating Myocardium.

There is considerable divergence among studies regarding the pathology of reversibly dyssynergic hibernating myocardium. At one extreme, some investigators believe that the myocardium is destined to undergo irreversible myocyte death, which is supported by data showing large amounts of fibrosis (>30% of the tissue) and greatly abnormal high-energy phosphate metabolism, as well as by retrospective analysis suggesting that the degree of fibrosis is related to the duration of hibernating myocardium.[35] At the other extreme, in some circumstances, fibrosis is not a prominent feature with normal myocardial energetics at rest, suggesting that hibernating myocardium can be sustained for long periods without progressive degeneration.[47,48] The factors that promote a path toward progressive degeneration versus adaptation are currently unknown but may be modulated by the superimposed neurohormonal activation and elevation in cytokine levels associated with advanced clinical heart failure, as well as intermittent irreversible injury that arises from intermittent reductions in coronary flow below the threshold required to maintain myocyte viability.

Future Perspectives

The major factors determining myocardial perfusion and oxygen delivery that were established over the last 40 years have been incorporated into the current management of angina and have withstood the test of time. The basic understanding of the fluid mechanical behavior of coronary stenoses also has been translated to the cardiac catheterization laboratory, where measurements of coronary pressure distal to a stenosis and coronary flow are routinely obtained. These physiologic concepts now facilitate routine

clinical decision making in a way that favorably affects outcomes.

Despite progress in advancing our mechanistic understanding of the coronary circulation and myocardial ischemia in health and disease, important gaps remain in basic knowledge as well as in the translation of this knowledge to clinical care. For example, why some patients develop coronary collaterals or intrinsic adaptations to repetitive ischemia whereas others undergo progressive structural degeneration remains unclear. Basic research has identified the importance of physical factors such as shear stress and local coronary pressure in regulating isolated coronary resistance vessels, but how these interact in a complex vascular network to bring about the phenomenon of autoregulation and metabolic coronary vasodilation remains unanswered. Finally, although abnormalities in coronary microcirculatory control may be as important as stenosis severity in determining symptoms of myocardial ischemia and the risk for subsequent coronary events, our understanding of the physiologic and cellular mechanisms responsible for microvascular dysfunction is limited. Continued bench-to-bedside translational investigation in these and other areas is needed to advance our fundamental knowledge of coronary circulatory control and improve the care of patients with chronic ischemic heart disease.

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58

ST-Elevation Myocardial Infarction

Pathophysiology and Clinical Evolution

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The pathologic diagnosis of myocardial infarction (MI) requires evidence of myocardial cell death caused by ischemia. Characteristic findings include coagulation necrosis and contraction band necrosis, often with patchy areas of myocytolysis at the periphery of the infarct. During the acute phase of MI, myocytes die in the infarct zone, with subsequent inflammation, clearance of necrotic debris, repair, and eventual scar formation.

Clinical diagnosis of MI requires a syndrome indicative of myocardial ischemia with some combination of myocardial necrosis detected by biochemical, electrocardiographic, or imaging

modalities. The sensitivity and specificity of the clinical tools for diagnosing MI vary considerably depending on the timing of evaluation after the onset of infarction. Cardiac professional societies have jointly established criteria for the diagnosis of MI (**Table 58.1**). The universal definition of *myocardial infarction* classifies MI into five types, depending on the circumstances in which the MI occurs (**Table 58.2**).[1] Successive revisions to the definition of MI and a shift to more sensitive biomarkers of myocardial injury have had important implications for the clinical care of patients, epidemiologic monitoring, public policy, and clinical trials.[2-4]

TABLE 58.1

Third Universal Definition of Myocardial Infarction (MI)

Criteria for Acute Myocardial Infarction

The term *acute MI* should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions, any of the following criteria meets the diagnosis for MI:
• Detection of a rise and/or fall in cardiac biomarker values (preferably cTn), with at least one value above the 99th percentile URL and with at least one of the following:
  • Symptoms of ischemia
  • New or presumed new significant ST-segment–T wave (ST-T) changes or new LBBB
  • Development of pathologic Q waves on the ECG
  • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  • Identification of an intracoronary thrombus by angiography or autopsy
• Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic changes on the ECG or new LBBB, but death occurred before cardiac biomarkers were determined or before cardiac biomarker values would be increased.
• PCI-related MI is arbitrarily defined by elevation of cTn values (to >5 × 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise in cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (1) symptoms suggestive of myocardial ischemia, (2) new ischemic changes on the ECG, (3) angiographic findings consistent with a procedural complication, or (4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality is required.
• Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall in cardiac biomarker values and at least one value higher than the 99th percentile URL.
• CABG-related MI is arbitrarily defined by elevation of cardiac biomarker values (to >10 × 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (1) new pathologic Q waves or new LBBB, (2) angiographically documented new graft or new native coronary artery occlusion, or (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality is required.

Criteria for Previous Myocardial Infarction
Any of the following criteria meets the diagnosis for prior MI: • Pathologic Q waves with or without symptoms in the absence of nonischemic causes. • Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract in the absence of a nonischemic cause. • Pathologic findings of previous MI.

CABG, Coronary artery bypass grafting; *cTn,* cardiac troponin; *LBBB,* left bundle branch block; *PCI,* percutaneous coronary intervention; *URL,* upper reference limit.

From Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581.

TABLE 58.2

Third Universal Myocardial Infarction (MI) Classification of Type

Type 1: Spontaneous Myocardial Infarction

Spontaneous MI related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries that leads to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion nonobstructive or no CAD.

Type 2: Myocardial Infarction Secondary to Ischemic Imbalance

In cases of myocardial injury with necrosis in which a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand (e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy/bradyarrhythmias, anemia, respiratory failure, hypotension, hypertension ± left ventricular hypertrophy).

Type 3: Myocardial Infarction Resulting in Death When Biomarker Values Are Unavailable

Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic changes on the ECG or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarkers could rise, or in rare cases, when cardiac biomarkers were not collected.

Type 4a: Myocardial Infarction Related to Percutaneous Coronary Intervention

MI associated with PCI is arbitrarily defined by elevation of cTn values to >5 × the 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise in cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (1) symptoms suggestive of myocardial ischemia, (2) new ischemic changes on the ECG or new LBBB, (3) angiographic loss of patency of a major coronary artery or a side branch or persistent slow flow or no flow or embolization, or (4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality is required.

Type 4b: Myocardial Infarction Related to Stent Thrombosis

MI associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall in cardiac biomarkers values with at least one value above the 99th percentile URL.

Type 5: Myocardial Infarction Related to Coronary Artery Bypass Grafting

MI associated with CABG is arbitrarily defined by elevation of cardiac biomarker values to >10 × the 99th percentile URL in patients with normal baseline cTn values (<99th percentile URL). In addition, either (1) new pathologic Q waves or new LBBB, (2) angiographically documented new graft or new native coronary artery occlusion, or (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality is required.

CAD, coronary artery disease; *cTn*, cardiac troponin; *LBBB*, left bundle branch block; *URL*, upper reference limit.

From Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581.

The contemporary approach to patients with new onset or worsening ischemic symptoms is to consider them as having an *acute coronary syndrome* (ACS), which encompasses the diagnoses of unstable angina, non–ST-segment elevation MI (NSTEMI), and ST-segment elevation MI (STEMI) (**Fig. 58.1**). The principal diagnostic tool for patients with suspected ACS is the 12-lead electrocardiogram (ECG), which identifies those with ST-segment elevation, the subject of this chapter and **Chapter 59**, and those without ST-segment elevation, the subject of **Chapter 60**.

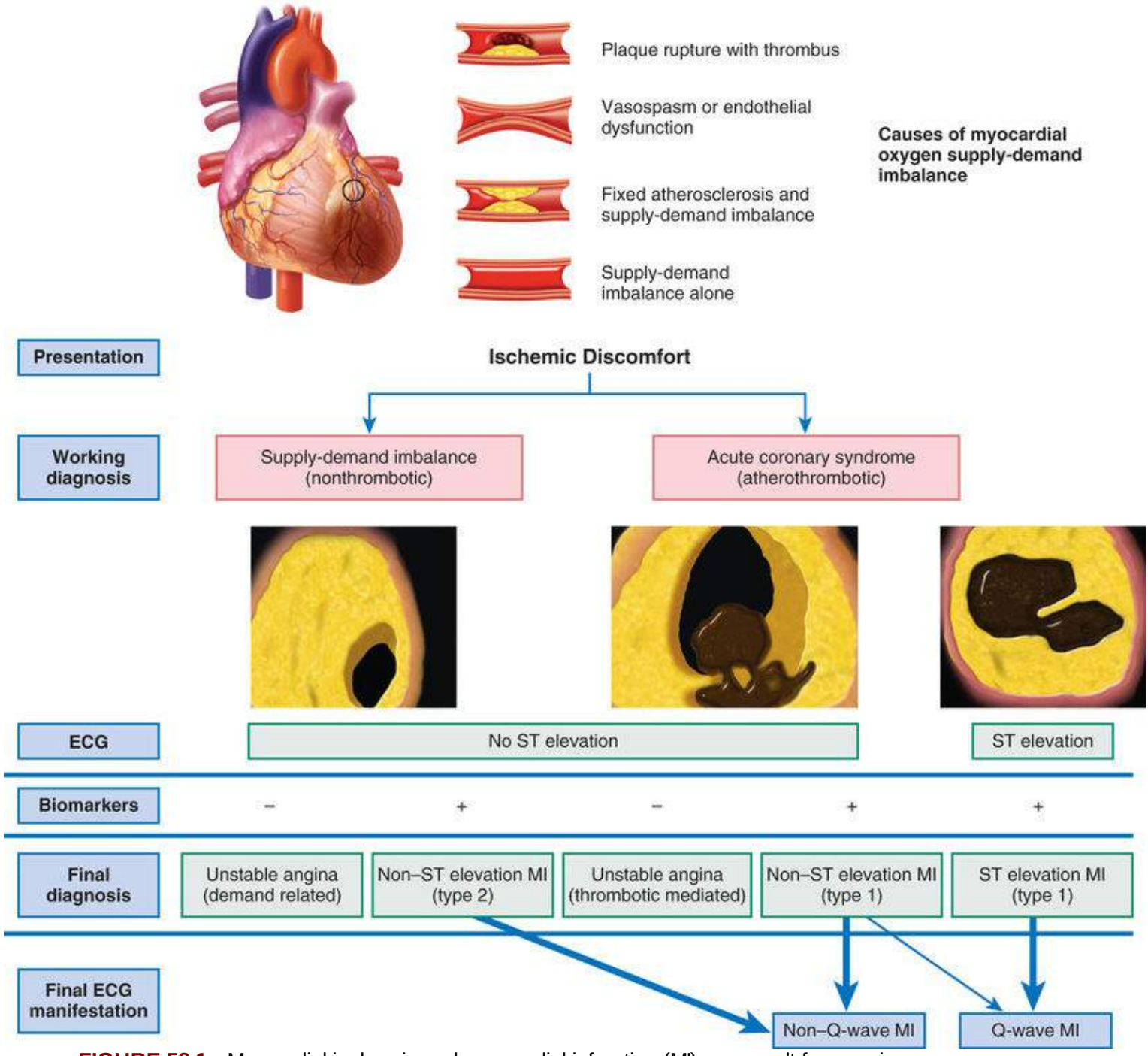
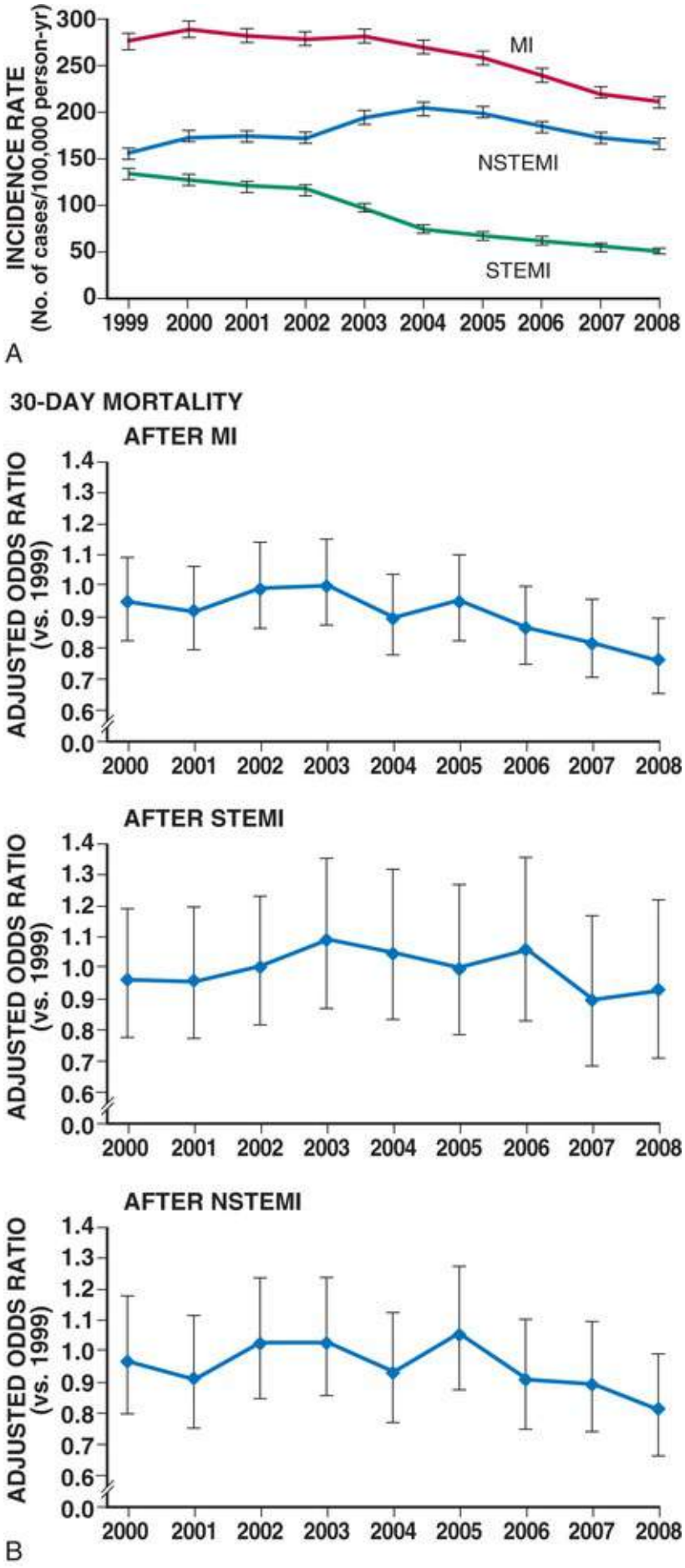


FIGURE 58.1 Myocardial ischemia and myocardial infarction (MI) can result from various coronary disease processes, including vasospasm, increased myocardial demand in the setting of a fixed coronary lesion, and erosion or rupture of vulnerable atherosclerotic plaque leading to acute thrombus formation and subsequent ischemia. All result in myocardial oxygen supply-demand mismatch and can precipitate ischemic symptoms, and all processes, when severe or prolonged, will lead to myocardial necrosis or infarction. Nonthrombotically mediated events (*bottom half, left side*) typically occur without ST-segment elevation (STE) on the ECG but can have elevated levels of cardiac biomarkers if the ischemia is severe and long enough, in which case they are classified as having type 2 MI. The atherothrombotic lesion is the hallmark pathobiologic event of an acute coronary syndrome (ACS). The reduction in flow may be caused by a completely occlusive thrombus (*bottom half, right side*) or by a subtotally occlusive thrombus (*bottom half, middle*). Ischemic discomfort may occur with or without STE on the ECG. Of patients with STE, Q wave MI ultimately develop in most, but not all patients, depending on the duration of ischemia and collateralization. Patients without STE have either unstable angina or non–ST-segment elevation MI (NSTEMI), a distinction that is ultimately made by the presence or absence of a serum or plasma cardiac marker (e.g., cardiac troponin) detected in blood. Non–Q wave MI ultimately develops in most patients with NSTEMI on the ECG; Q wave MI may develop in a few. MI that develops as the result of the atherothrombotic lesion of an ACS is classified as type 1 MI. (Modified from Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581.)

Changing Patterns in Incidence and Care

Despite advances in diagnosis and management, STEMI remains a major public health problem in the industrialized world and is on the rise in developing countries[5] (**see Chapter 1**). Each year in the United States alone, more than 1 million patients will be hospitalized for an MI or coronary heart death.[6] The rate of MI rises sharply in both men and women with increasing age, and racial differences exist, with MI occurring more frequently in black men and women compared to white, regardless of age. The proportion of patients with ACS events who have STEMI varies across observational studies but has declined over the past decade, in part due to the introduction of more sensitive assays of myocardial injury that increase the number of NSTEMI cases relative to STEMI.[6] This estimate does not include "silent" MI, which may not prompt hospitalization. Between 1999 and 2008, the proportion of patients with an ACS and STEMI declined by almost 50% (47.0% to 22.9%)[4] (**eFig. 58.1**). Although hospitalizations for MI have declined for patients older than 55 years old, there has not been a similar decline in the rates for younger patients, in particular in women.[7] Of particular concern from a global perspective, the burden of coronary disease in low- and middle-income countries has reached the rate affecting more affluent countries.[5] The limited resources available to treat STEMI in low- and middle-income countries mandate major international efforts to strengthen primary prevention programs.



EFIGURE 58.1 **A,** Age- and sex-adjusted incidence rates of acute myocardial infarction (MI) from 1999 to 2008. *I bars* represent 95% confidence intervals. **B,** Adjusted odds ratios are shown for 30-day mortality according to year after any MI (*top*), STEMI (*middle*), and NSTEMI (*bottom*). Models were adjusted for patient demographic characteristics, previous cardiovascular disease, cardiovascular risk factors, chronic lung disease, and systemic cancer. The reference year is 1999. (From Yeh RW, Sidney S, Chandra M, et al. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med 2010;362:2155.)

Improvements in Outcome

The overall number of deaths from STEMI has declined steadily over the past 30 years, but it has stabilized over the past decade[8] (**eFig. 58.1**). Both a decreased incidence of STEMI and a decline in the case-fatality rate after STEMI have contributed to this trend.[6] According to estimates from the American Heart Association (AHA), the short-term mortality rate of patients with STEMI ranges from 5% to 6% during the initial hospitalization and from 7% to 18% at 1 year.[8,9] The highest risk of ischemic complications following MI occurs within 180 days, after which the risk becomes fairly linear. This pattern is most evident in patients older than 80 years[10] (**Fig. 58.2**). Mortality rates in clinical trial populations tend to be approximately half of those observed in registries of consecutive patients, most likely because of the exclusion of patients with more extensive comorbidities.

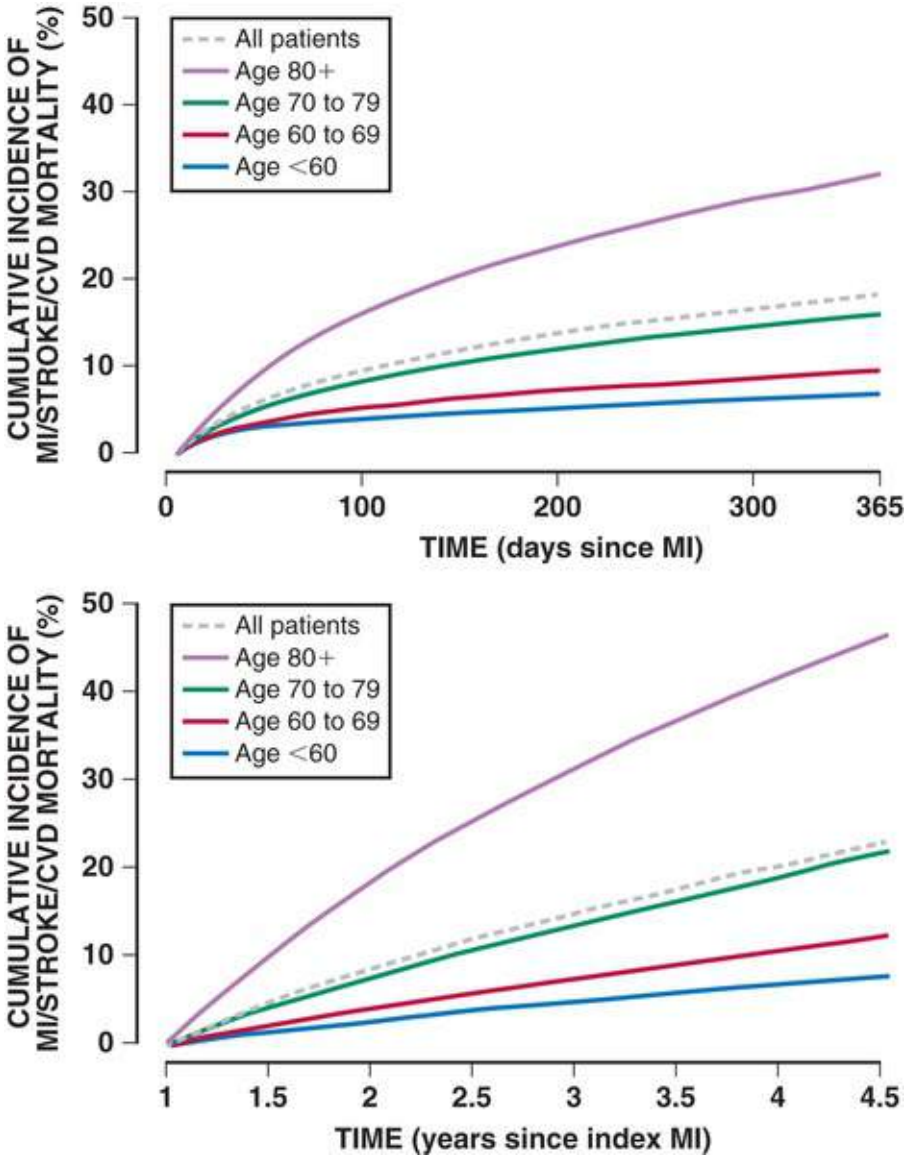


FIGURE 58.2 Cardiovascular risk after myocardial infarction (MI) by age. Kaplan-Meier estimate of the risk of the combined endpoint (MI, ischemic stroke, or cardiovascular disease [CVD] mortality) during the first 365 days after the index MI (*top*) and after 1 year from the initial infarction (*bottom*). (From Jernberg T, Hasvold P, Henriksson M, et al. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. Eur Heart J 2015;36:1163-70.)

Improvements in the management of patients with STEMI have occurred in several phases.[11,12] The "clinical observation phase" of coronary care consumed the first half of the 20th century and focused on detailed recording of physical and laboratory findings, with little active treatment of the infarction. The "coronary care unit phase" began in the mid-1960s and emphasized early detection and management of cardiac arrhythmias based on the development of monitoring and cardioversion/defibrillation capabilities. The "high-technology phase," heralded by the introduction of the pulmonary artery balloon flotation catheter, set the stage for bedside hemodynamic monitoring and directed hemodynamic management. The modern "reperfusion era" of STEMI care began with intracoronary and then intravenous fibrinolysis, increased use of aspirin (**see Chapter 59**), and subsequently the development and evolution of primary percutaneous coronary intervention (PCI) (**Chapter 62**).

Contemporary care of patients with STEMI has entered an "evidence-based coronary care phase," driven by professional society guidelines and performance measure benchmarks for clinical practice.[13,14] Implementation of guideline-directed medical treatment (GDMT) and regional quality initiatives has significantly decreased heterogeneity in care, increased compliance with evidence-based therapies, and improved outcomes.[15]

Limitations of Current Therapy

Rates of appropriate initiation of reperfusion therapy vary widely, with up to 30% of patients with STEMI who are eligible to receive reperfusion therapy not receiving this lifesaving treatment in some registries.[16] Care of another substantial proportion of patients does not meet the recommended door-to-reperfusion time.[17] This gap mandates initiatives to increase timely administration of guideline-directed reperfusion therapy[18] (**see Chapter 59**).

Management and outcomes of patients with STEMI appear to vary substantially depending on the volume of such patients cared for within a hospital system.[19] Hospitals with a high clinical volume, a high rate of invasive procedures, and a top ranking in quality reports have lower STEMI mortality rates. Conversely, patients with STEMI not cared for by a cardiovascular specialist have higher mortality rates. Variation also occurs in the treatment patterns of certain population subgroups with STEMI, including elderly, women,[20] blacks, and some high-risk patients (e.g., presenting with cardiogenic shock).

The advent of mandatory reporting for procedural complications and outcomes in STEMI has led to the establishment of benchmarks for procedural success and mortality rates and the ability to compare across different regions and hospitals.[15] However, public reporting of outcomes in STEMI may also have unintentionally led to lower rates of revascularization in the highest-risk patients, who would often benefit most from early revascularization (e.g., cardiogenic shock) because of the concern regarding higher case-fatality rates.[21]

Pathologic Findings

Almost all acute coronary syndromes result from coronary atherosclerosis, generally with superimposed coronary thrombosis caused by rupture or erosion of an atherosclerotic lesion[22] (**see Chapters 44 and 60**). Nonatherogenic forms of coronary artery disease are discussed later in this chapter, and causes of MI without coronary atherosclerosis are presented in **Table 58.3**.

TABLE 58.3

Causes of Myocardial Injury

Injury Related to Primary Myocardial Ischemia
Plaque rupture
Intraluminal coronary artery thrombus formation
Injury Related to the Supply-Demand Imbalance of Myocardial Ischemia
Tachyarrhythmias/bradyarrhythmias
Aortic dissection or severe aortic valve disease
Hypertrophic cardiomyopathy
Cardiogenic, hypovolemic, or septic shock
Severe respiratory failure
Severe anemia
Hypertension with or without left ventricular hypertrophy
Coronary spasm
Coronary embolism or vasculitis
Coronary endothelial dysfunction without significant coronary artery disease
Injury Not Related to Myocardial Ischemia
Cardiac contusion, surgery, ablation, pacing, or defibrillator shocks
Rhabdomyolysis with cardiac involvement
Myocarditis
Cardiotoxic agents (e.g., anthracyclines, trastuzumab [Herceptin])
Multifactorial or Indeterminate Myocardial Injury
Heart failure
Stress (takotsubo) cardiomyopathy
Severe pulmonary embolism or pulmonary hypertension
Sepsis and critically ill patients
Renal failure
Severe acute neurologic diseases (e.g., stroke, subarachnoid hemorrhage)
Infiltrative diseases (e.g., amyloidosis, sarcoidosis)
Strenuous exercise

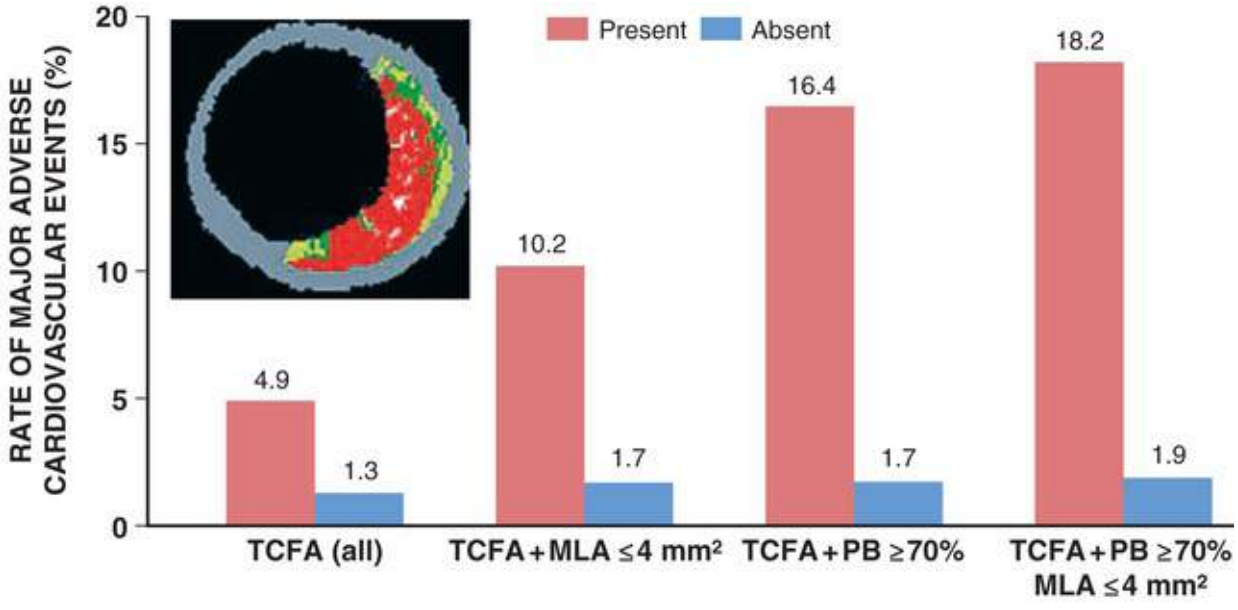
From Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581.

When acute coronary atherothrombosis occurs, the resulting intracoronary thrombus may obstruct partially, which generally leads to myocardial ischemia in the absence of ST elevation, or occlude completely and cause transmural myocardial ischemia and STEMI. Before the fibrinolytic era, clinicians typically divided patients with MI into those in whom a Q wave developed on the ECG and those with non–Q wave MI based on evolution of the ECG pattern over several days. The term *Q wave infarction* was frequently considered to be virtually synonymous with "transmural infarction," whereas *non–Q wave infarctions* were often referred to as "subendocardial infarctions." Contemporary studies using cardiac magnetic resonance imaging (CMR) indicate that the development of a Q wave on the ECG depends more on the size of the infarct than on the depth of mural involvement. Thus the use of *ACS* is the more appropriate, broad conceptual framework as it is anchored by the underlying unifying pathophysiology (**see Fig. 58.1**). Further classification of patients by the presence of ST-segment elevation (STEMI) or by its absence (non–ST-segment elevation ACS), rather than by the evolution of Q waves, permits immediate clinical triage decisions regarding the need for urgent revascularization (**see Chapter 59**).

Plaque Formation and Disruption

Plaques that precipitates ACS usually provoke thrombi caused by fibrous cap rupture, superficial erosion, or occasionally vasospasm or disruption caused by a calcified nodule. Some cases of ACS lack an evident culprit thrombus (**see Chapter 44**). Current clinical data have challenged the simplistic concept of the "vulnerable plaque." In a prospective study of 697 patients with ACS who underwent three-vessel coronary angiography and gray-scale radiofrequency intravascular ultrasonographic imaging after PCI found that less than 5% of plaques with ultrasound characteristics of a thin-capped fibroatheroma actually caused a clinical event during a 3.4-year follow-up[23] (**Fig. 58.3**). Thus, equating the lipid-rich, thin-capped plaque with "vulnerability" is a misnomer. Other morphologic characteristics associated with

rupture-prone plaque include expansive remodeling that minimizes luminal obstruction (mild stenosis by angiography), neovascularization (angiogenesis), plaque hemorrhage, adventitial inflammation, and a "spotty" pattern of calcification.[24]

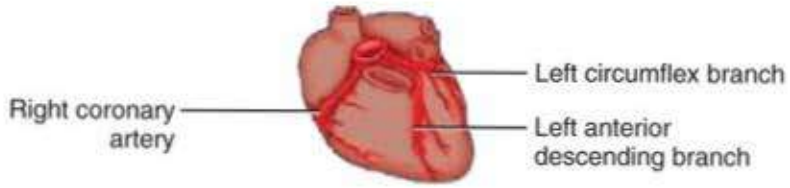


Lesion hazard ratio (95% CI)	3.90 (2.25–6.76)	6.55 (3.43–12.51)	10.83 (5.55–21.10)	11.05 (4.39–27.82)
P value	<0.001	<0.001	<0.001	<0.001
Prevalence (%)	46.7	15.9	10.1	4.2

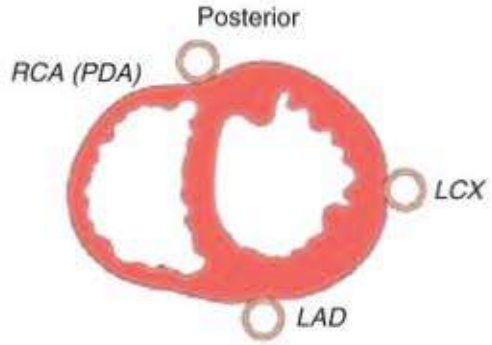
FIGURE 58.3 Comparison of cardiovascular event rates for lesions that were and those that were not thin-cap fibrothecomas (TCFAs). This figure shows the event rates associated with 595 nonculprit lesions that were characterized as TCFAs and 2114 that were not, by means of gray-scale radiofrequency intravascular ultrasonographic imaging according to minimal luminal area (MLA) and plaque burden (PB). Lesions that had a larger plaque burden, signifying greater atherosclerotic content, and smaller lumen were at greatest risk for subsequently triggering an acute coronary event. *Insert,* Example of a TCFA imaged by radiofrequency ultrasonography. *Red* indicates necrotic core, *dark green* indicates fibrous tissue, *white* indicates confluent dense calcium, and *light green* indicates fibrofatty tissue. CI, Confidence interval. (From Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226.)

Acute Coronary Syndromes

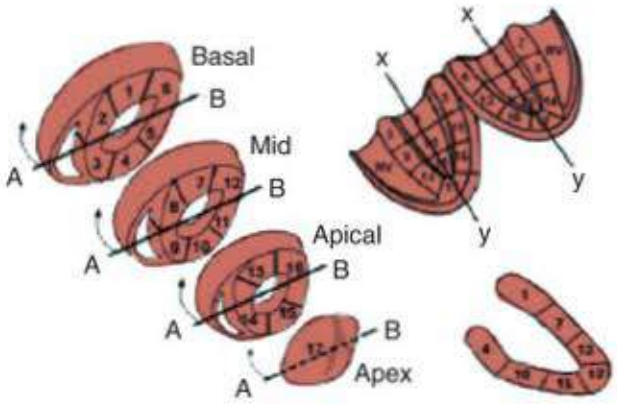
Plaque disruption exposes thrombogenic substances that may produce an extensive thrombus in the infarct-related artery (**see Fig. 58.1**). An adequate collateral network that prevents necrosis from occurring can result in clinically silent episodes of coronary occlusion; in addition, many plaque ruptures are asymptomatic if the thrombosis is not occlusive. Characteristically, completely occlusive thrombi lead to extensive injury to the ventricular wall in the myocardial bed subtended by the affected coronary artery (**Fig. 58.4**). Infarction alters the sequence of depolarization ultimately reflected as changes in the QRS complex. The most characteristic change in QRS that develops in most patients with STEMI is the evolution of Q waves in leads overlying the infarct zone. In a minority of patients with ST elevation, no Q waves develop but other abnormalities in the QRS complex occur frequently, such as diminution in R wave height and notching or splintering of the QRS (**see Chapter 12**). Patients who have ischemic symptoms without ST elevation are initially diagnosed as suffering either from unstable angina or, with evidence of myocardial necrosis, from NSTEMI.


Right coronary artery
Left circumflex branch
Left anterior descending branch

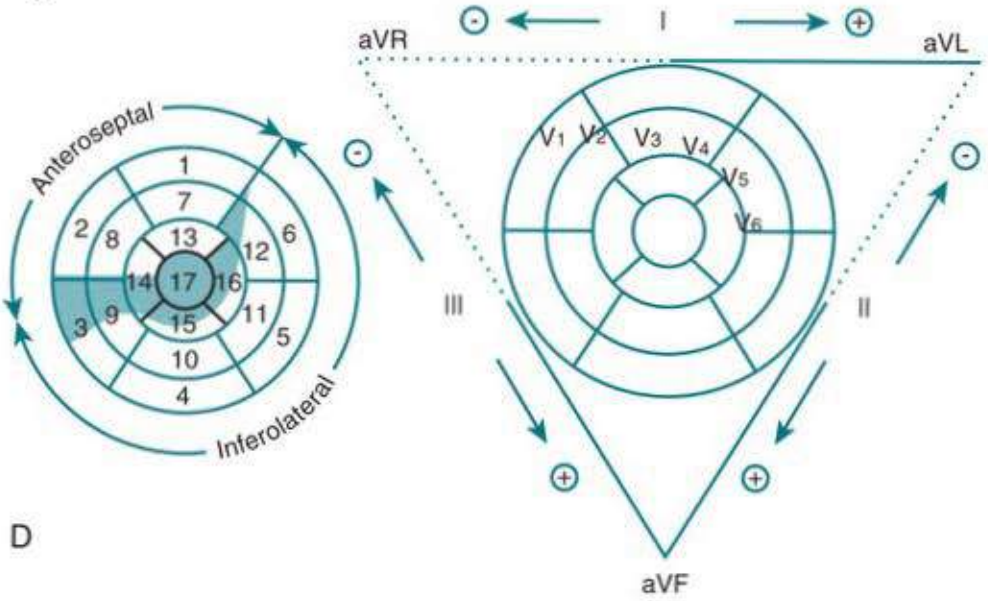
A


Posterior
RCA (PDA)
LCX
LAD
Anterior

B


Basal
Mid
Apical
Apex
A
B
x
y

C


aVR
I
aVL
Anteroseptal
Inferolateral
III
II
aVF
V1
V2
V3
V4
V5
V6

D

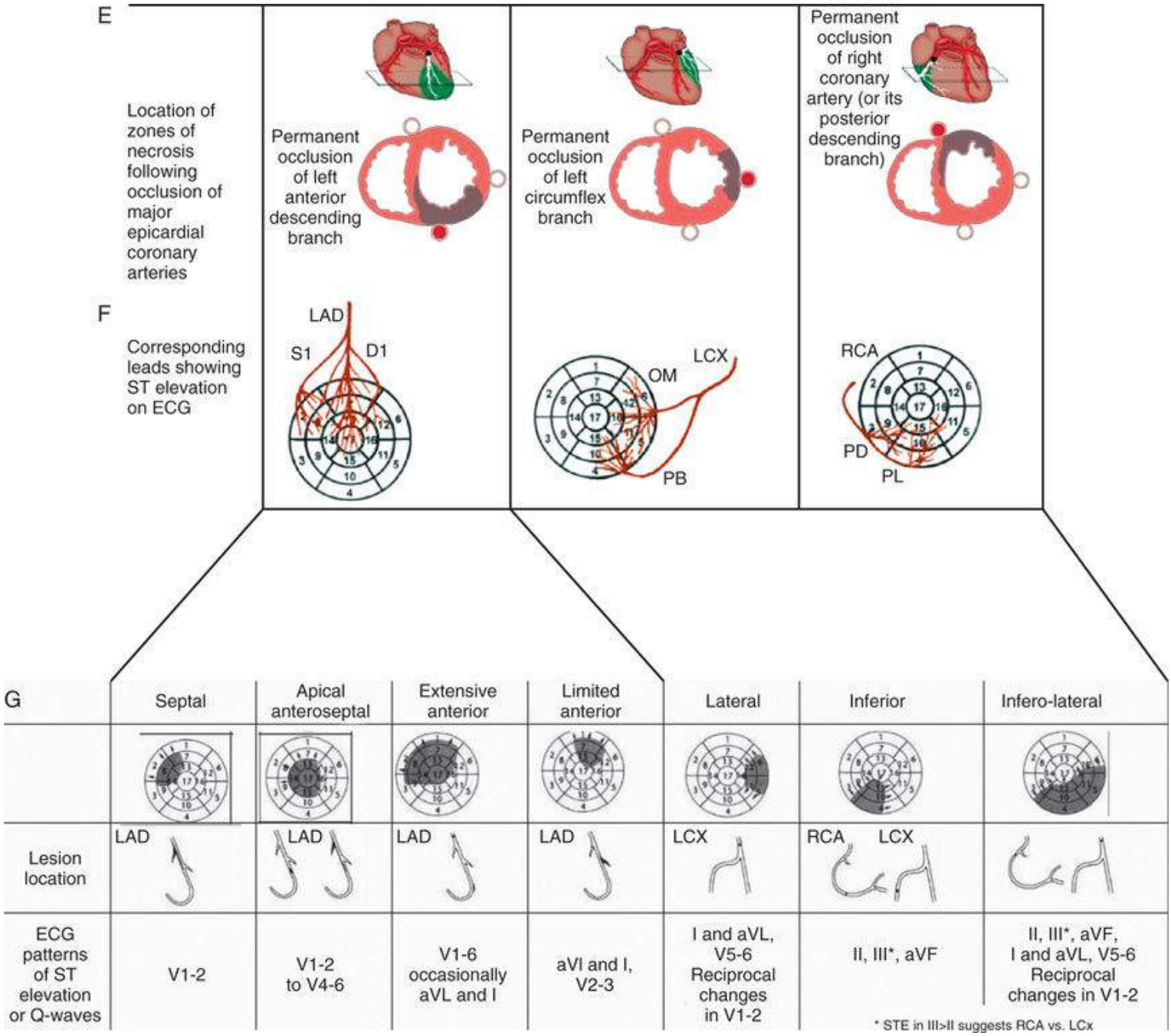


FIGURE 58.4 Correlation of sites of coronary occlusion, zones of necrosis, and abnormalities on the ECG. **A,** Schematic of the heart with location of major epicardial coronary arteries. **B,** Schematic depicts a short-axis view of the left and right ventricles and approximate location of the left anterior descending (LAD), left circumflex (LCX), and right coronary (RCA) arteries; the RCA gives rise to the posterior descending artery (PDA) in most patients. **C,** The 17 myocardial segments in a polar map format. **D,** Position of the standard ECG leads relative to the polar map. **E,** Location of zones of necrosis after occlusion. The infarct artery can be deduced by identifying the leads that show ST elevation and referencing that polar map format **(D). F,** Identification of the infarct artery from the 12-lead ECG is shown for the arterial supply provided by the LAD, LCX, and RCA. For example, ST elevation seen most prominently in the leads overlying segments 1, 2, 7, 8, 13, 14, and 17 indicates that the LAD is the infarct artery. *D1,* First diagonal; *OM,* obtuse marginal; *PB,* posterobasal; *PD,* posterior descending; *PL,* posterolateral; *S1,* first septal. **G,** Further localization of culprit arteries via differential ECG patterns will depend on the location of lesion (proximal versus distal) and branch artery inclusion. (Modified from Bayes-de-Luna A, Wagner G, Birnbaum Y, et al. A new terminology for the left ventricular walls and location of myocardial infarcts that present Q wave based on the standard of cardiac magnetic resonance imaging. Circulation 2006;114:1755.)

Patients with persistent ST-segment elevation are candidates for reperfusion therapy (either pharmacologic or catheter based) to restore flow in the occluded epicardial infarct-related artery.[13,14] ACS patients without ST-segment elevation are not candidates for pharmacologic reperfusion but should receive anti-ischemic and antithrombotic therapy, followed in most cases by PCI (**see Chapter 60**). Thus

the 12-lead ECG remains at the center of the decision pathway for the management of patients with ACS, to distinguish between those with ST elevation and those without it.[13,14]

Heart Muscle

The cellular effects of ischemia commence within seconds of the onset of hypoxia with the loss of adenosine triphosphate (ATP) production. Myocardial relaxation-contraction is compromised, and irreversible cell injury begins within as early as 20 minutes. Necrosis is usually complete in 6 hours unless reperfusion occurs or an extensive collateral circulation is present (**Fig. 58.5**).

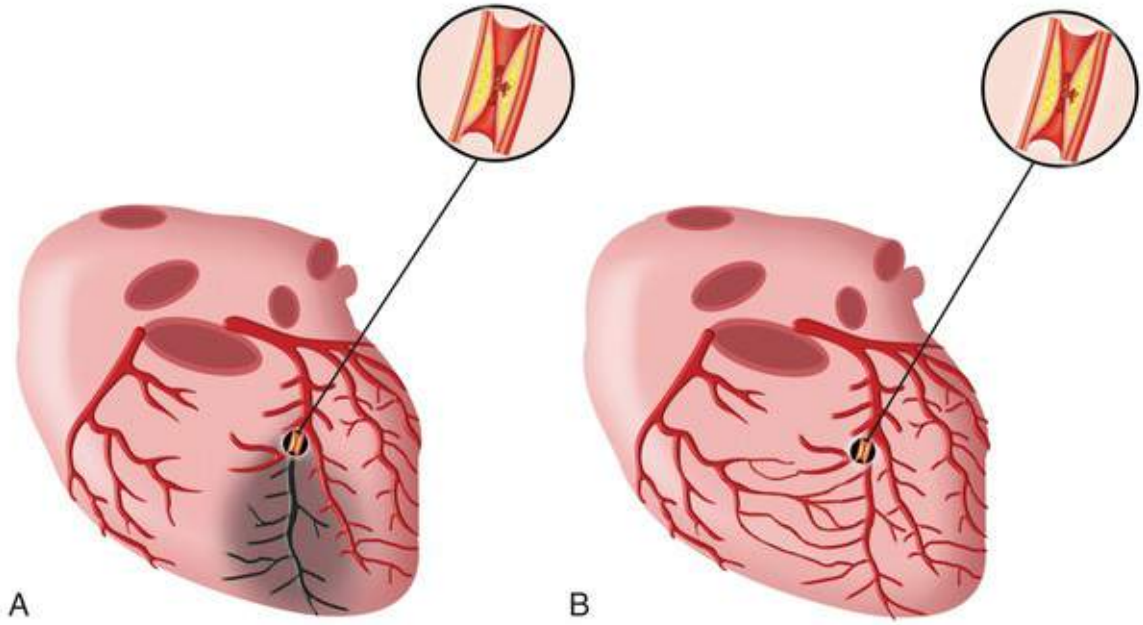


FIGURE 58.5 Schematic drawing of the coronary artery circulation without **(A)** and with **(B)** interarterial anastomoses between the right coronary artery and the occluded left anterior descending artery (LAD) (occluded downstream of the third diagonal branch). **A,** The *gray area* indicates the ischemic area at risk for MI (finally corresponding to infarct size) in the case of LAD occlusion and in the absence of collaterals. **B,** The area at risk for MI is equal to zero because of the extended collaterals. (From Traupe T, Gloekler S, de Marchi SF, et al. Assessment of the human coronary collateral circulation. Circulation 2010;122:1210.)

Gross Pathologic Findings

On gross inspection, MI falls into two major types: *transmural* infarcts, in which myocardial necrosis involves the full thickness (or almost full thickness) of the ventricular wall, and *subendocardial* (nontransmural) infarcts, in which the necrosis involves the subendocardium, the intramural myocardium, or both, without extending all the way through the ventricular wall to the epicardium (**Fig. 58.6**).

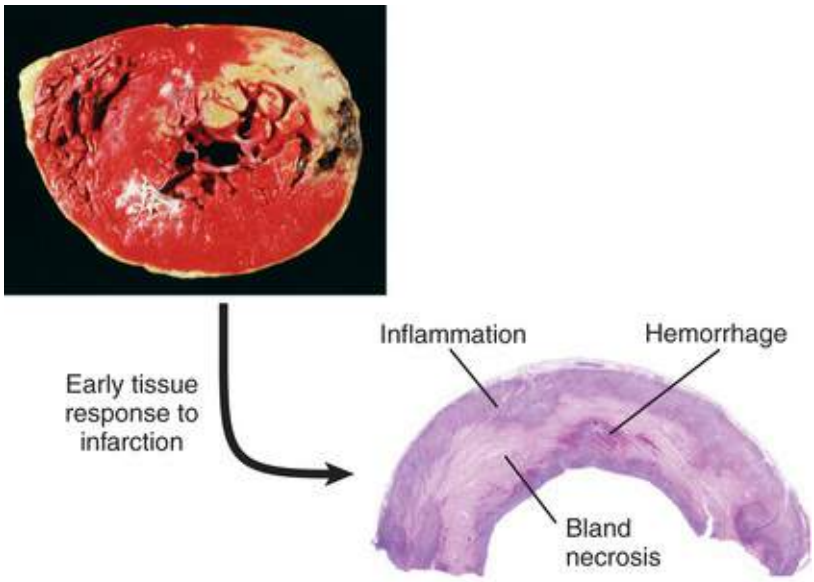
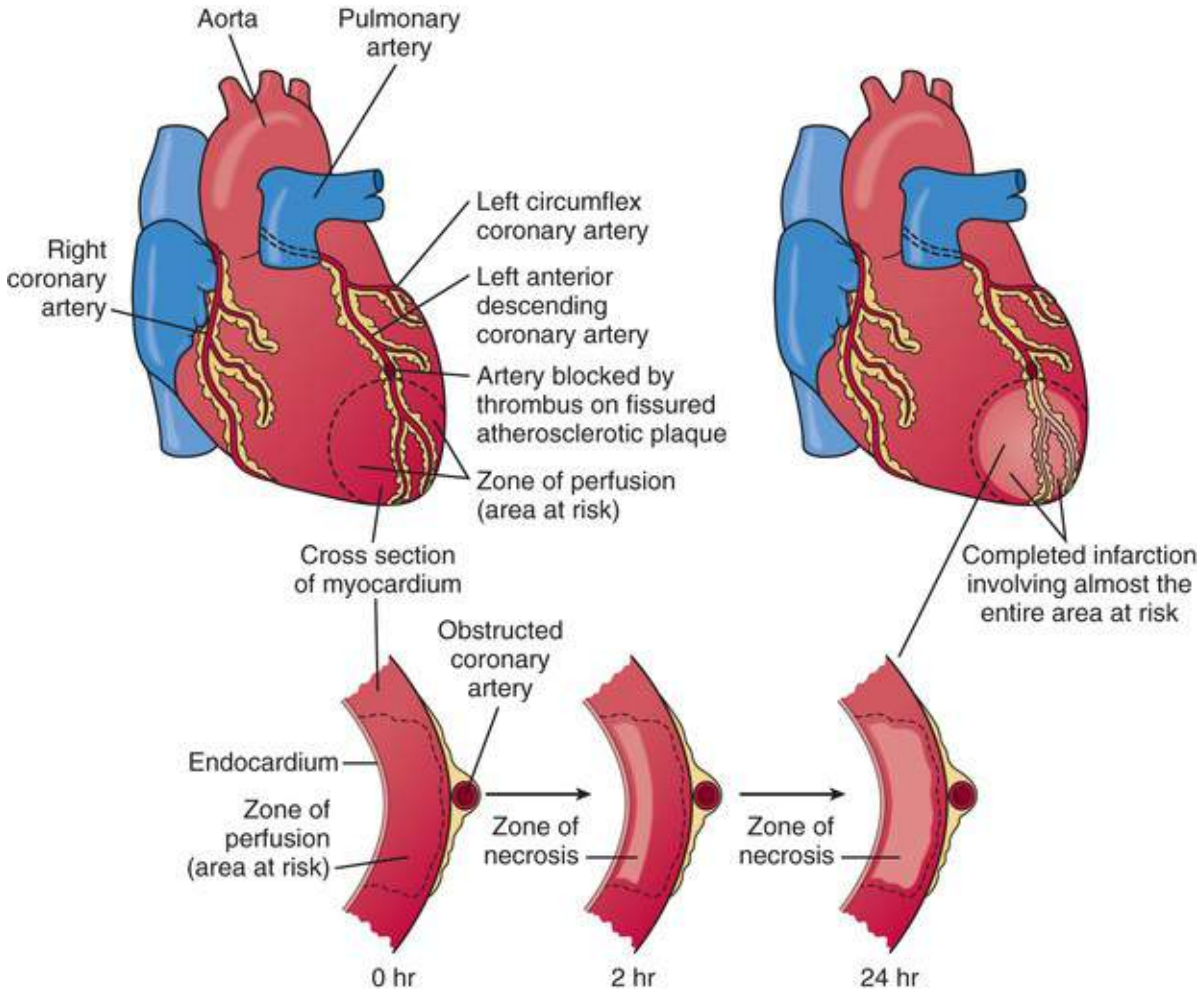


FIGURE 58.6 **Top,** Acute MI, predominantly of the posterolateral left ventricle, demonstrated histochemically by lack of staining with triphenyltetrazolium chloride in areas of necrosis. The staining defect is caused by leakage of the enzyme following cell death. The myocardial hemorrhage at one edge of the infarct was associated with cardiac rupture, and the anterior scar (*lower left*) was indicative of an old infarct. The specimen was oriented with the posterior wall at the top. **Bottom,** The early tissue response to the infarction process involves a mixture of bland necrosis, inflammation, and hemorrhage. (From Schoen FJ. The heart. In Kumar V, Abbas AK, Fausto N, editors. Robbins & Cotran Pathologic Basis of Disease. 8th ed. Philadelphia: Saunders; 2009.)

Occlusive coronary thrombosis appears to be much more common when the infarction is transmural and localized to the distribution of a single coronary artery (**see Fig. 58.4**). Nontransmural infarctions, however, frequently occur in the presence of severely narrowed but still patent coronary arteries, or when the infarcted region has sufficient collateral circulation. Patchy nontransmural MI may arise secondary to fibrinolysis or PCI of an originally occlusive thrombus, with restoration of blood flow *before* the wavefront of necrosis has extended from the subendocardium across the full thickness of the ventricular wall (**eFig. 58.2**).



EFIGURE 58.2 Schematic representation of the progression of myocardial necrosis after coronary artery occlusion. Necrosis begins in a small zone of the myocardium beneath the endocardial surface in the center of the ischemic zone. This entire region of myocardium (*dashed outline*) depends on the occluded vessel for perfusion and is the area at risk. A narrow zone of myocardium immediately beneath the endocardium is spared from necrosis because it can be oxygenated by diffusion from the ventricle.
(From Schoen FJ. The heart. In Kumar V, Abbas AK, Fausto N, editors. Robbins & Cotran Pathologic Basis of Disease. 8th ed. Philadelphia: Saunders; 2009.)

Histologic and Ultrastructural Findings

Gross alterations in the myocardium are difficult to identify until at least 6 to 12 hours has elapsed following the onset of necrosis (**Fig. 58.7**), but a variety of histochemical stains can identify zones of necrosis after only 2 to 3 hours. Subsequently, the infarcted myocardium undergoes a sequence of gross pathologic changes (**Fig. 58.8**). Within hours of death from MI, the presence of an infarct can often be detected by immersing slices of myocardium in triphenyltetrazolium chloride (TTC), which turns noninfarcted myocardium a brick-red color while the infarcted area remains unstained (**see Fig. 58.6**).

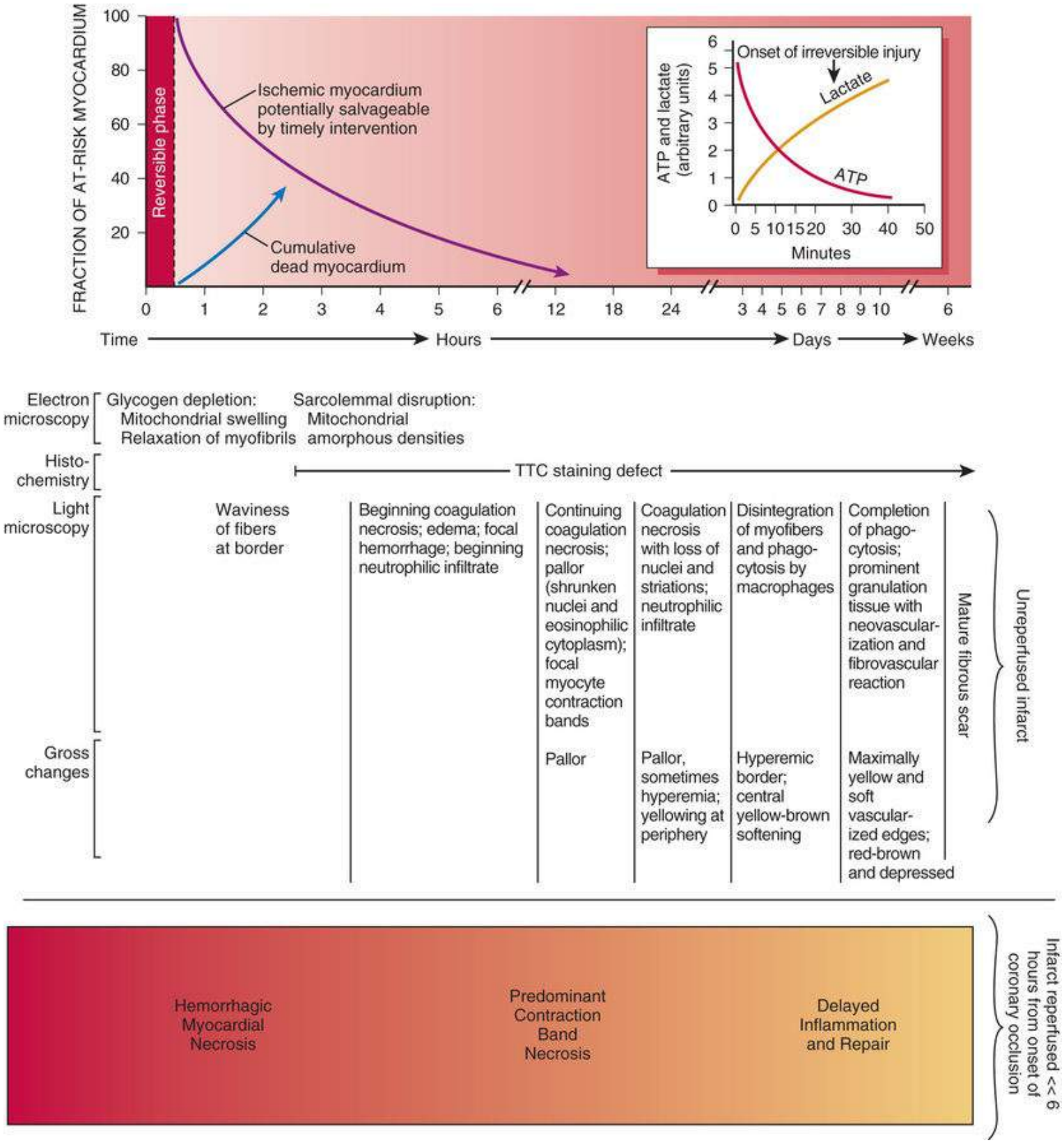


FIGURE 58.7 Temporal sequence of early biochemical, ultrastructural, histochemical, and histologic findings after the onset of myocardial infarction. **Top,** Schematics of the time frames for early and late reperfusion of the myocardium supplied by an occluded coronary artery. For approximately 30 minutes after the onset of even the most severe ischemia, myocardial injury is potentially reversible; after this point, progressive loss of viability occurs and is complete by 6 to 12 hours. The benefits of reperfusion are greatest when it is achieved early, with progressively smaller benefits occurring as reperfusion is delayed. Note the alterations in the temporal sequence in the reperfused infarct. The pattern of pathologic findings following reperfusion varies depending on the timing of reperfusion, previous infarction, and collateral flow. ATP, Adenosine triphosphate; TTC, triphenyltetrazolium chloride. (From Schoen FJ. The heart. In Kumar V, Abbas AK, Fausto N, editors. Robbins & Cotran Pathologic Basis of Disease. 8th ed. Philadelphia: Saunders; 2009.)

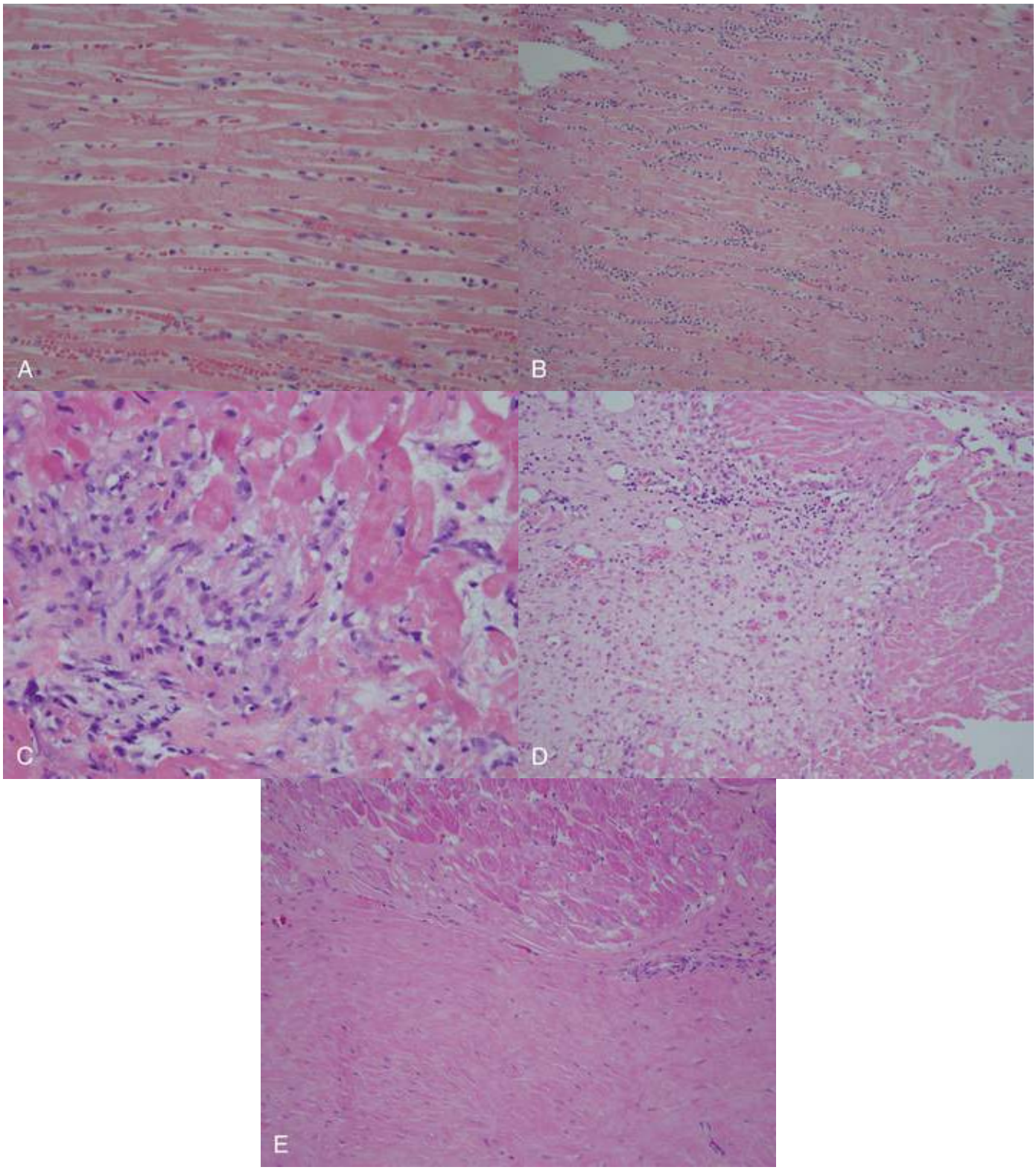


FIGURE 58.8 Microscopic features of myocardial infarction (MI). These histologic sections derived from the heart of a woman who suffered a stuttering reinfarction illustrate the histologic appearance of the injured myocardium and various phases of its healing. Times are estimated based on the clinical history and the typical pathologic findings of myocardial ischemic injury. **A,** At 8 hours post-MI, cross-striations are absent in some cardiac myocytes, and contraction bands are forming. There is myocardial interstitial edema, and leukocytes have begun to appear in the ischemically injured zone. **B,** At 36 hours post-MI, in the center of an ischemic area, most myocytes have lost cross-striations, contraction bands abound, and a predominantly polymorphonuclear leukocytic infiltrate has appeared. **C,** At 5 days post-MI, a few myocytes or fragments of myocytes persist with cross-striations. In the center of this micrograph, a predominantly monocytic leukocyte infiltrate surrounds the debris of dead myocytes. **D,** At 14 days following an acute ischemic insult, an island of granulation tissue has begun to form. There are numerous neovessels in areas of mononuclear cell accumulation. An organized extracellular matrix has begun to form. **E,** At 3 months following the acute ischemic event, an organized scar has formed in the matrix-rich and relatively hypocellular area on the bottom of this micrograph. Some surviving cardiac myocytes remain (*top* of micrograph). (Photomicrographs courtesy Dr. Robert F. Padera, Department of Pathology, Brigham and

Microscopic Findings

Histologic evaluation of MI reveals various stages of the healing process (**see Figs. 58.7 and 58.8**). In experimental infarction, the earliest ultrastructural changes in cardiac muscle after ligation of a coronary artery, noted within 20 minutes, consist of a reduction in the size and number of glycogen granules; intracellular edema; and swelling and distortion of the transverse tubular system, sarcoplasmic reticulum, and mitochondria. These early changes are reversible. Changes after 60 minutes of occlusion include myocyte swelling, swelling and internal disruption of mitochondria, development of amorphous (flocculent) aggregation and margination of nuclear chromatin, and relaxation of myofibrils. After 20 minutes to 2 hours of ischemia, the changes in some cells become irreversible, and progression of these alterations occurs.

Patterns of Myocardial Necrosis

Coagulation Necrosis

Coagulation necrosis results from severe, persistent ischemia and is usually present in the central region of infarcts; it causes arrest of muscle cells in the relaxed state and passive stretching of ischemic muscle cells. The tissue exhibits stretched myofibrils, many cells with pyknotic nuclei, congested microvessels, and phagocytosis of necrotic muscle cells (**see Fig. 58.7**). Mitochondrial damage with prominent amorphous (flocculent) densities occurs, but no calcification is evident.

Necrosis with Contraction Bands

This form of myocardial necrosis, also termed *contraction band necrosis* or *coagulative myocytolysis*, results primarily from severe ischemia followed by reflow. It is characterized by hypercontracted myofibrils with contraction bands and mitochondrial damage, frequently with calcification, marked vascular congestion, and healing by lysis of muscle cells. Necrosis with contraction bands is caused by increased influx of calcium ions (Ca^{2+}) into dying cells, which results in the arrest of cells in the contracted state in the periphery of large infarcts and, to a greater extent, in nontransmural than in transmural infarcts. The entire infarct may show this form of necrosis after reperfusion (**see Figs. 58.7 and 58.8**).

Myocytolysis

Ischemia without necrosis generally causes no acute changes visible on light microscopy, but severe prolonged ischemia can result in myocyte vacuolization, often termed *myocytolysis*. Prolonged severe ischemia, which is potentially reversible, causes cloudy swelling, as well as hydropic, vascular, and fatty degeneration.

Apoptosis

An additional pathway of myocyte death involves apoptosis, or programmed cell death. In contrast to coagulation necrosis, myocytes undergoing apoptosis exhibit shrinkage of cells, fragmentation of DNA, and phagocytosis, but without the usual cellular infiltrate indicative of inflammation. The role of apoptosis in the setting of MI is less well understood than that of classic coagulation necrosis. Apoptosis

may occur shortly after the onset of myocardial ischemia, but its major impact appears to be on late myocyte loss and ventricular remodeling after MI.

Current Concepts of the Cellular Events During Myocardial Infarction and Healing

Classic studies defined the sequence of cellular events that occur during human MI by careful histologic studies.[25] Accumulation of granulocytes characterized the first days following MI, then mononuclear phagocytes accumulated in the infarct in tissue. Granulation tissue characterized by neovascularization and accumulation of extracellular matrix (fibrosis) followed. Recent experimental work in mice has revealed a sequence of accumulation of subpopulations of mononuclear phagocytes.[25] The first wave, occurring about days 1 to 3 after coronary ligation, consists of a proinflammatory subset of monocytes characterized by high proteolytic and phagocytic capacity and elaboration of proinflammatory cytokines. During a later phase (days 3 to 7), less inflammatory monocytes predominate and produce the angiogenic mediator vascular endothelial growth factor (VEGF) and the fibrogenic mediator transforming growth factor beta (TGF-β) (**Fig. 58.9**). This highly orchestrated sequential recruitment of subpopulations of monocytes probably plays an important role in myocardial healing. The granulocytes arriving on the scene of ischemic injury function as “first responders.” They serve to initiate and amplify the acute local inflammatory response. The reactive oxygen species that they elaborate may contribute to endothelial damage, reperfusion injury, and the clinical phenomenon of “no-reflow.” The first wave of proinflammatory and phagocytically active mononuclear cells constitutes a “demolition crew” that can clear necrotic debris and pave the way for the second wave of less inflammatory monocytes, which contribute to healing by promoting the formation of granulation tissue (**Fig. 58.10**). These “repair” monocyte/macrophages elaborate a palette of mediators that stimulate angiogenesis and extracellular matrix production by surviving myocardial stromal cells. New microvessels and fibrosis are key constituents of granulation tissue, and these processes furnish the foundation for myocardial scar formation, ventricular remodeling, and infarct healing.

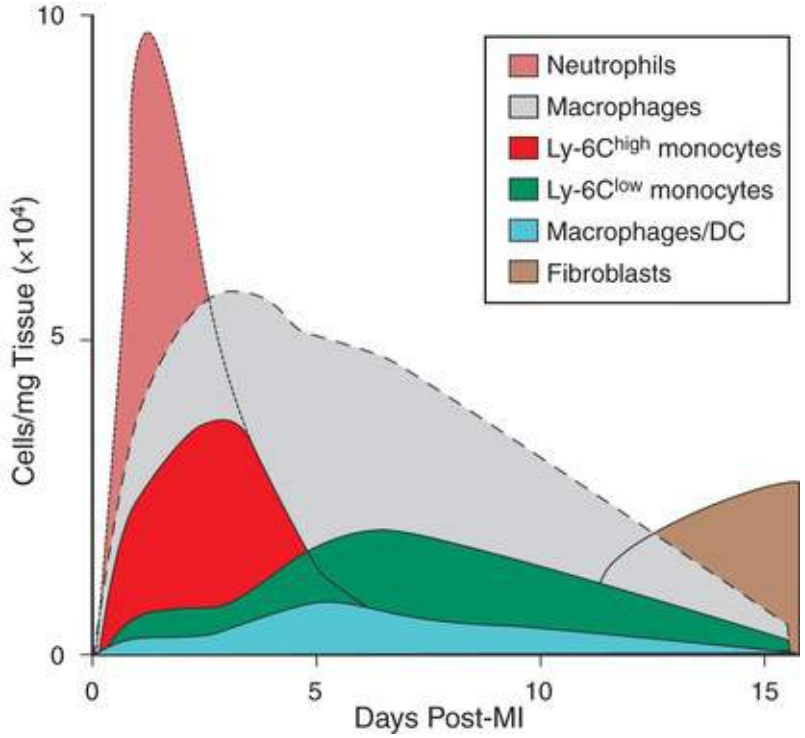


FIGURE 58.9 Sequencing waves of different cell types participate in myocardial infarction (MI) and healing. In the first hours to days following acute myocardial ischemia, neutrophils accumulate in the infarcting myocardium, as shown by the *salmon-colored* peak centered on days 1 and 2. Following this first wave of inflammatory cells, mononuclear phagocytes begin to accumulate in the ischemic tissue. Recent studies in mice have shown that in the early days of this monocytic infiltration, a particularly proinflammatory subset of mononuclear phagocytes characterized by high levels of the surface marker Ly-6C arrive first. In days 5 through 10, a reparative population of monocytes prevails (*green*), marked by low surface expression of Ly-6C. As the accumulation of leukocytes in the injured myocardium wanes, fibroblasts and related mesenchymal cells synthesize extracellular matrix (ECM) macromolecules such as collagen. ECM production contributes to repair and scar formation during healing of the ischemically-injured heart tissue. DC, Dendritic cells. (From Nahrendorf M et al. Mechanisms of myocardial ischemic injury, healing, and remodeling. In Morrow DA, editor. Myocardial Infarction: a Companion to Braunwald's Heart Disease. Philadelphia: Elsevier; 2017.)

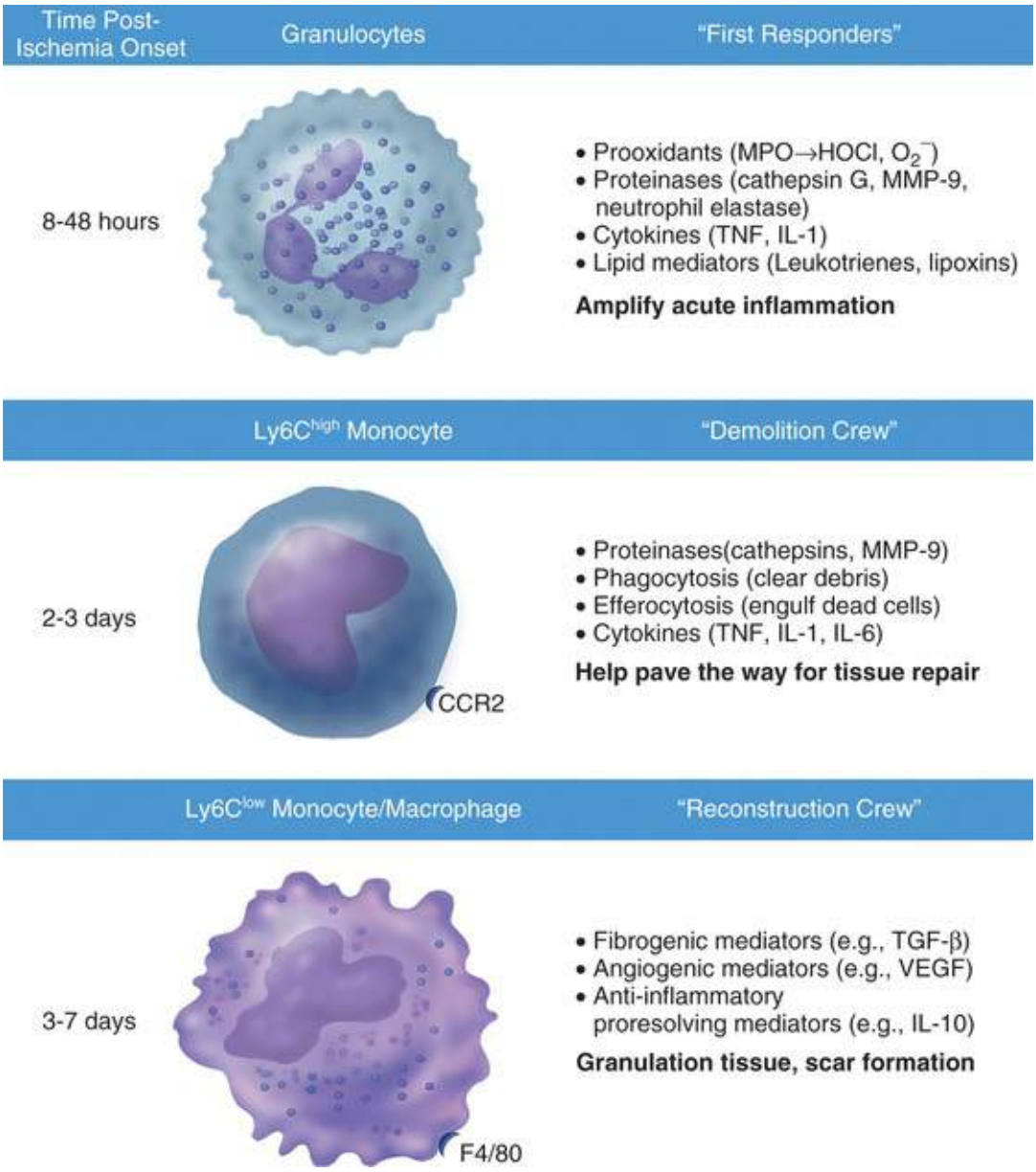


FIGURE 58.10 Temporal sequence and functions of leukocytes localizing in the infarcting myocardium. The leukocytes that predominate sequentially in the evolving myocardial infarct have specific sets of functions that govern the repair of the injured tissue. The granulocytes, "first responders," amplify the acute inflammatory response. The proinflammatory monocyte population functions as a "demolition crew" to pave the way for tissue repair. The reparative monocytes then engage in "reconstruction" to repair the injured tissue. CCR, CC chemokine receptor; HOCl, hypochlorous acid; IL, interleukin; MMP, matrix metalloproteinase; MPO, myeloperoxidase; O_2, superoxide anion; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor. (From Libby P, Nahrendorf M, Swirski FK. Leukocytes link local and systemic inflammation in ischemic cardiovascular disease: an expanded "cardiovascular continuum." J Am Coll Cardiol 2016;67:1091-103.)

The elucidation of this tightly orchestrated response to myocardial ischemic injury provides new perspectives on the pathophysiology of infarction, suggesting novel therapeutic targets to "tune" this local inflammatory response in any way that can favor salutary myocardial healing and prevent the adverse remodeling of the infarcted left ventricle associated with ischemic cardiomyopathy and poor outcomes. Recent experimental work has provided considerable new insight in this regard (**Fig. 58.11**). Sympathetic nervous activation caused by the pain and anxiety associated with the ACS can have far-reaching effects on the inflammatory response in addition to the well-recognized hemodynamic alterations produced by catecholamines. Beta-adrenergic stimulation can mobilize leukocyte progenitor cells from the bone marrow. Some of these cells can feed extra medullary hematopoiesis in the spleen. This "emergency hematopoiesis" can provide the leukocytes that participate in myocardial healing. In mice, mobilization of

a preformed pool of proinflammatory monocytes from the spleen depends in part on the role of angiotensin in signaling. This experimental observation may provide a mechanistic understanding of the ability of angiotensin-converting enzyme (ACE) inhibitors to combat adverse remodeling of the ischemic left ventricular (LV) myocardium. In addition to catecholamines, proinflammatory cytokines released during ACS can promote hematopoiesis and amplify the inflammatory response in the evolving infarct. In mice, interleukin (IL)-1β can stimulate the mobilization of precursors of leukocytes from the bone marrow. Inhibition of this proinflammatory cytokine does not change the size and experimental infarction but limits the decrement in contractile function in the infarcted ventricle.[26] This example illustrates how modulation of the inflammatory response in ischemic myocardium might influence the healing process.

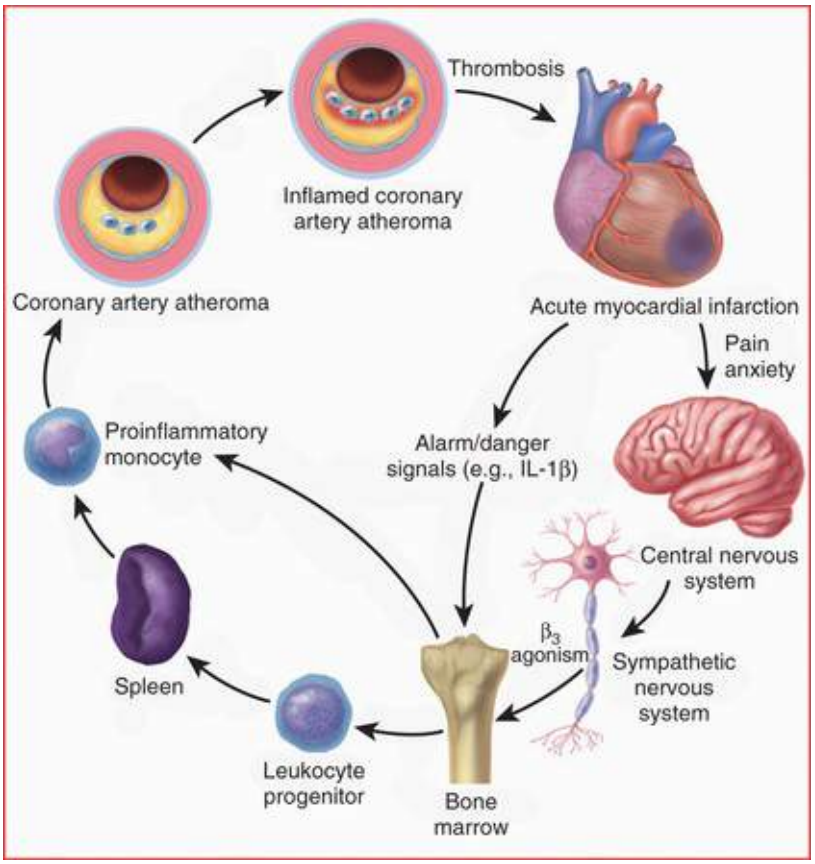


FIGURE 58.11 Leukocytes link local and systemic inflammation in ischemic cardiovascular disease. Myocardial infarction (MI) most often results from a disruption of a coronary artery atheroma that triggers thrombus formation. The sympathetic nervous system discharge in response to the pain and anxiety provoked by the acute MI evokes the mobilization of leukocyte progenitors from the bone marrow. Various humoral mediators, including the proinflammatory cytokine interleukin-1 beta (IL-1β) also help to recruit progenitor cells from the bone marrow. These progenitors can enter the bloodstream and make their way to the spleen, where they may engage in extramedullary leukopoiesis. The circulating proinflammatory monocytes can then home to atheromata that may localize remotely from the culprit lesion of the acute MI, setting the stage for a round of aggravated plaque evolution and recurrent events. This cyclic concept builds on the "cardiovascular continuum" concept promulgated by Dzau and Braunwald in 1991. (From Libby P, Nahrendorf M, Swirski FK. Leukocytes link local and systemic inflammation in ischemic cardiovascular disease: an expanded "cardiovascular continuum." J Am Coll Cardiol 2016;67:1091-103.)

Another insight bolstered by recent experimental work is the concept that inflammation in the myocardium can ignite inflammatory activity in remote atherosclerotic plaques, predisposing them to disrupt and provoke thrombosis. Such "echoes" of myocardial inflammation in plaques themselves may explain some of the early recurrent coronary events in patients with ACS. Moreover, this observation provides some mechanistic understanding of clinical observations that coronary atherosclerotic plaques

remote from the culprit lesion exhibit inflammatory activation not only in the non–infarct-related artery, but also in other arterial beds, such as the carotid circulation.

Although much of the information in **Fig. 58.11** emerged from murine experiments, imaging observations in humans lend credence to their clinical applicability. Uptake of the glucose analogue ^{18}F-deoxyglucose (FDG) monitors metabolic activity. Patients with ACS show increased uptake of FDG in bone marrow and in the spleen compared to stable patients. These observations support the clinical translatability of the mouse experiments that revealed bone marrow activation following coronary artery ligation and boosted inflammatory processes in the spleen. Indeed, those with increased splenic FDG uptake appear to have greater risk for recurrent events.[27] Thus a "cardiosplenic axis" of inflammatory signaling likely operates in humans as well as mice, furnishing new mechanistic insight into the pathogenesis of MI and uncovering novel therapeutic targets.

Modification of Pathologic Changes by Reperfusion

When reperfusion of myocardium undergoing the evolutionary changes from ischemia to infarction occurs sufficiently early (i.e., within 15 to 20 minutes), it can prevent necrosis from developing. Beyond this early stage, the number of salvaged myocytes—and therefore the amount of salvaged myocardial tissue (area of necrosis/area at risk)—is directly related to the duration of coronary artery occlusion, the level of myocardial oxygen consumption, and collateral blood flow (**Fig. 58.12**). Reperfused infarcts typically show a mixture of necrosis, hemorrhage within zones of irreversibly injured myocytes, coagulative necrosis with contraction bands, and distorted architecture of cells in the reperfused zone (**eFig. 58.3**). Reperfusion of infarcted myocardium accelerates the washout of leaked intracellular proteins, thereby producing an exaggerated and early peak value of substances such as the MB fraction of creatine kinase (CK-MB) and cardiac-specific troponin T and I (see later).[1]

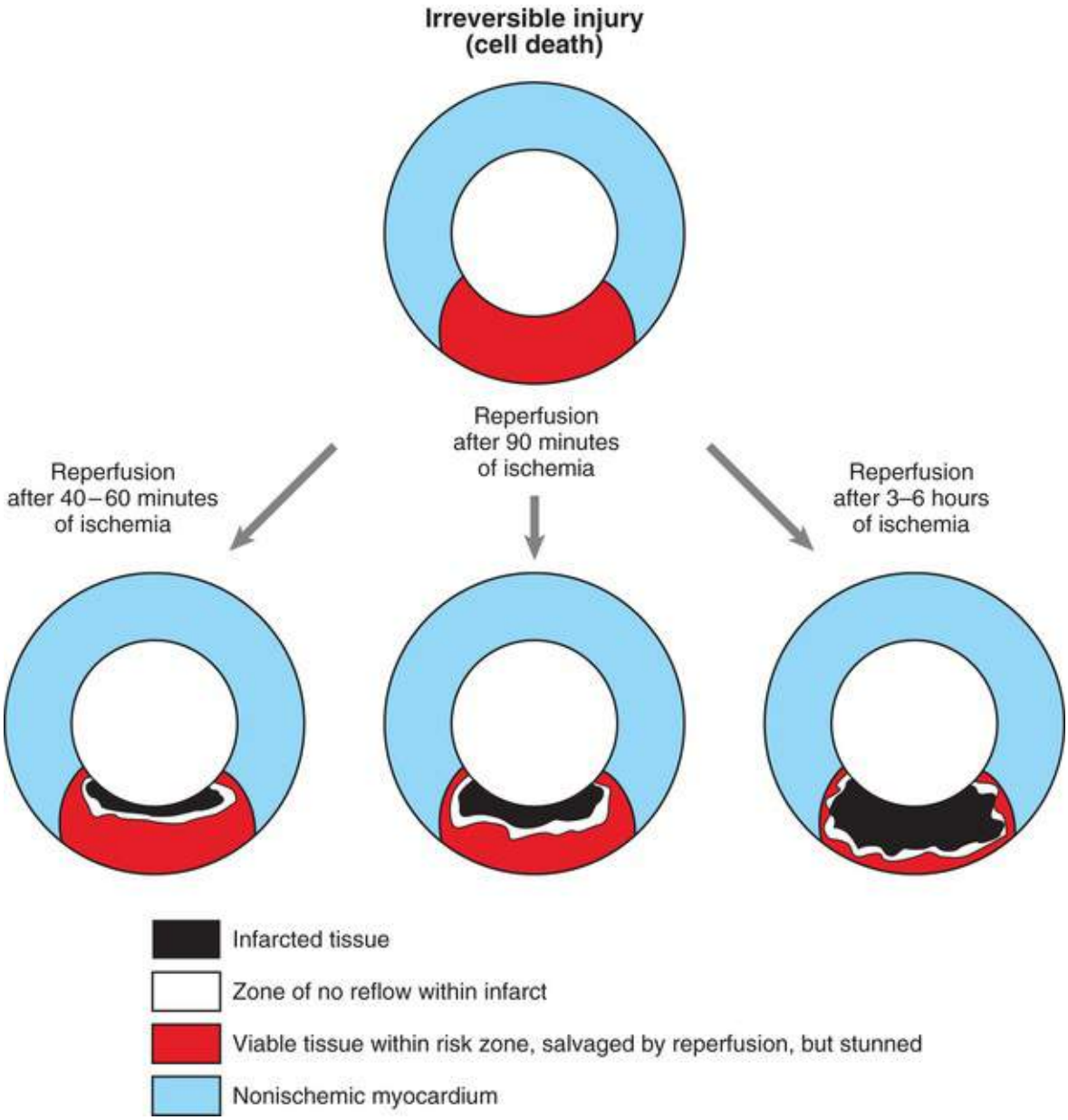
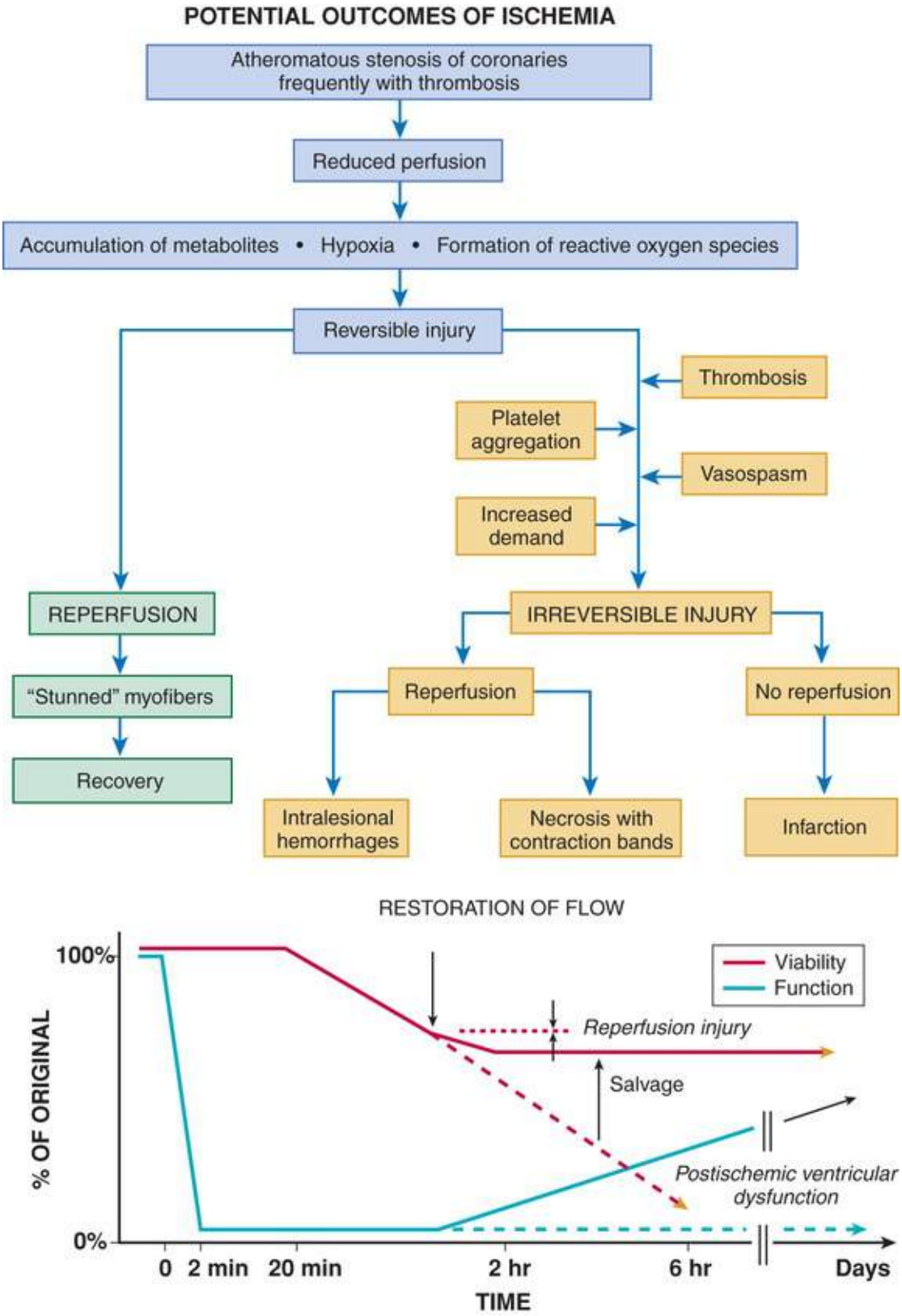


FIGURE 58.12 **Top,** Schematic of a transmural section of the heart after a short period of ischemia (≤20 minutes). Cell death does not occur (reversible injury), but tissue is stunned and reperfusion arrhythmias might ensue. **Middle** and **bottom,** Schematic of a transmural section of the left ventricle derived from studies in the anesthetized canine model of proximal coronary occlusion and reperfusion. After 40 to 60 minutes of ischemia, irreversible cell damage is confined to the subendocardium. A smaller area of no-reflow is present within the necrotic region. If reperfusion is delayed to 90 minutes, the necrotic region expands from the subendocardium to the midmyocardium within the ischemic risk zone, accompanied by an expansion of the no-reflow region. After 3 to 6 hours of ischemia, necrosis becomes nearly transmural, and the no-reflow region, although contained within the necrotic area, becomes larger. (From Kloner RA et al. Reperfusion injury: prevention and management. In Morrow DA, editor. Myocardial Infarction: a Companion to Braunwald's Heart Disease. Philadelphia: Elsevier; 2017.)



EFIGURE 58.3 Several potential outcomes of reversible and irreversible ischemic injury to the myocardium. The schematic diagram at the *bottom* depicts the timing of changes in function and viability. A key point is that although function drops dramatically after coronary occlusion, the tissue is still viable for a period. This is the basis for early aggressive efforts at reperfusion of patients with STEMI. (From Schoen FJ. The heart. In Kumar V, Abbas AK, Fausto N, editors. Robbins & Cotran Pathologic Basis of Disease. 8th ed. Philadelphia: Saunders; 2009.)

Coronary Anatomy and Location of Infarction

Angiographic studies performed in the earliest hours of STEMI find an approximately 90% incidence of total occlusion of the infarct-related vessel. Spontaneous fibrinolysis of the thrombotic occlusion can

occur in the period following the onset of MI. Pharmacologic fibrinolysis and PCI markedly increase the proportion of patients with a patent infarct-related artery early after STEMI.

A STEMI with transmural necrosis typically occurs distal to an acutely totally occluded coronary artery with thrombus superimposed on an eroded or ruptured plaque (**see Fig. 58.4**). Yet, total occlusion of a coronary artery does not always cause MI. Collateral blood flow and other factors, such as the level of myocardial metabolism, presence and location of stenoses in other coronary arteries, rate of development of the obstruction, and quantity of myocardium supplied by the obstructed vessel, all influence the viability of myocardial cells distal to the occlusion.

Studies of patients in whom STEMI ultimately develops after having undergone coronary angiography at some time before its occurrence have helped clarify the extent of coronary disease before infarction. Although high-grade stenoses more frequently lead to STEMI than do less obstructive lesions, STEMI can result from sudden thrombotic occlusion at the site of disruption of previously noncritically stenosed plaque. When collateral vessels perfuse an area of the ventricle, an infarct may occur at a distance from a coronary occlusion. For example, following gradual obliteration of the lumen of the right coronary artery (RCA), collateral vessels arising from the left anterior descending coronary artery (LAD) can keep the inferior wall of the left ventricle viable. Later, an occlusion of LAD may cause infarction of the distal inferior wall.

Right Ventricular Infarction

Approximately 30% to 50% of patients with inferior infarction have some involvement of the right ventricle.[28,29] RV infarction almost invariably develops in association with a large infarction of the adjacent septum and inferior LV walls, but isolated infarction of the right ventricle is seen in just 3% to 5% of autopsy-proven cases of MI. RV infarction occurs less often than would be anticipated from the frequency of atherosclerotic lesions involving the RCA. The classic presentation of an RV infarct is hypotension, clear lung fields, and elevated jugular venous pressures. Acute management of RV infarction complicated by cardiogenic shock includes judicious volume replacement, early revascularization, maintenance of atrioventricular synchrony, and in refractory cases, mechanical circulatory support (**see Chapter 59**). In contrast to the left ventricle, the right ventricle can sustain long periods of ischemia but still demonstrate excellent recovery of contractile function after reperfusion.

Atrial Infarction

Infarction of the atria occurs in up to 10% of patients with STEMI if PR-segment displacement is used as the criterion. Although isolated atrial infarction is observed in less than 5% of patients with STEMI at autopsy, it often occurs in conjunction with ventricular infarction and can cause rupture of the atrial wall.[30] This type of infarction is more common on the right than the left side, occurs more frequently in the atrial appendages than in the lateral or posterior walls of the atrium, and can result in thrombus formation. Atrial arrhythmias frequently accompany atrial infarction. Reduced secretion of atrial natriuretic peptide may ensue and lead to a low–cardiac output syndrome when RV infarction coexists.

Collateral Circulation in Acute Myocardial Infarction

Patients with occlusive coronary artery disease (CAD) frequently have a particularly well-developed coronary collateral circulation, especially those with reduction of the luminal cross-sectional area by more than 75% in one or more major vessels; patients with chronic hypoxia, as occurs in severe anemia, chronic obstructive pulmonary disease (COPD), and cyanotic congenital heart disease; and those with LV

hypertrophy[31] (**see Fig. 58.5 and Chapter 57**).

The magnitude of coronary collateral flow is a principal determinant of infarct size. Indeed, patients with abundant collateral vessels may have totally occluded coronary arteries without evidence of infarction in the distribution of that artery; thus survival of myocardium distal to such occlusions depends largely on collateral blood flow.[32] Even if the collateral perfusion existing at the time of coronary occlusion does not prevent infarction, it may still exert a beneficial effect by preventing the formation of LV aneurysms. The presence of a high-grade stenosis (90%), possibly with periods of intermittent total occlusion, probably permits the development of collateral vessels that remain only as potential conduits until a total occlusion occurs or recurs. Total occlusion then brings these channels into full operation. Patients with angiographic evidence of collateral formation have improved angiographic and clinical outcomes after MI.

Nonatherosclerotic Causes of Acute Myocardial Infarction

Numerous pathologic processes other than atherosclerosis can involve the coronary arteries and result in STEMI (**see Table 58.3**).[1] For example, coronary arterial occlusions can result from embolization into a coronary artery. The causes of coronary embolism are numerous: infective endocarditis and nonbacterial thrombotic endocarditis (**see Chapter 73**), mural thrombi, prosthetic valves, neoplasms, air introduced at cardiac surgery, and calcium deposits from manipulation of calcified valves at surgery. In situ thrombosis of coronary arteries can occur secondary to chest wall trauma or hypercoagulable states.

Spontaneous coronary artery dissection (SCAD), once thought to be a relatively rare event, is identified more frequently now with greater utilization of intracoronary imaging and may account for 10% to 30% of MIs in women younger than 50. Initial triage and evaluation of patients with suspected SCAD should follow standard ACS algorithms. A clear dissection flap and thrombosis may be visible at angiography, but often there is only an intramural hematoma, which can be mistaken for vasospasm or an atherosclerotic plaque unless intracoronary imaging is used. Revascularization strategies for SCAD diverge from standard ACS recommendations. Conservative management with oral and intravenous (IV) antithrombotic therapy alone is recommended if coronary flow is preserved because of high rates of PCI-related complications. Revascularization with PCI or coronary artery bypass grafting (CABG) should be considered for occlusive lesions, recognizing a higher risk of complications.[33]

Rarer causes include syphilitic aortitis, which can produce marked narrowing or occlusion of one or both coronary ostia, whereas Takayasu arteritis can result in obstruction of the coronary arteries. Necrotizing arteritis, polyarteritis nodosa, mucocutaneous lymph node syndrome (Kawasaki disease), systemic lupus erythematosus (**see Chapter 94**), and giant cell arteritis can cause coronary occlusion. Therapeutic levels of mediastinal radiation can result in coronary arteriosclerosis[34] with subsequent infarction. MI can also result from coronary arterial involvement in patients with amyloidosis (**see Chapter 77**), Hurler syndrome, pseudoxanthoma elasticum, and homocystinuria. Cocaine can cause MI in patients with normal coronary arteries, preexisting MI, documented coronary artery disease, or coronary artery spasm (**see Chapter 80**).

Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA)

MINOCA is defined as evidence of MI (positive cardiac biomarker and corroborative clinical evidence of infarction) with angiographically normal or near-normal coronary arteries (the absence of obstructive CAD on angiography, [i.e. no coronary artery stenosis ≥50%], in any potential infarct-related artery), and no other explanation for the presentation.[35,35a] Coronary artery spasm, plaque erosion or rupture, and

coronary dissection are common MINOCA etiologies affecting the epicardial arteries, as are plaque erosion and plaque rupture not discerned by standard angiography, whereas the two most common myocardial or microvascular mimickers of MI are acute myocarditis (**see Chapter 79**) and acute stress (takotsubo) cardiomyopathy.

Compared to patients with atherosclerotic-mediated MI, patients with MINOCA tend to be young and more often females, with relatively few coronary risk factors except a history of cigarette smoking. One third of patients with MINOCA present with STEMI.[36] Usually, they have no history of angina pectoris before the infarction. These patients do not generally have a prodrome before infarction, but the clinical, laboratory, and electrocardiographic features of STEMI otherwise resemble those present in the overwhelming majority of patients with STEMI, who have classic obstructive atherosclerotic CAD. Approximately half of patients with MINOCA have smooth vessels on angiography, whereas the other half has some nonobstructive irregularities that may predispose them to vasospasm or plaque erosions.

Additional causes MI in the setting of normal-appearing coronary arteries include (1) coronary emboli, perhaps from a small mural thrombus, prolapsed mitral valve, or myxoma; (2) CAD in vessels too small to be visualized on coronary arteriography or coronary arterial thrombosis with subsequent recanalization; (3) a hematologic disorder (e.g., polycythemia vera, cyanotic heart disease with polycythemia, sickle cell anemia, disseminated intravascular coagulation, thrombocytosis, thrombotic thrombocytopenic purpura) causing in situ thrombosis in the presence of normal coronary arteries; (4) augmented oxygen demand (e.g., thyrotoxicosis, amphetamine use); (5) hypotension secondary to sepsis, blood loss, or pharmacologic agents; and (6) anatomic variations, such as anomalous origin of a coronary artery, coronary arteriovenous fistula, or a myocardial bridge.[35a]

Prognosis in MINOCA

In general, patients who have survived STEMI without evidence of significant CAD have a better long-term outlook than those with atherosclerotic-mediated STEMI; in-hospital mortality is approximately 60% lower, and 1-year mortality, 40% lower.[36] However, the subsequent risk for patients presenting with MINOCA is largely based on the underlying etiology and comorbidities. Cardiac magnetic resonance imaging is recommended to exclude myocarditis in patients without clear cause of MINOCA.[35a]

Stress (Takotsubo) Cardiomyopathy

Acute stress cardiomyopathy, also termed *transient LV apical ballooning syndrome* or takotsubo cardiomyopathy, typically involves transient wall motion abnormalities involving the LV apex and midventricle (**Fig. 58.13**), although other patterns have been reported, including “reverse” takotsubo pattern. This syndrome occurs in the absence of obstructive epicardial CAD and can mimic STEMI.[37] Typically, an episode of physical or psychological stress precedes the development of takotsubo cardiomyopathy; although some cases lack an evident precipitant. More than half of patients presenting with takotsubo cardiomyopathy have an active or history of a neurologic or psychiatric disorder, potentially linking neurologic-mediated vasoconstriction. Initial ECGs demonstrate substantial and often diffuse ST-segment elevation, prompting, when coupled with the typical (frequently severe) chest discomfort, the appropriate immediate referral for coronary angiography. One proposed ECG algorithm for differentiating stress cardiomyopathy from STEMI found that different patterns of ST elevations across the different coronary territories could distinguish stress cardiomyopathy from ACS with excellent specificity. However, this observation requires validation and should not preclude urgent catheterization to exclude acute thrombotic lesions.[38]

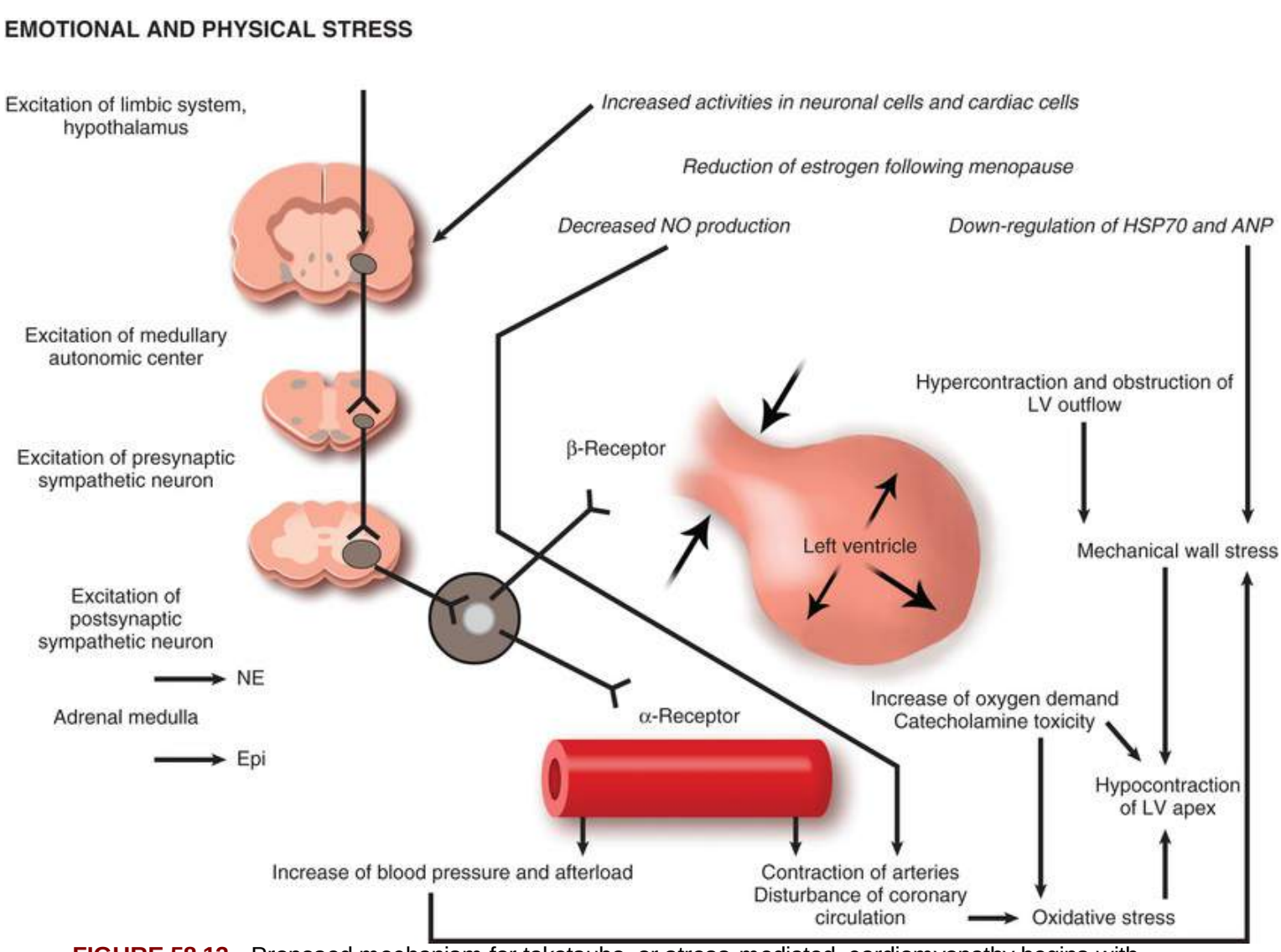


FIGURE 58.13 Proposed mechanism for takotsubo, or stress-mediated, cardiomyopathy begins with sudden and severe emotional stress, which activates central autonomic network neurons expressing estrogen receptors. Simultaneously, sympathetic neuronal and adrenomedullary hormonal outflow increases dramatically and results in release of epinephrine (*Epi*) from the adrenal medulla combined with the release of norepinephrine (*NE*) from cardiac and extracardiac sympathetic nerves, which stimulate adrenoceptors in the blood vessels of the heart. Contraction of resistance vessels rapidly increases systemic blood pressure and cardiac afterload. High circulating levels of NE and Epi can precipitate catecholamine toxicity in cardiomyocytes via occupation of adrenoceptors. The typical hypercontraction of the basal sections of the heart, which leads to functional basal obstruction of left ventricular (*LV*) outflow, further exacerbates LV wall stress and increases end-diastolic pressure. *ANP,* Atrial natriuretic peptide; *HSP70,* heat shock protein 70; *NO,* nitric oxide. (From Akashi YJ, Goldstein DS, Barbaro G, Ueyama T. Takotsubo cardiomyopathy: a new form of acute, reversible heart failure. Circulation 2008;118:2754.)

The etiology of stress-induced cardiomyopathy is not clear, but neurally activated or circulating catecholamine-mediated microvascular dysfunction, as well as myocardial stunning and injury, play important roles. Most patients with takotsubo cardiomyopathy will experience rapid recovery of ventricular function, although more than 20% of patients do suffer in-hospital complications, including heart failure, arrhythmias, and death, and at rates similar to patients with ACS.[37,39]

Pathophysiology

Left Ventricular Function

Systolic Function

On interruption of antegrade flow in an epicardial coronary artery, the zone of myocardium supplied by that vessel immediately loses its ability to shorten and perform contractile work (**Fig. 58.14**). Four abnormal contraction patterns develop in sequence: (1) *dyssynchrony,* or dissociation of the time course of contraction of adjacent segments; (2) *hypokinesis,* or a reduction in the extent of shortening; (3) *akinesis,* or cessation of shortening; and (4) *dyskinesis,* paradoxical expansion, and systolic bulging. Hyperkinesis of the remaining normal myocardium initially accompanies dysfunction of the infarct. The early hyperkinesis of the noninfarcted zones probably results from acute compensation, including increased activity of the sympathetic nervous system and the Frank-Starling mechanism. A portion of this compensatory hyperkinesis is ineffective work because contraction of the noninfarcted segments of myocardium causes dyskinesis of the infarct zone. The increased motion of the noninfarcted region subsides within 2 weeks of infarction, during which some degree of recovery often occurs in the infarct region as well, particularly if reperfusion of the infarcted area occurs and myocardial stunning diminishes.

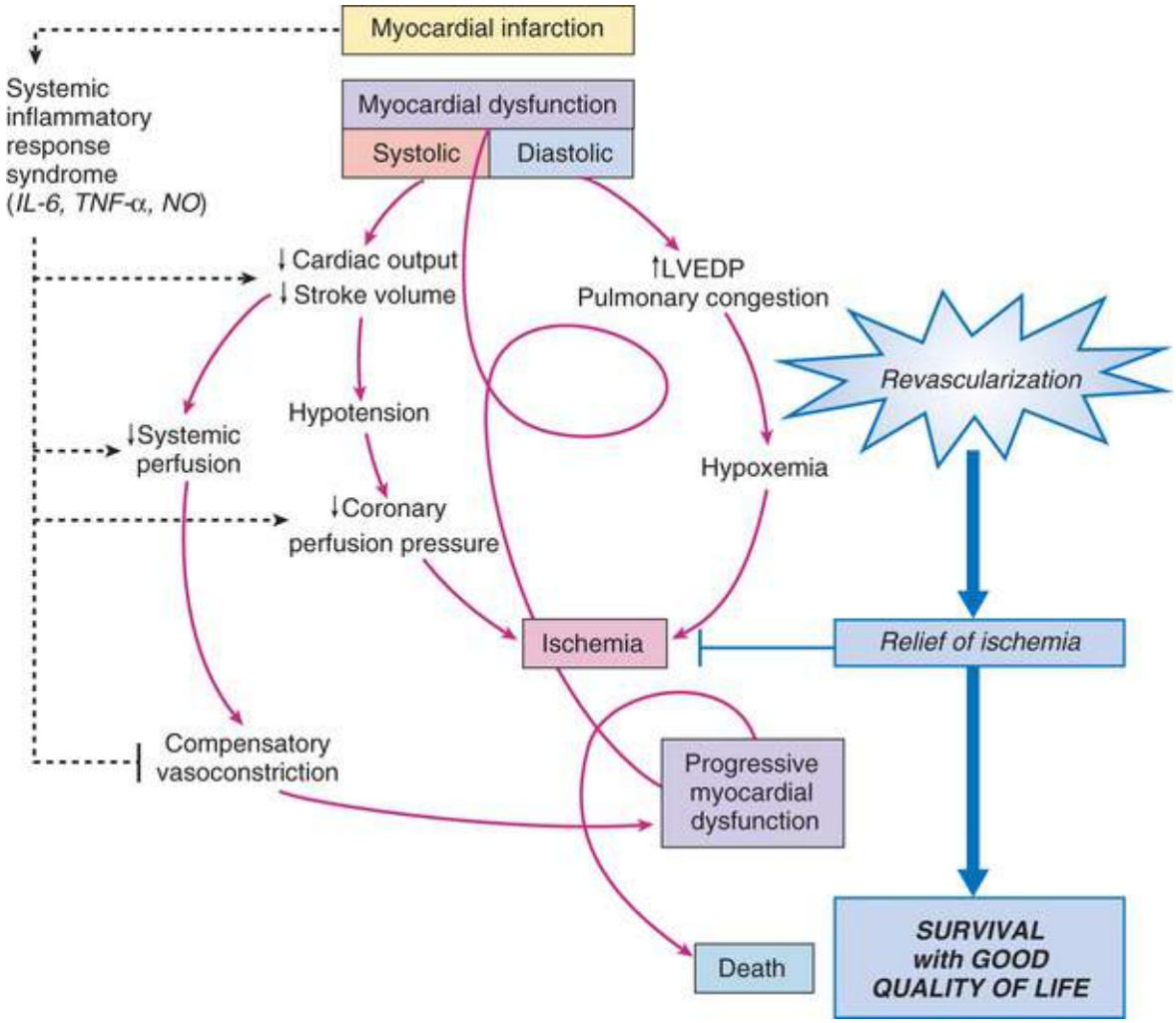


FIGURE 58.14 Pathophysiology of cardiogenic shock. Myocardial injury causes systolic and diastolic dysfunction. A decrease in cardiac output leads to a decrease in systemic and coronary perfusion. The decreased perfusion exacerbates ischemia and causes cell death in the infarct border zone and the remote zone of myocardium. Inadequate systemic perfusion triggers reflex vasoconstriction, which is usually insufficient. Systemic inflammation may play a role in limiting the peripheral vascular compensatory response and may contribute to the myocardial dysfunction. Whether inflammation plays a causal role or is only an epiphenomenon remains unclear. Revascularization leads to relief of ischemia. Demonstration of an increase in cardiac output or the LV ejection fraction as the mechanism of benefit of revascularization has not been possible, but revascularization significantly increases the likelihood of survival with good quality of life. *IL-6,* Interleukin-6; *LVEDP,* left ventricular end-diastolic pressure; *NO,* nitric oxide; *TNF,* tumor necrosis factor. (From Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. Circulation 2008;117:686, 2008.)

Patients with STEMI may also have reduced myocardial contractile function in noninfarcted zones. This finding may result from previous obstruction of the coronary artery supplying the noninfarcted region of the ventricle and loss of collaterals from the freshly occluded infarct-related vessel, a condition termed *ischemia at a distance*. Conversely, the development of collaterals before STEMI occurs may allow greater preservation of regional systolic function in an area of distribution of the occluded artery and improvement in the LV ejection fraction (EF) early after infarction[31] (**see Fig. 58.5**).

If a sufficient quantity of myocardium undergoes ischemic injury (**see Fig. 58.12**), LV pump function becomes depressed; cardiac output, stroke volume, blood pressure, and peak dP/dt decline; and end-systolic volume increases. The degree to which end-systolic volume increases is perhaps the most powerful hemodynamic predictor of mortality following STEMI.[40] Paradoxical systolic expansion of an area of ventricular myocardium further decreases LV stroke volume.[41] As necrotic myocytes slip past each other, the infarct zone thins and elongates, especially in patients with large anterior infarcts, thereby leading to expansion of the infarct (see later). In some patients a vicious circle of dilation begetting

further dilation ensues. Inhibitors of the renin-angiotensin-aldosterone system (RAAS) can limit the degree of ventricular dilation, which depends closely on infarct size, patency of the infarct-related artery, and RAAS activation, even in the absence of symptomatic LV dysfunction.[42] With time, edema and ultimately fibrosis (via mechanisms previously discussed; **see Fig. 58.9**) increase the stiffness of the infarcted myocardium back to and beyond preinfarct values. Increasing stiffness in the infarcted zone of myocardium improves LV function because it prevents paradoxical systolic wall motion (dyskinesia).

The likelihood of clinical symptoms developing correlates with specific parameters of LV function. The earliest abnormality is ventricular stiffness in diastole (see later), which occurs with infarcts involving only a small portion of the left ventricle. When the abnormally contracting segment exceeds 15% of the myocardium, the EF may decline, and LV end-diastolic pressure and volume may increase. The risk for the development of physical signs and symptoms of LV failure also increases in proportion to increasing areas of abnormal LV wall motion. Clinical heart failure accompanies areas of abnormal contraction exceeding 25%, and loss of more than 40% of the LV myocardium usually leads to cardiogenic shock, often fatal.

Unless extension of the infarct occurs, some improvement in wall motion takes place during the healing phase, with recovery of function occurring in initially reversibly injured (stunned) myocardium (**see Fig. 58.12 and eFig. 58.3**). Regardless of the age of the infarct, patients who continue to demonstrate abnormal wall motion involving 20% to 25% of the left ventricle will probably manifest hemodynamic signs of LV failure, with its attendant poor prognosis for long-term survival.

Diastolic Function

The diastolic properties of the left ventricle change in ischemic and infarcted myocardium (**see Chapters 22, 23, and 26**). These alterations are associated with a decrease in the peak rate of decline in LV pressure (peak—dP/dt), an increase in the time constant of the fall in LV pressure, and an initial rise in LV end-diastolic pressure. Over several weeks, end-diastolic volume increases, and diastolic pressure begins to fall toward normal. As with impairment of systolic function, the magnitude of the diastolic abnormality appears to relate to the size of the infarct.

Circulatory Regulation

Patients with STEMI have an abnormality in circulatory regulation. The process begins with an anatomic or functional obstruction in the coronary vascular bed that results in regional myocardial ischemia and, if the ischemia persists, in MI. If the infarct is of sufficient size, it depresses overall LV function such that LV stroke volume falls and filling pressure rises.[43] A marked depression in LV stroke volume ultimately lowers aortic pressure and, together with increased LV end-diastolic pressure,[44] reduces coronary perfusion pressure. This condition may intensify myocardial ischemia and thereby initiate a vicious cycle (**Fig. 58.14**), leading to cardiogenic shock, which occurs in 5% to 8% of patients with STEMI.[45,46]

Systemic inflammation secondary to myocardial injury leads to the release of cytokines that contribute to the vasodilation and decreased systemic vascular resistance.[47] The inability of the left ventricle to empty normally also increases preload; that is, it dilates the well-perfused, normally functioning portion of the left ventricle. This compensatory mechanism tends to restore stroke volume to normal levels, but at the expense of a reduced EF. Dilation of the left ventricle also elevates ventricular wall tension, because Laplace law dictates that at any given arterial pressure, the dilated ventricle must develop higher wall tension. This increased afterload not only depresses LV stroke volume but also elevates myocardial oxygen consumption, which in turn intensifies the myocardial ischemia. When regional myocardial

dysfunction is limited and the function of the remainder of the left ventricle is normal, compensatory mechanisms—especially hyperkinesis of the nonaffected portion of the ventricle—sustain overall LV function. If a large portion of the left ventricle ceases to function, pump failure ensues.

Ventricular Remodeling

As a consequence of STEMI, the changes in LV size, shape, and thickness involving both the infarcted and the noninfarcted segments of the ventricle described earlier occur and are collectively referred to as *ventricular remodeling*—which in turn can influence ventricular function and prognosis.[48] Changes in LV dilation combined with hypertrophy of residual noninfarcted myocardium cause remodeling. After infarct size, other important factors driving the process of LV dilation are ventricular volume, loading conditions, and infarct artery patency.[41,49] Elevated ventricular pressure contributes to increased wall stress and the risk for infarct expansion, but a patent infarct artery accelerates myocardial scar formation and increases tissue turgor in the infarct zone, thereby reducing the risk for infarct expansion and ventricular dilation. Inflammation, a key component in healing, may also govern the degree of adverse versus appropriate compensatory myocardial remodeling, as discussed.[25] Immediately post-MI, EF correlates only modestly with eventual LV volumes. Many large MIs do not evolve to a poorly remodeled heart, while a subset of patients with relatively smaller infarcts progress to significant adverse remodeling. Genetic or epigenetic differences in the regulation of the healing process resulting from a variable inflammatory response may explain in part the heterogeneous natural history of infarct healing[49] (**Fig. 58.15**). Exaggerated ventricular dilation, for example, may results from an inflammatory process with excessive matrix degradation, whereas greater scar deposition and less dilation may follow an inflammatory process that preferentially stimulates a more profibrotic healing process.[50]

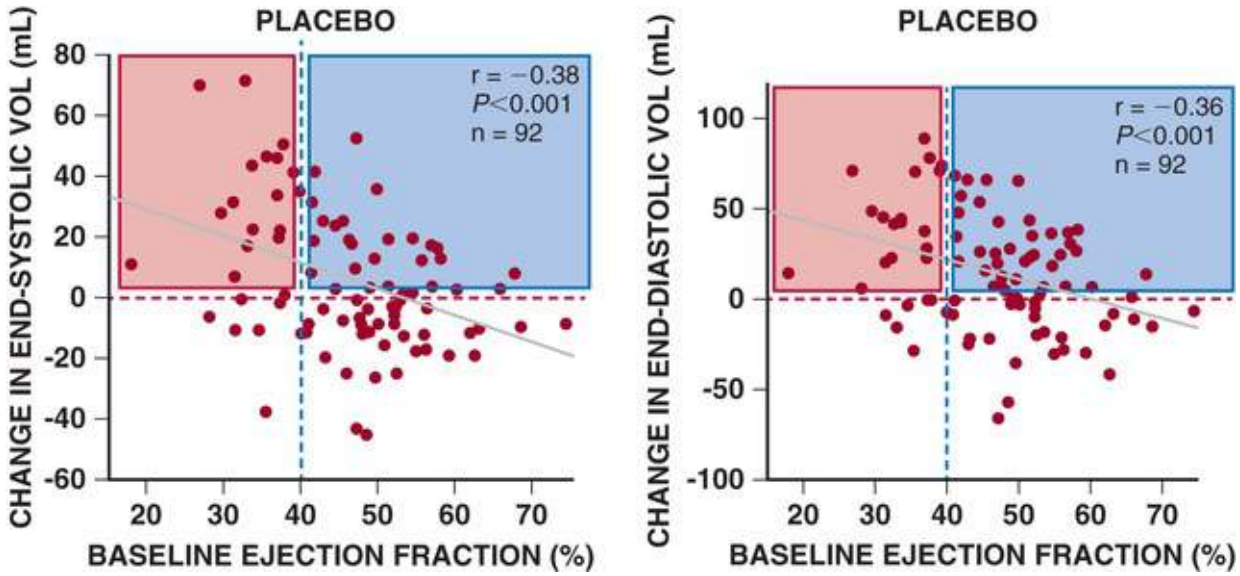


FIGURE 58.15 Relationship between baseline ejection fraction (EF) and subsequent change in left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV). LV angiography was performed 4.3 days after percutaneous coronary intervention and was repeated 4 months later. LV remodeling developed over time in both patients with reduced baseline EF (*orange area*) and in patients with normal baseline EF (*blue area*). Although a correlation exists between baseline EF and changes in systolic volumes, a number of patients with preserved EF will progress to ventricular dilation, while some with reduced EF will not. (From Westman PC, Lipinski MJ, Luger D, et al. Inflammation as a driver of adverse left ventricular remodeling after acute myocardial infarction. J Am Coll Cardiol 2016;67:2050-60.)

Infarct Expansion

An increase in the size of the infarcted segment, known as *infarct expansion*, is defined as "acute dilation and thinning of the area of infarction not explained by additional myocardial necrosis." Infarct expansion appears to result from a combination of slippage between muscle bundles, which reduces the number of myocytes across the infarct wall; disruption of normal myocardial cells; and destruction of extracellular matrix within the necrotic zone. Infarct expansion involves thinning and dilation of the infarct zone before the formation of a firm, fibrotic scar. The degree of infarct expansion appears to be related to preinfarction wall thickness, with existing hypertrophy possibly protecting against infarct thinning.

On a cellular level, the degree of expansion and worsening remodeling depends on the intensity of the inflammatory response to the necrotic cells. Suppression of cytokine expression and stimulation may minimize the degree of inflammation and thus final infarct size.[25,26,49,51]

The apex, the thinnest region of the left ventricle, is particularly vulnerable to infarct expansion. Infarction of the apex secondary to LAD occlusion causes the radius of curvature at the apex to increase, thereby exposing this normally thin region to a marked elevation in wall stress.

Infarct expansion associates with both higher mortality and a higher incidence of nonfatal complications, such as heart failure and ventricular aneurysm. Infarct expansion is best recognized as elongation of the noncontractile region of the ventricle on echocardiography or CMR. When the expansion is severe enough to cause symptoms, the most characteristic clinical findings are deterioration of systolic function, new or worsening pulmonary congestion, and development of ventricular arrhythmias.

Ventricular Dilation

Although infarct expansion plays an important role in the ventricular remodeling that occurs early after MI, remodeling is also caused by dilation of the viable portion of the ventricle, which commences immediately after STEMI and progresses for months or years thereafter. A shift of the pressure-volume curve of the left ventricle to the right, which results in a larger LV volume at any given diastolic pressure, may accompany dilation. This dilation of the noninfarcted zone can be viewed as a compensatory mechanism that maintains stroke volume in the presence of a large infarction. This chronic dilation may also be a manifestation of a chronic inflammatory process affecting the myocardium that began at the time of the large infarct, but never fully resolved.[51] Large STEMIs place an extra load on the residual functioning myocardium, a burden that presumably causes the compensatory hypertrophy of the noninfarcted myocardium. This hypertrophy could help compensate for the functional impairment caused by the infarct and may be responsible for some of the hemodynamic improvement seen in some patients in the months after infarction.

Effects of Treatment

Several factors can affect ventricular remodeling after STEMI, notably final infarct size (**see Fig. 58.12 and eFig. 58.3**). Acute reperfusion and other measures to restrict the extent of myocardial necrosis limit the increase in ventricular volume after STEMI. Multiple pharmacologic agents that target reperfusion injury or regenerative therapies aimed at limiting infarct size have undergone evaluation in clinical trials, although few have produced significant results in adequately powered phase III investigations[52] (**see Chapter 59**). Appropriate and timely scar formation in the infarct also affects the degree of LV remodeling post-MI. Glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs) given early after MI can cause scar thinning and greater infarct expansion, whereas RAAS inhibitors attenuate the ventricular enlargement. Additional beneficial consequences of inhibition of angiotensin II that may

contribute to myocardial protection include attenuation of endothelial dysfunction and direct antiatherogenic effects. Inhibition of aldosterone action may limit excessive fibrosis and decrease the development of ventricular arrhythmias.

Pathophysiology of Other Organ Systems

Pulmonary Function.
Increased pulmonary capillary hydrostatic pressure in the setting of STEMI can promote interstitial edema and result in arteriolar and bronchiolar compression that ultimately causes perfusion of poorly ventilated alveoli with resultant hypoxemia. In addition to hypoxemia, diffusion capacity decreases. Hyperventilation often occurs in patients with STEMI and may cause hypocapnia and respiratory alkalosis, particularly in restless, anxious patients with pain. Pulmonary extravascular (interstitial) water content, LV filling pressure, and the clinical signs and symptoms of LV failure are correlated. The increase in pulmonary extravascular water may cause the alterations in pulmonary mechanics observed in patients with STEMI: reduction in airway conductance, pulmonary compliance, forced expiratory volume, and midexpiratory flow rate and an increase in closing volume, presumably related to the widespread closure of small, dependent airways during the first 3 days after STEMI. Ultimately, severe increases in extravascular water may lead to pulmonary edema. Virtually all lung volume indices—total lung capacity, functional residual capacity, and residual volume, as well as vital capacity—fall during STEMI.

Reduction of Affinity of Hemoglobin for Oxygen.
In patients with MI, particularly when complicated by LV failure or cardiogenic shock, the affinity of hemoglobin for oxygen falls (i.e., P50 increases). The increase in P50 results from increased levels of erythrocyte 2,3-diphosphoglycerate, which is an important compensatory mechanism that mediates an estimated 18% increase in release of oxygen from oxyhemoglobin in patients with cardiogenic shock.

Endocrine Function

Glucose Homeostasis
(**see Chapter 51**). Hyperglycemia is common in patients presenting with STEMI and is associated with worse outcomes. Although patients with STEMI often have absolute concentrations of blood insulin in the normal range, these levels are usually inappropriately low for their blood sugar concentration, indicating insulin resistance. Patients with cardiogenic shock frequently have marked hyperglycemia with depressed levels of circulating insulin. Abnormalities in insulin secretion and the resultant impaired glucose tolerance appear to result from a reduction in pancreatic blood flow caused by the splanchnic vasoconstriction accompanying shock. In addition, increased activity of the sympathetic nervous system with augmented circulating catecholamines inhibits insulin secretion and increases glycogenolysis, which also contributes to elevated blood sugar.

Glucose permits the generation of ATP by anaerobic glycolysis, as opposed to free fatty acids (FFAs), which require aerobic conditions to furnish ATP. Because hypoxic heart muscle derives a considerable proportion of its energy from the metabolism of glucose (**see Chapter 22**), and because glucose uptake by the myocardium requires insulin, insulin deficiency can jeopardize the availability of energy. Despite these metabolic considerations, the most contemporary data indicate that maintaining glucose levels below 180 mg/dL, while avoiding hypoglycemia, is the safest post-MI glucose management strategy.[53]

Insulin-glucose infusions confer no benefit for patients with STEMI (**see Chapter 59**).

Adrenal Medulla.

Plasma and urinary catecholamine levels peak in the first 24 hours after onset of chest pain, with the greatest rise in plasma catecholamine secretion occurring during the first hour after onset of STEMI. These high levels of circulating catecholamines in patients with STEMI correlate with the occurrence of serious arrhythmias and result in an increase in myocardial oxygen consumption, both directly and indirectly, because of catecholamine-induced elevation of circulating FFAs. The concentration of circulating catecholamines correlates with the extent of myocardial damage and the incidence of cardiogenic shock, as well as with both early and late mortality.

Circulating catecholamines enhance platelet aggregation; when this occurs in the coronary microcirculation, release of the potent local vasoconstrictor thromboxane A_2 may further impair cardiac perfusion. The marked increase in sympathetic activity immediately following STEMI is both protective and potentially deleterious. Early inhibition of circulating catecholamines with IV beta-adrenergic receptor blockers can diminish cardiac function and worsen outcomes in patients with incipient or frank cardiogenic shock, whereas beta-adrenergic receptor blockade in stable patients and in the convalescent phase is a cornerstone of post-MI care (**see Chapter 59**). Beta blockers may also limit mobilization of leukocytes from the bone marrow and thus exert an anti-inflammatory effect that could benefit infarct healing and limit activation of atheromata.[25,54]

Activation of the Renin-Angiotensin-Aldosterone System

Noninfarcted regions of the myocardium appear to exhibit activation of the tissue RAAS with increased production of angiotensin II. Both locally and systemically generated A II can stimulate the production of various growth factors, such as platelet-derived growth factor and TGF-β, that promote compensatory hypertrophy in the noninfarcted myocardium, as well as control the structure and tone of the infarct-related coronary and other myocardial vessels. Additional potential actions of A II that could aggravate infarction include the release of endothelin, plasminogen activator inhibitor (PAI) 1, and aldosterone, which may cause vasoconstriction, impair fibrinolysis, and increase sodium retention, respectively.[51]

Natriuretic Peptides

The peptides atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are released from the cardiac atria in response to an elevation in atrial pressure. Atrial and ventricular myocardium secrete B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP). Given the larger mass of ventricular than atrial myocardium, the total amount of mRNA for BNP is higher in the ventricles than in the atria. Natriuretic peptides are released early after STEMI, with a peak at approximately 16 hours. The natriuretic peptides released from the left ventricle during STEMI originate both from the infarcted myocardium and from viable noninfarcted myocardium. The rise in BNP and NT-proBNP after STEMI correlates with infarct size and regional wall motion abnormalities. Measurement of natriuretic peptides can provide useful information both early and late in the course of STEMI.[55,56]

Adrenal Cortex

Plasma and urinary 17-hydroxycorticosteroids and ketosteroids, as well as aldosterone, rise markedly in patients with STEMI. Their concentrations correlate directly with the peak level of serum CK, thus implying an association between the stress imposed by larger infarcts and greater secretion of adrenal

steroids. The magnitude of the elevation in cortisol correlates with infarct size and mortality.

Thyroid Gland

Although patients with STEMI are generally euthyroid clinically, serum triiodothyronine (T_3) levels can decrease transiently, a fall that is most marked on approximately the third day after the infarct. A rise in reverse T_3 usually accompanies this fall in T_3, with variable changes or no change in thyroxine (T_4) and thyroid-stimulating hormone levels.[57] The alteration in peripheral T_4 metabolism appears to correlate with infarct size and may be mediated by the rise in endogenous levels of cortisol that accompanies STEMI.

Renal Function

Both prerenal azotemia and acute renal failure can complicate the marked reduction in cardiac output that occurs in cardiogenic shock.

Hematologic Alterations

Platelets

STEMI generally occurs in the presence of extensive coronary and systemic atherosclerotic plaque, which may serve as the site for the formation of platelet aggregates—a sequence suggested as an early step in the process of coronary thrombosis, coronary occlusion, and subsequent MI. Platelets from patients with STEMI have an increased propensity for aggregation both systemically and locally in the area of disrupted plaque and release vasoactive substances. Thus, platelets are key therapeutic targets for the initial antithrombotic management in STEMI.

Hemostatic Markers

Elevated levels of serum fibrinogen degradation products, an end product of thrombosis, as well as release of distinctive proteins when platelets are activated (e.g., platelet factor 4, beta-thromboglobulin), occur in some patients with STEMI. Fibrinopeptide A (FPA), a protein released from fibrin by thrombin, reflects ongoing thrombosis and increases during the early hours of STEMI. Marked elevation of hemostatic markers such as FPA, thrombin-antithrombin complex, and prothrombin fragment 1.2 is associated with an increased risk for mortality in patients with STEMI. Interpretation of coagulation test results in these patients may be complicated by elevated blood levels of catecholamines, concomitant shock, and venous thrombosis or embolism—conditions that may alter various tests of platelet and coagulation function. Additional factors that affect coagulation test results in patients with STEMI include the type and dosage of antithrombotic agent and reperfusion of the infarct artery.

Leukocytes

Leukocytosis usually accompanies STEMI in proportion to the magnitude of the necrotic process, elevated glucocorticoid levels, and possibly inflammation in the coronary arteries. The magnitude of the elevation in leukocyte count is associated with in-hospital mortality after STEMI. Experimental evidence suggests that the surge in catecholamines after coronary occlusion can mobilize leukocyte progenitors from bone marrow, thereby sustaining the inflammatory response following infarction.[25,54]

Blood Viscosity

Clinical and epidemiologic studies suggest that several hemostatic and hemorrheologic factors (e.g., fibrinogen, factor VII, plasma viscosity, hematocrit, red blood cell aggregation, total white blood cell count) participate in the pathophysiology of atherosclerosis and play an integral role in acute thrombotic events. An increase in blood viscosity also occurs in patients with STEMI and can be attributed to hemoconcentration during the first few days and later to elevated serum concentrations of $alpha_2$-globulin and fibrinogen, components of the acute-phase response to tissue necrosis that also cause the elevated sedimentation rate characteristic of STEMI.

Clinical Features

Predisposing Factors

Up to one third of patients with STEMI have an identifiable precipitating trigger or prodromal symptoms. Unusually heavy exercise (particularly in fatigued or habitually inactive patients), emotional stress, and acute illness are the most frequent triggers.[58,59] Such infarctions could result from marked increases in myocardial oxygen consumption in the presence of severe coronary arterial narrowing (a type 2 MI), or the acute hemodynamic stress on a fragile plaque from a catecholamine or blood pressure surge.

Accelerating angina and rest angina, two patterns of unstable angina, may culminate in STEMI (**see Fig. 58.1**). Noncardiac surgical procedures may also precede STEMI. Perioperative risk stratification and preventive measures may limit STEMI and cardiac-related mortality[60] (**see Chapter 11**). Reduced myocardial perfusion secondary to hypotension (e.g., hemorrhagic or septic shock) and the increased myocardial oxygen demands caused by aortic stenosis, fever, tachycardia, and agitation can also contribute to myocardial necrosis. Other factors reported to predispose to STEMI include respiratory infections, hypoxemia from any cause, pulmonary embolism, hypoglycemia, administration of ergot preparations, cocaine use, sympathomimetics, serum sickness, allergy, and rarely, wasp stings. In patients with Prinzmetal angina (**see Chapter 61**), STEMI may develop in the territory of the coronary artery that undergoes spasm.

Circadian Periodicity

The time of onset of STEMI has a pronounced circadian periodicity, with the peak incidence of events occurring in the morning.[61] Circadian rhythms affect many physiologic and biochemical variables; plasma catecholamines and cortisol and platelet aggregability increase in the early-morning hours. Patients receiving a beta-blocking agent or aspirin do not exhibit this characteristic circadian peak before the development of STEMI, consistent with precipitation by sympathetic stimuli or platelet activation. The concept of “triggering” a STEMI is complex and can involve the superimposition of multiple factors, such as the time of day, season, and the stress of natural disasters.

History

See also Chapters 10, 56, and 60.

Prodromal Symptoms

The patient's history remains crucial to establishing a diagnosis of STEMI. Chest discomfort resembling classic angina pectoris usually characterizes the prodrome, but it occurs at rest or with less activity than

usual. Yet the symptoms are often not disturbing enough to induce patients to seek immediate medical attention. A feeling of general malaise or frank exhaustion frequently accompanies other symptoms preceding STEMI.

Nature of the Pain

Pain in patients with STEMI varies in intensity; in most patients it is severe and in some instances is intolerable. The pain is prolonged—it generally lasts for more than 30 minutes and frequently for several hours if there is no reperfusion. The patient usually describes the discomfort as constricting, crushing, oppressing, or compressing and often complains of a sensation of a heavy weight or a squeezing in the chest. Although patients typically describe the discomfort as a choking, viselike, or heavy pain, it can also be characterized as a stabbing, knifelike, boring, or burning discomfort. The discomfort usually localizes retrosternally and frequently spreads to both sides of the anterior part of the chest, with a predilection for the left side. Often the pain radiates down the ulnar aspect of the left arm and produces a tingling sensation in the left wrist, hand, and fingers. Some patients note only a dull ache or numbness of the wrists in association with severe substernal or precordial discomfort. In some patients, pain from STEMI may begin in the epigastrium and simulate a variety of abdominal disorders, which often causes STEMI to be misdiagnosed as "indigestion." In other patients the discomfort of STEMI radiates to the shoulders, upper extremities, neck, jaw, and interscapular region, again usually favoring the left side. In patients with preexisting angina pectoris, the pain of infarction generally resembles that of angina with respect to location, but it is normally much more severe, lasts longer, and is not relieved by rest or nitroglycerin.

STEMI pain may subside by the time that the physician first encounters the patient (or the patient reaches the hospital), or it may persist for many hours until adequate reperfusion (**see Chapter 59**). Both angina pectoris and STEMI pain likely arise from nerve endings in ischemic or injured, but not necrotic myocardium. Thus, in cases of STEMI, stimulation of nerve fibers in an ischemic zone of myocardium surrounding the necrotic central area of infarction probably gives rise to the pain.

The pain often disappears suddenly and completely following restoration of blood flow to the infarct territory. Recurrent pain after initial reperfusion should prompt immediate evaluation for acute re-occlusion of the culprit lesion. The recognition that pain implies ischemia and not infarction heightens the importance of targeted anti-ischemic therapy and immediate reperfusion (typically by repeat coronary angiography) to relieve the ischemia, for which the pain is a marker. This finding suggests that clinicians should *not* be complacent about ongoing cardiac pain in any circumstances. In some patients—particularly older adults, patients with diabetes, and heart transplant recipients—STEMI can manifest clinically not by chest discomfort but rather by symptoms of acute LV failure and chest tightness or by marked weakness or frank syncope. Diaphoresis, nausea, and vomiting may accompany these symptoms. Women may experience symptoms of STEMI differently than men (**see Chapter 89**), requiring particular awareness and vigilance on the part of the interviewing physician.

Other Symptoms

Nausea and vomiting may occur, presumably because of activation of the vagal reflex or stimulation of LV receptors as part of the Bezold-Jarisch reflex. These symptoms occur more frequently in patients with inferior STEMI than with anterior STEMI. When the pain of STEMI is epigastric in location and associated with nausea and vomiting, the clinical picture can easily be confused with that of acute cholecystitis, gastritis, or peptic ulcer. Other symptoms include feelings of profound weakness, dizziness, palpitations, cold perspiration, and a sense of impending doom. On occasion, symptoms arising from an

episode of cerebral embolism or other systemic arterial embolism can herald STEMI. Chest discomfort may not accompany these symptoms.

Differential Diagnosis

STEMI pain may overlap with that caused by acute pericarditis, acute aortic syndromes, pulmonary, and musculoskeletal discomfort, as discussed in detail in **Chapter 56** (**see Table 56.1**).

Silent ST-Elevation Myocardial Infarction with Atypical Features

Nonfatal STEMI can go unrecognized by the patient and may manifest only on subsequent routine electrocardiographic, imaging, or postmortem examination. Of these unrecognized infarctions, approximately half are truly silent, with patients unable to recall any symptoms. The other portion of patients with so-called silent infarction can recall an event characterized by symptoms compatible with acute MI in response to leading questions after finding ECG or imaging abnormalities. Unrecognized or silent infarction occurs more often in patients without antecedent angina pectoris and in patients with diabetes and hypertension and typically manifests as new wall motion abnormalities, fixed perfusion defects, or pathologic Q waves.[62] Silent ischemia often follows silent STEMI (**see Chapter 61**). The prognosis of patients with silent and symptomatic manifestations of STEMI appear quite similar.[63]

Atypical features of STEMI include the following: (1) heart failure (i.e., dyspnea without pain beginning de novo or worsening of established failure), (2) classic angina pectoris without a particularly severe or prolonged episode, (3) atypical location of the pain, (4) central nervous system manifestations resembling those of stroke secondary to a sharp reduction in cardiac output in a patient with cerebral arteriosclerosis, (5) apprehension and nervousness, (6) sudden mania or psychosis, (7) syncope, (8) overwhelming weakness, (9) acute indigestion, and (10) peripheral embolization. Although women may more likely present with “atypical” features of STEMI than men, recent evidence suggests fewer differences between sexes than previously thought[64] (**see Chapter 89**).

Physical Examination

See also Chapter 10.

General Appearance

Patients suffering from STEMI often appear anxious and in considerable distress. An anguished facial expression is common, and—in contrast to patients with severe angina pectoris, who often lie, sit, or stand still because all forms of activity increase the discomfort—some patients suffering from STEMI may be restless and move about in an effort to find a comfortable position. They often massage or clutch their chests and frequently describe their pain with a clenched fist held against the sternum (Levine sign). In patients with LV failure and sympathetic stimulation, cold perspiration and skin pallor may be evident; they typically sit or are propped up in bed and gasp for breath. Between breaths they may complain of chest discomfort or a feeling of suffocation. Cough producing frothy, pink, or blood-streaked sputum may occur if pulmonary edema is present. Patients in cardiogenic shock often lie listlessly and make few spontaneous movements. Their skin is cool and clammy, with a bluish or mottled color over the extremities, and there is marked facial pallor with severe cyanosis of the lips and nailbeds. Depending on the degree of cerebral perfusion, a patient in shock may converse normally or may be confused.

Heart Rate

The heart rate can vary from marked bradycardia to a rapid regular or irregular tachycardia, depending on the underlying rhythm and degree of LV failure. Typically the pulse is rapid and regular initially (sinus tachycardia at 100 to 110 beats/minute) and slows as the patient's pain and anxiety are relieved; premature ventricular contractions are common. Tachycardia at presentation is associated with a higher risk for fatal complications of MI.

Blood Pressure

Most patients with uncomplicated STEMI are normotensive, although the reduced stroke volume accompanying the tachycardia can cause declines in systolic and pulse pressure and elevation of diastolic blood pressure (BP). In previously normotensive patients, a hypertensive response is occasionally seen during the first few hours, presumably because of adrenergic discharge secondary to pain, anxiety, and agitation. Previously hypertensive patients may become normotensive without treatment after STEMI, although many of them eventually regain their elevated BP levels, generally 3 to 6 months after infarction. In patients with massive infarction, arterial pressure falls acutely because of LV dysfunction and may be exacerbated by morphine and/or nitrates, which cause venous pooling; as recovery occurs, arterial pressure tends to return to preinfarction levels.

Patients in cardiogenic shock by definition have systolic pressure below 90 mm Hg and evidence of end-organ hypoperfusion. Hypotension alone does not necessarily signify cardiogenic shock; some patients with inferior infarction and activation of the Bezold-Jarisch reflex may also transiently have systolic BP below 90 mm Hg. Their hypotension eventually resolves spontaneously, although IV atropine (0.5 to 1 mg) and assumption of the Trendelenburg position can accelerate recovery. Other patients who are initially only slightly hypotensive may demonstrate gradually falling BP with a progressive reduction in cardiac output over several hours or days as cardiogenic shock develops because of increasing ischemia and extension of infarction (**see Fig. 58.14**). Evidence of autonomic hyperactivity is common and varies in type with the location of the infarction. More than half of patients with inferior STEMI have evidence of excess parasympathetic stimulation, with hypotension, bradycardia, or both evident during initial evaluation, whereas approximately half of patients with anterior STEMI show signs of sympathetic excess and have hypertension, tachycardia, or both.

Temperature and Respiration

Fever, a nonspecific response to tissue necrosis, develops in most patients with extensive STEMI within 24 to 48 hours of onset of infarction. Body temperature often begins to rise within 4 to 8 hours after onset of infarction, and rectal temperature may reach 38.3°C to 38.9°C (101°F to 102°F). The fever usually resolves by the fourth or fifth day after MI.

The respiratory rate may rise slightly soon after the development of STEMI; in patients without heart failure (HF), it results from anxiety and pain and returns to normal with treatment of the physical and psychological discomfort. Respiratory rates greater than 20 breaths/min augur heightened risk.[65] In patients with LV failure, respiratory rate correlates with severity of the failure; patients with pulmonary edema may have rates exceeding 40 breaths/min. However, the respiratory rate is not necessarily elevated in patients with cardiogenic shock. Cheyne-Stokes (periodic) respiration may occur in elderly individuals with cardiogenic shock or HF, particularly after opiate therapy or in the presence of cerebrovascular disease.

Jugular Venous Pulse

The jugular venous pulse is usually normal in STEMI involving the left ventricle. The *a* wave may be prominent in patients with pulmonary hypertension secondary to LV failure or reduced compliance. In contrast, RV infarction (regardless of whether it accompanies LV infarction) often results in marked jugular venous distention and, when complicated by necrosis or ischemia of RV papillary muscles, in the tall *c-v* waves of tricuspid regurgitation. Patients with STEMI and cardiogenic shock generally have elevated jugular venous pressure, although in the early phase, if RV function is relatively preserved, right-sided pressures may remain normal. In patients with STEMI, hypotension, and hypoperfusion (findings that may resemble those of patients with cardiogenic shock) without elevated jugular venous pressures, the depression in LV performance probably is related to hypovolemia, at least in part. Assessing LV performance with echocardiography or by measuring LV filling pressure with a pulmonary artery catheter can help determine the cause of hypotension.

Carotid Pulse

Palpation of the carotid arterial pulse provides a clue to LV stroke volume: a small pulse suggests reduced stroke volume, whereas a sharp, brief upstroke often occurs in patients with mitral regurgitation or a ruptured ventricular septum with a left-to-right shunt. Pulsus alternans reflects severe LV dysfunction.

The Chest

Moist rales are audible in patients in whom LV failure or reduction in LV compliance leads to pulmonary edema. Diffuse wheezing can occur in patients with severe LV failure. Cough with hemoptysis, suggesting pulmonary embolism with infarction, can also occur. In 1967, Thomas Killip proposed a prognostic classification scheme on the basis of the presence and severity of rales in patients with STEMI. Class I patients are free of rales and a third heart sound (S_3). Class II patients have rales, but only to a mild to moderate degree (<50% of lung fields), and may or may not have an S_3. Class III patients have rales in more than half of each lung field and frequently have pulmonary edema. Class IV patients have cardiogenic shock. Despite the overall improvement in the mortality rate that applies to each category, the Killip classification still remains useful for prognostication.[66]

Cardiac Examination

Palpation

Palpation of the precordium may yield normal results, but in patients with transmural STEMI, it more often reveals a presystolic pulsation synchronous with an audible fourth heart sound (S_4), a finding reflecting vigorous left atrial contraction filling a ventricle with reduced compliance. Patients with LV systolic dysfunction may have a diffuse or dyskinetic LV impulse, or an outward movement of the left ventricle palpable in early diastole, coincident with an S_3.

Auscultation

Heart Sounds.

The heart sounds, particularly the first sound, are frequently muffled and occasionally inaudible immediately after an infarct, and their intensity increases during convalescence. A soft first heart sound

(S_1) may also reflect prolongation of the PR interval. Patients with marked ventricular dysfunction and/or left bundle branch block (LBBB) may have paradoxical splitting of the second heart sound (S_2). An S_4 is almost universally present in patients in sinus rhythm with STEMI, but it has limited diagnostic value because it is usually audible in most patients with chronic ischemic heart disease and is recordable, although not often audible, in many normal individuals older than 45. An S_3 in patients with STEMI usually reflects severe LV dysfunction with elevated ventricular filling pressure. It reflects rapid deceleration of transmitral blood flow during protodiastolic filling of the left ventricle and is typically heard in patients with large infarctions. S_3 is detected best at the apex with the patient in the left lateral recumbent position. An S_3 may result not only from LV failure but also from increased inflow into the left ventricle, as occurs when mitral regurgitation or a ventricular septal defect complicates STEMI. S_3 and S_4 emanating from the left ventricle are heard best at the apex, and in patients with RV infarcts, can be heard along the left sternal border and increase on inspiration.

Murmurs.

Patients with STEMI typically have systolic murmurs, transient or persistent, that generally result from mitral regurgitation secondary to dysfunction of the mitral valve apparatus (papillary muscle dysfunction, LV dilation). A new, prominent, apical holosystolic murmur accompanied by a thrill may represent rupture of a head of a papillary muscle (**see Chapter 59**). Rupture of the interventricular septum produces similar findings, although the murmur and thrill are usually most prominent along the left sternal border and may be audible at the right sternal border as well. The systolic murmur of tricuspid regurgitation (from RV failure caused by pulmonary hypertension or RV infarction, or from infarction of an RV papillary muscle) is also heard along the left sternal border. It is characteristically intensified by inspiration and is accompanied by a prominent *c-v* wave in the jugular venous pulse and an RV fourth sound.

Friction Rubs.

Patients with STEMI may develop pericardial friction rubs. Rubs are notorious for their evanescence and thus are probably even more common than reported. Although friction rubs can be heard within 24 hours or as late as 2 weeks after onset of infarction, they occur most frequently on the second or third day. Occasionally, patients with extensive infarction can have a loud rub that lasts for many days. Patients with STEMI and a pericardial friction rub may have a pericardial effusion on echocardiographic study, but only rarely the classic ECG changes of pericarditis. Delayed onset of the rub and the associated discomfort of pericarditis (as late as 3 months after infarction) characterizes the now rare post-MI (Dressler) syndrome. Pericardial rubs are most readily audible along the left sternal border or just inside the apical impulse. Loud rubs may be audible over the entire precordium and even over the back. Occasionally, only the systolic portion of a rub is heard, which requires distinction from a systolic murmur, such as might result from rupture of the ventricular septum or mitral regurgitation.

Other Findings

Ocular Fundi

Hypertension, diabetes, and generalized atherosclerosis typically accompany STEMI and can produce characteristic changes in the fundus. A funduscopic (ophthalmoscopic) examination may provide information on the underlying vascular status, which can prove particularly useful in patients unable to provide a detailed history.

Abdomen

Patients often interpret pain in the abdomen associated with nausea, vomiting, restlessness, and even abdominal distention as a sign of "indigestion," leading to self-medication with antacids; it can also suggest an acute abdominal process to the physician. Right-sided HF, characterized by hepatomegaly and a positive abdominojugular reflux, is unusual in patients with acute LV infarction but occurs in patients with severe and prolonged LV failure or RV infarction.

Extremities

Coronary atherosclerosis is often associated with systemic atherosclerosis, and therefore patients with STEMI may have a history of intermittent claudication and may demonstrate the physical findings of peripheral vascular disease (**see Chapter 64**). Thus, patients with CAD may exhibit diminished peripheral arterial pulses, loss of hair, and atrophic skin in the lower extremities. Peripheral edema is a manifestation of RV failure and, as with congestive hepatomegaly, is unusual in patients with acute LV infarction. Cyanosis of the nailbeds is common in patients with severe LV failure and is particularly striking in patients with cardiogenic shock.

Neuropsychiatric Findings

Except for the altered mental status that occurs in patients with STEMI who have greatly reduced cardiac output and cerebral hypoperfusion, findings on neurologic examination are normal unless the patient has sustained a cerebral embolism secondary to mural thrombus. The association between these two conditions can be explained by systemic hypotension from STEMI precipitating a cerebral infarction, and vice versa, as well as by mural emboli from the left ventricle causing cerebral emboli. As discussed in **Chapter 59**, patients with STEMI frequently exhibit alterations in their emotional state, including intense anxiety, denial, and depression.

Laboratory Findings

Serum and Plasma Markers of Cardiac Damage

Proteins released into the blood from damaged myocardial cells can indicate myocardial injury. Even though the availability of serum and plasma cardiac markers with greatly enhanced sensitivity for myocardial injury has enabled clinicians to identify much lower levels of injury, biochemical tests of myocardial injury provide no direct insight into the cause of the damage.[67] MI is the diagnosis given to myocardial injury that results from ischemia[1] (**Fig. 58.16**). Other nonischemic insults, such as myocarditis or direct myocardial toxins, may result in myocardial injury but should not be labeled MI. Moreover, the enhanced ability to detect myocardial damage has increased the number of cases of myocardial injury that result from non–plaque-related clinical events, thus necessitating the establishment of new criteria for MI that place the injury in clinical context[1] (**see Tables 58.1 to 58.3**).

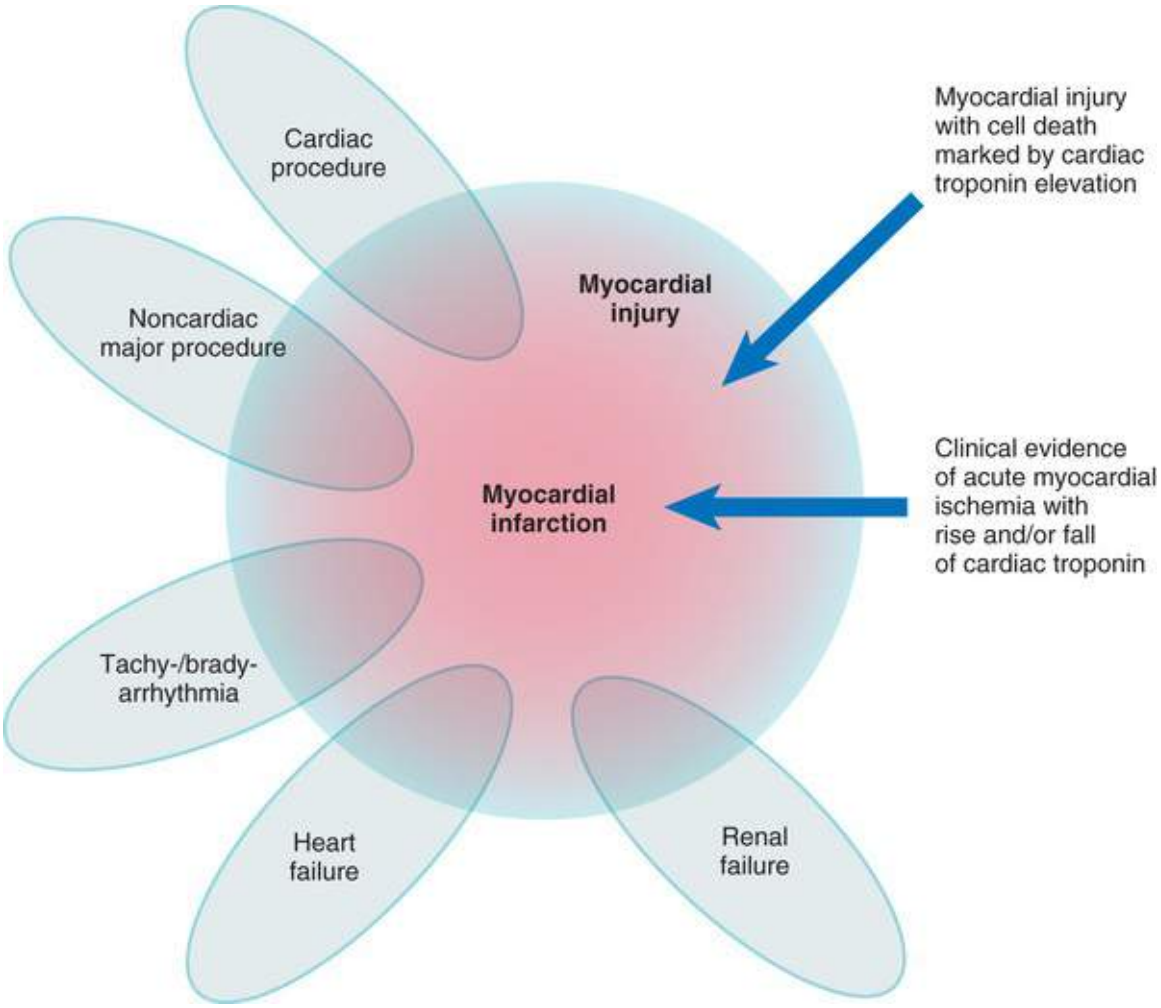


FIGURE 58.16 Myocardial ischemia and subsequent myocardial injury can result from a variety of clinical entities, including renal failure, heart failure, tachyarrhythmia or bradyarrhythmia, and cardiac or noncardiac procedures. Each of these scenarios can result in myocardial injury with cell death marked by the release of detectable circulating levels of cardiac troponin. However, each of these entities can also be associated with myocardial infarction when there is clinical evidence of acute myocardial ischemia with a typical rise and/or fall in cardiac troponin levels. (From Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581.)

Although this section applies more to diagnostic decision making for patients with suspected ACS without ST-segment elevation (**see Chapter 60**), this chapter contains a general discussion of cardiac biomarkers because of the overlapping pathophysiologic concepts and methodology regarding the use of biomarkers to evaluate patients with STEMI. Clinicians should *not* wait for the results of biomarker assays to initiate treatment of patients with STEMI. Given the urgency for reperfusion in patients with STEMI, a rapid clinical assessment and the 12-lead ECG should serve to initiate such strategies.

Necrosis compromises the integrity of the sarcolemmal membrane; intracellular macromolecules (serum and plasma cardiac markers) begin to diffuse into the cardiac interstitium and ultimately into the microvasculature and lymphatics in the region of the infarct (**Fig. 58.17; see Table 58.3**). The rate of appearance of these macromolecules in the peripheral circulation depends on several factors, including intracellular location, molecular weight, local blood and lymphatic flow, and the rate of elimination from blood.

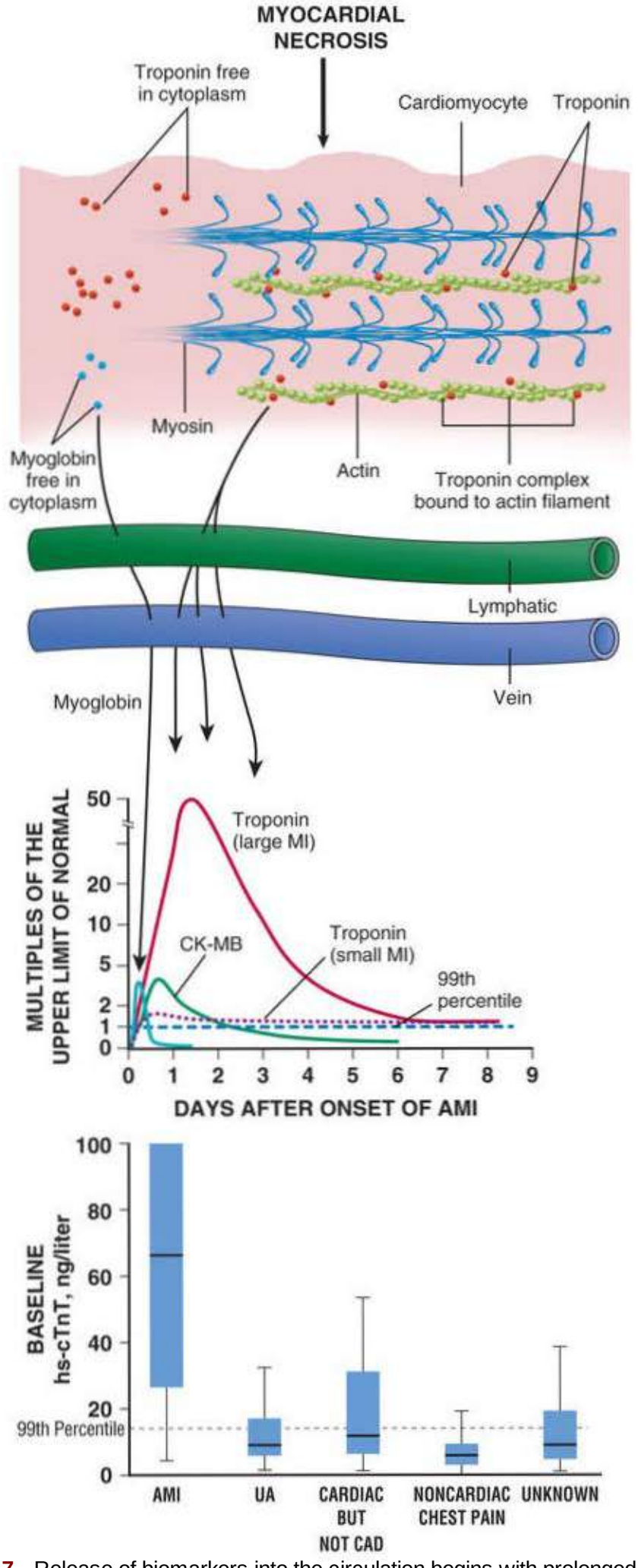


FIGURE 58.17 Release of biomarkers into the circulation begins with prolonged ischemia and

subsequent necrosis that results in loss of integrity of the cellular membranes. After disruption of the sarcolemmal membrane of the cardiomyocyte, the cytoplasmic pool of biomarkers is released first (*leftmost arrow* in **bottom** portion of the top panel). Markers such as myoglobin are released rapidly, and blood levels rise quickly above the cutoff limit. More protracted release of biomarkers from the disintegrating myofilaments follows and may continue for several days *(three-headed arrow).* Cardiac troponin levels rise to substantially higher multiples of the upper reference limit (the 99th percentile of values in a reference control group) compared with CK-MB in patients with acute myocardial infarction (MI) and sustain sufficient myocardial necrosis that results in abnormally elevated levels of CK-MB. Clinicians can now diagnose MI by more sensitive assays that detect even small elevations in cardiac troponin above the upper reference limit, even though levels of CK-MB and troponin determined from older generations of assays may still be below the MI decision limit. Other causes of myocardial injury, such as renal failure or pulmonary embolism, can lead to detectable levels of cardiac troponin even without any coronary artery disease **(lower panel).** AMI, Acute myocardial infarction; CAD, coronary artery disease; UA, unstable angina. (Modified from Antman EM. Decision making with cardiac troponin tests. N Engl J Med 2002;346:2079; Jaffe AS, Babiun L, Apple FS. Biomarkers in acute cardiac disease: the present and the future. J Am Coll Cardiol 2006;48:1; and Reichlin T et al. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. Arch Intern Med 2012;172:1211.)

Cardiac-Specific Troponins

The preferred biomarker to detect myocardial injury is cardiac troponin, which consists of three subunits that regulate the calcium-mediated contractile process of striated muscle. These subunits include troponin C, which binds Ca^{2+}; troponin I (TnI), which binds to actin and inhibits actin-myosin interactions; and troponin T (TnT), which binds to tropomyosin, thereby attaching the troponin complex to the thin filament (**Fig. 58.17**). Although most TnT is incorporated in the troponin complex, approximately 6% to 8% is dissolved in the cytosol; in contrast, approximately 2% to 3% of TnI is found in a cytosolic pool. Following myocyte injury, the initial release of cardiac-specific TnT and TnI is from the cytosolic pool, followed subsequently by release of the myofilament-bound protein.[68] Different genes encode TnT and TnI in cardiac and skeletal muscle, thus permitting the production of specific antibodies for the cardiac forms (cTnT and cTnI), which enables quantitative measurement.[69] Detection of a rise and fall in cTnT or cTnI in the appropriate clinical setting is the cornerstone of the diagnostic criteria for MI.[1]

When interpreting the results of assays for cTnT or cTnI, clinicians must recognize several analytic issues. Multiple manufacturers produce cTn assays using different troponin epitopes for detection, which has resulted in varying reference levels.[70] The release pattern of troponin complexes, conformational changes, and degradation into various troponin fragments may differentially affect the results of various commercial assays. Such post-translational modifications may provide insight into the underlying cause and timing of release (e.g., differentiating ischemia from myocarditis), but such applications have not emerged for clinical interpretation.

Cutoff Values.

Variations in the cutoff concentration for abnormal levels of cTn in the clinically available immunoassays result in part from the different specificities of the antibodies used for detecting free and complexed cTn. Thus, clinicians should apply evidence-based cutoff values for the particular assay used in their laboratory, which is defined as a value exceeding that of 99% of a reference control group. Assays that have a level of imprecision (i.e., coefficient of variation) of less than 10% at the specific 99th percentile cutoff are optimal for clinical practice.[1] In patients with MI, concentrations of cTnT and cTnI detected by conventional assays (non–high-sensitivity) can be detected approximately 3 hours after the onset of chest pain.[71] Because of continuous release from a degenerating contractile apparatus in necrotic myocytes, elevations in cTnI may persist for 7 to 10 days after MI; elevations in cTnT may persist for up to 10 to 14

days (**Fig. 58.17**). The prolonged time course of the elevation in cTnT and cTnI is advantageous for the late diagnosis of MI. Patients with STEMI who undergo successful recanalization of the infarct-related artery have a rapid release of cardiac troponins, which can indicate reperfusion (**Fig. 58.18**).

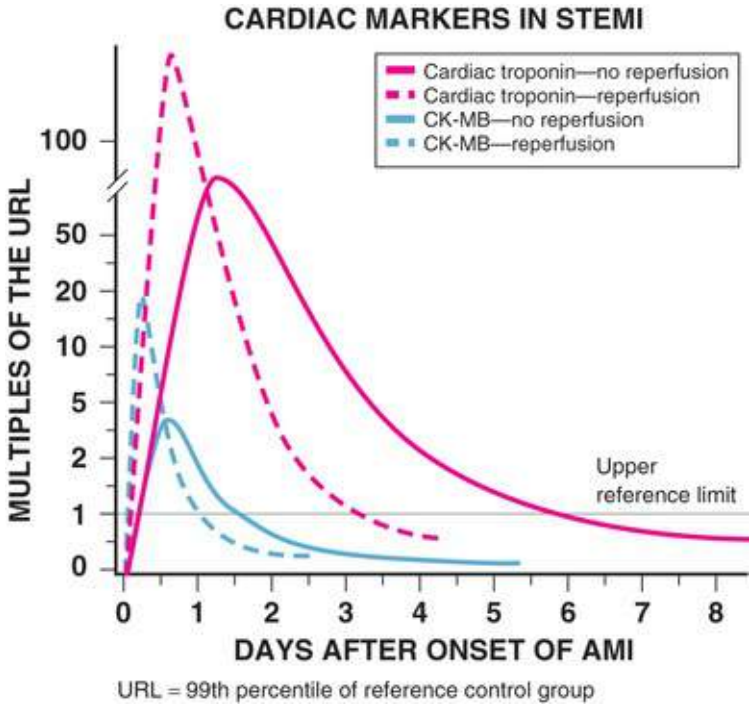


FIGURE 58.18 The kinetics of the release of CK-MB and cardiac troponin in patients who do not undergo reperfusion is shown in the *solid blue* and *red curves* as multiples of the upper reference limit (URL). When patients with STEMI undergo reperfusion, as depicted in the *dashed blue* and *red curves,* the cardiac biomarkers are detected sooner and rise to a higher peak value but decline more rapidly, which results in a smaller area under the curve and limitation of infarct size. AMI, Acute myocardial infarction. (Modified from Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction]. Circulation 2004;110:e82.)

High-Sensitivity Cardiac Troponin.

High-sensitivity assays deliver enhanced analytic performance, thus enabling more precise measurement of very low concentrations of cardiac-specific troponin. Experts recommend that the term *high-sensitivity troponin* (hsTn) be reserved for assays that can detect cardiac troponin in more than 50% of an apparently healthy population.[69,70] Such assays have greater sensitivity than previous-generation assays, but also have diminished clinical specificity for MI because they detect true myocardial injury in a variety of other clinical settings. In addition, high-sensitivity assays likely detect troponin release much earlier than older-generation assays. Nevertheless, in multiple studies of patients with nontraumatic chest pain, hsTn assays have improved overall diagnostic accuracy and enabled earlier detection of myocardial injury.[72,73] Moreover, hsTn assays facilitate the adoption of criteria for rapidly changing concentration of troponin over periods as short as 1 to 3 hours that aid in discriminating acute myocardial injury from chronically elevated values caused by underlying structural heart disease (e.g., left ventricular hypertrophy). Use of such “delta” criteria can improve the clinical specificity of diagnostic testing with cardiac troponin as well as permit rapid exclusion of MI in patients without changing values of hsTn.[73]

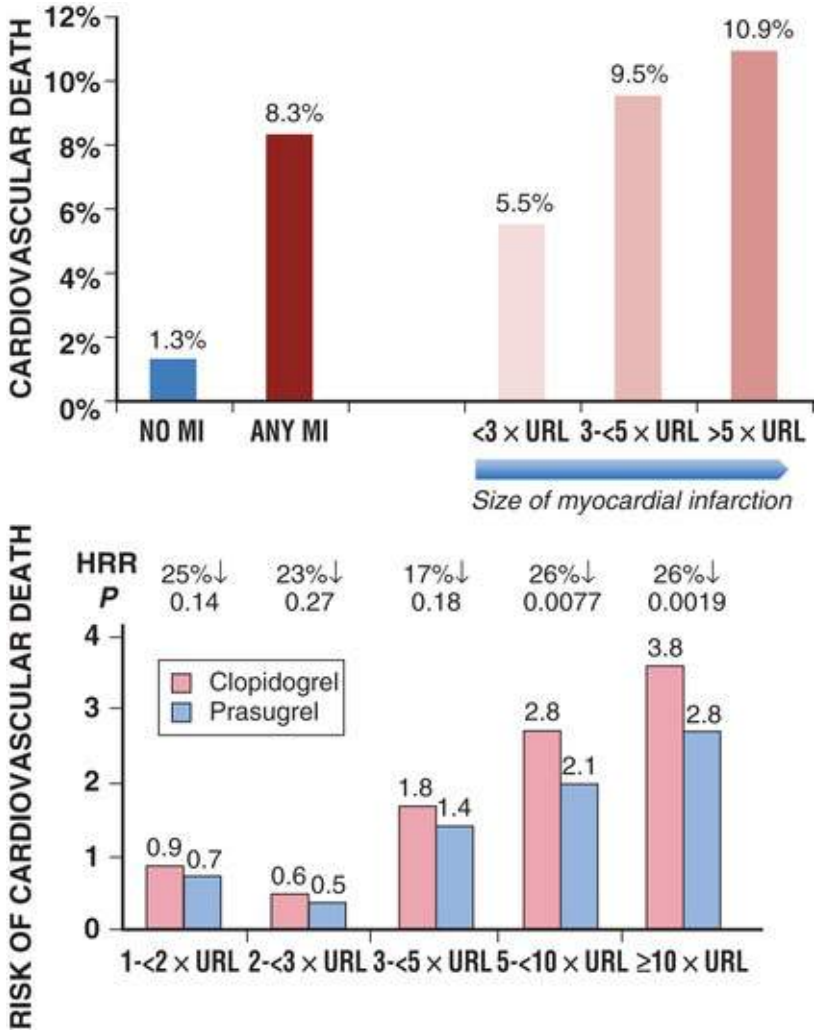
Creatine Kinase MB Isoenzyme

If a cardiac-specific troponin assay is not available, CK-MB measured with a mass assay is the best alternative. Cardiac muscle contains both the MM and the MB isoenzyme of CK. Other tissues can contain small quantities of CK-MB, including the small intestine, tongue, diaphragm, uterus, and prostate. Strenuous exercise, particularly in trained long-distance runners or professional athletes, can elevate both total CK and CK-MB. Because CK-MB can be detected in the blood of healthy persons, the cutoff value for abnormal elevation of CK-MB is usually set a few units above the upper reference limit (URL) for a given laboratory (**see Fig. 58.17**). As with cardiac-specific troponin, the diagnosis of MI requires a maximal concentration of CK-MB exceeding the 99th percentile of values for sex-specific reference levels on two successive samples in a rise-and-fall pattern.[1] CK-MB may rise in circumstances involving severe skeletal muscle injury.

Recommendations for Measurement of Circulating Markers

All patients with suspected MI should undergo measurement of cardiac-specific troponin as soon as possible at the initial encounter. In patients with STEMI, the results of biomarker assessment should not delay interventions to achieve immediate reperfusion. From a cost-effectiveness perspective, measuring both a cardiac-specific troponin and CK-MB is unnecessary.[1] Use of conventional troponin assays permit the routine diagnosis of MI by obtaining measurements at initial evaluation and then 3 to 6 hours later (**see Table 58.1**). The use of high-sensitivity assays can reduce the interval between testing to 1 to 2 hours in patients without diagnostic ECG changes.[73,74] Emerging data suggest that an initial hsTn value below the limit of detection may provide a sufficiently high sensitivity and negative predictive value to enable discharge. Later testing is required only when uncertainty exists regarding the onset of pain or when stuttering symptoms occur. Testing beyond 2 hours from hospital arrival should also be considered for patients who arrive very early (<2 hours) after symptom onset.

The universal definition of MI recommends classifying infarctions into five types (**see Table 58.2**), along with the magnitude of the infarction expressed as the fold elevation in cardiac biomarkers above the 99th percentile URL. For example, a clinical trial that compared prasugrel with clopidogrel as supportive antiplatelet therapy for moderate- to high-risk ACS patients undergoing PCI found benefit across infarct size as determined by biomarker elevation[2] (**eFig. 58.4**).



EFIGURE 58.4 **Top panel,** Risk for cardiovascular death associated with new or recurrent type I myocardial infarction (MI) stratified according to MI size. **Bottom panel,** Event rates with prasugrel versus clopidogrel with respect to the total number of new or recurrent MIs; the incidence of MI (%) is classified by using the biomarker categories recommended by the universal definition of MI (see Table 58.2). The biomarker categories are groupings of fold elevations above the upper reference limit (URL) of normal. The data shown for each *bar* are derived from Kaplan-Meier estimates for the incidence of MI; the percent reductions represent the relative reductions in the hazard ratio (HRR) for the development of an MI in the prasugrel versus clopidogrel groups. (From Morrow DA et al. Effect of the novel thienopyridine prasugrel compared with clopidogrel on spontaneous and procedural myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38. An application of the classification system from the universal definition of myocardial infarction. Circulation 2009;119:2758; and Bonaca MP et al. American College of Cardiology/American Heart Association/European Society of Cardiology/World Heart Federation universal definition of myocardial infarction classification system and the risk of cardiovascular death: observations from the TRITON-TIMI 38 trial [Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38]. Circulation 2012;125:577.)

Other Biomarkers

Other biomarkers may be used noninvasively to assess the potential causes and complications of MI. C-reactive protein (CRP) rises substantially in the setting of STEMI as a result of the inflammatory response to myocyte necrosis and is associated with the subsequent risk for death or HF. Natriuretic peptides reflect the hemodynamic impact of the MI and are associated with prognosis. Although both natriuretic peptides and CRP enhance risk assessment, no clear guidance is available on how to direct specific therapeutic maneuvers in the setting of STEMI based on these biomarkers.[75] Future studies evaluating novel biomarkers should focus on unmet clinical scenarios such as earlier detection of MI, differentiation of type I from type 2 MI, distinguishing the mechanism of thrombosis (e.g., plaque rupture versus erosion;

see Table 60.1), and improved risk stratification.

Other Laboratory Measurements

Serum Lipids

During the first 24 to 48 hours after admission, total cholesterol and high-density lipoprotein (HDL) cholesterol remain at or near baseline values, but they generally fall after that. The fall in HDL cholesterol after STEMI is greater than the fall in total cholesterol; thus the ratio of total cholesterol to HDL cholesterol is no longer useful for risk assessment unless measured early after MI. All patients with STEMI admitted within 24 hours of symptom onset should have a lipid profile,[76] although regardless of lipid levels and unless contraindicated, all patients with STEMI should receive high-intensity statin therapy. Lipid levels may still be clinically useful for patients admitted beyond 24 to 48 hours, but further measurements 4 to 8 weeks after MI provide more informative determination of serum lipid concentrations. Increased triglycerides may offer additional risk stratification beyond LDL and HDL cholesterol levels[77] (**see Chapter 48**).

Hematologic Findings

Elevation of the white blood cell count usually develops within 2 hours after the onset of chest pain, reaches a peak 2 to 4 days after infarction, and returns to normal in 1 week; the peak leukocyte count generally ranges between 12 and 15 × 10^3/mL but occasionally rises to as high as 20 × 10^3/mL in patients with large STEMI. Frequently, there is an increase in the percentage of polymorphonuclear leukocytes and a left shift of the differential count. In epidemiologic studies, higher white blood cell counts at initial evaluation in patients with an ACS are associated with an increased risk for adverse clinical outcomes.[78]

The erythrocyte sedimentation rate (ESR) is usually normal the first couple days after infarction. It then rises to a peak on the fourth or fifth day and may remain elevated for several weeks. The increase in the ESR does not correlate well with the size of the infarction or with prognosis. The hematocrit often increases during the first few days after infarction as a consequence of hemoconcentration. The hemoglobin value at initial evaluation of a patient with STEMI is strongly associated with the risk of recurrent major cardiovascular events following a J-shaped relationship. Cardiovascular mortality increases progressively as the initial hemoglobin value falls below 14 to 15 g/dL; conversely, it also rises as the hemoglobin level increases above 17 g/dL. The increased risk from anemia is probably related to diminished tissue delivery of oxygen, whereas the increased risk with polycythemia may be relates to an increase in blood viscosity.[79]

Electrocardiography

The ECG remains the most important diagnostic test in the evaluation of patients with suspected ischemic symptoms (**see Chapter 12**). Established criteria aid the diagnosis of STEMI in LBBB (**Table 58.4**), evidence of RBBB in setting of acute MI also portends a similar poor prognosis,[80] and should prompt consideration of urgent catheterization in setting of persistent ischemic settings and RBBB.[14] Patients with chest pain and ECG changes consistent with STEMI must be considered for immediate reperfusion.

TABLE 58.4

Electrocardiographic Manifestations of Myocardial Infarction

ELECTROCARDIOGRAPHIC MANIFESTATIONS OF ACUTE MYOCARDIAL ISCHEMIA (IN THE ABSENCE OF LEFT BUNDLE BRANCH BLOCK)	
ST Elevation	

New ST elevation at the J point in two contiguous leads with the following cut points:
• ≥0.1 mV in all leads (except V_2-V_3)
• In leads V_2-V_3 the following cut points apply:
  • ≥0.2 mV in men ≥40 years
  • ≥0.25 mV in men <40 years
  • ≥0.15 mV in women	

ST Depression and T Wave Changes	
• New horizontal or downsloping ST depression ≥0.05 mV in two contiguous leads • T-wave inversion ≥0.1 mV in two contiguous leads with a prominent R wave or R/S ratio >1	
ELECTROCARDIOGRAPHIC MANIFESTATIONS OF ISCHEMIA IN THE SETTING OF LEFT BUNDLE BRANCH BLOCK	
Electrocardiographic Criterion	**Points**
ST-segment elevation ≥1 mm and concordant with the QRS complex	5
ST-segment depression ≥1 mm in lead V_1, V_2, or V_3	3
ST-segment elevation ≥5 mm and discordant with the QRS complex	2
A score of ≥3 had a specificity of 98% for acute MI	
ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH PREVIOUS MYOCARDIAL INFARCTION (IN THE ABSENCE OF LEFT VENTRICULAR HYPERTROPHY AND LEFT BUNDLE BLOCK)	
Any Q wave in leads V_2-V_3 ≥0.02 sec or a QS complex in leads V_2 and V_3	
Q wave ≥0.03 sec and ≥0.1-mV deep or QS complex in leads I, II, aVL, aVF, or V_4-V_6 in any 2 leads of a contiguous lead grouping (I, aVL; V_1-V_6; II, III, aVF)	
R wave ≥0.04 sec in V_1-V_2 and R/S ≥1 with a concordant positive T wave in absence of a conductions defect	

Based on criteria from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78.

Analysis of the constellation of ECG leads showing ST elevation may also be useful for identifying the site of occlusion in the infarct artery[81] (**see Fig. 58.4**). The extent of ST deviation on the ECG, location of the infarction, and the QRS duration correlate with the risk for adverse outcomes. In addition to the diagnostic and prognostic information contained within the 12-lead ECG, the degree of ST-segment resolution provides valuable noninvasive information about the success of reperfusion for STEMI, regardless of whether it was achieved with fibrinolysis or primary coronary intervention[82] (**see Chapter 59**).

Although general agreement exists on electrocardiographic and vector cardiographic criteria for the recognition of infarction of the anterior and inferior myocardial walls, less agreement exists on criteria for lateral and posterior infarcts. Instead of “posterior,” the descriptor “lateral” may be more appropriate given the segmental anatomy of the heart as it sits in the thorax. The most recent universal definition of MI, however, retains the category of posterior MI.[1] Patients with an abnormal R wave in V_1 (0.04 second in duration and/or R/S ratio ≥1 in the absence of preexcitation or RV hypertrophy) and inferior or lateral Q waves have an increased incidence of isolated occlusion of a dominant left circumflex coronary artery without collateral circulation; such patients have a lower EF, increased end-systolic volume, and higher complication rate than do those with inferior infarction because of isolated occlusion of the right coronary artery. ST-segment elevations in aVR, reflecting the basal intraventricular septum, can be observed in up to 30% of STEMIs and identifies patients with a higher likelihood of left main coronary artery or multivessel disease and worse outcomes.[83]

Serial changes on the ECG develop in most patients with STEMI, but many factors limit the usefulness of the ECG in diagnosing and localizing MI: the extent of myocardial injury, age of the infarct, its location, presence of conduction defects, previous infarcts or acute pericarditis, and changes in electrolyte concentrations. Abnormalities in the ST segment and T wave can be quite nonspecific and may occur in a variety of conditions, including stable and unstable angina pectoris, ventricular hypertrophy,

acute and chronic pericarditis, myocarditis, early repolarization, electrolyte imbalance, shock, and metabolic disorders, as well as after administration of digitalis. Serial ECGs help in differentiating these conditions from STEMI, although for early triage decisions, concurrent imaging may help distinguish potential STEMI from other etiologies. Many patients bear the stigmata of a STEMI on the ECG for the rest of their lives, particularly if Q waves evolve, but in a substantial minority the typical changes disappear, the Q waves regress, and findings on the ECG can even return to normal. Conditions that may mimic the electrocardiographic features of MI by producing a pattern of "pseudoinfarction" include ventricular hypertrophy, conduction disturbances, preexcitation, primary myocardial disease, pneumothorax, pulmonary embolism, amyloid heart disease, hypertrophic cardiomyopathy, primary and metastatic tumors of the heart, traumatic heart disease, intracranial hemorrhage, hyperkalemia, pericarditis, early repolarization, forms of muscular dystrophy, and cardiac sarcoidosis.

Q Wave and Non–Q Wave Infarction

The presence or absence of Q waves on the surface ECG does not reliably distinguish between transmural and nontransmural (subendocardial) MI. Q waves on the ECG signify abnormal electrical activity but are not synonymous with irreversible myocardial damage, although Q waves are associated with worse outcomes.[84] Also, the absence of Q waves may simply reflect the insensitivity of the standard 12-lead ECG, especially in zones of the left ventricle supplied by the left circumflex artery (**see Fig. 58.4**).

Ischemia at a Distance

Patients with new Q waves and ST-segment elevation diagnostic of STEMI in one territory often have ST-segment depression in other territories. These additional ST-segment abnormalities, which imply a poor prognosis, result either from ischemia in a territory other than the area of infarction, termed *ischemia at a distance*, or from reciprocal electrical phenomena. ST-segment depression in the anterior leads in the setting of acute inferior STEMI may be caused by concurrent anterior ischemia, inferolateral wall infarction, or true reciprocal changes. Although precordial ST-segment depression is associated more often with extensive infarction of the lateral or inferior septal segments than with anterior wall subendocardial ischemia, imaging techniques such as echocardiography can evaluate the presence of an anterior wall motion abnormality.

Right Ventricular Infarction

ST-segment elevation in the right precordial leads (V_1, V_3R through V_6R) is a relatively sensitive and specific sign of RV infarction.[28,29] Occasionally, ST-segment elevation in V_2 and V_3 results from acute RV infarction; this appears to occur only when injury to the left inferior wall is minimal. Usually, the concurrent inferior wall injury suppresses this anterior ST-segment elevation resulting from RV injury. Similarly, RV infarction appears to reduce the anterior ST-segment depression often observed with inferior wall MI. A QS or QR pattern in V_3R and V_4R also suggests RV myocardial necrosis but has less predictive accuracy than ST-segment elevation in these leads.

Imaging

Noninvasive imaging provides important diagnostic and prognostic information in patients with MI. Most cases of STEMI, unless the ECG is nondiagnostic or the clinical scenario is questionable, do not require imaging for diagnosis. Imaging is key for determining the extent of the infarct, the presence of mechanical

complications, and the overall function of the right and left ventricles.

Radiography

The initial chest radiograph in patients with STEMI is almost invariably a portable film obtained in the emergency department or cardiac intensive care unit (**see Chapter 15**). Chest imaging should not delay primary reperfusion strategies, unless there is a reason to evaluate a particular suspected pulmonary pathology. When present, prominent pulmonary vascular markings on the radiograph reflect elevated LV end-diastolic pressure, but significant temporal discrepancies can occur because of *diagnostic lags* and *post-therapeutic lags*. Up to 12 hours can elapse before pulmonary edema accumulates after ventricular filling pressure has increased. The post-therapeutic phase lag represents a longer interval; up to 2 days is required for pulmonary edema to resolve and the radiographic signs of pulmonary congestion to clear after ventricular filling pressure have returned toward normal. The degree of congestion and the size of the left side of the heart on the chest film are useful for defining groups of patients with STEMI who have an increased risk for fatal complications.

Echocardiography

The relative portability of echocardiographic equipment makes this technique ideal for the assessment of patients with suspected MI[85] (**see Chapter 14**). In patients with active chest pain compatible with ischemia but with a nondiagnostic ECG, the finding on echocardiography of a regional wall motion abnormality supports the diagnosis of myocardial ischemia. Echocardiography can also aid the evaluation of patients with chest pain and a nondiagnostic ECG who are suspected of having aortic dissection. Identification of an intimal flap consistent with aortic dissection is a critical observation because it would drive changes in therapeutic strategy (**see Chapter 63**), but transthoracic echocardiography (TTE) has poor sensitivity for detecting aortic dissection compared with other imaging modalities, such as computed tomography (CT) angiography.

LV function estimated from an echocardiogram correlates well with measurements from angiography and is useful in establishing the prognosis after MI. Furthermore, early use of echocardiography can aid in early detection of potentially viable but stunned myocardium (contractile reserve), residual provocable ischemia, patients at risk for HF after MI, and mechanical complications of MI such as acute mitral or tricuspid regurgitation or ventricular septal defects. Newer techniques also provide information regarding the success of myocardial tissue-level reperfusion.[86] Although TTE is adequate in most patients, some patients have poor echocardiographic windows, especially if they are undergoing mechanical ventilation. In such patients, transesophageal echocardiography (TEE) or CMR can help in evaluating infarct size and location, ventricular septal defects, and papillary muscle dysfunction.

Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) has limited application during the acute phase because of long scan-times and the need to transport patients with MI to the MRI scanner, but it is a useful imaging technique during the subacute and chronic phases of MI. CMR permits exact localizing and sizing the area of infarction and a quantitative assessment of the severity of the ischemic insult (**see Chapter 17**). This modality is attractive because of its ability to assess perfusion of infarcted and noninfarcted tissue, as well as reperfused myocardium;[87] identify areas of jeopardized but not infarcted myocardium; identify myocardial edema, fibrosis, wall thinning, and hypertrophy; assess ventricular chamber size and segmental wall motion;[88,89] and identify the temporal transition between ischemia and infarction[90] (**Fig.**

58.19). Because of these capabilities, CMR may be particularly useful in the diagnostic assessment of possible MINOCA.

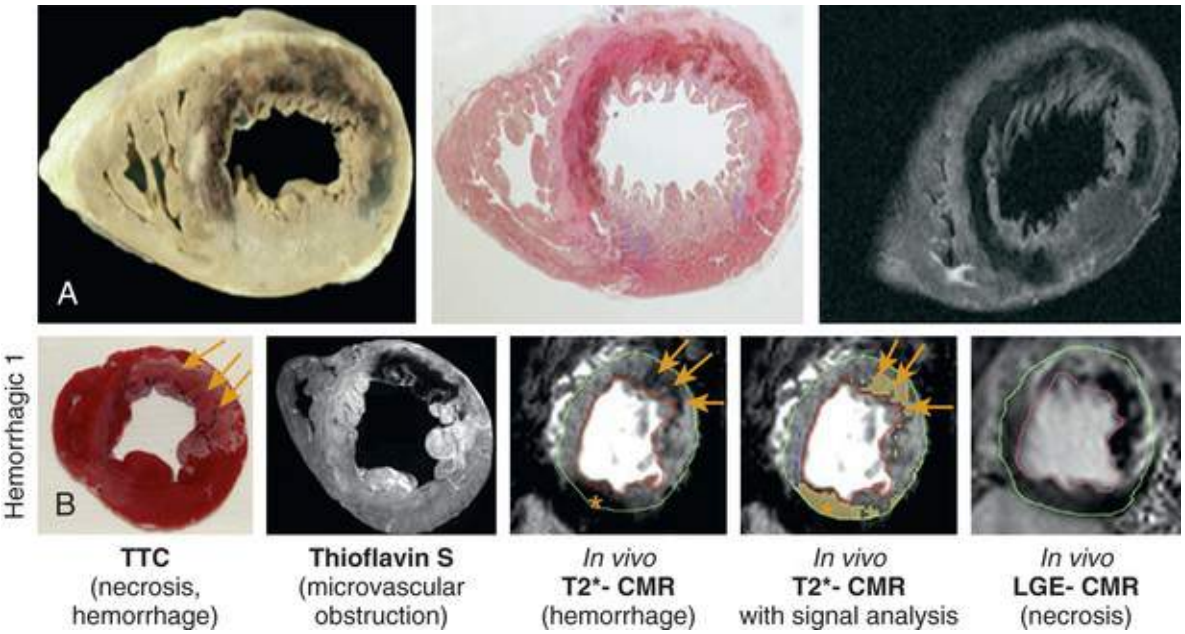


FIGURE 58.19 Cardiac magnetic resonance (CMR) images in myocardial infarction. **A,** *Left to right,* Gross anatomic image obtained at autopsy, histology image after staining with Heidenhain trichrome stain, and ex vivo T2-weighted CMR image from the short-axis slice. **B,** *Left to right,* Images from an experimentally induced MI in a dog. CMR was performed day 3 after reperfusion in which T2*-weighted gradient-echo imaging was performed. Ex vivo, thioflavin S imaging, and triphenyltetrazolium chloride (TTC) staining were performed to assess for microvascular obstruction (MVO), hemorrhage, and myocardial necrosis. LGE, Late gadolinium enhancement. (From Hamirani YS, Wong A, Kramer CM, Salerno M. Effect of microvascular obstruction and intramyocardial hemorrhage by CMR on LV remodeling and outcomes after myocardial infarction: a systematic review and meta-analysis. JACC Cardiovasc Imaging 2014;7:940-52.)

Contrast-enhanced CMR with gadolinium can define areas of myocardial necrosis accurately. The transmural extent of late gadolinium enhancement (LGE) in regions of dysfunctional myocardium accurately predicts the likelihood of recovery of contractile function after successful restoration of coronary flow by mechanical revascularization.[91] Numerous clinical studies have also demonstrated the high sensitivity of LGE ("delayed hyperenhancement") in detecting small amounts of myonecrosis. LGE accurately identifies the infarct zone compared with histologic examination. The best predictor of return to normal ventricular wall thickening is less than 25% transmurality of LGE. LGE is also a sensitive technique for detecting RV infarcts.[92]

In patients with a previous MI, estimation of the size of the peri-infarct zone by CMR with the delayed-enhancement technique provides incremental prognostic value beyond LV volume and EF. Besides detecting infarction, this imaging technique can characterize the presence and size of microvascular obstruction and intramyocardial hemorrhage as a result of infarction, which may be an even poorer prognostic finding than the extent of LGE.[87]

Nuclear Imaging

Radionuclide angiography, perfusion imaging, infarct-avid scintigraphy, and positron emission tomography (PET) can all evaluate patients with suspected ACS but have no role in the acute management of STEMI[85] (**see Chapter 16**). Nuclear cardiac imaging techniques can assess infarct size, collateral flow, and jeopardized myocardium; determine the effects of the infarct on ventricular function; and

establish the prognosis of patients with STEMI. However, echocardiography and CMR provide more relevant information regarding valvular and structural function than nuclear imaging. Stress nuclear imaging may be used to assess for ischemia in patients with residual obstructive CAD after initial reperfusion of the infarct-related artery.

Computed Tomography

CT can provide an assessment of cavity dimensions and wall thickness, can detect LV aneurysms, and—of particular importance in patients with STEMI—can identify intracardiac thrombi (**see Chapter 18**). In the acute setting, contrast-enhanced CT detects focal areas of MI as decreased areas of enhancement. Older infarcts show hyperenhancement.[93] Although cardiac CT is a less convenient technique, it is probably more sensitive than echocardiography for thrombus detection. Coronary CT angiography is sensitive in detecting coronary obstructions, particularly in the proximal third of the coronary anatomy, and may improve the diagnostic evaluation of patients with a low to intermediate probability of ACS, but it does not have a role in the management of suspected STEMI.[85]

Estimation of Infarct Size

Interest in limiting infarct size, largely because of the recognition that the quantity of infarcted myocardium has important prognostic implications, has focused attention on accurate determination of MI size. As reviewed earlier, the relationship between infarct size and subsequent changes in LV volumes and function is not directly linear. Other factors such as residual ischemia, inflammation, and therapy can affect eventual ventricular function and prognosis.[49] However, the degree of infarcted myocardium remains a strong predictor of subsequent outcomes.[94]

Electrocardiography.

The sum of ST-segment elevations measured from multiple precordial leads correlates with the extent of myocardial injury in patients with anterior MI. Moreover, a relationship exists between the number of ECG leads showing ST-segment elevation and the mortality rate: patients with 8 or 9 of 12 leads showing ST-segment elevation have three to four times the mortality of those with ST elevations in only 2 or 3.

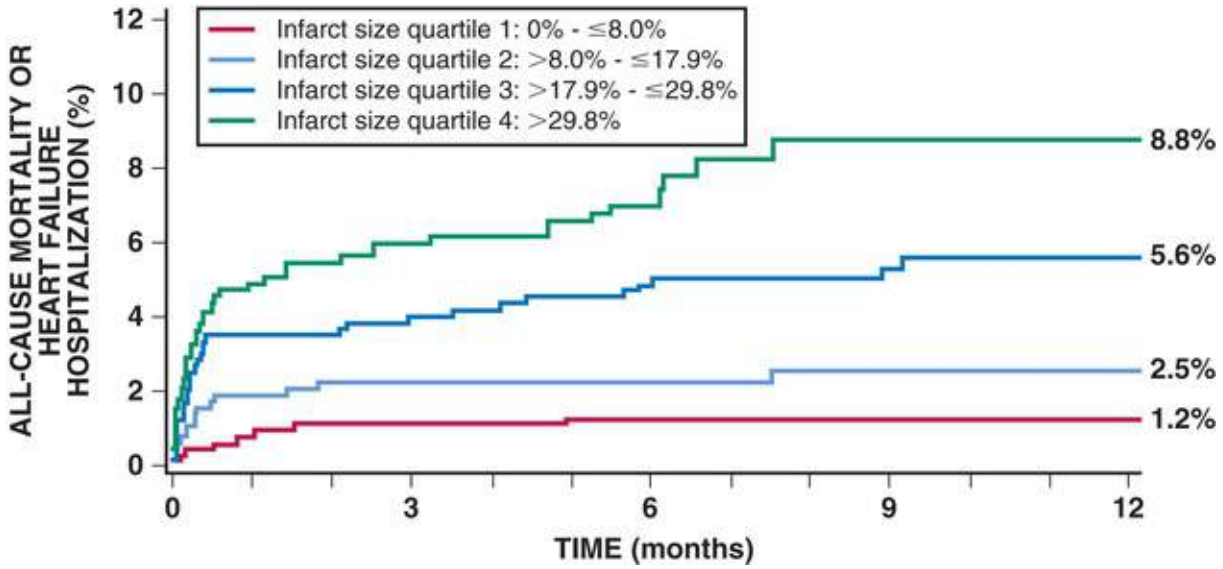
Cardiac Markers.

Estimation of infarct size by analysis of serum or plasma cardiac markers of necrosis requires accounting for the quantity of the marker lost from the myocardium, its volume of distribution, and its release ratio. Serial measurements of proteins released by necrotic myocardium can help to determine MI size. Clinically, the peak CK, CK-MB, or troponin level provides an approximate estimate of infarct size. Coronary artery reperfusion dramatically changes the washout kinetics of necrosis markers from myocardium, thereby resulting in early and exaggerated peak levels (**see Fig. 58.18**). Measuring a cardiac-specific troponin level several days after STEMI, even in cases of successful reperfusion, may provide a reliable estimate of infarct size because such late troponin measurements reflect delayed release from the myofilament-bound pool in damaged myocytes.

Noninvasive Imaging Techniques.

The imaging modalities previously discussed can aid in experimental and clinical assessment of infarct size.[85] Echocardiography remains the most frequently used modality for assessing infarct size and LV function, although contrast-enhanced CMR can detect smaller degrees of ischemia and identify

permanently damaged areas of the myocardium versus “stunned” regions, which may recover. Nuclear imaging and CMR can quantify the extent of infarct size more reliably than echocardiography. Even among patients undergoing primary PCI, the size of infarct is associated strongly with worse outcomes, in particular during the first 6 months[89] (**eFig. 58.5**). CMR can also discern the regional heterogeneity of infarction patterns in patients with persistently occluded infarct arteries or severe microvascular occlusion versus those with a successfully reperfused macrocirculation and microcirculation.



EFIGURE 58.5 Infarct size and outcomes after percutaneous coronary intervention (PCI). All-cause mortality and heart failure according to quartiles of infarct size (IS) assessed by CMR. (From Stone GW, Selker HP, Thiele H, et al. Relationship between infarct size and outcomes following primary pci: patient-level analysis from 10 randomized trials. J Am Coll Cardiol 2016;67:1674-83.)

Future Perspectives

The remarkable advances in understanding the cellular and molecular mechanisms of myocardial ischemic injury, coupled with recent insights into the mechanisms during repair and healing of the infarcted myocardium, have identified potential targets for “tuning” the healing response to optimize the repair process in ischemically injured myocardium and minimize adverse left ventricular remodeling. We still triage patients who present with ACS on the basis of the ECG, but we should strive toward a more mechanistically based categorization of ACS that reflects the underlying biologic basis of the acute ischemic insult. To fill this gap, we need to seek, refine, and validate biomarkers of the different pathologic pathways that provoke acute myocardial ischemia and then apply at point of care, more mechanistically based therapies. Such biomarker-guided personalized therapy would thus achieve more precision in the care of ACS patients. For example, markers that distinguish fibrous cap rupture from superficial erosion as triggers to thrombus formation might inform different management strategies. This hypothesis would require rigorous validation but could lead to a more personalized management strategy.

We understand more clearly the different pathways in formation of coronary thrombi, but not all acute ischemic events result from clot formation. Past research centered on epicardial coronary artery spasm as a contributor to acute ischemic event, but we now recognize that dysfunction of smaller intramyocardial arteries may also provoke ischemia without necessarily causing evident thrombosis.[95] The spectrum of ischemic processes ranging from MINOCA and in the extreme stress (takotsubo) cardiomyopathy highlight

the need for greater investigation into the microvasculature, to understand better the underlying mechanism of these diseases and identify novel therapeutic strategies. Thus, although we have made considerable inroads in understanding and treating ACS in the last decades, the residual risk remains unacceptable. We must strive to expand our mechanistic understanding of the pathophysiology of ACS to address this residual burden and achieve the promise of precision medicine.

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ST-Elevation Myocardial Infarction

Management

Erin A. Bohula, David A. Morrow

The care of patients with ST-elevation myocardial infarction (STEMI) has transformed in conjunction with major shifts in the approach to reperfusion therapy from primarily pharmacologic to catheter-based strategies.[1-4] With simultaneous advances in medical therapy, the case-fatality rate for patients with STEMI has continued to decline[4,5] (**Fig. 59.1**). Nevertheless, optimal management of patients at high risk for or with established major complications of STEMI remains critical to the care of this condition. A discussion of the management of STEMI can follow the clinical course of the patient. **Chapter 45** addresses primary and secondary prevention of coronary artery disease (CAD). **Chapter 56** reviews the emergency evaluation of patients with chest pain. This chapter deals with treatment at the time of onset of STEMI (prehospital issues, initial recognition and management in the emergency department, and reperfusion), hospital management (medications, complications, and preparation for discharge), and early secondary prevention after STEMI. **Chapter 62** discusses percutaneous coronary intervention (PCI) in patients with STEMI. **Chapter 41** describes the use of internal and external automated defibrillators for prevention of sudden cardiac death after myocardial infarction (MI). **Chapter 61** discusses the long-term management of the patient with established chronic stable ischemic heart disease, including patients with prior acute MI.

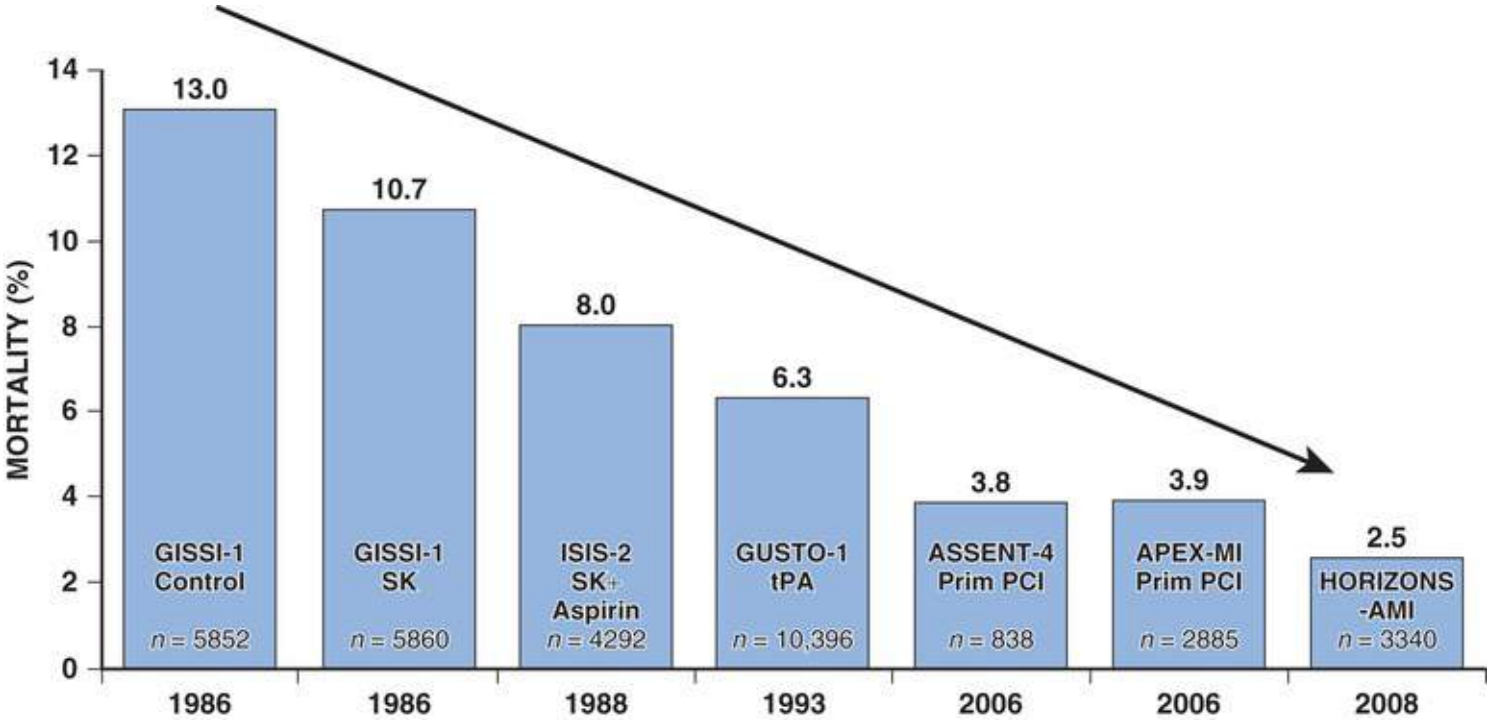


FIGURE 59.1 Early mortality rates have declined in major randomized trials of STEMI patients from 1986 to 2008 with the introduction and improvement in pharmacologic and/or mechanical reperfusion therapy. Prim PCI, Primary percutaneous coronary intervention; SK, streptokinase; tPA, tissue plasminogen activator. (From Van de Werf F. The history of coronary reperfusion. Eur Heart J 2014;35;2510-2515.)

Prehospital Management

Given the progressive loss of functioning myocytes with persistent occlusion of the infarct-related artery in STEMI (**see Chapter 58**), initial management aims to restore blood flow to the infarct zone as rapidly as possible. Primary PCI is generally the preferred option, provided that an experienced operator and team can perform it in timely fashion.[1,4,6] Missed opportunities for improvement in the care of STEMI include failure to deliver any form of reperfusion therapy in approximately 15% of patients and failure to minimize delays in reperfusion because of inefficient systems of care.[5,7,8] The "chain of survival" for STEMI involves a highly integrated strategy beginning with patient education about the symptoms of MI and early contact with the medical system, coordination of destination protocols in emergency medical service (EMS) systems, efficient practices in emergency departments to shorten door-to-reperfusion time, and expeditious implementation of the reperfusion strategy by a trained team.[9,10] The American Heart Association (AHA) launched a national initiative to engineer improved health care delivery for STEMI, including implementation of systems that shorten total ischemic time while emphasizing overall quality of care for STEMI[10] (**Tables 59.1 and 59.2**).

TABLE 59.1

Criteria for a System of Care for ST-Elevation Myocardial Infarction (STEMI)

1. The system should be registered with Mission: Lifeline.
2. Ongoing multidisciplinary team meetings should occur, including EMS, non-PCI hospitals/STEMI referral centers, and PCI hospitals/STEMI receiving centers, to evaluate outcomes and quality improvement data. Operational issues should be reviewed, problems identified, and solutions implemented.
3. Each STEMI system should include a process for prehospital identification and activation, destination protocols to STEMI receiving centers, and transfer for patients who arrive at STEMI referral centers and are primary PCI candidates, are ineligible for fibrinolytic therapy, and/or are in cardiogenic shock.
4. Each system should have a recognized system coordinator, physician champion, and EMS medical director.
5. Each system component (EMS, STEMI referral centers, and STEMI receiving centers) should meet the appropriate criteria.

EMS, Emergency medical services; *PCI,* percutaneous coronary intervention.

TABLE 59.2

Interventions to Improve Door-to-Device Times

1. A prehospital ECG for diagnosing STEMI is used to activate the PCI team while the patient is en route to the hospital.
2. Emergency physicians activate the PCI team.
3. A single call to a central page operator activates the PCI team.
4. A goal is set for the PCI team to arrive at the catheterization laboratory within 20 minutes after being paged.
5. Timely data feedback and analysis are provided to members of the STEMI care team.

From O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78.

Prehospital Care

The prehospital care of patients suspected of having STEMI bears directly on the likelihood of survival. Most deaths associated with STEMI occur within the first hour of its onset and usually result from ventricular fibrillation (VF) (**see Chapter 42**). Therefore, immediate implementation of resuscitative efforts and rapid transportation of the patient to a hospital have prime importance. Major components of the time from the onset of ischemic symptoms to reperfusion include (1) the time for the patient to recognize the problem and seek medical attention; (2) prehospital evaluation, treatment, and transportation; (3) the time for diagnostic measures and initiation of treatment in the hospital (e.g., “door-to-needle” time for patients receiving a fibrinolytic agent and “door-to-device” time for patients undergoing a catheter-based reperfusion strategy); and (4) the time from initiation of treatment to restoration of flow.

Patient-related factors that correlate with a longer delay until deciding to seek medical attention include older age; female sex; black race; low socioeconomic or uninsured status; history of angina, diabetes, or both; consulting a spouse or other relative; and consulting a physician.[1,11] Health care professionals should heighten the level of awareness of patients at risk for STEMI (e.g., those with hypertension, diabetes, history of angina pectoris). They should use each patient encounter as a “teachable moment” to review and reinforce with patients and their families the need to seek urgent medical attention for a pattern of symptoms that includes chest discomfort, extreme fatigue, and dyspnea. Patients should also be instructed in the proper use of sublingual nitroglycerin and to call emergency services if the ischemic-type discomfort persists for more than 5 minutes.[1]

Emergency Medical Service Systems

EMS systems have three major components: emergency medical dispatch, first response, and the EMS ambulance response (**see Chapter 56**). The expanded capability to record a prehospital 12-lead

electrocardiogram (ECG) represents a major advance in EMS systems (**Table 59.2**).[12] The ability to transmit such ECGs and to activate the STEMI care team before arrival at the hospital places EMS efforts at the center of the early response to STEMI.[13] Ongoing efforts to shorten the time until treatment of patients with STEMI include improvement in the medical dispatch component by expanding 911 coverage, providing automated external defibrillators to first responders, placing automated external defibrillators in critical public locations, and greater coordination of the EMS ambulance response. Well-equipped ambulances and helicopters staffed by personnel trained in the acute care of patients with STEMI allow definitive therapy to begin during transport to the hospital. Radiotelemetry systems that allow transmission of the electrocardiographic signal to a medical control officer facilitate the triage of patients with STEMI (**Fig. 59.2**).

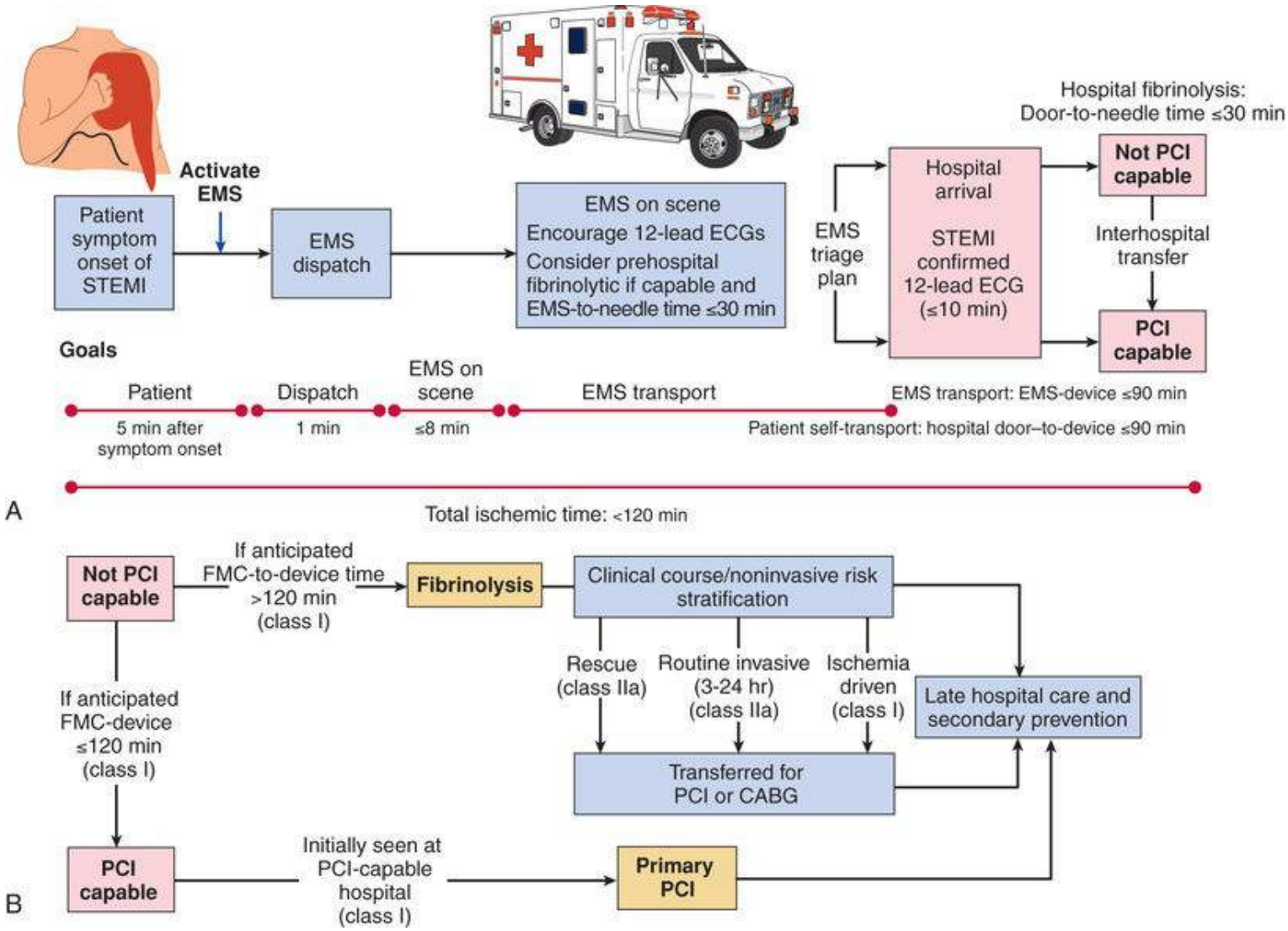


FIGURE 59.2 System goals and initial reperfusion treatment of patients with STEMI. Reperfusion in STEMI patients can be accomplished by pharmacologic (fibrinolysis) or catheter-based (primary PCI) approaches and may involve transfer from a non–PCI-capable to a primary PCI-capable center. **A,** Patient transported by the emergency medical services (EMS). The STEMI systems goal is to maintain a network of transportation and destination hospitals so that the total ischemic time is kept to less than 120 minutes. In addition to this overall goal, three additional time objectives exist. (1) If the EMS has fibrinolytic capability and the patient qualifies for therapy, prehospital fibrinolysis may be considered and, if used, should be started within 30 minutes of arrival of the EMS on scene. (2) For patients transported to a non–PCI-capable hospital where a fibrinolytic is to be administered, the hospital door–to-needle time should be 30 minutes or less. (3) If the patient is transported to a PCI-capable hospital, the time from first medical contact (FMC) to deployment of the first PCI device (FMC-to-device time) should be 90 minutes or less. Patient self-transportation is discouraged. If the patient arrives at a non–PCI-capable hospital and a

fibrinolytic is to be administered, the door-to-needle time should be 30 minutes or less. If the patient arrives at a PCI-capable hospital, the door-to-balloon time should be 90 minutes or less. The treatment options and time recommendations after arrival at the hospital are the same. Consideration of emergency interhospital transfer of the patient to a PCI-capable hospital for mechanical revascularization is also appropriate if use of a fibrinolytic is contraindicated or PCI can be initiated promptly (anticipated FMC-to-device time ≤120 minutes) or if fibrinolysis is unsuccessful (i.e., "rescue PCI"). Secondary nonemergency interhospital transfer can be considered for recurrent ischemia or routine invasive evaluation 3 to 24 hours after fibrinolysis. **B,** Reperfusion strategies for patients with STEMI, regardless of whether they go to a PCI-capable or to a non–PCI-capable hospital. The optimal strategy depends on the timing of the onset of symptoms, the patient's eligibility for fibrinolysis, and the options for timely transfer to a PCI-capable hospital. The denoted class I and class II recommendations are from the ACCF/AHA guidelines for the management of STEMI. For patients who receive fibrinolysis, noninvasive risk stratification is recommended to guide decisions regarding delayed coronary revascularization. CABG, Coronary artery bypass grafting. (Modified from Armstrong PW, Collen D, Antman E. Fibrinolysis for acute myocardial infarction: the future is here and now. Circulation 2003;107:2533; and O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78.)

In addition to prompt defibrillation, the efficacy of prehospital care appears to depend on several factors, including early relief of pain with its deleterious physiologic sequelae, reduction of excessive activity of the autonomic nervous system, and treatment of arrhythmias such as ventricular tachycardia (VT)—but these efforts must not delay rapid transfer to the hospital (**Fig. 59.2**).

Prehospital Fibrinolysis

Multiple observational studies and several randomized trials have evaluated the potential benefits of prehospital versus in-hospital fibrinolysis.[1,4] Although none of the individual trials showed a significant reduction in mortality with prehospital-initiated fibrinolytic therapy, earlier treatment generally provides greater benefit, and a meta-analysis of all the available trials demonstrated a 17% reduction in mortality.[1] The CAPTIM (Comparison of Primary Angioplasty and Pre-hospital Fibrinolysis in Acute Myocardial Infarction) trial, for example, reported a trend toward a lower mortality rate in patients with STEMI who received prehospital fibrinolysis compared with patients who received primary PCI, especially if they were treated within 2 hours of the onset of symptoms.[1] In the STREAM (Strategic Reperfusion Early After Myocardial Infarction) trial, prehospital fibrinolysis offered similar efficacy to primary PCI in 1892 patients with STEMI who presented within 3 hours of symptom onset and who could not undergo primary PCI within 1 hour of first medical contact. The primary endpoint of death, shock, heart failure, or reinfarction at 30 days occurred in 12.4% of the fibrinolysis arm and 14.3% in the primary PCI arm (**Fig. 59.3**).[14] Rescue or urgent PCI was required in 36% of patients initially receiving fibrinolysis, with the remainder undergoing coronary angiography per protocol a median of 17 hours after randomization. The rate of intracranial hemorrhage was higher in the fibrinolysis group, but nonintracranial bleeding rates were similar between the treatment groups. Based on these data, prehospital fibrinolysis is reasonable in settings in which substantial time can be saved by prehospital treatment because of long transportation times (60 to 90 minutes or longer), and physicians are present in the ambulance, or there is a well-organized EMS system with full-time paramedics who can obtain and transmit 12-lead ECG recordings from the field to an online medical command able to authorize prehospital fibrinolysis[4] (**see Fig. 59.2**).

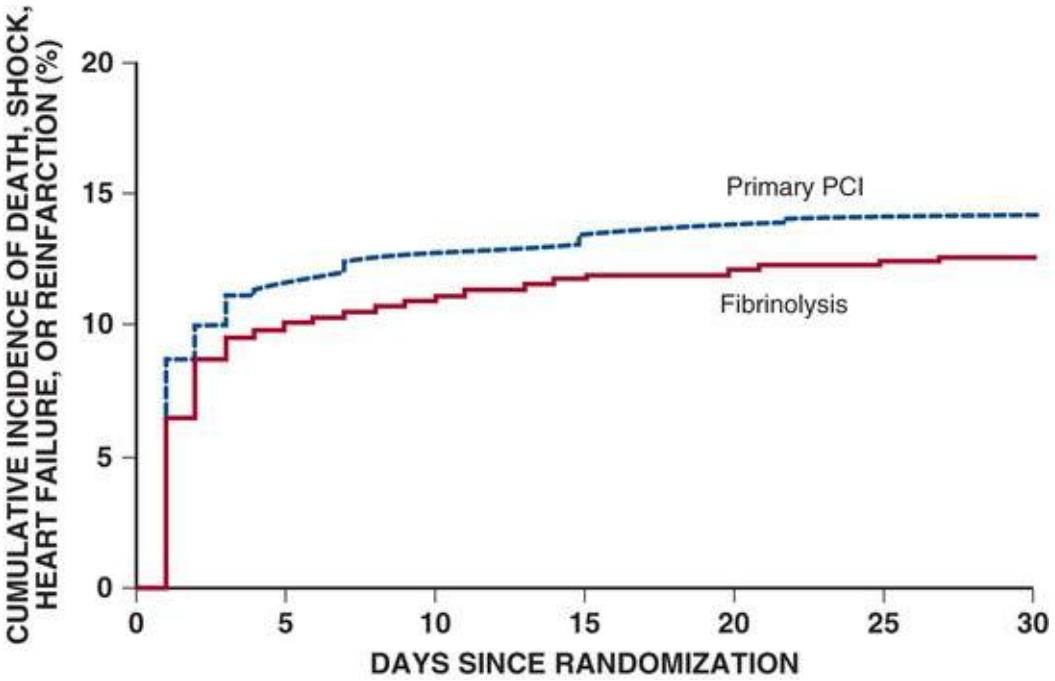


FIGURE 59.3 The STREAM (Strategic Reperfusion Early After Myocardial Infarction) study found that prehospital fibrinolysis offers similar efficacy to primary PCI in 1892 patients with STEMI who presented within 3 hours of symptom onset and who could not undergo primary PCI within 1 hour of FMC, where the primary endpoint of death, shock, heart failure, or reinfarction at 30 days occurred in 12.4% of the fibrinolysis arm and 14.3% in the primary PCI arm (hazard ratio, 0.68; confidence interval, 0.68 to 1.09; *P* = 0.21 by log-rank test). (Modified from Armstrong PW, Gershlick AH, Goldstein P, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. N Engl J Med 2013;368(15):1379-87.)

Management in the Emergency Department

When evaluating patients with chest pain in the emergency department (ED), physicians must confront the difficult tasks of rapidly identifying patients who require urgent reperfusion therapy, triaging lower-risk patients to the appropriate setting within the hospital, and not discharging patients inappropriately while avoiding unnecessary admissions. A history of ischemic-type discomfort and the initial 12-lead ECG are the primary tools for screening patients with possible acute coronary syndrome (ACS) for STEMI (**see Chapter 56**). Because the 12-lead ECG is at the center of the decision pathway for initiation of reperfusion therapy, it should be obtained promptly (≤10 minutes after hospital arrival) in patients with suspected ischemic symptoms.[1] More extensive use of prehospital 12-lead ECGs has also facilitated early triage of patients with STEMI.[12] Because lethal arrhythmias can occur suddenly in patients with STEMI, all patients should have bedside monitoring of the ECG and intravenous (IV) access.

The presence of ST-segment elevation on the ECG in a patient with ischemic discomfort highly suggests thrombotic occlusion of an epicardial coronary artery and should trigger a well-rehearsed sequence of rapid assessment of the patient for initiation of a reperfusion strategy.[1] Critical factors that weigh into selection of a reperfusion strategy include the time elapsed since the onset of symptoms, the risk associated with STEMI, the risk related to administering a fibrinolytic, and the time required to initiate an invasive strategy (**see Fig. 59.2**). In non–PCI-capable hospitals, the initial assessment should include evaluation of the contraindications to administration of a fibrinolytic (**Table 59.3**). Patients with an initial ECG that reveals ST-segment depression and/or T wave inversion without ST-segment elevation are not considered candidates for immediate reperfusion therapy unless a posterior injury current is suspected (**see Chapter 12**).

TABLE 59.3

Contraindications to and Cautions in the Use of Fibrinolytics for Treating ST-Elevation Myocardial Infarction*

Absolute Contraindications
Any previous intracranial hemorrhage
Known structural cerebral vascular lesion (e.g., arteriovenous malformation)
Known malignant intracranial neoplasm (primary or metastatic)
Ischemic stroke within 3 months *except* acute ischemic stroke within 4.5 hours
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed-head or facial trauma within 3 months
Intracranial or intraspinal surgery within 2 months
Severe uncontrolled hypertension (unresponsive to emergency therapy)
For streptokinase, previous treatment within the previous 6 months
Relative Contraindications
History of chronic, severe, poorly controlled hypertension
Significant hypertension at initial evaluation (SBP >180 mm Hg or DBP >110 mm Hg)†
History of previous ischemic stroke >3 months
Dementia
Known intracranial pathology not covered in Absolute Contraindications
Traumatic or prolonged (>10 minutes) cardiopulmonary resuscitation
Major surgery (<3 weeks)
Recent (within 2 to 4 weeks) internal bleeding
Noncompressible vascular punctures
Pregnancy
Active peptic ulcer
Oral anticoagulant therapy

*Viewed as advisory for clinical decision making and may not be all-inclusive or definitive.

†Could be an absolute contraindication in low-risk patients with MI.

DBP, Diastolic blood pressure; *SBP,* systolic blood pressure.

From O' Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78.

Given the importance of time to reperfusion,[4] emphasis has shifted to overall medical system goals, starting at the point of first medical contact with the patient.[1,15] Benchmarks for medical systems to use when assessing the quality of their performance are a door-to-needle time of 30 minutes or less for initiation of fibrinolytic therapy and a door-to-device time of 90 minutes or less for percutaneous coronary perfusion[1,2] (**Fig. 59.2**). In patients with a clinical history suggestive of STEMI (**see Chapter 56**) and an initial nondiagnostic ECG (i.e., no ST-segment deviation or T wave inversion), serial tracings should be obtained during evaluation in the ED. ED staff can seek the sudden development of ST-segment elevation by periodic visual inspection of the bedside electrocardiographic monitor, by continuous ST-segment recording, or by auditory alarms when the ST-segment deviation exceeds programmed limits. Decision aids such as computer-based diagnostic algorithms, identification of high-risk clinical indicators, rapid determination of cardiac biomarkers, echocardiographic evaluation for regional wall motion abnormalities, and myocardial perfusion imaging have greatest clinical usefulness when the findings on the ECG are not diagnostic.

General Treatment Measures

See also **Chapter 60** and **Table 60.5**.

Aspirin

Aspirin is effective across the entire ACS spectrum and is part of the initial management strategy for patients with suspected STEMI. Because low doses take several days to achieve a full antiplatelet effect,

162 to 325 mg should be administered at the first opportunity after initial medical contact.[1] To achieve therapeutic blood levels rapidly, the patient should chew a non–enteric-coated tablet to promote buccal absorption bypassing the gastric mucosa.

Control of Cardiac Pain

Initial management of patients with STEMI should target relief of pain and its associated heightened sympathetic activity. Control of cardiac pain is typically achieved with a combination of analgesics (e.g., morphine) and interventions to favorably improve the balance of myocardial oxygen supply and demand, including oxygen (in the setting of hypoxia), nitrates, and in appropriately selected patients, beta-adrenergic receptor–blocking agents (beta blockers).[1]

Analgesics

Although a wide variety of analgesic agents, including meperidine, pentazocine, and morphine, can treat the pain associated with STEMI, morphine remains the drug of choice, except in patients with well-documented morphine hypersensitivity. Doses of 4 to 8 mg administered intravenously initially, followed by doses of 2 to 8 mg repeated at intervals of 5 to 15 minutes have been recommended until the pain is relieved or side effects emerge—hypotension, depression of respiration, or vomiting.[1] Appropriate dosing of morphine sulfate will vary, however, depending on the patient's age, body size, blood pressure (BP), and heart rate (HR).

Reduction of anxiety with successful analgesia diminishes the patient's restlessness and the activity of the autonomic nervous system, with a consequent reduction in the heart's metabolic demands, and possible favorable effects on myocardial healing (**see Chapter 58**). Morphine has beneficial effects in patients with pulmonary edema as a result of peripheral arterial and venous dilation (particularly in those with excessive sympathoadrenal activity); it reduces the work of breathing and slows the HR secondary to combined withdrawal of sympathetic tone and augmentation of vagal tone. Counterbalancing these potential benefits, observational studies have suggested an association between the administration of morphine and adverse outcomes in patients with ACS, with the putative mechanism being a slowing of antiplatelet agent absorption.[16,17]

Maintaining the patient in a supine position and elevating the lower extremities if BP falls can minimize hypotension following the administration of nitroglycerin and morphine. Such positioning is undesirable in patients with pulmonary edema, but morphine rarely produces hypotension in these circumstances. IV administration of atropine may be helpful in treating excessive vagomimetic effects of morphine.

Nitrates

By virtue of their ability to enhance coronary blood flow by coronary vasodilation and to decrease ventricular preload by increasing venous capacitance, sublingual (SL) nitrates are indicated for most patients with an ACS. At present, the only groups of patients with STEMI in whom SL nitroglycerin should *not* be given are those with suspected right ventricular (RV) infarction[18] or marked hypotension (e.g., systolic BP <90 mm Hg), especially if accompanied by bradycardia.

Once hypotension is excluded, an SL nitroglycerin tablet should be administered and the patient observed for improvement in symptoms or change in hemodynamics. If an initial dose is well tolerated and appears to be beneficial, further nitrates should be administered while monitoring vital signs. Even small doses can produce sudden hypotension and bradycardia, a reaction that can usually be reversed with IV atropine. Long-acting oral nitrate preparations should be avoided in the early course of STEMI

because of the frequently changing hemodynamic status of the patient. In patients with a prolonged period of waxing and waning chest pain, IV nitroglycerin may help control the symptoms and correct the ischemia, but frequent monitoring of BP is required. Initiation of a reperfusion strategy in patients with STEMI should not be delayed while assessing the patient's response to SL or IV nitrates.

Beta-Adrenergic Blocking Agents

Beta blockers aid in the relief of ischemic pain, reduce the need for analgesics in many patients, and reduce infarct size and life-threatening arrhythmias. Avoiding early IV beta blockers in patients with Killip class II or greater is important, however, because of the risk of precipitating cardiogenic shock.[1] Routine use of IV beta blockers is no longer recommended in patients with STEMI, but IV administration of a beta blocker at the initial evaluation of patients with STEMI who are hypertensive and have ongoing ischemia is reasonable.[1]

A practical protocol for use of a beta blocker in this situation follows. First, exclude patients with heart failure (HF), hypotension (systolic BP <90 mm Hg), bradycardia (HR <60 beats/min), or significant atrioventricular (AV) block. Second, administer metoprolol in three 5-mg IV boluses. Third, observe the patient for 2 to 5 minutes after each bolus, and if HR falls below 60 beats/min or systolic BP falls below 100 mm Hg, do not administer any further drug. Fourth, if hemodynamic stability continues 15 minutes after the last IV dose, begin oral metoprolol tartrate, 25 to 50 mg every 6 hours for 2 to 3 days as tolerated, and then switch to 100 mg twice daily.[1] Lower doses may be used in patients who have a partial decline in BP with the initial dosing or who appear to be at higher risk (e.g., larger infarction) for development of HF because of poor left ventricular (LV) performance. Infusion of an extremely short-acting beta blocker, such as esmolol, 50 to 250 µg/kg/min, may be useful in patients with relative contraindications to the administration of a beta blocker and in whom HR slowing is considered highly desirable.[19]

Oxygen

Hypoxemia can occur in patients with STEMI and generally results from ventilation-perfusion abnormalities that are sequelae of LV failure; concomitant intrinsic pulmonary disease may also contribute to hypoxemia in some patients. Treating all patients hospitalized for STEMI with oxygen for at least 24 to 48 hours is common practice based on the empiric assumption of hypoxia and evidence that increased oxygen in the inspired air may protect ischemic myocardium. However, augmentation of the fraction of oxygen in inspired air (FIO_2) does not elevate O_2 delivery significantly in patients who are not hypoxemic. Furthermore, it may increase systemic vascular resistance and arterial pressure, promote coronary vasoconstriction, and result in greater oxidative stress. Moreover, in a randomized trial comparing oxygen (8 L/min) with no supplemental oxygen in 441 patients with STEMI but without hypoxia, compared with the control therapy, supplemental O_2 therapy demonstrated a trend toward increased early myocardial injury measured with cardiac troponin.[20] In a secondary analysis, O_2 supplementation was associated with increased myocardial infarct size assessed by cardiac magnetic resonance imaging (CMR) at 6 months.

In view of these considerations, arterial oxygen saturation (SaO_2)can be estimated by pulse oximetry, and O_2 therapy can be omitted if the oximetric findings are normal. On the other hand, patients with STEMI and arterial hypoxemia (e.g. SaO_2 <90%) should receive oxygen.[1] In patients with severe pulmonary edema, endotracheal intubation and mechanical ventilation may be necessary to correct the hypoxemia and reduce the work of breathing.

Limitation of Infarct Size

Infarct size is an important determinant of prognosis in patients with STEMI. Patients who succumb from cardiogenic shock generally exhibit either a single massive infarct or a moderate infarct superimposed on multiple previous infarctions.[21,22] Survivors with large infarcts frequently exhibit late impairment of ventricular function, and their long-term mortality rate is higher than that of survivors with small infarcts.[22] In view of the prognostic importance of infarct size, the possibility of modifying infarct size has attracted much experimental and clinical attention[4,23] (**see Chapter 58, Fig. 58.12**). Efforts to limit infarct size have used several different (sometimes overlapping) approaches: (1) early reperfusion, (2) reduction of myocardial energy demands, (3) manipulation of energy production sources in the myocardium, and (4) prevention of reperfusion injury.[24]

Dynamic Nature of Infarction

STEMI is a dynamic process that does not occur instantaneously but rather evolves over hours. The fate of jeopardized, ischemic tissue can be favorably affected by interventions that restore myocardial perfusion, reduce microvascular damage in the infarct zone, decrease myocardial oxygen requirements, inhibit accumulation or facilitate washout of noxious metabolites, augment the availability of substrate for anaerobic metabolism, or blunt the effects of mediators of injury that compromise the structure and function of intracellular organelles and constituents of cell membranes. Strong evidence in experimental animals and suggestive evidence in patients indicate that *ischemic preconditioning*, a form of endogenous protection against STEMI, before sustained coronary occlusion decreases infarct size and is associated with a more favorable outcome, along with decreased risk for extension of infarction and recurrent ischemic events. Brief episodes of ischemia in one coronary vascular bed may precondition myocardium in a remote zone and thereby attenuate the size of infarction in the latter when sustained coronary occlusion occurs.[25]

Perfusion of myocardium in the infarct zone appears to fall maximally immediately following coronary occlusion. Spontaneous recanalization of an occluded infarct-related artery occurs in up to one third of patients beginning at 12 to 24 hours. This delayed spontaneous reperfusion may enhance LV function because it improves healing of infarcted tissue, prevents ventricular remodeling, and reperfuses hibernating myocardium. Yet, strategies involving pharmacologically induced and catheter-based reperfusion of the infarct vessel can *maximize* the amount of salvaged myocardium by *accelerating* the process of reperfusion and also implementing it in patients who would otherwise have an occluded infarct-related artery. An overarching concept that applies to all methods of reperfusion is the critical importance of time. The earlier the infarct artery is reperfused, the greater the reduction in mortality[1] (**Fig. 59.4**).

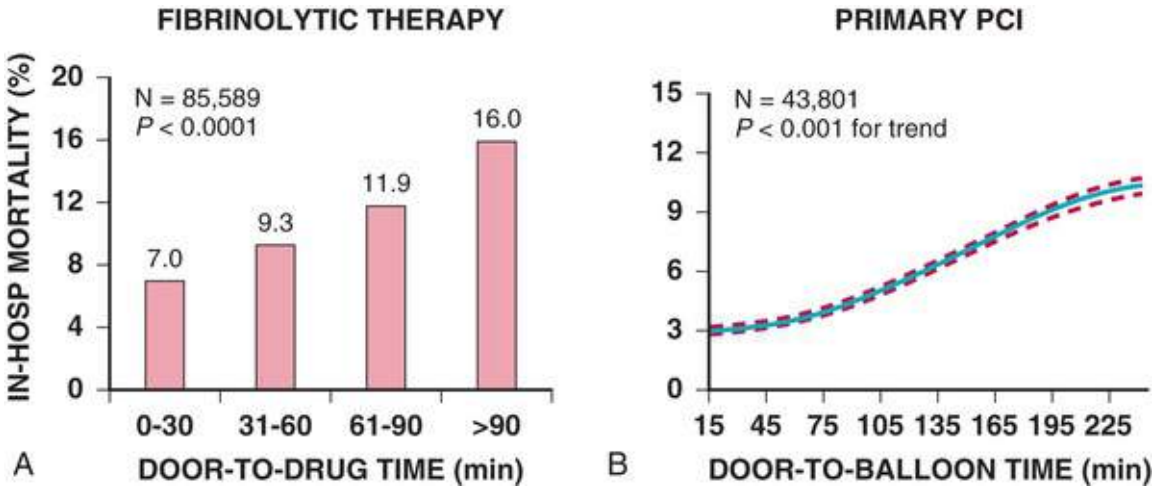


FIGURE 59.4 Importance of time to reperfusion in patients undergoing fibrinolysis **(A)** or primary PCI **(B)** for STEMI. **A,** Graph based on data from 85,589 patients treated with fibrinolysis. A progressive increase in the in-hospital mortality rate occurs for every 30-minute delay. **B,** Based on data from 43,801 patients, this graph depicts the adjusted in-hospital mortality rate as a function of door-to-balloon time. Estimated mortality ranged from 3% with a door-to-balloon time of 30 minutes to 10.3% in patients with a door-to-balloon time of 240 minutes. (Data from Cannon CP et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. JAMA 2000;283:2941; and Rathore SS et al. Association of door-to-balloon time and mortality in patients admitted to hospital with ST elevation myocardial infarction: national cohort study. BMJ 2009;338:b1807.)

Additional factors that may limit infarct size during reperfusion include relief of coronary spasm, prevention of damage to the microvasculature, improved systemic hemodynamics (augmentation of coronary perfusion pressure and reduced LV end-diastolic pressure), and collateral circulation. Prompt implementation of measures designed to protect ischemic myocardium and support myocardial perfusion may provide sufficient time for the development of compensatory mechanisms that limit the ultimate extent of infarction (**see Chapter 58**). Interventions designed to protect ischemic myocardium during the initial event may also reduce the extension of infarction or early reinfarction.

Routine Measures for Limitation of Infarct Size

Although timely reperfusion of ischemic myocardium is the most important technique for limiting infarct size, several routine measures to accomplish this goal apply to all patients with STEMI, regardless of whether they receive reperfusion therapy.[1] The treatment strategies discussed in this section can be initiated at first medical contact and can be continued throughout the hospital phase of care.

Myocardial oxygen consumption should be minimized by maintaining the patient at rest both physically and emotionally and by using mild sedation and a quiet atmosphere—in addition to the interventions already discussed. Administration of adrenergic agonists should be avoided whenever possible. All forms of tachyarrhythmia require prompt treatment because they increase myocardial oxygen needs. HF should also be treated swiftly to minimize increases in adrenergic tone and hypoxemia (see later, Left Ventricular Failure). If ongoing ischemia occurs, severe anemia (hemoglobin <7 g/dL) can be corrected by the cautious administration of packed red blood cells, accompanied by a diuretic if there is any evidence of LV failure. Associated conditions, particularly infections and accompanying tachycardia, fever, and elevated myocardial oxygen needs, require management.

Reperfusion Therapy

General Concepts

Although late spontaneous reperfusion occurs in some patients, thrombotic occlusion persists in most patients with STEMI. Timely reperfusion of jeopardized myocardium is the most effective way of restoring the balance between myocardial oxygen supply and demand.[26] The dependence of myocardial salvage on the time elapsed until treatment pertains to patients treated with either fibrinolysis or PCI[1,27,28] (**Fig. 59.5**). The efficacy of fibrinolytic agents decreases as coronary thrombi mature over time (**see Fig. 59.4**). Analyses adjusted for baseline risk also demonstrate a statistically significant increase in in-hospital and long-term mortality with progressive delays between the onset of symptoms and PCI.[1,28] Each 30-minute delay from symptom onset to PCI increases the relative risk (RR) for 1-year mortality by 8%.

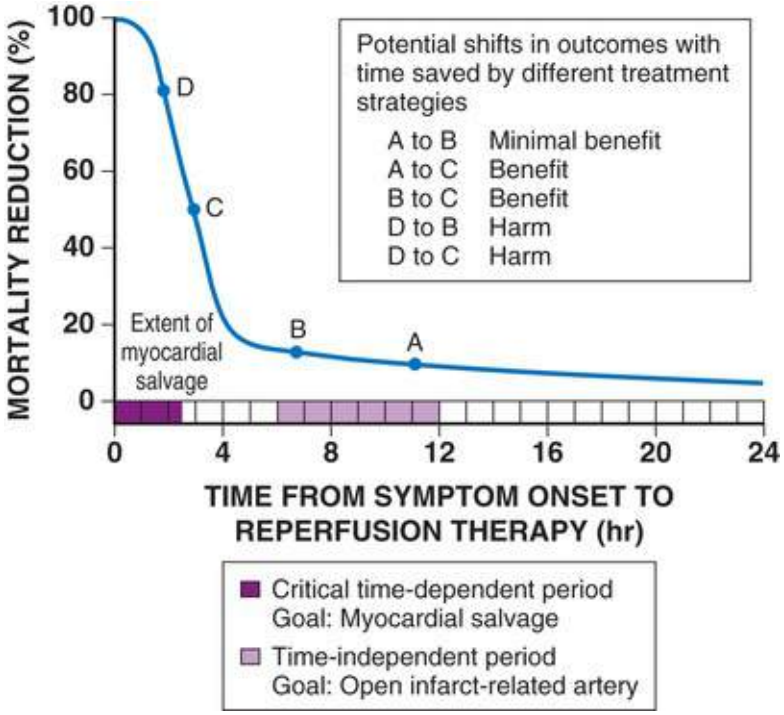


FIGURE 59.5 The reduction in mortality as a benefit of reperfusion therapy is greatest in the first 2 to 3 hours after the onset of symptoms of acute MI, most likely a consequence of myocardial salvage. The exact duration of this critical early period may be modified by several factors, including the presence of functioning collateral coronary arteries, ischemic preconditioning, myocardial oxygen demands, and the duration of sustained ischemia. After this early period, the magnitude of the mortality benefit is much reduced, and as the mortality reduction curve flattens, time to reperfusion therapy is less critical. The magnitude of the benefit depends on how far up the curve the patient can be shifted. The benefit of a shift from point A or B to point C would be substantial, but the benefit of a shift from point A to point B would be small. This schematic illustrates how a treatment strategy that delays therapy during the early critical period, such as transfer of a patient for PCI with a long transportation time, could be harmful (shift from point D to point C or point B). (Modified from Gersh BJ, Stone GW, White HD, Homes DR Jr. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: is the slope of the curve the shape of the future? JAMA 2005;293:979.)

In some patients, particularly those with cardiogenic shock, tissue damage occurs in a “stuttering” manner rather than abruptly. This scenario underscores the need for careful history taking to ascertain whether the patient appears to have had repetitive cycles of spontaneous reperfusion and reocclusion. Determining the precise time of onset of the infarction process in these patients, however, can be difficult and sometimes misleading. In such patients with waxing and waning ischemic discomfort, a rigid time interval from the first episode of pain should not be used when determining whether a patient is “outside the window” for benefit from acute reperfusion therapy.

Pathophysiology of Myocardial Reperfusion

Prevention of cell death by restoration of blood flow depends on the severity and duration of the preexisting ischemia. Substantial experimental and clinical evidence indicates that the earlier blood flow is restored, the more favorable the recovery of LV systolic function, improvement in diastolic function, and reduction in overall mortality.[1] Collateral coronary vessels also appear to influence LV function after reperfusion.[29] They provide sufficient perfusion of myocardium to slow cell death and probably have greater importance in patients undergoing reperfusion later than 1 to 2 hours after coronary occlusion. Even after successful reperfusion and despite the absence of irreversible myocardial damage, a period of postischemic contractile dysfunction can occur—a phenomenon called *myocardial stunning*.[24]

Reperfusion Injury

Reperfusion, although beneficial in terms of myocardial salvage, may cause adverse sequelae described by the term *reperfusion injury*[25] (**see Chapter 58**). Several types of reperfusion injury occur in experimental animals: (1) *lethal* reperfusion injury, which refers to reperfusion-induced death of cells that were still viable at restoration of coronary blood flow; (2) *vascular* reperfusion injury, which is progressive damage to the microvasculature such that there is an expanding area of no-reflow and loss of coronary vasodilatory reserve; (3) *stunned myocardium*, in which salvaged myocytes display a prolonged period of contractile dysfunction after restoration of blood flow because of abnormalities in intracellular metabolism, leading to reduced energy production; and (4) *reperfusion arrhythmias*, which refer to bursts of VT (and occasionally VF) that occur within seconds of reperfusion.[25] Vascular reperfusion injury, stunning, and reperfusion arrhythmias can all occur in patients with STEMI. The concept of lethal reperfusion injury to potentially salvageable myocardium remains controversial, both in animals and in humans.[30-32]

Microvasculature damage in the reperfused myocardium can lead to a hemorrhagic infarct (**see Chapter 58**). Fibrinolytic therapy appears more likely than catheter-based reperfusion to produce hemorrhagic infarction. Although there is concern that this hemorrhage may lead to extension of the infarct, this does not appear to be the case. Histologic study of patients not surviving despite successful reperfusion has revealed hemorrhagic infarcts, but this hemorrhage does not usually extend beyond the area of necrosis.

Protection Against Reperfusion Injury.

A variety of adjunctive therapies have been proposed to mitigate the injury that occurs after reperfusion, including modulators of nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) signaling, such as atrial natriuretic peptide, exenatide, and NO, and inhibitors of mitochondrial permeability and dysfunction, such as cyclosporine A.[25,33] Also, using antiplatelet agents and antithrombins to minimize embolization of atheroembolic debris, and prevention of subsequent inflammatory damage may serve to maintain microvascular integrity (**see Tables 60.4 and 60.5**). The effectiveness of interventions directed against reperfusion injury appears to decline rapidly the later that they are administered after reperfusion. In animals, no beneficial effect is detectable after 45 to 60 minutes of reperfusion has elapsed. Transient ischemia produced in other vascular beds may also reduce reperfusion injury, a concept called *remote ischemic conditioning* (RIC).[25,33] Application of this concept to patients undergoing coronary artery bypass grafting (CABG), using repeated cycles of prolonged BP cuff inflation on the upper extremity, reduced perioperative myocardial injury, but did not improve clinical outcomes in two randomized

trials.[34-36] Several studies have also identified a reduction in MI size in STEMI patients treated with RIC.[33] The ongoing CONDI2/ERIC-PPCI (Effect of Remote Ischaemic Conditioning on Clinical Outcomes in STEMI Patients Undergoing PPCI) trial of 4300 STEMI patients will address whether RIC can improve clinical outcomes.[37]

An alternative experimental approach to protection against reperfusion injury is called *postconditioning*, which involves introducing brief, repetitive episodes of ischemia alternating with reperfusion.[25,33] This appears to activate the cellular protective mechanisms centering around prosurvival kinases.[25] Many of these protective kinases are also activated during ischemic preconditioning. Several clinical studies in patients with STEMI undergoing PCI have provided evidence that postconditioning is associated with reduced infarct size and improvement in myocardial perfusion, but others have failed to show a benefit.[25] A study evaluating clinical outcomes after postconditioning in 1252 patients with STEMI is ongoing.[38]

Reperfusion Arrhythmias

Transient sinus bradycardia occurs in many patients with inferior infarcts at the time of acute reperfusion, often accompanied by some degree of hypotension. This combination of hypotension and bradycardia with a sudden increase in coronary flow may involve activation of the Bezold-Jarisch reflex. Premature ventricular contractions (PVCs), accelerated idioventricular rhythm, and nonsustained VT also usually follow successful reperfusion. Although some investigators have postulated that early afterdepolarizations participate in the genesis of reperfusion-related ventricular arrhythmias, they are present during both ischemia and reperfusion and therefore not likely to be involved in the development of reperfusion-associated VT or VF.

When present, rhythm disturbances may actually indicate successful restoration of coronary flow, but their specificity for successful reperfusion is limited. In general, clinical features are inaccurate markers of reperfusion, with no single clinical finding or constellation of findings being reliably predictive of angiographically demonstrated coronary artery patency.[1] Although reperfusion arrhythmias may show a temporal clustering at restoration of coronary blood flow in patients after successful fibrinolysis, this brief “electrical storm” is generally innocuous and therefore does not warrant prophylactic antiarrhythmic therapy or specific treatment, except in rare cases of symptomatic or hemodynamically significant reperfusion arrhythmias.[1]

Late Establishment of Patency of the Infarct Vessel

The improved survival and ventricular function after successful reperfusion may not result entirely from limitation of infarct size. Poorly contracting or noncontracting myocardium in a zone that is supplied by a stenosed infarct-related artery with slow anterograde perfusion may still contain viable myocytes. PCI can augment flow in the infarct-related artery and thus improve the function of the so-called hibernating myocardium.[39,40]

Fibrinolysis

Fibrinolysis can recanalize the thrombotic occlusion associated with STEMI, and when achieved, restoration of coronary flow reduces infarct size and improves myocardial function and survival over both the short and the long term.[28] Patients treated within the first 1 to 2 hours after the onset of symptoms seem to have the greatest potential for long-term improvement in survival with fibrinolysis.[1]

Assessment of Reperfusion

TIMI Flow Grade.

To provide a level of standardization both for clinical communication and for studies comparing various reperfusion regimens, most clinicians and investigators describe the flow in the infarct vessel according to the TIMI (Thrombolysis In Myocardial Infarction) trial grading system[41] (**Fig. 59.6**). However, an angiographic snapshot in time does not reflect the fluctuating status of flow in the infarct vessel, which may undergo repeated cycles of patency and reocclusion before or during fibrinolysis. When assessed 60 to 90 minutes after the start of fibrinolytic therapy,[1] the finding of TIMI grade 3 flow is far superior to grade 2 in terms of reduction of infarct size and both short-term and long-term mortality benefit. Therefore, TIMI grade 3 flow should be the goal for achieving reperfusion of the epicardial infarct artery (**Fig. 59.6**).

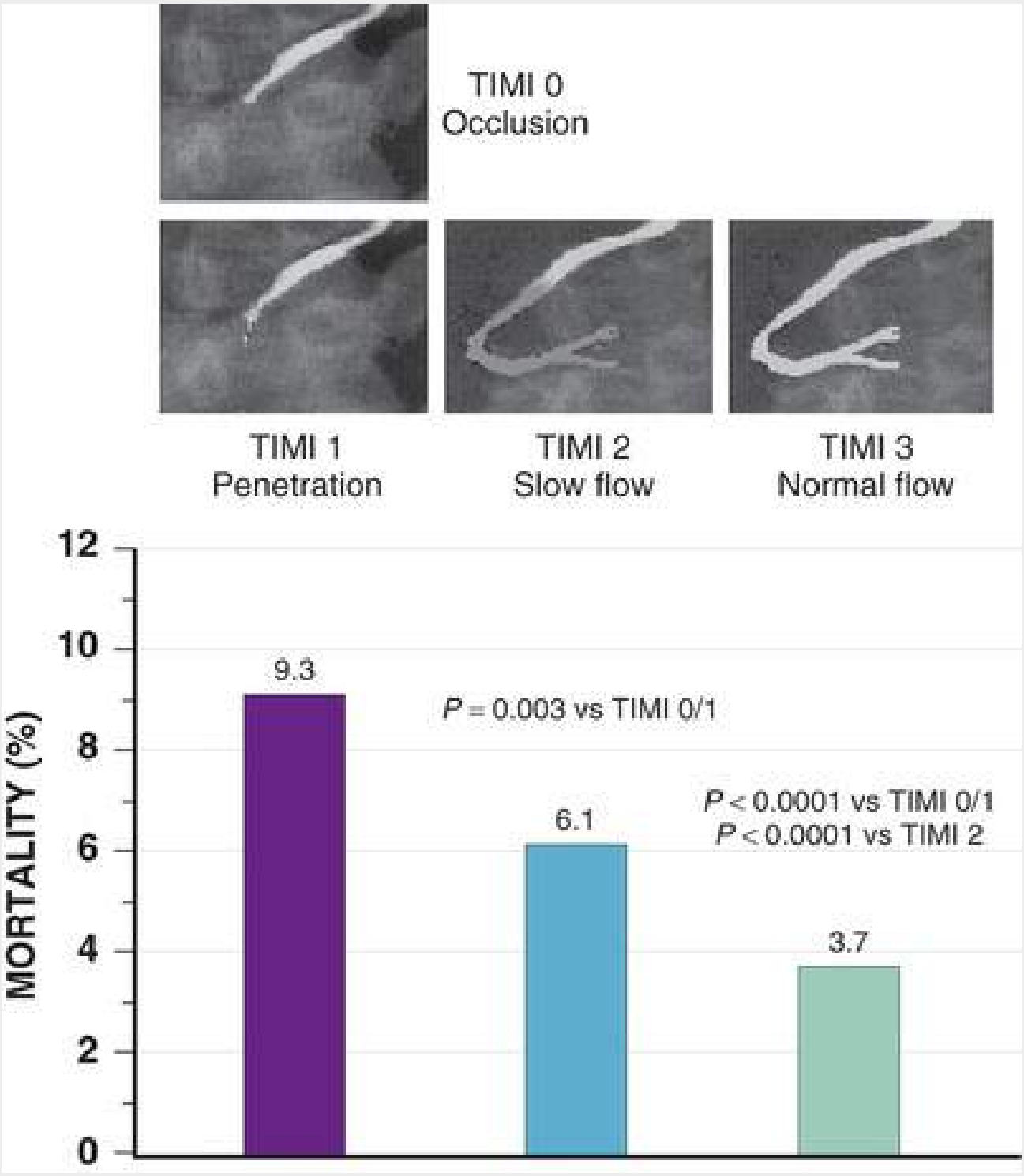


FIGURE 59.6 Correlation of TIMI (thrombolysis in myocardial infarction) flow grade and mortality. A pooled analysis of data from 5498 patients in several angiographic trials of reperfusion for STEMI showed a gradient of mortality when the angiographic findings were stratified by TIMI flow grade. Patients with TIMI 0 or TIMI 1 flow had the highest rate of mortality, TIMI 2 flow associated with an intermediate rate of mortality, and the lowest rate of mortality was observed in patients with TIMI 3 flow. (Courtesy Dr. Michael Gibson, personal communication.)

The TIMI Frame Count.

To provide a more quantitative statement of the briskness of coronary blood flow in the infarct artery and to account for differences in the size and length of vessels (e.g., left anterior descending versus right coronary artery) and interobserver variability, Gibson and coworkers developed the TIMI frame count—a simple count of the number of angiographic frames elapsed until the contrast material arrives in the distal bed of the vessel of interest.[42] This objective and quantitative index of coronary blood flow independently predicts in-hospital mortality from STEMI and also separates patients with TIMI grade 3

flow into low-risk and high-risk groups. The TIMI frame count can also be used to quantitate coronary blood flow (mL/sec), as calculated by:

$$21 \div (\text{Observed TIMI frame count}) \times 1.7$$

based on Doppler velocity wire data showing that normal flow equals 1.7 cm^3/sec, which 21 frames encompass. The calculated coronary perfusion relates to mortality in patients treated with fibrinolytics or primary PCI and can be used to assess various modalities for reperfusion in patients with STEMI.

Myocardial Perfusion.

Even patients with TIMI grade 3 flow in the culprit artery may not always achieve adequate myocardial perfusion (**eFig. 59.1**), especially if the delay between the onset of symptoms and restoration of epicardial flow is long.[42,43] The terms myocardial "no-reflow" and "coronary microvascular obstruction" describe a state of reduced myocardial perfusion after opening of an epicardial infarct-related artery.[42] The four major impediments to normalization of myocardial perfusion are ischemia-related injury, reperfusion-related injury, distal embolization, and individual susceptibility of the microcirculation to injury[42] (**Fig. 59.7**). Obstruction of the distal microvasculature in the downstream bed of the infarct-related artery results from platelet or microparticle microemboli and thrombi. Fibrinolysis may actually exacerbate microembolization of platelet aggregates because of the exposure of clot-bound thrombin, an extremely potent platelet agonist. Spasm can also occur in the microvasculature as a result of the release of substances from activated platelets. Reperfusion injury results in endothelial cell edema, production of reactive oxygen species, and calcium overload. In addition, cytokine activation leads to the accumulation of neutrophils and inflammatory mediators that contribute to tissue injury.[42] Interstitial edema from ischemia and reperfusion injury can compress vasculature, further compromising perfusion. Several techniques can evaluate the adequacy of myocardial perfusion.

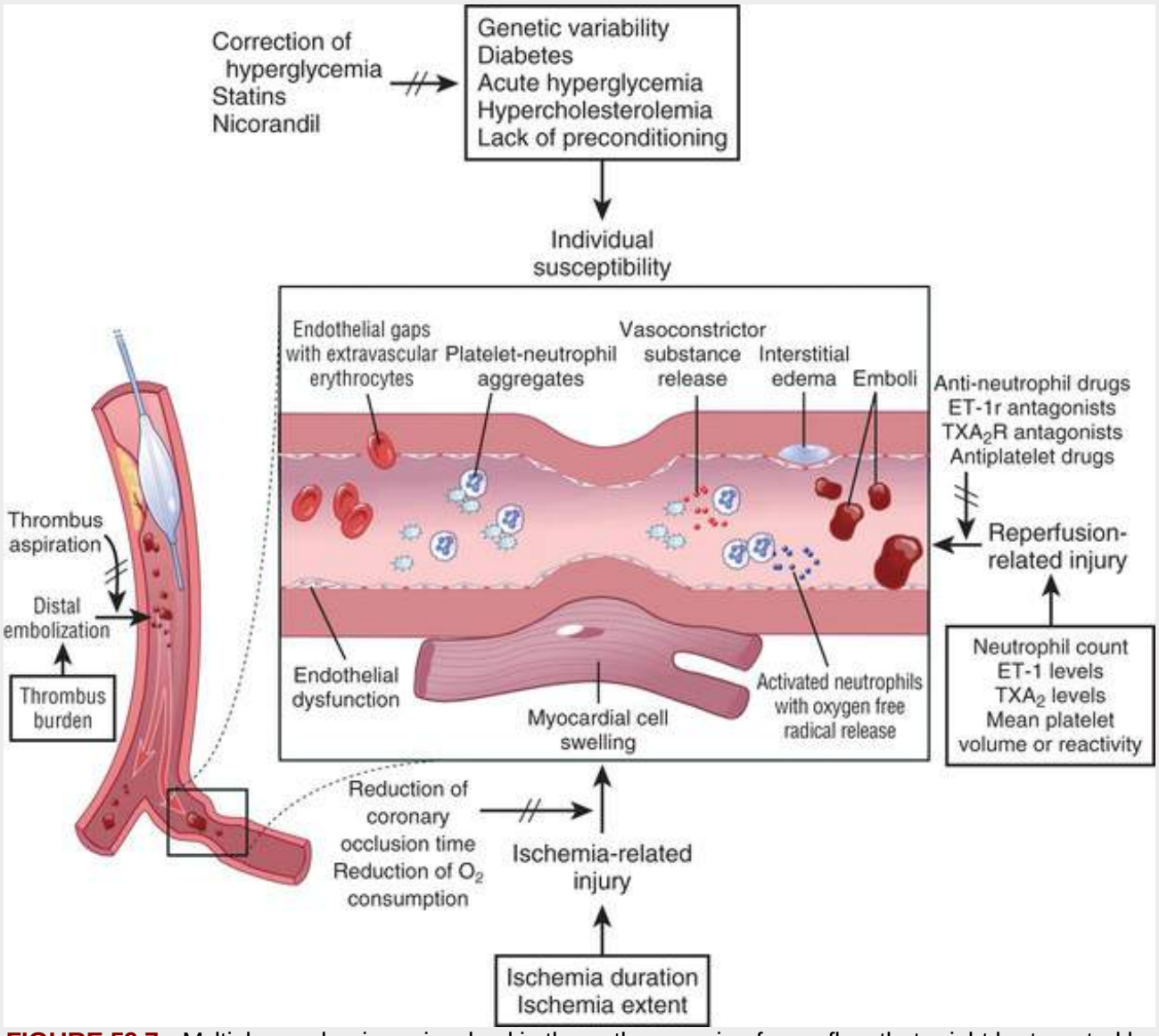
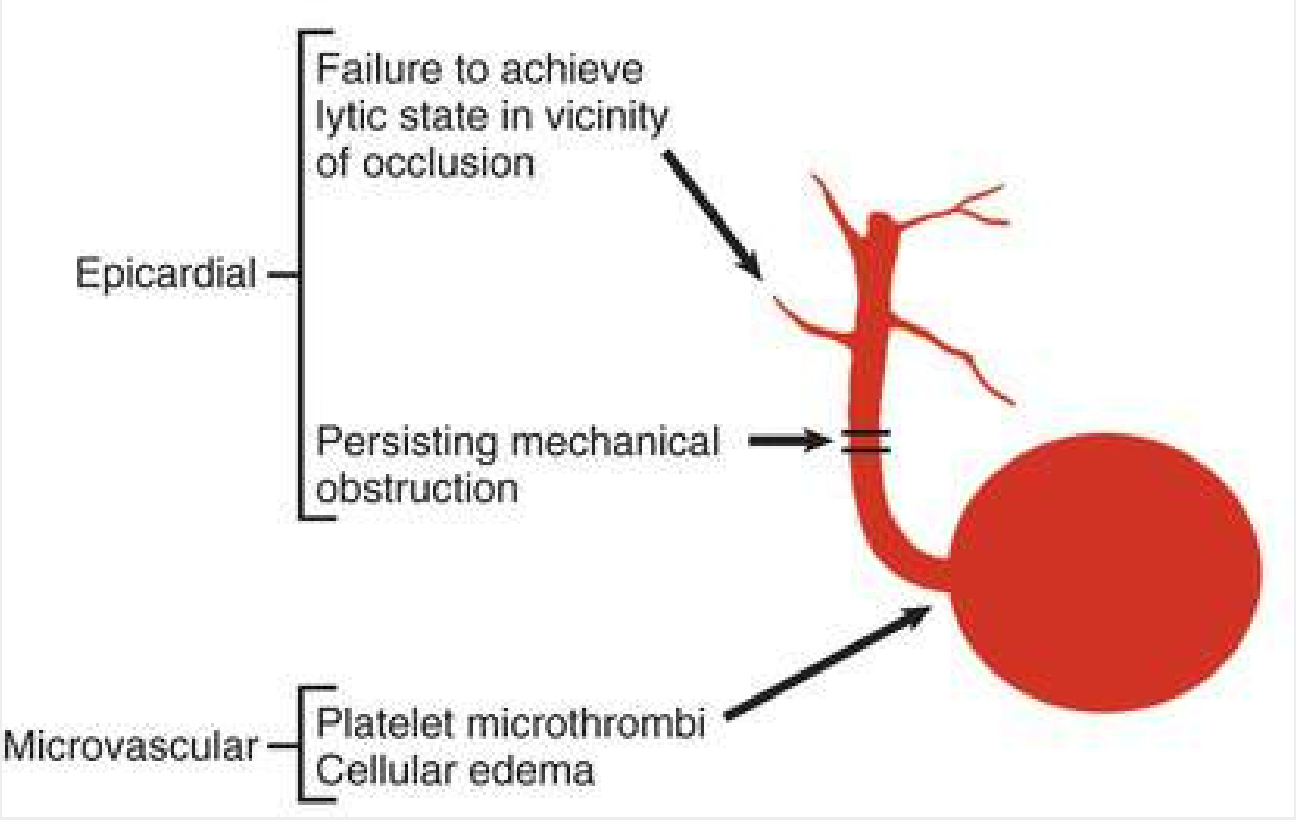


FIGURE 59.7 Multiple mechanisms involved in the pathogenesis of no-reflow that might be targeted by appropriate therapy. ET, Endothelin; TXA_2, thromboxane A_2. (Modified from Niccoli G, Burzotta F, Galiuto L, Crea F: Myocardial no-reflow in humans. J Am Coll Cardiol 2009;54:281.)



EFIGURE 59.1 Points of possible failure of reperfusion therapy. Complete reperfusion requires successful restoration of normal flow in both the epicardial coronary artery and the distal coronary microvasculature, termed *myocardial tissue–level reperfusion.* Failure of *epicardial* reperfusion can result from failure to induce a lytic state or from persistent mechanical obstruction at the site of occlusion. Failure of *microvascular* reperfusion is caused by a combination of platelet microthrombi followed by endothelial swelling and myocardial edema ("no reflow"). Reperfusion may fail because of persistent occlusion of the epicardial infarct-related artery (TIMI grades 0 and 1), patency of an epicardial artery in the presence of impaired (TIMI grade 2) flow, or microvascular occlusion in the presence of angiographically normal (TIMI grade 3) flow. Successful reperfusion requires a patent artery with an intact microvascular network. (Modified from Davies CH, Ormerod OJ. Failed coronary thrombolysis. Lancet 1998;351:1191.)

Electrocardiography.

Electrocardiographic ST-segment resolution, when present, has a high positive predictive value (PPV) of greater than 90% for infarct artery patency with, but persistent ST-segment elevation (i.e., lack of ST-segment resolution) is a poor predictor of infarct-related artery occlusion, with a negative predictive value (NPV) of approximately 50%. However, the persistence of ST-segment elevation after angiographically successful primary PCI identifies patients with a higher risk for LV dysfunction and mortality, presumably because of microvascular damage in the infarct zone.[44,45] Thus the 12-lead ECG can reflect the biologic integrity of myocytes in the infarct zone and indicate inadequate myocardial perfusion even in the presence of TIMI grade 3 flow.[46] The extent of ST-segment resolution provides powerful prognostic information early in the management of patients with STEMI.[45,47]

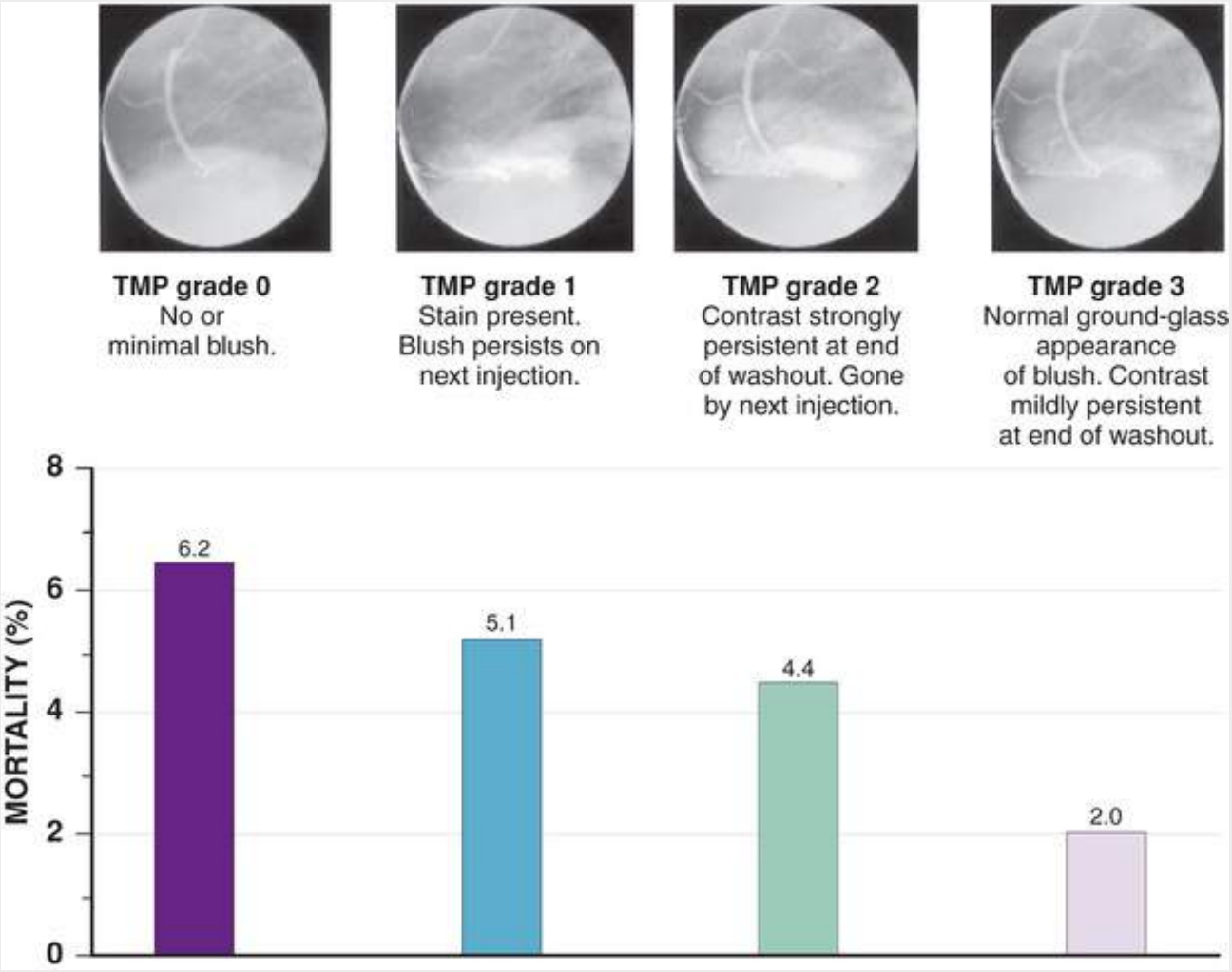
Noninvasive Imaging.

Defects in perfusion patterns seen with myocardial contrast-enhanced echocardiography correlate with regional wall motion abnormalities and lack of myocardial viability on dobutamine stress echocardiography[48] (**see Chapter 14**). Contrast-enhanced CMR can also identify regions of microvascular obstruction, which associate with an adverse long-term prognosis[49] (**see Chapter 17**).

Invasive Assessment.

Doppler flow wire studies can also define abnormalities in myocardial perfusion. In addition, Gibson and colleagues developed an angiographic method for assessing myocardial perfusion: the TIMI

myocardial perfusion (TMP) grade[47,50] (**eFig. 59.2**). Abnormalities associated with increasing myocardial perfusion, as assessed by the TMP grade, correlate with unfavorable ventricular remodeling and risk for mortality, even after adjusting for the presence of TIMI grade 3 flow or a normal TIMI frame count.[43,47]

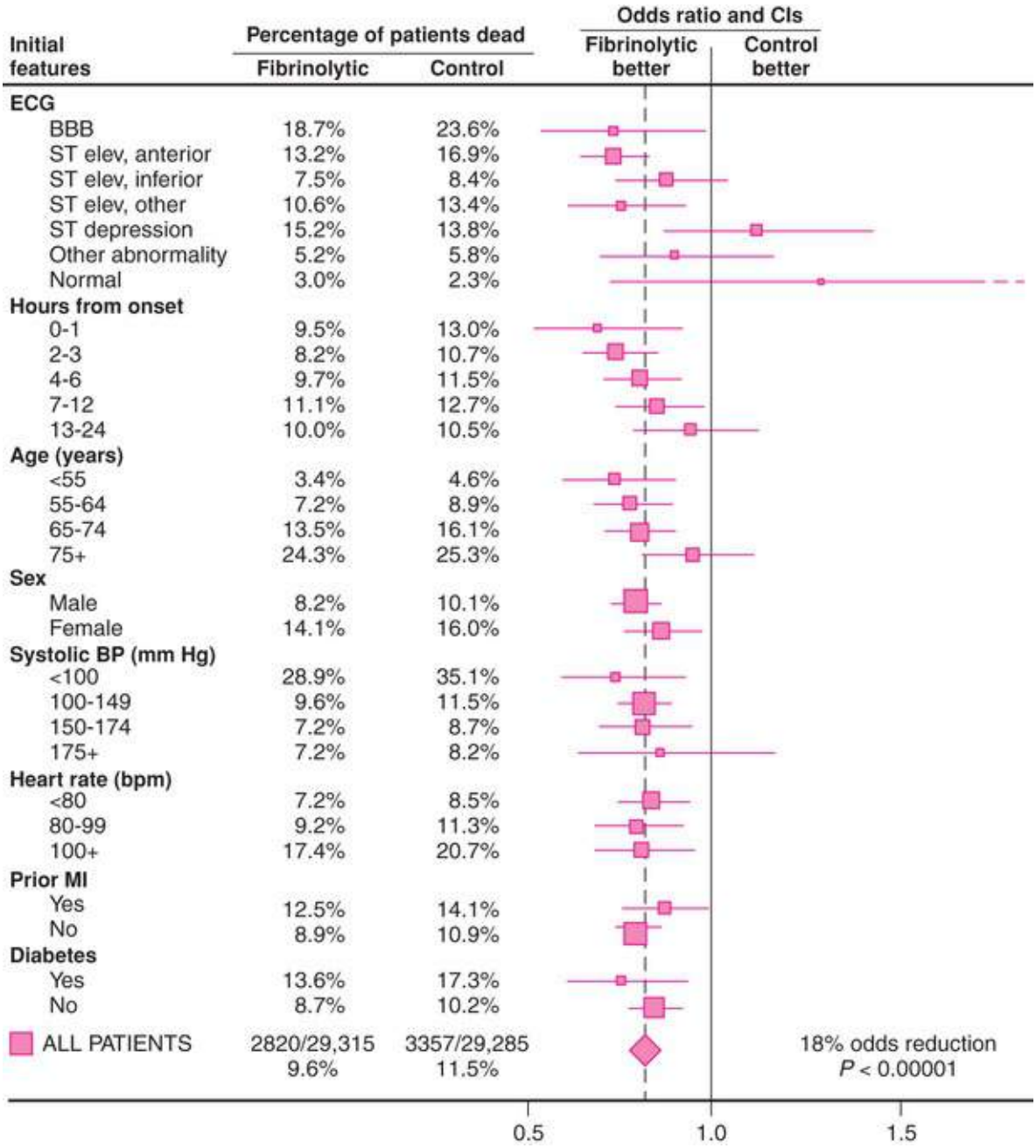


EFIGURE 59.2 Relationship between angiographic assessment of myocardial tissue–level reperfusion categorized by TIMI myocardial perfusion (TMP) grade and mortality. TMP grade 0 or no perfusion of the myocardium is associated with the highest rate of mortality. If a stain of the myocardium is present (grade 1), mortality is also high. A reduction in mortality is seen if the dye enters the microvasculature but is still persistent at the end of the washout phase (grade 2). The lowest mortality rate is observed in patients with normal perfusion (grade 3), with the dye being minimally persistent at the end of the washout phase. (From Gibson CM, Cannon CP, Murphy SA, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. Circulation 2000;101:125.)

Effect of Fibrinolytic Therapy on Mortality

Early intravenous fibrinolysis improves survival in patients with STEMI.[1] The Fibrinolytic Therapy Trialists' (FTT) Collaborative Group performed a comprehensive overview of nine trials of fibrinolytic therapy, each of which enrolled more than 1000 patients. The overall results indicated an 18% reduction in short-term mortality, but as much as a 25% reduction in mortality in the subset of 45,000 patients with ST-segment elevation or bundle branch block (**eFig. 59.3**). Two trials, LATE (Late Assessment of Thrombolytic Efficacy) and EMERAS (Estudio Multicéntrico Estreptoquinasa Repúblicas de América del Sur), when viewed together, provide evidence that a reduction in mortality may still be observed in

patients treated with thrombolytic agents between 6 and 12 hours after the onset of ischemic symptoms. Data from the LATE and EMERAS trials and the FTT overview form the basis for extending the window of treatment with fibrinolytics up to 12 hours after the onset of symptoms. As cited in the American College of Cardiology Foundation (ACCF)/AHA guidelines for the management of STEMI, Boersma and colleagues pooled the trials in the FTT overview, two smaller studies with data on time until randomization, and 11 additional trials.[1] Analysis of six time categories from the onset of symptoms to randomization showed a nonlinear relationship of treatment benefit to time, with the best outcome occurring in the first 1 to 2 hours after the onset of symptoms.[1]



EFIGURE 59.3 Differences in mortality during days 0 to 35, subdivided by initial features, in a collaborative overview of results from nine trials of thrombolytic therapy. Absolute mortality rates are shown for the fibrinolytic and control groups in the **center** of the figure for each of the clinical features at initial encounter, listed on the **left side** of the figure. The ratio of the odds of death in the fibrinolytic group to that in the control group is shown for each subdivision *(colored squares),* along with its 99% confidence interval (CI) *(horizontal line).* The summary odds ratio (OR) at the **bottom** of the figure corresponds to an 18% proportional reduction in 35-day mortality and is highly statistically significant. This translates to a reduction of 18 deaths per 1000 patients treated with thrombolytic agents. BBB, Bundle branch block; BP, blood pressure; SD, standard deviation. (From Fibrinolytic Therapy Trialists' [FTT] Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of mortality and major morbidity results from all randomized trials of more than 1000 patients. Lancet 1994;343:311.)

The effect of fibrinolytic therapy on mortality in elderly patients has been controversial. Although patients older than 75 years were initially excluded from randomized trials of fibrinolytic therapy, they eventually comprised approximately 15% of those studied in trials of fibrinolysis and 35% of those analyzed in registries of patients with STEMI.[51] Barriers to initiation of therapy in older patients with STEMI include a protracted period of delay in seeking medical care, a lower incidence of ischemic discomfort and greater incidence of atypical symptoms and concomitant illnesses, and an increased incidence of nondiagnostic findings on the ECG.[51] Younger patients with STEMI achieve a slightly greater

relative reduction in mortality than elderly patients, but the higher absolute mortality in elderly patients yielded similar absolute reductions in mortality (**eFig. 59.3**).

Several models have integrated the many clinical variables available before the administration of fibrinolytic therapy that affect a patient's risk for death. A convenient, simple, bedside risk-scoring system predicts 30-day mortality at initial evaluation of fibrinolytic-eligible patients with STEMI[52] (**Fig. 59.8**). Modeling of mortality risk cannot cover all clinical scenarios, however, and should supplement clinical judgment in individual cases. For example, patients with inferior STEMI who might otherwise be considered to have a low risk for mortality, and for whom many physicians have questioned the benefits of fibrinolytic therapy, might be in a higher mortality risk subgroup if their inferior infarction is associated with RV infarction, precordial ST-segment depression, or ST-segment elevation in the lateral precordial leads. The short-term survival benefit enjoyed by patients who receive fibrinolytic therapy endures after 1 to 10 years. Advances in adjunctive antiplatelet and antithrombin therapies have led to reductions in the rate of reinfarction after fibrinolysis for STEMI.[4]

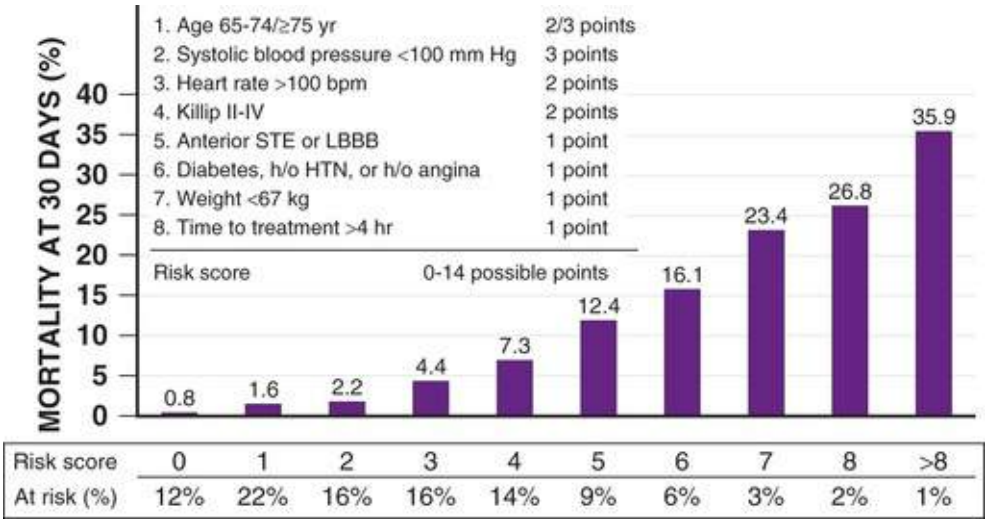


FIGURE 59.8 TIMI risk score for STEMI predicting 30-day mortality. h/o, History of; HTN, hypertension; LBBB, left bundle branch block. (From Morrow DA, Antman EM, Charlesworth A, et al. The TIMI risk score for ST elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: An In TIME II substudy. Circulation 2000;102:2031.)

Comparison of Fibrinolytic Agents

Table 59.4 presents the comparative features of the approved fibrinolytic agents for IV therapy. All fibrinolytic agents exert their effect by converting the proenzyme plasminogen to the active enzyme plasmin. The so-called fibrin-specific fibrinolytics are those that are relatively inactive in the absence of fibrin but in its presence substantially increase their activity on plasminogen (**see Chapter 93**).

TABLE 59.4

Comparison of Approved Fibrinolytic Agents

FIBRINOLYTIC AGENT	DOSE	FIBRIN SPECIFICITY*	FIBRINOGEN DEPLETION	ANTIGENIC	PATENCY RATE (90-min TIMI 2 OR 3 FLOW)
Fibrin Specific					
Tenecteplase (TNK)	Single IV weight-based bolus†	++++	Minimal	No	85%
Reteplase (r-PA)	10 units + 10-unit IV boluses given 30 min apart	++	Moderate	No	84%
Alteplase (t-PA)	90-min weight-based infusion‡	++	Mild	No	73-84%
Non–Fibrin Specific					
Streptokinase§	1.5 million units IV given over 30-60 min	No	Marked	Yes¶	60-68%

*Strength of fibrin specificity: ++++ is stronger; ++ is less strong.

†Bolus of 30 mg for weight less than 60 kg, 35 mg for 60 to 69 kg, 40 mg for 70 to 79 kg, 45 mg for 80 to 89 kg, and 50 mg for 90 kg or greater.

‡Bolus of 15 mg, infusion of 0.75 mg/kg for 30 minutes (maximum, 50 mg), then 0.5 mg/kg (maximum, 35 mg) over the next 60 minutes; the total dose not to exceed 100 mg.

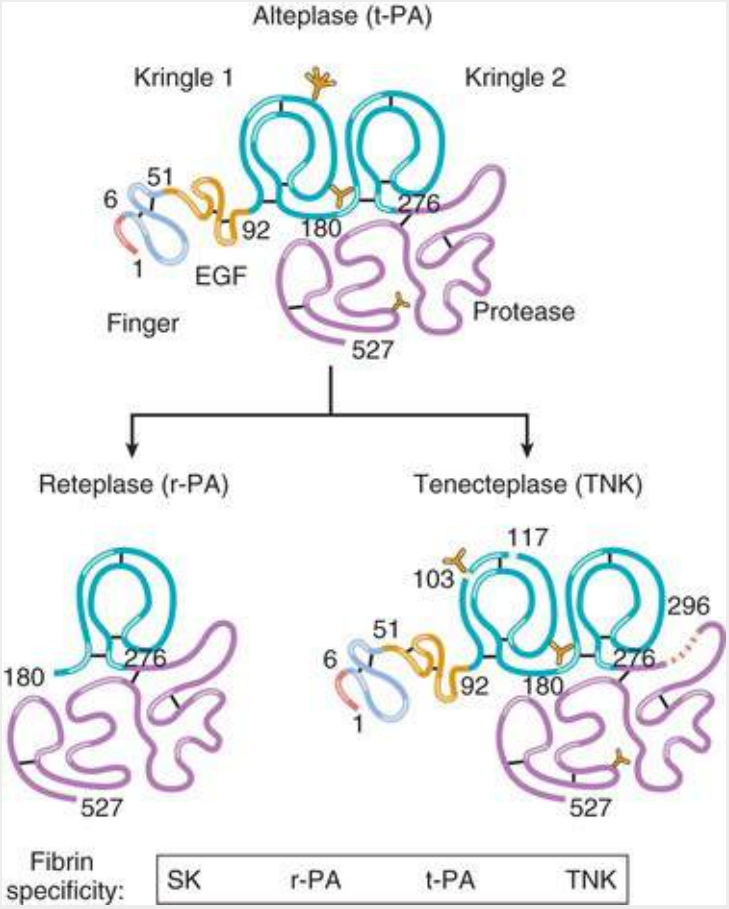
§Streptokinase is no longer marketed in the United States but is available in other countries.

¶Streptokinase is highly antigenic and absolutely contraindicated within 6 months of previous exposure because of the potential for serious allergic reaction.

r-PA, Reteplase plasminogen activator; *t-PA,* tissue plasminogen activator.

From O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78.

The tissue plasminogen activator (t-PA) molecule contains five domains[53] (**eFig. 59.4**). In the absence of fibrin, t-PA is a weak plasminogen activator; fibrin provides a scaffold on which t-PA and plasminogen are held in such a way that the catalytic efficiency of t-PA increases many-fold. A dose regimen of t-PA administered over a 90-minute period produces more rapid thrombolysis than a 3-hour fixed-rate infusion. Therefore the recommended dosage for t-PA is the 90-minute “accelerated” regimen.



EFIGURE 59.4 Molecular structure of alteplase (t-PA), reteplase (r-PA), and tenecteplase (TNK). Streptokinase (SK) is the least fibrin-specific thrombolytic agent in clinical use; the progressive increase in relative fibrin specificity for the various thrombolytics is shown at the *bottom.* See also Fig. 93.16. (Modified from Brener SJ, Topol EJ. Third-generation thrombolytic agents for acute myocardial infarction. In Topol EJ, editor. Acute Coronary Syndromes. New York: Marcel Dekker; 1998, p 169.)

Modifications in the native t-PA structure have yielded a group of fibrinolytic agents with prolonged plasma clearance that allows them to be administered as a bolus (**eFig. 59.4 and Table 59.4**) rather than as the bolus and infusion by which accelerated-dose t-PA is administered.[53] Reteplase (double fixed-dose bolus) and tenecteplase (single weight-based bolus) have both been compared with accelerated t-PA. Both these newer agents confer mortality benefits similar to that achieved with accelerated t-PA, but with more convenient dosing. In one large trial, tenecteplase had a lower rate of major bleeding than accelerated t-PA.

Other Fibrinolytic Agents.

Streptokinase, a protein derived from streptococci, binds and activates human plasminogen and is an inexpensive and effective fibrinolytic agent that is still used in some regions of the world. Urokinase is used for STEMI on rare occasions as an intracoronary infusion.

Effect on Left Ventricular Function

As with survival, improvement in global LV function is related to the time of initiation of fibrinolytic treatment, with the greatest improvement occurring with the earliest therapy. Although precise measurements of infarct size would be an ideal endpoint for clinical reperfusion studies, such measures have proved impractical. Attempts to use the LV ejection fraction (EF) as a surrogate for infarct size have not been productive because little difference is seen in EF between treatment groups that show a significant difference in mortality. Methods of assessing LV function, such as end-systolic volume or quantitative echocardiography, are more revealing because patients with smaller volumes and better-

preserved ventricular shape have improved survival. The *myocardial salvage index*, defined as the difference between the initial perfusion defect (e.g., by sestamibi scintigraphy or CMR) and the final perfusion defect, is a useful means for comparing the effectiveness of reperfusion therapies.[49,54] CMR can characterize LV volumes, the extent of scar by gadolinium delayed hyperenhancement, and the presence of ischemia with stress perfusion imaging, providing significant incremental prognostic information over other clinical variables.[49,55]

Complications of Fibrinolytic Therapy

Bleeding complications are most common, and intracranial hemorrhage is the most serious complication of fibrinolytic therapy; its frequency is generally less than 1% but varies with the clinical characteristics of the patient and the fibrinolytic agent used (**Fig. 59.9**).[1] Intracranial bleeding in the setting of fibrinolysis for STEMI is associated with a high case-fatality rate. Nonintracranial bleeding can also increase morbidity, but whether it causes higher overall mortality, after taking into account the higher-risk clinical characteristics that also predispose patients to bleeding during treatment of STEMI, is uncertain.[56,57]

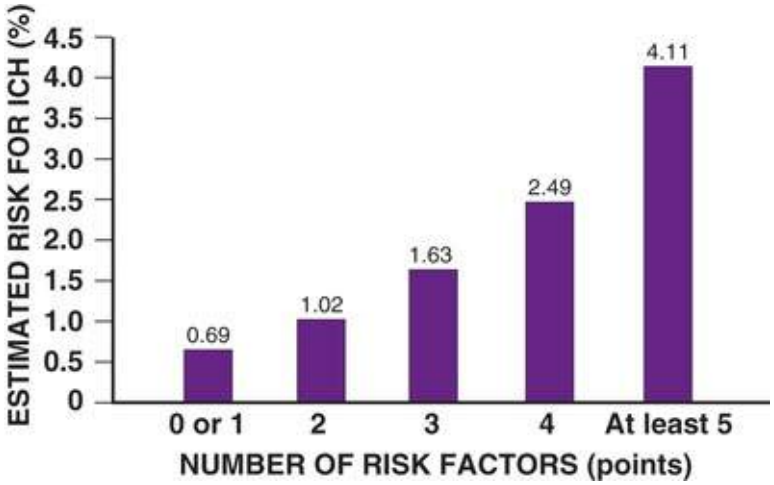


FIGURE 59.9 Estimation of risk for intracranial hemorrhage (ICH) with fibrinolysis. Common risk factors include increased age, low body weight, and hypertension on admission. See reference for further discussion. (Data from Brass LM, Lichtman JH, Wang Y, et al. Intracranial hemorrhage associated with thrombolytic therapy for elderly patients with acute myocardial infarction: results from the Cooperative Cardiovascular Project. Stroke 2000;31:1802.)

Reports have demonstrated an "early hazard" with fibrinolytic therapy—that is, an excess of deaths in the first 24 hours in fibrinolytic-treated patients compared with controls, especially in elderly patients treated more than 12 hours after symptom onset. However, this excess early mortality is more than offset by deaths prevented beyond the first day, with an average 18% (range, 13% to 23%) reduction in mortality by 35 days compared with offering no reperfusion therapy.[1] The mechanisms responsible for this early hazard are not clear but are probably multiple, including an increased risk for myocardial rupture, fatal intracranial hemorrhage, and possibly myocardial reperfusion injury.

Recent exposure to streptococci or streptokinase produces some degree of antibody-mediated resistance to streptokinase (and anistreplase) in most patients. Although such resistance is only rarely of clinical consequence, patients should not receive streptokinase for STEMI if they have been treated with a streptokinase product within the past 6 months.

Recommendations for Fibrinolytic Therapy

As described in the preceding sections, fibrinolytic therapy confers well-established benefits in patients with STEMI, with a time-dependent improvement in survival rates during the initial 12 hours after the onset of symptoms. When a patient arrives at a PCI-capable facility, primary PCI is the preferred mode of reperfusion therapy (see later, Selection of Reperfusion Strategy).[1,2] However, many health care facilities do not have ready access to timely PCI; if the delay from first medical contact to performing primary PCI is anticipated to exceed 120 minutes, administration of a fibrinolytic is indicated for the treatment of STEMI within 12 hours of onset in the absence of contraindications.[1] In addition, even when interhospital transport times are expected to be short, there may be advantages to immediate initiation of fibrinolytic therapy versus incurring any delay until primary PCI in patients with STEMI and low bleeding risk who present very early.[1]

Choice of Agent

The choice of fibrinolytic in hospital systems is generally driven by the desire to establish consistent protocols within the health care system by weighing ease of dosing, cost, and other institutional preferences. In patients seen early with acceptable bleeding risk, a high-intensity fibrin-specific regimen, such as accelerated t-PA, reteplase, or tenecteplase, is usually preferable.[1] In patients whose risk for death is low (e.g., young patient with small inferior MI) and whose risk for intracranial hemorrhage is increased (e.g., acute hypertension), administration of streptokinase is reasonable, but rarely done in the United States. In patients who are to be treated with a fibrin-specific fibrinolytic, we believe that clinicians should use a bolus fibrinolytic such as reteplase or tenecteplase. Bolus fibrinolytics have a lower chance of medication errors and are associated with less noncerebral bleeding—as well as offering the potential for prehospital treatment.[4,53]

Late Therapy

No mortality benefit was demonstrated in the LATE and EMERAS trials when fibrinolytics were routinely administered to patients between 12 and 24 hours, although we believe that it is still reasonable to consider fibrinolytic therapy when PCI is not available, for appropriately selected patients with clinical and electrocardiographic evidence of ongoing ischemia within 12 to 24 hours of symptom onset and a large area of myocardium at risk or hemodynamic instability. Persistent chest pain late after the onset of symptoms correlates with a higher incidence of collateral or anterograde flow in the infarct zone and is therefore a marker for viable myocardium that might be salvaged. Because elderly patients treated with fibrinolytic agents more than 12 hours after the onset of symptoms have an increased risk for cardiac rupture, we believe that restricting late administration of a fibrinolytic to patients younger than 65 years with ongoing ischemia is preferable. An elderly patient with ongoing ischemic symptoms but initially seen late (>12 hours) is better managed with PCI than with fibrinolytic therapy.

Intracoronary Fibrinolysis

In contemporary practice, patients are more likely to be treated with PCI. This evolution has revived the concept of delivering fibrinolytic agents by the intracoronary route, but current efforts are largely restricted to adjunctive use during complicated PCI procedures.

Catheter-Based Reperfusion Strategies

Catheter-based strategies can also achieve reperfusion of the infarct artery. This approach has evolved

from passage of a balloon catheter over a guidewire in the culprit vessel only to now include potent oral antiplatelet therapy, multiple options for anticoagulants, and coronary stents, with the possibility of multivessel revascularization.[1] PCI used as primary reperfusion therapy in patients with STEMI is referred to as direct or primary PCI (**see Fig. 59.2**). If fibrinolysis has failed to reperfuse the infarct vessel, or a severe stenosis is present in the infarct vessel after fibrinolysis, rescue PCI can be performed. A strategy of routine delayed angiography and PCI after successful fibrinolytic therapy may also be considered.[5] Finally, a conservative approach of elective PCI only when spontaneous or exercise-provoked ischemia occurs may be used to manage patients with STEMI, regardless of whether they have received a previous course of fibrinolytic therapy or no initial reperfusion therapy.[1] This chapter discusses decision making regarding the selection of initial reperfusion therapy and referral for PCI in patients who have undergone initial fibrinolysis.

The approach to primary PCI, including device selection, the technical approach to percutaneous revascularization, and decision making regarding non–culprit vessel disease are discussed in **Chapter 62**. As an alternative to pharmacologic reperfusion therapy, primary PCI has evolved significantly. Several randomized trials have suggested that a strategy of multivessel PCI, either at the time of primary PCI or as a planned, staged procedure, may be safe and may improve outcomes in hemodynamically stable patients with STEMI.[58-60] These findings have prompted a change in recommendation from class III to IIb for consideration of multivessel PCI in stable patients with STEMI. Aspiration thrombectomy at primary PCI now has a class III recommendation based on trial data showing no improvement in cardiovascular (CV) outcomes and a possible increase in stroke risk.[6,61] Radial artery access now tends to be favored over femoral artery access in primary PCI based on the MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX) trial, which demonstrated a reduction in bleeding and mortality.[62] Finally, studies suggest that newer-generation drug-eluting stents (DESs) may result in lower rates of repeat revascularization with equivalent rates of stent thrombosis compared to contemporary bare-metal stents (BMSs).[63]

Surgical Reperfusion

Providing surgical reperfusion in a timely fashion is usually not logistically possible. Therefore, patients with STEMI who are candidates for reperfusion should undergo either immediate fibrinolysis or PCI. However, patients with STEMI are currently referred for CABG for persistent or recurrent ischemia despite fibrinolysis or primary PCI with residual coronary disease not amenable to PCI, high-risk coronary anatomy (e.g., left main stenosis) discovered at initial catheterization, or a complication of STEMI such as ventricular septal rupture or severe mitral regurgitation caused by papillary muscle dysfunction. STEMI patients with continued severe ischemic and hemodynamic instability will probably benefit from emergency revascularization.

Patients who successfully undergo fibrinolysis but have important residual stenoses and on anatomic grounds are more suitable for surgical revascularization than for PCI have undergone CABG with quite low rates of mortality (approximately 4%) and morbidity, provided that the procedure is carried out more than 24 hours after STEMI; patients requiring urgent or emergency CABG within 24 to 48 hours of STEMI have mortality rates between 12% and 15%.[1] When surgery is performed under urgent conditions with active and ongoing ischemia or cardiogenic shock, operative mortality rates are higher, in large part reflecting the patient's overall condition that necessitated emergency surgery.

Selection of Reperfusion Strategy

When performed rapidly after arrival at an experienced center, primary PCI is superior to pharmacologic reperfusion therapy.[1,4,64] However, registry and randomized data remind us that very early fibrinolysis may be at least as effective as primary PCI.[14,65] Consequently, decision making for individual patients remains complex regarding the optimum form of reperfusion therapy, especially when a delay until PCI is anticipated.[1] Prehospital fibrinolysis may be as effective as PCI in patients early after symptom onset but requires significant infrastructure, including a trained EMS unit with direct physician support. This infrastructure may not be logistically feasible in many communities, particularly those without the resources to support 24-hour availability of primary PCI. At the same time, improvements in catheterization laboratory facilities, new stents, evolution of adjunctive antithrombotic therapy, and development of collaborative systems for rapid transfer for invasive therapy have improved the efficacy and safety of primary PCI in patients with STEMI, including those being transferred for primary PCI (**see Chapter 62**).[66] Selection of the optimal form of reperfusion therapy therefore involves judgments regarding both system resources and individual patient characteristics.

For patients who arrive at an experienced primary PCI center, primary PCI should be performed in those with STEMI who present within 12 hours of symptom onset and those with later arrival who have ongoing ischemia, HF, or shock. In patients taken to centers that are not PCI capable, the primary consideration is time required for transportation to a PCI-capable center. The greatest operational impediment to routine implementation of a PCI reperfusion strategy is the delay required for transportation to a skilled PCI center (**see Fig. 59.2 and Table 59.1**).[67] Trials conducted in health care systems with extremely short transportation and door-to-balloon times at PCI centers have demonstrated that referral to a PCI center can be superior to fibrinolysis administered at a local hospital.[67] If the delay to implementation of primary PCI is substantial, however, the mortality advantage over administration of a fibrin-specific agent is lost (**Fig. 59.10**). The best estimate of the time delay at which this advantage is lost is 1 to 2 hours, but it may vary depending on the timing of initial evaluation and the extent of myocardium at risk.[67]

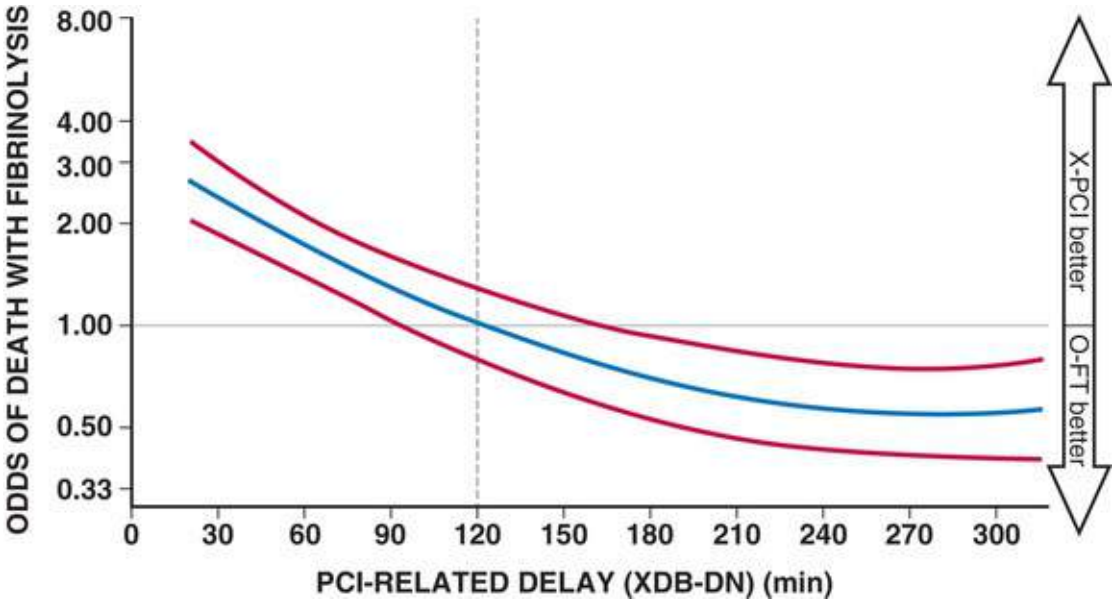


FIGURE 59.10 Relationship between PCI-related delay (minutes) during transfer from a non–PCI-capable hospital to a PCI-capable hospital and in-hospital mortality. The *red lines* represent 95% CIs. XDB-DN indicates transfer delay (transfer door-to-balloon minus door-to-needle time). With delays longer than 120 minutes between administration of a fibrinolytic on-site and balloon (or device) time at a receiving hospital, the on-site fibrinolytic strategy becomes preferable with respect to mortality risk when compared with transfer for PCI. O-FT, On-site fibrinolytic therapy; X-PCI, transfer PCI. (From Pinto DS, Frederick PD, Anjan K, et al. Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic as delays increase. Circulation 2011;124:2518.)

If the time from first medical contact to PCI is expected to be more than 120 minutes, fibrinolysis is recommended in the absence of (1) significant contraindications to fibrinolysis, (2) shock or acute severe heart failure, or (3) late presentation. Otherwise, transfer for primary PCI is generally favored if any of these conditions are present, even if the delay to revascularization will be greater than 120 minutes (**see Fig. 59.2 and Table 59.3**):

1. *High risk for bleeding.* In patients with an increased risk for bleeding, particularly intracranial hemorrhage, therapeutic decision making strongly favors a PCI-based reperfusion strategy. If PCI is unavailable, the benefit of pharmacologic reperfusion should be balanced against the risk for bleeding. A decision analysis suggests that when PCI is not available, fibrinolytic therapy should still be favored over no reperfusion treatment until the risk for life-threatening bleeding exceeds 4%.
2. *Presence of shock or acute severe heart failure.* Patients in cardiogenic shock have improved survival if they are treated with an early revascularization strategy of PCI and/or CABG. Therefore, immediate transfer to a PCI-capable hospital is recommended in patients with shock or acute severe HF regardless of the time delay.[68]
3. *Prolonged time from onset of symptoms to initiation of reperfusion therapy.* PCI is preferable in patients with late arrival, particularly those initially seen 12 to 24 hours after symptom onset. Fibrinolysis can be considered in the 12- to 24-hour window for patients with evidence of ongoing ischemia and where PCI is not available, although the benefit has not been established.[1]

When the diagnosis of STEMI is in doubt, an invasive strategy is clearly the preferred strategy because it not only provides key diagnostic information regarding the patient's symptoms, but does so without the risk for intracranial hemorrhage associated with fibrinolysis.

Referral for Angiography with Intent of Revascularization After Initial Fibrinolysis

Patients with STEMI who are initially managed by fibrinolysis at a non–PCI-capable center should be transferred urgently to a PCI-capable center if the patient develops cardiogenic shock or severe HF or has failed reperfusion with a fibrinolytic. Transfer should also be considered (class IIa) as a part of a pharmacoinvasive strategy in stable patients with the intention of performing angiography, and PCI as necessary, 3 to 24 hours after fibrinolysis[1,69] (**Table 59.5; see Fig. 59.2**).

TABLE 59.5

Indications for Coronary Angiography in Patients Who Were Managed with Fibrinolytic Therapy or Who Did Not Receive Reperfusion Therapy

RECOMMENDATION	COR	LOE
Cardiogenic shock or acute severe heart failure that develops after initial evaluation	I	B
Intermediate- or high-risk findings on predischarge noninvasive ischemia testing	I	B
Spontaneous or easily provoked myocardial ischemia	I	C
Failed reperfusion or reocclusion after fibrinolytic therapy	IIa	B
Stable* patients after successful fibrinolysis—before discharge and ideally between 3 and 24 hours	IIa	B

*Although individual circumstances vary, *clinical stability* is defined as the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.

COR, Class of recommendation; *LOE,* level of evidence.

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78.

Patients undergoing angiography and PCI after suspected failure of reperfusion with fibrinolysis tend to have a lower mortality rate and significantly lower rates of recurrent MI and HF compared with patients who continue medical therapy, including readministration of a fibrinolytic agent. In the REACT (Rapid Early Action for Coronary Treatment) study, patients with suspected failed reperfusion at 90 minutes by electrocardiographic criteria were randomly assigned to one of three treatment arms: rescue PCI, conservative care, or repeated fibrinolytic therapy. The composite of death, reinfarction, stroke, or severe HF at 6 months was significantly lower in patients randomly assigned to rescue PCI than in the two other treatment groups.[1] More minor bleeding, however, occurred in patients randomly assigned to rescue PCI.

The option of administration of a fibrinolytic agent at non–PCI-capable hospitals, followed by routine transfer for angiography and PCI if indicated, has been advanced as an attractive strategy to offer timely reperfusion therapy and arrange a “nonemergency” transfer for subsequent procedures to reduce the risk for subsequent reinfarction. Retrospective analyses of trials of fibrinolytic therapy indirectly support this approach because they suggest a lower risk for recurrent MI and a lower 2-year mortality rate in patients who subsequently undergo early PCI. The limited randomized trials evaluating a strategy of routine catheterization after fibrinolysis have provided mixed results. Nevertheless, overall, these trials have suggested improvement in clinical outcomes in patients transferred for early catheterization, particularly those at higher risk for death and recurrent ischemia (**Fig. 59.11 and eFig. 59.5**).[1] In the largest of these studies, TRANSFER-AMI (Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction; *n* = 1059), immediate transfer for angiography versus conservative care reduced the composite endpoint of death, recurrent MI, recurrent ischemia, new or

worsening HF, or shock at 30 days.[70] In a meta-analysis that included seven randomized trials of early transfer for catheterization, a strategy of routine early catheterization after fibrinolysis yielded a statistically significant 35% reduction in the incidence of death or MI at 30 days (odds ratio [OR], 0.65; 95% confidence interval [CI] 0.49 to 0.88) without an increase in the risk for major bleeding (**Fig. 59.11**).[69]

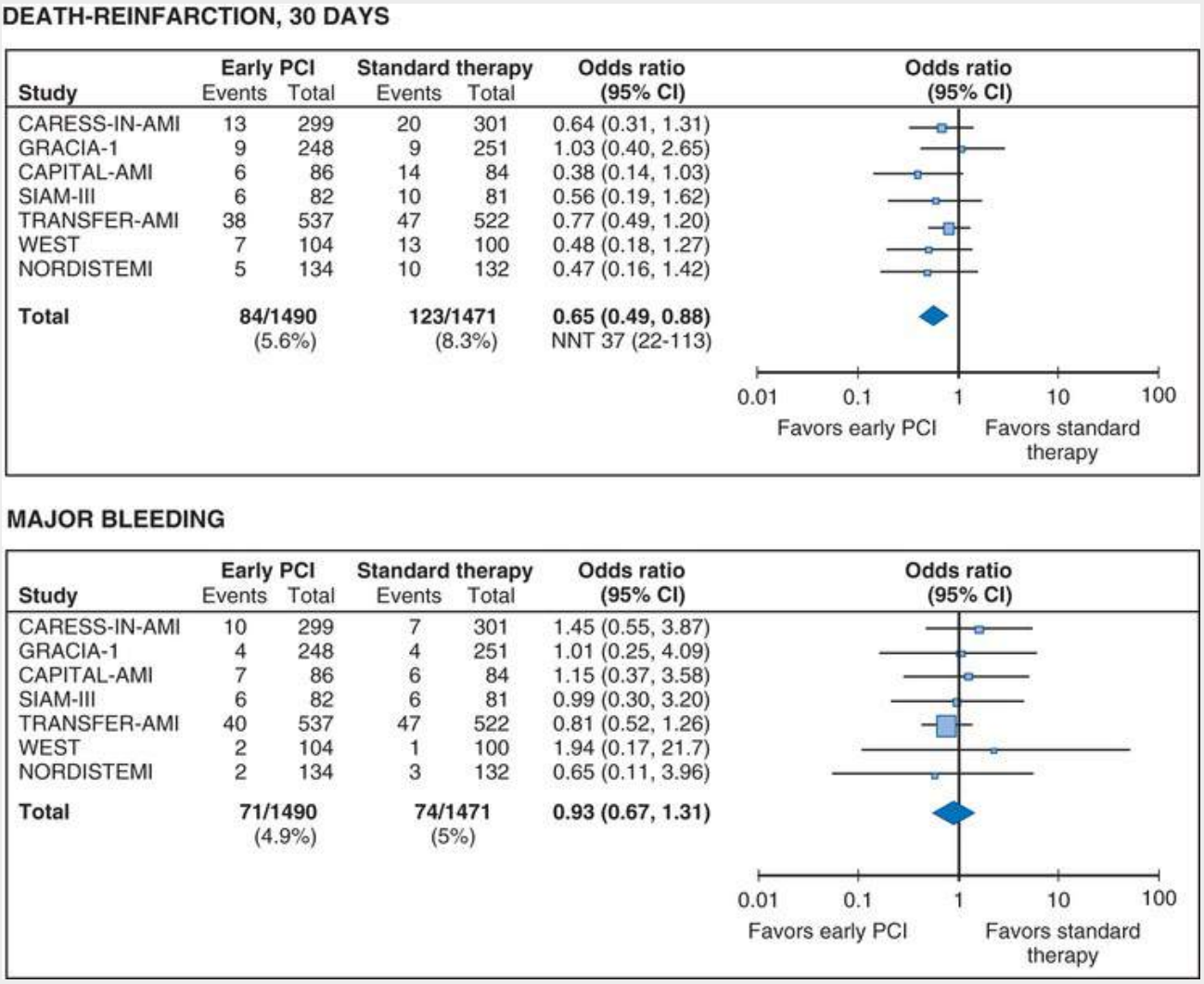
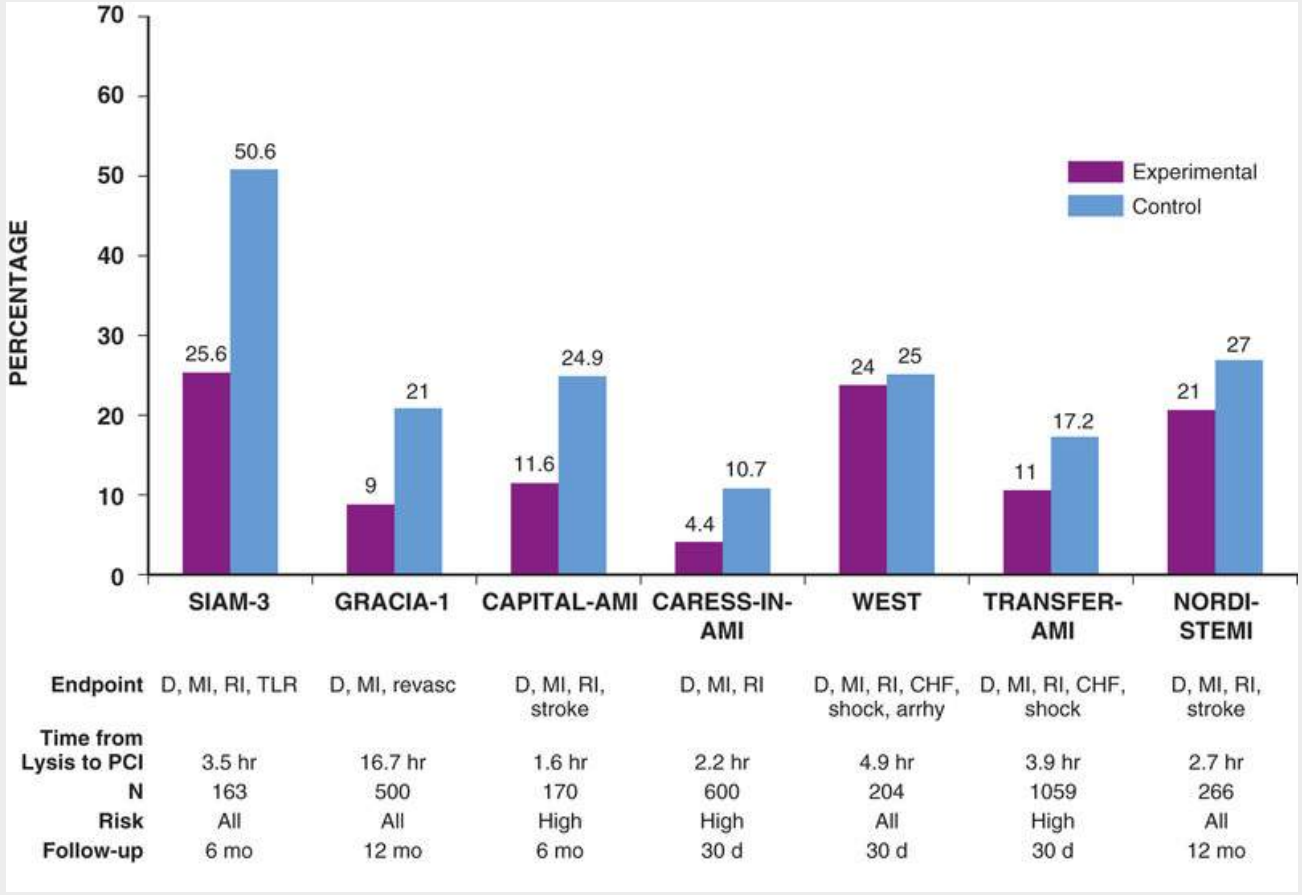


FIGURE 59.11 A meta-analysis of seven randomized trials of early transfer for catheterization, a strategy of routine early catheterization after fibrinolysis, was associated with a statistically significant 35% reduction in the incidence of death or MI at 30 days **(top)** with no increase in major bleeding **(bottom),** for combined death-reinfarction and recurrent ischemia between early PCI and standard therapy. Size of data markers indicates the weight of each trial. (Modified from Borgia, F., Goodman, SG., Halvorsen S, et al. Early routine percutaneous coronary intervention after fibrinolysis vs. standard therapy in ST-segment elevation myocardial infarction: a meta-analysis. Eur Heart J 2010:31(17):2156-69.)



EFIGURE 59.5 Primary outcome of trials of routine versus ischemia-driven (or delayed) catheterization and percutaneous coronary intervention (PCI) after fibrinolytic therapy. Trials comparing routine early catheterization after fibrinolytic therapy with either an ischemia-driven approach or routine delayed catheterization generally showed a consistent pattern of benefit with a strategy of routine transfer for invasive evaluation. The *darker bars* represent patients who underwent routine early catheterization after fibrinolytic therapy. The *lighter bars* represent patients who underwent either an ischemia-guided or routine delayed catheterization approach. arrhy, Arrhythmia; CHF, congestive heart failure; D, death; RI, recurrent ischemia; revasc, ischemia-driven revascularization; TLR, target lesion revascularization. CAPITAL-AMI, Combined Angioplasty and Pharmacological Intervention Versus Thrombolysis Alone in Acute Myocardial Infarction; CARESS-in-AMI, Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction; GRACIA, Grupo de Análisis de la Cardiopatía Isquémica Aguda; NORDISTEMI, Norwegian Study on District Treatment of ST-Elevation Myocardial Infarction; SIAM-3, Southwest German Interventional Study in Acute Myocardial Infarction; TRANSFER-AMI, Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction; WEST, Which Early ST-Elevated Myocardial Infarction Therapy. (Modified from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHAguideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e383.)

Notably, the clinical trials that assessed routine invasive evaluation after initial fibrinolysis used a time window of 0 to 24 hours for the “early invasive” strategy, thus supporting earlier transfer after administration of fibrinolytic therapy, even for patients without high-risk features. Although we believe that there will probably be continued benefit even beyond 24 hours in patients with a patent but stenotic infarct artery after initial successful reperfusion, later time windows have not been directly examined. Because of the associated increased bleeding risk, very early (<2 to 3 hours) catheterization after the administration of fibrinolytic therapy with the intent to perform revascularization should be reserved for patients with evidence of failed fibrinolysis and significant myocardial jeopardy, for whom rescue PCI would be appropriate. In addition, when STEMI is suspected to have occurred by a mechanism other than thrombotic occlusion at the site of atherosclerotic plaque, coronary angiography may provide diagnostic information and direct specific therapy.

In summary, delayed coronary angiography with PCI of the infarct artery is indicated in patients initially treated with a noninvasive strategy (i.e., with fibrinolysis or without reperfusion therapy) who become unstable with cardiogenic shock, acute severe HF, or unstable postinfarction angina, provided that invasive management is not considered futile or inappropriate (**Table 59.5**). Delayed PCI also appears to be reasonable in patients with failed fibrinolysis or reocclusion of the infarct artery or in those who demonstrate significant residual ischemia during hospitalization after initial noninvasive management. The benefits of routine (non–ischemia-driven) PCI on an angiographically significant stenosis in a patent infarct artery more than 24 hours after STEMI are less well established, and delayed PCI on a totally occluded infarct artery longer than 24 hours after STEMI should not be undertaken in clinically stable patients without evidence of severe ischemia.[1]

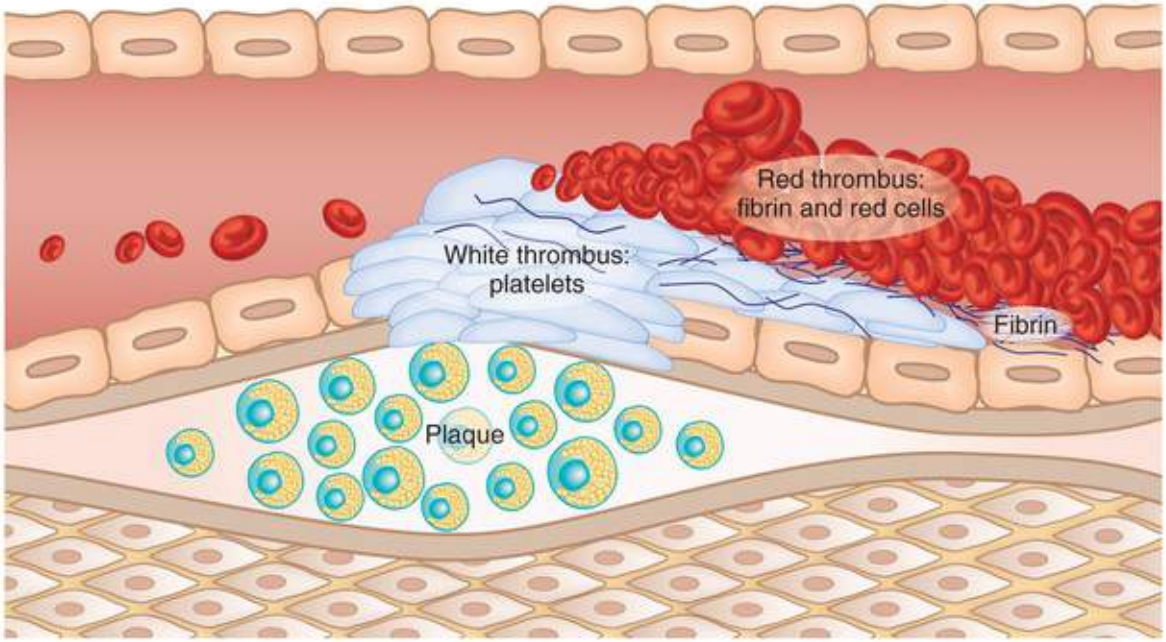
Patients Not Eligible for Reperfusion Therapy

Aspirin and antithrombin therapy can be prescribed for patients who are not candidates for acute reperfusion because of lack of availability of PCI and contraindications to fibrinolysis. In the setting of absolute contraindications to fibrinolysis (**see Table 59.3**) and lack of access to PCI facilities, antithrombotic therapy should be initiated because of the small but finite chance (approximately 10%) of restoring TIMI grade 3 flow in the infarct vessel and decreasing the chance of thrombotic complications of STEMI.

Anticoagulant and Antiplatelet Therapy

Anticoagulant Therapy

The rationale for administering anticoagulant therapy acutely to patients with STEMI includes establishing and maintaining patency of the infarct-related artery, regardless of whether a patient receives fibrinolytic therapy (**eFig. 59.6**), and preventing deep venous thrombosis, pulmonary embolism, ventricular thrombus formation, and cerebral embolization.



EFIGURE 59.6 Targets for therapy during reperfusion of patients with STEMI. This schematic view shows a longitudinal section of an infarct-related artery at the level of the obstructive thrombus. Following rupture of a vulnerable plaque (*bottom center*), the coagulation cascade activates, which ultimately leads to the deposition of fibrin strands; platelets also activate and begin to aggregate. Platelets that aggregate with incorporation of relatively few red cells form a white thrombus. The mesh of fibrin strands and platelet aggregates obstructs flow in the infarct-related artery. Pharmacologic reperfusion is a multipronged approach consisting of fibrinolytic agents that digest fibrin, anticoagulants that prevent the formation of thrombin and inhibit the activity of formed thrombin, and antiplatelet therapy. (Modified from Jackson SP. Arterial thrombosis—insidious, unpredictable, and deadly. Nat Med 2011;17:1423.)

Effect of Heparin on Mortality

Randomized trials of patients with STEMI conducted in the prefibrinolytic era showed a lower risk for reinfarction, pulmonary embolism, and stroke in those who received IV heparin, thus supporting the administration of heparin to STEMI patients not treated with fibrinolytic therapy. With the introduction of the fibrinolytic era and, importantly, after publication of the ISIS-2 (Second International Study of Infarct Survival) trial, the situation became more complicated because of strong evidence of a substantial reduction in mortality with aspirin alone and confusing and conflicting data regarding the risk/benefit ratio of heparin used as an adjunct to aspirin or in combination with aspirin and a fibrinolytic agent.[1] Nevertheless, a meta-analysis of trials in the fibrinolytic era suggested that for every 1000 patients treated with heparin versus aspirin alone, five fewer deaths ($P = 0.03$) and three fewer recurrent infarctions ($P = 0.04$) occur, but at the expense of three more major bleeding episodes ($P = 0.001$).[71]

Other Effects of Heparin.

Several angiographic studies have examined the role of heparin therapy in establishing and maintaining patency of the infarct-related artery in patients with STEMI. Although evidence favoring the use of heparin in conjunction with a fibrin-specific fibrinolytic agent for enhancing patency of the infarct artery is not conclusive, the suggestion of a mortality benefit and amelioration of LV thrombi after STEMI supports the use of heparin for at least 48 hours after fibrinolysis.[1]

The most serious complication of anticoagulant therapy is bleeding (**see Chapter 93**), especially intracranial hemorrhage. Major hemorrhagic events occur more frequently in patients with low body weight, advanced age, female sex, marked prolongation of the activated partial thromboplastin time

(APTT) (>90 to 100 seconds), and performance of invasive procedures.[72] Frequent monitoring of the APTT reduces the risk for major hemorrhagic complications in patients treated with heparin. During the first 12 hours after fibrinolytic therapy, however, the APTT may be elevated as a result of the fibrinolytic agent alone (particularly if streptokinase is administered), thus making it difficult to interpret accurately the effects of a heparin infusion on the patient's coagulation status.

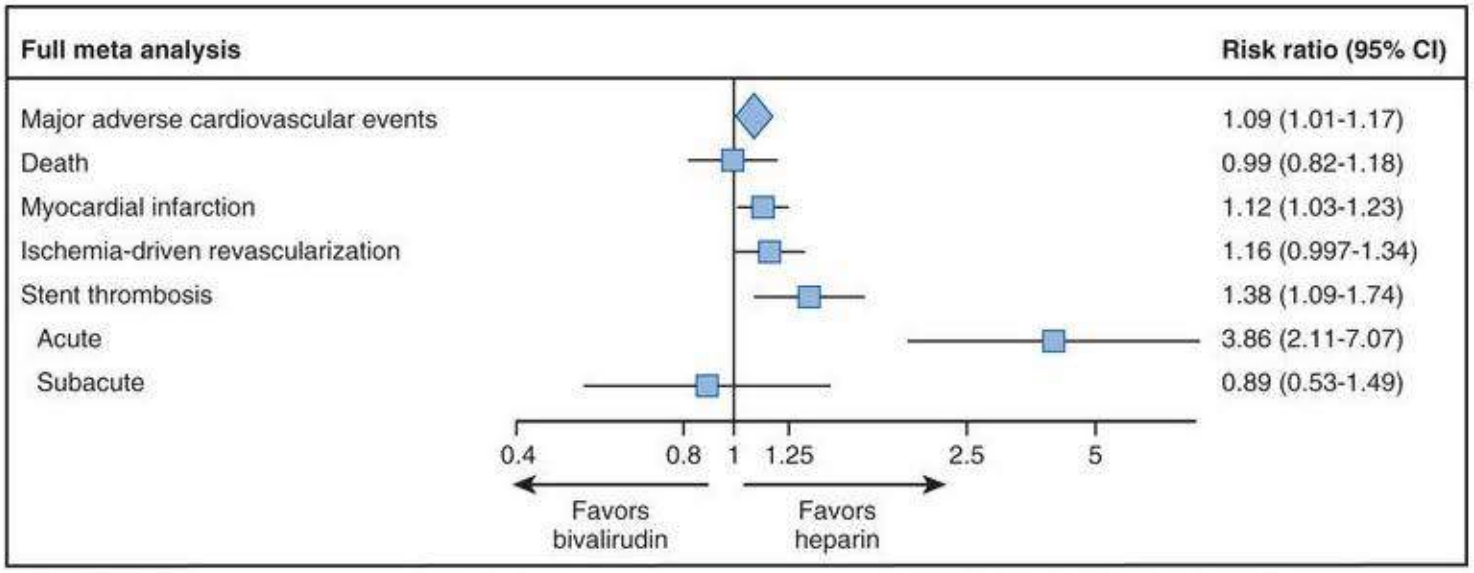
Disadvantages of Heparin.

Potential disadvantages of unfractionated heparin (UFH) include dependency on antithrombin III for inhibition of thrombin activity, sensitivity to platelet factor 4, inability to inhibit clot-bound thrombin, marked interpatient variability in therapeutic response, and the need for frequent monitoring of the APTT. Even with standardized weight-based dosing nomograms, less than 35% of initial APTT measurements are within the therapeutic range.[73] Several alternative anticoagulants can circumvent these disadvantages of UFH.

Hirudin and Bivalirudin

In patients undergoing fibrinolysis, direct thrombin inhibitors such as hirudin or bivalirudin reduce the incidence of recurrent MI by 25% to 30% compared with heparin but have not reduced mortality. In addition, both hirudin and bivalirudin cause higher rates of major bleeding than heparin when used with fibrinolytic agents.[74]

In contrast, when administered for a short period as an adjunct to primary PCI in the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial, bivalirudin (open label), versus heparin plus glycoprotein (GP) IIb/IIIa inhibitors, reduced the 30-day rate of major bleeding or major adverse CV events, including death, reinfarction, target vessel revascularization for ischemia, and stroke (RR, 0.76; 95% CI 0.63 to 0.92; $P = 0.005$), driven by a significant 40% reduction in major bleeding (**eFig. 59.7**). Treatment with bivalirudin significantly reduced mortality at 30 days and at 1 year, but increased the early risk for stent thrombosis .[72] Similarly, in the EUROMAX (European Ambulance Acute Coronary Syndrome Angiography) trial, when started during transport for primary PCI in STEMI, bivalirudin reduced the primary outcome of death or major bleeding compared to heparin with optional GP IIb/IIIa, with a reduction in major bleeding but increase in stent thrombosis.[75] However, there was no significant difference in mortality. A meta-analysis of 16 randomized controlled trials (RCTs), including four with predominantly STEMI patients, reported an increased risk of major adverse cardiovascular events (MACE) (RR, 1.09; 95% CI 1.01 to 1.17; $P = 0.0204$), primarily from increases in MI, ischemia-driven revascularization, and acute stent thrombosis (**Fig. 59.12**). There was no difference in mortality, and bleeding rates were generally lower with bivalirudin, with the magnitude of the reduction dependent on GP IIb/IIIa co-administration.[76] The findings were consistent in the subset with STEMI.



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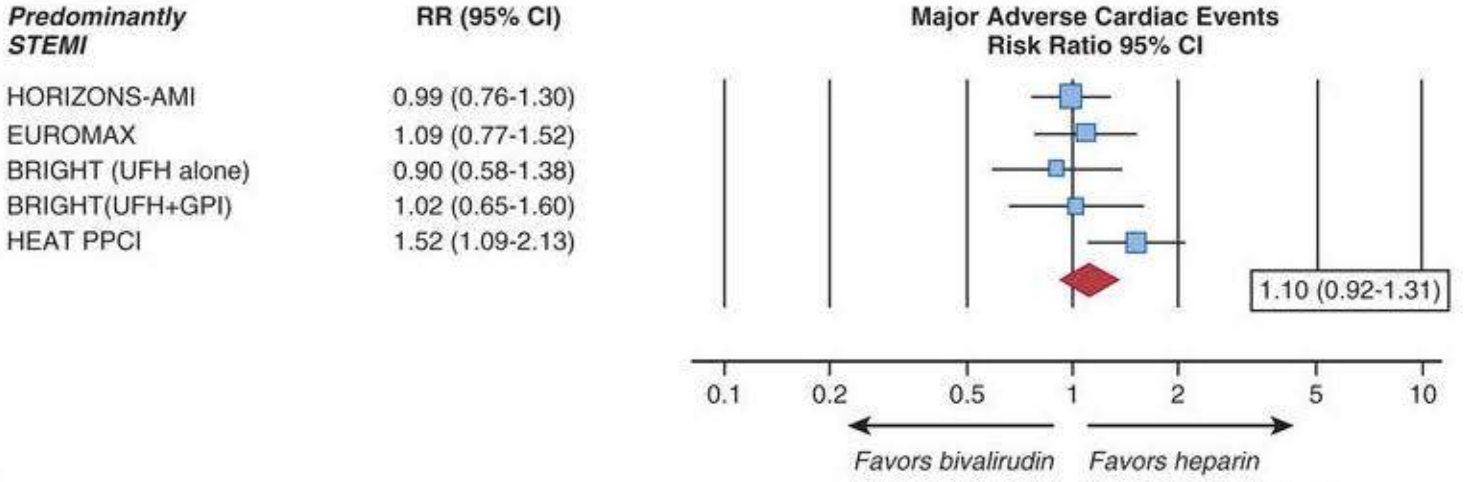

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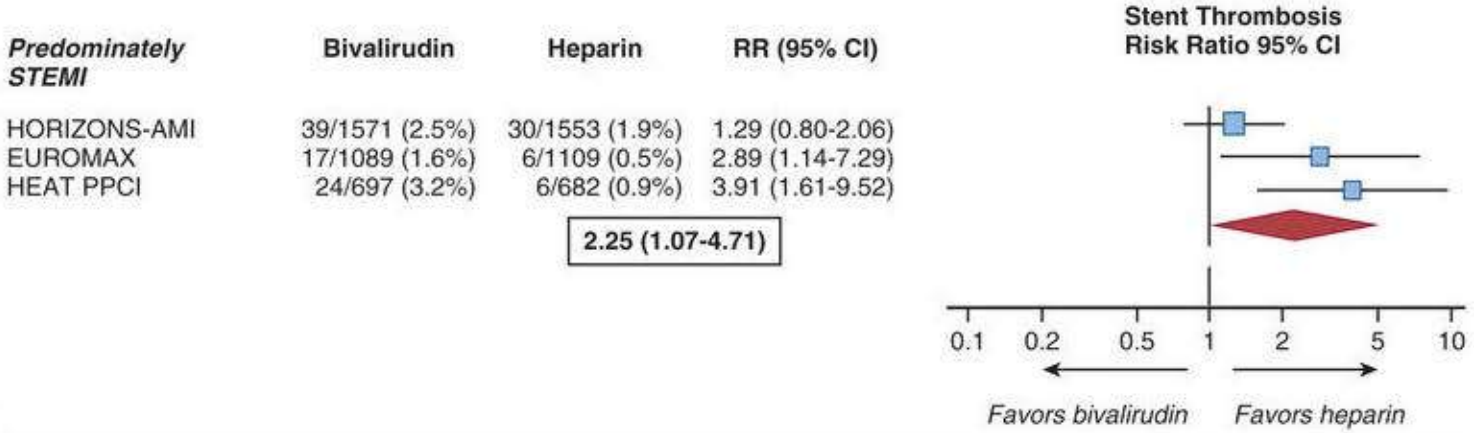

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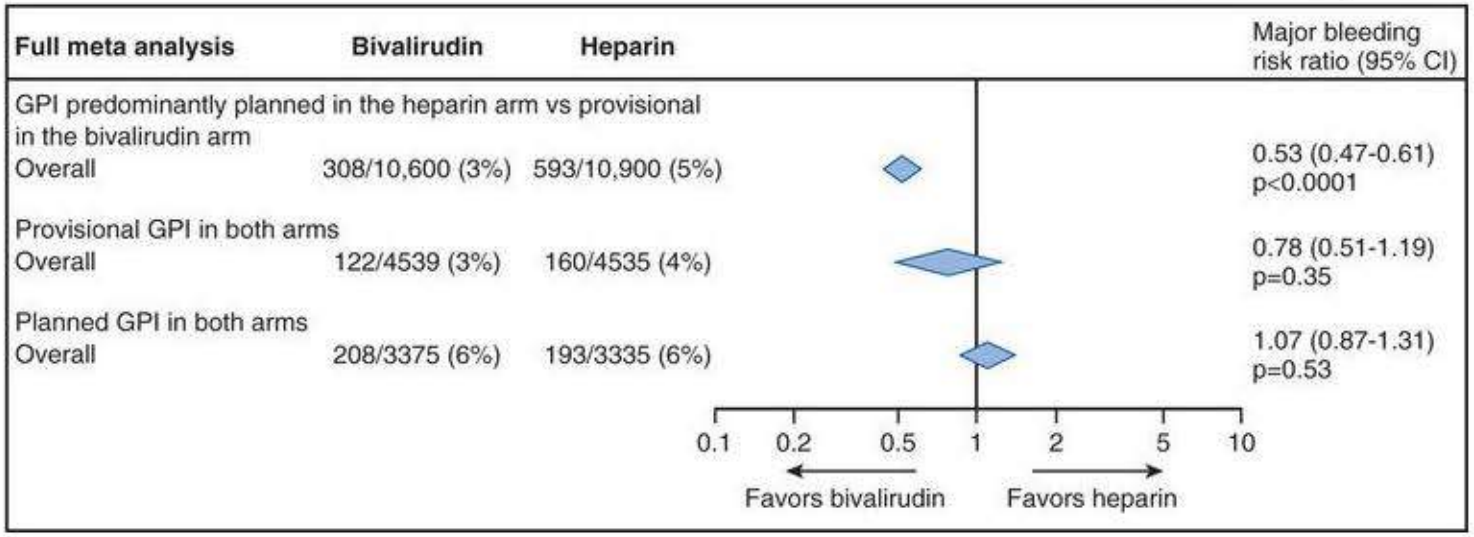
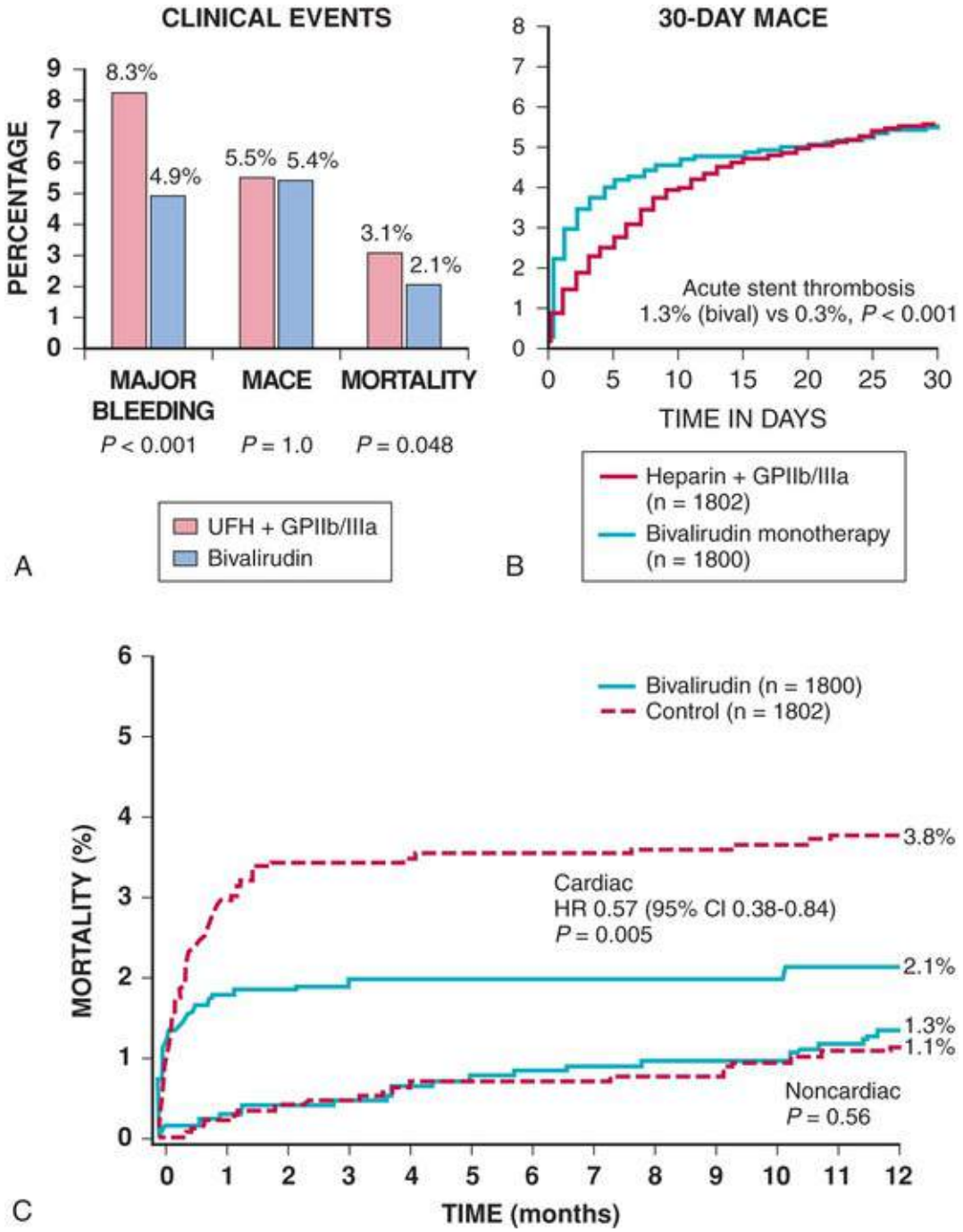


D

FIGURE 59.12 Meta-analysis of 33,958 patients from 16 randomized trials of bivalirudin versus heparin

during PCI. There was an increase in the risk of major adverse cardiac events (MACE) at 30 days with bivalirudin-based regimens compared with heparin-based regimens (risk ratio, 1·09; 95% CI 1·01 to 1·17; *P* = 0·0204) in the overall study population **(A).** While there was no difference in death or ischemia-driven revascularization, there was a significant increase in MI and acute stent thrombosis in the overall study population with bivalirudin-based regimens versus heparin-based regimens. There was a similar 10% increase in MACE **(B)** and numerically larger relative risk of stent thrombosis (risk ratio, 2.25; 95% CI 1.07 to 4.71) **(C)** in the four trials predominantly enrolling STEMI patients. Overall, bivalirudin-based regimens lowered the risk of major bleeding (risk ratio, 0.62; 95% CI 0.49 to 0.78; *P* < 0.0001), but the magnitude of this effect varied depending on whether glycoprotein IIb/IIIa inhibitors (GPI) were used predominantly in the heparin arm only, provisionally in both arms, or planned in both arms **(D).** (Modified from Cavender M, Sabatine MS. Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: a meta-analysis of randomised controlled trials. Lancet. 2014:384(9943):599-606.)



EFIGURE 59.7 Results of an open-label randomized clinical trial comparing bivalirudin to unfractionated heparin (UFH) and a GP IIb/IIIa receptor antagonist as adjunctive medical therapy to support primary PCI in patients with STEMI. **A,** Treatment with bivalirudin was associated with significantly lower rates of major bleeding and mortality at 30 days. **B,** Kaplan-Meier curves of the cumulative incidence of major adverse cardiac events (MACE) did not differ between the two strategies at 30 days. **C,** Acute stent thrombosis during the first 24 hours was higher in patients treated with bivalirudin alone, but cardiovascular mortality was reduced in the bivalirudin group after 1 year of follow-up, thus providing strong evidence for this treatment strategy. (From Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218; and Mehran R, Lansky AJ, Witzenbichler B. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomized controlled trial. Lancet 2009;374:1149.)

Low-Molecular-Weight Heparins

Advantages of low-molecular-weight heparins (LMWHs) include a stable, reliable anticoagulant effect, high bioavailability permitting administration via the subcutaneous (SC) route, and a high anti-Xa/anti-IIa ratio producing blockade of the coagulation cascade in an upstream location and greatly reducing thrombin generation. The primary role of LMWH for management of STEMI is as an adjunct to

fibrinolytic therapy. Although LMWHs do not improve the rate of early (60 to 90 minutes) reperfusion of the infarct artery, LMWH reduces rates of reocclusion of the infarct artery, reinfarction, or recurrent ischemic events.[77] This effect may underlie the significant reduction in recurrent MI with a strategy of extended anticoagulation with LMWHs, or a factor Xa antagonist versus standard therapy, in patients with STEMI undergoing fibrinolysis.

When compared with placebo, the LMWH reviparin significantly reduced the incidence of death, recurrent MI, or stroke at 30 days in 15,570 patients with STEMI, 73% of whom received a fibrinolytic (predominantly a non–fibrin-specific agent).[78] This important finding demonstrates not only that LMWHs are clinically effective for STEMI, but also that a clinical anticoagulant therapy provides benefit as part of a fibrinolytic reperfusion strategy.

Several trials have compared a LMWH with UFH as part of a pharmacologic reperfusion strategy and demonstrated the LMWH to be superior.[78] In the ASSENT (Assessment of the Safety and Efficacy of a New Thrombolytic) 3 trial, enoxaparin (30-mg IV bolus, followed by SC injections of 1 mg/kg every 12 hours until discharge from the hospital)[79] reduced 30-day mortality, in-hospital reinfarction, or in-hospital refractory ischemia compared with UFH (RR, 0.74; 95% CI 0.63 to 0.87). The rate of intracranial hemorrhage was similar with UFH and enoxaparin (0.93% versus 0.88%; $P = 0.98$). The ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction 25) trial tested in a double-blind, double-dummy design the hypothesis that a strategy of enoxaparin (adjusted for age and renal function) administered for the duration of the index hospitalization was superior to the conventional antithrombin strategy of UFH administration for 48 hours after fibrinolysis.[80] The primary endpoint of death or recurrent nonfatal MI through 30 days was reduced by 17% ($P = 0.001$; **Fig. 59.13A**) with enoxaparin compared with UFH, with a 33% reduction ($P = 0.001$) in reinfarction and a nonsignificant favorable trend on overall mortality ($P = 0.11$). This improvement in recurrent MI was balanced by an increase in the incidence of major bleeding (1.4% and 2.1%, $P = 0.001$). In a meta-analysis of trials of LMWH versus UFH, LMWH clearly reduced recurrent MI but with a pattern of increased bleeding (**Fig. 59.13B**).

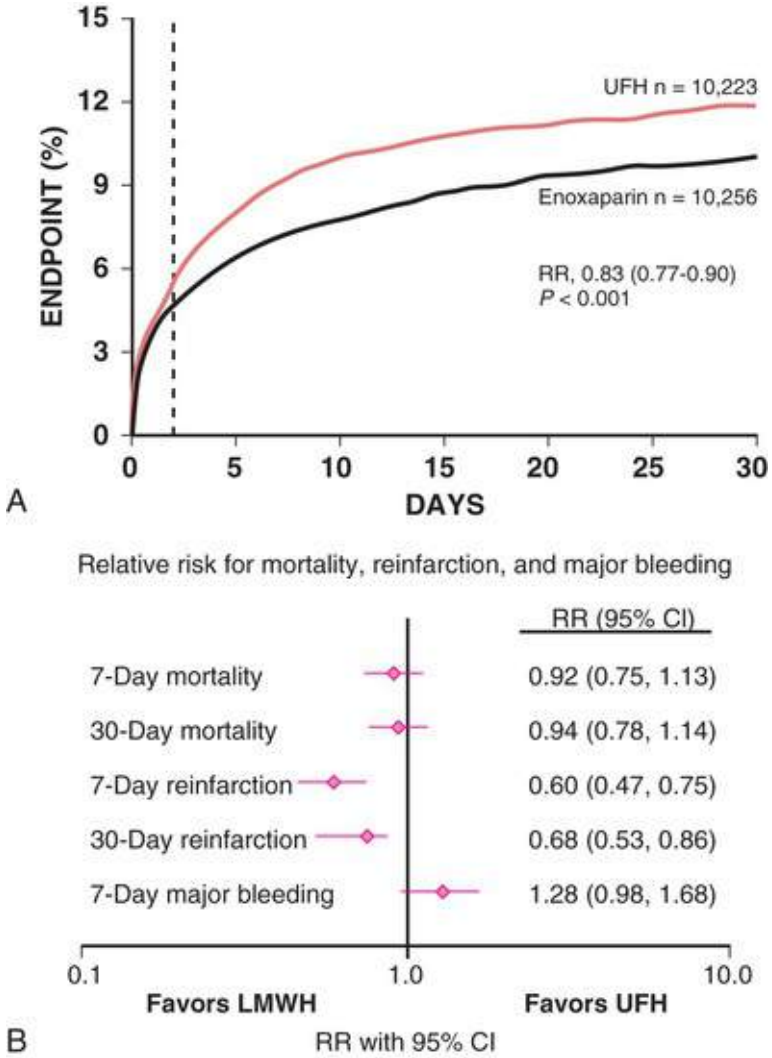


FIGURE 59.13 Comparison of enoxaparin with unfractionated heparin (UFH) as adjunctive therapy in patients with STEMI receiving fibrinolysis. **A,** Primary results from the ExTRACT-TIMI 25 trial showing that the rate of the primary endpoint (death or nonfatal MI) at 30 days was significantly lower in the enoxaparin group than in the UFH group (9.9% versus 12%, *P* <0.001 by log-rank test). The *dashed vertical line* indicates the comparison at day 2 (direct pharmacologic comparison), at which time a trend in favor of enoxaparin was seen. **B,** Results of a meta-analysis of seven randomized controlled clinical trials of low-molecular-weight heparin (LMWH) versus UFH, including 27,577 patents with STEMI. Individual outcomes of all-cause death, reinfarction, and major bleeding through 7 days are shown. (From Antman EM et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial Infarction. N Engl J Med 2006;354:1477; and Singh S et al. Adjunctive low molecular weight heparin during fibrinolytic therapy in acute ST-elevation myocardial infarction: a meta-analysis of randomized control trials. Clin Cardiol 2009;32:358.)

Parenteral Factor Xa Antagonists

The OASIS-6 (Organization for the Assessment of Strategies for Ischemic Syndromes) trial evaluated the specific factor Xa antagonist fondaparinux (2.5 mg subcutaneously) in 12,092 patients with STEMI.[81] The trial design compared fondaparinux given for 8 days with placebo in patients when the treating physician thought that UFH was not indicated (stratum I) and with UFH for 48 hours when the treating physician thought that heparin was indicated (stratum II). Fondaparinux reduced the composite of death or reinfarction in stratum I (hazard ratio [HR], 0.79; 95% CI, 0.68 to 0.92), but not in stratum II (HR, 0.96; 95% CI, 0.81 to 1.13). The outcome of patients in stratum II who underwent PCI tended to be worse with fondaparinux than with UFH, probably because of an increased risk for catheter thrombosis.

Oral Factor IIa and Factor Xa Antagonists

See later section, Secondary Prevention of Acute Myocardial Infarction.

Recommendations for Anticoagulant Therapy

Anticoagulation With Fibrinolysis.

Given the pivotal role of thrombin in the pathogenesis of STEMI (**eFig. 59.6**), antithrombotic therapy remains an important intervention. A regimen of an IV UFH bolus of 60 units/kg to a maximum of 4000 units, followed by an initial infusion at 12 units/kg/hr to a maximum of 1000 units/hr for 48 hours, adjusted to maintain the APTT at 1.5 to 2 times control (approximately 50 to 70 seconds), is effective in patients receiving fibrinolytic therapy.[1]

Both the ExTRACT-TIMI 25 and the OASIS-6 trials indicated that prolonged administration of an anticoagulant for the duration of hospitalization is beneficial compared with the previous practice of administering UFH only for 48 hours unless clear-cut indications for continued anticoagulation were present. Accordingly, patients managed with pharmacologic reperfusion therapy should receive anticoagulant therapy for a minimum of 48 hours and preferably for the duration of hospitalization after STEMI, up to 8 days. Enoxaparin or fondaparinux is preferred when administration of an anticoagulant for longer than 48 hours is planned in patients with STEMI treated with a fibrinolytic.[1] Enoxaparin should be administered according to age, weight, and creatinine clearance and be given as an IV bolus, followed in 15 minutes by SC injection for the duration of the index hospitalization, up to 8 days or until revascularization. Fondaparinux should be administered as an initial IV dose, followed in 24 hours by daily SC injections if the estimated creatinine clearance is higher than 30 mL/min. If PCI is performed in a patient treated with fondaparinux, co-administration of an additional antithrombin agent with anti–factor IIa activity is required to mitigate the risk of catheter-related thrombosis.

In patients with a known history of heparin-induced thrombocytopenia, bivalirudin in conjunction with streptokinase is a useful alternative to heparin.[1] For patients who are referred for CABG, UFH is the preferred antithrombin.

Adjunctive Anticoagulation for Primary PCI (See Chapter 62).

Either UFH or bivalirudin is recommended as an anticoagulant to support primary PCI, with preference for bivalirudin or heparin without a concomitant GP IIb/IIIa inhibitor for patients at high risk for bleeding.[1,76] Fondaparinux is not recommended as the sole anticoagulant in this setting.[1] LMWH has not had sufficient evaluation in primary PCI to formulate recommendations for treatment. Some investigators who have used enoxaparin to support primary PCI for STEMI administer 0.5 mg/kg intravenously at the time of the procedure.

Patients Treated Without Reperfusion Therapy.

Treatment with an anticoagulant is reasonable, and agents shown to be more effective than UFH in other groups with STEMI may be preferable. For example, in patients with STEMI not receiving reperfusion therapy, fondaparinux reduces the composite of death or recurrent MI without an increase in severe bleeding, compared with placebo or UFH.[82]

Antiplatelet Therapy

Platelets play a major role in the response to disruption of coronary artery plaque, especially in the early phase of thrombus formation. Fibrinolysis can activate platelets, and platelet-rich thrombi resist

fibrinolysis more than fibrin and erythrocyte-rich thrombi (**eFig. 59.6**). Thus a sound scientific basis exists for inhibiting platelet aggregation in *all* patients with STEMI, regardless of the reperfusion management strategy. The agent most extensively tested has been aspirin, and treatment with aspirin and a second antiplatelet agent, such as clopidogrel, prasugrel, ticagrelor, or cangrelor, has become the standard of care for patients with STEMI.

Antiplatelet Therapy with Fibrinolysis

The ISIS-2 study was the largest trial of aspirin in patients with STEMI; it provided the single strongest piece of evidence that aspirin reduces mortality in such patients.[83] In contrast to the observations of a time-dependent mortality effect of fibrinolytic therapy, the reduction in mortality with aspirin was similar in patients treated within 4 hours (25% reduction in mortality), between 5 and 12 hours (21% reduction), and between 13 and 24 hours (21% reduction). An overall 23% reduction in mortality with aspirin occurred in ISIS-2 that was largely additive to the 25% reduction in mortality from streptokinase, such that patients receiving both therapies experienced a 42% reduction in mortality. The reduction in mortality was as high as 53% in patients who received both aspirin and streptokinase within 6 hours of symptoms.

Obstructive platelet-rich arterial thrombi resist fibrinolysis and have an increased tendency for reocclusion after initial successful reperfusion in patients with STEMI. Despite inhibition of cyclooxygenase (COX) by aspirin, platelet activation leading to platelet aggregation and increased thrombin formation continues through thromboxane A_2–independent pathways. Adding other antiplatelet agents to aspirin has benefited patients with STEMI.[72] Inhibitors of the $P2Y_{12}$ adenosine diphosphate receptor help prevent the activation and aggregation of platelets. In the CLARITY-TIMI (Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction) 28 trial, addition of the $P2Y_{12}$ inhibitor clopidogrel to background treatment with aspirin in patients with STEMI who were younger than 75 years and received fibrinolytic therapy reduced the risk for clinical events (death, reinfarction, stroke) and reocclusion of a successfully reperfused infarct artery (**Fig. 59.14A**).[72] An ST Resolution (STRes) electrocardiographic substudy from CLARITY-TIMI 28 provided insight into the mechanism of the benefit of clopidogrel in STEMI. No difference was seen in the rate of complete STRes between the clopidogrel and placebo groups at 90 minutes (38.4% versus 36.6%). When patients were stratified by STRes category, treatment with clopidogrel resulted in greater benefit in those with evidence of early STRes, with greater odds of having an open artery at late angiography in patients with partial (OR, 1.4; $P = 0.04$) or complete (OR, 2.0; $P = 0.001$) STRes, but no improvement in those with no STRes evident at 90 minutes (OR, 0.89; $P = 0.48$) (P for interaction = 0.003). Clopidogrel also associated with a significant reduction in the odds for in-hospital death or MI in patients who achieved partial (OR, 0.30; $P = 0.003$) or complete STRes at 90 minutes (OR, 0.49; $P = 0.056$), whereas clinical benefit was not apparent in patients who had no STRes (OR, 0.98; $P = 0.95$) (P for interaction = 0.027). Thus it appears that clopidogrel did not increase the rate of complete opening of occluded infarct arteries when fibrinolysis was administered, but was effective in preventing reocclusion of an initially reperfused infarct artery.

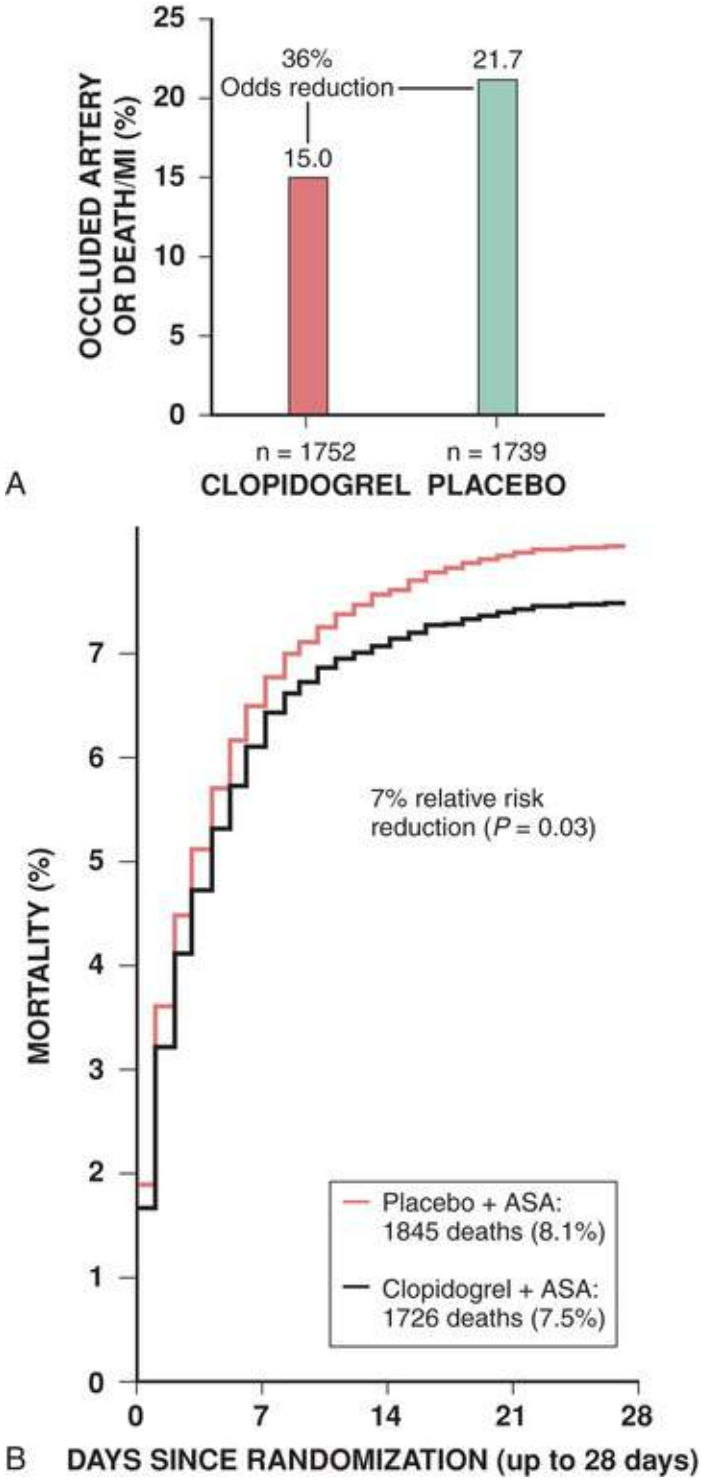


FIGURE 59.14 Impact of the addition of clopidogrel to aspirin (ASA) in patients with STEMI. **A,** Effects of the addition of clopidogrel in patients receiving fibrinolysis for STEMI. Patients in the clopidogrel group (*n* = 1752) had a 36% reduction in the odds of dying, sustaining a recurrent infarction, or having an occluded infarct artery compared with the placebo group (*n* = 1739) in the CLARITY-TIMI 28 trial. **B,** Effect of the addition of clopidogrel on in-hospital mortality after STEMI. These time-to-event curves show a 0.6% reduction in mortality in the group receiving clopidogrel plus aspirin (*n* = 22,961) versus placebo plus aspirin (*n* = 22,891) in the COMMIT trial. (**A,** Modified from Sabatine MS et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005;352:1179; **B,** modified from Chen ZM et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1607.)

In COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial), 45,852 patients with suspected MI were randomly assigned to clopidogrel, 75 mg/day (without a loading dose), or placebo in addition to aspirin, 162 mg/day[72] (**Fig. 59.14B**). Patients in the clopidogrel group had a lower rate of the composite endpoint of death, reinfarction, or stroke (9.2% versus 10.1%; *P* = 0.002). They also had a

significantly lower rate of death (7.5% versus 8.1%; *P* = 0.03). No excessive bleeding with clopidogrel occurred in this trial.

Combination Pharmacologic Reperfusion

Trials of GP IIb/IIIa inhibitors combined with either full or reduced doses of fibrinolytics showed improvements in reperfusion, including myocardial perfusion as reflected in enhanced STRes and faster angiographic frame counts. However, subsequent large outcomes trials revealed no significant effect on survival, and reductions in reinfarction were outweighed by the increases in bleeding.[79] The combination of a GP IIb/IIIa inhibitor and a fibrinolytic as a pharmacologic reperfusion regimen is therefore not recommended.[1]

Antiplatelet Therapy for PCI in ST-Elevation Myocardial Infarction

All patients with STEMI should receive aspirin as soon as possible after initial encounter in the absence of contraindications. Adding the $P2Y_{12}$ inhibitor clopidogrel to aspirin appears to offer additional benefit in patients undergoing PCI after STEMI. In patients undergoing either primary PCI or delayed PCI after initial therapy for STEMI, the more potent $P2Y_{12}$ inhibitor prasugrel was superior to clopidogrel in reducing the risk for CV death, MI, or stroke.[72] In the subgroup of patients with STEMI enrolled in TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction; *n* = 3534), the primary endpoint was lowered by 32% at 30 days with prasugrel compared with aspirin (6.5% versus 9.5%; *P* = 0.0017) and by 21% at 15 months (10.0% versus 12.4%; *P* = 0.022) (**Fig. 59.15**).[84] Prasugrel reduced definite or probable stent thrombosis by 42% compared with clopidogrel. Analogously, in the PLATO (Platelet Inhibition and Patient Outcomes) trial, compared with clopidogrel, treatment with the reversible $P2Y_{12}$ inhibitor ticagrelor in patients with STEMI undergoing primary PCI (*n* = 7544) tended to reduce the primary endpoint of CV death, recurrent MI, or stroke by 13%, a magnitude similar to that for the overall trial population (**Fig. 59.15**); there was a 26% reduction in definite or probable stent thrombosis and an 18% reduction in all-cause mortality.[85]

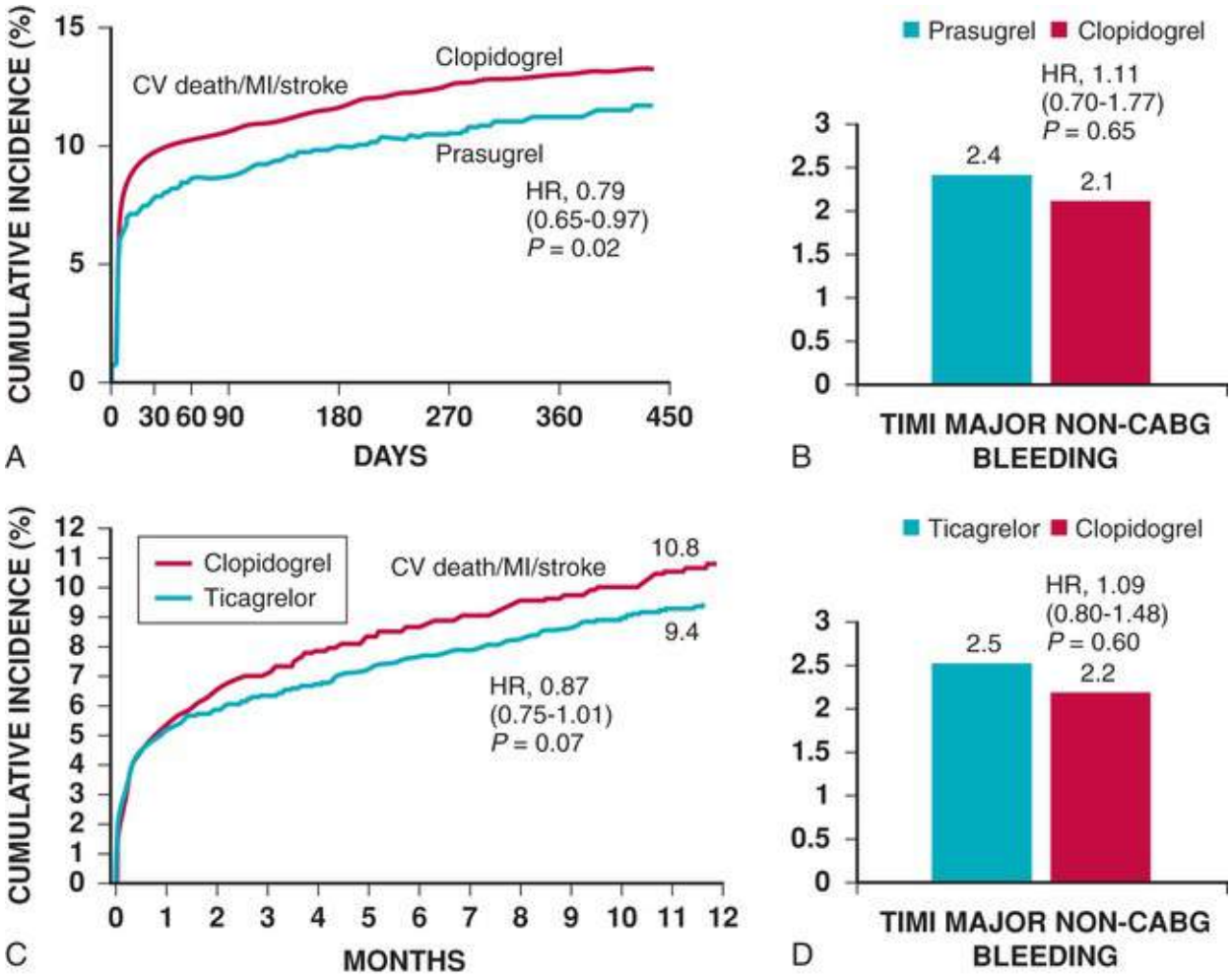


FIGURE 59.15 **A,** Efficacy of prasugrel in the subgroup of patients with STEMI enrolled in a randomized clinical trial of prasugrel versus clopidogrel in patients undergoing PCI after an ACS. Treatment with prasugrel associated with a 21% relative reduction in the risk for cardiovascular (CV) death, MI, or stroke during 15 months of follow-up. **B,** Major bleeding (TIMI non-CABG) increased with prasugrel in the trial overall, but did not reach statistical significance in patients with STEMI. **C,** Efficacy results for ticagrelor (versus clopidogrel) in patients with STEMI enrolled in the PLATO trial. The effect of ticagrelor on the primary endpoint (incidence of MI, stroke, or CV death) was consistent with the superiority of ticagrelor versus clopidogrel in the overall trial. **D,** Rates of major bleeding (TIMI non-CABG) are shown. CABG, Coronary artery bypass grafting. (**A, B,** From Montalescot G et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction [TRITON-TIMI 38]: double-blind, randomised controlled trial. Lancet 2009;373:723; **C, D,** from Steg PG et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation 2010;122:2131.)

Evidence regarding the appropriate timing of initiation of $P2Y_{12}$ inhibitor therapy before PCI for STEMI is mixed. As part of the PCI-CLARITY (PCI-Clopidogrel as Adjunctive Reperfusion Therapy) study, the investigators performed a meta-analysis of PCI-CLARITY, PCI-CURE (PCI-Clopidogrel in Unstable angina to prevent Recurrent Events), and CREDO (Clopidogrel for the Reduction of Events During Observation) and found that pretreatment with clopidogrel significantly reduced the risk for 30-day CV death or MI in a population that included both patients with STEMI and non–ST elevation ACS.[1,72] In a subsequent meta-analysis that included data from randomized trials and registries, higher-risk STEMI patients had a lower risk for major coronary events with clopidogrel pretreatment, but not a reduction in mortality or an increase in bleeding.[86] Prehospital administration of ticagrelor did not improve the primary endpoint of coronary reperfusion, but did reduce the secondary endpoint of stent thrombosis without any additional bleeding, compared to in-hospital administration in patients with STEMI undergoing primary PCI in the ATLANTIC trial (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery).[87] **Chapter**

62 discusses the use of GP IIb/IIIa inhibitors as part of adjunctive therapy for patients with STEMI undergoing PCI.

Recommendations for Antiplatelet Therapy

Patients who have not taken aspirin before the development of STEMI should chew non–enteric-coated aspirin, and the dose should be 162 to 325 mg initially. During the maintenance phase of antiplatelet therapy following STEMI, the dose of aspirin should be reduced to 75 to 162 mg to minimize the risk for bleeding.[1] Lower doses are preferable because of the increased risk for bleeding with higher doses reported in several studies; the CURRENT-OASIS 7 trial did not find differences in terms of efficacy or safety in STEMI patients randomly assigned to 81 versus 325 mg of aspirin. If true aspirin allergy is present, other antiplatelet agents such as clopidogrel or ticlopidine can be substituted.

The addition of a $P2Y_{12}$ inhibitor to aspirin is warranted in most patients with STEMI.[1] Based on the results of the COMMIT and CLARITY-TIMI 28 trials, clopidogrel, 75 mg/day orally, is an option for all patients with STEMI regardless of whether they receive fibrinolytic therapy, undergo primary PCI, or do not receive reperfusion therapy. The data available suggest that a loading dose of 300 mg of clopidogrel should be given to patients younger than 75 years who receive fibrinolytic therapy. Data are insufficient in elderly patients to recommend a loading dose in those 75 years or older who receive a fibrinolytic. When primary PCI is the mode of reperfusion therapy, an oral loading dose of 600 mg of clopidogrel before stent implantation is an established treatment, followed by 75 mg daily.[1,88] Interpatient variability in the response to clopidogrel can occur (**see Chapters 8, 60, and 93**), and individuals with lesser degrees of platelet inhibition have increased risk for death and ischemic complications.[89]

Prasugrel and ticagrelor generally achieve greater degrees of platelet inhibition than clopidogrel and can be used to treat patients with STEMI. On the basis of the results of TRITON-TIMI 38, prasugrel administered as an oral loading dose of 60 mg and 10 mg daily thereafter demonstrated benefit in patients with STEMI, but should not be used in patients with a history of cerebrovascular disease or who are at higher risk for life-threatening bleeding.[1] Ticagrelor also reduced CV events compared with clopidogrel, and in PLATO, ticagrelor was administered as an oral loading dose of 180 mg and then 90 mg twice daily.[1,85] When using ticagrelor, the recommended maintenance dose of aspirin is 81 mg daily.[1]

Hospital Management

Coronary Care and Intermediate Care Units

Development of the coronary care unit (CCU) established the practice of continuous monitoring of cardiac rhythm by highly trained nurses with the skills and authority to initiate immediate treatment of arrhythmias in the absence of physicians and with the availability of specialized equipment (defibrillators, pacemakers).[90] The clustering of patients with STEMI in the CCU greatly enhanced efficient use of the trained personnel, facilities, and equipment to improve patient outcomes.[90] These benefits of geographic clustering with specialized nursing contribute to the optimal care of patients with STEMI, and in some hospitals, such care can be provided in “intermediate care” telemetry units with well-trained staff outside the CCU.[91] Such intermediate care units, when equipped with continuous electrocardiographic monitoring and resuscitation equipment, may be appropriate for initial admission of STEMI patients with a low risk for mortality. This strategy has proved cost-effective and may reduce CCU use by one third, shorten hospital stays, and have no deleterious effect on patients' recovery.[1]

With increasing attention directed to limitations on resources and to the economic impact of intensive care, the proportion of appropriately selected patients with STEMI cared for in an intermediate care unit will likely increase. Nevertheless, a dedicated cardiac intensive care unit (CICU) plays a pivotal role in the management of patients with major complications of STEMI, who may require treatment of refractory arrhythmias, use of invasive hemodynamic monitoring, or mechanical circulatory support.[90] In patients with STEMI managed in a CICU, those with an uncomplicated status, such as patients without HF, hypotension, heart block, hemodynamically compromising ventricular arrhythmias, or persistent ischemic-type discomfort, can be safely transferred out of the CICU within 24 to 36 hours. In patients with complicated STEMI, the duration of the CICU stay should be dictated by the need for "intensive" care—that is, hemodynamic monitoring, close nursing supervision, IV vasoactive drugs, and frequent changes in the medical regimen.

General Measures

The managing clinical staff should be sensitive to patient concerns about prognosis and future productivity. A calm, quiet atmosphere can help allay anxiety and reduce adrenergic tone. Use of anxiolytic medications may be appropriate in some cases. To reduce the risk for nausea and vomiting early after infarction and to decrease the risk for aspiration, we find it prudent to limit the patient's diet to either nothing by mouth or clear liquids during the first 4 to 12 hours after admission. Thereafter, dietary intervention is an important component of an overall strategy for secondary prevention (**see Chapters 45 and 49**).

The results of laboratory tests should be scrutinized for any derangements potentially contributing to arrhythmias, such as disturbances in acid-base balance or electrolytes. Delirium can be provoked by medications frequently used in the hospital, including antiarrhythmic drugs, H_2 blockers, narcotics, and beta blockers. Use of potentially offending agents should be discontinued in patients with an abnormal mental status. Haloperidol, a butyrophenone, can be used safely in patients with STEMI. Stool softeners can prevent constipation and straining.

Physical Activity

In the absence of complications, stabilized patients with STEMI need not be confined to bed for more than 12 hours, and unless they are hemodynamically compromised, they may use a bedside commode shortly after admission. Progression of activity should be individualized depending on the patient's clinical status, age, and physical capacity. In patients without hemodynamic compromise, early mobilization (e.g., sitting in chair, standing, walking around bed) does not usually cause important changes in HR, BP, or pulmonary wedge pressure. As long as BP and HR are monitored, early mobilization offers considerable psychological and physical benefit without any clear medical risk.

Pharmacologic Therapy

Beta Blockers

Use of beta blockers for the treatment of patients with STEMI can cause both immediate effects (when the drug is given early in the course of infarction) and long-term effects (secondary prevention). Immediate IV administration of beta blockers reduces the cardiac index, HR, and BP.[92] The net effect is a reduction in myocardial oxygen consumption per minute and per beat. Favorable effects of acute IV administration of beta blockers on the balance of myocardial oxygen supply and demand are reflected in reductions in chest

pain, in the proportion of patients with threatened infarction in whom STEMI actually evolves, and in the development of ventricular arrhythmias. Because beta-adrenergic blockade diminishes circulating levels of free fatty acids (FFAs) by antagonizing the lipolytic effects of catecholamines, and because elevated FFA levels augment myocardial oxygen consumption and probably increase the incidence of arrhythmias, these metabolic actions of beta blockers may also benefit the ischemic heart. As noted earlier, because early administration of IV beta blockers can cause detrimental effects in some patients, the present guidelines omit this therapy for most patients.[1]

More than 52,000 patients have been randomly assigned to treatment in clinical trials studying beta-adrenergic blockade for acute MI.[1] These trials cover a range of beta blockers and timing of administration and were largely conducted in the era before reperfusion strategies were developed for STEMI. Data available in the pre-reperfusion era suggested favorable trends toward a reduction in mortality, reinfarction, and cardiac arrest. In the reperfusion era, adding an IV beta blockers to fibrinolytic therapy was not associated with a reduction in mortality but helped reduce the rate of recurrent ischemic events. Concern arose regarding the potential risk of provoking cardiogenic shock if early IV followed by oral beta-adrenergic blockade was routinely administered to all patients with STEMI. The largest trial of beta blockers in patients with acute MI was COMMIT, which randomly assigned 45,852 patients within 24 hours of MI to metoprolol given as sequential IV boluses of 5 mg up to 15 mg, followed by 200 mg/day orally, or to placebo.[1] The rate of the composite endpoint of death, reinfarction, or cardiac arrest in the metoprolol group (9.4%) did not differ from that in the placebo group (9.9%). Significant reductions occurred in reinfarction and episodes of VF in the metoprolol group, which translated into 5 fewer events for each of these endpoints per 1000 patients treated; yet there were 11 more episodes of cardiogenic shock in the metoprolol group per 1000 patients treated. Risk for the development of cardiogenic shock (recorded as part of COMMIT protocol, in contrast to earlier studies) was greatest in patients with moderate to severe LV dysfunction (Killip class II or greater).

The combined results of the low-risk patients from COMMIT and data from earlier trials provide an overview of the effects of early IV therapy followed by oral therapy with beta blockers (**Fig. 59.16**). A 13% reduction occurred in all-cause mortality (7 lives saved per 1000 patients treated), along with a 22% reduction in reinfarction (5 fewer events per 1000 patients treated) and a 15% reduction in VF or cardiac arrest (5 fewer events per 1000 patients treated). To achieve these benefits safely, early administration of beta blockers to patients with relative contraindications should be avoided (**Table 59.6**).

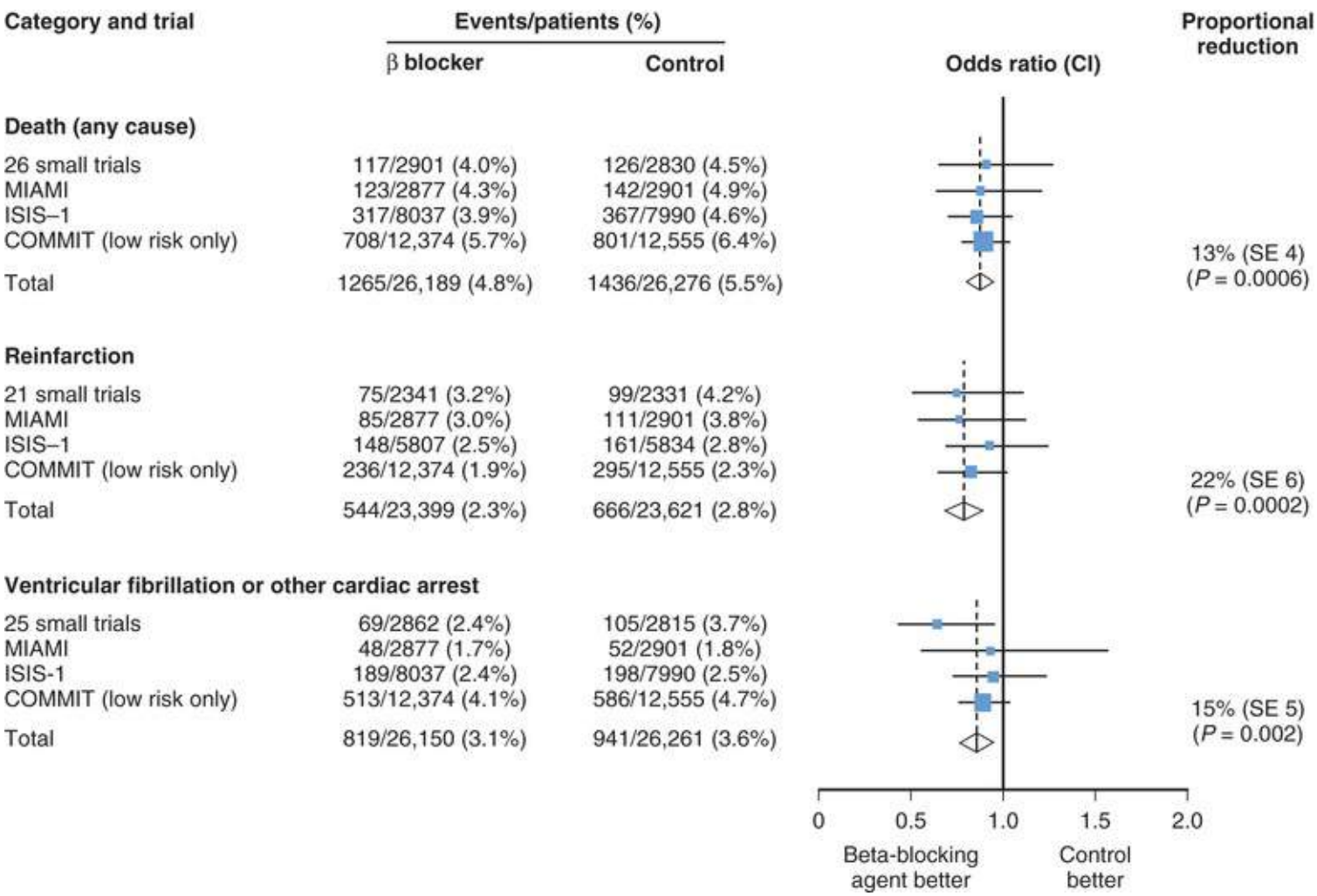


FIGURE 59.16 Meta-analysis of the effects of intravenous and then oral beta (β)-blocker therapy on death, reinfarction, and cardiac arrest during the scheduled treatment periods in 26 small randomized trials, MIAMI, ISIS-1, and the low-risk subset of COMMIT. For COMMIT, data are included only for patients with a systolic blood pressure higher than 105 mm Hg, a heart rate greater than 65 beats/min, and Killip class I (as in MIAMI). Five small trials included in the ISIS-1 report had no data on reinfarction. In the ISIS-1 trial, data on reinfarction in the hospital were available for the last three quarters of the study and involved 11,641 patients. ORs (odd ratios) in each (*blue squares* with the area proportional to the number of events) were determined by comparing outcomes in patients allocated to β-blocker therapy with those in patients allocated to control, along with 99% CIs (confidence intervals) *(horizontal lines).* Overall ORs and 95% CIs are plotted by the *diamonds,* with value and significance given alongside. (From Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1622.)

TABLE 59.6

Recommendations for Beta-Blocker Therapy for ST-Elevation Myocardial Infarction (STEMI)

RECOMMENDATION	COR	LOE
Oral beta blockers should be initiated in the first 24 hours in patients with STEMI who do not have any of the following: Signs of heart failure or evidence of a low-output state Increased risk for cardiogenic shock*: • Age >70 years • Systolic blood pressure <120 mm Hg • Sinus tachycardia >110 beats/min or heart rate <60 beats/min • Increased time since the onset of symptoms of STEMI Other relative contraindications to use of oral beta blockers: • PR interval longer than 0.24 second • Second- or third-degree heart block • Active asthma or reactive airways disease	I	B
Beta blockers should be continued during and after hospitalization for all patients with STEMI and no contraindications to their use.	I	B
Patients with initial contraindications to the use of beta blockers in the first 24 hours after STEMI should be reevaluated to determine their subsequent eligibility.	I	C
It is reasonable to administer IV beta blockers at initial encounter to patients with STEMI and no contraindications to their use who are hypertensive or have ongoing ischemia.	IIa	B

*The greater the number of risk factors present, the higher the risk for development of cardiogenic shock.

COR, Class of recommendation; *LOE,* level of evidence.

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78.

Recommendations

Given the evidence of a benefit of early administration of beta blockers for STEMI, patients without a contraindication, regardless of the administration of concomitant fibrinolytic therapy or performance of primary PCI, should receive *oral* beta blockers within the first 24 hours (**Table 59.6**). IV administration of beta-blocking therapy during this period is also reasonable if a tachyarrhythmia or hypertension is present, in the absence of signs of HF/low output, indicators of high risk for the development of shock, or other relative contraindications to beta blockers.[1]

Beta blockers are especially helpful in STEMI patients with significant residual unrevascularized CAD and evidence of recurrent ischemia or tachyarrhythmias early after the onset of infarction.[93] If adverse effects of beta blockers develop or if patients have complications of infarction that are contraindications to these agents, such as HF or heart block, beta blockers should be withheld. Unless there are contraindications (**Table 59.6**), beta blockers probably should be continued in patients in whom STEMI develops. Moreover, patients who initially have contraindications to a beta blockers, such as acute HF, should be reevaluated with respect to their candidacy for such therapy after 24 hours.[1]

Selection of Beta Blockers

Favorable effects have been reported with metoprolol, atenolol, carvedilol, timolol, and alprenolol; these benefits probably occur with propranolol and with esmolol, an ultrashort-acting agent, as well. In the absence of any favorable evidence supporting the benefit of agents with intrinsic sympathomimetic activity, such as pindolol and oxprenolol, and with some unfavorable evidence for these agents in secondary prevention, beta blockers with intrinsic sympathomimetic activity should probably not be chosen for treatment of STEMI. The CAPRICORN (Carvedilol Post Infarction Survival Control in Left Ventricular Dysfunction) trial randomly assigned 1959 patients with MI and systolic dysfunction (EF <40%) to carvedilol or placebo in addition to contemporary pharmacotherapy, including angiotensin-

converting enzyme (ACE) inhibitors in 98% of patients. All-cause mortality was reduced over a mean follow-up of 1.3 years by 23% with carvedilol compared to placebo ($P = 0.031$), with a similar pattern noted during the first 30 days.[22] Thus, CAPRICORN confirmed the benefit of administration of a beta blocker in addition to ACE inhibitor therapy in patients with transient or sustained LV dysfunction after MI.

Occasionally, clinicians may decide to proceed with therapy with a beta blocker even in patients with relative contraindications, such as a history of mild asthma, mild bradycardia, mild HF, or first-degree heart block. In this situation a trial of esmolol may help determine whether the patient can tolerate beta-adrenergic blockade. Because the hemodynamic effects of this drug (half-life of 9 minutes) disappear in less than 30 minutes, it offers an advantage over longer-acting agents when the risk for complications with a beta blocker is relatively high.

Inhibition of the Renin-Angiotensin-Aldosterone System

The rationale for inhibition of the renin-angiotensin-aldosterone system (RAAS) includes experimental and clinical evidence of a favorable impact on ventricular remodeling, improvement in hemodynamics, and a reduction in HF incidence. Unequivocal evidence from RCTs has shown that ACE inhibitors reduce mortality from STEMI.[1] These trials can be grouped into two categories. The first group *selected* MI patients for randomization on the basis of features indicative of increased mortality, such as left ventricular ejection fraction (LVEF) lower than 40%, clinical signs and symptoms of HF, anterior location of infarction, and abnormal wall motion score index (**Fig. 59.17**). The second group consisted of *unselective* trials that randomized all patients with MI provided that they had a minimum systolic BP of approximately 100 mm Hg (ISIS-4, GISSI-3 [Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico], CONSENSUS II [Cooperative New Scandinavian Enalapril Survival Study II], and Chinese Captopril Study) (**Fig. 59.18**). With the exception of the SMILE (Survival of Myocardial Infarction Long-Term Evaluation) study, all the selective trials initiated ACE inhibitor therapy between 3 and 16 days after MI and maintained it for 1 to 4 years, whereas the unselective trials all initiated treatment within the first 24 to 36 hours and maintained it for only 4 to 6 weeks.

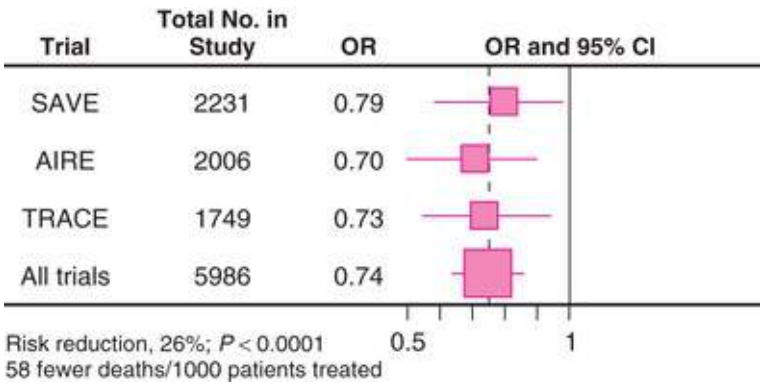


FIGURE 59.17 Effect of ACE inhibitors on mortality after MI—results from long-term trials. (From Gornik H, O'Gara PT. Adjunctive medical therapy. In Manson JE et al, editors. Clinical Trials in Heart Disease: a Companion to Braunwald's Heart Disease. Philadelphia: Saunders; 2004, p 114.)

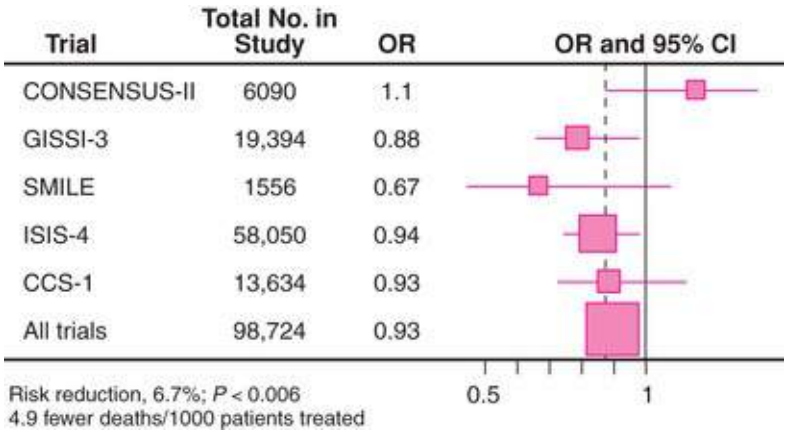


FIGURE 59.18 Effects of ACE inhibitors on mortality after MI—results from short-term trials. (From Gornik H, O'Gara PT. Adjunctive medical therapy. In Manson JE et al, editors. Clinical Trials in Heart Disease: a Companion to Braunwald's Heart Disease. Philadelphia: Saunders; 2004, p 114.)

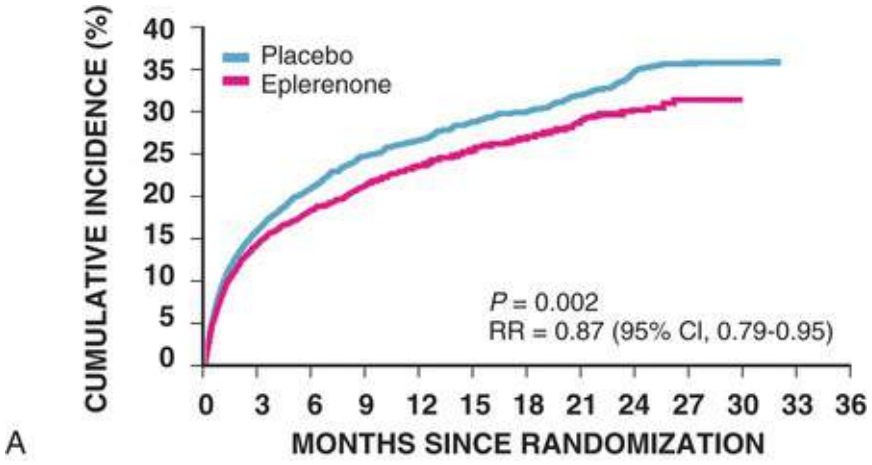
A consistent survival benefit was observed in all the trials already noted, except for CONSENSUS II, the one study that used an IV preparation early in the course of MI. An estimate of the mortality benefit of ACE inhibitors in the unselective trials with a short duration of therapy was 5 lives saved per 1000 patients treated. Analysis of these unselective short-term trials indicates that approximately one third of the lives saved occurred within the first 1 to 2 days. Certain subgroups, such as patients with anterior infarction, showed proportionately greater benefit with the early administration (11 lives saved per 1000) of ACE inhibitors. Not unexpectedly, greater survival benefits of 42 to 76 lives saved per 1000 patients treated were obtained in the selective trials with a long duration of therapy. Of note, a general 20% reduction in the risk for death attributable to ACE inhibitor treatment occurred in the selective trials. The reduction in mortality with ACE inhibitors was accompanied by significant reductions in the development of HF, thus supporting the underlying pathophysiologic rationale for administering this class of drugs to patients with STEMI. In addition, some data suggest that chronic administration of ACE inhibitors after STEMI reduces the incidence of ischemic events, including recurrent MI and the need for coronary revascularization.[26]

The mortality benefits of ACE inhibitors add to those achieved with aspirin and beta blockers. The benefits of ACE inhibition appear to be a class effect because several agents have been associated with reduced mortality and morbidity. To replicate these benefits in clinical practice, however, physicians should select a specific agent and prescribe the drug according to the protocols used in the clinical trials.[94] The major contraindications to ACE inhibitors in patients with STEMI include hypotension in the setting of adequate preload, known hypersensitivity, and pregnancy. Adverse reactions include hypotension, especially after the first dose, and intolerable cough; much less often, angioedema can occur.

An alternative method of pharmacologic inhibition of the RAAS is the administration of angiotensin II receptor–blocking agents (ARBs). The VALIANT (Valsartan in Acute Myocardial Infarction) trial compared the effects of the ARB valsartan, valsartan and captopril, and captopril alone on mortality in patients with acute MI complicated by LV systolic dysfunction and/or HF within 10 days of MI.[26] Mortality rates were similar in the three treatment groups: 19.9% with valsartan, 19.3% with valsartan plus captopril, and 19.5% with captopril alone. The combination of the ACE and the ARB caused more unwanted actions; thus drugs from these classes should not be combined.

Aldosterone blockade is another pharmacologic strategy for inhibition of the RAAS. The EPHESUS (Eplerenone Post-AMI Heart Failure Efficacy and Survival) trial randomly assigned 6642 patients with acute MI *complicated by left ventricular dysfunction and heart failure* to the selective aldosterone-blocking agent eplerenone or placebo in conjunction with contemporary postinfarction

pharmacotherapy.[95,96] During a mean follow-up of 16 months, a 15% reduction occurred in the RR for mortality in favor of eplerenone. Eplerenone also reduced CV mortality or hospitalization for CV events (**Fig. 59.19**). Serious hyperkalemia (serum potassium [K^+] concentration, 6 mmol/L) occurred in 5.5% of patients in the eplerenone group compared with 3.9% in the placebo group ($P = 0.002$). In contrast, in the ALBATROSS (Aldosterone Lethal Effects Blocked in Acute MI Treated with or without Reperfusion to Improve Outcome and Survival at Six Months Follow-up) trial, early mineralocorticoid antagonism versus placebo in an expanded population of patients with MI, *including both STEMI and non–ST elevation MI, and patients without left ventricular function or heart failure*, did not reduce the primary outcome of death, cardiac arrest, ventricular arrhythmia, implantable cardioverter-defibrillator (ICD) placement, or HF.[97] However, an exploratory analysis by MI type found a reduction in all-cause death (HR, 0.20; 95% CI 0.06 to 0.70) in the subgroup of patients with STEMI ($n = 1229$). Further studies are necessary to determine if a mineralocorticoid receptor antagonist (MRA) improves outcomes in all STEMI patients, regardless of HR or LV dysfunction.



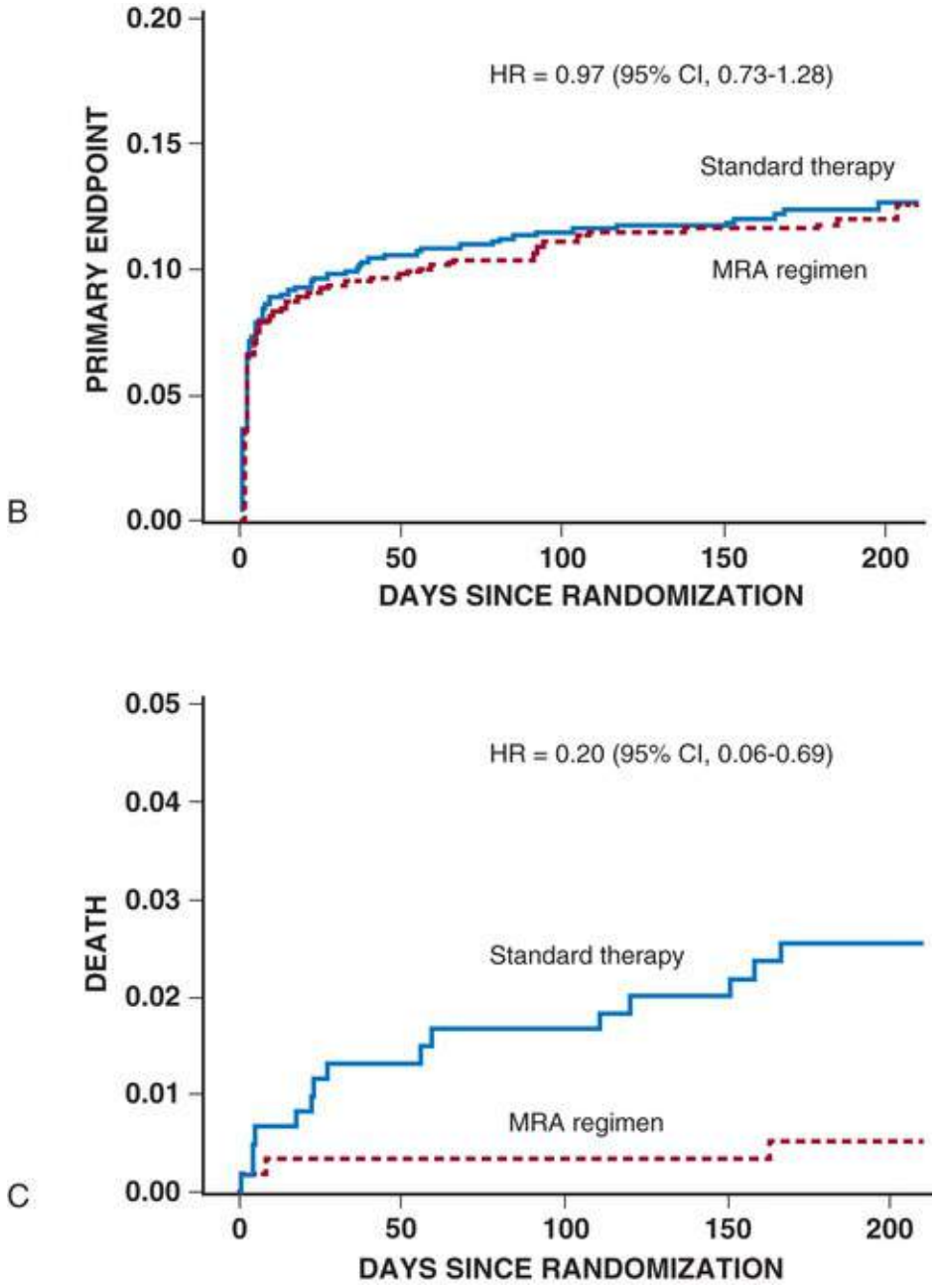


FIGURE 59.19 Mineralocorticoid receptor antagonism (MRA) following MI in patients with and without heart failure or left ventricular dysfunction. **A,** Eplerenone significantly reduced death from cardiovascular causes or hospitalization for cardiovascular events in the EPHESUS (Eplerenone Post-AMI Heart Failure Efficacy and Survival) trial in patients with acute MI *complicated by left ventricular dysfunction and heart failure*. **B,** The ALBATROSS (Aldosterone Lethal Effects Blocked in Acute MI Treated with or without Reperfusion to Improve Outcome and Survival at Six Months Follow-up) trial found no difference in the primary outcome of death, cardiac arrest, ventricular arrhythmia, ICD placement, or heart failure with early MRA versus placebo in acute MI *with or without left ventricular function or heart failure*. **C,** An exploratory subgroup analysis in patients with STEMI identified a reduction in all-cause death. (Modified from Pitt B et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:14, and Beygui F et al. Early aldosterone blockade in acute myocardial infarction: the ALBATROSS randomized clinical trial. J Am Coll Cardiol 2016;67(16):1917-27.)

Recommendations

After administration of aspirin and initiation of reperfusion strategies and, when appropriate, beta blockers, *all* patients with STEMI should be considered for inhibition of the RAAS. Although few disagree with the recommendation that high-risk STEMI patients (elderly, anterior infarction, previous infarction, Killip class II or greater, and asymptomatic patients with evidence of depressed global ventricular function on imaging) should receive lifelong treatment with ACE inhibitors, some have

proposed short-term (4 to 6 weeks) therapy for a broader group of patients on the basis of the pooled results of the unselective mortality trials.[1]

Considering all the data available, we favor a strategy of an initial trial of oral ACE inhibitors in all patients with STEMI and HF, as well as in hemodynamically stable patients, commencing within the first 24 hours. ACE inhibition therapy should be continued indefinitely in patients with HF, evidence of a reduction in global function, or a large regional wall motion abnormality. In patients without these findings, long-term treatment with ACE inhibitors is based on other considerations related to the potential benefits on secondary prevention. ARBs are a clinically effective alternative to ACE inhibitors. Although not yet studied specifically among patients with acute MI, an angiotensin receptor-neprilysin inhibitor (ARNI) can be considered over an ACE inhibitor or ARB for long-term management in patients with chronic symptomatic HF with reduced EF, including patients with ischemic cardiomyopathy from prior MI.[98] Finally, long-term aldosterone blockade should be instituted in high-risk patients following STEMI (EF <40%, clinical HF, diabetes mellitus) who are already receiving an ACE inhibitor and beta blocker and do not have contraindications. The small but definite increase in the risk for serious hyperkalemia when aldosterone blockade is prescribed, particularly when other measures for RAAS inhibition are used concurrently, warrants periodic monitoring of the serum K^+ level.[96]

Nitrates

The potential for reductions in ventricular filling pressure, wall tension, and cardiac work, coupled with improvement in coronary blood flow, especially in ischemic zones, and antiplatelet effects, makes nitrates a logical and attractive pharmacologic intervention in patients with STEMI.[1] Administration of nitrates reduces pulmonary capillary wedge pressure (PCWP) and systemic arterial pressure, LV chamber volume, infarct size, and the incidence of mechanical complications. Nevertheless, routine administration of nitrates does not alter survival in patients with STEMI. Although a meta-analysis of 10 trials conducted in the prefibrinolytic era showed nitrate therapy to be associated with a reduction in mortality,[71] two megatrials of nitrate therapy (GISSI-3 and ISIS-4) conducted in the reperfusion era demonstrated no benefit on major CV outcomes.[1]

With the aim of controlling hypertension or treating HF, IV nitroglycerin can be administered safely to patients with evolving STEMI as long as the dose is titrated to avoid induction of reflex tachycardia or systemic arterial hypotension. Patients with inferior wall infarction may be sensitive to an excessive fall in preload, particularly with concurrent RV infarction.[1] In such cases, nitrate-induced venodilation could impair cardiac output and reduce coronary blood flow, thus worsening rather than improving myocardial oxygenation.

Clinically significant methemoglobinemia, although rare, can develop when unusually large doses of nitrates are administered. This problem is important not only for its potential to cause symptoms of lethargy and headache, but also because elevated methemoglobin levels can impair the O_2-carrying capacity of blood and potentially exacerbate ischemia. Dilation of the pulmonary vasculature supplying poorly ventilated lung segments may produce a ventilation-perfusion mismatch. Tolerance to IV nitroglycerin (as manifested by increasing nitrate requirements) develops in many patients, often as soon as 12 hours after the infusion is started.

Recommendations

Nitroglycerin is indicated for the relief of persistent pain and as a vasodilator in patients with infarction associated with LV failure or hypertension. In the absence of recurrent angina or HF, we do not routinely

prescribe nitrates for patients with STEMI. Long-term nitrates have no clear benefit in asymptomatic patients, and we therefore do not prescribe them beyond the first 48 hours in patients without angina or LV failure.

Calcium Channel Antagonists

Despite sound experimental and clinical evidence of an anti-ischemic effect, calcium antagonists have not been helpful in the acute phase of STEMI, and several systematic overviews have raised concern about an increased risk for mortality when these agents, particularly short-acting dihydropyridines, are prescribed on a routine basis. Nondihydropyridine calcium channel–blocking agents (verapamil and diltiazem) can be given to slow a rapid ventricular response in atrial fibrillation in patients for whom beta blockers are ineffective. These agents should be avoided in patients with Killip class II or greater.

Other Therapies

Magnesium

A functional deficit in available magnesium may develop in patients with STEMI. Because of the risk for cardiac arrhythmias when electrolytes are deficient in the early phase of infarction, patients with STEMI should have their serum magnesium measured on admission. We advocate repleting magnesium deficits to maintain a serum magnesium level of 2 mEq/L or greater. In the presence of hypokalemia, the serum magnesium level should be rechecked and repleted if necessary because it is often difficult to correct a potassium deficit in the presence of a concurrent magnesium deficit. There is no indication for routine IV administration of magnesium to patients with STEMI.

Glucose Control During ST-Elevation Myocardial Infarction

During the acute phase of STEMI, catecholamine levels increase in both the blood and ischemic myocardium. Insulin levels remain low, whereas cortisol, glucagon, and FFA levels increase. These factors may contribute to an elevation in the blood glucose level, which should be measured routinely on admission. Intensive insulin therapy to control blood glucose strictly is no longer recommended routinely for patients with MI.[99] Blood glucose levels should be maintained below 180 mg/dL, if possible, while avoiding hypoglycemia[1] (**see Chapter 51**).

A series of small trials suggested that infusions of glucose-insulin-potassium (GIK) to patients with STEMI were beneficial, but the CREATE-ECLA (Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation–Estudios Cardiologicos Latinoamerica) investigators randomly assigned 20,201 patients with STEMI (83% of whom received reperfusion therapy) to GIK or placebo and found no impact on mortality (30-day mortality, 9.7% in control and 10% in GIK group).[100,101] In addition, prehospital administration of GIK did not improve the primary endpoint of progression to MI in patients with ACS.[102] Thus, in the contemporary era of management of STEMI in which other effective therapies (reperfusion, aspirin, ACE inhibitors) are administered, routine use of GIK infusions appears to have no benefit.

Other Agents

Multiple adjunctive pharmacotherapies to prevent inflammatory damage in the infarct zone have been investigated but have not shown clinical benefit. For example, *pexelizumab,* a monoclonal antibody against the C5 component of complement, had no effect on infarct size in patients with STEMI treated

with either fibrinolytics or PCI or on mortality in patients treated with primary PCI.[103] The anti-inflammatory agent *losmapimod*, a p38 mitogen-activated protein kinase (MAPK) inhibitor that reduces cytokine amplification in ACS, did not reduce the short-term risk of CV death, MI, or severe recurrent ischemia in 3503 patients with acute MI.[104] Similarly, *darapladib*, an oral, selective inhibitor of the lipoprotein-associated phospholipase A_2 enzyme, did not alter the composite of CV death, MI, or stroke in 13026 patients with acute MI in the SOLID-TIMI 52 (Stabilization of Plaques Using Darapladib) trial.[105]

Hemodynamic Disturbances

Hemodynamic Assessment

Patients with clinically uncomplicated STEMI do not require invasive hemodynamic monitoring because clinical evaluation can assess the status of the circulation. Routine assessments in patients with STEMI should include monitoring of the heart rate and rhythm, repeated measurement of systemic arterial pressure by cuff, repeated auscultation of the lung fields for pulmonary congestion, measurement of urine output, examination of the skin for evidence of the adequacy of perfusion, and monitoring for hypoxemia.

In patients with STEMI who have clinical signs and symptoms of HF, assessment of the degree of hemodynamic compromise is important. Central venous pressure (CVP) reflects right rather than LV function. RV function—and therefore systemic venous pressure—may be normal or almost so in patients with substantial LV failure. Conversely, patients with RV failure caused by RV infarction may exhibit elevated right atrial (RA) pressure and CVP despite normal LV function. Low values for RA pressure and CVP imply hypovolemia, whereas elevated RA pressure usually results from RV failure secondary to LV failure, pulmonary hypertension, RV infarction, or less often, tricuspid regurgitation or pericardial tamponade.

In select patients with complicated STEMI, it may be useful to monitor invasively with an intra-arterial catheter and a pulmonary artery (PA) catheter for measurement of PA, PA occlusive, and RA pressures, as well as estimation of cardiac output. In patients with hypotension, a Foley catheter should be considered for continuous measurement of urine output.

Monitoring of Pulmonary Artery Pressure

Accurate determination of hemodynamics by clinical assessment can be difficult in critically ill patients. Use of a PA catheter thus often leads to important changes in therapy. Before inserting a PA catheter into a patient with STEMI, the physician must believe that the potential benefit of the information that can obtained outweighs any potential risks. Major complications from PA catheters are uncommon, but severe problems can occur, including sepsis, pulmonary infarction, and PA rupture. Minimized duration of catheterization and strict adherence to aseptic technique can diminish the risk. Using antiseptic-impregnated dressings can also reduce catheter-related bloodstream infections.

Accumulating evidence from settings other than STEMI suggests that routine invasive hemodynamic monitoring does not improve outcomes. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) Trial demonstrated no difference in death or hospitalization at 6 months, but increased rates of adverse events (21.9% versus 11.5%; $P = 0.04$) in 433 patients with HF not accompanied by shock randomly assigned to placement of a PA catheter or to noninvasive standard care.[94] A meta-analysis of data for 5051 patients from 13 RCTs of PA

catheterization in patients undergoing surgery admitted to the ICU with advanced HF or diagnosed with acute respiratory distress syndrome (ARDS) or sepsis showed no difference in mortality.[94] Based on these limited data and expert consensus, placement of a PA catheter is recommended in only a subset of patients, including those with presumed cardiogenic shock and need for escalating vasopressor therapy or mechanical circulatory support; those exhibiting clinical decompensation with equivocal findings on assessment of filling pressures, perfusion, and vascular tone (i.e., to assist with determination of shock type); and patients with ongoing significant symptoms or dependence on inotropes despite attempts at noninvasive optimization of recommended therapies (**Table 59.7**). In the setting of STEMI, PA catheterization is reasonable for diagnostic and management purposes in patients with mechanical lesions (or suspected lesions) such as severe mitral regurgitation or a ruptured ventricular septum or RV infarction.[94,106] Noninvasive methods of determination of cardiac output, such as pulse contour analysis and thoracic electrical bioimpedance, are also available.[107]

TABLE 59.7

Indications for Hemodynamic Monitoring in Patients with ST-Elevation Myocardial Infarction

Management of complicated acute myocardial infarction
Shock with unclear clinical assessment of hemodynamics (e.g. filling pressures, vascular tone)
Ventricular septal rupture versus acute mitral regurgitation
Severe cardiogenic shock caused by right or left ventricular failure with a need for escalating vasopressor, inotropic, or mechanical circulatory support
Refractory ventricular tachycardia
Difficulty differentiating severe pulmonary disease from left ventricular failure with available noninvasive data
Assessment of cardiac tamponade

Data from Gore JM, Zwernet PL. Hemodynamic monitoring of acute myocardial infarction. In Francis GS, Alpert JS, editors. Modern Coronary Care. Boston: Little, Brown; 1990, p 138; and Yancy CW et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128(16):e240-327.

Hemodynamic Abnormalities

In 1976, Swan, Forrester, and associates measured cardiac output and wedge pressure simultaneously in a large series of patients with acute MI and identified four major hemodynamic subsets of patients (**Table 59.8**): (1) patients with normal systemic perfusion and without pulmonary congestion (normal cardiac output and normal wedge pressure), (2) patients with normal perfusion and pulmonary congestion (normal cardiac output and elevated wedge pressure), (3) patients with decreased perfusion but without pulmonary congestion (reduced cardiac output and normal wedge pressure), and (4) patients with decreased perfusion and pulmonary congestion (reduced cardiac output and elevated wedge pressure). This classification, which overlaps with a crude clinical classification proposed earlier by Killip and Kimball (**Table 59.8**), has proved quite useful, but it should be noted that patients frequently pass from one category to another with therapy and sometimes apparently even spontaneously.

TABLE 59.8

Hemodynamic Classification of Patients with Acute Myocardial Infarction

A. BASED ON CLINICAL EXAMINATION		B. BASED ON INVASIVE MONITORING	
Class	**Definition**	**Subset**	**Definition**
I	Rales and S_3 absent	I	Normal hemodynamics PCWP <18, CI >2.2
II	Crackles, S_3 gallop, elevated jugular venous pressure	II	Pulmonary congestion PCWP >18, CI >2.2
III	Frank pulmonary edema	III	Peripheral hypoperfusion PCWP <18, CI <2.2
IV	Shock	IV	Pulmonary congestion and peripheral hypoperfusion PCWP >18, CI <2.2

CI, Cardiac index; *PCWP,* pulmonary capillary wedge pressure.

A, Modified from Killip T, Kimball J. Treatment of myocardial infarction in a coronary care unit: a two-year experience with 250 patients. Am J Cardiol 1967;20:457; **B,** from Forrester J et al. Medical therapy of acute myocardial infarction by the application of hemodynamic subsets. N Engl J Med 1976;295:1356.

Hemodynamic Subsets

The hemodynamic groupings shown in **Tables 59.8 and 59.9** allow rational approaches to therapy. The goals of hemodynamic therapy include maintenance of ventricular performance, BP support, and protection of jeopardized myocardium. Because these goals may occasionally be at cross-purposes, recognition of the hemodynamic profile, as assessed clinically or as available from hemodynamic monitoring, may be needed to design an optimal therapeutic management strategy.

TABLE 59.9

Hemodynamic Patterns for Common Clinical Conditions

Cardiac Condition	CHAMBER PRESSURE (mm Hg)				
	RA	**RV**	**PA**	**PCW**	**CI**
Normal	0-6	25/0-6	25/0-12	6-12	≥2.5
AMI without LVF	0-6	25/0-6	30/12-18	≤18	≥2.5
AMI with LVF	0-6	30-40/0-6	30-40/18-25	>18	>2.0
Biventricular failure	>6	50-60/>6	50-60/25	18-25	>2.0
RVMI	12-20	30/12-20	30/12	≤12	<2.0
Cardiac tamponade	12-16	25/12-16	25/12-16	12-16	<2.0
Pulmonary embolism	12-20	50-60/12-20	50-60/12	<12	<2.0

AMI, Acute myocardial infarction; *CI,* cardiac index; *LVF,* left ventricular failure; *PA,* pulmonary artery; *PCW,* pulmonary capillary wedge; *RA,* right atrium; *RV,* right ventricle; *RVMI,* right ventricular myocardial infarction.

From Gore JM, Zwernet PL. Hemodynamic monitoring of acute myocardial infarction. In Francis GS, Alpert JS, editors. Modern Coronary Care. Boston: Little, Brown: 1990, pp 139-64.

Hypotension in the Prehospital Phase

Hypotension associated with bradycardia often reflects excessive vagotonia. Relative or absolute hypovolemia is often present when hypotension occurs with a normal or rapid HR. Marked diaphoresis, reduction of fluid intake, or vomiting during the period preceding and accompanying the onset of STEMI may contribute to the development of hypovolemia. Even if the effective vascular volume is normal, relative hypovolemia may be present because ventricular compliance is reduced in cases of STEMI, and LV filling pressure as high as 20 mm Hg may be necessary to provide optimal preload.

Management.

In the absence of HF, when hypotension is suspected to result from excessive vagotonia, patients should be placed in the reverse Trendelenburg position. In patients with sinus bradycardia and hypotension, atropine should be administered (0.3 to 0.6 mg intravenously, repeated at 3- to 10-minute intervals up to 2 mg). If these measures do not correct the hypotension, normal saline should be administered intravenously while monitoring for signs of HF. Because of the poor correlation between LV filling pressure and mean RA pressure, assessment of CVP can be of limited value as a guide to fluid therapy. Administration of positive inotropic or vasopressor agents is indicated during the prehospital phase if systemic hypotension persists despite correction of hypovolemia.

The Hyperdynamic State

When infarction is not complicated by hemodynamic impairment, no therapy other than general supportive measures and treatment of arrhythmias is necessary. However, if the hemodynamic profile involves a hyperdynamic state—that is, elevation of the sinus rate, arterial pressure, and CI, occurring singly or together in the presence of a normal or low LV filling pressure—treatment with beta blockers is indicated. Presumably, the increased HR and BP result from inappropriate activation of the sympathetic nervous system, possibly because of augmented release of catecholamines triggered by pain or anxiety.

Left Ventricular Failure

Left ventricular dysfunction is one of the most important predictors of mortality following STEMI[108-112] (**Fig. 59.20**). In patients with STEMI, either systolic dysfunction alone or both systolic and diastolic dysfunction can occur. LV diastolic dysfunction leads to pulmonary venous hypertension and pulmonary congestion. Clinical manifestations of LV failure become more common as the extent of injury to the left ventricle increases. In addition to infarct size, other important predictors of the development of symptomatic LV dysfunction include advanced age and diabetes.[110] Mortality increases in association with the severity of the hemodynamic deficit.[108]

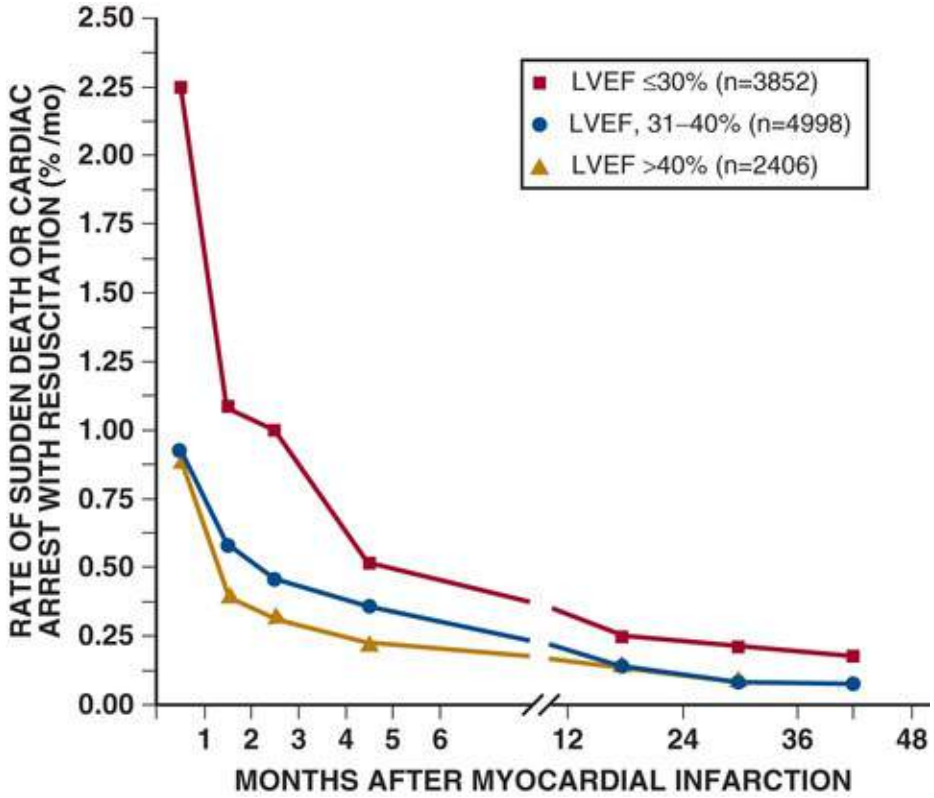


FIGURE 59.20 Rate of sudden death or cardiac arrest with resuscitation stratified by time from MI. The high rate of sudden death or cardiac arrest occurs within the first month after MI in all strata of left ventricular ejection fraction (LVEF) and declines exponentially to a plateau after 12 months. (From Zaman S, Kovoor P. Sudden cardiac death early after myocardial infarction: pathogenesis, risk stratification, and primary prevention. Circulation 2014;129(23):2426-35.)

Therapeutic Implications

Classification of patients with STEMI by hemodynamic subsets has therapeutic relevance. As already noted, patients with low to normal wedge pressure and hypoperfusion may benefit from infusion of fluids because the peak stroke volume value is not usually attained until LV filling pressure reaches 18 to 24 mm Hg. However, a low level of LV filling pressure does not necessarily imply that the LV damage is slight. Such patients may be relatively hypovolemic or may have an RV infarct with or without severe LV damage.

The relationship between ventricular filling pressure and cardiac index when preload is increased by infusion of fluid can provide valuable hemodynamic information in addition to that obtained from baseline measurements. For example, the ventricular function curve rises steeply (marked increase in cardiac index small increase in filling pressure) in patients with normal LV function and hypovolemia, whereas the curve rises gradually or remains flat in patients with a combination of hypovolemia and depressed cardiac function. Invasive hemodynamic monitoring can help guide therapy in patients with severe LV failure (PCWP >18 mm Hg and cardiac index <2.2 liters/min/m^2). Although positive inotropic agents can be useful, they do not represent the initial therapy of choice for patients with STEMI. Instead, HF, in the presence of elevated PCWP, is managed most effectively first by reducing ventricular preload and then, if possible, by lowering afterload. Arrhythmias can contribute to hemodynamic compromise and should be treated promptly in patients with LV failure.

Hypoxemia

In STEMI complicated by HF, a combination of pulmonary vascular engorgement (and in some cases,

pulmonary interstitial edema), diminished vital capacity, and in some patients, contributory respiratory depression from narcotic analgesics may cause hypoxemia. Hypoxemia can impair the function of ischemic tissue at the margin of the infarct and thereby contribute to establishing or perpetuating the vicious cycle. However, augmentation of F_{IO_2} in patients without hypoxemia may increase systemic vascular resistance (SVR) and arterial pressure, promote coronary vasoconstriction, and result in more oxidative stress and greater infarct size.[20] As a result, Sa_{O_2} can be estimated by pulse oximetry, and O_2 therapy can be omitted if the oximetric findings are normal (see earlier, General Treatment Measures).[1] On the other hand, in patients with STEMI and arterial hypoxemia, increasing F_{IO_2} by facemask should be used initially, but if Sa_{O_2} cannot be maintained above 85% to 90% with 100% F_{IO_2}, strong consideration should be given to endotracheal intubation and positive-pressure ventilation. Positive end-expiratory pressure (PEEP) may diminish systemic venous return and reduce effective LV filling pressure. This effect may require reducing the PEEP amount, initiating normal saline infusions to maintain LV filling pressure, or adjusting the rate of infusion of vasodilators (e.g., nitroglycerin). Because myocardial ischemia can occur during the return to unsupported spontaneous breathing, weaning should be accompanied by observation for signs of ischemia.

Diuretics

Mild HF in patients with STEMI frequently responds well to diuretics such as furosemide administered intravenously in doses of 10 to 40 mg, repeated at 3- to 4-hour intervals if necessary. The resultant decrease in PCWP reduces dyspnea, and the lowering of LV wall tension that accompanies the reduction in LV diastolic volume diminishes myocardial oxygen requirements and may lead to improvement in contractility and augmentation of EF, stroke volume, and cardiac output. The reduction in LV filling pressure may also enhance myocardial oxygen delivery by diminishing the impedance to coronary perfusion attributable to the elevated ventricular wall tension. It may also improve arterial oxygenation by reducing pulmonary vascular congestion.

IV furosemide reduces pulmonary vascular congestion and pulmonary venous pressure within 15 minutes, before renal excretion of sodium and water has occurred; presumably this action results from a direct dilating effect of this drug on the systemic venous bed. LV filling pressure generally should not be reduced much below 18 mm Hg, the lower range being associated with optimal LV performance in patients with STEMI, because this may reduce cardiac output further and cause arterial hypotension. Excessive diuresis may also result in hypokalemia and magnesium loss.

Afterload Reduction

Myocardial oxygen requirements depend on LV wall stress, which in turn is proportional to the product of the peak developed LV pressure, volume, and wall thickness. IV vasodilator therapy should be considered in patients with STEMI complicated by (1) HF unresponsive to treatment with diuretics, (2) hypertension, (3) mitral regurgitation (MR), or (4) ventricular septal defect (VSD). In these patients, treatment with vasodilator agents increases stroke volume and may reduce myocardial oxygen requirements and thereby lessens ischemia. Hemodynamic monitoring of systemic arterial pressure and in many cases PCWP and cardiac output in patients treated with these agents is generally indicated. Improvement in cardiac performance and energetics requires three simultaneous effects: (1) reduction of LV afterload, (2) avoidance of excessive systemic arterial hypotension to maintain effective coronary perfusion pressure, and (3) avoidance of excessive reduction of ventricular filling pressure with consequent diminution of cardiac output.

Vasodilator therapy is particularly useful when STEMI is complicated by MR or rupture of the ventricular septum. In such patients, vasodilators alone or in combination with intra-aortic balloon counterpulsation can sometimes provide sufficient hemodynamic stabilization to permit definitive studies, as well as to prepare the patient for early surgical intervention. Because of the precarious state of patients with complicated infarction and the need for meticulous adjustment of dosage, therapy is best initiated with agents that can be administered intravenously and have a short duration of action, such as nitroprusside or nitroglycerin.

Nitroglycerin

Animal experiments have shown this drug to be less likely than nitroprusside to produce "coronary steal" (i.e., diversion of blood flow from the ischemic to the nonischemic zone). Therefore, apart from consideration of its routine use in STEMI patients discussed earlier, it may be a particularly useful vasodilator in patients with STEMI complicated by LV failure. A dosage of 10 to 15 µg/min is infused, and the dose is increased by 10 µg/min every 5 minutes until the desired effect (improvement in hemodynamics or relief of ischemic chest pain) is achieved or a decline in systolic arterial pressure to 90 mm Hg or by more than 15 mm Hg has occurred. Although both nitroglycerin and nitroprusside lower systemic arterial pressure, systemic vascular resistance, and the heart rate–systolic blood pressure product, the reduction in LV filling pressure is more prominent with nitroglycerin because of its relatively greater effect than nitroprusside on venous capacitance vessels. Nevertheless, in patients with severe LV failure, cardiac output often increases despite the reduction in LV filling pressure produced by nitroglycerin.

Oral Vasodilators.

The use of oral vasodilators for the treatment of chronic HF is discussed in **Chapter 25**. Patients with STEMI and persistent HF should receive long-term RAAS inhibition, including an ACE inhibitor or ARB, and an aldosterone antagonist.[1,94,98] Treatment with an ARNI may be indicated in patients with reduced EF who develop chronic HF after MI; however, patients with recent ACS were excluded from the pivotal trial of sacubitril/valsartan.[113] The reduced ventricular load achieved with RAAS inhibition decreases the left ventricle remodeling that typically occurs after STEMI and reduces development of HF and risk for death.[94,98]

Digitalis (see Chapter 25).

Although digitalis increases the contractility and oxygen consumption of normal hearts, when HF is present, the diminution in heart size and wall tension frequently results in a net reduction of myocardial oxygen requirements. In animals, digoxin fails to improve ventricular performance immediately following experimental coronary occlusion, but can prove beneficial when administered several days later. The absence of early beneficial effects may result from the inability of ischemic tissue to respond to digitalis or the already maximal stimulation of contractility of the normal heart by circulating and neuronally released catecholamines.

Although the issue is still controversial, digitalis glycosides may increase the incidence of arrhythmias when given to patients in the first few hours after the onset of STEMI, particularly in the presence of hypokalemia. Administration of digitalis to patients with STEMI in the hospital phase should generally be reserved for the management of supraventricular tachyarrhythmias, such as atrial flutter and fibrillation, in the setting of poor LV function and HF persisting despite treatment with diuretics or

vasodilators.

Vasoactive Medications.

In addition to early coronary reperfusion, preservation of cardiac output, BP, and end-organ perfusion is paramount in patients with acute MI complicated by cardiogenic shock. Inotropes and vasopressors may be administered with the goal of maintaining perfusion so as to preserve end-organ function. To achieve this goal, therapy generally targets support of arterial pressure. Once BP is stabilized with resuscitation and vasopressor therapy, treatment can be tailored to address the underlying pathophysiology (e.g., addition of further inotropic support or vasodilator therapy). In general, the dose of vasopressor and inotropic therapy should be maintained at the minimal dose and duration of therapy necessary to achieve these aims, since these agents can have adverse consequences (e.g., increased myocardial oxygen consumption, arrhythmias).

Beta-Adrenergic Agonists.

When LV failure is severe, as manifested by marked a reduction in the cardiac index (<2.2 liters/min/m^2), and PCWP is at optimal (18 to 24 mm Hg) or excessive (>24 mm Hg) levels despite therapy with diuretics, beta-adrenergic agonists are indicated.[114] Dopamine, norepinephrine and dobutamine can be useful in patients with STEMI and reduced cardiac output, increased LV filling pressure, pulmonary vascular congestion, and hypotension.

Dopamine has dose-dependent stimulation of dopamine, $beta_1$ and $alpha_1$ receptors. At low doses, dopaminergic receptor stimulation predominates; at moderate doses, $beta_1$ activation results in augmentation of cardiac output and HR; at high doses, $alpha_1$ stimulation prevails, manifest as vasoconstriction (**Table 59.10**). Although "renal dosing" of dopamine was believed to improve urine output and renal protection in HF, this effect was not evident in an RCT of patients with acute HF and renal dysfunction.[115] Although dopamine is an important option as a vasopressor, particularly in patients with hypotension, it may cause tachycardia or tachyarrhythmias. Compared with norepinephrine, treatment with dopamine at doses up to 20 µg/kg/min was associated with a higher rate of tachyarrhythmias (24.1% versus 12.4%) among 1679 patients with shock in the SOAP (Sepsis Occurrence in Acutely Ill Patients) II trial. In a subgroup analysis of patients with cardiogenic shock (280, 17% of total trial population), dopamine was not only associated with more arrhythmic events but also with increased mortality (approximately 50% versus 40% at 28 days, log-rank *P* value = 0.03, *P* interaction by shock type = 0.87).[116]

TABLE 59.10

Inotropic and Vasopressor Agents: Indications, Dose Range, Receptor Binding, and Major Clinical Side Effects

			RECEPTOR BINDING*				
Drug	**Clinical Indication**	**Dose Range**	**A1**	**B1**	**B2**	**DA**	**Major Side Effects**
Catecholamines							
Dopamine	Shock (vasodilatory, cardiogenic) Symptomatic bradycardia unresponsive to atropine or pacing	2.0 to 20 (max 50) µg•kg^{-1}•min^{-1}	+++	++++	++	+++++	Severe hypertension (especially in patients taking nonselective beta blockers) Ventricular arrhythmias Cardiac ischemia Tissue ischemia, gangrene (high doses or caused by tissue extravasation)
Dobutamine	Low CO (decompensated HF, cardiogenic shock, sepsis-induced myocardial dysfunction)	2.0 to 20 (max 40) µg•kg^{-1}•min^{-1}	+	+++++	+++	N/A	Tachycardia Increased ventricular response rate in patients

	Symptomatic bradycardia unresponsive to atropine or pacing						with atrial fibrillation Ventricular arrhythmias Cardiac ischemia Hypotension
Norepinephrine	Shock (vasodilatory, cardiogenic)	0.01 to 3 μg•kg^{-1}•min^{-1}	+++++	+++	++	N/A	Arrhythmias Bradycardia Peripheral (digital) ischemia Hypertension (especially nonselective beta-blocker patients)
Epinephrine	Cardiac arrest Anaphylaxis Shock (cardiogenic, vasodilatory)	Infusion: 0.01 to 0.10 μg•kg^{-1}•min^{-1} Bolus: 1 mg IV every 3 to 5 min (max 0.2 mg/kg) IM: (1:1000):0.1 to 0.5 mg (max 1 mg)	+++++	++++	+++	N/A	Ventricular arrhythmias Severe hypertension Cardiac ischemia
Isoproterenol	Bradyarrhythmias (especially torsade des pointes) Brugada syndrome	2 to 10 μg/min	0	+++++	+++++	N/A	Ventricular arrhythmias Cardiac ischemia Hypertension
Phenylephrine	Hypotension (vagally mediated, medication induced) Increase MAP with aortic stenosis and hypotension Decrease left ventricular outflow tract gradient in HCM	Bolus: 0.1 to 0.5 mg IV every 10 to 15 min Infusion: 0.4 to 9.1 μg•kg^{-1}•min^{-1}	+++++	0	0	N/A	Reflex bradycardia Hypertension (especially with nonselective beta blockers) Severe peripheral and visceral vasoconstriction Tissue necrosis with extravasation
Phosphodiesterase Inhibitors (PDEIs)							
Milrinone	Low CO (decompensated HF, after cardiotomy)	Bolus: 50 μg/kg bolus over 10 to 30 min Infusion: 0.375 to 0.75 μg•kg^{-1}•min^{-1} (dose adjustment necessary for renal impairment)	N/A				Ventricular arrhythmias Hypotension Cardiac Ischemia Torsade des pointes
Amrinone	Low CO (refractory HF)	Bolus: 0.75 mg/kg over 2 to 3 min Infusion: 5 to 10 μg•kg^{-1}•min^{-1}	N/A				Arrhythmias; enhanced AV conduction (increased ventricular response rate in atrial fibrillation) Hypotension Thrombocytopenia Hepatotoxicity
Other Agents							
Vasopressin	Shock (vasodilatory, cardiogenic) Cardiac arrest	Infusion: 0.01 to 0.1 U/min (common fixed dose 0.04 U/min) Bolus: 40-U IV bolus	V1 receptors (vascular smooth muscle) V2 receptors (renal collecting duct system)				Arrhythmias Hypertension Decreased CO (at doses >0.4 U/min) Cardiac ischemia Severe peripheral vasoconstriction causing ischemia (especially skin) Splanchnic vasoconstriction
Levosimendan	Decompensated HF	Loading dose: 12 to 24 μg/kg over 10 min Infusion: 0.05 to 0.2 μg•kg^{-1}•min^{-1}	N/A				Tachycardia, enhanced AV conduction Hypotension

*0, Zero significant receptor affinity; + to +++++, minimal to maximal relative receptor affinity; *N/A,* not applicable.

A1, Alpha$_1$-adrenergic receptor; *AS,* aortic stenosis; *AV,* atrioventricular; *B1*, beta$_1$-adrenergic receptor; B2, beta$_2$-adrenergic receptor; *CO,* cardiac output; *DA*, dopamine receptors; *HCM,* hypertrophic cardiomyopathy; *HF,* heart failure; *IM,* intramuscular; *IV,* intravenous; *LVOT,* left ventricular outflow tract; *MAP,* mean arterial pressure; *max,* maximum.

From Overgaard CB, Dzavik V: Inotropes and vasopressors: review of physiology and clinical use in cardiovascular disease. *Circulation* 2008;118(10):1047-1056.

Norepinephrine increases myocardial oxygen consumption because of its peripheral vasoconstrictor and positive inotropic actions and thus had previously been avoided in patients with MI and shock (**Table 59.10**). However, based on the findings of SOAP-II, norepinephrine is generally recommended over dopamine, except in cases of relative bradycardia.

Dobutamine has a positive inotropic action comparable to that of dopamine, but a slightly less positive chronotropic effect, and vasodilatory rather than vasoconstrictor activity (**Table 59.10**).[114] As a result, it is useful in select patients whose HF persists despite treatment with diuretics, who are not hypotensive, and who are likely to benefit from both an enhancement in contractility and afterload reduction. As with all vasoactive medications, dobutamine must be given with constant monitoring of the ECG and systemic arterial pressure. In patients with STEMI who develop cardiogenic shock warranting treatment with dobutamine, we also generally place a PA catheter for assessment of PCWP and for frequent measurements of cardiac output. The dose should be reduced if significant tachycardia develops,

if supraventricular or ventricular tachyarrhythmias occur, or if ST-segment deviations increase.

Epinephrine is an activator of alpha- and beta-adrenergic receptors, resulting in increased HR, cardiac output, and vascular tone (**Table 59.10**). It is generally reserved for refractory shock as a second- or third-line agent, for anaphylaxis, or during cardiac arrest. Although epinephrine is recommended during cardiac arrest according to the advanced cardiovascular life support algorithm, studies suggest that those who received epinephrine in the setting of out-of-hospital cardiac arrest had higher rates of return of spontaneous circulation, but equivalent or even worse survival and neurologic function.[117,118]

Other Positive Inotropic Agents.

Milrinone is a noncatecholamine, nonglycoside, phosphodiesterase inhibitor with inotropic and vasodilating actions (**Table 59.10**).[114] Similar to dobutamine, it is useful in patients with cardiogenic shock without significant hypotension. Milrinone has a longer half-life than dobutamine (approximately 2.5 hours versus 2 minutes, with normal renal function) and also tends to correlate with greater pulmonary vasodilatation and fewer arrhythmic events. Calcium-sensitizing agents, such as levosimendan, may have some beneficial effects on CV outcomes, but these medications have shown little incremental value in randomized trials.[119]

Vasopressors.

Vasopressor therapy may be required to stabilize BP in cardiogenic or mixed shock. *Vasopressin,* or antidiuretic hormone (ADH), results in arterial smooth muscle contraction through V1 receptor agonism on the systemic vasculature (**Table 59.10**). Vasopressin is typically used for refractory vasodilatory shock, particularly septic shock. However, we also occasionally use vasopressin as a part of an "adrenergic-sparing" approach in patients with severe HF, particularly in the setting of mixed cardiogenic and vasodilatory shock, based on the hypothesis that endogenous vasopressin may be depleted over time in critically ill patients. Clinical trial data of outcomes are limited with vasopressin use in cardiogenic shock. *Phenylephrine,* a synthetic, selective $alpha_1$ agonist, is rarely used in cardiogenic shock because of potent vasoconstriction.

Cardiogenic Shock

Congestion and inadequate tissue or end-organ perfusion secondary to cardiac insufficiency characterize cardiogenic shock. This reduction in perfusion decreases O_2 and nutrient delivery to tissues, which if severe or protracted, can lead to multiorgan dysfunction and death. Cardiogenic shock complicating MI most often results from LV dysfunction (approximately 80%); the remainder have a mechanical defect (e.g., VSD, papillary muscle rupture) or predominant RV infarction[108,110] (**Fig. 59.21**). Patients with cardiogenic shock complicating STEMI are more likely to be older; to have a history of diabetes mellitus, previous MI, or HF; and to have sustained an anterior infarction at the time of development of shock. In the past, cardiogenic shock occurred in up to 20% of patients with STEMI, but estimates from recent large trials and observational data bases report an incidence rate of 5% to 8%.[120] When shock occurs, the prognosis remains poor, with in-hospital mortality rates of 40% to 60%, and few interventions, with the exception of prompt coronary revascularization, conclusively provide benefit.[108,109]

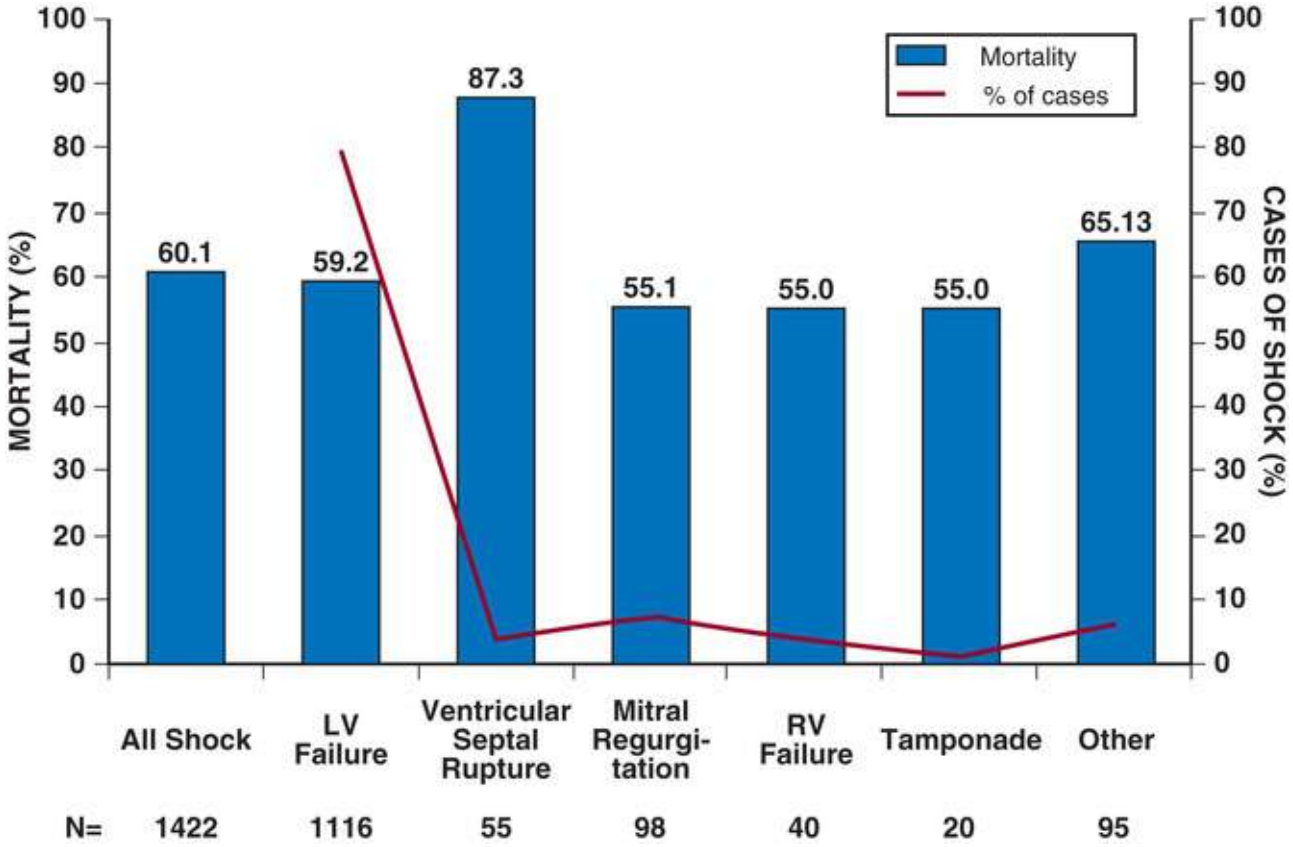


FIGURE 59.21 Mortality by etiology of cardiogenic shock following acute myocardial infarction (AMI). In-hospital mortality rates are shown for various primary etiologic conditions associated with death due to cardiogenic shock after AMI: left ventricular (LV) failure, ventricular septal rupture, acute severe mitral regurgitation, isolated right ventricular (RV) failure, cardiac tamponade/rupture (tamp), and "other" (includes previous severe valvular heart disease and excessive beta or calcium channel blockade). The proportion of patients in each category is shown. (Modified from Hochman JS et al. Cardiogenic shock complicating acute myocardial infarction—etiologies, management and outcome: a report from the SHOCK Trial Registry. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock? J Am Coll Cardiol 2000;36(3 Suppl A):1063-70.)

Pathologic Findings

At autopsy, more than two thirds of patients with cardiogenic shock demonstrate multivessel coronary disease, usually including the left anterior descending coronary artery (LAD). Almost all patients with cardiogenic shock exhibit thrombotic occlusion of the artery supplying the major region of recent infarction, with loss of 40% or more of LV mass.[108,110] Patients who die of cardiogenic shock often have "piecemeal" necrosis, that is, progressive myocardial necrosis from marginal extension of the infarct into an ischemic zone bordering the infarction. This finding is generally associated with persistent elevation of cardiac biomarkers. Such extensions and focal lesions probably result in part from the shock state itself. Early deterioration of LV function secondary to apparent extension of the infarction in some cases may result from expansion of the necrotic zone of myocardium without actual extension of the necrotic process. The hydrodynamic force that develops during ventricular systole can disrupt necrotic myocardial muscle bundles, with resultant expansion and thinning of the akinetic zone of myocardium, which in turn results in deterioration of overall LV function.

Pathophysiology

The shock state in patients with STEMI appears to be the result of a vicious cycle, as demonstrated in **Fig. 58.14**.

Diagnosis

Generally accepted criteria for cardiogenic shock include (1) frank or relative hypotension, defined by a systolic BP below 80 or 90 mm Hg or a reduction in mean arterial pressure (MAP) of 30 mm Hg; (2) inadequate cardiac index, defined as less than 1.8 liters/min/m^2 without mechanical or pharmacologic support, or less than 2.2 liters/min/m^2 with support; (3) elevated end-diastolic pressures on the right (>10 to 15 mm Hg) and/or left (>18 mm Hg) side of the heart; and (4) evidence of end-organ hypoperfusion.[108,120] End-organ hypoperfusion may manifest as altered mental status, decreased urine output, acute kidney injury, cool or mottled extremities, acute liver injury, or lactic acidosis.

Spurious estimates of LV end-diastolic pressure based on measurements of PA wedge pressure can occur in patients with marked MR, in which the tall *v* wave in the left atrial (and PA wedge) pressure tracing elevates the MAP above LV end-diastolic pressure. Accordingly, MR and other mechanical lesions (e.g., VSD, ventricular aneurysm, pseudoaneurysm) must be excluded before making the diagnosis of cardiogenic shock caused by impairment of ventricular function. Mechanical complications should be suspected in any patient with STEMI in whom circulatory collapse occurs. Patients with cardiogenic shock merit immediate hemodynamic, angiographic, and echocardiographic evaluation. It is important to exclude mechanical complications because primary therapy for such lesions usually requires immediate invasive treatment with intervening mechanical support of the circulation.

Medical Management

In cardiogenic shock caused by impaired ventricular function, inotropic and vasopressor agents can provide pharmacologic support to maintain MAP and augment cardiac output; these agents should be administered at the lowest possible doses. Although inotropes generally improve hemodynamics in these patients, unfortunately they do not appear to improve hospital survival significantly. Similarly, vasodilators may elevate cardiac output and reduce LV filling pressure, but lowering the already markedly reduced coronary perfusion pressure can compromise further myocardial perfusion and accelerate the vicious cycle illustrated in **Fig. 58.14**. Vasodilators may nonetheless be used in conjunction with mechanical circulatory support (see next section) and inotropic agents to increase cardiac output while sustaining or elevating coronary perfusion pressure.

Patients with cardiogenic shock usually have elevated SVR, although cardiogenic shock can be complicated by a systemic inflammatory response syndrome (SIRS) and a vasodilatory state, particularly with shock of longer duration or more profound severity.[108] When SVR is not elevated (i.e., <1800 dynes/sec/cm^5) in patients with cardiogenic shock, *inopressors*, or agents with inotropic and vasopressor properties, can be useful to maintain perfusion through preservation of MAP and augmentation of cardiac output.

Mechanical Circulatory Support

The theoretical benefits of mechanical circulatory support (MCS) include the ability to (1) maintain end-organ perfusion and prevent the progressive shock spiral, (2) reduce intracardiac filling pressures and congestion, (3) reduce LV volumes, wall stress, and myocardial oxygen consumption, (4) augment coronary perfusion, (5) support the circulation during complex coronary interventions, (6) allow time for recovery of stunned or hibernating myocardium, and (7) limit infarct size[121] (**see Chapter 29**). No definitive evidence has yet shown that MCS following MI improves outcomes, and data are lacking to define the optimal strategy for timing and choice of device.[121] As a result, based primarily on expert consensus, early placement of MCS may be considered in those with cardiogenic shock who fail to

stabilize quickly after initial interventions (e.g., reperfusion) and for those undergoing high-risk PCI (e.g., multivessel or unprotected left main) with severe HF or LV dysfunction[121] (**Fig. 59.22**).

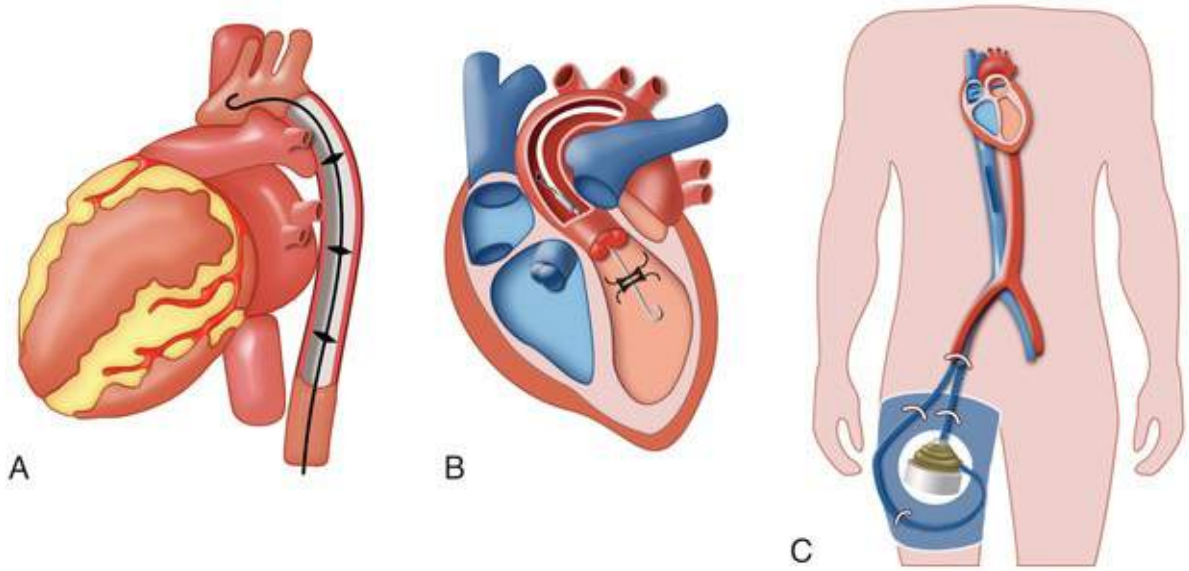
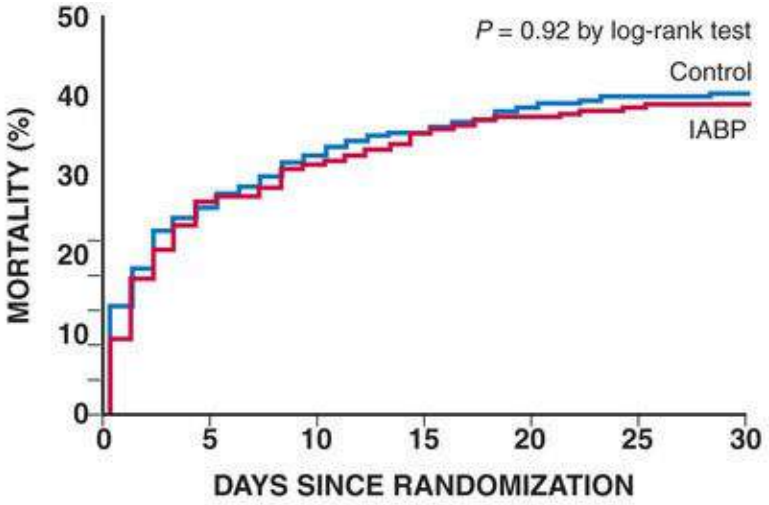


FIGURE 59.22 Schematic representation of examples of major categories of nonsurgical mechanical circulatory support. **A,** Intra-aortic balloon pump inserted into the descending aorta between the arch vessels and renal arteries. **B,** Impella Recover (Abiomed, Aachen, Germany). This rotational flow device is percutaneously inserted through the femoral artery and positioned across the aortic valve, with flow intake in the left ventricle and outflow in the aorta. **C,** TandemHeart (CardiacAssist, Pittsburgh). A cannula is inserted percutaneously through the right femoral vein and advanced toward the right atrium, where it is introduced by transatrial septal perforation, to establish inflow into an external rotational motor. A cannula in either femoral artery then provides the outflow. (Modified from Desai NR, Bhatt DL. Evaluating percutaneous support for cardiogenic shock: data shock and sticker shock. Eur Heart J 2009;30:2073.)

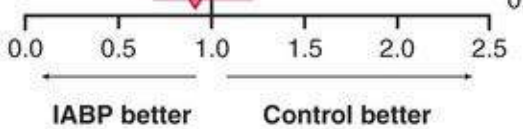
Intra-Aortic Balloon Counterpulsation

Intra-aortic balloon (IAB) counterpulsation continues to be used for the treatment of STEMI in three groups of patients: (1) those with hemodynamic instability who require support of the circulation for the performance of cardiac catheterization and angiography to assess lesions that are potentially correctable surgically or by angioplasty, (2) those with cardiogenic shock that does not respond to medical management, and rarely, (3) those with refractory ischemia that is not alleviated by other treatments, or who await definitive revascularization. In experimental animals, IAB counterpulsation decreases preload, increases coronary blood flow, and improves cardiac performance. Unfortunately, the improvement is often only temporary in patients with cardiogenic shock. Although a response to IAB counterpulsation correlates with better outcomes in observational studies and small randomized trials, in the largest randomized trial conducted to date, counterpulsation alone did not improve overall survival in patients with cardiogenic shock secondary to MI[122] (**Fig. 59.23**). Also, no benefit was observed in any clinically relevant subgroups. Nevertheless, IAB counterpulsation is reasonable in patients with cardiogenic shock whose condition does not stabilize with other interventions, and as a bridge to recovery or more advanced therapies.[1]



A

Baseline variable	No. of patients	IABP 30-day mortality (%)	Control 30-day mortality (%)	Relative risk (95% CI)	P value for interaction
Sex					0.61
Female	187	44.4	43.2	1.03 (0.74-1.43)	
Male	411	37.3	40.5	0.92 (0.72-1.18)	
Age					0.09
<50 yr	70	19.4	44.1	0.44 (0.21-0.95)	
50-75 yr	334	34.6	36.5	0.95 (0.71-1.27)	
>75 yr	194	53.7	50.0	1.07 (0.81-1.41)	
Diabetes					0.82
Yes	195	42.9	46.7	0.92 (0.67-1.26)	
No	399	37.2	38.9	0.96 (0.74-1.23)	
Hypertension					0.05
Yes	410	42.9	40.4	1.06 (0.84-1.34)	
No	183	28.9	43.0	0.67 (0.45-1.01)	
Type of MI					0.76
STEMI/LBBB	412	41.0	42.9	0.96 (0.77-1.21)	
Non-STEMI	177	37.5	38.3	0.98 (0.67-1.43)	
STEMI type					0.14
Anterior	216	35.4	43.7	0.81 (0.58-1.13)	
Nonanterior	196	48.3	42.2	1.16 (0.85-1.57)	
Previous infarction					0.04
Yes	131	47.9	33.3	1.44 (0.93-2.21)	
No	466	37.3	43.3	0.86 (0.39-1.07)	
Hypothermia					0.31
Yes	226	48.1	44.2	1.09 (0.82-1.44)	
No	372	35.1	39.3	0.89 (0.68-1.16)	
Blood pressure					0.76
<80 mm Hg	161	50.7	46.4	1.09 (0.79-1.50)	
≥80 mm Hg	432	35.9	39.2	0.92 (0.72-1.17)	



B

FIGURE 59.23 Primary result of a randomized trial of routine insertion of an intra-aortic balloon pump (IABP) versus standard care in patients with acute MI and cardiogenic shock. **A,** In this randomized trial of 600 patients, the primary endpoint of death from any cause did not differ between the randomized treatment groups. **B,** There was no convincing benefit of the routine use of IABP for shock in any of the major subgroups examined. LBBB, Left bundle branch block. (From Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med 2012;367:1287.)

Percutaneous Left Ventricular Assist Devices

A percutaneous left ventricular assist device (LVAD) may be placed by cannulation of the left femoral vein and advancement to the left atrium by transseptal puncture (**see Fig. 59.22**). Blood from the left atrium returns into the femoral artery via a nonpulsatile motor. This system may provide up to 5 liters/min of flow. Small randomized trials have not revealed any mortality advantage over IAB counterpulsation, but hemodynamic improvement is greater with the percutaneous LVAD.[121] Another percutaneous alternative is a motorized device placed across the aortic valve that delivers continuous flow of blood from the left ventricle into the aorta and provides hemodynamic support superior to that achieved with an IAB in patients with MI.[121,123] Extracorporeal membrane oxygenation (ECMO) is another percutaneous circulatory support option that provides biventricular support as well as oxygenation. The aim of temporary mechanical support with LVADs is to allow time for recovery of stunned or hibernating myocardium or for a bridge to more durable devices. Surgically placed LVADs as a bridge to transplantation or as a destination therapy are discussed in **Chapter 28**.

Complications

Complications of MCS include vascular damage, ischemia distal to the site of insertion for devices requiring femoral arterial cannulation, thrombocytopenia, hemolysis, atheroemboli, infection, mechanical failure, and bleeding in the setting of anticoagulation.

Revascularization

Of the five therapies frequently used to treat patients with cardiogenic shock—inotropes/vasopressors, MCS, fibrinolysis, PCI, and CABG—the first two are useful temporizing maneuvers. Revascularization, however, appears to improve survival.

The SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock?) study evaluated early revascularization for the treatment of patients with MI complicated by cardiogenic shock.[108] Patients with shock caused by LV failure complicating STEMI were randomly assigned to emergency revascularization (n = 152), accomplished by either CABG or angioplasty, or to initial medical stabilization (n = 150). In 86% of patients in both groups, IAB counterpulsation was performed. The primary endpoint was all-cause mortality at 30 days; a secondary endpoint was mortality at 6 months. At 30 days the overall mortality rate was 46.7% in the revascularization group, not significantly different from the 56% mortality observed in the medical therapy group (P = 0.11). Subgroups of patients in the SHOCK study who showed benefit from the early revascularization strategy (i.e., reduced 6-month mortality) were those younger than 75 years, those with a previous MI, and those randomly assigned less than 6 hours from the onset of infarction. Long-term survival improved significantly in patients with cardiogenic shock who underwent early revascularization (**Fig. 59.24**). A subsequent observational study of patients with MI complicated by shock indicated that well-selected elderly patients undergoing PCI had a 1-year survival similar to that in younger patients undergoing early revascularization.[124]

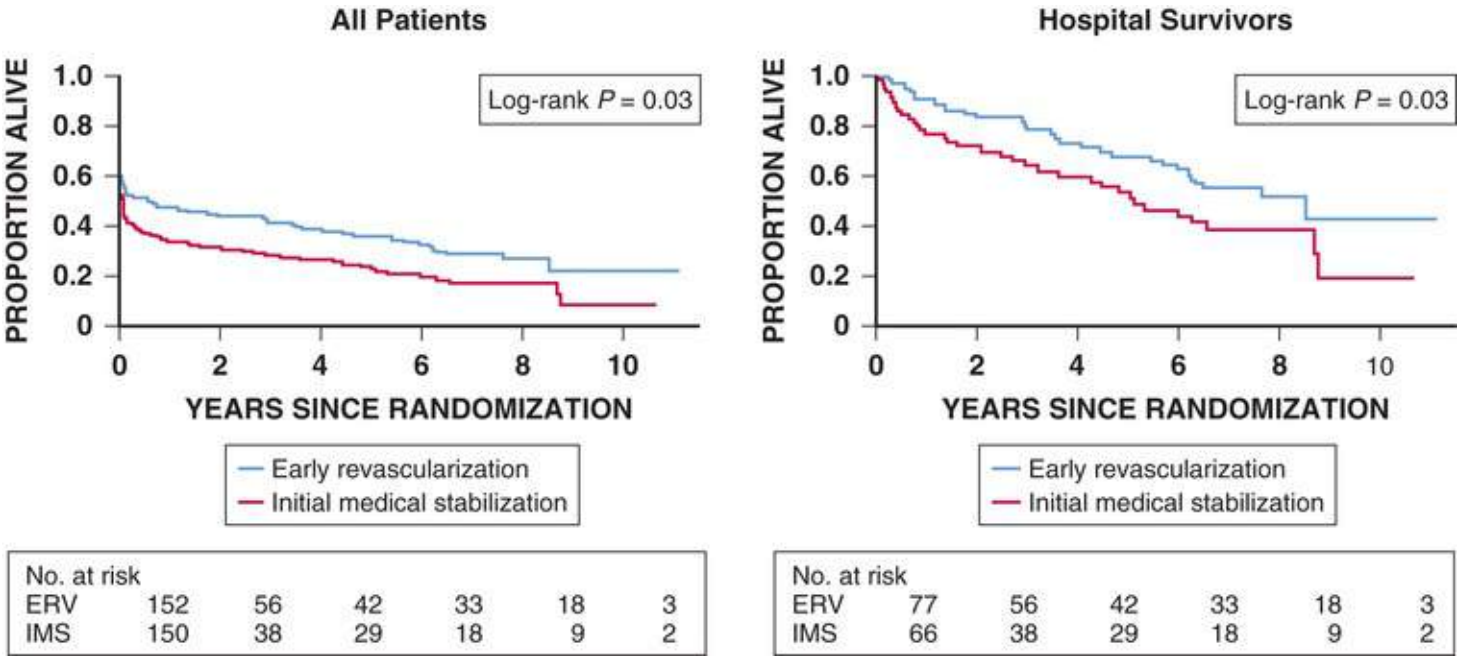


FIGURE 59.24 Impact of revascularization in patients in the SHOCK trial. Among all patients, survival rates in the early revascularization (ERV) and initial medical stabilization (IMS) groups, respectively, were 41.4% and 28.3% at 3 years and 32.8% and 19.6% at 6 years. Among hospital survivors, survival rates in the ERV and IMS groups, respectively, were 78.8% and 64.3% at 3 years and 62.4% and 44.4% at 6 years. (From Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. JAMA 2006;295:2511.)

Multivessel disease affects 70% to 90% of patients with cardiogenic shock and acute MI, but the optimal extent of the initial revascularization is not yet known.[122] Although multiple recent small studies demonstrated robust reductions in recurrent CV events with multivessel or complete revascularization compared to infarct artery–only revascularization in patients with STEMI, all these studies excluded patients with cardiogenic shock[58-60] (see earlier, Catheter-Based Reperfusion Strategies). In a prospective observational study of 169 participants with resuscitated cardiac arrest and cardiogenic shock, multivessel PCI was associated with decreased mortality compared with culprit vessel–only PCI[125] (**Fig. 59.25**). However, in the substantially larger CULPRIT-SHOCK (Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock) trial among 706 patients with cardiogenic shock onset within 12 hours in the setting of acute MI (ST- and non–ST-elevation MI) that randomized patients to infarct artery–only or acute multivessel revascularization, patients allocated to infarct artery-only PCI had a lower 30-day rate of death or severe renal failure leading to renal replacement therapy (RR 0.83; 95% CI 0.71 to 0.96; P = 0.01).[1,126,126a] Moreover, the risk of death was lower in patients randomized to culprit-only PCI (P = 0.03).[126a]

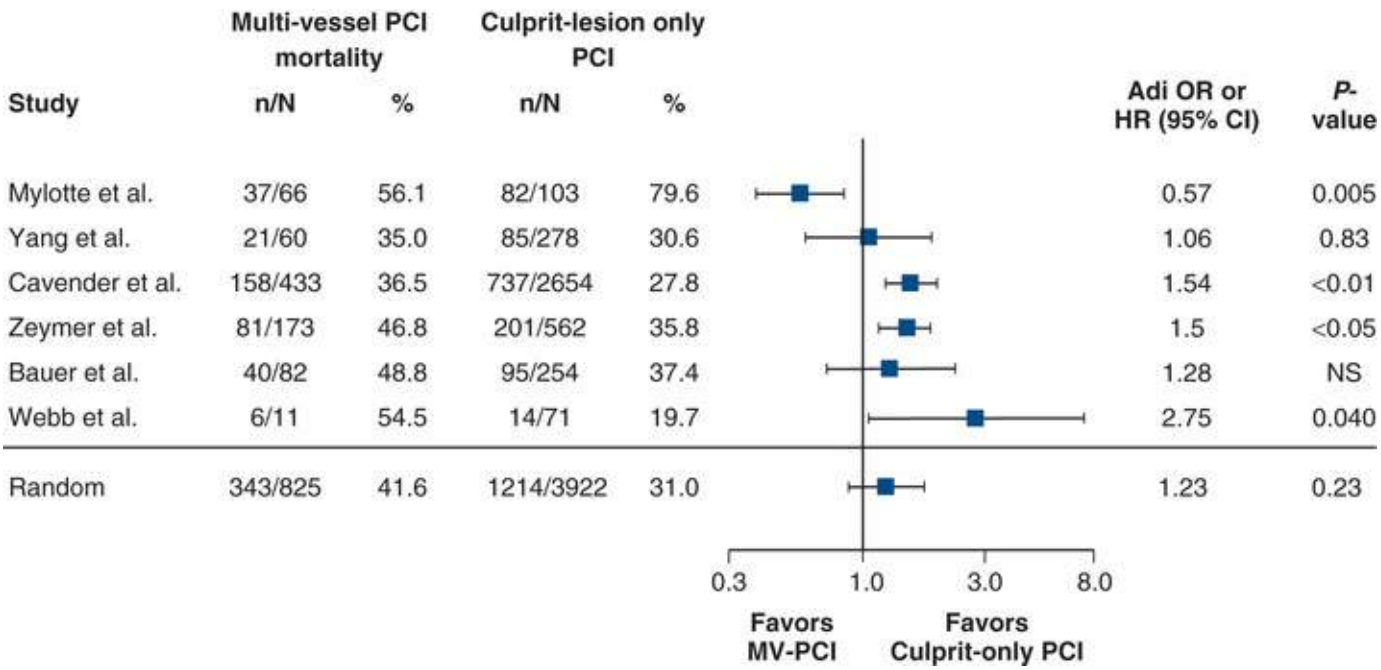


FIGURE 59.25 Mortality for multivessel (*MV*) versus culprit vessel–only percutaneous coronary intervention (*PCI*) in several registries of patients with cardiogenic shock. Meta-analysis using random effects modeling (*Random*) displayed. *HR,* Hazard ratio; *NS,* not significant; *OR,* odds ratio. (Data from Thiele H, Ohman EM, Desch S, et al. Management of cardiogenic shock. Eur Heart J 2015;36:1223-30.)

Recommendations

We recommend individualized assessment of patients to determine their desire for aggressive care and overall candidacy for further treatment (e.g., age, mental status, comorbid conditions). Patients with shock who are potential candidates for revascularization of the culprit artery should be revascularized. Routine revascularization of nonculprit arteries in the same procedure as the primary PCI does not appear indicated and may be associated with worsened outcomes. In patients with STEMI and shock, in whom PCI or CABG is not suitable, fibrinolytic agents can be given unless they have a contraindication.[1] IAB counterpulsation and LVADs may aid patients with refractory shock whose condition does not stabilize with other therapies.

Right Ventricular Infarction

The clinical features of RV infarction range from mild RV dysfunction to cardiogenic shock. Clinically significant RV infarction, which accompanies approximately one third of inferior LV infarctions, produces characteristic electrocardiographic manifestations and hemodynamic patterns (**Fig. 59.26**). Right-sided heart filling pressures (CVP, RA, RV end-diastolic) are elevated, whereas LV filling pressure is normal or only slightly raised; RV systolic and pulse pressures are decreased, and cardiac output is often greatly depressed.

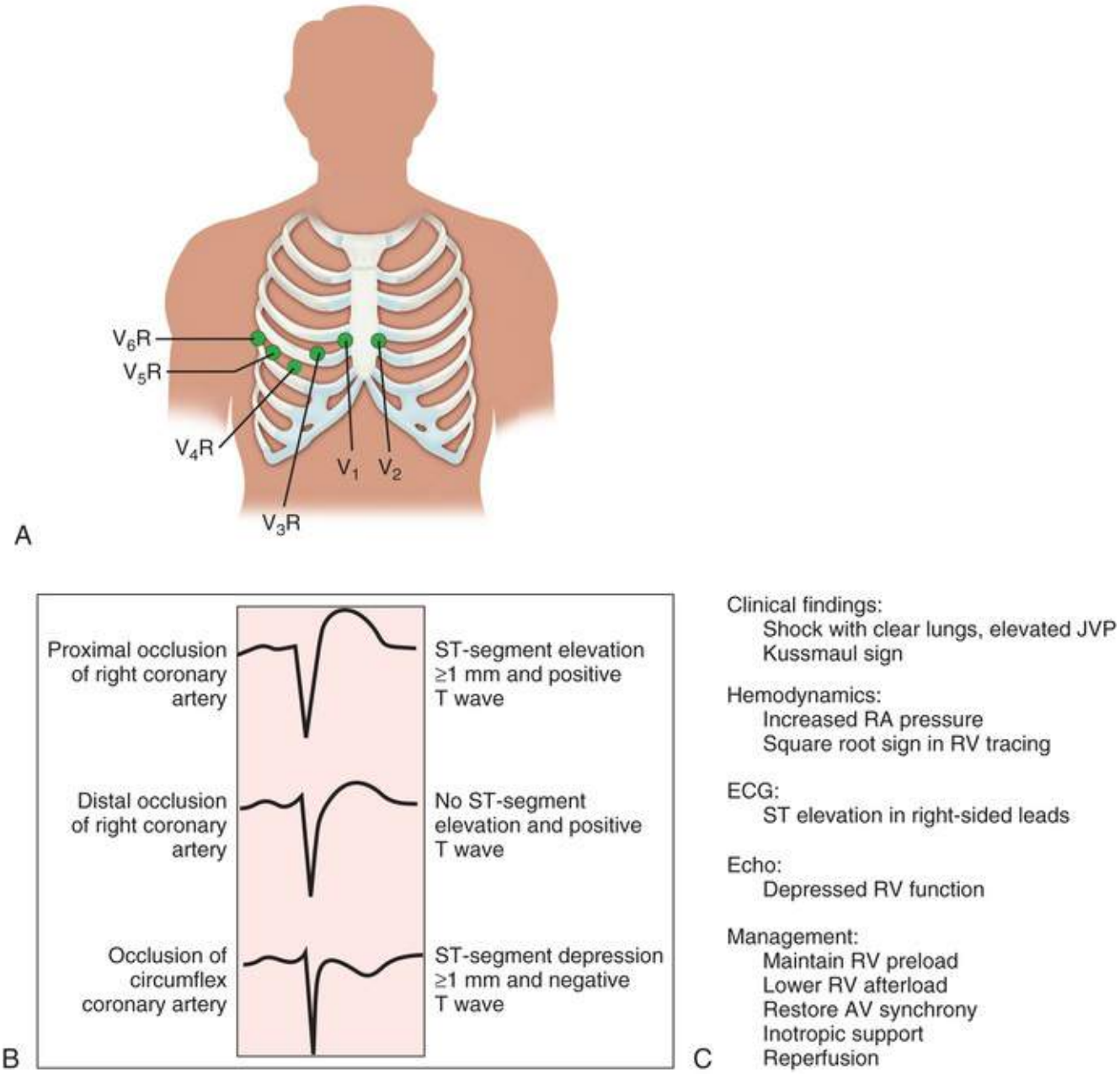


FIGURE 59.26 Right ventricular (RV) infarction: diagnosis, clinical features, and management. **A,** Placement of right-sided leads for electrocardiographic evaluation of RV infarction. **B,** ST elevation is seen in the right-sided ECG leads (e.g., V_4R), with variation in the repolarization pattern depending on the infarct artery and the location of the occlusion. **C,** Patients with hemodynamically significant RV infarction have shock but clear lungs and elevated jugular venous pressure (JVP). Management is directed at maintaining adequate RV preload and lowering pulmonary artery pressure to unload the right ventricle. Inotropic therapy may be necessary in some cases. Echo, Echocardiogram; RA, right atrial. (Modified from Wellens HJ. The value of the right precordial leads of the electrocardiogram. N Engl J Med 1999;340:381; and Antman EM et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction]. J Am Coll Cardiol 2004;44(3):e1.)

Diagnosis

Many patients with the combination of a normal LV filling pressure and depressed cardiac index have RV infarcts (with accompanying inferior LV infarcts). The hemodynamic picture may superficially resemble that seen in patients with pericardial disease (**see Chapter 83**) and includes elevated RV filling pressure; a steep, right atrial *y* descent; and an early diastolic drop and plateau (resembling the square root sign) in the RV pressure tracing. Moreover, patients with RV infarction may display the Kussmaul sign (increase

in jugular venous pressure with inspiration) and pulsus paradoxus (decrease in systolic BP >10 mm Hg with inspiration) (**Fig. 59.26C**). In fact, the Kussmaul sign in the setting of inferior STEMI is highly predictive of RV involvement.

The ECG can provide the first clue to RV involvement in patients with inferior STEMI (**Fig. 59.26B**). Most patients with RV infarction have ST-segment elevation in lead V_4R (right precordial lead in the V_4 position).[1] Transient elevation of the ST segment in any of the right precordial leads can occur with RV MI, and the presence of ST-segment elevation of 0.1 mV or greater in any one or a combination of leads V_4R, V_5R, and V_6R in patients with the clinical picture of acute MI points to the diagnosis of RV MI. In addition to noting the presence or absence of convex upward ST elevation in V_4R, clinicians should determine whether the T wave is positive or negative; such distinctions help distinguish proximal versus distal occlusion of the right coronary artery versus occlusion of the left circumflex artery (**Fig. 59.26B**). Elevation of the ST segments in leads V_1 through V_4 caused by RV infarction can be confused with elevation caused by anteroseptal infarction. Although the elevated ST segments orient anteriorly in both cases, the frontal plane can provide important clues: the ST segments orient to the right with RV infarction (e.g., +120 degrees), whereas they orient to the left with anteroseptal infarction (e.g., −30 degrees).

Noninvasive Assessment

Echocardiography helps in the differential diagnosis because in patients with RV infarction, in contrast to pericardial tamponade, little or no pericardial fluid accumulates. The echocardiogram shows abnormal wall motion of the right ventricle, as well as RV dilation and depression of the RV ejection fraction.[127] MRI can also aid in recognition of RV infarction. Impaired RV function delineated by either modality is associated with increased mortality after MI.[127,128] Additionally, shock from isolated RV dysfunction carries almost as high a mortality risk as LV shock; serial studies have shown, however, some degree of ventricular recovery more frequently with RV infarction than with LV infarction.[18]

Treatment

Because of their ability to reduce preload, medications routinely prescribed for LV infarction may produce profound hypotension in patients with RV infarction. Specifically, nitrates, morphine, and diuretics should be avoided. In patients with hypotension caused by RV MI, hemodynamics can improve with a combination of expansion of plasma volume to augment RV preload and cardiac output and, when LV failure is present, arterial vasodilators.[1] If hypotension has not responded to brisk administration of 1 or more liters of fluid, however, consideration should be given to hemodynamic monitoring with a PA catheter because further volume infusion may be of little use and could produce pulmonary congestion. Arterial vasodilators reduce the impedance to LV outflow and, in turn, LV diastolic, left atrial, and pulmonary (arterial) pressure, thereby lowering impedance to RV outflow and enhancing RV output.

Right ventricular infarction is common in patients with inferior LV infarction. Therefore, otherwise unexplained systemic arterial hypotension with diminished cardiac output or marked hypotension in response to small doses of nitroglycerin in patients with inferior infarction should lead to prompt consideration of this diagnosis. In patients requiring pacing, ventricular pacing may fail to increase cardiac output, and AV sequential pacing may be needed. Successful reperfusion of the right coronary artery significantly improves RV mechanical function and lowers in-hospital mortality in patients with RV infarction.[18] Replacement of the tricuspid valve and repair of the valve with annuloplasty rings can treat severe tricuspid regurgitation caused by RV infarction.

Mechanical Causes of Heart Failure

The most dramatic complications of STEMI involve tearing or rupture of acutely infarcted tissue (**Fig. 59.27**). The clinical characteristics of these lesions vary considerably and depend on the site of rupture, which may involve the free wall of either ventricle, the interventricular septum, or the papillary muscles. The overall incidence of these complications, although difficult to assess because clinical and autopsy series differ considerably, appears to have decreased initially with the introduction of reperfusion therapy and subsequently decreased substantially with the widespread adoption of primary PCI.[129] **Table 59.11** shows the comparative clinical profile of these complications, as gathered from different studies.

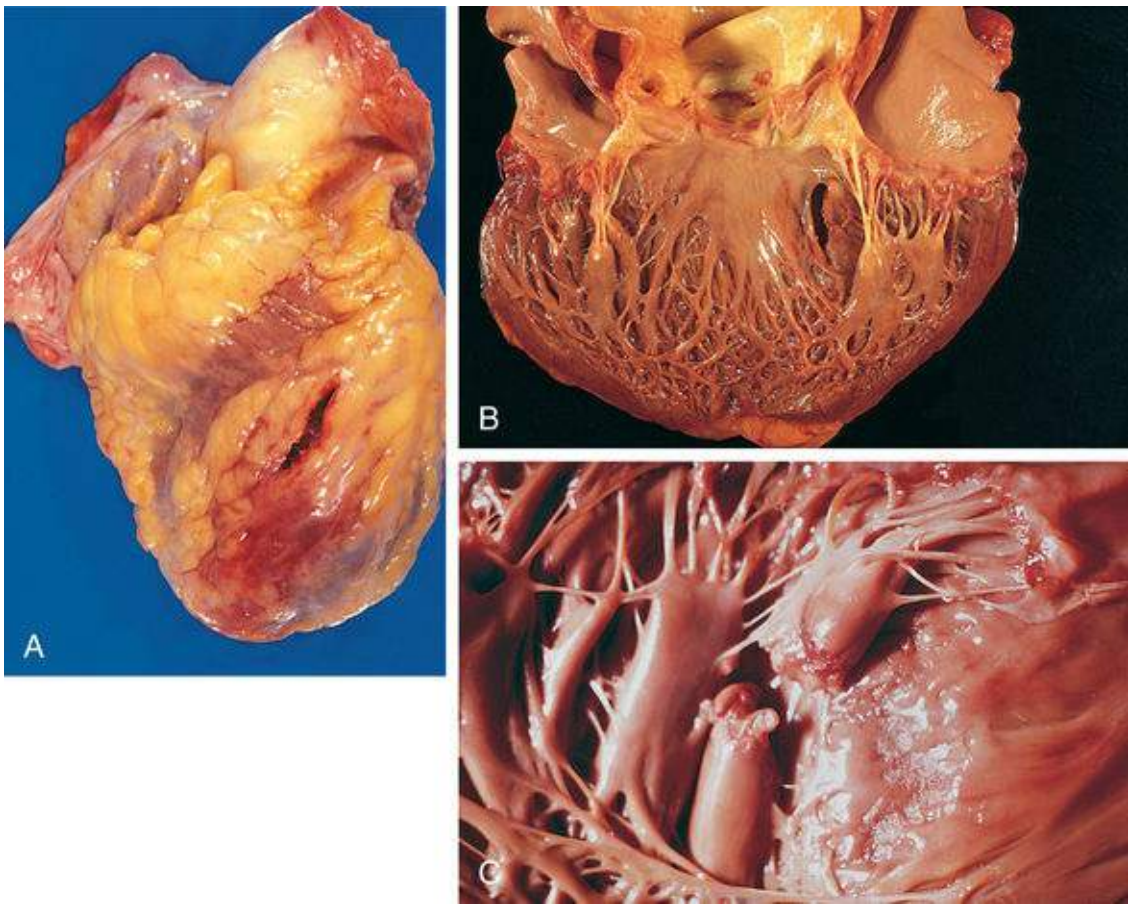


FIGURE 59.27 Cardiac rupture syndromes complicating STEMI. **A,** Anterior myocardial rupture in an acute infarct. **B,** Rupture of the ventricular septum. **C,** Complete rupture of a necrotic papillary muscle.
(From Schoen FJ: The heart. In Kumar V, Abbas AK, Fausto N, editors. Robbins & Cotran Pathologic Basis of Disease. 7th ed. Philadelphia: Saunders; 2005.)

TABLE 59.11

Characteristics of Ventricular Septal Rupture, Rupture of the Ventricular Free Wall, and Papillary Muscle Rupture

CHARACTERISTIC	VENTRICULAR SEPTAL RUPTURE	RUPTURE OF THE VENTRICULAR FREE WALL	PAPILLARY MUSCLE RUPTURE
Incidence	1-3% without reperfusion therapy, 0.2-0.34% with fibrinolytic therapy, 3.9% in patients with cardiogenic shock	Approximately 1%; fibrinolytic therapy does not reduce risk; primary PCI seems to reduce risk	Approximately 1% (posteromedial more frequent than anterolateral papillary muscle rupture)
Time course	Bimodal peak; within 24 hr and 3-5 days; range, 1-14 days	Bimodal peak; within 24 hr and 3-5 days; range, 1-14 days	Bimodal peak; within 24 hr and 3-5 days; range, 1-14 days
Clinical manifestations	Chest pain, shortness of breath, hypotension	Anginal, pleuritic, or pericardial chest pain; syncope; hypotension; restlessness; sudden death	Abrupt onset of shortness of breath and pulmonary edema; hypotension
Physical findings	Harsh holosystolic murmur, thrill, S_3, accentuated S_2, pulmonary edema, RV and LV failure, cardiogenic shock	Jugular venous distention (29% of patients), pulsus paradoxus (47%), electromechanical dissociation, cardiogenic shock	A soft murmur in some cases, no thrill, variable signs of RV overload, severe pulmonary edema, cardiogenic shock
Echocardiographic findings	Ventricular septal rupture, left-to-right shunt on color flow Doppler echocardiography through the ventricular septum, pattern of RV overload	>5 mm pericardial effusion not visualized in all cases; layered, high-acoustic echoes within the pericardium (blood clot); direct visualization of tear; signs of tamponade	Hypercontractile LV, torn papillary muscle or chordae tendineae, flail leaflet, severe mitral regurgitation on color flow Doppler echocardiography
Right-heart catheterization	Increase in oxygen saturation from the RA to RV, large *v* waves	Ventriculography insensitive, classic signs of tamponade not always present (equalization of diastolic pressures in the cardiac chambers)	No increase in oxygen saturation from the RA to RV, large *v* waves,* very high PCWP

*Large *v* waves are from the pulmonary capillary wedge pressure (PCWP).

LV, Left ventricle/left ventricular; *PCI,* percutaneous coronary intervention; *RA,* right atrium; *RV,* right ventricle/right ventricular.

Data from Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004;110(9):e82.

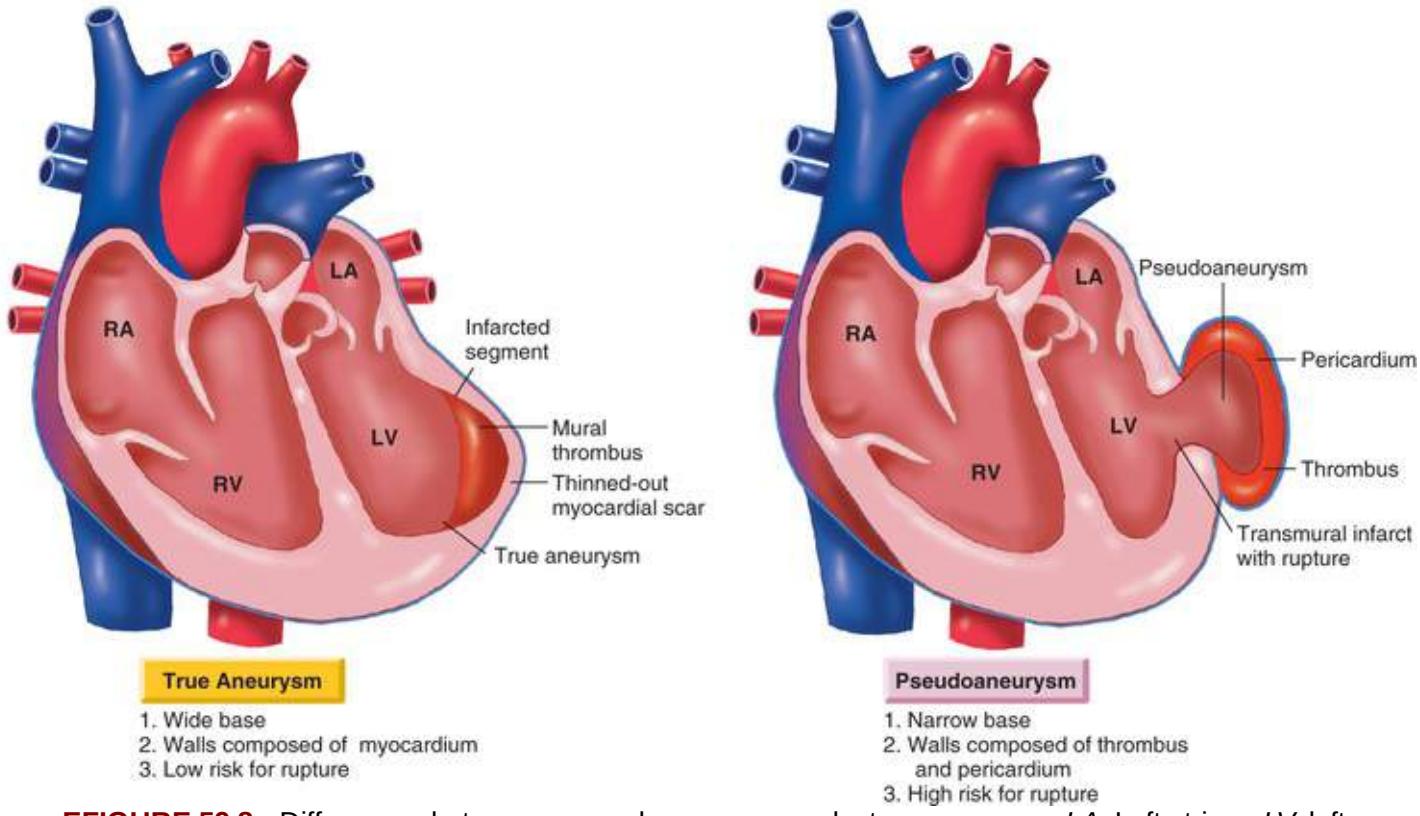
Free Wall Rupture

The clinical course of rupture varies from *catastrophic*, with an acute tear leading to tamponade and immediate death, to *subacute,* with nausea, hypotension, and pericardial discomfort the major clinical clues to its presence (**Fig. 59.27 and Table 59.11**). The tear is usually preceded by a large infarct with subsequent expansion, sometimes with a dissecting hematoma, and occurs near the junction of the infarct and normal muscle. Rupture is more common in the left ventricle (specifically, the anterior or lateral wall) than in the right ventricle and seldom occurs in the atria. Other features associated with rupture include reperfusion with a fibrinolytic agent versus PCI, older age, female sex, hypertension, single-vessel disease without collateral circulation, and an anterior or first MI.[129] Mortality rates can be as high as 75% to 90% following free wall rupture. Survival depends on recognition of this complication, and most importantly, on prompt surgical repair.[1]

Pseudoaneurysm

Incomplete rupture of the heart may occur when organizing thrombus and hematoma, together with pericardium, seal a rupture of the left ventricle and thus prevent the development of hemopericardium (**eFig. 59.8**). With time, this area of organized thrombus and pericardium can become a pseudoaneurysm (false aneurysm) that maintains communication with the cavity of the left ventricle. In contrast to true aneurysms, which always contain some myocardial elements in their walls, the walls of pseudoaneurysms are composed of organized hematoma and pericardium and lack any elements of the original myocardial wall. Pseudoaneurysms can become quite large, even equaling the true ventricular cavity in size, and they communicate with the LV cavity through a narrow neck. Frequently, pseudoaneurysms contain significant quantities of old and recent thrombi, the superficial portions of which can cause arterial emboli.

Pseudoaneurysms can drain off a portion of each ventricular stroke volume, exactly as do true aneurysms. The diagnosis of pseudoaneurysm can usually be made by echocardiography, contrast-enhanced angiography, CMR, or computed tomography (CT), although differentiation between a true aneurysm and a pseudoaneurysm can sometimes be difficult with any imaging technique.[68,127]



EFIGURE 59.8 Differences between a pseudoaneurysm and a true aneurysm. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (From Shah PK: Complications of acute myocardial infarction. In Parmley W, Chatterjee K, editors. Cardiology. Philadelphia: Lippincott; 1987.)

Diagnosis

Myocardial free wall rupture is usually accompanied by sudden profound shock, often rapidly leading to pulseless electrical activity caused by pericardial tamponade. Immediate pericardiocentesis can confirm the diagnosis. If the patient's condition is sufficiently stable, echocardiography can establish the diagnosis of tamponade.[127]

Treatment

In patients with critically compromised hemodynamics, establishment of the diagnosis should be followed immediately by surgical resection of the necrotic and ruptured myocardium with primary reconstruction. When the rupture is subacute and a pseudoaneurysm is suspected or present, prompt elective surgery is indicated because the risk of rupture approaches 50% in untreated cases.[68]

Rupture of Interventricular Septum

As in rupture of the free wall of the ventricle, transmural infarction underlies rupture of the ventricular septum. The perforation can range in length from one to several centimeters (**Fig. 59.27**). It can be a direct through-and-through opening or more irregular and serpiginous. Rupture of the septum with an anterior

infarction tends to be apical in location, whereas inferior infarctions are associated with perforation of the basal septum and have a worse prognosis than those in an anterior location.

Clinical features associated with increased risk for rupture of the interventricular septum include lack of development of a collateral network, advanced age, female sex, and chronic kidney disease (**Table 59.11**). Because previous ischemia induces myocardial preconditioning, thereby decreasing the likelihood of transmural myocardial necrosis and septal rupture, patients with evidence of hypertension, diabetes mellitus, chronic angina, or previous MI are less likely to experience rupture.[110]

A new, harsh, loud holosystolic murmur heard best at the lower left sternal border, usually accompanied by a thrill, characterizes a ruptured interventricular septum. Biventricular failure generally ensues within hours to days. The defect can also be recognized by echocardiography with color flow Doppler imaging (**Fig. 59.28**) or by insertion of a PA balloon catheter to document the left-to-right shunt. Rupture of the interventricular septum after STEMI carries a poor prognosis, with mortality of 40% to 75%.[129] The likelihood of survival depends on the degree of impairment of ventricular function and the size of the defect, but because the rupture site can expand, prompt repair is necessary even in hemodynamically stable patients.[1] Septal rupture is most often repaired surgically (**Fig. 59.29**), although transcatheter closure may be considered, particularly when the patient is deemed inoperable and the anatomy is amenable to application of a closure device.[130]

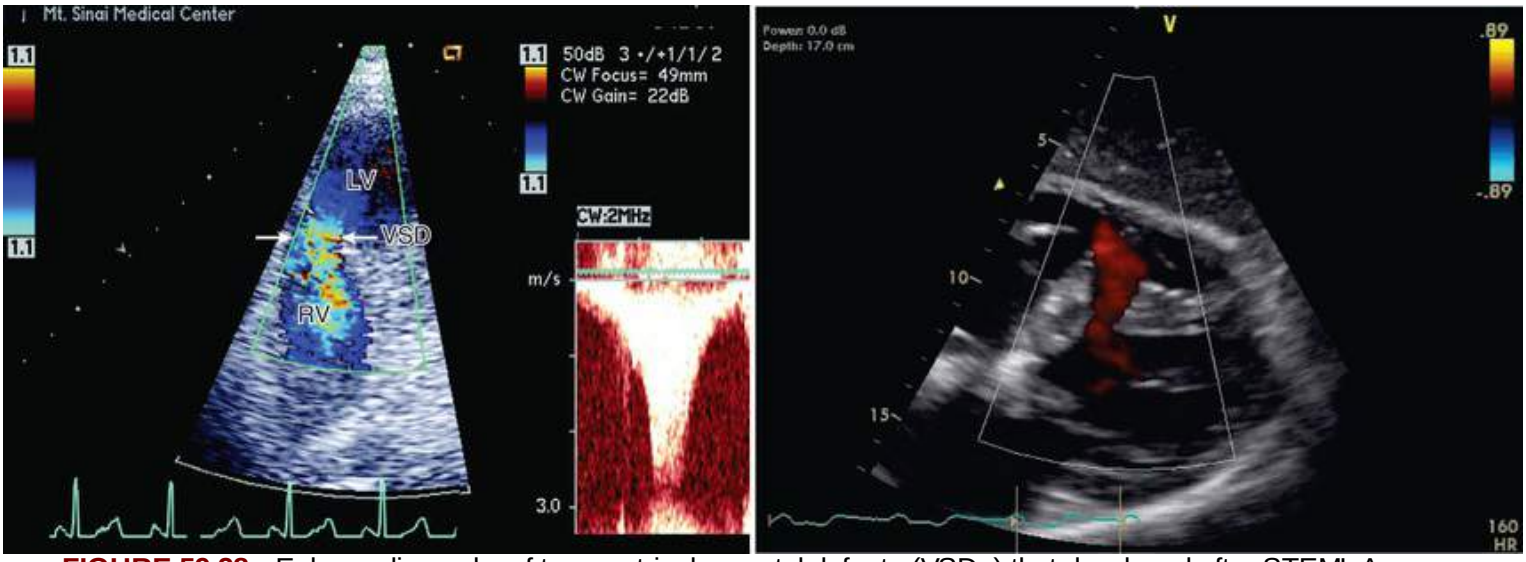


FIGURE 59.28 Echocardiography of two ventricular septal defects (VSDs) that developed after STEMI. A close-up of the ventricular septum demonstrates turbulent systolic color flow Doppler across a VSD (*white arrows*), and continuous-wave Doppler demonstrates systolic flow across a VSD **(left)**. A subcostal view demonstrates color flow Doppler across a VSD **(right)**. *LV,* Left ventricle; *RV,* right ventricle. (**Left,** From Kamran M, Attari M, Webber G. Images in cardiovascular medicine. Ventricular septal defect complicating an acute myocardial infarction. Circulation 2005;112:e337; **Right,** from Brigham and Women's Hospital, 2013.)

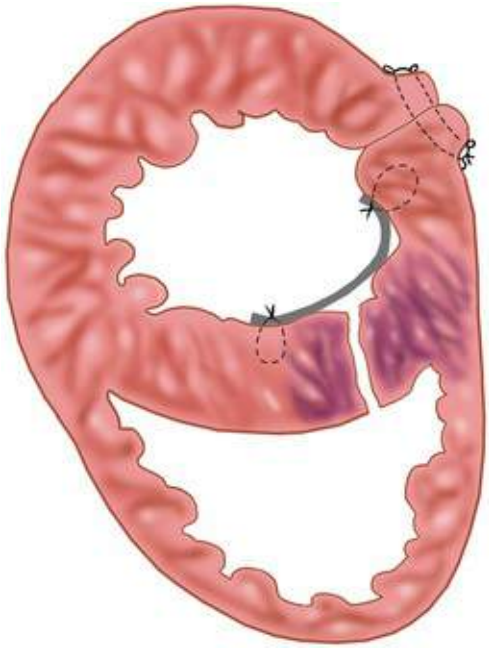


FIGURE 59.29 Repair of an ischemic ventricular septal defect. The infarct typically involves a free wall and septum. Repair of the defect is performed through an incision in the ventricular wall infarct. The septal defect is closed with a prosthetic patch, and a second patch is used to close the incision in the free wall.
(Courtesy Dr. David Adams, Mt. Sinai Hospital, New York.)

Rupture of a Papillary Muscle

Partial or total rupture of a papillary muscle is a rare but often fatal complication of transmural MI[131] (**see Fig. 59.21**). Complete transection of a LV papillary muscle is incompatible with life because the sudden massive MR that develops cannot be tolerated. Rupture of a portion of a papillary muscle, usually the tip or head of the muscle, that results in severe, although not necessarily overwhelming MR, is much more frequent and is not immediately fatal (**Fig. 59.30**). Inferior wall infarction can lead to rupture of the posteromedial papillary muscle, which because of its singular blood supply, occurs more frequently than rupture of the anterolateral muscle, a consequence of anterolateral MI. Unlike rupture of the ventricular septum, which occurs with large infarcts, papillary muscle rupture occurs with a relatively small infarction in approximately half of cases. These patients may have a modest extent of CAD as well. Rupture of a RV papillary muscle is unusual but can cause massive tricuspid regurgitation and RV failure. In a small number of patients, rupture of more than one cardiac structure is noted clinically or at postmortem examination; all possible combinations of rupture of the LV free wall, the interventricular septum, and the papillary muscles can occur.

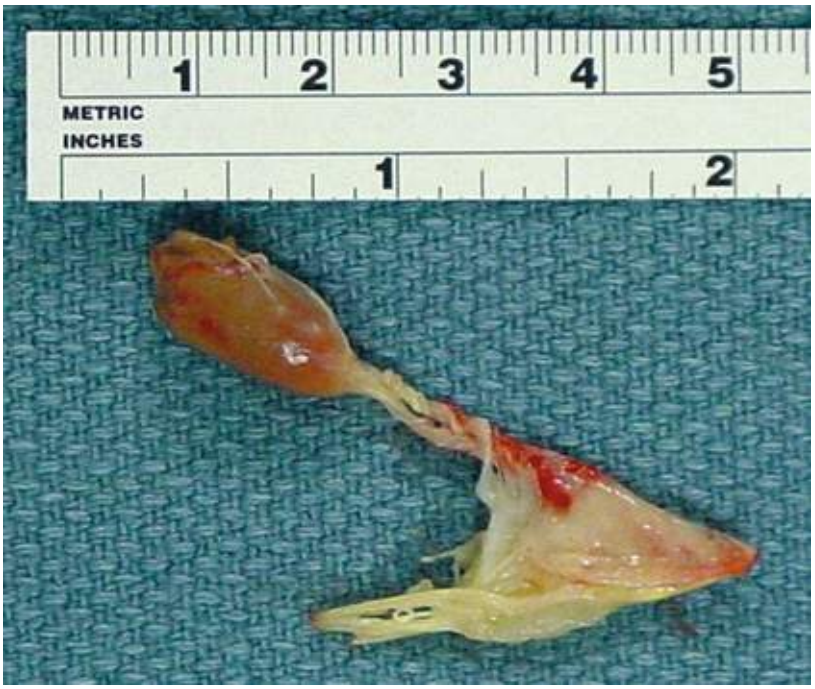


FIGURE 59.30 Surgical specimen showing a papillary muscle (*top left*), chordae, and anterior mitral leaflet (*bottom right*) from a patient who had a partial rupture of the papillary muscle and underwent mitral valve replacement for severe mitral regurgitation after STEMI. (Courtesy Dr. John Byrne, Brigham and Women's Hospital, Boston.)

As with patients who have a ruptured VSD, those with papillary muscle rupture manifest with increasingly severe HF. These patients may also have a holosystolic murmur, but because of rapid equalization of pressures between the left atrium and ventricle, patients with torrential acute MR may have an unimpressive or absent murmur.[131] In either ventricular or papillary muscle rupture, the murmur may become softer or may disappear as arterial pressure falls. Echocardiography can promptly recognize MR secondary to partial or complete rupture of a papillary muscle and distinguish it from other, generally less severe forms of MR that occur with STEMI. Color flow Doppler imaging is particularly helpful in distinguishing acute MR from VSD in the setting of STEMI (**Table 59.11**).[1] However, acute severe MR may be difficult to diagnose with transthoracic echocardiography (TTE) in cases with narrow eccentric jets with rapid equalization of pressures; therefore, transesophageal echocardiography (TEE) should be employed when suspicion is high because of its greater diagnostic accuracy.

Differentiation Between Ventricular Septal Rupture and Mitral Regurgitation

Distinguishing on clinical grounds between acute MR and rupture of the ventricular septum in patients with STEMI in whom a loud systolic murmur suddenly develops may be difficult. Such differentiation can be made most readily by color flow Doppler echocardiography. In addition, right-heart catheterization can readily distinguish between these two complications. Patients with ventricular septal rupture demonstrate a “step-up” in SaO_2 in blood samples from the right ventricle and PA compared with those from the right atrium. Patients with acute MR lack this step-up; they may demonstrate tall *c-v* waves in both the pulmonary capillary and pulmonary arterial pressure tracings.

Management

We recommend initiation of invasive monitoring in most cases once there is recognition of a major mechanical complication of STEMI. RV and LV filling pressures (RA pressure and PCWP) guide fluid

administration or the use of diuretics, whereas measurements of cardiac output and MAP permit calculation of SVR to direct vasodilator therapy. For acute MR and VSDs, unless systolic BP is below 90 mm Hg, vasodilator therapy, usually nitroglycerin or nitroprusside, should be instituted as soon as possible once hemodynamic monitoring is available. Inotropes may also be needed to support adequate cardiac output. These interventions may be critically important for stabilizing the patient's condition in preparation for further diagnostic studies and repair. If pharmacologic therapy is not tolerated or fails to achieve hemodynamic stability, IAB counterpulsation should be instituted rapidly. IAB counterpulsation as a bridge to definitive repair should be considered for most patients with acute mechanical complications of STEMI.

Operative intervention is most successful in patients with STEMI and circulatory collapse when a surgically correctable mechanical lesion (e.g., VSD, ruptured papillary muscle) can be identified and addressed (**Fig. 59.31**). In most cases, surgery should not be delayed in patients with a correctable lesion who agree to an aggressive management strategy and require pharmacologic and mechanical (counterpulsation) support.[1] In such patients a serious complication frequently develops—infection, ARDS, extension of the infarct, or renal failure—if surgery is delayed. Early surgery, short duration of shock, and mild degrees of RV and LV impairment predict surgical survival.[1] In a subset of patients whose hemodynamic status remains stable, the operation may be postponed for 2 to 4 weeks to allow some healing of the infarct. Such complex decisions regarding the optimal timing of surgery require integration of multiple aspects of the clinical course and anatomy of the mechanical complication by a multidisciplinary “heart” team. These situations also require careful consideration of the goals of care with the patient or proxies to ensure respecting the patient's wishes and values, particularly in cases with a high degree of futility (**see Chapter 31**).

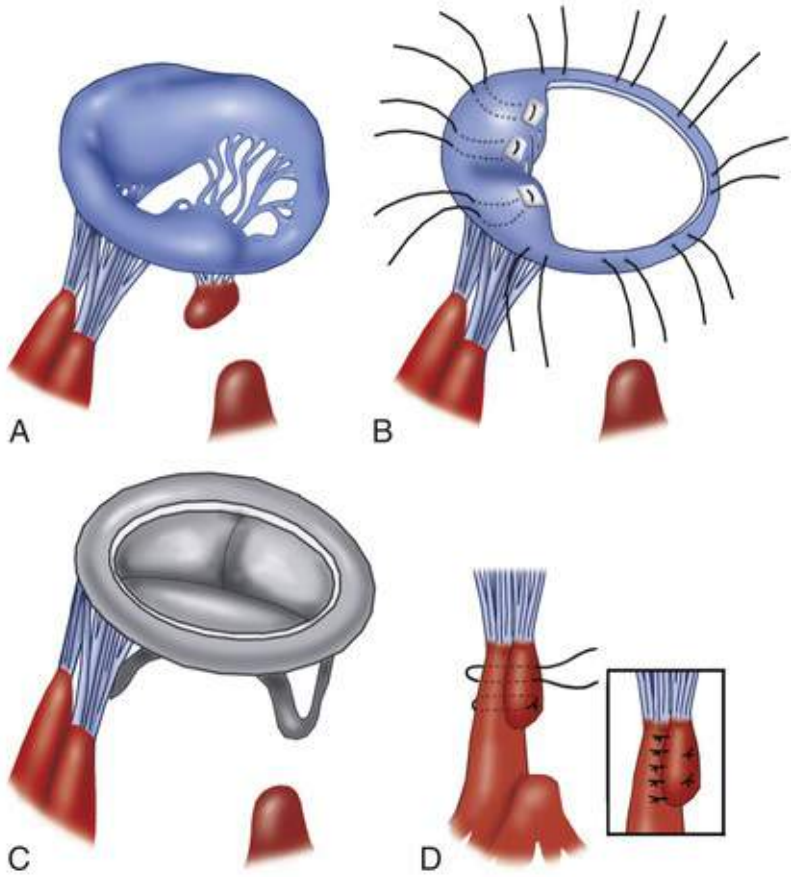


FIGURE 59.31 Surgical management of mitral regurgitation (MR) caused by a ruptured papillary muscle. **A,** Acute papillary muscle rupture results in severe MR as a result of leaflet and commissural prolapse. Mitral valve replacement is usually necessary. **B,** Mitral débridement with retention of the unruptured commissural and leaflet segment is performed to preserve partial continuity of the annular papillary muscle. **C,** Mitral valve replacement is then performed. **D,** Occasionally, mitral valve repair can be performed by transfer of a papillary head to a nonruptured segment. (Courtesy Dr. David Adams, Mt. Sinai Hospital, New York.)

Catheter-based options for VSD repair may be appropriate in patients who are not candidates for early definitive surgical correction.[1,130] We sometimes undertake early catheter-based repair with the aim of temporizing the defect until a later definitive surgical repair, when more infarct healing has occurred. However, because the initial closure of the defect is almost always incomplete, and the device requires time to thrombose and endothelialize, in most patients with hemodynamically significant mechanical complications, surgical management is the best option.[1,130]

Arrhythmias

Arrhythmias can complicate the course of patients with STEMI (**Table 59.12**). Many serious arrhythmias develop before hospitalization, even before the patient is monitored. Some abnormality in cardiac rhythm also occurs in many patients with STEMI treated in the hospital. These arrhythmias can include both tachycardic and bradycardic episodes, either of which can provoke hemodynamic consequences. (See also Part V in this textbook.)

TABLE 59.12

Cardiac Arrhythmias and Management During Acute Myocardial Infarction

CATEGORY	ARRHYTHMIA	OBJECTIVE OF TREATMENT	THERAPEUTIC OPTIONS
1. Electrical instability	Ventricular premature beats	Correction of electrolyte deficits and minimization of sympathetic tone	Potassium and magnesium solutions, beta blocker
	Ventricular tachycardia	Prophylaxis against ventricular fibrillation, restoration of hemodynamic stability	Antiarrhythmic agents, beta blocker; cardioversion/defibrillation; revascularization
	Ventricular fibrillation	Urgent reversion to sinus rhythm	Defibrillation; amiodarone, lidocaine; revascularization
	Accelerated idioventricular rhythm	Observation unless hemodynamic function is compromised	Increase sinus rate (atropine, atrial pacing); antiarrhythmic agents
	Nonparoxysmal atrioventricular junctional tachycardia	Search for precipitating cause (e.g., digitalis intoxication); suppress arrhythmia only if hemodynamic function is compromised	Atrial overdrive pacing; antiarrhythmic agents; cardioversion relatively contraindicated if digitalis intoxication present
2. Pump failure, excessive sympathetic stimulation	Sinus tachycardia	Reduce heart rate to diminish myocardial oxygen demands	Antipyretics; analgesics; consider beta blocker unless heart failure present
	Atrial fibrillation and/or atrial flutter	Reduce ventricular rate; restore sinus rhythm	Verapamil, digitalis glycosides; amiodarone; treat heart failure; cardioversion
	Paroxysmal supraventricular tachycardia	Reduce ventricular rate; restore sinus rhythm	Vagal maneuvers; verapamil, cardiac glycosides, beta blockers; cardioversion
3. Bradyarrhythmias, conduction disturbances	Sinus bradycardia	Acceleration of the heart rate only if hemodynamic function is compromised	Atropine; atrial pacing
	Junctional escape rhythm	Acceleration of the sinus rate only if loss of atrial "kick" causes hemodynamic compromise	Atropine; atrial pacing
	Atrioventricular block, intraventricular block		Insertion of a pacemaker

Modified from Antman EM, Rutherford JD, editors. Coronary Care Medicine: a Practical Approach. Boston: Martinus Nijhoff; 1986, p 78.

Hemodynamic Consequences

Patients with LV dysfunction have a relatively fixed stroke volume and depend on changes in HR to alter cardiac output. However, the range of HR with maximal cardiac output is narrow: either faster or slower rates can cause reductions in output. Thus, all forms of tachycardia and bradycardia can depress cardiac output in patients with STEMI. Although optimal cardiac output may require a rate higher than 100 beats/min, because HR is one of the major determinants of myocardial oxygen consumption, more rapid HRs elevate myocardial energy needs to levels that can adversely affect ischemic myocardium. In patients with STEMI, therefore, the optimal rate is usually lower, in the range of 60 to 80 beats/min.

A second factor to consider in assessing the hemodynamic consequences of a particular arrhythmia is loss of the atrial contribution to ventricular preload. Studies of patients without STEMI have demonstrated that loss of atrial transport decreases LV output by 15% to 20%. In patients with reduced diastolic LV compliance of any cause (including STEMI), however, atrial systole is of greater importance for LV filling. In patients with STEMI, atrial systole boosts end-diastolic volume by approximately 15%, end-diastolic pressure by 30%, and stroke volume by 35%.

Ventricular Arrhythmias (See Chapter 39)

Ventricular Premature Depolarizations

Before the widespread use of reperfusion therapy, aspirin, and beta blockers for the management of STEMI, frequent ventricular premature complexes (VPCs) (>5/min), VPCs with a multiform configuration, early coupling ("R-on-T" phenomenon), and repetitive patterns in the form of couplets or salvoes were thought to presage VF. However, as many patients who do not develop fibrillation have such "warning arrhythmias" as those who do. Primary VF (see later) can occur without antecedent warning arrhythmias and may even develop despite their suppression. Both primary VF and VPCs, especially R-on-T beats, occur during the early phase of STEMI, a period of considerable heterogeneity in electrical activity. Although R-on-T beats expose this heterogeneity and can precipitate VF in a small minority of patients, the ubiquitous nature of VPCs in patients with STEMI and the extremely infrequent nature of VF in the current era of STEMI management result in unacceptably low sensitivity and specificity of the electrocardiographic patterns observed on monitoring systems for identifying patients at risk for VF.

Management

The incidence of VF in patients with STEMI seen in CICUs over the past three decades appears to have declined. The previous practice of prophylactic suppression of ventricular premature beats with antiarrhythmic drugs is not indicated and may actually increase the risk for fatal bradycardic and asystolic events.[1] We therefore pursue a conservative course in patients with STEMI with VPCs and do not routinely prescribe antiarrhythmic drugs, other than beta blockers, but instead correct any recurrent ischemia or electrolyte or metabolic disturbances.[1] When VPCs accompany sinus tachycardia at the inception of an infarction, augmented sympathoadrenal stimulation often contributes and can be treated by beta blockers. In fact, early administration of an IV beta blocker effectively reduces the incidence of VF in evolving MI.[132]

Accelerated Idioventricular Rhythm

An accelerated idioventricular rhythm typically occurs during the first 2 days, with about equal frequency in anterior and inferior infarctions. Most episodes are brief. Accelerated idioventricular rhythm often follows when successful reperfusion has been established with fibrinolytic therapy. However, the frequent occurrence of this rhythm in patients without reperfusion limits its reliability as a marker of the restoration of patency of the infarct-related coronary artery and may have different implications following primary PCI.[133] In contrast to rapid VT, accelerated idioventricular rhythm is thought not to affect prognosis, and we do not routinely treat accelerated idioventricular rhythms.

Ventricular Tachycardia and Ventricular Fibrillation

A leading hypothesis for a major mechanism of ventricular arrhythmias in the acute phase of coronary occlusion is reentry caused by inhomogeneity of the electrical characteristics of ischemic myocardium[133] (**Fig. 59.32**). The cellular electrophysiologic mechanisms for reperfusion arrhythmias appear to include washout of various ions such as lactate and potassium and toxic substances that have accumulated in the ischemic zone. VT or VF occurring late in the course of STEMI is more common in patients with transmural infarction and LV dysfunction and is more frequently associated with hemodynamic deterioration.

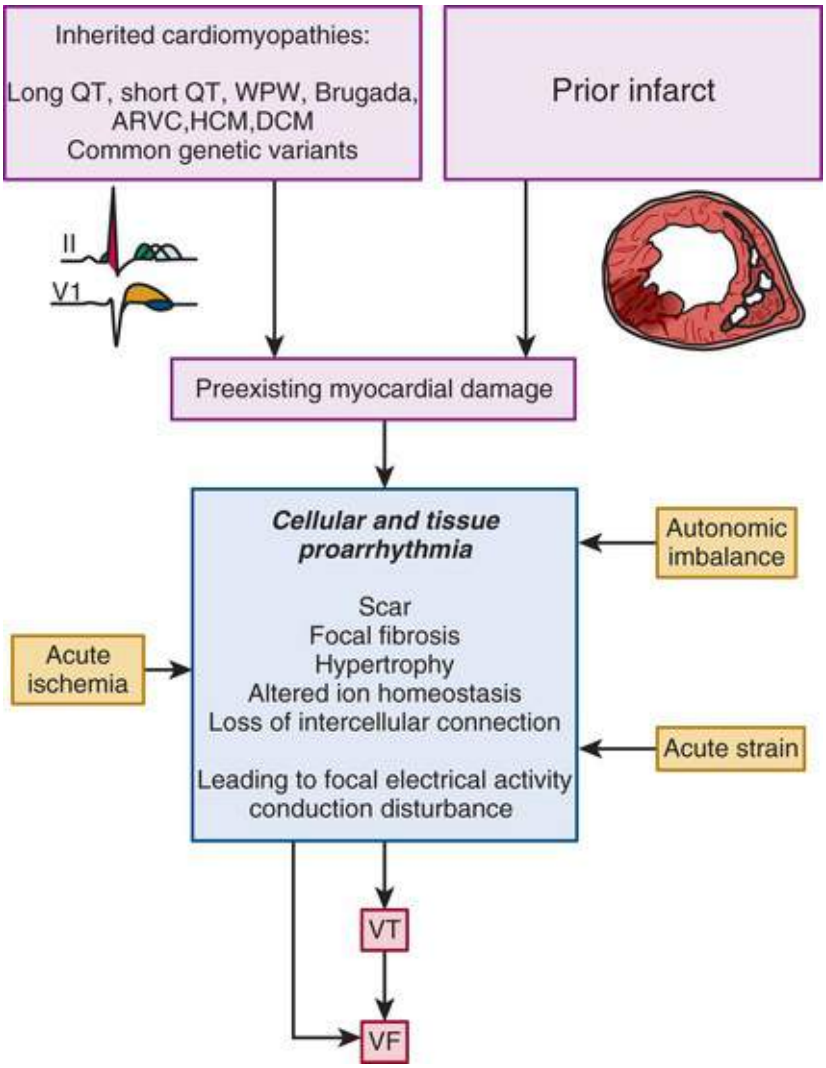


FIGURE 59.32 Drivers of arrhythmias in acute coronary syndromes. A preexisting substrate for ventricular arrhythmias, secondary to prior MI, cardiomyopathy, or a genetic predisposition, together with acute ischemia, autonomic tone, and acute ventricular strain, creates triggered activity and arrhythmias. ARVC, Arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolf-Parkinson-White syndrome. (Adapted from Kirchhof P, Breithardt G, Eckardt L. Primary prevention of sudden cardiac death. Heart 2006;92:1873–8, Copyright BMJ Publishing Group Ltd; and from Basso C, Rizzo S, Thiene G. The metamorphosis of myocardial infarction following coronary recanalization. Cardiovasc Pathol 2010;19:22–8.)

Prophylaxis

Because hypokalemia can increase the risk for development of VT, low serum potassium levels require prompt identification and treatment after admission for STEMI.[134] Despite the lack of a consistent relationship between hypomagnesemia and ventricular arrhythmias, magnesium deficits may still link to risk because patients with STEMI have reduced intracellular magnesium levels not adequately reflected by serum measurements. As noted earlier, magnesium should be repleted to achieve a serum level of 2 mEq/L. Early beta-blocker use has reduced VF and can be instituted in patients who lack a contraindication.[1] Lidocaine prophylaxis to prevent primary VF is no longer advised.[1]

Management

Treatment of unstable VT or VF consists of electrical cardioversion implemented as rapidly as possible.[135] IV administration of amiodarone can also facilitate management of unstable ventricular arrhythmias or prevention of refractory recurrent episodes. After reversion to sinus rhythm, every effort

should be made to correct any underlying abnormalities, such as hypoxia, hypotension, acid-base or electrolyte disturbances, or digitalis excess. Urgent revascularization is warranted if ventricular arrhythmias are ongoing and caused by ischemia. The use of extended antiarrhythmic therapy, such as amiodarone or lidocaine, is discussed in **Chapters 36 and 39**. In patients with sustained VT or VF at a time *after* successful reperfusion, we generally continue antiarrhythmic therapy, most often amiodarone, until a defibrillator is placed.

Prognosis

Among patients who underwent fibrinolytic therapy in the GUSTO-I (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) study, approximately 10% experienced VT/VF. In the APEX-AMI (Assessment of Pexelizumab in Acute Myocardial Infarction) study, which included patients treated with primary PCI, sustained VT/VF developed in 5.7%. Patients with VT/VF had worse clinical outcomes than those without VT/VF. Additionally, mortality rates were higher in those with late versus early VT/VF; specifically, when compared with patients without VT/VF, the adjusted risk of mortality at 90 days increased twofold or sixfold in patients with early or late VT/VF, respectively.[133] In patients in whom sustained VT/VF develops later in the course after STEMI (e.g., >48 hours) without evidence of a reversible cause, ICD therapy for secondary prevention should be considered before discharge.[1] This situation differs from that in patients with VT/VF *before* reperfusion therapy, in whom antiarrhythmic therapy other than a beta blocker is not indicated. Indications for insertion of an ICD for *primary* prevention in patients with a reduced LVEF after STEMI are discussed later.

Bradyarrhythmias (See Chapters 40 and 41)

Sinus Bradycardia

Sinus bradycardia frequently occurs during the early phases of STEMI, particularly in patients with inferior and posterior infarctions. On the basis of data from experimental infarction and some clinical observations, the increased vagal tone that produces sinus bradycardia during the early phase of STEMI may actually be beneficial, perhaps because it reduces myocardial oxygen demand. Thus the acute mortality rate in patients with sinus bradycardia appears similar to that in those without this arrhythmia.[1]

Management

Isolated sinus bradycardia, unaccompanied by hypotension or ventricular ectopy, should be observed rather than treated. In the first 4 to 6 hours after infarction, if the sinus rate is extremely low (<40 to 50 beats/min) and associated with hypotension, IV atropine in doses of 0.3 to 0.6 mg every 3 to 10 minutes (with total dose not exceeding 3 mg) can be administered to bring the heart rate up to approximately 60 beats/min.

Atrioventricular and Intraventricular Block

Ischemic injury can produce conduction block at any level of the AV or intraventricular conduction system. Such blocks can occur in the AV node and the bundle of His and produce various grades of AV block, in either main bundle branch and produce right or left bundle branch block, and in the anterior and posterior divisions of the left bundle and produce left anterior or left posterior (fascicular) divisional blocks. Conduction disturbances can occur in various combinations. **Table 59.13** summarizes the clinical

features of proximal and distal AV conduction disturbances in patients with STEMI.

TABLE 59.13

Atrioventricular Conduction Disturbances in Acute Myocardial Infarction

	LOCATION OF ATRIOVENTRICULAR (AV) CONDUCTION DISTURBANCE	
	Proximal	**Distal**
Site of block	Intranodal	Infranodal
Site of infarction	Inferoposterior	Anteroseptal
Compromised arterial supply	RCA (90%), LCX (10%)	Septal perforators of LAD
Pathogenesis	Ischemia, necrosis, hydropic cell swelling, excessive parasympathetic activity	Ischemia, necrosis, hydropic cell swelling
Predominant type of AV nodal block	First-degree (PR >200 msec) Mobitz type I second-degree	Mobitz type II second-degree Third-degree
Common premonitory features of third-degree AV block	First- or second-degree AV block Mobitz I pattern	Intraventricular conduction block Mobitz II pattern
Features of escape rhythm following third-degree block		
Location	Proximal conduction system (His bundle)	Distal conduction system (bundle branches)
QRS width	<0.12/sec*	>0.12/sec
Rate	45-60/min but may be as low as 30/min	Often <30/min
Stability of escape rhythm	Rate usually stable; asystole uncommon	Rate often unstable with moderate to high risk for ventricular asystole
Duration of high-grade AV block	Usually transient (2-3 days)	Usually transient but some form of AV conduction disturbance and/or intraventricular defect may persist
Associated mortality rate	Low unless associated with hypotension and/or with power failure or ventricular arrhythmias	High because of extensive infarction associated heart failure
Pacemaker therapy		
Temporary	Rarely required; may be considered for bradycardia associated with left ventricular power failure, syncope, or angina	Should be considered in patients with anteroseptal infarction and acute bifascicular block
Permanent	Almost never indicated because the conduction defect is usually transient	Indicated for patients with high-grade AV block and block in the His-Purkinje system and those with a transient advanced AV block and associated bundle branch block

*Some studies suggest that a wide QRS escape rhythm (>0.12 second) following high-grade AV block in inferior infarction is associated with a worse prognosis.

LAD, Left anterior descending coronary artery; *LCX,* left circumflex coronary artery; *RCA,* right coronary artery.

Modified from Antman EM, Rutherford JD, editors. Coronary Care Medicine: a Practical Approach. Boston: Martinus Nijhoff; 1986; and Dreifus LS et al. Guidelines for implantation of cardiac pacemakers and antiarrhythmia devices. J Am Coll Cardiol 1991;18:1.

First-Degree Atrioventricular Block

A first-degree AV block does not generally require specific treatment. Beta blockers and calcium antagonists (other than dihydropyridines) prolong AV conduction and may be responsible for first-degree AV block as well, but discontinuation of the use of these drugs in the setting of STEMI could increase ischemia and ischemic injury. Therefore, we generally do not decrease the dosage of these drugs unless the PR interval is longer than 0.24 second. These agents should be stopped only if a higher-degree block or hemodynamic impairment occurs. If the block is a manifestation of excessive vagotonia and is associated with sinus bradycardia and hypotension, administration of atropine, as already outlined, may be helpful. Continued electrocardiographic monitoring is important in such patients in view of the possible progression to higher degrees of block.

Second-Degree Atrioventricular Block

First-degree and type I second-degree AV blocks do not appear to affect survival, are most often associated with occlusion of the right coronary artery, and result from ischemia of the AV node (**Table 59.13**). Specific therapy is not required in patients with type I second-degree AV block when the ventricular rate exceeds 50 beats/min and PVCs, HF, and bundle branch block are absent. If these complications develop, however, or if HR falls below approximately 50 beats/min and the patient is

symptomatic, immediate treatment with atropine (0.3 to 0.6 mg) is indicated. Temporary pacing systems are almost never needed in the management of this arrhythmia.

Type II second-degree AV block in the setting of inferior or posterior STEMI is usually temporary and is manifested as a narrow-complex, junctional escape rhythm. These arrhythmias can typically be managed conservatively. With anterior or lateral STEMI, a type II second-degree AV block usually originates from a lesion in the conduction system below the bundle of His (**Table 59.13**). Because of its potential for progression to complete heart block, patients with type II second-degree AV block in this setting should be treated with a temporary external or transvenous demand pacemaker.[1]

Complete (Third-Degree) Atrioventricular Block

Complete AV block can occur in patients with either inferior or anterior infarction, although it is more common in inferior than in anterior MI. Complete heart block in patients with inferior infarction usually develops gradually, often progressing from a first-degree or type I second-degree block.[133] The escape rhythm is typically stable without asystole and often junctional, with a rate exceeding 40 beats/min and a narrow QRS complex in 70% of cases and a slower rate and wide QRS complex in the others. This form of complete AV block is often transient, may respond to pharmacologic antagonism of adenosine with methylxanthines, and resolves in most patients within a few days (**Table 59.13**).

Patients with inferior infarction often have concomitant ischemia or infarction of the AV node secondary to hypoperfusion of the AV node artery, but the His-Purkinje system usually escapes injury. Patients with inferior STEMI and AV block have larger infarcts and more depressed RV and LV function than patients with an inferior infarct and no AV block. As already noted, junctional escape rhythms with narrow QRS complexes occur frequently in this setting.

Pacing is not generally necessary in patients with inferior wall infarction and complete AV block because this is often transient in nature. Pacing is indicated, however, if symptoms related to a ventricular rate emerge, if ventricular arrhythmias or hypotension is present, or if pump failure develops. Atropine rarely proves adequate in these patients. Only when complete heart block develops in less than 6 hours after the onset of symptoms is atropine likely to abolish the AV block or cause acceleration of the escape rhythm. In such cases the AV block is more likely to be transient and related to increases in vagal tone, as opposed to the more persistent block seen later in the course of STEMI, which generally requires cardiac pacing.

In patients with anterior infarction, third-degree AV block can occur suddenly 12 to 24 hours after the onset of infarction, although it is usually preceded by intraventricular block and often a type II (not first-degree or type I) second-degree AV block. Such patients typically have unstable escape rhythms with wide QRS complexes and rates less than 40 beats/min; ventricular asystole may occur quite suddenly. In patients with anterior infarction, AV block generally develops as a result of extensive septal necrosis involving the bundle branches. The high mortality rate in these patients with a slow idioventricular rhythm and wide QRS complex is caused by extensive myocardial necrosis resulting in severe LV failure and frequently shock (**Table 59.13**).

Whether temporary transvenous pacing per se improves survival in patients with anterior STEMI remains controversial. Some physicians contend that ventricular pacing has limited efficacy when used to correct a complete AV block in patients with anterior infarction, in view of the poor prognosis in this group regardless of therapy. However, pacing protects against asystole and may protect against transient hypotension, with its attendant risks of extending the infarction and precipitating malignant ventricular tachyarrhythmias.

Intraventricular Block

The right bundle branch and the left posterior division have a dual blood supply from the left anterior descending and right coronary arteries, whereas the left anterior division is supplied by septal perforators originating from the LAD. Not all conduction blocks in patients with STEMI are complications of infarcts, because almost half are already present at the first ECG recording and may represent antecedent conduction abnormalities. Compared with patients without conduction defects, those with STEMI and bundle branch blocks have higher peak biomarker levels, lower EF, and increased in-hospital and long-term mortality rates.[133,136-138] In the prefibrinolytic era, intraventricular conduction disturbances (i.e., block within one or more of the three subdivisions [fascicles] of the His-Purkinje system: anterior and posterior divisions of the left bundle and the right bundle) occurred in 5% to 10% of patients with STEMI. More recent series in the reperfusion era suggest that intraventricular blocks occur in approximately 2% to 5% of patients with MI.[1]

Isolated Fascicular Blocks

An isolated left anterior divisional block is unlikely to progress to a complete AV block. Mortality is increased in these patients, although not as much as in those with other forms of conduction block. The posterior fascicle is larger than the anterior fascicle, and in general, a larger infarct is required to block it. As a consequence, mortality is markedly increased. Complete AV block is an uncommon complication of either form of isolated divisional block.

Right Bundle Branch Block

Right bundle branch block (RBBB) alone can lead to AV block because it is often a new lesion associated with anteroseptal infarction. Isolated RBBB is associated with increased mortality risk in patients with anterior STEMI, even if complete AV block does not occur, but this appears to be the case only if accompanied by HF.[136,137]

Bifascicular Block, Including Left Bundle Branch Block

The combination of RBBB with either left anterior or left posterior divisional block or the combination of left anterior and posterior divisional blocks (i.e., LBBB) is known as *bidivisional* or *bifascicular block*. If a new block occurs in two of the three divisions of the conduction system, the risk for development of a complete AV block is quite high. Mortality is also high because of the occurrence of severe pump failure secondary to the extensive myocardial necrosis required to produce such an extensive intraventricular block.[1]

Preexisting bundle branch block or divisional block is less often associated with the development of complete AV block in patients with STEMI than conduction defects acquired during the course of the infarct. Bidivisional block in the presence of prolongation of the PR interval (first-degree AV block) may indicate disease of the third subdivision rather than disease of the AV node and entails a greater risk for complete heart block than if first-degree AV block is absent.

Complete bundle branch block (either left or right), the combination of RBBB and left anterior divisional (fascicular) block, and any of the various forms of trifascicular block are all associated more often with anterior than with inferoposterior infarction. All these forms are more common with large infarcts and in older patients and have a higher incidence of other accompanying arrhythmias than seen in patients without bundle branch block.

Use of Pacemakers in Patients with Acute Myocardial Infarction (See Chapter 41)

Temporary Pacing

As with complete AV block, transvenous ventricular pacing has not resulted in a statistically demonstrable improvement in prognosis in STEMI patients who develop intraventricular conduction defects. Temporary pacing is advisable in some patients, however, because of the high risk for complete AV block. This category includes patients with new bilateral (bifascicular) bundle branch block (i.e., RBBB with left anterior or posterior divisional block and alternating right and left BBB); first-degree AV block adds to this risk. An isolated new block in only one of the three fascicles, even with PR prolongation and preexisting bifascicular block and a normal PR interval, poses somewhat less risk; these patients should be monitored closely, with insertion of a temporary pacemaker deferred unless a higher-degree AV block occurs.

Asystole

The presence of apparent ventricular asystole on monitor displays of continuously recorded ECGs may be misleading because the rhythm may actually be fine VF. The predominance of VF as the cause of cardiac arrest in this setting suggests electrical countershock as initial therapy, even if definitive electrocardiographic documentation of this arrhythmia is not available.

Permanent Pacing

The advisability of permanent pacemaker insertion is complicated because not all sudden deaths in patients with STEMI and conduction defects result from high-grade AV block. A high incidence of late VF occurs in survivors with anterior STEMI complicated by either RBBB or LBBB. Therefore, rather than asystole caused by failure of AV conduction and infranodal pacemakers, VF could be responsible for late sudden death.

Long-term pacing may be indicated when complete heart block persists throughout the hospital phase in a patient with STEMI, when sinus node function is greatly impaired, or when type II second-degree or third-degree block occurs intermittently.[139] High-grade AV block associated with newly acquired BBB or other criteria for conduction system impairment may justify prophylactic long-term pacing as well. Additional considerations that drive the decision to insert a permanent pacemaker include whether the patient is a candidate for an ICD or has severe HF that might be improved with biventricular pacing (**see Chapters 25 and 39**).

Supraventricular Tachyarrhythmias (See Chapters 37 and 38)

Sinus Tachycardia

Sinus tachycardia is typically associated with augmented sympathetic activity and may provoke transient hypertension or hypotension. Common causes are anxiety, persistent pain, LV failure, fever, pericarditis, hypovolemia, pulmonary embolism, and drugs (e.g., epinephrine, dopamine); rarely, it occurs in patients with atrial infarction. Sinus tachycardia is particularly common in patients with anterior infarction, especially in those with significant accompanying LV dysfunction. It is an undesirable rhythm in patients with STEMI because it augments myocardial oxygen consumption and reduces the time in diastole

available for coronary perfusion, thereby intensifying the myocardial ischemia and external myocardial necrosis. Persistent sinus tachycardia can signify persistent HF and, in these circumstances, connotes a poor prognosis and excess mortality. An underlying cause should be sought and appropriate treatment instituted, such as analgesics for pain; diuretics for HF; oxygen, beta blockers, and nitroglycerin for ischemia; and aspirin for fever or pericarditis. Treating sinus tachycardia caused by pain, anxiety, or fever with beta blockers is reasonable, but these agents are contraindicated in patients who are tachycardic because of pump failure.

Atrial Flutter and Fibrillation

Atrial flutter and atrial fibrillation (AF) are usually transient in patients with STEMI; these arrhythmias typically result from augmented sympathetic stimulation of the atria and often occur in patients with LV failure, pulmonary emboli, or atrial infarction and aggravate the hemodynamic deterioration in these states (**see Table 59.11**). The increased ventricular rate and loss of the atrial contribution to LV filling can reduce cardiac output considerably. AF during STEMI is associated with increased mortality and stroke, particularly in patients with anterior infarction.[140-143] Because it is more common in patients with clinical and hemodynamic manifestations of extensive infarction and a poor prognosis, AF is probably a marker of a poor prognosis, and several studies have found at least a small, independent contribution to increased mortality.[141-143]

Management

Atrial flutter and AF in patients with STEMI are treated as in other settings (**see Chapter 38**). If the arrhythmia causes ongoing hypotension, ischemia, or HF, cardioversion should be considered. In stabilized patients and in the absence of contraindications, a beta blocker should be administered after STEMI; in addition to several other benefits, these agents help slow the ventricular rate should AF recur. Digitalis may also help slow the ventricular rate when AF develops after STEMI in the setting of ventricular dysfunction. In addition, amiodarone may aid management. Patients with recurrent episodes of AF should be treated with oral anticoagulants (to reduce the risk for stroke), even if sinus rhythm is present at hospital discharge, because no antiarrhythmic regimen can completely suppress AF.

Other Complications

Recurrent Chest Discomfort

Evaluation of postinfarction chest discomfort may be complicated by previous abnormalities on the ECG and a vague description of the discomfort by the patient, who either may be exquisitely sensitive to fleeting discomfort or may deny a potential recrudescence of symptoms. Clinicians face the critical task of distinguishing recurrent angina or infarction from nonischemic causes of discomfort that might result from infarct expansion, pericarditis, pulmonary embolism, and non–cardiac-related conditions. Ischemic causes to consider include acute reocclusion of an initially recanalized or stented vessel, mechanical or thrombotic occlusion of a side branch or distal vessel during an initial PCI, new ischemia in a non–infarct-related coronary artery that was also stenosed but not occluded, and coronary spasm. Important diagnostic maneuvers include repeated physical examination, repeated ECG, and assessment of the response to SL nitroglycerin. (The use of noninvasive diagnostic evaluation for recurrent ischemia in patients whose symptoms appear only with moderate or higher levels of exertion is also discussed later in

this chapter.)

Recurrent Ischemia and Reinfarction

Patients undergoing primary PCI for STEMI versus fibrinolysis have less postinfarction angina and reinfarction. Additionally, in high-risk patients with STEMI who were treated with fibrinolysis, transfer for PCI within 6 hours after fibrinolysis is also associated with significantly fewer ischemic complications than treatment with fibrinolysis alone.[69] More effective antiplatelet and antithrombin therapies have also reduced the rate of recurrent ischemic events following STEMI.[1] Consequently, the incidence of early recurrent ischemic events in STEMI patients treated by immediate or delayed PCI now is less than 5%.[4,69]

Diagnosis

Extension of the original zone of necrosis or reinfarction into a separate myocardial zone can be a difficult diagnosis, especially within the first 24 hours after the index event. Diagnostic criteria have been established,[144] but discrimination of a new MI discrete from the initial STEMI is often challenging, because cardiac markers may remain elevated as a result of the initial infarction, and distinguishing changes of the normal evolution after the index infarction from those caused by recurrent infarction may not be possible on the ECG. Recurrent infarction should be strongly considered, however, with dynamic recurrence of ST-segment elevation.

Pericarditis should also be considered in such patients. The presence of a rub and lack of responsiveness to nitroglycerin may be useful in distinguishing pericardial discomfort, but doing so on clinical grounds is frequently challenging, and diagnostic coronary angiography may be necessary to exclude acute native vessel or stent thrombosis. The predominant angiographic predictors of reinfarction in patients undergoing primary PCI include a final coronary stenosis greater than 30%, post-PCI coronary dissection, and post-PCI intracoronary thrombus, multivessel disease, and greater total stent length.[145,146]

Prognosis

Regardless of whether postinfarction angina is persistent or limited, its presence is important because of the associated higher short-term morbidity rate. Reinfarction links to higher rates of in-hospital complications (e.g., HF, AV block) and early and long-term mortality.[145]

Management

Patients with repeat ST-segment elevation and the appropriate clinical findings should undergo urgent catheterization and PCI (**see Fig. 59.2**), unless pericarditis or other post-MI complications are the cause; repeated fibrinolysis can be considered if PCI is not available. In patients believed to have recurrent ischemia in the absence of ST elevation concerning for ongoing injury and who do not have evidence of hemodynamic compromise, an attempt should be made to control symptoms with SL or IV nitroglycerin and IV beta blocker to slow HR to 60 beats/min. Hypotension, HF, or ventricular arrhythmias developing during recurrent ischemia usually warrant urgent catheterization and revascularization.

High-risk patients with STEMI who undergo fibrinolysis may benefit from a strategy of routine referral for catheterization and revascularization (3 to 24 hours; **see eFig. 52.5**).[69] Trials that compared primary PCI with PCI performed as soon as possible after establishing a preparatory pharmacologic regimen, however, have not shown such a facilitated-PCI approach to be more effective than primary PCI, and mortality may even increase because of excessive bleeding in the facilitated-PCI group.[1]

Finally, with increasing use of PCI for the management of patients with STEMI, clinicians should be alert to the problem of stent thrombosis as a cause of recurrent ischemia. Stent thrombosis can occur acutely (hours to days after stent deployment) or late (many months after stent deployment) (**see Chapter 62**).

Pericardial Effusion and Pericarditis (See Chapter 83)

Pericardial Effusion

Effusions are generally detected echocardiographically, and their incidence varies with imaging modality and technique, criteria, and laboratory expertise. Effusions are more common in patients with anterior or lateral STEMI, larger infarcts, more microvascular obstruction, greater LV dysfunction, no reperfusion, and higher rates of HF.[147-149] Most pericardial effusions after STEMI do not cause hemodynamic compromise. The reabsorption rate of a postinfarction pericardial effusion is slow, with resolution often taking several months. An effusion does not necessarily indicate pericarditis; although they may coexist, most effusions develop without other evidence of pericarditis. When tamponade does occur, it is usually caused by ventricular rupture or hemorrhagic pericarditis.[150]

Pericarditis

Pericarditis can produce pain as early as the first day and as late as 8 weeks after STEMI. The pain of pericarditis may be confused with that resulting from postinfarction angina, recurrent infarction, or both. An important distinguishing feature is radiation of the pain to either trapezius ridge, a finding that is almost pathognomonic of pericarditis and rarely seen with ischemic discomfort. Additionally, the discomfort of pericarditis usually worsens during a deep inspiration but can be relieved or diminished by sitting up and leaning forward.

Transmural MI, by definition, extends to the epicardial surface and can cause local pericardial inflammation. An acute fibrinous pericarditis, *pericarditis epistenocardica,* occurs frequently after transmural infarction, but most patients do not report any symptoms from this process. Although transient pericardial friction rubs are relatively common within the first 48 hours in patients with transmural infarction, pain or electrocardiographic changes occur much less often. The development of a pericardial rub, however, appears to correlate with a larger infarct and greater hemodynamic compromise.

Although anticoagulation clearly increases the risk for hemorrhagic pericarditis early after STEMI, this complication does not occur with sufficient frequency during heparinization or after fibrinolytic therapy to warrant absolute prohibition of such agents when a rub is present. Nevertheless, detection of a significant (≥1 cm) or enlarging pericardial effusion usually should indicate discontinuation of anticoagulation. Patients in whom continuation or initiation of anticoagulant therapy is strongly indicated (e.g., during cardiac catheterization) should have heightened monitoring of clotting parameters and observation for clinical signs of possible tamponade. Late pericardial constriction caused by anticoagulant-induced hemopericardium has been reported.

Treatment of pericardial discomfort consists of aspirin, but usually in doses higher than prescribed routinely following infarction—doses of 650 mg orally as often as every 4 hours may be necessary. Nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids should be avoided because they may interfere with myocardial scar formation.[151]

Dressler Syndrome

Also known as *post–myocardial infarction syndrome*, Dressler syndrome usually occurs 1 to 8 weeks after infarction. Dressler cited an incidence of 3% to 4% of all patients with MI in 1957, but the incidence has decreased dramatically since that time. Clinically, patients with Dressler syndrome have malaise, fever, pericardial discomfort, leukocytosis, an elevated erythrocyte sedimentation rate (ESR), and a pericardial effusion. At autopsy, individuals with this syndrome usually demonstrate localized fibrinous pericarditis containing polymorphonuclear leukocytes (PMNs). The cause of post-MI syndrome is not clearly established, although detection of antibodies to cardiac tissue suggests an immunopathologic process. Treatment is with aspirin, 650 mg as often as every 4 hours, may be effective.[151] Glucocorticosteroids and NSAIDs are best avoided in patients with Dressler syndrome within 4 weeks of STEMI because of their potential to impair infarct healing, cause ventricular rupture, and increase coronary vascular resistance.[151]

Venous Thrombosis and Pulmonary Embolism

Almost all peri-MI pulmonary emboli originate from thrombi in the veins of the lower extremities; much less frequently, they originate from mural thrombi overlying an area of RV infarction. Bed rest and HF predispose to venous thrombosis and subsequent pulmonary embolism (PE), and both these conditions often occur in patients with STEMI, particularly in those with large infarcts. At a time when patients with STEMI were routinely subjected to prolonged bed rest, more than 20% examined at autopsy had PE, and massive PE accounted for 10% of deaths from MI. In contemporary practice, with early mobilization and the widespread use of low-dose anticoagulant prophylaxis, PE has become an uncommon cause of death in patients with STEMI. When PE does occur in patients with STEMI, management is generally similar to that for patients without infarction (**see Chapter 84**).

Left Ventricular Aneurysm

The term *left ventricular aneurysm* (often called *true aneurysm*) is generally reserved for a discrete, dyskinetic area of the LV wall with a broad neck (to differentiate it from a pseudoaneurysm caused by a contained myocardial rupture) (**eFig. 59.8**). Dyskinetic or akinetic areas of the left ventricle are much more common than true aneurysms after STEMI. True LV aneurysms probably develop in less than 5% of all patients with STEMI.[1] The wall of a true aneurysm is thinner than that of the rest of the left ventricle (**eFig. 59.8**), and it is usually composed of fibrous tissue, as well as necrotic muscle occasionally mixed with viable myocardium.

Pathogenesis

Aneurysm formation presumably occurs when intraventricular tension stretches the noncontracting infarcted heart muscle and thus produces expansion of the infarct, a relatively weak, thin layer of necrotic muscle, and fibrous tissue that bulges with each cardiac contraction. With the passage of time, the wall of the aneurysm becomes more densely fibrotic, but it continues to bulge with systole and renders some of the LV stroke volume during each systole ineffective.

Total occlusion of a poorly collateralized LAD is associated with aneurysm formation after anterior STEMI. An aneurysm rarely occurs with multivessel disease when either extensive collaterals or a patent LAD. Aneurysms occur approximately four times more often at the apex and in the anterior wall than in the inferoposterior wall. The overlying pericardium generally adheres densely to the wall of the aneurysm, which may even become partially calcified after several years. True LV aneurysms (in contrast

to pseudoaneurysms) rarely rupture.

Diagnosis

The presence of persistent ST-segment elevation in an electrocardiographic area of infarction, classically thought to suggest aneurysm formation, indicates a large infarct with a regional wall motion abnormality but does not necessarily imply an aneurysm. The diagnosis of aneurysm is best made by echocardiography, CMR, CT, or left ventriculography at cardiac catheterization.

Prognosis and Treatment

A LV aneurysm increases the risk for mortality, even compared with that in patients with a comparable LVEF. Death in these patients is frequently sudden and presumably related to the relatively high incidence of ventricular tachyarrhythmias that occur with aneurysms.[152] With loss of shortening from the area of the aneurysm, the remainder of the ventricle may become hyperkinetic to compensate, but with relatively large aneurysms, complete compensation is impossible. Stroke volume falls, or if maintained, it is at the expense of an increase in end-diastolic volume, which in turn leads to increased wall tension and myocardial oxygen demand. Heart failure may ensue, and angina may appear or worsen.

Aggressive management of STEMI, including prompt reperfusion, may diminish the incidence of ventricular aneurysms. Surgical aneurysmectomy generally succeeds only if contractile performance in the nonaneurysmal portion of the left ventricle is relatively preserved. In such circumstances, when the operation is performed for worsening HF or angina, operative mortality is relatively low, and clinical improvement can be expected.[94] Compared with CABG alone, adding surgical ventricular reconstruction for patients with LVEF of 35% or less reduced LV volume but did not improve symptoms, exercise tolerance, or the endpoint of death or hospitalization for cardiac causes.[153] A transcatheter approach for aneurysm exclusion is currently under investigation; to date, device implantation has been generally successful, but outcome data are limited.[154,155] Because of the risk for mural thrombosis and systemic embolization, patients with a residual LV aneurysm after STEMI may warrant long-term oral anticoagulation.

Left Ventricular Thrombus and Arterial Embolism

Endocardial inflammation and the relative stasis of blood during the acute phase of infarction probably provide a thrombogenic surface for clots to form in the left ventricle. With extensive transmural infarction of the septum, however, mural thrombi may overlie infarcted myocardium in both ventricles. The incidence of LV thrombus formation after STEMI appears to have dropped from approximately 20% to 5% with more aggressive use of antithrombotic strategies, but variation in imaging techniques will influence detection rates.[156] Prospective studies have suggested that patients in whom a mural thrombus develops early (within 48 to 72 hours of infarction) have an extremely poor early prognosis, with a high rate of mortality from the complications of a large infarction (shock, reinfarction, rupture, and ventricular tachyarrhythmia), rather than emboli from the LV thrombus.

Even though a mural thrombus adheres to the endocardium overlying the infarcted myocardium, superficial portions can become detached and embolize systemically. Although estimates vary because of patient selection, approximately 10% of mural thrombi result in systemic embolization.[156] Echocardiographic risk factors for thrombus embolization include increased mobility and protrusion into the ventricular chamber, visualization on multiple views, and contiguous zones of akinesis and

hyperkinesis. CMR techniques can also characterize LV thrombi and assist in prediction of the risk for embolism.

Management

Data from previous trials with limited sample sizes suggested that anticoagulation (IV heparin or high-dose SC heparin) reduces the development of LV thrombi by 50%. However, because of a low event rate, precluded demonstrating reduced systemic embolism.[156] Fibrinolysis reduces the rate of thrombus formation. However, antithrombotic therapy with heparin cloud the interpretation of data from fibrinolytic trials. Recommendations for anticoagulation vary considerably, and fibrinolysis has precipitated fatal embolization. Moreover, few data from the era of dual-antiplatelet therapy after primary PCI are available to guide decisions. Nevertheless, anticoagulation for 3 to 6 months with warfarin is reasonable for many patients with demonstrable mural thrombi. Patients with STEMI and anterior apical akinesis or severe dyskinesis may also merit a limited course of anticoagulant therapy.[1]

Convalescence, Discharge, and Post–Myocardial Infarction Care

The transition to outpatient care after STEMI is a critical one. Posthospital systems of care designed to reduce hospital readmissions can facilitate coordinated, evidence-based outpatient care for all patients with STEMI.[1] (**See also Chapter 54**.)

Timing of Hospital Discharge

In practice, the timing of discharge from the hospital is variable. Patients with STEMI have risk for late in-hospital mortality from recurrent ischemia or infarction, hemodynamically significant ventricular arrhythmias, and severe HF. Risk indicators for mortality in the hospital include clinical HF, as evidenced by persistent sinus tachycardia and pulmonary congestion, recurrent VT and VF, new AF or atrial flutter, intraventricular conduction delays or heart block, anterior location of infarction, and recurrent episodes of angina with marked ST-segment abnormalities at low activity levels (see later, Risk Stratification after ST-Elevation Myocardial Infarction).

Aggressive reperfusion protocols with PCI or fibrinolytics can reduce the length of hospital stay without compromising mortality after discharge.[157,158] In patients with apparently successful reperfusion, absence of early sustained ventricular tachyarrhythmias, hypotension, or HF, coupled with a well-preserved LVEF, predicts a low risk for late complications in the hospital. Such patients appear to be suitable candidates for hospital discharge less than 5 days from the onset of symptoms; current practice in U.S. hospitals is discharge in 3 days or less for many patients who have undergone successful primary PCI.[158] Most complications that would preclude early discharge occur within the first 3 days of admission, permitting identification of patients suitable for expedited discharge early during the hospitalization. Several controlled trials and many uncontrolled trials of early discharge after STEMI have shown no increase in risk in patients appropriately selected for early discharge.[157,158]

Following STEMI, patients are often eager for information, anxious, in need of reassurance, confused by misinformation and previous impressions, and capable of counterproductive denial. The hospitalization after STEMI provides ample opportunities to begin the rehabilitation process. The decision regarding timing of discharge for patients with uncomplicated STEMI should consider the

patient's psychological state after STEMI, the adequacy of dose titration for essential drugs such as beta blockers and RAAS inhibitors, and the availability and timing of follow-up with visiting nurses and the primary care physician. In patients who have experienced a complication, discharge is deferred until their condition has been stable for several days and they clearly have responded appropriately to any interventions.

Counseling

Before discharge from the hospital, all patients should receive detailed instruction concerning physical activity. Initially, this should consist of walking at home but avoidance of isometric exercise such as lifting. The patient should be given fresh nitroglycerin tablets and instructed in their use (**see Chapter 61**). The patient should also be educated regarding all other medications prescribed. Graded resumption of activity should be encouraged, ideally as part of a monitored cardiac rehabilitation program (**see Chapter 54**). Many approaches have been used, ranging from formal rigid guidelines to general advice advocating moderation and avoidance of any activity that evokes symptoms. Sexual activity counseling, often overlooked during recovery from STEMI, should be included in the educational process.[159] In addition, physicians should explicitly discuss the risk associated with continued smoking and offer assistance in cessation, along with nicotine replacement therapy in appropriate patients.[1,160]

Some evidence indicates that behavioral alteration is possible after recovery from STEMI and may improve the prognosis. Patients with STEMI should be referred to a postdischarge cardiac rehabilitation program with supervised physical exercise and an educational component.[161] Given the relationship between depression and STEMI, psychosocial intervention programs can decrease symptoms of depression and are a useful adjunct to standard cardiac rehabilitation programs after STEMI[162] (**see Chapters 54 and 96**).

Risk Stratification after ST-Elevation Myocardial Infarction

The process of risk stratification following STEMI occurs in several stages: initial findings, in-hospital course, and at hospital discharge. The tools used to form an integrated and dynamic assessment of the patient consist of baseline demographic information; serial ECGs and serum and plasma cardiac biomarker measurements; hemodynamic monitoring data; a variety of noninvasive tests; and if performed, the findings at cardiac catheterization. These findings, integrated with the occurrence of in-hospital complications, can provide information regarding survival.

Initial Findings.

Certain demographic and historical factors portend a worse prognosis in patients with STEMI, including age older than 65, history of diabetes mellitus, previous angina pectoris, and previous MI (**eFig. 59.3**). Diabetes mellitus in particular appears to confer a more than 40% increase in adjusted risk for death by 30 days[163] (**see Chapter 51**). Surviving diabetic patients also experience a more complicated post-MI course, including a greater incidence of postinfarction angina, infarct extension, and HF. These higher rates of complications are probably related to the extensive accelerated atherosclerosis and higher risk for thrombosis and HF associated with diabetes mellitus.

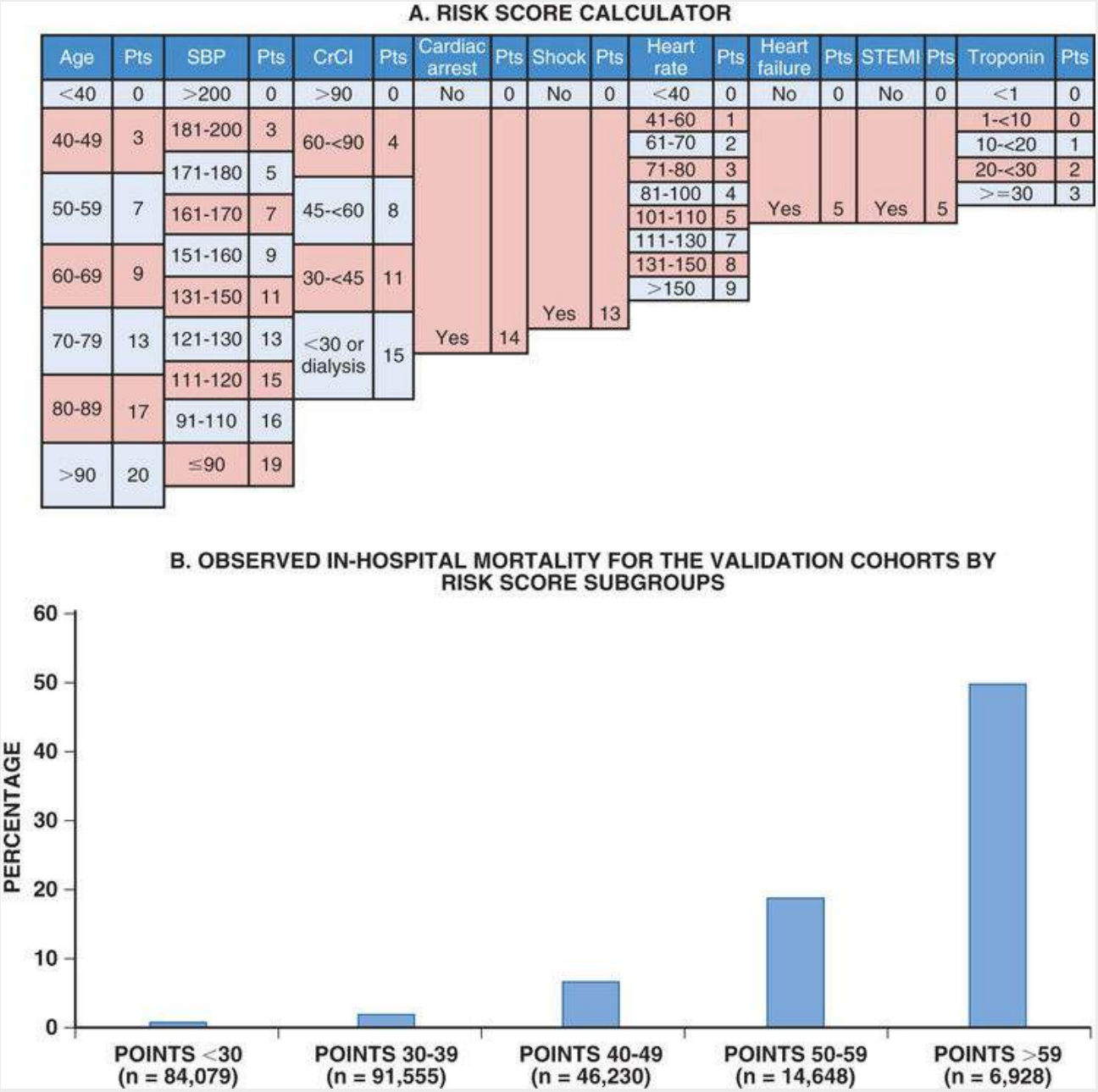
In addition to playing a central role in the decision pathway for the management of patients with ACS based on the presence or absence of ST-segment elevation, the 12-lead ECG provides important prognostic information.[52] Mortality is greater in patients experiencing anterior wall STEMI than in those with inferior STEMI, even when corrected for infarct size. Patients with RV infarction complicating

inferior infarction, as suggested by ST-segment elevation in V_4R, have higher mortality than patients sustaining an inferior infarction without RV involvement. Patients with multiple leads showing ST elevation and a high sum of ST-segment elevation have increased mortality, especially if their infarct is anterior. Patients whose ECGs demonstrate persistent advanced heart block (e.g., type II second-degree or third-degree AV block) or new intraventricular conduction abnormalities (bifascicular or trifascicular) in the course of STEMI have a worse prognosis than patients without these abnormalities (see earlier, Atrioventricular and Intraventricular Block). The influence of high degrees of heart block has particular importance in patients with RV infarction because such patients have a greatly increased mortality risk.[52] Other electrocardiographic findings that augur poorly are persistent horizontal or downsloping ST-segment depression, Q waves in multiple leads, ST-segment depression in anterior leads in patients with inferior infarction, and atrial arrhythmias, especially AF.

Several validated clinical risk stratification tools may be used at initial evaluation to assess the short-term and long-term risk for death after MI.[52] In addition to the patient's age and historical factors such as diabetes and previous MI, clinical signs of HF, including tachycardia and hypotension, are common in many of these clinical risk assessment scores.

Hospital Course.

Hospital mortality from STEMI depends directly on the severity of LV dysfunction. Risk stratification incorporating abnormalities of vital signs (e.g. HR, systolic BP); presence of HF, shock, or cardiac arrest; estimation of infarct size; and in appropriate patients, invasive hemodynamic monitoring provides an assessment of the likelihood of a complicated hospital course and may also identify important abnormalities, such as hemodynamically significant mitral regurgitation, that convey an adverse long-term prognosis[164] (**see Table 59.8 and eFig. 59.9**). In particular, the development of HF and LV dysfunction after MI entails a higher risk for sudden cardiac death.[112] Recurrent infarction and new stroke during hospitalization for STEMI also, not surprisingly, confer a higher risk for death.



EFIGURE 59.9 Using contemporary patient-level data from a large database of 243,440 patients (ACTION [Acute Coronary Treatment and Intervention Outcomes Network] Registry–GWTG [Get with the Guidelines]), a multivariate hierarchical logistic regression model was developed to predict in-hospital mortality in patients presenting with acute myocardial infarction (AMI) using demographic, clinical, and laboratory parameters **(A).** Observed in-hospital mortality rates for the validation cohort varied substantially by risk score **(B),** ranging from as low as 0.4% in the lowest-risk group (score <30) to 49.5% in the highest-risk group (score >59). CrCl, Creatinine clearance; Pts, points; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction. (From McNamara RL et al. Predicting in-hospital mortality in patients with acute myocardial infarction. J Am Coll Cardiol 2016;68(6):626-35.)

Assessment at Hospital Discharge

Both short-term and long-term survival after STEMI depend on three major factors: resting LV function, residual potentially ischemic myocardium, and susceptibility to serious ventricular arrhythmias. The most important of these factors is the state of LV function[52] (**see Fig. 59.20**). The second most important factor is how the severity and extent of the obstructive lesions in the coronary vascular bed perfusing residual viable myocardium affect the risk for recurrent infarction and serious ventricular arrhythmias. Thus, survival is related to the quantity of myocardium that has become necrotic and the portion remaining in ischemic jeopardy. The third risk factor, susceptibility to serious arrhythmias, is reflected in ventricular

ectopic activity and other indicators of electrical instability, such as reduced HR variability or baroreflex sensitivity and abnormal findings on a signal-averaged ECG.[52] All these factors identify patients at increased risk for death.

Assessment of Left Ventricular Function

The left ventricular ejection fraction (LVEF), a readily assessed measurement of LV function, is extremely useful for risk stratification. However, imaging of the left ventricle at rest may not adequately distinguish among infarcted, irreversibly damaged, and stunned or hibernating myocardium. To circumvent this difficulty, various techniques have been investigated to assess the extent of residual viable myocardium and degree of microvascular obstruction, including exercise and pharmacologic stress echocardiography, stress radionuclide perfusion imaging, positron emission tomography, and gadolinium-enhanced CMR.[127,165,166] All these techniques can be performed safely in postinfarction patients. Because no study has clearly shown one imaging modality to be superior to the others, clinicians should be guided in their selection of ventricular imaging technique by the availability and level of expertise with a given modality at their local institution.[166]

Assessment of Myocardial Ischemia

Because of the adverse consequences of recurrent MI after STEMI, assessing a patient's risk for future ischemia and infarction is important. Noninvasive testing for ischemia, usually before discharge, provides valuable information about the presence of residual ischemia in patients who have not undergone coronary angiography during the initial management of STEMI. It may also be useful in assessing the functional significance of any coronary stenoses identified at angiography but not revascularized (**see Table 59.5**). In the latter case, stress imaging to localize ischemia may be useful.

Exercise Testing.

An exercise test also offers an opportunity to formulate a more precise exercise prescription and helps boost patients' confidence in their ability to conduct their daily activities after discharge. Patients who are unable to exercise can be evaluated by a pharmacologic stress protocol with echocardiography or perfusion imaging. Treadmill exercise testing after STEMI has traditionally used a submaximal protocol that requires the patient to exercise until symptoms of angina appear, electrocardiographic evidence of ischemia is seen, or a target workload (5 metabolic equivalents) has been reached, whichever comes first (**see Chapters 13 and 54**). Symptom-limited exercise tests can be performed safely before discharge in patients with an uncomplicated course after infarction. Variables derived from exercise tests after STEMI that have been evaluated for their ability to predict the occurrence of death or recurrent nonfatal infarction include the development and magnitude of ST-segment depression, the development of angina, exercise capacity, and the systolic BP response during exercise.[52]

Assessment for Electrical Instability

After STEMI, patients have the greatest risk for development of sudden cardiac death (SCD) from malignant ventricular arrhythmias in the first 1 to 2 years.[52] Multiple techniques may stratify patients into those who are at increased risk for SCD after STEMI. These include measurement of QT dispersion (variability in QT intervals between ECG leads), ambulatory ECGs for detection of ventricular arrhythmias (Holter monitoring), invasive electrophysiologic testing, recording of a signal-averaged ECG (a measure of delayed, fragmented conduction in the infarct zone), and measurement of HR variability

(beat-to-beat variability in R-R intervals) or baroreflex sensitivity (slope of a line relating beat-to-beat change in the sinus rate in response to alteration of blood pressure). However, none of these approaches has proved sufficiently useful for routine practice.[52]

Despite the increased risk for arrhythmic events following STEMI in patients who have abnormal results on one or more of the noninvasive tests described, several points merit emphasis. The low positive predictive value (<30%) of the noninvasive screening tests limits their usefulness when viewed in isolation. Although the predictive value of screening tests can be improved by combining several tests, the therapeutic implications of an increased risk profile for arrhythmic events have not been established. The reductions in mortality achievable with the general use of beta blockers, ACE inhibitors, aspirin, and revascularization, when appropriate after infarction, coupled with concerns about the efficacy and safety of antiarrhythmic drugs and the cost of implanted defibrillators, leave considerable uncertainty about the therapeutic implications of an abnormal noninvasive test result for electrical instability in an asymptomatic patient. Action by clinicians on the results of an abnormal finding in asymptomatic patients should await additional data on patient outcomes. Management of patients with sustained, hemodynamically compromising arrhythmias is discussed in Part V.

Prophylactic Antiarrhythmic Therapy

Although antiarrhythmic therapy can control atrial and ventricular arrhythmias effectively in many patients, routine use of prophylactic antiarrhythmic drug therapy, with the exception of beta blockers, does not improve outcome and, with some agents, increases the risk for death.[1] The most notable postinfarction trial in this area was CAST (Cardiac Arrhythmia Suppression Trial), which tested whether encainide, flecainide, or moricizine for suppression of ventricular arrhythmias detected on ambulatory electrocardiographic monitoring would reduce the risk for cardiac arrest and death; however, CAST was stopped prematurely because of increased mortality in the active treatment groups. The SWORD (Survival with Oral D-Sotalol) trial was similarly stopped prematurely because of increased mortality in the active treatment group. In contrast, CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) showed that amiodarone reduces the frequency of ventricular premature depolarization in patients with recent MI, and that this reduction correlated with lowering of arrhythmic death or resuscitation from VF. However, 42% of patients discontinued use of amiodarone during maintenance therapy in CAMIAT because of intolerable side effects. EMIAT (European Amiodarone Myocardial Infarction Trial) showed a reduction in arrhythmic death after MI in patients with depressed LV function, but total mortality and other CV-related mortality did not decrease.

The routine use of antiarrhythmic agents (including amiodarone) therefore cannot be recommended. Although trials that included post-STEMI patients in the study population have shown significant reductions in mortality in those randomly assigned to ICD implantation versus conventional medical therapy (**see Chapter 41**), early implantation of an ICD in the first few weeks after MI has not shown benefit.[167] Routine risk stratification to guide ICD placement early after STEMI is therefore not recommended; reassessment of LV function 40 days or longer after STEMI can guide consideration of an ICD for primary prevention of SCD[167] (**Fig. 59.33**). Trials of strategies for prevention and treatment of arrhythmias, including the use of wearable external defibrillators,[168] during the early period after STEMI are ongoing. Wearable cardiac defibrillators can be considered in the immediate post-MI period (e.g., 40 days) in patients with LV dysfunction based on small studies demonstrating efficacy for detection and termination of VT/VF, but without proven survival benefit.[169]

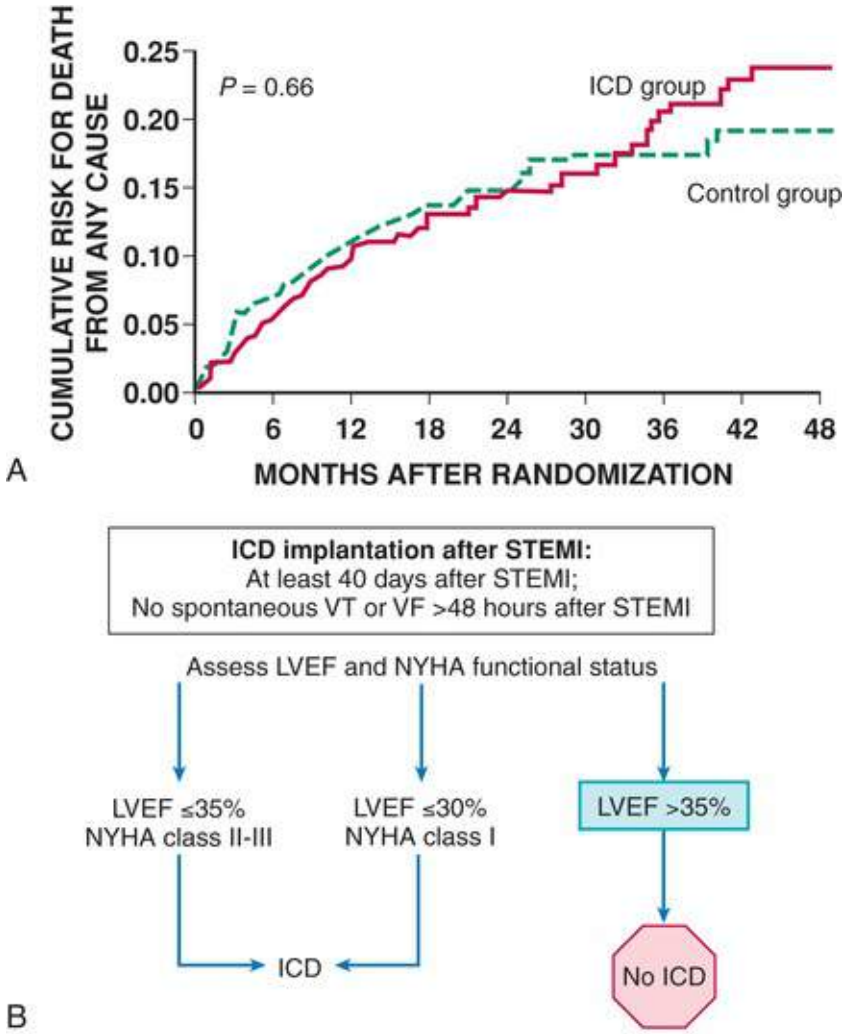


FIGURE 59.33 **A,** DINAMIT trial and algorithm for placement of an implantable cardioverter-defibrillator (ICD) in patients with STEMI but without ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) more than 48 hours after STEMI. DINAMIT, a randomized, open-label study, compared ICD with no ICD therapy 6 to 40 days after an MI in 674 patients who also had a left ventricular ejection fraction (LVEF) of 35% or less and impaired cardiac autonomic function. The study concluded that ICD therapy reduced the rate of death from arrhythmias but that this advantage was offset by an increase in deaths from other causes. **B,** The appropriate management path is based on measurement of LVEF; measurements obtained 3 days or less after STEMI should be repeated before proceeding with the algorithm. Patients with LVEF less than 35% at least 40 days after STEMI are referred for insertion of an ICD if they are in New York Heart Association (NYHA) Class II or III. Patients with a more depressed LVEF less than 30% are referred for ICD implantation even if they are NYHA Class I because of their increased risk for sudden cardiac death. Patients with LVEF less than 40% who have nonsustained VT and inducible VT on electrophysiological study are discussed in Chapter 42. Patients with preserved left ventricular function (LVEF >40%) do not receive an ICD and are treated with medical therapy after STEMI. (**A,** From Hohnloser SH et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med 2004;351:2481; **B,** modified from Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the ACCF/AHA Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation.* 2017.

Secondary Prevention After Acute Myocardial Infarction

Patients who survive the initial course of STEMI still have considerable risk for recurrent events, thus rendering preventive efforts imperative. (See also Part VI.)

Cardiac Rehabilitation (See Chapter 54)

Contemporary exercise-based cardiac rehabilitation after STEMI aims to increase functional capacity,

reducing disability, improving quality of life, modifying coronary risk factors, and limit morbidity and mortality.[161,170] The key components of cardiac rehabilitation include patient assessment; ongoing medical surveillance; nutritional counseling; management of hypertension, lipids, and diabetes mellitus; cessation of smoking; psychosocial counseling; physical activity counseling; exercise training; and pharmacologic treatment, as appropriate. When compared with usual care, cardiac rehabilitation is associated with lower total and cardiac mortality, but despite these outcomes, cardiac rehabilitation services remain vastly underused.[171]

Lifestyle Modification (See Chapter 45)

Efforts to improve survival and quality of life after MI are related to lifestyle modification of known risk factors. Of these, cessation of smoking and control of hypertension are probably the most important. Use of hospital-based smoking cessation programs and referral to cardiac rehabilitation programs have led to successful smoking cessation.[1]

Depression (See Chapter 96)

Physicians caring for patients following STEMI need to acknowledge the prevalence of major depression after infarction. This problem is associated independently with higher mortality. In addition, lack of an emotionally supportive network in the patient's environment after discharge increases risk for recurrent cardiac events. The precise mechanisms relating depression and lack of social support to a worse prognosis after STEMI are not clear, but one possibility is lack of adherence to prescribed treatments, a behavior associated with increased risk for post-MI mortality. Therefore, a comprehensive cardiac rehabilitation program that includes primary health care personnel who counsel patients and make home visits can reduce the rate of rehospitalization for recurrent ischemia and infarction.[171]

Modification of Lipid Profile (See Chapters 45 and 48)

Obtaining a lipid profile on admission is reasonable in all patients admitted with acute MI. Total cholesterol levels may fall 24 to 48 hours after infarction. We continue to ascribe to a long-term target low-density lipoprotein (LDL) cholesterol level of less than 70 mg/dL for patients who experience an ACS, as recommended in many guidelines.[172] High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use.[1] Ezetimibe, a nonstatin lipid-lowering agent, may be added during hospitalization for STEMI based on IMPROVE-IT (Improved Reduction of Outcome: Vytorin Efficacy International Trial), which demonstrated a reduction in recurrent CV events when added to statin therapy.[172,173] Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors result in decreased LDL receptor degradation and can be considered for chronic lipid-lowering therapy as an adjunct to statin therapy, based on proven efficacy for event reduction.[172,173a] CV outcomes trials with PCSK9 inhibitors are ongoing, and their place in therapy is not yet well defined.[174]

Antiplatelet Agents (See Chapter 93)

On the basis of compelling data from the Antiplatelet Trialists' Collaboration of a 22% reduction in the risk for recurrent infarction, stroke, or vascular death in high-risk vascular patients receiving prolonged antiplatelet therapy, all patients with STEMI without contraindications should receive 75 to 325 mg of aspirin daily indefinitely, with 81 mg the preferred maintenance dose.[1] Additional benefits of long-term aspirin therapy that can accrue in patients with STEMI include an increased likelihood of patency of the infarct artery and smaller infarcts if MI recurs. Patients with true aspirin allergy can receive clopidogrel

(75 mg once daily). In the absence of contraindications, all patients after STEMI should receive a platelet inhibitor in addition to aspirin for 12 months according to one of the following regimens: clopidogrel (75 mg/day) in patients with STEMI treated with medical therapy alone, lytic therapy, or PCI; prasugrel (10 mg/day) in patients treated with PCI; or ticagrelor (90 mg twice daily) in patients treated with medical therapy alone or PCI[1,175] (**Fig. 59.34**). *Cangrelor,* a potent, fast-acting reversible, IV $P2Y_{12}$ inhibitor, can be used during PCI in patients who have not received a $P2Y_{12}$ inhibitor before PCI, based on CHAMPION-PHOENIX (A Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention) findings demonstrating a lower rate of death, MI, revascularization, or stent thrombosis, compared with clopidogrel, in patients undergoing PCI, including primary PCI for STEMI.[176]

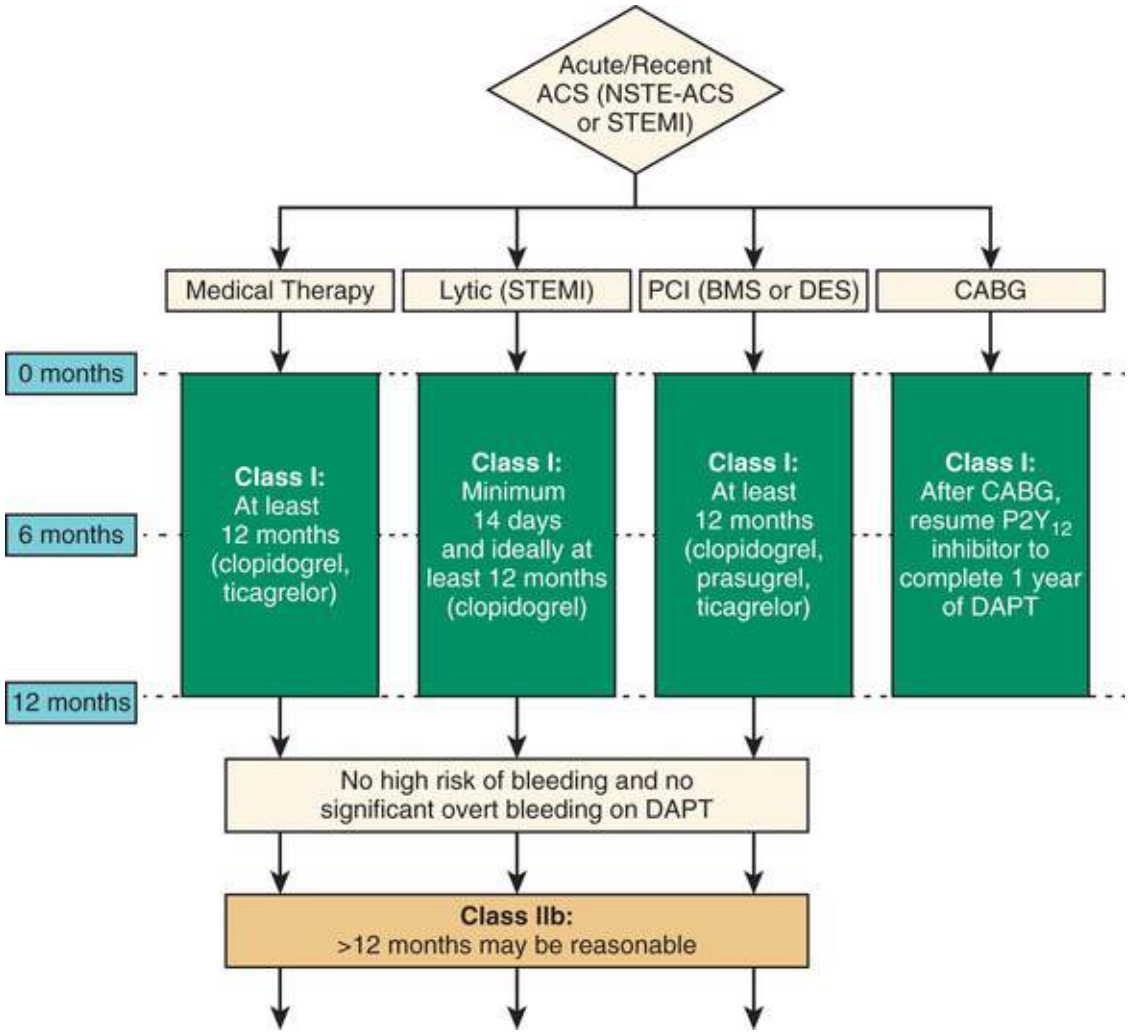


FIGURE 59.34 ACC/AHA guideline recommendation for duration and choice of antiplatelet agent in patients with recent acute coronary syndrome (ACS), including STEMI. Aspirin therapy is generally continued indefinitely post-ACS. In patients treated with dual-antiplatelet therapy (DAPT) after DES implantation who have a high risk of bleeding (e.g. use of oral anticoagulant therapy, major intracranial surgery) or develop significant overt bleeding, discontinuation of P2Y12 inhibitor therapy after 6 months for ACS may be reasonable. The optimal duration of prolonged DAPT is not established. BMS, Bare-metal stent; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DES, drug-eluting stent; Hx, history; lytic, fibrinolytic therapy; NSTE-ACS, non–ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention. (Modified from Levine GN et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. J Am Coll Cardiol 2016;68(10):1082-115.)

Aspirin therapy should be maintained indefinitely. In the absence of significant overt bleeding or risk factors for bleeding, it is reasonable to continue dual-antiplatelet therapy for more than 12 months based

on the DAPT (Dual Antiplatelet Therapy) and PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin) trials.[177,178] The PEGASUS-TIMI 54 study, which randomized 21,162 patients with MI in the preceding 1 to 3 years to ticagrelor versus placebo, demonstrated a reduction in the composite of CV death, MI, or stroke at the cost of increased bleeding.[178] The DAPT study demonstrated a reduction in death, MI, and stroke as well as stent thrombosis with continuation of a thienopyridine (clopidogrel or prasugrel) on background therapy with aspirin for 30 months versus 12 months in patients undergoing drug-eluting stent (DES) placement, including 1045 STEMI patients.[177] A large RCT of the thrombin receptor antagonist *vorapaxar* in stable patients with prior MI, ischemic stroke, or symptomatic peripheral artery disease provided additional evidence for a benefit of more potent oral antiplatelet therapy than aspirin alone for long-term secondary prevention.[179] In particular, among patients with prior MI, the addition of vorapaxar to standard antiplatelet therapy reduced the risk of CV death, MI, or stroke by a relative 20% (HR, 0.80; 95% CI 0.72 to 0.89; $P < 0.001$).[180] This benefit was counterbalanced by an increased risk of bleeding with the addition of vorapaxar. A similar reduction in major atherothrombotic events with oral anticoagulants lend additional support to the concept of expanded antithrombotic therapy for long-term secondary prevention (see Anticoagulants). Risk stratification can aid in personalization of antiplatelet therapy in patients with stable ischemic heart disease based on balancing the risk of recurrent atherothrombotic events with the risk of bleeding.[181,182]

In patients treated with PCI, prasugrel and ticagrelor have proved superior to clopidogrel and are recommended as preferred in some guidelines.[2,175] However, in some practice environments, economic or formulary barriers may render access to prasugrel or ticagrelor difficult for some patients. Given the critical importance of dual-antiplatelet therapy in patients who have received DESs, access to a $P2Y_{12}$ inhibitor must be ensured.

Inhibition of the Renin-Angiotensin-Aldosterone System

To prevent late remodeling of the left ventricle and to decrease the likelihood of recurrent ischemic events, we advocate indefinite therapy with an ACE inhibitor in patients with HF, a moderate decrease in global EF, or a large regional wall motion abnormality, even in the presence of a normal global EF. (See earlier, Pharmacologic Therapy, Inhibition of the Renin-Angiotensin-Aldosterone System.)

Beta-Adrenergic Blocking Agents

Meta-analyses of trials from the prethrombolytic era involving more than 24,000 patients who received beta blockers in the convalescent phase of STEMI have shown a 23% reduction in long-term mortality. In most patients who have beta blockade initiated during the convalescent phase of STEMI, the reduction in long-term mortality probably results from the combination of an antiarrhythmic effect (prevention of SCD) and prevention of reinfarction.

Despite the well-documented benefits of therapy with a beta blocker, this treatment continues to be underused, especially in high-risk groups such as older adults. Patients with a relative contraindication to beta blockers (e.g., bradyarrhythmias) should undergo a monitored trial of therapy in the hospital. The dosage should be sufficient to blunt the HR response to stress or exercise. Much of the impact of beta blockers in preventing mortality occurs in the first weeks; consequently, treatment should commence as soon as possible. Programs that provide physician feedback to improve adherence to guidelines should be used.

Some controversy exists regarding how long patients should be treated. The collective data from five

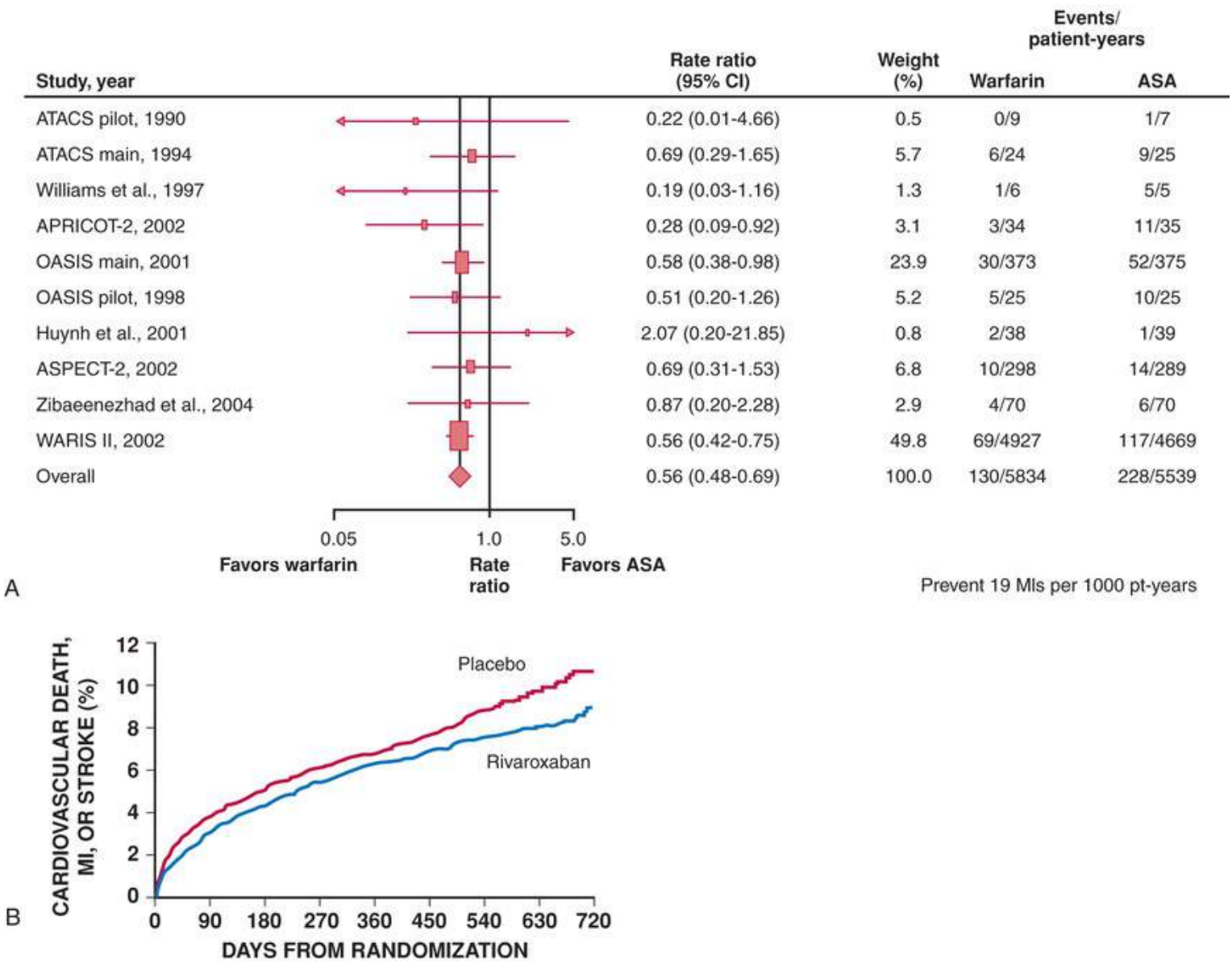
trials on long-term follow-up of patients treated with beta blockers after infarction suggest that therapy should be continued for at least 2 to 3 years. At that time, if the beta blocker is well tolerated and there is no reason to discontinue therapy, such therapy probably should be continued in most patients (**see Chapter 61**).

Nitrates

Although nitrates are suitable for the management of specific conditions after STEMI (e.g., recurrent angina) or as part of a treatment regimen for HF, little evidence indicates that nitrates reduce mortality over the long term when prescribed on a routine basis to all MI patients.

Anticoagulants (See Chapter 93)

After several decades of evaluation, the weight of evidence now suggests that anticoagulants have a favorable effect on late mortality, stroke, and reinfarction in patients hospitalized with STEMI (**eFig. 59.10**). Nevertheless, given the multiple alternatives for antithrombotic therapy for long-term secondary prevention, clinicians must weigh the potential benefits of treatment with an OAC based on established indications for anticoagulation, the use of other antithrombotic therapies, including long-term DAPT, and the risk for bleeding.



EFIGURE 59.10 Outcomes with extended oral anticoagulant therapy for secondary prevention in patients with STEMI. **A,** Meta-analysis of trials of warfarin versus placebo with respect to the outcome of recurrent MI showing the potential to prevent 19 MIs per 1000 patients treated. **B,** Primary result of the ATLAS ACS 2–TIMI 51 trial, in which 15,526 patients with acute coronary syndrome (ACS) were randomly assigned to one of two doses of the oral factor Xa inhibitor rivaroxaban or placebo for a mean of 13 months. Rivaroxaban lowered the rate of cardiovascular death, MI, or stroke by 16%. This benefit was present in patients with STEMI (*n* = 7727), who showed a 15% reduction in the primary endpoint. ASA, Acetylsalicylic acid.

At least three theoretical reasons exist for anticipating that anticoagulants might be beneficial in the long-term management of patients after STEMI. First, because the coronary occlusion responsible for STEMI is often caused by a thrombus, anticoagulants might be expected to halt progression, slow progression, or prevent the development of new thrombi elsewhere in the coronary arterial tree. Second, anticoagulants might be expected to diminish the formation of mural thrombi and resultant systemic embolization. Third, anticoagulants might reduce the incidence of venous thrombosis and pulmonary embolization.

Alternative OACs to warfarin that have the advantage of more predictable anticoagulation with stable oral dosing, such as the oral factor Xa inhibitors, have undergone evaluation in patients with ACS, including STEMI. The ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in

Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction) trial tested two low doses of the oral factor Xa inhibitor *rivaroxaban* versus placebo. Rivaroxaban at doses of both 2.5 and 5 mg twice daily significantly reduced CV death, MI, or stroke compared to placebo (8.9% versus 10.7%; $P = 0.008$; **eFig. 59.10**).[183] Both doses also reduced stent thrombosis. The group receiving the 2.5-mg dose demonstrated a significant reduction in CV mortality (2.7% versus 4.1%; $P = 0.002$) compared with placebo, which was not seen with 5 mg. Rivaroxaban resulted in an increase in major bleeding (2.1% versus 0.6%; $P < 0.001$) without a significant increase in fatal bleeding.

The risk-benefit profile of low dose oral anticoagulant therapy with rivaroxaban for secondary prevention after STEMI has been supplemented by the results of a large trial of secondary prevention in patients with stable atherosclerosis, including prior MI. In the COMPASS (Cardiovascular OutcoMes for People Using Anticoagulation StrategieS) trial, 27,2395 patients with established stable CAD or peripheral artery disease were randomized to treatment with rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once daily).[183a] Patients with CAD qualified for participation with either a history of MI in the past 20 years or multivessel CAD. Compared with aspirin alone, rivaroxaban 2.5 mg twice daily plus aspirin reduced the risk of CV death, MI, or stroke by 24% (HR 0.76; 95% CI, 0.66 to 0.86; P < 0.001). Major bleeding was increased by the addition of rivaroxaban from 1.9% to 3.1% (HR 1.70; 95% CI, 1.40 to 2.05; P < 0.001). However, there were fewer deaths overall in the rivaroxaban 2.5 mg twice daily plus aspirin group compared with aspirin alone (HR 0.82; 95% CI, 0.71 to 0.96; nominal P = 0.01). Rivaroxaban 5 mg twice daily without aspirin did not significantly reduce the primary endpoint compared with aspirin alone. COMPASS did not study patients receiving an ADP antagonist in any treatment arm. The role of the available options for long-term antithrombotic therapy in addition to aspirin (e.g. ticagrelor, rivaroxaban, or vorapaxar) are likely to be refined with clinical experience, additional research, and review by professional society guidelines committees.

Despite similar findings in the ACS phase II studies with rivaroxaban (ATLAS ACS-TIMI 46) and with another oral factor Xa inhibitor, *apixaban* (APPRAISE, Apixaban for Prevention of Acute Ischemic Events), the phase III APPRAISE-2 study, which tested apixaban versus placebo in patients following an ACS, was terminated early because of an increase in major bleeding without a significant improvement in efficacy.[72,184] The divergent results of the ATLAS ACS 2-TIMI 51 and APPRAISE-2 studies may be related to a higher baseline risk of the patients and concordant competing risks, the inclusion of patients with previous stroke or transient ischemic attack, and higher degrees of anticoagulation in APPRAISE-2.

Calcium Channel Antagonists.

We do *not* recommend the routine use of calcium antagonists for secondary prevention of MI. A possible exception is a patient who cannot tolerate a beta blocker because of adverse effects on bronchospastic lung disease but who has well-preserved LV function. Such patients may be candidates for a rate-slowing calcium antagonist such as diltiazem or verapamil.

Hormone Therapy (See Chapters 45 and 89).

The decision to prescribe hormone therapy is often complex and involves the desire to suppress postmenopausal symptoms versus the risk for breast and endometrial cancer and vascular events. At present, we recommend that hormone therapy with estrogen plus progestin should *not* be started after STEMI and should be discontinued in postmenopausal women after STEMI.

Antioxidants (See Chapter 45).

Dietary supplementation with omega-3 polyunsaturated fatty acids has associated with a reduction in

coronary death and reinfarction after MI. Contemporary randomized studies, however, have shown no convincing benefit in the context of guideline-based medical therapy.[185,186] Current data therefore do not support the use of antioxidant therapy for secondary prevention after STEMI.

Nonsteroidal Anti-Inflammatory Drugs

Evidence has emerged that COX-2–selective drugs and NSAIDs with varying COX-1/COX-2 inhibitory ratios promote a prothrombotic state, and that their use is associated with an increased risk for atherothrombotic events.[1] Given the desire not to interfere with the beneficial pharmacologic actions of low-dose aspirin after STEMI, and reports of increased mortality and reinfarction when NSAIDs are used after MI, clinicians should avoid prescribing NSAIDs to patients recovering from STEMI.[1] If NSAIDs must be prescribed for relief of pain, the lowest dose required to control symptoms should be administered for the shortest time required.

Future Perspectives and Emerging Therapies

Although the case-fatality rate of patients with STEMI has declined substantially, considerable opportunities for improvement remain. Of these, we emphasize three major directions: (1) mitigation of reperfusion injury and impaired myocardial tissue perfusion, (2) management of cardiogenic shock after STEMI, and (3) amelioration of the adverse remodeling.

Although PCI usually restores flow through epicardial arteries, many patients do not achieve adequate nutrient flow at the myocardial level in the infarct zone because of impaired microvascular flow (**see Fig. 59.7 and eFig. 59.1**). Despite effective restoration of flow in the culprit epicardial artery, patients with impaired microvascular reperfusion have reduced survival.[42] Identification of therapies that reliably improve microvascular perfusion in the setting of primary PCI and pharmacologic reperfusion has proved challenging. For example, although thrombus aspiration was hypothesized to improve outcomes through a reduction in microvascular obstruction due to distal embolization, improvements in ST-segment resolution did not translate to a reduction in recurrent CV events.[61,187,188]

Reperfusion injury to the microvasculature can also extend myocardial injury beyond the initial ischemic zone. To date, multiple candidate interventions to reduce reperfusion injury that appeared promising in initial studies have failed in definitive randomized trials. Amelioration of the reperfusion injury that contributes to long-term myocardial dysfunction remains an unmet clinical need. Therefore, therapies that target microvascular obstruction and reperfusion injury merit ongoing investigation.[25,42]

Even if reperfusion were achieved in timely fashion and microvascular obstruction were minimized, patients with STEMI inevitably lose some myocytes. When ventricular failure or severe mechanical disruption results, cardiogenic shock may ensue. Mortality from cardiogenic shock remains in excess of 40%. Improvement in the outcomes of patients in whom shock develops after STEMI remains a vexing clinical challenge.[108] The disappointing results of trials of percutaneous mechanical support have challenged common clinical assumptions.[122,189,190] Novel therapies and strategies for the management of shock are an area of unmet clinical need.

In addition to the early risk for ventricular failure because of acute myocardial injury, secondary damage to the left ventricle can also occur in the long term as a result of ventricular remodeling after STEMI. Treatments to minimize ventricular remodeling include the standard approaches to disruption of the RAAS and potential new therapies such as ARNIs, reducing the amount of central nervous system generation of aldosterone, enhancing the synthesis of endothelial nitric oxide synthase, modulating beta-

adrenergic signaling, and minimizing the processes that lead to cardiac apoptosis.[191] Novel approaches using biologic and mechanical interventions to improve ventricular structure are under investigation.[192,193] Moreover, myocytes are capable of entering the cell cycle and dividing[194] (**see Chapter 30**). Cardiac regenerative measures merit rigorous evaluation regarding efficacy in ameliorating the adverse ventricular remodeling or myocardial repair by use of either endogenous or exogenous sources of cells that give rise to myocytes (**Fig. 59.35**).[195]

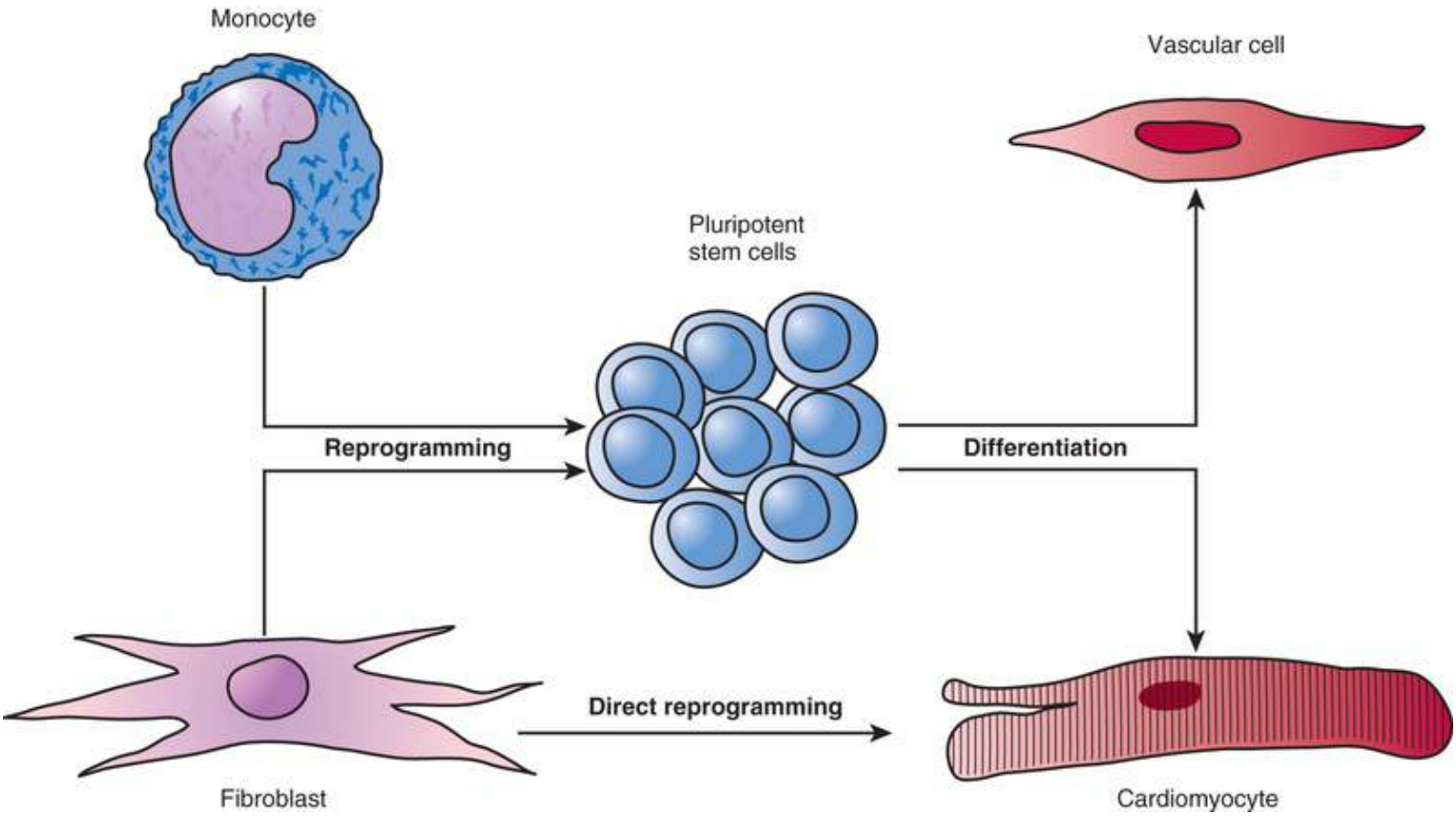


FIGURE 59.35 Not only can embryonic stem cells give rise to multiple cell types, but cells such as monocytes and fibroblasts can undergo reprogramming to differentiate into cardiovascular cells. (From Lee RT, Walsh K. The future of cardiovascular regenerative medicine. Circulation 2016;133(25):2618.)

Acknowledgment

The authors wish to acknowledge the previous contributions of Drs. Elliott M. Antman and Jessica L. Mega, which have laid the foundation for this chapter.

Guidelines

Management of Patients with ST-Elevation Myocardial Infarction

Stephen D. Wiviott

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) updated guidelines for the diagnosis and management of patients with ST-elevation myocardial infarction (STEMI) in 2013.[1] This guideline has not been updated *in full* since this publication, but two other documents provide substantial additional information to guide management of patients with STEMI: the 2015 Focused update on Primary Percutaneous Coronary Intervention[2] and the 2016 Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease.[3] As with other ACCF/AHA guidelines, these documents place recommendations into the customary four classes and ratings for the level of evidence (LOE.)

Definition and Diagnosis

STEMI is defined by symptoms of myocardial ischemia associated with persistent electrocardiographic evidence of ST elevation and subsequent elevation of biologic markers of myocardial necrosis. According to the universal definition of myocardial infarction (MI), ST elevation in the absence of either left bundle branch block (LBBB) or left ventricular (LV) hypertrophy is defined as new ST elevation of at least 2 mm in men or 1.5 mm in women in at least two contiguous leads.[4] New or presumably new LBBB at initial evaluation should not be considered diagnostic of MI. Interpretation of the electrocardiogram (ECG) may be obscured by previous LBBB, paced rhythm, LV hypertrophy, or Brugada syndrome.

Onset of Myocardial Infarction

Time until treatment is paramount in the management of STEMI, and early recognition, transport, and treatment can improve outcomes in patients with this syndrome.

Patient-Related Delays and Initial Treatment

Time delays in seeking care tend to be longer in women, blacks, and older adults. Delays may result from failure to recognize symptoms, uncertainty of the severity of symptoms, and lack of understanding of the importance of rapid treatment. The STEMI guidelines emphasize the importance of anticipatory planning, including the need to activate the emergency medical service (EMS) system and early aspirin treatment. Patients should learn warning signs, develop a survival plan, and discuss risk reduction with their physicians.

Mode of Transport to the Hospital

Patients with ischemic symptoms should be transported to the hospital by ambulance rather than by friends or family. Ambulance transport associates with earlier recognition of STEMI, faster reperfusion, and lower mortality. The benefits of ambulance transport are increased by prehospital communication of the diagnosis of STEMI and by transfer to hospitals capable of performing prompt percutaneous coronary intervention (PCI).

Community Preparedness and Systems Goals for Reperfusion Therapy

Time until appropriate reperfusion therapy is one key to the treatment of STEMI. Community-based systems designed for the rapid management of patients with STEMI should facilitate rapid reperfusion. **Fig. 59G.1** outlines the major strategies and decision points for the management of patients with STEMI.

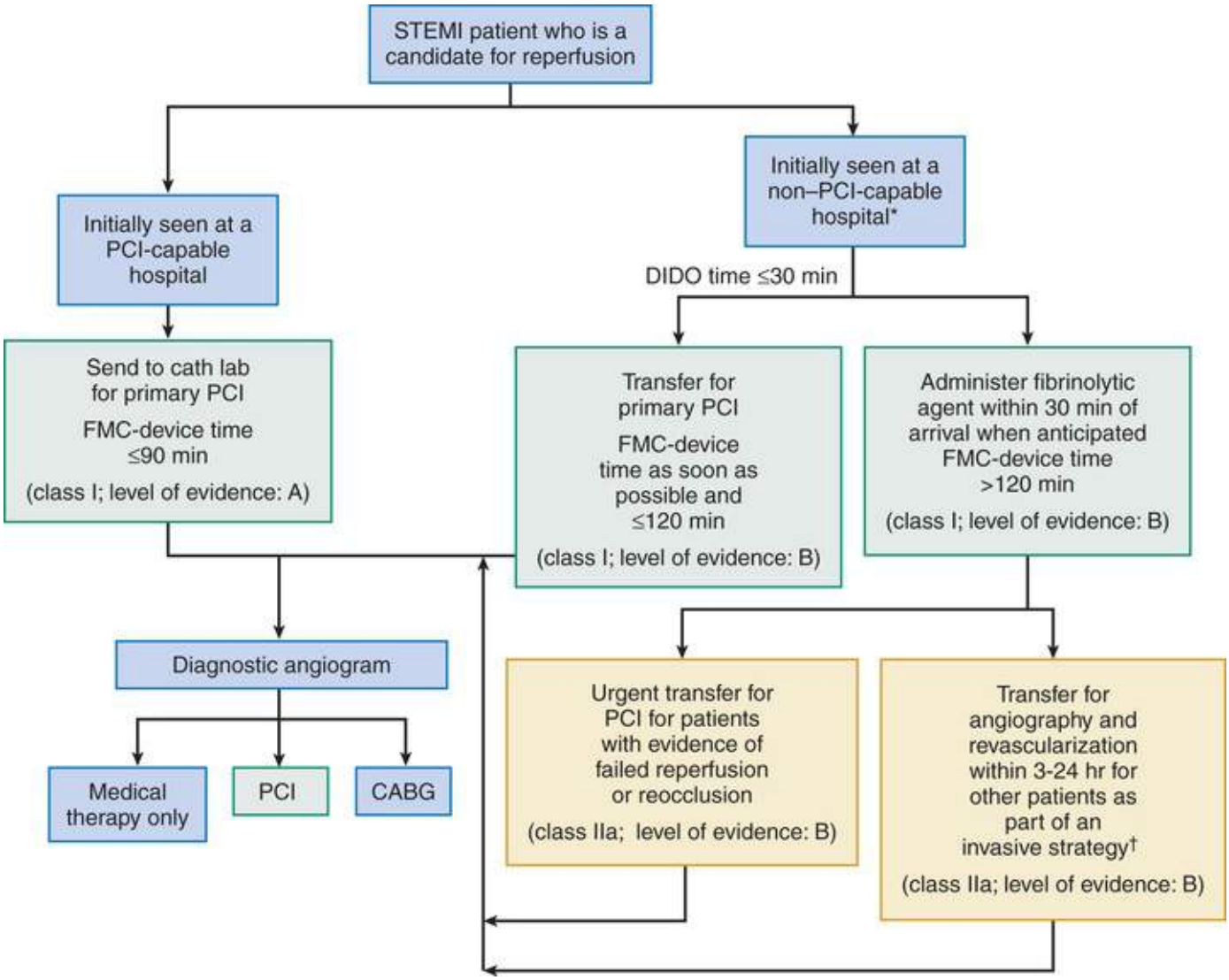


FIGURE 59G.1 Reperfusion therapy for patients with ST-segment elevation myocardial infarction (STEMI). The *bold arrows* and *boxes* are the preferred strategies. Performance of percutaneous coronary intervention (PCI) is dictated by an anatomically appropriate culprit stenosis. *Patients with cardiogenic shock or severe heart failure initially seen at a non–PCI-capable hospital should be transferred for cardiac catheterization and revascularization as soon as possible, irrespective of the delay in time after the onset of MI (class I; LOE: B). †Angiography and revascularization should not be performed within the first 2 to 3 hours after the administration of fibrinolytic therapy. *CABG,* Coronary artery bypass graft surgery; *DIDO,* door in–door out; *FMC,* first medical contact. (Modified from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61(4):e78.)

Class I recommendations include the following:

- Communities should create and maintain regional systems of STEMI care that includes assessment and quality improvement of EMS and hospital-based activities (LOE: B).
- A 12-lead ECG should be performed by EMS personnel at the site of first medical contact (FMC) in patients with symptoms consistent with STEMI (LOE: B).
- Reperfusion therapy should be administered to all eligible patients

with STEMI in whom the onset of symptoms began within the previous 12 hours (LOE: A).
• Primary PCI is the recommended method of reperfusion when experienced operators can perform it within timely fashion (LOE: A).
• EMS transport directly to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI, with an ideal FMC-to-device time goal of 90 minutes or less (LOE: B).
• Immediate transfer to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI who initially arrive at or are transported to a non–PCI-capable hospital, with an FMC-to-device time goal of 12 minutes or less (LOE: B).
• Without contraindications, fibrinolytic therapy should be administered to patients with STEMI at non–PCI-capable hospitals when the anticipated FMC-to-device time at a PCI-capable hospital exceeds 120 minutes because of unavoidable delays (LOE: B).
• When fibrinolytic therapy is indicated or chosen as the primary reperfusion strategy, it should be administered within 30 minutes of hospital arrival (LOE: B).

When selecting reperfusion therapy, the provider must consider several features in relation to these recommendations, including time from the onset of symptoms, risk for STEMI-related complications, risk for bleeding, presence of heart failure or shock, and time required for the administration of fibrinolytics versus the time needed for transfer to a PCI-capable hospital. Patients best suited for transfer to PCI-capable hospitals include those with congestive heart failure (CHF) or shock, high bleeding risk, longer than 3 to 4 hours after onset of symptoms, and short transfer times to PCI-capable hospitals. Those best suited for initial fibrinolytic therapy include patients with low bleeding risk, very early after the onset of symptoms, and longer delays until the performance of PCI.

Relationship Between Sudden Cardiac Death and ST-Elevation Myocardial Infarction

STEMI is inexorably linked to sudden cardiac death: approximately 70% of deaths attributable to coronary heart disease occur with out-of-hospital arrest. The STEMI guidelines offer some key recommendations for the evaluation and management of patients with STEMI and out-of-hospital cardiac arrest, including the following class I recommendations:

• Therapeutic hypothermia should be started as soon as possible in comatose patients with STEMI and out-of-hospital cardiac arrest

caused by ventricular fibrillation or pulseless ventricular tachycardia, including patients who undergo primary PCI (LOE: B).

• Immediate angiography and PCI, when indicated, should be performed in resuscitated patients with out-of-hospital cardiac arrest whose initial ECG shows STEMI (LOE: B).

Reperfusion at a Hospital Capable of Performing Percutaneous Coronary Interventions

The 2013 STEMI guidelines are divided into sections describing appropriate care at PCI-capable hospitals versus non–PCI-capable hospitals.[1]

Primary Percutaneous Coronary Intervention (Table 59G.1)

Primary PCI is generally preferable to fibrinolytic therapy when time until treatment is short and the patient arrives at a high-volume, well-equipped center with experienced operators and support staff. When compared with fibrinolysis, primary PCI produces higher rates of TIMI (thrombolysis in myocardial infarction) grade 3 flow and patent infarct-related arteries and lower rates of recurrent ischemia, urgent revascularization, recurrent MI, and death. Primary PCI, when successful, can also enable early hospital discharge and return to activities. Such improvements are less or absent in low-volume centers or with low-volume operators.

TABLE 59G.1

Primary Percutaneous Coronary Intervention (PCI) for ST-Elevation Myocardial Infarction

	COR	LOE
Ischemic symptoms <12 hr	I	A
Ischemic symptoms <12 hr and contraindications to fibrinolytic therapy irrespective of delay in time after FMC	I	B
Cardiogenic shock or acute severe heart failure irrespective of delay in time after the onset of myocardial infarction	I	B
Evidence of ongoing ischemia 12-24 hr after the onset of symptoms	IIa	B
PCI on a noninfarct artery at the time of primary PCI in patients without hemodynamic compromise	III: Harm	B

COR, Class of recommendation; *FMC,* first medical contact; *LOE,* level of evidence.

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61(4):e78.

Procedural Considerations

The 2013 STEMI guidelines offered a class IIa recommendation for manual aspiration thrombectomy in patients undergoing primary PCI, although subsequent trial data do not show that this procedure reduces 30-day mortality in patients with STEMI.[5] The 2015 focused update on primary PCI changed this recommendation to class III (LOE: A) as a routine strategy and class IIb for selective bailout in the setting of unsatisfactory results.

The 2013 guidelines listed non–culprit vessel PCI in hemodynamically stable patients with multivessel CAD at the time of primary PCI as class III (LOE B), discouraging such procedures. The results of subsequent randomized controlled trials (RCTs) suggesting benefit in certain circumstances led to an

upgraded recommendation of class IIb (LOE B).

Class I indications are given for the use of intracoronary stents at primary PCI (LOE: A). Either drug-eluting stents (DESs) or bare-metal stents (BMSs) can be used, but when patients are anticipated to be at high bleeding risk or are probably not compliant with dual-antiplatelet therapy (DAPT) for other reasons, a class I indication is given for the use of BMSs and a class III indication for DESs—because of the risk for delayed stent thrombosis in DESs with premature discontinuation of DAPT. **Table 59G.2** summarizes the adjunctive antithrombotic therapy for primary PCI, including antiplatelet therapy and anticoagulant therapy.

TABLE 59G.2

Adjunctive Antithrombotic Therapy to Support Reperfusion with Primary Percutaneous Coronary Intervention (PCI)

	COR	LOE
Antiplatelet Therapy		
Aspirin		
• 162- to 325-mg loading dose before the procedure	I	B
• 81- to 325-mg daily maintenance dose (indefinite)*	I	A
• 81 mg daily is the preferred maintenance dose*	IIa	B
$P2Y_{12}$ Inhibitors		
Loading Doses		
• Clopidogrel: 600 mg as early as possible or at the time of PCI	I	B
• Prasugrel: 60 mg as early as possible or at the time of PCI	I	B
• Ticagrelor: 180 mg as early as possible or at the time of PCI	I	B
Maintenance Doses		
Drug-eluting stents (DESs) placed: continue therapy for 1 yr with:		
• Clopidogrel: 75 mg daily	I	B
• Prasugrel: 10 mg daily	I	B
• Ticagrelor: 90 mg twice a day	I	B
Bare-metal stents (BMSs)† placed: continue therapy for 1 yr with:		
• Clopidogrel: 75 mg daily	I	B
• Prasugrel: 10 mg daily	I	B
• Ticagrelor: 90 mg twice a day	I	B
DESs placed		
• Patients with STEMI and previous stroke or TIA: prasugrel	III: Harm	B
Intravenous Glycoprotein IIb/IIIa Receptor Antagonists in Conjunction with Unfractionated Heparin or Bivalirudin in Selected Patients		
• Abciximab: 0.25-mg/kg IV bolus, then 0.125 µg/kg/min (maximum, 10 µg/min)	IIa	A
• Tirofiban (high bolus dose): 25-µg/kg IV bolus, then 0.15 µg/kg/min	IIa	B
• In patients with CrCl <30 mL/min, reduce the infusion by 50%		
• Eptifibatide (double bolus): 180-µg/kg IV bolus, then 2 µg/kg/min; a second 180-µg/kg bolus is administered 10 min after the first bolus	IIa	B
• In patients with CrCl <50 mL/min, reduce the infusion by 50%		
• Avoid in patients on hemodialysis		
• Pre–catheterization laboratory administration of IV GP IIb/IIIa receptor antagonist	IIb	B
• Intracoronary abciximab: 0.25-mg/kg bolus	IIb	B
Anticoagulant Therapy		
• Unfractionated heparin (UFH)		
• With a GP IIb/IIIa receptor antagonist planned: 50- to 70-unit/kg IV bolus to achieve therapeutic ACT‡	I	C
• With no GP IIb/IIIa receptor antagonist planned: 70- to 100-unit/kg bolus to achieve a therapeutic ACT§	I	C
• Bivalirudin: 0.75-mg/kg IV bolus, then 1.75-mg/kg/hr infusion with or without previous treatment with UFH. An additional bolus of 0.3 mg/kg may be given if needed	I	B
• Reduce the infusion to 1 mg/kg/hr with estimated an CrCl <30 mL/min		
• Preferred over UFH with a GP IIb/IIIa receptor antagonist in patients at high risk for bleeding	IIa	B
• Fondaparinux: not recommended as the sole anticoagulant for primary PCI	III: Harm	B

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.

†Balloon angioplasty without stent placement may be used in selected patients. It might be reasonable to provide $P2Y_{12}$ inhibitor therapy to patients with STEMI undergoing balloon angioplasty alone according to the recommendations listed for BMSs (LOE: C).

‡The recommended ACT with planned GP IIb/IIIa receptor antagonist treatment is 200 to 250 seconds.

§The recommended ACT with no planned GP IIb/IIIa receptor antagonist treatment is 250 to 300 seconds (HemoTec device) or 300 to 350 seconds (Hemochron device).

ACT, Activated clotting time; *CrCl,* creatinine clearance; *COR,* class of recommendation; *GP,* glycoprotein; *IV,* intravenous; *LOE,* level of evidence; *STEMI,* ST-elevation myocardial infarction.

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61(4):e78.

For antiplatelet therapy, class I recommendations include aspirin and $P2Y_{12}$ receptor antagonists.

Aspirin

• Aspirin (162 to 325 mg) should be given before primary PCI (LOE: B).
• After PCI, aspirin should be continued indefinitely (LOE: B). *Note:* An 81-mg dose of aspirin is recommended for maintenance (class IIa; LOE: B) instead of higher doses.

$P2Y_{12}$ Antagonists

• A loading dose of a $P2Y_{12}$ receptor inhibitor should be given as early as possible or at the time of primary PCI in patients with STEMI (LOE: B), with options including clopidogrel, 600 mg (LOE: B); prasugrel, 60 mg (LOE: B); or ticagrelor, 180 mg (LOE: B).
• Patients with STEMI who receive a stent should receive a $P2Y_{12}$ antagonist. Options include clopidogrel, 75 mg daily (LOE: B); prasugrel, 10 mg daily (LOE: B); or ticagrelor, 90 mg twice daily (LOE: B). The 2016 focused update on duration of DAPT indicates that it is reasonable to use ticagrelor (class IIa, LOE: B) or prasugrel (class IIa, LOE: B) in preference to clopidogrel. *Note:* Prasugrel should not be used (class III, LOE: B) in patients with high bleeding risk or a history of transient ischemic attack (TIA) or stroke.

Anticoagulant Therapy

For anticoagulant therapy, key recommendations include supportive anticoagulation with unfractionated heparin (UFH), with dosing based on the activated clotting time (ACT: class I, LOE: C), or with bivalirudin in patients who have not been treated previously with UFH (class I, LOE: B). In patients with a high risk for bleeding, bivalirudin is generally recommended instead of heparin plus a glycoprotein IIb/IIIa receptor antagonist (class IIa, LOE: B), and fondaparinux should *not* be used as the sole anticoagulant (class III, LOE: B).

Reperfusion at a Hospital Not Capable of Performing Percutaneous Coronary Interventions

The guidelines categorize the management of patients at a non–PCI-capable hospital into three phases: fibrinolytic therapy, assessment of patency, and transfer to a PCI-capable hospital.

Fibrinolytic Therapy When the Delay Anticipated Is Within 120 Minutes

Table 59G.3 summarizes the key recommendations for the indications for fibrinolytic therapy with a

delay of longer than 120 minutes from FMC to primary PCI. The 2013 STEMI guidelines recommend fibrin-specific agents over non–fibrin-specific agents when available.[1] Fibrin-specific regimens include single-bolus tenecteplase (TNK tissue plasminogen activator [t-PA]), double-bolus reteplase (r-PA), or infusion of alteplase (t-PA). Streptokinase administered over a 30- to 60-minute period is the only nonspecific agent recommended. The choice of fibrinolytic agent depends on a risk-benefit analysis that integrates time from the onset of symptoms, clinical features, comorbid conditions, delay until performance of PCI, and potential contraindications (**Table 59G.4**). **Table 59G.5** summarizes antithrombotic therapy for STEMI treated with fibrinolytic therapy.

TABLE 59G.3

Indications for Fibrinolytic Therapy When the Delay from First Medical Contact to Primary Percutaneous Intervention Is Longer than 120 Minutes

	COR	LOE
Ischemic symptoms <12 hr	I	A
Evidence of ongoing ischemia 12-24 hr after the onset of symptoms and a large area of myocardium at risk or hemodynamic instability	IIa	C
ST-segment depression except if true posterior (inferobasal) MI is suspected or when associated with ST-segment elevation in lead aVR	III: Harm	B

COR, Class of recommendation; *LOE,* level of evidence.

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61(4):e78.

TABLE 59G.4

Contraindications to Fibrinolytic Therapy for ST-Elevation Myocardial Infarction

Absolute Contraindications
Any previous intracranial hemorrhage
Known structural cerebral vascular lesion
Known malignant intracranial neoplasm
Ischemic stroke within 3 months (except ischemic stroke within 4.5 hours)
Suspected aortic dissection
Active bleeding or bleeding diathesis
Significant closed-head or facial trauma within 3 months
Intracranial or intraspinal surgery within 2 months
Severe uncontrolled hypertension (not responsive to emergency therapy)
For streptokinase, previous treatment within 6 months
Relative Contraindications
History of chronic, severe, poorly controlled hypertension
Significant hypertension at initial evaluation (SBP, >180 mm Hg, DBP >110 mm Hg)
History of ischemic stroke >3 months
Dementia
Known intracranial pathology not covered in Absolute Contraindications
Traumatic or prolonged cardiopulmonary resuscitation (>10 minutes)
Major surgery within 3 weeks
Recent internal bleeding (within 2-4 weeks)
Noncompressible vascular puncture
Pregnancy
Active peptic ulcer
Oral anticoagulant therapy

DBP, Diastolic blood pressure; *SBP,* systolic blood pressure.

TABLE 59G.5

Adjunctive Antithrombotic Therapy to Support Reperfusion with Fibrinolytic Therapy

	COR	LOE
Antiplatelet Therapy		
Aspirin		
• 162- to 325-mg loading dose	I	A
• 81- to 325-mg daily maintenance dose (indefinite)	I	A
• 81 mg daily is the preferred maintenance dose	IIa	B
P2Y$_{12}$ Receptor Inhibitors		
• Clopidogrel:	I	A
• Age ≤75 yr: 300-mg loading dose		
• Followed by 75 mg daily for at least 14 days	I	A
• Age >75 yr: no loading dose, give 75 mg	I	A
• Followed by 75 mg daily for at least 14 days	I	A (14 days)
Anticoagulant Therapy		
• Unfractionated heparin (UFH):	I	C
• Weight-based IV bolus and infusion adjusted to obtain an APTT of 1.5-2.0 times control for 48 hr or until revascularization. IV bolus of 60 units/kg (maximum, 4000 units) followed by an infusion of 12 units/kg/hr (maximum, 1000 units) initially, adjusted to maintain the APTT at 1.5-2.0 times control (≈50-70 sec) for 48 hr or until revascularization		
• Enoxaparin:	I	A
• If age <75 yr: 30-mg IV bolus, followed in 15 min by 1 mg/kg subcutaneously every 12 hr (maximum, 100 mg for the first 2 doses)		
• If age ≥75 yr: no bolus, 0.75 mg/kg subcutaneously every 12 hr (maximum, 75 mg for the first 2 doses)		
• Regardless of age, if CrCl <30 mL/min, 1 mg/kg subcutaneously every 24 hr		
• Duration: For the index hospitalization, up to 8 days or until revascularization		
• Fondaparinux:	I	B
• Initial dose of 2.5 mg IV, then 2.5 mg subcutaneously daily starting the following day, for the index hospitalization up to 8 days or until revascularization		
• Contraindicated if CrCl <30 mL/min		

APTT, Activated partial thromboplastin time; *COR,* class of recommendation; *CrCl,* creatinine clearance; *LOE,* level of evidence.

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61(4):e78.

Antiplatelet Therapy

- A loading dose of aspirin (162 to 325 mg) and clopidogrel (300 mg in patients ≤75 years of age; 75 mg in patients >75 years of age) should be administered with fibrinolytic therapy (class I, LOE: A).
- Aspirin should be continued indefinitely at 81 to 100 mg, and clopidogrel should be continued at 75 mg. *Note:* A dose of 81 mg of aspirin is preferred instead of higher maintenance dosing (class IIa, LOE: B).

Anticoagulant Therapy

Patients with STEMI treated with fibrinolytic therapy for reperfusion should receive anticoagulant therapy for a minimum of 48 hours and preferably for the duration of hospitalization, up to 8 days or until revascularization is performed (class I, LOE: A). Acceptable regimens include UFH for up to 48 hours (LOE: C), enoxaparin for up to 8 days (LOE: A), or fondaparinux for up to 8 days (LOE: B).

Transfer to a Hospital Capable of Performing PCI after Fibrinolytic Therapy

Table 59G.6 summarizes key recommendations for transfer to a PCI-capable hospital for angiography. The only class I indication for immediate transfer in the 2013 STEMI guidelines is for patients with severe heart failure or cardiogenic shock, but the general recommendation is for all patients who have failed reperfusion or suffered reocclusion (class IIa, LOE: B) to be transferred urgently and for stable patients to be transferred routinely (class IIa, LOE: B).

TABLE 59G.6

Indications for Transfer for Angiography after Fibrinolytic Therapy

	COR	LOE
Cardiogenic shock or acute severe heart failure that develops after initial evaluation	I	B
Intermediate- or high-risk findings on predischarge noninvasive ischemia testing	I	B
Spontaneous or easily provoked myocardial ischemia	I	C
Failed reperfusion or reocclusion after fibrinolytic therapy	IIa	B
Stable* patients after successful fibrinolysis, before discharge and ideally between 3 and 24 hr	IIa	B

*Although individual circumstances vary, *clinical stability* is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.

COR, Class of recommendation; *LOE,* level of evidence.

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61(4):e78.

Delayed Invasive Management

Coronary Angiography and PCI in Patients Initially Managed with Fibrinolytic Therapy or in Those with No Reperfusion (Table 59G.7)

PCI should be performed when angiography identifies significant stenosis in the infarct-related arteries. Class I indications relate to high-risk clinical features (cardiogenic shock, severe CHF), recurrent spontaneous or provoked ischemia, or high-risk features on noninvasive testing. PCI on non–infarct-related arteries should be based on spontaneous symptoms (class I, LOE: C) or high-risk features on noninvasive testing (class IIa, LOE: B) suggestive of ischemia in the territory of the non-infarct–related artery. One study published after the guidelines suggested a benefit of PCI on non–infarct-related arteries.[6]

TABLE 59G.7

Indications for Percutaneous Coronary Intervention (PCI) on an Infarct Artery in Patients Who Were Managed with Fibrinolytic Therapy or Who Did Not Receive Reperfusion Therapy

	COR	LOE
Cardiogenic shock or acute severe heart failure	I	B
Intermediate- or high-risk findings on predischarge noninvasive ischemia testing	I	C
Spontaneous or easily provoked myocardial ischemia	I	C
Patients with evidence of failed reperfusion or with reocclusion after fibrinolytic therapy (as soon as possible)	IIa	B
Stable* patients after successful fibrinolysis, ideally between 3 and 24 hr	IIa	B
Stable* patients >24 hr after successful fibrinolysis	IIb	B
Delayed PCI on a totally occluded infarct artery >24 hr after STEMI in stable patients	III: No benefit	B

*Although individual circumstances vary, *clinical stability* is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.

COR, Class of recommendation; *LOE,* level of evidence; *STEMI,* ST-elevation myocardial infarction.

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61(4):e78.

Adjunctive Antithrombotic Agents to Support Delayed PCI

Table 59G.8 summarizes adjunctive antiplatelet therapy and anticoagulant therapy to support delayed PCI. Antiplatelet and anticoagulant therapies in patients in whom PCI is delayed are similar to those in patients who undergo PCI early, but the timing and dosing of $P2Y_{12}$ antagonists differ depending on the time interval and type of fibrinolytic agent given. Notably, a loading dose of 300 mg of clopidogrel should be administered (if not already given with fibrinolysis) for PCI performed within 24 hours, and for PCI performed after 24 hours, a 600-mg loading dose. Prasugrel should be used at standard dosing, but not within 48 hours of fibrinolytic therapy. Anticoagulant therapy can consist of UFH (class I, LOE: C) or enoxaparin (class I, LOE: B), but fondaparinux should *not* be used as a stand-alone anticoagulant (class III, LOE: B).

TABLE 59G.8

Adjunctive Antithrombotic Therapy to Support Percutaneous Intervention (PCI) after Fibrinolytic Therapy

	COR	LOE
Antiplatelet Therapy		
Aspirin		
• 162- to 325-mg loading dose given with a fibrinolytic agent (before PCI)	I	A
• 81- to 325-mg daily maintenance dose after PCI (indefinite)	I	A
• 81 mg daily is the preferred daily maintenance dose	IIa	B
$P2Y_{12}$ Receptor Inhibitors		
Loading Doses		
For patients who received a loading dose of clopidogrel with fibrinolytic therapy:		
• Continue clopidogrel, 75 mg daily, without an additional loading dose	I	C
For patients who have not received a loading dose of clopidogrel:		
• If PCI is performed ≤24 hr after fibrinolytic therapy: clopidogrel, 300-mg loading dose before or at the time of PCI	I	C
• If PCI is performed >24 hr after fibrinolytic therapy: clopidogrel, 600-mg loading dose before or at the time of PCI	I	C
• If PCI is performed >24 hr after treatment with a fibrin-specific agent or >48 hr after a non–fibrin-specific agent: prasugrel, 60 mg at the time of PCI	IIa	B
For patients with previous stroke/TIA: prasugrel	III: Harm	B
Maintenance Doses		
Drug-eluting stents (DESs) placed: continue therapy for at least 1 yr with:		
• Clopidogrel: 75 mg daily	I	C
• Prasugrel: 10 mg daily	IIa	B
Bare-metal stents (BMSs) placed: continue therapy for at least 30 days and up to 1 yr with:*		
• Clopidogrel: 75 mg daily	I	C
• Prasugrel: 10 mg daily	IIa	B
Anticoagulant Therapy		
• Continue UFH throughout PCI while administering additional IV boluses as needed to maintain a therapeutic ACT, depending on use of a GP IIb/IIIa receptor antagonist†	I	C
• Continue enoxaparin throughout PCI: • No additional drug if the last dose was given within the previous 8 hr • 0.3-mg/kg IV bolus if the last dose was given 8-12 hr earlier	I	B
• Fondaparinux: • As sole anticoagulant for PCI	III: Harm	C

*Balloon angioplasty without stent placement may be used in selected patients. It might be reasonable to provide $P2Y_{12}$ inhibitor therapy to patients with STEMI undergoing balloon angioplasty after fibrinolysis alone according to the recommendations listed for BMSs (LOE: C).

†The recommended ACT with no planned GP IIb/IIIa receptor antagonist treatment is 250 to 300 seconds (HemoTec device) or 300 to 350 seconds (Hemochron device).

ACT, Activated clotting time; *COR,* class of recommendation; *IV,* intravenous; *LOE,* level of evidence.

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61(4):e78.

Coronary Artery Bypass Graft Surgery

The 2013 STEMI guidelines accord coronary artery bypass grafting (CABG) a relatively limited role in the management of patients with STEMI. The only class I indications for CABG in patients with STEMI include the management of those whose coronary anatomy is not amenable to PCI; those who have ongoing or recurrent ischemia, shock, severe heart failure, or other high-risk features (LOE: B); and patients at the time of operative repair of mechanical defects, such as a ventricular septal defect (LOE: B).

In general, aspirin should be continued throughout the pre-CABG and peri-CABG periods. With the understanding that CABG is often urgent in the setting of STEMI, clopidogrel or ticagrelor should be discontinued for at least 24 hours when possible. In stable settings, clopidogrel and ticagrelor should be stopped for 5 days and prasugrel stopped for 7 days before CABG, but earlier surgery may be considered if the benefits outweigh the risks (class IIb).

Duration of Dual-Antiplatelet Therapy

The focused update on dual-antiplatelet therapy provides guidance on duration of therapy in patients with acute coronary syndrome (ACS), including both STEMI and non-STEMI (**Fig. 59G.2**). In this guideline, aspirin, in the absence of any contraindication, is continued indefinitely at a maintenance dose of 75 to 100 mg.

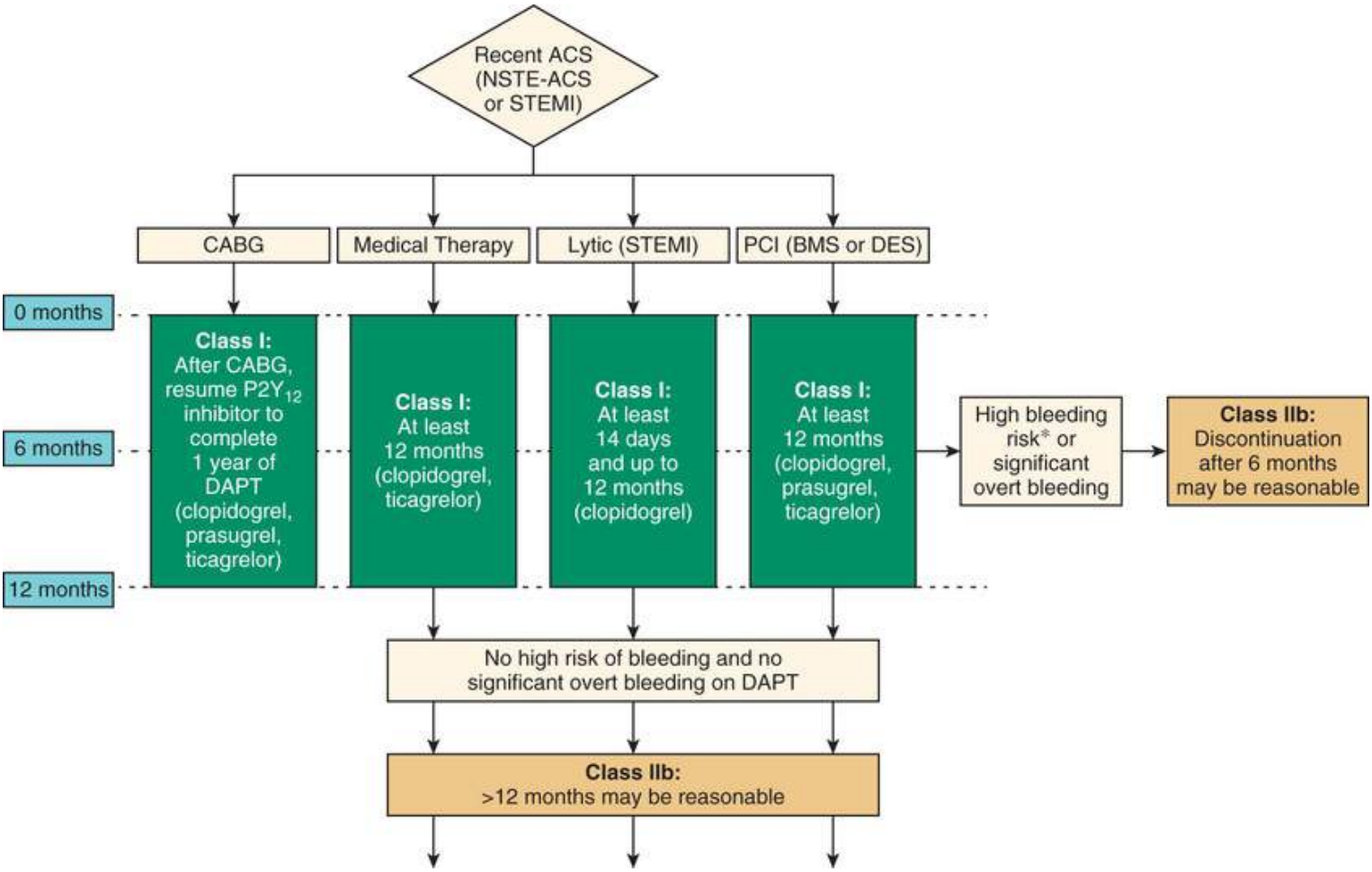


FIGURE 59G.2 Treatment algorithm for duration of $P2Y_{12}$ inhibitor therapy in patients with recent acute coronary syndrome (NSTE-ACS or STEMI). Colors correspond to class of recommendation in Table 59G.1. *Arrows* at the **bottom** of the figure denote that the optimal duration of prolonged DAPT is not established. Aspirin therapy is almost always continued indefinitely in patients with coronary artery disease. *High bleeding risk denotes those who have or develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy) or are at increased risk of severe bleeding complication (e.g., major intracranial surgery). *BMS,* Bare-metal stent; *CABG,* coronary artery bypass graft surgery; *DAPT,* dual-antiplatelet therapy; *DES,* drug-eluting stent; *lytic,* fibrinolytic therapy; *NSTE-ACS,* non–ST-elevation acute coronary syndrome; *PCI,* percutaneous coronary intervention; *STEMI,* ST-segment elevation myocardial infarction. (From Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2016;134(10):e141.)

• For patients with ACS treated with PCI (either primary or delayed), in general, treatment with clopidogrel, prasugrel, or ticagrelor should be given for at least 12 months (class I, LOE: B). In those who have

tolerated 12 months of treatment without a bleeding complication and who are not at high risk for bleeding (e.g., coagulopathy, oral anticoagulant use) longer durations of DAPT may be reasonable (class IIb, LOE: A). In contrast, discontinuation of DAPT at 6 months, even in patients with DESs, may be reasonable if patients develop overt bleeding or are at high risk for severe bleeding (class IIb, LOE: C).

- In patients treated with fibrinolytic therapy clopidogrel should be continued for a minimum of 14 days (class I, LOE: A) and ideally at least 12 months (class I, LOE: C). In such patients who have tolerated 12 months of treatment without bleeding complication and who are not at high risk for bleeding, DAPT for longer than 12 months may be reasonable (class IIb; LOE: A).
- In patients with ACS treated with CABG, DAPT should be resumed following CABG to complete 12 months of therapy (class I, LOE: C).
- In patients with ACS treated with medical therapy alone (without fibrinolytic or revascularization), clopidogrel or ticagrelor should be continued for at least 12 months (class I, LOE B). It is reasonable to use ticagrelor in preference to clopidogrel (class IIa, LOE: B). In such patients who have tolerated 12 months of treatment without bleeding complication and who are not at high risk for bleeding, DAPT for longer than 12 months may be reasonable (class IIb, LOE: A).

Routine Medical Therapies

Pharmacologic management of STEMI is covered in this chapter. **Table 59G.9** summarizes the indications and cautions for routine medical therapies in patients following STEMI, as based on the 2013 guidelines.

TABLE 59G.9

Indications and Cautions for Adjunctive Medical Therapies for Patients with ST-Elevation Myocardial Infarction

THERAPY	INDICATIONS	CAUTIONS
Beta-adrenergic receptor–blocking agents	Oral: All patients without contraindication IV: Patients with refractory hypertension or ongoing ischemia without contraindication	Signs of congestive heart failure Low-output state Increased risk for cardiogenic shock Prolonged first-degree or high-grade atrioventricular block Reactive airways disease
Angiotensin-converting enzyme (ACE) inhibitors	Anterior myocardial infarction and LVEF ≤0.40 or congestive heart failure All patients without contraindication	Hypotension Renal failure Hyperkalemia
Angiotensin receptor–blocking agents (ARBs)	Intolerant of ACE inhibitors	Hypotension Renal failure Hyperkalemia
Statins	All patients without contraindications	With drugs metabolized via CYP3A4, fibrates Monitor for myopathy, hepatotoxicity Adjust dose for lipid targets
Nitroglycerin	Ongoing chest pain Hypertension and congestive heart failure	Suspected right ventricular infarction SBP <90 (or 30 mm Hg below baseline) Recent use of a type 5 PDE inhibitor
Oxygen	Clinically significant hypoxemia (SpO_2 <90) Congestive heart failure Dyspnea	Chronic obstructive pulmonary disease and CO_2 retention
Morphine	Pain Anxiety Pulmonary edema	Lethargic or moribund patient Hypotension Bradycardia Known hypersensitivity

IV, Intravenous; *LVEF,* left ventricular ejection fraction; *PDE,* phosphodiesterase; *SBP,* systolic blood pressure.

Risk Assessment after ST-Elevation Myocardial Infarction

Post-STEMI risk assessment allows the clinician's initial impression to be updated based on data occurring during the hospital stay, such as successful reperfusion, angiographic parameters, clinical heart failure or arrhythmia, and ventricular function; noninvasive testing may be helpful. Testing for the presence of residual ischemia may be helpful in patients following STEMI. The only class I recommendation is to use noninvasive testing for ischemia before discharge in patients who did not undergo angiography and who did not have high-risk features for which coronary angiography would be warranted. (LOE: B.)

Because LV function strongly predicts outcome in patients with STEMI, a class I indication recommends that all patients with STEMI undergo measurement of their LV ejection fraction (LVEF). Echocardiography is the most commonly used modality and can assess mechanical complications, in addition to ventricular function. Patients with significant ventricular dysfunction should have a repeat examination more than 40 days after MI to evaluate the potential need for an implantable cardioverter-defibrillator (ICD).

In the absence of a reversible cause, late (defined as >48 hours after MI) in-hospital sustained ventricular tachycardia or ventricular fibrillation is an indication (class I; LOE: B) for ICD therapy. In patients who do not have an indication for ICD therapy based on late life-threatening arrhythmias, evaluation of LVEF to determine the need for an ICD for primary prevention of sudden cardiac death should be performed with sufficient time to allow any LV stunning to resolve. Based on the 2013 STEMI guidelines, patients with an LVEF of 0.40 or lower should have echocardiography repeated more than 40 days after MI. If the LVEF remains 0.35 or lower and the patient has a Class II or III New York Heart Association classification of CHF or an LVEF of 0.30 or lower independent of symptoms, an ICD is indicated.

Posthospitalization Plan of Care

Transition from hospital to outpatient care requires a careful discharge and follow-up plan. Class I indications for posthospital care planning include the following:

- Posthospital care systems should be used to facilitate the transition to effective, coordinated outpatient care for all patients with STEMI. (LOE: B.)
- Exercise-based cardiac rehabilitation/secondary prevention programs are recommended for patients with STEMI. (LOE: B.)
- A clear, detailed, evidence-based plan of care that promotes adherence to medication, timely follow-up with the health care team, appropriate dietary and physical activities, and compliance with interventions for secondary prevention should be provided to patients with STEMI. (LOE: C.)
- Encouragement and advice to stop smoking and to avoid secondhand smoke should be provided to patients with STEMI. (LOE: A.)

Key components in the plan of care should include medications, physical activity/rehabilitation, risk factor modification, lifestyle interventions, attention to management of comorbid conditions and psychosocial factors, provider follow-up, patient and family education, and socioeconomic factors.

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60

Non–ST Elevation Acute Coronary Syndromes

Robert P. Giugliano, Eugene Braunwald

Ischemic heart disease may manifest clinically as either chronic stable angina (**see Chapter 61**) or an acute coronary syndrome (ACS).[1] The spectrum of ACS includes ST-segment elevation myocardial infarction (STEMI) (**see Chapter 58 and 59**), and the non–ST elevation acute coronary syndromes (NSTE-ACS). The latter consist of non–ST elevation myocardial infarction (NSTEMI), and unstable angina (UA) (**Fig. 60.1**), which have indistinguishable clinical presentations at the initial evaluation.

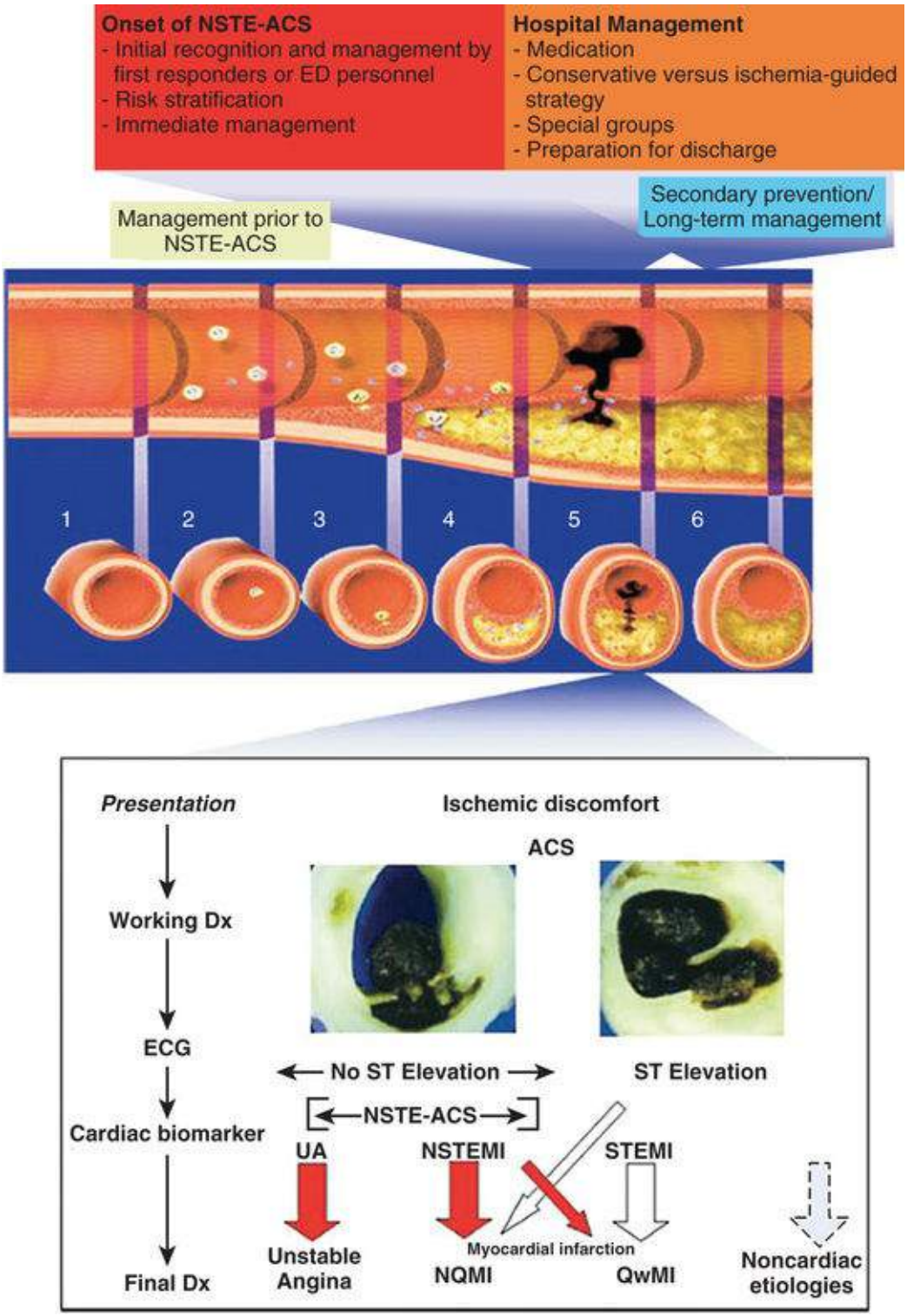


FIGURE 60.1 Acute coronary syndrome (ACS). The **top** half of the figure illustrates the progression of plaque formation and onset and complications of non–ST elevation (NSTE)-ACS, with management at each stage. The numbered section of an artery depicts the process of atherogenesis from (*1*) normal artery to (*2*) extracellular lipid in the suboptimal to (*3*) fibrofatty stage to (*4*) procoagulant expression and weakening of the fibrous cap. ACS develops with (*5*) disruption of the fibrous cap, which is the stimulus for thrombogenesis. (*6*) Thrombus resorption may be followed by collagen accumulation and smooth muscle cell growth. Thrombus formation and possible coronary vasospasm reduce blood flow in the affected coronary artery and cause ischemic chest pain. The **bottom** half of the figure illustrates the clinical, pathologic, electrocardiographic, and biomarker correlates in ACS and the general approach to management. Flow reduction may be related to a completely occlusive thrombus (*right side*) or subtotally occlusive thrombus (*left side*). Most patients with ST-segment elevation (*thick white arrow*) develop QwMI, and a few (*thin white arrow*) develop NQMI. Those without ST-elevation have either UA or NSTEMI (*thick red arrows*), a distinction based on cardiac biomarkers. Most patients presenting with NSTEMI develop NQMI; a few may develop QwMI. The spectrum of clinical presentations including UA, NSTEMI, and STEMI is referred to as ACS. This NSTE-ACS CPG includes sections on initial management before NSTE-ACS, at the onset of NSTE-ACS, and during the hospital phase. Secondary prevention and plans for long-term management begin early during the hospital phase. Patients with noncardiac etiologies make up the

largest group presenting to the ED with chest pain (*dashed arrow*). *CPG,* Clinical practice guideline; *Dx,* diagnosis; *ECG,* electrocardiogram; *ED,* emergency department; *MI,* myocardial infarction; *NQMI,* non–Q wave myocardial infarction; *NSTEMI,* non–ST elevation myocardial infarction; *QwMI,* Q wave myocardial infarction; *STEMI,* ST-elevation myocardial infarction; *UA,* unstable angina. (From Amsterdam EA et al. 2014 ACC/AHA non-ST-segment elevation ACS guideline. J Am Coll Cardiol 2014;64(24):e139-228; and Libby P et al. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation 2001;104:365-72.)

Several features help to differentiate ACS from chronic stable angina, including (1) sudden onset of symptoms at rest (or with minimal exertion) that last at least 10 minutes unless treated promptly; (2) severe pain, pressure, or discomfort in the chest; and (3) an accelerating pattern of angina that develops more frequently, with greater severity, or that awakens the patient from sleep. The 12-lead electrocardiogram (ECG) and markers of myocardial necrosis are essential tools in distinguishing between the three types of ACS. Patients with typical symptoms (**see Chapter 56**) *without* persistent (>20 minutes continuously) ST-segment elevation in at least two contiguous electrocardiographic leads, but with elevation of myocardial biomarkers >99% percentile of normal, are classified as having NSTEMI. Patients without typical symptoms and serial negative markers of myocardial necrosis are classified as having UA, a diagnosis that carries a better prognosis.

Epidemiology

Despite the decline in cardiovascular disease (CVD) mortality over the past three decades,[2,3] cardiovascular and circulatory diseases remain the leading causes of death in the world, responsible for more than 54 million deaths in 2013.[4] In 2016 in the United States, it is estimated that more than 1.1 million patients will experience an ACS event, of whom 72% will have a myocardial infarction (MI).[5] The fraction of ACS attributed to NSTEMI continues to increase, while that for STEMI is declining, for several reasons: (1) wider use of preventive measures such as aspirin, statins, and smoking cessation; (2) aging of the population, with greater prevalence of diabetes and chronic kidney disease (CKD) and lower rates of smoking; and (3) broader use of troponin assays with higher sensitivity for myocardial necrosis, which shifts the diagnosis from UA to NSTEMI.[6]

Pathophysiology

The pathogenesis of NSTE-ACS involves four processes operating singly or in various combinations: (1) disruption of an unstable atheromatous plaque, which may be driven at least in part by inflammation[1] (**Fig. 60.2**); (2) coronary arterial vasoconstriction; (3) gradual intraluminal narrowing of an epicardial coronary artery caused by progressive atherosclerosis or restenosis after stenting; and (4) oxygen supply-demand mismatch (**see Chapter 57**). Our understanding of the complex interactions between these pathways continues to evolve. For example, recent studies have identified increased levels of proprotein convertase subtilisin/kexin type 9 (PCSK9) as a risk factor for more severe atherosclerosis, a marker for vulnerable plaques, and a contributor to plaque destabilization resulting in ACS.[7,8] (**See also Chapters 44 and 58**.)

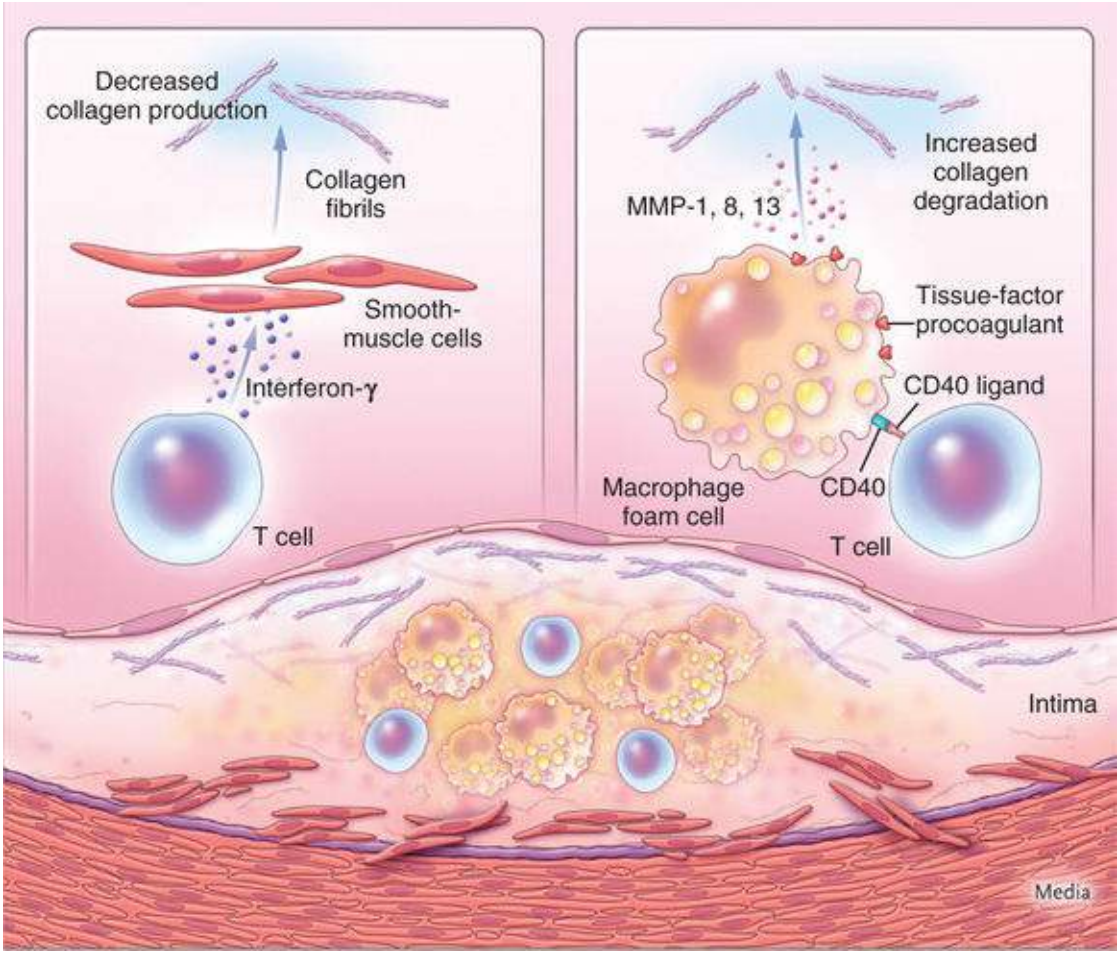


FIGURE 60.2 Inflammatory pathways predisposing coronary arteries to rupture and thrombosis. A cross section of an atheromatous plaque at the **bottom** of the figure shows the central lipid core containing macrophage foam cells (*yellow*) and T cells (*blue*). Arterial smooth muscle cells (*red*) present in the intima and media are the source of arterial collagen (triple helical structures). Activated T cells secrete cytokine interferon-gamma, which inhibits the production of the new, interstitial collagen required to repair and maintain the plaque's protective fibrous cap **(top left).** T cells may also activate macrophages in the intima by expressing CD40 ligand, which engages the CD40 receptor on the phagocyte. This inflammatory signaling causes overproduction of matrix metalloproteinases (*MMP*) 1, 8, and 13, which catalyze the initial rate-limiting step in collagen breakdown **(top right).** CD40 ligand also causes macrophages to overproduce tissue-factor procoagulant. These multiple consequences of inflammatory signaling each contribute to the instability of the plaque's fibrous cap. (From Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 2013;368:2004-13.)

Three forms of disruptions of coronary artery plaques can precipitate thrombosis: plaque rupture, plaque erosion, and disruptive nodular calcification protruding into the lumen (**Fig. 60.3**).[9] Plaque rupture remains the most common, but plaque erosion has become responsible for an increasing proportion of ACS events.[10] **Table 60.1** summarizes differences in the main characteristics between plaque rupture and superficial erosion as the causes of ACS. Vasoconstriction causing dynamic obstruction of coronary arterial flow may result from spasm of the epicardial coronary arteries (Prinzmetal angina) or from constriction of small, intramural muscular coronary arteries. The latter may result from vasoconstrictors released by platelets, from endothelial dysfunction (cardiac syndrome X; **see Chapter 89**), adrenergic stimuli, cold, cocaine, or amphetamines (**Chapter 80**). More than one of these mechanisms may operate simultaneously.

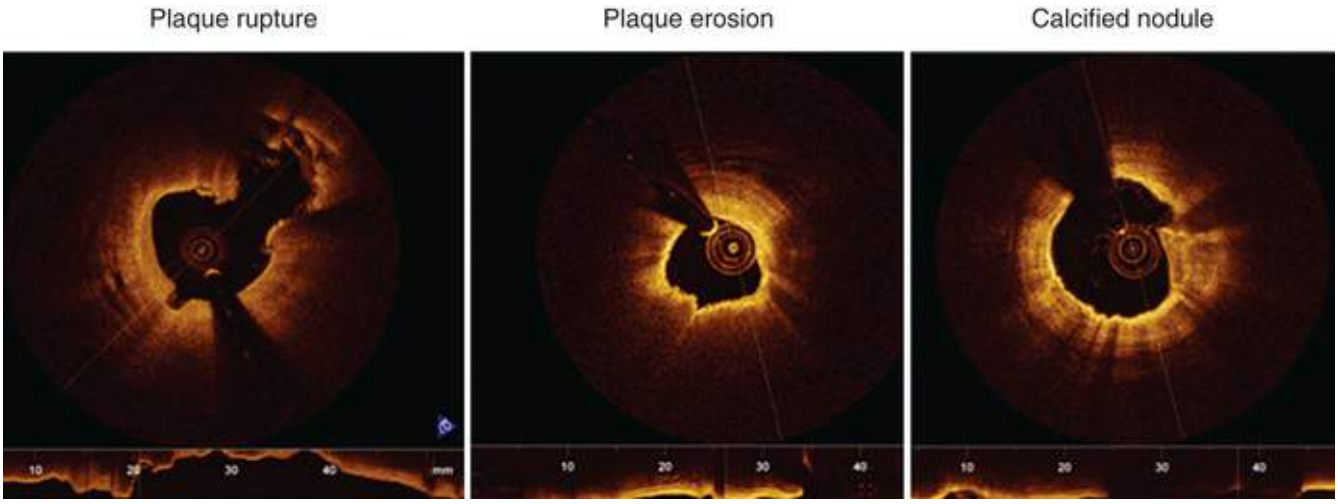


FIGURE 60.3 Representative optical coherence tomography images of underlying plaque morphologies. **Left,** Plaque rupture of a necrotic core with an overlying thin ruptured cap represents the most frequent pathophysiologic process leading to an acute coronary syndrome. **Center,** Plaque erosion with a thrombus in direct contact with an intimal plaque that is rich in smooth muscle cells and proteoglycan matrix. **Right,** The least common plaque morphology resulting in an acute coronary syndrome (ACS) is the calcified nodule, a heavy calcified plaque with a surrounding area of fibrosis. There are breaks in the calcified plate of the plaque with bone formation and interspersed fibrin, with a disrupted fibrous cap and overlying thrombus. A calcified nodule as the basis of ACS is more common in older men than in women or younger patients. (From Eisen A, Giugliano RP, Braunwald E. Update on acute coronary syndrome. JAMA Cardiol 2016;1(6):718-30.)

TABLE 60.1

Main Characteristics of Plaque Rupture and Superficial Erosion

PLAQUE RUPTURE	PLAQUE EROSION
Lipid rich	Lipid poor
Collagen poor, thin fibrous cap	Proteoglycan and glycosaminoglycan rich
Interstitial collagen breakdown	Nonfibrillar collagen breakdown
Abundant inflammation	Few inflammatory cells
Smooth muscle cell apoptosis	Endothelial cell apoptosis
Macrophage predominance	Secondary neutrophil involvement
Male predominance	Female predominance
High level of low-density lipoprotein cholesterol	High level of triglycerides

Modified from Libby P, Pasterkamp G. Requiem for the "vulnerable plaque." Eur Heart J 2015;36:2984-87.

Activation of the coagulation cascade and platelets play central roles in the formation of thrombus following plaque disruption (**see Chapter 93**). The first step in thrombus formation is vascular injury that causes *adhesion* of platelets to the arterial wall via binding of platelet glycoprotein (GP) Ib to subendothelial von Willebrand factor. Exposure of platelets to subendothelial collagen and/or circulating thrombin causes platelet *activation*, which induces platelets to change shape and results in their degranulation with release of adenosine diphosphate (ADP) and thromboxane A_2 (TxA_2), which in turn cause further platelet activation and expression of platelet GP IIb/IIIa. In parallel, tissue factor expressed within the lipid-rich core of atherosclerotic plaque, when exposed to circulating blood, activates the *coagulation cascade*. A complex of tissue factor and coagulation factors VIIa and Va leads to the formation of activated factor X (factor Xa), which in turn amplifies the production of activated factor IIa (thrombin). This cascade proceeds with thrombin-induced conversion of fibrinogen to fibrin. The platelet and coagulation systems converge as thrombin also potently activates platelets. Platelet GP IIb/IIIa binds circulating fibrinogen, thereby causing platelet aggregation and ultimately producing a platelet-fibrin thrombus, portions of which may embolize distally and cause myocardial necrosis.

Four observations support the central role of coronary artery thrombosis in the pathogenesis of NSTE-ACS: (1) autopsy findings of thrombi in the coronary arteries typically localized to a ruptured or eroded atherosclerotic plaque, (2) visualization by optical coherence tomography (**Fig. 60.3**) or computed tomographic angiography (CTA) of plaque ulceration and/or irregularities in the fibrous cap of atherosclerotic plaque, consistent with plaque rupture and thrombus formation; (3) elevation of serum markers of platelet activity, thrombin generation, and fibrin formation; and (4) improvement in clinical outcome with antiplatelet and anticoagulant therapies.

Clinical Assessment

History

NSTE-ACS resulting from atherosclerosis is relatively uncommon in men younger than 40 and women younger than 50 in the absence of genetic disorders such as familial hypercholesterolemia, but the incidence rises steadily thereafter. Patients with ACS frequently have traditional risk factors for coronary heart disease (CHD) (**see Chapter 45**). However, while coronary risk factors reliably assess risk in populations, they are less helpful in the assessment of individual patients.

The initial symptom of NSTE-ACS is typically described as retrosternal pressure, heaviness, or frank pain (**see Chapter 56**), and although it resembles stable exertional angina, it is usually more intense and lasts longer (>10 minutes). Radiation to the ulnar aspect of the upper left arm, either shoulder, the neck, or the jaw is common, but symptoms may localize anywhere between the ear and epigastrium.[11] Symptoms such as diaphoresis, nausea, abdominal pain, dyspnea, and syncope may accompany the discomfort. Features that support the diagnosis include exacerbation of symptoms by physical exertion; precipitation by severe anemia, infection, inflammation, fever, or metabolic or endocrinologic (e.g., thyroid) disorders. Atypical manifestations, such as dyspnea without chest discomfort, pain limited to the epigastrium, or indigestion, represent “anginal equivalents.” These atypical findings are more prevalent in women, older adults, and patients with diabetes, CKD, or dementia and can lead to underrecognition, undertreatment, and worse outcomes. Chest pain that is pleuritic, positional, or described as “stabbing” is generally not caused by myocardial ischemia. The clinical manifestations may appear suddenly, with severe, new-onset symptoms occurring during minimal exertion (Canadian Cardiovascular Society Class [CCSC] III) or at rest (CCSC IV), an accelerating pattern of angina (more frequent, more intense, longer lasting), or angina occurring shortly after a completed MI.[12]

Physical Examination

Findings on physical examination may be normal, although patients with large territories of myocardial ischemia may have audible third and/or fourth heart sounds or pulmonary rales. Rarely, hypotension, pale cool skin, sinus tachycardia, or frank cardiogenic shock can occur; these findings are much more common with STEMI than with NSTE-ACS. Potential precipitating causes of ACS, such as fever, resistant hypertension, tachycardia, profound bradycardia, thyroid disease, and gastrointestinal (GI) bleeding, can sometimes be identified. Findings such as pulse deficits, tachypnea, and tachycardia in the presence of clear lung fields and pulsus paradoxus with jugular venous distention may lead to alternative life-threatening diagnoses, such as aortic dissection, pulmonary embolism, or cardiac tamponade.

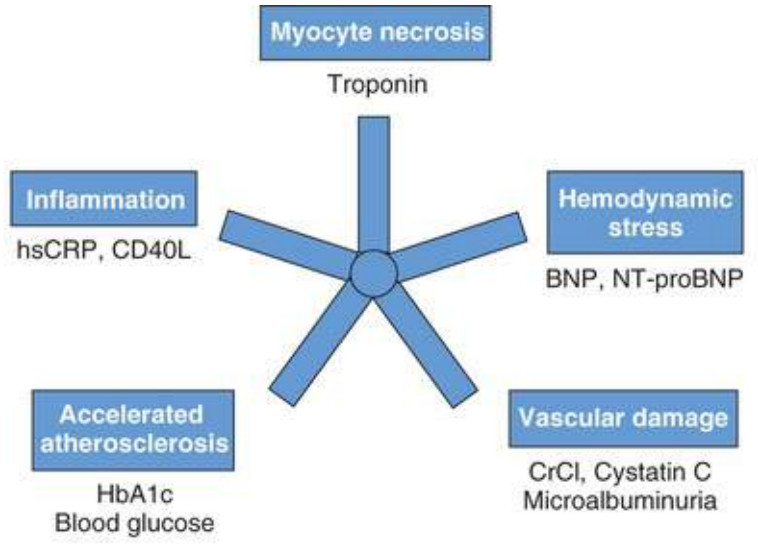
Electrocardiography

The most common abnormalities on the 12-lead ECG are ST-segment depression and T wave inversion, which are more likely to be present while the patient is symptomatic. Comparison with a recent ECG is important because dynamic ST-segment depressions as little as 0.05 mV are a sensitive (but not specific) marker for NSTE-ACS. Greater degrees of ST-segment depression predict poorer outcomes. Transient ST-segment elevation lasting less than 20 minutes occurs in up to 10% of patients and suggests either UA or coronary vasospasm. Deep (>0.2 mV) T wave inversions are compatible with, but not necessarily diagnostic of, NSTE-ACS, whereas isolated T wave inversions of lesser magnitude are not particularly helpful given their low specificity. More than half of patients with definite NSTE-ACS may have normal or nondiagnostic ECGs. Because ischemia may occur in a territory that is not well represented on the standard 12-lead ECG (see later), or because the patient may have episodic ischemia that is missed on the initial ECG, tracings should be repeated every 20 to 30 minutes until the symptoms resolve, or the diagnosis of MI is established or excluded.

Coronary angiography identifies a culprit lesion in the circumflex coronary artery in one third of patients with high-risk NSTE-ACS.[13] Because the standard 12-lead ECG does not represent this territory well, assessment of posterior leads V_7 through V_9 (with the gain increased to 20 mm/mV) should be considered in patients with a history suggestive of ACS and a nondiagnostic initial ECG. Similarly, ACS caused by isolated involvement of an acute marginal branch of the right coronary artery is often not apparent on the standard 12-lead ECG but may be suspected from leads V_3R and V_4R. Therefore, it is useful to obtain these extra leads in patients suspected of having ACS but with normal findings on a 12-lead ECG. Continuous monitoring of the ECG in the days following NSTE-ACS can identify patients at higher risk for recurrent events. ST-segment depressions noted on such monitoring within the first week after NSTE-ACS are associated with an increased risk for reinfarction and death.

Laboratory Testing: Biomarkers

A number of biomarkers reflecting the diverse causes of NSTE-ACS are useful for prognostication. These include markers of myocyte necrosis, hemodynamic stress, vascular damage (particularly renovascular), acceleration of atherosclerosis, and inflammation (**Fig. 60.4**). Cardiac-specific troponins I (cTnI) and T (cTnT) are the biomarkers of choice to identify myocardial necrosis, thus distinguishing between NSTE-ACS and UA. Since the sensitivities of different troponin assays in clinical practice vary, the consensus recommendation is to define MI by an elevation in cTnI or cTnT >99th percentile of the normal range of the specific assay used,[14] with a typical temporal rise and fall occurring in a patient with a clinical presentation consistent with ACS. However, although troponin elevation in the presence of ischemic discomfort often signifies myocardial necrosis, there are numerous other mechanisms of troponin release, including apoptosis, cellular release of proteolytic degradation products of troponin, increased cellular wall permeability, and normal myocyte turnover.[15] Furthermore, a wide variety of clinical conditions can be associated with troponin elevation that are not MI (**Table 60.2**). Even with less sensitive troponin assays, 60% to 70% of persons with chest discomfort seen in the emergency department (ED) will have detectable cTn, but only a minority are diagnosed with acute MI.[16] As high-sensitivity troponin (hsTn) assays[17] that can detect ultralow concentrations of troponin in approximately 90% of healthy individuals become increasingly available, consideration of the clinical context of a troponin elevation will become even more important in avoiding misdiagnosis and improper triage in management of patients. (**See also Chapters 56 and 58**.)



Biomarker	Independent predictor of risk	Useful as a component in a multimarker strategy	Therapeutic implication
Troponin	+++	++	+++
BNP	+++	++	0
Renal dysfunction	++	+	+
Glucose metabolism*	+	0	+
CRP	++	++	++

FIGURE 60.4 Multimarker approach for risk stratification in ACS. *Glucose metabolism** = Hyperglycemia or elevated glycated hemoglobin (HbA1c); BNP, brain natriuretic peptide; CD40L, CD40 ligand; CrCl, creatinine clearance; hsCRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-BNP. (Modified from Morrow DA, Braunwald E. Future of biomarkers in acute coronary syndromes: moving toward a multimarker strategy. Circulation 2003;108:250.)

TABLE 60.2

Causes of Elevated Troponin Reflecting Direct Myocardial Damage Other Than Spontaneous Myocardial Infarction (Type 1)

CARDIAC	NONCARDIAC OR SYSTEMIC
Tachyarrhythmias	Pulmonary embolism, pulmonary hypertension
Congestive heart failure	Trauma (e.g., electrical shock, burns, blunt chest wall)
Hypertensive emergencies	Hypo- or hyperthyroidism
Infection, inflammation (e.g., myocarditis, pericarditis)	Toxicity (e.g., anthracyclines, snake venom)
Stress cardiomyopathy (takotsubo cardiomyopathy)	Renal failure
Structural heart disease (e.g., aortic stenosis)	Sepsis, shock
Aortic dissection	Stroke or other acute neurologic event
Coronary spasm	Extreme endurance efforts (e.g., ultramarathon)
Cardiac procedures (endomyocardial biopsy, ablation, coronary artery bypass grafting, percutaneous coronary intervention)	Rhabdomyolysis
Infiltrative diseases (e.g., amyloidosis, hemochromatosis, malignancy)	

Modified from Newby LK et al. JACC 2012;60:2427-63 and Roffi M et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent st-segment elevation. Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology. Eur Heart J 2016;37:267-315.

Fourth-generation cTn assays currently used in the United States are less sensitive than hsTn assays available in some European countries. Thus, two negative cTn assays at least 6 hours apart are needed to exclude MI with these less sensitive assays. However, with newer hsTn assays (approved in the United States in 2017), it is possible with a single measurement at presentation of less than 5 ng/L to classify almost two thirds of patients presenting to the ED with suspected ACS as “very low risk” for MI or cardiac death in the next 30 days (negative predictive value [NPV], 99.6%).[18] Absolute changes in hsTn greater than 9.2 ng/L are even more predictive of acute MI than a single measure or relative changes

between two measurements.[19] Use of absolute changes in hsTn allow for rapid protocols as brief as 1 hour to rule in or rule out MI in up to 77% of unselected patients presenting to the ED with acute chest pain,[20,21] with results comparable to a 3-hour approach.[22] In addition to their utility in early diagnosis and prognostication, cTn levels following ACS aid intermediate-term risk stratification over the subsequent 6 months. When hsTn assays are not available, the 2015 European Society of Cardiology (ESC) guidelines[23] recommend assessment of *copeptin*, the C-terminal part of the vasopressin prohormone, to improve the sensitivity in diagnosing acute MI.[24]

Several other biomarkers may be useful to determine prognosis and help guide care. Of these, the natriuretic peptides (i.e., brain natriuretic peptide [BNP] and N-terminal pro-BNP) have been most widely used in patients with NSTE-ACS. Natriuretic peptides (NPs) rise in proportion to the degree of ventricular distention (strain) and correlate with the risk of adverse events, including death, heart failure (HF), and MI, in a graded fashion. More importantly, elevation of a baseline NP identifies patients who are more likely to benefit from more intensive anti-ischemic and lipid-lowering regimens and early coronary revascularization. Similarly, C-reactive protein (CRP), a marker of inflammation, is elevated following NSTE-ACS, and the degree of elevation correlates with long-term cardiovascular (CV) outcomes. In addition, CRP may identify patients with NSTE-ACS who require more intensive management of risk factors, including lipids, glucose, blood pressure, and weight. Other promising novel biomarkers in ACS are summarized in **eTable 60.1**.

ETABLE 60.1

Novel Biomarkers in Acute Coronary Syndromes (ACS)

BIOMARKER	DESCRIPTION
Markers Predicting Death and/or Ischemic Events	
Chemokine ligand-5 and ligand-18	Mediators of monocyte recruitment induced by ischemia[a]
Interleukin-6	Stimulator of hepatic synthesis of C-reactive protein[b]
Interleukin-17 (IL-17)	Produced by CD4+ T cells, IL-17 plays a role in host immunity and development of an unstable plaque[c]
Growth differentiation factor-15	Member of the transforming growth factor-beta cytokine superfamily that is released from cardiomyocytes after ischemia and reperfusion injury[d]
Heart-type fatty acid–binding protein	Cytoplasmic protein involved in intracellular uptake and buffering of free fatty acids in the myocardium[e]
Membrane attack complex	Ischemia leads to changes in myocardial cell surface molecule expression, rendering the cell membrane a target for the complement system, ultimately leading to cell lysis[f]
Myeloperoxidase	Hemeprotein released during degranulation of neutrophils and some monocytes[g]
Pentraxin 3	Inflammatory marker associated with thin-cap vulnerable plaques[h]
Pregnancy-associated plasma protein A	Zinc-binding metalloproteinase found in vulnerable plaques that cause destabilization of the fibrous plaque[i]
Placental growth factor	Member of the vascular endothelial growth factor family that is strongly upregulated in atherosclerotic lesions and acts as a primary inflammatory instigator of atherosclerotic plaque instability [j]
Secretory phospholipase A_2	Hydrolyzes phospholipids to generate lysophospholipids and fatty acids, thereby enhancing susceptibility of the vessel atherosclerosis[k]
Markers Predicting Heart Failure	
Copeptin	Peptide fragment of provasopressin[l]
Midregional proadrenomedullin	Peptide fragment of the vasodilatory peptide adrenomedullin[l]
Midregional proatrial natriuretic peptide	Peptide fragment of atrial natriuretic peptide[l]
Neopterin	Marker of monocyte activation[m]
Osteoprotegerin	Modulator of immune function and inflammation[n]

[a]Kraaijeveld AO, de Jager SC, de Jager WJ, et al. CC chemokine ligand-5 (CCL5/RANTES) and CC chemokine ligand-18 (CCL18/PARC) are specific markers of refractory unstable angina pectoris and are transiently raised during severe ischemic symptoms. Circulation 2007;116:1931-1941.

[b]Beygui F, Silvain J, Pena A, et al. Usefulness of biomarker strategy to improve GRACE score's prediction performance in patients

with non-ST-segment elevation acute coronary syndrome and low event rates. Am J Cardiol 2010;106:650-8.

[c]Simon T, Taleb S, Danchin N, et al. Circulating levels of interleukin-17 and cardiovascular outcomes in patients with acute myocardial infarction. Eur Heart J 2013;34:570-7.

[d]Kato ET, Morrow DA, Cannon CP, et al. Growth differentiation factor-15 (GDF-15) for risk stratification in patients after an acute coronary syndrome: insights from the SOLID-TIMI 52 trial. Circulation 2015;132:A14844.

[e]Viswanathan K, Kilcullen N, Morrell C, et al. Heart-type fatty acid–binding protein predicts long-term mortality and re-infarction in consecutive patients with suspected acute coronary syndrome who are troponin-negative. J Am Coll Cardiol 2010;55:2590-8.

[f]Lindberg S, Pedersen SH, Mogelvang R, et al. Soluble form of membrane attack complex independently predicts mortality and cardiovascular events in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. Am Heart J 2012;164:786-92.

[g]Morrow DA, Sabatine MS, Brennan ML, et al. Concurrent evaluation of novel cardiac biomarkers in acute coronary syndrome: myeloperoxidase and soluble CD40 ligand and the risk of recurrent ischaemic events in TACTICS-TIMI 18. Eur Heart J 2008;29:1096-102.

[h]Koga S, Ikeda S, Yoshida T, et al. Elevated levels of systemic pentraxin 3 are associated with thin-cap fibroatheroma in coronary culprit lesions: assessment by optical coherence tomography and intravascular ultrasound. JACC Cardiovasc Interv 2013;6:945-54.

[i]Bonaca MP, Scirica BM, Sabatine MS, et al. Prospective evaluation of pregnancy-associated plasma protein A and outcomes in patients with acute coronary syndromes. J Am Coll Cardiol 2012;60:332-8.

[j]Lenderink T, Heeschen C, Fichtlscherer S, et al. Elevated placental growth factor levels are associated with adverse outcomes at four-year follow-up in patients with acute coronary syndromes. J Am Coll Cardiol 2006;47:307-11.

[k]Mallat Z, Steg PG, Benessiano J, et al. Circulating secretory phospholipase A_2 activity predicts recurrent events in patients with severe acute coronary syndromes. J Am Coll Cardiol 2005;46:1249-57.

[l]O'Malley RG, Bonaca MP, Scirica BM, et al. Prognostic performance of multiple biomarkers in patients with non-ST-segment elevation acute coronary syndrome: analysis from the MERLIN-TIMI 36 trial (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes-Thrombolysis in Myocardial Infarction 36). J Am Coll Cardiol 2014;63:1644-53.

[m]Nazer B, Ray KK, Sloan S, et al. Prognostic utility of neopterin and risk of heart failure hospitalization after an acute coronary syndrome. Eur Heart J 2011;32:1390-7.

[n]Omland T, Ueland T, Jansson AM, et al. Circulating osteoprotegerin levels and long-term prognosis in patients with acute coronary syndromes. J Am Coll Cardiol 2008;51:627-33.

Multimarker approaches (e.g., simultaneous assessment of cTn, hs-CRP, and BNP) can further improve risk stratification of patients with NSTE-ACS.[25] While lipid measurements are less helpful for individual prognostication, assessment of the low-density lipoprotein cholesterol (LDL-C) and triglycerides, along with glucose or hemoglobin (Hb) A_{1c} can identify uncontrolled risk factors that with proper management, could reduce the risk of future CV events (**see Chapter 45**). Likewise, routine assessments of arterial oxygenation, hematocrit, and thyroid function may identify treatable conditions that can cause secondary ACS.[26]

Noninvasive Testing

Noninvasive testing in patients with established or suspected NSTE-ACS plays a number of important roles: (1) establishing the presence (or absence) of significant CHD; (2) diagnosing CHD as the cause of cTn elevation in patients who may have other explanations (see earlier); (3) evaluating the extent of residual ischemia after initiation of medical therapy, helping to guide future management; (4) localizing the territory of ischemia before revascularization in a patient with multivessel disease; and (5) assessing left ventricular (LV) function.

The safety of early stress testing in patients with NSTE-ACS has been debated, but symptom-limited or pharmacologic stress testing appear to be safe after at least 24 hours of stabilization without symptoms of

active ischemia or other signs of hemodynamic or electrical instability. The merits of various modalities of stress testing have been compared (**see Chapter 13**). Exercise stress myocardial perfusion imaging with nuclear isotopes and stress echocardiography with dobutamine have greater sensitivity than electrocardiographic exercise stress testing without imaging (**see Chapters 14 and 16**). A practical approach is to select the modality of stress testing based on individual patient characteristics and preferences, as well as local availability and expertise. For most patients, electrocardiographic exercise stress testing is recommended if the ECG at rest lacks significant baseline abnormalities (e.g., ST depressions, bundle-branch block, electronic pacing). If significant baseline ECG abnormalities are present, stress perfusion or echocardiographic imaging should be performed before and immediately after exercise. In patients who cannot achieve a significant workload during exercise, pharmacologic stress testing with imaging is recommended. High-risk findings on the stress test (e.g., severe ischemia as reflected by ST-segment depression ≥0.2 mV before stage 3, hypotension with exercise, ventricular tachyarrhythmia, new or worsening LV dysfunction) are indications to proceed rapidly with coronary angiography with the intent to perform coronary revascularization, if possible.

Echocardiography is useful in the assessment of LV systolic and diastolic function and can also identify left atrial dilation, functional mitral regurgitation, tricuspid annular plane systolic excursion, diastolic dysfunction, ventricular mechanical dyssynchrony, and ultrasound “lung comets” (extravascular lung fluid observed on thoracic ultrasound scanning). Each of these is associated with an adverse prognosis in patients with NSTE-ACS.

Contrast-enhanced coronary CTA (CCTA) in patients with or suspected of having NSTE-ACS can help: (1) recognize or exclude the presence of epicardial CHD, (2) identify which vessel(s) have coronary atherosclerosis, (3) assist in risk stratification and prognosis (**see Chapter 18**). Three large randomized trials have shown that CCTA compared to standard evaluation expedites the triage of patients presenting with chest discomfort in the ED, thereby shortening length of stay.[27-29] Additional benefits include reductions in costs,[30,31] and of return visits to the ED.[31] A randomized trial comparing standard of care with versus without CCTA in 4146 patients with suspected angina demonstrated that CCTA better clarified the diagnosis of angina due to CHD, reduced the need for stress testing, but increased the use of coronary angiography.[32] These studies and others led the American College of Radiology and the American College of Cardiology to recommend use of CCTA in the ED in patients with chest discomfort and suspected ACS who are at low risk at presentation[33,34] (**Table 60.3**).

TABLE 60.3

Appropriateness of Coronary Computed Tomographic Angiography (CTA) in Patients with Acute Chest Pain Syndromes

Appropriate Indications
Electrocardiogram negative or indeterminate for myocardial ischemia
Low-intermediate pretest likelihood by risk stratification tools
TIMI risk score of 0-2 (low risk) ideal or TIMI score of 3-4 (intermediate) in some cases
HEART score <3
≥1 Negative troponin value, including point-of-care assays
Equivocal or inadequate previous functional testing during index ED or within previous 6 months
Equivocal Indications
High clinical likelihood of ACS by clinical assessment and standard risk criteria (e.g., TIMI score >4)
Previously known coronary artery disease
Known calcium score ≥400
Relative Contraindications
History of allergic reaction to iodinated contrast
Estimated glomerular filtration rate (eGFR) 30 to <60 mL/min/1.73 m^2
Factors likely to lead to nondiagnostic scans; specific will vary with scanner technology and site capabilities
Heart rate greater than site maximum for reliably diagnostic scans after beta blockers (usually 70-80 bpm)
Contraindications to beta blockers and heart rate not controlled
Atrial fibrillation or other markedly irregular rhythm
Body mass index >39 kg/m^2
Absolute Contraindications
Known acute coronary syndromes
eGFR <30 unless on long-term dialysis
Previous anaphylaxis after iodinated contrast administration
Previous episode of contrast allergy after adequate steroid/antihistamine preparation
Pregnancy or uncertain pregnancy status in premenopausal women

ACS, Acute coronary syndrome; *ED,* emergency department; *eGFR,* estimated glomerular filtration rate; *TIMI,* Thrombolysis in Myocardial Infarction.

Modified from Hollander JE, Than M, Mueller C. State-of-the-art evaluation of emergency department patients presenting with potential acute coronary syndromes. Circulation 2016;134:547-64.

In hospitals that have hsTn assays available, the benefit of CCTA is less clear,[35] although some studies suggest CCTA may improve risk stratification in patients in whom hsTn levels do not conclusively rule in or rule out MI.[36,37] The benefits of CCTA may extend beyond the ED, permitting more rapid and accurate identification of high-risk patients who may benefit from early, intensive therapies.[32,38]

Cardiac magnetic resonance imaging (CMR) using a rapid-scan protocol can provide precise measurements of ventricular volumes and function, evaluate ventricular wall edema, identify areas of infarcted versus hibernating myocardium, establish the presence of myocardial perfusion, quantify wall motion, and identify myocardium at risk in patients with NSTE-ACS.[39] These detailed assessments can help guide coronary revascularization in several common clinical scenarios, as when the stenosis is of borderline significance, the culprit lesion is uncertain because of multivessel disease, or myocardial viability in a territory at risk is in question (**see Chapter 17**).

Invasive Imaging

Invasive coronary angiography has been the standard technique for imaging the coronary arterial tree for nearly six decades. The culprit lesion in NSTE-ACS typically exhibits an eccentric stenosis with scalloped or overhanging edges and a narrow neck (**see Chapter 20**). These angiographic findings may represent disrupted atherosclerotic plaque or thrombus. Features suggesting thrombus include globular intraluminal masses with a rounded or polypoid shape; “haziness” of a lesion suggests the presence of thrombus, but this finding is not specific.

Approximately 85% of patients with a clinical diagnosis of NSTE-ACS have significant coronary obstruction (i.e., >50% stenosis of luminal diameter, in at least one major coronary artery). Most have

obstructive disease, including multiple epicardial arteries—approximately 10% with left main coronary artery disease, 35% with three-vessel disease, and 20% with two-vessel disease—whereas only approximately 20% have single-vessel disease. The remaining 15% have no significant coronary obstruction, a finding that is more common in women and minorities. In such patients, NSTE-ACS may be related to microvascular coronary obstruction, endothelial dysfunction, or coronary artery spasm and may have a more favorable prognosis. In 37,101 patients enrolled in eight clinical trials of NSTE-ACS, the 30-day rate of death or MI was 2.2% in those with no obstructive coronary artery disease (CAD) compared to 13.3% in patients with obstructive disease.[40]

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are two invasive cross-sectional imaging techniques that can provide details regarding plaque morphology (**see Fig. 60.3**). In the clinical setting, IVUS and OCT are used most commonly to guide coronary stent placement (**see Chapter 20**). These techniques and others (e.g., near-infrared spectroscopy, intravascular magnetic resonance imaging, angioscopy) can provide detailed plaque morphology and establish the pathophysiologic etiology of ACS, although the clinical utility of such additional information is uncertain.

Risk Assessment

Residual Risk

The risk for recurrent ischemic events following an episode of ACS depends as much on the presence and stability of multifocal lesions as on the culprit lesion responsible for the initial event.[41] Aggressive medical management of the remaining plaques and prevention of new ones is required to prevent recurrent events.[41] The percentage of patients with more than one active plaque on angiography correlates with the level of high-sensitivity (hs) CRP. These findings provide an important pathophysiologic link among inflammation, more diffuse active CAD, and recurrent cardiac events in the months to years following a clinical ACS event.

Natural History

Patients with UA have lower short-term mortality (<2.0% at 30 days) than do those with NSTEMI or STEMI. However, with the increasing use of hsTn, the fraction of patients with NSTE-ACS diagnosed with UA is declining.[6]

The early mortality risk with NSTEMI is related to the extent of myocardial damage and resulting hemodynamic compromise and is lower than in patients with STEMI, who usually have larger infarcts.[42] In contrast, long-term outcomes with respect to both mortality and nonfatal events are worse in patients with NSTE-ACS. This finding probably results from the greater age, extent of CAD, previous MI, comorbid condition (e.g., diabetes, impaired renal function), and likelihood of recurrence of ACS in patients with NSTE-ACS than in those with STEMI.

Risk Assessment Scores

Several risk scores that integrate clinical variables and findings on the ECG and from serum biomarkers have been developed for patients with NSTE-ACS.[43-45] The TIMI (Thrombolysis in Myocardial Ischemia) risk score for UA/NSTEMI identifies seven independent risk factors; their sum correlates directly with death or recurrent ischemic events[43] (**Fig. 60.5**). This simple, rapid assessment at the initial evaluation identifies high-risk patients who can derive benefit from an early invasive strategy and more intensive antithrombotic therapy. The GRACE (Global Registry of Acute Coronary Events) risk score[45] uses a

larger number of weighted risk factors to predict mortality after NSTE-ACS; however, it is more complex than the TIMI risk score and is not easily calculated by hand. For longer-term prognostication in patients after ACS, a risk score based on nine independent clinical predictors identifies a gradient of risk for recurrent atherothrombotic events, the TIMI stable ischemic CAD risk score (**Fig. 60.6**). It distinguishes patients with greater absolute benefit with more intensive antithrombotic and lipid-lowering therapies.[46,47]

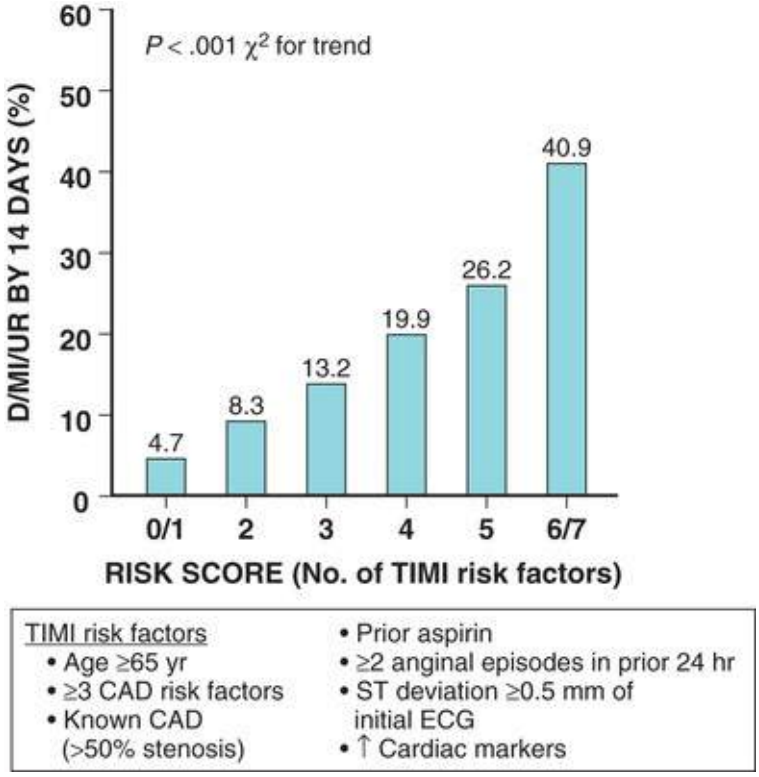


FIGURE 60.5 Thrombolysis in Myocardial Infarction (TIMI) risk score for UA/NSTE-MI (NSTE-ACS). The number of risk factors present is counted. CAD, Coronary artery disease; D/MI/UR, death, myocardial infarction, or urgent revascularization. (Modified from Antman EM, Cohen M, Bernink PJ, et al: The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000;284:835.)

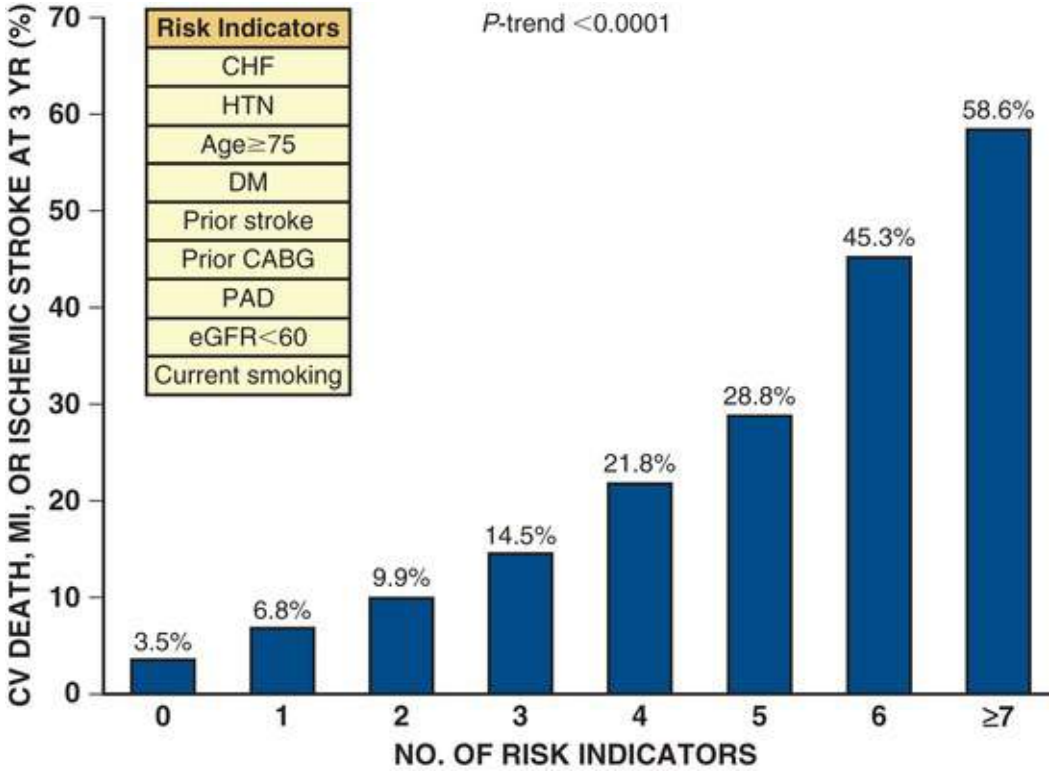


FIGURE 60.6 Long-term risk stratification after myocardial infarction using the TIMI Stable Ischemic CAD Risk Score. Nine independent factors, when combined in a simple long-term risk score, can identify a broad range of future risk of the composite of cardiovascular (CV) death, myocardial infarction (MI), or ischemic stroke. CABG, Coronary artery bypass grafting; CHF, coronary heart disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HTN, hypertension; PAD, peripheral artery disease.
(From Bohula EA, Bonaca MP, Braunwald E, et al: Atherothrombotic risk stratification and the efficacy and safety of vorapaxar in patients with stable ischemic heart disease and prior myocardial infarction. Circulation 2016;134(4):304-313.)

Management

Management of patients with NSTE-ACS consists of an acute phase focused on the clinical symptoms and stabilization of the culprit lesion(s) and a longer-term phase that involves therapies directed at the prevention of disease progression and future plaque rupture/erosion. Retrospective angiographic studies[48] and a prospective natural history study of patients with NSTE-ACS managed with PCI[41] have shown that plaques that cause more severe stenosis have a higher risk of rupture leading to an ACS event. However, since plaques with less severe stenosis are more prevalent, these less obstructive lesions are responsible for about half of the future ACS events.

General Measures

Patients with new or worsening chest discomfort or an anginal equivalent symptom suggestive of ACS should be transported rapidly to the ED by ambulance, if possible, and evaluated immediately.[49] The initial evaluation should include a directed history and physical examination and ECG performed within 10 minutes of arrival.[23] If possible, the ECG should be obtained in the ambulance. Blood specimens for cTn or, if possible, hsTn assay should be obtained with expedited assessment via either a point-of-care device or laboratory measurement that can provide results within 60 minutes. Additional laboratory studies, such as natriuretic peptide, a complete blood count, serum electrolytes, creatinine, and glucose, can help guide early management treatments and strategy.

Patients with elevated cTn or new ST-segment abnormalities or deemed to be at moderate or high risk

based on a validated risk score should be admitted to a specialized cardiovascular intensive care unit (ICU). Patients with UA but without elevated cTn and ischemic electrocardiographic changes should be admitted to a monitored bed, preferably in a CV step-down unit.[11] In these settings, continuous electrocardiographic monitoring with telemetry detects tachyarrhythmias, alterations in atrioventricular (AV) and intraventricular conduction, and changes in ST-segment deviation. Patients should be placed on bed rest and inhaled oxygen provided to patients with arterial oxygen saturation (SaO_2) less than 90% and those with HF and pulmonary rales. Ambulation, as tolerated, is permitted if the patient has been stable without recurrent chest discomfort or ECG changes for at least 12 to 24 hours. Patients with atypical symptoms and low risk or those who have symptoms more consistent with another noncardiac cause may be observed in the ED or a short-stay unit. A second cTn assay should be performed 3 to 6 hours after the first, and further assessment with noninvasive imaging or stress testing may be considered to permit rapid exclusion of ACS.

Anti-Ischemic Therapy

Guidelines emphasize the early use of anti-ischemic therapies to improve the balance between oxygen supply and demand.[11,23] The goals of anti-ischemic therapy include relief of symptoms and prevention of early sequelae of ACS, including recurrent MI, HF, arrhythmias, and death. **Table 60.4** summarizes traditional and newer/experimental pharmacologic anti-ischemic therapies.

TABLE 60.4

Pharmacologic Anti-Ischemic Therapies in Non–ST Elevation Acute Coronary Syndromes (NSTE-ACS)

CLASS OF MEDICATION	MECHANISM OF ACTION	CLINICAL EFFECTS IN NSTE-ACS
Traditional Therapies		
Beta blockers	Decrease heart rate, blood pressure, and contractility through antagonism of $beta_1$ receptors	Decrease mortality[51]
Nitrates	Decrease preload through venodilation; vasodilate coronary arteries	No benefit on mortality
Calcium channel blockers	May vasodilate, reduce heart rate, or decrease contractility depending on specific drug	No clear benefit on mortality or reinfarction Increased reinfarction rate when short-acting nifedipine is used alone
Newer and Experimental Therapies		
Ranolazine	Inhibits late inward sodium current	Decreases recurrent ischemia and arrhythmias
Trimetazidine	Shifts myocardial metabolism from fatty acid to glucose use	Decreases short-term mortality
Nicorandil	Activates ATP-sensitive K^+ channels and dilates arterioles; may have ischemic precondition-like effect	Decreases arrhythmias and transient ischemia
Cyclosporine	Inhibitor of the mitochondrial permeability transition pore involved in reperfusion injury	Reduces infarct size in small studies;* larger clinical trial in progress

*Mewton N, Croisille P, Gahide G, et al. Effect of cyclosporine on left ventricular remodeling after reperfused myocardial infarction. J Am Coll Cardiol 2010;55(12):1200-5.

From American Heart Association; Soukouli V, Boden WE, Smith SC Jr, O'Gara PT. Nonantithrombotic medical options in acute coronary syndromes: old agents and new lines on the horizon. Circ Res 2014;114:1944-58.

Nitrates

Nitrates are vasodilators that increase myocardial blood flow (coronary vasodilation of atherosclerotic and normal vessels), reduce myocardial oxygen requirements by lowering cardiac preload (systemic venodilation), reduce cardiac afterload (systemic arterial dilation) thereby diminishing ventricular wall stress, and may have a mild antiplatelet effect. Reflex increases in heart rate (HR) and contractility that increase myocardial oxygen demand can be mitigated by concomitant use of a beta blocker. Well-

controlled clinical trials have not shown a reduction in cardiac events with nitrates; however, the rationale for nitrate use in NSTE-ACS is extrapolated from pathophysiologic principles and extensive clinical observations demonstrating their clinical effectiveness in relief of pain or other discomfort caused by myocardial ischemia.

In symptomatic patients without hypotension, the initial administration of rapidly acting nitroglycerin (sublingual or buccal, 0.3 to 0.6 mg at 5-minute intervals) is recommended, beginning before hospital arrival whenever possible. Intravenous (IV) nitroglycerin (5 to 10 µg/min, titrated to a maximum of 200 µg/min as needed) should be initiated in patients with hypertension and in patients with persistent or recurrent ischemic symptoms or HF, provided the systolic blood pressure (SBP) is at least 90 to 100 mm Hg. Tolerance to nitrates may develop within 12 to 24 hours and can be mitigated by nitrate-free intervals (if symptoms permit) or increasing the dose (if symptoms persist). Abrupt discontinuation of high doses of IV nitrates is not advised because this may precipitate recurrent ischemia and/or rebound hypertension; instead, IV nitrates should be weaned over several hours.

Important contraindications to nitrates include hypotension and recent use of a phosphodiesterase type 5 (PDE-5) inhibitor, sildenafil or vardenafil (within 24 hours), or tadalafil (within 48 hours). Since the catalytic site of PDE-5 normally degrades cyclic guanosine monophosphate, inhibitors of PDE-5 potentiate the endogenous levels of cGMP, possibly resulting in exaggerated, prolonged, and dangerous vasodilatory effects of nitrates. Relative contraindications to nitrates include hypotension (SBP <90 mm Hg), severe obstruction to LV outflow, large right ventricular infarction, or hemodynamically significant pulmonary embolism. In such patients, nitrates should be used with caution, if at all.

Beta-Adrenergic Receptor–Blocking Agents

Beta blockers competitively inhibit the myocardial effects of neuronally released and circulating catecholamines and reduce myocardial oxygen consumption by lowering HR, BP, and myocardial contractility. The evidence supporting beta blockers derives largely from older studies of patients with acute MI (generally STEMI) or new left bundle branch block (LBBB), before the current era of reperfusion therapy. In clinical trials of patients with acute MI, beta blockers reduce reinfarction, ventricular arrhythmias, and death. The findings from these trials, some of which included patients without ST elevation, have been extrapolated to patients with UA and NSTEMI.

A systematic review that pooled data on approximately 4700 patients with UA from five trials performed before 1986 showed that beta blockers reduced the risk for progression to MI.[50] Whether beta blockers would have similar efficacy in the modern era of intensive pharmacologic management with an early invasive strategy is unclear. Two more recent nonrandomized analyses from large registries of patients with NSTE-ACS demonstrated risk-adjusted decreases in predischarge[51] and longer-term[52] survival among patients treated with a beta blocker.

Oral beta blockers in doses used for chronic stable angina (**see Chapter 61**) should be initiated within the first 24 hours[11,23] with the following exceptions: (1) acute or severe HF; (2) low cardiac output; (3) hypotension; and (4) contraindications to beta-blocker therapy (e.g., high-degree AV block, active bronchospasm). Patients with initial contraindications to beta blockers should be reevaluated to determine subsequent eligibility to receive one of these agents. If ischemia persists despite IV nitrate therapy, IV beta blockers (5 mg over 1 to 2 min, repeated every 5 min for a total initial dose of 15 mg) may be used cautiously, generally following initial oral administration. IV beta blockers should be avoided in hypotensive patients.[53] Beta blockers should be avoided in patients with coronary vasospasm or acute intoxication with cocaine or methamphetamine because unopposed alpha-mediated coronary vasoconstriction may occur, worsening coronary spasm. Beta blockers with intrinsic sympathomimetic

activity (e.g., acebutolol, pindolol) should generally be avoided because they may increase the risk of ventricular tachycardia (VT) and fibrillation (VF).

Morphine

In the absence of contraindications (e.g., hypotension, allergy), it is reasonable to administer IV morphine (1 to 5 mg) if there is ongoing ischemic discomfort or pain despite treatment with maximally tolerated anti-ischemic medications (nitrates, beta blockers), with the caveat that morphine may slow intestinal absorption of oral platelet inhibitors. The morphine dose may be repeated every 5 to 30 minutes to relieve symptoms and maintain the patient's comfort. Morphine may act as both an analgesic and an anxiolytic; its venodilator effects may be beneficial by reducing preload (particularly in patients with acute pulmonary edema), and mildly reduces HR and BP by increasing vagal tone. Morphine may cause hypotension; supine positioning and IV saline may be used to restore BP. Naloxone (0.4 to 2.0 mg IV) may be administered for morphine overdose with respiratory or circulatory depression. In patients with morphine allergy, meperidine can be substituted.

Calcium Channel Blockers

Calcium channel blockers (CCBs) have vasodilatory effects and reduce arterial pressure. Some CCBs, such as verapamil and diltiazem, also slow HR, reduce myocardial contractility, and thereby reduce myocardial oxygen requirements. CCBs have been effective in reducing ischemia in patients with NSTE-ACS and persistent ischemia despite treatment with full-dose nitrates and beta blockers, as well as in patients with contraindications to beta blockers and in those with hypertension.[10,25] Such patients should receive nondihydropyridine CCBs that lower HR. The short-acting formulation of the dihydropyridine nifedipine, which accelerates HR, can cause harm in patients with ACS when not co-administered with a beta blocker. No harm has been observed with long-term treatment with the long-acting dihydropyridines—amlodipine and felodipine—in patients with documented LV dysfunction and CAD, suggesting that these agents may be safe in patients with NSTE-ACS and LV dysfunction. In patients with suspected/confirmed vasospastic angina (see later), CCBs and nitrates should be considered and beta blockers avoided. Contraindications to nondihydropyridine CCBs include significant LV dysfunction, increased risk for cardiogenic shock, PR interval longer than 0.24 second, and high-degree AV block.

Antiplatelet Therapy

See **Fig. 60.7** and **Table 60.5**.

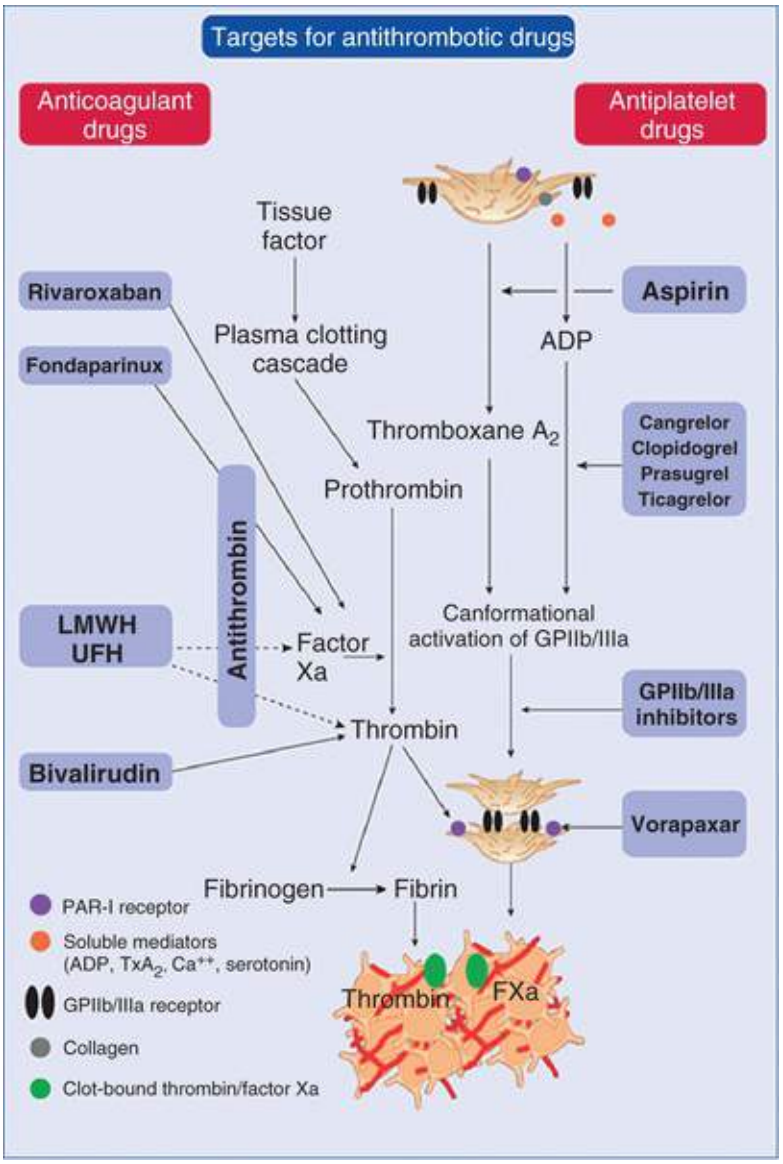


FIGURE 60.7 Targets of available antithrombotic drugs for NSTE-ACS can be used to inhibit blood coagulation and platelet aggregation during and after thrombus formation. *ADP,* Adenosine diphosphate; *GP,* glycoprotein; *LMWH,* low-molecular-weight heparin; *Tx,* thromboxane; *UFH,* unfractionated heparin; *vorapaxar* is a protease-activated receptor 1 (*PAR-1*) blocker. (From Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, Eur Heart J 2016;37:267-315.)

TABLE 60.5

2014 Guideline Recommendations for Antithrombotic Agents in Patients with Non–ST Elevation Acute Coronary Syndromes

Antiplatelet Therapy
Non–enteric-coated, chewable aspirin (162 to 325 mg) should be given to all patients without contraindications on presentation, and a maintenance dose of aspirin (81 to 325 mg/day) continued indefinitely.
In patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel (300 or 600 mg) followed by a daily maintenance dose of 75 mg should be substituted.
Either clopidogrel or ticagrelor can be used initially with either an early invasive or ischemic guided strategy (COR I, LOE: B).
Ticagrelor may be preferred over clopidogrel as the initial treatment (COR IIa, LOE: B).
In patients treated with ticagrelor, the preferred aspirin maintenance dose is 81 mg/day.
Use prasugrel only in patients receiving coronary stents (COR I, LOE: B).
The use of glycoprotein IIb/IIIa receptor inhibitors is reserved mainly to the time of PCI in high-risk patients who were not adequately pretreated with $P2Y_{12}$ inhibitors (COR I, LOE: A) or in those patients who were adequately pretreated with $P2Y_{12}$ inhibitors but have a high-risk profile (COR IIa, LOE: B).
Clopidogrel and ticagrelor should be discontinued at least 5 days (COR I, LOE: B) and prasugrel at least 7 days (COR I, LOE: C) before major surgery.
Anticoagulant Therapy
Enoxaparin is recommended at presentation (COR I, LOE: A); other option include unfractionated heparin (UFH) (COR I, B) and fondaparinux (COR I, LOE: B). If an early invasive strategy is planned, bivalirudin (COR I, LOE: B) is also an option.
If fondaparinux is used initially, add UFH or bivalirudin just before or during PCI to prevent catheter-related thrombosis (COR I, LOE: B).
Bivalirudin is preferred over UFH plus GP IIb/IIIa inhibitor in patients undergoing PCI who are at high risk of bleeding (COR IIa, LOE: B).
It is reasonable to use enoxaparin during PCI if it was used as the initial anticoagulant (COR IIb, LOE: B).

COR, Class of recommendation; *LOE,* level of evidence; *PCI,* percutaneous coronary intervention.

Modified from Eisen A, Giugliano RP. Antiplatelet and anticoagulation treatment in patients with non-ST-segment elevation acute coronary syndrome: comparison of the updated North American and European guidelines. Cardiol Rev 2016;24:170-6; and Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64: e139-228.

Oral Antiplatelet Drugs

Aspirin (Acetylsalicylic Acid, ASA)

ASA acetylates platelet cyclooxygenase 1 (COX-1), thereby blocking the synthesis and release of thromboxane A_2 (TxA_2), a platelet activator, and decreasing platelet aggregation and arterial thrombus formation. Because the inhibition of COX-1 by ASA is irreversible, the antiplatelet effects last for the lifetime of the platelets, approximately 7 to 10 days. Several placebo-controlled trials have demonstrated the benefit of ASA in patients with NSTE-ACS.[54] In addition to reducing adverse clinical events early in treatment, ASA also reduces the frequency of ischemic events in secondary prevention. It is a cornerstone of antiplatelet therapy in patients with all forms of ACS, as well as those with chronic CHD.[11]

Even though doses of ASA have ranged from 50 to 1300 mg/day in randomized trials, there does not appear to be a dose-response effect on efficacy, but GI bleeding is increased at higher doses.[54] The CURRENT OASIS-7 (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Symptoms)[55] trial randomly assigned 25,086 patients with ACS to receive high-dose (300 to 325 mg/day) or low-dose (75 to 100 mg/day) ASA for 30 days (and to high-dose versus regular-dose clopidogrel; see later). No difference in the risk for CV death, MI, or stroke was observed between the two doses of ASA, but GI bleeding increased with the higher dose. Guidelines recommend that in patients with NSTE-ACS who have not been taking ASA, the initial loading dose should be 162 to 325 mg of non–enteric-coated ASA, followed by a maintenance dose of 75 to 100 mg daily.[11] Enteric-coated ASA should be avoided initially because it delays and reduces absorption.[56] Data from PLATO (Study of Platelet Inhibition and Patient Outcomes), a large trial of ticagrelor, an oral antiplatelet agent that inhibits the receptor $P2Y_{12}$, provides another reason to favor low-dose ASA.[57] High-dose (≥160 mg) aspirin was associated with increased GI bleeding risk in the

absence of improved outcomes, compared to low-dose (<160 mg) aspirin.[58] Most nonsteroidal anti-inflammatory drugs (NSAIDs) bind reversibly to COX-1, preventing this enzyme's inhibition by aspirin, and may cause prothrombotic effects; thus NSAIDs should be avoided.

So-called ASA resistance may occur during chronic therapy, with 2% to 8% of patients exhibiting a limited antiplatelet effect (i.e., minimal change in inhibition of platelet aggregation). These patients tend to have a greater risk for recurrent cardiac events. Causes of ASA resistance are varied and include poor compliance (pseudoresistance), reduced absorption, interaction with ibuprofen or other NSAIDs, overexpression of COX-2 mRNA, and use of enteric-coated forms. Rarely, a genetic or other intrinsic reason for minimal response to ASA is present. No evidence supports the routine monitoring of antiplatelet effects with adjustment of the ASA dose.[59]

Contraindications to ASA include documented allergy (e.g., ASA-induced asthma), nasal polyps, active bleeding, or a known platelet disorder. Dyspepsia or other GI symptoms with long-term ASA therapy (i.e., ASA intolerance) do not usually preclude therapy in the short term. In patients who have an allergy to ASA, desensitization or substituting clopidogrel, prasugrel, or ticagrelor is recommended.[11] Clopidogrel may be substituted in place of ASA in patients who cannot tolerate ASA because of GI bleeding.

$P2Y_{12}$ Inhibitors

Management of ACS now routinely includes dual-antiplatelet therapy (DAPT) consisting of both ASA and a $P2Y_{12}$ inhibitor (**Table 60.5**). The latter includes the oral thienopyridines (ticlopidine, clopidogrel, prasugrel), which irreversibly block ADP binding to the surface of the platelet $P2Y_{12}$ receptor, as well as a cyclopentyltriazolopyrimidine (ticagrelor), which is a reversible ADP inhibitor. Thienopyridines are prodrugs that require oxidation by the hepatic cytochrome P-450 (CYP) system to form the active metabolites. Thus drugs that inhibit the CYP system reduce the formation of the active form of thienopyridines, unlike ticagrelor, which does not depend on the CYP system. In addition to inhibition of platelet activation and aggregation, thienopyridines also reduce fibrinogen, blood viscosity, and erythrocyte deformability and aggregability through mechanisms that appear to be independent of ADP.

Clopidogrel

Clopidogrel largely avoids the hematologic complications (neutropenia and, rarely, thrombotic thrombocytopenic purpura) associated with ticlopidine, the first widely used thienopyridine. When clopidogrel is absorbed, approximately 85% is hydrolyzed by circulating esterases and thus rendered inactive. The remaining clopidogrel must be oxidized by the hepatic CYP system to generate the active metabolites that inhibit the $P2Y_{12}$ receptor.

The addition of clopidogrel to ASA was studied in the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial of 12,562 patients with NSTE-ACS who were treated with ASA, unfractionated heparin (UFH), or low-molecular-weight heparin (LMWH), and other standard therapies and randomly assigned to receive either a 300-mg loading dose of clopidogrel followed by 75 mg daily or a placebo.[60] The addition of clopidogrel to ASA reduced CV death, MI, or stroke by 20% in both low- and high-risk patients with NSTE-ACS, regardless of whether they were managed with medical therapy, PCI, or coronary artery bypass grafting (CABG) (**Fig. 60.8**). Benefit was seen as early as 24 hours, with Kaplan-Meier curves beginning to diverge after just 2 hours.[61] Moreover, the reduction in MI or CV death was similar before and after PCI, through a mean follow-up of 8 months.[62] Addition of clopidogrel results in a small increase in bleeding, including a nonsignificant increase in both life-threatening and fatal

bleeding.[60]

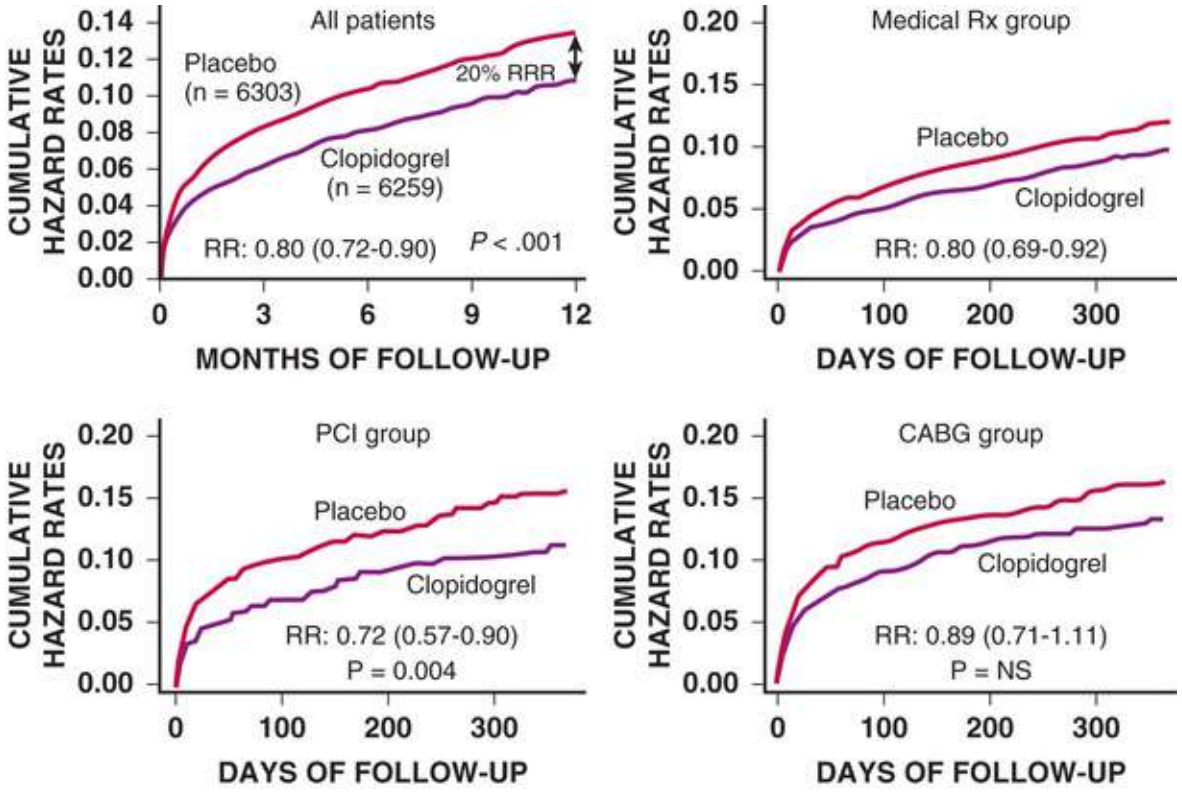


FIGURE 60.8 Benefit of clopidogrel in reducing cardiovascular death, MI, or stroke in patients with NSTE-ACS in the CURE trial and in patients managed medically or with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). P-value or interaction among strata 0.53. RR, relative risk; RRR, relative risk ratio; Rx, drug. (From Yusuf Set al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494; and Fox KAet al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome. The Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial. Circulation 2004;110:1202.)

These and similar findings in other trials led to a class I recommendation in both North American[11] and European[63] guidelines to administer clopidogrel prior to PCI. In patients undergoing CABG, those who had received clopidogrel within 5 days of surgery had an increased risk for major bleeding and the need for reoperation, which led to the recommendation that clopidogrel be discontinued at least 5 days before major surgery, if possible.[11,63]

In NSTE-ACS patients the initial loading dose of 300 to 600 mg clopidogrel should be followed by a maintenance dose of 75 mg daily. Use of a 600-mg loading dose achieves a steady-state level of platelet inhibition after just 2 hours, more rapidly than the 300-mg dose. Thus, 600-mg clopidogrel is the preferred loading dose for patients with NSTE-ACS undergoing PCI.[11,23] Two strategies for initiating clopidogrel therapy in patients with NSTE-ACS have evolved: (1) starting clopidogrel at arrival or hospital admission or (2) delaying treatment with clopidogrel until after coronary angiography and then administering the drug on the catheterization table if PCI is performed. The early treatment strategy is preferred because it affords the benefits of reducing early ischemic events, but at the cost of an increase in bleeding in the minority of patients who undergo CABG instead of or immediately after PCI.

Although DAPT reduces recurrent ischemic events in patients with NSTE-ACS compared to ASA alone,

up to 10% of patients treated with ASA plus clopidogrel have events within the first year of ACS, including definite stent thrombosis in up to 2% of patients at 1 year.[64] As with ASA, hyporesponders to clopidogrel have been identified and are at higher risk for recurrent cardiac events, including stent thrombosis, MI, and death.[59] The incidence of patients not achieving the expected pharmacologic response to clopidogrel ranges from 5% to 30%, depending on the population and the definition used to assess response.[59] Hyporesponsiveness to clopidogrel is more common in patients with diabetes, as well as in those with obesity, advanced age, and with certain genetic polymorphisms of the CYP system. Patients with a minimal antiplatelet response to clopidogrel have lower concentrations of the active metabolite, thus indicating failure of this necessary conversion.

Several polymorphisms of the gene encoding for the CYP2C19 enzyme have been associated with reduced production of the active metabolite of clopidogrel (**see Chapter 8**). These polymorphisms (especially the reduced-function *C2 allele) occur in approximately one third of white individuals and up to half of Asians and have been associated with increased adverse clinical outcomes in patients treated with clopidogrel. In other studies, reduced-function alleles are associated with increased stent thrombosis. Testing for these polymorphisms in patients who are candidates for thienopyridine treatment can identify those who are likely to be unresponsive or hyporesponsive to the standard dose of clopidogrel and are candidates for alternative antiplatelet regimens. Three randomized trials that evaluated more aggressive antiplatelet regimens in patients with high platelet reactivity after standard dose of ASA and clopidogrel, however, did not show a significant reduction in clinical CV events with higher doses of antiplatelet drugs versus standard doses.[65-67] Data from a study of patients with UA undergoing PCI showed that a daily maintenance dose of 225 mg or more of clopidogrel (at least three times the standard dose) is necessary in heterozygote carriers of the CYP2C19*2 allele to achieve the same level of platelet inhibition as that in noncarriers who receive 75 mg daily.[68] Thus the three aforementioned trials may have failed to show clinical benefit with more intensive antiplatelet regimens in patients with high platelet reactivity, in part because of insufficiently high clopidogrel doses. Proton pump inhibitors (PPIs) modestly reduce the antiplatelet effect of clopidogrel when assessed by platelet function assays[69] because of competition for metabolism by the CYP3A4 enzyme. However, a randomized, double-blind trial[70] indicated that a clinically significant interaction between clopidogrel and PPIs is unlikely.

Prasugrel

Similar to clopidogrel, prasugrel is a prodrug requiring hepatic oxidation to form an active metabolite that irreversibly inhibits the platelet $P2Y_{12}$ receptor. However, unlike clopidogrel, formation of the active metabolite of prasugrel requires only one step and is generated within 30 minutes of ingestion. While the active metabolites of clopidogrel and prasugrel exert equal antiplatelet effects in vitro, the generation of the prasugrel metabolite is approximately 10 times as great as the clopidogrel metabolite, which results in approximately a 10-fold greater potency.

Prasugrel (60-mg loading dose, 10-mg daily maintenance dose) was compared to clopidogrel (300-mg loading dose, 75-mg daily maintenance dose) in 10,074 patients with NSTE-ACS with known anatomy coronary anatomy in the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38) trial.[71] The primary composite of CV death, MI, or stroke was reduced by 19% in the patients randomized to prasugrel through 15 months of follow-up.(**Fig. 60.9A**) The benefit driven by a significant 24% reduction in MI and was particularly striking in patients with diabetes (30% reduction).[72] In addition, prasugrel

markedly reduced the rate of definite or probable stent thrombosis (by 52%), particularly in patients with drug-eluting stents (64%)[73]; thus prasugrel should be considered in patients who present with stent thrombosis despite compliance with clopidogrel therapy.[23]

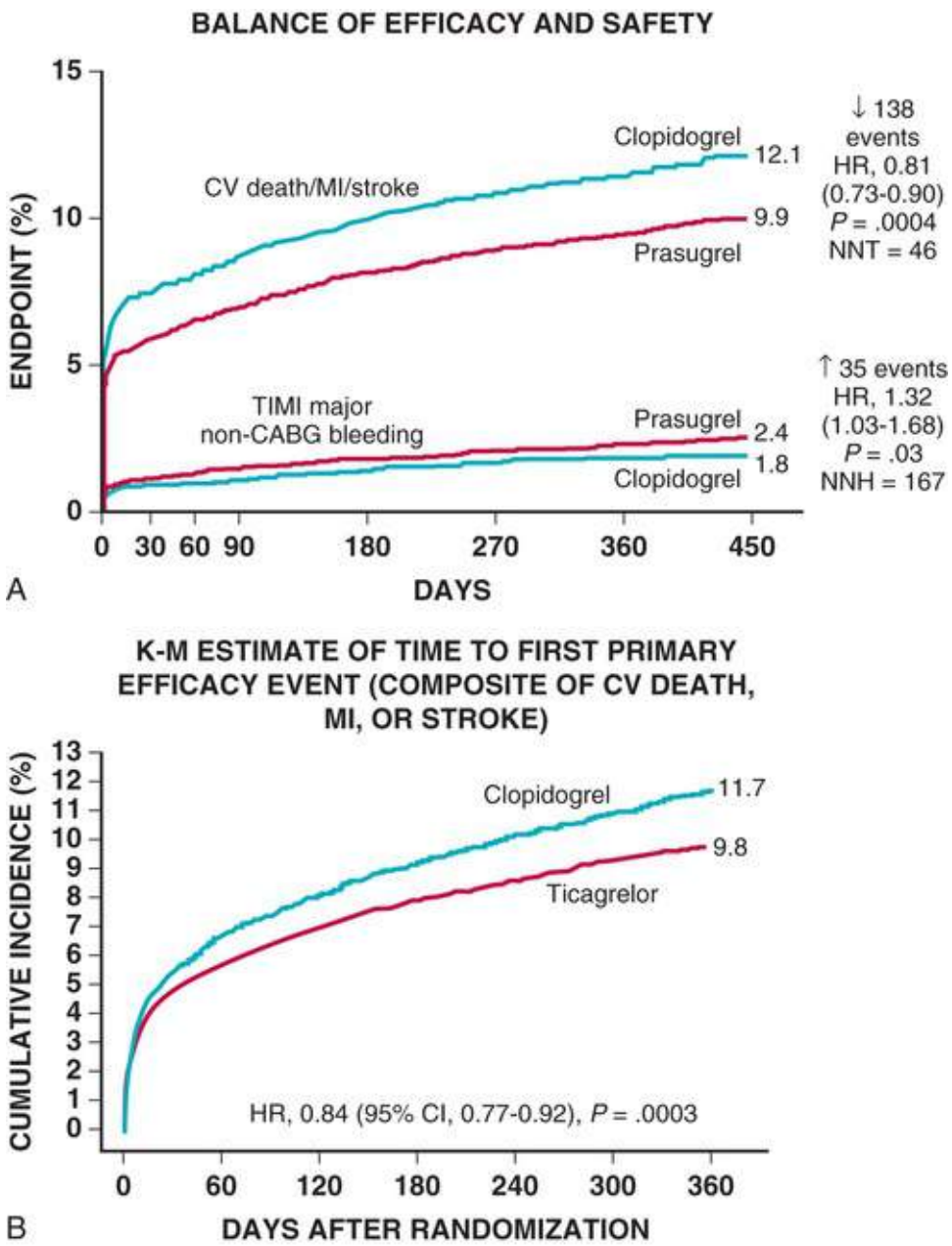


FIGURE 60.9 Comparison of more potent adenosine diphosphate (ADP) inhibitors versus clopidogrel. **A,** Comparison of the efficacy and safety of prasugrel versus clopidogrel in the TRITON-TIMI 38 trial in patients with ACS undergoing PCI. HR, Hazard ratio; NNT, number of patients needed to prevent one primary endpoint event; NNH, number of patients needed to be treated to cause harm (TIMI major bleeding). **B,** The primary endpoint of the PLATO trial—a composite of death from vascular causes, myocardial infarction (MI), or stroke—occurred significantly less often in the ticagrelor group than in the clopidogrel group. CV, Cardiovascular; K-M, Kaplan-Meier curve. (**A,** From Wiviott SD et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;347:2001; **B,** from Wallentin L et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045.)

Severe bleeding complications were more common with prasugrel, including non-CABG major (**Fig. 60.9A**), spontaneous, and fatal bleeding events. Prasugrel is contraindicated in patients with prior stroke or transient ischemic attack (TIA) due to evidence of net harm in this group in TRITON-TIMI 38. Bleeding rates were especially high in elderly patients (≥75 years) and those with reduced body weight

(<60 kg [132 lb]). Thus, prasugrel should be avoided in such patients unless they are at high risk for thrombosis, in which case a 5-mg maintenance dose is preferred. In patients younger than 75 who weighed at least 60 kg and had no prior stroke or TIA—the "core" group of patients for whom the U.S. Food and Drug Administration (FDA) approved its use—prasugrel was associated with a 26% reduction in the primary endpoint.[74] Prasugrel should be discontinued at least 7 days before cardiac surgery whenever possible.[11]

Prasugrel (10 mg daily) was compared to clopidogrel (75 mg daily) on a background of ASA and other standard therapies in 7243 patients under age 75 with NSTE-ACS managed with an ischemia-guided strategy in the TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) randomized trial.[75] There was no benefit of treatment with prasugrel over clopidogrel, and bleeding rates were similar. The ACCOAST (A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non–ST-Elevation Myocardial Infarction) trial of high-risk patients with NSTE-ACS managed with an early invasive strategy randomized to prasugrel versus clopidogrel *prior to angiography*.[76] There was no significant difference in the composite primary efficacy endpoint, but prasugrel did increase bleeding compared to clopidogrel. Given the totality of the evidence from these three randomized trials, prasugrel is most suitable in patients younger than 75 years without a prior stroke or TIA who have had coronary angiogram and in whom PCI is planned. Prasugrel is not recommended for use in patients with NSTE-ACS before angiography.[10,25]

Ticagrelor

Ticagrelor is the first nonthienopyridine ADP blocker approved for use. It is a *reversible* inhibitor (half-life approximately 12 hours) of the $P2Y_{12}$ platelet receptor, in contrast to the oral thienopyridines, which are irreversible inhibitors. Both the parent drug and its metabolite are active and have similar potency; thus, similar to prasugrel, inhibition of $P2Y_{12}$-mediated platelet aggregation is nearly complete and more rapid than with clopidogrel. Since ticagrelor does not require metabolism via the CYP2C19 pathway to generate its active metabolite, the variability of antiplatelet activity described with clopidogrel in patients does not apply to ticagrelor.

The phase 3 PLATO trial compared ticagrelor (180-mg loading dose, 90-mg twice-daily maintenance dose) with clopidogrel (300- or 600-mg loading dose, 75-mg daily maintenance dose) on a background of ASA. In PLATO, 11,067 (59%) of the 18,624 patients had NSTE-ACS.[77] Ticagrelor significantly reduced the primary endpoint (CV death, MI, or stroke) by 16% (**Fig. 60.9B**) and also reduced stent thrombosis by 33%, CV death by 21%, and total mortality by 22%. A broad array of subgroups demonstrated consistent benefit with ticagrelor over clopidogrel, including patients age 75 or older, weight less than 60 kg, with a prior history of stroke or TIA, and those managed with a noninvasive strategy. However, there was no benefit of ticagrelor in patients enrolled in the United States, in whom the dose of ASA was higher on average than in other countries.[57] Whether this finding is related to chance, more frequent use of higher-dose ASA (e.g. 325 mg daily), or some other aspect of care that differed in the United States remains uncertain. Nevertheless, the FDA has recommended that low-dose ASA (75 to 100 mg daily) be used in combination with ticagrelor.

Safety events were similar between ticagrelor and clopidogrel, with three important exceptions that were more common with ticagrelor: non–CABG-related major bleeding (4.5% versus 3.8%; $P = 0.03$), dyspnea (13.8% versus 7.8%; $P < 0.001$), and pauses in sinus rates in the first week lasting longer than 3 seconds (5.8% versus 3.6%; $P = 0.01$).[77] Although a reversible $P2Y_{12}$ inhibitor with a shorter effective

half-life than clopidogrel, ticagrelor achieves a higher level of platelet inhibition and thus should be discontinued at least 5 days before major surgery.[11]

Long-term use of ticagrelor with ASA in patients who had experienced MI 1 to 3 years earlier was evaluated in the PEGASUS-TIMI 54 trial.[78] Compared to placebo, both the standard maintenance dose of ticagrelor (90 mg twice daily) and a lower dose (60 mg twice daily) reduced the rate of the primary composite endpoint (CV death, MI, or stroke) by 15% and 16%, respectively. Although the rates of TIMI major bleeding were higher with ticagrelor, rates of intracranial and fatal bleeding were not increased. Major bleeding rates were lower and tolerability better with the 60-mg twice-daily dose,[79] which was FDA approved for the prevention of CV death, MI, and stroke in stable patients with a history of stroke.

Protease-Activated Receptor-1 Antagonists

The oral protease-activated receptor-1 (PAR-1) antagonist *vorapaxar*, which inhibits thrombin-mediated platelet activation, was not effective in patients with NSTE-ACS.[80] In the TRA-2P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–TIMI) trial of 26,449 stable patients with a history of MI, ischemic stroke, or peripheral vascular disease, the addition of vorapaxar to standard therapies reduced ischemic events while increasing bleeding compared to placebo.[81] Patients enrolled 2 weeks to 1 year after MI had a 20% reduction in CV death, MI, or stroke. The efficacy and safety profile of vorapaxar were similar whether patients were or were not taking a concomitant thienopyridine.[82] This PAR-1 antagonist may play a role in secondary prevention in stable patients following an NSTEMI.

Intravenous Antiplatelet Agents

Glycoprotein IIb/IIIa Inhibitors

The glycoprotein (GP) IIb/IIIa inhibitors block the final common pathway of platelet aggregation—fibrinogen-mediated cross-linkage of platelets—caused by a variety of stimuli (e.g., thrombin, ADP, collagen, serotonin) (**see Fig. 60.7**) and were more frequently used in the era before the introduction of potent oral and IV $P2Y_{12}$ inhibitors. Three agents in this class are available: abciximab, a monoclonal antibody approved only in patients undergoing PCI, and eptifibatide and tirofiban, both of which are reversible small-molecule inhibitors approved for use in patients with ACS and in those undergoing PCI (**see Table 98.4**).

Several trials, mostly on a background of ASA without $P2Y_{12}$ inhibitor, have shown benefit of GP IIb/IIIa inhibition in the management of patients with NSTE-ACS, with an overall small (9%) but statistically significant relative reduction in death or MI at 30 days in a large meta-analysis,[83] with greater benefit in high-risk patients with ST-segment changes and/or elevated troponin concentration or diabetes.[83,84] However, the rates of major hemorrhage were significantly higher in patients treated with GP IIb/IIIa inhibitors, occurring in 2.4% compared to 1.4% of those given placebo, and severe thrombocytopenia (<50,000/mm^3) was also increased.[85] Two large trials have examined routine early administration at initial evaluation versus delayed provisional use of GP IIb/IIIa inhibitors just before PCI in patients who also received a $P2Y_{12}$ inhibitor (most commonly pre-PCI) and found no significant benefit with an increased risk of bleeding.[86,87] Based on the totality of the evidence, the routine administration of GP IIb/IIIa inhibitors to patients with NSTE-ACS who receive DAPT with ASA and a $P2Y_{12}$ inhibitor (i.e., triple-antiplatelet therapy) is not recommended. However, selective use in patients at high risk for ischemic complications, such as those with diabetes or angiographic evidence of thrombus, and at low

risk for bleeding who are to undergo PCI, or in the management of thrombotic complications during PCI, appears more prudent.

Cangrelor

Cangrelor is an IV direct-acting $P2Y_{12}$ inhibitor that blocks ADP-induced platelet activation and aggregation. The parent compound exhibits an almost immediate onset of action and short half-life of 3 to 6 minutes.[88] Three large outcome studies have evaluated cangrelor in more than 25,000 patients undergoing PCI across a broad spectrum of clinical presentations (stable angina, UA, NSTEMI, STEMI). In a patient-level meta-analysis, cangrelor reduced the risk of the primary composite outcome of death, MI, ischemia-driven revascularization, and stent thrombosis at 48 hours by 18% (2.9 versus 3.5%; P = 0.04) relative to control among the 14,282 patients who underwent PCI after NSTE-ACS.[89] There was an excess of 3 per 1000 non-CABG bleeds with cangrelor (1.0 versus 0.7%).

Since cangrelor is administered intravenously and has a rapid onset and offset of action, it has the potential to overcome several practical limitations of oral $P2Y_{12}$ inhibitors in patients with NSTE-ACS undergoing PCI. These limitations include (1) a slower onset action of oral delivery; (2) delayed absorption of oral agents in patients who have decreased GI perfusion, nausea, or receive opiates; and (3) the need to postpone CABG for 5 to 7 days after an oral $P2Y_{12}$ inhibitor to reduce the risk of bleeding. Cangrelor was approved in the United States and Europe in 2015 as an adjunct to PCI for reducing the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis in patients in who have not been treated with a $P2Y_{12}$ platelet inhibitor and who are not being given a GP IIb/III inhibitor.

Anticoagulant Therapy

Once the diagnosis of NSTE-ACS has been made, a parenteral anticoagulant should be initiated in addition to DAPT, unless the patient has an absolute contraindication (e.g., uncontrolled bleeding) (**see Fig. 60.7**).

Heparin

Unfractionated heparin is a mixture of polysaccharide chains of different lengths that prevent coagulation by blocking thrombin (factor IIa) and factor Xa. UFH also binds to circulating plasma proteins, acute-phase reactants, and endothelial cells and thus has an unpredictable anticoagulant effect. Because of its short half-life, UFH must be administered as an IV infusion to ensure a stable level of anticoagulation.

A meta-analysis of 1353 patients in six trials showed a 33% reduction in death or MI with UFH plus ASA versus ASA alone.[90] Daily monitoring of the anticoagulant response via the activated partial thromboplastin time (APTT) is recommended, with titrations made according to a standardized nomogram to achieve an APTT of 50 to 70 seconds or 1.5 to 2.5 times control.[23] The ACC/AHA guidelines recommend a weight-adjusted dose of UFH (60-unit/kg bolus and 12-unit/kg/hr infusion), as well as frequent monitoring of the APTT (every 6 hours until the target range is reached and every 12 to 24 hours thereafter) and adjustment of the dose if necessary.[11] Adverse effects include bleeding, especially when the APTT is excessively elevated. Immunogenic heparin-induced thrombocytopenia (HIT) is an infrequent but serious complication that can cause thrombosis and bleeding and may even be fatal. In patients with HIT, a direct thrombin inhibitor (e.g., argatroban, 2-μg/kg/min infusion to achieve APTT 1.5 to 3 times control[91]) or fondaparinux (see later) should be substituted.

Heparin Reversal

Protamine sulfate binds heparin to form a stable salt, thus quickly reversing the anticoagulant effect of UFH. Because the half-life of UFH is approximately 1 to 1.5 hours, the dose of protamine necessary to reverse an infusion of UFH should be based on the total UFH dose administered in the previous 2 to 3 hours. Approximately 1 mg neutralizes 100 units of UFH. A slow IV infusion is recommended to avoid hypotension or bradycardia. Protamine reverses approximately 60% of the anticoagulant effect of LMWH but does not completely neutralize its anti-Xa activity.

Low-Molecular-Weight Heparin

The low-molecular-weight forms of heparin are enriched with shorter polysaccharide chains, which results in a more predictable anticoagulant effect than with UFH. LMWH has several potential advantages over UFH: (1) its greater anti–factor Xa activity (relative to factor IIa) inhibits thrombin generation more effectively; (2) LMWH induces greater release of tissue factor pathway inhibitor than UFH, and it is not neutralized by platelet factor 4; (3) LMWH less frequently causes HIT; (4) the high and consistent bioavailability of LMWH allows subcutaneous (SC) administration; (5) monitoring of the anticoagulation level is not necessary; and (6) LMWH binds less avidly to plasma proteins than UFH and therefore has a more consistent anticoagulant effect.

Although several LMWHs have been approved, the weight of evidence supports the choice of *enoxaparin.*[11,23] The standard dose of enoxaparin is 1 mg/kg subcutaneously every 12 hours, with dosing only once daily for patients with a creatinine clearance (CrCl) less than 30 mL/min. Administration of enoxaparin for up to 8 days (or until hospital discharge) was found effective in patients with ACS, whereas extending therapy to 6 weeks did not reduce ischemic events further in patients with NSTE-ACS.[92] In the event of bleeding, the anticoagulant effect of LMWH can be reversed partially with protamine. LMWH should not be used in patients with a history of HIT. In patients with NSTE-ACS treated with ASA, LMWH reduced the incidence of death or MI by 66% compared with placebo. In a meta-analysis of 21,945 patients from six trials of patients with NSTE-ACS in which enoxaparin was compared with UFH, new or recurrent MI occurred less frequently with enoxaparin, whereas the rate of major bleeding was similar between the drugs.[93]

Direct Thrombin Inhibitors

The direct thrombin inhibitors have a potential advantage over indirect thrombin inhibitors such as UFH or LMWH in that they do not require antithrombin and can inhibit clot-bound thrombin. Direct thrombin inhibitors do not interact with plasma proteins, provide a very stable level of anticoagulation, and do not cause thrombocytopenia, thus making them an excellent choice for anticoagulation in patients with a history of HIT.

Bivalirudin, the drug in this class most widely used in patients with ACS or undergoing PCI, binds reversibly to thrombin and has a half-life of approximately 25 minutes. In the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial,[94] patients with NSTE-ACS randomized to bivalirudin without a GP IIb/IIIa inhibitor experienced less bleeding in comparison to the combination of a GP IIb/IIIa inhibitor with either UFH or enoxaparin. However, there were no differences in major bleeding between anticoagulants (UFH or enoxaparin versus bivalirudin) in patients taking a GP IIb/IIIa inhibitor, and there were no differences in ischemic events between the three treatment arms.[94] A meta-analysis of four trials enrolling predominantly patients with NSTE-ACS showed that heparin-based regimens slightly reduced major adverse cardiovascular events (MACE) compared to bivalirudin-based

regimens (relative risk [RR], 1.10; 95% confidence interval [CI] 0.99 to 1.23).[95]

Subsequently, in the Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiomax (MATRIX) study,[96] 7213 patients with ACS (44% with high-risk NSTE-ACS) in whom PCI was planned were randomized to either bivalirudin or UFH in an open-label fashion. Rates of MACE (death, MI, stroke), net adverse clinical events (MACE or major bleeding), and mortality did not differ between the treatment groups in the entire population or among the 3203 patients with NSTE-ACS. Major bleeding was reduced significantly in the bivalirudin group by almost 50% among patients with NSTE-ACS. However, use of GP IIb/IIIa inhibitors in the study was more frequent in the UFH group (26% versus 5%), as designated by the trial design, and likely contributed to the increased bleeding in the UFH group.

The use of bivalirudin monotherapy (with ASA and a $P2Y_{12}$ inhibitor but without a GP IIb/IIIa inhibitor) is now considered an acceptable alternative to heparin-based regimens in patients with NSTE-ACS managed with an early invasive strategy and may be preferred in patients with increased risk for bleeding who are undergoing PCI.[11] In patients with NSTE-ACS before angiography, the recommended dose of bivalirudin is a 0.10-mg/kg IV bolus followed by an infusion of 0.25 mg/kg/hr. If started during the procedure, a 0.75-mg/kg bolus dose of bivalirudin should be administered, followed by an infusion at 1.75 mg/kg/hr during PCI.[11] It may be discontinued shortly after PCI to permit removal of arterial access sheaths. In patients with renal dysfunction and a CrCl less than 30 mL/min, the infusion rate should be reduced to 1 mg/kg/hr.

Factor Xa Inhibitors

Both parenteral and oral factor Xa inhibitors have been studied in patients with NSTE-ACS.

Fondaparinux

This synthetic pentasaccharide indirectly inhibits factor Xa and requires the presence of antithrombin for its action. The OASIS-5 trial compared daily SC fondaparinux (2.5 mg) with standard-dose enoxaparin in 20,078 patients with high-risk NSTE-ACS.[97] No difference was found in the primary ischemic composite through 9 days, although fondaparinux did reduce major bleeding by nearly half, and mortality at 30 days tended to be lower with fondaparinux. In patients undergoing PCI, however, fondaparinux was associated with a greater than threefold increased risk for catheter-related thrombi. Supplemental UFH at catheterization (85 units/kg if no GP IIb/IIIa inhibitor was used; 60 units/kg with concomitant GP IIb/IIIa inhibitor) appeared to minimize the risk of this problem with fondaparinux.[98] Thus, fondaparinux is an alternative for patients with NSTE-ACS managed noninvasively, particularly in patients at high risk for bleeding.[11,23]

Oral Factor Xa Inhibitors

Two oral direct factor Xa inhibitors, *rivaroxaban* and *apixaban,* have been studied in phase 3 trials of patients with ACS. In the ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary syndrome–Thrombolysis in Myocardial Infarction) trial, low-dose rivaroxaban (5 mg twice daily) and very-low-dose rivaroxaban (2.5 mg twice daily) reduced the primary composite (death, MI, or stroke) significantly by 16% compared to placebo on a background of DAPT.[99] Bleeding, including intracranial hemorrhage, was significantly increased with the addition of rivaroxaban to DAPT. Because the 2.5-mg twice-daily dose had a more favorable safety profile and also significantly reduced death, it was approved by the European Medicines Agency in 2013

for the prevention of atherothrombotic events in post–acute MI patients. However, rivaroxaban has not been approved for use after ACS by the FDA. Studies with apixaban in combination wtih antiplatelet agents demonstrated increased bleeding without a reduction in ischemic events; thus this indication was not pursued further.

Longer-Term Oral Anticoagulant and Antiplatelet Therapy

Approximately 10% of patients presenting with NSTE-ACS have an indication for ongoing oral anticoagulation, such as atrial fibrillation (AF), mechanical heart valves, or recent venous thromboembolism. Since the combination of oral anticoagulation with DAPT is associated with a threefold to fourfold increase in bleeding requiring hospitalization[100] the management of such patients is complicated and remains controversial. Current consensus statements provide variable recommendations ranging from 1 to 12 months for the duration of triple therapy (ASA, ADP inhibitor, and anticoagulant), depending on the bleeding and thromboembolic risk and type of coronary stent.[101] The desire to avoid prolonged interruptions in oral anticoagulation needs to be balanced by the increased risk of bleeding when patients with NSTE-ACS require coronary angiography and revascularization.[102]

In patients with NSTE-ACS receiving DAPT who had been receiving prior oral anticoagulation, it is reasonable to transition to a parenteral anticoagulant at or shortly after presentation (i.e., once therapeutic anticoagulation has waned). If immediate angiography is required, radial access is the preferred choice because it may reduce the risk of access site bleeding. After the procedure the duration of triple therapy should be minimized. Since most of the available data with triple therapy are in patients who have received ASA, clopidogrel, and a vitamin K antagonist (VKA), current guidelines[11,23] favor low-dose ASA (75 to 100 mg daily), clopidogrel, and VKA targeting an international normalized ratio (INR) of 2.0 to 2.5, although ongoing studies are evaluating different combinations of ADP inhibitors and oral anticoagulants (warfarin and non–vitamin K antagonist oral anticoagulants [NOACs]), with and without ASA. Use of bare-metal stents (which require a shorter duration of DAPT than drug-eluting stents) should be considered, and gastric protective agents[103] are recommended to reduce the risk of bleeding. An approach to antithrombotic therapy in patients with AF and NSTE-ACS minimizes bleeding while providing protection from thrombosis and ischemia (**Fig. 60.10**).

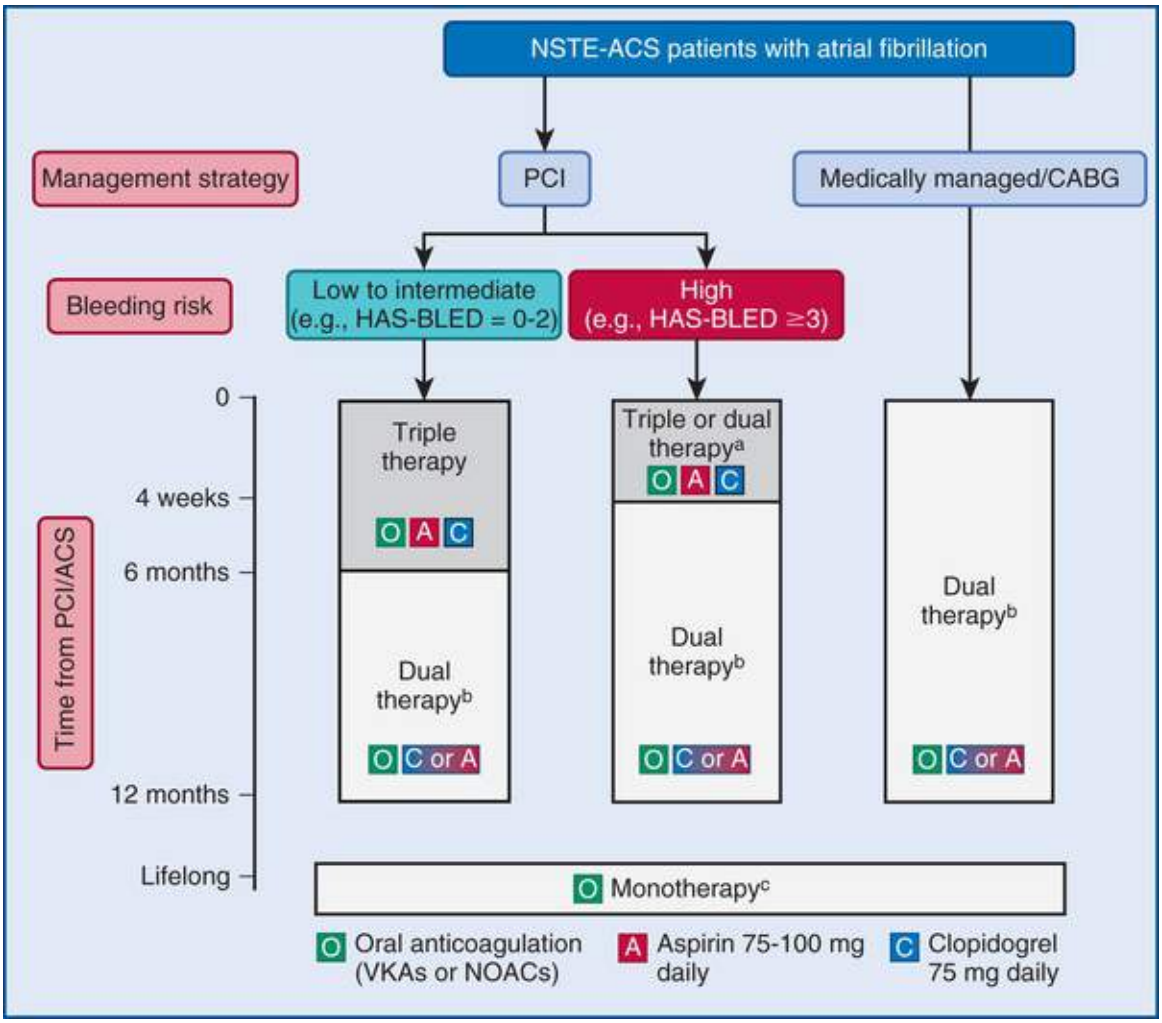


FIGURE 60.10 Antithrombotic strategies in patients with non–ST elevation acute coronary syndrome (NSTE-ACS) and nonvalvular atrial fibrillation (AF). CABG, Coronary artery bypass graft; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years (2 points), diabetes, stroke, or systemic arterial embolism (2 points)–vascular disease, age 65-74, sex category; DAPT, dual-antiplatelet therapy; NOACs, non–vitamin K antagonist oral anticoagulants; PCI, percutaneous coronary intervention; VKAs, vitamin K antagonists. [a]Dual therapy with oral anticoagulation and clopidogrel may be considered in select patients (low ischemic risk). [b]Aspirin as an alternative to clopidogrel may be considered in patients on dual therapy (i.e., oral anticoagulation plus single antiplatelet); triple therapy may be considered up to 12 months in very select patients at high risk of ischemic events (e.g., prior stent thrombosis on adequate antiplatelet therapy, stenting in the left main or last remaining patent coronary artery, multiple stenting in proximal coronary segments, two stents bifurcation treatment, or diffuse multivessel disease, especially in diabetic patients). [c]Dual therapy with oral anticoagulation and an antiplatelet agent (aspirin or clopidogrel) beyond 1 year may be considered in patients at very high risk of coronary events. In patients undergoing coronary stenting, dual-antiplatelet therapy may be an alternative to triple or a combination of anticoagulants and single-antiplatelet therapy if the CHA_2DS_2-VASc score is 1 (males) or 2 (females). (Modified from Lip GY, Windecker S, Huber K, et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions. Eur Heart J 2014;35:3155-79.)

Subsequent to the release of the previous guidelines, the results of a trial[104] in 2124 patients with AF undergoing coronary stenting randomized to low-dose rivaroxaban (15 mg once daily) plus a P_2Y_{12} inhibitor for 12 months, very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months, or dose-adjusted VKA (once daily) plus DAPT for 1, 6, or 12 months were reported. The rates of clinically significant bleeding were approximately 40% lower in the two groups receiving rivaroxaban than in the group receiving VKA plus DAPT. The rates of death from CV causes, MI, or stroke were similar in the three groups, although events were infrequent and confidence intervals broad. Both rivaroxaban-based regimens were associated with fewer deaths and less hospitalization for adverse events compared to the group randomized to VKA plus DAPT.[105]

Bleeding: Risk Assessment, Prevention, and Treatment

Severe bleeding is the most common complication of antithrombotic therapy and is associated with poorer outcomes in patients with ACS undergoing PCI,[102] although the magnitude of the independent contribution to mortality that can be attributed to bleeding remains controversial.[106] Regardless, efforts to minimize the risk of bleeding are recommended and include (1) assessment of bleeding (and ischemic) risk using an established risk score, such as the HAS-BLED score;[23] (2) dose adjustment of antithrombotic drugs according to body weight and renal function (**see Table 98.5**); (3) selection of anticoagulants (e.g., fondaparinux in medically managed patients or bivalirudin without a GP IIb/IIIa inhibitor in patients managed invasively) and antiplatelet (e.g., low-dose ASA + clopidogrel) regimens with a lower-risk bleeding profile;[107] (4) avoidance of other therapies that increase the risk for bleeding (e.g., NSAIDs); (5) use of radial arterial access,[96] smaller sheath sizes, timely removal of arterial sheaths, and femoral closure devices;[108] (6) use of bare-metal stents to permit a shorter duration (1 month) of DAPT; and (7) prophylactic administration of gastroprotective agents, in particular PPIs,[103] in patients at increased risk of upper GI bleeding.

Decisions regarding the number and duration of antithrombotic agents after NSTE-ACS are complex and require individual assessment of risk and benefit. Use of a clinical prediction rule to estimate the benefit and harm of DAPT beyond 12 months after PCI may help to identify which patients should continue long-term DAPT.[109] Patients receiving an oral anticoagulant who present with NSTE-ACS represent a particularly high-risk group who require careful management of the antithrombotic regimen. The following steps are recommended[23]: 1) do not use heparin in patients with INR greater than 2.5 taking a VKA; (2) in patients taking a NOAC, use reduced-dose parenteral anticoagulant (e.g., UFH, 60 U/kg, or enoxaparin, 0.5 mg/kg) periprocedurally; (3) avoid pretreatment with a $P2Y_{12}$ inhibitor; and (4) limit use of GP IIb/IIIa inhibitors to only periprocedural complications.

In case of major bleeding, the European Society of Cardiology (ESC) provides the following recommendations[23]: (1) interrupt both anticoagulant and antiplatelet therapies, unless bleeding can be adequately controlled by specific hemostatic measures; (2) neutralize anticoagulant therapy; (3) consider platelet transfusion to neutralize antiplatelet agents; (4) since blood transfusions may have deleterious effects on outcome, individual assessment of the risk/benefit ratio is recommended, and transfusions should be withheld in hemodynamically stable patients with hemoglobin above 7 g/dL; (5) erythropoietin is not indicated as a treatment for acute anemia or blood loss, because it may increase the risk of arterial or venous thromboembolism; and (6) minor bleeding should be managed without interruption of antithrombotic therapies.

Invasive Versus Conservative Management

Two general approaches to cardiac catheterization and revascularization can be used to manage patients with NSTE-ACS: (1) an early invasive strategy involving routine early (within 48 hours of initial evaluation) cardiac catheterization, followed by PCI, CABG, or continuing medical therapy, depending on the coronary anatomy, and (2) an ischemia-guided (or selective invasive) approach, with initial medical management and catheterization being reserved for patients with hemodynamic instability or recurrent ischemia, either at rest or on a noninvasive stress test, followed by revascularization if the anatomy is suitable. An early invasive strategy is *not* recommended in patients with extensive comorbidities in whom the risks of revascularization outweigh the potential benefits, or in patients with acute chest pain with low clinical likelihood of ACS and a negative troponin assay.[11]

A meta-analysis of seven trials confirmed an overall significant 25% reduction in mortality and a 17% reduction in nonfatal MI after 2 years of follow-up in patients managed with an early invasive strategy.[110] Similar findings were reported in an individual patient-level meta-analysis from three contemporary randomized trials involving 5467 patients who were followed for 5 years.[111] The benefit of an early invasive strategy also applied to key subgroups who traditionally were less likely to undergo early angiography, including older adults,[112] patients with CKD,[113] and women,[114] although one analysis in women did not show benefit.[115] A sex-specific meta-analysis demonstrated benefit of an invasive strategy in all men and in high-risk women but not in low-risk women.

Thus, an early invasive strategy, in the absence of contraindication, is recommended in patients with NSTE-ACS who have ST-segment changes and/or positive troponin assay on admission, or in whom these high-risk features develop over the subsequent 24 hours. Other high-risk indicators, such as recurrent ischemia or evidence of congestive heart failure, also indicate an early invasive strategy.[11,23] An early invasive strategy is also advised in patients with NSTE-ACS previously treated with CABG[11] and in patients who have had NSTE-ACS within 6 months of a previous PCI and in whom restenosis may be the cause.[23] Indications for an initial conservative strategy include patients with life-threatening comorbid conditions or in whom the risks outweigh the potential benefits, and in low-risk patients without recurrent symptoms.[11,23]

Timing of an Invasive Approach

A meta-analysis of four trials involving 4013 patients with NSTE-ACS compared an early invasive strategy (time to angiography, 1.2 to 14 hours following hospital presentation) with a delayed invasive strategy (time to angiography, 21 to 86 hours). Mortality and MI rates in the two strategies did not differ,[116] but the early invasive approach was associated with significant reductions in recurrent ischemia (41%) and duration of hospital stay (28%) and with favorable trends with respect to bleeding and the composite of CV death, MI, or stroke. These findings were confirmed in a more recent study of NSTEMI patients in whom randomization to a strategy of immediate angiography (median, 1.4 hours from admission) followed by PCI, when appropriate, significantly reduced death or MI at 30 days (4.3 versus 13.0%; $P = 0.008$) compared to a delayed invasive strategy (median, 61 hours).[117] Although relatively uncommon (<3% incidence), patients who develop cardiogenic shock post-NSTEMI represent a particularly high-risk subgroup, with an in-hospital mortality of 35% in a U.S. national database of over 2.2 million patients admitted with NSTEMI.[118] The risk-adjusted mortality was reduced by more than 50% with an invasive strategy in these patients.

Predischarge Risk Stratification in Patients Managed With an Ischemia-Guided Strategy

In stable patients managed with an ischemia-guided strategy, noninvasive stress testing is recommended after at least 12 to 24 hours following the most recent symptoms.[11] Options include exercise testing (in patients without resting ST-segment abnormalities), exercise testing with imaging modalities in patients with ST-segment changes, or pharmacologic stress testing in patients unable to exercise. An additional benefit of imaging studies is the assessment of LV function, which should be ascertained in all patients with definite ACS.[11]

Percutaneous Coronary Intervention (See also Chapter 62)

Angiographic success (TIMI epicardial grade 2 or 3 flow) can be achieved in a large majority (95%) of

patients with NSTE-ACS who undergo PCI, even in those considered to be at high risk.[119] However, the development of intraprocedural complications, such as transient or sustained loss of a side branch, abrupt closure, distal embolization, or development of the no-reflow phenomenon, may entail a four- to fivefold increase in the risk for ischemic complications and death over the next 30 days.[119] Although use of drug-eluting stents (DESs) reduces the risk for restenosis, there is a risk for late stent thrombosis following DES implantation, especially when DAPT (i.e., ASA and $P2Y_{12}$ inhibitor) is discontinued. This serious complication can be reduced in the long term in patients with DESs, by continuing DAPT beyond 12 months after stenting.[109]

The newer stents coated with everolimus have demonstrated consistent benefits compared to earlier-generation stents coated with sirolimus or paclitaxel[120,121] and to bare-metal stents (BMSs).[122] Given reductions in stent thrombosis, restenosis, and other ischemic events following placement of an everolimus-eluting stent, the need for prolonged (≥12 months) DAPT is less clear, and shorter durations of DAPT may be possible. Ongoing innovation in stent technology (e.g., polymer-free drug-coated stents[123]) to reduce the risk of stent failure (e.g., bioabsorbable polymer-coated stents)[124] and the need for prolonged DAPT are being developed, but have not yet been tested in large numbers of patients with NSTE-ACS. Radial arterial access reduces bleeding compared to femoral access, achieves similar procedural and clinical success,[96] and should become the standard of care for patients with ACS undergoing coronary angiography.

Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting

Several trials have compared PCI and CABG in patients with stable CHD, but no large studies have randomized patients with NSTE-ACS to different modes of revascularization. Based on the results from patients with stable CHD, CABG is recommended in patients with disease of the left main coronary artery (LMA), as well as for those with multivessel disease (involving all three major epicardial vessels or the proximal left anterior descending artery [LAD] plus a second artery) and an LV ejection fraction (EF) less than 40% and/or diabetes mellitus (DM). In a study of 1900 patients with DM and multivessel CAD (27% of whom had NSTE-ACS), when compared to PCI, CABG significantly reduced the composite endpoint of death, MI, or stroke.[125] However, as experience with multivessel and LMA PCI grows, an increasing number of nondiabetic patients with this more complex coronary anatomy may also be suitable for PCI. For other patients with less severe CAD, and with suitable coronary anatomy, although PCI is associated with slightly lower initial morbidity and mortality and lower rates of stroke than CABG,[125] it is associated with a higher need for repeat PCI[125-127] and somewhat less relief of angina.[128]

Both North American[11] and European[23] guidelines recommend using a “heart team” approach to guide decisions regarding revascularization that includes input from interventional cardiologists and cardiothoracic surgeon in patients with lLMA and complex CAD. Factors that favor CABG include multiple and complex coronary lesions, presence of DM, LV systolic dysfunction, and DAPT intolerance. Factors favoring PCI include high risk of operative mortality, prior thoracotomy, and advanced CKD.[11]

Lipid-Lowering Therapy (See Also Chapters 45 and 48)

In a meta-analysis of 13 randomized controlled trials (RCTs) involving 17,963 patients with ACS (a mixture of STEMI and NSTE-ACS), early (on average 4 days after admission), intensive statin therapy compared to control, usually placebo, decreased the rate of death and CV events over 2 years of follow-

up by 19%.[129] The benefit began to emerge between 4 and 12 months, achieving statistical significance by 12 months. The prespecified subgroup of 3260 patients with UA in the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) trial experienced a 26% reduction in total mortality with pravastatin compared to placebo.[130] However, intensive statin (atorvastatin, 80 mg) was even more effective than pravastatin (40 mg) in the 2724 patients post-NSTE-ACS enrolled in the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial,[131] reducing the composite of CV death, MACE, or stroke by 20% relative (5% absolute) over an average of 2 years of follow-up. Atorvastatin (80 mg) not only achieved a lower on-treatment LDL than pravastatin (40 mg) (mean, 62 versus 95 mg/dL), but was also more effective in reducing hsCRP (median, 1.3 versus 2.1 mg/dL), which may have also contributed to the early divergence of the event curves beginning at 2 weeks after randomization.[132]

More recently IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) for the first time demonstrated the added clinical benefit of adding a nonstatin therapy (*ezetimibe,* a cholesterol absorption inhibitor) to background statin therapy. In the overall trial population of 18,144 patients with ACS (71% of whom had NSTE-ACS), ezetimibe significantly reduced the risk of CV death, MACE, or stroke by 6.4% relative (2% absolute) at 7 years.[133] MI and stroke fell significantly by 13% and 21%, respectively. Specifically, in the 12,941 patients with NSTE-ACS at presentation, there was the same 2% absolute reduction in events with ezetimibe (36.6% versus 34.4%; number needed to treat [NNT] = 50).[133] Despite a low time-weighted average LDL-C during the trial (54 mg/dL with ezetimibe + simvastatin versus 70 mg/dL with placebo + simvastatin), ezetimibe was well tolerated with no increase in serious side effects.[133] On the basis of the IMPROVE-IT results, a recent Expert Consensus Decision Pathway[134] has recommended the use of ezetimibe in patients with ACS who (1) have a recurrent CV event despite maximally tolerated statin, (2) have an inadequate response to maximally tolerated statin, or (3) are intolerant of several statins. The benefits of ezetimibe were most prominent in post-ACS patients at high risk of MACE, including patients with DM and those older than 75 years.[133] An especially high-risk group were patients who developed an ACS despite having previously undergone CABG. In these patients, treatment patients managed with the standard of care, including simvastatin (40 to 80 mg), had a 60% rate of MACE or stroke at a median of 6 years, despite achieving an average LDL-C less than 70 mg/dL.[47] However, addition of ezetimibe (which reduced the LDL-C to 54 mg/dL on average) resulted in a 20% relative reduction in MACE (NNT = 11) (**Fig. 60.11**).

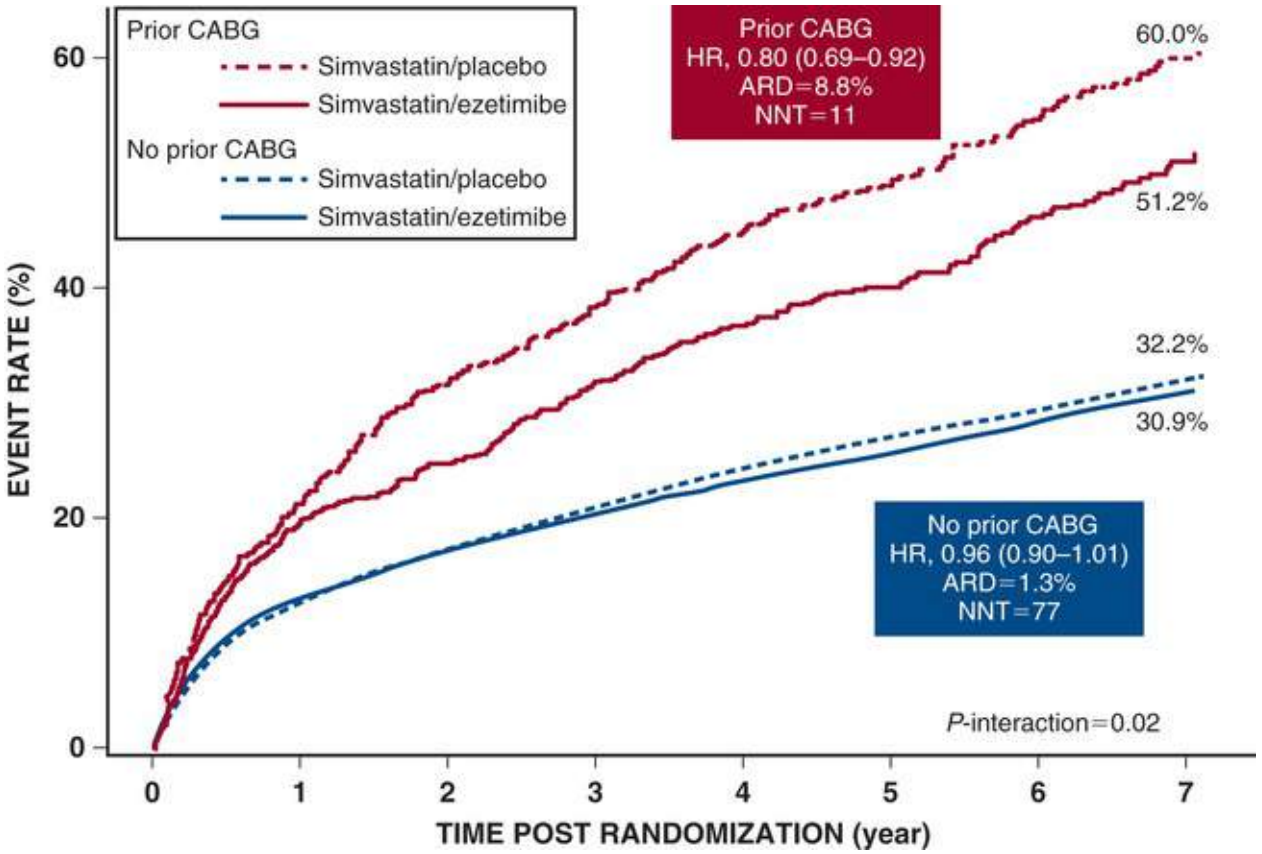


FIGURE 60.11 Benefit of ezetimibe in addition to statin in patients with acute coronary syndrome (ACS) and prior coronary artery bypass graft surgery (CABG). Shown are the cumulative event rates for the primary composite endpoint of death from cardiovascular (CV) disease, a major coronary event (nonfatal myocardial infarction, documented unstable angina requiring hospital admission, or coronary revascularization occurring at least 30 days after randomization), or nonfatal stroke in the intention-to-treat population during the overall study period in IMPROVE-IT. Patients with prior CABG are shown in *red* and those without prior CABG are in *blue*. Among patients with a prior CABG, ezetimibe reduced the primary CV composite endpoint by 20% relative to placebo. ARD, Absolute risk differences; HR, hazard ratio; NNT, number needed to treat. (From Eisen A, Cannon CP, Blazing MA, et al. The benefit of adding ezetimibe to statin therapy in patients with prior coronary artery bypass graft surgery and acute coronary syndrome in IMPROVE-IT. Eur Heart J 2016;37(48):3576-84.)

These findings underscore the importance of initiating intensive lipid-lowering therapy as soon as possible after admission with NSTE-ACS to achieve a 50% reduction in LDL-C.[23] Given the ongoing benefit seen during follow-up in the ACS trials as well as later divergence of the curves in patients with stable CHD, lipid-lowering therapy should be continued indefinitely, without reducing the dose in patients who are tolerating the therapy regardless of how low the LDL-C falls.[134a] An additional potential benefit of early high-intensity statin in patients with NSTE-ACS is protection from contrast-induced nephropathy. In 504 statin-naive patients with NSTE-ACS managed with an early invasive strategy, patients randomized to rosuvastatin (40 mg) at admission followed by 20 mg daily had a 62% relative reduction in contrast-induced acute kidney injury (6.7% versus 15.1%; $P = 0.003$) and fewer than half the number of adverse CV and renal events (3.6 versus 7.9%; $P = 0.04$) compared to placebo.[135]

Discharge and Posthospital Care

The time of hospital discharge following ACS affords a “teachable moment” for the patient, when the physician and staff can review and optimize the medical regimen for long-term treatment. Patients with NSTE-ACS and those with STEMI should receive secondary prevention approaches (**see Chapters 45, 54, and 59**).

Subgroups of Special Interest

Older Adults (See Also Chapter 88)

Patients age 75 or older have a higher incidence, prevalence, and rates of adverse outcomes of NSTE-ACS.[5,136,137] Advanced age is accompanied by a greater degree of comorbidity; age- and disease-related changes in physiology can affect pharmacokinetics/dynamics, volume of distribution, drug sensitivity; and polypharmacy (increasing the risk of drug-drug interactions), each of which poses additional challenges to the management of NSTE-ACS. Elderly patients are more likely to present with atypical symptoms (e.g., dyspnea rather than chest pain or discomfort), and with ECG abnormalities that are less diagnostic than those seen in younger patients.[138] Nevertheless, elderly patients with NSTE-ACS derive similar or even greater benefit from guideline-directed therapy than younger patients, yet, paradoxically, they are less likely to receive such proven therapies. Among the guideline therapies, several practical suggestions can reduce the risk of bleeding in the elderly patient, including (1) exclusive use of low-dose maintenance ASA, 75 to 100-mg; (2) selection of an ADP inhibitor other than prasugrel; (3) use of bivalirudin rather than UFH plus GP IIb/IIIa inhibitor; and (4) avoidance of abciximab if a GP IIb/IIIa inhibitor is needed to manage a peri-PCI thrombotic complication.[139]

In addition, it is critically important to dose-adjust therapies according to body weight and renal function to avoid excess dosing of antithrombotics in older patients, which can lead to excess bleeding.[23,140] Reliance on the serum creatinine alone may underestimate the true extent of renal dysfunction, since age contributes importantly to determining creatinine clearance. Guidelines recommend assessment of renal function in all patients at the time of ACS and during long-term follow-up at an interval in months equal to the CrCl (in mL/min) divided by 10 (e.g., for a CrCl of 30 mg/dL, reassess renal function in 30/10 = 3 months).[141]

Since older patients are more likely to have more severe and extensive CAD, they are more likely to have coronary anatomy amenable to revascularization than younger patients with NSTE-ACS. However, since elderly patients are at higher risk for procedural complications and bleeding, patients and physicians often exercise more caution regarding invasive procedures, resulting in lower rates of revascularization. A meta-analysis[142] of three randomized trials demonstrated a 29% reduction (HR, 0.71; 95% CI 0.55 to 0.91) in death or MI at 5 years in patients age 75 or older with an early invasive strategy. More recently, a randomized trial of 457 patients 80 or older (median 85) demonstrated a 47% reduction (HR, 0.53; 95% CI 0.41 to 0.69) in the composite of MI, need for urgent revascularization, stroke, and death over a median follow-up of 1.5 years with an early invasive strategy versus a conservative strategy (optimum medical treatment alone).[143] Barring comorbidities that prove to be contraindications, advanced age should not deter otherwise-indicated comprehensive treatment of NSTE-ACS, including the use of an early invasive strategy and revascularization.[11] An approach in the elderly patient that carefully considers the potential risks and benefits, estimated life expectancy, comorbidities, quality of life, frailty, and patient values and preferences is recommended.[23]

Women (See Also Chapter 89)

Cardiovascular disease is the leading cause of death in women in the United States[5] and worldwide.[4] Since 1984, the annual mortality rate for CVD has been higher for women than men, yet CVD remains understudied, underdiagnosed, and undertreated in women.[144] Similar to older patients with NSTE-ACS, when compared to men, women are more likely to present with atypical symptoms[137] and to have more

comorbidities,[114,145] and are less likely to be referred for cardiac testing, including coronary angiography.[137,145] However, younger women, in contrast to men and older women, are more likely to have nonatherosclerotic causes of angina, such as microvascular dysfunction and abnormal vascular reactivity. In addition, the biochemical profile of women with NSTE-ACS differs from men in that women are more likely to have abnormal BNP and hsCRP levels and less likely to have an elevated troponin assay. Nevertheless, women with NSTE-ACS should receive the same pharmacologic therapy as men in both the acute care and the secondary prevention phase, and women with NSTE-ACS with high-risk features should undergo an early invasive strategy.[11] In contrast, low-risk women with NSTE-ACS should not routinely undergo an early invasive strategy because of the lack of benefit and potential for harm. In a pooled analysis of 3550 patients with NSTE-ACS from eight trials, women are more likely than men to have nonobstructive CAD on coronary angiography.[40] Although rates of MACE are lower in patients with nonobstructive disease compared to those with obstructive CAD, they are not negligible (16% at 5 years in women participating in the WISE registry[146]), and therefore secondary preventive measures should not be withheld in either women or men with nonobstructive CHD.

Because women on average have lower body weight and are older than their male counterparts, they are more likely to have impaired renal function and are at greater risk for excess dosing of antithrombotic therapies that require renal dose adjustment. Although older studies showed that women had higher rates of contrast-induced nephropathy (CIN) and vascular complications than men, recent data from the MATRIX study demonstrated a similar advantage of radial over femoral arterial access in women as in men.[96] Furthermore, analyses from ACS registries suggest that the poorer early outcomes in women were associated with lower rates of evidence-based care than men.[136] Women are also more likely to experience adverse cardiovascular outcomes after discharge and to experience higher rates of readmission for angina.[147] This may in part be explained by the lower rates of evidence-based therapies (beta blockers, statins, ACE inhibitors) in women, particularly women younger than 55.[148] Thus, strategies to promote guideline adherence and greater awareness of the similar CV risk in patients with NSTE-ACS, regardless of sex, are needed.[144]

Diabetes Mellitus and Glucose Intolerance (See Also Chapter 51)

More than 30 million Americans live with DM, and another 84 million have prediabetes.[149] The prevalence of diagnosed DM in adults age 65 and older was 26% in 2012, and an additional 51% (>20 million) had prediabetes based on fasting glucose, oral glucose tolerance testing (OGTT), or HbA_{1c}. CHD causes 75% of deaths in patients with DM.

Since more than 30% of patients with NSTE-ACS have DM and such patients have higher rates of adverse CV outcomes,[150] all patients presenting with NSTE-ACS should be screened for DM during hospitalization. Patients with known DM or glucose intolerance should receive the medical therapies established in those with normal glucose metabolism, and in addition, should have frequent glucose monitoring through discharge. Glucose-lowering therapies should be considered in most patients with blood glucose greater than 180 mg/dL, while avoiding hypoglycemia (<90 mg/dL), because there is a U-shaped relationship between glucose levels and outcomes in patients with DM and ACS. Patients with DM have a blunted response to standard antiplatelet regimens, including clopidogrel and ASA.[151] Subgroup analyses comparing outcomes in patients with and without DM have suggested incrementally greater benefit of some more potent antiplatelet agents, including prasugrel[72] and GP IIb/IIIa inhibitors, in

patients with DM.

With regard to revascularization, the ESC NSTE-ACS guidelines[23] recommend an early invasive strategy and a preference for CABG over PCI in patients with DM and complex (e.g., multivessel or LMA) CAD.[125] When PCI is selected, a newer-generation DES should be employed.[63] Renal function should be closely monitored for 2 to 3 days after coronary angiography or PCI in patients with renal dysfunction or who are treated with metformin. If renal function deteriorates, metformin should be held for at least 48 hours until renal function improves.

A pooled analysis of 15,459 patients with NSTE-ACS enrolled in 11 TIMI trials demonstrated that DM is associated independently with higher risk of mortality at 30 days (HR, 1.78; 95% CI 1.24 to 2.56) and at 1 year (HR, 1.65; 95% CI 1.30 to 2.10).[152] This increased risk also extended to patients with undiagnosed DM and those with newly identified glucose intolerance.[153] Despite poorer outcomes, patients with DM and NSTE-ACS are less likely to receive guideline-directed therapies and revascularization.[150]

Chronic Kidney Disease (See Also Chapter 98)

In 2017, the prevalence of CKD had increased to 15% (>30 million) of the adults in the United States.[154] Patients with impaired renal function and NSTE-ACS are older on average and more likely to have additional comorbid conditions, including DM, peripheral arterial disease (PAD), and HF. Thus, they have increased risk for recurrent ischemic events,[155] including stent thrombosis and post-PCI ischemic events,[156] and for treatment complications;[157] are underrepresented in clinical trials; and are often undertreated in clinical practice.[155,157,158] All patients admitted with NSTE-ACS should have renal function measured at presentation to permit informed decisions regarding management and proper dosing of antithrombotic agents.

Data on patients with advanced CKD (stages IV or V) and ACS are limited as most randomized trials excluded patients with CrCl less than 30 mL/min or estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2. A meta-analysis of five trials of 1453 patients with NSTE-ACS and CKD (all with eGFR <60 mL/min/1.73 m^2) demonstrated favorable trends in all-cause mortality, the composite of death or nonfatal MI, and rehospitalization with an early invasive strategy compared to conservative management.[113] Thus, coronary angiography should be considered in patients with CKD, and the benefits of prompt revascularization should be weighed against the risks of bleeding and CIN. In patients with CKD undergoing PCI, newer-generation DESs are preferred over BMSs.[23] In patients with multivessel CHD, acceptable surgical risk, and life expectancy longer than 1 year, CABG is preferred over PCI, whereas in patients with high surgical risk or shorter life expectancy, PCI is recommended.[23]

Patients with CKD have a greater risk of bleeding because of impaired platelet function and excess dosing with antithrombotic therapy[159] (**Table 98.5**). In patients with CKD, the dosage of renally cleared medications requires adjustment; such medications include enoxaparin, bivalirudin, eptifibatide, and tirofiban. In addition, patients with CKD have increased risk for CIN following angiography and revascularization. Current guidelines recommend that the risk for CIN be assessed by measurement of the ratio of contrast volume to eGFR and that this ratio not exceed 3.7.[63] Adequate hydration with isotonic saline from 12 hours before to 24 hours after dye exposure is essential.

Heart Failure

Both the AHA/ACC[11] and ESC[23] guidelines provide specific new recommendations regarding patients

with NSTE-ACS complicated by heart failure (HF). An early invasive approach is recommended if possible because these patients are at increased risk of major morbidity and death, and revascularization, particularly CABG, improves outcomes.[160,161] Echocardiography is recommended prior to coronary angiography to evaluate LV systolic function, extent and degree of wall motion abnormalities, and associated valvular dysfunction and to identify possible mechanical complications. The revascularization strategy should be determined by coronary anatomy, degree of LV and valvular dysfunction, comorbidities, and surgical risk. In patients with prior CABG or anatomy not suitable for CABG, PCI may be considered. If there is a large territory of myocardial ischemia and severe LV systolic dysfunction, LV support (e.g., percutaneous ventricular assist devices) may be necessary for hemodynamic support peri-PCI.[162]

Although cardiogenic shock is less common in patients with NSTEMI-ACS than in STEMI patients, in NSTEMI the shock tends to occur later in the hospitalization and in patients with more comorbidities, extensive CAD, and recurrent ischemia/infarction. When possible, early revascularization with PCI is recommended to improve chances of survival; emergency CABG is recommended if the coronary anatomy is not suitable for PCI. Short-term use of mechanical circulatory support should be considered in patients with hemodynamic instability caused by mechanical complications. However, routine use of intra-aortic balloon counterpulsation in patients without mechanical complications is not recommended, given the lack of proven benefit.[163] A percutaneous LV assist device (LVAD) may be considered in select patients as a bridge to cardiac transplantation or to an implanted LVAD.[164] Patients who emerge from the acute episode stable, but with persistent LV systolic dysfunction, should receive management as outlined in **Chapter 25**.

Prinzmetal Variant Angina

In 1959, Prinzmetal and colleagues described a syndrome of ischemic pain that occurred at rest, accompanied by ST-segment elevation.[165] Prinzmetal variant angina (PVA) may be associated with acute MI, VT or VF, and sudden cardiac death (SCD). Spasm of a proximal coronary artery with resultant transmural ischemia and abnormalities in LV function are the diagnostic hallmarks of PVA. Patients with PVA tend to be younger than those with NSTE-ACS attributable to coronary atherosclerosis, and many do not exhibit the classic coronary risk factors, except they are frequently heavy cigarette smokers. Angina is often extremely severe, tends to cluster between midnight and 8 AM, and may be accompanied by syncope related to AV block,[166] asystole, or ventricular tachyarrhythmia.[167] Increased QT dispersion appears to be a risk marker for SCD in these patients.

Approximately one third of patients with PVA also exhibit severe fixed coronary obstruction and may have a combination of exertion-induced angina with ST-segment depression and episodes of angina at rest with ST-segment elevation.[168] Rarely, PVA appears to be a manifestation of a generalized vasospastic disorder associated with migraine and/or Raynaud phenomenon. PVA can also develop in association with aspirin-induced asthma and administration of 5-fluorouracil and cyclophosphamide. The ergot derivatives used to treat migraine headache and serotonin antagonists used to treat depression can precipitate episodes of PVA. The incidence of PVA has always been greater in Japan than in Western countries, but across the world, the incidence appears to have fallen markedly over the past three decades, possibly related in part to the widespread use of calcium antagonists.

The key to diagnosis of PVA lies in the detection of episodic ST-segment elevation, often accompanied by severe chest pain, usually occurring at rest. Multiple asymptomatic episodes of (silent) ST-segment elevation occur in many patients. ST-segment deviations may be present in any leads, depending on the artery involved. Patients with no or mild fixed coronary obstruction tend to experience a more benign course than do patients with PVA and associated severe obstructive lesions.[167]

Three provocative tests for coronary spasm can be performed at coronary angiography—hyperventilation, intracoronary acetylcholine, and intracoronary ergonovine—although the third test is no longer available in the United States. Acetylcholine, according to a fixed protocol, is now most widely used.[169] These provocative maneuvers should be used only in patients without obstructive CHD and in whom PVA is suspected, but not yet confirmed. Their use has been declining over the past three decades, in part related to the induction of rare but sometimes fatal arrhythmias.

Management.

Patients with PVA should be strongly urged to discontinue smoking. The mainstay of therapy is a calcium antagonist, alone or preferably in combination with a long-acting nitrate. Sublingual or IV nitroglycerin often abolishes attacks of PVA promptly, while the long-acting nitrates are useful in preventing attacks. The response to beta blockade in patients with PVA is variable. Some patients, particularly those with associated fixed obstructions, show a reduction in the frequency of exertion-induced angina caused primarily by augmentation of myocardial oxygen requirements. In others, however, nonselective beta-blocking agents may actually be detrimental because blockade of $beta_2$ receptors, which mediate coronary dilation, may allow unopposed alpha receptor–mediated coronary vasoconstriction. In a study of 640 Japanese patients with vasospastic angina confirmed by acetylcholine provocation testing and no significant coronary stenosis, statin therapy significantly reduced the risk of MACE.[170] Prevention of plaque formation or progression may explain part of the benefit of statins, but the pleiotropic effects of statins, such as the amelioration of endothelial dysfunction, suppression of inflammation, and inhibition of the Rho A/Rho-kinase pathway, may also pertain.

PCI and occasionally CABG may be indicated in patients with PVA associated with discrete, proximal, fixed obstructive lesions, but revascularization is contraindicated in patients with isolated coronary artery spasm without accompanying fixed obstructive disease. Patients who have experienced ischemia-associated VF and continue to manifest ischemic episodes despite maximal medical treatment should receive an implantable cardioverter-defibrillator (ICD).

Many patients with PVA pass through an acute, active phase, with frequent episodes of angina and cardiac events occurring during the first 6 months after diagnosis. The extent and severity of the underlying CAD and the tempo of the syndrome have a major effect on the incidence of late mortality and MI. Remission occurs more frequently in patients without significant fixed coronary artery stenoses and in those who have discontinued smoking. For unclear reasons, some patients, after a relatively quiescent period of months or even years, experience a recrudescence of vasospastic activity with frequent and severe episodes of ischemia. Fortunately, these patients generally respond to retreatment with calcium antagonists and nitrates. Clinical outcomes are excellent in patients with isolated coronary spasm and no underlying CAD, with no cardiac death or MI occurring in 76 patients monitored for 3 years in the CASPAR (Coronary Artery Spasm in Patients with Acute Coronary Syndrome) study, although about half these patients experienced angina frequently.[171]

Cardiac Syndrome X (See Also Chapter 89)

Approximately 15% of patients with NSTE-ACS have no obstructive epicardial coronary artery disease,

although they may have electrocardiographic evidence of myocardial ischemia. This condition is sometimes still referred to as “cardiac syndrome X.” It must be distinguished from metabolic syndrome (**see Chapter 45**).

Cocaine and Amphetamines (See Also Chapter 80)

Cocaine use causes a marked increase in sympathetic tone by blocking the reuptake of norepinephrine from synapses by preganglionic neurons, thereby resulting in increased myocardial oxygen demand and decreased supply. This may cause acute myocardial ischemia and may manifest as ACS. This condition, which has similar findings as amphetamine abuse, occurs more frequently in younger persons and should be especially considered in males younger than 30 years.[172] The use of psychoactive “street” drugs known as “bath salts” that contain synthetic cathinones with cocaine-like actions may also cause CV complications, including ACS.[173]

Patients with NSTE-ACS and a recent history of cocaine or methamphetamine use should be treated similar to those without recent stimulant use, except that patients with signs of acute intoxication (e.g., euphoria, tachycardia, hypertension) should not receive beta blockers because of the risk of coronary spasm.[11] Vasodilators and CCBs are preferred agents, and benzodiazepines alone or in combination with nitroglycerin may also be used to manage hypertension.

Future Perspectives

NSTE-ACS is a heterogeneous syndrome, not a specific disease. Subgroups of patients who respond to specific therapies should be identified. Specifically, there is considerable variation in the responses to antiplatelet agents and anticoagulants, in terms of both efficacy and safety. Efforts should be elevated to identify predictors of responses to these agents. In addition to phenotypic subgroups of patients with NSTE-ACS, the “omics” technologies, especially genomics, proteomics, and metabolomics, will play critically important roles in this effort. For example, the inflammatory biomarker hsCRP is used to identify patients with NSTE-ACS with active or persistent inflammation. These patients are at substantially high risk of recurrent ACS and should receive intensive secondary prevention. Since inflammation appears to play a key role in the development of unstable atherosclerotic plaques, the use of potent anti-inflammatory agents that can be administered safely over prolonged periods in patients at high risk of plaque disruption should be considered. Two large trials of anti-inflammatory drugs—canakinumab, which blocks interleukin-1,[174] a proinflammatory cytokine, and methotrexate[175]—are now underway. Colchicine is another anti-inflammatory drug that is useful in the treatment of acute pericarditis and should also be tested in NSTE-ACS. **Table 60.6** summarizes important additional unanswered questions regarding NSTE-ACS.

TABLE 60.6

Key Unanswered Questions in Non–ST Elevation Acute Coronary Syndromes (NSTE-ACS)

Pathophysiology
• Will superficial plaque erosion continue to rise to become the dominant pathophysiology? • Should patients be treated differently based on their underlying pathophysiology? • What are the critical determinants that cause one vulnerable plaque to cause a clinical event but another vulnerable plaque to be silent and heal?
Diagnosis
• What will be the role of concomitant use of coronary computed tomographic angiography and high-sensitivity troponin (hsTn) assays in evaluating patients with suspected ACS? • Will shorter rule-out algorithms with hsTn assays improve patient outcomes? • What will be the role of genetic testing to individualize treatment and improve patient outcomes?
Acute Treatment
• What is the preferred antithrombotic regimen peri-PCI? • What is the optimal combination of and timing for administering high-potency lipid-lowering therapies? • What is the optimal timing and dosing for administering beta blockers? • What is the optimal timing of oral antiplatelet administration in patients undergoing an early invasive strategy? • What are the indications for and timing of revascularization of obstructed nonculprit lesions? • What is the role of FFR-guided PCI? • What are the contemporary benefits of CABG versus PCI in patients with multivessel disease? • Will novel pharmacologic and mechanical circulatory support strategies improve survival in patients with cardiogenic shock? • What is the desired hemoglobin level, and what is the optimal timing for blood transfusion?
Chronic Treatment
• What is the optimal duration and regimen of antiplatelet therapy, and how does this differ if an oral anticoagulant is needed? • Will newer-generation stents allow shortening of the duration of antiplatelet therapy? • Can dual-antiplatelet therapy be replaced by a single potent $P2Y_{12}$ inhibitor? • What is the role of PCSK9 inhibitors in patients admitted with ACS?
Prognosis and Secondary Prevention
• Can we improve prediction of the risk of sudden cardiac death and identify who might benefit more from prevention strategies? • How can the rate of recurrent ischemic cardiovascular events be further reduced? • What is the role of cardiac regenerative medicine in patients with left ventricular dysfunction after MI?

Modified from Eisen A, Giugliano RP, Braunwald E, Update on acute coronary syndrome, JAMA Cardiol 2016. doi:10.1001/jamacardio.2016.2049.

Guidelines

Non–ST Elevation Acute Coronary Syndromes

Robert P. Giugliano and Eugene Braunwald

In 2014 the American Heart Association (AHA) and American College of Cardiology (ACC) issued a new guideline on the Management of Patients with Non–ST Elevation Acute Coronary Syndromes (NSTE-ACS).[1] The European Society of Cardiology (ESC) guideline on the same topic followed in 2015.[2] These guidelines cover the entire spectrum of issues related to management of patients with NSTE-ACS, including definitions, pathophysiology, epidemiology, diagnosis, risk assessment, biomarkers, treatment, and quality of care. New to this pair of guidelines are sections on additional high-risk groups, performance measures, registries, and gaps in evidence. This chapter uses the standard system—class of recommendation (COR) I to III, level of evidence (LOE): A to C—to summarize the key recommendations for the management of patients with NSTE-ACS from the 2014 AHA/ACC 2014 guideline.[1]

Initial Evaluation

The initial evaluation of patients with suspected ACS should incorporate features of the patient's history, risk factors, symptoms, electrocardiographic findings, and troponin to identify the likelihood of ACS and help guide the diagnosis (**Fig. 60G.1**).

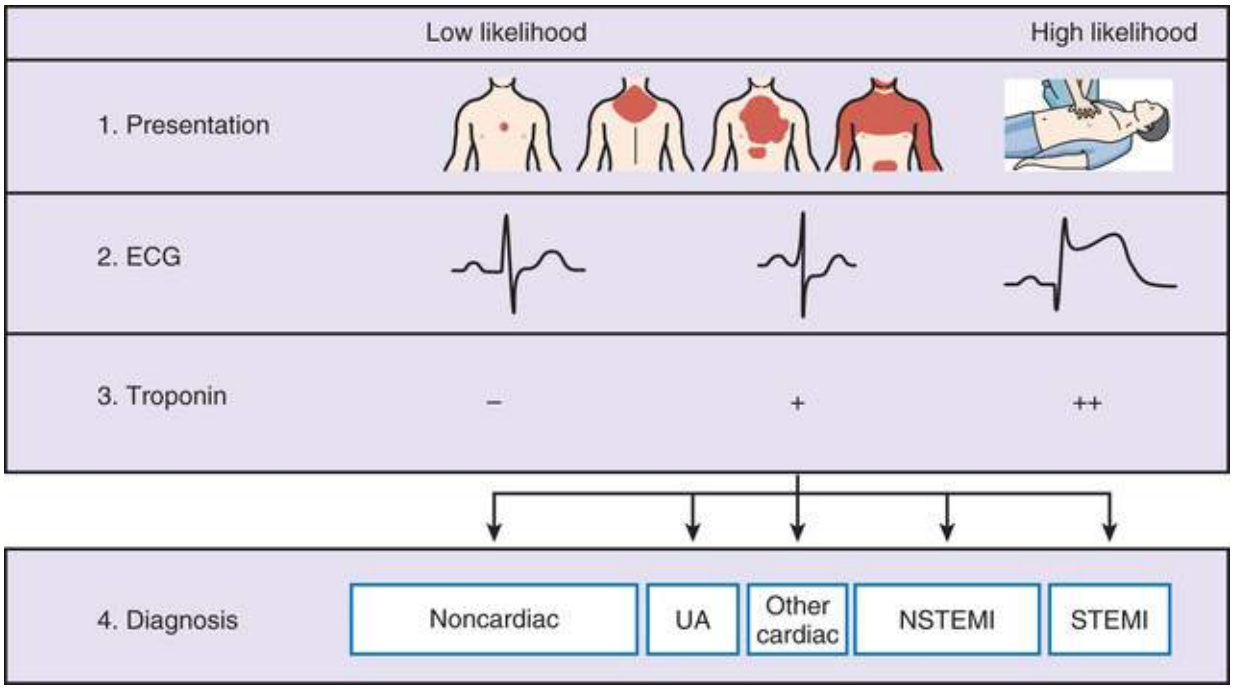


FIGURE 60G.1 Initial assessment of patients with suspected acute coronary syndrome (ACS). The initial assessment is based on the integration of low-likelihood and/or high-likelihood features derived from the clinical presentation (i.e., symptoms, vital signs), 12-lead ECG, and cardiac troponin. The proportion of the final diagnoses derived from the integration of these parameters is visualized by the size of the respective boxes. "Other cardiac" includes myocarditis, takotsubo cardiomyopathy, tachyarrhythmias, and a variety of addition noncoronary cardiac diagnoses (**see Table 60.2**). "Noncardiac" refers to thoracic diseases such as pneumonia or pneumothorax. Cardiac troponin should be interpreted as a quantitative marker; the higher the level, the higher the likelihood for the presence of myocardial infarction. In patients presenting with cardiac arrest or hemodynamic instability of presumed cardiovascular origin, echocardiography should be performed and interpreted by trained physicians immediately following a 12-lead ECG. If the initial evaluation suggests aortic dissection[11] or pulmonary embolism,[12] other diagnostic studies (e.g., computed tomographic angiography) are recommended. STEMI, ST-elevation myocardial infarction; NSTEMI, non–ST elevation myocardial infarction; UA, unstable angina. (From Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology. Eur Heart J 2016;37:267-315.)

Early Risk Stratification

AHA/ACC Class I Recommendations[1]

1. In patients with chest pain or other symptoms suggestive of ACS, a 12-lead ECG should be performed and evaluated for ischemic changes within 10 minutes of the patient's arrival at an emergency facility (LOE: C).
2. If the initial ECG is not diagnostic but the patient remains symptomatic and there is a high clinical suspicion for ACS, serial ECGs (e.g., 15- to 30-minute intervals during the first hour) should be performed to detect ischemic changes (LOE: C).
3. Serial cardiac troponin I or T levels (when a contemporary assay is used) should be obtained at presentation and 3 to 6 hours (1 to 3 hours if hsTn) after symptom onset in all patients who present with symptoms consistent with ACS, to identify a rising and/or falling pattern of values (LOE: A).
4. Additional troponin levels should be obtained beyond 6 hours after symptom onset in patients with normal troponin levels on serial examination when changes on ECG and/or clinical

presentation confer an intermediate or high index of suspicion for ACS (LOE: A).

5. The presence and magnitude of troponin elevations are useful for short- and long-term prognosis (LOE: B).
6. Risk scores should be used to assess prognosis in patients with NSTE-ACS (LOE: A).

Early Hospital Care

The key recommendations from the AHA/ACC[1] for standard medical therapies during the early hospital care phase are summarized in **Table 60G.1**. These therapies include oxygen, nitrates, morphine, antithrombotic therapy, beta blockers, calcium channel blockers (CCBs), and high-intensity statins.

TABLE 60G.1

Summary of Recommendations for Standard Medical Therapy in the Early Hospital Care Phase of Management of Patients with Non–ST Elevation Acute Coronary Syndromes (NSTE-ACS)

RECOMMENDATIONS	COR	LOE
Oxygen		
Administer supplemental oxygen only with oxygen saturation <90%, respiratory distress, or other high-risk features for hypoxemia.	I	C
Nitrates		
Administer sublingual NTG every 5 min × 3 for continuing ischemic pain and then assess need for IV NTG.	I	C
Administer IV NTG for persistent ischemia, HF, or hypertension.	I	B
Nitrates are contraindicated with recent use of a phosphodiesterase inhibitor.	III: Harm	B
Analgesic Therapy		
IV morphine sulfate may be reasonable for continued ischemic chest pain despite maximally tolerated anti-ischemic medications.	IIb	B
NSAIDs (except aspirin) should not be initiated and should be discontinued during hospitalization for NSTE-ACS because of the increased risk of MACE associated with their use.	III: Harm	B
Beta-Adrenergic Blockers		
Initiate oral beta blockers within the first 24 hr in the absence of HF, low-output state, risk for cardiogenic shock, or other contraindications to beta blockade.	I	A
Use of sustained-release metoprolol succinate, carvedilol, or bisoprolol is recommended for beta-blocker therapy with concomitant NSTE-ACS, *stabilized* HF, and reduced systolic function.	I	C
Reevaluate to determine subsequent eligibility in patients with initial contraindications to beta blockers.	I	C
It is reasonable to continue beta-blocker therapy in patients with normal LV function with NSTE-ACS.	IIa	C
IV beta blockers are potentially harmful when risk factors for shock are present.	III: Harm	B
Calcium Channel Blockers (CCBs)		
Administer initial therapy with nondihydropyridine CCBs with recurrent ischemia and contraindications to beta blockers in the absence of LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 sec, or second- or third-degree atrioventricular block without a cardiac pacemaker.	I	B
Administer oral nondihydropyridine calcium antagonists with recurrent ischemia after use of beta blocker and nitrates in the absence of contraindications.	I	C
CCBs are recommended for ischemic symptoms when beta blockers are not successful, are contraindicated, or cause unacceptable side effects.*	I	C
Long-acting CCBs and nitrates are recommended for patients with coronary artery spasm.	I	C
Immediate-release nifedipine is contraindicated in the absence of a beta blocker.	III: Harm	B
Cholesterol Management		
Initiate or continue high-intensity statin therapy in patients with no contraindications.	I	A
Obtain a fasting lipid profile, preferably within 24 hr.	IIa	C

*Short-acting dihydropyridine calcium channel antagonists should be avoided.

COR, Class of recommendation; *HF,* heart failure; *IV,* intravenous; *LOE,* level of evidence; *LV,* left ventricular; *MACE,* major adverse cardiovascular events; *N/A,* not available; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *NTG,* nitroglycerin.

From Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-st-elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Am Coll Cardiol 2014;64:e139-228.

Initial Antithrombotic Therapy

Once the diagnosis of ACS has been established, patients should be promptly treated with an anticoagulant, aspirin, and in the majority of patients, a $P2Y_{12}$ inhibitor (**Table 60G.2**). Important

differences exist between clopidogrel and the newer $P2Y_{12}$ inhibitors, prasugrel and ticagrelor (**Table 60G.3**). Cangrelor is an intravenous $P2Y_{12}$ inhibitor with rapid onset and offset now approved for use in patients undergoing PCI.

TABLE 60G.2

Summary of Recommendations for Antithrombotic Therapy

RECOMMENDATIONS	DOSING, SPECIAL CONSIDERATIONS	COR	LOE
Aspirin			
Non–enteric-coated aspirin to all patients promptly after presentation	162-325 mg	I	A
Aspirin maintenance dose continued indefinitely	81-325 mg/day*	I	A
$P2Y_{12}$ Inhibitors			
Clopidogrel loading dose followed by daily maintenance dose in patients unable to take aspirin	75 mg	I	B
$P2Y_{12}$ inhibitor, in addition to aspirin, for up to 12 mo for patients treated initially with either an early invasive or initial ischemia-guided strategy:		I	B
• Clopidogrel	300- or 600-mg loading dose, then 75 mg/day		
• Ticagrelor	180-mg loading dose, then 90 mg twice daily		
$P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) continued for at least 12 mo in post-PCI patients treated with coronary stents	N/A	I	B
Ticagrelor in preference to clopidogrel for patients treated with an early invasive or ischemia-guided strategy	N/A	IIa	B
Glycoprotein (GP) IIb/IIIa Inhibitors			
GP IIb/IIIa inhibitor in patients treated with an early invasive strategy and DAPT with intermediate/high-risk features (e.g., positive troponin)	Preferred options are eptifibatide or tirofiban	IIb	B
Parenteral Anticoagulant and Fibrinolytic Therapy			
SC enoxaparin for duration of hospitalization or until PCI is performed	1 mg/kg SC every 12 hr (reduce dose to 1 mg/kg/day SC in patients with CrCl <30 mL/min) Initial 30-mg IV loading dose in select patients	I	A
Bivalirudin until diagnostic angiography or PCI is performed in patients with early invasive strategy only	Loading dose 0.10 mg/kg loading dose followed by 0.25 mg/kg/hr Only provisional use of GP IIb/IIIa inhibitor in patients also treated with DAPT	I	B
SC fondaparinux for the duration of hospitalization or until PCI is performed	2.5 mg SC daily	I	B
Administer additional anticoagulant with anti-IIa activity if PCI is performed while patient is on fondaparinux	N/A	I	B
IV UFH for 48 hr or until PCI is performed	Initial loading dose 60 IU/kg (max 4000 IU) with initial infusion 12 IU/kg/hr (max 1000 IU/hr) Adjusted to therapeutic APTT range	I	B
IV fibrinolytic treatment not recommended in patients with NSTE-ACS	N/A	III: Harm	A

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.[10]

APTT, activated partial thromboplastin time; *COR,* class of recommendation; *CrCl,* creatinine clearance; *DAPT,* dual antiplatelet therapy; *IV,* intravenous; *LOE,* level of evidence; max, maximum; *N/A,* not available; *NSTE-ACS,* non–ST elevation acute coronary syndromes; *PCI,* percutaneous coronary intervention; *SC,* subcutaneous; *UFH,* unfractionated heparin.

Modified from Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Am Coll Cardiol 2014;64:e139-228.

TABLE 60G.3

$P2Y_{12}$ Inhibitors

	CLOPIDOGREL	PRASUGREL	TICAGRELOR	CANGRELOR
Chemical class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolopyrimidine	Stabilized ATP analogue
Administration	Oral	Oral	Oral	Intravenous
Dose	300-600 mg orally, then 75 mg/day	60 mg orally, then 10 mg/day	180 mg orally, then 90 mg twice daily	30-μg/kg bolus and 4-μg/kg/min infusion
Dosing in chronic kidney disease (CKD)				
• Stage 3 (eGFR 30-59)	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
• Stage 4 (eGFR 15-29)	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
• Stage 5 (eGFR <15)	Use only for selected indications (e.g., stent thrombosis prevention)	Not recommended	Not recommended	No dose adjustment
Binding reversibility	Irreversible	Irreversible	Reversible	Reversible
Activation	Prodrug, with variable liver metabolism	Prodrug, with predictable liver metabolism	Active drug with additional active metabolite	Active drug
Onset of loading dose effect[a]	2-6 hr[b]	30 min[b]	30 min[b]	2 min
Duration of effect	3-10 days	7-10 days	3-5 days	1-2 hr
Withdrawal before surgery	5 days[c]	7 days[c]	5 days[e]	1 hr
Plasma half-life of active $P2Y_{12}$ inhibitor[d]	30-60 min	30-60 min[e]	6-12 hr	5-10 min
Inhibition of adenosine reuptake	No	No	Yes	Yes ("inactive" metabolite only)

[a]50% inhibition of ADP-induced platelet aggregation.

[b]Onset of effect may be delayed if intestinal absorption is delayed (e.g., by opiates).

[c]Shortening may be considered if indicated by platelet function tests and low bleeding risk.

[d]Affecting the response to platelet transfusion.

[e]The distribution phase half-life is reported since it most likely reflects duration of clinically relevant plasma levels, whereas the corresponding elimination-phase half-life is approximately 7 hours.

ADP, Adenosine diphosphate; *ATP,* adenosine triphosphate; *eGFR,* estimated glomerular filtration rate (in mL/min/1.73 m^2).

Modified from Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology. Eur Heart J 2016;37:267-315.

Ischemia-Guided Strategy Versus Early Invasive Strategies

The two treatment strategies have emerged for managing patients with NSTE-ACS (**Fig. 60G.2**). In both strategies, patients should receive optimal medical therapy, as previously described (**Tables 60G.1 to 60G.3**). On presentation, patients who are very-high risk, such as those with hemodynamic instability (**Table 60G.4**), should be referred for an immediate (within 2 hours of presentation) invasive coronary angiogram. At the other extreme, patients without recurrent symptoms and who are deemed to be at low risk for subsequent ischemic events may be managed with an ischemia-guided strategy, including a noninvasive stress test (preferably with imaging) to assess for inducible ischemia. In particular, patients with acute chest pain and a low likelihood of ACS who are troponin negative (LOE: C), especially women (LOE: B), should preferentially be managed with an ischemia-guided strategy.

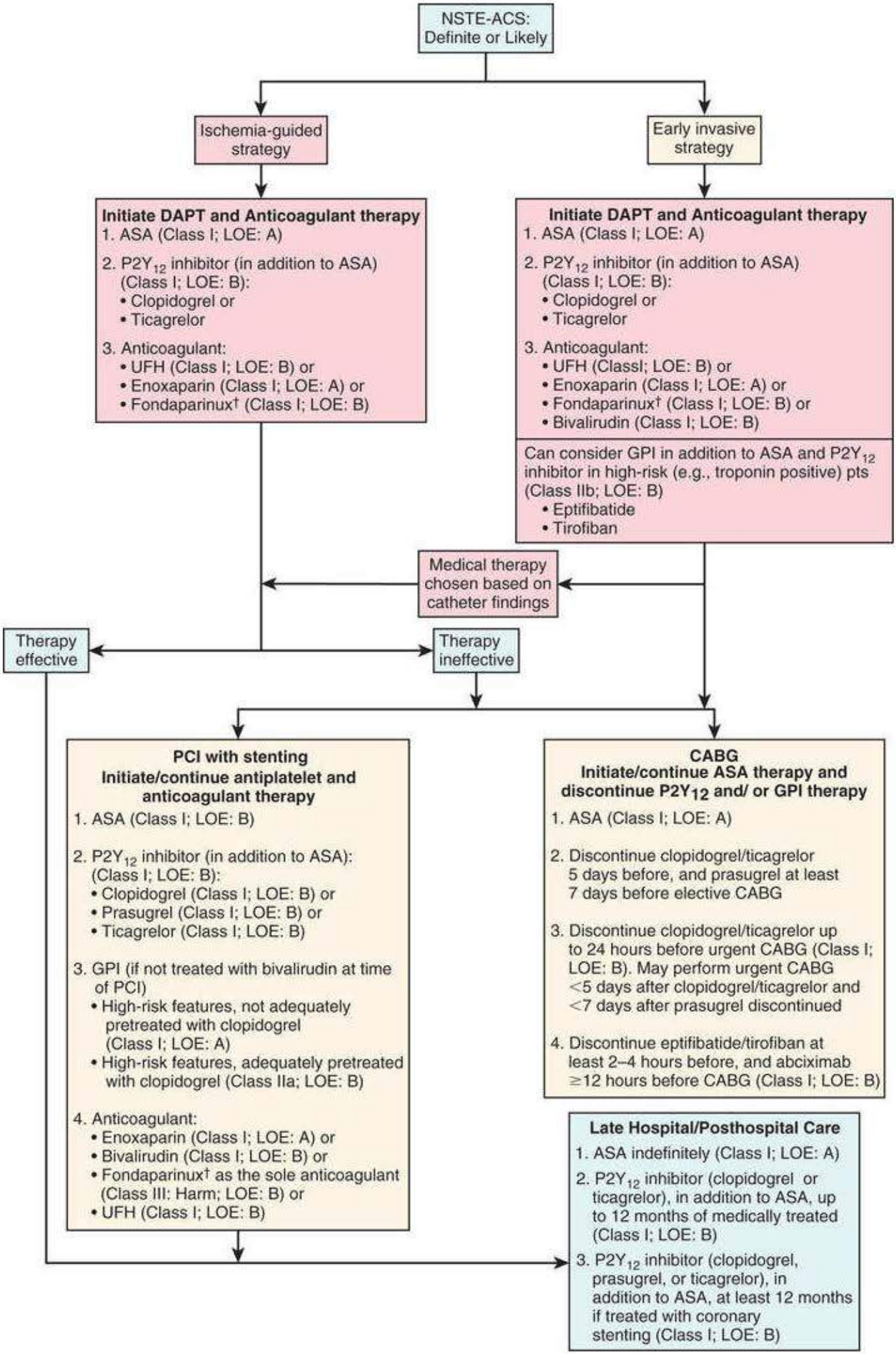

NSTE-ACS: Definite or Likely
Ischemia-guided strategy
Early invasive strategy
Initiate DAPT and Anticoagulant therapy
1. ASA (Class I; LOE: A)
2. P2Y12 inhibitor (in addition to ASA) (Class I; LOE: B):
• Clopidogrel or
• Ticagrelor
3. Anticoagulant:
• UFH (Class I; LOE: B) or
• Enoxaparin (Class I; LOE: A) or
• Fondaparinux† (Class I; LOE: B)
Initiate DAPT and Anticoagulant therapy
1. ASA (Class I; LOE: A)
2. P2Y12 inhibitor (in addition to ASA) (Class I; LOE: B):
• Clopidogrel or
• Ticagrelor
3. Anticoagulant:
• UFH (ClassI; LOE: B) or
• Enoxaparin (Class I; LOE: A) or
• Fondaparinux† (Class I; LOE: B) or
• Bivalirudin (Class I; LOE: B)
Can consider GPI in addition to ASA and P2Y12 inhibitor in high-risk (e.g., troponin positive) pts (Class IIb; LOE: B)
• Eptifibatide
• Tirofiban
Medical therapy chosen based on catheter findings
Therapy effective
Therapy ineffective
PCI with stenting
Initiate/continue antiplatelet and anticoagulant therapy
1. ASA (Class I; LOE: B)
2. P2Y12 inhibitor (in addition to ASA): (Class I; LOE: B):
• Clopidogrel (Class I; LOE: B) or
• Prasugrel (Class I; LOE: B) or
• Ticagrelor (Class I; LOE: B)
3. GPI (if not treated with bivalirudin at time of PCI)
• High-risk features, not adequately pretreated with clopidogrel (Class I; LOE: A)
• High-risk features, adequately pretreated with clopidogrel (Class IIa; LOE: B)
4. Anticoagulant:
• Enoxaparin (Class I; LOE: A) or
• Bivalirudin (Class I; LOE: B) or
• Fondaparinux† as the sole anticoagulant (Class III: Harm; LOE: B) or
• UFH (Class I; LOE: B)
CABG
Initiate/continue ASA therapy and discontinue P2Y12 and/ or GPI therapy
1. ASA (Class I; LOE: A)
2. Discontinue clopidogrel/ticagrelor 5 days before, and prasugrel at least 7 days before elective CABG
3. Discontinue clopidogrel/ticagrelor up to 24 hours before urgent CABG (Class I; LOE: B). May perform urgent CABG <5 days after clopidogrel/ticagrelor and <7 days after prasugrel discontinued
4. Discontinue eptifibatide/tirofiban at least 2–4 hours before, and abciximab ≥12 hours before CABG (Class I; LOE: B)
Late Hospital/Posthospital Care
1. ASA indefinitely (Class I; LOE: A)
2. P2Y12 inhibitor (clopidogrel or ticagrelor), in addition to ASA, up to 12 months of medically treated (Class I; LOE: B)
3. P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor), in addition to ASA, at least 12 months if treated with coronary stenting (Class I; LOE: B)

FIGURE 60G.2 Algorithm for management of patients with definite of likely non-ST-elevation acute coronary syndromes (NSTE-ACS). See text and **Table 60G.2** for selecting between the two management strategies (ischemia-guided and early invasive). †In patients who have been treated with fondaparinux (as upfront therapy) who undergo percutaneous coronary intervention (PCI), an additional anticoagulant with anti-IIa activity should be administered at the time of PCI because of the risk of catheter thrombosis. ASA, Acetylsalicylic acid (aspirin); CABG, coronary artery bypass grafting; DAPT, dual-antiplatelet therapy; GPI, glycoprotein inhibitor; LOE, level of evidence; UFH, unfractionated heparin. (From Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e139-228.)

TABLE 60G.4
Risk Criteria in Patients with NSTE-ACS

Very-High-Risk Criteria
• Hemodynamic instability or cardiogenic shock • Recurrent or ongoing chest discomfort refractory to optimal medical therapy • Life-threatening arrhythmias or cardiac arrest • Mechanical complications of MI • Acute heart failure • Recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation
High-Risk Criteria
• Rise and fall in cardiac troponin compatible with MI • Dynamic ST-T wave changes without symptoms (silent) • Elevated TIMI (>4) or GRACE (>140) risk score
Intermediate-Risk Criteria
• Diabetes mellitus • Renal insufficiency (eGFR <60 mL/min/173 m^2) • LVEF <40% or congestive heart failure • Early post-MI angina • Prior PCI • Prior CABG • TIMI (2-3) or GRACE (109-140) risk score
Low-Risk Criteria
• None of the characteristics mentioned above

CABG, Coronary artery bypass graft; *eGFR,* estimated glomerular filtration rate; *GRACE,* Global Registry of Acute Coronary Events; *LVEF,* left ventricular ejection fraction; *PCI,* percutaneous coronary intervention; *MI,* myocardial infarction; *TIMI,* thrombolysis in myocardial infarction.

Modified from Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology. Eur Heart J 2016;37:267-315.

If any of the following occur, the patient is considered to have failed initial ischemia-guided strategy and should be referred for invasive angiography: (1) refractory angina at rest or with minimal exertion despite optimal medical therapy, (2) objective evidence of ischemia (e.g., dynamic ST-segment changes on ECG, ischemia demonstrated on noninvasive stress imaging study), or (3) very high prognostic risk score.

Coronary Revascularization

See **Chapter 62**.

Late Hospital Care, Hospital Discharge, and Posthospital Care

Goals of care in the phase of the management of patients with NSTE-ACS include prevention of recurrent ACS, late complications of infarction, and progression of atherosclerosis with lifestyle and aggressive

risk modification, as well as restoring the patient to normal activities.

AHA/ACC Class I Recommendations[1]

Anti-Ischemic Therapies

1. Medications required in the hospital to control ischemia (e.g., beta blockers, CCBs, nitrates) should be continued after hospital discharge in patients with NSTE-ACS who do not undergo coronary revascularization, patients with incomplete or unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Titration of the doses may be required. (LOE: C.)
2. All patients who are post–NSTE-ACS should be given sublingual (SL) or spray nitroglycerin with oral and written instructions for its use (LOE: C). For patients who are post–NSTE-ACS and have initial angina lasting more than 1 minute, nitroglycerin (1 dose SL or spray) is recommended if angina does not subside within 3 to 5 minutes; call emergency medical services (EMS) immediately (LOE: C).

Antiplatelet Therapy

1. Aspirin should be continued indefinitely. The maintenance dose should be 81 mg daily (although up to 325 mg daily maybe used in special circumstances). (LOE: A.)
2. In addition to aspirin, a $P2Y_{12}$ inhibitor should be continued for up to 12 months in all patients with NSTE-ACS without contraindications. Options include:
    - Clopidogrel: 75 mg daily (LOE: B) *or*
    - Ticagrelor: 90 mg twice daily (LOE: B) *or*
    - Prasugrel 10 mg daily (LOE: B), only if coronary stenting was performed

Combined Postdischarge Oral Anticoagulant and Antiplatelet Therapy

1. The duration of triple-antithrombotic therapy with a vitamin K antagonist (VKA), aspirin, and a $P2Y_{12}$ receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding (LOE: C).
2. Proton pump inhibitors (PPIs) should be prescribed in patients with NSTE-ACS with a history of gastrointestinal bleeding who require triple-antithrombotic therapy with a VKA, aspirin, and a $P2Y_{12}$ receptor inhibitor[3] (LOE: C).

Renin-Angiotensin-Aldosterone Inhibitors

1. Angiotensin-converting enzyme inhibitors (ACEIs) should be started and continued indefinitely in all patients with left ventricular ejection fraction (LVEF) less than 40% and in those with diabetes mellitus (DM), hypertension, or stable chronic kidney disease (CKD), unless contraindicated (LOE: A). Angiotensin receptor blockers (ARBs) are recommended in who are ACEI intolerant (LOE: A).

2. Aldosterone blockade is recommended in patients after MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (>5.0 mEq/L) who are receiving therapeutic doses of ACEI and beta blocker and have an LVEF of 40% or less, DM, or heart failure (LOE: A).

Education

1. Before hospital discharge, patients with NSTE-ACS should be informed about symptoms of worsening myocardial ischemia and MI and should be given oral and written instructions about how and when to seek emergency care for such symptoms (LOE: C).
2. Before hospital discharge, patients who are post–NSTE-ACS and/or designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use (LOE: C).
3. If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or occurs at rest), patients should contact their clinician without delay to assess the need for additional treatment or testing (LOE: C).
4. Before discharge, patients should be educated about modification of cardiovascular risk factors (LOE: C).

Risk Factor Modification

1. All eligible patients with NSTE-ACS should be referred to a comprehensive cardiovascular rehabilitation program either before hospital discharge or during the first outpatient visit (LOE: B). Patients who have undergone PCI or CABG derive benefit from risk factor modification and should receive counseling that revascularization does not obviate the need for lifestyle changes (LOE: C).
2. Patients should be educated about appropriate cholesterol management, blood pressure (BP), smoking cessation, and lifestyle management[4,5] (LOE: C).
3. The pneumococcal vaccine is recommended for patients age 65 and older and in high-risk patients with cardiovascular disease[6] (LOE: B).

In addition, NSAIDs and hormones should be avoided because of the potential for harm, and there is no proven benefit for antioxidant vitamins or folic acid for secondary prevention of ACS.

Special Patient Groups

The AHA/ACC provide the following class I recommendations for select special patient groups.

Older Patients

1. Patients ≥75 years of age should be treated with guideline-directed medical therapy, an early invasive strategy, and revascularization as appropriate[7] (LOE: A).

2. Pharmacotherapy should be individualized and dose adjusted by weight and/or creatinine clearance to reduce adverse events caused by age-related changes in pharmacokinetics/dynamics, volume of distribution, comorbidities, drug interactions, and increased drug sensitivity (LOE: A).
3. Management decisions should be patient centered and should consider patient preferences/goals, comorbidities, functional and cognitive status, and life expectancy[8] (LOE: B).

Women

1. Women with NSTE-ACS should be managed with the same pharmacologic therapy as men for acute care and for secondary prevention, with attention to weight and renally calculated doses of antiplatelet and anticoagulant agents to reduce bleeding risk (LOE: B).
2. Women with NSTE-ACS and high-risk features (e.g., troponin elevation) should undergo an early invasive strategy (LOE: A).
3. Women with low-risk features should not undergo early invasive treatment because of lack of benefit and the possibility of harm (COR III, LOE: B).

Patients with Heart Failure

1. Patients with a history of heart failure (HF) and NSTE-ACS should be treated according to the same risk stratification guidelines and recommendations for patients without HF[9] (LOE: B).
2. Selection of a specific revascularization strategy should be based on the degree, severity, and extent of coronary artery disease (CAD); associated cardiac lesions; extent of LV dysfunction; and history of prior revascularization procedures[9] (LOE: B).
3. Early revascularization is recommended in suitable patients with cardiogenic shock caused by cardiac pump failure after NSTE-ACS (LOE: B).

Diabetes Mellitus

Medical treatment in the acute phase of NSTE-ACS and decisions to perform stress testing, angiography, and revascularization should be similar in patients with and without DM (LOE: A).

Post–Coronary Artery Bypass Graft Surgery

Patients with prior CABG and NSTE-ACS should receive antiplatelet and anticoagulant therapy according to guideline-directed medical therapy and should be strongly considered for early invasive strategy because of their increased risk (LOE: B).

Chronic Kidney Disease

1. The creatinine clearance should be estimated in patients with NSTE-ACS at the time of presentation, and doses of renally cleared medications should be adjusted according to the pharmacokinetic data for specific medications (LOE: B).
2. Patients undergoing coronary and left ventricular angiography should receive adequate hydration

(LOE: C).

Use of Performance Measures and Registries

Participation in a standardized quality-of-care data registry designed to track and measure outcomes, complications, and performance measures can be beneficial in improving the quality of NSTE-ACS care (LOE: B). National systems for ACS and standardization of quality-of-care data registries are critical to permit assessment of care and quality improvement. **Table 60G.5** lists 10 performance measures from the ESC[2] that are useful for monitoring and improving the standards of care in NSTE-ACS.

TABLE 60G.5

Ten Performance Measures in Patients with NSTE-ACS

1. Use of aspirin
2. Use of an oral $P2Y_{12}$ inhibitor
3. Use of fondaparinux, bivalirudin, UFH, or enoxaparin
4. Use of beta blocker at discharge for patients with LV dysfunction
5. Use of statins
6. Use of ACEI or ARB in patients with systolic LV dysfunction or heart failure, hypertension, or diabetes
7. Use of early invasive procedures in intermediate- to high-risk patients
8. Smoking cessation advice/counseling
9. Enrollment in a secondary prevention or cardiac rehabilitation program
10. Development of regional and/or national programs to measure performance indicators systematically and provide feedback to individual hospitals

ACE, Angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; *LV,* left ventricular; *UFH,* unfractionated heparin.

Modified from Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology. Eur Heart J 2016;37:267-315.

Evidence Gaps

Despite decades of high-quality clinical trials, data from well-conducted registries, and other controlled studies that provide the large body of evidence supporting guideline-directed management of NSTE-ACS, challenges and gaps in optimal care remain. Optimal medical therapy remains underutilized, particularly in high-risk subgroups. Comparative effectiveness studies lag behind the landmark trials establishing the efficacy and safety of novel therapies.

The paradox of newer and more potent antithrombotic and anticoagulant drugs that reduce major adverse cardiac outcomes but increase bleeding risk represents a particularly difficult challenge for patients at increased risk for bleeding (e.g., elderly, CKD) and those receiving oral anticoagulation. An unmet need is to distinguish which higher-risk patients are candidates for an ischemia-guided strategy compared with an early invasive management strategy, since these patients were typically underrepresented in the landmark clinical trials.

At the extreme, a sizable minority of patients (more often women than men) with NSTE-ACS have nonobstructive CAD, yet the prognosis is not benign. There appear to be multiple mechanisms of ACS postulated, and rigorous evaluation of treatment for this condition is lacking. **See Table 60.6** for additional unanswered questions.

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61

Stable Ischemic Heart Disease

David A. Morrow, James A. de Lemos

The spectrum of stable ischemic heart disease (SIHD) is broad and includes individuals with chronic stable angina, asymptomatic ischemia, prior myocardial infarction, prior coronary revascularization, as well as individuals with nonobstructive coronary atherosclerosis. SIHD is most frequently caused by

atheromatous plaque that obstructs or gradually narrows the epicardial coronary arteries. The pathogenesis of atherosclerosis is described in **Chapter 44**. However, other contributors, such as endothelial dysfunction, microvascular disease, and vasospasm, may also exist alone or in combination with coronary atherosclerosis and may be the dominant cause of myocardial ischemia in some patients (**Fig. 61.1**). Thus, the concept that ischemic heart disease (IHD) is synonymous with "obstructive coronary atherosclerosis" is an overly simplified view.[1-3]

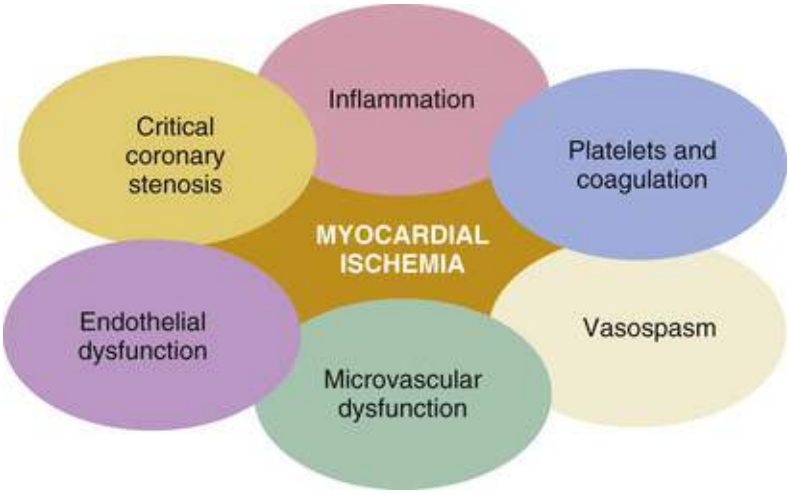


FIGURE 61.1 Pathophysiology of ischemic heart disease (IHD). The idea that IHD is synonymous with critical stenoses of epicardial coronary arteries is an oversimplification. The potential contributors to IHD are multiple. (Modified from Marzilli M, Bairey Merz CN, Boden WE, et al. Obstructive coronary atherosclerosis and ischemic heart disease: an elusive link. J Am Coll Cardiol 2012;60:951.)

Factors that predispose to coronary atherosclerosis are discussed in **Chapter 45**, control of coronary blood flow in **Chapter 57**, percutaneous coronary revascularization in **Chapter 62**, ST-segment elevation myocardial infarction (MI) in **Chapters 58 and 59**, non–ST-segment elevation acute coronary syndrome (ACS) in **Chapter 60**, and sudden cardiac death, another significant consequence of IHD, in **Chapter 42**.

The presenting symptoms in patients with IHD are highly variable. Chest discomfort is usually the predominant symptom in chronic (stable) angina, unstable angina, Prinzmetal (variant) angina, microvascular angina, and acute MI. However, manifestations of IHD also occur in which chest discomfort is absent or not prominent, such as asymptomatic (silent) myocardial ischemia, heart failure, cardiac arrhythmias, and sudden death. Notably, IHD may also present with atypical angina or anginal equivalents, such as midepigastric discomfort, dyspnea, effort intolerance, and excessive fatigue, which are observed more frequently in women, older adults, and individuals with diabetes.

Coronary arteries may also become obstructed by nonatherosclerotic mechanisms, including extrinsic compression, myocardial bridging, coronary arteritis in association with systemic vasculitis, and radiation-induced coronary artery disease (CAD). Myocardial ischemia and angina pectoris may also occur in the setting of extreme myocardial oxygen (O_2) demand with or without underlying obstructive CAD, as in the case of aortic valve disease (**see Chapter 68**), hypertrophic cardiomyopathy (**Chapter 78**), dilated nonischemic cardiomyopathies (**Chapter 77**), or pulmonary hypertension (**Chapter 85**).

Magnitude of the Problem

The importance of IHD in contemporary society is attested to by the large number of persons afflicted

(**see Chapter 1**). It is estimated that 15,400,000 Americans have IHD, 7,800,000 of whom have angina pectoris and 7,600,000 have had MI.[4] Based on data from the Framingham Heart Study, the lifetime risk for IHD among individuals with an optimal risk factor profile is 3.6% for men and less than 1% for women; whereas among individuals with two or more major risk factors, the lifetime risk is 37.5% for men and 18.3% for women. In 2013, IHD accounted for 46% of all deaths caused by cardiovascular disease (CVD) and was the single most frequent cause of death in American men and women, resulting in more than one in seven deaths in the United States. The economic cost of IHD is formidable, estimated to be $207.3 billion in the United States in 2011 to 2012.

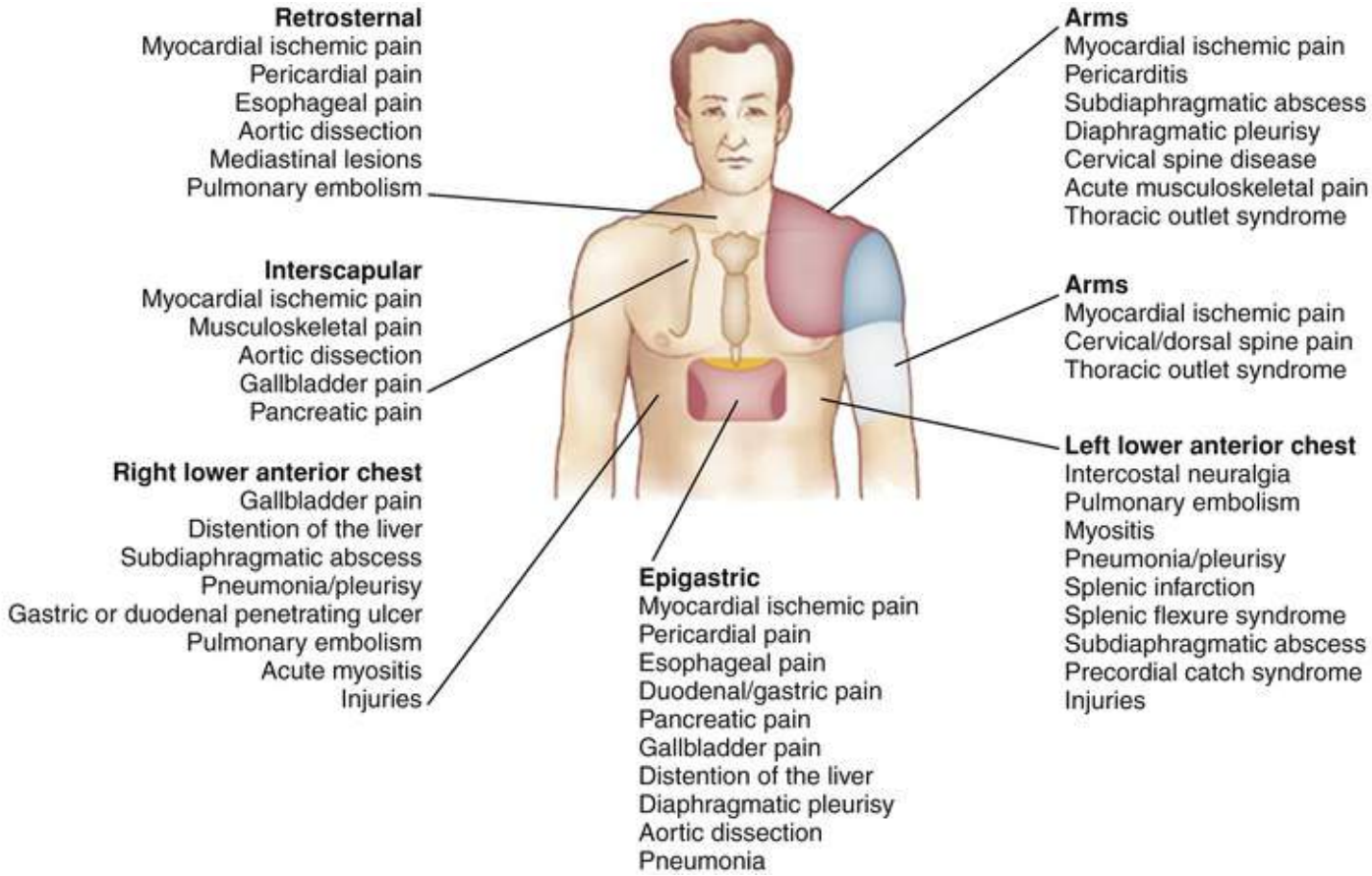
Despite a steady decline in age-specific mortality from CAD over the past several decades, IHD is the leading cause of death worldwide, and it is expected that the rate of CAD will only accelerate in the coming decades. Moreover, with a decline in case-fatality rate of MI, the prevalence of survivors with SIHD has increased despite a relatively stable rate of incident MI. At the same time, the burden of IHD is shifting progressively to lower socioeconomic groups with contributory factors that include aging of the population, increases in the worldwide prevalence of obesity and type 2 diabetes, and a rise in cardiovascular risk factors in younger generations. The World Health Organization (WHO) has estimated that by 2030, the global number of deaths from IHD will have risen from 7.4 million in 2012 to 9.2 million.

Stable Angina Pectoris

Clinical Manifestations

Characteristics of Angina (See Chapter 56)

Angina pectoris is a discomfort in the chest or adjacent areas caused by myocardial ischemia. It is usually precipitated by exertion but may also be initiated by emotional distress. Angina that is prolonged, occurs at rest, or occurs in an accelerating pattern of increasing frequency and tempo is indicative of unstable IHD, including unstable angina and acute MI (**see Chapters 58 and 60**). Heberden's initial description of angina as conveying a sense of “strangling and anxiety” is still remarkably pertinent. Other adjectives frequently used to describe this distress include constricting, suffocating, crushing, heavy, and squeezing. In other patients the quality of the sensation can be vague and described as a mild pressure-like discomfort, tightness, an uncomfortable numbness, or a burning sensation. The site of the discomfort is usually retrosternal, but radiation is common and generally occurs down the ulnar surface of the left arm; the right arm and the outer surfaces of both arms may also be involved (**eFig. 61.1**). Epigastric discomfort alone or in association with chest pressure may occur and can masquerade as indigestion. Anginal discomfort above the mandible or below the epigastrium is rare. Anginal equivalents (i.e., symptoms of myocardial ischemia other than angina), such as dyspnea, faintness, fatigue, and frequent belching, are more commonly seen in women and older adults. A history of abnormal exertional dyspnea may be an indicator of IHD even when angina is absent. Nocturnal angina may be a manifestation of unstable angina but should also raise suspicion of sleep apnea (**see Chapter 87**). Postprandial angina, presumably caused by redistribution of coronary blood flow to the splanchnic circulation, may be a marker of severe IHD.



EFIGURE 61.1 Location of discomfort and cause of chest symptoms. The location of angina is usually retrosternal, but radiation is common. An epigastric location of angina may also occur.

The typical episode of angina pectoris usually begins gradually and reaches its maximum intensity over a period of minutes before dissipating. It is unusual for angina pectoris to reach its maximum severity within seconds, and it is characteristic that patients with angina generally prefer to rest, sit, or stop walking during episodes. Chest discomfort while walking in the cold or uphill is suggestive of angina. Features suggesting the absence of angina pectoris include pain that is pleuritic, sharp or stabbing in quality, or reproduced by movement or palpation of the chest wall or arms (**eFig. 61.1**). Constant pain lasting many hours or, alternatively, very brief episodes of pain lasting seconds are also unlikely to result from angina. Typical angina pectoris is relieved within minutes by rest or the use of short-acting nitroglycerin. Response to the latter is often a useful diagnostic tool, although it should be remembered that esophageal pain may also respond to nitroglycerin. A delay of more than 5 to 10 minutes before relief is obtained with rest and nitroglycerin suggests that the symptoms are either not caused by ischemia or are caused by severe ischemia, as with acute MI or unstable angina. The phenomenon of *warm-up angina* is used to describe the ability of some patients in whom angina develops with exertion to continue subsequently at the same or even greater level of exertion without symptoms after an intervening period of rest. This attenuation of myocardial ischemia observed with repeated exertion has been postulated to be caused by ischemic preconditioning (**see Chapter 57**).

Assessment and Classification of Angina Pectoris

A system of grading the severity of angina pectoris proposed by the Canadian Cardiovascular Society (CCS) is widely used. The system is a modification of the New York Heart Association (NYHA) functional classification and allows patients to be categorized in more specific terms. Other grading systems include a specific activity scale developed by Goldman and associates that is based on the metabolic cost of specific activities. A limitation of all these grading systems is their dependence on

accurate reporting by patients in the context of patients' widely varying tolerance of symptoms. Functional estimates based on the CCS criteria have shown a reproducibility that is only moderate and that do not correlate well with objective measures of exercise performance.

More recent developments incorporate measures of the impact of angina on quality of life, which can be assessed using general instruments such as the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) or the disease-specific Seattle Angina Questionnaire (SAQ). Although these objective measurements have typically only been used in the research setting, a short, seven-question version of the SAQ may be more practical for the clinical setting. In the future, embedding simple, objective, patient-centered disease measurements into the clinical encounter is likely to become increasingly important for chronic diseases such as SIHD.

Mechanisms of Anginal Pain.

The mechanisms of cardiac pain and the neural pathways involved are poorly understood. It is presumed that angina pectoris results from ischemic episodes that excite chemosensitive and mechanosensitive receptors in the heart. Stimulation of these receptors results in the release of adenosine, bradykinin, and other substances that excite the sensory ends of sympathetic and vagal afferent fibers. The afferent fibers traverse the nerves that connect to the upper five thoracic sympathetic ganglia and the upper five distal thoracic roots of the spinal cord. Impulses are transmitted by the spinal cord to the thalamus and then to the neocortex. Data from animal studies have identified the vanilloid receptor-1 (VR1), also known as the transient receptor potential vanilloid-1 receptor (TRPV1) receptor, an important sensor for somatic nociception, to be present on sensory nerve endings in the heart and have suggested that VR1 functions as a transducer of myocardial tissue ischemia and may play a role in ischemic preconditioning.

Within the spinal cord, cardiac sympathetic afferent impulses may converge with impulses from somatic thoracic structures, which may be the basis for referred cardiac pain, such as to the chest. In comparison, cardiac vagal afferent fibers synapse in the nucleus tractus solitarius of the medulla and then descend to excite the upper cervical spinothalamic tract cells, which may contribute to the anginal pain experienced in the neck and jaw. Moreover, vagal input in the nucleus tractus solitarius may lead to stimulation of efferent impulses in the autonomic system that contribute to nausea and emesis. Positron emission tomography (PET) of the brain in persons with silent ischemia suggests that failed transmission of signals from the thalamus to the frontal cortex may contribute to this phenomenon, along with impaired afferent signaling, such as that caused by autonomic neuropathy. Silent ischemia in diabetic patients, for example, has been proposed to be related to failed development of the cardiac sensory system because of reduced nerve growth factor.

Differential Diagnosis of Chest Pain

Esophageal Disorders

Common disorders that may simulate or coexist with angina pectoris are gastroesophageal reflux and disorders of esophageal motility, including diffuse spasm. To compound the difficulty in distinguishing between angina and esophageal pain, both may be relieved by nitroglycerin. However, esophageal pain is often relieved by milk, antacids, foods, or occasionally, warm liquids.

Esophageal Motility Disorders

Esophageal motility disorders are not uncommon in patients with retrosternal chest pain of unclear cause. In addition to chest pain, most such patients have dysphagia. Both IHD and esophageal disease are common clinical entities that may coexist. Diagnostic evaluation for an esophageal disorder may be indicated in patients with IHD who have a poor symptomatic response to antianginal therapy in the absence of documented ischemia.

Biliary Colic

Although visceral symptoms are often associated with myocardial ischemia (particularly acute inferior MI; **see Chapter 56**), biliary colic and related hepatobiliary disorders may also mimic ischemia and should always be considered in patients with atypical chest discomfort, particularly in patients with diabetes. The pain is steady, usually lasts 2 to 4 hours, and subsides spontaneously, without any symptoms between attacks. It is generally most intense in the right upper abdominal area but may also be felt in the epigastrium or precordium. This discomfort is often referred to the scapula, may radiate around the costal margin to the back, or in rare cases may be felt in the shoulder and may suggest diaphragmatic irritation.

Costochondritis

In 1921, Tietze first described a syndrome of local pain and tenderness, generally limited to the anterior chest wall and associated with swelling of costal cartilage. The full-blown Tietze syndrome (i.e., pain associated with tender swelling of the costochondral junctions) is uncommon, whereas costochondritis causing tenderness of the costochondral junctions (without swelling) is relatively common. Pain on palpation of these joints is usually well localized and is a useful clinical sign, although deep palpation may elicit pain in the absence of costochondritis. Although palpation of the chest wall often reproduces pain in patients with various musculoskeletal conditions, it should be appreciated that chest wall tenderness does not exclude symptomatic CAD.

Other Neurologic and Musculoskeletal Disorders

Cervical radiculitis may be confused with angina. This condition may occur as a constant ache and sometimes results in a sensory deficit. The pain may be related to motion of the neck, just as motion of the shoulder triggers attacks of pain from bursitis. Occasionally, pain mimicking angina can be caused by compression of the brachial plexus by the cervical ribs, and tendinitis or bursitis involving the left shoulder may also cause angina-like pain. Physical examination may also detect pain triggered by movement of an arthritic shoulder or a calcified shoulder tendon. Herpes zoster, caused by recrudescence of the varicella-zoster virus, can manifest as pain across the chest and should be recognized by its dermatomal distribution and associated blistering or crusting rash. The pain of zoster (shingles) may begin several days before a rash is apparent. Postherpetic neuralgia may persist in the absence of a rash.

Other Causes of Angina-Like Pain

Severe pulmonary hypertension may be associated with exertional chest pain with the characteristics of angina pectoris, and indeed, this pain is thought to be caused by right ventricular (RV) ischemia that develops during exertion (**see Chapter 85**). Other associated symptoms include exertional dyspnea, dizziness, and syncope. Related findings on physical examination, such as a parasternal lift, a palpable and loud pulmonary component of the second sound, and RV hypertrophy on the electrocardiogram (ECG), are usually readily recognized.

Pulmonary embolism is initially characterized by dyspnea as the cardinal symptom, but chest pain may

also be present (**see Chapter 84**). Pleuritic pain suggests pulmonary infarction, and a history of exacerbation of the pain with inspiration, along with a pleural friction rub, if present, helps distinguish it from angina pectoris.

The pain of acute pericarditis may at times be difficult to distinguish from angina pectoris (**see Chapter 83**). However, pericarditis tends to occur in younger patients, and the diagnosis depends on the combination of chest pain not relieved by rest or nitroglycerin, exacerbation by movement or deep inspiration, and lying flat; a pericardial friction rub, which may be evanescent; and changes on the ECG, notably PR-segment depression and/or diffuse ST elevation.

The classic symptom of aortic dissection is a severe, often sharp pain that radiates to the back (**see Chapter 63**).

Physical Examination

Most patients with SIHD have normal findings on cardiac examination, and thus the single best clue to the diagnosis of angina is the clinical history. Nonetheless, careful examination can exclude other conditions that mimic angina and may reveal atherosclerosis in noncoronary vascular territories, evidence of risk factors for coronary atherosclerosis (e.g., acanthosis nigricans, tendon xanthomas), or the consequences of myocardial ischemia (**see Chapter 10**).

Pathophysiology

Angina pectoris results from myocardial ischemia, which is caused by an imbalance between myocardial O_2 requirements and myocardial O_2 supply. The former may be elevated by increases in heart rate (HR), left ventricular (LV) wall stress, and contractility (**see Chapter 22**); the latter is determined by coronary blood flow and coronary arterial O_2 content (**Fig. 61.2**). The clinical precipitants and manifestations of supply-demand imbalance are discussed in this section. The pathobiology of atherosclerosis is discussed in **Chapter 44**. See Chest Pain with a Normal Coronary Arteriogram later in this chapter and **Chapter 57** for discussion of other abnormalities in coronary function and contributors to myocardial ischemia in the absence of critical coronary obstruction.

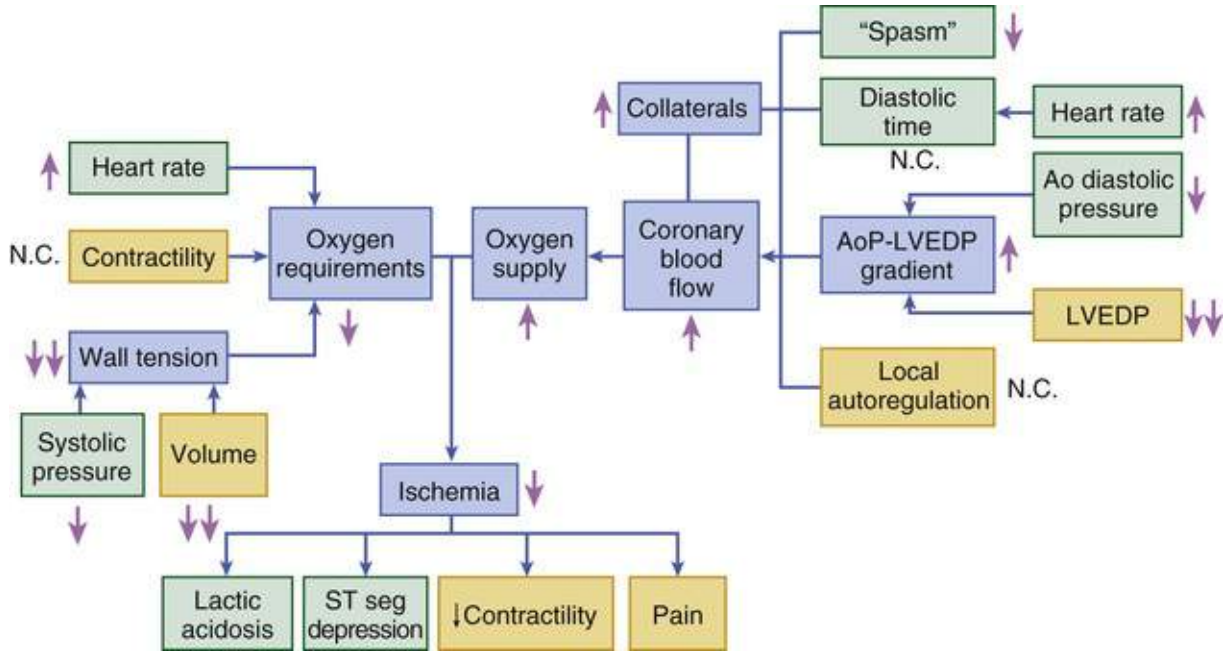


FIGURE 61.2 Factors influencing the balance between myocardial O_2 requirement (*left*) and supply (*right*). *Arrows* indicate effects of nitrates. In relieving angina pectoris, nitrates exert favorable effects by reducing O_2 requirements and increasing supply. Although a reflex increase in heart rate would tend to reduce the time for coronary flow, dilation of collaterals and enhancement of the pressure gradient for flow to occur as left ventricular end-diastolic pressure (LVEDP) falls tend to increase coronary flow. AoP-LVEDP, Aortic pressure minus LVEDP; N.C., no change. (From Frishman WH: Pharmacology of the nitrates in angina pectoris. Am J Cardiol 1985;56:8I.)

Angina Caused by Increased Myocardial Oxygen Requirements

In this condition, sometimes termed *demand angina*, the myocardial O_2 requirement increases in the presence of a constant and usually restricted O_2 supply. The increased O_2 requirement usually results from a physiologic response to exertion, emotional duress, or mental stress. Of great importance to the myocardial O_2 requirement is the rate and intensity at which any physical task is carried out. Mental and emotional stress may precipitate angina, presumably by increased hemodynamic and catecholamine responses to stress, increased adrenergic tone, and reduced vagal activity. The combination of physical exertion and emotion in association with sexual activity may precipitate angina. Other precipitants of angina include physical exertion after a heavy meal and the excessive metabolic demands imposed by chills, fever, thyrotoxicosis, tachycardia from any cause, uncontrolled hypertension, exposure to the cold, and hypoglycemia.

Angina Caused by Transiently Decreased Oxygen Supply

As with unstable angina, chronic stable angina may be caused by transient reductions in O_2 supply, a condition sometimes termed *supply angina*, as a consequence of coronary vasoconstriction that results in dynamic stenosis. In the presence of atherosclerotic stenoses, platelet thrombi and leukocytes may elaborate vasoconstrictor substances such as serotonin and thromboxane A_2. In addition, endothelial damage in atherosclerotic coronary arteries decreases production of vasodilator substances, resulting in an abnormal vasoconstrictor response to exercise and other stimuli. A variable threshold of myocardial ischemia in patients with chronic stable angina may be caused by dynamic changes in smooth muscle tone and also by constriction of arteries distal to the stenosis. Patients with resulting "variable-threshold angina" may have good days, when they are capable of substantial physical activity, as well as bad days,

when even minimal activity can cause clinical and/or electrocardiographic evidence of myocardial ischemia or angina at rest. They often complain of a circadian variation in angina that is more common in the morning. Angina on exertion and sometimes even at rest may be precipitated by cold temperature, emotion, and mental stress.

In rare instances, severe dynamic obstruction may develop alone in patients without organic obstructing lesions and can cause myocardial ischemia and angina at rest (see later, Prinzmetal Variant Angina; **see also Chapters 57 and 60**). On the other hand, in patients with severe fixed obstruction in one or more epicardial coronary arteries, only a minor increase in dynamic obstruction is necessary for coronary blood flow to fall below a critical level and cause myocardial ischemia.

Importance of Pathophysiologic Considerations in Configuring Therapy

The pathophysiologic and clinical correlations of ischemia in patients with SIHD may have important implications for the selection of anti-ischemic agents, as well as for their timing. The greater the contribution from increased myocardial O_2 demand associated with tachycardia or increased contractility, the greater is the likelihood that beta-blocking agents will be effective; nitrates and calcium channel–blocking agents, at least hypothetically, are more likely to be effective in episodes caused primarily by coronary vasoconstriction. The finding that an increase in myocardial O_2 requirement precedes episodes of ischemia in most patients with chronic stable angina—that is, that they have demand angina—argues in favor of controlling the HR and blood pressure (BP) as a primary therapeutic approach.

Evaluation and Management

Biochemical Tests

In patients with SIHD, metabolic abnormalities that are risk factors for the development of CAD are frequently detected. Such abnormalities include dyslipidemia (**see Chapter 48**) and insulin resistance. Moreover, chronic kidney disease is strongly associated with risk for atherosclerotic vascular disease (**see Chapter 98**). All patients with established or suspected CAD warrant evaluation of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, serum creatinine (leading to estimation of glomerular filtration rate [eGFR]), fasting blood glucose levels, and measurement of hemoglobin (Hb) A_{1c}.

Measurement of other lipid elements that are particularly atherogenic, such as apolipoprotein B and small dense LDL, appears to add prognostic information to the measurement of total cholesterol and LDL and may be considered a secondary target for therapy in patients who have achieved therapeutic targets for LDL.[5,6] However, no consensus has been reached regarding routine measurement, and a simple approach based on calculation of non-HDL cholesterol (particularly in patients with triglyceride levels >200 mg/dL) may capture most of the important information related to other atherogenic lipid particles. Similarly, lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is associated with risk for coronary heart disease (CHD), as well as for recurrent events, independent of traditional risk factors. However, despite this association, inhibitors of Lp-PLA_2 have not proved useful for the treatment of IHD.[7,8] Present prevention guidelines do not recommend Lp-PLA_2 for routine risk assessment. Lipoprotein (a) [Lp(a)] is a highly heritable lipid-related risk factor that should be considered for measurement in selected individuals with premature CAD, as well as those with recurrent ischemic events despite standard preventive therapies, particularly if a strong family history of CAD is present. After decades of study, large genetic studies have now clearly established Lp(a) as a causal risk factor for CAD. Although niacin is the only widely available treatment shown to lower Lp(a), proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors also lower Lp(a) and may emerge as a therapeutic option.[9]

Although homocysteine has also been linked to atherogenesis, prospective studies suggest, at most, a modest increase in risk associated with elevated homocysteine levels and have not consistently demonstrated a relationship independent of traditional risk factors or other biochemical markers.[10] Moreover, placebo-controlled trials have failed to demonstrate clinical benefit associated with folate and B vitamin replacement therapies as an intervention to mitigate the adverse effects of increased homocysteine levels.[11] Therefore, general screening for elevated homocysteine levels is not recommended.

Biomarkers of Myocyte Injury, Ischemia, and Hemodynamic Stress

Blood levels of cardiac troponins T and I are typically used to differentiate patients with acute MI from those with SIHD. However, with the development of high-sensitivity assays, low levels of circulating troponins are now detectable in most patients with SIHD and demonstrate a graded relationship with the subsequent risk for cardiovascular (CV) mortality and heart failure.[12,13] Moreover, patients with SIHD who have small increases in high-sensitivity troponin (hsTn) levels over time are at increased risk for adverse outcomes, even in the absence of an evident change in clinical status (**Fig. 61.3**). Potential emerging applications of cardiac troponin in SIHD are reviewed in depth elsewhere.[14]

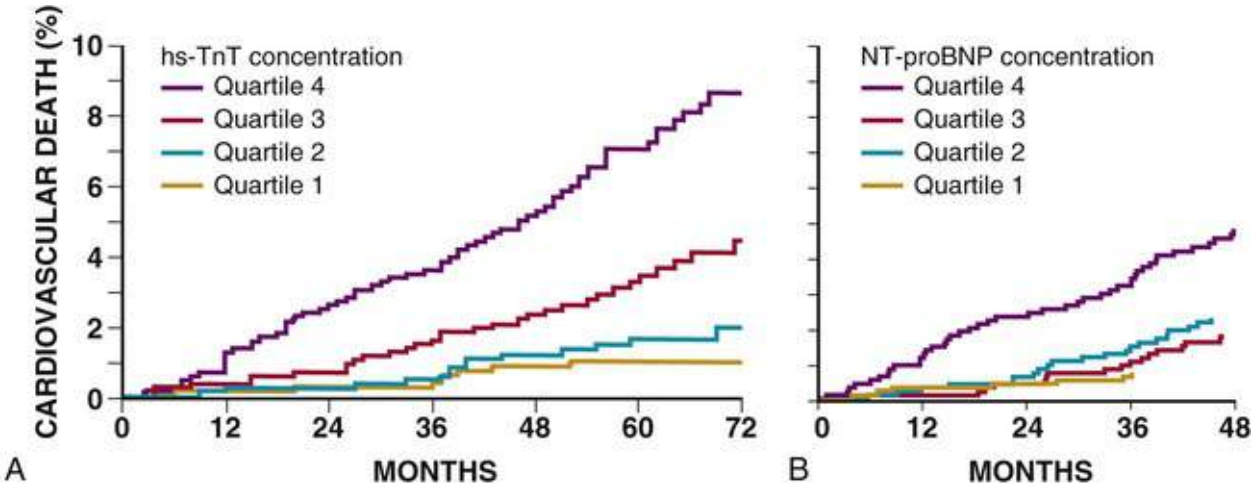


FIGURE 61.3 Incidence of cardiovascular (CV) death according to the concentration of high-sensitivity troponin T (hs-TnT) **(A)** and N-terminal pro–B-type natriuretic peptide (NT-proBNP) **(B)** in patients with stable coronary artery disease (CAD) subgrouped by quartiles of biomarker concentration. **A,** Circulating cardiac troponin T was detected in 97.7% of individuals by hs-TnT assay, with 11.1% having a concentration that exceeded the 99th percentile reference limit. During a median follow-up of 5.2 years, the incidence of CV death was associated with the baseline concentration of hs-TnT. This relationship was apparent at concentrations of hs-TnT below the 99th percentile reference limit (0.013 µg/L). **B,** The NT-proBNP concentration was also strongly associated with risk for CV mortality; prognostic accuracy improved when NT-proBNP was considered alongside traditional clinical risk indicators. (**A,** From Omland T et al. A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med 2009;361:2538; **B,** from Omland T et al. Prognostic value of B-type natriuretic peptides in patients with stable coronary artery disease. J Am Coll Cardiol 2007;50:201.)

Biomarkers of neurohormonal activation have also been extensively studied in patients with SIHD. For example, the plasma concentration of brain (B-type) natriuretic peptide (BNP) increases in response to spontaneous or provoked ischemia. Although BNP and N-terminal pro-BNP (NT-proBNP) do not have sufficient specificity to aid in the diagnosis of SIHD, higher concentrations of these peptides are strongly associated with risk for CV events in those at risk for and with established CAD. As has been shown with hsTn, serial measurements of natriuretic peptides also provide incremental prognostic information in patients with SIHD, suggesting a potential future role of outpatient monitoring with these tests.[14] Despite the promising results of studies to date, routine measurement of troponins and natriuretic peptides is not yet warranted in patients with SIHD, because the optimal strategies to reduce levels of these biomarkers, or to lower risk for patients with elevated levels, have not been determined. However, intensive secondary preventive therapies, such as treatment with high-intensity statin regimens, reduce risk in those with elevated troponin, with absolute risk reductions that are heightened given the high risk status of these patients.[15-17]

Growth differentiation factor-15,[18] ST2, fibroblast growth factor-23,[19] and galectin-3[20] are also biomarkers that may putatively reflect myocardial ischemia or its consequences and have been associated with CV outcomes in clinical studies of patients with SIHD. Other novel biomarkers of hemodynamic stress, such as midregional proadrenomedullin (MR-proADM) and midregional pro–atrial natriuretic peptide (MR-proANP), can also provide information regarding the risk for CV death in patients with SIHD.[21] However, insufficient information is available to demonstrate that these measurements provide robust incremental information beyond natriuretic peptide and hsTn measurements, which have emerged as the strongest candidate biomarkers for clinical application in patients with SIHD.

Inflammatory Biomarkers

Advances in understanding of the pathobiology of atherothrombosis have generated interest in

inflammatory biomarkers as noninvasive indicators of underlying atherosclerosis and CV risk (**see Chapter 44**). Measurement of the acute-phase protein high-sensitivity C-reactive protein (hsCRP) has shown a consistent relationship to risk for incident CV events. (**see Chapter 45**). The prognostic value of hsCRP is additive to traditional risk factors, including lipids; however, its incremental clinical value for screening among individuals without known vascular disease continues to be debated.[22] The role of hsCRP testing among individuals with SIHD has also been extensively studied, with multiple studies confirming independent associations of hsCRP with adverse cardiac events. Also, two studies have shown that hsCRP may be an important biomarker reflecting residual risk among patients following ACS who are treated to low LDL goals with statin therapy. Patients who achieved low LDL cholesterol levels (<70 mg/dL) but with hsCRP levels above 2 mg/L were at higher risk for subsequent ischemic events than patients with low levels of both LDL and hsCRP. Moreover, hsCRP has been used to select potential candidates for antiinflammatory pharmacotherapy.[22a] In head-to-head comparison studies, the strength of the association of hsCRP with outcomes has been less than that seen with natriuretic peptides and cardiac troponins.

Although other biomarkers of inflammation, such as interleukin-6, myeloperoxidase, growth factors, cytokines, and metalloproteinases, remain under study as potential biomarkers reflecting inflammatory pathways contributing to atherosclerosis,[23] given their lack of cardiac specificity, they are unlikely to emerge as clinically useful biomarkers.

Genetic and Transcriptomic Biomarkers

Large-scale genetic mapping programs, utilizing genome-wide association studies (GWASs) and more recently next-generation genome sequencing have identified more than 50 unique genetic variants contributing to IHD (**see Chapter 7**). These studies have contributed to the identification of many new potential pathogenic targets and have also allowed testing for large numbers of genetic variations simultaneously at relatively low cost. Because the genes contributing to IHD individually explain only a small amount of the variation in disease, combining multiple variants in genetic risk scores is presently thought to be the only viable strategy by which genetic risk prediction could enter clinical practice. However, the genetic risk scores have only marginally improved risk prediction in individuals without known IHD and did not improve risk prediction in patients with previous CAD.[24] Larger genetic risk scores, incorporating additional variants identified with finer gene-mapping strategies, may improve performance in the future. It is more likely that genetic testing will enter routine practice as a tool to guide therapeutic drug selection (pharmacogenomics; **see Chapter 6**). Two studies have demonstrated that individuals with high genetic risk scores, identifying a genetic predisposition to IHD, derive greater reduction in risk with statin therapy than do individuals with low genetic risk scores.[25]

It is now also possible to study multigene expression from peripheral blood cells, so called transcriptomics.[26] For example, a peripheral blood gene expression score based on expression values for 23 genes from peripheral blood cells has been developed and validated to assess the risk for obstructive CAD; a high negative predictive value (NPV) with a very low rate of major adverse cardiac events (MACE) over a 1-year period was demonstrated in patients with a low gene expression score.[26]

Noninvasive Testing

Resting Electrocardiogram

Findings on the resting ECG are normal in approximately half of patients with SIHD, and even patients

with severe CAD may have a normal tracing at rest (**see Chapter 12**). A normal resting ECG suggests the presence of normal resting LV function and is an unusual finding in a patient with an extensive previous MI. The most common abnormalities on the ECG in patients with SIHD are nonspecific ST-T wave changes with or without abnormal Q waves. In patients with known CAD, however, the occurrence of ST-T wave abnormalities on the resting ECG (particularly if obtained during an episode of angina) can correlate with the severity of the underlying heart disease. This correlation explains the adverse association of ST-T wave changes with prognosis in these patients. In contrast, a normal resting ECG is a more favorable long-term prognostic sign in patients with suspected or definite CAD.

Interval ECGs may reveal the development of Q wave MIs that have gone unrecognized clinically. Various conduction disturbances, most frequently left bundle branch block (LBBB) and left anterior fascicular block, may occur in patients with SIHD. They are often associated with impairment of LV function, reflect multivessel CAD, and are an indicator of a relatively poor prognosis. Various arrhythmias, especially premature ventricular contractions (PVCs), may be present on the ECG, but these also have low sensitivity and specificity for accurately detecting CAD. LV hypertrophy on the ECG is associated with a worse prognosis in patients with chronic stable angina. This finding implies the presence of underlying hypertension, aortic stenosis, hypertrophic cardiomyopathy, or previous MI with remodeling and warrants further evaluation, such as echocardiography to assess LV size, wall thickness, and function.

During an episode of angina pectoris, ECG findings become abnormal in 50% or more of patients with normal resting ECGs. The most common finding is ST-segment depression, although ST-segment elevation and normalization of previous resting ST-T wave depression or inversion (pseudonormalization) may develop. Ambulatory ECG monitoring (see later, Silent Myocardial Ischemia) provides a quantitative estimate of the frequency and duration of ischemic episodes during routine activities; however, its sensitivity for detecting CAD is less than that of exercise electrocardiography.

Resting Echocardiogram

Assessment of global LV function is one of the most valuable aspects of echocardiography. Identification of regional wall motion abnormalities may be suggestive of CAD, whereas other findings such as valvular stenosis or pulmonary hypertension may suggest alternative diagnoses. U.S. and European guidelines differ notably regarding recommendations for routine echocardiography in patients with SIHD. European Society of Cardiology (ESC) guidelines recommend routine echocardiography (class I, level of evidence [LOE]: B) for patients with SIHD,[27] whereas American College of Cardiology/American Heart Association (ACC/AHA) guidelines do not recommend routine echocardiography for all patients with angina pectoris (class III, LOE: C); rather, echocardiography is recommended for patients with a history of MI, ST-T wave abnormalities, or conduction defects or Q waves on the ECG (class I, LOE: B).[28] We also believe echocardiography is appropriate for patients with persistent elevation in cardiac biomarkers such as BNP (or NT-proBNP) or cardiac troponin (cTn).

Chest Radiograph (See Chapter 15)

The chest roentgenogram is generally within normal limits in patients with SIHD, particularly if they have normal findings on the resting ECG and have not experienced MI. If present, cardiomegaly is indicative of severe CAD with previous MI, preexisting hypertension, or an associated nonischemic condition such as concomitant valvular heart disease or cardiomyopathy.

Stress Testing (See Chapters 13, 14, and 16)

Noninvasive stress testing can provide useful and often indispensable information to establish the diagnosis and estimate the prognosis in patients with suspected stable angina. However, indiscriminate use of such tests yields limited incremental information beyond that provided by the physician's detailed and thoughtful clinical assessment. Appropriate application of noninvasive tests requires consideration of bayesian principles, which state that the negative and positive predictive values of any test are defined not only by its sensitivity and specificity but also by the prevalence of disease (or pretest probability) in the population under study. Noninvasive testing should be performed only if the incremental information provided by a test is likely to alter the planned management strategy. The value of noninvasive stress testing is greatest when the pretest likelihood is intermediate because the test result is likely to have the greatest effect on the post-test probability of CAD and thus on clinical decision making.

Traditionally, the pretest probability of CAD has been estimated using a classification scheme developed by Diamond and Forrester over 40 years ago that incorporates age, sex, and whether symptoms are typical, atypical, or nonanginal. However, the performance of this classification scheme has been diminished by changing risk factor profiles, leading to substantial overestimation of the probability of obstructive CAD in contemporary cohorts.[29,30] Two newer algorithms for predicting CAD have been developed by a European consortium and calibrated in more modern cohorts. These two CAD consortium scores—a basic score (**Table 61.1**) and a more detailed clinical score—are now recommended in the ESC guidelines on the management of SIHD.[27] A head-to-head comparison of the Diamond-Forrester and CAD consortium scores demonstrated substantial improvement in the prediction of obstructive CAD with the two newer scores, suggesting that use of these scores could reduce unnecessary referrals for diagnostic testing.[31]

TABLE 61.1

Pretest Likelihood of Coronary Artery Disease (CAD) in Symptomatic Patients According to Age, Sex, and Symptom Quality

AGE (yr)	NONANGINAL PAIN		ATYPICAL ANGINA		TYPICAL ANGINA	
	Women (%)	Men (%)	Women (%)	Men (%)	Women (%)	Men (%)
30-39	5	18	10	29	28	59
40-49	8	25	14	38	37	69
50-59	12	34	20	49	47	77
60-69	17	44	28	59	58	84
70-79	24	54	37	69	68	89
>80	32	65	47	78	76	93

Modified from Genders TS et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. Eur Heart J 2011;32(11):1316-30.

Exercise Electrocardiogram (See Chapter 13)

Diagnosis of Coronary Artery Disease.

The exercise ECG is particularly helpful in patients with chest pain syndromes who are considered to have a moderate probability of CAD and in whom the resting ECG is normal, provided that they are capable of achieving an adequate workload.[32] Although the incremental diagnostic value of exercise testing is limited in patients in whom the estimated prevalence of CAD is high or low, the test provides useful additional information about the degree of functional limitation in both groups of patients and

about the severity of ischemia and prognosis in patients with a high pretest probability of CAD. Interpretation of the exercise test should include consideration of the patient's exercise capacity (duration and metabolic equivalents) and clinical, hemodynamic, and electrocardiographic responses.

Asymptomatic Persons.

Exercise testing in asymptomatic individuals without known CAD is not usually recommended. Exercise testing may be appropriate for asymptomatic individuals at high cardiac risk who plan to begin vigorous exercise, those with high-risk professions (e.g., airline pilots), and those with evidence of extensive atherosclerosis on other noninvasive testing, such as severe coronary calcifications on cardiac computed tomography (CT).

Risk Stratification.

One of the most important and consistent prognostic markers is maximal exercise capacity, regardless of whether it is measured by exercise duration or by workload achieved or whether the test was terminated because of dyspnea, fatigue, or angina.[23] After adjustment for age, the peak exercise capacity measured in metabolic equivalents is among the strongest predictors of mortality in patients with CVD. Other factors identified with exercise treadmill testing associated with a poor prognosis in patients with SIHD include the presence and magnitude of ST depression, and abnormal HR and BP response.

Regardless of the severity of symptoms, patients with high-risk stress test results have a high likelihood of CAD and, if they have no obvious contraindications to revascularization, should undergo coronary arteriography.[33] Such patients, even if asymptomatic, are at risk for left main or triple-vessel CAD, and many have impaired LV function. By contrast, patients with clearly negative exercise test results, regardless of symptoms, have an excellent prognosis that cannot usually be improved by revascularization. If they do not have other high-risk features or refractory symptoms, coronary arteriography is not generally indicated. Similarly, patients in whom objective evidence of mild ischemia (e.g., 1-mm ST-segment depression) develops at a high workload (e.g., >9 to 10 minutes on a Bruce protocol) may not necessarily warrant coronary arteriography before an adequate trial of medical therapy is first administered.

Influence of Antianginal Therapy.

Antianginal therapy may reduce the sensitivity of exercise testing as a screening tool. If the purpose of the exercise test is to *diagnose* ischemia, it should be performed, if possible, in the absence of antianginal medications, particularly long-acting beta-blocking agents, which should be omitted for 2 to 3 days before testing. For long-acting nitrates, calcium antagonists, and short-acting beta blockers, discontinuing use of the medications the day before testing usually suffices. If the test is being performed for *risk stratification* in a patient with known CAD, discontinuation of medications is not necessary.

Controversy Regarding the Routine Use of Adjunctive Imaging *(see later, **Nuclear Cardiology Techniques** and **Stress Echocardiography**)*.

Important differences exist between U.S. and European guidelines regarding the routine addition of adjunctive imaging to exercise stress testing. In the U.S. guidelines, a regular exercise ECG is recommended to be considered first in patients with chest pain and a normal resting ECG for screening and detection of CAD, whereas in the European guidelines, stress imaging is recommended as the initial test option if local expertise and availability permit.[27] These differences reflect differing interpretations of exercise-ECG studies and their limitations, as well as the cost-effectiveness of routine imaging. The European guideline authors highlight the problem of verification bias, by which the sensitivity of exercise ECG may be artificially inflated and specificity decreased when only patients with positive exercise tests are referred for coronary angiography. When studies with verification bias are not included

(including those using CT angiography), the sensitivity and specificity of exercise ECG change from approximately 70% to 75% sensitivity and specificity to 50% sensitivity and 90% specificity (**Table 61.2**).

TABLE 61.2

ACC/AHA 2012 and ESC 2013 Guidelines: Selected Sensitivity and Specificity of Noninvasive Tests for Detection of Coronary Artery Disease (CAD)

	SENSITIVITY		SPECIFICITY	
	ACC/AHA 2012	ESC 2013	ACC/AHA 2012	ESC 2013
Exercise ECG	0.68	0.45-0.50*	0.77	0.85-0.90*
Echocardiography				
Exercise or pharm	0.76		0.88	
Exercise		0.80-0.85		0.80-0.88
Pharm		0.79-0.83		0.82-0.86
Single-Photon Emission Computed Tomography				
Exercise or pharm	0.88		0.77	
Exercise		0.73-0.92		0.63-0.87
Pharm		0.90-0.91		0.75-0.84
Positron Emission Tomography				
Exercise or pharm	0.91		0.82	
Pharm		0.81-0.97		0.74-0.91
Cardiac Magnetic Resonance Imaging				
Dobutamine		0.79-0.88		0.82-0.86
Vasodilator		0.67-0.94		0.61-0.85
CCTA		0.95-0.99		0.64-0.93

*Corrected for referral bias.

CCTA, Coronary computed tomographic angiography; Pharm, pharmacological.

American College of Cardiology/American Heart Association (ACC/AHA) 2012 estimates modified from Garber and Solomon, 1999.

European Society of Cardiology (ESC) 2013 estimates were collated from multiple studies and modified from Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the Management of Stable Coronary Artery Disease of the European Society of Cardiology. Eur Heart J 2013;34:2949-3003.

Sex Differences in Exercise Testing for Diagnosis of CAD *(see Chapters 13 and 89)*.

On the basis of earlier studies that indicated a much higher frequency of false-positive stress test results in women than in men, it is generally accepted that electrocardiographic stress testing is not as reliable in women.[32,34] However, the prevalence of CAD in women in the patient populations under study was low, and the lower positive predictive value (PPV) of an exercise ECG in women can be accounted for, in large part, on the basis of bayesian principles (**see Table 61.1**). Once men and women are stratified appropriately according to the pretest prevalence of disease, the results of stress testing are similar, although the specificity is probably slightly less in women. Exercise imaging modalities have greater diagnostic accuracy than exercise electrocardiography in men and women.[35] Nevertheless, the standard exercise stress test is recommended by the ACC/AHA as the initial stress test of choice in most patients who can exercise, including women. Again, the ESC guidelines favor use of adjunctive cardiac imaging. In support of the U.S. recommended approach, a trial of symptomatic women randomly assigned to exercise ECG or single-photon emission computed tomography (SPECT) perfusion imaging demonstrated no difference in the 2-year rate of MACE but significantly lower costs with the exercise ECG strategy.[36]

Nuclear Cardiology Techniques (See Chapter 16)

Stress Myocardial Perfusion Imaging.

Exercise myocardial perfusion imaging (MPI) with simultaneous ECG recording is generally considered to be superior to an exercise ECG alone in detecting CAD, in identifying multivessel CAD, in localizing

diseased vessels, and in determining the magnitude of ischemic and infarcted myocardium. Exercise SPECT yields higher sensitivity and specificity than exercise electrocardiography alone (**see Table 61.2**).[37]

Stress MPI is particularly helpful in the diagnosis of CAD in patients with abnormal resting ECGs and in those in whom ST-segment responses cannot be interpreted accurately, such as patients with repolarization abnormalities caused by LV hypertrophy and those receiving digitalis. Because stress MPI is a relatively expensive test (three to four times the cost of an exercise ECG) and is associated with radiation exposure, stress MPI should *not* be used as a screening test in patients in whom the prevalence of CAD is low.[38]

MPI with Pharmacologic Vasodilator Stress.

For patients unable to exercise adequately, pharmacologic vasodilator stress with adenosine derivatives (and rarely dipyridamole) may be used. As a general rule, a patient should be able to walk up two flights of stairs without stopping in order to complete a standard exercise stress test. The need for pharmacologic stress should be considered for patients who are older or have claudication, pulmonary disease, orthopedic problems, or severe obesity. In most nuclear cardiology laboratories, vasodilator studies account for approximately 40% to 50% of those referred for perfusion imaging. Although the diagnostic accuracy of pharmacologic vasodilator stress perfusion imaging is comparable to that achieved with exercise perfusion imaging (**see Table 61.2**), treadmill testing is preferred for patients who are capable of exercising because the exercise component of the test provides additional diagnostic and prognostic information, including ST-segment changes, effort tolerance, symptomatic response, and HR and BP response (**Table 61.3**). For patients unable to tolerate adenosine or regadenoson, dobutamine MPI can be performed.

TABLE 61.3

Risk Stratification Based on Noninvasive Testing

High Risk (>3% Annual Risk for Death or Myocardial Infarction)
1. Severe resting left ventricular dysfunction (LVEF <35%) not readily explained by noncoronary causes
2. Resting perfusion abnormalities involving ≥10% of the myocardium without previous known MI
3. High-risk stress findings on the ECG, including • ≥2-mm ST-segment depression at low workload or persisting into recovery • Exercise-induced ST-segment elevation • Exercise-induced VT/VF
4. Severe stress-induced LV dysfunction (peak exercise LVEF <45% or drop in LVEF with stress ≥10%)
5. Stress-induced perfusion abnormalities encumbering ≥10% of the myocardium or stress segmental scores indicating multiple vascular territories with abnormalities
6. Stress-induced LV dilation
7. Inducible wall motion abnormality (involving >2 segments or 2 coronary beds)
8. Wall motion abnormality developing at a low dose of dobutamine (≤10 mg/kg/min) or at a low heart rate (<120 beats/min)
9. Multivessel obstructive CAD (≥70% stenosis) or left main stenosis (≥50% stenosis) on CCTA
Intermediate Risk (1-3% Annual Risk for Death or Myocardial Infarction)
1. Mild to moderate resting LV dysfunction (LVEF of 35% to 49%) not readily explained by noncoronary causes
2. Resting perfusion abnormalities involving 5-9.9% of the myocardium in patients without a history or previous evidence of MI
3. ≥1-mm ST-segment depression occurring with exertional symptoms
4. Stress-induced perfusion abnormalities encumbering 5-9.9% of the myocardium or stress segmental scores indicating 1 vascular territory with abnormalities but without LV dilation
5. Small wall motion abnormality involving 1-2 segments and only 1 coronary bed
6. 1-vessel CAD with ≥70% stenosis or moderate CAD stenosis (50-69% stenosis) in ≥2 arteries on CCTA
Low Risk (<1% Annual Risk for Death or Myocardial Infarction)
1. Low-risk treadmill score (score ≥5) or no new ST-segment changes or exercise-induced chest pain symptoms when achieving maximal levels of exercise
2. Normal or small myocardial perfusion defect at rest or with stress encumbering <5% of the myocardium*
3. Normal stress or no change in limited resting wall motion abnormalities during stress
4. No coronary stenosis >50% on CCTA

*Although the published data are limited, patients with these findings will probably not be at low risk in the presence of either a high-risk treadmill score or severe resting LV dysfunction (LVEF <35%).

CCTA, Cardiac computed tomography angiography; *LVEF,* left ventricular ejection fraction; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia.

Assessment of coronary artery calcium (CAC) can also be used to contribute to risk assessment.

Modified from Fihn SD, Gardin JM, Abrams J, ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation 2012;126:e354.

Vasodilator stress agents are also used with positron emission tomography (PET) to diagnose CAD and determine its severity (**see Chapter 16**). PET is associated with improved diagnostic accuracy compared with SPECT (**see Table 61.2**),[39] as well as lower radiation dose because of the shorter half-life of the radiotracers typically used. However, PET is less widely available. Both SPECT and PET are valuable for assessing myocardial viability in patients with regional or global LV dysfunction and thus may be useful to help identify candidates with ischemic cardiomyopathy who will most benefit from revascularization (see later, Myocardial Hibernation).

High-Risk Findings on MPI.

The prognostic value of stress MPI is now well established. In particular, the ability of MPI to identify patients at low (<1% with a normal MPI study), intermediate (1% to 5%), or high (>5%) risk for future cardiac events is valuable in patient management decisions (**Table 61.3**). The prognostic data obtained from MPI, including LV ejection fraction (EF) as well as the size and distribution of perfusion abnormalities, are incremental to clinical and treadmill exercise data in predicting future cardiac events.[37]

Stress Echocardiography (See Chapter 14).

Two-dimensional echocardiography is useful for the evaluation of patients with chronic CAD because it can be used to assess global and regional LV function under basal conditions and during ischemia, as

well as to detect LV hypertrophy and associated valve disease. Stress echocardiography may be performed with exercise or pharmacologic stress and allows detection of regional ischemia by identifying wall motion abnormalities induced by ischemia. Adequate images can be obtained in more than 85% of patients, and the test is highly reproducible in expert centers. Numerous studies have shown that exercise echocardiography can detect the presence of CAD with an accuracy similar to that of stress MPI and is superior to exercise electrocardiography alone (**see Table 61.2**).[40] Stress echocardiography is also valuable in localizing and quantifying ischemic myocardium. Limitations imposed by poor visualization of endocardial borders in a sizable subset of patients have been reduced by use of myocardial contrast agents, three-dimensional imaging, and strain-rate echocardiography (**see Chapter 14**). Although less expensive than nuclear perfusion imaging, stress echocardiography is more expensive than and not as widely available as exercise electrocardiography. Pharmacologic stress with dobutamine is an effective alternative for patients unable to exercise.

As with perfusion imaging, stress echocardiography also provides important prognostic information about patients with known or suspected CAD. The presence or absence of inducible regional wall motion abnormalities and the response of the EF to exercise or pharmacologic stress provide incremental prognostic information to that provided by the resting echocardiogram. Moreover, a negative stress echocardiographic result portends a low risk for future events (<1% per person-year; **see Table 61.3**).

Computed Tomography (See Chapter 18)

Cardiac CT has made substantial advances as a noninvasive approach to imaging atherosclerosis and its consequences.[41,42] In addition to being a highly sensitive method for detecting coronary calcification, which is a good marker of the total coronary atherosclerotic burden, cardiac CT can also provide angiography of the coronary arterial tree and quantification of ventricular function. Emerging applications allow assessment of myocardial perfusion and even functional assessment of the hemodynamic significance of coronary stenoses (fractional flow reserve).[43,44]

Coronary artery calcification (CAC) can be detected with a rapid noncontrast CT that utilizes only low doses of ionizing radiation. CAC screening does not have a role in the diagnosis of obstructive CAD in symptomatic patients with a high pretest probability of CAD. However, screening of *asymptomatic* individuals at intermediate risk for CAD events may be reasonable in selected individuals, because a high calcium score may reclassify an individual as being at higher risk and thereby lead to more intense risk factor modification.[43] Routine CAC screening in low-risk individuals is not recommended.

As an alternative to noncontrast CT to identify coronary calcification, coronary computed tomographic angiography (CCTA) can be used to diagnosis CAD in patients with an indication for diagnostic testing.[45] CT technology has progressed such that in select individuals, high-quality images of the coronary arteries may be obtained at relatively low overall radiation exposure. Consequently, CCTA may be reasonable in symptomatic patients at intermediate risk for CAD after initial evaluation, in particular, those with indeterminate results of stress testing.[46] The accuracy of CCTA for estimating the severity of luminal stenosis is limited in patients with tachycardia unable to be controlled adequately with beta blockers, heavy coronary calcification, or in the region of previously placed coronary stents. Sensitivity and specificity of CCTA compare favorably to other noninvasive techniques (**see Table 61.2**).

In a randomized trial of 10,003 symptomatic patients without known CAD, CCTA was compared with functional testing as an initial evaluation strategy. Clinical outcomes and costs were similar in the CCTA and functional testing arms over a median follow-up of 2 years (**Fig. 61.4**). Patients randomized to CCTA underwent more cardiac catheterizations but were less likely to be found to have no obstructive disease

on invasive angiography.[30] An important finding from this study was the low rate of CV events in both treatment arms, highlighting the possibility that deferral of all testing may be reasonable for many lower-risk individuals.

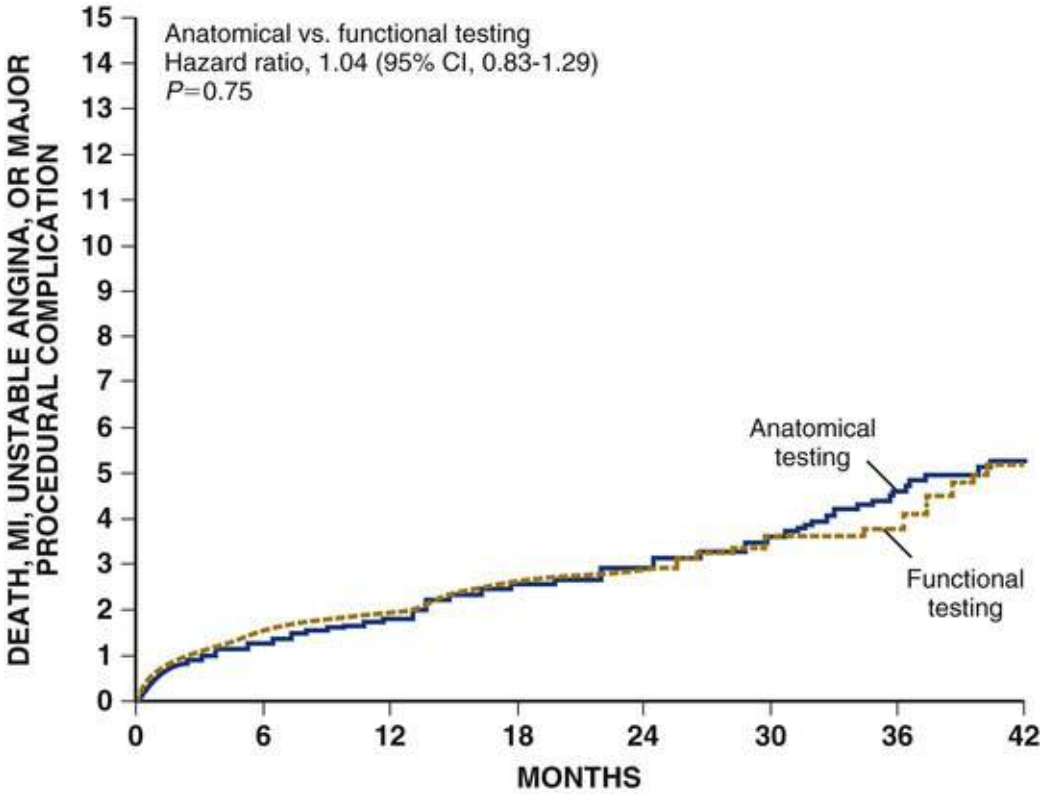


FIGURE 61.4 Outcome of patients with symptoms suggestive of coronary artery disease undergoing initial anatomic versus functional testing. Among 10,003 patients randomized to a strategy of anatomic testing (coronary computed tomographic angiography) or to functional testing (exercise electrocardiography, nuclear stress testing, or stress echocardiography), the composite primary end point of death, myocardial infarction (MI), hospitalization for unstable angina, or major procedural complication did not differ between the two diagnostic strategies (Modified from Douglas PS, Hoffman U, Patel MR et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 2015;372:1298.)

Stress myocardial CT perfusion imaging is an emerging technique that provides both anatomic and physiologic information that can be combined with CCTA in a single protocol with a radiation dose similar to that of nuclear perfusion imaging.[47,48] In a study of 381 patients across 16 centers, CT perfusion imaging sensitivity and specificity for the diagnosis of CAD (≥50% stenosis) were 88% and 55%, respectively, compared with 62% and 67% for SPECT, with overall superior accuracy for CT (0.74 versus 0.64; $P = 0.001$).[45]

In experienced centers with advanced technology, CT has also been used to characterize plaque composition and, when paired with PET in a hybrid PET/CT scanner, can offer an assessment of coronary anatomy concurrent with information regarding myocardial blood flow and metabolism.[49] Nevertheless, the capacity of CT for determination of plaque composition is currently not sufficient for routine application.[50,51] Fractional flow reserve (FFR) can also now be estimated from CT angiogram images using complex computational algorithms (CTA-FFR), but these currently require off-line processing using proprietary software. The PLATFORM study compared patient care guided by CTA plus CTA-FFR versus usual care and reported a reduction in the probability of finding no obstructive CAD in the group who underwent CTA-FFR before angiography.[44] Further technological enhancements will be required before CTA-FFR is suitable for routine clinical use.

Currently, the clinical strength of CCTA remains its ability to exclude significant CAD with a high NPV. The rapid pace of innovation and clinical investigation of cardiac CT is likely to lead to further evolution of its role and integration into the assessment and management of SIHD.[44]

Cardiac Magnetic Resonance Imaging (See Chapter 17)

CMR is established as a valuable clinical tool for imaging the aorta and cerebral and peripheral arterial vasculature and is evolving as a versatile noninvasive cardiac imaging modality that has multiple applications in patients with SIHD. Clinical use of CMR for assessment of myocardial viability has grown because of evidence demonstrating its ability to predict functional recovery after percutaneous or surgical revascularization and its very good correlation with PET. Pharmacologic stress perfusion imaging with CMR compares favorably with SPECT (**Table 61.2**) and also offers accurate characterization of LV function, as well as delineation of patterns of myocardial disease that are often useful in discriminating ischemic from nonischemic myocardial dysfunction.[52]

Because of its ability to visualize arteries in three dimensions and differentiate tissue constituents, CMR has received interest as a method to characterize arterial atheroma and assess vulnerability to rupture on the basis of compositional analysis. Characterization of arterial plaque has been achieved in the aorta and carotid arteries in humans and has been shown to be predictive of subsequent vascular events.[53] Moreover, CMR coronary angiography is established as a modality to characterize congenital coronary anomalies (**see Chapter 75**) and has shown promise in detecting stenoses in the proximal and middle segments of major epicardial vessels or surgical bypass grafts.

Invasive Assessment

Catheterization, Angiography, and Coronary Arteriography

The clinical examination and noninvasive techniques described earlier are extremely valuable in establishing the diagnosis of CAD and are indispensable to the overall assessment of patients with this condition. Currently, however, precise assessment of the anatomic severity of CAD still requires invasive coronary arteriography (**see Chapters 19 and 20**). Nevertheless, it should be remembered that myocardial ischemia may occur in the absence of epicardial CAD (see later, Chest Pain with a Normal Coronary Arteriogram).[1,2] In patients with chronic stable angina referred for coronary arteriography, older series suggested that approximately 25% each had single-, double-, or triple-vessel anatomically significant CAD (i.e., >70% luminal diameter narrowing). From 5% to 10% had obstruction of the left main coronary artery, and in approximately 15%, no critical obstruction was detectable. In a contemporary report from the National Cardiovascular Data Registry (NCDR) that included almost 400,000 patients without known CAD, the proportion of individuals who reported angina but had no obstructive disease on coronary angiography was much higher, approaching 50%.[54]

LV function can be assessed by contrast ventriculography (**see Chapter 19**). Global abnormalities in LV systolic function are reflected by elevations in LV end-diastolic and end-systolic volume and depression of the EF. These changes are nonspecific, however, and can occur in many forms of heart disease. Abnormalities in regional wall motion (e.g., hypokinesis, akinesis, dyskinesis) are more characteristic of CAD.

High-Risk Findings from Coronary Angiography.

The independent impact of multivessel CAD and LV dysfunction and their interaction on the prognosis of patients with CAD is well established (**Fig. 61.5**).

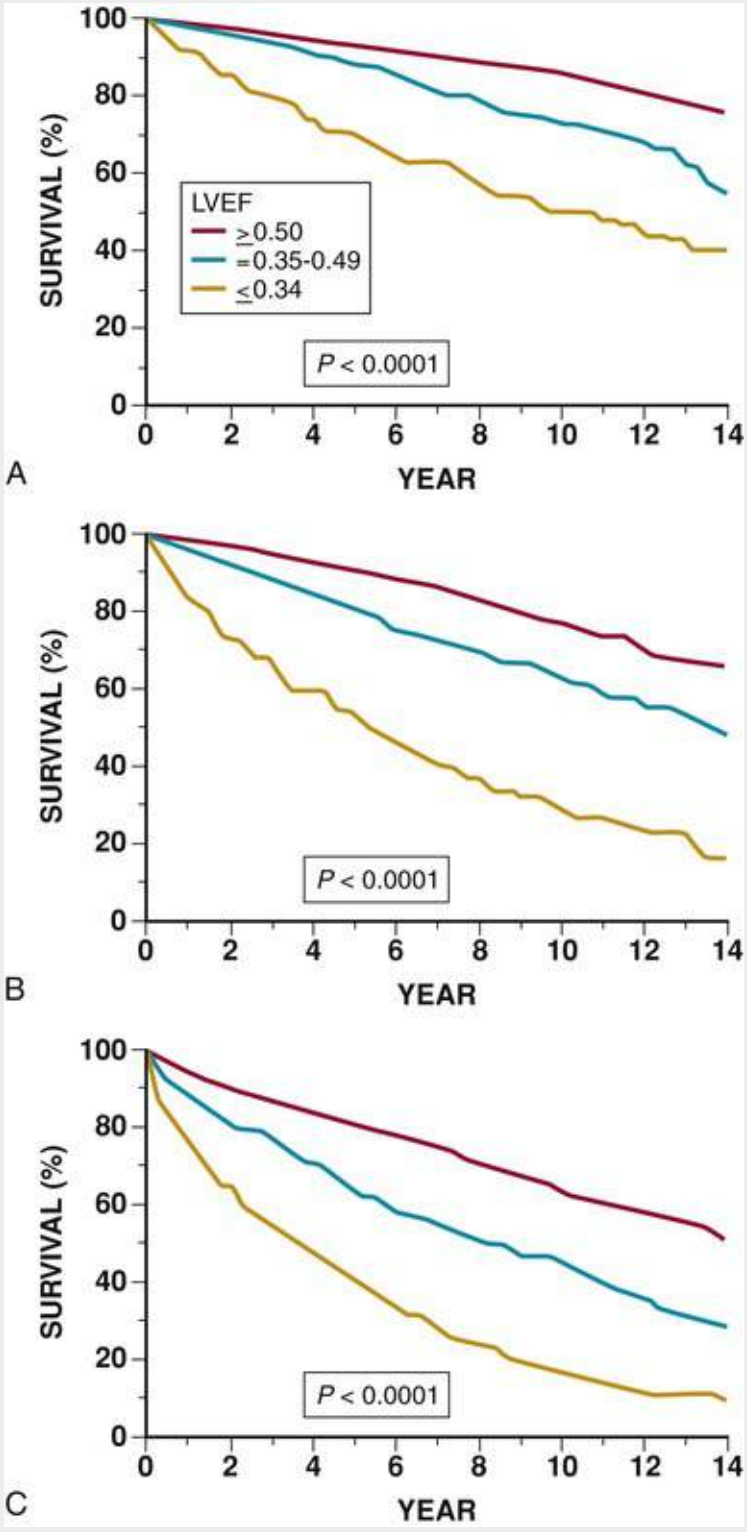
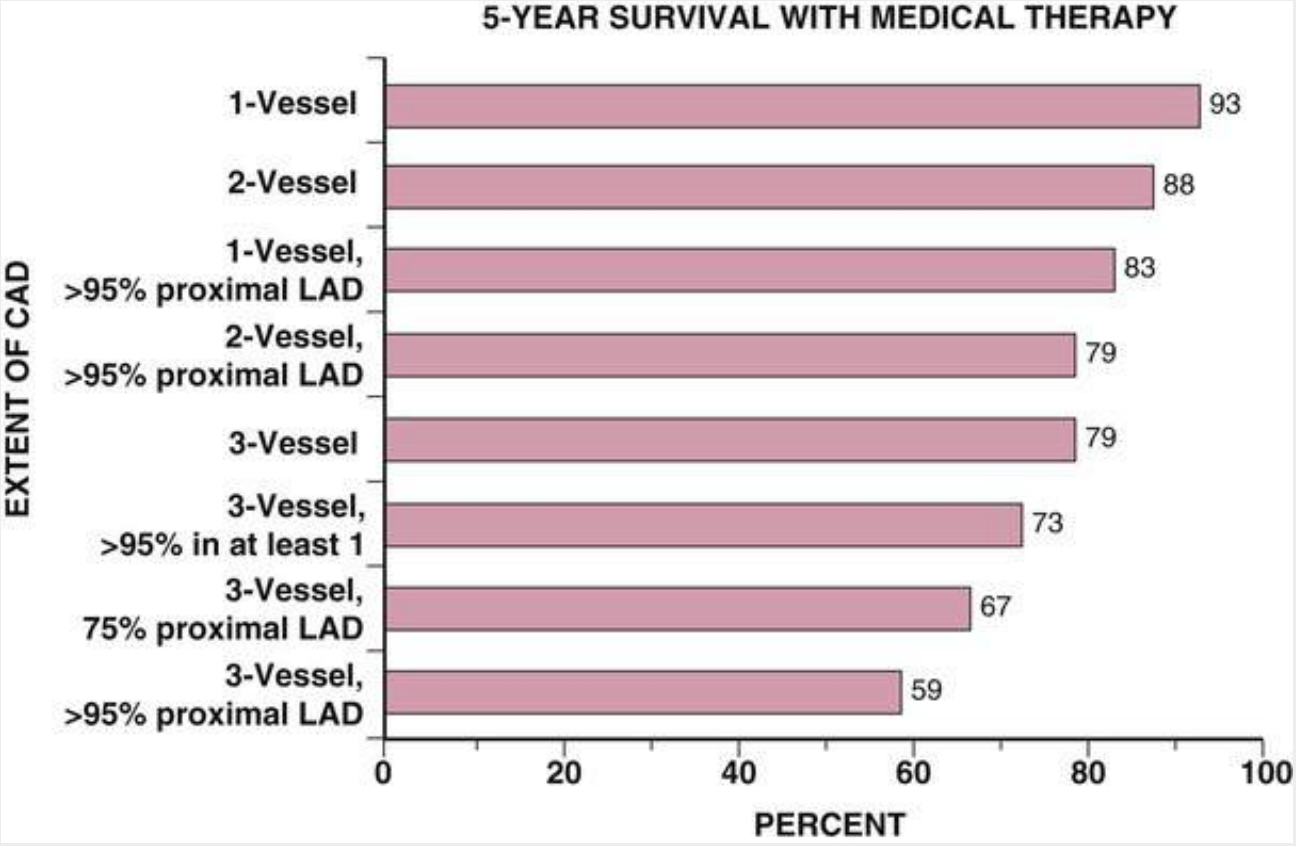


FIGURE 61.5 Graphs showing survival of medically treated patients in CASS stratified by normal, moderately, or severely reduced left ventricular ejection fraction (LVEF). **A,** Patients with single-vessel coronary disease. **B,** Patients with double-vessel coronary disease. **C,** Patients with triple-vessel coronary disease. (From Emond M, Mock MB, Davis KB, et al. Long-term survival of medically treated patients in the Coronary Artery Surgery Study [CASS] Registry. Circulation 1994;90:2651.)

Extent of Coronary Artery Disease.

Although several indices have been used to quantify the extent or severity of CAD, the simple

classification of disease into single-, double-, or triple-vessel or left main CAD is the most widely used and is effective. Additional prognostic information is provided by the severity of the obstruction and its location, whether proximal or distal. The concept of the gradient of risk is illustrated in **eFig. 61.2**. The importance to survival of the quantity of myocardium that is jeopardized is reflected in the observation that an obstructive lesion proximal to the first septal perforating branch of the left anterior descending (LAD) coronary artery was associated with a 5-year survival rate of 90%, versus 98% in patients with more distal lesions. More sophisticated scoring systems, such as the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score, capture a more detailed assessment of the full extent and severity of epicardial CAD.[55]



EFIGURE 61.2 Angiographic extent of coronary artery disease (CAD) and subsequent survival with medical therapy. A gradient of mortality risk is established based on the number of diseased vessels and the presence and severity of disease of the proximal left anterior descending (LAD) coronary artery. (Data from Califf RM, Armstrong PW, Carver JR, et al. Task Force 5. Stratification of patients into high-, medium-, and low-risk subgroups for purposes of risk factor management. J Am Coll Cardiol 1996;27:964.)

High-grade lesions of the left main coronary artery or its equivalent, as defined by severe proximal LAD and proximal left circumflex CAD, are particularly life threatening. In natural history studies before the era of aggressive coronary revascularization, mortality in medically treated patients with severe left main CAD was reported to be 29%, with a 3-year mortality rate as high as 59% in patients with left main stenosis greater than 70%.

Limitations of Angiography.

Coronary angiography provides information principally about the degree of luminal stenosis of the coronary arteries. However, the pathophysiologic significance of coronary stenoses lies in their impact on resting and exercise-induced blood flow and their potential for plaque rupture with superimposed thrombotic occlusion. Coronary angiography is not a reliable indicator of the functional significance of

stenosis. Furthermore, coronary angiographic determinants of the severity of stenosis are based on a decrease in the caliber of the lumen at the site of the lesion relative to adjacent reference segments, which are considered, often erroneously, to be relatively free of disease. This approach may lead to significant underestimation of the severity and extent of atherosclerosis. The recent evolution in invasive diagnostics that frequently include measurement of FFR to assess the functional severity of lesions and to guide revascularization is an important step addressing this limitation of coronary angiography.

The most serious limitation to the routine use of coronary angiography for prognosis in patients with SIHD is its inability to identify which coronary lesions can be considered to be at high risk, or vulnerable, for future events, such as MI or sudden cardiac death (SCD). Although it is widely accepted that MI is the result of thrombotic occlusion at the site of plaque rupture or erosion (**see Chapter 58**), it is clear that it is not necessarily the plaque causing the most severe stenosis that subsequently ruptures. Lesions causing mild obstruction can rupture, thrombose, and occlude, thereby leading to MI and SCD. In fact, two thirds to three quarters of all acute MIs emanate from antecedent coronary stenoses that involve less than 50% of the luminal diameter. Approaches to quantifying the extent of CAD, inclusive of nonobstructive lesions, appear to offer additional prognostic information.

In summary, angiographic documentation of the extent of CAD provides useful information for assessment of the patient's risk for death and future ischemic events and is an indispensable step in the selection of patients for coronary revascularization, particularly if the interaction among the anatomic extent of disease, LV function, and severity of ischemia is taken into account. However, angiography often underestimates the burden of coronary atherosclerosis and is not helpful in predicting sites of subsequent plaque rupture or erosion that can precipitate MI or SCD. Additional tools that improve structural and functional assessment of coronary stenoses are discussed next.

Advanced Structural Coronary Imaging

Advanced invasive imaging techniques such as intravascular ultrasonography (IVUS) provide a more comprehensive evaluation of the coronary wall and have substantially enhanced the detection and quantification of coronary atherosclerosis, as well helping to characterize the vulnerability of coronary atheroma to rupture[56,57] (**see Chapter 20**). Studies incorporating both coronary angiography and IVUS have demonstrated that IVUS detects the presence of atherosclerosis missed by angiography alone. Although clinical use of IVUS for assessment of borderline stenoses has been largely supplanted by FFR measurement, IVUS continues to have a role in assessing left main coronary stenoses and bifurcation lesions and in optimizing stent deployment.[58] Virtual-histology (VH) IVUS uses ultrasound backscatter data to identify plaque components, including calcification, fibrous, and fibrofatty tissue. In several studies, VH-IVUS–defined thin-capped fibroatheroma (VH-TCFA) was associated with future MACE.[59,60]

Intravascular optical coherence tomography (OCT) is a light-based technology that provides much higher-resolution images of the coronary atheroma (10 to 15 μ versus 100 to 150 μ with IVUS), but penetration is limited to 1 to 3 mm in depth. OCT is particularly useful for measuring fibrous cap thickness and assessing coronary dissections and endothelial coverage of stent struts. Coronary angioscopy and thermography are exclusively research tools that have not emerged as clinically useful.[23,61,62]

Functional Assessment

Fractional flow reserve has emerged as the most important invasive tool to complement coronary angiography, providing a functional assessment of the hemodynamic impact of a coronary stenosis. The

measurement is simple to perform and highly reproducible. The primary role of FFR is in guiding decisions regarding percutaneous coronary intervention (PCI) for stenoses that appear intermediate in severity on angiography. FFR is determined as the ratio of pressure distal to a stenosis to pressure before the stenosis under conditions of maximal hyperemia, which is usually achieved with adenosine (**see Fig. 62.1**). For practical purposes, the proximal pressure measurement is performed in the aorta using a guiding catheter. A stenosis with FFR values less than 0.75 is highly likely to be associated with ischemia on nuclear perfusion imaging, whereas stenoses with FFR greater than 0.8 are rarely associated with ischemia. FFR of 0.75 to 0.8 represents a "gray zone." Recently a new measurement, the instantaneous wave free ratio (iFR), has been developed that allows characterization of the hemodynamic significance of coronary stenoses without administration of adenosine. This technique measures the gradient across a coronary stenosis at a point in diastole when microvascular resistance is minimal and stable.[62a]

Additional options for functional assessment include measurement of *coronary flow reserve* (maximum flow divided by resting flow) and endothelial function. These measurements frequently produce abnormal results in patients with CAD and play an important role in detecting microvascular dysfunction, particularly in those without obstructive epicardial disease.[63-65] The *index of microcirculatory resistance* (IMR) is a newer tool to interrogate the coronary microcirculation.[66,67] IMR incorporates the measured pressure gradient divided by coronary flow, is easier to perform than coronary flow reserve, and can be performed simultaneously with FFR using the same equipment. (See later, Patient Selection for Revascularization, and **Chapters 57 and 62**.)

Other Angiographic Findings

Coronary Artery Ectasia and Aneurysms.

Patulous aneurysmal dilation involving most of the length of a major epicardial coronary artery is present in approximately 1% to 3% of patients with obstructive CAD at autopsy or angiography. Most coronary artery ectasia and aneurysms are caused by coronary atherosclerosis (50%), and the rest are caused by congenital anomalies and inflammatory conditions such as Kawasaki disease.[68] Despite the absence of overt obstruction, 70% of patients with multivessel fusiform coronary artery ectasia or aneurysms have demonstrated evidence of cardiac ischemia.

Coronary ectasia should be distinguished from discrete coronary artery aneurysms, which are almost never found in arteries without severe stenosis, are most common in the LAD coronary artery, and are usually associated with extensive CAD. These discrete atherosclerotic coronary artery aneurysms do not appear to rupture and do not warrant resection.

Coronary Collateral Vessels *(see Chapter 20)*.

Provided that they are of adequate size, collateral vessels may protect against MI when total occlusion occurs. In patients with abundant collateral vessels, MI size is smaller than in patients without collaterals, and total occlusion of a major epicardial artery may not lead to LV dysfunction. In patients with chronic occlusion of a major coronary artery but without MI, collateral-dependent myocardial segments show almost normal baseline blood flow and O_2 consumption but severely limited flow reserve. This finding helps explain the ability of collateral vessels to protect against resting ischemia but not against exercise-induced angina.

Myocardial Bridging.

Bridging of coronary arteries is observed during coronary angiography at a rate of less than 5% in otherwise angiographically normal coronary arteries and ordinarily does not constitute a hazard.

Occasionally, compression of a portion of a coronary artery by a myocardial bridge can be associated with clinical manifestations of myocardial ischemia during strenuous physical activity and may even result in MI or initiate malignant ventricular arrhythmias. In an autopsy study, increased myocardial bridge thickness and length, as well as proximal vessel location, correlated with increased risk for MI, proposed to result from promotion of proximal atherosclerosis.[69] The functional consequences of myocardial bridging may be characterized with intracoronary Doppler measurements or MPI (**see Chapter 20**).

Natural History and Risk Stratification

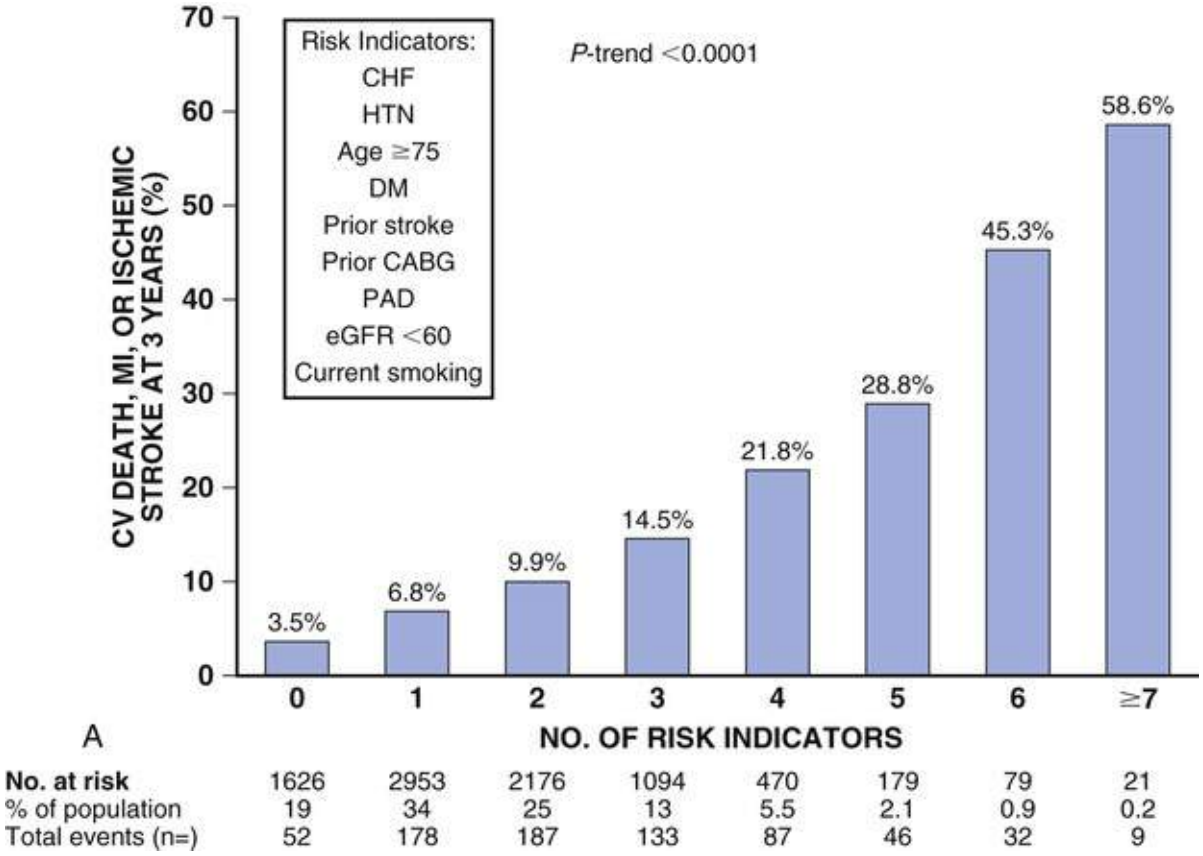
Up to 30% of patients with a history of stable angina experience angina one or more times per week. Stable angina is associated with physical limitation and worse quality of life. The frequency of reported angina varies substantially between providers, suggesting significant heterogeneity in identifying, characterizing, and managing angina.[70] Women have a similar incidence of stable angina as men, and angina in both sexes is associated with higher risk for mortality than is seen in the general population. Data from the Framingham Study, obtained before the widespread use of aspirin, beta-blocking agents, and aggressive modification of risk factors, revealed an average annual mortality rate of 4% in patients with SIHD. The combination of these treatments has improved the prognosis, with a current annual mortality rate of 1% to 3% and a rate of major ischemic events of 1% to 2%. For example, among 38,602 outpatients with SIHD enrolled in the REACH Registry, the 1-year rate of CV death was 1.9% (95% confidence interval [CI] 1.7% to 2.1%), that of all-cause mortality was 2.9% (95% CI 2.6% to 3.2%), and that of CV death, MI, or stroke was 4.5% (95% CI 4.2% to 4.8%).[71,72] Clinical, noninvasive, and invasive tools are useful for refining the estimated risk in individual patients with SIHD. Moreover, noninvasively acquired information is valuable in identifying patients who are candidates for invasive evaluation with cardiac catheterization.

Risk Stratification and Risk Models

Risk stratification is an integral component of the assessment and management of patients with SIHD. Risk assessment should be considered an iterative process, by which the estimation of risk is continually updated as new clinical or test information becomes available or symptoms change. Clinical characteristics, including older age, male sex, diabetes mellitus (DM), previous MI, and the presence of symptoms typical of angina, are predictive of the presence of CAD and associated with a higher risk of MACE in patients with SIHD.[23] A number of studies have attested to the adverse prognostic implications of heart failure (HF) in patients with SIHD. The severity of angina, especially the tempo of intensification, and the presence of dyspnea are also important predictors of outcome. Each of the noninvasive and invasive tests that assesses the extent of CAD, burden of ischemia, and LV function also provides powerful prognostic information (see later).

Several risk scores that integrate widely available clinical risk indicators have been developed to aid in prognostication with the aim of directing follow-up and therapeutic decision making. Patients with SIHD and prior MI vary in their risk for recurrent CV events. The Thrombolysis in Myocardial Ischemia (TIMI) Risk Score for Secondary Prevention (TRS 2°P) is a pragmatic integer score based on nine routinely assessed clinical characteristics—age, DM, hypertension, smoking, peripheral arterial disease (PAD), prior stroke, prior coronary artery bypass grafting (CABG), history of HF, and renal dysfunction—that exhibited a clear graded relationship with the risk for CV death, MI, or ischemic stroke in a population of 8598 patients with established coronary or peripheral atherosclerosis (**Fig. 61.6A**).[73] Also,

this risk score identified a pattern of increasing absolute benefit from treatment with the novel platelet inhibitor vorapaxar. In a second validation cohort in the IMPROVE IT trial of ezetimibe, the TRS 2°P performed similarly for risk stratification and also identified patients with a significantly greater absolute and relative risk reduction with the addition of ezetimibe to simvastatin (**Fig. 61.6B**).[74] Although the discriminatory capacity of the TRS 2°P was only moderate (C-statistic, 0.68) in both datasets, the demonstrated role for estimating benefit from more than one specific therapy lends clinical relevance.



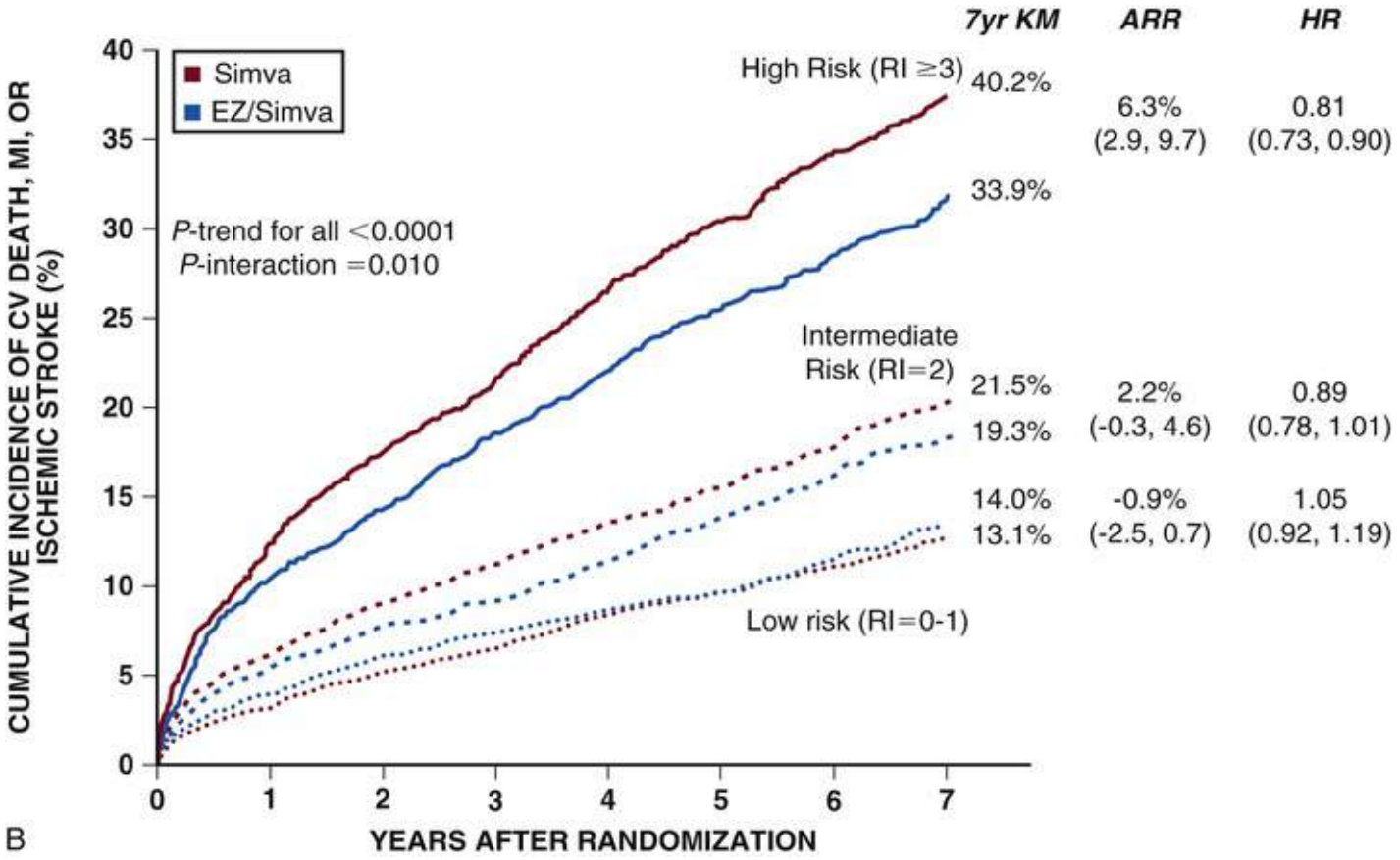


FIGURE 61.6 The TIMI Risk Score for Secondary Prevention. This risk score (http://www.timi.org/index.php?page=trs2p) was developed as a pragmatic nine-variable risk stratification tool among 8589 stable patients with a history of prior myocardial infarction (MI), prior stroke, or symptomatic peripheral artery disease (PAD). **A,** The 3-year risk of cardiovascular (CV) death, MI, or ischemic stroke is shown by risk score group along with the proportion of the development population that fell within each group. CABG, Coronary artery bypass grafting; CHF, Coronary heart disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HTN, hypertension. **B**, The risk score was applied prospectively to 17,717 patients stabilized after an acute coronary syndrome and randomized to ezetimibe/simvastatin (EZ/Simva) or simvastatin (simva) alone. The cumulative incidence of CV death, MI, or ischemic stroke is shown by risk category and treatment group, demonstrating a pattern of increasing benefit of ezetimibe with higher risk categories defined by the score. ARR, absolute risk reduction; HR, hazard ratio; KM, Kaplan-Meier event rate; RI, risk index. (**A,** From Bohula EA et al. Atherothrombotic risk stratification and the efficacy and safety of vorapaxar in patients with stable ischemic heart disease and previous myocardial infarction. Circulation 2016;134:304-13; **B,** from Bohula EA et al. Atherothrombotic risk stratification and ezetimibe use in IMPROVE-IT. J Am Coll Cardiol 2016;67:2129.)

In addition, two risk scores have been developed for patients who have undergone PCI to aid in decision making regarding the use of dual-antiplatelet therapy (DAPT).[75,76] The DAPT risk score estimates net clinical outcome (balancing reductions in ischemia with increases in bleeding) with extending the duration of DAPT from 12 to 30 months after stenting.[76] The PARIS risk score was developed as a weighted integer score to predict new coronary thrombotic events (MI or stent thrombosis) in patients who had undergone PCI. The PARIS risk variables are consistent with the TRS 2°P, including PCI for ACS, revascularization before the qualifying PCI, DM, renal dysfunction, and current smoking. Patients are stratified into three bins of coronary thrombotic risk ranging from 1.8% to 10% at 2 years.[75]

Medical Management

Comprehensive management of SIHD has five aspects: (1) identification and treatment of associated diseases that can precipitate or worsen angina and ischemia, (2) reduction of coronary risk factors, (3)

application of pharmacologic and nonpharmacologic interventions for secondary prevention, (4) pharmacologic management of angina, and (5) revascularization by PCI or CABG, when indicated. Although discussed individually in this chapter, all five of these approaches must be considered, often simultaneously, in each patient. Of the medical therapies, aspirin, statins, and angiotensin-converting enzyme (ACE) inhibitors have been shown to reduce mortality and morbidity in patients with SIHD. Other therapies, such as nitrates, beta blockers, calcium antagonists, and ranolazine, have been shown to improve symptoms and exercise performance, but their effect, if any, on survival in patients with SIHD has not been demonstrated.[77]

In stable patients with LV dysfunction following MI, ACE inhibitors and beta-blocking agents reduce both mortality and the risk for repeat MI, and these agents are recommended in all such patients, with or without chronic angina, along with aspirin, statins, and in select individuals, aldosterone antagonists.

Treatment of Associated Diseases

Several common medical conditions that can increase myocardial O_2 demand or reduce O_2 delivery may contribute to the onset of new angina pectoris or exacerbation of previously stable angina. Such conditions include anemia, occult thyrotoxicosis, fever, infections, and tachycardia. Cocaine can cause acute coronary spasm and MI. In patients with CAD, by causing cardiac dilation, HF, increases in filling pressures, or tachyarrhythmias, including sinus tachycardia, can increase myocardial O_2 need and increase the frequency and severity of angina. Identification and treatment of these conditions are critical to the management of SIHD.

Reduction of Coronary Risk Factors

Hypertension (See Chapters 46 and 47)

Epidemiologic links between increased blood pressure and CAD severity and mortality are well established. For individuals 40 to 70 years of age, risk for IHD doubles for each 20–mm Hg increment in systolic BP across the entire range of 115 to 185 mm Hg.[78] Hypertension predisposes to vascular injury, accelerates the development of atherosclerosis, increases myocardial O_2 demand, and intensifies ischemia in patients with preexisting obstructive CAD. Although the relationship between hypertension and CAD is linear, LV hypertrophy is a stronger predictor of MI and CAD death than is the actual degree of BP increase. A meta-analysis of clinical trials of treatment of mild to moderate hypertension has shown a statistically significant 16% reduction in CAD events and mortality in patients receiving antihypertensive therapy. This treatment effect is almost twice as great in older as in younger persons. It is logical to extend these observations about the benefits of antihypertensive therapy to patients with established CAD. Moreover, the number of individuals treated to avoid one death is lower in patients with established CV disease. Therefore, BP control is an essential component of the management of patients with SIHD, with a goal of less than 140/90 mm Hg.[78-80] However, there is also evidence for a “J” shaped risk relationship, reflecting adverse outcomes in patients who achieve a very low BP on therapy. Therefore, in patients who have CAD with evidence of myocardial ischemia, the BP should be lowered slowly and, given concern of an increase risk at low ranges of diastolic BP, it is recommended to avoid diastolic BP below 60 mm Hg in elderly patients. Newer and emerging options for the treatment of hypertension are discussed in **Chapter 47**.[81]

Although there has been an assumed incremental risk for increased CV events in hypertensive patients with SIHD and a belief that more intensive BP lowering would reduce clinical events, the data from

randomized trials examining systolic BP targets below 140 mm Hg have had mixed results. Among patients with SIHD and DM, the ACCORD-BP study did not reveal an additional benefit of lowering systolic BP below 120 mm Hg in type 2 DM patients compared with lowering BP to less than 140 mm Hg.[5,82] However, in a trial of 9361 patients with hypertension and a high risk indicator other than DM, patients randomized to a systolic BP target of less than 120 mm Hg compared with below 140 mm Hg had a significantly reduced rate of the primary endpoint of ACS, stroke, HF, or death (1.65%/yr versus 2.19%/yr; hazard ratio [HR], 0.75; 95% CI 0.64 to 0.89) as well as all-cause mortality (HR, 0.73; 95% CI 0.60 to 0.90).[83]

Cigarette Smoking

Smoking remains one of the most powerful risk factors for the development of CAD in all age-groups (**see Chapter 45**). In patients with CAD, cigarette smokers have a higher 5-year risk for SCD, MI, and all-cause mortality than do those who have stopped smoking. Cigarette smoking may be responsible for aggravating angina other than through the progression of atherosclerosis. It may increase myocardial O_2 demand and reduce coronary blood flow by means of an alpha-adrenergically mediated increase in coronary artery tone and thereby cause acute ischemia. Moreover, passive exposure to cigarette smoke has adverse CV effects that are almost as great as those of active smoking. Smoking cessation lessens the risk for MACE in patients with established CAD and is one of the most effective and cost-saving approaches to prevention of disease progression.[79,84] Strategies for smoking cessation are discussed in **Chapter 45**.[85] Studies of nicotine medications and smokeless tobacco suggest that the risks of nicotine without tobacco combustion products are low compared with cigarette smoking, but are still of concern in people with CVD. The health implications of electronic cigarette use are as yet incompletely understood.[86]

Management of Dyslipidemia (See Chapter 48)

Clinical trials in patients with established atherosclerotic vascular disease have demonstrated a significant reduction in subsequent CV events in patients with a wide range of serum cholesterol and LDL cholesterol levels treated with statins. In the aggregate, angiographic trials of cholesterol lowering in patients with chronic CAD have shown that its effects on coronary obstruction are modest in comparison to the substantive reduction in CV events, thus suggesting that regression of atherosclerosis is not the primary mechanism of benefit. Nonetheless, in angiographic trials using IVUS, intensive statin therapy has led to regression of coronary atherosclerotic burden. Furthermore, several, but not all, studies have shown that statins significantly improve endothelium-mediated responses in the coronary and systemic arteries of patients with hypercholesterolemia or known atherosclerosis.

Lipid lowering with statins has been shown to reduce circulating levels of hsCRP, decrease thrombogenicity, and favorably alter the collagen and inflammatory components of arterial atheroma; these effects do not appear to correlate well with the change in serum LDL cholesterol level and suggest anti-atherothrombotic properties of statins. These pleiotropic properties may contribute to plaque stabilization, improvement in blood flow, reduction of inducible myocardial ischemia, and a decrease in coronary events in patients treated with statins.

Results from secondary prevention trials of patients with a history of SIHD, unstable angina, or previous MI have provided convincing evidence that effective lipid-lowering therapy significantly improves overall survival and reduces CV mortality in patients with CAD, regardless of baseline cholesterol levels. Moreover, trials in patients with established IHD have provided evidence of greater

reduction in MACE with intensive-dose compared with moderate-dose statin therapy. The 2013 ACC/AHA guidelines for cholesterol management advocate high-intensity statin therapy in all patients with established IHD who are younger than 75 years, in the absence of contraindications, with less emphasis on specific LDL target goals than in prior cholesterol guidelines.[87-89]

Since these 2013 guidelines were published, several additional studies of LDL-lowering agents other than statins have been completed. Among 18,144 patients stabilized after an ACS and who had a baseline LDL cholesterol (LDL-C) level between 50 to 100 mg/dL and were randomized to simvastatin (40 mg) plus ezetimibe or simvastatin (40 mg) alone, the addition of ezetimibe lowered the composite of CV death, MI, unstable angina requiring hospitalization, or coronary revascularization by a relative 6.4% (2% absolute difference at 7 years; $P = 0.016$).[90] In addition, combined analyses of multiple small trials of PCSK9 inhibitors with lipid lowering as the primary endpoint suggested that this class of agents that potently lowers LDL-C improved CV outcomes.[91,92] Subsequently, a randomized placebo-controlled trial of the PCSK9 inhibitor evolocumab in 27,564 patients with established atherosclerotic vascular disease demonstrated a 15% reduction in the composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization (3yr rate, 12.6% vs. 14.6%; P < 000.1).[92a] A decision pathway developed by the ACC recognizes that if a patient with known atherosclerotic vascular disease treated with a statin has a less-than-anticipated response (i.e., <50% reduction in LDL-C or on-treatment LDL-C ≥100 mg/dL, or LDL-C ≥70 mg/dL for those with additional risk indicators), additional clinical approaches are warranted. In our practice, we also continue to view achieving an LDL-C less than 70 mg/dL as optimal in patients with established IHD. After addressing adherence to a high-intensity statin regimen, the clinician should consider the addition of a nonstatin medication to the current regimen, weighing risks, benefits, costs, and preferences with the individual patient.[93]

Low High-Density Lipoprotein Cholesterol.

Patients with established CAD and low levels of HDL cholesterol (HDL-C) represent a subgroup at considerable risk for future coronary events, even when LDL-C is low.[94,95] Low HDL levels are often associated with obesity, hypertriglyceridemia, insulin resistance, and hypertension. The constellation of these findings—often referred to as metabolic syndrome—typically signifies the presence of small lipoprotein remnants and small, dense, LDL particles, which are thought to be particularly atherogenic (**see Chapter 48**). Therapies to raise HDL have focused on diet and exercise, as well as smoking cessation. Whether HDL itself should be a target for pharmacologic therapies remains a controversial question.[96] Data on fibric acid derivatives, which lower triglycerides and raise HDL, have provided conflicting results, and no benefit was seen in the most contemporary trial that combined fenofibrate with statin therapy.[97,98] Moreover, two randomized trials of extended-release niacin failed to show benefit when niacin was added to contemporary therapy, despite marked increases in HDL-C among niacin-treated patients.[99,100] A trial of extended-release niacin versus placebo in 3414 patients with atherosclerotic vascular disease who had low baseline levels of HDL (<40 mg/dL for men; <50 mg/dL for women) and well-controlled LDL-C values (<70 mg/dL) while taking a statin, with or without ezetimibe, found no incremental clinical benefit of the addition of niacin to statin therapy during a mean 3-year follow-up.[99] In addition, a secondary prevention trial involving 25,673 IHD patients (Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events) reported no significant reduction in a composite of major vascular events during a mean 4 years of treatment with simvastatin combined with extended-release niacin and laropiprant, a prostaglandin D_2 receptor-1 antagonist used to retard cutaneous flushing during niacin therapy, compared with statin-based therapy alone.[100]

Inhibitors of cholesterol ester transport protein (CETP) have also been disappointing. In two large

randomized trials, torcetrapib, a CETP inhibitor, increased HDL-C by 61% and reduced LDL-C by 20% but did not decrease progression of atherosclerosis and was associated with an increase in ischemic events, which may be explained by increased BP with torcetrapib.[101] In addition, a large outcomes trial of the CETP inhibitor dalcetrapib was stopped early because of a lack of clinically meaningful efficacy, and a multinational randomized trial of evacetrapib among 12,092 patients at high vascular risk demonstrated no effect on MACE compared with placebo.[102,103] In the last of this series of large outcomes trials with CETP inhibitors, among 30,449 patients with atherosclerosis followed for a median of 4.1 years, anacetrapib increased HDL by 104% and lowered LDL by 18% with a 1% absolute reduction in the risk of a major coronary event commensurate with the effect of lowering LDL without an additional benefit of raising HDL.[103a] Even though CETP inhibitors may raise plasma levels of HDL significantly, these agents can produce qualitatively dysfunctional, large HDL particles that may not be associated with a reduction in cardiac events. These trials have raised questions regarding the treatment of HDL-C as a target for secondary prevention.

Management of Diabetes Mellitus (See Chapter 51).

Patients with DM are at significantly higher risk for atherosclerotic vascular disease. Although a favorable impact of control of glycemia on microvascular complications of diabetes has been established, the effect on macrovascular complications (including CAD) is unclear. During a mean follow-up of 17 years in participants in the Diabetes Control and Complications Trial, patients with type 1 DM assigned to intensive glycemic therapy were at lower risk for CV complications. However, the results of studies of glycemic therapy with a shorter duration of follow-up, principally in patients with type 2 DM, are mixed.[104] Several large trials evaluating the effects of oral hypoglycemic agents on CV outcomes have shown no reduction in MACE.[105,106] Moreover, three large randomized trials comparing tight versus standard glucose control strategies failed to demonstrate benefit of more aggressive treatment. One of the trials, ACCORD (Action to Control Cardiovascular Risk in Diabetes) was stopped prematurely due to excess mortality in the group randomized to tight glucose control.[107] Thus, although a near-normal HbA_{1c} level (i.e., <7% [53 mmol/L]) is optimal to minimize microvascular complications, for older patients and those with preexisting CVD, a less stringent HbA_{1c} target of 8% or lower is recommended[108] Weight management, physical activity, BP control, and lipid management are recommended for all patients with SIHD and diabetes.[28,79]

Given reported CV risks of some oral hypoglycemic agents, the CV safety and efficacy of pharmacologic approaches to lowering blood glucose have garnered substantial attention from clinicians and researchers, particularly as new agents have become available. Guidance from U.S. and European regulatory authorities has required that large outcomes trials be performed to establish the CV safety of these new agents. Thus, new data are becoming available on the CV effects of these drugs, several of which have recently shown improvements in CV outcomes. The EMPA-REG Outcomes trial compared two doses of empagliflozin versus placebo in 7020 patients with type 2 DM and established CVD.[109] Empagliflozin is an inhibitor of sodium-glucose transporter 2 (SGLT2) that lowers blood glucose by promoting glucosuria; it also has diuretic and natriuretic effects. The primary endpoint of CV death, MI, or stroke was reduced by 14% in the combined empagliflozin groups, a finding driven by a 38% reduction in CV death (HR, 0.62; 95% CI 0.49 to 0.78; $P < 0.001$). Significant reductions were also seen in all-cause mortality (5.7 versus 8.3%; HR, 0.68; 95% CI 0.57 to 0.82) and HF hospitalization (HR, 0.65; 95% CI 0.50 to 0.85; $P < 0.001$). Similarly, canagliflozin lowered the rate of CV death, MI, or

stroke by 14% among 10,142 patients with diabetes and high cardiovascular risk.[109a] CV benefits have also emerged with the glucagon-like peptide-1 (GLP-1) GLP-1 agonist liraglutide. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results–A Long Term Evaluation (LEADER) trial, liraglutide reduced MACE by a relative 13% (HR, 0.87; 95% CI 0.78 to 0.97; $P < 0.001$) and CV death by 22% (HR, 0.78; 95% CI 0.66 to 0.93; $P = 0.007$) among 9340 patients with type 2 DM and elevated CV risk.[110] Semaglutide, a once-weekly administered GLP-1 agonist, was also shown to reduce the rates of CV death, MI, and stroke compared with placebo (HR, 0.74; 95% CI, .58 to 0.95; $P < 0.02$).[110a] Multiple other large cardiovascular outcomes studies are ongoing evaluating novel therapies for type 2 DM.

Estrogen Replacement.

In view of the collective data from randomized clinical trials, it is *not* advised that hormone replacement therapy be initiated or continued for secondary CV prevention in women with CAD (**see Chapter 89**).[28,79]

Exercise (see Chapter 54)

The conditioning effect of exercise on skeletal muscles allows a greater workload at any level of total-body O_2 consumption. By decreasing the HR at any level of exertion, higher cardiac output can be achieved at any level of myocardial O_2 consumption. The combination of these two effects of exercise conditioning permits patients with chronic stable angina to increase physical performance substantially following institution of a continuing exercise program.[111]

Most of the information about the physiologic effects of exercise and their effect on prognosis in patients with IHD has come from studies on patients entered into cardiac rehabilitation programs, many of whom previously sustained an MI. Less information is available on the benefits of exercise in patients with SIHD without a previous MI. Collectively, small randomized trials evaluating exercise training in patients with SIHD indicate improved effort tolerance, O_2 consumption, and quality of life and reduced evidence of ischemia on MPI.[111] In addition, exercise training reduced hospitalizations and revascularization procedures and was associated with favorable changes in inflammatory and hemostatic mediators of CV risk in proportion to the intensity of exercise. Whether exercise accelerates the development of collateral vessels in patients with chronic CAD is unclear.

Exercise is safe if increased gradually, and if survivors of MI can be used as a yardstick, it is probably cost-effective.[112] The psychological benefits of exercise are difficult to evaluate. However, a single nonrandomized study demonstrated significant improvement in well-being scores and positive affect scores, as well as a reduction in disability scores, in patients in a structured exercise program. Patients who are involved in exercise programs are also more likely to be health conscious, to pay attention to diet and weight, and to discontinue cigarette smoking. For all these reasons, patients should be urged to participate in regular exercise programs, usually walking, in conjunction with their drug therapy.[79,112]

Obesity (See Chapters 50 and 51)

Obesity is both an independent contributor to the risk for IHD and is associated with a constellation of other risk factors, including hypertension, dyslipidemia, and abnormal glucose metabolism. Weight loss can improve or prevent many of the metabolic consequences of obesity.[113,114] However, the association of obesity with outcomes among patients with established SIHD is complex, with the most favorable outcomes consistently seen among individuals with overweight or mild-moderate obesity, and worse

outcomes among normal-weight individuals and those with extreme obesity (body mass index [BMI] ≥40 kg/m^2).[115] The explanation for the "obesity paradox" by which mild-moderate obesity appears protective in observational studies has not been fully elucidated.

Inflammation (See Chapters 44 and 45)

Atherothrombosis has been recognized as an inflammatory disease.[116,117] Markers of systemic inflammation, of which hsCRP is the most extensively studied, identify patients with established vascular disease who are at higher risk for death and future ischemic events. Moreover, the lower levels of hsCRP achieved with statin therapy in patients with established IHD are associated with a better long-term prognosis.[118] Targeting of inflammation as a potential objective for therapeutic intervention in patients with IHD is discussed in **Chapter 48**. Additional research is ongoing to clarify whether inflammation should be a target for routine strategies of risk reduction or novel therapeutic agents in patients with atherosclerosis.[119] At least one adequately sized outcomes trial has demonstrated the potential for an agent specifically targeting inflammation for secondary prevention. In the randomized placebo-controlled Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS), canakinumab, a monoclonal antibody targeting interleukin-1β, reduced the composite of CV death, MI, or stroke at the cost of an increased rate of fatal infections (**see Chapter 48**).[22a]

Pharmacotherapy for Secondary Prevention

Aspirin *(see Chapters 45, 59, and 93)*.

Aspirin reduces the incidence of MACE in men and women with previous MI or stroke, and after CABG. Moreover, small studies have supported the benefit of aspirin in patients with chronic stable angina but without a history of MI.[28] Therefore administration of aspirin daily is advisable in patients with SIHD and no contraindications to this drug. Dosing at 75 to 162 mg daily appears to have comparable effects on secondary prevention as dosing at 160 to 325 mg daily and is associated with lower bleeding risk. Even among patients with intracoronary stenting, low-dose aspirin has been shown to be preferable to higher-dose aspirin. Thus, aspirin, 75 to 162 mg daily, is preferred for secondary prevention.[28]

Other Oral Platelet Inhibitors.

Other orally acting antiplatelet agents have been studied in patients with SIHD, including patients with or without a prior MI and patients managed with or without prior coronary stenting. Clopidogrel, a thienopyridine derivative, may be substituted for aspirin in patients with aspirin hypersensitivity or in those who cannot tolerate aspirin (**see Chapter 93**).[28] In a randomized comparison between clopidogrel and aspirin in patients with established atherosclerotic vascular disease (the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events [CAPRIE] trial), treatment with clopidogrel resulted in a modest 8.7% relative reduction in the risk for vascular death, ischemic stroke, or MI ($P = 0.043$) over 2 years. Studies evaluating the addition of adenosine diphosphate (ADP) receptor antagonists such as clopidogrel, prasugrel, and ticagrelor to aspirin in patients with ACS or after PCI have demonstrated important risk reductions. Therefore, DAPT combining aspirin with one of these agents is routine in patients with ACS. In contrast, the treatment of patients with SIHD with DAPT should be more individualized because the clinical data suggest important risk/benefit trade-offs.[120]

When studied in a population that included patients with clinically evident CVD ($n = 12,153$) or asymptomatic individuals with multiple risk factors ($n = 3284$) enrolled in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance) trial, the

addition of clopidogrel to aspirin showed no significant benefit with respect to the primary endpoint of CV death, MI, or stroke over a median of 28 months. However, in the large subgroup of those with established vascular disease, the addition of clopidogrel was associated with a 1% absolute reduction in these events (6.9% versus 7.9%; $P = 0.046$), thus supporting the hypothesis of a potential benefit from clopidogrel in patients with SIHD taking aspirin. In a subsequent study, patients were who had received a coronary stent were randomized to discontinuation of thienopyridine therapy at 12 months or continuation of DAPT through 30 months. Studied in this manner, continuation of long-term DAPT reduced the risk of death, MI, or stroke by 13% (absolute difference 1.6%) and stent thrombosis by 72% (absolute 1%) at the cost of a significant increase in bleeding (0.9%).[121] The balance of ischemia reduction and bleeding was more favorable among individuals in this trial who underwent PCI for an ACS event than those who underwent elective PCI.[122]

In a multinational randomized placebo-controlled trial (RCT) of ticagrelor in patients 1 to 3 years after a prior MI, whether managed medically or with revascularization, the addition of ticagrelor to aspirin reduced the rate of CV death, MI, or stroke, balanced against an increased rate of bleeding.[123] A combined analysis of these and other trials of long-term DAPT, predominantly in patients with prior ACS, revealed a significant reduction in CV mortality.[124] As such, treatment with long-term DAPT may be reasonable for patients at high risk of recurrent thrombosis, particularly those with a prior ACS event, provided they have an acceptable risk of bleeding.[120]

Importantly, patients at lower risk for ischemic events, including most patients undergoing PCI for SIHD symptoms who have not had a prior ACS, may not have a favorable balance of risk/benefit with extending the duration of DAPT. Indeed, some studies evaluating optimal DAPT duration for elective stenting for SIHD have suggested that *shorter* durations than 1 year are associated with similar ischemic outcomes along with expectedly lower rates of bleeding than longer durations of treatment.[125] As such, the most recent DAPT guideline from ACC/AHA recommends that the standard duration of DAPT be at least 6 months for most patients receiving stents for SIHD.[120] Risk scores weighing these competing risks for ischemic events and bleeding may be useful in decision making. Patients who are at higher risk of atherothrombotic events with acceptable bleeding risk may be considered for DAPT longer than 6 to 12 months.[73,75,76]

A large study of the oral platelet inhibitor vorapaxar has provided additional support that more potent antiplatelet therapy than aspirin alone reduces recurrent atherothrombosis in patients with SIHD who have had a prior MI. In a randomized, double-blinded, placebo-controlled trial of vorapaxar, an antagonist of the platelet-activating action of thrombin, vorapaxar reduced the risk for recurrent MACE in the overall trial; driven by a large subgroup of 17,779 patients enrolled with MI in the prior year.[126,127] However, a significant increase in the risk for bleeding with vorapaxar underscores the need for tailoring treatment to the individual patient based on the competing risks for increased thrombotic events versus increased bleeding.

Low-Dose Oral Anticoagulation.

When studied as therapy for secondary prevention in IHD, vitamin K antagonists reduced the risk of recurrent atherothrombotic events at a cost of significantly increased risk of bleeding. As a result of this risk and the challenges of long-term administration, vitamin K antagonists have not been routinely used for secondary prevention in SIHD. Direct oral anticoagulants offer the potential for a more favorable balance of efficacy and safety. In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, 27,2395 patients with established stable CAD or peripheral artery disease were randomized to treatment with rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once daily). Patients with CAD qualified for

participation with either a history of MI in the past 20 years or multivessel CAD. Patients with CAD who were <65 years of age were also required to have documentation of atherosclerosis involving at least two vascular beds or to have at least two additional risk factors (current smoking, diabetes mellitus, an estimated glomerular filtration rate <60 mL/min, heart failure, or nonlacunar ischemic stroke ≥1 month earlier). Patients with peripheral artery disease qualified with either prior lower extremity artery revascularization, symptomatic claudication with an abnormal diagnostic test for PAD, or documented carotid artery disease. Compared with aspirin alone, rivaroxaban 2.5 mg twice daily plus aspirin reduced the risk of CV death, MI, or stroke by 24% (HR, 0.76; 95% CI, 0.66 to 0.86; $P < 0.001$). Major bleeding was increased by the addition of rivaroxaban from 1.9% to 3.1% (HR, 1.70; 95% CI, 1.40 to 2.05; $P < 0.001$). However, there were fewer deaths overall in the rivaroxaban 2.5 mg twice daily plus aspirin group compared with aspirin alone (HR, 0.82; 95% CI, 0.71 to 0.96; nominal $P = 0.01$). Rivaroxaban 5 mg twice daily without aspirin did not significantly reduce the primary endpoint compared with aspirin alone. This result provides a clear demonstration of the benefit of low-dose anticoagulation with rivaroxaban as an option for secondary prevention in SIHD. However, COMPASS did not study patients receiving an ADP antagonist in any treatment arm. The roles of the available options for long-term antithrombotic therapy in addition to aspirin (e.g. ticagrelor, rivaroxaban, or vorapaxar) are likely to be refined with clinical experience, additional research, and review by professional society guidelines committees.[127a]

Patients with Other Indications for Chronic Oral Anticoagulation.

Patients with SIHD who have indications for treatment with oral anticoagulation (OAC), because of atrial fibrillation (AF), venous thromboembolic disease, or mechanical heart valves, present challenging decisions regarding management (**see Chapter 93**). As a result of prior ACS or coronary stenting, such patients usually have indications for one or two antiplatelet agents in addition to OAC. However, the addition of even a single antiplatelet agent increases major bleeding rates by more than 50%, whereas bleeding is more than doubled among those requiring “triple therapy” with OAC, aspirin, and clopidogrel.[128]

For patients with strong indications for OAC who are at relatively low ischemic risk (i.e., no recent MI or stent), it may be reasonable to omit antiplatelet therapy altogether, particularly if bleeding risk is increased.

For patients with AF, reassessment of the risks and benefits of OAC should be performed after considering the increased bleeding risk associated with combination therapy. For example, among patients at lower stroke risk, it may be preferable to defer OAC after MI and/or stenting and reinitiate OAC once the patient can safely be withdrawn from DAPT. When triple therapy is necessary, recommendations include (1) limiting exposure to triple therapy to the shortest possible duration, (2) targeting the lower range of international normalized ratio (INR) for warfarin, (3) avoiding the more potent $P2Y_{12}$ antagonism of prasugrel and ticagrelor (i.e., clopidogrel is preferred in combination with OAC), and (4) routinely administering proton pump inhibitors (PPIs) to prevent gastrointestinal (GI) bleeding.[129] In addition, a small trial has shown that withdrawing aspirin after coronary stenting is associated with favorable bleeding and efficacy compared with triple therapy.[130]

Two subsequent trials have further advanced this strategy using reduced dose direct oral anticoagulants. In the PIONEER AF-PCI trial, reduced dose rivaroxaban (15 mg) plus P2Y12 inhibitor, without aspirin, was associated with markedly lower major bleeding rates at 1 year than standard triple therapy with warfarin, aspirin, and P2Y12 inhibitor (16.8 vs 26.7%, $P < 0.001$).[130a] Similarly, in the RE-DUAL PCI trial, reduced dose daibigatran plus P2Y12 inhibitor (without aspirin) resulted in similar bleeding reduction at 1 year compared to the triple-therapy regimen with warfarin (15.4% vs 26.9%, $P <$

0.001).[130b] No differences in ischemic outcomes or stroke were observed for either of the less-intensive regimens. These findings suggest that for patients with atrial fibrillation undergoing PCI, dual therapy with an oral anticoagulant (preferably a reduced dose of a direct oral anticoagulant) and clopidogrel, without aspirin, provides the best balance of safety and efficacy.

Beta-Blocking Agents.

The value of beta adrenoceptor–blocking drugs (beta-blocking agents) in reducing death and recurrent MI in patients who have experienced MI is well established (**see Chapters 59 and 60**), as is their usefulness in the treatment of angina. However, the optimal duration of treatment after MI is not clear, particularly for patients without LV dysfunction. Moreover, whether these drugs are also of value in preventing MI and SCD in patients with SIHD without previous MI is less certain, and there have been no prospective controlled trials involving placebo.[131] Findings from observational studies are mixed, with one of the largest studies reporting no reduction in mortality in patients with SIHD receiving beta-blocking agents[132] (**Fig. 61.7**). However, such observational studies are limited by the high potential for uncontrolled confounding. Moreover, the favorable effects of beta blockers on ischemia and arrhythmias evident in randomized trials among patients with prior MI or reduced LVEF may extend to other patients with SIHD. Therefore, although the use of beta blockers as first-line therapy for uncomplicated hypertension has been questioned, it is sensible to use these drugs when angina, hypertension, or both are present in patients with SIHD and when these drugs are well tolerated.[28]

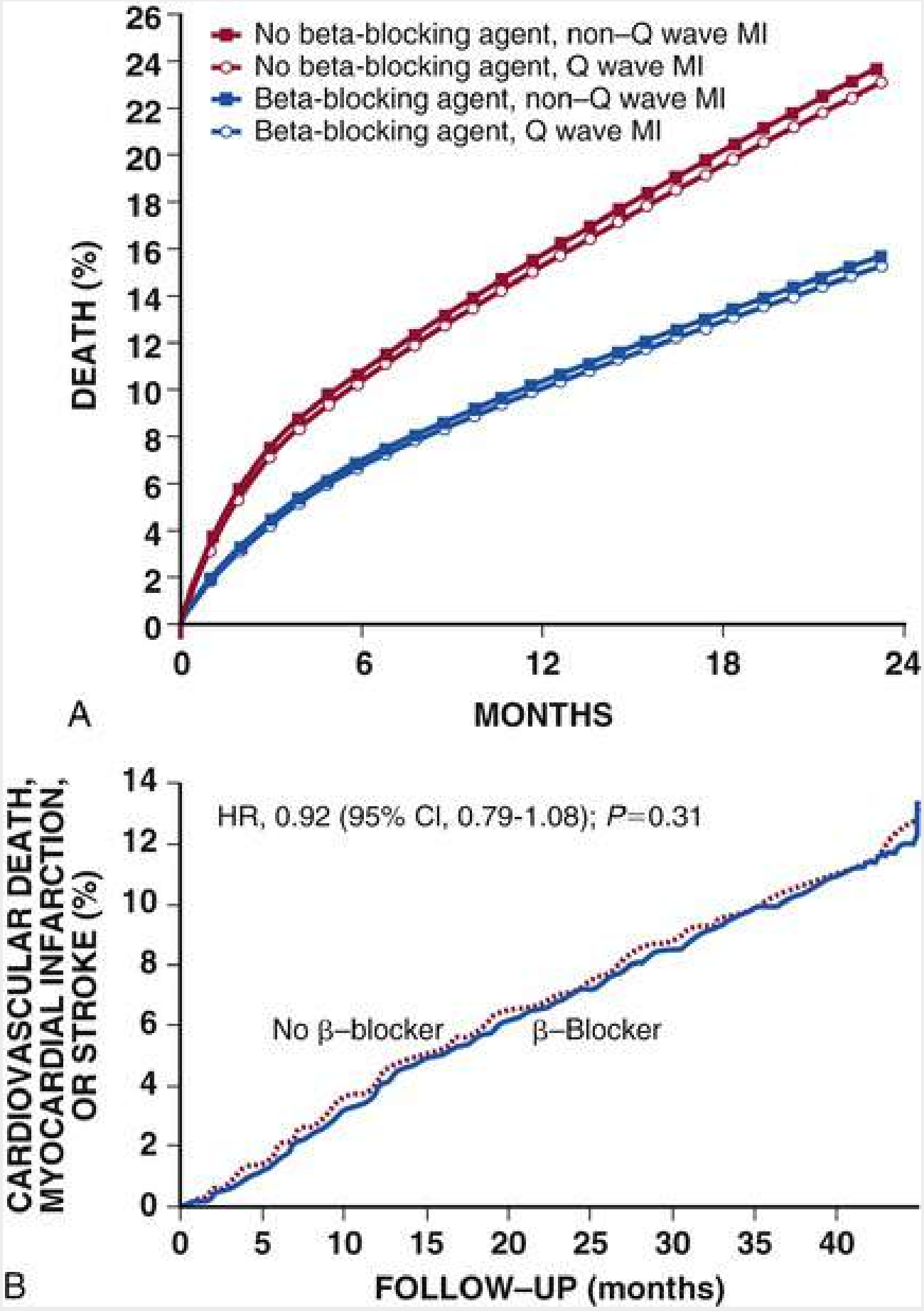


FIGURE 61.7 **A,** Assessment of the association between administration of a beta-blocking agent and the mortality rate in 201,752 individuals with previous myocardial infarction (MI) followed in a Medicare-based registry of patients discharged in 1994 to 1995 after MI. In patients with uncomplicated MI, prescription of a beta blocker was associated with a 40% relatively lower mortality rate. **B,** Longitudinal, observational study of patients in the REACH (Reduction of Atherothrombosis for Continued Health) registry in which a subgroup of 12,012 patients with known coronary artery disease (CAD) and no previous MI were monitored. In a propensity-matched analysis, the rate of cardiovascular death, MI, or stroke did not differ

between those treated with or without a beta blocker (*n* = 3599) in each matched group; hazard ratio (HR), 0.92; 95% CI 0.79 to 1.08; *P* = 0.31. (**A,** From Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. N Engl J 1998;Med 339:493; **B,** from Bangalore S et al. Beta-blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. JAMA2012;308:1340.)

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers.

Although inhibitors of the renin-angiotensin-aldosterone system (RAAS) are not indicated for the treatment of angina, these drugs appear to have important benefits in reducing the risk for future ischemic events in some patients with CVD.[28] Potentially beneficial effects of ACE inhibitors include reductions in LV hypertrophy, vascular hypertrophy, progression of atherosclerosis, plaque rupture, and thrombosis, in addition to a potentially favorable influence on myocardial O_2 supply-and-demand relationships, cardiac hemodynamics, sympathetic activity, and coronary endothelial vasomotor function. Furthermore, in vitro experiments have shown that angiotensin II induces inflammatory changes in human vascular smooth muscle cells and that treatment with ACE inhibitors can reduce signs of inflammation in animal models of atherosclerosis.

Two trials have provided strong evidence supporting the therapeutic benefit of ACE inhibitors in patients with normal LV function and absence of HF (**Fig. 61.8**). In the HOPE (Heart Outcomes Protection Evaluation) study, ramipril significantly decreased the risk for major vascular events by a relative 22% in 9297 patients with atherosclerotic vascular disease or DM. EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Stable CAD) similarly showed a 20% relative reduction in the risk for CV death, MI, or cardiac arrest in 13,655 patients with stable CAD in the absence of HF. In contrast, in the PEACE (Prevention of Events with Angiotensin Converting Enzyme Inhibition) trial, trandolapril showed no effect on the risk for CV death, MI, or coronary revascularization in 8290 patients with stable CAD and preserved LV function who were receiving intensive preventive therapy (**Fig. 61.8**).[28] ACE inhibitors are recommended for all patients with CAD and LV dysfunction and for those with hypertension, DM, or chronic kidney disease. ACE inhibitors may be considered for optional use in all other patients with SIHD, including those with a normal LVEF, well-controlled CV risk factors in whom revascularization has been performed.[28] Investigation to identify reliable indicators of which patients with SIHD will derive particular benefit from treatment is ongoing; such indicators include renal dysfunction, biomarkers of myocardial stress, and genetic polymorphisms.[21,133]

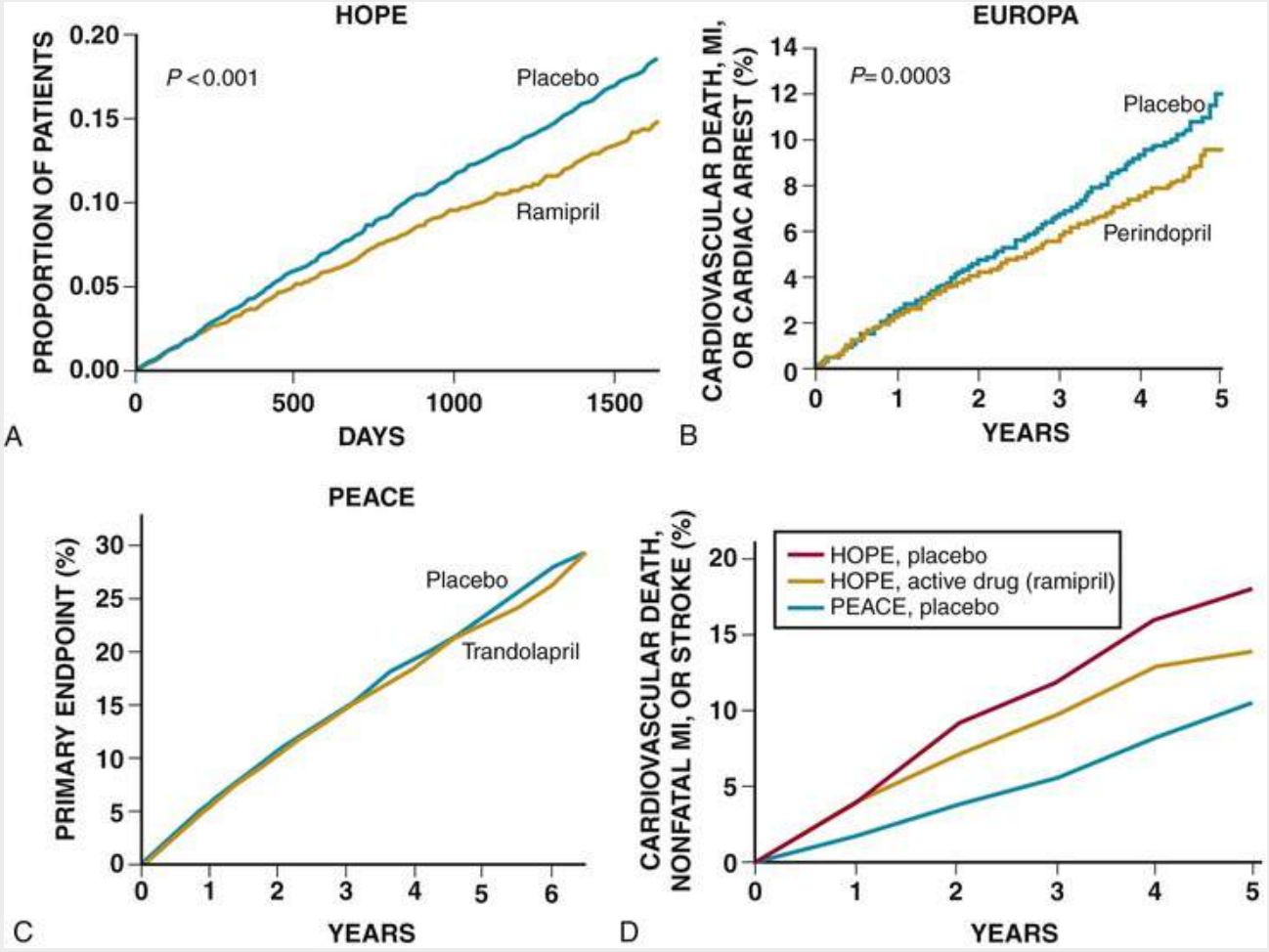


FIGURE 61.8 Kaplan-Meier time-to-event curves for the primary endpoint of three large randomized, placebo-controlled trials of angiotensin-converting enzyme (ACE) inhibitors for patients at high risk for or with established cardiovascular (CV) disease without heart failure. **A,** Cumulative incidence of CV death, MI, or stroke with ramipril versus placebo in patients in the HOPE trial. **B,** Cumulative incidence of CV death, MI, or cardiac arrest with perindopril or placebo in EUROPA. **C,** Cumulative incidence of CV death, MI, or coronary revascularization with trandolapril or placebo in the PEACE trial. **D,** Comparison of CV death, MI, or stroke in the HOPE and PEACE trials. The cumulative incidence of major CV events was lower in patients treated with placebo in the PEACE trial than in patients treated with ramipril in the HOPE trial. (**A,** From HOPE Study Investigators. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high risk patients. N Engl J Med 2000;342:145; **B,** from EUROPA Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized double-blind, placebo-controlled, multicenter trial [the EUROPA study]. Lancet 2003;363:782; and **C,** From PEACE Trial Investigators. Angiotensin-converting enzyme inhibition in stable coronary artery disease. N Engl J Med 2004;351:2058.)

In patients with established vascular disease or high-risk diabetes, angiotensin receptor blockers (ARBs) appear to provide similar secondary prevention benefits as ACE inhibitors and thus are suitable alternatives for patients intolerant of ACE inhibitors. However, ARBs should generally not be used in combination with ACE inhibitors because the combination provides no additional benefit over the individual agents and results in an increased rate of complications.[134]

Antioxidants and Vitamins *(see Chapter 44)*.

Oxidized LDL particles are strongly linked to the pathophysiology of atherogenesis, and observational studies have suggested that high dietary intake of antioxidant vitamins (A, C, and beta-carotene) and flavonoids (polyphenolic antioxidants), naturally present in vegetables, fruits, tea, and wine, is associated with a decrease in CAD events. However, in multiple large randomized trials of antioxidant supplements, including vitamin E, vitamin C, beta-carotene, folic acid, and vitamins B_6 and B_{12}, the risk for MACE was not reduced. Similarly, despite multiple observational studies suggesting that low levels of vitamin D are associated with increased CV risk, several randomized trials have failed to show

reduction in CV risk factors or subclinical disease with vitamin D supplementation.[135] Several additional large randomized trials are ongoing that should provide a clearer picture of the risks and benefits of vitamin D supplementation (www.clinicaltrials.gov; NCT01169259, NCT00736632). Thus, according to current evidence, there is no basis for recommending that individuals with IHD take supplemental folate, vitamin E, vitamins C, D, or E, or beta-carotene for the purpose of improving CV outcomes.[28]

Counseling and Changes in Lifestyle

The psychosocial issues faced by patients in whom stable angina develops are similar to, although usually less intense than, those experienced by patients with acute MI. Depressive symptoms are strongly associated with health status as reported by the patient, including the burden of symptoms and overall quality of life, independent of LV function and the presence of ischemia.[136] In addition, the association between depressive symptoms and IHD may reflect a causal relationship between the former and atherothrombosis inasmuch as depressive symptoms are associated with higher levels of circulating biomarkers of inflammation.[137] In conjunction with counseling, treatment with a selective serotonin reuptake inhibitor (SSRI) appears to be safe and effective in managing depression in patients with IHD.[138] Thus, efforts to evaluate and treat depression in patients with CAD are an important element of the overall management of such patients. Moreover, psychosocial stress at work, home, or both is associated with an increased risk for MI and may be a target for preventive interventions.[139] In a small RCT, physical exercise complemented antidepressant pharmacotherapy in reducing depressive symptoms.[140]

An important aspect of the physician's role is to counsel patients with respect to dietary habits, goals for physical activity, the types of work that they can do, and their leisure activities.[141] Certain changes in lifestyle may be helpful, such as modifying strenuous activities if they consistently and repeatedly produce angina. A history of CAD and stable angina is not inconsistent with the ability for physical exertion, which is important not only in regard to recreational activities and lifestyle, but also when some physical exertion is required in the patient's employment. However, isometric activities such as weightlifting and other activities such as snow shoveling, which involves an energy expenditure of 60% to 65% of peak O_2 consumption, and cross-country skiing may be undesirable. In addition, these latter activities expose the individual to the detrimental effects of cold on the O_2 demand-and-supply relationship.

Eliminating or reducing the factors that precipitate anginal episodes is of obvious importance. Patients learn their usual threshold by trial and error. Patients should avoid sudden bursts of activity, particularly after long periods of rest or inactivity, after meals, and in cold weather. Both chronic angina and unstable angina exhibit a circadian rhythm characterized by a lower angina threshold shortly after arising. The stress of sexual intercourse is approximately equal to that of climbing one flight of stairs at a normal pace or any activity that induces an HR of approximately 120 beats/min. Most patients with stable angina are able to continue satisfactory sexual activity. Patients with SIHD may use sildenafil and other phosphodiesterase inhibitors to treat impotence, but these agents cannot be used in conjunction with nitrates, since this combination may promote life-threatening hypotension.[142]

Although from a perspective of both quality of life and avoiding prolonged ischemia, it is desirable to minimize the number of bouts of angina, occasional angina is not to be feared. Indeed, unless patients occasionally reach their angina threshold, they may not appreciate the extent of their exercise capacity. An important dimension to effective angina control relates to the benefits of prophylactic use of short-acting nitrates (either sublingual nitroglycerin or nitrolingual pump spray). If there is a clear pattern of effort angina, prophylactic use of short-acting nitrates several minutes before engaging in the offending activity may provide sufficient vasodilation to prevent an anginal episode.

Pharmacologic Management of Angina

Beta Adrenoceptor–Blocking Agents

Beta-blocking agents constitute a cornerstone of therapy for angina.[143] In addition to their anti-ischemic properties, beta-blocking agents are modestly effective antihypertensives (**see Chapter 47**) and antiarrhythmics (**Chapter 36**). They have also been shown to reduce mortality and reinfarction in patients after MI (**Chapter 59**) and to reduce mortality in patients with HF with reduced EF (**Chapter 25**). Beta blockers reduce the frequency of anginal episodes and raise the anginal threshold, both when given alone and when added to other antianginal agents. This combination of actions makes them extremely useful in the management of SIHD.

The beneficial actions of these drugs depend on their ability to competitively inhibit the effects of neuronally released and circulating catecholamines on beta adrenoceptors (**Tables 61.4 and 61.5**). Beta blockade reduces myocardial O_2 requirements, primarily by slowing the HR; the slower HR in turn increases the fraction of the cardiac cycle occupied by diastole, with a corresponding increase in the time available for coronary perfusion (**Fig. 61.9; see also Table 61.4**). In addition, these drugs reduce exercise-induced increases in BP and limit exercise-induced increases in contractility. Thus, beta-blocking agents reduce myocardial O_2 demand primarily during activity or excitement, when surges of increased sympathetic activity occur. In the presence of impaired myocardial perfusion, the effects of beta blockers on myocardial O_2 demand may critically and favorably alter the imbalance between supply and demand and thereby mitigate ischemia.

TABLE 61.4

Effects of Antianginal Agents on Indices of Myocardial Oxygen Supply and Demand

Index	Nitrates	BETA-ADRENOCEPTOR–BLOCKING AGENTS				CALCIUM ANTAGONISTS		
		ISA		Cardioselective				
		No	Yes	No	Yes	Nifedipine	Verapamil	Diltiazem
Supply								
Coronary resistance								
Vascular tone	↓↓	↑	0	↑	0↑	↓↓↓	↓↓↓	↓↓↓
Intramyocardial diastolic tension	↓↓↓	↑	0	↑	↑	↓↓	0	0
Coronary collateral circulation	↑	0	0	0	0	↑	0	↑
Duration of diastole	0 (↓)	↑↑↑	0↓	↑↑↑	↑↑↑	0↑ (↓↓)	↑↑↑ (↓)	↑↑ (↓)
Demand								
Intramyocardial systolic tension								
Preload	↓↓↓	↑	0	↑	↑	↓0	↑0↓	0↓
Afterload (peripheral vascular resistance)	↓	↑	↑	↑↑	↑	↓↓	↓	↓
Contractility	0 (↑)	↓↓↓	↓	↓↓↓	↓↓↓	↓ (↑↑)*	↓↓ (↑)*	↓ (↑)*
Heart rate	0 (↑)	↓↓↓	0↓	↓↓↓	↓↓↓	0 (↑↑)	↓↓ (↑)	↓↓ (↑)

*Effect of calcium entry on LV contractility, as assessed in the intact animal model. The net effect on LV performance is variable because it is influenced by alterations in afterload, reflex cardiac stimulation, and the underlying state of the myocardium.

↑ = increase; ↓ = decrease; 0 = little or no definite effect. The number of arrows represents the relative intensity of effect. Symbols in parentheses indicate reflex-mediated effects. *ISA,* Intrinsic sympathomimetic activity.

From Shub C, Vlietstra RE, McGoon MD. Selection of optimal drug therapy for the patient with angina pectoris. Mayo Clin Proc 1985;60:539.

TABLE 61.5

Physiologic Actions of Beta-Adrenergic Receptors

ORGAN	RECEPTOR TYPE	RESPONSE TO STIMULUS
Heart		
Sinoatrial node	$Beta_1$	Increased heart rate
Atria	$Beta_1$	Increased contractility and conduction velocity
AV node	$Beta_1$	Increased automaticity and conduction velocity
His-Purkinje system	$Beta_1$	Increased automaticity and system conduction velocity
Ventricles	$Beta_1$	Increased automaticity, contractility, and conduction velocity
Arteries		
Peripheral	$Beta_2$	Dilation
Coronary	$Beta_2$	Dilation
Carotid	$Beta_2$	Dilation
Other	$Beta_2$	Increased insulin release Increased liver and muscle glycogenolysis
Lungs	$Beta_2$	Dilation of bronchi
Uterus	$Beta_2$	Smooth muscle relaxation

From Abrams J. Medical therapy of stable angina pectoris. In Beller G, Braunwald E, editors. Chronic Ischemic Heart Disease. Atlas of Heart Disease. Vol 5. Philadelphia: Saunders; 1995, p 7.19.

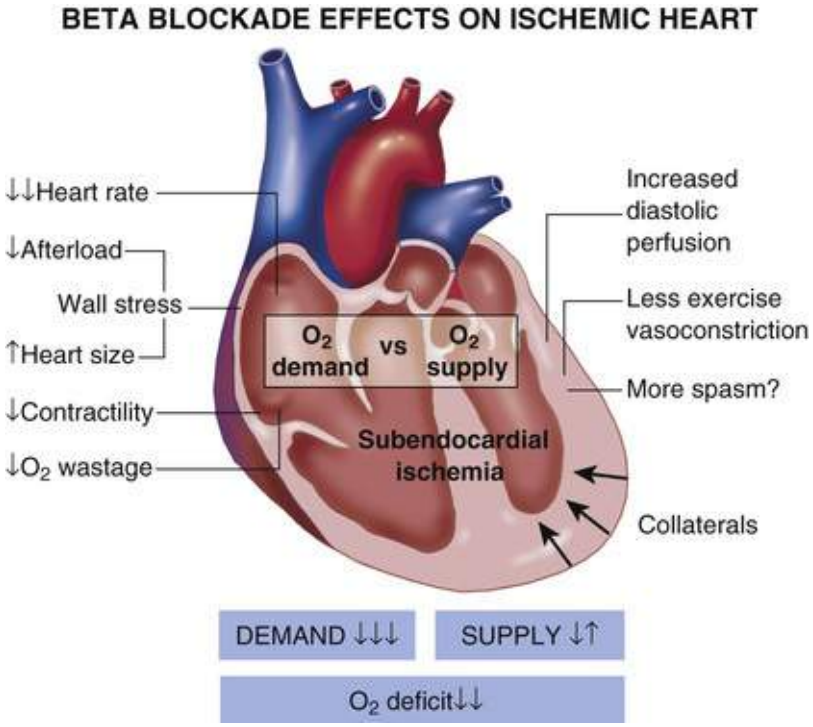


FIGURE 61.9 Effects of beta blockade on an ischemic heart. Beta blockade has a beneficial effect on ischemic myocardium unless (1) the preload rises substantially, as in left-sided heart failure, or (2) vasospastic angina is present, in which case spasm may be promoted in some patients. Note the suggestion that beta blockade diminishes exercise-induced vasoconstriction. (Modified from Opie LH: Drugs for the Heart. 4th ed. Philadelphia: Saunders; 1995, p 6.)

Beta-blocking agents may reduce blood flow to most organs by means of the combination of unopposed alpha-adrenergic vasoconstriction and $beta_2$ receptor blockade (**Table 61.5**). Complications are relatively minor, but in patients with peripheral vascular disease, the reduction in blood flow to skeletal muscles with the use of nonselective beta-blocking agents may decrease maximal exercise capacity. In patients with preexisting LV dysfunction, beta blockade may increase LV volume and thereby enhance O_2 demand.

Characteristics of Different Beta-Blocking Agents

Selectivity.

Two major subtypes of beta receptors, designated $beta_1$ and $beta_2$, are present in different proportions in different tissues. $Beta_1$ receptors predominate in the heart, and stimulation of these receptors leads to an increase in HR, atrioventricular (AV) conduction, and contractility; release of renin from juxtaglomerular cells in the kidneys; and lipolysis in adipocytes. $Beta_2$ stimulation causes bronchodilation, vasodilation, and glycogenolysis. Nonselective beta-blocking drugs (e.g., propranolol, nadolol, penbutolol, pindolol, sotalol, timolol, carteolol) block both $beta_1$ and $beta_2$ receptors, whereas cardioselective beta-blocking agents (e.g., acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, nebivolol) block $beta_1$ receptors while having less effect on $beta_2$ receptors. Thus, cardioselective beta blockers reduce myocardial O_2 requirements while tending not to block bronchodilation, vasodilation, or glycogenolysis. However, as the doses of these drugs are increased, this cardioselectivity diminishes. Because cardioselectivity is only relative, the use of cardioselective beta blockers in doses sufficient to control angina may still cause bronchoconstriction in some susceptible patients. Nevertheless, beta blockers are relatively well tolerated by most patients with obstructive pulmonary disease.

Some beta-blocking agents also cause vasodilation. Such drugs include labetalol (an alpha-adrenergic–blocking agent and $beta_2$-agonist; **see Chapter 47**), carvedilol (with alpha- and $beta_1$-blocking activity), bucindolol (a nonselective beta blocker that causes direct [non–alpha-adrenergic–mediated] vasodilation), and nebivolol (a cardioselective beta blocker with a direct stimulatory effect on endothelial nitric oxide synthase [eNOS]).

Intrinsic Sympathomimetic Activity.

Beta-blocking agents with intrinsic sympathomimetic activity (ISA), such as acebutolol, bucindolol, carteolol, celiprolol, penbutolol, and pindolol, are partial beta-agonists that also produce blockade by shielding beta receptors from more potent beta-agonists. Pindolol and acebutolol produce low-grade beta stimulation when sympathetic activity is low (at rest), whereas these partial agonists behave more as conventional beta blockers when sympathetic activity is high. Agents with ISA may not be as effective as those without this property in reducing HR or the frequency, duration, and magnitude of ambulatory ST-segment changes or increasing the duration of exercise in patients with severe angina.

Potency.

Potency can be measured by the ability of beta blockers to inhibit the tachycardia produced by isoproterenol. All drugs are considered in reference to propranolol, which is given a value of 1.0 (**Table 61.6**). Timolol and pindolol are the most potent agents, and acebutolol and labetalol are the least potent.

TABLE 61.6

Pharmacokinetics and Pharmacology of Some Beta Adrenoceptor–Blocking Agents

CHARACTERISTIC	ATENOLOL	METOPROLOL/XL	NADOLOL	PINDOLOL	PROPRANOLOL/LA	TIMOLOL	ACEBUTOLOL	LA
Extent of absorption (%)	≈50	>95	≈30	>90	>90	>90	≈70	>90
Extent of bioavailability (% of dose)	≈40	≈50/77	≈30	≈90	≈30/20	75	≈50	≈25
Beta-blocking plasma concentration	0.2-0.5 μg/mL	50-100 ng/mL	50-100 ng/mL	50-100 ng/mL	50-100 ng/mL	50-100 ng/mL	0.2-2.0 μg/mL	0.7-
Protein binding (%)	<5	12	≈30	57	93	≈10	30-40	≈50
Lipophilicity*	Low	Moderate	Low	Moderate	High	Low	Low	Lov
Elimination half-life (hr)	6-9	3-7	14-25	3-4	3.5 to 6/8-11	3-4	3-4†	≈6
Drug accumulation in renal disease	Yes	No	Yes	No	No	No	Yes‡	No
Route of elimination	RE (mostly HM unchanged)	HM	RE	RE (40% unchanged and HM)	HM	RE (20% unchanged and HM)	HM‡	HM
Beta-blockade potency ratio (propranolol = 1)	1.0	1	1.0	6.0	1	6.0	0.3	0.3
Adrenoreceptor-blocking activity	β_1‖	β_1‖	β_1/β_2	β_1/β_2	β_1/β_2	β_1/β_2	β_1‖	β_1/β
Intrinsic sympathetic activity	0	0	0	+	0	0	+	0
Membrane-stabilizing activity	0	0	0	+	++	0	+	0
Usual maintenance dose	50-100 mg/day	50-100 mg bid-qid/50-400 mg/day	40-80 mg/day	10-40 mg/day (bid-tid)	80-320 mg/day (bid-tid)/80-160 mg/day	10-30 mg bid	200-600 mg bid	100
FDA-Approved Indications:								
Hypertension	Yes	Yes/Yes	Yes	Yes	Yes/Yes	Yes	Yes	Yes
Angina	Yes	Yes/Yes	Yes	No	Yes/Yes	No	No	No
After MI	Yes	Yes/No	No	No	Yes/No	Yes	No	No
Heart failure	No	Yes/Yes	No	No	No/No	No	No	No

*Determined by the distribution ratio between octanol and water.

†The half-life of the active metabolite diacetolol is 12 to 15 hours.

‡Acebutolol is eliminated mainly by the liver, but its major metabolite diacetolol is excreted by the kidney.

§Rapid metabolism by esterases in the cytosol of red blood cells.

‖Beta$_1$ selectivity is maintained at lower doses, but beta$_2$ receptors are inhibited at higher doses.

FDA, U.S. Food and Drug Administration; *HM,* hepatic metabolism; *MI,* myocardial infarction; *RE,* renal excretion.

Lipid Solubility.

The hydrophilicity or lipid solubility of beta-blocking agents is a major determinant of their absorption and metabolism (**Table 61.6**). The lipid-soluble (lipophilic) beta blockers propranolol, metoprolol, and pindolol are readily absorbed from the GI tract and metabolized predominantly by the liver. Water-soluble beta blockers, such as atenolol, are usually eliminated unchanged by the kidneys. Lipid-soluble agents are often preferable in patients with significant renal dysfunction, for whom clearance of water-soluble agents is reduced. Greater lipid solubility is associated with greater penetration into the central nervous system (CNS) and may contribute to the side effects (e.g., lethargy, depression, hallucinations) that are not clearly related to beta-blocking activity.

Alpha Adrenoceptor–Blocking Activity.

The alpha-blocking potency of oral labetalol (approximately 10% that of phentolamine) is approximately 20% of its beta-blocking potency (**Table 61.6**). Labetalol's combined alpha- and beta-blocking effects make it a particularly useful antihypertensive agent (**see Chapter 47**), and it is especially useful in patients with hypertension and angina. The major side effects of labetalol are postural hypotension and retrograde ejaculation. Carvedilol also possesses alpha-adrenergic–blocking activity with an alpha$_1$-to-

beta–blocking ratio of approximately 1:10, and thus may be preferable to other beta blockers when additional BP lowering is desired.

Genetic Polymorphisms.

The metabolism of metoprolol, carvedilol, and propranolol may be influenced by genetic polymorphisms or other medications that influence hepatic metabolism. Oxidative metabolism of metoprolol occurs primarily through the cytochrome P-450 enzyme CYP2D6 and exhibits the debrisoquin type of genetic polymorphism; poor hydroxylators or metabolizers (≤10% of white individuals) have significant prolongation of the elimination half-life of the drug in comparison to extensive hydroxylators or metabolizers. Thus, angina might be controlled by a single daily dose of metoprolol in poor metabolizers, whereas extensive metabolizers require the same dose two or three times daily. If a patient exhibits an exaggerated clinical response (e.g., extreme bradycardia) after the administration of metoprolol, propranolol, or other lipid-soluble beta blockers, it may be the result of prolongation of the elimination half-life because of slow oxidative metabolism. Metabolism of metoprolol may also be altered by drugs that interact with CYP2D6. Preliminary evidence suggests differences in survival in patients with unstable IHD and provoked ischemia in those with SIHD treated with beta-blocking agents based on polymorphisms of the $beta_2$-adrenergic receptor (*ADRB1* and *ADRB2*).[144,145]

Effects on Serum Lipid Levels.

Therapy with beta blockers (those lacking ISA) usually causes no significant changes in total or LDL-C levels but increases triglyceride and reduces HDL-C levels. The most studied drug has been propranolol, which can increase plasma triglyceride concentrations by 20% to 50% and reduce HDL-C levels by 10% to 20%. Increasing $beta_1$ selectivity is associated with lesser effects on lipid levels. Adverse effects on the lipid profile may be more common with nonselective than with $beta_1$-selective–blocking agents.

Adverse Effects and Contraindications

Most of the adverse effects of beta-blocking agents occur as a consequence of the known properties of these drugs and include cardiac effects (e.g., severe sinus bradycardia, sinus arrest, AV block, reduced LV contractility), bronchoconstriction, fatigue, mental depression, nightmares, GI upset, sexual dysfunction, intensification of insulin-induced hypoglycemia, and cutaneous reactions (**Table 61.7; see also Table 61.5**). Lethargy, weakness, and fatigue may be caused by reduced cardiac output or may arise from a direct effect on the CNS. In patients who already have impaired LV function, HF may be exacerbated (**see Chapter 25**). Pindolol, because of its ISA activity, may be preferable in patients with sinus node dysfunction. Carvedilol has been shown to exhibit modest insulin-sensitizing properties and can relieve some manifestations of metabolic syndrome.[146] Blockade of $beta_2$ receptors also inhibits the vasodilating effects of catecholamines in peripheral blood vessels and leaves the constrictor (alpha-adrenergic) receptors unopposed, thereby enhancing vasoconstriction. Noncardioselective beta blockers may precipitate episodes of Raynaud phenomenon in patients with this condition. Reduced flow to the limbs may also occur in patients with peripheral vascular disease.

TABLE 61.7

Candidates for Use of Beta-Blocking Agents for Angina

Ideal Candidates
Prominent relationship of physical activity to attacks of angina
Coexistent hypertension
History of supraventricular or ventricular arrhythmias
Previous myocardial infarction
LV systolic dysfunction
Mild to moderate heart failure symptoms (NYHA Functional Class II and III)
Prominent anxiety state
Poor Candidates
Asthma or reversible airway component in patients with chronic lung disease
Severe LV dysfunction with severe heart failure symptoms (NYHA Functional Class IV)
History of severe depression
Raynaud phenomenon
Symptomatic peripheral artery disease
Severe bradycardia or heart block
Diabetes with frequent hypoglycemic episodes

LV, Left ventricular; *NYHA,* New York Heart Association.

Modified from Abrams JA. Medical therapy of stable angina pectoris. In Beller G, Braunwald E, editors. Chronic Ischemic Heart Disease. Atlas of Heart Disease. Vol 5. Philadelphia: Saunders; 1995, p 7.22.

Abrupt withdrawal of beta blocker after prolonged administration can result in increased total ischemic activity in patients with chronic stable angina. Chronic beta-blocker therapy can be safely discontinued by slowly withdrawing the drug in a stepwise manner over 2 to 3 weeks. If abrupt withdrawal of beta blockers is required, patients should be instructed to reduce exertion and manage angina episodes with sublingual nitroglycerin and/or substitute a calcium antagonist.

Calcium Antagonists

The critical role of calcium ions (Ca^{2+}) in the normal contraction of cardiac and vascular smooth muscle is discussed in **Chapters 22 and 57**. The calcium antagonists (**see Chapter 47**) are a heterogeneous group of compounds that inhibit movement of Ca^{2+} through slow channels in cardiac and smooth muscle membranes by noncompetitive blockade of voltage-sensitive L-type calcium channels. The three major classes of calcium antagonists are the dihydropyridines (nifedipine is the prototype), the phenylalkylamines (verapamil is the prototype), and the modified benzothiazepines (diltiazem is the prototype). Amlodipine and felodipine are additional dihydropyridines that are among the most commonly used calcium antagonists in the United States. The two predominant effects of calcium antagonists result from blocking the entry of Ca^{2+} and slowing recovery of the channel. Phenylalkylamines have a marked effect on recovery of the channel and thereby exert depressant effects on cardiac pacemakers and conduction, whereas dihydropyridines, which do not impair channel recovery, have little effect on the conduction system.

Mechanism of Action.

The efficacy of calcium antagonists in patients with angina pectoris is related to the reduction in myocardial O_2 demand and the increase in O_2 supply (**see Table 61.4**). The latter effect is particularly important in patients with conditions in which a prominent vasospastic or vasoconstrictor component may be present, such as Prinzmetal variant angina (**see Chapters 57 and 60**). Calcium antagonists may be effective on their own or in combination with beta-blocking agents and nitrates in patients with chronic stable angina. Several calcium antagonists are effective for the treatment of angina pectoris

(**Table 61.8**). Each relaxes vascular smooth muscle in the systemic arterial and coronary arterial beds. In addition, blockade of the entry of calcium into myocytes results in a negative inotropic effect, which is counteracted to some extent by peripheral vascular dilation and by activation of the sympathetic nervous system in response to drug-induced hypotension. However, the negative inotropic effect must be taken into consideration in patients with significant LV dysfunction.

TABLE 61.8

Pharmacokinetics of Some Calcium Antagonists Used for Angina Pectoris

	DILTIAZEM/SR	NICARDIPINE	NIFEDIPINE/SR	VERAPAMIL/SR	AMLODIPINE	FELODIPINE	ISRADIPINE	NISOLDI
Usual adult dose	30-90 mg tid-qid SR: 60-180 mg bid CD: 120-480 mg/day	20-40 mg tid SR: 30-60 mg bid	IR: 10-30 mg tid SR: 90 mg/day	80-120 mg tid-qid SR: 180-480 mg/day	2.5-10 mg/day	SR: 2.5-100 mg/day	CR: 2.5-10 mg bid	SR: 10-40 m
Extent of absorption (%)	80-90	100	90	90	>90	>90	>90	ND
Extent of bioavailability (%)	40-70	30	65-75/86	20-35	60-90	20	25	5
Onset of action	30-60 min	20 min	20 min	30 min	0.5-1.0 hr	2 hr	20 min	1-3 hr
Time to peak serum concentration (hr)	2-3/6-11	0.5-2.0	0.5/6	IV: 3-5 min Oral: 1-2 SR: 7-9	6-12	2-5	1.5	6-12
Therapeutic serum levels (ng/mL)	50-200	30-50	25-100	80-300	5-20	1-5	2-10	ND
Elimination half-life (hr)	3.5/5-7	2.0-4.0	2.0-5.0	3.0-7.0*	30-50	11-16	8	7-12
Elimination pass, hepatic	60% metabolized by the liver; remainder excreted by the kidneys	High first-pass hepatic metabolism	High first-pass hepatic metabolism	85% eliminated by first-pass hepatic metabolism	Hepatic	High first-pass hepatic metabolism	High first-pass hepatic metabolism	Hepatic
Heart rate	↓	↑	↑↑	↓	0	↑	0	0
Peripheral vascular resistance	↓	↓↓↓	↓↓↓	↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓
FDA-Approved Indications								
	IR– SR		IR–SR	IR–SR				
Hypertension	No–Yes	Yes†	No–Yes	Yes–Yes	Yes	Yes	Yes	Yes
Angina	Yes–Yes	Yes	Yes–Yes	Yes–No	Yes	No	No	Yes
Coronary spasm	Yes–No	No	Yes–Yes	Yes–No	Yes	No	No	No

*Half-life of 4.5 to 12 hours with multiple dosing; may be prolonged in older adults.

†The sustained-release formulation may be preferred for hypertension.

CD, Combination drug; *CR,* controlled release; *IR,* immediate release; *ND,* no data; *SR,* sustained release; *FDA,* U.S. Food and Drug Administration.

Potential Antiatherogenic Actions.

Hyperlipidemia-induced changes in the permeability of smooth muscle cells to calcium may play a role in atherogenesis. Experimental work with calcium channel–blocking drugs, in particular, work with more lipophilic second-generation agents such as amlodipine, has demonstrated improved endothelial function and inhibition of smooth muscle cell proliferation and migration, in addition to ameliorating unfavorable membrane alterations. Although data from small randomized trials suggested reduced progression of coronary atherosclerosis and improved coronary endothelial function with amlodipine and nifedipine, several larger trials have failed to confirm an effect of calcium antagonists on atherosclerosis burden. Thus the hypothesis that calcium antagonists might inhibit atherogenesis has been explored since the 1970s but has not yet been definitively answered.[147]

First-Generation Calcium Antagonists

Nifedipine.

Nifedipine, a dihydropyridine, is a particularly effective dilator of vascular smooth muscle and is a more potent vasodilator than diltiazem or verapamil. The beneficial effects of nifedipine in the treatment of angina result from its capacity to reduce myocardial O_2 requirements because of its afterload-reducing effect and to increase myocardial O_2 delivery as a result of its dilating action on the coronary vascular bed (**see Table 61.4**). Because immediate-release formulations can precipitate hypotension and adverse events, an extended-release formulation should be used when nifedipine is administered. A meta-analysis of 15 studies of long-acting calcium channel antagonists, including nifedipine, in patients with CAD demonstrated significant reductions in angina, stroke, and HF, with no improvement in other CV outcomes. Long-acting nifedipine should be considered an effective and safe antianginal drug for the treatment of symptomatic patients with angina who are already receiving beta-blocking agents, with or without nitrates.

Adverse Effects.

These occur in 15% to 20% of patients and require discontinuation of medication in approximately 5%. Most adverse effects are related to systemic vasodilation and include headache, dizziness, palpitations, flushing, hypotension, and leg edema (unrelated to HF). In rare cases in patients with extremely severe, fixed coronary obstructions, nifedipine aggravates angina, presumably by lowering arterial pressure excessively with subsequent reflex tachycardia. For this reason, combined treatment of angina with nifedipine and a beta-blocking agent is particularly effective and superior to nifedipine alone. Nifedipine has been reported to worsen HF in patients with preexisting chronic HF and is contraindicated in patients who are hypotensive or have severe aortic valve stenosis.

Verapamil.

Verapamil dilates systemic and coronary resistance vessels and large coronary conductance vessels. It slows the HR and reduces myocardial contractility. This combination of actions results in a reduction in the myocardial O_2 requirement, which is the basis for the drug's efficacy in the management of chronic stable angina (**Table 61.8**). When evaluated in INVEST (International Verapamil-Trandolapril Study), a strategy combining sustained-release verapamil and trandolapril versus atenolol and a diuretic for the treatment of patients with hypertension and CAD, including those with previous MI, showed equivalent outcomes with respect to death, MI, or stroke.[147]

In patients with cardiac dysfunction, verapamil may reduce cardiac output, increase LV filling pressure, and cause clinical HF. Verapamil slows the HR and AV conduction. Therefore, it is contraindicated in patients with preexisting AV nodal disease or sick sinus syndrome, HF, and suspected digitalis or quinidine toxicity. Verapamil should generally not be used together with a beta-blocking agent due to the risk for bradycardia or heart block. The bioavailability of verapamil is increased by cimetidine and carbamazepine, whereas verapamil may increase plasma levels of cyclosporine and digoxin.

Adverse effects of verapamil are noted in approximately 10% of patients and are related to systemic vasodilation (hypotension and facial flushing), GI symptoms (constipation, nausea), and CNS reactions such as headache and dizziness. A rare side effect is gingival hyperplasia, which appears after 1 to 9 months of therapy.

Diltiazem.

The actions of diltiazem are intermediate between those of nifedipine and verapamil. In clinically useful doses, diltiazem's vasodilator effects are less profound than those of nifedipine, and its cardiac depressant action on the sinoatrial and AV nodes and myocardium is less than that of verapamil. This profile may explain the remarkably low incidence of adverse effects of diltiazem. Diltiazem is a systemic vasodilator that lowers arterial pressure at rest and during exertion and increases the workload required to produce myocardial ischemia, but it may also increase myocardial O_2 delivery. Although it causes little vasodilation of epicardial coronary arteries under basal conditions, diltiazem may enhance perfusion of the subendocardium distal to a flow-limiting coronary stenosis; it also blocks exercise-induced coronary vasoconstriction.

Major side effects of diltiazem are similar to those of the other calcium channel–blocking agents and are related to vasodilation, but they are relatively infrequent, particularly if the dosage does not exceed 240 mg daily. As with verapamil, diltiazem should be prescribed with caution for patients with sick sinus syndrome or AV block. In patients with preexisting LV dysfunction, diltiazem may exacerbate or precipitate HF.

Diltiazem interacts with other drugs, including beta-blocking agents (causing enhanced negative inotropic, chronotropic, and dromotropic effects), flecainide, and cimetidine (which increases the bioavailability of diltiazem). Diltiazem has been associated with increased plasma levels of substrates of CYP3A4, including apixaban, atorvastatin, simvastatin, cilostazol, dofetilide, ivabradine, and ranolazine, as well as non-CYP3A4 substrates, including carbamazepine and cyclosporine. Diltiazem may cause excessive sinus node depression if administered with disopyramide and may reduce digoxin clearance, especially in patients with renal failure.

Second-Generation Calcium Antagonists

The second-generation calcium antagonists (e.g., nicardipine, isradipine, amlodipine, felodipine) are mainly dihydropyridine derivatives, with nifedipine being the prototypic agent. Experience has also accumulated with nimodipine, nisoldipine, and nitrendipine. These agents differ in potency, tissue specificity, and pharmacokinetics and generally are potent vasodilators because of the greater vascular selectivity than seen with the first-generation antagonists (e.g., verapamil, nifedipine, diltiazem).

Amlodipine.

Less lipid soluble than nifedipine, amlodipine has a slow, smooth onset and ultralong duration of action (plasma half-life of 36 hours). It causes marked coronary and peripheral dilation and may be useful in the treatment of patients with angina accompanied by hypertension. It may be used as a once-daily hypotensive or antianginal agent. In a series of randomized placebo-controlled studies in patients with stable exercise-induced angina pectoris, amlodipine was shown to be effective and well tolerated. In two trials involving patients with established CAD, amlodipine reduced the risk for MACE. Amlodipine has little if any negative inotropic action and may be especially useful in patients with chronic angina and LV dysfunction.

The usual dosage of amlodipine is 5 to 10 mg once daily. Downward adjustment of the starting dose is appropriate for patients with liver disease and elderly patients. Significant changes in BP are typically not evident until 24 to 48 hours after initiation. Steady-state serum levels are achieved at 7 to 8 days. Amlodipine should not be co-administered with simvastatin because it increases drug levels of this statin and may increase risk for myopathy.

Nicardipine.

Although it has a half-life similar to that of nifedipine (2 to 4 hours), nicardipine appears to have greater vascular selectivity. Nicardipine may be used as an antianginal and antihypertensive agent and requires administration three times daily, although a sustained-release formulation is available for twice-daily dosing in patients with hypertension. For chronic stable angina pectoris, nicardipine appears to be as effective as verapamil or diltiazem, and its efficacy is enhanced when combined with a beta-blocking agent.

Felodipine and Isradipine.

In the United States, both these drugs are approved by the U.S. Food and Drug Administration (FDA) for the treatment of hypertension, but not for angina pectoris. One study has documented similar efficacy between felodipine and nifedipine in patients with chronic stable angina. Felodipine has also been reported to be more vascular selective than nifedipine and to have a mild positive inotropic effect as a result of calcium channel agonist properties. Isradipine has a longer half-life than nifedipine and demonstrates greater vascular sensitivity.

Nitrates

Mechanism of Action

The action of nitrates is to relax vascular smooth muscle. The vasodilator effects of nitrates are evident in systemic (including coronary) arteries and veins, but they appear to be predominant in the venous circulation. The venodilator effect reduces ventricular preload, which in turn reduces myocardial wall tension and O_2 requirements. The action of nitrates in reducing preload and afterload makes them useful in the treatment of HF (**see Fig. 61.2**), as well as angina. By reducing the heart's mechanical activity, volume, and O_2 consumption, nitrates increase exercise capacity in patients with IHD, thereby allowing greater total-body workload to be achieved before the angina threshold is reached. Thus, in patients with stable angina, nitrates improve exercise tolerance and time to ST-segment depression during treadmill exercise tests. When used in combination with calcium channel–blocking agents and/or beta-blocking agents, the antianginal effects appear to be greater.[28]

Effects on the Coronary Circulation (See Table 61.4).

Nitroglycerin causes dilation of epicardial stenoses. Even a small increase in a narrowed arterial lumen can produce a significant reduction in resistance to blood flow across obstructed segments. Nitrates may also exert a beneficial effect in patients with impaired coronary flow reserve by alleviating the vasoconstriction caused by endothelial dysfunction of resistance vessels.

Redistribution of Blood Flow.

Nitroglycerin causes blood flow to be redistributed from normally perfused segments to ischemic areas, particularly in the subendocardium. This redistribution may be mediated in part by an increase in collateral blood flow and in part by lowering of LV diastolic pressure, thereby reducing subendocardial compression. Nitroglycerin appears to reduce coronary vascular resistance preferentially in viable myocardium with ischemia, as detected by SPECT. Nitroglycerin alters myocardial perfusion by preferentially increasing flow to areas of reduced perfusion, with little or no change in global myocardial

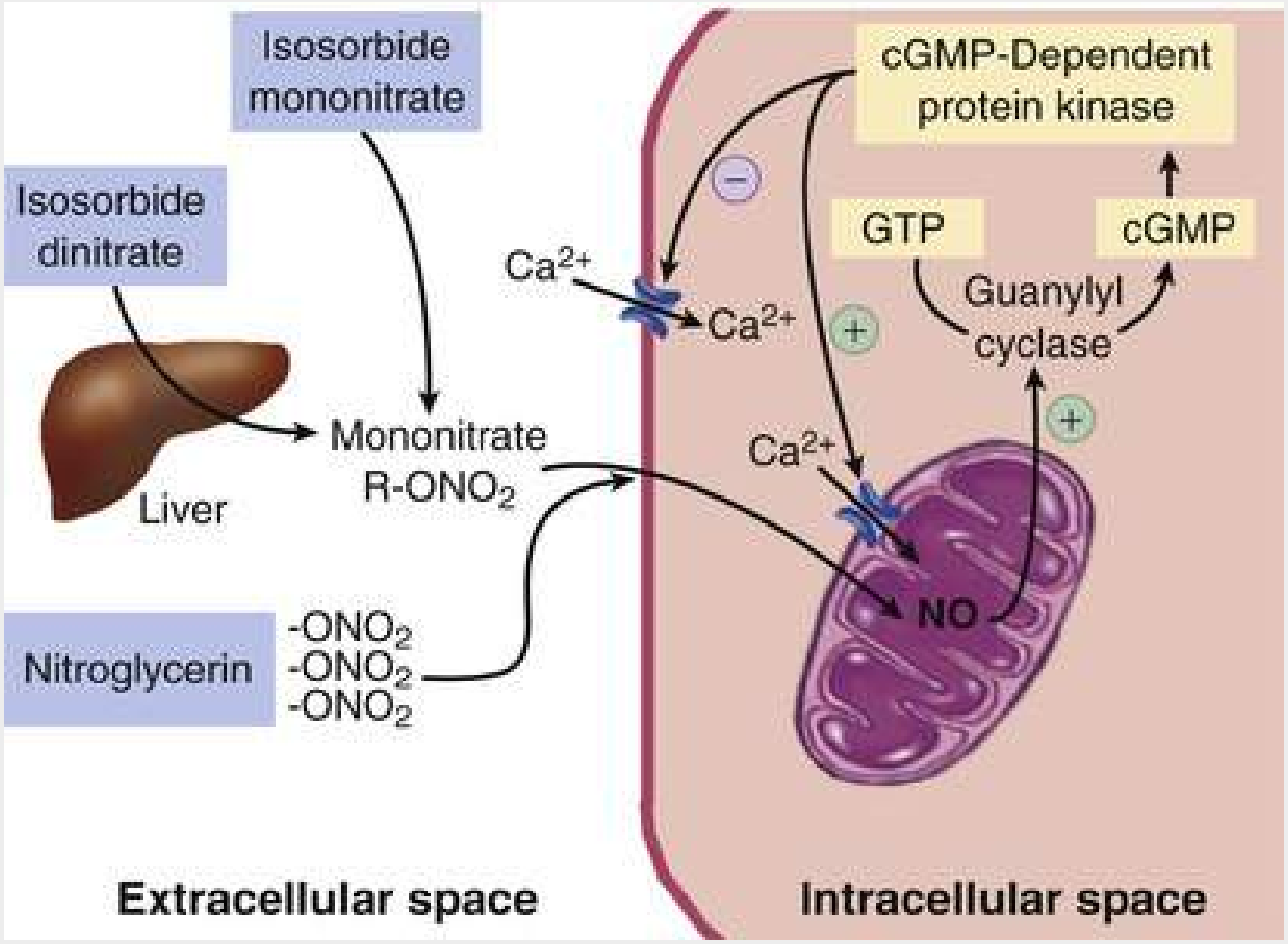
perfusion.

Antithrombotic Effects.

Stimulation of guanylate cyclase by nitric oxide (NO) results in inhibitory action on platelets in addition to vasodilation. Although antithrombotic effects of intravenous (IV) nitroglycerin have been demonstrated in patients with unstable angina and in those with SIHD, the clinical significance of these actions is not clear as nitrates have not been shown to lower the rate of MI.

Cellular Mechanism of Action.

Nitrates have the ability to cause vasodilation, regardless of whether the endothelium is intact. After entering the vascular smooth muscle cell, nitrates are converted to reactive NO or *S*-nitrosothiols, which activate intracellular guanylate cyclase to produce cyclic guanosine monophosphate (cGMP), which in turn triggers smooth muscle relaxation and antiplatelet aggregator effects (**eFig. 61.3**). Evidence now exists that biotransformation of nitroglycerin occurs via mitochondrial aldehyde dehydrogenase and that inhibition of this enzyme may contribute to the development of tolerance.[148] Subsequent studies have also shown cytosolic bioactivation by aldehydrogenase-2. Although the aggregate evidence supports release of NO as the major cellular mechanism of action of oral nitrates, experimental data have challenged this conclusion. In particular, the arterial vasodilatory effects of nitroglycerin in vitro depend, at least in part, on endothelial calcium-activated potassium channels.



EFIGURE 61.3 Mechanism of action of nitrates. Evidence exists that biotransformation of mononitrates occurs through the action of mitochondrial aldehyde reductase in producing nitric oxide (NO). NO activates soluble guanylyl cyclase, which results in increased production of cyclic guanosine monophosphate (cGMP). The second messenger cGMP reduces cytoplasmic calcium (Ca^{2+}) by inhibiting inflow and stimulating mitochondrial uptake of calcium, thus mediating the relaxation of smooth muscle cells and causing vasodilation. Isosorbide dinitrate is metabolized by the liver, whereas the liver is bypassed by mononitrates. GTP, Guanosine triphosphate. R-ONO_2, mononitrate. (Modified from Gori T, Parker JD. Nitrate tolerance: a unifying hypothesis. Circulation 2002;106:2510; and Opie LH. Drugs for the Heart. 4th ed. Philadelphia: Saunders; 1995, p 33.)

Potential for Adverse Effects During Long-Term Administration.

Experimental data have raised questions regarding the potentially competing long-term effects of oral nitrates.[148] Multiple animal experiments and at least one human study have demonstrated that extended exposure to nitrates can impair endothelial-dependent vasodilation through increases in endothelin-1 and the generation of free radical species.[149] This effect appears to be reversed by antioxidant therapy. Long-term studies in humans are necessary to determine the clinical relevance of these findings.

Types of Preparations and Routes of Administration

Short-acting nitroglycerin administered sublingually (either by tablet or spray) remains the drug of choice for the treatment of acute angina episodes (**Table 61.9**). Because sublingual (SL) administration avoids first-pass hepatic metabolism, a transient but effective concentration of the drug rapidly appears in the circulation. Within 30 to 60 minutes, hepatic breakdown has abolished the hemodynamic and clinical effects. SL nitroglycerin is also useful when taken prophylactically shortly before undertaking physical activities that are likely to cause angina. When used for this purpose, it may prevent angina for up to 40 minutes.

TABLE 61.9

Recommended Dosing Regimens for Long-Term Nitrate Therapy

PREPARATION OF AGENT	DOSE	SCHEDULE
Nitroglycerin*		
Ointment	0.5-2 inches	2 or 3 times daily
Transdermal patch	0.2-0.8 mg/hr	Every 24 hr; remove at bedtime for 12-14 hr
Sublingual tablet	0.3-0.6 mg	As needed, up to 3 doses 5 min apart
Spray	1 or 2 sprays	As needed, up to 3 doses 5 min apart
Isosorbide Dinitrate*		
Oral	10-40 mg	2 or 3 times daily
Oral sustained release	80-120 mg	Once or twice daily (eccentric schedule)
Isosorbide 5-Mononitrate		
Oral	20 mg	Twice daily (given 7-8 hr apart)
Oral sustained release	30-240 mg	Once daily

*A 10- to 12-hour nitrate-free interval is recommended.

Adverse Reactions.

Adverse reactions are common and include headache, flushing, and hypotension. The last is rarely severe, but in some patients with volume depletion and in an upright posture, nitrate-induced hypotension is accompanied by a paradoxical bradycardia, consistent with a vasovagal or vasodepressor response. This reaction is more common in older adults, who are less able to tolerate hypovolemia, and may be magnified in hot weather. Methemoglobinemia is a rare complication of very large doses of nitrates; commonly used doses of nitrates cause small elevations in methemoglobin levels that are probably not of clinical significance.

Short-Acting Nitroglycerin (Nitroglycerin Tablets and Oral Spray).

Nitrate preparations are available in SL, buccal, oral, spray, and ointment forms (**Table 61.9**). An oral nitroglycerin spray that dispenses metered, aerosolized doses of 0.4 mg may be better absorbed than the SL form in patients with dry mucosal membranes. It can also be quickly sprayed onto or under the tongue. For prophylaxis, the spray should be used 5 to 10 minutes before angina-provoking activities. An additional advantage of the pump spray preparation is a longer shelf life (up to 2 years) than that of SL nitroglycerin (which is approximately 6 months).

Isosorbide Dinitrate.

This drug is available in tablets for SL use, in chewable form, in tablets for oral use, and in sustained-release (SR) capsules. Partial or complete nitrate tolerance (see later) develops with regimens of isosorbide dinitrate administered as 30 mg three or four times daily. A dosage schedule should be adopted that allows a 12-hour or longer nitrate-free interval. If the drug is administered on a three-times-daily schedule (e.g., at 8 AM, 1 PM, and 6 PM), the antianginal benefit lasts for approximately 6 hours, and the magnitude of the antianginal benefit decreases with each successive dose.

Isosorbide 5-Mononitrate.

Plasma levels of isosorbide 5-mononitrate reach their peak between 30 minutes and 2 hours after ingestion, and the drug has a plasma half-life of 4 to 6 hours. A single 20-mg tablet still exhibits activity 8 hours after administration. Tolerance has not been demonstrated with once-daily or eccentric dosing intervals but does occur with a twice-daily dosing regimen at 12-hour intervals. The only SR preparation of isosorbide 5-mononitrate is Imdur, which is given once daily at 30 to 240 mg. Presumably, this

preparation avoids tolerance by providing a sufficiently low nitrate level or a duration of action of 12 hours or less. Once-daily dosing of oral nitrates improves compliance and may offer better efficacy in reducing angina.

Topical Nitroglycerin.

Nitroglycerin may be applied as a transdermal patch. Application of a silicone gel or polymer matrix impregnated with nitroglycerin results in absorption for 24 to 48 hours at a rate determined by various methods of preparation of the patch. Transdermal nitroglycerin therapy has been shown to increase exercise duration and maintain its anti-ischemic effects for 12 hours after patch application throughout 30 days of therapy, without significant evidence of nitrate tolerance or rebound phenomena, provided that the patch is not applied for more than 12 of 24 hours.

Nitrate Tolerance.

A major problem with the use of nitrates is the development of nitrate tolerance, which has been demonstrated with all forms of nitrate administration that deliver continuous, relatively stable blood levels of the drug. Although nitrate tolerance is rapid in onset, renewed responsiveness is easily established after a short, nitrate-free interval. The problem of tolerance applies to most nitrate preparations. Nitrate tolerance appears to be limited to capacitance and resistance vessels and has not been noted in large conductance vessels, including the epicardial coronary arteries and radial arteries, despite continuous administration of nitroglycerin for 48 hours.

Mechanisms.

Several mechanisms of nitrate tolerance have been proposed. Evidence has supported the hypothesis that increased generation of vascular superoxide anion (O_2^-) is central to the process.[148,150] There are multiple possible contributors to the generation of oxygen free radicals, including the effects of nitroglycerin on eNOS uncoupling and counterregulatory neurohormonal activation. The increased O_2^- formation has a number of consequences, including plausible links to many of the proposed mechanisms of nitrate tolerance: (1) plasma volume expansion and neurohormonal activation, (2) impaired biotransformation of nitrates to NO, and (3) decreased end-organ responsiveness to NO.

Management.

The primary strategy for managing nitrate tolerance is to prevent it by providing a nitrate-free interval. The optimal interval is unknown, but with patches or ointment or preparations of isosorbide dinitrate or isosorbide 5-mononitrate, a 12-hour off-period is recommended. Experimental data suggest that nitrate-induced oxidative stress, nitrate tolerance, and endothelial dysfunction may be mitigated by an ARB.[151] In addition, pentaerythrityl tetranitrate is an organic nitrate that may have lesser detrimental effects on mitochondrial aldehyde dehydrogenase.[152]

Nitrate Withdrawal.

A common form of nitrate withdrawal (rebound) is observed in patients whose angina is intensified after discontinuation of large doses of long-acting nitrates. In this situation, patients may also have heightened sensitivity to constrictor stimuli. The potential for rebound can be modified by adjusting the dose and timing of administration, in addition to the use of other antianginal drugs.

Interaction With Cyclic Guanosine Monophosphate–Specific Phosphodiesterase Type 5 Inhibitors.

The combination of nitrates and phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil, and

vardenafil) may cause serious, prolonged, and potentially life-threatening hypotension.[142] Nitrate therapy is an absolute contraindication to the use of these agents, and vice versa. Patients who want to take a PDE5 inhibitor should be aware of the serious nature of this adverse drug interaction and be warned about taking any of these agents within 24 hours of any nitrate preparation, including short-acting SL nitroglycerin tablets.

Other Pharmacologic Agents

Ranolazine

Ranolazine is a piperazine derivative that was approved in 2006 in the United States for use in patients with chronic stable angina.[153] Ranolazine is unique among currently approved antianginals in that its anti-ischemic effects are achieved without a clinically meaningful change in HR or BP. When studied at high concentrations with in vitro experiments, ranolazine was shown to shift myocardial substrate uptake from fatty acid to glucose and thus was considered to be a potential myocardial metabolic modulator. However, subsequent studies at concentrations of ranolazine consistent with doses tested in clinical trials have indicated that ranolazine exerts favorable effects on ischemia through a reduction in calcium overload in ischemic myocytes via inhibition of the late inward sodium current (I_{Na}).[154] In animal models of ischemia and reperfusion, ranolazine preserves tissue levels of adenosine triphosphate (ATP) and improves myocardial contractile function.

An SR formulation of ranolazine has been studied in four RCTs and improved exercise performance and increased the time to ischemia during exercise treadmill testing when used as monotherapy or in combination with the most frequently used doses of atenolol, amlodipine, or diltiazem. Ranolazine also decreases angina frequency and nitroglycerin use when used in conjunction with a beta-blocking agent or calcium channel–blocking agent, and in patients with DM.[153,155]

Despite the favorable effect of ranolazine on ischemic symptoms, in two multinational outcomes RCTs, ranolazine has not reduced major CV events. When studied in 6560 patients with non–ST-segment elevation ACS, ranolazine, administered for an average of approximately 1 year, did not add to standard therapy in secondary prevention of MACE. However, ranolazine reduced the incidence of recurrent ischemia, in particular, worsening angina, in a more diverse population with CAD than studied previously (**Fig. 61.10**). Consistent with previous studies, the reduction in angina and improvement in exercise performance were evident only in patients with a history of chronic angina and was no less in women than in men.[156] When studied in 2651 patients with incomplete revascularization after PCI, ranolazine had no demonstrable effect on ischemia-driven revascularization or hospitalization (HR, 0.95; 95% CI 0.82 to 1.10; $P = 0.48$)[157] or on quality of life.[158]

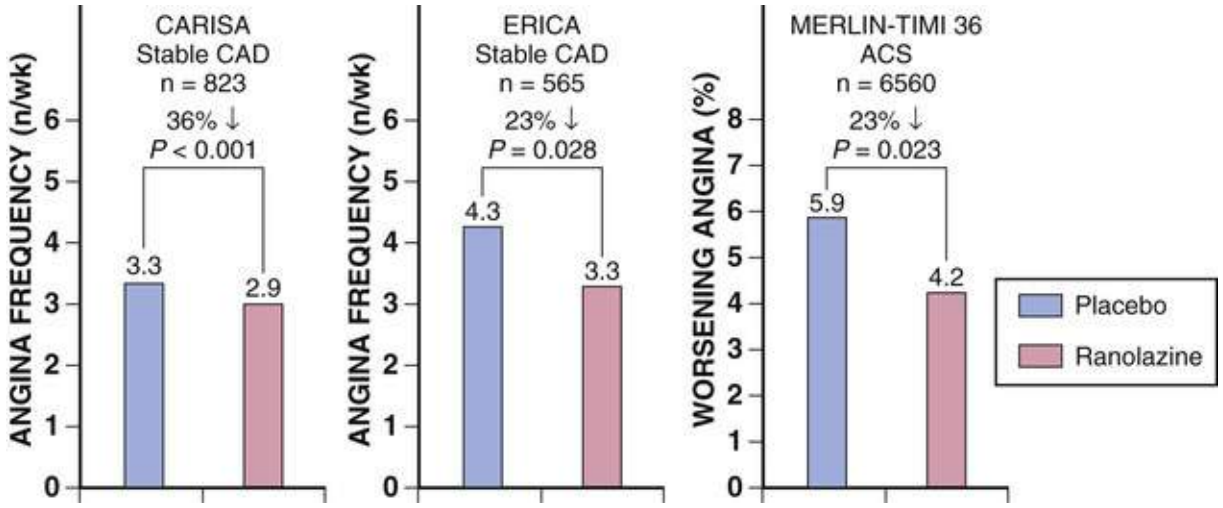


FIGURE 61.10 Reduction in the frequency of angina in three randomized, double-blind, placebo-controlled trials of ranolazine in patients with established coronary artery disease (CAD). Patients with stable CAD and early positive stress testing treated with standard doses of atenolol, amlodipine, or diltiazem were studied in the CARISA (Combination Assessment of Ranolazine in Stable Angina) trial. Patients with stable CAD and at least three episodes of angina per week despite amlodipine, 10 mg daily, were studied in the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. After the diagnosis of non–ST-elevation ACS, patients were studied for an average of 12 months in the MERLIN (Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes) trial. In each trial, ranolazine reduced the frequency of angina. (Data from Chaitman BR et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. JAMA 2004;291:309; Stone PS et al. Antianginal efficacy of ranolazine when added to treatment with amlodipine. J Am Coll Cardiol 2006;48:566; and Morrow DA et al. Effects of ranolazine on recurrent cardiovascular events in patients with non–ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. JAMA 2007;297:1775.)

Because of its proposed mechanism of action on cardiac myocytes rather than modulation of the HR or BP, ranolazine has been studied in patients with angina and ischemia without obstructive epicardial CAD. In a pilot study of 20 women with angina and no obstructive CAD but with impaired coronary flow reserve on CMR, ranolazine reduced symptoms, with evidence of an improved myocardial perfusion reserve index.[159] However, a subsequent study in 128 women with evidence of microvascular dysfunction in the absence of obstructive CAD showed no benefit of ranolazine with respect to symptoms or myocardial perfusion abnormalities.[160]

The half-life of the SR formulation of ranolazine is approximately 7 hours. A steady state is generally achieved within 3 days of twice-daily dosing. Ranolazine is metabolized primarily through the CYP3A4 pathway, and thus the plasma concentration is increased if administered in combination with moderate (e.g., diltiazem) or strong (e.g., ketoconazole, macrolide antibiotic) inhibitors of this system. Verapamil increases the absorption of ranolazine by inhibition of P-glycoprotein. Plasma concentrations of simvastatin are increased approximately twofold after the administration of ranolazine, and it should not be co-administered with ranolazine in doses greater than 20 mg daily.

Ranolazine should be started at 500 mg twice daily and may be increased to a maximum of 1000 mg twice daily in patients with persistent angina. The most commonly reported adverse effects in clinical studies are nausea, generalized weakness, and constipation. Dizziness has also been reported, as has a small, dose-related increase in the corrected QT (QTc) interval, an average of 2 to 5 milliseconds in the dosage range of 500 to 1000 mg twice daily. In contrast to beta blockers and calcium antagonists, ranolazine does not have adverse effects on LV contractility.

The electrophysiologic effects of ranolazine include inhibition of the delayed rectifier current and inhibition of I_{Na}; the net effect is to shorten the action potential duration and suppress early afterdepolarizations.[161,162] Thus, ranolazine does not have the electrophysiologic profile observed with

QT-prolonging drugs associated with torsades de pointes. Rather, ranolazine appears to have favorable electrophysiologic effects on ventricular and atrial arrhythmias. For example, in patients with recent ACS, ranolazine reduced the incidence of arrhythmias detected on ambulatory electrocardiographic monitoring compared with placebo. Subsequent experimental and small human studies have revealed possible favorable effects on AF, suppression of torsades de pointes, and recurrence of internal defibrillator discharges. Ranolazine has been investigated for its potential clinical antiarrhythmic effects alone and in combination with other agents.[163,164] Nevertheless, because of its effect on the QT interval, ranolazine is contraindicated in patients with preexisting QT prolongation, in patients receiving other QT-prolonging medications, or in those with hepatic impairment, which has been associated with a steeper relationship between ranolazine and the QTc.

In addition to these electrophysiologic effects, ranolazine also appears to have favorable glycometabolic effects, including a modest reduction in HbA_{1c}.[165,166]

Ivabradine.

Ivabradine is a specific and selective inhibitor of the I_f ion channel, the principal determinant of the sinoatrial (SA) node pacemaker current.[167,168] Ivabradine reduces the spontaneous firing rate of SA pacemaker cells and thus slows HR through a mechanism not associated with negative inotropic effects. Although approved for use in the United States and Europe for patients with chronic HF with an HR not optimally controlled on maximally tolerated beta-blocker therapy,[168] ivabradine does not currently have a role in patients with SIHD.

Ivabradine reduces the peak HR during exercise, increases the time to limiting angina compared with placebo, and is equivalent to atenolol with respect to exercise performance and time to ischemic ST-segment depression in patients with stable angina undergoing exercise testing. Ivabradine has also been shown to reduce the HR without any effect on ventilatory parameters in patients with obstructive pulmonary disease and to be tolerated in patients with CAD and LV dysfunction. Ivabradine reduced CV death or hospitalization for worsening HF in patients with chronic HF, reduced EF, and HR of 70 beats/min or higher (**see Chapter 25**).[169] However, in a randomized trial of 10,917 patients with CAD and decreased LV function, ivabradine did not reduce the primary endpoint of CV death, hospitalization for MI, or hospitalization for HF. Moreover, in a subsequent trial in 19,102 patients who had SIHD without clinical HF and an HR of 70 beats/min or higher, ivabradine did not reduce the rate of CV death or MI or its components in the overall population or in prespecified subgroups.[170] Rather, there was a possible adverse effect of ivabradine on the incidence of CV death or MI in the subgroup of patients with a history of activity-limiting angina.[170]

Nicorandil.

Nicorandil is a nicotinamide ester that dilates peripheral and coronary resistance vessels via action on ATP-sensitive potassium channels and possesses a nitrate moiety that promotes systemic venous and coronary vasodilation.[171] As a result of these dual actions, nicorandil reduces preload and afterload and results in an increase in coronary blood flow. In addition to these effects, nicorandil may have cardioprotective actions mediated through the activation of potassium channels. Nicorandil has also been studied as a coronary vasodilator for hyperemic testing and for renal protection during PCI. Nicorandil has been associated with ulcerations of the GI tract.[172]

Nicorandil has antianginal efficacy similar to that of beta-blocking agents, nitrates, and calcium channel–blocking agents. In a randomized clinical trial (n = 5126), nicorandil reduced the risk for

cardiac death, MI, or hospital admission for angina (HR, 0.83; $P = 0.014$) in comparison to placebo when added to standard antianginal therapy. Nicorandil is not approved for use in the United States.

Metabolic Agents.

Agents aimed at increasing the metabolic efficiency of cardiac myocytes have also been studied in patients with chronic stable angina. Partial inhibitors of fatty acid oxidation appear to shift myocardial metabolism to more oxygen-efficient pathways. Trimetazidine and perhexiline are drugs that have been shown to inhibit fatty acid metabolism and reduce the frequency of angina without hemodynamic effects in patients with chronic stable angina.[173] These agents are not available for clinical use in the United States but are prescribed in other regions of the world.[174]

Other Considerations of Medical Management of Angina Pectoris

Choice of Initial Therapy

Selection of initial therapy for angina pectoris is reasonably based on an individualized approach to each patient that considers other CV conditions such as hypertension, tachyarrhythmias, conduction system disease, PAD, and LV dysfunction, as well as other non–cardiac-related medical conditions such as severe reactive airways disease, DM, or depression. Comparative studies of antianginal agents have not shown any meaningful difference in efficacy to differentiate one specific class of agents from another for patients with SIHD and no previous MI. Rather, selection of the optimal agent is usually based on overall consideration of the management of coexisting conditions, tolerability, and cost. For most patients, beta-blocking agents or calcium channel antagonists, which are effective and low cost, remain the first line of therapy.

Relative Advantages of Beta-Blocking Agents and Calcium Antagonists

The choice between a beta-blocking agent and a calcium channel antagonist as initial therapy in patients with chronic stable angina is controversial because both classes of agents are effective in relieving symptoms and reducing ischemia[28] (**Table 61.10**). Trials comparing beta blockers and calcium antagonists have not shown any difference in the rate of death or MI,[70] although in some studies, beta blockers appeared to have greater clinical efficacy and less frequent discontinuation because of side effects. Because long-term administration of beta blockers has been demonstrated to prolong life in patients after acute MI (**see Fig. 61.7A**), it is reasonable to consider beta blockers over calcium antagonists as the agents of choice in treating patients with SIHD.[28] Nevertheless, as highlighted by a large observational study, definitive evidence to support this preference is not available (**see Fig. 61.7B**).[132] In addition, these drugs may produce fatigue, depression, and sexual dysfunction. In contrast, although calcium antagonists do not show these adverse effects, their long-term administration has *not* been shown to improve long-term survival after acute MI.

TABLE 61.10

Recommended Use of Beta-Blocking Agents or Calcium Antagonists in Patients Who Have Angina in Conjunction with Other Medical Conditions

CLINICAL CONDITION	RECOMMENDED DRUG
Cardiac Arrhythmia or Conduction Disturbance	
Sinus bradycardia	Nifedipine, amlodipine
Sinus tachycardia (not caused by cardiac failure)	Beta-blocking agent
Supraventricular tachycardia	Beta-blocking agent, verapamil, or diltiazem
AV block	Nifedipine or amlodipine
Rapid atrial fibrillation	Beta-blocking agent, verapamil, or diltiazem
Ventricular arrhythmia	Beta-blocking agent
Left Ventricular Dysfunction	
Heart failure	Beta-blocking agent
Miscellaneous Medical Conditions	
Systemic hypertension	Beta-blocking agent or calcium antagonist
Severe preexisting migraine headaches	Beta-blocking agent, verapamil or diltiazem
COPD with bronchospasm or asthma	Nifedipine, amlodipine, verapamil, or diltiazem
Hyperthyroidism	Beta-blocking agent
Raynaud syndrome	Nifedipine or amlodipine
Claudication	Calcium antagonist
Severe depression	Calcium antagonist

COPD, Chronic obstructive pulmonary disease.

Selection of Therapy

The choice of drug with which to initiate therapy for management of angina is influenced by a number of clinical factors[28] (**Table 61.10**):

1. In patients with a history of asthma or chronic obstructive lung disease with wheezing on clinical examination, in whom beta-blocking agents, even relatively selective agents, may not be tolerated, calcium antagonists or nitrates are preferred, and ranolazine is an option. A trial of a beta blocker should be considered if the patient has a history of previous MI or LV dysfunction.
2. Nifedipine (long acting), amlodipine, and nicardipine are the calcium antagonists of choice in patients with chronic stable angina and sick sinus syndrome, sinus bradycardia, or significant AV conduction disturbances, whereas beta blockers and verapamil should be used only with great caution in such patients. In patients with symptomatic conduction disease, neither a beta blocker nor a heart rate–lowering calcium antagonist should be used unless a pacemaker is in place. If a beta blocker is required in patients with asymptomatic evidence of conduction disease, pindolol, which has the greatest ISA, is useful. In the case of calcium channel–blocking agents in patients with conduction system disease, amlodipine, nifedipine or nicardipine are preferable to verapamil and diltiazem. Nitrates and ranolazine are alternatives.
3. Calcium antagonists or long-acting nitrates are preferred for patients with suspected Prinzmetal variant angina; beta blockers may even aggravate angina under these circumstances.
4. Calcium antagonists may be preferred over beta blockers in patients with significant, symptomatic peripheral artery disease because the latter may cause peripheral vasoconstriction.
5. Beta-blocking agents should usually be avoided in patients with a history of significant depressive illness and should be avoided or monitored for exacerbation of symptoms in patients with sexual dysfunction, sleep disturbance, nightmares, fatigue, or lethargy.
6. The beneficial effects of beta blockers on survival in patients with LV dysfunction after MI, coupled with their beneficial effects on survival and LV performance in patients with heart failure, have established beta-blocking agents as the drug class of choice for the treatment of

angina in patients with LV dysfunction, with or without symptoms of HF, together with ACE inhibitors or ARBs. If a beta blocker is not tolerated or angina persists despite beta blockade and nitrates, amlodipine can be administered. Ranolazine is also an option for such patients. In countries where it is available, ivabradine may be considered in patients with angina in conjunction with LV dysfunction and HR above 70 beats/min who are receiving beta-blocker therapy. Verapamil, nifedipine, and diltiazem should be avoided.

7. Hypertensive patients with angina pectoris do well with either beta blockers or calcium antagonists because both have antihypertensive effects, and an ACE inhibitor should strongly be considered for all patients with CAD and hypertension. Although less effective as antihypertensive agents, present professional society guidelines favor use of beta blockers in patients with angina and hypertension, with nondihydropyridine calcium channel blockers as an alternative if symptom relief or control of hypertension is inadequate with the beta blocker. Carvedilol has a more robust effect than metoprolol on BP and is better tolerated than labetalol, so carvedilol may be the preferred beta blocker for patients with angina and hypertension.

Combination Therapy

A combination of multiple agents is widely used for the management of chronic stable angina, with options that include a beta blocker, calcium antagonist, long-acting nitrate, or ranolazine, which may be particularly useful when the HR, BP, or LV dysfunction limits escalation of other therapy. In patients with moderate or severe LV dysfunction, sinus bradycardia, or AV conduction disturbances, combination therapy with nondihydropyridine calcium antagonists and beta blockers should be avoided or should be initiated with caution. The negative inotropic effects of calcium antagonists are not usually a problem in combined therapy with low doses of beta blockers but can become significant with higher doses. With such doses, amlodipine is the calcium antagonist of choice, but it should be used cautiously. Ranolazine may be useful in such patients who do not tolerate other agents.

Synthesis of Integrated Approach to Management of Patients with Chronic Angina

1. Identify and treat precipitating factors, such as anemia, uncontrolled hypertension, thyrotoxicosis, tachyarrhythmias, uncontrolled heart failure, and concomitant valvular heart disease.
2. Initiate risk factor modification, physical exercise, diet, and lifestyle counseling. Commence therapy with a high-intensity statin regimen.
3. Begin pharmacotherapy with aspirin and a beta blocker or calcium antagonist. Initiate an ACE inhibitor in all patients with an LV ejection fraction of 0.40 or lower and in those with hypertension, diabetes, or chronic kidney disease. In addition, an ACE inhibitor should be considered for all other patients.
4. Use sublingual nitroglycerin for alleviation of anginal symptoms and for prophylaxis, if needed.
5. If angina persists, the next step is usually the addition of a second agent: a calcium antagonist or beta blocker, or long-acting nitrate with dosing schedules that prevent nitrate tolerance. The need to treat concomitant hypertension or the presence of LV dysfunction and symptoms of HF may be an indication for the use of one of these agents, even in patients in whom episodes of symptomatic angina are infrequent. Ranolazine is an alternative for some patients, particularly those in whom initiation or titration of other agents is limited by low HR or BP.

6. If angina persists despite two antianginal agents (usually a beta blocker with a long-acting nitrate preparation or a calcium antagonist), add a third antianginal agent. Selection of the agent will be guided by potential side effects and the presence or absence of concomitant hypertension, relative hypotension, conduction system disease, tachyarrhythmias, or LV dysfunction.
7. Coronary angiography, with a view to considering coronary revascularization, is indicated in patients with refractory symptoms or ischemia despite guideline-directed medical therapy. Coronary angiography should also be carried out in patients with high-risk noninvasive test results (**see Table 61.3**) and in those whose occupation or lifestyle requires a more aggressive approach.

Nonpharmacologic Treatment Approaches.

These therapies are generally considered only for patients who have refractory ischemic symptoms after failing medical therapy with multiple agents and coronary revascularization (see later, Revascularization Approaches in Stable Ischemic Heart Disease).

Enhanced External Counterpulsation.

The use of enhanced external counterpulsation (EECP) is another alternative treatment of refractory angina.[175] EECP is generally administered as 35 1-hour treatments over 7 weeks. Observational data have suggested that EECP reduces frequency of angina and use of nitroglycerin and improves exercise tolerance and quality of life, and responses can last for up to 2 years. In a randomized, double-blind, sham-controlled study of EECP for patients with chronic stable angina, active counterpulsation was associated with an increase in time to ST-segment depression during exercise testing and a reduction in angina, as well as an improvement in health-related quality of life that extended to at least 1 year. There are no definitive data that EECP reduces the extent of ischemia as determined by MPI.

The mechanisms underlying the effects of EECP are poorly understood. Possible mechanisms include (1) durable hemodynamic changes that reduce myocardial O_2 demand; (2) improvement in myocardial perfusion caused by the capacity of increased transmyocardial pressure to open collaterals; and (3) elaboration of various substances that improve endothelial function and vascular remodeling caused by augmented flow through the arterial vascular bed, thereby resulting in an improvement in systemic arterial compliance.[176] Finally, the possibility of placebo effects should be recognized; most of the evidence demonstrating favorable effects of EECP is derived from uncontrolled studies, and data from sham-controlled studies are few.

Spinal Cord Stimulation.

An option for patients with refractory angina who are not candidates for coronary revascularization is spinal cord stimulation using a specially designed electrode inserted into the epidural space.[177] The beneficial effects of neuromodulation on pain with this technique are based on the gate theory, in which stimulation of axons in the spinal cord that do not transmit pain to the brain will reduce input to the brain from axons that do transmit pain. Regardless of the mechanism, several observational studies have reported success rates of up to 80% in terms of reducing the frequency and severity of angina. Small randomized trials, including one sham-controlled study, have indicated improvements in symptoms and functional status.[178] Less easily explained is an apparent anti-ischemic effect of this technique.[179] This approach should be reserved for patients in whom all other treatment options have been exhausted.

Transmyocardial Revascularization.

See later, Transmyocardial Laser Revascularization.

Gene (Angiogenesis) Therapy.
See Chapter 30.

Revascularization Approaches in Stable Ischemic Heart Disease (See Chapter 62)

Approach to Decision Making Regarding Revascularization

Ischemic heart disease represents as a dynamic continuum of disease with a variable natural history that may, over decades, encompass many phases of clinical expression ranging from asymptomatic periods, development of chronic exertional angina, subsequent quiescent periods, progression to accelerating angina, and culmination in unstable angina, acute MI, HF, or SCD (**see Chapters 23, 42, 58, and 60**). Therefore, the approach to treatment should be tailored to the individual patient's clinical status. Atherosclerosis is typically a diffuse or multifocal process that requires a comprehensive, systemic approach to management. Moreover, myocardial ischemia may also occur in the absence of obstructive CAD. In general, the principles guiding patient management are predicated on addressing two simultaneous goals, if possible: (1) use of disease-modifying therapies or approaches to prolong life and reduce major adverse cardiovascular events (MACE) such as acute MI, hospitalization for ACS, or HF, and (2) optimization of the patient's health status, quality of life, and functional capacity such that angina or ischemia do not have an adverse impact on activities of daily living (ADLs).[28]

The benefits of revascularization on the natural history of SIHD are proportional to the patient's underlying risk, which makes it essential to quantify the patient's prognosis as accurately as possible (**see Table 61.3**). In addition to the patient's MACE risk, sociodemographic factors such as age, physical capacity, ability to adhere to prescribed treatments and lifestyle interventions, overall quality of life, other medical conditions, and patient preferences should be considered. Each of these aspects should be integrated in considering how best to achieve these two fundamental goals of therapy for patients with SIHD. Revascularization approaches are an integral component of an overall management strategy to improve outcomes and are used when needed in addition to guideline-directed medical therapy (GDMT). The success of catheter-based or surgical treatment is predicated on the overall success of GDMT and lifestyle intervention as a platform for the management of all patients with SIHD. Decisions regarding the best mode of revascularization (catheter based or surgical) should follow a thoughtful assessment of whether and when revascularization is necessary to achieve these goals of therapy and are best made by a multidisciplinary heart team that includes a noninterventional cardiologist, an interventional cardiologist, and a cardiac surgeon. Patients are also critical participants in decision making in terms of their preferences.[180]

Patient Selection for Revascularization

Each of the following considerations may be used to guide decisions regarding the indications for, as well as the approach to, revascularization: (1) the presence and severity of symptoms, (2) physiologic significance of the coronary lesions and other anatomic considerations, (3) extent of myocardial ischemia and presence of LV dysfunction, and (4) other medical conditions that influence the risks associated with percutaneous or surgical revascularization and longevity after revascularization.

Presence and Severity of Symptoms

A goal of therapy is complete elimination of angina and resumption of full physical function to the extent

possible.[28] Coronary revascularization (catheter based or surgical) should be considered if ischemic symptoms persist after intensification of medical therapy, or if unacceptable side effects or the patient's therapeutic preferences limit antianginal therapy (see earlier, Assessment and Classification of Angina Pectoris).

Significance of Coronary Lesions (and Other Anatomic Considerations)

Seventy percent or greater stenosis of an epicardial coronary artery is considered to be anatomically significant (≥50% for left main coronary stenosis). Thus the professional guidelines that have influenced clinical practice regarding revascularization have been framed principally around these anatomic criteria —number of diseased vessels and extent and severity of anatomic disease—together with integration of functional considerations: magnitude and distribution of ischemia and amount of threatened myocardium.[28] Data from the large, prospective Clinical Outcomes Utilization Revascularization and Aggressive Drug Evaluation (COURAGE) randomized trial of PCI versus medical therapy examined the relationship between the severity of stenosis and the extent of angiographic CAD by using quantitative coronary angiography in a core laboratory, and contrary to conventional wisdom, no anatomic subset of CAD stenosis severity (including patients with 70% to 90% narrowing and >90% narrowing of LAD) was found to benefit from PCI versus medical therapy with respect to long-term clinical events.[28]

Moreover, clinicians also face clinical uncertainty regarding the potential significance of “borderline” visual coronary stenoses, nominally defined as lesions in the 50% to 70% range. It is widely acknowledged that angiographically determined stenosis severity expressed as the percentage of luminal narrowing is often an inaccurate measure of a lesion's functional significance.[2,3,65,181] Even though cardiac surgeons have considered 50% or greater stenosis as the criterion for “significant,” many factors other than visual stenosis severity (e.g., lesion eccentricity, tortuosity, presence of plaque rupture or asymmetric luminal filling defects, presence of additional serial lesions) can potentially render a 50% to 70% stenosis “functionally or hemodynamically significant.” Multiple additional techniques, such as IVUS, OCT, and coronary pressure/flow measurements (see earlier, Invasive Assessment, and **Chapter 20**), provide enhanced assessment of the anatomic and functional significance of specific coronary lesions and may complement stress testing to aid in decision-making judgments on the potential benefits of revascularization.

Other anatomic features, in addition to lesion severity, also influence the likelihood of success and the approach to revascularization for a given patient.[33] Such features include vessel size, extent of calcification, tortuosity, and relationships to side branches (**see Chapter 62**). Patients with diffuse severe disease of the distal coronary arteries may be poor candidates for any revascularization procedure.

Fractional Flow Reserve

Measurement of FFR is extremely useful for guiding appropriate decisions regarding revascularization of intermediate stenoses[65,182] (see earlier, Invasive Assessment, and **Chapters 57 and 62**). In a study of 325 patients with an intermediate stenosis scheduled for PCI, patients with an FFR higher than 0.75 (56%) were randomly assigned to PCI or medical therapy. Patients managed medically had a risk for cardiac death or MI that was less than 1% per year over the first 5 years and was not increased relative to the group who underwent stenting through 15-years of follow-up.[183] Subsequently, FFR was evaluated in the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial, in which patients were randomly assigned to conventional PCI, guided by visual assessment of the angiogram, or FFR-guided PCI (with PCI performed only in lesions with FFR ≤0.8). The results showed a lower 2-year rate

of death or MI with the FFR-guided strategy. From 2 to 5 years, the risks with the two strategies were similar. Therefore, at 5 years, outcomes in the two treatment groups were also similar; however, the FFR-guided group had a lower number of stented arteries and less resource use.[184] Nonetheless, the FAME trial did not include a comparison group that received GDMT without revascularization. The FAME 2 trial did include a comparison group receiving GDMT without revascularization[64] (see later, Comparisons between Percutaneous Coronary Intervention and Medical Therapy). The FAME 3 trial is testing use of FFR to guide multivessel PCI and is comparing FFR-guided PCI with contemporary drug-eluting stents to CABG in patients with three-vessel disease.[185]

Extent of Ischemia and Presence of Left Ventricular Dysfunction

The three major determinants of risk in patients with CAD are the extent of ischemia, the number of vessels diseased, and LV function.[23] The extent of ischemia on noninvasive testing is an important predictor of subsequent adverse outcomes and identifies patients in whom revascularization may provide clinical benefit over that of medical therapy beyond the relief of symptoms. The magnitude of the benefit with revascularization versus medical therapy is enhanced in the setting of LV dysfunction. Moreover, the greatest survival benefits of CABG, as well as symptomatic and functional improvements, are evident in patients with impaired LV function (generally defined as LVEF <0.40) (**Tables 61.11 and 61.12**).

TABLE 61.11

Impact of Coronary Artery Bypass Surgery Versus Medical Therapy on Survival*

CATEGORY OF RISK	NUMBER OF VESSELS DISEASED	SEVERITY OF ISCHEMIA	EJECTION FRACTION	RESULTS OF SURGERY ON SURVIVAL
Mild	2	Mild	>0.50	Unchanged†
	3			Unchanged†
Moderate	2	Mod. to severe	>0.50	Unchanged†
	3			Improved†
	2	Mild	<0.50	Unchanged†
	3			Improved‡
High	2	Mod. to severe	<0.50	Improved‡
	3			Improved‡

*In subsets of patients studied in the CASS randomized trial and registry studies.

†Randomized trial.

‡Survival improved with surgery versus medicine. In the European Coronary Surgery Trial, patients with double-vessel disease and involvement of the proximal left anterior descending (LAD) coronary artery had improved survival with surgery regardless of left ventricular function.

TABLE 61.12

Effects of Coronary Artery Bypass Grafting (CABG) on Survival in Coronary Artery Bypass Surgery Trialists Collaboration Analysis From 1994*

SUBGROUP	MEDICAL TREATMENT MORTALITY RATE (%)	*P* VALUE FOR CABG VERSUS MEDICAL TREATMENT
Vessel Disease		
One vessel	9.9	0.18
Two vessels	11.7	0.45
Three vessels	17.6	<0.001
Left main artery	36.5	0.004
No Left Anterior Descending Coronary Artery Disease		
One or two vessels	8.3	0.88
Three vessels	14.5	0.02
Left main artery	45.8	0.03
Overall	12.3	0.05
Left Anterior Descending Coronary Artery Disease Present		
One or two vessels	14.6	0.05
Three vessels	19.1	0.009
Left main artery	32.7	0.02
Overall	18.3	0.001
Left Ventricular Function		
Normal	13.3	<0.001
Abnormal	25.2	0.02
Exercise Test Status		
Missing	17.4	0.10
Normal	11.6	0.38
Abnormal	16.8	<0.001
Severity of Angina		
Class 0, I, II	12.5	0.005
Class III, IV	22.4	0.001

*Systematic overview of the effect of CABG versus medical therapy on survival based on data from seven randomized trials comparing a strategy of initial CABG with one of initial medical therapy. Subgroup results at 5 years are shown.

From Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass surgery on survival: overview of 10-year results from randomized trials by the Coronary Artery Bypass Surgery Trialists Collaboration. Lancet 1994;344:563.

Risks Associated with the Procedure

Patients with SIHD may have other medical conditions, such as renal dysfunction, peripheral atherosclerosis, or pulmonary disease, that may influence the patient's suitability for surgical or percutaneous revascularization. For example, in a patient with a history of GI bleeding, the potential need for long-term DAPT after a procedure should be considered. Moreover, a patient with three-vessel CAD and impaired LV function who might derive a more durable survival benefit from CABG may be too high risk clinically to undergo surgery and might be a better candidate for multivessel PCI.

In addition, the following general principles regarding the choice of treatment in patients with SIHD should be considered:

1. For most patients with stable angina, revascularization should not constitute the initial management strategy before evidence-based medical therapy (pharmacologic antianginal therapy, disease-modifying treatments, and therapeutic lifestyle intervention) is initiated and optimized.[28]
2. When improvement in survival is not a relevant consideration, the severity of angina or impairment in health status should play a significant role in determining whether revascularization is appropriate to enhance quality of life (i.e., limiting angina while undergoing GDMT is a more compelling indication than episodic, exertional angina occurring on minimal medical therapy).
3. The patient's treatment preferences should always be a primary consideration in guiding which

treatment strategy should be used.

4. In certain clinical circumstances, it may be difficult to reliably ascertain whether anginal symptoms or anginal equivalents such as exertional dyspnea or fatigue are a direct manifestation of underlying CAD, especially in patients with significant obesity, those who are sedentary, or those who may have coexisting chronic obstructive pulmonary disease. In such settings, symptoms that are either atypical for or nondiagnostic of obstructive CAD may not necessarily improve with revascularization, even when such symptoms coexist with physiologically significant CAD.
5. The decision to proceed with coronary revascularization in a patient with SIHD should entail a thoughtful, transparent discussion of all potential treatment options, with full disclosure of the anticipated benefits and potential risks associated with PCI or CABG relative to GDMT. In an elective setting where urgent/emergency PCI is not being contemplated to reduce the possibility of death or MI, use of a “heart team,” as cited earlier, is both prudent and clinically appropriate. Although ad hoc PCI is typically done once the patient's coronary anatomy is defined in the catheterization laboratory, it is frequently difficult to have the type of discussion that would involve a complete review of the potential risks and benefits of all treatment options by the heart team in this setting.
6. In summary, treatment decisions must be individualized according to the specific clinical features and personal preferences of a given patient (often in collaboration with family members and referring physician), along with informed discussion about the potential risks and benefits of all three therapeutic options.

Percutaneous Coronary Intervention

PCI, which includes percutaneous transluminal coronary angioplasty (PTCA), intracoronary stenting, and related techniques, has continued to evolve significantly over the past three decades. PTCA has been largely supplanted by stenting with the advent of bare-metal stents (BMSs) in the mid-1990s, followed by the introduction of drug-eluting stents (DESs) in 2003 and subsequent evolutions in stent design to include thinner struts and improved drug-eluting platforms and delivery systems to minimize both restenosis and acute, subacute, and late/very late stent thrombosis. Moreover, the practice of interventional cardiology has evolved significantly with improved adjunctive pharmacotherapy and advances in technology other than stenting, such as devices directed at specific technical issues (e.g., rotablation and atherectomy catheters).[186,187] PCI is an important treatment modality in patients with SIHD, particularly in those with chronic angina who remain symptomatic despite optimal GDMT.

Chapter 62 discusses the technical aspects, early outcomes, and long-term outcomes of PCI. This section focuses on comparisons of PCI with medical therapy and when to select PCI as part of a therapeutic strategy.

Among the many desirable features of PCI is the fact that it can be performed during the same clinical encounter as diagnostic angiography. Stable patients can often be discharged on the same or next day, and clinical recovery is usually complete within 1 week. In many patients, relief of symptoms may be immediate and dramatic. Such attributes can motivate some patients to elect to undergo PCI even when medical therapy alone may lower overall risk with equivalent long-term outcomes.

Early Outcome.

Continued improvement in the technical aspects of PCI (predominantly coronary stenting), as well as increasing operator experience, has had a favorable impact on the rate of primary success and the rate of reductions in complications. The ACC National Cardiovascular Data Registry (ACC-NCDR) has reported an angiographic success rate of 96% and a procedural success rate (angiographic success without death, heart attack, or emergency revascularization) of 93% in patients undergoing PCI. The incidence of death before hospital discharge is less than 1%, and emergency CABG is required in 0.3% of cases. The ACC-NCDR has also reported a periprocedural MI rate of 1%. Although studies using routine assessment of cardiac biomarkers have reported higher rates, the significance of increases in these periprocedural biomarkers is debated.[188] With modern-generation DESs, the rate of restenosis is now less than 10%, with a corresponding approximately 20% decrease in the need for repeat revascularization procedures relative to the era of BMSs. Outcomes in specific challenging subgroups of patients, such as those with chronic total occlusions or left main coronary stenosis, are discussed in **Chapter 62**. Advances in technology have improved success rates in both these anatomic settings; for example, technical success rates greater than 70% have been reported for PCI of chronic total occlusions, supporting this approach as a reasonable alternative (class IIa) in patients with appropriate clinical indications and suitable anatomy when performed by operators with appropriate experience.[189]

Long-Term Outcome

Stenting versus Angioplasty.

Compared with balloon angioplasty, coronary stenting reduces MACE by approximately 40% as a result of reduced repeat revascularization, without a detectable decrease in mortality or rate of MI.[33]

Restenosis and Late Stent Thrombosis.

See Chapter 62.

Comparisons Between Percutaneous Coronary Intervention and Medical Therapy

Studies comparing balloon angioplasty with medical therapy in the present era are of uncertain clinical relevance today because both PCI and medical treatments have undergone profound changes over the past two decades. Moreover, randomized clinical trials comparing PCI with medical therapy are few in number and have involved fewer than 9000 patients (in total). Most have enrolled patients with predominantly single-vessel disease and were completed before the routine use of coronary stenting and enhanced adjunctive pharmacotherapy. In aggregate, the results of these 16 trials have supported better control of angina, improved exercise capacity, and improved quality of life in patients treated with angioplasty versus medical therapy.[28,190] However, a meta-analysis of eight trials of stenting versus medical therapy indicated that the initial improvement in relief of angina with PCI over medical therapy is not sustained in the era of contemporary medical therapy[28,190] (**Fig. 61.11**). In addition, no randomized trial or meta-analysis has demonstrated a reduction in death or MI with PCI versus medical therapy for patients with SIHD.

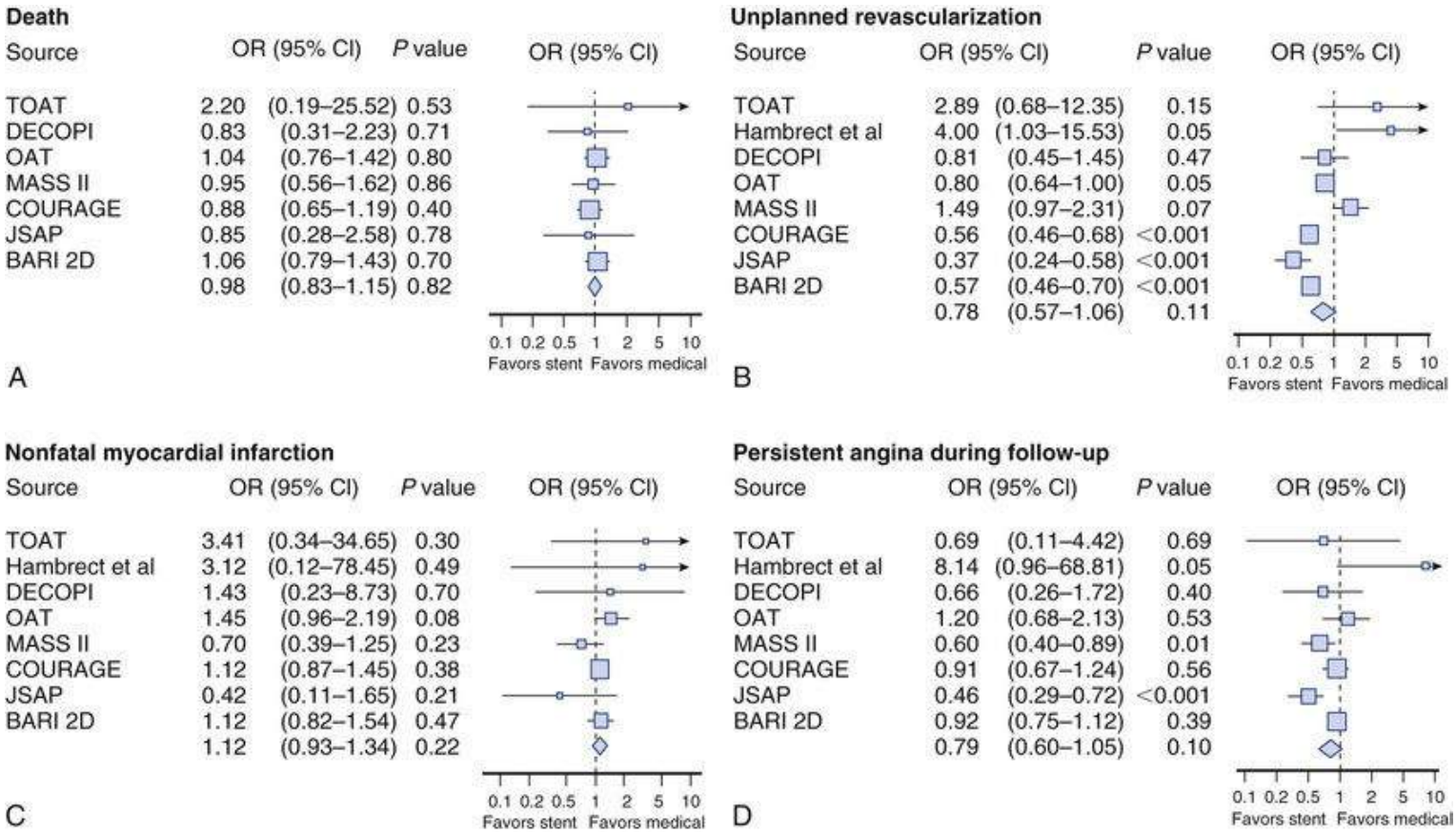


FIGURE 61.11 Meta-analysis of coronary stent implantation versus medical therapy. Data are developed in eight trials enrolling 7229 patients, including three trials of stable patients after myocardial infarction (MI), and five studies enrolled patients with stable angina and/or ischemia on stress testing. Mean weighted follow-up was 4.3 years. There was no evidence of benefit of initial coronary stenting compared with initial medical therapy for prevention of death **(A),** unplanned revascularization **(B),** nonfatal MI **(C),** or persistent angina **(D).** OR, Odds ratio. (Modified from Stergiopoulos K, Brown DL. Initial coronary stent implantation with medical therapy vs medical therapy alone for stable coronary artery disease: meta-analysis of randomized controlled trials. Arch Intern Med 2012;172:312-9.)

Between 1999 and 2004, 2287 patients with objective evidence of ischemia and proximal angiographic CAD (≥70% visual stenosis) were randomized to GDMT with or without PCI in the COURAGE trial.[28] Its goal was to test a strategy of routine, anatomically driven PCI plus GDMT versus a strategy of PCI, if needed, for failure of initial GDMT. During a median follow-up of 4.6 years, death or MI occurred with similar frequency in both arms (HR for PCI + GDMT versus GDMT, 1.05; 95% CI 0.87 to 1.27; P = 0.62) (**Fig. 61.12**). Thus the main study findings indicated that as an initial management strategy in patients with SIHD, PCI did not reduce death, MI, or other MACE when added to GDMT. Patients initially treated with PCI had less angina at 1 and 3 years, but not at 5 years, than did patients initially treated without initial PCI. As expected, in patients who received GDMT initially, subsequent PCI was performed more frequently than in those initially treated with PCI, although only 16.5% of GDMT patients required revascularization during the first year of follow-up, whereas the remaining 16.1% of patients crossed over to revascularization between years 1 and 7.

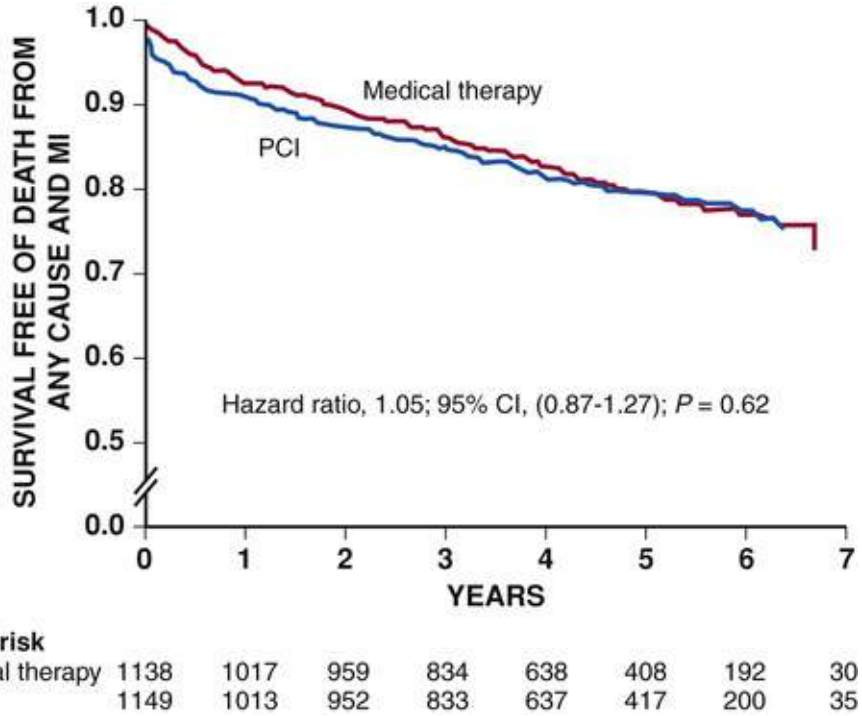


FIGURE 61.12 Outcome in 2287 patients with objective evidence of myocardial infarction (MI) and significant coronary artery disease enrolled in the COURAGE trial and randomly assigned to percutaneous coronary intervention (PCI) and optimal medical therapy (OMT) or to OMT alone. No difference in the primary endpoint of death from any cause or MI was observed between the two treatment groups. (From Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503.)

Subgroup analyses of the COURAGE trial revealed consistency among clinically relevant special populations: no difference between PCI plus OMT versus GDMT in patients with multivessel CAD, low LVEF, CCS class II or III angina, or diabetes. The primary endpoint (death or MI) was similar in the two treatment groups for the subsets with either no to mild ischemia (18% and 19%, respectively, $P = 0.92$) or moderate to severe ischemia (19% and 22%, respectively; $P = 0.53$; interaction P value = 0.65). Moreover, there was no graded increase in events for the overall cohort based on the extent of ischemia. Thus the premise that severe ischemia may identify an important subset of patients with SIHD who may derive clinical benefit from PCI remains unproven.

Although it is plausible results would be different with newer-generation DESs, which are both safer (less stent thrombosis) and more effective (reduced restenosis) than PCI techniques used in COURAGE, no RCTs are yet available comparing newer-generation DESs with GDMT.

Fractional Flow Reserve Strategy

An FFR-guided PCI strategy plus the best available medical therapy was compared with best available medical therapy alone in the FAME 2 trial.[64,182] In this trial, patients who had lesions with an FFR of 0.8 or less in one or more visually stenotic coronary arteries (≥50% stenosis) were randomly assigned to medical therapy alone or PCI plus medical therapy. The plan was to enroll 1632 patients in the study with a projected minimum 2-year follow-up; however, the trial was terminated prematurely after enrollment of 888 patients with a mean follow-up of 7 months, at the recommendation of the data monitoring committee because of a highly significant reduction in the composite primary endpoint of death, MI, or urgent revascularization. The final analysis revealed a 68% relative risk reduction in the primary endpoint from 12.7% in the medical therapy group to 4.3% in the PCI group (HR, 0.32; 95% CI, 0.19 to 0.53; $P < 0.001$). Notably, the difference in this open-label trial was driven solely by a lower rate of urgent revascularization in the PCI group than in the medical therapy group (1.6% versus 11.1%; HR, 0.13; 95%

CI 0.06 to 0.30; $P < 0.001$), with no significant difference in death or MI[182] (**Fig. 61.13**).

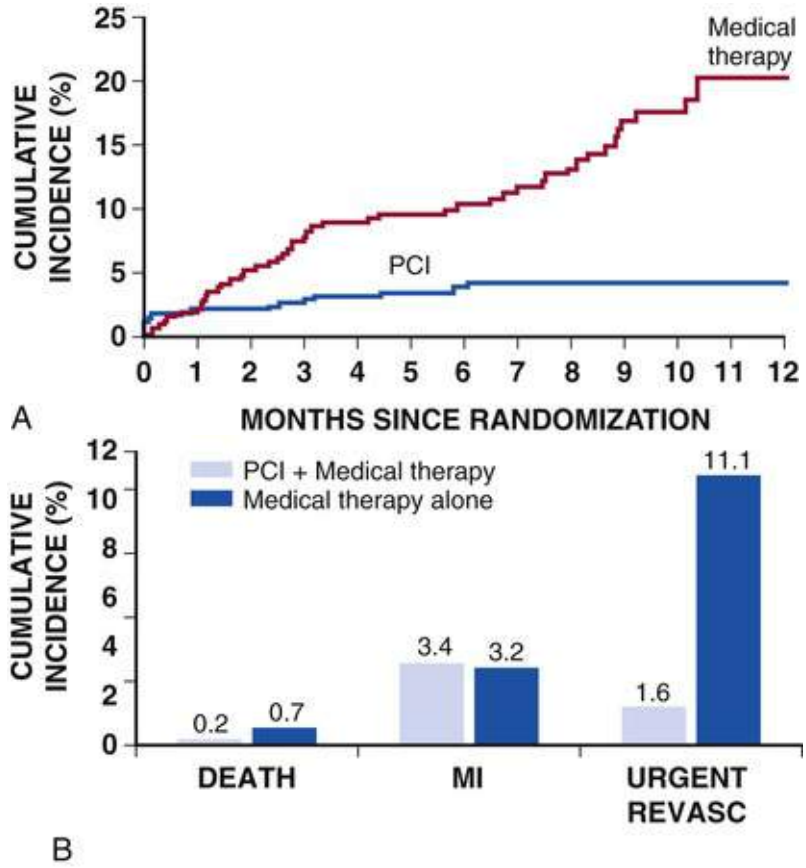


FIGURE 61.13 Outcome of death, myocardial infarction (MI), or urgent revascularization in 888 patients with stable coronary artery disease (CAD) for whom percutaneous coronary intervention (PCI) was being considered. The patients underwent assessment of all stenoses by fractional flow reserve (FFR) and were randomly assigned to FFR-guided PCI plus best available medical therapy or the best available medical therapy alone. **A,** Enrollment was halted prematurely because of a significant reduction in the primary endpoint in patients treated with an FFR-guided revascularization strategy: 4.3% in the PCI group and 12.7% in the medical therapy group (HR with PCI, 0.32; 95% CI 0.19 to 0.53; $P < 0.001$). **B,** However, this effect on the primary endpoint was driven entirely by a reduction in unplanned revascularization (Revasc) rather than by death or MI. (Modified from De Bruyne B, Piljs NH, Kalesan B et al. Fractional flow reserve–guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:998.)

Findings from both the COURAGE and FAME 2 studies show that PCI reduces ischemic symptoms and the need for future revascularization. Neither the FAME 2 trial (with a mean 7 months of follow-up) nor the COURAGE trial (with a mean 55 months of follow-up) showed a reduction in the rate of death or MI with PCI versus GDMT. Although FAME 2 did not test use of FFR versus not used, the findings lend indirect support to current guidelines for the selective use of FFR to guide PCI decision making for borderline visual lesions (50% to 70% stenosis).[182]

Recently two randomized controlled trials compared PCI guided by the newer instantaneous wave-free ratio (iFR) vs. PCI guided by FFR. Randomization to iFR, which allows assessment of the hemodynamic consequences of a stenosis without the use of adenosine vasodilation, was associated with similar major adverse cardiac event rates, but fewer side effects and shorter procedure times.[182a,182b]

In summary, to date, meta-analyses of randomized trials of PCI versus medical therapy for SIHD have demonstrated that mortality, MI, severity and extent of ischemia, and long-term angina do not differ between these two strategies.[28] Nevertheless, the question of whether PCI can reduce the risk for CV death or MI in select patients at higher risk for ischemia remains under investigation. ISCHEMIA

(International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; ClinicalTrials.gov, NCT01471522), funded by the National Heart, Lung and Blood Institute (NHLBI), is presently underway and is designed to evaluate whether revascularization plus GDMT is superior to GDMT alone with respect to CV death or MI in patients with SIHD and documented moderate to severe myocardial ischemia.[191]

At present, based on the best available data from randomized trials, it appears reasonable to pursue a strategy of initial medical therapy for most patients with SIHD and CCS class I or II symptoms and to reserve revascularization for those with persistent and/or more severe symptoms despite GDMT or those with high-risk criteria on noninvasive testing, such as inducible ischemia involving a moderate or large territory of myocardium.[28]

Selection of Percutaneous Coronary Intervention for Revascularization

In addition to general considerations regarding the indications and approach to revascularization (see earlier, Approach to Decision Making Regarding Revascularization), additional factors that need to be weighed in selecting PCI as an option for therapy include the following:

1. The likelihood of successful catheter-based revascularization based on the angiographic characteristics of the lesion.
2. The ability to achieve complete revascularization based on the extent of CAD and the volume of myocardium and the severity of ischemia in the distribution of the artery or arteries amenable to PCI.
3. Although advances in technology have significantly reduced the rates of both acute failure of PCI and target lesion restenosis, consideration of these risks and their potential consequences remain relevant to decision making regarding PCI. The percentage of viable myocardium at risk, the presence of impaired LV function, and the diffuseness and anatomic complexity of CAD, including specific angiographic factors such as small vessel diameter, long lesion length, total occlusion, and saphenous vein graft disease, may be relevant to the potential risks and benefit of PCI.

Percutaneous Coronary Intervention in Specific Subgroups of Patients with Stable Ischemic Heart Disease

Diabetes Mellitus.

Patients with DM are at substantially higher risk for complications after PCI (**see Chapter 51**). Possible explanations for the higher rate of adverse outcomes include a greater burden of coronary atherosclerosis, an altered vascular biologic response to balloon and stent injury, rapid progression of disease in nonrevascularized segments, and higher platelet reactivity. The diabetic atherosclerotic milieu is characterized by a procoagulant state, decreased fibrinolytic activity, increased proliferation, and inflammation. Restenosis is more frequent in patients with diabetes, as is disease progression. For this reason, CABG, which bypasses most of the vessel instead of a specific lesion, may offer a better intermediate- to long-term outcome for patients with multivessel CAD. The optimal strategy for revascularization in patients with DM is discussed later. A strategy of initial GDMT appears to be reasonable for most patients with diabetes and SIHD.[192]

Left Ventricular Dysfunction.

Despite advances in interventional cardiology, LV dysfunction remains independently associated with higher in-hospital and long-term mortality after PCI. Specifically, in patients with stable CAD and estimated EF of 40% or less, 41% to 49%, and 50% or higher in the NHLBI Dynamic Registry, mortality at 1 year after PCI was 11.0%, 4.5%, and 1.9%, respectively. Contemporary trials of PCI versus medical therapy have included too few patients with impaired LV function to guide therapeutic decision making in this important subset of patients.

Women and Older Patients.

Specific issues related to PCI in women and older adults are discussed in **Chapters 88 and 89**. Observational studies have shown higher rates of complications, particularly bleeding, among women compared with men undergoing invasive management. A post hoc study from the COURAGE trial showed that the 40% of the patients 65 years or older had a twofold higher rate of death or MI than younger patients, although no age-related differences in clinical outcomes were noted in patients randomly assigned to PCI or GDMT. Of note, despite the potential increased risk for complications in older patients undergoing PCI, no such increased rate of comorbid conditions (e.g., local vascular complications, worsening renal function, bleeding) was observed.[193]

Renal Dysfunction.

Patients with impaired renal function (generally those with an eGFR <60 mL/min), particularly those with diabetes, are at increased risk for worsening azotemia (**see Chapter 98**), and this is often an important consideration in the physician's decision of whether to proceed with coronary angiography and PCI in such patients. A post hoc analysis from the COURAGE trial showed that patients with decreased renal function had a significantly higher long-term rate of CV events than did those whose eGFR was 60 mL/min or higher, but there was neither evidence of clinical benefit nor harm in patients with reduced renal function who underwent PCI versus GDMT, thus suggesting that treatment decisions in such patients should be appropriately individualized on the basis of anticipated benefits and risks.

Previous Coronary Bypass Grafting.

CABG and PCI are often considered competitive procedures, but it is more appropriate to view them as complementary. An increasing number of patients who have treated with CABG and later have recurrent ischemia undergo revascularization with PCI. The technical aspects and procedural outcomes of PCI in patients with venous bypass grafts are discussed in **Chapter 62**.

Coronary Artery Bypass Grafting

In 1964, Garrett, Dennis, and DeBakey first used CABG as a “bailout” procedure. Widespread use of the technique by Favoloro and Johnson and their respective collaborators followed in the late 1960s. Use of an internal mammary artery (IMA) graft was pioneered by Kolessov in 1967 and by Green and colleagues in 1970. CABG evolved over the next five decades and currently remains an important treatment modality for many patients with SIHD. Most bypass operations continue to be performed through a median sternotomy using cardiopulmonary bypass (CPB) and cardioplegic cardiac arrest, with a smaller number performed without bypass on a beating heart. Less invasive approaches have been developed for select patients who may be appropriate candidates for more limited coronary revascularization, including anterior and lateral thoracotomies, partial sternotomies, and epigastric incisions. The technical goal of bypass surgery is to achieve, whenever possible, complete revascularization by grafting all coronary arteries of sufficient caliber that have physiologically significant proximal stenoses. CABG has been documented to prolong survival, relieve angina, and improve quality of life in specific subgroups of patients with CAD.[194-196]

The annual number of CABG operations in the United States rose steadily over the first three decades, with a peak in the late 1990s. Since then, however, rates of CABG have steadily declined, which is probably related to growth of the use of PCI, particularly in patients with multivessel CAD.[4] CABG provides excellent short- and intermediate-term results in the management of SIHD; its long-term results are affected by failure of venous grafts. Long-term data with totally arterial surgical revascularization (i.e., using bilateral IMA grafts) are few.

Minimally Invasive Coronary Artery Bypass Surgery.

Less invasive or minimally invasive approaches may be divided into four major categories based on the approach and use of CPB.[194] *Port-access* CABG is performed through limited incisions with femoral-femoral CPB and cardioplegic arrest. Port-access technology has also now enabled *totally endoscopic, robotically assisted* CABG (TECAB) surgery to be performed on the arrested heart.[197] *Off-pump* CABG (OPCAB) is performed by using a standard median sternotomy, with generally small skin incisions, and stabilization devices to reduce motion of the target vessels while anastomoses are performed without CPB.[198-200] Finally, *minimally invasive direct coronary artery bypass* (MIDCAB) is performed through a left anterior thoracotomy without CPB. Thus, off-pump approaches to CABG include both OPCAB and MIDCAB techniques.

Potential advantages of the minimally invasive approaches include less postoperative patient discomfort, reduced risk for wound infection, and shorter recovery times. Avoidance of CPB may mitigate the risk for bleeding, systemic thromboembolism, renal insufficiency, myocardial stunning, and stroke. Also, the damaging neurologic effects of CABG may result in cognitive impairment, particularly in older adults and those with heavily calcified aortas. Amelioration of the systemic inflammatory response that occurs after CPB is viewed as an additional advantage that may affect these clinical outcomes.

Initial short-term clinical and angiographic outcomes studies suggested that the less invasive techniques could achieve results comparable to those of traditional CABG.[201,202] In 2009, however, a comparative trial of OPCAB versus CABG plus CPB in 2203 patients revealed no difference in death or complications at 30 days (7.0% versus 5.6%, respectively; $P = 0.19$) but a significantly worse 1-year composite outcome of all-cause mortality, nonfatal MI, and need for repeat revascularization in off-pump versus on-pump procedures (9.9% versus 7.4%, respectively; $P = 0.04$). Additionally, in patients undergoing follow-up angiography, the graft patency rate was significantly lower in OPCAB recipients, with no treatment-based differences in neuropsychological outcomes or short-term resource use. Thirty-day outcomes of off-pump versus on-pump CABG in CORONARY (CABG Off or On Pump Revascularization Study) had similar results in 4752 patients randomly assigned to OPCAB versus traditional CABG. Although the duration of the operation and subsequent mechanical ventilation were both reduced, as was the incidence of postoperative bleeding and acute kidney injury, the primary composite outcome of death, MI, stroke, or renal failure requiring dialysis did not differ between groups (9.8% versus 10.3%; HR, 0.95; 95% CI 0.79 to 1.14; $P = 0.59$), but the need for early revascularization was increased.[203] In addition, data on long-term outcomes after OPCAB are conflicting,[202] with concern remaining that poorer graft patency and incomplete revascularization may contribute to a hazard associated with OPCAB. Therefore, although most datasets support reductions in blood loss and transfusion requirements, fewer wound infections, less postoperative AF, lower indices of myocardial injury, shorter duration of mechanical ventilation, and earlier hospital discharge with OPCAB, long-term outcome studies are concerning, and additional data on long-term survival and neurocognitive function are needed to assess the comparative effectiveness of these two approaches.[200]

Novel approaches to coronary revascularization combine a minimally invasive surgical CABG

procedure on the LAD coronary artery (i.e., a left IMA implant to the proximal LAD using OPCAB) with PCI on the remaining vessels.[204] Additional experience with these so-called hybrid revascularization procedures is needed to further clarify appropriate selection criteria and to determine whether this strategy offers important advantages over multivessel CABG alone. Despite initial enthusiasm for TECAB, robotic-assisted CABG remains less than 1% of total CABG volume.[197]

Arterial and Venous Conduits.

The current standard for bypass grafting advocates routine use of an IMA for grafting the LAD and supplemental saphenous vein grafts to other vessels.[205,206] Although the benefits of a single IMA graft over a saphenous vein graft alone are not in dispute, the superiority of bilateral IMA grafts over a single IMA graft is less well accepted. Initial enthusiasm for the use of bilateral IMA grafts was tempered by a higher rate of postoperative complications, including bleeding, wound infection, and prolonged ventilatory support. Wound infection, most notably deep sternal wound infection, has been of particular concern but remains modest in frequency (<3%), except in patients who are obese or have diabetes or those who require prolonged ventilatory support. In a randomized trial of 3102 patients undergoing CABG, the use of bilateral IMA grafts conferred similar CV outcomes at 30 days, 1 year, and 5 years as the use of a single IMA graft, but higher rates of sternal complications.[207] Current professional society guidelines recommend use of bilateral IMA grafts as reasonable (class IIa) in younger patients in the absence of excessive risk of sternal complications.[206,208] Nevertheless, given the increased technical demands and longer operative times of bilateral IMA grafting, it has not been adopted widely. Studies attempting to differentiate patency and outcomes with radial artery grafts versus the right IMA have been inconclusive, and thus either approach is a reasonable option as a second arterial conduit to native arteries with severe stenoses. The uncertainty may be reflected in the variable strength of recommendation from professional societies ranging from class IIb[196] to class I,[208] with a class IIa recommendation in 2015 guidelines from the Society of Thoracic Surgeons.[206]

Patency of Venous and Arterial Grafts.

Early occlusion (before hospital discharge) occurs in 8% to 12% of venous grafts, and by 1 year, 15% to 30% have become occluded. After the first year the annual occlusion rate is 2% and rises to approximately 4% annually between years 6 and 10. Patency rates with IMA grafts are superior. Data regarding patency of radial artery grafts are mixed; although, a network meta-analysis of trials with a minimum of 4 years of follow-up indicates improved patency compared with venous grafts.[209] Arterial grafts are more susceptible to failure because of competitive flow from native blood vessels than saphenous vein grafts (SVGs); thus, arterial grafts should not be used to revascularize borderline stenoses without clear evidence of flow limitation.

Distal Vasculature.

The state of the distal coronary vasculature is important for the fate of bypass grafts. Late patency of grafts is related to coronary arterial runoff, as determined by the diameter of the coronary artery into which the graft is inserted, the size of the distal vascular bed, and the severity of coronary atherosclerosis distal to the site of insertion of the graft. The highest graft patency rates are found when the lumina of vessels distal to the graft insertion are larger than 1.5 mm in diameter, perfuse a large vascular bed, and are free of atheroma obstructing more than 25% of the vessel lumen. For saphenous veins, optimal patency rates are achieved with a lumen of 2.0 mm or larger.

Progression of Disease in Native Arteries.

The rate of disease progression appears to be highest in arterial segments already showing evidence of disease, and it is between three and six times higher in grafted native coronary arteries than in nongrafted

native vessels. These data suggest that bypassing an artery with minimal disease, even if initially successful, may ultimately be harmful to patients, who incur both a risk for graft closure and an increased risk for accelerated obstruction of native vessels. Lesions in the native vessel that are long (>10 mm) and greater than 70% in diameter are at increased risk for progressing to total occlusion.

Effects of Therapy on Vein Graft Occlusion and Native Vessel Progression.

Measures aimed at enhancing long-term patency are generally directed at delaying the overall process of atherosclerosis and thus may have several additional benefits.[210] Secondary preventive therapy, in particular aspirin and lipid-lowering treatment, is important in reducing the risk for failure of venous grafts. Chronic anticoagulant therapy has not been convincingly shown to alter outcomes.

Antiplatelet Therapy.

Several trials have demonstrated the efficacy of aspirin therapy for maintaining early graft patency when started within 24 hours preoperatively, but the benefit is lost when aspirin is started more than 48 hours postoperatively. Aspirin, 75 to 325 mg daily, should be continued indefinitely for long-term secondary prevention. Although the addition of clopidogrel to aspirin is indicated after CABG for patients with ACS, in a trial of 113 patients with SIHD, the addition of clopidogrel to aspirin did not influence the progression of SVG intimal hyperplasia.[211] Thus, routine DAPT after CABG in patients with SIHD (without ACS) is not recommended. Clopidogrel monotherapy should be used for patients who have an allergy or are intolerant to aspirin.

Lipid-Lowering Therapy.

Three randomized trials of lipid-lowering therapy have shown a favorable impact on the development of graft disease. High-intensity statin therapy is indicated for post-CABG patients, since clinical trials comparing intensive versus moderate statin doses confirm similar relative benefit in subgroups with prior CABG.

Patient Selection

Indications for CABG are centered on evidence demonstrating improvement in the quality and duration of life.[194,196,212] The decision to perform revascularization with PCI or CABG is determined largely from the coronary anatomy, LV function, comorbidities that may affect the patient's risk associated with either revascularization procedure, and patient preference (see earlier). CABG is indicated, regardless of symptoms, for patients with CAD in whom survival is likely to be prolonged and for those with multivessel CAD in whom noninvasive testing suggests high risk (**see Table 61.11**). Patients with more extensive and severe CAD have an increasing magnitude of benefit from CABG over medical therapy (**Fig. 61.14 and eFig. 61.4; see also Table 61.12**). Patients with left main and/or three-vessel CAD and, in particular, those with multivessel CAD and LV systolic dysfunction should be considered candidates for CABG to prolong life, whereas similar data support the benefits of CABG in diabetic patients with multivessel CAD if revascularization is needed. Other factors that must always be considered in the decision are general health and non–coronary-related comorbid conditions that influence both the risks associated with surgery and the likelihood of durable functional benefit.

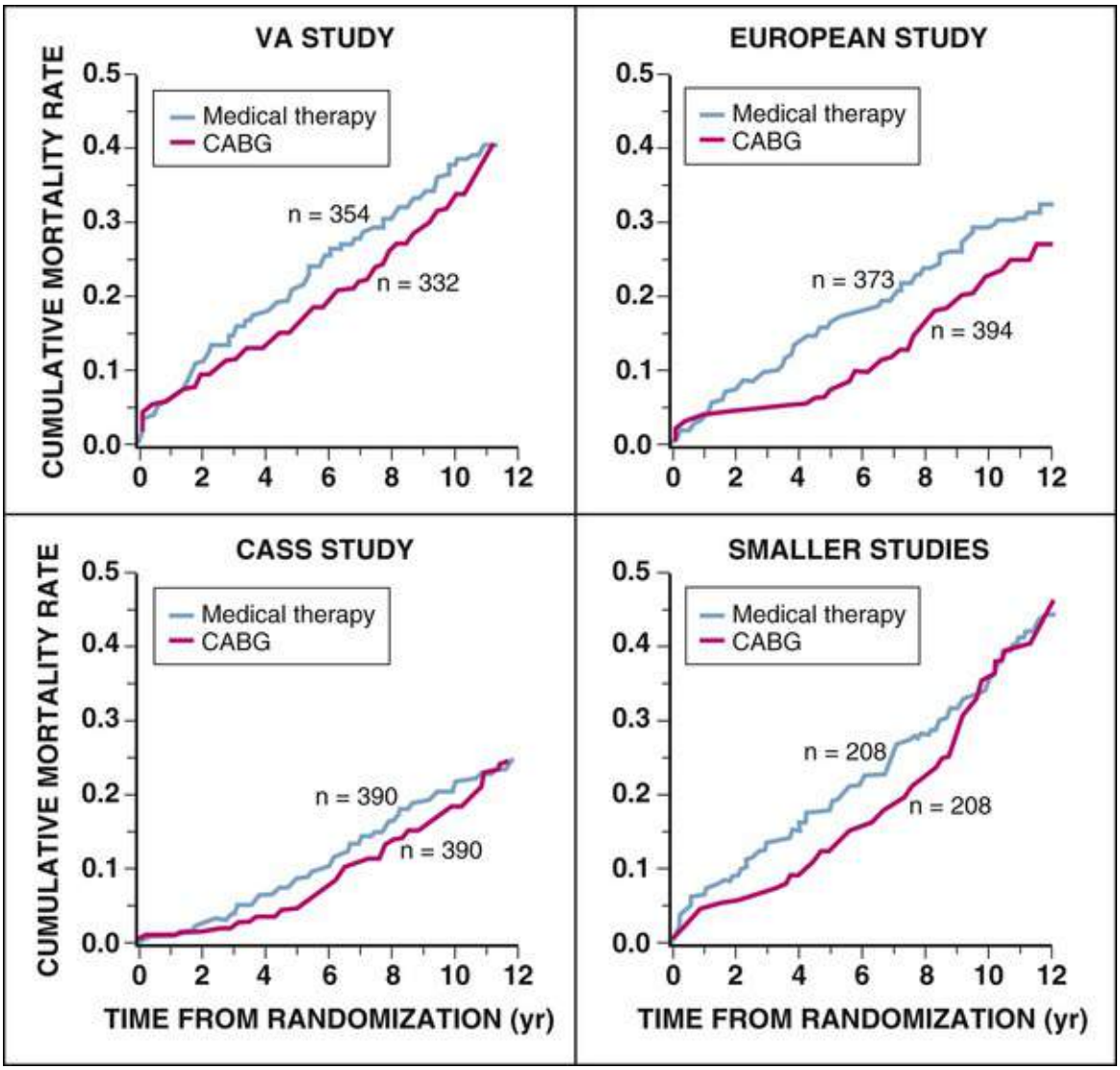
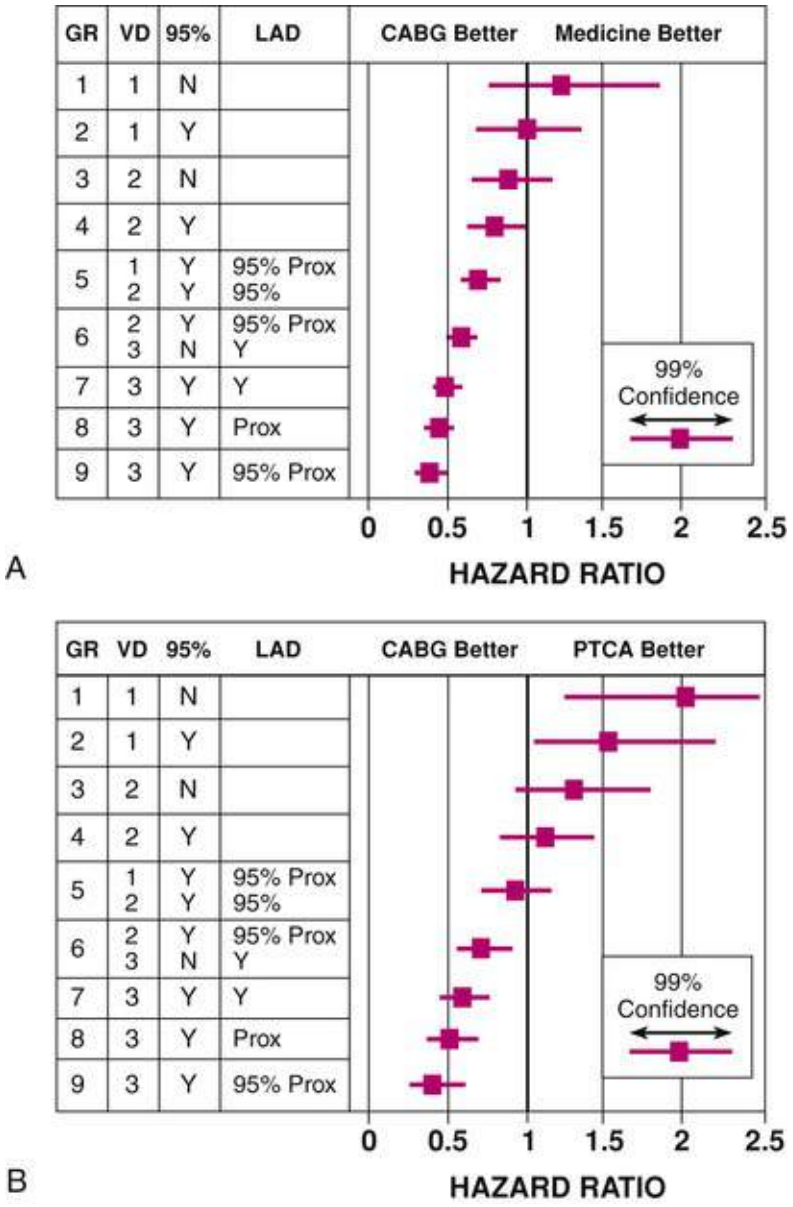


FIGURE 61.14 Survival curves of three large randomized trials of medical therapy versus coronary artery bypass grafting (CABG) and four smaller studies combined. (From Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA guidelines for coronary artery bypass graft surgery: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to Revise the 1991 Guidelines for Coronary Artery Bypass Graft Surgery]. J Am Coll Cardiol 1999;34:1262.)



EFIGURE 61.4 **A,** Adjusted hazard (mortality) ratios comparing CABG surgery and medical therapy for nine coronary anatomy severity groups (GR) according to the number of vessels diseased (VD), the presence or absence of a 95% proximal stenosis, and involvement of the left anterior descending (LAD) coronary artery. **B,** Adjusted hazard (mortality) ratios comparing coronary artery bypass graft (CABG) surgery and percutaneous transluminal coronary angioplasty (PTCA) for nine coronary anatomy groups according to the number of vessels diseased, the presence or absence of a 95% proximal stenosis, and LAD involvement. In patients with the least severe categories of disease, 5-year survival appears to be better with PTCA (single-vessel disease without proximal stenosis and without LAD involvement), whereas for patients with triple-vessel disease and higher grade, more complex double-vessel disease, a survival benefit is noted with surgery. For other subsets of patients with double-vessel disease, no difference in survival was seen in those treated with CABG surgery or PTCA, and many of these patients are probably similar to those included in the randomized trials. (From Jones RH, Kesler K, Phillips HR III, et al. Long-term survival benefits of coronary artery bypass grafting and percutaneous transluminal angioplasty in patients with coronary artery disease. J Thorac Cardiovasc Surg 1996;111:1013.)

Surgical Outcomes and Long-Term Results

The patient population undergoing CABG has been changing over time, particularly with the wider use of PCI. Compared with the 1970s, patients undergoing CABG at present are older, include a higher percentage of women, and are sicker in that a greater proportion have unstable angina, three-vessel CAD, previous coronary revascularization with either CABG or PCI, LV dysfunction, and comorbidities, including hypertension, diabetes, and peripheral vascular disease. Despite the increasing risk profile of

this population, outcomes with CABG have generally remained stable or have improved.

Operative Mortality

Robust multivariable models have been developed and refined with the objective of predicting perioperative mortality. In particular, the Society of Thoracic Surgeons (STS) risk estimator (riskcalc.sts.org) and the European System for Cardiac Operative Risk Evaluation (EuroSCORE, www.euroscore.org) are well-validated risk estimation tools that are available with convenient on-line calculators. Risk indicators for death following CABG that are shared across the available risk tools include (1) preoperative CV factors, including the number of coronary vessels diseased, presence of left main CAD, recent acute MI or ACS event, prior CABG, hemodynamic instability, LV dysfunction, concomitant valvular heart disease, pulmonary hypertension with or without right-sided heart failure, and associated carotid or peripheral vascular disease; (2) preoperative noncardiac comorbid conditions and demographic factors such as older age at surgery, female sex, DM, and pulmonary and renal disease, as well as overall frailty; and (3) intraoperative factors such as ischemic damage and failure to use IMA grafts.

The cumulative mortality in almost 1.6 million isolated CABG operations recorded in the STS database declined from 3.05% between 1997 and 1999 to approximately 2% in 2008 and has remained at that rate through 2015.[213] Moreover, CABG-related mortality has declined substantially over the past two decades when adjusted for changes in clinical risk profile.

Perioperative Complications.

Perioperative morbidity has increased because of a larger fraction of higher-risk patients. The rates of major morbidity in the 144,940 CABG-only operations recorded in the STS database in 2014 were 1.3% for stroke, 2.0% for renal failure, 0.3% for mediastinitis, and 23.4% for AF. Approximately 10% of patients required rehospitalization within 30 days.[213]

Myocardial Infarction.

Perioperative MI, particularly if associated with hemodynamic or arrhythmic complications or with preexisting LV dysfunction, has a major adverse effect on early and late prognosis. The reported incidence varies widely (0% to >10%), in large part because of heterogeneous diagnostic criteria, with a median of 2.9%. The diagnostic criteria for MI in the setting of CABG have been revised and are now based on elevation of cardiac troponin (cTn) or a myocardial creatine kinase (CK) MB isoenzyme level more than 10 times the upper limit of normal in association with objective evidence of new myocardial dysfunction or graft occlusion based on noninvasive imaging or angiography.[214]

Cerebrovascular Complications.

Neurologic abnormalities following cardiac surgery are dreaded complications and are associated with higher long-term mortality.[215,216] Postulated mechanisms include emboli from atherosclerosis of the aorta or other large arteries (potentially precipitated by aortic cross-clamping), emboli from the CPB machine circuit and its tubing, and intraoperative hypotension, particularly in patients with preexisting hypertension.[215] Type I injury is associated with major neurologic deficits, stupor, and coma, and type II injury is characterized by deterioration in intellectual function and memory. The incidence of neurologic abnormalities is variably estimated, depending on how the deficits are defined. Findings of perioperative silent brain injury detected by magnetic resonance imaging (MRI) are present in 25% to 50% of patients after CABG.[217] The incidence of stroke reported in the Northern New England Cardiovascular Disease

Study Group database between 1992 to 2001 was 1.6%, with a higher rate documented in prospective studies (1.5% to 5%). Studies aimed at careful evaluation of neurologic deficits report more frequent neurologic sequelae; type I deficits have been documented in 6% of patients early after CABG, with short-term cognitive decline occurring in 33% to 83%. A prospective long-term study using sophisticated neurocognitive testing revealed cognitive decline in 53% of patients at the time of hospital discharge, in 36% at 6 weeks, and in 24% at 6 months. Older age, in addition to other comorbidities (particularly diabetes), and intraoperative manipulation of the aorta are powerful predictors of the neurologic sequelae of CPB, including stroke, delirium, and neurocognitive dysfunction.[215] In most but not all studies, atherosclerosis of the proximal aorta has also been a strong predictor of stroke, as has use of an intra-aortic balloon pump (IABP). CABG performed without CPB may be associated with reduced risk for stroke.

Atrial Fibrillation.

This arrhythmia is one of the most frequent complications of CABG.[218,219] AF occurs in up to 40% of patients, primarily within 2 to 3 days. In the early postoperative period, rapid ventricular rates and loss of atrial transport may compromise systemic hemodynamics, increase the risk for embolization, and lead to a significant increase in the duration and cost of the hospital stay. AF is associated with a twofold to threefold increase in postoperative stroke. Older age, hypertension, previous AF, and HF are associated with a higher risk for AF after cardiac surgery. Statin therapy may be accompanied by less frequent postoperative AF.[220] Off-pump techniques may be associated with less frequent postoperative AF.

Prophylactic use of beta-blocking agents reduces the frequency of postoperative AF; such drugs should be administered routinely before and after CABG to patients without contraindications. Amiodarone is also effective in prophylaxis against postoperative AF and may be considered in patients at high risk for its development (**see Chapter 38**). However, when the rhythm occurs perioperatively, a strategy of rhythm control is not superior compared to one of rate control with respect to days of hospitalization, complications, or AF rates at 60 days.[218] Up to 80% of patients spontaneously revert to sinus rhythm within 24 hours without treatment other than agents used for controlling the ventricular rate. At 60 days, 94% of the patients in the rate-control group and 98% of those in the rhythm-control group had had a stable heart rhythm without AF for the previous 30 days ($P = 0.02$).[218]

Renal Dysfunction.

The incidence of renal failure requiring dialysis after CABG remains low (0.5% to 1.0%) but is associated with significantly greater morbidity and mortality[221,222] (**see Chapter 98**). Less severe postoperative renal dysfunction is much more common, particularly in patients with advanced age, DM, preexisting renal dysfunction, and HF. Patients with preoperative renal dysfunction and a serum creatinine level that rises to above 2.5 mg/dL appear to be at increased risk for the need for hemodialysis and may be candidates for alternative approaches to revascularization. *N*-acetylcysteine does not appear to prevent the development of renal dysfunction in patients undergoing cardiac surgery. Other interventions proposed to reduce postoperative renal dysfunction, such as treatment with fenoldopam or high-dose statin therapy have also failed.[200,223,224]

Relief of Angina

All the major randomized trials have demonstrated greater relief of angina, better exercise performance, and a lower requirement for antianginal medications at 5 years in surgically treated than in medically treated patients. Independent predictors of recurrence of angina include female sex, obesity, and lack of use of the IMA as a conduit. In patients with three-vessel CAD undergoing CABG, the completeness of

revascularization is a significant determinant of the relief of symptoms at 1 year and over a 5-year period. After 5 years, approximately 75% of surgically treated patients can be predicted to be free of an ischemic event, SCD, occurrence of MI, or recurrence of angina; approximately 50% remain free for approximately 10 years and 15% for 15 or more years.

Effects on Survival

Clinical practice has been shaped by three major randomized trials of CABG versus medical therapy in which patients were enrolled between 1972 and 1984: the VA (Veterans Affairs) trial, the European Cardiac Society Study (ECSS), and the NHLBI-supported CASS[194,196] (**see Fig. 61.14**). The evidence base consists of data from 2649 patients participating in these and several smaller trials and has important limitations with respect to application to current practice because the risk profile of patients referred for surgery, as well as the available surgical and medical interventions, have evolved substantially since these trials were conducted. In particular, these trials antedated the widespread use of IMAs and the disease-modifying therapies (e.g., aspirin, statins, RAS inhibitors) that currently comprise GDMT.

Nevertheless, major points guiding clinical practice have been drawn from a meta-analysis of these trials. In each of the trials, a survival benefit of CABG emerged during midterm follow-up (2 to 6 years), an advantage that eroded during long-term follow-up. Considered together, the results of these trials supported a reduction in long-term mortality (10 years), an absolute 4.1% lowering of mortality rates at the time, with CABG compared with medical therapy ($P = 0.03$). Subgroup analyses revealed several high-risk criteria that identify patients who are likely to sustain a more substantial survival benefit: (1) left main CAD, (2) single- or double-vessel CAD with proximal LAD disease, (3) LV systolic dysfunction, and (4) a composite evaluation that indicates high risk, including severity of symptoms, high-risk exercise tolerance test, history of previous MI, and presence of ST depression on resting ECG.

The combined results of all the trials and registries indicate that the sicker the patient—based on the severity of symptoms or ischemia, presence of DM, number of vessels diseased, and presence of LV dysfunction—the greater the benefit of surgical over medical therapy on survival (**see Table 61.12 and eFig. 61.4**). CABG prolongs survival compared with medical therapy alone in patients with significant left main CAD regardless of symptoms and in patients with three-vessel CAD that includes the proximal LAD irrespective of LV function. The preponderance of evidence indicates that surgical therapy prolongs life in patients with three- and two-vessel CAD with impaired LV function, particularly those with proximal narrowing of one or more coronary arteries and severe angina. Patients with angina or evidence of ischemia at a low or moderate level of exercise, especially those with obstruction of the proximal LAD, may benefit from coronary revascularization by PCI or CABG.

Patients with Depressed Left Ventricular Function (See Chapter 57).

Depressed LV function is one of the most powerful predictors of perioperative and late mortality. In the New York State CABG registry, an EF of 25% or less was associated with 6.5% in-hospital mortality, compared with 1.4% in those with EF greater than 40%.[196] As the population ages and the proportion undergoing reoperation increases, the number of patients with preoperative LV dysfunction and clinical HF will increase. In the CABG Patch trial confined to patients with EF of 35% or less, perioperative mortality was 3.5% for patients without clinical signs of HF versus 7.7% for those with NYHA Classes I to IV HF.[196]

Although the effect of a reduced EF on operative mortality cannot be eliminated, careful attention to

intraoperative metabolic, inotropic, and mechanical support, including preoperative intra-aortic balloon counterpulsation in some patients, may decrease perioperative mortality compared to the mortality rates expected from prediction models. Thus, in experienced centers, in-hospital mortality for patients with severe LV dysfunction is less than 4% to 5%.[225]

The powerful association between preoperative EF and late survival emphasizes that currently the presence of LV dysfunction has changed from a relative contraindication to CABG to a potential indication.[196,226] This shift in perspective occurred in concert with the recognition that viable dysfunctional myocardium may improve after coronary revascularization. Indeed, in the largest meta-analysis of randomized trials of CABG versus medical therapy, the most striking survival benefits of CABG, as well as symptomatic and functional improvements, were shown by patients with impaired LV function, in whom the prognosis with medical therapy is poor.[196]

This conclusion is also supported by large contemporary registries and long-term follow-up of patients with LV dysfunction randomized to CABG plus medical therapy versus medical therapy alone. In a propensity-adjusted observational analysis comparing survival with CABG versus medical therapy in patients with an LVEF less than 35% and no left main stenosis greater than 50%, a survival advantage was observed through 10 years of follow-up.[227] In the randomized STICH (Surgical Treatment for Ischemic Heart Failure) trial of predominantly on-pump CABG versus medical therapy in 1212 patients with CAD amenable to revascularization and EF of 35% or less in the absence of left main CAD or severe (class III) angina, the rate of death from any cause at an average of 56 months after randomization was 36% in patients assigned to CABG and 41% in those assigned to medical therapy (HR, 0.86; 95% CI 0.72 to 1.04; $P = 0.12$). However, the combined endpoint of death or hospitalization for CV causes was significantly lower (58%) in the CABG group than in the medical therapy group (68%; HR, 0.74; 95% CI 0.64 to 0.85; $P < 0.001$; **eFig. 61.5**).[228] Moreover, in the STITCH Extension Study (STICHES), in which follow-up was extended to 10 years, a significant mortality difference emerged favoring the CABG arm (58.9% versus 66.1%; HR, 0.84; 95% CI 0.73 to 0.97; $P = 0.02$ (**Fig. 61.15**).[229]

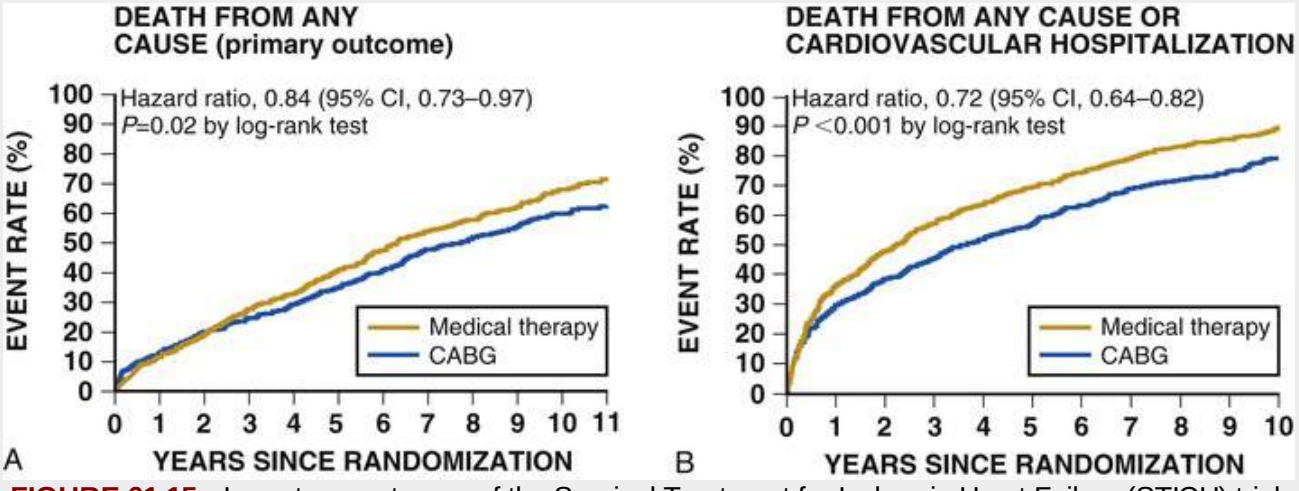
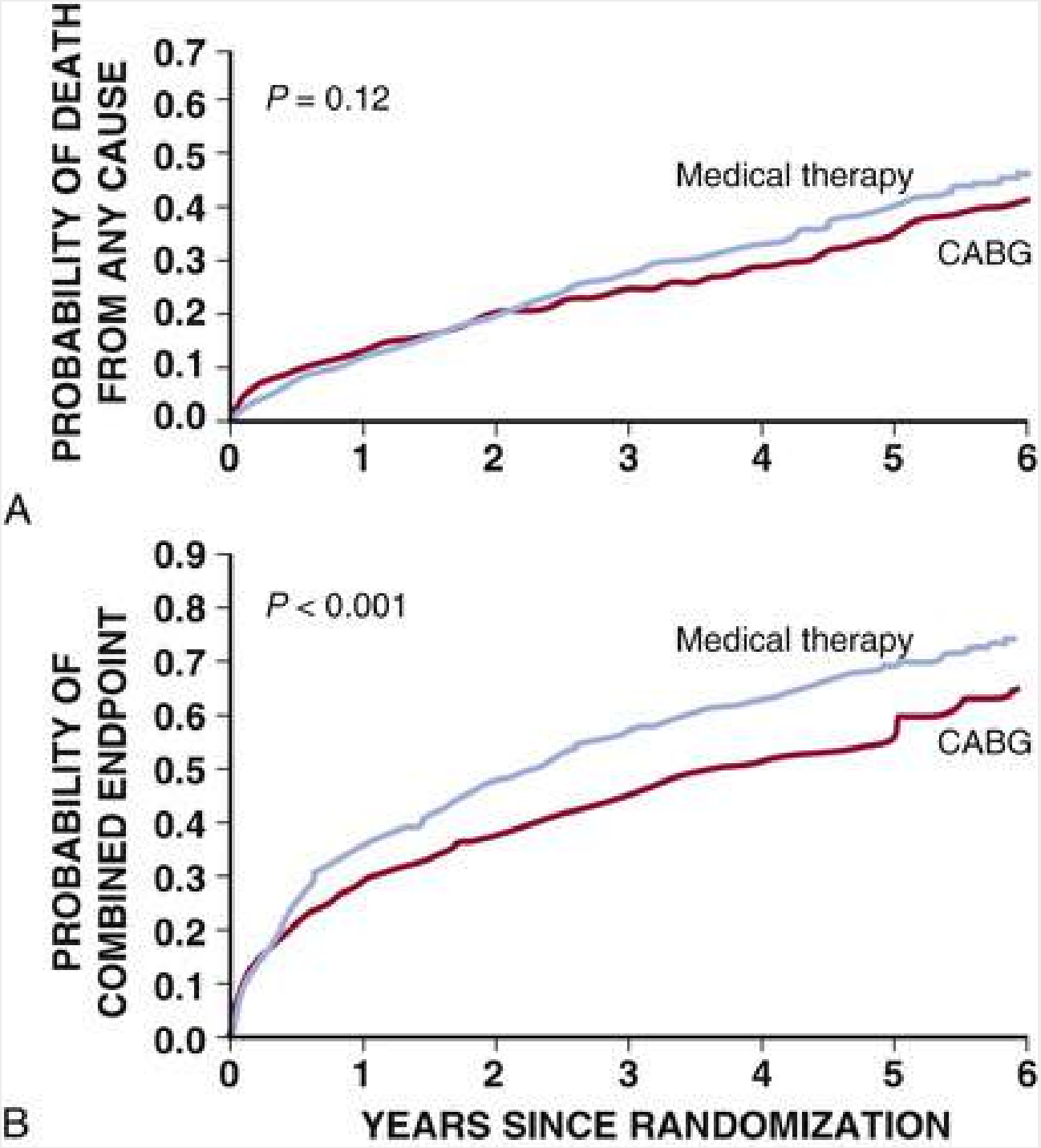


FIGURE 61.15 Long-term outcome of the Surgical Treatment for Ischemic Heart Failure (STICH) trial. The STICH trial included a 1212 patients with an ejection fraction of 35% or less and coronary artery disease amenable to coronary artery bypass grafting (CABG) who were randomly assigned to undergo CABG plus medical therapy or medical therapy alone and followed for 10-years. **A,** Death from any cause occurred in 58.9% of the CABG group and 66.1% in the medical-therapy group (HR, 0.84; 95% CI 0.73 to 0.97; $P = 0.02$ by log-rank test). **B,** Death from any cause or cardiovascular hospitalization was similarly reduced by CABG compared with medical therapy alone. (Modified from Velazquez EJ, Lee KL, Jones RH, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. N Engl J Med 2016;374:1511-20.)



EFIGURE 61.5 Patients (*n* = 1212) with CAD amenable to coronary artery bypass grafting (CABG) and an ejection fraction of 0.35 or less were randomly assigned to medical therapy alone or medical therapy plus CABG. **A,** There was no significant difference in the rate of death from any cause, which occurred in 41% of the medical therapy group and 36% in the CABG group (HR, 0.86; 95% CI, 0.72 to 1.04; *P* = 0.12). **B,** The secondary combined endpoint of death from any cause or hospitalization for cardiovascular causes was lower in the CABG group (58% versus 68%; HR with CABG, 0.74; 95% CI, 0.64 to 0.85; *P* < 0.001). (Modified from Velazquez E, Lee KL, Deja MA, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med 2012;364:1607.)

Although preoperative LV dysfunction creates the potential for significant benefit, the perioperative risk must be considered and weighed in shared decision making with the patient,[226] Despite the absence of a clear impact of myocardial viability on outcomes with CABG in the STICH trial,[230] selective evaluation of patients for viable myocardium may be a reasonable strategy when considering CABG for high-risk patients with severe LV dysfunction.[225]

Myocardial Hibernation (see Chapter 57).

Successful reperfusion of viable but noncontractile or poorly contracting myocardium is a goal of

coronary revascularization in patients with LV dysfunction.[225] Two related pathophysiologic conditions have been described to explain the reversible ischemic contractile dysfunction: (1) *myocardial stunning*, which describes prolonged but temporary postischemic LV dysfunction without myocardial necrosis, and (2) *myocardial hibernation*, or persistent LV dysfunction when myocardial perfusion is chronically reduced (or repetitively stunned) but sufficient to maintain the viability of tissue. The reduction in myocardial contractility in hibernating myocardium conserves metabolic demands and may be protective, but more prolonged and severe hibernation may lead to severe ultrastructural abnormalities, irreversible loss of contractile units, and apoptosis.

Hibernating myocardium can cause abnormal systolic or diastolic LV function, or both. Studies involving PET, thallium-201, and dobutamine echocardiography have demonstrated that patients with LV dysfunction and evidence of hibernating myocardium have a high mortality rate when treated with medical therapy alone. The predominant clinical feature of myocardial ischemia in these patients may not be angina but dyspnea secondary to increased LV end-diastolic pressure. Symptoms of HF resulting from chronic LV dysfunction may be inappropriately ascribed to myocardial necrosis and scarring when the symptoms may in fact be reversible if the chronic ischemia is relieved by coronary revascularization.

Detection of Hibernating Myocardium.

Several clinical and imaging markers may be used to determine the likelihood that a dysfunctional myocardial segment is viable or nonviable (**Table 61.13**). The presence of angina and the absence of Q waves on the ECG and a history of previous MI are useful clues. A severe reduction in the diastolic wall thickness of dysfunctional LV segments is indicative of scarring. On the other hand, akinetic or dyskinetic segments with preserved diastolic wall thickness may represent a mixture of scarred and viable myocardium. Imaging tools that may be used for this assessment (dobutamine echocardiography, PET, contrast-enhanced CMR, CT, thallium rest-redistribution imaging) are discussed in **Chapters 14, 16, and 17**.

TABLE 61.13

Markers of Viable Myocardium

CLINICAL INDICATOR	FEATURE SUGGESTING VIABILITY/NONVIABILITY	DIAGNOSTIC TEST	ALTERNATIVE TEST
Diastolic wall thickness	Wall thickness <6 mm is highly suggestive of nonviable scar.	Standard Echo	CT, CMR
Regional wall motion	Improved wall motion after stimulation with low-dose dobutamine (i.e., contractile reserve) suggests viability.	Low-dose dobutamine Echo	CT, CMR, gated SPECT
Regional blood flow	Late redistribution or redistribution with second tracer injection suggests viability.	SPECT	PET, CMR
Myocardial metabolism	Mismatch between flow (low) and metabolism (active) suggests viability.	PET	SPECT
Myocardial fibrosis	Scar limited to subendocardium suggests viability, whereas transmural or near-transmural scar indicates nonviability.	CMR	CT

CMR, Cardiac magnetic resonance imaging; *CT,* computed tomography; *Echo,* echocardiography; *PET,* positron emission tomography; *SPECT,* single-photon emission computed tomography.

Surgical Treatment in Special Groups

Women (See Chapter 89)

Women are less likely than men to be referred for coronary angiography and subsequent revascularization.[231] In some studies, sex-based differences in referral for revascularization are explained fully by clinical factors. Moreover, it has not been established whether sex-based differences represent underuse of CABG in women, overuse in men, or both. Compared with men, women who undergo CABG

are sicker, as defined by age, comorbid conditions, severity of angina, and history of HF. In-hospital mortality and perioperative morbidity after CABG have remained, on average, 1.5 to 2 times higher in women than in men. However, when adjusted for the greater risk profile of women referred for CABG, short-term mortality rates, as well as long-term outcomes, are similar to those for men in most but not all studies, with similar advantages of CABG over multivessel PCI.[232] With generally similar long-term outcomes after surgical revascularization with risk adjustment, female sex should not be a significant factor in decisions regarding whether to offer CABG.

Older Patients (see Chapter 88)

The aging of the population, in combination with marked improvement in perioperative care and in the outcomes of CABG has resulted in a burgeoning population of elderly patients with extensive CAD undergoing such surgery.[233] The number of individuals older than 75 years in the United States is expected to quadruple in the next 50 years, with CVD the leading cause of morbidity and mortality in this population. Many such individuals are likely to become candidates for CABG.

Older patients are sicker than their younger counterparts in that they have a greater frequency of comorbidities, including peripheral vascular and cerebrovascular disease; more extensive triple-vessel and left main CAD; and a higher frequency of LV dysfunction and history of HF.[196] Not unexpectedly, these differences translate into higher perioperative mortality and complication rates, with a sharp increase in the slope of the curve relating mortality to age in patients older than 70 years. Despite these differences, in-hospital mortality for older adults has declined over time to 7% to 9% in those undergoing CABG only and has been reported as low as 3% to 4% in the subgroup of octogenarians without significant medical comorbid conditions. However, elderly patients with high indices of frailty and disability are at significantly higher risk for major morbidity and mortality during CABG.[234] Given the marked variation in outcomes in older patients undergoing revascularization, decisions should be based on individual risk and needs assessment.

Renal Disease

Cardiovascular disease is the major cause of mortality in patients with end-stage renal disease (ESRD) and accounts for 54% of deaths (**see Chapter 98**). Patients with ESRD, as well as those with less severe renal insufficiency, have numerous risk factors that not only accelerate the development of CAD but also complicate its medical management. These risk factors include diabetes, hypertension with LV hypertrophy, systolic and diastolic dysfunction, abnormal lipid metabolism, anemia, and increased homocysteine levels. Therefore, mild or more severe renal dysfunction is prevalent in as many as 50% of patients undergoing CABG. Coronary revascularization with PCI or CABG is frequently performed in patients with ESRD, but mortality and complication rates are increased. Patients with milder degrees of renal insufficiency who are not dependent on dialysis are also at higher risk for major perioperative complications, longer recovery times, and lower rates of short-term and midterm survival. Observational data have suggested that in patients undergoing chronic dialysis, CABG is the preferred strategy for revascularization over PCI for patients with multivessel CAD.[235-237] However, randomized data are few, and 30-day mortality in patients with ESRD undergoing CABG ranges from 9% to as high as 20%.

Patients with Diabetes (see Chapter 51)

Diabetes is an important independent predictor of mortality in patients undergoing surgical revascularization. Patients with DM have smaller distal vessels, which are deemed to be poorer targets

for bypass grafting. Nevertheless, the patency of arterial and venous grafts appears to be similar in diabetic and nondiabetic patients. Despite these higher risks with operative intervention, because of the potential long-term benefits of CABG in patients with DM and severe CAD, such patients should be considered candidates for CABG[238,239] (see later, Comparisons between Percutaneous Coronary Intervention and Coronary Artery Bypass Surgery).

Coronary Bypass Surgery in Patients with Associated Vascular Disease.

Management of patients with combined CAD and peripheral vascular disease involving the carotid arteries, the abdominal aorta, or vessels of the lower extremities presents many challenges (**see Chapter 64**).

Impact of Combined Coronary Artery Disease and Peripheral Artery Disease.

Clinically apparent CAD occurs frequently in patients with peripheral artery disease (PAD). In patients undergoing peripheral vascular surgery, late outcomes are dominated by cardiac causes of morbidity and mortality. Conversely, in patients with CAD, presence of PAD, even if asymptomatic, is associated with an adverse prognosis, presumably because of the greater total atherosclerotic burden borne by these patients.[240]

Because patients with CAD and peripheral atherosclerosis tend to be older and have more widespread vascular disease and end-organ damage than patients without peripheral atherosclerosis, the perioperative mortality and morbidity consequent to CABG are high and the late outcome is not as favorable. In the Northern New England Cardiovascular database, in-hospital and long-term mortality after CABG were 2- to 2.5-fold greater in patients with peripheral vascular disease than in those without it, with augmented risk for those with lower extremity disease. Diffuse atheroembolism is a particularly serious complication of CABG in patients with aortic atherosclerosis. It is a major cause of perioperative death, stroke, neurocognitive dysfunction, and multiorgan dysfunction after CABG. Nevertheless, given the diffuse nature of CAD in patients with peripheral vascular disease, CABG may have advantages over PCI in many such patients.

Carotid Artery Disease.

In patients with stable CAD and carotid artery disease in whom carotid endarterectomy or stenting is planned, consideration of coronary revascularization can usually be performed after the carotid surgery. The prevalence of significant carotid disease in an increasingly older population being considered for CABG is high; approximately 20% have 50% or greater stenosis, 6% to 12% have 80% or greater stenosis, and the percentage is higher in patients with left main CAD. In patients for whom surgical treatment is being considered for both carotid artery disease and CAD, the merits of a combined versus a staged approach have been debated.[241] Moreover, it remains uncertain whether asymptomatic carotid disease significantly increases the risk for stroke during CABG. Neither the combined nor staged approaches has been demonstrated to be unequivocally superior to the other, and an individualized approach, depending on the patient's initial condition, severity of symptoms, anatomy of the coronary and carotid vessels, and individual institutional experience, is most appropriate. Preoperative or simultaneous carotid stenting is under investigation as an alternative approach to combined carotid endarterectomy and CABG.[242]

Management of Patients with Associated Vascular Disease *(see **Chapter 64**)*.

Patients with severe or unstable CAD requiring revascularization can be categorized into two groups according to the severity and instability of the accompanying vascular disease. When the noncoronary

vascular procedures are elective, they can generally be postponed until the cardiac symptoms have stabilized, either by intensive medical therapy or by revascularization. A combined procedure is necessary in patients with both unstable CAD and an unstable vascular condition, such as frequent recurrent transient ischemic attacks or a rapidly expanding abdominal aortic aneurysm. In some patients in this category, PCI offers the potential for stabilizing the patient's cardiac condition before proceeding with a definitive vascular repair. A problem is posed by the use of clopidogrel after stenting; this will increase bleeding unless surgery is performed at least 5 days after discontinuation of clopidogrel.

Patients Requiring Reoperation

In some centers, as many as 20% of isolated CABG surgeries are cardiac reoperations,[243] with the major indication for reoperation being late disease of SVGs. An added factor underlying recurrent symptoms is progression of disease in native vessels between the first and second operations. Several series have emphasized the sicker preoperative status of patients undergoing reoperation, including older age, more serious comorbid conditions, associated valvular heart disease, and a greater prevalence of LV dysfunction and greater extent of ischemic jeopardized myocardium.

Not unexpectedly, the mortality associated with reoperation is significantly higher than that of initial CABG procedures. At a time when mortality in STS risk estimates was 2.6% for urgent and 6% for emergency first CABG operations, the corresponding rates were 7.4% and 13.5% in patients undergoing repeated CABG. As a result of the higher risk and operative complexity of redo CABG, PCI is increasingly being considered as the first-line option in patients with SVG failure. In such cases, PCI of the native coronary vessels is preferred to SVG PCI because of lower complication rates and better long-term patency. When the native coronary artery has a chronic total occlusion (CTO), revascularization decisions can be challenging. Many CTOs, which previously required redo CABG, can now be successfully revascularized by expert PCI operators in specialized referral centers. However, it has not been demonstrated that CTO PCI improves clinical outcomes.

Comparisons Between Percutaneous Coronary Intervention and Coronary Artery Bypass Surgery

Observational Studies

In observational studies of CABG versus balloon angioplasty, over 1 to 5 years of follow-up, rates of mortality and MI were not significantly different between treatment strategies. However, recurrent events, including angina and the need for repeat revascularization procedures, were significantly more frequent in the PTCA than in the CABG group, largely because of incomplete revascularization and restenosis. More recent studies have compared CABG with coronary stenting. In an analysis of approximately 60,000 patients with multivessel CAD treated with coronary stenting or CABG and recorded in the New York State Registry between 1997 and 2000, CABG was found to be associated with higher survival after adjustment for medical comorbidities in patients with two or more diseased vessels, with or without involvement of the LAD.[196] Results were similar among more than 100,000 propensity-matched Medicare beneficiaries who underwent CABG or multivessel PCI between 1992 and 2008.[244] Similarly, in an analysis of approximately 600,000 patients with multivessel CAD enrolled in the ACC-NCDR and STS databases, the observed 1-year mortality rates were similar between patients who underwent CABG and those who underwent PCI. However, 4-year mortality was significantly lower in the CABG group in multiple sensitivity analyses of potential confounders.[245] A propensity-matched analysis of approximately

18,000 patients who underwent PCI with second-generation DESs (everolimus) or CABG for multivessel CAD showed similar risk of death in the two groups but a higher risk of MI and need for repeat revascularization among patients treated with PCI.[246] The similarity of the rates of survival highlights the role of clinical judgment in selecting the optimal therapy for the individual patient and the ability to achieve good outcomes in appropriately selected patients with multivessel CAD, particularly those without involvement of the proximal LAD coronary artery.

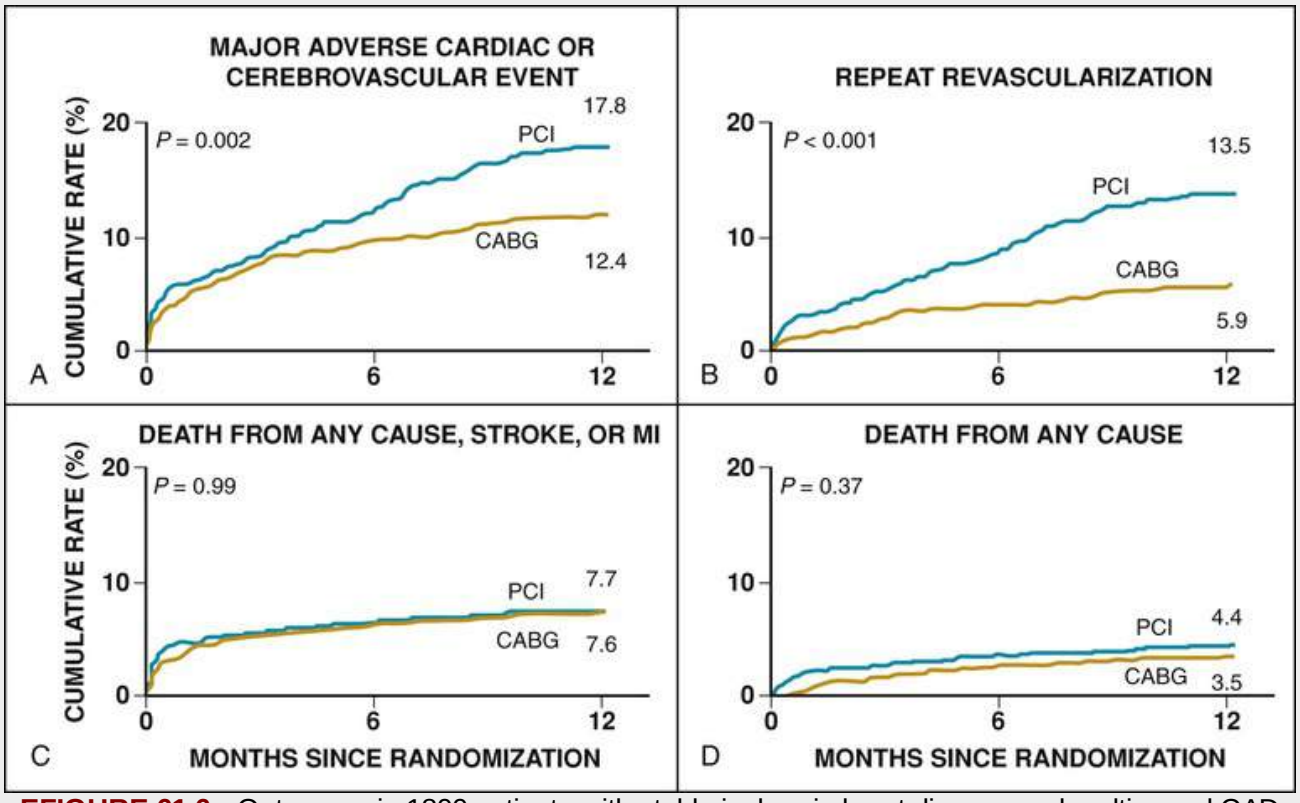
Randomized Trials

Overall, the findings from randomized trials indicate that in selected patients with multivessel CAD and preserved ejection fraction, CABG results in fewer repeat revascularizations and fewer symptoms without a significant difference in survival when compared with multivessel PCI.

Percutaneous Coronary Intervention Versus Coronary Artery Bypass Surgery in Patients with Multivessel Disease.

At least 10 published randomized studies have compared PCI with CABG in patients with multivessel CAD. Despite the heterogeneity of the trials in regard to design, methods, and the patient population enrolled, the results are generally comparable and provide a consistent perspective of CABG and PCI in select patients with multivessel CAD. Nevertheless, limitations should be recognized. Conducted over several decades, the trials evolved substantially with respect to the technology used for both procedures and disease-modifying preventive therapy. Moreover, most patients entered into the trials had preserved LV function. Therefore, patients enrolled in these trials were at relatively low risk, with predominantly double-vessel CAD and a normal LVEF—that is, a high proportion of patients in whom CABG had not previously been shown to be superior to medical therapy in regard to survival. Thus, one would not expect a significant mortality difference between PCI and CABG.[28]

With progressive improvements in stent technology, patients with higher-risk coronary anatomy have been enrolled in trials. In the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial conducted between 2005 and 2007, 1800 patients with three-vessel or left main CAD were randomly assigned to undergo CABG or PCI after a "multidisciplinary team" consisting of a local cardiac surgeon and interventional cardiologist determined that equivalent anatomic revascularization could be achieved with either treatment.[247] The primary outcome measure was a noninferiority comparison of the two groups for major adverse cardiac or cerebrovascular events (MACCE; i.e., death from any cause, stroke, MI, or repeat revascularization) during the 12-month period after randomization. Rates of MACCE at 12 months were significantly higher in the PCI group (17.8% versus 12.4% for CABG; $P = 0.002$) (**eFig. 61.6**), in large part because of an increased rate of repeat revascularization (13.5% versus 5.9%; $P < 0.001$); thus the criterion for noninferiority was not met. At 12 months the rates of death and MI were similar between the two groups. However, stroke was significantly more likely to occur with CABG (2.2% versus 0.6% with PCI; $P = 0.003$). With longer follow-up in this trial, MACCE rates were lower in CABG-treated patients than those treated with PCI, both at 3 years (20.2% with CABG versus 28.0% with PCI; $P < 0.001$) and at 5 years (26.9% with CABG versus 37.3% with PCI; $P < 0.001$).[248] At 5 years, rates for MI (3.8% with CABG versus 9.7% with PCI; $P < 0.0001$) and repeat revascularization (13.7% with CABG versus 25.9% with PCI; $P < 0.0001$) were significantly lower in the CABG group, whereas rates of all-cause mortality (11.4% with CABG versus 13.9% with PCI; $P = 0.10$) and stroke (3.7% with CABG versus 2.4% with PCI; $P = 0.09$) did not significantly differ between groups.



EFIGURE 61.6 Outcomes in 1800 patients with stable ischemic heart disease and multivessel CAD randomly assigned to coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). **A,** CABG was superior to PCI at 1 year with respect to the primary outcome measure of death from any cause, myocardial infarction (MI), stroke, or repeat revascularization. **B,** This result was driven by the need for repeat revascularization, which was reduced significantly in the CABG group. **C, D,** There was no difference in the rate of death, MI, or stroke or death from any cause in the two treatment groups. (Modified from Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961.)

The comparative effectiveness of CABG versus PCI differs based on the anatomic complexity and severity of the CAD, as determined by the SYNTAX score. This score considers the number, location, and complexity of the coronary stenoses. Among patients with intermediate or high SYNTAX scores, CABG was clearly superior to PCI for major CV events, but among those with low scores, outcomes were similar (**Fig. 61.16**). Therefore, CABG should remain the standard of care for patients with complex coronary lesions (high or intermediate SYNTAX scores), whereas for patients with less complex CAD (low SYNTAX scores) or left main CAD (with low or intermediate SYNTAX scores), PCI remains an acceptable alternative. In a meta-analysis of 10 randomized trials, long-term mortality was similar after CABG or PCI in most subgroups with multivessel CAD. However, CABG appears to be better in patients with diabetes or older age, in whom mortality was more favorable in the CABG group.[196,247,249,250] Moreover, patients with diabetes with multivessel disease and low surgical risk may be appropriate candidates for CABG with increasing benefit with longer follow-up time[251] (**eFig. 61.7**). In-hospital costs are lower for patients undergoing PCI, but need for recurrent hospitalization and repeat revascularization procedures over the long term contributes to an increase in postdischarge cost in patients treated with PCI, which resulted in similar overall cost over 3 to 5 years.

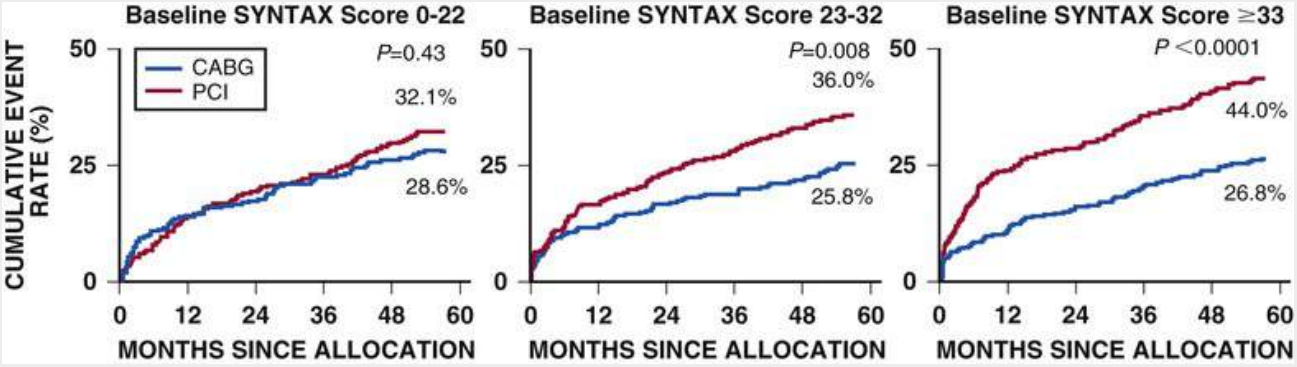
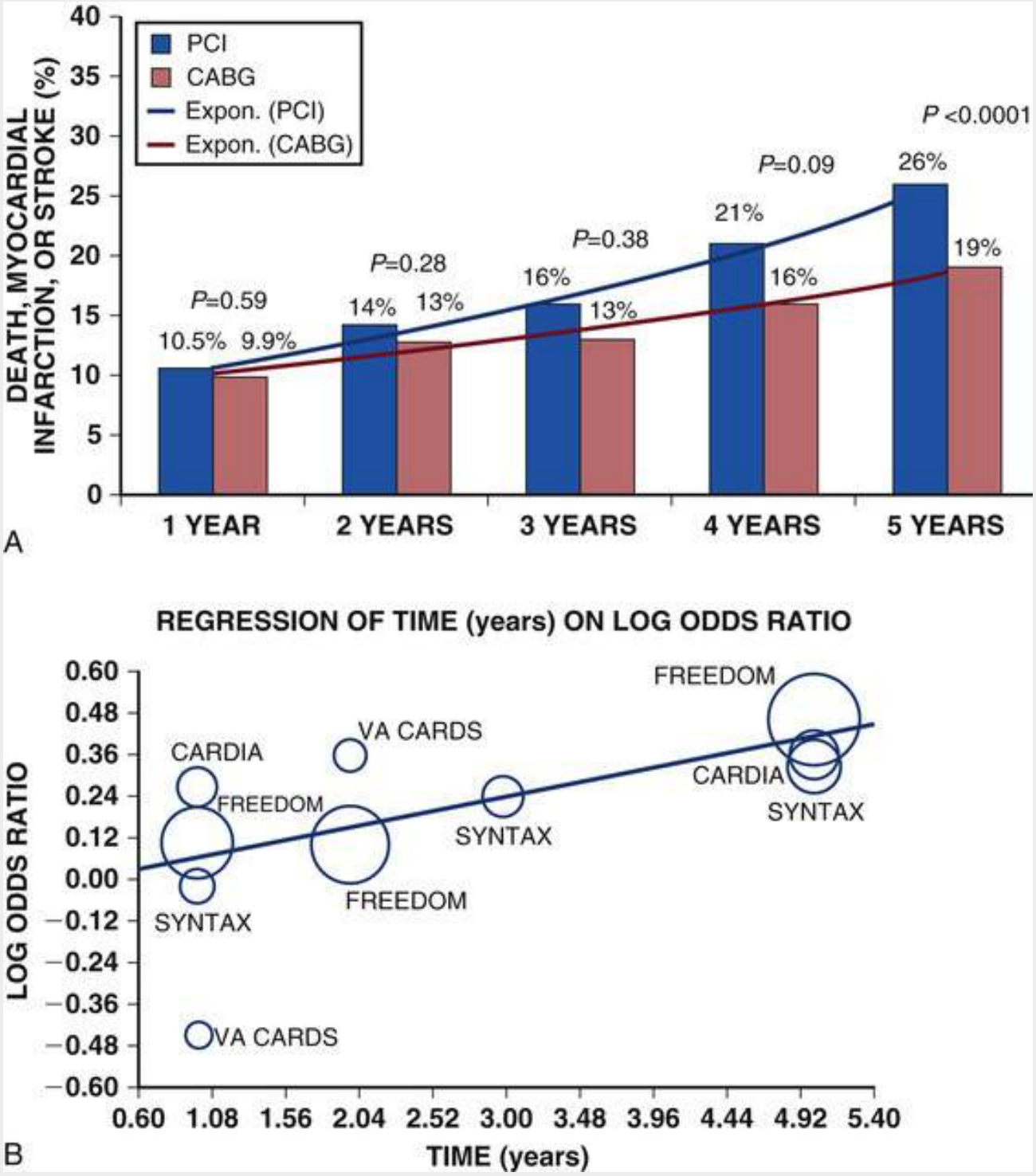


FIGURE 61.16 Major adverse cardiac and cerebral events at 5 years follow-up in the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. Patients are stratified by baseline SYNTAX score tertiles. The SYNTAX trial compared coronary artery bypass graft (CABG) surgery with percutaneous coronary intervention (PCI) in patient with left main or three-vessel coronary artery disease (CAD). The SYNTAX score describes the location, extent, and complexity of angiographic CAD, with low scores reflecting less complex disease and high scores more complex disease. CABG and PCI yielded similar outcomes among individuals in the lowest SYNTAX score tertile, but CABG was superior among individuals in the upper two tertiles, with the largest difference favoring CABG seen among patients with the most complex disease. (Modified from Mohr FW, Morice M-C, Kapetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;381:629-38.)



EFIGURE 61.7 Meta-analysis of four randomized trials (*n* = 3052) comparing percutaneous coronary intervention (PCI) with drug-eluting stents versus coronary artery bypass grafting (CABG) in diabetic patients with multivessel CAD. The primary endpoint (major adverse cardiac events) was a composite of death, myocardial infarction (MI), and stroke at a mean follow-up of 4 years. **A,** Display of the pooled rate of the primary endpoint across the duration of follow-up by CABG or PCI, demonstrating an increasing advantage of CABG with longer duration of follow-up. **B,** Metaregression plot for log odds ratio of the primary endpoint for PCI versus CABG as a function of time (in years). Markers above the regression line favor CABG and below the line favor PCI. The size of the data markers represents the weight of each trial. (Hakeem A, Garg N, Bhatti S, et al. Effectiveness of percutaneous coronary intervention with drug-eluting stents compared with bypass surgery in diabetics with multivessel coronary disease: comprehensive systematic review and meta-analysis of randomized clinical data. J Am Heart Assoc 2013;2:e000354.)

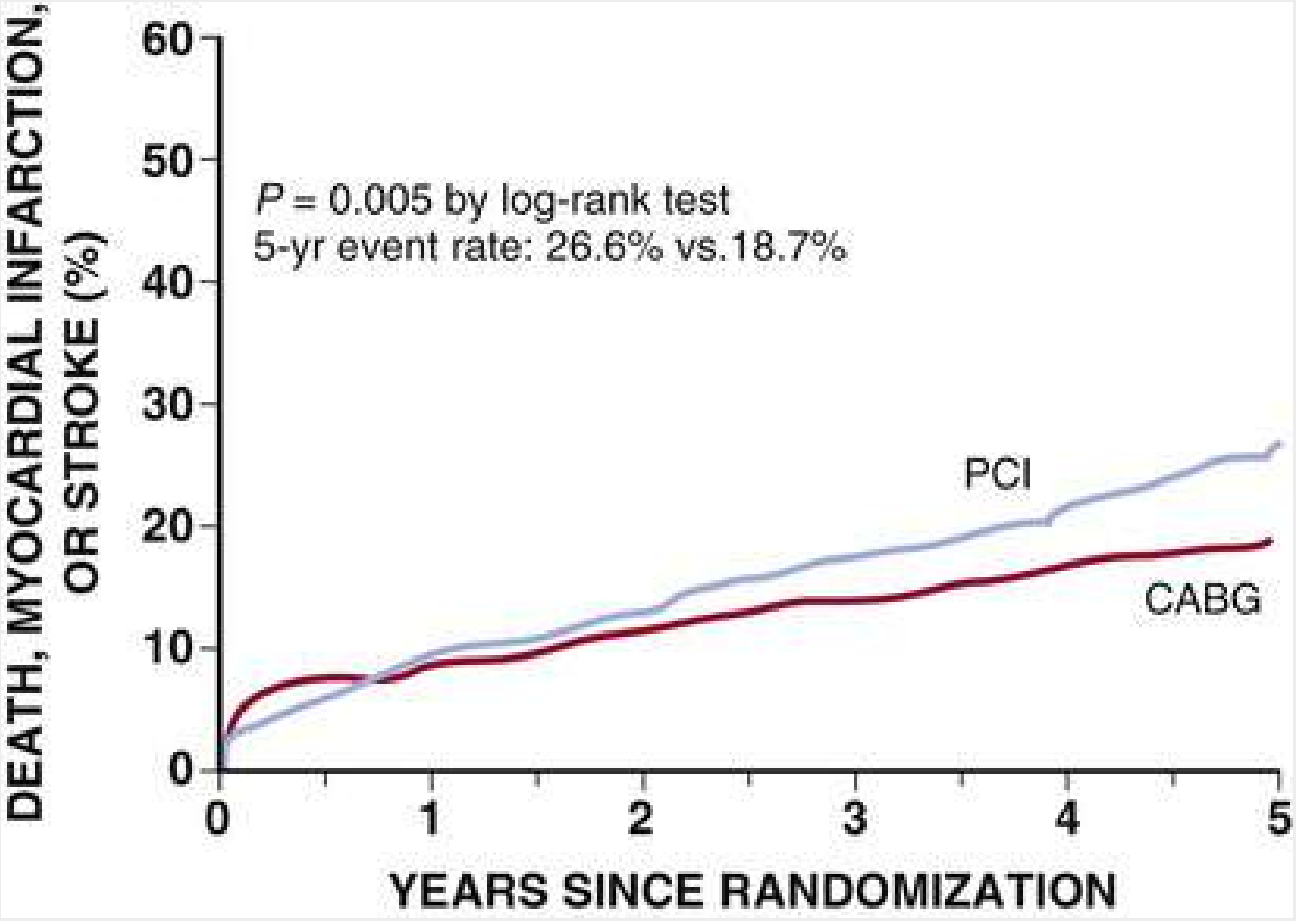
Patients with Diabetes (see Chapter 51).

An initially unexpected finding in the BARI (Bypass Angioplasty Revascularization Investigation) trial was that patients with previously treated DM who underwent PTCA had a 5-year mortality of 34.5% versus 19.4% for those who underwent CABG (P = 0.003). This advantage of CABG over PTCA for

patients with DM became more robust by 10 years of follow-up in the BARI trial and was supported in other studies. More rapid progression of atherosclerosis and high rates of restenosis in patients undergoing PCI were plausibly major contributors to this difference. In a collaborative meta-analysis of individual patient data from 7812 patients in 10 trials of PCI versus CABG, total mortality was significantly reduced by 30% with CABG in the subset of 1233 diabetic patients—findings that persisted even after exclusion of the BARI trial.[196,252]

The findings of the BARI-2D trial did not directly compare PCI and CABG but provide additional information and indirect comparisons for revascularization in patients with DM.[196] In the BARI-2D trial, 2368 patients with established diabetes and CAD were randomly assigned to prompt revascularization (PCI or CABG) versus delayed/no revascularization and OMT. A notable feature of the prompt-revascularization strategy was prespecification to PCI or CABG before randomization, with patients who had more severe CAD being allocated to CABG. Approximately two thirds of patients in BARI-2D were assigned to PCI, with the remainder who displayed more extensive CAD undergoing CABG based on "heart team" consensus decision making. At the 5-year follow-up, all-cause mortality did not differ between these two treatment groups. However, two prespecified analyses of a secondary composite endpoint (death, MI, or stroke) provide important insight: (1) compared with GDMT without revascularization, the CABG cohort had a significantly lower rate of death, MI, or stroke driven mainly by a reduction in nonfatal MI but also accompanied by a nonsignificant 16% relative decrease in mortality, and (2) in contrast to CABG, there was no difference in either the primary survival or secondary composite endpoints in patients treated with PCI or GDMT. Of note, in BARI-2D, only 35% of patients received a DES.[196]

Subsequently, the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial of 1900 patients with multivessel CAD who were randomly assigned to either DES treatment or CABG showed a convincing clinical benefit in diabetic patients who underwent CABG. In particular, the trial findings showed significant reductions in all-cause mortality and the composite of death or MI in CABG-treated diabetic patients[253] (**eFig. 61.8**). The results of the FREEDOM trial add to the growing body of scientific information that patients with SIHD and diabetes, especially those with 3-vessel CAD, have better long-term clinical outcomes with CABG than with PCI, even when using DESs. A potential advantage of CABG over PCI is that bypass grafts to the mid–coronary vessel both treat the culprit lesion (regardless of anatomic complexity) and may afford prophylaxis against new proximal disease progression, whereas stents treat only suitable stenotic segments with no benefit against the development of new disease.[194]



EFIGURE 61.8 Patients (*n* = 1900) with diabetes and multivessel CAD suitable for revascularization either by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) were randomly assigned to undergo either PCI with drug-eluting stents or CABG and monitored for a minimum of 2 years. The primary endpoint of death, MI, or stroke was significantly lower in the CABG group than in those randomly assigned to PCI (18.7% versus 26.6% at 5 years, *P* = 0.005). Both myocardial infarction and death were significantly reduced with the CABG strategy. However, stroke was more frequent in the CABG group. (From Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;20:367.)

Choosing Among Percutaneous Coronary Intervention, Coronary Artery Bypass Surgery, and Medical Therapy

Optimal medical therapy for SIHD involves a reduction in reversible risk factors, counseling in lifestyle alteration, treatment of conditions that intensify angina, and pharmacologic management of ischemia. Unlike the situation in ACS patients,[33] revascularization has not been shown to reduce the rate of death or MI when used in patients with SIHD (with the exception of CABG in patients meeting specific anatomic criteria). Recommendations for either PCI or CABG should be based on both the extent and the severity of ischemia (by noninvasive stress testing or invasive assessment of the hemodynamic significance of anatomic stenosis) and the severity of anginal symptoms or functional impairment. When an unacceptable level of angina persists despite medical management, the patient has troubling side effects from the anti-ischemic drugs, or the patient exhibits a high-risk result on noninvasive testing, the coronary anatomy should be defined to allow selection of the appropriate technique for revascularization. When one method of revascularization is preferred over the other for improved survival, this consideration generally takes precedence over improved symptoms. The patient should understand when the procedure is being performed in an attempt to improve symptoms, survival, or both. After elucidation of the coronary anatomy, selection of the technique of revascularization should be made as described next[33,196] (**Table**

61.14; see also eFig. 61.4).

TABLE 61.14

Comparison of Revascularization Strategies in Multivessel Disease

ADVANTAGES	DISADVANTAGES
Percutaneous Coronary Intervention	
Less invasive Shorter hospital stay Lower initial cost Easily repeated Effective in relieving symptoms	Restenosis High incidence of incomplete revascularization Understudied in patients with severe LV dysfunction Less favorable outcome in diabetic persons Limited to specific anatomic subsets Requires adherence with long-term DAPT
Coronary Artery Bypass Graft Surgery	
Effective in relieving symptoms Improved survival in certain subsets Ability to achieve complete revascularization Wider applicability (anatomic subsets)	Cost Morbidity Higher periprocedural mortality Higher risk for stroke and neurocognitive complications

DAPT, Dual-antiplatelet therapy; *LV,* left ventricular.

Modified from Faxon DP. Coronary angioplasty for stable angina pectoris. In Beller G, Braunwald E, editors. Chronic Ischemic Heart Disease. Atlas of Heart Disease. Vol 5. Philadelphia: Saunders; 1995, p 9.15.

Single-Vessel Disease

In patients with single-vessel disease in whom revascularization is deemed necessary and the lesion is anatomically suitable, PCI is almost always preferred over CABG.

Multivessel Disease

The first step is to assess the extent of CAD and its complexity while considering whether the patient falls into a subset of patients for whom surgical revascularization may confer a survival benefit. Most of the patients included in randomized trials comparing PCI to CABG were at lower risk, as defined by double-vessel CAD and well-preserved LV function. Moreover, several trials required that equivalent degrees of revascularization be achievable by both techniques. Most patients with chronically occluded coronary arteries were excluded, and of those who were clinically eligible, approximately two thirds were excluded for angiographic reasons. Although there was no significant difference in mortality at 5 years between PCI- and CABG-treated patients with left main and/or multivessel CAD in the SYNTAX trial, rates of both MI and repeat revascularization were significantly higher in patients who underwent PCI.

For patients who either refuse surgery or are not deemed suitable candidates for CABG, PCI remains a reasonable treatment option over medical therapy, provided that the patient accepts the possibility of symptom recurrence and the need for repeat revascularization. Patients with focal stenoses in each affected vessel (i.e., low SYNTAX score) and preserved LV function generally fare best with PCI. Additional anatomic factors, such as the presence of severe proximal LAD disease, should also be considered and weigh in favor of surgery (**see eFig. 61.4**). For patients with left main CAD or severe three-vessel CAD and LV dysfunction, CABG is generally the best approach and is recommended (class I) in professional society guidelines.[28,194,248] However, in selected patients with left main CAD, excellent technical and clinical results can still be obtained with PCI, but with a greater need for repeated revascularization procedures than with CABG. With newer-generation DES, outcomes for left main PCI have improved, and PCI now represents a suitable alternative to CABG if anatomic features are favorable (i.e., disease does not involve the bifurcation, and diffuse CAD is not present). PCI for unprotected left main disease is reasonable (class IIa) in patients whose coronary anatomy is consistent with a low risk of

PCI procedural complications and a high likelihood of good long-term outcome (i.e., low SYNTAX score of ≤22, ostial or trunk left main CAD), particularly if the risk of adverse surgical outcomes is high (e.g., STS-predicted risk of operative mortality ≥5%).[28] In general, for all patients with complex multivessel CAD for whom revascularization is being contemplated, there should be a thorough review and discussion of treatment options with the patient by a team that includes a cardiac surgeon and interventional cardiologist to reach a consensus on which approach is best suited for a particular patient.

Need for Complete Revascularization

Complete revascularization is an important goal in patients with LV dysfunction and/or multivessel CAD. The major advantage of CABG over PCI is its greater ability to achieve complete revascularization, particularly in patients with triple-vessel CAD, in addition to providing a conduit to the distal native vessel downstream of future de novo coronary stenoses. In patients with borderline LV function (EF of 0.40 to 0.50) and milder degrees of ischemia, PCI may provide adequate revascularization, even if it is not complete anatomically.

In many patients, either method of revascularization is suitable. Other factors to consider include the following:

1. Access to a high-quality team and operator (surgeon or interventional cardiologist).
2. Patient preference. Some patients are reluctant to remain at risk for recurrence of symptoms and reintervention; such patients are better candidates for surgical treatment. Other patients are attracted by the less invasive nature and more rapid recovery from PCI; these patients prefer to have PCI as their initial revascularization, with the plan of undergoing CABG if the symptoms persist and/or excellent revascularization has not been achieved.
3. Advanced patient age and comorbidity. Frail, very elderly patients and those with comorbid conditions are often better candidates for PCI.
4. Need for chronic oral anticoagulation. CABG may be preferable in patients with higher bleeding risk to avoid the risks of triple therapy with aspirin, clopidogrel, and an oral anticoagulant.

Patients with Diabetes (see Chapter 51)

The BARI-2D trial results reinforced the principal finding of the COURAGE trial that an initial strategy of PCI provides no incremental clinical benefit over GDMT, even in patients with diabetes.[238,239] However, in patients who remain symptomatic despite GDMT or when significant ischemia or extensive CAD is demonstrated, a revascularization strategy is warranted. Either PCI or CABG may be reasonable choices, depending on the anatomic complexity of the disease. However, based on the findings of BARI-2D, FREEDOM, and recent meta-analyses, CABG is regarded as the preferred revascularization approach in patients with multivessel CAD and DM when reduction of clinical events is the principal goal of treatment[238] (**Fig. 61.17**).

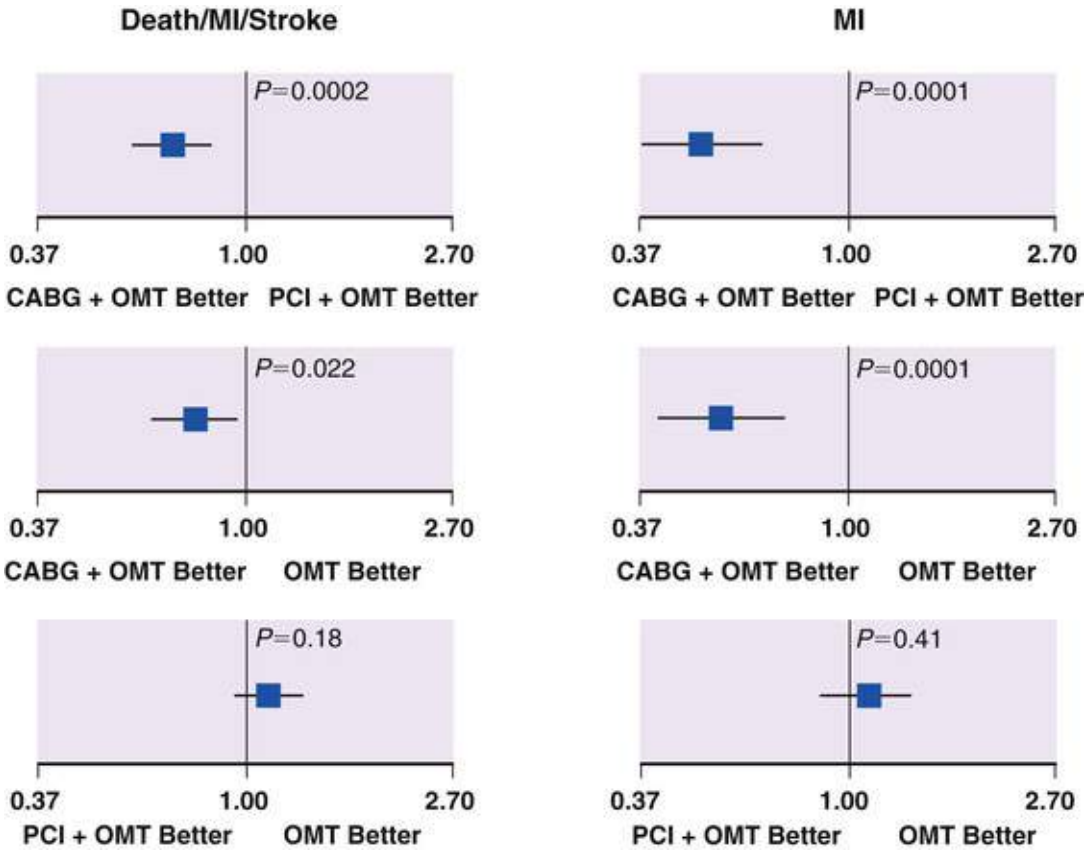


FIGURE 61.17 Meta-analysis of randomized trials comparing different revascularization strategies for patients with coronary artery disease and type 2 diabetes mellitus. Trial-adjusted hazard ratios are reported for comparisons of coronary artery bypass graft (CABG) surgery versus percutaneous coronary intervention (PCI), CABG versus optimal medical therapy (OMT), and PCI versus OMT. CABG was superior to PCI and to OMT for both the composite outcome as well as the individual MI endpoint. In contrast, PCI was not superior to OMT for either outcome. (From Mancini GB, Farkouh ME, Brooks MM, et al. Medical Treatment and Revascularization Options in Patients With Type 2 Diabetes and Coronary Disease. J Am Coll Cardiol 2016;68:985-95.)

Summary of Indications for Coronary Revascularization

1. Certain anatomic subsets of patients are candidates for CABG, regardless of the severity of symptoms or LV dysfunction. Such patients include those with significant left main CAD and most patients with three-vessel CAD that includes the proximal LAD, especially those with LV dysfunction (EF <50%). Patients with chronic stable angina and two-vessel CAD with significant proximal disease of the LAD and either LV dysfunction or high-risk findings on noninvasive testing may also be best considered for CABG.[28]
2. The results of the long-term extension (STICHES) of the STICH trial[229] as well as other aggregate data support the benefits of CABG in patients with LV dysfunction and multivessel CAD, regardless of symptoms, provided that they do not have other conditions likely to reduce life expectancy. In patients whose dominant symptom is HF without severe angina, the benefits of coronary revascularization are less well defined, but this approach should be considered in those who also have evidence of severe ischemia (regardless of angina symptoms), particularly in the presence of a significant extent of potentially viable dysfunctional (hibernating) myocardium.[196]
3. The primary objective of coronary revascularization in patients with single-vessel disease is relief of significant symptoms or objective evidence of severe ischemia. For most of these patients, PCI is the revascularization modality of choice.

4. In patients with angina who are not considered to be at high risk, survival is similar with surgery, PCI, and medical management.
5. All the indications discussed earlier relate to the potential benefits of CABG over medical therapy on survival. Coronary revascularization with PCI or CABG is highly efficacious in relieving symptoms and may be considered for patients with moderate to severe ischemic symptoms whose condition is not controlled by and/or who are dissatisfied with medical therapy, even if they are not in a high-risk subset. For such patients, the optimal method of revascularization is selected on the basis of LV function and arteriographic findings and the likelihood of technical success.

Transmyocardial Laser Revascularization

Transmyocardial laser revascularization (TMLR) is performed by placing a laser on the epicardial surface of the left ventricle, exposed through a lateral thoracotomy, and creating small channels from the epicardial to the endocardial surfaces. Failure of two sham-controlled trials of percutaneous laser myocardial revascularization to show any benefit has diminished interest in TMLR. However, the potential to enhance stem cell engraftment has led to investigation of TMLR in conjunction with stem cell therapy.[254]

Other Manifestations of Coronary Artery Disease

Prinzmetal Variant Angina

See Chapters 57 and 60.

Chest Pain with a Normal Coronary Arteriogram

The syndrome of angina or angina-like chest discomfort with normal findings on coronary arteriography, previously termed *syndrome X* (to be differentiated from "metabolic syndrome X") (**see Chapter 45**), is an important clinical entity that is often associated with clinical and electrocardiographic evidence of myocardial ischemia and has previously been underrecognized. Better described as "angina without flow-limiting epicardial coronary stenosis," this syndrome was generally regarded as having a benign long-term prognosis but is now recognized to be associated with an increased risk for adverse outcomes in certain subsets of patients.[1,2,181] For decades, angina with normal findings on coronary arteriography in the absence of underlying conditions such as severe aortic stenosis or hypertrophic cardiomyopathy was largely viewed by clinicians as unrelated to true myocardial ischemia, but rather a manifestation of undetected noncardiac reasons. Potential explanations for angina in the absence of flow-limiting CAD offered historically include vasospastic angina, misinterpreted coronary angiogram, potential misdiagnosis of flush (or stump) coronary occlusions at sites of major arterial bifurcations, increased subendocardial pressure leading to coronary artery compression, and hyperdynamic ventricular contraction with an elevated EF resulting in a supply-demand imbalance. In some patients, particularly premenopausal women, when exercise-induced ST-segment depression during treadmill exercise triggered referral for diagnostic coronary angiography that resulted in normal angiographic findings, these abnormal noninvasive test results were dismissed as being "false positives." However, steady accumulation of experimental and clinical data has provided a sound scientific basis for recognizing that

myocardial ischemia may occur without critical coronary stenosis and may be explained by overlapping effects of concealed diffuse coronary atherosclerosis revealed by FFR or IVUS, endothelial dysfunction, microvascular dysfunction, coronary spasm, and in some cases myocardial bridging.[2,181,255,256]

Patients with chest pain and normal findings on coronary arteriography may represent as many as 10% to 30% of those undergoing coronary arteriography because of clinical suspicion of angina.[181] This proportion may be substantially higher in women. For example, in the initial WISE (Women's Ischemic Syndrome Evaluation) study, approximately two thirds of women with chest pain and other findings suggestive of SIHD had no critical coronary stenoses detected with angiography.[256] Data from 388 U.S. hospitals participating in the ACC-NCDR revealed that at least 50% of women and 30% of men referred for coronary angiography had no obstructive CAD.[256] True myocardial ischemia, as reflected by the production of lactate by the myocardium during exercise or pacing, is present in some of these patients. In addition, coronary artery reactivity testing demonstrates evidence of endothelial and microvascular dysfunction in a substantial proportion of such individuals.[257] The incidence of coronary calcification on CT is significantly higher than that in normal controls (53% versus 20%) but lower than that in patients with angina secondary to obstructive CAD (96%). Moreover, observational data have established that their outcome is not as uniformly excellent as suggested by early cohort studies.[34,258] In addition, abnormal measures of endothelial and microvascular function in these patients are associated with a higher risk for death, MI, or hospitalization for HF.

The causes of the syndrome are probably multiple and not homogeneous across individuals.[3] Vascular (endothelial and microvascular) dysfunction, coronary vasospasm, and myocardial metabolic abnormalities, as previously noted, have each been implicated. Included in this syndrome are patients in whom angina may be the direct consequence of subendocardial ischemia as a result of abnormalities in the coronary microvasculature (or arteriolar resistance vessels), the small caliber of which would be beyond the resolution of coronary angiography. This condition is frequently termed *microvascular angina.* Alternatively, in some individuals, chest discomfort without ischemia may be caused by abnormal pain perception or sensitivity. Furthermore, IVUS studies have demonstrated anatomic and physiologic heterogeneity in such patients, with a spectrum ranging from completely normal epicardial coronary arteries to vessels with intimal thickening and atheromatous plaque and non–flow-limiting obstructions (10% to 30% diameter reductions)—insufficient to cause angina on the basis of coronary luminal narrowing alone, but in the setting of superimposed dynamic coronary vasomotor tone, such ischemic symptoms could readily occur. Lastly, it may be difficult to distinguish patients with angina and normal findings on coronary arteriography in whom chest pain is caused by ischemia from patients with noncardiac pain. However, an approach of assuming a favorable prognosis and dismissing symptoms in all such patients is clearly not justified by the evidence.

Microvascular Dysfunction (Impaired Coronary Flow Reserve).

Many patients with evidence of myocardial ischemia do not have visible coronary atherosclerosis at angiography, and conversely, some patients with severe coronary atherosclerotic obstructions neither experience chest discomfort nor have any objective findings of myocardial ischemia.[35,259] Atherosclerosis is just one element of a complex myriad of potential impediments to coronary flow that includes inflammation, microvascular coronary dysfunction, endothelial dysfunction, and thrombosis. Accordingly, patients with chest pain, angiographically normal coronary arteries, and no evidence of large-vessel spasm, even after an acetylcholine challenge, may demonstrate an abnormally decreased capacity to

reduce coronary resistance and increase coronary flow in response to stimuli such as exercise, adenosine, dipyridamole, and atrial pacing. Discordance between epicardial coronary function (by FFR) and microvascular function (by coronary flow reserve [CFR] or the index of microcirculatory resistance [IMR]) can provide insight into coronary microvascular function. The finding of a normal FFR, indicating no obstructive epicardial stenosis, but reduced CFR or IMR, indicating predominant microvascular disease, is associated with a particularly unfavorable prognosis.[260] As such, coronary flow evaluation may be useful in the investigation of the functional severity of coronary pathology.[3,181]

Patients with microvascular angina also have an exaggerated response of small coronary vessels to vasoconstrictor stimuli and an impaired response to intracoronary vasodilators. Abnormal endothelium-dependent vasoreactivity has been associated with regional myocardial perfusion defects on SPECT, PET, and CMR.[261] It has been reported that patients with angina and angiographically normal coronary anatomy also have impaired vasodilator reserve in forearm vessels and airway hyperresponsiveness, which suggests that the smooth muscle of systemic arteries and other organs may be affected in addition to that of the coronary circulation.

Endothelial dysfunction and endothelial cell activation, reported in patients with microvascular angina, may participate in the release of cellular adhesion molecules, proinflammatory cytokines, and constricting mediators that induce changes in the arterial wall and result in microvascular coronary dysfunction and higher risk for the future development of obstructive CAD.

Evidence of Ischemia.

Despite the general acceptance that microvascular or endothelial dysfunction is present in many patients with angina and normal findings on coronary arteriography, whether ischemia is in fact the putative cause of the symptoms in all patients is not clear. For this reason, studies of transmyocardial production of lactate have generated mixed results. The development of LV dysfunction and electrocardiographic or scintigraphic abnormalities during exercise in some of these patients supports an ischemic cause. Moreover, stress echocardiography with dobutamine detects regional contraction abnormalities consistent with ischemia in a subset of patients. More sensitive techniques, such as perfusion analysis with CMR, have demonstrated that subendocardial perfusion abnormalities, in particular, may be associated with angina with normal angiographic findings.

Abnormal Pain Perception.

The lack of definitive evidence of ischemia in many patients with angina and normal coronary angiographic findings has focused attention on alternative nonischemic causes of cardiac-related pain, including a decreased threshold for pain perception. This hypersensitivity may result in an awareness of chest pain in response to stimuli such as arterial stretch or changes in heart rate, rhythm, or contractility. A sympathovagal imbalance with sympathetic predominance in some of these patients has also been postulated. At cardiac catheterization, some patients with angina are unusually sensitive to intracardiac instrumentation, with the typical chest pain being consistently produced by direct right atrial stimulation and saline infusion. Measurements of regional cerebral blood flow at rest and during chest pain have suggested differential handling of afferent stimuli between such patients and those with obstructive CAD.

Clinical Features

The syndrome of angina or angina-like chest pain with no obstructive disease of the epicardial arteries occurs more frequently in women (**see Chapter 89**), many of whom are premenopausal, whereas obstructive CAD is found more often in men and postmenopausal women (**Fig. 61.18**). Similarly to women with critical epicardial CAD, many women with microvascular angina will experience dyspnea

or fatigue or may have a preponderance of symptoms such as nausea, and midepigastric pain. Although the features are frequently atypical, the chest pain may nonetheless be severe and disabling. Angina in the absence of obstructive CAD may have markedly adverse effects on quality of life, employment, and use of health care resources.

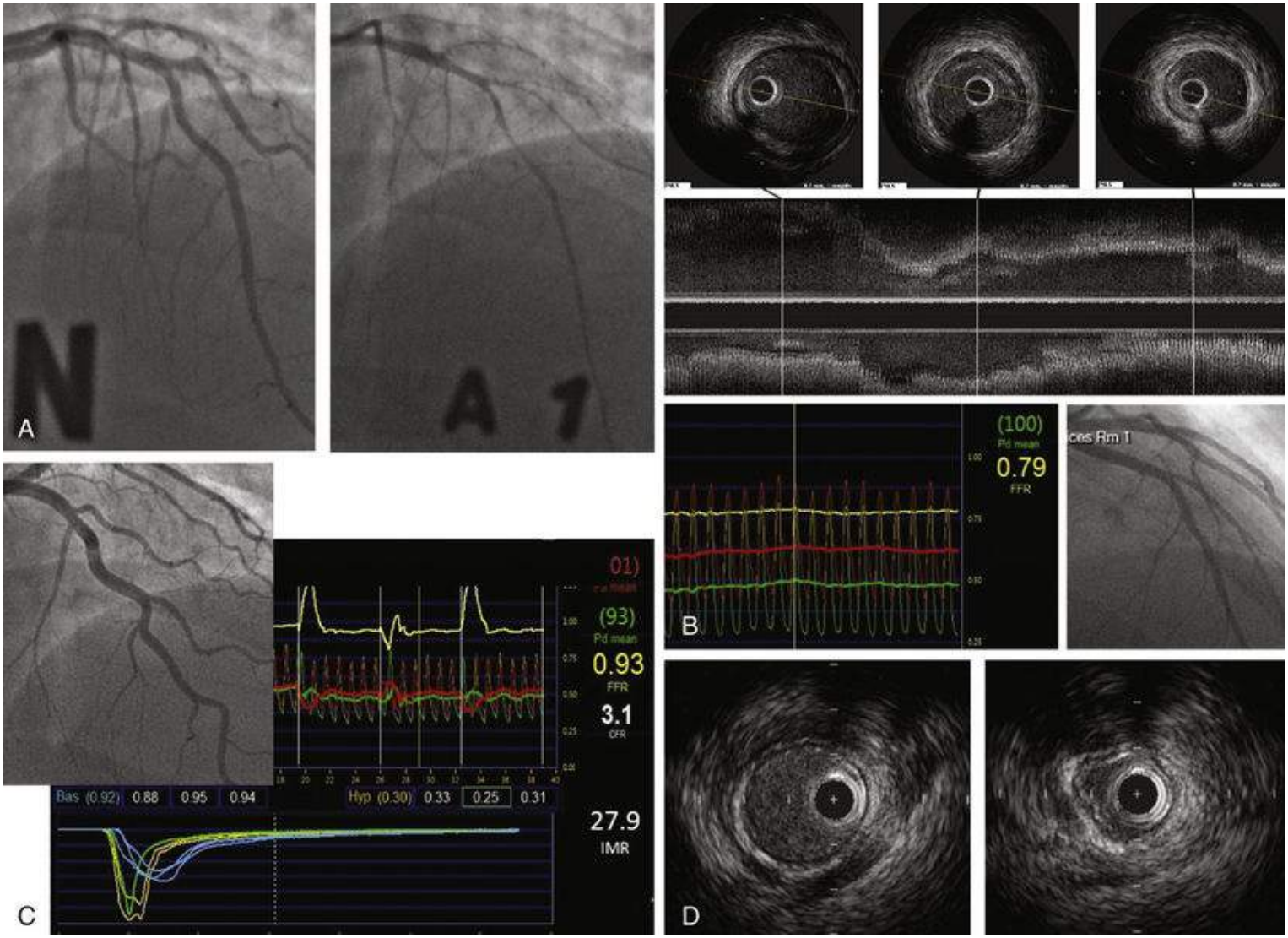


FIGURE 61.18 Evaluation of patients with chest pain in the absence of coronary artery obstruction. **A,** Baseline coronary angiogram and subsequent angiogram after intracoronary acetylcholine, demonstrating diffuse endothelial dysfunction with vasoconstriction. **B,** Cross-sectional and longitudinal intravascular ultrasound images demonstrating diffuse atherosclerosis, and coronary pressure tracing revealing an abnormal fractional flow reserve in a normal-appearing left anterior descending coronary artery (LAD) on angiography. **C,** Coronary angiogram revealing a normal LAD with a pressure tracing showing an abnormal index of microcirculatory resistance. **D,** Cross-sectional intravascular ultrasound images of a myocardial bridge segment. (With permission from Lee BK, Lim HS, Fearon WF, et al. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. Circulation 2015;131:1054-60.)

Clinical and Diagnostic Assessment

Abnormal physical findings reflecting ischemia are uncommon in these patients. The resting ECG may be normal, but nonspecific ST-T wave abnormalities are often observed, sometimes occurring in association with the chest pain. Approximately 20% to 30% of patients with chest pain and normal coronary angiographic findings have positive exercise test results. However, many patients with this syndrome do not complete the exercise test because of fatigue or mild chest discomfort. LV function is usually normal at

rest and during stress, unlike the situation in obstructive CAD, in which function often becomes impaired during stress.

Comprehensive invasive assessment of patients with evidence of myocardial ischemia on noninvasive testing can provide diagnostic information in more than 75% of those without obstructive CAD. Such a comprehensive invasive assessment may include FFR to evaluate epicardial obstructive disease that was not apparent from the angiogram, endothelial function testing with acetylcholine, IMR with adenosine, and IVUS to assess for diffuse structural abnormalities and myocardial bridging. In some series, IVUS revealed diffuse coronary atherosclerosis in all such patients evaluated.[3] Such findings may be useful to guide management.

Prognosis

Accumulating data suggest that the prognosis in patients with chest pain without obstructive CAD is more heterogeneous than once thought. In patients with EF of 50% or greater in the CASS registry, the 7-year survival rate was 96% for those with normal arteriographic findings and 92% for those whose arteriographic study revealed mild CAD (50% luminal stenosis). However, subsequent studies have shown that the prognosis is not as favorable in some groups of patients.[1,2,181] For example, an ischemic response to exercise is associated with increased mortality. Moreover, in women with angina and no obstructive CAD enrolled in the WISE investigations, persistence of symptoms was associated with more than a twofold higher risk for CV events. Such patients may be appropriate candidates for formal studies of vascular function and aggressive risk factor modification (**see Chapter 89**).

Management

No specific guideline-recommended therapy is available for patients with signs and symptoms of IHD who do not have obstructive CAD (**see Fig. 61.18**). Risk factors for atherosclerotic vascular disease should be managed, and for those with established atherosclerosis, even if nonobstructive, GDMT should be instituted.[181] For those with ischemic symptoms, a trial of anti-ischemic therapy with nitrates, calcium antagonists, and beta blockers is logical, but the response to this therapy is variable. Perhaps because of the heterogeneity of this population, studies testing these antianginal therapies have produced conflicting results. For example, beta blockers may be most effective in such patients who also have evidence of a hyperadrenergic state characterized by increased sympathetic nervous system activity (e.g., hypertension, tachycardia, reduced HR variability). SL nitroglycerin has shown paradoxical effects on blood flow and exercise tolerance in some studies and beneficial effects in others. Observational studies of calcium antagonists have in general resulted in disappointing outcomes with respect to amelioration of symptoms. Although a small pilot study of women with well-documented microvascular angina and myocardial ischemia treated with ranolazine showed an improvement in functional status and quality of life,[159] no benefit from ranolazine was seen in a subsequent placebo-controlled trial performed in patients with angina and MR evidence of impaired CFR.[160]

ACE inhibitors have favorable effects on endothelial function, vascular remodeling, and sympathetic tone that may be relevant to the pathophysiology of the underlying myocardial ischemia in some of these patients. Preliminary data on ACE inhibitors in this population are promising. Similarly, *estrogen* has been shown to attenuate the normal coronary vasomotor responses to acetylcholine, increase coronary blood flow, and potentiate endothelium-dependent vasodilation in postmenopausal women. Studies of estrogen replacement in postmenopausal women with angina but without critical epicardial CAD have demonstrated improvement in symptoms and exercise performance; however, the role of exogenous

estrogen in treatment of this group remains in question. Treatment with imipramine (50 mg daily) and structured psychological intervention targeted to the altered somatic and visceral pain perception of certain patients have been reported to be helpful.

Silent Myocardial Ischemia

Epidemiologic studies of sudden cardiac death (SCD), as well as clinical and postmortem studies of patients with silent MI, have suggested that many patients with severe IHD never experience angina pectoris (**see Chapter 42**). These patients may be considered to have a defective anginal warning system in that they may not be subjectively aware of myocardial ischemia when it is present. In addition, up to one third of patients with chronic stable angina also exhibit episodes of silent (asymptomatic) ischemia. The total ischemic burden in these patients refers to the total period of ischemia, both symptomatic and asymptomatic.

Analysis of ambulatory electrocardiographic recordings in patients with CAD who had both symptomatic and silent myocardial ischemia has shown that 85% of ambulant ischemic episodes occur without chest pain, and 66% of angina reports were unaccompanied by ST-segment depression. Their frequency suggests that overt angina pectoris is merely the "tip of the ischemic iceberg." Episodes of silent ischemia may be present in approximately one third of all treated patients with angina, although a higher prevalence has been reported in diabetic persons (**see Chapter 51**).

Mechanisms.
Differences in both peripheral and central neural processing of pain have been proposed as important factors underlying silent ischemia. PET of cerebral blood flow during painful versus silent ischemia indicates differences in the CNS handling of afferent signals. Specifically, overactive gating of afferent signals in the thalamus may reduce the cortical activation necessary for perception of pain from the heart. *Autonomic neuropathy* has also been implicated in the reduced sensation of pain during ischemia, supporting the belief that diabetic patients with dysautonomia may manifest myocardial ischemia without anginal symptoms more often than nondiabetic persons.

Prognosis.
Although some controversy remains, ample evidence has supported the view that episodes of myocardial ischemia, regardless of whether they are symptomatic or asymptomatic, are of prognostic importance in patients with CAD.[262] In asymptomatic patients, the presence of exercise-induced ST-segment depression has been shown to predict a four- to fivefold higher cardiac mortality compared to patients without this finding. Similarly, in patients with stable angina or previous MI, the presence of inducible ischemia, evident by ST depression or reversible myocardial perfusion abnormalities during exercise testing, is associated with unfavorable outcomes regardless of whether symptoms are present. The strength of this association is greatest when the ischemia is found to occur at a low workload. A study of stress nuclear imaging revealed that a threshold of ischemia in 7.5% or greater of the myocardium was associated with a higher risk for cardiac death or MI in asymptomatic patients without known CAD.

Detection and Management.
Ambulatory ECG monitoring, while feasible, is not justified as a widespread screening tool for silent ischemia. The exercise ECG can be used to identify most patients likely to have significant ischemia during their daily activities (**see Chapter 13**). In addition, silent ischemia may be discovered by a

positive scintigraphic perfusion scan undertaken in patients with known angiographic CAD, or in asymptomatic individuals with suspected high-risk CAD. However, we emphasize that routine stress testing or nuclear perfusion studies are not indicated for patients with SIHD in the absence of a change in clinical status. Noninvasive studies have been overused in some countries, despite the lack of evidence to support benefit.[263]

In such patients with a defective anginal warning system, it is reasonable to assume that *asymptomatic* ischemia has a prognostic significance similar to that of symptomatic ischemia, and that their management is similar with respect to disease-modifying preventive therapy. Studies evaluating revascularization for silent ischemia have yielded conflicting results. A post hoc analysis of the COURAGE trial evaluated clinical outcomes in patients with silent myocardial ischemia and in those with symptomatic ischemia during a 5-year follow-up.[264] A total of 283 patients with SIHD qualified for enrollment on the basis of objective baseline findings of inducible ischemia and significant flow-limiting coronary stenoses (>70%) but who lacked anginal symptoms. No overall differences were detected in patients with silent ischemia between those randomly assigned to PCI or medical therapy for the endpoints of death or MI.[264] When these results were combined with the ACIP (Asymptomatic Cardiac Ischemia Pilot) trial and the earlier SWISSI-II study, the pooled analysis of 1042 patients with silent ischemia revealed a statistically significant 64% reduction in the composite endpoint of death or MI in PCI-treated patients and a significant 56% reduction in death alone. In contrast, in a propensity-adjusted analysis of patients undergoing repeated revascularization in the setting of asymptomatic ischemia noted on MPI, all-cause mortality was not improved during a mean 5.7-year follow-up.[265] A nuclear substudy from the COURAGE trial was undertaken in 1381 randomly assigned patients (GDMT alone = 699 patients; PCI + GDMT = 682 patients) who underwent stress myocardial perfusion SPECT at baseline only (with or without a repeated follow-up scan), with the results interpreted locally by the on-site investigators. At baseline, moderate to severe ischemia was present in one third of patients (n = 468), and the incidence was comparable in both treatment groups (P = 0.36). The primary endpoint (death or MI) was similar in the two treatment groups for the subsets with either no to mild ischemia (18% and 19%, respectively; P = 0.92) or moderate to severe ischemia (19% and 22%, respectively; P = 0.53; interaction P value = 0.65).[266]

In summary, although suppression of ischemia in asymptomatic patients with SIHD appears to be a worthwhile objective, at present it is not clear whether treatment should be guided by symptoms or by ischemia as determined by noninvasive testing. Nevertheless, it seems reasonable to use anti-ischemic and disease-modifying pharmacologic therapy in patients with well-documented myocardial ischemia, even if symptoms are lacking. Whether revascularization improves outcomes among patients with large ischemic burden, with or without symptoms, absent other indications for revascularization, remains to be determined. The NHLBI-sponsored ISCHEMIA is currently randomizing 8000 patients with SIHD and moderate to severe ischemia to either optimal medical therapy or OMT plus revascularization. This trial should provide further insights into the role of ischemia (and ischemia monitoring) for targeting coronary revascularization in patients with SIHD.

Heart Failure in Ischemic Heart Disease (See Chapter 23)

Currently, the leading cause of HF in developed countries is CAD. In the United States, CAD and its complications account for two thirds to three fourths of all cases of HF. In many patients the progressive nature of HF reflects the advancing nature of the underlying CAD.

Ischemic Cardiomyopathy

In 1970, Burch and colleagues first used the term *ischemic cardiomyopathy* to describe the condition in which CAD results in severe myocardial dysfunction, with clinical manifestations often being indistinguishable from those of primary dilated cardiomyopathy (**see Chapter 77**). Symptoms of HF caused by ischemic myocardial dysfunction and hibernation, diffuse fibrosis, or multiple MIs, alone or in combination, may dominate the clinical picture of CAD. In some patients with chronic CAD, angina may be the principal clinical manifestation at one time, but later this symptom diminishes or even disappears as HF becomes more prominent. Other patients with ischemic cardiomyopathy have no history of angina or MI, and it is in this subgroup that ischemic cardiomyopathy is most often confused with dilated cardiomyopathy. When angina coexists with ischemic cardiomyopathy, outcomes appear particularly poor.[267]

It is important to recognize hibernating myocardium in patients with ischemic cardiomyopathy because symptoms resulting from chronic LV dysfunction may be incorrectly thought to result from necrotic and scarred myocardium rather than from a reversible ischemic process[268] (see earlier, Myocardial Hibernation). Hibernating myocardium may be present in patients with known or suspected CAD and a degree of cardiac dysfunction or HF not readily accounted for by previous MIs.

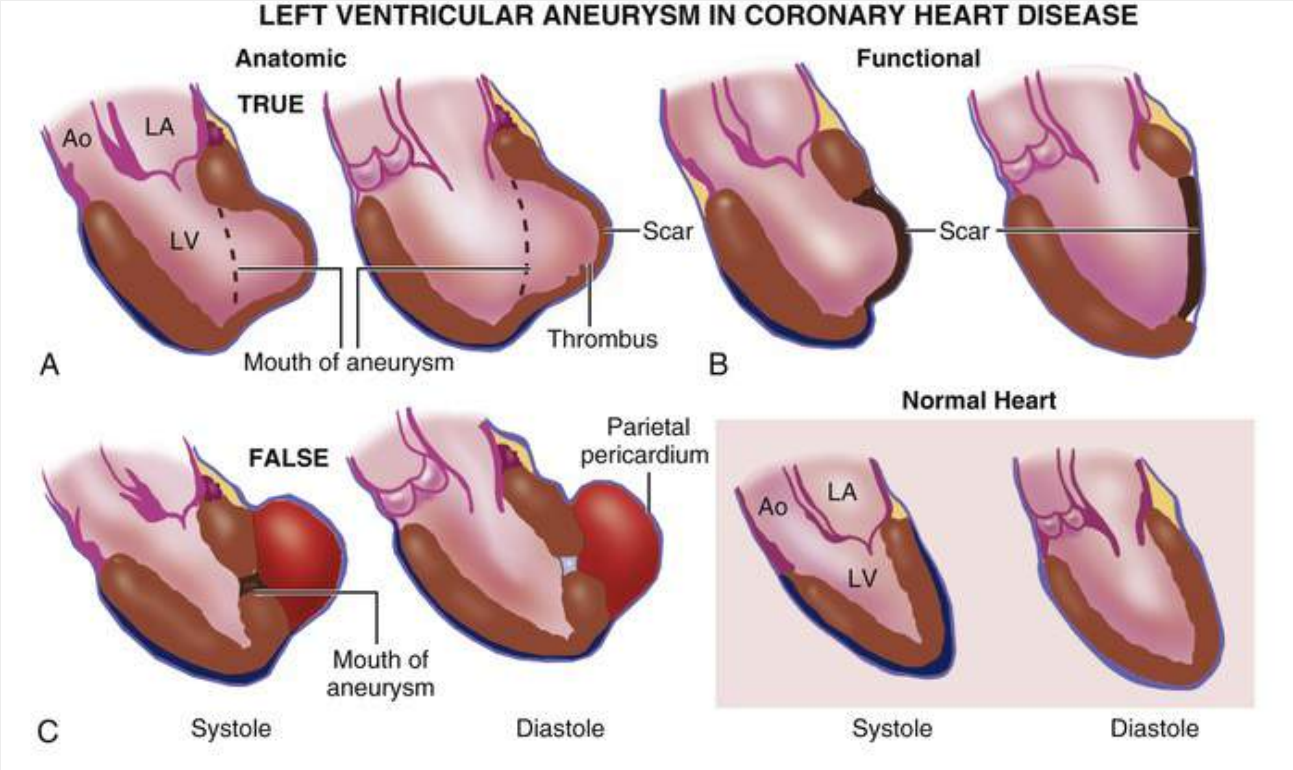
The outlook for patients with ischemic cardiomyopathy treated medically is poor, and revascularization or cardiac transplantation may be considered.[230] The prognosis is particularly poor for patients in whom ischemic cardiomyopathy is caused by multiple MIs, in those with associated ventricular arrhythmias, and in those with an extensive amount of hibernating myocardium. However, this last group of patients, whose HF, even if severe, is caused by large segments of reversibly dysfunctional but viable myocardium, may have a better prognosis and relief of HF symptoms after revascularization. Thus the key to management of patients with ischemic cardiomyopathy, in addition to providing evidence-based medical therapy for HF, is careful selection of patients who may be appropriate candidates for revascularization[269] (see earlier, Coronary Artery Bypass Grafting, Patients with Depressed Left Ventricular Function).

Although seemingly of intuitive value, the role of viability testing to guide revascularization decisions in patients with ischemic cardiomyopathy is not clear. Observational studies have suggested that patients with ischemic cardiomyopathy who have extensive multivessel CAD and viable myocardium may derive a survival advantage with CABG, whereas those with little or no viable myocardium should usually be managed similar to those with dilated cardiomyopathy (**see Chapters 25 and 77**). Nonetheless, in the randomized STICH trial, viability testing did not appear to identify patients in whom CABG provided incremental survival benefit.[230] Similarly, the small PARR-2 (PET and Recovery Following Revascularization-2) study of 430 patients randomly assigned to PET-guided management versus standard care did not demonstrate an advantage of revascularization when viability testing was used as a guide.[225] Additional, rigorous, adequately sized observational studies and RCTs are needed to define the role of viability testing.

Left Ventricular Aneurysm.

LV aneurysm is usually defined as a segment of the ventricular wall that exhibits paradoxical (dyskinetic) systolic expansion. Chronic fibrous aneurysms interfere with LV performance principally through loss of contractile tissue. Aneurysms made up largely of a mixture of scar tissue and viable myocardium or of thin scar tissue also impair LV function by a combination of paradoxical expansion and loss of effective contraction. False aneurysms (pseudoaneurysms) represent localized myocardial rupture in which the

hemorrhage is limited by pericardial adhesions, and they have a mouth that is considerably smaller than the maximal diameter (**eFig. 61.9**). True and false aneurysms may coexist, although the combination is extremely rare.



EFIGURE 61.9 Hearts in systole and diastole with true and false anatomic and functional left ventricular (LV) aneurysms and healed MI. A normal heart in systole and diastole is shown for comparison **(inset). A,** True anatomic LV aneurysm protrudes during both systole and diastole, has a mouth that is as wide as or wider than the maximal diameter, has a wall that was formerly the wall of the left ventricle, and is composed of fibrous tissue with or without residual myocardial fibers. A true aneurysm may or may not contain thrombus and very rarely ruptures once the wall is healed. **B,** A functional LV aneurysm protrudes during ventricular systole but not during diastole and consists of fibrous tissue with or without myocardial fibers. **C,** False anatomic LV aneurysm protrudes during both systole and diastole, has a mouth that is considerably smaller than the maximal diameter of the aneurysm and represents a myocardial rupture site, has a wall made up of parietal pericardium, almost always contains thrombus, and often ruptures. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle. (From Cabin HS, Roberts WC. Left ventricular aneurysm, intra-aneurysmal thrombus, and systemic embolus in coronary heart disease. Chest 1980;77:586.)

The frequency of LV aneurysms depends on the incidence of transmural MI and HF in the population studied. LV aneurysms and the need for aneurysmectomy have declined dramatically during the past 5 to 10 years in concert with the expanded use of acute reperfusion therapy for evolving MI (**see Chapter 59**). More than 80% of LV aneurysms are located anterolaterally near the apex. They are often associated with total occlusion of the LAD coronary artery and poor collateral blood supply. Approximately 5% to 10% of aneurysms are located posteriorly. Three fourths of patients with LV aneurysms have multivessel CAD.

Approximately 50% of patients with moderate or large aneurysms have symptoms of HF, with or without associated angina; 33% have severe angina alone; and 15% have symptomatic ventricular arrhythmias that may be intractable and life threatening. Mural thrombi are found in almost half of patients with chronic LV aneurysms and can be detected by angiography and two-dimensional echocardiography (**see Chapter 14**). Systemic embolic events in patients with thrombi and an LV aneurysm tend to occur early after MI. In patients with a chronic LV aneurysm (documented at least 1

month after MI), subsequent systemic emboli were extremely uncommon (0.35 per 100 patient-years in those not receiving anticoagulants).

Detection.

Clues to the presence of an aneurysm include persistent ST-segment elevations on the resting ECG (in the absence of chest pain) and a characteristic bulge of the silhouette of the left ventricle on a chest radiograph. Marked calcification of the LV silhouette may be present. These findings, when clear-cut, are relatively specific, but they have limited sensitivity. Two-dimensional echocardiography can readily demonstrate LV aneurysms and is helpful in distinguishing between true and false aneurysms based on the demonstration of a narrow neck in relation to cavity size in false aneurysm. Color flow echocardiographic imaging is useful in establishing the diagnosis because flow “in and out” of the aneurysm, as well as abnormal flow within the aneurysm, can be detected, and pulsed Doppler imaging can reveal a “to-and-fro” pattern with characteristic respiratory variation in the peak systolic velocity. CMR may be emerging as the preferred noninvasive technique for the preoperative assessment of LV shape, thinning, and resectability.

Left Ventricular Aneurysmectomy.

True LV aneurysms do not rupture, and operative excision is carried out to improve the clinical manifestations, most often HF but sometimes also angina, embolization, and life-threatening tachyarrhythmias.[269,270] CABG is frequently performed along with aneurysmectomy, especially in patients with angina accompanying HF.

A large LV aneurysm in a patient with HF symptoms, particularly if angina pectoris is also present, is a possible indication for surgery. The operative mortality rate for LV aneurysmectomy is approximately 8% (range, 2% to 19%), with rates as low as 3% being reported in more recent series. Improvement in LV function has been reported in survivors of resection of LV aneurysms. Anterior ventricular restoration has the potential to reverse the adverse remodeling, realign contractile fibers, and decrease LV wall stress and thus has been of interest as a possible intervention to mitigate the progression of ischemic cardiomyopathy. Small, unblinded series have suggested that surgical ventricular restoration (SVR) could result in improvement in both LV function and quality of life.[270] The value of SVR for patients with ischemic cardiomyopathy who do not have frank LV aneurysms was tested in the STICH trial and shown not to improve rates of death or cardiac hospitalization: 56% for CABG and 57% for CABG plus SVR. Thus, in the absence of new data, use of SVR remains an unproven strategy in the management of HF patients.[270,271]

Mitral Regurgitation Secondary to Coronary Artery Disease

Mitral regurgitation (MR) is an important cause of HF in some patients with CAD. Rupture of a papillary muscle or the head of a papillary muscle usually causes severe acute MR in the course of acute MI (**see Chapters 58 and 69**). The cause of chronic MR in patients with CAD is multifactorial, and the geometric determinants are complex; these include papillary muscle dysfunction from ischemia and fibrosis, in conjunction with a wall motion abnormality and changes in LV shape in the region of the papillary muscle and/or dilation of the mitral annulus. Enlargement of the mitral annulus at end-systole is asymmetric, with lengthening primarily involving the posterior annular segments and leading to prolapse of leaflet tissue tethered by the posterior papillary muscle and restriction of leaflet tissue attached to the anterior leaflet. Most patients with chronic CAD and MR previously had an MI. Clinical features that help identify MR secondary to papillary muscle dysfunction as the cause of acute pulmonary edema or milder symptoms of left-sided HF include a loud systolic murmur and demonstration of a flail mitral valve leaflet on

echocardiography. In some patients with severe MR into a small, noncompliant left atrium, the murmur may be unimpressive or inaudible. Doppler echocardiography is helpful in assessing the severity of the regurgitation (**see Chapter 14**). As in MR of other causes, the left atrium is not usually greatly enlarged unless MR has been present for more than 6 months. The ECG is nonspecific, and most patients have angiographic evidence of multivessel CAD.

Management

In patients with severe MR, the indications for surgical correction, usually in association with CABG, are fairly clear-cut.[272] Because of progression of underlying LV dysfunction and resultant structural abnormalities, mitral valve (MV) repair is not always durable. In a randomized trial from the NHLBI Cardiothoracic Surgery Network (CTSN), MV replacement was equivalent to repair in producing reverse LV remodeling and resulted in more durable correction.[273] The decision for MV surgery is based on the anatomic characteristics of the structures forming the MV apparatus, the urgency of the need for surgery, and the severity of LV dysfunction.

A more complex and frequently encountered problem has involved the indications for MV surgery in patients undergoing a CABG procedure in whom the severity of MR is moderate. In a trial comparing CABG alone with CABG plus MV repair in 301 patients with moderate ischemic MR, MV repair reduced the 2-year rate of moderate or severe residual MR (11.2% versus 32.3%; $P < 0.001$) but did not result in a significant difference in the left ventricular end-systolic volume index (LVESVI) or survival at 1 year or 2 years of follow-up[274] (**Fig. 61.19**). Individual treatment decisions require balancing the risks of an increased rate of adverse perioperative events with combined surgery against uncertain benefits of a lower incidence of postoperative moderate or severe MR (**see Chapter 69**).

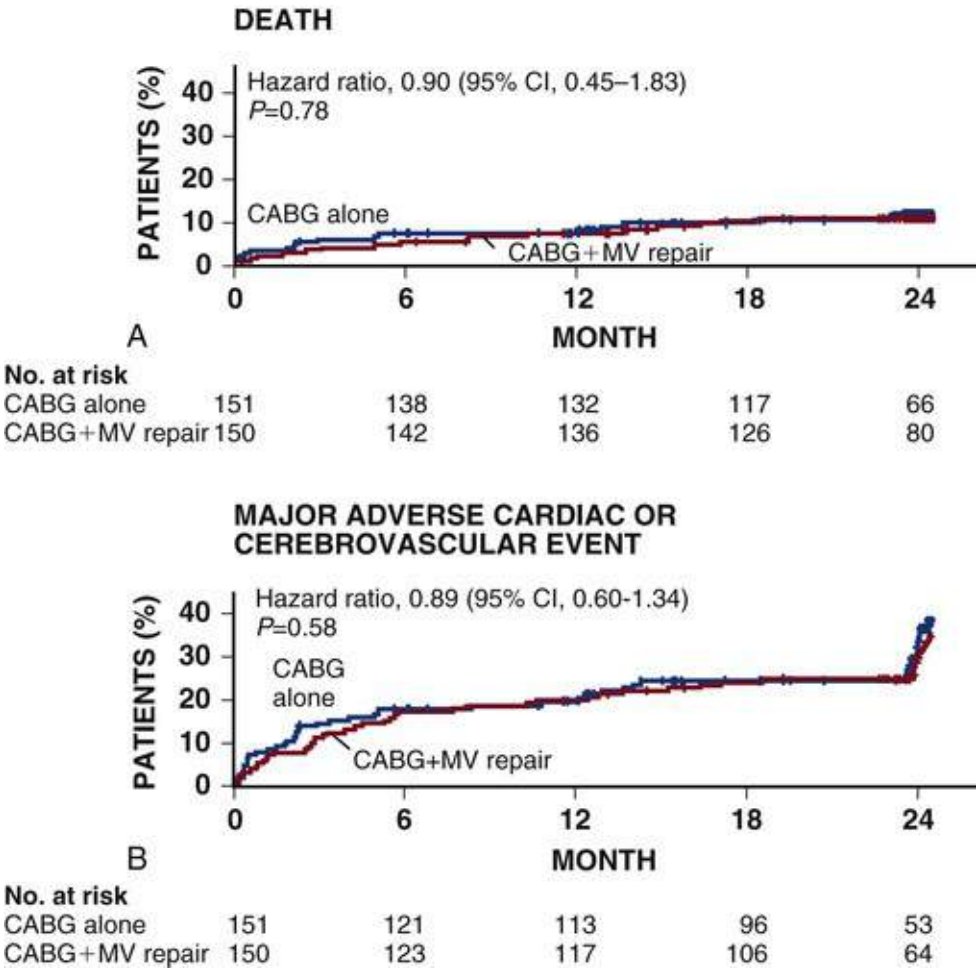


FIGURE 61.19 Outcomes after surgery in patients with moderate ischemic mitral regurgitation (MR). In a randomized trial, 301 patients with moderate ischemic MR undergoing planned coronary-artery bypass grafting (CABG) were allocated to either CABG alone or CABG plus mitral valve (MV) repair. Over 2 years of follow-up, MV repair provided a more durable correction of MR but did not significantly improve survival or reduce major adverse cardiac or cerebrovascular events. (From Michler RE, Smith PK, Parides MK, et al. Two-year outcomes of surgical treatment of moderate ischemic mitral regurgitation. N Engl J Med 2016;374:1932-41.)

In 2015, mortality associated with combined CABG and MV repair was less than 6%.[213] Predictors of early mortality include the need for replacement versus repair (in some but not all series) but also may include other variables, such as age, comorbid conditions, the urgency of surgery, and LV function. Late results are strongly influenced by the pathophysiologic mechanisms underlying MR and are poorer in patients with regurgitation resulting from annular dilation or restrictive leaflet motion than in patients with chordal or papillary muscle rupture. It is encouraging that despite the relatively high operative mortality, long-term outcomes of hospital survivors are excellent. In patients with very poor LV function and dilation of the mitral annulus, MR can intensify the severity of LV failure. In such patients the risk associated with surgery is high and the long-term benefit not established, and a trial of intensive medical therapy, including afterload reduction, beta blockade, and biventricular pacing may be worthwhile (**see Chapters 25 and 27**), because favorable remodeling may reduce the severity of MR without the need for surgery. For patients undergoing CABG, the procedural risks associated with combined CABG and MV repair may outweigh the benefit of reduced MR in those at highest perioperative risk.[272]

Cardiac Arrhythmias.

In some patients with CAD, cardiac arrhythmias are the dominant clinical manifestation of the disease. Various degrees and forms of ventricular ectopic activity are the most common arrhythmias in patients

with CAD, but serious ventricular arrhythmias may be a major component of the clinical findings in other subgroups. The clinical features of arrhythmias and their management in patients with CAD are discussed in **Chapters 35 and 36**.

Nonatheromatous Coronary Artery Disease.

Although atherosclerosis is by far the most common cause of CAD, other conditions may also be responsible. These include congenital abnormalities in the origin or distribution of the coronary arteries (**see Chapters 20 and 75**), the most important of which are anomalous origin of a coronary artery (usually the left) from the pulmonary artery, origin of both coronary arteries from either the right or the left sinus of Valsalva, and coronary arteriovenous fistula.[275] An anomalous origin of the left main coronary artery or right coronary artery from the aorta, with subsequent coursing between the aorta and pulmonary trunk, is a rare and sometimes fatal coronary arterial anomaly. Coronary anomalies are reported to cause between 12% and 19% of sports-related deaths in U.S. high school and college athletes and account for one third of cardiac anomalies in military recruits with nontraumatic sudden death.

Myocardial Bridging.

This cause of systolic compression of the LAD coronary artery is a well-recognized angiographic phenomenon of questionable clinical significance.[276]

Connective Tissue Disorders.

Several inherited connective tissue disorders are associated with myocardial ischemia (**see Chapter 7**), including Marfan syndrome (causing aortic and coronary artery dissection), Hurler syndrome (causing coronary obstruction), Ehlers-Danlos syndrome (causing coronary artery dissection), and pseudoxanthoma elasticum (causing accelerated CAD).

Spontaneous Coronary Artery Dissection.

This is a rare cause of MI and SCD that is much more common in women than men and is often unrecognized or misdiagnosed.[277] Chronic dissection manifesting as HF has been described. Some cases are associated with atherosclerosis. Emerging data suggest that fibromuscular dysplasia may be an important cause of this syndrome, and screening of the renal arteries with angiography or CCTA is recommended. Other contributing factors include estrogen use and hypertension. In the acute phase, a conservative strategy is recommended because PCI failure rates are high, iatrogenic dissection is common, and complete healing may lead to a favorable outcome without intervention.[277] In survivors of spontaneous coronary artery dissection, the subsequent 3-year mortality is approximately 20%, and 10% to 15% of patients have a recurrent dissection.

Coronary Vasculitis and Vasculopathy.

Connective tissue diseases or autoimmune forms of vasculitis, including polyarteritis nodosa, giant cell (temporal) arteritis, or vasculopathy (e.g., scleroderma), can involve the coronary arteries (**see Chapter 94**). Kawasaki disease, a mucocutaneous lymph node syndrome, may cause coronary artery aneurysms and ischemic heart disease in children. Coronary arteritis is seen at autopsy in approximately 20% of patients with rheumatoid arthritis but is rarely associated with clinical manifestations. The incidence of CAD is increased in women with systemic lupus erythematosus (SLE). In patients with SLE, CAD has been attributed to vasculitis, immune complex–mediated endothelial damage, and coronary thrombosis from antiphospholipid antibodies, as well as accelerated atherosclerosis. Antiphospholipid syndrome, characterized by arterial and venous thrombosis and the presence of antiphospholipid antibodies, may be associated with MI, angina, and diffuse LV dysfunction. Luetic (syphilitic) aortitis may also produce myocardial ischemia by causing coronary ostial obstruction.

Takayasu Arteritis.

In rare cases, Takayasu arteritis is associated with angina, MI, and cardiac failure in patients younger than 40 years (**see Chapter 94**). Coronary blood flow may be decreased by involvement of the ostia or proximal segments of the coronary arteries, but disease in distal coronary segments is rare. The average age at the onset of symptoms is 24 years, and the event-free survival rate 10 years after diagnosis is approximately 60%. CCTA has been shown to be useful in detecting involvement of the coronary arteries in Takayasu arteritis.

Postmediastinal Irradiation.

The occurrence of CAD and morbid cardiac events in young individuals after mediastinal irradiation is highly suggestive of a cause-and-effect relationship.[278] Pathologic changes include adventitial scarring and medial hypertrophy with severe intimal atherosclerotic disease. Radiation injury may be latent and may not manifest clinically for many years after therapy. Contributory factors include higher doses than those currently administered and the presence of cardiac risk factors. In patients without risk factors who receive an intermediate total dose of 30 to 40 Gy, the risk for cardiac death and MI is low.

Cardiac Transplantation–Associated Coronary Arteriopathy

See Chapters 28 and 44.

Future Perspectives

Despite Heberden aptly describing “angina” almost two and a half centuries ago, our understanding of the syndrome, its causes, and optimal management continues to evolve. Three major areas are in need of continued investigation. First, the complex and probably heterogeneous causes of myocardial ischemia in the absence of obstructive epicardial coronary disease require continued exploration. Substantial data challenge the paradigm that ischemic heart disease requires critical epicardial coronary atherosclerosis or other structural heart disease that results in dramatically increased myocardial oxygen demand. Preclinical, translational, and clinical epidemiologic data have all demonstrated abnormalities in coronary artery function that may result in myocardial ischemia in the absence of atherosclerotic obstruction. As yet, however, therapies proposed to address this important syndrome appear to be insufficient. Additional insight into the pathobiology of ischemia in these circumstances may lead to new therapeutic directions. Second, although it is clear that an initial approach of guideline-directed medical therapy is the best approach for most patients with SIHD, clinical equipoise remains regarding whether patients with moderate or severe ischemia on noninvasive testing should routinely undergo coronary revascularization in the absence of symptoms that are refractory to medical therapy. Moreover, the role of invasive functional testing of coronary blood flow in decision making regarding coronary revascularization will no doubt continue to evolve. Third, definitive evidence regarding the value of using viability and ischemia assessments to guide the management of patients with SIHD and concomitant severe LV dysfunction remains elusive. Despite our wealth of experience with stable ischemic heart disease, important questions remain unanswered.

Guidelines

Stable Ischemic Heart Disease

David A. Morrow and James A. de Lemos

The American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) published updated guidelines for the diagnosis and management of patients with stable ischemic heart disease (SIHD) in 2012 and a focused update of this guideline in 2014.[1,2] In addition, a new ACCF/AHA guidelines document was published in 2016 providing new recommendations for the duration of dual-antiplatelet therapy (DAPT) for patients with SIHD undergoing percutaneous coronary intervention (PCI).[3] The European Society of Cardiology (ESC) published guidelines for management of stable coronary artery disease in 2013.[4] We refer to the ACCF/AHA guidelines except in cases where the U.S. and European guidelines disagree. The tables and figures reflect only the ACCF/AHA guidelines.

Populations addressed include patients with "ischemic equivalents" such as dyspnea or arm pain with exertion and patients with IHD who have become asymptomatic. Patients with unstable ischemic syndromes are not included in these guidelines (see guidelines summarized in **Chapter 60**).

Overview

The ACCF/AHA guidelines emphasize the importance of a detailed symptom history, focused physical examination, and directed risk factor assessment for patients with chest pain to estimate the probability of IHD before additional testing. For patients without symptoms or findings suggestive of high risk, noninvasive evaluation rather than invasive coronary angiography is recommended (**Fig. 61G.1**). For patients with an intermediate probability of coronary artery disease (CAD), noninvasive testing should be considered to refine the diagnostic assessment of patients. Noninvasive testing is also indicated to inform risk stratification in patients with a high probability of or established SIHD (**Fig. 61G.2**).

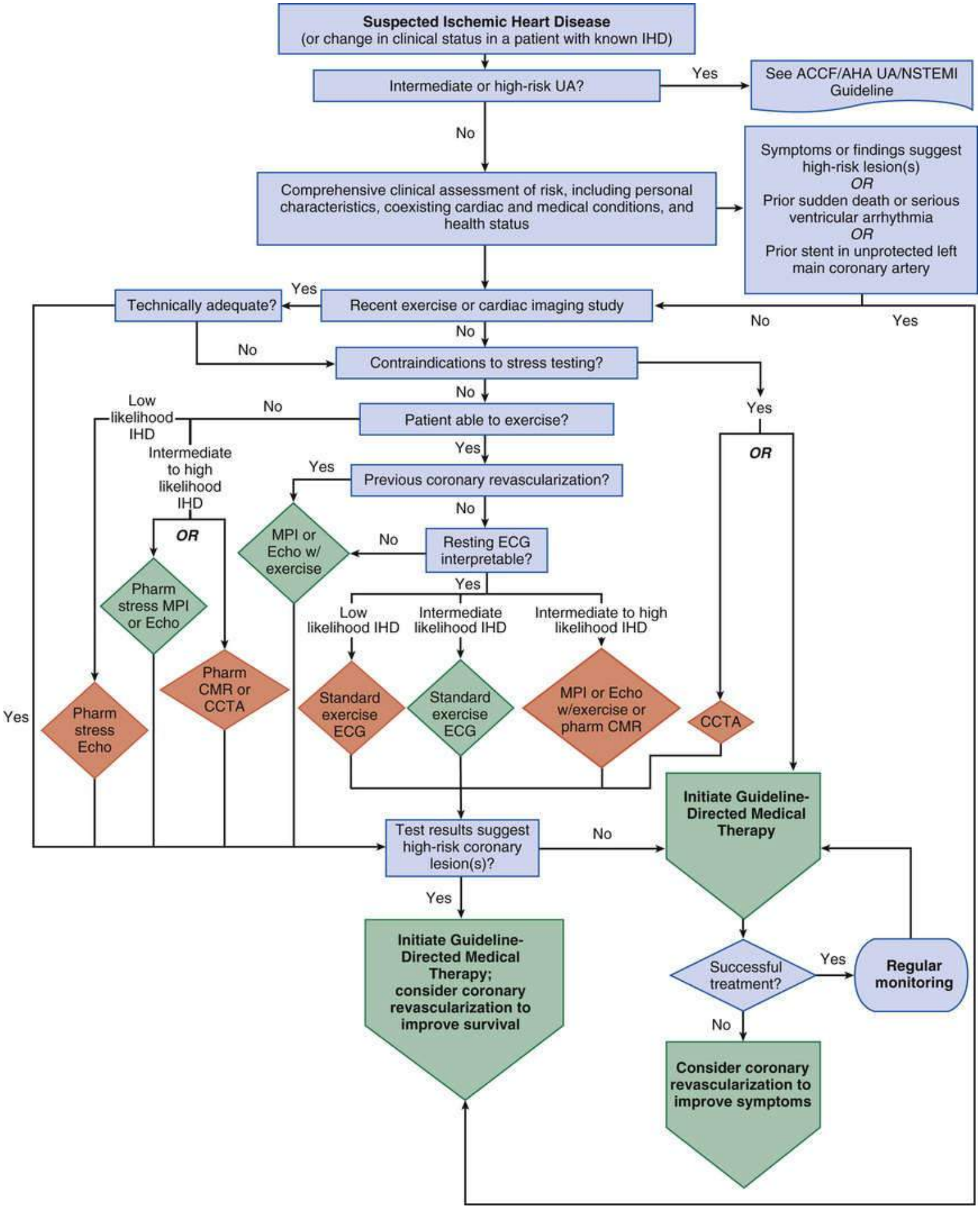


FIGURE 61G.1 Diagnosis of patients with suspected stable ischemic heart disease (SIHD). Colors correspond to the class of recommendations: *green,* class 1; *orange,* class IIa. The algorithms do not represent a comprehensive list of recommendations (see full guidelines for all recommendations). CCTA, Cardiac computed tomographic angiography; CMR, cardiac magnetic resonance imaging; ECG, electrocardiography; Echo, echocardiography; MPI, myocardial perfusion imaging; NSTEMI, non–ST-segment elevation myocardial infarction; Pharm, pharmacologic; UA, unstable angina. (From Fihn SD, Gardin

JM, Abrams J, et al: 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: Areport of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 60:2564, 2012.)

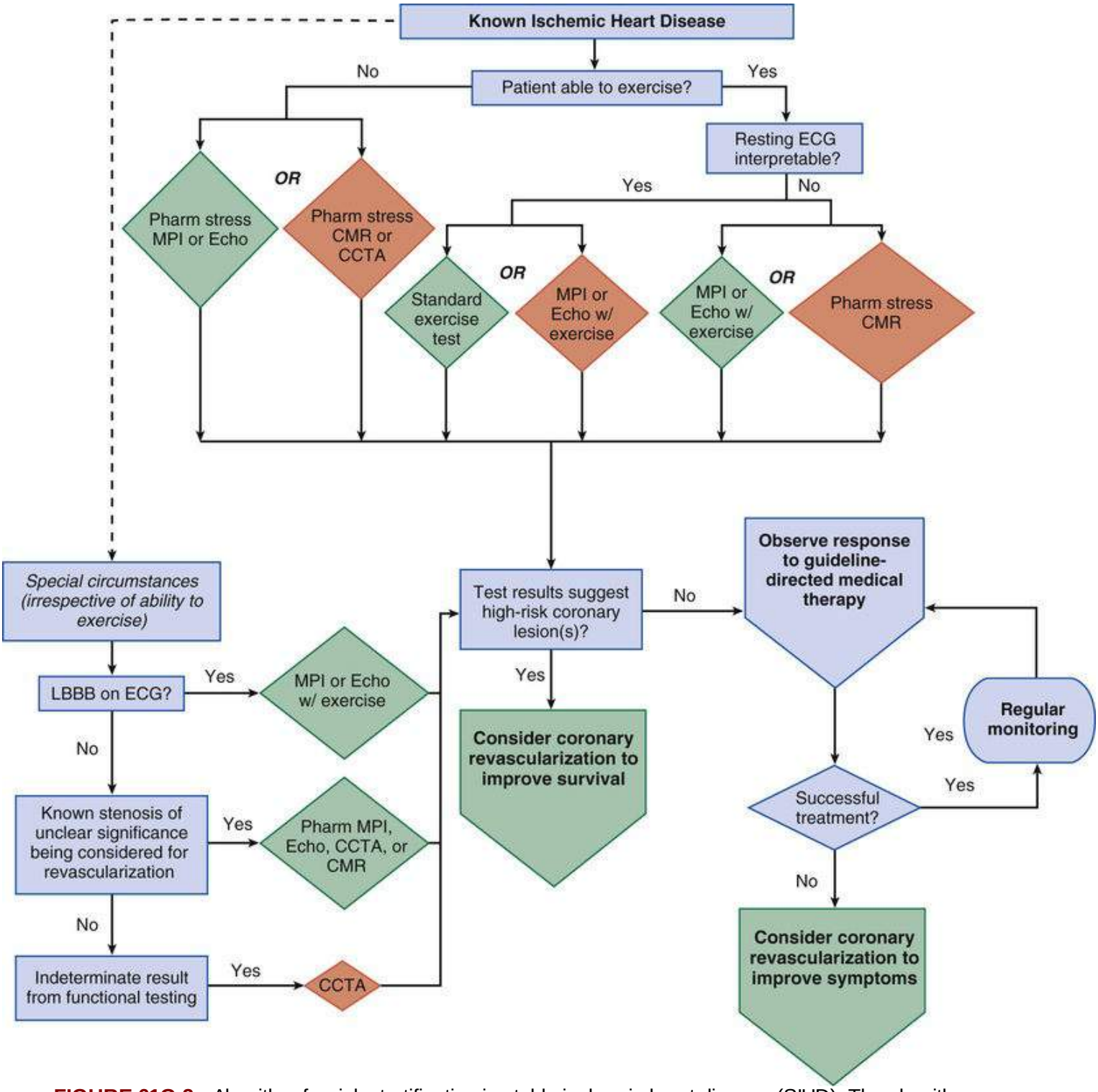


FIGURE 61G.2 Algorithm for risk stratification in stable ischemic heart disease (SIHD). The algorithms do not represent a comprehensive list of recommendations (see full guideline text for all recommendations). CCTA, Cardiac computed tomographic angiography; CMR, coronary magnetic resonance imaging; ECG, electrocardiography; Echo, echocardiography; LBBB, left bundle branch block; MPI, myocardial perfusion imaging; Pharm, pharmacologic. (From Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60:2564.)

The treatment algorithm recommended by the ACCF/AHA guidelines emphasizes the importance of patient education about CAD, prevention of progression of atherosclerosis through risk factor management, and improvement in health status by treatment of ischemic symptoms (**Fig. 61G.3**). In particular, the patient should be included in decision making such that choices about diagnostic and

therapeutic options are made through a process of shared decision making, with discussion of risks, benefits, and costs to the patient.

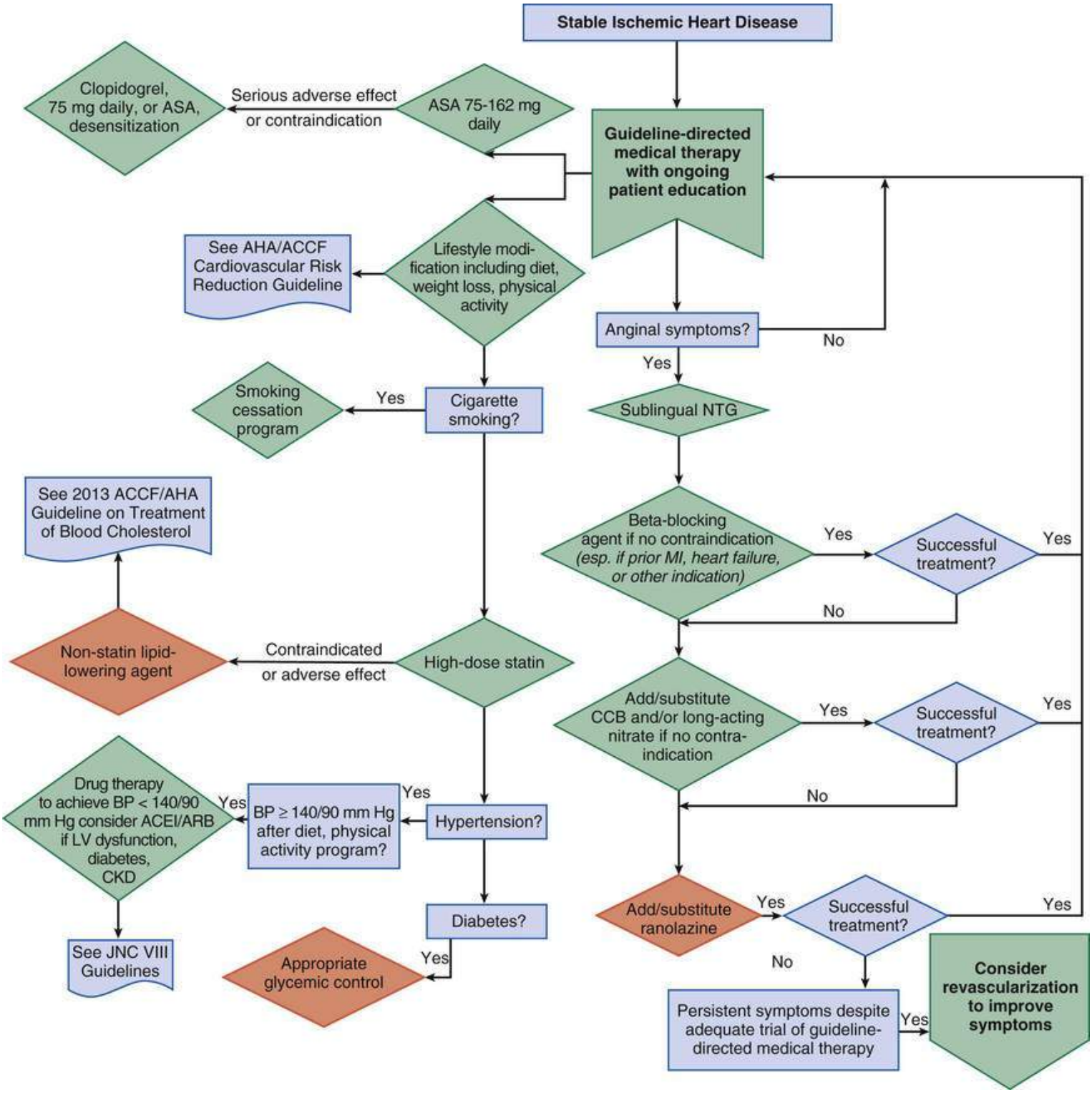


FIGURE 61G.3 Algorithm for guideline-directed medical therapy for patients with stable ischemic heart disease. The algorithms do not represent a comprehensive list of recommendations (see full guideline text for all recommendations). ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocking agent; ASA, aspirin; ATP III, Adult Treatment Panel III; BP, blood pressure; CCB, calcium channel blocking agent; CKD, chronic kidney disease; JNC VIII, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; NHLBI, National Heart, Lung and Blood Institute; NTG, nitroglycerin. (From Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60:2564.)

Diagnosis

Noninvasive Studies

Resting Electrocardiography

A resting electrocardiogram (ECG) is recommended in patients undergoing evaluation for symptoms who do not have an obvious, noncardiac cause of chest pain. Any of the following abnormalities on the ECG are associated with a poorer prognosis: evidence of previous myocardial infarction (MI); persistent ST-segment depression or T wave inversion (especially in leads V_1 to V_3); left bundle branch block (LBBB), bifascicular block, or high-degree atrioventricular (AV) block; or left ventricular (LV) hypertrophy.[1,2]

Exercise Electrocardiography

Exercise testing is considered most valuable for diagnosis in patients with an intermediate probability of CAD. The ACCF/AHA guidelines recommend exercise ECGs unless the baseline ECG shows abnormalities likely to render the exercise tracing uninterpretable or patients are unable to exercise (**see Fig. 61G.1**). Exercise ECG is also reasonable in patients with a low pretest probability of obstructive CAD who do require testing (**Table 61G.1**). In contrast, the ESC guidelines recommend routine addition of adjunctive imaging if such testing is available with local expertise, regardless of baseline ECG findings. This important difference in guidelines reflects a differing interpretation of the guideline committees regarding the influence of test verification bias on the sensitivity and specificity of the exercise ECG.

TABLE 61G.1

ACCF/AHA Guidelines for Stress Testing and Advanced Imaging for Initial Diagnosis in Patients with Suspected Stable Ischemic Heart Disease Who Require Noninvasive Testing

TEST	EXERCISE STATUS		ECG INTERPRETABLE		PRETEST PROBABILITY OF IHD			COR	LOE
	Able	Unable	Yes	No	Low	Intermediate	High		
Patients Able to Exercise									
Exercise ECG	X		X			X		I	A
Exercise ECG with MPI or Echo	X			X		X	X	I	B
Exercise ECG	X		X		X			IIa	C
Exercise ECG with MPI or Echo	X		X			X	X	IIa	B
Pharmacologic stress CMR	X			X		X	X	IIa	B
CCTA	X		Either			X		IIb	B
Exercise Echo	X		X			X		IIb	C
Pharmacologic stress with nuclear MPI, Echo, or CMR	X		X			Any		III	C
Exercise stress with MPI	X		X		X			III	C
Patients Unable to Exercise									
Pharmacologic stress with nuclear MPI or Echo		X	Either			X	X	I	B
Pharmacologic stress Echo		X	Either		X			IIa	C
CCTA		X	Either		X	X		IIa	B
Pharmacologic stress CMR		X	Either			X	X	IIa	B
Exercise ECG		X		X		Any		III	C
Other Reasons for Cardiac Computed Tomography Angiography									
Continued symptoms after normal test results Inconclusive stress test results Unable to undergo stress test	Either		Either			X		IIa	C
CAC	Either		Either		X			IIb	C

COR, Class of recommendation; *LOE,* level of evidence; *CAC,* coronary artery calcium (imaging); *CCTA,* coronary computed tomographic angiography; *CMR,* cardiac magnetic resonance imaging; *ECG,* electrocardiography; *Echo,* echocardiography; *IHD,* ischemic heart disease; *MPI,* myocardial perfusion imaging.

Stress Imaging Studies

The ACCF/AHA guidelines recommend stress imaging (exercise or pharmacologic) as opposed to an exercise ECG when the ECG is uninterpretable, such as in (1) patients who have complete LBBB, electronically paced ventricular rhythm, preexcitation syndrome, and other conduction abnormalities; (2) patients who have more than 1 mm of ST-segment depression at rest, including those with LV hypertrophy or taking drugs such as digitalis; and (3) patients who are unable to exercise to a sufficient level for meaningful exercise ECG results. Stress imaging is also reasonable in patients with CAD who have undergone previous revascularization, for whom localizing ischemia is important. It is reasonable also in patients with an intermediate to high pretest probability of obstructive CAD, even those with an interpretable ECG and moderate or better physical functioning (**Table 61G.1**). As previously noted, the ESC guideline recommends more broad use of stress imaging even among patients with interpretable baseline ECGs.

The guidelines specify that exercise stress is preferable to pharmacologic stress when the patient can exercise adequately. **Table 61G.1** summarizes the appropriate indications for stress imaging in patients who are and who are not able to exercise. As with the exercise ECG, these tests are considered most useful for diagnosis in patients with an intermediate probability of disease.

Coronary Computed Tomography Angiography

The ACCF/AHA guidelines indicate that coronary computed tomographic angiography (CCTA; **see Chapter 18**) is reasonable (class IIa) for patients with a low to intermediate pretest probability of CAD who are incapable of exercising or have persistent symptoms after other testing has provided normal or inconclusive results (**Table 61G.1**). CCTA may be reasonable (class IIb) for patients with an intermediate pretest probability of CAD who are capable of exercising. A recent large comparative effectiveness trial demonstrating generally equivalent outcomes for CCTA versus standard stress testing[5] may lead to a stronger recommendation for CCTA in the next update to the SIHD guidelines.

Specific Patient Subsets

Although treadmill ECG testing is less accurate for diagnosis in women than in men, the ACCF/AHA guidelines note that “there currently are insufficient data to justify replacing standard exercise testing with stress imaging in the initial evaluation of women.” In contrast, the ESC guidelines recommend routine adjunctive imaging in women, provided testing is available with local expertise.

Coronary Angiography

In the 2012 ACCF/AHA guidelines, invasive coronary angiography plays a very limited role in the diagnosis of CAD. The guidelines do support coronary angiography for diagnosis in patients with suspected SIHD who (1) have survived sudden death or serious ventricular arrhythmias or (2) have symptoms or findings that suggest high-risk coronary lesions (**see Fig. 61G.1**). Use of invasive coronary angiography for risk assessment and to enable coronary revascularization is discussed next.

Risk Stratification

The ACCF/AHA guidelines emphasize the following four factors that predict survival for patients with CAD: (1) LV function, (2) anatomic extent and severity of coronary atherosclerosis, (3) presence of recent plaque rupture, and (4) the patient's general health and noncoronary comorbidity.

Assessment of Left Ventricular Function and Other Structural Heart Disease

The guidelines consider echocardiographic assessment of LV function and evaluation for myocardial, valvular, or pericardial abnormalities (class I) appropriate in patients with known or suspected IHD and symptoms or signs of heart failure (HF), a history of previous MI, pathologic Q waves on the ECG, complex ventricular arrhythmias, or an undiagnosed heart murmur. Echocardiography may be considered (class IIb) for patients with hypertension or diabetes mellitus (DM) and abnormal findings on an ECG. In contrast, the ESC guidelines recommend routine resting echocardiography in *all* patients (class I) to exclude alternative causes of angina, assess regional wall motion abnormalities, measure LV ejection fraction (EF), and assess diastolic function.

Noninvasive Tests for Ischemia

Noninvasive testing provides valuable information regarding ischemic burden and prognosis and helps identify candidates for coronary revascularization. Standard treadmill exercise testing is recommended in the ACCF/AHA guidelines for assessment of prognosis in all patients who are able to exercise, except those with an uninterpretable ECG (**Table 61G.2**), in whom nuclear myocardial perfusion imaging (MPI) or echocardiography is indicated. Pharmacologic stress imaging is discouraged in patients who are able to exercise.

TABLE 61G.2

ACCF/AHA Guidelines for Stress Testing and Advanced Imaging for Patients with Known Stable Ischemic Heart Disease Who Require Noninvasive Testing for Risk Assessment

TEST	EXERCISE STATUS		ECG INTERPRETABLE		ADDITIONAL CONSIDERATIONS	COR	LOE
	Able	Unable	Yes	No			
Patients Able to Exercise							
Exercise ECG	X		X			I	B
Exercise ECG with MPI or Echo	X			X	Abnormalities other than LBBB or ventricular pacing	I	B
Exercise ECG with MPI or Echo	X		X			IIa	B
Pharmacologic stress CMR	X			X		IIa	B
CCTA	X			X		IIb	B
Pharmacologic stress imaging or CCTA	X		X			III	C
Patients Unable to Exercise							
Pharmacologic stress with nuclear MPI or Echo		X	Either			I	B
Pharmacologic stress CMR		X	Either			IIa	B
CCTA		X	Either		Without previous stress test	IIa	C
Regardless of Ability to Exercise							
Pharmacologic stress with nuclear MPI or Echo	Either			X	LBBB present	I	B
Exercise or pharmacologic stress with nuclear MPI, Echo, or CMR	Either		Either		Known coronary stenosis being considered for revascularization	I	B
CCTA	Either		Either		Indeterminate result of functional testing	IIa	C
	Either		Either		Unable to undergo stress imaging	IIb	C
	Either		Either		Alternative to invasive coronary angiography when functional testing indicates moderate to high risk	IIb	C

COR, Class of recommendation; *LOE,* level of evidence; *CCTA,* coronary computed tomographic angiography; *CMR,* cardiac magnetic resonance imaging; *ECG,* electrocardiography; *Echo,* echocardiography; *LBBB,* left bundle branch block; *MPI,* myocardial perfusion imaging.

Coronary Angiography

In the ACCF/AHA guidelines the decision to proceed to coronary angiography should be based on

symptomatic status and risk estimation derived from clinical data and noninvasive test results. Coronary angiography is a necessary step for the management of patients in whom coronary revascularization is likely to be beneficial because of a high risk for complications with medical therapy alone. Thus the guidelines support coronary angiography in patients with suspected SIHD who (1) have survived sudden death, (2) have signs or symptoms of HF, (3) have a high likelihood of severe IHD and the potential benefits are deemed to exceed the risk, or (4) have persistent symptoms despite an adequate trial of guideline-directed medical therapy (GDMT) (**Table 61G.3; see also Fig. 61G.3**).

TABLE 61G.3

ACCF/AHA Guidelines for Coronary Angiography to Assess Risk in Patients with Known or Suspected Stable Ischemic Heart Disease (SIHD)

COR	INDICATION	LOE
I (indicated)	1. Patients with SIHD who have survived sudden cardiac death or potentially life-threatening ventricular arrhythmia should undergo coronary angiography to assess cardiac risk.	B
	2. Patients with SIHD in whom symptoms and signs of heart failure develop should be evaluated to determine whether coronary angiography should be performed for risk assessment.	B
	3. Coronary angiography is recommended for patients with SIHD whose clinical characteristics and results of noninvasive testing indicate a high likelihood of severe IHD and when the benefits are deemed to exceed risk.	C
IIa (good supportive evidence)	1. Coronary angiography is reasonable to further assess risk in patients with SIHD who have depressed LV function (EF <50%) and moderate-risk criteria on noninvasive testing with demonstrable ischemia.	C
	2. Coronary angiography is reasonable to further assess risk in patients with SIHD and inconclusive prognostic information after noninvasive testing or in patients for whom noninvasive testing is contraindicated or inadequate.	C
	3. Coronary angiography for risk assessment is reasonable for patients with SIHD who have unsatisfactory quality of life because of angina, have preserved LV function (EF >50%), and have intermediate-risk criteria on noninvasive testing.	C
III (no benefit)	1. Coronary angiography for risk assessment is not recommended in patients with SIHD who elect not to undergo revascularization or who are not candidates for revascularization because of comorbid conditions or individual preferences.	B
	2. Coronary angiography is not recommended to further assess risk in patients with SIHD who have preserved LV function (EF >50%) and low-risk criteria on noninvasive testing.	B
	3. Coronary angiography is not recommended to assess risk in patients who are at low risk according to clinical criteria and who have not undergone noninvasive risk testing.	C
	4. Coronary angiography is not recommended to assess risk in asymptomatic patients with no evidence of ischemia on noninvasive testing.	C

COR, Class of recommendation; *LOE,* level of evidence; *EF,* ejection fraction; *LV,* left ventricular.

The ACCF/AHA guidelines conclude that there is no benefit of coronary angiography in patients who are at low risk according to clinical criteria and have not undergone or have no evidence of ischemia on noninvasive testing.

Treatment

The ACCF/AHA guidelines for medical therapy in patients with SIHD are oriented toward preventing death while maximizing health and function. More specific objectives are shown in **Table 61G.4**. Coronary revascularization is recommended in specific patient subsets in whom it has been shown to extend life, but in many settings there are a variety of reasonable options, including GDMT, PCI (**see Chapter 62**), and coronary artery bypass grafting (CABG) (**Fig. 61G.3**). Cost-effectiveness and patient preference are considered important components in decision making.

TABLE 61G.4

ACCF/AHA Goals for Management of Stable Ischemic Heart Disease (SIHD)

1. Reduce premature cardiovascular death.
2. Prevent complications of SIHD that directly or indirectly impair patients' functional well-being, including nonfatal acute myocardial infarction and heart failure.
3. Maintain or restore a level of activity, functional capacity, and quality of life that are satisfactory to the patient.
4. Completely or almost completely eliminate ischemic symptoms.
5. Minimize the cost of health care, in particular by eliminating avoidable adverse effects of tests and treatments and by preventing hospital admissions.

The guidelines identify five complementary strategies: (1) educate patients about the cause, manifestations, and treatment options for IHD; (2) identify and treat conditions that contribute to, worsen, or complicate IHD; (3) modify risk factors for IHD (see next); (4) use evidence-based pharmacologic treatments to improve health status and survival; and (5) use coronary revascularization when there is clear evidence of the potential to improve health status and survival.

Risk Factor Modification

The ACCF/AHA guidelines support lifestyle modifications, including daily physical activity and weight management, for all patients with SIHD (**Table 61G.5**) and also recommend intensive management of risk factors, including hypertension (target blood pressure <140/90 mm Hg), cigarette smoking, diabetes, low-density lipoprotein (LDL) cholesterol, and obesity (**Table 61G.6; see also Table 61G.5**). The 2013 ACCF/AHA cholesterol guidelines[6] support dietary therapy for all patients and high-intensity statin therapy in the absence of contraindications or documented adverse effects for all patients with established coronary heart disease (CHD). For elderly patients age 75 or older, moderate rather than high-dose statin therapy is a reasonable option.

TABLE 61G.5

ACCF/AHA Guidelines for Risk Factor Modification for Patients with Stable Ischemic Heart Disease (SIHD)

COR	INDICATION	LOE
Lipid Management		
I (indicated)	1. Lifestyle modifications, including daily physical activity and weight management, are strongly recommended for all patients with SIHD.	B
	2. Dietary therapy for all patients should include reduced intake of saturated fats (to <7% of total calories), trans fatty acids (to <1% of total calories), and cholesterol (to <200 mg/day).	B
	3. In addition to therapeutic lifestyle changes, high-intensity statin therapy should be prescribed in the absence of contraindications or documented adverse effects. For patients older than 75 years, moderate-intensity statin therapy may be considered.	A
IIa (good supportive evidence)	For patients who do not tolerate statins, LDL cholesterol–lowering therapy with bile acid sequestrants, niacin, or both is reasonable. Ezetimibe or PCSK9 inhibitors are also alternatives.	B
Blood Pressure (BP) Management		
I (indicated)	1. All patients should be counseled about the need for lifestyle modification: weight control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products.	B
	2. In patients with SIHD and a BP of 140/90 mm Hg or higher, antihypertensive drug therapy should be instituted in addition to or after a trial of lifestyle modifications.	A
	3. The specific medications used for the treatment of high BP should be based on specific patient characteristics and may include ACE inhibitors and/or beta-blocking agents, as well as the addition of other drugs such as thiazide diuretics or calcium channel blocking agents if needed to achieve a goal BP of less than 140/90 mm Hg.	B
Physical Activity		
I (indicated)	1. For all patients, clinicians should encourage 30 to 60 minutes of moderate-intensity aerobic activity at least 5 days and preferably 7 days per week, supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, household work) to improve cardiorespiratory fitness and move patients out of the least-fit, least-active, high-risk cohort (bottom 20%).	B
	2. For all patients, risk assessment with a physical activity history and/or an exercise test is recommended to guide prognosis and prescription.	B
	3. Medically supervised programs (cardiac rehabilitation) and physician-directed, home-based programs are recommended for at-risk patients at first diagnosis.	A
IIa (good supportive evidence)	It is reasonable for clinicians to recommend complementary resistance training at least 2 days per week.	C
Weight Management		
I (indicated)	1. BMI and/or waist circumference should be assessed at every visit, and clinicians should consistently encourage weight maintenance or reduction through an appropriate balance of lifestyle physical activity, structured exercise, caloric regulation, and formal behavioral programs	B
	2. The initial goal of weight loss therapy should be to reduce body weight by approximately 5% to 10% from baseline. With success, further weight loss can be attempted if indicated.	C
Smoking Cessation		
I (indicated)	Smoking cessation and avoidance of exposure to environmental tobacco smoke at work and home should be encouraged for all patients with SIHD. Follow-up, referral to special programs, and pharmacotherapy are recommended, as is a stepwise strategy for smoking cessation (Ask, Advise, Assess, Assist, Arrange, Avoid).	B
Management of Psychological Factors		
IIa (good supportive evidence)	It is reasonable to consider screening patients with SIHD for depression and to refer or treat when indicated.	B
IIb (weak supportive evidence)	Treatment of depression has not been shown to improve cardiovascular disease outcomes but might be reasonable for its other clinical benefits.	C
Alcohol Consumption		
IIb (weak supportive evidence)	In patients with SIHD who drink alcohol, it might be reasonable for nonpregnant women to have 1 drink (4 oz of wine, 12 oz of beer, or 1 oz of spirits) a day and for men to have 1 or 2 drinks a day unless alcohol is contraindicated (e.g., patients with history of alcohol abuse or dependence, patients with liver disease).	C
Exposure to Air Pollution		
IIa (good supportive evidence)	It is reasonable for patients with SIHD to avoid exposure to increased air pollution to reduce their risk for cardiovascular events.	C

COR, Class of recommendation; *LOE,* level of evidence; *ACE,* angiotensin-converting enzyme; *BMI,* body mass index; *LDL,* low-density lipoprotein.

The management of diabetes mellitus in patients with established atherosclerosis is discussed in **Chapter 51**.

TABLE 61G.6

ACCF/AHA Guidelines for Medical Therapy to Prevent Myocardial Infarction (MI) and Death

COR	INDICATION	LOE
Antiplatelet Therapy		
I (indicated)	1. Treatment with aspirin, 75 to 162 mg daily, should be continued indefinitely in the absence of contraindications in patients with SIHD.	A
	2. Treatment with clopidogrel is reasonable when aspirin is contraindicated in patients with SIHD.	B
IIb (weak supportive evidence)	3. Treatment with aspirin, 75 to 162 mg daily, and clopidogrel, 75 mg daily, might be reasonable in certain high-risk patients with SIHD.	B
Beta-Blocking Therapy		
I (indicated)	1. Beta-blocking therapy should be started and continued for 3 years in all patients with normal LV function after MI or ACS.	B
	2. Beta-blocking therapy should be used in all patients with LV systolic dysfunction (EF <40%) and heart failure or previous MI unless contraindicated. (Use should be limited to carvedilol, metoprolol succinate, or bisoprolol, which have been shown to reduce the risk for death.)	A
IIb (weak supportive evidence)	Beta-blocking agents may be considered as chronic therapy for all other patients with coronary or other vascular disease.	C
Renin-Angiotensin-Aldosterone Blocker Therapy		
I (indicated)	1. ACE inhibitors should be prescribed in all patients with SIHD who also have hypertension, diabetes mellitus, LVEF of 40% or less, or CKD unless contraindicated.	A
	2. ARBs are recommended for patients with SIHD who have hypertension, diabetes mellitus, LV systolic dysfunction, or CKD who are intolerant of ACE inhibitors.	A
IIa (good supportive evidence)	1. Treatment with an ACE inhibitor is reasonable in patients with both SIHD and other vascular disease.	B
	2. It is reasonable to use ARBs in other patients who are intolerant of ACE inhibitors.	C
Other Therapies		
III (not indicated)	1. Estrogen therapy is not recommended in postmenopausal women with SIHD with the intent of reducing cardiovascular risk or improving clinical outcomes.	A
	2. Vitamin C, vitamin E, and beta-carotene supplementation is not recommended with the intent of reducing cardiovascular risk or improving clinical outcomes in patients with SIHD.	A
	3. Treatment of elevated homocysteine with folate or vitamins B_6 and B_{12} is not recommended with the intent of reducing cardiovascular risk or improving clinical outcomes in patients with SIHD.	A

COR, Class of recommendation; *LOE,* level of evidence; *ACE,* angiotensin-converting enzyme; *ACS,* acute coronary syndrome; *ARB,* angiotensin receptor blocker; *CKD,* chronic kidney disease; *EF,* ejection fraction; *LV,* left ventricular; *SIHD,* stable ischemic heart disease.

Pharmacologic Therapy

The guidelines emphasize the importance of low-dose aspirin (75 to 162 mg) for patients with SIHD in the absence of contraindications (class I, level of evidence [LOE]: A) (**Table 61G.6**). In the absence of contraindications, beta-blocking agents are recommended for 3 years in all patients after an acute coronary syndrome (ACS) who have normal LV function and indefinitely in all patients with SIHD and LV systolic dysfunction. The evidence for beta blockers as chronic therapy in other patients with SIHD is weaker (class IIb, LOE: C). Absolute contraindications to beta blockers include severe bradycardia, preexisting high degree of AV block, sick sinus syndrome, and decompensated LV failure; relative contraindications include asthma and bronchospastic disease, severe depression, and peripheral vascular disease.

Angiotensin-converting enzyme (ACE) inhibitors are recommended (class I; **Table 61G.6**) for patients with SIHD who also have diabetes, hypertension, chronic kidney disease, and/or LV systolic dysfunction and may be considered in other patients with CAD (class IIa).

The AHA/ACC guidelines recommend beta-blocking agents as initial therapy for relief of symptoms of myocardial ischemia in patients with SIHD (**Table 61G.7**). Long-acting nitrates and/or calcium antagonists (class I) or ranolazine (class IIa) should be used (or added) for symptom control when beta blockers are contraindicated, not tolerated, or ineffective. The ESC guidelines provide different recommendations for antianginal drug selection, recommending beta blockers and/or calcium antagonists as first-line therapy (class I), with long-acting nitrates, ivabradine, or ranolazine (class IIa) or

trimetazidine (class IIb) considered as second-line additions. Annual influenza vaccination is recommended for patients with SIHD.

TABLE 61G.7

ACCF/AHA Guidelines for Medical Therapy for Relief of Symptoms

COR	INDICATION	LOE
I (indicated)	1. Beta-adrenergic blocking agents (beta blockers) should be prescribed as initial therapy for relief of symptoms in patients with SIHD.	B
	2. Calcium channel–blocking agents* or long-acting nitrates should be prescribed for relief of symptoms when beta blockers are contraindicated or cause unacceptable side effects in patients with SIHD.	B
	3. Calcium channel–blocking agents* or long-acting nitrates, in combination with beta blockers, should be prescribed for relief of symptoms when initial treatment with beta blockers is unsuccessful in patients with SIHD.	B
	4. Sublingual nitroglycerin or nitroglycerin spray is recommended for immediate relief of angina in patients with SIHD.	B
IIa (good supportive evidence)	1. Treatment with a long-acting nondihydropyridine calcium channel blocker (verapamil or diltiazem) instead of a beta blocker as initial therapy for relief of symptoms is reasonable in patients with SIHD.	B
	2. Ranolazine can be useful when prescribed as a substitute for a beta blocker for relief of symptoms in patients with SIHD if initial treatment with beta blockers leads to unacceptable side effects or is ineffective or if initial treatment with beta blockers is contraindicated.	B
	3. Ranolazine in combination with beta blockers can be useful when prescribed for relief of symptoms when initial treatment with beta blockers is not successful in patients with SIHD.	A
IIb weak supportive evidence)	1. Enhanced external counterpulsation may be considered for relief of refractory angina in patients with SIHD.	B
	2. Spinal cord stimulation may be considered for relief of refractory angina in patients with SIHD.	C
III (not indicated)	Acupuncture should not be used for the purpose of improving symptoms or reducing cardiovascular risk in patients with SIHD.	C

*Short-acting dihydropyridine calcium antagonists should be avoided.

COR, Class of recommendation; *LOE,* level of evidence.

Revascularization

The ACCF/AHA guidelines for revascularization focus on improvement of survival in patients with SIHD and high clinical risk for mortality with GDMT (**Fig. 61G.4 and Table 61G.8**) and in those who have inadequate control of symptoms and quality of life despite GDMT (**Table 61G.9; see also Fig. 61G.4**). Recommendations include CABG for patients with significant left main CAD, triple-vessel CAD, or CAD involving the proximal left anterior descending (LAD) plus one other major coronary artery. CABG is reasonable (class IIa) for patients with double-vessel CAD who have evidence of severe or extensive myocardial ischemia or mild to moderate LV systolic dysfunction with viable myocardium in the region of intended revascularization. CABG is given preference over PCI (class IIa) in patients with complex three-vessel disease and those with DM.

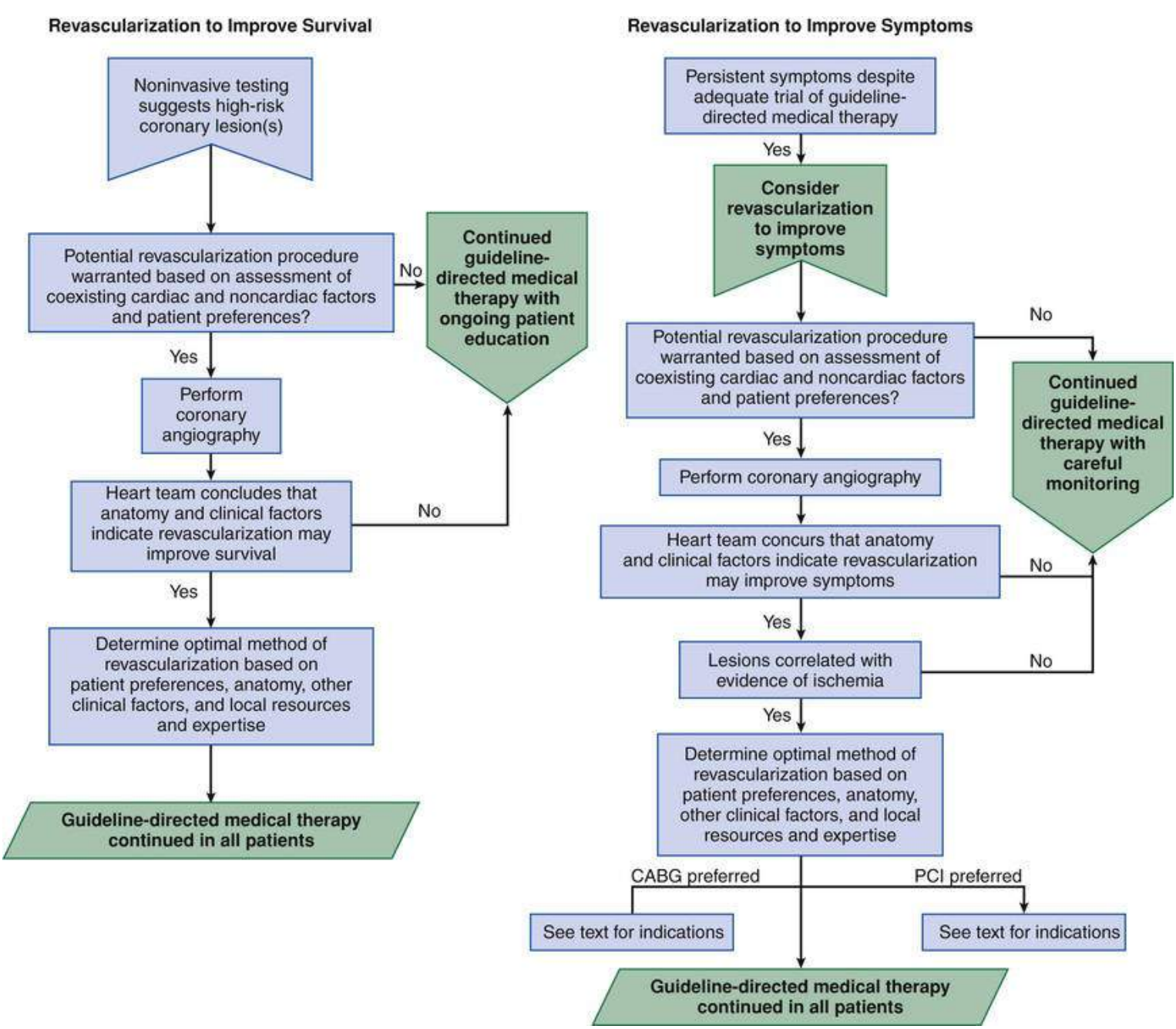


FIGURE 61G.4 Algorithm for revascularization to improve survival (*left*) and symptoms (*right*) in patients with stable ischemic heart disease. The algorithms do not represent a comprehensive list of recommendations (see full guideline text for all recommendations. CABG, Coronary artery bypass graft surgery; PCI, percutaneous coronary intervention. (From Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60:2564.)

TABLE 61G.8

ACCF/AHA Guidelines for Revascularization to Improve Survival Versus Medical Therapy in Patients with Stable Ischemic Heart Disease (SIHD)

ANATOMIC SETTING	COR	RECOMMENDATION	LOE
Unprotected Left Main or Complex Coronary Artery Disease (CAD)			
CABG and PCI	I	Heart team approach	C
CABG and PCI	IIa	Calculation of STS and SYNTAX Scores	B
Unprotected Left Main			
CABG	I		B
PCI	IIa	For SIHD when both the following are present: 1. Anatomic conditions associated with a low risk for PCI procedural complications and a high likelihood of a good long-term outcome 2. Clinical characteristics that predict a significantly increased risk for adverse surgical outcomes	B
	IIb	For SIHD when both the following are present: 1. Anatomic conditions associated with a low to intermediate risk for PCI procedural complications and an intermediate to high likelihood of a good long-term outcome 2. Clinical characteristics that predict increased risk for adverse surgical outcomes (e.g., STS-predicted operative mortality >2%)	B
	III	For SIHD in patients (versus performing CABG) with unfavorable anatomy for PCI and who are good candidates for CABG	B
Three-Vessel CAD with or Without Proximal Left Anterior Descending CAD			
CABG	I		B
	I	CABG is generally recommended in preference to PCI to improve survival in patients with diabetes mellitus and three-vessel CAD, particularly if a LIMA graft can be anastomosed to the LAD, provided the patient is a good candidate for surgery.	
	IIa	It is reasonable to choose CABG over PCI in patients with complex three-vessel CAD (e.g., SYNTAX score ≥22) who are good candidates for CABG.	B
PCI	IIb		B
Two-Vessel CAD with Proximal Left Anterior Descending CAD			
CABG	I		B
CABG	I	CABG is generally recommended in preference to PCI to improve survival in patients with diabetes mellitus and complex two-vessel CAD with proximal LAD involvement, particularly if a LIMA graft can be anastomosed to the LAD, provided the patient is a good candidate for surgery.	B
PCI	IIb		B
Two-Vessel CAD Without Proximal Left Anterior Descending CAD			
CABG	IIa	With extensive ischemia	B
	IIb	Without extensive ischemia	C
PCI	IIb		B
One-Vessel Proximal Left Anterior Descending CAD			
CABG	IIa	With LIMA	B
PCI	IIb		B
One-Vessel CAD Without Proximal Left Anterior Descending CAD			
CABG	III	Harm	B
PCI	III	Harm	B
Left Ventricular Dysfunction			
CABG	IIa	EF of 35% to 50%	B
CABG	IIb	EF <35% without significant left main disease	B
PCI	N/A	Insufficient data	
Survivors of Sudden Cardiac Death with Presumed Ischemia-Mediated Ventricular Tachycardia			
CABG	I		B
PCI	I		C
No Anatomic or Physiologic Criteria for Revascularization			
CABG	III	Harm	B
PCI	III	Harm	B

COR, Class of recommendation; *LOE,* level of evidence; *CABG,* coronary artery bypass grafting; *EF,* ejection fraction; *LAD,* left anterior descending coronary artery; *LIMA,* left internal mammary artery; *N/A,* not applicable; *PCI,* percutaneous coronary intervention; *STS,* Society of Thoracic Surgeons; *SYNTAX,* Synergy between PCI with Taxus and Cardiac Surgery.

TABLE 61G.9

ACCF/AHA Guidelines for Revascularization to Improve Symptoms in Patients with Significant Anatomic (>50% Left Main or >70% Non–Left Main Coronary Artery Disease) or Physiologic (Fractional Flow Reserve <0.80) Coronary Artery Stenoses

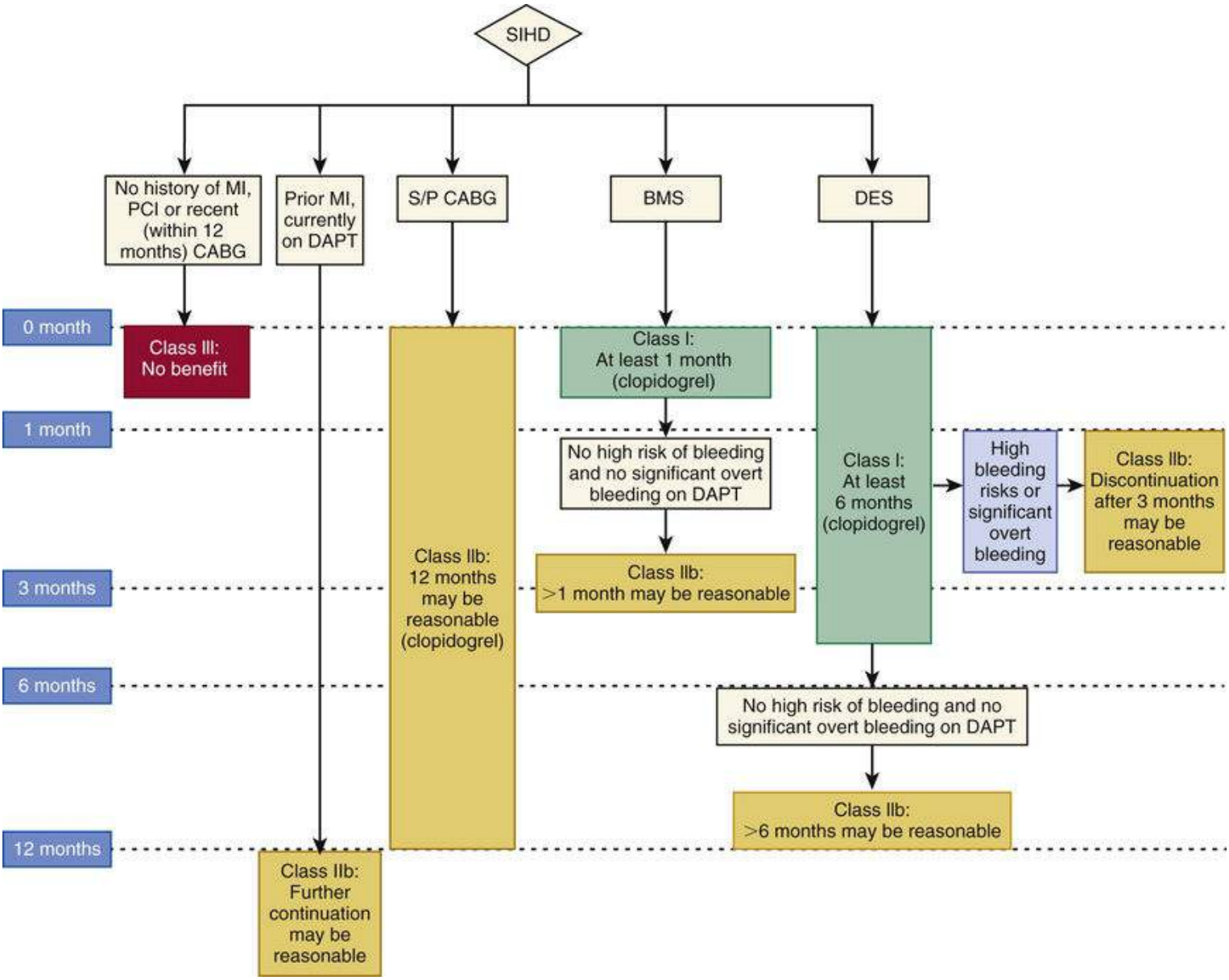
CLINICAL SETTING	RECOMMENDATION		LOE
≥1 significant stenosis amenable to revascularization and unacceptable angina despite GDMT	I	CABG or PCI	A
≥1 significant stenoses and unacceptable angina in whom GDMT cannot be implemented because of medication contraindications, adverse effects, or patient preferences	IIa	CABG or PCI	C
Previous CABG with ≥1 significant stenosis associated with ischemia and unacceptable angina despite GDMT	IIa	PCI	C
	IIb	CABG	C
Complex three-vessel CAD (e.g., SYNTAX score ≥22) with or without involvement of the proximal left anterior descending coronary artery and a good candidate for CABG	IIa	CABG preferred over PCI	B
No anatomic or physiologic criteria for revascularization	III	Neither CABG nor PCI	C

LOE, Level of evidence; *CABG,* coronary artery bypass grafting; *GDMT,* guideline-directed medical therapy; *PCI,* percutaneous coronary intervention; *SYNTAX,* Synergy between PCI with Taxus and Cardiac Surgery.

The ACCF/AHA guidelines discourage the use of PCI or CABG for single- or double-vessel CAD without significant involvement of the proximal LAD artery unless lifestyle limiting angina remains after an adequate trial of GDMT, particularly if noninvasive testing data indicate that they have only a small area of viable myocardium or do not have extensive ischemia or reduced LVEF (**Tables 61G.8 and 61G.9**).

Dual-Antiplatelet Therapy After PCI for SIHD

The 2016 ACCF/AHA guideline update on DAPT for patients with CAD[3] represents a substantial change from previous guidelines, in that different durations of DAPT are now recommended for patients undergoing PCI for SIHD than for those undergoing PCI for ACS. For SIHD treated with drug-eluting stents (DES), the recommended duration of therapy has been shortened to at least 6 months (class I), with even shorter durations (a least 3 months) reasonable for patients at high bleeding risk (class IIb) and longer durations (>6 months) reasonable for selected patients at low bleeding risk who have done well for the initial 6-month period (class IIb) (**eFig. 61G.1**). For patients receiving bare metal stents (BMS), the recommended duration of therapy is at least 1 month (class I), with longer durations reasonable for patients at low bleeding risk (class IIb). For patients with ACS, the recommended duration of DAPT remains at least 12 months (class I) in the absence of high bleeding risk. Also, a class IIb recommendation supports extending the duration of DAPT beyond 12 months from PCI for ACS patients at low risk for bleeding who had no overt bleeding during the initial 12-month course of DAPT.



EFIGURE 61G.1 Treatment algorithm for duration of P2Y12 inhibitor therapy in patients with stable ischemic heart disease (SIHD), without acute coronary syndrome (ACS) within the past several years. Colors correspond to class of recommendation. Patients with a history of ACS >1 year prior who have since remained free of recurrent ACS are considered to have transitioned to SIHD. Clopidogrel is the only currently used $P2Y_{12}$ inhibitor studied in patients with SIHD undergoing percutaneous coronary intervention (PCI). Aspirin therapy is almost always continued indefinitely in patients with coronary artery disease. High bleeding risk denotes those who have or develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy) or are at increased risk of severe bleeding complication (e.g., major intracranial surgery). BMS, Bare metal stent; CABG, coronary artery bypass graft surgery; DES, drug-eluting stent; Hx, history; MI, myocardial infarction; S/P, status post. (From Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. An update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation 2016;134:e123-55.)

Patient Follow-Up

The ACCF/AHA guidelines recommend that patients with SIHD have follow-up evaluations at least annually for assessment of symptoms and clinical function, surveillance of complications of SIHD,

monitoring of cardiac risk factors, and assessment of the adequacy of and adherence to lifestyle interventions and GDMT (**Table 61G.10**). Assessment of LVEF is recommended for patients with SIHD and new or worsening HF or evidence of intervening MI. The guidelines urge restraint in the use of routine testing in the follow-up of patients with SIHD if they have not had a change in clinical status (**Table 61G.11**).

TABLE 61G.10

ACC/AHA Guidelines for Follow-Up Noninvasive Testing in Patients with Known Stable Ischemic Heart Disease: New, Recurrent, or Worsening Symptoms (Not Consistent with Unstable Angina)

TEST	EXERCISE STATUS		ECG INTERPRETABLE		ADDITIONAL CONSIDERATIONS	COR	LOE
	Able	Unable	Yes	No			
Patients Able to Exercise							
Exercise ECG	X		X			I	B
Exercise ECG with MPI or Echo	X			X		I	B
Exercise ECG with MPI or echo	X		Either		Previous requirement for imaging or known to be at high risk for multivessel CAD	IIa	B
Pharmacologic stress MPI, Echo, or CMR	X		X			III	C
Patients Unable to Exercise							
Pharmacologic stress with nuclear MPI or Echo		X	Either			I	B
Pharmacologic stress CMR		X	Either			IIa	B
Exercise ECG		X		X		III	C
Regardless of Ability to Exercise							
Coronary computed tomographic angiography	Either		Either		To assess patency of coronary stent or bypass graft ≥3 mm in diameter	IIb	C
	Either		Either		In absence of known moderate or severe calcification and to assess coronary stent <3 mm in diameter	IIb	C
	Either		Either		Known moderate or severe calcification or assessment of stent <3 mm in diameter	III	C

COR, Class of recommendation; *LOE,* level of evidence; *CAD,* coronary artery disease; *CMR,* cardiac magnetic resonance imaging; *ECG,* electrocardiography; *Echo,* echocardiography; *MPI,* myocardial perfusion imaging.

TABLE 61G.11

ACC/AHA Guidelines for Follow-Up Noninvasive Testing in Patients with Known Stable Ischemic Heart Disease: Asymptomatic or Stable Symptoms

TEST	EXERCISE STATUS		ECG INTERPRETABLE		PRETEST PROBABILITY OF ISCHEMIA	ADDITIONAL CONSIDERATIONS	COR	LOE
	Able	Unable	Yes	No				
Exercise or pharmacologic stress with MPI, Echo, or CMR at ≥2-year intervals		X		X	Previous evidence of silent ischemia or at high risk for recurrent event	Unable to exercise, uninterpretable ECG, or incomplete revascularization	IIa	C
Exercise ECG at ≥1-year intervals	X		X		Previous silent ischemia or at high risk for recurrent event		IIb	C
Exercise ECG	X		X		No previous silent ischemia and not at high risk for recurrent events		IIb	C
Exercise or pharmacologic stress imaging or CCTA	Either		Either			<5-year intervals after CABG or <2-year intervals after PCI	III	C

ECG, Electrocardiography; *CABG,* coronary artery bypass grafting; *CCTA,* coronary computed tomographic angiography; *CMR,* cardiac magnetic resonance imaging; *Echo,* echocardiography; *MPI,* myocardial perfusion imaging; *PCI,* percutaneous coronary intervention.

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Percutaneous Coronary Intervention

Laura Mauri, Deepak L. Bhatt

The use of percutaneous coronary intervention (PCI) to treat ischemic coronary artery disease (CAD) has expanded dramatically over the past three decades. In the absence of left main or complex multivessel CAD, PCI is the preferred method of revascularization in the United States for most patients with ischemic CAD. The estimated 600,000 PCI procedures performed annually in the United States exceed the number of coronary artery bypass graft (CABG) procedures.[1] Over the past several years, however, the growth of PCI has slowed because of the effectiveness of risk factor modification, prevention of restenosis with drug-eluting stents, and a better understanding of the patients who will benefit from revascularization.[2] The number of PCIs is expected to grow modestly (1% to 5%) over the next decade as a result of the aging U.S. population and an increased frequency of obesity and diabetes. Other key enablers of the expanded use of PCI in patients with complex CAD include improvements in equipment design (e.g., catheters with lower profile and enhanced deliverability), development of adjunctive pharmacologic strategies (e.g., adenosine diphosphate [ADP] receptor antagonists and direct thrombin inhibitors) to improve safety, and better hemodynamic support devices in “ultrahigh”-risk patients. Additionally, some types of CAD previously difficult to treat with PCI (e.g., left main disease, chronic total occlusions) have benefited from advances in technology and clinical studies that demonstrate good safety and efficacy in select patients.

This chapter reviews the indications and clinical considerations for the selection of patients for PCI; discusses the current array of coronary devices, antithrombotic therapy, vascular access approaches, and vascular closure devices used for PCI; details the short- and long-term outcomes of PCI; and summarizes the requirements for operator and institutional proficiency.

Coronary balloon angioplasty, or percutaneous transluminal coronary angioplasty (PTCA), was first performed by Andreas Gruentzig in 1977 with a fixed-wire balloon catheter. The procedure was initially limited to the fewer than 10% of patients with symptomatic CAD who had a single, focal, noncalcified lesion in a proximal coronary vessel. As equipment design and operator experience evolved over the next decade, the use of PCI expanded to encompass an increasing spectrum of coronary anatomy, including multivessel CAD, total occlusions, diseased saphenous vein grafts, and acute ST-segment elevation myocardial infarction (STEMI) (**see Chapter 59**). Two limitations prevented the widespread use of balloon angioplasty for CAD: abrupt closure of the treated vessel occurred in 5% to 8% of cases and required emergency CABG in 3% to 5%, and restenosis resulted in recurrence of symptoms in 30% of patients within the following year.

New coronary devices were developed in the late 1980s to overcome the limitations associated with balloon angioplasty. Coronary stents act as a scaffold on the inner arterial wall to prevent early and late vascular remodeling. Rotational atherectomy ablates calcific atherosclerotic plaque and was developed as stand-alone therapy for nondilatable coronary stenoses or for use in combination with coronary stents following the ablation of calcific plaque. By the early 2000s, several devices had been developed to protect the distal circulation from atherothrombotic embolization (i.e., embolic protection devices). Aspiration and thrombectomy catheters were developed to remove medium and large thrombi from within the coronary artery, thereby preventing distal embolization. The term *percutaneous coronary intervention* now encompasses the broad array of balloons, stents, and adjunctive devices required to perform safe and effective percutaneous revascularization in complex coronary artery lesions.

Indications

Clinical Presentations

The major value of percutaneous or surgical coronary revascularization is relief of the symptoms and signs of ischemic CAD (**see Chapters 59 and 61** and PCI Guidelines at the end of this chapter). PCI reduces the risk for mortality and subsequent myocardial infarction (MI) compared with medical therapy in patients with acute coronary syndromes (ACS). Optimal medical therapy (OMT) appears to be as effective as PCI in reducing death and MI in patients with stable angina, although relief of symptoms and improvement of ischemia are better with PCI. Greater than 5% improvement in the ischemic burden is achieved more often with PCI, and the magnitude of the residual ischemia correlates with less frequent death and MI. Further studies comparing the use of coronary arteriography and PCI in patients with moderate degrees of myocardial ischemia are ongoing (e.g., ISCHEMIA, International Study of Comparative Health Effectiveness with Medical and Invasive Approaches),[3] and recent randomized trials requiring physiologic evidence of ischemia, as measured by fractional flow reserve (FFR), have identified a benefit of PCI over medical therapy in preventing urgent revascularization.[4] Irrespective of the indication for revascularization, PCI should be coupled with OMT after the procedure, such as control of hypertension and diabetes, exercise, and smoking cessation (**see Chapter 45**). Lipid management, particularly statin use, is also an important component of OMT.

Compared with PCI alone, CABG is associated with a late mortality benefit in certain high-risk medical and anatomic subsets, such as patients with left main disease, three-vessel CAD, and extensive markers of higher anatomic risk for PCI, such as determined by a SYNTAX (Synergy Between PCI with TAXUS and Cardiac Surgery) score,[5] or patients with diabetes and significant multivessel disease.[6] These benefits are manifested beyond 1 year after treatment and for up to 5 years of follow-up, but the early periprocedural risks, particularly for stroke, are higher with CABG, and patients have a longer in-hospital recovery period. The risks and benefits associated with coronary revascularization therefore need careful review with the patient and family, and the relative options of PCI, CABG, or OMT should be discussed before performing these procedures. Patients with left main or multivessel disease benefit from joint consultation with a cardiac surgeon, an interventional cardiologist, and the referring cardiologist, and consideration of patient preferences in weighing diverse factors is valuable. A task force of the American College of Cardiology (ACC) and American Heart Association (AHA) has published guidelines for the performance of PCI and CABG procedures,[7-9] and a multispecialty writing committee has developed appropriate use criteria for revascularization in several clinical and lesion-specific subsets (see later, PCI Guidelines).[10,11]

Asymptomatic or Minimally Symptomatic Patients.
Asymptomatic patients or those who have only mild symptoms are generally best treated with medical therapy unless one or more high-grade lesions subtend a moderate to large area of viable myocardium, the patient prefers to maintain a very active lifestyle or has a high-risk occupation, and the procedure can be performed with a high chance of success and low likelihood of complications.[11] Patients who are minimally symptomatic or asymptomatic should not undergo coronary revascularization if only a small area of myocardium is at risk, if no objective evidence of ischemia can be detected, or if the likelihood of success is low or the chance of complications is high.[10]

Patients with Moderate to Severe Angina (see Chapter 61).
Patients with Canadian Cardiovascular Society (CCS) class III angina, particularly those who are refractory to medical therapy, can benefit from coronary revascularization, provided that the lesion subtends a moderate to large area of viable myocardium, as determined by noninvasive testing.[8] Patients with recurrent symptoms while receiving medical therapy are candidates for revascularization even if they have a higher risk for an adverse outcome with revascularization. Patients with class III symptoms should not undergo revascularization without noninvasive evidence of myocardial ischemia or a trial of medical therapy, particularly if only a small region of myocardium is at risk, the likelihood of success is low, or the chance of complications is high.[10]

Patients with Unstable Angina, NSTEMI, and STEMI (see Chapters 59 and 60).
Cardiac catheterization and coronary revascularization in moderate- to high-risk patients with unstable angina (UA) or non–ST-segment elevation MI (NSTEMI) may improve mortality and reduce the rate of reinfarction.[12] In a meta-analysis of seven trials with 8375 patients monitored for up to 2 years, the all-cause mortality rate was 4.9% in the early invasive group versus 6.5% in the conservative group (risk ratio [RR], 0.75; $P = 0.001$). The 2-year incidence of nonfatal MI was 7.6% in the invasive group and 9.1% in the conservative group (RR, 0.83; $P = 0.012$). At a mean of 13 months of follow-up, rehospitalization for UA was reduced as well (RR, 0.69; $P < 0.0001$). Current guidelines suggest that an early invasive strategy should be pursued in patients with recurrent ischemia despite therapy, elevated troponin levels, new ST-segment depression, new or worsening symptoms of heart failure (HF), depressed left ventricular (LV) function, hemodynamic instability, sustained ventricular tachycardia (VT), or a recent PCI or CABG procedure.[12]

Specific clinical recommendations pertain to patients with STEMI, including primary PCI, rescue PCI, facilitated PCI, and PCI following successful thrombolysis[13] (see Guidelines). Timely PCI in patients with STEMI improves survival over that achieved with medical therapy, provided that it is performed by a physician who routinely performs PCI, and that the hospital has sufficient PCI volume to support its proficiency. Patients with cardiogenic shock or severe HF also benefit from primary PCI, regardless of their age at initial evaluation.

Left Main and Three-Vessel Coronary Artery Disease

The SYNTAX trial randomly assigned 1800 patients with multivessel disease ($n = 1709$) or left main disease to PCI with a drug-eluting stent (DES) versus CABG.[2] Complete revascularization was the goal for both study groups, and the average number of treated vessels and stents in patients undergoing PCI for left main or multivessel disease was 3.6 lesions and 4.6 stents. One-year outcomes did not differ between the PCI and CABG groups in all-cause mortality or MI. However, rates of major adverse cardiovascular or cerebrovascular events (MACCE) were significantly higher with PCI, mainly attributable to the significantly higher rates of target lesion revascularization in the PCI group. Five-year outcomes were similar to these findings, with no significant difference in all-cause mortality, but a persistently elevated rate of target lesion revascularization was associated with PCI, as was MI.[5] These findings were based on the SYNTAX score, an angiographic grading system to quantify the complexity of PCI (**see Chapter 20**). With low scores (≤22), there was no significant difference in the primary outcome between PCI and CABG patients, but with intermediate or with high scores (>33), MACCE rates were lower with CABG.

Patients with Diabetes Mellitus

The largest trial to date devoted to studying outcomes after revascularization in patients with diabetes

mellitus (DM) and multivessel disease is FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease), a randomized controlled trial (RCT) that compared the outcomes of PCI and CABG in patients with DM and multivessel disease.[6] In this trial, diabetic patients requiring revascularization with angiographically proven multivessel disease and lesions amenable to either PCI or CABG were randomly assigned to complete coronary revascularization with one of these techniques. The primary outcome (all-cause mortality, nonfatal MI, or nonfatal stroke) at 5 years was worse in patients treated with PCI than in those who underwent CABG (26.6% versus 18.7%; $P = 0.005$). Considering individual components of the primary outcome, there was a significantly increased long-term risk for all-cause mortality and nonfatal MI with PCI as opposed to CABG. CABG, however, was associated with an increased risk for nonfatal stroke, and the severity of strokes in the CABG group was twice as likely to disable a patient severely as were strokes occurring in the PCI group.

The results of the FREEDOM trial have largely validated smaller studies, subgroup analyses, and meta-analyses attempting to compare methods of revascularization in diabetic patients with multivessel disease. The CARDia (Coronary Artery Revascularization in Diabetes) randomized trial compared PCI with CABG; although smaller in size, it was dedicated to patients with DM, and a significant fraction had multivessel disease.[14] The trial lacked sufficient power to compare mortality. As in the FREEDOM trial, however, CARDia revealed an increased risk for stroke in the CABG group. Similarly, even though most patients were treated with DESs in this trial, the need for repeated revascularization procedures was significantly increased with PCI.

Patients Without Options for Revascularization

Patients with substantial angina but who are poor candidates for conventional revascularization have limited therapeutic options. These patients generally either have occlusion of a single proximal vessel that subtends a large amount of myocardium or have undergone one or more previous CABG operations with stenoses or occlusions of the saphenous vein grafts (SVGs), which are poorly suited for conventional repeated revascularization. “Limited-option” patients account for approximately 4% to 12% of those undergoing coronary angiography; a larger group (20% to 30%) of patients have incomplete revascularization because the coronary anatomy is unsuitable for surgical or percutaneous techniques. Better techniques and equipment for crossing chronic total occlusions have helped some of these patients (see later). Antianginal medications such as ranolazine may also be particularly useful in this subset (**see Chapter 61**).

Patient-Specific Considerations

Assessment of the potential risks and benefits of PCI must address five fundamental patient-specific risk factors: extent of jeopardized myocardium, baseline lesion morphology, underlying cardiac function (e.g., LV function, rhythm stability, coexisting valvular heart disease), presence of renal dysfunction, and preexisting medical comorbid conditions that may place the patient at higher risk for PCI. Each of these factors contributes independently to the risks and benefits attributable to PCI. Proper planning for a PCI procedure requires careful attention to each of these factors.

Extent of Jeopardized Myocardium

The proportion of viable myocardium subtended by the treated coronary artery is the principal

consideration in assessing the acute risk associated with the PCI procedure. PCI interrupts coronary blood flow for a period of seconds to minutes, and the ability of patients to hemodynamically tolerate a sustained coronary occlusion depends on both the extent of "downstream" viable myocardium and the presence and grade of collaterals to the ischemic region. Although the risk for abrupt closure has been reduced substantially with the availability of coronary stents, when other procedural complications develop—such as a large side branch occlusion, distal embolization, perforation, or no-reflow—rapid clinical deterioration may occur that is proportionate to the extent of jeopardized myocardium. In the unlikely event that out-of-hospital stent thrombosis develops, the clinical sequelae of the episode are related to the extent of myocardium subtended by the occluded stent. Predictors of cardiovascular collapse with a failed PCI include the magnitude of myocardium at risk, the severity of the baseline stenosis, multivessel CAD, and the presence of diffuse disease.

Complete Versus Ischemia-Targeted Intervention for Multivessel Disease

The treatment approaches for PCI and CABG compared in randomized trials have essentially all focused on the strategy of complete revascularization. Data supporting complete revascularization of all angiographic lesions during treatment of multivessel disease with PCI or CABG have been observational (nonrandomized) and thus limited by selection bias in that patients in whom full revascularization is feasible are also those who are at lower risk for procedural and future adverse events. The concept of targeted treatment of vessels with only physiologically significant—not just angiographically significant—stenosis may be one that allows improved outcomes in patients with multivessel disease being treated with either PCI or CABG.

The FFR technique involves placement of a pressure wire across a potentially significant lesion, and under conditions of maximal coronary blood flow, the ratio of pressure distal to versus proximal to a lesion or series of sequential lesions is measured in a given artery (**Fig. 62.1**) (**see Chapters 57 and 61**). In contrast to traditional angiography, which can provide only an anatomic evaluation, FFR provides a functional assessment of the presence of a reduction in flow that correlates well with ischemia as detected by nuclear scintigraphy. The FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial compared angiography with FFR guidance for selection of lesions during DES PCI in more than 1000 patients.[15] Only lesions with an FFR of 0.8 or less were considered to warrant PCI in the FFR arm. FFR guidance resulted in fewer overall stented lesions, and a 2-year analysis revealed significantly reduced mortality or MI with the use of FFR versus pure angiographic guidance, thus corroborating not only the simple procedural benefit of FFR but also the morbidity and mortality advantages of stenting across physiologically relevant lesions.[16]

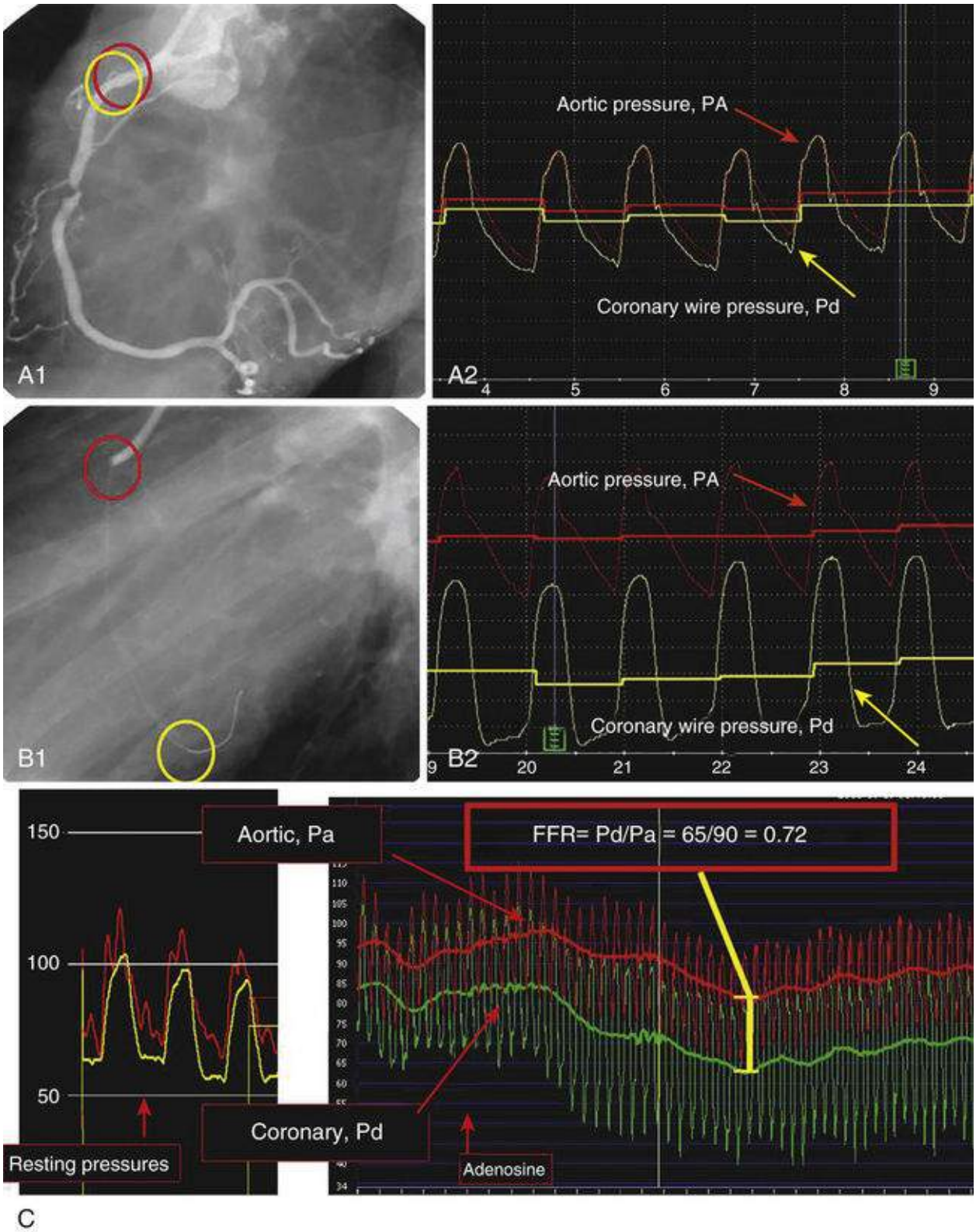


FIGURE 62.1 Method of fractional flow reserve (FFR) measurement. The first step is always to advance the pressure wire up to the tip of the catheter **(A1)** to be absolutely sure that the pressures are superimposed **(A2).** Then, the wire is advanced across the stenosis **(B1)** and obtains a corresponding FFR **(B2). C**, Mild resting gradient **(left panel)** becomes larger with hyperemia **(right panel).** FFR is calculated as Pd/Pa at the nadir of distal pressure presumed to be the point of maximal hyperemia. In this example, FFR = 0.72. (From Kern, MJ. Fractional flow reserve. In Bhatt DL, editor. Cardiovascular Intervention: A Companion to Braunwald's Heart Disease. Philadelphia: Elsevier; 2016.)

In patients with STEMI, revascularization of only the culprit infarct–related artery has generally been recommended,[10] unless there is ongoing cardiogenic shock because of jeopardized myocardium in other regions. However, recent guideline changes now suggest that PCI of a noninfarct artery may be considered in select patients with STEMI and multivessel disease who are hemodynamically stable.[17] Recent trials of

modest size have suggested that there may be reduction in future need for revascularization, and potentially even "hard" outcomes, with a strategy of complete revascularization[18] (**Fig. 62.2**). A larger trial is underway to determine whether nonculprit severe lesions should be treated even in the absence of shock.

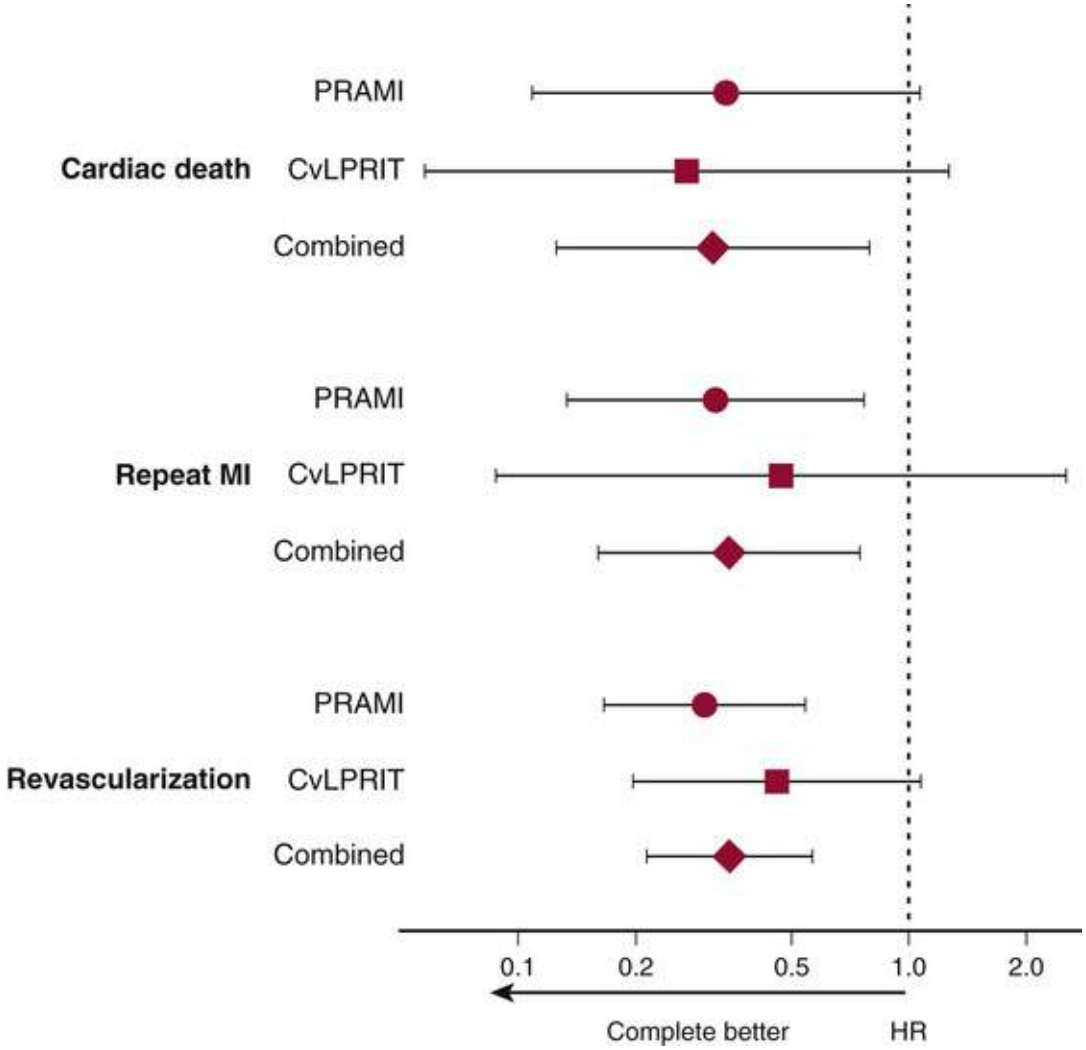


FIGURE 62.2 Reduction in the need for future revascularization and possibly "hard" events with a strategy of complete revascularization versus culprit-only revascularization in primary percutaneous coronary intervention for ST-elevation myocardial infarction. *CvLPRIT,* Complete versus Lesion-only Primary PCI Trial; *HR,* Hazard ratio; *MI,* myocardial infarction; *PRAMI,* Preventive Angioplasty in Acute Myocardial Infarction. (From Bhatt DL. Do we really know the CvLPRIT in myocardial infarction? Or just stent all lesions? J Am Coll Cardiol 2015;65:973-5.)

Baseline Lesion Morphology.

Several angiographic findings increase the technical complexity of PCI and elevate the risk for acute and long-term complications. The initial ACC/AHA lesion classification system has been refined with use of the Society for Cardiovascular Angiography and Interventions (SCAI) risk system, which further characterizes risk by the presence or absence of total occlusion. Although coronary stents have reduced the need for emergency CABG from 3% to 8% with balloon angioplasty to less than 1% with the availability of coronary stents, they have not eliminated the risk for periprocedural MI, stent thrombosis, or distal embolization and "no reflow." Vessel patency and lesion complexity remain important

predictors of outcome in patients undergoing coronary stent placement. Reviews of registry data have confirmed the impact of high-risk lesion features on procedural success rates and the risk for short- and long-term complications. Most recently, the SYNTAX angiographic scoring system, when combined with clinical factors, has become a method of deciding between complex PCI and CABG.[19] An online calculator is available (www.syntaxscore.com).

Chronic Total Occlusions.

Chronic coronary occlusions occur in many patients with severe (>70% stenosis) CAD and are the most important factor leading to referral for CABG procedures rather than PCI. The inability of guidewires to recanalize total coronary occlusions is related to duration of the occlusion, presence of bridging collaterals, occlusion length greater than 15 mm, and absence of a "beak" to assist in guidewire advancement. Although approaches such as retrograde crossing via collaterals and newer guidance technologies have been used to recanalize refractory occlusions, better guidewires and wire techniques have accounted for much of the improvement in successfully crossing occlusions over recent years.[20] Once the chronic total occlusion (CTO) has been crossed, DESs may be used to reduce late clinical recurrence.

Saphenous Vein Grafts.

SVG interventions account for approximately 8% of PCI procedures and pose an increased risk for postprocedural MI as a result of the atheroembolization that occurs during PCI. When no-reflow occurs, administration of arterial vasodilators (e.g., nitroprusside, verapamil, adenosine) into the SVG may improve flow into the distal native circulation, but the risk for death or MI is still substantially increased. More extensive SVG degeneration and bulkier lesions are associated with higher complication rates than are SVGs that have less extensive disease. In the setting of "high-risk" SVG anatomy, alternative approaches using the native coronary artery should be pursued whenever possible. Lower rates of restenosis in SVG lesions occur after coronary stent placement than after balloon angioplasty. Although DESs provide lower restenosis rates in SVGs that are 4.0 mm or less, they are currently not available for SVGs larger than 4.5 mm in diameter, and bare-metal stents (BMSs) are reasonable in this setting. Embolic protection devices are strongly recommended in patients treated for SVG stenoses to lessen the risk for distal embolization of atherothrombotic debris.

Bifurcation Lesions.

Optimal management of lesions involving both branches of a coronary bifurcation remains controversial. "Snowplowing" of plaque into the adjacent parent vessel or side branch is a major limitation of conventional balloon angioplasty. Atheroablative procedures such as rotational atherectomy have not reduced this risk. Risk stratification for bifurcation PCI includes assessment of the extent of atherosclerotic disease in both vessels, estimation of relative vessel size and distribution in the parent vessel and side branch, and determination of the orientation of the vessels to one another. Side branch compromise may also occur in up to 30% of bifurcation lesions without apparent branch vessel disease.

Stent placement in one vessel rather than in both parent vessel and side branch is generally preferred. In a meta-analysis of six randomized trials that included 1642 patients with coronary bifurcation lesions who were randomly selected to undergo PCI involving either double or single stenting, the risk for MI increased with double stenting (RR, 1.78; $P = 0.001$).[21]

When extensive disease occurs in both vessels, various strategies have been used, including simultaneous "kissing" stents (**Fig. 62.3**) and "crush," culotte, T stenting, and TAP ("T and small protrusion") techniques. Irrespective of the bifurcation stenting strategy used, a final kissing balloon inflation in the parent vessel and side branch should generally be performed. DESs appear to have lower

restenosis rates than BMSs do, but when recurrence develops in patients treated with a DES, it generally occurs at the origin of the side branch. New dedicated bifurcation stents and side branch access main vessel stents are in development. Determination of the FFR of an angiographically narrowed side branch can be useful if it demonstrates no significant impairment of flow and therefore no need to place a stent.

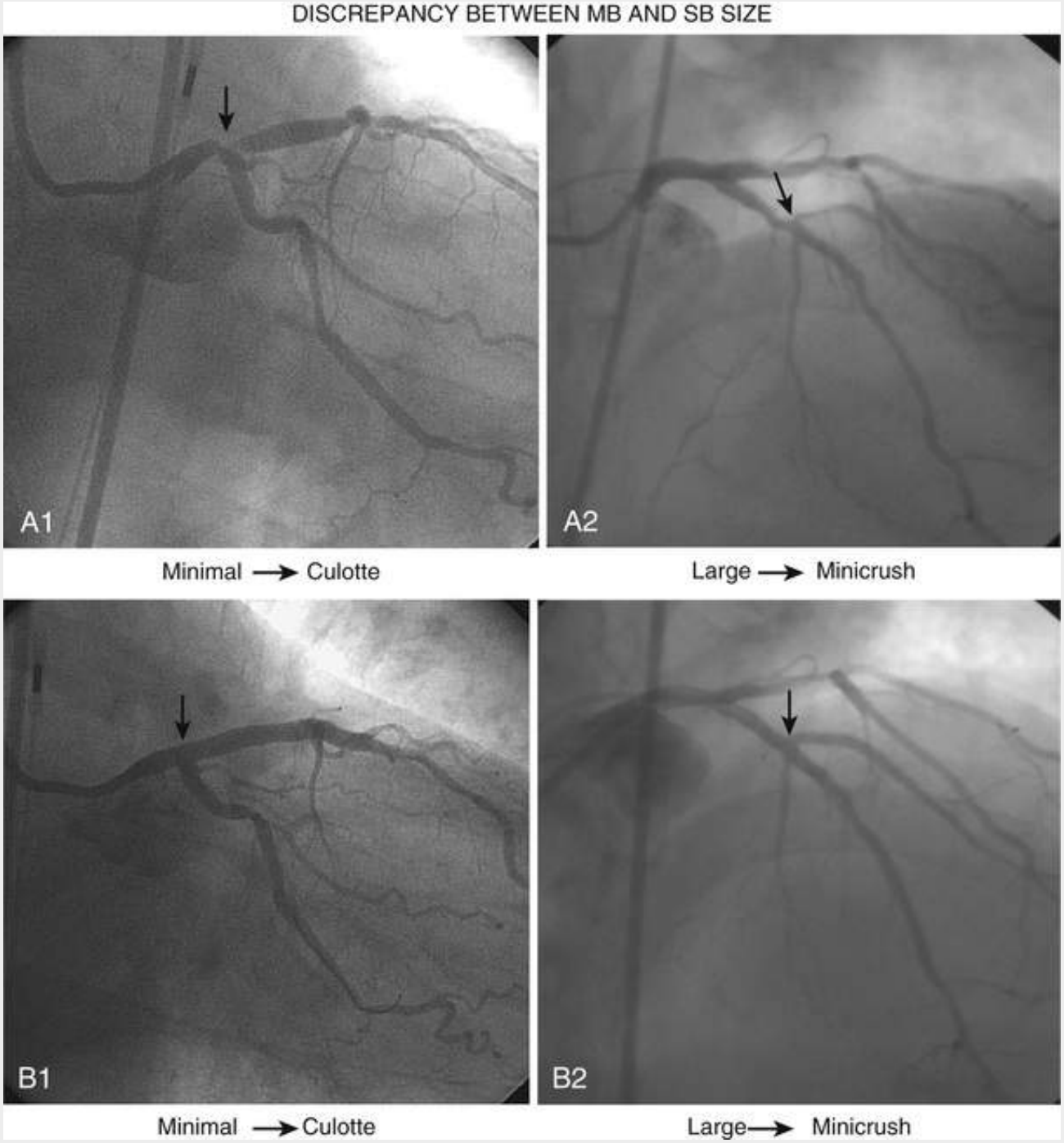


FIGURE 62.3 Angiography demonstrating a left main coronary artery bifurcation with minimal discrepancy between distal left main and circumflex size **(A1)** that would be suitable for culotte stenting **(B1)** compared with an left anterior descending coronary artery (LAD)–diagonal bifurcation with a large discrepancy between LAD and diagonal **(A2)** that would not be suitable for culotte stenting but should rather be treated with a minicrush technique **(B2).** *MB,* main branch; *SB,* side branch. (From Colombo A, Latib A. Bifurcations. In Bhatt DL, editor. Cardiovascular Intervention: A Companion to Braunwald's Heart Disease. Philadelphia: Elsevier; 2016.)

Lesion Calcification.

The presence of extensive coronary calcification poses unique challenges for PCI because calcium in the

vessel wall leads to irregular and inflexible lumens, thus making delivery of guidewires, balloons, and stents much more challenging. Extensive coronary calcification also renders the vessel wall rigid, which necessitates higher balloon inflation pressure to achieve complete stent expansion and, on occasion, leads to “undilatable” lesions that resist any balloon expansion pressure that can be achieved. Rotational atherectomy effectively ablates the vessel wall calcification and facilitates stent delivery and complete stent expansion (**Fig. 62.4**).

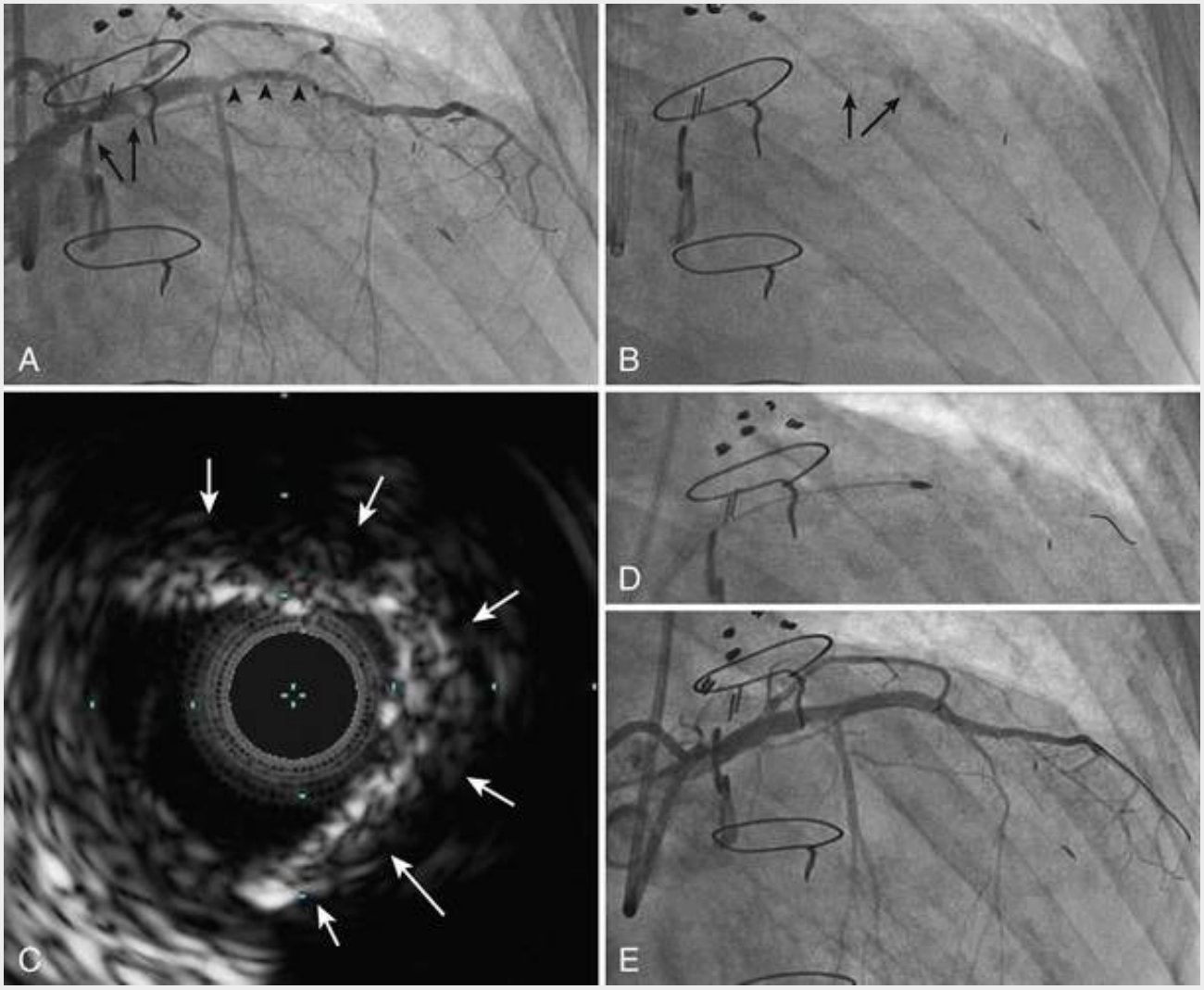


FIGURE 62.4 Rotational atherectomy of the left anterior descending coronary artery (LAD)/diagonal. **A,** Initial angiogram demonstrates severe calcified stenosis in the proximal (*arrow*) and mid-LAD (*arrowheads*) extending to the diagonal. **B,** Fluoroscopy alone shows the severe calcification (*arrows*). **C,** Intravascular ultrasound demonstrates 270-degree calcification (*arrows*) with echo dropout behind the calcium. **D,** Rotaburr in the mid-LAD. **E,** Final angiogram after stent placement. (From Krishnaswamy A, Whitlow PL. Calcified lesions. In Bhatt DL, editor. Cardiovascular Intervention: A Companion to Braunwald's Heart Disease. Philadelphia: Elsevier; 2016.)

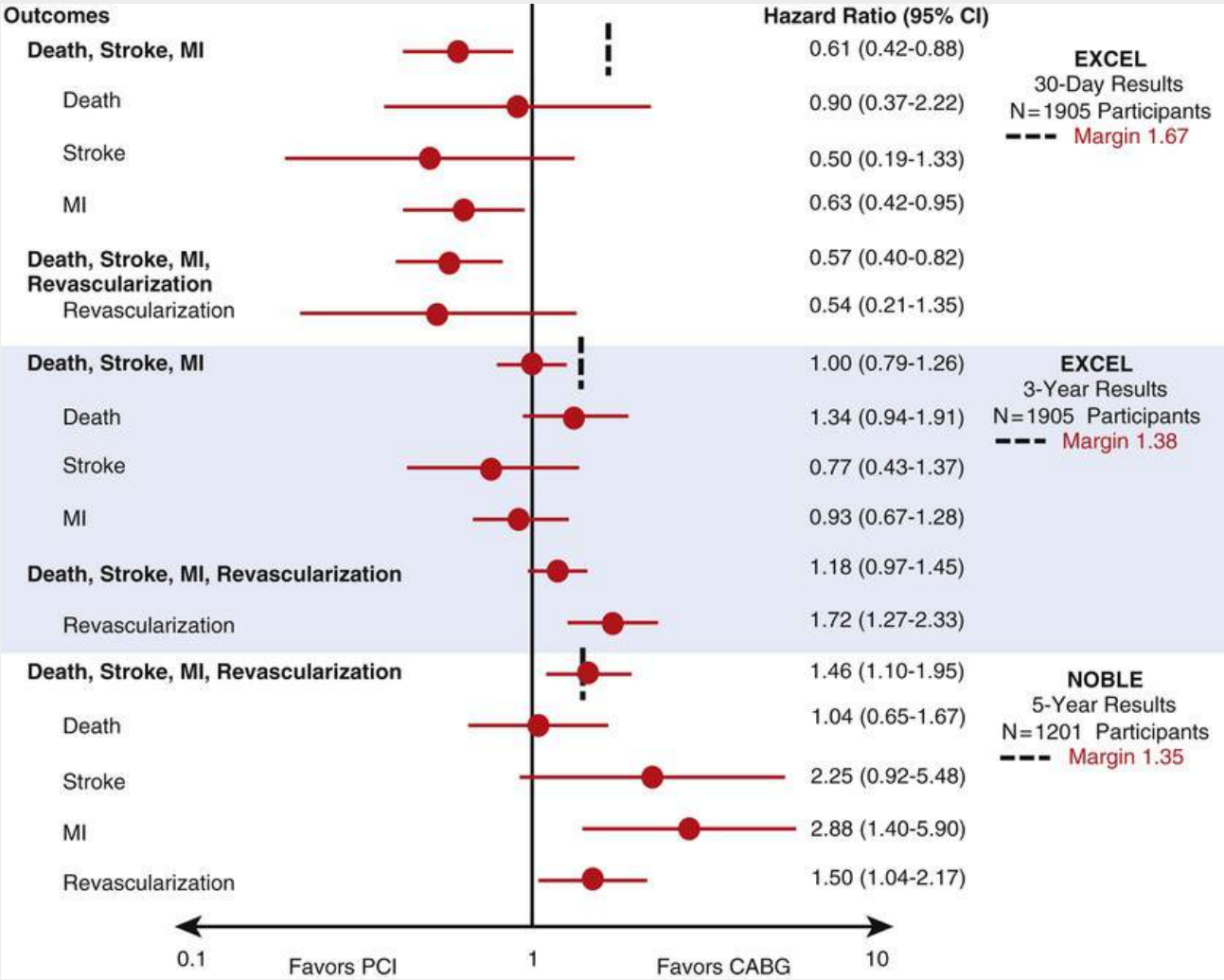
Thrombus.

Conventional angiography has poor sensitivity for the detection of coronary thrombus, but the presence of a large, angiographically apparent coronary thrombus heightens the risk for procedural complications. Large coronary thrombi may fragment and embolize during PCI or may extrude through gaps between stent struts placed in the vessel, thereby risking lumen compromise or thrombus propagation and acute thrombosis of the treated vessel. In addition, large coronary thrombi can embolize to other coronary branches or vessels or dislodge and compromise the cerebral or other vascular beds. In the setting of

contemporary primary PCI for STEMI, routine manual catheter aspiration of thrombus appears to have no significant effect on mortality and may increase the risk of stroke,[22] but it may be helpful in select patients with visible thrombus.[3]

Left Main Coronary Artery Disease.

The presence of left main CAD has been an accepted indication for CABG because of the potential for hemodynamic collapse in the setting of acute complications, stent thrombosis, or restenosis involving the body of the left main coronary artery or its extension into the left anterior descending or left circumflex coronary artery. Registry and randomized studies have suggested that rates of death or MI are similar in patients undergoing CABG or PCI,[3,23,24] although the need for repeated revascularization is higher in patients treated with PCI with additional vessel disease.[3,25] The use of PCI for left main CAD has been elevated to a class IIb indication (see PCI Guidelines at the end of this chapter). The Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) and Nordic-Baltic-British Left Main Revascularization (NOBLE) trials each evaluated the noninferiority of PCI versus CABG for left main coronary artery stenosis (**eFig. 62.1**).[25a,25b] EXCEL, which had a composite primary endpoint of death, stroke, or myocardial infarction, concluded noninferiority of PCI at a median follow-up of 3 years.[25a] NOBLE, which had a composite primary endpoint of death, stroke, myocardial infarction, or revascularization, assessed at 5 years, did not conclude that PCI was noninferior and did conclude that CABG was superior.[25b] The additional endpoint component included in the NOBLE trial resulted in the differing conclusions, indicating that close inspection of the details and timing of the assessment are critical for study interpretation, as well as consideration of the balance of risk and benefit in patients with left main stenosis.[25c]



EFIGURE 62.1 Two noninferiority trials comparing percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG). The EXCEL trial (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) primary composite endpoint was death, stroke, or myocardial infarction at 3 years. The NOBLE trial (Nordic–Baltic–British Left Main Revascularization) composite primary endpoint was death from any cause, nonprocedural myocardial infarction, any coronary revascularization, or stroke. Although the noninferiority margins were roughly similar in the two trials, the EXCEL results led to the conclusion that PCI was superior to CABG at 30 days and was noninferior at 3 years, and the NOBLE findings, based on longer follow-up and a more inclusive primary endpoint, led to the conclusion that CABG was superior at 5 years. In the EXCEL trial, the early benefit of PCI was due to avoidance of periprocedural infarction. The late benefit of CABG, on the basis of extended follow-up, was largely due to lower rates of spontaneous myocardial infarction (not shown: 4.3% with PCI vs. 2.7% with CABG; hazard ratio [HR] with PCI, 1.60; 95% confidence interval [CI], 0.95 to 2.70; P = 0.07 for the superiority of CABG) and revascularization (12.9% vs. 7.6%; HR, 1.72; 95% CI, 1.27 to 2.33; P < 0.001 for the superiority of CABG). Similarly, the NOBLE trial showed that PCI, as compared with CABG, was associated with higher rates of nonprocedural myocardial infarction (7% vs. 2%; HR, 2.88; 95% CI, 1.40 to 5.90; P = 0.004 for the superiority of CABG) and revascularization (16% vs. 10%; HR, 1.50; 95% CI, 1.04 to 2.17; P = 0.03 for the superiority of CABG) at 5 years, leading to the conclusion that CABG was superior (rate of major adverse cardiovascular and cerebrovascular events, 29% with PCI vs. 19% with CABG; HR, 1.48; 95% CI, 1.11 to 1.96; P = 0.007 for the superiority of CABG). (Modified from Mauri L, D'Agostino RB. Challenges in the design and interpretation of noninferiority trials. N Engl J Med 2017;377:1357-67.)

Underlying Cardiac Function

Left ventricular function is an important predictor of outcome during PCI. For each 10% decrement in resting LV ejection fraction (EF), the risk for in-hospital mortality following PCI increases approximately twofold. Associated valvular disease or ventricular arrhythmia further increases the risk associated with PCI in the setting of LV dysfunction. Intra-aortic balloon pump (IABP) support may be useful when LV

function is severely compromised (i.e., EF <35%) or when the PCI target lesion supplies a substantial portion of viable myocardium. Routine use of IABPs has limited benefit in patients with STEMI,[26] although they are recommended for patients in cardiogenic shock. Other percutaneous cardiopulmonary support devices that do not effectively reduce LV pressure have been replaced by percutaneous LV assist devices that are positioned in the left atrium (e.g., TandemHeart, CardiacAssist, Pittsburgh, Pa)[27,28] or directly in the left ventricle (Impella, Abiomed, Danvers, Mass)[29-31] (**Fig. 62.5**). These devices may permit very-high-risk PCI with less chance of hemodynamic collapse during the procedure, although current data do not show them to be superior to IABPs.[32] Peripheral extracorporeal membrane oxygenation (ECMO) support through large-bore arterial and venous access may be useful in cases of cardiovascular collapse.

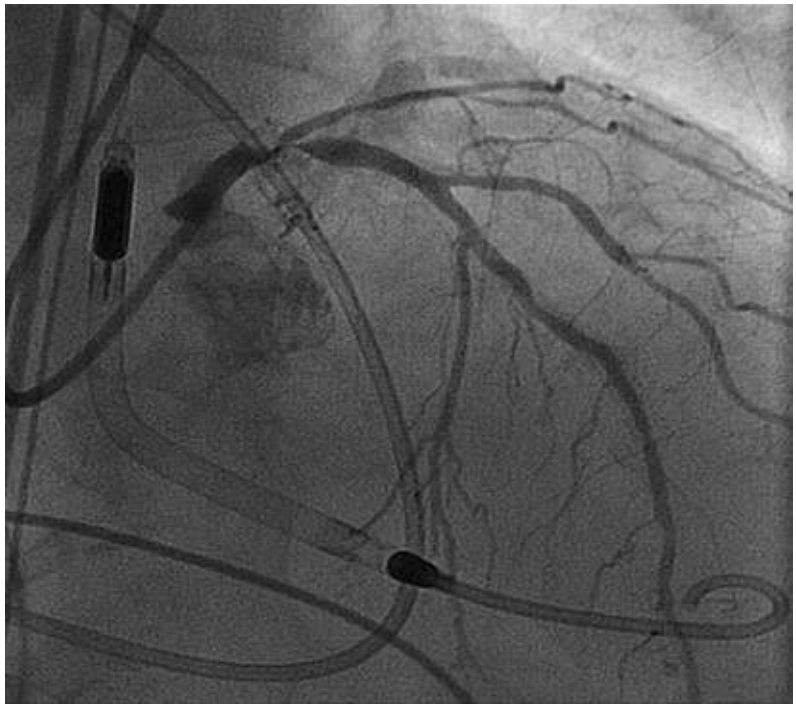


FIGURE 62.5 Position of the Impella device in the left ventricle before left main coronary intervention in a sole remaining artery.

Renal Insufficiency

The morbidity and mortality associated with PCI are directly related to the extent of baseline renal disease (**see also Chapter 98**). Patients with evidence of mild renal dysfunction have a 20% higher risk for death at 1 year following PCI than do those with preserved renal function. Renal dysfunction following the administration of contrast material during angiography may be related to contrast-induced nephropathy (**see Chapter 19**), to cholesterol embolization syndrome (**see Chapter 64**), or to both. The risk for nephropathy is dependent on the dose of the contrast agents used, hydration status at the time of the procedure, preexisting renal function of the patient, age, hemodynamic stability, anemia, and diabetes. The risk for cholesterol embolization syndrome is related to manipulation of the catheter in an ascending or descending atherosclerotic aorta from which cholesterol crystals are released. Although the risk associated with hemodialysis is less than 3% in cases of uncomplicated contrast-induced nephropathy, in-hospital mortality in the setting of hemodialysis exceeds 30%. Mild renal dysfunction is associated with an up to fourfold increased risk for death at 1 year after PCI compared with patients with preserved renal

function, although this association is probably not causal.

Associated Medical Comorbid Conditions

A bleeding diathesis or need for chronic warfarin therapy may preclude patients from tolerating long-term combination aspirin and clopidogrel therapy after placement of a DES, thereby placing them at higher risk for stent thrombosis. The need for discontinuation of dual-antiplatelet therapy (DAPT) before impending non–cardiac-related surgery soon after stent implantation may also predispose to stent thrombosis. In each of these circumstances, BMS placement may be the preferred approach, particularly if the surgery can be deferred for approximately 6 weeks after placement of the stent[33,34] (**Fig. 62.6**).

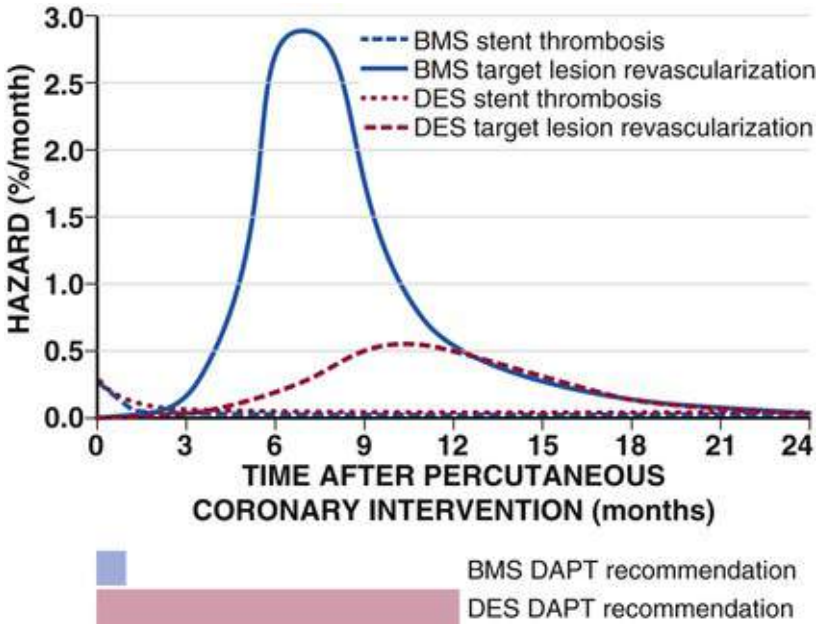


FIGURE 62.6 Hazard of stent thrombosis and target lesion revascularization over time according to the type of stent. BMS, Bare-metal stent; DAPT, dual-antiplatelet therapy; DES, drug-eluting stent. (From Matteau A, Mauri L. Optimal timing of noncardiac surgery after stents. Circulation 2012;126:1322.)

Vascular Access

The most frequently used vascular access sites for PCI include the common femoral artery, the brachial artery, and increasingly, the radial artery (**see Chapters 19 and 20**). The *femoral approach* (either right or left sided) is the most commonly used vascular access site in the United States and provides the advantages of large vessel size (typically 6 to 8 mm in diameter) and the ability to accommodate larger (>6 French [F]) sheath sizes, including IABPs. In addition, because of the typically straight path from the femoral artery to the ascending aorta, the femoral approach provides excellent guide catheter support and manipulability and access to the venous system through the adjacent femoral vein. The presence of severe peripheral arterial disease or peripheral vascular bypass grafts and the requirement for immobilization after the procedure limit use of the femoral approach in some patients.

The *brachial approach* was historically used as the principal alternative to femoral access, but because the brachial artery provides the only circulation to the forearm and hand (i.e., it is a functional end-artery), any compromise of the brachial artery can lead to severe ischemic complications in the hand.

The *radial approach* has gained in popularity as an alternative to femoral access in patients with

significant peripheral vascular disease, particularly in obese patients, in whom direct compression of the radial artery reduces bleeding complications.[35,36] The radial approach provides direct access to the ascending aorta and has the unique advantage of allowing immediate mobilization following PCI. An Allen test may be useful to assess flow to the hand before radial artery cannulation. Tortuosity of the brachiocephalic trunk may limit use of the radial approach in 2% to 3% of patients. The small size of the radial artery limits the size of guiding catheters that can be used during PCI (typically 5F or 6F for women and 7F for men, although larger, sheathless guides are entering practice). Transradial access is associated with a generally lower rate (2%) of vascular complications.[37] A meta-analysis suggested that radial access reduced major bleeding in comparison to femoral access.[38] In the RIVAL (Radial vs Femoral Access for Coronary Intervention) trial, which randomly assigned patients to either femoral or radial access, no significant difference was found in the primary endpoint of major ischemic events or bleeding[39] (**Table 62.1**), but the rate of vascular complications was significantly reduced with the radial approach.

TABLE 62.1

Outcomes in Radial Versus Femoral Access in RIVAL Trial

OUTCOME	FEMORAL (*n* = 3514)	RADIAL (*n* = 3507)	*P* VALUE
Composite of death, myocardial infarction, stroke, or non-CABG–related major bleeding at 30 days*	4.0%	3.7%	0.50
Death at 30 days	1.5%	1.3%	0.47
Myocardial infarction at 30 days	1.9%	1.7%	0.65
Stroke at 30 days	0.4%	0.6%	0.30
Percutaneous coronary intervention success	95.2%	95.4%	0.83
Access site crossover	2.0%	7.6%	<0.0001
Major vascular complications	3.7%	1.4%	<0.0001
Access site major bleeding	0.3%	0.2%	Not provided
Symptomatic radial occlusion	NA	0.2%	NA
Procedure time (min)	35	34	0.62
Fluoroscopy time (min)	8.0	9.3	<0.0001
Contrast volume (mL)	180	181	0.87
Patient prefers radial access for next procedure	50.7%	90.2%	<0.0001

*Primary endpoint.

CABG, Coronary artery bypass graft; *NA,* not applicable.

Modified from Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. Lancet 2011;377:1409.

Complications

Vascular access site complications occur after 3% to 7% of femoral PCIs and lead to significantly increased length of hospital stay, total cost, and morbidity and mortality. Complications range from relatively minor access site hematomas, to life-threatening retroperitoneal bleeding requiring emergency blood transfusion, to damage to the vasculature necessitating prompt surgical intervention. Factors predisposing patients to increased risk for serious vascular complications after PCI include older age, female sex, larger vascular sheath size, low body mass index, renal insufficiency, and degree of anticoagulation during the procedure. The location of the entry point for transfemoral access predicts the risk and type of vascular complication (**see Chapter 19**). If the access site is above the level of the inguinal ligament, the risk for retroperitoneal hemorrhage increases substantially. If the access site is distal to the femoral bifurcation, pseudoaneurysms (0.4%) and arteriovenous fistulas (0.2%) may occur. Major vascular complications of the femoral approach include limb-threatening ischemia (0.1%) and retroperitoneal hemorrhage (0.4%), which are associated with a 2- to 10-fold increased risk for death in

the first 30 days after PCI.

Vascular Closure Devices

Vascular access closure devices were introduced in the mid-1990s as a new way of managing access sites following femoral access procedures. Vascular closure devices reduce the time to ambulation, increase patient comfort after PCI, and facilitate efficient case flow in the catheterization laboratory.

Currently approved vascular closure devices fall into three categories: (1) sealant devices, including collagen-based and thrombin-based systems, which leave no mechanical anchor inside or outside the vessel; (2) mechanical closure devices, including suture-mediated and nitinol clip–based systems, which provide immediate secure closure to the vessel; and (3) hybrid closure devices, such as the dissolvable AngioSeal device (St. Jude Medical, Minneapolis), which use a combination of collagen sealant and internal mechanical closure to induce rapid hemostasis.[40] Although each device has proved to be relatively safe and effective, a lack of comparative data prohibits evaluation of the relative risks and benefits associated with each device. Meta-analyses have concluded that vascular closure devices do not lower the risk for vascular complications compared with manual hemostasis, but infections may occur more often with suture-based closure devices, and occlusions are found more often with hybrid devices. Registry analyses have suggested that closure devices reduce bleeding complications in select patients,[41] but randomized clinical trials are necessary to validate this finding.

Coronary Devices

Over the past three decades, steady improvements in the equipment used for coronary revascularization (e.g., reductions in device profile and improvements in catheter flexibility) have been supplemented by the introduction of periodic "transformational technology," such as coronary stents and, more recently, drug-eluting stents, which have extended the scope and breadth of clinical practice. The type of lesions amenable to PCI has become progressively more complex over this period, and the outcomes associated with the use of these devices have progressively improved. A brief overview of currently available coronary devices follows.

Balloon Angioplasty

Balloon angioplasty expands the coronary lumen by stretching and tearing the atherosclerotic plaque and vessel wall and, to a lesser extent, by redistributing atherosclerotic plaque along its longitudinal axis. Elastic recoil of the stretched vessel wall generally leaves a 30% to 35% residual diameter stenosis, and the vessel expansion can result in propagation of coronary dissections and lead to abrupt vessel closure in 5% to 8% of patients. Although stand-alone balloon angioplasty is rarely used other than for very small (<2.25 mm) vessels, balloon angioplasty remains integral to PCI for predilating lesions before stent placement, deploying coronary stents, and further expanding stents after deployment.

Most enhancements in balloon technology are related to the development of *low-profile* (deflated diameter = 0.7 mm) balloons that can be tracked more readily through tortuous anatomy and *noncompliant* balloons that can be inflated to pressures in excess of 20 atm without overexpansion or rupture. A modification of balloon angioplasty includes a focused-force dilation in which a scoring blade or guidewire external to the balloon concentrates the dilating force and resists balloon slippage during inflation. The Cutting Balloon (Boston Scientific, Natick, Mass) and the AngioScore catheter (AngioScore, Fremont, Calif) are focused-force balloon angioplasty systems that are currently used in a

small minority (<5%) of PCIs. They are sometimes useful in restenotic stent lesions to prevent slippage of the balloon during inflation.

Coronary Atherectomy

Atherectomy refers to removal (rather than simple displacement) of the obstructing atherosclerotic plaque. By removing plaque or improving lesion wall compliance in calcified or fibrotic lesions, atherectomy can provide a larger final minimal lumen diameter than can be achieved by balloon angioplasty alone. Atherectomy was performed in 30% of interventional procedures between 1992 and 1994, but its use fell dramatically with the availability of coronary stents. Fewer than 5% of current procedures involve the use of atherectomy, most often rotational atherectomy in combination with coronary stents.

The Rotablator Rotational Atherectomy System (Boston Scientific) is the most commonly used atherectomy device and removes atheromatous plaque by abrasion of the inelastic calcified plaque with microscopic (20 to 50 µm) diamond chips embedded on the surface of a rapidly rotating (160,000 rpm) olive-shaped atherectomy burr. Such abrasion generates 2- to 5-µm microparticles that pass through the coronary microcirculation for removal by the reticuloendothelial system. The burrs travel over a specialized 0.009-inch guidewire and are available in diameters ranging from 1.25 to 2.50 mm. In the setting of severe calcification, smaller-diameter (1.25 mm) burrs can be used initially, followed by larger burrs in 0.25- to 0.50-mm increments up to 70% of the reference vessel diameter. Aggressive rotational atherectomy techniques do not provide a restenosis advantage over more conservative methods and tend to increase acute procedural complications such as distal embolization or coronary perforation. Rotational atherectomy does not appear to reduce restenosis in noncalcified vessels any more than balloon angioplasty does. Rotational atherectomy is currently reserved for ostial and heavily calcified lesions that cannot be dilated with balloon angioplasty or those that prevent the delivery of coronary stents. Rotational atherectomy is generally limited to abrasion of superficial calcification with a single 1.5- or 1.75-mm burr to improve lesion compliance (plaque modification) before the lesion is treated definitively by balloon dilation and stent placement. Rotational atherectomy is presently used in fewer than 5% of PCI procedures (**Fig. 62.7**). Orbital atherectomy is a variant of rotational atherectomy that has recently been introduced into coronary and peripheral intervention.

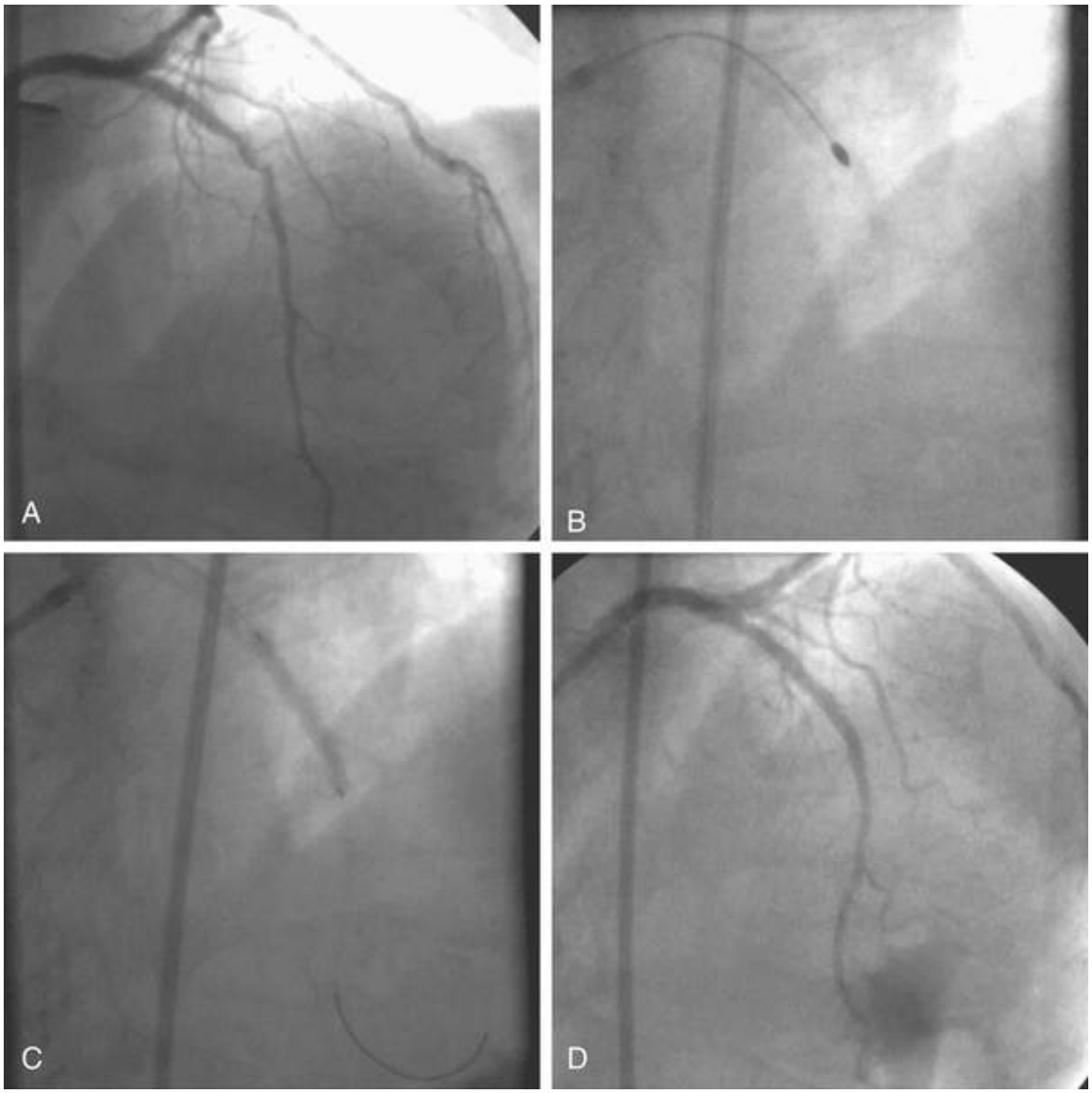


FIGURE 62.7 Rotational atherectomy of an undilatable left anterior descending coronary artery (LAD). **A,** Heavily calcified diffuse lesion in LAD is generally considered undilatable with conventional balloon techniques. **B,** A 1.5-mm rotational atherectomy burr revolving at 160,000 rpm is advanced to ablate the calcified lesion. **C,** A 3-mm × 28-mm stent can then be advanced across the blockage and inflated to 16 atm. Full stent expansion is unlikely to occur without pretreatment with rotational atherectomy. **D,** Final angiographic result shows no residual stenosis and normal flow into the distal vessel.

Thrombectomy and Aspiration Devices

The AngioJet rheolytic thrombectomy catheter (Possis Medical, Minneapolis) was introduced as a dedicated device for thrombus removal through dissolution and aspiration of the thrombus. High-speed saline jets within the tip of the catheter create intense local suction by the Venturi effect; surrounding blood, thrombus, and saline are pulled into the lumen of the catheter opening, and the debris is propelled proximally through the catheter lumen. Rheolytic thrombectomy was superior to a prolonged intraluminal urokinase infusion in patients with a large thrombus, but its routine use in patients with STEMI was not associated with improvement in infarct size on single-photon emission computed tomography (SPECT) imaging and may have caused more complications. Rheolytic thrombectomy may still be useful in clinical practice when a large angiographic thrombus is located in a native vessel or SVG.

Newer, aspiration catheters that use 6F guiding catheters have been developed as alternatives to rheolytic thrombectomy in patients with thrombus-containing lesions. Although simpler to use, these

techniques may be slightly less effective (particularly with partially organized thrombus) than rheolytic thrombectomy. In a multicenter study of 1071 patients with STEMI who were randomly assigned to a thrombus aspiration group or a conventional PCI group, a myocardial blush grade of 0 or 1 occurred in 17.1% of the patients in the thrombus aspiration group and in 26.3% of those in the conventional PCI group ($P < 0.001$). At 30 days the rate of death in patients with a myocardial blush grade of 0 or 1, 2, and 3 was 5.2%, 2.9%, and 1.0%, respectively ($P = 0.003$), and the rate of adverse events was 14.1%, 8.8%, and 4.2%, respectively ($P < 0.001$).[42] Meta-analysis of older data had suggested that simple manual thrombus aspiration before PCI reduced mortality in patients undergoing primary PCI, but larger randomized clinical trials in the present era demonstrated no significant reduction.[22]

Embolic Protection Devices

The advent of embolic protection systems has reduced the risk for postprocedural adverse events following SVG PCI. Although embolization of atherosclerotic debris was not considered a major complication during the early years of native coronary balloon angioplasty, it is now recognized as a potential cause of distal myocardial necrosis after PCI, particularly in friable SVG lesions. Distal embolization causes postprocedural elevation of cardiac enzymes in almost 20% of patients after SVG PCI, and this enzyme elevation is associated with substantial morbidity and mortality. Numerous additional occlusive and filter-based distal protection systems, as well as proximal occlusion devices, have undergone evaluation for use in SVG interventions,[43] but currently the filter devices are most commonly available. Despite their potential benefit in preventing thromboembolization in patients with STEMI, none of the embolic protection devices has reduced MI size with primary intervention.

Distal Embolic Filters.

Distal filters are advanced across the target lesion in their smaller collapsed state, and withdrawal of the retaining sheath allows the filters to open and expand against the vessel wall. The filters then remain in place to catch any liberated embolic material larger than the pore size (usually 120 to 150 μm) of the filter during intervention. At the end of the intervention the filters are collapsed by using a sheath, and the captured embolic material is removed from the body. This type of device has the advantage of maintaining anterograde flow during the procedure and allowing intermittent injection of contrast material to visualize the underlying anatomy, but it has the potential disadvantage of allowing debris with a diameter smaller than the pore size of the filter to pass (**Fig. 62.8**).

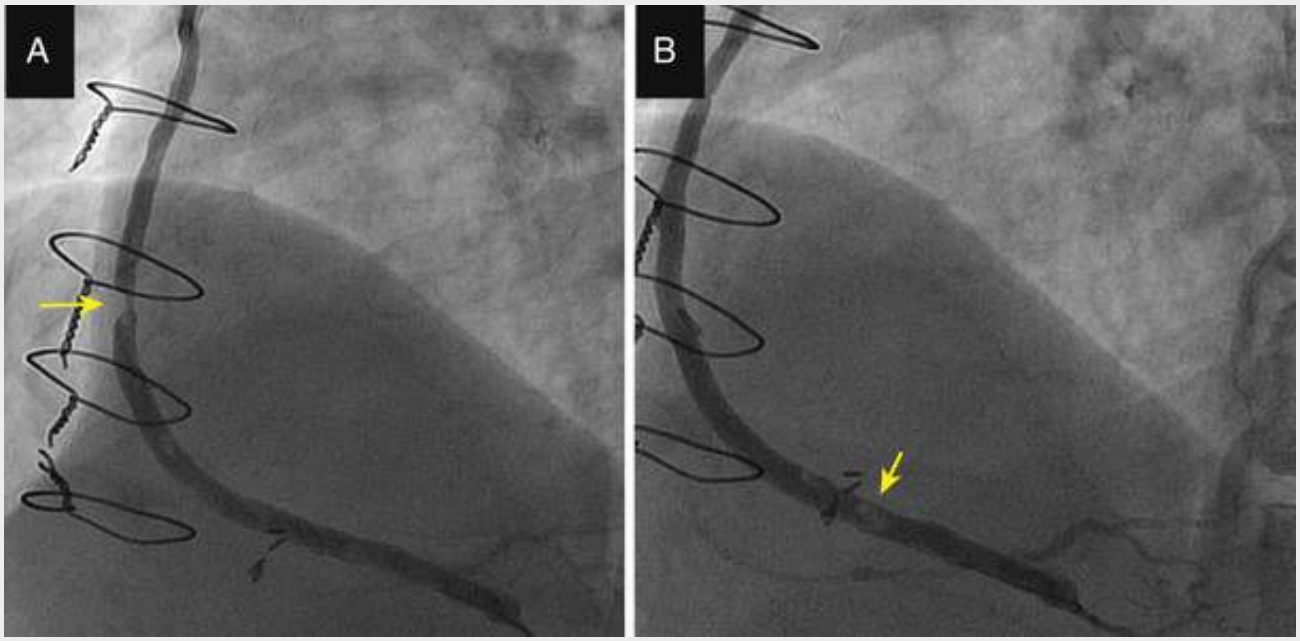


FIGURE 62.8 Examples of debris capture by a filter. **A,** FilterWire placed distally to eccentric saphenous vein graft body lesion. **B,** During PCI, debris embolized distally and was captured within the filter. (From Brilakis ES, Banerjee S. Bypass graft interventions. In Bhatt DL (ed.): Cardiovascular Intervention: A Companion to Braunwald's Heart Disease. Philadelphia, Elsevier, 2016.)

Coronary Stents

Coronary stents have emerged as the predominant form of PCI and are currently used in more than 90% of PCI procedures worldwide. Coronary stents act as scaffolds for arterial dissection flaps, thereby lowering the incidence of vessel closure and need for emergency CABG; they also lessen the frequency of restenosis because of their effect in preventing arterial recoil, which is the primary mechanism of restenosis with balloon angioplasty. Despite the late clinical improvement in comparison to balloon angioplasty, restenosis after coronary stent placement occurs in some patients as a result of excessive intimal hyperplasia within the stent. Second-generation balloon-expandable stents introduced between 1997 and 2003 vary in metallic composition (i.e., cobalt chromium or layered metals versus solid 316 L stainless steel), strut design, stent length, delivery and deployment system, and arterial surface coverage. These modifications enhanced flexibility and ease of delivery of the stent while also improving vessel scaffolding and side branch access.

The early use of coronary stents was limited by high (3% to 5%) subacute thrombosis rates despite aggressive antithrombotic therapy with aspirin, dipyridamole, periprocedural low-molecular-weight dextran, and an uninterrupted transition from intravenous (IV) heparin to oral warfarin. Subacute thrombosis produced profound clinical consequences that resulted in an untoward outcome (e.g., death, MI, or emergency revascularization) in virtually every such patient. Lower frequencies of subacute stent thrombosis (approximately 0.5% to 1.0%) have resulted from the use of high-pressure stent deployment and with a drug regimen that includes aspirin and an ADP receptor antagonist (clopidogrel, prasugrel, or ticagrelor, and/or IV cangrelor) started just before or after stent placement (**see Chapter 93**).

Even though coronary BMSs reduce the incidence of angiographic and clinical restenosis compared with balloon angioplasty, angiographic restenosis (follow-up diameter stenosis >50%) still occurs in 20% to 30% of patients, and clinical restenosis (recurrent angina caused by restenosis in the treated segment) develops in 10% to 15% of patients in the first year after treatment. Restenosis with BMSs occurs more often in patients with small vessels, long lesions, and DM, among other factors. Adjunctive

pharmacologic therapy has not prevented restenosis after stent placement.

Mechanical treatments of in-stent restenosis have included balloon redilation, removal of in-stent hyperplasia by means of atherectomy, and repeated BMS placement. Brachytherapy using beta or gamma sources modestly improved this outcome for in-stent restenosis, but brachytherapy has several limitations, including the requirement for a radiation therapist, a tendency for late "catch-up" restenosis, and inhibition of endothelialization, which greatly increases the risk for thrombosis if another stent is implanted in the same vessel segment. Brachytherapy was found to be inferior to DES placement for treating restenosis in two randomized studies.[44,45]

BMSs are currently used in 10% to 20% of patients undergoing PCI, most often because of an inability to take long-term DAPT. However, the data actually suggest superiority of current-generation DESs over BMSs even in patients at high risk of bleeding.[46]

Drug-Eluting Stents

DESs were developed in the early 2000s to provide sustained local delivery of an antiproliferative agent at the site of vessel wall injury. The three components of current DESs are a balloon-expandable stent, a durable or resorbable polymer coating that provides sustained drug delivery, and the pharmacologic agent used to limit intimal hyperplasia.

DESs have proven efficacy in patients with focal, de novo, and "workhorse" lesions that include reference vessel diameters of 2.5 to 3.5 mm and lesion lengths of 15 to 30 mm. Additional randomized trials and registries have also demonstrated the benefit of DESs in patients with long (>30 mm in length) and small (<2.5 mm) vessels, CTOs, SVG and internal mammary artery disease, in-stent restenosis, and STEMI.[47] Current DESs show lower risk of stent thrombosis than the first DESs[48,49] and consistent prevention of restenosis compared with BMSs, as well as improved deliverability because of lower-profile materials. Stent thrombosis is now rare compared with risk of MI unrelated to prior stents. Recent randomized comparisons of current DESs to BMSs indicate similar or lower rates of stent thrombosis with DESs, both early[48] and beyond 1 year.[49]

With current DESs, guidelines now recommend 6 months or longer of DAPT in patients without ACS who are not at high risk of bleeding and who tolerated DAPT without a bleeding complication.[50] Guidelines have also been updated regarding longer-duration DAPT based on recently published trials and indicate that 12 months or longer may be reasonable for patients who do not have a high risk of bleeding and who have tolerated DAPT without a bleeding complication.[51] Although low stent thrombosis risks with DESs are further reduced with extended therapy, the recommendations are largely based on reduction in the risk of late MI unrelated to the stent, rather than stent thrombosis.[52-54]

Sirolimus-Eluting Stents

The CYPHER stent (Cordis, Warren, NJ) contains sirolimus, a naturally occurring immunosuppressive agent that causes cytostatic inhibition of cell proliferation. Sirolimus is released from a biostable polymer over 30 days. The pivotal SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) trial included 1058 patients with workhorse lesions who were randomly assigned to treatment with a sirolimus-eluting stent or a BMS. The primary clinical endpoint of 8-month target vessel failure, which included target-vessel revascularization, death, or MI, was reduced from 21% in patients treated with BMSs to 8.6% in patients treated with sirolimus-eluting stents ($P < 0.001$). The rate of target-vessel revascularization was reduced from 16.6% in BMSs to 4.1% in sirolimus-eluting stents at 1 year ($P < 0.001$) and was sustained at 5 years.[55,56] The cumulative incidence of MI or revascularization attributed to

remote segments of the target vessel did not differ between the two groups. Even though manufacture of the CYPHER stent ceased in 2011, other sirolimus-eluting stents continue to be manufactured and sold outside the United States.

Paclitaxel-Eluting Stents

The TAXUS stent (Boston Scientific) is composed of a stainless steel stent platform, a polyolefin polymer derivative, and the microtubular stabilizing agent paclitaxel, which has anti-inflammatory effects while also inhibiting both cell migration and division. Release of paclitaxel is completed within 30 days of implantation, although a substantial portion (>90%) of the paclitaxel remains within the polymer indefinitely. The pivotal TAXUS-IV trial randomly assigned 1314 patients with single de novo coronary lesions to either a TAXUS stent or an identical-appearing BMS. The rate of ischemia-driven target-vessel revascularization at 9 months was reduced from 11.3% to 3% and remained significantly reduced at 12 months (from 17.1% to 7.1%) in patients with paclitaxel-eluting stents ($P < 0.001$). The TAXUS stent is no longer manufactured.

Zotarolimus-Eluting Stents

Zotarolimus (also known as ABT-578) is another rapamycin analogue released from a phosphorylcholine (PC)-coated stent that has been evaluated in the Endeavor stent (Medtronic Vascular, Santa Rosa, Calif). In the ENDEAVOR-II trial, 1197 patients were assigned to treatment with the Endeavor zotarolimus-eluting PC polymer–coated stent or with the same BMS without the drug or the polymer coating.[57] The 9-month primary endpoint of target-vessel failure was reduced from 15.1% with the BMS to 7.9% with the Endeavor stent ($P < 0.0001$).[57] The ENDEAVOR-IV trial was a prospective, randomized, single-blind, controlled trial in which the safety and efficacy of the zotarolimus-eluting stent was compared with that of the paclitaxel-eluting stent in 1548 patients with single de novo coronary lesions. The primary endpoint was a composite of cardiac death, MI, or target-vessel revascularization, and the Endeavor stent was noninferior to the TAXUS stent. In addition, fewer periprocedural MIs occurred with zotarolimus-eluting stents (0.5% versus 2.2%; $P = 0.007$) because of less side branch occlusion in patients with these stents.[58] A large randomized trial compared stent thrombosis between the Endeavor and Cypher stents and showed no difference at the primary endpoint of definite or probable stent thrombosis at 3 years,[59] but did show a difference at 4 years (1.6% vs. 2.6%, $P = 0.003$).[60] The Endeavor stent is currently being manufactured but less widely available than the more recently approved Resolute zotarolimus-eluting stent. In the RESOLUTE All Comers Trial of 2,292 patients, the Resolute zotarolimus-eluting stent was found to be noninferior to the everolimus-eluting stent (8.2% versus 8.3%, respectively; $P < 0.001$ for noninferiority) with respect to the primary endpoint of target-lesion failure.[61] At 5 years of follow-up, there were no significant differences between stents in target-lesion failure, its components, or stent thrombosis.[62]

Everolimus-Eluting Stents

The XIENCE stent (Abbott Vascular) uses the cobalt chromium Vision stent, a durable fluoropolymer, and everolimus, a rapamycin analogue that has both immunosuppressive and antiproliferative effects. Based on initial studies in which the use of an absorbable poly-L-lactic acid (PLA) polymer was evaluated, the SPIRIT program has shown a reduction in late lumen loss comparable to that achieved with the CYPHER stent. SPIRIT III was a prospective, single-blind RCT that enrolled 1002 patients undergoing PCI for lesions 28 mm or less in length and with a reference vessel diameter of between 2.5 and 3.75 mm.[63] Angiographic in-segment late loss was significantly less in the everolimus-eluting stent group than in the

paclitaxel group (0.14 versus 0.28 mm; $P \leq 0.004$).[63] The everolimus stent was noninferior to the paclitaxel stent in terms of the rate of target-vessel failure at 9 months (7.2% versus 9.0%, respectively; $P < 0.001$ for noninferiority). The everolimus stent was associated with significant reductions in composite major adverse cardiac events (MACE) at 9 months compared with the paclitaxel stent (4.6% versus 8.1%; $P = 0.03$) and at 1 year (6.0% versus 10.3%; $P = 0.02$) because of fewer MIs and target-lesion revascularization procedures.[63] SPIRIT IV, a larger randomized comparison of the everolimus and paclitaxel stents in 3687 patients, found similar benefits of the everolimus stent, with significantly lower rates of target-lesion failure, MI, stent thrombosis, and ischemia-driven target-lesion revascularization at 2 years.[64] At 3 years of follow-up, similar results were found in a meta-analysis of the SPIRIT II, III, and IV trials (target-lesion failure, 8.9% versus 12.5%; $P = 0.0002$; MI, 3.2% versus 5.1%; $P = 0.002$; stent thrombosis, 0.7% versus 1.7%; $P = 0.003$; ischemia-driven target-lesion revascularization, 6.0% versus 8.2%; $P = 0.004$).[65]

Bioabsorbable Polymers and Drug-Eluting Stents

Bioabsorbable polymers have the potential benefit of no polymer remaining after the period required for drug suppression of neointimal hyperplasia, therefore limiting possible vascular reaction and toxicity. These polymers have been used on conventional metal stents to elute drug,[66,67] as well as in combination with fully bioabsorbable scaffolds.[68,69] The EVOLVE II trial found that the SYNERGY stent, which contains an bioabsorbable everolimus-eluting polymer on a cobalt chromium stent, was noninferior to a durable polymer everolimus-eluting stent in target-lesion failure at 12 months (6.7% versus 6.5%, respectively; P for noninferiority = 0.0005) in 1687 patients.[70] Clinical studies are underway to determine whether shorter durations of DAPT may be reasonable in patients at higher bleeding risk treated with this stent, since the drug and polymer are resorbed within 3 to 4 months after stent implantation.[71]

DESs that are completely bioabsorbable several years after implantation are now available.[72] In the ABSORB III trial, the primary endpoint of target-lesion failure at 1 year occurred in 7.8% of patients treated with an everolimus-eluting bioabsorbable scaffold (ABSORB) and in 6.1% of patients treated with a durable polymer everolimus-eluting stent (noninferiority $P = 0.007$; difference $P = 0.16$).[73] In a meta-analysis of six randomized trials with 3738 patients, ABSORB was associated with a greater risk of definite/probable thrombosis than the durable polymer everolimus-eluting stent (odds ratio, 1.99; 95% confidence interval [CI] 1.00 to 3.98; $P = 0.05$).[73] Currently, these stents are being considered primarily for proximal, simple large-vessel stenoses, to avoid higher risks of scaffold thrombosis in smaller or more complex lesions.

Antiplatelet Agents

See also Chapter 93.

Aspirin

Aspirin irreversibly inhibits cyclooxygenase (COX) and thus blocks the synthesis of thromboxane A_2 (TxA_2), a vasoconstriction agent that promotes platelet aggregation.[74] Aspirin substantially reduces periprocedural MI caused by thrombotic occlusions compared with placebo and is standard for all patients undergoing PCI. The inhibitory effect of aspirin occurs within 60 minutes, and its effect on platelets lasts for up to 7 days after discontinuation. Although the minimum effective aspirin dosage in the

setting of PCI remains uncertain, patients maintained on a regimen of daily chronic aspirin therapy should receive 81 to 325 mg of aspirin before PCI. Patients not already taking daily long-term aspirin therapy should be given 325 mg of aspirin at least 2 hours and preferably 24 hours before PCI is performed. After PCI, aspirin should be continued indefinitely in patients without allergy, and a lower dose (e.g., 81 mg) may be preferable to decrease the risk for gastrointestinal bleeding risk (see Guidelines).

Adenosine Diphosphate Receptor Antagonists

Thienopyridine derivatives cause irreversible platelet inhibition through their effects on the $P2Y_{12}$ ADP receptor, which can activate the glycoprotein (GP) IIb/IIIa complex. Because aspirin and the thienopyridines have distinct mechanisms of action, their combination inhibits platelet aggregation to a greater extent than either agent alone. Use of the combination of aspirin and clopidogrel (or previously, ticlopidine) for 14 to 28 days was essential to prevent stent thrombosis after BMS placement. The combination of aspirin and clopidogrel was also found to reduce death, MI, and urgent revascularization within 12 months in patients undergoing PCI in the setting of NSTEMI and UA and in those undergoing elective PCI. Recent studies suggest that a loading dose of 600 mg of clopidogrel rather than 300 mg results in more rapid (<2 hours) platelet inhibition and improved clinical outcomes, including lower rates of stent thrombosis. Additional clopidogrel loading with 300 or 600 mg may also be used in patients being treated with chronic maintenance clopidogrel therapy, although whether this actually improves clinical outcomes is unclear.[75] The need for pretreatment with clopidogrel is more controversial in that the improved clinical outcomes need to be balanced against the potential risk for bleeding should CABG be necessary. Current guidelines recommend that a 600-mg loading dose of clopidogrel be administered before or during PCI. All post-PCI patients treated with a DES should receive clopidogrel (75 mg daily) for at least 6 months if they do not have a high risk for bleeding. For post-PCI patients receiving a BMS, current guidelines recommend clopidogrel for a minimum of 1 month and ideally up to 12 months (unless the patient has an increased risk for bleeding, in whom it should be given for a minimum of 2 weeks). However, recent studies comparing BMSs to current DESs do not indicate greater safety with BMS, with similar or higher risks of stent thrombosis and higher risks of repeat revascularization within 12 months.[76,77]

Prasugrel, a thienopyridine, is a more potent $P2Y_{12}$ ADP receptor inhibitor with a more rapid onset of action and higher levels of platelet inhibition than higher-dose clopidogrel.[78] In a study of 13,608 patients with moderate- to high-risk ACS undergoing scheduled PCI and randomly assigned to receive prasugrel (60-mg loading dose and 10-mg daily maintenance dose) or clopidogrel (300-mg loading dose and 75-mg daily maintenance dose) for 6 to 15 months, the primary efficacy endpoint—a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke—occurred in 12.1% of patients receiving clopidogrel and in 9.9% of those receiving prasugrel ($P < 0.001$).[79] Prasugrel was also associated with significant reductions in rates of MI (9.7% for clopidogrel versus 7.4% for prasugrel; $P < 0.001$), urgent target-vessel revascularization (3.7% versus 2.5%; $P < 0.001$), and stent thrombosis (2.4% versus 1.1%; $P < 0.001$).[79] On the other hand, major bleeding was observed in 2.4% of patients receiving prasugrel and in 1.8% of patients receiving clopidogrel ($P = 0.03$), with more frequent rates of life-threatening bleeding occurring in the prasugrel group (1.4% versus 0.9% with clopidogrel; $P = 0.01$), including fatal bleeding (0.4% versus 0.1%, respectively; $P = 0.002$).[79,80] Among patients treated with clopidogrel, carriers of reduced-function *CYP2C19* alleles had significantly lower levels of active metabolite, diminished platelet inhibition, and higher rates of adverse cardiovascular events.[81] Such a relationship was not found in patients treated with prasugrel. Further research will be necessary to determine whether point-of-care

platelet assays or determination of genetic polymorphisms can help in allocating therapy, although to date this type of testing does not appear to be clinically useful.[82] In patients with an ACS undergoing PCI who are at low bleeding risk, prasugrel may be given in a 60-mg loading dose as soon as possible after definition of the coronary anatomy, with 10 mg daily continued for 12 months after stent placement.

Ticagrelor, a reversible oral $P2Y_{12}$ receptor antagonist, provides faster, greater, and more consistent ADP receptor inhibition than clopidogrel.[83] In a multicenter double-blind trial, 18,624 patients with ACS, with or without ST-segment elevation, were randomly assigned to treatment with ticagrelor (180-mg loading dose, then 90 mg twice daily) or clopidogrel (300- to 600-mg loading dose, then 75 mg daily) for 12 months. The primary endpoint—a composite of death from vascular causes, MI, or stroke at 12 months—occurred in 9.8% of patients receiving ticagrelor and in 11.7% of those receiving clopidogrel (hazard ratio, 0.84; $P < 0.001$).[84] Ticagrelor was also associated with significant reductions in MI alone (5.8% versus 6.9% in clopidogrel group; $P = 0.005$) and in death from vascular causes (4.0% versus 5.1%, respectively; $P = 0.001$).[84] No significant difference in overall rates of major bleeding was observed between the ticagrelor and clopidogrel groups (11.6% and 11.2%, respectively; $P = 0.43$), but ticagrelor was associated with a higher rate of major bleeding not related to CABG (4.5% versus 3.8%; $P = 0.03$).[84]

Current evidence suggests that in the absence of risk factors for bleeding, DAPT should continue for at least 12 months after stent placement.[51] The DAPT score was developed to help further refine individualized treatment by determining which patients are most likely to benefit from or be harmed by continuation of DAPT beyond 12 months.[85] Prolonged ADP receptor antagonist therapy not only reduces late stent thrombosis but also prevents MI remote from the initial intervention. Nonetheless, in patients with elevated bleeding risk, it may be reasonable to consider shorter durations of therapy (6 months) with current DES. Indefinite aspirin and clopidogrel therapy is recommended in patients undergoing brachytherapy, and long-term higher doses (150 mg daily) of clopidogrel, or alternatively, prasugrel or ticagrelor, may be considered in patients in whom stent thrombosis may be catastrophic, such as those with unprotected left main coronary artery stenting or with stenting of the last remaining vessel.[10] It is important to note that the patients in these trials did not receive anticoagulant therapy, and that there are multiple ongoing trials examining antiplatelet therapy in conjunction with warfarin or novel anticoagulants for patients with atrial fibrillation undergoing coronary stent treatment.[86,87] IV cangrelor is now approved for use in elective and urgent PCI and is an attractive option for patients who have not been pretreated with oral ADP receptor antagonists.[88,89]

Glycoprotein IIB/IIIA Inhibitors

Thrombin and collagen are potent platelet agonists that can cause release of ADP and serotonin and activate GP IIb/IIIa receptors on the platelet surface (**see Chapter 93**). Functionally active GP IIb/IIIa has a role in the "final common pathway" of platelet aggregation by binding fibrinogen and other adhesive proteins that bridge adjacent platelets. Three intravenous GP IIb/IIIa inhibitors are approved for clinical use. Studies supporting the use of these agents during PCI were performed before the widespread use of DAPT, however, and use of these agents has been reevaluated in this context.

Abciximab is a chimeric human-murine monoclonal antibody that irreversibly binds to the platelet GP IIb/IIIa receptor on human platelets. It also binds to the vitronectin ($\alpha_v\beta_3$) receptor found on platelets and to vessel wall endothelial and smooth muscle cells. The recommended dosage of abciximab is a 0.25 mg/kg by IV bolus, followed by a continuous IV infusion of 0.125 µg/kg/min (to a maximum of 10 µg/min) for 12 hours. Abciximab can be administered safely in patients with renal insufficiency, and

platelet infusions can reverse the effect of this agent (although repeated transfusions may be necessary).

Eptifibatide is a cyclic peptide derivative that reversibly binds GP IIb/IIIa. The double eptifibatide bolus (180-µg/kg boluses 10 minutes apart) and infusion dose (2.0 µg/kg/min for 18 to 24 hours) result in sufficient platelet inhibition to prevent ischemic events in patients undergoing PCI. Addition of eptifibatide to a 600-mg loading dose of clopidogrel also causes incremental platelet inhibition. The eptifibatide infusion must be reduced to 1 µg/kg/min in patients with a creatinine clearance lower than 50 mL/min. Platelet transfusions do not reverse the platelet inhibition with eptifibatide, although by 4 hours after cessation of the infusion, patients have safely undergone CABG.

Tirofiban, a small peptidomimetic molecule, has also undergone evaluation for its adjunctive benefit during urgent PCI but was found to be inferior to abciximab for prevention of ischemic events during PCI. The recommended dosage of tirofiban is an initial rate of 0.4 µg/kg/min for 30 minutes and then continued at 0.1 µg/kg/min. Patients with severe renal insufficiency (creatinine clearance <30 mL/min) should receive half the usual rate of infusion. Subsequent studies have suggested that the tirofiban bolus dose given in the initial PCI studies may not have produced an optimal antiplatelet effect during PCI, and that larger bolus doses can improve the inhibition of platelet aggregation.

The GP IIb/IIIa inhibitors have demonstrated improvement in clinical outcomes within the first 30 days after PCI, primarily by reducing ischemic complications, including periprocedural MI and recurrent ischemia. They are particularly useful in patients with troponin-positive ACS but have no consistent effect in reducing late restenosis. Although GP IIb/IIIa inhibitors differ in their structure, reversibility, and duration, two meta-analyses found no difference between their clinical effects in patients undergoing primary PCI.[90,91] Bleeding is the major risk associated with GP IIb/IIIa inhibitors, and therefore downward adjustment of the unfractionated heparin dose has been recommended. GP IIb/IIIa inhibitors are recommended in patients with NSTEMI and UA who are *not* pretreated with clopidogrel, and it is reasonable to administer them to patients with troponin-positive ACS who have also been pretreated with clopidogrel.[92,93]

Antithrombin Agents

Unfractionated heparin (UFH) is the most commonly used thrombin inhibitor during PCI. Point-of-care activated clotting time (ACT) monitoring has facilitated heparin dose titration during PCI, and retrospective studies on balloon angioplasty have related the ACT value to clinical outcome after PCI. An ACT in the range of 350 to 375 seconds provided the lowest composite ischemic event rate, although any level of ACT longer than 250 seconds was not associated with any further reductions in ischemic complications with the concomitant use of GP IIb/IIIa inhibitors. More recent studies in the thienopyridine era have failed to correlate ischemic outcomes with the level of anticoagulation achieved with UFH during coronary stent placement. Weight-adjusted heparin dosing regimens of 50 to 70 IU/kg help avoid "overshooting" the ACT. Sufficient UFH should be administered during PCI to achieve an ACT longer than 250 to 300 seconds if no GP IIb/IIIa inhibitor is given, and longer than 200 to 250 seconds if a GP IIb/IIIa inhibitor is given. Routine use of IV heparin after PCI is no longer indicated. If no closure device has been used, early sheath removal is encouraged when the ACT falls to less than 150 to 180 seconds. (**See also Chapter 93**.)

Low-Molecular-Weight Heparin

Enoxaparin is considered a reasonable alternative to UFH in patients with non–ST-segment elevation

ACS undergoing PCI (**see Chapter 60**), but difficulty monitoring the levels of anticoagulation in the event that PCI is performed has limited its clinical use at many centers.[94] The SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors) trial prospectively randomly assigned 10,027 high-risk patients with non–ST-elevation ACS with an intended early invasive strategy to treatment with subcutaneous enoxaparin or to IV UFH. The 30-day primary efficacy outcome, a composite clinical endpoint of all-cause death or nonfatal MI occurred in 14% of the enoxaparin patients and in 14.5% of the UFH patients. More TIMI (thrombolysis in myocardial infarction) major bleeding was observed in patients treated with enoxaparin (9.1% versus 7.6%; $P = 0.008$). Risk for bleeding was highest in patients who received "crossover" therapy with UFH and enoxaparin. When enoxaparin is given before PCI, empiric dose algorithms have been designed to guide additional anticoagulation therapy during PCI. If the last dose of enoxaparin was administered less than 8 hours before PCI, no additional antithrombin is needed. If the last dose of enoxaparin was given between 8 and 12 hours, a 0.3-mg/kg bolus of IV enoxaparin should be administered. If the dose was administrated more than 12 hours before PCI, conventional anticoagulation therapy is indicated.

Bivalirudin

Bivalirudin is a direct thrombin inhibitor that has been used as an alternative to UFH in patients undergoing PCI. Bivalirudin generally causes fewer bleeding complications than UFH because of its shorter half-life (25 minutes) and more predictable bioavailability. Bivalirudin is also accessible to clot-bound thrombin, because its anticoagulant effect does not depend on binding with antithrombin. Bivalirudin was not inferior to the combination of UFH and GP IIb/IIIa inhibitor in 6010 "low-risk" patients in the REPLACE-2 (Second Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events) trial. In a larger study of 13,819 patients with UA and NSTEMI, bivalirudin alone was compared with bivalirudin plus a GP IIb/IIIa inhibitor and with heparin plus a GP IIb/IIIa inhibitor. Using a composite ischemia endpoint of death, MI, or unplanned revascularization for ischemia and major bleeding to determine the net clinical benefit, bivalirudin alone, versus heparin plus a GP IIb/IIIa inhibitor, showed noninferiority in the composite ischemia endpoint (7.8% and 7.3%, respectively) and significantly reduced rates of major bleeding (3.0% versus 5.7%; $P < 0.001$), which resulted in a better net clinical outcome (10.1% versus 11.7%; $P = 0.02$). Bivalirudin is considered a reasonable alternative to UFH in low-risk patients undergoing PCI and may reduce bleeding complications in higher-risk patients with UA and NSTEMI. Bivalirudin may be safely substituted for UFH in patients with ACS[95] and is a cost-effective alternative to UFH plus a GP IIb/IIIa inhibitor. In a randomized study of 3602 patients with STEMI undergoing primary PCI, anticoagulation with bivalirudin alone, versus heparin plus GP IIb/IIIa inhibitors, resulted in significantly reduced 30-day rates of major bleeding and net adverse clinical events, including a lower rate of mortality.[93] Adjunctive oral ADP-blocking agents should be given as soon as possible before PCI in patients with ACS.

Factor Xa Inhibitors

Fondaparinux is a pentasaccharide that has anti–factor Xa activity without effects on factor IIa and may cause less bleeding when used to treat patients with ACS.[96] The OASIS-5 (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes) trial randomly assigned 20,078 patients with ACS to receive either fondaparinux (2.5 mg daily) or enoxaparin (1 mg/kg of body weight twice daily) for a mean of 6 days. Occurrence of the 9-day primary study endpoint (death, MI, or refractory ischemia) was similar in

the two groups (5.8% with fondaparinux and 5.7% with enoxaparin), although the risk for major bleeding at 9 days was markedly lower with fondaparinux than with enoxaparin (2.2% versus 4.1%; $P < 0.001$). This reduction in bleeding was accompanied by an improvement in late mortality in patients treated with fondaparinux. Potential limitations of this approach are the relatively long half-life of fondaparinux and the need for adjunctive anticoagulation with heparin during PCI to avoid the development of catheter thrombi. Fondaparinux was not effective in reducing ischemic events in patients undergoing primary PCI for STEMI.

Outcomes After Percutaneous Coronary Intervention

Procedural success and complication rates are used to measure outcomes after PCI. Early (<30 day) success (e.g., relief of angina; freedom from death, MI, urgent revascularization) is generally related to the safety and effectiveness of the initial procedure, whereas late (30 days to 1 year) success (e.g., freedom from angina recurrence, target-vessel revascularization, MI, death) depends on both clinical restenosis and progressive atherosclerosis at remote sites. Substantial improvements in coronary devices (e.g., DESs), in the adjunctive antithrombotics used during PCI (e.g., ADP antagonists, GP IIb/IIIa inhibitors, direct thrombin inhibitors), and in secondary prevention after PCI (e.g., therapy with lipid-lowering agents, beta-adrenergic blockers, antiplatelet drugs; **see Chapter 45**) have greatly improved early and late clinical outcomes after PCI.

Early Clinical Outcomes

Anatomic (or angiographic) *success* after PCI is defined as attainment of a residual diameter stenosis of less than 50%, which is generally associated with at least a 20% improvement in diameter stenosis and relief of ischemia. With the widespread use of coronary stents, the angiographic criterion for success is 20% stenosis or less when stents are used. Procedural success is defined as angiographic success without the occurrence of major complications (death, MI, or CABG) within 30 days of the procedure. *Clinical success* is defined as procedural success without the need for urgent repeated PCI or surgical revascularization within the first 30 days of the procedure. Several clinical, angiographic, and technical variables can be used to predict the risk for procedural failure in patients undergoing PCI. Major complications include death, MI, or stroke, and minor complications include transient ischemic attacks, vascular complications, contrast-induced nephropathy, and angiographic complications.

Mortality

Although mortality after PCI is rare (<1%), it is higher in the setting of STEMI, in cardiogenic shock, and in patients with previously poor LV function in whom an occlusion develops. Several risk factors for early mortality after PCI have been identified.[97,98]

Myocardial Infarction

Periprocedural MI is one of the most common complications of PCI.[99] Two classification systems were previously used to classify MI after PCI: the World Health Organization (WHO) classification system, which defines MI as an elevation in total creatine kinase (CK) more than two times normal in association with elevation of the CK-myocardial band (MB) isoform, and a second system, more frequently used for evaluation of adjunctive pharmacologic agents by the U.S. Food and Drug Administration (FDA), in

which MI is defined as an elevation in CK-MB three times normal or higher after the procedure. A consensus definition of periprocedural MI now uses a troponin level elevated more than five times normal when it occurs in conjunction with clinical evidence of MI with symptoms, changes on the electrocardiogram (ECG), angiographic findings, or a new imaging abnormality.[100] In clinical practice, asymptomatic CK-MB elevation (<5 times upper limit of normal) occurs after 3% to 11% of technically successful PCIs and has little apparent clinical consequence. Larger degrees of myonecrosis (CK-MB 5 to 8 times upper limit of normal) are associated with higher 1-year mortality rates and should be considered a periprocedural MI. Many of these clinically silent infarcts may reflect a higher atherosclerotic burden in patients with such events and may not be truly causal. Troponin T and I elevations occur more often than CK-MB elevations, but their prognostic significance over that of CK-MB elevation is not as well established. Spontaneous MI after PCI has much more prognostic importance than periprocedural enzyme elevation.[101]

Urgent Revascularization

Emergency or urgent CABG following PCI is now uncommon and, in the era of coronary stents, results from catastrophic complications during PCI, such as coronary perforation or severe dissection and abrupt closure. Chest pain after PCI is relatively common, and evaluation requires an immediate 12-lead ECG. Recurrent ischemia after PCI, as manifested by chest pain, ECG abnormalities, and elevated levels of cardiac biomarkers, may result from acute or subacute stent thrombosis, residual dissections, plaque prolapse, side branch occlusion, or thrombus at the treatment site or may be related to residual disease not treated during the initial procedure. In the presence of suspected recurrent ischemia, coronary arteriography is the most expeditious way to identify the cause of the residual ischemia.

Angiographic Complications

Complications that occur during PCI, depending on their severity and duration, may result in periprocedural MI (Videos 62.1 and 62.2). If coronary dissections that extend deeper into the media or adventitia begin to compromise the true lumen of the vessel, clinical ischemia may develop. Even though most intraprocedural dissections can be treated promptly by stenting, significant residual dissections of the treated artery occur in 1.7% of patients. These residual dissections increase the risk for postprocedural MI, need for emergency CABG, and the incidence of stent thrombosis and increase mortality threefold.[102] In addition to barotrauma-induced dissections, dissections attributable to the guiding catheter represent another mechanism for disrupting the coronary vessel and compromising distal flow.

Coronary perforation develops in 0.2% to 0.5% of patients undergoing PCI and is more common with atheroablative devices and hydrophilic wires than with balloon angioplasty or conventional guidewires. Depending on the rate of flow through the vessel perforation, cardiac tamponade and hemodynamic collapse can occur within minutes, thus requiring immediate recognition and treatment of the perforation. Strategies for controlling coronary perforations include reversal of intraprocedural anticoagulation and prolonged inflation (at least 10 minutes) of an oversized balloon at low pressure at the site of the perforation to encourage sealing of the tear in the vessel. Management strategies for perforations include the use of perfusion balloons, which provide a small amount of distal perfusion, and the use of polytetrafluoroethylene (PTFE)-covered stents, which may control free perforations, in addition to decompression of pericardial pressure with prompt pericardiocentesis. Approximately one third of patients with PCI-associated coronary artery perforation require emergency cardiac surgery.

No-reflow is defined as reduced anterograde perfusion in the absence of a flow-limiting stenosis and occurs in up to 2% to 3% of PCI procedures, typically during interventions on degenerated SVGs, during rotational atherectomy, and during acute MI interventions. No-reflow is probably caused by distal embolization of atheromatous and thrombotic debris dislodged by balloon inflation, atherectomy, or stent implantation. Once it occurs, no-reflow can cause severe short- and long-term consequences, including a fivefold increased risk for periprocedural MI and a threefold increased risk for death. Although numerous pharmacologic strategies (e.g., intracoronary sodium nitroprusside) have been used to treat no-reflow, their efficacy in reducing the frequency of subsequent adverse events is still debated.

Stent Thrombosis.

With the routine use of a high-pressure stent after dilation and DAPT after stent implantation, the rate of stent thrombosis has declined to approximately 1% within the first year after stenting, although it can be higher in patients with STEMI or after complex PCI. Certain clinical, angiographic, and procedural factors predispose to its development. Lesion-specific factors that increase the likelihood of stent thrombosis include a residual dissection at the margin of the stent, impaired flow into or out of the stent, small stent diameter (<3 mm), long stent length, and treatment of acute MI. Patient noncompliance with DAPT, resistance to the antiplatelet effects of aspirin and clopidogrel, and hypercoagulability may also play important roles in the development of stent thrombosis (**Table 62.2**).

TABLE 62.2

Variables Associated with Stent Thrombosis

Clinical Variables
Acute myocardial infarction
Clopidogrel noncompliance and discontinuation
Clopidogrel bioavailability
Diabetes mellitus
Renal failure
Congestive heart failure
Previous brachytherapy
Anatomic Variables
Long lesions
Smaller vessels
Multivessel disease
Acute myocardial infarction
Bifurcation lesions
Procedural Factors
Stent underexpansion
Incomplete wall apposition
Residual inflow and outflow disease
Margin dissections
Crush technique
Overlapping stent
Polymer materials

The timing of stent thrombosis is defined as acute (<24 hours), subacute (24 hours to 30 days), late (30 days to 1 year), and very late (>1 year). Traditional definitions of stent thrombosis have included only episodes associated with an ACS and angiographic or pathologic demonstration of thrombosis within the stent or its margins. The Academic Research Consortium has proposed criteria for documentation of all possible stent thrombosis in clinical studies, including the categories of definite, probable, and possible.

Early reports suggested an incremental risk (0.2% to 0.5% per year) for very late stent thrombosis occurring 1 year or longer after DES implantation.[103] Inhibition of endothelialization caused by the potent antiproliferative effect of the drugs delivered by DESs may significantly prolong the period of risk for

the development of stent thrombosis. Although concerning, these events have not yet been shown to cause a significant increase in late morbidity or mortality, probably because of the benefits of DESs in reducing the need for repeated revascularization procedures and avoidance of the complications associated with the development of in-stent restenosis.[1,104-106] Ongoing evaluation of the long-term safety of DESs has engendered intense investigation, with efforts focused on determining whether patient- and lesion-specific risk factors, such as insensitivity to aspirin or clopidogrel, may contribute; whether these risks are device-specific or drug-specific phenomena; and whether prolonged DAPT may ameliorate these risks. Preliminary data suggest that second-generation DESs have lower rates of stent thrombosis than first-generation DESs. IV antiplatelet agents, such as the ADP receptor antagonist cangrelor, have the potential to further reduce the rate of periprocedural stent thrombosis.[107]

The not-infrequent scenario of a patient requiring noncardiac surgery in the weeks following PCI can markedly increase the risk for stent thrombosis. Studies of outcomes in patients undergoing noncardiac surgery soon after BMS PCI have documented stent thrombosis occurring in up to 8% in the first 2 weeks after PCI, with risks declining to baseline rates by 8 weeks. This increased risk probably results from the frequent cessation of ADP receptor antagonist treatment before surgery, as well as the hypercoagulable state in the perioperative period.

Late Clinical Outcomes

Ischemic events within the first year after PCI result from one of three processes. *Lumen renarrowing* requiring repeated target-lesion revascularization occurs in 20% to 30% of patients undergoing balloon angioplasty because of reparative arterial constriction, also known as “negative remodeling.” *Clinical restenosis* after stent implantation is less common (10% to 20%) and attributable to intimal hyperplasia within the stent. *Clinical recurrence* caused by restenosis is least common (3% to 5%) after DES placement because of focal tissue growth within the stent or at its margins. Yet another cause of clinical events after PCI is progression of coronary atherosclerosis at a site remote from that treated earlier by PCI. Death and MI can also result from sudden rupture of a plaque that is remote from the site of the initial intervention.

These processes can be partially distinguished by the timing of their occurrence. Clinical restenosis resulting from lumen renarrowing at the site of PCI generally develops within the first 6 to 9 months after PCI, whereas death and MI because of plaque instability may occur at any point after PCI at a low but constant rate (1% to 2% risk per year). Predictors of higher risk for all-cause late mortality include advanced age, reduced LV function, congestive heart failure, DM, a higher number of diseased vessels, inoperable disease, or severe comorbid conditions. A 95% 10-year survival rate can be expected in patients with single-vessel CAD, and an 80% survival rate after PCI can be achieved in those with multivessel CAD. In a 5-year follow-up study of patients treated with the TAXUS stent, target-vessel revascularization during the first year was driven by target-lesion revascularization, and target-vessel revascularization after 1 year involved similar numbers of target-lesion and non–target-lesion revascularization events, primarily as a result of progression of atherosclerotic disease. The annualized hazard ratio for non–target-lesion revascularization and other major adverse events (including death, MI, and stent thrombosis) was relatively constant beyond 1 year and not significantly different between paclitaxel-eluting stents and BMSs.[108]

Outcomes Benchmarking and Procedural Volumes

Along with CABG, PCI ranks among the most studied of all procedures in the United States. National structured outcomes registries, such as the National Heart, Lung and Blood Institute (NHLBI) Dynamic Registry and the ACC National Cardiovascular Data Repository (NCDR), have been examined.[9,109-111] The NCDR CathPCI registry also provides contemporary risk-adjusted outcomes benchmarked to hundreds of participating institutions. Participants in such national, regional, or statewide outcomes-reporting initiatives can compare their risk-adjusted clinical outcomes with those at institutions with similar patient mix and size. The detailed nature of these datasets, in which the data collected span the range of patient clinical characteristics, lesion descriptors, and device-level information, provides centers with a comprehensive comparison of their practice patterns and outcomes with those at peer institutions. More than 50% of U.S. hospitals participate in the NCDR CathPCI registry. Participation in a prospective quality assessment and outcomes registry is recommended for centers performing PCI.

Guidelines recommend that physicians undergo a 3-year comprehensive cardiac training program with 12 months of training in diagnostic catheterization, during which the trainee performs 300 diagnostic catheterizations, including 200 as the primary operator. Interventional training requires a fourth year of training, including more than 250 interventional procedures, a level that is also required for physicians to be eligible for the American Board of Internal Medicine certifying examination in interventional cardiology.

The guidelines favor performance of PCI by higher-volume operators, defined as those performing more than 75 procedures per year at high-volume centers (those in which more than 400 procedures are performed each year). These recommendations are based on the dated observations that higher-volume operators have lower adverse event rates than do lower-volume operators.[112] In one analysis of 1338 PCIs performed in the United States and Canada, operators with fewer than 100 cases per year had higher rates of 30-day death, MI, or target-vessel revascularization (13.2% versus 8.7%; $P = 0.18$) and large MI (7.7% versus 3.3%; $P = 0.06$) than did those with 100 or more cases per year.[112] However, a more contemporary analysis of primary PCI found no relationship between hospital PCI volume and mortality in hospitals participating in a quality improvement initiative.[113]

Although PCI has traditionally been performed at centers that offer on-site surgical backup, more recent analyses have shown that PCI for STEMI and elective PCI can be performed safely, provided that PCI is performed by high-volume operators with minimal institutional volume requirements.[9,114-116] Off-site PCI is best suited for underserved areas that are geographically far removed from major centers.

Institutions must have a system for quality measurement and improvement that includes valid peer review. The guidelines recommend that quality assessment reviews take into consideration risk adjustment, statistical power, and national benchmark statistics. They should also include tabulation of adverse event rates for comparison with benchmark values, as well as case review of complicated procedures and some uncomplicated procedures.

Future Perspectives

After three decades of rapid growth and dissemination of coronary interventional techniques and the associated dramatic refinement in the devices used for revascularization, many challenges still remain for the percutaneous treatment of CAD. Ongoing large-scale multicenter randomized trials will assess the safety and efficacy of PCI with DESs in patients with unprotected left main coronary artery stenosis. Additional technologies are currently in clinical testing for the treatment of complex bifurcation stenosis with dedicated bifurcation stent systems. Better techniques to treat chronic total occlusions are being

developed.

DES design is continually evolving in an attempt to optimize effective early endothelialization of the stented segment without sacrificing the long-term benefits of DESs in reducing target-lesion revascularization. Theoretically, advances in stent, polymer, and drug design could lead to improvements in restenosis and thrombosis rates, which in turn may reduce rates of MI and even death (**Fig. 62.9**). Of course, this concept would need to be tested prospectively in adequately powered trials of sufficient duration, but it could lead to reexamination of the relative merits of PCI versus medical therapy or CABG in a variety of settings.

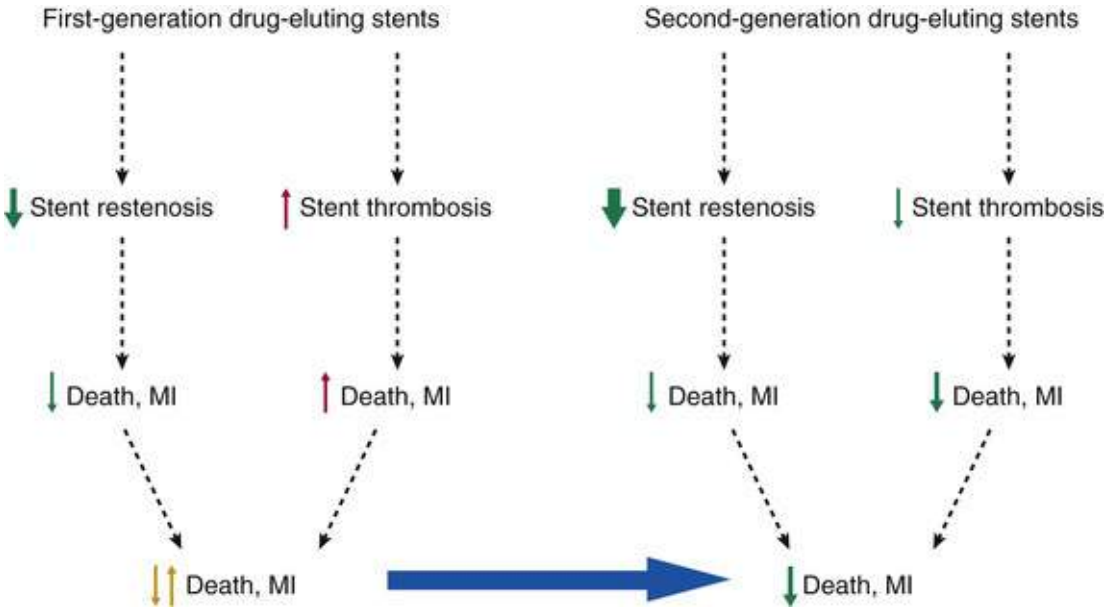


FIGURE 62.9 Theoretical framework by which second-generation drug-eluting stents (DESs) might decrease the risk for myocardial infarction (MI) and cardiovascular death in comparison to bare-metal stents, even though first-generation DESs did not. (From Bhatt DL. Examination of new drug-eluting stents—top of the class! Lancet 2012;380:1453.)

Determination of the optimal duration of antiplatelet therapy following DES deployment requires ongoing study. Bioabsorbable stents, produced from bioerodible polymers or magnesium alloys, show promise as a mechanism of providing short-term scaffolding to prevent abrupt closure of the vessel while leaving nothing permanent in the vessel wall after several months, thereby potentially reducing the risk for very late stent thrombosis, although this has not been proved to date.

Early investigations of myocardial regeneration following acute MI by percutaneous delivery of autologous stem cell or progenitor cell lines have generated great interest in the potential of such therapies to improve myocardial recovery (**see Chapter 30**), but more clinical data are needed. Continued refinement of ventricular support devices offers hope for myocardial recovery in the patient with severe myocardial dysfunction.

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Guidelines

Percutaneous Coronary Intervention

Laura Mauri and Deepak L. Bhatt

The American College of Cardiology/American Heart Association (ACC/AHA) published their initial guidelines for the performance of percutaneous coronary intervention (PCI) in 2001 and have since provided a series of focused updates that revised selected recommendations based on the ever-expanding clinical evidence base and evolving practice patterns.[1-3] In aggregate, these guidelines have provided clinicians with the tools required to enhance clinical decision making for patients undergoing percutaneous revascularization.

As with other ACC/AHA guidelines, they use the standard ACC/AHA classification system for indications (class of recommendation, COR):

I: Conditions for which there is evidence and/or general agreement that the test is useful and effective.
II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness or efficacy of performing the test.
IIa: Weight of evidence or opinion is in favor of usefulness or efficacy.
IIb: Usefulness or efficacy is less well established by evidence and/or opinion.
III: Conditions for which there is evidence and/or general agreement that the test is not useful or effective and in some cases may be harmful.

Three levels are used to rate the level of evidence (LOE) on which recommendations have been based:

A: Recommendations are derived from data from multiple randomized clinical trials.
B: Recommendations are derived from a single randomized trial or nonrandomized studies.
C: Recommendations are based on the consensus opinion of experts.

Clinical Features

Guidelines relevant to the use of PCI to improve survival over that achieved with medical therapy (**Table 62G.1**) and to improve symptoms in patients with significant anatomic or physiologic coronary artery stenoses (**Table 62G.2**) and ST-elevation myocardial infarction (STEMI) (**Table 62G.3**) are provided.

TABLE 62G.1

ACC/AHA Recommendations for Percutaneous Coronary Intervention (PCI) to Improve Survival Over That Achieved with Medical Therapy[3]

ANATOMIC SETTING	COR	RECOMMENDATION	LOE
Unprotected left main or complex CAD	I	Heart team approach recommended	C
	IIa	Calculation of STS and SYNTAX scores	B
Unprotected left main	IIa	PCI for SIHD when both the following are present: anatomic conditions associated with a low risk for procedural complications (e.g., low SYNTAX score of ≤22, ostial or trunk left main CAD) *and* clinical characteristics that predict a significantly increased risk for adverse surgical outcomes, such as an STS-predicted risk for operative mortality ≥5%	C
	IIa	PCI for UA/NSTEMI if not a CABG candidate	B
	IIa	PCI for STEMI when distal coronary flow is TIMI flow grade <3 and PCI can be performed more rapidly and safely than CABG	C
	IIb	PCI for SIHD when both the following are present: anatomic conditions associated with a low to intermediate risk for procedural complications and an intermediate to high likelihood of good long-term outcome (e.g., low to intermediate SYNTAX score of <33, bifurcation left main CAD) *and* clinical characteristics that predict an increased risk for adverse surgical outcomes, such as moderate to severe COPD and disability from previous stroke or previous cardiac surgery, as well as an STS-predicted risk for operative mortality >2%	B
Three-vessel disease	IIb	PCI of uncertain benefit relative to CABG	B

COR, Class of recommendation; *LOE,* level of evidence; *CABG,* coronary artery bypass grafting; *CAD,* coronary artery disease; *COPD,* chronic obstructive pulmonary disease; *NSTEMI,* non–ST-segment elevation myocardial infarction; *SIHD,* stable ischemic heart disease; *STEMI,* ST-segment elevation myocardial infarction; *STS,* Society of Thoracic Surgeons; *SYNTAX,* Synergy Between PCI with TAXUS and Cardiac Surgery; *TIMI,* Thrombolysis in Myocardial Infarction; *UA,* unstable angina.

TABLE 62G.2

ACC/AHA Recommendations for Percutaneous Coronary Intervention (PCI) to Improve Symptoms in Patients with Significant Anatomic or Physiologic Coronary Artery Stenosis[3]

ANATOMIC SETTING	COR	RECOMMENDATION	LOE
≥1 significant stenosis and unacceptable angina despite GDMT	I	PCI or CABG	A
≥1 significant stenosis and unacceptable angina in patients in whom GDMT cannot be implemented	IIa	PCI or CABG	C
Previous CABG with ≥1 significant stenosis associated with ischemia and unacceptable angina despite GDMT	IIa	PCI	C
Complex three-vessel CAD (e.g., SYNTAX score >22) and a good candidate for CABG	IIa	CABG preferred over PCI	B

COR, Class of recommendation; *LOE,* level of evidence; *CABG,* coronary artery bypass grafting; *CAD,* coronary artery disease; *GDMT,* guideline-directed medical therapy.

TABLE 62G.3

ACC/AHA Recommendations for Percutaneous Coronary Intervention (PCI) in Patients with ST-Segment Elevation Myocardial Infarction (STEMI)[2,3]

INDICATION	COR	RECOMMENDATION	LOE
Primary PCI	I	STEMI symptoms within 12 hours	A
		Severe heart failure or cardiogenic shock	B
		Contraindications to fibrinolytic therapy with ischemic symptoms <12 hours	B
	IIa	Clinical and/or electrocardiographic evidence of ongoing ischemia between 12 and 24 hours after symptom onset	B
	IIb	PCI of noninfarct artery may be considered in selected patients with STEMI and multivessel disease who are hemodynamically stable, either at the time of primary PCI or as a planned staged procedure	B-R
Delayed or elective PCI	IIa	Clinical evidence of fibrinolytic failure or infarct artery reocclusion	B
		Ischemia on noninvasive testing	B
	IIb	Hemodynamically significant stenosis in a patent infarct artery >24 hours after STEMI	B
	III (no benefit)	Totally occluded infarct artery >24 hours after STEMI in a hemodynamically stable asymptomatic patient without evidence of severe ischemia	B

COR, Class of recommendation; *LOE,* level of evidence.

Adjunctive Pharmacotherapy

Guidelines for duration of antiplatelet therapy after PCI have recently been updated, based on data from randomized clinical trials assessing the duration of dual-antiplatelet therapy (DAPT) with aspirin plus a $P2Y_{12}$ inhibitor (**Table 62G.4**). Overall, extended-duration DAPT is associated with lower risks of myocardial infarction (MI) and stent thrombosis and a higher risk of nonfatal bleeding. Balancing the benefits of reduced ischemic events with the risks of increased bleeding events is recommended for individual patients when determining the duration of treatment (**Table 62G.5**). The expanding number of antiplatelet and antithrombin agents available for use during PCI has provided clinicians with a number of competing therapeutic options. Guidelines for antiplatelet therapy and antithrombin therapy during PCI have been provided (**Table 62G.6**). Guidelines for antiplatelet therapy after PCI have also been provided (**Table 62G.7**). In addition, there is increasing awareness that providing optimal medical therapy following PCI is mandatory, including secondary risk factor modifications such as lipid-lowering therapy (**see Chapter 45**).

TABLE 62G.4

ACC/AHA Recommendations on Duration of Dual-Antiplatelet Therapy (DAPT) for Patients Undergoing Percutaneous Coronary Intervention (PCI)[10]

COR	RECOMMENDATION	LOE
I	After PCI, in patients with stable ischemic heart disease, treat with clopidogrel for at least 1 month in patients treated with a BMS.	A
I	After PCI, in patients with stable ischemic heart disease, treat with clopidogrel for at least 6 months in patients treated with a DES.	B-R
IIb	After PCI, in patients with stable ischemic heart disease with no high risk of bleeding and no significant overt bleeding on DAPT, treatment for more than 1 month may be reasonable for patients treated with a BMS, and treatment for more than 6 months may be reasonable for patients treated with a DES.	A
IIB	In patients with stable ischemic heart disease treated with DAPT after DES who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after 3 months may be reasonable.	C-LD
I	In patients with acute or recent ACS (non–ST-elevation ACS or NSTEMI) treated with PCI with DES or BMS, treat with at least 12 months of clopidogrel, prasugrel, or ticagrelor.	B-R
IIa	In patients with acute or recent ACS (non–ST-elevation ACS or NSTEMI) treated with DAPT after coronary stent implantation, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance $P2Y_{12}$ inhibitor therapy.	B-R
IIa	In patients with acute or recent ACS (non–ST-elevation ACS or NSTEMI) treated with DAPT after coronary stent implantation, who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel for maintenance $P2Y_{12}$ inhibitor therapy.	B-R
IIB	In patients with acute or recent ACS (non–ST-elevation ACS or NSTEMI) treated with DAPT after DES who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months may be reasonable.	C-LD
IIB	In patients with acute or recent ACS (non–ST-elevation ACS or NSTEMI) treated with PCI (DES or BMS) and not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), treatment for more than 12 months with clopidogrel, prasugrel, or ticagrelor may be reasonable.	A
III	Prasugrel should not be administered to patients with a prior history of stroke or TIA.	B-R

COR, Class of recommendation; *LOE,* level of evidence (B-R, moderate-quality evidence from one or more randomized clinical trials; *C-LD,* randomized or nonrandomized observational/registry studies or a meta-analysis); *ACS,* acute coronary syndrome; *BMS,* bare-metal stent; *DES,* drug-eluting stent; *NSTEMI,* non–ST-elevation myocardial infarction; *TIA,* transient ischemic attack.

TABLE 62G.5

Dual-Antiplatelet Therapy (DAPT) Score*

CLINICAL PREDICTION SCORE VARIABLE	POINTS
Age ≥75 years	−2
Age 65 to <75 years	−1
Age <65 years	0
Cigarette smoking	1
Diabetes mellitus	1
Myocardial infarction at presentation	1
Prior percutaneous coronary intervention or prior myocardial infarction	1
Paclitaxel-eluting stent	1
Stent diameter <3 mm	1
Congestive heart failure, or left ventricular ejection fraction <30%	2
Vein graft stent	2
Total score range	**−2 to 10**

*Scores of 2 or higher may indicate that extended-duration DAPT is associated with a reduction in MI or stent thrombosis that is greater than the increase in moderate or severe bleeding. Conversely, scores lower than 2 may indicate that extended-duration DAPT is associated with an increase in bleeding that is greater than the reduction in MI or stent thrombosis.

Modified from Levine GN, Bates ER, Bittl JA, et al. ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. Circulation 2016;134:e123.

TABLE 62G.6

ACC/AHA Recommendations for Antiplatelet and Antithrombin Pharmacotherapy During Percutaneous Coronary Intervention (PCI)[3]

INDICATION	COR	RECOMMENDATION	LOE
Aspirin (ASA)	I	Patients already taking daily long-term ASA therapy should take 81 to 325 mg of ASA before PCI is performed.	B
		Patients not taking ASA therapy should be given nonenteric ASA, 325 mg, before PCI.	B
$P2Y_{12}$ inhibitors Clopidogrel, prasugrel, ticagrelor	I	A loading dose of clopidogrel, generally 600 mg, should be administered before or when PCI is performed.	A
		Clopidogrel: a 600-mg loading dose is recommended.	B
		Prasugrel: generally not recommended in patients >75 years of age; FDA suggests consideration of using a lower maintenance dose in patients weighing <60 kg.	B
		Ticagrelor: issues of patient compliance may be especially important because it is given twice daily.	B
	III	Prasugrel is contraindicated in patients with previous TIA/CVA.	B
Glycoprotein (GP) IIb/IIIa inhibitors	I	If no clopidogrel pretreatment, and UA/NSTEMI with high-risk features.	A
	IIa	If no clopidogrel pretreatment and STEMI, most appropriate with large anterior MI and/or large thrombus burden.	A
		If no clopidogrel pretreatment and stable ischemic heart disease.	B
	IIa	If clopidogrel pretreatment and STEMI, most appropriate with large anterior MI and/or large thrombus burden.	C
	IIa	If clopidogrel pretreatment and UA/NSTEMI with high-risk features.	B
	IIb	If clopidogrel pretreatment and stable ischemic heart disease.	B
	III	Precatheterization laboratory administration of GP inhibitor for STEMI.	B
Unfractionated heparin	I	Dosing based on whether GP inhibitor was given.	C
Bivalirudin	I	The lower bleeding rates associated with bivalirudin are mitigated when used with a GPI	B
Enoxaparin	I	An additional dose of 0.3 mg/kg of IV enoxaparin should be administered at the time of PCI to patients who have received <2 therapeutic SC doses (e.g., 1 mg/kg) or received the last SC enoxaparin dose 8-12 hours before PCI.	B
	IIb	Recommendations for IV enoxaparin during PCI apply to patients who have not received previous antithrombin therapy or who have received "upstream" SC enoxaparin therapy for UA/NSTEMI.	B
	III (harm)	Patients treated with SC enoxaparin within 12 hours of PCI should not receive additional treatment with UFH during PCI.	B
Fondaparinux	III (harm)	PCI should not be performed with fondaparinux as the sole antithrombin agent in patients treated with upstream fondaparinux. An additional anticoagulant with anti–factor IIa activity should be administered.	C

COR, Class of recommendation; *LOE,* level of evidence; *CVA,* cerebrovascular accident; *FDA,* U.S. Food and Drug Administration; *MI,* myocardial infarction; *IV,* intravenous; *NSTEMI,* non–ST-elevation myocardial infarction; *SC,* subcutaneous; *TIA,* transient ischemic attack; *STEMI,* ST-segment elevation myocardial infarction; *UA,* unstable angina; *UFH,* unfractionated heparin.

TABLE 62G.7

ACC/AHA Postprocedure Recommendations for Aspirin and Proton Pump Inhibitor (PPI) Therapy in Patients Undergoing Percutaneous Coronary Intervention[3]

INDICATION	COR	RECOMMENDATION	LOE
Aspirin (ASA)	I	After PCI, use of aspirin should be continued indefinitely.	A
	IIa	After PCI, it is reasonable to use ASA, 81 mg/day, in preference to higher maintenance doses.	B
PPI	IIa	Use of PPIs is reasonable in patients with an increased risk for GI bleeding who require DAPT.	C
	III (no benefit)	Routine use of a PPI is not recommended for patients at low risk for GI bleeding.	C

COR, Class of recommendation; *LOE,* level of evidence; *ACS,* acute coronary syndrome; *BMS,* bare-metal stent; *DAPT,* dual-antiplatelet therapy; *DES,* drug-eluting stent; *GI,* gastrointestinal; *NSTEMI,* non–ST-elevation myocardial infarction; *STEMI,* ST-segment elevation myocardial infarction.

Appropriateness Criteria for Percutaneous Coronary Intervention

An ongoing challenge for the application of guidelines to clinical practice is to construct expert opinion for the appropriateness of revascularization based on integration of the clinical findings, noninvasive testing, coronary anatomy, and the intensiveness of medical therapy. Appropriateness criteria for revascularization based on a consensus opinion of interventionalists, cardiac surgeons, and noninvasive cardiologists were published in 2009[4] and updated in 2012.[5] Risk stratification for cardiac events was established (**Table 62G.8**), and a series of clinical scenarios were graded on a scale of 1 to 9 based on the following appropriateness definitions:

TABLE 62G.8

Noninvasive Risk Stratification

High Risk (>3% Annual Mortality Rate)
1. Severe resting LV dysfunction (LVEF <35%)
2. High-risk treadmill score (−11 or less)
3. Severe exercise-induced LV dysfunction (exercise LVEF <35%)
4. Stress-induced large perfusion defect (particularly if anterior)
5. Stress-induced multiple perfusion defects of moderate size
6. Large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-201)
7. Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (thallium-201)
8. Echocardiographic wall motion abnormality (involving >2 segments) developing with low-dose dobutamine (≤10 mg/kg/min) or at a low heart rate (<120 beats/min)
9. Stress echocardiographic evidence of extensive ischemia
Intermediate Risk (1-3% Annual Mortality Rate)
1. Mild to moderate resting LV dysfunction (LVEF = 35-49%)
2. Intermediate-risk treadmill score (greater than −11 to <5)
3. Stress-induced moderate perfusion defect without LV dilation or increased lung uptake (thallium-201)
4. Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses of dobutamine involving ≤2 segments
Low Risk (<1% Annual Mortality Rate)
1. Low-risk treadmill score (≥5)
2. Normal or small myocardial perfusion defect at rest or with stress
3. Normal stress echocardiographic wall motion, no change, or limited resting wall motion abnormalities during stress

LV, Left ventricular; *LVEF,* LV ejection fraction.

Modified from Patel MR, Dehmer GJ, Hirshfeld JW, et al. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 appropriateness criteria for coronary revascularization: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology: Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2009;53:530.

- Score of 7 to 9: *Appropriate* (A) when the expected benefits, in terms of survival or health outcomes (symptoms, functional status, and/or quality of life), exceed the expected negative consequences of the procedure.
- Score of 4 to 6: *Uncertain* (U) for the indication provided, which means that coronary revascularization may be acceptable and may be a reasonable approach for the indication, but with uncertainty implying that more research and/or patient information is needed to further classify the indication.
- Score of 1 to 3: *Inappropriate* (I) for the indication provided, which means that coronary revascularization is not generally acceptable and not a reasonable approach for the indication and is unlikely to improve the patient's health outcomes or survival.

The appropriateness for revascularization in various manifestations of acute coronary syndromes (ACS) is listed in **Table 62G.9**. In general, the guidelines support a very prominent role for revascularization in patients with ACS. The criteria for stable coronary artery disease (CAD) are based on extent of disease in the coronary arteries, complexity of the coronary anatomy, severity of angina, degree of ischemia, and extent of antianginal medical therapy (**Tables 62G.10 to 62G.12**). These key factors must all be weighed before deciding on the appropriateness of revascularization. Patients who have previously undergone coronary artery bypass grafting (CABG) and require repeated revascularization merit special consideration because the risks associated with repeated bypass surgery are higher than with the initial surgery. In patients who have previously undergone CABG, the guidelines recommend revascularization for severe angina (Canadian class III or IV), especially with large areas of ischemia and when medical therapy has already been maximized. The appropriate mode of revascularization by PCI or CABG for various anatomic subsets incorporates the burden of CAD and the presence of total occlusion (which may be measured by the SYNTAX score[6]) into the decision making. Importantly, in the 2012 focused update, two revisions resulted in a higher appropriateness rating for PCI than in the initial 2009 appropriateness criteria, based largely on the positive results of the SYNTAX (Synergy Between PCI with TAXUS and Cardiac Surgery) randomized trial in these subgroups of patients.[7] Three-vessel disease is categorized as *appropriate* for PCI when there are three focal stenoses or a low SYNTAX score, but categorized as *uncertain* in appropriateness for PCI if multiple diffuse lesions or an intermediate to high SYNTAX score is present (**Table 62G.13**).[5] Isolated left main stenosis and left main disease with a low burden of CAD are classified as uncertain appropriateness for treatment by PCI.

TABLE 62G.9

Appropriate Use Criteria for Revascularization in Patients with Acute Coronary Syndromes[4,5]

	INDICATION	APPROPRIATE USE SCORE* (1-9)
1	• STEMI • ≤12 hours from onset of symptoms • Revascularization of the culprit artery	A (9)
2	• STEMI • Onset of symptoms within the previous 12-24 hours • Severe HF, persistent ischemic symptoms, or hemodynamic or electrical instability present	A (9)
3	• STEMI • >12 hours from symptom onset • Asymptomatic; no hemodynamic instability and no electrical instability	I (3)
4	• STEMI with presumed successful treatment by fibrinolysis • Evidence of HF, recurrent ischemia, or unstable ventricular arrhythmias present • One-vessel CAD, presumed to be the culprit artery	A (9)
5	• STEMI with presumed successful treatment by fibrinolysis • Asymptomatic; no HF, no recurrent ischemic symptoms, or no unstable ventricular arrhythmias • Normal LVEF • One-vessel CAD presumed to be the culprit artery	U (5)
6	• STEMI with presumed successful treatment by fibrinolysis • Asymptomatic; no HF, no recurrent ischemic symptoms, or no unstable ventricular arrhythmias at evaluation • Depressed LVEF • Three-vessel CAD • Elective/semielective revascularization	A (8)
7	• STEMI with successful treatment of the culprit artery by primary PCI or fibrinolysis • Asymptomatic; no HF, no evidence of recurrent or provocable ischemia, and no unstable ventricular arrhythmias during the index hospitalization • Normal LVEF • Revascularization of a non–infarct-related artery during the index hospitalization	I (2)
8	• STEMI or NSTEMI and successful PCI of the culprit artery during the index hospitalization • Symptoms of recurrent myocardial ischemia and/or high-risk findings on noninvasive stress testing performed after the index hospitalization • Revascularization of 1 or more additional coronary arteries	A (8)
9	• UA/NSTEMI and low-risk features associated with short-term risk for death or nonfatal MI • Revascularization of the presumed culprit artery	U (6)
10	• UA/NSTEMI and intermediate-risk features associated with short-term risk for death or nonfatal MI • Revascularization of the presumed culprit artery	A (8)
11	• UA/NSTEMI and high-risk features associated with short-term risk for death or nonfatal MI • Revascularization of the presumed culprit artery	A (9)
12	• UA/NSTEMI and high-risk features associated with short-term risk for death or nonfatal MI • Revascularization of multiple coronary arteries when the culprit artery cannot clearly be determined	A (9)
13	• Patients with acute MI (STEMI or NSTEMI) • Evidence of cardiogenic shock • Revascularization of 1 or more coronary arteries	A (8)

**A,* Appropriate; *I,* inappropriate; *U,* uncertain.

CAD, coronary artery disease; *HF,* heart failure; *LVEF,* left ventricular ejection fraction; *MI,* myocardial infarction; *NSTEMI,* non–ST-segment elevation MI; *PCI,* percutaneous coronary intervention; *STEMI,* ST-segment elevation; MI; *UA,* unstable angina.

TABLE 62G.10A

Low-Risk Findings on Noninvasive Testings[4,5]

SYMPTOMS MEDICAL THERAPY	CTO OF 1 VESSEL; NO OTHER DISEASE	1-2 VESSELS; NO OTHER DISEASE; NO PROXIMAL LAD DISEASE	1-VESSEL DISEASE OF PROXIMAL LAD	2-VESSEL DISEASE WITH PROXIMAL LAD DISEASE	3-VESSEL DISEASE; NO LEFT MAIN DISEASE
Class III or IV Maximum treatment	U	A	A	A	A
Class I or II Maximum treatment	U	U	A	A	A
Asymptomatic Maximum treatment	I	I	U	U	U
Class III or IV No/minimal treatment	I	U	A	A	A
Class I or II No/minimal treatment	I	I	U	U	U
Asymptomatic No/minimal treatment	I	I	U	U	U

A, Appropriate; *CTO,* chronic total occlusion; *I,* inappropriate; *LAD,* left anterior descending artery; *U,* uncertain.

TABLE 62G.10B

Low-Risk Findings in Asymptomatic Patients[4,5]

EXERCISE STRESS TEST MEDICAL THERAPY	CTO OF 1 VESSEL; NO OTHER DISEASE	1-2 VESSELS; NO OTHER DISEASE; NO PROXIMAL LAD DISEASE	1-VESSEL DISEASE OF PROXIMAL LAD	2-VESSEL DISEASE WITH PROXIMAL LAD DISEASE	3-VESSEL DISEASE; NO LEFT MAIN DISEASE
High risk Maximum treatment	U	A	A	A	A
High risk No/minimal treatment	U	U	A	A	A
Intermediate risk Maximum treatment	U	U	U	U	A
Intermediate risk No/minimal treatment	I	I	U	U	A
Low risk Maximum treatment	I	I	U	U	U
Low risk No/minimal treatment	I	I	U	U	U

A, Appropriate; *CTO,* chronic total occlusion; *I,* inappropriate; *LAD,* left anterior descending artery; *U,* uncertain.

TABLE 62G.11A

Intermediate-Risk Findings on Noninvasive Study[4,5]

SYMPTOMS MEDICAL THERAPY	CTO OF 1 VESSEL; NO OTHER DISEASE	1-2 VESSELS; NO OTHER DISEASE; NO PROXIMAL LAD DISEASE	1-VESSEL DISEASE OF PROXIMAL LAD	2-VESSEL DISEASE WITH PROXIMAL LAD DISEASE	3-VESSEL DISEASE; NO LEFT MAIN DISEASE
Class III or IV Maximum treatment	A	A	A	A	A
Class I or II Maximum treatment	U	A	A	A	A
Asymptomatic Maximum treatment	U	U	U	U	A
Class III or IV No/minimal treatment	U	U	A	A	A
Class I or II No/minimal treatment	U	U	U	A	A
Asymptomatic No/minimal treatment	I	I	U	U	A

A, Appropriate; *CTO,* chronic total occlusion; *I,* inappropriate; *LAD,* left anterior descending artery; *U,* uncertain.

TABLE 62G.11B

Intermediate-Risk Findings in Patients with Canadian Cardiovascular Society Class I or II Angina[4,5]

EXERCISE STRESS TEST MEDICAL THERAPY	CTO OF 1 VESSEL; NO OTHER DISEASE	1-2 VESSELS; NO OTHER DISEASE; NO PROXIMAL LAD DISEASE	1-VESSEL DISEASE OF PROXIMAL LAD	2-VESSEL DISEASE WITH PROXIMAL LAD DISEASE	3-VESSEL DISEASE; NO LEFT MAIN DISEASE
High risk Maximum treatment	A	A	A	A	A
High risk No/minimal treatment	U	A	A	A	A
Intermediate risk Maximum treatment	U	A	A	A	A
Intermediate risk No/minimal treatment	U	U	U	A	A
Low risk Maximum treatment	U	U	A	A	A
Low risk No/minimal treatment	I	I	U	U	U

A, Appropriate; *CTO,* chronic total occlusion; *I,* inappropriate; *LAD,* left anterior descending artery; *U,* uncertain.

TABLE 62G.12A

High-Risk Findings on Noninvasive Study[4,5]

SYMPTOMS MEDICAL THERAPY	CTO OF 1 VESSEL; NO OTHER DISEASE	1-2 VESSELS; NO OTHER DISEASE; NO PROXIMAL LAD DISEASE	1-VESSEL DISEASE OF PROXIMAL LAD	2-VESSEL DISEASE WITH PROXIMAL LAD DISEASE	3-VESSEL DISEASE; NO LEFT MAIN DISEASE
Class III or IV Maximum treatment	A	A	A	A	A
Class I or II Maximum treatment	A	A	A	A	A
Asymptomatic Maximum treatment	U	A	A	A	A
Class III or IV No/minimal treatment	A	A	A	A	A
Class I or II No/minimal treatment	U	A	A	A	A
Asymptomatic No/minimal treatment	U	U	A	A	A

A, Appropriate; *CTO,* chronic total occlusion; *I,* inappropriate; *LAD,* left anterior descending artery; *U,* uncertain.

TABLE 62G.12B

High-Risk Findings in Patients with Canadian Cardiovascular Society Class III or IV Angina[4,5]

EXERCISE STRESS TEST MEDICAL THERAPY	CTO OF 1 VESSEL; NO OTHER DISEASE	1-2 VESSELS; NO OTHER DISEASE; NO PROXIMAL LAD DISEASE	1-VESSEL DISEASE OF PROXIMAL LAD	2-VESSEL DISEASE WITH PROXIMAL LAD DISEASE	3-VESSEL DISEASE; NO LEFT MAIN DISEASE
High risk Maximum treatment	A	A	A	A	A
High risk No/minimal treatment	A	A	A	A	A
Intermediate risk Maximum treatment	A	A	A	A	A
Intermediate risk No/minimal treatment	U	U	A	A	A
Low risk Maximum treatment	U	A	A	A	A
Low risk No/minimal treatment	I	U	A	A	A

A, Appropriate; *CTO,* chronic total occlusion; *I,* inappropriate; *LAD,* left anterior descending artery; *U,* uncertain.

TABLE 62G.13

Appropriateness of Coronary Artery Bypass Grafting (CABG) and Percutaneous Coronary Intervention (PCI)[5]

ANATOMIC SETTING	CABG*	PCI*
Two-vessel CAD with proximal LAD stenosis	A	A
Three-vessel CAD with low CAD burden (i.e., three focal stenoses, low SYNTAX score)	A	A
Three-vessel CAD with intermediate to high CAD burden (i.e., multiple diffuse lesions, presence of CTO, or high SYNTAX score)	A	U
Isolated left main stenosis	A	U
Left main stenosis and additional CAD with low CAD burden (i.e., additional involvement of one or two vessels or low SYNTAX score)	A	U
Left main stenosis and additional CAD with intermediate to high CAD burden (i.e., three-vessel involvement, presence of CTO, or high SYNTAX score)	A	I

*A, Appropriate; *I,* inappropriate; *U,* uncertain.

CAD, Coronary artery disease; *CTO,* chronic total occlusion; *LAD,* left anterior descending coronary artery; *SYNTAX,* Synergy Between PCI with TAXUS and Cardiac Surgery.

The terms *Appropriate*, *Uncertain,* and *Inappropriate* have been recently updated and replaced with the terms *Appropriate*, *May Be Appropriate,* and *Rarely Appropriate*.

Guidelines for Training

The guidelines recommend that physicians undergo a 3-year comprehensive cardiac training program before dedicated interventional training in an accredited program. Interventional training requires a fourth year of training, including more than 250 interventional procedures, a level that is required for physicians to be eligible for the American Board of Internal Medicine certifying examination in interventional cardiology.[8,9] Maintenance of certification requires that 150 procedures be performed in the 2 years before the 10-year certification lapses (or a procedural log including the outcomes of 25 consecutive cases as the primary operator), in addition to retaking the Added Qualification Examination in Interventional Cardiology.[8,9]

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63

Diseases of the Aorta

Alan C. Braverman, Marc Schermerhorn

The Normal Aorta

Anatomy and Physiology

The aorta, the largest artery in the body, has thoracic and abdominal components (**Fig. 63.1**). The thoracic aorta is divided into the ascending, arch, and descending segments, and the abdominal aorta, into the

suprarenal and infrarenal segments. The ascending aorta has two distinct portions. The *aortic root* begins at the aortic valve and extends to the sinotubular junction. The aortic root supports the bases of the aortic valve leaflets, which bulge outward into the sinuses of Valsalva during systole. The right and left coronary arteries arise from the sinuses of Valsalva. The upper portion of the ascending aorta begins at the sinotubular junction and rises to join the aortic arch. The proximal portion of the ascending aorta lies within the pericardial cavity, anterior to the pulmonary artery bifurcation. The aortic arch gives rise to the innominate, left common carotid, and left subclavian arteries. The descending thoracic aorta begins distal to the left subclavian artery. The ligamentum arteriosum marks the point at which the aortic arch joins the descending aorta, denoted the *aortic isthmus*. The aortic isthmus is vulnerable to deceleration trauma because this site marks the transition between the mobile ascending aorta and arch and the descending aorta, which is relatively fixed to the thoracic cage. The descending aorta gives rise to posterior paired intercostal arteries at multiple levels of the spine. Distally, the thoracic aorta passes through the diaphragm, becoming the abdominal aorta. The abdominal aorta gives rise to the celiac artery and the superior mesenteric artery anteriorly, followed by the typically posterolateral origins of the left and anterolateral right renal arteries. This part of the aorta is called the *suprarenal* or *visceral* segment. The infrarenal aorta lies anterior to the lumbar spine, where paired lumbar artery braches arise posteriorly. The aorta ends by bifurcation into common iliac arteries.

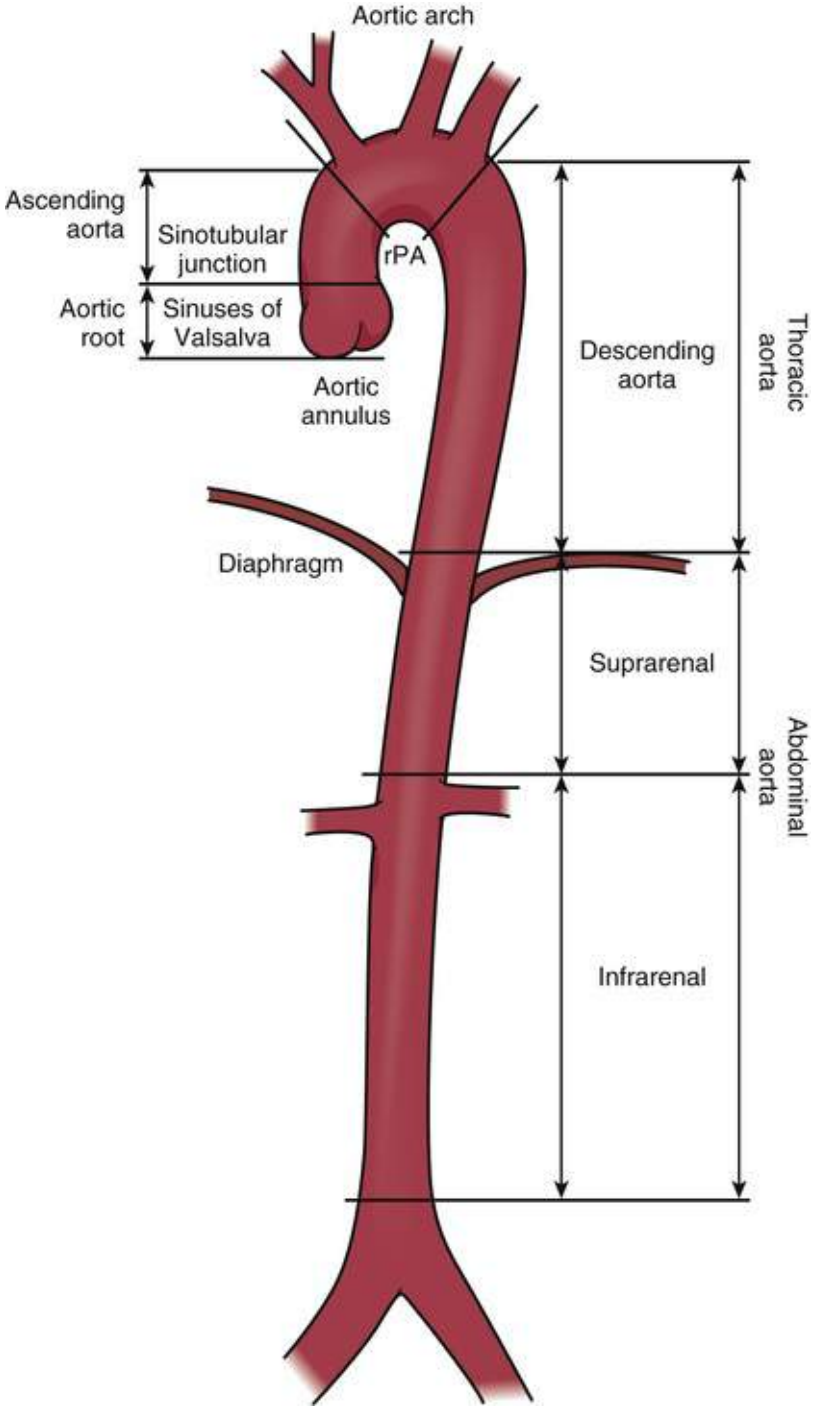


FIGURE 63.1 Anatomic segments of the aorta; *rPA,* right pulmonary artery. (From Erbel R, Aboyans V, Boileau C, et al. 2014 ESC guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2873-926.)

Microscopic Structure.

The aortic wall includes three layers: the *intima*, the *tunica media*, and the *tunica adventitia* (**Fig. 63.2**) (**see Chapter 44**). The internal elastic lamina demarcates the intima, lined by endothelial cells, from the media. The media has concentric layers of elastic fibers alternating with vascular smooth muscle cells (SMCs). Each layer of elastin and SMCs constitutes a "lamellar unit." The media gives the aorta its circumferential resilience (elasticity), which resists hemodynamic stress. The external elastic lamina delineates the abluminal portion of the media from the adventitia. The adventitia contains collagen fibers, fibroblasts, nerves, and vasa vasorum. The adventitial collagen fibers ultimately govern the tensile

strength of the aortic wall.

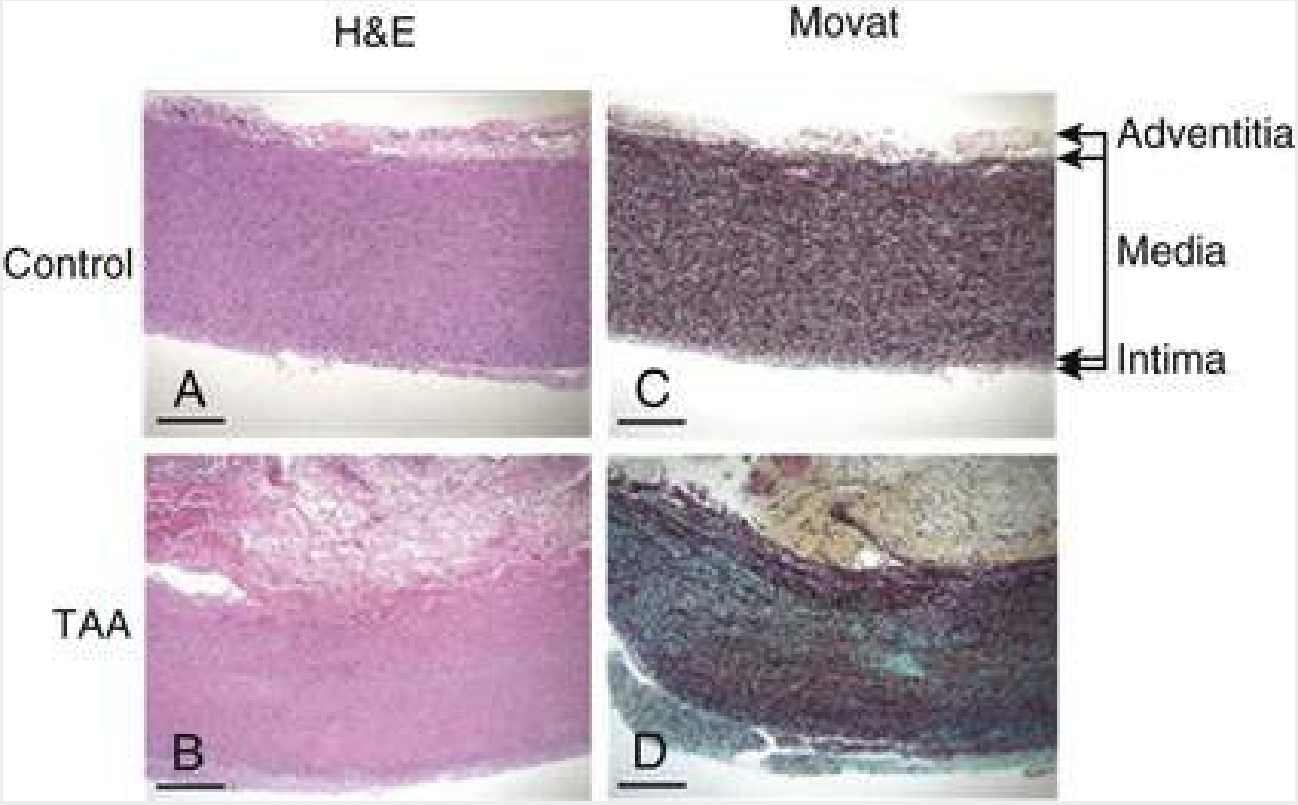


FIGURE 63.2 Aortic histology and pathology associated with thoracic aortic aneurysm (TAA) involving the ascending aorta. All panels are identically oriented with the adventitia at the top and the intima at the bottom. Hematoxylin and eosin (H&E) staining of aortic sections from a control **(A)** and a patient **(B)** with a TAA demonstrates medial degeneration with the fragmentation of elastic fibers, accumulation of proteoglycans, and regions of smooth muscle cell loss. Movat staining of aortic sections from control **(C)** and patient with an aneurysm **(D)** shows fragmentation of elastic fibers (stained *black*), loss of smooth muscle cells (cells stained *red* and nuclei stained *violet*), and accumulation of proteoglycans (stained *blue*) in the medial layer. 40× magnification; *scale bars* represent 500 µg. (Modified from Milewicz DM et al. Genetic basis of thoracic aortic aneurysms and dissections: focus on smooth muscle cell contractile dysfunction. Ann Rev Genomics Hum Genet 2008;9:283-02; and Hiratzka LF et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. J Am Coll Cardiol 2010;55:e27-129.)

The ascending aorta normally contains approximately 55 to 60 elastic lamellae, with a gradual decrease in the number of elastic lamellae down the length of the aorta to approximately 26 at the aortic bifurcation. Oxygen and nutrients reach the aortic wall by simple diffusion from the lumen, at least in segments of the aorta that contain up to approximately 29 elastic lamellae. In the proximal aortic segments, the *vasa vasorum* supply additional nutrients to the outer third of the thoracic aortic media. The infrarenal aorta normally lacks an independent microvascular supply.

The compliance of the aortic wall under normal conditions results from reversible extension of the elastic lamellar units in the media. At mechanical strain levels that exceed the extensile capacity of the medial elastic fibers, aortic tensile strength becomes dependent on the collagen fiber meshwork of the media and adventitia. Although not functionally significant under normal circumstances or in systemic hypertension, the dependence on adventitial collagen in accommodating greater hemodynamic stress can contribute to abdominal aortic aneurysms (AAAs), in which the wall tension within the dilated segment may exceed by orders of magnitude higher that in a normal aorta. In AAAs, collagen fibers reorganize to accommodate higher degrees of tensile stress.

Physiology

The aorta as an elastic conduit transmits pulsatile arterial blood pressure (BP) to all points in the arterial tree. The biomechanical properties of the aorta, including resilience to cyclic deformation, derive from the elastin and collagen in the media and adventitia. The aortic wall pressure-diameter relationship is nonlinear; a more distensible component is demonstrated at lower pressures and a stiffer component at higher pressures, with the transition from distensible to stiff behavior occurring at pressures higher than 80 mm Hg.

The pressure-diameter curve of the aorta becomes less steep with increasing age (i.e., aorta stiffens and aortic diameter increases). The aortic diameter is generally less than 40 mm at the root and becomes smaller distally. Aortic diameters depend on age, sex, body size, and BP and increase in size by 0.9 mm in men and 0.7 mm in women per decade.[1]

Evaluation of the Aorta

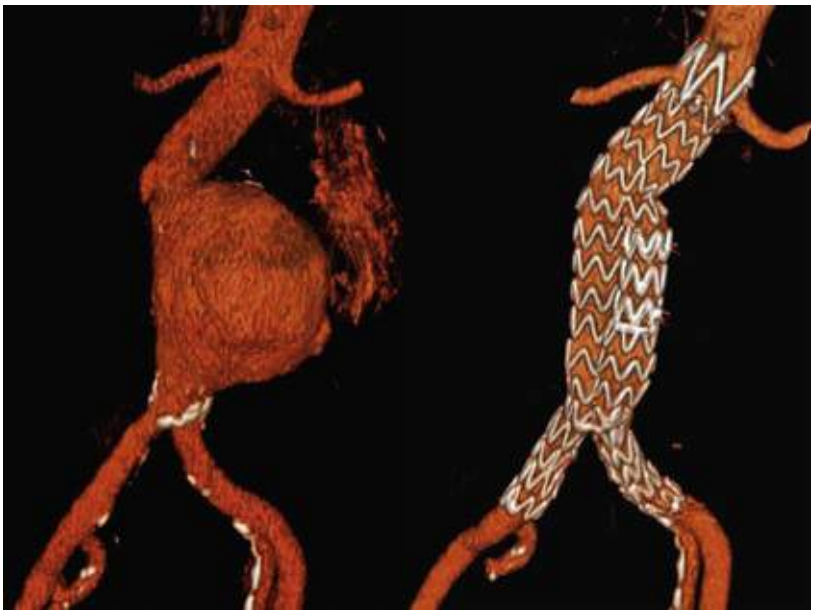
In some nonobese individuals the aorta can be palpated in the midabdominal region. The bifurcation typically occurs at the level of the umbilicus and the fourth lumbar (L4) vertebral body. Plain radiography is insensitive in evaluating the thoracic and abdominal aorta, but much more diagnostic detail regarding the aorta can be obtained with ultrasound (including echocardiography), computed tomography (CT), magnetic resonance imaging (MRI), and less frequently, aortography.

Aortic Aneurysms

The term *aortic aneurysm* refers to a pathologic segment of aortic dilation that expands and can eventually rupture. One criterion for abnormal aortic dilation is an increase in diameter of at least 50% greater than expected for the same aortic segment in unaffected individuals of the same age and sex.[2] Aortic aneurysms are described by their size, location, morphology, and cause. Aortic aneurysms can be either fusiform or saccular. *Fusiform* aneurysms, the more common type, are symmetrically dilated with involvement of the entire aortic circumference. *Saccular* aneurysms exhibit a focal outpouching. These lesions represent “true” aneurysms, with an intact but dilated aortic wall involving all layers. In contrast, in *pseudoaneurysms* (“false” aneurysms), bleeding has occurred through the aortic wall and resulted in a contained periaortic hematoma in continuity with the aortic lumen. Pseudoaneurysms may result from trauma or contained rupture of an aortic aneurysm, dissection, or penetrating ulcer.

Abdominal Aortic Aneurysms

AAAs are defined by an abdominal aorta greater than 3.0 cm in diameter.[3] AAAs occur in 3% to 9% of men older than 50 years and are the most common form of aortic aneurysms. Most AAAs (>80%) arise in the infrarenal aorta (**eFig. 63.1**), but up to 10% may involve the pararenal or visceral aorta and may extend into the thoracoabdominal segment. AAAs are approximately five times more prevalent in men than in women and are strongly associated with age, with most occurring in those older than 60 years.[4] AAAs also are strongly associated with cigarette smoking; current and former smokers have a fivefold increased risk compared to nonsmokers. Other risk factors include emphysema, hypertension, and hyperlipidemia. Up to 20% of patients with AAAs describe a family history of AAA, denoting a heritable component.



EFIGURE 63.1 Three-dimensional computed tomographic angiogram demonstrating a ruptured infrarenal abdominal aortic aneurysm with extravasation managed by way of successful endovascular stent-graft treatment. (From Steuer J, Lachat M, Veith FJ, Wanhainen A. Endovascular grafts for abdominal aortic aneurysm. Eur Heart J 2016;37:145-51. Picture courtesy Kevin Mani, Uppsala, Sweden.)

Pathogenesis

AAA formation is associated with chronic aortic wall inflammation, increased local expression of proteinases, and degradation of structural connective tissue proteins (**Fig. 63.3**). Aneurysmal dilation and rupture result from mechanical failure of medial elastin and adventitial collagen. Inflammatory cells commonly infiltrate the aortic wall. Patients with “inflammatory AAAs” may exhibit extension of this process to the periaortic retroperitoneal tissues. Matrix-degrading enzymes released by inflammatory cells lead to medial degeneration and play a role in dilation and rupture.[5] Inflammatory cells may enter the media in response to signals elaborated by medial SMCs as a result of hemodynamic stress, ischemia, autoimmune processes, or extension of intimal atherosclerosis. Proinflammatory cytokines may play a role. Although a response to both foreign antigens and microbial infection has been postulated in the development of AAAs, evidence shows that the chronic inflammation in aneurysm tissue also exhibits features of an autoimmune response. Destruction of medial elastin and a marked decrease in the concentration of elastin characterize AAAs. Experimental studies have demonstrated that damage to the elastic lamellae leads to aneurysmal dilation, and elastolytic proteinases may play a critical role. The tensile strength of the aortic wall results principally from interstitial collagen, and AAAs generally is associated with increased collagen content. Enzymes such as matrix metalloproteinases (MMPs) and elastolytic cathepsins can degrade the arterial extracellular matrix (ECM) constituents and contribute to aneurysm expansion and rupture.[5] Treatment of animals with tetracyclines and other MMP inhibitors can suppress experimental aneurysm development.[5]

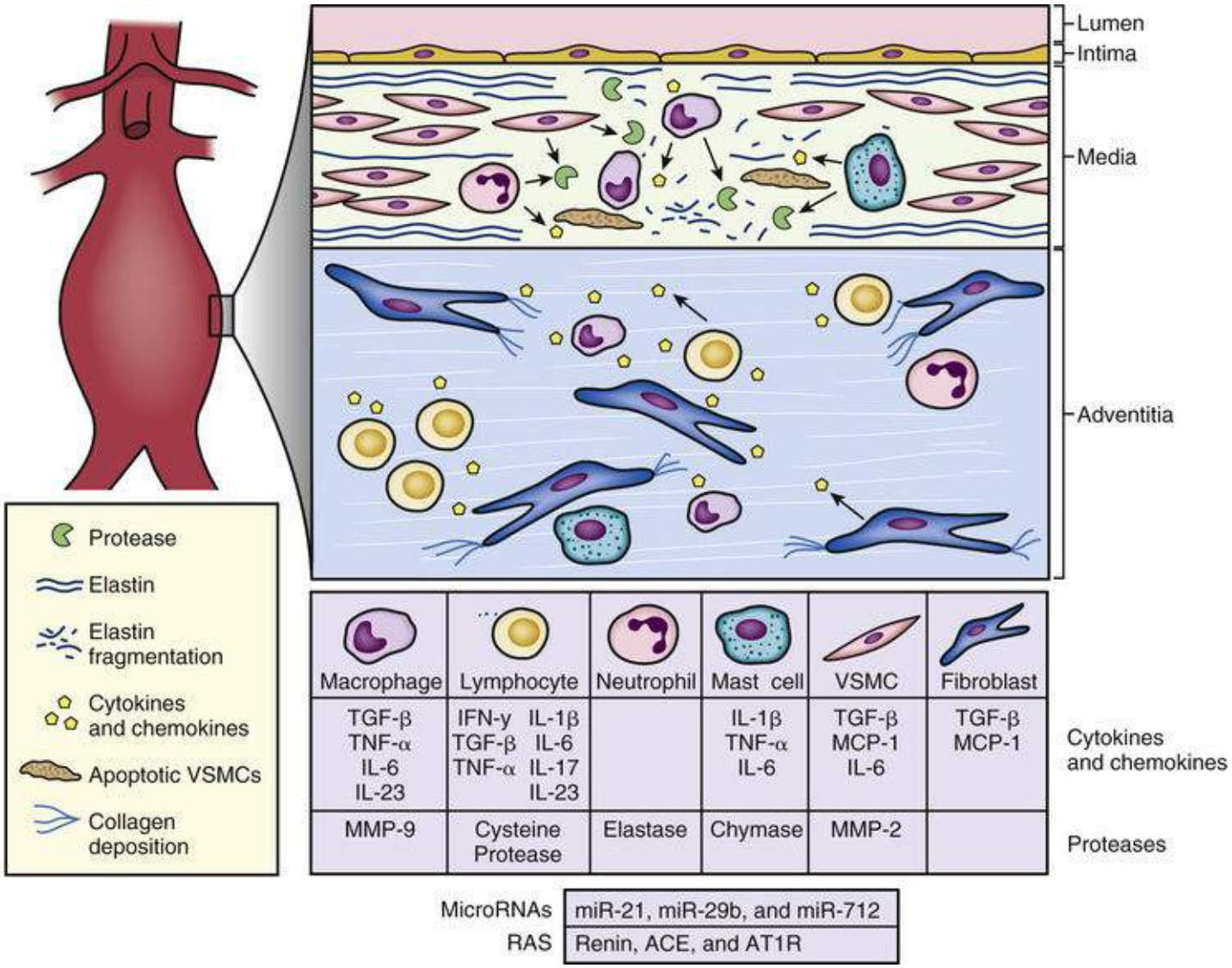


FIGURE 63.3 Pathophysiology and therapeutic targets of abdominal aortic aneurysm (AAA). Progressive dilation of the aortic wall is associated with recruitment of leukocytes, macrophage activation, and production of proinflammatory cytokines. Over years, apoptosis and cellular senescence of smooth muscle cells occurs in conjunction with infiltration of lymphocytes, mast cells, and neutrophils. Macrophages and vascular smooth muscle cells (VSMCs) also produce proenzyme forms of proteases that are activated in the extracellular space and degrade extracellular matrix proteins (elastin and interstitial collagens). Adventitial fibroblasts are presumed to promote structural repair, but the interstitial collagen becomes disorganized. The table legend illustrates major cell types involved in AAA pathogenesis, as well as select examples of future therapeutic targets that are involved in AAA pathogenesis. AT1R, Angiotensin type 1 receptor; IFN, interferon; IL, interleukin; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; miR, microRNA; RAS, renin-angiotensin system; TGF, transforming growth factor; TNF, tumor necrosis factor. (From Davis FM, Rateri DL, Daugherty A. Mechanisms of aortic aneurysm formation: translating preclinical studies into clinical therapies. Heart 2014;100:1498-505.)

The natural history of AAAs involves a balance between degradative and reparative processes. Because vascular SMCs normally produce elastin and collagen during aortic development and SMCs predominate within the elastic media, they may mediate repair of connective tissue within AAAs. Depletion of medial SMCs characterizes AAAs. Mechanisms underlying the loss of SMCs in AAAs include *apoptosis*, which may be initiated by medial ischemia, signaling molecules, or cellular immune responses. In the absence of vasa vasorum, the nutrient supply to the media of the distal aorta depends on diffusion from the lumen, which may be jeopardized by intimal thickening and atherosclerotic plaque.

Clinical Features

AAAs develop insidiously over several years and rarely cause symptoms in the absence of distal

thromboembolism, rapid expansion, or rupture. Although large AAAs are at substantial risk of rupturing, the vast majority of AAAs are small. Most AAAs are detected by screening studies or as an incidental finding on imaging studies performed for another purpose.

Physical examination is insensitive in detecting AAAs, but abdominal palpation may reveal a pulsatile epigastric or periumbilical mass. Only 30% to 40% of AAAs are noted on physical examination, although aneurysms larger than 5 cm are detected in approximately 75% of patients, depending on body habitus.[4] The mural thrombi associated with AAAs may lead to thromboembolism, occurring in 2% to 5% of patients. AAA is present in up to 85% of patients with a femoral artery aneurysm and 60% of patients with a popliteal artery aneurysm.[4] Patients with AAA may have coexisting thoracic aortic aneurysm (TAA) disease (25%) and an increased prevalence of iliac and popliteal aneurysms.[1]

Diagnostic Imaging

Abdominal ultrasound (US) can detect AAAs with high accuracy and is preferred over CT in screening for AAAs because US is inexpensive, noninvasive, and avoids radiation and contrast agents.[4] Because US-derived measurements of AAA diameter are less accurate than by CT or MRI, many use US for follow-up of small AAAs and CT or MRI for larger AAAs. Abdominal CT is accurate in both detection of AAAs and measurement of aneurysm diameter. When combined with radiographic contrast enhancement, thin-slice techniques, and three-dimensional reconstructions with measurements obtained perpendicular to the centerline of the aorta, CT angiography (CTA) is more accurate than US. CTA is especially useful in demonstrating the relationship of the AAA to the renal, visceral, and iliac arteries and patterns of mural thrombus, calcification, or coexisting occlusive atherosclerosis, which might influence AAA repair. Three-dimensional reconstructions enhance visualization of the AAA before endovascular aneurysm repair (EVAR) (**eFig. 63.1**). CT can also assess AAA variants, such as inflammatory AAAs and mycotic aneurysms. Magnetic resonance angiography (MRA) also has high accuracy in detecting AAAs, measuring aneurysm diameter, and planning treatment. MRA avoids exposure to radiation and iodine-based contrast material. CTA has superseded aortography in the evaluation and management of AAAs. In patients undergoing EVAR, aortography is an initial step in the operative procedure. It is also used in subsequent interventions following EVAR, such as embolization of the lumbar or iliac artery branches.

Screening

Screening for AAAs with ultrasound, coupled with repair of AAAs above a size threshold, has reduced AAA-related deaths.[3,4] The incidence of screening-detected AAAs ranges from 1 per 1000 in adults younger than 60 years to 7 per 1000 in those in their mid-60s, but it may be as high as 10% in those with risk factors such as older age, male sex, smoking, family history, history of other aneurysms, hypertension, and atherosclerosis. Aneurysm screening is associated with a 50% reduction in rupture and a 50% decrease in aneurysm-related mortality.[3,4] Despite the cost-effectiveness of AAA screening in men 65 to 74 years of age, routine screening for AAAs in women remains controversial[3] and has not demonstrated a survival benefit.[4] AAAs occur about 10 years later in women than men, and rates of rupture and mortality from rupture are both higher in women. The U.S. Preventive Services Task Force (PSTF) recommended a one-time ultrasound screening for AAAs in men 65 to 75 years of age with a history of smoking.[3,4] The Society for Vascular Surgery (SVS) recommends a one-time screening for AAAs in all men and women 65 or older with a history of tobacco use or a family history of AAA.

Genetics/Molecular Genetics

Several genetic disorders are associated with thoracic aortic aneurysms (TAAs), including Marfan syndrome, Loeys-Dietz syndrome, and vascular Ehlers-Danlos syndrome, but less frequently with aneurysms of the abdominal aorta. Up to 20% of patients with an infrarenal AAA have a family history of AAAs, suggesting an inherited component. Several genetic variants, including *DAB2IP*, *LRP1*, *CDKN2B-AS1*, *CNTN3*, *LAP*, *IL6R*, and the *SORT1* locus, are associated with AAA.[6]

Natural History

AAAs gradually expand over years at an average rate for AAAs 3.0 to 5.5 cm in diameter of 0.2 to 0.3 cm/year, increasing as aortic diameter increases.[3] Not all AAAs follow a linear or consistent rate of expansion. Although the aneurysm diameter is most important in predicting rupture, size alone may not predict risk for rupture. Wall tension, wall stiffness, and peak wall stress may all contribute. Some have suggested that aortic diameter indexed to body surface area (aortic size index) may be a better predictor of rupture for women than diameter alone.[7] The estimated 1-year risk for rupture is 10% to 20% for AAAs 6.0 to 7.0 cm in diameter, 20% to 40% for AAAs 7.0 to 8.0 cm, and 30% to 50% for AAAs larger than 8.0 cm. The 5-year risk for rupture is approximately 5% for AAAs 3.0 to 4.0 cm in diameter, 10% to 20% for AAAs 4.0 to 5.5 cm, 30% to 40% for AAAs 5.5 to 6.0 cm, and greater than 80% for AAAs larger than 7.0 cm.[4]

Ruptured Abdominal Aortic Aneurysm

Symptoms directly attributable to AAAs usually relate to rupture of the aneurysm or rapid expansion and impending rupture. Rupture of AAAs into the peritoneal cavity results in acute hemorrhage, severe abdominal pain, and hypotension caused by exsanguination (**eFig. 63.1**). Rupture into the retroperitoneum may result in a temporarily contained periaortic hematoma, with severe abdominal or back pain that may radiate to the flank or groin. A tender pulsatile abdominal or flank mass may be present, along with hypotension and/or syncope. Approximately 30% to 50% of patients with ruptured AAAs die before hospitalization, and an additional 30% to 40% die after reaching a hospital but before treatment.[4] The operative mortality rate for open surgical repair (OSR) after AAA rupture is 40% to 50%, but may be lower with EVAR.[3,4] Stable patients with symptomatic but apparently unruptured AAAs should undergo CT to determine whether rupture has occurred. Because emergency repair entails a much higher mortality rate, in the absence of rupture, it may be prudent in certain cases to delay surgical repair for 4 to 24 hours to optimize conditions under close monitoring.[4]

Management

Surveillance and Medical Therapy

Patients with small AAAs can be observed safely with imaging surveillance. In general, repair should be considered for asymptomatic aneurysms greater than 5.0 to 5.5 cm in diameter.[3,4] Symptomatic aneurysms and those with rapid growth (>1 cm/yr) require more urgent consideration. In patients with AAAs larger than 4.5 cm, CT is preferred over US for more accurate measurement of AAA size. Surveillance of aneurysms until the diameter exceeds 5.5 cm yields a low rate of rupture (approximately 1% per year).[4] The SVS suggests the following surveillance imaging strategy for AAAs of various sizes: 2.5 to 2.9 cm, every 7 years; 3.0 to 3.9 cm, every 3 years; 4.0 to 4.9 cm, every 12 months; and 5.0 to 5.4 cm, every 6 months. Uncertainty exists regarding the ultimate therapy for AAAs between 4.5 and 5.4 cm, and recommendations must be individualized. Young, healthy patients—especially women—with AAAs

between 5 and 5.4 cm may benefit from early repair.[4]

Several steps are recommended for patients with AAAs to help minimize the risk for expansion of the aneurysm. Smoking cessation is important because ongoing tobacco use is linked to more rapid rates of AAA expansion and rupture. Patients with AAAs and coexisting atherosclerotic disease will likely benefit from statin therapy, which might also slow AAA growth.[5] Patients with small AAAs should exercise regularly because moderate physical activity does not adversely influence the risk for rupture and may limit AAA growth.

Experimental Therapy.

The potential use of pharmacologic therapies to suppress the growth rate of small AAAs is of great interest.[5] One of the earliest approaches suggested was the use of beta-adrenergic receptor–blocking agents (beta blockers) to diminish aortic stress. Although successful in animal models of AAAs, clinical trials demonstrated no benefit of propranolol in patients with small AAAs.[4] Suppression of proteinases involved in ECM degradation is another approach.[5] Further investigation is needed to determine whether MMP inhibitors such as doxycycline can reduce the rate of AAA expansion in humans. Clinical trials have not demonstrated any utility of angiotensin-converting enzyme (ACE) inhibitors in slowing the growth of small AAAs.[8]

Surgery

The decision to undergo elective repair of an asymptomatic AAA depends on life expectancy and the estimated risk for rupture, balanced against the estimated risks associated with AAA repair. Patients with AAAs often have underlying coronary artery disease (CAD), and because postoperative myocardial infarction (MI) increases subsequent perioperative morbidity and mortality, attention is directed toward CAD before elective AAA repair. Current guidelines state that in the absence of an active cardiac condition, further noninvasive testing is indicated only if it will change management. Some patients benefit from preoperative evaluation for coronary ischemia and treatment (**see Chapter 11**). Perioperative medical management to reduce cardiac risk in patients undergoing AAA repair may include continuation of beta blockers, statins, and/or aspirin. AAAs can be treated surgically by OSR or EVAR. Selection of the approach depends on the individual anatomy and on secondary factors such as patient age and estimated risks associated with anesthesia and surgery, with most patients currently undergoing EVAR.[3,4]

Techniques and Outcomes.

For OSR of infrarenal AAAs, the abdominal aorta is approached through a transperitoneal or left retroperitoneal exposure using a tube or bifurcated prosthetic graft. The operative mortality rate for OSR ranges from 1% to 4% in reports from single-institution centers of excellence, and mortality rates in large databases range from 4% to 8%.[4] Operative complication rates range from 10% to 30%, with morbidity related to cardiac, pulmonary, and renal complications and colonic ischemia. Because outcomes with OSR relate to hospital and surgeon volumes, OSR for AAAs should optimally be performed at centers with demonstrable operative mortality rates lower than 5%. Late complications develop in as many as 15% to 30% of patients in long-term follow-up after OSR for AAAs. Such complications include problems related to the abdominal incision (including hernia and bowel obstruction), perianastomotic aneurysms (including false aneurysms secondary to disruption of the suture line and true aneurysms secondary to proximal aortic degeneration), graft infection, graft-enteric fistula, and graft limb occlusions

with lower extremity ischemia. Late aneurysm formation at anastomotic sites after OSR is uncommon and affects 1%, 5%, and 20% of patients, respectively, at 5, 10, and 20 years postoperatively.[4] After open AAA repair, patients should generally have clinical follow-up with CT at 5-year intervals.

Endovascular Abdominal Aortic Aneurysm Repair.

In patients with suitable anatomy, EVAR offers a less invasive alternative to OSR. EVAR requires adequate nonaneurysmal proximal and distal attachment sites.[4] Randomized controlled trials (RCTs) comparing EVAR with OSR for asymptomatic infrarenal AAAs have demonstrated a lower 30-day mortality rate with EVAR than with OSR.[3,9] A significantly higher number of repeated interventions, however, occurred in the EVAR group.[9,10] In an analysis of 79,932 Medicare patients, EVAR had a similar early benefit in perioperative mortality (1.6% versus 5.2%) and complications, demonstrating the generalizability of the RCT data.[9] At long-term (8-year) follow-up, however, AAA-related or all-cause mortality did not differ significantly between EVAR and OSR.[9] EVAR patients had more aneurysm-related reinterventions.[9]

Observational studies report a mortality benefit of EVAR over OSR in ruptured AAA[10] (**eFig. 63.1**). The IMPROVE trial randomized ruptured AAAs to an EVAR-first strategy versus OSR and demonstrated no improvement in 30-day mortality.[10] Although RCTs have yet to demonstrate a survival benefit of EVAR for ruptured AAA, guidelines recommend treatment of ruptured AAA in centers with a protocol for rapid evaluation and management, preferably with EVAR for suitable patients.

Appropriate patient selection permits low perioperative mortality (1% to 2%) and complication (10% to 15%) rates with EVAR for elective AAA repair.[4] Currently, the options of EVAR and OSR are considered in “medically fit” patients with suitable anatomy. Most patients select EVAR because of its early perioperative advantages and the “less invasive” nature of the procedure. At follow-up after 6 and 8 years in the DREAM and EVAR-1 studies, EVAR had more late complications and secondary reinterventions, and the initial reduction in mortality with EVAR did not persist after a few years.[4,9,10]

“Endoleaks” (persistent blood flow in the aneurysm sac outside the endograft) develop in almost 25% of patients at follow-up and can cause of aortic rupture after EVAR.[4] Type I endoleaks, which result from loss of complete sealing at the proximal (type Ia) or distal (type Ib) end of the stent-graft, lead to increased pressure in the aneurysm sac and are associated with increased risk for rupture[3] (**Fig. 63.4**). Type II endoleaks, the most common, result from retrograde filling of the aneurysm sac by the lumbar or inferior mesenteric arteries. Type III endoleaks are caused by separation of components or disruption of the endograft fabric and require treatment, usually by relining with a stent graft. Type IV endoleaks are related to blood seeping through porous graft material and are self-limited. *Endotension,* an enlarging AAA after EVAR without a demonstrated endoleak and with a diameter increased to greater than 10 mm, usually requires repair. Late complications of EVAR (endograft migration, limb thrombosis), implant-related complications, and graft infection can also occur. Monitoring the durability of the clinical results requires long-term radiographic surveillance. Imaging with contrast-enhanced CTA is typically performed at 1 month and annually after implantation of the device.[3] The presence of endoleak may mandate more frequent surveillance. Color duplex ultrasonography to detect endoleaks and AAA enlargement may be used in those with stable imaging findings after 1 year. In conditions that limit the use of contrast material, duplex ultrasound may be combined with non–contrast-enhanced CT.

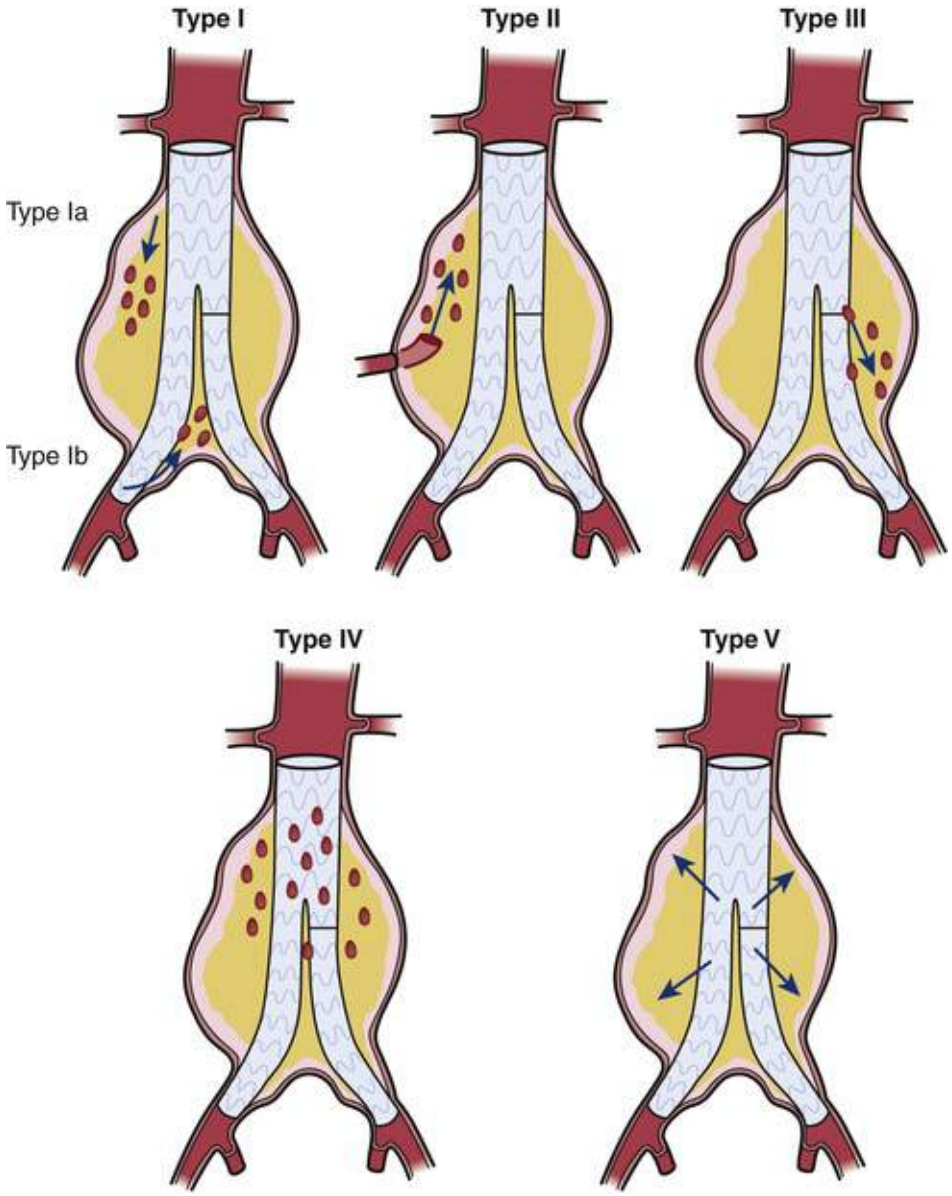


FIGURE 63.4 Classification of endoleaks. **Type I:** Leak at graft attachment site above, below, or between graft components (*Ia*: proximal attachment site; *Ib*: distal attachment site; *Ic*: iliac occluder). **Type II:** Branch leaks without attachment site leaks. Retrograde filling of aneurysm sac through single-branch (*IIa*) or multiple-branch (*IIb*) vessels. **Type III:** Leak through mechanical defect in graft, mechanical failure of the stent-graft by junctional separation of the modular components (*IIIa*), or fractures or fabric holes in the endograft (*IIIb*). **Type IV:** Leak through graft fabric as a result of graft porosity. **Type V:** Continued expansion of aneurysm sac without demonstrable leak on imaging (endotension, controversial). A primary endoleak is present from time of graft placement. A secondary endoleak appears after a prior negative computed tomographic angiogram. (Modified from White GH, May J, Petrasek P. Specific complications of endovascular aortic repair. Semin Interv Cardiol 2000;5:35-46.)

Widespread use of EVAR has demonstrated a reduction in early morbidity and mortality in patients with AAAs, especially in older adults. This advantage does not persist in long-term follow-up, however.[9] EVAR should ideally be performed at centers with very low in-hospital mortality (<3%) and a primary conversion rate to OSR of less than 2% for elective repair.[4] The development of fenestrated and branched endografts is extending EVAR to increasingly challenging aneurysms that extend more proximally to involve the renal and mesenteric vessels.

Thoracic Aortic Aneurysms

TAAs have an estimated incidence of at least 5 to 10 per 100,000 person-years.[11] The cause, natural history, and treatment vary depending on the location of the TAA. Aortic root or ascending aortic

aneurysms are most common (approximately 60%), followed by aneurysms of the descending aorta (approximately 35%) and aortic arch (<10%).[2] *Thoracoabdominal aortic aneurysm* (approximately 10%) refers to descending thoracic aneurysms that extend distally to involve the abdominal aorta.

Cause and Pathogenesis

Causes of TAAs include heritable disorders, genetic (congenital) disorders, and degenerative (formerly known as "atherosclerotic"), mechanical, inflammatory, and infectious diseases. Many of the genetic disorders preferentially involve the aortic root and ascending aorta, but some may involve the arch and descending aorta. Risk factors for TAAs include smoking, hypertension, age, COPD, CAD, and family history. In series of AAA, 20% to 27% of patients had either synchronous or metachronous TAA.[1] *Cystic medial degeneration* (CMD) describes degeneration and fragmentation of elastic fibers, loss of SMCs, increase in deposition of collagen, and replacement with interstitial "cysts" of mucoid-appearing basophilic-staining ECM (**see Fig. 63.2**). Patients with Marfan syndrome and many other genetically triggered TAA diseases have aortic CMD. Aging is associated with some degree of CMD, a process that may be accelerated by hypertension. These changes lead to progressive weakening of the aortic wall and may result in dilation and aneurysm formation.

Genetically Triggered Thoracic Aortic Aneurysm Disorders

Many disorders of the thoracic aorta are related to a genetic or heritable disorder, some of which are associated with multisystem syndromic features and others with thoracic aortic disease and branch vessel disease alone (nonsyndromic)[12] (**Table 63.1**). The phenotype in certain conditions may be subtle, and intrafamilial variability is common, highlighting the importance of a careful physical examination.[13] These disorders are associated with abnormalities in the aortic media, ECM proteins, vascular SMCs, or contractile proteins.[6,12] Such disorders include Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, familial thoracic aortic aneurysm and dissection syndrome, bicuspid aortic valve disease, Turner syndrome, and the aortopathy associated with many congenital heart diseases. The timing of prophylactic surgery for aneurysm disease in patients with these conditions depends on the gene defect and other factors, including aortic diameter, rate of aortic growth, family history, age, sex, and patient and physician preferences[12] (**Table 63.2**).

TABLE 63.1

Thoracic Aortic Aneurysm (TAA) Syndromes and Diseases from a Heritable or Genetic Cause

GENE (PROTEIN)	SYNDROME OR DISEASE	CLINICAL FEATURES
Extracellular Matrix Protein Genes		
FBN1 (fibrillin-1)	Marfan syndrome	Aortic root aneurysm, AD, TAA, MVP, long bone overgrowth, scoliosis, pectus deformities, ectopia lentis, myopia, tall stature, PTX
FBN2 (fibrillin-2)	Congenital contractural arachnodactyly, Beals syndrome	MVP, arachnodactyly, marfanoid habitus, digital contractures, mild aortic dilation
COL3A1 (type 3 procollagen)	Vascular Ehlers-Danlos syndrome	TAA, AAA, arterial rupture, AD, MVP, bowel and uterine rupture, PTX, translucent skin, atrophic scars, small joint hypermobility, easy bruising
EFEMP2 (fibulin-4)	Cutis laxa	TAA, arterial tortuosity, arterial stenosis, hypertelorism, arachnodactyly
MFAP5 (microfibrillar-associated protein 5)	FTAAD, AAT9	TAA, AD
TGF-β Signaling Pathway Genes		
TGFBR1 (TGF-β receptor 1)	Loeys-Dietz syndrome type 1, Furlong syndrome, FTAAD, AAT5	TAA, branch vessel aneurysms, AD, arterial tortuosity, craniosynostosis, hypertelorism, bluish sclera, bifid/broad uvula, translucent skin, visible veins, MVP, clubfoot, easy bruising
TGFBR2 (TGF-β receptor 2)	Loeys-Dietz syndrome type 2, FTAAD, AAT3	TAA, branch vessel aneurysms, AD, arterial tortuosity, craniosynostosis, hypertelorism, bluish sclera, bifid/broad uvula, translucent skin, visible veins, MVP, clubfoot, easy bruising
SMAD3 (SMAD3)	Aneurysm-osteoarthritis syndrome, LDS 3	TAA, branch vessel aneurysms, AD, arterial tortuosity, overlapping phenotype with LDS 1 and 2 and marfanoid features, bifid uvula, premature osteoarthritis, osteoarthritis dissecans
TGFB2 (TGF-β 2)	FTAAD, LDS 4	TAA, arterial tortuosity, AD, MVP, PDA, overlapping features of MFS and LDS, bifid uvula, hypertelorism
TGFB3 (TGF-β 3 ligand)	Rienhoff syndrome, LDS 5	TAA, AAA, AD, hypertelorism, bifid uvula, overlapping features of MFS and LDS, MVP
SKI (v-SKI sarcoma oncogene homolog)	Shprintzen-Goldberg syndrome (velocardiofacial syndrome)	TAA, marfanoid habitus, craniosynostosis, intellectual disability, skeletal muscle hypotonia
SLC2A10 (glucose transporter 10)	Arterial tortuosity syndrome	Widespread aortic and branch vessel tortuosity, TAA, aortic and arterial dissection, keratoconus, marfanoid habitus, joint contractures
SMAD2 (SMAD2)	FTAAD	TAA, AD, cervicocranial arterial dissection
SMAD4 (SMAD4)	Juvenile polyposis syndrome, HHT, FTAAD	Telangiectasia, AVMs, TAA, AD
Vascular Smooth Muscle Contraction Components or Cytoskeleton Genes		
ACTA2 (α-smooth muscle actin)	FTAAD, AAT6	TAA, AD, BAV, moyamoya disease, premature CAD and CVD, livedo reticularis, iris flocculi
MYH11 (myosin heavy chain-11)	FTAAD, AAT4	TAA, AD, PDA
MYLK (myosin light chain kinase)	FTAAD, AAT7	AD at relatively small aortic size
PRKG1 (protein kinase cGMP-dependent)	FTAAD, AAT8	Aortic root aneurysm and AD
MAT2A (MAT IIα)	FTAAD	TAA, AD, BAV
FLNA (filamin A)	EDS with periventricular nodular heterotopia and cardiac valve dysplasia	X-linked, TAA, BAV, MV disease, seizures, joint hypermobility
Bicuspid Aortic Valve–Associated Ascending Aortic Aneurysm		
NOTCH1 (NOTCH1)	BAV with TAA	Aortic stenosis, TAA
TGFBR1, TGFBR2, TGFB2, TGFB3, ACTA2, MAT2A, GATA5, SMAD6, LOX	BAV with TAA	Syndromic and nonsyndromic FTAA with increased frequency of BAV
XO, Xp	Turner syndrome	BAV, COA, TAA, AD, short stature, lymphedema, webbed neck, premature ovarian failure; affects 1 in 2500 live-born girls

AAA, Abdominal aortic aneurysm; *AAT,* aortic aneurysm syndrome; *AD,* aortic dissection; *AVM,* arteriovenous malformation; *BAV,* bicuspid aortic valve; *CAD,* coronary artery disease; *COA,* coarctation of the aorta; *CVD,* cerebrovascular disease; *EDS,* Ehlers-Danlos syndrome; *FTAAD,* familial thoracic aortic aneurysm and dissection syndrome; *HHT,* hereditary hemorrhagic telangiectasia; *LDS,* Loeys-Dietz syndrome; *MFS,* Marfan syndrome; *MV,* mitral valve; *MVP,* mitral valve prolapse; *PDA,* patent ductus arteriosus; *PTX,* pneumothorax; *TAA,* thoracic aortic aneurysm; *TGF,* transforming growth factor.

TABLE 63.2

Size Threshold for Prophylactic Aortic Root or Ascending Aortic Aneurysm Resection for Various Conditions

CONDITION	SIZE THRESHOLD*
Degenerative aneurysm	≥5.5 cm
Bicuspid aortic valve	≥5.5 cm
Bicuspid aortic valve with risk factors or low surgical risk†	≥5.0 cm
Bicuspid aortic valve requiring aortic valve replacement	>4.5 cm
Marfan syndrome	≥5.0 cm
Marfan syndrome with risk factors‡	>4.5 cm
Loeys-Dietz syndrome§	4.0 to 4.5 cm
Familial thoracic aortic aneurysm syndromes¶	4.5 to 5.0 cm
Turner syndrome	>2.5 cm/m^2

*Lower thresholds for intervention may be considered according to body surface area in patients of small stature or in the case of rapid growth of the aorta. Age, body size, rapid growth, family history, risk of surgery, and patient and physician wishes may influence aortic size threshold.

†Family history of aortic dissection or aortic growth rate of 0.5 cm or more per year or if the patient is at low surgical risk (<4%) and the surgery is performed by an experienced aortic surgical team in a center with established expertise in these procedures. Other risk factors for aortic dissection include coarctation of the aorta, hypertension, and the root phenotype of bicuspid aortic valve.

‡Family history of aortic dissection or rapid aortic growth (>3 mm/yr), or severe aortic or mitral regurgitation. If pregnancy desired, consider prophylactic aortic surgery for aortic diameter of 4.0 to 4.5 cm.

§It is reasonable to consider surgical repair of the aorta in adults with Loeys-Dietz syndrome or a confirmed *TGFBR1* or *TGFBR2* mutation with aortic diameter of 4.2 cm or more by transesophageal echocardiogram or 4.4 to 4.6 or more by CT or MRI. Aortic surgery at smaller diameters may be recommended when there are severe craniofacial features, rapid growth, or a family history of aortic dissection.

¶Surgical thresholds vary depending on the specific gene mutation involved. TAA caused by *ACTA2*, *SMAD3*, and *MYLK* may lead to aortic dissection at relatively small aortic diameters.

Modified from Erbel R et al. 2014 ESC guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2873-926; Hiratzka LF et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. Circulation 2010;121:e266-369; and Hiratzka et al. Surgery for aortic dilatation in patients with bicuspid aortic valves: a statement of clarification from the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;67:724-31.

Marfan syndrome (MFS), an autosomal dominant disorder of connective tissue, results from abnormal fibrillin-1 caused by mutations in the *FBN1* gene.[12] Aortic dilation in MFS affects most prominently the sinuses of Valsalva (**Fig. 63.5**) (Video 63.1), but distal aortic aneurysms and dissections may occur. In addition to directing elastogenesis and providing structural support to tissues, fibrillin-1 interacts with latent transforming growth factor beta (TGF-β)–binding proteins and controls the activation and signaling of TGF-β. The abnormal fibrillin-1 in MFS leads to excess free TGF-β, which promotes aortic disease (**Fig. 63.6**). Angiotensin interacts with TGF-β signaling, and blocking TGF-β, whether by neutralizing antibody or by the angiotensin receptor blocker (ARB) losartan, attenuates or prevents aortic aneurysm formation in MFS mice.[12] In children with MFS and aggressive aortic disease, ARB therapy stabilized aortic root size.[14] However, in randomized trials, there was no significant difference in rate of aortic dilation in Marfan patients treated with atenolol or losartan[14,15] (**eFig. 63.2**). In the Dutch Marfan trial comparing the addition of losartan to standard care (using beta blocker in >70%), losartan therapy did reduce aortic growth rate.[1,16] At present, maximal-dose beta-blocker therapy or ARB treatment in MFS is recommended to lessen aortic growth rate. An upcoming meta-analysis will explore subsets of patients who may benefit from a specific treatment.[14,15]

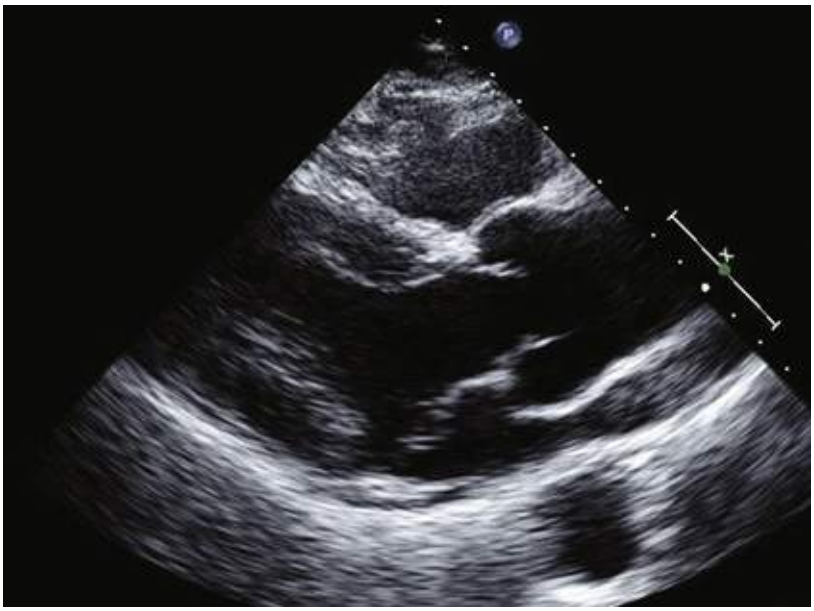


FIGURE 63.5 Transthoracic echocardiogram of a dilated aortic root in a patient with Marfan syndrome. The dilation is most pronounced in the sinuses of Valsalva, and the aorta narrows above the sinotubular junction.

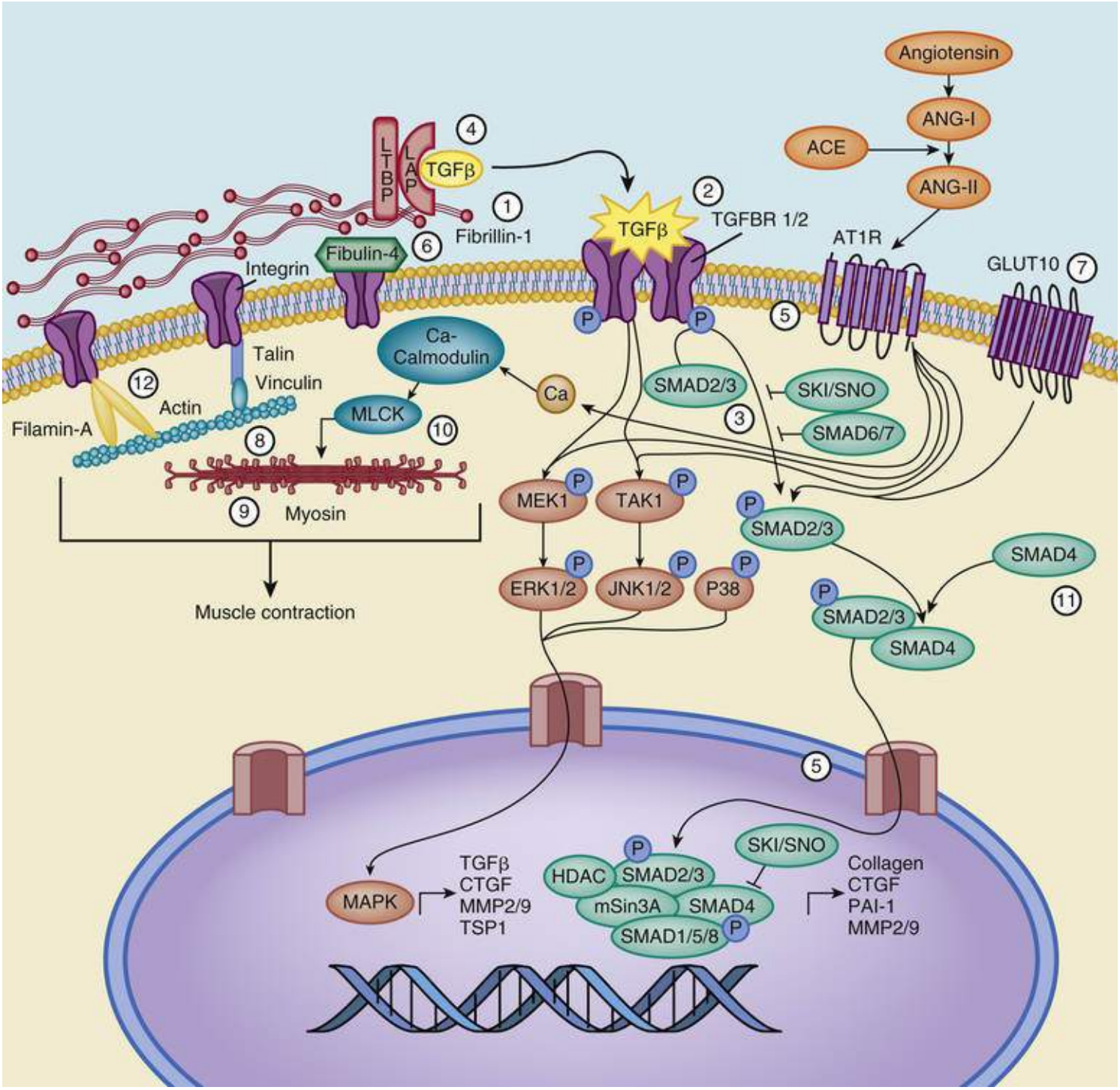
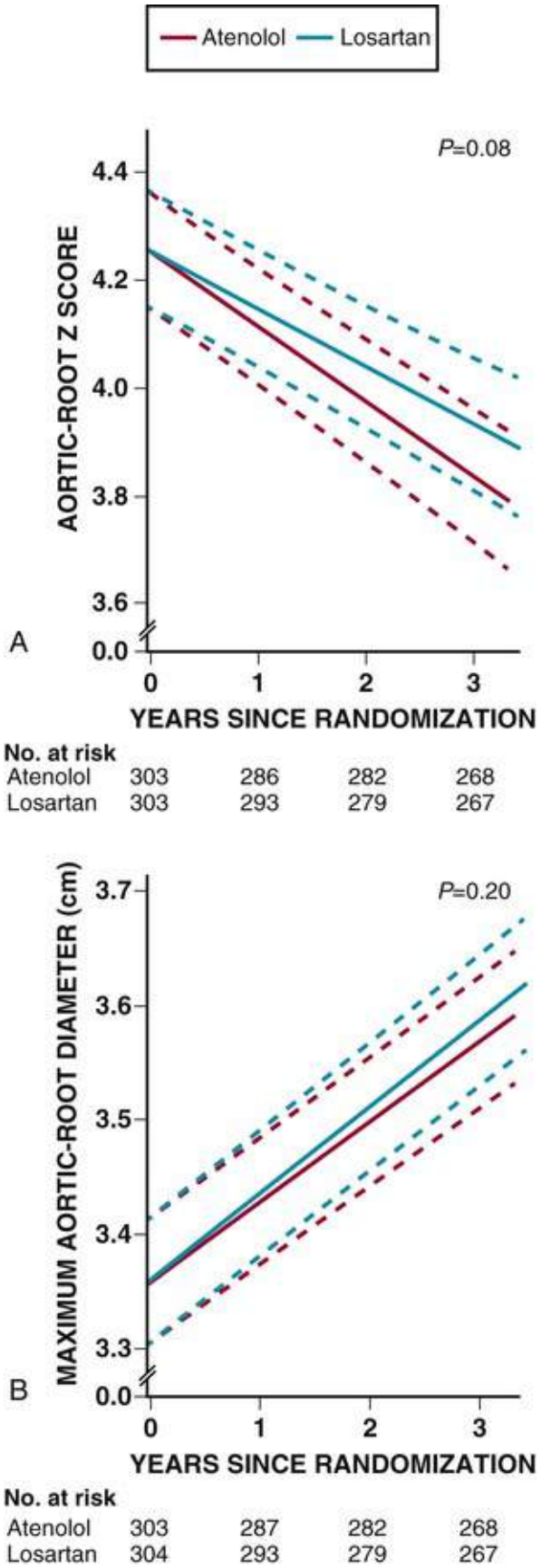


FIGURE 63.6 Pathways implicated in heritable thoracic aortic aneurysm diseases (**see also Table 63.1**). *Numbers* indicate the corresponding syndrome caused by mutations in the protein: *1,* Marfan syndrome; *2,* Loeys-Dietz syndrome type 1 or 2; *3,* Loeys-Dietz syndrome type 3; *4,* Loeys-Dietz syndrome type 4; *5,* Shprintzen-Goldberg syndrome; *6,* cutis laxa type 1B; *7,* arterial tortuosity syndrome; *8, 9,* and *10,* familial thoracic aortic aneurysms and dissections; *11,* Myhre syndrome, juvenile polyposis syndrome, and hemorrhagic telangiectasia syndrome; *12,* Ehlers-Danlos–related syndrome with periventricular nodular heterotopia. *ACE,* Angiotensin-converting enzyme; *ANG,* angiotensin; *ERK,* extracellular signal–regulated kinase; *HDAC,* histone deacetylase; *JNK,* Jun N-terminal kinase; *MAPK,* mitogen-activated protein kinase; *MEK,* mitogen-activated protein kinase/extracellular signal–regulated kinase; *MLCK,* myosin light chain kinase; *MMP,* matrix metalloproteinase; *PAI,* plasminogen activator inhibitor; *TAK,* transforming growth factor-β–activated kinase; *TGF,* transforming growth factor; *TGFBR,* transforming growth factor-β receptor; *TSP,* thrombospondin. (From Gillis E, Van Laer L, Loeys BL. Genetics of thoracic aortic aneurysm: at the crossroads of transforming growth factor-beta signaling and vascular smooth muscle contractility. Circ Res 2013;113:327-40.)



EFIGURE 63.2 Atenolol versus losartan in Marfan syndrome trial. Change in aortic-root *z* score **(A)** and aortic-root diameter **(B),** according to treatment group. Both treatment arms demonstrated a reduction in aortic-root *z* scores over time, consistent with a reduction in aortic growth rate relative to body growth.
(From Lacro RV, Dietz HC, Sleeper LAet al. Atenolol versus losartan in children and young adults with Marfan's syndrome. N Engl J Med 2014;371:2061-71.)

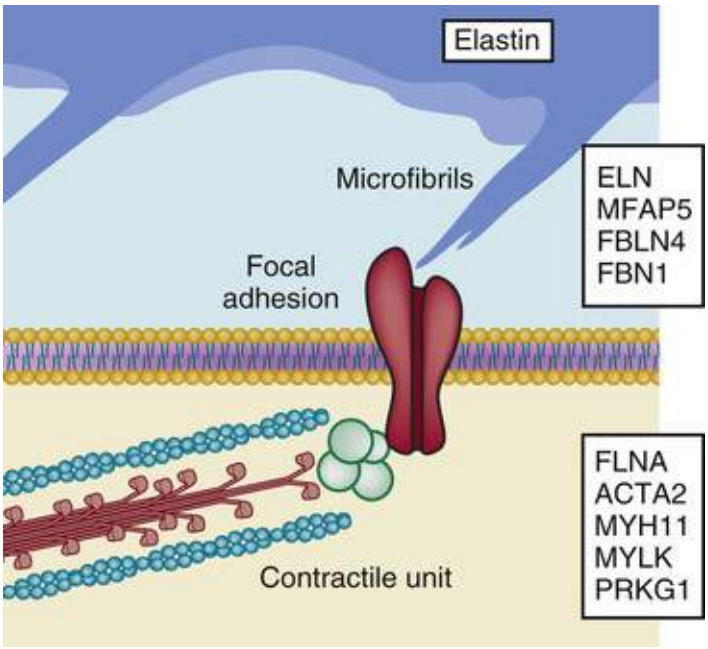
Loeys-Dietz syndrome (LDS), caused by mutations in *TGFBR1* and *TGFBR2*, has craniofacial abnormalities (hypertelorism, bifid/broad uvula, cleft palate, craniosynostosis), arterial tortuosity, and aneurysms and dissections of the aorta and branch vessels.[1,12,17] Patients with LDS may have cutaneous

features, including easy bruisability, hyperlucent skin with easily visible veins, and facial milia. The diseased tissues of patients with LDS exhibit excess TGF-β signaling[12] (**Fig. 63.6**). LDS has a more aggressive vascular phenotype than MFS, with dissections occurring at smaller sizes and younger ages. *TGFBR2* mutations may have a more aggressive phenotype than *TGFBR1* mutations, especially in men.[12] Aortic surgery is recommended at aortic root dimensions of 4 to 4.5 cm, especially when more severe craniofacial features are present.[1,17]

Aneurysms-osteoarthritis syndrome (AOS), also called *LDS3* and familial thoracic aortic aneurysm and dissection syndrome (FTAAD), results from *SMAD3* mutations and involves early severe osteoarthritis and osteochondritis dissecans, skeletal and cutaneous features of LDS, and arterial tortuosity, aneurysms, and dissections of the aorta and branch vessels.[1,17] AOS also may have an aggressive aortic phenotype and may merit aortic surgery at smaller aortic root dimensions.[1,12]

Vascular Ehlers-Danlos syndrome (vEDS) is caused by mutations in *COL3A1* that result in abnormal type III procollagen synthesis and is associated with aortic aneurysms and dissection. Individuals with vEDS have risk for spontaneous arterial dissection and rupture, often involving medium-sized arteries. Aortic root disease is less common, with more frequent involvement of the descending and abdominal aorta and branch vessels. Unlike MFS and LDS, the abnormal arteries in patients with vEDS are friable, thus making surgical repair more difficult. vEDS significantly reduces life span because of arterial disease and rupture of visceral organs.

In the absence of other phenotypic features (nonsyndromic), TAAs may be familial, with up to 20% of patients having an affected first-degree relative.[1,6,12,17] This disorder, *familial thoracic aortic aneurysm and dissection* (TAAD), is inherited as an autosomal dominant trait with decreased penetrance and variable expression (especially in women).[6] An ever-increasing number of genes have been identified that can cause familial TAAD, some of which are also associated with AAA and cerebral aneurysm[1,6,17] (**see Table 63.1**). Although TGF-β signaling abnormalities underlie the pathogenesis in certain aneurysm syndromes, defects in SMC contractile function leading to aortic aneurysm and dissection are related to *ACTA2*, *MYH11*, *MYLK*, *FLNA*, and *PRKG1* mutations[12] (**Fig. 63.6 and eFig. 63.3**). Fibrillin-1 microfibrils may participate in mechanotransduction in vascular SMCs, thereby linking fibrillin-1 in the matrix to intracellular actin filaments. *ACTA2* encodes smooth muscle alpha-actin, and mutation of this gene is the most common cause of familial TAAD; *ACTA2* mutations account for 14% of familial TAAD and is associated with livedo reticularis, iris flocculi, premature coronary and cerebrovascular disease, patent ductus arteriosus (PDA), and bicuspid aortic valves.[12,18] Aortic dissection at diameters or less than 5 cm are described, and approximately 50% of *ACTA2* patients have aortic events, with cumulative risk estimated at 76% by age 85 years.[18] First-degree relatives of individuals with unexplained TAA or dissection should undergo aortic imaging or genetic testing with mutation analysis when a known mutation is present in the family.[1,6,17]



EFIGURE 63.3 Elastin-contractile unit in smooth muscle cells. The altered genes that predispose to thoracic aortic aneurysms and acute aortic dissections are indicated (**see Table 63.1**). The location of the gene indicates where its protein product is located in the elastin-contractile unit. (From Karimi A, Milewicz D. Structure of the elastin-contractile units in the thoracic aorta and how genes that cause thoracic aortic aneurysms and dissections disrupt this structure. Can J Cardiol 2016;32:26-34.)

Bicuspid aortic valve (BAV) *disease* affects approximately 1% of the population and may be associated with ascending aortic aneurysm, coarctation of the aorta, and aortic dissection[19] (Video 63.2). The BAV exhibits abnormal leaflet folding, wrinkling, and increased leaflet doming, which can result in turbulence even in the absence of a stenotic or regurgitant lesion. Abnormal aortic wall shear stress due to helical flow patterns in the setting of bicuspid aortic valves may underlie the aortopathy of BAV disease[20,21] (**Fig. 63.7**). Ascending TAAs associated with BAVs may develop independent of valve function and may develop late after aortic valve replacement (AVR) (Video 63.3). There are multiple aortic phenotypes in BAV aortopathy, and the root phenotype (present in 10%) may have a higher aortic risk[21] (Video 63.4). The aortic dilation in BAV disease occurs most often in the proximal to middle ascending aorta, making imaging of the entire ascending aorta important in patients with BAVs.[17] CMD underlies the aortic aneurysm and risk for dissection associated with BAVs.[21] When BAV and TAA coexist, there is more CMD associated with the regurgitant than with the stenotic BAV.[21] Compared with tricuspid aortic valve (TAV) aneurysms, BAV aneurysms exhibit increased apoptosis, increased MMP-2 activity, and abnormalities in TGF-β and protein kinase C–signaling pathways.[19] The lifetime risk of aortic dissection for the BAV patient is four to eight times higher than the risk in the general population.[21] However, the risk of dissection in BAV patients followed longitudinally and undergoing elective aneurysm surgery is relatively low. Of 416 patients with BAV (age at diagnosis, 35 ±12 years) followed for a mean of 16 years, aortic dissection incidence was 3.1 cases per 10,000 patient-years, with an age-adjusted relative risk of 8.4 compared with the general population.[21] Higher rates were observed in patients age 50 or older at baseline (17.4 cases per 10,000 patient-years) and in patients with ascending aortic aneurysm at baseline (44.9 cases per 10,000 patient-years, versus age matched population risk of 0.31 per 10,000 person-years). The risk of aortic dissection in patients with BAV and an ascending aorta aneurysm of 5.3 cm is approximately 4%.[22] BAVs and ascending aortic aneurysm may be familial, inherited as an autosomal dominant disorder with variable expressivity and incomplete penetrance.[12] Gene mutations associated with BAV and TAA are listed in **Table 63.1**. Genetic heterogeneity, complexity of the trait, noncoding sequence variants, and epigenetic factors may explain the lack of an underlying

genetic pathogenesis in BAV TAA disease.[12] First-degree relatives of a patient with BAV, especially with aortopathy, should undergo evaluation for BAVs and ascending TAA.[17]

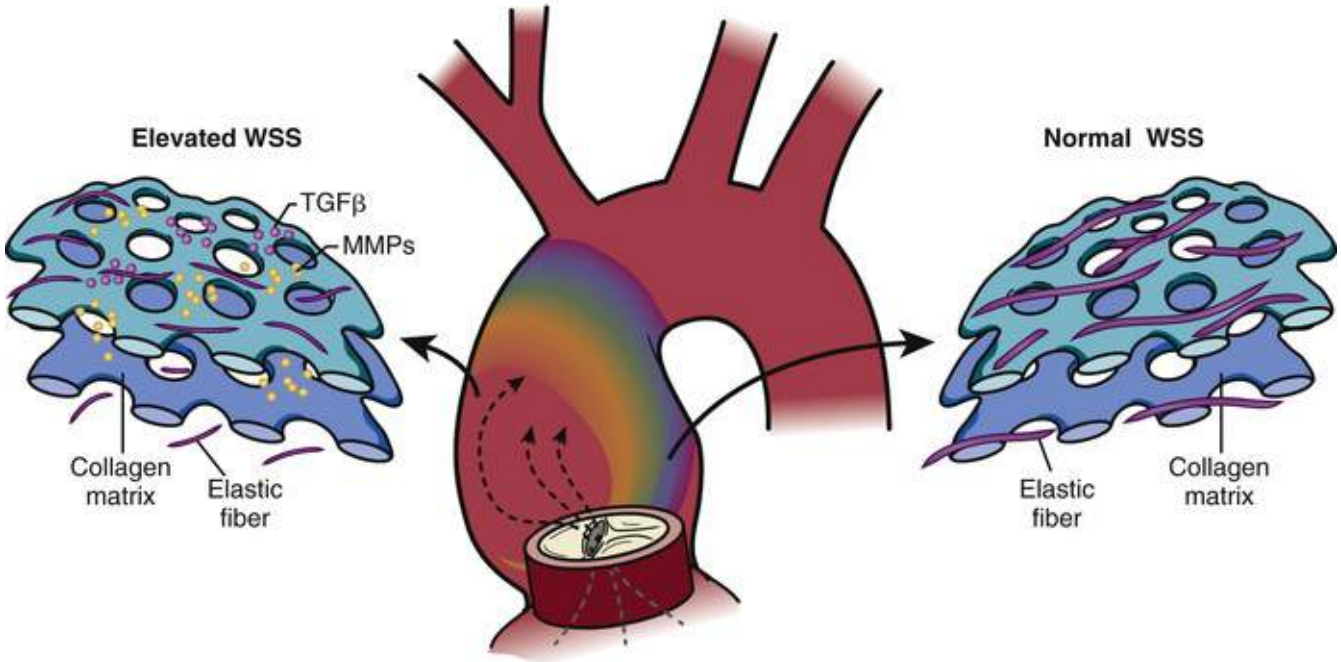
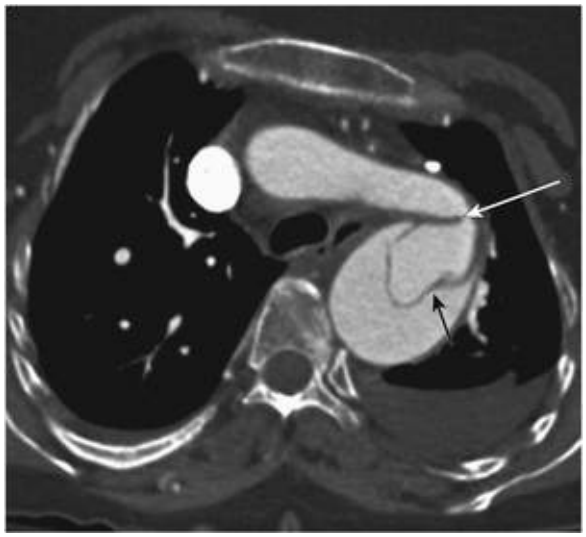


FIGURE 63.7 Bicuspid aortic valve (BAV) aortopathy is related to abnormal aortic flow and elevated wall shear stress. Four-dimensional flow cardiac magnetic resonance imaging (4D flow CMR) is used to assess the relation between wall shear stress (WSS) and regional aortic tissue remodeling in BAV patients. Elevated aortic WSS generated by aberrant flow from cusp fusion corresponds to more severe extracellular matrix (ECM) dysregulation than adjacent regions of normal WSS in the same patient's aorta. Elastic fiber degeneration is more severe in regions of elevated WSS (less elastin, thinner fibers, and greater distances between laminae), where higher concentrations of mediators of ECM dysregulation (matrix metalloproteinases [MMPs] and transforming growth factor beta [TGFβ]) are also observed. These data implicate valve-related hemodynamics as a contributing factor to BAV aortopathy. (From Guzzardi DG, Barker AJ, van Ooij P, et al. Valve-related hemodynamics mediate human bicuspid aortopathy insights from wall shear stress mapping. J Am Coll Cardiol 2016;66:892-900.)

Turner syndrome (TS), which affects 1 in 2000 live-born girls, results from complete or partial loss of a second sex chromosome (XO, Xp). Approximately 50% to 75% of patients with TS have cardiovascular (CV) defects, including BAVs in 30%, coarctation of the aorta in 12%, elongation of the transverse arch in 30%, and ascending aortic dilation 33%.[23] Abnormal TGF-β signaling may contribute to the aortic disease in TS. Patients with TS have an estimated 100-fold greater risk for aortic dissection than do age-matched controls.[23] Most women with TS who develop aortic dissection have risk factors, including aortic dilation, BAV, coarctation of the aorta, and systemic hypertension[23] (**eFig. 63.4**). Women with TS but without risk factors for aortic dissection should undergo reevaluation of the aorta every 5 to 10 years or when clinically indicated (e.g., contemplating pregnancy).[17] Women with risk factors or known CV defects require more frequent imaging. Because patients with TS have short stature, ascending aortic dimensions should be evaluated in relation to body surface area (BSA). TS patients have increased aortic diameter relative to BSA and a higher risk for dissection at smaller absolute aortic diameters.[23,24]



EFIGURE 63.4 Contrast-enhanced computed tomography scan in 47-year-old woman with Turner syndrome demonstrating an elongated aortic arch, coarctation of the aorta (*white arrow*), dilated proximal descending aorta, and acute type B aortic dissection (*black arrow*).

Aortic enlargement and CMD are associated with other congenital heart diseases, including coarctation of the aorta, transposition of the great vessels, ventricular septal defect, and tetralogy of Fallot.

Degenerative Aneurysms

Degenerative ("atherosclerotic") aneurysms are less common in the ascending aorta and are associated with diffuse aortic atherosclerosis. Isolated arch aneurysms may be degenerative or related to penetrating aortic ulcers, CMD, and rarely, syphilis or other infections. Most descending TAAs are degenerative but may also result from genetic disorders. These aneurysms tend to originate just distal to the origin of the left subclavian artery, may be either fusiform or saccular, and may extend into the abdominal aorta or coexist with AAAs.

Aortic Dissection

Dissection is a common cause of aneurysm of the descending thoracic aorta and the arch. Frequently, aneurysm formation develops during the chronic stage of dissection and thus involves the ascending aorta less often, since this segment is almost always surgically replaced during the acute stage (see later).

Syphilis and Aortitis

Cardiovascular syphilis occurs in the tertiary stage and typically involves the ascending aorta and arch. Aortitis rarely occurs today because of antibiotic treatment of syphilis early in its course. CV *syphilis* becomes evident after a latent period of at least 10 to 25 years. Pathologic features include lymphocytic and plasma cell inflammation in the adventitia, with the classic appearance of a "tree bark" or wrinkled appearance of the aortic intima. Ascending aortic aneurysm formation occurs in 40% of cases. Tertiary syphilis may cause aortic valvulitis, aortic regurgitation (AR), and coronary ostial stenosis.

Infectious *aortitis* (typically bacterial, less often fungal) is discussed later (**see also Chapter 73**). Other causes of TAAs include noninfectious aortitis such as giant cell arteritis, other vasculitides, and idiopathic aortitis and IgG4 disease. Noninfectious aortitis may underlie aortic aneurysms in 2% to 8% of TAAs.

Clinical Manifestations

Most TAAs are asymptomatic and are discovered incidentally. Physical findings such as AR may suggest TAA. Symptoms of TAAs usually are related to a local mass effect, progressive AR, or systemic embolization caused by mural thrombus or atheroembolism. Obstruction of the superior vena cava or innominate vein may result from ascending aorta or arch aneurysms. TAAs may compress the trachea, bronchus, or esophagus. Persistent chest or back pain may occur because of a direct mass effect from the TAA, with compression of intrathoracic structures or erosion into bones. The most serious complications of TAAs are rupture and dissection (**Fig. 63.8 and eFig. 63.5**). Aortic rupture leads to sudden severe chest or back pain. Rupture into the pleural cavity (usually left) or into the mediastinum is associated with hypotension; rupture into the esophagus leads to hematemesis; and rupture into the bronchus or trachea results in hemoptysis. Infected TAAs are associated with pain, fever, and fistulas. Acute aortic expansion, contained rupture, and pseudoaneurysm can cause severe chest or back pain. Thoracic aortic dissection (see later) is more common than rupture.

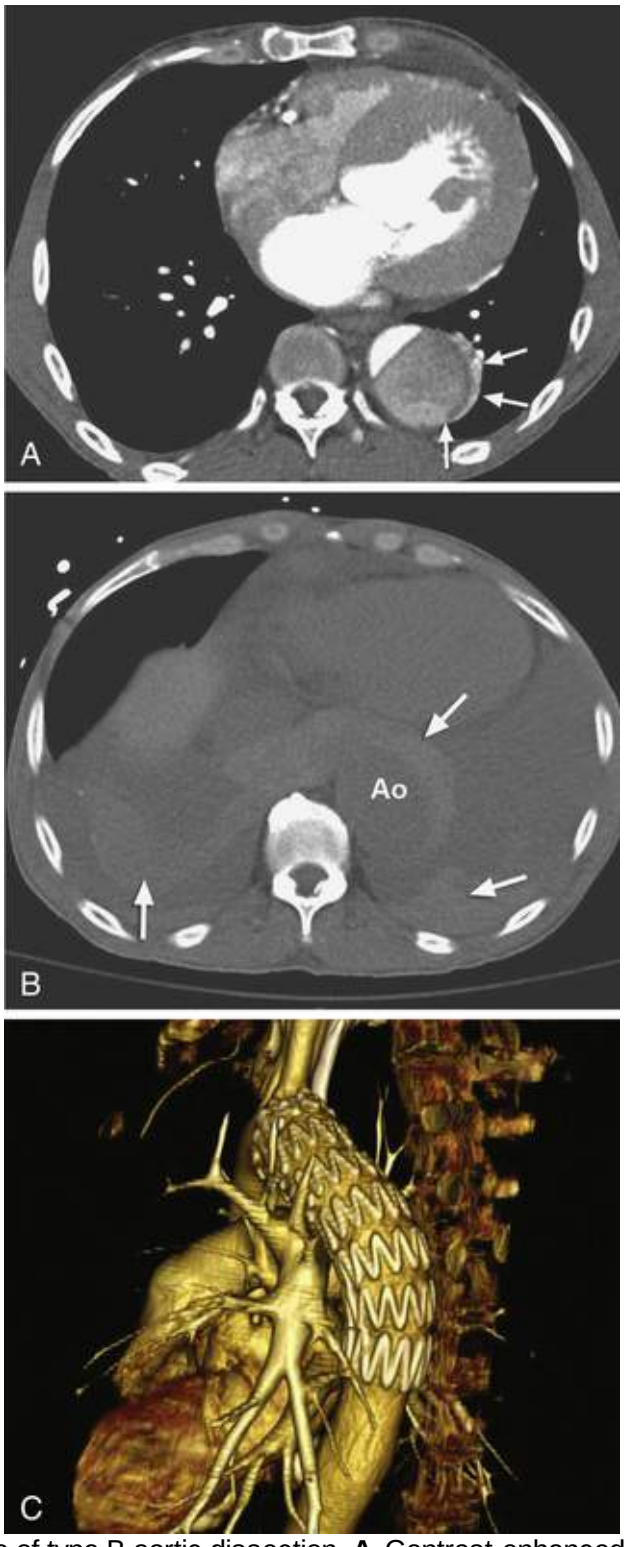
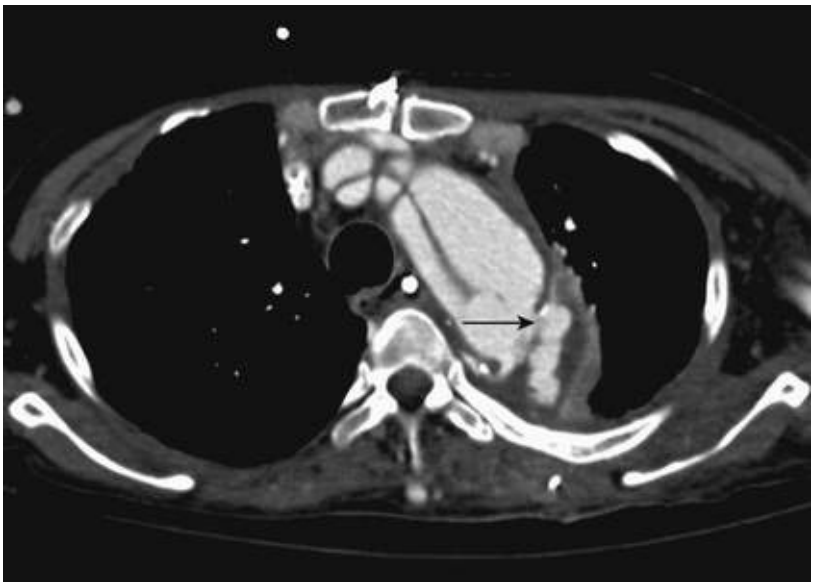


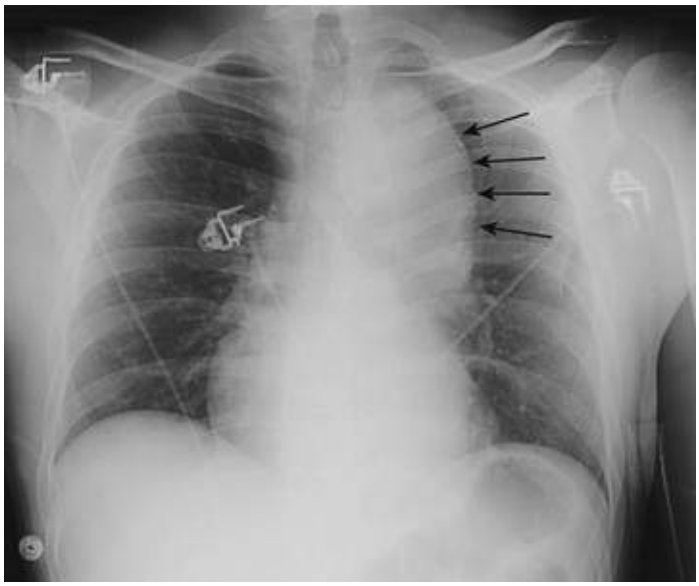
FIGURE 63.8 Rupture of type B aortic dissection. **A,** Contrast-enhanced computed tomography demonstrating early leakage of blood from the dilated false lumen (*arrows*). The small true lumen is densely opacified with contrast material. **B,** Non–contrast-enhanced CT demonstrating acute hemorrhage from the ruptured type B dissection (*arrows*); *Ao,* aorta. **C,** Three-dimensional reconstruction of the descending thoracic aorta after emergency endovascular repair of the ruptured aortic dissection.



EFIGURE 63.5 Contrast-enhanced computed tomography scan in a patient with acute type A aortic dissection complicated by acute rupture of the aortic arch and active mediastinal bleeding (*arrow*). The dissection flap is visualized in the arch. (From Braverman AC. Aortic dissection. In Levine GN, editor. Color Atlas of Cardiovascular Disease. New Delhi, India: Jaypee Brothers Medical Publishers; 2015, pp 895-903.)

Diagnosis

Many TAAs are evident on chest radiographs (**eFig. 63.6**), with features including a widened mediastinum, prominent aortic knob, or displaced trachea. Smaller aneurysms may not be visible on x-ray films. Aneurysms involving the sinuses of Valsalva and aortic root may not be seen on chest radiographs, being "hidden" behind the sternum, mediastinal structures, and vertebrae. Aortic tortuosity and unfolding in older adults may also mimic or mask TAAs. Thus, chest radiography cannot exclude the diagnosis of TAA.



EFIGURE 63.6 Chest radiograph demonstrating a large descending thoracic aortic aneurysm (*black arrows*).

Transthoracic echocardiography (TTE) can visualize TAAs involving the sinuses of Valsalva and often the proximal ascending aorta, aortic arch, and proximal descending aorta[2] (**see Fig. 63.5** and Videos 63.1

and 63.4). Aortic root size varies with age, height or BSA, and sex, and nomograms provide normal ranges.[2,17] Although TTE does not thoroughly characterize the aortic arch and descending TAAs, transesophageal echocardiography (TEE) can image most of the thoracic aorta (Video 63.5).

Contrast-enhanced CT and MRA provide outstanding detail of aortic and branch vessel anatomy in TAA disease. In the setting of a tortuous aorta, axial images alone can be misleading and may "overstate" the true dimension of the aorta.[2] When the axial images cut through the descending aorta at a plane that is off-axis, it results in a falsely large aortic diameter. Multidetector CTA and MRA allow reconstruction of the axial data into three-dimensional images, permitting aortic measurement in a true cross section to obtain an accurate diameter[2] (**Fig. 63.9 and eFig. 63.7**). The echocardiogram generally measures the internal diameter, whereas CT and MRI measure the external diameter of the aorta, which is expected to be 0.2 to 0.4 cm larger than the internal diameter.[2,17]

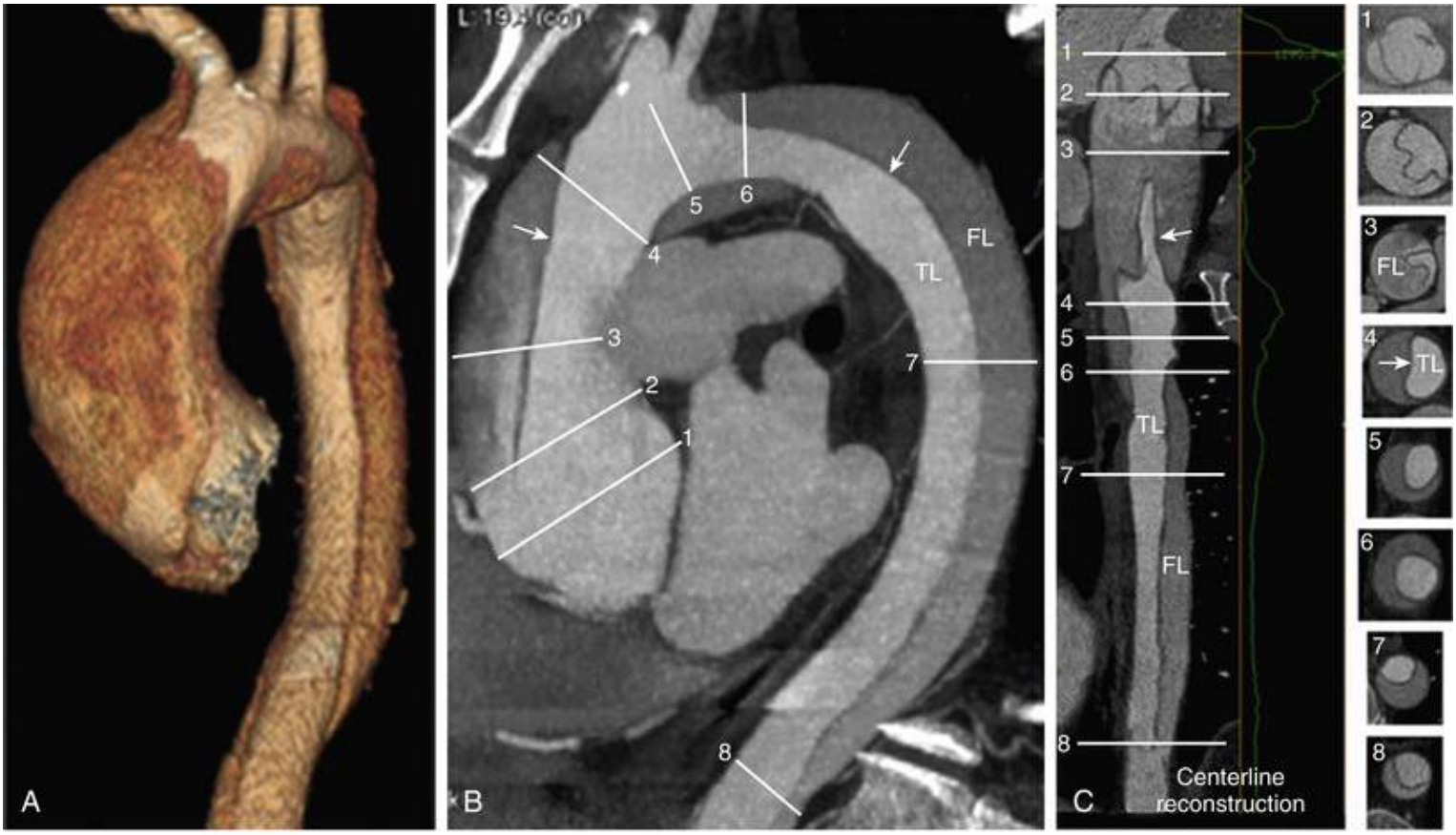
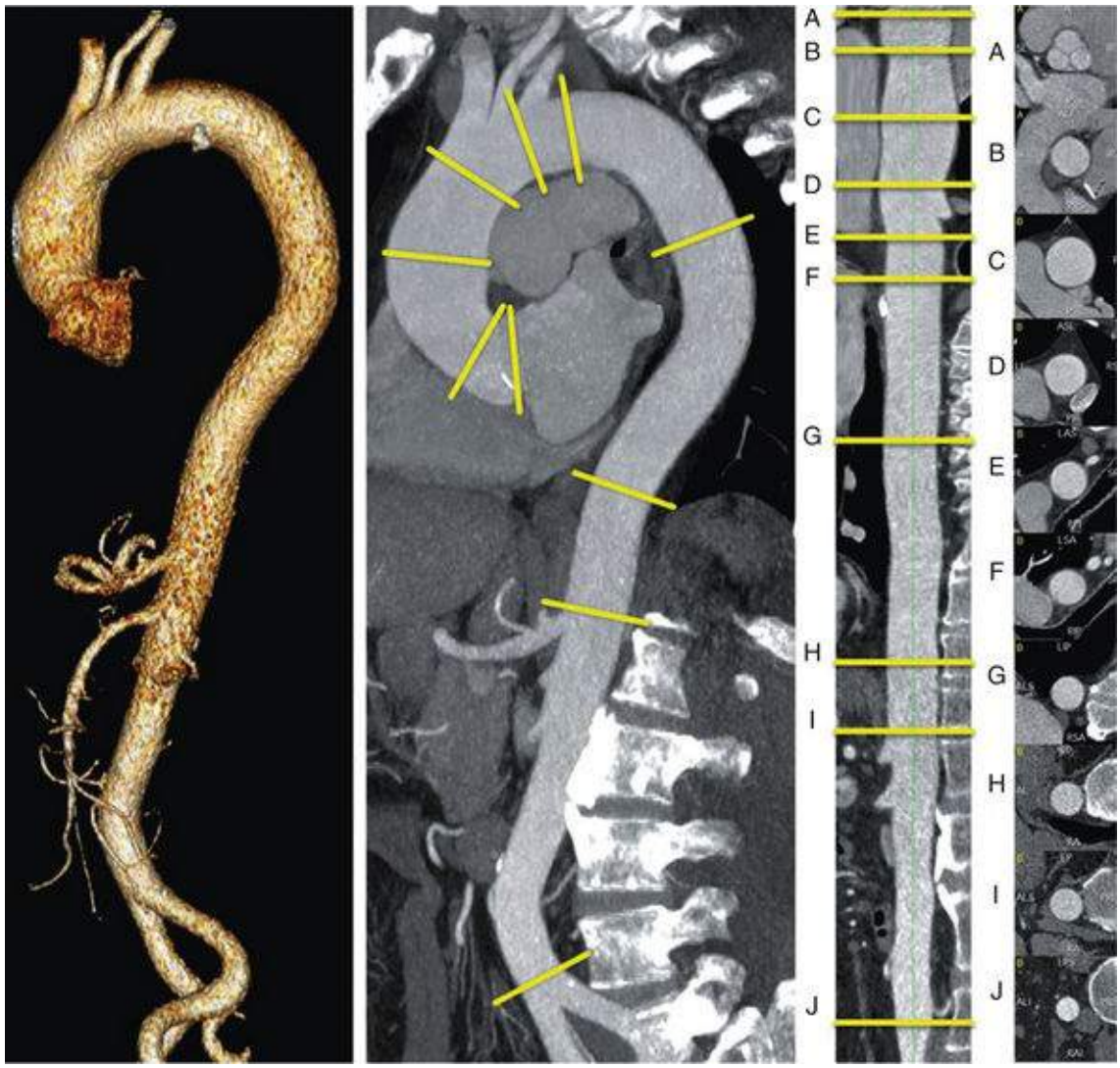


FIGURE 63.9 Computed tomographic angiography (CTA) of the thoracic aorta. **A,** Three-dimensional volume rendering. **B,** Oblique coronal view of the aorta. Note linear gating artifacts. **C,** Centerline reconstruction of the aorta as a straight vessel, eliminating tortuosity and allowing for measurement in true short axis (*right panel*). Corresponding levels of measurements are shown on **B** and **C:** *1,* sinuses of Valsalva; *2,* sinotubular junction; *3,* proximal ascending aorta; *4,* distal ascending aorta; *5,* aortic arch; *6,* aortic isthmus; *7,* mid–descending aorta; *8,* distal descending aorta at diaphragm. Type A aortic dissection flap (*arrows*), true lumen (*TL*), and false lumen (*FL*) are shown in **B** and **C.** (From Mongeon FP, Marcotte F, Terrone DG. Multimodality noninvasive imaging of thoracic aortic aneurysms: time to standardize? Can J Cardiol 2016;32:48-59.)



EFIGURE 63.7 Thoracic and abdominal aorta in a three-dimensional reconstruction **(left),** parasagittal multiplanar reconstruction (MPR) along the centerline **(middle),** and straightened MPR along the centerline with given landmarks (*A* to *J*) **(right),** orthogonal to the centerline-orientated cross sections at the landmarks. Landmarks *A* to *J* should be used to report aortic diameters: *A,* sinuses of Valsalva; *B,* sinotubular junction; *C,* mid–ascending aorta (as indicated); *D,* proximal aortic arch (aorta at the origin of the brachiocephalic trunk); *E,* mid–aortic arch (between left common carotid and subclavian arteries); *F,* proximal descending thoracic aorta (approximately 2 cm distal to left subclavian artery); *G,* mid–descending aorta (level of the pulmonary arteries as easily identifiable landmarks, as indicated); *H,* at diaphragm; *I,* at the celiac axis origin; *J,* right before aortic bifurcation. (Provided by F. Nensa, Institute of Diagnostic and Interventional Radiology, Essen. From Erbel R, Aboyans V, Boileau C, et al. 2014 ESC guidelines on the diagnosis and treatment of aortic diseases. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2873-926.)

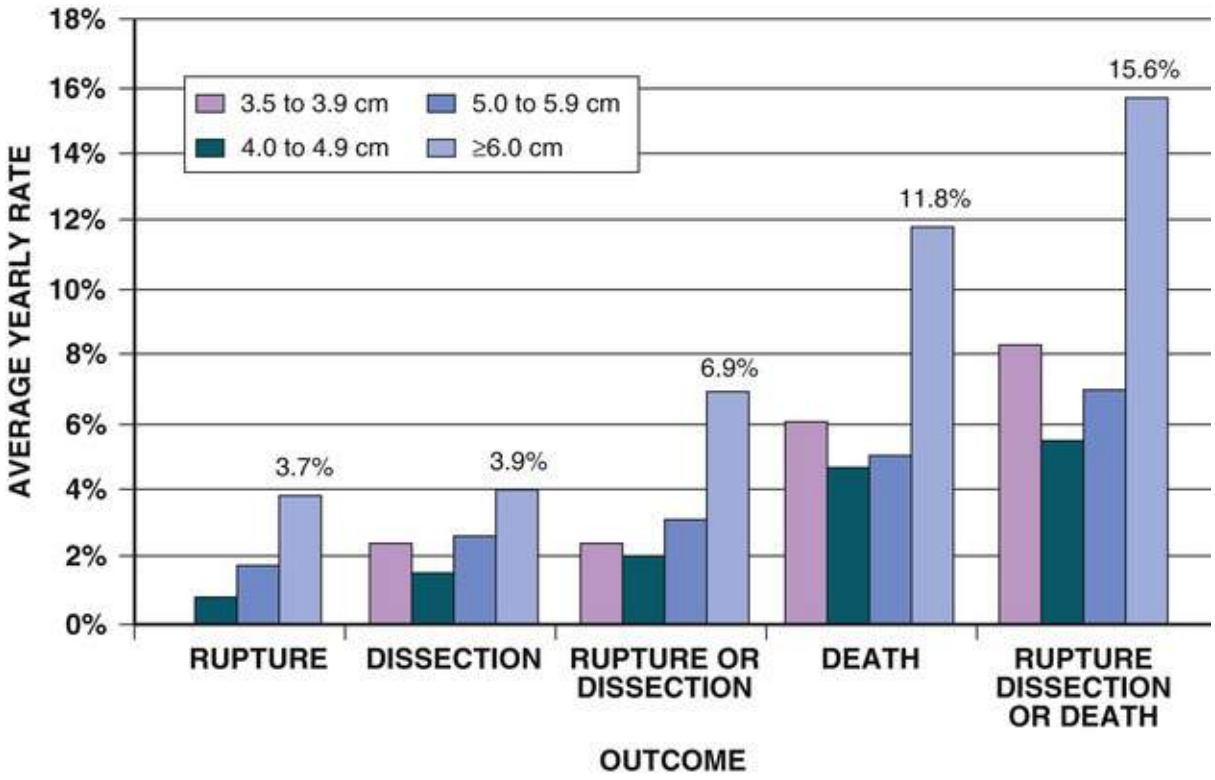
Natural History

Many factors influence the natural history of TAAs. Patients with MFS and BAV disease have a more rapid aneurysm growth rate than those with degenerative aneurysms.[11] The location and size of the TAA also affect its rate of growth and likelihood of rupture or dissection. TAAs are relatively indolent, with a growth rate of approximately 1 to 2 mm/yr and marked individual variability.[1,11] Larger aneurysms grow faster than smaller ones. Aneurysms of the descending aorta have a greater growth rate (approximately 2 mm/year) than those of the ascending aorta (1 mm/yr), and dissected TAAs grow more rapidly than those without dissection.[11]

Rupture and acute dissection are the major complications of TAAs (**see Figs. 63.8 and 63.9 and eFigs. 63.4 and 63.5**). Less than half of patients with rupture arrive at the hospital alive; mortality at 24 hours

reaches 75%. Aortic diameter and the underlying disease determine risks of aortic complications. For ascending aortic aneurysms larger than 6 cm, the risk for rupture, dissection, or death is 15.6%.[1,25] A series of patients with MFS had a risk of aortic dissection of 0.3% per year at an aortic root diameter 4.5 to 4.9 cm and 1.33% per year at 5.0 to 5.4 cm.[26] Among BAV patients, the risk of aortic dissection was approximately 3.8% for those with an ascending aortic diameter of 5.3 cm and 10% when the ascending aorta is 6 cm.[22] For LDS, certain familial TAA syndromes, and vEDS, the aortic diameter is less predictive, and dissection may occur at smaller aortic sizes. In patients with degenerative descending or thoracoabdominal aortic aneurysms, the estimated risks of definite aortic events (dissection, rupture, or death) were 5.5%, 7.2%, 9.3%, and 15.4% at aortic diameters of 50, 55, 60, and 70 mm, respectively.[27]

Risk factors for increased growth and rupture of TAAs include older age, chronic obstructive pulmonary disease (COPD), hypertension, cigarette smoking, rapid aneurysm growth, aortic dissection, and a positive family history.[17] Aortic diameter is the most important risk factor for aneurysm complications (**eFig. 63.8**). Sex and BSA may also predict complications of aneurysms.[17,25,27] Some have proposed using aortic cross-sectional area and body height,[17] and the Aortic Risk Calculator uses height, weight, and aortic diameter to calculate a yearly risk for rupture or dissection.[25]



EFIGURE 63.8 Yearly rates of rupture, dissection, or death related to aortic size. Note that the likelihood of rupture, dissection, or death within the coming year also jumps sharply for aneurysms that reach 6 cm or larger. (The rates indicated for rupture or dissection and for rupture, dissection, or death are lower than the sum of the rates in individual categories because patients with multiple complications were counted only once in the combined categories). (From Elefteriades JA, Farkas EA. Thoracic aortic aneurysm: clinically pertinent controversies and uncertainties. J Am Coll Cardiol 2010;55:841-57. Illustration by Rob Flewell.)

Surgical thresholds for TAA repair depend on the disease present and patient-specific factors (**Table 63.2**). For degenerative aneurysms, surgical replacement of the aorta is recommended when the aortic root or ascending aortic diameter reaches 5.5 cm; the arch >5.5 to 6 cm; and the descending or thoracoabdominal aorta reaches >5.5 to 6 cm.[1,17,27] Surgery is recommended in MFS when the aortic root diameter is 50 mm or larger, with a lower threshold for those with rapid aortic growth or a family history

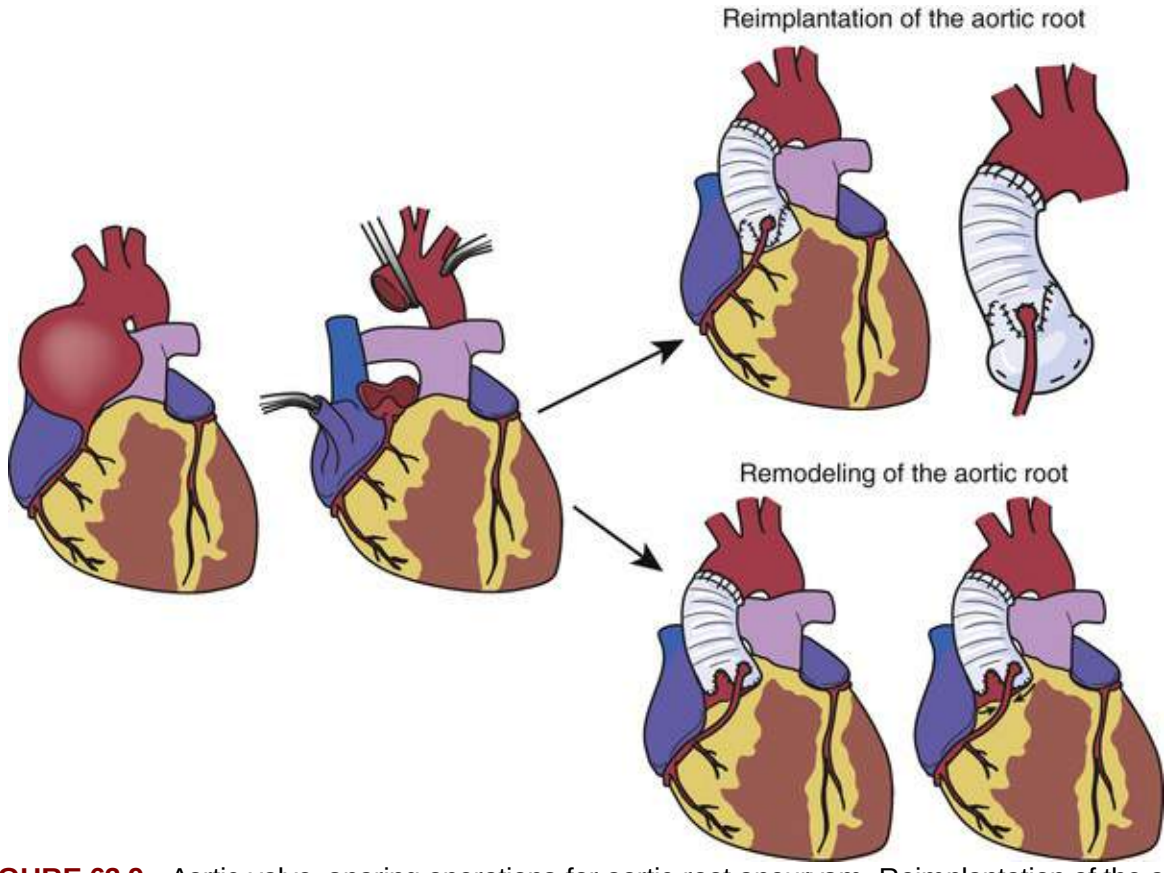
of aortic dissection;[1,17] in familial TAA syndromes at 4.5 to 5 cm;[1] in BAV aneurysm at 5.5 cm or larger, and at 5.0 cm or larger if there are risk factors for aortic dissection (family history of dissection, rapid aortic growth (>3 to 5 mm/year), coarctation of the aorta, or hypertension) or if the patient is at low surgical risk.[1,24] If surgery is being performed on the BAV, aortic aneurysm surgery may be performed in acceptable candidates at aortic diameter greater than 4.5 cm.[24] Adults with LDS should have surgery when the aortic root measures 4.0 to 4.5 cm, although some recommend surgery in patients with LDS once the aortic root is larger than 4 cm, especially when accompanied by a high craniofacial index.[1,12,17] In TS, prophylactic surgery should be considered when the ascending aortic size index is 2.5 cm/m^2 or greater.[23,24] Surgical timing also depends on the family history, sex, rate of aneurysm growth, body size, coexisting aortic valve disease, need for other heart surgery, comorbid conditions, and patient and physician preference. Because aortic complications occur at diameters lower than surgical thresholds, physicians must individualize management based on surgical risk and other factors. Endovascular approaches for some conditions may lead to earlier therapy for appropriate candidates, but genetically triggered aneurysm disease generally limits thoracic endovascular aortic repair to emergencies or hybrid procedures involving surgical grafts as landing zones.

Management

Surgical Treatment

Ascending Thoracic Aortic Aneurysms.

Treatment of ascending TAAs involves opening the ascending aorta and placement of a prosthetic graft with or without concomitant AVR. A composite graft consisting of a Dacron tube with a prosthetic aortic valve sewn into one end (the modified Bentall procedure) is generally the method of choice in treating ascending TAAs involving the root and associated with significant aortic valve disease. The valve and graft are sewn directly into the aortic annulus, and the coronary arteries are reimplanted into the Dacron graft. For elective aneurysm repair, the risk for death or stroke ranges from 1% to 5% depending on the disease, patient population, and surgical experience.[1,17] The risk for morbidity and mortality increases with the need for arch dissection. Emergency operations on the proximal aorta carry much higher risk. Patients with structurally normal aortic valve leaflets and those whose AR is secondary to dilation of the sinotubular junction or aortic annulus may be able to undergo a valve-sparing root replacement—reimplanting the native valve within a Dacron graft (David procedure) or by remodeling the aortic root (Yacoub procedure) (**eFig. 63.9**). The reimplantation technique is preferable to the remodeling technique because it stabilizes the annulus and limits aortic dilation and late AR.[28]



EFIGURE 63.9 Aortic valve–sparing operations for aortic root aneurysm. Reimplantation of the aortic valve is performed with a tubular graft or with tailored graft to recreate the aortic sinuses, whereas remodeling of the aortic root was performed by tailoring a tubular polyester fabric graft in such a way as to recreate the aortic sinuses and suturing it to the remnants of aortic sinuses and aortic annulus. (From David TE, David CM, Manlhiot C, et al. Outcomes of aortic valve-sparing operations in Marfan syndrome. J Am Coll Cardiol 2015;66:1445-53.)

A pulmonary autograft (the Ross procedure) is an alternative to a composite aortic graft in appropriate candidates. This procedure involves replacing the native aortic valve and root with the patient's own pulmonary root, inserted into the aortic position. The pulmonary root is replaced with a cryopreserved homograft root. The Ross procedure carries risks of late autograft aneurysm formation and should not be used in patients with genetically triggered aortic root diseases; its use is controversial in the setting of BAV and aortic disease. Another alternative is the use of cryopreserved aortic allografts (cadaveric aortic root and proximal ascending aorta), but durability issues and late aortic calcification limit this choice. Estimates of risk for mortality for thoracic aortic elective repair follow: composite valve graft, 1% to 5%; separate AVR and ascending aortic repair, 1% to 5%; valve-sparing root replacement, less than 1% to 1.5%; and BAV and ascending aortic repair, 1.5%.[17]

Aortic Arch Aneurysms.

Aortic arch aneurysms are more difficult to treat surgically because reconstruction of the aortic arch vessels requires interruption of blood flow to these vessels.[17] One approach uses a *hemiarch resection*—the arch vessels remain intact, with the descending aorta as a roof, and the remaining arch is replaced. Extended arch resection requires either removing the entire arch and using branched grafts to replace the arch and great vessels, by using bypasses constructed to each great vessel, or reimplanting an island of arch tissue that includes the origins of the great vessel.[17] Cerebral protection during arch surgery can use several methods, traditionally deep hypothermic circulatory arrest. If the aneurysm extends partially into the descending thoracic aorta, the polyester graft is extended as an elephant trunk into the descending portion of the aneurysm, necessitating a second procedure to complete the repair.[17,29] In this procedure the

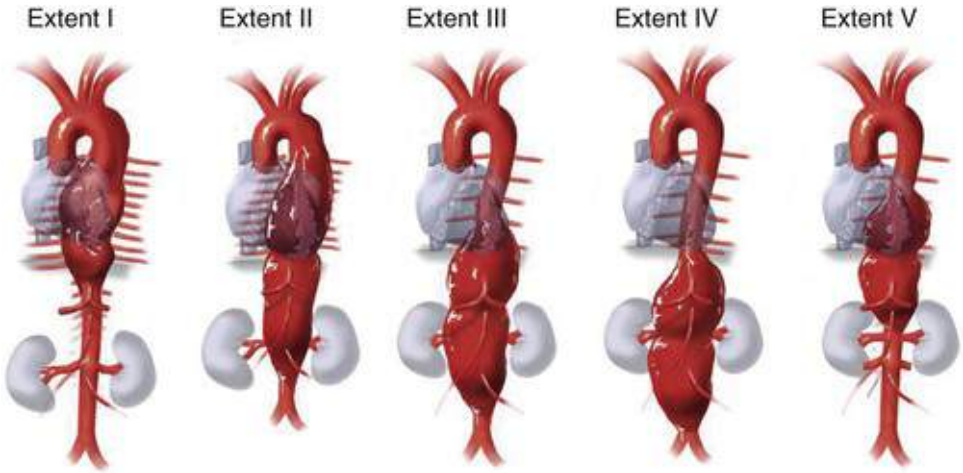
distal anastomosis is created to the midportion of a graft and the distal graft is within the lumen of the aorta and thus can be retrieved without manipulation of the arch. A recent modification of this procedure uses a covered endovascular stent-graft attached to a vascular graft to allow fixation of the stent-graft within the descending aorta and vascular graft reconstruction of the aortic arch.[30] This “frozen elephant trunk” procedure allows total replacement of the arch and descending aortic in a single stage for complex aneurysms, as well as treatment of acute type A dissection.[29] Spinal cord injury occurs in 9% of frozen elephant trunk procedures performed for extensive chronic aortic dissection.[29] Arch aneurysm surgery has a morbidity and mortality rate of 2% to 7% risk for both death and stroke.[1,17] Endovascular techniques and extra-anatomic reconstructions can treat complex aortic arch aneurysms and complete elephant trunk procedures.[17,29] Surgery for arch aneurysms is considered when aneurysm diameter is greater than 55 mm. Increased operative risk merits consideration of debranching procedures with thoracic endovascular aortic repair (TEVAR) as a hybrid approach. However, this approach involves higher risk of a retrograde type A aortic dissection.[1]

Descending Thoracic Aneurysms.

Treatment paradigms for descending TAAs have changed because of the rapid development of TEVAR.[1] Mortality for descending TAA repair is lower early after TEVAR compared to OSR, whereas midterm survival rates are similar.[1] The European Society of Cardiology (ESC) guidelines suggest consideration of TEVAR for descending TAA at diameter greater than 55 mm, and OSR at greater than 60 mm when it is the only option for an appropriate candidate.[1] Lower thresholds for may apply to connective tissue disorders, including MFS and LDS. TEVAR has a higher risk of complications in MFS and other connective tissue disorders and is typically reserved for urgent complications, very-high-risk patients, or with proximal and distal hand-sutured grafts to “land” the endograft.[1] Treatment of descending TAAs involves replacement of the aneurysmal segment with a polyester graft. The procedures are performed with partial femorofemoral bypass or atriofemoral bypass to maintain retrograde perfusion to critical arterial branches; these procedures are associated with a perioperative mortality of 10% or less and a paraplegia rate of approximately 2%, depending on the extent of repair.[17] Five-year survival rates after descending TAA resection approach 70%. TEVAR is discussed later.

Thoracoabdominal Aneurysms.

Thoracoabdominal aortic aneurysms (TAAAs) can extend from the subclavian artery to the iliac vessels. The Crawford classification (modified by Safi) describes the extent of the aneurysm, and this predicts morbidity, mortality, and risk for paralysis with repair[31] (**eFig. 63.10**). Surgical therapy and outcomes with TAAA are further discussed in the online supplement for this chapter.



EFIGURE 63.10 Schematic representation of the modified Crawford classification scheme for thoracoabdominal aortic aneurysm extents. (From Frederick JR, Woo YJ. Thoracoabdominal aortic aneurysm. Ann Cardiothorac Surg 2012;1:277-85.)

Endovascular Repair of Thoracic Aneurysms.

TEVAR is a much less invasive alternative to OSR of descending TAAs, with lower morbidity and mortality rates, but the aorta must have adequate proximal and distal landing zones of at least 20 to 25 mm in length and diameters that accommodate the endograft and adequate vascular access.[1,17] Stent-graft trials in the TEVAR arms reported rates of 1.9% to 2.1% for mortality, 2.4% to 4% for stroke, 4.4% to 7.2% for paraparesis, and 1.3% to 3% for paralysis.[32] In the OSR groups, mortality and neurologic morbidity rates ranged from 5.7% to 11.7% for mortality, 4.3% to 8.6% for permanent stroke, 5.7% for paraparesis, and 3.4% to 8.5% for paralysis.[32]

The anatomic configuration of the ascending aorta and transverse arch makes applying these techniques and devices challenging in these proximal segments. Hybrid techniques using extra-anatomic bypass procedures can create an appropriate proximal landing zone for the endovascular graft in the aorta without the need for major open thoracic surgery. In up to 50% of TEVAR procedures, the stent-graft intentionally covers the left subclavian artery.[17] Transposition of the left subclavian artery or a left carotid-to-subclavian bypass can be performed to allow attachment and seal of an endovascular graft across the takeoff of the subclavian artery. Subclavian artery occlusion without reconstruction is associated with an increased risk for cerebrovascular complications, including stroke, which can be mitigated by reconstruction before endovascular exclusion of the subclavian artery.[1]

If all the branches of the aortic arch need to be excluded for appropriate endovascular repair of an arch aneurysm, other options are available. Complete extra-anatomic aortic arch debranching can be performed, with reconstruction of the arch branches and subsequent carotid and subclavian bypasses as necessary. Another option is to perform an elephant trunk procedure under cardiopulmonary arrest; a prosthetic graft is sutured to the healthy portion of the ascending aorta and aortic arch, and branches of the aortic arch are left intact. This approach creates a proximal attachment zone that can be extended distally with an endovascular graft to complete the aneurysm repair. Bypasses to all the aortic arch branches can also be performed from the proximal ascending aortic arch in select patients, with a healthy portion left in the ascending aorta for attachment and seal of an endovascular graft. Branched devices developed to manage patients with complex thoracic and thoracoabdominal aneurysms are undergoing early evaluation. Debranching procedures involving visceral vessels may be performed before proceeding with endograft implantation, although the morbidity and mortality of this hybrid approach have not been found to be lower than standard OSR for the visceral aorta.[17] Open and endovascular repair of TAAs is associated

with a variety of significant risks, including cardiac, pulmonary, renal, and cerebrovascular complications. Spinal cord dysfunction with the development of paraparesis or paraplegia is a major source of morbidity. Drainage of cerebrospinal fluid (CSF) has been used in combination with a mean arterial pressure (MAP) of at least 70 mm Hg to lessen spinal cord complications.[17]

Rupture of a descending TAA is often fatal before hospital admission. TEVAR of ruptured descending TAAs is associated with a lower in-hospital mortality rate (19%) than OSR (33%).[33] Up to 10% of device-related complications occur in the first 30 days after TEVAR.[17] Endoleaks are the most common complication of endovascular repairs and occur in 10% to 20% of patients.[17] Serial imaging surveillance is required after TEVAR. Over a 5-year follow-up, the mean aortic diameter after TEVAR decreased from 61 to 55 mm.[33] The rate of freedom from reintervention on the aortic segment treated was 85% at 10 years.

Medical Management

Treating hypertension and smoking cessation are important because they are risk factors for TAA development, expansion, and rupture.[17] Patients with degenerative TAAs should receive cholesterol-lowering therapy. Beta blockers or ARBs are recommended for patients with MFS.[12,15] Despite the absence of data from randomized trials, many use beta blockers in non-MFS patients with TAAs and in patients after aneurysm repair. Because TGF-β signaling is related to the pathogenesis of some heritable TAA disorders, drugs affecting this signaling pathway, such as ARBs, may provide benefit.[17]

Long-term imaging surveillance of the aorta is imperative. After discovery of an aneurysm, patients should be reevaluated in 6 months to assess the aneurysm status. In general, for degenerative TAAs, annual imaging is recommended when the aorta is between 4.0 and 4.5 cm, and imaging at 6- to 12-month intervals for aneurysms of 4.5 to 5.4 cm, depending on size and growth rate. For relatively small aneurysms that are stable from year to year, imaging may be performed every 2 to 3 years.[17] In patients with MFS and familial TAAD, annual imaging is recommended for aortic sizes of 3.5 to 4.4 cm and annual or biannual imaging for 4.5 to 5 cm. For BAV with aortic dilation, annual imaging is recommended depending on size. In LDS and in some familial TAA diseases, imaging from the head to the pelvis is recommended because of the potential for widespread aneurysms.[6,12,17]

Lifestyle modification is necessary for patients with TAAs, including awareness of the condition and the risk for aortic dissection and rupture. Avoidance of strenuous physical activity, especially isometric exercise and weightlifting, is important and may impact work-related recommendations.[34,35] Pregnancy is associated with an increased risk for aortic dissection in those with MFS and other heritable aneurysm diseases, and management strategies must encompass this risk.[17] Because many diseases that lead to TAAs are familial, aortic imaging is recommended for first-degree relatives of patients with TAAs or aortic dissection to identify those with asymptomatic disease. If a patient has a mutant gene (**see Table 63.1**), first-degree relatives should undergo counseling and mutation testing.[17] Then, only relatives with the genetic mutation should undergo aortic imaging. In the absence of an identified mutation, first-degree relatives should have evaluation and imaging. If a first-degree relative has thoracic aortic disease, second-degree relatives should also be screened.[17]

Aortic Dissection

Acute aortic syndromes include classic aortic dissection, aortic intramural hematoma (IMH), and penetrating atherosclerotic aortic ulcer (PAU)[1,2,17] (**Fig. 63.10**). In 80% to 90% of acute aortic syndromes, classic aortic dissection is present, with intimal disruption leading to a dissection plane in the media that may propagate anterograde (or less often retrograde) throughout the length of the aorta (see Video 63.18). Adventitial disruption may lead to rupture, or more frequently, a distal tear(s) results in blood reentering the aortic lumen. In classic aortic dissection an intimal flap exists between the two lumens (true and false lumens). From 10% to 20% of acute aortic syndromes result from IMH, where bleeding in the aortic wall occurs without evidence of an intimal tear or dissection flap.[1,2] PAUs also lead to acute aortic syndromes in approximately 5% of cases.

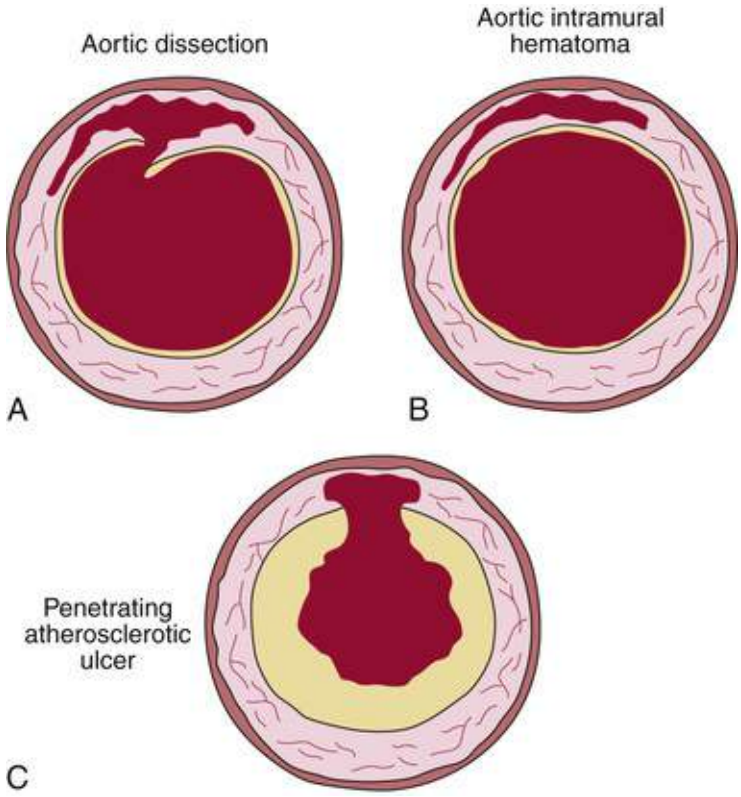


FIGURE 63.10 Acute aortic syndromes. **A,** Classic aortic dissection. There is a tear in the intima with blood entering the media and a dissecting cleavage plane propagating for variable distances anterograde (and occasionally retrograde) throughout the aortic wall. **B,** Aortic intramural hematoma (IMH). A spontaneous hemorrhage of the vasa vasorum leads to bleeding within the media in the absence of an intimal tear or intimal flap. **C,** Penetrating atherosclerotic aortic ulcer (PAU). An ulcerated aortic plaque ruptures into the media, leading to an outpouching or ulceration in the aortic wall. This may be associated with IMH formation, pseudoaneurysm, or a focal, thick-walled aortic dissection.

Ascertaining the exact incidence of aortic dissection is difficult as many patients die before the condition is recognized. U.S. population studies estimate the incidence of aortic dissection at 2 to 6 cases per 100,000 person-years.[1] In Sweden the incidence of dissection in men is reported to be 16 per 100,000 yearly.[17] In autopsy series the prevalence of aortic dissection ranges from 0.2% to 0.8%. Aortic dissection occurs at least twice as often in males as in females. Patients with acute aortic dissection have very high early mortality, with up to 1% per hour reported in the first 24 hours before surgery for type A dissection.[17,36] Type A aortic dissection occurs most often in individuals age 50 to 60 years, with type B

dissection more at a peak of 60 to 70 years.

There are two main hypotheses for acute aortic dissection: (1) a primary tear in the aortic intima with blood from the aortic lumen penetrating into the diseased media and leading to dissection and creation of the true and false lumens and (2) primary rupture of the vasa vasorum leading to hemorrhage in the aortic wall, with subsequent intimal disruption creating the intimal tear and aortic dissection. Distention of the false lumen with blood causes the intimal flap to compress the true lumen and narrow its caliber and may lead to malperfusion syndromes.

Classification

The two major classification schemes for aortic dissection, DeBakey and Stanford, are based on the location of the dissection (**Fig. 63.11 and Table 63.3**). The ascending aorta is proximal to the brachiocephalic artery, and the descending aorta begins distal to the left subclavian artery. The DeBakey classification divides dissections into types I, II, and III. DeBakey type I dissections originate in the ascending aorta and extend at least to the aortic arch and often to the descending aorta—frequently all the way to the iliac arteries. Type II dissections involve the ascending aorta alone. Type III dissections begin in the descending aorta, usually just distal to the left subclavian artery, and may be classified further according to whether the dissection stops above the diaphragm [IIIa] or extends below the diaphragm [IIIb]. The Stanford classification categorizes dissections into type A and type B based on whether the ascending aorta is involved. Type A dissections involve the ascending aorta, with or without extension into the descending aorta. Type B dissections do not involve the ascending aorta. Thus, dissections that involve the aortic arch but not the ascending aorta are characterized as type B in the Stanford classification. Others classify dissections as “ascending” or “descending.”

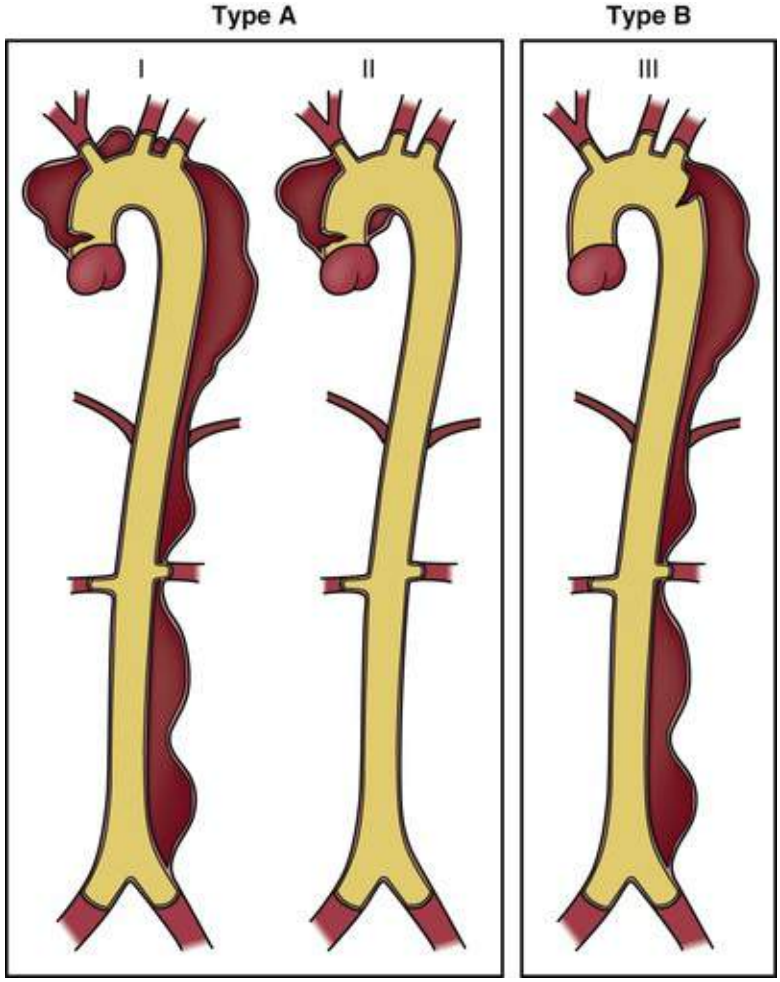


FIGURE 63.11 Classification schemes of acute aortic dissection. **DeBakey classification:** *Type I* dissection originates in the ascending aorta and extends at least to the aortic arch and often to the descending aorta (and beyond). *Type II* dissection originates in the ascending aorta and is confined to this segment. *Type III* dissection originates in the descending aorta, usually just distal to the left subclavian artery, and extends distally. **Stanford classification:** *Type A* dissection involves the ascending aorta (with or without extension into the descending aorta). *Type B* dissection does not involve the ascending aorta.
(From Braverman AC. Aortic dissection. prompt diagnosis and emergency treatment are critical. Cleve Clin J Med 2011;78:1695-704.)

TABLE 63.3

Classification Schemes of Acute Aortic Dissection

TYPE	DESCRIPTION
DeBakey Classification	
I	Dissection originates in the ascending aorta and extends at least to the aortic arch and often to the descending aorta (and beyond).
II	Dissection originates in the ascending aorta and is confined to this segment.
III	Dissection originates in the descending aorta, usually just distal to the left subclavian artery, and extends distally.
Stanford Classification	
A	Dissection involves the ascending aorta (with or without extension into the descending aorta).
B	Dissection does not involve the ascending aorta.

Modified from Braverman AC. Aortic dissection. prompt diagnosis and emergency treatment are critical. Cleve Clin J Med 2011;78:1695-704.

Most type A dissections begin within a few centimeters of the aortic valve, and most type B dissections begin just distal to the left subclavian artery. Approximately 65% of intimal tears occur in the ascending aorta, 30% in the descending aorta, less than 10% in the aortic arch, and approximately 1% in the abdominal aorta. Treatment depends on the site, with emergency surgery being recommended for acute type A dissections and initial medical therapy recommended for type B dissections. Aortic dissection is

also classified according to its duration, with the classic definition of “acute” when present for less than 2 weeks and “chronic” when present for longer than 2 weeks. A new classification system by the International Registry of Acute Aortic Dissection (IRAD) takes into account that the morbidity and mortality associated with acute dissection are highest in the first 2 weeks, especially the first 24 to 48 hours.[1,17,36] The IRAD classification includes hyperacute (<24 hours), acute (2 to 7 days), subacute (8 to 30 days), and chronic (>30 days) (**Fig. 63.12**).[36] Others classify dissections as acute (<2 weeks), subacute (2 to 6 weeks), or chronic (>6 weeks)[17] (**Table 63.4**). The DISSECT system of classification divides patients into subsets of importance for endovascular management.[37]

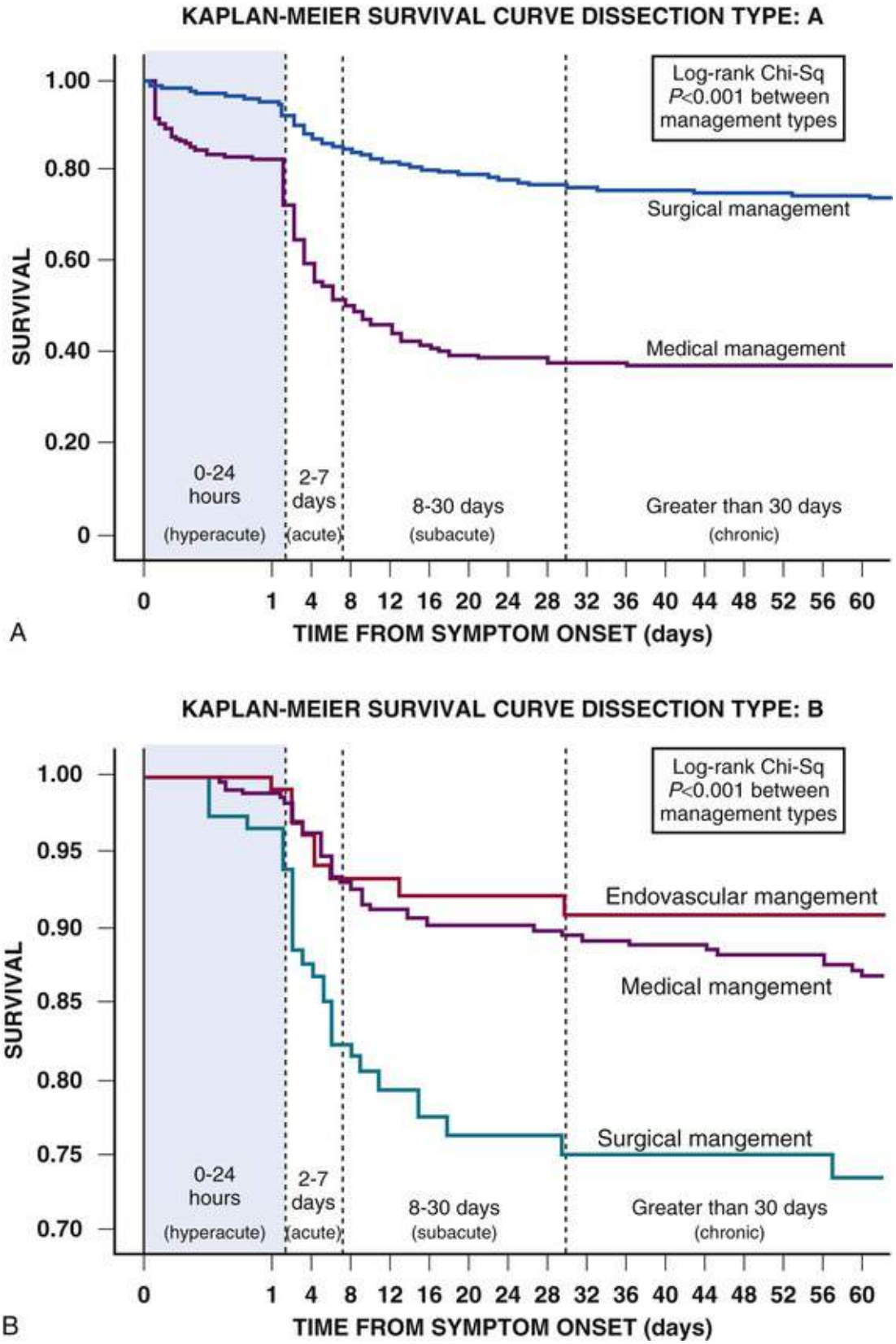


FIGURE 63.12 International Registry of Acute Aortic Dissection (IRAD) classification system of survival after aortic dissection. Kaplan-Meier survival curves for type A dissection **(A)** and type B dissection **(B)** stratified by treatment type. (From Booher AM, Isselbacher EM, Nienaber CA, et al. The IRAD classification system for characterizing survival after aortic dissection. Am J Med 2013;126:730 e19-24.)

TABLE 63.4

Aortic Dissection Classification Based on Duration from Symptom Onset

CLASSIC DEFINITION	TAD GUIDELINES[1]	IRAD CLASSIFICATION[2]	ESC GUIDELINES[3]
Acute: <14 days Chronic: >14 days	Acute: <14 days Subacute: <2-6 weeks Chronic: >6 weeks	Hyperacute: <24 hours Acute: 2-7 days Subacute: 8-30 days Chronic: >30 days	Acute: <14 days Subacute: 14-90 days Chronic: >90 days

[1]Hiratzka LF, Bakris GL, Beckman JA, et al. Guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation 2010;121:e266-369.

[2]Booher AM, Isselbacher EM, Nienaber CA, et al. The IRAD classification system for characterizing survival after aortic dissection. Am J Med 2013;126:730 e19-24.

[3]Erbel R, Aboyans V, Boileau C, et al. 2014 ESC guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2873-926.

TAD, Thoracic Aortic Diseases; *IRAD,* International Registry of Acute Aortic Dissection; *ESC,* European Society of Cardiology.

Cause and Pathogenesis

Several conditions predispose the aorta to dissection (**Table 63.5**), most from disruption of the integrity of the aortic wall or marked increases in aortic wall circumferential stress (see earlier discussion on TAAs). Approximately 75% of all patients with aortic dissection have hypertension. Hypertension may affect the elastic properties of the arterial wall and increase stiffness, predisposing to aneurysm or dissection. However, hypertension alone is not usually associated with significant aortic dilation, and the vast majority of hypertensive patients never have aortic dissection. In the IRAD registry of 4428 patients, conditions associated with dissection included: hypertension (77%), atherosclerosis (27%), previous cardiac surgery (16%), known aortic aneurysm (16%), MFS (4%), and iatrogenic condition (3%).[38]

TABLE 63.5

Risk Factors for Aortic Dissection

Hypertension
Heritable or genetic thoracic aortic disease and syndromes (**see Table 63.1**)
Marfan syndrome
Loeys-Dietz syndrome
Familial thoracic aortic aneurysm syndromes
Vascular Ehlers-Danlos syndrome
Turner syndrome
Congenital diseases/syndromes
Bicuspid aortic valve
Coarctation of the aorta
Tetralogy of Fallot
Atherosclerosis
Penetrating atherosclerotic ulcer
Trauma, blunt or iatrogenic
Catheter/guidewire
Intra-aortic balloon pump
Aortic/vascular surgery
Motor vehicle accident
Coronary artery bypass grafting/aortic valve replacement/TAVR
Thoracic endovascular aneurysm repair (TEVAR)
Cocaine/methamphetamine use
Inflammatory/infectious diseases
Giant cell arteritis
Takayasu arteritis
Behçet disease
Aortitis
Syphilis
Pregnancy (with underlying aortopathy)
Weightlifting (with underlying aortopathy)

TAVR, Transcatheter aortic valve replacement.

Genetically triggered aortic syndromes, congenital heart diseases, inflammatory vascular diseases, and cocaine and methamphetamine use are also risk factors for aortic dissection. CMD commonly underlies aortic dissection but does not indicate the cause (**see Fig. 63.2**). Excessive signaling in the TGF-β pathway and abnormalities in function of the SMC contractile element may underlie certain aortic aneurysm syndromes[6,12,17] (**see Table 63.1, Fig. 63.6, and eFig. 63.2**). Patients with MFS have a high risk for aortic root aneurysm and especially type A aortic dissection. Despite being present in only 1 in 5000 individuals, MFS accounts for approximately 4% of all aortic dissections and a significant proportion of aortic dissection in young patients.[17,38] After elective root replacement in MFS, there is a 1.5% annual risk of type B aortic dissection.[39] Recognition of genetic mutations as a cause of aortic aneurysms and dissections has increased.[6,12] Variants at the rs2118181 locus on the *FBN1* gene and mutations in the *KIF6* gene also predispose to aortic dissection.[40]

BAV is an important risk factor for ascending aortic aneurysm and dissection[19,21,22] (see Videos 63.2 and 63.3). Aortic dissection is also associated with Noonan syndrome, unicuspid aortic valve, supravalvular aortic stenosis, aberrant right subclavian artery (Kommerell diverticulum), right-sided aortic arch, polycystic kidney disease, and Alport syndrome (in males).[1,17]

Aortic dissection may complicate aortitis, particularly giant cell arteritis. Nonspecific aortitis, Takayasu arteritis, IgG4 disease, and Behçet syndrome all are associated with aortic dissection. Syphilitic aortitis is a rare cause of dissection. Cocaine use accounts for less than 2% of cases of aortic dissection, more often presenting with hypertension and small aortic diameters.[41] Underlying elastic medial abnormalities and the biomechanical stress related to hypertension and tachycardia may play a role. Aortic dissection may also occur with intense weightlifting, but generally in the setting of an underlying aortopathy.

Aortic dissection can occur during late pregnancy or in the early postpartum period.[26] The relationship between pregnancy and aortic dissection is difficult to attribute solely to hemodynamic factors, and

hormonally induced changes in aortic wall composition during pregnancy may contribute. Although most pregnancy-related aortic dissections are caused by underlying aortopathy, the syndrome is not diagnosed in many until after dissection occurs.[42] Women with aortopathy from many disorders, including MFS, LDS, familial TAAD, vEDS, TS, and BAV disease with aneurysm, have increased risk for acute aortic dissection related to pregnancy.[17,26] In MFS the risk for type A dissection is greatest when the aortic root is enlarged, at an estimated 1% when the aortic diameter is less than 40 mm, and 10% in high-risk patients (aortic diameter >40 mm, rapid dilation, or previous aortic dissection).[26] Even after root replacement, pregnancy carries a risk of dissection in women with aortopathy.[43]

Blunt aortic trauma usually leads to localized tears or periaortic or frank aortic transection and only rarely causes classic aortic dissection. Iatrogenic trauma accounts for approximately 3% of aortic dissections.[38] Intra-arterial catheterization and interventions may induce aortic dissection because of disruption of the intima. Iatrogenic type A dissection related to coronary artery interventions are rare, and when limited and stable on imaging, it may often be treated conservatively.[44] Cardiac surgery entails a very small risk for acute aortic dissection related to aortic cannulation, crossclamps, aortic anastomosis, and retrograde dissection as a result of femoral cannulation. Aortic dissection may occur late (months to years) after cardiac surgery, with those undergoing AVR or with a previous aneurysm or dissection having the highest risk. Retrograde ascending aortic dissection occurs in approximately 1% to 2% of patients undergoing TEVAR for acute or chronic type B aortic dissection.

Individuals with TAA have risk for aortic dissection, with risk for dissection and rupture increasing as aneurysm size increases. However, many aortic dissections occur in patients with aortic dimensions that are not greatly dilated.[45] The dissection process leads to an acute increase in aortic diameter during the dissection.[46] Thus, for many with acute dissection, the aortic diameter immediately beforehand was smaller. Of type A aortic dissections in the IRAD registry, aortic diameter averaged 5.3 cm, with approximately 60% smaller than 5.5 cm and 40% smaller than 5.0 cm (**Fig. 63.13**).[45] In addition to aortic diameter, age, sex, body size, and rate of aortic growth, mechanical and hemodynamic factors also play a role. The mechanisms responsible for individual susceptibility to acute dissection at a certain aortic diameter are not well understood.

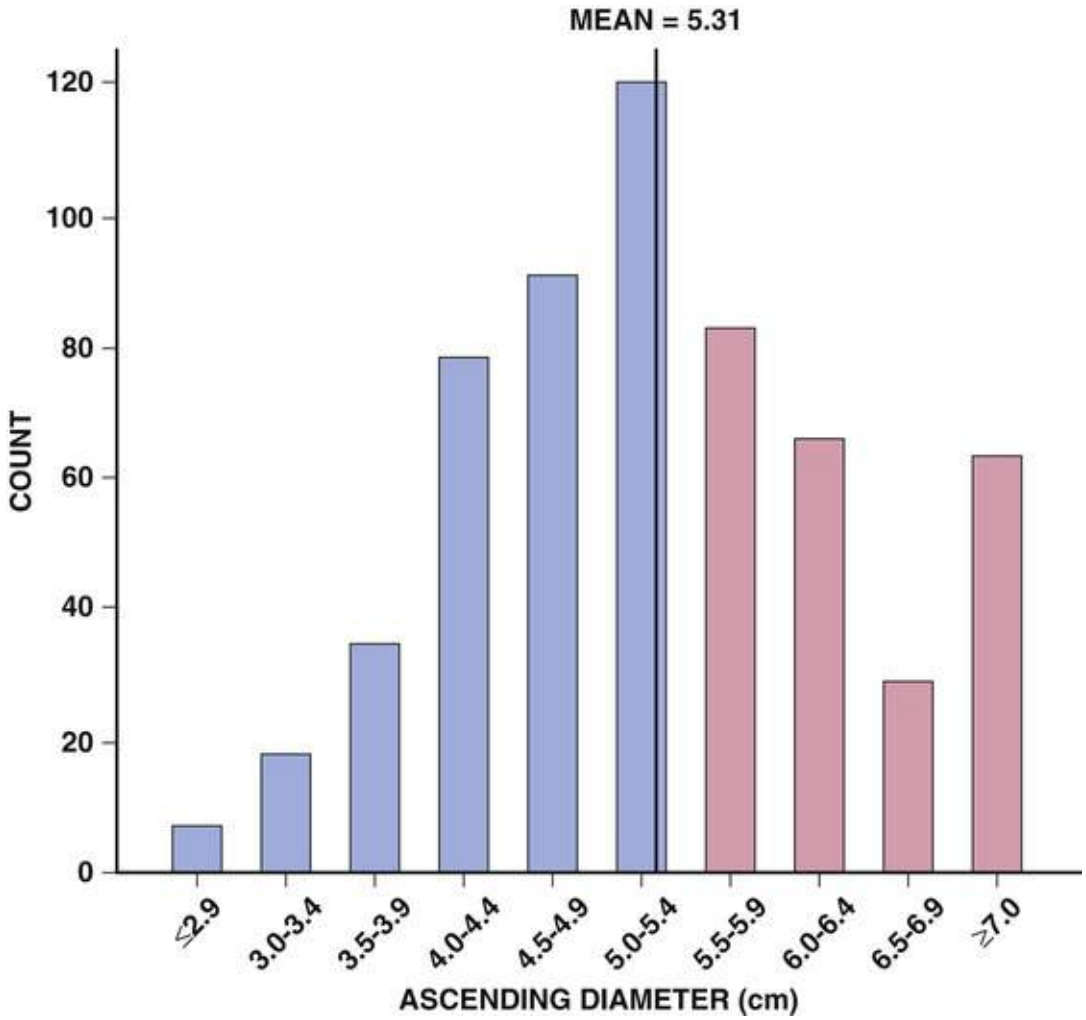


FIGURE 63.13 Distribution of aortic size (in cm) at the time of presentation with acute type A aortic dissection from IRAD. *Blue/purple bars* indicate patients with diameters less than 5.5 cm. (From Elefterades JA, Farkas EA. Thoracic aortic aneurysm: clinically pertinent controversies and uncertainties. J Am Coll Cardiol 2010;55:841-57. Modified from Pape L, Tsai TT, Isselbacher EM, et al. Aortic diameter ≥5.5 cm is not a good predictor of type A aortic dissection: observations from the International Registry of Acute Aortic Dissection (IRAD). Circulation 2007;116:1120-7. Illustration by Rob Flewell.)

Clinical Manifestations

Symptoms

The symptoms of aortic dissection can be variable and may mimic those of more common conditions, thus emphasizing the importance of a high index of suspicion. Abrupt onset of severe chest or back pain is the most classic feature.[1,38] Distinct from the discomfort of coronary ischemia, the pain is described as severe in approximately 90% of patients and usually of sudden onset, with maximum intensity occurring at its inception. The pain may be accompanied by a "sense of doom." The quality of the pain is most commonly described as "sharp," "severe," or "stabbing," and adjectives such as "tearing" or "ripping" are used less often.[1,17,38] Symptoms highly suggestive of aortic dissection, such as a feeling of being "stabbed in the chest with a knife" or "hit in the back with a baseball bat," may be reported, but some describe chest burning, pressure, or pleuritic pain. The pain may lessen or resolve which makes diagnosis even more challenging. In some patients the symptoms related to a complication (e.g., syncope, heart failure, stroke) dominate, and the pain is not mentioned or is downplayed. Factors associated with delay in diagnosis include female gender, transfer from another hospital, fever, and normal BP.[37]

The pain of acute aortic dissection is migratory in approximately 17% of cases and tends to follow the

path of the dissection through the aorta.[1,38] The pain of dissection may radiate from the chest to the back, or vice versa. Pain in the neck, throat, jaw, or head predicts involvement of the ascending aorta (and often the great vessels), whereas pain in the back, abdomen, or lower extremities usually indicates descending aortic involvement.

Other clinical features at presentation include congestive heart failure (CHF) (<10%), syncope (9%), acute stroke (6%), acute MI, paraplegia, and cardiac arrest or sudden death.[47] Acute CHF related to type A dissection may result from acute severe AR. Syncope in patients with type A dissection is usually associated with hemopericardium, rupture, or stroke. Patients with aortic dissection infrequently have predominantly abdominal pain, which may lead to delays in diagnosis. “Painless” aortic dissection occurs in 6% of patients and is more common in those with diabetes, previous aortic aneurysm, and prior cardiac surgery.[47]

Physical Findings

Findings on physical examination and organ system complications in patients with acute aortic dissection are highly variable and range from virtually unremarkable to full cardiac arrest secondary to hemopericardium or rupture. The findings may demonstrate complications related to the dissection, such as AR, abnormal peripheral pulses, stroke, or CHF (**Table 63.6**). The presence of these findings must heighten clinical suspicion for aortic dissection,[17] but their absence does not exclude dissection and should not dissuade pursuit of the diagnosis when suspected. Hypertension occurs in approximately 70% of patients with acute aortic dissection.[38] Although most patients with type B dissection are hypertensive, many with type a dissection are normotensive or hypotensive on initial evaluation.[1,17,38,47] Hypotension complicating acute dissection may result from cardiac tamponade, acute aortic rupture, or CHF related to acute severe AR.

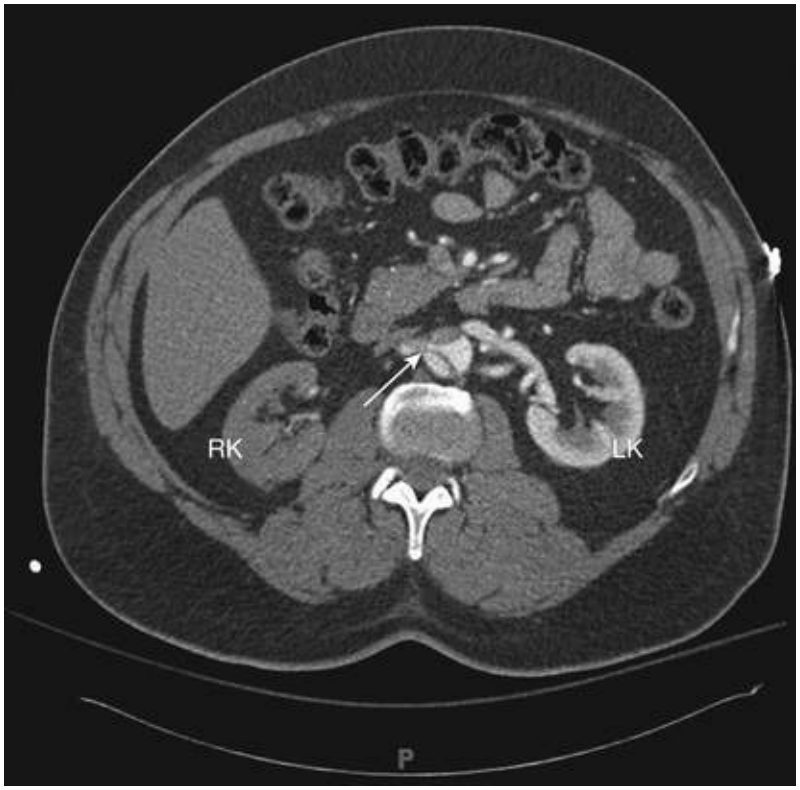
TABLE 63.6

Organ System Complications of Acute Aortic Dissection

Cardiovascular	Cardiac arrest Syncope Aortic regurgitation Congestive heart failure Coronary ischemia Myocardial infarction Cardiac tamponade Pericarditis
Pulmonary	Pleural effusion Hemothorax Hemoptysis (from an aortotracheal or bronchial fistula)
Renal	Acute renal failure Renovascular hypertension Renal ischemia or infarction
Neurologic	Stroke Transient ischemic attack Paraparesis or paraplegia Encephalopathy Coma Spinal cord syndrome Ischemic neuropathy
Gastrointestinal	Mesenteric ischemia or infarction Pancreatitis Hemorrhage (from aortoenteric fistula)
Peripheral vascular	Upper or lower extremity ischemia
Systemic	Fever

The physical findings typically associated with aortic dissection—pulse deficits, AR, and neurologic manifestations—are more characteristic of ascending than descending dissection. A pulse deficit is

reported in 31% of type A dissections and 19% of type B dissections, with frank limb ischemia less common.[1,38] Malperfusion may be dynamic, static, or mixed. Dynamic malperfusion is most common and results from the overpressurized false lumen pushing the septum toward the true lumen, leading to collapse of the true lumen and obstruction of branch vessels. Static malperfusion results from stenosis or occlusion of a branch artery caused by the dissection flap, hematoma, embolism, or thrombosis[17,48] (**eFig. 63.11**).



EFIGURE 63.11 Contrast-enhanced computed tomography scan demonstrating malperfusion of the right kidney (*RK*) because of acute aortic dissection. The dissection flap involves the right renal artery (*arrow*). The left kidney (*LK*) demonstrates normal perfusion and opacification, whereas the RK has poor perfusion with contrast material, consistent with malperfusion.

Aortic regurgitation (AR), a key diagnostic feature of type A dissection, occurs in 41% to 76% of patients[17,38,47] (**Fig. 63.14**) (Video 63.6). The murmur of AR varies in intensity, depending on BP and the degree of heart failure, and may be inaudible in some cases. Potential mechanisms of AR include (1) incomplete coaptation of the aortic leaflets caused by concurrent dilation of the aortic root and annulus or by acute aortic dilation from an expanding false lumen leading to central aortic regurgitation; (2) aortic leaflet prolapse caused by the dissection flap propagating into the aortic leaflets or commissures or by distortion of proper leaflet alignment by an asymmetric dissection flap (**Fig. 63.14**) (Videos 63.7 and 63.8); (3) an extensive or circumferential dehiscing intimal flap prolapsing into the left ventricular outflow tract during diastole and interfering with valve coaptation (Videos 63.9 and 63.10); or (4) preexisting AR resulting from an underlying aortic root aneurysm or BAV disease[17] (Video 63.11).

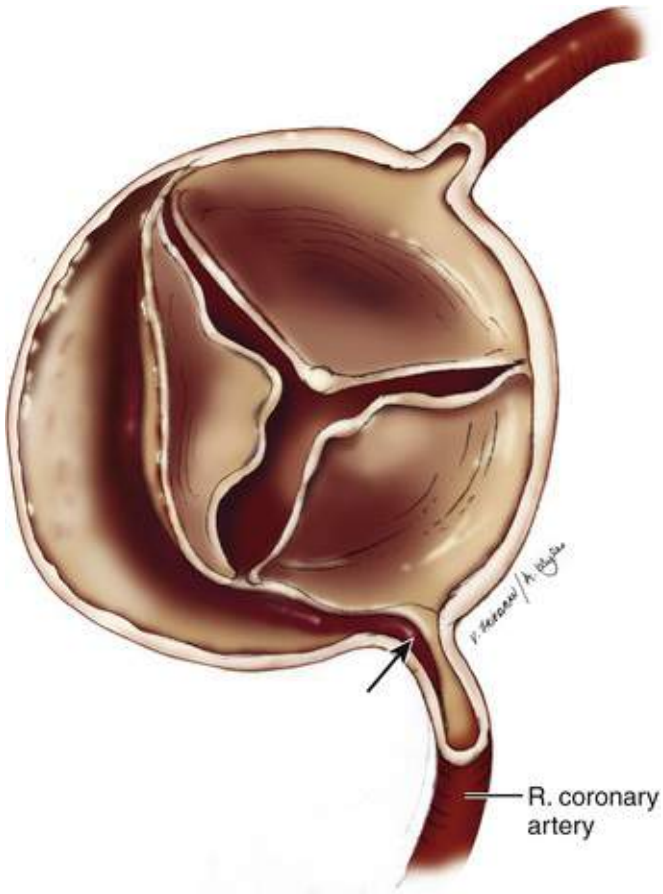


FIGURE 63.14 Aortic regurgitation complicating acute type A aortic dissection. The dissection flap distorts the normal aortic leaflet alignment, thereby leading to malcoaptation of the aortic valve and subsequent aortic regurgitation. In this example the dissection flap extends into the ostium of the right coronary artery (*arrow*).

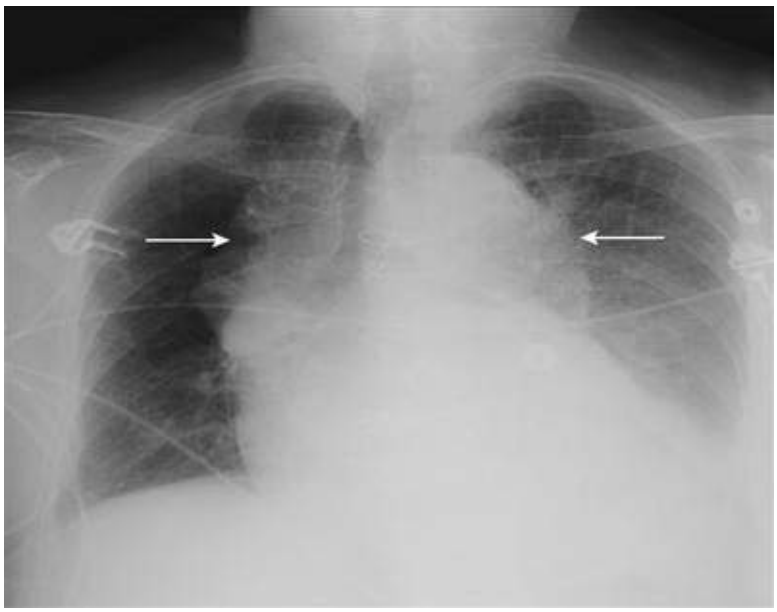
Neurologic manifestations occur in 17% to 40% of patients with aortic dissection and are more common with type A dissections.[49] Neurologic syndromes include persistent or transient ischemic stroke, spinal cord ischemia, ischemic neuropathy, and hypoxic encephalopathy and are related to malperfusion of one or more branches supplying the brain, spinal cord, or peripheral nerves. Ischemic stroke occurs in approximately 6% of patients with type A dissection.[47] Syncope occurs in 19% of type A and 3% of type B aortic dissection and may be related to acute hypotension (caused by cardiac tamponade, severe AR, or aortic rupture), obstruction of a cerebral vessel, or activation of cerebral baroreceptors and carries an increased mortality rate.[17,38,47] Less common neurologic manifestations of dissection include seizures, transient global amnesia, ischemic neuropathy, disturbances in consciousness and coma, and paraparesis or paraplegia related to spinal cord ischemia. Coma and cerebral malperfusion are associated with poor outcomes,[49] but some studies have failed to identify brain malperfusion as an independent risk factor for an adverse outcome after surgical repair.[17,47]

Acute MI related to the false lumen compressing the coronary ostium or the dissection flap involving the coronary artery complicates 1% to 2% of patients with acute type A aortic dissection.[1] It most frequently involves the right coronary artery (**Fig. 63.14**) and leads to acute inferior MI. Troponin elevations and electrocardiographic changes may occur in acute dissection.[1] Aortic dissection may not be suspected as a cause of coronary ischemia, and misdiagnosis may lead to inappropriate therapy and delays in treatment. Considering aortic dissection in the differential diagnosis of patients with acute coronary ischemia or infarction, especially when their risk factors, symptoms, or findings on examination are compatible with this diagnosis, is important. When coronary angiography in a patient with ST-segment elevation myocardial infarction (STEMI) shows no culprit lesion, aortic dissection should be excluded.[17]

Aortic dissection may extend into the abdominal aorta and result in vascular complications and malperfusion. Renal artery involvement occurs in at least 5% to 10% of patients and may lead to renal ischemia, infarction, or renal insufficiency or refractory hypertension (**eFig. 63.11**). Mesenteric ischemia occurs in less than 5% of patients with aortic dissection and is associated with a marked increase in mortality. The symptoms may be insidious, associated with nonspecific abdominal complaints, and a high index of suspicion must be maintained for this complication.[1,17] Aortic dissection may lead to a left-sided pleural effusion, usually related to an inflammatory response. Acute hemothorax may result from rupture. Type A aortic dissection may be accompanied by acute pericarditis but more often is a bland pericardial effusion. Acute cardiac tamponade as a result of rupture with hemopericardium complicates approximately 9% of type A dissections and is related to worse outcomes.[17] Isolated abdominal aortic dissection is rare (approximately 1% of dissections) and is associated with an existing AAA or an iatrogenic cause.

Laboratory Findings

The chest radiograph may be the first clue to the diagnosis of aortic dissection (**eFig. 63.12**), but the findings are nonspecific and in many cases, completely normal. The dissected aorta may not be dilated, and its image may not be displaced or widened on x-ray film. The most common abnormality seen is an abnormal aortic contour or widening of the aortic silhouette, which appears in approximately 80% of cases (83% of type A; 72% of type B).[47] Pleural effusions occur in approximately 20% of dissections. In the most recent IRAD survey, normal chest x-ray findings on presentation were found in 29% of type A and 36% of type B dissections.[38] Thus, a normal chest radiograph cannot exclude the presence of an aortic dissection. Laboratory tests important to obtain when evaluating for complications of aortic dissection include complete blood count, comprehensive metabolic profile, lactic acid, troponin, lactate dehydrogenase, and creatine kinase levels.



EFIGURE 63.12 Chest x-ray film of a patient with acute type A aortic dissection demonstrating a widened mediastinum and enlargement of the ascending and descending aortic shadows (*arrows*).

The electrocardiographic findings in patients with aortic dissection are nonspecific but may indicate acute complications such as myocardial ischemia or infarction related to coronary artery involvement or low-voltage QRS complexes related to hemopericardium. Ten percent of type B dissection patients have

electrocardiographic signs of ischemia.[1] Acute MI occurs in 1% to 2% of patients with type A dissections.

Biomarkers.
Reliable biomarkers for the diagnosis or exclusion of acute aortic dissection have stirred great interest. Release of smooth muscle proteins (calponin), soluble elastin fragments, myosin heavy chain and the BB isoform of creatine kinase, fibrin degradation products, and TGF-β occurs after aortic dissection.[37] These markers have limited usefulness because of sensitivity, specificity, or time delay and are not currently appropriate for clinical use. Patients with acute aortic dissection have elevated D-dimer levels reaching very high levels in many patients, making this a very useful biomarker for classic acute dissection.[1,17,37] In patients seen within the first 24 hours of onset, a D-dimer level lower than 500 ng/mL had a negative likelihood ratio of 0.07 and a negative predictive value of 95%. D-dimer is reported as having a sensitivity of 97% and a specificity of 47%.[37] Notably, normal D-dimer levels can occur with aortic dissection and a thrombosed false lumen, as well as with aortic IMH and PAU.[17] Additionally, patients may initially be seen longer than 24 hours after symptom onset, which affects D-dimer levels. Although a negative D-dimer result in low-suspicion patients may be useful, the negative likelihood ratio provided by the D-dimer assay is not sufficient in high-risk individuals and cannot “rule out” the disease in these patients.[17]

Diagnostic Techniques

When aortic dissection is suspected, expedient and accurate confirmation of the diagnosis is important. Diagnostic methods available to diagnose aortic dissection include contrast-enhanced CT, MRI, TEE, and TTE. TEE, helical CT, and MRI have very high diagnostic accuracy for suspected aortic dissection.[1,2,17] Each modality has advantages and disadvantages with respect to diagnostic ability, speed, convenience, and risk.[2] The choice of imaging study depends on the availability and expertise in the individual institution. If the probability of dissection is high and initial testing is negative or nondiagnostic, a second diagnostic test should be performed. When comparing imaging modalities, one must consider the diagnostic information needed. Besides diagnosing the type and location of dissection, additional useful information includes anatomic features and complications related to the dissection, including its extent, entry sites, and reentry sites; patency of the false lumen; involvement of branch vessels; severity of AR; hemopericardium; coronary artery involvement; malperfusion; and rupture (**eTable 63.1**).

ETABLE 63.1

Diagnostic Information from Imaging of Acute Aortic Dissection

1. Establish the presence of aortic dissection or variant (aortic IMH, PAU)
2. Location of the dissection (type A, type B)
3. Anatomic features a. Extent of dissection b. Sites of entry and reentry c. False lumen patency, partial thrombosis, thrombosis
4. Complications of dissection a. Type A i. Aortic regurgitation ii. Coronary artery involvement iii. Pericardial effusion/hemopericardium b. Aortic rupture or leakage c. Branch vessel involvement d. Malperfusion e. Aneurysmal enlargement

IMH, Intramural hematoma; *PAU,* penetrating atherosclerotic aortic ulcer.

Computed Tomography

Contrast-enhanced computed tomography (CECT) is the modality most often used for evaluating aortic dissection and is best performed with an electrocardiogram (ECG)-gated, multidetector scanner, which may eliminate aortic pulsation motion artifacts.[2] On CECT, aortic dissection is diagnosed by the presence of two distinct lumens with a visible intimal flap or by detection of two lumens by their differing rates of opacification with contrast material (**Fig. 63.15; see also Fig. 63.9 and eFigs. 63.4, 63.5, and 63.11**). If the false lumen is completely thrombosed, it demonstrates low attenuation. The false lumen usually has slower flow and a larger diameter than the true lumen.[1,2] CECT is highly accurate in diagnosing aortic dissection, with a sensitivity and specificity of 98% to 100%.[2,17] Spiral (helical) CECT allows three-dimensional reconstruction for evaluation of the dissection and branch vessels and is critical for planning endovascular repair. CT requires intravenous (IV) contrast material, and without contrast enhancement, aortic dissection may go undetected (**eFig. 63.13**). CT can identify the presence of thrombus in the false lumen and detect hemopericardium, aortic rupture, branch vessel involvement, and blood supply from the true and false lumens. Major limitations of CT include an inability to evaluate the coronary arteries and aortic valve reliably, motion artifact related to cardiac movement, streak artifact related to implanted devices, and complications associated with the use of contrast agents, especially nephropathy (**see Chapter 98**).

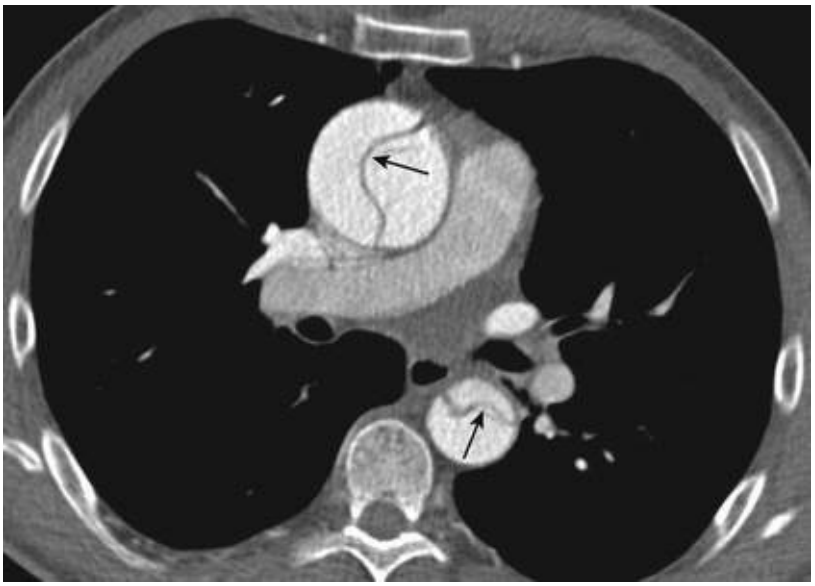
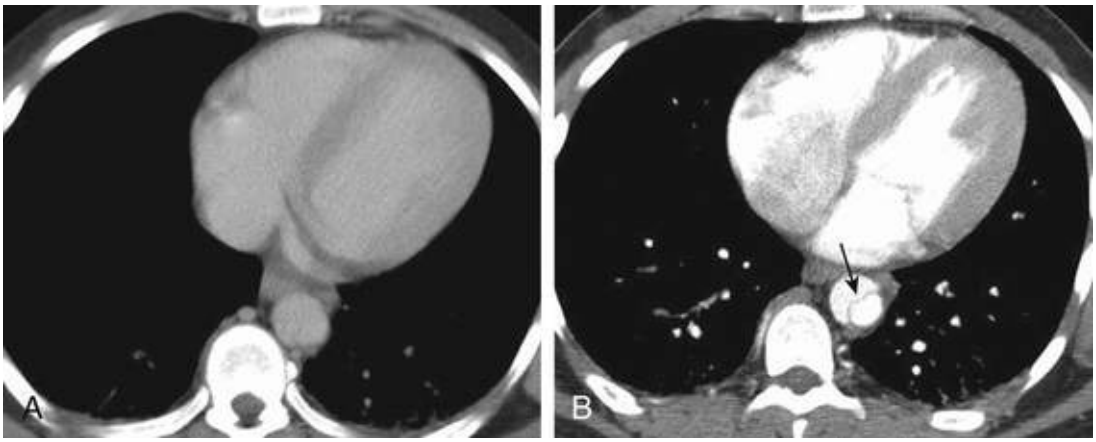


FIGURE 63.15 Contrast-enhanced computed tomography scan of acute type A aortic dissection. The ascending aorta is dilated, and a complex dissection flap is visualized in the ascending aorta (*upper arrow*) and descending aorta (*lower arrow*).



EFIGURE 63.13 Importance of contrast-enhanced computed tomography (CECT) in aortic dissection. CT scan of type B aortic dissection. **A,** Non-CECT fails to identify the dissection or intimal flap. **B,** CECT identifies the intimal flap *(arrow).*

Magnetic Resonance Imaging

MRI is highly accurate in evaluating aortic dissection, with sensitivity and specificity of 98%, and does not require IV iodinated contrast material or ionizing radiation[1,2,17] (**Fig. 63.16**). MRI permits multiplanar imaging with three-dimensional reconstruction and cine-MRI for visualization of blood flow, differentiation of slow flow and clot, evaluation of intimal flap mobility, and detection of AR. MRI can assess branch vessel morphology when combined with contrast-enhanced MRA. MRI may detect pericardial effusion, aortic rupture, entry points, and exit points with a high level of accuracy; MRA may detect and quantify AR. MRI has important limitations in evaluating acute aortic dissection. It is contraindicated in patients with certain implantable devices (pacemaker, defibrillator) and other metallic implants. MRI has limited availability on an emergency basis, and more time is needed to acquire images than with CT. Thus, MRI is infrequently used as the initial test for evaluation of acute dissection, but given its imaging detail and lack of ionizing radiation, it is particularly attractive for the long-term follow-up of aortic dissection.

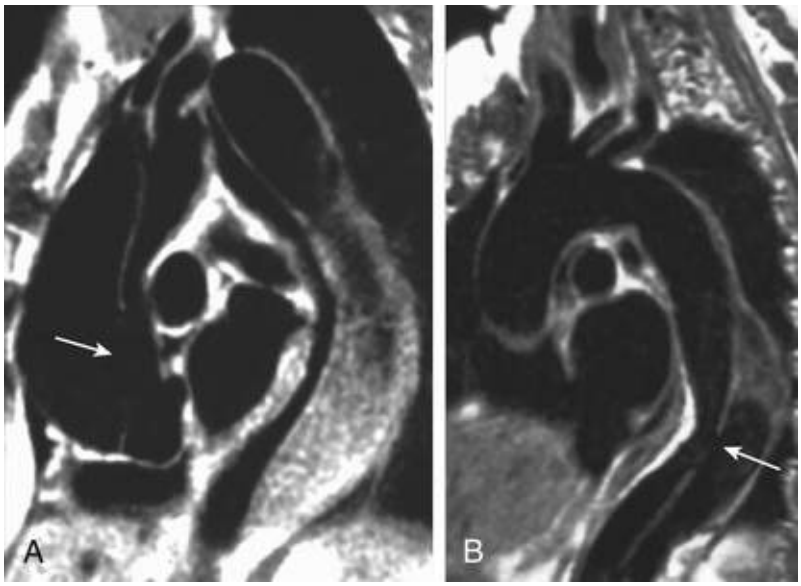


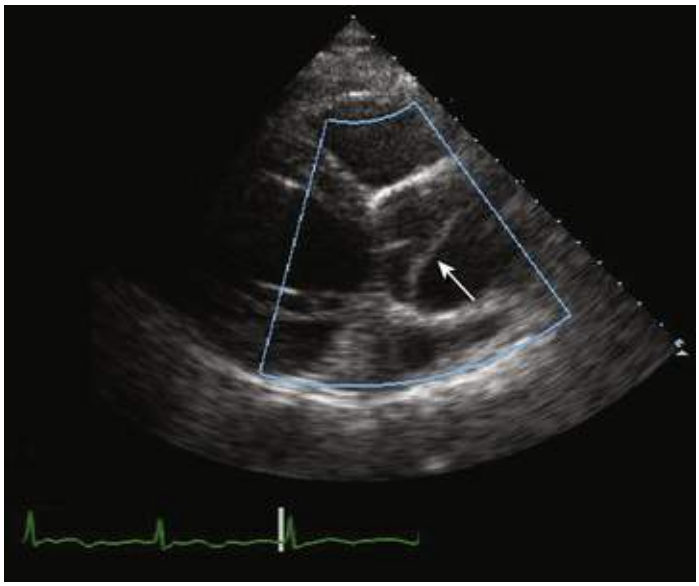
FIGURE 63.16 Spin-echo magnetic resonance images. **A,** Type A dissection. **B,** Type B dissection. The entry site is visualized as focal interruption of the linear image of the intimal flap (*arrows*). (From Baliga RB, Nienaber CA, Bossone E, et al. The role of imaging in aortic dissection and related syndromes. JACC Cardiovasc Imaging 2014;7:406-24.)

Ultrasound

The sonographic diagnosis of aortic dissection is based on the presence of an undulating intimal flap with independent motion within the aortic lumen that separates the true and false lumens[1,2] (Videos 63.12 to 63.19; also see Videos 63.2, 63.3, and 63.6 to 63.11). Color flow Doppler demonstrates differential flow in the two lumens and can detect intimal tears. When the false lumen is thrombosed, displacement of intimal calcification or thickening of the aortic wall suggests aortic dissection.

Transthoracic Echocardiography

TTE has sensitivity of 70% to 80% and specificity of 93% to 96% for the identification of type A aortic dissection, but it is much less sensitive (31% to 55%) than other modalities for the diagnosis of type B aortic dissection[17] (**eFig. 63.14** and Videos 63.12 to 63.14). Advanced imaging techniques and contrast enhancement can increase the accuracy of TTE for the diagnosis of type A aortic dissection.[1,2] Because TTE has a reduced sensitivity of detecting aortic dissection, negative findings do not exclude acute aortic dissection, but certain clues, including a dilated aorta, AR, or pericardial effusion, may suggest this diagnosis.



EFIGURE 63.14 Transthoracic echocardiogram of a type A aortic dissection. A dissection flap *(arrow)* is present in the dilated aortic root.

Transesophageal Echocardiography

TEE is highly accurate in the evaluation and diagnosis of acute aortic dissection (sensitivity, approximately 98%; specificity, 95%), but its accuracy is operator dependent (**Fig. 63.17**) (see Videos 63.2, 63.3, 63.7 to 63.10, and 63.15 to 63.18). TEE may not completely visualize the distal ascending aorta and proximal aortic arch, but it interrogates the remaining thoracic aortic segments well. TEE may visualize the intimal tear in 75% to 100% of cases, differentiate the true and false lumens, and identify fenestrations in the intimal flap (**eFig. 63.15**) (see Video 63.16). Features of the true lumen on TEE include a smaller lumen, systolic expansion, systolic anterograde flow, communication from the true to the false lumen in systole, and early and fast contrast-enhanced echocardiographic flow.[1,2] TEE is 100% sensitive in detecting AR complicating dissection and may define its mechanism (see Videos 63.6 to 63.11). TEE provides information about left ventricular function, the proximal coronary arteries, and pericardial effusion and may assist with endovascular treatment (see Videos 63.17 and Video 63.18).

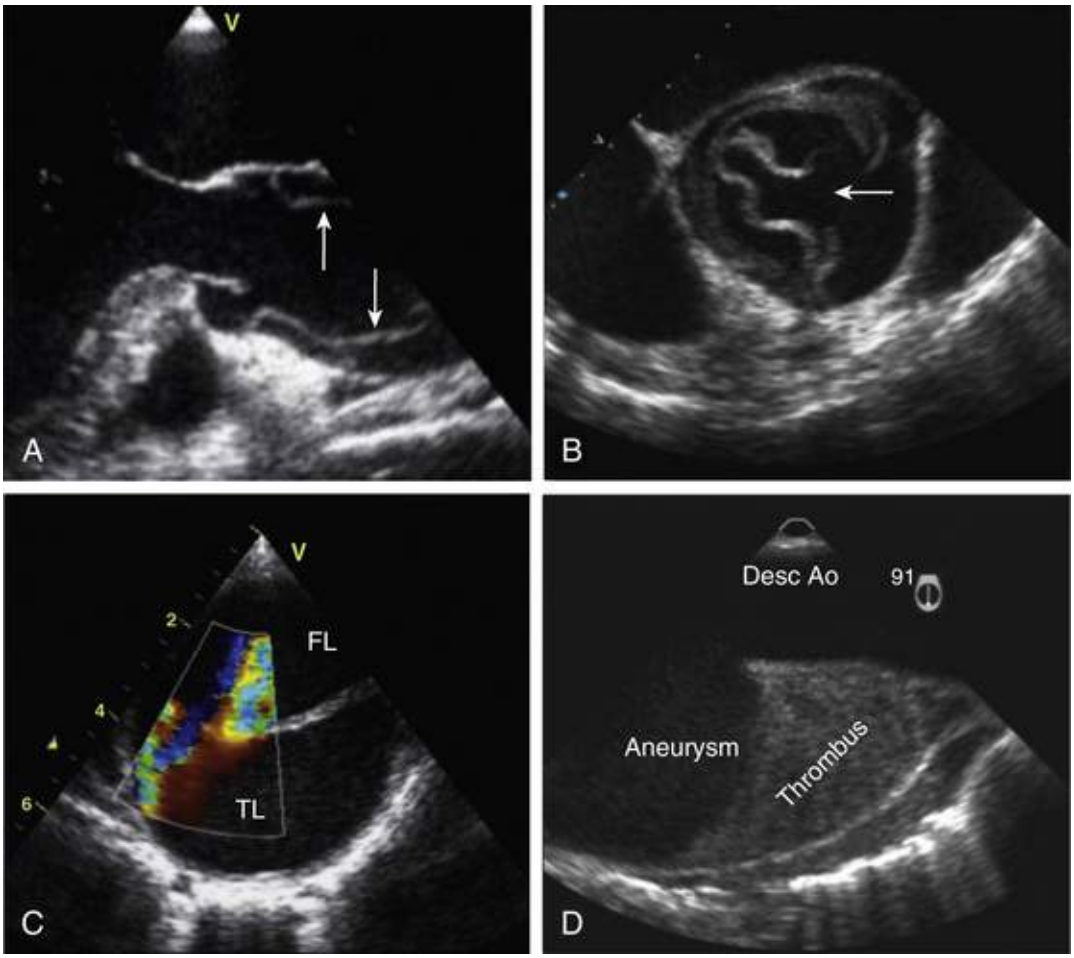
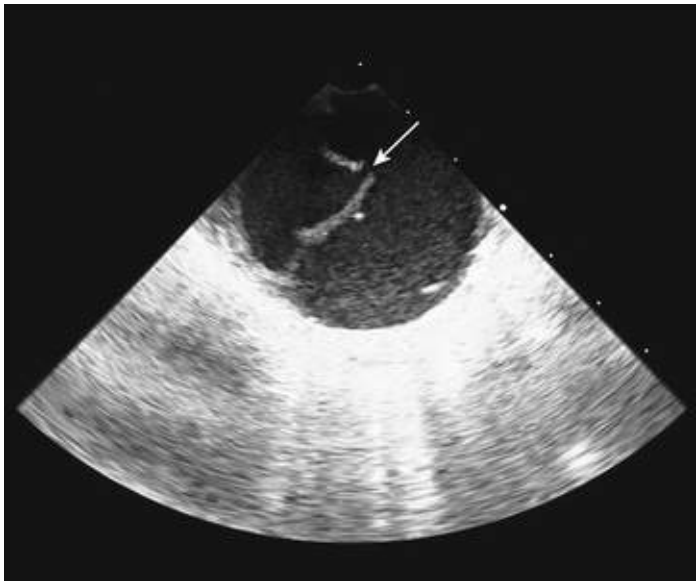


FIGURE 63.17 Transesophageal echocardiographic assessment of thoracic aortic disease. Acute type A dissection visualized in longitudinal and short-axis views; *arrows* indicate dissection lamella **(A)** and an intimal tear close to the aortic leaflets **(B). C,** Color flow mapping in a patient with chronic type B dissection shows vigorous flow into the false lumen (*FL*), demonstrating the communication between true lumen (*TL*) and FL. **D,** Partial thrombosis in aneurysmal FL in chronic type B dissection. (From Baliga RB, Nienaber CA, Bossone E, et al. The role of imaging in aortic dissection and related syndromes. JACC Cardiovasc Imaging 2014;7:406-24.)



EFIGURE 63.15 Transthoracic echocardiogram of a type B aortic dissection demonstrating the dissection flap and a small fenestration *(arrow)*.

Aortography

Aortography is no longer used for the initial diagnosis of suspected acute aortic dissection and is now used mainly during endovascular repair or coronary angiography. Findings of dissection on aortography include two lumens or an intimal flap, an undulating deformation of the aortic lumen, aortic wall thickening, branch vessel involvement, and AR. Compared with other imaging modalities, aortography has less accuracy in diagnosing aortic dissection. A false-negative aortogram may result from thrombosis of the false lumen, from equal opacification of both the true and false lumens, and from IMH.

Selecting an Imaging Modality

Because of its availability on an emergency basis, CECT is usually the first choice for the diagnosis of aortic dissection. The risk for contrast-induced nephropathy may complicate the decision about which test to perform when TEE or MRI is unavailable. Importantly, non–contrast-enhanced CT might fail to diagnose aortic dissection (**eFig. 63.13**). Non–contrast-enhanced MRA may diagnose aortic dissection when gadolinium contrast is contraindicated. TTE may be able to diagnose aortic dissection but does not have sufficient sensitivity to exclude aortic dissection. If TEE or MRI is not available on an urgent basis, the clinician must weigh the risks associated with IV contrast material versus the potential fatal consequences of failing to diagnose aortic dissection.

Role of Coronary Angiography

Routine coronary angiography is not recommended before surgery for acute type A aortic dissection because of concern about delay in emergency surgery.[17] Besides the delay incurred, coronary angiography may be technically difficult in the patient with dissection. Arterial access may fail to gain entry into the true lumen, and injury to the aorta from the catheter or guidewire may cause extension of the dissection or perforation of the aorta. In patients undergoing surgery for acute type A dissection, coronary artery involvement by the dissection can most often be corrected intraoperatively, and angiography is not required.

Evaluation and Management Algorithms

The thoracic aortic disease guidelines provide an algorithm for the management of patients with presentations compatible with acute aortic dissection[17,50] (**Fig. 63.18**). A bedside risk assessment determines whether the patient has any of three high-risk features: (1) *high-risk condition* (MFS or related disorder, familial TAA, family history of aortic disease, known aortic valve disease such as BAV, recent aortic manipulation, or known TAA); (2) *high-risk pain features*, including chest, back, or abdominal pain described as abrupt in onset, severe in intensity, and of ripping/tearing/sharp or stabbing quality; and (3) *high-risk examination features*, including perfusion deficit (pulse deficit, BP differential, focal neurologic deficit), murmur of AR, or hypotension. The presence of two or more high-risk features strongly suggests aortic dissection. Patients considered highly likely to have acute aortic dissection require emergency surgical consultation and expedited imaging. Patients whose features suggest aortic dissection and who do not have an alternative diagnosis require expedited imaging. Those with lower-risk profiles are evaluated for alternative diagnoses, but when none is considered likely or confirmed, aortic imaging is recommended. Further study is needed prospectively to validate the accuracy of this risk score.

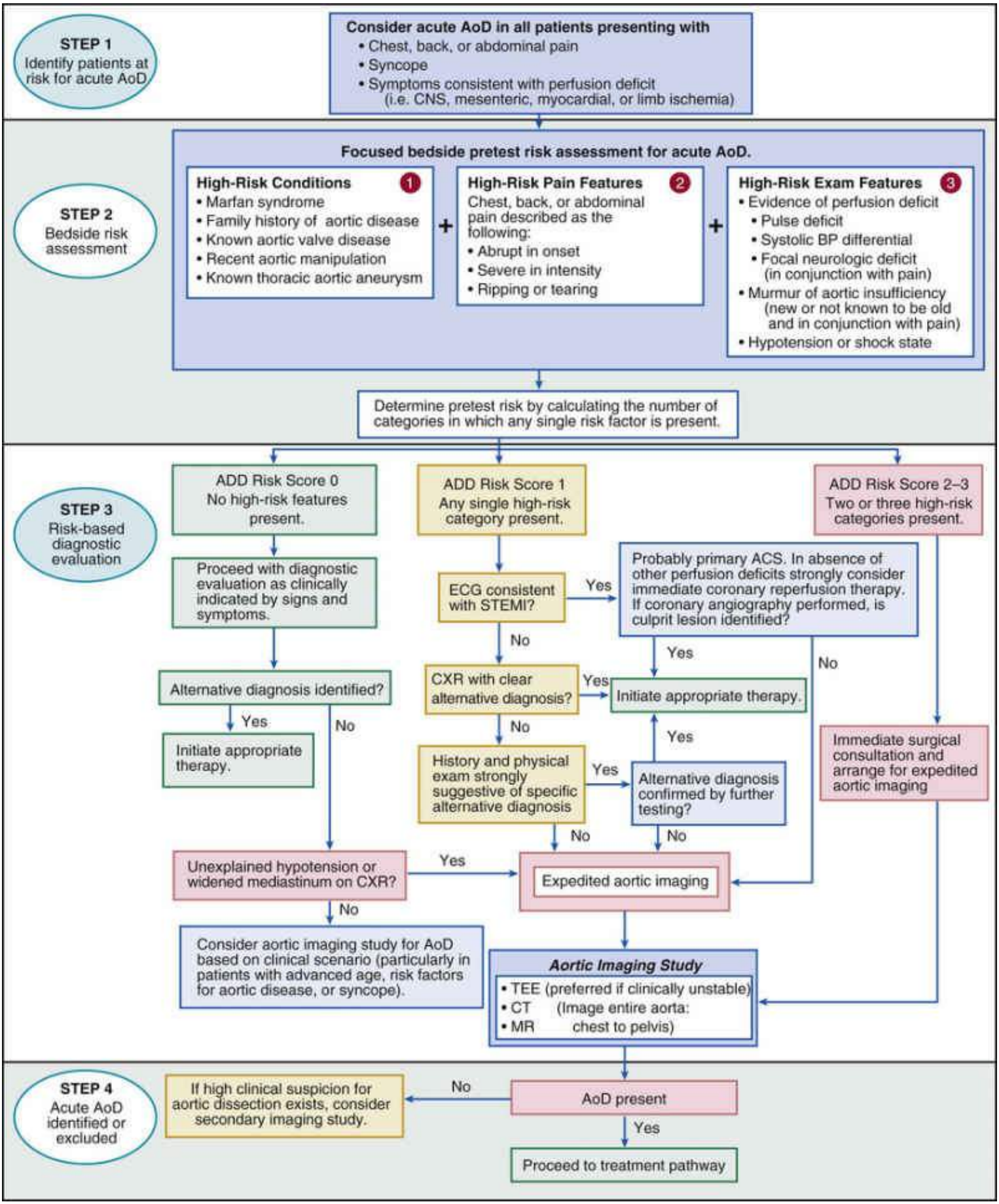


FIGURE 63.18 Evaluation pathway for aortic dissection (AoD). ACS, Acute coronary syndrome; ADD, aortic dissection detection; BP, blood pressure; CNS, central nervous system; CXR, chest x-ray film; STEMI, ST-segment elevation myocardial infarction. (Adapted from Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional

Management

The thoracic aortic disease guidelines suggest a management pathway for patients with acute aortic dissection (**Fig. 63.19**).[17] Initial medical management includes stabilizing the patient, controlling pain, and lowering BP with beta blockers to reduce the rate of rise in the force (dP/dt) of left ventricular contraction. These measures should commence immediately while the patient is undergoing diagnostic evaluation. Lowering BP may help prevent further propagation of the dissection and lessen the risk for aortic rupture. Aortic dissection has high mortality rate. In the IRAD initial report, medical management of acute type A dissection had a mortality of 20% in the first day and 30% by 48 hours.[47] A recent IRAD update reported survival for medically managed type A dissections to be 82% at 24 hours, 51% at 7 days, 40% at 30 days, and 38% at 60 days.[36] Emergency surgery leads to improved survival in patients with acute type A dissection, with an 18% in-hospital mortality for surgically treated type A dissection and 56% mortality for medically treated patients[38] (**see Fig. 63.12**). Age alone should not be an exclusion criterion for surgical treatment.[1] Initial medical therapy is recommended for acute type B dissections. Patients with acute aortic dissection require urgent multidisciplinary evaluation and management. Emergency transfer to a tertiary medical center with access to cardiovascular surgery, vascular surgery, interventional radiology, and cardiology is recommended for patients with acute dissection.[1,17] Hospitals with higher procedural volumes for surgically managed patients with acute type A and B dissections have lower mortality rates.[1,51]

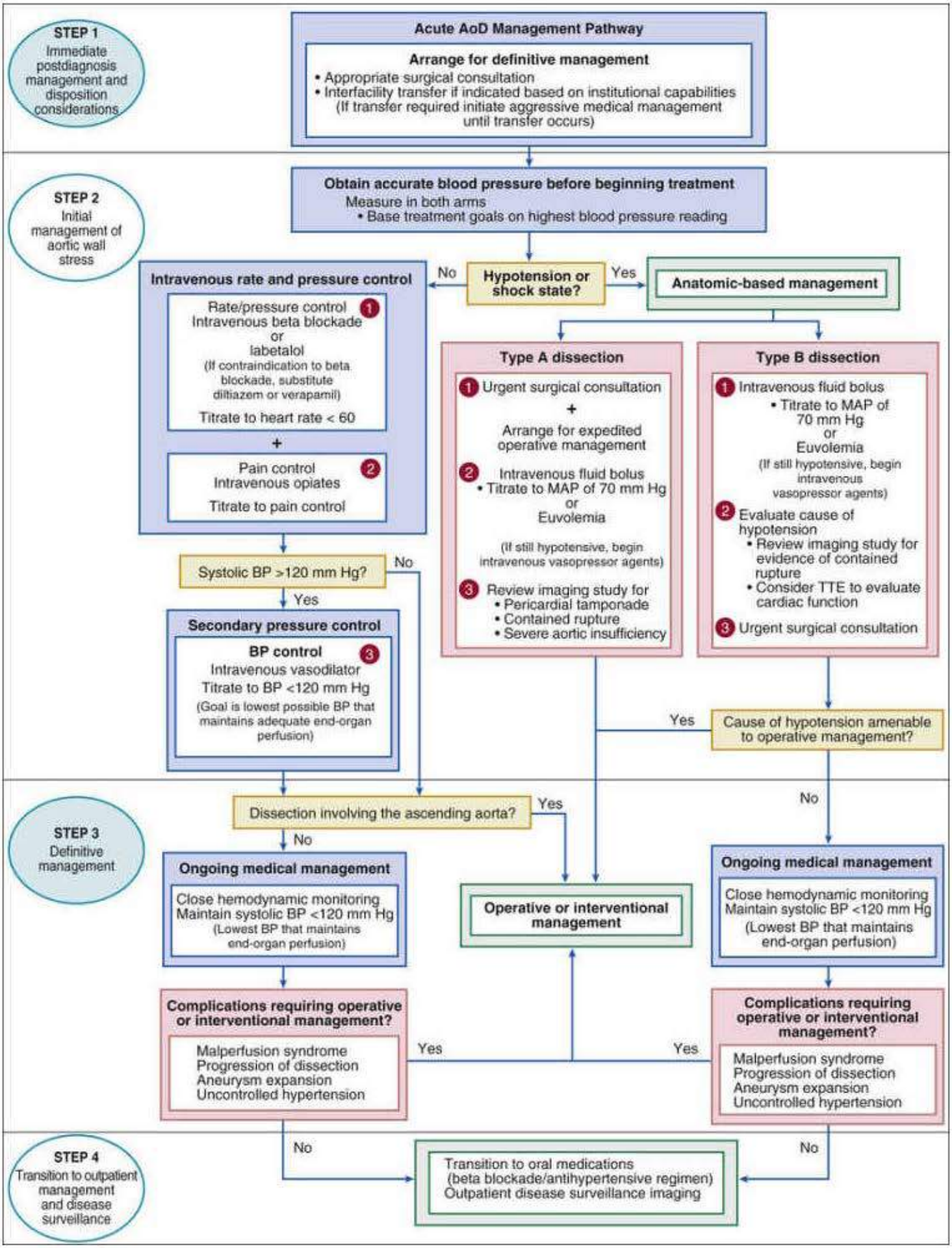


FIGURE 63.19 Management pathway for acute aortic dissection. AoD, Aortic dissection; BP, blood pressure; MAP, mean arterial pressure. (From Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: executive summary. Areport of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American

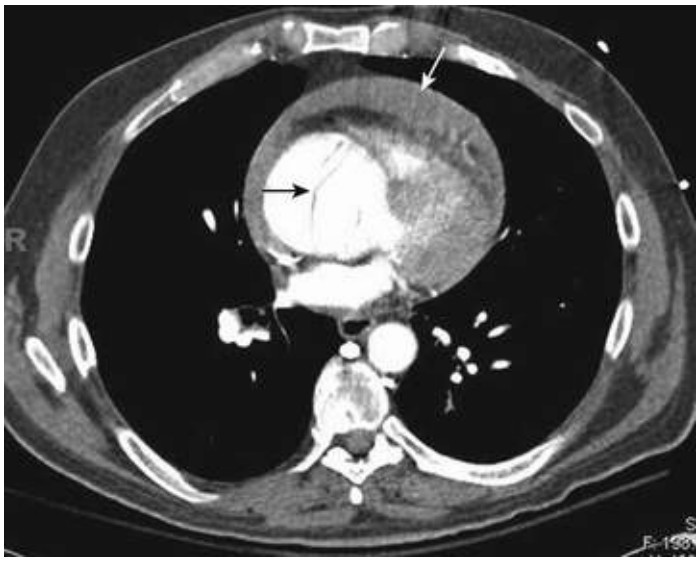
Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation 2010;121:e266.)

Blood Pressure Reduction

Reduction of systolic BP to levels of approximately 100 to 120 mm Hg or the lowest level necessary for adequate perfusion and a heart rate (HR) of 60 to 80 beats/min is recommended.[37] Beta blockers should be administered even if the patient does not have hypertension. For rapid administration of agents to reduce the rate of rise in ventricular force (dP/dt) and stress on the aorta, IV beta blockers may be given. Esmolol is given as an initial bolus of 1000 µg/kg and then as a continuous infusion of 150 to 300 µg/kg/min. Labetalol is given at an initial IV dose of 20 mg over 2 minutes and then at 40 to 80 mg every 10 minutes (maximum dose, 300 mg) until the desired response is achieved. Labetalol is then administered by continuous infusion at a rate of 2 to 10 mg/min, up to 300 mg total cumulative dose. Sodium nitroprusside leads to rapid reduction of BP but also may result in an increase in dP/dt; thus it must be used together with a beta blocker in the setting of acute aortic dissection. Sodium nitroprusside is initiated at a dose of 0.3 to 0.5 µg/kg/min, uptitrating by 0.5 µg/kg/min as required. Adequate control of BP and HR in patients with acute aortic dissection often requires multiple agents. IV ACE inhibitors and IV nitroglycerin may be useful. Other IV medications for severe hypertension include nicardipine (5 mg/hr, can be increased to a maximum of 15 mg/hr). When evaluating refractory hypertension in acute dissection, the clinician must consider renal artery malperfusion, which may require endovascular therapy (**eFig. 63.11**). The need for multiple antihypertensive agents to control BP acutely may wane after the first several days. Persistence of severe hypertension or signs of renal ischemia should prompt evaluation for renal artery involvement.

Management of Cardiac Tamponade

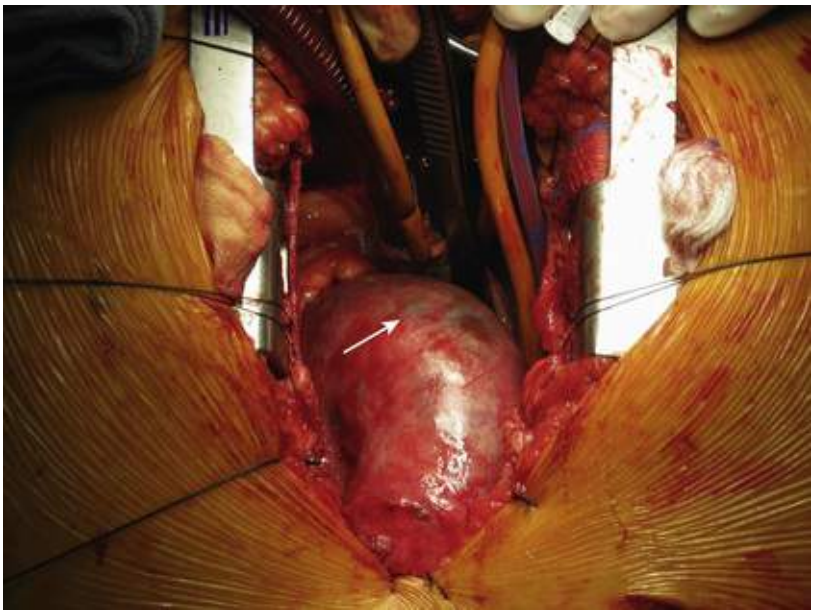
Cardiac tamponade, which occurs in 8% to 31% of acute type A dissections, is one of the most common mechanisms of death in patients with dissection[1,17,52] (**eFig. 63.16** and Video 63.13). Patients with tamponade may present with hypotension, syncope, or altered mental status and have double the in-hospital mortality rate as those without tamponade (54% versus 25%).[52] Pericardiocentesis for acute hemopericardium in patients with dissection can result in recurrent bleeding and acute hemodynamic collapse, especially if a larger volume of fluid is removed and increased BP leads to further brisk bleeding into the pericardial space. Therefore, in a relatively stable patient with acute type A dissection and cardiac tamponade, the risks associated with pericardiocentesis probably outweigh its benefits. Asian studies report the safety of pericardiocentesis for cardiac tamponade complicating IMH.[17] Hypotension or shock from hemopericardium secondary to ascending dissection requires emergency aortic surgery. However, for patients who will not survive until surgery, pericardiocentesis with aspiration of only enough pericardial fluid to stabilize the patient before surgery may be lifesaving and should be considered a treatment option in this setting.[17,52]



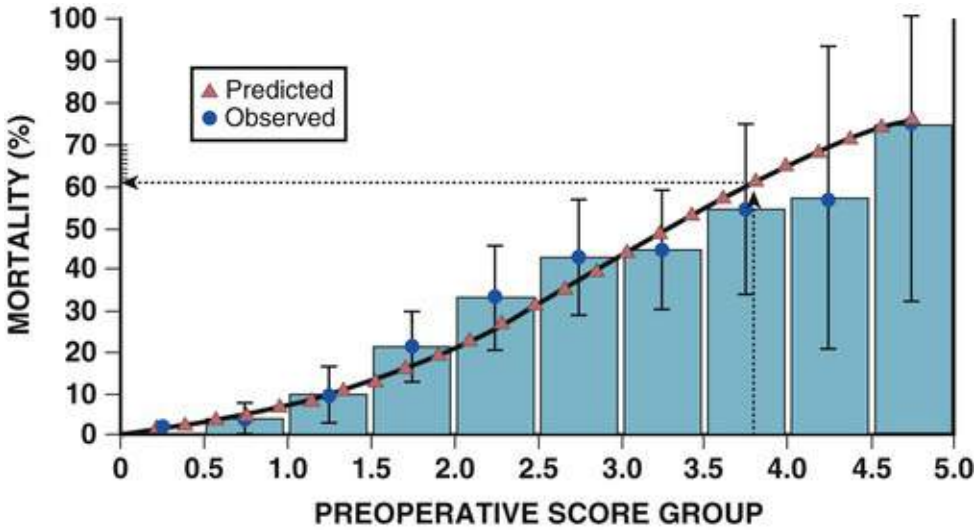
EFIGURE 63.16 Contrast-enhanced computed tomography scan of a dilated ascending aorta with acute type A aortic dissection *(black arrow)* complicated by hemopericardium *(white arrow).*

Definitive Therapy

Definitive therapy for acute aortic dissection includes emergency surgery for type A dissection in patients considered surgical candidates (**eFig. 63.17**). Patients with acute type A aortic dissection are at risk for aortic rupture, AR with heart failure, stroke, cardiac tamponade, and visceral ischemia. Compared to medical therapy, immediate surgical treatment improves survival in patients with acute type A aortic dissection.[17,38,47] In the most recent era of IRAD, the mortality rate of patients with type A aortic dissection undergoing surgery was 18%, versus 56% in those treated medically (typically because of advanced age and comorbid conditions)[36,38] (**see Fig. 63.12**). In experienced centers, 30-day surgical mortality for acute type A dissection is 10% to 35%.[37,38,47,49] Factors increasing mortality included shock, heart failure, cardiac tamponade, MI, renal failure, age, and malperfusion.[17,47,49,53] Type A aortic dissection surgery had a mortality rate of 16% in septuagenarians and 35% in octogenarians.[49] Although shock in type A dissection is associated with a high mortality rate, survivors with or without shock demonstrated a similar long-term mortality.[54] A bedside preoperative and postoperative risk prediction tool for mortality permits estimation of the risks associated with surgery for acute type A aortic dissection[55] (**eFig. 63.18 and eTable 63.2**).



EFIGURE 63.17 Intraoperative photograph of acute ascending aortic dissection demonstrating a dilated aortic root and ascending aorta. The aorta has a bluish discoloration (*arrow*) typical of underlying aortic dissection. (Photograph courtesy Dr. Nicholas Kouchoukos.)



EFIGURE 63.18 Observed versus model probabilities of death by preoperative score. Example: A 77-year-old woman had migrating chest pain, preoperative cardiac tamponade, a pulse deficit, and ST elevation. Her model score is 0.7 (age >70) + 0.9 (migratory chest pain) + 1.0 (preoperative cardiac tamponade) + 0.6 (pulse deficit) + 0.6 (ST elevation). Total score = 3.8. Estimated surgical mortality risk = 61%. (From Rampoldi V, Trimarchi S, Eagle KA, et al. Simple risk models to predict surgical mortality in acute type A aortic dissection: the International Registry of Acute Aortic Dissection score. Ann Thorac 2007;83:55.)

ETABLE 63.2

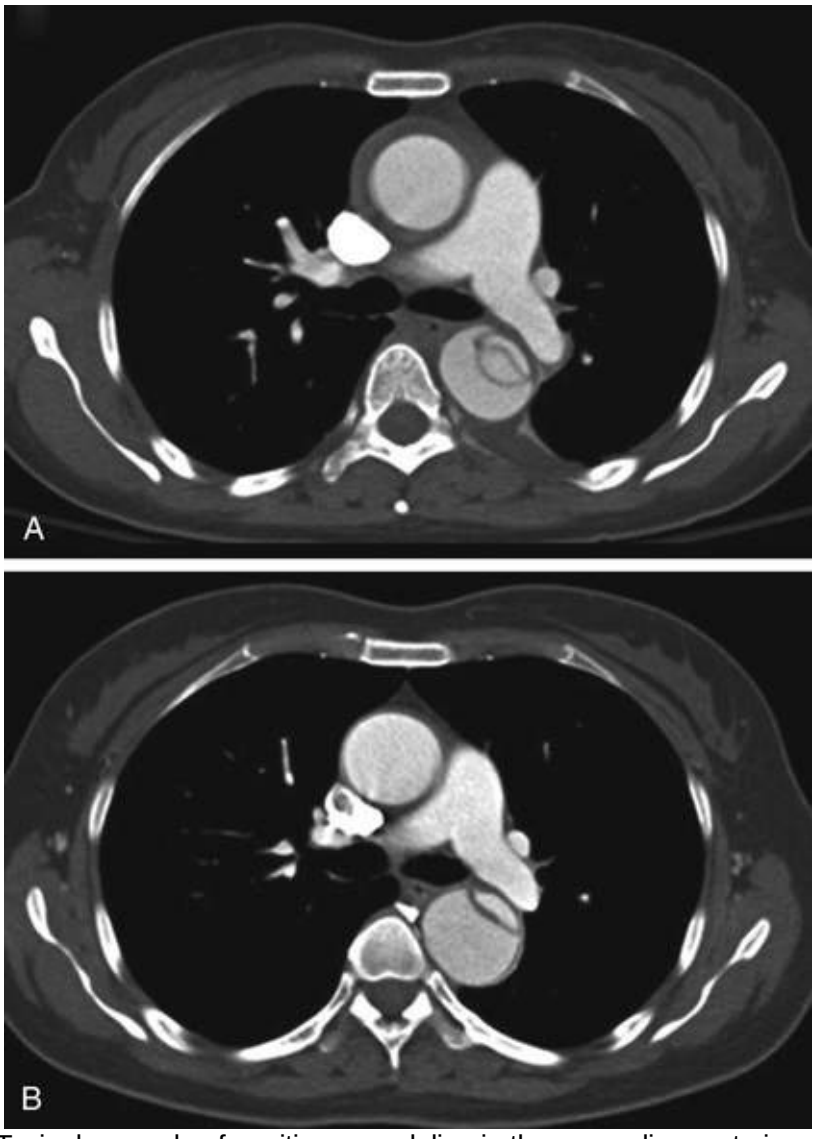
Preoperative Prediction Model of Risk for Surgical Mortality

VARIABLE	OVERALL TYPE A (%)	% IN SURVIVORS	% IN THOSE WHO DIED	COEFFICIENT	SCORE ASSIGNED	*P* VALUE	OR* FOR DEATH (95% CI)
Age ≥70 years	27.3	24.1	37.4	0.68	0.7	<0.01	1.98 (1.19-3.29)
History of aortic valve replacement	4.5	3.8	6.6	1.44	1.5	<0.01	4.21 (1.56-1.34)
Initially seen with hypotension, shock, or tamponade	28.8	22.4	49.0	1.17	1.2	<0.01	3.23 (1.95-5.37)
Migrating chest pain	13.8	12.1	19.3	0.88	0.9	<0.01	2.42 (1.32-4.45)
Preoperative cardiac tamponade	15.5	11.7	28.2	0.97	1.0	<0.01	2.65 (1.48-4.75)
Any pulse deficit	28.6	25.7	37.8	0.56	0.6	0.03	1.75 (1.06-2.88)

**OR,* Odds ratio; *CI,* confidence interval.

From Rampoldi V, Trimarchi S, Eagle KA, et al. Simple risk models to predict surgical mortality in acute type A aortic dissection: the International Registry of Acute Aortic Dissection score. Ann Thorac Surg 2007;83:55-61.

Select patients with type A dissection have undergone successful TEVAR and hybrid treatment, but more data are required in this area because of technical and anatomic restrictions.[37] Acute retrograde type A dissection with a primary intimal tear in the descending aorta is usually treated surgically. A favorable outcome has been reported for a few carefully selected patients treated with initial medical therapy and timely interventions when the ascending aortic extension is thrombosed and not aneurysmal[56] (**eFig. 63.19**).



EFIGURE 63.19 Typical example of positive remodeling in the ascending aorta is seen in a 48-year-old woman with acute retrograde type A aortic dissection. **A,** At initial presentation, maximal diameter of the ascending aorta was 43.6 mm with the thickness of thrombosed false lumen of 8.7 mm. **B,** After 15.6 months, the thrombosed false lumen in the ascending aorta disappeared, whereas the diameter of the ascending aorta decreased to 36.3 mm. (From Kim JB, Choo SJ, Kim WK, et al. Outcomes of acute retrograde type A aortic dissection with an entry tear in descending aorta. Circulation 2014;130[Suppl 1]:S39-44.)

Patients with acute type B aortic dissection have a lower acute mortality rate than those with acute type A dissection, with overall in-hospital mortality rates of approximately 10%.[38,57] In uncomplicated type B dissection, the in-hospital mortality rate is much lower—as low as 1% to 6% in those requiring only medical therapy[37,38]—but complicated type B dissection carries a much higher mortality rate, especially when accompanied by shock or malperfusion.[57] In the IRAD era, 57% of patients with acute type B dissection were treated medically, 32% received endovascular therapy, and 7% were treated with OSR, with in-hospital mortality rates of 10%, 14%, and 21%, respectively.[38] (**see Fig. 63.12**). National database trends report in-hospital mortality rates of 14.3% for type B dissection treated surgically and 7.9% treated with TEVAR.[51] Increasing age, female sex, hypotension/shock, periaortic hematoma, aortic diameter larger than 5.5 cm, and malperfusion are associated with increased mortality rates. A model using these variables may predict in-hospital mortality.[57] Typical indications for TEVAR in patients with complicated type B aortic dissection include visceral or limb ischemia, rupture or impending rupture, rapid expansion of the aortic diameter, uncontrollable pain, or retrograde extension of the dissection into the ascending aorta (**Table 63.7**). The preferred therapy for most complications is endovascular therapy.[1,37]

TABLE 63.7

Indications for Thoracic Endovascular Aortic Repair for Type B Aortic Dissection*

Rupture
Impending rupture
Malperfusion
Hemorrhagic pleural effusion
Refractory pain
Refractory hypertension
Aneurysmal dilation (>55 mm)
Rapid increase in diameter
Recurrent symptoms

*Or open surgical repair if anatomy is unsuitable for TEVAR.

Primary arch dissections are uncommon, and management of this condition must be individualized. Surgical repair of acute arch dissection has a mortality rate between 15% and 29%. If the ascending aorta is involved, the dissection is classified as type A, and emergency surgery is recommended. Many advocate initial medical therapy for primary arch dissections that do not involve the ascending aorta, whereas others recommend emergency surgery for some primary arch dissections, especially if aneurysmal enlargement is present. Type B dissections that extend retrogradely into the transverse arch have been managed variably; initial medical therapy is recommended for most. Isolated abdominal aortic dissections are rare and associated with hypertension, preexisting aneurysm disease, or genetic disorders. Most are spontaneous, but some are related to trauma or iatrogenic causes.

Surgical Management.

Operative therapy for acute aortic dissection is technically very demanding (see Video 63.18). The aortic wall is thin and friable, and Teflon felt and sutures with pledgets are used to buttress the wall and prevent the sutures from tearing the fragile aortic wall.

Type A Aortic Dissection.

OSR, performed as expediently as possible, is the treatment of choice for acute type A aortic dissection to prevent life-threatening complications.[1,17] An inverse relationship exists between hospital/surgeon volume and operative mortality for patients with acute type A dissection.[48] One must weigh the risks of surgery in a low-volume center versus the risk associated with a delay in transfer to a site with expertise. Surgical therapy aims to treat or prevent the common complications of dissection, including cardiac tamponade, AR, aortic rupture, stroke, and visceral ischemia. The immediate surgical goals are to excise the intimal tear; to obliterate the false channel by oversewing the edges of the aorta; and to reconstitute the aorta, directly or more often with placement of an interposition graft. In type A dissection, AR is also treated by resuspension of the aortic valve leaflets or by prosthetic AVR. Although some controversy surrounds the timing of directly treating malperfusion, the general consensus when this complication accompanies acute type A dissection is to repair the aorta first because this will correct the malperfusion in most patients.[1,17,48] Patient-specific therapeutic decisions must be made depending on the mechanism of malperfusion.[53] When severe malperfusion syndrome due to mesenteric ischemia or descending aortic pseudocoarctation is present, some have proposed that initial TEVAR to the descending aorta be performed.[48] However, this approach is associated with delay in definitive surgery and interim rupture rates of 5% to 23%.[48]

A median sternotomy is performed, and cannulation for cardiopulmonary bypass generally involves the axillary artery (**eFig. 63.20**) or less often the femoral approach (**eFig. 63.21**), to avoid trauma to the

weakened aortic wall.[48,58] A woven polyester vascular graft replaces the ascending aorta, and surgeon-specific methods to support the anastomosis are used[58] (**Fig. 63.20**). Most patients can be treated by obliteration of the false lumen by placement of Teflon felt as a neomedia and resuspension of the native aortic valve (**eFigs. 63.22 and 63.23**). Intraoperative aortic valve inspection and TEE guidance assist in managing the aortic valve in patients with proximal aortic dissection.[58] When AR complicates dissection, repair of the aortic wall, decompression of the false lumen, and resuspension of the commissures to the aortic wall will usually restore valve competence. In approximately 20% to 25% of patients who undergo conservative valve management, root dilation or progressive AR may develop late and require AVR or root replacement.[58] When aortic leaflet disease precludes repair, AVR plus associated ascending aortic replacement is indicated. When the sinuses are dilated, composite valve and root replacement is often performed via the modified Bentall procedure. If the sinus of Valsalva is involved by dissection, it is preferable to replace the aortic root to prevent late AR.[1] When the aortic root is dilated but the aortic leaflets are normal, many have achieved success by performing a reimplantation with valve-sparing root replacement[17,48] (**Fig. 63.20 and eFig. 63.9**). This complex process requires a longer procedure and surgical expertise, and for many, composite valve and root replacement is more appropriate. For dissections with a tear localized to the ascending aorta, with a normal-size arch without distal malperfusion, surgical repair involves a hemiarch replacement with an open distal anastomosis under circulatory arrest[48,58] (**eFig. 63.24**).

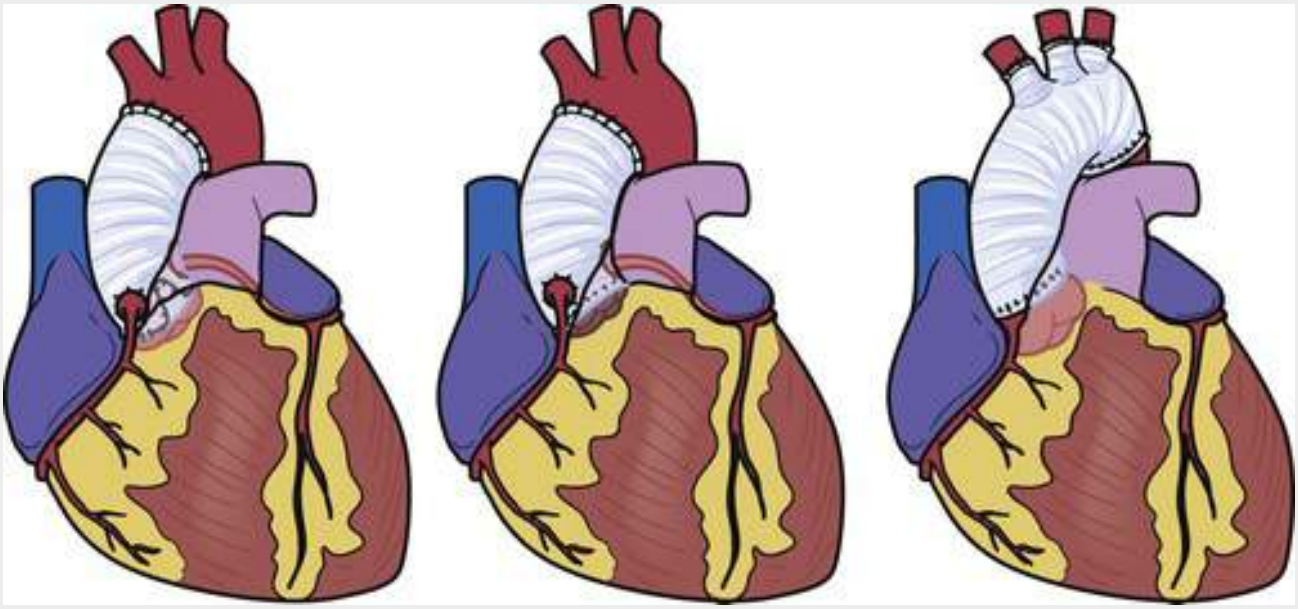
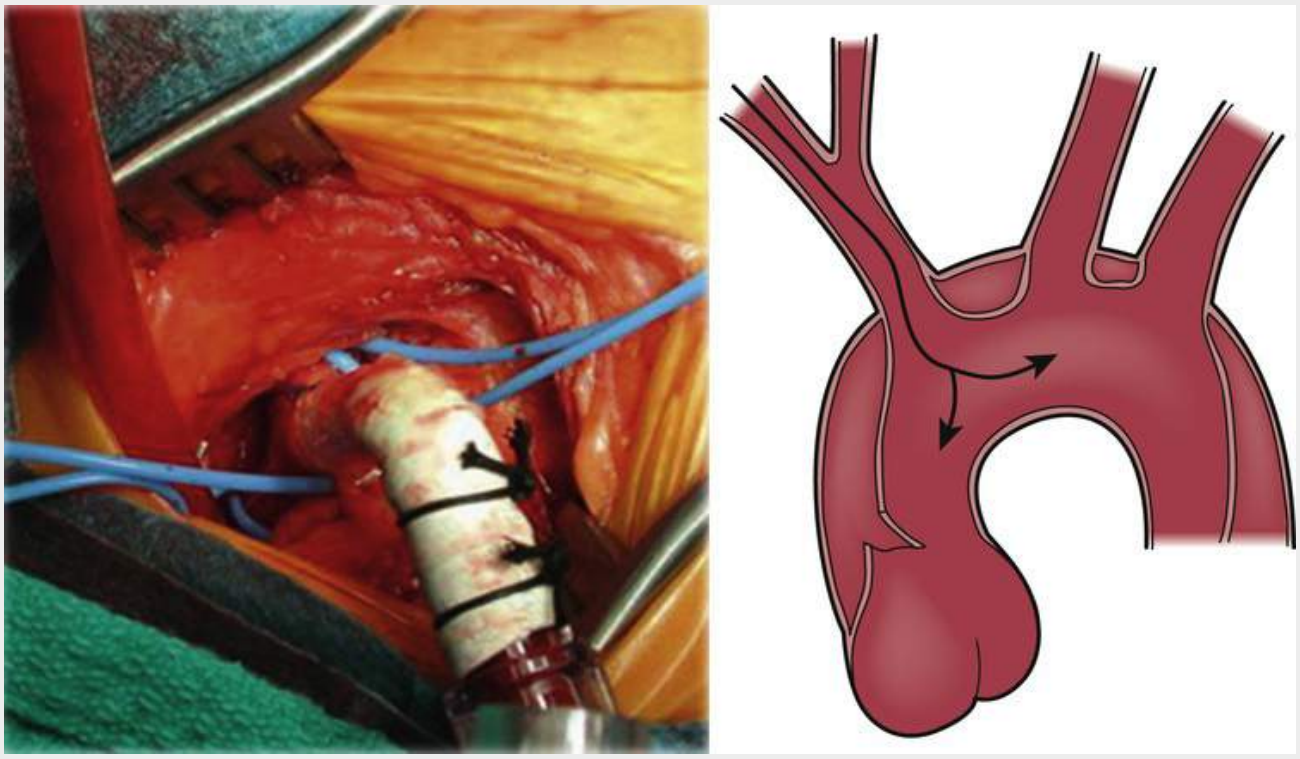
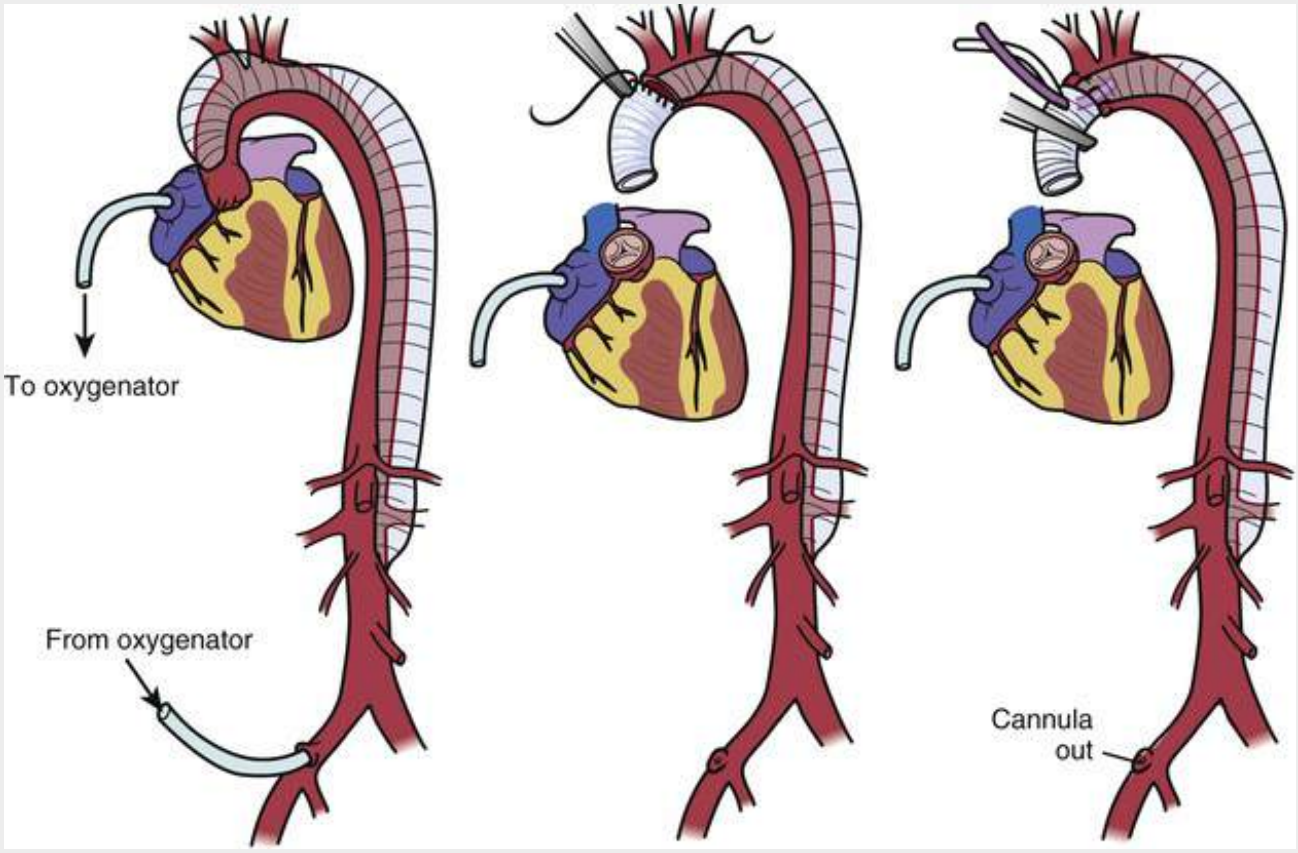


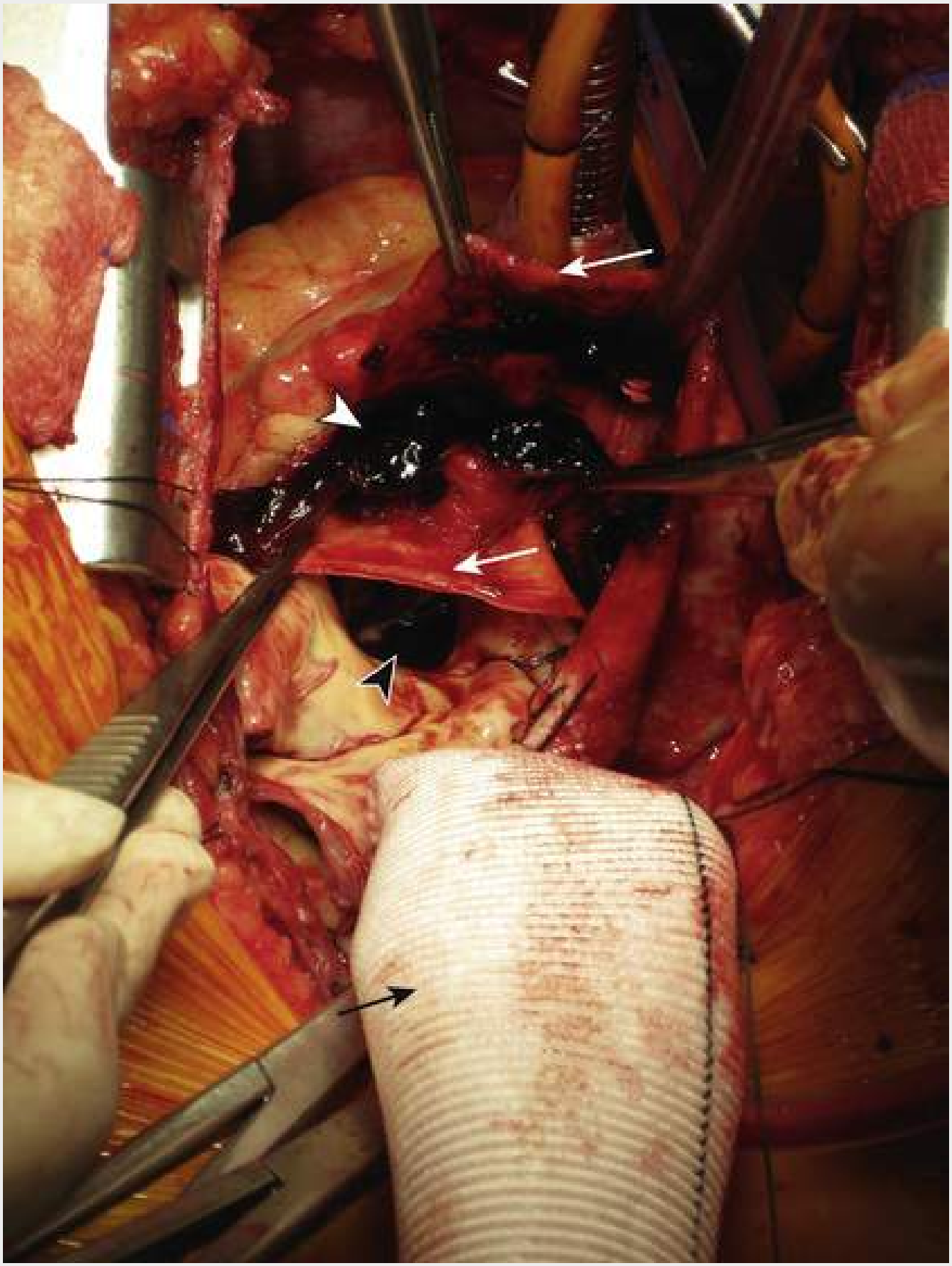
FIGURE 63.20 Different surgical procedures to repair proximal aortic dissection (type A). **Left to right,** DAVID procedure with reinsertion of coronary arteries and preservation of native aortic valve, replacement as both the ascending aorta and the native aortic valve, and total arch replacement with anastomoses to all head vessels. (From Nienaber CA, Divchev D, Palisch H, et al. Early and late management of type B aortic dissection. Heart 2014;100:1491-7.)



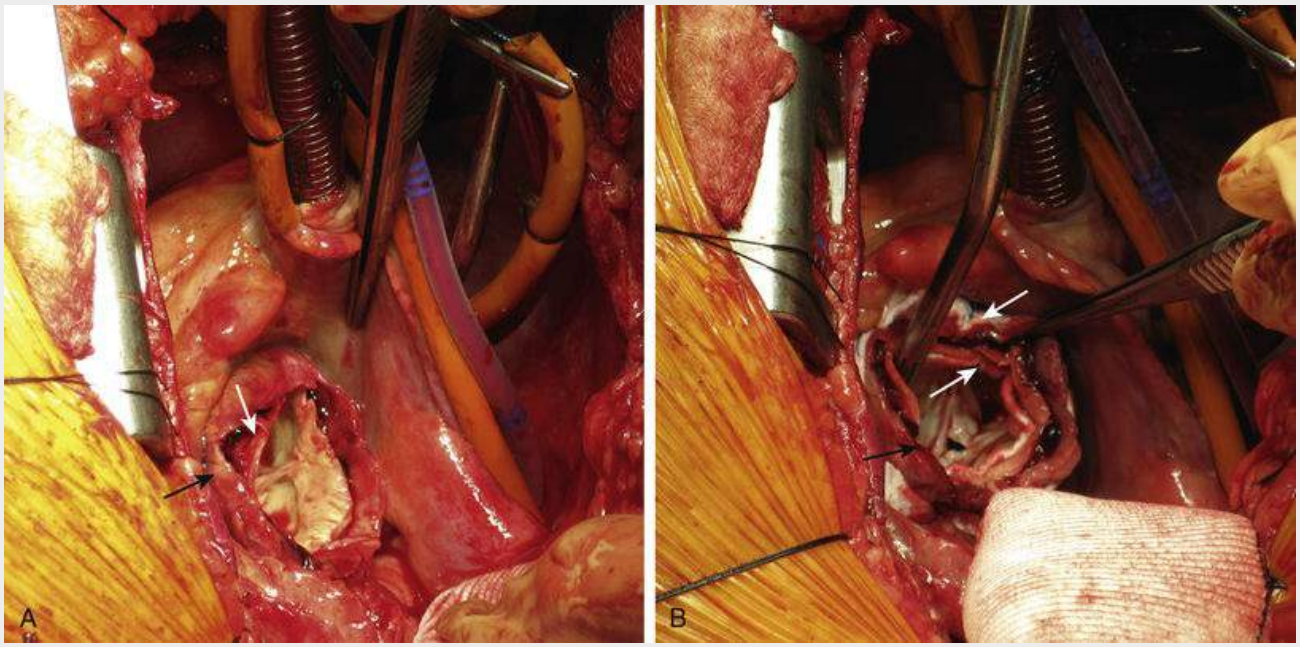
EFIGURE 63.20 Axillary artery perfusion in acute type A aortic dissection. Axillary artery perfusion may prevent malperfusion because blood is pumped into the true lumen. With this type of arterial return during cardiopulmonary bypass, the ascending aorta may be clamped without increasing the risk of malperfusion. (From David TE. Surgery for acute type A aortic dissection. J Thorac Cardiovasc Surg 2015;150:279-83.)



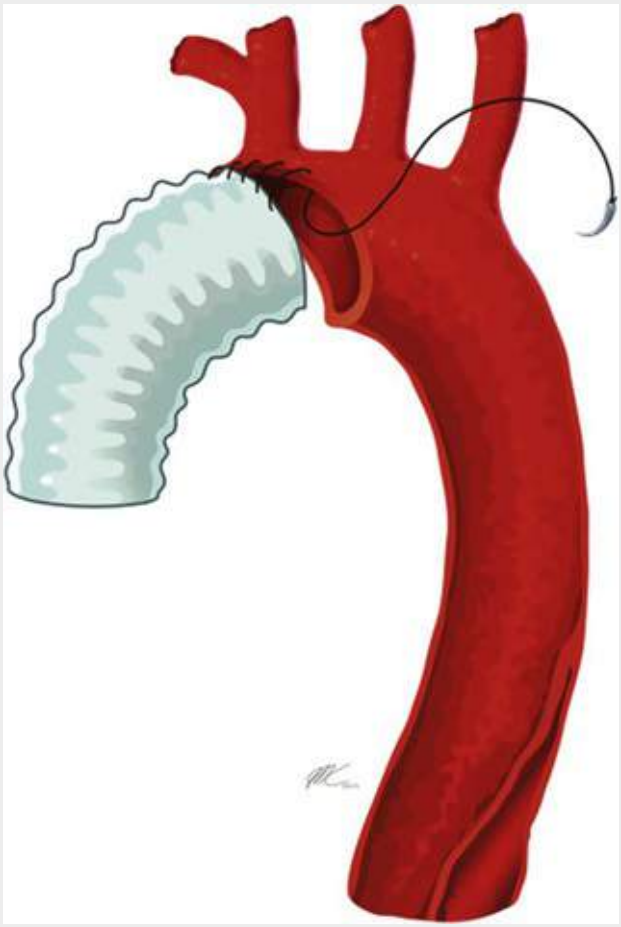
EFIGURE 63.21 Surgery for acute type A aortic dissection. Femoral artery perfusion reverses the flow in the false lumen, and aortic clamping should be avoided to reduce the risk of malperfusion. The distal anastomosis should be performed under circulatory arrest. The femoral cannula should be removed and inserted into the polyester fabric graft for antegrade perfusion after completion of the distal anastomosis.
(From David TE. Surgery for acute type A aortic dissection. J Thorac Cardiovasc Surg 2015;150:279-83.)



EFIGURE 63.22 Intraoperative photograph of the aortic root in acute ascending aortic dissection repair. The aortic valve is in the center (*black arrowhead*). The pickup is on the intimal flap (*upper white arrow*). Forceps elevate the outer wall of the false lumen (*lower white arrow*). Thrombus is visualized in the false lumen (*white arrowhead*). The aorta is being prepared for repair using a polyester graft (*black arrow*).
(Photograph courtesy Dr. Nicholas Kouchoukos.)



EFIGURE 63.23 Surgical repair of acute type A aortic dissection. **A,** Intraoperative photograph of surgical repair of acute type A aortic dissection. The aorta has been transected above the aortic commissures, and the inner (*white arrow*) and outer (*black arrow*) layers are approximated after removal of thrombus from the false lumen. **B,** The aortic valve has been suspended by three sutures placed at the top of each commissure (*black arrow*). A strip of polytetrafluoroethylene felt is placed within the true aortic lumen (*lower white arrow*), and another strip is placed outside the aorta (*upper white arrow*). A polyester graft will be sutured to the aorta, incorporating the two layers of the aorta and the two strips of felt. (Photograph courtesy Dr. Nicholas Kouchoukos.)



EFIGURE 63.24 Standard surgical repair involving hemiarch replacement and open distal anastomosis under circulatory arrest for patients with tears localized to the ascending aorta, a normal-caliber aortic arch, and no evidence of distal malperfusion. (From El-Hamamsy I, Ouzounian M, Demers P, et al. State-of-the-art surgical management of acute type Aaortic dissection. Can J Cardiol 2016;32:100-9. Image courtesy Dr. Jehangir Appoo.)

The aortic arch is dissected in more than 70% of type A dissections, and arch vessel involvement in the dissection process is reported in 28% to 73%.[1,17,49,58] Arch replacement, with the patient under deep hypothermic circulatory arrest, is also performed if the intimal tear is extensive throughout the arch and arch vessels and is not amenable to primary resection, if the aortic arch is aneurysmal or ruptured, if a primary arch tear is identified at surgery, and in some patients with hereditary aneurysm syndromes. Prolonged circulatory arrest times increase morbidity and mortality. Branched-graft techniques are preferred in managing arch vessels involved.[48] Although more complex procedures in which the entire aortic arch is replaced may reduce patency of the false lumen, this complex procedure carries higher risk than hemiarch or ascending aortic surgery. However, the German Registry for Acute Aortic Dissection Type A (GERAADA) study reported no difference in 30-day mortality comparing hemiarch and total arch versus no arch procedures.[49]

Extended distal repair may be performed to seal tears extending to the descending aorta and to improve obliteration of the false lumen distally.[48] The elephant trunk and the frozen elephant trunk procedures (see earlier section on TAAs) may be performed in acute type A dissection requiring extensive distal repair with multiple techniques available, including open, closed, and hybrid procedures[48,58] (**Fig. 63.21**).

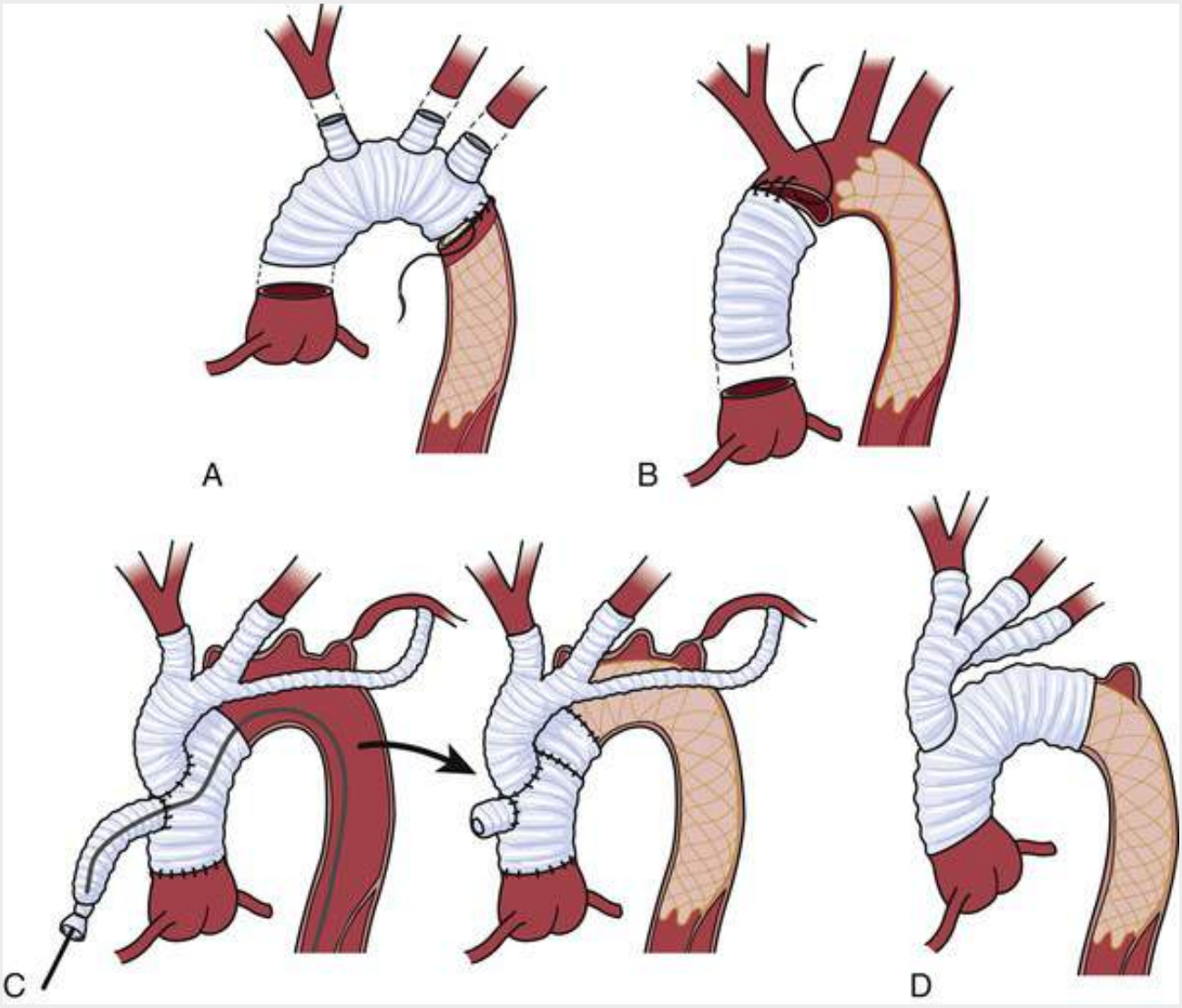
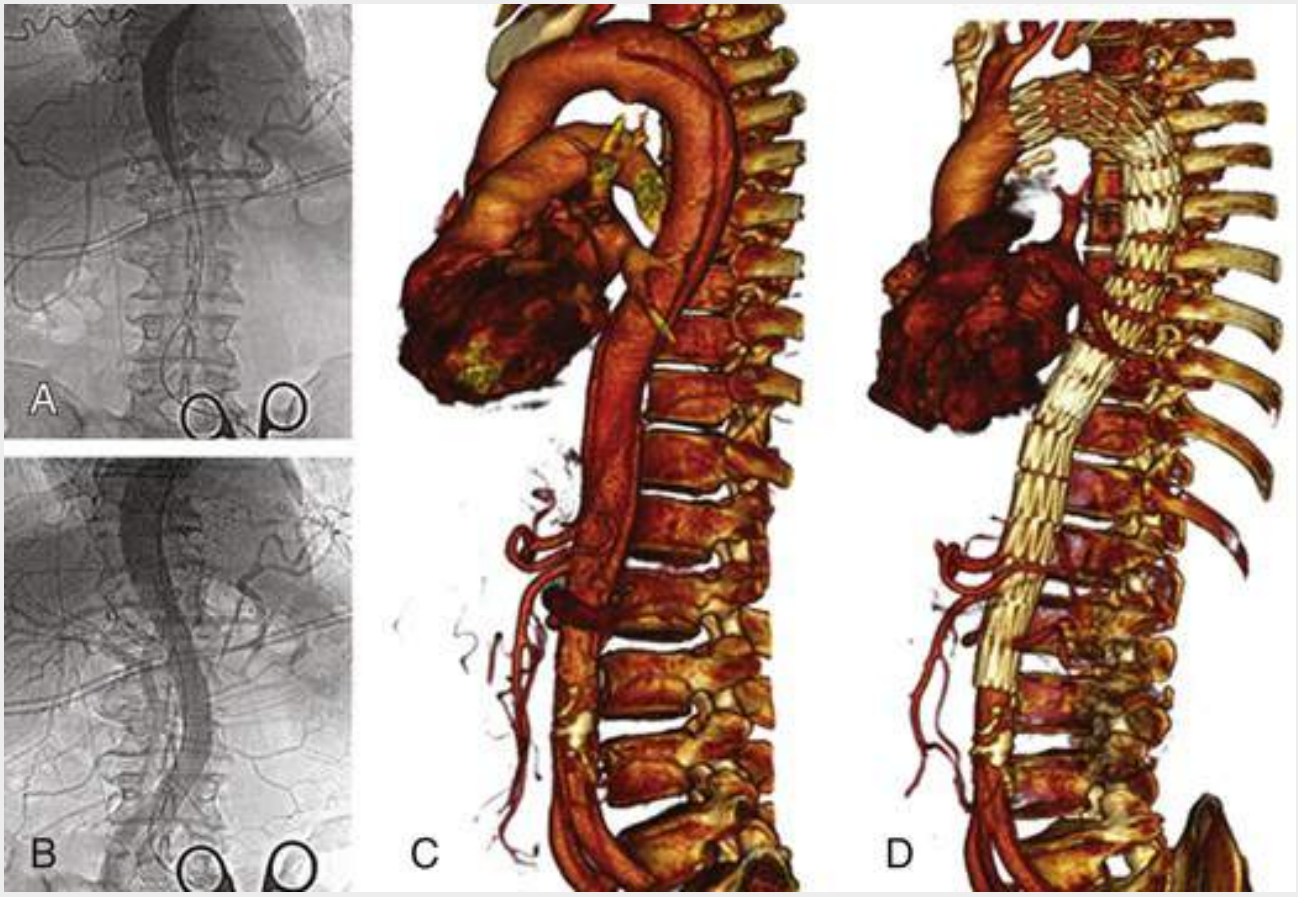


FIGURE 63.21 Approaches to extended distal repair for acute type A aortic dissection. **A,** Open stent graft and total arch replacement with antegrade stent-graft placed in descending thoracic aorta at circulatory arrest. **B,** Open stent-graft and hemiarch replacement with antegrade stent-graft placed in the descending thoracic aorta at circulatory arrest. **C,** Closed stent-graft with hybrid arch. Proximal rerouting of arch vessels to sinotubular junction and endovascular stent graft deployment into ascending aortic graft with fluoroscopy after weaning from cardiopulmonary bypass. **D,** Closed stent-graft with hybrid arch replacement. Arch replaced surgically to level of left subclavian artery and polyester proximal landing zone created for stent-graft in transverse arch. (From El-Hamamsy I, Ouzounian M, Demers P, et al. State-of-the-art surgical management of acute type A aortic dissection. Can J Cardiol 2016;32:100-9. Images courtesy Dr. Jehangir Appoo.)

Type B Aortic Dissection.

Treatment of patients with type B aortic dissections is evolving with the increased use of endovascular devices. Because of the high mortality rates associated with OSR, stable patients with uncomplicated type B dissection usually receive nonoperative treatment.[1,17,37] Patients with complicated type B aortic dissection secondary to aortic rupture, intractable pain, aneurysmal enlargement, or end-organ ischemia as a result of aortic branch vessel involvement should receive TEVAR, which entails lower morbidity and mortality than OSR[1,37] (**see Fig. 63.8**) (**eFig. 63.25**). Of 1476 patients with type B dissection in the IRAD registry, 63% were treated medically, with mortality rate of 8.7%; 23% received endovascular repair, with mortality of 12%; and 13% underwent OSR, with mortality of 17%.[38] Other large registries report a mortality rate of approximately 32% for OSR in acute type B dissection.[37] The STABLE trial is evaluating the treatment of complicated type B dissection with endovascular grafts compiling a 30-day mortality rate of 4.7%. Favorable aortic remodeling occurred and follow-up through 5-years is ongoing.[59] The DISSECTION trial treated complicated type B dissection with TEVAR, reporting a 30-

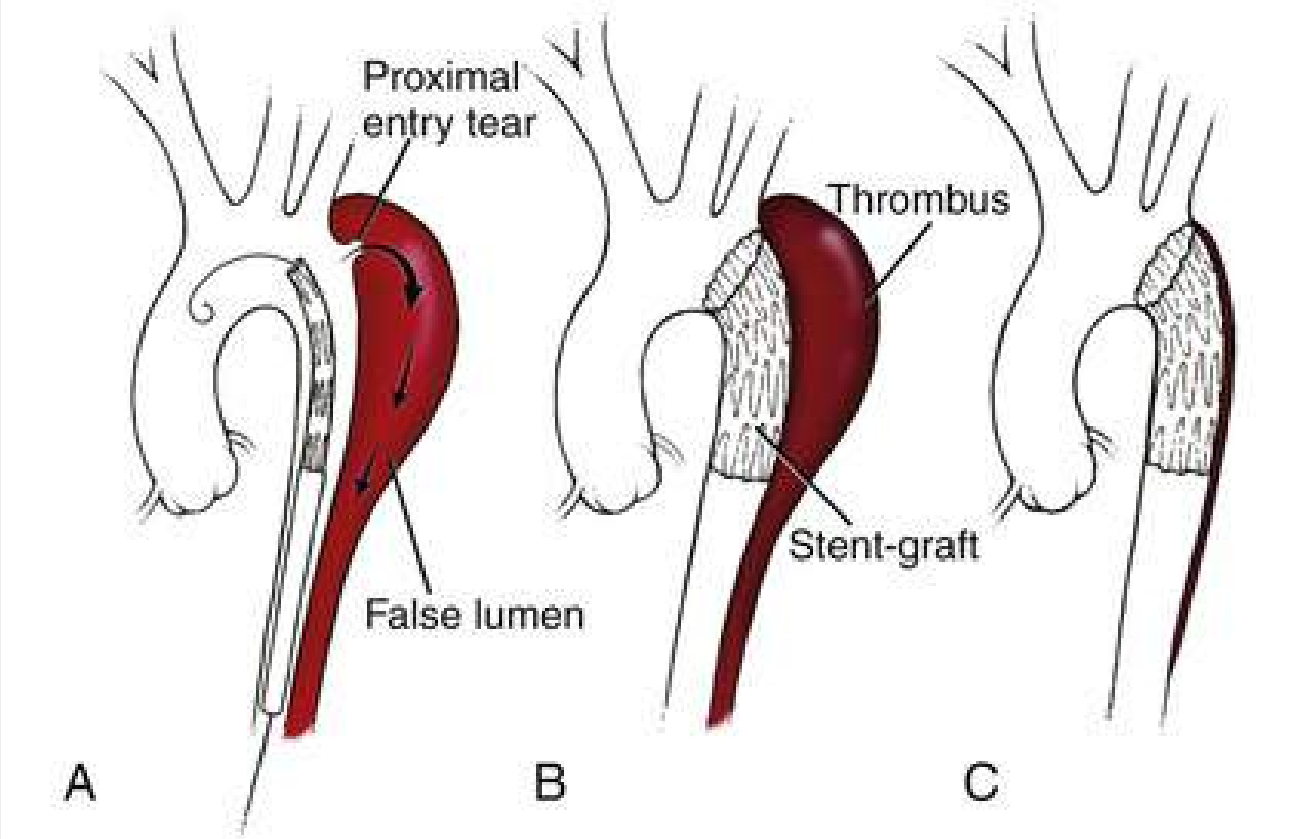
day mortality of 8% and 12-month mortality of 15%.[60]



EFIGURE 63.25 Complicated acute type B aortic dissection with aortic malperfusion above the renal arteries before and after emergency stent-graft implantation. **A,** Aortogram with no-flow to the abdominal aorta. **B,** Aortogram demonstrating markedly improved distal flow after stent-graft placement. **C,** Three-dimensional reconstruction of the complicated type B dissection before thoracic endovascular aneurysm repair (TEVAR). **D,** After stent-graft placement. (From Akin I, Kische S, Tehders TC, et al. TEVAR, the solution to all aortic problems? Herz 2011;36:539.)

When a dead-end false lumen leads to dynamic compression of the true lumen, balloon fenestration of the intimal flap allows blood to flow from the false into the true lumen, decompressing the distended false lumen. However, fenestration and branch vessel stenting alone may not relieve malperfusion, and TEVAR may be required.[1]

TEVAR covers the area of the primary intimal tear and redirects flow to the true lumen, promoting thrombosis of the false lumen and allowing aortic remodeling (**eFig. 63.26**). This treatment often corrects malperfusion syndromes and branch vessel ischemia (**eFig. 63.25**) and is useful in the treatment of enlarging symptomatic dissections and ruptured aortas. At present, endovascular devices are approved for the treatment of type B dissections (acute, chronic, complicated, or uncomplicated). Up to two thirds of patients so treated have persistence of a perfused false lumen, which can require reintervention and surgical conversion. If malperfusion of a branch vessel persists, branch vessel stenting or the technique of *provisional extension to induce complete attachment* (PETTICOAT)—in which the entry point is sealed with an endograft and the remaining thoracic aorta, abdominal aorta, and/or branch vessels are stented open—may correct the problem.[37] Hybrid approaches (TEVAR and OSR) of dissections involving the arch and descending aorta may have lower risk than OSR. Retrograde ascending dissection is a potentially lethal complication that may occur during TEVAR for type B dissection, emphasizing the requirement for an OSR team at institutions performing endografts for aortic dissection.[17]



EFIGURE 63.26 Thoracic endovascular aneurysm repair (TEVAR) after aortic dissection in the setting of aneurysmal enlargement of the false channel. **A,** Endograft is advanced to cover the proximal entry tear into the false channel. **B,** Sealing of the entry tear promotes thrombosis in the false lumen. **C,** Remodeling of the aorta occurs with expansion of the true lumen and a smaller, thrombosed false lumen.

Patients with uncomplicated type B aortic dissection have a risk for long-term complications, including aneurysm formation and late rupture (**eFig. 63.27**). Whether early TEVAR of uncomplicated type B dissection changes the morbidity and mortality of uncomplicated type B dissection is under investigation. The INSTEAD trial reported no difference in all-cause mortality between patients with uncomplicated chronic type B dissection treated with TEVAR versus medical therapy.[61] Patients treated with TEVAR had a significantly higher rate of aortic remodeling, including false lumen thrombosis and true lumen expansion (91% versus 19% for TEVAR versus medical therapy) (**Fig. 63.22**). The 5-year all-cause mortality was not different between groups, but aorta-related mortality was significantly less in TEVAR treated patients, as was progressive aneurysmal enlargement[61] (**Fig. 63.23**). The ADSORB trial comparing TEVAR with medical therapy in uncomplicated type B dissection found that TEVAR improved aortic remodeling compared to medical therapy, but with no difference in rupture or in dissection-related or overall mortality after 1 year;[62] 3-year data are forthcoming. Typical indications for TEVAR (or OSR) in chronic type B aortic dissection include progressive aortic enlargement (>10 mm/yr), aneurysmal enlargement (>55 mm), malperfusion syndromes, and recurrent pain.[1,37] Management of chronic type B aortic dissection is complex because data from a recent meta-analysis demonstrates high rates of operative mortality (OSR, 5.6% to 21%; TEVAR, 0 to 14%) and complications (stroke: OSR, 0 to 13%; TEVAR, 0 to 12%; spinal cord ischemia: OSR, 0 to 16%; TEVAR, 0 to 13%; renal failure: OSR, 0 to 33%; TEVAR, 0 to 34%).[63] Reintervention rates were also high (OSR, 6% to 29%; TEVAR, 4% to 47%). Currently, OSR is reserved for patients with aortic diameters larger than 55 mm who are good surgical candidates and at greater than 60 mm for reasonable candidates, whereas those at high surgical risk should be considered for endovascular repair at dedicated centers (European Society for Vascular

Surgery guideline).

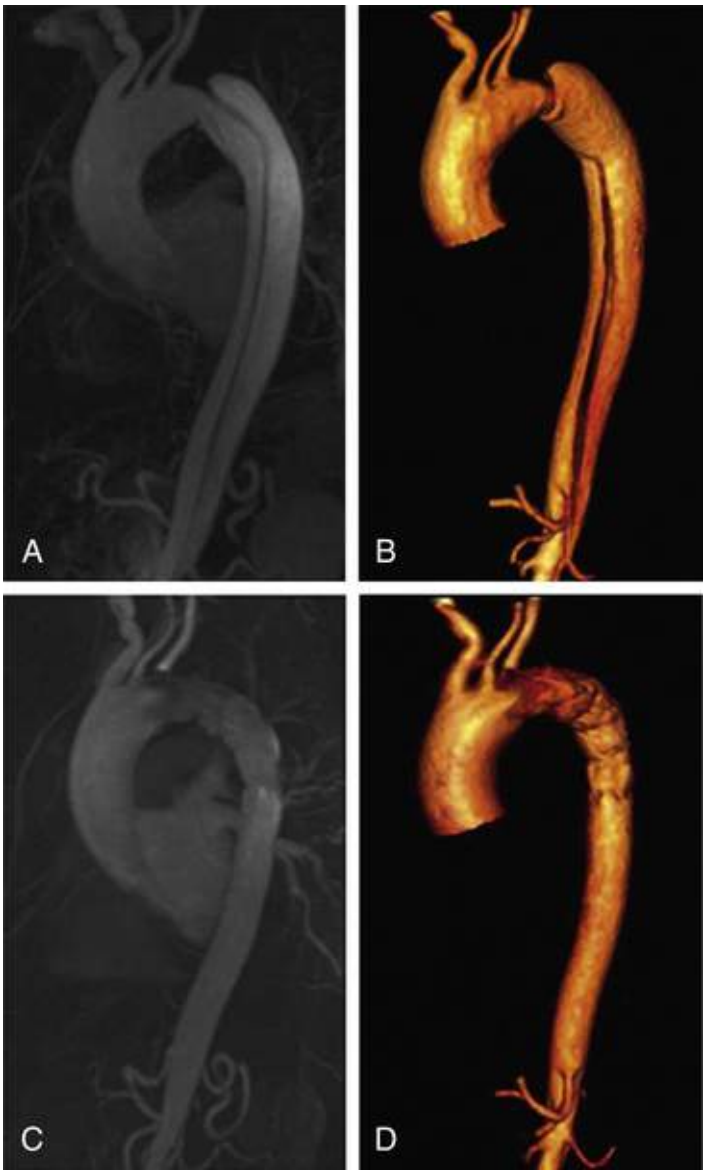
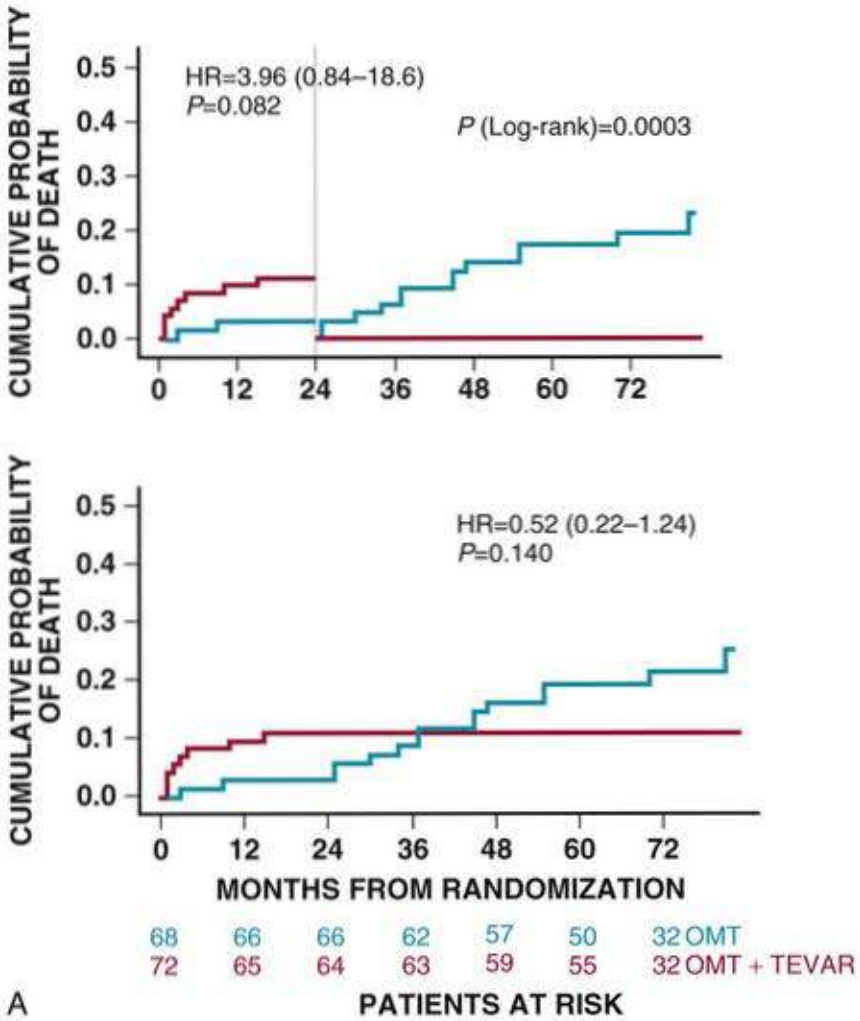
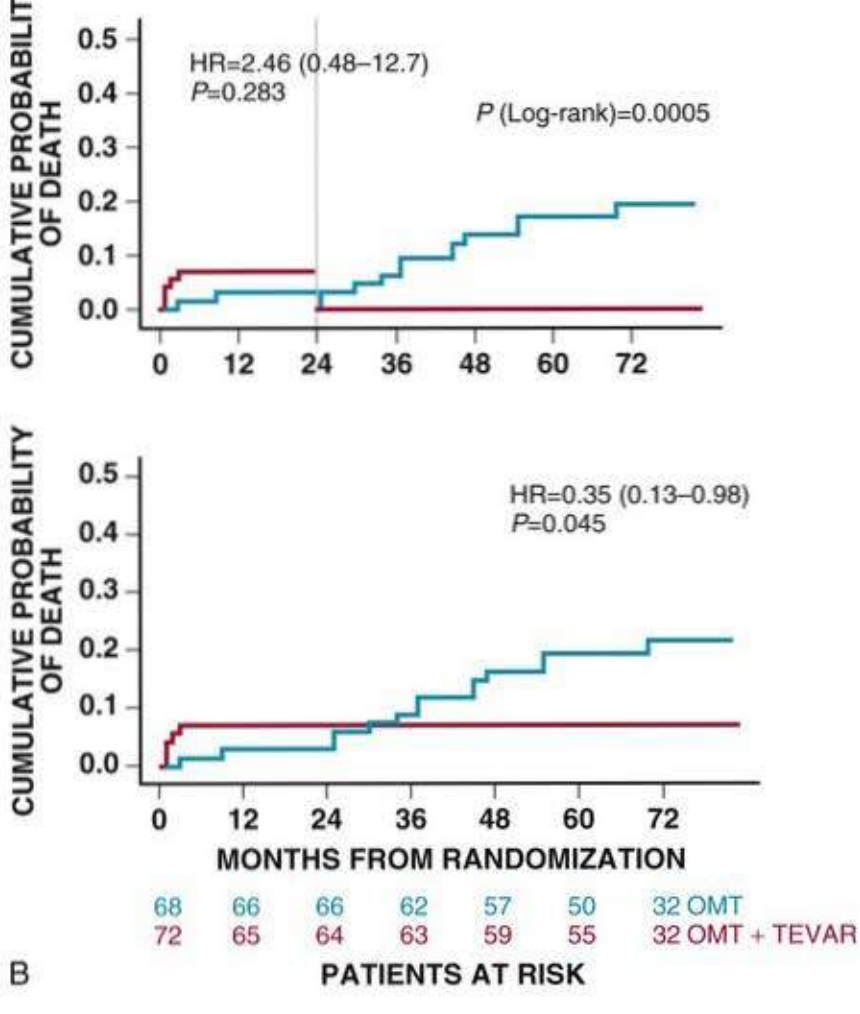


FIGURE 63.22 Gadolinium-enhanced sagittal magnetic resonance angiograms of type B dissection before randomization **(A, B)** and 5 years after endovascular repair **(C, D).** Sagittal maximum intensity projection **(A** and **C)** and three-dimensionally reconstructed scans **(B** and **D)** show complete aortic remodeling with time; the left subclavian artery is filled by collaterals after intentional coverage with the endograft. (From Nienaber CA, Kische S, MD, Rousseau H, et al; INSTEAD-XL trial. Long-term results of the randomized Investigation of Stent Grafts in Aortic Dissection Trial. Circulation Cardiovasc Interv 2013;6:407-16.)


CUMULATIVE PROBABILITY OF DEATH
0.5
0.4
0.3
0.2
0.1
0.0
HR=3.96 (0.84–18.6)
P=0.082
P (Log-rank)=0.0003
0
12
24
36
48
60
72
HR=0.52 (0.22–1.24)
P=0.140
MONTHS FROM RANDOMIZATION
68 66 66 62 57 50 32 OMT
72 65 64 63 59 55 32 OMT + TEVAR
PATIENTS AT RISK

A


CUMULATIVE PROBABILITY OF DEATH
0.5
0.4
0.3
0.2
0.1
0.0
HR=2.46 (0.48–12.7)
P=0.283
P (Log-rank)=0.0005
0
12
24
36
48
60
72
HR=0.35 (0.13–0.98)
P=0.045
MONTHS FROM RANDOMIZATION
68 66 66 62 57 50 32 OMT
72 65 64 63 59 55 32 OMT + TEVAR
PATIENTS AT RISK

B

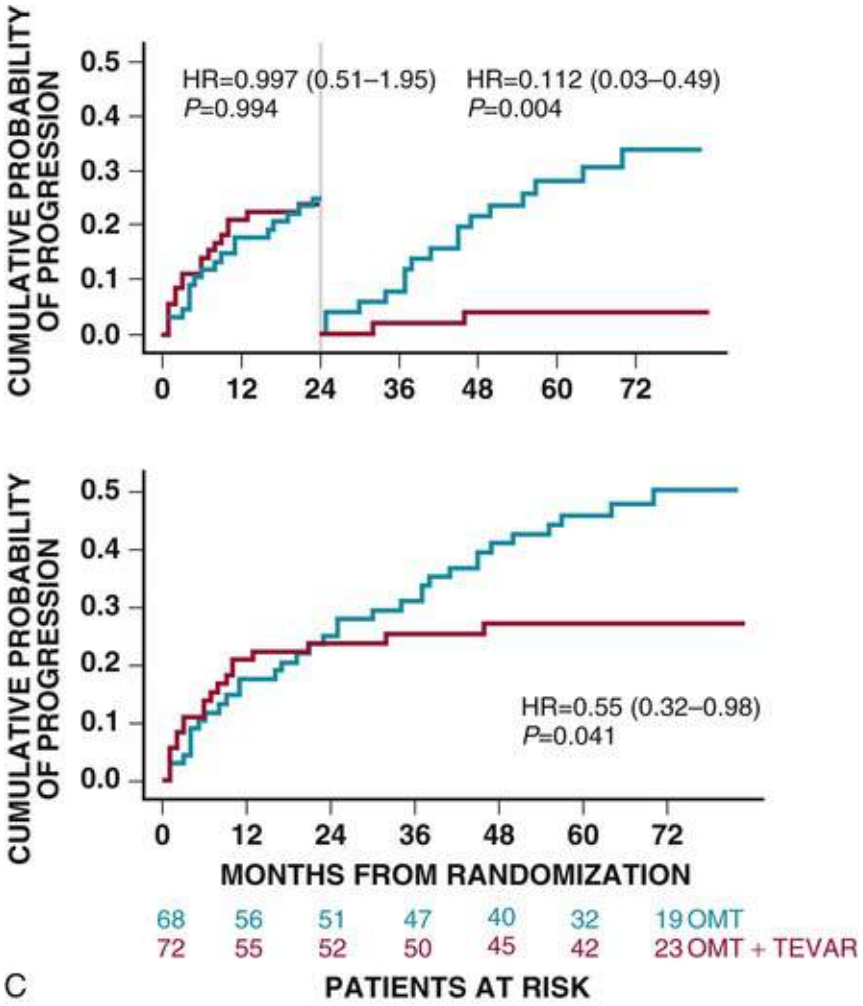
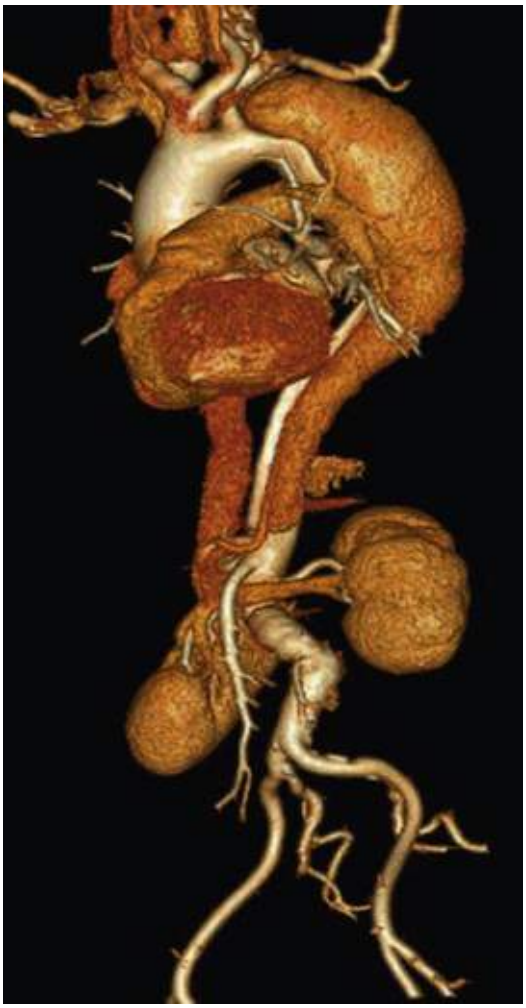


FIGURE 63.23 Cardiovascular mortality from INSTEAD-XL trial comparing endovascular therapy to medical treatment in uncomplicated type A aortic dissection. **A,** Kaplan-Meier estimates of all-cause mortality (death) and Landmark analysis with a breakpoint at 24 months after randomization to the end of the trial are shown for optimal medical treatment (OMT) and OMT plus thoracic endovascular aortic repair (TEVAR) groups. After 2 years of follow-up, TEVAR revealed beneficial prognostic benefit. **B,** Kaplan-Meier estimates of aorta-specific mortality (death) and Landmark analysis with the breakpoint at 24 months after randomization to the end of the trial are shown for OMT and OMT + TEVAR groups. After 2 years of follow-up, the observed mortality was lower with TEVAR than with OMT alone. **C,** Kaplan-Meier estimates of a combined endpoint of progression and adverse events (aorta-related death, conversion, and ancillary interventions, including the second stent-graft procedure, access revision, peripheral interventions) with a breakpoint at 24 months are shown for OMT and OMT + TEVAR. With TEVAR, less progression of disease was observed in the late phase of follow-up compared with OMT. HR, Hazard ratio. (From Nienaber CA, Kische S, MD, Rousseau H, et al; INSTEAD-XL trial. Long-term results of the randomized Investigation of Stent Grafts in Aortic Dissection Trial. Circulation Cardiovasc Interv 2013;6:407-16.)



EFIGURE 63.27 Three-dimensional computed tomography image of aneurysmal dilation 3 years after an uncomplicated type B aortic dissection. (From Nienaber CA, Divchev D, Palisch H, et al. Early and late management of type B aortic dissection. Heart 2014;100:1491-7.)

Long-Term Therapy and Follow-Up

Short- and long-term survival rates for type A aortic dissection range between 52% and 94% at 1 year and between 45% and 88% at 5 years.[17] Others report that patients with type A dissection who survive surgery have survival rates of approximately 90% at 1 year, 75% at 5 years, and 54% at 10 years.[58] In single-center studies of long-term follow-up after type A aortic dissection, the 10-year survival rate was 55% to 59% and the 20-year survival rate, 24% to 30%.[64,65]

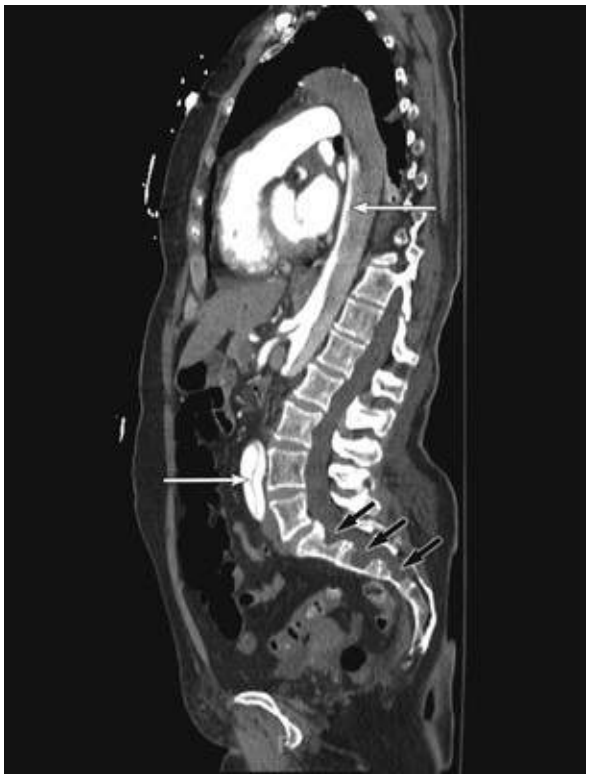
Medically treated patients with type A aortic dissection have a very high mortality rate, in excess of 20% by 24 hours and 50% in the first week after diagnosis.[38,47] Few data exist about the natural history of medically managed chronic type A aortic dissection. Some studies report dismal survival with medical therapy alone, even in patients who survive the initial hospitalization, but IRAD reported a 38% survival rate at 60 days.[36] Of patients with type A dissection surviving hospitalization with medical therapy, the 1-year survival rate has been quite variable, ranging from less than 20% to 88%, and 3-year survival has been reported as high as 68%.[66] A few patients are initially seen in the subacute stage and should undergo surgery. On occasion, patients are incidentally discovered to have a chronic type A dissection during evaluation for AR or a dilated ascending aorta. Surgical treatment is recommended for appropriate candidates with chronic type A dissection, especially those with an ascending aortic aneurysm greater than 5.5 cm, AR, or symptoms.[46]

Long-term survival rates in patients with acute type B dissection range from 56% to 92% at 1 year and

48% to 82% at 5 years.[66] These studies have included single-center reports with heterogeneous enrollment criteria and lack of endovascular therapy. Nonetheless, findings at long-term follow-up after type B aortic dissection are worse than after type A dissection. Previous studies have demonstrated that many deaths in follow-up are related to subsequent aortic complications such as rupture, extension of the dissection, and the risks associated with subsequent aortic and vascular surgery. The 1- to 3-year survival rates of patients discharged after initial hospitalization for acute type B aortic dissection were 78%, 83%, and 77% to 98% for patients treated medically, surgically, or with endovascular therapy, respectively.[36]

Long-term management after aortic dissection includes medical therapy, BP control, screening the patient and first-degree relatives for heritable disorders associated with aortic dissection, serial imaging of the aorta, lifestyle modifications, and education.[34,42] One important long-term management goal after dissection is treating hypertension, with a BP goal of lower than 120/80 mm Hg in most individuals. Poorly controlled hypertension is associated with an increase in late morbidity and mortality.[65,67] There are no randomized trials comparing specific medications after chronic aortic dissection. Beta blockers are the most commonly used drugs after dissection and may be associated with improved survival (specifically with type A dissection).[1,68] Beta blockers are the drugs of first choice because of their effect on aortic stress and dP/dt and are recommended even in patients without hypertension.[17] Beta-blocker therapy is associated with a lower requirement for late surgery in follow-up.[65,67] Calcium channel blockers may improve survival after type B dissection,[68] and ACE inhibitors may be associated with lower rates of late aortic events.[67] Smoking cessation and risk factor modification for degenerative disease are also important.[17]

Many patients with dissection will eventually be found to have an underlying genetic predisposition to aortic disease. Some have syndromic features recognized as MFS or LDS; features of these disorders should be sought on examination.[13] Recognition of *dural ectasia*—widening or enlargement of the dural canal, usually in the lumbosacral spine—on CT or MRI often indicates an underlying genetic aneurysm syndrome (e.g., MFS, LDS) (**eFig. 63.28**). Some patients will have an underlying BAV, a familial condition in 9% of cases; other patients will have nonsyndromic familial TAA or dissection syndromes.[12] Comprehensive family studies recognize that 20% of individuals with a TAA or dissection will have another first-degree relative with thoracic aortic disease, and thus the importance of family screening, as previously described.[17]



EFIGURE 63.28 Dural ectasia as a sign of underlying connective tissue disease in aortic dissection. A sagittal computed tomography scan demonstrates acute aortic dissection (*white arrows*) and dural ectasia (*black arrows*) in the lumbosacral spine of a woman with previously undiagnosed Marfan syndrome.

Long-term management after dissection includes regular imaging of the aorta and its branches for complications, especially aneurysmal enlargement (**eFig. 63.27**). The distal arch and the proximal descending aorta are the areas at highest risk for late aneurysm formation after acute aortic dissection. Between 2% and 13% of patients require reoperation within 5 years, and the risk associated with repeated surgery or intervention 10 years after type A aortic dissection ranges from 16% to 25%.[58] Typical protocols for follow-up after acute dissection include imaging with CT or MRA at 1 to 3, 6, 12, 18, and 24 months and yearly thereafter, with intervals depending on the size of the aorta and changes in aortic dimension over time.[1,17] MRA should be considered for long-term follow-up to avoid repeated radiation exposure.

Risk factors for late aneurysm formation include aortic dilation, hypertension, nonresection of the false lumen, larger false lumen diameter (>22 mm), entry tear diameter larger than 10 mm, and partial false lumen thrombosis.[37] A patent false lumen and a dilated descending aorta (>45 mm) are risk factors for aneurysm and reintervention.[2] Patients with partial false-lumen thrombosis have higher mortality at follow-up than those with a completely patent or completely thrombosed false lumen.[66] Increased pressure may occur in the false lumen in the setting of partial thrombosis because of the lack of distal reentry tears and may lead to subsequent expansion and increased risk for rupture.[66] Ulcerlike projections (localized blood-filled pouches) protruding into the thrombosed false lumen on CT are associated with late aortic events. MRI using four-dimensional phase-contrast imaging may identify patients at risk for aortic dilation.[37]

Many late deaths following surgery for aortic dissection result from rupture of the aorta at the site of previous dissection or from rupture of another aneurysm at a remote site. Aneurysms related to expansion of the false lumen have relatively thin walls and are at higher risk for rupture than degenerative aneurysms. Rapid aortic growth (>5 mm/yr) or aortic diameter greater than 60 mm are risk factors for rupture.[2] The timing of repair for aneurysmal involvement of the residual aorta depends on several factors, including the patient's age and general medical condition, comorbid conditions, underlying

disease process, rate of aneurysmal enlargement, and absolute size of the aorta. In general, patients with a descending aorta diameter after dissection that exceeds 5.5 to 6 cm, or if the rate of aortic expansion exceeds 1 cm/yr, should have evaluation for repair.[1,17] In patients at relatively lower risk and in those with certain genetically triggered TAA diseases, open surgical repair at a smaller aortic diameter is appropriate.

Lifestyle modifications are necessary after aortic dissection. Isometric activities, including weightlifting, lead to increased BP and aortic wall stress.[34] Many need to change jobs, modify their work activities, or be considered disabled as a result of aortic dissection and/or underlying aortic disease, because of limitations placed on physical activity. However, low to moderate levels of many types of physical activity, including sex, are considered safe, and participation in exercise may lessen depression and lower BP.[34]

Aortic Dissection Variants

In addition to acute aortic dissection, aortic IMH and PAU are included in the acute aortic syndromes (**see Fig. 63.10**). These disorders may be identical to classic aortic dissection in their manifestations and may cause acute chest or back pain, but they have important differences in their imaging and management. IMH is associated with many of the same risk factors as classic aortic dissection, whereas PAU is more common in the descending aorta and is associated with heavy calcification and atherosclerosis.

Aortic Intramural Hematoma

Aortic IMH is a type of acute aortic syndrome in which a hematoma develops in the medial layer of the aortic wall with no evidence of an intimal flap or false lumen.[1,2,17,69] Imaging studies demonstrate a circular or crescentic thickening of 5 mm or more in the aortic wall. From 10% to 20% of acute aortic syndromes are caused by an IMH, with higher incidence in Asian studies than Western cohorts.[70-72] IMH involves the ascending aorta in 30%, the arch in 10%, and the descending aorta in 60% to 70% of cases. IMH may result from rupture of the vasa vasorum and subsequent mural hemorrhage. Supporting this theory is the location of IMH in the outer aortic media, versus the inner medial location of a classic dissection. Micro–intimal tear may initiate IMH, with the intimal tear too small to detect by routine CT. This feature may lead to negligible reentry into the true lumen and a thrombosed false lumen.[1,71]

IMH is classified as type A or type B as for classic aortic dissection. Symptoms and risk factors of IMH resemble those of aortic dissection, with acute chest and/or back pain predominating. Ascending IMH may lead to AR, hemopericardium, or rupture, but malperfusion is less common. The proximity of the IMH to the adventitia may explain the frequent coexistence of pleural effusion, pericardial effusion, and periaortic hematoma and underlies the higher risk for aortic rupture.[1,72]

Imaging studies useful for the diagnosis of IMH include TEE, CT, and MRI.[2] TTE has a very low sensitivity. TEE features of IMH include focal crescentic or circumferential aortic wall thickening of 5 mm or more, an eccentric aortic lumen, displaced intimal calcification, and areas of echolucency within the aortic wall and no intimal flap or flow in the aortic wall[2] (**Fig. 63.24**) (**eFig. 63.29** and Videos 63.19 to 63.21). On non–contrast-enhanced CT, IMH appears as an area of high attenuation (due to bleeding) in the wall of the aorta (**eFig. 63.30**), whereas on CECT, the aortic wall demonstrates low attenuation, because no contrast material enters the wall (**Fig. 63.24**). MRI demonstrates focal thickening of the aortic wall, with phase-contrast cine and gradient echocardiography demonstrating no-flow in the aortic wall (**eFig. 63.31**). High signal intensity on T2-weighted MR images may be visualized because of blood in the aortic wall with acute IMH. Ulcerlike projections (ULP; localized blood-filled pouch protruding into hematoma in aortic wall that may be caused by micro–intimal defects), focal contrast enhancement within the hematoma, thick hematoma, and a large aortic diameter are associated with a higher risk of complications in IMH[1,69,71] (**eFig. 63.32**).

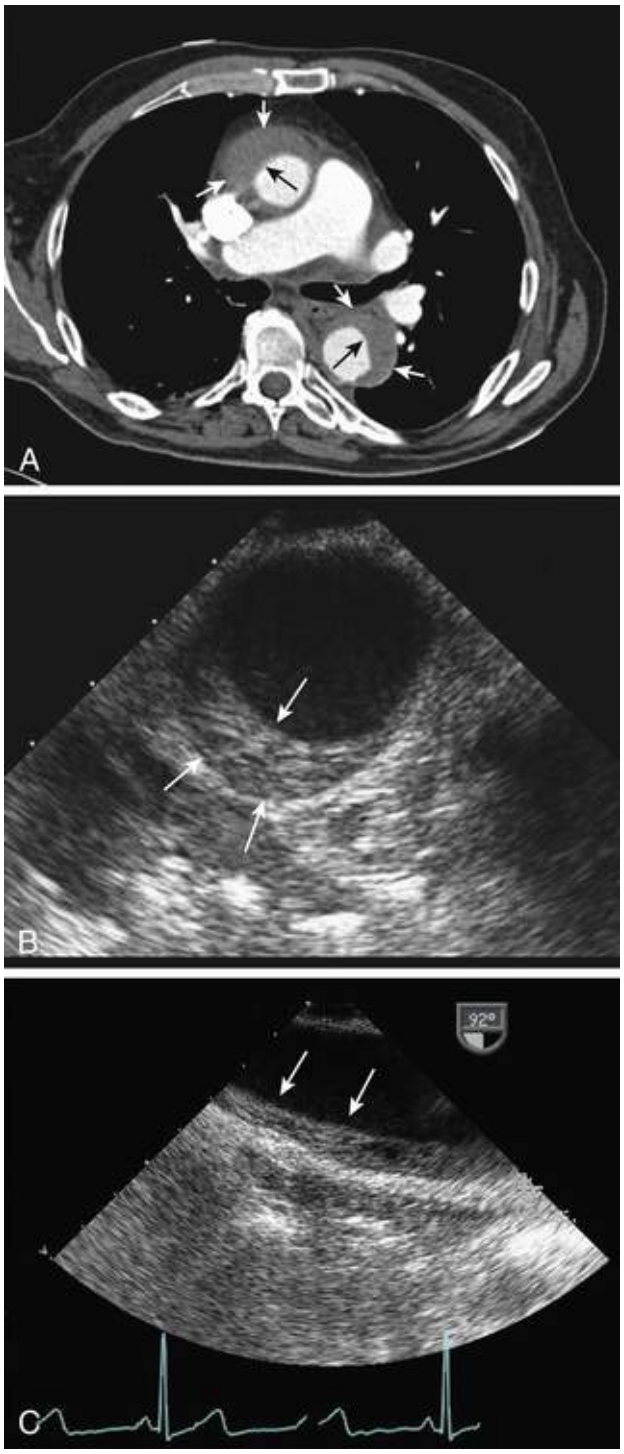
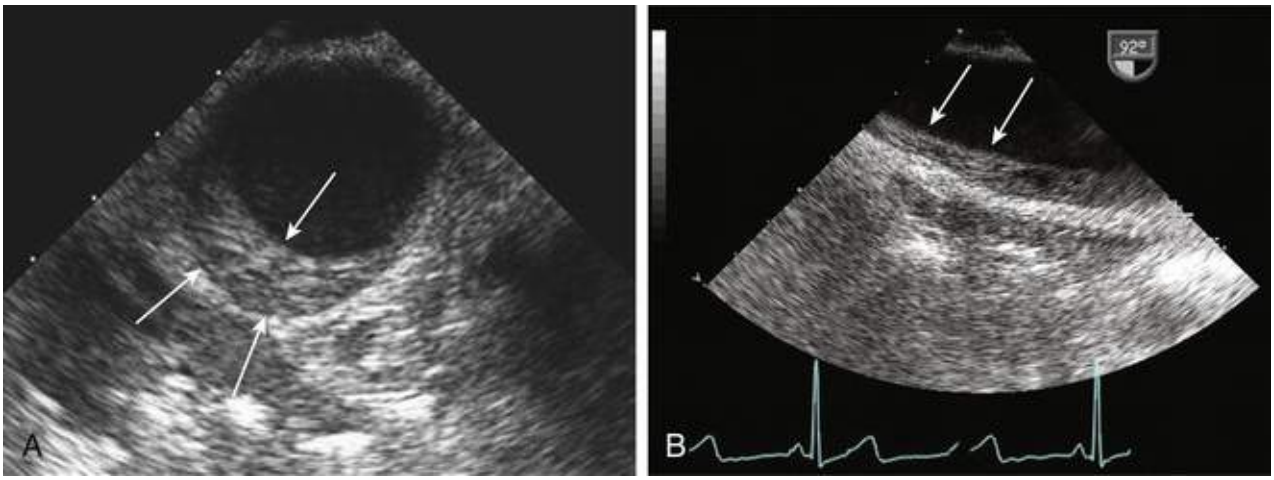
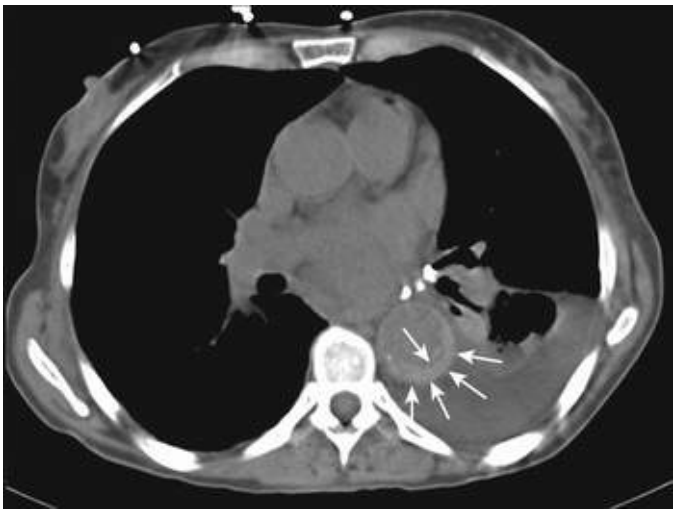


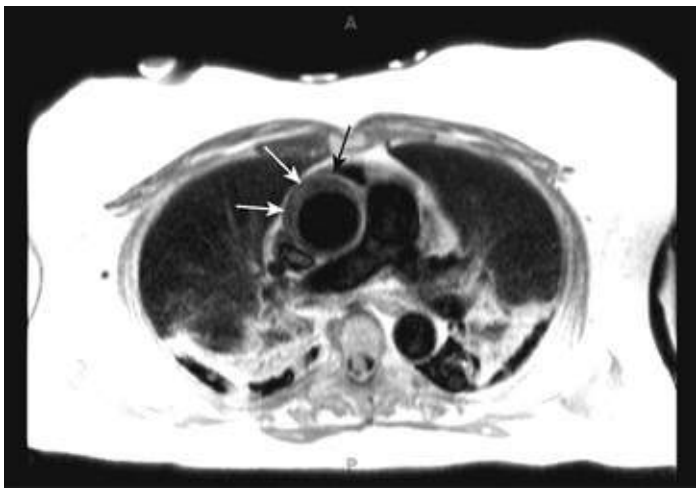
FIGURE 63.24 Intramural hematoma (IMH) of the aorta. **A,** Contrast-enhanced computed tomography scan demonstrating type A IMH of the aorta. Note the circumferential hematoma involving the ascending aorta (*upper arrows*) and the crescentic hematoma involving the descending aorta (*lower* arrows). **B,** Transesophageal echocardiogram short-axis view of the descending aorta demonstrating typical crescentic thickening of the aortic wall (*arrows*) in acute type B IMH. **C,** Transesophageal echocardiogram longitudinal view of the aorta demonstrating IMH (*arrows*).



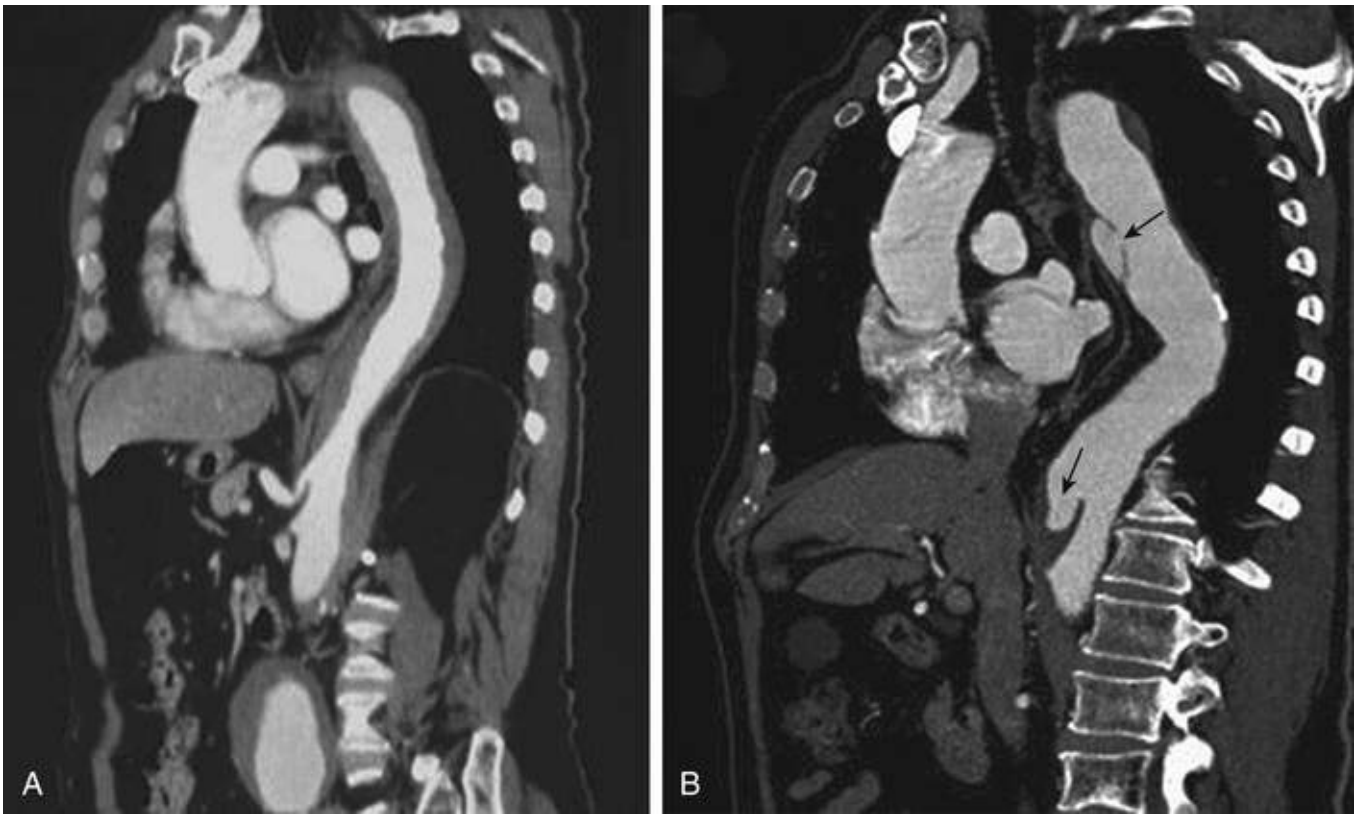
EFIGURE 63.29 Transesophageal echocardiograms of acute type B aortic intramural hematoma (IMH). **A,** Short-axis view of the descending aorta demonstrating typical crescentic thickening of the aortic wall (*arrows*) with IMH. **B,** Longitudinal view of the aorta demonstrating IMH (*arrows*).



EFIGURE 63.30 Non–contrast-enhanced computed tomography scan revealing type B intramural hematoma with crescentic thickening of the aortic wall (*arrows*) and associated left pleural effusion.

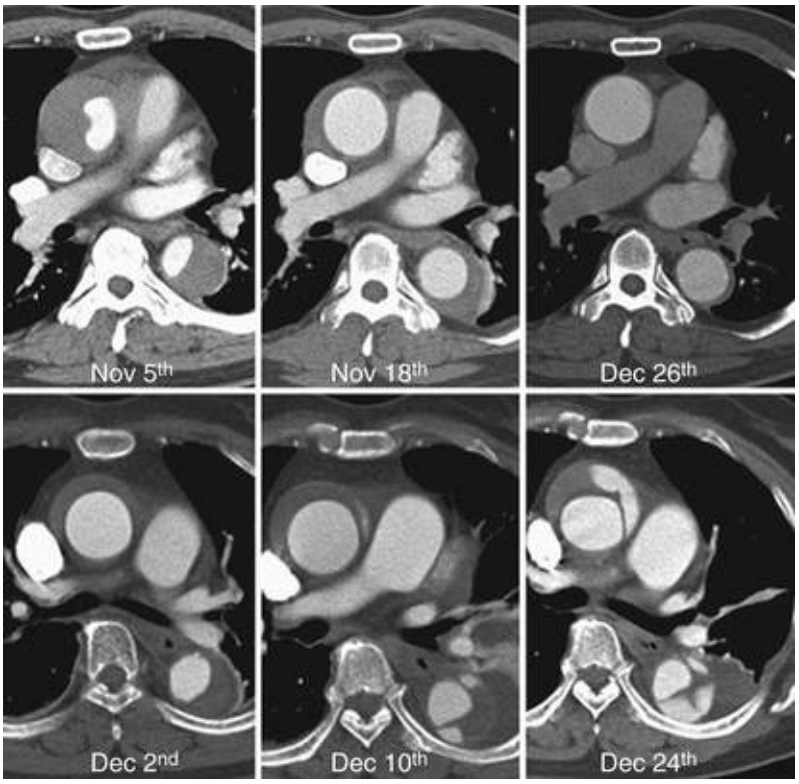


EFIGURE 63.31 Magnetic resonance image of type A intramural hematoma of the aorta. The crescentic thickening of the aortic wall hematoma is denoted by *arrows*.



EFIGURE 63.32 **A,** Computed tomography image of intramural hematoma (IMH) in descending thoracic aorta at diagnosis of acute aortic syndrome. **B,** Development of two ulcerlike projections in the same patient at 6 months (*black arrows*). (From Evangelista A, Czerny M, Nienaber C, et al. Interdisciplinary expert consensus on management of type B intramural haematoma and penetrating aortic ulcer. Eur J Cardiothorac Surg 2015;47:209-17.)

Distinct from an aneurysm with mural thrombus, IMH has a smooth lumen and curvilinear wall (**Fig. 63.24**) (**eFigs. 63.29 to 63.33**). In certain cases, differentiating IMH from aortic dissection with thrombosis of the false lumen, mural thrombus within an aortic aneurysm, or severe aortic atherosclerosis may be difficult. On TEE, identifying the intima—often calcified and echodense—helps in making this distinction. Thickening beneath the intima suggests IMH, whereas thickening above the intima (on the luminal side) occurs with mural thrombus in an aneurysm. In contrast to aortic atherosclerosis, IMH is not typically associated with diffuse irregularities in the aortic intima surface unless related to a penetrating ulcer.



EFIGURE 63.33 Computed tomography images showing complete resorption of a proximal hematoma **(upper panels)** and development of typical aortic dissection during medical treatment **(lower panels).**
(From Song JK. Aortic intramural hematoma: aspects of pathogenesis 2011. Herz 2011;36:488-97.)

Early studies from Europe and the United States reported that patients with type A IMH were at high risk for complications, including aortic dissection (25% to 50%), hemopericardium, and rupture, with mortality in excess of 30% with medical therapy alone.[72] Reports from Asia have suggested a much different approach to the management of type A IMH—medical therapy, serial imaging, and careful observation with prolonged hospitalization as an initial strategy—and have reported low mortality rates for many patients.[71] With this approach, however, many patients with type A IMH have progressed to frank dissection (30% to 40%), hemopericardium, or rupture requiring emergency surgery, complications associated with high mortality[1,2,70,72] (**eFig. 63.33**). Given the potential for unpredictable and catastrophic complications, surgical therapy is recommended for type A IMH and medical management for patients with type B IMH.[1,17,69,72] (See Videos 63.20 and 63.21.)

Descending IMH may progress to frank dissection and late aneurysm formation or may be reabsorbed completely. Predictors of complications from IMH are listed in **eTable 63.3**. Management of localized arch IMH must be individualized, with some advocating initial medical therapy for this group. The average 30-day mortality rate in type B IMH is 4% in medically treated patients and 16% in those requiring surgery. Mortality at 3 years was 14% in medically treated patients and 23% for surgically treated patients.[1] Patients with type B IMH require continued surveillance after surgery and while receiving medical therapy. Complete resolution of type B IMH has been described in more than 50% in some series, whereas others have progressed to frank dissection (5%), localized dissection or ULP (25%), rupture (4%), or late aneurysm formation (27%).[1] Frequent imaging follow-up is recommended when ULP is visualized. Predictors of resolution of type B IMH have included younger age, smaller aortic diameter (<4 to 4.5 cm), hematoma thickness less than 1 cm, and postoperative use of beta blockers.[1,69,72] Surgery or TEVAR for type B IMH is reserved for complications such as persistent pain, aortic aneurysm, progression, impending rupture, or rupture.[1,69] The role of TEVAR is unclear in this disorder because there is no intimal defect or patent false lumen, although midterm results for select patients has been favorable.[69,70]

ETABLE 63.3

High-risk Features of Type B Intramural Hematoma (IMH)

HIGH-RISK FEATURE	CUTOFF OR SIGN OF COMPLICATED EVOLUTION
Age (years)	>70
Initial aortic diameter (mm)	>45
Mean aortic diameter growth rate (mm/yr)	≥5
Wall thickness of involved segment (mm)	≥10
Pleural effusion	Presence
Aortic ulcer	Presence
Ulcerlike projection	Presence

Modified from Evangelista A, Czerny M, Nienaber C et al. Interdisciplinary expert consensus on management of type B intramural haematoma and penetrating aortic ulcer. Eur J Cardiothorac Surg 2015;47:209-17.

Penetrating Atherosclerotic Aortic Ulcer

In PAU, an atherosclerotic lesion penetrates through the internal elastic lamina into the media, often associated with a variable degree of IMH formation.[1,2,17,69] PAUs may lead to pseudoaneurysm, aortic rupture, or late aneurysm. Aortic ulcers may be single or multiple and range from 5 to 25 mm in diameter and 4 to 30 mm in depth. PAUs are more common in the middle to distal descending aorta than in the arch or ascending or abdominal aorta.[1,2] PAUs occur in 2% to 7% of symptomatic patients with acute aortic syndrome.[1,69,73] Patients with PAUs are typically elderly and have coexisting vascular disease and many have concomitant aneurysmal dilation of the aorta elsewhere, especially in the abdominal aorta. Even though up to 25% of PAUs are found incidentally on imaging studies, typical symptoms of PAUs include acute chest or back pain, similar in description to that of classic aortic dissection. Although PAUs may lead to aortic dissection, most patients do not have AR, pulse deficits, or visceral ischemia.

Imaging techniques for PAUs include CT, MRI, TEE, and aortography. Findings on CT include focal aortic ulceration, associated IMH, and a calcified, displaced intima[1,2] (**Fig. 63.25**). Typically, a craterlike outpouching with irregular edges occurs in the setting of heavy atherosclerosis. In some cases, it may be difficult to differentiate PAU with an IMH from an IMH with ulcerlike projection.[1,2] CT may also demonstrate pleural effusions, mediastinal hemorrhage, coexisting aneurysms, contained rupture, pseudoaneurysm, and frank rupture. Most patients have some degree of IMH formation. When a PAU is associated with aortic dissection, the dissection often involves a short segment of aorta and has a thick intimal flap. MRI findings in patients with PAUs include localized areas of high signal intensity in the aorta wall consistent with IMH, focal intimal thickening, and ulcerlike projections.[2] TEE demonstrates aortic atherosclerosis with focal ulceration of the intima, often with hematoma.[2]

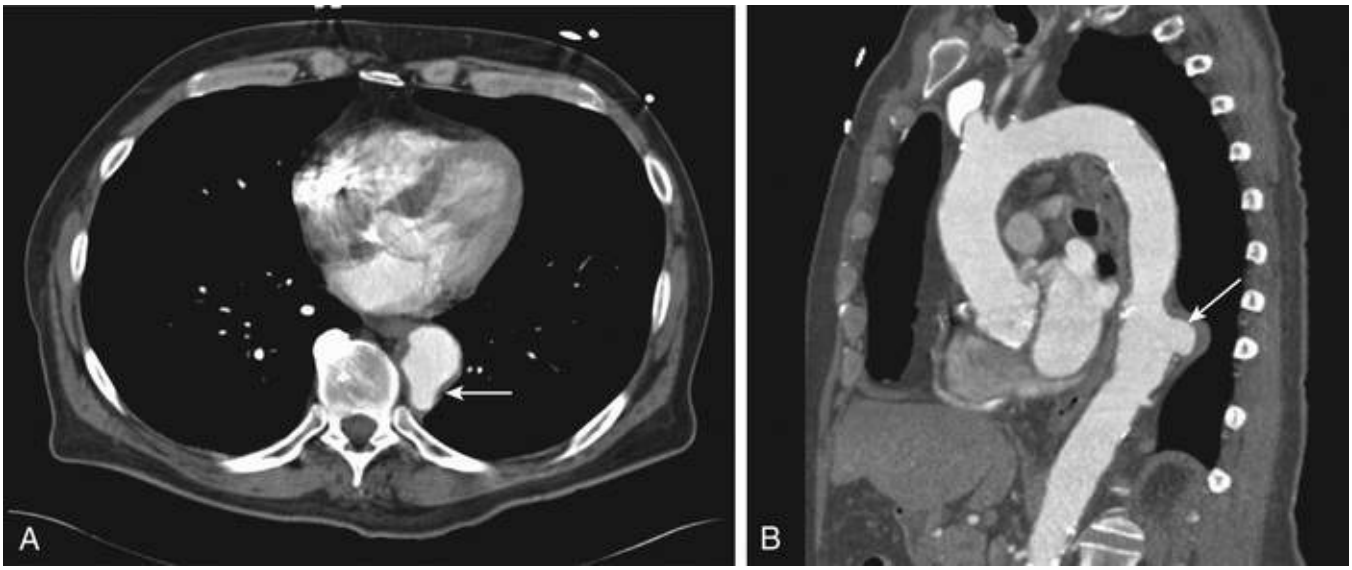


FIGURE 63.25 Contrast-enhanced computed tomography scan demonstrating an acute penetrating atherosclerotic aortic ulcer (PAU). **A,** Axial image demonstrating the typical focal outpouching of the aortic ulcer (*arrow*). **B,** Sagittal image demonstrating the PAU (*arrow*) with associated intramural hematoma. Symptomatic PAU has an increased risk of aortic rupture and is often amenable to endovascular repair. (From Braverman AC. Aortic dissection. In Levine GN, editor. Color Atlas of Cardiovascular Disease. New Delhi, India: Jaypee Brothers Medical Publishers; 2015, pp 895-903.)

PAUs have an uncertain natural history, with variability in the literature depending on patient selection. A PAU may "stabilize" or lead to complications, including IMH, distal embolization, aortic rupture, pseudoaneurysm (contained rupture), aortic dissection, or development of a saccular or fusiform aneurysm.[1] In one study the annual growth rate of PAUs was 0.31 cm/yr. Some studies report gradual aortic enlargement and a low incidence of life-threatening complications, whereas others report a high incidence of acute complications.[69,73] In general, patients with ascending PAUs undergo surgical resection. Stable patients with type B PAUs may be managed medically, with close follow-up and serial imaging. When an asymptomatic PAU is discovered, serial imaging studies are required to document stability.[69] Patients with refractory or recurrent pain, overlying IMH or periaortic hemorrhage, or rapid increase in size are at increased risk of rupture and should undergo invasive treatment.[1,17,69,73] Indications for TEVAR or surgery may include the development of hemorrhage, periaortic hematoma, expanding pseudoaneurysm, saccular aneurysm formation, continued pain, or rupture.[69] Predictors of disease progression include increasing aortic wall thickness, ulcer craters greater than 15 to 20 mm in diameter or 10 mm in depth, increasing aortic hematoma, and increasing pleural effusion.[69,74] The short segment involved and the high-risk patient population make TEVAR preferable to OSR.[69,73] Of 310 patients with PAU treated with TEVAR, the 30-day mortality was 5% and 1-year survival, 91%.[73] Endoleaks may complicate TEVAR for PAU in 5% to 20% of cases, with more recent studies reporting lower risk.[69,73,74] In-hospital mortality for PAU requiring TEVAR is estimated at 4% to 11%,[74] and aortic-related mortality of 4% at 18 months is reported.[73] Others report a 5-year survival of 65% after TEVAR for PAU.[1,69]

Aortoarteritis Syndromes

Bacterial Infections of the Aorta

Infected aortic aneurysms (*mycotic aneurysms*) are a rare but lethal condition and account for less than 1% of all aneurysms undergoing surgery.[75] Infection may result from contiguous spread from adjacent thoracic tissues, such as mediastinitis, abscess, infected lymph nodes, empyema, or paravertebral

abscess. Other causes include septic emboli from endocarditis and hematogenous dissemination of bacteria in the setting of sepsis or IV drug abuse. Infection most often arises in a diseased aorta, whether aneurysmal, atherosclerotic, or traumatized as a result of previous aortic cannulation or suturing.[75] Even though the disease may be insidious in onset, it may also have a fulminant course with frequent aneurysm rupture (>50%) and a high mortality rate (>25% to 50%). Standard treatment has involved resection of the aneurysm, débridement of infected soft tissue, antibiotics, and arterial reconstruction. Most patients undergo in situ aortic grafting, whereas others undergo extra-anatomic bypass. TEVAR is feasible and for many patients, especially those at high risk, may be a reasonable option.[75-77]

The classic triad of an infected aortic aneurysm includes fever; abdominal, back, or chest pain; and a pulsatile tender mass. Most patients, however, do not have these pathognomonic findings. Patients are febrile and have markers of inflammation. Bacteremia is common, but blood cultures may be negative in more than 25% of cases, especially after antibiotic therapy, and in some patients the organism is established only during surgery by culture and Gram stain of the aortic wall.[76,77] Patients often have a comorbid condition (e.g., diabetes, other chronic disease) or an immunocompromised state or may be receiving chronic corticosteroid therapy. Many have recently undergone gastrointestinal operations or invasive procedures. Infected aneurysms typically involve the infrarenal aorta. Infected TAAs are less common, usually affecting the descending aorta and accompanied by rupture or pseudoaneurysm.[77] Infections of prosthetic aortic grafts occur in 1% to 2% of patients. Aortic graft–enteric erosion and fistula are common complications.

The most common microorganisms associated with infected aortic aneurysms include *Staphylococcus aureus* and *Streptococcus* and *Salmonella* species, but infections with gram-negative bacilli and fungi can occur.[75] Even though *Salmonella* can infect an underlying atherosclerotic aortic aneurysm, this microbe may directly penetrate an intact intima of a normal aortic wall and lead to arteritis and aneurysm formation. Thus the clinician should always suspect underlying aortic seeding when *Salmonella* bacteremia occurs.

CT, MRI, and aortography may be diagnostic in patients with infected aortic aneurysms. Saccular aneurysms resulting from rapid focal arterial wall degeneration are most common[75] (**Fig. 63.26 and eFig. 63.34**). Features on CT include disruption of calcification, irregular wall thickening, periaortic mass, rim enhancement, and periaortic stranding. The presence of gas and vertebral body erosion is highly suggestive of infection. Aortocaval or aortoenteric fistulas may complicate infected aneurysms. Infected aneurysms may expand rapidly and have a propensity to rupture. Because most descending or abdominal aneurysms are atherosclerotic, lack of calcium in an involved aorta may suggest infection. MRI features of infected aneurysms include a soft tissue mass, stranding, and rim enhancement. Nuclear imaging studies with ^{111}In-labeled white blood cell scans have also been used. Fluorodeoxyglucose positron emission tomography (FDG-PET) may assist in diagnosing mycotic aneurysms and graft infections by detecting hypermetabolic activity and can monitor response to antibiotic therapy.[2,75]

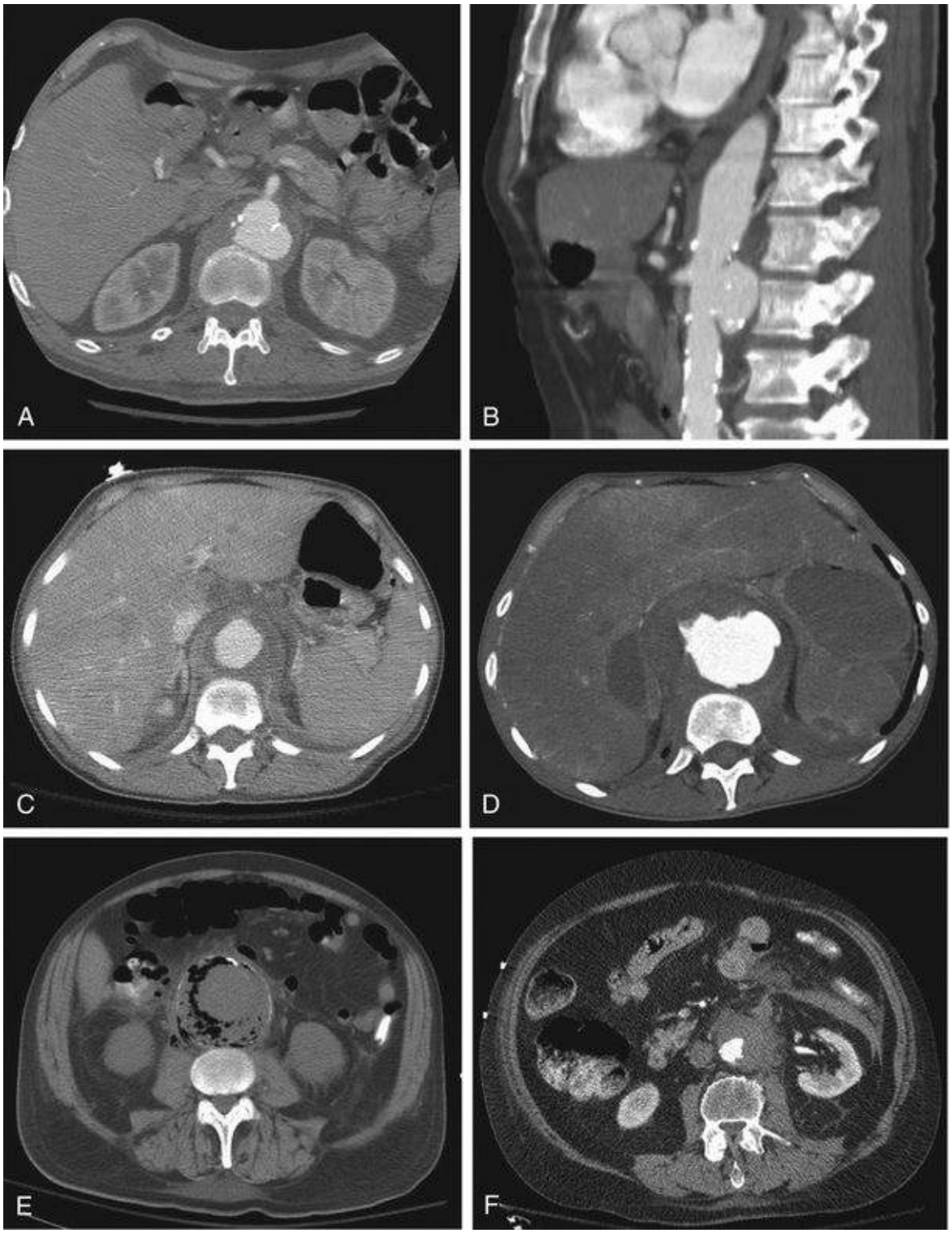
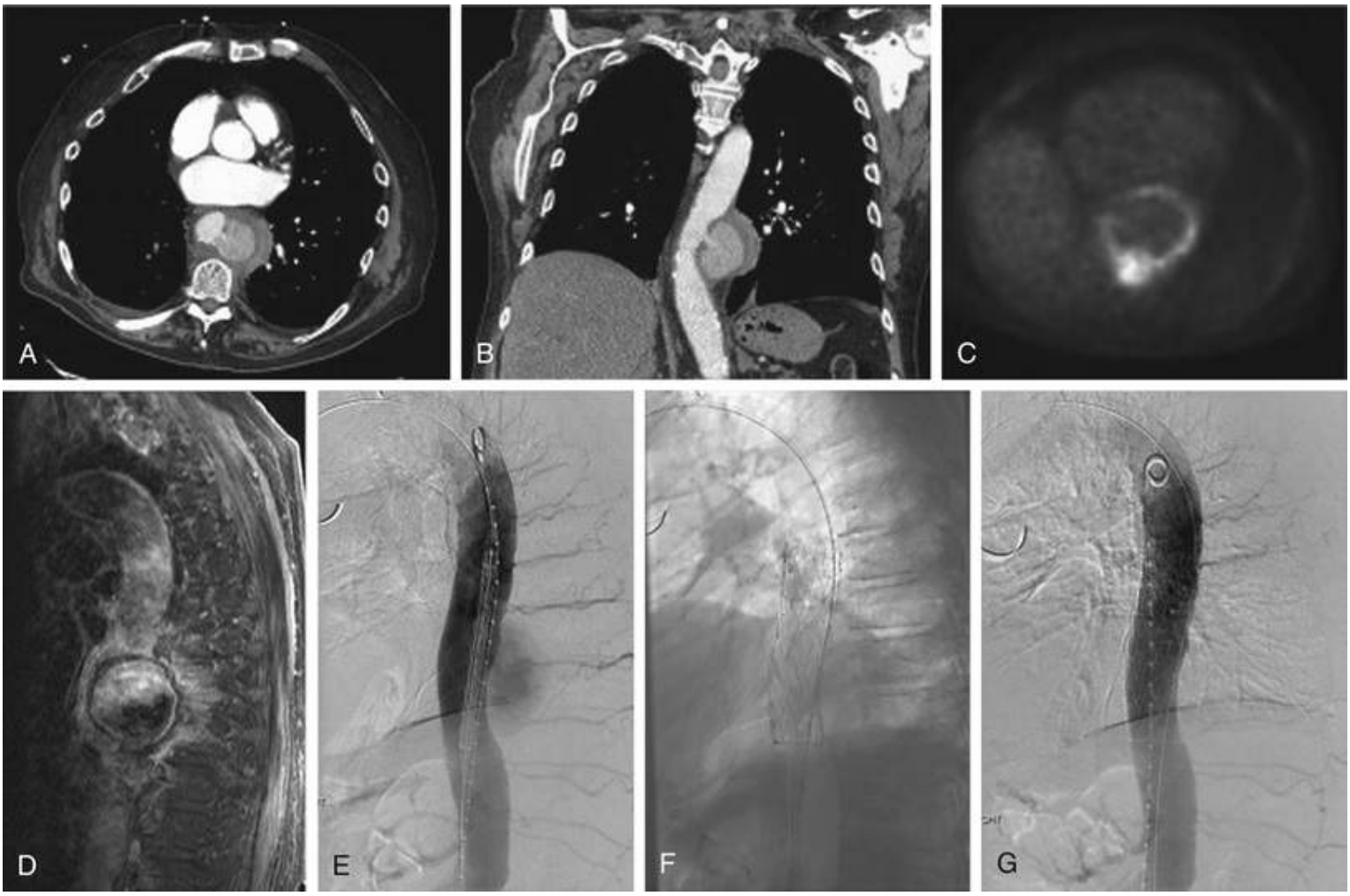


FIGURE 63.26 Typical features of mycotic aneurysms (MAs) on computed tomography. **A, B,** MAs classically present as focal outpouchings of the vascular wall, as seen on axial **(A)** and sagittal **(B)** images. In this case, there is calcification of the aortic wall, which may have been a nidus for infection. **C, D,** MAs tend to grow rapidly, as in this case, with images at initial presentation **(C)** and 2 weeks later **(D).** Also noted is irregularity of the aortic wall and mural thrombus. **E,** Inflammatory changes are common, as in this case with gas in the aortic wall in an MA due to infection by adjacent diverticulitis. **F,** MAs are prone to rupture. (From Deipolyi AR, Rho J, Khademhosseini A, Oklu R. Diagnosis and management of mycotic aneurysms. Clin Imaging 2016;40:256-62.)



EFIGURE 63.34 Example of mycotic aortic aneurysm (MA) treated with endovascular repair. Axial **(A)** and coronal **(B)** contrast-enhanced computed tomography images demonstrate a focal saccular outpouching, with surround inflammatory changes and rupture. **C,** Positron emission tomography demonstrates uptake in the aortic wall and in an adjacent vertebral body, concerning for extension of infection. **D,** Sagittal T2-weighted magnetic resonance image shows high signal in the adjacent vertebrae and discs, consistent with associated discitis/osteomyelitis. Again, MA is shown as a focal saccular outpouching with inflammatory changes. **E,** Aortogram demonstrates filling of the focal outpouching in the distal thoracic aorta. A stent graft is in position, just prior to being deployed. **F,** The covered stent has been deployed and postdilated. **G,** Completion aortogram demonstrates exclusion of the aneurysm by the stent. (From Deipolyi AR, Bailin A, Khademhosseini A, Oklu R. Imaging findings, diagnosis, and clinical outcomes in patients with mycotic aneurysms: single center experience. Clin Imaging 2016;40:512-6.)

Untreated infected aortic aneurysms generally expand and eventually rupture, often with rapid progression. *Salmonella* and other gram-negative infections have a greater tendency for early rupture and death.[77] Overall mortality from infected aortic aneurysms exceeds 50% with medical therapy alone. Treatment of infected AAAs involves excision or exclusion of the infected aortic tissue, in situ or extra-anatomic bypass of the aorta and branches, débridement of infected periaortic tissue, and prolonged antibiotic therapy. Many infected aneurysms are in locations not amenable to conventional extra-anatomic reconstruction. When infrarenal AAAs are associated with extensive aortic and periaortic purulence, extra-anatomic bypass is performed. In situ bypass is more often performed in the patient with suprarenal aneurysms or infrarenal aneurysms with minimal purulence. Recent surgical series have reported a short-term mortality of 10% to 40%, and higher mortality with OSR of thoracic aortic mycotic aneurysm.[75-77] Two-year survival is reported at 60%.[77] Subsequent graft infections complicate approximately 10% of patients, with extra-anatomic bypass resulting in worse outcomes compared to in situ repair.[77] Because many patients have a high risk for complications of surgery for infected aortic aneurysms, some advocate endovascular repair for select patients who are not suitable for OSR, either as a bridge to open repair or

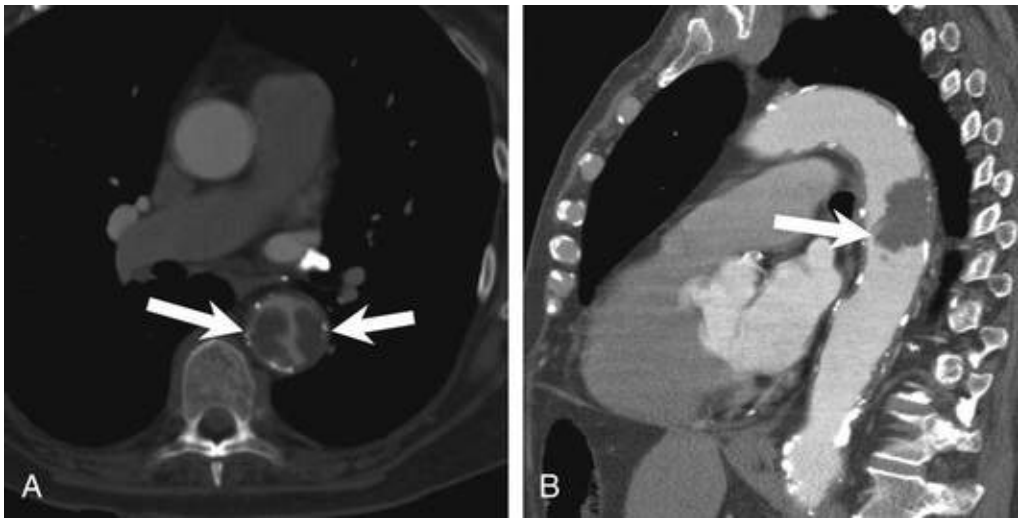
as definitive therapy[77] (**eFig. 63.34**). In a series of 130 aortic mycotic aneurysms treated with endovascular repair, infection-related mortality was 19%, with survival of 91%, 75%, 55%, and 41% after 1 month, 12 months, 60 months, and 120 months, respectively.[77]

Endovascular abdominal stent-graft infections are uncommon, with an incidence of 0.05% to 5%.[78] Pseudoaneurysm and aneurysm expansion and rupture may occur. Treatment includes removal of the infected stent-graft. Antibiotic-soaked in situ grafting is most frequently used, and some patients require axillofemoral bypass with total graft excision and oversewing of the aorta stump.[78]

Primary Tumors of the Aorta

Tumors that affect the thoracic aorta usually arise secondarily from direct invasion by adjacent cancer or metastases, especially from the lung and esophagus. Primary aortic sarcomas are very rare and are usually unsuspected until histologic analysis reveals malignancy. The average age at diagnosis is 60 years, with a male preponderance.[79] High-grade tumors (87%), arterial embolization (47%), and metastatic disease at diagnosis (45%) are common.[79] These tumors most often localize in the descending thoracic and abdominal aorta. Symptoms include pain, embolism, claudication, visceral ischemia, or constitutional symptoms. Less frequently, these tumors may cause hemorrhage or invade adjacent structures. Three categories of tumors have been described: *intraluminal* (polypoid), *intimal* (derived from endothelial cells or myofibroblasts), and *adventitial* (mural, fibrosarcomas). Intraluminal and intimal tumors are the most common and spread along the inner wall of the aorta, appearing polypoid on imaging. They may be accompanied by acute arterial embolization, with the embolus a mixture of tumor and thrombus, or may lead to arterial obstruction or involvement of visceral arteries. Widely metastatic emboli may occur. Adventitial (mural) tumors are rare and grow to involve periaortic tissue and adjacent organs.

Aortic tumors are of mesenchymal origin and include angiosarcoma (37%), leiomyosarcoma (13%), fibrous tumor (7%), and undifferentiated sarcoma (39%). CT may detect intimal tumors (**eFig. 63.35**), but the findings may mimic protruding atheroma. MRI is considered the most reliable imaging modality and may differentiate between tumor and atheromatous material. If no metastases are present, resection with prosthetic graft replacement is recommended. Because of difficulty in achieving wide margins, tumors may recur locally. Palliative treatment of obstructive tumors includes endarterectomy, endovascular grafts, and extra-anatomic bypass. Chemotherapy and radiation therapy have been used in some cases with limited success. The median survival is 11 months, with 1-, 3-, and 5-year survival rates of 47%, 17%, and 9%, respectively.[79]



EFIGURE 63.35 Intimal sarcoma of the descending thoracic aorta in a 70-year-old woman. Contrast-enhanced computed tomography shows an irregular low-density mass (*arrows*) partially filling the aortic lumen in the axial **(A)** and sagittal **(B)** planes. Extensive atherosclerotic calcifications appear throughout the aortic wall. (From Restrepo CS, Betancourt SL, Martinez-Jimenez S, et al. Aortic tumors. Semin Ultrasound CT MR 2012;33:265.)

Future Perspectives

Aortic disease has witnessed remarkable advances through discoveries in basic science, animal experimentation, genetics, clinical consortiums and registries, and translational research. Multiple trials of pharmacotherapy in degenerative AAA disease and heritable TAA disorders have advanced translational science and stimulated new proposals into pathogenesis, identifying potential targets for therapy. Partnerships with patient advocacy organizations have improved awareness of aortic disease. Recent management guidelines for thoracic aortic disease have furthered the evaluation and treatment of these disorders. Large registries, including IRAD, GERAADA, and GenTAC, provide important clinical and translational platforms for understanding aortic disease.

Advances in imaging the aorta structurally and functionally, with techniques to understand the biomechanical forces, four-dimensional flow characteristics, and biologic activity in the aortic wall, hold promise in understanding and managing patients with aortic disease. Remarkable advances in endovascular, hybrid, and open surgical repair have reduced morbidity and mortality for many aortic diseases. The role of endovascular therapy for aneurysm disease and acute and chronic dissection is likely to evolve over time as branched grafts and lower-profile delivery systems become available. Treatment of uncomplicated type B dissection with TEVAR may change the natural history of this disorder.

Surgical Therapy and Outcomes with Thoracoabdominal Aortic Aneurysms

Crawford type I involves the entire thoracic aorta and the upper abdominal aorta extending from the proximal descending aorta above the T6 vertebra to the level of the renal arteries (~25 of TAAAs); type II is the highest risk group, with the aneurysm involving the entire thoracic and most or all of the abdominal aorta extending from the proximal descending aorta above T6 to below the renal arteries, often to the iliac bifurcation (30% of TAAAs); type III aneurysms involve the distal half of the descending thoracic aorta below T6 and extend into the abdominal aorta (<25% of TAAAs); and type IV extends from the diaphragm and involves most of the abdominal aorta to the aortic bifurcation (<25% of TAAAs).

Crawford type V aneurysms arise in the distal half of the descending aorta (below T6) and extend into the abdominal aorta, but are limited to the visceral segment.[1] Repair of Crawford types I-III aneurysms is complex and usually performed through an extensive thoracoabdominal incision. The procedure requires bypass to maintain perfusion of the lower extremities and the mesenteric vessels. Spinal fluid drainage and other techniques, as for thoracic aneurysms, may diminish the risk for paraplegia and paraparesis. The mortality rate in low-risk patients is 3% to 10%, with a paraplegia rate of 3% to 5%, depending on the extent of the repair. Morbidity and mortality with repair of Crawford type IV aneurysms is intermediate between AAA and type I-III TAAA. Emergency surgery for rupture or leak carries a mortality rate of 80%.[1]

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Guidelines

Diseases of the Aorta

Alan C. Braverman and Marc Schermerhorn

Recommendations on Imaging of the Aorta[2]

Class I

1. It is recommended that diameters be measured at prespecified anatomic landmarks, perpendicular to the longitudinal axis. (*Level of evidence: C*)
2. In the case of repetitive imaging of the aorta over time, to assess change in diameter, it is recommended that the imaging modality with the lowest iatrogenic risk be used. (*Level of evidence: C*)
3. In the case of repetitive imaging of the aorta over time to assess change in diameter, it is recommended that the same imaging modality be used, with a similar method of measurement. (*Level of evidence: C*)

Class IIb

Aortic diameters may be indexed to the body surface area, especially for the outliers in body size.

(*Level of evidence: B*)

Recommendation in Patients with Aortic Aneurysm[2]

Class IIa

In cases of abdominal aortic aneurysm (AAA), duplex ultrasound for screening for peripheral artery disease and peripheral aneurysms should be considered. (*Level of evidence: C*)

Evaluation and Management of Acute Thoracic Aortic Disease

Recommendations for Screening Tests

Class I

1. An electrocardiogram (ECG) should be obtained in all patients with symptoms that may represent acute aortic dissection.[1]
    a. Given the relative infrequency of dissection-related coronary artery occlusion, the presence of ST-segment elevation suggestive of myocardial infarction (MI) should be treated as a primary cardiac event without delay for definitive aortic imaging unless the patient is at high risk for aortic dissection. *(Level of evidence: B)*
2. Urgent and definitive imaging of the aorta with transesophageal echocardiography (TEE), computed tomography (CT), or magnetic resonance imaging (MRI) is recommended to identify or exclude aortic dissection in patients determined to be at high risk for the disease by initial screening.[1] *(Level of evidence: B)*

Class IIa

1. In case of suspicion of acute aortic syndrome (AAS), the interpretation of biomarkers should always be considered along with the pretest clinical probability.[2] (*Level of evidence: C*)
2. In case of low clinical probability of AAS, negative D-dimer levels should be considered as ruling out the diagnosis.[2] (*Level of evidence: B*)
3. In case of intermediate clinical probability of AAS with positive (point-of-care) D-dimer test, further imaging tests should be considered.[2] (*Level of evidence: B*)

Class III

1. A negative finding on chest radiography should not delay definitive aortic imaging in patients determined to be high risk for aortic dissection by initial screening.[1] *(Level of evidence: C)*
2. In patients with high probability (risk score 2 or 3) of aortic dissection, testing of D-dimers is not recommended.[2] (*Level of evidence: C*)

Recommendations for Diagnostic Imaging Studies

Class I

1. Selection of a specific imaging modality (CT, MRI, TEE, TTE[2]) to identify or exclude aortic dissection should be based on patient variables and institutional capabilities, including immediate availability.[1,2] *(Level of evidence: C)*
2. If high clinical suspicion exists for acute aortic dissection but the findings on initial aortic imaging are negative, a second imaging study should be obtained.[1,2] (*Level of evidence: C*)
3. In case of uncomplicated type B aortic dissection treated medically, repeated imaging (CT or MRI) during the first days is recommended.[2] (*Level of evidence: C*)

Recommendations for Intramural Hematoma (IMH) Without Intimal Defect or Penetrating Aortic Ulcer (PAU)

Class I

1. In all patients with IMH or PAU, medical therapy including pain relief and blood pressure control is recommended.[2] (*Level of evidence: C*)
2. In cases of type A IMH or PAU, urgent surgery is indicated.[2] (*Level of evidence: C*)
3. In cases of type B IMH or PAU, initial medical therapy under careful surveillance is recommended.[2] (*Level of evidence: C*)

Class IIa

1. It is reasonable to treat IMH similar to aortic dissection in the corresponding segment of the aorta.[1] *(Level of evidence: C)*
2. In complicated type B IMH or PAU, thoracic endovascular aortic repair (TEVAR) should be considered.[2] (*Level of evidence: C*)

Class IIb

In complicated type B IMH or PAU, surgery may be considered.[2] (*Level of evidence: C*)

Surgical and Endovascular Treatment by Location of Disease

Ascending Aorta and Aortic Sinuses

Recommendations for Asymptomatic Patients with Ascending Aortic Aneurysms

Class I

1. Asymptomatic patients with a degenerative thoracic aortic aneurysm (TAA), chronic aortic dissection, IMH, PAU, mycotic aneurysm, or pseudoaneurysm who are otherwise suitable

candidates and in whom the diameter of the ascending aorta or aortic sinus is 5.5 cm or greater should be evaluated for surgical repair.[1] *(Level of evidence: C)*

2. Surgery is indicated in patients who have aortic root aneurysm, with maximal aortic diameter of 50 mm or more for patients with Marfan syndrome.[2] (*Level of evidence: C*)
3. Patients undergoing aortic valve repair or replacement and who have an ascending aorta or aortic root larger than 4.5 cm should be considered for concomitant repair of the aortic root or replacement of the ascending aorta.[1] *(Level of evidence: C)*

Class IIa

1. Elective aortic replacement is reasonable for patients with Marfan syndrome, other genetic diseases, or bicuspid aortic valve (BAV) when the ratio of maximal ascending or aortic root area in square centimeters divided by the patient's height (in meters) exceeds 10.[1] *(Level of evidence: C)*
2. It is reasonable for patients with Loeys-Dietz syndrome or a confirmed *TGFBR1* or *TGFBR2* mutation to undergo aortic repair when the aortic diameter reaches 4.2 cm or greater by TEE (internal diameter) or 4.4 to 4.6 cm or greater by CT or MRI (external diameter).[1] *(Level of evidence: C)*
3. In short-statured patients with Turner syndrome and BAV disease, absolute measurement of aortic root or ascending aortic diameter may not predict the risk of aortic dissection, as well as aortic diameter index greater than 2.5 cm/m^2. In addition, in a study of patients with BAV disease, a maximum aortic cross-sectional area-to-height ratio greater than 10 cm^2/m was also a predictor of aortic dissection.[1] (*Level of evidence: B-NR*)

Recommendations for Aortic Arch Aneurysms

Class IIa

For patients with low operative risk in whom an isolated degenerative aneurysm of the aortic arch is present, operative treatment is reasonable for asymptomatic patients when the diameter of the arch exceeds 5.5 cm.[1,2] *(Level of evidence: B)*

Descending Thoracic Aorta and Thoracoabdominal Aorta

Recommendations for Descending Thoracic Aorta and Thoracoabdominal Aortic Aneurysms

Class I

1. For patients with chronic dissection, particularly if associated with a connective tissue disorder, no significant comorbid disease, and a descending thoracic aortic diameter greater than 5.5 cm, open repair is recommended.[1] *(Level of evidence: B)*
2. For patients with degenerative or traumatic descending TAAs exceeding 5.5 cm, saccular aneurysms, or postoperative pseudoaneurysms, TEVAR should be strongly considered when

feasible.[1] *(Level of evidence: B)*

3. For patients with thoracoabdominal aneurysms in whom TEVAR options are limited and surgical morbidity is elevated, elective surgery is recommended if the aortic diameter exceeds 6.0 cm—or less if a connective tissue disorder such as Marfan or Loeys-Dietz syndrome is present.[1] *(Level of evidence: C)*

Class IIa

1. TEVAR should be considered in patients who have descending TAA with maximal diameter of 55 mm or more.[2] *(Level of evidence: C)*
2. When TEVAR is not technically possible, surgery should be considered in patients who have descending TAA with maximal diameter of 60 mm or more. *(Level of evidence: C)*

Counseling and Management of Chronic Aortic Diseases in Pregnancy

Recommendations for Counseling and Management of Chronic Aortic Diseases in Pregnancy[1]

Class I

1. Women with Marfan syndrome and aortic dilation, as well as patients without Marfan syndrome who have known aortic disease, should be counseled about their risk for aortic dissection, in addition to the heritable nature of the disease, before pregnancy. *(Level of evidence: C)*
2. For pregnant women with known thoracic aortic dilation or a familial or genetic predisposition to aortic dissection, strict blood pressure control, specifically to prevent stage II hypertension, is recommended. *(Level of evidence: C)*
3. For all pregnant women with known aortic root or ascending aortic dilation, monthly or bimonthly echocardiographic measurement of ascending aortic dimensions until birth is recommended to detect aortic expansion. *(Level of evidence: C)*
4. Pregnant women with aortic aneurysms should undergo delivery at locations where cardiothoracic surgery is available. *(Level of evidence: C)*

Class IIa

Fetal delivery via cesarean section is reasonable for patients with significant aortic enlargement, dissection, or severe aortic valve regurgitation. *(Level of evidence: C)*

Class IIb

If progressive aortic dilation or advancing aortic valve regurgitation is documented, prophylactic surgery may be considered. *(Level of evidence: C)*

Recommendations for Surveillance of Thoracic Aortic Disease or Previously Repaired Patients[1]

Class IIa

1. CT or MRI of the thoracic aorta is reasonable after a type A or B aortic dissection or after prophylactic repair of the aortic root/ascending aorta. *(Level of evidence: C)*
2. CT or MRI of the aorta is reasonable at 1, 3, 6, and 12 months after dissection and, if stable, annually thereafter so that any threatening enlargement can be detected in timely fashion. *(Level of evidence: C)*

Diagnosis and Management of Patients With Thoracic Aortic Disease: Genetic Syndromes Associated with Thoracic Aortic Aneurysms and Dissection

Recommendations for Genetic Syndromes[1]

Class I

1. An echocardiogram is recommended at diagnosis of Marfan syndrome to determine aortic root and ascending aortic diameters, and at 6 months thereafter to determine the rate of enlargement of the aorta. *(Level of evidence: C)*
2. Annual imaging is recommended for patients with Marfan syndrome if stability of the aortic diameter is documented. If the maximal aortic diameter is 4.5 cm or greater or if the aortic diameter shows significant growth from baseline, more frequent imaging should be considered. *(Level of evidence: C)*
3. Patients with Loeys-Dietz syndrome or a confirmed genetic mutation known to predispose to aortic aneurysms and aortic dissections (e.g., *TGFBR1*, *TGFBR2*, *FBN1*, *ACTA2*, *MYH11*) should undergo complete aortic imaging at initial diagnosis and 6 months thereafter to establish whether enlargement is occurring. *(Level of evidence: C)*

Class IIa

For women with Marfan syndrome contemplating pregnancy, it is reasonable to replace prophylactically the aortic root and ascending aorta if the diameter exceeds 4.0 cm. *(Level of evidence: C)*

Class IIb

In patients with Turner syndrome and additional risk factors, including a BAV, coarctation of the aorta, or hypertension, and in patients who attempt to become pregnant or who become pregnant, it may be reasonable to perform imaging of the heart and aorta to help determine the risk for aortic

dissection. *(Level of evidence: C)*

Recommendations on Genetic Testing in Aortic Diseases

Class I

1. Aortic imaging is recommended for first-degree relatives of patients with TAA and/or dissection to identify those with asymptomatic disease.[1] *(Level of evidence: B)*
2. If the mutant gene associated with aortic aneurysm or dissection is identified in a patient, first-degree relatives should undergo counseling and testing. Then, only relatives with the genetic mutation should undergo aortic imaging.[1] *(Level of evidence: C)*
3. It is recommended to investigate first-degree relatives of a patient with thoracic aortic aneurysm and dissection syndrome (TAAD) to identify a familial form in which relatives all have a 50% chance of carrying the familial mutation.[2] *(Level of evidence: C)*
4. Once a familial form of TAAD is highly suspected, it is recommended to refer the patient to a geneticist for family investigation and molecular testing.[2] *(Level of evidence: C)*

Variability of age of onset warrants screening every 5 years of “healthy” at-risk relatives until diagnosis (clinical or molecular) is established or ruled out.[2] *(Level of evidence: C)*

Class IIa

1. If one or more first-degree relatives of a patient with known TAA and/or dissection are found to have thoracic aortic dilation, aneurysm, or dissection, imaging of second-degree relatives is reasonable.[1] *(Level of evidence: B)*
2. In familial nonsyndromic TAAD, screening for aneurysm should be considered, not only in the thoracic aorta, but also throughout the arterial tree, including cerebral arteries.[2] *(Level of evidence: C)*

Class IIb

Sequencing of genes known to cause familial TAAs and/or dissection may be considered in patients with a family history and clinical features associated with mutations in these genes.[1] *(Level of evidence: B)*

Recommendations for Bicuspid Aortic Valve and Associated Congenital Variants in Adults[1]

Class I

1. First-degree relatives of patients with a BAV, premature onset of thoracic aortic disease with minimal risk factors, or a familial form of TAA and dissection should be evaluated for the

presence of a BAV and asymptomatic thoracic aortic disease. *(Level of evidence: C)*

2. All patients with a BAV should have both the aortic root and ascending thoracic aorta evaluated for evidence of aortic dilation. *(Level of evidence: B)*

Recommendation for Employment and Lifestyle in Patients with Thoracic Aortic Disease[1]

Class IIa

For patients with a current TAA or dissection or previously repaired aortic dissection, employment and lifestyle restrictions are reasonable, including avoidance of strenuous lifting, pushing, or straining that would require a Valsalva maneuver. *(Level of evidence: C)*

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Aortic Dissection

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64

Peripheral Artery Diseases

Marc P. Bonaca, Mark A. Creager

Peripheral artery disease (PAD) generally refers to acute or chronic obstruction of the arteries supplying the lower or upper extremities that, when severe, results in downstream ischemia and potentially tissue loss.[1] Most often caused by atherosclerosis, PAD may also result from thrombosis, embolism, vasculitis, fibromuscular dysplasia, or entrapment. The term *peripheral vascular disease* is less specific because it encompasses a group of diseases affecting blood vessels that include other atherosclerotic conditions, such as renal artery disease and carotid artery disease, as well as vasculitides, vasospasm, venous thrombosis, venous insufficiency, and lymphatic disorders.

Atherosclerotic PAD correlates strongly with risk for major adverse cardiovascular events (MACE) because it is frequently associated with coronary and cerebral atherosclerosis.[1] Patients with PAD and concomitant symptomatic cerebrovascular or coronary disease are at particularly high risk. Patients with PAD also have limb morbidity, including intermittent claudication, chronic critical limb ischemia, acute limb ischemia, and tissue loss.[2,3] The limb morbidity impacts quality of life and independence and, in its severe forms, is associated with increased mortality.[4]

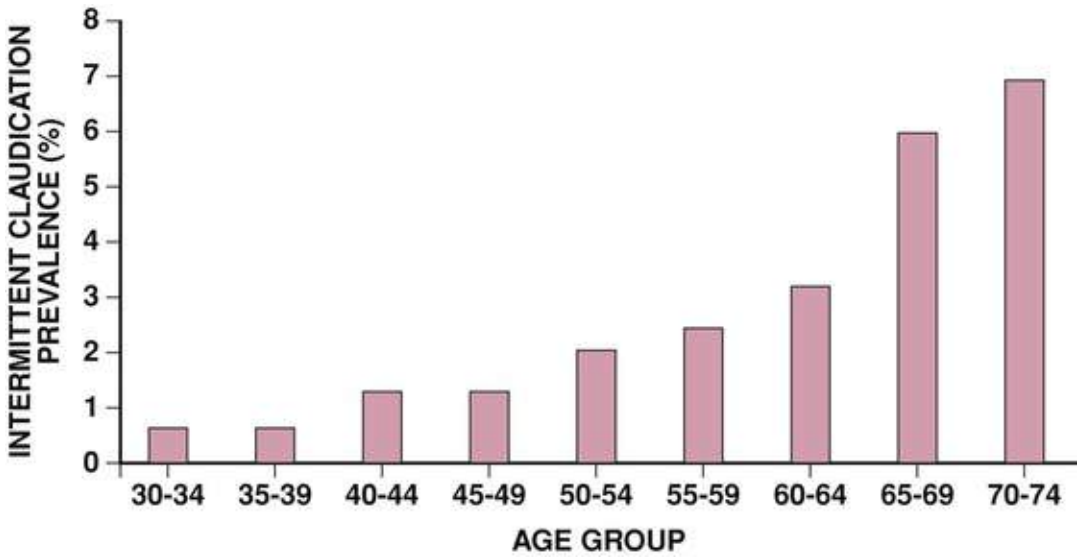
PAD is underdiagnosed, and use of indicated therapies is low.[5] As a manifestation of atherosclerosis associated with increased cardiovascular risk, cardiologists have increasing interest in its diagnosis and management. Clinicians treating patients with PAD not only must be skilled in application of strategies to reduce systemic ischemic risk, but also must know how to characterize the severity of limb disease and use therapies to optimize function and reduce the risk of tissue loss. This chapter provides a framework for the diagnosis and management of patients with PAD.

Epidemiology

The prevalence of PAD varies according to the population studied, the diagnostic method used, and

whether symptoms are included to derive estimates. Most epidemiologic studies have used a noninvasive measurement, the *ankle-brachial index* (ABI), to diagnose PAD. The ABI is the ratio of ankle to brachial systolic blood pressure (see later). The prevalence of PAD based on abnormal ABI values ranges from approximately 6% in persons 40 years and older to 15% to 20% in those 65 years and older.[6,7] PAD affects 8 to 10 million individuals in the United States and more than 200 million people worldwide.[8] The prevalence of PAD is greater in men than in women in most studies. Taking into consideration the total number of women and men in the U.S. population, however, there are more women than men with PAD.[9] Blacks have a higher prevalence of PAD than non-Hispanic whites.[10]

Questionnaires specifically designed to elicit symptoms of *intermittent claudication* can serve to assess the prevalence of symptomatic disease in these populations. Overall, the estimated prevalence of claudication ranges from 1.0% to 4.5% in a population older than 40 years.[1,6] The prevalence and incidence of claudication increase with age and are greater in men than in women in most studies[10] (**eFig. 64.1**). Estimates vary by age and sex but generally indicate that 10% to 30% of patients with PAD have claudication. The incidence of *critical limb ischemia* (CLI) is approximately 22 per 100,000 per year, affecting 1% to 2% of patients with PAD.[1,11] Less information is available on the prevalence and incidence of *acute limb ischemia* (ALI), with estimates among patients with symptomatic PAD of approximately 1% to 2% per year.[3,12] The incidence of *amputation* ranges from 112 to 250 per million per year.



EFIGURE 64.1 Age-related prevalence of intermittent claudication derived from large population-based studies. (From Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease [TASC II]. Eur J Vasc Endovasc Surg 2007;33:S1.)

Risk Factors for Peripheral Artery Disease

The well-known modifiable risk factors associated with coronary atherosclerosis also contribute to atherosclerosis of the peripheral circulation (**see Chapter 45**). The risk factors most strongly associated with the greatest risk of PAD are cigarette smoking and diabetes mellitus (DM); dyslipidemia, hypertension, chronic kidney disease, and inflammation, as measured by C-reactive protein (CRP) concentration, are also associated with increased risk for PAD (**Table 64.1**). Data from several observational studies indicate a twofold to fourfold increase in the prevalence of PAD in current smokers

in comparison to never smokers, with smoking cessation associated with better outcomes.[13,14] A dose-response relationship exists between lifetime exposure to cigarettes and the incidence of symptomatic PAD. In the Women's Health Study the hazard ratio for incident symptomatic PAD in smokers of more than 15 cigarettes per day was 17 (95% confidence interval [CI] 11 to 27); the risk decreased following smoking cessation.[13] Patients with DM often have extensive and severe PAD and a greater propensity for arterial calcification.[15] Metabolic syndrome is also associated with PAD.[16] Involvement of the femoral and popliteal arteries resembles that in nondiabetic persons, but distal disease affecting the tibial and peroneal arteries occurs more frequently. Among patients with PAD, diabetic patients are more likely than nondiabetic patients to have critical limb ischemia or to undergo an amputation.[15] Abnormalities in lipid metabolism are associated with PAD. Elevations in total or low-density lipoprotein (LDL) cholesterol increase the risk for PAD and claudication in most studies. Hypertriglyceridemia predicts risk for PAD when considered as an independent variable, but its effect diminishes when considered in the context of other lipid fractions.[11,17] In addition, hypertension increases the risk for PAD by 1.3- to 2.2-fold.[17,18] The risk for development of PAD and intermittent claudication increases progressively with the number of risk factors.

TABLE 64.1

Odds Ratio of Peripheral Artery Disease in Persons With Risk Factors

RISK FACTOR	ODDS RATIO (95% CI)
Cigarette smoking	4.46 (2.25-8.84)
Diabetes mellitus	2.71 (1.03-7.12)
Hypertension	1.75 (0.97-3.13)
Hypercholesterolemia	1.68 (1.09-2.57)
Hyperhomocysteinemia	1.92 (0.95-3.88)
Chronic kidney disease	2.00 (1.08-3.70)
Insulin resistance	2.06 (1.10-4.00)
C-reactive protein	2.20 (1.30-3.60)

Data derived from reports of the National Health and Nutrition Examination Survey (NHANES): Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from NHANES, 1999–2000. Circulation 2004;110:738; Pande RL, Perlstein TS, Beckman JA, Creager MA. Association of insulin resistance and inflammation with peripheral arterial disease: NHANES, 1999–2004. Circulation 2008;118:33; O'Hare AM, Glidden DV, Fox CS, Hsu CY. High prevalence of peripheral arterial disease in persons with renal insufficiency: results from NHANES, 1999–2000. Circulation 2004;109:320; and Guallar E et al. Confounding of the relation between homocysteine and peripheral arterial disease by lead, cadmium, and renal function. Am J Epidemiol 2006;163:700.)

The pathobiology of PAD involves inflammation, as does atherosclerosis in other tissue beds.[19] High concentrations of fibrinogen are associated with an increased risk of developing PAD, most likely a reflection of increased inflammation rather than a procoagulant effect. Levels of leukocyte adhesion molecules and characteristics of leukocyte-platelet aggregates correlate with the development and extent of PAD.[20,21] Levels of CRP, monocytes, and lipoprotein-associated phospholipase A_2 in peripheral blood are independently associated with PAD, consistent with a role of innate immunity and chronic inflammation in its pathogenesis.[19,22] Conversely, serum bilirubin, an endogenous antioxidant with anti-inflammatory properties, is associated with reduced PAD prevalence. Inflammation provides the mechanistic link between many of the common risk factors for atherosclerosis and the pathophysiologic processes in the arterial wall that lead to PAD.

Pathophysiology of Peripheral Artery Disease

Intermittent claudication results from an oxygen (O_2) supply-demand mismatch analogous to angina in

patients with stable angina. Impairment in O_2 delivery capacity coupled with dysfunction in O_2 extraction and utilization at the muscular level result in ischemic pain through activation of local sensory receptors by accumulation of lactate or other metabolites (**Fig. 64.1**). Patients with intermittent claudication may have single or multiple occlusive lesions in the arteries supplying the limb. Blood flow and leg O_2 consumption are normal at rest, but the obstructive lesions limit blood flow and O_2 delivery during exercise such that the metabolic needs of the exercising muscle outstrip the available supply of O_2 and nutrients. Patients with critical limb ischemia typically have multiple occlusive lesions such that even the resting blood supply cannot meet the nutritional needs of the limb, leading to rest pain and tissue loss.

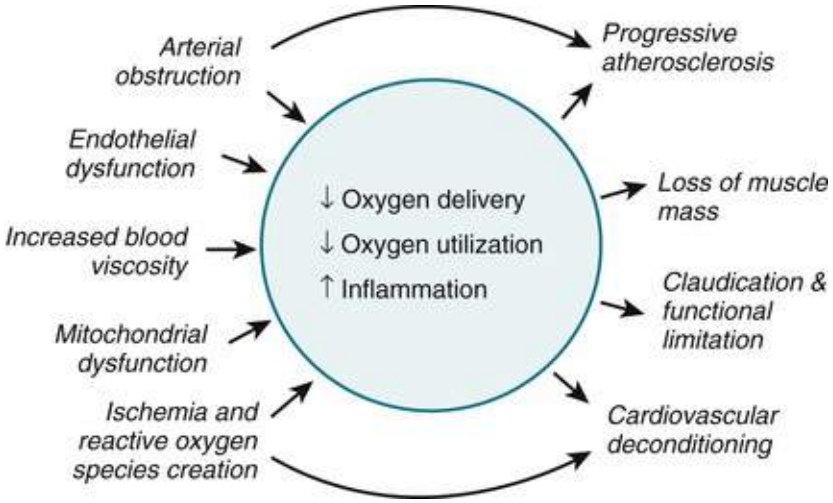


FIGURE 64.1 Mechanisms for functional limitations in peripheral artery disease (PAD). (Modified from Bonaca MP, Creager MA. Pharmacological treatment and current management of peripheral artery disease. Circ Res 2015;116:1579-98.)

Factors Regulating Blood Supply

Flow through an artery is directly related to perfusion pressure and inversely related to vascular resistance (**see Chapter 57**). Stenoses reduce flow through the artery (**Fig. 64.2**), as described in the Poiseuille equation:

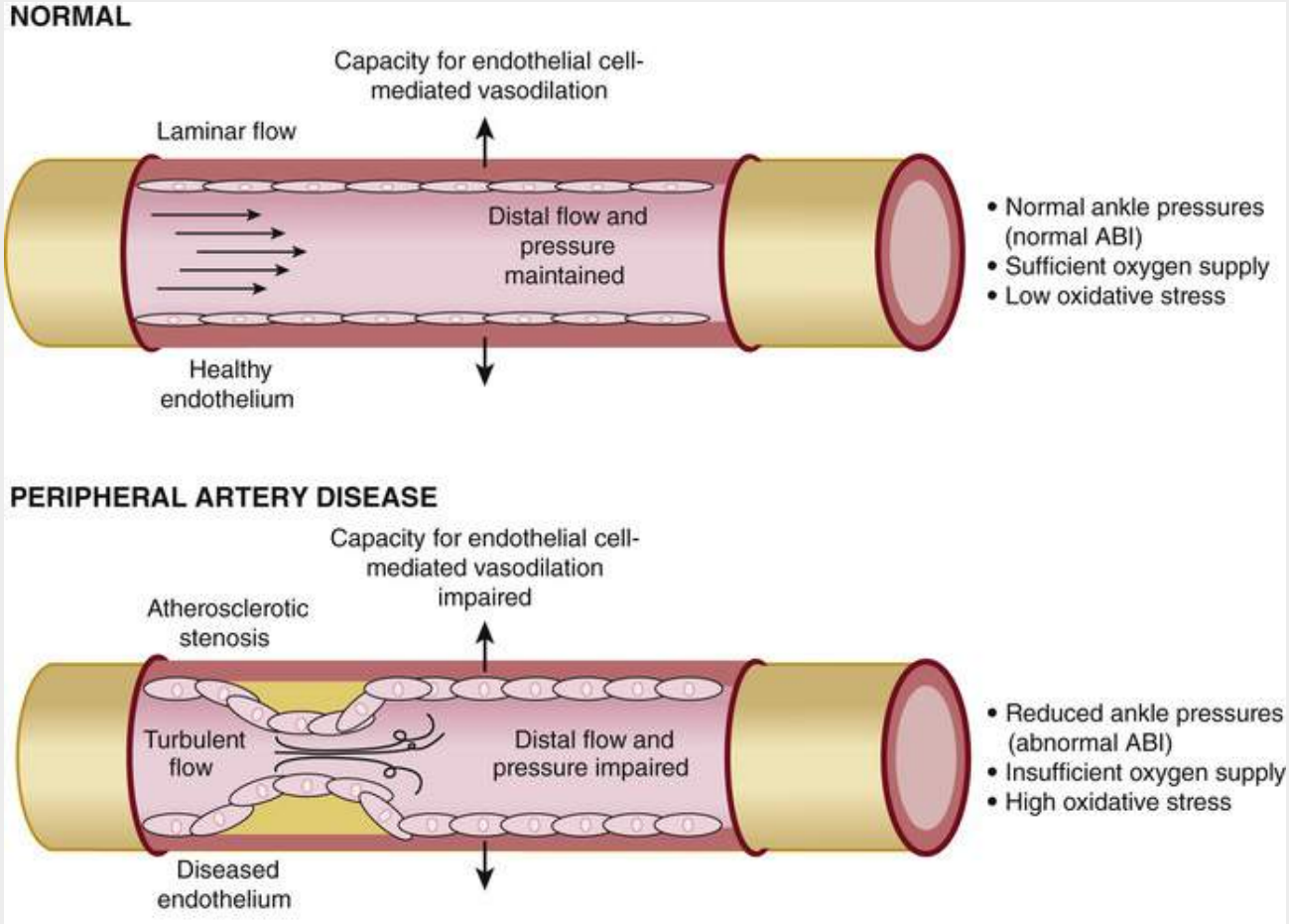


FIGURE 64.2 Pathophysiology of intermittent claudication. In healthy arteries **(top)**, flow is laminar, and endothelial function is normal; therefore blood flow and oxygen delivery match muscle metabolic demand at rest and during exercise. Muscle metabolism is efficient and results in low oxidative stress. In contrast, in PAD **(bottom)**, arterial stenosis results in disturbed flow, and the loss of kinetic energy results in a drop in pressure across the stenosis. Collateral vessels have high resistance and only partially compensate for the arterial stenosis. In addition, endothelial function is impaired, thereby resulting in further loss of vascular function. These changes limit the blood flow response to exercise and result in a mismatch of oxygen delivery to muscle metabolic demand. Changes in skeletal muscle metabolism further compromise the efficient generation of high-energy phosphates. Oxidant stress, the result of inefficient oxidation, further impairs endothelial function and muscle metabolism. ABI, Ankle-brachial index.

$$Q = \frac{\Delta P \pi r^4}{8 \eta l}$$

where ΔP is the pressure gradient across the stenosis, *r* is the radius of the residual lumen, η is blood viscosity, and *l* is the length of the vessel affected by the stenosis. As the severity of a stenotic lesion increases, flow falls progressively. The pressure gradient across the stenosis increases in a nonlinear manner, thus emphasizing the importance of a stenosis at high blood flow rates. Usually, a blood pressure gradient exists at rest if the stenosis reduces the diameter of the lumen by more than 50% because as distorted flow develops, kinetic energy is lost. A stenosis that does not cause a pressure gradient at rest may cause one during exercise when blood flow increases because of the higher cardiac output and decreased vascular resistance. Consequently, as flow through a stenosis increases, distal perfusion pressure drops. As the metabolic demand of exercising muscle outstrips its blood supply, local metabolites (including adenosine, nitric oxide [NO], potassium [K^+]), and hydrogen ion [H^+]) accumulate, and peripheral resistance vessels dilate. Perfusion pressure then drops further because the

stenosis limits flow. In addition, intramuscular pressure rises during exercise and may exceed the arterial pressure distal to an occlusion and halt blood flow. Flow through collateral blood vessels can usually meet the resting metabolic needs of skeletal muscle tissue at rest but does not suffice during exercise.

Functional abnormalities in vasomotor reactivity may also interfere with blood flow. Patients with peripheral atherosclerosis have reduced vasodilator capability of both conduit and resistance vessels. Normally, arteries dilate in response to pharmacologic and biochemical stimuli, such as acetylcholine, serotonin, thrombin, and bradykinin, as well as in response to shear stress induced by increases in blood flow. This vasodilator response results from the release of biologically active substances from the endothelium, particularly NO. The vascular relaxation of a conduit vessel that occurs after a flow stimulus, such as that induced by exercise, may facilitate the delivery of blood to exercising muscles in healthy persons. The atherosclerotic femoral arteries and calf resistance vessels of patients with PAD have impaired endothelium-dependent vasodilation in response to flow or pharmacologic stimuli. This failure of vasodilation might prevent an increase in nutritive blood supply to exercising muscle because endothelium-derived NO can contribute to hyperemic blood flow after an ischemic stimulus.

Abnormalities in the microcirculation also contribute to the pathophysiology of CLI. Patients with severe limb ischemia have a reduced number of perfused skin capillaries. Other potential causes of decreased capillary perfusion in CLI include reduced red blood cell deformability, increased leukocyte adhesiveness, platelet aggregates, fibrinogen, microvascular thrombosis, excessive vasoconstriction, and interstitial edema. Intravascular pressure may also decrease because of precapillary arteriolar dilation secondary to locally released vasoactive metabolites.[23]

Skeletal Muscle Structure and Metabolic Function

Electrophysiologic and histopathologic examination has found evidence of partial axonal denervation of skeletal muscle in legs affected by PAD. Type I, oxidative slow-twitch fibers are preserved, but type II, glycolytic fast-twitch fibers are lost in the skeletal muscle of patients with PAD. The loss of type II fibers correlates with decreased muscle strength and reduced exercise capacity. In skeletal muscle distal to PAD, the shift to anaerobic metabolism occurs earlier during exercise and persists longer after exercise. Patients with claudication have increased lactate release and accumulation of acylcarnitines during exercise and slowed O_2 desaturation kinetics, indicative of ineffective oxidative metabolism.[23] Moreover, mitochondrial respiratory activity and phosphocreatine and adenosine triphosphate (ATP) recovery time are delayed in the calf muscles of PAD patients, as assessed after submaximal exercise by ^{31}P magnetic resonance spectroscopy.[23a]

Clinical Features

Symptoms

The cardinal symptoms of PAD include limb pain either with exercise (intermittent claudication) or at rest. The term *claudication* is derived from the Latin *claudicare*, “to limp.” Intermittent claudication refers to a pain, ache, sense of fatigue, or other discomfort that occurs in the affected muscle group with exercise, particularly walking, and resolves with rest. The location of the symptom is often related to the site of the most proximal stenosis. Buttock, hip, or thigh claudication typically occurs in patients with obstruction of the aorta and iliac arteries. Calf claudication is caused by femoral or popliteal artery stenoses. The gastrocnemius muscle consumes more oxygen during walking than other muscle groups in

the leg do and thus causes the most frequent symptoms reported by patients. Ankle or foot claudication occurs in patients with tibial and peroneal artery disease. Similarly, stenoses of the subclavian, axillary, or brachial arteries may cause shoulder, biceps, or forearm claudication, respectively. The symptoms should resolve several minutes after cessation of effort. Episodic calf or thigh pain that occurs during rest, such as nocturnal cramps, should not be confused with claudication and are not symptoms of PAD. The history obtained from persons reporting claudication should note the walking distance, speed, and incline that precipitate claudication. Such baseline assessment serves to evaluate disability and provides an initial qualitative measure with which to determine stability, improvement, or deterioration during subsequent encounters with the patient. PAD may result in functional limitations beyond those caused by pain. Patients with PAD walk more slowly and have less walking endurance than do patients without PAD.[24]

Several questionnaires can be used to assess the presence and severity of claudication. The Rose Questionnaire was developed initially to diagnose both angina and intermittent claudication in epidemiologic surveys. It questions whether pain develops in either calf with walking and whether the pain occurs at rest, while walking at an ordinary or hurried pace, or on walking uphill. Several modifications of this questionnaire have been developed, including the Edinburgh Claudication Questionnaire and the San Diego Claudication Questionnaire,[24] both of which are more sensitive and specific than a physician's diagnosis of intermittent claudication based on walking distance, walking speed, and nature of the symptoms. Another validated instrument, the Walking Impairment Questionnaire, asks a series of questions and derives a point score based on walking distance, walking speed, and nature of the symptoms.[23,25,26]

Symptoms resembling limb claudication occasionally result from nonatherosclerotic causes of artery obstruction (**Table 64.2**), including arterial embolism; vasculitides such as thromboangiitis obliterans, Takayasu arteritis, and giant cell arteritis; aortic coarctation; fibromuscular dysplasia; irradiation; endofibrosis of the external iliac artery; and extravascular compression as a result of arterial entrapment or an adventitial cyst (**see Chapter 94**). Several nonvascular causes of exertional leg pain should be considered in the differential diagnosis of intermittent claudication. Lumbosacral radiculopathy resulting from degenerative joint disease, spinal stenosis, and herniated discs can cause pain in the buttock, hip, thigh, calf, or foot with walking, often after very short distances or even with standing. This symptom has been called *neurogenic pseudoclaudication*. Lumbosacral spine disease and PAD both preferentially affect the elderly population and thus may coexist in the same individual. Positional changes in symptoms or attenuation of pain while walking stooped forward, such as with a shopping cart, are suggestive of a neurogenic rather than a vascular cause of symptoms. Arthritis of the hips and knees also provokes leg pain with walking. Typically, the pain is localized to the affected joint and can be elicited on physical examination by palpation and range-of-motion maneuvers. *Exertional compartment syndrome* most often occurs in athletes with large calf muscles; increased tissue pressure during exercise limits microvascular flow and results in calf pain or tightness. Symptoms improve after cessation of exercise. Rarely, skeletal muscle disorders such as myositis can cause exertional leg pain. *Glycogen storage disease type V,* also known as McArdle syndrome, in which skeletal muscle phosphorylase is deficient, can cause symptoms mimicking the claudication of PAD. Patients with chronic venous insufficiency sometimes report leg discomfort with exertion, a condition designated *venous claudication.* Venous hypertension during exercise increases arterial resistance in the affected limb and limits blood flow. In the case of venous insufficiency, elevated extravascular pressure caused by interstitial edema further diminishes capillary perfusion. Peripheral edema, venous stasis pigmentation, and occasionally venous varicosities demonstrated on physical examination may provide clues for this unusual cause of exertional leg pain.

TABLE 64.2

Differential Diagnosis of Exertional Leg Pain

Vascular Causes
Atherosclerosis
Thrombosis
Embolism
Vasculitis
Thromboangiitis obliterans
Takayasu arteritis
Giant cell arteritis
Aortic coarctation
Fibromuscular dysplasia
Irradiation
Endofibrosis of the external iliac artery
Extravascular compression
Arterial entrapment (e.g., popliteal artery entrapment, thoracic outlet syndrome)
Adventitial cysts
Nonvascular Causes
Lumbosacral radiculopathy
Degenerative arthritis
Spinal stenosis
Herniated disc
Arthritis
Hips, knees
Venous insufficiency
Myositis
Glycogen storage disease type V (McArdle syndrome)

Symptoms or tissue loss occur at rest in patients with CLI. Typically, patients complain of pain or paresthesias in the foot or toes of the affected extremity. This discomfort worsens with leg elevation and improves with leg dependency, as might be anticipated by the effect of gravity on perfusion pressure. The pain can be particularly severe at sites of skin fissuring, ulceration, or necrosis. Frequently, the skin is very sensitive, and even the weight of bedclothes or sheets elicits pain. Patients may sit on the edge of the bed and dangle their legs to alleviate the discomfort. In contrast, patients with neuropathy can experience little or no pain despite the presence of severe ischemia.

Critical limb and digital ischemia can result from arterial occlusions from a variety of etiologies besides atherosclerosis, including conditions such as thromboangiitis obliterans, vasculitides such as systemic lupus erythematosus (SLE) or scleroderma, vasospasm, atheromatous embolism, and acute arterial occlusion secondary to thrombosis or embolism (see later). Acute gouty arthritis, trauma, and sensory neuropathy such as that caused by DM, lumbosacral radiculopathies, and complex regional pain syndrome (previously known as “reflex sympathetic dystrophy”) can cause foot pain. Leg ulcers also occur in patients with venous insufficiency or sensory neuropathy, particularly that related to diabetes. These ulcers appear to be distinct from those caused by PAD. The ulcer of venous insufficiency usually localizes near the medial malleolus and has an irregular border and a pink base with granulation tissue. In general, they produce milder pain than those caused by PAD. *Neurotrophic ulcers* occur at sites of pressure or trauma, usually on the sole of the foot. These ulcers are deep, frequently infected, and not generally painful because of the loss of sensation.

Physical Findings

A complete cardiovascular examination includes palpation of the peripheral pulses, inspection of the extremities, including the feet, and auscultation of accessible arteries for bruits. Pulse abnormalities and bruits increase the likelihood of PAD.[23,24] Readily palpable pulses in healthy individuals include the brachial, radial, and ulnar arteries in the upper extremities and the femoral, popliteal, dorsalis pedis, and posterior tibial arteries in the lower extremities. The aorta can also be palpated in thin people. A

decreased or absent pulse indicates diminished pressure from a more proximal stenosis. For example, a normal right femoral pulse but absent left femoral pulse suggests the presence of left iliofemoral arterial stenosis. A normal femoral artery pulse but absent popliteal artery pulse would indicate a stenosis in the superficial femoral artery or proximal popliteal artery. A palpable popliteal artery pulse with absent dorsalis pedis or posterior tibial artery pulses indicates disease of the anterior and posterior tibial arteries, respectively.

Bruits are often a sign of accelerated blood flow velocity and flow disturbance at sites of stenosis. A stethoscope should be used to auscultate the supraclavicular and infraclavicular fossae for evidence of subclavian artery stenosis; the abdomen, flank, and pelvis for evidence of stenoses in the aorta and its branch vessels; and the inguinal region for evidence of femoral artery stenoses. Pallor can be elicited on the soles of the feet of some patients with PAD by performing a maneuver in which the feet are elevated above the level of the heart and the calf muscles are exercised by repeated dorsiflexion and plantar flexion of the ankle. The legs are then placed in the dependent position, and the time until the onset of hyperemia by evident rubor and venous distention is measured. Each of these variables depends on the rate of blood flow, which in turn reflects the severity of stenosis and adequacy of collateral vessels.

The legs of patients with chronic aortoiliac disease may show muscle atrophy. Additional signs of chronic low-grade ischemia include hair loss, dystrophic, thickened and brittle toenails, smooth and shiny skin, and atrophy of the subcutaneous fat of the digital pads. Patients with severe limb ischemia have cool skin and may also have petechiae, persistent cyanosis or pallor, dependent rubor, pedal edema resulting from prolonged dependency, skin fissures, ulceration, or gangrene. The ulcers caused by PAD typically have a pale base with irregular borders and usually involve the tips of the toes or the heel of the foot or develop at sites of pressure (**Fig. 64.3**). These ulcers vary in size and may be as small as 3 to 5 mm.

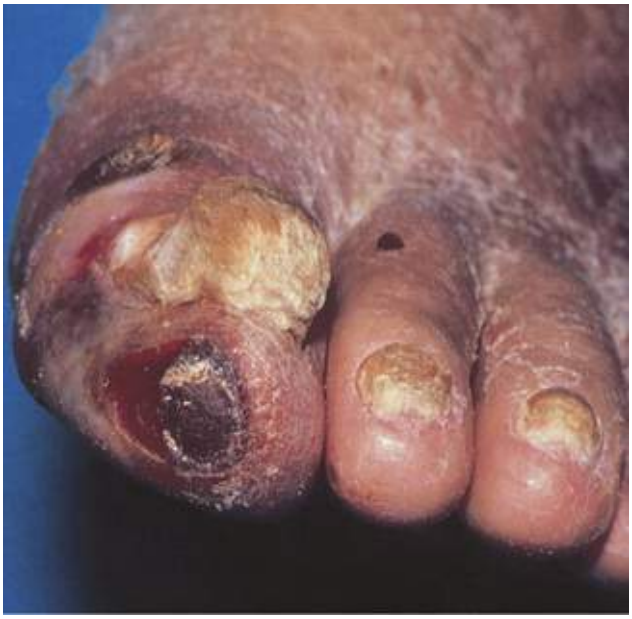


FIGURE 64.3 Typical arterial ulcer. It is a discrete, circumscribed, necrotic ulcer located on the great toe.

Categorization

Classification of patients with PAD depends on the severity of the symptoms and abnormalities detected on physical examination. Categorization of the clinical manifestations of PAD helps to characterize risk

and provides a basis for the types and intensity of therapeutic intervention. Fontaine described one widely used scheme that classifies patients into one of four stages, progressing from asymptomatic to CLI (**Table 64.3**). Several professional vascular societies have adopted the Rutherford scale, a contemporary, more descriptive classification that includes asymptomatic patients, three grades of claudication, and three grades of CLI ranging from rest pain alone to minor and major tissue loss[23,24,27] (**Table 64.4**).

TABLE 64.3

Fontaine Classification of Peripheral Artery Disease

STAGE	SYMPTOMS
I	Asymptomatic
II	Intermittent claudication
IIa	Pain free, claudication walking >200 m
IIb	Pain free, claudication walking <200 m
III	Rest and nocturnal pain
IV	Necrosis, gangrene

TABLE 64.4

Clinical Categories of Chronic Limb Ischemia

GRADE	CATEGORY	CLINICAL DESCRIPTION
	0	Asymptomatic
I	1	Mild claudication
	2	Moderate claudication
	3	Severe claudication
II	4	Ischemic rest pain
	5	Minor tissue loss: nonhealing ulcer, focal gangrene with diffuse pedal ulcer
III	6	Major tissue loss extending above the transmetatarsal level, functional foot no longer salvageable

Modified from Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg 1997;26:517.

Testing for Peripheral Artery Disease

Patients with signs or symptoms suggestive of PAD should have testing to confirm the diagnosis and to characterize the distribution and severity of disease. In patients with risk factors, clinicians should be aware of atypical symptoms, perform a vascular physical examination, and perform diagnostic testing in those with a history or examination suggestive of PAD.

Segmental Pressure Measurement

Measurement of systolic blood pressure (SBP) along sequential segments of each extremity is one of the simplest noninvasive measures for ascertaining the presence and severity of stenoses in the peripheral arteries. In the lower extremities, pneumatic cuffs are placed on the upper and lower portions of the thigh, on the calf, above the ankle, and often over the metatarsal area of the foot. Similarly, for the upper extremities, pneumatic cuffs are placed on the upper part of the arm over the biceps, on the forearm below the elbow, and at the wrist. SBP at each respective limb segment is measured by first inflating the pneumatic cuff to suprasystolic pressure and then determining the pressure at which blood flow occurs during deflation of the cuff. The onset of flow is assessed by placing a Doppler ultrasound flow probe over an artery distal to the cuff. In the lower extremities, it is most convenient to place the Doppler probe

on the foot over the posterior tibial artery, because it courses inferior and posterior to the medial malleolus, or over the dorsalis pedis artery on the dorsum of the metatarsal arch. In the upper extremities the Doppler probe can be placed over the brachial artery in the antecubital fossa or over the radial and ulnar arteries at the wrist.

Left ventricular contraction imparts kinetic energy to blood, which is maintained throughout the large and medium-sized vessels. SBP may be higher in the more distal vessels than in the aorta and proximal vessels because of amplification and reflection of blood pressure (BP) waves. A stenosis can cause loss of pressure energy because of increased frictional forces and disturbance of flow at the site of the stenosis. Approximately 90% of the cross-sectional area of the aorta must be narrowed before a pressure gradient develops. In smaller vessels, such as the iliac and femoral arteries, a 70% to 90% decrease in cross-sectional area will cause a resting pressure gradient sufficient to decrease SBP distal to the stenosis. Taking into consideration the precision of this noninvasive method and the variability in BP during even short periods, a BP gradient in excess of 20 mm Hg between successive cuffs is generally used as evidence of arterial stenosis in the lower extremity, whereas a gradient of 10 mm Hg indicates a stenosis between sequential cuffs in the upper extremity. SBP in the toes and fingers is approximately 60% of SBP at the ankle and wrist, respectively, because pressure diminishes further in the smaller distal vessels. **Fig. 64.4** provides examples of leg segmental BP measurements in a patient with left calf claudication. In the right leg, there are no pressure gradients between the upper and lower parts of the thigh or between the calf and ankle. In the left leg, pressure gradients between the upper and lower parts of the thigh, between the lower part of the thigh and calf, and between the calf and ankle indicate stenoses in the superficial femoral and popliteal arteries and in the tibioperoneal arteries.

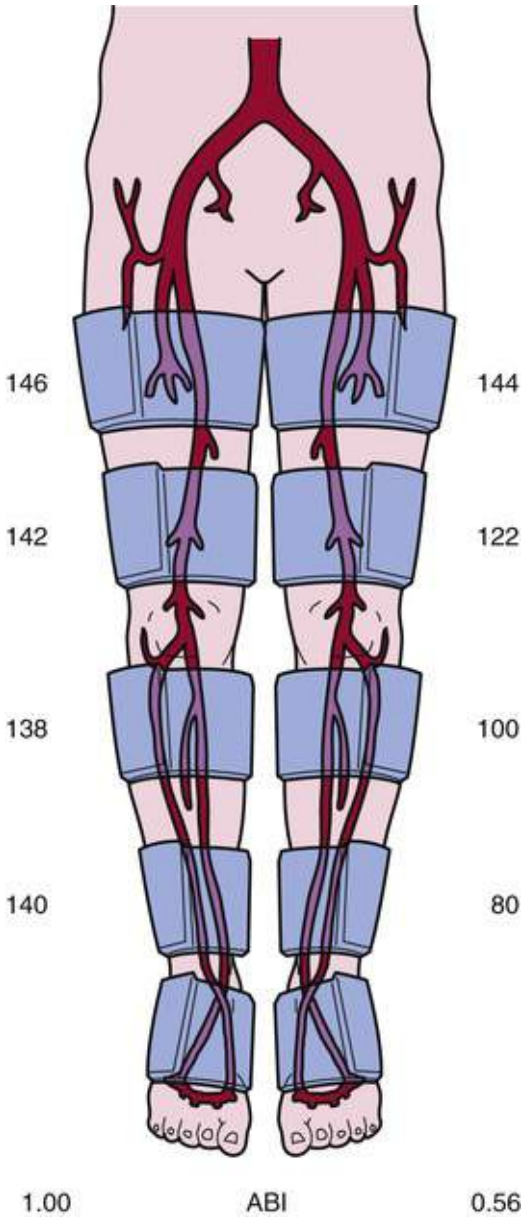


FIGURE 64.4 Segmental pressure measurements in a patient with intermittent claudication of the left calf. A pressure gradient is present between the left upper and lower thigh cuffs, lower thigh and calf cuffs, and calf and ankle cuffs, consistent with multisegmental disease affecting the femoral-popliteal and tibial arteries. The left ankle-brachial index (ABI) is 0.56, which is abnormal. Segmental pressure measurements and the ABI in the right leg are normal.

Ankle-Brachial Index

Determination of the ABI is a simplified application of leg segmental BP measurements that can readily be used at the bedside. This index is the ratio of SBP measured at the ankle to SBP measured at the brachial artery.[28] A pneumatic cuff placed around the ankle is inflated to suprasystolic pressure and subsequently deflated while the onset of flow is detected with a Doppler ultrasound probe placed over the dorsalis pedis and posterior tibial arteries, thus denoting ankle SBP. Brachial artery SBP can be assessed in a routine manner with either a stethoscope to listen for the first Korotkoff sound or a Doppler probe to listen for the onset of flow during cuff deflation. The *normal* ABI range is 1.00 to 1.40. An ABI value of 0.91 to 0.99 is *borderline*, and an ABI of 0.90 or less is *abnormal*.[28,29] An ABI of 0.90 or lower has a specificity of 83% to 99% and a sensitivity of 69% to 73% in detecting stenoses greater than 50%.[28] The sensitivity of an ABI less than 1.0 approaches 100%. The ABI is often used to gauge the severity of PAD. Patients with symptoms of leg claudication often have an ABI ranging from 0.5 to 0.8, and patients

with CLI usually have an ABI lower than 0.5. A low ABI is associated with shorter walking distance and lower speed. Less than 40% of patients whose ABI is lower than 0.40 can complete a 6-minute walk.[24,30] In patients with skin ulcerations, an ankle SBP less than 55 mm Hg predicts poor ulcer healing. Leg BP recordings are not reliable in patients with calcified vessels, as might occur in those with DM or renal insufficiency. Inflation of the pneumatic cuff cannot compress the calcified vessel; the Doppler probe consequently indicates continuous blood flow, even when the pressure exceeds 250 mm Hg. An ABI higher than 1.40 indicates a noncompressible artery, and the test is not informative for either confirming or excluding PAD. In this case, a *toe-brachial-index* (TBI) may be informative, with a ratio of 0.70 or higher reflecting normal perfusion pressure.

Treadmill Exercise Testing

Treadmill exercise testing can be used to evaluate the clinical significance of peripheral artery stenoses and provide objective evidence of the patient's walking capacity. The *claudication onset time* is when symptoms of claudication first develop, and the *peak walking time* occurs when the patient can no longer continue walking because of severe leg discomfort. This standardized and more objective measure of walking capacity supplements the patient's history and provides a quantitative assessment of the patient's disability, as well as a metric for monitoring therapeutic interventions. Treadmill exercise protocols use a motorized treadmill that incorporates fixed or progressive speeds and angles of incline. A fixed workload test usually maintains a constant grade of 12% and a speed of 1.5 to 2.0 mph. A progressive, or graded, treadmill protocol typically maintains a constant speed of 2 mph while the grade gradually increases by 2% every 2 to 3 minutes. Repeated treadmill test results have better reproducibility with progressive than with constant-grade protocols.

Treadmill testing can determine whether arterial stenoses contribute to the patient's symptoms of exertional leg pain. During exercise, blood flow through a stenosis increases as vascular resistance falls in the exercising muscle. According to the Poiseuille equation, described previously, the pressure gradient across the stenosis increases in direct proportion to flow. Thus, ankle and brachial SBP is measured during resting conditions before treadmill exercise, within 1 minute after exercise, and repeatedly until baseline values are reestablished. Normally, the BP increase that occurs during exercise should be the same in both the upper and the lower extremities, with a constant ABI of 1.0 or greater being maintained. In the presence of peripheral artery stenoses, however, the ABI decreases because the BP increase observed in the arm is not matched by a comparable increase in ankle BP. A 25% or greater decrease in the ABI after exercise in a patient whose walking capacity is limited by claudication is considered diagnostic and implicates PAD as a cause of the patient's symptoms. This provocative test should be considered in patients with risk factors and symptoms suggestive of vascular claudication but with normal resting ABI, as may occur in those with proximal disease.[31]

Pulse Volume Recording

The pulse volume recording graphically illustrates the volumetric change in a segment of the limb that occurs with each pulse. Plethysmographic instruments, typically using strain gauges or pneumatic cuffs, can transduce volumetric changes in the limb, which can be displayed on a graphic recorder. These transducers, placed strategically along the limb, record the pulse volume in its different segments, such as the thigh, calf, ankle, metatarsal region, and toes, or the upper part of the arm, forearm, and fingers. The normal pulse volume contour depends on both local arterial pressure and vascular wall distensibility and

resembles a BP waveform. It consists of a sharp systolic upstroke rising rapidly to a peak, a dicrotic notch, and a concave downslope that drops off gradually toward the baseline. The contour of the pulse wave changes distal to a stenosis, with loss of the dicrotic notch, a slower rate of rise, a more rounded peak, and a slower descent. The amplitude becomes lower with increasing severity of disease, and the pulse wave may not be recordable at all in a critically ischemic limb. Segmental analysis of the pulse wave may indicate the location of an arterial stenosis, which probably resides in the artery between a normal and an abnormal pulse volume recording. The pulse volume wave also provides information about the integrity of blood flow when BP measurements cannot be obtained accurately because of noncompressible vessels.

Doppler Ultrasonography

Continuous-wave and pulsed-wave Doppler systems transmit and receive high-frequency ultrasound signals. The Doppler frequency shift caused by moving red blood cells varies directly with the velocity of blood flow. Typically, the perceived frequency shift is between 1 and 20 kHz and is within the audible range of the human ear. Therefore, placement of a Doppler probe along an artery enables the examiner to hear whether blood flow is present and the vessel is patent. Processing and graphic recording of the Doppler signal permit a more detailed analysis of the frequency components.

Doppler instruments can be used without or with gray-scale imaging to evaluate an artery for the presence of stenoses. The Doppler probe is positioned at approximately a 60-degree angle over the common femoral, superficial femoral, popliteal, dorsalis pedis, and posterior tibial arteries. The normal Doppler waveform has three components: a rapid forward-flow component during systole, a transient flow reversal during early diastole, and a slow anterograde component during late diastole. The Doppler waveform becomes altered if the probe is placed distal to an arterial stenosis and is characterized by deceleration of systolic flow, loss of the early diastolic reversal, and diminished peak frequencies. Arteries in a limb with critical ischemia may not show any Doppler frequency shift. As with pulse volume recordings, change from a normal to an abnormal Doppler waveform as the artery is interrogated more distally suggests the location of a stenosis.

Duplex Ultrasound Imaging

Duplex ultrasound imaging provides a direct, noninvasive means of assessing both the anatomic characteristics of peripheral arteries and the functional significance of arterial stenoses. The methodology incorporates gray-scale B-mode ultrasound imaging, pulsed Doppler velocity measurements, and color coding of the Doppler shift information (**Fig. 64.5**). Real-time ultrasonographic scanners emit and receive high-frequency sound waves, typically ranging from 2 to 10 MHz, to construct an image. The acoustic properties of the vascular wall differ from those of the surrounding tissue, thus enabling them to easily be imaged. Atherosclerotic plaque may be present and visible on gray-scale images. Pulsed-wave Doppler systems emit ultrasound beams at precise times and can therefore sample the reflected ultrasound waves at specific depths to enable the examiner to determine blood cell velocity within the lumen of the artery. By positioning the pulsed Doppler beam at a known angle; the examiner can calculate blood flow velocity according to the following equation:

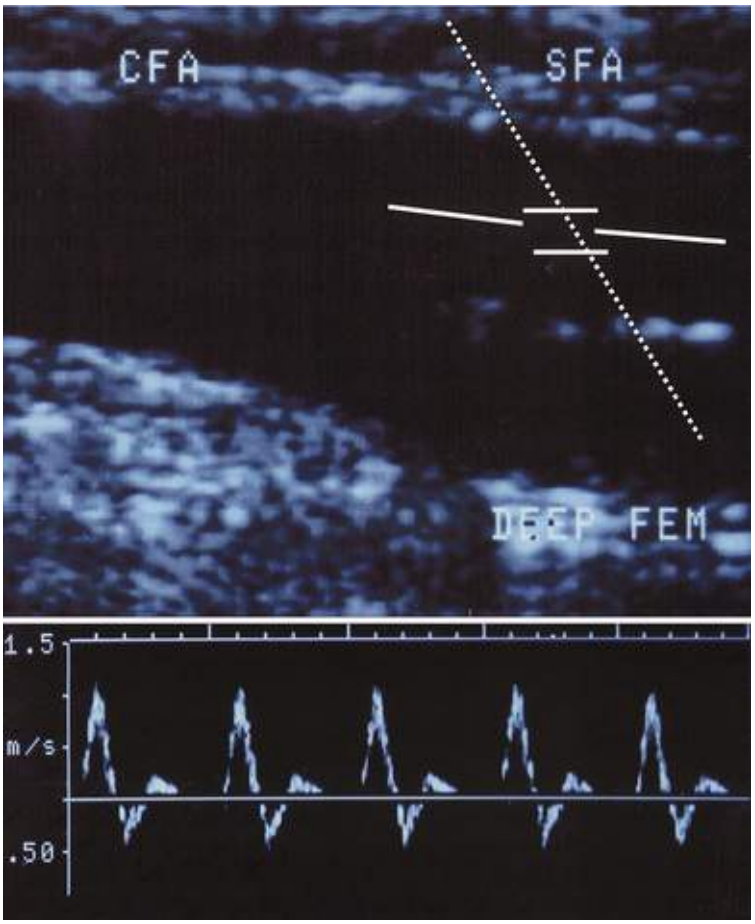


FIGURE 64.5 Duplex ultrasonogram of the common femoral artery (CFA) bifurcation into the superficial femoral artery (SFA) and deep femoral artery. The **upper image** shows a normal gray-scale image of the artery in which the intima is not thickened and the lumen is widely patent. The **lower image** is a recording of the pulse Doppler velocity sampled from the superficial femoral artery. The triphasic profile is apparent, the envelope is thin, and peak systolic velocity is within normal limits.

$$\mathrm{Df} = 2\mathrm{VF}\cos\theta/C$$

where Df is the frequency shift, V is the velocity, F is the frequency of the transmitted sound, θ is the angle between the transmitted sound and the velocity vector, and C is the velocity of sound and tissue. For optimal measurements, the angle of the pulsed Doppler beam should be less than 60 degrees. With color Doppler, the frequency shift information within the entire field sampled by the ultrasound beam can be superimposed on the gray-scale image. This approach provides a composite real-time display of flow velocity within the vessel.

Color-assisted duplex ultrasound imaging is an effective means of localizing peripheral arterial stenoses (**Fig. 64.6**). Normal arteries have laminar flow, with the highest velocity occurring at the center of the artery. The corresponding color image is usually homogeneous with relatively constant hue and intensity. In the presence of an arterial stenosis, blood flow velocity increases through the narrowed lumen. As the velocity increases, there is progressive desaturation of the color display, and flow disturbance distal to the stenosis causes changes in hue and color. Pulsed Doppler velocity measurements can be made along the length of the artery and particularly at areas of flow abnormalities suggested by the color images. A twofold or greater increase in peak systolic velocity at the site of an atherosclerotic plaque indicates a 50% or greater stenosis (**Fig. 64.6**). A threefold increase in velocity suggests a 75% or greater stenosis. An occluded artery generates no Doppler signal. Duplex ultrasound imaging for

identification of sites of arterial stenosis has approximately 89% to 99% specificity and 80% to 98% sensitivity.[32] Measurement of sequential peak systolic velocities enables evaluation of restenosis of peripheral stents or bypass grafts and to determine the need to consider reintervention to preserve vessel patency.

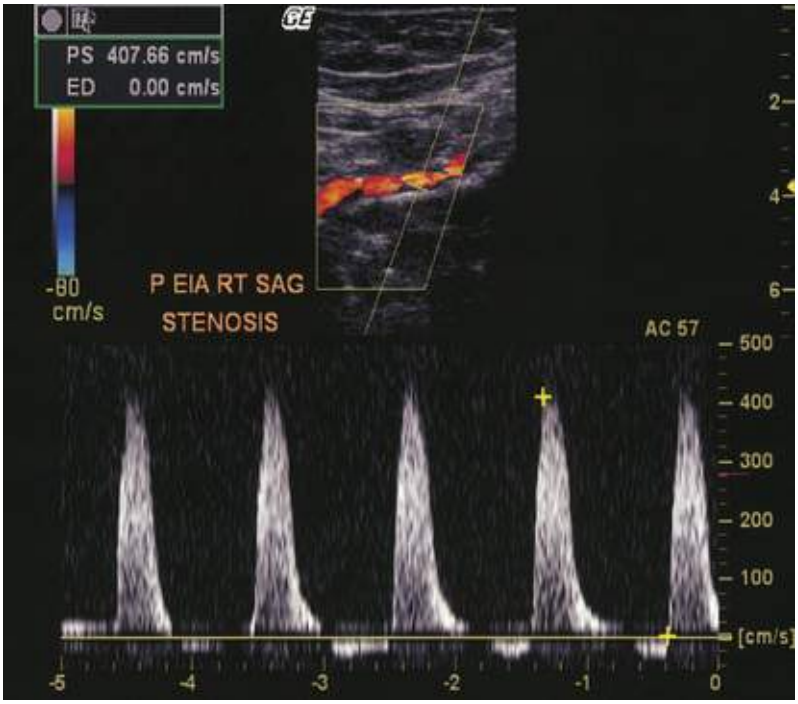
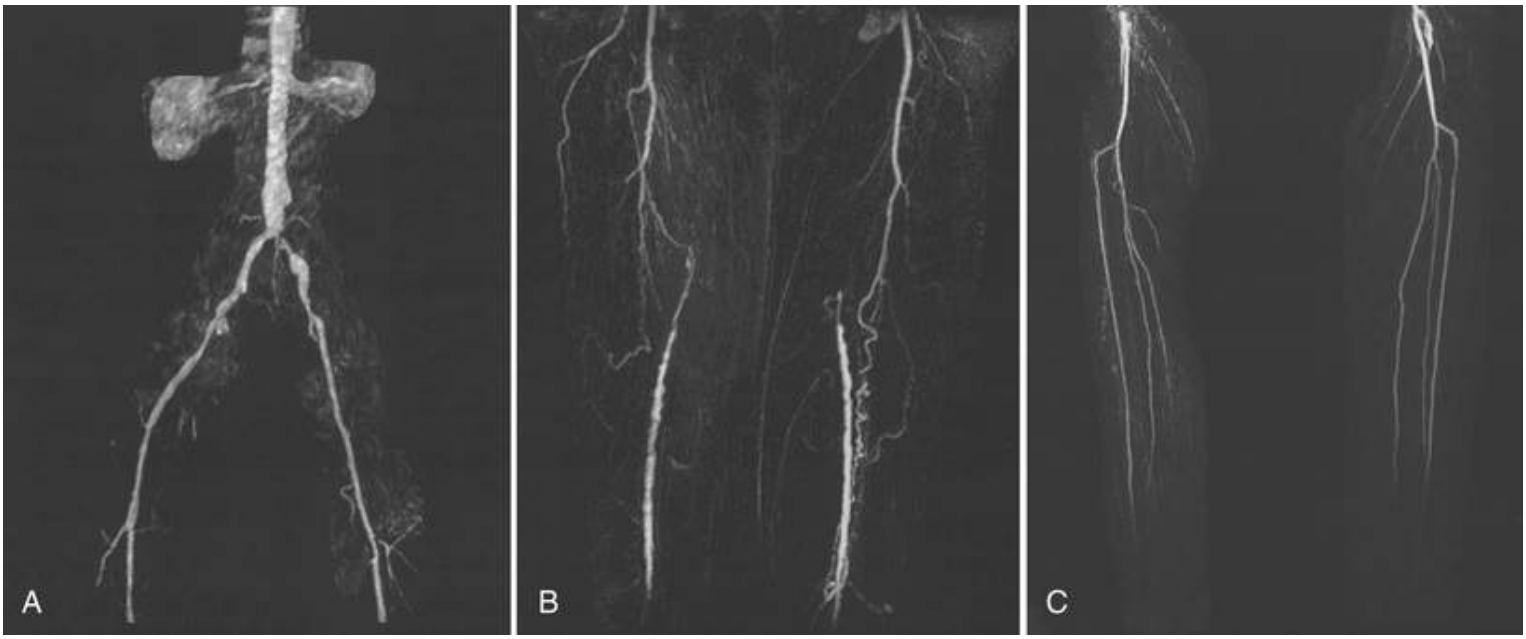


FIGURE 64.6 Duplex ultrasonogram of the external iliac artery. The **upper image** is a color image of the artery in which there is heterogeneity and desaturation of color, indicative of high-velocity flow through a stenosis. The **lower image** is a recording of the pulse Doppler velocity sampled from the right external iliac artery. The peak velocity of 350 cm/sec is elevated. These features are consistent with a significant stenosis.

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) can be used to noninvasively visualize the aorta and peripheral arteries (**see Chapters 17 and 66**). Resolution of the vascular anatomy with gadolinium-enhanced MRA approaches that of conventional contrast-enhanced digital subtraction angiography (DSA) (**eFig. 64.2**). A meta-analysis of 32 studies comparing MRA with intra-arterial DSA found a sensitivity of 95% and a specificity of 96% for detecting segmental stenotic and occlusive lesions.[33] MRA currently has its greatest usefulness in the evaluation of symptomatic patients to assist in decision making before endovascular and surgical intervention or in patients at risk for renal, allergic, or other complications during conventional angiography.



EFIGURE 64.2 Gadolinium-enhanced two-dimensional magnetic resonance angiography (MRA) of the aorta and both legs extending from the thighs to above the ankle. **A,** Aortoiliac atherosclerosis with a stenosed left common iliac artery. **B,** Bilateral superficial femoral artery occlusion with reconstitution of the distal portion of the right and left superficial femoral arteries. **C,** Anterior tibial, posterior tibial, and peroneal arteries, which are patent in each leg.

Computed Tomographic Angiography

Computed tomography (CT) scanners use multidetector technology to acquire cross-sectional images (**see Chapter 18**). This permits imaging of peripheral arteries with excellent spatial resolution during a relatively short time and with a reduced amount of radiocontrast material (**Fig. 64.7**). Image reconstructions in three dimensions permit rotation to optimize visualization of arterial stenoses. Compared with conventional contrast-enhanced angiography, the sensitivity and specificity for stenoses greater than 50% or occlusion reported for computed tomographic angiography (CTA) using multidetector technology are 95% and 96%, respectively.[34] CTA offers advantages over MRA because it can be used in patients with stents, metal clips, and pacemakers, although it has the disadvantage of requiring radiocontrast material and ionizing radiation.

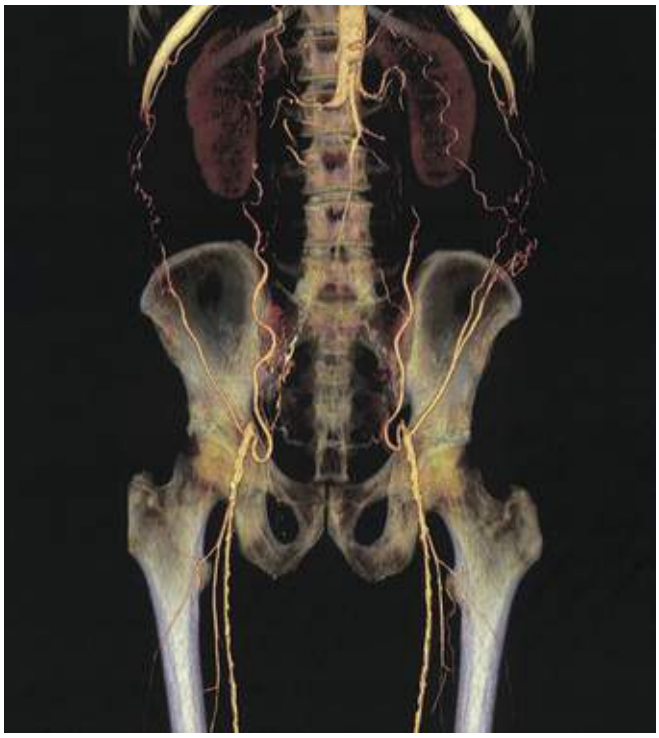


FIGURE 64.7 Computed tomographic angiogram (CTA) in a patient with complete occlusion of the aorta and both iliac arteries. The common femoral arteries have been reconstituted. (Courtesy 3D and Image Processing Center of Brigham and Women's Hospital, Boston.)

Contrast-Enhanced Angiography

Conventional angiography can aid in evaluation of the arterial anatomy before a revascularization procedure. It still has occasional usefulness when the diagnosis is in doubt. Most contemporary angiography laboratories use digital subtraction techniques after intra-arterial administration of contrast material to enhance resolution. Injection of the contrast material into the aorta permits visualization of the aorta and iliac arteries, and injection of contrast material into the iliofemoral segment of the involved leg permits optimal visualization of the femoral, popliteal, tibial, and peroneal arteries (**Fig. 64.8**).

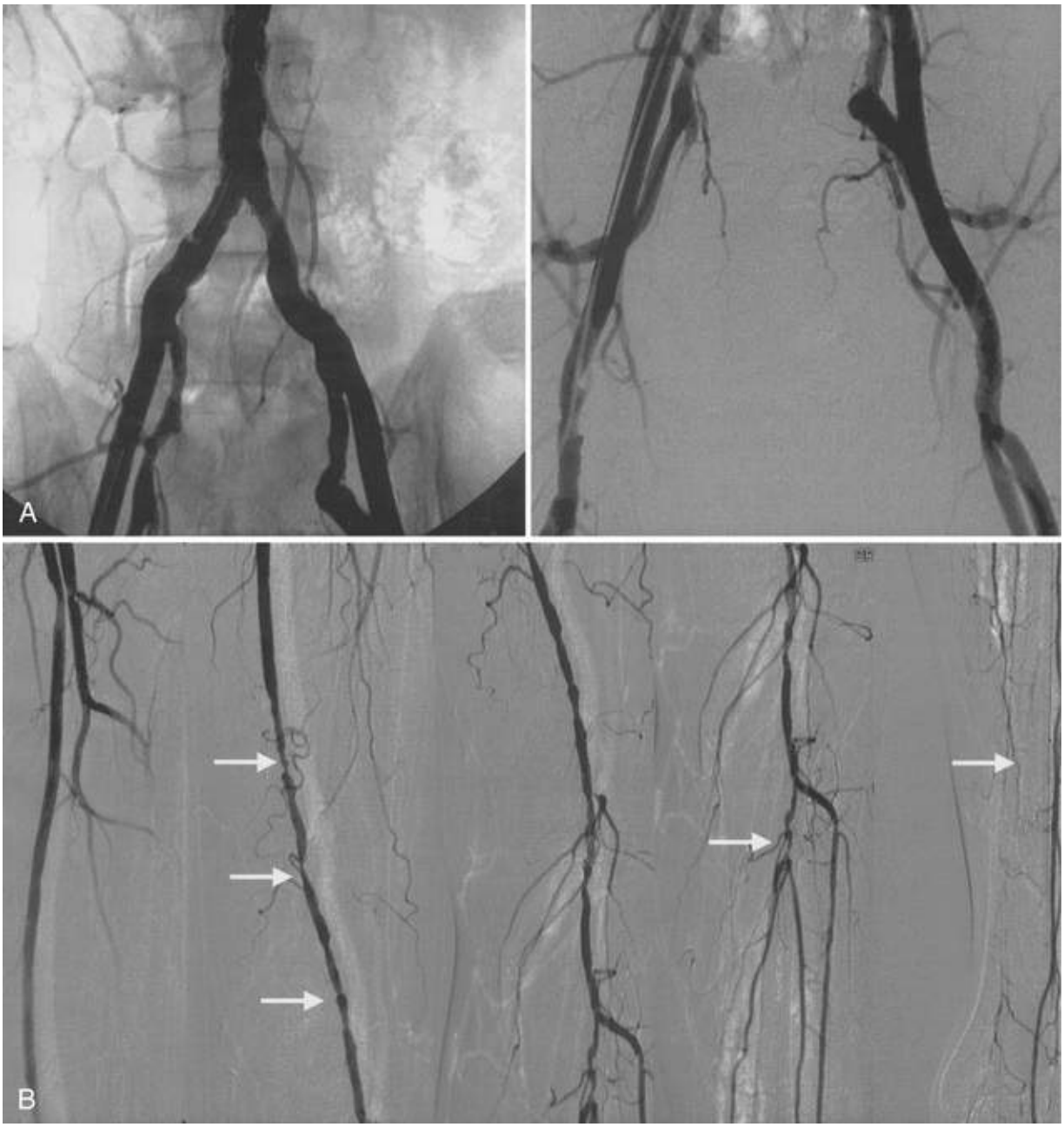


FIGURE 64.8 Angiogram of a patient with disabling left calf claudication. **A,** The aorta and bilateral common iliac arteries are patent. **B,** The left superficial femoral artery has multiple stenotic lesions (*arrows at left*). Significant stenosis of the left tibioperoneal trunk and left posterior tibial artery (*arrows at right*) is present.

Prognosis

Patients with PAD have increased risk for adverse cardiovascular (CV) events, as well as for limb loss and impaired quality of life[2,7] (**Fig. 64.9 and eFig. 64.3**). Such patients frequently have concomitant coronary artery disease (CAD) and cerebrovascular disease.[35] Patients with an abnormal ABI are twofold to fourfold more likely than those with a normal ABI to have a history of myocardial infarction (MI), angina, congestive heart failure, or cerebrovascular ischemia.[36] Angiographically significant CAD occurs in approximately 60% to 80% of patients with PAD, and 15% to 25% of patients with PAD have significant carotid artery stenoses, as detected by duplex ultrasonography. In the REACH (Reduction of Atherothrombosis for Continued Health) Registry, 62% of the patients with PAD had either or both coronary and cerebrovascular disease. The specificity of an abnormal ABI in predicting future CV events is approximately 90%.[28] The risk for death from CV causes increases 2.5- to 6-fold in patients with PAD,

and their annual mortality rate is 4.3% to 4.9%.[17,36] Patients with PAD and prior MI have a particularly poor CV prognosis, with a 3-year risk of CV death, MI, or stroke approaching 20%, reflecting a 60% increase in risk relative to those with prior MI but no PAD[37,38] (**eFig. 64.4**). Those with the most severe PAD have the greatest risk for death, and mortality correlates with decreasing ABI (**Fig. 64.10**).[7] Approximately 25% of patients with CLI die within 1 year, and the 1-year mortality rate in patients who have undergone amputation for PAD may be as high as 45%.[39]

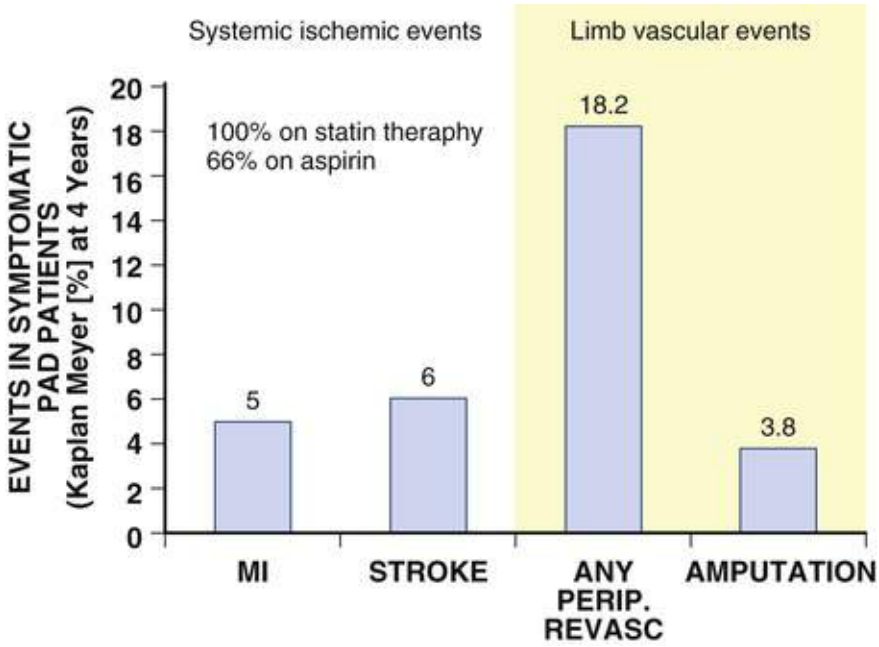


FIGURE 64.9 Event rates in patients with PAD at 4 years in the REACH Registry. MI, Myocardial infarction; Perip. Revasc, peripheral artery revascularization. (Modified from Kumbhani DJ, Steg PG, Cannon CP, et al. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry. Eur Heart J 2014;35:2864-72.)

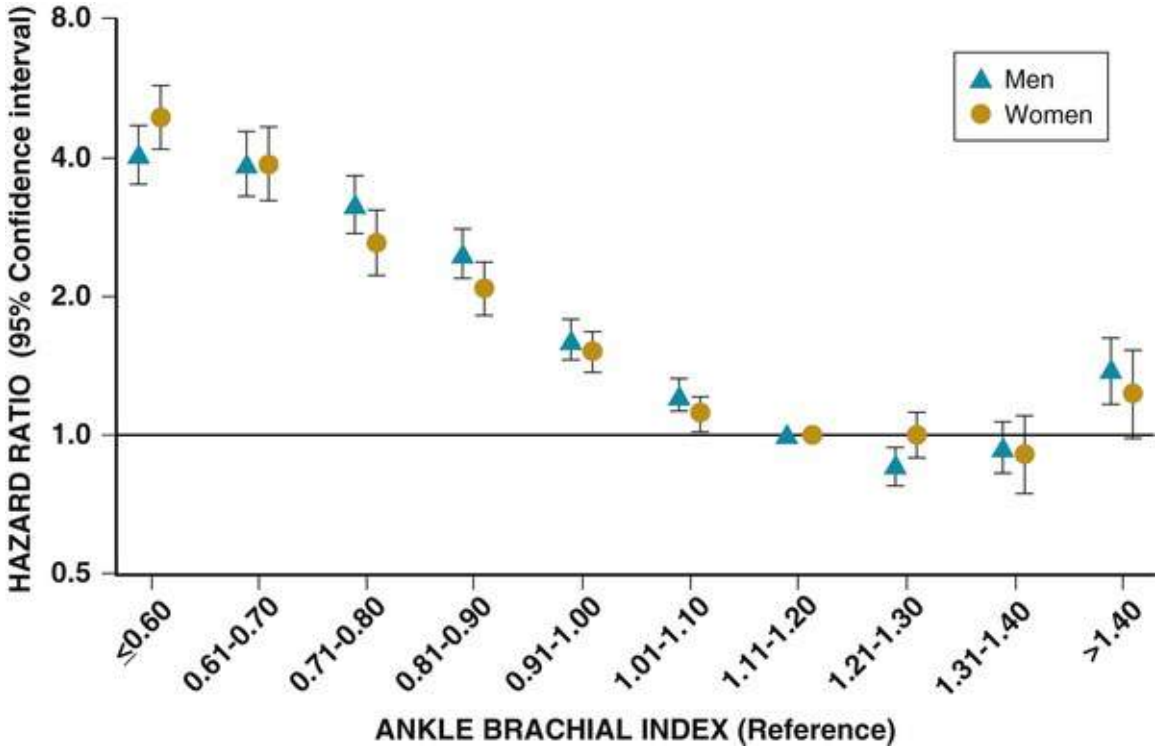
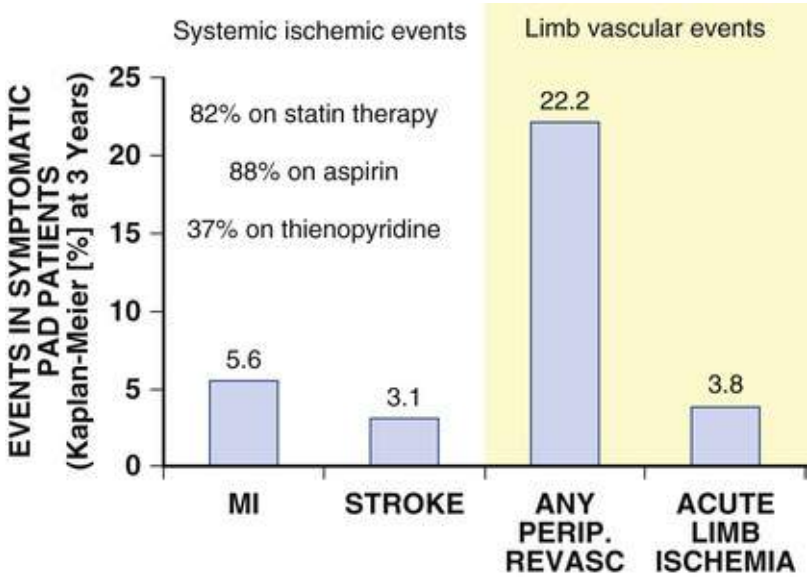
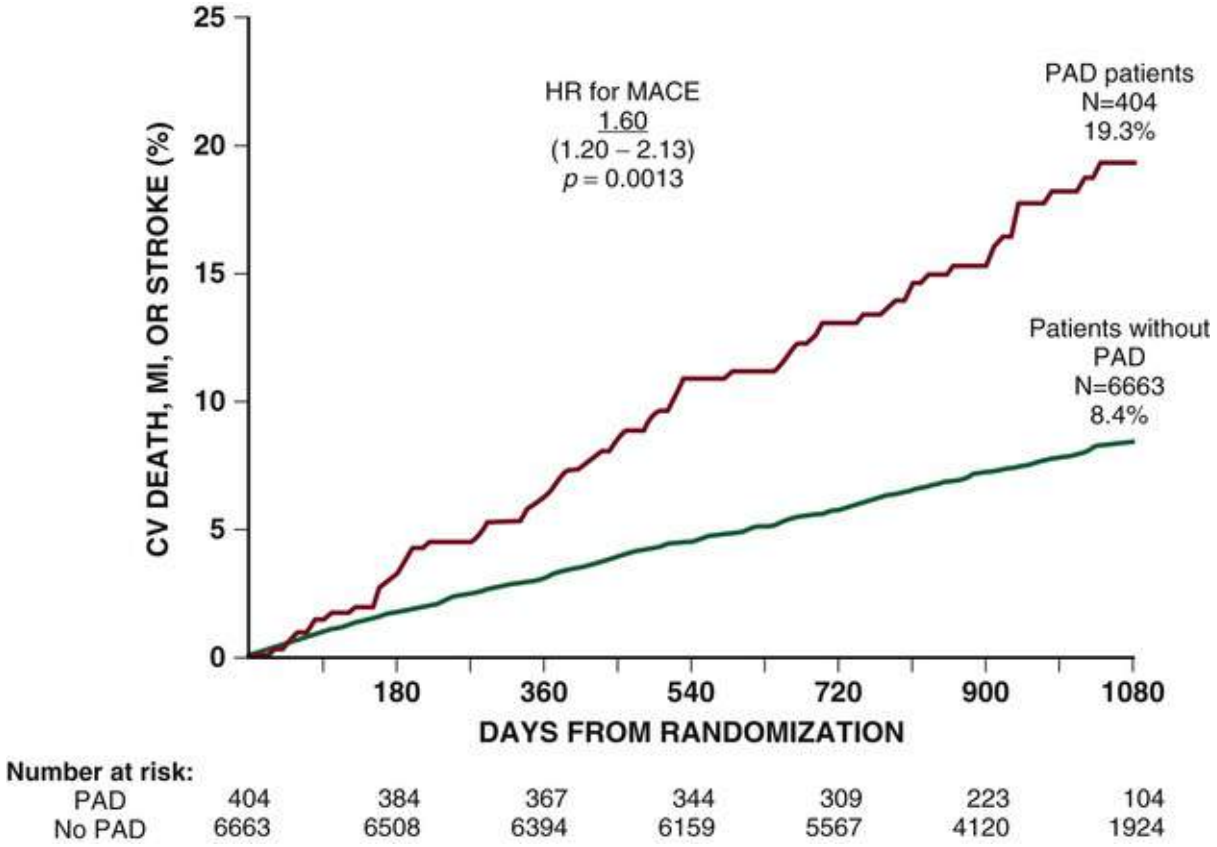


FIGURE 64.10 Association of ankle-brachial index (ABI) with all-cause mortality in a meta-analysis of 16 cohort studies. (From Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008;300:197.)



EFIGURE 64.3 Rates of major adverse cardiovascular events and limb vascular events in patients with PAD at three years in TRA2°P-TIMI 50. MI, Myocardial infarction; Perip. Revasc, peripheral artery revascularization. (Modified from Bonaca MP, Gutierrez JA, Creager MA, et al. Acute limb ischemia and outcomes with vorapaxar in patients with peripheral artery disease: results from the Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients with Atherosclerosis–Thrombolysis in Myocardial Infarction 50 (TRA2°P-TIMI 50). Circulation 2016;133:997-1005.)



EFIGURE 64.4 Rate of cardiovascular (CV) death, myocardial infarction (MI), or stroke in patients with prior MI and concomitant PAD (*orange*) or without PAD (*green*). HR, Hazard ratio; MACE, major adverse cardiovascular events. (Modified from Bonaca MP, Bhatt DL, Storey RF, et al. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. J Am Coll Cardiol 2016;67:2719-28.)

Worsening symptoms develop in approximately 25% of patients with claudication, and over 3 years, approximately 20% will require an intervention to improve lower extremity perfusion (**see Fig. 64.9 and eFig. 64.3**). Moreover, loss of mobility occurs more often in patients with PAD than in those without PAD, even in patients without classic symptoms of claudication.[24] Both smoking and DM independently predict progression of disease.[15,40] Those with DM have at least a 12-fold higher likelihood of amputation than nondiabetic persons.[7] The risk for limb loss is higher in PAD patients with CLI in whom revascularization fails or is not feasible and approximates 40% by 6 months.[11]

Treatment

Treatment of PAD aims to reduce CV morbidity and mortality, as well as improve quality of life by decreasing symptoms of claudication, eliminating rest pain, and preserving limb viability. Therapeutic considerations therefore include modification of risk factors by alterations in lifestyle and use of pharmacologic therapy to reduce the risk for adverse CV events such as MI, stroke, and death, as well as to decrease limb morbidity. Symptoms of claudication can improve with pharmacotherapy or exercise rehabilitation. Optimal management of CLI often includes endovascular interventions or surgical reconstruction to improve blood supply and maintain limb viability. Revascularization can aid some patients with disabling symptoms of claudication that persist despite exercise therapy and pharmacotherapy.[1]

Risk Factor Modification

Lipid-lowering therapy reduces the risk of CV events (**see Chapters 45 and 48**). The Heart Protection Study found that lipid-lowering therapy with simvastatin reduced the risk for adverse CV outcomes by 25% in patients with atherosclerosis, including more than 6700 patients with PAD.[41] Pooled results from 17 trials found that lipid-lowering therapy reduced the risk for CV events in patients with PAD by 26%.[41] Recent lipid-lowering guidelines recommend high- or moderate-intensity statin therapy for all patients with PAD, depending on age.[42,43] Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have shown promising preliminary results in reducing CV risk in patients with atherosclerosis and are under investigation in large CV outcomes trials that include patients with symptomatic PAD.[44]

Smoking Cessation

Prospective trials examining the benefits of smoking cessation are lacking, but observational evidence unequivocally shows that cigarette smoking increases the risk for atherosclerosis and its clinical sequelae. Nonsmokers with PAD have lower rates of MI and mortality than those who have smoked or continue to smoke, and PAD patients who discontinue smoking have approximately twice the 5-year survival rate of those who continue to smoke. In addition to frequent physician advice, pharmacologic interventions that effectively promote smoking cessation include nicotine replacement therapy, bupropion, and varenicline.[14,41]

Treatment of Diabetes

Aggressive treatment of diabetes decreases the risk for microangiopathic events such as nephropathy and retinopathy (**see Chapter 51**), but most classes of glucose-lowering drugs have not shown a reduction of macrovascular events.[45] In several trials, intensive glucose control versus standard therapy has not reduced ischemic risk associated with increased mortality.[45] Long-term follow-up of the UKPDS (United Kingdom Prospective Diabetes Study) of patients with type 2 DM, however, did find that intensive treatment was associated with a 15% reduction in MI, suggesting a positive glycemic legacy in patients with newly diagnosed diabetes and without prior CV events.[46] Recent studies have shown that certain glucose-lowering agents can reduce CV risk in patients with atherosclerosis. In the EMPA-REG trial, the sodium-glucose transporter 2 (SGLT2) inhibitor inhibitor *empagliflozin* reduced all-cause mortality by 32% in patients with type 2 DM at increased risk of CV events, including more than 600 patients with PAD.[47] The observations of increased rates of leg and foot amputation in ongoing studies with a related agent, however, indicate caution and warrant further study for limb risk in patients with PAD.[48] The glucagon-like protein (GLP)-1 agonists liragulitide and semaglutide improved macrovascular outcomes in patients with type 2 DM and either established CV disease or at heightened CV risk.[49,50] Selection of specific agents may supersede glucose targets in high-risk populations where treating to lower targets alone has associated with harm.[45]

Blood Pressure Control

Antihypertensive therapy reduces the risk for stroke, CAD, and vascular death (**see Chapters 46 and 47**). In patients with PAD, the intensity of antihypertensive treatment must take into consideration benefits of reduced risk of CV events and the potential to exacerbate limb symptoms. Although several studies have suggested that intensive BP control (versus moderate BP control) reduce CV events in diabetic patients with PAD, data with regard to specific targets are mixed.[15] A post hoc analysis of the International

Verapamil-SR/Tandolapril study found that PAD associated with higher ischemic risk, but there appeared to be a J-shaped relationship between SBP and outcome, suggesting that patients with PAD might require specific targets.[51] In the SPRINT trial, a target SBP of 120 mm Hg or less resulted in a significant reduction in CV events, but outcomes specific to patients with PAD were not reported.[52] There are no comparative studies of specific antihypertensive agents in patients with PAD, but findings from several clinical trials support the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients with atherosclerosis, including those with PAD. In the HOPE (Heart Outcomes Prevention Evaluation) study, the ACE inhibitor ramipril decreased the risk for vascular death, MI, or stroke by 22%, with 44% having PAD.[41] Other ACE inhibitors as well as ARBs have shown similar benefits.[41] Although in theory, beta blockers could worsen lower extremity symptoms in PAD, a systematic review that included six studies of beta blocker therapy found no significant impairment of walking capacity.[53] Thus, if clinically indicated for other conditions, these drugs should not be withheld in patients with PAD.

Antiplatelet Therapy

Substantial evidence supports the use of antiplatelet agents to reduce ischemic risk in patients with atherosclerosis (**see Chapter 93**). The Antithrombotic Trialists' (ATT) Collaboration Meta-analysis of more than 9000 patients with symptomatic PAD showed a 23% reduction in vascular death, MI, or stroke with antiplatelet monotherapy.[54] Although the findings are often taken as evidence supporting the use of aspirin, the trials included several classes of antiplatelet agents (e.g., aspirin, thienopyridines, dipyridamole, picotamide). The benefits were counterbalanced by a 60% increase in major extracranial bleeding. Moreover, any conclusions regarding aspirin therapy from this analysis cannot be extrapolated to patients who have asymptomatic PAD. Both the POPADAD (Prevention of Progression of Arterial Disease And Diabetes) and AAA (Aspirin for Asymptomatic Atherosclerosis) trials found no difference in CV outcomes with long-term aspirin in otherwise healthy patients with an abnormal ABI but no symptoms of PAD.[55,56] A meta-analysis including 18 randomized trials comprising 5269 patients with PAD (including asymptomatic patients) found that aspirin did not reduce the risk of CV mortality or MI versus placebo.[41,56]

The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial compared clopidogrel with aspirin in reducing ischemic events in patients with recent MI, recent ischemic stroke, or PAD. Overall, clopidogrel reduced vascular death, MI or stroke by 8.7% versus aspirin.[41,56] Notably, among the 6452 patients in the PAD subgroup, clopidogrel treatment appeared to be associated with a greater 23.8% relative risk reduction. Recently, in the EUCLID (Examining Use of Ticagrelor in PAD) trial, ticagrelor, a novel potent $P2Y_{12}$ inhibitor, did not reduce CV death, MI, or stroke versus clopidogrel in patients with symptomatic PAD, including those with prior peripheral revascularization.[57,58] Taken together, these data demonstrate that antiplatelet monotherapy reduces CV risk in patients with symptomatic PAD, but it is of uncertain benefit in those with a marginally low ABI and no symptoms.

The efficacy of dual or more antiplatelets in PAD has been studied in several trials. The CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial evaluated the addition of clopidogrel to aspirin (DAPT) vs. aspirin alone in patients with established CAD, cerebrovascular disease, or PAD, as well as in patients with multiple risk factors. Overall, dual-antiplatelet therapy (DAPT) produced no significant benefit over aspirin, although a post hoc analysis suggested benefit in those with established CV disease, particularly prior MI.[41] The TRA2°P-TIMI 50 trial studied vorapaxar, an antagonist of protease-activated receptor 1 (PAR-1), in addition to aspirin

and/or clopidogrel, in stable patients with established atherosclerosis. PAR-1 localizes on platelets, endothelium, and vascular smooth muscle. Overall, vorapaxar reduced the risk of MI, stroke, and CV death but was associated with an increase in moderate or severe bleeding.[59,60] Benefit was greatest in patients with MI or PAD, whereas there was overall harm in patients with prior stroke. In the PEGASUS-TIMI 54 trial (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin) the addition of ticagrelor, 60 mg, to aspirin resulted in a 5.2% absolute risk reduction in CV death, MI, or stroke, with significant reductions in both CV and all-cause mortality in patients with PAD and prior MI.[37] The PRODIGY trial, which investigated prolonged DAPT after coronary stenting, showed consistent benefits in the PAD subgroup.[38]

Anticoagulant Therapy

The WAVE (Warfarin Antiplatelet Vascular Evaluation) trial compared combination antiplatelet and oral anticoagulant therapy with antiplatelet therapy alone in patients with PAD.[61] Anticoagulation with warfarin did not reduce the primary composite endpoint of MI, stroke, or CV death, but there was a greater than threefold increase in life-threatening bleeding. Trials investigating direct non–vitamin K–dependent oral anticoagulants at various doses alone or in combination with antiplatelet therapy are in progress and should provide information regarding the efficacy and safety of these agents in patients with PAD.

Treatment of Symptoms and Prevention of Limb Vascular Events

Limb morbidity adversely affects quality of life. Treatment strategies should include those measures that improve functional capacity, alleviate symptoms, preserve limb viability, and reduce the risk of limb loss.

Exercise Training

Exercise training is the most effective noninvasive intervention for improving limb-related symptoms. Postulated mechanisms of benefit include the formation of collateral vessels and improvement in endothelium-dependent vasodilation, hemorheology, muscle structure and metabolism, and walking efficiency[25] (**Fig. 64.11**). Exercise increases the expression of angiogenic factors, particularly in hypoxic tissue. Exercise training also improves endothelium-dependent vasodilation. Improvement in calf blood flow has not been demonstrated consistently in patients with claudication; however, some studies have found that exercise training increased capillary density in calf muscle and that this change preceded the improvement in maximal O_2 consumption.[62,63] To date, no imaging studies have demonstrated increased collateral blood vessels after exercise training in patients with PAD.

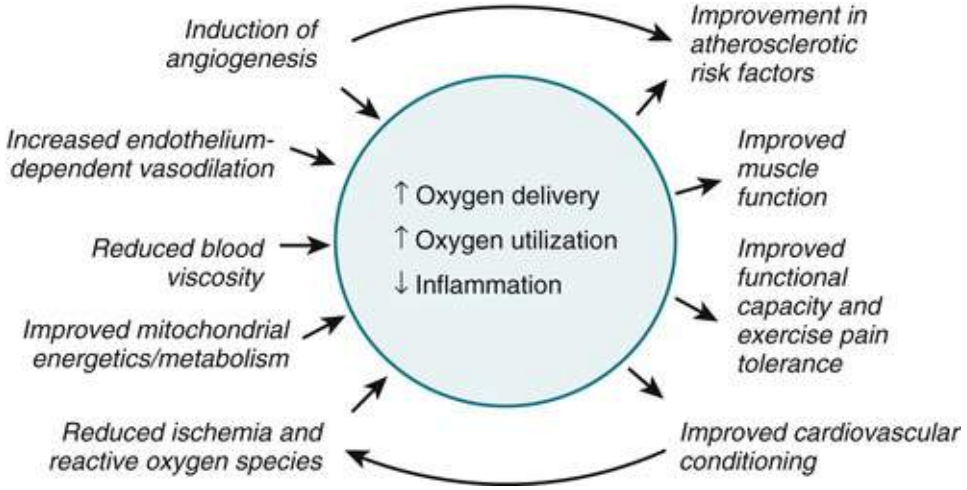


FIGURE 64.11 Mechanisms underlying the benefit of exercise in PAD. (Modified from Bonaca MP, Creager MA. Pharmacological treatment and current management of peripheral artery disease. Circ Res 2015;116:1579-98.)

Much of the benefit of exercise training likely results from changes in skeletal muscle structure or function, such as increased muscle mitochondrial enzyme activity, oxidative metabolism, and ATP production rate (**Fig. 64.11**). Improvement in exercise performance is associated with a decrease in plasma and skeletal muscle short-chain acylcarnitine concentrations, which indicates improvement in oxidative metabolism and increased peak O_2 consumption. Higher physical activity levels are associated with greater calf muscle area and density.[23,24] Training may also enhance biomechanical performance and enable patients to walk more efficiently with less energy expenditure. Supervised exercise training increases maximal walking time by 50% to 200%.[64] Exercise therapy is effective and durable, with the best results achieved with supervised exercise followed by home-based programs (**Fig. 64.12**). The greatest benefit occurs when sessions are at least 30 minutes in duration, when sessions take place at least three times per week for 6 months, and when walking is the mode of exercise. Home-based exercise training, when governed with a step-activated monitor, also improves walking time in patients with claudication[65,66] (**Fig. 64.12**). Leg strength training improves walking time, although not as much as does treadmill exercise training.[24] Arm ergometry also improves walking performance.[67] In the CLEVER (Claudication Exercise versus Endoluminal Revascularization) trial of patients with iliac artery stenosis, supervised exercise training improved mean walking time more than endovascular intervention, and both were more effective than optimal medical therapy; however, quality-of-life measures improved more in the endovascular intervention group[65] (**eFig. 64.5**). In the ERASE (Endovascular Revascularization and Supervised Exercise) trial, the combination of endovascular revascularization and exercise in selected patients was shown to be superior to exercise alone and may be considered a therapeutic strategy for select patients with aortoiliac or femoropopliteal disease.[68] Current guidelines recommend that patients with intermittent claudication undergo supervised exercise rehabilitation as initial therapy.[1,43]

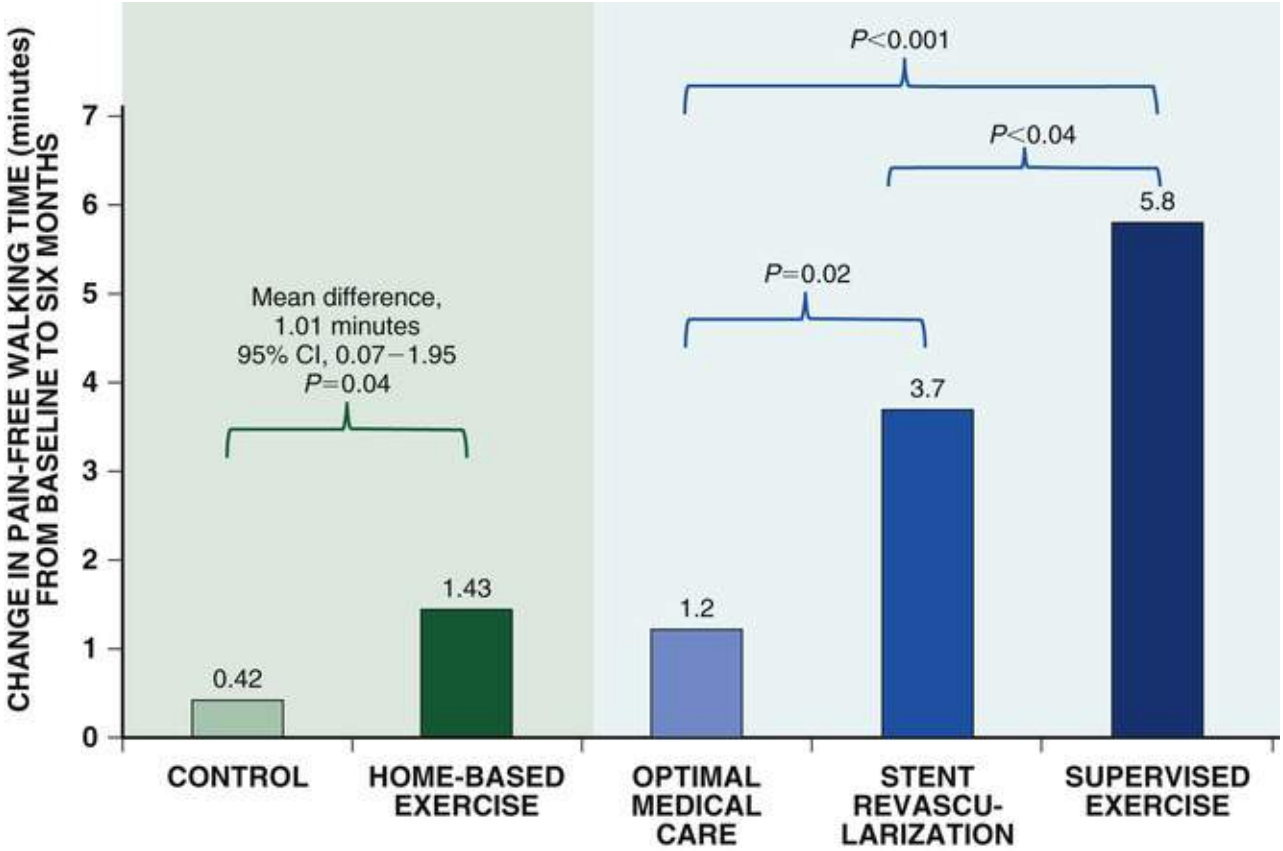
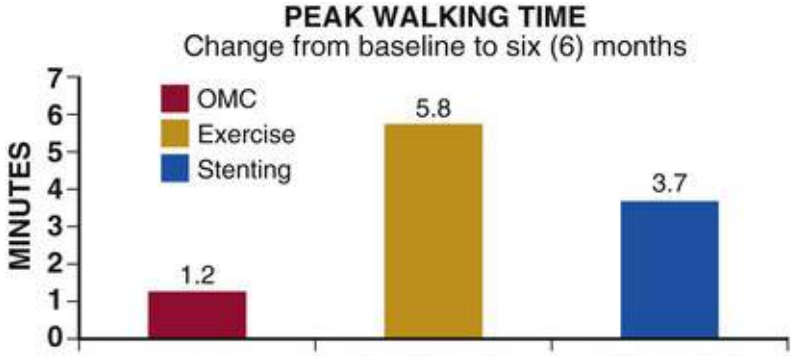


FIGURE 64.12 The relative efficacy of medical care alone, home based exercise, supervised exercise, and stent revascularization in patients with PAD. (Modified from McDermott MM et al. Home-based walking exercise intervention in peripheral artery disease: a randomized clinical trial. JAMA 2013;310:57-65; and Murphy TP et al. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the claudication: exercise versus endoluminal revascularization (CLEVER) study. Circulation 2012;125:130-9.)



PAIR-WISE COMPARISONS

	Difference (minutes)	*P* value
Exercise vs. OMC	4.6 (95% CI, 2.7–6.5)	<0.001
Stenting vs. OMC	2.5 (95% CI, 0.6–4.4)	0.02
Exercise vs. Stenting	2.1 (95% CI, 0.0–4.2)	0.04

EFIGURE 64.5 Effect of optimal medical care (OMC), exercise training, and endovascular intervention on peak walking time at 6 months in patients with iliac artery stenosis. Supervised exercise training improved mean walking time more than endovascular intervention, and both were more effective than OMC. (Modified from Murphy TP, Cutlip DE, Regensteiner JG, et al. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the Claudication: Exercise Versus Endoluminal Revascularization [CLEVER] study. Circulation 2012;125:130.)

Smoking Cessation

Smoking cessation reduces the risk for developing symptomatic PAD and lessens the risk of progression to CLI and amputation in those with PAD.[40,41]. Smoking before limb bypass is associated with early graft failure, and smoking cessation reduces this risk.[69]

Pharmacotherapy to Improve Claudication

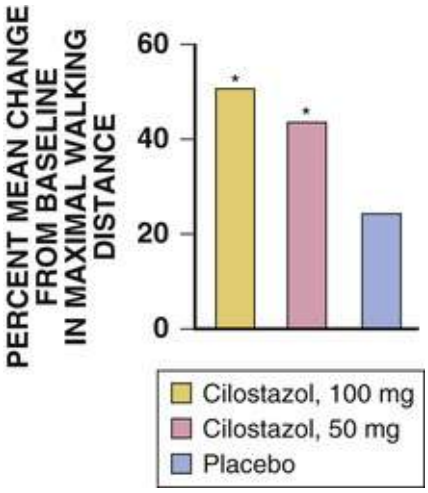
Both pentoxifylline and cilostazol are available for the treatment of claudication in patients with PAD (**Table 64.5**). *Pentoxifylline* is a xanthine derivative with benefits thought to be mediated through its hemorheologic properties, including its ability to decrease blood viscosity and to improve erythrocyte flexibility.[41] It has marginal efficacy.[41] *Cilostazol* is a quinolinone derivative that inhibits phosphodiesterase 3 (PDE3), thereby decreasing degradation of cyclic adenosine monophosphate and increasing its concentration in platelets and blood vessels. Although cilostazol inhibits platelet aggregation and causes vasodilation in experimental animals, its mechanism of action in patients with PAD is not known. Meta-analyses have found that cilostazol improves absolute claudication distance by 40% to 50% in comparison to placebo[70] (**eFig. 64.6**). Quality-of-life measures, as assessed by the 36-Item Short-Form Medical Outcomes Scale (SF-36) and Walking Impairment Questionnaire, also demonstrate improvement. A U.S. Food and Drug Administration (FDA) advisory states that cilostazol should not be used in patients with congestive heart failure because other PDE3 inhibitors decrease survival in these patients. A long-term safety trial found that cilostazol (versus placebo) did not increase the risk for total or CV mortality, but the study was limited because more than 60% of the patients discontinued treatment before completion of the study.[71]

TABLE 64.5

Approved Medical Therapies for Patients With Peripheral Artery Disease (PAD)

INDICATIONS						
Therapy	**Mechanism of Action**	**Key Clinical Trials**	**European Medicines Agency**	**European Society of Cardiology**	**FDA**	**ACC/AHA**
Statin (Class effect)	Cholesterol lowering HMG-CoA reductase inhibitor	Heart Protection Study 13% RRR with simvastatin 40 mg daily vs. placebo in all-cause mortality, 18% RRR in coronary heart death Approval for PAD based on subgroup of 6748 patients, 2700 had PAD and no CHD	Reduction in MACE and mortality	Class I for lipid lowering with LDL <2.5 mmol/L, optimally <1.8 mmol/L	Reduction in MACE and mortality	Class I, LOE A
ACEI or ARB (Class effect)	Blood pressure lowering and other vascular effects Renin-angiotensin system inhibition	HOPE 22% RRR with ramipril 10 mg daily vs. placebo for composite of MI, stroke, or CV death Approval for PAD based on subgroup of 4051 patients, 1725 with "clinical PAD"	Reduction in MACE	Class I for blood pressure lowering to ≤140/90 mm Hg	Reduction in MACE	Class I, LOE A for antihypertensive therapy Class IIa, LOE A for ACEI/ARB specifically
Clopidogrel	Antiplatelet $P2Y_{12}$ inhibitor	CAPRIE 8.7% RRR vs. aspirin for composite of ischemic stroke, MI, or vascular death Approval for PAD based on subgroup of 6452 patients	As monotherapy Reduction in MACE	Class I monotherapy for risk reduction Class I added to ASA after lower extremity stenting	As monotherapy Reduction in MACE	Class I, LOE A for monotherapy Class IIb, LOE B-R, C-LD, when added to aspirin as DAPT
Vorapaxar	Antiplatelet PAR-1 antagonist	TRA2P-TIMI 50 20% RRR vs. placebo for composite of MI, stroke, or CV death Approval for PAD based on subgroup of 3787 patients	Added to aspirin or clopidogrel Reduction in MACE, limb benefits mentioned	Approved after most recent guidelines	Added to aspirin and/or clopidogrel Reduction in MACE	Class IIb, LOE B-R added to aspirin and/or clopidogrel
Pentoxifylline	Decreases blood viscosity Mechanism not fully understood	Meta-analysis of six studies including 788 patients showed minimal increase in maximal walking distance with (+59 m)	Improve function and symptoms in patients with intermittent claudication	Described but no clear recommendation	Improve function and symptoms in patients with intermittent claudication	Class III, LOE B-R
Cilostazol	Antiplatelet and vasodilator Mechanism not fully understood	50 mg bid (n = 303), 100 mg bid (n = 998), and placebo (n = 973) Improvement in maximal walking distance with 100 mg bid, expressed as the percent mean change from baseline, 28% to 100% vs. placebo, which were −10% to 41%	Reduction of symptoms of intermittent claudication, as indicated by an increased walking distance	Class I for symptoms	Reduction of symptoms of intermittent claudication, as indicated by an increased walking distance	Class I, LOE A

FDA, U.S. Food and Drug Administration; *ACC/AHA,* American College of Cardiology/American Heart Association; *ACEI,* angiotensin-converting enzyme inhibitor; *ARB,* angiotensin receptor blocker; *bid,* twice daily; *CHD,* coronary heart disease; *CV,* cardiovascular; *DAPT,* dual-antiplatelet therapy; *LDL,* low-density lipoprotein; *LOE,* level of evidence *(B-R,* moderate-quality evidence from one or more randomized clinical trials; *C-LD,* randomized or nonrandomized observational/registry studies or a meta-analysis); *MACE,* major adverse cardiovascular events; *MI,* myocardial infarction; *PAR-1,* protease-activated receptor 1; *RRR,* relative risk reduction.



EFIGURE 64.6 Effect of cilostazol versus placebo on maximal walking distance based on a meta-analysis of nine randomized trials. (Modified from Pande RL, Hiatt WR, Zhang P, et al. A pooled analysis of the durability and predictors of treatment response of cilostazol in patients with intermittent claudication. Vasc Med 2010;15:181.)

Antithrombotic Therapy

Studies evaluating the benefits of antithrombotic therapy in patients with atherosclerosis, including patients with PAD, have generally focused on outcomes of MI, stroke, and vascular death, with limb-vascular outcomes variably reported.[54] Two studies in stable patients with asymptomatic PAD showed no benefit of aspirin in reducing incident CLI or amputation.[41,56] A trial of ticlopidine, a $P2Y_{12}$ inhibitor, versus placebo in patients with PAD showed that it reduced limb events and mortality.[41] In CAPRIE, clopidogrel reduced CV risk relative to aspirin, but there were more amputations with clopidogrel (52 versus 47).[41] EUCLID showed no reduction in ALI or limb events with ticagrelor versus clopidogrel in patients without prior revascularization.[57,58] It is therefore unclear whether aspirin or clopidogrel as monotherapy provides limb-vascular benefit.

Many patients with PAD receive DAPT after intervention. Randomized trials to support this practice are lacking. In the CASPAR (Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Artery Disease) trial, DAPT versus aspirin did not reduce the primary composite endpoint of graft occlusion, revascularization, amputation, or death in patients undergoing below-knee bypass surgery for PAD.[72] In TRA2°P-TIMI 50, vorapaxar, added to aspirin, clopidogrel, or DAPT, decreased ALI by 42%, with associated reductions in risk of graft thrombosis, stent thrombosis, and de novo thrombosis.[73] In PEGASUS-TIMI 54, ticagrelor added to aspirin reduced acute adverse limb events including ALI by 35%.[37] In the WAVE trial, there was no reduction in limb ischemia with warfarin.[61] The Dutch Bypass Oral Anticoagulants or Aspirin Study similarly found no benefit for limb outcomes with warfarin after infrainguinal bypass surgery.[41] Several ongoing trials of direct oral anticoagulants at lower doses are ongoing and include ALI in the primary or secondary endpoints.

Statins

In addition to systemic CV risk reduction, statins may improve symptoms of claudication and reduce the risk of tissue loss.[2,41] In the TREADMILL (Treatment of Peripheral Atherosclerotic Disease with Moderate or Intensive Lipid Lowering) trial, atorvastatin (80 mg) increased pain-free walking distance by more than 60% versus a 38% increase with placebo, and additional trials support these findings.[41] A propensity-adjusted analysis from the REACH Registry observed a reduction in amputations with statin use in patients with PAD.[2] The Heart Protection Study reported that simvastatin reduced the risk of a first

acute peripheral vascular event, defined retrospectively as the first occurrence of a noncoronary revascularization, aneurysm repair, major amputation, or death from PAD.[41]

Vasodilators

Most studies of vasodilators have failed to demonstrate any efficacy in patients with intermittent claudication. Several pathophysiologic explanations may account for the failure of vasodilator therapy in patients with PAD. During exercise, resistance vessels distal to a stenosis dilate in response to ischemia. Vasodilators would have minimal if any effect on these endogenously dilated vessels, but would decrease resistance in other vessels and create a relative steal phenomenon, thereby reducing blood flow and perfusion pressure to the affected leg. Moreover, in contrast to their effects on myocardial O_2 consumption in patients with CAD (because of afterload reduction), vasodilators do not reduce skeletal muscle O_2 demand.

Other Medical Therapies

Other classes of drugs, including serotonin (5-HT_2) antagonists, alpha-adrenergic antagonists, L-arginine, carnitine derivatives, vasodilator prostaglandins, antibiotics, and angiogenic growth factors, have been studied for the treatment of either claudication or CLI.[41] Overall, these therapies have not proved useful in improving PAD symptoms.[1] Angiogenic growth factors yielded encouraging preliminary findings in patients with CLI. However, large phase 3 clinical trials did not demonstrate improvement in the rate of amputation-free survival in patients with CLI or improvement in walking time in patients with intermittent claudication[74,75] In initial reports, stem cell–based therapies for PAD improved ABI, rest pain, and pain-free walking time and prevented amputation in some patients with chronic limb ischemia.[76,77] The response to cell therapy, however, may depend on patient selection, with some suggestion that patients with advanced CLI are poor candidates.[78] The findings from these preliminary trials require confirmation with additional clinical trials.

Percutaneous Transluminal Angioplasty and Stents

Peripheral catheter–based interventions are indicated for patients with lifestyle-limiting claudication despite a trial of exercise rehabilitation or pharmacotherapy[79] (**see Chapter 66**). Patients with CLI with anatomy amenable to catheter-based therapy may also be candidates for endovascular intervention. A large clinical trial is comparing the efficacy of endovascular intervention with surgical revascularization on limb outcomes in patients with critical limb ischemia.[80]

Peripheral Artery Surgery

Surgical revascularization improves symptoms in patients with disabling claudication and is indicated to relieve rest pain and preserve limb viability in patients with critical limb ischemia that is not amenable to percutaneous interventions. The specific operation must take into account the anatomic location of the arterial lesions and the presence of comorbid conditions. Planning for surgical procedures requires identification of the arterial obstruction by imaging to ensure sufficient arterial inflow to and outflow from the graft to maintain patency. *Aortobifemoral bypass* is the most frequent operation performed in patients with aortoiliac disease. Typically, a knitted or woven prosthesis made of Dacron or polytetrafluoroethylene (PTFE) is anastomosed proximally to the aorta and distally to each common

femoral artery.[81] On occasion the iliac artery is used for the distal anastomosis to maintain anterograde flow into at least one hypogastric artery. A systematic review of 29 studies from 1970 to 2007 that compared 5738 patients who underwent aortobifemoral bypass surgery found an operative mortality rate of 4%,[82] although high-volume centers in the United States report lower mortality rates. Five-year patency rates for aortobifemoral bypass grafts exceed 80%.[83]

Extra-anatomic surgical reconstructive procedures for aortoiliac disease include axillobifemoral bypass, iliobifemoral bypass, and femoral-femoral bypass. These bypass grafts circumvent the aorta and iliac arteries and are generally used in high-risk patients with CLI. Five-year patency rates range from 50% to 70% for axillobifemoral bypass operations and from 70% to 80% for femoral-femoral bypass grafts.[83] The operative mortality rate for extra-anatomic bypass procedures is 3% to 5% and reflects, in part, the serious comorbid conditions and advanced atherosclerosis in many of the patients who undergo these procedures.

Reconstructive surgery for infrainguinal arterial disease includes femoral-popliteal and femoral-tibial or femoral-peroneal artery bypass. Infrainguinal bypass uses in situ or reversed autologous saphenous veins or synthetic grafts made of PTFE as conduits. Patency rates for autologous saphenous vein bypass grafts exceed those with PTFE grafts,[83] Grafts with the distal anastomosis placed in the popliteal artery above the knee have better patency rates than those placed below the knee. Five-year primary patency rates for femoral-popliteal reconstruction in patients with claudication are approximately 80% and 75% for autogenous vein grafts and PTFE grafts, respectively, and approximately 65% and 45%, respectively, in patients with CLI. For femoral below-knee bypass, including tibioperoneal artery reconstruction, the 5-year patency rates for saphenous vein grafts in patients with claudication or CLI are similar to those for femoral-popliteal above-knee grafts (60% to 80%). The 5-year patency rate for PTFE grafts in the infrapopliteal position is considerably lower, approximately 65% in patients with claudication and 33% in patients with CLI. The operative mortality rate for infrainguinal bypass operations is 2% to 3%.

Graft stenoses can result from technical errors at surgery, such as retained valve cuffs or intimal flap or valvotome injury; from fibrous intimal hyperplasia, usually within 6 months of surgery; or from atherosclerosis, which usually occurs within the vein graft at least 1 to 2 years after surgery. Institution of graft surveillance protocols with the use of color-assisted duplex ultrasonography has enabled the identification of graft stenoses, thereby prompting graft revision and avoiding complete graft failure.[1] Routine ultrasonographic surveillance improves graft outcome.

Fig. 64.13 provides an overview of medical therapy for patients with PAD. **Table 64.5** details medical therapies approved for PAD patients.

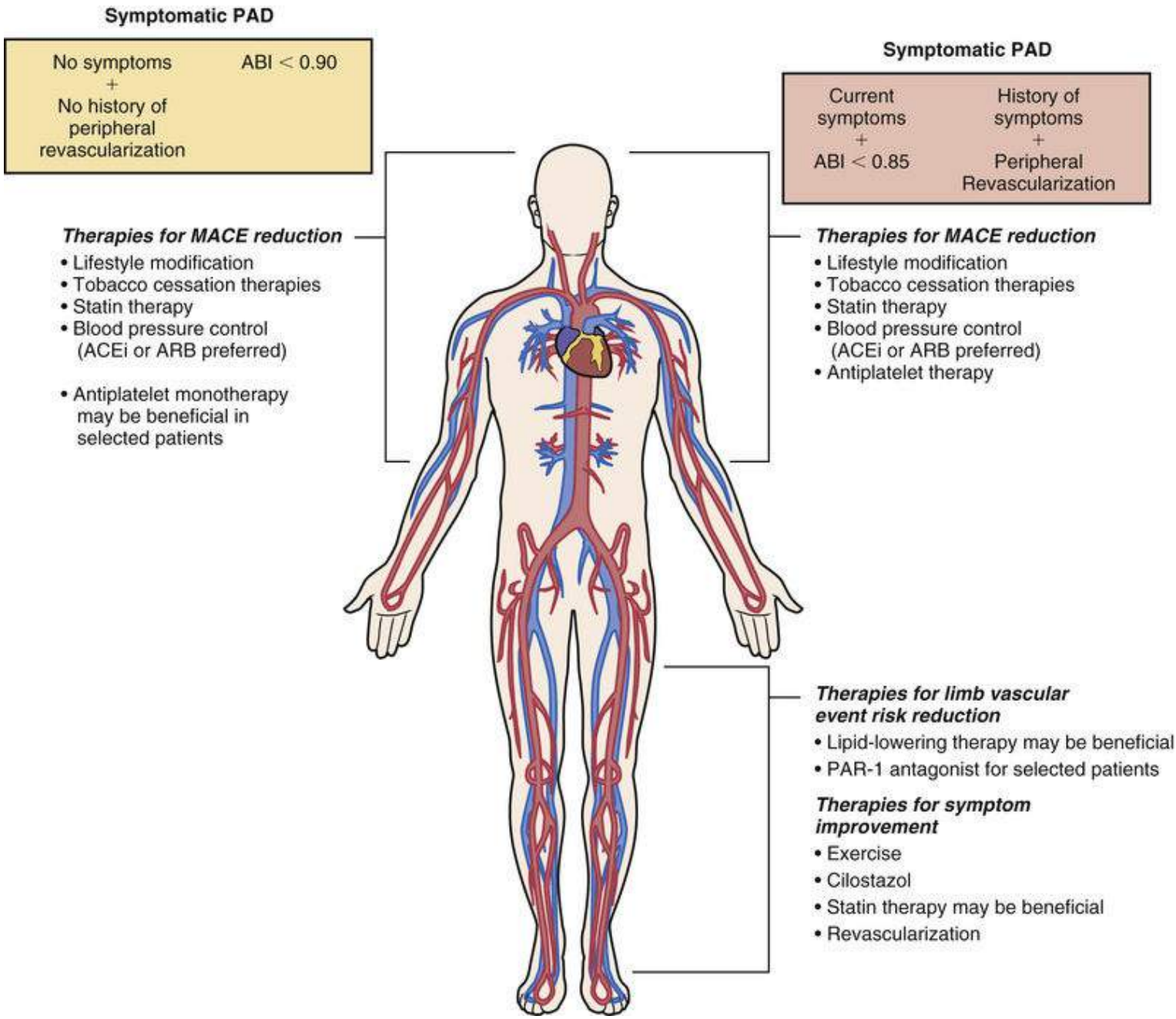


FIGURE 64.13 Summary of medical management of patients with peripheral artery disease (PAD). *ABI,* Ankle-brachial index; *ARB,* angiotensin receptor blocker; *ACEi,* angiotensin-converting enzyme inhibitor; *MACE,* major adverse cardiovascular events; *PAR-1,* protease-activated receptor 1. (Modified from Bonaca MP, Creager MA. Pharmacological treatment and current management of peripheral artery disease. Circ Res 2015;116:1579-98.)

Vasculitis

See Chapter 94.

Thromboangiitis Obliterans

Thromboangiitis obliterans (TAO), a segmental vasculitis that involves the distal arteries, veins, and nerves of the upper and lower extremities, typically affects younger persons who smoke.[84,85]

Pathology and Pathogenesis

TAO primarily affects the medium and small vessels of the arms, including the radial, ulnar, palmar, and digital arteries, and their counterparts in the legs, including the tibial, peroneal, plantar, and digital arteries. Involvement can extend to the cerebral, coronary, renal, mesenteric, aortoiliac, and pulmonary arteries.[85] Pathologic findings include an occlusive, highly cellular thrombus that incorporates polymorphonuclear leukocytes, microabscesses, and occasionally multinucleated giant cells. The inflammatory infiltrate can also affect the vascular wall, but the internal elastic membrane remains intact. In the chronic phase of the disease, the thrombus becomes organized and the vascular wall becomes fibrotic.

The precise cause of TAO is not known. Tobacco use or exposure is present in virtually every patient. Hypercoagulability, immunologic mechanisms, and endothelial dysfunction may contribute to the pathogenesis of TAO. Potential immunologic mechanisms include increased cellular sensitivity to types I and III collagen and the presence of antiendothelial cell antibodies. $CD4^+$ T cells have been identified in the cellular infiltrates of vessels of patients with TAO.[84] Decreased endothelium-dependent vasodilation can occur in both the affected and the unaffected limbs of patients with TAO. Some reports have found increased frequency of a prothrombin gene mutation, elevated plasma homocysteine concentration, or increased levels of anticardiolipin antibodies in patients with TAO.

Clinical Features

The prevalence of TAO is greater in Asia than in North America or Western Europe. In the United States, TAO occurs in approximately 13 per 100,000. Symptoms develop in most before 45 years of age, and 75%-90% are men. Patients can have claudication of the hands, forearms, feet, or calves. Most patients with TAO have pain at rest and digital ulcerations; frequently, more than one extremity is affected. Raynaud phenomenon occurs in approximately 45% of patients, and superficial thrombophlebitis, which may be migratory, develops in approximately 40%. The risk for amputation within 5 years is approximately 25%.[85] The radial, ulnar, dorsalis pedis, and posterior tibial pulses may be absent. Two thirds of patients have abnormal Allen test results. The distal aspects of the extremities may have discrete, tender, erythematous subcutaneous cords, indicative of superficial thrombophlebitis.

Diagnosis

No specific laboratory tests, other than biopsy, can diagnose TAO. Most tests therefore aim to exclude other diseases that might have similar clinical features, including autoimmune diseases such as scleroderma or SLE, hypercoagulable states, DM, and acute arterial occlusion secondary to embolism. Acute-phase indicators, such as the erythrocyte sedimentation rate (ESR) or CRP, are usually normal. Serum immunologic markers, including antinuclear antibodies and rheumatoid factor, should not be present, and serum complement levels should be normal. If clinically indicated, a proximal source of embolism should be excluded by imaging. Arteriography of an affected limb supports the diagnosis of TAO if there is segmental occlusion of small and medium arteries, absence of atherosclerosis, and corkscrew collateral vessels circumventing the occlusion (**Fig. 64.14**). These same findings, however, can occur in patients with scleroderma, SLE, mixed connective tissue disease, and antiphospholipid antibody syndrome. The conclusive test is a biopsy specimen showing the classic pathologic findings. This procedure is rarely indicated, however, and biopsy sites may fail to heal because of severe ischemia. The diagnosis therefore usually depends on an age at onset of younger than 45 years, a history of tobacco use, physical examination demonstrating distal limb ischemia, exclusion of other diseases, and if necessary, angiographic demonstration of typical lesions.

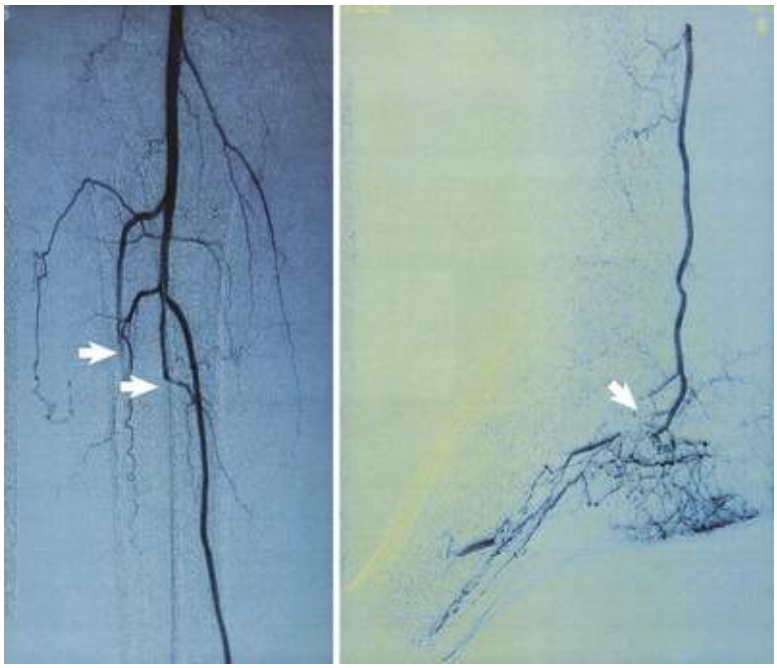


FIGURE 64.14 Angiograms of a young woman with thromboangiitis obliterans. **Left,** Occlusion of anterior tibial and peroneal arteries (*arrows*). **Right,** Occlusion of distal portion of posterior tibial artery (*arrow*) with bridging collateral vessels.

Treatment

The cornerstone of TAO treatment is cessation of tobacco use. Patients without gangrene who stop smoking rarely require amputation.[84] In contrast, one or more amputations may ultimately be required in 40%-45% of those who continue to smoke. No definitive drug therapy is available for TAO. Intravenous iloprost, a prostacyclin analogue, may be more effective than aspirin for rest pain and ischemic ulcers, but oral iloprost is not effective.[86] There is insufficient evidence to support the use of other vasodilator prostaglandin analogues in this setting.[86] Vascular reconstructive surgery is not usually a viable option because of the segmental nature of this disease and the involvement of distal vessels. An autogenous saphenous vein bypass graft can be considered if a target vessel for the distal anastomosis is available.

Takayasu Arteritis and Giant Cell Arteritis

See Chapter 94.

Fibromuscular Dysplasia

Fibromuscular dysplasia (FMD) is a noninflammatory disorder that affects medium and large arteries, typically the renal, carotid, and vertebral arteries. It also may involve the arteries supplying the leg, particularly the iliac arteries and less often the femoral, popliteal, tibial, and peroneal arteries.[87] FMD rarely causes intermittent claudication or CLI. It most often affects women but can occur at any age in both sexes. Although traditionally thought to occur in young women, recent registries have described occurrence primarily in middle-aged women.[87] In addition, while historically described as affecting the renal arteries with the highest frequency, registries describe similar involvement of the carotid, vertebral, and renal arteries, with approximately 65% of patients having multivessel involvement. Aneurysm or dissection is present in more than 40% of patients at diagnosis.[88] Spontaneous coronary artery dissection

(SCAD) is an uncommon presentation of FMD. The most frequent presenting signs and symptoms are hypertension, headache, pulsatile tinnitus, and dizziness illustrating clinical scenarios that should prompt consideration of FMD (**Table 64.6**).[87]

TABLE 64.6

Clinical Circumstances Prompting Consideration of Fibromuscular Dysplasia

Hypertension <35 years old or resistant hypertension at any age
Epigastric bruit and hypertension
Transient ischemic attack, stroke, or cervical bruit in a patient <60 years old
Symptomatic PAD in a woman < 60 years old without atherosclerotic risk factors
Subarachnoid hemorrhage
Pulsatile tinnitus
Severe and recurrent headaches
Peripheral artery dissection or spontaneous coronary artery dissection
Visceral or intracranial aneurysm
Aortic aneurysm in a patient <60
Renal infarction

Modified from Olin JW, Froehlich J, Gu X, et al. The United States Registry for Fibromuscular Dysplasia: results in the first 447 patients. Circulation 2012;125:3182-90.

In patients with suspected FMD, the diagnosis is confirmed by imaging including CT, MRI, and Duplex ultrasound. DSA is generally reserved for patients with a high clinical suspicion and nondiagnostic noninvasive imaging. FMD can be distinguished from atherosclerosis by imaging and patient characteristics (younger, lack of atherosclerosis risk factors) and from vasculitis by the absence of clinical signs, symptoms, or testing suggesting inflammation (e.g., elevated ESR or CRP).

Histopathologic examination shows fibroplasia most often affecting the media, but it can involve the intima or adventitia. The histologic classification of FMD includes the medial subtypes (medial fibroplasia, perimedial fibroplasia, and medial hyperplasia), as well as intimal fibroplasia and adventitial hyperplasia.[89] Depending on the histopathologic type, stenosis results from hyperplasia of the fibrous or muscular components of the vessel wall. Angiography can be classified into two subtypes. The first, *multifocal* FMD, is more common and presents with the classic “string of beads” and has been pathologically associated with intimal fibroplasia, medial hyperplasia, and to perimedial fibroplasia. The second, *focal* FMD, appears as a tubular stenosis, is less common, and is pathologically associated with medial hyperplasia and periarterial hyperplasia (**Fig. 64.15**). As many as one third of cases cannot be classified using angiographic criteria, and the pathologic subtypes overlap considerably. The lack of routine histopathology in the clinical setting and limitations of angiographic criteria have prompted consideration of alternative classification systems.[87]

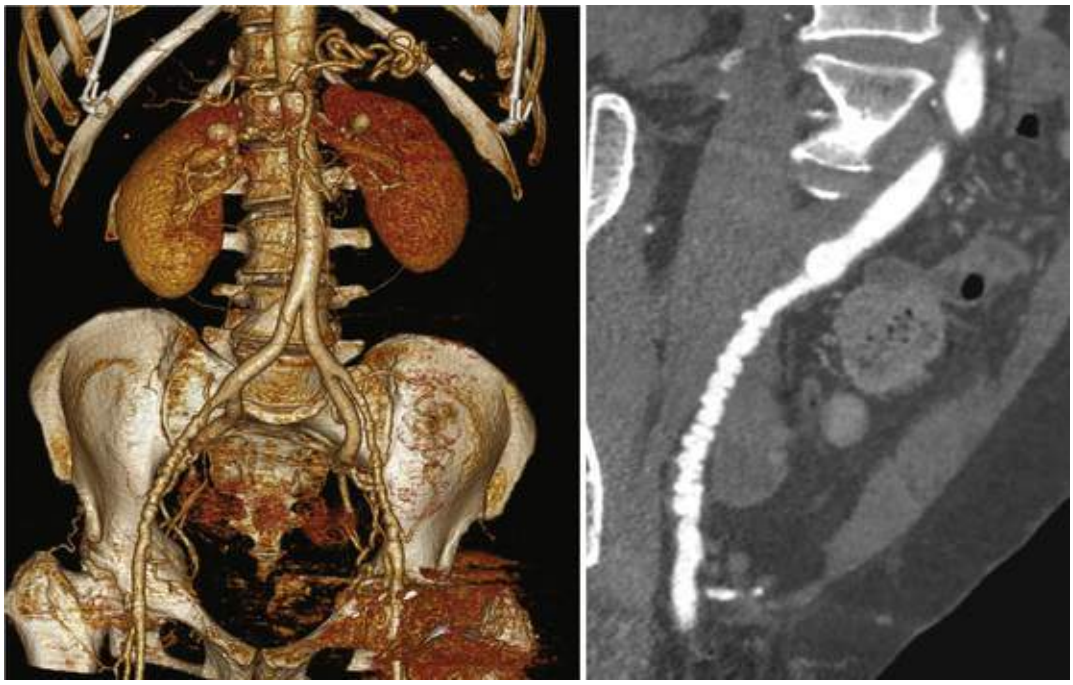


FIGURE 64.15 Angiograms of a patient with fibromuscular dysplasia (FMD). **Left,** Three-dimensional volume-rendered angiogram demonstrating bilateral external iliac FMD. **Right,** Maximum intensity projection of the external iliac artery . (Images courtesy Jeffrey Olin, MD.)

Symptomatic FMD patients can undergo angioplasty. All patients should receive medical therapy to treat any conventional risk factors (e.g., antihypertensive medications) and should have serial clinical evaluations with laboratory testing and/or imaging when indicated, based on clinical assessment. In general, medication use varies based on vascular bed involvement.[90] Smoking is associated with worse outcomes, underscoring the importance of cessation.[91]

Popliteal Artery Entrapment Syndrome

Popliteal artery entrapment syndrome is an uncommon cause of intermittent claudication. It occurs when an anatomic variation in the configuration or insertion of the medial head of the gastrocnemius muscle compresses the popliteal artery.[92] The popliteus muscle also can compress the popliteal artery and cause this syndrome. Popliteal artery entrapment is bilateral in approximately one third of affected patients. It should be suspected when a young, typically athletic, usually male person is evaluated for claudication. Potential consequences include popliteal artery thrombosis, embolism, and aneurysm formation.

Findings on peripheral pulse examination may be normal unless provocative maneuvers are performed. Walking or repeated ankle dorsiflexion and plantar flexion maneuvers may cause attenuation or disappearance of the pedal pulses and a decrease in the ABI in patients with popliteal artery entrapment. Imaging studies such as duplex ultrasonography, CTA, MRA, or conventional angiography, performed at rest and during ankle flexion maneuvers, can confirm the diagnosis. Treatment of popliteal artery entrapment syndrome involves release of the popliteal artery, which may require division and reattachment of the medial head of the gastrocnemius muscle. On occasion, occlusion of the popliteal artery requires surgical bypass. Five-year patency rates for surgical treatment exceed 80%.[93]

Acute Limb Ischemia

Acute limb ischemia (ALI) occurs when an arterial occlusion suddenly reduces blood flow to the arm or

leg.[94] The metabolic needs of the tissue outstrip perfusion, thereby jeopardizing limb viability. Pain may develop quickly and affect the part of the extremity distal to the site of obstruction. It is not necessarily confined to the foot or toes or the hand or fingers, as is usually the case with chronic limb ischemia (CLI). Concurrent ischemia of peripheral nerves causes sensory loss and motor dysfunction. Findings on physical examination can include absence of pulses distal to the occlusion, cool skin, pallor, delayed capillary return and venous filling, diminished or absent sensory perception, and muscle weakness or paralysis. This constellation of symptoms and signs is often recalled as the “six Ps”: pain, paresthesias, pallor, pulselessness, poikilothermia, and paralysis.

Prognosis

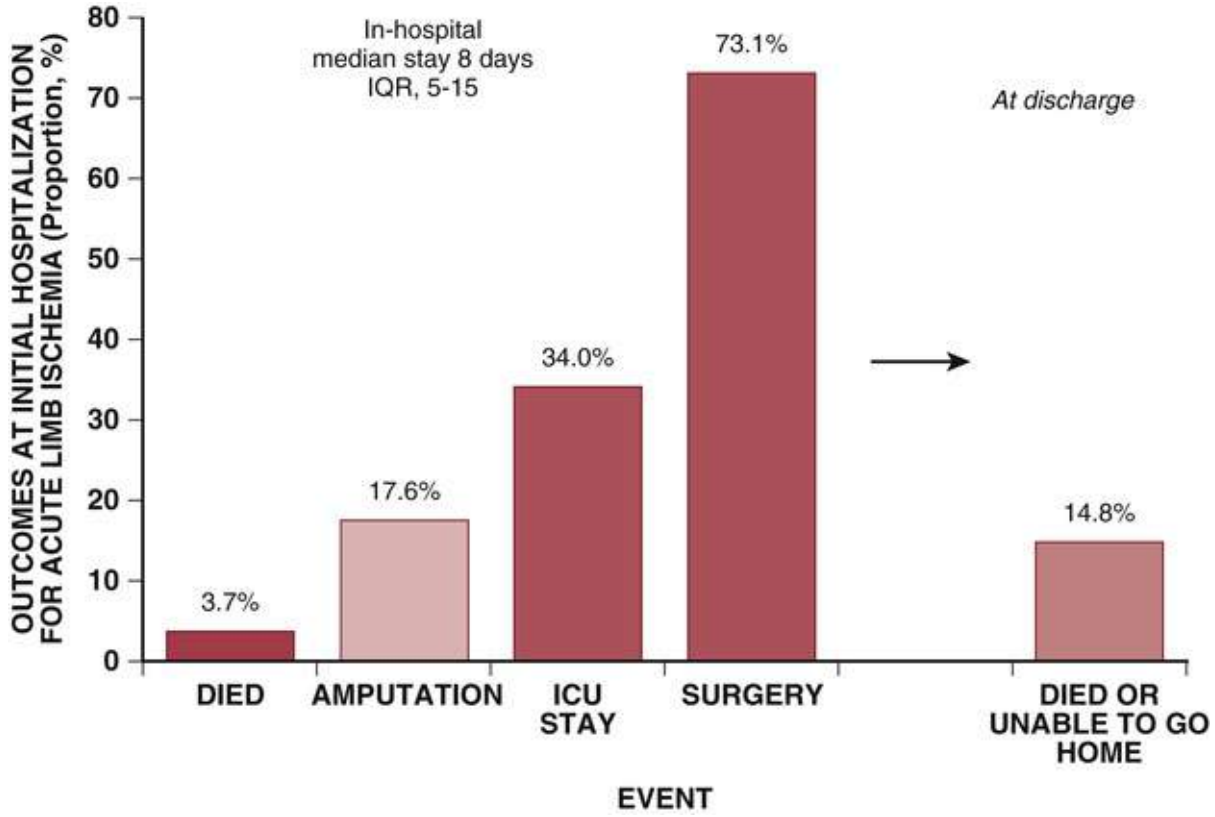
Patients with ALI usually have comorbid CV disorders, which may even be responsible for the ischemia. The risk for limb loss depends on the severity of the ischemia and the time elapsed before revascularization. Among patients with atherosclerosis presenting with ALI in a recent study, approximately 18% required amputation, and 15% either died or were unable to return home after hospitalization[73] (**eFig. 64.7**). The Society for Vascular Surgery and the International Society for Cardiovascular Surgery developed a classification that takes into consideration the severity of ischemia and the viability of the limb, along with related neurologic findings and Doppler signals[95] (**eTable 64.1**).

ETABLE 64.1

Clinical Categories of Acute Limb Ischemia

CATEGORY	DESCRIPTION, PROGNOSIS	FINDINGS		DOPPLER SIGNALS	
		Sensory Loss	Muscle Weakness	Arterial	Venous
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
A. Marginally	Salvageable if treated promptly	Minimal (toes) or none	None	(Often) inaudible	Audible
B. Immediately	Salvageable with immediate revascularization	More than toes, rest pain	Mild, moderate	(Usually) inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

Modified from Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg 1997;26:517. Erratum in J Vasc Surg 2001;33:805.



EFIGURE 64.7 Outcomes in patients presenting with acute limb ischemia. *ICU,* Intensive care unit; *IQR,* interquartile range. (Modified from Bonaca MP, Gutierrez JA, Creager MA, et al. Acute limb ischemia and outcomes with vorapaxar in patients with peripheral artery disease: results from the Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients with Atherosclerosis–Thrombolysis in Myocardial Infarction 50 (TRA2°P-TIMI 50). Circulation 2016;133:997-1005.)

Pathogenesis

Causes of ALI include embolism, thrombosis in situ, dissection, and trauma. A large proportion are embolic[96,97] (**Fig. 64.16**). Most arterial emboli arise from thrombotic sources in the heart, as occurs in atrial fibrillation, or other sources such as prosthetic cardiac valves, paradoxical embolism, and cardiac tumors such as left atrial myxomas. Aneurysms of the aorta or peripheral arteries may lead to embolization of thrombus to more distal arterial sites and usually lodge at branch points where the artery decreases in size. In patients with established PAD, causes of ALI include in-situ atherothrombosis, graft thrombosis, or stent thrombosis[73] (**Fig. 64.16**). Thrombosis in situ occurs in atherosclerotic peripheral arteries, infrainguinal bypass grafts, peripheral artery aneurysms, and normal arteries of patients with hypercoagulable states. In patients with PAD, thrombosis in situ may complicate plaque rupture and cause acute arterial occlusion and limb ischemia, as occurs in the coronary arteries of patients with acute MI. One of the most common causes of ALI in patients with PAD is thrombotic occlusion of an infrainguinal bypass graft. Acute thrombotic occlusion of a normal artery is unusual but may occur in patients with acquired thrombophilic disorders such as antiphospholipid antibody syndrome, heparin-induced thrombocytopenia, disseminated intravascular coagulation, and myeloproliferative diseases. There is limited evidence that inherited thrombophilic disorders such as activated protein C resistance (factor V Leiden), prothrombin *G20210* gene mutation, or deficiencies of antithrombin III and protein C and S increase the risk for acute peripheral arterial thrombosis.

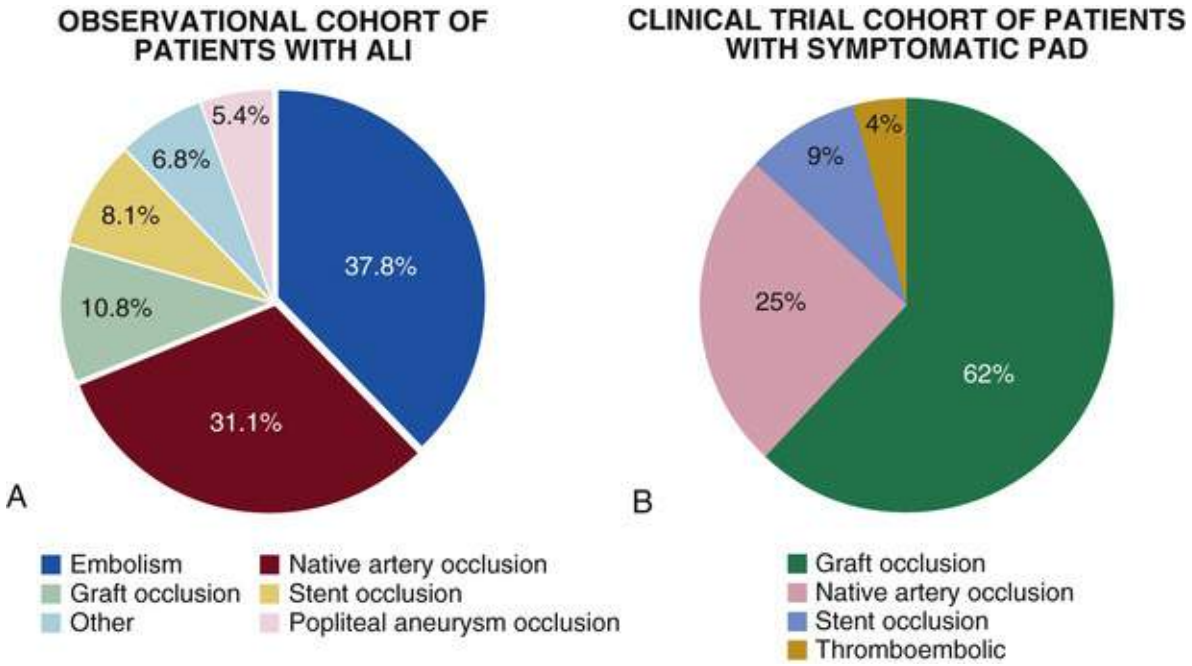


FIGURE 64.16 Etiologies of acute limb ischemia (ALI) in an All Comers registry **(A)** and in patients with symptomatic peripheral artery disease (PAD) not requiring anticoagulation **(B).** (**A,** Modified from Duval S et al. The impact of prolonged lower limb ischemia on amputation, mortality, and functional status: the FRIENDS registry. Am Heart J 2014;168:577-87; **B,** modified from Bonaca MP et al. Acute limb ischemia and outcomes with vorapaxar in patients with peripheral artery disease: results from the Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients with Atherosclerosis–Thrombolysis in Myocardial Infarction 50 (TRA2°P-TIMI 50). Circulation 2016;133:997-1005.)

Diagnostic Tests

The history and physical examination usually establish the diagnosis of ALI. Tests should not delay urgent revascularization procedures to rescue a limb with threatened viability. Pressure in the affected limb and corresponding ABI can be measured if flow is detectable by Doppler ultrasonography. A Doppler probe can assess the presence of blood flow in peripheral arteries, even when pulses are not palpable. Color-assisted duplex ultrasonography can determine the site of occlusion, particularly to evaluate the patency of infrainguinal bypass grafts. MRA, CTA, and conventional arteriography can demonstrate the site of occlusion and provide an anatomic guide for revascularization.

Treatment

For patients with acute leg ischemia, the bed should be positioned such that the feet are lower than chest level, thereby increasing limb perfusion pressure by hydrostatic effects. Effort should be made to reduce pressure on the heels, on bone prominences, and between the toes by appropriate placement of soft material on the bed (e.g., sheepskin) and between the toes (e.g., lamb's wool). Heparin should be administered intravenously immediately.[94] The dose should maintain the partial thromboplastin time at 2.0 to 2.5 times control values to prevent propagation of thrombi or recurrent embolism.

Revascularization is indicated when the viability of the limb is threatened or when symptoms of ischemia persist (**Fig. 64.17**). Options for restoration of blood flow include endovascular revascularization, intra-arterial thrombolytic therapy, and surgical revascularization. Catheter-directed intra-arterial thrombolysis plus thrombectomy is an initial treatment option for patients with either category I or II acute limb ischemia if they have no contraindication to thrombolysis.[94] Identification and repair of a graft stenosis after successful thrombolysis improve long-term graft patency. The thrombolytic regimens currently used include the recombinant tissue plasminogen activators alteplase, reteplase, and

tenecteplase. Catheter-based thrombolytic therapy should generally be continued for 24 to 48 hours to achieve optimal benefit and to limit the risk for bleeding. Adjuvant use of platelet glycoprotein IIb/IIIa inhibitors shortens thrombolysis time but does not improve outcome. Percutaneous, catheter-based mechanical thrombectomy, with devices that remove thrombus via aspiration, fragmentation, or high-energy ultrasound, can be used alone or in addition to pharmacologic thrombolysis to treat patients with ALI. Surgical revascularization, including thromboembolectomy and bypass of the occluded area, is an option for restoration of blood flow to an ischemic limb. Five prospective randomized trials have compared the benefits and risks of thrombolysis and surgical reconstruction in ALI patients. Overall, the two interventions did not differ in the rate of death or amputation during the 1 year between, although patients undergoing thrombolysis had a greater risk for major bleeding. Findings from the individual trials suggest that catheter-based thrombolysis is an appropriate initial option in patients with viable or marginally threatened limbs and when the ischemia is of less than 14 days' duration, whereas surgical revascularization is more appropriate in those with immediately threatened limbs and in those whose symptoms have lasted for more than 14 days. Patients with irreversible injury require amputation (**Fig. 64.17**).

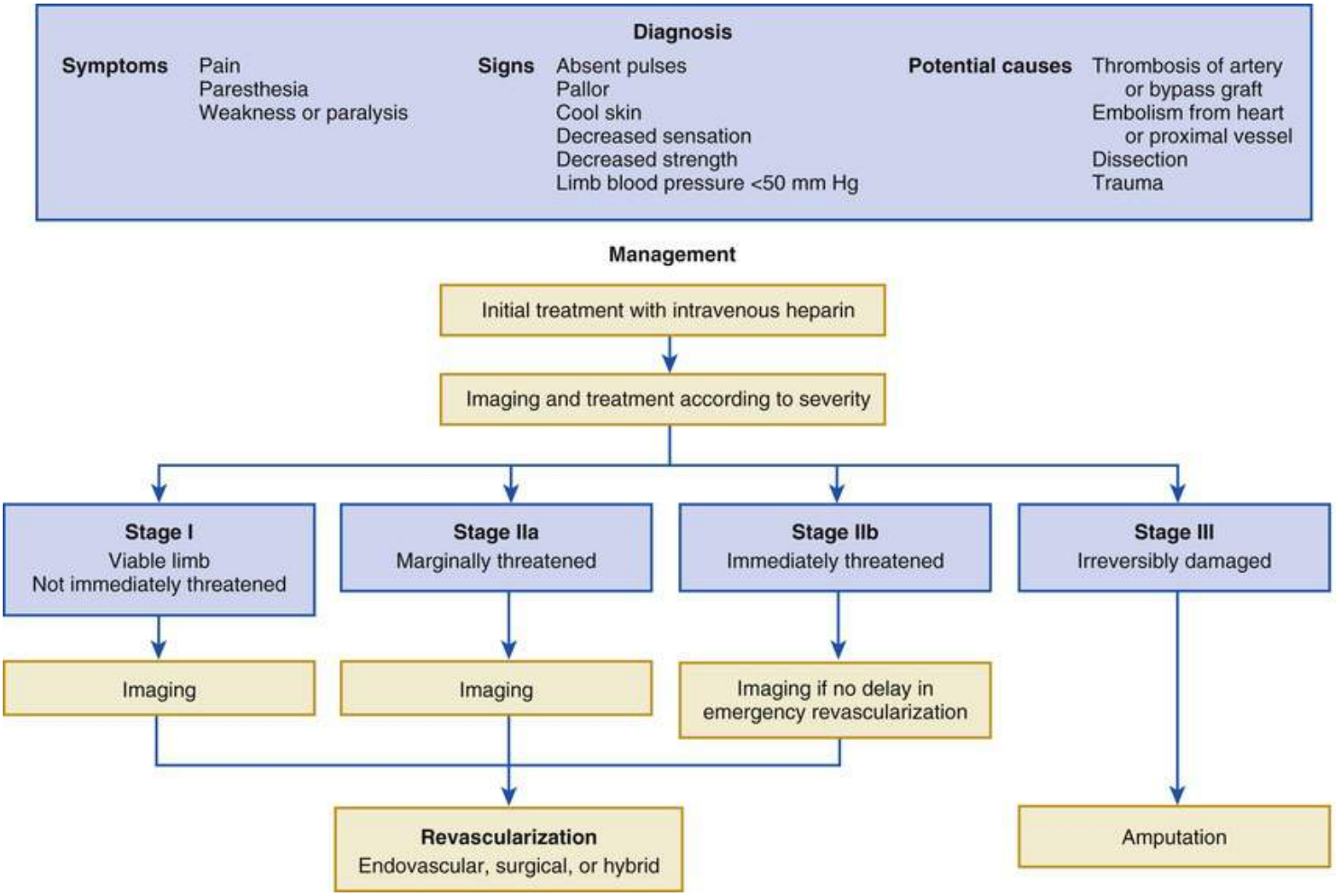


FIGURE 64.17 Diagnostic and treatment approach for patients presenting with acute limb ischemia.

The optimal long-term antithrombotic strategy in patients with ALI remains uncertain. Long-term anticoagulant therapy is usually indicated for patients with an embolic source, such as atrial fibrillation. For patients with symptomatic PAD who develop ALI from thrombotic complications in the limbs (e.g., graft occlusion, stent thrombosis, in situ thrombosis), intensive antiplatelet therapy may be more effective

than aspirin alone in reducing recurrent events.[3,37] Warfarin has not proved beneficial in secondary prevention of nonembolic ALI and is generally only indicated based on the underlying etiology (e.g., atrial fibrillation).

Atheroembolism

Atheroembolism refers to occlusion of arteries resulting from detachment and embolization of atheromatous debris, including fibrin, platelets, cholesterol crystals, and calcium fragments. Other terms include *atherogenic embolism* and *cholesterol embolism.* Atheroemboli originate most frequently from "shaggy," protruding atheroma of the aorta and less frequently from atherosclerotic branch arteries (**eFig. 64.8**). The atheroemboli typically occlude small downstream arteries and arterioles of the skin, extremities, brain, eyes, kidneys, or mesentery. Most affected individuals are men older than 60 years with clinical evidence of atherosclerosis.

EFIGURE 64.8 Atherosclerotic aorta of a patient with atheroemboli. Multiple, protruding, shaggy atheromas with superimposed mural thrombi are present. (Courtesy R.N. Mitchell, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

Pathogenesis

Patients with aortic atherosclerosis characterized by large complex atheromas have the greatest risk for atheroembolism. Identification of large, protruding atheromas by transesophageal ultrasound predicts future embolic events. Catheter manipulation may also cause atheroemboli, in approximately 1% to 2% of patients undergoing endovascular procedures. Similarly, surgical manipulation of the aorta during cardiac or vascular operations may precipitate atheroembolism. Controversy remains whether anticoagulants or thrombolytic drugs contribute to atheroembolism. Recent clinical trials of anticoagulants have found a relatively low incidence of atheroembolism in patients with large aortic plaques.

Clinical Features

The most notable clinical features of atheroembolism involving the extremities include painful cyanotic toes, called “blue toe syndrome” (**Fig. 64.18**). Livedo reticularis occurs in approximately 50% of patients. Local areas of erythematous or violaceous discoloration may be present on the lateral aspects of the feet and the soles, as well as on the calves. Other findings include digital and foot ulcerations, nodules, purpura, and petechiae. Pedal pulses are typically present because the emboli tend to lodge in the more distal digital arteries and arterioles. Symptoms and signs indicating additional organ involvement with atheroemboli should be sought. Renal involvement, manifested by increased BP and azotemia, typically occurs in patients with peripheral atheroemboli. Patients also sometimes show evidence of mesenteric or bladder ischemia and splenic infarction.

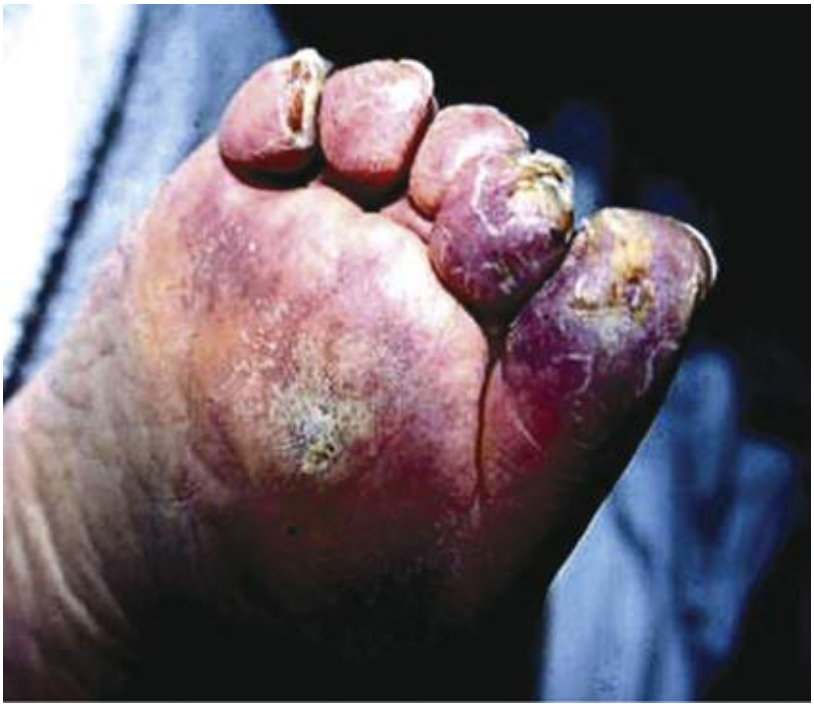


FIGURE 64.18 Atheroemboli involving the foot, or “blue toe syndrome.” There is cyanotic discoloration of the toes along with localized areas of violaceous discoloration. (Modified from Beckman JA, Creager MA. Peripheral artery disease: clinical evaluation. In Creager MA, Beckman JA, Loscalzo J, editors. Vascular Medicine: A Companion to Braunwald's Heart Disease. 2nd ed. Philadelphia: Elsevier; 2013, p 231.)

The clinical setting and findings usually suffice for the diagnosis of atheroembolism, but other diseases may have some of the manifestations of atheroemboli. Hypersensitivity vasculitides secondary to connective tissue diseases, infections, drugs, polyarteritis nodosa, or cryoglobulinemia generally involve multiple organ systems and cause cutaneous findings of purpura, ulcers, and digital ischemia, similar to those resulting from atheroemboli (**see Chapter 94**). Procoagulant disorders such as antiphospholipid antibody syndrome, heparin-induced thrombocytopenia, and myeloproliferative disorders such as essential thrombocythemia can cause digital artery thrombosis with resultant digital ischemia, cyanosis, and ulceration.

Diagnostic Tests

Laboratory findings consistent with atheroembolism include an elevated ESR, eosinophilia, and eosinophiluria. Other findings may include anemia, thrombocytopenia, hypocomplementemia, and

azotemia. Imaging of the aorta with TEE, MRA, or CTA may identify sites of severe atherosclerosis indicating a source of the atheroemboli. The only definitive test for atheroembolism is pathologic confirmation on skin or muscle biopsy specimens. Pathognomonic findings include elongated needle-shaped clefts in small arteries caused by cholesterol crystals and often accompanied by inflammatory infiltrates composed of lymphocytes and possibly giant cells and eosinophils, intimal thickening, and perivascular fibrosis.

Treatment

No definitive treatment has been established for atheroembolism. Local foot care should be provided as with acute limb ischemia. It may be necessary to excise or amputate necrotic areas.

Risk factor modification, such as lipid-lowering therapy with statins and smoking cessation, can favorably affect the overall outcome of atherosclerosis, but whether such intervention will prevent recurrent atheroembolism is unknown. The efficacy of antiplatelet therapy in preventing recurrence is unknown, although antiplatelets are generally indicated in patients with atherosclerosis. The use of warfarin is controversial, and some have even suggested that anticoagulants precipitate atheroemboli, whereas others have found that warfarin reduces atheroembolic events, particularly in patients with mobile aortic atheroma. The use of corticosteroids to treat atheroembolism is also controversial.

Surgical removal of the source should be considered in patients with atheroembolism, particularly in those with recurrence. Surgical procedures include excision and replacement of affected portions of the aorta, endarterectomy, and bypass operations. Operative intervention targets the site of the aorta and iliac or femoral arteries with aneurysm formation or evidence for mobile atherosclerotic plaque. Frequently, diffuse aortic disease makes it difficult to identify the precise segment responsible for the atheroembolism. Several small case series have reported endovascular placement of stents and stent grafts to prevent recurrent atheroembolism.

Guidelines

Peripheral Artery Diseases

Marc P. Bonaca and Mark A. Creager

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Task Force on Practice Guidelines published its most recent guidelines for the management of patients with peripheral artery disease (PAD) in 2016.[1] This summary presents salient features and important recommendations from these guidelines. We omit some recommendations superseded by more recent statements or data.

Vascular History and Physical Examination

The ACCF/AHA guidelines state that practitioners should query patients at risk for PAD about limitations in walking caused by symptoms of fatigue, aching, numbness, or pain in the buttocks, thighs, calves, or feet and about leg discomfort associated with exertion and rest. Additional questions can determine whether the patient has pain even at rest or poorly healing or nonhealing wounds of the legs or feet. The guidelines recommend performance of a comprehensive pulse examination and careful inspection of the

feet. This includes measurement of blood pressure in both arms; auscultation of the carotid arteries, abdomen, and femoral arteries for bruits; and palpation of the brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial artery pulses. The feet are inspected to assess skin color, temperature, integrity, and the presence of ulcerations (**Tables 64G.1 and 64G.2; see also Table 64G.6**).

TABLE 64G.1

ACCF/AHA Guidelines for Vascular History and Physical Examination of Patients With Peripheral Artery Disease (PAD)

COR	INDICATION	LOE
I	1. Patients at increased risk of PAD should undergo a comprehensive medical history and a review of symptoms to assess for exertional leg symptoms.	B-NR
	2. Patients at increased risk of PAD should undergo vascular examination, including palpation of lower extremity pulses (i.e., femoral, popliteal, dorsalis pedis, and posterior tibial), auscultation for femoral bruits, and inspection of the legs and feet.	B-NR
	3. Patients with PAD should undergo noninvasive blood pressure measurement in both arms at least once during the initial assessment.	B-NR

COR, Class of recommendation; *LOE,* level of evidence; *B-NR,* moderate-quality evidence from one or more nonrandomized clinical trials.

TABLE 64G.2

ACCF/AHA Guidelines for Longitudinal Follow-Up in Patients With Peripheral Artery Disease

COR	INDICATION	LOE
I	1. Patients with PAD should be followed up with periodic clinical evaluation, including assessment of cardiovascular risk factors, limb symptoms, and functional status.	C-EO
	2. Patients with PAD who have undergone lower extremity revascularization (surgical and/or endovascular) should be followed up with periodic clinical evaluation and ABI measurement.	C-EO
IIa	1. Duplex ultrasound can be beneficial for routine surveillance of infrainguinal, autogenous vein bypass grafts in patients with PAD.	B-R
	2. Duplex ultrasound is reasonable for routine surveillance after endovascular procedures in patients with PAD.	C-LD
IIb	The effectiveness of duplex ultrasound for routine surveillance of infrainguinal prosthetic bypass grafts in patients with PAD is uncertain.	B-R

COR, Class of recommendation; *LOE,* level of evidence; *B-R,* moderate-quality evidence from one or more randomized clinical trials; *C-EO,* consensus of expert opinion; *C-LD,* randomized or nonrandomized observational/registry studies or a meta-analysis.

Diagnostic Tests

Noninvasive vascular diagnostic techniques provide adjunctive diagnostic information to the history and physical examination. Such tests include physiologic measurements and imaging studies. Noninvasive physiologic assessment may include the ankle-brachial and toe-brachial indices, segmental pressure measurements, Doppler waveform analysis, pulse volume recordings, and exercise testing (**Table 64G.3; see Chapter 64**).

TABLE 64G.3

ACCF/AHA Guidelines for Diagnostic Testing, Anatomic Assessment and Screening of Other Arterial Beds in Patients With Peripheral Artery Disease

COR	INDICATION	LOE
I	1. In patients with history or physical examination findings suggestive of PAD, the resting ankle-brachial index (ABI), with or without segmental pressures and waveforms, is recommended to establish the diagnosis.	B-NR
	2. Resting ABI results should be reported as abnormal (ABI ≤0.90), borderline (ABI 0.91 to 0.99), normal (1.00 to 1.40), or noncompressible (ABI >1.40).	C-LD
	3. Toe-brachial index (TBI) should be measured to diagnose patients with suspected PAD when the ABI is greater than 1.40.	B-NR
	4. Patients with exertional non–joint-related leg symptoms and normal or borderline resting ABI (>0.90 and ≤1.40) should undergo exercise treadmill ABI testing to evaluate for PAD.	B-NR
	5. Duplex ultrasound, CTA, or MRA of the lower extremities is useful to diagnose anatomic location and severity of stenosis for patients with symptomatic PAD in whom revascularization is considered.	B-NR
	6. Invasive angiography is useful for patients with CLI in whom revascularization is considered.	C-EO
IIa	1. In patients at increased risk of PAD but without history or physical examination findings suggestive of PAD, measurement of the resting ABI is reasonable.	B-NR
	2. In patients with PAD and an abnormal resting ABI (≤0.90), exercise treadmill ABI testing can be useful to objectively assess functional status.	B-NR
	3. In patients with normal (1.00 to 1.40) or borderline (0.91 to 0.99) ABI in the setting of nonhealing wounds or gangrene, it is reasonable to diagnose CLI by using TBI with waveforms, $TcPO_2$, or SPP.	B-NR
	4. In patients with PAD with an abnormal ABI (≤0.90) or with noncompressible arteries (ABI >1.40 and TBI ≤0.70) in the setting of nonhealing wounds or gangrene, TBI with waveforms, $TcPO_2$, or SPP can be useful to evaluate local perfusion.	B-NR
	5. Invasive angiography is reasonable for patients with lifestyle-limiting claudication with an inadequate response to GDMT for whom revascularization is considered.	C-EO
	6. A screening duplex ultrasound for AAA is reasonable in patients with symptomatic PAD.	B-NR
III	1. In patients not at increased risk of PAD (**see Table 64.1**) and without history or physical examination findings suggestive of PAD, the ABI is not recommended.	B-NR
	2. Invasive and noninvasive angiography (CTA, MRA) should not be performed for the anatomic assessment of patients with asymptomatic PAD.	B-R

COR, Class of recommendation; *LOE,* level of evidence; *AAA,* abdominal aortic aneurysm; *CLI,* critical limb ischemia; *CTA,* computed tomographic angiography; *GDMT,* guideline-directed medical therapy; *MRA,* magnetic resonance angiography.

Medical Management of Patients With Peripheral Artery Disease

Medical treatment of patients with PAD is directed toward reducing adverse cardiovascular events and improving symptoms of intermittent claudication. Drugs, other risk factor–modifying measures, and antiplatelet agents can decrease the risk for myocardial infarction (MI), stroke, and cardiovascular death (**Table 64G.4**). Exercise and cilostazol both improve walking distance in patients with claudication (**Table 64G.5**). Medical therapies have not been demonstrated to preserve limb viability in patients once they develop critical limb ischemia, and these patients should undergo urgent evaluation for revascularization (**Tables 64G.6 to 64G.8**).

TABLE 64G.4

ACCF/AHA Guidelines for Medical Therapy for Patients With Peripheral Artery Disease

COR	INDICATION	LOE
I	1. Antiplatelet therapy with aspirin alone (range, 75 to 325 mg/day) or clopidogrel alone (75 mg/day) is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD.	A
	2. Treatment with a statin medication is indicated for all patients with PAD.	A
	3. Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death.	A
	4. Patients with PAD who smoke cigarettes or use other forms of tobacco should be advised at every visit to quit.	A
	5. Patients with PAD who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy (varenicline, bupropion, and/or nicotine replacement therapy) and/or referral to a smoking cessation program.	A
	6. Patients with PAD should avoid exposure to environmental tobacco smoke at work, at home, and in public places.	B-NR
	7. Management of diabetes mellitus in the patient with PAD should be coordinated between members of the health care team.	C-EO
	8. Cilostazol is an effective therapy to improve symptoms and increase walking distance in patients with claudication.	A
	9. Patients with PAD should have an annual influenza vaccination.	C-EO
IIa	1. In asymptomatic patients with PAD (ABI ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death.	C-EO
	2. The use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers can be effective to reduce the risk of cardiovascular ischemic events in patients with PAD.	A
	3. Glycemic control can be beneficial for patients with CLI to reduce limb-related outcomes.	B-NR
IIb	1. In asymptomatic patients with borderline ABI (0.91 to 0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain.	B-R
	2. The effectiveness of dual-antiplatelet therapy (aspirin and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established.	B-R
	3. Dual-antiplatelet therapy (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization.	C-LD
	4. The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain.	B-R
	5. The usefulness of anticoagulation to improve patency after lower extremity autogenous vein or prosthetic bypass is uncertain.	B-R
III	1. Anticoagulation should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD.	A
	2. Pentoxifylline is not effective for treatment of claudication.	B-R
	3. Chelation therapy (e.g., ethylenediaminetetraacetic acid) is not beneficial for treatment of claudication.	B-R
	4. B-complex vitamin supplementation to lower homocysteine levels for prevention of cardiovascular events in patients with PAD is not recommended.	B-R

COR, Class of recommendation; *LOE,* level of evidence; *ABI,* ankle-brachial index; *CLI,* critical limb ischemia; *MI,* myocardial infarction.

TABLE 64G.5

ACCF/AHA Guidelines for Exercise Therapy in Patients With Peripheral Artery Disease

COR	INDICATION	LOE
I	1. In patients with claudication, a supervised exercise program is recommended to improve functional status and quality of life and to reduce leg symptoms.	A
	2. A supervised exercise program should be discussed as a treatment option for claudication before possible revascularization.	B-R
IIa	1. In patients with PAD, a structured community- or home-based exercise program with behavioral change techniques can be beneficial to improve walking ability and functional status.	A
	2. In patients with claudication, alternative strategies of exercise therapy, including upper-body ergometry, cycling, and pain-free or low-intensity walking that avoids moderate to maximum claudication while walking, can be beneficial to improve walking ability and functional status.	A

COR, Class of recommendation; *LOE,* level of evidence.

TABLE 64G.6

ACCF/AHA Guidelines for Minimizing Tissue Loss in Patients With Peripheral Artery Disease

COR	INDICATION	LOE
I	1. Patients with PAD and diabetes mellitus should be counseled about self–foot examination and healthy foot behaviors.	C-LD
	2. In patients with PAD, prompt diagnosis and treatment of foot infection are recommended to avoid amputation.	C-LD
IIa	1. In patients with PAD and signs of foot infection, prompt referral to an interdisciplinary care team can be beneficial.	C-LD
	2. It is reasonable to counsel patients with PAD without diabetes mellitus about self–foot examination and healthy foot behaviors.	C-EO
	3. Biannual foot examination by a clinician is reasonable for patients with PAD and diabetes mellitus.	C-EO

COR, Class of recommendation; *LOE,* level of evidence.

TABLE 64G.7

ACCF/AHA Guidelines for Revascularization of Patients With Peripheral Artery Disease

COR	INDICATION	LOE
I	1. In patients with CLI, revascularization should be performed when possible to minimize tissue loss.	B-NR
	2. An evaluation for revascularization options should be performed by an interdisciplinary care team before amputation in the patient with CLI.	C-EO
	3. Endovascular procedures are recommended to establish in-line blood flow to the foot in patients with nonhealing wounds or gangrene.	B-R
	4. Surgical procedures are recommended to establish in-line blood flow to the foot in patients with nonhealing wounds or gangrene.	C-LD
	5. When surgery is performed for CLI, bypass to the popliteal or infrapopliteal arteries (i.e., tibial, pedal) should be constructed with suitable autogenous vein.	A
	6. Endovascular procedures are effective as a revascularization option for patients with lifestyle-limiting claudication and hemodynamically significant aortoiliac occlusive disease.	A
	7. When surgical revascularization is performed, bypass to the popliteal artery with autogenous vein is recommended in preference to prosthetic graft material.	A
IIa	1. Revascularization is a reasonable treatment option for the patient with lifestyle-limiting claudication with an inadequate response to GDMT.	A
	2. Endovascular procedures are reasonable as a revascularization option for patients with lifestyle-limiting claudication and hemodynamically significant femoropopliteal disease.	B-R
	3. Surgical procedures are reasonable as a revascularization option for patients with lifestyle-limiting claudication with inadequate response to GDMT, acceptable perioperative risk, and technical factors suggesting advantages over endovascular procedures.	B-NR
	4. A staged approach to endovascular procedures is reasonable in patients with ischemic rest pain.	C-LD
	5. Evaluation of lesion characteristics can be useful in selecting the endovascular approach for CLI.	B-R
	6. In patients with CLI for whom endovascular revascularization has failed and a suitable autogenous vein is not available, prosthetic material can be effective for bypass to the below-knee popliteal and tibial arteries.	B-NR
	7. A staged approach to surgical procedures is reasonable in patients with ischemic rest pain.	C-LD
IIb	1. The usefulness of endovascular procedures as a revascularization option for patients with claudication due to isolated infrapopliteal artery disease is unknown.	C-LD
	2. Use of angiosome-directed endovascular therapy may be reasonable for patients with CLI and nonhealing wounds or gangrene.	B-NR
III	1. Endovascular procedures should *not* be performed in patients with PAD solely to prevent progression to CLI.	B-NR
	2. Surgical procedures should *not* be performed in patients with PAD solely to prevent progression to CLI.	B-NR
	3. Femoral-tibial artery bypasses with prosthetic graft material should not be used for the treatment of claudication.	B-R

COR, Class of recommendation; *LOE,* level of evidence; *CLI,* critical limb ischemia; *GDMT,* guideline-directed medical therapy.

TABLE 64G.8

ACCF/AHA Guidelines for Wound Healing Therapies for Patients With Critical Limb Ischemia (CLI)

COR	INDICATION	LOE
I	1. An interdisciplinary care team should evaluate and provide comprehensive care for patients with CLI and tissue loss to achieve complete wound healing and a functional foot.	B-NR
	2. In patients with CLI, wound care after revascularization should be performed with the goal of complete wound healing.	C-LD
IIb	1. In patients with CLI, intermittent pneumatic compression (arterial pump) devices may be considered to augment wound healing and/or ameliorate severe ischemic rest pain.	B-NR
	2. In patients with CLI, the effectiveness of hyperbaric oxygen therapy for wound healing is unknown.	C-LD
III	Prostanoids are not indicated in patients with CLI.	B-R

COR, Class of recommendation; *LOE,* level of evidence.

Revascularization Strategies for Patients With Peripheral Artery Disease

Revascularization procedures can improve symptoms and preserve limb viability. These procedures are broadly categorized as endovascular interventions and surgical reconstruction, although hybrid procedures consisting of both endovascular and surgical revascularization are also used. In determining the type of revascularization procedure, one important consideration is the location of the obstruction, which is broadly categorized as *inflow,* involving the aorta and iliac arteries; *outflow,* including the femoral and popliteal arteries; or *run-off,* affecting the tibial and peroneal arteries. The decision to perform endovascular or surgical procedures also depends on the clinical context and the morphologic features and distribution of the stenotic and occlusive lesions. Endovascular interventions may involve percutaneous transluminal angioplasty (PTA) with balloon dilation, stents, atherectomy, and thrombolysis. Surgical procedures include aortobifemoral bypass; iliac endarterectomy; extra-anatomic bypass, such as

femoral-femoral and axillobifemoral bypass; and infrainguinal bypass procedures, such as femoral-popliteal and femoral-tibial bypass. Infrainguinal bypass procedures generally use saphenous veins for the bypass conduit, but other veins or synthetic material may also be used, such as polytetrafluoroethylene (PTFE) (**Table 64G.7**).

Management of Acute Limb Ischemia

The ACCF/AHA guidelines state that patients with symptoms and signs of acute limb ischemia should undergo emergency evaluation and treatment to preserve viability in a salvageable extremity. Revascularization strategies include catheter-based thrombolysis/thrombectomy or surgical revascularization. Considerations for determining the type of revascularization procedure used to treat acute limb ischemia include the cause of acute arterial occlusion, the duration of time since the onset of symptoms, and the severity of limb ischemia (**Table 64G.9**).

TABLE 64G.9

ACCF/AHA Guidelines for Management of Patients With Acute Limb Ischemia (ALI)

COR	INDICATION	LOE
I	1. Patients with ALI should be emergently evaluated by a clinician with sufficient experience to assess limb viability and implement appropriate therapy.	C-EO
	2. In patients with suspected ALI, initial clinical evaluation should rapidly assess limb viability and potential for salvage and does not require imaging.	C-LD
	3. In patients with ALI, systemic anticoagulation with heparin should be administered unless contraindicated.	C-EO
	4. In patients with ALI, the revascularization strategy should be determined by local resources and patient factors (e.g., etiology, degree of ischemia).	C-LD
	5. Catheter-based thrombolysis is effective for patients with ALI and a salvageable limb.	A
	6. Amputation should be performed as the first procedure in patients with a nonsalvageable limb.	C-LD
	7. Patients with ALI should be monitored and treated (e.g., fasciotomy) for compartment syndrome after revascularization.	C-LD
	8. In the patient with ALI, a comprehensive history should be obtained to determine the cause of thrombosis and/or embolization.	C-EO
IIa	1. In patients with ALI with a salvageable limb, percutaneous mechanical thrombectomy can be useful as adjunctive therapy to thrombolysis.	B-NR
	2. In patients with ALI due to embolism and with a salvageable limb, surgical thromboembolectomy can be effective.	C-LD
	3. In the patient with a history of ALI, testing for a cardiovascular cause of thromboembolism can be useful.	C-EO
IIb	The usefulness of ultrasound-accelerated catheter-based thrombolysis for patients with ALI with a salvageable limb is unknown.	C-LD

COR, Class of recommendation; *LOE,* level of evidence.

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Acute Limb Ischemia

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65

Prevention and Management of Ischemic Stroke

Larry B. Goldstein

Each year, more than 795,000 Americans have strokes (cerebrovascular accidents), and more than 150,000 die. In 2013, stroke fell from the fourth to the fifth leading cause of death in the United States.[1] Approximately 6.6 million Americans age 20 years or older have had a stroke, a leading cause of severe, long-term disability. Stroke disproportionately affects minority populations. In 2013, 58% of stroke-related deaths occurred in women, and women are less than half as likely as men to be able to live independently after stroke. Although age is a major risk factor for stroke, approximately 10% of strokes occur in persons 18 to 50 years of age.[1] Risk factors for stroke overlap with those for coronary artery disease (CAD) and peripheral artery disease (PAD), yet stroke can reflect diverse pathophysiologic processes, and therapies can confer different levels of benefit and risk than for other vascular diseases.[2] This discussion focuses on therapeutic interventions that have particular relevance for cardiologists. The American Heart Association/American Stroke Association (AHA/ASA) provides detailed, current evidence-based guidelines for prevention of a first stroke,[2] prevention of recurrent stroke,[3] and emergency management of patients with ischemic stroke.[4-6]

This chapter reviews various aspects of medical therapy for ischemic stroke. Readers are directed to AHA guidelines reviewing the use of carotid endarterectomy and angioplasty/stenting for primary and secondary prevention of stroke[2,3,7] and to **Chapter 66**.[7]

Medical Therapy for Prevention of Stroke

Approximately 78% of strokes are first events, which makes primary prevention of paramount importance.[1] Approximately 18% of survivors will have a second stroke within 4 years. After a transient ischemic attack (TIA), patients have a risk for ischemic stroke of approximately 11% over 90 days, with the highest risk in the first week.[1] TIA is a frequently misdiagnosed condition defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. A study that used systems dedicated to the urgent evaluation and management of patients with TIA found a much lower 90-day risk (3.7%).[8] The ABCD2 score was developed to help assess the short-term risk for stroke in patients with TIA[9] (**Table 65.1**). The risk for stroke within 2 days is low (1%) in those with a score of 0 to 3, moderate (4%) in those with a score of 4 to 5, and high (8%) in those with a score of 6 to 7.[9] Even those at apparent low risk, however, may require urgent treatment.[10] Indeed, 22% of strokes occur in patients with an ABCD2 score of less than 4.[8]

TABLE 65.1

ABCD2 Score

FACTOR	POINTS
Age >60 years	1
Blood pressure >140/90 mm Hg	1
Clinical Features	
Speech deficit, no weakness	1
Unilateral weakness	2
Diabetes	1
Duration	
10-59 minutes	1
>60 minutes	2

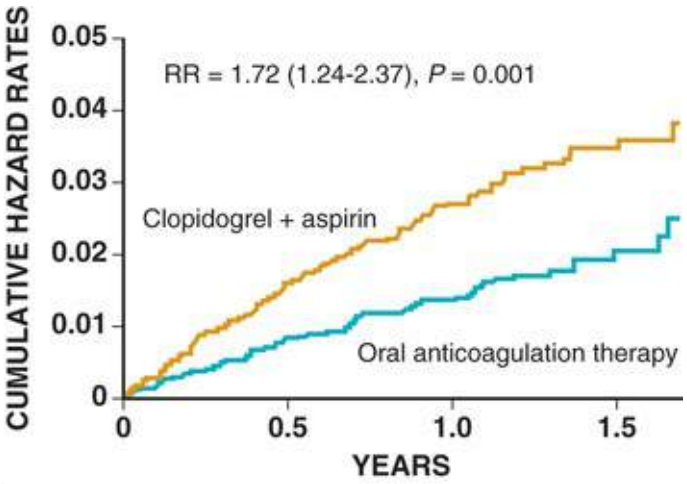
Platelet Antiaggregants

Primary Prevention

The use of platelet antiaggregants for preventing a first stroke depends on the patient's global risk for cardiovascular (CV) events and stroke, as assessed by any of several instruments (**see Chapter 45**). The benefit of aspirin for primary CV prophylaxis outweighs its associated risk for bleeding complications in persons with a 10-year risk greater than 10%. There is no evidence that platelet antiaggregants reduce the risk for stroke in persons at low risk, or in those with diabetes in the absence of other major risk factors, and aspirin is not recommended for these purposes[2] (**see Chapter 45**).

The Women's Health Study found no reduction in its prespecified primary endpoint (nonfatal myocardial infarction [MI], nonfatal stroke, or CV death) with aspirin (100 mg on alternate days), but there was a 17% reduction in stroke, although with an increase in the risk for bleeding.[11] This benefit occurred primarily in women who had stroke risk factors (e.g., hypertension, diabetes). Thus, aspirin may be considered for primary stroke prevention in women whose risk for stroke outweighs its associated bleeding risk.[2]

Patients with atrial fibrillation (AF) should generally receive anticoagulation for prevention of stroke.[3,12] In addition to warfarin, additional agents are available for prevention of a first and recurrent stroke in patients with nonvalvular AF[3] (see later and **Chapters 38 and 93**). Aspirin or the combination of aspirin and clopidogrel is inferior to warfarin for stroke prevention in patients with AF and should only be considered in those who cannot take anticoagulants[13] (**eFig. 65.1**).

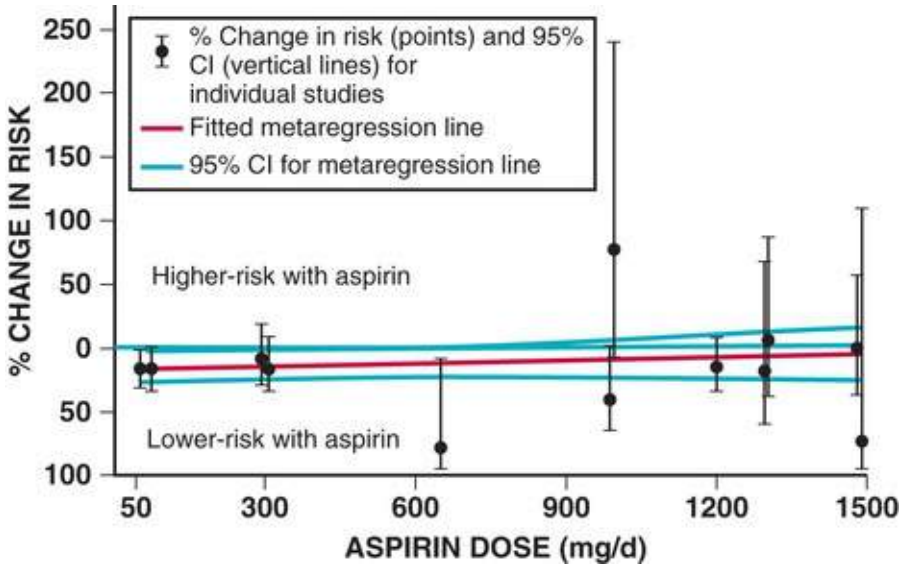


No. at risk				
Clopidogrel + aspirin	3335	3168	2419	941
Oral anticoagulation therapy	3371	3232	2466	930

EFIGURE 65.1 Clopidogrel plus aspirin versus anticoagulation in patients with atrial fibrillation and risk for stroke. RR, Risk ratio (relative risk). (From Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006;367:1903.)

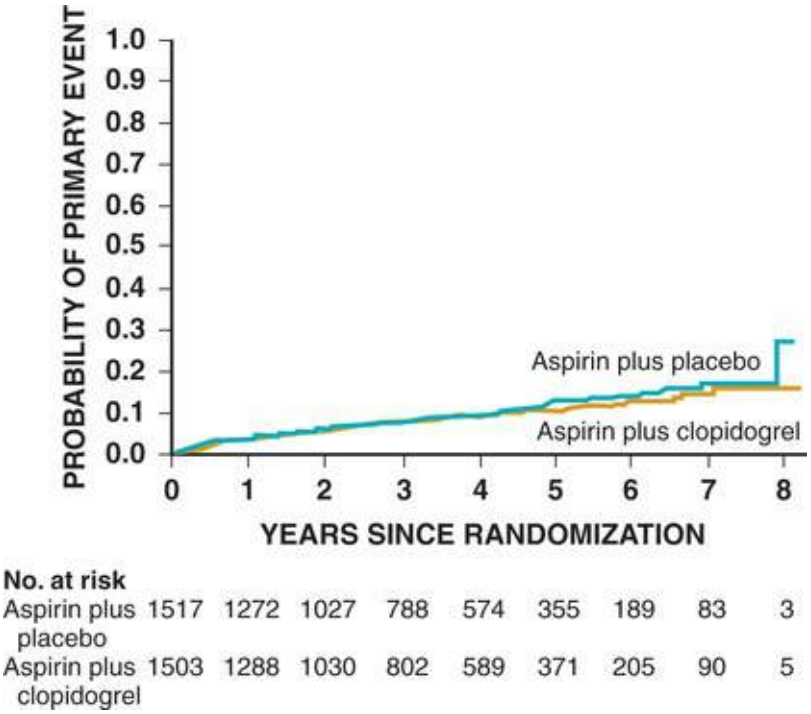
Secondary Prevention

Aspirin (lowest efficacious dose in comparison to placebo, 50 mg/day) lowers the risk of recurrent stroke by approximately 15% (95% confidence interval [CI] 6% to 23%) in persons with noncardioembolic ischemic stroke with little or no increase in stroke recurrence with higher doses[3,14] (**eFig. 65.2**). Sustained-release (SR) *dipyridamole* (200 mg twice daily) is as efficacious as aspirin in reducing the risk for recurrent stroke, with a further reduction (37%) when the two drugs are combined; the combination reduces the risk of stroke by 23% compared to aspirin alone.[3,15] Cardiologists are often concerned that dipyridamole might increase the risk of cardiac ischemia, but clinical trials have not substantiated this reservation.



EFIGURE 65.2 Megaregression analysis showing no difference in the effect of aspirin in reducing stroke risk for doses ranging between 50 and 1500 mg daily. (From Johnson ES, Lanes SF, Wentworth CE, et al. A metaregression analysis of the dose-response effect of aspirin on stroke. Arch Intern Med 1999;159:1248.)

Clopidogrel monotherapy given to patients with a history of MI, stroke, or symptomatic PAD reduces the combined risk of MI, stroke, or vascular death by 8.7% (95% CI 0.3% to 16.5%; $P = 0.043$) compared with aspirin.[3] Although based on a potentially underpowered subgroup analysis, there is no evidence of a significant reduction in stroke in those with previous stroke. The combination of clopidogrel and aspirin does reduce the rate of myocardial infarction, stroke, or death from CV causes more than aspirin alone in patients with cardiovascular disease (CVD, including stroke) or multiple risk factors.[16] When tested specifically in patients with a history of stroke, the combination of clopidogrel and aspirin was associated with an increase in bleeding complications without a reduction in ischemic stroke.[17] SPS3 (Stroke Prevention Study 3) similarly found a higher risk for hemorrhage with no reduction in ischemic events after lacunar stroke in those treated with the combination versus aspirin alone[18] (**Fig. 65.1**).



No. at risk									
Aspirin plus placebo	1517	1272	1027	788	574	355	189	83	3
Aspirin plus clopidogrel	1503	1288	1030	802	589	371	205	90	5

FIGURE 65.1 Aspirin plus clopidogrel versus aspirin for secondary prevention of stroke in patients with lacunar stroke. Probability of the primary outcome is shown. The hazard ratio for the primary outcome, recurrent stroke, was 0.92 (95% CI 0.72 to 1.2). (From SPS3 Investigators. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. N Engl J Med 2012;367:817.)

The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, conducted in China, compared clopidogrel plus aspirin versus aspirin alone starting within 24 hours of minor ischemic stroke or high-risk TIA, with the combination continued for 21 days.[19] The combination reduced the risk of stroke (8.2% versus 11.7%; hazard ratio [HR], 0.68; 95% CI 0.57 to 0.81; $P < 0.001$) with no difference in hemorrhage (**Fig. 65.2**). Pending the results of similar trial in the United States, a short course of clopidogrel and aspirin started within 24 hours can be considered in patients with noncardioembolic minor stroke or high-risk TIA.[3] Long-term clopidogrel plus aspirin should not be used for stroke prophylaxis in patients at high risk or in patients with recent major stroke.[3]

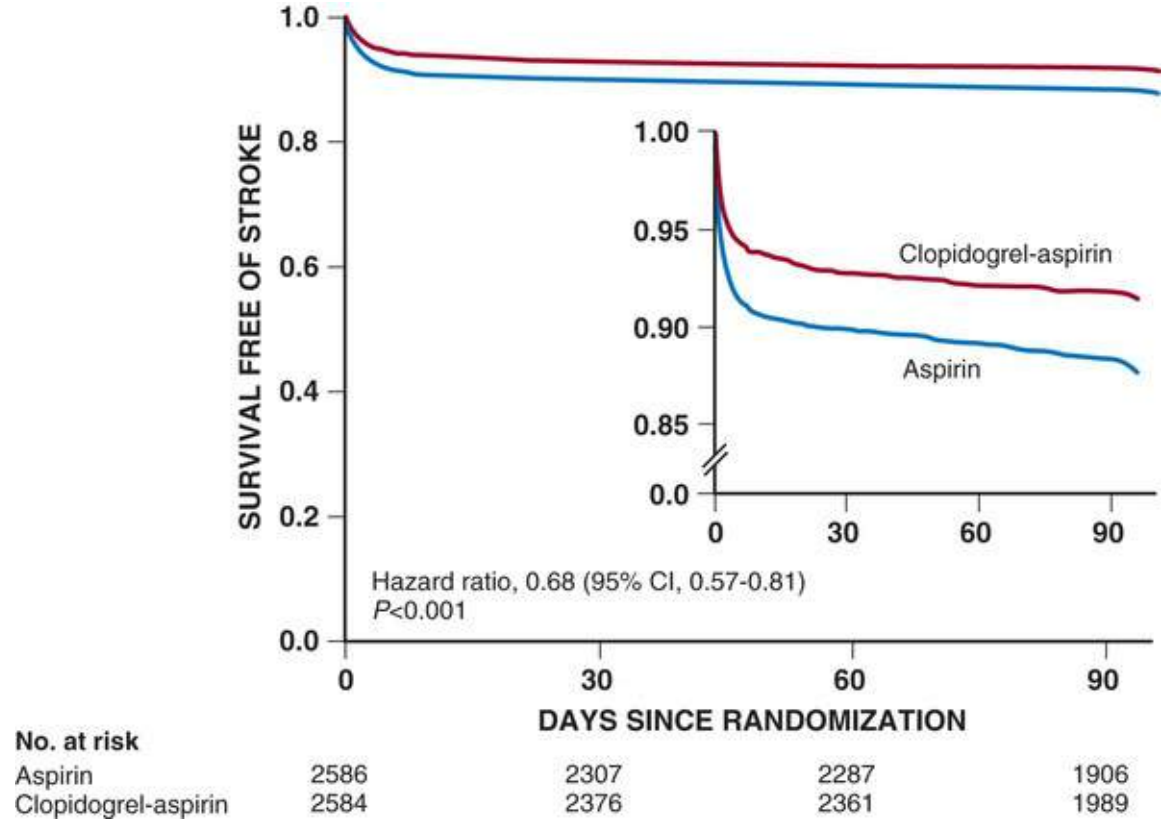
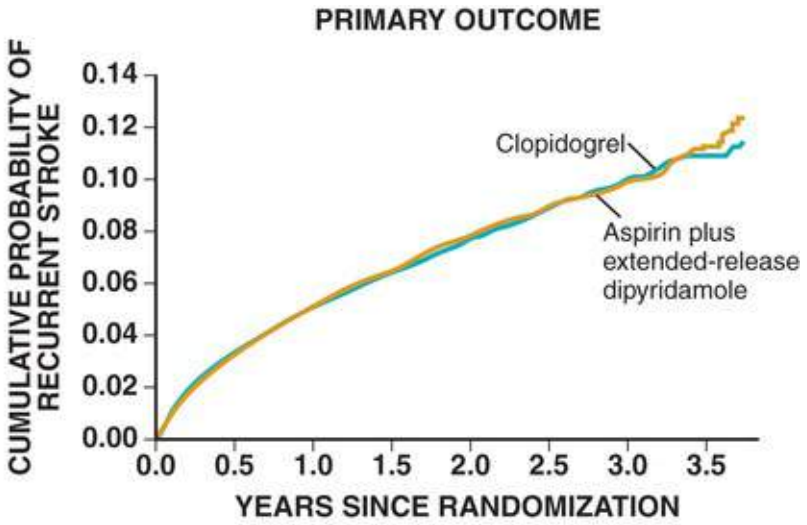


FIGURE 65.2 Effect of clopidogrel at an initial dose of 300 mg, followed by 75 mg/day for 90 days, plus aspirin (75 mg/day for first 21 days), versus placebo plus aspirin (75 mg/day for 90 days), on 90-day stroke risk in patients with minor stroke or TIA, with therapy started within 24 hours. (From Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 2013;369:11.)

A direct comparison found that aspirin plus dipyridamole was comparable to clopidogrel monotherapy for secondary stroke prevention in patients with noncardioembolic stroke[20] (**eFig. 65.3**). Aspirin, aspirin plus SR dipyridamole, and clopidogrel are reasonable options for secondary stroke prevention in these patients.[3]



No. at risk								
Aspirin plus extended-release dipyridamole	10,181	9715	9431	9146	6970	4426	2332	1060
Clopidogrel	10,151	9677	9371	9137	6934	4435	2331	1037

EFIGURE 65.3 Clopidogrel versus aspirin plus extended-release dipyridamole (ERDP) for secondary stroke prevention. The primary outcome is time to first recurrent stroke. (From Sacco RL, Diener HC, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. N Engl J Med 2008;359:1238.)

No prospective randomized trials available have assessed different antithrombotic regimens in patients who have a recurrent event while receiving an antiplatelet drug. A prospective registry study found a reduced composite of stroke, MI, and vascular death in patients who had a stroke while taking aspirin who were either switched to a different antiplatelet drug or who had a second antiplatelet added to aspirin[21] (**Fig. 65.3**)

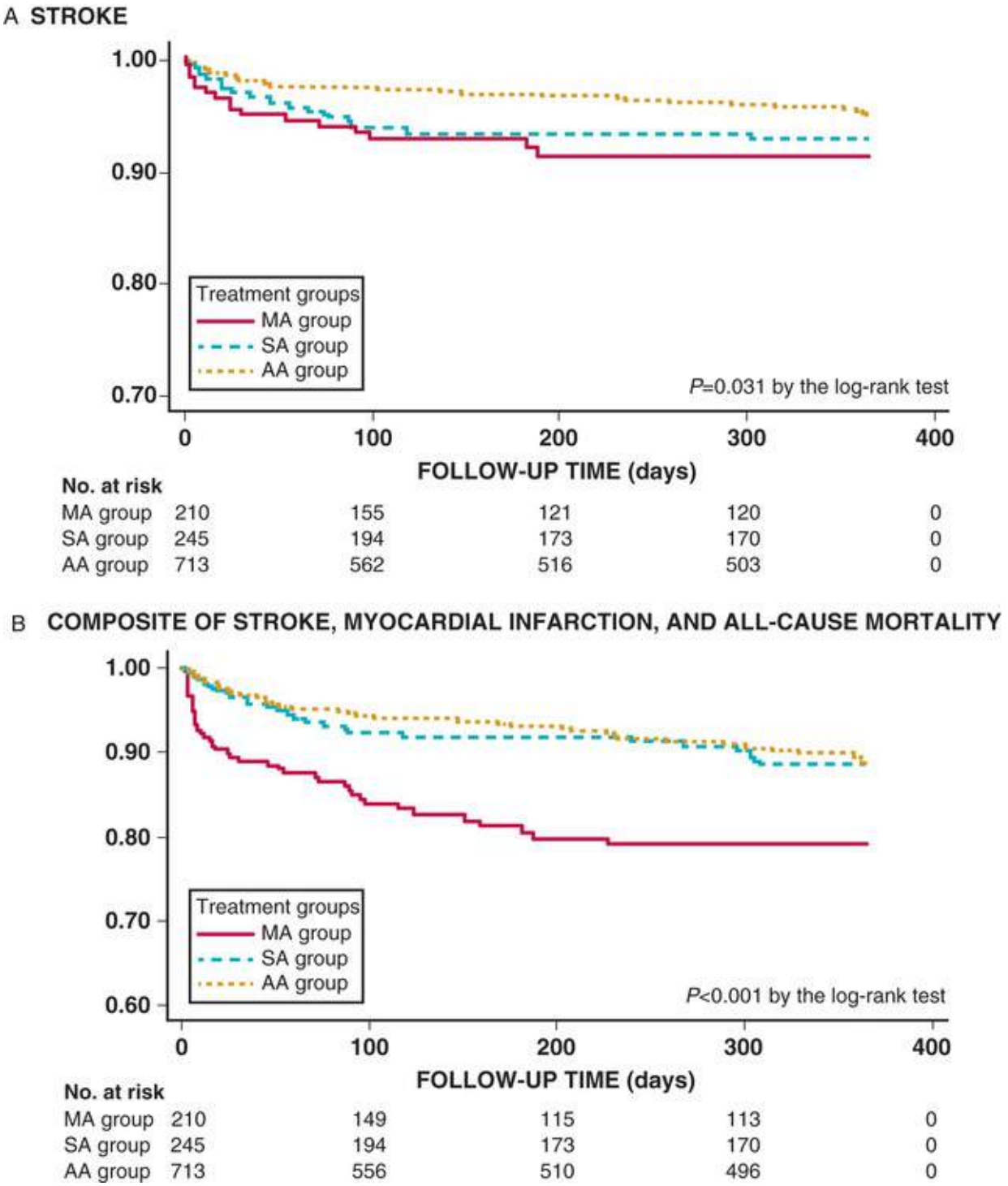


FIGURE 65.3 Effect of maintaining aspirin versus changing antiplatelet therapy in patients who had an ischemic stroke while on aspirin therapy, based on analysis of data from a prospective registry. **A,** Primary endpoint of stroke. **B,** Composite endpoint of stroke, myocardial infarction, and all-cause mortality. AA, Add another antiplatelet agent; MA, Maintain aspirin therapy; SA, Switch aspirin to a different anti-platelet agent. (From Kim JT, Park MS, Choi KH, et al. Different antiplatelet strategies in patients with new ischemic stroke while taking aspirin. Stroke 2016;47:128.)

Anticoagulation

Primary Prevention

The use of long-term anticoagulation to reduce the risk for a first cardiogenic embolism in patients at increased risk because of conditions such as mechanical heart valves, AF, and cardiomyopathy is addressed in **Chapters 25, 38, 63, and 93** and in **Part VIII**.

Secondary Prevention

Evidence supporting the use of anticoagulation for prevention of recurrent stroke in patients without AF or other high-risk cardiogenic sources is uncertain, or the evidence suggests that the benefit does not outweigh the risk for warfarin-associated bleeding complications. Thus, patients who have had a noncardioembolic ischemic stroke or TIA should receive antiplatelet agents rather than oral anticoagulation to reduce the risk for recurrent stroke and other CV events.[3]

Although based on a post hoc analysis, data from Warfarin-Aspirin Recurrent Stroke Study (WARSS) addressed "aspirin nonresponders." This term is used variably to refer to patients taking aspirin who have no measurable platelet antiaggregant effect or to patients who have a recurrent ischemic event such as stroke despite treatment. The WARSS analysis used the latter definition. Despite a high rate of recurrent stroke in patients failing aspirin therapy who were subsequently treated with aspirin, there was no advantage to switching from aspirin to warfarin (and as previously reviewed, no randomized trials have assessed the benefit of switching to an alternative platelet antiaggregant regimen in this setting).

The WASID (Warfarin-Aspirin Symptomatic Intracranial Disease) trial compared warfarin (international normalized ratio [INR] of 2 to 3) with aspirin (1300 mg/day).[22] The rate of recurrent ischemic stroke, intracerebral hemorrhage, or non–stroke-related vascular death did not differ between the two treatment regimens (22% with warfarin versus 21% with aspirin; $P = 0.83$), but the rate of major hemorrhage was higher with warfarin (8.3% versus 3.2%; $P = 0.01$). Because of a lack of efficacy and a higher rate of bleeding complications, warfarin should not generally be used for patients with symptomatic large-vessel intracranial steno-occlusive disease.[3] The SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) trial further showed superiority of aggressive medical management to angioplasty/stenting in patients with symptomatic, large-vessel intracranial steno-occlusive disease because of a high, early risk for stroke with endovascular treatment[23] (**Fig. 65.4**). Further work shows that intracranial atherosclerotic stenosis can regress with modern medical therapy.[24]

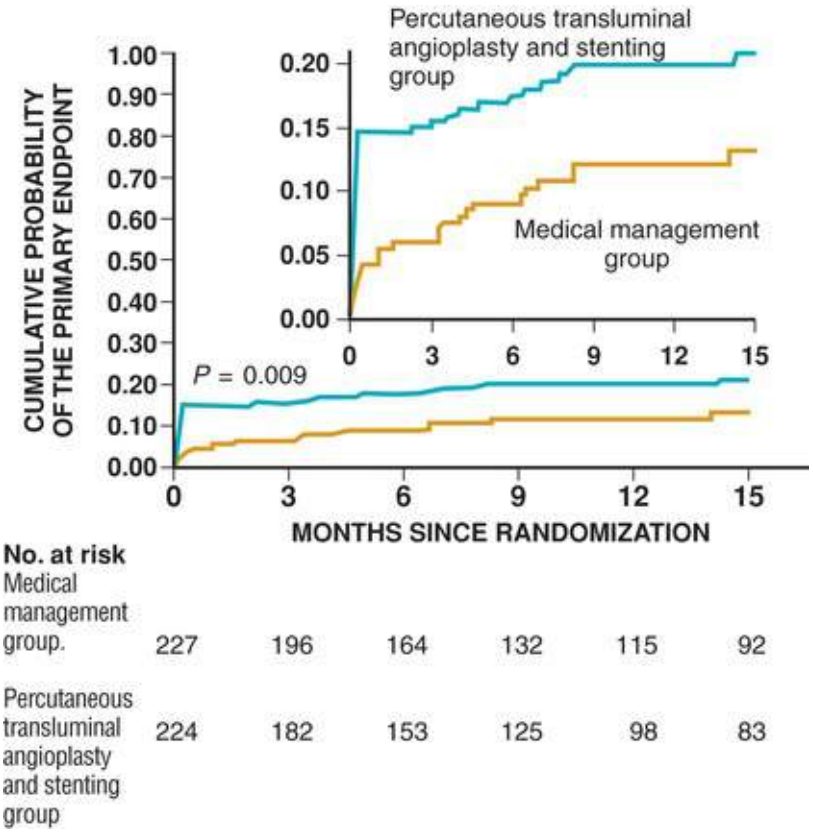


FIGURE 65.4 Percutaneous transluminal angioplasty and stenting plus medical therapy versus medical therapy alone in patients with symptomatic, high-grade intracranial stenosis. Kaplan-Meier curves for the cumulative probability of the primary endpoint according to treatment assignment are shown. The primary endpoint was stroke or death within 30 days after enrollment or after a revascularization procedure for the qualifying lesion during the follow-up period, or stroke in the territory of the qualifying artery beyond 30 days. The curves were truncated at 15 months, because relatively few patients have been followed beyond this time, and only two primary endpoint events have occurred beyond 15 months, both in the group receiving percutaneous transluminal angioplasty and stenting (PTAS) (one at 26.1 months and one at 26.2 months). The maximum duration of follow-up is 28.9 months for the group receiving medical management only and 28.1 months for the PTAS group. The **inset** shows the same data on an enlarged segment of the *y* axis. (From Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med 2011;365:993.)

Angioplasty and stenting in patients with an intracranial stenosis who "fail" medical therapy may still be considered under the U.S. Food and Drug Administration (FDA) Humanitarian Device Exemption with local institutional review board approval. The use of the procedure is restricted to those who have had a recurrent stroke in the territory of the stenosed artery despite medical therapy and should be avoided in the setting of an acute stroke.

Although a patent foramen ovale (PFO, with or without an atrial septal aneurysm) is found more frequently in young patients with cryptogenic stroke, optimal therapy for secondary stroke prophylaxis is uncertain. Indeed, the relationship between the presence of a PFO (whether large or small and with or without an atrial septal aneurysm) and the risk for *recurrent* stroke and death is not clear. A systematic literature review of 129 articles identified four meeting the minimal quality criteria and found, compared to those without a PFO, no significant increase in recurrent stroke or death for those with a PFO (odds ratio [OR], 0.95; 95% CI 0.62 to 1.44), a small PFO (OR, 1.23; 95% CI 0.76 to 2.00), a large PFO (OR, 0.59; 95% CI 0.28 to 1.24), or a combined PFO and atrial septal aneurysm (OR, 2.10; 95% CI 0.86 to 5.06).[25] This finding agrees with the results of the subsequently reported PICSS (PFO in Cryptogenic Stroke Study), which found almost identical rates of recurrent stroke or death regardless of the presence of a PFO.[26] An index was developed to help identify patients with cryptogenic stroke in whom a PFO is more likely pathogenic than incidental.[27]

Essentially no prospective randomized trials have compared antiplatelet and anticoagulant therapy in patients with cryptogenic stroke in the setting of PFO. In an exploratory analysis, PICSS investigators reported almost identical rates of recurrent stroke or death with aspirin or warfarin in those with and without a PFO.[26] Patients with a cryptogenic ischemic stroke or TIA and a PFO who do not have a venous source of paradoxical embolism or other indication for anticoagulation should receive antiplatelet therapy.[27]

Several randomized trials have assessed the potential benefits of endovascular PFO closure versus medical therapy and found no statistical benefit of closure (**see Chapter 75**). No individual trial of endovascular PFO closure to prevent recurrent stroke met its primary, prespecified endpoint, and meta-analysis did not show superiority of PFO closure to medical therapy for secondary prevention of cryptogenic stroke in patients with PFO[28] (**Fig. 65.5**). Transcatheter PFO closure is not recommended for secondary stroke prevention.[27] The current FDA Humanitarian Device Exemption for endovascular PFO closure with a device designed for that purpose requires the patient to have failed best medical therapy. Whether endovascular PFO closure benefits even this population is uncertain.

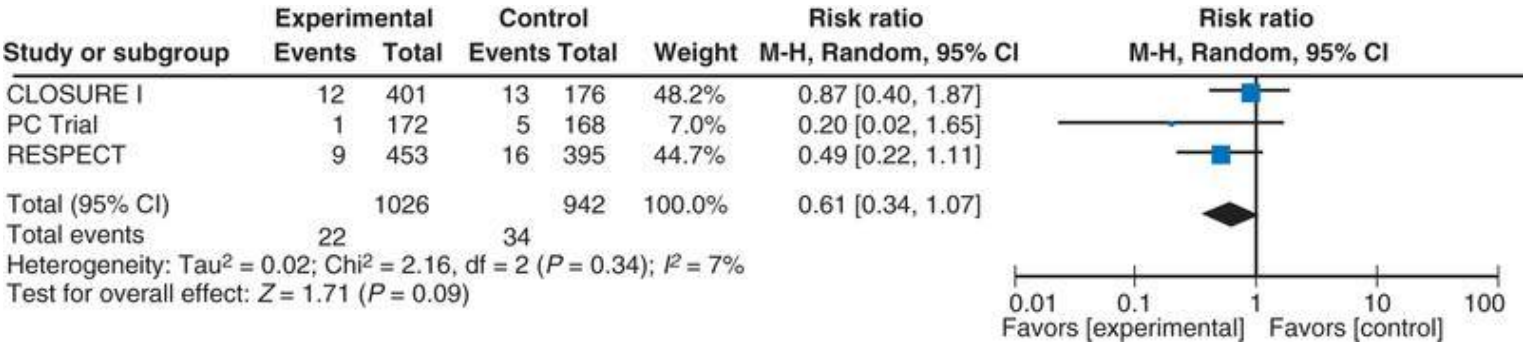


FIGURE 65.5 Meta-analysis of the risk of nonfatal ischemic stroke with patent foramen ovale closure versus medical therapy in patients with cryptogenic stroke. M-H, Mantel-Haenszel method. (From Spencer FA, Lopes LC, Kennedy SA, Guyatt G. Systematic review of percutaneous closure versus medical therapy in patients with cryptogenic stroke and patent foramen ovale. BMJ Open 2014;4:e004282.)

Patients with low–ejection fraction (EF) congestive heart failure (CHF) also have risk for systemic embolization, but data from large prospective randomized trials have not identified the optimal antithrombotic therapy for these patients. The WATCH (Warfarin and Antiplatelet Therapy in Chronic Heart Failure) trial compared open-label warfarin (target INR of 2.5 to 3.0) and double-blind treatment with either clopidogrel or aspirin in patients in sinus rhythm who had chronic CHF (EF <35%).[29] No differences were found between warfarin and aspirin (HR, 0.98; 95% CI 0.86 to 1.12; $P = 0.77$), between warfarin and clopidogrel (HR, 0.89; 95% CI 0.68 to 1.16; $P = 0.39$), or between clopidogrel and aspirin (HR, 1.08; 95% CI 0.83 to 1.40; $P = 0.57$) for the primary outcome (time until nonfatal stroke, nonfatal MI, or death). No evidence shows superiority of warfarin over aspirin or of clopidogrel over aspirin for prevention in stroke in patients with low-EF CHF. The WARCEF (Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction) trial compared warfarin (target INR of 2.0 to 3.5) with aspirin (325 mg/day) in patients in normal sinus rhythm who had a reduced left ventricular (LV) EF.[30] Ischemic stroke, intracerebral hemorrhage, or death from any cause (primary outcome) occurred at a rate of 7.47 events per 100 patient-years with warfarin versus 7.93 with aspirin (HR with warfarin, 0.93; 95% CI 0.79 to 1.10; $P = 0.40$). A reduction in ischemic stroke with warfarin was balanced by an increase in intracranial hemorrhage (**Fig. 65.6**). Taken together, WATCH and WARCEF found no reduction in stroke with warfarin versus aspirin in patients with CHF or low LVEF.

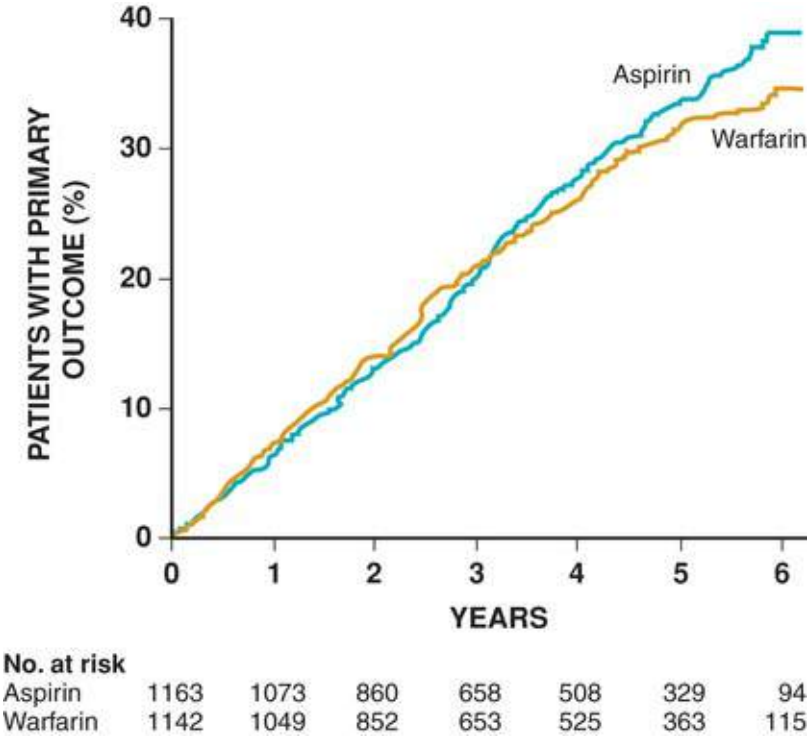


FIGURE 65.6 Warfarin versus aspirin in patients with heart failure and no atrial fibrillation. Cumulative incidence of the primary outcome is shown. The primary outcome was time to the first event in the composite endpoint of ischemic stroke, intracerebral hemorrhage, or death from any cause. (From Homma S, Thompson JLP, Pullicino PM, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med 2012;366:1859.)

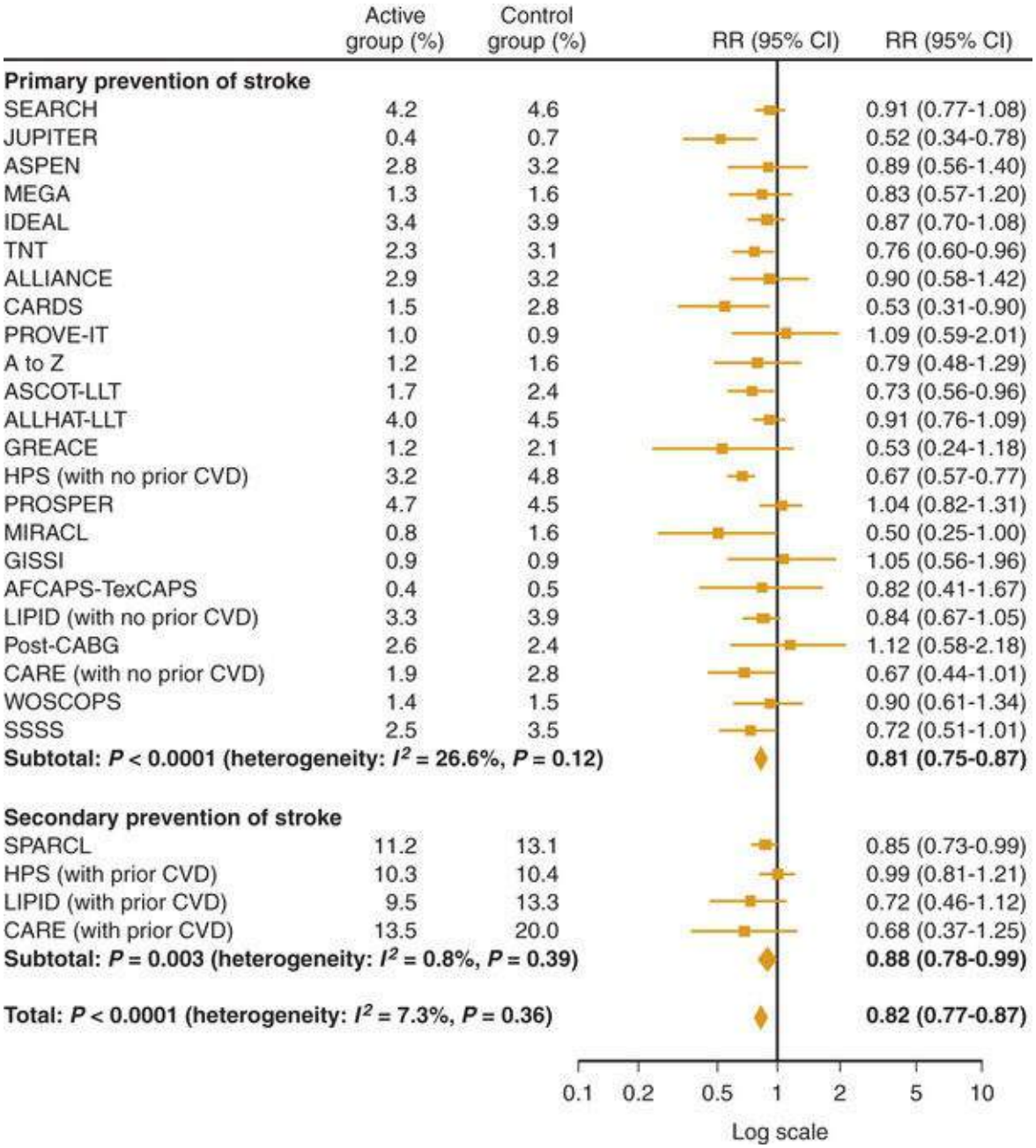
The various inherited (e.g., protein C, protein S, or antithrombin III deficiency; factor V Leiden; prothrombin G20210A mutation) and acquired (e.g., lupus anticoagulant, anticardiolipin or antiphospholipid antibodies) coagulopathies are more often associated with venous than with arterial thrombosis[31,32] (**see also Chapter 93**). Despite clear instances in which these types of disorders associate with ischemic stroke, particularly in children or young adults, causal relationships remain controversial. For example, in APASS (Antiphospholipid Antibody Stroke Study), another substudy of WARSS, 41% of 1770 participants were positive for one or more antiphospholipid antibody.[33] Rates of recurrent thromboembolic events were somewhat higher in those positive for antiphospholipid antibody, but outcomes did not differ between antibody-positive patients treated with warfarin or with aspirin. Patients with venous thromboembolic events who have an underlying coagulopathy or those with stroke or TIA otherwise fulfilling the criteria for antiphospholipid antibody syndrome (venous and arterial occlusive disease in multiple organs, miscarriages, and livedo reticularis) appropriately receive warfarin. Because thrombophilias (especially the genetic forms previously listed) are more frequently associated with venous thrombosis, cryptogenic stroke in this setting should prompt an evaluation for potential sources of paradoxical embolism. The yield of magnetic resonance imaging (MRI) of the pelvis and lower extremities is higher than that of Doppler ultrasound, and MRI should be considered in patients with a presumed paradoxical embolus.[34] In the absence of antiphospholipid antibody syndrome, those with arterial stroke who are found to have only elevated antiphospholipid antibody levels may reasonably be treated with antiplatelet therapy.[27]

Statins (See Chapters 45 and 48)

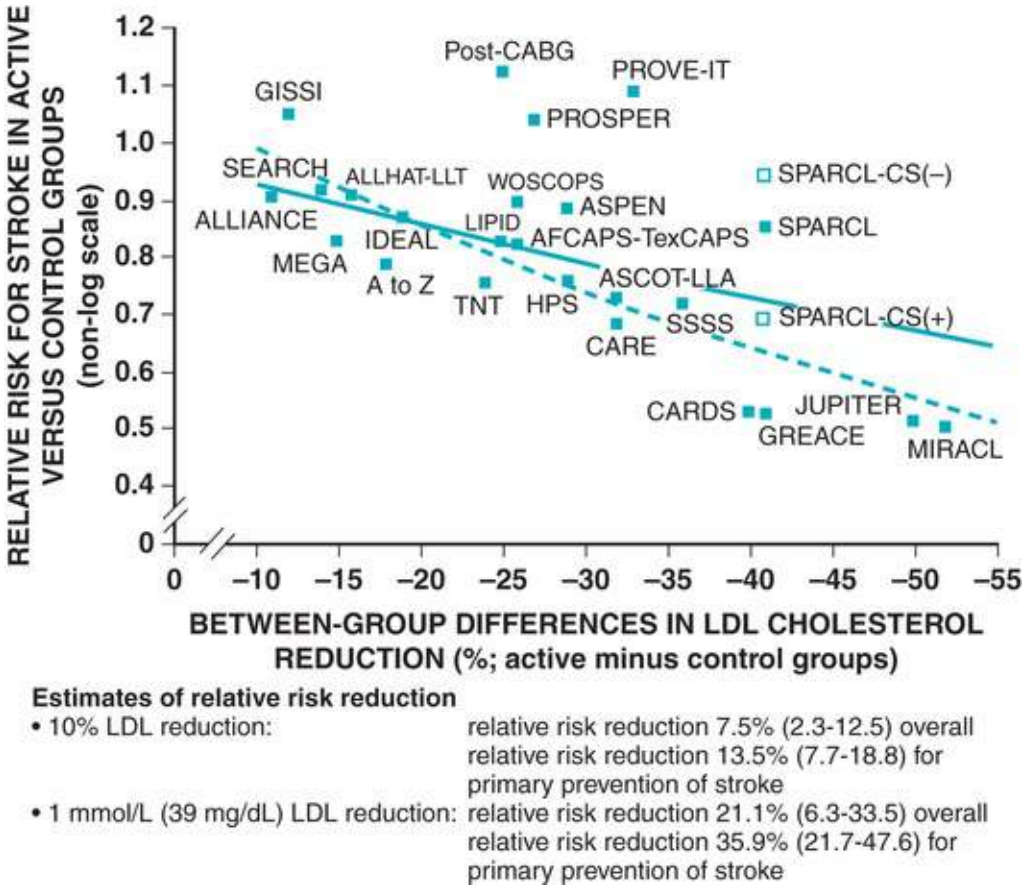
Primary Prevention

Treatment of patients with coronary heart disease (CHD) or those at elevated risk for CHD with

hydroxymethylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors (statins) reduces not only cardiac events, but also the risk for a first stroke[35] (**eFig. 65.4**). A meta-analysis of randomized trials of statins that included 165,792 participants found that each 40-mg/dL decrease in low-density lipoprotein (LDL) cholesterol was associated with a 21.1% (95% CI 6.3% to 33.5%; $P = 0.009$) reduction in the risk for a first stroke[35] (**eFig. 65.5**). Specific studies show a reduction in the risk for first stroke with statin treatment in patients with diabetes,[36,37] those with hypertension,[38] and older adults.[39]

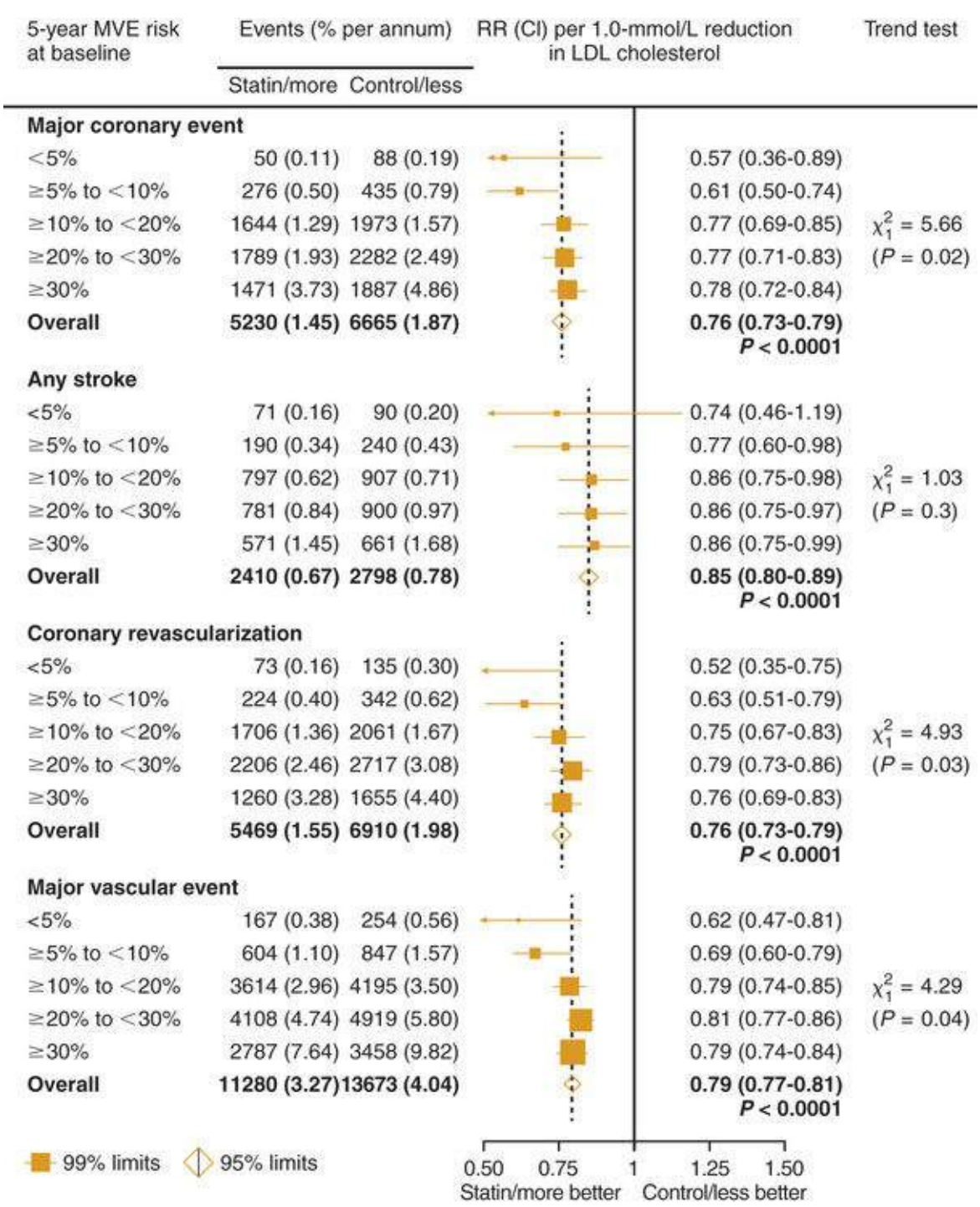


EFIGURE 65.4 Meta-analysis of the effects of statins on stroke prevention. Results are from 24 trials that included 165,792 patients with fatal and nonfatal stroke. CVD, Cardiovascular disease; RR, risk ratio. (From Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet Neurol 8:453, 2009; data on LIPID and CARE with or without prior CVD from Vergouwen MD, de Haan RJ, Vermeulen M, Roos YB: Statin treatment and the occurrence of hemorrhagic stroke in patients with a history of cerebrovascular disease. Stroke 2008;39:497.)



EFIGURE 65.5 Cholesterol lowering with statins and risk for stroke. Inverse variance-weighted regression lines have been plotted after including all 24 trials (165,792 patients; *solid line*) and excluding those with clearly identified groups of patients in secondary stroke prevention (SPARCL; HPS, LIPID, and CARE subgroups with previous cerebrovascular disease; *dashed line*). The underlying causes of stroke are important when considering the association between lipid and stroke risk, so the SPARCL results are also shown in accordance with the presence or absence of documented CS. Data for the SEARCH trial were presented at the 2008 American Heart Association meeting. CS, Carotid stenosis; LDL, low-density lipoprotein. (From Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet Neurol 2009;8:453.)

JUPITER (Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin) evaluated the effect of a statin in persons with higher than median (>2 mg/dL) level of high-sensitivity C-reactive protein who were not otherwise candidates for statin treatment.[40] In this group, statin treatment reduced stroke by approximately 50%. The benefit of stroke reduction with statin therapy may extend to those at lower (5% to 10% 5-year) risk for vascular events[41] (**eFig. 65.6**). The Heart Outcomes Prevention Evaluation (HOPE)–3 trial assessed the effect of rosuvastatin (10 mg daily) in CVD-free patients at intermediate (approximately 1% per year) risk.[42] Over 5.6 years, randomization to treatment led to a reduction death from CV causes, nonfatal MI, or nonfatal stroke from 4.8% to 3.7% (HR, 0.76; 95% CI 0.64 to 0.9; $P = 0.002$). Revascularization procedures, heart failure, and resuscitated cardiac arrest were reduced from 5.7% to 4.4% (HR, 0.75; 95% CI 0.64 to 0.88; $P < 0.001$). Stroke was reduced from 1.6% to 1.1% (HR, 0.70; range, 0.52 to 0.95). The AHA/American College of Cardiology (ACC) global risk calculator can be used to identify patients who are most likely to benefit from statin treatment.[43,44]



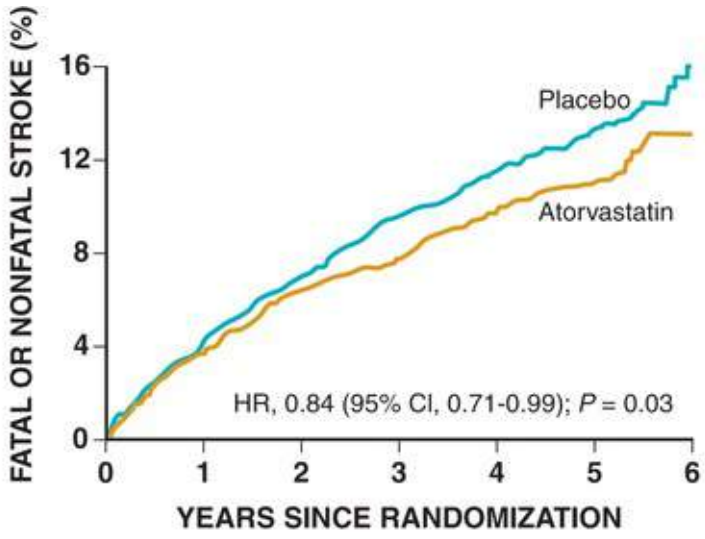
EFIGURE 65.6 Effects on major coronary events, strokes, coronary revascularization procedures, and major vascular events per 1.0-mmol/L reduction in low-density lipoprotein (LDL) cholesterol at different levels of risk. MVE, Major vascular event; RR, relative risk. (From Cholesterol Treatment Trialists' [CTT] Collaborators: The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581.)

Secondary Prevention

The HPS (Heart Protection Study) included 3280 patients with a history of stroke (including 1820 with stroke and no history of CHD) who were treated with either a statin or placebo.[45] In those with a previous history of stroke, statin treatment reduced the frequency of major vascular events (MVEs: MI, stroke, revascularization procedure, or vascular death) by 20%, but did not lower the risk for recurrent stroke (occurring in 10.5% of placebo versus 10.4% of statin group). The most important explanation might be that patients were randomized an average of approximately 4 years after the index event. Most recurrent strokes occur soon (within the first few years), so those randomized in the HPS had a relatively low risk

for recurrent stroke.

The SPARCL (Stroke Prevention with Aggressive Reduction in Cholesterol Levels) trial randomly assigned more than 4700 patients within 6 months of a noncardioembolic stroke or TIA and no known CHD to high-dose statin or placebo for a primary endpoint of the first occurrence of a nonfatal or fatal stroke.[46] Those randomized to high-dose statin treatment had a 16% relative reduction in nonfatal or fatal stroke, as well as a 35% relative reduction in major coronary events. Added to the previous data on prevention of a first stroke, SPARCL showed that treatment with a high-dose statin can reduce the risk for recurrent stroke after stroke or TIA (**eFig. 65.7**). On the basis of this trial, patients with atherosclerotic ischemic stroke or TIA and without known CHD should receive high-intensity statin therapy to reduce the risk for stroke and other CV events.[3]



EFIGURE 65.7 Effect of statin therapy on stroke in patients with a recent stroke or TIA. The Kaplan-Meier curve for stroke or TIA in SPARCL is shown. The data report an intention-to-treat analysis with prespecified adjustments for geographic region, entry event, time since the entry event, sex, and baseline age for the first occurrence of a fatal or nonfatal stroke or TIA. HR, Hazard ratio. (From Amarenco P, Bogousslavsky J, Callahan AIII, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549.)

Antihypertensives (See Chapters 46 and 47)

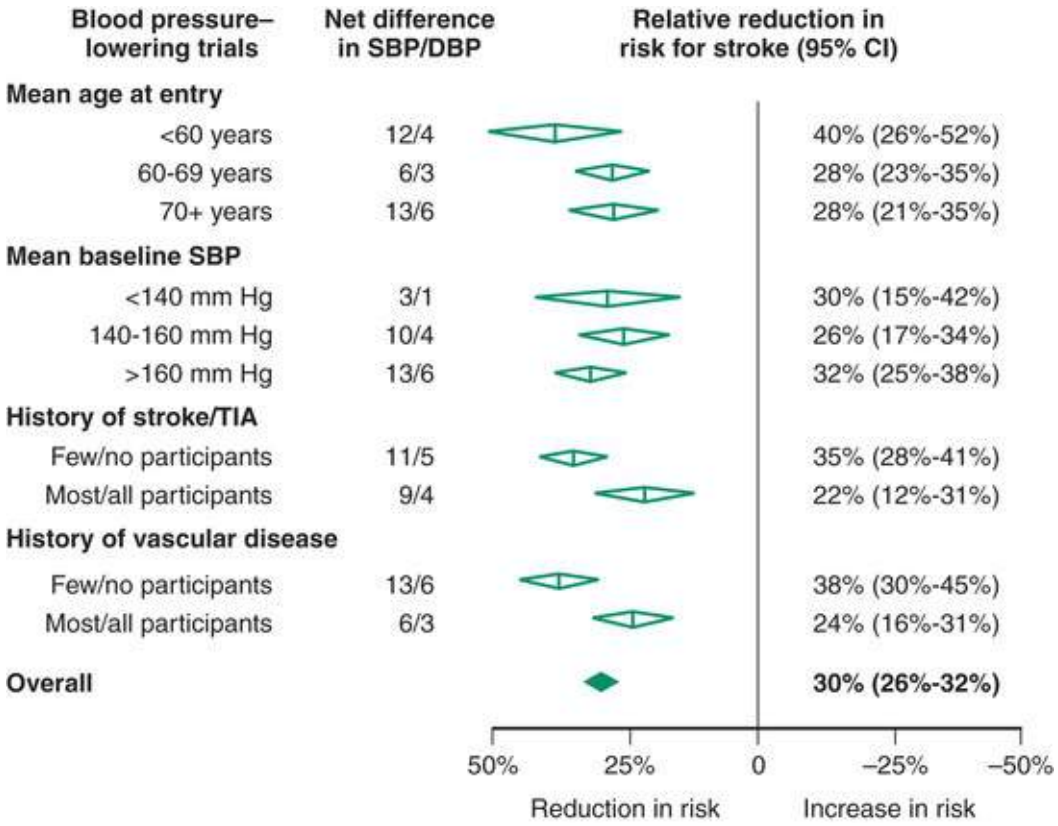
Primary Prevention

Hypertension is one of the most important treatable risk factors for both ischemic stroke and parenchymal intracerebral hemorrhage. Although a specific antihypertensive regimen must be individualized, reduction in blood pressure (BP) is generally more important than the specific agent or agents used.[31,47]

The Systolic Blood Pressure Intervention Trial (SPRINT) compared the benefit of treatment of systolic blood pressure (SBP) to a target of lower than 120 mm Hg with treatment to a target of lower than 140 mm Hg in patients at increased risk of CV events who had SBP of 130 to 180 mm Hg.[48] Stroke fell from 1.5% to 1.3% annually, but the difference was not significant (HR, 0.89; 95% CI 0.63 to 1.25; $P = 0.50$). The HOPE-3 trial also evaluated an antihypertensive regimen in people at intermediate risk without CVD and showed no overall benefit.[49] Explanations for this neutral result include the choice of

antihypertensives (candesartan and hydrochlorothiazide) and the small reduction in BP with treatment (mean, 6/3 mm Hg).

An earlier meta-analysis of randomized controlled trials (RCTs) comparing antihypertensive drugs with placebo or no treatment with more than 73,500 participants who had almost 2900 stroke events found similar risk reductions with angiotensin-converting enzyme (ACE) inhibitors (28%), beta-adrenergic receptor blockers (beta blockers) or diuretics (35%), and calcium channel antagonists (39%), with average BP reduction of 5/2, 13/6, and 10/5 mm Hg, respectively[50] (**eFig. 65.8**). Subsequent work suggests that stroke reduction may be less in the setting of higher BP variability.[51,52] Beta blockers are associated with greater BP variability than other classes of antihypertensives and may be less effective.[53] Chlorthalidone may be more effective than hydrochlorothiazide in reducing CV events.[54]



EFIGURE 65.8 Randomized controlled trials comparing antihypertensive drugs with a placebo (or no treatment) by subgroup. The meta-analyses of blood pressure–lowering trials were stratified into subgroups on the basis of mean age of trial participants at entry, baseline systolic blood pressure (SBP) level, and whether trial participants predominantly had a history of stroke/transient ischemic attack (TIA) or vascular disease. The *diamonds* are centered on the pooled estimate of effect and represent 95% CIs. The *solid diamond* represents the pooled relative risk and 95% CI for all contributing trials. DBP, Diastolic blood pressure. (From Lawes CM, Bennett DA, Feigin FL, Rodgers A. Blood pressure and stroke: an overview of published reviews. Stroke 2004;35:1024.)

Secondary Prevention

A meta-analysis including 16 RCTs of BP lowering for secondary prevention of stroke in 40,292 participants found an 18% (95% CI 9% to 26%) relative risk reduction in recurrent stroke with treatment[55] (**Fig. 65.7**). Each 10–mm Hg reduction in SBP is associated with a 33% (95% CI 9% to 51%) reduction in recurrent stroke. Data on the relative benefits of specific antihypertensive regimens for secondary prevention of stroke are sparse. Another meta-analysis found a reduction in recurrent stroke with diuretics (32%) and with diuretics plus ACE inhibitors (45%), but not with beta blockers or ACE

inhibitors used alone.[56] The overall reductions in both stroke and all vascular events were related to the degree of BP lowering.

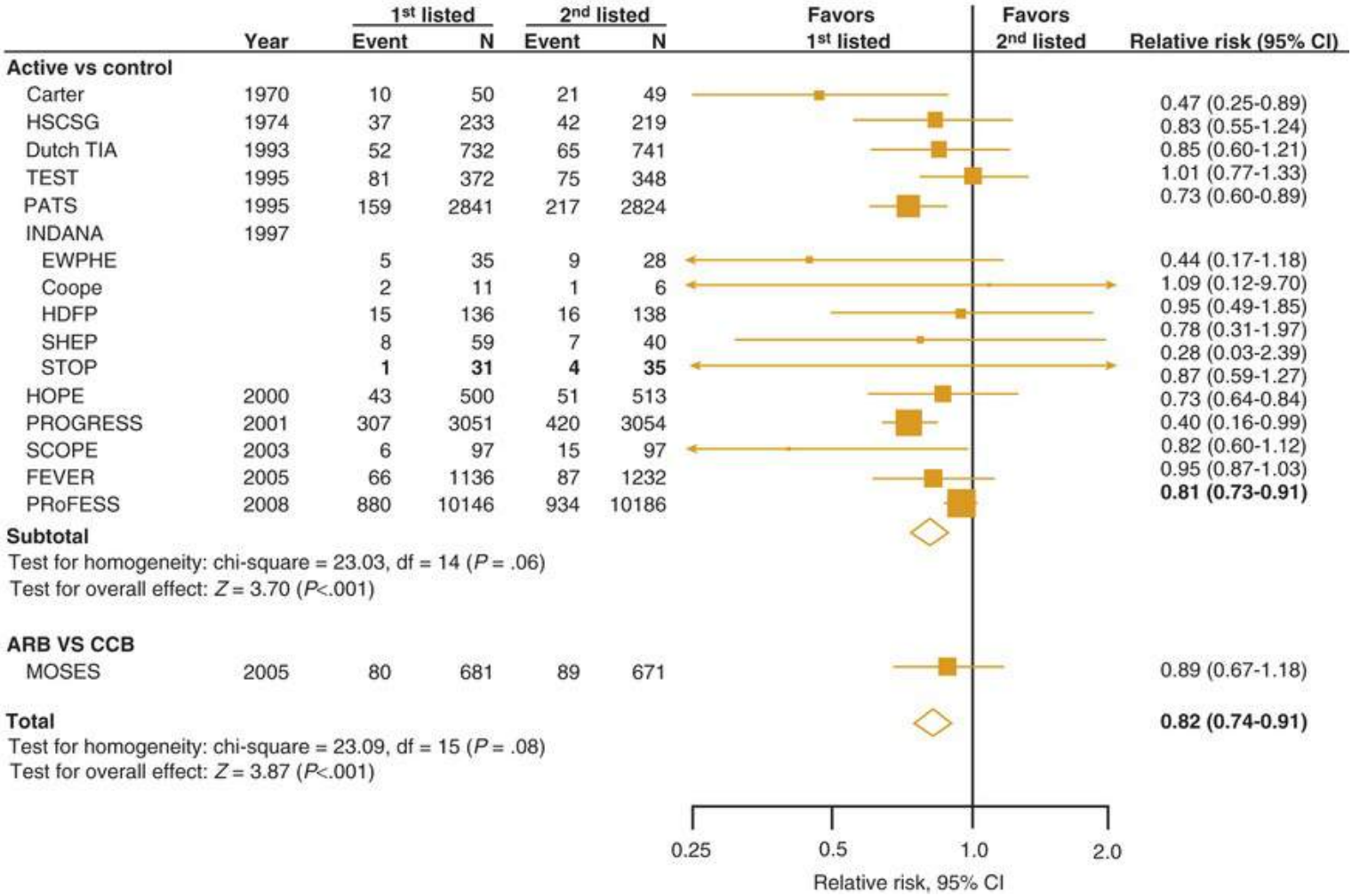


FIGURE 65.7 Meta-analysis of randomized controlled trials of blood pressure lowering for secondary prevention of stroke. ARB, Angiotensin receptor blocker; CCB, calcium channel blocker. (From Arima H, Chalmers J. PROGRESS: prevention of recurrent stroke. J Clin Hypertens 2011;13:693.)

Whether ACE inhibitors have a specific benefit in reducing recurrent stroke risk also remains uncertain. The HOPE study compared the effects of an ACE inhibitor and placebo in high-risk persons and found a 24% reduction in the risk for stroke, MI, or vascular death in 1013 patients with a history of stroke or TIA.[57] PROGRESS (Perindopril Protection Against Recurrent Stroke Study) tested the effects of a BP-lowering regimen, including an ACE inhibitor, in 6105 patients with stroke or TIA within the previous 5 years.[3] Randomization was stratified by intention to use single (ACE inhibitor) or combination (ACE inhibitor plus diuretic indapamide) therapy in hypertensive (>160 mm Hg systolic or >90 mm Hg diastolic) and in nonhypertensive patients. The combination, which reduced BP by an average of 12/5 mm Hg, led to a 43% reduction in recurrent stroke and a 40% reduction in MVEs, with the effect present in both hypertensive and normotensive groups. Monotherapy with either agent showed no significant benefit. Specific patient characteristics and comorbid conditions should guide the choice of a specific antihypertensive regimen.

Diabetes and Glucose Intolerance

There remains no evidence that tight control of diabetes decreases stroke risk in primary or secondary prevention settings. As previously reviewed, management of BP and use of statins reduce stroke risk in patients with diabetes.

The Insulin Resistance Intervention after Stroke (IRIS) trial tested the hypothesis that pioglitazone reduces the rates of stroke and MI after ischemic stroke or TIA in patients without diabetes who have insulin resistance.[58] Over 4.8 years, stroke or MI occurred in 9.0% of the pioglitazone group and 11.8% of the placebo group (HR in pioglitazone group, 0.76; 95% CI 0.62 to 0.93; $P = 0.007$) (**Fig. 65.8**). The primary complications of treatment were a greater frequency of more than 4.5 kg of weight gain (52.2% versus 33.7%; $P < 0.001$), edema (35.6% versus 24.9%; $P < 0.001$), and bone fracture requiring surgery or hospitalization (5.1% versus 3.2%; $P = 0.003$).

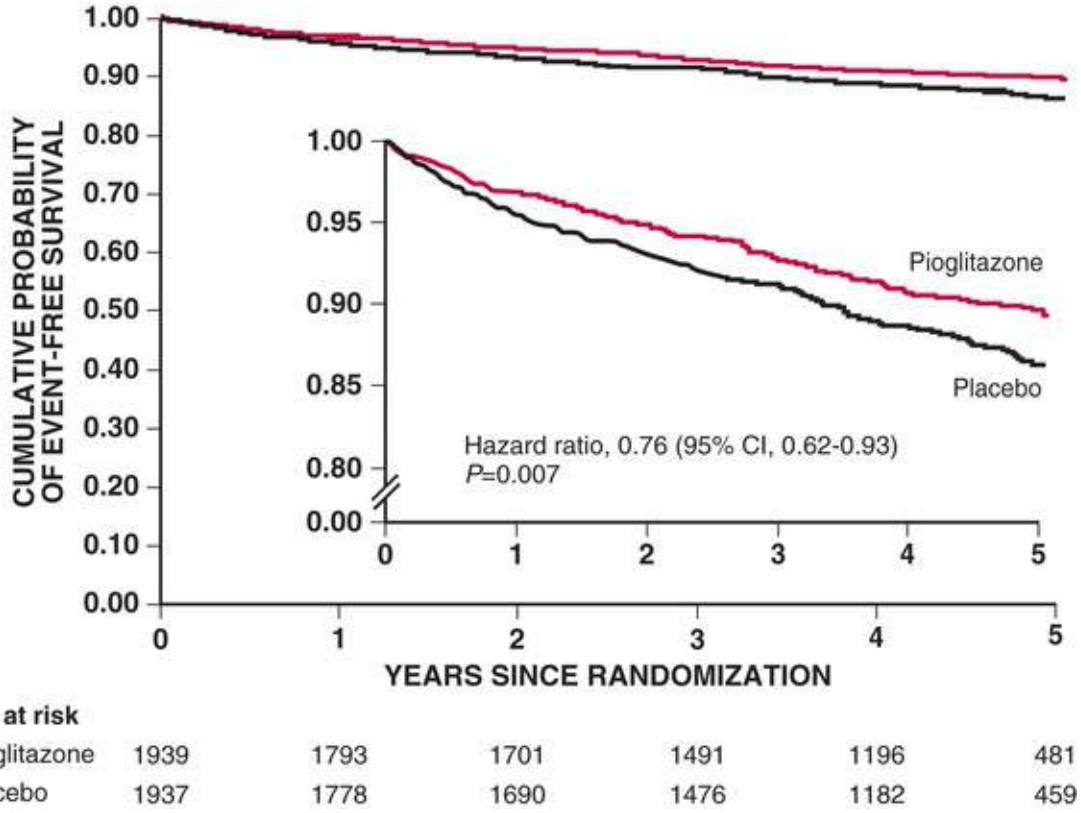


FIGURE 65.8 Effect of pioglitazone on the risk of stroke and myocardial infarction in patients with insulin resistance but no diabetes who had a recent stroke or transient ischemic attack. (From Kernan WN, Viscoli CM, Furie KL, et al. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med 2016;374:1321.)

Management of Acute Ischemic Stroke

In patients presenting with a neurologic deficit suggesting an acute ischemic stroke, we use the approach shown in **Fig. 65.9**. As with acute coronary syndromes (ACS), time is of the essence in the treatment of patients with acute ischemic stroke. Stroke has numerous causes and potential pathophysiologic mechanisms that provide the rationale for tailoring secondary preventive therapies. A variety of conditions may cause symptoms and signs that can be mistaken for those of a stroke. The onset of ischemic symptoms mandates a prompt evaluation of whether the patient should receive reperfusion therapy (**Fig. 65.9**).

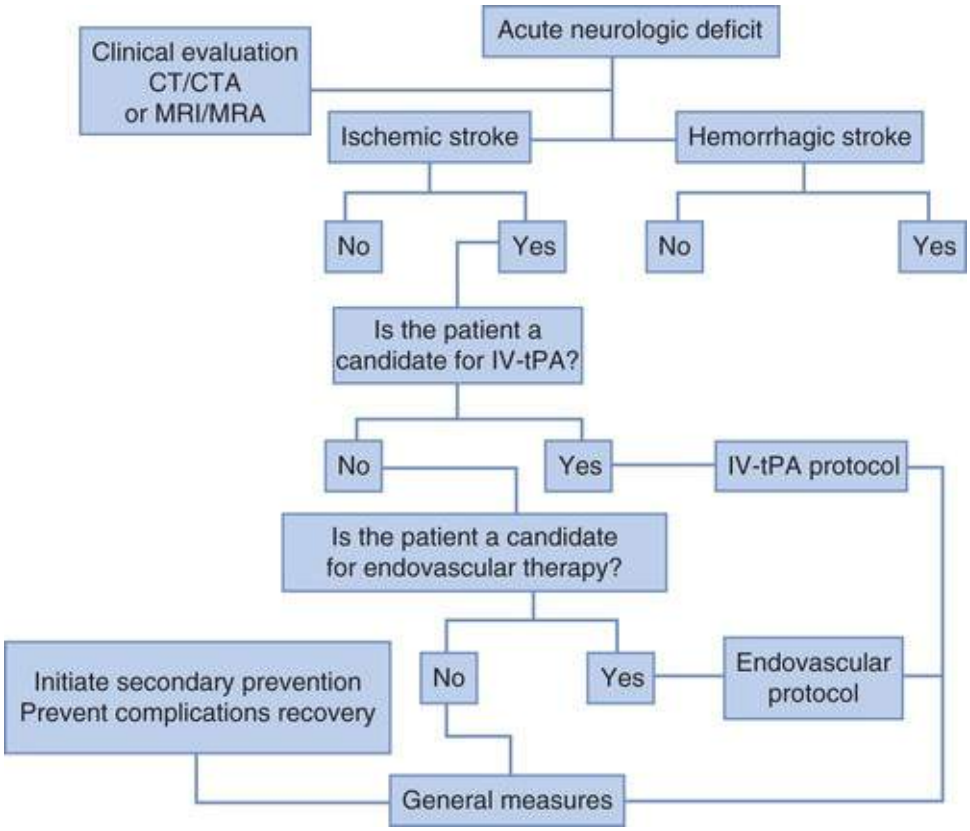


FIGURE 65.9 Example of approach to patients with symptoms suggestive of acute ischemic stroke. Patients presenting with an acute neurologic deficit are first rapidly evaluated to exclude other conditions and brain hemorrhage. This includes neuroimaging, as well as vascular imaging to guide further intervention and management, particularly in those with suspected large artery occlusion who might be candidates for endovascular therapy. CT, Computed tomography; CTA, CT angiography; IV-tPA, intravenous tissue plasminogen activator; MRI, magnetic resonance imaging; MRA, MR angiography. (Modified from Goldstein LB. Modern medical management of acute ischemic stroke. Methodist DeBakey Cardiovasc J 2014;10:39.)

The reliable and valid National Institutes of Health Stroke Scale (NIHSS) serves as a measure of stroke severity. It is used to monitor stroke patients for clinical worsening or improvement and to help determine a patient's candidacy for intravenous tissue plasminogen activator (IV t-PA).[59]

Intravenous Recombinant Tissue Plasminogen Activator

Only IV recombinant t-PA (rt-PA, alteplase) has received FDA approval for pharmacologic treatment of acute ischemic stroke. Treatment of appropriate patients with rt-PA thrombolytic therapy is associated with an approximate 13% absolute (32% relative) increase in the proportion of patients who are free of disability 3 months later.[4] Benefits are similar in those with ischemic stroke involving small penetrating arteries and in those with occlusion of larger intracranial arteries. Although this treatment is also associated with an increased risk for hemorrhage (6.4% risk for symptomatic intracerebral hemorrhage with treatment versus 0.6% with placebo; 2.9% risk for fatal hemorrhage versus 0.3% with placebo), the strategy yields net clinical benefit (improvement in outcomes previously cited includes adverse bleeding effects). Based on national guidelines, alteplase must be given within 4.5 hours of the onset of symptoms, which means that the patient must generally arrive at a properly equipped and organized hospital within 3.5 hours of symptom onset to have the necessary evaluations completed, including brain computed tomography (CT) to exclude hemorrhage or other conditions (**Fig. 65.9**). Within this “window,” the sooner treatment can be initiated, the greater the likelihood of a favorable response[60] (**Fig. 65.10**). Although there is a trend toward an increased risk of intracerebral hemorrhage with IV t-PA within this period, the effect

is not significant.

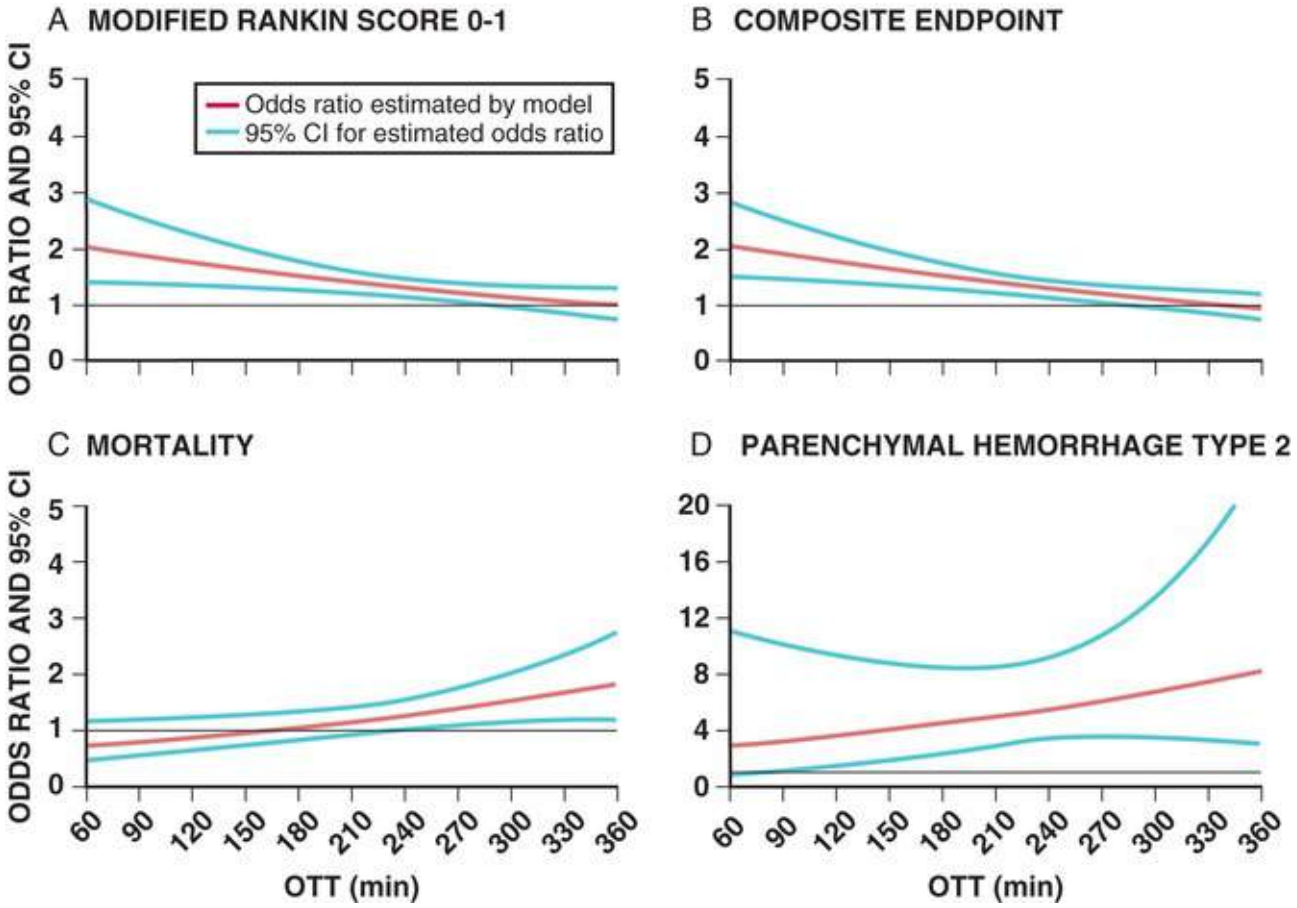


FIGURE 65.10 Pooled clinical trial analysis of the relationship between lag between stroke onset to start of treatment (OTT) with intravenous tissue plasminogen activator (t-PA) on the treatment effect after adjustment for prognostic variables. (From Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010;375:1695.)

Clinical guidelines for treatment with IV t-PA initially reflected a strict protocol that closely followed those used in the clinical trials on which the use of alteplase was based.[61] These guidelines were revised based on subsequent data and extensive clinical experience[6] (**Tables 65.2 and 65.3**). Many of decisions rely on clinical judgment. Furthermore, guideline-based recommendations do not align completely with the FDA product labeling. For example, although AHA/ASA guidelines endorse treatment of selected patients up to 4.5 hours after symptom onset, the FDA approval is limited to those who can be treated within 3 hours (**Table 65.2**). The development of organized systems of stroke care should optimize prompt clinical evaluations, minimize delays in treatment, ensure institution of other interventions that improve outcomes, and ensure that patients receive appropriate secondary prevention.[62]

TABLE 65.2

Comparison of Recommendations for Treatment with Intravenous Alteplase (T-PA)

2013 AHA/ASA GUIDELINE[61]	2016 AHA/ASA REVISION[6]	2016 FDA LABELING
Inclusion		
Ischemic stroke causing measurable neurologic deficit	Ischemic stroke causing measurable neurologic deficit. (Class I, LOE A)	Acute ischemic stroke; exclude acute ICH
Onset of symptoms <4.5 hr before beginning treatment	<3 hr (Class I, LOE A) 3-4.5 hr (Class I, LOE B)	Onset of symptoms <3 hr before beginning treatment
Age ≥18 yr	For patients ≥18 years old, treatment equally recommended for	Pediatric use not established; age

	those <80 and >80 years; older patients have poorer outcomes, higher mortality, and higher rates of sICH than those <80 years, but compared with controls, treatment provides a better chance of being independent at 3 mo across all age-groups. (Class I, LOE A) The efficacy and risk of treatment in neonates, children, and adolescents <18 yo are not well established. (Class IIb, LOE B)	>77 yr is one of several interrelated baseline characteristics associated with increased risk of ICH; data suggest a reduced but still favorable clinical outcome.
Exclusions		
Previous stroke <3 mo	Treatment may be harmful. (Class III, LOE B) The potential for increased risk of sICH and associated morbidity and mortality exists but is not well established. (Class IIb, LOE B)	None
Significant head trauma <3 mo	Contraindicated	Contraindicated
Major trauma <14 days	Treatment may be considered; weigh the risks of bleeding from trauma-related injuries against the severity and potential disability from the stroke. (Class IIb; LOE C)	None
Symptoms suggesting SAH	Contraindicated (Class III; LOE C)	Contraindicated
Arterial puncture at noncompressible <7 days	Safety and efficacy are uncertain. (Class IIb, LOE C)	None
History of ICH	Treatment in setting of cerebral microbleeds is reasonable. (Class IIa, LOE B) Treatment of patients with a history of ICH is potentially harmful. (Class III, LOE C)	None
Intracranial neoplasm, AVM, or aneurysm	Treatment is reasonable and probably recommended in patients with a <10 mm unruptured and unsecured intracranial aneurysm. (Class IIa, LOE C) Usefulness and risks with larger aneurysms are not well established. (Class IIb, LOE C) Usefulness and risks with AVM are not well established (Class IIb, LOE C); treatment may be considered in setting of severe deficits and high likelihood of morbidity and mortality that would outweigh anticipated risk of ICH. (Class IIb, LOE C) Probably recommended in setting of extra-axial intracranial neoplasm. (Class IIa, LOE C) Potentially harmful in setting of an intra-axial intracranial neoplasm. (Class III, LOE C)	Contraindicated in the presence of intracranial conditions that may increase the risk of bleeding
Intracranial or intraspinal surgery <3 mo	Potentially harmful (Class III, LOE C)	Contraindicated
Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)	Treat if BP can be lowered to <185/110 mm Hg with antihypertensive agents with assessment of stability of BP before starting treatment. (Class I, LOE B) BP should be maintained <180/105 mm Hg for at least the first 24 hours after treatment. (Class I, LOE B)	Contraindicated in setting of current severe uncontrolled hypertension; no specific BP values; warning for BP >175/110 mm Hg
Active internal bleeding	-	Contraindicated
Acute bleeding diathesis, including but not limited to: platelets <100,000/mm^3, heparin <48 hr with APTT greater than ULNl, anticoagulant with INR >1.7 or PT >15 sec; current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (APTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)	Treatment not recommended if platelets <100,000/mm^3, INR >1.7, APTT >40 sec, or PT >15 sec. (Class III, LOE C) Treatment in patients who received dose of LMWH (prophylactic or therapeutic) <24 hr is not recommended. (Class III, LOE B) Treatment of patients taking direct thrombin inhibitors or direct factor Xa inhibitors is not recommended unless laboratory tests such as APTT, INR, platelet count, ECT, TT, or appropriate direct factor Xa activity assays are normal, or patient has not received dose of these agents for >48 hr (assuming normal renal function). (Class III, LOE C) It is reasonable not to delay treatment pending hematologic or coagulation testing if there is no reason to suspect abnormal test. (Class IIa, LOE B)	Contraindicated for bleeding diathesis (no laboratory values or specific examples)
Blood glucose concentration <50 mg/dL or >400 mg/dL	Hypoglycemia and hyperglycemia may mimic acute stroke; blood glucose should be checked before treatment, (Class III, LOE B) Recommended with initial glucose levels >50 mg/ dL. (Class I, LOE A) Treatment may be reasonable if initial glucose is >400 mg/dL and subsequently normalizes. (Class IIb, LOE C)	None
CT demonstrating multilobar infarction (hypodensity > 1/3 cerebral hemisphere)	Recommended in the setting of mild to moderate early ischemic changes (other than frank hypodensity). (Class I, LOE A) Evidence is insufficient to identify a threshold of hypoattenuation severity or extent that affects treatment response; however, treatment in the setting CT brain imaging showing extensive regions of clear hypoattenuation is not recommended. (Class III, LOE A)	None
Severe stroke	Benefit remains despite increased risk of hemorrhagic transformation. (Cass I, LOE A)	None
Relative Exclusions		
Minor symptoms	No exclusion for mild but disabling stroke symptoms. (Cass I, LOE A) Treatment for nondisabling symptoms can be considered. (Class IIb, LOE C)	None
Rapidly improving symptoms	Reasonable in setting of moderate to severe stroke and early improvement, but with continued moderate and potentially disabling symptoms. (Class IIa, LOE A) Delaying treatment to monitor for continued improvement not recommended. (Class III, LOE C)	None

Pregnancy	May be treated when anticipated benefits of treating moderate to severe stroke outweigh anticipated increased risks of uterine bleeding. (Class IIb, LOE C) Safety and efficacy <14 days after delivery have not been well established. (Class IIb, LOE C)	Pregnancy category C
Seizure at onset with postictal residual neurologic impairments	Treatment is reasonable if the residual impairments are thought secondary to stroke and not a postictal phenomenon. (Class IIa, LOE C)	None
Major surgery or serious trauma <14 days	The potential increased risk of surgical site hemorrhage should be weighed against anticipated benefits of reduced stroke-related neurologic deficits. (Class IIb, LOE C)	None
GI or urinary tract hemorrhage <21 days	Patients with structural GI malignancy or bleeding <21 days should be considered high risk; treatment is potentially harmful. (Class III, LOE C) Treatment of patients with past GI/GU bleeding may be reasonable. (Class IIb, LOE C)	Warning for GI or GU bleeding
Acute MI <3 months)	Reasonable if the recent MI was non-STEMI. (Class IIa, LOE C) Reasonable if the recent MI was STEMI involving right or inferior myocardium. (Class IIa, LOE C) May be reasonable if the recent MI was STEMI involving left anterior myocardium. (Class IIb, LOE C) For patients with concurrent acute ischemic stroke and acute MI, treatment with IV t-PA at the dose appropriate for stroke, followed by PTCA and stenting if indicated, is reasonable. (Class IIa, LOE C)	None
Additional Relative Exclusions 3 to 4.5 Hours*		
Aged >80 years	Treatment is safe and can be as effective as in younger patients. (Class IIa, LOE B)	NA
NIHSS >25	Benefit is uncertain. (Class IIb, LOE C)	NA
Taking oral anticoagulant regardless of INR	Safe and may be beneficial if taking warfarin with an INR<1.7. (Class IIb, LOE B)	NA
History of both diabetes and prior ischemic stroke	May be as effective as treatment in the 0- to 3-hr window and may be a reasonable option. (Class IIb, LOE B)	NA

*Treatment not FDA approved between 3 and 4.5 hours.

AHA/ASA, American Heart Association/American Stroke Association; *FDA,* US Food and Drug Administration; *LOE,* Level of evidence; *APTT,* activated partial thromboplastin time; *AVM,* arteriovenous malformation; *CT,* computed tomography; *ECT,* ecarin clotting time; *GI,* gastrointestinal; *GU,* genitourinary; *ICH,* intracranial/cerebral hemorrhage; *sICH,* subdural ICH; *INR,* international normalized ratio; *IV t-PA,* intravenous tissue plasminogen activator; *LMWH,* low-molecular-weight heparin; *MI,* myocardial infarction; *NA,* not applicable; *NIHSS,* National Institutes of Health Stroke Scale; *PT,* prothrombin time; *PTCA,* percutaneous transluminal coronary angioplasty; *SAH,* subarachnoid hemorrhage; *sICH,* symptomatic intracerebral hemorrhage; *STEMI,* ST-segment elevation MI; *TT,* thrombin time.

TABLE 65.3

Treatment with Intravenous Alteplase (t-PA) in Other Settings

Intracardiac Thrombus
Treatment may be reasonable for patients with major acute ischemic stroke likely to produce severe disability and known left atrial or ventricular thrombus. (Class IIb, LOE C) Treatment is of uncertain benefit for patients with moderate acute ischemic stroke likely to produce mild disability and known left atrial or ventricular thrombus. (Class IIb, LOE C)
Infective Endocarditis
Treatment is not recommended because of the increased risk of intracranial hemorrhage. (Class III, LOE C)
Serious Comorbid Conditions
End-Stage Renal Disease
Treatment is recommended in patients with end-stage renal disease on hemodialysis and a normal APTT. (Class I, LOE C)
Dementia
Patients with preexisting dementia may benefit treatment; individual considerations such as life expectancy and premorbid level of function are important to determine whether treatment may offer a clinically meaningful benefit. (Class IIb, LOE B)
Current Malignancy
Treatment of patients with current malignancy and reasonable (>6 mo) life expectancy may benefit from treatment if other contraindications such as coagulation abnormalities, recent surgery, or systemic bleeding do not coexist. (Class IIb, LOE C)
Preexisting Disability
Preexisting disability does not independently increase the risk of sICH but may be associated with less neurologic improvement and higher mortality; treatment with preexisting disability (mRS score ≥2) may be reasonable, but decisions should take into account quality of life, social support, place of residence, need for a caregiver after treatment, patient and family preferences, and goals of care. (Class IIb, LOE B)
Hemorrhagic Retinopathy
Treatment in patients with a history of diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions is reasonable, but the potential increased risk of visual loss should be weighed against the anticipated benefits of reduced stroke-related neurologic deficits. (Class IIa; LOE B)
Intracardiac Mass
Treatment may be reasonable for patients with major acute ischemic stroke likely to produce severe disability and cardiac myxoma. (Class IIb, LOE C) Treatment may be reasonable for patients with major acute ischemic stroke likely to produce severe disability and papillary fibroelastoma. (Class IIb, LOE C)
Sickle Cell Disease
Treatment is not well established. (Class IIb, LOE C)
Wake-up Stroke
Treatment is not recommended if time last known to be at baseline is >4.5 hr or unknown. (Class III, LOE B) Use of imaging criteria to select patients who awoke with stroke or have unclear time of symptom onset to guide treatment is not recommended outside a clinical trial. (Class III, LOE B)
Menstruation and Menorrhagia: Recommendations
Treatment is probably indicated in women who are menstruating and do not have a history of menorrhagia; however, women should be warned that treatment could increase the degree of menstrual flow. (Class IIa, LOE C) Treatment may be considered in women with recent or active history of menorrhagia without clinically significant anemia or hypotension because the potential benefits of treatment probably outweigh the risks of serious adverse effects. (Class IIb, LOE C) Emergent consultation with a gynecologist is probably indicated before a decision about treatment is made in the setting of a history of recent or active vaginal bleeding causing clinically significant anemia. (Class IIa, LOE C) Women who are menstruating or have active vaginal bleeding who are treated with IV t-PA should be monitored for vaginal bleeding for 24 hr. (Class I, LOE C)
Aortic Arch and Cervicocephalic Arterial Dissection
Treatment of patients with known or suspected aortic arch dissection is not recommended and is potentially harmful. (Class III, LOE C) Treatment of patients with known or suspected extracranial cervical arterial dissection is reasonably safe within 4.5 hr and is probably recommended. (Class IIa, LOE C) The usefulness and hemorrhagic risk of treatment in the setting of known or suspected intracranial arterial dissection is not well established. (Class IIb, LOE C)
Dural Puncture Within 7 Days
Treatment may be considered in patients who had a lumbar dural puncture in the preceding 7 days. (Class IIb, LOE C)
Psychogenic/Conversion/Malingering
The risk of symptomatic intracranial hemorrhage is quite low and treatment is probably recommended in preference over delaying treatment to pursue additional diagnostic studies. (Class IIa, LOE B)
Catheterization Laboratory Environment/ Endovascular Complications
Treatment is reasonable depending on the usual eligibility criteria. (Class IIa, LOE A)
Cocaine Use
Treatment is reasonable in instances of illicit drug use–associated acute ischemic stroke in patients with no other exclusions. (Class IIa, LOE C)

APTT, Activated partial thromboplastin time; *sICH,* subdural intracranial hemorrhage; *IV t-PA,* intravenous tissue plasminogen activator; *mRS,* modified Rankin scale.

Up to one third of patients may have arterial reocclusion early after IV thrombolysis. One study suggested facilitation of clot lysis by concomitant exposure to the ultrasound waves provided by transcranial Doppler, which also serves to monitor clot dissolution.[63] None of a variety of adjunctive neuroprotective strategies has proved effective.[64]

Endovascular Therapy

Catheter-based endovascular approaches for acute reperfusion of patients with large-vessel occlusions (LVOs) yield proven benefit in patients with acute ischemic stroke.[5] Early trials used either intra-arterial t-PA and first-generation clot retriever devices, alone or in combination, and failed to show an overall

benefit of the approach. More recent trials employing stent retrievers reported improved patient outcomes; almost all patients first received IV t-PA, and the majority had proximal middle cerebral artery (MCA) or internal carotid artery (ICA) occlusions. The stent retriever-based studies found benefit despite differences in patient selection and imaging protocols; several used the Alberta Stroke Program Early CT Score (ASPECTS) to exclude patients with large, established areas of infarction deemed unlikely to benefit from reperfusion.[5,65,66] Regardless of mode of treatment, as with IV-tPA, reestablishing circulation to ischemic tissue as soon as possible confers a greater likelihood of achieving improved patient outcomes.[66] The AHA has issued guidelines for endovascular therapy[5] (**Table 65.4**).

TABLE 65.4

AHA Recommendations for Endovascular Therapy in Patients with Acute Ischemic Stroke[5]

Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria (class I; level of evidence, A):

1. Prestroke modified Rankin Score 0 to 1 (functionally independent).
2. Acute ischemic stroke receiving intravenous recombinant tissue plasminogen activator within 4.5 hours of onset according to guidelines from professional medical societies.
3. Causative occlusion of the internal carotid artery or proximal middle cerebral artery.
4. Age 18 years or older.
5. National Institutes of Health Stroke Scale (NIHSS) score of 6 or greater.
6. Alberta Stroke Program Early CT Score (ASPECTS) of 6 or greater.
7. Treatment can be initiated (groin puncture) within 6 hours of symptom onset

Other Measures for Treatment of Stroke

Several other important questions often arise in the management of patients with acute ischemic stroke, as well as regarding the use of other interventions that lack definitive supporting data.

Anticoagulation and Platelet Antiaggregant Therapy

The indications for the acute anticoagulation of patients with ischemic stroke are extremely limited. The most recent AHA guidelines reflect this view and specifically advise against emergency anticoagulation with the goal of improving neurologic outcomes or preventing early recurrent stroke in patients with acute ischemic stroke, because of a high risk for intracranial bleeding complications, and discourage the initiation of anticoagulant therapy within 24 hours of treatment with IV rt-PA.[61] Patients with AF-associated stroke benefit from long-term anticoagulation, unless contraindicated because of high bleeding risk (e.g., previous intracerebral hemorrhage).[3] The risk for early recurrence in patients with stroke related to AF is generally low (0.3% to 0.5%/day for first 2 weeks), so the timing of initiation of anticoagulation needs to be balanced against the risk for bleeding. Those with large strokes and those with uncontrolled hypertension generally have the highest risk for spontaneous hemorrhagic transformation of an ischemic stroke.

The use of anticoagulants in patients with stroke related to infective endocarditis is problematic (**see Chapter 73**). Systemic embolization occurs in 22% to 50% of patients with infective endocarditis, with up to 65% of emboli affecting the central nervous system, most of which (90%) involve the MCA.[67] Anticoagulation has shown no benefit in patients with native valve endocarditis, and it is not generally recommended for at least the first 2 weeks of antibiotic therapy in patients with stroke related to *Staphylococcus aureus* prosthetic valve endocarditis.[67] Of particular concern is the possible development of *mycotic intracranial aneurysms*. These aneurysms are often multiple and can be either asymptomatic, associated with focal neurologic signs, or because they most commonly affect distal branches of the

MCA, associated with signs and symptoms of subarachnoid hemorrhage or a sterile meningitis.[67] Although CT angiography (CTA) or MR angiography (MRA) can screen patients with symptoms suggesting the presence of a mycotic aneurysm, because distal portions of the artery are most commonly affected, catheter angiography remains the definitive modality for detection of these lesions (distal portions of MCA can be difficult to visualize with CTA or MRA). Many intracranial mycotic aneurysms regress with antibiotic treatment. Surgical clipping or endovascular obliteration can also be considered. Anticoagulation should be generally avoided in these patients, as mycotic aneurysms have propensity to rupture.

As noted earlier, platelet antiaggregants reduce the risk for recurrent stroke in patients with a history of ischemic stroke or TIA. In the acute setting, aspirin initiated within 48 hours of acute ischemic stroke may provide benefit (platelet antiaggregants are prohibited for first 24 hours in patients treated with IV rt-PA). A combined analysis of two relevant trials found that treatment with aspirin (160 mg or 325 mg daily) was associated with a small but statistically significant benefit, with 9 (±3) fewer deaths or nonfatal strokes per 1000 treated patients.[68] The CHANCE trial, conducted in China, suggests that a short course of aspirin plus clopidogrel decreases the risk of early recurrent stroke in patients with minor ischemic stroke or high-risk TIA compared to aspirin alone.[19] Whether these results extend to other populations is uncertain. A secondary analysis of data from CHANCE found that the benefit of clopidogrel (a prodrug) was limited to those who were not carriers of the *CYP2C19* loss-of-function allele (i.e., could metabolically activate clopidogrel).[69] Population-based differences in allele frequency could lead to different trial results in different regions.

Blood Pressure Management

Management of BP in the setting of acute ischemic stroke remains largely empiric. Treatment of elevated BP in patients who might otherwise be candidates for IV t-PA differs from that in patients who are not thrombolytic candidates and follows a specific protocol[4] (**Tables 65.5 and 65.6**). Patients who have been treated with a thrombolytic merit relatively aggressive treatment of elevated BP because of an increased risk for bleeding complications associated with uncontrolled hypertension.

TABLE 65.5

Potential Approaches to Arterial Hypertension in Patients with Acute Ischemic Stroke Who Are Potential Candidates for Acute Reperfusion Therapy

Patient otherwise eligible for acute reperfusion therapy except that BP is >185/110 mm Hg:
Labetalol, 10-20 mg IV over 1-2 min, may repeat once, *or*
Nicardipine, 5 mg/hr IV, titrate up by 2.5 mg/hr every 5-15 min, maximum 15 mg/hr; when desired BP reached, lower to maintain BP in proper limits, *or*
Other agents (e.g., hydralazine, enalaprilat) may be considered when appropriate.
If BP is not maintained at or below 185/110 mm Hg, do not administer rt-PA.
Management of BP during and after rt-PA or other acute reperfusion therapy:
Monitor BP every 15 min for 2 hr from start of rt-PA therapy; then every 30 min for 6 hr and then every hour for 16 hr.
If systolic BP 180-230 mm Hg or diastolic BP 105-120 mm Hg:
Labetalol, 10 mg IV, followed by continuous IV infusion 2-8 mg/min, *or*
Nicardipine, 5 mg/hr IV; titrate up to desired effect by 2.5 mg/hr every 5-15 min (max, 15 mg/hr).
If BP not controlled or diastolic BP >140 mm Hg, consider sodium nitroprusside

BP, Blood pressure; *IV,* intravenous(ly); *rt-PA,* recombinant tissue plasminogen activator.

From Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke. Stroke 2013;44:870-947. Copyright 2013 American Heart Association, Inc.

TABLE 65.6

Approach to Arterial Hypertension in Patients with Acute Ischemic Stroke Who Are *Not* Potential Candidates for Acute Reperfusion Therapy

Consider lowering BP in patients with acute ischemic stroke if systolic BP >220 mm Hg or diastolic BP >120 mm Hg.
Consider BP reduction as indicated for other concomitant organ system injury:
Acute myocardial infarction
Congestive heart failure
Acute aortic dissection
A reasonable target is to lower BP by 15% to 25% within the first day.

BP, Blood pressure.

From Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke. Stroke 2013;44:870-947.

Several lines of evidence suggest cautious BP management in non–thrombolytic-treated patients with acute ischemic stroke who do not have malignant hypertension (i.e., in patients with hypertensive encephalopathy, aortic dissection, acute renal failure, acute pulmonary edema, acute MI, or high BP >220/120 mm Hg).[4] Abruptly lowering BP may further compromise an already ischemic brain and potentially increase the size of the stroke. If treatment is necessary, precipitous drops should be avoided. In a single-blind study with blinded outcome assessments, the China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) randomly assigned over 4000 patients to receive antihypertensive treatment (target reduction of 10% to 25% within first 24 hours) or to discontinue all antihypertensive medications during hospitalization.[70] BP reduction did not reduce death or major disability at 14 days or hospital discharge.

Stroke After Percutaneous Coronary Interventions and Thrombolytic Treatment of Myocardial Infarction

Although infrequent, stroke can complicate percutaneous coronary interventions (PCIs). The same principles outlined for the management of acute stroke in other settings apply. The patient could receive IV rt-PA and could be evaluated for endovascular therapy, provided that all the other inclusion criteria are met and the patient has no other contraindications to the therapy. It is important to establish systems to ensure the rapid evaluation and treatment of patients with stroke after PCI.

Intracerebral hemorrhage following administration of a thrombolytic for acute MI or pulmonary embolism is another serious treatment-related complication. The infusion should be stopped and heparin discontinued in any patient in whom acute neurologic symptoms develop. Because these symptoms might result from either hemorrhage or ischemia, a brain-imaging study is mandatory before proceeding with further treatment. Treatments to reduce the amount of thrombolytic-associated intracerebral hemorrhage once it has occurred are not well established. Administration of cryoprecipitate and/or fresh-frozen plasma has been advocated. Those with brainstem compression related to cerebellar hemorrhage may benefit from surgical evacuation of the hematoma. Such patients require prompt transfer to a setting with expertise in neurologic intensive care.

Future Perspectives

Much of the greater than 40% reduction in stroke mortality that has occurred in the United States over the last decade is associated with more effective prevention. One analysis found that 10 potentially

modifiable risk factors account for 90% of the population-attributable risk of stroke.[71] Continued emphasis on prevention promises to have the greatest impact on further improvements. Establishing the clinical usefulness of advanced neuroimaging to optimize selection of patients for acute reperfusion interventions requires additional work. New approaches to poststroke recovery offer the potential of improved outcomes in those with functional deficits that persist after the acute period.

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66

Treatment of Noncoronary Obstructive Vascular Disease

Scott Kinlay, Deepak L. Bhatt

Peripheral vascular disease is a general term that includes pathologic processes affecting arteries, veins, and lymphatics (**see Chapter 64**). This chapter focuses on catheter-based endovascular treatment of large

and medium-sized arteries predominantly affected by atherosclerosis, as well as large-vein obstruction secondary to chronic disease. Although *peripheral artery disease* (PAD) refers to lower limb arterial disease, sometimes the term is used to describe disease in the large and medium arteries of the upper limbs, neck, and aortomesenteric arteries. The incidence and prevalence of PAD increase with age and with other risk factors for atherosclerosis. Thus, these two demographic forces will likely lead to a global increase in PAD (**see Chapter 1**).

Increasing awareness of PAD, the impact that PAD has on cardiovascular (CV) risk and quality of life, and the rapid development of percutaneous techniques for revascularization continue to accelerate the number of endovascular procedures for PAD. Appropriate use of this expensive technology requires a clear understanding of the goals of medical and revascularization therapies.

Approach to the Patient With Peripheral Artery Disease

Chronic PAD may be asymptomatic or may manifest as claudication, critical limb ischemia, or embolic infarction of a distal organ (e.g., stroke). Asymptomatic disease is common. In the lower extremities, asymptomatic disease occurs in at least half and in as many as 80% of patients with abnormal functional test results indicative of obstructive arterial disease (e.g., abnormal ankle-brachial index [ABI]). Even asymptomatic disease indicates elevated CV risk.[1-5] These considerations warrant intensive modification of atherosclerosis risk factors as a prime goal of therapy to reduce the risk for myocardial infarction (MI) and stroke, the most common causes of death in patients with PAD.[1,4-8]

Claudication classically refers to leg discomfort or pain related to exercise and relieved by rest, but it also describes discomfort in the upper limbs caused by effort-related ischemia. Claudication affects function (the ability to walk or use a limb) and quality of life. Therefore, treatment of claudication aims to improve function and reduce discomfort at the maximum level of activity desired by a patient. Stopping cigarette smoking and starting a regular walking regimen are the two most important lifestyle interventions for claudication. Together, these interventions reduce the mechanisms responsible for the progression of disease and favorably change arterial biologic state, including vasodilator function, muscle metabolism, and angiogenesis.[1,5,6,8] It is important to tell patients that the pain or discomfort associated with claudication is not harmful, and that once this discomfort abates with rest, they should continue to push their activity again to improve endurance. Revascularization strategies aim to improve arterial blood flow in obstructed large and medium-sized arteries when noninvasive therapies fail. Catheter-based interventions, when indicated, should be deployed together with lifestyle and medical treatment.[9]

Critical limb ischemia (CLI) refers to PAD with ischemic pain at rest or tissue loss (e.g., ulcer or gangrene).[1,4,5,10] This scenario has clinical urgency because of near-term risk for limb jeopardy requiring major amputation. *Major* amputation in the lower limbs refers to amputation at or above the level of the ankle and requires a prosthesis for the patient to walk.[10] Amputation is disfiguring and at higher levels has greater impact on functional independence of the patient. In contrast, *minor* amputations (e.g., toe or transmetatarsal) usually have little impact on the patient's ability to walk. Catheter-based therapies for CLI are used to improve blood flow and heal ischemic tissue, to salvage the limb (prevent major amputation), or to enable a lower level of amputation that might have less impact on the patient's ability to walk.

Cervical carotid, vertebral, and subclavian disease, although often asymptomatic, can lead to artery-to-artery embolism with transient ischemic attack (TIA) and stroke. The risk for major stroke is high shortly

after a symptomatic event but less so several months after an event or with asymptomatic disease.[11] Mesenteric and renal artery disease affects organ function. Chronic ischemia of the gut causes postprandial abdominal discomfort and food avoidance leading to weight loss, but it may progress to frank mesenteric infarction with a high mortality rate.[12] Renal artery stenosis can precipitate hypertensive crises associated with pulmonary edema, hypertension resistant to treatment, and rapidly worsening renal dysfunction.[13]

Symptomatic disease that threatens a distal organ (e.g., CLI, TIA, mesenteric angina) justifies a more aggressive approach because these manifestations entail the highest risk for functional loss and death without treatment. PAD associated with less-threatening clinical scenarios (e.g., claudication) may allow a less aggressive approach, with more time to assess the response to lifestyle and medical therapies (**Fig. 66.1**). There is rarely justification for catheter-based or surgical revascularization of asymptomatic lower or upper limb PAD, mesenteric disease, or subclavian or vertebral artery disease. Revascularizing asymptomatic extracranial carotid disease beyond medical therapy has uncertain value, although recent guidelines support such interventions for patients at higher risk for stroke and low risk for periprocedural adverse events.[11]

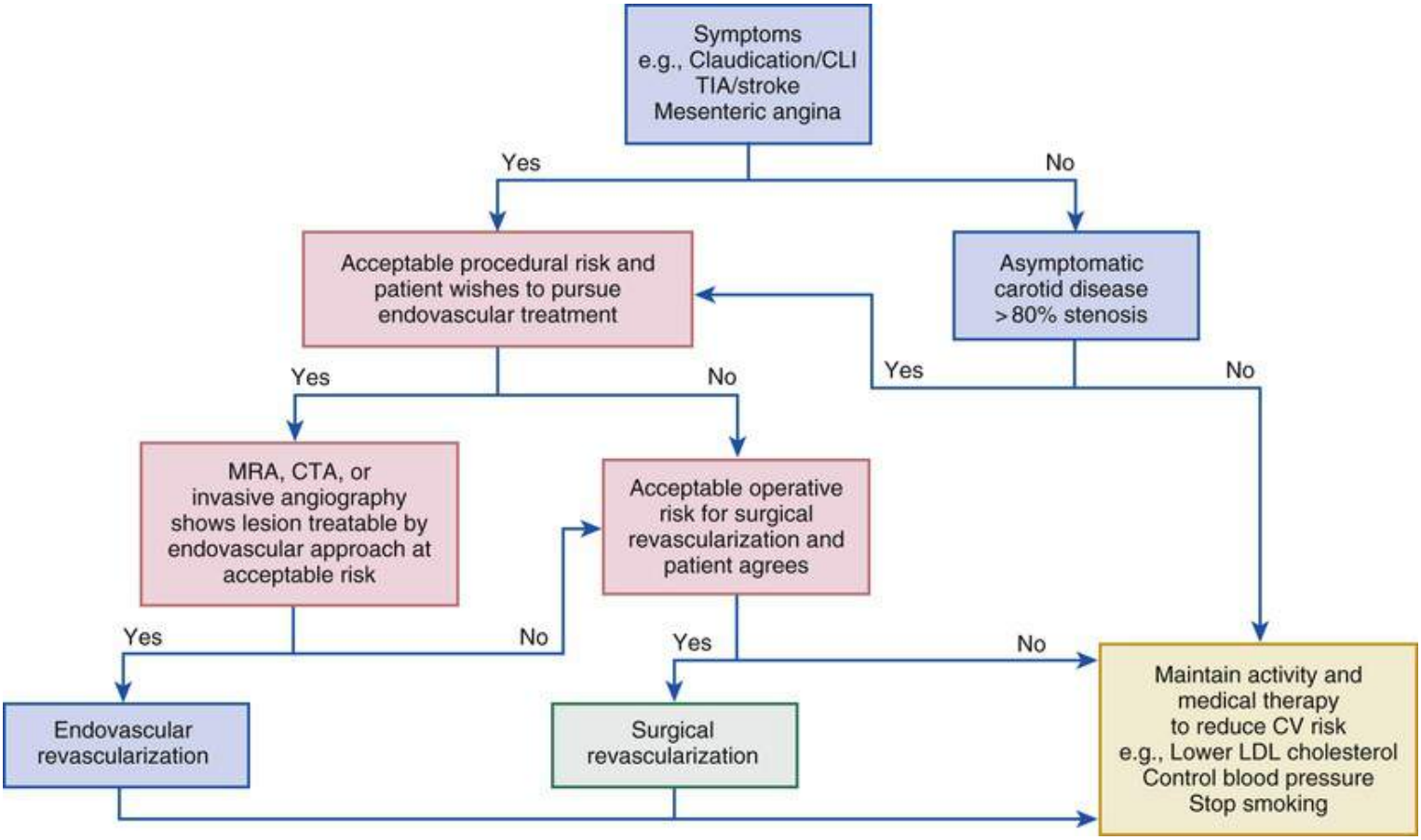

FIGURE 66.1 Approach to a patient with peripheral artery disease. This strategy is based on assessment of the risk for adverse events with and without treatment by taking into consideration procedural or operative risks and the patient's informed decision to proceed with revascularization. CLI, Critical limb ischemia; CTA, computed tomographic angiography; CV, cardiovascular; LDL, low-density lipoprotein; MRA, magnetic resonance angiography; TIA, transient ischemic attack.

Quality of Evidence Evaluating Endovascular Treatments

In contrast to coronary disease, few well-controlled studies have evaluated endovascular treatment of PAD and venous disease. Many studies are single arm, and most focus on patency (lack of restenosis) and repeated revascularization over a relatively short period. Although these endpoints provide information on the mechanisms likely to lead to improved control of symptoms, function, quality of life, and tissue preservation, they do not provide direct guidance on symptoms and function in patients with claudication or CLI. Interventionalists should recognize the limitations in many studies and encourage future studies to address patient-oriented endpoints and adjudicated CV outcomes.[14-16]

Endovascular Technologies

Balloon Angioplasty

Balloon angioplasty remains the mainstay of endovascular intervention for PAD and venous disease[17,18] (**Fig. 66.2**). Angioplasty remodels the artery by expansion and accommodates the atherosclerotic plaque to expand the vessel lumen. This procedure usually causes dissection of the plaque that may or may not impair blood flow. Angioplasty is limited in the short term by acute recoil of the artery and flow-limiting dissections, which may cause abrupt closure of the artery. In the intermediate time frame, overexuberant neointimal hyperplasia and negative remodeling of the artery may lead to symptomatic restenosis. Despite these limitations, balloon angioplasty can achieve durable results, particularly with shorter lesions, and is less likely than stenting to obstruct side branches associated with the lesion. Most operators use prolonged inflations (at least 1 minute or more). Both rapid-exchange and over-the-wire platforms are available, as well as short and long shaft lengths for lesions close to or farther from the access site.

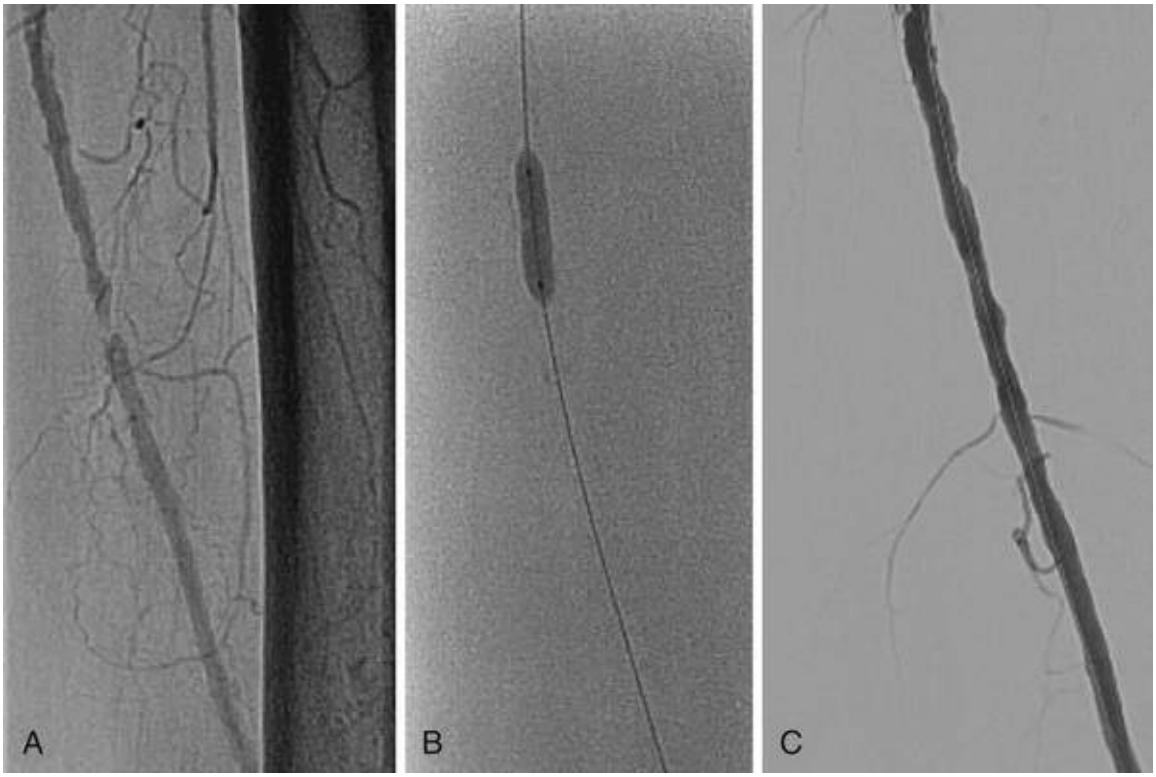

FIGURE 66.2 Treatment of a mid–superficial femoral artery stenosis **(A),** with balloon angioplasty alone **(B),** with an excellent final result **(C).**

Bare-Metal Stents

Bare-metal stents (BMSs) come in two types: balloon-expandable stents (**Fig. 66.3**) and self-expanding stents[17,18] (**Fig. 66.4**). Stent implantation requires aspirin therapy and an adenosine receptor antagonist (i.e., clopidogrel), although the evidence for dual-antiplatelet therapy (DAPT) is largely derived by extrapolation from the coronary stent literature.

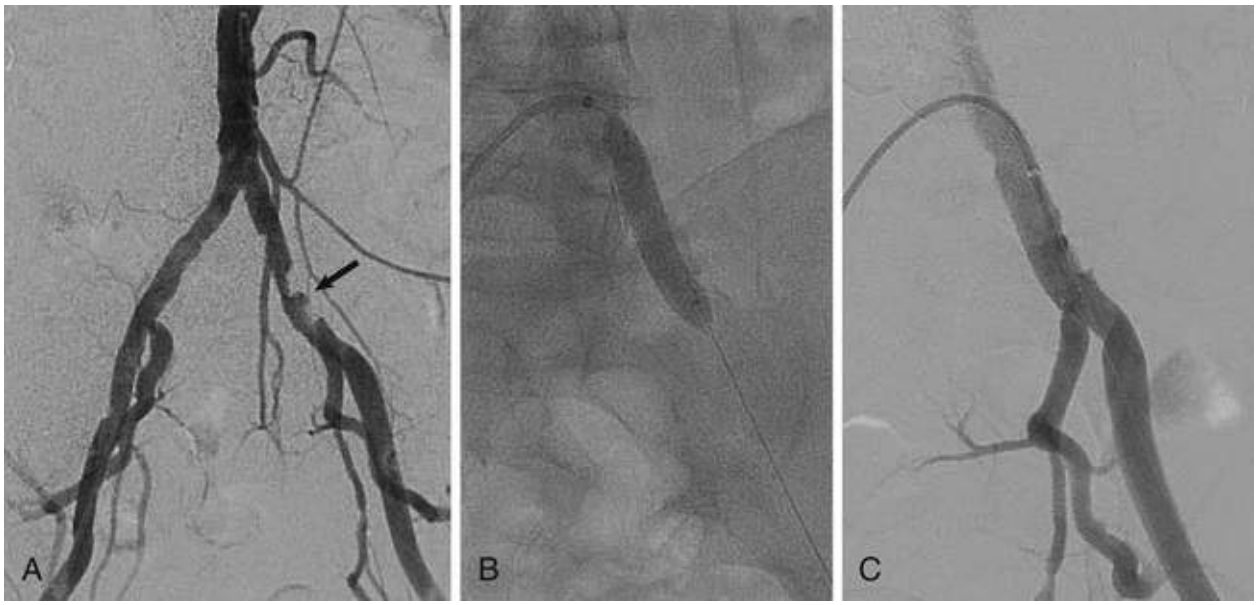

FIGURE 66.3 Treatment of left common iliac stenosis with a balloon-expandable stent from the contralateral right femoral artery. **A,** Serial stenoses in the left common iliac artery (*arrow*). **B,** Balloon-expandable stent deployment. **C,** Final angiogram.

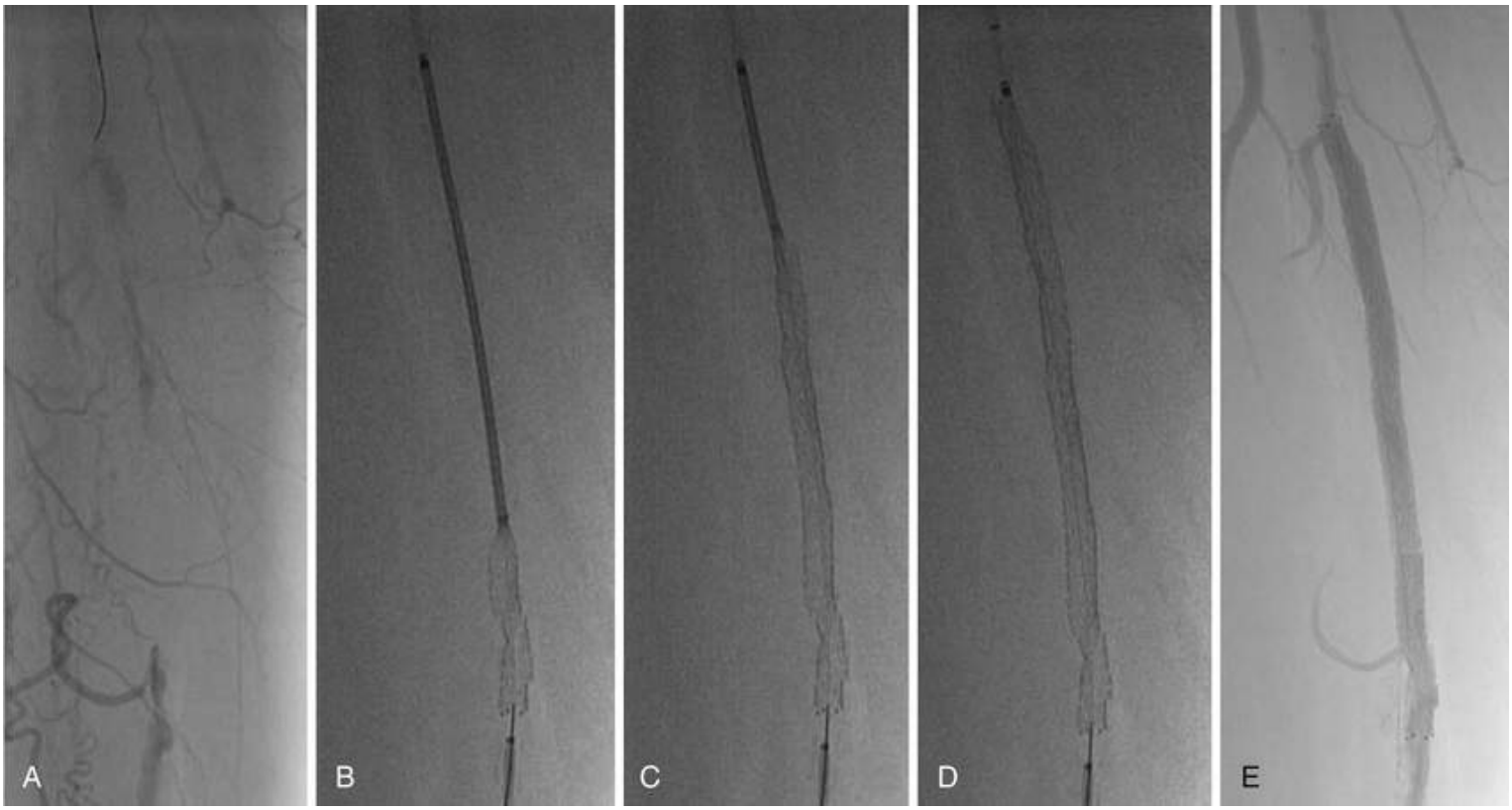

FIGURE 66.4 Treatment of a superficial femoral artery occlusion with a self-expandable nitinol stent. **A,** A wire approaches the occluded segment. **B-D,** The delivery catheter is pulled back to release the self-expanding stent. **E,** Final angiogram.

Balloon-expandable stents have greater radial strength and are less likely to move on deployment, which is important for ostial placement. Such stents can be crushed by external compression and are therefore avoided outside the torso. They are sometimes used to treat tibial disease, but only for critical limb ischemia, for which long-term patency may be less of an issue once tissue healing has occurred.

Self-expanding stents were originally made of stainless steel but are now usually made of nitinol.[17] Nitinol stents reexpand on compression and are therefore used outside the torso, where external compression is more likely to occur. They may also be used in tortuous arteries, where they probably conform better than balloon-expandable stents. Their lower radial strength, however, increases the risk for recoil. More recent self-expanding stent designs are more durable and less likely to fracture.[17,18] Nitinol stents cannot be overdilated if the stent is undersized for the artery, which may lead to stent malapposition or even embolization.

Drug-Eluting Peripheral Stents

Earlier attempts at coating peripheral self-expanding stents were initially associated with less restenosis in the short term but were unsuccessful in longer follow-up, partly because of inferior stent platforms prone to fracture. More durable stent designs[17-19] and drug elution with everolimus[20] or paclitaxel[21] offer lower rates of restenosis. The 5-year follow-up of the Zilver PTX study demonstrated a sustained benefit from self-expanding drug-eluting stents (DESs) over balloon angioplasty and BMSs on freedom from clinical symptoms of ischemia (80% versus 59%) and repeat revascularization (66% versus 43%) in femoral-popliteal arteries.[22] The duration of DAPT required for these stents is uncertain, but recent randomized trials have generally used 2 to 6 months of treatment with an adenosine receptor antagonist.[20,21]

Covered Stents

Stents covered with or sandwiching a polymer such as polytetrafluoroethylene (PTFE) have proved very useful for treating perforations related to endovascular treatment or excluding aneurysms (**Fig. 66.5**). Results from randomized trials are inconsistent; some studies show no benefit over BMSs,[23] and others suggest lower restenosis at 12 months when treating femoral and iliac artery disease.[24,25] In one series, covered stents that cross the knee joint were associated with higher rates of occlusion and major amputation than those deployed above the knee (34% versus 10%).[26] Disadvantages of covered stents include unintentional[21] occlusion of important branch vessels, concerns about the risk for late stent thrombosis, and whether restenosis was merely delayed rather than prevented.

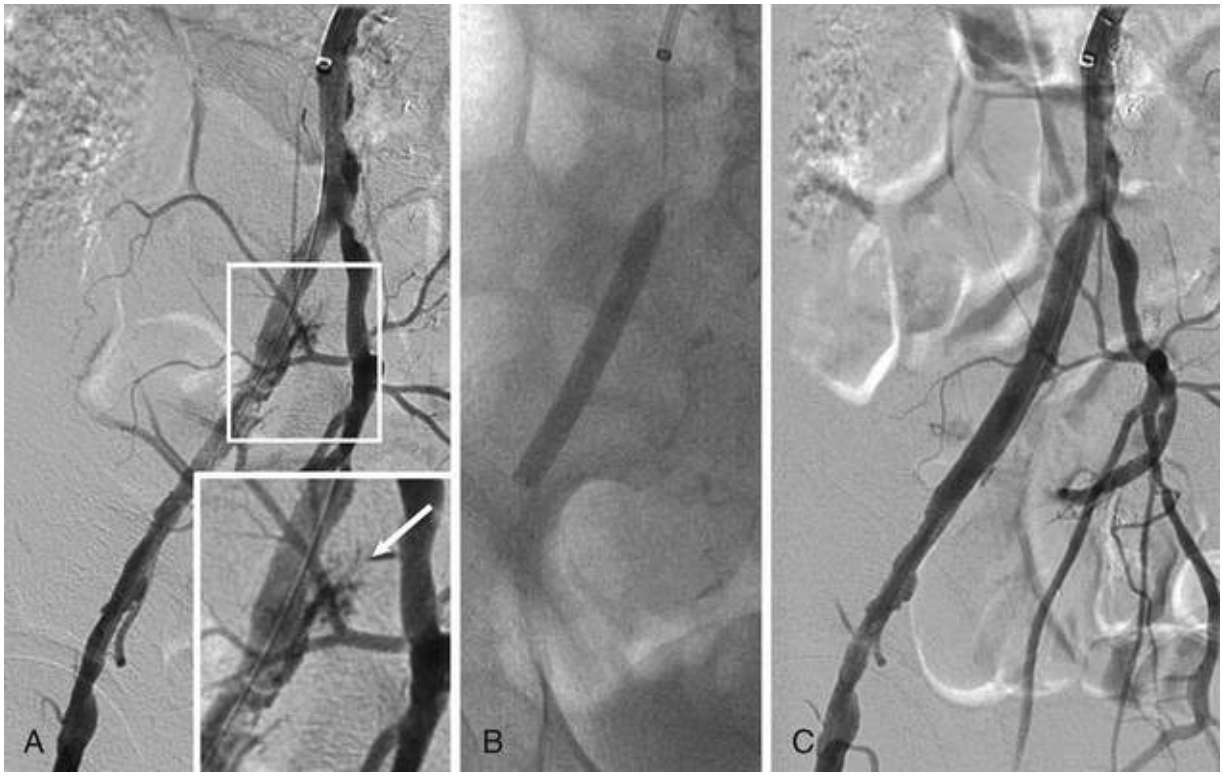

FIGURE 66.5 Treatment of a perforated external iliac artery with a covered stent. **A,** Perforation after directional atherectomy shown enlarged in the lower right box (*arrow*). **B,** Deployment of a balloon-expandable covered stent. **C,** Final angiogram with the perforation sealed.

Drug-Coated Balloons

Balloons coated with antirestenosis agents (drug-eluting balloons) represent an exciting development. This technology uses a non–stent-related method to deliver drugs such as paclitaxel into the arterial wall after conventional angioplasty treatments. Compared with plain balloon angioplasty, drug-coated balloons have less restenosis and repeat revascularization in the femoral-popliteal arteries.[27-30] Drug-coated balloons also offer a lower risk of restenosis compared with plain balloon angioplasty for treating in-stent restenosis lesions.[31] Late follow-up of two randomized trials at 2 and 5 years shows a sustained benefit on patency and repeat revascularization with drug-coated versus plain balloon angioplasty in femoral-popliteal arteries, without safety concerns of aneurysm or late stenoses.[30,32] The duration of DAPT with drug-coated balloons in the femoral-popliteal arteries is uncertain but varies between 1 and 6 months in most randomized trials.

The effect of drug-coated balloons in below-knee angioplasty, primarily for CLI, is less certain. Compared to plain balloon angioplasty, one randomized trial showed a lower risk for repeat revascularization but no effect on major amputation or mortality.[33] The only other randomized trial, the IN.PACT DEEP study, showed no difference in restenosis and a trend to increasing risk of amputation, leading the sponsor to withdraw that drug-coated balloon from the market.[34] Differences in drug-coating techniques and eluting agents could explain the lackluster results of drug-coated balloons below the knee, and the question of their value requires further evaluation.[18]

Thrombolysis and Thrombectomy

Catheter-directed thrombolysis is an important adjunctive therapy for arterial thrombosis, stent thrombosis, and occlusive thrombotic venous disease. Thrombolysis may be indicated for acute thrombosis with a threatened but viable extremity, but an immediately threatened limb (e.g., with sensory or early motor deficits) is more often treated by surgical revascularization,[35] which offers more rapid reperfusion, the ability to débride devitalized tissue, and the opportunity to relieve compartment syndromes. Much of the experience with catheter-based thrombolysis comes from its use for acute limb ischemia (ALI), venous thrombosis, or pulmonary embolism. It serves as an adjunctive treatment of semiacute manifestations such as peripheral stent thrombosis. Long-term results tend to be better when thrombolysis reveals an anatomic stenosis that probably precipitated the thrombosis and is treatable, for example, by repeated angioplasty.

Catheter-directed thrombolysis is more effective than intravenous thrombolysis only if an infusion catheter (with multiple infusion holes) is inserted into the thrombosed vessel. It is also less effective if given more than 14 days after thrombosis.[5,18] Typically, the infusion continues for 12 to 24 hours, because treatment over 48 hours is associated with depletion of circulating fibrinogen and a higher risk for major bleeding.[36] Catheter-based thrombolysis with or without angioplasty or stenting also reduces the incidence of post-thrombotic syndrome in patients with proximal (iliac) deep venous thrombosis,[35,37] and it is used as adjunctive therapy for massive pulmonary emboli[38,39] (**see Chapter 84**).

Any thrombolysis regimen increases risk for fatal or major bleeding. Absolute contraindications to thrombolysis[38] include (1) a cerebrovascular event less than 2 months previously, (2) active bleeding, (3) gastrointestinal bleeding less than 10 days previously, and (4) neurosurgery (intracranial or spinal surgery) or trauma less than 3 months previously. Relative contraindications include (1) cardiopulmonary resuscitation less than 10 days previously, (2) nonvascular surgery or trauma less than 10 days previously, (3) uncontrolled hypertension (sustained systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg), (4) puncture of a noncompressible vessel, (5) intracranial tumor, and (6) recent eye surgery.

Catheter aspiration thrombectomy uses catheters with a rapid-exchange port to direct the catheter to the thrombus and a large aspiration port to aspirate the catheter with a large syringe. These catheters can aspirate smaller thrombi but are generally inadequate for a large burden of thrombus (e.g., long femoral stent thrombosis).

Mechanical thrombectomy uses a variety of devices that may include thrombolytic agents to help break up thrombus before suction by an aspiration catheter or catheters using the Venturi effect.[39] Although mechanical thrombectomy is a more rapid treatment than catheter-directed thrombolysis, embolization

can occlude the distal arterial bed and lead to infarction and tissue loss, although combination with an embolic protection device might theoretically reduce this risk.

Atherectomy and Other Treatments

Atherectomy devices, although conceptually attractive, have not proved better than angioplasty in direct comparisons in most arterial beds.[17,18] A recent Cochrane review of four trials comparing atherectomy to established treatments for PAD found no evidence to support atherectomy as an alternative to balloon angioplasty.[40] Atherectomy is one of several niche tools and serves best in heavily calcified arteries to improve balloon and stent expansion or in regions where vessels encounter repetitive flexion or torsion, such as over joints, and where stents are avoided (because of kinking and increased fracture). In these settings, atherectomy may improve the distensibility of an artery to permit adequate expansion by balloon angioplasty without flow-limiting dissection. Drug-eluting balloons have renewed interest in this technology because they may reduce the contribution of excessive intimal hyperplasia to restenosis. This strategy needs formal testing in clinical trials.

Coronary rotational atherectomy devices (Rotablator) are generally too small for the larger peripheral arteries, and it is uncertain how a large amount of plaque ablated from a long peripheral lesion would affect the downstream microcirculation (**Fig. 66.6**). *Peripheral rotational* atherectomy devices include the Jetstream, which has a 2.0-, 3.1-, and 3.5-mm cutting profile (**Fig. 66.7**), and the Diamondback, which uses an eccentric location to achieve a larger cutting arc.[17,18] *Directional* atherectomy devices include the Silverhawk device[17,18] (**Fig. 66.8**). All the peripheral devices have a tendency to embolize plaque into microvessels. Distal embolic protection devices may reduce this complication.

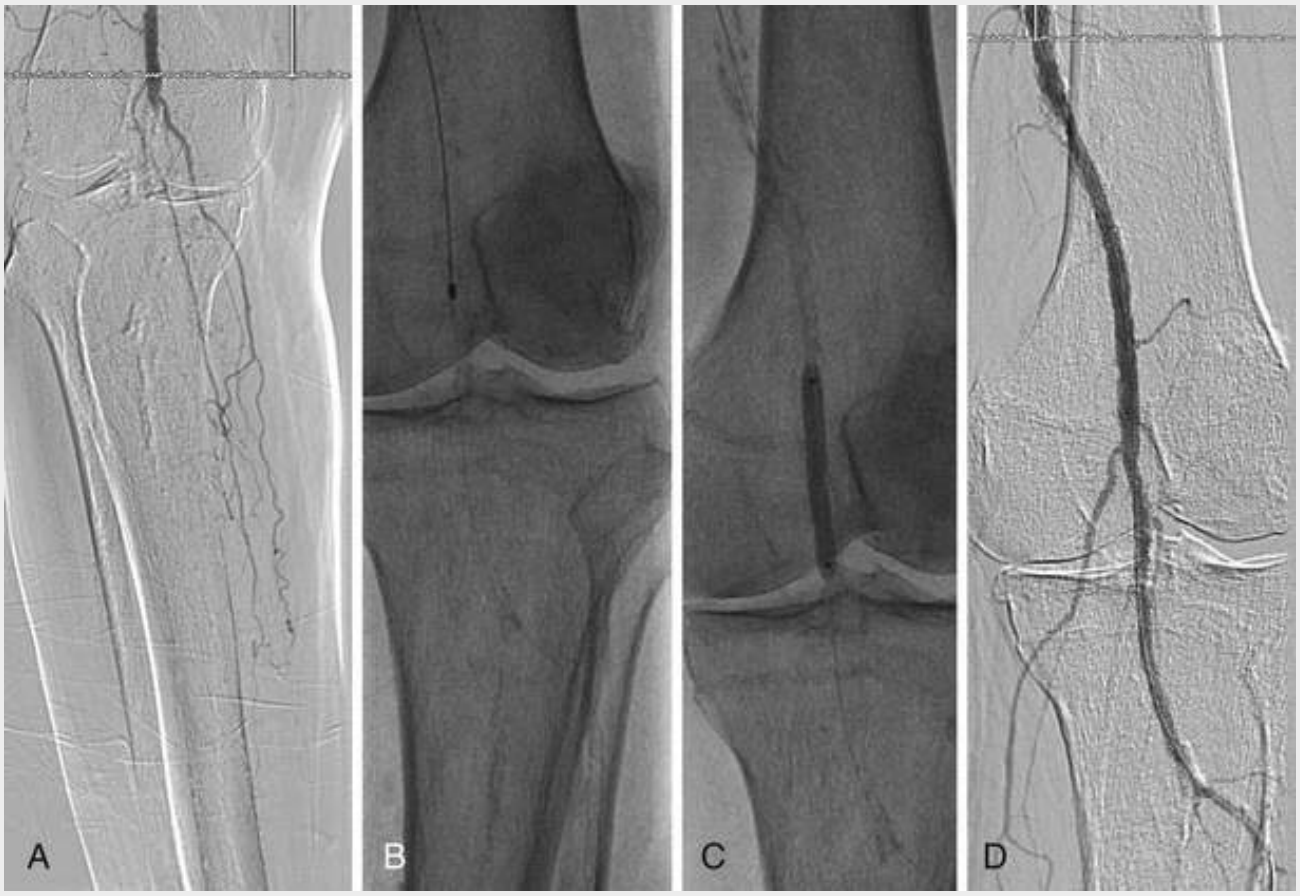

FIGURE 66.6 Occluded popliteal artery treated with a Rotablator and balloon angioplasty. **A,** Occluded artery. **B,** Rotaburr during rotablation. **C,** Balloon angioplasty. **D,** Final result.

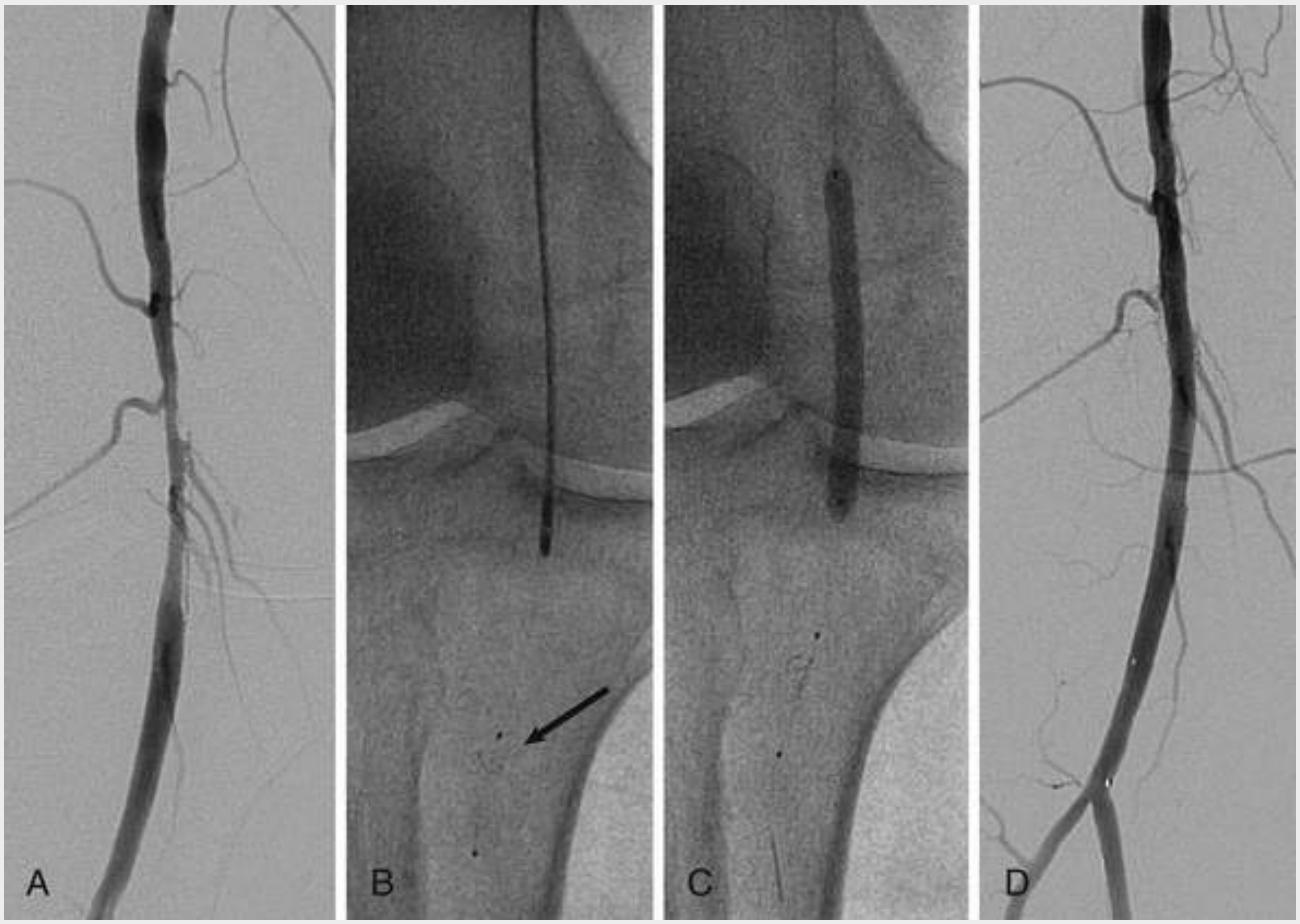

FIGURE 66.7 Stenosis in a popliteal artery treated by Jetstream rotational atherectomy. **A,** Popliteal stenosis. **B,** Jetstream catheter over a filter embolic protection device (*arrow*). **C,** Adjunctive balloon angioplasty. **D,** Final angiogram.

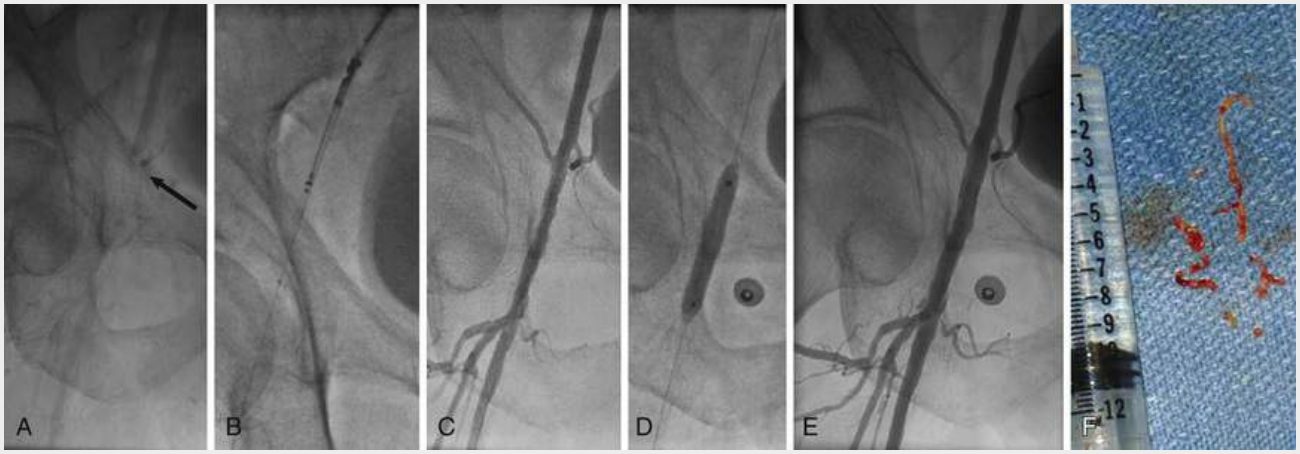

FIGURE 66.8 Common femoral artery occlusion treated with directional atherectomy. **A,** Occlusion in the right common femoral artery (*arrow*). **B,** Directional atherectomy catheter. **C,** After eight cutting runs. **D,** Adjunctive balloon angioplasty. **E,** Final angiogram. **F,** Atheromatous material removed by the atherectomy device.

Cryoplasty involves the use of proprietary balloon and inflation technology to inflate the balloon with nitrous oxide, which chills on expansion to −10°C (**Fig. 66.9**). One pilot study suggested lower rates of restenosis in the femoral arteries when used with nitinol stents compared to balloon angioplasty,[41] but longer-term outcomes are uncertain and larger studies are needed.

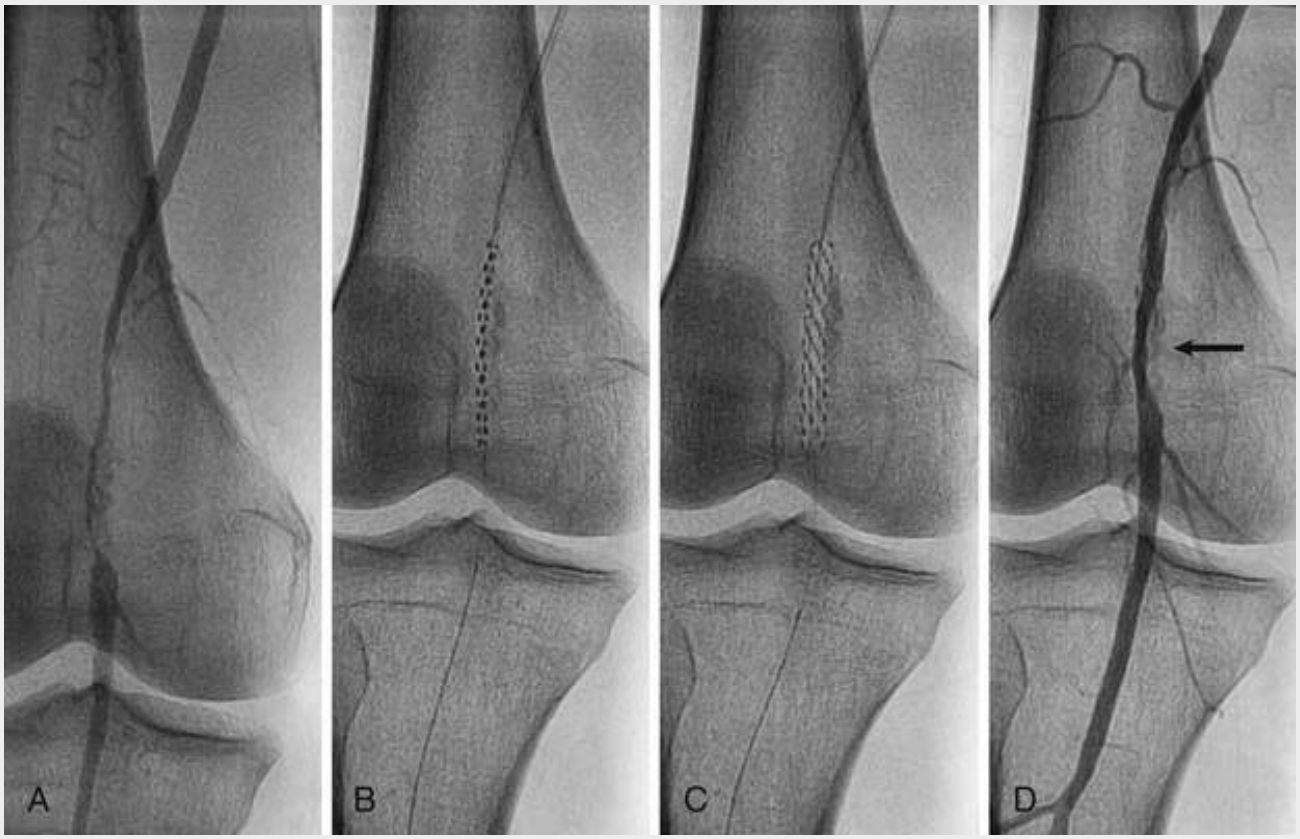

FIGURE 66.9 Cryoplasty of a popliteal artery stenosis. **A,** Popliteal artery stenosis. **B,** Cryoplasty balloon predilation. **C,** Cryoplasty balloon during inflation. **D,** Final angiogram with some residual narrowing because of recoil adjacent to a heavily calcified segment of the popliteal artery (*arrow*).

Planning an Intervention

Vascular Imaging

Vascular imaging is the first stage of planning an endovascular intervention[4,5,10,18] (**Fig. 66.10**). Traditionally, invasive angiography served to determine the extent and severity of obstructive disease. Conventional angiography can use lower frame rates than needed for coronary angiography because most peripheral arteries are relatively static. Digital subtraction angiography (DSA) images remove bone and soft tissue from the image while leaving the contrast-enhanced image of the artery for more clarity, provided that the limb remains still during acquisition.

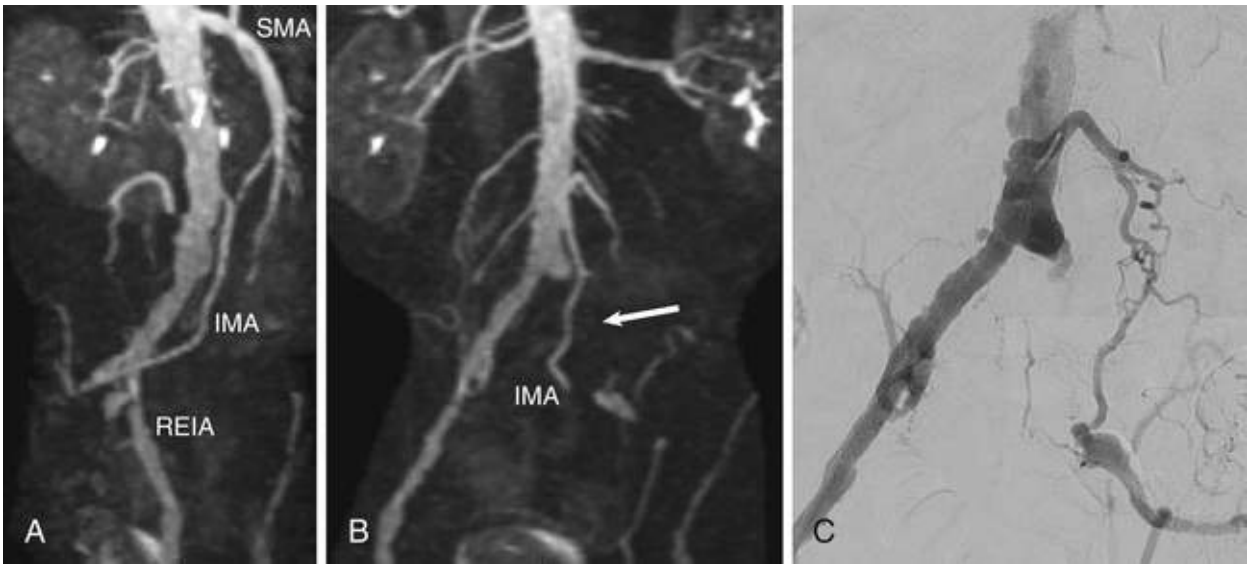

FIGURE 66.10 Comparison of magnetic resonance angiography (MRA) and digital subtraction angiography (DSA). **A,** Lateral rotation of a maximum intensity projection (MIP) image of the lower aorta and iliac arteries; *IMA,* Inferior mesenteric artery; *REIA,* right external iliac artery; *SMA,* superior mesenteric artery. **B,** Anterior-posterior rotation from a MIP showing the left common iliac occlusion (*arrow*) and the IMA supplying collaterals to the left external iliac artery. **C,** Corresponding image from conventional angiography with DSA.

Noninvasive imaging is used to plan the vascular access and the tools probably required for the procedure.[10,18,42] Magnetic resonance imaging (MRI) uses gadolinium or other contrast agents or time-of-flight techniques, which rely on laminar blood flow and have the advantage of not requiring contrast material, which can rarely cause serious adverse effects in patients with renal insufficiency (e.g., nephrogenic sclerosing fibrosis). However, time-of-flight techniques may overestimate the severity of disease in regions of disturbed flow near obstructive or nonobstructive plaque. Computed tomographic angiography (CTA) using iodinated contrast material provides more rapid imaging, but heavy calcification can mask stenoses and make interpretation of lesion severity more difficult. Iodinated contrast agents can cause reactions or impair renal function.

MRI cannot be used in patients who have retained ferric metals (e.g., most pacemakers, shrapnel). Most contemporary stents are compatible with MRI but leave a flow void that does not allow interpretation of obstructive disease. High-resolution contrast-enhanced computed tomography (CT) scans offers advantages for assessing stent patency. Both MRI and CT tend to overestimate the severity of stenosis compared with conventional invasive angiography.

Duplex ultrasound is very useful for imaging arteries in the limbs and the cervical arteries and veins. This modality does require considerable time to map out large arterial systems, however, explaining the more common use of magnetic resonance angiography (MRA) and CTA as noninvasive techniques to plan endovascular interventions.

Vascular Access

Vascular access can use either antegrade or retrograde approaches (**Fig. 66.11**).[10] The contralateral common femoral artery (CFA) furnishes the most common vascular access for the lower limb. A catheter enters the access side over the bifurcation of the aorta and into the target iliac arteries through a support wire. A sheath is directed up and over the aortic bifurcation and pointed into the target iliac artery (**Fig. 66.12**). This approach is familiar to many operators and provides access to the CFA at its most superficial location. It also allows compression of the artery against the femoral head to aid in manual

hemostasis after removal of the sheath.

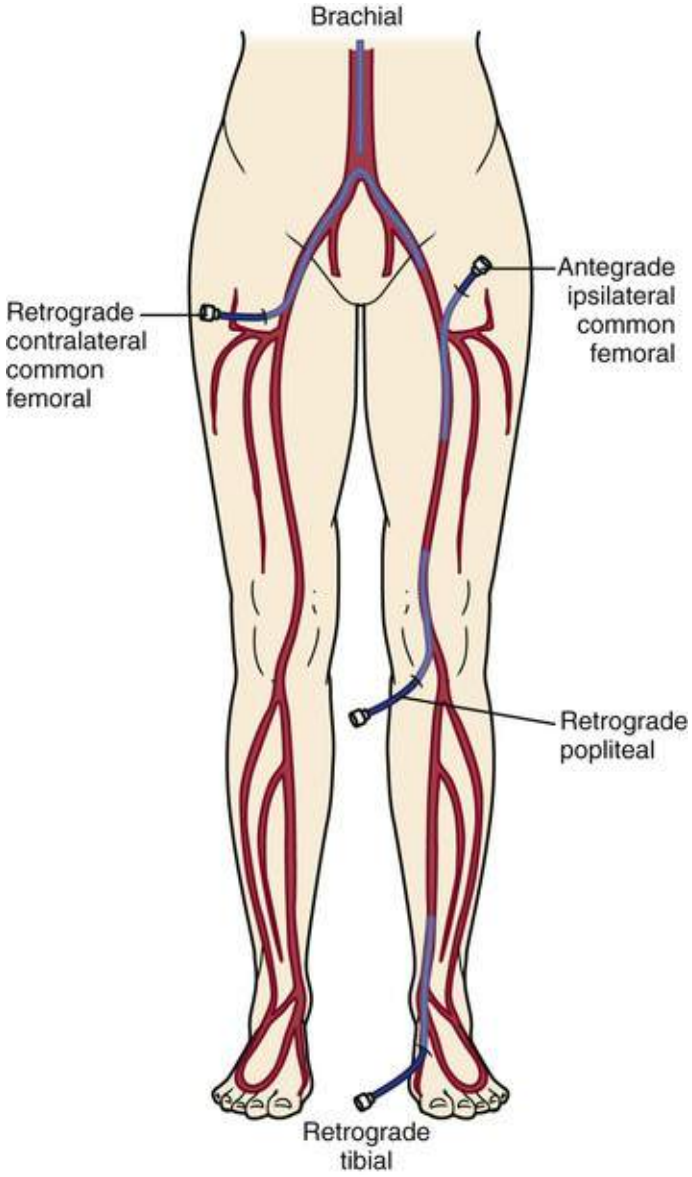

FIGURE 66.11 Antegrade and retrograde arterial access for lower extremity interventions. (From Kinlay S. Management of critical limb ischemia. Circ Cardiovasc Interv 2016;9:e001946.)

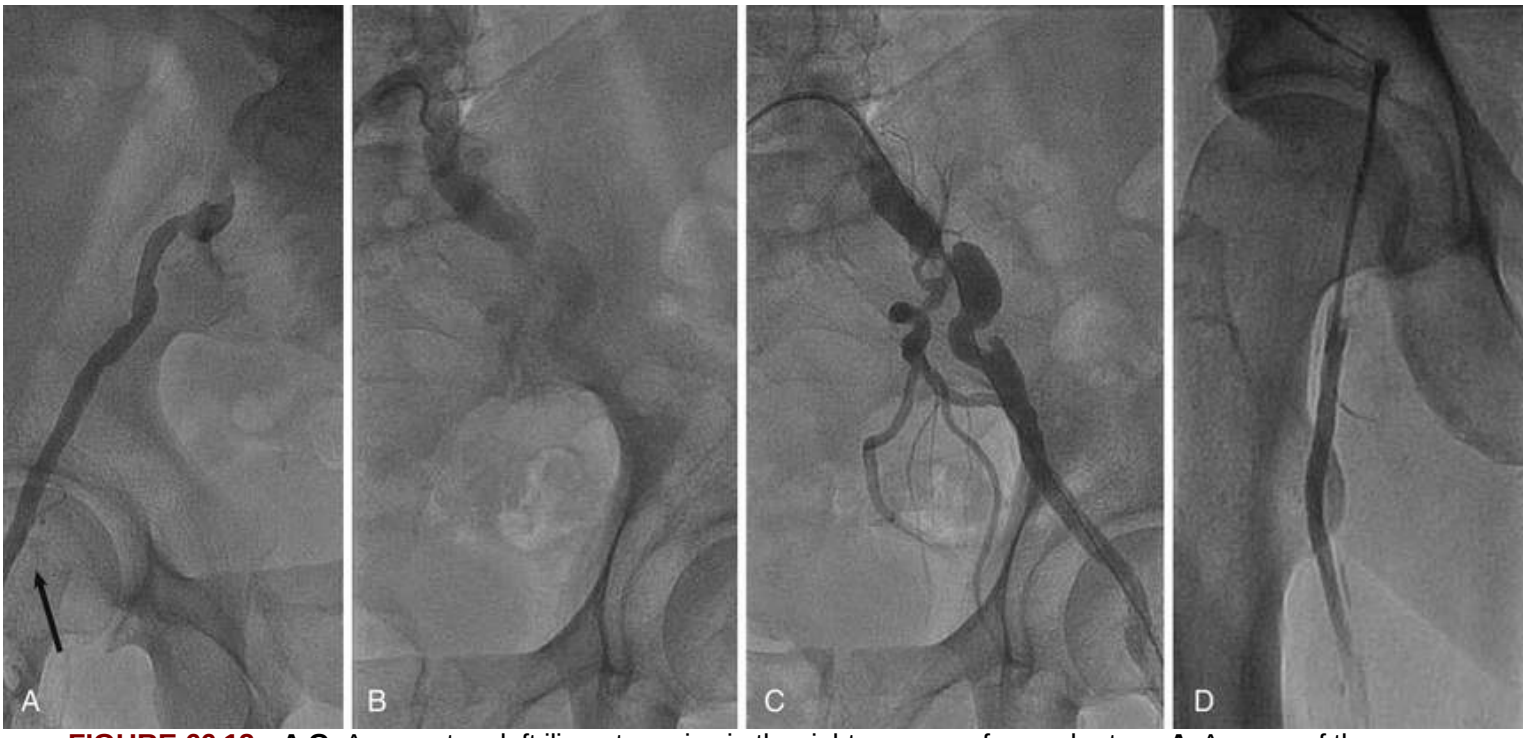

FIGURE 66.12 **A-C,** Access to a left iliac stenosis via the right common femoral artery. **A,** Access of the right femoral artery. The *arrow* indicates the access site of the femoral sheath. **B,** An Omniflush catheter is directed from the right iliac artery into the origin of the left iliac artery. **C,** A support wire is used to direct a sheath into the left common iliac artery for the intervention. **D,** Anterograde access of the common femoral artery with the tip of the sheath directed into the superficial femoral artery.

The anterograde femoral approach involves skin access several centimeters cranial to the CFA and angles toward the femoral head (**Fig. 66.12**). This approach offers greater pushability for total occlusions and is closer to distal tibial lesions, but it is difficult in overweight patients, in whom the access needle must traverse a large depot of subcutaneous fat.

Rarely, retrograde access from the popliteal artery or from a tibial artery can assist in crossing a total occlusion that cannot be crossed from an anterograde approach[10,18,43] (**Figs. 66.13 and 66.14**). Retrograde access has the disadvantages of the potential to cause injury to the distal access site because of the smaller artery size (tibial arteries) or more difficult hemostasis from a deeper location (popliteal). Techniques that combine retrograde and anterograde approaches can assist in crossing difficult total occlusions. An unsuccessful procedure from a retrograde access site, however, could lead to a nonhealing ulcer and CLI, and thus it is generally used as a "last resort."

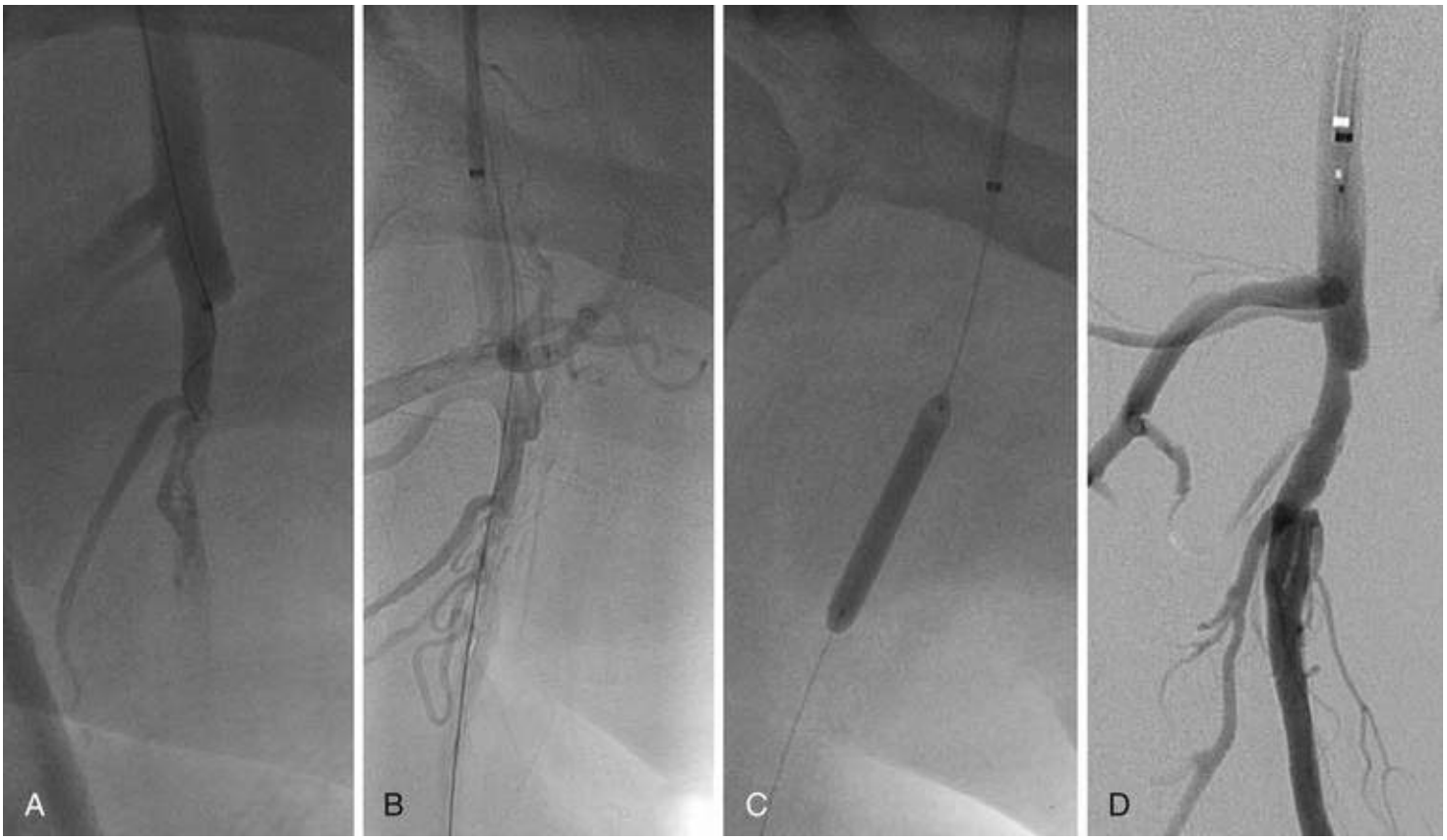

FIGURE 66.13 Anterograde and retrograde approach to a brachial artery stenosis. **A,** Unable to cross the stenosis from the anterograde approach, with a shuttle sheath directed into the brachial artery from the femoral approach. **B,** Successful wire crossing retrogradely from the radial approach. The wire was snared into the shuttle sheath. **C,** Balloon angioplasty performed anterogradely from the shuttle sheath. **D,** Final angiogram with an excellent long-term functional result.

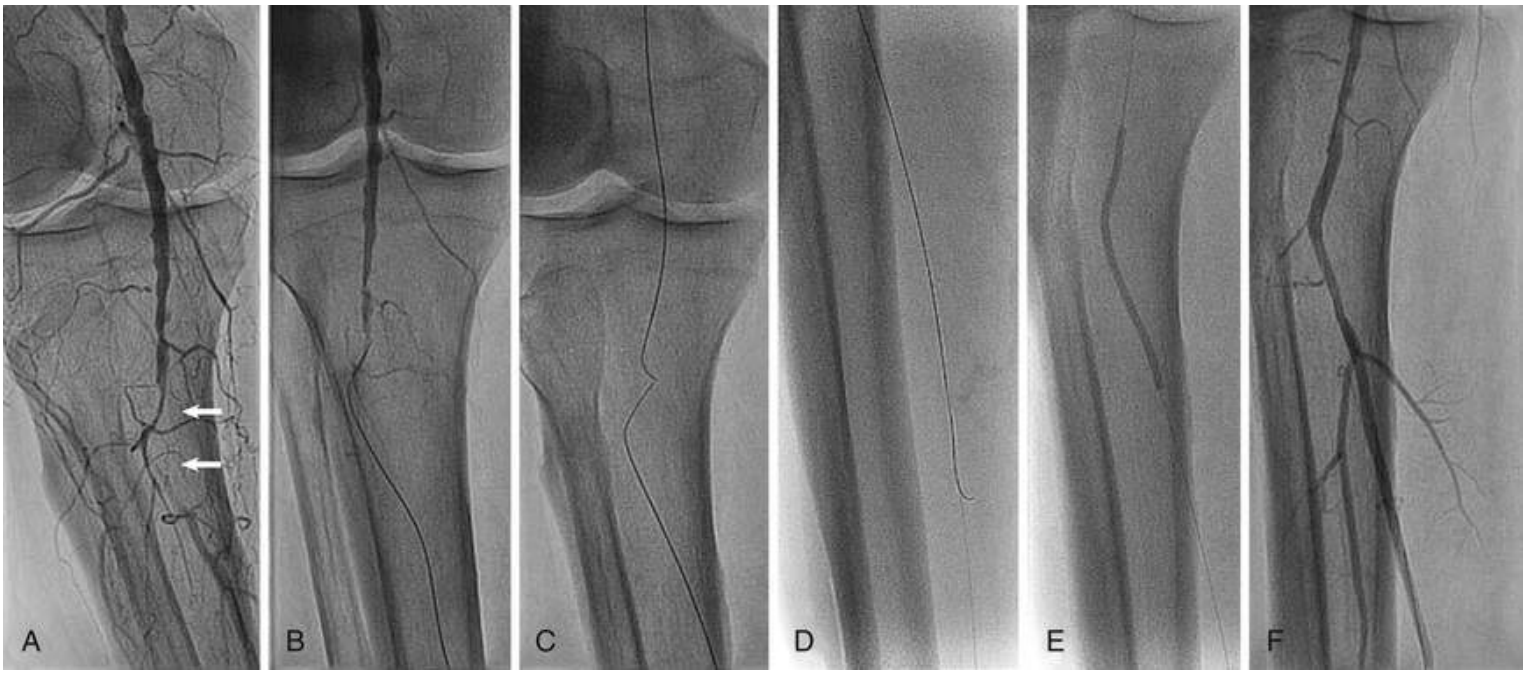

FIGURE 66.14 Anterograde and retrograde approach to an occluded below-knee popliteal and posterior tibial artery. **A,** Occluded segment (*arrows*). **B,** Retrograde wire from the posterior tibial artery accessed at the ankle. **C,** Anterograde and retrograde wires crossing the occlusion. **D,** The anterograde wire crossed the occlusion into the distal posterior tibial artery. **E,** Balloon angioplasty was followed by a short stent in the occluded segment. **F,** Final angiogram.

The brachial artery approach can permit access to the iliac arteries, but it is usually too far a distance from the superficial femoral arteries for most balloons and stent delivery devices. A shuttle sheath from the femoral approach or retrograde access from the radial or brachial approach can be used to access upper limb lesions. Brachial or radial artery access often provides better support for the mesenteric and renal arteries because these arteries typically angulate caudally.

Endovascular Treatment of Arterial Disease

Peripheral Artery Disease of the Lower Extremities

The clinical history and physical examination can generally differentiate PAD from other causes of leg discomfort. Physiologic tests such as the ABI are quick and easy to perform, but segmental leg pressures can indicate the level of obstructive disease. Infrainguinal disease usually diminishes distal pulses and impairs the resting ABI. Typical symptoms of PAD with a normal resting ABI should raise suspicion for iliac or aortic disease, in which case an exercise ABI is generally abnormal (**see Chapter 64**). More advanced imaging such as MRA, CTA, or invasive angiography is generally indicated only if revascularization is being considered. MRI or CT can help identify the level, extent, and severity of PAD and help indicate the likelihood of endovascular success versus surgical treatment, as well as access site and adjunctive endovascular technologies. In general, treatment of proximal disease offers higher long-term durability than does treatment of distal disease.

Aortoiliac Disease

Aortoiliac disease is approached from the ipsilateral femoral artery, contralateral femoral artery, or brachial artery. An ipsilateral femoral approach is more direct and associated with greater wire pushability through an occlusion. Many operators will often gain contralateral femoral access with a small sheath, because this will provide quick access to the aorta or proximal iliac artery for temporary balloon occlusion in the event of perforation and rapid hemorrhage. Although plain balloon angioplasty produces a very durable result, balloon-expandable stents are now preferred for their better long-term durability, particularly with long lesions.[3-5] “Kissing stents” are a well-described option for disease involving the distal aorta, but in many cases of iliac disease, landing stents at the ostium of the iliac artery yields a good response and preserves contralateral access if arterial interventions are required for a leg in the future. Balloon-expandable stents are usually preferable for most lesions involving ostia because of their greater radial strength and precision of placement, but self-expanding stents may be better in more tortuous lesions (**Fig. 66.15**). Although covered stents prevent plaque prolapse, they have uncertain added value and the potential disadvantage of occluding the opposite iliac artery if deployed too high or occluding the ipsilateral internal iliac artery if deployed too low. They also appear to have a higher risk of thrombosis. Covered stents are useful for treating aneurysms and potentially lifesaving for treating vessel rupture or perforation.[17,18] Occlusions involving the distal aorta generally undergo surgical treatment, although percutaneous transluminal angioplasty and stenting offer an option to patients with prohibitive surgical risk and CLI.

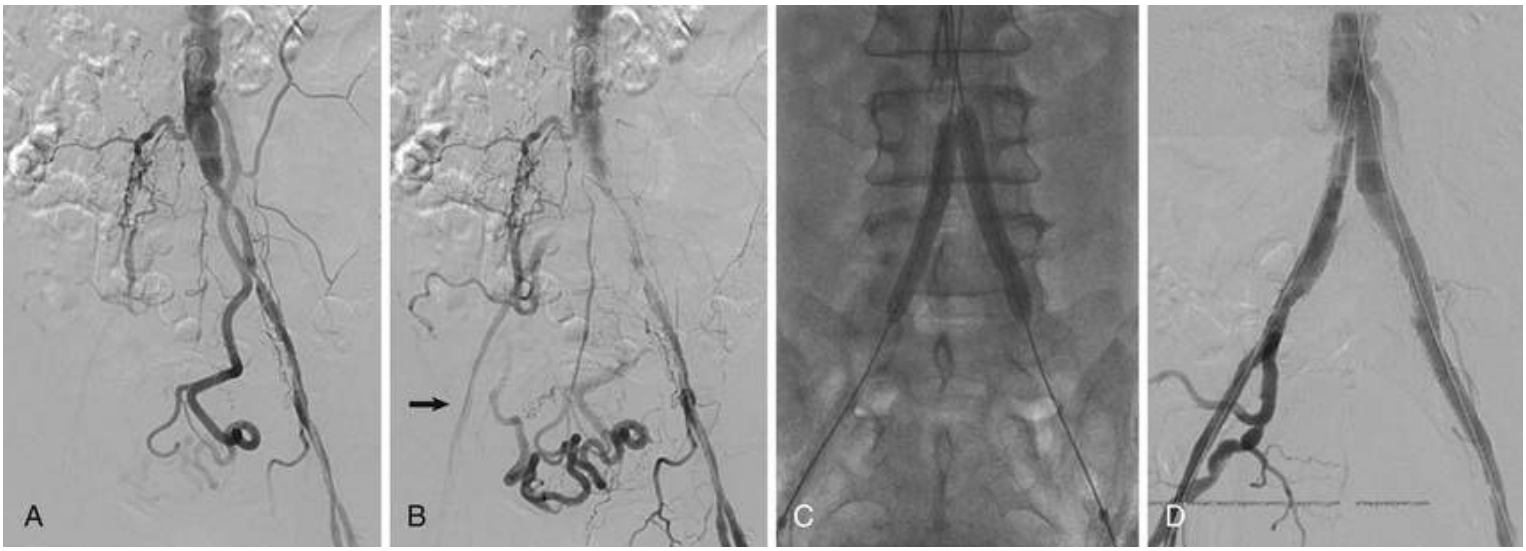

FIGURE 66.15 Aortoiliac intervention for an occluded right common iliac artery and serial stenoses in the left iliac artery. **A,** Early-phase angiogram showing occlusion of the right common iliac artery. **B,** Late-phase angiogram showing a patent right external iliac artery (*arrow*). **C,** Bilateral kissing balloon-expandable stents in the common iliac arteries. **D,** Composite angiogram showing the final result.

The external iliac artery rises out of the pelvis and joins the CFA just above the femoral head. This ascent out of the pelvis is deceptive on angiography, which may be related to the higher risk for perforation or dissection with endovascular treatment. Once the artery leaves the pelvis, it can undergo external compression, prompting consideration of self-expanding stents. Endovascular angioplasty and stenting, particularly for shorter and common iliac lesions, has very good technical success with excellent durability (>80% patency) over a 5-year period, similar to results with surgical revascularization.[3,4,17]

Femoral-Popliteal Artery Disease

Obstructive atherosclerosis is more common in the superficial femoral than the popliteal or common femoral arteries. Usually, the profunda femoris serves as an important source of collateral blood flow to the leg in patients with obstructive superficial femoral artery disease. The CFA is more difficult to treat because it is subject to greater flexion and extension with movement of the hip, and complications that occlude the CFA are likely to lead to an acutely threatened limb as a result of obstruction of the profunda and superficial femoral arteries. Even though balloon angioplasty can successfully treat obstructive CFA disease secondary to atherosclerosis or complications of CFA access for other procedures, surgical repair with patch angioplasty is the standard of care for most patients with acceptable surgical risk. Balloon-expandable stents should not be used in this location because of repetitive compression during movement of the hip, and self-expanding stents should be avoided because of concerns of durability and loss of a site of potential future vascular access. The profunda femoris is a smaller artery with a thinner wall than the superficial femoral artery, and the risk for complications and evidence of long-term success with catheter-based intervention are uncertain.

Most percutaneous femoral interventions involve the superficial femoral and popliteal arteries, and interventional techniques are similar with both arteries. PAD typically involves these arteries, which are subject to torsion and stretch with movement of the leg. The popliteal artery is particularly subject to torsion and kinking, and stents are generally avoided below the level of the top of the patella and above the tibial metaphyseal plate when viewed with the leg straight (**Fig. 66.16**). Stenting between this region subjects stents to extreme flexion, compression, and torsion and is associated with stent fracture, restenosis, and poor long-term durability. As a result, stenting across the knee should be considered only in patients with CLI and a poor angioplasty result and in those with prohibitive surgical risk.

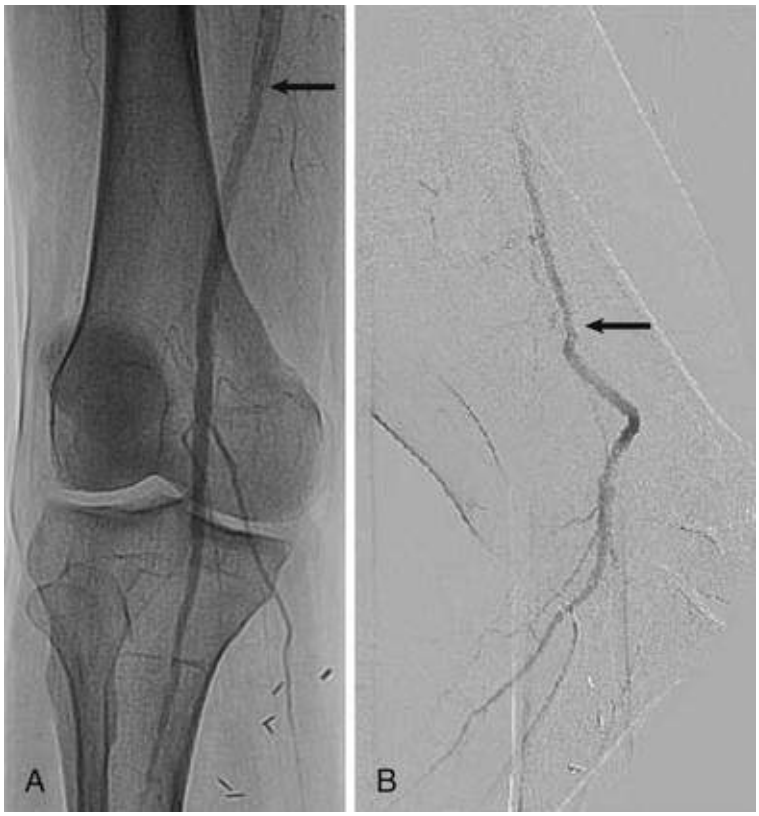

FIGURE 66.16 The popliteal artery is subject to torsion and kinking on bending the knee. **A,** Popliteal angiogram in the anteroposterior view with the knee straight. **B,** Popliteal artery showing increased tortuosity in a rotated view with the knee flexed to 90 degrees. The *arrows* indicate the distal margin of a superficial femoral self-expanding stent.

Acute procedural success rates with catheter-based interventions now approach 90%, in part because of a wide variety of wires, crossing catheters, and reentry catheters for total occlusions. Restenosis rates are higher than in the iliac artery and may require repeated interventions. Catheter-based therapies should be considered part of a long-term strategy of surveillance for recurrent and new disease and repeated interventions when needed.[44-46] Balloon angioplasty alone has durability similar to that of primary stenting for short lesions (<50 to 100 mm in length),[3,8,17] and in this setting, provisional stenting for abrupt closure, flow-limiting dissection, or poor expansion (residual stenosis >30% to 50%) is an acceptable strategy. For longer lesions (>100 mm), primary stenting with self-expanding nitinol stents offer better durability and walking function than balloon angioplasty with provisional stenting[3,8,17] (**Fig. 66.17; see also Fig. 66.4**) (see Videos 66.1 through 66.10). Drug-eluting nitinol self-expanding stents offer less restenosis than does balloon angioplasty with and without provisional stenting with nitinol BMSs.[22] Further studies with longer drug-eluting nitinol stents and comparisons to routine bare-metal stenting with or without drug-coated balloons will determine their value.

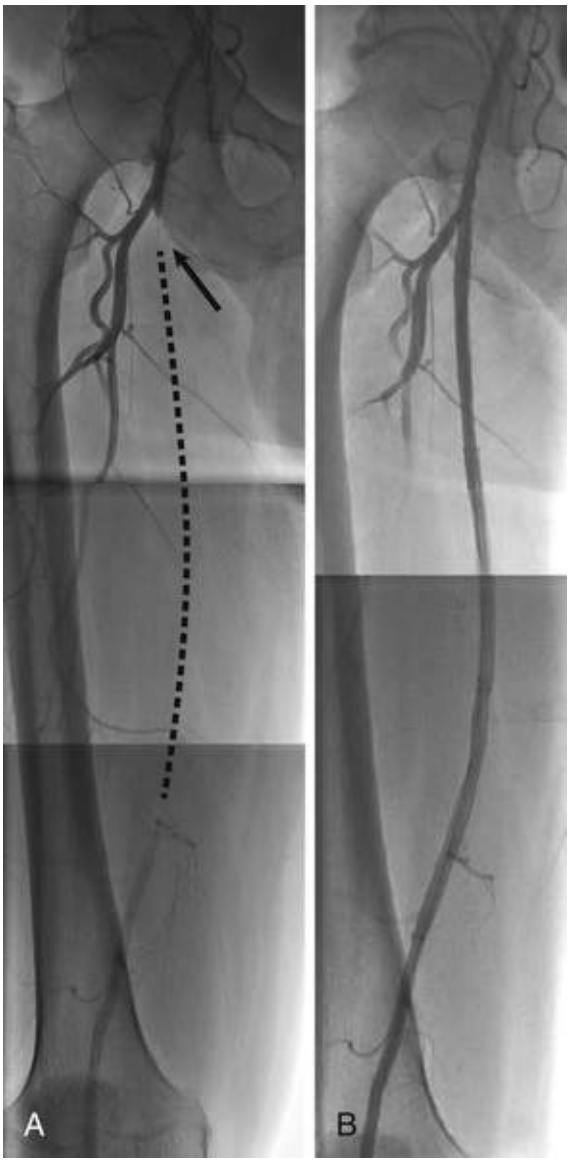

FIGURE 66.17 Composite angiograms showing a long occlusion of the right superficial femoral artery (*arrow* and *dashed line* in **A**). **B,** Three nitinol self-expanding stents were deployed in the superficial femoral artery to restore flow in this artery.

Atherectomy (directional, rotational, or laser), cutting balloons, and cryotherapy offer little routine advantage despite their theoretical value.[3,5,18,40] However, atherectomy may permit greater luminal expansion with balloons and stents in calcified disease. Emboli occur in some cases with atherectomy, and many operators recommend embolic protection devices, but without evidence from randomized controlled trials (RCTs). There are no randomized direct comparisons of adjunctive techniques to balloon angioplasty or stenting in the femoral artery, but based on the evidence available and extrapolation from the coronary experience, their routine use does not reduce long-term risks for restenosis. Drug-eluting balloons offer lower restenosis rates than balloon angioplasty[27-29,31,47] and may provide a durable result with or without atherectomy in regions where stents should be avoided, such as over joints. Interventionalists need to establish systems to monitor patients for recurrent or new disease and treat atherosclerosis risk factors intensively. Collaboration with surgical colleagues and vascular medicine specialists should improve outcomes.

Tibial Disease

The popliteal artery divides into three tibial arteries: the anterior tibial, which becomes the dorsalis pedis in the foot; the posterior tibial, which forms the pedal arcade with the anterior tibial artery; and the

peroneal artery, which usually ends just above the ankle but can be an important collateral to the foot. In general, claudication is rare with loss of even two of the three tibial arteries. Catheter-based interventions have high rates of restenosis, in part because of the small diameter and long lesion length, and are rarely justified in patients with claudication. Frequently, correction of obstructive proximal disease will resolve the claudication even with extensive residual tibial disease.

In contrast, treating severe tibial disease in patients with CLI can promote wound healing, resolve pain at rest, and prevent major amputation (**Fig. 66.18**). Vascular access is more limited for distal tibial disease, because a contralateral femoral approach or a brachial approach (**see Fig. 66.11**)[10] is often too distant for most equipment based on 130- to 150-mm shaft lengths. Antegrade CFA access can allow equipment to reach to foot if needed and often gives greater pushability to drive through long occlusions. The retrograde pedal approach (**see Fig. 66.11**)[10] uses noninvasive ultrasound and a micropuncture needle to access one of the tibial arteries at the foot or ankle. Access from above (e.g., antegrade CFA) allows a retrograde wire from the foot to be snared and exteriorized and provides a rigid rail for angioplasty balloons (**see Fig. 66.14**). A pedal access site may become a nonhealing ulcer if the intervention is unsuccessful, so this approach is often used as a last resort.[10]

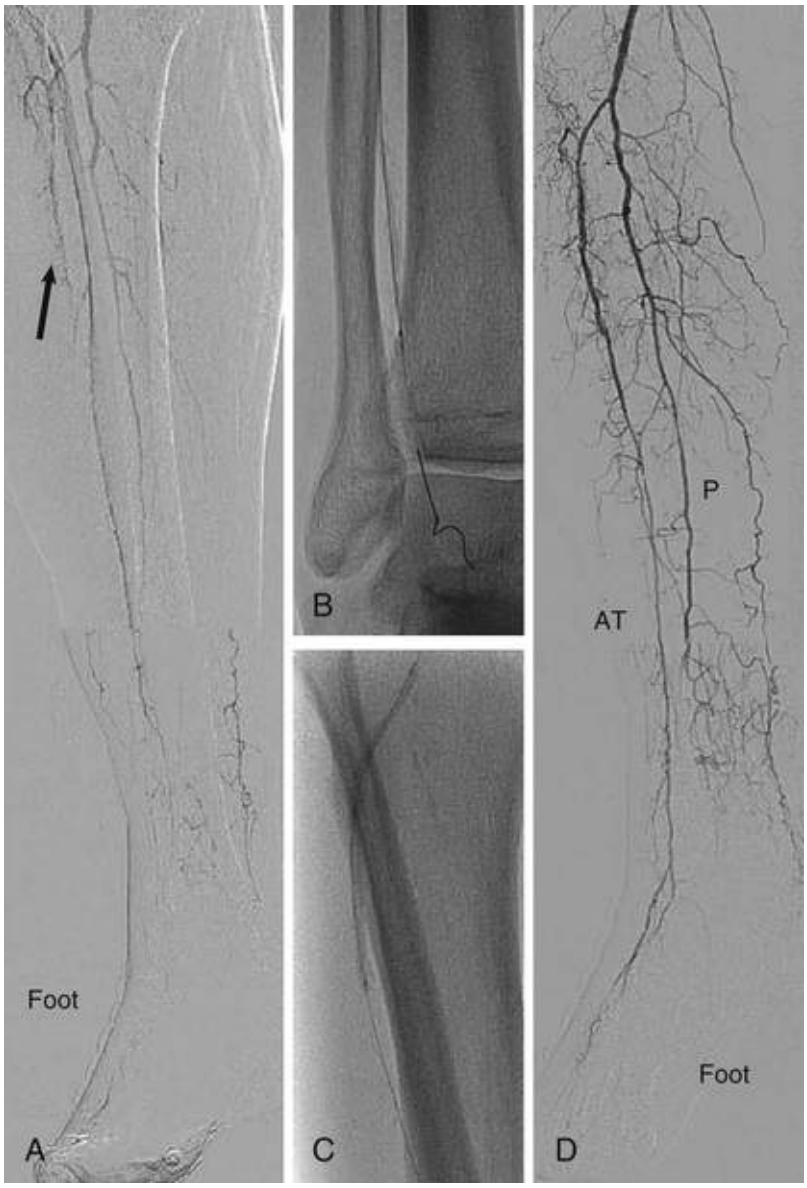

FIGURE 66.18 Revascularization of a totally occluded anterior tibial artery in a patient with a nonhealing ulcer on the right big toe. **A,** Proximal occlusion of the anterior tibial artery (*arrow*) with no flow into the foot. **B,** Wire traversing the anterior tibial artery at the ankle. **C,** Balloon angioplasty of the whole anterior tibial artery (the image shows a balloon at the proximal anterior tibial artery). **D,** Final angiogram. *AT,* Anterior tibial artery; *P,* peroneal artery.

Angiosome-directed revascularization refers to revascularization of a tibial artery that supplies the area of a nonhealing ulcer or gangrene (**Fig. 66.19**).[10] The value of angiosome-directed revascularization versus restoring any straight flow to the foot is debated. In observational studies, wound healing was better and amputation lower with angiosome-directed rather than indirect (nonangiosome) tibial revascularization.[48] These observations may be confounded, however, because indirect revascularization may be a marker for more complex tibial disease and poorer limb outcomes.[10] In one study, changes in foot microcirculation assessed by skin perfusion pressures improved to a similar degree in angiosome and nonangiosome tibial revascularization.[49]

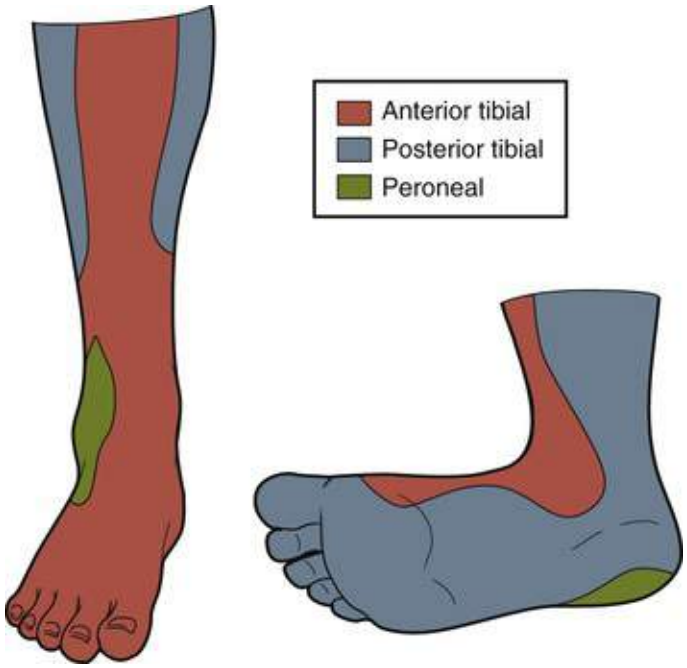

FIGURE 66.19 Angiosome distributions showing regions supplied by the three below-knee arteries. (From Kinlay S. Management of critical limb ischemia. Circ Cardiovasc Interv 2016;9:e001946.)

Tibial disease is most often treated by prolonged balloon inflation, but stents are used as bail-out treatment of flow-limiting dissection[10,18] (**Fig. 66.20; also see Fig. 66.14**). Although balloon-expandable coronary stents are used, they are prone to external compression. Randomized trials of coronary DESs offer greater patency and less reintervention for restenosis than BMSs,[50,51] plain balloon angioplasty,[52] or drug-coated balloon angioplasty.[53] Most of these studies do not show an effect on major amputation or survival, but they may be underpowered for these endpoints. As mentioned, newer drug-coated balloons are under development and testing for tibial interventions.

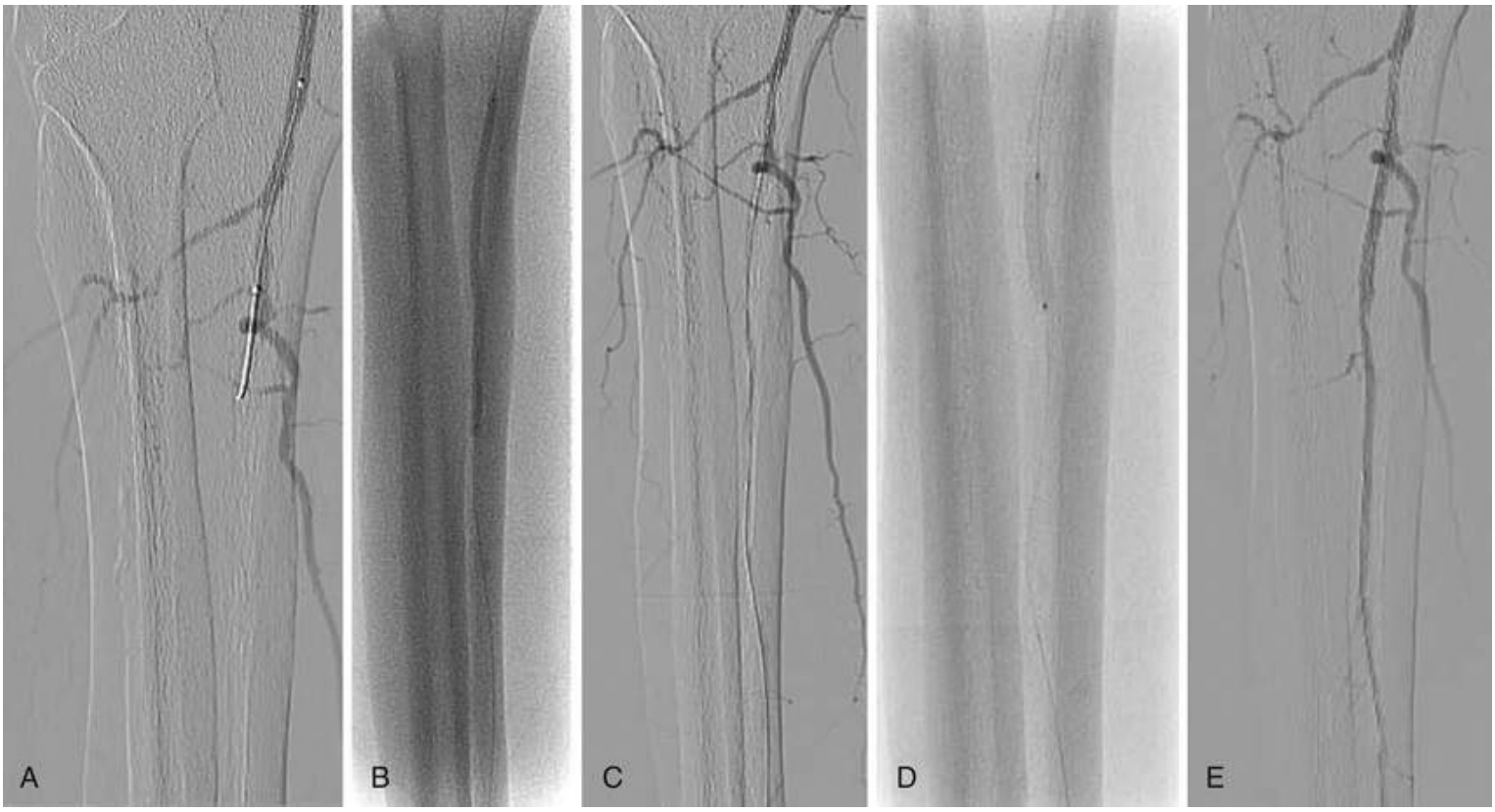

FIGURE 66.20 Bail-out stenting in patient with critical limb ischemia and gangrene of the toes. **A,** Wire traversing occluded peroneal artery. Anterior tibial and posterior tibial arteries were occluded. **B,** Balloon angioplasty of peroneal artery. **C,** Dissection and recoil of proximal peroneal artery. **D,** Stent deployment. **E,** Final angiogram of peroneal artery.

Multiple catheter-based interventions over several months may be required to heal an ulcer because restenosis slows healing. Once healed, however, restenosis may be less of an issue, given the use of adequate foot care and protection to prevent skin breakdown. Managing CLI with ulceration or gangrene requires close follow-up to débride dead tissue in ulcerated areas and aid healing. Gangrenous toes can be left dry until they mummify and autoamputate or can be surgically amputated once viable and devitalized tissue are clearly demarcated. Infected gangrene does require surgical amputation to avoid osteomyelitis. These complexities mandate a team approach to care that includes wound specialists, podiatrists, surgeons, and prosthesis specialists for optimum management.

Cervical Artery Disease

Extracranial Carotid Disease

Extracranial disease of the internal and common carotid artery is a potential source of artery-to-artery embolism, one of the causes of ischemic stroke (**see Chapter 65**). Over the last two decades, improvements in catheter-based techniques have enabled patients at increased risk for stroke from this cause to be treated with outcomes similar to those of traditional carotid endarterectomy.[11]

Symptoms are the most important factor related to the risk for disabling stroke and the indication for revascularization. “Symptomatic disease” refers to patients with a minor stroke or TIA. In the carotid circulation, symptoms are typically dysphasia, contralateral hemiparesis or hemiparesthesia, or ipsilateral transient monocular blindness (amaurosis fugax).[54] Symptoms lasting less than 24 hours and without infarction noted on imaging are classified as TIAs. Minor strokes are classified as “mild clinical deficits” or “no clinical residual deficits” with evidence of infarction on imaging.[54] The higher sensitivity of newer imaging techniques (e.g., diffusion-weighted MRI) compared with older technologies may have

increased the likelihood of finding small infarcts with no residual clinical deficits.[54]

The second factor related to stroke risk is the *severity of stenosis* of the extracranial internal carotid artery. For patients with recent symptoms and stenosis greater than 70%, the risk for stroke over the subsequent 5 years is up to 30%, with a risk of approximately 10% within the first 3 months.[5,11,54] After 3 months, however, the risk for stroke declines and approaches the risk in asymptomatic patients with a similar degree of stenosis (2% to 3% per year).[55]

Carotid endarterectomy and stenting both entail a small procedural/operative risk for stroke, and this limits their benefit to patients at low risk for perioperative events but at higher risk for stroke in the long term without revascularization (**Tables 66.1 and 66.2**). Based on trials of surgery versus medical therapy from 20 years ago, carotid endarterectomy is recommended for symptomatic patients with greater than 50% to 99% stenosis by invasive angiography or greater than 70% stenosis by noninvasive imaging and with a periprocedural risk for stroke and death of less than 6%.[5,11,54] For asymptomatic patients, indications include 80% to 99% stenosis in those with a periprocedural risk for stroke or death of less than 3%.[5,11]

TABLE 66.1

Factors Associated with Increased Risk for Complications with Carotid Artery Stent Placement

Tortuous aortic arch
Platelet or clotting disorder
Difficult vascular access
Lesion or heavy vessel calcification
Visible thrombus
Advanced age (>75-80 yr)*

*The risk for a cerebrovascular accident (stroke) with carotid artery stent placement is increased, and the risk for myocardial infarction with carotid endarterectomy is increased.

TABLE 66.2

Factors Associated with Increased Risk from Carotid Artery Surgery

Anatomic Criteria
High cervical or intrathoracic lesion
Previous neck surgery or radiation therapy
Contralateral carotid artery occlusion
Previous ipsilateral carotid endarterectomy
Contralateral laryngeal nerve palsy
Tracheostomy
Medical Comorbidities
Age >80 yr*
Class III or IV congestive heart failure
Class III or IV angina pectoris
Left main coronary disease
Two- or three-vessel coronary artery disease
Need for open heart surgery
Ejection fraction ≤30%
Recent myocardial infarction
Severe chronic obstructive lung disease

*The risk for a cerebrovascular accident (stroke) with carotid artery stent placement is increased, and the risk for myocardial infarction with carotid endarterectomy is increased.

Carotid stenting with embolic protection has evolved as a treatment that is equivalent to surgical carotid endarterectomy based on direct comparisons in randomized trials of patients with high and average risk for periprocedural CV events from surgery.[56-59] Long-term follow-up of randomized trials show no difference in outcomes over 5 to 10 years between surgical endarterectomy and carotid stenting

for symptomatic and asymptomatic patients with carotid disease.[56,57] Acceptably low periprocedural risk depends on adequate training of operators and selection of patients at low risk for complications.[5,55,60] Potential indications for carotid stenting are the same as those listed earlier for endarterectomy. As with endarterectomy, several factors determine the success of carotid stenting. Patient selection is very important in asymptomatic patients or those several months after symptoms, who have a lower absolute benefit from surgical endarterectomy or stenting than those with recent symptoms.[5,11]

In asymptomatic patients, the reduction in risk with revascularization accrues slowly over the long term and needs to offset the small but important periprocedural/operative risk. This benefit usually takes several years to accrue, and asymptomatic patients need to have reasonable 5-year survival for a realistic chance of achieving a net benefit from revascularization. Patients with a low risk for periprocedural stroke, MI, or death are also selected to maximize the net long-term benefit. For carotid stenting, this includes patients without severe vessel tortuosity, heavy calcification, or significant cognitive deficits.[55] Patients older than 80 years have a higher risk for perioperative adverse events with stenting or surgery. The primary outcome of the CREST study of patients at average surgical risk suggested no difference in outcomes at 2.5 years[61] or 10 years with stenting versus surgery.[57]

Carotid stenting starts with access to the common carotid artery with a diagnostic catheter and then a delivery sheath. Embolic protection consists of distal protection using filters or obstructive balloons deployed distal to the carotid stenosis or proximal occlusion devices deployed proximal to the stenosis. Filters allow blood flow to the brain to continue and theoretically lead to less brain ischemia if the circle of Willis is incomplete. Self-expanding stents using delivery systems on a 0.014-inch platform can avoid external compression (**Figs. 66.21 and 66.22**).

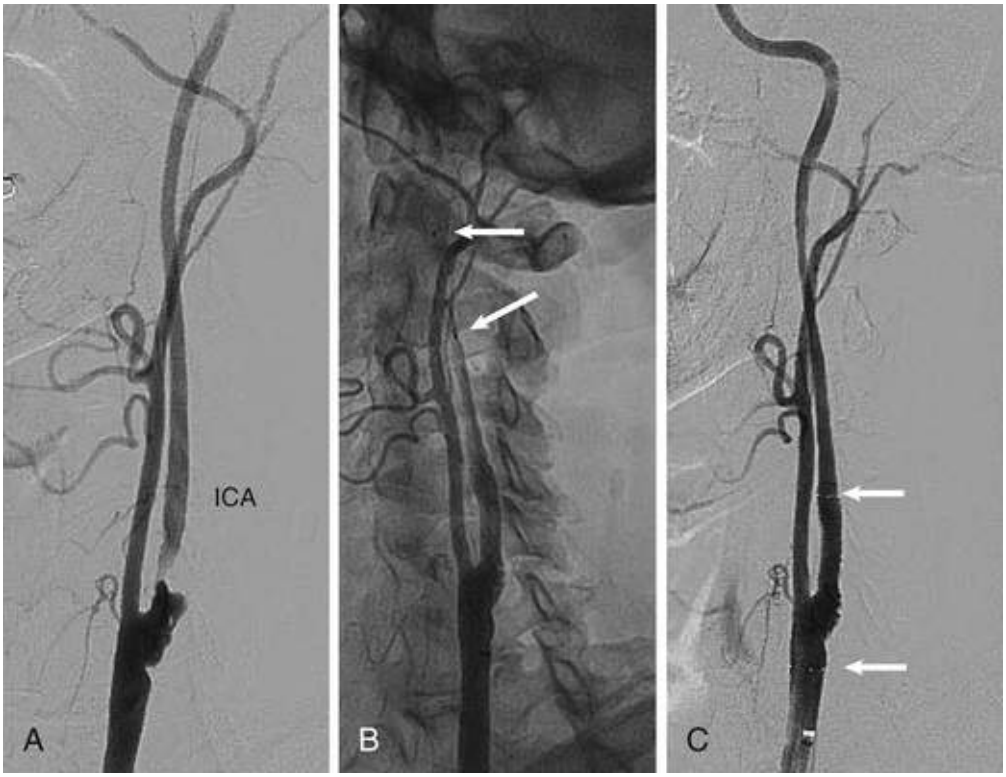

FIGURE 66.21 Carotid stenting for symptomatic carotid stenosis. **A,** Stenosis at origin of left internal carotid artery. **B,** Stent deployed. *Arrows* indicate markers of embolic protection filter. **C,** Final angiogram with *arrows* indicating the margins of the stent.

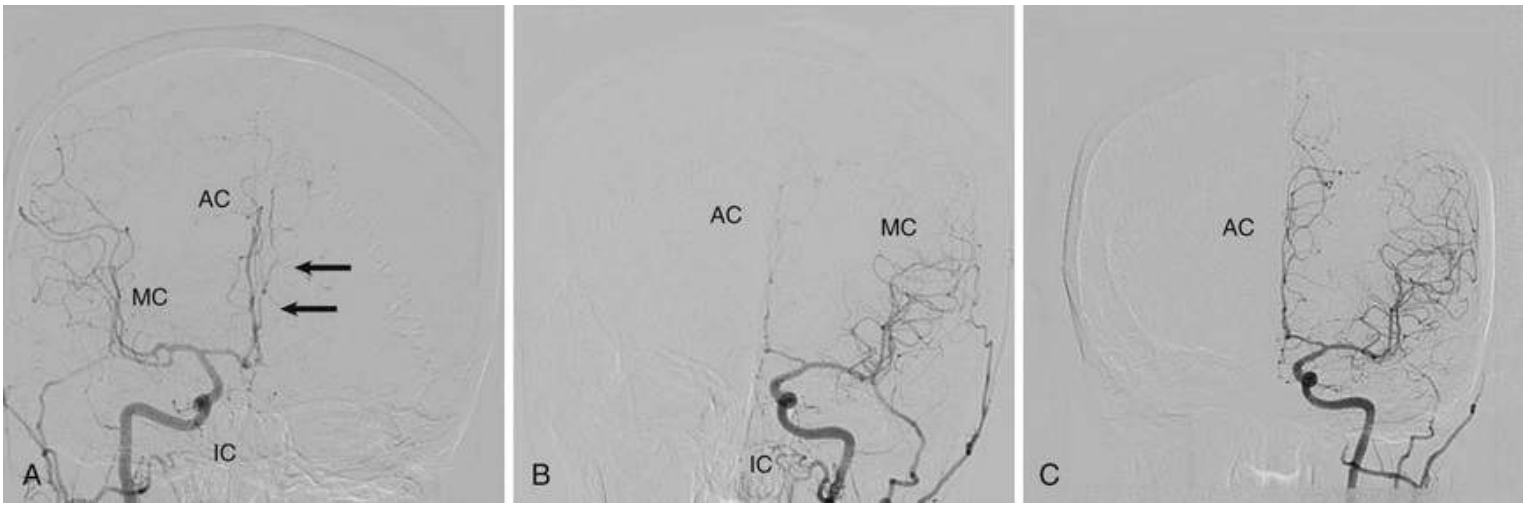

FIGURE 66.22 Intracranial angiograms from the patient in Fig. 66.21. **A,** Right carotid angiogram showing the right internal carotid artery (*IC*), middle cerebral artery (*MC*), and anterior cerebral artery (*AC*). There is crossover filling through the anterior communicating artery into the left anterior cerebral artery because of poor left-sided perfusion from the left cervical internal carotid stenosis. **B,** Left carotid angiogram showing poor filling of the left AC relative to the MC. **C,** Improved perfusion of the left AC after stenting the left internal carotid artery.

Vertebral and Subclavian Disease

The left and right vertebral arteries usually arise from the left and right subclavian arteries, course through the upper vertebrae into the posterior of the skull, and join together as the basilar artery. One vertebral artery is often larger (dominant) than the other, and loss of one such artery is usually well tolerated. Diagnosis of vertebrobasilar insufficiency is clinical with symptoms affecting the brainstem and cerebellum, including dizziness, ataxia, diplopia, and syncope.[5,54] Atherosclerosis usually affects the proximal vertebral arteries, but more extensive proximal disease in the subclavian or brachiocephalic arteries can cause vertebrobasilar insufficiency. Patients with vertebrobasilar insufficiency have a 5-year risk for stroke of approximately 30% without any treatment.

Medical treatment of vertebral artery disease includes antiplatelet agents and 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors. Blood pressure (BP) control to reduce ischemic stroke requires careful titration to avoid hypotension and hypoperfusion, which can precipitate symptoms. Surgical therapy consisting of transection and reimplantation into an adjacent subclavian artery entails considerable morbidity, including Horner syndrome (2%), lymphocele (10% to 15%), chylothorax (<1%), and thrombosis (5% to 10%), as well as high mortality (5%). Extracranial percutaneous treatment, particularly with stenting, has much lower morbidity and short-term mortality, and long-term mortality resembles that of surgery (10% to 20% at 3 years), partly related to the high prevalence of other comorbid conditions.[62]

Subclavian stenosis more often affects the left subclavian origin than the brachiocephalic or right subclavian arteries. This predilection may result from more disturbed blood flow at the origin of the left subclavian artery. Subclavian stenosis usually causes a 15 mm Hg or greater difference in noninvasive brachial BP between the two arms,[5] in the absence of significant bilateral disease. Most subclavian stenosis, however, is asymptomatic and does not need investigation or revascularization. Symptoms from subclavian stenosis include arm claudication with activity, angina in patients with a left internal mammary/thoracic artery graft from previous coronary artery bypass surgery (**Fig. 66.23**), vertebrobasilar insufficiency with arm activity because of vertebral steal, or ischemic (hand) steal syndrome in patients with a dialysis fistula. Although noninvasive imaging can identify reverse flow in the vertebral artery

distal to a subclavian stenosis, this physiologic abnormality does not always lead to symptoms, particularly if it involves a nondominant vertebral artery or blood flow in the contralateral vertebral artery is not impeded. Thus, physiologic reversal of flow in the vertebral artery without symptoms is not an indication for revascularization.

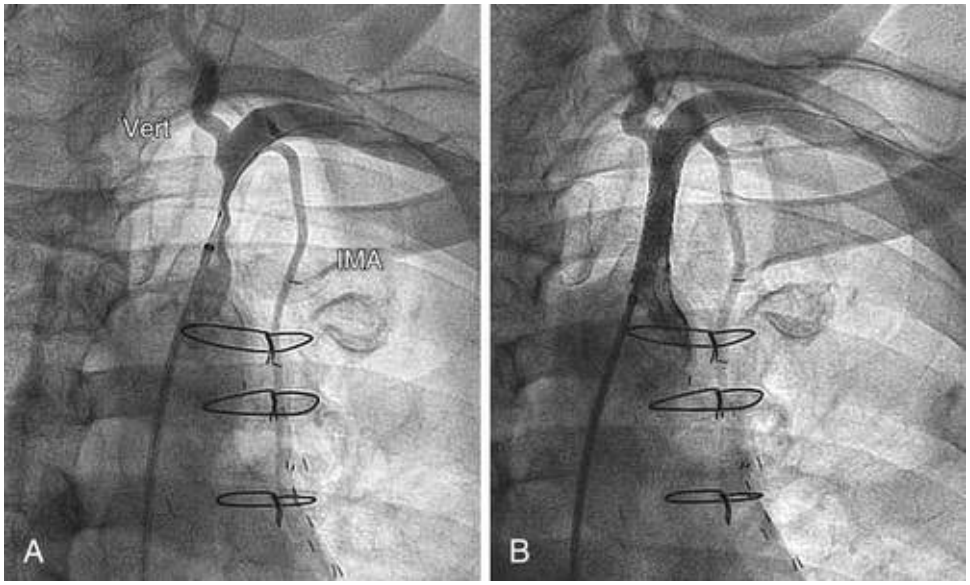

FIGURE 66.23 Stenting a left subclavian stenosis in a patient with angina and ischemia of the anterior left ventricular wall noted on stress testing. **A,** Shuttle sheath placed at the origin of the subclavian artery and stenosis. *IMA,* Internal mammary artery; *Vert,* vertebral artery. **B,** Stent deployed to improve blood flow to the IMA.

Medical therapy targets the progression of atherosclerosis (e.g., antiplatelet agents, HMG-CoA reductase inhibitors, BP control). Because most subclavian disease is proximal or ostial, surgical revascularization usually involves subclavian-to-common carotid bypass, a procedure associated with a 5% risk for morbidity, including stroke. This explains the more common use of percutaneous revascularization with stents to treat symptomatic subclavian disease. Balloon-expandable stents are generally used because they allow more precise placement to cover the ostium of the artery and avoid the vertebral and left internal mammary artery origins. In the event that these distal branches are covered by "snowplowing" of plaque into the branch vessel, balloon-expandable stents permit dilation through the stent struts into the branch vessel. Embolic stroke is rare, possibly because of reverse flow down the vertebral artery during balloon dilation and stenting. Thus, embolic protection is infrequently used for vertebral and subclavian artery stenting. The long-term results of stenting subclavian and brachiocephalic disease are excellent (>90% overall patency).[5]

Mesenteric and Renal Artery Disease

Mesenteric Artery

Three arteries supply the mesenteric viscera: the celiac artery, superior mesenteric artery, and inferior mesenteric artery. Although advanced atherosclerosis of the aorta is common, mesenteric angina or infarction is very uncommon, probably because of the multiple collateral networks in the mesentery. Acute mesenteric ischemia with infarction is a surgical emergency because it is usually associated with infarction of the small or large intestine.[12] An embolus (e.g., from thrombus in the heart associated with atrial fibrillation) is a common cause and typically lodges in the proximal mesenteric artery (usually the

superior mesenteric artery). Urgent surgery within 24 hours is required to resect dead bowel and revascularize ischemic bowel, with death in virtually all cases treated beyond this time.

Chronic mesenteric ischemia is a more insidious syndrome that causes discomfort or frank abdominal pain on eating and substantial weight loss because of food avoidance.[12] Classically, more than two mesenteric arteries are stenosed or occluded. The disease is usually adjacent and involves advanced atherosclerosis of the aorta and origins of the mesenteric arteries. Asymptomatic disease of the mesenteric arteries does not require revascularization.

Bowel endoscopy can detect changes associated with ischemia, but noninvasive arterial imaging with duplex ultrasound or MRA or CTA generally identifies the extent of disease. Invasive angiography usually requires a lateral aortogram to identify clearly the origins of the mesenteric arteries. Surgical revascularization with reimplantation of the arteries has high mortality and morbidity (10% to 15%) because of the advanced age and other vascular comorbid conditions. Percutaneous angioplasty with stenting has lower mortality (<5%) and morbidity and achieves good resolution of symptoms in about 70% to 80% of patients over several years (**Fig. 66.24**).[12] Restenosis may require further intervention and can be identified by duplex ultrasound and CTA or MRA.

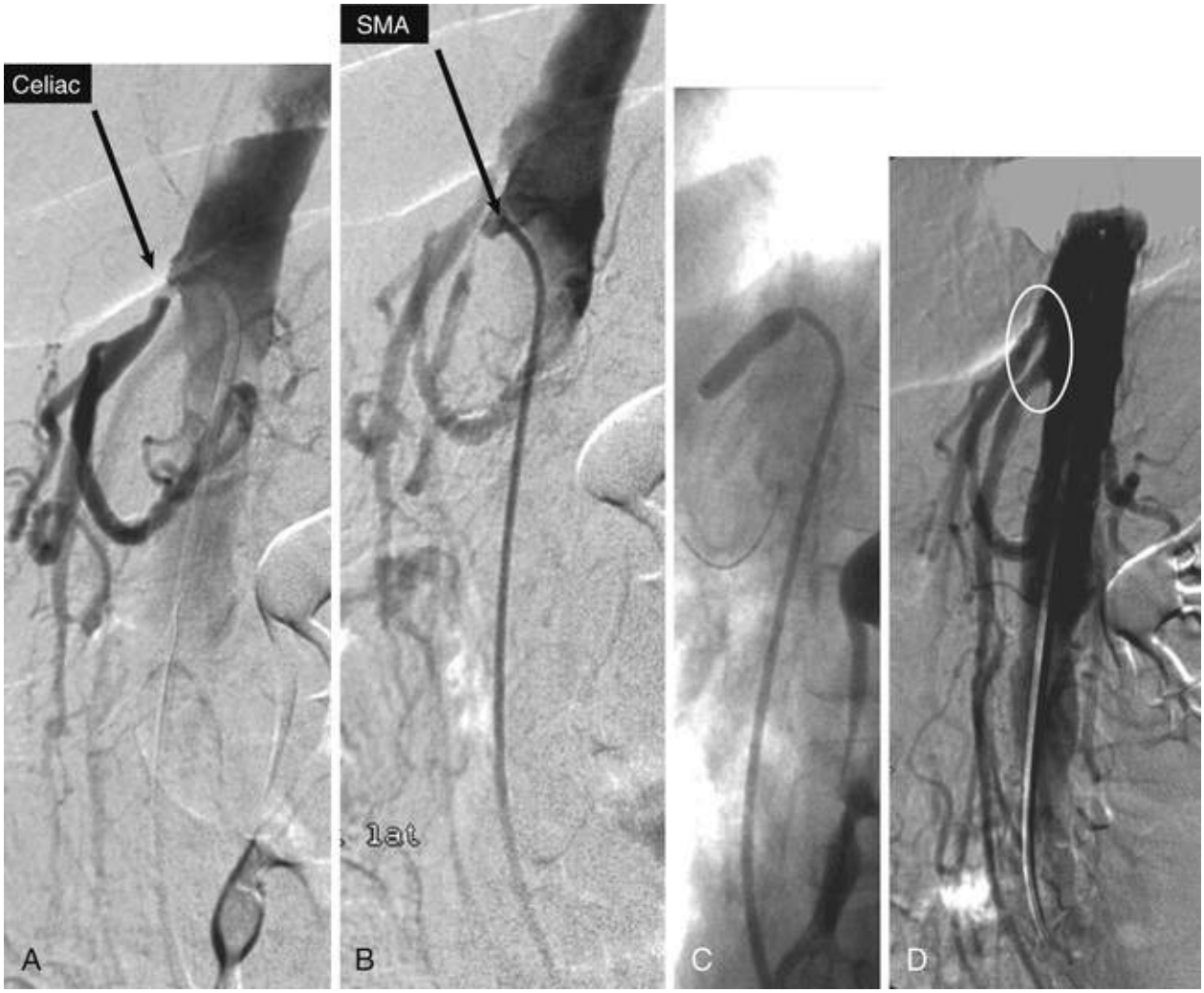

FIGURE 66.24 Mesenteric stenosis. **A, B,** Both these vessels proved to be critically stenosed. *SMA,* Superior mesenteric artery. **C,** The celiac artery and SMA were treated interventionally to restore wide patency in both, as outlined in **D.** The patient's symptoms abated, and she began to gain weight.

Renal Artery

Renal artery stenosis can cause secondary hypertension or rapidly deteriorating renal function. Clinical clues to the diagnosis of renal artery stenosis include onset of hypertension before 55 years of age, resistant or malignant hypertension (particularly in a previously well-controlled patient), rapidly increasing creatinine level over a several-month period or earlier, and sudden pulmonary edema without a clear cardiac cause (e.g., because of sudden hypertension with or without acute mitral regurgitation). Imaging with duplex ultrasound or with MRA, CTA, or invasive angiography can identify renal artery stenosis.

Although renal artery stenosis is relatively common, determining whether it is a reversible cause of hypertension or declining renal function is difficult. Screening outside the aforementioned clinical scenarios probably offers low yield and justification because treatment does not usually impact BP control or renal function.[63,64] Although some patients with renal impairment and significant stenosis may have improved renal function with stenting, approximately one third of patients see no improvement, and in another 20% to 30% of patients, renal function worsens, possibly because of atheroembolization. Even though many operators use embolic protection devices during renal stenting, these devices have unknown value in preventing atheroemboli or worsening renal function.

Three randomized trials of stenting renal arteries with greater than 40% to 60% stenosis by angiography to control resistant hypertension or preserve renal function showed no effect on BP control, preservation of renal function, or CV events.[63,65] In the CORAL study, even the subgroup of participants with a renal artery stenosis of at least 80% did not benefit from renal artery stenting.[65] As a result, the enthusiasm for renal artery stenting has waned considerably, although there is still some support for stenting renal artery stenosis in the presence of “flash” pulmonary edema without cardiac causes, rapidly decreasing renal function, and some cases of accelerating or resistant hypertension, based mainly on case reports and case series (**Fig. 66.25**).[66] In particular, there may still be value for stenting in bilateral renal artery stenosis and unilateral stenosis to a sole remaining kidney.

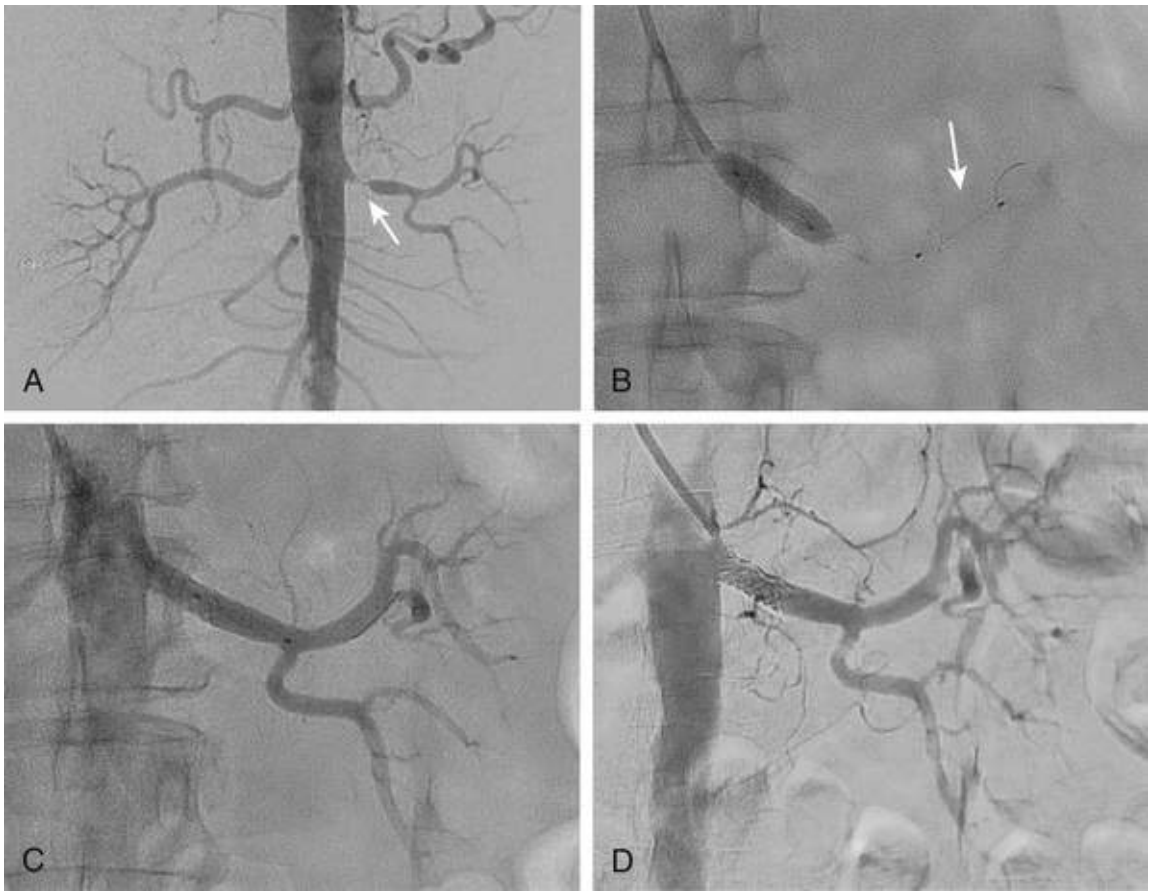

FIGURE 66.25 Left renal artery stent for rapid deterioration in renal function associated with hypertension. **A,** Aortogram showing left renal artery stenosis (*arrow*) with delayed filling of the left kidney compared to the right kidney. **B,** Stent deployment with some overhang into the aorta using an embolic protection filter (*arrow*). **C,** Post-stent deployment angiogram. **D,** Final angiogram after removal of filter.

Fibromuscular dysplasia (FMD) is a rarer cause of renal artery stenosis and hypertension more often seen in younger patients, with a higher prevalence in women.[67] Although defined histologically in the past, a recent classification based on imaging (multifocal "beading" versus unifocal) disease has some prognostic value.[68] FMD typically involves the middle or distal renal artery, whereas atherosclerosis usually involves the ostium or proximal renal artery. FMD often accompanies similar disease in other arterial beds (e.g., carotid arteries).[67] This diagnosis has particular importance in that balloon angioplasty without stenting often very effectively controls BP with a durable response.

Resistant hypertension despite multiple antihypertensive agents is a marker of elevated CV risk.[69] Recognition that the rich plexus of sympathetic nerves in the adventitia of renal arteries may contribute to resistant hypertension led to a number of catheter-based technologies to ablate the sympathetic nerves to lower BP and CV risk (**see Chapters 46 and 47**.) Although early uncontrolled studies suggested marked BP lowering in selected patients, the large sham-controlled SYMPLICITY HTN-3 trial showed no significant effect of renal artery denervation on BP or CV events.[70]

Endovascular Treatment of Venous Disease

Extremity Deep Venous Thrombosis

Upper and lower extremity deep venous thrombosis (DVT) results from multiple factors often encompassed in the Virchow triad: abnormalities in coagulation, hemodynamic flow, and endothelial injury (**see Chapter 84**). Such factors include hypercoagulable states, venous stasis, external obstruction, scarring or congenital abnormalities of veins, or injury to veins.

Lower extremity DVT is treated primarily medically with anticoagulation, but endovascular treatment is an option for patients with proximal venous thrombosis defined as being at the level of the common femoral vein or higher. Thrombosis at this site occurs in about one third of all cases of lower extremity DVT[38] and obstructs venous return from the lower limb. Proximal DVT occurs more frequently in the left leg as a result of compression of the left iliac vein by the overlying right iliac artery (May-Thurner syndrome). Acute severe proximal deep venous occlusion, characterized by a blue limb, pain, and limb ischemia (phlegmasia cerulea dolens) is often associated with malignancy. Chronic post-thrombotic syndrome occurs over several years in about half the patients with iliofemoral DVT[37] and involves limb swelling, heaviness, and pain. Medical treatment includes compression stockings and anticoagulation. Endovascular treatment of proximal DVT by catheter-directed thrombolysis with or without balloon angioplasty and self-expanding stents reduces the incidence of post-thrombotic syndrome by about 20%[37] (**Fig. 66.26**).

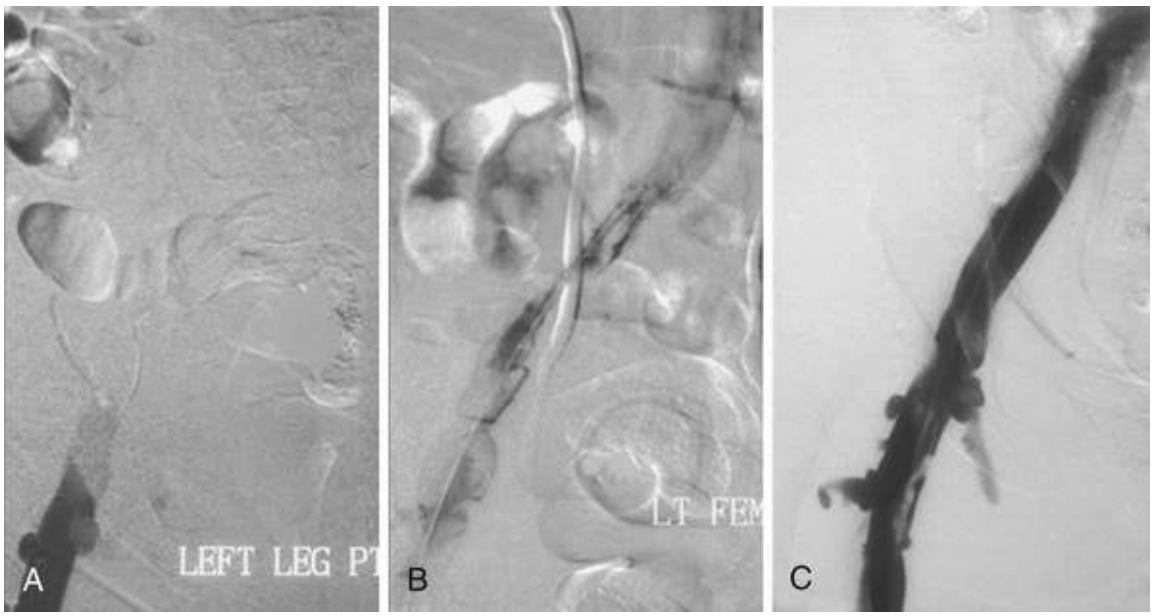

FIGURE 66.26 Venogram and intervention. A venogram of the left femoral vein was obtained after gaining access to the popliteal vein under ultrasound guidance. The patient is lying face down on the table to allow access to the popliteal vein. **A,** Baseline showing occlusion of the left femoral vein. **B,** Multihole catheter across the venous occlusion; administration of lytic agents is started. **C,** Four hours after lysis following percutaneous transluminal angioplasty and placement of a self-expanding stent to restore patency.

Upper extremity DVT is related to effort-related proximal vein thrombosis in athletes (Paget-Schroetter syndrome), venous thoracic outlet syndrome, catheter-related thrombosis, or malignancy.[71] Effort-related thrombosis is usually associated with vigorous arm exercise (e.g., weightlifting). *Venous thoracic outlet syndrome* is related to compression of the subclavian vein as it exits the thoracic cage between the clavicle, first rib, costoclavicular ligament, and subclavian and anterior scalene muscles. Catheter-related thrombosis is associated with indwelling catheters, ports, and pacemaker or defibrillator leads. Malignancy with external obstruction is more frequently associated with superior vena cava syndrome (see next). Anticoagulation is the most common treatment of upper extremity DVT, but endovascular therapy can provide relief from post-thrombotic syndrome. Endovascular therapy includes catheter-directed thrombolysis and treatment of any precipitating cause. For example, thoracic outlet syndrome generally requires surgical decompression (resection of the first rib or other structures) and venoplasty soon after thrombolysis because stents usually crush or fracture in this location. Central venous catheters

should be removed if they are no longer required, or the patient should be maintained on a long-term anticoagulation regimen.

Superior Vena Cava Syndrome

Superior vena cava syndrome results from obstruction of the superior vena cava with impairment of venous return from the head and upper limbs (**see Chapters 81 and 84**). Typical causes include external compression, invasion from a tumor, or thrombosis related to an indwelling central catheter (e.g., for chemotherapy) or leads from pacemakers or defibrillators. Symptoms include swelling and fullness in the head, headache, dyspnea, and a sense of choking. Angioplasty alone rarely relieves this condition successfully because of vessel recoil, but stenting very effectively reduces symptoms. Thrombosis often accompanies stenosis and requires catheter-directed thrombolytic therapy before balloon and stent therapy (**Fig. 66.27**). The stent usually needs to be oversized and extended well above and partly below the lesion so that it remains anchored and less likely to embolize. Anticoagulation is generally prescribed, often indefinitely for superior vena cava obstruction or thrombosis associated with malignancy. Symptoms usually respond rapidly within 24 hours. Ideally, indwelling catheters and pacemaker leads should be removed before stenting and reimplanted afterward if required. Long-term outcomes depend more on the cause of the superior vena cava obstruction, but in nonmalignant cases, high patency rates (>80%) over several years prevail.[72,73]

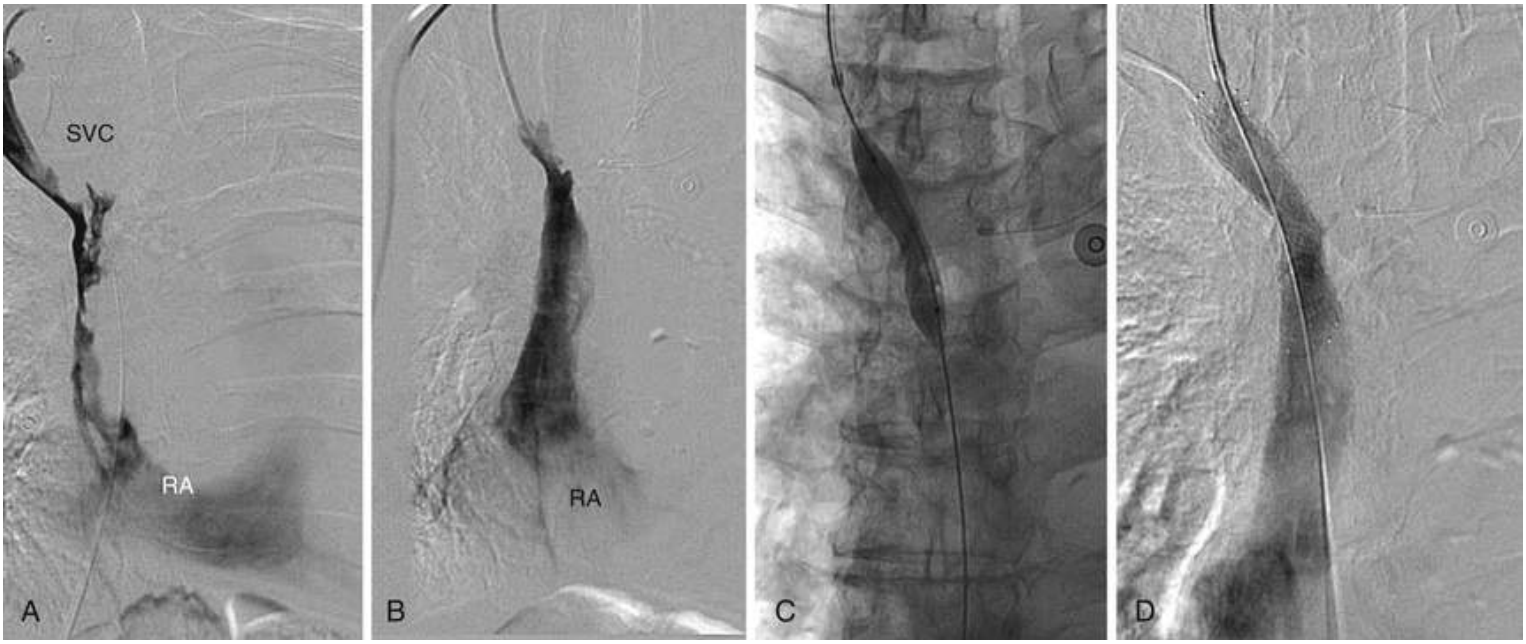

FIGURE 66.27 Superior vena cava syndrome secondary to external compression of the SVC by a lung tumor and thrombosis of the SVC. **A,** Initial venogram showing compression of the superior vena cava (*SVC*) and filling defects because of thrombus; *RA,* right atrium. **B,** Venogram after 24 hours of catheter-directed thrombolysis with resolution of the thrombus but residual stenosis. **C,** Balloon venoplasty. **D,** Final angiogram after deployment of a self-expanding stent.

Future Perspectives

New technologies have advanced endovascular treatment of noncoronary vascular disease into the mainstream. In many cases, adapting techniques from interventional cardiology has revolutionized the

ability to treat patients with complex peripheral vascular disease through minimally invasive endovascular means. In coming years, an even greater proportion of peripheral vascular disease may be treated in the angiography suite instead of in the operating room.

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PART VIII
Diseases of the Heart Valves

OUTLINE

67

Approach to the Patient with Valvular Heart Disease

Catherine M. Otto, Robert O. Bonow

Over the lifetime of a patient with valvular heart disease (VHD), the most important aspects of medical care are

1. An accurate diagnosis of the cause and severity of VHD
2. Measures to prevent further valve dysfunction through prevention of rheumatic fever and endocarditis
3. Education about the natural history of disease, including anticipated type and timing of symptom

onset
4. Primary and secondary prevention of atherosclerotic cardiovascular disease (CVD)
5. Interval medical evaluation and imaging to monitor disease progression
6. Prompt recognition and treatment of associated cardiac conditions, including atrial fibrillation (AF), hypertension, coronary artery disease (CAD), endocarditis, and aortic dilation
7. Optimal timing of surgical or transcatheter intervention to correct or ameliorate valve dysfunction.

Although much attention is focused on the timing and type of intervention, the other aspects of standard medical care in these patients likely have comparable or greater benefit in improving quality and length of life. As clinicians, we follow patients with VHD for many years before and after intervention; a surgical or transcatheter intervention is only one (although major) episode in each patient's medical journey. We also need to consider that most of our interventions leave the patient with a new disease: a prosthetic valve. Surgical and transcatheter interventions are transformative technologies that prevent premature death and disability, but patients still have VHD after intervention and continue to require medical therapy, as discussed in this chapter.

The Heart Valve Clinic

The clinical presentation, diagnosis, natural history, and optimal timing of interventions for patients with VHD depend on the specific valve lesion (**see Chapters 68 to 70**). However, many of the principles of patient evaluation and medical therapy are common to all VHD patients. Patients with VHD now are classified by disease stage as follows[1,2]:

Stage A: Patients at risk for development of VHD
Stage B: Asymptomatic patients with progressive VHD (mild to moderate severity)
Stage C: Asymptomatic patients with severe VHD with *either*
Normal right or left ventricular systolic function (stage C1) *or*
Decompensated ventricular function (stage C2)
Stage D: Symptomatic patients with severe VHD

Patients with significant VHD are best evaluated in a heart valve clinic, functioning as part of the heart valve team (**Fig. 67.1**), given the complexity of diagnosis and clinical decision making in these patients.[3,4] However, the initial diagnosis of VHD relies on detection by the primary care provider or general cardiologist. VHD patients may present with new cardiac symptoms, but often the diagnosis is made in asymptomatic patients based on the presence of a murmur on physical examination or findings on echocardiography requested for other reasons.

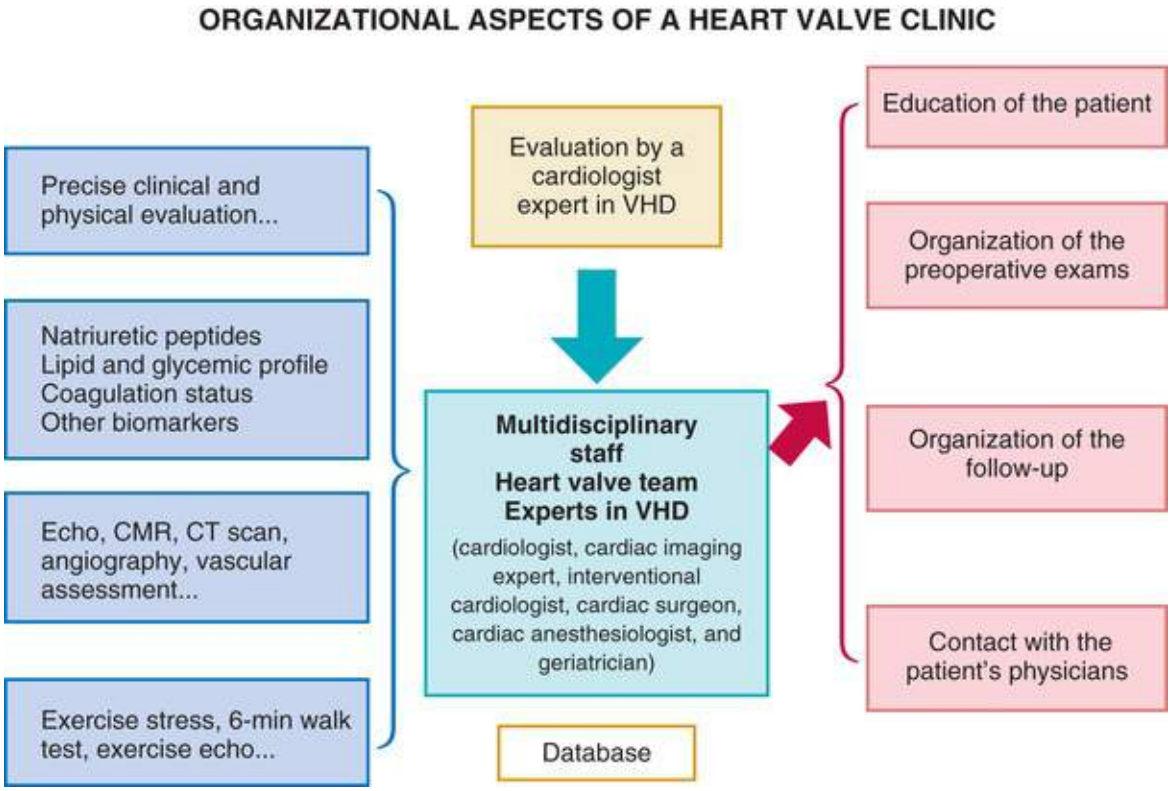


FIGURE 67.1 Functioning of the advanced heart valve clinic. CMR, Cardiac magnetic resonance imaging; CT, computed tomography; Echo, echocardiography; VHD, valvular heart disease. (From Lancellotti P, Rosenhek R, Pibarot P, et al: ESC Working Group on Valvular Heart Disease position paper. Heart valve clinics: organization, structure, and experiences. Eur Heart J 2013;34:1597.)

Clinical History

In a patient with suspected or known VHD, the clinical history is the most important element for diagnosis and clinical decision making (**see Chapter 10**). Patient demographics provide important clues about the likelihood and type of VHD based on the epidemiology of these conditions. For example, the asymptomatic young man with a diastolic murmur most likely has a bicuspid aortic valve; the pregnant patient with heart failure (HF) who is from an area with endemic rheumatic heart disease most likely has rheumatic mitral stenosis (MS); a middle-aged man with a loud systolic murmur and decreased exercise tolerance likely has mitral valve prolapse (MVP); and the elderly man with a systolic murmur and HF likely has calcific aortic stenosis (AS).

Risk Factors.

Potential risks for VHD include genetic, clinical, and infectious factors. Although specific genetic causes have not yet been identified, a positive family history often is present in patients with a bicuspid aortic valve or MVP, as well as in patients with VHD secondary to a connective tissue disorder, such as Marfan syndrome. Clinical factors associated with calcific valve disease include older age, male gender, hypertension, hyperlipidemia, smoking, diabetes, and renal insufficiency.[5] Only approximately 50% of those with rheumatic valve disease are aware of having had rheumatic fever in the past, so rheumatic valve disease should be considered in any patient who has resided in an area with a high prevalence of rheumatic fever[6] (**see Chapter 74**).

Symptoms.

Symptoms caused by VHD include frank HF, angina, and syncope, although the initial symptoms typically

are subtler with decreased exercise tolerance, exertional dizziness, or dyspnea. Because VHD typically progresses slowly over many years with adaptive cardiac changes, patients may gradually reduce activities without recognizing that limitation is caused by a medical condition and thus may deny symptoms, even when exercise capacity is severely reduced. In contrast, acute valve regurgitation from endocarditis, chordal rupture, or aortic dissection presents acutely with cardiogenic shock, pulmonary edema, or HF.

Exercise Capacity.
Clinicians should specifically ask patients to compare their current level of physical activity to activity levels in the past, in order to detect decreased exercise capacity in the apparently "asymptomatic" patient.[7] With careful questioning and education of the patient about the expected symptoms of VHD, many patients then will realize that symptoms are present and will report this at the next follow-up visit. If in doubt about symptom status, exercise testing may be helpful (**see Chapters 68 and 69**).

Other Considerations.
Clinical decision making in the VHD patients involves numerous factors other than the presence and severity of VHD. Thus the clinical history also should include comorbid cardiac and noncardiac conditions, functional status, cognitive function, family and social support, and a discussion of patient preferences and values.

Physical Examination

Physical examination is important in patients with known or suspected VHD (**see Chapter 10**). A cardiac murmur is a defining characteristic of VHD and the most common reason for making the initial diagnosis. In addition, discrepancies between physical examination findings and diagnostic testing may prompt additional evaluation. However, reliability of physical examination is low for determining the exact cause and severity of VHD. Thus, although it is an intellectual challenge to listen to the murmur, evaluate changes with maneuvers, and so on, the real value of physical examination is for monitoring the patient's general appearance; looking for signs of HF; evaluating frailty, physical activity levels, and cognitive function; and detecting findings to suggest a systemic disease process associated with VHD. In clinical practice the wide availability of echocardiography ensures that a correct diagnosis of valve anatomy and function is possible in every patient (**see Chapter 14**).

Cardiac Murmurs

The murmur characteristics, loudness, radiation, and associated findings provide useful clues about which valve is involved and whether the valve is stenotic or regurgitant. However, with a few exceptions, clinical studies have demonstrated that physical examination is unreliable for evaluation of the severity of VHD and remains unreliable even with higher levels of education and training. Thus, echocardiography is recommended for (1) any murmur associated with cardiac symptoms, (2) a grade 3 or louder systolic murmur, and (3) any diastolic murmur.

Murmur Location

The location on the chest wall where the murmur is loudest, the direction of radiation, the timing of the murmur and associated changes in the first and second heart sounds all are closely related to the anatomy and hemodynamics of the valve lesion (**Fig. 67.2**). Systolic murmurs are caused by stenosis of a semilunar

(aortic or pulmonic) valve or regurgitation of an atrioventricular (mitral or tricuspid) valve, with a differential diagnosis that includes other abnormal systolic cardiac flows (e.g., ventricular septal defect) (**Table 67.1**). Diastolic murmurs are caused by regurgitation of a semilunar (aortic or pulmonic) valve or stenosis of an atrioventricular (mitral or tricuspid) valve.

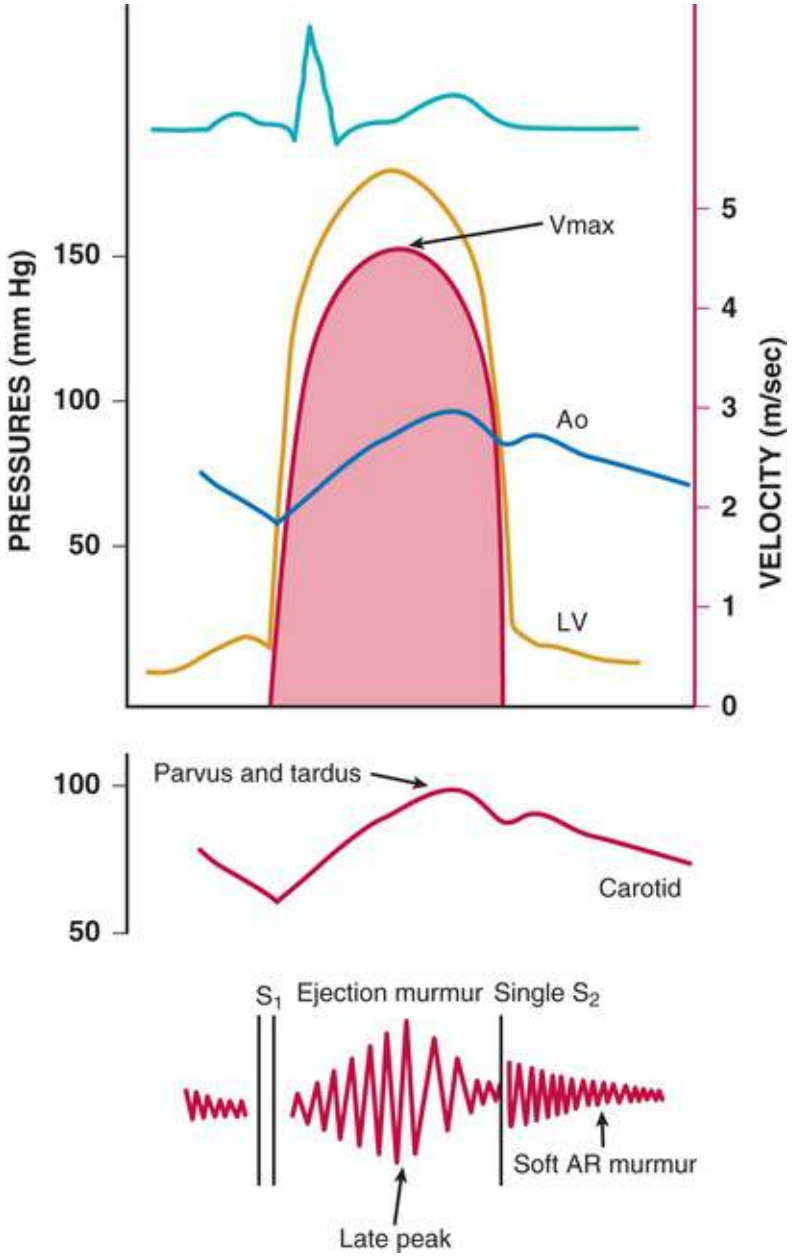


FIGURE 67.2 The close relationship among cardiac hemodynamics, Doppler flow velocities, and physical examination findings is evident in this diagram of the ECG (*top*), aortic (Ao) and left ventricular (LV) pressure tracings, aortic flow velocity (*red shaded area*), carotid pulse contour, and auscultatory findings (*bottom*) in valvular aortic stenosis. AR, Aortic regurgitation; Vmax, Maximum velocity.

TABLE 67.1

Physical Examination Characteristics of Murmurs Caused by Valve Disease

CONDITION	CHARACTERISTICS AND TIMING	LOCATION	RADIATION	EFFECTS OF MANEUVERS	ASSOCIATED FINDINGS	DIFFERENTIAL DIAGNOSIS
Innocent flow murmur	Soft midsystolic	Base	Variable or none	No change	None	A flow murmur is common during pregnancy and in patients with a high output state (e.g., fever, anemia).
Aortic stenosis (AS)	Crescendo-decrescendo systolic	Base (right second ICS)	Usually to carotid arteries but sometimes to apex in older adults	Decrease with handgrip or standing	Single S_2, delayed and decreased carotid upstroke, midsystolic click with congenital AS	HCM murmur peaks in late systole and increases with standing or strain phase of Valsalva maneuver.
Mitral regurgitation (MR)	Holosystolic	Apex	Radiation to back or axilla with posteriorly directed jet, to LSB or head with anteriorly directed jet	Increase with handgrip	Hyperdynamic apical impulse	Ventricular septal defect murmur usually loudest (with palpable thrill) at LSB and does not change with handgrip. Acute MR may have a very soft or inaudible murmur.
Tricuspid regurgitation (TR)	Holosystolic with respiratory variation	Left lower sternal border	Right lower sternal border	Increase with inspiration	Prominent v waves in JVP, pulsatile liver	—
Pulmonic stenosis (PS)	Crescendo-decrescendo systolic	Left second ICS	None	No change	Ejection click if mobile valve leaflets	A pulmonic flow murmur due to increased flow volume may be present with ASD in the absence of PS.
Aortic regurgitation (AR)	High-pitched diastolic decrescendo	Best heard at LSB with patient sitting up and leaning forward at end-expiration	None	Increase with handgrip	Wide pulse pressure, displaced and enlarged apical impulse	Acute AR murmur may be harsh and short in duration and the pulse pressure may be narrow with a normal size apical impulse.
Mitral stenosis (MS)	Low-pitched diastolic rumble, presystolic accentuation	Apex Murmur best heard with patient in steep left lateral position with stethoscope bell on apical impulse	None	Best heard in left lateral decubitus position	Loud S_1 with opening snap in early to middle diastole	—
Pulmonic regurgitation (PR)	Soft decrescendo diastolic	Left second ICS	LSB	May increase with inspiration	RV heave if severe PR has resulted in RV dilation	—
Tricuspid stenosis (TS)	Low-pitched diastolic rumble	Right sternal border	Right upper abdomen	Increase with inspiration	Increased JVP, peripheral edema, ascites	—

ASD, Atrial septal defect; *HCM,* hypertrophic cardiomyopathy; *ICS,* intercostal space; *JVP,* jugular venous pressure; *LSB,* left sternal border; *RV,* right ventricular.

Murmur Timing

The timing of onset and offset and the changing loudness of the murmur over the cardiac cycle reflect valve hemodynamics. A murmur of AS starts after the first heart sound (S_1), increases and then decreases in loudness with a peak in midsystole to late systole, and ends before the second heart sound (S_2). The visual analogy for this crescendo-decrescendo murmur is a diamond-shaped or ejection-type murmur. In contrast, the murmur of mitral regurgitation (MR) obscures S_1 and S_2 because backflow across the mitral valve starts sooner and ends later than flow across the aortic valve. An MR murmur typically is uniform in loudness from onset to offset, a pattern called *holosystolic.* In patients with MVP, the MR murmur may be only late systolic, and S_1 is clearly audible.

Murmur Loudness

Murmurs tend to be loudest over the anatomic location of the affected valve, for example, the upper right second intercostal space at the cardiac base for the aortic valve and the left ventricular (LV) apex for the

mitral valve. Right-sided, but not left-sided, valve lesions vary in loudness with respiration. In general, the loudness of a murmur correlates with severity; more severe AS is associated with a louder murmur in many patients, but this relationship is not a reliable indicator of disease severity. For example, a MR murmur may be loud with only mild valve leakage, and conversely, severe AS may be present with a soft murmur if cardiac output is low or sound transmission to the chest wall is poor.

Murmur Radiation

Murmurs can also be heard distal to the valve lesion, usually with a reduced loudness. The “radiation” of a murmur follows the blood flow direction: AS murmurs radiate to the carotid arteries; MR murmurs radiate to the axilla. However, there is wide variation in physical examination findings. The murmur of AS radiates to the apex in some, often elderly, patients (the Gallavardin phenomenon). The MR murmur may radiate to the back with a posteriorly directed MR jet or superiorly, if the jet is aimed in that direction.

Changes in First and Second Heart Sounds

The relationship of the murmur to S_1 and S_2 and the sounds themselves also provide information about the presence of valve disease. With AS, the aortic component of S_2 is reduced; an absent aortic closure sound is a relatively sensitive and specific finding in patients with severe AS. With MS, an opening snap precedes the diastolic murmur, with the interval between S_2 and the opening snap reflecting the severity of valve obstruction. Other valve lesions are associated with other changes (**see Table 67.1**).

Other Cardiac Findings

Examination of the neck veins is helpful for estimating right atrial filling pressure and for detection of abnormal venous pulsations, such as the *v* wave caused by tricuspid valve regurgitation, which can be associated with a lateral motion of the head with each heart beat in severe cases. The carotid artery impulse is bounding in patients with severe aortic regurgitation (AR) and may be associated with a rhythmic bobbing of the head in synchrony with the heart beat due to the increased pulse pressure (de Musset sign). A delayed onset of the carotid upstroke with a slow rate of rise in systole is specific for severe aortic valve obstruction. However, this finding is not sensitive for detection of AS because carotid pulsations may be brisk if there is concurrent increased vessel stiffness or AR, even when severe AS is present. Other standard components of the cardiovascular examination in patients with VHD include examination of the lungs, abdomen, and extremities.

Diagnostic Testing

Cardiac imaging is central to diagnosis and management of patients with VHD. Chest radiography is used for evaluation of acute decompensation but is not routinely used for diagnosis or monitoring. The 12-lead electrocardiogram (ECG) and various types of ambulatory monitoring are used for diagnosis and management of arrhythmias, as in any patient with heart disease, but ECG diagnosis of chamber hypertrophy or dilation largely has been replaced by direct imaging.[8]

Imaging

Echocardiography (See Chapter 14)

Echocardiography is the primary modality for diagnosis of the cause of VHD, severity of valve dysfunction, LV size and systolic function, and associated findings such as pulmonary hypertension and left atrial enlargement.[9] Standard echocardiographic approaches are appropriate for the initial diagnosis of VHD, but more precise evaluation and quantitation of valve disease require special expertise. Not all echocardiography laboratories or echocardiographers have the training and experience to perform these measurements reliably, and thus imaging is best performed at the heart valve center. Advanced imaging approaches, including three-dimensional imaging and strain rate imaging, as well as transesophageal echocardiography (TEE), have further expanded clinical indications for echocardiography. Echocardiography is essential both for optimal timing of surgical or transcatheter intervention (**see Chapter 72**), and for monitoring progressive disease (**Table 67.2**).

TABLE 67.2

Frequency of Echocardiograms in Asymptomatic Patients with Valvular Heart Disease and Normal Left Ventricular Function*

Stage	VALVE LESION			
	Aortic Stenosis†	Aortic Regurgitation	Mitral Stenosis	Mitral Regurgitation
Stage B (progressive)	Mild (V_{max} 2.0-2.9 m/sec) Every 3-5 yr	Mild Every 3-5 yr depending on valve and sinus anatomy	Mild (MVA >1.5 cm^2) Every 3-5 yr	Every 3-5 yr (mild severity)
	Moderate (V_{max} 3.0-3.9 m/sec) Every 1-2 yr	Moderate Every 1-2 yr	—	Every 1-2 yr (moderate severity)
Stage C (severe)	Every 6 mo to 1 yr (V_{max} ≥4 m/sec)	Every 6-12 mo More frequently if LV dilation present.	Every 1-2 yr (MVA 1.0-1.5 cm^2) Every 1 yr (MVA <1 cm^2)	Every 6-12 mo More frequently if LV dilation present.

*Patients with mixed-valve disease may require serial evaluations at intervals earlier than recommended for single-valve lesions.

†With normal stroke volume.

LV, Left ventricle; *MVA,* mitral valve area; V_{max}, maximum aortic jet velocity.

Modified from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57-185.

Cardiac Magnetic Resonance Imaging (See Chapter 17)

Cardiac magnetic resonance imaging (CMR) provides more accurate and reproducible measures of LV volumes and ejection fraction (EF), but few use this approach for prediction of outcomes in VHD patients. CMR also allows quantitation of AR and MR, which may be helpful if echocardiography is nondiagnostic or when the degree of LV dilation seems out of proportion to regurgitant severity. CMR is less helpful for evaluation of AS because maximum velocity may be underestimated. However, CMR evaluation of LV myocardial fibrosis provides insights into the disease process and may be clinically relevant in the future.

Computed Tomography (See Chapter 18)

Both CMR and computed tomography (CT) are useful in VHD patients who have associated aortic dilation. In patients with a bicuspid aortic valve, a baseline CMR or CT aortic study is recommended, unless the ascending aorta is well visualized on echocardiography, and is the primary modality for

following progressive aortic dilation in affected patients[1,10] (**see Chapters 63 and 68**). CT also has value for evaluating prosthetic valve dysfunction, allowing accurate visualization of mechanical leaflet occluder motion and detection of thrombus or pannus formation (**see Chapter 71**). CT also is useful in patients with endocarditis for visualizing the full extent of aortic or ventricular pseudoaneurysms and other complications. Combined positron emission tomography (PET) and CT have also been used in assessing the site of ongoing inflammatory changes in endocarditis (**see Chapters 16 and 73**).

Stress Testing

Stress testing is used in patients with VHD for several reasons[7,11] (**Table 67.3**):

TABLE 67.3

Primary Indications for Stress Testing in Valvular Heart Disease

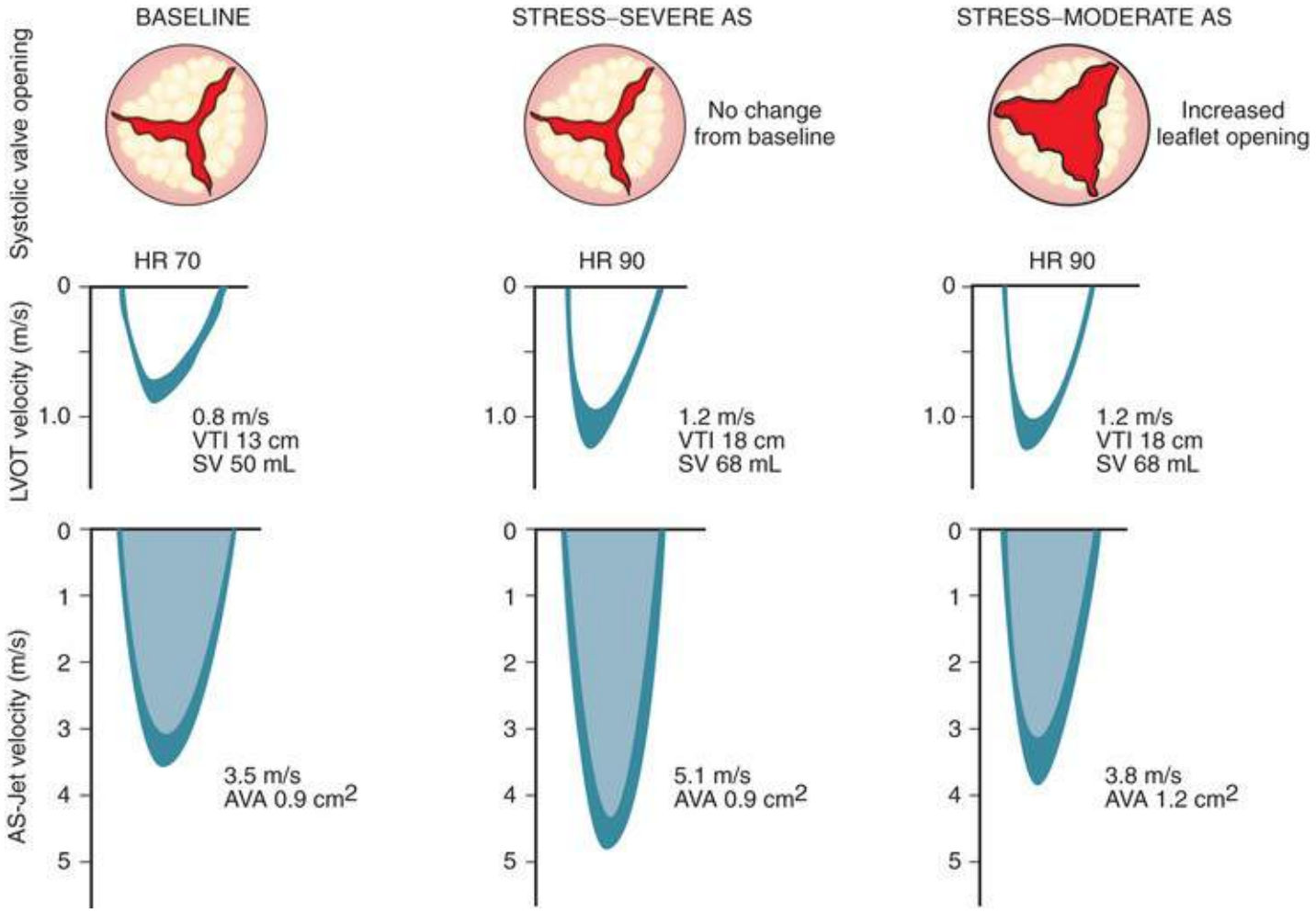
INDICATION	STRESS TYPE	ECHO DATA ACQUISITION	PARAMETERS USED IN CLINICAL DECISION MAKING	COMMENTS
Aortic stenosis (AS): symptom status	Exercise treadmill	Optional	Exercise duration Symptoms Blood pressure response	—
Low-output, low-gradient AS*	Low-dose dobutamine	Aortic jet velocity (CWD) LV outflow velocity (PDE) Ejection fraction (2D)	Severe AS is present if: V_{max} >4.0 m/sec or mean ΔP >40 mm Hg with AVA ≤1.0 cm^2 at any flow rate	Contractile reserve is defined as ↑ejection fraction or ↑transaortic stroke volume >20%
Mitral stenosis	Exercise treadmill or supine bicycle	TR jet velocity (CWD)	PA systolic pressure > 60 mm Hg with exercise	—
Mitral regurgitation	Exercise treadmill or supine bicycle	TR jet velocity (CWD)	PA systolic pressure > 60 mm Hg with exercise	—

*Defined as AVA <1.0 cm^2 with LV ejection fraction <40% and mean ΔP <30-40 mm Hg with stroke volume index 35 ml/m^2 or less.

2D, Two-dimensional imaging; *AVA,* aortic valve area; *CWD,* continuous-wave Doppler; *LV,* left ventricular; *ΔP,* pressure gradient; *PA,* pulmonary artery; *PDE,* pulsed Doppler echocardiography; *TR,* tricuspid regurgitation; *Vmax,* maximum aortic jet velocity.

Modified from Otto CM, Owens DS: Stress testing for structural heart disease. In Gillam LD, Otto CM, editors. Advanced Approaches in Echocardiography: Practical Echocardiography Series. Philadelphia: Saunders; 2012.

1. Treadmill exercise testing is used for evaluation of exercise capacity, blood pressure response, and symptoms when symptom status is unclear on the clinical history (**see Chapter 13**).
2. Low-dose dobutamine stress echocardiography is used for evaluation of AS severity when concurrent LV dysfunction is present (**eFig. 67.1; see Chapters 14 and 68**).
3. Bicycle or treadmill stress testing, with Doppler echocardiographic evaluation of pulmonary pressures, is used in patients with mitral valve disease and exertional symptoms despite only moderate disease at rest (**see Chapter 69**).



EFIGURE 67.1 Changes in aortic valve opening and Doppler flows with dobutamine stress echocardiography for low-output low-gradient aortic stenosis (AS). The baseline data show a hypothetical patient with an ejection fraction (EF) of 35% and limited aortic valve systolic opening, an aortic jet velocity (AS-jet) of 3.5 m/sec, and aortic valve area (AVA) of 0.9 cm^2. If true severe AS is present **(middle panel),** as EF increases from 35% to 45%, the transaortic flow rate increases but the aortic opening is fixed, resulting in a marked increase in aortic velocity (and pressure gradient) with no change in valve area. In a patient with the same baseline data but "pseudosevere AS," the increase in EF and transaortic stroke volume (SV) "push" the aortic leaflets to open more so that there is a smaller increase in aortic velocity in association with an increase in AVA. Current diagnostic testing relies on Doppler data with dobutamine stress testing because direct imaging of valve anatomy is not adequate for the visualization of the exact systolic orifice. LVOT, Left ventricular outflow tract; HR, heart rate, VTI, velocity-time integral. (From Otto CM, Owens DS: Stress testing for structural heart disease. In Gillam LD, Otto CM, editors. Advanced Approaches in Echocardiography: Practical Echocardiography Series. Philadelphia: Saunders; 2012.)

Caution is needed in using any type of stress testing for diagnosis of CAD in patients with VHD. Coronary blood flow is abnormal in patients with significant VHD, and the accuracy of stress testing for diagnosis of CAD in this population has not been well established. For example, myocardial oxygen supply-demand mismatch in patients with AS may result in "balanced ischemia" without evidence of regional dysfunction, even when significant epicardial CAD is present. Coronary angiography is recommended when CAD is suspected in patients with VHD.

Cardiac Catheterization

Concomitant CAD frequently is present in patients with VHD. Coronary angiography is recommended before surgical or transcatheter valve intervention in the following groups[1]:

1. In patients with symptoms of angina, objective evidence of ischemia, decreased LV systolic

function, history of CAD, or coronary risk factors (including men age >40 years and postmenopausal women)

2. In patients with chronic severe secondary MR (**see Chapter 69**)
3. In select patients undergoing surgical valve procedures with a low or intermediate pretest probability of CAD, CT coronary angiography is a reasonable alternative to invasive angiography (**see Chapter 18**). An abnormal coronary CT angiogram (the presence of any epicardial CAD) mandates further evaluation by cardiac catheterization.
4. When emergency surgery is needed for acute valve regurgitation, disease of the aortic sinuses or ascending aorta, or infective endocarditis, it is appropriate to proceed directly to surgery without coronary angiography.

Basic Principles of Medical Therapy

Medical therapy in all patients with VHD includes prevention of progressive valvular dysfunction, primary and secondary prevention for atherosclerotic CVD, and treatment of concurrent cardiac conditions.

Prevention of Rheumatic Valve Disease

On a worldwide basis, primary and secondary prevention of rheumatic valve disease is key to reducing the overall burden of VHD (**see Chapter 74**). Even though less common in developed countries because of primary prevention by treatment of streptococcal pharyngitis, secondary prevention is important for all patients with a diagnosis of rheumatic valve disease.[6]

Endocarditis Prophylaxis

Optimal dental hygiene and regular dental care are critical for prevention of infective endocarditis (**see Chapter 73**); all patients should be educated about the importance of endocarditis prevention, the signs and symptoms of early endocarditis, and the need to report promptly any unexplained fever or other symptoms.[12-15] Patients should be encouraged to request blood cultures first when a primary care provider recommends antibiotic therapy for any indication. In addition, antibiotic prophylaxis at the time of dental procedures is recommended in patients with all types of prosthetic heart valves and valve repairs, as well as other high-risk conditions.[15,16]

Prevention and Treatment of Coronary Artery Disease

Risk factors for development of calcific valve disease are similar to the risk factors for atherosclerotic CVD (**see Chapter 45**). Thus, appropriate evaluation and management of conventional CVD risk factors is important in management of patients with VHD. CAD is common in patients with VHD and should be treated with guideline-based medical, interventional, and surgical therapy (**see Chapter 61**). Revascularization at the time of surgical or interventional procedures for VHD should be considered to relieve symptoms and improve long-term outcomes.

Atrial Fibrillation

Atrial fibrillation often accompanies mitral valve disease, presumably related to increased pressure and size and of the left atrium, and may herald symptom onset. Medical management of AF associated with mitral valve disease may include transcatheter or surgical ablation procedures to restore sinus rhythm is some patients as an alternative to medical therapy for rate or rhythm control (**see Chapter 38**). Anticoagulation to prevent embolic events is recommended in all patients with AF and mitral valve

disease (**Table 67.4**). When rheumatic disease is present, particularly MS, vitamin K antagonist therapy is needed given the extremely high embolic risk, whereas current guidelines suggest direct oral anticoagulation (**see Chapter 93**) is reasonable in patients with MR and AF.[17-20] AS often is accompanied by AF, particularly in older adults. Management focuses on rate control and prevention of embolic events, although select patients may be considered for ablation procedures.

TABLE 67.4

Anticoagulation for Atrial Fibrillation in Patients with Valvular Heart Disease (VHD)

PATIENT GROUP	RECOMMENDATION	RATIONALE
VHD plus atrial fibrillation (AF)	Anticoagulant therapy should be individualized using shared decision making after discussion of benefits and risks, and taking into account patient preferences and values.	With new data showing equivalence of direct oral anticoagulant versus vitamin K antagonist therapy for patients with AF and VHD in prevention of embolic events, a shared decision-making approach should be followed to determine the anticoagulation therapy for each individual patient.
Mitral stenosis (MS)	Anticoagulation (vitamin K antagonist or heparin) is indicated for patients with MS and AF (paroxysmal, persistent, or permanent).	Patients with MS and AF are at the highest risk of embolic events with a high prevalence of left atrial thrombi, even when in sinus rhythm. Clinical trials of direct oral anticoagulants versus warfarin excluded patients with MS.
Other native valve disease	In patients with native aortic valve disease, tricuspid valve disease, or mitral valve regurgitation, antithrombotic therapy for AF should follow standard AF guidelines.	Randomized clinical trials of direct oral anticoagulants versus warfarin, which included subgroups of patients with native valve disease (except MS), showed equivalence of these therapies.
Bioprosthetic valves	In patients with a bioprosthetic valve, antithrombotic therapy for AF should follow standard AF guidelines, as well as recommendations for management after valve implantation (**see Chapter 71**).	Randomized clinical trials of direct oral anticoagulants versus warfarin, which included subgroups of patients with bioprosthetic valves, showed equivalence of these therapies.
Mechanical valves	Patients with a mechanical prosthetic valve should be treated with vitamin K antagonists or heparin as recommended for the prosthetic valve regardless of the presence of AF.	Patients with mechanical valves require warfarin therapy (or heparin) for prevention of thromboembolic events. Guidelines for prosthetic valves address whether the goal INR should be increased when concurrent AF is present (**see Chapter 72**).

INR, International normalized ratio.

Hypertension

Hypertension also typically is present in patients with VHD and should be treated using guideline-based medical therapy[21] (**see Chapter 47**). In patients with AS, medical therapy may need to be initiated at lower doses and titrated upward slowly but usually is well tolerated. It is especially important to measure transvalvular velocity, gradient, and area when the patient is normotensive because hypertension can result in underestimation of AS severity (**see Chapter 68**).

Left Ventricular Dysfunction

Left ventricular dysfunction caused by VHD is an indication for intervention. However, many patients have LV dysfunction from CAD or a primary cardiomyopathy in conjunction with mild or moderate VHD. In particular, amyloid heart disease may be present in elderly adults with calcific valve disease (**see Chapter 77**). Thus a complete evaluation for other causes of LV dysfunction is recommended, particularly when the degree of LV systolic dysfunction, hypertrophy, or diastolic dysfunction seems out of proportion to the severity of VHD. This evaluation helps guide decision making in predicting the likely effects of interventions on recovery of LV function. Management of HF with preserved or reduced EF in patients with valve disease follows the same general principles as for other patients (**see Chapters 25 and 26**), with the caveat that management of volume status may be challenging because there is only a narrow range of LV filling volumes/pressures that allow an adequate forward cardiac output without an excessive rise in filling pressures, often referred to as a “narrow preload window.” Patients often rapidly swing back and forth between pulmonary congestion and low-output symptoms. Meticulous outpatient medical management is needed in these patients.

Aortic Disease

Aortic dilation frequently accompanies aortic valve disease (**see Chapter 68**). Bicuspid aortic valve disease is accompanied by an aortopathy in many patients with progressive aortic dilation and an increased risk of aortic dissection (**see Chapter 63**). Additional imaging and monitoring of aortic anatomy and size is needed in these patients. Some patients with calcific aortic valve disease also have aortic dilation, often in conjunction with systemic hypertension, again with the need for additional imaging and follow-up in select patients.

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68

Aortic Valve Disease

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Aortic Stenosis

Epidemiology

In recent population-based echocardiographic studies, 1% to 2% of persons age 65 or older and 12% of persons 75 or older had calcific aortic stenosis (AS)[1,2] (**see Chapter 88**). Among those older than 75, 3.4% (95% confidence interval [CI] 1.1% to 5.7%) have severe AS.[2] The prevalence of aortic valve sclerosis without stenosis, defined as irregular thickening or calcification of the aortic valve leaflets, increases with age and ranges from 9% in populations with a mean age of 54 years to 42% in populations with a mean age of 81 years.[1,3] The rate of progression from aortic sclerosis to stenosis is 1.8% to 1.9% per year.[3] With the aging of the population, the number of individuals with AS is expected to increase twofold to threefold in developed countries in the coming decades.[1,3,4]

Causes and Pathology

Valvular AS has three principal causes: a congenital bicuspid valve with superimposed calcification, calcification of a normal trileaflet valve, and rheumatic disease (**Fig. 68.1**). In a U.S. series of 933 patients undergoing aortic valve replacement (AVR) for AS, a bicuspid valve was present in more than 50%, including two thirds of those younger than 70 years and 40% of those older than 70 (see Classic References, Roberts and Ko).

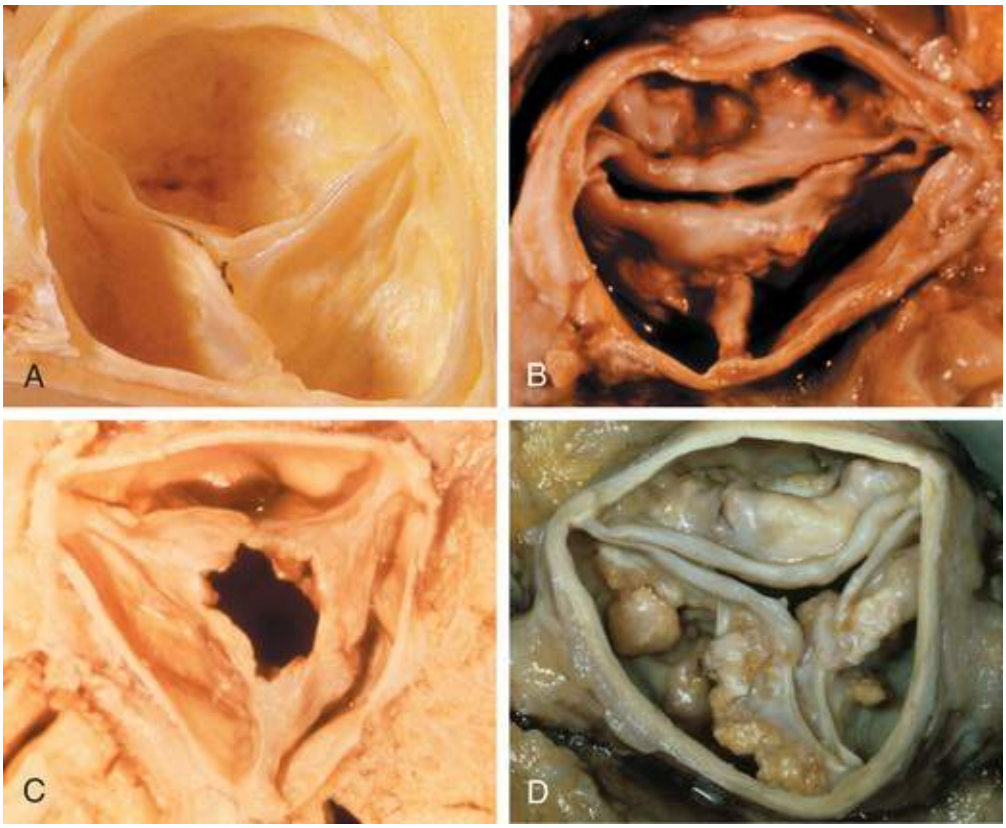


FIGURE 68.1 Major types of aortic valve stenosis. **A,** Normal aortic valve. **B,** Congenital bicuspid aortic stenosis. A false raphe is present at 6 o'clock. **C,** Rheumatic aortic stenosis. The commissures are fused with a fixed central orifice. **D,** Calcific degenerative aortic stenosis. (**A,** From Manabe H, Yutani C, editors. Atlas of Valvular Heart Disease. Singapore: Churchill Livingstone; 1998, pp 6, 131; **B-D,** courtesy Dr. William C. Roberts, Baylor University Medical Center, Dallas.)

In addition, AS may be caused by a congenital valve stenosis manifesting in infancy or childhood. Rarely, AS is caused by severe atherosclerosis of the aorta and aortic valve; this form of AS occurs most

frequently in patients with severe hypercholesterolemia and is observed in children with homozygous type II hyperlipoproteinemia. Rheumatoid involvement of the valve is a rare cause of AS and results in nodular thickening of the valve leaflets and involvement of the proximal portion of the aorta. Ochronosis with alkaptonuria is another rare cause of AS.

Fixed obstruction to left ventricular (LV) outflow also may occur above the valve (supravalvular stenosis) or below the valve (discrete subvalvular stenosis; **see Fig. 14.45**) (Video 68.1A and 68.1B). Dynamic subaortic obstruction may be caused by hypertrophic cardiomyopathy (**see Chapter 78**).

Congenital Aortic Valve Disease.

Congenital malformations of the aortic valve may be unicuspid, bicuspid, or tricuspid, or the anomaly may manifest as a dome-shaped diaphragm (**see Fig. 14.44** and **Chapter 75**). Unicuspid valves typically produce severe obstruction in infancy and are the most common malformations found in fatal valvular AS in children younger than 1 year, but also may be seen in young adults with an anatomy that mimics bicuspid valve disease. Congenitally bicuspid valves rarely are responsible for serious narrowing of the aortic orifice during childhood,[5] but do cause significant aortic regurgitation (AR) requiring valve surgery in young adulthood in a subset of patients. Most affected patients, however, have normal valve function until late in life, when superimposed calcific changes result in valve obstruction (see later, Bicuspid Aortic Valve Disease).

Calcific Aortic Valve Disease.

Calcific (formerly “senile” or “degenerative”) aortic valve disease affecting a congenital bicuspid or normal trileaflet valve is now the most common cause of AS in adults. Aortic sclerosis, identified by either echocardiography or computed tomography (CT), is the initial stage of calcific valve disease and, even in the absence of valve obstruction or known cardiovascular disease, is associated with an increased risk of myocardial infarction (MI) and cardiovascular and all-cause mortality.[3,6] Epidemiologic associations have been documented between cardiovascular risk factors and calcific aortic valve disease, suggesting that treating or preventing these risk factors may lessen the risk of developing AS (**Table 68.1**).

TABLE 68.1

Strength of Associations in Observational and Epidemiologic Studies of Clinical Risk Factors and Calcific Aortic Valve Disease (CAVD)

Risk Factor	CAVD ANALYSIS		
	Cross-Sectional	Incident	Progression
Age	+++	+++	+++
Male sex	++/−	++	0
Height	++	++	0
Body mass index	++	++	0
Hypertension	++	++	0
Diabetes	+++	+++	0
Metabolic syndrome	++	++	+
Dyslipidemia	++	++	0
Smoking	++	++	+
Renal dysfunction	+	0	0
Inflammatory markers	+	0	0
Phosphorus levels	++	0	N/A
Calcium levels	0	0	N/A
Baseline calcium score	N/A	N/A	+++

+, Weak positive association; ++, modest positive association; +++, strong positive association; −, weak negative association; 0, no association seen; *N/A,* no/insufficient data available.

From Owens DS, O'Brien KD: Clinical and genetic risk factors for calcific valve disease. In Otto CM, Bonow RO, editors. Valvular Heart Disease: A Companion to Braunwald's Heart Disease. 4th ed. Philadelphia: Saunders; 2013, pp 53-62.

Although calcific AS once was considered to represent the result of years of normal mechanical stress on an otherwise normal valve (“wear and tear”), it is now clear that an active biology underlies the initiation and progression of calcific aortic valve disease (**Fig. 68.2**).[7] Differences in the biology driving the initiation and progression phases of calcific aortic valve disease could have important implications for medical therapies aimed at preventing, slowing, or reversing the path from aortic sclerosis to severe stenosis, both in terms of which pathways are relevant to target and when along the disease spectrum drugs targeting them are most likely to be effective.

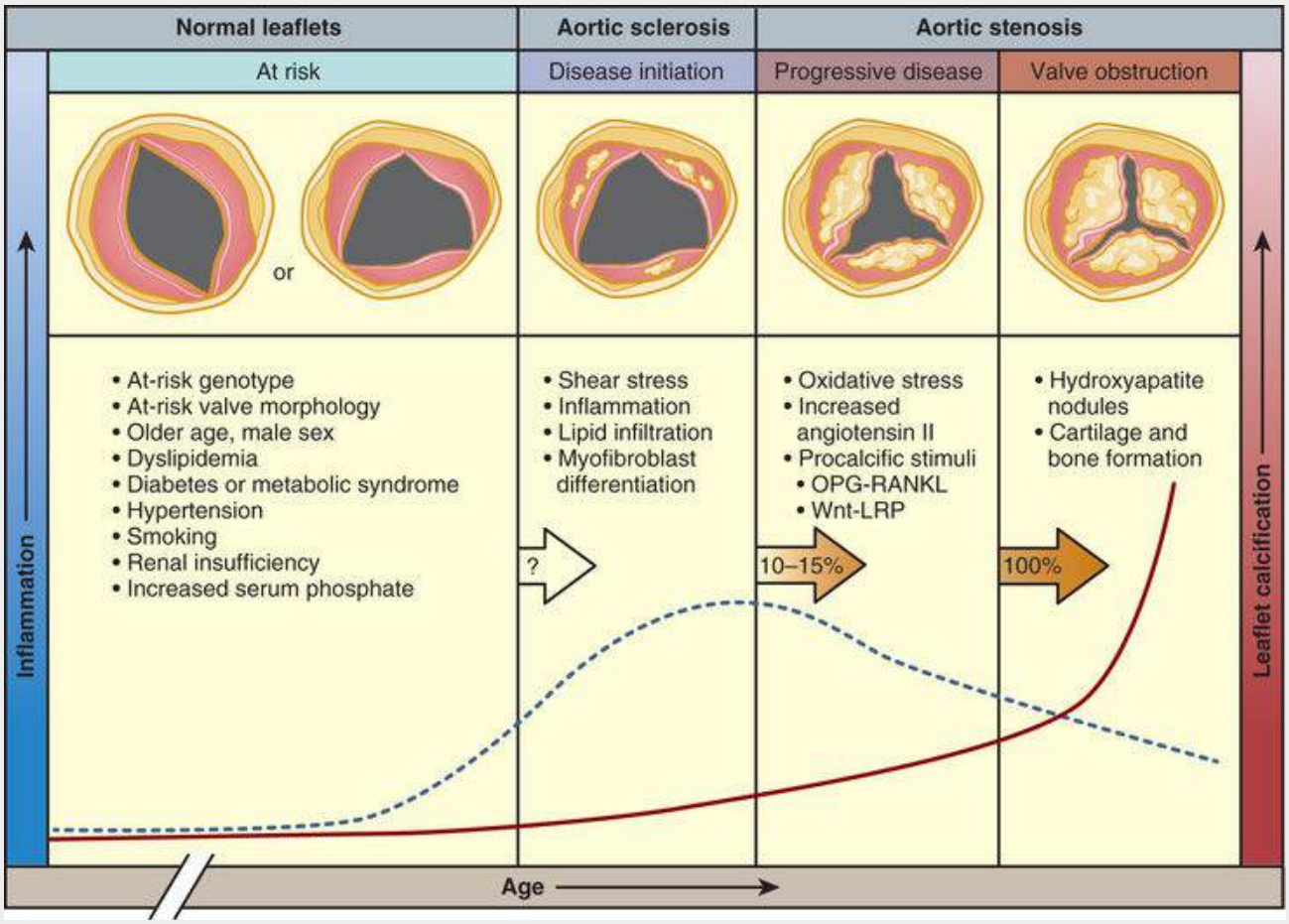


FIGURE 68.2 Disease mechanisms and time course of calcific aortic stenosis (AS): relationship among disease stage, valve anatomy, clinical risk factors, mechanisms of disease, and patient's age. Endothelial disruption with inflammation (*dashed line*) and lipid infiltration are key elements in the initiation of disease. There are few data on the prevalence of disease initiation in at-risk patients, and progressive disease develops in only a subgroup of these patients. Progressive leaflet disease, which is associated with several disease pathways, develops in approximately 10% to 15% of patients with AS. Once these disease mechanisms are activated, leaflet calcification results in severe AS in almost all patients. With end-stage disease, tissue calcification (*red line*) is the predominant tissue change, resulting in valve obstruction. Current imaging approaches are reliable only when substantial leaflet changes are present (in patients with progressive disease or valve obstruction), which limits clinical studies of interventions to prevent or slow the progression of early disease. LRP, Lipoprotein receptor–related protein complex; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor-κB ligand. (From Otto CM, Prendergast B. Aortic-valve stenosis: from patients at risk to severe valve obstruction. N Engl J Med 2014;371:744-56.)

Normal valve leaflets are comprised of the fibrosa (facing the aorta), ventricularis (facing the ventricle), and spongiosa (located between the fibrosa and ventricularis). *Valve interstitial cells* (VICs) are the most predominant cell type; endothelial and smooth muscle cells are also present. Through a complex interplay of molecular events, the pliable, flexible valve becomes stiff and immobile, characterized grossly by fibrosis and calcification. The process is initiated by lipid infiltration and oxidative stress, which attract and activate inflammatory cells and promote the elaboration of cytokines (**Fig. 68.3**).[4] VICs undergo osteogenic reprogramming that promotes the mineralization of the extracellular matrix and the progression of fibrocalcific remodeling of the valve.

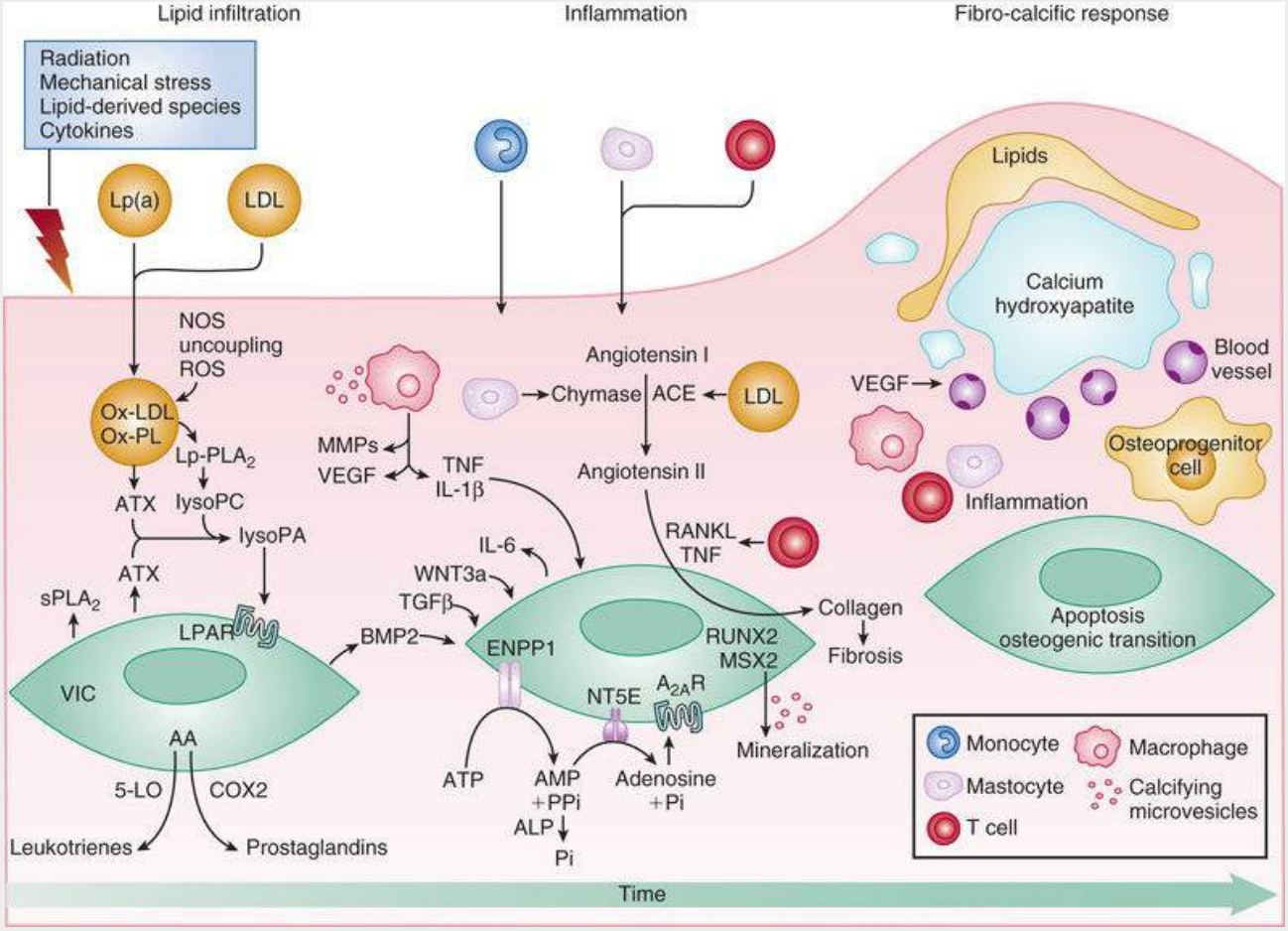


FIGURE 68.3 Pathogenesis of calcific aortic stenosis. Endothelial damage allows infiltration of lipids, specifically low-density lipoprotein (*LDL*) and lipoprotein(a) [*Lp(a)*], into the fibrosa and triggers the recruitment of inflammatory cells into the aortic valve. Endothelial injury can be triggered by several factors, including lipid-derived species, cytokines, mechanical stress, and radiation injury. The production of reactive oxygen species (*ROS*) is promoted by the uncoupling of nitric oxide synthase (*NOS*), which increases the oxidation of lipids and further intensifies the secretion of cytokines. Enzymes transported in the aortic valve by lipoproteins (i.e., LDL, Lp[a]) such as lipoprotein-associated phospholipase A_2 (*Lp-PLA*$_2$) and ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2), also known as autotoxin (*ATX*), produce lysophospholipid derivatives. ATX, which is also secreted by valve interstitial cells (*VIC*), transforms lysophosphatidylcholine (*lysoPC*) into lysophosphatidic acid (*lysoPA*). Several factors, including lysoPA, the receptor activator of nuclear factor-κB ligand (*RANKL*; also known as TNFSF11), and WNT3a, promote the osteogenic transition of VIC. Arachidonic acid (*AA*) generated by cytosolic PLA_2 promotes the production of eicosanoids such as prostaglandins and leukotrienes through prostaglandin G/H synthase 2 (PTGS2; also known as cyclooxygenase 2 [*COX2*]) and 5-lipoxygenase (*5-LO*) pathways, respectively. In turn, eicosanoids promote inflammation and mineralization. Chymase and angiotensin-converting enzyme (*ACE*) promote production of angiotensin II, which increases synthesis and secretion of collagen by VIC. Because of increased production of matrix metalloproteinases (*MMPs*) and decreased synthesis of tissue inhibitors of metalloproteinases (TIMPs), disorganized fibrous tissue accumulates within the aortic valve. Microcalcification begins early in the disease, driven by microvesicles secreted by VIC and macrophages. In addition, overexpression of ectonucleotidases—ENPP1, 5′-nucleotidase ecto (*NT5E*), and alkaline phosphatase (*ALP*)—promotes both apoptosis and osteogenic-mediated mineralization. Bone morphogenetic protein 2 (*BMP2*) leads to osteogenic transdifferentiation, which is associated with the expression of bone-related transcription factors (e.g., runt-related transcription factor 2 [*RUNX2*] and homeobox protein MSX2). Osteoblast-like cells subsequently coordinate calcification of the aortic valve as part of a highly regulated process analogous to skeletal bone formation. Deposition of mineralized matrix is accompanied by fibrosis and neovascularization, which is abetted by vascular endothelial growth factor (*VEGF*). In turn, neovascularization increases the recruitment of inflammatory cells and bone marrow–derived osteoprogenitor cells. *$A_{2A}R$,* Adenosine A_{2A} receptor; *$sPLA_2$,* secreted phospholipase A_2; *LPAR,* lysophosphatidic acid receptor; *Ox-PL,* oxidized phospholipid; *Ox-LDL,* oxidized LDL; *TGFβ,* transforming growth factor beta; *TNF,* tumor necrosis factor. (From Lindman BR, Clavel M-A, Mathieu P, et al. Calcific aortic stenosis. *Nat Rev Dis Primers*. 2016;2:16006.)

Familial clustering of calcific AS also has been described, suggesting a possible genetic

predisposition to valve calcification.[8,9] Genetic polymorphisms have been linked to the presence of calcific AS, including those involving the vitamin D receptor, interleukin (IL)-10 alleles, estrogen receptor, transforming growth factor (TGF)-ß receptor, and the apolipoprotein E4 allele.[10] In a genome-wide association study (GWAS) based on a meta-analysis of data on nearly 7000 patients from three population-based cohorts, a single-nucleotide polymorphism (SNP) in the locus for low-density lipoprotein (LDL) was associated with aortic valve calcification, serum lipoprotein(a) [Lp(a)] levels, and incident AS (hazard ratio [HR], 1.68; CI 1.32 to 2.15).[11] This correlation was confirmed by review of a large Danish registry of more than 77,000 patients in whom two Lp(a) genotypes were significantly associated with incident AS.[12] Recent evidence suggests a potential link between Lp(a) and AS through lipoprotein-associated phospholipase A_2 (Lp-PLA_2) and ectonucleotide pyrophosphatase/phosphodiesterase family member 2 (ENPP2), also known as *autotaxin*.[13-17] Lp(a) transports both Lp-PLA_2 and autotaxin, and each of these is found in increased abundance in stenotic aortic valves.[15,16,18] Lp-PLA_2 transforms oxidized phospholipids species into lysophosphatidylcholine (lysoPC); in turn, autotaxin transforms lysoPC into lysophosphatidic acid (lysoPA), which appears to play a role in the osteogenic reprogramming of VICs.[16,17]

Rheumatic Aortic Stenosis.

Rheumatic AS results from adhesions and fusions of the commissures and cusps and vascularization of the leaflets of the valve ring, leading to retraction and stiffening of the free borders of the cusps. Calcific nodules develop on both surfaces, and the orifice is reduced to a small, round or triangular opening (**Fig. 68.1C**). As a consequence, the rheumatic valve often is regurgitant as well as stenotic. Patients with rheumatic AS invariably have rheumatic involvement of the mitral valve (**see Chapter 74**). With the decline in rheumatic fever in developed nations, rheumatic AS is decreasing in frequency, although it continues to be a major problem on a worldwide basis.

Pathophysiology

Valve Obstruction

In adults with calcific AS, a significant burden of leaflet disease is present before obstruction to outflow develops. However, once even mild obstruction is present, hemodynamic progression occurs in almost all patients, with the interval from mild to severe obstruction ranging from less than 5 to more than 10 years (**Fig. 68.4**). In infants and children with congenital AS, the valve orifice shows little change as the child grows, thereby contributing to the relative obstruction over time. **Table 68.2** provides the clinical stages reflecting the progression of aortic stenosis.

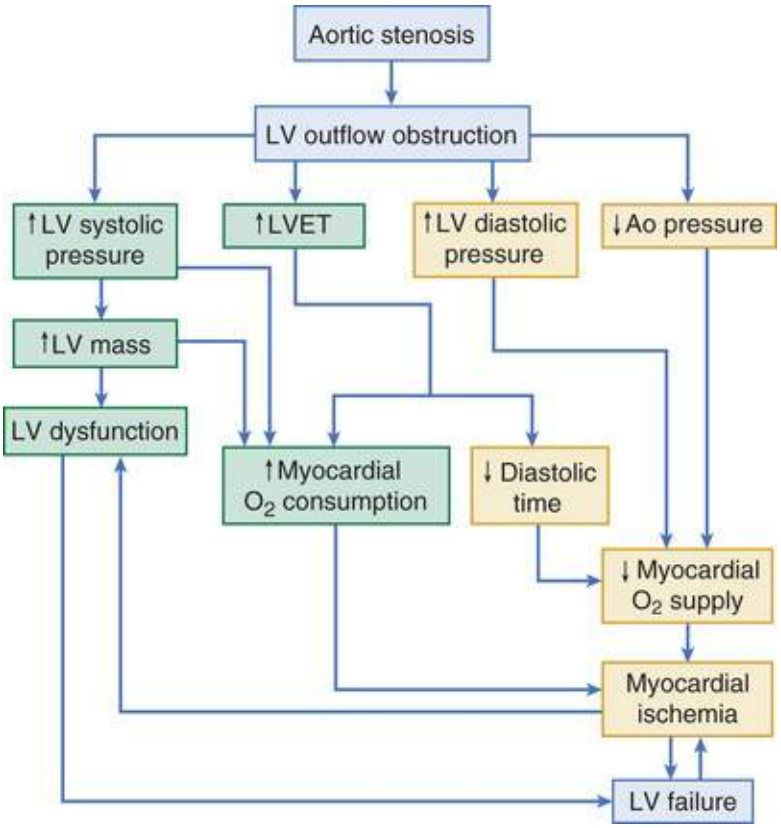


FIGURE 68.4 Pathophysiology of aortic stenosis. Left ventricular (LV) outflow obstruction results in an increased LV systolic pressure, increased LV ejection time (LVET), increased LV diastolic pressure, and decreased aortic (Ao) pressure. Increased LV systolic pressure with LV volume overload increases LV mass, which may lead to LV dysfunction and failure. Increased LV systolic pressure, LV mass, and LVET increase myocardial oxygen (O_2) consumption. Increased LVET results in a decrease of diastolic time (myocardial perfusion time). Increased LV diastolic pressure and decreased Ao diastolic pressure decrease coronary perfusion pressure. Decreased diastolic time and coronary perfusion pressure decrease myocardial O_2 supply. Increased myocardial O_2 consumption and decreased myocardial O_2 supply produce myocardial ischemia, which further deteriorates LV function. (From Boudoulas H, Gravanis MB: Valvular heart disease. In Gravanis MB, editor. Cardiovascular Disorders: Pathogenesis and Pathophysiology. St Louis; Mosby; 1993, p 64.)

TABLE 68.2

Stages of Valvular Aortic Stenosis (AS)

STAGE	DEFINITION	VALVE ANATOMY	VALVE HEMODYNAMICS	HEMODYNAMIC CONSEQUENCES	SYMPTOMS
A	**At risk of AS**	Bicuspid aortic valve (or other congenital valve anomaly) Aortic valve sclerosis	Aortic Vmax <2 m/sec	None	None
B	**Progressive AS**	Mild to moderate leaflet calcification of a bicuspid or trileaflet valve with some reduction in systolic motion *or* Rheumatic valve changes with commissural fusion	***Mild AS:*** Aortic Vmax 2.0-2.9 m/sec or mean ΔP <20 mm Hg ***Moderate AS:*** Aortic Vmax 3.0-3.9 m/sec or mean ΔP 20-39 mm Hg	Early LV diastolic dysfunction may be present. Normal LVEF	None
C	**Asymptomatic severe AS**				
C1	Asymptomatic severe AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	***Severe AS:*** Aortic Vmax ≥4 m/sec or mean ΔP ≥40 mm Hg AVA typically is ≤1 cm^2 (or AVAi ≤0.6 cm^2/m^2) Very severe AS is an aortic Vmax ≥5 m/sec, or mean ΔP ≥ 60 mm Hg	LV diastolic dysfunction Mild LV hypertrophy Normal LVEF	None Exercise testing is reasonable to confirm symptom status
C2	Asymptomatic severe AS with LV dysfunction	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	Aortic Vmax ≥4 m/sec or mean ΔP ≥40 mm Hg AVA typically is ≤1 cm^2 (or AVAi ≤0.6 cm^2/m^2)	LVEF <50%	None
D	**Symptomatic severe AS**				
D1	Symptomatic severe high-gradient AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	***Severe AS:*** Aortic Vmax ≥4 m/sec, or mean ΔP ≥40 mm Hg AVA typically is ≤1 cm^2 (or AVAi ≤0.6 cm^2/m^2), but may be larger with mixed AS/AR	LV diastolic dysfunction LV hypertrophy Pulmonary hypertension may be present.	Exertional dyspnea or decreased exercise tolerance Exertional angina Exertional syncope or presyncope
D2	Symptomatic severe low-flow, low-gradient AS with reduced LVEF	Severe leaflet calcification with severely reduced leaflet motion	AVA ≤1 cm^2 with resting aortic Vmax <4 m/sec, or mean ΔP <40 mm Hg Dobutamine stress echo shows AVA ≤1 cm^2 with Vmax ≥4 m/sec at any flow rate	LV diastolic dysfunction LV hypertrophy LVEF <50%	HF Angina Syncope or presyncope
D3	Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS	Severe leaflet calcification with severely reduced leaflet motion	AVA ≤1 cm^2 with aortic Vmax ≤4 m/sec, or mean ΔP <40 mm Hg AVAi ≤0.6 cm^2/m^2 Stroke volume index <35 mL/m^2 Measured when patient is normotensive (systolic BP <140 mm Hg)	Increased LV relative wall thickness Small LV chamber with low stroke volume Restrictive diastolic filling LVEF ≥50%	HF Angina Syncope or presyncope

AVA, Aortic valve area; *AVAi,* AVA indexed to body surface area; *BP,* blood pressure; *HF,* heart failure; *LVEF,* left ventricular ejection fraction; Δ*P,* pressure gradient; *Vmax,* maximum aortic jet velocity.

From Nishimura RA, Otto CM, Bonow RO, et al, 2014 AHA/ACCF guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57.

Severe obstruction to LV outflow usually is characterized by the following: (1) an aortic jet velocity of 4 m/sec or greater; (2) a mean transvalvular pressure gradient at least 40 mm Hg in the presence of a normal flow; or (3) an effective aortic orifice (calculated by the continuity equation; **see Fig. 14.48**) no greater than 1.0 cm^2 in an average-sized adult (i.e., ≤0.6 cm^2/m^2 of body surface area), which is approximately 25% of the normal aortic orifice of 3.0 to 4.0 cm^2.[19] *Moderate* AS is characterized by an aortic jet velocity of 3.0 to 3.9 m/sec or mean transvalvular pressure gradient of 20 to 39 mm Hg, usually with an aortic valve orifice area (AVA) of 1.0 to 1.5 cm^2. *Mild* AS is characterized by an aortic jet velocity of 2.0 to 2.9 m/sec or mean transvalvular pressure gradient less than 20 mm Hg, usually with

aortic orifice of 1.5 to 2.0 cm^2 (**Table 68.2**).[4,19-21]

The degree of stenosis associated with symptom onset varies among patients, however, and no single number defines severe or critical AS in an individual patient. Clinical decisions are based on consideration of symptom status and the LV response to chronic pressure overload, in conjunction with hemodynamic severity. In some cases, additional measures of hemodynamic severity, such as the energy loss index, valvular impedance, or evaluation with changing loading conditions (e.g., dobutamine stress) or with exercise, are necessary for full evaluation of disease severity.[22-26]

Hypertrophic Myocardial Remodeling

Maintenance of cardiac output in the face of an obstructed aortic valve imposes a chronic increase in LV pressure. In response, the ventricle typically undergoes hypertrophic remodeling characterized by myocyte hypertrophy and increased wall thickness (**Fig. 68.5**). LV remodeling may manifest as concentric remodeling, concentric hypertrophy, or eccentric hypertrophy. Based on LaPlace law, LV remodeling reduces wall stress (afterload) and is considered one of the important compensatory mechanisms to maintain LV ejection performance, which is directly affected by afterload (see Classic References, Grossman).

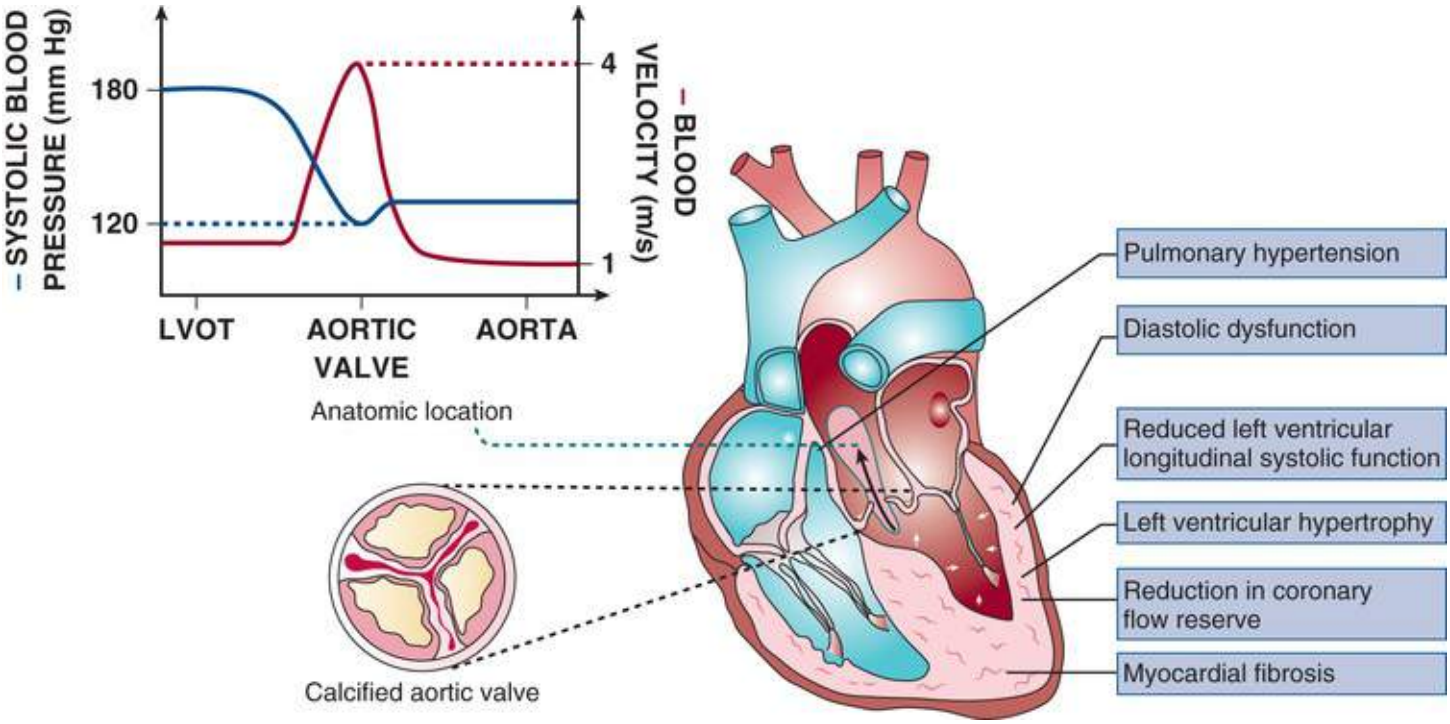


FIGURE 68.5 Maladaptive remodeling and impaired function of the left ventricle in response to pressure overload from aortic stenosis. The narrowing of the aortic valve orifice causes an acceleration of the blood flow velocity with a concomitant decrease in systolic blood pressure between the left ventricular outflow tract (LVOT) and the aorta. The increased LV pressure imposed by AS results in LV hypertrophy (augmentation of LV myocardial mass), reduced coronary flow reserve, myocardial fibrosis, diastolic dysfunction, and decreased longitudinal systolic shortening, although the ejection fraction remains normal in most patients. Left atrial enlargement is common because of elevated LV filling pressures, which often lead to secondary pulmonary hypertension and right ventricular dysfunction in the more advanced stages of the disease. (From Lindman BR, Clavel M-A, Mathieu P, et al. Calcific aortic stenosis. Nat Rev Dis Primers 2016;2:16006.)

However, LV hypertrophy is not simply related to increased afterload. Preclinical studies have demonstrated that blocking the hypertrophic response to pressure overload did not have deleterious

effects on LV performance despite increased wall stress (see Classic References, Hill). In patients with AS, several studies have now documented that increased LV hypertrophic remodeling is associated with more severe ventricular dysfunction and heart failure (HF) symptoms, as well as higher mortality.[27-29] Thus, while it may reduce wall stress, LV hypertrophic remodeling also may have longer-term deleterious effects that translate into impaired ventricular performance and worse clinical outcomes.

Cardiac hypertrophy in response to pressure overload involves both adaptive and maladaptive processes.[30] In addition, hypertrophic remodeling in patients with AS is determined by several factors other than the severity of valve obstruction, including sex, genetics, vascular load, and metabolic abnormalities.[31,32] Moreover, the degree to which LV hypertrophic remodeling is maladaptive versus adaptive and the resulting functional and clinical effects is not simply an issue of total LV mass and geometry; composition and energetics of the myocardium also are important.[30]

Left Ventricular Diastolic Function

Hypertrophic remodeling also impairs diastolic myocardial relaxation and increases stiffness,[33,34] as modulated by cardiovascular and metabolic comorbidities.[35] Higher cardiomyocyte stiffness, increased myocardial fibrosis, advanced-glycation end products, and metabolic abnormalities each contribute to increased chamber stiffness and higher end-diastolic pressures.[33] Atrial contraction plays a particularly important role in filling of the left ventricle in AS because it increases LV end-diastolic pressure without causing a concomitant elevation of mean left atrial pressure. This “booster pump” function of the left atrium prevents the pulmonary venous and capillary pressures from rising to levels that would produce pulmonary congestion, while maintaining LV end-diastolic pressure at the elevated level necessary for effective contraction of the hypertrophied left ventricle. Loss of appropriately timed, vigorous atrial contraction, as occurs in atrial fibrillation (AF) or atrioventricular dissociation, may result in rapid clinical deterioration in patients with severe AS. After surgical relief of AS, diastolic dysfunction may revert toward normal with regression of hypertrophy, but some degree of long-term diastolic dysfunction typically persists.

Left Ventricular Systolic Function

Left ventricular systolic function, as measured by the ejection fraction (EF), remains normal until late in the disease process in most patients with AS.[4] Nonetheless, more subtle systolic dysfunction can be detected as reduced longitudinal systolic strain before a reduction in the EF[36,37] (**see Chapter 14**). The development and severity of systolic dysfunction is the result of a complex interplay of factors, including the severity of valve obstruction, metabolic abnormalities, vascular load, inadequate hypertrophy (given the inverse correlation between wall stress and systolic performance), maladaptive hypertrophy (resulting in impaired contractility), ischemia, and fibrosis.[4,32,38] Eventually, a subset of patients develop overt systolic dysfunction manifested by a reduced LVEF. In these patients, systolic function usually improves after the ventricle is unloaded by AVR; the amount of recovery depends on many factors, including the degree to which systolic dysfunction was affected by afterload mismatch versus altered contractility.[39,40]

Myocardial Fibrosis.

Cardiac fibrosis is an emerging risk factor for adverse clinical outcomes in patients with AS.[41-44] As a part of the hypertrophic remodeling process, diffuse and replacement myocardial fibrosis (not fibrosis from prior MI) may develop,[41] although the incidence and extent of fibrosis are variable and

unpredictable and the underlying biologic mechanisms not yet clarified. Importantly, patients with severe fibrosis, despite a normal EF, are more likely to have worse preoperative HF symptoms and less likely to experience improvement in symptoms midterm after valve replacement, compared to those with no or minimal fibrosis before valve replacement.[42]

Pulmonary and Systemic Vasculature.

The hypertrophied and pressure overloaded left ventricle transmits increased pressure to the pulmonary vasculature, which leads to pulmonary hypertension in many patients with AS, becoming severe in 15% to 20%.[45] While patients may initially manifest pulmonary venous hypertension alone, some will go on to develop increased pulmonary vascular resistance, perhaps influenced by specific comorbidities and chronicity of pulmonary venous hypertension.[46-48] Among asymptomatic patients, exercise induced pulmonary hypertension is associated with decreased event-free survival.[49] Among patients undergoing surgical or transcatheter AVR, the presence and severity of pulmonary hypertension is associated with increased postoperative mortality.[46,48,50]

The systemic vasculature also makes an important contribution to total LV afterload. Hemodynamic studies with agents that dilate the systemic vasculature show an acute increase in LV stroke volume, underscoring that changes in vascular properties can unload the left ventricle despite no change in the valvular obstruction[47,51] (see Classic References, Khot). Measures of increased vascular load, including vascular stiffness, global load (integrating both valvular and vascular load), and systolic blood pressure, have been associated with adverse LV remodeling, impaired LV function, and worse clinical outcomes.[38,52-54]

Myocardial Ischemia.

In patients with AS, the hypertrophied left ventricle, increased systolic pressure, and prolongation of ejection all elevate myocardial oxygen (O_2) consumption. At the same time, even in the absence of epicardial coronary disease, decreased myocardial capillary density in the hypertrophied ventricle, increased LV end-diastolic pressure, and a shortened diastole all serve to decrease the coronary perfusion pressure gradient and myocardial blood flow. Together, this creates an imbalance between myocardial O_2 supply and demand, with the ischemia most pronounced in the subendocardium (**see Fig. 68.4**). As valve obstruction becomes more severe, coronary flow reserve progressively decreases.[55] Exercise or other states of increased O_2 demand may exacerbate this imbalance and cause angina indistinguishable from that caused by epicardial coronary obstruction.

Clinical Presentation

Symptoms

The cardinal manifestations of acquired AS are exertional dyspnea, angina, syncope, and ultimately HF.[20,56] Most patients now are diagnosed before symptom onset on the basis of the finding of a systolic murmur on physical examination, with confirmation of the diagnosis by echocardiography. Symptoms typically begin at age 50 to 70 years with bicuspid aortic valve stenosis and in those older than 70 with calcific stenosis of a trileaflet valve, although even in this age group approximately 40% of patients with AS have a congenital bicuspid valve (see Roberts and Ko).

The most common clinical presentation in patients with a known diagnosis of AS who are followed prospectively is a gradual decrease in exercise tolerance, fatigue, or dyspnea on exertion. The mechanism of exertional dyspnea may be LV diastolic dysfunction, with an excessive rise in end-diastolic pressure leading to pulmonary congestion. Alternatively, exertional symptoms may be a result of the limited ability

to increase cardiac output with exercise. More severe exertional dyspnea, with orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema, reflects various degrees of pulmonary venous hypertension. These are relatively late symptoms in patients with AS, and in current practice, intervention typically is undertaken before this disease stage.

Angina is a frequent symptom of patients with severe AS and usually resembles the angina observed in patients with coronary artery disease (CAD) in that it is usually precipitated by exertion and relieved by rest (**see Chapters 56 and 61**). In patients without CAD, angina results from the combination of the increased O_2 needs of hypertrophied myocardium and reduction of O_2 delivery secondary to the excessive compression of coronary vessels. In patients with CAD, angina is caused by a combination of epicardial coronary artery obstruction and the O_2 imbalance characteristic of AS. Very rarely, angina results from calcific emboli to the coronary vascular bed.

Syncope most often is caused by the reduced cerebral perfusion that occurs during exertion when arterial pressure declines because of systemic vasodilation and an inadequate increase in cardiac output related to valvular stenosis. Syncope also has been attributed to malfunction of the baroreceptor mechanism in severe AS (**see Chapter 99**), as well as to a vasodepressor response to a greatly elevated LV systolic pressure during exercise. Premonitory symptoms of syncope are common. Exertional hypotension also may be manifested as “graying-out spells” or dizziness on effort. Syncope at rest may be caused by transient AF with loss of the atrial contribution to LV filling, which causes a precipitous decline in cardiac output, or to transient atrioventricular (AV) block caused by extension of the calcification of the valve into the conduction system.

Gastrointestinal (GI) bleeding may develop in patients with severe AS, often associated with angiodysplasia (most frequently of the right colon) or other vascular malformations. This complication arises from shear stress–induced platelet aggregation with a reduction in high-molecular-weight multimers of von Willebrand factor and increases in proteolytic subunit fragments.[57] These abnormalities correlate with the severity of AS and are correctable by AVR.

An increased risk of infective endocarditis has been documented in patients with aortic valve disease, particularly in younger patients with a bicuspid valve (**see Chapter 73**). Cerebral emboli resulting in stroke or transient ischemic attacks (TIAs) may be caused by microthrombi on thickened bicuspid valves. Calcific AS rarely may cause embolization of calcium to various organs, including the heart, kidneys, and brain.

Physical Examination.

The key features of the physical examination in patients with AS are palpation of the carotid upstroke, evaluation of the systolic murmur, assessment of splitting of the second heart sound (S_2), and examination for signs of HF (**see Chapters 10 and 67**).

The carotid upstroke directly reflects the arterial pressure waveform. The expected finding with severe AS is a slow-rising, late-peaking, low-amplitude carotid pulse, the *parvus and tardus* carotid impulse. When present, this finding is specific for severe AS. However, many adults with AS have concurrent conditions, such as AR or systemic hypertension, that affect the arterial pressure curve and the carotid impulse. Thus an apparently normal carotid impulse is not reliable for excluding the diagnosis of severe AS. Also with severe AS, radiation of the murmur to the carotid arteries may result in a palpable thrill or carotid shudder.

Auscultation.

The ejection systolic murmur of AS typically is late-peaking and heard best at the base of the heart, with radiation to the carotids. Cessation of the murmur before A_2 is helpful in differentiation from a pansystolic mitral murmur. In patients with calcified aortic valves, the systolic murmur is loudest at the base of the heart, but high-frequency components may radiate to the apex—the so-called *Gallavardin phenomenon,* in which the murmur may be so prominent that it is mistaken for the murmur of mitral regurgitation (MR). In general, a louder and later-peaking murmur indicates more severe stenosis. However, although a systolic murmur of grade 3 intensity or greater is relatively specific for severe AS, this finding is insensitive, and many patients with severe AS have only a grade 2 murmur. When the left ventricle fails and stroke volume falls, the systolic murmur of AS becomes softer; rarely, it disappears altogether.

Splitting of S_2 is helpful in excluding the diagnosis of severe AS, because normal splitting implies the aortic valve leaflets are flexible enough to create an audible closing sound (A_2). With severe AS, S_2 may be single because (1) calcification and immobility of the aortic valve make A_2 inaudible, (2) closure of the pulmonic valve (P_2) is buried in the prolonged aortic ejection murmur, or (3) prolongation of LV systole makes A_2 coincide with P_2.

Dynamic Auscultation.

The intensity of the systolic murmur varies from beat to beat when the duration of diastolic filling varies, as in AF or after a premature contraction. This characteristic is helpful in differentiating AS from MR, in which the murmur usually is unaffected. The murmur of valvular AS is augmented by squatting, which increases stroke volume. It is reduced in intensity during the strain of the Valsalva maneuver and on standing, both of which reduce transvalvular flow.

Diagnostic Testing

Echocardiography

Echocardiography is the standard approach for evaluating and following patients with AS and selecting them for operation (**see Chapter 14** and **Figs. 14.46 to 14.49**). Echocardiographic imaging allows accurate definition of valve anatomy, including the cause of AS and the severity of valve calcification, and sometimes allows direct imaging of the orifice area using three-dimensional imaging.[58-60] Echocardiographic imaging also is invaluable for the evaluation of LV hypertrophy and systolic function, with calculation of EF, measurement of aortic sinus dimensions, and detection of associated mitral valve disease.[60] Longitudinal systolic strain imaging has emerged as a more sensitive measure of LV function and predicts adverse clinical events, including mortality.[36,61-63]

Doppler echocardiography allows measurement of *transaortic jet velocity,* which is the most useful measure for following disease severity and predicting clinical outcome. The stenotic orifice area is calculated using the continuity equation, and mean transaortic pressure gradient is calculated using the modified Bernoulli equation[60] (**see Fig. 14.48**). Both AVA and pressure gradient calculations from Doppler data have been well validated compared with invasive hemodynamics and in terms of their ability to predict clinical outcome. However, the accuracy of these measures requires an experienced laboratory with meticulous attention to technical details.

The combination of pulsed, continuous-wave, and color flow Doppler echocardiography is helpful in detecting and determining the severity of AR (which coexists in approximately 75% of patients with predominant AS) and in estimating pulmonary artery pressure. In some patients, additional measures of AS severity may be necessary, such as correction for poststenotic pressure recovery or three-dimensional

transesophageal echocardiography (TEE) of valve anatomy. Evaluation of AS severity is affected by the presence of systemic hypertension, and reevaluation after blood pressure (BP) control may be necessary.[64] In patients with LV dysfunction and low cardiac output, assessing the severity of AS can be enhanced by assessing hemodynamic changes during dobutamine infusion (see later).

Exercise Stress Testing

Because patients may tailor their lifestyle to minimize symptoms or may ascribe fatigue and dyspnea to deconditioning or aging, they may not recognize early symptoms as important warning signals, although these symptoms often can be elicited by a careful history. Exercise testing may be helpful in apparently asymptomatic patients to unmask symptoms or demonstrate limited exercise capacity or an abnormal BP response.[65] Exercise stress testing should be absolutely avoided in symptomatic patients.

Cardiac Computed Tomography

The use of CT is expanding in patients with calcific aortic valve disease (**see Chapter 18**). CT is useful for evaluating aortic dilation in patients with evidence or suspicion of aortic root disease on echocardiography or chest radiography, particularly those with a bicuspid valve. Measurement of aortic dimensions at several levels, including the sinuses of Valsalva, sinotubular junction, and ascending aorta, is necessary for clinical decision making and surgical planning. Beyond this, CT is increasingly used to assess valve calcification to predict the rate of disease progression or, more often, when the severity of the stenosis is in doubt, particularly in those with low-flow, low-gradient AS.[66,67] CT is also a routine part of the preprocedural evaluation of patients having AVR, principally to look for a porcelain aorta, as well as determine appropriate valve sizing and assess aortic and peripheral vascular anatomy when a transcatheter approach is considered[68] (**see Figs. 18.15 and 72.5**).

Cardiac Catheterization

In almost all patients, the echocardiographic examination provides the important hemodynamic information required for patient management. Cardiac catheterization is now recommended only when noninvasive tests are inconclusive, when clinical and echocardiographic findings are discrepant, and for coronary angiography before surgical intervention[19,69-71] (**see Chapters 19 and 20**).

Other Imaging Modalities

Cardiac Magnetic Resonance Imaging (see Chapter 17).

CMR is useful for assessing LV volume, function, and mass, especially in settings where this information cannot be obtained readily from echocardiography.[72] CMR is also excellent for assessing aortic dimensions in patients with a bicuspid valve, particularly to avoid radiation when serial imaging is needed over many years. Given the adverse prognosis associated with the presence and severity of myocardial fibrosis, CMR with late gadolinium enhancement (LGE) may be used to risk-stratify patients with AS (**Fig. 68.6**). CMR is also sometimes used instead of CT to assess valve morphology, vascular anatomy, and annular dimensions in preparation for transcatheter aortic valve replacement, although MRI is not recommended for assessment of stenosis severity because of underestimation of transvalvular velocities.[73]

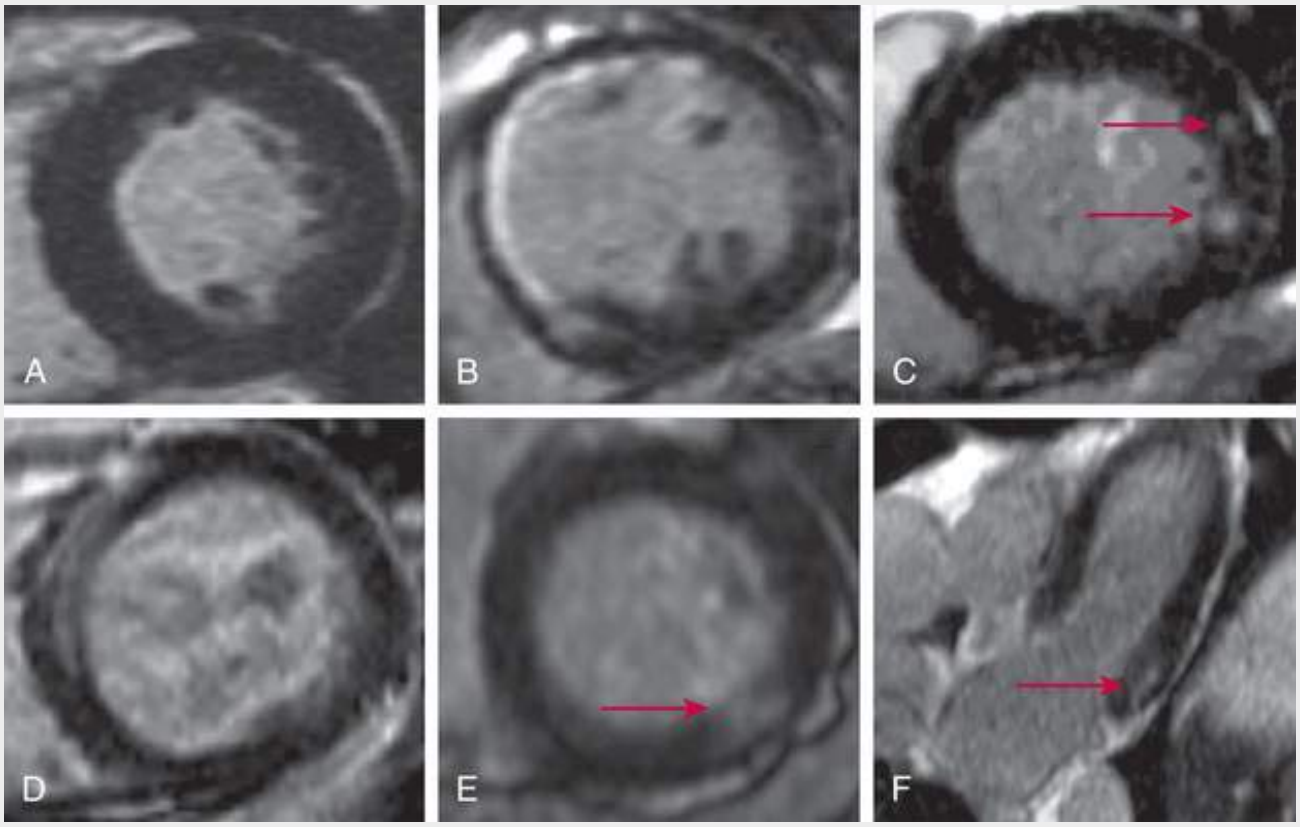


FIGURE 68.6 Cardiac magnetic resonance images showing different patterns of late gadolinium enhancement (LGE) observed in patients with aortic stenosis. **A,** No LGE. **B,** Infarct LGE with subendocardial pattern observed in septum and anterior wall. **C,** Two focal areas of midwall LGE in lateral wall of left ventricle (*red arrows*). **D,** Midwall LGE in a more linear pattern, affecting the septum. **E,** Short-axis view, and **F,** long-axis view, of midwall LGE (*red arrows*) of the inferolateral wall in the same patient. (Dweck MR, Joshi S, Murigu T, et al. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. J Am Coll Cardiol 2011;58:1271-9.)

Positron Emission Tomography (see Chapter 16).

Active uptake of ^{18}F–sodium fluoride in the aortic valve on positron emission tomography (PET) identifies active tissue calcification and predicts change in aortic valve calcification on follow-up CT 1 to 2 years later.[74-76] The new calcification is observed in a similar distribution as the baseline uptake of ^{18}F–sodium fluoride (**Fig. 68.7**). This may become a useful surrogate endpoint for trials testing therapies to slow the progression of calcific aortic valve disease, but further studies are needed.

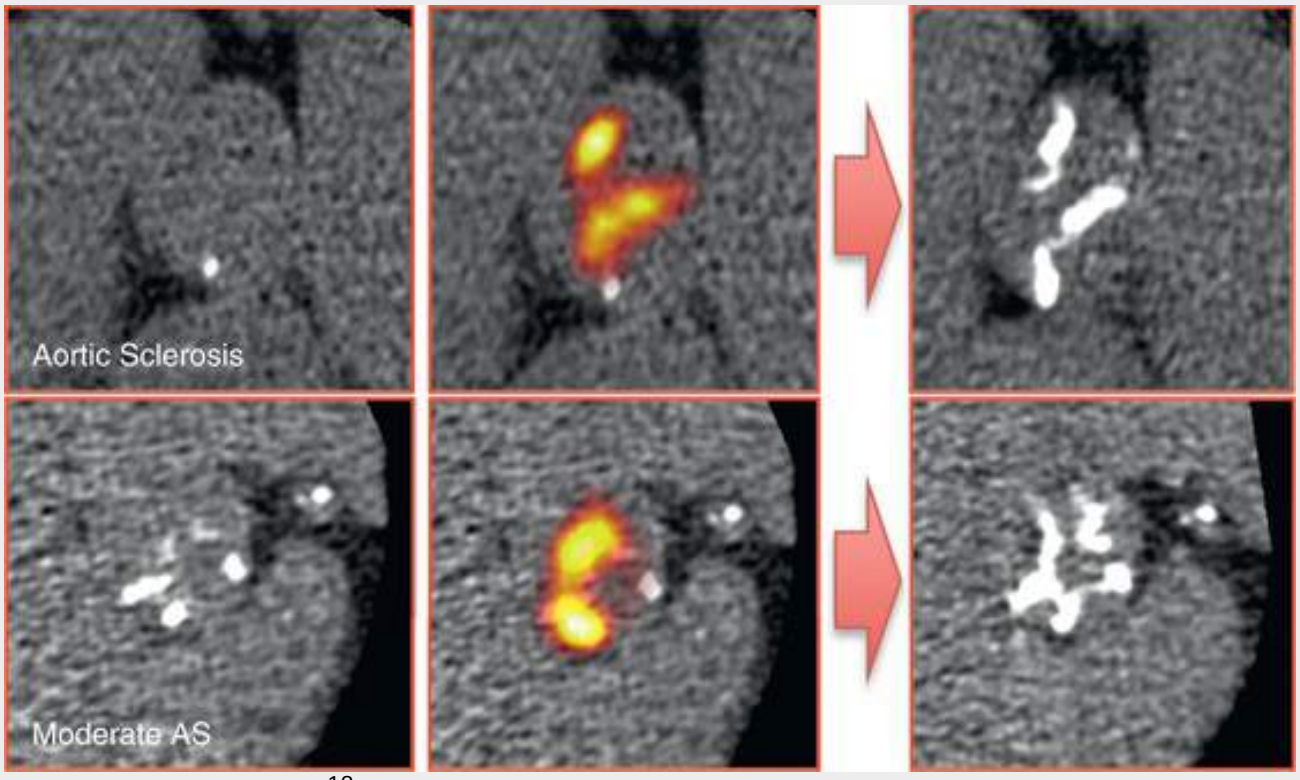


FIGURE 68.7 Valvular ^{18}F-fluoride uptake predicts the progression of calcification in aortic stenosis (AS). Two patients with calcific aortic valve disease. **Left,** Baseline computed tomography (CT) images. **Middle,** Fused positron emission tomography (PET)/CT images showing increased ^{18}F-fluoride valvular uptake (*red/yellow areas*). **Right,** Repeat CT scans after 2 years with new areas of macroscopic calcium (*white areas*) in a similar distribution to that of baseline PET uptake. (Jenkins WS, Vesey AT, Shah AS, et al. Valvular (18)F-fluoride and (18)F-fluorodeoxyglucose uptake predict disease progression and clinical outcome in patients with aortic stenosis. J Am Coll Cardiol 2015;66:1200-1.)

Disease Course

Asymptomatic Patients

The diagnosis of AS is most often made on auscultation of a murmur suggestive of AS, followed by confirmation with echocardiography. When AS is not severe and symptoms are absent, patients are reevaluated clinically and with echocardiography based on the AS severity. Generally, repeat imaging is performed every 6 to 12 months for severe AS, every 1 to 2 years for moderate AS, and every 3 to 5 years for mild AS, unless a change in signs or symptoms prompts repeat imaging sooner.[19,69]

The severity of outflow tract obstruction gradually increases over 10 to 15 years, so the clinical course includes a long latent period during which stenosis severity is only mild to moderate and clinical outcomes are similar to those for age-matched normal patients.[77,78] The rate of progression of AS is highly variable and difficult to predict. In clinical studies the factors associated with more rapid hemodynamic progression included older age, more severe leaflet calcification, renal insufficiency, hypertension, obesity, metabolic syndrome, smoking, hyperlipidemia, and elevated circulating levels of Lp(a) and increased activity of Lp-PLA_2.[4,13,14]

Of patients with mild valve thickening but no obstruction to outflow (e.g., aortic sclerosis), 16% will have valve obstruction at 1 year of follow-up, but only 2.5% will develop severe valve obstruction at an average of 8 years after the diagnosis of aortic sclerosis. Disease progression may be related to different factors than for initiation of disease.[79]

Once moderate to severe AS is present, prognosis remains excellent provided the patient remains

asymptomatic.[80] The progressive nature of the disease, however, warrants close follow-up. Although stenosis is on average more severe in symptomatic than in asymptomatic patients, marked overlap is evident in all measures of severity between these two groups. Prospective studies evaluating the rate of progression to symptomatic AS in initially asymptomatic patients are summarized in **eTable 68.1**. The strongest predictor of progression to symptoms is the Doppler aortic jet velocity.[20,81,82] Survival free of symptoms is 84% at 2 years when aortic velocity is less than 3 m/sec, compared with only 21% when velocity is greater than 4 m/sec (**Fig. 68.8**). In adults with severe AS (Doppler velocity >4 m/sec), outcome can be further predicted by the magnitude of the Doppler velocity (**Fig. 68.8B**), as well as by the severity of aortic valve calcification.[63,83,84] In such studies, most events consisted of the development of symptoms prompting AVR and not sudden death in otherwise asymptomatic patients. However, retrospective studies have reported some cases of sudden death in apparently asymptomatic adults with severe AS. A prospective observational study of initially asymptomatic Japanese patients with severe AS compared outcome in those who underwent early surgery versus a "watchful waiting" strategy.[85] With propensity matching to adjust for baseline differences between the two groups, the survival rate was significantly higher in the 291 patients with early surgery compared to the 291 initially followed conservatively. However, it is noteworthy that 31% of patients in the conservative group who developed symptoms did not undergo AVR, and this accounted for 17% of the deaths during "watchful waiting." Thus the role of early surgical intervention in asymptomatic patients remains unresolved and can only be determined with a prospective randomized controlled trial (RCT).

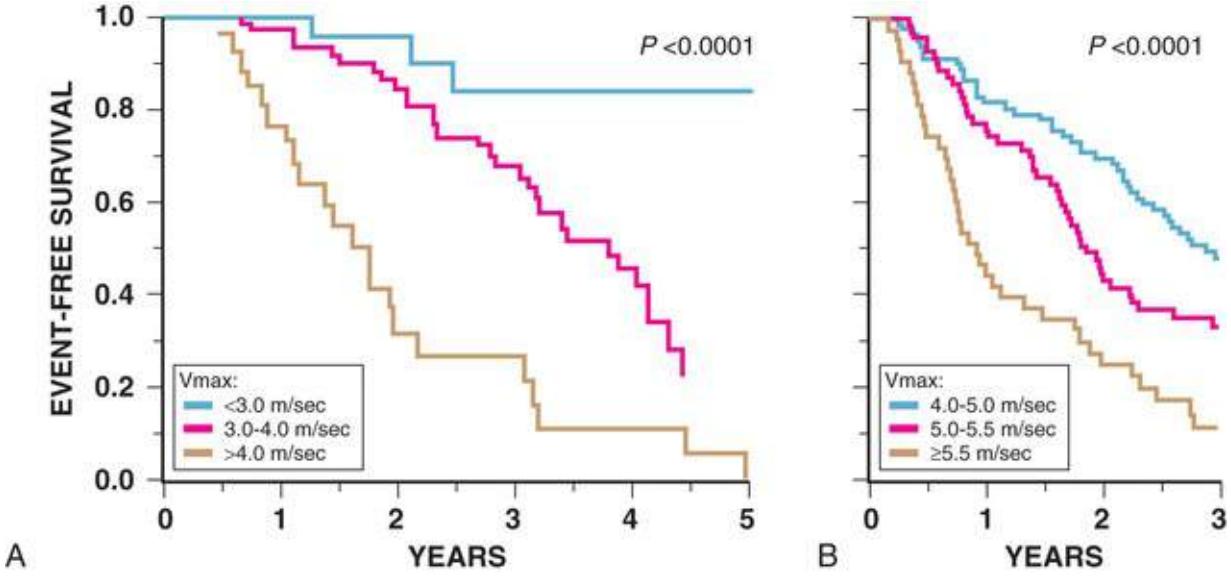


FIGURE 68.8 **A,** Natural history as reflected by event-free survival in asymptomatic patients with aortic stenosis. Initial peak aortic jet velocity (Vmax) stratifies patients according to the likelihood that symptoms requiring valve replacement will develop over time. **B,** Outcomes with very severe AS. Kaplan-Meier event-free survival rate for patients with Vmax of 4.0 m/sec or greater. In both **A** and **B,** most "events" consisted of the onset of symptoms warranting aortic valve replacement. (**A,** From Otto CM et al. A prospective study of asymptomatic valvular aortic stenosis: clinical, echocardiographic, and exercise predictors of outcome. Circulation 1997;95:2262; **B,** from Rosenhek R et al. Natural history of very severe aortic stenosis. Circulation 2010;121:151.)

ETABLE 68.1

Clinical Outcomes in Prospective Studies of Asymptomatic Aortic Stenosis in Adults

	SEVERITY OF	MEAN

STUDY	PATIENTS (*n*)	AORTIC STENOSIS	AGE (yr)	FOLLOW-UP	EVENT-FREE SURVIVAL WITHOUT SYMPTOMS
Kelly et al, 1988	51	Vmax >3.6 m/sec	63 ±8	5-25 mo	Overall: 59% at 15 mo
Pellikka et al, 1990	113	Vmax ≥4.0 m/sec	40-94	20 mo	Overall: 86% at 1 yr, 62% at 2 yr
Kennedy et al, 1991	66	AVA = 0.7-1.2 cm^2	67 ±10	35 mo	Overall: 59% at 4 yr
Otto et al, 1997	123	Vmax >2.6 m/sec	63 ±16	2.5 ±1.4 yr	Overall: 93% ±5% at 1 yr, 62% ±8% at 3 yr; 26% ±10% at 5 yr *Subgroups:* Vmax <3 m/sec: 84% ±16% at 2 yr Vmax, 3-4 m/sec: 66% ±13% at 2 yr Vmax >4 m/sec: 21% ±18% at 2 yr
Rosenhek et al, 2000	128	Vmax >4.0 m/sec	60 ±18	22 ±18 mo	Overall: 67% ±5% at 1 yr, 56% ±55% at 2 yr, 33% ±5% at 4 yr *Subgroups:* No or mild Ca^{2+}: 75% ±9% at 4 yr Moderate-severe Ca^{2+}: 20% ±5% at 4 yr
Rosenhek et al, 2004	176	Vmax 2.5-3.9 m/sec LVEF >50%	58 ±19	48 ±19 mo	95% at 1 yr 75% at 2 yr 60% at 5 yr
Pellikka et al, 2005	622	Vmax ≥4.0 m/sec	72 ±11	5.4 ±4.0 yr	Overall: 82% at 1 yr, 67% at 2 yr, 33% at 5 yr
Rossebo et al, 2008	1873	Vmax 2.5-4.0 m/sec	68 ±9	52 mo (median)	Event-free survival 65% at 5 years No effect of statin therapy on major CV events
Lancellotti et al, 2010	163	AVAi ≤0.6 cm^2/m^2 No AS symptoms LVEF ≥55%	70 ±10	20 ±19 mo	Event-free survival 50% at 2 years, 44% at 4 years Multivariate predictors of clinical outcome were Vmax ≥4.4 m/sec, LV longitudinal deformation ≤15.9%, valvuloarterial impedance ≥4.9 mm Hg/m^2, and LA area ≥12.2 cm^2/m^2.
Kang et al, 2010	95	AVA 0.75 cm^2 PLUS Vmax ≥4.5 m/sec *or* ΔP_{mean} ≥50 mm Hg	63 ±12	50 mo	71% ±5% at 2 yr 47% ±5% at 4 yr 28% ±6% at 6 yr Multivariate predictors of survival were Vmax ≥5 m/sec, age, male sex, EuroScore, and degree of valve calcification.
Stewart et al, 2010	183	Vmax >3 m/sec LVEF >50%	70	31 mo (median)	Probability of symptom-free survival at 3 yr (95% CI): Vmax <3.5 m/sec: 0.72 (0.61-0.84) Vmax 3.5-4.0 m/sec: 0.46 (0.30-0.62) Vmax >4.0 m/sec: 0.32 (0.20-0.44)
Rosenhek et al, 2010	116	Vmax ≥5.0 m/sec	67 ±15	41 mo (median)	Vmax 5.0-5.5 m/sec: 43% at 2 yr Vmax ≥5.5 m/sec: 25% at 2 yr Vmax but not AVA predicted outcome
Jander et al, 2011	435	*Low-gradient "severe" AS:* AVA <1 cm^2 with ΔP_{mean} ≤40 mm Hg	70 ±9	46 ±14 mo	No difference in event rates between groups Low-gradient "severe" AS, defined as an AVA <1 cm^2 with ΔP_{mean} ≤40 mm Hg, was *not* a predictor of clinical outcome.
	184	*Moderate AS:* AVA 1-1.5 cm^2, ΔP_{mean} 25-40 mm Hg	67 ±9	46 ±14 mo	
Saito et al, 2012	103	AVA <1.0 cm^2	72 ±11	36 ±27 mo	AVA index <0.6 cm^2/m^2: 41% at 3 yr AVA index ≥0.6 cm^2/m^2: 86% at 3 yr *Multivariate analysis:* AVAi <0.6 cm^2/m^2 (HR, 2.6; 95% CI 11.1-6.3) Vmax >4.0 m/sec (HR, 2.6; 95% CI 1.2-5.8) AVA <0.75 cm^2 did *not* predict outcome (mean BSA 1.50 ±0.15 m^2).

AVA, Aortic valve area; *AVAi,* AVA indexed for body surface area; *BNP,* blood natriuretic peptide level (pg/mL); *BSA,* body surface area; *Ca^{2+},* aortic valve calcification; *CV,* cardiovascular; *ln,* logarithm; *Mod,* moderate; *ΔP_{mean},* mean pressure gradient; *Vmax,* maximum aortic velocity.

Data from Kelly TA et al. Comparison of outcome of symptomatic to symptomatic patients older than 20 years of age with valvular aortic stenosis. Am J Cardiol 1988;61:123; Pellikka PA et al. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. J Am Coll Cardiol 1990;15:1012; Kennedy KD et al. Natural history of moderate aortic stenosis. J Am Coll Cardiol 1991;17:313; Otto CM et al. A prospective study of asymptomatic valvular aortic stenosis: clinical, echocardiographic, and exercise predictors of outcome. Circulation 1997;95:2262; Rosenhek R et al. Predictors of outcome in severe asymptomatic aortic valve stenosis. N Engl J Med 2000;343:611; Pellikka PA et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation 2005;111:3290; Monin JL et al. Risk score for predicting outcome in patients with asymptomatic aortic stenosis. Circulation 2009;120:69; Rosenhek R et al. Mild and moderate aortic stenosis: natural history and risk stratification by echocardiography. Eur Heart J 2004;25:199; Pellikka PA et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation 2005;21;3290; Rossebo AB et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 2008;359:1343; Lancellotti P et al. Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay. Heart 2010;96:1364; Kang DH et al. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. Circulation 2010;121:1502; Stewart RA et al. Left ventricular systolic and diastolic function assessed by tissue Doppler imaging and outcome in asymptomatic aortic stenosis. Eur Heart J 2010;31:2216; Rosenhek R et al. Natural history of very severe aortic stenosis. Circulation 2010;121:151; Jander N et al. Outcome of patients with low-gradient "severe" aortic stenosis and preserved

ejection fraction. Circulation 2011;123:887; Saito T et al. Prognostic value of aortic valve area index in asymptomatic patients with severe aortic stenosis. Am J Cardiol 2012;110:93.

Because of the variability in hemodynamic severity at symptom onset, and because many patients fail to recognize symptom onset resulting from the insidious rate of disease progression, both exercise testing and serum B-type natriuretic peptide (BNP) levels have been evaluated as measures of disease progression and predictors of symptom onset. Exercise testing monitored by a physician is safe in adults with severe AS when symptom status is unclear, and patients who develop symptoms or exhibit a decrease in blood pressure with exertion should be considered to have symptomatic disease.[65] An elevated BNP level may be helpful when symptoms are equivocal or when stenosis severity is only moderate, but the role of BNP monitoring in the evaluation of disease progression has not been fully defined.[86] **Table 68.3** lists other factors that are useful for risk stratification to predict symptom onset and event-free survival.

TABLE 68.3

Risk Stratification of Patients with Severe Aortic Stenosis (AS)

ASYMPTOMATIC PATIENTS*	SYMPTOMATIC PATIENTS†
Abnormal exercise test	Lack of contractile reserve in patients with low-flow, low-gradient, low-EF AS
Elevated BNP	Very low mean gradient (<20 mm Hg)
Moderate to severe valve calcification	Very elevated BNP
Very high aortic velocity (>5 or 5.5 m/sec)	Severe ventricular fibrosis
Rapid increase in aortic velocity	O_2-dependent lung disease
Increased hypertrophic LV remodeling	Frailty
Reduced LV longitudinal systolic strain	Advanced renal dysfunction
Myocardial fibrosis	Very high STS score
Pulmonary hypertension	

*Markers of increased rate of disease progression and/or decreased event-free survival.

†Markers of increased risk and/or potential futility.

BNP, Brain (B-type) natriuretic peptide; *EF,* ejection fraction; *LV,* left ventricular; *STS,* Society of Thoracic Surgeons.

From Lindman BR, Bonow RO, Otto CM. Current management of calcific aortic stenosis. Circ Res 2013;113:223.

Symptomatic Patients

Once even mild symptoms are present, survival is poor unless outflow obstruction is relieved. Expected survival for patients with severe symptomatic AS will differ somewhat based on the age, number of comorbidities, and severity of HF of the cohort examined, but average survival without AVR is only 1 to 3 years after symptom onset.[87,88] In the PARTNER (Placement of Transcatheter Aortic Valves) study, outcomes were very poor for patients with severe symptomatic AS deemed unsuitable candidates for surgery who were randomly assigned to conventional therapy (e.g., medical therapy without transcatheter AVR), with a 1-year mortality of 50.9% and a 2-year mortality of 68%.[88,89] Among symptomatic patients with severe AS, the outlook is poorest when the left ventricle has failed and the cardiac output and transvalvular gradient are both low. The risk of sudden death is high with symptomatic severe AS, so these patients should be promptly referred for AVR. In patients who do not undergo AVR, recurrent hospitalizations for angina and decompensated HF are common, associated with significant consumption of health care resources.[90]

Classification of Severe Aortic Stenosis.

Severe AS is defined as AVA of 1.0 cm^2 or greater, mean gradient of 40 mm Hg or higher, or a peak jet velocity of 4 m/sec or more (**see Table 68.2**). When aortic velocity or gradient meet this criteria, severe AS is present and classified as stage C in asymptomatic patients and stage D1 in symptomatic patients. Classification of stenosis severity is more complex when AVA is 1.0 cm^2 or less, but mean pressure gradient is less than 40 mm Hg and peak jet velocity less than 4 m/sec. Many patients with these apparently "discordant" data have moderate AS. However, it is important to consider the diagnosis of low-gradient severe AS, particularly if symptoms consistent with AS are present. First, measurement errors should be excluded, particularly an undermeasured LV outflow tract dimension, since this will yield a calculated AVA that is smaller than the actual AVA (**see Chapter 14**). Indexing AVA for body size may be helpful in small patients but is not recommended in normal-size and larger adults. The next steps are to measure LVEF and stroke volume, evaluate valve anatomy and degree of leaflet calcification, and then consider further testing.

Severe Low-Flow, Low-Gradient Aortic Stenosis with Reduced LVEF.

Classic low-flow, low-gradient AS (stage D2) is defined as AVA of 1.0 cm^2 or less with an aortic velocity less than 4.0 m/sec or mean gradient less than 40 mm Hg, and LVEF less than 50% (**see Table 68.2**). Patients with HF symptoms and stage D2 AS often create a diagnostic dilemma for the clinician because their clinical presentation and hemodynamic data may be indistinguishable from those of patients with a dilated cardiomyopathy and a calcified valve that is not severely stenotic.[91,92] Severe AS can be distinguished from moderate AS with primary LV dysfunction based on the changes in valve hemodynamics during transient increases in flow, usually by increasing cardiac output with dobutamine[92,93] (**see Chapter 14**). Severe AS is present if there is an increase in aortic velocity to at least 4 m/sec at any flow rate, with AVA that remains less than 1.0 cm^2.[58] Dobutamine echocardiography also provides evidence of myocardial contractile reserve (increase in stroke volume >20% from baseline), which is an important predictor of operative risk and survival after AVR in these patients.[92,94-96] However, even in patients with a lack of contractile reserve, AVR should be considered if the mean gradient is greater than 20 mm Hg, because survival after AVR is better (approximately 50% at 5 years) than with medical therapy.[96,97] In those without contractile reserve, the projected AVA at a transvalvular flow rate of 250 mL/sec, or cardiac CT to assess valve calcification, may be useful to improve discrimination between truly severe AS versus moderate AS with myocardial dysfunction.[95]

Severe Low-Flow, Low-Gradient Aortic Stenosis with Preserved LVEF.

Low-flow, low-gradient AS also can occur with a normal LVEF (≥50%) (**see Table 68.2**), typically in elderly patients with a small, hypertrophied left ventricle or those with concurrent hypertension. This is often referred to as "paradoxical" low-flow, low-gradient AS (ACC/AHA stage D3; AVA ≤1.0 cm^2 with aortic velocity <4.0 m/sec or mean gradient <40 mm Hg, and LVEF ≥50%) because despite a normal EF, transaortic flow is low (stroke volume index <35 mL/m^2).[19,98] Distinguishing truly severe AS from moderate AS can be challenging. Measurement errors should be ruled out and small body size accounted for (an indexed AVA ≤0.6 cm^2/m^2 is consistent with severe AS). Dobutamine has been used to augment flow to distinguish truly severe AS from pseudosevere AS, but is less preferred in these patients with a hypertrophied ventricle, small LV cavity, and marked diastolic dysfunction.[99] Evaluation of valve hemodynamics after the treatment of hypertension can be helpful and, increasingly, CT assessment of valve calcification is being used to identify patients with a severely calcified valve.[64,66]

Treatment

Medical Management

Medical therapy has not been shown to affect disease progression in patients with AS.[4,7,20] Furthermore, both observational studies and RCTs convincingly demonstrate that AVR is superior to medical therapy in patients with severe symptomatic AS.[88,100] The risk of sudden death increases dramatically once symptoms are present, and patients should be advised to report promptly the development of any symptoms possibly related to AS. In asymptomatic patients with AS of any degree, evaluation and treatment for conventional cardiovascular risk factors is recommended in accordance with established guidelines (**see Chap. 45**).

Hypertension accompanies AS in a majority of patients.[101] Because of traditional teaching that AS is a disease with fixed afterload, there has often been reluctance to treat hypertension because of concerns that vasodilation would not be offset by an increase in stroke volume. However, several studies have demonstrated that vasodilation is accompanied by increases in stroke volume, even in patients with severe AS[47] (see Classic References, Khot). Hypertension imposes an additional load on the left ventricle and is associated with more adverse hypertrophic LV remodeling.[53] Although treatment of hypertension may not reduce AS-related events, it should be treated according to established guidelines (**see Chapter 47**) because of the known adverse association between hypertension and vascular events and mortality.[53,54] There is no one class of medicines established as the preferred treatment of hypertension in patients with AS, but because the renin-angiotensin system is upregulated in the valve and ventricle of patients with AS, angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) may preferentially considered. Small studies have demonstrated their safety, and some suggest a clinical benefit, but larger-scale randomized studies are needed.[20]

The presence of concomitant CAD is related to the patient's age but is common in patients with AS. Primary and secondary prevention guidelines should be followed and the decision of whether to prescribe a statin medication should not be influenced by the presence of AS. RCTs testing the use of statins in patients with mild AS to more advanced disease were adequately powered and showed no improvement in mortality, time to AVR, or rate of AS progression in the treatment versus placebo groups.[102]

Atrial fibrillation (AF) or atrial flutter may also develop in up to one third of older patients with AS, perhaps exacerbated by left atrial enlargement related to diastolic dysfunction. When such an arrhythmia is observed in a patient with AS, the possibility of associated mitral valvular disease should be considered. When AF occurs, the rapid ventricular rate may cause angina pectoris. The loss of the atrial contribution to LV filling and a sudden fall in cardiac output may cause serious hypotension. If this occurs, AF should be treated promptly, usually with cardioversion. New-onset AF in a previously asymptomatic patient with severe AS may be a marker of impending symptom onset.[103]

In patients with heart failure (HF) and volume overload, AVR is indicated, but diuretics may reduce congestion and provide some symptomatic relief prior to valve replacement. Patients with decompensated HF may benefit from medical therapy as a bridge to definitive therapy with valve replacement. Nitroprusside has been used during hemodynamic monitoring in the intensive care unit to unload the left heart, reduce congestion, and improve forward flow. Similarly, phosphodiesterase type 5 inhibition has been shown to provide acute improvements in pulmonary and systemic hemodynamics resulting in biventricular unloading.[47] These medications may improve the patient's hemodynamic status, allowing the AVR procedure to be performed more safely.

Balloon Aortic Valvuloplasty

AVR is the procedure of choice for relief of outflow obstruction in adults with valvular AS. Balloon aortic valvuloplasty has only a modest hemodynamic effect in patients with calcific AS. It can provide

short-term improvement in survival and quality of life, but these benefits are not sustained.[104] Accordingly, balloon aortic valvuloplasty is not recommended as an alternate to valve replacement for calcific AS. In selected cases, it might be reasonable as a bridge to definitive treatment with AVR in unstable patients or as a palliative procedure in patients who are not candidates for AVR.[105]

Aortic Valve Replacement

AVR is recommended for adults with symptomatic severe AS, even if symptoms are mild (**Fig. 68.9**). Despite this clear guideline recommendation,[19,69] many patients with symptomatic AS are not referred appropriately for surgery, even when the operative risk is low.[87] AVR also is recommended for severe AS with a LVEF less than 50% and for patients with severe asymptomatic AS who are undergoing coronary bypass grafting (CABG) or other forms of heart surgery.[19,20,69] In addition, AVR is appropriate for apparently asymptomatic patients with severe AS when exercise testing provokes symptoms or a fall in BP. Outcomes are similar in patients with mixed AS and AR, and standard criteria for intervention are applicable in this patient group.[106,107] In asymptomatic patients with severe AS and a low operative risk, AVR may be considered when markers of rapid disease progression are present (e.g., severe valve calcification) or when AS is very severe, depending on patient preferences regarding the risk of earlier intervention versus careful monitoring with intervention promptly at symptom onset. Once a decision is made that AVR is indicated, a surgical approach or transcatheter approach may be considered (**see Fig. 68.9**).[108]

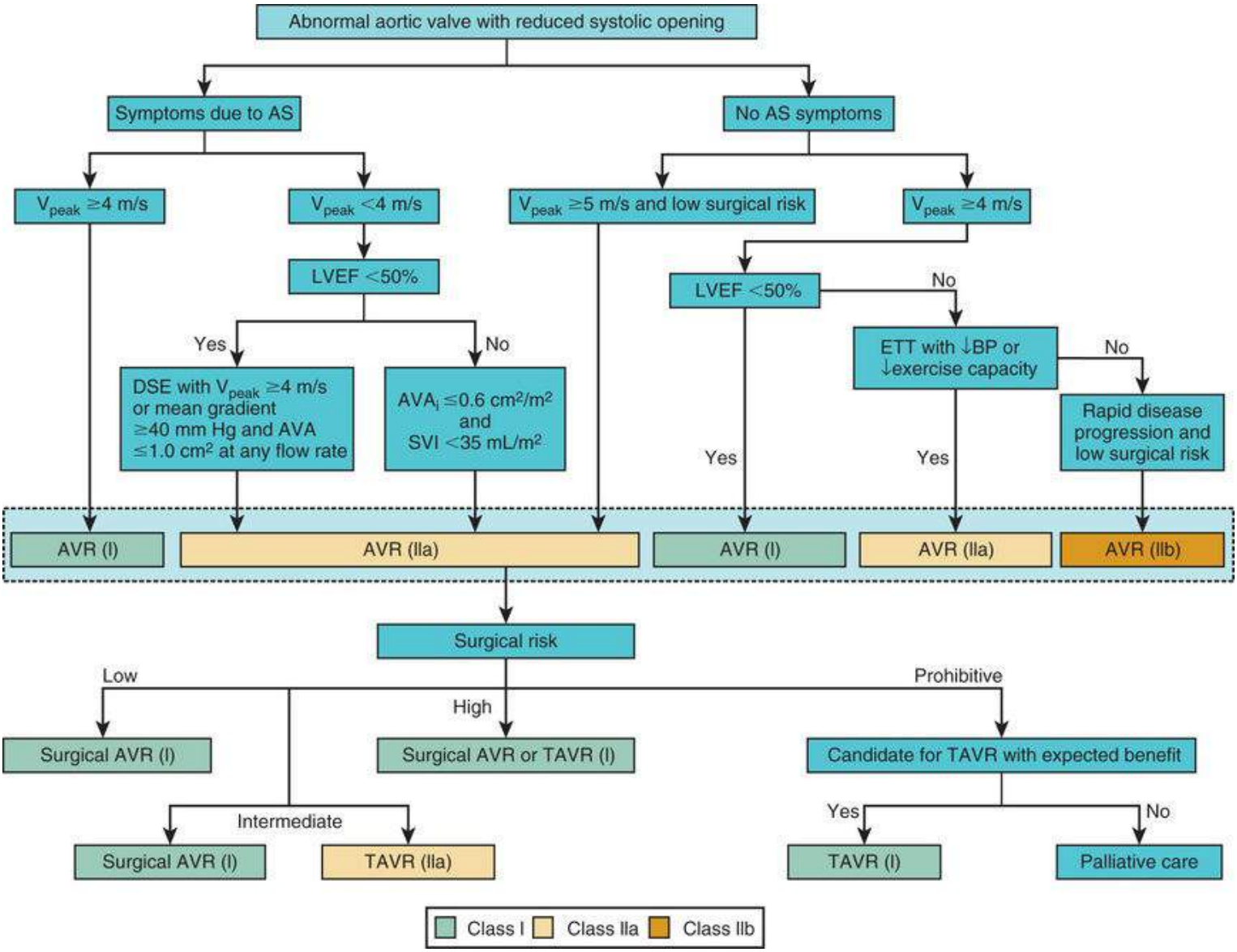


FIGURE 68.9 Algorithm for management of aortic stenosis (AS) recommended by 2014 American College of Cardiology/American Heart Association guidelines for indications for aortic valve replacement (AVR) for severe AS, including the 2017 update for considerations for surgical AVR and transcatheter AVR (TAVR). AVA, Aortic valve area; AVAi, AVA indexed for body surface area; BP, blood pressure; DSE, dobutamine stress echocardiography; ETT, exercise treadmill test; LVEF, left ventricular ejection fraction; SVI, stroke volume index; V_{peak}, peak aortic jet velocity. (Modified from Lindman BR, Clavel M-A, Mathieu P, et al. Calcific aortic stenosis. Nat Rev Dis Primers 2016;2:16006.)

After AVR, symptoms of pulmonary congestion (exertional dyspnea) and myocardial ischemia (angina pectoris) are relieved in almost all patients, and most patients will exhibit an improvement in exercise tolerance, even if it was only mildly reduced before surgery. A reduced EF often improves and even normalizes after AVR, but impaired longitudinal strain may still be evident.[109] LV hypertrophy tends to regress after AVR, but the rate and extent of reversal varies and is often incomplete. Myocardial fibrosis regresses more slowly than myocyte hypertrophy, and thus diastolic dysfunction may improve but still persist for years after successful valve replacement.

Surgical Aortic Valve Replacement

Since the first successful surgical AVR (SAVR) in 1960, improvements in valve design, surgical techniques, and perioperative management have decreased surgical morbidity and mortality despite the increasing age and comorbidities of patients treated. The Society of Thoracic Surgeons (STS) National Database Committee reported an overall operative mortality rate of 3.2% in 67,292 patients undergoing

isolated AVR and 5.6% in 66,074 patients undergoing AVR and CABG.[110-112] In patients younger than 70 with minimal comorbidities, the operative risk of mortality is less than 1% in many centers. Medicare data from the past decade indicate that the 30-day mortality after surgical AVR in patients age 65 and older in the United States has decreased, from 7.6% in 1999 to 4.2% in 2011, with the most marked decrease in patients age 85 and older, in whom the 30-day mortality has decreased from 12.3% to 5.8%.[113] Therefore, advanced age should not be considered a contraindication to operation.[114] The 30-day mortality rate also is significantly related to the number of AVR procedures performed at each hospital. Risk factors associated with a higher mortality rate include a high New York Heart Association (NYHA) functional class, impaired LV function, advanced age, the presence of associated CAD, and other comorbidities.[115-118]

Transcatheter Aortic Valve Replacement

Over the last decade, transcatheter AVR (TAVR) has transformed the treatment of patients with calcific AS.[119] First, it was shown to be superior to medical therapy (usually accompanied by balloon aortic valvuloplasty) in patients who were not candidates for surgery.[88-100] Subsequently, in patients deemed high risk for surgery, TAVR was shown to be noninferior and perhaps superior to SAVR.[120-122] More recently, in intermediate-risk patients, TAVR has been shown to compare favorably to SAVR.[123-125] Randomized trials are ongoing to compare TAVR and SAVR in low-risk patients. The most common approach to valve implantation is *transfemoral*, particularly as sheath size progressively decreases. The long-term durability of transcatheter valves remains to be determined, which is particularly relevant as we move toward treating younger, lower-risk patients (**see Chapter 72**).

Patient Selection for TAVR or SAVR.

The choice of SAVR versus TAVR should come after a decision that AVR is indicated (**see Fig. 68.9**).[108] Given the complexity of issues to consider, it is recommended that these decisions occur through a heart valve team of cardiac surgeons, interventional cardiologists, clinical and imaging experts in valve disease, as well as nurses, anesthetists, and geriatricians as needed.[126] The overall procedural risk for the patient for SAVR or TAVR depends on multiple factors, including age, comorbidities, frailty, LV function, and anatomic issues (**Table 68.4**). The landscape for these decision pathways is rapidly changing as successive trials are reported (**see Chapter 72**). Currently, TAVR is approved in the United States for patients at extreme, high, or intermediate risk for surgery, as reflected in the 2017 update of the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of patients with valvular heart disease;[127] results from low-risk trials are anticipated in the next few years. In a novel approach to developing a clinical practice guideline, recommendations were recently provided for transcatheter versus surgical valve replacement[128-131] (**Fig. 68.10**). For patients at higher risk, the potential benefit versus futility of TAVR needs careful consideration[132] (**Fig. 68.11**). Although TAVR reduces mortality compared to medical therapy, a sizable subgroup of patients dies soon after TAVR or has no improvement in their quality of life.[133] If poor health status is driven more by comorbidities and frailty than by symptomatic AS, AVR may yield no clinical benefit, and palliative care should be considered.

TABLE 68.4

Factors to Consider for Patient Selection for Transcatheter versus Surgical Aortic Valve Replacement

Age (both in terms of procedural risk and anticipated postprocedure survival with implanted prosthesis)
Left ventricular function
Valve anatomy (bicuspid versus tricuspid)
Number of comorbidities
Pulmonary function
Renal function
Liver function
Frailty
Disability
Anatomy (e.g., porcelain aorta, septal bulge, femoral vessel size, aortic atheroma, “hostile chest,” graft anatomy)
Coronary disease: need for revascularization, optimal strategy
Concomitant significant mitral or tricuspid valve disease and likelihood of improvement if only aortic stenosis is treated
Likelihood of particular complications (e.g., paravalvular leak, coronary obstruction, heart block, stroke, acute kidney injury)

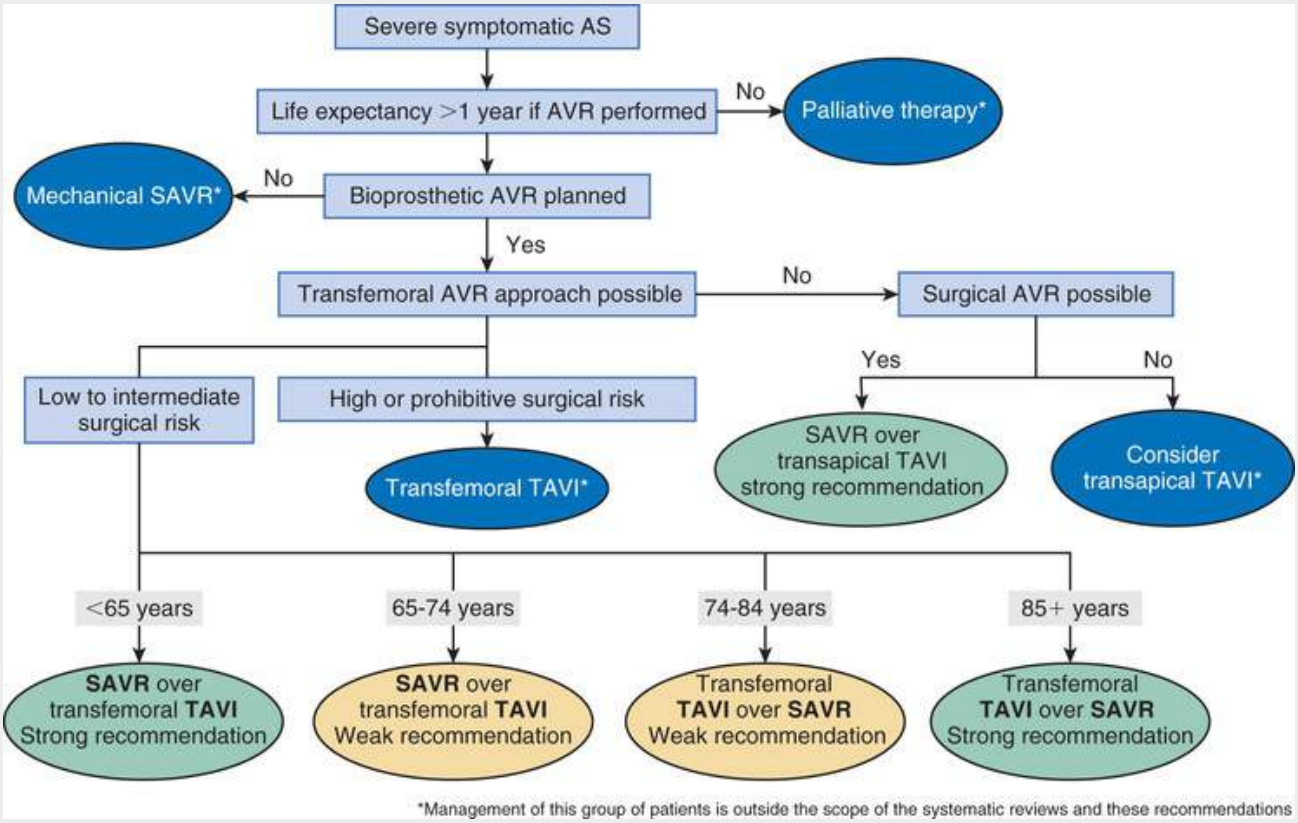


FIGURE 68.10 Algorithm for management of severe aortic stenosis (AS). *Colored boxes* represent the recommendations covered by this study. AVR, Aortic valve replacement; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve insertion. (From Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. BMJ 2016;354:i5085.)

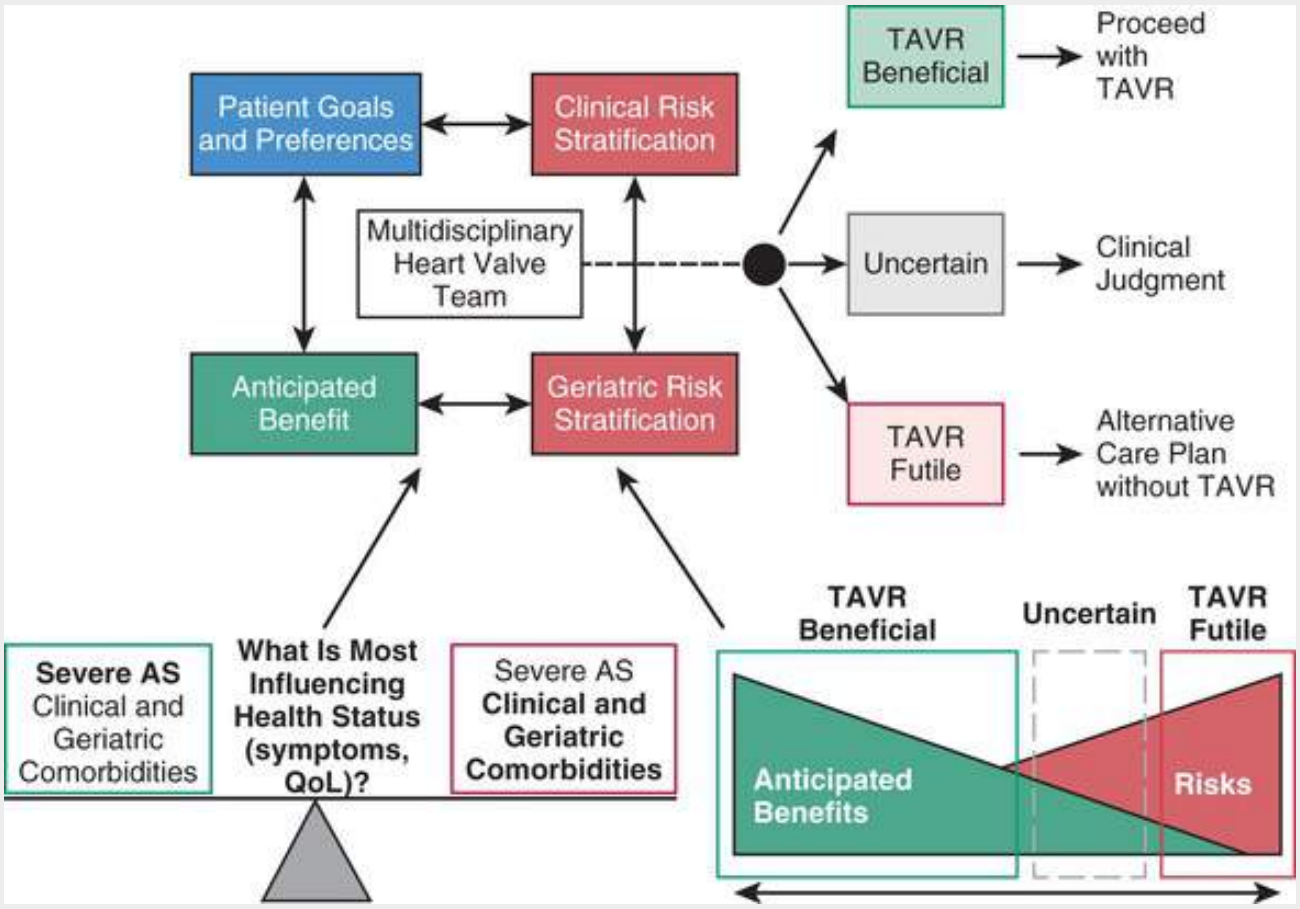


FIGURE 68.11 Decision making by multidisciplinary heart valve team on patients referred for transcatheter aortic valve replacement (TAVR). The team considers and weighs the various factors shown and makes a decision regarding whether TAVR will likely be beneficial or futile. Areas of uncertainty require clinical judgment. The factors thought most to influence the patient's current health status affect assessment of the anticipated benefit of TAVR. Anticipated benefits or risks may clearly outweigh each other, but in some cases, there is uncertainty when patient goals and preferences are especially important to incorporate into decision making regarding whether to perform TAVR. AS, Aortic stenosis; QoL, quality of life. (From Lindman BR, Alexander KP, O'Gara PT, Afilalo J. Futility, benefit, and transcatheter aortic valve replacement. JACC Cardiovasc Interv 2014;7:707-16.)

Aortic Regurgitation

Causes and Pathology

Aortic regurgitation may be caused by primary disease of the aortic valve leaflets and/or the wall of the aortic root[106] (**Fig. 68.12**). Among patients with isolated AR who undergo AVR, the percentage with aortic root disease has been increasing steadily during the past few decades; it now represents the most common cause and accounts for more than 50% of all such patients in some series.

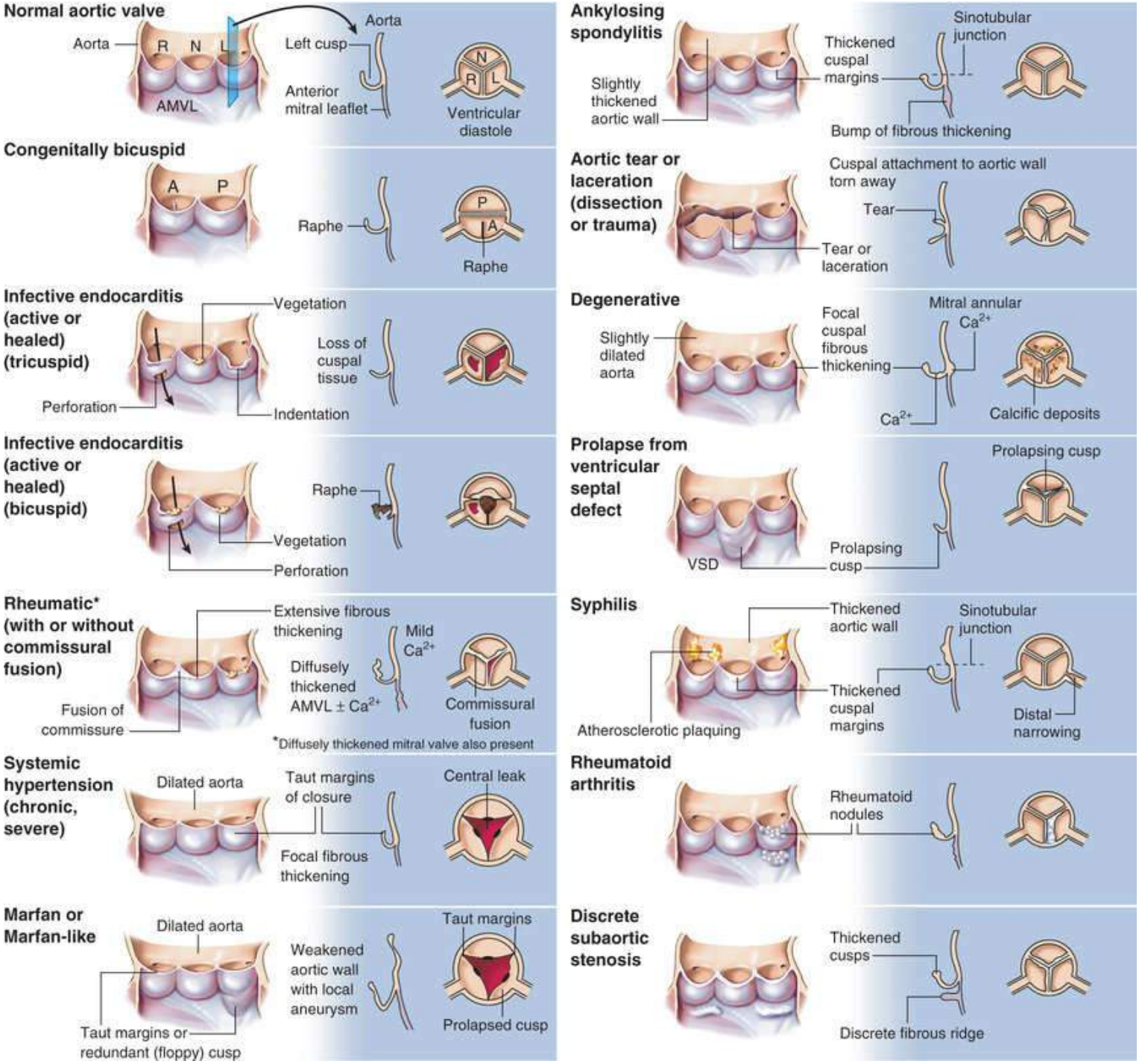


FIGURE 68.12 Diagram of various causes of pure aortic regurgitation. *A,* Anterior; *AMVL,* anterior mitral valve leaflet; *Ca^{2+},* calcification; *L,* left coronary cusp; *N,* noncoronary cusp; *P,* posterior; *R,* right coronary cusp; *VSD,* ventricular septal defect. (From Waller BF. Rheumatic and nonrheumatic conditions producing valvular heart disease. Cardiovasc Clin 1986;16:30.)

Valvular Disease

Primary valvular causes of AR include (1) calcific AS in older patients, who have some degree (usually mild) of AR (75% of patients); (2) infective endocarditis (**see Chapter 73**), in which the infection may destroy or cause perforation of a leaflet, or the vegetations may interfere with proper coaptation of the cusps; and (3) trauma that results in a tear of the ascending aorta, in which loss of commissural support can cause prolapse of an aortic cusp. Although the most common complication of a congenitally bicuspid valve in adults is stenosis, incomplete closure or prolapse of a bicuspid valve may also cause isolated AR or a combination of AS and AR.[5] Rheumatic fever remains a common cause of AR worldwide. The

cusps become infiltrated with fibrous tissue and retract, which prevents cusp apposition during diastole; this usually leads to AR through a defect in the center of the valve (**see Fig. 68.1C**). The associated fusion of the commissures may restrict the opening of the valve, resulting in combined AS and AR; associated mitral valve involvement is also common (**see Chapter 74**). Progressive AR may occur in patients with a large ventricular septal defect, as well as in patients with membranous subaortic stenosis (**see Chapter 75**), and as a complication of percutaneous balloon aortic valvuloplasty. Progressive AR also may occur in patients with myxomatous proliferation of the aortic valve. An increasingly common cause of valvular AR is structural deterioration of a bioprosthetic valve (**see Chapter 71**).

Less common valvular causes of AR include various forms of congenital AR, such as unicommissural and quadricuspid valves, or rupture of a congenitally fenestrated valve, particularly in the presence of hypertension. Other, less common causes of AR occur in association with systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, Jaccoud arthropathy, Takayasu disease, Whipple disease, Crohn disease, and in the past the use of certain anorectic drugs. Isolated congenital AR is an uncommon lesion on necropsy studies but, when present, is usually associated with a bicuspid valve.

Aortic Root Disease

Aortic regurgitation secondary to marked dilation of the ascending aorta is now more common than primary valve disease in patients undergoing AVR for isolated AR[134] (**see Chapter 63**). The conditions responsible for aortic root disease include age-related (degenerative) aortic dilation, cystic medial necrosis of the aorta (either isolated or associated with classic Marfan syndrome), aortic dilation related to bicuspid valves,[5] aortic dissection, osteogenesis imperfecta, syphilitic aortitis, ankylosing spondylitis, Behçet syndrome, psoriatic arthritis, arthritis associated with ulcerative colitis, relapsing polychondritis, reactive arthritis, giant cell arteritis, and systemic hypertension, as well as exposure to some appetite-suppressant drugs.

When the aortic annulus becomes greatly dilated, the aortic leaflets separate and AR may ensue. Dissection of the diseased aortic wall may occur and aggravate the AR. Dilation of the aortic root also may have secondary effects on the aortic valve because dilation causes tension and bowing of the individual cusps, which may thicken and retract. This defect leads to intensification of the AR, further dilating the ascending aorta and leading to a vicious cycle in which, as for MR, more regurgitation leads to more regurgitation (**see Chapter 69**).

Pathophysiology of Chronic Aortic Regurgitation

Left Ventricular Remodeling and Function.

In contrast to MR, in which a fraction of the LV stroke volume is ejected into the low-pressure left atrium, in AR the entire LV stroke volume is ejected into a high-pressure chamber (i.e., the aorta), although the low aortic diastolic pressure does facilitate ventricular emptying during early systole (**Fig. 68.13**). In MR, especially acute MR, the reduction of wall tension (i.e., reduced afterload) allows more complete systolic emptying; in AR, the increase in LV end-diastolic volume (i.e., increased preload) provides hemodynamic compensation.

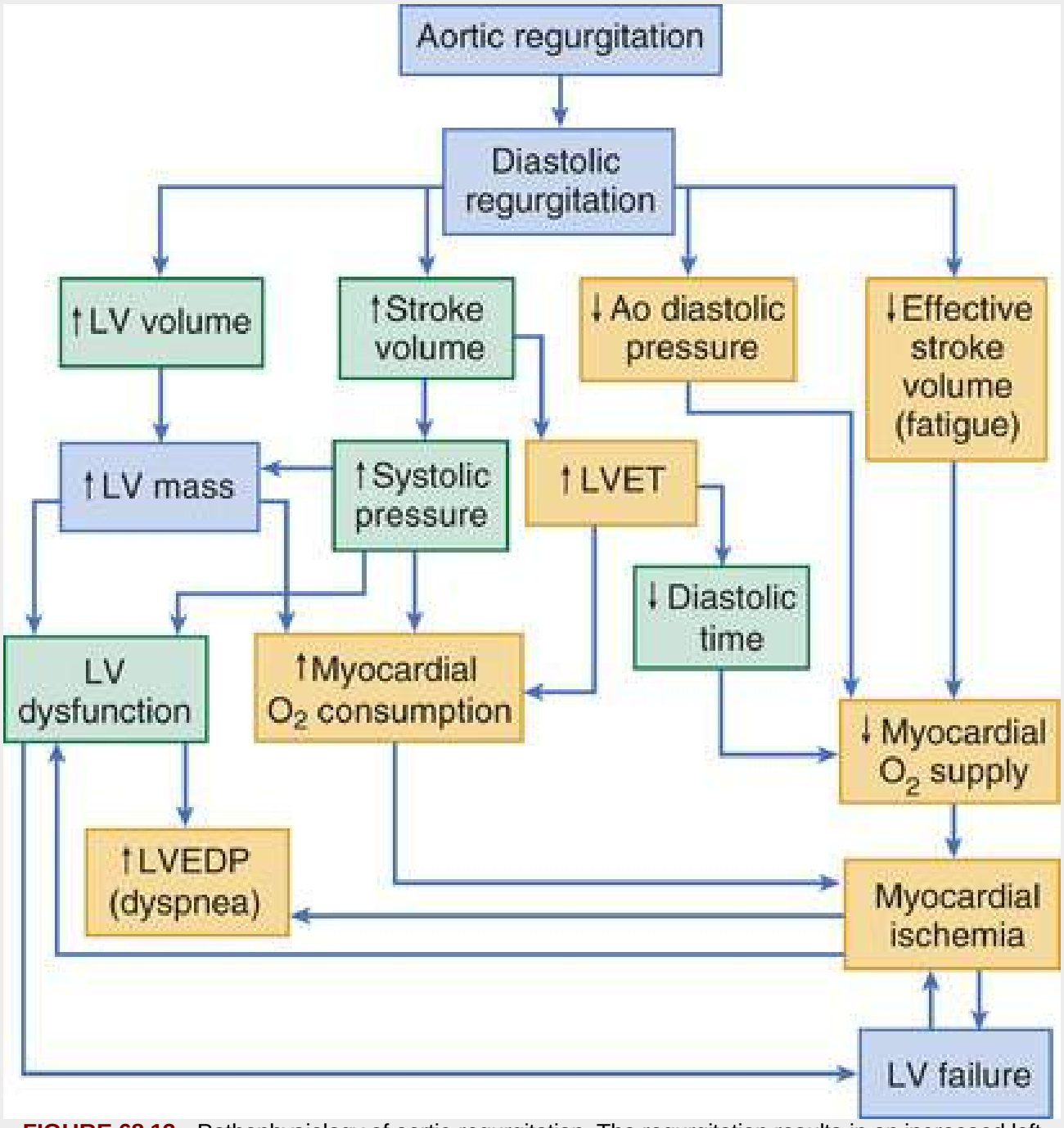


FIGURE 68.13 Pathophysiology of aortic regurgitation. The regurgitation results in an increased left ventricular (LV) volume, increased stroke volume, increased aortic (Ao) systolic pressure, and decreased effective stroke volume. Increased LV volume results in an increased LV mass, which may lead to LV dysfunction and failure. Increased LV stroke volume increases systolic pressure and prolongation of LV ejection time (LVET). Increased LV systolic pressure results in a decrease in diastolic time. Decreased diastolic time (myocardial perfusion time), diastolic aortic pressure, and effective stroke volume lead to reduced myocardial O_2 supply. Increased myocardial O_2 consumption and decreased myocardial O_2 supply produce myocardial ischemia, which further impairs LV function. LVEDP, LV end-diastolic pressure. (From Boudoulas H, Gravanis MB: Valvular heart disease. In Gravanis MB, editor. Cardiovascular Disorders: Pathogenesis and Pathophysiology. St Louis: Mosby; 1993, p 64.)

Severe AR may occur with a normal effective forward stroke volume and a normal LVEF (forward + regurgitant stroke volume/end-diastolic volume), together with an elevated LV end-diastolic volume, pressure, and stress[106] (**Fig. 68.14**). In accord with Laplace law—wall tension is related to the product of the intraventricular pressure and radius divided by wall thickness (**see Chapter 22**)—LV dilation also increases the LV systolic tension required to develop any level of systolic pressure. Thus, in AR, there is an increase in both preload and afterload. LV systolic function is maintained through the combination of chamber dilation and hypertrophy. This leads to eccentric hypertrophy, with replication of sarcomeres in

series and elongation of myocytes and myocardial fibers (see Classic References, Grossman). In compensated AR, sufficient wall thickening results in a normal ratio of LV wall thickness to cavity radius. Under these conditions, end-diastolic wall stress is maintained at or returns to normal levels. In AS, by contrast, changes include pressure overload (concentric) hypertrophy with replication of sarcomeres, largely in parallel, and an increased ratio of wall thickness to radius, but in both AR and AS, an increase in interstitial connective tissue develops. In AR, LV mass usually is greatly increased, often to levels even higher than in isolated AS. As AR persists and increases in severity over time, however, wall thickening fails to keep pace with the hemodynamic load, and end-systolic wall stress rises. At this point, the afterload mismatch results in a decline in systolic function, and the LVEF falls (**see Fig. 68.14**).

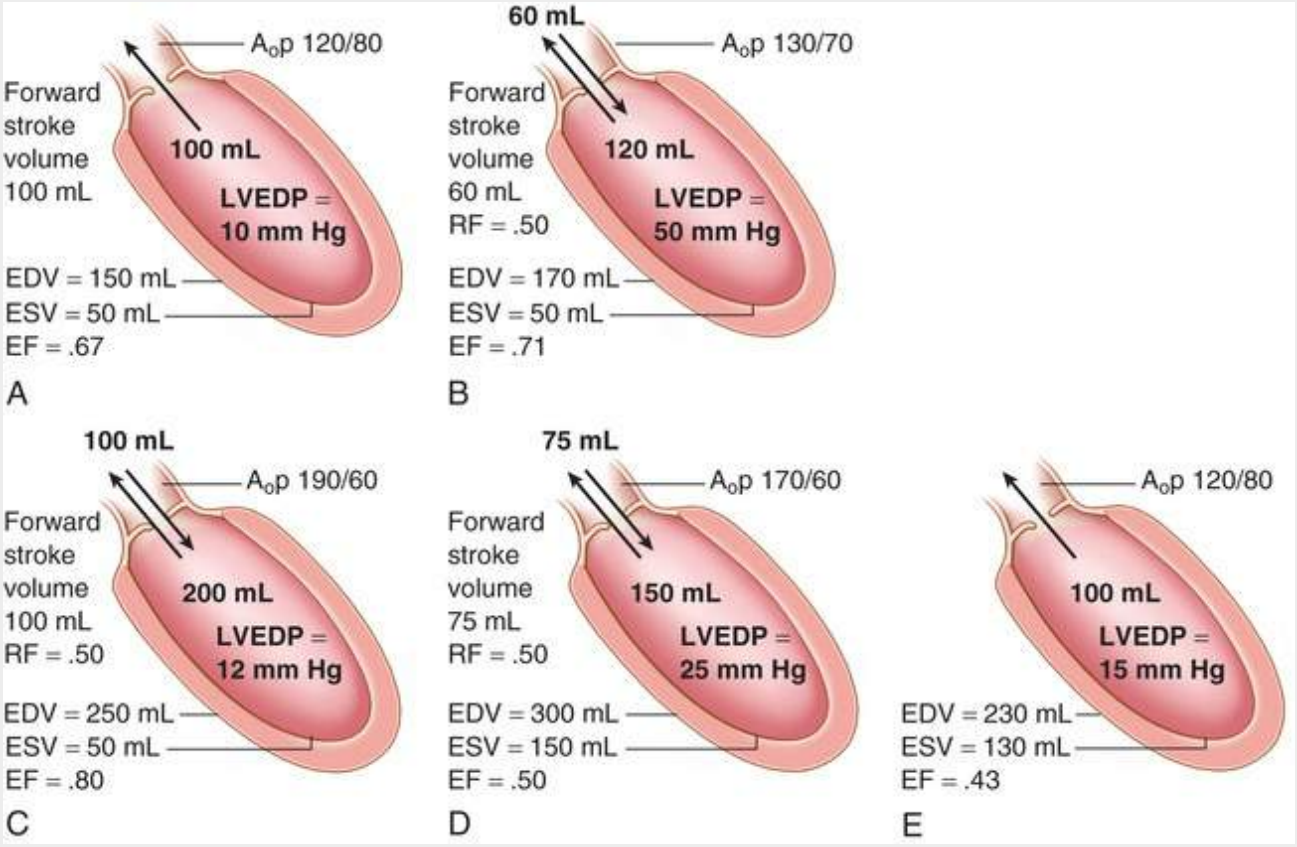


FIGURE 68.14 Hemodynamics of aortic regurgitation (AR). **A,** Normal conditions. **B,** The hemodynamic changes that occur in severe acute AR. Although total stroke volume is increased, forward stroke volume is reduced. Left ventricular end-diastolic pressure (LVEDP) rises dramatically. **C,** Hemodynamic changes occurring in chronic compensated AR. Eccentric hypertrophy produces increased end-diastolic volume (EDV), which permits an increase in total, as well as forward, stroke volume. The volume overload is accommodated, and LV filling pressure is normalized. Ventricular emptying and end-systolic volume (ESV) remain normal. **D,** In chronic decompensated AR, impaired LV emptying produces an increase in ESV and a fall in ejection fraction (EF), total stroke volume, and forward stroke volume. Further cardiac dilation and reelevation of LV filling pressure occur. **E,** Immediately after valve replacement, preload estimated by EDV decreases, as does filling pressure. ESV also is decreased, but to a lesser extent. The result is an initial fall in EF. Despite these changes, elimination of AR leads to an increase in forward stroke volume, and with time, EF increases. A_oP, Aortic pressure; RF, regurgitant fraction. (From Carabello BA. Aortic regurgitation: hemodynamic determinants of prognosis. In Cohn LH, DiSesa VJ, editors. Aortic Regurgitation: Medical and Surgical Management. New York: Marcel Dekker; 1986, pp 99-101.)

Patients with severe chronic AR have the largest LV end-diastolic volumes of any form of heart disease, resulting in so-called cor bovinum. However, end-diastolic pressure is not uniformly elevated (i.e., LV compliance often is increased; **see Fig. 68.14**). The adaptive response to gradually increasing,

chronic AR permits the ventricle to function as an effective high-compliance pump, handling a large stroke volume, often with little increase in filling pressure. During exercise, peripheral vascular resistance declines and, with an increase in heart rate, diastole shortens and the regurgitation per beat decreases, facilitating an increment in effective (forward) cardiac output without substantial increases in end-diastolic volume and pressure. The EF and related ejection phase indices are often within normal limits, both at rest and during exercise, even though MI, as reflected in the slope of the end-systolic pressure-volume relationship, is depressed.

As the left ventricle decompensates, interstitial fibrosis increases, compliance declines, and LV end-diastolic pressure and volume rise (**see Fig. 68.14**). In advanced stages of decompensation, left atrial, pulmonary artery wedge, pulmonary arterial, right ventricular (RV), and right atrial pressures rise, and the effective (forward) cardiac output falls, at first during exercise and then at rest. The normal decline in LV end-systolic volume or the rise in EF fails to occur during exercise. Symptoms of HF develop, particularly those secondary to pulmonary congestion.

Myocardial Ischemia.

When acute AR is induced experimentally, myocardial O_2 requirements rise substantially, secondary to an increase in wall tension. In patients with chronic severe AR, total myocardial O_2 requirements also are augmented by the increase in LV mass. Because the major portion of coronary blood flow occurs during diastole, when aortic pressure is lower than normal in AR, coronary perfusion pressure is reduced. Studies in experimentally induced AR have shown a reduction in coronary flow reserve, with a change in forward coronary flow from diastole to systole. The result—a combination of increased O_2 demands and reduced supply—sets the stage for the development of myocardial ischemia, especially during exercise. Thus, patients with severe AR exhibit a reduction of coronary reserve, which may be responsible for myocardial ischemia, which may in turn play a role in the deterioration of LV function.

Clinical Presentation of Chronic Aortic Regurgitation

The clinical stages of chronic AR demonstrate the progressive nature of the disease (**Table 68.5**).

TABLE 68.5

Stages of Chronic Aortic Regurgitation (AR)

STAGE	DEFINITION	VALVE ANATOMY	VALVE HEMODYNAMICS	HEMODYNAMIC CONSEQUENCES	SYMPTOMS
A	**At risk of AR**	Bicuspid aortic valve (or other congenital valve anomaly) Aortic valve sclerosis Diseases of the aortic sinuses or ascending aorta History of rheumatic fever or known rheumatic heart disease IE	AR severity none or trace	None	None
B	**Progressive AR**	Mild to moderate calcification of a trileaflet valve or bicuspid aortic valve (or other congenital valve anomaly) Dilated aortic sinuses Rheumatic valve changes Previous IE	***Mild AR:*** Jet width <25% of LVOT Vena contracta <0.3 cm RVol <30 mL/beat RF <30% ERO <0.10 cm^2 Angiography grade 1+ ***Moderate AR:*** Jet width 25-64% of LVOT Vena contracta 0.3-0.6 cm RVol 30-59 mL/beat RF 30-49% ERO 0.10-0.29 cm^2 Angiography grade 2+	Normal LV systolic function Normal LV volume or mild LV dilation	None
C	**Asymptomatic severe AR**	Calcific aortic valve disease Bicuspid valve (or other congenital abnormality) Dilated aortic sinuses or ascending aorta Rheumatic valve changes IE with abnormal leaflet closure or perforation	***Severe AR:*** Jet width ≥65% of LVOT Vena contracta >0.6 cm Holodiastolic flow reversal in proximal abdominal aorta RVol ≥60 mL/beat RF ≥50% ERO ≥0.3 cm^2 Angiography grade 3+ to 4+ In addition, diagnosis of chronic severe AR requires evidence of LV dilation.	*C1:* Normal LVEF (≥50%) and mild-to-moderate LV dilation (LVESD ≤50 mm) *C2:* Abnormal LV systolic function with depressed LVEF (<50%) or severe LV dilation (LVESD >50 mm or indexed LVESD >25 mm/m^2)	None; exercise testing is reasonable to confirm symptom status
D	**Symptomatic severe AR**	Calcific valve disease Bicuspid valve (or other congenital abnormality) Dilated aortic sinuses or ascending aorta Rheumatic valve changes Previous IE with abnormal leaflet closure or perforation	***Severe AR:*** Doppler jet width ≥65% of LVOT Vena contracta >0.6 cm Holodiastolic flow reversal in the proximal abdominal aorta RVol ≥60 mL/beat RF ≥50% ERO ≥0.3 cm^2 Angiography grade 3+ to 4+ In addition, diagnosis of chronic severe AR requires evidence of LV dilation.	Symptomatic severe AR may occur with normal systolic function (LVEF ≥50%), mild to moderate LV dysfunction (LVEF 40-50%), or severe LV dysfunction (LVEF <40%). Moderate to severe LV dilation is present.	Exertional dyspnea or angina, or more severe HF symptoms

ERO, Effective regurgitant orifice; *HF,* heart failure; *IE,* infective endocarditis; *LVEF,* left ventricular ejection fraction; *LVESD,* left ventricular end-systolic dimension; *LVOT,* left ventricular outflow tract; *RF,* regurgitant fraction; *RVol,* regurgitant volume.

From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACCF guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57.

Symptoms

In chronic severe AR, the left ventricle gradually enlarges while the patient remains asymptomatic.[134,135] Symptoms of reduced cardiac reserve or myocardial ischemia develop, most often in the fourth or fifth decade of life, and usually only after considerable cardiomegaly and myocardial dysfunction have occurred. The principal manifestations—exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea—usually develop gradually. Angina pectoris is prominent late in the course; nocturnal angina may be troublesome and often is accompanied by diaphoresis, which occurs when the heart rate slows and arterial diastolic pressure falls to extremely low levels. Patients with severe AR often complain of an uncomfortable awareness of the heartbeat, especially on lying down, and thoracic discomfort caused by pounding of the heart against the chest wall. Tachycardia, occurring with emotional stress or exertion, may cause palpitations and head pounding. Premature ventricular contractions (PVCs) are particularly distressing because of the great heave of the volume-loaded left ventricle during the postextrasystolic beat. These complaints may be present for many years before symptoms of overt LV dysfunction develop.

Physical Examination.

In patients with chronic, severe AR, the head may bob with each heartbeat (Musset sign), and water-hammer pulses, with abrupt distention and quick collapse (Corrigan pulse), are evident. The arterial pulse often is prominent and can be best appreciated by palpation of the radial artery with the patient's arm elevated (**see Chapters 11 and 67**). A bisferiens pulse may be present and is more readily recognized in the brachial and femoral arteries than in the carotid arteries. A variety of auscultatory findings provide confirmation of a wide pulse pressure. The Traube sign (also known as “pistol shot” sounds) refers to booming systolic and diastolic sounds heard over the femoral artery, the Müller sign consists of systolic pulsations of the uvula, and the Duroziez sign is a systolic murmur heard over the femoral artery when it is compressed proximally and a diastolic murmur when it is compressed distally. Capillary pulsations (Quincke sign) can be detected by transmitting a light through the patient's fingertips or exerting gentle pressure on the tip of a fingernail.

Systolic arterial pressure is elevated, and diastolic pressure is abnormally low. Korotkoff sounds often persist to zero even though the intra-arterial pressure rarely falls below 30 mm Hg. The point of change in Korotkoff sounds (i.e., the muffling of these sounds in phase IV) correlates with the diastolic pressure. As HF develops, peripheral vasoconstriction may occur and arterial diastolic pressure may rise, even though severe AR is present.

The apical impulse is diffuse and hyperdynamic and is displaced laterally and inferiorly. A rapid ventricular filling wave often is palpable at the apex. The augmented stroke volume may create a systolic thrill at the base of the heart or suprasternal notch and over the carotid arteries. In many patients, a carotid shudder is palpable.

Auscultation.

The diastolic murmur, the principal physical finding in AR, is of high frequency and begins immediately after A_2. It may be distinguished from the murmur of pulmonic regurgitation by its earlier onset (i.e., immediately after A_2 rather than after P_2) and usually by the presence of a widened pulse pressure. The murmur is heard best with the diaphragm of the stethoscope while the patient is sitting up and leaning forward, with the breath held in deep exhalation. In severe AR, the murmur reaches an early peak and then shows a dominant decrescendo pattern throughout diastole.

The severity of AR correlates better with the duration than with the intensity of the murmur. In mild AR, the murmur may be limited to early diastole and typically is high-pitched and blowing. In severe AR

the murmur is holodiastolic and may have a rough quality. When the murmur is musical ("cooing dove" murmur), it usually signifies eversion or perforation of an aortic cusp. In patients with severe AR and LV decompensation, equilibration of aortic and LV pressures in late diastole abolishes the late diastolic component of the regurgitant murmur. When AR is caused by primary valvular disease, the diastolic murmur is heard best along the left sternal border in the third and fourth intercostal spaces. However, when it is caused mainly by dilation of the ascending aorta, the murmur often is more readily audible along the right sternal border.

Many patients with chronic AR have a harsh systolic outflow murmur caused by the increased total LV stroke volume and ejection rate, which often radiates to the carotid vessels. The systolic murmur often is more readily audible than the diastolic murmur. It may be higher-pitched and less rasping than the murmur of AS but often is accompanied by a systolic thrill. Palpation of the carotid pulses will elucidate the cause of the systolic murmur and differentiate it from the murmur of AS.

A third heart sound (S_3) correlates with an increased LV end-diastolic volume. Its development may be a sign of impaired LV function, which is useful in identifying patients with severe AR who are candidates for surgical treatment. A mid-diastolic and late diastolic apical rumble, the *Austin Flint murmur*, is common in severe AR and may occur in the presence of a normal mitral valve. This murmur appears to be created by severe AR impinging on the anterior leaflet of the mitral valve or the free LV wall; convincing evidence for obstruction to mitral inflow in these patients is lacking.

Diagnostic Testing

Echocardiography

Echocardiography is helpful in identifying the cause of AR (**Fig. 68.15**) and may demonstrate a bicuspid valve, thickening of the valve cusps, other congenital abnormalities, prolapse of the valve, a flail leaflet, or vegetation (**see Chapter 14**). In addition to leaflet anatomy and motion, the size and shape of the aortic root can be evaluated, although visualization of the ascending aorta is not always adequate, necessitating additional imaging tests in some cases. Transthoracic echocardiography (TTE) usually is satisfactory, but transesophageal echocardiography (TEE) often provides more detail, particularly of the aortic root. TTE is useful for the measurement of LV end-diastolic and end-systolic dimensions and volumes, EF, and mass[59,134] (Videos 68.2A and 68.2B). Two-dimensional image–guided M-mode measurements of LV dimensions are recommended when possible, because the high temporal resolution of this modality allows more accurate identification of endocardial borders. Care is needed to ensure that measurements are not oblique and are at the same site on subsequent studies. When the M-line is oblique, two-dimensional measurements are made in conjunction with the calculation of biplane ventricular end-diastolic and end-systolic volumes. Recent studies have suggested that LV end-systolic volume is a strong predictor of adverse clinical outcomes.[135-138] These measurements, when made serially, are of great value in selecting the optimal time for surgical intervention.

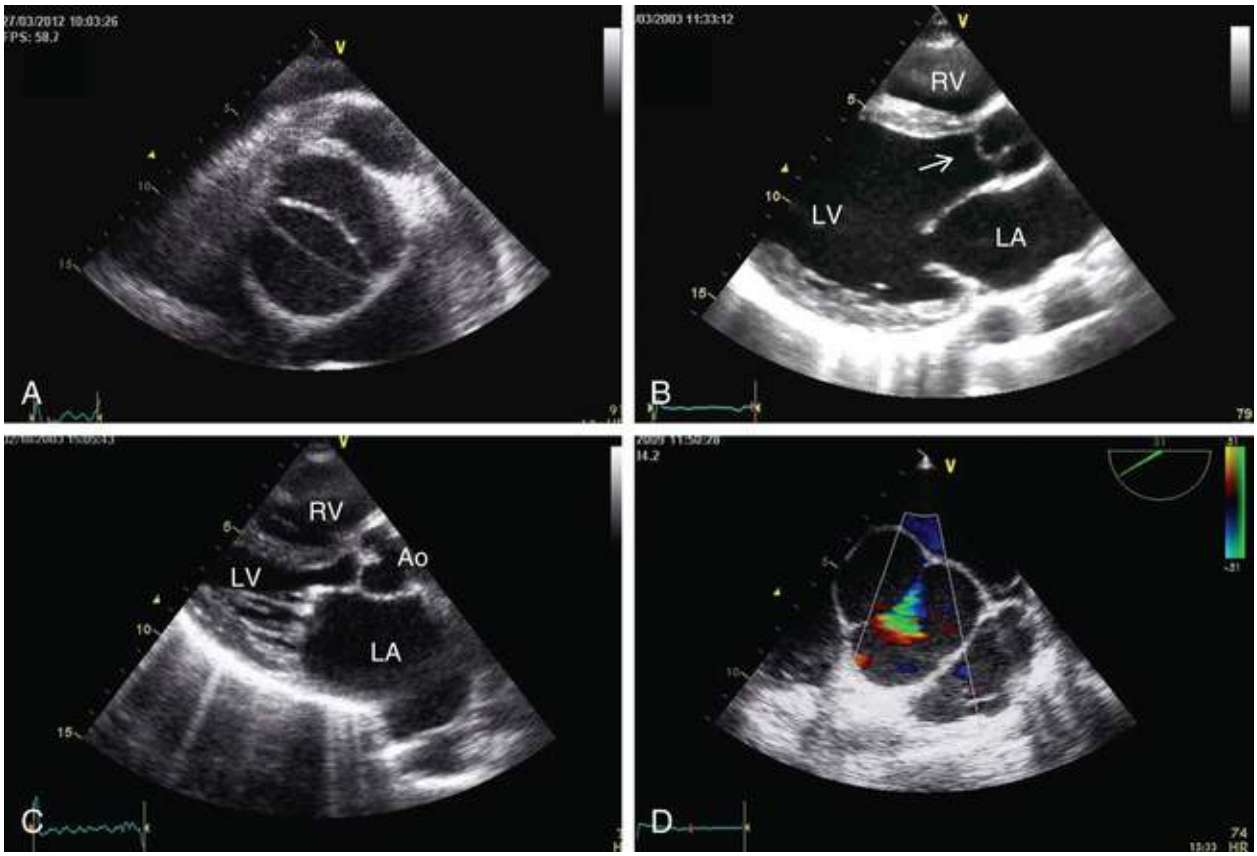


FIGURE 68.15 Role of echocardiography in etiologic investigation of aortic regurgitation. **A,** Transthoracic parasternal short-axis view showing a bicuspid aortic valve. **B,** Myxomatous aortic valve with a prolapse of the right coronary cusp (*arrow*). **C,** Rheumatic valvular disease with mitral and aortic involvement. **D,** Transesophageal image showing a central regurgitant orifice secondary to annuloaortic ectasia. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle. (From Tornos P, Evangelista A, Bonow RO. Aortic regurgitation. In Otto CM, Bonow RO, editors. Valvular Heart Disease: A Companion to Braunwald's Heart Disease. 4th ed. Philadelphia: Saunders; 2013, pp 163-78.)

High-frequency fluttering of the anterior leaflet of the mitral valve during diastole may be seen in acute and chronic AR. However, it does not develop when the mitral valve is rigid, as occurs with rheumatic involvement. This sign, unlike the Austin Flint murmur, is present even in mild AR and results from the movement imparted to the anterior leaflet of the mitral valve by the jet of blood regurgitating from the aorta.

Doppler echocardiography and color flow Doppler imaging are the most sensitive and accurate noninvasive techniques for the diagnosis and evaluation of AR. They readily detect mild degrees of AR that may be inaudible on physical examination. Both aortic regurgitant orifice size and aortic regurgitant flow can be estimated quantitatively[59,139] (**see Fig. 14.50** and Video 68.3A and 68.3B), and such determinations are strongly recommended.[19,140] These quantitative data provide the basis for the definitions of mild, moderate, and severe AR (**see Table 68.5** and Videos 68.4, 68.5A and 68.5B, and 68.6A and 68.6B). Serial studies permit determination of the progression of AR and its effect on the left ventricle.

Cardiac Magnetic Resonance Imaging.

CMR provides accurate measurements of regurgitant volumes and the regurgitant orifice in AR (**Fig. 68.16**). It is the most accurate noninvasive technique for assessing LV end-systolic volume, diastolic volume, and mass (**see Chapter 17**). CMR accurately quantifies the severity of AR on the basis of the antegrade and retrograde flow volumes in the ascending aorta and is recommended when

echocardiographic evaluation of regurgitation is suboptimal.[73,141-143]

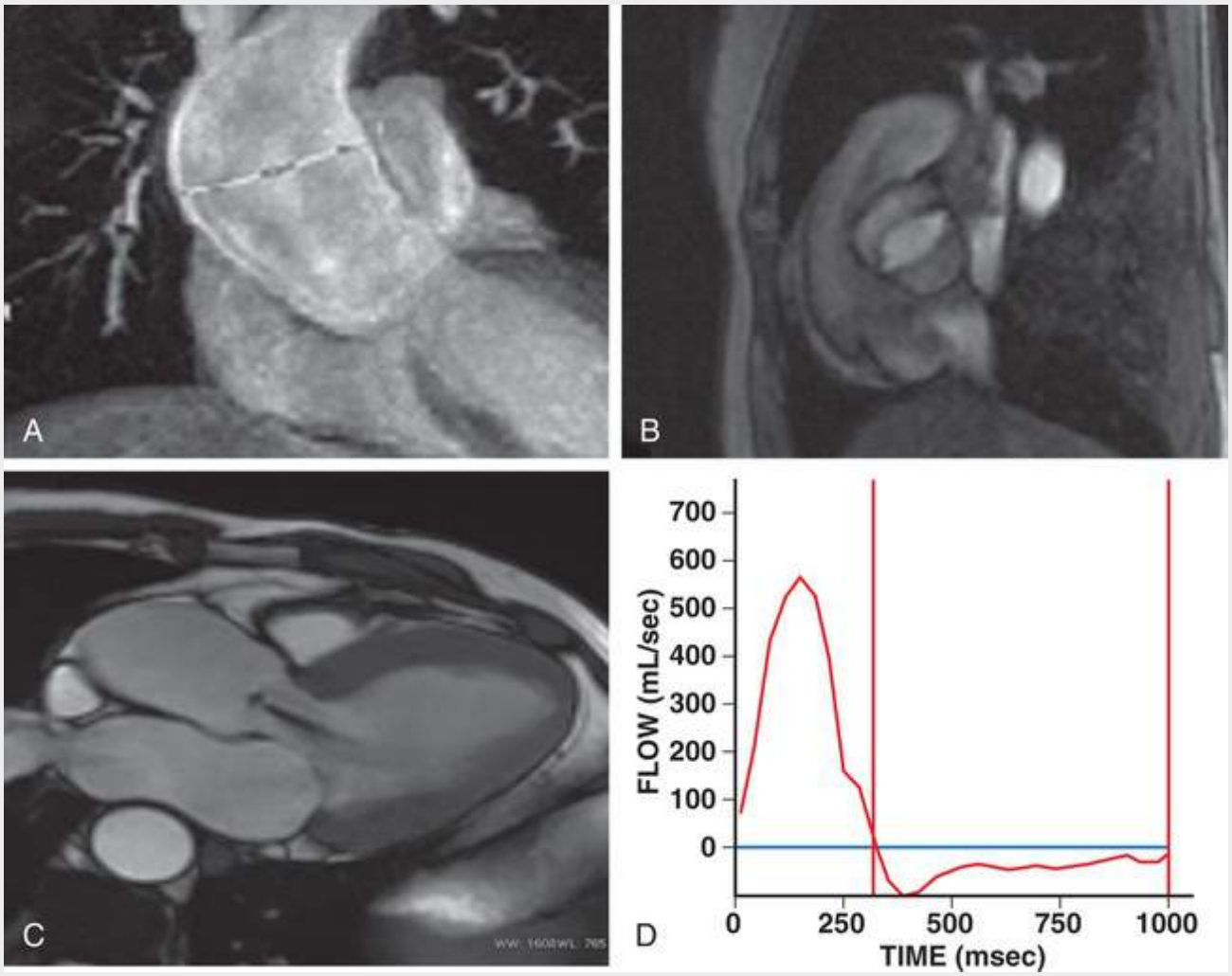


FIGURE 68.16 Cardiac magnetic resonance images showing a bicuspid aortic valve with aortic regurgitation and ascending aorta dilation. **A,** Fast single-shot steady-state free precession (SSFP) image in a coronal view. **B,** Retrospectively reconstructed magnitude image from a phase-contrast sequence showing a bicuspid aortic valve. **C,** Balanced SSFP image. Oblique axial left ventricle inflow-outflow view, showing grade 2 AR. **D,** Flow-versus-time plot for the ascending aorta. Antegrade flow was calculated at 140 mL/beat, retrograde flow at 40 mL/beat, and aortic regurgitant fraction of 33%. (From Tornos P, Evangelista A, Bonow RO. Aortic regurgitation. In Otto CM, Bonow RO, editors. Valvular Heart Disease: A Companion to Braunwald's Heart Disease. 4th ed. Philadelphia: Saunders; 2013, pp 163-78.)

Angiography.

For angiographic assessment of AR, contrast material should be injected rapidly (i.e., at 25 to 35 mL/sec) into the aortic root, and filming should be carried out in the right and left anterior oblique projections (**see Chapter 19**). Opacification may be improved by filming during a Valsalva maneuver.

Disease Course

Asymptomatic Patients with Chronic Aortic Regurgitation

Patients with mild or moderate AR who are asymptomatic with normal or only minimally increased cardiac size require no therapy but should be followed clinically and by echocardiography every 12 or 24 months. Asymptomatic patients with chronic severe AR and normal LV function should be examined at intervals of approximately 6 months. In addition to clinical examination, serial echocardiographic

assessments of LV size and EF should be made. CMR usually is not necessary but may be useful in patients whose noninvasive test results are inconclusive or discordant with clinical findings or when further evaluation of aortic size is needed (**Fig. 68.16**). Patients with mild to moderate AR and those with severe AR with a normal LVEF and only mild ventricular dilation may engage in aerobic forms of exercise. However, patients with AR who have limitations of cardiac reserve and evidence of declining LV function should not engage in competitive sports or strenuous activities.[144]

Moderately severe or even severe chronic AR often is associated with a generally favorable prognosis for many years. Quantitative measures of AR severity predict clinical outcome, and LV size and systolic function also are strong predictors of clinical outcome. In a study of 251 asymptomatic patients (mean age, 61 years), the 10-year survival was 94% ±4% in those with mild AR, compared with 69% ±9% in those with severe AR (**Fig. 68.17**).[137] By contrast, in series involving younger asymptomatic patients (mean age, 39 years) with severe AR and a normal LVEF, the mortality rate was less than 1% per year,[19,135] and more than 45% of the patients remained asymptomatic with normal LV function at 10 years. The average rate of developing symptoms or LV systolic dysfunction in these latter series was less than 6% per year (**Fig. 68.18**; **see eTable 68.2**).

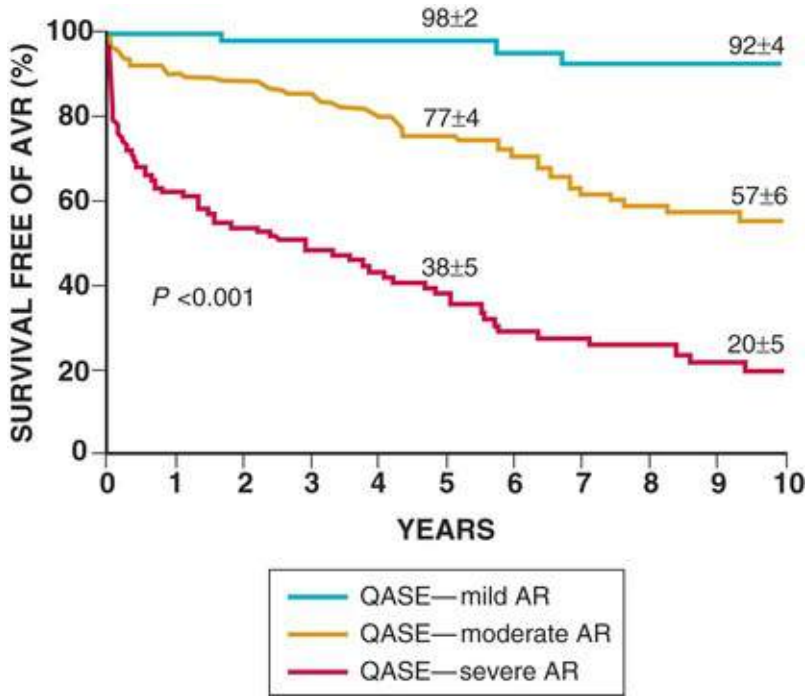


FIGURE 68.17 Composite endpoint of survival free of surgery for aortic regurgitation after diagnosis in asymptomatic patients; AVR, aortic valve replacement. Patients are stratified according to quantitative criteria of the American Society of Echocardiography (QASE) for AR grading. The QASE–severe AR is defined as regurgitant volume (RV) greater than 60 mL/beat or effective regurgitant orifice (ERO) greater than 30 mm^2. The QASE–mild AR is defined as RV less than 30 mL/beat and ERO less than 10 mm^2, and QASE–moderate AR as greater than mild but not reaching QASE–severe criteria. The 5- and 10-year rates of the endpoint (± standard error) are indicated. Note the wide difference in outcomes according to QASE grading at baseline. (From Detaint D, Messika-Zeitoun D, Maalouf J, et al. Quantitative echocardiographic determinants of clinical outcome in asymptomatic patients with aortic regurgitation: a prospective study. J Am Coll Cardiol Imaging 2008;1:1.)

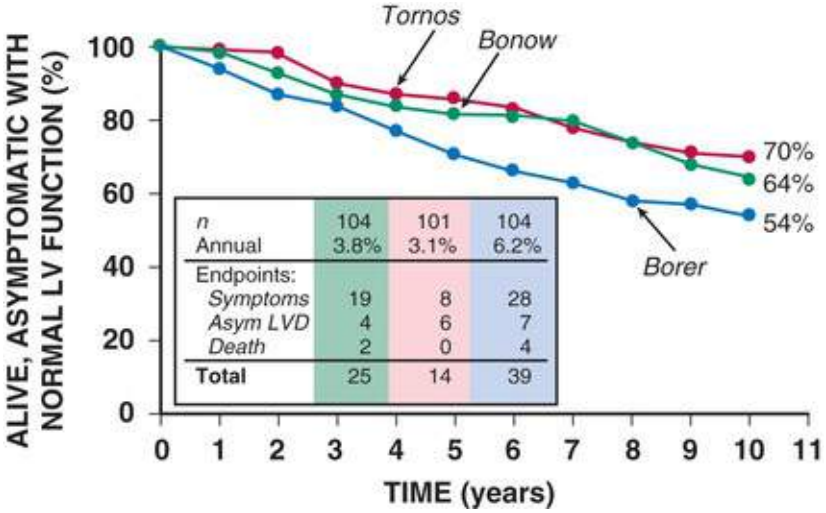


FIGURE 68.18 Three series examining the natural history of chronic asymptomatic aortic regurgitation in patients with normal LV ejection fraction at rest, each comprising more than 100 patients. At 10 years, 54% to 70% of patients remained asymptomatic with normal left ventricular (LV) function, such that the risk of developing symptoms, LV dysfunction (LVD), or death is approximately 3% to 6% per year. The endpoints encountered in these series are indicated. Most patients who deteriorated developed symptoms leading to aortic valve replacement. However, 25% to 30% of the endpoints, either asymptomatic LVD (Asym LVD) or death, occurred without warning symptoms. (From Bonow RO. Chronic mitral regurgitation and aortic regurgitation: have indications for surgery changed? J Am Coll Cardiol 2013;61:693. Data modified from Bonow RO et al. Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. Circulation 1991;84:1625; Tornos MP et al. Clinical outcome of severe asymptomatic chronic aortic regurgitation: a long term prospective follow up study. Am Heart J 1995;130:333; and Borer JS et al. Prediction of indications for valve replacement among asymptomatic and minimally symptomatic patients with chronic aortic regurgitation and normal left ventricular performance. Circulation 1998;97:525.)

ETABLE 68.2

Studies of the Natural History of Asymptomatic Aortic Regurgitation (AR)

Study	PROGRESSION TO SYMPTOMS, DEATH, OR LV DYSFUNCTION			PROGRESSION TO ASYMPTOMATIC LV DYSFUNCTION			Comments
	Patients (*n*)	Mean Follow-up (yr)	Rate/yr (%)	Patients (*n*)	Rate/yr (%)	Mortality: (Patients, *n*)	
Bonow et al, 1983, 1991	104	8.0	3.8	4	0.5	(2)	Outcome predicted by LV ESD, EDD, change in EF with exercise, rate of change in ESD, and EF at rest with time.
Scognamiglio et al, 1986	30	4.7	2.1	3	2.1	0	Three patients developing asymptomatic LV dysfunction initially had lower PAP/ESV ratios and a trend toward higher LV ESD and EDD and lower FS.
Siemienczuk et al, 1989	50	3.7	4.0	1	0.5	0	Patients included those receiving placebo and medical dropouts in a randomized drug trial; included some patients with NYHA FC II symptoms; outcome predicted by LV ESV, EDV, change in EF with exercise, and end-systolic wall stress.
Scognamiglio et al, 1994	74	6.0	5.7	15	3.4	0	All patients received digoxin as part of a randomized trial.
Tornos et al, 1995	101	4.6	3.0	6	1.3	0	Outcome predicted by pulse pressure, LV ESD, EDD, and EF at rest.
Ishii et al, 1996	27	14.2	3.6	—	—	0	Development of symptoms predicted by systolic BP, LV ESD, EDD, mass index, and wall thickness; LV function not reported in all patients.
Borer et al, 1998	104	7.3	6.2	7	0.9	(4)	20% of patients in NYHA FC II; outcome predicted by initial FC II symptoms, change in LV EF with exercise, LV ESD, and LV FS.
Tarasoutchi et al, 2003	72	10	4.7	1	0.1	0	Development of symptoms predicted by LV ESD and EDD; LV function not reported in all patients.
Evangelista et al, 2005	31	7	3.6	—	—	(1)	Placebo control group in 7-year vasodilator clinical trial.
Detaint et al, 2008	251	8.0	5.0	17	2.1	(33)	10-year actuarial survival free of AVR: 92% ±4% with mild AR (RVol <30 mL and ERO <0.1 cm^2) 57% ±5% with moderate AR 20% ±5% with severe AR (RVol ≥60 mL and ERO ≥0.3 cm^2)
Pizzaro et al, 2011	294	3.5	10%	—	2.8%	1.7%	Adverse outcomes associated with BNP >130 pg/mL, RVol, EROA, and ESD, EDD, ESV, and EDV indices.
Olsen et al, 2011	35	1.6	14.3%	—	—	0%	Disease progression associated with reduced myocardial systolic strain, systolic strain rate, and early diastolic strain rate.

BNP, B-type (brain) natriuretic peptide level; *BP,* blood pressure; *EDD,* end-diastolic dimension; *EDV,* end-diastolic volume; *EF,* ejection fraction; *ESD,* end-systolic dimension; *ERO,* effective regurgitant orifice; *ESV,* end-systolic volume; *FC,* Functional Class; *FS,* fractional shortening; *LV,* left ventricular; *NYHA,* New York Heart Association; *PAP,* pulmonary artery pressure; *RVol,* regurgitant volume.

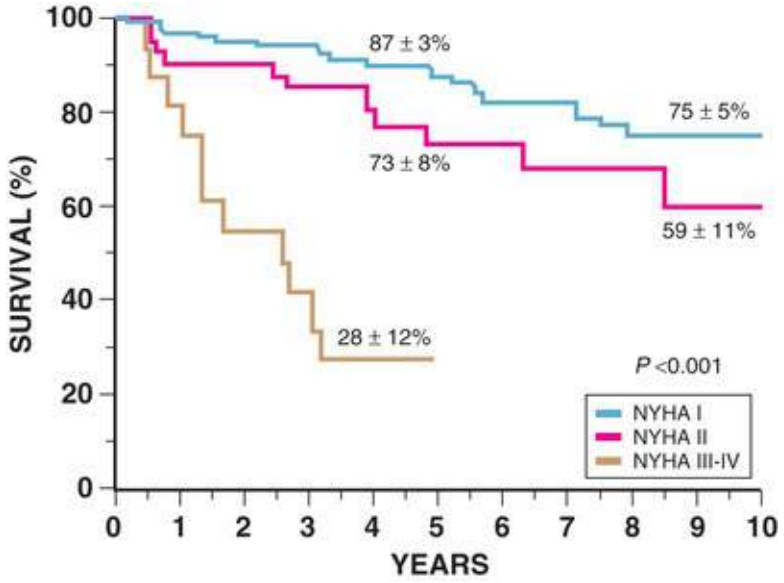
Data from Bonow RO et al. The natural history of asymptomatic patients with aortic regurgitation and normal left ventricular function. Circulation 1983;68:509; Bonow RO et al. Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. Circulation 1991;84:1625; Scognamiglio R et al. Progression of myocardial dysfunction in asymptomatic patients with severe aortic insufficiency. Clin Cardiol 1986;9:151; Siemienczuk D et al. Chronic aortic insufficiency: factors associated with progression to aortic valve replacement. Ann Intern Med 1989;110:587; Scognamiglio R et al. Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function. N Engl J Med 1994;331:689; Tornos MP et al. Clinical outcome of severe asymptomatic chronic aortic regurgitation: a long-term prospective follow-up study. Am Heart J 1995;130:333; Ishii K et al. Natural history and left ventricular response in chronic aortic regurgitation. Am J Cardiol 1996;78:357; Borer JS et al. Prediction of indications for valve replacement among asymptomatic or minimally symptomatic patients with chronic aortic regurgitation and normal left ventricular performance. Circulation 1998;97:525; Tarasoutchi F et al. Ten-year clinical laboratory follow-up after application of a symptom-based therapeutic strategy to patients with severe chronic aortic regurgitation of predominant rheumatic etiology. J Am Coll Cardiol 2003;41:1316; Evangelista A et al. Long-term vasodilator therapy in patients with severe aortic regurgitation. N Engl J Med 2005;353:1342; Detaint D et al. Quantitative echocardiographic determinants of clinical outcome in asymptomatic patients with aortic regurgitation: a prospective study. J Am Coll Cardiol Imaging 2008;1:1; Pizzaro R et al. Prospective validation of the prognostic usefulness of B-type natriuretic peptide in asymptomatic patients with chronic aortic regurgitation. J Am Coll Cardiol 2011;58:1705; Olsen NT et al. Speckle tracking echocardiography for predicting outcome in chronic aortic regurgitation during conservative management and after surgery. J Am Coll Cardiol Imaging 2011;4:223.

Gradual deterioration of LV function may occur even during the asymptomatic period, and some patients may incur significant impairment of systolic function before the onset of symptoms (**see Table 68.5**). Numerous surgical series over the past two decades have indicated that depressed LVEF is among the most important determinants of mortality after AVR, particularly since LV dysfunction may become

irreversible and may not improve after AVR.[19,69,135] LV dysfunction is more likely to be reversible if detected early, before EF becomes severely depressed, before the left ventricle becomes markedly dilated, and before significant symptoms develop. It is therefore important to intervene surgically before these changes have become irreversible.[134] Measures of LV systolic volume and systolic function are the most important predictors of clinical course in asymptomatic patients[135-137] (**see eTable 68.2**). Biomarkers such as BNP[145] and assessment of myocardial strain[146] also may play a role in the future in identifying high-risk patients, based on small series published to date, but more work is necessary before these additional measures are recommended for routine management.

Symptomatic Patients with Chronic Aortic Regurgitation

As with AS, however, once the patient with AR becomes symptomatic, the downhill course becomes rapidly progressive. Congestive heart failure, punctuated by episodes of acute pulmonary edema, and sudden death may occur, usually in previously symptomatic patients who have considerable LV dilation. Data compiled in the presurgical era indicate that without surgical treatment, death usually occurred within 4 years after the development of angina pectoris and within 2 years after the onset of HF. Even in the current era, 4-year survival without surgery in patients with NYHA Class III or IV symptoms is only approximately 30% (**see eFig. 68.1**).



EFIGURE 68.1 Survival without surgery in 242 patients with chronic aortic regurgitation, demonstrating the importance of symptoms in determining outcome. Patients with New York Heart Association (NYHA) Class III or IV symptoms had a survival of only 28% at 4 years. By contrast, the 10-year survival in patients in NYHA Class I was 75%, which was identical to that for an age-matched normal population. (From Dujardin KS, Enriquez-Sarano M, Schaff HV, et al. Mortality and morbidity of aortic regurgitation in clinical practice: a long-term follow-up study. Circulation 1999;99:1851.)

Treatment of Chronic Aortic Regurgitation

Medical Therapy

No specific therapy to prevent disease progression in chronic AR is currently available. Uncertainty remains about whether patients with chronic AR and evidence of significant volume overload (increased end-diastolic dimension or volume) should be considered for vasodilator therapy to alter the natural

history of chronic LV volume overload.[147] Short-term studies spanning 6 months to 2 years have demonstrated beneficial hemodynamic effects of oral hydralazine, nifedipine, felodipine, and ACE inhibitors. However, prospective RCTs have not shown consistent clinical benefit in terms of LV function or delay in need for AVR. In view of this equipoise, definitive recommendations regarding the indications for long-active nifedipine or ACE inhibitors are not possible.[134]

It is conceivable that blockade of the renin-angiotensin system may provide additional myocardial benefits beyond peripheral vasodilation by direct mechanisms to reduce interstitial fibrosis and remodeling. Such promising effects have been demonstrated in animal models[148] but are yet to be tested in prospective RCTs. A retrospective Scottish registry study of 2266 patients with at least moderate AR reported a 44% reduction in all-cause mortality (HR, 0.56; 95% CI 0.64 to 0.89; $P < 0.01$) over a mean 4.4-year period in the 876 patients taking ACE inhibitors or ARBs compared with the 1390 patients who did not receive these drugs.[149] Patients taking ACE inhibitors/ARBs were younger, however, with significantly greater use of other drugs (including aspirin, statins, beta blockers, and calcium channel blockers) that might affect outcome, because most events were considered cardiovascular and not directly related to AR. Nevertheless, ACE inhibitor/ARB therapy was associated with a 32% reduction in AR events (AVR, HF hospitalization, HF death) ($P < 0.01$). Another retrospective study reported beneficial effects of beta-blocker therapy on survival in patients with AR.[150] However, patients receiving beta blockers were younger than those not taking beta blockers and also more frequently had concomitant therapy with ACE inhibitors, statins, aspirin, and calcium channel blockers that might have influenced outcome. More than two thirds of patients in this study had HF and 25% had AF, so extrapolation to asymptomatic patients is difficult. Moreover, interpretation of the survival results is complicated by greater intervention with AVR and CABG in those taking beta blockers. Thus, these studies are not definitive and indicate the need for prospectively designed RCTs before ACE inhibitor or beta-blocker therapy can be considered in asymptomatic patients with chronic AR.

Although there is no specific therapy to improve clinical outcomes in patients with chronic AR, it is recommended to treat hypertension (systolic BP >140 mm Hg), CAD, atrial arrhythmias, and any other cardiovascular comorbidities according to established guidelines. For symptomatic patients, chronic medical therapy may be necessary for some patients who refuse surgery or who are considered to be inoperable because of comorbid conditions. These patients should receive an aggressive HF regimen (**see Chapter 25**) with ACE inhibitors (and perhaps other vasodilators), diuretics, and salt restriction; beta blockers may also be beneficial.[150] Even though nitroglycerin and other nitrates are not as helpful in relieving anginal pain in patients with AR as in patients with CAD or AS, these are reasonable therapies to try. In patients who are surgical candidates but who have severely decompensated LV dysfunction, vasodilator therapy may be particularly helpful to stabilize them before AVR.

Surgical Aortic Valve Replacement

Indications for Valve Replacement

Fig. 68.19 shows a proposed management strategy for patients with chronic severe AR.[19] Because of their excellent prognosis in the short and medium term, surgical correction should be deferred in patients with chronic severe AR who are asymptomatic, exhibit good exercise tolerance, and have an EF greater than 50% without severe LV dilation (i.e., end-systolic diameter ≤50 mm) or progressive LV dilation on serial echocardiograms. In the absence of obvious contraindications or serious comorbidity, surgical treatment is advisable for symptomatic patients with severe AR and for asymptomatic patients either with EF of

50% or less or with severe LV dilation (end-systolic diameter >50 mm or 25 mm/m^2 when indexed to body size).[19,69] Between these ends of the clinical-hemodynamic spectrum are many patients in whom it may be difficult to balance the immediate risks of AVR and the continuing risks of an implanted prosthetic valve against the hazards of allowing a severe volume overload to damage the left ventricle.[134,135]

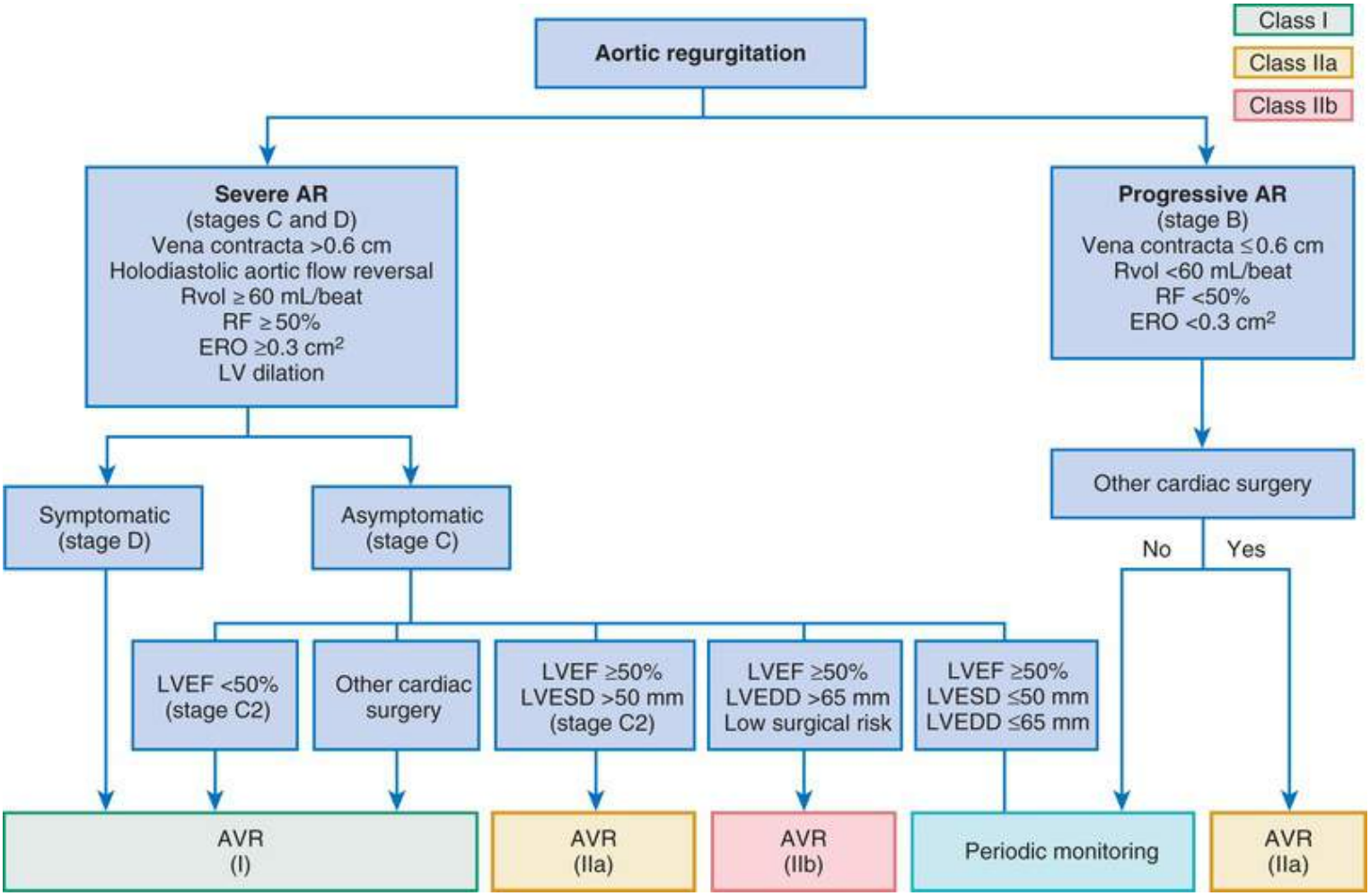


FIGURE 68.19 Management strategy for patients with chronic severe aortic regurgitation. AVR, Aortic valve replacement (valve repair may be appropriate in selected patients); ERO, effective regurgitant orifice; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; RF, regurgitant fraction; RVol, regurgitant volume. (From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACCF guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57.)

Because severe symptoms (NYHA Class III or IV) and LV dysfunction with an EF less than 50% are independent risk factors for poor postoperative survival (**Fig. 68.20**), surgery should be carried out in patients with even mild symptoms (NYHA Class II) before severe LV dysfunction has developed.[19,70,134,135] Even after successful correction of AR, patients with severe LV dysfunction may have persistent cardiomegaly and depressed LV function. Such patients often exhibit persistent histologic changes in the left ventricle, including massive fiber hypertrophy and increased interstitial fibrous tissue. Therefore, surgery is highly desirable for patients before irreversible LV changes have occurred.

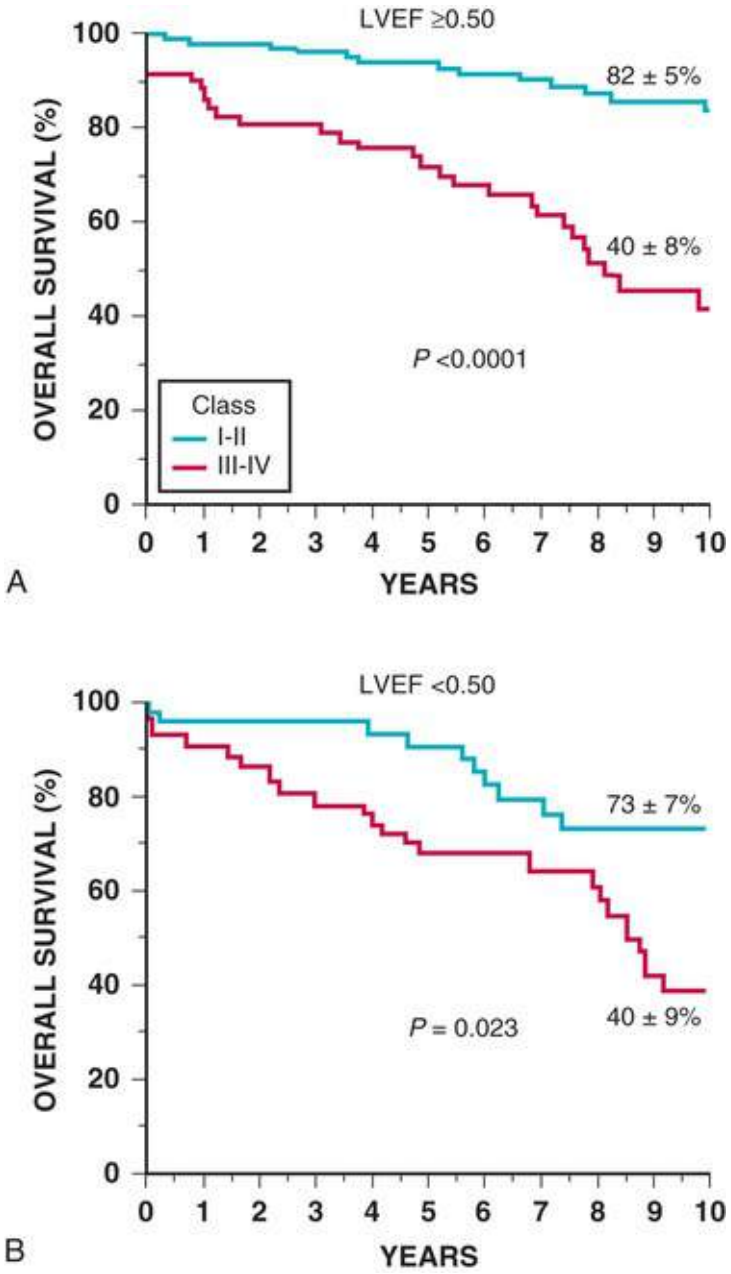


FIGURE 68.20 Long-term postoperative survival in patients with aortic regurgitation, stratified according to the severity of preoperative symptoms and preoperative left ventricular ejection fraction (LVEF). Patients with NYHA Class III or IV symptoms experienced significantly worse survival than those with Class I or II symptoms, whether the echocardiographic LVEF was higher than 0.50 **(A)** or less than 0.50 **(B),** without associated coronary artery disease. (From Klodas E, Enriquez-Sarano M, Tajik AJ, et al. Optimizing timing of surgical correction in patients with severe aortic regurgitation: role of symptoms. J Am Coll Cardiol 1997;30:746.)

Because AR has complex effects on preload and afterload, the selection of appropriate indices of ventricular contractility to identify patients for operation is challenging. The relationship between end-systolic wall stress and LVEF or percentage of fractional shortening is a useful measurement,[56] as are more load-independent measures of LV contractility. However, in the absence of such complex measurements, serial changes in LV end-diastolic and end-systolic volumes or dimensions can be used to detect the relative deterioration of LV function.[134] Although strongly influenced by loading conditions, LV end-diastolic and end-systolic volumes and ejection phase indices (e.g., EF, fraction shortening) are still useful empiric predictors of postoperative function.

Serial echocardiograms should be obtained to detect changes in LV size and function in asymptomatic patients with severe AR (**see Fig. 68.19**). Impaired LV function at rest is the basis for selecting patients for operation; normal LV function at rest with failure of the EF to rise normally with exercise is not considered an indication for surgery, but it is an early warning sign of impaired function at rest.

Echocardiographic measurements of LV size also are important, with M-mode LV end-diastolic and end-systolic dimensions, when possible, and with biplane apical calculations of the end-systolic volume index. Echocardiographic measurements should be made with side-by-side comparison of previous serial studies. A consistent change in dimensions or volumes, greater than measurement variability, must be ensured before recommending AVR for asymptomatic patients on the basis of these numbers alone.

Asymptomatic patients with severe AR but normal LV function have an excellent prognosis and do not require prophylactic operation (**see eTable 68.2**). On average, less than 6% of patients each year require surgery because of the development of symptoms or of LV dysfunction (**see Fig. 68.18**), although the rate of symptom development is higher in patients older than 60 years.[137] The LV end-systolic dimension determined by echocardiography is valuable in predicting outcome in asymptomatic patients. Patients with severe AR and an end-systolic diameter less than 40 mm almost invariably remain stable and can be followed without need for surgery in the near term. However, patients with an end-systolic diameter of more than 50 mm have a 19% likelihood per year of developing symptoms of LV dysfunction, and those with an end-systolic diameter more than 55 mm are at increased risk for development of irreversible LV dysfunction if they do not undergo AVR. Postoperative function and survival in this latter group are determined by the severity of symptoms and degree and duration of LV dysfunction.[134,135] Indexed end-systolic dimension (ESDI) or volume (ESVI) may be a more robust indicator for timing of surgical intervention.[136,137] Patients with an ESDI of 2.5 cm/m^2 or ESVI of 45 mL/m^2 or greater are at higher risk for adverse outcomes.[19,137] Further data on the use of EDVI and ESVI are needed before this approach becomes standard. Recent findings suggest that lower thresholds of EDVI should be considered to optimize long-term survival after AVR.[138]

In summary, the following considerations apply to the selection of patients with chronic AR for surgical treatment.[19,69] Operation should be deferred in asymptomatic patients with normal and stable LV function and should be recommended for symptomatic patients (**see Fig. 68.19**). In asymptomatic patients with LV dilation or dysfunction, a decision should be based not on a single abnormal measurement but rather on several observations of depressed performance and impaired exercise tolerance, carried out at intervals of 2 to 4 months. If evidence of LV dysfunction is borderline or inconsistent, continued close follow-up is indicated. If abnormalities are progressive and consistent (i.e., LVEF <50% or LV end-systolic diameter rises to >50 mm), AVR should be strongly considered, even in asymptomatic patients. Symptomatic patients with severe AR who have normal, mildly depressed, or moderately depressed LV function should undergo AVR. Even patients with severely depressed LV function have acceptable operative and long-term survival.[151] Ventricular assist device or transplant may also be considered as an alternative, particularly in those with longstanding severe LV dysfunction, but medical therapy is associated with a dismal prognosis.

The indications for AVR for patients with severe AR secondary to aortic sinus or ascending aortic disease are similar to those for patients with primary valvular disease. In addition, concomitant surgery to repair the aortic sinuses or replace the ascending aorta is indicated if the amount of aortic dilation is greater than 45 mm.[19,152] As for patients with other valvular lesions, adult surgical candidates who may have underlying CAD, based on symptoms, age, sex, and risk factors, should undergo preoperative coronary angiography. Those with significant coronary artery stenoses should undergo revascularization at the time of AVR.

Operative Procedures

The standard surgical approach for chronic AR is AVR. Concurrent aortic root replacement is performed when aortic dilation is the cause of or accompanies valve dysfunction. However, experience is

accumulating with surgical aortic valve repair, which is a viable option for select patients in experienced centers.[153-156] Occasionally, when a leaflet has been torn from its attachments to the aortic annulus by trauma, surgical repair may be possible, and in patients with AR secondary to prolapse of an aortic leaflet, aortic cusp resuspension or cusp resection may be used. When AR is caused by leaflet perforation resulting from healed infective endocarditis, a pericardial patch can be used for repair. However, unlike patients with chronic MR, the large majority of patients with pure AR will require AVR rather than repair. Transcatheter AVR for AR is under investigation but is not an established approach.[157,158]

Because an increasing proportion of patients with severe isolated AR coming to operation now have primary aortic root rather than primary valvular disease, an increasing number can be treated surgically by correcting the dilated aortic root.[155,156] Aneurysmal dilation of the ascending aorta requires excision, replacement with a graft that includes a prosthetic valve, and reimplantation of the coronary arteries. In some patients with aortic root disease, the native valve can be spared when the aortic root is replaced or repaired (**Fig. 68.21**).

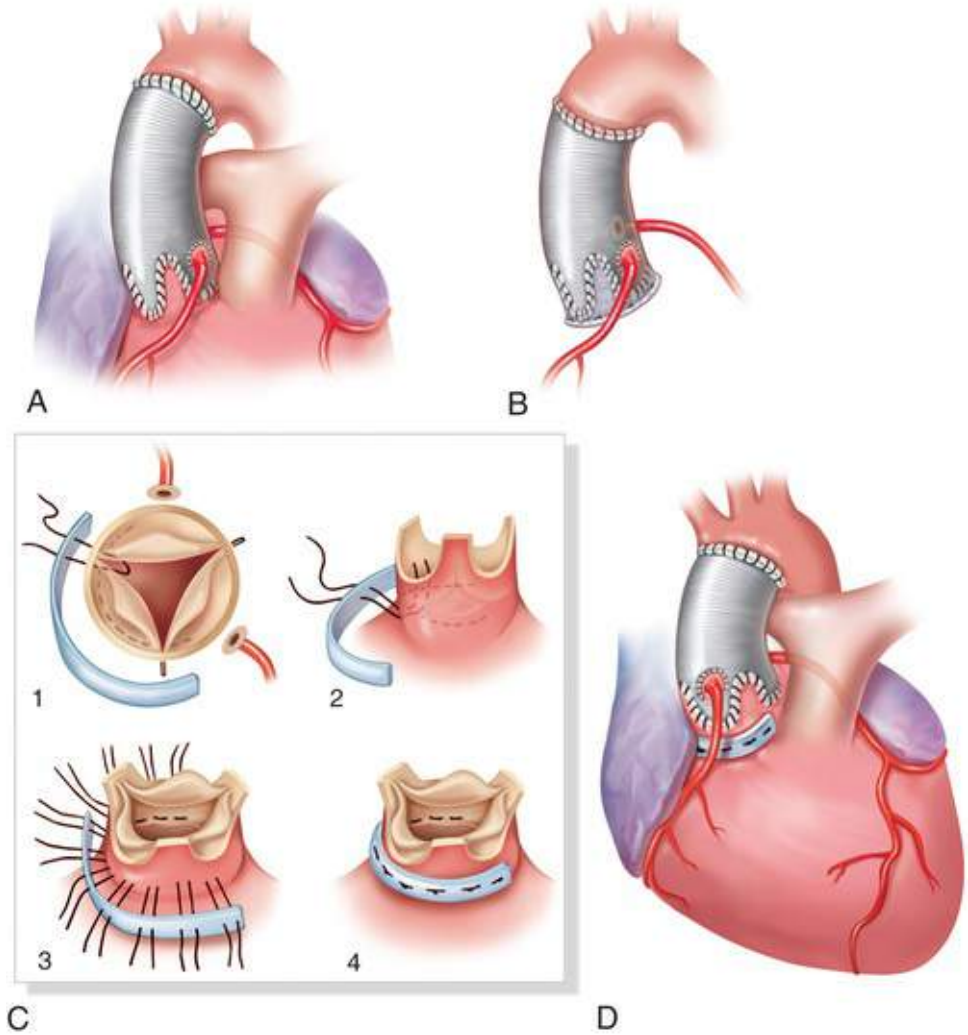


FIGURE 68.21 Repair of aortic regurgitation caused by aortic root dilation. **A,** Remodeling of the aortic root with replacement of all three aortic sinuses. **B,** Reimplantation of the aortic valve in patients with annuloaortic ectasia and aortic root aneurysm. **C, D,** Aortic annuloplasty in patients with annuloaortic ectasia. (From David TE. Aortic root aneurysms: remodeling or composite replacement? Ann Thorac Surg 1997;64:1564.)

When AVR is performed in patients with severe AR, the aortic annulus often is larger than in patients with AS. Thus a larger prosthetic valve can be inserted, and mild postoperative obstruction to LV outflow is less of a problem than it is in some patients with AS. In general, the associated risks and results of AVR

in patients with AR are similar to those in patients with AS, with a large proportion of patients exhibiting striking relief of symptoms. Substantial reductions in heart size and in LV diastolic volume and mass occur in most patients. Exceptions are seen in patients with NYHA Class III or IV HF and patients with severe LV dysfunction preoperatively. As for patients with AS, the operative risk of AVR for patients with AR depends on the general condition of the patient, the state of LV function, and the skill and experience of the surgical team. Mortality ranges from 3% to 8% in most medical centers. A late mortality of approximately 5% to 10%/year is observed in survivors who had marked cardiac enlargement and/or prolonged LV dysfunction preoperatively. Follow-up studies have shown both early rapid and then slower, long-term reductions in LV mass, EF, myocyte hypertrophy, and ventricular fibrosis content after surgical relief of AR. By extending the indications for operation to symptomatic patients with normal LV function, as well as to asymptomatic patients with LV dysfunction, early and late results are improving. With the continued improvement of surgical techniques and results, it probably will become possible to extend the surgical recommendation to asymptomatic patients with severe AR, normal LV systolic function, and only mild LV dilation. However, in view of the risks of operation and the long-term complications of currently available prosthetic valves, we do not believe that the time for such a policy has yet arrived.

Acute Aortic Regurgitation

Pathophysiology and Clinical Presentation.

Acute AR is caused most often by infective endocarditis, aortic dissection, or trauma[159] (**see Chapters 63 and 73**). The characteristic features of acute AR are tachycardia and an increase in LV diastolic pressure. In contrast with the pathophysiologic events in chronic AR just described, in which the left ventricle can adapt over time to the increased hemodynamic load, in acute AR the regurgitant volume fills a ventricle of normal size that cannot accommodate the combined large regurgitant volume and inflow from the left atrium. Because the ability of total stroke volume to rise acutely is limited, forward stroke volume declines. The sudden increase in LV filling causes the LV diastolic pressure to rise rapidly above left atrial pressure during early diastole (**see Fig. 68.14**), causing the mitral valve to close prematurely in diastole. The tachycardia may compensate for the reduced forward stroke volume, and the LV and aortic systolic pressures may exhibit little change. However, acute severe AR may cause profound hypotension and cardiogenic shock. In light of the limited ability of the left ventricle to tolerate acute severe AR, patients with this valvular lesion often develop clinical manifestations of sudden cardiovascular collapse, including weakness, severe dyspnea, and profound hypotension secondary to the reduced stroke volume and elevated left atrial pressure. In some patients, the aortic diastolic pressure equilibrates with the elevated LV diastolic pressure.

Physical Examination.

Patients with acute severe AR characteristically appear gravely ill, with tachycardia, severe peripheral vasoconstriction, cyanosis, and sometimes pulmonary congestion and edema. Depending on the etiology of the acute AR, signs suggestive of endocarditis or aortic dissection may be present. The peripheral signs of AR are often not impressive and certainly not as dramatic as in patients with chronic AR. The normal or only slightly widened pulse pressure may lead to significant underestimation of the severity of the valvular lesion. The LV impulse is normal or almost normal, and the rocking motion of the chest characteristic of chronic AR is not apparent. S_1 may be soft or absent because of premature closure of the mitral valve, and the sound of mitral valve closure in mid- or late diastole occasionally is audible.

Closure of the mitral valve may be incomplete, however, and diastolic MR may occur.

The early diastolic murmur of acute AR is lower-pitched and of shorter duration compared with that of chronic AR, because as LV diastolic pressure rises, the (reverse) pressure gradient between the aorta and left ventricle is rapidly reduced. A systolic murmur is common, resulting in to-and-fro sounds. The Austin Flint murmur often is present but is of brief duration and ceases when LV pressure exceeds left atrial pressure in diastole. With premature diastolic closure of the mitral valve, the presystolic portion of the Austin Flint murmur is eliminated.

Echocardiography.

In acute AR, the echocardiogram reveals a dense, diastolic Doppler signal with an end-diastolic velocity approaching zero and premature closure and delayed opening of the mitral valve. Diastolic MR may be seen. LV size and EF are usually normal, although contractility may be enhanced and EF increased because of the compensatory adrenergic surge. These findings contrast with those in chronic AR, in which end-diastolic dimensions and wall motion are increased. Occasionally, with equilibration of aortic and LV pressures in diastole, premature opening of the aortic valve may be detected. TEE is often useful to clarify the underlying reason for the acute regurgitation, particularly to identify an ascending aortic dissection or endocarditis.

Electrocardiography.

In acute AR, the ECG will usually show sinus tachycardia. If endocarditis is a possible etiology, progressive severity of heart block on serial ECGs may indicate the presence and expansion of an accompanying aortic root abscess.

Radiography.

In acute AR, radiographic examination often reveals evidence of marked pulmonary edema. The cardiac silhouette usually is remarkably normal, although left atrial enlargement may be present, and depending on the cause of the AR, enlargement of the ascending aorta may be seen.

Management.

Because early death caused by LV failure is common in patients with acute severe AR, prompt surgical intervention is indicated. Even a normal ventricle cannot sustain the burden of acute, severe volume overload. Therefore the risk of acute AR is much greater than that of chronic AR. While the patient is being prepared for surgery, treatment with an intravenous positive inotropic agent (dopamine or dobutamine) and/or a vasodilator (nitroprusside) often is necessary. The agent and dosage should be selected on the basis of arterial pressure (**see Chapter 24**). Beta blockers and intra-aortic balloon counterpulsation are contraindicated, because either lowering the heart rate or augmenting peripheral resistance during diastole can lead to rapid hemodynamic decompensation. In hemodynamically stable patients with acute AR secondary to active infective endocarditis, operation may be deferred to allow 5 to 7 days of intensive antibiotic therapy (**see Chapter 73**). However, AVR should be undertaken at the earliest sign of hemodynamic instability, or if there is any evidence of abscess formation. If an acute aortic dissection is the cause for the AR, the aorta will also need to be fixed during surgery.

Bicuspid Aortic Valve Disease

Epidemiology

A congenital bicuspid aortic valve (BAV) is present in approximately 1% to 2% of the population and is more prevalent in men, accounting for 70% to 80% of cases. In a subset of patients with BAV, familial

clustering consistent with an autosomal dominant inheritance with incomplete penetrance has been documented.[5] In some families with BAV and associated congenital anomalies, a mutation in the *NOTCH1* gene has been described.

Pathophysiology

The most prevalent anatomy for a bicuspid valve is two cusps with a right-left systolic opening, consistent with congenital fusion of the right and left coronary cusps, seen in 70% to 80% of patients (**Fig. 68.22**; **see also Figs. 68.15 and 14.44**) (Videos 68.7A, 68.7B, and 68.7C). An anterior-posterior orientation, with fusion of the right and noncoronary cusps, is less common, seen in approximately 20% to 30% of patients.[160,161] Fusion of the left and noncoronary cusps is rarely seen. A prominent ridge of tissue or raphe may be present in the larger of the two cusps so that the closed valve in diastole may mimic a trileaflet valve. Echocardiographic diagnosis relies on imaging the systolic leaflet opening with only two aortic commissures (Videos 68.8A and 68.8B). Unicuspid valves are distinguished from a bicuspid valve by having only one aortic commissure.

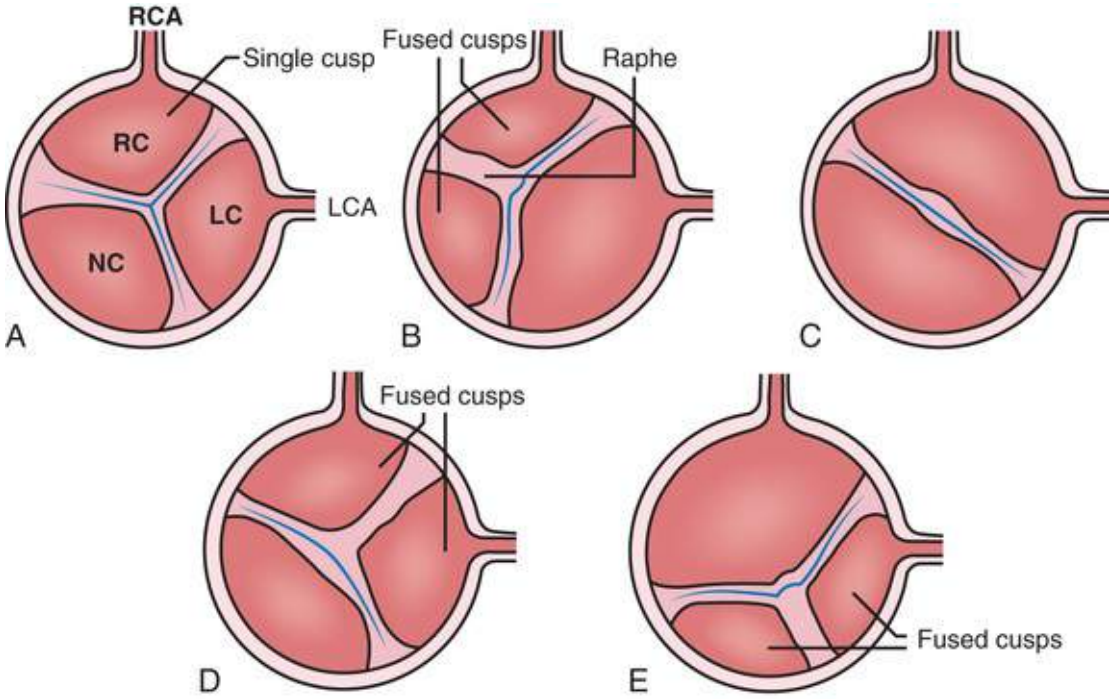
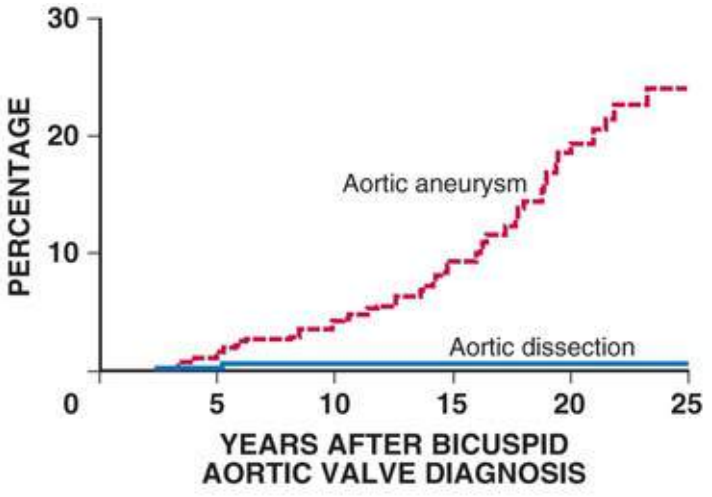


FIGURE 68.22 Comparison of tricuspid and bicuspid aortic valve structures. **A,** Schematic representation of a normal tricuspid aortic valve with the three cusps. *LC,* Left coronary; *LCA,* left coronary artery; *NC,* noncoronary; *RC,* right coronary; *RCA,* right coronary artery. **B,** Bicuspid valve with right noncoronary cusp fusion and one raphe (the line of union between the fused cups). **C,** Bicuspid valve with fusion of the right and left coronary cusps and no raphe. **D,** Bicuspid valve with right-left coronary cusp fusion and one raphe. **E,** Bicuspid valve with fusion of the left and noncoronary cups and one raphe. (From Lindman BR, Clavel M-A, Mathieu P, et al. Calcific aortic stenosis. Nat Rev Dis Primers 2016;2:16006.)

Bicuspid aortic valve disease is associated with an aortopathy, with dilation of the ascending aorta related to accelerated degeneration of the aortic media[5,161-163] (**see Chapter 63**). The presence, location, and severity of aortic dilation are related to valve morphology (**see Fig. 17.16**), but do not appear to be related to the severity of valve dysfunction.[164,165] The risk of aortic dissection in patients with BAV is five to nine times higher than the general population, but the absolute risk is still quite low (**Fig. 68.23**).[5,166,167] Some studies have also suggested an association between BAV disease (anterior-posterior leaflet

opening) and mitral valve prolapse (MVP).[168]



No. at risk						
Aortic aneurysm	384	352	309	186	88	39
Aortic dissection	416	387	348	209	110	53

FIGURE 68.23 Risk of aneurysm formation and aortic dissection after definite bicuspid aortic valve diagnosis. Kaplan-Meier risk of aortic aneurysm (*dashed red line*) 25 years after echocardiographic diagnosis in 384 patients (32 patients with baseline aneurysm excluded) and risk of aortic dissection (*blue bar*) 25 years after echocardiographic diagnosis in 416 patients. (From Michelena HI, Khanna AD, Mahoney D, et al. Incidence of aortic complications in patients with bicuspid aortic valves. JAMA 2011;306:1104-12.)

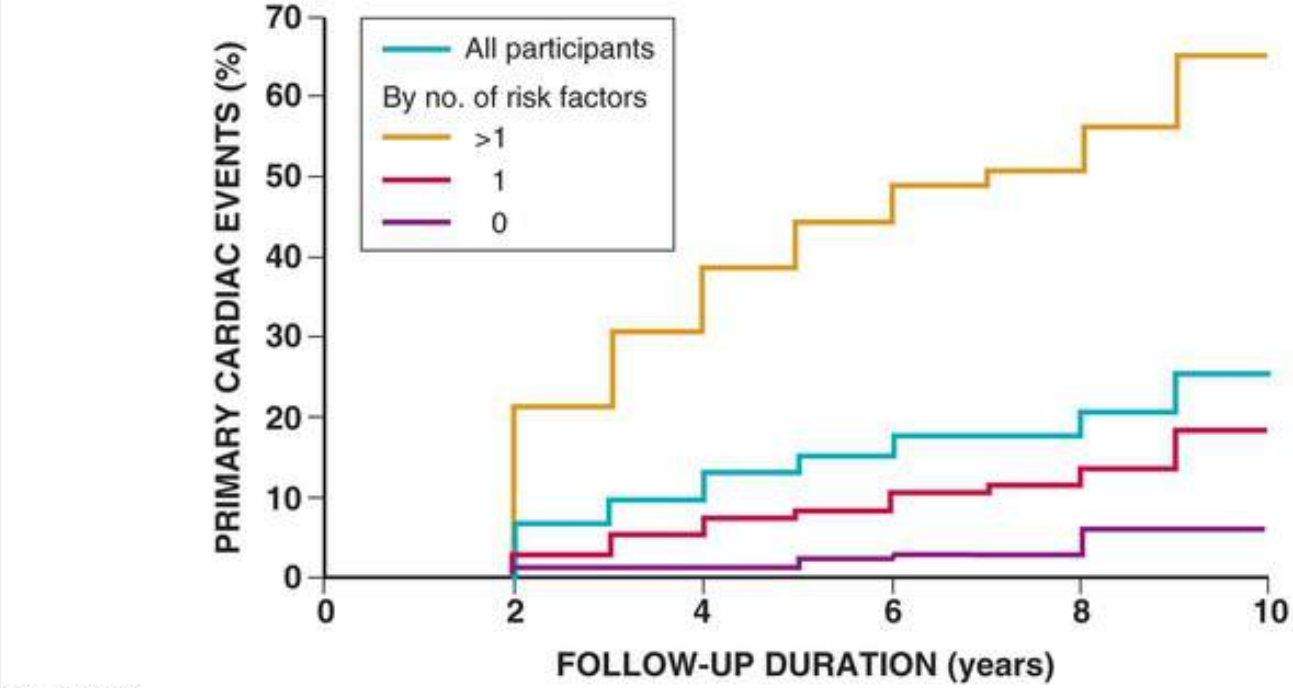
Clinical Presentation

Patients with BAV may be diagnosed at any age on the basis of the presence of an aortic ejection sound or a systolic or diastolic murmur. Some patients, however, are initially diagnosed on echocardiography requested for other reasons, and others are diagnosed through a family history of BAV disease.[169] Often, the diagnosis is unknown until the physical examination reveals manifestations of valve dysfunction or the patient develops symptoms.

Disease Course

Most bicuspid valves function normally until late in life, although a subset of patients present in childhood or adolescence with valve dysfunction. Overall, survival is no different from population estimates.[167,170,171] Over a mean follow-up of 9 years, primary cardiac events occurred in 25% of 642 ambulatory adults with BAV. Events included aortic valve or root replacement (22%), hospitalization for HF (2%), and cardiac death (3%). Risk factors for cardiac events were age greater than 30 years, and moderate or severe AR or AS (**Fig. 68.24**). In another series of 212 patients with BAV and no or mild valve dysfunction at diagnosis, aortic valve surgery, ascending aortic surgery, or any cardiovascular surgery occurred in 24%, 5%, and 27%, respectively, over 20 years of follow-up.[171] Patients with BAV also are at increased risk for endocarditis (0.4 per 100,000), accounting for approximately 1200 deaths per year in the United States. However, most patients with BAV develop calcific valve stenosis later in life, typically presenting with severe AS after the age of 50 years. Although the histopathologic features of calcific stenosis of a BAV are no different from those of a trileaflet valve, the turbulent flow and increased leaflet stress caused by the abnormal architecture are postulated to result in accelerated valve

changes, explaining the earlier average age at presentation in patients with a bicuspid, compared with trileaflet, stenotic valve. BAV disease accounts for greater than 50% of AVRs in the United States and is a common cause of calcific AS, even in older persons.



No. at risk						
All participants	642	639	533	413	309	198
By no. of risk factors						
>1	142	141	95	66	51	36
1	306	305	261	204	153	93
0	194	193	177	143	105	69

FIGURE 68.24 Outcome of patients with bicuspid aortic valves. The frequency of primary cardiac events in patients with more than one risk factor at baseline (*n* = 142) was 65% (standard deviation [SD], 5%); in all participants (*n* = 642), 25% (SD, 2%); in patients with one risk factor at baseline (*n* = 306), 18% (SD, 3%); and in patients with no risk factors at baseline (*n* = 194), 6% (SD, 2%). The risk factors for primary cardiac events were age older than 30 years, moderate or severe aortic regurgitation, and moderate or severe aortic stenosis. (From Tzemos N, Therrien J, Yip J, et al. Outcomes in adults with bicuspid aortic valves. JAMA 2008;300:1317.)

The aortopathy associated with BAV disease often results in aortic dilation and carries an increased risk of aortic dissection. The magnitude of risk appears to vary depending on valve and aortic morphology and on a family history of aortic involvement.[162,172,173]

Management

The management of BAV disease is directed toward the hemodynamic consequences of valve dysfunction—AS or AR—as discussed earlier. Currently, there are no effective medical therapies to prevent progressive valve deterioration when a bicuspid valve is diagnosed. In addition to appropriate follow-up for valve dysfunction, evaluation of the ascending aorta is needed, often with CT or CMR to ensure adequate visualization and accurate measurement of the aortic sinuses and ascending aorta (**see Fig. 68.16**).[174] If AVR is needed for stenosis or regurgitation, concurrent aortic root replacement is recommended if the maximum aortic dimension (measured at end-diastole) exceeds 45 mm.[152] Even in the

absence of aortic valve disease, aortic root replacement is recommended when the aortic dimension is 55 mm or greater in adults with BAV and may be considered with an aortic diameter of 50 mm if there is a family history of dissection or evidence of rapid progression.[152]

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69

Mitral Valve Disease

James D. Thomas, Robert O. Bonow

Mitral Stenosis

Causes and Pathology

The predominant cause of mitral stenosis (MS) is rheumatic fever,[1] with rheumatic changes present in 99% of stenotic mitral valves excised at the time of mitral valve replacement. Approximately 25% of all patients with rheumatic heart disease have isolated MS, and approximately 40% have combined MS and mitral regurgitation (MR). Multivalve involvement is seen in 38% of patients with MS, with the aortic valve affected in approximately 35% and the tricuspid valve in approximately 6%. The pulmonic valve is rarely affected. Two thirds of all patients with rheumatic MS are female. The interval between the initial episode of rheumatic fever (**see Chapter 74**) and clinical evidence of mitral valve obstruction is variable, ranging from a few years to more than 20 years.

Rheumatic fever results in characteristic changes of the mitral valve; diagnostic features are thickening at the leaflet edges, fusion of the commissures, and chordal shortening and fusion[2] (**Fig. 69.1**). With acute rheumatic fever, the changes include inflammation and edema of the leaflets, with small fibrin-platelet thrombi along the leaflet contact zones. Subsequent scarring leads to the characteristic valve deformity, with obliteration of the normal leaflet architecture by fibrosis, neovascularization, and increased collagen and tissue cellularity. *Aschoff bodies*, the pathologic hallmark of rheumatic disease, are seen most frequently in the myocardium, not the valve tissue, with Aschoff bodies identified in only 2% of autopsied patients with chronic valve disease.

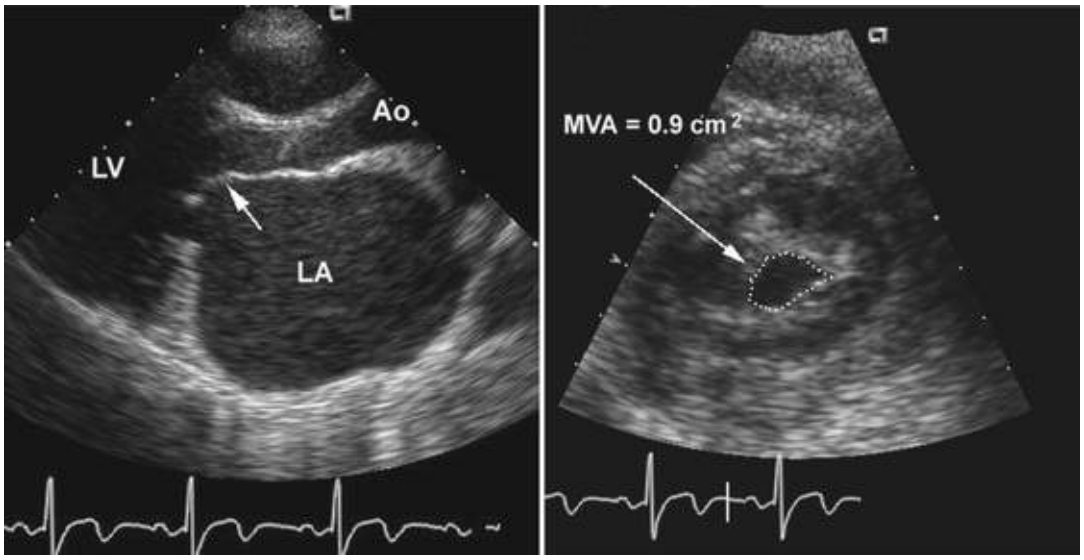


FIGURE 69.1 Parasternal long-axis **(left)** and short-axis **(right)** two-dimensional echocardiographic views showing the characteristic findings in rheumatic mitral stenosis. Note the commissural fusion that results in doming of the leaflets in the long-axis view and in a decrease in the width of the mitral orifice in the short-axis view. The patient has relatively thin, flexible leaflets with little subvalvular involvement. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *MVA,* mitral valve area. (From Otto CM. Valvular Heart Disease. Philadelphia: Saunders; 2004.)

These anatomic changes lead to a typical functional appearance of the rheumatic mitral valve. In earlier stages of the disease, the relatively flexible leaflets snap open in diastole into a curved shape because of restriction of motion at the leaflet tips (**see Fig. 69.1**; **see also Fig. 14.36**). This sudden restriction of leaflet opening in diastole is responsible for the characteristic opening snap (OS) on auscultation, and the interval between the second heart sound (S_2) and OS bears an inverse relationship with left atrial (LA) pressure. This "diastolic doming" is most evident in the motion of the anterior leaflet and becomes less prominent as the leaflets become more fibrotic and calcified, which also muffles the OS. The symmetric fusion of the commissures results in a small, central oval orifice in diastole that on pathologic specimens is shaped like a fish mouth or buttonhole because the anterior leaflet is not in the physiologic open position (**Fig. 69.2**; **see also Fig. 69.1, right, and Fig. 14.37**). With end-stage disease, the thickened leaflets may be so adherent and rigid that they cannot open or shut, with consequent reduction in or, rarely, even abolition of the first heart sound (S_1), and leading to combined MS and MR. When rheumatic fever results exclusively or predominantly in contraction and fusion of the chordae tendineae, with little fusion of the valvular commissures, dominant MR results.

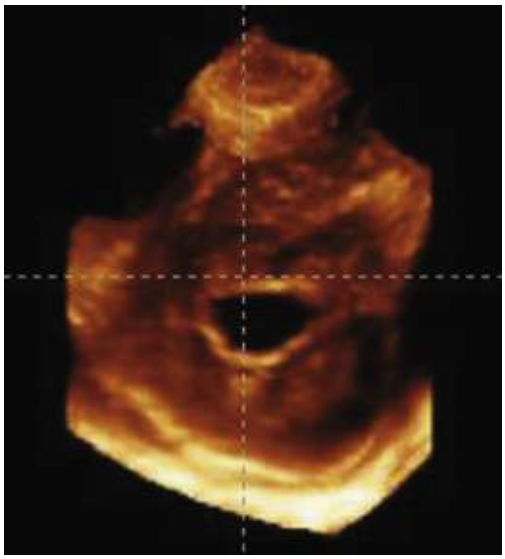


FIGURE 69.2 Three-dimensional imaging of rheumatic mitral stenosis, obtained by intraoperative epicardial echocardiography. Commissural fusion leaves the mitral valve with a small, circular orifice that has been likened to a fish mouth.

Debate continues about whether the anatomic changes of severe MS result from recurrent episodes of rheumatic fever or from a chronic autoimmune process caused by cross-reactivity between a streptococcal protein and valve tissue (**see Chapter 74**), or whether calcific valve disease is superimposed. Evidence supporting recurrent infection as an important factor in disease progression includes the correlation between the geographic variability in the prevalence of rheumatic heart disease and the age when patients present with severe MS. In North America and Europe, with approximately 1 case per 100,000 population, patients present with severe valve obstruction in the sixth decade of life. By contrast, in Africa, with a disease prevalence of 35 per 100,000, severe disease often is seen in teenagers. Conversely, evidence favoring superimposed calcific valve disease is the observation that restenosis after mitral valvuloplasty is caused by leaflet thickening and fibrosis, rather than representing recurrent commissural fusion.[3]

Congenital MS is uncommon and typically is diagnosed in infancy or early childhood (**see Chapter 75**), often as part of the Shone complex. MS is a rare complication of malignant carcinoid disease, generally seen only with pulmonary metastases or right-to-left shunting, systemic lupus erythematosus (SLE), rheumatoid arthritis, and mucopolysaccharidoses of the Hunter-Hurler phenotype, Fabry disease, and Whipple disease. Methysergide therapy is an unusual but documented cause of MS, as was the association with the diet drug fenfluramine (most notoriously in the combination drug Fen-Phen). The association of atrial septal defect with rheumatic MS is called Lutembacher syndrome.

Other conditions may result in obstruction to left ventricular (LV) inflow, including an LA tumor, particularly myxoma (**see Chapter 95**), ball valve thrombus in the left atrium (usually associated with MS), infective endocarditis with large vegetations (**Chapter 73**), or a congenital membrane in the left atrium (i.e., cor triatriatum; **Chapter 75**). In older patients, extensive mitral annular calcification may result in restriction of the size and motion of the annulus and may extend onto the base of the mitral leaflets, resulting in functional MS, although obstruction rarely is severe.[4] Mitral annular calcification often develops in patients with calcific aortic valve disease.[5] A particularly troublesome form of MS is seen following radiotherapy for chest or breast cancer. Characterized by heavy calcification and thickening of the aortomitral curtain,[6] it often requires multimodality imaging for full characterization.[7]

Pathophysiology

The most useful descriptor of the severity of mitral valve obstruction is the degree of valve opening in diastole, or the mitral valve orifice area. In normal adults the cross-sectional area of the mitral valve orifice (MVA) is 4 to 6 cm^2 (**Table 69.1**). When the orifice is reduced to approximately 2 cm^2, which is considered to represent mild MS, blood can flow from the left atrium to the left ventricle only if propelled by a small, although abnormal, pressure gradient. When the mitral valve opening is reduced to 1 cm^2, which is considered to represent severe MS,[8] a left atrioventricular (AV) pressure gradient of approximately 20 mm Hg (and therefore, with normal LV diastolic pressure, a mean LA pressure >25 mm Hg) is required to maintain normal cardiac output at rest (**Fig. 69.3**; **see also Fig. 19.13**).

TABLE 69.1

Stages of Mitral Stenosis (MS)

STAGE	DEFINITION	VALVE ANATOMY	VALVE HEMODYNAMICS*	HEMODYNAMIC CONSEQUENCES	SYMPTOMS
A	**At risk for MS**	Mild valve doming during diastole	Normal transmitral flow velocity	None	None
B	**Progressive MS**	Rheumatic valve changes with commissural fusion and diastolic doming of mitral valve leaflets Planimetered MVA >1.5 cm^2	Increased transmitral flow velocities MVA >1.5 cm^2 Diastolic pressure half-time <150 msec	Mild to moderate LA enlargement Normal pulmonary pressure at rest	None
C	**Asymptomatic severe MS**	Rheumatic valve changes with commissural fusion and diastolic doming of mitral valve leaflets Planimetered MVA ≤1.5 cm^2 (MVA ≤1 cm^2 with very severe MS)	MVA ≤1.5 cm^2 (MVA ≤1 cm^2 with very severe MS) Diastolic pressure half-time ≥150 msec (Diastolic pressure half-time ≥220 msec with very severe MS)	Severe LA enlargement Elevated PASP >30 mm Hg	None
D	**Symptomatic severe MS**	Rheumatic valve changes with commissural fusion and diastolic doming of mitral valve leaflets Planimetered MVA ≤1.5 cm^2	MVA ≤1.5 cm^2 (MVA ≤1 cm^2 with very severe MS) Diastolic pressure half-time ≥150 msec (Diastolic pressure half-time ≥220 msec with very severe MS)	Severe LA enlargement Elevated PASP >30 mm Hg	Decreased exercise tolerance Exertional dyspnea

*The transmitral mean pressure gradient should be obtained to determine the full hemodynamic effect of the MS and usually is greater than 5 to 10 mm Hg in severe MS; however, because of the variability of the mean pressure gradient with heart rate and forward flow, it has not been included in the criteria for severity.

LA, Left atrial; *MVA,* mitral valve area; *PASP,* pulmonary artery systolic pressure.

From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACCF guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57-185.

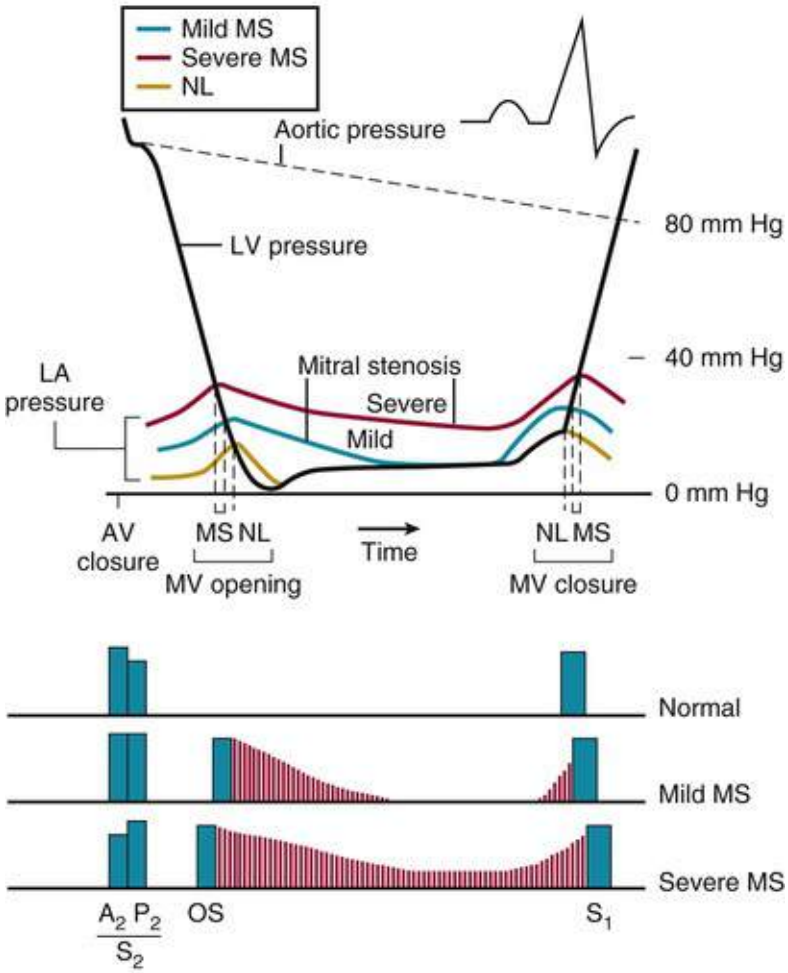


FIGURE 69.3 Schematic representation of left ventricular (LV), aortic, and left atrial (LA) pressures, showing normal (NL) relationships and alterations with mild and severe mitral stenosis (MS). Corresponding classic auscultatory signs of MS are shown at the *bottom* of the diagram. The higher left atrial *v* wave of severe MS causes earlier pressure crossover and earlier mitral valve (MV) opening, leading to a shorter interval between aortic valve (AV) closure and the opening snap (OS). The higher LA end-diastolic pressure with severe MS also results in later closure of the MV. With severe MS, the diastolic rumble becomes longer, and there is accentuation of the pulmonic component (P_2) of the second heart sound (S_2) in relation to the aortic component (A_2).

The transvalvular pressure gradient for any given valve area is a function of the square of the transvalvular blood velocity (v) in the simplified Bernoulli equation, balancing the potential energy of pressure with the kinetic energy of $\frac{1}{2}\rho v^2$, where ρ is blood density. Given that velocity is approximately equal to the instantaneous flow rate Q divided by MVA, the pressure gradient clearly is proportional to the square of the flow and inversely proportional to the square of valve area.[8] Thus a doubling of flow rate quadruples the pressure gradient, and any further reduction in valve area only exacerbates this. The elevated LA pressure in turn raises pulmonary venous and capillary pressures, resulting in exertional dyspnea. The first bouts of dyspnea in patients with MS usually are precipitated by tachycardia resulting from exercise, pregnancy, hyperthyroidism, anemia, infection, or atrial fibrillation (AF). All these (1) increase the rate of blood flow across the mitral orifice, resulting in further elevation of the LA pressure, and (2) decrease the diastolic filling time, resulting in a reduction in forward cardiac output. Because diastole shortens proportionately more than systole as heart rate increases, the time available for flow across the mitral valve is reduced at higher heart rates. At any given stroke volume, therefore, tachycardia results in a higher instantaneous volume flow rate and higher transmitral pressure gradient, which elevates LA pressures further. This higher transmitral gradient, often in combination with inadequate LV filling (because of the shortened diastolic filling time), explains the sudden occurrence of dyspnea and

pulmonary edema in previously asymptomatic patients with MS who develop AF with a rapid ventricular rate. It also accounts for the equally rapid clinical improvement in these patients when the ventricular rate is slowed. Compounding the direct impact of LA pressure on pulmonary capillary wedge pressure (PCWP) is the development of reflex pulmonary arterial vasospasm, which may further elevate pulmonary arterial pressure, leading to right-sided heart failure (HF).[9]

Atrial contraction augments the presystolic transmitral valvular gradient by approximately 30% in patients with MS (**Fig. 69.3**). AF is common in patients with MS, with an increasing prevalence with age. In patients with severe MS younger than 30 years, only approximately 10% are in AF, compared with approximately 50% of those older than 50s. Withdrawal of atrial transport when AF develops reduces cardiac output by approximately 20%, often resulting in symptom onset.

Obstruction at the mitral valve level has other hemodynamic consequences, which account for many of the adverse clinical outcomes associated with MS. Elevated LA pressure results in pulmonary artery hypertension, with secondary effects on the pulmonary vasculature and right-sided cardiac chambers. In addition, LA enlargement and stasis of blood flow are associated with an increased risk of thrombus formation and systemic embolism. Typically, the left ventricle is relatively normal or even small, unless there is coexisting MR, with the primary LV abnormalities being a small, underfilled chamber and paradoxical septal motion caused by right ventricular (RV) enlargement and dysfunction.

Hemodynamic Consequences of Mitral Stenosis

Pulmonary Hypertension.

In patients with MS and sinus rhythm, mean LA pressure is elevated (**see Fig. 69.3**), and the LA pressure curve shows a prominent atrial contraction (*a* wave), with a gradual pressure decline after mitral valve opening (*y* descent). In patients with mild to moderate MS without elevated pulmonary vascular resistance (PVR), pulmonary artery pressure (PAP) may be normal or only minimally elevated at rest but rises during exercise (**see eFig. 19.12**). However, in patients with severe MS and those with significantly increased PVR, PAP is elevated when the patient is at rest. Rarely, in patients with extremely elevated PVR, PAP may exceed systemic arterial pressure. Further elevations of LA and pulmonary vascular pressures occur during exercise and tachycardia, particularly with the onset of AF.

Pulmonary hypertension in patients with MS results from (1) passive backward transmission of the elevated LA pressure; (2) pulmonary arteriolar constriction, which presumably is triggered by LA and pulmonary venous hypertension (reactive pulmonary hypertension); and (3) organic obliterative changes in the pulmonary vascular bed, which may be considered a complication of longstanding and severe MS (**see Chapter 85**). With moderately elevated PAP (systolic pressure 30 to 60 mm Hg), RV performance is usually maintained. In time, severe pulmonary hypertension results in right-sided HF, with dilation of the right ventricle and its annulus, secondary tricuspid regurgitation, and sometimes pulmonic regurgitation. These changes in the pulmonary vascular bed may also exert a protective effect; the elevated precapillary resistance makes the development of symptoms of pulmonary congestion less likely by tending to prevent blood from surging into the pulmonary capillary bed and damming up behind the stenotic mitral valve. This protection, however, occurs at the expense of a reduced cardiac output. In patients with severe MS, pulmonary vein–bronchial vein shunts occur. Their rupture may cause hemoptysis. Patients with severe MS exhibit a reduction in pulmonary compliance, increase in the work of breathing, and redistribution of pulmonary blood flow from base to apex.

Left Ventricular Function.

The LV chamber typically is normal or small, with normal systolic function and normal LV end-diastolic pressure. However, coexisting MR, aortic valve lesions, systemic hypertension, ischemic heart disease, and cardiomyopathy all may be responsible for elevations of LV diastolic pressure.

Exercise Hemodynamics.

At any given severity of stenosis, the clinical picture is dictated largely by the levels of cardiac output and PVR with exertion. The response to a given degree of mitral obstruction may be characterized at one end of the hemodynamic spectrum by a normal cardiac output and high left AV pressure gradient or, at the opposite end of the spectrum, by a greatly reduced cardiac output and low transvalvular pressure gradient. Thus, in some patients entering the *severe* range of MS (with MVA of 1.0 to 1.5 cm^2), cardiac output may be normal at rest and rises normally during exertion. However, the high transvalvular pressure gradient with exertion elevates LA and pulmonary capillary pressures, leading to pulmonary congestion during exertion. By contrast, in other patients with MS in this range, there is an inadequate rise in cardiac output during exertion, resulting in a smaller rise in pulmonary venous pressure. In these patients, symptoms are caused by a low cardiac output rather than by pulmonary congestion. In patients with *critical* MS (MVA <1 cm^2), particularly when PVR is elevated, cardiac output usually is depressed at rest and may fail to rise at all during exertion. These patients frequently have resting weakness and fatigue secondary to a low cardiac output, with low-output and pulmonary congestion symptoms with exercise.

Left Atrial Changes.

The combination of mitral valve disease and atrial inflammation secondary to rheumatic carditis causes (1) LA dilation, (2) fibrosis of the atrial wall, and (3) disorganization of the atrial muscle bundles. These changes lead to disparate conduction velocities and inhomogeneous refractory periods. Premature atrial activation, caused by an automatic focus or reentry, may stimulate the left atrium during the vulnerable period, thereby precipitating AF. The development of this arrhythmia correlates independently with the severity of the MS, degree of LA dilation, and height of the LA pressure. However, in most studies of patients with severe MS undergoing percutaneous balloon mitral valvotomy (BMV), the strongest predictor of AF is older age. AF often is episodic at first but then becomes more persistent. AF causes diffuse atrophy of atrial muscle, further atrial enlargement, and further inhomogeneity of refractoriness and conduction (**see Chapter 38**). These changes lead in turn to irreversible AF.

Clinical Presentation

Symptoms

Dyspnea

The most common presenting symptoms of MS are dyspnea, fatigue, and decreased exercise tolerance.[3] Symptoms may be caused by a reduced ability to increase cardiac output normally with exercise or elevated pulmonary venous pressures and reduced pulmonary compliance. Dyspnea may be accompanied by cough and wheezing. Vital capacity is reduced, presumably because of the presence of engorged pulmonary vessels and interstitial edema. Patients who have critical obstruction to LA emptying and dyspnea with ordinary activity (New York Heart Association [NYHA] Functional Class III) generally have orthopnea as well and are at risk for attacks of frank pulmonary edema. The latter may be precipitated by effort, emotional stress, respiratory infection, fever pregnancy, or AF with a rapid ventricular rate or other tachyarrhythmia. Pulmonary edema may be caused by any condition that increases

the flow rate across the stenotic mitral valve, either because of an increase in total cardiac output or a reduction in the time available for blood flow across the mitral orifice to occur. In patients with a markedly elevated PVR, RV function often is impaired, and the presentation also may include symptoms and signs of right-sided HF.

MS is a slowly progressive disease, and many patients remain seemingly asymptomatic merely by readjusting their lifestyles to a more sedentary level. Usually, symptom status can be accurately assessed by a directed history, asking the patient to compare current levels of maximum exertion with those at specific times in the past. Interviewing the family may reveal limitations that the patient does not acknowledge. Exercise testing may be useful for selected patients to determine functional status objectively and may be combined with Doppler echocardiography (see later) to assess exercise hemodynamics.

Hemoptysis

Hemoptysis is rare in patients with a known diagnosis of MS because intervention usually is performed before severe obstruction becomes chronic. When hemoptysis does occur, it can be sudden and severe, caused by rupture of thin-walled, dilated bronchial veins, usually because of a sudden rise in LA pressure, or it may be milder, with only blood-stained sputum associated with attacks of paroxysmal nocturnal dyspnea. The pink, frothy sputum characteristic of acute pulmonary edema with rupture of alveolar capillaries also may develop in these patients. Hemoptysis also may be caused by pulmonary infarction, a late complication of MS associated with HF.

Chest Pain

Chest pain is not a typical symptom of MS, but a small proportion, perhaps 15%, of patients with MS experience chest discomfort that is indistinguishable from that of angina pectoris. This symptom may be caused by severe RV hypertension secondary to the pulmonary vascular disease or by concomitant coronary atherosclerosis. Rarely, chest pain may be secondary to coronary obstruction caused by coronary embolization. In many patients, however, a satisfactory explanation for the chest pain cannot be uncovered, even after complete hemodynamic and angiographic studies.

Palpitations and Embolic Events

Patients with MS often are initially diagnosed when they present with AF or an embolic event.

Other Symptoms

Compression of the left recurrent laryngeal nerve by a greatly dilated left atrium, enlarged tracheobronchial lymph nodes, and dilated pulmonary artery may cause hoarseness (Ortner syndrome). A history of repeated hemoptysis is common in patients with pulmonary hemosiderosis. Systemic venous hypertension, hepatomegaly, edema, ascites, and hydrothorax are all signs of severe MS with elevated PVR and right-sided HF.

Physical Examination

The most common findings on physical examination in patients with MS are an irregular pulse caused by AF and signs of left- and right-sided HF (**see Chapter 10**). The classic diastolic murmur and loud S_1 often are difficult to appreciate. Patients with severe chronic MS, a low cardiac output, and systemic

vasoconstriction may exhibit the so-called mitral facies, characterized by pinkish purple patches on the cheeks. The arterial pulse is usually normal, but in patients with a reduced stroke volume, the pulse may be low in volume. The jugular venous pulse (JVP) usually exhibits a prominent *a* wave in patients with sinus rhythm and elevated PVR. In patients with AF, the *x* descent of the JVP disappears, and there is only one crest, a prominent *v* or *c-v* wave, per cardiac cycle. Palpation of the cardiac apex usually reveals an inconspicuous left ventricle; the presence of a palpable presystolic expansion wave or an early diastolic rapid filling wave speaks strongly against serious MS. A readily palpable, tapping S_1 suggests that the anterior mitral valve leaflet is pliable. When the patient is in the left lateral recumbent position, a diastolic thrill of MS may be palpable at the apex. Often, a RV lift is felt in the left parasternal region in patients with pulmonary hypertension. A greatly enlarged right ventricle may displace the left ventricle posteriorly and produce a prominent RV apex beat that can be confused with a LV lift. A loud P_2 may be palpable in the second left intercostal space in patients with MS and pulmonary hypertension.

Auscultation

The auscultatory features of MS (**see Fig. 69.3**) include an accentuated S_1 with prolongation of the Q-S_1 interval, correlating with the level of the LA pressure. Accentuation of S_1 occurs when the mitral valve leaflets are flexible. It is caused in part by the rapidity with which LV pressure rises at the time of mitral valve closure, as well as by the wide closing excursion of the leaflets. Marked calcification and/or thickening of the mitral valve leaflets reduce the amplitude of S_1, probably because of diminished motion of the leaflets. As PAP rises, P_2 at first becomes accentuated and widely transmitted and often can be readily heard at both the mitral and the aortic areas. With further PAP elevation, splitting of S_2 narrows because of reduced compliance of the pulmonary vascular bed, with earlier pulmonic valve closure. Lastly, S_2 becomes single and accentuated. Other signs of severe pulmonary hypertension include a nonvalvular pulmonic ejection sound that diminishes during inspiration, because of dilation of the pulmonary artery, a systolic murmur of tricuspid regurgitation, a Graham Steell murmur of pulmonic regurgitation, and an S_4 originating from the right ventricle. An S_3 gallop originating from the left ventricle is absent in patients with MS unless significant MR or aortic regurgitation coexists.

Opening Snap.

The mitral OS is caused by a sudden tensing of the valve leaflets after the valve cusps have completed their opening excursion. The OS occurs when the movement of the mitral dome into the left ventricle suddenly stops. It is most readily audible at the apex, using the diaphragm of the stethoscope. The OS usually can be differentiated from P_2 because the OS occurs later, unless right bundle branch block is present. In addition, the OS usually is loudest at the apex, whereas S_2 is best heard at the cardiac base. The mitral valve cannot be totally rigid if it produces an OS, so an OS usually is accompanied by an accentuated S_1. Calcification confined to the tip of the mitral valve leaflets does not preclude an OS, although calcification of the body and tip does. The mitral OS follows A_2 by 0.04 to 0.12 second; this interval varies inversely with the LA pressure (**see Fig. 69.3**). A short A_2-OS interval is a reliable indicator of severe MS, but accurate estimation of this time interval requires considerable experience.

Diastolic Murmur.

The diastolic, low-pitched, rumbling murmur of MS is best heard at the apex, with the bell of the stethoscope (low-frequency mode on electronic stethoscopes) and with the patient in the left lateral

recumbent position. When this murmur is soft, it is limited to the apex but, when louder, may radiate to the left axilla or the lower left sternal area. Although the intensity of the diastolic murmur is not closely related to the severity of stenosis, the pitch and duration of the murmur are a guide to the severity of mitral valve narrowing. The murmur persists for as long as the left AV pressure gradient exceeds approximately 3 mm Hg, and it is higher in pitch for higher-velocity (and higher-gradient) transmitral jets. The murmur usually commences immediately after the OS. In mild MS the early diastolic murmur is brief but, in the presence of sinus rhythm, resumes in presystole. In severe MS the murmur persists until end-diastole, with presystolic accentuation while sinus rhythm is maintained (**see Fig. 69.3**).

Other Auscultatory Findings.

A pansystolic murmur of tricuspid regurgitation and a S_3 originating from the right ventricle may be audible in the fourth intercostal space in the left parasternal region in patients with severe MS. These signs, which are secondary to pulmonary hypertension, may be confused with the findings of MR. However, the inspiratory augmentation of the murmur and of the S_3 and the prominent *v* wave in the jugular venous pulse aid in establishing that the murmur originates from the tricuspid valve. A high-pitched decrescendo diastolic murmur along the left sternal border in patients with MS and pulmonary hypertension may be audible pulmonic regurgitation (Graham Steell murmur) but more often is caused by concomitant aortic regurgitation.

Diagnosis and Evaluation

Differential Diagnosis

Mitral stenosis is a rare diagnosis in developed countries, and most apical diastolic murmurs have other causes. In older patients, an apical diastolic rumble is most likely to be caused by mitral annular calcification, and 90% of patients with a diastolic apical murmur have no significant stenosis on echocardiography. In patients with a normally functioning mitral prosthesis, a diastolic murmur is a frequent finding. In severe MR—indeed, in any condition in which flow across a nonstenotic mitral valve is increased (e.g., a ventricular septal defect)—there may also be a short diastolic murmur following an S_3. LA myxoma (**see Chapter 95**) may produce auscultatory findings similar to those in rheumatic valvular MS. A diastolic rumble may also be present in some patients with hypertrophic cardiomyopathy (HCM), caused by early diastolic flow into the hypertrophied, nondistensible left ventricle (**see Chapter 78**).

Echocardiography

Echocardiography is the most accurate approach to the diagnosis and evaluation of MS[8,10] (**see Chapter 14**). It is recommended for all patients with MS at initial presentation, for reevaluation of changing symptoms or signs, and at regular intervals (depending on disease severity) for monitoring disease progression (**see Table 69.1**). Imaging shows the characteristic anatomy with leaflet thickening and restriction of opening caused by symmetric fusion of the commissures, resulting in "doming" of the leaflets in diastole (**see Fig. 69.1**; **see also Fig. 14.36** and Videos 69.1A and 69.2A). As disease becomes more severe, thickening extends from the leaflet tips toward the base, with further restriction of motion and less curvature of the leaflet in diastole. The mitral chords are variably thickened, fused, and shortened, with superimposed calcification of the valve apparatus in many cases.

Mitral valve area is measured by direct planimetry from two-dimensional short-axis images (**see Fig.**

69.1, right, and Fig. 14.38; Videos 69.1B and 69.2B) and calculated by the Doppler pressure half-time and proximal isovelocity surface area (PISA) methods (**see Figs. 14.39 and 14.40**; Video 69.3), each of which has technical challenges.[11] The transmitral gradient also is calculated and any coexisting MR quantitated on the basis of the accepted guidelines.[12,13] Three-dimensional echocardiography is playing an increasing role in assessing mitral valve morphology and quantifying severity of MS[14-18] (**see Fig. 69.2**; **see also Fig. 14.38**; Videos 69.4 and 69.5). Evaluation of the morphology of the valve is helpful for predicting the hemodynamic results and outcome of percutaneous BMV. The Wilkins score consists of four components summed together, graded 0 to 4+ for leaflet thickness, mobility, calcification, and chordal involvement to provide an overall score that is favorable (low) or unfavorable (high) for valvuloplasty (**see Table 14.9**). Confirming earlier reports, the Wilkins score continues to predict long-term outcome after BMV[19] (**see Fig. 72.7**). Other important anatomic features of the valve are the degree of anterior leaflet doming, symmetry of commissural fusion, and distribution of leaflet calcification.[8]

Other key features on echocardiography are LA size, PAP, LV size and systolic function, and RV size and systolic function. When pulmonary hypertension is present, the right ventricle frequently is dilated, with reduced systolic function. Tricuspid regurgitation may be secondary to RV dysfunction and annular dilation or may be caused by rheumatic involvement of the tricuspid valve (**see Chapter 70**). Complete evaluation of aortic valve anatomy and function also is important because the aortic valve is affected in approximately one third of patients with MS. When transthoracic images are suboptimal, transesophageal echocardiography (TEE) is appropriate. TEE also is necessary to exclude LA thrombus and to evaluate MR severity when percutaneous BMV is considered.

Exercise Testing with Doppler Echocardiography

Exercise testing is useful for many patients with MS to ascertain the level of physical conditioning and elicit covert cardiac symptoms. The exercise test can be combined with Doppler echocardiography to assess exercise pulmonary pressure,[20] usually with the Doppler examination performed at rest after termination of treadmill exercise, but sometimes performed during bicycle exercise (**see Chapter 14**). Exercise Doppler testing is recommended when a discrepancy exists between resting echocardiographic findings and severity of clinical symptoms.[21] Useful parameters on exercise testing include exercise duration, blood pressure and heart rate response, change in mitral peak and (especially) mean gradient, and increase in pulmonary pressures with exercise, compared with the expected normal changes. An exercise pulmonary systolic pressure greater than 60 mm Hg can be a key data point in the management of these patients.

Other Diagnostic Evaluation Modalities

Electrocardiography.

The electrocardiogram (ECG) is relatively insensitive for detecting mild MS but does show characteristic changes in moderate or severe obstruction (**see Chapter 12**). LA enlargement (P wave duration in lead II >0.12 second and/or a P wave axis between +45 and −30 degrees) is a principal ECG feature of MS and is found in 90% of patients with significant MS and sinus rhythm. The ECG signs of LA enlargement correlate more closely with LA volume than with LA pressure and often regress after successful valvotomy. AF is common with longstanding MS, as noted.

ECG evidence of RV hypertrophy correlates with RV systolic pressure. When RV systolic pressure is 70 to 100 mm Hg, approximately 50% of patients exhibit ECG criteria for RV hypertrophy, including a

mean QRS axis greater than 80 degrees in the frontal plane and R:S ratio greater than 1 in lead V_1. Other patients with this degree of pulmonary hypertension have no frank evidence of RV hypertrophy, but the R:S ratio fails to increase from the right to the midprecordial leads. When RV systolic pressure is greater than 100 mm Hg in patients with isolated or predominant MS, ECG evidence of RV hypertrophy is consistently found.

Radiography.

Patients with hemodynamically significant MS almost invariably have evidence of LA enlargement on the lateral and left anterior oblique views (**see Fig. 15.3**), although the cardiac silhouette may be normal in the frontal projection. Extreme LA enlargement rarely occurs in isolated MS; when present, MR usually is severe. Enlargement of the pulmonary artery, right ventricle, and right atrium (as well as the left atrium) is commonly seen in patients with severe MS causing pulmonary hypertension. Occasionally, calcification of the mitral valve is evident on the chest radiograph, but more often fluoroscopy is required to detect valvular calcification.

Radiologic changes in the lung fields indirectly reflect the severity of MS. Interstitial edema, an indication of severe obstruction, is manifested as Kerley B lines (dense, short, horizontal lines most frequently seen in costophrenic angles) (**see Fig. 15.5**). This finding is present in 30% of patients with resting PCWP less than 20 mm Hg and in 70% with pressure greater than 20 mm Hg. Severe longstanding mitral obstruction often results in Kerley A lines (straight, dense lines up to 4 cm in length, running toward the hilum), as well as the findings of pulmonary hemosiderosis and rarely, parenchymal ossification.

Cardiac Computed Tomography and Magnetic Resonance Imaging.

Cardiac CT scanning can provide MVA estimates in MS by planimetry after multiplanar reconstruction, although these typically are somewhat larger than those obtained by echocardiography or catheterization.[22,23] Cardiac magnetic resonance imaging (CMR) can also estimate the stenotic valve area, either by planimetry or continuity, with closer agreement to echocardiographic values than CT.[23,24] These tomographic techniques can also provide information on LA cavity and appendage thrombi.

Cardiac Catheterization.

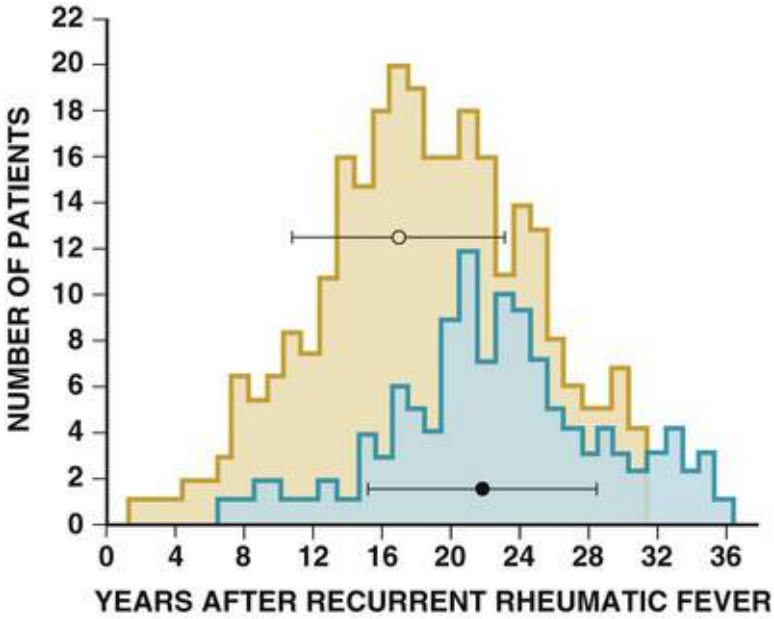
Catheter-based measurement of LA and LV pressures shows the expected hemodynamics (**see Fig. 19.13**) and allows measurement of the mean transmitral pressure gradient and, in conjunction with measurement of transmitral volume flow rate, calculation of the valve area using the Gorlin formula. Occasionally, diagnostic cardiac catheterization is necessary when echocardiography is nondiagnostic or results are discrepant with clinical findings. More often, these measurements now are recorded for monitoring before, during, and after percutaneous BMV. Routine diagnostic cardiac catheterization is not recommended for the evaluation of MS.

Disease Course

Interval Between Acute Rheumatic Fever and Mitral Valve Obstruction

In temperate zones, such as the United States and Western Europe, patients who develop acute rheumatic fever have an asymptomatic period of approximately 15 to 20 years before symptoms of MS develop (**see eFig. 69.1**). It then takes approximately 5 to 10 years for most patients to progress from mild disability (i.e., early NYHA Class II) to severe disability (NYHA Class III or IV). The progression is much more rapid in patients in tropical and subtropical areas, in Polynesians, and in Native Alaskans. In India, critical MS may be present in children as young as 6 to 12 years of age. In North America and Western

Europe, however, symptoms develop more slowly, with onset usually between ages 45 and 65 years. The most likely causes for these differences are the relative prevalence of rheumatic fever and lack of primary and secondary prevention in developing countries, resulting in recurrent episodes of valve scarring (**see Chapter 74**).



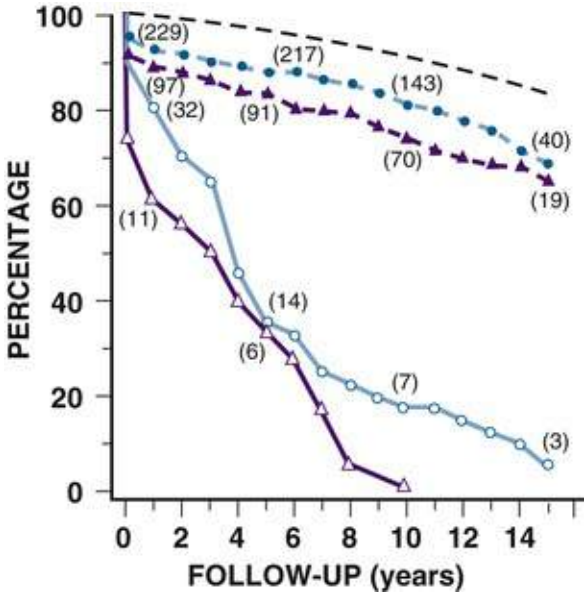
EFIGURE 69.1 Interval between active rheumatic fever and clinical symptoms of valve disease in 177 patients with mitral stenosis (*yellow bars*) and 121 with aortic stenosis (*blue bars*). (From Horstkotte D, Niehues R, Strauer BE. Pathomorphological aspects, aetiology, and natural history of acquired mitral valve stenosis. Eur Heart J 1991;12[Suppl B]:55-60.)

Hemodynamic Progression

Serial echocardiographic data have described the rate of hemodynamic progression in patients with mild MS.[3,8] The two largest series had a combined total of 153 adults, with a mean age of approximately 60 years, with an average follow-up of slightly more than 3 years. As in most series of patients with MS, 75% to 80% were women. The initial MVA was 1.7 ±0.6 cm^2, and the overall rate of progression was a decrease in valve area of 0.09 cm^2/yr. Approximately one third of patients showed rapid progression, defined as a decrease in MVA of more than 0.1 cm^2/yr. These data apply to the older patients with MS seen in developed countries. Few data are available on the rate of hemodynamic progression of rheumatic MS in underdeveloped countries, where the age at symptom onset is much younger.

Clinical Outcomes

Natural history data obtained in the presurgical era indicate that symptomatic patients with MS have a poor outlook, with 5-year survival rates of 62% for MS patients in NYHA Class III but only 15% in Class IV. Data from unoperated patients in the surgical era still reported a 5-year survival rate of only 44% in patients with symptomatic MS who refused valvotomy (**eFig. 69.2**).



EFIGURE 69.2 Natural history of the respective valvular lesion in 159 patients with isolated mitral stenosis (MS) (*solid blue line*) or mitral regurgitation (MR) (*solid purple line*) who did not have surgery, even though operation was indicated, compared with patients treated with valve replacement for MS (*dashed blue line*) or MR (*dashed purple line*). The expected survival rate in the absence of mitral valve disease is indicated by the *upper curve* (*dashed black line*). (From Horstkotte D, Niehues R, Strauer BE. Pathomorphological aspects, aetiology, and natural history of acquired mitral valve stenosis. Eur Heart J 1991;12[Suppl B]:55-60.)

Overall clinical outcomes are greatly improved in patients who undergo surgical or percutaneous relief of valve obstruction on the basis of current guidelines.[21,25] However, longevity is still shortened compared with that expected for age, largely because of complications of the disease process (AF, systemic embolism, pulmonary hypertension) and side effects of therapy (e.g., prosthetic valves, anticoagulation).

Complications

Atrial Fibrillation

The most common complication of MS is AF (**see Chapter 38**).[3] The prevalence of AF in patients with MS is related to the severity of valve obstruction and patient age. In historical series, AF was present in 17% of patients age 21 to 30 years, 45% age 31 to 40 years, 60% age 41 to 50, and 80% older than 51. Even when MS is severe, the prevalence of AF is related to age. In more recent BMV studies, prevalence of AF ranged from 4% in a series of 600 patients from India (mean age, 27 years) to 27% in 4832 patients from China (mean age, 37) to 40% in 1024 patients from France (mean age, 49).

AF may precipitate or worsen symptoms caused by loss of the atrial contribution to filling and to a short diastolic filling period when the ventricular rate is not well controlled. In addition, AF predisposes affected patients to LA thrombus formation and systemic embolic events. AF conveys a worse overall prognosis in MS patients than in the general population. In patients with AF and MS, 5-year survival is only 64%, compared with 85% in patients with AF but without MS.

Systemic Embolism

Systemic embolism in patients with MS is caused by LA thrombus formation. Although systemic embolization most often occurs in patients with AF, 20% of patients with MS and a systemic embolic event are in sinus rhythm. When embolization occurs in patients in sinus rhythm, the possibility of transient AF or underlying infective endocarditis should be considered. However, up to 45% of patients with MS who are in normal sinus rhythm demonstrate prominent spontaneous LA contrast (a marker of

embolic risk; Video 69.6) on TEE (**see Chapter 14**). Atrial thrombi have been documented in a few patients with MS in sinus rhythm, and many patients with new-onset AF have LA thrombi. It is postulated that the loss of atrial appendage contractile function, despite electrical evidence of sinus rhythm, leads to blood flow stasis and thrombus formation. Additional evidence implicates inflammatory markers, endothelial dysfunction, and platelet activation as inciting mechanisms for thromboembolism.[26,27]

The risk of embolism correlates directly with patient age and LA size[28] and inversely with the cardiac output. Before the advent of surgical treatment, this serious complication of MS developed in at least 20% of patients at some time during the course of their disease. Before the era of anticoagulant therapy and surgical treatment, approximately 25% of all fatalities in patients with MS were secondary to systemic embolism.

Approximately half of all clinically apparent emboli are found in the cerebral vessels. Coronary embolism may lead to myocardial infarction (MI) and angina pectoris, and renal emboli may be responsible for the development of systemic hypertension. Emboli are recurrent and multiple in approximately 25% of patients who develop this complication. Rarely, massive thrombosis develops in the left atrium, resulting in a pedunculated ball-valve thrombus, which may suddenly aggravate obstruction to LA outflow when a specific body position is assumed or may cause sudden death. Similar consequences occur in patients with free-floating thrombi in the left atrium. These two conditions usually are characterized by variability in the physical findings, often on a positional basis. They are very hazardous and necessitate surgical treatment, often on an emergency basis.

Infective Endocarditis

MS is a predisposing factor for endocarditis in less than 1% of cases in clinical series of bacterial endocarditis (**see Chapter 73**). The estimated risk of endocarditis in patients with MS is 0.17 per 1000 patient-years, which is much lower than the risk in patients with MR or aortic valve disease.

Medical Management

Drug Treatment

The medical management of MS is directed primarily toward (1) prevention of recurrent rheumatic fever, (2) prevention and treatment of complications of MS, and (3) monitoring disease progression to allow intervention at the optimal time.[3] Patients with MS caused by rheumatic heart disease should receive penicillin prophylaxis for beta-hemolytic streptococcal infections to prevent recurrent rheumatic fever, per established guidelines (**see Chapter 74**). Prophylaxis for infective endocarditis is no longer recommended (**Chapter 73**). Anemia and infections should be treated promptly and aggressively in patients with valvular heart disease. Of note, however, blood cultures should always be considered before initiation of antibiotic therapy in patients with valve disease, because the presentation of endocarditis often is mistaken for a noncardiac infection.

Anticoagulation with vitamin K antagonists (VKAs) for prevention of systemic embolism is warranted in any patient with MS and AF, prior embolism, or known thrombus in the LA cavity or appendage.[21] Anticoagulation also may be considered for patients with severe MS and sinus rhythm when there is severe LA enlargement (diameter >55 mm) or spontaneous contrast on echocardiography. Treatment with warfarin is used to maintain the international normalized ratio (INR) between 2 and 3.[29] Few data address the safety and utility of novel oral anticoagulants (NOACs) in MS, because such patients were generally excluded from all NOAC trials (**see Chapter 93**), although there has been a recent publication calling for

a randomized trial to test VKAs and NOACs in patients with MS.[30]

Asymptomatic patients with mild to moderate rheumatic mitral valve disease should have a history and physical examination annually, with echocardiography every 3 to 5 years for mild stenosis, every 1 to 2 years for moderate stenosis, and annually for severe stenosis. More frequent evaluation is appropriate for any change in signs or symptoms. All patients with significant MS should be advised to avoid occupations requiring strenuous exertion.

In patients with severe MS, with persistent symptoms after intervention or when intervention is not possible, medical therapy with oral diuretics and the restriction of sodium intake may improve symptoms. Digitalis glycosides do not alter the hemodynamics and usually do not benefit patients with MS and sinus rhythm, but these drugs are of value in slowing the ventricular rate in patients with AF and in treating patients with right-sided HF. Hemoptysis is managed by measures designed to reduce pulmonary venous pressure, including sedation, assumption of the upright position, and aggressive diuresis. Beta-adrenergic blocking agents and rate-slowing calcium antagonists may increase exercise capacity by reducing heart rate in patients with sinus rhythm, especially in patients with AF.

Treatment of Arrhythmias.

AF is a frequent complication of severe MS. Management of AF for patients with MS is similar to management for AF of any cause (**see Chapter 38**). However, it typically is more difficult to restore and maintain sinus rhythm because of pressure overload of the left atrium in conjunction with effects of the rheumatic process on atrial tissue and the conducting system.

Immediate treatment of AF includes administration of intravenous (IV) heparin followed by oral warfarin. The ventricular rate should be slowed, as stated in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of AF,[29] initially with an IV beta blocker or nondihydropyridine calcium channel antagonist, followed by long-term rate control with oral doses of these agents. When these medications are ineffective or when additional rate control is necessary, digoxin or amiodarone may be considered. Digoxin alone for long-term management of AF may be considered in patients with concurrent LV dysfunction or a sedentary lifestyle. An effort should be made to reestablish sinus rhythm by a combination of pharmacologic treatment and cardioversion. If cardioversion is planned in a patient who has had AF for more than 24 hours before the procedure, anticoagulation with warfarin for more than 3 weeks is indicated. Alternatively, if TEE results show no atrial thrombus, immediate cardioversion can be carried out provided the patient is effectively anticoagulated with IV heparin before and during the procedure and with warfarin chronically thereafter. Paroxysmal AF and repeated conversions, spontaneous or induced, carry the risk of embolization. In patients who cannot be converted or maintained in sinus rhythm, beta blockers or digitalis should be used to maintain the ventricular rate at rest at approximately 60 beats/min. Beta blockers are particularly helpful in preventing rapid ventricular responses that develop during exertion. Multiple repeat cardioversions are not indicated if the patient fails to sustain sinus rhythm while receiving adequate doses of an antiarrhythmic.

Patients with chronic AF who undergo surgical mitral valve repair or replacement may undergo the maze procedure. More than 80% of patients undergoing this procedure can be maintained in sinus rhythm postoperatively and can regain normal atrial function, including a satisfactory success rate in those with significant LA enlargement. Early intervention with percutaneous valvotomy may prevent the development of AF.

Mitral Valvotomy

Percutaneous Balloon Mitral Valvotomy

Patients with mild to moderate MS who are asymptomatic frequently remain so for years, and clinical outcomes are similar to those in age-matched normal individuals. Severe or symptomatic MS, however, is associated with poor long-term outcomes if the stenosis is not relieved mechanically (**see eFig. 69.2**). Percutaneous BMV is the procedure of choice for the treatment of MS; surgical intervention is now reserved for patients who require intervention and are not candidates for a percutaneous procedure[8] (**see Chapter 72**).

BMV is recommended for symptomatic patients with moderate to severe MS (i.e., MVA <1 cm^2/m^2 of body surface area [BSA] or <1.5 cm^2 in normal-sized adults) and with favorable valve morphology, no or mild MR, and no evidence of LA thrombus (**Fig. 69.4**). Even mild symptoms, such as a subtle decrease in exercise tolerance, are an indication for intervention because the procedure relieves symptoms and improves long-term outcome with a low procedural risk. In addition, BMV is a reasonable option for asymptomatic patients with very severe MS (<1 cm^2) with favorable valve anatomy or when mitral valve obstruction has resulted in AF.[21] Of note, AF precipitates symptoms in most patients with significant MS.

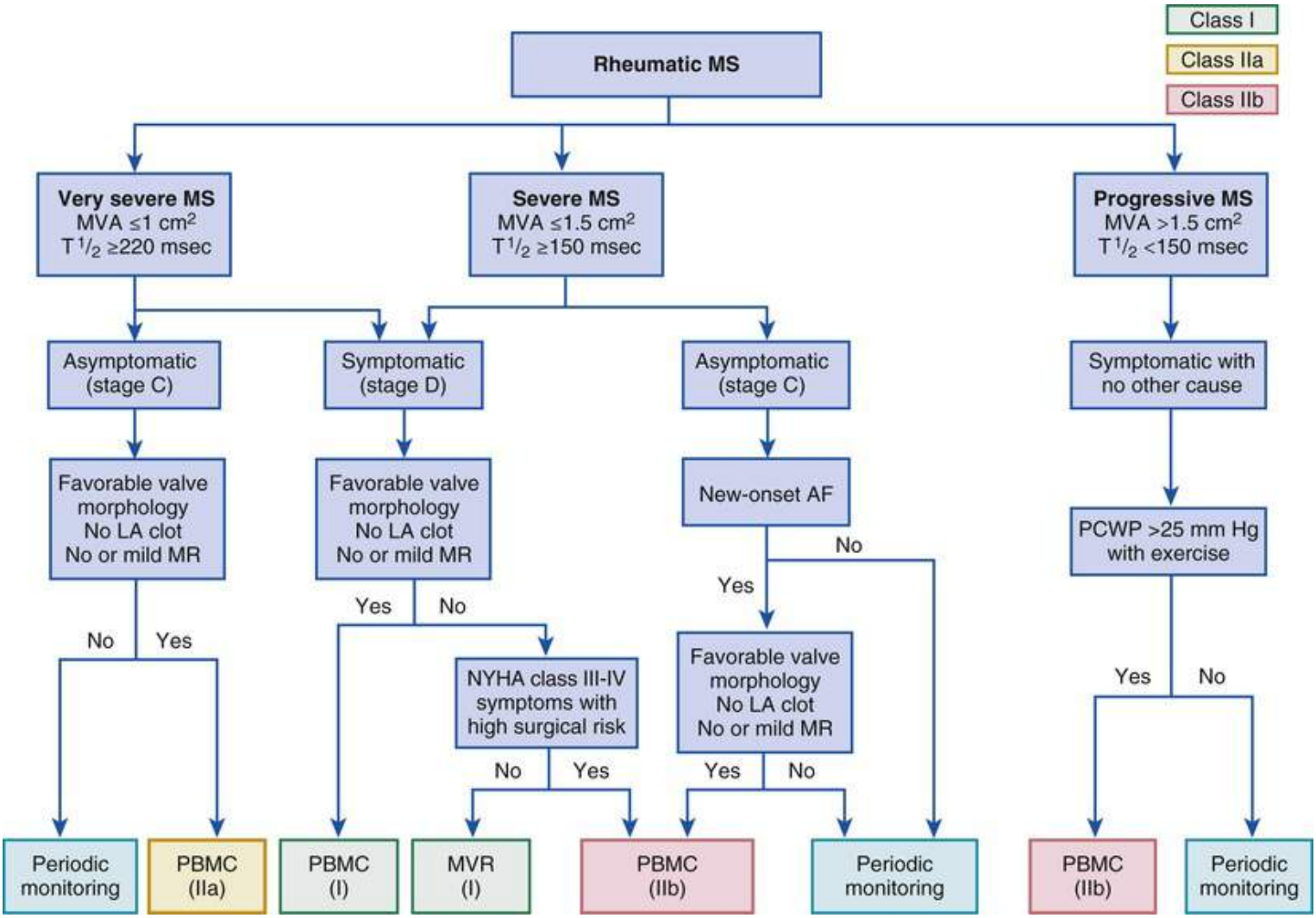


FIGURE 69.4 Indications for intervention for rheumatic mitral stenosis (MS). AF, Atrial fibrillation; LA, left atrial; MR, mitral regurgitation; MVA, mitral valve area; MVR, mitral valve surgery (repair or replacement); PBMC, percutaneous balloon mitral commissurotomy; PCWP, pulmonary capillary wedge pressure; $T_{1/2}$, pressure half-time. (From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACCF guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57-185.)

BMV also may be considered in symptomatic patients in whom surgery carries high risk for adverse events or outcomes, even when valve morphology is not ideal, including patients with restenosis after a previous BMV or previous surgical commissurotomy who are unsuitable candidates for surgery because of very high risk. These include very old, frail patients; patients with associated severe ischemic heart disease; patients in whom MS is complicated by pulmonary, renal, or neoplastic disease; women of childbearing age in whom mitral valve replacement is undesirable; and pregnant women with MS.

BMV may be further considered for patients with mild MS in whom symptoms cannot be explained by other causes and who experience pulmonary hypertension (PCWP >25 mm Hg) with exercise (**see Fig. 69.4**). In this last group, it is likely that valve obstruction is the cause of pulmonary hypertension, even when stenosis severity does not meet the valve area criteria for severe obstruction.

This percutaneous technique consists of advancing a small balloon flotation catheter across the interatrial septum (after transseptal puncture), enlarging the opening, advancing a large (23- to 25-mm) hourglass-shaped (Inoue) balloon, and inflating it within the orifice[19,31] (**Fig. 69.5**; **see also Fig. 72.6**; Video 69.7). Alternatively, two smaller (15- to 20-mm) side-by-side balloons across the mitral orifice may be used. A third technique involves retrograde, nontransseptal dilation of the mitral valve, in which the balloon is positioned across the mitral valve using a steerable guidewire.

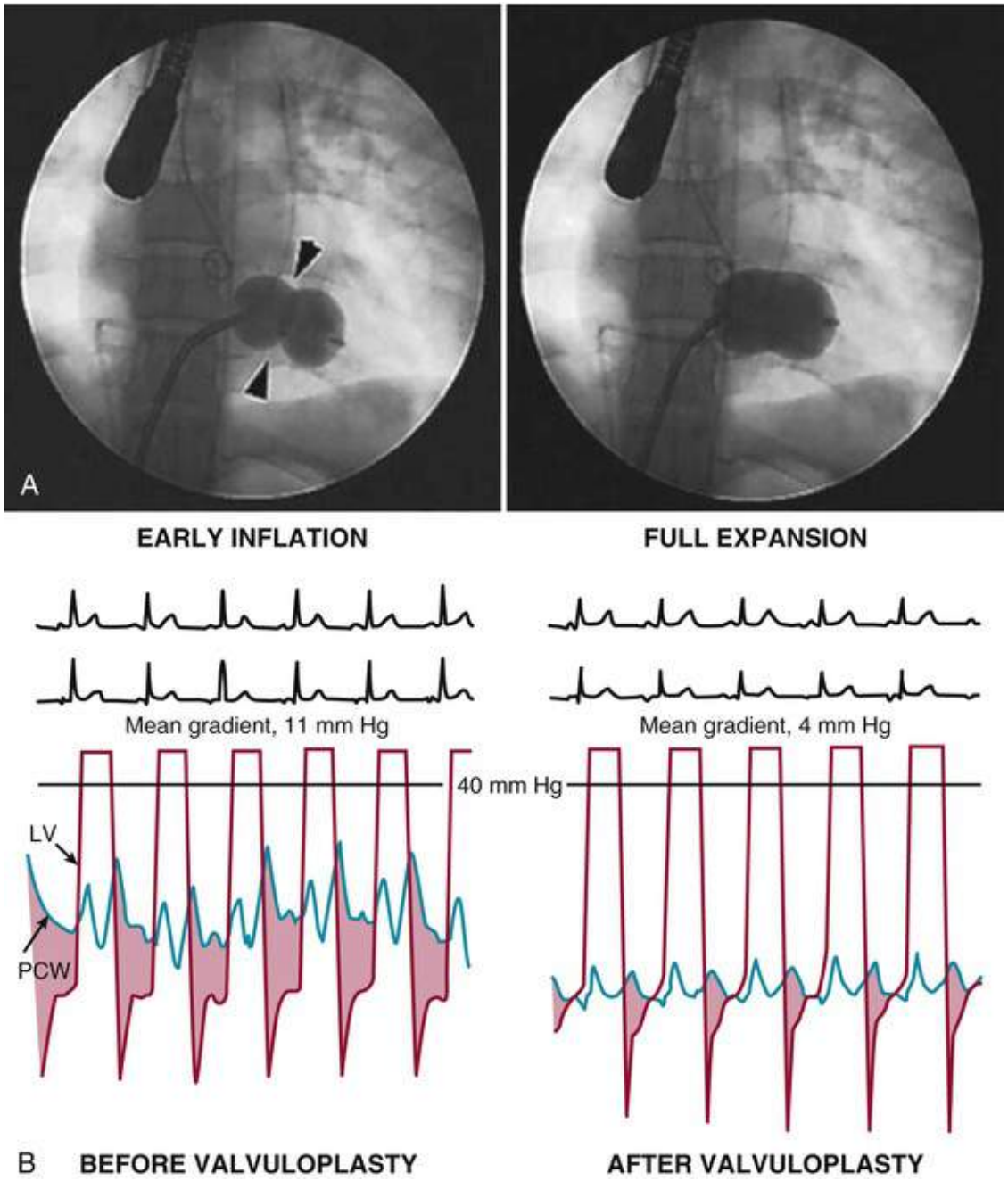
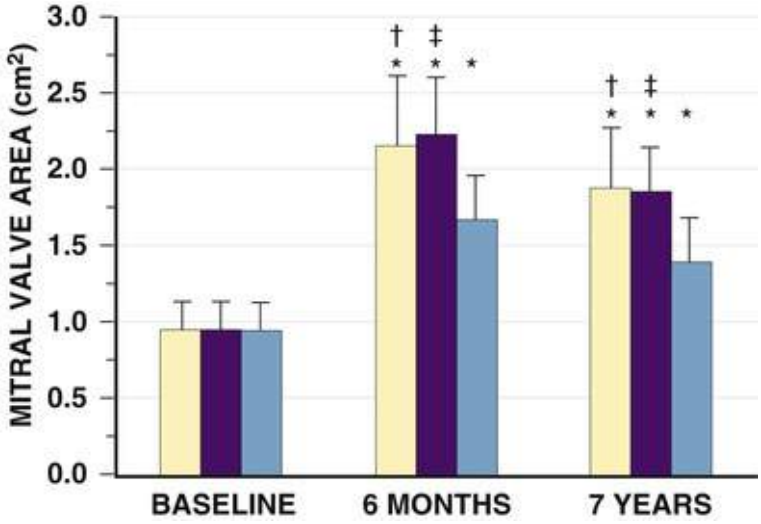


FIGURE 69.5 Percutaneous balloon mitral valvotomy (BMV) for mitral stenosis using the Inoue technique (**see Chapter 72**). **A,** The catheter is advanced into the left atrium using the transseptal technique and guided in antegrade fashion across the mitral orifice. As the balloon is inflated, its distal portion expands first; this is pulled back so that it fits snugly against the orifice (*arrowheads*). With further inflation, the proximal portion of the balloon expands to center the balloon within the stenotic orifice **(left).** Further inflation expands the central "waist" portion of the balloon **(right),** resulting in commissural splitting and enlargement of the orifice. **B,** Successful BMV results in significant increase in mitral valve area, as reflected by a reduction in the diastolic pressure gradient between left ventricle (*magenta*) and pulmonary capillary wedge (PCW) (*blue*) pressure, as indicated by the *shaded* area. (From Delabays A, Goy JJ. Images in clinical medicine: percutaneous mitral valvuloplasty. N Engl J Med 2001;345:e4.)

Commissural separation and fracture of nodular calcium appear to be the mechanisms responsible for improvement in valvular function. In several series, the hemodynamic results of BMV have been favorable (**eFig. 69.3**), with reduction of the transmitral pressure gradient from an average of approximately 18 to 6 mm Hg (**see Chapter 72**), a small (average, 20%) increase in cardiac output, and an average doubling of the calculated MVA, from 1 to 2 cm^2.[8,19,31] Results are especially impressive in younger patients without severe valvular thickening or calcification (**see Fig. 69.1**). Elevated PVR declines rapidly, although usually not completely. The reported mortality rate has ranged from 1% to 2%. Complications include cerebral emboli and cardiac perforation, each in approximately 1% of patients,

and development of MR severe enough to require operation in another 2% (approximately 15% develop lesser, but still undesirable, degrees of MR).[32] Approximately 5% of patients are left with a small, residual atrial septal defect (ASD), but this closes or decreases in size in most. Rarely, the ASD is large enough to cause right-sided HF; this complication most often is seen in conjunction with an unsuccessful mitral valvotomy.



EFIGURE 69.3 Mitral valve area before and 6 months and 7 years after valvotomy in a prospective, randomized trial of balloon mitral valvotomy (BMV) (*yellow bars*), open surgical mitral commissurotomy (OMC) (*purple bars*), and closed mitral commissurotomy (CMC) (*blue bars*). At 6 months and 7 years, results with BMV were equivalent to those with OMC and superior to those with CMC. *P < 0.001 compared to baseline value; †*P* < 0.001 for BMV versus CMC; ‡*P* < 0.001 for OMC versus CMC. (From Ben Farhat B, Ayari M, Maatouk F, et al. Percutaneous balloon versus surgical closed and open mitral commissurotomy: seven-year follow-up results of a randomized trial. Circulation 1998;97:245-50.)

The likelihood of hemodynamic benefit and the risk of complication with BMV are predicted by anatomic features of the stenosed valve (Video 69.8). Rigid thickened valves with extensive subvalvular fibrosis and calcification lead to suboptimal results. One echocardiographic scoring system divides patients into three groups: those with a pliable, noncalcified anterior leaflet and minimal chordal disease (group 1); those with a pliable, noncalcified anterior leaflet but with chordal thickening and shortening (<10 mm long) (group 2); and those with fluoroscopic evidence of calcification of any extent of the valve apparatus (group 3).[8] Event-free survival at 3 years is highest for group 1 (89%), compared with group 2 (78%) or group 3 (65%). With an alternate echocardiographic scoring system (Wilkins score), leaflet rigidity, leaflet thickening, valvular calcification, and subvalvular disease are each scored from 0 to 4 (**see Table 14.9**).[3,19,21] A score of 8 or lower usually is associated with an excellent immediate- and long-term result, whereas scores exceeding 8 are associated with less impressive results (**Fig. 69.6**; **see also Fig. 72.7**), including increased risk of development of MR. Commissural calcification also is a predictor of poor outcomes.

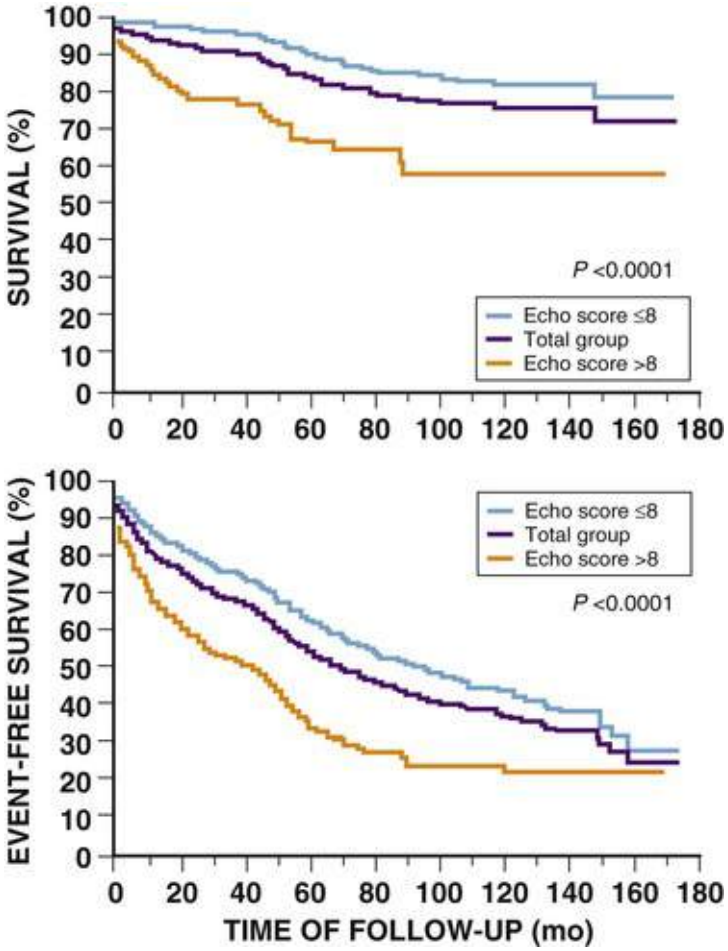


FIGURE 69.6 Long-term survival **(top)** and event-free survival **(bottom)** after balloon mitral valvotomy (BMV) for 879 patients who were stratified by baseline echocardiographic (Echo) morphology score of 8 or less (*blue line*) or more than 8 (*gold line*). Events include death, repeat BMV, and surgical mitral valve replacement. Patients with the lower Echo score had a significantly better outcome initially and over the next 12 to 13 years. (From Palacios IF, Sanchez PL, Harrell LC, et al. Which patients benefit from percutaneous mitral balloon valvuloplasty? Prevalvuloplasty and postvalvuloplasty variables that predict long-term outcome. Circulation 2002;105:1465-71.)

TEE should be performed just before BMV to exclude LA thrombus and confirm that MR is not moderate or severe. TEE also is appropriate for evaluating MS severity and mitral valve morphology when transthoracic images are suboptimal, although the chordal apparatus on TEE is less well visualized compared with transthoracic imaging. During the procedure, transthoracic, transesophageal, or intracardiac echocardiography is used to monitor placement of the catheters and balloon, assess hemodynamic results after each inflation, and detect complications such as MR.

In patients with suitable anatomic findings, long-term results are favorable, with excellent survival rates without functional disability or need for surgery or repeat BMV.[3,31] Patients with severe MS randomly assigned to undergo BMV, closed surgical valvotomy, or open surgical valvotomy had similar clinical outcomes for BMV and open surgery that were superior to closed surgical valvotomy. After 7 years, MVA was equivalent in the BMV and open surgery groups, both significantly greater than in the closed valvotomy group (**eFig. 69.3**). In another randomized study that included older patients with less favorable valve morphology, compared with open surgical commissurotomy, patients randomly assigned to undergo BMV had a smaller increase in MVA and higher likelihood of restenosis (28% versus 18% at 4 years). Excellent results also have been reported in children and adolescents in developing nations, where patients tend to be younger. These young patients usually have pliable valves, which are ideal for BMV. It has also been shown that suitable candidates who have restenosed after prior commissurotomy can still be effectively treated with BMV.[33]

Surgical Valvotomy

Three operative approaches are available for the treatment of rheumatic MS: (1) closed mitral valvotomy (CMV) using a transatrial or transventricular approach; (2) open valvotomy (i.e., valvotomy done under direct vision with the aid of cardiopulmonary bypass [CPB]), which may be combined with other repair techniques, such as leaflet resection or augmentation, chordal procedures, and annuloplasty when MR is present; and (3) mitral valve replacement (**Table 69.2**).[34] Surgical intervention for MS is recommended for patients with severe MS and significant symptoms (NYHA Class III or IV) when BMV is not available, when BMV is contraindicated because of persistent LA thrombus or moderate to severe MR, or when the valve is calcified and surgical risk is acceptable. The preferred surgical approach is valve repair (open valvotomy, with or without additional procedures) whenever possible, although since patients referred for surgery often have poor morphology for BMV, valve replacement is often the best choice. Surgery also is reasonable for patients with severe MS and severe pulmonary hypertension when BMV is not possible and may be considered for patients with moderate to severe MS with recurrent embolic events despite anticoagulation.

TABLE 69.2

Approaches to Mechanical Relief of Mitral Stenosis

APPROACH	ADVANTAGES	DISADVANTAGES
Closed surgical valvotomy	Inexpensive Relatively simple Good hemodynamic results in selected patients Good long-term outcome	No direct visualization of valve Only feasible with flexible, noncalcified valves Contraindicated with MR grade higher than 2+ Surgical procedure with general anesthesia
Open surgical valvotomy	Visualization of valve allows directed valvotomy. Concurrent annuloplasty for MR is feasible.	Best results with flexible, noncalcified valves Surgical procedure with general anesthesia
Valve replacement	Feasible in all patients regardless of extent of valve calcification or severity of MR	Surgical procedure with general anesthesia Effect of loss of annular-papillary muscle continuity on LV function Prosthetic valve Chronic anticoagulation
Balloon mitral valvotomy	Percutaneous approach Local anesthesia Good hemodynamic results in selected patients Good long-term outcome	No direct visualization of valve Only feasible with flexible noncalcified valves Contraindicated with MR grade higher than 2+

LV, Left ventricular; *MR,* mitral regurgitation.

Closed Mitral Valvotomy.

CMV is rarely used now in the United States, having been replaced by BMV, which is more effective in patients who are CMV candidates. CMV is more popular in developing nations, where the expense of open heart surgery and even of balloon catheters for BMV is an important factor, and where patients with MS are younger and therefore have more pliable valves. However, even in these nations, CMV is being replaced by BMV, with balloon resterilization to keep the procedure economical.

CMV is performed without CPB but with the aid of a transventricular dilator. It is an effective operation, provided that MR, atrial thrombosis, or valvular calcification is not serious and that chordal fusion and shortening are not severe. Echocardiography is useful for selecting suitable candidates for CMV by identifying patients without valvular calcification or dense fibrosis. If possible, CMV should be carried out with pump standby; if the surgeon is unable to achieve a satisfactory result, the patient can be placed on CPB and the valvotomy performed under direct vision or the valve replaced.

On average, MVA is increased by 1 cm^2, with only 20% to 30% of patients requiring mitral valve

replacement within 15 years. The hospital mortality rate is 1% to 2% in experienced centers. Marked symptomatic improvement occurs in most patients, and those selected with low echocardiographic scores have excellent long-term survival. Long-term follow-up has shown that the results are best if the operation is carried out before chronic AF, severe pulmonary hypertension, or HF has occurred,[34] and complication rates are higher when valves are calcified or severely thickened.

Open Mitral Valvotomy.

Most surgeons now prefer to carry out direct-vision or open valvotomy. This operation is most frequently performed in patients with MS whose mitral valves are too distorted or calcified for BMV. CPB is established and, to obtain a dry, quiet heart, body temperature is usually lowered, the heart is arrested, and the aorta is occluded intermittently. Thrombi are removed from the left atrium and its appendage, and the latter often is amputated to remove a potential source of postoperative emboli. The commissures are incised, and when necessary, fused chordae tendineae are separated, the underlying papillary muscle is split, and the valve leaflets are débrided of calcium. Mild or even moderate MR may be corrected using similar repair approaches as for primary MR. Intraoperative echocardiography (or, if not available, LA and LV pressures) is used after bypass has been discontinued to confirm that the valvotomy has been effective. When it has not been effective, another attempt can be made. If repair is not possible—usually because of severe distortion and calcification of the valve and subvalvular apparatus, with accompanying MR that cannot be corrected—mitral valve replacement (MVR) should be done. In patients with AF, an LA maze or AF ablation procedure typically is done at surgery to increase the likelihood of maintaining long-term sinus rhythm. Open valvotomy is feasible and successful in more than 80% of patients referred for this procedure, with an operative mortality of 1%, rate of reoperation for MVR of 0% to 16% at 36 to 53 months, and 10-year actuarial survival rates of 81% to 100%.

Restenosis After Valvotomy

Mitral valvotomy, whether percutaneous or operative and open or closed, is palliative rather than curative and, even when successful, there is some degree of residual mitral valve dysfunction. Because the valve is not normal postoperatively, turbulent flow usually persists in the paravalvular region, and the resultant trauma may play a role in restenosis. These changes are analogous to the gradual development of obstruction in a congenitally bicuspid aortic valve and are not usually the result of recurrent rheumatic fever. It is likely that the process of superimposed leaflet calcification and increased stiffness superimposed on the rheumatic valve is similar to the calcific changes seen in aortic valve stenosis.

On clinical grounds alone, based on the reappearance of symptoms, the incidence of restenosis has been estimated to range widely, from 2% to 60%. Recurrence of symptoms is often not caused by restenosis but may be caused by one or more of the following conditions: (1) an inadequate first procedure with residual stenosis; (2) increased severity of MR, either at operation or developing consequently, sometimes from infective endocarditis; (3) progression of aortic or tricuspid valve disease; or (4) development of coronary artery disease (CAD). True restenosis occurs in less than 20% of patients who are followed for 10 years.[3]

Thus, in properly selected patients, mitral valvotomy, however performed—percutaneous BMV, closed or open surgical valvotomy—is a low-risk procedure that results in a significant increase in the size of the mitral orifice and favorably alters the clinical course of an otherwise progressive disease. PAP falls promptly and decisively when mitral obstruction is effectively relieved. Most patients maintain clinical improvement for 10 to 15 years of follow-up. When a second procedure is required because of symptomatic deterioration, the valve is usually calcified and more seriously deformed than at the first

operation, and adequate reconstruction may not be possible. Accordingly, MVR often is necessary at that time, although in suitable patients, repeat commissurotomy can be quite effective.[33]

Mitral Valve Replacement

MVR is recommended for symptomatic patients with severe MR when BMV or surgical mitral valve repair is not possible. Usually, MVR is required for patients with combined MS and moderate or severe MR, those with extensive commissural calcification, severe fibrosis, and subvalvular fusion, and those who have undergone previous valvotomy. The operative mortality rate for isolated MVR ranges from 3% to 8% in most centers and averaged 6.04% in 16,105 such operations for patients with MS and/or MR reported in the Society of Thoracic Surgeons (STS) National Database.[35] Prosthetic valves are associated with increased risk because of valve deterioration and chronic anticoagulation, so the threshold for operation should be higher in patients in whom preoperative evaluation suggests that MVR may be required than in patients in whom valvotomy alone appears to be indicated.

Generally, a mechanical valve is preferred when MVR for MS is necessary and AF is present because of the need for chronic anticoagulation. In patients younger than 65 years who are in sinus rhythm, a mechanical valve is reasonable because of the risk of tissue valve deterioration and likely need for a second operation in the future. However, some younger patients may choose a bioprosthetic valve for lifestyle considerations, despite the risk of valve deterioration. A bioprosthetic valve is appropriate in patients who cannot take warfarin and is reasonable in all patients older than 65 years. The development of percutaneous options for MVR, particularly valve-in-valve insertion into dysfunctional mitral bioprostheses,[36] has complicated decision making in the initial operation, with some younger patients preferring bioprostheses.

MVR is indicated in patients with MS and MVA smaller than 1.5 cm^2 in NYHA Class III or IV whose valves are not suitable for valvotomy (**see Fig. 69.4**). Because the operative mortality risk may be high (10% to 20%) in NYHA Class IV patients, surgery should be carried out before patients reach this stage if possible. On the other hand, even such high-risk patients should not be denied this option unless they have comorbid conditions that preclude surgery or a satisfactory outcome.

Percutaneous Mitral Valve Replacement in Mitral Stenosis

Unlike the dramatic progress seen in the application of transcatheter aortic valve replacement (TAVR) for treatment of aortic stenosis, the development of percutaneous valve repair or replacement for MS is still in the early stages (**see Chapter 72**). Mitral clipping, approved for high-risk patients with organic MR, has no role in mitral stenosis, since the clipping only makes the valve area smaller. There have been a few case reports published where balloon-expandable transcutaneous aortic prostheses have been inserted into stenotic mitral valve, either transapically[37] or transseptally,[38] with reasonable results, but utility on a broader scale is unproved as yet.

Mitral Regurgitation

Causes and Pathology

The mitral valve apparatus involves the mitral leaflets, chordae tendineae, papillary muscles, and mitral annulus (**Fig. 69.7** and Video 69.9). Abnormalities of any of these structures may cause MR.[12,39-41] The major causes of MR include myxomatous degeneration (mitral valve prolapse [MVP] and ruptured mitral chordae), rheumatic heart disease, infective endocarditis, HCM, annular calcification, dilated cardiomyopathy (DCM), and ischemic heart disease (**eTable 69.1**). Less common causes of MR include collagen vascular diseases, trauma, the hypereosinophilic syndrome, carcinoid, and exposure to certain drugs.

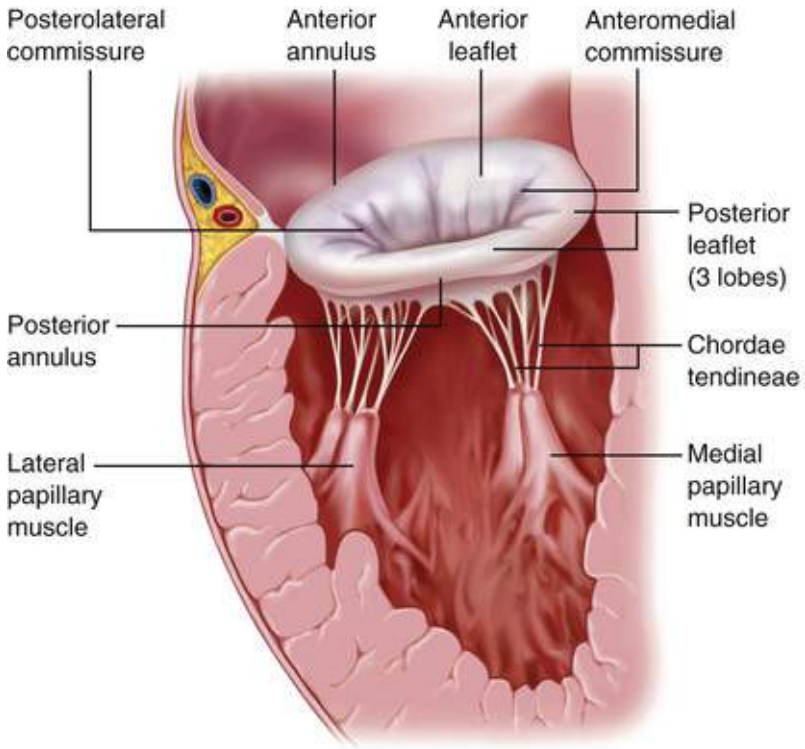


FIGURE 69.7 Continuity of the mitral apparatus and the left ventricular (LV) myocardium. Mitral regurgitation (MR) may be caused by any condition that affects the leaflets or the structure and function of the left ventricle. Similarly, a surgical procedure that disrupts the mitral apparatus in an attempt to correct MR will have adverse effects on LV geometry, volume, and function. (From Otto CM. Evaluation and management of chronic mitral regurgitation. N Engl J Med 2001;345:740-6.)

ETABLE 69.1

Causes of Acute and Chronic Mitral Regurgitation

Acute
Mitral Annulus Disorders
• Infective endocarditis (abscess formation) • Trauma (valvular heart surgery) • Paravalvular leak caused by suture interruption (surgical technical problems or infective endocarditis)
Mitral Leaflet Disorders
• Infective endocarditis (perforation or interfering with valve closure by vegetation) • Trauma (tear during percutaneous balloon mitral valvotomy or penetrating chest injury) • Tumors (atrial myxoma) • Myxomatous degeneration • Systemic lupus erythematosus (Libman-Sacks lesion)
Rupture of Chordae Tendineae
• Idiopathic (e.g., spontaneous) • Myxomatous degeneration (mitral valve prolapse, Marfan syndrome, Ehlers-Danlos syndrome) • Infective endocarditis • Acute rheumatic fever • Trauma (percutaneous balloon valvotomy, blunt chest trauma)
Papillary Muscle Disorders
• Coronary artery disease (causing dysfunction and rarely rupture) • Acute global left ventricular dysfunction • Infiltrative diseases (amyloidosis, sarcoidosis) • Trauma
Primary Mitral Valve Prosthetic Disorders
• Porcine cusp perforation (endocarditis) • Porcine cusp degeneration • Mechanical failure (strut fracture) • Immobilized disc or ball of the mechanical prosthesis
Chronic
Inflammatory
• Rheumatic heart disease • Systemic lupus erythematosus • Scleroderma
Degenerative
• Myxomatous degeneration of mitral valve leaflets (Barlow click-murmur syndrome, prolapsing leaflet, mitral valve prolapse) • Marfan syndrome • Ehlers-Danlos syndrome • Pseudoxanthoma elasticum • Calcification of mitral valve annulus
Infective
• Infective endocarditis affecting normal, abnormal, or prosthetic mitral valves
Structural
• Ruptured chordae tendineae (spontaneous or secondary to myocardial infarction, trauma, mitral valve prolapse, endocarditis) • Rupture or dysfunction of papillary muscle (ischemia or myocardial infarction) • Dilation of mitral valve annulus and left ventricular cavity (congestive cardiomyopathies, aneurysmal dilation of left ventricle) • Hypertrophic cardiomyopathy • Paravalvular prosthetic leak
Congenital
• Mitral valve clefts or fenestrations • Parachute mitral valve abnormality in association with: Endocardial cushion defects Endocardial fibroelastosis Transposition of great arteries Anomalous origin of left coronary artery

Data from Jutzy KR, Al-Zaibag M. Acute mitral and aortic valve regurgitation. In Al-Zaibag M, Duran CMG, editors. Valvular Heart Disease. New York: Marcel Dekker; 1994, pp 345-62; and Haffajee CI. Chronic mitral regurgitation. In Dalen JE, Alpert JS, editors. Valvular Heart Disease. 2nd ed. Boston: Little, Brown; 1987, p 112.

The many potential causes of MR can be broadly categorized by the type of leaflet motion abnormality proposed by Carpentier (**Fig. 69.8**), because these mechanisms also suggest strategies for surgical correction.[39] Leaflet motion is normal in type I, increased in type II, and restricted in type III (restricted opening in IIIa and restricted closure in IIIb). In general, types II and IIIa usually are caused by primary disorders of the valve leaflets, whereas types I and IIIb have relatively normal leaflets, which are distorted by LV and annular remodeling causing secondary MR. The surgeon's view of the mitral valve in classic views of these four conditions is shown in **Fig. 69.9**. For clinical purposes, MR is classified as *primary* (or organic or degenerative) MR, caused by intrinsic disease of the mitral leaflets, and *secondary* (or functional) MR, caused by diseases of the left ventricle and/or mitral annulus. *Ischemic*

MR is a subset of secondary MR caused by regional ventricular dysfunction from prior MI. Primary and secondary MR are two distinctly different disease conditions, with different pathophysiologies, outcomes, and management considerations.

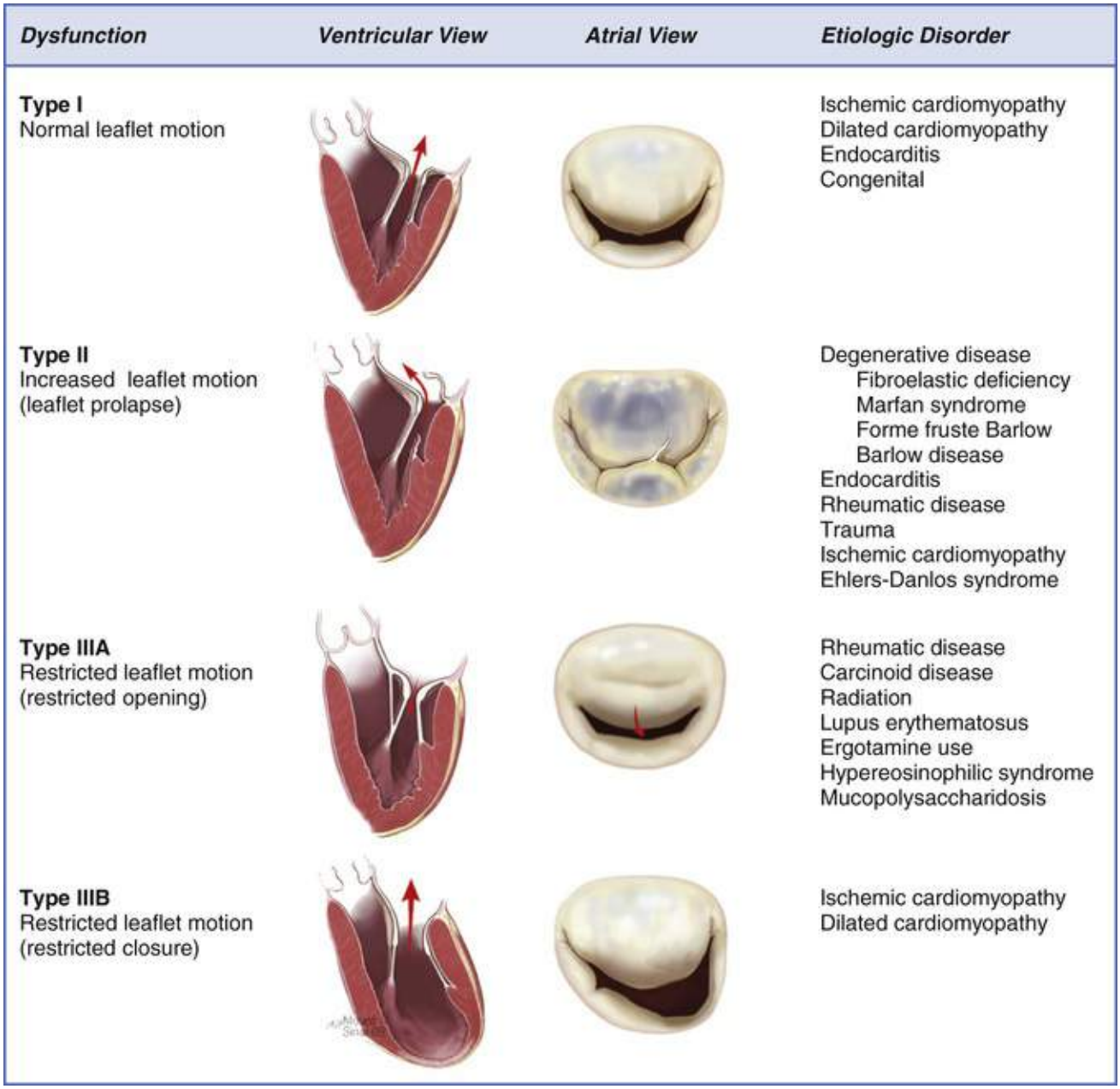


FIGURE 69.8 Pathophysiologic triad approach to mitral regurgitation (MR) and its multifactorial etiology. The mechanism of leaflet dysfunction defines the three types of MR. (From Castillo JG, Adams DH. Mitral valve repair and replacement. In Otto CM, Bonow RO, editors. Valvular Heart Disease: A Companion to Braunwald's Heart Disease. Philadelphia: Saunders; 2013, pp 327-340.)

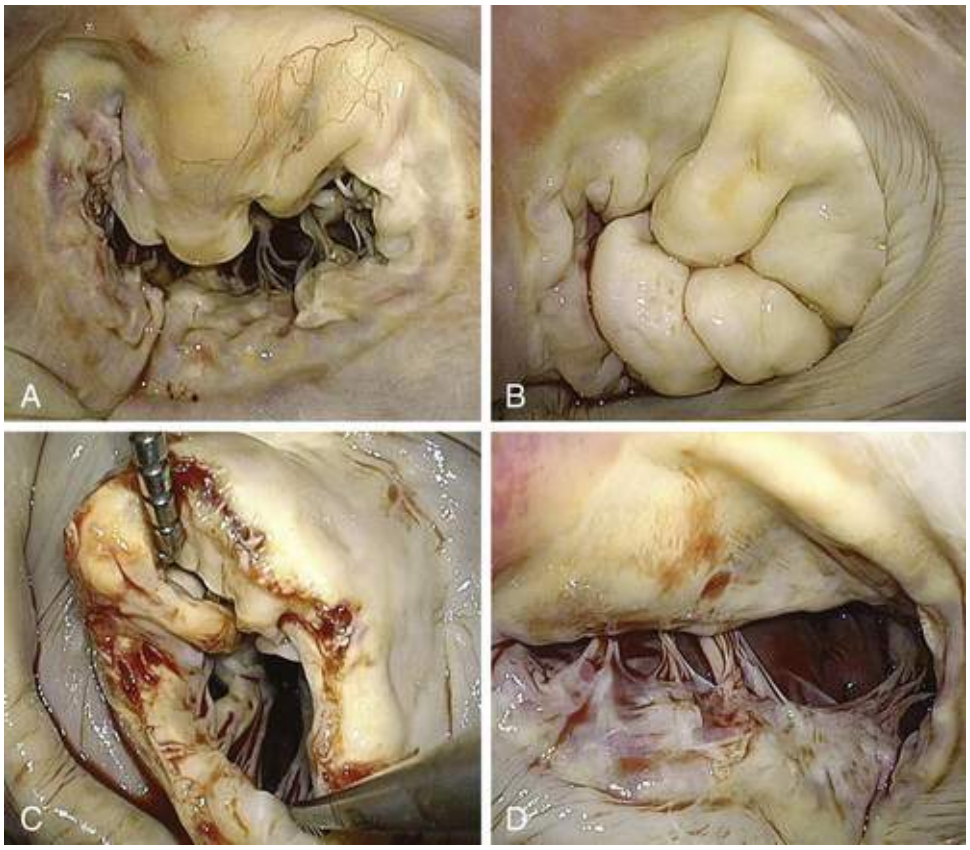


FIGURE 69.9 Valve lesions in mitral regurgitation. **A,** Severe annular dilation leading to type I dysfunction. **B,** Severe myxomatous changes with redundant, thick, and bulky segments in a patient with Barlow disease and type II dysfunction. **C,** Rheumatic mitral valve disease with classic "fish mouth" appearance and type IIIA dysfunction. **D,** Ischemic mitral valve disease caused by severe tethering of the P_3 scallop leading to type IIIB dysfunction. (From Castillo JG, Adams DH: Mitral valve repair and replacement. In Otto CM, Bonow RO, editors. Valvular Heart Disease: A Companion to Braunwald's Heart Disease. Philadelphia: Saunders; 2013, pp 327-340.)

Abnormalities of Valve Leaflets.

MR caused by primary abnormalities of the valve leaflets occurs in many situations.[39,42] In the developed world, myxomatous degeneration is the leading cause of organic MR. Intensive work in the past decade has demonstrated the mitral valve to be a dynamic structure with protein turnover and remodeling continuing throughout life. The normal mitral valve is a thin (<3 mm) endothelium-lined bileaflet structure with dense collagen on the ventricular side (fibrosa), a less stiff layer of collagen and elastin on the atrial side (atrialis), and in between a loose connective tissue layer with abundant glycosaminoglycans (spongiosa). Interspersed among the spongiosa are valvular interstitial cells (VICs), derived from endocardial endothelium, which normally are inactive.[42] In myxomatous degeneration, these VICs can be transformed to myofibroblasts, which secrete excess glycosaminoglycans and matrix metalloproteinases, leading to fragmentation of the fibrosa and atrialis and thickening of the spongiosa (**Fig. 69.10**). In turn, this reduces the tensile strength of the MV, making it prone to prolapse into the left atrium with repetitive application of ventricular pressure.[43]

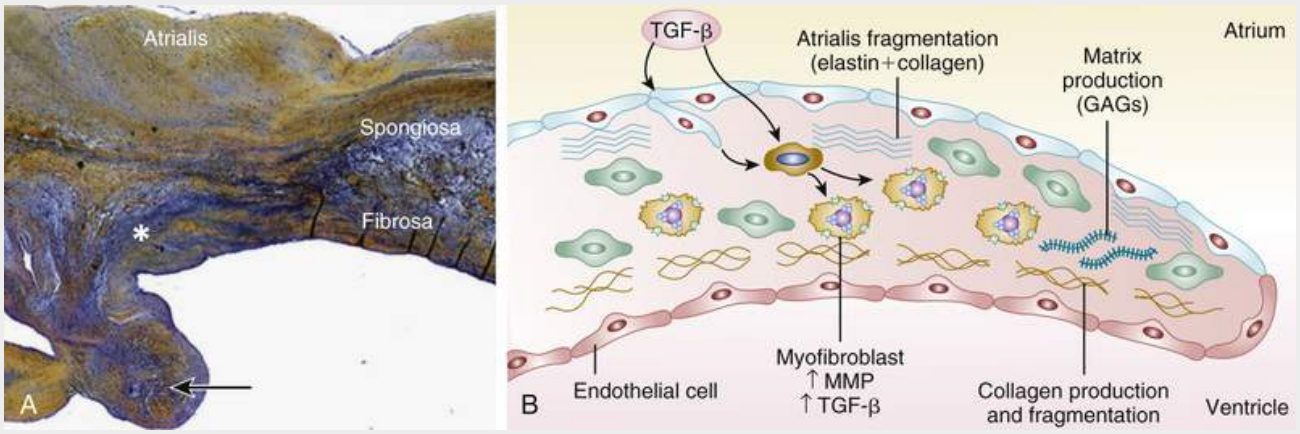


FIGURE 69.10 Mechanisms of mitral valve prolapse (MVP). **A,** Mitral valve stained with hematoxylin and eosin to define the lesion of MVP as disruption of the fibrosa by myxoid extracellular matrix (*), which also infiltrates the collagen core of the chordae tendineae, one of which was ruptured (*arrow*). The elastin lamina beneath the atrialis is also disrupted. **B,** Schematic showing the mechanism of myxomatous degeneration, with activation of valve interstitial cells to myofibroblasts that increase matrix production and turnover, secrete MMPs that drive collagen and elastin fragmentation, and release transforming growth factor (TGF)-β, which in turn promotes further cell proliferation and myofibroblast differentiation. GAGs, Glycosaminoglycans; MMP, matrix metalloproteinase. (From Levine RA, Hagege AA, Judge DP, et al. Mitral valve disease: morphology and mechanisms. Nat Rev Cardiol 2015;12:689-710.)

A minority of myxomatous degeneration cases have a clear genetic component, with MVP frequently seen in connective tissue disorders such as Marfan, Loeys-Dietz, and Ehlers-Danlos syndromes and pseudoxanthoma elasticum (**see Chapter 7**).[44] A common thread in these syndromes appears to be excessive transforming growth factor beta (TGF-β) stimulation. The more common, nonsyndromic MVP can have a genetic component, with familial clustering demonstrated in the Framingham study, but this likely involves many genes with incomplete penetrance. Although parental MVP conveyed a fivefold increased risk of MVP, the overall prevalence in the offspring was only 5.4%.[45]

Myxomatous disease occurs on a spectrum that depends on the relative degree of leaflet thickening and redundancy versus weakness in the chordae tendineae. On one extreme is *Barlow syndrome* (**see Fig. 69.9B**), with gross leaflet thickening and redundancy, multiscalloped deep prolapse, and severe regurgitation arising from multiple points along the valve closure line. At the other extreme is *fibroelastic deficiency,* with relatively thin leaflets, presenting with isolated flail of a single scallop and very focal regurgitation, which still may be severe. Intermediate forms may lie between these two extremes.[46]

Infective endocarditis can cause MR by perforating valve leaflets (**see Chapter 73**). Vegetations can prevent leaflet coaptation, and valvular retraction during the healing phase of endocarditis can cause MR. Destruction of the mitral valve leaflets can also occur in patients with penetrating and nonpenetrating trauma.

In the developing world, chronic rheumatic heart disease remains a common cause of MR. In contrast with MS, rheumatic MR is more frequent in men than in women. It is a consequence of shortening, rigidity, deformity, and retraction of one or both mitral valve cusps and is associated with shortening and fusion of the chordae tendineae and papillary muscles.

MR can also occur with exposure to certain drugs, which cause fibrotic changes in the valve leaflets.[47] Drugs associated with MR include the ergot alkaloids methysergide and ergotamine, the anorexigens (dex)fenfluramine and benfluorex, the dopamine agonists pergolide and cabergoline; and 3,4-methylenedioxymethamphetamine (MDMA, “Ecstasy”). The thickened, rigid leaflets are similar to those usually seen in the right heart in patients with carcinoid and suggest a common pathophysiologic cause of overstimulation of the serotonin 2B receptor. In carcinoid confined to the gastrointestinal tract, the excess

serotonin is metabolized in the lungs, and mitral involvement is not seen. However, with lung metastases or right-to-left shunting, mitral and aortic thickening and regurgitation may develop.

Abnormalities of the Mitral Annulus

Dilation.

In normal adults the mitral annulus measures approximately 10 cm in circumference. It is soft and flexible, and contraction of the surrounding LV muscle during systole causes the annular constriction that contributes importantly to valve closure.[2] Smooth muscle cells within the annulus and mitral leaflets themselves can also exert a sphincter action on the valve.[48] MR secondary to dilation of the mitral annulus can occur in any form of heart disease characterized by dilation of the left ventricle and/or atrium, especially DCM and longstanding AF.[49,50] LV submitral aneurysm has been reported as a cause of annular MR in sub-Saharan Africa and appears to result from a congenital defect in the posterior portion of the annulus. In addition, primary diseases of the leaflets, such as myxomatous disease, are associated with annular dilation and abnormal annular motion, which may aggravate severity of MR.[51,52]

Calcification.

Idiopathic (degenerative) calcification of the mitral annulus is often found at autopsy, generally of little functional consequence. However, when severe (**see eFig. 15.7**), it may cause MR and may even encroach on the orifice enough to cause significant MS. Mitral annular calcification shares common risk factors with atherosclerosis, including systemic hypertension, hypercholesterolemia, and diabetes; is associated with coronary and carotid atherosclerosis, as well as aortic valve calcification; and identifies patients at higher risk for cardiovascular morbidity and mortality. Annular calcification may also be accelerated by an intrinsic defect in the fibrous skeleton of the heart, as in Marfan and Hurler syndromes, where annular dilation further contributes to MR. The incidence of mitral annular calcification is also increased in patients who have chronic renal failure with secondary hyperparathyroidism, as well as with rheumatic involvement.

Abnormalities of the Chordae Tendineae.

Abnormalities of the chordae tendineae are important causes of MR (**see Fig. 14.30**). Lengthening and rupture of the chordae tendineae are cardinal features of the MVP syndrome (**see Fig. 14.40**), particularly fibroelastic deficiency. The chordae may be congenitally abnormal; rupture may be spontaneous (primary) or may result from infective endocarditis, trauma, rheumatic fever, or rarely, osteogenesis imperfecta or relapsing polychondritis. In most patients, no cause for chordal rupture is apparent other than increased mechanical strain on thin, myxomatous chordae. Chordae to the posterior leaflet rupture more frequently than those to the anterior leaflet. Depending on the number of chordae involved in rupture and the rate at which rupture occurs, the resultant MR may be mild, moderate, or severe and acute, subacute, or chronic. Chordal rupture may also occur secondary to trauma from percutaneous circulatory support devices.[53]

Involvement of the Papillary Muscles.

Diseases of the LV papillary muscles can also cause MR. Because these muscles are perfused by the terminal portion of the coronary vascular bed, they are particularly vulnerable to ischemia, and any disturbance in coronary perfusion may result in papillary muscle dysfunction. When transient, ischemia results in temporary papillary muscle dysfunction and may cause transient episodes of MR that are sometimes associated with attacks of angina pectoris or pulmonary edema. When severe and prolonged, ischemia causes papillary muscle dysfunction and scarring, as well as chronic MR. The posterior papillary muscle, which is supplied by the posterior descending branch of the right coronary artery, becomes ischemic and infarcted more frequently than the anterolateral papillary muscle; the latter is

supplied by diagonal branches of the left anterior descending coronary artery and often by marginal branches from the left circumflex artery as well. Ischemia of the papillary muscles usually is caused by coronary atherosclerosis but also may occur in patients with severe anemia, shock, coronary arteritis of any cause, or an anomalous left coronary artery. MR occurs frequently in patients with healed myocardial infarcts and most frequently is caused by regional dysfunction of the LV myocardium at the base of a papillary muscle, usually in the right coronary or left circumflex territories, resulting in tethering of the mitral leaflets and incomplete leaflet coaptation.[54,55] Although necrosis of a papillary muscle is a frequent complication of MI, frank rupture of the full papillary muscle is much less common and is often fatal because of the extremely severe MR that it produces (**see Chapters 58 and 59**). However, rupture of one or two of the apical heads of a papillary muscle can result in a flail leaflet (**see Fig. 14.29A**) with a lesser degree of MR (but still usually severe), which makes survival possible, usually with prompt surgical therapy,[56,57] although percutaneous repairs have also been reported.[58]

Various other disorders of the papillary muscles also may be responsible for the development of MR (**see Chapters 23, 61, and 77**). These disorders include congenital malposition of the muscles; absence of one papillary muscle, resulting in the so-called parachute mitral valve syndrome; and involvement or infiltration of the papillary muscles by a variety of processes, including abscesses, granulomas, neoplasms, amyloidosis, and sarcoidosis.

Left Ventricular Dysfunction.

Ischemic LV dysfunction and DCM are important causative factors in the development of MR and represent the second leading cause of MR after MVP in the United States.[55] LV dilation from any cause, including ischemia, can alter the spatial relationships between the papillary muscles and chordae tendineae and thereby result in functional MR (**see Fig. 69.6**; **see also Figs. 14.31B and 14.41**). In general, for a given amount to LV dilation, MR is greater when there is asymmetric tethering of the mitral valve from inferior and inferolateral ventricular scarring than from symmetric dilation in DCM (**Fig. 69.11**).[54]

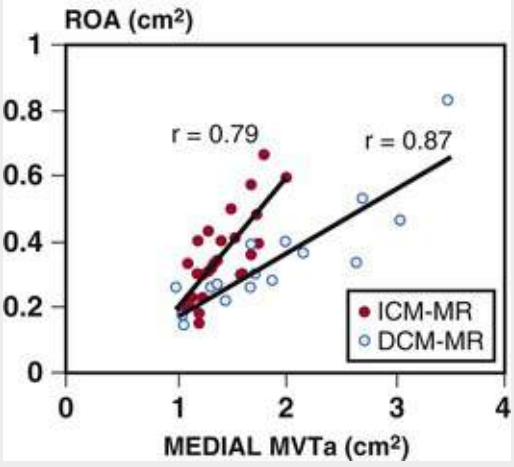


FIGURE 69.11 Significant correlations between mitral valve tethering area (MVTa) and effective regurgitant orifice area (ROA) in patients with secondary mitral regurgitation related to ischemic cardiomyopathy (ICM-MR) versus dilated cardiomyopathy (DCM-MR). For a given MVTa, patients with ICM have more severe MR than patients with DCM. (From Kwan J, Shiota T, Agler DA, et al. Geometric differences of the mitral apparatus between ischemic and dilated cardiomyopathy with significant mitral regurgitation: real-time three-dimensional echocardiography study. Circulation 2003;107:1135-40.)

Some degree of MR is found in approximately 30% of patients with CAD being considered for coronary artery bypass graft surgery (CABG). In most of these patients, MR develops from tethering of

the posterior leaflet because of regional LV dysfunction. The outlook for the patient with ischemic MR is substantially worse than for the patient with MR from other causes, because of the associated CAD, LV remodeling, and systolic dysfunction. Other pathologic changes may include additional ischemic damage to the papillary muscles, dilation of the mitral valve ring, and loss of systolic annular contraction, contributing further to MR. In most of these patients, MR is mild; however, any degree of MR is associated with a worse prognosis than in patients without MR. The incidence and severity of regurgitation vary inversely with the LV ejection fraction (EF) and vary directly with the LV end-systolic volume. MR occurs in approximately 20% of patients after acute MI and, even when mild, is associated with a higher risk of adverse outcomes.[55,59,60]

Other causes of MR include obstructive HCM (**see Chapter 78**), the hypereosinophilic syndrome, endomyocardial fibrosis, trauma affecting the leaflets and papillary muscles, Kawasaki disease, LA myxoma, and various congenital anomalies, including cleft anterior leaflet and ostium secundum ASD (**Chapters 75 and 94**).

Chronic Primary Mitral Regurgitation

Pathophysiology

Because the regurgitant mitral orifice is functionally in parallel with the aortic valve, the impedance to ventricular emptying is reduced in patients with MR. Consequently, MR enhances LV emptying. A significant proportion of the regurgitant volume is ejected into the left atrium before the aortic valve opens and after it closes. The volume of MR flow depends on a combination of the instantaneous size of the regurgitant orifice and the (reverse) pressure gradient between the left ventricle and left atrium.[61] Both the orifice size and the pressure gradient are labile. LV systolic pressure, and therefore the LV-LA gradient, depends on SVR, and LA pressure may rise dramatically with severe MR, sometimes reducing the LV-LA gradient to zero by end-systole. For patients in whom the mitral annulus has normal flexibility, the cross-sectional area of the mitral annulus may be altered by many interventions. Thus, increases in preload and afterload and depression of contractility increase LV size and enlarge the mitral annulus and thus the regurgitant orifice. When LV size is reduced by treatment with positive inotropic agents, diuretics, and particularly vasodilators, the regurgitant orifice size decreases, and the volume of regurgitant flow declines, as reflected in the height of the *v* wave in the LA pressure pulse and in the intensity and duration of the systolic murmur. Conversely, LV dilation, regardless of cause, may increase MR.

Left Ventricular Compensation

The left ventricle initially compensates for the development of acute MR by emptying more completely and by increasing preload (i.e., through Frank-Starling principle). Because acute MR reduces late systolic LV pressure and radius, LV wall tension declines markedly (and proportionately to a greater extent than LV pressure), permitting a reciprocal increase in the extent and velocity of myocardial fiber shortening and leading to a reduced end-systolic volume (ESV) (**Fig. 69.12**). When MR, particularly severe MR, becomes chronic, the LV end-diastolic volume (EDV) increases and the ESV returns to normal. By means of the Laplace principle, which states that myocardial wall tension is related to the product of intraventricular pressure and radius divided by wall thickness, the elevated LVEDV increases wall tension to normal or supranormal levels in the “chronic compensated stage” of severe MR. The resultant increase in LVEDV and mitral annular diameter may create a vicious circle in which MR leads to more MR. In patients with chronic MR, LVEDV and LV mass are increased; that is, typical volume overload

(eccentric) hypertrophy develops. However, the degree of hypertrophy is often not proportional to the degree of LV dilation, so the ratio of LV mass/EDV may be less than normal, increasing wall stress. Nonetheless, the reduced afterload permits maintenance of EF in the normal to supranormal range, giving false reassurance, as the "effective ejection fraction" (EFE, forward stroke volume divided by LVEDV) may be quite depressed, often unmasked after mitral surgery.[62,63] The reduced LV afterload allows a greater proportion of the contractile energy of the myocardium to be expended in shortening than in tension development, and explains how the left ventricle can adapt to the load imposed by MR.

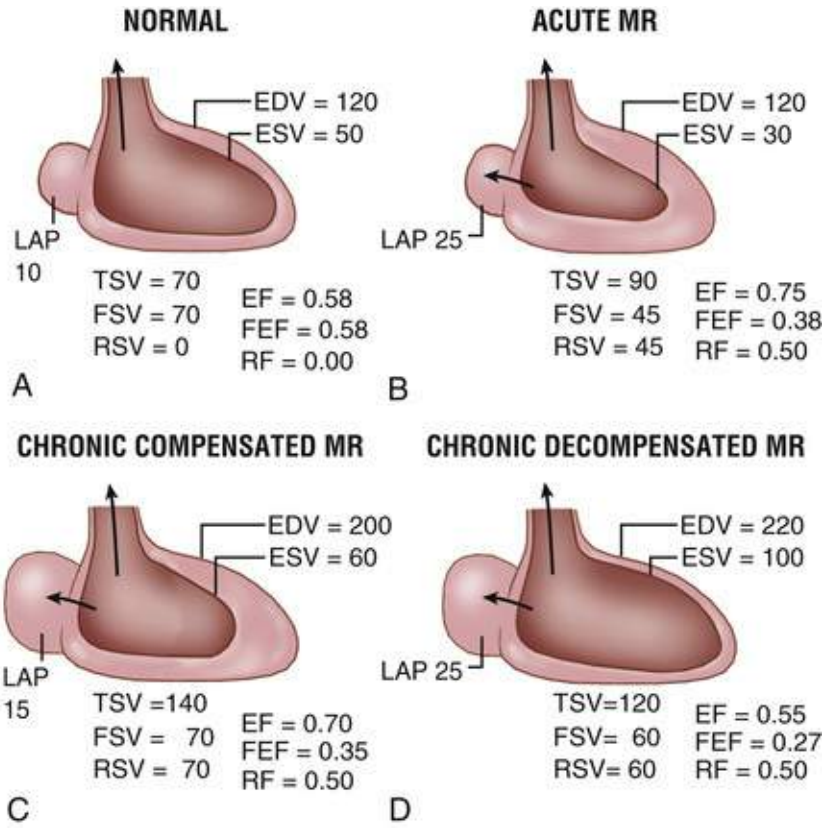


FIGURE 69.12 Three phases of mitral regurgitation are depicted and compared with **A,** normal physiology. **B,** In acute MR an increase in preload and a decrease in afterload cause an increase in end-diastolic volume (EDV) and a decrease in end-systolic volume (ESV), producing an increase in total stroke volume (TSV). Forward stroke volume (FSV) is diminished, however, because 50% of the TSV regurgitates as the regurgitant stroke volume (RSV), resulting in an increase in left atrial pressure (LAP). Although the left ventricular (LV) ejection fraction (EF) appears preserved at 0.75, in reality the forward or "effective" EF (FEF, defined as FSV/EDV) is only 0.38 with a regurgitant fraction (RF, defined as RSV/TSV) of 0.50. **C,** In the chronic compensated phase, eccentric hypertrophy has developed and EDV is now increased substantially. Afterload has returned toward normal as the radius term of the Laplace relationship increases with the increase in EDV. Normal muscle function and a large increase in EDV permit a substantial increase in TSV from the acute phase. This in turn permits a normal FSV. Left atrial enlargement now accommodates the regurgitant volume at lower LAP. EF remains greater than normal, but FEF demonstrates the inefficiency of the cardiac function. **D,** In the chronic decompensated phase, muscle dysfunction has developed, impairing EF, diminishing both TSV and FSV. The EF, although still normal, has decreased to 0.55, with FEF even lower at 0.27, and LAP is reelevated because less volume is ejected during systole, causing a higher ESV. RF has remained at 0.50 in all three regurgitation scenarios. (Illustration modified to show FEF and RF.) (Modified from Carabello BA. Progress in mitral and aortic regurgitation. Curr Probl Cardiol 2003;28:553-82.)

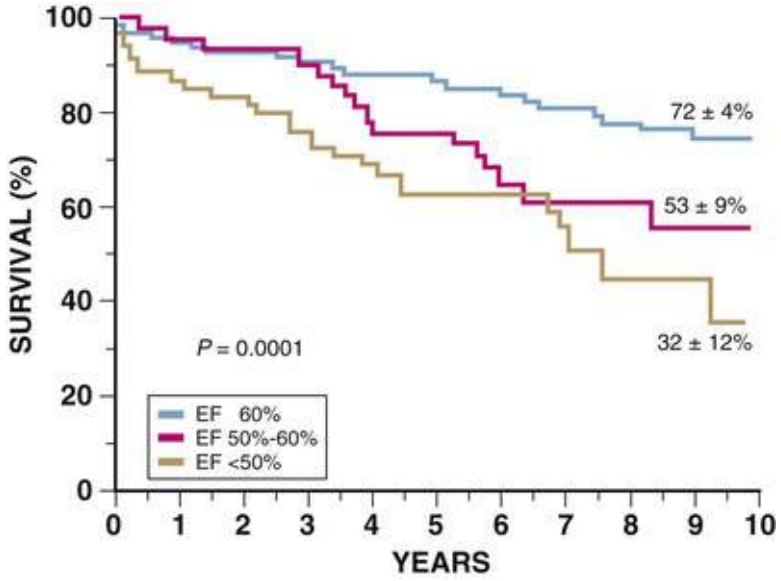
The eccentric LV hypertrophy that accompanies the elevated EDV of chronic MR is secondary to new sarcomeres laid down in series. A shift to the right (greater volume at any pressure) occurs in the LV diastolic pressure-volume curve in patients with chronic MR. With decompensation, chamber stiffness increases, raising the diastolic pressure at any volume.

In most patients with severe primary MR, compensation is maintained for years, but in some patients the prolonged hemodynamic overload ultimately leads to myocardial decompensation.[61] ESV, preload, and afterload all increase, whereas EF and stroke volume decline. In such patients, there is evidence of neurohormonal activation and elevation of circulating proinflammatory cytokines. Plasma natriuretic peptide (NP) levels also increase in response to the volume load[64]—more in patients with symptomatic decompensation.

Coronary flow rates may be increased in patients with severe MR, but the increases in myocardial oxygen consumption (MVO_2) are relatively modest compared with patients with AS and AR, because myocardial fiber shortening, which is elevated in patients with MR, is not one of the principal determinants of MVO_2 (**see Chapter 22**). One of these determinants, mean LV wall tension, may actually be reduced in patients with MR, whereas the other two, contractility and heart rate, may be minimally affected. Thus, patients with MR have a low incidence of clinical manifestations of myocardial ischemia, compared with the much higher incidence in those with AS and AR, conditions in which MVO_2 is greatly augmented.

Assessment of Myocardial Contractility

Because the ejection phase indices of myocardial contractility are inversely correlated with afterload, patients with early MR (with reduced LV afterload) often exhibit elevations in ejection phase indices of myocardial contractility, such as EF, fractional fiber shortening, and velocity of circumferential fiber shortening (VCF).[63] Many patients ultimately develop symptoms because of elevated LA and pulmonary venous pressures related to the regurgitant volume and with no change in these ejection phase indices, which remain elevated. In other patients, however, major symptoms reflect serious contractile dysfunction, at which time EF, fractional shortening, and mean VCF have declined to low-normal or below-normal levels (**see Fig. 69.12**). As MR persists, the reduction in afterload, which increases myocardial fiber shortening and the aforementioned ejection phase indices, is opposed by the impairment of myocardial function characteristic of severe chronic diastolic overload. However, even in patients with overt HF secondary to MR, the EF and fractional shortening may be only modestly reduced. Therefore, values in the low-normal range for the ejection phase indices of myocardial performance in patients with chronic MR may actually reflect impaired myocardial function, whereas moderately reduced values (e.g., EF, 40% to 50%) generally signify severe, often irreversible, impairment of contractility, identifying patients who may do poorly after surgical correction of the MR (**eFig. 69.4**). In such patients, parameters of longitudinal shortening, such as global longitudinal strain (GLS), may better predict postoperative LV dysfunction than EF.[62] An EF of less than 35% in patients with chronic severe organic MR usually represents advanced myocardial dysfunction; such patients are high operative risks and may not experience satisfactory improvement after MVR.



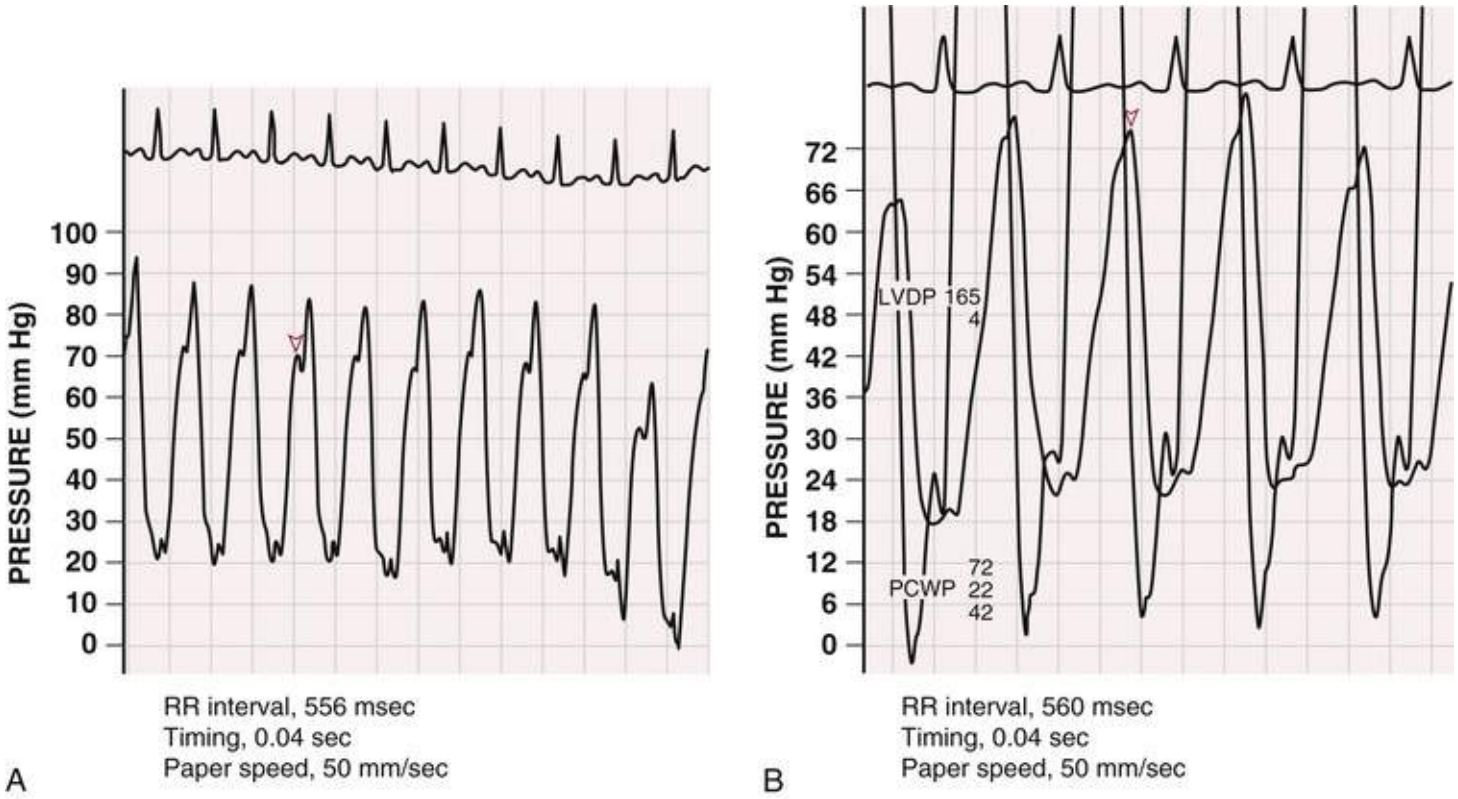
EFIGURE 69.4 Late survival of patients after surgical correction of mitral regurgitation. Patients are subdivided on the basis of the preoperative echocardiographic ejection fraction (EF). (From Enriquez-Sarano M, Tajik AJ, Schaff HV, et al. Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. Circulation 1994;90:833-7.)

End-Systolic Volume.

Preoperative myocardial contractility is an important determinant of the risk of operative death, cardiac failure perioperatively, and postoperative level of LV function. It is not surprising, therefore, that the end-systolic pressure-volume (or stress-dimension) relationship has emerged as a useful index for evaluating LV function in patients with MR. The simple measurement of end-systolic volume or diameter has been found to be a useful predictor of function and survival after mitral valve surgery.[61,65] A preoperative LV end-systolic diameter that exceeds 40 mm identifies a patient with a high likelihood of impaired LV systolic function after surgery.[21] GLS magnitude (**see Chapter 14**) less than 19.3% (a normal value in the absence of severe MR) has been shown to be more strongly predictive for postoperative LV dysfunction than traditional parameters such as EF and end-systolic diameter.[62]

Hemodynamics.

Effective (forward) cardiac output and EF are usually depressed in symptomatic patients with severe MR, whereas total LV output (the sum of forward and regurgitant flow) usually is elevated until late in the patient's course. The cardiac output achieved during exercise, not the regurgitant volume, is the principal determinant of functional capacity. The atrial contraction *a* wave in the LA pressure pulse usually is not as prominent in MR as in MS, but the *v* wave is characteristically much taller (**see Chapter 19**) because it is inscribed during ventricular systole, when the left atrium is being filled with blood from the pulmonary veins and from the left ventricle. Occasionally, backward transmission of the tall *v* wave into the pulmonary arterial bed may result in an early diastolic pulmonary arterial *v* wave (**eFig. 69.5**). In patients with isolated MR, the *y* descent in the PCWP pulse is particularly rapid because the distended left atrium empties rapidly during early diastole. However, in patients with combined MS and MR, the *y* descent is gradual. Although a left AV pressure gradient persisting throughout diastole signifies the presence of significant associated MS, a brief early diastolic gradient may occur in patients with isolated severe MR as a result of the rapid flow of blood across a normal-sized mitral orifice early in diastole, often accompanied by an early diastolic murmur at the apex.



EFIGURE 69.5 Hemodynamic tracings in a 45-year-old woman with acute mitral regurgitation from bacterial endocarditis. **A,** Pulmonary artery pressure. **B,** Simultaneous left ventricular diastolic pressure (LVDP) and pulmonary capillary wedge pressure (PCWP). The PCWP tracing demonstrates a markedly elevated *v* wave (*arrowhead*, **B**) that transmits to the pulmonary artery pressure (*arrowhead*, **A**). (Modified from Wisse B, Sniderman AD. Severe mitral regurgitation. N Engl J Med 2000;343:1386.)

Left Atrial Compliance.

The compliance of the left atrium (and pulmonary venous bed) is an important determinant of the hemodynamic and clinical picture in patients with severe MR. Three major subgroups of patients with severe MR based on LA compliance have been identified and are characterized next. These also usually correlate with the chronicity of severe regurgitation.

When severe MR develops acutely (e.g., with rupture of chordae tendineae, infarction of a papillary muscle head, leaflet disruption from trauma or endocarditis), the left atrium is initially normal in size and compliance. The pressure-volume relationship of the relaxed atrium is curvilinear, and the sudden volume load from the MR forces it to operate on a steeper portion of this curve, with an exaggerated rise in pressure (*v* wave) for a given regurgitant volume. This marked elevation of mean LA pressure leads to pulmonary congestion as a prominent symptom. Sinus rhythm usually is present, at least initially. Over time, the left atrium dilates, and its wall becomes hypertrophied to maintain contractile function. Chamber dilation shifts the pressure-volume curve to the right, increasing compliance at a given volume, whereas hypertrophy has the opposite effect, shifting the curve upward. The balance of these two remodeling processes will determine the overall impact on mean LA pressure and the *v* wave. As severe MR becomes chronic, dilation predominates, and the *v* wave may fall with an increase in operating compliance. If symptoms are tolerated (or nonexistent), this stage may last years, with progressive LA enlargement, which increases the risk of AF. At the extremes, patients may present with massive atrial enlargement and greatly increased compliance, with relatively modest LA pressure elevation. AF is likely, and the atrial wall may largely be replaced by fibrous tissue.

Clinical Presentation

The clinical stages of primary chronic degenerative MR demonstrate the progressive nature of the disease (**Table 69.3**).

TABLE 69.3

Stages of Chronic Primary Mitral Regurgitation (MR)

STAGE	DEFINITION	VALVE ANATOMY	VALVE HEMODYNAMICS*	HEMODYNAMIC CONSEQUENCES	SYMPTOMS
A	**At risk for MR**	Mild MVP with normal coaptation Mild valve thickening and leaflet restriction	No MR jet or small central jet area <20% LA on Doppler Small vena contracta <0.3 cm	None	None
B	**Progressive MR**	Severe MVP with normal coaptation Rheumatic valve changes with leaflet restriction and loss of central coaptation Previous IE	Central jet MR 20-40% LA or late systolic eccentric jet MR Vena contracta <0.7 cm RVol <60 mL RF <50% ERO <0.40 cm^2 Angiographic grade 1-2+	Mild LA enlargement No LV enlargement Normal pulmonary pressure	None
C	**Asymptomatic severe MR**	Severe MVP with loss of coaptation or flail leaflet Rheumatic valve changes with leaflet restriction and loss of central coaptation Previous IE Thickening of leaflets with radiation heart disease	Central jet MR >40% LA or holosystolic eccentric jet MR Vena contracta ≥0.7 cm RVol ≥60 mL RF ≥50% ERO ≥0.40 cm^2 Angiographic grade 3-4+	Moderate or severe LA enlargement LV enlargement Pulmonary hypertension may be present at rest or with exercise. *C1*: LVEF >60% and LVESD <40 mm *C2*: LVEF ≤60% and LVESD ≥40 mm	None
D	**Symptomatic severe MR**	Severe MVP with loss of coaptation or flail leaflet Rheumatic valve changes with leaflet restriction and loss of central coaptation Previous IE Thickening of leaflets with radiation heart disease	Central jet MR >40% LA or holosystolic eccentric jet MR Vena contracta ≥0.7 cm RVol ≥60 mL RF ≥50% ERO ≥0.40 cm^2 Angiographic grade 3-4+	Moderate or severe LA enlargement LV enlargement Pulmonary hypertension present	Decreased exercise tolerance Exertional dyspnea

*Several valve hemodynamic criteria are provided for assessment of MR severity, but not all criteria for each category will be present in each patient. Classification of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.

ERO, Effective regurgitant orifice; *IE,* infective endocarditis; *LA,* left atrium; *LVEF,* left ventricular ejection fraction; *LVESD,* left ventricular end-systolic dimension; *MVP,* mitral valve prolapse; *RF,* regurgitant fraction; *RVol,* regurgitant volume.

From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACCF guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57-185.

Symptoms

The nature and severity of symptoms in patients with chronic MR are functions of a combination of interrelated factors, including the severity of MR; rate of its progression; level of LA, pulmonary venous, and pulmonary arterial pressures; presence of episodic or chronic atrial tachyarrhythmias; and presence of associated valvular, myocardial, or coronary artery disease. In addition, there may be symptoms related to the underlying pathogenic cause of the MR (e.g., endocarditis, SLE, Marfan syndrome). Many patients with severe MR remain completely asymptomatic, although close questioning of the patient or family may reveal subtle reductions in functional capacity. Symptoms may occur with preserved LV contractile function in patients with chronic MR who have severely elevated pulmonary venous pressures or AF. In other patients, symptoms herald LV decompensation. In patients with rheumatic MR, the time between the initial attack of rheumatic fever and development of symptoms tends to be longer than in those with MS, often more than two decades. Hemoptysis and systemic embolization are less common in patients with isolated or predominant MR than in those with MS. The development of AF affects the course adversely but perhaps not as dramatically as in MS. Conversely, chronic weakness and fatigue secondary to a low cardiac output are more prominent features in MR.

In patients with severe chronic MR who have a greatly enlarged left atrium and relatively mild LA hypertension (patients with increased LA compliance), PVR does not usually rise markedly. Instead, the major symptoms, fatigue and exhaustion, are related to the depressed cardiac output. Right-sided HF, characterized by congestive hepatomegaly, edema, and ascites, may be prominent in patients with acute MR, elevated PVR, and pulmonary hypertension. Angina pectoris is rare unless CAD coexists.

The vast majority of patients with myxomatous degeneration and MVP are asymptomatic and remain so throughout life. Although early studies called attention to a MVP syndrome, with a characteristic systolic nonejection click and various nonspecific symptoms, such as fatigability, palpitations, postural orthostasis, and anxiety and other neuropsychiatric symptoms, as well as symptoms of autonomic dysfunction, these associations have not been confirmed in carefully controlled studies.[66] How and even whether these symptoms are related to the presence of MVP is not clear. Patients may complain of syncope, presyncope, palpitations, chest discomfort, and when MR is severe, symptoms of exertional dyspnea and diminished cardiac reserve. Chest discomfort may be typical of angina pectoris but is more often atypical in that it is prolonged, not clearly related to exertion, and punctuated by brief attacks of severe stabbing pain at the apex. The discomfort may be secondary to abnormal tension on papillary muscles. In patients with MVP and severe MR, the symptoms of the latter (fatigue, dyspnea, and exercise limitation) typically predominate. Patients with MVP also may develop symptomatic arrhythmias (see later).

Physical Examination

Palpation of the arterial pulse is helpful in differentiating aortic stenosis (AS) from MR, both of which may produce a prominent systolic murmur at the base of the heart and apex (**see Chapter 10**). The carotid arterial upstroke is sharp in severe MR and delayed in AS; the volume of the pulse may be normal or reduced in the presence of HF. The cardiac impulse, as with the arterial pulse, is brisk and hyperdynamic. It is displaced to the left, and a prominent LV filling wave is frequently palpable in thin patients.

Auscultation.

When chronic severe MR is caused by defective valve leaflets, S_1, produced by mitral valve closure, is usually diminished. Wide splitting of S_2 is common and results from the shortening of LV ejection and an earlier A_2 because of reduced resistance to LV ejection. In patients with severe pulmonary hypertension, P_2 is louder than A_2. The abnormal increase in the flow rate across the mitral orifice during the rapid filling phase is often associated with a third heart sound (S_3), which should not be interpreted as a feature of HF in these patients, and this may be accompanied by a brief diastolic rumble.

The systolic murmur is the most prominent physical finding; it must be differentiated from the systolic murmur of AS, tricuspid regurgitation (TR), and ventricular septal defect (VSD). In most patients with severe MR, the systolic murmur commences immediately after the soft S_1 and continues beyond and may obscure the A_2 because of the persisting LV-LA pressure difference after aortic valve closure. The holosystolic murmur of chronic MR is usually constant in intensity, blowing, high-pitched, and loudest at the apex, with frequent radiation to the left axilla and left infrascapular area, particularly with posteriorly directed jets. Radiation toward the sternum or aortic area, however, may occur with abnormalities of the posterior leaflet and is particularly common in patients with MVP and flail involving this leaflet. The murmur shows little change, even in the presence of large beat-to-beat variations of LV stroke volume, as in AF. This finding contrasts with that in most midsystolic (ejection) murmurs, such as in AS, which vary greatly in intensity with stroke volume and therefore with the duration of diastole. Little correlation has

been found between the intensity of the systolic murmur and severity of MR. In patients with severe MR caused by LV dilation, acute MI, or paraprosthetic valvular regurgitation, or in those who have marked emphysema, obesity, chest deformity, or a prosthetic heart valve, the systolic murmur may be barely audible or even absent, a condition referred to as “silent” MR.

The murmur of MR may be holosystolic, late systolic, or early systolic. When the murmur is confined to late systole, the regurgitation usually is secondary to MVP and may follow one or more midsystolic clicks and typically is not severe. Such late systolic MR is often associated with a normal S_1 because initial closure of the mitral valve cusps may be unimpaired. Occasionally, a late systolic murmur of papillary muscle dysfunction may be noted, becoming louder or holosystolic during acute myocardial ischemia, and may disappear when ischemia is relieved. A midsystolic click preceding a mid- to late systolic murmur, and the response of that murmur to a number of maneuvers, helps establish the diagnosis of MVP (discussed later). Early systolic murmurs are typical of acute MR. When the LA *v* wave is greatly elevated in acute MR, the murmur may diminish or disappear in late systole as the reverse pressure gradient declines. As noted, a short, low-pitched diastolic murmur following S_3 may be audible in patients with severe MR, even without accompanying MS.

Dynamic Auscultation.

Auscultation during positional changes or the Valsalva maneuver can be quite helpful in characterizing the MR murmur. When MR is holosystolic, it typically varies little during respiration. However, sudden standing usually diminishes the murmur, whereas squatting augments it. The late systolic murmur of MVP behaves in the opposite direction, decreasing in duration with squatting and increasing in duration with standing. Similarly, with the Valsalva maneuver, MVP clicks may occur earlier in systole with lengthening of the murmur. Holosystolic MR murmur is often softer during the strain of the Valsalva maneuver and shows a left-sided response (i.e., a transient overshoot that occurs six to eight beats after release of the strain). The murmur of MR usually is intensified by isometric exercise, differentiating it from the systolic murmurs of valvular AS and obstructive HCM, both of which are reduced by this intervention. The murmur of MR caused by LV dilation decreases in intensity and duration after effective therapy with cardiac glycosides, diuretics, rest, and particularly vasodilators.

Diagnosis and Evaluation

Differential Diagnosis

The holosystolic murmur of MR resembles that produced by a VSD, but the latter is usually loudest at the sternal border and is often accompanied by a thrill in the parasternal area. The murmur of MR may also be confused with that of TR, but the latter is usually lower in pitch and is heard best along the left sternal border, with augmentation during inspiration and a prominent *v* wave and *y* descent in the JVP.

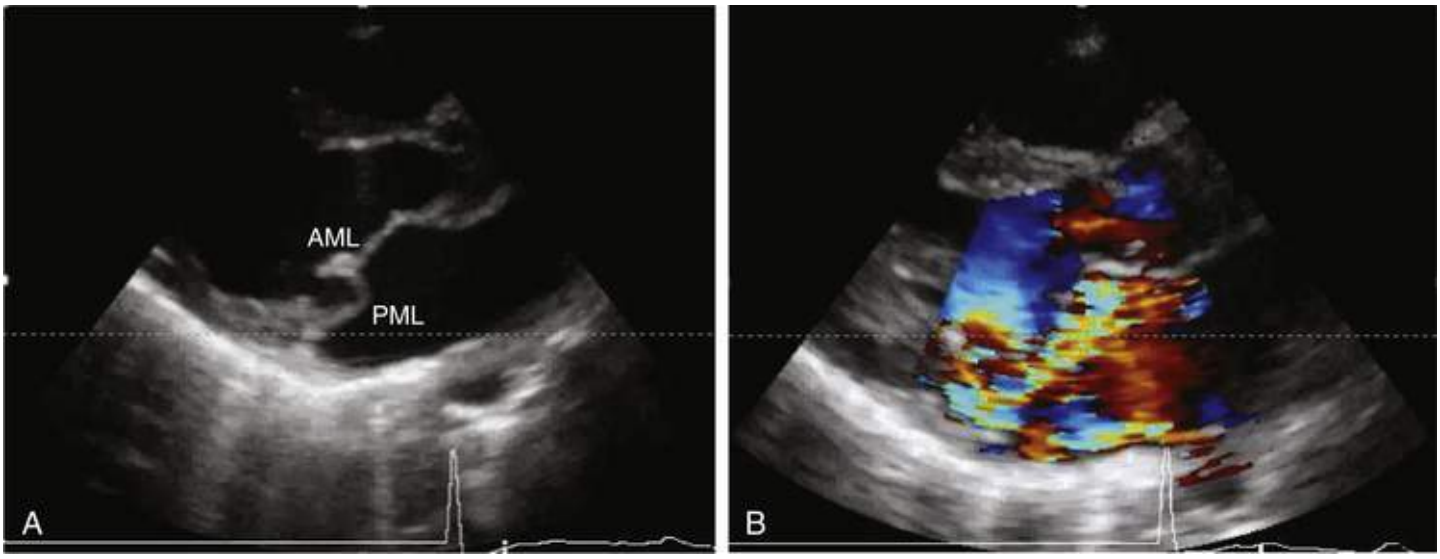
When the chordae tendineae to the posterior leaflet of the mitral valve rupture, the regurgitant jet is often directed anteriorly, so that it impinges on the atrial septum adjacent to the aortic root and causes a prominent systolic murmur at the base of the heart, which can be confused with that of AS. On the other hand, when the chordae tendineae to the anterior leaflet rupture, the jet usually is directed to the posterior wall of the left atrium, and the murmur radiates to the axilla and may be transmitted to the spine or even the top of the head.

Patients with rheumatic disease of the mitral valve exhibit a spectrum of abnormalities, ranging from pure MS to pure MR. The presence of a S_3, a rapid LV filling wave and prominent LV impulse on

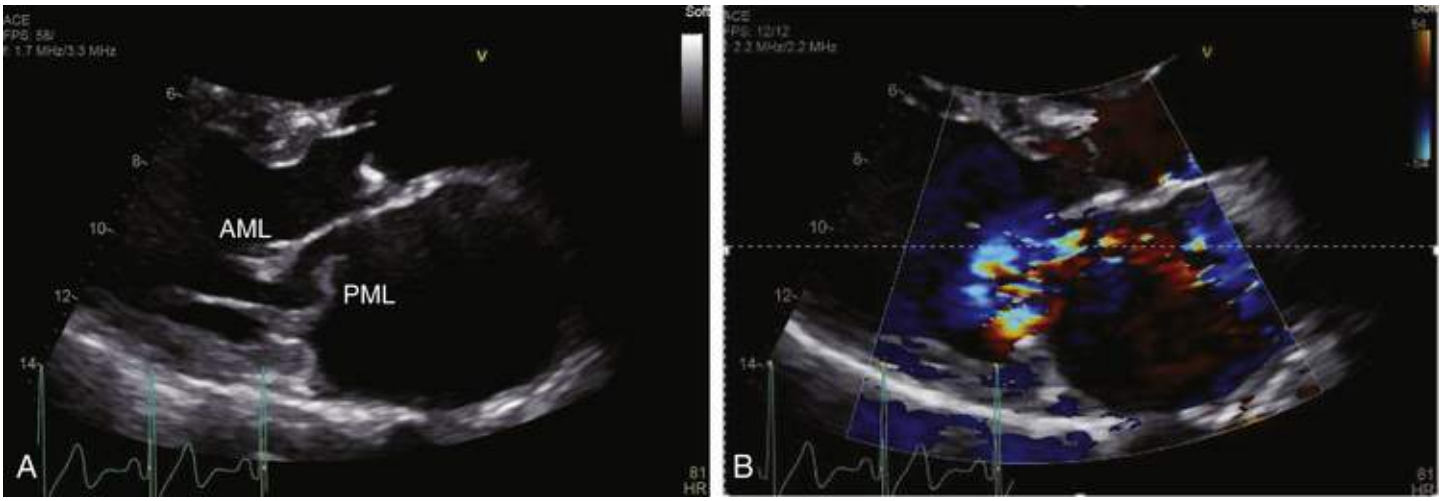
palpation, and a soft S_1 all favor predominant MR. By contrast, an accentuated S_1, a prominent OS with a short A_2-OS interval, and a soft, short systolic murmur all indicate predominant MS. Elucidation of the predominant valvular lesion may be complicated by the presence of a holosystolic murmur of TR in patients with pure MS and pulmonary hypertension; this murmur may sometimes be heard at the apex when the right ventricle is greatly enlarged and may therefore be mistaken for the murmur of MR.

Echocardiography

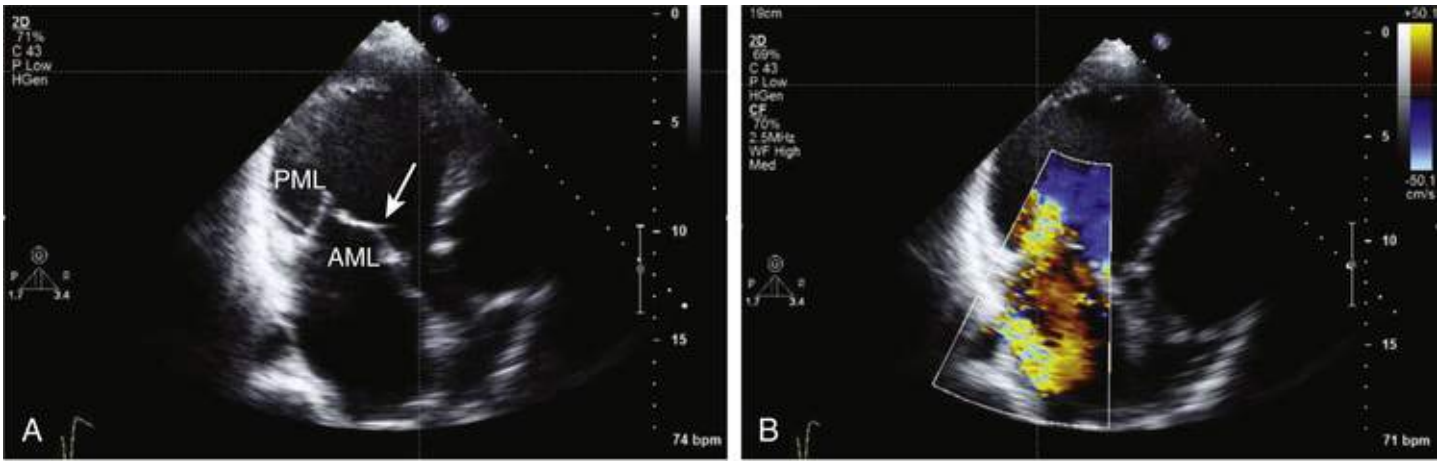
Echocardiography plays a central role in the diagnosis of MR, in determining its cause and potential for repair, and in quantifying its severity (**see Chapter 14**). In patients with severe MR, echocardiographic imaging shows enlargement of the left atrium and left ventricle, with increased systolic motion of both chambers. The underlying cause of the regurgitation, such as rupture of chordae tendineae, in MVP (**eFig. 69.6** and Video 69.10; **see Fig. 14.40**), rheumatic mitral disease, a flail leaflet (**eFig. 69.7** and Videos 69.11 and 69.12), vegetations (**see Chapter 73**), and regional or global LV dilation with leaflet tethering (**eFig. 69.8** and Video 69.13) can often be determined on transthoracic echocardiography (TTE). It also may show calcification of the mitral annulus as a band of dense echoes between the mitral apparatus and posterior wall of the heart. This technique also is useful for estimating the hemodynamic effects of MR on the left atrium and left ventricle; in patients with LV dysfunction, EDV and ESV are increased, and EF and shortening rate may decline.[12,65,67-69]



EFIGURE 69.6 Mitral valve prolapse. **A,** Parasternal long-axis view showing deep prolapse of the posterior mitral leaflet. **B,** Anteriorly directed mitral regurgitation. *AML,* anterior mitral leaflet; *PML,* posterior mitral leaflet.



EFIGURE 69.7 Flail mitral leaflet. **A,** Parasternal long-axis view showing severe flail of the posterior mitral leaflet. **B,** Anteriorly directed mitral regurgitation. *AML,* anterior mitral leaflet; *PML,* posterior mitral leaflet.



EFIGURE 69.8 Functional mitral regurgitation. **A,** Apical long-axis view showing a large posterior myocardial infarction, which is tethering the posterior leaflet preventing the anterior leaflet from closing. **B,** This causes a posteriorly directed jet of mitral regurgitation. *AML,* anterior mitral leaflet; *PML,* posterior mitral leaflet; arrow indicates tenting of the AML caused by tethering of the secondary chordae.

Doppler echocardiography in MR characteristically reveals a high-velocity jet in the left atrium during systole.[67] The severity of the regurgitation is reflected in the width of the jet across the valve and the size of the left atrium. Qualitative assessment using color flow Doppler imaging or pulsed techniques correlates reasonably well with quantitative methods in estimating the severity of MR. However, color flow jet areas are significantly influenced by the driving pressure (LV-LA gradient), jet eccentricity, and a host of instrument factors, such as transmit power and frequency, receiver gain, Nyquist limit, and wall filter (Videos 69.14 and 69.15), thereby limiting the accuracy of this approach. Importantly, however, the jet morphology can give important clues as to the mechanism of the MR. In organic MR the jet generally goes away from the most significant anatomic lesion, so posterior prolapse or flail typically produces an anterior jet, and vice versa. This rule breaks down in functional MR, where the typical cause is the anterior leaflet overriding a tethered posterior leaflet and producing a posteriorly directed jet.

Quantitative methods to measure regurgitant fraction, regurgitant volume, and regurgitant orifice area have greater accuracy when done carefully[70] (**Fig. 69.13**; **see also Figs. 14.42 and 14.43**), and these methods are strongly recommended (**see Table 69.3**).[12,21,71]

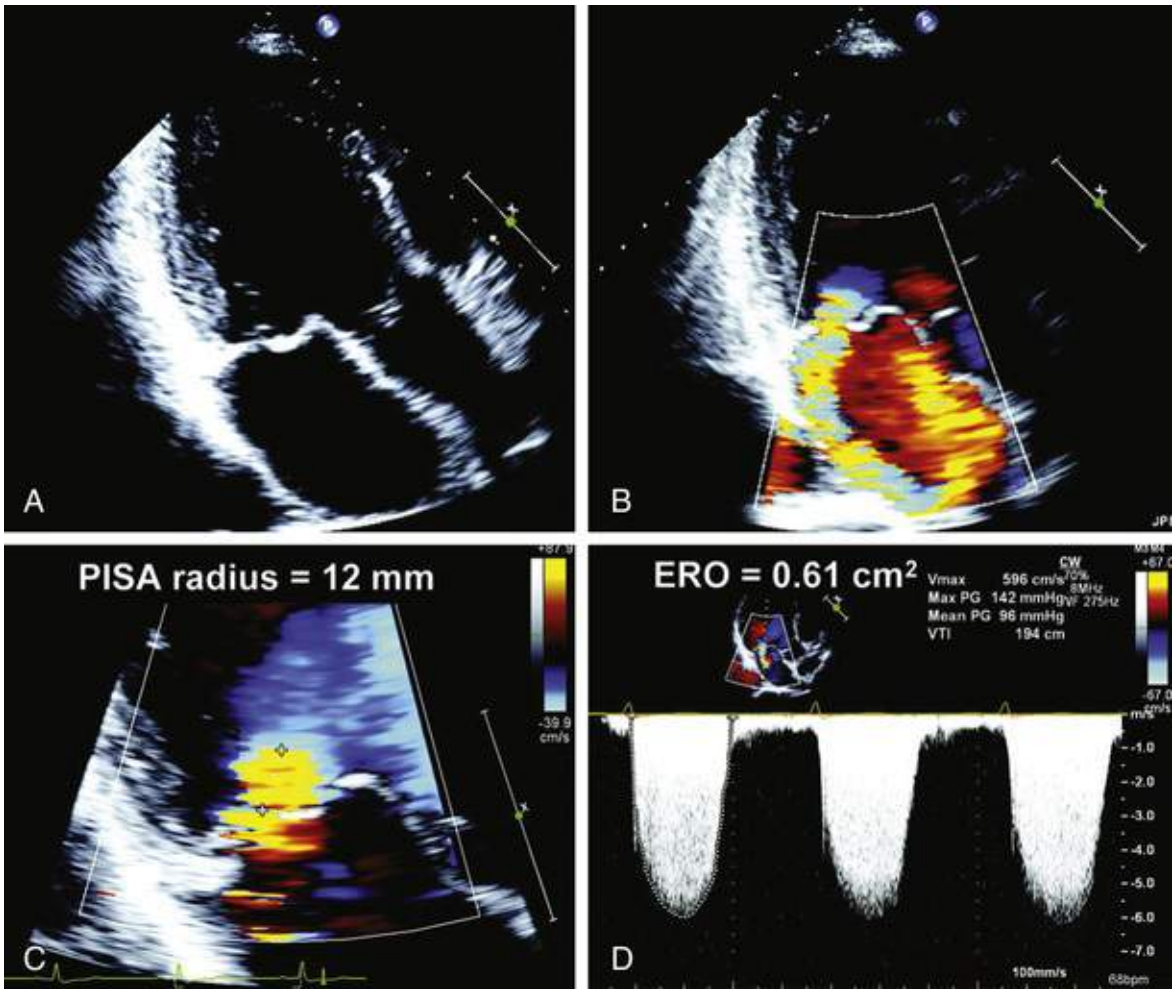


FIGURE 69.13 Severe mitral regurgitation caused by prolapse of the mitral valve with quantitative determination of effective regurgitant orifice area (ERO) on echocardiography. **A, B,** Severe prolapse of the mitral valve with severe MR. **C, D,** ERO was calculated with the proximal isovelocity surface area (PISA) radius and peak velocity of the MR jet. (From Kang DH, Kim JH, Rim JH, et al. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation. Circulation 2009;119:797-804.)

Regurgitant volume (RVol) is theoretically simple concept but challenging in practice. In principle, stroke volume is measured in two locations, one that includes the MR (forward flow across mitral annulus or total LV stroke volume) and one that does not (forward flow though LV outflow tract [if no AR] or right-sided stroke volume). Unfortunately, each of these stroke volumes requires multiple measurements, with any error propagating throughout the calculation, compounded at the end by needing to subtract one large number from another. The vena contracta, defined as the narrowest cross-sectional area of the regurgitant jet as mapped by color flow Doppler echocardiography, also predicts the severity of MR (**see Fig. 69.13**) but may suffer from "color blooming" artifact and limitation of lateral resolution.

The *proximal isovelocity surface area* (PISA) method may be the most practical quantitative method for daily use (**see Chapter 14**). It exploits the predictable flow acceleration leading into the mitral valve, which forms roughly hemispheric isovelocity shells that can be highlighted by shifting the aliasing velocity of the color display and identified where the color changes from blue to red (**see Fig. 14.42**). If the radial distance is r from the vena contracta to the contour with velocity v, the flow rate Q will be given by:

$$Q = 2\pi r^2 v$$

from which the *effective regurgitant orifice area* (EROA) can be obtained by dividing Q by the

maximal velocity through the orifice obtained by continuous-wave (CW) Doppler (Vmax). A simplification that works in the majority of cases assumes approximately 100 mm Hg of driving pressure across the regurgitant orifice (with Bernoulli equation, leading to a 5-m/sec Vmax). If the aliasing velocity is set to (approximately) 40 cm/sec, the calculation simplifies to EROA = $r^2/2$. An approximation to RVol can be obtained by multiplying EROA by the velocity time integral (VTI) of the regurgitant CW signal. **Fig. 69.14** shows how this simplified approach can be done in practice.

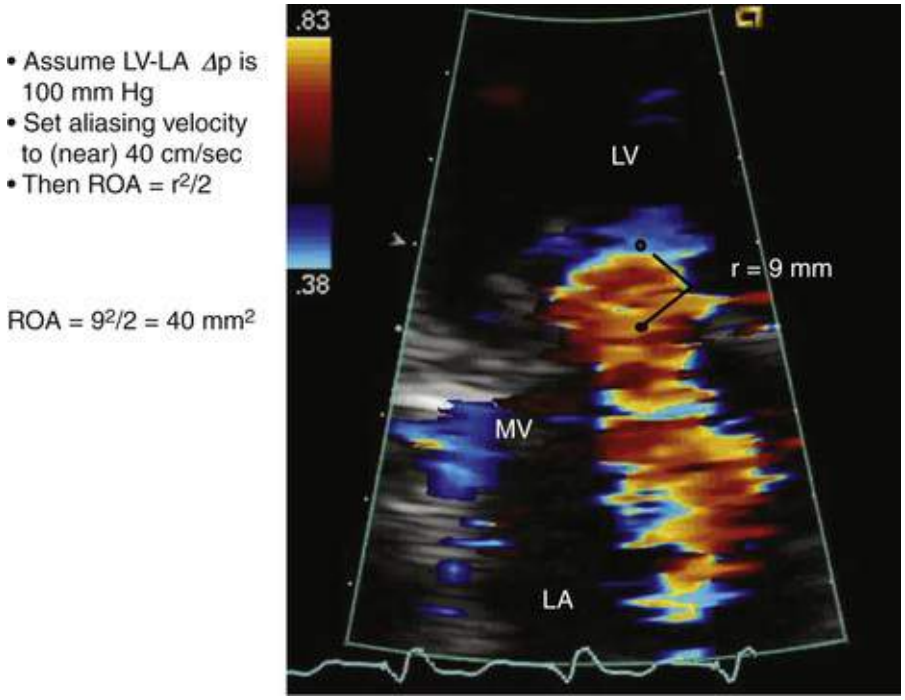


FIGURE 69.14 Simplified approach to estimating the regurgitant orifice area (ROA) using the proximal convergence method. The method assumes that the pressure difference is approximately 100 mm Hg between the left ventricle (LV) and the left atrium (LA) in systole (producing a 5-m/sec regurgitant jet velocity) and sets the color aliasing velocity to approximately 40 cm/sec. Then, by measuring the radius *r* from the *red-blue area* to the orifice (aided by switching the color off and on), the effective ROA (EROA) is given simply by $r^2/2$. This was validated against the complete formula in Pu M, Prior DL, Fan X, et al. Calculation of mitral regurgitant orifice area with use of a simplified proximal convergence method: initial clinical application. J Am Soc Echocardiogr 2001;14:180-5.

The most important caveat with the PISA equation involves nonholosystolic jets. **Fig. 69.15** shows a large proximal convergence zone with an EROA of 0.6 cm^2, but the CW Doppler demonstrates that this is a case of MVP where the regurgitation does not begin until the latter half of systole, so the regurgitation is much less severe than a single frame showing the largest jet, vena contracta, or convergence zone would imply (Video 69.16). When calculating RVol, one should multiply EROA by the VTI from the dense part of the CW signal, not including the faint, early systolic portion when regurgitation is mild. Nonholosystolic jets are quite common in MVP (without flail) and in functional MR where the MR is most prominent during early systole and isovolumic relaxation, with relatively little in midsystole when the mitral valve is firmly closed by LV pressure. Additional pitfalls of the PISA method include slight flow underestimation (on the order of v/v_{max}) as contours flatten out approaching the orifice; some overestimation as convergence zones are distorted by surrounding walls (a problem generally confined to already-severe MR); and further underestimation when the regurgitant orifice is elongated, as is common in functional MR.

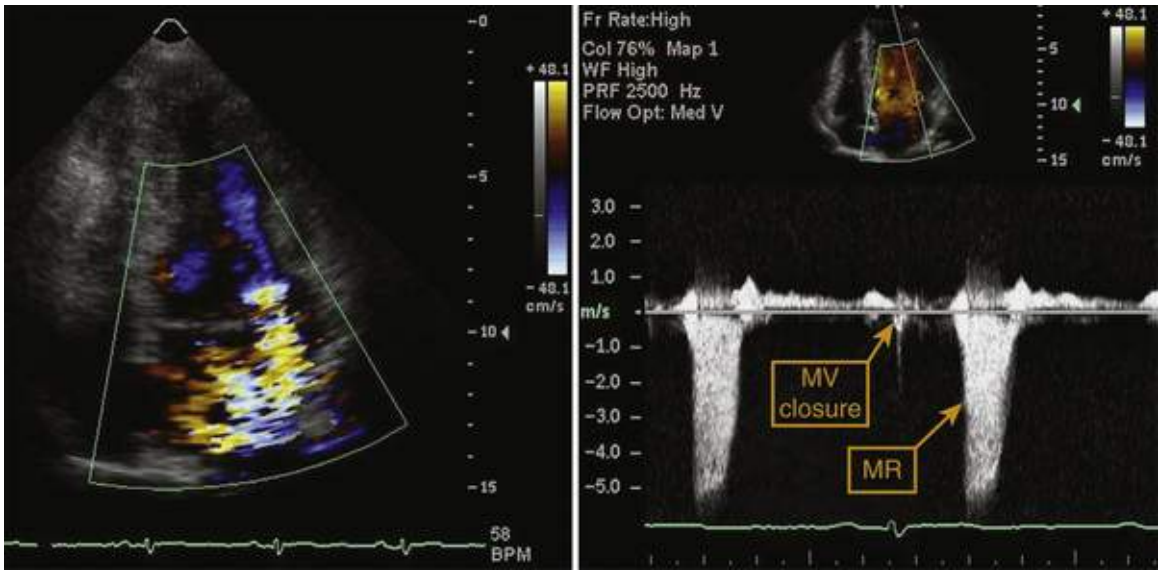


FIGURE 69.15 Limitation of the proximal isovelocity surface area (PISA) method when mitral regurgitation (MR) is not holosystolic. Although there is a large proximal convergence zone with an effective regurgitant orifice area (EROA) of 0.6 cm^2 **(left panel),** the continuous-wave Doppler (CWD) pattern **(right panel)** demonstrates that the regurgitation does not begin until the latter half of systole, which is very common in mitral valve (MV) prolapse. Thus the regurgitation is much less severe than a single frame showing the largest jet, vena contracta, or convergence zone would imply. When calculating regurgitant volume, one should multiply EROA by the velocity time integral (VTI) from the dense part of the CWD signal, not including the faint, early systolic portion when MR is mild.

Supportive evidence for MR severity can be found in pulmonary venous flow, where a normal-pattern systolic (S) wave greater than diastolic (D) wave generally indicates mild MR, and frank systolic reversal indicates severe MR, but the common "blunted" pattern (S < D) may be seen in all degrees of MR. A transmitral E wave greater than 1.2 m/sec is supportive of severe MR, whereas a pattern with E < A virtually excludes severe MR. Doppler echocardiography also is an important tool to estimate the systolic PAP and to determine the presence and severity of associated aortic regurgitation (AR) or TR.

In interrogating the mitral valve, it is important to localize the origin and direction of the regurgitant jet. The parasternal and apical long-axis views identify pathology of the posterior versus anterior leaflet and jet direction, whereas the often-neglected parasternal short-axis and apical two-chamber views can show where along the commissural closure line the dominant jet originates (**Fig. 69.16**).

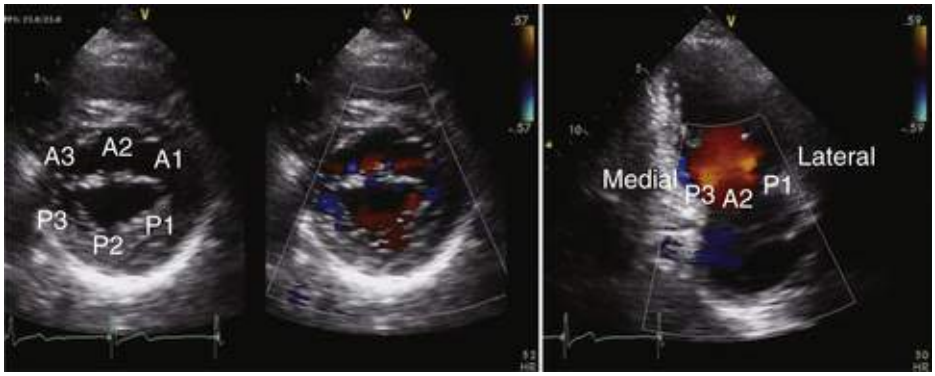


FIGURE 69.16 When examining the mitral valve echocardiographically, it is crucial to obtain anatomically oriented images that localize the origin of the regurgitant jet, particularly along the medial-lateral extent of the commissural closure line. The parasternal short-axis view **(left)** and apical two-chamber view **(right)** both allow this delineation. Localizing the proximal convergence zone in these views can be particularly helpful in assessing the mechanism.

Three-dimensional echocardiography is assuming a more central role in MR assessment, with LV

volumes routinely available, and surface rendering of the valve directly demonstrating the pathology. Multiplane imaging allows structured interrogation of the valve for optimally localizing the pathology.

TEE may be needed in addition to TTE for assessment of the detailed anatomy of the regurgitant mitral valve (**see Figs. 14.35 and 14.40** and Video 69.17) and the severity of MR in some patients. TEE is useful when the TTE images are suboptimal and also in determining whether mitral valve repair or clipping is feasible or whether MVR is necessary. Three-dimensional imaging and three-dimensional color Doppler[2,52,72] help elucidate the mechanism of MR (Video 69.18). **Fig. 69.17** shows how multiplane imaging can explore the full medial-lateral extent of the valve to localize jet origin.

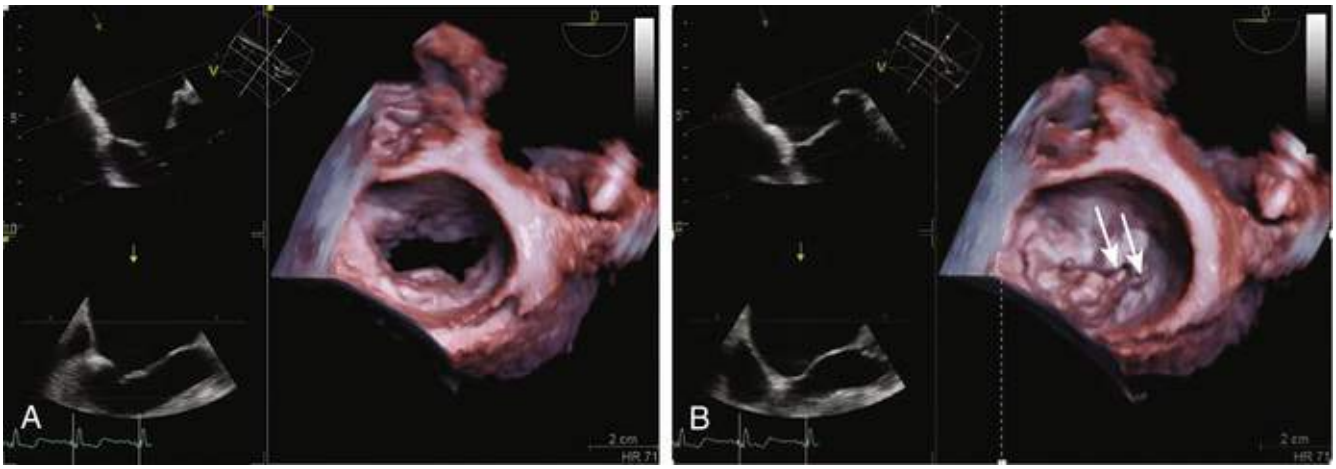


FIGURE 69.17 Three-dimensional echocardiography now allows direct visualization of the pathology, here demonstrating ruptured chordae to P_2 and P_3 (*arrows*). **A,** Ventricular diastole; **B,** systole.

Exercise echocardiography can be extremely helpful in determining severity of MR and hemodynamic abnormalities (e.g., pulmonary hypertension) during exercise.[73-75] This is a useful objective means to evaluate symptoms in patients who appear to have only mild MR at rest and, alternatively, to determine functional status and dynamic changes in hemodynamics in patients who otherwise appear stable and asymptomatic. Particularly helpful is an observation that late systolic MR becomes more holosystolic with exercise, particularly if PAP rises significantly. When ordering a treadmill exercise echocardiogram, the physician should provide guidance to the sonographer as to the priority for the various datasets to be obtained after exercise, because it is often impossible to obtain diagnostic mitral and tricuspid imaging as well as wall motion assessment while heart rate is still optimally high. If the focus is on the mitral valve, rapid acquisition of mitral color flow and CW Doppler and tricuspid CW Doppler images will usually be a priority. If the exercise is on a supine bicycle, comprehensive imaging can be obtained of all relevant parameters. Dobutamine echocardiography has little role in assessing organic MR but may be useful for ischemia or viability assessment in functional MR.

Other Diagnostic Evaluation Modalities

Electrocardiography.

The principal ECG findings are LA enlargement and AF. ECG evidence of LV enlargement occurs in approximately one third of patients with severe MR. Approximately 15% of patients exhibit ECG evidence of RV hypertrophy, a change that reflects the presence of pulmonary hypertension of sufficient severity to counterbalance the hypertrophied left ventricle of MR.

Radiography.

Cardiomegaly with LV enlargement, and particularly with LA enlargement, is a common finding in patients with chronic severe MR. Although the left atrium may be severely enlarged, little correlation has been found between LA size and pressure. Interstitial edema with Kerley B lines frequently is seen in patients with acute MR or with progressive LV failure.

In patients with combined MS and MR, overall cardiac enlargement and particularly LA dilation are prominent findings. Predominant MS is suggested by relatively mild cardiomegaly (principally straightening of the left cardiac border) and significant changes in the lung fields, whereas predominant MR is more likely when the heart is greatly enlarged and the changes in the lungs are relatively inconspicuous. Calcification of the mitral annulus, an important cause of MR in older adults, is most prominent in the posterior third of the cardiac silhouette. The lesion is best visualized on chest films exposed in the lateral or right anterior oblique projections (**see eFig. 15.7**), in which it appears as a dense, coarse, C-shaped opacity.

Cardiac Magnetic Resonance Imaging.

CMR provides accurate measurements of regurgitant flow that correlates well with quantitative Doppler imaging.[76] It also is the most accurate noninvasive technique for measuring LV EDV, ESV, and mass,[77] and has recently been included in guidelines for imaging in valvular regurgitation.[12] Although detailed visualization of mitral valve structure and function is obtained more reliably with echocardiography, particularly TEE, CMR offers a promising approach for more accurate assessment of regurgitant severity and its impact on chamber size.[78,79]

Cardiac Computed Tomography.

Cardiac CT imaging can provide useful structural information about the regurgitant mitral valve,[80-83] with particular value in sizing the mitral annulus and quantifying the degree of annular calcification.[84] CT appears to be particularly useful in planning for percutaneous MVR[85] and has been used in conjunction with three-dimensional printing to ensure an adequate fit of the proposed valve within the mitral apparatus.[86,87] Some have proposed CT imaging for quantification of the actual regurgitant severity, specifically the planimetered size of the EROA, but this will likely remain adjunctive given the availability of echocardiography and CMR.[88]

Left Ventricular Angiography.

Again, given the availability of echocardiography and CMR, there is little reason to perform left ventriculography to characterize MR. The prompt appearance of contrast material in the left atrium after its injection into the left ventricle indicates the presence of MR. The injection should be rapid enough to permit LV opacification but slow enough to avoid the development of premature ventricular contractions (PVCs), which can induce spurious regurgitation. The RVol can be determined from the difference between the total LV stroke volume, estimated by angiocardiography, and the simultaneous measurement of the effective forward stroke volume by the Fick method. In patients with severe MR, the RVol may approach or even exceed the effective forward stroke volume. Qualitative but clinically useful estimates of the severity of MR may be made by cineangiographic observation of the degree of opacification of the left atrium and pulmonary veins after the injection of contrast material into the left ventricle.

Disease Course

The natural history of chronic primary MR is highly variable and depends on a combination of the volume of regurgitation, state of the myocardium, and cause of the underlying disorder. Asymptomatic patients with mild primary MR usually remain in a stable state for many years. Severe MR develops in only a

small percentage of these patients, usually because of intervening infective endocarditis or rupture of the chordae tendineae. In patients with mild MR related to MVP, the rate of progression in severity of MR is highly variable; in most cases, progression is gradual unless a ruptured chorda causing flail leaflet supervenes. Regurgitation tends to progress more rapidly in patients with connective tissue diseases, such as Marfan syndrome, than in those with chronic MR of rheumatic or myxomatous origin. In asymptomatic patients with severe MR, the rate of progression to symptoms, LV dysfunction, pulmonary hypertension, or AF is 30% to 40% at 5 years[89] (**Fig. 69.18**). Acute rheumatic fever is a frequent cause of isolated severe MR among adolescents in developing nations, and these patients often have a rapidly progressive course.

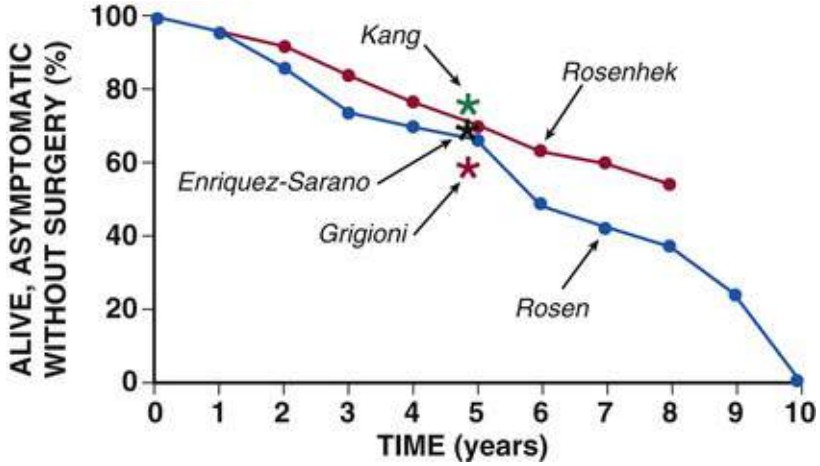
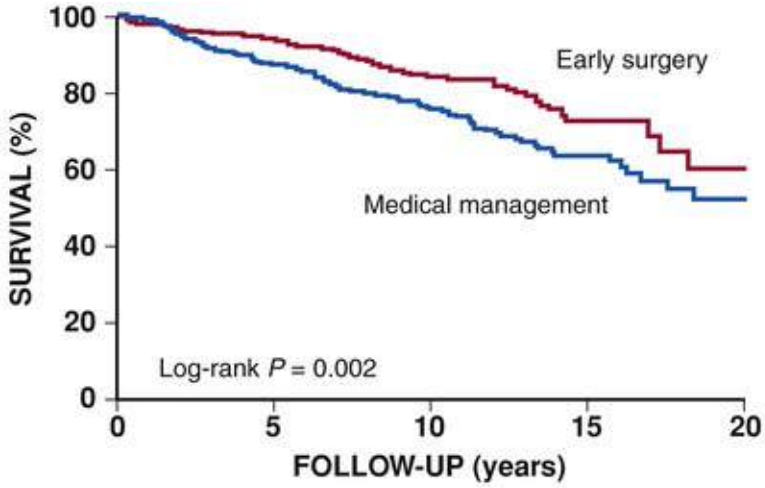


FIGURE 69.18 Five series examining the natural history of primary degenerative mitral regurgitation in patients who initially were asymptomatic with normal left ventricular systolic function. (From Bonow RO. Chronic mitral regurgitation and aortic regurgitation: have indications for surgery changed? J Am Coll Cardiol 2013;61:693-701. Data modified from Rosen SF et al. Natural history of the asymptomatic patient with severe mitral regurgitation secondary to mitral valve prolapse and normal right and left ventricular performance. Am J Cardiol 1994;74:374-80; Enriquez-Sarano M et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. N Engl J Med 2005;352:875-83; Rosenhek R et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. Circulation 2006;113:2238-44; Grigioni F et al. Outcomes in mitral regurgitation due to flail leaflets: a multicenter European study. J Am Coll Cardiol Imaging 2008;1:133-41; and Kang DH et al. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation. Circulation 2009;119:797-804.)

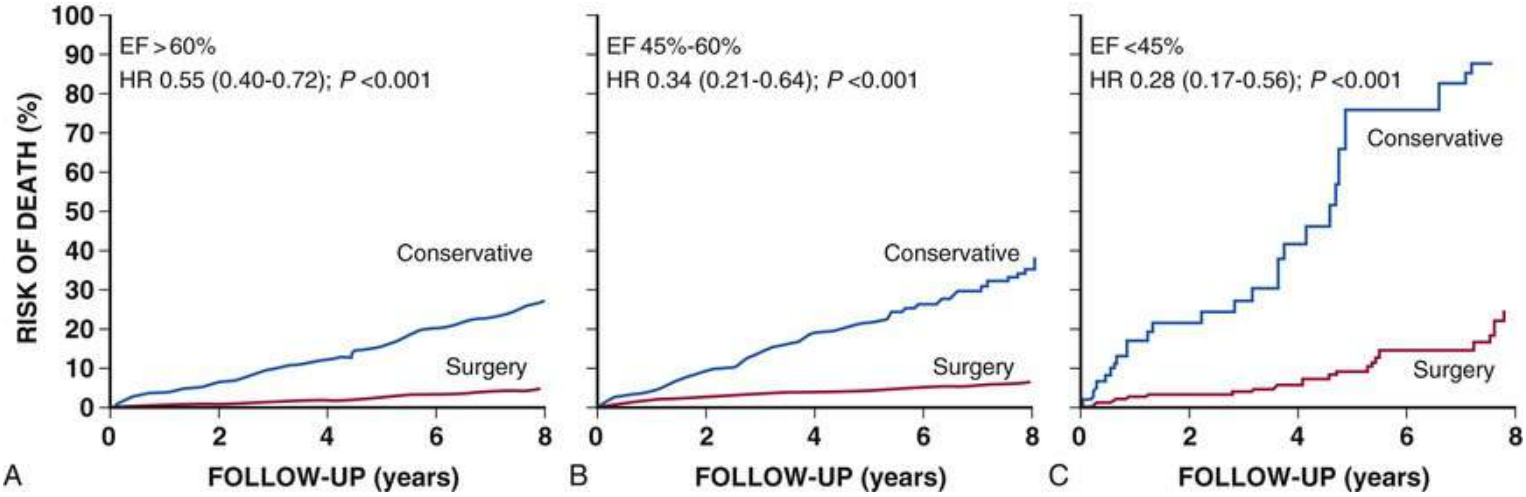
AF is a common arrhythmia in patients with chronic MR, associated with age and LA dilation, and its onset is a marker for disease progression. Patients with AF have an adverse outcome compared with patients who remain in sinus rhythm,[61] and development of AF is considered an indication for operative intervention, especially in patients who are candidates for mitral valve repair.[21]

Because the natural history of severe MR has been altered greatly by surgical intervention, it is difficult now to predict the clinical course in patients who receive medical therapy alone. However, a 5-year survival of only 30% was reported in patients who were candidates for operation, presumably because of symptoms, but who declined surgery (**see eFig. 69.2**). Among patients with severe MR resulting from flail leaflets, the annual mortality rate without surgery is as high as 3%,[90,91] and at 20 years, 60% will have died (**Fig. 69.19**). The mortality is particularly high in those with LV systolic dysfunction, defined as LVEF of 60% or less[91] (**see eFig. 69.9**).



No. at Risk					
Medical management	324	276	157	53	8
Early surgery	324	295	160	35	10

FIGURE 69.19 Long-term survival in patients with severe mitral regurgitation related to flail leaflets, comparing outcomes in patients who underwent early surgery (within 3 months of detection) and in those who initially were managed medically. The medically treated group either never underwent surgery or underwent surgery at a later date. Data are shown after propensity matching to adjust for age and comorbidity. (From Suri RM, Vanoverschelde JL, Grigioni F, et al. Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets. JAMA 2013;310:609-16.)



EFIGURE 69.9 Survival of patients with severe mitral regurgitation related to flair leaflets after treatment with early surgery (within 3 months of detection) or with initial medical management. Outcomes are shown for patients with normal left ventricular ejection fraction (EF) **(A)** and for patients with mild **(B)** and severe **(C)** left ventricular systolic dysfunction. HR, Hazard ratio. (From Tribouilloy C, Rusinaru D, Grigioni F, et al. Long-term mortality associated with left ventricular dysfunction in mitral regurgitation due to flail leaflets: a multicenter analysis. Circ Cardiovasc Imaging 2014;7:363.)

Whether patients with severe MR who are asymptomatic and have normal LV function are at risk of death is a subject of debate.[61,89,92,93] In a study of 286 asymptomatic patients with severe MR and normal LV function followed without surgery, the annual mortality was less than 1% (5% mortality at 7 years). However, in 127 propensity score-matched patients in that study, the estimated actuarial 7-year survival was 99% ±1% in those treated with early surgery, compared with only 85% ±4% for those treated according to current guidelines for watchful waiting. Another study of patients with flail leaflets, noted earlier,[91] reported similar annual mortality rates of less than 1% in those with preserved LV systolic function (mortality <6% at 8 years; **see eFig. 69.9A**).

Mortality arguments aside, however, all studies uniformly indicate that among asymptomatic patients

with initially normal LVEF, severe MR is associated with a high likelihood of requiring surgery over the next 6 to 10 years because of HF symptoms, LV dysfunction, or AF (**see Fig. 69.18**). Moreover, long-term survival after successful surgical repair of primary degenerative MR is reduced in patients with even mild preoperative symptoms or LV dysfunction compared with those who undergo surgery when asymptomatic[94] (**Fig. 69.20**). These considerations have prompted recommendations for earlier surgery in patients who are candidates for repair,[21,37,61,89,92,95] especially in the setting of flail leaflets. Care should always be taken that the regurgitation is indeed severe. A common confounder is MR in MVP confined to late systole, which may look severe on an individual frame, but is actually mild or moderate on volumetric quantitation. These patients have been shown to have a better long-term prognosis than those with holosystolic MR.[96]

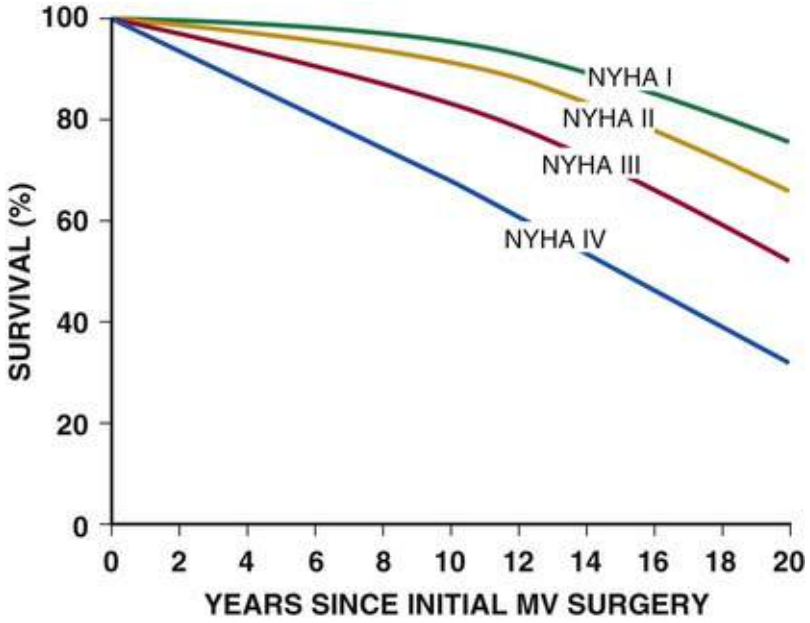


FIGURE 69.20 Long-term survival after mitral valve (MV) repair based on preoperative New York Heart Association (NYHA) functional status in 840 patients with primary degenerative mitral regurgitation. The median follow-up was 10.4 years. (From David TE, Armstrong S, McCrindle BW, Manlhiot C. Late outcomes of mitral valve repair for mitral regurgitation due to degenerative disease. Circulation 2013;127:1485-92.)

Medical Treatment of Primary Mitral Regurgitation

The role of pharmacologic therapy for MR remains another subject of uncertainty and debate. Although afterload reduction therapy undoubtedly is indicated and may be lifesaving in patients with acute MR and secondary forms of chronic MR (see later), the indications for such therapy in patients with chronic primary valvular MR are much less clear. Because afterload is not excessive in most patients with chronic MR, in whom systolic shortening is facilitated by the reduced systolic wall stress, systemic vasodilator therapy to reduce afterload further may not provide additional benefit. Acute administration of nitroprusside, nifedipine, and angiotensin-converting enzyme (ACE) inhibitors to severely symptomatic patients has been demonstrated to alter hemodynamics favorably in some studies, but these effects may not pertain to asymptomatic patients with preserved systolic function. Several small studies of chronic therapy with ACE inhibitors, ranging in duration from 4 weeks to 6 months, have failed to provide evidence of hemodynamic benefit, and no long-term studies or randomized trials have been done to make definitive recommendations. At present, convincing data are lacking that vasodilator therapy affects LV volumes or systolic function favorably in the absence of symptoms or hypertension, and current guidelines

do not recommend the use of these agents for chronic therapy of primary degenerative MR.[21,25]

On the basis of animal models of MR and evidence in patients with chronic MR of neuroendocrine activation and increased sympathetic activity, data from retrospective studies and a small prospective trial indicate that beta blockers may delay the progression of LV dysfunction and improve patient outcomes.[97,98] However, in the absence of definitive clinical trials, such therapy is not currently recommended. An exception would be patients with severe chronic MR, with symptoms or LV dysfunction (or both) who are not candidates for surgical or transcatheter treatment because of age or other comorbid conditions or contributing factors. These patients should receive standard, aggressive management for HF with ACE inhibitors and beta blockers (**see Chapter 25**). Routine antibiotic prophylaxis to prevent infective endocarditis is no longer recommended for patients with MR (**see Chapter 73**). All patients with AF, paroxysmal or chronic, should receive chronic anticoagulation, and appropriate measures should be taken to control the ventricular response rate and restore sinus rhythm, if possible.

Surgical Treatment of Primary Mitral Regurgitation

Surgical treatment should be considered for patients with functional disability and for patients with no symptoms or only mild symptoms but with progressively deteriorating LV function or progressively increasing LV dimensions, as documented by noninvasive studies.[21,25,61,89] In patients considered for surgery, two-dimensional TTE or TEE with Doppler evaluation and color flow Doppler imaging provide detailed assessment of mitral valve structure and function.[65] Left-heart catheterization and coronary arteriography are indicated principally to determine the presence and extent of CAD. In selected cases, right-heart catheterization and left ventriculography may be helpful resolving discrepancies between echocardiographic findings and the clinical picture, as well as detecting and assessing the severity of other associated valvular lesions.

Without surgical treatment, the prognosis for patients with MR and HF is poor (**see eFig. 69.2**), so mitral valve repair or replacement is indicated for symptomatic patients. When operative treatment is being considered, the chronic and often slowly but relentlessly progressive nature of MR must be weighed against the immediate risks and long-term uncertainties attendant on surgery, especially if MVR is required. Surgical mortality depends on the patient's clinical and hemodynamic status, particularly LV function; age[99,100] (**see Chapter 88**); presence of comorbid conditions such as renal, hepatic, or pulmonary disease;[101] and the skill and experience of the surgical team.[37,102] The decision to replace or to repair the valve is of critical importance, and mitral valve repair is strongly recommended whenever possible (**Fig. 69.21**). Replacement involves the operative risk, as well as the risks of thromboembolism and anticoagulation in patients receiving mechanical prostheses, of late structural valve deterioration in patients receiving bioprostheses, and of late mortality, especially in patients with associated CAD who require CABG. Mitral repair is more likely to occur in a surgical center doing more than 20 MR procedures per year, emphasizing the critical importance of surgical experience and expertise.[103] Surgical mortality in patients requiring MVR does not depend significantly on which of the currently used tissue or mechanical valve prostheses is selected.

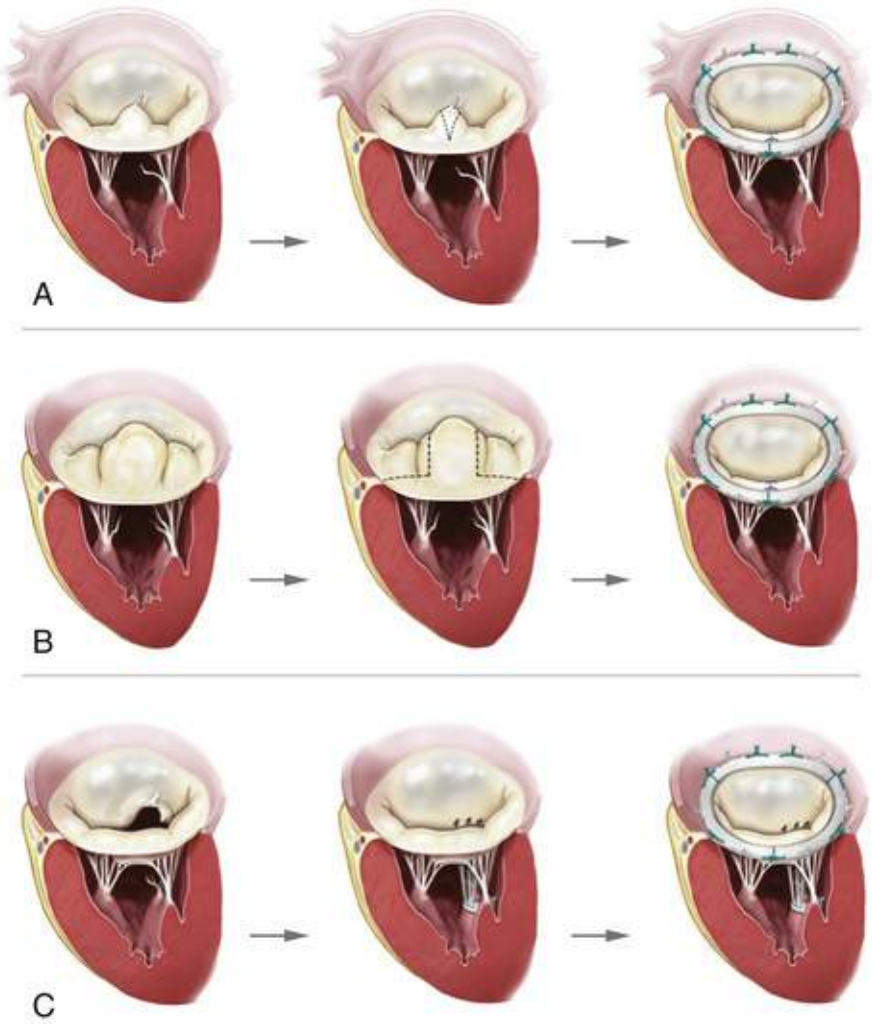
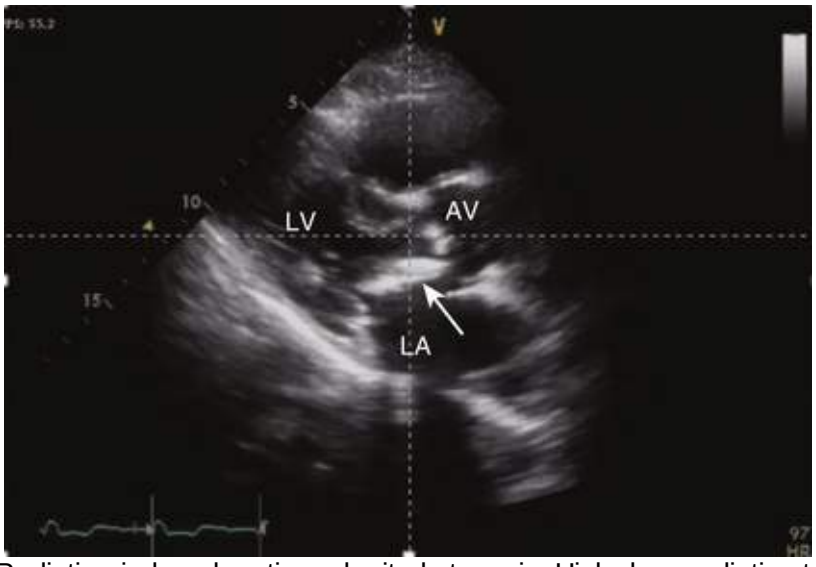


FIGURE 69.21 Most frequently applied surgical approaches currently used for repair of posterior leaflet prolapse. **A,** Triangular resection; **B,** quadrangular resection and sliding leaflet plasty; **C,** neochordoplasty with polytetrafluoroethylene sutures. *Dashed lines* represent the area of leaflet to be excised. (From Castillo JG, Adams DH. Mitral valve repair and replacement. In Otto CM, Bonow RO, editors. Valvular Heart Disease: ACompanion to Braunwald's Heart Disease. Philadelphia: Saunders; 2013, pp 327-340.)

Repair of primary degenerative MR most often is successful in (1) children and adolescents with pliable valves, (2) adults with MR secondary to MVP, (3) cases with annular dilation, (4) cases with chordal rupture, and (5) cases with perforation of a mitral leaflet caused by infective endocarditis. These clinical categories represent the vast majority of patients with MR in the United States and other developed countries. These procedures are less likely to be successful in older patients with the rigid, calcified, deformed valves of rheumatic or radiation heart disease (**eFig. 69.10** and Video 69.19) or in those with severe subvalvular chordal thickening and major loss of leaflet substance, many of whom require MVR. The presence of severe mitral annular calcification poses a challenge to both repair and replacement strategies.[104] However, younger patients who have severe rheumatic MR in the absence of active carditis may undergo successful repair.[37,102] This consideration is particularly important in developing countries.



EFIGURE 69.10 Radiation-induced aortic and mitral stenosis. High-dose radiation to the chest induces severe fibrosis and calcification of the aortic and mitral valves. A characteristic finding is heavy calcification along the aorto-mitral curtain (*arrow*). *LV,* left ventricle; *LA,* left atrium; *AV,* aortic valve.

Mitral valve repair for degenerative MR consists of reconstruction of the valve, which usually is accompanied by a mitral annuloplasty using a rigid or flexible prosthetic ring (**see Fig. 69.21**).[105] Prolapsed valves causing severe MR usually are treated with resection of the prolapsing segment(s) with plication and reinforcement of the annulus. Replacing, reimplanting, elongating, or shortening of the chordae tendineae, splitting the papillary muscles, and repairing the subvalvular apparatus have been successful in select patients with pure or predominant MR in whom subvalvular pathology contributes to the MR.[37,105] Repair of anterior and posterior prolapsing leaflets has been successful in experienced centers, although results are less successful than where pathology is confined to one leaflet. Deep clefts are sometimes found between scallops, which can simply be closed. Intraoperative TEE with Doppler is critical for assessing the adequacy of mitral valve repair.[106] In the minority of patients with persistent significant MR in whom the operative results are unsatisfactory, the problem usually can be corrected immediately or, if necessary, the valve can be replaced. LV outflow tract obstruction caused by systolic anterior motion of the mitral valve occurs in 5% to 10% of patients after mitral valve repair for degenerative MR.[39] The causes are multifactorial but may include excess valvular tissue with severe leaflet redundancy and/or an interventricular septum bulging into a small, hyperdynamic left ventricle. These complications also may be recognized intraoperatively on TEE, guiding treatment with volume loading and beta blockers, which often is helpful. The obstruction usually disappears with time; if it does not, a second pump run and repeat repair or MVR may be necessary. Recognizing the risk for outflow tract obstruction in the preoperative TEE allows prophylactic surgical strategies: a sliding annuloplasty for excessive posterior leaflet length (detachment of the leaflet and reattachment to shorten it); reefing to pull back the free margin of an excessively long anterior leaflet; and myomectomy for an upper septal bulge.[107]

Preoperative AF is an independent predictor of reduced long-term survival after mitral valve surgery for chronic MR. The persistence of AF postoperatively requires long-term anticoagulation, thereby partially nullifying the advantages of mitral valve repair. In patients who have developed AF, whether chronic or paroxysmal, outcomes are improved if a maze procedure is performed at the time of mitral valve repair or replacement,[61,108] with reduced risk of postoperative stroke. The decision to perform a maze procedure should be based on surgical expertise as well as patient age and comorbid conditions, because this procedure may add to the length and complexity of the operation. The technique consists of electrically isolating portions of the atria from each other and the pulmonary veins using either suture

lines (“cut and sew”), radiofrequency energy, or cryotherapy.[109,110]

Mitral Valve Repair Versus Replacement.

Although mitral valve replacement (MVR) has been used successfully in treating MR for almost six decades, some dissatisfaction with the results of this operation has been reported. First, LV function often deteriorates after MVR, contributing to early and late mortality and late disability. The increase in afterload consequent to abolishing the low impedance leak was first believed to be responsible, but now it is clear that the loss of annular-chordal-papillary muscle continuity (**see Fig. 69.7**) interferes with LV geometry, volume, and function in patients who have undergone MVR. This limitation does not occur after mitral valve repair. Animal experiments have shown convincingly that the normal function of the mitral valve apparatus primes the left ventricle for normal contraction that is prevented when surgery causes discontinuity of this apparatus. Animal experiments and human trials indicate that preservation of the papillary muscle and its chordal attachments to the mitral annulus is beneficial to postoperative LV function after mitral valve reconstruction and replacement. Thus, preservation of these tissues, whenever possible, is now considered a critical feature of MVR.[39,105,109,110]

A second disadvantage of MVR is inherent problems with the prosthesis itself, including the risks of thromboembolism or hemorrhage associated with mechanical prostheses, late structural deterioration of bioprostheses, and infective endocarditis with all prostheses. Outcomes after mitral valve repair are more favorable than those with MVR in comparative studies,[100] although this benefit has never been subjected to a prospective randomized trial in organic MR (see later for a randomized trial in functional MR). For these reasons, increasing efforts are being made to repair the mitral valve whenever possible in patients with isolated or predominant MR.[39,89,102,105,111,112]

With growing experience in mitral valve repair for degenerative causes of MR, including MVP and rupture of chordae tendineae, the number of patients having valve reconstruction is increasing each year. In many centers in the United States, more than two thirds of all patients requiring operation for pure or predominant MR now undergo mitral valve repair. This percentage has steadily increased, and currently 69% of patients in the STS database undergoing surgery for isolated primary MR undergo mitral valve repair.[103] However, many patients who are candidates for repair continue to undergo MVR, and most mitral valve operations in the United States continue to be performed by low-volume surgeons, in whom the likelihood of performing a successful mitral valve repair is lower than that of higher-volume valve surgeons.[113] Mitral valve repair is a technically more demanding procedure than MVR, with a distinct learning curve for the surgeon. In addition, MR recurs after mitral valve repair in a subset of patients with degenerative valve disease that is predicted in part by the presence of residual MR immediately after repair.[114,115] Thus there is growing emphasis on referral of patients requiring surgery for pure MR to centers of excellence in performing mitral valve repair.[21,25,39,89,116]

Minimally invasive surgical techniques using a small, low, asymmetric sternotomy or anterior thoracotomy and percutaneous CPB[117] have been found to be less traumatic and can be used for mitral valve repair and replacement. This approach has been reported to reduce cost, improve cosmetic results, and shorten the recovery time. However, it also is demanding technically and is successfully performed by only a minority of cardiac surgeons. Recent advances in robotic surgery have allowed this approach to be used for a wide range of mitral valve procedures, but the learning curve is also quite steep and technically demanding.[118]

Percutaneous Mitral Valve Repair.

In 2013 the U.S. Food and Drug Administration (FDA) approved the MitraClip system for percutaneous mitral valve repair in patients with organic MR and a prohibitive risk for open heart surgery (predicted mortality >8%). It was subsequently given a class IIb indication in the 2014 valve guideline and has now been used in more than 30,000 patients (**see Chapter 72**).

Surgical Results

Operative mortality rates of 1% to 9% are now common in many centers for patients with pure or predominant MR (NYHA Class II or III) who undergo elective isolated mitral valve repair or replacement. The overall mortality rate was 3.0% in the STS database of 77,836 patients undergoing isolated mitral valve surgery between 2002 and 2010,[119] with a significant increase in the percentage of patients undergoing mitral valve repair from 54.8% (2002–2006) to 61.8% (2007–2010). Mortality was significantly lower in the repair than replacement patients (1.4% vs 5.4% in 2007-10). Patients undergoing mitral valve repair are younger and less symptomatic and have considerably fewer comorbid conditions than those undergoing MVR, and these factors contribute to the observed differences in operative mortality. It also is not possible in the STS database to differentiate patients undergoing surgery for primary forms of MR from those with LV dysfunction and secondary MR. Among the 22,786 patients undergoing mitral valve repair in 2007 to 2010 with a STS predicted risk of mortality (PROM) score of 0 to 4%, the operative mortality was 0.9%.

The combination of mitral valve surgery with CABG was associated with an mortality rate of 6.2% between 2011 and 2014,[120] and even higher (up to 25%) in patients with severe LV dysfunction, especially when pulmonary or renal function is impaired, or when the operation must be carried out on an emergency basis. A strong gradient was found between surgical centers of the highest (three-star) rating, with 2.6% risk-adjusted mortality to 11.1% in one-star centers. Age per se is no barrier to successful surgery; mitral valve repair or replacement can be performed in patients older than 75 years if their general health status is adequate,[99,100,121] although surgery in these patients carries higher risk than in younger patients (**see Chapter 88**). Medicare data covering 2000 through 2009 indicate an operative mortality of 3.9% for patients older than 65 undergoing mitral valve repair and 8.9% for those undergoing MVR.[122] The 1-, 5-, and 10-year survival rates were 90.9%, 77.1%, and 53.6%, respectively, in patients undergoing mitral valve repair and 82.6%, 64.7%, and 37.2%, respectively, in those undergoing MVR. As in the STS database, Medicare patients undergoing mitral valve repair were younger and had fewer comorbid conditions than those undergoing MVR. These favorable outcomes of elderly patients undergoing mitral valve surgery, especially repair, support the earlier identification and surgical referral in this age-group.

Surgical treatment substantially improves survival in patients with symptomatic MR. Preoperative factors, such as age younger than 60 years, NYHA Class I or II, cardiac index exceeding 2.0 liters/min/m^2, LV end-diastolic pressure less than 12 mm Hg, and a normal EF (which should be >60% in patients with severe primary MR) and ESV, all correlate with excellent immediate and long-term survival rates. Both preoperative LVEF (**see eFigs. 69.4 and 69.9**) and end-systolic diameter are important predictors of short- and long-term outcomes.[61] Excellent outcome is anticipated in patients with end-systolic diameter less than 40 mm and EF of 60% or more. Intermediate outcomes are observed in patients with end-systolic diameter of 40 to 50 mm and EF of 50% to 60%. Poor outcomes are associated with values beyond these limits. With improved echocardiographic and magnetic resonance technology, including three-dimensional imaging, it is now possible to have more accurate ventricular volumes to guide timing of surgery, as detailed in a recent guideline,[12] although long-term data are limited. A recent magnetic resonance study showed a greater likelihood for progressing to a need for surgery among those with

LVEDV index greater than 100 mL/m^2, RVol greater than 55 mL, and regurgitant fraction of 40%. One parameter that will probably gain increasing importance in guiding timing of intervention is global longitudinal strain. In a study of 233 patients undergoing mitral valve repair for organic MR, GLS was the best predictor of a postoperative LV dysfunction, with values closer to zero than −19.9% predicting LVEF less than 50% at 1 year after surgery, with sensitivity and specificity of 90% and 79%, respectively.[62]

A large proportion of operative survivors exhibit improved clinical status, quality of life, and exercise tolerance after mitral valve repair or replacement.[112] Severe pulmonary hypertension is reduced, LVEDV and LV mass decrease, and coronary flow reserve increases. Depressed contractile function improves, especially if the papillary muscles and chordal attachment to the annulus remain intact. However, patients with MR who have marked LV dysfunction preoperatively sometimes remain symptomatic, with depressed LV function, despite a technically satisfactory surgical procedure. Progressive LV dysfunction and death from HF may occur, presumably because LV dysfunction may be advanced and largely irreversible by the time patients with pure MR develop serious symptoms. Thus, every effort should be made to operate on patients before they develop serious symptoms, and even asymptomatic patients with severe MR may be considered for surgery in an experienced center if there is a high likelihood (>95%) that the valve can be repaired successfully without residual MR.[21,25,61,89,95,123]

Even though surgical results are suboptimal in patients with MR who have developed severe symptoms or marked LV dysfunction,[61,90] an operation is still indicated for most of these patients because conservative therapy has little to offer. Postoperative survival rates are lower in patients in AF than in those in sinus rhythm.[21,61] As with patients with MS, the arrhythmia by itself does not unfavorably influence outcome but is a marker for older age and other clinical and hemodynamic features associated with less optimal results.

Indications for Surgery

The proposed management strategy for patients with chronic severe primary MR from the 2014 valve guideline[21] was modified slightly by the 2017 focused update[124] (**Fig. 69.22**). The threshold for surgical treatment of primary MR is decreasing because of a reduction in operative mortality, improvement in mitral valve repair procedures, long-term results indicating durability of repair in experienced centers, and the recognition of the poor long-term results in many patients when severe primary MR is corrected only after a long history of symptoms, impaired LV function, AF, or pulmonary hypertension. A detailed echocardiographic examination should be done to assess the likelihood that mitral valve repair, rather than replacement, is possible, and the difference in outcomes between these procedures should be weighed in deciding whether or not to proceed.

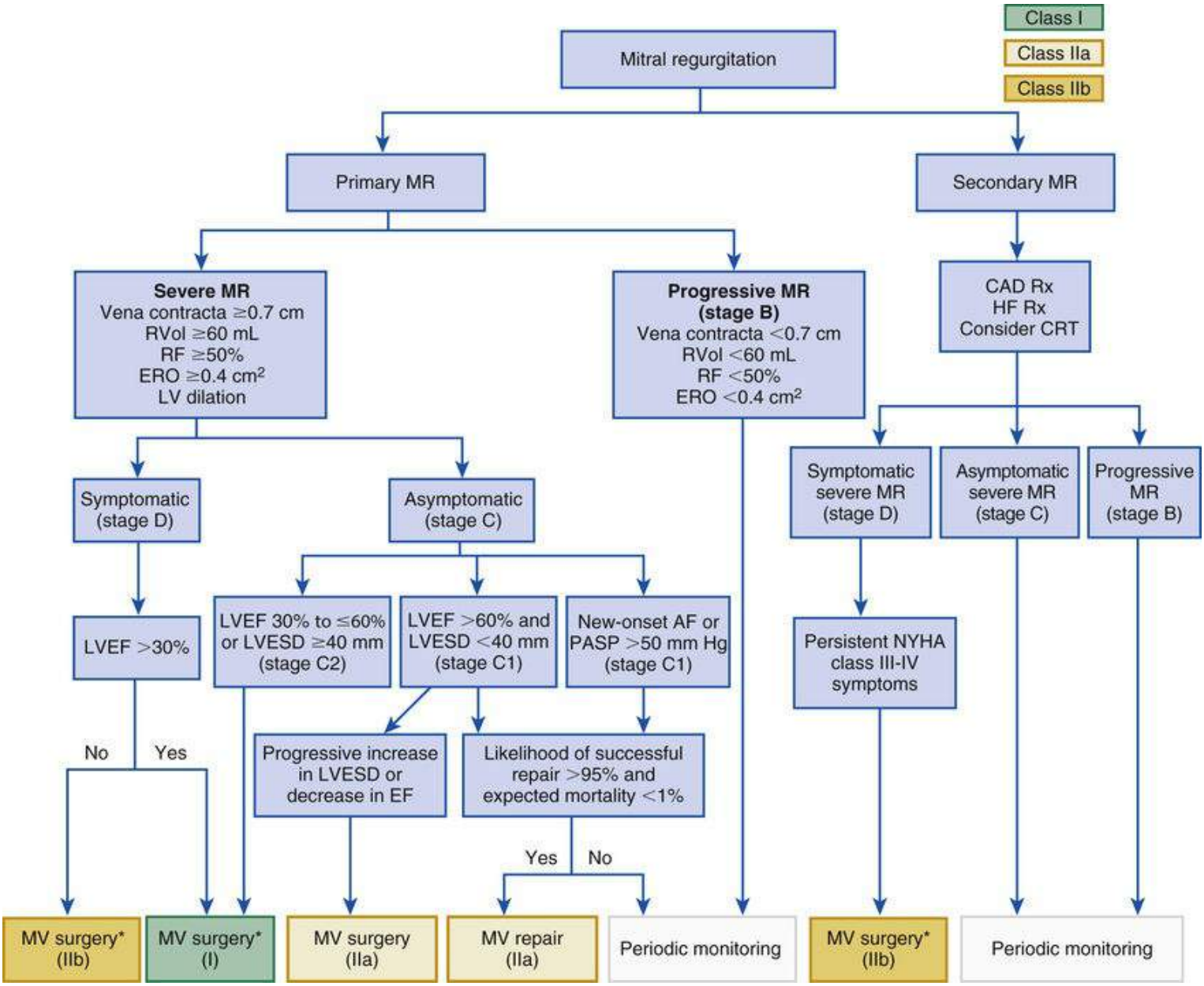


FIGURE 69.22 Updated 2017 indications for mitral valve (MV) surgery for chronic severe mitral regurgitation (MR). *Mitral valve repair preferred over mitral valve replacement when possible. AF, Atrial fibrillation; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; ERO, effective regurgitant orifice; HF, heart failure; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; Rx, therapy. (From Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e1159-95.)

Asymptomatic Patients.

Asymptomatic patients (NYHA Class I) should be considered for mitral valve repair if they have LV systolic dysfunction (EF ≤60% and/or LV end-systolic diameter of 40 mm).[21] It also is reasonable to consider mitral valve repair in asymptomatic patients when AF or pulmonary hypertension is present. Critical in such patients is certainty that the MR is truly severe. Special caution should be exercised in patients with MVP and late systolic MR (**see Fig. 69.15**), since instantaneous parameters of MR magnitude (jet area, ERO by proximal convergence) may appear severe, while the brief duration of the regurgitation makes volumetric magnitude only moderate. Exercise echocardiography may be helpful risk-stratifying such patients.[96]

A number of centers are moving toward a more aggressive surgical approach in which mitral valve

repair is recommended to all patients with severe MR, independent of symptoms or LV function.[39,61,89,123] This approach is supported by data indicating that patients who undergo mitral valve repair while asymptomatic have significantly greater long-term survival rates than patients with even mild (NYHA Class II) preoperative symptoms (**see Fig. 69.20**).[94] In addition, patients with severe MR related to flail leaflets have greater long-term survival if they undergo prompt surgery rather than waiting for development of more severe symptoms or more severe hemodynamic compromise (**see Fig. 69.19**).[90] However, this recommendation for mitral valve repair in asymptomatic patients should be considered only for those with truly severe MR[12] (**see Table 69.3**) who are referred to centers where the surgical experience indicates a high degree of certainty of successful mitral valve repair.[39,105] Unfortunately, successful mitral valve repair cannot be guaranteed, and even in the best of circumstances, some young asymptomatic patients may be subjected to the risks of prosthetic valves prematurely and unnecessarily with this approach.

When mitral valve repair is not recommended, asymptomatic patients with normal LV function should be followed clinically and by echocardiography every 6 to 12 months with vigilance for any decline in functional capacity. A careful history or an exercise test often reveals that these patients are not truly asymptomatic.

If mitral valve replacement is likely to be necessary, a higher threshold for clinical and hemodynamic impairment should be used than if mitral valve repair is contemplated, and there are few indications for MVR in truly asymptomatic patients other than LV systolic dysfunction (**see Fig. 69.22**). Because of the higher operative mortality, older patients (>75 years) should generally undergo surgery only if they are symptomatic. In the setting of excessive operative risk, percutaneous intervention in primary MR with mitral clipping can be considered.

Symptomatic Patients.

Patients with severe primary MR and moderate or severe symptoms (NYHA Class II, III, and IV) should generally be considered for surgery. One exception is that of patients in whom the LVEF is less than 30% and echocardiography suggests that MVR will be required and that the subvalvular apparatus cannot be preserved. Because of the high risk of operation and the poor long-term results in these patients, medical therapy may be advised, but the outcome is poor in any event. However, when mitral valve repair appears possible, even patients with serious LV dysfunction may be considered for operation (**see Fig. 69.22**).[125]

Transcatheter Mitral Valve Repair

There is growing interest in the development of percutaneous approaches to mitral valve repair using either the edge-to-edge technique or the coronary sinus approach for percutaneous mitral annuloplasty[126] (**see Chapter 72**). The edge-to-edge method has generated the greatest clinical experience, mirroring the concept of the surgical Alfieri method for repair of MR by stitching the two mitral leaflets to create a double mitral orifice.[127] The transcatheter MitraClip device (Abbot Vascular) has received regulatory approval in both Europe and the United States. This device is delivered through an atrial transseptal approach and joins the tips of the anterior and posterior mitral leaflets, reducing and in some cases eliminating the MR (**see Fig. 72.8**). Data from clinical registries and a prospective clinical trial demonstrate successful implantation of the device in most patients in experienced centers,[128,129] although a second clip is needed in many patients to achieve effective reduction in MR. The reduction in MR is associated with favorable LV remodeling and amelioration of symptoms, both immediately and up to 4 years, with clinical results equivalent to those achieved surgically,[130,131] with worse results noted in those

with complex valve pathology.[132] Longer-term outcomes are not yet available. In view of the excellent and durable results with surgical repair of primary MR, including that in elderly patients, the MitraClip has been FDA approved only for those patients considered at prohibitive surgical risk because of extensive medical comorbidity. Data in this particular subset of patients treated with the edge-to-edge device have shown effectiveness in functional improvement and symptom relief.[133] Of note, whereas the MitraClip is approved in Europe for both primary and secondary MR, the FDA has only approved it for primary MR in the United States.

Chronic Secondary Mitral Regurgitation

Secondary MR stemming from LV dilation and systolic dysfunction (Video 69.20), often with concomitant mitral annular dilation, is a common consequence of ischemic and nonischemic cardiomyopathies[55] (**see Chapters 61 and 77**). **Table 69.4** outlines the clinical stages of secondary MR, updated to reflect the 2017 valve guideline,[124] which reestablished a single scale of severity for MR regardless of etiology, also reflected in the updated American Society of Echocardiography guideline for grading valve regurgitation.[12] Numerous studies have shown that secondary MR identifies patients with HF at higher risk for hemodynamic deterioration and death than those without MR (**see Chapter 23**). Even mild degrees of MR that would be well tolerated for decades in patients with primary MR stemming from MVP are associated with increased mortality over 3 to 5 years.[59,60] Because the mechanism of ischemic and nonischemic (or functional) MR is related to the magnitude of LV remodeling, patients with MR generally have lower EF and higher ESV than those without MR, and MR of greater severity is associated with more severe LV dysfunction and remodeling. Thus, MR is a marker of significant regional or global LV dysfunction. What is less clear is whether secondary MR, once established, contributes to progression of LV dysfunction and plays a causative role in the observed worse outcomes or is more a marker for poor outcome even if the MR was not present. Thus, whether secondary MR should be a target for surgical or device intervention remains uncertain.

TABLE 69.4

Stages of Chronic Secondary Mitral Regurgitation (MR)

STAGE	DEFINITION	VALVE ANATOMY	VALVE HEMODYNAMICS*	ASSOCIATED CLINICAL FINDINGS	SYMPTOMS
A	**At risk of MR**	Normal valve leaflets, chords, and annulus in a patient with coronary disease or cardiomyopathy	No MR jet or small central jet area <20% LA on Doppler Small vena contracta <0.30 cm	Normal or mildly dilated LV size with fixed (infarction) or inducible (ischemia) regional wall motion abnormalities Primary myocardial disease with LV dilation and systolic dysfunction	Symptoms caused by coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy.
B	**Progressive MR**	Regional wall motion abnormalities with mild tethering of mitral leaflet Annular dilation with mild loss of central coaptation of the mitral leaflets	ERO† <0.40 cm^2 RVol <60 mL RF <50%	Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction caused by primary myocardial disease	Symptoms caused by coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy.
C	**Asymptomatic severe MR**	Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet Annular dilation with severe loss of central coaptation of the mitral leaflets	ERO† ≥0.40 cm^2 RVol ≥60 mL RF ≥50%	Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction caused by primary myocardial disease	Symptoms caused by coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy.
D	**Symptomatic severe MR**	Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet Annular dilation with severe loss of central coaptation of mitral leaflets	ERO† ≥0.40 cm^2 RVol ≥60 mL RF ≥50%	Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction caused by primary myocardial disease	HF symptoms caused by MR persist even after revascularization and optimization of medical therapy. Decreased exercise tolerance Exertional dyspnea

*Several valve hemodynamic criteria are provided for assessment of MR severity, but not all criteria for each category will be present in each patient. Categorization of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.

†The measurement of the proximal isovelocity surface area (PISA) by two-dimensional transthoracic echocardiography (TTE) in patients with secondary MR underestimates the true ERO because of the crescentic shape of the proximal convergence.

ERO, Effective regurgitant orifice; *HF,* heart failure; *LA,* left atrium; *LV,* left ventricular; *RF,* regurgitant fraction; *RVol,* regurgitant volume.

From Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e1159-95.

Clinical Presentation

Symptoms

Patients with secondary MR related to LV dysfunction often present with HF symptoms, but many are asymptomatic (at least with regard to the MR), with MR detected incidentally on physical examination or echocardiography. AF is common.

Physical Examination

An apical S_3 is a common finding. As noted previously, the systolic murmur of secondary MR related to LV dilation may be soft and barely audible, particularly in patients with nonholosystolic MR that becomes minimal in midsystole. Thus the physical examination can be misleading regarding the presence and severity of secondary MR. The murmur of papillary muscle dysfunction may occur in late systole and is highly variable, often accentuated or holosystolic during acute myocardial ischemia and absent when ischemia is relieved.

Diagnosis and Evaluation

Echocardiography

Echocardiography is important in identifying the degree of LV dilation and systolic dysfunction, the presence and severity of MR (Video 69.21), and mechanisms responsible for secondary MR[2,55,134] (**see Chapter 14**). MR develops as a result of annular dilation and tethering of the mitral leaflets from geometric displacement or traction of the papillary muscles, and this tethering results in restricted leaflet closure with incomplete coaptation during systole (**see Figs. 14.31B and 14.41**). Most often the posterior leaflet is more severely restricted in closure, allowing the anterior leaflet to override it, producing a posteriorly directed jet of MR that may arise broadly along the commissural closure line. Because the magnitude of MR can vary so widely with loading conditions and ischemia, evaluation with exercise echocardiography can be informative.[54]

Cardiac Magnetic Resonance Imaging

CMR is useful in assessing severity of LV remodeling and contractile dysfunction, as well as the pattern of myocardial fibrosis as it relates to regional dysfunction and papillary muscle dysfunction.[12,135]

Medical Management of Secondary Mitral Regurgitation.

Patients with secondary MR stemming from LV dilation and dysfunction should undergo aggressive evidence-based medical management for LV systolic dysfunction (**see Chapter 25**). Beneficial reverse remodeling with medical therapy, especially with beta blockers, will reduce the severity of MR in many patients.

Resynchronization Therapy.

In patients with a dilated or ischemic cardiomyopathy and secondary MR, successful reverse remodeling with resynchronization therapy by biventricular chamber pacing (**see Chapters 25 and 26**) significantly reduces MR severity.[136,137] The mechanism of this effect probably is similar to that achieved in some patients with medical management, namely, LV remodeling with a reduction in ventricular size and associated improvement in alignment of the papillary muscles. This leads to improved leaflet coaptation and decreased regurgitant flow across the mitral valve.

Surgical Treatment of Secondary Mitral Regurgitation

Ischemic MR secondary to regional LV dysfunction with annular dilation may be treated by annuloplasty[138] (**see Chapter 28**), with rings designed to reduce the annular dilation and restore annular shape (**Fig. 69.23**). Annuloplasty also is successful in many patients with significant functional MR resulting from DCM. In select patients, mitral valve surgery improves symptomatic status.[139,140] Episodic MR caused by transient ischemia often is eliminated by coronary revascularization, whereas moderate to severe chronic MR secondary to ischemic heart disease usually requires mitral valve repair or replacement.[39,55] In patients undergoing CABG, some investigators recommend that concomitant mitral valve repair be considered for even mild MR. Several randomized trials have provided conflicting data on this subject. In the POINT study, a prospective trial of CABG versus CABG plus mitral valve repair in 102 patients with ischemic MR, those receiving mitral valve repair showed greater symptomatic improvement and higher LVEF and lower LV dimensions and PAP compared with those receiving CABG

alone, but no difference in survival between the two groups was demonstrated.[55,141] Subsequently, the RIME trial of CABG versus CABG plus mitral valve repair in 73 patients with ischemic MR of moderate severity reported higher peak oxygen consumption, lower LVESV index, and lower B-type natriuretic peptide (BNP) levels in patients receiving mitral valve repair, but once more, survival did not differ between the two groups.[142] Countering these small studies is the Cardiothoracic Surgical Trials Network (CTSN) trial of 301 patients with moderate MR (defined as ROA of 0.2 to 0.4 cm^2) all requiring CABG and randomized to mitral valve repair (with annuloplasty) versus CABG alone. Although significantly more patients had moderate or greater MR at 12 months in the no-repair group (31.0% versus 11.2%; $P < 0.001$), for the prespecified primary endpoint of postoperative ESV, there was no difference, nor was there any difference in mortality or major adverse cardiac events.[143] Similar results have been reported at follow-up to 2 years (**Fig. 69.24**).[144]

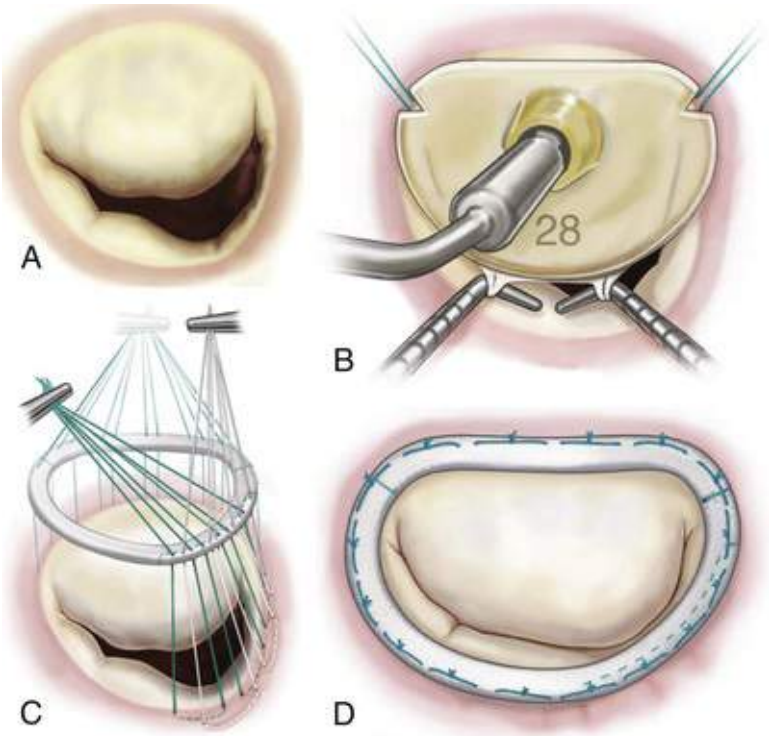


FIGURE 69.23 Surgical approach to ischemic mitral regurgitation. **A,** Typical findings with leaflet restriction predominantly in the P_2-P_3 region resulting in malcoaptation of the mitral leaflets. **B,** Sizing the annulus with a Carpentier-Edwards sizer is based primarily on the surface area and height of the anterior leaflet. **C,** Suturing the annuloplasty ring. **D,** After placement of a full remodeling annuloplasty ring, surface of coaptation is restored. (Modified from Carpentier A, Adams DH, Filsoufi F, editors. Carpentier's Reconstructive Valve Surgery. Philadelphia: Saunders; 2010.)

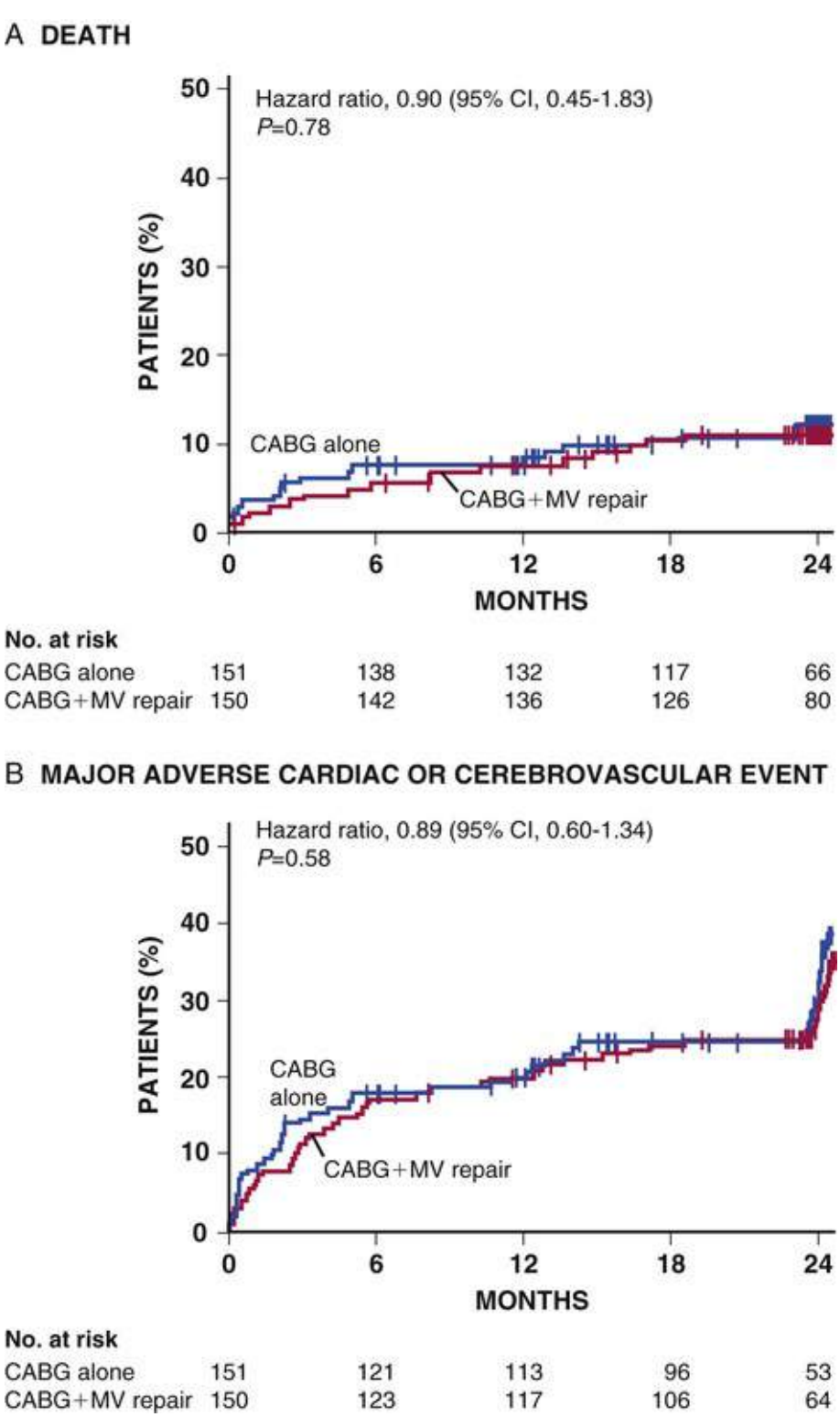


FIGURE 69.24 Two-year outcomes of patients with moderate mitral regurgitation undergoing coronary artery bypass surgery (CABG) who were randomized to CABG alone versus CABG plus mitral valve (MV) repair. **A,** Death. **B,** Composite endpoint of major adverse cardiac or cerebrovascular events. (From Michler RE, Smith PK, Parides MK, et al. Two-year outcomes of surgical treatment of moderate ischemic mitral regurgitation. N Engl J Med 2016;374:1932-41.)

These trials illustrate that in patients with functional MR, the primary problem is disease of the LV myocardium, and prognosis is strongly influenced by the degree of LV dysfunction and residual ischemia. Mitral valve repair or replacement in these latter patients has a less beneficial effect on long-term outcome, particularly in those with ischemic MR, than in patients with degenerative MR. Thus the indications for mitral valve surgery are less clear for secondary MR than for primary MR, exemplified by there being no class I or IIa indications for isolated surgery in secondary MR (**see Fig. 69.22**). Moreover, unlike repair of primary MR caused by myxomatous disease or fibroelastic deficiency, in which an

experienced surgeon can produce results that are durable for decades, mitral valve repair of secondary MR is often not durable because of progression of the underlying LV myocardial disease.[145] This has fueled suggestions that mitral valve replacement might provide a more durable surgical solution to secondary MR with reduced recurrence rates.[146] This was addressed in a retrospective, propensity-matched study of MVR versus mitral valve repair in 1006 patients with ischemic MR.[147] Survival did not differ between the two groups, but patients undergoing mitral valve repair had a significantly greater likelihood of requiring reoperation. These results were further confirmed in a CTSN prospective randomized clinical trial of mitral valve repair versus replacement in 251 patients with severe ischemic MR,[148] which demonstrated that MVR achieved equivalent degrees of reduction in LV volume with replacement and repair, with less recurrent MR during the follow-up period, now confirmed to 2 years[149] (**Fig. 69.25**). This equipoise was driven largely by the 32.6% of repair patients who had recurrent moderate or greater MR at 1 year (rising to 58.8% at 2 years). Among the patients with recurrent MR, LV end-systolic volume index was significantly larger than in those without recurrence (62.6 ±26.9 and 42.7 ±26.4 mL, respectively; $P < 0.001$). These data have informed predictive models to identify patients most likely to fail a mitral valve repair,[150] including those with larger EROA, outward tethering of the valve, and those with inferobasal aneurysms. In multivariate analysis, the ratio of LV end-systolic diameter to the annuloplasty ring diameter was most predictive of recurrent MR.[151] Such patients appear to be better served by a chordal-sparing MVR.

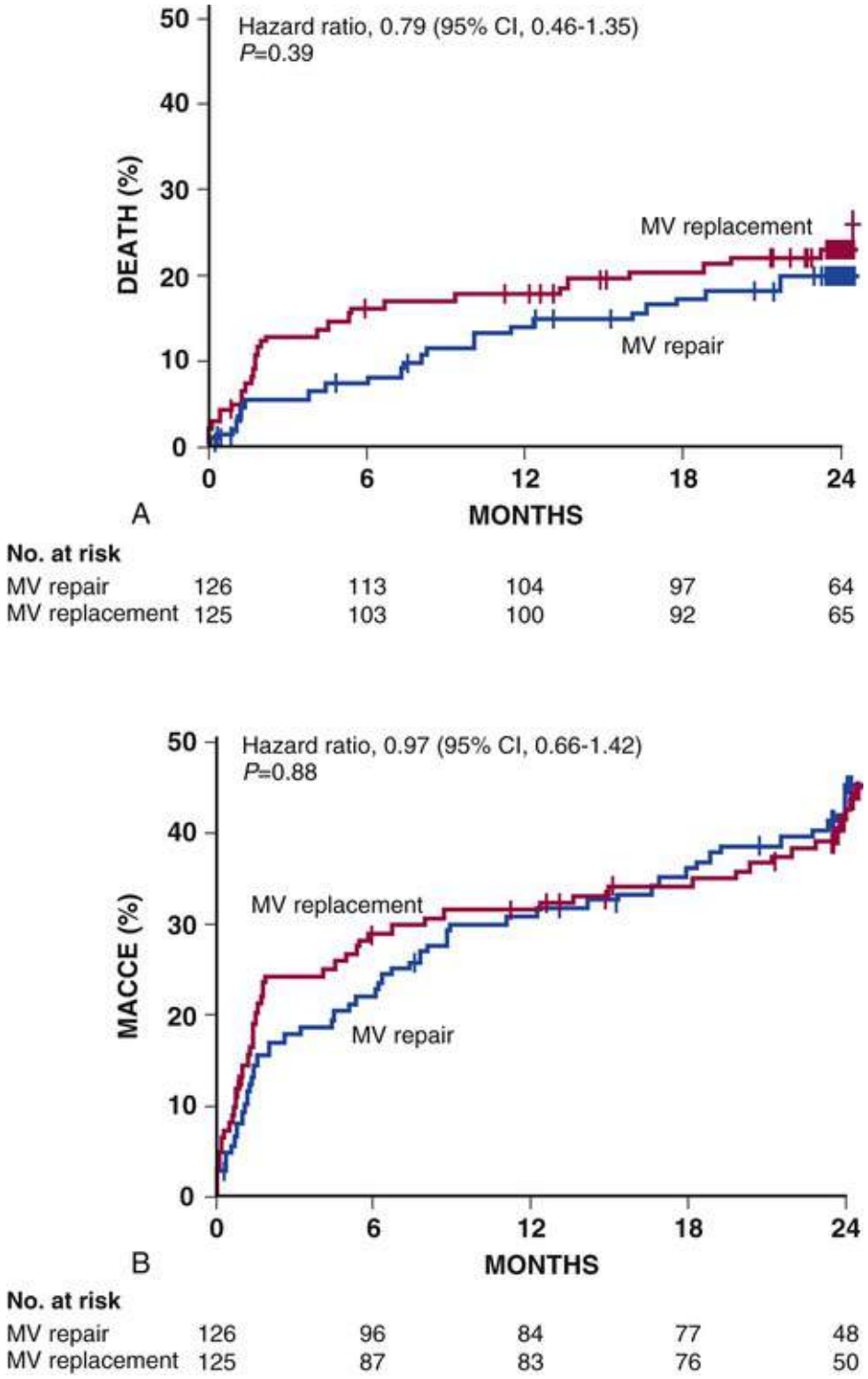


FIGURE 69.25 Postoperative outcomes of patients with ischemic mitral regurgitation randomly assigned to mitral valve (MV) repair versus replacement. **A,** Mortality. **B,** Composite endpoint of death, stroke, repeat MV surgery, hospitalization for heart failure, and increase in NYHA functional class by 1 or more; MACCE, major adverse cardiac or cerebrovascular events. (From Goldstein D, Moskowitz AJ, Gelijns AC, et al. Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. N Engl J Med 2016;374:344-53.)

Transcatheter Treatment of Secondary Mitral Regurgitation.

Considering the high mortality and morbidity associated with secondary MR in the setting of LV dysfunction, whether medically or surgically treated, and evidence of symptomatic improvement among some patients after surgical mitral valve repair or replacement, a less invasive intervention to reduce or eliminate MR is appealing. In Europe, where the MitraClip is an approved device for all MR etiologies,

approximately two thirds of device implantations are in patients with secondary MR,[152] with registry data indicating substantial reduction in MR severity and improved symptom status,[129] with similar results in patients with functional MR from ischemic and nonischemic etiologies[153] (**see Chapter 72**). One European study reported improved symptoms and beneficial reverse LV remodeling after MitraClip implantation in patients with severe MR and HF who had not responded to previous beta blockade and resynchronization therapy.[154] The MitraClip is not yet approved in the United States for secondary forms of MR, pending results of ongoing prospective clinical trials in this condition.

Acute Mitral Regurgitation

The causes of acute MR are diverse and represent acute manifestations of disease processes that may, under other circumstances, cause chronic MR (**see eTable 69.1**). Especially important causes of acute MR are spontaneous rupture of chordae tendineae, infective endocarditis with disruption of valve leaflets or chordal rupture, ischemic dysfunction or rupture of a papillary muscle, and malfunction of a prosthetic valve.

Clinical Presentation

Acute severe MR causes a marked reduction in forward stroke volume, a slight reduction in ESV, and an increase in EDV. One major hemodynamic difference between acute and chronic MR derives from the differences in LA compliance. Patients who develop acute severe MR usually have a normal-sized left atrium, with normal or reduced LA compliance. The LA pressure rises abruptly, which often leads to pulmonary edema, marked elevation of PVR, and right-sided HF.

Because the *v* wave is markedly elevated in patients with acute severe MR, the reverse pressure gradient between the left ventricle and left atrium declines at the end of systole, and the murmur may be decrescendo rather than holosystolic, ending well before A_2. It usually is lower-pitched and softer than the murmur of chronic MR. A left-sided S_4 frequently is found. Pulmonary hypertension, which is common in patients with acute MR, may increase the intensity of P_2, and the murmurs of pulmonic regurgitation and TR also may develop, along with a right-sided S_4. In patients with severe, acute MR, a *v* wave (late systolic pressure rise) in the PAP pulse (**see eFig. 69.5**) may rarely cause premature closure of the pulmonic valve, an early P_2, and paradoxical splitting of S_2. Acute MR, even if severe, often does not increase overall cardiac size, as seen on the chest radiograph, and may produce only mild LA enlargement despite marked elevation of LA pressure. In addition, the echocardiogram may show little initial increase in the LV or LA internal diameter, but increased LV systolic motion is prominent. Characteristic features on Doppler echocardiography are the severe jet of MR (**see Fig. 14.30**) and elevation of the systolic PAP. Similar to the physical examination, the high atrial *v* wave can lead to early cessation of MR and a triangular-shaped CW Doppler profile instead of the usual parabolic shape. Careful interrogation of the valve by both TTE and TEE is essential to identify the mechanism and underlying etiology of the acute valve dysfunction.

In severe MR secondary to acute MI, pulmonary edema, hypotension, and frank cardiogenic shock may develop. It is essential to determine the cause of the MR, which may be a ruptured papillary muscle (**see Fig. 14.30**), annular dilation from severe LV dilation, or papillary muscle displacement with leaflet tethering.[155]

Medical Management of Acute Mitral Regurgitation

Afterload reduction is particularly important in treating patients with acute MR. IV nitroprusside may be lifesaving in patients with acute MR caused by rupture of the head of a papillary muscle complicating an acute MI. It may permit stabilization of clinical status, thereby allowing coronary arteriography and surgery to be performed with the patient in optimal condition. In patients with acute MR who are hypotensive, an inotropic agent such as dobutamine should be administered with the nitroprusside. Intra-aortic balloon counterpulsation may be necessary to stabilize the patient while preparations for surgery are made.

Surgical Treatment of Acute Mitral Regurgitation

Emergency surgical treatment may be required for patients with acute LV failure caused by acute severe MR. Emergency surgery is associated with higher mortality rates than for elective surgery for chronic MR.[119] However, unless patients with acute severe MR and HF are treated aggressively, a fatal outcome is almost certain.

Acute papillary muscle rupture requires emergency surgery with mitral valve repair or replacement. In patients with papillary muscle dysfunction, initial treatment should consist of hemodynamic stabilization, usually with the aid of an intra-aortic balloon pump, and surgery should be considered for those patients who do not experience improvement with aggressive medical therapy. If patients with MR can be stabilized by medical treatment, it is preferable to defer operation until 4 to 6 weeks after the infarction, if possible. Vasodilator treatment may be useful during this period. However, medical management should not be prolonged if multisystem (renal and/or pulmonary) failure develops.

Surgical mortality rates also are higher in patients with acute MR and refractory HF (NYHA Class IV), those with prosthetic valve dysfunction, and those with active infective endocarditis (of a native or prosthetic valve). Despite the higher surgical risks, the efficacy of early operation has been established in patients with infective endocarditis complicated by medically uncontrollable congestive heart failure and recurrent emboli (**see Chapter 73**).

Percutaneous Treatment of Acute Mitral Regurgitation

Experience is limited with percutaneous approaches to acute MR, although early reports support the selective use of the MitraClip in postinfarct MR[156] and even endocarditis, once the infection has been cleared.[157]

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70

Tricuspid, Pulmonic, and Multivalvular Disease

Patricia A. Pellikka

Tricuspid Stenosis

Causes and Pathology

Tricuspid stenosis (TS) is almost always rheumatic in origin, although rheumatic valve disease more frequently affects left-sided valves.[1] Other causes of obstruction to right atrial (RA) emptying are unusual and include congenital tricuspid atresia (**see Chapter 75**); RA tumors, which may produce a clinical picture suggesting rapidly progressive TS (**Chapter 95**); and device leads, which more often are associated with tricuspid regurgitation (TR), but can become looped and fused to the tricuspid valve apparatus and, particularly if multiple, cause obstruction. The carcinoid syndrome (**see Chapter 77**) and use of ergot-related drugs more frequently produce TR, which if severe contributes to a gradient across the tricuspid valve[2] (Video 70.1C). Dysfunction, including thrombosis, of a tricuspid mechanical or bioprosthetic valve can result in stenosis. Rarely, obstruction to right ventricular (RV) inflow can be caused by endomyocardial fibrosis, tricuspid valve vegetations, or extracardiac tumors.

Most patients with rheumatic tricuspid valve disease have TR or a combination of TS and TR. Isolated rheumatic tricuspid valve disease is uncommon, and this lesion generally accompanies mitral valve disease, which dominates the presentation (**see Chapter 69**). In many patients with TS, the aortic valve also is involved (i.e., trivalvular stenosis is present). TS is found at autopsy in approximately 15% of patients with rheumatic heart disease but is of clinical significance in only approximately 5%. Organic tricuspid valve disease is more common in India, Pakistan, and other developing nations near the equator than in North America or Western Europe. The anatomic changes of rheumatic TS resemble those of mitral stenosis (MS), with fusion and shortening of the chordae tendineae and fusion of the leaflets at their edges, producing a diaphragm with a fixed central aperture. However, valvular calcification is rare. As with MS, TS is more common in women. The right atrium often is greatly dilated in TS, and its walls are thickened. There may be evidence of severe passive congestion, with enlargement of the liver and spleen.

Pathophysiology

A diastolic pressure gradient between the right atrium and ventricle—the hemodynamic expression of TS—is augmented when the transvalvular blood flow increases during inspiration or exercise. A relatively modest diastolic pressure gradient (i.e., a mean gradient of only 5 mm Hg) usually is sufficient to elevate the mean RA pressure to levels that result in systemic venous congestion and, unless sodium intake has been restricted or diuretics have been given, is associated ultimately with jugular venous distention (JVD), ascites, and edema.

In patients with sinus rhythm, the RA *a* wave may be very tall. Resting cardiac output usually is markedly reduced and fails to rise during exercise. This accounts for the normal or only slightly elevated left atrial (LA), pulmonary artery, and RV systolic pressures, despite the presence of accompanying mitral valvular disease.

A mean diastolic pressure gradient across the tricuspid valve as low as 2 mm Hg, and the typical echocardiographic appearance of leaflet restriction or “doming” is sufficient to establish the diagnosis of TS. Exercise, deep inspiration, and the rapid infusion of fluids or administration of atropine may greatly enhance a borderline pressure gradient in a patient with TS. The diagnosis is generally made with transthoracic echocardiography (TTE); occasionally, transesophageal echocardiography (TEE) or other imaging is necessary. Rarely is invasive assessment necessary.

Clinical Presentation and Diagnosis

Symptoms.

The low cardiac output characteristic of TS causes fatigue, and patients often experience discomfort caused by hepatomegaly, ascites, and anasarca (**Table 70.1**). The severity of these symptoms, which are secondary to an elevated systemic venous pressure, is out of proportion to the degree of dyspnea. Some patients complain of a fluttering discomfort in the neck, caused by giant *a* waves in the jugular venous pulse (JVP). Occasionally, the symptoms of MS (severe dyspnea, orthopnea, and paroxysmal nocturnal dyspnea) may be masked in the presence of severe TS because the latter prevents surges of blood into the pulmonary circulation behind the stenotic mitral valve. The absence of symptoms of pulmonary congestion in a patient with obvious MS should suggest the possibility of TS.

TABLE 70.1

Clinical and Laboratory Features of Rheumatic Tricuspid Stenosis

History
Progressive fatigue, edema, anorexia
Minimal orthopnea, paroxysmal nocturnal dyspnea
Rheumatic fever in two thirds of patients
Female preponderance
Pulmonary edema and hemoptysis rare
Physical Findings
Signs of multivalvular involvement
Diastolic rumble at lower left sternal border, increasing in intensity with inspiration
Often confused with mitral stenosis
Peripheral cyanosis
Neck vein distention, with prominent *a* waves and slow *y* descent
Absent right ventricular lift
Associated murmurs of mitral and aortic valve disease
Hepatic pulsation
Ascites, peripheral edema
Imaging Findings
Electrocardiogram: Tall right atrial P waves and no right ventricular hypertrophy
Chest radiograph: Dilated right atrium without enlarged pulmonary artery segment
Echocardiogram: Diastolic doming of tricuspid valve leaflets, thickening of valve, diastolic pressure gradient across tricuspid valve, right atrial enlargement

Modified from Ockene IS. Tricuspid valve disease. In Dalon JE, Alpert JS, editors. Valvular Heart Disease. 2nd ed. Boston: Little Brown; 1987, pp 356, 390.

Physical Examination.

Because MS occurs frequently in patients with TS and the two valvular lesions have similar physical findings, and because the physical findings in TS are subtle, echocardiography is essential for the diagnosis of TS. The physical findings of TS may be attributed to MS, which is more common and associated with a louder murmur. Therefore a high index of clinical suspicion is required to detect TS. In the presence of sinus rhythm, the *a* wave in the JVP is tall, and a presystolic hepatic pulsation often is palpable. The *y* descent is slow and barely appreciable. The lung fields are clear, and despite engorged neck veins and the presence of ascites and anasarca, the patient may be comfortable while lying flat. Thus the diagnosis of TS may be suspected from inspection of the JVP in a patient with MS but without clinical evidence of pulmonary hypertension. This suspicion is strengthened when a diastolic thrill is palpable at the lower left sternal border, particularly if the thrill appears or becomes more prominent during inspiration.

The auscultatory findings of the accompanying MS usually are prominent and often overshadow the more subtle signs of TS. A tricuspid opening snap (OS) may be audible but often is difficult to distinguish from a mitral OS. However, the tricuspid OS usually follows the mitral OS and is localized to the lower left sternal border, whereas the mitral OS usually is most prominent at the apex and radiates more

widely. The diastolic murmur of TS is also usually heard best along the lower left parasternal border in the fourth intercostal space and usually is softer, higher-pitched, and shorter in duration than the murmur of MS. The presystolic component of the TS murmur has a scratchy quality and a crescendo-decrescendo configuration that diminishes before the first heart sound (S_1). The diastolic murmur and OS of TS both are augmented by maneuvers that increase transtricuspid valve flow, including inspiration, the Müller maneuver (forced inspiration against a closed glottis), assumption of the right lateral decubitus position, leg raising, inhalation of amyl nitrite, squatting, and isotonic exercise. The murmur and OS are reduced during expiration or the strain of the Valsalva maneuver and return to control levels immediately (i.e., within two or three beats) after Valsalva release.

Electrocardiography.

In the absence of atrial fibrillation (AF) in a patient with valvular heart disease, TS is suggested by the presence of electrocardiographic evidence of RA enlargement (**see Chapter 12**). The P wave amplitude in leads II and V_1 exceeds 0.25 mV. Because most patients with TS have mitral valve disease, the electrocardiographic signs of biatrial enlargement are often seen. The amplitude of the QRS complex in lead V_1 may be reduced by the dilated right atrium.

Radiography.

The key radiologic finding is marked cardiomegaly with conspicuous enlargement of the right atrium (i.e., prominence of the right heart border), which extends into a dilated superior vena cava and azygos vein, but without conspicuous dilation of the pulmonary artery. The vascular changes in the lungs characteristic of mitral valvular disease may be masked, with little or no interstitial edema or vascular redistribution, but LA enlargement may be present.

The stenotic tricuspid valve can also be visualized with cardiac magnetic resonance imaging (CMR) or computed tomography (CT) and RA and RV volumes quantified.

Echocardiography

The tricuspid valve should be carefully inspected at echocardiography in any patient with known or suspected rheumatic heart disease or other valve disease known to affect multiple valves. The echocardiographic changes (**see Chapter 14**) of the tricuspid valve in rheumatic TS resemble those observed in the mitral valve in rheumatic MS.[3] Two-dimensional echocardiography characteristically shows diastolic doming of the leaflets (**see Fig. 14.51**), thickening and restricted motion of the other leaflets, reduced separation of the tips of the leaflets, and a reduction in diameter of the tricuspid orifice. The presence of commissural fusion and the anatomy of the valve and subvalvular apparatus should also be assessed, because these features may impact therapy. TEE allows added delineation of the details of valve structure (see Video 70.2, which shows thickening and stenosis of the tricuspid valve and associated thrombus on the lateral aspect of the right atrium), and Doppler echocardiography can be helpful in assessing severity of TS when two-dimensional images are suboptimal. In TS, Doppler echocardiography shows a prolonged slope of antegrade flow and compares well with cardiac catheterization in the quantification of TS and assessment of associated TR. Doppler evaluation of TS has largely replaced the need for catheterization to assess severity. Severe TS is characterized by a valve area of 1 cm^2 or less, as assessed by the continuity equation. The pressure half-time is generally greater than 190 milliseconds, and the right atrium and inferior vena cava are dilated. The mean pressure gradient across the tricuspid valve varies with heart rate, but a mean gradient of 5 mm Hg or greater is consistent with significant TS.[4] Additional assessment of valve morphology may be provided by three-dimensional echocardiography, which allows en face views of the tricuspid valve and simultaneous views of all three

leaflets.[3]

Cardiac Catheterization

Invasive hemodynamic assessment of TS is rarely needed but is appropriate in the symptomatic patient in whom the physical findings and noninvasive data are discordant. It may occasionally be undertaken in patients undergoing invasive hemodynamic assessment for another indication. RA and RV pressures can be recorded simultaneously, using two catheters or a single catheter with a double lumen, with one lumen opening on either side of the tricuspid valve.

Management

Although the fundamental approach to the management of severe TS is surgical treatment, intensive sodium restriction and diuretic therapy may diminish symptoms secondary to accumulation of excess salt and water. If AF is present, ventricular rate control is needed to improve diastolic filling. A preparatory period of diuresis may diminish hepatic congestion, thereby improving hepatic function sufficiently to diminish the risks of subsequent operation.

Most patients with TS have coexisting valvular disease that requires surgery. Surgical treatment of TS should be done at mitral valve repair or replacement in TS patients with mean diastolic pressure gradient exceeding 5 mm Hg and tricuspid orifice less than approximately 2.0 cm^2. The final decision concerning surgical treatment is sometimes made at the operating table.

Because TS almost always is accompanied by some TR, simple finger fracture valvotomy may not result in significant hemodynamic improvement, and may merely substitute severe TR for TS. However, open valvotomy or commissurotomy in which the stenotic tricuspid valve is converted into a functionally bicuspid valve may result in improvement, but annuloplasty may also be necessary if annular dilation is present.[5] The commissures between the anterior and septal leaflets and between the posterior and septal leaflets are opened. It is not advisable to open the commissure between the anterior and posterior leaflets because of the concern of producing severe TR. If open valvotomy does not restore reasonably normal valve function, the tricuspid valve may have to be replaced. A large bioprosthesis is preferred to a mechanical prosthesis in the tricuspid position because of the high risk of thrombosis of the latter and the longer durability of bioprostheses in the tricuspid than in the mitral or aortic positions. Tricuspid balloon valvuloplasty is feasible, but has limited efficacy and may result in significant TR. It may be considered in the rare patient without TR, but because of lack of long-term outcome data, surgical therapy is preferred.

Tricuspid Regurgitation

Causes and Pathology

A trivial to mild amount of TR is frequently seen with echocardiography in patients with a normal right heart and structurally normal tricuspid valve. This is of no consequence and, under normal conditions, does not increase in severity. However, various conditions can lead to greater degrees of TR. The most common cause of TR is *not* intrinsic involvement of the valve itself (i.e., primary TR) but rather dilation of the right ventricle and of the tricuspid annulus causing secondary (functional) TR[6-8] (**Table 70.2**; **see also Fig. 14.52**). Right-sided heart dilation may result from volume overload as seen with left-to-right shunts in atrial septal defects (ASDs) or anomalous pulmonary venous connections. Dilation may be a

complication of RV failure of any cause. It is observed in patients with RV hypertension secondary to any form of cardiac or pulmonary vascular disease. Thus, secondary TR may be seen in mitral valve disease,[8,9] acute or chronic pulmonary thromboembolic disease, or chronic obstructive lung disease. In general, RV systolic pressure greater than 55 mm Hg will cause functional TR. TR can also result from RV infarction, congenital heart disease (e.g., pulmonic stenosis and pulmonary hypertension secondary to Eisenmenger syndrome; **see Chapter 75**), primary pulmonary hypertension (**Chapter 85**), and cor pulmonale. In infants, TR may complicate RV failure secondary to neonatal pulmonary diseases and pulmonary hypertension with persistence of the fetal pulmonary circulation. In all these cases, TR reflects the presence of, and in turn aggravates, severe RV failure. Functional TR may diminish or disappear as the right ventricle decreases in size with the treatment of heart failure. TR can also result from dilation of the annulus in Marfan syndrome, in which RV dilation secondary to pulmonary hypertension is not present.

TABLE 70.2
Causes and Mechanisms of Pure Tricuspid Regurgitation

Causes			
Anatomically Abnormal Valve			
Rheumatic			
Nonrheumatic			
Infective endocarditis			
Ebstein anomaly			
Floppy (prolapse)			
Congenital (non-Ebstein anomaly)			
Carcinoid			
Papillary muscle dysfunction			
Trauma			
Connective tissue disorders (Marfan syndrome)			
Rheumatoid arthritis			
Radiation injury			
Anatomically Normal Valve (Functional, Dilated Annulus)			
Elevated right ventricular systolic pressure			
Chronic atrial fibrillation			
Restrictive cardiomyopathy			
Mechanisms			
Condition	**Leaflet Area**	**Annular Circumference**	**Leaflet Insertion**
Floppy	↑	↑	Normal
Ebstein anomaly	↑	↑	Abnormal
Pulmonary/right ventricular systolic hypertension	Normal	↑	Normal
Papillary muscle dysfunction	Normal	Normal	Normal
Carcinoid	↓/Normal	Normal	Normal
Rheumatic	↓/Normal	Normal	Normal
Infective endocarditis	↓/Normal	Normal	Normal

Modified from Waller BF. Rheumatic and nonrheumatic conditions producing valvular heart disease. In Frankl WS, Brest AN, editors. Cardiovascular Clinics. Valvular Heart Disease: Comprehensive Evaluation and Management. Philadelphia: FA Davis; 1989, pp 35, 95.

A variety of disease processes can affect the tricuspid valve apparatus directly and lead to regurgitation (primary TR).[1,10] Organic TR may occur on a congenital basis (**see Chapter 75**), as part of Ebstein anomaly, defects involving the atrioventricular canal, when the tricuspid valve is involved in the formation of an aneurysm of the ventricular septum, or in corrected transposition of the great arteries, or it may occur as an isolated congenital lesion. Rheumatic fever may involve the tricuspid valve directly. When this occurs, it usually causes scarring of the valve leaflets and chordae tendineae, leading to limited leaflet mobility and either isolated TR or a combination of TR and TS. Rheumatic involvement of the mitral, and often the aortic, valve coexists.

TR may result from prolapse of the tricuspid valve caused by myxomatous changes in the valve and chordae tendineae; mitral valve prolapse (MVP) is usually present in these patients as well. Tricuspid valve prolapse has been estimated to occur in 20% of all patients with MVP, but compared to MVP,

diagnostic criteria are less well defined. Tricuspid valve prolapse also may be associated with ASD.

Distortion of the tricuspid leaflets by transvenous pacemaker and defibrillator leads is an increasingly common cause of clinically significant TR.[11] Injury to the tricuspid valve or subvalvular apparatus may complicate endomyocardial biopsy.

TR or the combination of TR and TS is an important feature of the *carcinoid syndrome* (**Fig. 70.1; see also Fig. 14.53**), which leads to focal or diffuse deposits of fibrous tissue on the endocardium of the valvular cusps and cardiac chambers, as well as on the intima of the great veins and coronary sinus. The white, fibrous carcinoid plaques are most extensive on the right side of the heart, where they usually are deposited on the ventricular surfaces of the tricuspid valve and cause the cusps to adhere to the underlying RV wall, thereby producing TR. A similar process may affect the tricuspid valve in patients who have used drugs that increase serotonin levels or simulate its effect on serotonin receptors (see Video 70.1). These include the anorectic drugs fenfluramine and phentermine, ergot derivatives used for treating migraine headaches (ergotamine, methysergide) or Parkinson disease (pergolide, cabergoline), or the synthetic stimulant and hallucinogen 3,4-methylenedioxymethamphetamine (MDMA, “Ecstasy”).

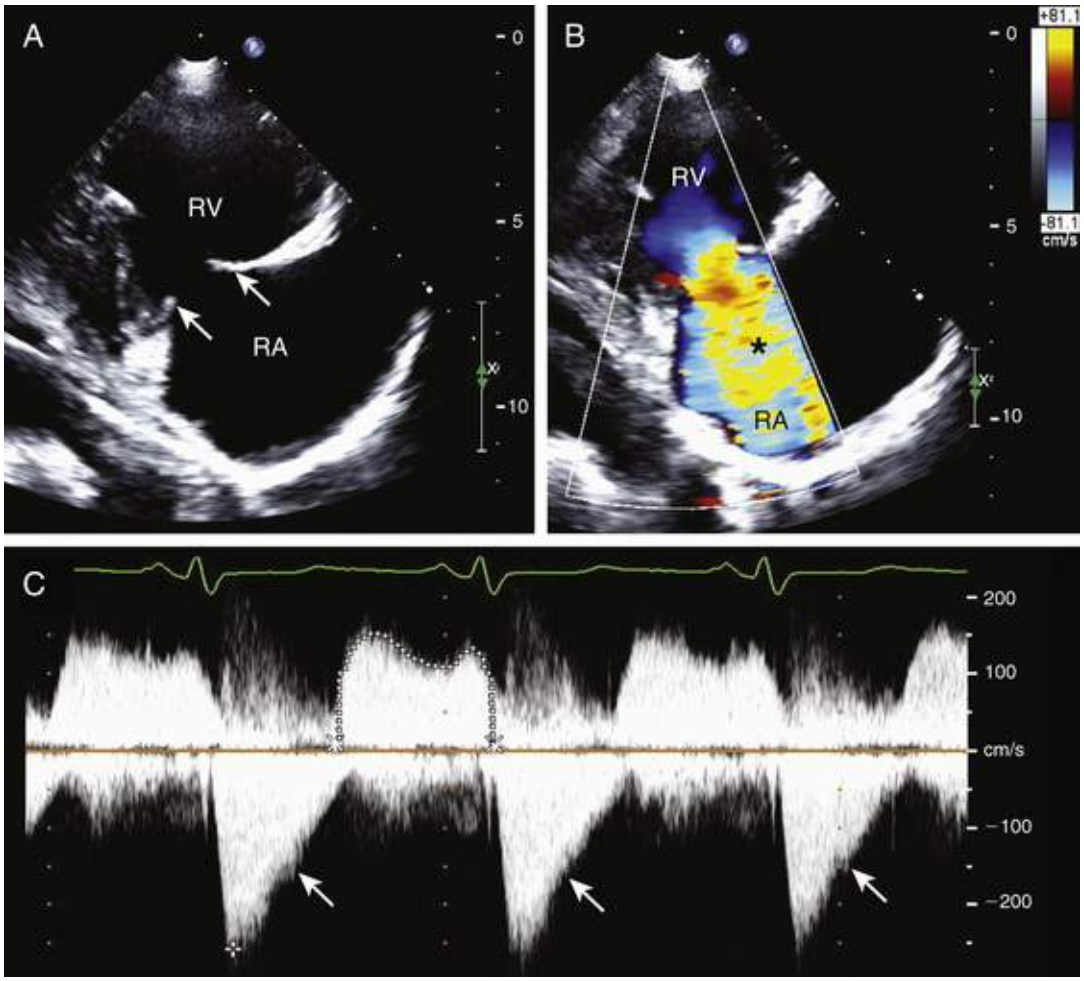

FIGURE 70.1 Transthoracic echocardiographic images of the tricuspid valve in a patient with carcinoid valvular heart disease. **A,** Two-dimensional parasternal long-axis image of the tricuspid valve inflow view in midsystole demonstrates a marked thickening and retraction of the tricuspid valve leaflets (*arrow*), resulting in failure of leaflet closure. **B,** Color Doppler imaging of the tricuspid valve in the parasternal long-axis tricuspid valve inflow view in midsystole demonstrates a broad regurgitant jet that occupies the entire right atrium, consistent with severe tricuspid valve regurgitation (*). *RA,* Right atrium; *RV,* right ventricle. **C,** Continuous-wave Doppler imaging across the tricuspid valve demonstrates a dense, systolic, dagger-shaped tricuspid regurgitant jet consistent with severe TR (*arrow*). Less severe forms of TR are typically associated with parabolic-shaped regurgitant jets. (From Luis SA, Pellikka PA. Carcinoid heart disease: diagnosis and management. Best Pract Res Clin Endocrinol Metab 2016;30:149.)

Other causes of TR include penetrating and nonpenetrating trauma,[12] dilated cardiomyopathy, and infective endocarditis (IE), particularly staphylococcal endocarditis in intravenous (IV) drug users. Endomyocardial fibrosis with shortening of the tricuspid leaflets and chordae tendineae is an important cause of TR in tropical Africa. Less common causes of TR include cardiac tumors (particularly RA myxoma), endomyocardial fibrosis, methysergide-induced valvular disease, and systemic lupus erythematosus involving the tricuspid valve.

Clinical Presentation and Diagnosis

The clinical stages of TR are outlined in **Table 70.3**.[13]

TABLE 70.3

Stages of Tricuspid Regurgitation (TR)

STAGE	DEFINITION	VALVE ANATOMY	VALVE HEMODYNAMICS*	HEMODYNAMIC CONSEQUENCES	SYMPTOMS
A	**At risk of TR**	*Primary:* Mild rheumatic change Mild prolapse Other (e.g., IE with vegetation, early carcinoid deposition, radiation) *Intra-annular:* RV pacemaker or ICD lead Postcardiac transplantation (biopsy related) *Functional:* Normal Early annular dilation	No or trace TR	None	None or in relation to other left heart or pulmonary/pulmonary vascular disease
B	**Progressive TR**	*Primary:* Progressive leaflet deterioration/destruction Moderate to severe prolapse, limited chordal rupture *Functional:* Early annular dilation Moderate leaflet tethering	*Mild TR:* Central jet area <5 cm^2 Vena contracta width not defined CW jet density and contour: soft and parabolic Hepatic vein flow: systolic dominance *Moderate TR:* Central jet area 5-10 cm^2 Vena contracta width not defined, but <0.70 cm CW jet density and contour: dense, variable contour Hepatic vein flow: systolic blunting	*Mild TR:* RV/RA/IVC size normal *Moderate TR:* No RV enlargement No or mild RA enlargement No or mild IVC enlargement with normal respirophasic variation Normal RA pressure	None or in relation to other left heart or pulmonary/pulmonary vascular disease
C	**Asymptomatic, severe TR**	*Primary:* Flail or grossly distorted leaflets *Functional:* Severe annular dilation (>40 mm or 21 mm/m^2) Marked leaflet tethering	*Severe TR:* Central jet area >10 cm^2 Vena contracta width >0.7 cm CW jet density and contour: dense, triangular with early peak Hepatic vein flow: systolic reversal	RV/RA/IVC dilated with decreased IVC respirophasic variation Elevated RA pressure with "*c-v*" wave Diastolic interventricular septal flattening may be present.	None, or in relation to other left-heart or pulmonary/pulmonary vascular disease
D	**Symptomatic, severe TR**	Same as for stage C	Same as for stage C	Same as for stage C Right ventricular systolic function eventually reduced	Fatigue, palpitations, dyspnea, abdominal bloating, anorexia, edema

*Several valve hemodynamic criteria are provided for assessment of TR severity, but not all criteria for each category will necessarily be present in every patient. Classification of TR severity as mild, moderate, or severe also depends on image quality an integration of these parameters with clinical findings.

CW, Continuous-wave; *ICD,* implantable cardioverter-defibrillator; *IE,* infective endocarditis; *IVC,* inferior vena cava; *RA,* right atrium; *RV,* right ventricle.

From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACCF guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57.

Symptoms.

In the absence of pulmonary hypertension or RV failure, TR generally is well tolerated. When pulmonary hypertension and TR coexist, cardiac output declines and the manifestations of right-sided heart failure become intensified. Thus the symptoms of TR result from a reduced cardiac output and from ascites, painful congestive hepatomegaly, and massive edema. Occasionally, patients exhibit throbbing pulsations in the neck, which intensify on effort and are caused by JVD, and systolic pulsations of the eyeballs also have been described. In the many patients with TR who have mitral valve disease, the symptoms of the

latter usually predominate. Symptoms of pulmonary congestion may abate as TR develops but are replaced by weakness, fatigue, and other manifestations of a depressed cardiac output.

Physical Examination.

In patients with severe TR, evidence of weight loss and cachexia, cyanosis, and jaundice are often present on inspection. AF is common. JVD also is evident, the normal *x* and *x*′ descents disappear, and a prominent systolic wave—a *c*-*v* wave (or *s* wave)—is apparent. The descent of this wave, the *y* descent, is sharp and becomes the most prominent feature of the venous pulse, except with coexisting TS, in which case it is slowed. A venous systolic thrill and murmur in the neck may be present in patients with severe TR. The RV impulse is hyperdynamic and thrusting in quality. Systolic pulsations of an enlarged tender liver are frequently present initially. However, in patients with chronic TR and congestive cirrhosis, the liver may become firm and nontender. Ascites and edema are common.

With auscultation, the murmur of mild TR may be very subtle and of short duration. When TR occurs in the absence of pulmonary hypertension (e.g., in IE or after trauma), the murmur usually is of low intensity and limited to the first half of systole. With greater degrees of TR, auscultation usually reveals a S_3 originating from the right ventricle, which is accentuated by inspiration. When TR is associated with and secondary to pulmonary hypertension, P_2 is accentuated as well, and the systolic murmur usually is high-pitched, pansystolic, and loudest in the fourth intercostal space in the parasternal region (but occasionally is loudest in the subxiphoid area). When the right ventricle is greatly dilated and occupies the anterior surface of the heart, the murmur may be prominent at the apex and difficult to distinguish from that produced by mitral regurgitation (MR).

The response of the systolic murmur to respiration and other maneuvers is of considerable aid in establishing the diagnosis of TR. The murmur characteristically is augmented during inspiration (Carvallo sign), with inspiration associated with an increase in RV size and tricuspid valve annulus dimension, as well as an increase in regurgitant orifice area.[14] However, when the failing ventricle can no longer increase its stroke volume with the patient in the recumbent or sitting position, the inspiratory augmentation may be elicited by standing. The murmur also increases during the Müller maneuver (see earlier), exercise, leg raising, and hepatic compression. It demonstrates an immediate overshoot after release of the Valsalva strain but is reduced in intensity and duration in the standing position and during the strain of the Valsalva maneuver. Increased atrioventricular flow across the tricuspid orifice in diastole may cause a short, early diastolic flow rumble in the left parasternal region following the third heart sound (S_3). Tricuspid valve prolapse, as with MVP, causes nonejection systolic clicks and late systolic murmurs. In tricuspid valve prolapse, however, these findings are more prominent at the lower left sternal border. With inspiration, the clicks occur later, and the murmurs intensify and become shorter in duration.

Electrocardiography.

Changes on the electrocardiogram (ECG) usually are nonspecific and characteristic of the lesion causing TR. Incomplete right bundle branch block, Q waves in lead V_1, and AF are often found.

Radiography.

In patients with functional TR, marked cardiomegaly usually is evident, and the right atrium is prominent. Evidence of elevated RA pressure may include distention of the azygos vein and the presence of a pleural effusion. Ascites with upward displacement of the diaphragm may be present. Systolic RA pulsations may be present on fluoroscopy.

Echocardiography

The goal of echocardiography is to estimate the severity of TR and assess pulmonary artery pressure (PAP) and RV function[6,15] (**see Chapter 14**). In patients with TR secondary to dilation of the tricuspid annulus, the right atrium, right ventricle, and tricuspid annulus all usually are greatly dilated on echocardiography.[15-17] There is evidence of RV diastolic overload with paradoxical motion of the ventricular septum similar to that observed in ASD. Exaggerated motion and delayed closure of the tricuspid valve are evident in patients with Ebstein anomaly. Prolapse of the tricuspid valve caused by myxomatous degeneration may be evident on echocardiography. Echocardiographic indications of tricuspid valve abnormalities, especially TR by Doppler examination, can be detected in the vast majority of patients with carcinoid heart disease (**see Fig. 70.1**). A similar appearance of the tricuspid valve may be seen in patients who have used drugs that increase serotonin levels or simulate its effect on serotonin receptors (see Video 70.1). In patients with TR caused by endocarditis, echocardiography may reveal vegetations on the valve or a flail valve. TEE enhances detection of TR. Doppler echocardiography is a sensitive technique for visualizing the TR jet. The magnitude of TR can be quantified using techniques similar to those used to evaluate MR.[14,17,18]

Cardiac Magnetic Resonance Imaging

CMR is useful for determining the three-dimensional geometric relationships between the right ventricle and the tricuspid annulus and leaflets in patients with functional TR.[19,20]

Hemodynamic Findings

The RA and RV end-diastolic pressures often are elevated in TR, whether the condition is caused by organic disease of the tricuspid valve or is secondary to RV systolic overload. The RA pressure tracing usually reveals absence of the *x* descent and a prominent *v* or *c-v* wave (ventricularization of the atrial pressure). Absence of these findings essentially excludes moderate or severe TR. As the severity of TR increases, the contour of the RA pressure pulse increasingly resembles that of the RV pressure pulse. A rise or no change in RA pressure on deep inspiration, rather than the usual fall, is a characteristic finding.[21] Determination of the pulmonary artery (or RV) systolic pressure may be helpful in deciding whether the TR is primary or secondary to RV dilation. A pulmonary artery or RV systolic pressure less than 40 mm Hg favors a primary cause, whereas a pressure greater than 55 mm Hg suggests that TR is secondary.

Management

TR in the absence of pulmonary hypertension usually is initially well tolerated and may not require surgical treatment. However, if TR is severe and sustained, eventually right-sided heart failure will ensue; thus appropriate consideration of and timing for surgery are indicated (**see Chapter 72**, Guidelines). Functional TR in the setting of pulmonary hypertension is associated with heart failure and poor survival[22,23] (**see Chapter 85**).

Surgical treatment of acquired TR secondary to annular dilation was greatly improved with the development of annuloplasty techniques, with or without an annuloplasty ring.[5,24] Repair rates have increased, especially over the past decade, and tricuspid valve surgery, usually concomitant with another cardiac operation, is the third most frequently performed valve surgery in North America.[8] Tricuspid valve repair accounts for 73% of tricuspid valve operations. For tricuspid valve replacement (TVR),

bioprostheses are increasingly being used and now account for 46% of TVRs.[25] At mitral valve surgery in patients with TR secondary to pulmonary hypertension, the severity of the TR should be assessed. It should be determined whether the TR is secondary to pulmonary hypertension, in which case the valve is normal, or whether it is secondary to other disease processes. Patients with mild TR without annular dilation usually do not require surgical treatment; pulmonary vascular pressures decline after successful mitral valve surgery, and the mild TR tends to disappear. However, even mild TR should be repaired if there is dilation of the tricuspid annulus, because the TR is likely to progress in severity if left untreated.[26]

Excellent results have been reported in patients with mild to moderate TR with the use of suture annuloplasty of the posterior (unsupported) portion of the annulus. Patients with severe TR require ring annuloplasty.[24,27] Surgical mortality rates in the Society of Thoracic Surgeons (STS) National Database decreased from 10.6% in 2000 to 8.2% in 2010 despite increased patient comorbidity.[8] Concomitant surgical procedures, renal and hepatic dysfunction, and preoperative symptomatic status are the principal determinants of surgical risk.[8,19,28] Reoperation is associated with in-hospital mortality of 13.9% but improvement in functional class in survivors.[29] Residual TR after tricuspid annuloplasty is determined principally by the degree of preoperative tricuspid leaflet tethering.[27,30] If these procedures do not provide a good functional result at the operating table, as assessed by TEE, TVR using a large bioprosthesis may be required. Transcatheter approaches to tricuspid valve repair and replacement using various methods and devices are feasible and currently being studied in clinical trials[31,32] (**see Chapter 72**).

When organic disease of the tricuspid valve (Ebstein anomaly or carcinoid heart disease) causes TR severe enough to require surgery, TVR usually is needed. The risk of thrombosis of mechanical prostheses is greater in the tricuspid than in the mitral or the aortic position, presumably because pressure and flow rates are lower in the right side of the heart. For this reason, a bioprosthesis is the valve of choice for the tricuspid position in adults. Graft durability of more than 10 years has been established. Postoperative vitamin K antagonist therapy is recommended after bioprosthetic TVR in patients with carcinoid heart disease because of a potential for thrombosis.[33]

In treating the difficult problem of tricuspid endocarditis in IV drug users (**see Chapter 73**), total excision of the tricuspid valve without immediate replacement generally can be tolerated by these patients, who usually do not have associated pulmonary hypertension. However, management decisions should be made by a heart valve team, including cardiology, cardiac surgery, and infectious disease specialists. Diseased valvular tissue should be excised to eradicate the endocarditis, and antibiotic treatment can then be continued. RV dysfunction will eventually occur if the resultant severe TR is untreated. A bioprosthetic valve may therefore be inserted several months after valve excision and control of the infection.

Pulmonic Stenosis

Causes and Pathology

Congenital pulmonic stenosis (PS) is the most common etiologic type of PS (**see Chapter 75**), with an estimated worldwide birth prevalence of 0.5 per 1000 live births, and a higher prevalence in Asia.[34] Noonan syndrome is associated with PS, and PS may be seen with tetralogy of Fallot, Williams syndrome, and with other congenital heart defects. The pulmonic valve may be bicuspid, unicommissural, acommissural, or dysplastic. Rheumatic inflammation of the pulmonic valve is very uncommon, usually is associated with involvement of other valves, and rarely leads to serious deformity. Carcinoid heart disease often involves the pulmonic valve, and plaques, similar to those involving the tricuspid valve, are

often present in the outflow tract of the right ventricle of patients with malignant carcinoid. The plaques result in constriction of the pulmonic valve annulus, retraction, thickening and fusion of the valve cusps, and a combination of PS and pulmonic regurgitation (PR) (**Fig. 70.2**).[35] Another cause of PS is extrinsic compression by cardiac tumors or by aneurysm of the sinus of Valsalva.

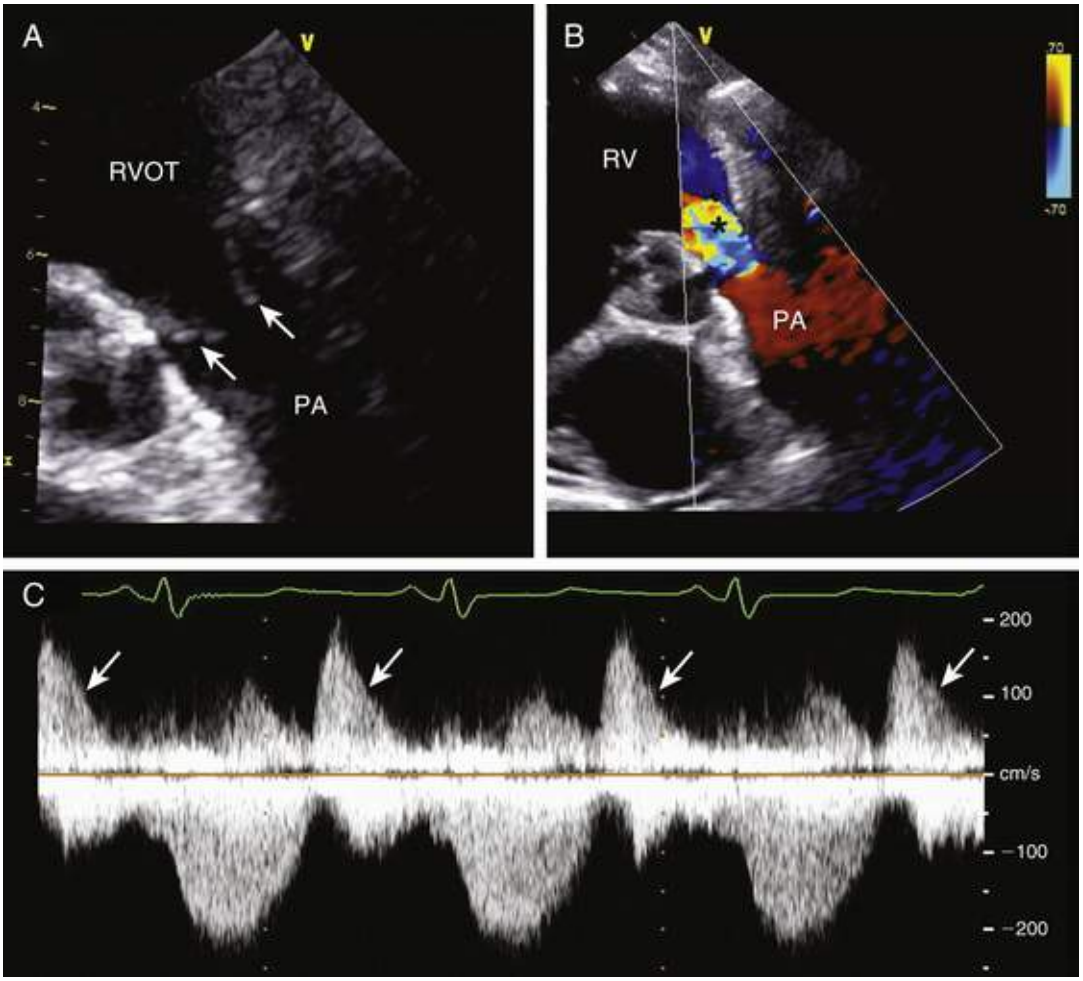

FIGURE 70.2 Transthoracic echocardiography images of the pulmonic valve in a patient with carcinoid heart disease. **A,** Zoomed two-dimensional parasternal short-axis image at the level of the aortic valve shows the pulmonic valve in long axis in mid-diastole, demonstrating a marked thickening with retraction of the pulmonic valve leaflets (*arrow*) and resulting in failure of leaflet closure. **B,** Color Doppler imaging of the pulmonic valve in the same view shows a broad regurgitant jet occupying the entire width of the right ventricular outflow tract (*RVOT*), consistent with severe pulmonic valve regurgitation (*). *RV,* Right ventricle; *PA,* pulmonary artery. **C,** Continuous-wave Doppler imaging across the pulmonic valve demonstrates a dense, diastolic, pulmonary regurgitant jet that returns to baseline before the end of diastole, consistent with severe PR (*arrow*). (From Luis SA, Pellikka PA. Carcinoid heart disease: diagnosis and management. Best Pract Res Clin Endocrinol Metab 2016;30:149.)

Clinical Presentation

Not until PS is severe do symptoms develop, including fatigue, dyspnea, exertional presyncope or syncope, and eventually, right-sided heart failure. The systolic ejection murmur of PS is heard at the left base and increases with inspiration. With increasing severity of PS, the ejection click moves closer to S_1; the click disappears in severe PS. With severe PS, the JVP shows a prominent *a* wave, and a RV lift becomes palpable.

Management

Management of congenital PS focuses on balloon dilation when PS is severe or the patient is symptomatic. For the mixed PS and PR of carcinoid involvement of the pulmonic valve, patch annuloplasty at pulmonic valve replacement (PVR) is frequently advisable.[33] Transcatheter PVR is increasingly being used for PS, atresia, or PR[36] (**see Chapter 72**). Long-term outcome after surgical treatment of PS is excellent.[37]

Pulmonic Regurgitation

Causes and Pathology

Pulmonic regurgitation can result from dilation of the valve ring secondary to pulmonary hypertension (of any cause) or from dilation of the pulmonary artery. IE can involve the pulmonic valve, resulting in valve regurgitation. As more patients with congenital heart disease survive to adulthood (**see Chapter 75**), there is an increasing population of young adults with residual PR after surgical treatment of tetralogy of Fallot (**Fig. 70.3**) or surgical or transcatheter treatment of congenital PS (**see Fig. 14.54**). PR also may result from various lesions that directly affect the pulmonic valve. These include congenital malformations, such as absent, malformed, fenestrated, or supernumerary leaflets. These anomalies may occur as isolated lesions but more often are associated with other congenital anomalies, particularly tetralogy of Fallot, ventricular septal defect (VSD), and valvular PS. Less common causes include trauma; carcinoid syndrome, in which leaflet thickening and retraction result in mixed stenosis and regurgitation (**see Fig. 70.2**); rheumatic involvement; injury produced by a pulmonary artery flow–directed catheter; syphilis; and chest trauma.

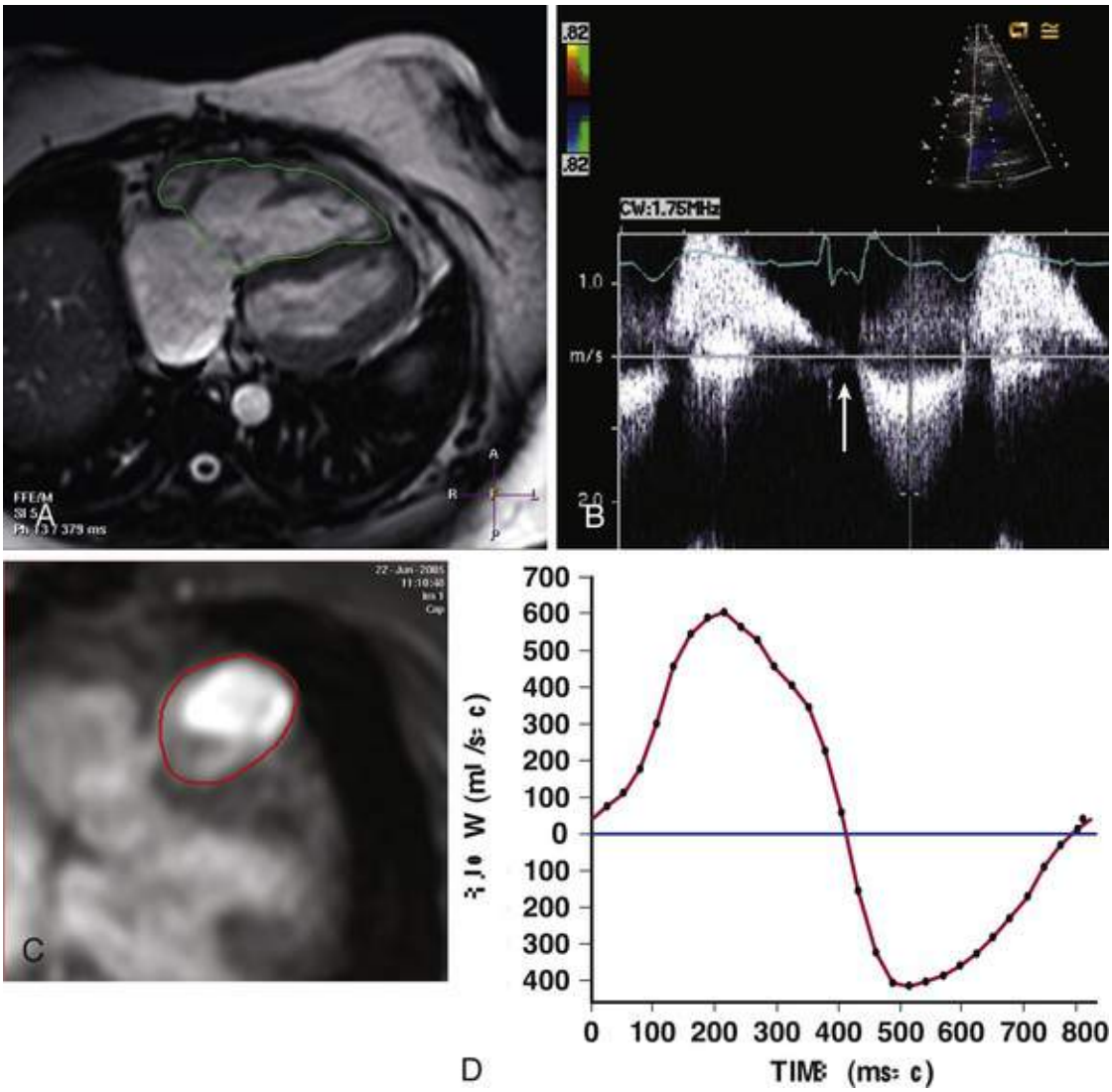

FIGURE 70.3 Cardiac magnetic resonance imaging (CMR) and Doppler echocardiographic evaluation in a 40-year-old woman who underwent repair of tetralogy of Fallot as a child. She was asymptomatic, but significant right ventricular (RV) enlargement was seen on echocardiography. **A,** RV dilation (*green circled area*) is confirmed in the CMR images, with a calculated RV end-diastolic volume of 444 mL. **B,** Doppler tracing shows a dense signal in diastole with a steep deceleration slope that reaches the baseline before the end of diastole (*arrow*). **C,** Interrogation of pulmonary artery flow in the CMR phase-velocity images is performed by drawing a region of interest (*red*) around the pulmonary artery. **D,** Graph of the pulmonary artery flow within the region of interest indicated in **C** demonstrates both antegrade and retrograde flow. The total RV stroke volume was 245 mL, with antegrade flow of 98 mL, yielding a regurgitant fraction of 67%.

Clinical Presentation

As in TR, isolated PR causes RV volume overload and may be tolerated for many years without difficulty unless it complicates, or is complicated by, pulmonary hypertension. In this case, PR usually is accompanied by and aggravates RV failure. Patients with PR caused by IE who develop septic pulmonary emboli and pulmonary hypertension often exhibit severe RV failure. In most patients, the clinical manifestations of the primary disease are severe and usually overshadow the PR.

Physical Examination.

The right ventricle is hyperdynamic and produces palpable systolic pulsations in the left parasternal area, and an enlarged pulmonary artery often produces systolic pulsations in the second left intercostal space.

Sometimes systolic and diastolic thrills are felt in the same area. A tap reflecting pulmonic valve closure usually is easily palpable in the second intercostal space in patients with pulmonary hypertension and secondary PR.

Auscultation.

P_2 is not audible in patients with congenital absence of the pulmonic valve; however, this sound is accentuated in patients with PR secondary to pulmonary hypertension. Wide splitting of S_2 caused by prolongation of RV ejection accompanying the augmented RV stroke volume may be noted. A nonvalvular systolic ejection click generated by the sudden expansion of the pulmonary artery by the augmented RV stroke volume frequently initiates a midsystolic ejection murmur, most prominent in the second left intercostal space. An S_3 and S_4 originating from the right ventricle often are audible, most readily in the fourth intercostal space at the left parasternal area, and are augmented by inspiration.

In the absence of pulmonary hypertension, the diastolic murmur of PR is low-pitched and usually is heard best at the third and fourth left intercostal spaces adjacent to the sternum. The regurgitant murmur reflects the diastolic pressure gradient between the pulmonary artery and the right ventricle; because these pressures are usually lower than left-sided pressures, the murmur of PR is less likely to be heard than that of a similar grade of aortic regurgitation (AR). The PR murmur commences when pressures in the pulmonary artery and right ventricle diverge, approximately 0.04 second after P_2. The murmur becomes louder during inspiration.

When systolic PAP exceeds approximately 55 mm Hg, dilation of the pulmonic annulus results in a high-velocity regurgitant jet, causing the audible murmur of PR, or Graham Steell murmur. This murmur is high-pitched, blowing, and decrescendo, beginning immediately after P_2, and is most prominent in the left parasternal region in the second to fourth intercostal spaces. Thus, although it resembles the murmur of AR, it usually is accompanied by severe pulmonary hypertension—that is, an accentuated P_2 or fused S_2, an ejection sound, and a systolic murmur of TR—and not by a widened arterial pulse pressure. Sometimes, a low-frequency presystolic murmur is present, originating from increased diastolic flow across the tricuspid valve.

The murmur of PR secondary to pulmonary hypertension usually increases in intensity with inspiration, is diminished during the Valsalva strain, and returns to baseline intensity almost immediately after release of the Valsalva strain. This PR murmur resembles and may be confused with the diastolic blowing murmur of AR. However, a diastolic blowing murmur along the left sternal border in patients with rheumatic heart disease and pulmonary hypertension (even in the absence of peripheral signs of AR) usually is caused by AR rather than PR.

Electrocardiography.

In the absence of pulmonary hypertension, PR often results in an ECG that reflects RV diastolic overload—an rSr (or rsR) configuration in the right precordial leads. PR secondary to pulmonary hypertension is usually associated with electrocardiographic evidence of RV hypertrophy.

Radiography.

Both the pulmonary artery and right ventricle are usually enlarged, but these signs are nonspecific. Fluoroscopy may demonstrate pronounced pulsation of the main pulmonary artery.

Cardiac Magnetic Resonance Imaging.

CMR may be used to assess pulmonic valve anatomy, recognize any obstruction above or below the valve, measure pulmonary artery dilation, and quantify PR severity (**see Fig. 70.3**). CMR also is useful in evaluating RV dilation and systolic function.[38]

Echocardiography

A trivial or mild degree of PR can be detected by Doppler echocardiography in most normal patients. With more severe degrees, two-dimensional echocardiography shows RV dilation and, in patients with pulmonary hypertension, RV hypertrophy as well. RV function can be evaluated. Abnormal motion of the septum characteristic of volume overload of the right ventricle in diastole and septal flutter may be evident. The motion of the pulmonic valve may point to the cause of the PR. Absence of *a* waves and systolic notching of the posterior leaflet suggest pulmonary hypertension; large *a* waves indicate PS. Doppler echocardiography is extremely accurate in detecting PR and in helping estimate its severity (**see Figs. 70.2 and 70.3; see also Fig. 14.54**). Severe PR is associated with a reduced pressure half-time, indicating rapid equalization of pressure in the right ventricle and pulmonary artery. Additionally, the density of the Doppler profile of the jet is increased, and reversal of flow in the pulmonary artery by color flow imaging can be detected a distance from the valve. Abnormal Doppler signals in the RV outflow tract, with velocity sustained throughout diastole, are generally observed in patients in whom PR is caused by dilation of the valve ring secondary to pulmonary hypertension. When the velocity falls during diastole, PAP is usually normal, and the regurgitation is caused by an abnormality of the valve itself.

Management

Except in patients with previous surgery for tetralogy of Fallot or similar RV outflow obstruction or for carcinoid heart disease, PR alone is seldom severe enough to require specific treatment. Treatment of the primary condition, such as IE, or the lesion responsible for the pulmonary hypertension, such as surgery for mitral valvular disease, often ameliorates the PR. The timing of surgery for severe PR is based on the degree of RV dilation and evidence of systolic dysfunction.[13,39] In these patients, PVR may be carried out, preferably with a pulmonary allograft. There is growing experience with catheter-based approaches to PVR in native pulmonic valve disease and in PR after surgical correction of congenital heart defects[36] (**see Chapter 72**).

Multivalvular Disease

Various clinical and hemodynamic syndromes can be produced by different combinations of valvular abnormalities. Multivalvular involvement has diverse causes (**Table 70.4**). It frequently is caused by rheumatic fever but is also seen with congenital heart disease, carcinoid heart disease, radiation heart disease, and connective tissue disorders. Myxomatous MR and MVP may be associated with tricuspid valve prolapse and TR, or with pulmonary hypertension, tricuspid annulus dilation, and TR. Marfan syndrome and other connective tissue disorders may cause multivalve prolapse and dilation, resulting in multivalvular regurgitation. Degenerative calcification of the aortic valve may be associated with degenerative mitral annular calcification, resulting in concomitant aortic stenosis (AS) and MR. Different pathologic conditions may affect two valves in the same patient (e.g., IE on the aortic valve causing AR and ischemia causing MR).

TABLE 70.4
Causes of Multivalvular Heart Disease

Acquired
Systemic diseases
Infective endocarditis
Carcinoid heart disease
Systemic lupus erythematosus
Cardiac diseases
Infective endocarditis
Rheumatic heart disease
Degenerative
Calcific diseases, increased with age, prior radiation, chronic kidney disease
Iatrogenic
Adverse drug effects: ergot-related antagonists
Radiation therapy
Functional (annulus dilatation), caused by:
Ischemic heart disease
Hypertensive heart disease
Chronic arrhythmia
Pulmonary hypertension
Cardiomyopathy
Congenital
Connective tissue disorders
Marfan syndrome
Ehlers-Danlos syndrome
Other
Trisomy 18, 13, and 15
Shone syndrome
Ochronosis
Mixed
Multiple conditions may contribute to valve dysfunction, such as:
Degenerative diseases may lead to associated functional disease.
Congenital heart disease may predispose to infective endocarditis or degenerative disease.

In patients with multivalvular disease, the clinical manifestations depend on the relative severity of each of the lesions. When the valvular abnormalities are of approximately equal severity, clinical manifestations produced by the more proximal (upstream) of the two valvular lesions (i.e., the mitral valve in patients with combined mitral and aortic valvular disease and the tricuspid valve in patients with combined tricuspid and mitral valvular disease) are generally more prominent than those produced by the distal lesion. Thus the proximal lesion tends to mask the distal lesion.

It is important to recognize multivalvular involvement preoperatively because failure to correct all significant valvular disease at the time of operation increases mortality. Specific guideline recommendations exist for concomitant valve surgery in patients undergoing surgery on another valve.[13,40] In patients with multivalvular disease, the relative severity of each lesion may be difficult to estimate by clinical examination because one lesion may mask the manifestations of the other. Therefore, patients with suspected multivalvular involvement being considered for surgical treatment should undergo careful clinical evaluation and full Doppler echocardiographic evaluation. Stress echocardiography is well suited for the assessment of multivalvular disease and may be especially useful when the patient's symptoms are disproportionate to the resting hemodynamics. Mixed stenotic and regurgitant lesions can be assessed with a combination of two- and three-dimensional imaging, including planimetry of stenotic orifices, color flow imaging, and Doppler. Multiple valves can be systematically assessed during exercise;[41] this is particularly helpful in assessing the patient with exertional symptoms, especially when these seem disproportionate to findings on imaging at rest. Right and left cardiac catheterization may occasionally be necessary. If there is any question concerning the presence of significant AS in patients undergoing mitral valve surgery, the aortic valve should be inspected, because overlooking this condition can lead to a high perioperative mortality. Similarly, it is useful to palpate the tricuspid valve at mitral valve surgery. Intraoperative TEE is also important for assessing the impact of repair of one valve lesion on another.

Mitral Stenosis and Aortic Valve Disease

Aortic valve involvement is present in approximately one third of patients with rheumatic MS. Rheumatic aortic valve disease may result in primary regurgitation, stenosis, or mixed stenosis and regurgitation. AR is evident on physical examination in approximately two thirds of patients with severe MS, but is severe in only approximately 10%. Since a proximal lesion may mask signs of a distal lesion on physical examination, significant AR may be missed in patients with severe MS because the widened pulse pressure may be absent. An accentuated S_1 and an OS in a patient with AR should suggest mitral valvular disease. AS is evident on physical examination based on the typical murmur, even when MS is present; however, cardiac output tends to be reduced more than in patients with isolated AS. On physical examination, an S_4 (which is common in patients with pure AS) usually is not present. The midsystolic murmur characteristic of AS may be reduced in intensity and duration because the stroke volume is reduced by the MS.

Echocardiography is of decisive value in the evaluation of patients with rheumatic disease and allows accurate diagnosis of the presence and severity of multivalve involvement, taking into consideration the altered flow conditions with serial lesions. For example, the gradient across the stenotic aortic valve may be relatively low when MS is present because of a low cardiac output; valve area calculations are especially helpful in this setting.

Because double-valve replacement is associated with increased short- and long-term risks, balloon mitral valvuloplasty (BMV) can be the first procedure if MS is the predominant lesion, with subsequent aortic valve replacement (AVR) when needed. If percutaneous BMV is not an option or concurrent AVR is needed, surgical valvotomy may be considered as an option.

It is vital to recognize the presence of hemodynamically significant aortic valvular disease (i.e., AS, AR) preoperatively in patients who are to undergo BMV. This procedure may be hazardous because it can impose a sudden hemodynamic load on the left ventricle that had previously been protected by the MS and may lead to acute pulmonary edema.

Aortic Stenosis and Mitral Regurgitation

AS is often accompanied by MR caused by MVP, annular calcification, rheumatic disease, or functional MR. The increased LV pressure secondary to LV outflow obstruction may augment the volume of MR flow, whereas the presence of MR may diminish the ventricular preload necessary for maintenance of the LV stroke volume in patients with AS. The result is a reduced forward cardiac output and marked LA and pulmonary venous hypertension. Significant MR is one explanation for low-output AS[42] (**see Chapter 68**). The development of AF (caused by LA enlargement) has an adverse hemodynamic effect in the presence of AS. Physical findings may be confusing because it may be difficult to recognize two distinct systolic murmurs. However, on echocardiography, the cause and severity of AS and MR can be accurately diagnosed. In most patients, MR is mild to moderate, and it is appropriate to treat AS alone. When MR is severe or there is significant structural mitral valve disease, concurrent mitral repair (whenever possible) or valve replacement at the time of AVR should be considered.

Aortic and Mitral Regurgitation

The relatively infrequent combination of AR and MR may be caused by rheumatic heart disease, prolapse of both the aortic and the mitral valves secondary to myxomatous degeneration, or dilation of both annuli in patients with connective tissue disorders. The clinical features of AR usually predominate, and it is sometimes difficult to determine whether the MR is caused by organic involvement of this valve or by

dilation of the mitral valve ring secondary to LV enlargement. When both valvular leaks are severe, this combination of lesions is poorly tolerated. The normal mitral valve ordinarily serves as a backup to the aortic valve, and premature (diastolic) closure of the mitral valve limits the volume of reflux that occurs in patients with acute AR. With severe combined regurgitant lesions, regardless of the cause of the mitral lesion, blood may reflux from the aorta through both chambers of the left side of the heart into the pulmonary veins. Physical and laboratory examinations usually show evidence of both lesions. An S_3 and a brisk arterial pulse frequently are present. The relative severity of each lesion can be assessed best by Doppler echocardiography, especially using proximal isovelocity surface area (PISA) or vena contracta methods, three-dimensional imaging, or contrast angiography. This combination of lesions leads to severe LV dilation. MR that occurs in patients with AR secondary to LV dilation often regresses after AVR alone. If severe, the MR may be corrected by annuloplasty at AVR. An intrinsically normal mitral valve that is regurgitant because of a dilated annulus should not be replaced.

Surgical Treatment of Multivalvular Disease

Replacement or repair of multiple valves presently comprises 12% of valve procedures and usually is associated with a higher risk and poorer survival than replacement of either of the valves alone.[43] The operative risk of double-valve replacement is approximately 70% higher than for single-valve replacement. The STS National Database Committee has reported an overall operative mortality rate of 9.6% for multivalve (usually double-valve) replacement in 3840 patients, compared with 3.2% and 5.7% for isolated AVR and mitral valve replacement, respectively.[44,45] The long-term survival depends strongly on the preoperative functional status. Patients operated on for combined AR and MR have poorer outcomes than patients undergoing double-valve replacement for any of the other combinations of lesions, presumably because both AR and MR may produce irreversible LV damage. Mitral valve repair or, in the case of MS, BMV performed in combination with AVR may be preferable to double-valve replacement and should be considered. Moreover, it should be expected that most patients will experience some decrease in functional MR severity after AVR. In the setting of planned AVR, management of coexistent MR should take into consideration the severity of MR, its mechanism, operative risks and comorbidities.[46] Risk factors that reduce long-term survival after double-valve replacement include advanced age, less favorable functional status, decreased LV ejection fraction, greater LV enlargement, and accompanying ischemic heart disease requiring coronary artery bypass grafting.[45,47]

In view of the higher risks, a higher threshold is required for multivalvular versus single-valve surgery. Thus patients generally are advised not to undergo multivalvular surgery until they reach late New York Heart Association (NYHA) Class II or III, unless they exhibit evidence of declining LV function. Despite a detailed noninvasive and invasive workup, the decision to treat more than one valve often is made on the basis of findings on palpation or direct inspection at the operating table, or the findings on intraoperative TEE.

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71

Prosthetic Heart Valves

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The past six decades have witnessed significant advancements in patient survival and functional outcomes following heart valve replacement surgery.[1] Continued refinements in prosthetic valve design and

performance, operative techniques, myocardial preservation, systemic perfusion, cerebral protection, and anesthetic management have enabled the application of surgical and transcatheter valve therapy to an increasingly wider spectrum of patients. Minimally invasive surgical approaches and the aggressive use of primary valve repair when anatomically appropriate are now routine practice in the vast majority of high-volume centers. Heart valve teams have been formed to provide multidisciplinary assessment and treatment of complex patients, including with the use of transcatheter heart valve replacement or repair when appropriate[2] (**see Chapter 72**). More than 43,000 aortic or mitral valve replacement operations (with or without coronary artery bypass) were reported to the Society of Thoracic Surgeons (STS) National Adult Cardiac Database in 2015.[3] Familiarity with the specific hemodynamic attributes, durability, thrombogenicity, and inherent limitations of currently available heart valve substitutes, as well as their potential for long-term complications, is critical to appropriate clinical decision making for patients in whom repair is not appropriate or feasible. The choice of valve prosthesis is inherently a trade-off between durability and risk of thromboembolism, with the associated hazards and lifestyle limitations of anticoagulation. The ideal heart valve substitute remains an elusive goal.

Types of Prosthetic Heart Valves

Mechanical Valves

The three basic types of mechanical prosthetic valves are bileaflet, tilting disc, and caged ball (**Fig. 71.1**; **see also Fig. 14.55**). The St. Jude bileaflet valve was first used in 1977 and is the most frequently implanted mechanical prosthesis worldwide. It consists of two pyrolytic semicircular “leaflets” or discs with a slitlike central orifice between the two leaflets and two larger semicircular orifices laterally. The opening angle of the leaflets relative to the annulus plane ranges from 75 to 90 degrees. The CarboMedics valve is a variation of the St. Jude prosthesis that can be rotated to prevent limitation of leaflet excursion by subvalvular tissue. For a given valve annulus size, effective orifice area (EOA) is generally larger and transprosthetic pressure gradient lower for the bileaflet mechanical valves compared to the tilting disc valves. Because the central orifice is smaller than the lateral orifices in bileaflet valves, the blood flow velocity may be locally higher within the inflow aspect of the central orifice; this phenomenon may lead to overestimation of gradient and underestimation of EOA by transthoracic echocardiography (TTE)[4,5] (**see Chapter 14**). Bileaflet valves typically have a small amount of normal regurgitation (“washing jet”), designed in part to decrease the risk of thrombus formation. A small, central jet and two converging jets emanating from the hinge points of the discs can be visualized on color Doppler flow imaging.

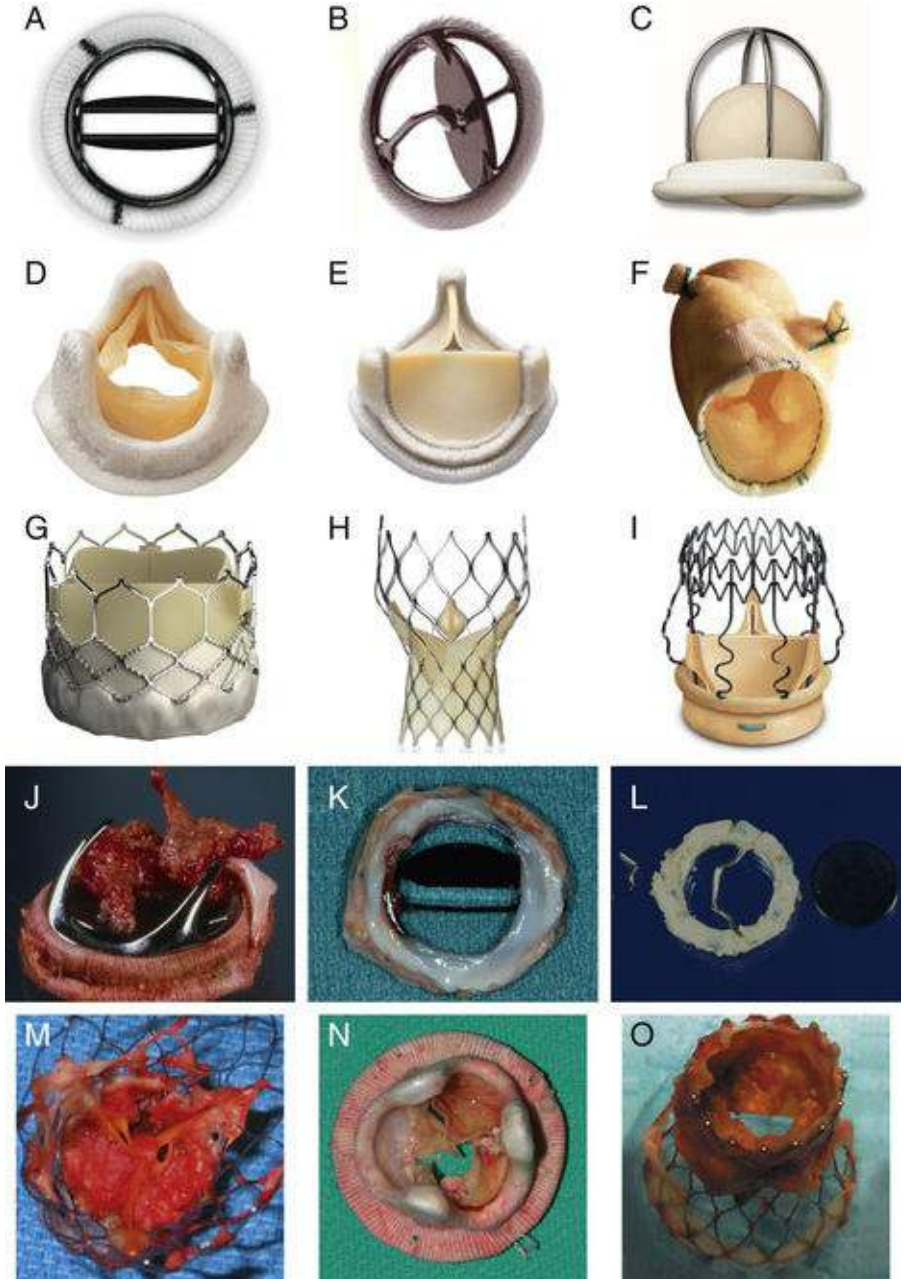

FIGURE 71.1 Different types of prosthetic valve models and complications. **A,** Bileaflet St. Jude mechanical valve. **B,** Monoleaflet Medtronic Hall mechanical valve. **C,** Caged-ball Starr-Edwards mechanical valve. **D,** Stented porcine Medtronic Mosaic bioprosthetic valve. **E,** Stented bovine pericardial Edwards Magna bioprosthetic valve. **F,** Stentless porcine Medtronic Freestyle bioprosthetic valve. **G,** Transcatheter balloon-expandable Edwards SAPIEN 3 bioprosthetic valve. **H,** Transcatheter self-expanding Medtronic CoreValve Evolut bioprosthetic valve. **I,** Sutureless Sorin Perceval bioprosthetic valve. **J,** Obstructive thrombus on a tilting disc prosthetic valve. **K,** Pannus ingrowth interacting with leaflet opening in bileaflet mechanical valve. **L,** Rupture of outlet strut and leaflet escape in Björk-Shiley prosthesis. **M,** Thrombosis in self-expanding transcatheter aortic valve. **N,** Leaflet calcific degeneration and tear in porcine bioprosthesis. **O,** Leaflet calcific degeneration and stenosis in self-expanding transcatheter aortic valve. (**F,** From Seeburger J, Weiss G, Borger MA, Mohr FW. Structural valve deterioration of a CoreValve prosthesis 9 months after implantation. Eur Heart J 2013;34:1607; **I,** Courtesy LivaNova PLC/Sorin Group; **K,** courtesy Dr. Christian Couture, Québec Heart & Lung Institute; **M,** from American Heart Association. Latib A, Naganuma T, Abdel-Wahab M, et al. Treatment and clinical outcomes of transcatheter heart valve thrombosis. Circ Cardiovasc Interv 2015;8:1-8; **N,** courtesy Gosta Petterson, Cleveland Clinic.)

Tilting disc or monoleaflet valves use a single, circular disc that rotates within a rigid annulus to occlude or open the valve orifice. The disc is secured by lateral or central metal struts. The opening angle of the disc relative to the valve annulus ranges from 60 to 80 degrees, resulting in two orifices of different size. The nonperpendicular opening angle of the valve occluder tends to slightly increase the resistance to blood flow, particularly in the major orifices. Tilting disc valves also have a small amount of

regurgitation, arising from small gaps at the perimeter of the valve.

The bulky Starr-Edwards ball-in-cage valve, the oldest commercially available prosthetic heart valve first used in 1965, is now very rarely implanted. The ball-cage valve is more thrombogenic and has less favorable hemodynamic performance characteristics than either bileaflet or tilting disc valves.

Currently available mechanical valves have excellent, long-term durability, with up to 45 years for the Starr-Edwards valve and more than 30 years for the St. Jude valve. Structural deterioration, exemplified by some older-generation Björk-Shiley (strut fracture with disc embolization) and Starr-Edwards (ball variance) prostheses, is now extremely rare. Ten-year freedom from valve-related death exceeds 90% for both St. Jude and CarboMedics bileaflet valves. All patients with mechanical valves require lifelong anticoagulation with a vitamin K antagonist (VKA). Long-term issues associated with mechanical valves include infective endocarditis, paravalvular regurgitation (PVR), hemolytic anemia, thromboembolism/valve thrombosis, pannus ingrowth, and hemorrhagic complications related to anticoagulation.

Tissue Valves

Tissue or biologic valves include stented and stentless bioprostheses (porcine, bovine), homografts (or allografts) from human cadaveric sources, and autografts of pericardial or pulmonic valve origin (**see Fig. 71.1**; **see also Fig. 14.57**). Tissue valves provide an alternative, less thrombogenic heart valve substitute that does not require long-term anticoagulation in the absence of additional risk factors for thromboembolism.

Stented Bioprosthetic Valves

The traditional design of a heterograft valve consists of three biologic leaflets made from the porcine aortic valve or bovine pericardium treated with glutaraldehyde to reduce its antigenicity. The leaflets are mounted on a metal or polymeric stented ring; they open to a circular orifice in systole, resembling the anatomy of the native aortic valve (**see Fig. 71.1**). The vast majority of bioprosthetic valves are treated with anticalcifying agents or processes. The newer generations of bovine pericardial valves (Carpentier-Edwards Magna or St. Jude Trifecta) offer improved hemodynamic performance compared with earlier-generation bioprostheses. A small degree of regurgitation can be detected by color Doppler flow imaging in 10% of normally functioning bioprostheses. One limitation of earlier generations of bioprosthetic valves was their limited durability due to *structural valve deterioration* (SVD), typically beginning within 5 to 7 years after implantation, but varying by position and age at implant, with tissue changes characterized by calcification, fibrosis, tears, and perforations. SVD occurs earlier for mitral than for aortic bioprosthetic valves, perhaps because of exposure of the mitral prosthesis to relatively higher left ventricular (LV) closing pressures. The process of SVD is accelerated in younger patients, in those with disordered calcium metabolism (end-stage renal disease), and possibly in pregnant women, independent of younger age. With newer-generation bioprosthetic pericardial valves, the durability is excellent, with SVD rates of 2% to 10% at 10 years, 10% to 20% at 15 years, and 40% at 20 years.[6,7]

Stentless Bioprosthetic Valves

The rigid sewing ring and stent-based construction of certain bioprostheses allow for easier implantation and maintenance of the three-dimensional relationships of the leaflets. However, these features also contribute to impaired hemodynamic performance. Stentless porcine valves were developed in part to

address these issues (**see Fig. 71.1**). Their use has been restricted to the aortic position. Implantation is technically more challenging, whether deployed in a subcoronary position or as part of a miniroot, and thus these valves are preferred by only a minority of surgeons. Early postoperative mean gradients can be less than 15 mm Hg, with further improvement in valve performance over time from aortic root remodeling, lower peak exercise transvalvular gradients, and more rapid reduction in LV mass.[8] Sutureless bioprosthetic valves have also been developed to decrease the complexity and duration of implantation of bioprosthetic valves (**see Fig. 71.1**).

Homografts

Aortic valve homografts are harvested from human cadavers within 24 hours of death and are treated with antibiotics and cryopreserved at −196°C. They are now usually implanted in the form of a total root replacement with reimplantation of the coronary arteries. Homograft valves appear resistant to infection and are preferred by some surgeons for management of aortic valve and root endocarditis in the active phase. Neither immunosuppression nor routine anticoagulation is required. Despite earlier expectations, long-term durability beyond 10 years is not superior to that for current-generation pericardial valves,[9] and reoperation may be technically more challenging.

Autografts

In the Ross procedure the patient's own pulmonic valve or autograft is harvested as a small tissue block containing the pulmonic valve, annulus, and proximal pulmonary artery and is inserted in the aortic position, usually as a complete root replacement with reimplantation of the coronary arteries.[9] The pulmonic valve and right ventricular outflow tract are then replaced with either an aortic or pulmonic homograft. Thus the procedure requires two separate valve operations, a longer time on cardiopulmonary bypass, and a steep learning curve. With appropriate selection of young patients by expert surgeons at experienced centers of excellence, operative mortality rates are less than 1% and 20-year survival rates as high as 95%, similar to the general population.[10] Advantages of the autograft include the ability to increase in size during childhood growth, excellent hemodynamic performance characteristics, lack of thrombogenicity, and resistance to infection. The hemodynamic performance characteristics of the pulmonary autograft are similar to those of a normal, native aortic valve. The procedure is usually reserved for children and young adults, but should be avoided in patients with dilated aortic roots, given the unacceptably high incidence of accelerated degeneration, pulmonary autograft dilation, and significant regurgitation.

Transcatheter Bioprosthetic Valves

Transcatheter aortic valve replacement (TAVR) is a valuable alternative to surgical aortic valve replacement in patients with symptomatic severe aortic stenosis (AS) considered to be at extreme, high, or intermediate surgical risk (**see Chapter 72**). Two main types of transcatheter aortic valves are currently used: balloon-expandable valves and self-expanding valves (**see Fig. 71.1**).

The Edwards SAPIEN XT and SAPIEN 3 balloon-expandable valves consist of a three-leaflet pericardial bovine valve mounted in a cobalt chromium frame. These valves are available in 20, 23, 26 and 29 mm sizes. Common access routes for TAVR are transfemoral, transapical, and transaortic. Approximately 75% to 80% of TAVR procedures are now performed by a transfemoral approach. As catheter sheath sizes decrease (now 14F or 16F for most valves), the balance is anticipated to shift even more toward the transfemoral approach. The transfemoral approach is associated with lower mortality

and quicker recovery compared to alternative access approaches.

The CoreValve balloon-expandable valve consists of three leaflets of porcine pericardium seated relatively higher in a nitinol frame to provide true supra-annular placement and is available in 26, 29, and 31 mm sizes. The CoreValve is most frequently implanted using the transfemoral approach.

For a given aortic annulus size, transcatheter valves have larger EOAs and lower gradients compared to surgical bioprosthetic valves.[11] PVR, however, occurs much more often following TAVR (**see Fig. 14.61**) and has adverse long-term consequences.[12] Mild regurgitation occurs in 25% to 60% of patients and moderate or severe regurgitation in 3% to 20%.[13,14] Moderate or severe PVR is associated with a 2.0- to 2.5-fold increase in mortality.[13] The most recent transcatheter balloon-expandable valve (SAPIEN 3) was designed with a skirt to reduce PVR. The rate of moderate or severe regurgitation has dropped to less than 3% with its use.[15] Some studies suggest that self-expanding valves have slightly larger EOAs and lower gradients but somewhat higher rates of PVR than balloon-expandable valves.[16]

Comparison of Mechanical and Tissue Valves

Obvious differences between valve types relate to durability (i.e., indefinite for mechanical versus limited for tissue valves) and need for anticoagulation (i.e., obligatory for mechanical versus none for tissue valves absent other risk factors for thromboembolism). Short- to intermediate-term hemodynamic performance characteristics with low-profile mechanical prostheses (e.g., St. Jude) are comparable to those with stented tissue valves of similar size. There are no important differences in rates of *prosthetic valve endocarditis* (PVE) (**see Chapter 73**), although some series have suggested a higher incidence of early (<1 year) infection with mechanical valves versus bioprostheses.[17] In the U.S. Veterans Affairs randomized trial conducted between 1977 and 1982, patients undergoing aortic valve replacement (AVR) had a better 15-year survival with a mechanical valve than with a bioprosthetic valve, whereas there was no difference in survival with mechanical versus biologic mitral valve replacement (MVR) (see Classic Reference, Hammermeister). With AVR, the increased mortality among patients allocated a bioprosthesis was driven largely by the higher rate of SVD. There was an increased risk of bleeding with mechanical valve replacement, but no significant differences were observed for other valve-related complications such as thromboembolism or PVE. A more recent, smaller randomized trial of patients 55 to 70 years of age with aortic valve disease also showed no difference in late survival between newer-generation mechanical and bioprosthetic valves, with higher rates of SVD and reoperation in patients with bioprostheses but no other differences in secondary endpoints.[18] In an analysis of more than 39,000 AVR patients age 65 to 80 years reported to the STS Adult Cardiac Surgery Database and linked to Medicare, patients receiving a bioprosthesis had a similar adjusted risk for death, higher risks for reoperation and endocarditis, and lower risks for stroke and bleeding, compared with patients receiving a mechanical valve.[19] Two propensity-matched analyses from New York's Statewide Planning and Research Cooperative System (SPARCS) reported no survival differences for patients 50 to 69 years of age undergoing mechanical versus bioprosthetic, AVR or MVR.[20,21] Rates of stroke and bleeding were higher, whereas rates of reoperation were lower, among mechanical valve recipients. A survival advantage among patients in this age-group who underwent mechanical rather than bioprosthetic valve replacement, however, was reported from the Swedish system for the Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry.[22] Stroke risk was similar between the groups, although bleeding rates were higher and the need for reoperation was lower after mechanical valve replacement.

Comparison of Surgical and Transcatheter Valves

TAVR is well established for the treatment of high-risk and inoperable patients with symptomatic severe AS[2,12,23] (**see Chapter 72**). Furthermore, recent trials have shown that TAVR is equivalent or superior to surgical AVR in patients at intermediate surgical risk.[15,24,25] In these trials, TAVR with transfemoral access resulted in a lower incidence of death or stroke, whereas with transthoracic access, outcomes were similar for surgical and transcatheter valve replacement. TAVR also resulted in larger EOAs and lower rates of acute kidney injury, severe bleeding, and new-onset atrial fibrillation than did surgical AVR. Surgical AVR resulted in fewer major vascular complications and less paravalvular aortic regurgitation.

Choice of Valve Replacement Procedure and Prosthesis

Once the indication for valve replacement is established, the next step is to select the type of procedure (repair versus replacement) and the type of prosthetic valve should replacement be necessary.[2] The 2014 American Heart Association and American College of Cardiology (AHA/ACC) guidelines for the management of patients with valvular heart disease advocate shared (patient-cardiologist–cardiac surgeon) decision making on the choice of intervention (repair or replacement, transcatheter or surgical) as well as the type of prosthetic valve (mechanical valve or bioprosthesis).[2,26] This choice is based on consideration of several factors, including valve durability, expected hemodynamics for a specific valve type and size, surgical or interventional risk, the potential need for long-term anticoagulation, and patient preferences.

Choice of Procedure

In patients with severe AS having an indication for AVR (**see Chapter 68**), the choice between surgical AVR versus TAVR is based on the predicted surgical risk, which is assessed by combining the STS-PROM estimate (http://riskcalc.sts.org/stswebriskcalc/), patient frailty, major organ system dysfunction, and procedure-specific impediments.[2] TAVR is recommended in patients who meet an indication for AVR for severe AS and who have a prohibitive surgical risk and a predicted post-AVR survival longer than 1 year. Surgical AVR or TAVR is recommended for patients with high surgical risk, depending on patient-specific procedural risks and preferences. TAVR is a reasonable alternative to surgical AVR for intermediate-risk patients, whereas surgical AVR is recommended for patients with low surgical risk.[26]

In patients with chronic severe primary mitral regurgitation (MR) who meet an indication for mitral valve surgery (**see Chapter 69**), mitral valve repair is recommended over MVR when a successful and durable repair can be accomplished.[2] In patients with chronic secondary MR, MVR may actually be superior to mitral valve repair because it is associated with lower rates of recurrent MR.[27]

Tricuspid valve annuloplasty repair is frequently performed at left-sided valve surgery when tricuspid regurgitation (TR) is severe or when there is significant tricuspid annular dilation (>40 mm) despite only mild or moderate degrees of TR[2] (**see Chapter 70**). Tricuspid valve replacement is undertaken for severe disease that cannot be repaired, such as with advanced rheumatic disease, carcinoid, or destructive endocarditis.

Surgical or transcatheter pulmonic valve replacement in the adult is rare.

Choice of Prosthetic Valve

A bioprosthesis is recommended in patients of any age in whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired.[2,26] A mechanical prosthesis is reasonable for AVR or MVR in patients younger than 50 who do not have a contraindication to anticoagulation, whereas a bioprosthesis is reasonable in patients older than 70 years.[26] Either a bioprosthetic or a mechanical valve is reasonable in patients between 50 and 70 years old. A bioprosthesis is reasonable for young women contemplating pregnancy to avoid the hazards of anticoagulation in this setting.

Medical Management and Surveillance After Valve Replacement

Antithrombotic Therapy

General Principles

Table 71.1 presents the antithrombotic regimen that is recommended in the 2014 AHA/ACC guideline for the different types of procedures and prosthetic valves.[2] All patients with mechanical heart valves require lifelong anticoagulation with a VKA, the intensity of which varies as a function of valve type or thrombogenicity, valve position and number, and the presence of additional risk factors for thromboembolism, such as atrial fibrillation, LV systolic dysfunction, a history of thromboembolism, and hypercoagulable state. Anticoagulant therapy with oral direct thrombin inhibitors or anti-Xa agents should not be used in patients with mechanical prostheses[2] (**see Chapter 93**). Although there is no clear consensus, a VKA may be used even in the absence of risk factors for thromboembolism for the first 3 to 6 months after bioprosthetic AVR or MVR.[26] Longer-term treatment of low-risk bioprosthetic AVR and MVR patients consists of low-dose aspirin, although there are no data to support this practice.

TABLE 71.1

Antithrombotic Therapy in Patients with Prosthetic Valves

PROSTHETIC VALVE	VKA (TARGET INR)	ASPIRIN (75-100 mg)	CLOPIDOGREL (75 mg)	CLASS
Mechanical Valves				
AVR: Bileaflet or current-generation single–tilting disc valves and no risk factors for thromboembolism*	Yes (INR: 2.5)	Yes	No	I
AVR: Older-generation valves† and/or any risk factor for thromboembolism*	Yes (INR: 3.0)	Yes	No	I
MVR: Mechanical valves	Yes (INR: 3.0)	Yes	No	I
AVR: On-X valve and no risk factors for thromboembolism	Yes (INR: 1.5-2.0)	Yes	No	IIb
Bioprosthetic Valves				
AVR or MVR: first 3 to 6 months	Yes (INR 2.5)	Yes	No	IIa
AVR or MVR: after first 3 to 6 months	No	Yes	No	I
Transcatheter Aortic Valves				
First 3 months	Yes	Yes	Yes	IIb
First 3-6 months	No	Yes	Yes	IIb
After first 6 months	No	Yes	No	IIb

*Risk factors for thromboembolism: atrial fibrillation, left ventricular (LV) dysfunction (LV ejection fraction ≤35%), left atrial (LA) dilation (LA diameter ≥50 mm), previous thromboembolism, and hypercoagulable condition.

†Ball-in-cage valves, older generation of single–tilting disc valves.

AVR, Aortic valve replacement; *MVR*, mitral valve replacement; *INR*, international normalized ratio; *VKA*, vitamin K antagonist.

From Nishimura RA, Otto CM, Bonow RO et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline on the management of patients with valvular heart disease. J Am Coll Cardiol 2017;70:252-89.

Interruption of Antithrombotic Therapy

In the planned interruption of VKA therapy for noncardiac surgery, the following must be taken into account: the nature of the procedure; the magnitude of risk of thromboembolism based on valve type, position, and number; underlying patient risk factors; and the competing risk of periprocedural hemorrhage.[2] Low-risk patients with low-profile bileaflet or tilting disc valves in the aortic position can usually stop VKA therapy 3 to 5 days before noncardiac surgery and then resume it postoperatively as soon as considered safe, without the need for a heparin "bridge." In all other patients, either low-molecular-weight heparin (LMWH) or intravenous unfractionated heparin (UFH) should be given both before and after surgery, as directed by the surgeon. The use of LMWH avoids the need for preoperative hospitalization. Randomized trial data are sparse and institutional/operator variability is great regarding the use of bridging strategies for noncardiac surgery in such patients.

Pregnancy

Pregnant patients with prosthetic valves should be followed carefully because of the increased hemodynamic burden that can cause or worsen heart failure if there is prosthetic valve dysfunction or if the hypercoagulable state related to pregnancy increases the risk of valve thrombosis (**see Chapter 90**). All antithrombotic regimens carry an increased risk to the fetus, an increased risk of miscarriage, and hemorrhagic complications for the mother. Therefore, patients require appropriate counseling, close monitoring, and adjustment of anticoagulation therapy. In pregnant patients with mechanical valves, warfarin is reasonable (class IIa) in the first trimester if the dose is 5 mg/day or less and is recommended (class I) to achieve a therapeutic international normalized ratio (INR) target in the second and third

trimesters. Discontinuation of warfarin with initiation of intravenous UFH is recommended before planned vaginal delivery in pregnant patients with a mechanical valve.

Infective Endocarditis Prophylaxis

Patients with prosthetic valves are at increased risk for infective endocarditis because of the foreign valve surface and sewing ring. Antibiotic prophylaxis is only indicated (class IIa) for patients with prosthetic valves who undergo dental procedures that involve manipulation of gingival tissue, the periapical region of teeth, or perforation of the oral mucosa (**see Chapter 73**) Prophylaxis is no longer recommended for nondental procedures such as transesophageal echocardiography (TEE), esophagogastroduodenoscopy, colonoscopy, or cystoscopy (unless there is active infection in these areas).[17,26]

Clinical Assessment

Postoperative visits should begin approximately 3 to 4 weeks after valve implantation. The first visit is focused on ensuring a smooth transition from hospital/rehabilitation facility to home, reconciling medications, and assessing neurocognitive function, wound healing, volume status, heart rhythm, and the auscultatory characteristics of prosthetic valve function. The history at subsequent visits is tailored to detect symptoms suggestive of heart failure or reduced functional capacity, arrhythmia, thromboembolism, or infection. Adherence to the recommended schedule of INR determinations and the relative time spent in the therapeutic range should be assessed in all anticoagulated patients. Problems with bleeding should be identified. A focused cardiovascular examination is repeated at each visit. Instructions regarding antibiotic prophylaxis are repeated. After the 6-month mark, follow-up visits can be conducted annually unless interim problems arise.

A chest radiograph is obtained by the surgeon at the first visit to assess for residual pleural fluid, pneumothorax, lung aeration, and heart size. An electrocardiogram (ECG) is routinely obtained and should be reviewed for rhythm, conduction, and dynamic repolarization changes. Postoperative baseline values for hemoglobin, hematocrit, lactate dehydrogenase (LDH), and bilirubin should be established for patients with mechanical heart valves, allowing future comparisons should hemolysis be suspected. It is less useful to follow the serum haptoglobin. Other laboratory studies are performed as clinically relevant.

Doppler Echocardiography.
An initial TTE examination performed 6 weeks to 3 months after prosthetic valve implantation is recommended to assess the results of surgery and serve as a baseline for comparison should complications or deterioration occur later. Repeat TTE as well as TEE is recommended if there is a change in clinical symptoms or signs suggesting valve dysfunction. In patients with a bioprosthetic valve, routine annual TTE follow-up is recommended after year 5 by the American Society of Echocardiography (ASE),[4] but not until year 10 in the 2014 AHA/ACC guideline.[2] Recent studies estimate that 25% to 30% of patients with a bioprosthesis implanted for less than 10 years in the aortic position have some degree of valve degeneration or dysfunction.[7] In patients with mechanical valves, routine annual echocardiography is not indicated in the absence of a change in clinical status.[2]

A complete echocardiogram includes two-dimensional imaging of the prosthetic valve, evaluation of the valve leaflet/occluder morphology and mobility, measurement of the transprosthetic velocity and

gradients, valve EOA, Doppler velocity index, estimation of degree of regurgitation, evaluation of LV size and systolic function, and calculation of systolic pulmonary artery pressure[4,5] (**see Chapter 14**). PVR is more common following TAVR than surgical AVR, and measurement of valve EOA is more challenging in transcatheter valves than in surgical valves because of the valve stent in the LV outflow tract.[26,28] Given that transcatheter valves are relatively new devices, more frequent follow-up is recommended, with specific recommendations provided by ASE and the Valve Academic Research Consortium (VARC) for Doppler-echocardiographic evaluation of these new valves.[28]

Evaluation and Treatment of Prosthetic Valve Dysfunction and Complications

The suspicion of prosthetic valve dysfunction may be the appearance of a new murmur or symptom in a patient with a prosthetic valve or the incidental finding of abnormally high flow velocities and gradients detected during a routine echocardiography. Doppler-echocardiography is the method of choice to evaluate prosthetic valve function, identify and quantitate prosthetic valve stenosis or regurgitation, and identify patient-prosthesis mismatch[4,5] (**Figs. 71.2 and 71.3**). Cinefluoroscopy and multidetector computed tomography (MDCT) (**see Chapter 18**) may also be very helpful to evaluate leaflet mobility in mechanical and bioprosthetic valves, respectively.[5] Prosthetic valve stenosis may be caused by thrombus formation, pannus ingrowth (or a combination of both), leaflet calcification in the case of bioprosthetic valves, and vegetations related to PVE. Prosthetic valve regurgitation may be caused by thrombus formation (mechanical valves), leaflet tear (bioprostheses), vegetations, or PVR.

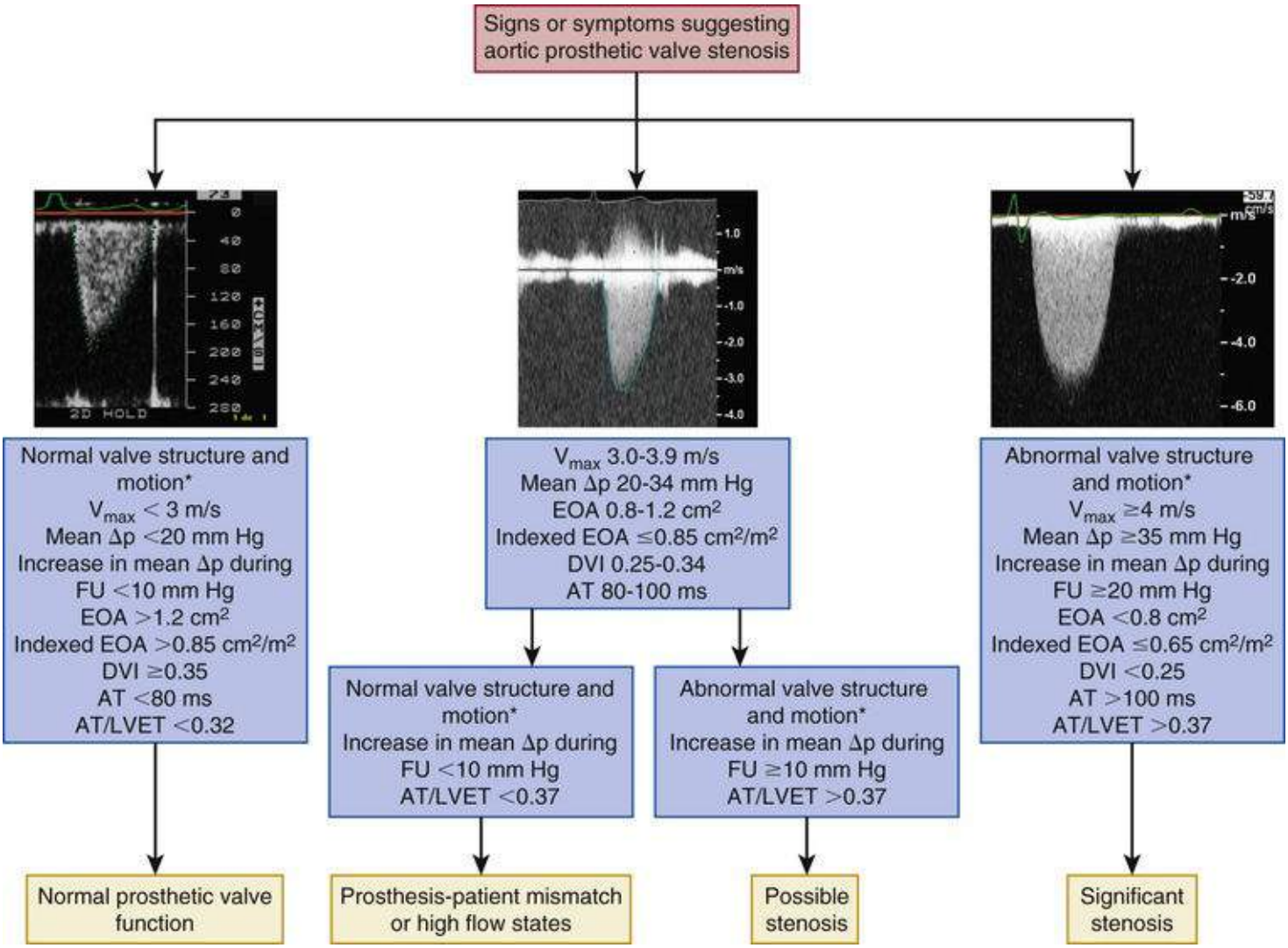

FIGURE 71.2 Evaluation of aortic prosthetic valve stenosis begins with standard measures of stenosis severity, including maximal velocity (V_{max}), mean pressure gradient (Δp), effective orifice area (EOA), and Doppler velocity index (DVI), the ratio of left ventricular (LV) outflow tract to aortic velocity. Normal values for each valve type and size should be referenced, but simple thresholds of 3 and 4 meters per second (m/s) for V_{max} and 20 and 35 mm Hg for mean Δp are a quick first step. For patients with intermediate measures of stenosis severity, the assessment of valve structure and motion and of the changes in Δp, EOA, and DVI during follow-up (FU) can be helpful to differentiate normal prosthetic valve function from concomitant prosthesis-patient mismatch or high flow states versus prosthetic valve stenosis. The shape of the velocity curve may also be helpful, with a triangular shape (short acceleration time [AT, i.e., time to peak velocity; ms, milliseconds] relative to LV ejection time [LVET]), suggesting normal valve function and a rounded waveform (increased AT/LVET ratio) suggesting significant stenosis. *Additional imaging, including transesophageal echocardiography, cinefluoroscopy, or computed tomography, may be needed to assess valve leaflet structure and motion.

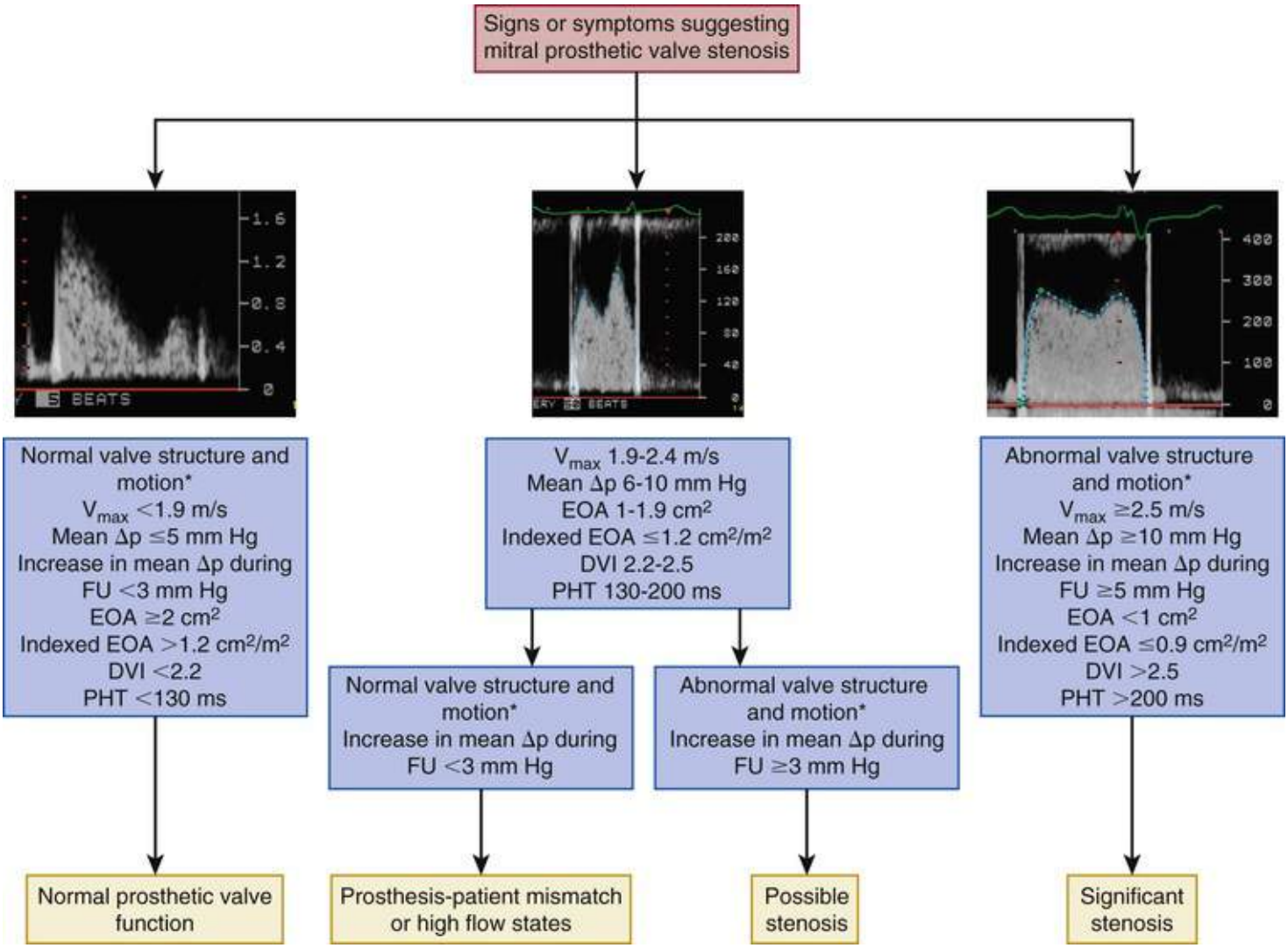

FIGURE 71.3 Evaluation of mitral prosthetic valve stenosis starts with standard measures of stenosis severity, including maximal velocity (V_{max}; m/s, meters per second), mean pressure gradient (mean Δp), effective orifice area (EOA), and pressure half-time (PHT; ms, milliseconds); FU, follow-up. Doppler velocity index (DVI) is the ratio of mitral to left ventricular (LV) outflow tract velocity, and therefore a value greater than 2.2 is abnormal. Normal values for each valve type and size should be referenced, but the thresholds shown are a quick first step. In patients with intermediate measures of stenosis severity, the differential diagnosis includes significant stenosis, prosthesis-patient mismatch, and a high flow state. *Additional imaging, including transesophageal echocardiography, cinefluoroscopy, or computed tomography, may be needed to assess valve leaflet structure and motion.

Prosthesis-Patient Mismatch

Patient-prosthesis mismatch (PPM) occurs when the size of a normally functioning prosthetic valve is too small in relation to the patient's body size, and thus to the patient's cardiac output requirements, resulting in abnormally high postoperative gradients. PPM is defined as an indexed EOA less than 0.85 cm^2 (severe, <0.65 cm^2) for aortic prosthetic valves and less than 1.2 cm^2 (severe, <0.9 cm^2) for mitral prosthetic valves. The prevalence of moderate PPM ranges from 20% to 70% and severe PPM from 2% to 10% after AVR or MVR.[29] Patients with aortic PPM have worse functional class and exercise capacity, reduced regression of LV hypertrophy, more adverse cardiac events, and increased risk of both perioperative and late mortality after AVR compared with patients who do not have PPM.[29] Patients with mitral PPM have persisting pulmonary hypertension and increased incidence of heart failure and death. A greater clinical impact of aortic PPM is also observed in specific groups of patients such as those with preexisting LV dysfunction or severe LV hypertrophy, and/or concomitant MR, as well as in those younger

than 65 to 70 years. PPM is less common with TAVR compared to surgical AVR, particularly in the subset of patients with a small aortic annulus.[11,30] **Figs. 71.2 and 71.3** provide algorithms for differentiating between normal prosthetic valve function, PPM, and intrinsic valve dysfunction caused by SVD, thrombus, or pannus.

Structural Valve Deterioration

Mechanical prostheses have an excellent durability, and SVD is extremely rare with contemporary valves, although mechanical failure (e.g., strut fracture, leaflet escape, occluder dysfunction caused by lipid adsorption) occurred with some models in the past. On the other hand, SVD from leaflet calcification or collagen fiber disruption is the major cause of bioprosthetic valve failure. SVD may lead to leaflet stiffening and progressive stenosis or leaflet tear with ensuing transvalvular regurgitation (**Fig. 71.4**; **see also Fig. 14.60**). Although SVD of bioprostheses has long been considered a purely passive degenerative process, more recent studies suggest that active and potentially modifiable processes may be involved, including lipid infiltration, inflammation, immune rejection, and active mineralization. Transcatheter valve-in-valve implantation offers a valuable alternative to surgery for patients with failed bioprosthetic valves who are at high or extreme surgical risk for reoperation[26,31] (**see Chapter 72**).

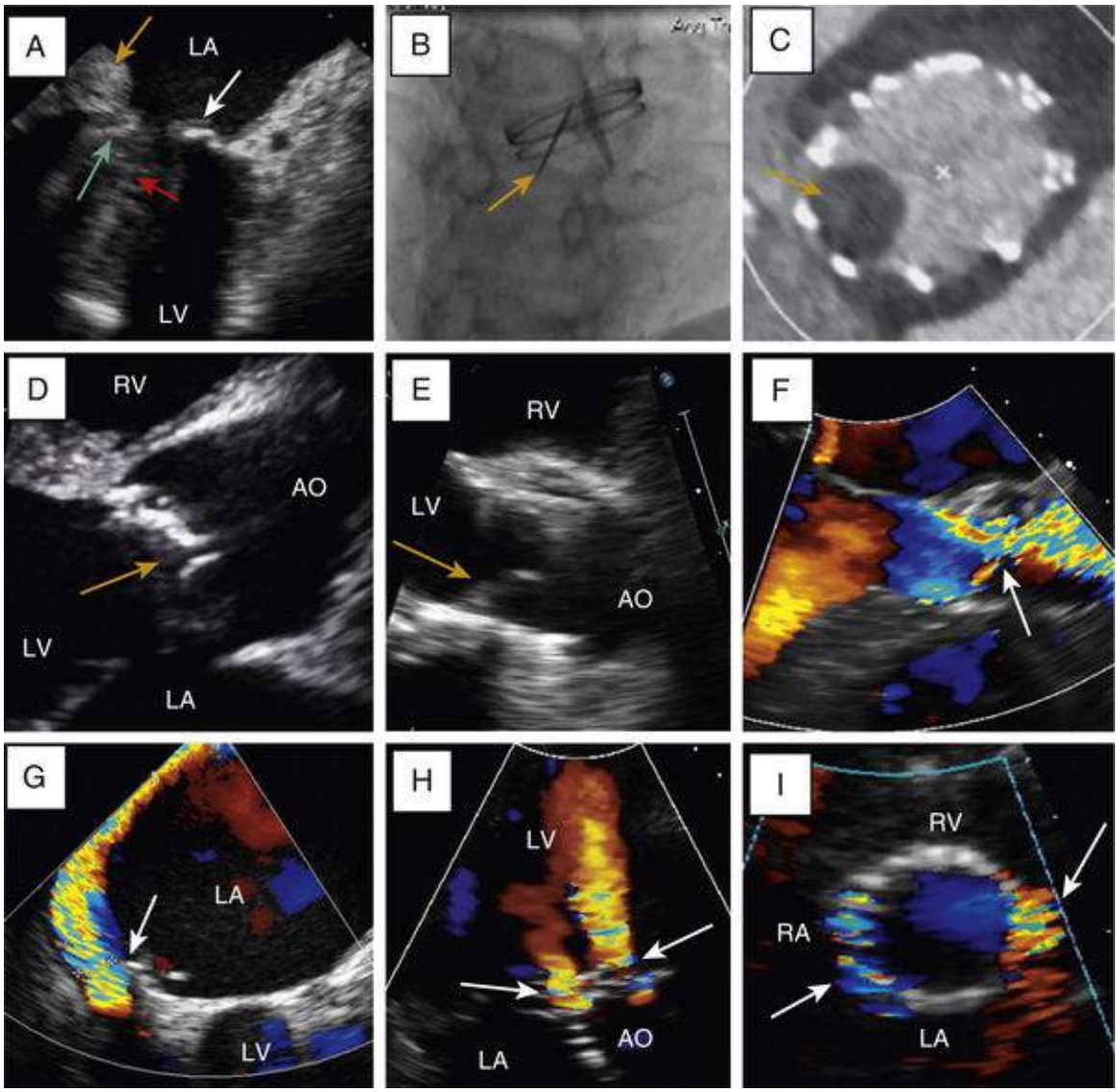

FIGURE 71.4 Imaging of prosthetic valve dysfunction. *AO,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. **A,** Transesophageal echocardiography (TEE) view of obstructed mitral bileaflet mechanical valve; *orange arrow,* large thrombus; *white arrow,* pannus; *red arrow,* mobile leaflet; *green arrow,* immobile leaflet (see Video 71.1). **B,** Cinefluoroscopy of bileaflet mechanical valve showing an immobile leaflet (*orange arrow*). **C,** Multidetector computed tomography with contrast injection showing area of hypoattenuation (*orange arrow*) indicating a thrombus on one of the leaflets of a balloon-expandable transcatheter valve. **D,** Transthoracic echocardiography (TTE) view of stented bioprosthetic valve with calcific degeneration, thickening, and reduced mobility of the leaflets (*orange arrow*) (see Video 71.2). **E, F,** TTE views of obstructive valve thrombosis in a balloon-expandable transcatheter aortic valve. The leaflets are thickened (**E,** *orange arrow*), and the width of the transprosthetic jet is narrowed (**F,** *white arrow*) (see Video 71.3). **G,** Color Doppler TEE view of severe paravalvular leak (*white arrow*) in mitral mechanical valve. **H,** Apical three-chamber, and **I,** parasternal short-axis, color Doppler TTE views of two paravalvular regurgitant jets (*white arrows*) in a transcatheter aortic valve (see Video 71.4). (**D,** Courtesy John Chambers, Guy's and St. Thomas Hospitals, London, and **G,** courtesy Arsène Basmadjian, Montreal Heart Institute.)

Paravalvular Regurgitation

Paravalvular regurgitation (PVR) occurs external to the prosthetic valve at the interface between the sewing ring and the native valve annulus (**Fig. 71.4**). It can occur as a result of inadequate technique, suture dehiscence, compromised native tissue integrity (dense calcification, extensive myxomatous degeneration), infection, or chronic abrasion of the sewing ring against a calcified or rigid annulus. The magnitude of the regurgitant volume will depend on the size of the orifice. A small, hemodynamically inconsequential paravalvular leak is usually discovered incidentally during routine TTE with color

Doppler flow imaging, with no change in management indicated. However, small paravalvular leaks may be associated with significant intravascular hemolysis and anemia as red blood cells are forced through a narrow orifice at high velocity. Despite a high clinical index of suspicion in this circumstance, a new, regurgitant murmur may not be audible. TEE may be necessary to differentiate PVR from transvalvular regurgitation and to visualize the defect appropriately, especially with mitral prostheses. Larger paravalvular leaks may result in significant volume overload and heart failure, to an extent that reoperation might be indicated. Significant PVR may develop during the late postoperative period and is often the result of endocarditis. Experience with transcatheter closure devices in patients with clinically important PVR has increased, but results to date have been mixed.[32] Management can prove challenging, and a conservative approach with medical therapy is often chosen, in part related to the risks associated with reoperation in some patients.

PVR occurs more frequently after transcatheter than surgical AVR; its incidence is significantly lower with newer-generation TAVR prostheses. Because PVR jets after transcatheter AVR are often multiple, irregular, and eccentric, the imaging and grading of PVR can be challenging (**Fig. 71.4**; **see also Fig. 14.61**). A multiwindow, multiparametric, integrative approach is essential to assess the severity of PVR by Doppler echocardiography.[14,28] Other imaging modalities, such as cineangiography, cardiac CT, and cardiac magnetic resonance imaging (**see Chapters 17 and 18**), as well as serum biomarkers, may also be useful to complement or corroborate the findings on echocardiography.[5,14,33] Corrective procedures such as repeat balloon dilation, valve-in-valve implantation, and transcatheter leak closure may be considered depending on the severity of PVR and the risk of procedural complications.[14]

Thromboembolism and Bleeding

Thromboemboli are a major source of morbidity in patients with prosthetic heart valves. The incidence of clinically recognizable events ranges from 0.6% to 2.3% per patient-year,[2] an estimate that does not account for any subclinical episodes that might be detected with sensitive imaging techniques.[34] Thromboembolic incidence rates are similar for non-anticoagulated patients with bioprostheses and appropriately anticoagulated patients with mechanical valves. Risk factors for thromboembolism include the inherent thrombogenicity of the prosthesis, valve position (mitral > aortic), valve number, time spent out of the therapeutic range of anticoagulation, a history of thromboembolism, hypercoagulable state, atrial fibrillation, left atrial enlargement, and LV systolic dysfunction. The risk of bleeding, estimated at 1% per patient-year, increases with age and the intensity of anticoagulation. In patients with uncontrollable bleeding who require reversal of anticoagulation, administration of fresh-frozen plasma or prothrombin-complex concentrate is reasonable.

Management of a thromboembolic event in patients with mechanical valves generally proceeds as follows[2]:

- For patients whose INR is subtherapeutic, the dose of the VKA is advanced to achieve the intended INR range.
- For patients whose INR is in the therapeutic range, the dose of the VKA is advanced to achieve a higher INR range, *and/or* low-dose aspirin is provided if not already used.
- The patient and family are informed about the increased risks of

bleeding.
- The potential for drug interactions is reviewed.

Reoperation to implant a less thrombogenic valve is rarely undertaken for patients with recurrent thromboemboli despite aggressive antithrombotic therapy.

Prosthetic Valve Thrombosis

The incidence of mechanical valve thrombosis is estimated at 0.3% to 1.3% per patient-year in developed countries, but as high as 6% per patient-year in developing countries.[2] Thrombosis of a mechanical heart valve can have devastating consequences (**see Figs. 71.1 and 71.4**). Bioprosthetic (surgical or transcatheter) valve thrombosis is less common, with a reported incidence of 0.03% to 0.5% per patient-year.[35] However, recent studies suggest that subclinical thrombosis may occur in 5% to 15% of patients within the first 2 years after TAVR.[36-38]

Clinical suspicion of prosthetic valve thrombosis should be raised by symptoms of heart failure, thromboembolism, or low cardiac output, coupled with a decrease in the intensity of the valve closure sounds (mechanical valves), new and pathologic murmurs, or documentation of inadequate anticoagulation. Thrombosis is more common in the mitral and tricuspid positions than in the aortic position. Although differentiation from pannus formation can be difficult, the clinical context usually allows accurate diagnosis. Evaluation with TTE/TEE can help guide management decisions[4,5] (**see Fig. 14.59**). In patients with mechanical valves, confirmation of abnormal leaflet or disc excursion in the presence of an occluding thrombus can also be obtained with cinefluoroscopy.[5] MDCT can be useful to identify leaflet thickening and reduced mobility after valve replacement with a bioprosthesis[36] (**see Fig. 71.4**).

Emergency surgery is reasonable for patients with left-sided prosthetic valve thrombosis and shock or New York Heart Association (NYHA) Functional Class III or IV symptoms and for patients with a large thrombus burden (≥0.8 cm^2 on TEE).[2] Fibrinolytic therapy is reasonable for patients with recent-onset (<2 weeks) NYHA Class I or II symptoms and small thrombus burden (<0.8 cm^2) and for sicker patients with larger thrombi when surgery is either not available or inadvisable. Fibrinolytic therapy is generally recommended for patients with right-sided prosthetic valve thrombosis.[2] Some patients with no or minimal symptoms and small thrombi can often be managed with intravenous UFH alone and then converted to fibrinolytic therapy if unsuccessful. An encouraging report of the efficacy of low-dose, slow-infusion tissue plasminogen activator in pregnant women with prosthetic valve thrombosis should prompt investigation of this approach in other patient subsets.[39] Any course of fibrinolytic therapy is followed at the appropriate interval by a continuous infusion of UFH during the transition to VKA therapy targeted to a higher INR, with or without low-dose aspirin. Serial TTE studies are useful to assess the response to treatment. In patients with suspected or confirmed bioprosthetic valve thrombosis who are hemodynamically stable and have no contraindications to anticoagulation, initial treatment with a VKA is reasonable.[26,35,36,38]

Infective Endocarditis

Prosthetic valve endocarditis is the most severe form of infective endocarditis (IE) and occurs in 1% to 6% of patients with valve prostheses, accounting for 10% to 30% of all IE cases[17] (**see Chapter 73**).

PVE is an extremely serious condition with high mortality (30% to 50%). The diagnosis, based on the Modified Duke Criteria, relies predominantly on the combination of positive blood cultures and echocardiographic evidence of prosthetic valve infection, including vegetations, paravalvular abscess, or a new PVR.[17] TEE is essential in patients with prosthetic valves because of its greater sensitivity in detecting these abnormalities. Recent studies suggest that increased uptake of ^{18}F-fluorodeoxyglucose measured by positron emission tomography combined with computed tomography (PET-CT) may improve the early diagnosis of PVE[40] (**see Fig. 16.47**). Despite prompt and appropriate antibiotic treatment, many patients with PVE will eventually require surgery. Medical treatment alone is more likely to succeed in late PVE (>6 months after surgery) and in nonstaphylococcal infections. Surgery should be considered in patients with heart failure; failure of antibiotic treatment; hemodynamically significant prosthetic valve regurgitation, especially if associated with deterioration of LV function; large vegetations (>10 mm); persistently positive blood cultures on therapy; recurrent emboli with persistent vegetations; and intracardiac fistula formation[2] (**see Fig. 73.4**). PVE after TAVR occurs predominantly within the first year after the procedure; its incidence is low (1%/patient-year), but in-hospital (approximately 35%) and 2-year (67%) mortality rates are high,[41] likely reflective of patient age and comorbidities.

Hemolytic Anemia

The development of a nonimmune hemolytic anemia after valve replacement or repair is usually attributable to PVR with intravascular red blood cell destruction. Diagnosis is based on a high index of suspicion, coupled with laboratory evidence of hemolysis, including the characteristic changes in red blood cell morphology (schistocytes), elevated indirect bilirubin and LDH, a high reticulocyte count, and depressed serum haptoglobin. Reoperative surgery or catheter closure of the defect is indicated when heart failure, a persistent transfusion requirement, or poor quality of life intervenes. Empiric medical measures include iron and folic acid replacement therapy and beta-adrenoreceptor blockers. It is important to exclude PVE as a cause.

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Transcatheter Therapies for Valvular Heart Disease

Howard C. Herrmann, Michael J. Mack

The impetus for the development of transcatheter therapies for valvular heart disease (VHD) arises from two major factors. First, a transcatheter therapy can avoid the risks associated with more invasive surgical approaches, particularly those associated with cardiopulmonary bypass and median sternotomy, while preserving or enhancing outcomes. Second, the patient wants to avoid the invasiveness and prolonged recovery associated with major surgery. However, these factors must always be balanced with the efficacy of the transcatheter approach. In this regard, the patient will always prefer a transcatheter approach that is less invasive, provides a faster patient recovery, and has similar efficacy to a more invasive surgical approach. However, a less efficacious approach, even if safer and associated with faster recovery, will require more complex decision making that takes into account the patient's age, comorbidities, and goals of care.

Historically, the first and quite successful transcatheter therapy for VHD was balloon valvuloplasty for congenital pulmonic stenosis, developed by Dr. Jean Kan in 1982. That led to a decade of extension of balloon therapies to the treatment of mitral stenosis (MS) and aortic stenosis (AS) and opened the door to other transcatheter therapies for regurgitation lesions, such as MitraClip (Abbott Vascular, Santa Clara, California) repair for mitral regurgitation (MR). More recently, the success of transcatheter aortic valve replacement (TAVR) with both balloon-expandable and self-expanding prostheses for severe, symptomatic AS has ushered in an entire medical specialty focused on transcatheter therapy of VHD. This chapter addresses the indications, techniques, clinical, and investigational therapies available for AS, MS, MR, and tricuspid regurgitation (TR).

Aortic Stenosis (See Chapter 68)

Paul Dudley White stated in 1931 that “there is no treatment for aortic valve disease.” In 1952, however, Hufnagel implanted a “ball and cage” prosthesis in the descending aorta for the treatment of aortic regurgitation (AR). The subsequent pioneering work of Harken, Braunwald, and Starr led to the treatment of patients with severe AS with surgical aortic valve replacement (SAVR) using a mechanical valve in 1960 (see Classic References, Harken). Currently, a wide variety of mechanical and bioprosthetic valves are used for the treatment of AS, with more than 90% of SAVRs performed with tissue valves (**see Chapter 71**).

Balloon Aortic Valvuloplasty

Transcatheter treatment of AS began in 1985 with balloon aortic valvuloplasty (BAV) by Cribier (see Classic References). Early feasibility and safety were accomplished with a modicum of success and modest improvement in valve area and clinical symptomatic relief. Although extensively employed for a number of years, BAV was largely abandoned because of the minimal duration of benefit, with symptomatic relief for only months, and restenosis rates of more than 80% at 1 year and no prolongation of patient survival (see Classic References, NHLBI).

However, there currently remains a role for BAV primarily as “bridge” therapy. Although there is occasionally a role for palliation in the elderly or premorbid patient, BAV is most frequently used for clinical decision making in two situations.[1,2] First, as a diagnostic tool, BAV can help clarify the cause of symptoms, such as chronic obstructive lung disease or heart failure as the cause of dyspnea in a patient with AS. In this setting, both the risks of BAV and the modest improvement in valve area must be factored into the expected benefit. Second, in addition to its role as a “bridge to decision,” BAV also has a limited role as a “bridge to therapy.” In patients with recent acute decompensated heart failure, acute renal failure, or decompensated left ventricular (LV) function, treatment with BAV as temporizing therapy can allow end-organ and cardiac recovery.

Transcatheter Aortic Valve Replacement

The idea of implanting a prosthetic valve to prevent restenosis after balloon valvuloplasty is credited to Henning Andersen, a Danish cardiologist who fashioned a stent from stainless steel surgical wires and mounted a bioprosthetic valve inside the stent. His initial animal experiments demonstrating feasibility were presented at the European Society of Cardiology in 1992 (see Classic References, Andersen). The ensuing decade led to improvements in valve and stent design along with development of a delivery system, culminating in the first successful human implantation by Cribier in 2002 (see Classic References). Although additional implants were performed over the next few years, efforts to expand to other centers and broaden experience were plagued by difficulties in safely reproducing Cribier's original antegrade transseptal delivery. The development of the *retrograde transfemoral* arterial route by Webb and colleagues[3] and the *antegrade transapical* approach by Walther and associates[4] allowed expansion of the procedure to other operators and centers. Progress was facilitated by the development of smaller-caliber and steerable delivery systems.

Two main types of stent design are used for TAVR: balloon-expandable and self-expanding (**Fig. 72.1**). One of each type is approved by the U.S. Food and Drug Administration (FDA) for use in the United

States. The Edwards Sapien Valve (Edwards Lifesciences, Irvine, California) is a cobalt chromium balloon-expandable valve with the valve leaflets made of treated bovine pericardium. The original Sapien THV valve was replaced by the second-generation Sapien XT valve and now the third-generation Sapien 3 valve. Most other TAVR valve designs are self-expanding nitinol valves. CoreValve (Medtronic, Minneapolis, Minnesota) is the most common self-expanding valve, now in its third generation as the Evolut-PRO valve. Both these valves are FDA approved for commercial use in the United States, with more than 75,000 commercial implants by late 2016.[5] Numerous other valves have received commercial approval for use in Europe and are in investigational device exemption (IDE) trials in the United States.

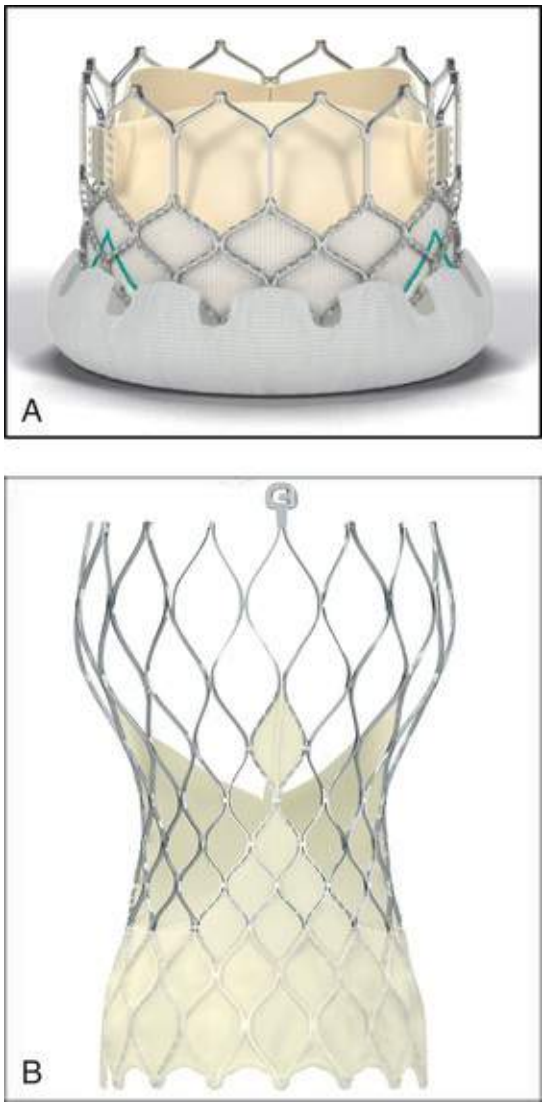

FIGURE 72.1 Transcatheter aortic valves currently approved for use in the United States. **A,** Sapien 3 balloon-expandable valve. **B,** Third-generation CoreValve (Evolut-PRO) self-expanding valve.

Currently, 85% to 90% of all TAVR valves are implanted by a transfemoral approach.[5] For patients in whom a transfemoral approach is not feasible, a number of other "alternative access" routes are used. The original transapical delivery is now seldom used for TAVR, as is the direct transaortic route, which is performed by an upper partial sternotomy or limited right anterior thoracotomy. The more preferred alternative access approach currently is a *subclavian* approach, usually the left, which can be facilitated by a side graft sewn onto the artery. Other innovative alternative access approaches include transcarotid, transcaval, and transmediastinal.

Evidence Base

A robust evidence base has compared TAVR to the standard of care for AS (**Table 72.1**). The series of PARTNER trials began with PARTNER 1B, which demonstrated superiority of TAVR to medical therapy in inoperable patients, with an absolute survival advantage of 23% at 5 years.[6] The PARTNER 1Al and CoreValve trials randomized high–surgical risk patients between TAVR and SAVR.[7,8] Both trials were noninferiority trials and showed either no difference or improved survival with TAVR at 1 year. Patients in PARTNER 1A have been followed to 5 years with no survival difference seen.[9]

TABLE 72.1

Randomized Trials of Transcatheter Aortic Valve Replacement

RISK	TRIAL	TAVR (*n*)	COMPARATOR (*n*)	OUTCOME
Inoperable	PARTNER 1B	179	Medical (179)	TAVR superior to medical
High risk	PARTNER 1A	348	SAVR (351)	TAVR = SAVR
	CoreValve	394	SAVR (401)	TAVR superior to SAVR
Intermediate risk	PARTNER 2A	1011	SAVR (1021)	TAVR = SAVR
	SURTAVI	864	SAVR (796)	TAVR = SAVR
Low risk*	PARTNER 3	TAVR vs. SAVR, total enrollment = 1228		
	CoreValve Evolut-R	TAVR vs. SAVR, total enrollment = 1200		

*The low-risk trials are ongoing.

Two multicenter randomized trials have compared TAVR to SAVR in symptomatic patients at intermediate surgical risk. The PARTNER 2A trial[10] randomized 2036 patients to the balloon-expandable Sapien valve versus SAVR, and the SURTAVI trial[11] randomized 1746 patients to a self-expanding TAVR (84% CoreValve, 16% Evolut-R) versus SAVR. The results of both trials demonstrated noninferiority of TAVR to SAVR for the composite endpoint of death and stroke at 2 years.

The mortality rate of TAVR has consistently improved over the past decade. More centers are gaining experience and surmounting a learning curve. Improvements in delivery systems, with smaller-caliber devices, allow a higher percentage of patients to be candidates for treatment with a transfemoral approach. Better patient selection is also a major contributor to improved outcomes. Clinical experience has defined the patient group with severe AS who have excessive frailty, comorbidities, and disability and are thus unlikely to improve after the procedure (“cohort C patients”). In a large registry of symptomatic, intermediate-risk patients who underwent TAVR using the balloon-expandable Sapien 3 system, survival was markedly superior to the surgical arm of PARTNER 2A.[12] (Importantly, PARTNER 2A was not a prospective randomized trial but used historic surgical controls.) Trials comparing TAVR to SAVR in low-risk patients are currently underway.

Complications.

The complications associated with TAVR have been somewhat addressed by improvements in devices, delivery, technique, and patient selection. These complications include stroke, paravalvular leak, need for a new, permanent pacemaker, and valve thrombosis.

An early concern of TAVR was an increased risk of stroke associated with the procedure. The incidence of clinically evident stroke both in randomized trials when examined by a neurologist and in clinical commercial registries ranges from 2% to 9%.[13] However, the use of sophisticated neuroimaging with diffusion-weighted (DW) magnetic resonance imaging (MRI) demonstrates the presence of embolic lesions in the brain in 68% to 100% of patients undergoing TAVR[9] (**Fig. 72.2**). This has led to the

development of cerebral protection devices that either capture or deflect emboli during the procedure. Results to date have been mixed; some studies have shown a decrease in both number and volume of lesions detected by DW MRI, but a recent major randomized trial of cerebral protection failed to meet its primary endpoint.[14] Nonetheless, this device (Sentinal, Claret Medical, Santa Rosa, California) recently received FDA approval. What remains unclear is the clinical relevance and significance of these radiographic lesions. Evidence in other clinical situations suggests that these findings are associated with long-term neurocognitive decline.

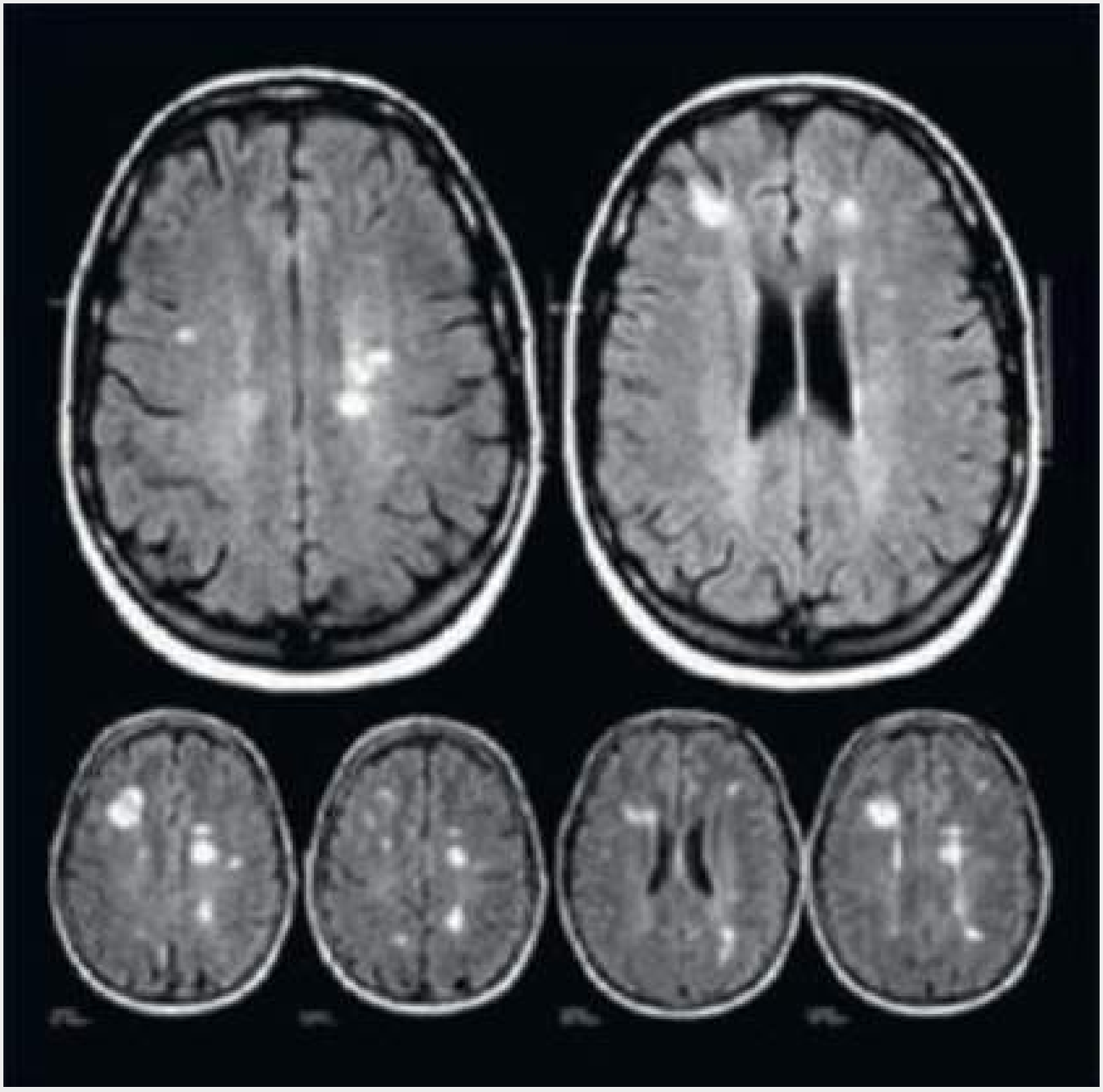

FIGURE 72.2 Typical findings on diffusion-weighted MRI after transcatheter aortic valve replacement (TAVR) showing multiple embolic lesions.

The incidence of moderate to severe paravalvular leak was significantly problematic in the initial trials of TAVR. However, improvements in valve design and increased availability of additional valve sizes, as well as the routine use of three-dimensional (3D) computed tomography (CT) reconstruction for preprocedural planning (**see Chapter 18**), allowing a more accurate selection of appropriate valve size (**Fig. 72.3; see also Fig. 18.15**), have decreased the incidence of moderate to severe paravalvular leak to

the range of 3% to 6% in current experience, although mild paravalvular regurgitation occurs in up to one third of patients.[15,16]

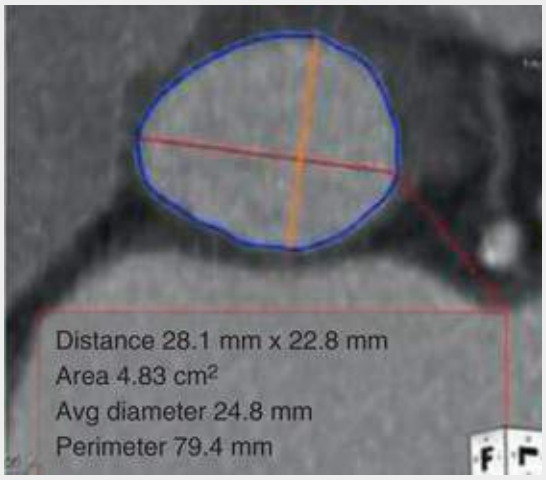

FIGURE 72.3 Three-dimensional reconstruction of a multislice CT scan for annular sizing for TAVR.

The requirement for a new, permanent pacemaker in many patients continues to be an issue with TAVR. The incidence ranges from approximately 10% to 30%, with most current studies closer to the lower end of this range.[17-19] Patients with preexisting conduction system abnormalities are particularly prone to develop increased conduction system block after TAVR and thus require a new, permanent pacemaker. This requirement may gain increasing importance as TAVR becomes more frequently employed in younger patients with a longer life expectancy. On the other hand, younger patients are less likely to have preexisting conduction system disease and therefore may be less likely to require a new pacemaker. Avoidance of valve oversizing and overinflation during deployment as well as slightly higher valve placement all may be beneficial in reducing the need for a new pacemaker.

Another concern associated with TAVR is valve leaflet thickening and thrombosis. This issue was initially discovered by using sophisticated imaging with four-dimensional reconstruction of multislice CT (4D CT) scans during research trials and registries.[20] The subsequent expanded use of these imaging modalities in surveillance studies revealed an incidence of approximately 7% to 10%.[21] Numerous studies have also shown resolution of these imaging abnormalities with anticoagulation, indicating valve thrombosis as the etiology[22] (**Fig. 72.4**). Current recommendations include the use of CT for detection whenever a clinical situation arises suggesting leaflet thrombosis, including an increase in mean transvalvular gradient, new or persistent heart failure, or stroke occurring beyond the periprocedural period.

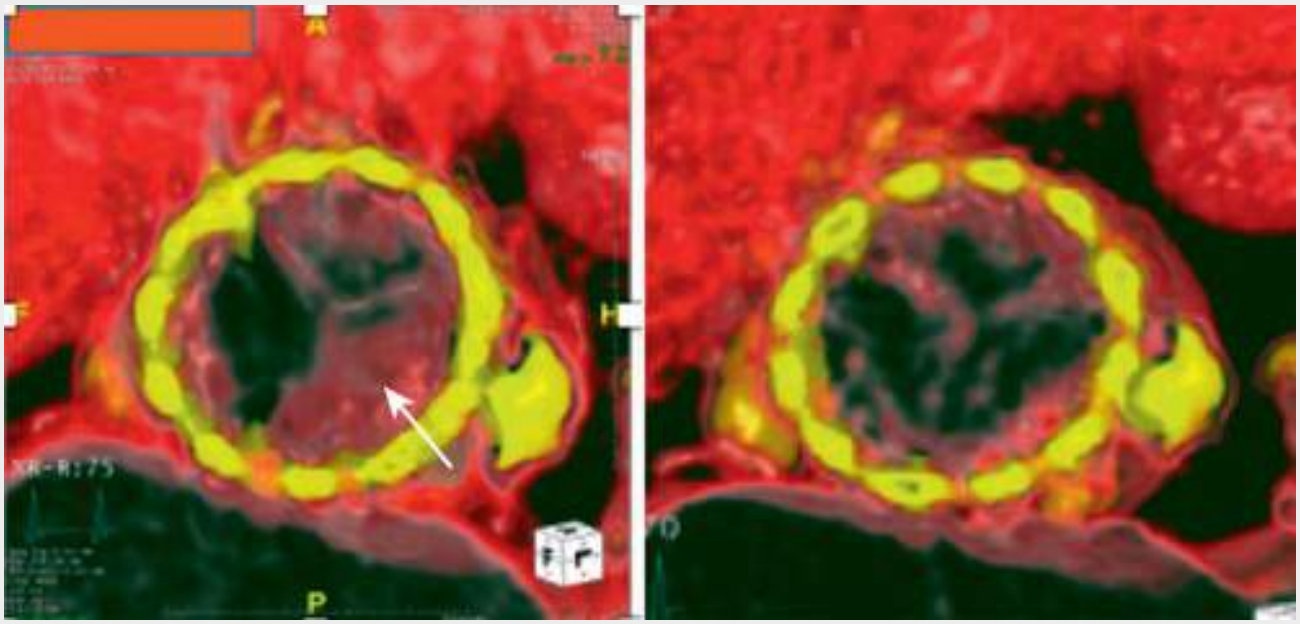

FIGURE 72.4 Four-dimensional CT scan demonstrating thrombus (*arrow*) on TAVR valve **(left)** with resolution after 30 days of warfarin therapy **(right).**

Valve Durability.

The question of valve durability remains unanswered with TAVR. Randomized studies to 5 years and single-center experience up to 10 years have not yet shown a major reason for concern regarding durability.[9,23] However, all the studies are subject to survivorship bias, and with small numbers of patients alive at 5 years or longer after the procedure, the ultimate issue of durability with surgical valves remains undetermined.

Imaging

Sophisticated imaging techniques are crucial to the success of a TAVR program. The use of high-quality transthoracic echocardiography (TTE) for initial determination of the diagnosis and severity of AS is mandatory (**see Chapter 14**), and the use of multislice CT scanning is critical for preprocedural planning (**Chapter 18**). Determination of annular size, height of coronary arteries, and presence of ascending aortic and LV outflow tract calcification are all critical to procedural success (**Fig. 72.5**). The use of transesophageal echocardiography (TEE) for diagnosis may be helpful when determining whether bicuspid valve disease is present and when chronic kidney disease precludes CT imaging. The use of TTE for patient follow-up and the "for cause" use of 4D CT or TEE have become routine practice.

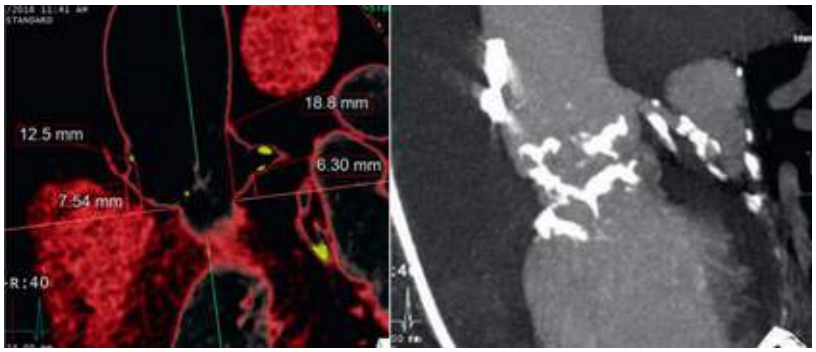

FIGURE 72.5 Three-dimensional CT scans. **Left,** Coronary height relative to the aortic annulus. **Right,** Calcification of the aortic root, annulus, and left ventricular outflow tract.

Heart Team Approach

The use of the multidisciplinary heart team has been an important part of the introduction of TAVR into clinical practice[24] (**see Chapter 67**). The members of the heart team include interventional cardiologists, cardiac surgeons, imaging specialists, anesthesiologists, midlevel providers, research coordinators, fellows-in-training, and geriatricians. Recent concerns are that the heart team is logistically unwieldly and has somewhat outlived its usefulness because patient decision making has become more straightforward.[25] However, as the role of TAVR becomes greater in intermediate-risk and possibly low-risk patients with AS, and transcatheter therapies are applied to other valvular lesions, the role of the heart team in patient-centered decision making will be even more important.

Minimalist Techniques

TAVR procedures are now usually performed percutaneously through a transfemoral approach, obviating the need for general anesthesia. The "minimalist approach," in which the procedures is performed under local anesthesia with mild to moderate sedation and without the routine use of intraprocedural TEE, has resulted in less resource utilization without jeopardizing outcomes.[26] Currently, this approach is used in approximately 15% to 20% of TAVR procedures in the United States, with as high as 90% in some centers.[5]

Future Perspectives.

The future bodes well for TAVR procedures. Currently, two randomized trials are ongoing in low–surgical risk patients between TAVR and SAVR. The two trials also include a subgroup of patients undergoing surveillance 4D CT scans for valve thrombosis to determine the true incidence, predisposing factors, and clinical relevance of the imaging abnormalities previously noted. Other ongoing registry studies include the role of TAVR in bicuspid aortic valves, and aortic and mitral "valve-in-valve" placement in degenerated bioprosthetic surgical valves (**see Chapter 71**). Both FDA-approved devices have received indications for high-risk patients with structurally degenerated aortic bioprostheses. Later-generation TAVR valves in completed or ongoing studies are likely to be introduced into clinical practice in the near future.

The role of adjunctive therapy remains in question. Although the use of dual-antiplatelet therapy has become routine, no strong evidence base supports DAPT. Clinical trials of the novel oral anticoagulants rivaroxaban and apixaban, alone and in combination with antiplatelet regimens, are ongoing. Cost-effectiveness of TAVR also remains an open question. The high cost of the device, approximately $32,000, has raised questions about the ultimate cost-effectiveness of the procedure. However, some evidence shows that the decreased utilization of resources, including a shorter hospital stay, now 1 to 2 days in major programs, offsets the higher device costs.[27]

Mitral Stenosis (See Chapter 69)

In the patient with severe and symptomatic MS, TTE is key to diagnose and confirm the functional severity of the stenosis (**see Chapter 14**).

Mitral Balloon Valvuloplasty

Determining the morphology of the mitral valve and subvalvular apparatus is important in preprocedural planning for mitral balloon valvuloplasty (MBV). The suitability of a valve for MBV can be determined using a morphologic score; the most widely used is the system of Wilkins (see Classic References), which assigns a score of 1 to 4 for leaflet mobility, valve thickening, calcification, and subvalvular thickening (**see Table 14.9**). The severity of concomitant MR is also a key determining factor for MBV, both as it relates to the final result, which may increase up to 1 grade, and to confirm that the patient's symptoms are indeed caused by valvular obstruction and not concomitant regurgitation. In the latter case, mitral valve replacement may be a better option for symptomatic relief. TEE is a final step to assess further the severity of MR and valve morphology and to ensure the absence of left atrial (LA) thrombus before MBV.

Indications

MBV is indicated in symptomatic MS patients who have at least moderate to severe MS, favorable valve morphology, the absence of LA thrombus, and less than moderate to severe MR. In patients with rheumatic MS and calcified nonpliable valves who are at high-risk or unsuitable for open surgery, MBV may be a reasonable alternative to provide palliative symptomatic relief. MBV may also be considered in asymptomatic patients with moderate to severe MS and new-onset atrial fibrillation after excluding LA thrombus (class IIb). In patients with symptoms and mild MS (mitral valve area [MVA] >1.5 cm^2), MBV can be considered if there is evidence of significant MS with exercise testing (class IIb).[28] The mechanism of benefit is separation of the fused commissures, which relieves the physical obstruction, thereby reducing the gradient and increasing MVA.

Procedure.

The transvenous antegrade transseptal route is typically used to gain access to the left atrium to perform MBV. Inoue first used a self-positioning latex balloon wrapped with a nylon mesh to allow phased balloon expansion in 1982 and described the technique in 1984 (see Classic References). The double-balloon technique involves two peripheral arterial balloons tracked over separate guidewires placed in the left ventricle and simultaneously inflated.

The double-balloon technique was the first one used in the United States. Following transseptal catheterization and therapeutic anticoagulation, a balloon-tipped end-hole catheter is used to traverse the mitral valve via the transseptal puncture site. This catheter is navigated to the apex of the left ventricle, and once positioned, a 260-cm guidewire is placed in the LV apex or looped across the aortic valve into the descending aorta. A second guidewire is placed using a similar technique or by using a dual-lumen catheter. Two 18- or 20-mm dilation balloons are tracked and positioned on the wires and inflated simultaneously to dilate the valve.

The Inoue technique has mostly replaced the double-balloon technique, in part because there is no risk of LV perforation with the Inoue balloon (**Fig. 72.6**). The initial size of the Inoue balloon is based on

patient's height. Once inserted over a guidewire into the left atrium, it can be steered across the mitral valve orifice with an internal stylet and then sequentially inflated multiple times over a 4-mm diameter range, with both hemodynamic and echocardiographic results assessed, to achieve the maximal dilation with the least increase in grade of MR. As such, it is important to evaluate carefully for severe commissural calcium preprocedurally. Calcium does not split with balloon inflation but does increase the potential for tearing the leaflets creating MR.

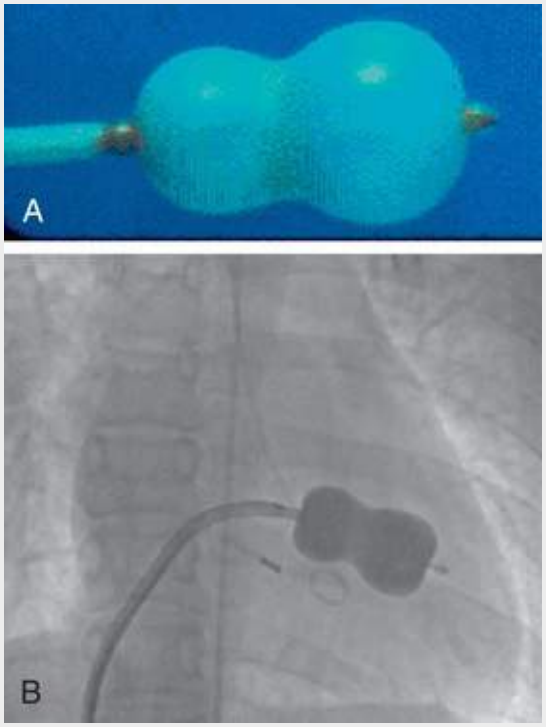

FIGURE 72.6 **A,** Inoue mitral balloon valvuloplasty catheter and three-stage balloon. **B,** Partially inflated Inoue balloon positioned across the mitral valve.

A reduction in mean mitral valve gradient by 50% or an increase in MVA greater than 1.5 cm^2 is considered a successful result and can be achieved in more than 80% of appropriately selected patients. An increase in MR by more than 1 grade after balloon inflation should signal an end to the procedure despite a residual gradient. Event-free survival after MBV is influenced by valve morphology. In a large study of 879 North American patients with a mean follow-up of 4.2 ±3.7 years, there was a greater immediate increase in MVA after MBV and improved long-term survival (82% versus 57%; $P < 0.0001$) in patients with a Wilkins score of 8 or less (**Fig. 72.7**). Patients with higher echocardiographic scores have more events in the long term, including need for repeat MBV, need for mitral valve surgery, and death (**Fig. 72.7B**). In multivariate analysis, age, post-MBV MR grade of 3+ or higher, prior surgical commissurotomy, New York Heart Association (NYHA) Class IV symptoms, and elevated post-MBV pulmonary artery systolic pressure were all independently associated with worse outcome at follow-up.

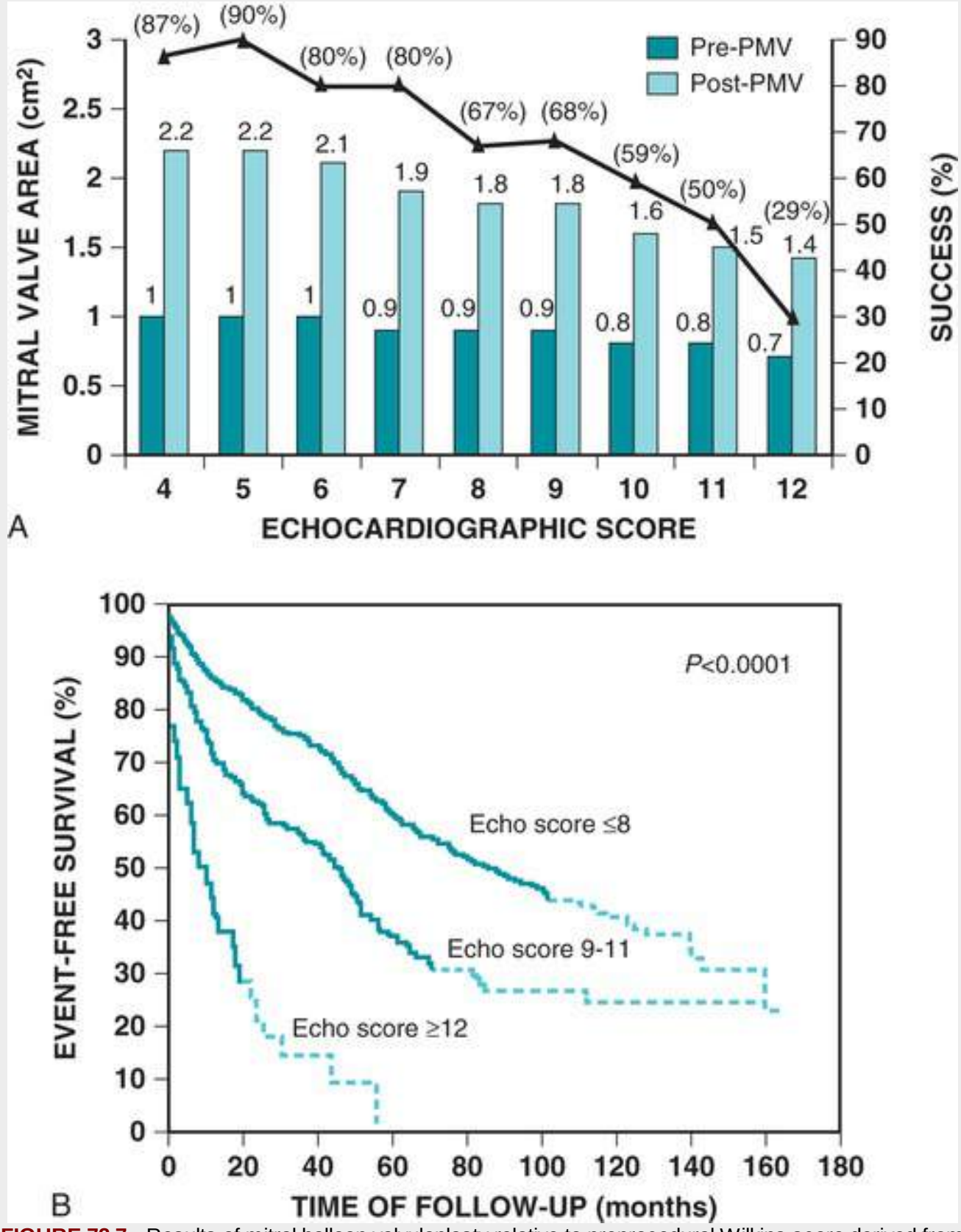

FIGURE 72.7 Results of mitral balloon valvuloplasty relative to preprocedural Wilkins score derived from echocardiography. **A,** *Bars* indicate mitral valve area before and after percutaneous mitral valvuloplasty (PMV) as a function of the echocardiographic score, and the connected *triangles* indicate procedural success rate. **B,** Association between echocardiographic score and postprocedural event-free survival. (From Palacios IF, Sanchez PL, Harrell LC, et al. Which patients benefit from percutaneous mitral valvuloplasty? Prevalvuloplasty and postvalvuloplasty variables that predict long-term outcome. Circulation 2002;105:1465-71. Copyright 2002 American Heart Association Inc.)

The most common complication from MBV, severe MR, occurs in 2% to 10% of patients, with no significant difference between the Inoue and double-balloon techniques. Overall procedural mortality is approximately 1%. Other, less common procedural complications include pericardial tamponade,

embolic events, vascular complications, arrhythmias, bleeding, stroke, myocardial infarction, residual atrial septal defect, and LV perforation.

Echocardiography is essential for many aspects of MBV, including the transseptal puncture and assessment of postprocedural results and complications (**see Chapter 14**). TEE is considered the gold standard, and 3D TEE has been shown to be superior to TTE in reducing fluoroscopy time and the interval from first transseptal puncture to first balloon inflation.[29] Intracardiac echocardiography can also be used, with the advantage of avoiding the endotracheal intubation and general anesthesia usually required for TEE.

Mitral Regurgitation

Unlike MS, which is primarily caused by rheumatic fever, MR is a more diverse disease that results from dysfunction of any of the portions of the complex mitral valve apparatus, including the leaflets, chords, annulus, and left ventricle. As discussed in **Chapter 69**, MR is often further classified into *primary* (organic or degenerative) disease, which affects the leaflets (e.g., fibromuscular dysplasia, mitral valve prolapse, rheumatic disease), and *secondary* (ischemic or functional) disease, which spares the leaflets (e.g., diseases of atrium and ventricle, including ischemic dysfunction and dilated cardiomyopathy). Patients with severe MR have decreased survival, whether symptomatic or not, and surgery is often recommended.[30] In asymptomatic patients with primary MR and preserved LV function, a "watchful waiting" or "active surveillance" approach can be considered until the development of symptoms, LV dysfunction, pulmonary hypertension, or atrial fibrillation,[31] and current guidelines recommend surgery in patients who have reached these endpoints.[28] Surgery may also be considered for asymptomatic patients with normal LV function in whom there is a high likelihood of successful mitral valve repair.[28]

Rationale for Transcatheter Therapy

Surgery improves survival in observational studies but is associated with mortality rates of 1% to 5% and additional morbidity rates of 10% to 20%, including stroke, reoperation, renal failure, and prolonged ventilation.[32] The risks of surgery are particularly high in patients who are elderly or have LV dysfunction and secondary MR. In one study of more than 30,000 patients undergoing mitral valve replacement, mortality increased from 4.1% in those younger than 50 years to 17.0% in octogenarians,[33] although these outcomes improved in a more recent report.[34] The risks and morbidity of surgery coupled with patient preference have stimulated attempts to develop less invasive solutions.

When considering percutaneous or transcatheter approaches for mitral repair, it is useful to classify them according to the major structural abnormality that they address.[35] Unlike the extensive toolbox available to the mitral surgeon, transcatheter approaches are much more limited and often able to address only a single major element of the dysfunctional valve that contributes to MR.[36]

Table 72.2 lists some of the devices, their manufacturers, and current state of development.

TABLE 72.2

Devices for Transcatheter Mitral Valve Repair and Replacement

TYPE/INDICATION	BRAND NAME	MANUFACTURER	STATUS
Leaflet/chordal	MitraClip	Abbott Vascular, Abbott Park, Ill	CE Mark FDA approved
	NeoChord DS1000 System	NeoChord, Eden Prairie, Minn	CE Mark U.S. IDE trial
	Harpoon NeoChord	Edwards LifeSciences, Irvine, Calif	Phase 1 (OUS)
	Mitra-Spacer	Cardiosolutions, West Bridgewater, Mass	Phase 1 (OUS)
	MitraFlex	TransCardiac Therapeutics, Atlanta, Ga	Preclinical
	Middle Peak Medical	Middle Peak Medical, Palo Alto, Calif	Phase 1 (OUS)
Indirect annuloplasty	CARILLON XE2 Mitral Contour System	Cardiac Dimensions, Kirkland, Wis	CE Mark
	Kardium MR	Kardium, Richmond, British Columbia, Canada	Preclinical
	Cerclage annuloplasty	National Heart, Lung and Blood Institute, Bethesda, Md	Phase 1 (OUS)
Direct or left ventricular annuloplasty	Mitralign Percutaneous Annuloplasty System	Mitralign, Tewksbury, Mass	CE Mark
	GDS Accucinch System	Guided Delivery Systems, Santa Clara, Calif	Phase 1 (OUS)
	Boa RF Catheter	QuantumCor, Laguna Niguel, Calif	Preclinical
	Cardioband	Valtech Cardio, Or Yehuda, Israel	CE Mark
	Millipede System	Millipede, Santa Rosa, Calif	Phase 1 (OUS)
	Arto System	MVRx, Belmont, Calif	Phase 1 (OUS)
Hybrid surgical	Adjustable Annuloplasty Ring	Mitral Solutions, Fort Lauderdale, Fla	Phase 1 (OUS)
	enCor ring	MiCardia Corporation, Irvine, Calif	CE Mark Phase 1
Left ventricular remodeling	The Basal Annuloplasty of the Cardia Externally (BACE)	Mardil Medical, Minneapolis, Minnesota	Phase 1 (OUS)
	Tendyne Repair	Tendyne Holdings, Baltimore, Md	Preclinical
	MitraSpacer	Cardiosolutions, Stoughton, Mass	Phase 1 (OUS)
Replacement	CardiAQ-Edwards	Edwards Lifesciences, Irvine, Calif	Phase 1 (OUS) U.S. EFS
	Tendyne	Abbott Vascular, Chicago	Phase 1 (OUS) U.S. EFS
	Tiara	Neovasc, Richmond, British Columbia, Canada	Phase 1 (OUS) U.S. EFS
	Intrepid (Twelve)	Medtronic, Minneapolis, Minn	Phase 1 (OUS) U.S. EFS
	Caisson	Caisson Interventional, Maple Grove, Minn	U.S. EFS

CE, Conformité Européenne [European Union]; *EFS,* early feasibility study; *FDA,* U.S. Food and Drug Administration; *IDE,* investigational device exemption; *OUS,* outside United States.

Leaflet Repair with MitraClip Device

MitraClip (Abbott Vascular) was the first transcatheter mitral valve repair technology to receive CE (Conformité Européenne) Mark approval (European Union) and has now also received limited FDA approval for patients with primary (degenerative) MR and prohibitive surgical risk (**Fig. 72.8**). This system replicates the Alfieri stitch operation, in which the middle scallops of the posterior and anterior leaflets (P2 and A2, respectively) are sutured together to create a double-orifice mitral valve. The operation, although usually performed with adjunctive ring annuloplasty, has proved effective and durable in a wide variety of pathologies as well as in select patients without annuloplasty.[37]

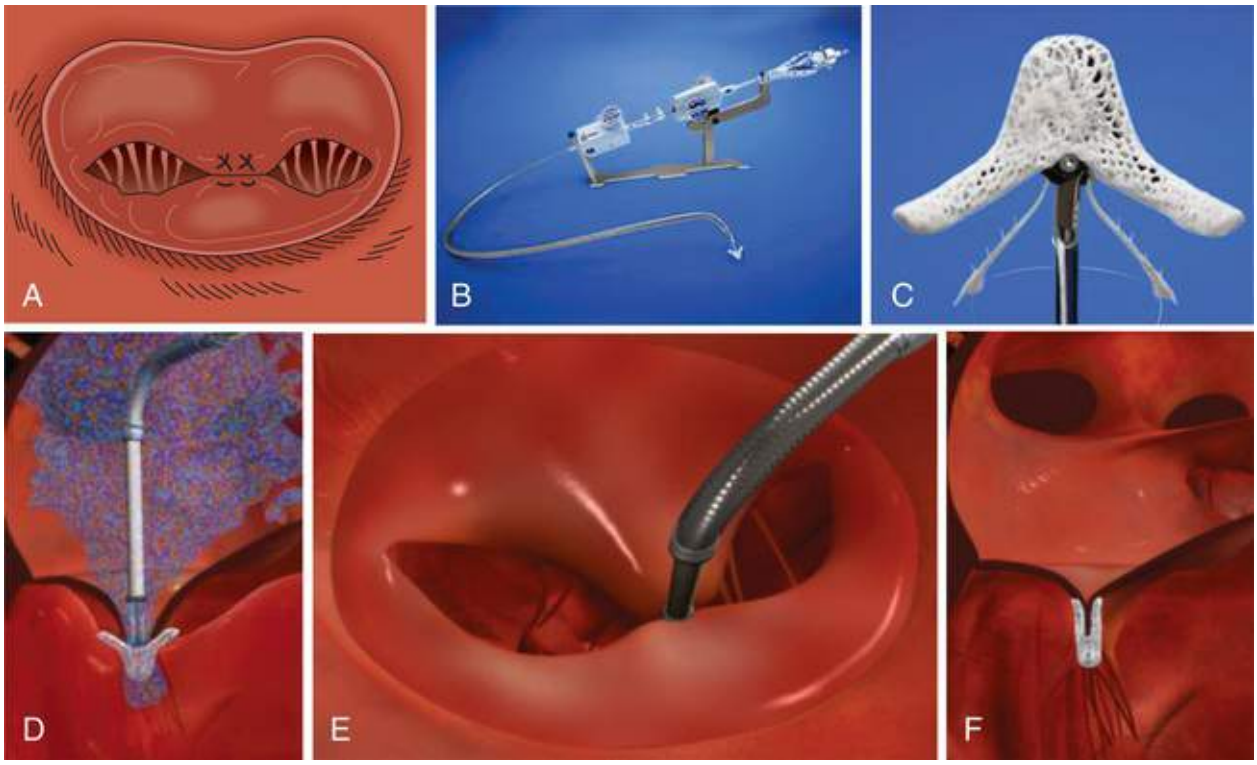

FIGURE 72.8 MitraClip leaflet coaptation system (Abbott Vascular) creates a bridge between the P2 and A2 segments of the mitral valve similar to the Alfieri stitch operation **(A)** utilizing a clip delivery system **(B)** and the MitraClip NT **(C)**. **D,** Side view, and **E,** left atrial view, of the clip delivery system as it is advanced through the mitral valve in the open position prior to grasping of the leaflets. **F,** The final result is illustrated after the clip has been released and the delivery system removed. (Courtesy Abbott Vascular, Inc.)

Trials with MitraClip have confirmed its feasibility (e.g., Endovascular Valve Edge-to-Edge Repair Study [EVEREST] I), and its safety and efficacy were compared with those of surgical repair in a randomized trial (EVEREST II).[38] The procedure is performed with standard catheterization techniques using a transseptal approach from the right femoral vein.[39] The clip delivery system is introduced through a 24F sheath into the left atrium, where it can be guided by TEE using a series of turning knobs through the mitral valve into the left ventricle. A properly aligned and oriented clip can grasp the P2 and A2 segments of the leaflets from the ventricular side to create leaflet apposition. Once leaflet insertion is confirmed by echocardiography, the clip can be released. If a suboptimal grasp occurs, the leaflet can be released, allowing repositioning before a second grasp attempt. Additionally, a second or more clips can be placed as needed for optimal MR reduction.

In the randomized EVEREST II trial, 184 patients received MitraClip therapy and 95 underwent surgical repair or replacement.[40] These patients were almost a decade older (mean age, 67 years) than in usual surgical series and had more comorbidities. Major adverse events at 30 days were significantly less frequent with MitraClip therapy (9.6% versus 57% with surgery; $P < 0.0001$), although much of the difference could be attributed to the greater need for blood transfusions with surgery. The freedom from the combined outcome of death, mitral valve surgery, and MR severity greater than 2+ at 12 months was higher with surgery (73%) than with MitraClip therapy (55%; $P = 0.0007$). In patients with acute MitraClip therapy success, the result appears durable, with a very low rate of later mitral valve surgery.[41]

Subsequent analyses of this study and additional registries have demonstrated persistent reductions in MR grade, improvement in NYHA functional class, and reduction in LV dimensions with MitraClip therapy.[41] Other studies have shown a lack of MS, no effect of initial rhythm on results, and importantly, greater benefit than with surgery for higher-risk patients[42] (**Fig. 72.9**).

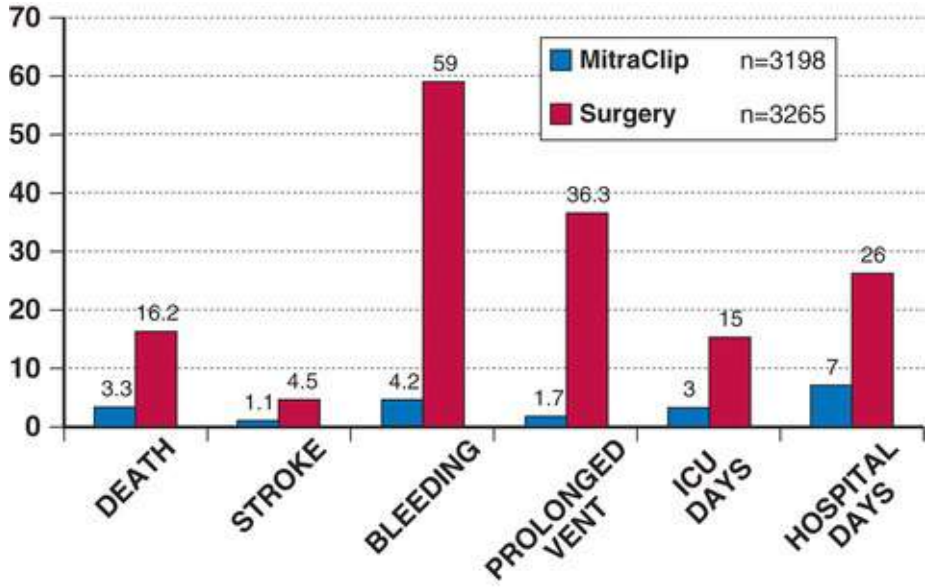

FIGURE 72.9 Meta-analysis of outcomes of the MitraClip compared to mitral valve surgery in high-risk patients. ICU, Intensive care unit; Vent, ventilation. (From Philip F, Athappan G, Tuzcu EM, et al. MitraClip for severe symptomatic mitral regurgitation in patients at high surgical risk. Catheter Cardiovasc Interv 2014;84:581-90.)

Although the EVEREST II trial failed to demonstrate efficacy equivalent to that of surgery for a diverse group of patients with varied risk and etiology, the EVEREST High-Risk Registry and prohibitive-risk patient subset, combined with the experience outside the United States, indicate a more appropriate role in high-risk patients and those with secondary functional and ischemic MR. In addition to improved symptoms, a 50% to 70% reduction in hospitalization for heart failure in the year after versus the year before MitraClip implantation has been observed, prompting a randomized trial, COAPT (Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for High Surgical Risk Patients), to compare the device with medical therapy in patients with secondary MR.[42] Several other devices, designed to provide leaflet repair, including NeoChord, Mitra-Spacer, and MitraFlex, are in preclinical or phase 1 evaluation (**see Table 72.2**).

Indirect Annuloplasty

The venous anatomy of the heart is of particular interest for treating MR because of the ease of access (from the right internal jugular vein) and the location of the great cardiac vein in proximity to the posterior mitral annulus. Some of the first attempts to treat MR without surgery did so by mimicking surgical ring annuloplasty through placement of devices in the coronary sinus, so-called indirect or percutaneous coronary sinus annuloplasty. The goal of this approach is to remodel the posterior annulus, cinching the great cardiac vein or pushing on the posterior annulus from the vein to improve leaflet coaptation.

The CARILLON XE2 Mitral Contour System (Cardiac Dimensions) has CE Mark and uses anchors placed in the coronary sinus that are pulled toward each other with a cinching device to reduce the mitral annular dimension by traction (**Fig. 72.10**). Early evaluation in the Amadeus study demonstrated feasibility, with implantation in 30 of 48 patients and modest improvement in quantitative measures of MR with a small risk of coronary compromise (15%) and death (one patient). More recently, a redesigned device was tested in the TITAN (Transcatheter Implantation of Carillon Mitral Annuloplasty Device) trial.[43] Of 65 patients with secondary MR (62% ischemic), the device was implanted successfully in 36 patients, with a mean age of 62 years, mean ejection fraction (EF) of 29%,

predominantly NYHA Functional Class III symptoms, and 2+ (30%), 3+ (55%), or 4+ (15%) grade MR. Quantitative measures of MR were better at 6 and 12 months than in 17 patients who did not receive implants.

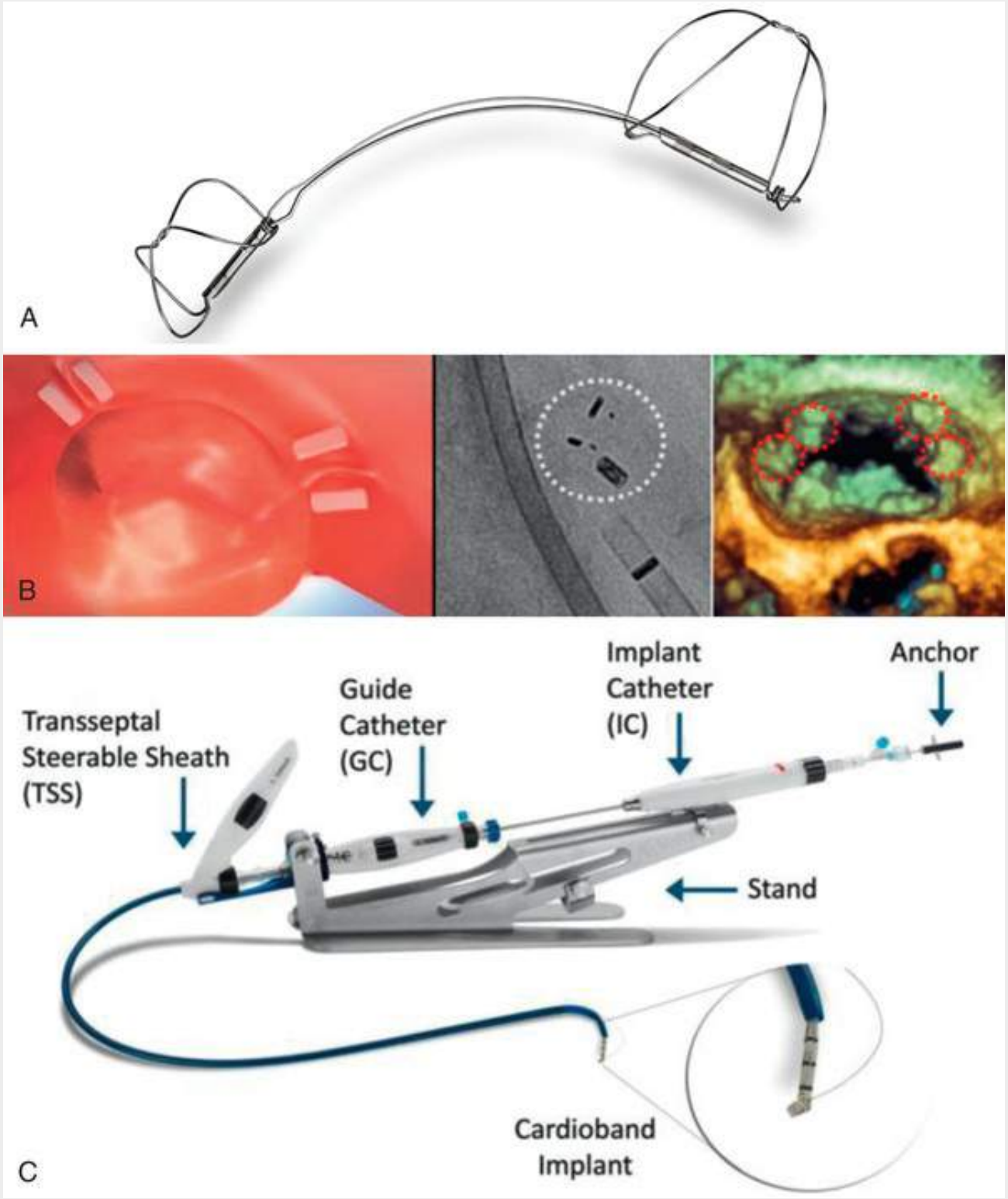

FIGURE 72.10 Evolving devices for mitral valve repair. **A,** Carillon XE2 Mitral Contour System (Cardiac Dimensions) **B,** Mitralign Percutaneous Annuloplasty System (Mitralign, Tewksbury, Mass). **C,** Cardioband annuloplasty system (Valtech Cardio, Or Yehuda, Israel). (From Nickenig G, Schueler R, Dager A, et al. Treatment of functional mitral valve regurgitation with a percutaneous annuloplasty system. J Am Coll Cardiol 2016;67:2927-2936.)

In general, indirect annuloplasty devices may be able to provide modest MR reduction in select patients, but likely less than that achievable surgically with a complete ring placed directly on the

annulus. The limited efficacy is related to the location of the coronary sinus relative to the annulus (up to 10 mm more cranial), great individual anatomic variability, and limited benefit of partial annular remodeling. Whether this level of efficacy will result in sufficient symptomatic improvement and LV remodeling to justify the procedure requires further study. Some “super-responders” may be identified on the basis of anatomic considerations before the procedure. The risks of this approach must also be considered. In addition to the risk for damage to the cardiac venous system, devices in this location can compress the left circumflex or diagonal coronary arteries, which traverse between the coronary sinus and the mitral annulus in most patients.[43]

In this regard, one novel indirect approach to reduce the septal-lateral dimension that deserves further consideration is the *cerclage annuloplasty* technique, which recently entered clinical evaluation. This approach attempts to create a more complete circumferential annuloplasty by placing a suture from the coronary sinus through a septal perforator vein into the right atrium or ventricle, where it is snared and tensioned with the proximal end from the right atrium to create a closed pursestring suture.[44] The procedure is guided by cardiac MRI and also uses a novel rigid protection device to avoid coronary compression.

Direct Annuloplasty and Left Ventricular Remodeling Techniques

Several devices have been developed to remodel more directly the mitral annulus, in part because of the limitations of indirect coronary sinus annuloplasty described earlier (**see Table 72.2**). The Mitralign Percutaneous Annuloplasty System (Mitralign) was originally based on the surgical techniques of Paneth's posterior suture plication. In this procedure a transaortic catheter is advanced to the left ventricle and used to deliver pledgeted anchors through the posterior annulus that can be pulled together to shorten (plicate) the annulus up to 17 mm (with two implants) (**Fig. 72.10B**). In 50 of 71 patients successfully treated in a phase 1 trial, septal-lateral dimension was reduced about 2 mm, MR grade at 6 months was reduced by a mean of 1.3 grades in 50% of patients, and modest symptomatic improvement was observed.[45] A CE Mark trial is underway. The Accucinch (Guided Delivery Systems) device utilizes a catheter approach to place up to 12 anchors along the ventricular surface of the posterior mitral annulus. A cable running through the anchors is tensioned to create posterior annular plication. In a later development the anchors are placed in the ventricular myocardium just below the valve plane (percutaneous ventriculoplasty).

More recently, the Cardioband annuloplasty system (Valtech Cardio, Or Yehuda, Israel) received CE Mark. This is an adjustable, catheter-delivered, sutureless device that is inserted transseptally and directly anchored on the atrial side of the annulus with subsequent adjustment (**Fig. 72.10C**). In a phase 1 European study, 31 high-risk patients with severe secondary MR received treatment.[46] Mean septal-lateral dimension was reduced from 37 to 29 mm, with initial reduction in MR grade to “trace” or “mild” in 93% of patients and to moderate MR or less at 30 days in 88%.[46]

The basis for devices to treat MR by affecting the shape of the left ventricle arises from the pathophysiology of secondary ischemic or functional MR (**see Chapter 69**). Changes in the inferior and lateral left ventricle from infarction can lead to tethering or tenting of the posterior leaflet, allowing anterior leaflet override as the mechanism of MR. Similarly, failure of leaflet coaptation from global LV enlargement causing annular distention is the major mechanism for MR in dilated cardiomyopathy.[42] Although ring annuloplasty can often ameliorate MR caused by LV distortion, procedures that also address the underlying LV pathology may be more beneficial. The Basal Annuloplasty of the Cardia Externally (BACE) device (Mardil) is a surgically implanted external tension band placed around the heart externally to treat ischemic MR at the time of coronary artery bypass graft (CABG) surgery. In a

preliminary report of 11 patients treated in India, MR grade was reduced acutely from grade 3.3 to 0.6. Preclinical work with a transcatheter approach to approximate the papillary muscles is also in development (Tendyne Repair).

Transcatheter Mitral Valve Replacement

The rationale for transcatheter mitral valve replacement (TMVR) is based on several lessons learned from surgical valve replacement[47] and results thus far with transcatheter mitral valve repair. With the current state of technologic development and clinical experience, transcatheter repairs do not appear to reduce MR to the same extent as surgical repairs. Moreover, in patients with secondary ischemic MR, mitral valve replacement (MVR) appears to provide more complete and durable elimination of MR than valve repair. In a surgical trial of 251 patients with severe ischemic MR randomized to mitral repair versus chordal-sparing MVR,[48] recurrent moderate or severe MR was higher at 12 months in the repair group (32.6%) than the replacement group (2.3%).

Early experience with valve-in-valve treatment using TAVR devices in previously implanted degenerating surgical mitral bioprostheses and annuloplasty rings has confirmed the feasibility of this approach. Balloon-expandable TAVR prostheses were initially implanted in degenerating bioprostheses and surgical annuloplasty rings via a transapical approach.[49] Subsequently, the feasibility of transseptal delivery and transatrial delivery has been demonstrated. Complications, including valve embolization, bleeding, and death, have been reported, but the early results have generally been favorable, with excellent reduction in MR grade and low residual transmitral gradients, resulting in the Sapien 3 device receiving FDA approval for this indication.[5]

Despite these initial demonstrations of the feasibility of transcatheter mitral valve-in-valve implantation, de novo placement of such devices in native valves, even those with mitral annular calcification, has proved more challenging.[50] Compared to TAVR, mitral devices need to be larger, and fixation to the diseased mitral apparatus is hampered by the greater valve complexity, lack of calcium, potential need for orientation, and noncircular annular shape.

Most current designs use a stent-based bioprosthesis that is self-expanding, anchors to attach to the annulus and/or leaflets, and a sealing skirt. Because the size of the mitral annulus requires a large prosthesis, initial experience has been with transapical delivery systems, although early experience with several transseptal and transatrial delivery approaches is underway. Novel devices that use a two-stage deployment with separate anchoring and valve portions are also being tested.

At least five TMVR devices have entered early feasibility investigation clinically in the United States (**Fig. 72.11; see also Table 72.2**), and more than 30 are in early development. The initial experience with TMVR has been challenging, in part from inclusion of compassionately treated patients with multiple comorbidities and predominantly treated with a relatively invasive transapical approach. Current trials are therefore targeting high-risk, but not inoperable, patients with both primary and secondary MR. Phase 2 study investigators will address that most patients with secondary MR do not have high short-term mortality and therefore are frequently medically managed. Overcoming procedural complications of TMVR will be essential to realize the symptomatic benefits compared to medical care. Patient comorbidities, cardiac and noncardiac, could hamper and confound comparative evaluations.

FIGURE 72.11 Transcatheter mitral valve replacement devices in early U.S. feasibility evaluation. *Top row,* CardiAQ-Edwards Transcatheter Mitral Valve (Edwards Lifesciences, Irvine, Calif) and Tendyne (Courtesy Abbott). *Bottom row,* Intrepid (Medtronic, Minneapolis), Tiara (Neovasc, Richmond, BC, Canada), and Caisson (Caisson Interventional, Maple Grove, Minn).

In the largest study of such a device to date, Muller and colleagues[51] treated 30 patients at high risk for surgery with a transcatheter transapical self-expanding nitinol prosthesis supporting a trileaflet porcine pericardial valve (Tendyne Mitral Valve System, Abbott Vascular, Roseville, Minnesota). The device was successfully implanted in 28 patients (93%) and was retrieved without complications in the other two patients. Grade 0 MR was reported in all but one patient. There were no device embolizations, strokes, or LV outflow tract obstruction. At 30 days, one patient died from pneumonia, and only one patient had mild MR. Overall freedom from major adverse events was 83%, and there was significant improvement in NYHA class, walk time, and quality of life.

It is hoped that improvements in devices, operator and procedural experience, and patient selection will lead to better outcomes. The potential advantages of this approach include the avoidance of both the surgical incision and the effects of cardiopulmonary bypass. Such devices could be fully sparing of the subvalvular apparatus and provide MR reduction that is equivalent to that achieved with surgical valve replacement. However, the early high mortality, although in very-high-risk patients receiving the device as a compassionate approach, has tempered some of the early enthusiasm for TMVR.[52]

In this regard, it is useful to emphasize that TMVR is not a “mitral TAVR.”[52,53] The mitral valve is more complex than the aortic valve, and MR has a vast array of etiologies. Unlike AS, MR is not as often a disease of elderly persons, and repair (not replacement) is the preferred surgical therapy, especially for patients with primary MR. Replacement may have less favorable effects on normal vortex flow and LV remodeling than successful repair.[54] Transcatheter prostheses in the mitral position will likely have lower durability, more risks associated with paravalvular leak,[55] and a greater risk of embolization, LV outflow tract obstruction, and thrombosis. Finally, the more frequent association with TR, which may need to be addressed, and the lower short-term mortality will be impediments to the design of rigorous clinical trials.[52,53]

Tricuspid Regurgitation

Moderate or severe TR affects approximately 1.6 million U.S. patients, but less than 1% undergo surgery.[56] Current guidelines recommend concomitant tricuspid repair or replacement during left-sided heart surgery for severe TR and for nonsevere TR with annular dilation.[28] A number of transcatheter devices to treat TR are under development, some of which are in early clinical feasibility evaluation.[57] Several are based on prior transcatheter mitral approaches (MitraClip, Mitralign), while others use more novel approaches. The TriCinch device places a corkscrew annular anchor tensioned to a stent in the inferior vena cava. The FORMA device fills the orifice with a balloon to reduce the effective regurgitant orifice area. Several companies are developing analogs of ring annuloplasty placed directly on the valve (Millipede) or implanted externally via the pericardial space (Triapta). Additionally, caval valve implants with current TAVR devices and novel devices specifically designed for this purpose (Tric Valve) are under evaluation.

Conclusion

Transcatheter therapy of valvular heart disease is an exciting area of cardiovascular medicine. The initial success of balloon valvuloplasty for stenotic lesions leading to the more recent growth of TAVR has revolutionized the modern approach to aortic stenosis. The complexity of the mitral valve apparatus and the myriad causes of mitral regurgitation have slowed the development of transcatheter mitral valve repair and replacement. Fueled by the ever-growing prevalence of heart failure in the aging U.S. population[58]—most of these older patients with heart failure have significant MR—and aided by the ingenuity of physicians and engineers, we can anticipate that transcatheter mitral and tricuspid valve therapies will soon become an available option for many patients in the near future.

Guidelines

Management of Valvular Heart Disease

Robert O. Bonow and Catherine M. Otto

The American College of Cardiology and the American Heart Association (ACC/AHA) first published guidelines for the management of patients with valvular heart disease (VHD) in 1998. These were revised in 2006, updated in 2008, and then completely revised in 2014.[1] The guidelines were updated once more in 2017.[2] Some materials from the 2014 guidelines and the 2017 update are presented in this chapter and **Chapters 68 to 71**. In addition to the guidelines, recommendations for the evaluation and management of VHD are included in appropriate use criteria (AUC) for echocardiography from the ACC and other organizations,[3] as well as ACC recommendations for assessment of athletes with cardiovascular abnormalities.[4] ACC and partner organizations have also published AUC criteria for management of patients with aortic stenosis.[5] The 2014 ACC/AHA guidelines and the 2017 update are summarized in this chapter. The European Society of Cardiology and European Association for Cardio-Thoracic Surgery have also published guidelines for management of patients with VHD.[6] There are slight differences between the U.S. and European guidelines, but most recommendations are concordant.

As with other ACC/AHA guidelines, these recommendations use the standard ACC/AHA classification system for indications:

Class I: Conditions for which there is evidence and/or general agreement that the test is useful and effective

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness or efficacy of performing the test

Class IIa: Weight of evidence or opinion in favor of usefulness or efficacy

Class IIb: Usefulness or efficacy less well established by evidence or opinion

Class III: Conditions for which there is evidence and/or general agreement that the test is not useful or effective and in some cases may be harmful (specifying “no benefit” or “harmful”)

Three levels are used to rate the evidence on which recommendations have been based:

Level A recommendations are derived from data from multiple randomized clinical trials.

Level B recommendations are derived from moderate-quality evidence from one or more randomized trials or meta-analyses (B-R) or nonrandomized, observational, or registry studies (B-NR).

Level C recommendations are based on nonrandomized observational studies with limitations of design (C-LD) or the consensus opinion of experts (C-EO).

The ACC/AHA guidelines define stages of progression of VHD to include patients at risk, asymptomatic patients with established mild to severe VHD, and symptomatic patients with VHD (**Table 72G.1; see also Tables 68.2, 68.5, 69.1, 69.3, 69.4, and 70.3**). The guidelines further emphasize that the clinical assessment should be based on the patient's symptomatic status and findings from the physical examination. Cardiac auscultation remains the most widely used method of screening for VHD. The chest radiograph and electrocardiogram (ECG), if normal, can often provide reassurance that a murmur is clinically insignificant. Echocardiography should be considered after assessment of these more routine data, and echocardiography is determined to be inappropriate for the evaluation of murmurs that experienced observers consider innocent or functional. In contrast, echocardiography is considered appropriate even in asymptomatic patients with murmurs suggesting significant valvular disease or with other signs or symptoms of cardiovascular disease (**Table 72G.2**), and there is emphasis on the use of Doppler echocardiography to quantify the severity of valvular stenosis and regurgitation. The recommended frequency of echocardiography in asymptomatic patients is shown in **Table 67.2**. In some cases, cardiac magnetic resonance imaging (CMR), cardiac catheterization and angiography, and exercise stress testing (**see Table 67.3**) are appropriate. For patients with severe aortic stenosis and low cardiac output (low-flow, low-gradient aortic stenosis), dobutamine stress echocardiography may be a reasonable tool for evaluation.

TABLE 72G.1

Stages of Progression of Valvular Heart Disease (VHD)[1]

STAGE	DEFINITION	DESCRIPTION
A	At risk	Patients with risk factors for the development of VHD
B	Progressive	Patients with progressive VHD (mild to moderate severity and asymptomatic)
C	Asymptomatic severe	Asymptomatic patients who have reached the criteria for severe VHD
		C1: Asymptomatic patients with severe VHD in whom the left or right ventricle remains compensated
		C2: Asymptomatic patients who have severe VHD, with decompensation of the left or right ventricle
D	Symptomatic severe	Patients who have developed symptoms as a result of VHD

TABLE 72G.2

ACC/AHA Guidelines for Diagnostic Testing in Patients with Valvular Heart Disease[1]

CLASS	INDICATION	LOE
General Indications for Valvular Heart Disease (VHD)		
I	TTE in the initial evaluation of patients with known or suspected VHD to confirm the diagnosis, establish etiology, determine severity, assess hemodynamic consequences, determine prognosis, and evaluate for timing of intervention.	B
	TTE in patients with known VHD with any change in symptoms or physical examination findings.	C
	Periodic monitoring with TTE in asymptomatic patients with known VHD at intervals depending on valve lesion, severity, ventricular size, and ventricular function.	C
	Cardiac catheterization for hemodynamic assessment in symptomatic patients with VHD when noninvasive tests are inconclusive or when there is a discrepancy between the findings on noninvasive testing and physical examination regarding severity of the valve lesion.	C
	Coronary angiography before valve intervention in patients with VHD with symptoms of angina, objective evidence of ischemia, decreased LVEF, history of CAD, or CAD risk factors (including men age >40 years and postmenopausal women).	C
IIa	Exercise testing is reasonable in selected patients with asymptomatic severe VHD to (1) confirm the absence of symptoms, (2) assess the hemodynamic response to exercise, or (3) determine prognosis (note class I recommendation for MS).	B
Indications for Specific Valve Diseases		
I	TTE in patients with dilated aortic sinuses or ascending aorta or with a BAV (stages A and B) to evaluate the presence and severity of AR.	B
	TEE in patients with MS considered for percutaneous mitral balloon commissurotomy to assess the presence or absence of left atrial thrombus and to further evaluate the severity of MR.	B
	TEE for evaluation of patients with chronic primary MR (stages B to D) in whom noninvasive imaging provides nondiagnostic information regarding severity of MR, mechanism of MR, and/or status of LV function.	C
	Intraoperative TEE to establish the anatomic basis for chronic primary MR (stages C and D) and to guide repair.	B
	CMR in patients with moderate or severe VHD (stages B, C, and D) and suboptimal TTE images for the assessment of LV systolic function, systolic and diastolic volumes, and assessment of VHD severity.	B
	MRA or CTA in patients with BAV when morphology of the aortic sinuses, sinotubular junction, or ascending aorta cannot be assessed accurately or fully by TTE.	C
	Serial TTE, MRA, or CTA to evaluate the size and morphology of the aortic sinuses and ascending aorta in patients with BAV and an aortic diameter greater than 4.0 cm, with the examination interval determined by the degree and rate of progression of aortic dilation and by family history. In patients with aortic diameter greater than 4.5 cm, this evaluation should be performed on an annual basis.	C
	Exercise testing with Doppler or invasive hemodynamic assessment in patients with MS to evaluate the response of the mean mitral gradient and pulmonary artery pressure when there is a discrepancy between resting Doppler echocardiographic findings and clinical symptoms or signs.	C
	Noninvasive imaging (stress nuclear/positron emission tomography, CMR, or stress TTE), coronary CTA, or cardiac catheterization, including coronary arteriography, is useful to establish etiology of chronic secondary MR (stages B to D) and/or assess myocardial viability, which in turn may influence management of functional MR.	C
IIa	Low-dose dobutamine stress testing using echocardiographic or invasive hemodynamic measurements is reasonable in patients with stage D2 AS with all the following: Calcified aortic valve with reduced systolic opening LVEF less than 50% Calculated valve area of 1.0 cm^2 or less Aortic velocity less than 4 m/sec or mean pressure gradient less than 40 mm Hg	B
III	Exercise testing should not be performed in symptomatic patients with AS when the aortic velocity is 4 m/sec or greater or the mean pressure gradient is 40 mm Hg or greater (stage D).	B

LOE, Level of evidence; *AR,* aortic regurgitation; *AS,* aortic stenosis; *BAV,* bicuspid aortic valve; *CAD,* coronary artery disease; *CMR,* cardiac magnetic resonance imaging; *CTA,* computed tomographic angiography; *LVEF,* left ventricular ejection fraction; *MR,* mitral regurgitation; *MRA,* magnetic resonance angiography; *MS,* mitral stenosis; *TEE,* transesophageal echocardiography; *TTE,* transthoracic echocardiography.

Aortic Stenosis (see Chapter 68)

The guidelines include limited indications for medical therapy for aortic stenosis (AS) other than control of blood pressure (**Table 72G.3**).

TABLE 72G.3

ACC/AHA Guidelines for Medical Management of Valvular Heart Disease[1]

DISEASE	CLASS	INDICATION	LOE
Aortic stenosis (AS)	I	Hypertension in patients at risk for development of AS (stage A) and in patients with asymptomatic AS (stages B and C) should be treated according to standard GDMT, started at a low dose and gradually titrated upward as needed with frequent clinical monitoring.	B
	IIb	Vasodilator therapy may be reasonable if used with invasive hemodynamic monitoring in the acute management of patients with severe decompensated AS (stage D) with NYHA Class IV HF symptoms.	C
	III	Statin therapy is not indicated for prevention of hemodynamic progression of AS in patients with mild to moderate calcific valve disease (stages B to D).	A
Aortic regurgitation (AR)	I	Treatment of hypertension (systolic BP >140 mm Hg) is recommended in patients with chronic AR (stages B and C), preferably with dihydropyridine calcium channel blockers or ACE inhibitors/ARBs.	B
	IIa	Medical therapy with ACE inhibitors/ARBs and beta blockers is reasonable in patients with severe AR who have symptoms and/or LV dysfunction (stages C2 and D) when surgery is not performed because of comorbidities.	B
Mitral stenosis (MS)	I	Anticoagulation (vitamin K antagonist or heparin) is indicated in patients with (1) MS and AF (paroxysmal, persistent, or permanent), (2) MS and prior embolic event, or (3) MS and left atrial thrombus.	B
	IIa	Heart rate control can be beneficial in patients with MS and AF and fast ventricular response.	C
	IIb	Heart rate control may be considered for patients with MS in normal sinus rhythm and symptoms associated with exercise.	B
Mitral regurgitation (MR)	I	Patients with chronic secondary MR (stages B to D) and HF with reduced LVEF should receive standard GDMT therapy for HF, including ACE inhibitors, ARBs, beta blockers, and/or aldosterone antagonists as indicated.	A
		Cardiac resynchronization therapy with biventricular pacing is recommended for symptomatic patients with chronic severe secondary MR (stages B to D) who meet the indications for device therapy.	A
	IIa	Medical therapy for systolic dysfunction is reasonable in symptomatic patients with chronic primary MR (stage D) and LVEF less than 60% in whom surgery is not contemplated.	B
	III	Vasodilator therapy is not indicated for normotensive asymptomatic patients with chronic primary MR (stages B and C1) and normal systolic LV function.	B
Tricuspid regurgitation (TR)	IIa	Diuretics can be useful for patients with severe TR and signs of right-sided HF (stage D).	C
	IIb	Medical therapies to reduce elevated pulmonary artery pressures and/or pulmonary vascular resistance might be considered in patients with severe functional TR (stages C and D).	C

LOE, Level of evidence; *ACE,* angiotensin-converting enzyme; *AF,* atrial fibrillation; *ARBs,* angiotensin receptor blockers; *AS,* aortic stenosis; *GDMT,* guideline-directed medical therapy; *HF,* heart failure; *LVEF,* left ventricular ejection fraction.

Aortic Valve Replacement

Surgery is recommended for patients with severe AS who have symptoms or left ventricular (LV) systolic dysfunction or are undergoing other forms of cardiac surgery (**Table 72G.4**). The ACC/AHA guidelines are generally supportive (class IIa) of aortic valve replacement (AVR) for asymptomatic patients with very severe AS (peak aortic valve velocity >5 m/sec) and those with moderate AS who are undergoing other forms of cardiac surgery. A class IIa recommendation is also given for patients with symptomatic low-flow, low-gradient AS with either normal or depressed LV systolic function, while stressing the care required to be certain that the AS is severe and is likely the cause of the symptoms. The 2017 guidelines update[2] provides the updated recommendations for selection of surgical AVR versus transcatheter AVR or aortic balloon valvotomy (**Table 72G.5**)

TABLE 72G.4

ACC/AHA Guidelines for Aortic Valve Replacement (AVR) for Aortic Stenosis (AS)[1]

CLASS	INDICATION	LOE
I	AVR with severe high-gradient AS who have symptoms by history or on exercise testing (stage D1).	B
	AVR for asymptomatic patients with severe AS (stage C2) and LVEF less than 50%.	B
	AVR for patients with severe AS (stage C or D) when undergoing other cardiac surgery.	B
IIa	AVR is reasonable for asymptomatic patients with very severe AS (stage C1, aortic velocity ≥5 m/sec) and low surgical risk.	B
	AVR is reasonable in asymptomatic patients (stage C1) with severe AS and decreased exercise tolerance or an exercise fall in blood pressure.	B
	AVR is reasonable in symptomatic patients with low-flow/low-gradient severe AS with reduced LVEF (stage D2) with a low-dose dobutamine stress study that shows an aortic velocity of 4 m/sec or more (or mean pressure gradient ≥40 mm Hg) with a valve area of 1.0 cm^2 or less at any dobutamine dose.	B
	AVR is reasonable in symptomatic patients with low-flow, low-gradient severe AS (stage D3) who are normotensive and have LVEF of 50% or greater, if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms.	C
	AVR is reasonable for patients with moderate AS (stage B) (aortic velocity, 3.0 to 3.9 m/sec) who are undergoing other cardiac surgery.	C
IIb	AVR may be considered for asymptomatic patients with severe AS (stage C1) and rapid disease progression and low surgical risk.	C

LOE, Level of evidence; *LVEF,* left ventricular ejection fraction.

TABLE 72G.5

Updated ACC/AHA Guidelines for Choice of Surgical Versus Transcatheter Treatment of Aortic Stenosis (AS)[2]

CLASS	INDICATION	LOE
I	For patients in whom TAVR or high-risk surgical AVR is being considered, members of a heart valve team should collaborate to provide optimal patient care.	C
	Surgical AVR in symptomatic and asymptomatic patients with severe AS who meet an indication for AVR (listed in Table 72G.4) when surgical risk is low or intermediate. (*Modified 2017*)	B
	TAVR in patients who meet an indication for AVR for AS who have a prohibitive surgical risk and a predicted post-TAVR survival >12 months. (*Modified 2017*)	A
	TAVR or surgical AVR in patients with severe AS who meet an indication for AVR and who have high surgical risk. (*Modified 2017*)	A
IIa	TAVR is a reasonable alternative to surgical AVR for symptomatic patients with severe AS and an intermediate surgical risk. (*New 2017*)	B
IIb	Percutaneous aortic balloon dilation may be considered as a bridge to surgical or transcatheter AVR in severely symptomatic patients with severe AS.	C
III	TAVR is not recommended in patients in whom the existing comorbidities would preclude the expected benefit from correction of AS.	B

LOE, Level of evidence; *AVR,* aortic valve replacement; *TAVR,* transcatheter AVR.

Chronic Aortic Regurgitation

The ACC/AHA guidelines consider vasodilator therapy appropriate for patients with hypertension, with weak endorsement for those with severe aortic regurgitation (AR), normal LV function, and evidence of LV dilation (**see Table 72G.3**). However, there is no endorsement for long-term vasodilator therapy in normotensive patients with normal LV function and mild AR. Vasodilator therapy is not an alternative to surgery for patients who are appropriate candidates for valve replacement, including those with asymptomatic LV dysfunction, but might be considered in those who have prohibitively high risks for surgery because of medical comorbidities.

Aortic Valve Replacement

The 2014 ACC/AHA guidelines recommend AVR for patients with severe AR and symptoms (**Table 72G.6**), as well as asymptomatic patients with LV systolic dysfunction (ejection fraction [EF] <50%) or those undergoing other forms of cardiac surgery. The guidelines were not supportive of surgery solely because of a decline in EF during exercise. Class IIa indications include patients with severe AR and normal LV function who have severe LV dilation (LV end-systolic dimension >50 mm) and those with moderate AR undergoing other forms of cardiac surgery. A class IIb recommendation includes those patients with severe AR, normal LV systolic function, and LV end-diastolic dimension greater than 65 mm, particularly if there is evidence of progressive LV dilation.

TABLE 72G.6

ACC/AHA Guidelines for Aortic Valve Replacement (AVR) for Chronic Aortic Regurgitation (AR)[1]

CLASS	INDICATION	LOE
I	AVR for symptomatic patients with severe AR regardless of LV systolic function (stage D).	B
	AVR for asymptomatic patients with chronic severe AR and LV systolic dysfunction (LVEF <50%) (stage C2).	B
	AVR for patients with severe AR (stage C or D) while undergoing cardiac surgery for other indications.	C
IIa	AVR is reasonable for asymptomatic patients with severe AR with normal LV systolic function (LVEF ≥50%), but severe LV dilation (stage C2, LVESD >50 mm).	B
	AVR is reasonable in patients with moderate AR (stage B) who are undergoing other cardiac surgery.	C
IIb	AVR may be considered for asymptomatic patients with severe AR and normal LV systolic function (stage C1, LVEF ≥50%) but severe LV dilation (LVEDD >65 mm) if surgical risk is low.*	C

*Particularly in the setting of progressive LV enlargement.

LOE, Level of evidence; *LV,* left ventricular; *LVEDD,* LV end-diastolic dimension; *LVEF,* LV ejection fraction; *LVESD,* LV end-systolic dimension.

Bicuspid Aortic Valve With Dilated Ascending Aorta

In patients with bicuspid aortic valve (BAV), CMR or computed tomography (CT) should be used when echocardiography cannot adequately assess the aortic sinuses or ascending aorta, or to quantify the severity of dilation and involvement of the ascending aorta further (**see Table 72G.2**). Recommendations for surgical repair or replacement were updated in 2016.[7] Surgery is indicated if the diameter of the aortic root or ascending aorta is greater than 5.5 cm (or smaller in patients of small stature), is greater than 5.0 cm in patients with risk factors for dissection (family history of aortic dissection or aortic growth rate of 0.5 cm/year or more), or if the patient is at low surgical risk and the surgery is performed by an experienced aortic surgical team in a center with established expertise in these procedures (**Table 72G.7**). Aortic surgery is also reasonable in patients with a BAV undergoing aortic valve surgery because of severe AS or AR (**see Tables 72G.4 and 72G.6**) if the diameter of the ascending aorta is greater than 4.5 cm.

TABLE 72G.7

Updated ACC/AHA Guidelines for Aortic Surgery in Patients with Bicuspid Aortic Valve (BAV)[7]

CLASS	INDICATION	LOE
I	Surgery to repair the aortic sinuses or replace the ascending aorta in patients with BAV if the diameter of the aortic sinuses or ascending aorta is greater than 5.5 cm.	B
IIa	Operative intervention to repair the aortic sinuses or replace the ascending aorta is reasonable in patients with BAV if the diameter of the aortic sinuses or ascending aorta is greater than 5.0 cm and a risk factor for dissection is present (family history of aortic dissection or if the rate of increase in diameter is ≥0.5 cm/year) or if the patient is at low surgical risk and surgery is performed by an experienced aortic surgical team in a center with established expertise in these procedures. (*Modified 2017*)	B
	Replacement of the ascending aorta is reasonable in patients with a BAV undergoing aortic valve surgery because of severe AS or AR (see Tables 72G.4 and 72G.6) if the diameter of the ascending aorta is greater than 4.5 cm.	C

LOE, Level of evidence; *AR,* aortic regurgitation; *AS,* aortic stenosis.

Mitral Stenosis (see Chapter 69)

Patients with more than mild mitral stenosis (MS) should be counseled to avoid unusual physical stresses. Anticoagulation is recommended for patients with MS if they have a history of atrial fibrillation, prior embolic event, or left atrial (LA) thrombus (**see Table 72G.3; see also eTable 67.1**). The guidelines are

not strongly supportive of anticoagulation on the basis of LA size alone.

Percutaneous Mitral Balloon Valvotomy

In centers with skilled operators, the guidelines recommend percutaneous mitral balloon commissurotomy (PMBC) as the initial procedure of choice for symptomatic patients with moderate or severe MS and favorable valve morphology and for asymptomatic patients with pulmonary hypertension (**Table 72G.8**). PMBC is not indicated for patients with mild MS, LA thrombus, or moderate to severe mitral regurgitation (MR).

TABLE 72G.8

ACC/AHA Guidelines for Intervention for Mitral Stenosis (MS)[1]

CLASS	INDICATION	LOE
I	PMBC for symptomatic patients with severe MS (MVA ≤1.5 cm^2, stage D) and favorable valve morphology in the absence of contraindications.	A
	Mitral valve surgery in severely symptomatic patients (NYHA Class III/IV) with severe MS (MVA ≤1.5 cm^2, stage D) who are not high risk for surgery and who are not candidates for or failed previous PMBC.	B
	Concomitant mitral valve surgery for patients with severe MS (MVA ≤1.5 cm^2, stages C or D) undergoing other cardiac surgery.	C
IIa	PMBC is reasonable for asymptomatic patients with very severe MS (MVA ≤1 cm^2, stage C) and favorable valve morphology in the absence of contraindications.	C
	Mitral valve surgery is reasonable for severely symptomatic patients (NYHA Class III/IV) with severe MS (MVA ≤1.5 cm^2, stage D) provided there are other operative indications.	C
IIb	PMBC may be considered for asymptomatic patients with severe MS (MVA ≤1.5 cm^2, stage C) and favorable valve morphology who have new onset of AF in the absence of contraindications.	C
	PMBC may be considered for symptomatic patients with MVA greater than 1.5 cm^2 if there is evidence of hemodynamically significant MS during exercise.	C
	PMBC may be considered for severely symptomatic patients (NYHA Class III/IV) with severe MS (MVA ≤1.5 cm^2, stage D) who have suboptimal valve anatomy and are not candidates for surgery or at high risk for surgery.	C
	Concomitant mitral valve surgery may be considered for patients with moderate MS (MVA, 1.6 to 2.0 cm^2) undergoing other cardiac surgery.	C
	Mitral valve surgery and excision of the left atrial appendage may be considered for patients with severe MS (MVA ≤1.5 cm^2, stages C and D) who have had recurrent embolic events while receiving adequate anticoagulation.	C

LOE, Level of evidence; *MVA,* mitral valve area; *NYHA,* New York Heart Association; *PMBC,* percutaneous mitral balloon commissurotomy.

Surgical Options

When possible, mitral valve repair is indicated for patients with symptomatic, moderate or severe MS when PMBC is not possible. Mitral valve repair may be considered for asymptomatic patients who experience recurrent embolic events despite adequate anticoagulation (class IIb). Mitral valve replacement (MVR) is an option when repair is not feasible.

Chronic Primary Mitral Regurgitation

In patients with chronic primary MR, transesophageal echocardiography (TEE) is considered most appropriate for intraoperative guidance and when transthoracic studies are inadequate (**see Table 72G.2**).

Surgery and Transcatheter Intervention

The ACC/AHA guidelines consider mitral valve repair to be the operation of choice for patients with suitable valves when performed by an experienced operator (**Table 72G.9**). Class I recommendations for repair are preferred to MVR in patients with primary MR limited to the posterior mitral leaflet and in patients with primary MR involving the anterior leaflet or both leaflets, when a successful and durable repair can be accomplished.

TABLE 72G.9

Updated ACC/AHA Guidelines for Intervention for Chronic Primary Mitral Regurgitation (MR)[2]

CLASS	INDICATION	LOE
I	MV surgery for symptomatic patients with severe primary MR (stage D) and LVEF greater than 30%.	B
	MV surgery for asymptomatic patients with severe primary MR and LV dysfunction (LVEF 30% to 60% and/or LVESD ≥40 mm, stage C2).	B
	MV repair in preference to MVR when surgical treatment for patients with severe primary MR limited to the posterior leaflet.	B
	MV repair in preference to MVR when surgical treatment for patients with severe primary MR involving the anterior leaflet or both leaflets when a successful and durable repair can be accomplished.	B
	Concomitant MV repair or replacement in patients with severe primary MR undergoing cardiac surgery for other indications.	B
IIa	MV repair is reasonable in asymptomatic patients with severe primary MR (stage C1) with preserved LV function (LVEF >60% and LVESD <40 mm) in whom the likelihood of a successful and durable repair without residual MR is greater than 95% with an expected mortality less than 1% when performed at a Heart Valve Center of Excellence.	B
	MV surgery is reasonable for asymptomatic patients with severe primary MR and preserved LV function (LVEF >60% and LVESD <40 mm) with a progressive increase in LV size or decrease in LVEF on serial imaging studies. (*New 2017*)	C
	MV repair is reasonable for asymptomatic patients with severe nonrheumatic primary MR (stage C1) and preserved LV function in whom there is a high likelihood of a successful and durable repair with (1) new onset of AF or (2) resting pulmonary hypertension (PA systolic pressure >50 mm Hg).	B
	Concomitant MV repair is reasonable in patients with moderate primary MR (stage B) undergoing cardiac surgery for other indications.	C
IIb	MV surgery may be considered in symptomatic patients with severe primary MR and LVEF of 30% or less (stage D).	C
	Transcatheter MV repair may be considered for severely symptomatic patients (NYHA Class III/IV) with severe primary MR (stage D) who have a reasonable life expectancy, but a prohibitive surgical risk because of severe comorbidities.	B
III	MVR should not be performed for the treatment of isolated severe primary MR limited to less than one half of the posterior leaflet unless MV repair has been attempted and was unsuccessful.	B

LOE, Level of evidence; *AF,* atrial fibrillation; *LV,* left ventricular; *LVEF,* LV ejection fraction; *LVESD,* LV end-systolic dimension; *MV,* mitral valve; *MVR,* mitral valve replacement; *NYHA,* New York Heart Association; *PA,* pulmonary artery.

Surgery is recommended for patients with chronic severe primary MR with symptoms independent of LV function and in asymptomatic patients when there is evidence of LV dysfunction (EF 30% to 60% and/or end-systolic dimension >40 mm). The guidelines also support mitral valve repair in asymptomatic patients with severe primary MR and normal LV function, with the recommendation that it is reasonable (class IIa) to perform surgery in such patients in the setting of an experienced Heart Valve Center of Excellence in which the likelihood of successful repair without residual MR is greater than 95% and with an anticipated operative mortality less than 1%. Surgery is also reasonable (class IIa) in patients with new-onset atrial fibrillation or pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg at rest).

Transcatheter mitral valve repair may be considered for severely symptomatic patients with severe primary MR (stage D) who have a reasonable life expectancy, but a prohibitive surgical risk because of severe comorbidities.

Chronic Secondary Mitral Regurgitation

Management of patients with chronic secondary forms of MR is focused primarily on treatment of the underlying LV dysfunction with medical and device therapies (**see Table 72G.3**). Indications for surgical intervention are less certain (**Table 72G.10**), but it is reasonable (class IIa) to perform mitral valve repair or MVR for patients with chronic severe secondary MR (stages C and D) who are undergoing coronary artery bypass grafting (CABG) or AVR. Mitral valve repair or replacement may be considered (class IIb) in patients with severe secondary MR and heart failure symptoms who have not responded to guideline-directed medical therapy (GDMT) for heart failure, including cardiac resynchronization therapy in appropriate patients. Updated guideline recommendations for secondary MR[2] incorporate results of randomized clinical trials that it is reasonable to choose chordal-sparing MVR over downsized annuloplasty repair if operation is considered for severely symptomatic patients. Moreover, the usefulness of mitral valve repair is uncertain in patients with chronic, moderate, ischemic MR undergoing CABG. Transcatheter mitral valve repair is not yet approved in the United States for secondary ischemic

or functional MR.

TABLE 72G.10

Updated ACC/AHA Guidelines for Intervention for Chronic Secondary Mitral Regurgitation (MR)[2]

CLASS	INDICATION	LOE
IIa	MV surgery is reasonable for patients with chronic severe secondary MR (stages C and D) who are undergoing CABG or AVR.	C
	It is reasonable to choose chordal-sparing MVR over downsized annuloplasty repair if operation is considered for severely symptomatic patients (NYHA Class III/IV) with chronic severe ischemic MR (stage D) and persistent symptoms despite GDMT for heart failure. (*New 2017*)	B
IIb	MV surgery may be considered for severely symptomatic patients (NYHA class III-IV) with chronic severe secondary MR (stage D).	B
	In patients with chronic, moderate, or ischemic MR (stage B) undergoing CABG, the usefulness of mitral valve repair is uncertain. (*Modified 2017*)	B

LOE, Level of evidence; *AVR,* aortic valve replacement; *CABG,* coronary artery bypass graft surgery; *GDMT,* guideline-directed medical therapy; *MV,* mitral valve; *NYHA,* New York Heart Association.

Tricuspid Valve Disease (see Chapter 70)

Tricuspid valve repair is appropriate for correcting severe tricuspid regurgitation (TR) in patients with mitral valve disease requiring valve repair or replacement (**Table 72G.11**). Tricuspid valve replacement or annuloplasty is considered reasonable for patients with symptomatic severe primary TR unresponsive to medical therapy, which consists primarily of diuretics. Annuloplasty may be considered for patients with mild to moderate TR who are undergoing surgery for mitral valve disease if they have pulmonary hypertension or dilation of the tricuspid annulus.

TABLE 72G.11

ACC/AHA Guidelines for Intervention for Tricuspid Valve Disease[1]

CLASS	INDICATION	LOE
I	Tricuspid valve surgery is recommended for patients with severe TR (stages C and D) undergoing left-sided valve surgery.	C
	Tricuspid valve surgery is recommended for patients with severe TS at operation for left-sided valve disease.	C
	Tricuspid valve surgery is recommended for patients with isolated, symptomatic severe TS.	C
IIa	Tricuspid valve repair can be beneficial for patients with mild, moderate, or greater functional TR (stage B) at left-sided valve surgery with either tricuspid annular dilation or prior evidence of right-sided heart failure.	B
	Tricuspid valve surgery can be beneficial for patients with symptoms due to severe primary TR that are unresponsive to medical therapy (stage D).	C
IIb	Tricuspid valve repair may be considered for patients with moderate functional TR (stage B) and pulmonary artery hypertension at left-sided valve surgery.	C
	Tricuspid valve surgery may be considered for asymptomatic or minimally symptomatic patients with severe primary TR (stage C) and progressive degrees of moderate or greater RV dilation and/or systolic dysfunction.	C
	Reoperation for isolated tricuspid valve repair or replacement may be considered for persistent symptoms caused by severe TR (stage D) in patients who have undergone previous left-sided valve surgery and who do not have severe pulmonary hypertension or significant RV systolic dysfunction.	C
	Percutaneous balloon tricuspid commissurotomy might be considered in patients with isolated, symptomatic severe TS without accompanying TR.	C

LOE, Level of evidence; *RV,* right ventricular; *TR,* tricuspid regurgitation; *TS,* tricuspid stenosis.

Prosthetic Heart Valves (see Chapter 71)

Choices in Valve Surgery

Numerous options are available for the surgical management of VHD. The ACC/AHA guidelines generally favor mitral valve repair over replacement. The standard surgical approach usually entails a median sternotomy with cardiopulmonary bypass. However, numerous alternatives are gaining acceptance. These include minimally invasive approaches to valve repair such as ministernotomy, small right thoracotomy, and robotic surgery. Transcatheter AVR (TAVR) and percutaneous approaches to mitral valve repair are approved procedures in the United States and Europe.

When replacement is necessary, several variables influence the selection of a bioprosthetic versus a mechanical valve (**Table 72G.12**). Patient preference plays an important role in determining the choice of a prosthetic valve. The class I recommendations are important considerations. First, choice of valve intervention and prosthetic valve type should be a shared decision process that hinges importantly on the desires of the patient. Second, a bioprosthesis is recommended in patients of any age for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired. In the 2017 guidelines update,[2] bioprosthetic valves are considered reasonable (class IIa) for patients 70 years and older, and a mechanical prosthesis is reasonable for AVR or MVR in patients younger than 50 who do not have a contraindication to anticoagulation. For patients age 50 to 70, it is reasonable to individualize the choice of mechanical or bioprosthetic valve prosthesis on the basis of individual patient factors and preferences, after full discussion of the trade-offs involved.

TABLE 72G.12

Updated ACC/AHA Guidelines for Selection of Prosthetic Heart Valves[2]

CLASS	INDICATION	LOE
I	Choice of valve intervention and prosthetic valve type should be a shared decision process with patient.	C
	A bioprosthesis is recommended in patients of any age for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired.	C
IIa	A mechanical prosthesis is reasonable for AVR or MVR in patients younger than 50 who do not have a contraindication to anticoagulation. (*Modified 2017*)	B
	A bioprosthesis is reasonable in patients older than 70.	B
	For patients age 50 to 70, it is reasonable to individualize the choice of either a mechanical or a bioprosthetic valve prosthesis on the basis of individual patient factors and preferences, after full discussion of the trade-offs involved. (*Modified 2017*)	B
IIb	Replacement of the aortic valve by a pulmonary autograft (the Ross procedure), when performed by an experienced surgeon, may be considered in young patients when anticoagulation with a VKA is contraindicated or undesirable.	C

LOE, Level of evidence; *AVR,* aortic valve replacement; *MVR,* mitral valve replacement; *VKA,* vitamin K antagonist.

Imaging Prosthetic Heart Valves

Table 72G.13 provides recommendations for imaging in patients with prosthetic heart valves.

TABLE 72G.13

ACC/AHA Guidelines for Imaging of Prosthetic Heart Valves[1]

CLASS	INDICATION	LOE
I	An initial TTE study in patients after prosthetic valve implantation for evaluation of valve hemodynamics.	B
	Repeat TTE in patients with prosthetic heart valves if there is a change in clinical symptoms or signs suggesting valve dysfunction.	C
	TEE is recommended when clinical symptoms or signs suggest prosthetic valve dysfunction.	C
IIa	Annual TTE is reasonable in patients with a bioprosthetic valve after the first 10 years, even in the absence of a change in clinical status.	C

LOE, Level of evidence; *TEE,* transesophageal echocardiography; *TTE,* transthoracic echocardiography.

Anticoagulation Therapy

The ACC/AHA guidelines recommend warfarin therapy for patients with mechanical valves (**Table 72G.14**). For patients with aortic valve prostheses, those with bileaflet mechanical valves and Medtronic-Hall valves should maintain an international normalized ratio (INR) between 2 and 3, whereas those with Starr-Edwards valves or mechanical disc valves should maintain INR between 2.5 and 3.5. The same target is indicated after MVR with a mechanical valve. In the 2017 guidelines update,[2] INR of 1.5 to 2.0 is considered a reasonable target in patients with mechanical On-X AVR and no thromboembolic risk factors. For bioprostheses, short-term anticoagulation with warfarin (INR, 2.5) is reasonable for AVR and MVR (3 to 6 months after surgery) and TAVR (3 months after implantation) in

patients at low risk of bleeding. Low-dose aspirin (75 to 100 mg/day) is recommended in addition to warfarin (class I) for all patients with mechanical heart valves and is reasonable (class IIa) in those with biologic valves. Clopidogrel may be considered for those who cannot take aspirin.

TABLE 72G.14

Updated ACC/AHA Guidelines for Antithrombotic Therapies for Prosthetic Heart Valves[2]

CLASS	INDICATION	LOE
I	Anticoagulation with a VKA and INR monitoring in patients with a mechanical prosthetic valve.	A
	Anticoagulation with a VKA to achieve an INR of 2.5 in patients with a mechanical AVR (bileaflet or current-generation single tilting disc) and no risk factors for thromboembolism.	B
	Anticoagulation with a VKA to achieve an INR of 3.0 in patients with a mechanical AVR and additional risk factors for thromboembolic events (AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions) or an older-generation mechanical AVR (e.g., ball-in-cage).	B
	Anticoagulation with a VKA to achieve an INR of 3.0 in patients with a mechanical MVR.	B
	Aspirin, 75 to 100 mg daily, in addition to anticoagulation with a VKA in patients with mechanical valve prosthesis.	A
IIa	Aspirin, 75 to 100 mg daily, is reasonable in all patients with a bioprosthetic aortic or mitral valve.	B
	Anticoagulation with a VKA to achieve a target INR of 2.5 is reasonable for the first 3 months and for as long as 6 months after bioprosthetic MVR or AVR in patients at low risk of bleeding. (*Modified 2017*)	B
IIb	A lower target INR of 1.5 to 2.0 may be reasonable in patients with mechanical On-X AVR and no thromboembolic risk factors. (*New 2017*)	B
	Anticoagulation with a VKA with a goal INR of 2.5 may be reasonable for the first 3 months after TAVR in patients at low risk of bleeding. (*New 2017*)	B
	Clopidogrel, 75 mg daily, may be reasonable for the first 6 months after a TAVR, in addition to lifelong aspirin, 75 to 100 mg daily.	C
III	Anticoagulant therapy with oral direct thrombin inhibitors or anti-Xa agents should not be used in patients with mechanical valve prostheses.	B

LOE, Level of evidence; *AF,* atrial fibrillation; *AVR,* aortic valve replacement; *INR,* international normalized ratio; *MVR,* mitral valve replacement; *TAVR,* transcatheter AVR; *VKA,* vitamin K antagonist.

Bridging Therapy

Antithrombotic medications must sometimes be interrupted in patients with mechanical valve prostheses for noncardiac surgery, invasive procedures, or dental care. In patients at low risk of thrombosis, warfarin should be stopped 48 to 72 hours before the procedure and started no more than 24 hours after the procedure (**Table 72G.15**). The ACC/AHA guidelines indicate that the use of heparin is usually unnecessary for patients at low risk of thrombosis, defined as those with a bileaflet mechanical aortic valve prosthesis with no risk factors. In the 2017 guidelines update,[2] bridging anticoagulation during the interval when INR is subtherapeutic preoperatively is reasonable on an individualized basis, with the risks of bleeding weighed against the benefits of thromboembolism prevention, for patients who are undergoing invasive or surgical procedures with a (1) mechanical AVR and any thromboembolic risk factor, (2) older-generation mechanical AVR, or (3) mechanical MVR. The recommended bridging therapy is intravenous unfractionated heparin or subcutaneous doses of low-molecular weight heparin.

TABLE 72G.15

Updated ACC/AHA Guidelines for Bridging Antithrombotic Therapies for Mechanical Heart Valves[2]

CLASS	INDICATION	LOE
I	Continuation of VKA anticoagulation with a therapeutic INR is recommended in patients with mechanical heart valves undergoing minor procedures (e.g., dental extractions, cataract removal) where bleeding is easily controlled.	C
	Temporary interruption of VKA anticoagulation, without bridging agents while INR is subtherapeutic is recommended in patients with a bileaflet mechanical AVR and no other risk factors for thrombosis who are undergoing invasive or surgical procedures.	C
IIa	Bridging anticoagulation therapy during the interval when INR is subtherapeutic preoperatively is reasonable on an individualized basis, with the risks of bleeding weighed against the benefits of thromboembolism prevention, for patients who are undergoing invasive or surgical procedures with a (1) mechanical AVR and any thromboembolic risk factor, (2) older-generation mechanical AVR, or (3) mechanical MVR. (*Modified 2017*)	C
	Administration of fresh-frozen plasma or prothrombin-complex concentrate is reasonable in patients with mechanical valves receiving VKA therapy who require emergency noncardiac surgery or invasive procedures.	C

LOE, Level of evidence; *AVR,* aortic valve replacement; *INR,* international normalized ratio; *MVR,* mitral valve replacement; *VKA,* vitamin K antagonist.

Prosthetic Valve Thrombosis

Emergency surgery is most reasonable for patients with a thrombosed left-sided prosthetic valve and moderate to severe symptoms (NYHA Class III or IV) or a large clot burden. Fibrinolytic therapy may be considered for patients with less severe symptoms, smaller clot burdens, or when surgery is high risk or unavailable (**Table 72G.16**).

TABLE 72G.16

Updated ACC/AHA Guidelines for Management of Prosthetic Valve Thrombosis[2]

CLASS	INDICATION	LOE
Diagnosis and Follow-Up		
I	Urgent evaluation with multimodality imaging is indicated in patients with suspected mechanical prosthetic valve thrombosis to assess valvular function, leaflet motion, and the presence and extent of thrombus. (*Modified 2017*)	B
Medical Therapy		
I	Fibrinolytic therapy is reasonable for patients with a thrombosed left-sided prosthetic heart valve, recent onset (<14 days) of NYHA Class I or II symptoms, and a small thrombus (<0.8 cm^2).	B
IIa	Fibrinolytic therapy is reasonable for thrombosed right-sided prosthetic heart valves.	B
Indications for Intervention		
I	Urgent initial treatment with either slow-infusion low-dose fibrinolytic therapy or emergency surgery is recommended for patients with a thrombosed left-sided mechanical prosthetic heart valve presenting with symptoms of valve obstruction. (*Modified 2017*)	B

LOE, Level of evidence; *NYHA,* New York Heart Association.

Prosthetic Valve Stenosis and Regurgitation

The 2017 guidelines update[2] includes recommendations for transcatheter valve-in-valve treatment of severe bioprosthetic AS or AR in patients judged by the heart team to be at high or prohibitive risk for surgical therapy, in whom improvement in hemodynamics is anticipated (**Table 72G.17**).

Table 72G.17

Updated ACC/AHA Guidelines for Management of Prosthetic Valve Stenosis and Regurgitation[2]

CLASS	INDICATION	LOE
Prosthetic Valve Stenosis		
I	Repeat valve replacement is indicated for severe symptomatic prosthetic valve stenosis.	C
IIa	In patients with suspected or confirmed bioprosthetic valve thrombosis who are hemodynamically stable and have no contraindications to anticoagulation, initial treatment with a VKA is reasonable. (*New 2017*)	C
	For severely symptomatic patients with bioprosthetic AS judged by the heart team to be at high or prohibitive risk of reoperation, and in whom improvement in hemodynamics is anticipated, a transcatheter valve-in-valve procedure is reasonable. (*New 2017*)	B
Prosthetic Valve Regurgitation		
I	Surgery is recommended for operable patients with mechanical heart valves who have intractable hemolysis or HF caused by severe prosthetic or paraprosthetic regurgitation.	B
IIa	Surgery is reasonable for asymptomatic patients with severe bioprosthetic regurgitation if operative risk is acceptable. (*Modified 2017*)	C
	Percutaneous repair of paravalvular regurgitation is reasonable in patients with prosthetic heart valves and intractable hemolysis or NYHA Class III/IV HF who are at high risk for surgery and have anatomic features suitable for catheter-based therapy when performed in centers with procedural expertise.	B
	For severely symptomatic patients with bioprosthetic AR judged by the heart team to be at high or prohibitive risk for surgical therapy, in whom improvement in hemodynamics is anticipated, a transcatheter valve-in-valve procedure is reasonable. (*New 2017*)	B

LOE, Level of evidence; *AR,* aortic regurgitation; *AS,* aortic stenosis; *HF,* heart failure; *NYHA,* New York Heart Association; *VKA,* vitamin K antagonist.

Valvular Heart Disease in Pregnancy

Native Valve Disorders

Table 72G.18 provides the management considerations for patients with VHD who want to become pregnant or who have become pregnant.

TABLE 72G.18

ACC/AHA Guidelines for Management of Valvular Heart Disease (VHD) in Pregnancy[1]

CLASS	INDICATION	LOE
General Considerations		
I	All patients with suspected VHD should undergo a clinical evaluation and TTE before pregnancy.	C
	All patients with severe VHD (stages C and D) should undergo prepregnancy counseling by a cardiologist with expertise in managing patients with VHD during pregnancy.	C
	All patients referred for a valve operation prior to pregnancy should receive prepregnancy counseling by a cardiologist with expertise in managing patients with VHD during pregnancy regarding the risks and benefits of all options for operative interventions, including mechanical prosthesis, bioprosthesis, and valve repair.	C
	Pregnant patients with severe VHD (stages C and D) should be followed in a tertiary care center with a dedicated heart valve team of cardiologists, surgeons, anesthesiologists, and obstetricians with expertise in the management of high-risk cardiac patients during pregnancy.	C
	Exercise testing is reasonable in asymptomatic patients with severe VHD prior to pregnancy.	C
III	ACE inhibitors and ARBs should *not* be given to pregnant patients with valve disease.	B
	Valve operation should *not* be performed in pregnant patients with valve stenosis in the absence of severe symptoms.	C
Indications for Medical Therapy for Native Valve Stenosis		
IIa	Anticoagulation should be given to pregnant patients with MS and AF unless contraindicated	C
	Use of beta blockers as required for rate control is reasonable for pregnant patients with MS in the absence of contraindication, if tolerated.	C
IIb	Use of diuretics may be reasonable for pregnant patients with MS and heart failure symptoms (stage D).	C
Interventions for Native Valve Stenosis		
I	Valve intervention for symptomatic patients prior to pregnancy with severe AS (aortic velocity ≥4 m/sec or mean pressure gradient ≥40 mm Hg, stage D).	C
	Valve intervention for symptomatic patients prior to pregnancy with severe MS (mitral valve area ≤1.5 cm^2, stage D).	C
	PMBC for asymptomatic patients prior to pregnancy with severe MS (mitral valve area ≤1.5 cm^2, stage C) who have valve morphology favorable for PMBC.	C
IIa	Valve intervention is reasonable for asymptomatic patients prior to pregnancy with severe AS (aortic velocity ≥4 m/sec or mean pressure gradient ≥40 mm Hg, stage C).	C
	PMBC is reasonable for pregnant patients with severe MS (mitral valve area ≤1.5 cm^2, stage D) with valve morphology favorable for PMBC who remain symptomatic with NYHA Class III or IV symptoms despite medical therapy.	B
	Valve intervention is reasonable for pregnant patients with severe MS (mitral valve area ≤1.5 cm^2, stage D) and valve morphology not favorable for PMBC only if there are refractory NYHA Class IV symptoms.	C
	Valve intervention is reasonable for pregnant patients with severe AS (mean pressure gradient ≥40 mm Hg, stage D) only if there is hemodynamic deterioration or NYHA Class III or IV symptoms.	B
III	Valve operation should *not* be performed in pregnant patients with valve stenosis in the absence of severe symptoms.	C
Interventions for Native Valve Regurgitation		
I	Valve repair or replacement is recommended prior to pregnancy for symptomatic women with severe valve regurgitation (stage D).	C
IIa	Valve operation for pregnant patients with severe valve regurgitation is reasonable only if there are refractory NYHA Class IV symptoms (stage D).	C
IIb	Valve repair prior to pregnancy may be considered in the asymptomatic patient with severe MR (stage C) and a valve suitable for valve repair, but only after detailed discussion with the patient regarding the risks and benefits of the operation and its outcome on future pregnancies.	C

LOE, Level of evidence; *ACE,* angiotensin converting enzyme; *AF,* atrial fibrillation; *ARBs,* angiotensin receptor blockers; *AS,* aortic stenosis; *MR,* mitral regurgitation; *MS,* mitral stenosis; *NYHA,* New York Heart Association; *PMBC,* percutaneous mitral balloon commissurotomy; *TTE,* transthoracic echocardiography.

Prosthetic Heart Valves

Table 72G.19 outlines the management of patients with prosthetic heart valves during pregnancy, including management of anticoagulation in patients with mechanical heart valves.

TABLE 72G.19

ACC/AHA Guidelines for Management of Prosthetic Heart Valves in Pregnancy[1]

CLASS	INDICATION	LOE
Indications for Evaluation		
I	All patients with a prosthetic valve should undergo a clinical evaluation and baseline TTE prior to pregnancy.	C
	All patients with a prosthetic valve should undergo prepregnancy counseling by a cardiologist with expertise in managing patients with VHD during pregnancy.	C
	TTE should be performed in all pregnant patients with a prosthetic valve if not previously done prior to pregnancy.	C
	Repeat TTE should be performed in all pregnant patients with a prosthetic valve who develop symptoms.	C
	TEE should be performed in all pregnant patients with a mechanical prosthetic valve who have prosthetic valve obstruction or experience an embolic event.	
	Pregnant patients with a mechanical prosthesis should be followed in a tertiary care center with a dedicated Heart Valve Team of cardiologists, surgeons, anesthesiologists, and obstetricians with expertise in the management of high-risk cardiac patients.	C
Indications for Antithrombotic Therapy		
I	Therapeutic anticoagulation with frequent monitoring is recommended for all pregnant patients with a mechanical prosthesis.	B
	Warfarin is recommended in pregnant patients with a mechanical prosthesis to achieve a therapeutic INR in the second and third trimester.	B
	Discontinuation of warfarin with initiation of intravenous UFH (with APTT >2 times control) is recommended before planned vaginal delivery in pregnant patients with a mechanical prosthesis.	C
	Low-dose aspirin, 75 to 100 mg daily, is recommended for pregnant patients in the second and third trimesters with a mechanical valve or a bioprosthesis.	C
IIa	Continuation of warfarin during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin to achieve a therapeutic INR is 5 mg or less daily, after full discussion with the patient regarding risks and benefits.	B
	Dose-adjusted LMWH at least twice daily (with target anti-Xa level of 0.8 to 1.2 U/mL, 4 to 6 hours after dose) during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is greater than 5 mg/day to achieve a therapeutic INR.	B
	Dose-adjusted continuous intravenous UFH (with APTT at least 2 times control) during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is greater than 5 mg per day to achieve a therapeutic INR.	B
IIb	Dose-adjusted LMWH at least twice daily (with target anti- Xa level of 0.8 to 1.2 U/mL, 4 to 6 hours after dose) during the first trimester may be reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is 5 mg or less daily to achieve a therapeutic INR.	B
	Dose-adjusted continuous infusion of UFH (with APTT at least 2 times control) during the first trimester may be reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is 5 mg or less daily to achieve a therapeutic INR.	B
III	LMWH should *not* be administered to pregnant patients with mechanical prostheses unless anti-Xa levels are monitored 4 to 6 hours after administration.	B

LOE, Level of evidence; *APTT,* activated partial thromboplastin time; *INR,* international normalized ratio; *LMWH,* low-molecular-weight heparin; *TEE,* transesophageal echocardiography; *TTE,* transthoracic echocardiography; *UFH,* unfractionated heparin.

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Cardiovascular Infections

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Historically, the focus of cardiovascular infections has been on infective endocarditis (IE) as the primary syndrome. In this chapter, infections that involve cardiovascular devices, including permanent pacemakers, implantable cardioverter-defibrillators, coronary stents, and ventricular assist devices, also are addressed, because infection is a frequent complication with some devices, often necessitating their removal. Moreover, the indications for devices continue to expand, involving an increasing number of patients, particularly among aging populations in many developed countries. These devices may be lifesaving and improve quality of life, but device removal generally is required for infection cure, and removal procedures are associated with notable morbidity and mortality. Certain aspects of antimicrobial therapy also are unique, because IE often is caused by multidrug-resistant organisms acquired in the health care setting. Consequently, fewer drugs are available for treating these infections, with an increased likelihood of drug-related toxicities. In addition, longer durations of therapy may be needed, which can increase the rate of drug-induced adverse events.

Infective Endocarditis

Before the pandemic of human immunodeficiency virus (HIV) infection, IE was the syndrome for which the expertise of infectious diseases physicians was almost universally requested. IE has the proclivity to cause complications both at the cardiac valve site and at extracardiac locations that can predispose affected patients to serious morbidity and mortality. Management of IE therefore requires a team approach, which generally includes specialists in infectious diseases, cardiovascular medicine, and cardiovascular surgery with particular expertise in IE. Thus, every patient with IE should be managed in the inpatient setting of a medical center with experienced medical and surgical specialists to provide care, which often includes emergent diagnostic and surgical interventions.

Epidemiology

The global burden of disease from IE is largely unknown. Much of the world's population lives in developing countries, where many people do not have routine access to advanced medical care, and usually no local or national infrastructure exists for disease reporting (**see Chapter 1**). Thus the clinical characterization of IE is biased, shaped by the collective experiences at large teaching facilities in countries where patient access is available and disease reporting is done. However, even in many developed countries, including the United States, IE is not included among the diagnoses requiring mandatory reporting to public health agencies that would define a statewide or national disease incidence or burden.

IE is a heterogeneous syndrome that is heavily influenced by the epidemiology of the infection. For example, in developing countries where rheumatic fever is still endemic, younger adults with longstanding rheumatic heart disease frequently present with a subacute clinical course spanning several weeks that involves left-sided native valve infection caused by viridans group streptococci. By contrast, in large, teaching, tertiary care centers in developed countries, patients with previous health care exposure frequently present with an acute illness that can be measured in days and is caused by *Staphylococcus aureus*, with numerous anatomic sites of metastatic foci of infection and worse

outcomes.

The incidence of IE is influenced by multiple host factors that modify the risk of infection. Such factors include the underlying anatomic (usually valvular) cardiac conditions that result in turbulent blood flow and endothelial cell disruption (see later, Pathogenesis). In addition, aging of the population in developed countries has resulted in more patients with myxomatous degeneration of the mitral valve, with subsequent prolapse and insufficiency (**see Chapter 69**). At the same time, a dramatic fall in the incidence of rheumatic fever has reduced the overall risk of IE in younger persons. Advances in medicine also alter the incidence of IE. For example, reduced use of tunneled catheters and increasing use of arteriovenous fistulas for chronic hemodialysis will reduce the risk of bloodstream infection. Improvement in oral health in developed countries also may affect the incidence of IE, but this remains to be determined.

Population-based studies[1,2] have been used to estimate both the incidence of IE and its clinical characterization, but complete case ascertainment is difficult to secure. For example, in the United States, patients may receive medical care in locations that are not in their place of residence. Thus, large medical centers that have unique expertise in endocarditis management may be unable to obtain complete case ascertainment in a population because of changing referral patterns or second-party coverage. Data generated from a population-based investigation will have limited applicability (generalizability) if the cohort under study is not representative of other populations in demographic or clinical features.

Incidence studies of IE are limited in number and in geographic coverage of populations.[1,2] The incidence reported among surveys from Western Europe and Olmsted County, Minnesota, has been stable for many years, at fewer than 10 cases per 100,000 person-years, with the exception of one analysis[3] from northwestern Italy that demonstrated a small but statistically significant increase in incidence. Historically, a sex predilection has been noted, with males more often affected by IE. This results in part from a major contribution of injection drug use (IDU), which more frequently is reported among men, but even in cohorts with IE and a low frequency of reported IDU, males still predominate. This male predominance may be fading, as reported in a recent analysis[2] in which the female incidence had increased, with a high level of health care exposure cited as a predisposing condition for the development of IE. Thus, access to health care can influence the epidemiology of IE.

Health care exposure, including both nosocomial and non-nosocomial exposure, has been recognized only recently[2,4] as a major contributor to the development of IE. Not only do indwelling central venous catheters and hemodialysis predispose to bloodstream infection, but infection with antimicrobial resistant pathogens is more likely to occur as a consequence of health care–related exposure. The virulence of some of these pathogens, in particular methicillin-resistant *S. aureus* (MRSA), is notable and is associated with increased mortality in patients with IE.

Injection drug users are a unique group at increased risk for IE. Thus the modified Duke criteria (see Classic References, Li) include IDU as a “minor” criterion to satisfy a case definition of IE. These patients, who tend to be young, male, and otherwise healthy, account for a large proportion of IE cases in inner-city medical centers in developed countries.[5] Their contact with the health care system often is limited to short stays in an emergency department (ED). Some patients, however, harbor chronic bloodborne viral infections, including those caused by hepatitis viruses and HIV, often unrecognized until the affected person presents with manifestations of IE and undergoes subsequent screening for viral infections not directly related to heart valve infection. The predominant pathogen involving IDU patients with IE is *S. aureus*; less common is a panoply of other organisms, including aerobic gram-negative bacilli and anaerobic and aerobic oral flora, with polymicrobial infections also seen in a minority of patients. Patients tend to delay seeking medical care and present with systemic complications of

infection. Because the right side of the heart, especially the tricuspid valve associated with heroin use,[5] usually is involved, patients often present with pulmonary complications, including septic pulmonary emboli, empyema, and lung abscesses. In a minority of patients, bilateral IE develops, with complications involving both the pulmonary and systemic circulations. Although outcomes of IDU patients with right-sided IE generally are good, these patients are well recognized to be at risk for recurrent bouts of IE, particularly if they continue injecting illicit drugs and if prosthetic valve placement was required to treat the previous valve infection.

Microbiology

Any of a vast array of bacteria and fungi can cause IE,[6] as is evident in novel case reports and literature reviews of IE caused by unusual organisms. Although changes in the prevalence of pathogens causing IE have emerged in recent years because of critical changes in the epidemiology of IE in developed countries,[2,7] the overall distribution of infecting organisms has remained the same, with gram-positive cocci being predominant. These include streptococcal, staphylococcal, and enterococcal species. Important virulence factors unique to each genus group appear to be operative in infection pathogenesis (see later). It is therefore not surprising that the modified Duke criteria (see Classic References, Li) listed only these three groups of pathogens as "typical microorganisms" in the designation of the major criterion of "blood culture positive" for IE.

Streptococcal Species

Among streptococci, the viridans group streptococci (VGS) are the predominant organisms that cause IE. A "subacute" presentation is typical, with symptoms of infection present for weeks to a few months, with low-grade fever, night sweats, and fatigue being common. These organisms normally are found in the mouth of humans and tend to cause indolent infections. Sustained bacteremia due to this group of bacteria should prompt a consideration of the diagnosis of IE, as few other infection syndromes cause sustained bloodstream infection. The viridians group includes several evolving species of streptococci and currently includes *sanguis, oralis* (*mitis*), *salivarius, mutans, intermedius, anginosus,* and *constellatus*. The latter three species have been referred to the *Streptococcus anginosus or S. milleri* group and are unique in that they have a proclivity to produce abscess formation and metastatic infection foci, both within the heart and in extracardiac locations in patients with IE.

The VGS also include species of *Gemella, Abiotrophia*, and *Granulicatella*. For *Gemella,* one species designated as *morbillorum* was previously listed in the *Streptococcus* genus. These organisms can cause IE and exhibit metabolic characteristics similar to those of the "nutritionally variant streptococci," which have now been reassigned to the *Abiotrophia* and *Granulicatella* genera. The recommended medical therapy for infections caused by these unique organisms is discussed later (see Antimicrobial Therapy).

The VGS constitute the predominant cause of native valve infection acquired in the community setting, in both developing and developed nations. A common substrate for infection from these organisms has been rheumatic valvular disease, but as mentioned, the incidence of acute rheumatic fever has fallen dramatically in developed countries.

Similar to other bacteria, VGS have developed resistance to some antibiotics. Fortunately, resistance to penicillin is seen in a minority of IE isolates. Resistance is not based on beta-lactamase production, and the definitions used[6] to characterize strains as being "penicillin resistant" are not the same as the break points recommended by the Clinical and Laboratory Standards Institute (CLSI). This distinction can be confusing for some clinicians, because selection of antibiotic therapy is based on in vitro susceptibility

results.

Unlike VGS, beta-hemolytic streptococci typically cause an acute presentation of IE. Injection drug users and elderly persons are two at-risk groups. Complications are common and often involve valve destruction and distant sites, frequently musculoskeletal, of infection. The prevalence of beta-hemolytic streptococci among cases of IE is less than 10%. Beta-hemolytic streptococci have remained uniquely susceptible to penicillin, with extremely rare exception. Nevertheless, it is prudent to obtain susceptibility testing on all isolates. Surgery is often required for management of severe valvular and perivalvular involvement.

Streptococcus gallolyticus (formerly known as *S. bovis*) deserves particular attention. The organism usually is found in the gastrointestinal (GI) tract, and when recovered from blood culture, whether related to IE or not, an examination for an underlying GI lesion, including colon cancer, should be performed. Although it currently is the cause of less than 10% of cases of IE, the expectation is that it will become more prominent in aging populations and those with increasing restrictions on cancer prevention screening.

Historically, IE from *Streptococcus pneumoniae* has received considerable attention. Although it continues to be a common cause of community-acquired bloodstream infection that often is related to pneumonia, it is a rare cause of IE today. When *S. pneumoniae* does cause IE, the clinical presentation usually is that of an acute syndrome associated with valve destruction. It can be associated with meningitis as well as other intracranial complications. Invasive isolates of pneumococci tend to be penicillin susceptible, but susceptibility testing is required to confirm this impression. As with IE from beta-hemolytic streptococci, surgery often is required to address valve-related complications.

Staphylococcal Species

The staphylococci are the second group of gram-positive cocci that are well recognized as causes of IE. *S. aureus* is a common cause of both native and prosthetic valve endocarditis.[6,7] The presentation in cases caused by *S. aureus* is acute in onset and associated with considerable systemic toxicity. In cases of left-sided heart infection, morbidity and mortality rates are high, despite appropriate therapy, including surgical intervention. Right-sided heart infection, predominantly of the tricuspid valve in injection drug users, has a much higher cure rate than that for left-sided heart infection, and mortality rates are low, unless bilateral infection is present. Unfortunately, the rate of IE from *S. aureus* is increasing, in part because of an increased exposure to health care. In addition, resistance to oxacillin and other antibiotics also has increased, which has made treatment more difficult.

Although coagulase-negative staphylococci are recognized as frequent pathogens of prosthetic valve infection, they also can cause native valve infection in a minority of IE cases. Although these infections usually are subacute in presentation, the morbidity and mortality associated with IE caused by coagulase-negative staphylococci are considerable. Of the more than 30 species of coagulase-negative staphylococci, two deserve special attention. *Staphylococcus epidermidis* is the most commonly identified species to cause bacteremia and IE. *Staphylococcus lugdunensis* is another species that causes both native and prosthetic valve endocarditis and tends to be more virulent than the other species of coagulase-negative staphylococci. Because this group of organisms is the most common cause of contaminated blood cultures, a delay in diagnosis can result from misinterpretation of blood culture results. Multiple sets of blood culture specimens should therefore be collected to better distinguish contamination from bloodstream infection. Except for *S. lugdunensis*, many strains of which remain penicillin susceptible, coagulase-negative staphylococci are more drug resistant than *S. aureus*; accordingly, fewer treatment options are available.

Enterococcal Species

Age is strongly associated with the development of IE caused by enterococcal species, with the prevalence of these organisms in IE cases doubling among elderly persons compared with young adults. A majority of infections are caused by *Enterococcus faecalis* and are associated with genitourinary (GU) tract abnormalities. In the past, enterococcal IE was community acquired, and enterococci were well recognized as part of the normal gut flora in humans. More recently, enterococcal species associated with health care exposure and central venous catheter use have contributed to infection predisposition. With this group of organisms, a subacute IE presentation is typical, and antibiotic therapy requires penicillin or ampicillin combined with an aminoglycoside, usually gentamicin. Multidrug-resistant enterococcal species, in particular *Enterococcus faecium*, can cause IE that is difficult to cure; this includes infection caused by vancomycin-resistant strains collectively termed *vancomycin-resistant enterococci* (VRE).

HACEK Organisms

The HACEK organisms are fastidious gram-negative bacilli comprising *Haemophilus* species (other than *H. influenzae*); *Aggregatibacter actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans*) and *Aggregatibacter aphrophilus* (formerly *Haemophilus aphrophilus*); *Cardiobacterium hominis*; *Eikenella corrodens*; and *Kingella kingae* and *K. denitrificans*. They colonize in the oropharynx and upper respiratory tract, causing subacute IE presentation that is community acquired. Most of the organisms in blood cultures may require several days of incubation. Because of the indolent clinical course, diagnosis often is delayed, with the formation of large vegetations observed at echocardiography. As a result, embolism to the brain or other systemic sites occurs frequently.

Aerobic Gram-Negative Bacilli

In view of their universal causation of bloodstream infection, it is noteworthy that IE caused by aerobic gram-negative bacilli is rare. This observation attests to the unique virulence factors that characterize gram-positive cocci in IE pathogenesis and are not found in gram-negative bacilli. This group includes *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., *Pseudomonas* spp., and others. In cases of IE caused by these organisms, presentations generally have been acute and sometimes associated with systemic toxicity, including sepsis and its complications. IE can be either community or health care associated. Outcomes of IE caused by aerobic gram-negative bacilli are characterized by increased morbidity and mortality rates.

Fungi

Fungi are extremely rare causes of IE. Identification of these organisms often is difficult because some do not grow in routine blood culture media. Even when selected culture media are used, fungal isolation may not be achieved. Thus, fungi can cause either blood culture–positive or culture-negative IE.

The bulk of these infections are caused by *Candida* spp., although a broad array of fungi may cause IE. These infections usually are health care associated and involve prosthetic valves, often arising as a result of a central venous catheter infection. An indwelling right-heart catheter, such as a flotation catheter, can denude a valve and nonvalvular endothelial surface, predisposing the patient to fungal (or bacterial) right-sided IE. In addition, IDU is a well-recognized risk factor for fungal IE.

Clinical presentations range in severity from acute to subacute. Complications are frequent, and surgical intervention is recommended as a routine intervention, particularly with infections caused by molds such as *Aspergillus* spp. Because relapsing IE is a concern and can be delayed in onset, many

clinicians advocate the use of lifelong oral antifungal suppressive therapy, usually with an azole, after initial parenteral therapy is completed.

Culture-Negative Endocarditis

For a majority of cases that are designated as blood culture–negative endocarditis, the pathogen is not recovered from blood cultures, because the patient's recent exposure to an antimicrobial had suppressive or killing activity against the pathogen. In addition, with some uncommon causes of culture-negative endocarditis, the pathogen either will not grow in routine blood culture media or grows slowly in the media and is not detected in the time used for blood cultures. In the former scenario, nothing can be done. In the latter, blood cultures can be held for an extended period, at least 14 days, to determine if an isolate is recovered. Other techniques, such as special culture methods or serologic studies, also are used to isolate or identify infection. Organisms that should be included in this category include fungi, *Coxiella burnetii*, *Bartonella* spp., *Brucella* spp., *Tropheryma whippelii*, and *Legionella* spp.

Pathogenesis

Investigations that examine pathogenic mechanisms will likely lead to the development of future novel therapies, many of them unrelated to the traditional activities of antimicrobial agents that will be used in the management and prevention of IE.

Two overarching aspects of endocarditis pathogenesis have been identified.[6] Already noted is a primary predilection for development of IE from an underlying valvular or nonvalvular cardiac structural abnormality that results in blood flow turbulence, endothelial disruption, and platelet and fibrin deposition. This lesion, termed *nonbacterial thrombotic endocarditis* (NBTE), serves as a nidus for subsequent adhesion by bacteria or fungi in the bloodstream. This pathway is thought to account for a majority of cases of IE, most often related to left-sided valvular stenosis or regurgitation. This picture of pathogenesis is mirrored, in many ways, by the animal model of endocarditis that has been used for decades to examine the pathogenesis, treatment, and prevention of IE. The microbiologic and histopathologic findings in infected animals reflect those seen in humans. A second factor is that infection may involve normal valves. Some reservations regarding this pathway of infection seem appropriate, because it is impossible to know if a valve is completely normal, including its endothelial surface, before onset of valve infection. In addition, animals do not develop experimental endocarditis after an intravascular challenge with a relatively large inoculum of virulent organisms, in particular *S. aureus*, in the absence of a previous disruption of the cardiac endothelial surface. Nevertheless, in vitro endothelial cell cultures studies have demonstrated uptake of organisms by endothelial cells.

The predominance of gram-positive cocci as causing IE deserves additional comment. Advances in molecular biologic techniques have resulted in the ability to define virulence factors that are unique to these organisms (see Classic References, Moreillon). Infectivity studies that have compared “wild-type” parent strains to molecularly “engineered” strains using an experimental IE model have been of critical importance in defining virulence factors among strains of staphylococci, streptococci, and enterococci. Some of these factors serve as “adhesins” and are largely responsible for initial bacterial attachment to an NBTE nidus or to endothelial cells. They also are responsible for the attachment to medical devices, including prosthetic valves and cardiovascular implantable electronic device (CIED) leads. In this regard, biofilm formation occurs with some of these organisms and is important in both native tissue and prosthetic valve infections, in the context of factors responsible for the propagation of IE after initial

bacterial attachment.

The findings from these investigations are expected to affect future treatment and prevention of IE. Novel vaccines containing bacterial proteins that function as adhesins and are good immunogens are being examined, for example, and already have proved to be efficacious in the prevention of experimental IE. In this case, the protein (FimA) is expressed by several VGS species in the pathogenesis of IE. In addition, it is conceivable that work focusing on treatment and prevention of dental caries by VGS could have some role in the management and prevention of IE.

Clinical Presentation

Predisposing Cardiac Conditions

Predisposing conditions to IE have evolved over the decades since early clinical series were reported. More recently, the International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS)[7] has detailed the clinical presentation in 2781 patients with definite IE. Native valve IE was predominant (72%), followed by prosthetic valve endocarditis (21%) and pacemaker or implantable cardioverter-defibrillator (ICD) IE (7%). Consistent with numerous earlier series, this international cohort study found that IE manifests with definite vegetations most frequently in the mitral valve position (41%), followed by the aortic valve position (38%), whereas the tricuspid (12%) and pulmonary (1%) valves were much less frequently involved.[7]

Preexisting valvular regurgitant lesions are much more prone to infection than stenotic lesions. It has been suggested that the incidence of IE is directly related to the impact of pressure on the closed valve, with shear stress disruption of the valvular endothelium in the vicinity of the egressing regurgitant jet. In the presence of the Venturi effect, circulating organisms are deposited within the high-velocity, lowered-pressure eddy zones of the regurgitant orifice of the receiving chamber, leading to the typical localization of vegetations on the upstream aspect of the infected valve.

Mitral regurgitation associated with degenerative mitral valve prolapse (MVP), particularly with advanced myxomatous leaflet thickening, is the most common predisposing condition for IE and is far more common than rheumatic mitral valve disease.[7] A recent population-based study demonstrated that an increased incidence of IE in patients with MVP was associated with either preexisting mitral regurgitation of at least moderate severity, or flail mitral leaflet.[8] Functional mitral regurgitation, associated with left ventricular (LV) remodeling causing malcoaptation of intrinsically normal mitral leaflets in a low-pressure, low-cardiac-output state (**see Chapter 69**), is quite uncommonly complicated by IE. The second most common native valve lesion predisposing to IE is aortic regurgitation. The risk of IE in patients with bicuspid aortic valve (BAV) is low (**see Chapter 68**), with an incidence of approximately 2% during follow-up periods ranging from 9 to 20 years.[9,10] BAV, however, is relatively common (16% to 43%) in case series of confirmed aortic valve IE,[11,12] is associated with a high incidence of periannular complications of IE (50% to 64%), and is a strong independent predictor of perivalvular extension of infection.[11] In patients older than 65 years of age, nonrheumatic aortic stenosis is seen as the aortic valve lesion in IE at a rate almost three times that of younger patients (28% and 10%, respectively).[13] Structurally normal valves may also be affected in IE, with risk associations of advanced age, renal failure requiring hemodialysis, and infection caused by *S. aureus* or enterococci.[14]

Congenital heart disease (**see Chapter 75**), other than BAV disease, is a predisposing condition to IE in approximately 5% to 12% of cases.[1,7,15] Unrepaired ventricular septal defects are the most frequent congenital heart disease lesions associated with IE, followed by ventricular outflow tract obstructive lesions, such as with tetralogy of Fallot.[16] Any highly turbulent shunt lesion can predispose affected

patients to IE, as can the presence of prosthetic material employed for palliative shunts, conduits, or shunt closures, particularly if a residual shunt is present after surgical intervention. Low-velocity, low-turbulence shunt lesions, such as secundum atrial septal defect, are much less prone to endocardial disruption and are associated with a very low incidence of IE.[16]

Additional conditions contribute to the anatomic cardiac lesions in the predisposition to risk of IE. These include a history of previous IE, the presence of chronic intravenous (IV) access, IV drug abuse, and indwelling endocavitary devices. Predisposing general medical conditions include diabetes mellitus, underlying malignancy, renal failure requiring hemodialysis, and chronic immunosuppressive therapy.[7,15] A history of an invasive or dental procedure can be identified in approximately 25% of patients within 60 days of clinical presentation with IE.[7] A history of cardiac disease may be present in approximately 50% to 65% of patients.[17] Superimposed and of mounting concern is the increasing frequency of health care–associated IE. In a report from the ICE-PCS investigators,[18] 19% of the cases in a study cohort of 1622 patients with IE were considered to be nosocomial (defined as related to hospitalization for more than 2 days before presentation with IE). An additional 16% of cases were related to non-nosocomial health care (e.g., outpatient hemodialysis, IV chemotherapy, wound care, or residence in a long-term care facility) received within 30 days of onset of symptoms of IE.

A recent study demonstrated that a portal of pathogen entry responsible for IE could be identified in almost 75% of patients if a systematic search was pursued.[19] In this study, the most common entry site was cutaneous (40%), associated with health care delivery, such as vascular access or a surgical site, or sites used for intravenous drug abuse. The second most common (29%) portal of entry was oral/dental, with an active infection implicated much more frequently than a prior dental procedure. Thirdly, a GI source was detected in 23% of patients, in the majority with colonic neoplasm, or less commonly, ulcerative or inflammatory disease. Far less (<5%) frequently, a GU, otorhinolaryngologic, or respiratory portal of entry was detected.[19]

Symptoms

The presentation of IE encompasses a broad spectrum of symptoms and is influenced by multiple contributing factors. These factors would include (1) the virulence of the infecting organism and persistence of bacteremia, (2) extent of local tissue destruction of the involved valve(s) and hemodynamic sequelae, (3) perivalvular extension of infection, (4) septic embolization to any organ in the systemic arterial circulation or to the lungs, as in the case of right-sided IE, and (5) the consequences of circulating immune complexes and systemic immunopathologic factors.

The diverse potential symptoms associated with IE are listed in **Table 73.1**. The frequency of symptoms has been approximated from numerous clinical series in both the older and more contemporary literature. Fever (>38°C) is the most common presenting symptom in up to 95% of patients, but may be absent in up to 20% of cases, particularly in elderly persons,[13] the immunocompromised, patients treated with previous empiric antibiotic therapy, or patients with CIED infections.[20,21] Fever defervescence usually occurs within 5 to 7 days of appropriate antibiotic therapy. Persistence of fever may indicate progressive infection with perivalvular extension such as abscess, septic embolization, an extracardiac site of infection (native or prosthetic), infected indwelling catheters or devices, inadequate antibiotic treatment of a resistant organism, or even an adverse reaction to the antibiotic therapy itself.

TABLE 73.1

Symptoms in Infective Endocarditis

SYMPTOM	PATIENTS AFFECTED (%)
Fever	80-95
Chills	40-70
Weakness	40-50
Malaise	20-40
Sweats	20-40
Anorexia	20-40
Headache	20-40
Dyspnea	20-40
Cough	20-30
Weight loss	20-30
Myalgia/arthralgia	10-30
Stroke	10-20
Confusion/delirium	10-20
Nausea/vomiting	10-20
Edema	5-15
Chest pain	5-15
Abdominal pain	5-15
Hemoptysis	5-10
Back pain	5-10

Other nonspecific constitutional symptoms of infection, such as chills, sweats, cough, headache, malaise, nausea, myalgias, and arthralgias, are less common accompanying symptoms and may be noted in approximately 20% to 40% of patients. In more protracted subacute cases of IE, symptoms and signs such as anorexia, weight loss, weakness, arthralgias, and abdominal pain may also occur in 5% to 30% of patients, misleading the clinician to pursue incorrect diagnoses such as malignancy, connective tissue disease, or other chronic infection or systemic inflammatory disorders.

Symptoms of dyspnea are important to recognize because they may indicate a severe hemodynamic lesion, usually left-sided valvular regurgitation. Associated symptoms of orthopnea and paroxysmal nocturnal dyspnea herald the onset of heart failure (HF). Early recognition of HF symptoms is imperative because it is the most common complication of IE, has the greatest impact on prognosis, is the most frequent indication for surgical intervention, and is the most important predictor of poor outcome with surgical therapy for IE.[22] HF complicates the course of approximately 30% to 50% of patients with IE,[7,15,23,24] and even with early surgical intervention, still doubles in-hospital mortality to almost 25%.[24]

A variety of chest pain syndromes can accompany IE. Pleuritic chest pain may result from septic pulmonary embolization and infarction complicating tricuspid IE. Much less common is angina pectoris related to embolization of vegetation fragments into the coronary circulation, which complicates IE in approximately 1% of the cases. Musculoskeletal chest symptoms related to systemic infection or superimposed infectious pneumonitis also would be in the differential diagnosis.

Physical Examination

Potential findings on physical examination are delineated in **Table 73.2**. These data are approximated from both older and more recently reported clinical series.[7,15,18,22-24] A definite murmur is audible in at least 80% of patients on presentation, particularly with left-sided IE. In the large ICE-PCS collaboration, the murmur was new in almost 50% of the patients.[7] The same cohort study found that worsening of a preexisting murmur occurred in 20% of cases. The presence of a new heart murmur also is noted more frequently in patients with IE complicated by HF,[22] and an S_3 gallop and pulmonary rales would further substantiate this diagnosis. Murmurs are detected in less than half of patients with IE complicating an implanted cardiac device[20] and are infrequently heard in patients with right-sided IE. Heart murmurs associated with acute IE complicated by extensive left-sided valvular destruction with acute, severe

regurgitation may also be deceptively unimpressive because of the nature of the decompensated hemodynamics in these unstable patients. Precipitous HF, pulmonary edema, and cardiogenic shock are most often associated with severe acute aortic regurgitation associated with IE, less so by severe acute mitral regurgitation. Severe tricuspid regurgitation, even as an acute complication of IE, is much better tolerated.

TABLE 73.2

Physical Findings in Infective Endocarditis

FINDING	PATIENTS AFFECTED (%)
Fever	80-90
Heart murmur	75-85
New murmur	10-50
Changing murmur	5-20
Central neurologic abnormality	20-40
Splenomegaly	10-40
Petechiae/conjunctival hemorrhage	10-40
Splinter hemorrhages	5-15
Janeway lesions	5-10
Osler nodes	3-10
Retinal lesion or Roth spot	2-10

A central neurologic abnormality usually is identified, and focal deficits consistent with stroke may be detected in 10% to 20% of patients[7,22] (**see Chapter 65**). In subacute, indolent IE, an acute stroke typically is the event that prompts the patient to seek medical attention. Most frequently, the stroke is cardioembolic in nature but may infrequently result from complications of intracranial cerebrovascular mycotic aneurysm, such as hemorrhagic rupture. Seizures, visual deficits, cranial nerve deficits, subarachnoid hemorrhage, and toxic encephalopathy are other potential neurologic complications of IE. The development of neurologic deterioration during the course of IE is associated with significantly increased mortality.

Abdominal examination may elicit nonspecific findings of tenderness and discomfort, particularly in the left upper quadrant, suggestive of splenic embolization and infarction, particularly if complicated by splenic abscess. The spleen is a common site of septic embolization. This most often is not identified by localized symptoms or findings but is discovered incidentally on computed tomography (CT) or using other imaging techniques. Splenomegaly usually is associated with a more protracted course of subacute IE and generally is reported in approximately 10% of patients in more recent clinical series in which the diagnosis is established earlier in the course of the disease.[7,15,18]

As a result of advances leading to earlier diagnosis and therapy, the classic peripheral manifestations of IE are now infrequently observed. Petechiae are the most common, occurring on the conjunctivae, oral mucosa, or extremities. Janeway lesions are painless hemorrhagic macules with a predilection for the soles or palms and are sequelae of peripheral septic embolization, most often associated with staphylococcal IE. Splinter subungual hemorrhages also are painless, dark-red linear lesions in the proximal nailbed and may coalesce. Brown distal splinter lesions at the tips of the nails are quite common in patients who perform manual labor and are caused by trauma, not infection. *Osler nodes* are painful, erythematous, nodular lesions usually located in the pads of the fingers and toes and are the result of immune complex deposition and focal vasculitis. *Roth spots* are retinal hemorrhages with a pale center of coagulated fibrin and also are related to immune complex–mediated vasculitis secondary to IE. An immune complex–mediated diffuse glomerulonephritis rarely may be associated with these findings. Both Osler nodes and Roth spots can be observed with other disorders, such as systemic lupus erythematosus (SLE), leukemia, and nonbacterial endocarditis. Aside from petechiae and conjunctival

hemorrhage, these peripheral findings were detected in less than 10% of patients in the recent ICE-PCS cohort.[7] A recent multicenter prospective cohort study of 1804 patients with IE confirmed similar results as pertains to the spectrum of clinical presentations and physical examination findings.[25]

Diagnosis

The protean clinical presentations and manifestations of IE encompass a broad differential diagnosis in the patient presenting with fever without a readily apparent cause. Other primary cardiac diagnoses that may potentially mimic IE include acute rheumatic fever, left atrial myxoma, antiphospholipid antibody syndrome, and nonbacterial thrombotic or marantic endocarditis. A number of connective tissue disorders, including SLE, reactive arthritis, polymyalgia rheumatica, and vasculitides, may be additional diagnostic considerations in select patients, as well as many other serious syndromes of infectious disease. The index of clinical suspicion for IE incrementally increases in the presence of predisposing cardiac conditions, new or changing murmurs, bloodstream infection, clinical evidence of embolic phenomena, and evolving HF or certain other hemodynamic abnormalities.

In 1994, Durack and associates proposed diagnostic criteria, subsequently known as the Duke criteria, to establish the diagnosis of definite or possible IE, and also to reject the diagnosis of IE. These criteria incorporated direct histopathologic evidence of IE or major clinical criteria, namely, blood culture positivity and evidence of endocardial involvement, supplemented by minor clinical criteria, for the definite diagnosis of IE. Thereafter, multiple clinical series using the Duke criteria for the diagnosis of IE reported the sensitivity to be in the range of 80%, with both specificity and negative predictive value (NPV) exceeding 90%.[6,22] Recognizing the increasing impact of *S. aureus* IE, the potential for IE associated with Q fever *Coxiella burnetii* infection, and the evolving role of transesophageal echocardiography (TEE) in the diagnosis of IE, Li and colleagues (see Classic References) proposed the modified Duke criteria (**Table 73.3**). *Major clinical criteria* include (1) blood culture positivity for bacteria typically associated with IE, or persistently positive cultures for organisms uncommonly associated with IE, or a blood culture or serology clearly positive for *C. burnetii* and (2) evidence of endocardial involvement by echocardiographic imaging demonstrating vegetation, significantly new valvular regurgitation, dehiscence of a prosthetic valve, or findings consistent with perivalvular extension of infection, such as abscess. *Minor clinical criteria* include (1) predisposing cardiac conditions or IV drug use; (2) persistent fever with temperatures greater than 38°C without an alternative explanation; (3) vascular phenomena such as systemic or pulmonary embolism, mycotic aneurysm, or intracranial or cutaneous hemorrhagic lesions; (4) immunologic phenomena such as Osler nodes, Roth spots, or glomerulonephritis; and (5) positive blood culture status not meeting major criteria or serologic evidence of active infection with an organism that could be associated with IE. By this diagnostic classification, a *definite* clinical diagnosis of IE is established in the presence of (a) two major criteria or (b) one major and three minor criteria, or (c) five minor criteria. A *possible* clinical diagnosis of IE is appropriate in the presence of (a) one major and one minor criterion or (b) three minor criteria. The diagnosis of IE is *rejected* if clinical evaluation (a) does not meet criteria for possible IE or (b) reveals complete resolution of a suspected IE syndrome or absence of anatomic evidence for IE on a course of antibiotic therapy for 4 days or less, or if (c) an alternative diagnosis explaining the initial presentation is confirmed.

TABLE 73.3

Definition of Infective Endocarditis (IE): Modified Duke Criteria

Definite Infective Endocarditis
Pathologic Criteria
• Microorganisms demonstrated by results of cultures or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; *or* • Pathologic lesions; vegetation, or intracardiac abscess confirmed by results of histologic examination showing active endocarditis
Clinical Criteria
• 2 major criteria, *or* • 1 major criterion and 3 minor criteria, *or* • 5 minor criteria
Possible Infective Endocarditis
• 1 major criterion and 1 minor criterion, *or* • 3 minor criteria
Rejected Diagnosis of Infective Endocarditis
• Firm alternate diagnosis explaining evidence of suspected IE, *or* • Resolution of IE syndrome with antibiotic therapy for ≤4 days, *or* • No evidence of IE at surgery or autopsy, on antibiotic therapy for ≤4 days, *or* • Does not meet criteria for possible IE
Definition of Terms Used in the Modified Duke Criteria for Diagnosis of Infective Endocarditis
Major Criteria
• Blood culture findings positive for IE Typical microorganisms consistent with IE from two separate blood cultures: • Viridans streptococci, *Streptococcus gallolyticus* (formerly known as *S. bovis*), *Staphylococcus aureus*, HACEK group, *or* • Community-acquired enterococci, in the absence of a primary focus, *or* Microorganisms consistent with IE from persistently positive blood culture findings, defined as: • ≥2 positive culture findings of blood samples drawn >12 hours apart, *or* • 3 or most of ≥4 separate culture findings of blood (with first and last sample drawn ≥1 hour apart) • Single positive blood culture for *Coxiella burnetii* or anti–phase I IgG titer ≥1 : 800 • Evidence of endocardial involvement Echocardiographic findings positive for IE (TEE recommended in patients with prosthetic valves, rated at least possible IE by clinical criteria or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows: • Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, *or* • Abscess, *or* • New partial dehiscence of prosthetic valve New valvular regurgitation; worsening or changing of preexisting murmur not sufficient
Minor Criteria
• Predisposition, predisposing heart condition, or intravenous drug use • Fever—temperature >38°C • Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions • Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor • Microbiologic evidence: positive blood culture finding but does not meet a major criterion as noted above (excludes single positive culture findings for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organism consistent with IE

TEE, Transesophageal echocardiography; *TTE,* transthoracic echocardiography.

Modified from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633.

Since their publication in 2000, the modified Duke criteria have been validated in subsequent investigations of diagnostic accuracy (confirmed to be high) and also clinical and epidemiologic utility and have been endorsed by guideline documents pertinent to the evaluation and management of the patient with IE.[6,22] In view of the vast heterogeneity of the clinical presentations of IE, the modified Duke criteria must always be used in combination with circumspect clinical judgment.

Basic Laboratory Testing

Microbiology

The microbiology and epidemiology of the pathogens associated with IE are detailed earlier in this chapter. As determined from data summarized from contemporary cohort series,[7,18,26-29] the organisms identified in patients with IE in a variety of clinical settings are listed in **Table 73.4**. In community-acquired IE, viridans group streptococci remain the most frequently isolated organism, followed closely by *S. aureus*, which is the predominant organism implicated in health care–associated IE, accounting for more than 40% of cases both in and out of the hospital environment. A defined portal of entry, such as an

intravascular catheter or tissue disruption from a recent surgical or dental procedure, can be implicated in 25% to 67% of such cases.[15,18,26] MRSA IE is much more common in health care–associated than in community-acquired IE (47% versus 12%, respectively).[18] In IE associated with IV drug abuse, *S. aureus* accounts for almost 70% of cases.[7]

TABLE 73.4
Microbiology of Infective Endocarditis (IE)

ORGANISM	NATIVE VALVE				PROSTHETIC VALVE	
	Health Care–Associated IE (%)					
	Community-Acquired IE (%) (*n* = 1201)[19,26]	Nosocomial (*n* = 370)[18,26]	Nonnosocomial (*n* = 254)[18]	Intravenous Drug Users with IE (%) (*n* = 237)[7]	Early IE (%) (*n* = 140)[27-29]	Late IE (%) (*n* = 390)[27,29]
Staphylococcus aureus	21	45	42	68	34	19
Coagulase-negative staphylococci	6	12	15	3	28	20
Enterococcus species	10	14	16	5	10	13
Viridans group streptococci	26	10	6	10	1	11
*Streptococcus gallolyticus**	10	3	3	1	1	7
HACEK	3	0	0	0	0	2
Fungi	0	2	2	1	6	3
Other	13	7	10	7	6	15
Negative blood culture	11	7	6	5	14	10

*Formerly *Streptococcus bovis.*

HACEK, *Haemophilus* spp., other than *H. influenzae*; *Aggregatibacter actinomycetemcomitans* [formerly *Actinobacillus actinomycetemcomitans*], *Aggregatibacter aphrophilus* [formerly *Haemophilus aphrophilus*]; *Cardiobacterium hominis*; *Eikenella corrodens*; *Kingella kingae* and *K. denitrificans.*

In patients with prosthetic valves (**see Chapter 71**), early prosthetic valve endocarditis has been defined as occurring as early as 60 days or less[27] up to 1 year[22,28,29] after surgery. *S. aureus* also is the leading pathogen in early prosthetic valve endocarditis (PVE), accounting for approximately 35% of cases, of which approximately one fourth are MRSA,[27] followed closely by coagulase-negative staphylococci. Streptococcal early PVE is unusual. Late PVE is caused less often by staphylococci, which nevertheless are still the most common infecting organism, and a higher occurrence of infections with both VGS and *Streptococcus gallolyticus* (formerly *S. bovis*) has been documented. As with community-acquired native valve IE, enterococcal infections account for approximately 10% of cases of both early and late PVE.

Negative blood culture results are observed in approximately 5% to 15% of the cases for both native and prosthetic valve IE. The most common cause for this discrepancy is the administration of antibiotic therapy before blood culture samples are drawn, as noted previously, and often such antibiotic therapy is directed empirically toward poorly defined symptoms of infection well before IE is considered. In the large ICE-PCS, 62% of patients with culture-negative IE had received antibiotic therapy within 7 days of obtaining the initial blood culture.[7] Other reasons for blood culture negativity would include IE caused by fastidious organisms or unusual pathogens such as *Bartonella* or *Legionella* spp., *C. burnetii*, or fungi. Rapid detection of pathogens associated with IE by polymerase chain reaction (PCR) techniques may become a reliable alternative to standard blood culture techniques in such cases.[30]

Other Blood Testing

The complete blood count often is abnormal in IE. In patients with subacute IE, a normochromic normocytic anemia of variable severity is detected in a majority of patients, often with low serum iron and total iron-binding capacity. Even with the systemic infection of IE, a leukocytosis with a left differential shift may be detected in only 50% to 60% of patients[23] and is more common with acute than with subacute IE. Leukopenia also may infrequently occur with subacute IE and usually is associated with splenomegaly. Thrombocytopenia may occur in approximately 10% of patients and has been found to be a predictor of early adverse outcome in IE. Sy and colleagues[31] reported a hazard ratio (HR) of approximately 1.13 for each 20×10^9/L decrement in the platelet count as a multivariate predictor of mortality from days 1 to 15 after presentation with IE.[31]

The erythrocyte sedimentation rate (ESR) usually is elevated in patients with IE, and in ICE-PCS, was elevated in 61% of patients. This large cohort study found that an elevated ESR was independently associated with a decreased risk of in-hospital death, presumably because of an association with subacute IE with a more indolent course.[7] The same study found that the C-reactive protein (CRP) also was elevated in approximately 60% of patients, whereas the rheumatoid factor concentration was abnormal in 5%[7]—the latter usually a feature of protracted subacute IE, not acute IE. Inclusion of ESR and CRP in the minor modified Duke criteria for the diagnosis of IE has been proposed, but is not endorsed by current guideline recommedations.[6]

Procalcitonin (PCT) is another protein that rises in response to a proinflammatory stimulus, particularly with severe bacterial infection. A meta-analysis of six studies, including 1006 patients with suspected IE, found PCT to be only 64% sensitive and 73% specific for the diagnosis of IE, and was less accurate than CRP.[32] PCT and other bacteremia-activated markers, such as cellular and vascular adhesion molecules, are currently not recommended as routine biomarkers for the diagnosis of IE.[33]

A new elevation in serum creatinine occurs in 10% to 30% of patients with IE[22] and may be related to multifactorial reasons including renal hypoperfusion from severe sepsis or HF, embolic renal infarction, immune complex–mediated glomerulonephritis, and toxicity from either antibiotic therapy or contrast agents used for imaging. Renal dysfunction developing within the first 8 days of presentation is independently predictive of early IE mortality, with HR of 1.13 per incremental increase in serum creatinine of 0.23 mg/dL,[31] and persistent serum creatinine elevation to greater than 2 mg/dL is predictive of 2-year mortality.[25] Urinalysis usually demonstrates hematuria and proteinuria. In cases of immune complex glomerulonephritis, red blood cell casts are evident, associated with depressed serum complement levels.

Limited studies conducted with small numbers of patients have assessed the prognostic value of cardiac biomarkers in IE. The cardiac troponins may be elevated from ventricular wall stress in HF, myocardial injury with myocardial abscess or embolic infarction, or septicemia alone. An increase in troponin I level to greater than 0.4 ng/mL significantly increases the risk of in-hospital mortality and need for early valve replacement.[34] A subset analysis of ICE-PCS demonstrated that in patients with IE, a troponin T level of 0.08 ng/mL or higher was associated with increased risk of cardiac abscess, central nervous system (CNS) events, and death IE (see Classic References, Stancoven). An elevation of the B-type natriuretic peptide (BNP) level to 400 pg/mL or higher also has been associated with a fourfold risk of the same three complications of IE, even with exclusion of patients with LV dysfunction or severe left-sided valve regurgitation.[35] In another study, elevation of the NT-proBNP level to 1500 pg/mL or higher at hospital admission was an independent predictor of need for surgical intervention or death within 30 days.[36]

Electrocardiogram

The 12-lead electrocardiogram (ECG) usually demonstrates nonspecific findings in patients with uncomplicated IE. Because of the close proximity of the atrioventricular node and proximal intraventricular conduction system to the aortic valve and root, perivalvular extension of infection from this location is the most common cause of new atrioventricular block (AVB) of any degree or bundle branch block (BBB). With perivalvular extension of infection, the incidence of AVB ranges from 10% to 20%, whereas new BBB occurs in approximately 3%.[18,28] The occurrence of a new conduction abnormality also is a multivariate risk predictor for death associated with IE.[18] More uncommonly, perivalvular extension complicating aortic valve IE may compromise proximal coronary artery patency, or emboli from aortic valve vegetations may cause damage, resulting in ischemic ECG changes or even ST-segment elevation acute coronary syndromes.[22] Other atrial and ventricular arrhythmias may potentially complicate structural or hemodynamic complications of IE. In a recent investigation that included 507 patients with left-sided native valve IE, new-onset atrial fibrillation was independently associated with HF and in-hospital mortality.[37]

Imaging

Imaging for Diagnosis of Infective Endocarditis

With use of the modified Duke criteria, a major clinical criterion for the diagnosis of IE is the demonstration of endocardial involvement with vegetations, perivalvular extension of infection, or evidence of disruption of the integrity of either native or prosthetic valves (**see Table 73.3**). Over the past several decades, echocardiography has been established as the imaging modality of choice for this purpose (**see Chapter 14**). Using early-generation imaging systems, initial studies reported the sensitivity of transthoracic echocardiography (TTE) to be in the range of 40% to 60% for the detection of native valvular vegetations, and substantially less for prosthetic valve vegetations.[38] With evolving advances in harmonic imaging and numerous other techniques to improve spatial image resolution, the sensitivity of current TTE imaging techniques for detection of native valve IE recently has been shown to be 82% and as high as 89% if high-quality TTE images are available (**Fig. 73.1; see also Fig. 14.77A**).[39] The specificity for TTE in the diagnosis of IE has been reported to be in the range of 70% to 90%.[24,38-40]

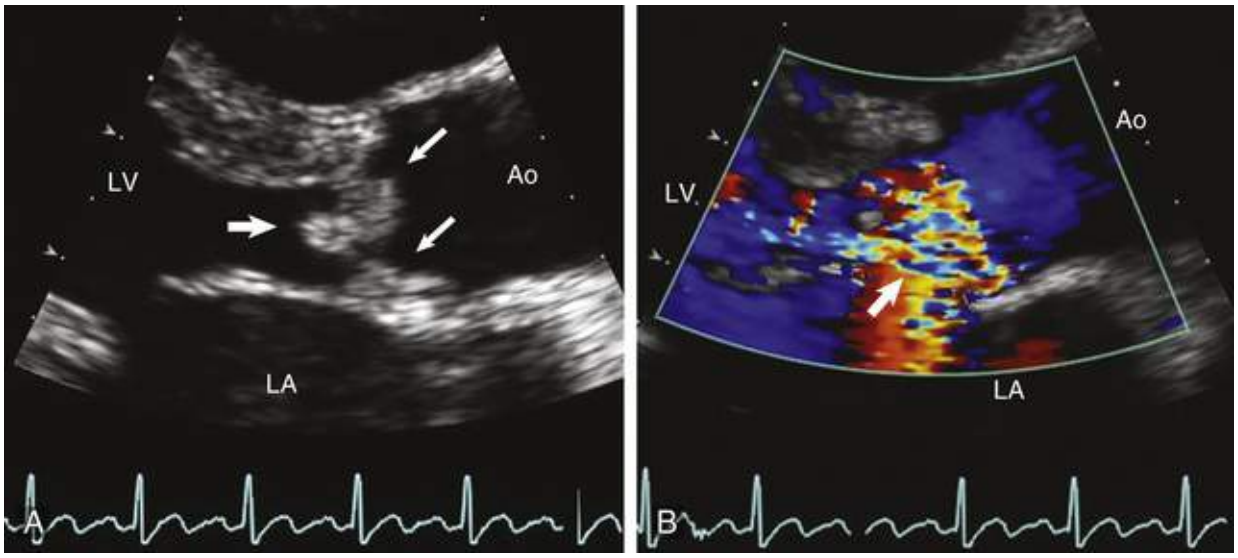

FIGURE 73.1 Infective endocarditis of the native aortic valve. **A,** Transthoracic echocardiography shows vegetations (*small arrows*) attached to the left ventricular aspects of the valve cusps and prolapsing into the left ventricular outflow tract (*large arrow*) during diastole. **B,** Severe aortic regurgitation (*arrow*) is shown by color Doppler. *Ao,* Ascending aorta; *LA,* left atrium; *LV,* left ventricle.

TEE circumvents multiple potential impediments to TTE imaging, such as body habitus, pulmonary disease, and other sources of acoustic interference between the chest wall and heart. Owing to much closer proximity of the transducer to the heart, TEE is performed with higher-frequency imaging, greatly enhancing spatial resolution (**Fig. 73.2; see also Fig. 14.77B**). With numerous imaging projections available, multiplane two-dimensional and three-dimensional TEE can characterize vegetations with a resolution size of approaching 2 to 3 mm, with sensitivity in the range of 90% to 100% and specificity exceeding 90%.[38-41] PVE, characterized by a lower incidence of valvular vegetations (60 to 70%) and higher incidence of periannular infection and associated complications (30 to 50%), is difficult to detect with TTE, generally with a sensitivity of less than 50%.[22] Valvular vegetations have been more frequently identified with IE involving transcatheter-implanted aortic bioprostheses (**see Chapter 72**), with perivalvular complications less common than for surgically implanted prostheses.[42,43] With sensitivity reported in the range of 80% to 95% and specificity greater than 90%,[24,44] TEE clearly is the imaging procedure of choice for the evaluation of suspected PVE (**Figs. 73.3 and 73.4**).

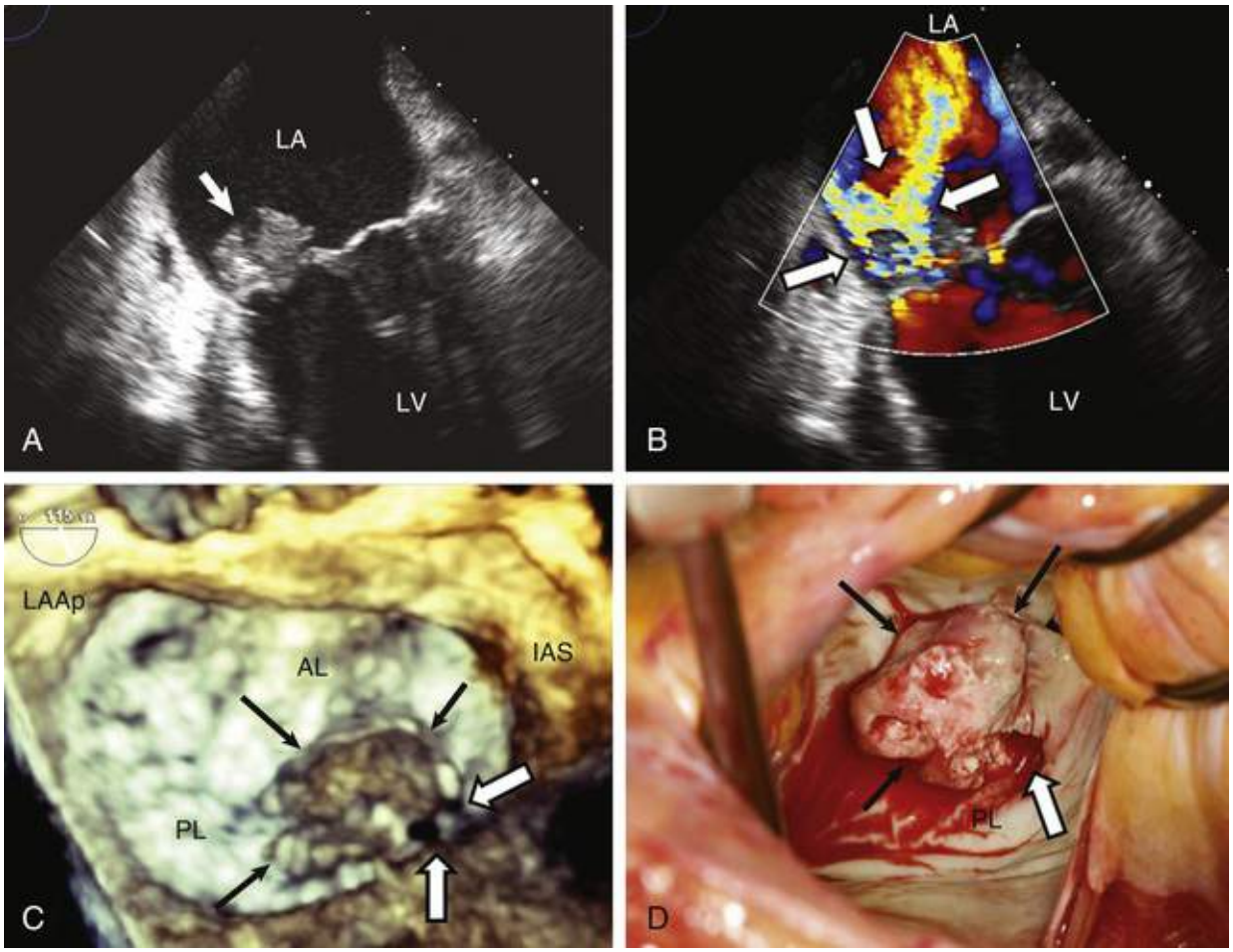

FIGURE 73.2 Infective endocarditis involving the mitral valve. **A,** Transesophageal echocardiography (TEE) image shows a large vegetation (*arrow*) attached to the atrial aspect of the posterior leaflet. **B,** Color Doppler image demonstrates a complex jet of mitral regurgitation (*arrows*) coursing through the body of the posterior mitral leaflet and vegetative mass, consistent with leaflet perforation. **C,** Three-dimensional TEE image of the mitral valve, as viewed from the left atrium (*LA*). Large vegetations (*black arrows*) are attached to the medial aspect of the posterior leaflet (*PL*), with perforation (*white arrows*) at the margin of the posteromedial commissure. **D,** Intraoperative visualization of the mitral valve as viewed from the left atriotomy. The large vegetative mass (*black arrows*) is attached to the posterior leaflet, and the posteromedial perforation (*white arrow*) is confirmed. *AL,* Anterior leaflet; *IAS,* interatrial septum; *LAAp,* left atrial appendage; *LV,* left ventricle.

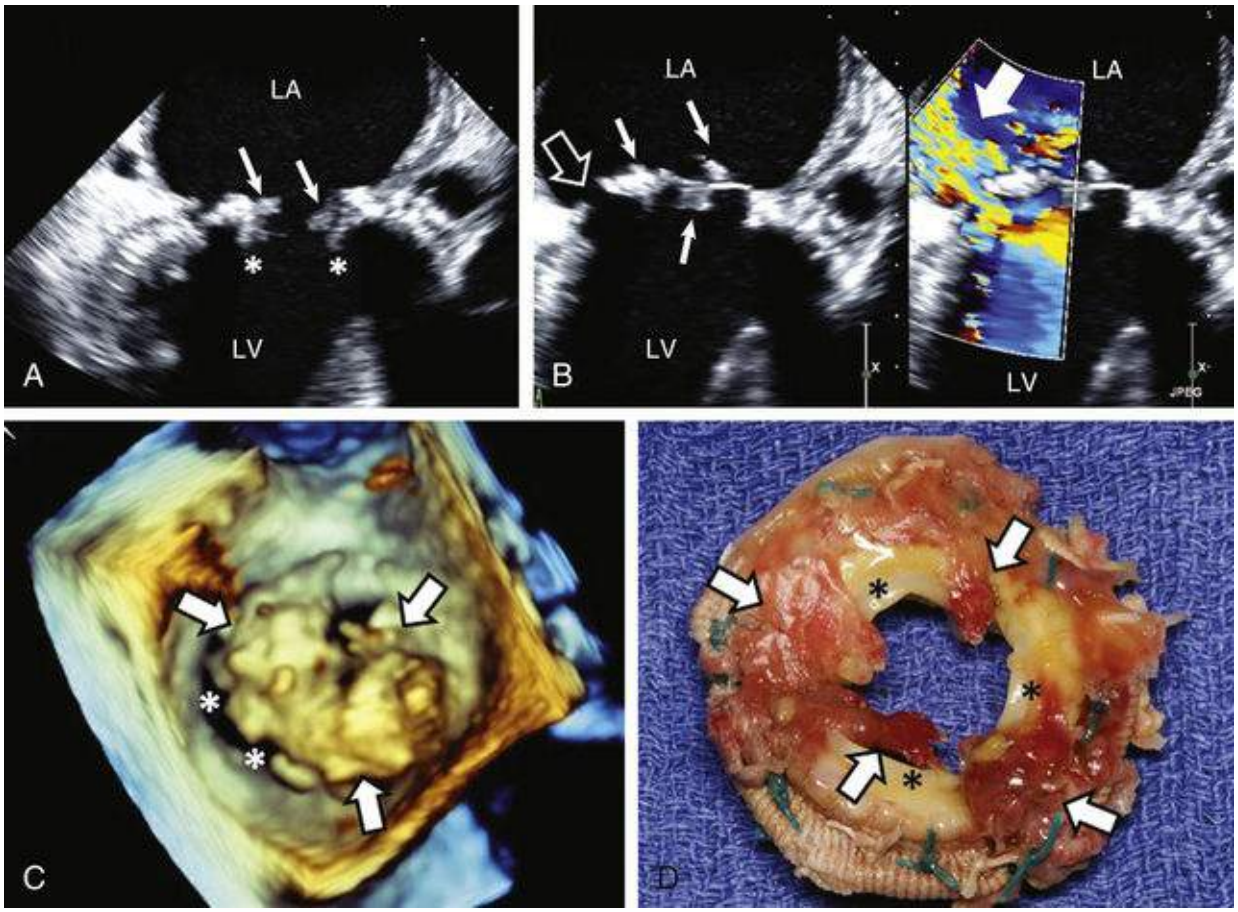

FIGURE 73.3 Infective endocarditis of a mitral bioprosthesis. **A,** On transesophageal echocardiography (TEE), multiple vegetations (*arrows*) can be seen within the inflow orifice of the bioprosthesis (*) during diastole. **B, Left,** During systole, a zone of inferolateral periannular prosthetic dehiscence (*large open arrow*) is evident with rocking motion of the prosthesis. Vegetations are present on the closed bioprosthetic leaflets and prosthetic annulus (*small arrows*). **Right,** Color Doppler image shows severe, eccentric periprosthetic mitral regurgitation (*large white arrow*) emanating from the zone of periannular dehiscence. *LA,* Left atrium; *LV,* Left ventricle. **C,** Three-dimensional TEE view from the left atrium shows an extensive mass of vegetations encompassing the periannular margins (*arrows*), which was not fully appreciated by two-dimensional imaging. A large crescentic zone of periannular dehiscence (*) is well visualized. **D,** The surgically excised mitral bioprosthesis shows extensive vegetations (*arrows*) attached to the atrial aspects of the prosthesis. Pannus ingrowth (*) into the prosthetic orifice also is present.

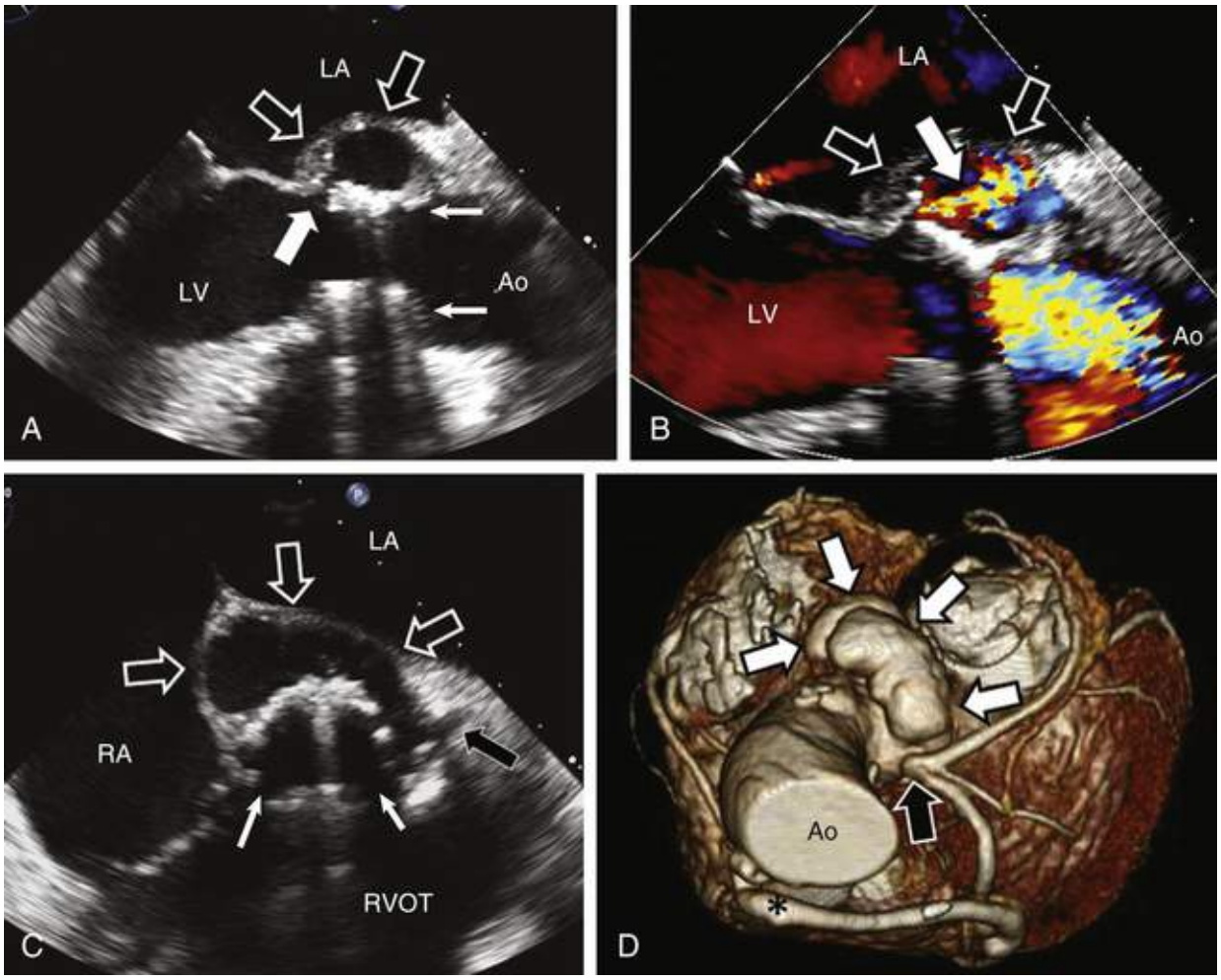

FIGURE 73.4 Periannular extension of infection complicating mechanical aortic prosthetic valve endocarditis. **A,** Transesophageal echocardiography (TEE) image shows a large, mycotic false aneurysm (*open arrows*) within the mitral-aortic intervalvular fibrosa adjacent to the prosthesis (*small arrows*). Communication with the left ventricular outflow tract is evident (*large white arrow*). **B,** Color Doppler image demonstrates flow communication (*arrow*) into the mycotic false aneurysm (*open arrows*) during systole, at which time the larger, color flow signal exits the aortic prosthesis into the ascending aorta (*Ao*). **C,** Short-axis TEE imaging of the mechanical aortic prosthesis (*small arrows*) indicates that the large mycotic false aneurysm (*large open arrows*) extends posteriorly adjacent to the left atrium (*LA*), bulges toward the right atrium (*RA*), and extends to the left main coronary artery (*black arrow*). **D,** Computed tomography with three-dimensional reconstruction, viewed from above and tilted anteriorly to show the posterior aortic root, shows the large posterolateral mycotic false aneurysm (*white arrows*) extending from the aortic root and encroaching upon the left main coronary artery (*black arrow*). A saphenous vein bypass graft (*) to the left anterior descending coronary artery also is seen. *LV,* Left ventricle; *RVOT,* right ventricular outflow tract.

In general, TTE is more readily available, and TTE may be more helpful in suspected cases of tricuspid valve endocarditis and in quantitating hemodynamic function manifested by valvular regurgitation, ventricular dysfunction, and elevated left and right ventricular filling pressures and pulmonary artery pressure. Because TTE and TEE provide complementary information, the most recent AHA guidelines[6] recommend both TTE and TEE be obtained in cases of suspected IE (**Fig. 73.5**). Variably mobile echodensities may be observed with echocardiography, particularly TEE. A differential diagnosis would include degenerative changes in a native valve, such as Lambl excrescences, endocardial fenestrations, ruptured or retracted chordae, and even acoustic artifacts reflected by calcified tissue. Valvular thickening, myxomatous changes, and sclerotic lesions move in concert with leaflet or cusp motion, without independent mobility of a vegetation, but may be difficult to discern from sessile vegetations. Filamentous valvular strands may be seen on both native and prosthetic valves. Thrombus associated with prosthetic valves may or may not be infected. Valvular neoplasms, such as papillary

fibroelastoma or rarely myxomas, also are included in the differential. Vegetations of IE typically are located on the upstream, lower-pressure side of the regurgitant valve, have soft tissue echocardiographic density (particularly early in the course of infection) and often are multiple and lobulated, with motion independent of the valve structure. Hyperrefractile, discretely nodular, or filamentous echodensities located on the downstream side of the valve are much less likely to represent vegetations associated with IE.

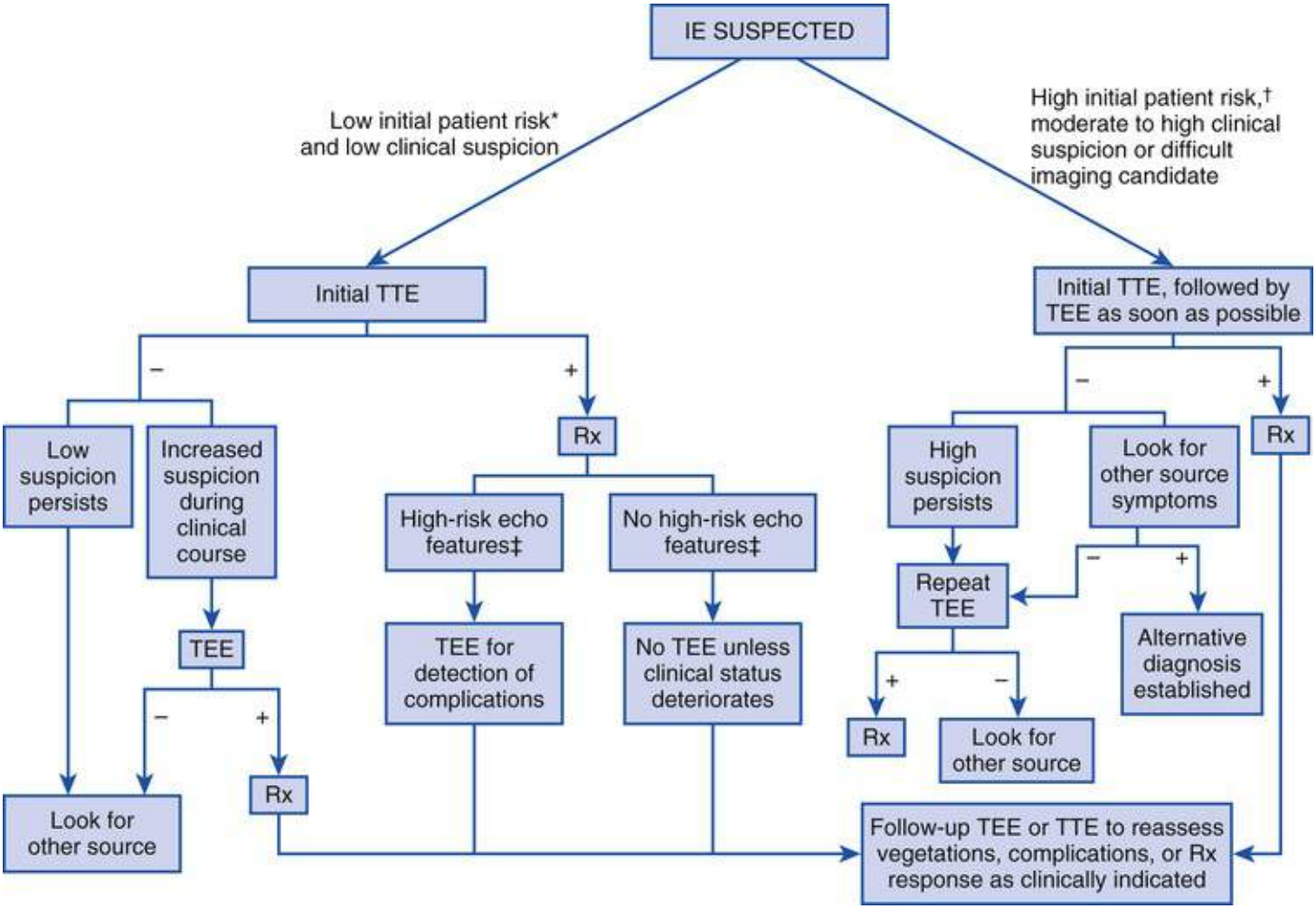

FIGURE 73.5 An approach to the diagnostic use of echocardiography (echo). Rx, Prescription; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography. *For example, a patient with fever and a previously known heart murmur and no other stigmata of infective endocarditis (IE). †High initial patient risks include prosthetic heart valves, many congenital heart diseases, previous endocarditis, new murmur, heart failure, or other stigmata of endocarditis. ‡High-risk echocardiographic features include large or mobile vegetations, valvular insufficiency, suggestion of perivalvular extension, or secondary ventricular dysfunction (see text). (Modified from Baddour LM et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. Ascientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435; and Habib G et al. 2015 ESC guidelines for the management of infective endocarditis. The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology. Eur Heart J 2015;36:3075.)

In addition to confirming the diagnosis of IE, echocardiography provides important information regarding complications of IE that indicate the potential need for surgery (**Table 73.5**).

TABLE 73.5

Echocardiographic Features That Suggest Potential Need for Surgical Intervention

Vegetation
Persistent vegetation after systemic embolization
Anterior mitral valve leaflet vegetation, particularly if it is highly mobile with size >10 mm*
One or more embolic events during the first 2 weeks of antimicrobial therapy*
Increase in vegetation size despite appropriate antimicrobial therapy*†
Valvular Dysfunction
Acute aortic or mitral insufficiency with signs of ventricular failure†
Heart failure unresponsive to medical therapy†
Valve perforation or rupture†
Perivalvular Extension
Valvular dehiscence, rupture, or fistula†
New heart block†‡
Large abscess or extension of abscess despite appropriate antimicrobial therapy†

*Surgery may be required because of risk of embolization.

†Surgery may be required because of heart failure or failure of medical therapy.

‡Echocardiography should not be the primary modality used to detect or monitor heart block.

See text for more complete discussion of indications for surgery based on vegetation characterizations.

Imaging for Delineation of Complications of Endocarditis

Local Valvular Destruction.

Caused most frequently by left-sided valvular regurgitant lesions, heart failure may complicate the course of approximately 30% to 40% of patients with IE, is three times more common in native than in prosthetic valve IE, and is the primary indication for early surgery in at least 50% to 60% of these patients.[22,24,40,45] New York Heart Association (NYHA) Functional Class III or IV HF complicating IE has the greatest impact on both medical and surgical prognosis, with reported in-hospital mortality rates in the range of 55% and 25%, respectively, in ICE-PCS.[45] HF most frequently is associated with aortic valve IE (30%), followed by mitral valve (20%) and tricuspid valve (<10%).[6]

New, moderate to severe valvular regurgitation may be detected by TEE in up to 70% of patients presenting with IE.[15] On imaging with TTE, and particularly with TEE, mechanisms contributing to valvular regurgitation include perforation, prolapse, and flail of the involved cusp or leaflet. Native valve perforations develop in 10% to 30% of patients with IE.[11,15,23,46] Even with TEE, which is much more sensitive than TTE (90% versus 45%), perforations can be difficult to visualize using two-dimensional imaging alone. Three-dimensional TEE imaging can significantly enhance detection of valvular perforations complicating IE (**see Fig. 73.2**).[41] Color Doppler imaging can readily identify a perforation, with color flow convergence entraining into the perforation from the exiting chamber and a regurgitant jet traversing through the body of a cusp or leaflet. Saccular mycotic aneurysms, most often present on the atrial aspect of the mitral valve, may rupture, leaving a large defect in the leaflet. Extensive vegetations may also impede valvular coaptation, leading to regurgitation, or rarely may cause stenosis.

Infectious destruction of left-sided native valvular cusp or leaflet integrity and disruption of the valvular support apparatus can lead to acute severe valvular regurgitation complicated by precipitous HF, pulmonary edema, and hemodynamic instability (**see Chapters 68 and 69**). In addition to identifying the mechanism(s) of regurgitation, echocardiographic imaging typically demonstrates normal LV size and ejection fraction (EF). In acute severe aortic regurgitation, Doppler assessment will demonstrate evidence of rapid elevation of LV diastolic filling pressures with very short aortic regurgitant pressure half-times and a restrictive pattern of mitral inflow. Such hemodynamics are associated with premature

closure of the mitral valve before the onset of systole. In acute severe mitral regurgitation, truncation of the usual parabolic continuous-wave Doppler regurgitant signal indicates late-systolic LV and left atrial (LA) pressure equilibration, consistent with a giant *v* wave noted on LA catheterization. Quantitative Doppler methods are quite useful to confirm the presence of acute severe regurgitation, because qualitative color flow jets may be complex, eccentric, or rapidly dissipating because of the loss of transvalvular pressure gradients.

Perivalvular Extension of Infection.

Perivalvular extension in IE includes the complications of periannular or intramyocardial abscess, mycotic false aneurysm, and fistula. The incidence of perivalvular extension ranges from 10% to almost 30% in native valve IE and at least 30% to 55% in PVE[15,27] (**see Figs. 73.3 and 73.4**). IE involving a transcatheter-implanted aortic bioprosthesis has been reported to have a lower incidence of complications from perivalvular extension of infection, such as abscess (15%), aortic mycotic pseudoaneurysm (4%), or aortoatrial fistula (4%).[42] Earlier series have reported the incidence of perivalvular extension of infection to approach 100% for aortic PVE.[6,22] Independent predictors of perivalvular extension are PVE, aortic valve involvement, and staphylococcal infection (from both coagulase-negative strains and *S. aureus*).[6,22] Periannular abscess has been reported in up to 50% of patients with native bicuspid aortic valve IE (**see Fig. 14.77C**), versus 20% in those with a tricuspid aortic valve.[11] Persistent fever, ongoing bacteremia despite appropriate antibiotic therapy, chest pain, a new heart murmur, recurrent embolism, or HF all should alert the clinician to the possible presence of perivalvular extension. After HF, perivalvular extension of infection is the second most common indication for early surgical intervention for IE, and although surgery clearly confers an early survival benefit,[46] perivalvular extension remains an independent predictor of increased in-hospital and 1-year mortality.[7,22,23,45] In left-sided native valve *S. aureus* IE, the echocardiographic findings of perivalvular extension of infection, such as intracardiac abscess, and LVEF less than 40% have been strong independent predictors of in-hospital early mortality.[47]

It is recognized that the sensitivity of TTE for the diagnosis of perivalvular extension is at best 50%, and even less in PVE. TEE has a reported sensitivity of 80% to 90%, specificities of greater than 90%, with positive predictive value (PPV) and NPV of 85% to 90% for diagnosis of perivalvular extension.[6,40] Although TEE is quite sensitive for the diagnosis of aortic perivalvular extension, mitral annular calcification may obscure small regions of mitral perivalvular extension, particularly in the posterior aspects of the annulus.[48] On echocardiographic imaging, early perivalvular abscess usually appears as a nonhomogeneous, soft tissue, echodense thickening that distorts the margins of normal periannular anatomy.

With IE in the aortic valve position, a high predilection for perivalvular extension of infection to involve the *mitral-aortic intervalvular fibrosa* (MAIF) has been recognized. The MAIF is the fibrous zone of continuity between the noncoronary cusp of the aortic valve and insertion of the anterior mitral valve leaflet. Being one of the least vascular structures of the heart, the MAIF is more susceptible to infection and mycotic false aneurysm formation. On echocardiographic imaging of these false aneurysms, systolic expansion of an echolucent cavity can be appreciated within the infected MAIF (**see Fig. 73.4**), with color Doppler flow communication usually evident from the subvalvular LV outflow tract. Potential complications of MAIF mycotic false aneurysms include fistulous communications into the left atrium or aorta, extension around the aortic root, compression of the proximal left coronary arteries with resultant myocardial ischemia, systemic embolization, and rupture into the pericardial space.[49] Fistulas from aortic perivalvular extension of infection may track into any cardiac chamber and are best identified with TEE

color flow Doppler techniques. Mitral valve IE complicated by perivalvular extension is less common, with much lower frequency of structural and conduction system sequelae. Prosthetic valve dehiscence is another manifestation of perivalvular extension of infection and usually is seen without impressive vegetations on the prosthesis itself (**see Fig. 73.3**). Imaging by TEE demonstrates crescentic defect adjacent to the sewing ring, variable rocking of the prosthesis, and periprosthetic regurgitation.

Cardiac 64-slice CT has been shown to be an accurate alternative imaging procedure for the evaluation of IE and perivalvular extension of infection (**see Chapter 18**). In a small group of patients with suspected IE, cardiac CT was 96% sensitive for the detection of valvular vegetations, identical in this respect to multiplanar TEE, compared with surgery.[50] Both imaging techniques had specificity and PPV/NPV exceeding 95%. Excellent correlation was found between cardiac CT and TEE in the determination of vegetation size and mobility; however, TEE was superior for the detection of small vegetations (≤4 mm) and valvular perforations. The sensitivity of cardiac CT for the detection of perivalvular extension of infection confirmed at surgery was 100%, versus 89% for TEE, and CT provided additional information regarding the extent of perivalvular extension not detected by TEE.[50] Similar findings have been reported in a series of patients with aortic prosthetic valve endocarditis, with good accuracy of 64-slice cardiac CT in the detection of early perivalvular extension of infection (**see Fig. 73.4**), periannular abscess, false aneurysm, and prosthetic valve dehiscence compared with TEE and surgery.[51]

Recently, positron emission tomography (PET)/CT imaging with fluorine 18–fluorodeoxyglucose (^{18}F-FDG) has incrementally improved the diagnostic accuracy in evaluation of suspected PVE, particularly CIED IE, increasing the sensitivity from approximately 60% to 70% with the modified Duke criteria with TEE imaging alone to 87% to 97% with the addition of ^{18}F-FDG PET/CT[52,53] (**see Fig. 16.47**). This resulted primarily from enhanced identification of infection in the tissue spaces adjacent to the prosthetic valve or implanted device, and less from the identification of sites of secondary infection. This imaging technique has been proposed as an additional major Duke criterion for the diagnosis of prosthetic device IE,[52] but because of the current lack of large studies, routine use of ^{18}F-FDG PET/CT has not been endorsed by guideline-writing committees to date.[6,22] Moreover, ^{18}F-FDG PET/CT has not been shown to be of incremental value in the diagnosis of native valve IE.[54]

Embolism.

Embolic events are common early in the course of IE, particularly before the institution of appropriate antibiotic therapy. Over the past two decades, numerous studies have reported an overall incidence of embolic events ranging from 20% to 50%.[6,22] In more recent clinical series, the reported incidence of acute stroke complicating IE ranged from 10% to 23%,[7,13,15,18,23] with rates of 15% to 25% reported for other embolic events not causing stroke.[7,11,13] Both stroke and other embolic events complicating IE occur more frequently in patients younger than 65 years[13] and are adverse predictors of outcome and survival in IE.[6,22] In a multicenter study using admission-screening CT imaging in 384 patients presenting with IE, 26% had one site of embolism, and another 9% had multiple sites of embolism in the following distribution: CNS (38%), spleen (30%), renal (13%), lung (10%), peripheral artery (6%), mesenteric (2%), and coronary (1%). The embolic event was clinically silent in 15% of all patients. The incidence of cerebral embolic events probably is significantly underestimated by clinical assessment. In a study of 130 patients with definite or possible IE by the modified Duke criteria, cerebral magnetic resonance imaging (MRI) found acute ischemic lesions in 52% of patients, whereas only 12% had acute neurologic symptoms.[55] In this study, MRI also demonstrated cerebral microhemorrhages in 57%, other hemorrhagic lesions in 8%, asymptomatic mycotic aneurysms in 8%, and abscesses in 6%. Screening cerebral MRI led

to significant modification of the diagnosis or treatment plan in 28% of the entire study group.[55]

Peripheral embolization with or without metastatic infection also may be detected with PET/CT, and clinically unsuspected lesions of this nature were observed in 28% of patients in one small series.[56] Imaging with PET/CT also is useful in the detection of perivalvular extension of infection, particularly of the aortic root, and for identification of CIED infections.

Numerous studies have examined the ability of echocardiographic characterization of vegetations to predict risk of embolic events in IE. More recent analyses have consistently shown that vegetations more than 10 mm in greatest dimension are independent predictors of embolism, with considerably higher risk with dimensions above 15 mm.[6,40,57-59] Before initiation of appropriate antibiotic therapy, such large vegetations are associated with a greater than 40% risk of a clinically evident or silent embolic event. Pedunculated and highly mobile vegetations also are independently associated with embolic risk.[40] Both vegetation length of more than 10 mm and severe vegetation mobility are multivariate predictors of embolism, even after initiation of antibiotic therapy. Mitral valve vegetations, particularly on the anterior leaflet in native valve IE, are more likely to embolize than those in the aortic position; the embolic risk generally is equivalent in native and in prosthetic valve IE.[6,40,60]

The infecting organism also has an impact on embolic risk. *Staphylococcus aureus* IE has been consistently implicated as an independent risk predictor for embolism; IE from *Streptococcus gallolyticus* and VGS is less implicated.[60] The presence of intracardiac perivalvular abscess is another independent risk for stroke associated with IE.[51]

Prediction of symptomatic embolism in IE has been proposed with the derivation and validation of a risk calculator employing the variables of age, diabetes mellitus, atrial fibrillation, embolism before initiation of antibiotic therapy, vegetation length, and the presence of *S. aureus* infection. This calculator, known as the Embolic Risk French Calculator, is available online. Employing this calculator, a 70-year-old patient with *S. aureus* IE, having all clinical risk variables present and vegetation size greater than 10 mm in length, would have an estimated 7-day embolic risk of 23%. The same-age patient with *S. aureus* IE but no clinical risk variables and vegetation size less than 10 mm would have an estimated 2% 7-day embolic risk.[61]

Over the past several decades, multiple clinical series have shown that the risk of embolism decreases dramatically, generally to less than 10% to 15%, within 1 week after initiation of appropriate antibiotic therapy.[6,22] The occurrence of stroke has been shown to fall to 3% after the first week of antibiotic therapy, with the overall incidence decreasing from 4.82 to 1.71 per 1000 patient-days during the second week of therapy.[60] With this documented response to antibiotic therapy, preemptive surgical intervention for potentially high-embolic-risk vegetations has not been previously advised unless there are recurrent embolic events despite ongoing appropriate antibiotic therapy.[6,22] This position has been challenged by a small study of patients with left-sided vegetations greater than 10 mm in diameter randomized to conventional management versus early surgery (within 48 hours).[62] On admission, almost 30% of each group had evidence of cerebral emboli and had no other indications for urgent surgical intervention. In patients randomized to conventional therapy, recurrent cerebral embolic events occurred in 13%, with an overall embolic event rate of 21% at 6 weeks, compared to a 0% over the same period for the early surgical patients; the in-hospital mortality was 3% for both groups.[62]

Recurrent embolic events or progressive increase in vegetation size despite appropriate antibiotic therapy, especially in the presence of significant perivalvular extension of infection or HF, would constitute clear indications for early surgical intervention.[6,22]

Thus far, no randomized controlled trials (RCTs) support the initiation of either antiplatelet or anticoagulant therapy to decrease embolic risk in IE. A retrospective analysis has suggested a lower

occurrence of embolic events in patients who continue to receive antiplatelet therapy taken before the onset of IE.[63] In a larger prospective cohort analysis, established antiplatelet therapy did not reduce the incidence of cerebrovascular complications associated with IE, but also did not increase the occurrence of hemorrhagic complications.[64] The investigators for the larger analysis reported that previously prescribed warfarin therapy, continued through the clinical course of left-sided native valve IE, was associated with a lower incidence of stroke, transient ischemic attack (TIA), and cerebral infections compared with those not receiving warfarin therapy (6% versus 26%, respectively), with the incidence of hemorrhagic complications being 2% in both groups.[65]

Approach to Echocardiographic Imaging.

Clinical risk assessment of the patient with suspected IE is the first step in deciding which echocardiographic imaging modality to use for evaluation (**Fig. 73.5** and **Table 73.6**). Patients with undifferentiated febrile syndromes, a chronic unchanged murmur, no physical examination findings suggestive of IE, and no high-risk cardiac anatomy (e.g., prosthetic valves or complex congenital heart disease [CHD]) are characterized as being at initially low patient risk with a lower pretest likelihood of IE. High initial patient risk characteristics that present a high pretest probability of IE and likelihood of adverse outcome include clinical findings of a significant new heart murmur, peripheral stigmata of IE, new HF, *S. aureus* bacteremia, and high-risk cardiac anatomy, including the presence of a prosthetic valve or complex CHD.[2,6] Independent risk factors for IE (established in 10% to 15% of cases) in the presence of *S. aureus* bacteremia include community-acquired status, IV drug abuse, significant preexisting native valve disease, intracardiac prosthesis or CIED, prolonged (>72 hours) bacteremia, secondary foci of infection, and embolic event.[66-68]

TABLE 73.6

Use of Echocardiography During Diagnosis and Treatment of Infective Endocarditis (IE)

Early
Echocardiography as soon as possible (<12 hours after initial evaluation) TEE preferred; obtain TTE views of any abnormal findings for later comparison TTE if TEE is not immediately available TTE may be sufficient in small children
Repeat Echocardiography
TEE after positive TTE as soon as possible in patients at high risk for complications TEE 7-10 days after initial TEE if suspicion exists without diagnosis of IE or with worrisome clinical course during early treatment of IE
Intraoperative
Prepump
Identification of vegetations, mechanism of regurgitation, abscesses, fistulas, and pseudoaneurysms
Postpump
Confirmation of successful repair of abnormal findings
Assessment of Residual Valve Dysfunction
Elevated afterload if necessary to avoid underestimating valve insufficiency or presence of residual abnormal flow
Completion of Therapy
Establish new baseline for valve function and morphology and ventricular size and function TTE usually adequate; TEE or review of intraoperative TEE may be needed for complex anatomy to establish new baseline

TEE, Transesophageal echocardiography; *TTE,* transthoracic echocardiography.

As shown in **Fig. 73.5**, patients at low initial risk should undergo TTE. In the absence of significant preexisting native valve disease or any prosthetic or implanted devices, adequate- or better-quality images detecting no vegetations exclude the diagnosis of IE, with NPV of 97% and sensitivity exceeding 90%.[69] With preexisting valve disease, the sensitivity approaches 60%, but with a similar NPV if TTE image quality is adequate.[70] Even with *S. aureus* bacteremia, initial TTE imaging is reasonable in the

absence of the previous risk factors.[6,66-68] If TTE images are limited or inadequate, TEE should be pursued. If TTE detects high-risk findings such as large (>10 mm in diameter) or highly mobile vegetations, suggests the presence of perivalvular extension of infection, or identifies new grade III to IV valvular regurgitation or new LV dysfunction, TEE should be promptly performed for further evaluation. Patients at high risk (e.g., new-onset HF, significant new murmur, clinical stigmata of IE, prior IE, prosthetic heart valves/devices, complex CHD, *S. aureus* bacteremia) should undergo initial imaging with TEE (**Fig. 73.5**), with supplemental TTE for complete semiquantitation of valvular regurgitation and delineation of left- and right-sided hemodynamics and ventricular function. If TEE is not immediately possible or available, TTE should be pursued first to avoid delay in imaging evaluation and diagnosis.

Provided that initial TTE images are of diagnostic quality and are negative for IE, if a low clinical suspicion for IE persists, other diagnoses should be pursued (**Fig. 73.5**). With increased clinical suspicion for IE throughout the patient's clinical course, an initially negative TTE should be followed up with TEE. If the initial TTE is positive for IE but high-risk findings as noted previously are lacking, TEE should not be mandatory, unless the patient is clinically unresponsive to antibiotic therapy or deteriorates during the clinical course. Any high-risk finding on TTE would warrant further evaluation with TEE.

As outlined in **Fig. 73.5**, if the initial TEE is negative for IE and there is diminishing clinical suspicion of IE, other diagnoses should be evaluated. If IE remains high in the differential diagnosis, repeat TEE should be performed in 3 to 5 days, recognizing that NPV of two sequential TEE studies is 98%.[6] After an initial TEE is positive for IE, it should be repeated throughout the patient's course as clinically indicated, to assess response to antibiotic therapy or evaluate clinical or hemodynamic deterioration.

At the completion of antibiotic therapy, repeat echocardiography is indicated to establish a new post-treatment baseline study of valvular morphology, residual vegetations, valvular regurgitation, and other hemodynamic factors and to assess ventricular function (**Table 73.6**). Provided that images are of diagnostic quality, TTE should be adequate for this purpose. With complex anatomy, or if prosthetic valve function remains in question, TEE usually is indicated.

Antimicrobial Therapy

Not only is it important to diagnose IE, but it also is critical that an etiologic diagnosis be obtained to ensure that optimal antimicrobial therapy is provided for attempted cure.[6,71] Because of the rarity of presentation, diagnosis of IE often eludes nonspecialists, which results in the administration of empiric therapy for a variety of more common febrile illnesses. This empiricism can greatly reduce the sensitivity of subsequent blood cultures when the IE diagnosis is eventually considered. Thus, initial empiricism results in a blood culture–negative presentation, which prompts administration of empiric antimicrobial therapy for IE. This scenario is a bane of infectious diseases specialists, who have traditionally cared for patients with IE. The antimicrobial regimen selected for therapy on the basis of the culture-negative state may not be curative. Moreover, the empiric regimen may include drugs, in particular aminoglycosides, that pose toxicity risks that might have been avoided had a pathogen been identified. Ultimately, this could result in a worst-case scenario in which a microbiologic cure is not achieved and irreversible toxicity occurs.

Some of the regimens employed in the treatment of IE are based on clinical trials with small numbers (dozens) of patients. Many of the regimens, however, are based on consensus opinion that is outlined in guidelines promulgated by societies or associations worldwide. Not surprisingly, these guidelines differ in their recommendations, which can be confusing for the practicing clinician.

Several tenets of medical management are important in defining an optimal antimicrobial regimen in

each case of IE. First, consultation with a physician who is experienced in the care of patients with IE is mandatory; this usually involves a specialist trained in infectious diseases. Second, selection and dosing of antimicrobial therapy are based on both pharmacokinetic and pharmacodynamic characteristics of specific drugs and in vitro susceptibility testing results of an isolated pathogen in blood or tissue specimen culture-positive cases. Third, antimicrobial treatment needs to be prolonged (over weeks), high dose, parenteral, and “cidal” in its activity against a patient's isolate. These aspects of medical therapy are necessary primarily because organisms in infected vegetations downregulate their metabolism once a relatively high concentration of organisms accumulate in vegetation tissue, which is an avascular structure.

Streptococci

Viridans Group Streptococci and *Streptococcus Gallolyticus*

Treatment regimens vary, depending on type of valve (native or prosthetic) and whether the streptococcal isolate is penicillin susceptible or not.[6] Regarding the latter issue, the definition of susceptibility to penicillin, as addressed previously, is based on minimum inhibitory concentrations (MICs) that are specific to treatment of the syndrome of IE; *highly penicillin-susceptible* status is defined as that of an isolate with an MIC of 0.12 µg/mL to penicillin. Therapy with either aqueous crystalline penicillin G sodium or ceftriaxone sodium should be microbiologically curative in 98% or more of patients with native valve IE who complete 4 weeks of treatment (**Table 73.7**). Because of the ease of administration of one dose per day of ceftriaxone parenterally, the bulk of therapy is with this agent rather than with intravenously administered aqueous crystalline penicillin G, which requires four to six doses per day. The once-a-day dosing of ceftriaxone sodium has been pivotal in some cases in allowing patients to avoid nursing home placement for multiple doses of antibiotic administration on a daily basis. In these patients the administration of one dose of ceftriaxone sodium each day has been done in a variety of outpatient venues that routinely administer parenteral medications.

TABLE 73.7

Therapy of Native Valve Endocarditis Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and *Streptococcus gallolyticus*

REGIMEN	DOSE* AND ROUTE	DURATION (wk)	STRENGTH OF RECOMMENDATION	COMMENTS
Aqueous crystalline penicillin G sodium	12-18 million U/24 hr IV either continuously or in 4 or 6 equally divided doses	4	Class IIa, LOE: B	Preferred in most patients >65 yr or patients with impairment of eighth cranial nerve function or renal function Ampicillin, 2 g IV every 4 hr, is reasonable alternative to penicillin if a penicillin shortage exists.
or				
Ceftriaxone sodium	2 g/24 hr IV/IM in 1 dose	4	Class IIa, LOE: B	
Aqueous crystalline penicillin G sodium	12-18 million U/24 hr IV either continuously or in 6 equally divided doses	2	Class IIa, LOE: B	Two-week regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 mL/min, impaired eighth cranial nerve function, or *Abiotrophia*, *Granulicatella*, or *Gemella* spp. infection; gentamicin dose should be adjusted to achieve peak serum concentration of 3-4 µg/mL and trough serum concentration of <1 µg/mL when 3 divided doses are used; there are no optimal drug concentrations for single daily dosing.†
or				
Ceftriaxone sodium	2 g/24 hr IV or IM in 1 dose	2	Class IIa, LOE: B	
plus				
Gentamicin sulfate‡	3 mg/kg/24 hr IV or IM in 1 dose	2		
Vancomycin hydrochloride§	30 mg/kg/24 hr IV in 2 equally divided doses	4	Class IIa, LOE: B	Vancomycin therapy is reasonable only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dose should be adjusted to a trough concentration range of 10-15 µg/mL.

*Doses recommended are for patients with normal renal function.

†Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of infective endocarditis (IE) exist.

‡Other potentially nephrotoxic drugs (e.g., nonsteroidal anti-inflammatory drugs) should be used with caution in patients receiving gentamicin therapy. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis caused by viridans group streptococci, as a second option, gentamicin can be administered daily in 3 equally divided doses.

§Vancomycin dosages should be infused during the course of at least 1 hour to reduce the risk of histamine-release "red man" syndrome.

Minimum inhibitory concentration (MIC) is ≤0.12 µg/mL. The subdivisions differ from Clinical and Laboratory Standards Institute–recommended break points that are used to define penicillin susceptibility.

IM, Intramuscularly; *IV,* intravenously; *LOE,* level of evidence.

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. A scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435-86.

Vancomycin is recommended in patients who cannot tolerate penicillin or cephalosporin therapy because of a history of immunoglobulin E (IgE)–mediated allergic reactions (**Table 73.7**). Before the preferred therapies of aqueous crystalline penicillin G or ceftriaxone are abandoned, consultation with an allergy specialist should be obtained, which may include skin testing to confirm that beta-lactam regimens are not a treatment option. Vancomycin should be administered intravenously for 4 weeks with serial, usually weekly monitoring of serum trough levels, if the dose is stable and the renal status is not changing. The desired serum trough level is 10 to 15 µg/mL; serum peak vancomycin levels are not required for treatment.

For selected patients, a 2-week treatment regimen can be used, but this should be based on input from an infectious diseases specialist. The combination regimen includes either aqueous crystalline penicillin G sodium or ceftriaxone sodium plus gentamicin sulfate (**Table 73.7**). The 2-week regimen should be limited to cases of uncomplicated native valve IE caused by VGS or *S. gallolyticus* strains that are highly susceptible to penicillin. The regimen would not be appropriate in patients with underlying renal or eighth

cranial nerve dysfunction. If the ceftriaxone-containing regimen is used, the single daily dose of the drug should be administered immediately before or after gentamicin dosing. No recommended guidelines for monitoring serum gentamicin concentrations are currently available.

Penicillin resistance is divided into two categories for VGS and *S. gallolyticus* infection in patients with native valve IE. In one group, relative resistance to penicillin is defined as a penicillin MIC greater than 0.12 µg/mL, to 0.5 µg/mL or less. In this group, 4 weeks of therapy is recommended with either aqueous crystalline penicillin G or ceftriaxone plus gentamicin once daily for the first 2 weeks of treatment (**Table 73.8**). Vancomycin can be used in patients who are not candidates for beta-lactam therapy. In the other group, penicillin resistance is defined as a penicillin MIC above 0.5 µg/mL. Fortunately, native valve IE due to these penicillin-resistant strains is rarely seen. In patients with these infections, a more aggressive course of therapy is recommended and is the same regimen as that used in the treatment of native valve IE caused by penicillin- and aminoglycoside-susceptible enterococci (**see Table 73.7**). Monotherapy with vancomycin should be administered in patients who are not candidates for the combination regimen.

TABLE 73.8

Therapy of Native Valve Endocarditis Caused by Strains of Viridans Group Streptococci (VGS) and *Streptococcus gallolyticus* Relatively Resistant to Penicillin

REGIMEN	DOSE* AND ROUTE	DURATION (WK)	STRENGTH OF RECOMMENDATION	COMMENTS
Aqueous crystalline penicillin G sodium	24 million U/24 hr IV either continuously or in 4–6 equally divided doses	4	Class IIa, LOE: B	It is reasonable to treat patients with IE caused penicillin-resistant (MIC ≥0.5 µg/mL) VGS strains with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal IE with infectious diseases consultation. (Class IIa, LOE: C) Ampicillin, 2 g IV every 4 hr, is a reasonable alternative to penicillin if a penicillin shortage exists.
plus				
Gentamicin sulfate†	3 mg/kg/24 hr IV or IM in 1 dose	2		Ceftriaxone may be a reasonable alternative treatment option for VGS isolates that are susceptible to ceftriaxone. (Class IIb, LOE: C)
Vancomycin hydrochloride‡	30 mg/kg/24 hr IV in 2 equally divided doses	4	Class IIa, LOE: C	Vancomycin therapy is reasonable only for patients unable to tolerate penicillin or ceftriaxone therapy.

*Doses recommended are for patients with normal renal function.

†**See Table 73.7** for appropriate dose of gentamicin. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis caused by VGS, as a second option, gentamicin can be administered daily in 3 equally divided doses.

‡**See Table 73.7** for appropriate dosage of vancomycin.

Minimum inhibitory concentration (MIC) is >0.12 to <0.5 µg/mL for penicillin. The subdivisions differ from Clinical and Laboratory Standards Institute–recommended break points that are used to define penicillin susceptibility.

IE, Infective endocarditis; *IM,* intramuscularly; *IV,* intravenously *LOE,* level of evidence.

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. A scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435-86.

Patients who have IE involving a prosthetic valve or prosthetic material (e.g., annuloplasty ring) due to VGS or *S. gallolyticus* should receive 6 weeks of antibiotic therapy (**Table 73.9**). In those infected with strains that are highly susceptible to penicillin (MIC <0.12 µg/mL), the addition of gentamicin for the first 2 weeks of either penicillin or ceftriaxone therapy is optional. In patients infected with streptococci that harbor any level of resistance to penicillin (MIC >0.12 µg/mL), combination therapy for 6 weeks is recommended. In patients who do not tolerate beta-lactam therapy, vancomycin as monotherapy should be administered for 6 weeks.

TABLE 73.9

Therapy for Endocarditis of Prosthetic Valves or Other Prosthetic Material Caused by Viridans Group Streptococci (VGS) and *Streptococcus gallolyticus*

REGIMEN	DOSE* AND ROUTE	DURATION (WK)	STRENGTH OF RECOMMENDATION	COMMENTS
Penicillin-Susceptible Strain (≤0.12 μg/mL)				
Aqueous crystalline penicillin G sodium	24 million U/24 hr IV either continuously or in 4-6 equally divided doses	6	Class IIa, LOE: B	Penicillin or ceftriaxone together with gentamicin has not demonstrated superior cure rates compared with monotherapy with penicillin or ceftriaxone for patients with highly susceptible strain. Ampicillin, 2 g IV every 4 hr, is reasonable alternative to penicillin if a penicillin shortage exists.
or				
Ceftriaxone	2 g/24 hr IV or IM in 1 dose	6	Class IIa, LOE: B	
with or without				
Gentamicin sulfate†	3 mg/kg/24 hr IV or IM in 1 dose	2		Gentamicin therapy should not be administered to patients with creatinine clearance <30 mL/min.
Vancomycin hydrochloride‡	30 mg/kg/24 hr IV in 2 equally divided doses	6	Class IIa, LOE: B	Vancomycin is reasonable only for patients unable to tolerate penicillin or ceftriaxone.
Penicillin Relatively or Fully Resistant Strain (MIC >0.12 μg/mL)				
Aqueous crystalline penicillin sodium	24 million U/24 hr IV either continuously or in 4-6 equally divided doses	6	Class IIa, LOE: B	Ampicillin, 2 g IV every 4 hr, is a reasonable alternative to penicillin if a penicillin shortage exists.
or				
Ceftriaxone	2 g/24 hr IV/IM in 1 dose	6	Class IIa, LOE: B	
plus				
Gentamicin sulfate	3 mg/kg per 24 hr IV/IM in 1 dose	6		
Vancomycin hydrochloride	30 mg/kg/24 hr IV in 2 equally divided doses	6	Class IIa, LOE: B	Vancomycin is reasonable only for patients unable to tolerate penicillin or ceftriaxone.

*Doses recommended are for patients with normal renal function.

†**See Table 73.7** for appropriate dose of gentamicin. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis resulting from VGS, as a second option, gentamicin can be administered daily in 3 equally divided doses.

‡See text and **Table 73.7** for appropriate dose of vancomycin.

IM, Intramuscularly; *IV,* intravenously; *LOE,* level of evidence.

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. A scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435-86.

Bacteria Formerly Known as “Nutritionally Variant Streptococci”

Because of their previous designation as “nutritionally variant streptococci,” a discussion of organisms now included in nonstreptococcal categories is warranted, although the prevalence of these organisms causing IE is low. *Abiotrophia defectiva* and *Granulicatella* spp. and *Gemella* spp. have unusual metabolic characteristics that can result in diminished activity of cell wall–active antibiotics to kill these organisms and thus decreased cure rates. Moreover, because of this characteristic, the ability to perform in vitro susceptibility testing is adversely affected, with potentially unreliable results. Thus a regimen recommended for treatment of native valve IE is advocated (**see Table 73.7**).

Beta-Hemolytic Streptococci

Unlike IE caused by VGS and *S. gallolyticus*, IE caused by beta-hemolytic streptococci typically is characterized by an acute onset with rapid valve destruction and other complications that often require cardiovascular surgical intervention. Consultation with a specialist in infectious diseases and cardiology is recommended. Because IE is infrequently caused by these organisms, prospective clinical trial data for therapeutic decisions are lacking. Nevertheless, recommended therapy for IE caused by *Streptococcus*

pyogenes (group A) includes either aqueous crystalline penicillin G or ceftriaxone or cefazolin, and treatment is for at least 4 weeks. For the other types (groups B, C, F, and G) of beta-hemolytic streptococcal infections, gentamicin is advocated by some clinicians for the first 2 weeks of treatment.

Staphylococci

As noted previously, staphylococci have become more prominent as agents of IE in developed countries. In addition, antibiotic resistance has dramatically increased over the years, and for many patients, therapeutic choices are limited, although use of these agents has been largely unexamined in prospective clinical trials.

Infections caused by oxacillin-susceptible staphylococci can be treated with either nafcillin or oxacillin that is administered intravenously over 6 weeks for left-sided native valve IE or complicated right-sided IE (**Table 73.10**). Although previously included as an optional agent to be given over the first 3 to 5 days of therapy,[6] gentamicin is no longer advocated because of nephrotoxicity risk.[72] In the infrequent event that an isolate is penicillin susceptible (MIC ≤0.1 µg/mL with negative result on screening for beta-lactamase production), aqueous crystalline penicillin G can be given. Cefazolin is an option for patients with left-sided infection who are intolerant of penicillins but have not had an IgE-mediated allergic reaction to penicillins.

TABLE 73.10

Therapy for Endocarditis Caused by Staphylococci in the Absence of Prosthetic Materials

REGIMEN	DOSE* AND ROUTE	DURATION (wk)	STRENGTH OF RECOMMENDATION	COMMENTS
Oxacillin-Susceptible Strains				
Nafcillin or oxacillin	12 g/24 hr IV in 4-6 equally divided doses	6	Class I, LOE: C	For complicated right-sided IE and for left-sided IE. For uncomplicated right-sided IE, 2 wk (see text).
For penicillin-allergic (nonanaphylactoid-type) patients:				Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin.
Cefazolin	6 g/24 hr IV in 3 equally divided doses	6	Class I, LOE: B	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases.
Oxacillin-Resistant Strains				
Vancomycin†	30 mg/kg/24 hr IV in 2 equally divided doses	6	Class I, LOE: C	Adjust vancomycin dose to achieve trough concentration of 10-20 µg/mL (see text for vancomycin alternatives).
Daptomycin	≥8 mg/kg/dose	6	Class IIb, LOE: B	Await additional study data to define optimal dosing.

*Doses recommended are for patients with normal renal function.

†For specific dosing adjustment and issues concerning vancomycin, **see Table 73.7** footnotes.

IE, Infective endocarditis; *IV,* intravenously; *LOE,* level of evidence.

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. A scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435-86.

For uncomplicated right-sided native valve IE caused by oxacillin-susceptible staphylococci, 2 weeks of antibiotic therapy with nafcillin or oxacillin is an option. For patients who are intolerant of beta-lactam therapy, vancomycin can be used, but many favor a longer treatment. Daptomycin, 6 mg/kg/day intravenously, is another treatment option in patients intolerant of beta-lactam therapy.

Defining an optimal treatment regimen for native valve IE, including left- and right-sided infection, caused by oxacillin-resistant staphylococci is a more difficult task. Currently, IV vancomycin is recommended, but cure rates are less than desired. Daptomycin and ceftaroline are treatment options in patients intolerant of or nonresponsive to vancomycin, but prospective trial data including large cohorts

are lacking.

Therapy for PVE caused by staphylococci involves more complex regimens because of the difficulty in curing infections involving prosthetic valve material. For oxacillin-susceptible strains, nafcillin or oxacillin is given for at least 6 weeks in combination with rifampin, which can be administered either intravenously or orally (**Table 73.11**). Cefazolin can be used if the patient is intolerant of penicillins and has not had an IgE-mediated allergic reaction. Gentamicin is recommended for the initial 2 weeks of treatment as well. In patients intolerant of gentamicin, or if the infecting isolate is resistant to gentamicin and other aminoglycosides, levofloxacin can be given, provided that the isolate is susceptible to this agent. For PVE caused by oxacillin-resistant strains, IV vancomycin should be given in combination with rifampin for at least 2 weeks and gentamicin for 2 weeks.

TABLE 73.11

Therapy for Endocarditis of Prosthetic Valves or Other Prosthetic Material Caused by Staphylococci

REGIMEN	DOSE* AND ROUTE	DURATION (WK)	STRENGTH OF RECOMMENDATION	COMMENTS
Oxacillin-Susceptible Strains				
Nafcillin or oxacillin	12 g/24 hr IV in 6 equally divided doses	≥6	Class I, LOE: B	Vancomycin should be used in patients with immediate-type hypersensitivity reactions to β-lactam antibiotics (**see Table 73.7** for dosing guidelines). Cefazolin may be substituted for nafcillin or oxacillin in patients with non–immediate-type hypersensitivity reactions to penicillins.
plus				
Rifampin	900 mg/24 hr IV or orally in 3 equally divided doses	≥6		
plus				
Gentamicin†	3 mg/kg/24 hr IV or IM in 2 or 3 equally divided doses	2		
Oxacillin-Resistant Strains				
Vancomycin	30 mg/kg/24 hr in 2 equally divided doses	≥6	Class I, LOE: B	Adjust vancomycin to a trough concentration of 10-20 μg/mL.
plus				
Rifampin	900 mg/24 hr IV/PO in 3 equally divided doses	≥6		
plus				
Gentamicin	3 mg/kg/24 hr IV/IM in 2 or 3 equally divided doses	2		See text for gentamicin alternatives.

*Doses recommended are for patients with normal renal function.

†Gentamicin should be administered in close proximity to vancomycin, nafcillin, or oxacillin dosing. **See Table 73.7** for appropriate dose of gentamicin.

IM, Intramuscularly; *IV,* intravenously; *LOE,* level of evidence.

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. A scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435-86.

Enterococci.

Enterococci are common causative organisms in IE, particularly in the elderly population, and treatment requires both penicillin or ampicillin and an aminoglycoside (usually gentamicin) for attempted cure of infection. Because of the recommended 4 to 6 weeks of therapy, it often is difficult to complete the aminoglycoside-containing regimen in these older patients without the development of nephrotoxicity and/or ototoxicity. These adverse events are a greater concern in patients who are not candidates for penicillin therapy, usually because of previous allergic reaction, in whom vancomycin is combined with an aminoglycoside.

For native valve IE caused by strains that are susceptible to both penicillin and gentamicin, 4 weeks of antibiotic treatment is recommended in patients with symptoms for 3 months or less; 6 weeks is recommended for symptoms of IE longer than 3 months or for PVE (**eTable 73.1**). If an isolate is gentamicin resistant and streptomycin susceptible, streptomycin should be given with either ampicillin or penicillin (**eTable 73.2**). When the isolate is resistant to all aminoglycosides or the patient is unable to tolerate an aminoglycoside-containing regimen, a combination of "high-dose" ceftriaxone (4 g daily in two divided doses) with ampicillin has been successfully used,[73,74] but no head-to-head trials have been conducted to determine if the double–beta-lactam regimen is comparable in efficacy to the aminoglycoside-containing regimen. Nevertheless, historical data suggest comparable outcomes with the two regimens; thus double–beta-lactam therapy for IE caused by *Enterococcus faecalis* is a treatment option.[6,22] The beta-lactam combination should be administered for 6 weeks.

ETABLE 73.1

Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Resulting From *Enterococcus* Spp. Caused by Strains Susceptible to Penicillin and Gentamicin in Patients Who Can Tolerate β-Lactam Therapy*

REGIMEN	DOSE† AND ROUTE	DURATION (wk)	STRENGTH OF RECOMMENDATION	COMMENTS
Either				
Ampicillin sodium	2 g IV every 4 hr	4–6	Class IIa, LOE: B	Native valve: 4-wk therapy recommended for patients with symptoms of illness <3 mo; 6-wk therapy recommended for native valve symptoms >3 mo and for patients with prosthetic valve or prosthetic material. Recommended for patients with creatinine clearance >50 mL/min.
or				
Aqueous penicillin G sodium	18-30 million U/24 hr IV either continuously or in 6 equally divided doses	4–6	Class IIa, LOE: B	
plus				
Gentamicin sulfate‡	3 mg/kg ideal body weight in 2-3 equally divided doses	4–6		
or				
Double β-lactam:			Class IIa, LOE: B	Recommended for patients with initial creatinine clearance <50 mL/min or who develop creatinine clearance <50 mL/min during therapy with gentamicin-containing regimen.
Ampicillin	2 g IV every 4 hr	6		
plus				
Ceftriaxone	2 g IV every 12 hr	6		

*For patients unable to tolerate a β-lactam, **see eTable 73.3**.

†Doses recommended are for patients with normal renal and hepatic function.

‡Dose of gentamicin should be adjusted to achieve a peak serum concentration of 3 to 4 µg/mL and a trough concentration of <1 µg/mL.

IV, Intravenously; LOE, level of evidence.

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. A scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435-86.

ETABLE 73.2

Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Resulting from *Enterococcus* spp. Caused by a Strain Susceptible to Penicillin and Resistant to Aminoglycosides or a Streptomycin-Susceptible Gentamicin-Resistant Strain in Patients Able to Tolerate β-Lactam Therapy*

REGIMEN	DOSE† AND ROUTE	DURATION (wk)	STRENGTH OF RECOMMENDATION	COMMENTS
Double β-lactam:				Double β-lactam is reasonable for patients with normal or impaired renal function abnormal cranial nerve VIII function or if the laboratory is unable to provide rapid results of streptomycin serum concentration; native valve infection with symptoms of infection <3-mo duration may be treated for 4 wk with the streptomycin-containing regimen. PVE, NVE with symptoms >3 mo, or treatment with a double β-lactam regimen requires a minimum of 6 wk of therapy.
Ampicillin	2 g IV every 4 hr	6	Class IIa, LOE: B	
plus				
Ceftriaxone	2 g IV every 12 hr			
Alternative for Streptomycin-Susceptible Gentamicin-Resistant Strain				
Either				
Ampicillin sodium	2 g IV every 4 hr	4-6	Class IIa, LOE: B	Use is reasonable only for patients with availability of rapid streptomycin serum concentrations. Patients with creatinine clearance <50 mL/min or who develop creatinine clearance <50 mL/min during treatment should be treated with double–β-lactam regimen. Patients with abnormal cranial nerve VIII function should be treated with double–β-lactam regimen.
or				
Aqueous penicillin G sodium	18-30 million U/24 hr IV either continuously or in 6 equally divided doses			
plus				
Streptomycin sulfate‡	15 mg/kg ideal body weight per 24 hr IV or IM in 2 equally divided doses			

*For patients unable to tolerate a β-lactam, **see eTable 73.3**.

†Doses recommended for patients with normal renal and hepatic function.

‡Streptomycin dose should be adjusted to obtain a serum peak concentration of 20 to 35 µg/mL and a trough concentration of <10 µg/mL.

IM, Intramuscularly; *IV,* intravenously; *NVE,* native valve infective endocarditis; *PVE,* prosthetic valve infective endocarditis.

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. A scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435-86.

Some enterococcal isolates are penicillin resistant; most do not produce beta-lactamase as the mechanism of penicillin resistance and should be treated with a combination of vancomycin plus gentamicin. For the extremely rare isolate that produces beta-lactamase, ampicillin-sulbactam can be used with gentamicin (**eTable 73.3**). For enterococcal strains resistant to vancomycin (VRE) and penicillin, optimal treatment regimens are undefined, and therapy should be defined by a consulting infectious diseases expert. Often, daptomycin or linezolid is selected for use with other agents, depending on additional susceptibility results, which may require sending an isolate to a reference laboratory.

ETABLE 73.3

Vancomycin-Containing Regimens for Vancomycin- and Aminoglycoside-Susceptible Penicillin-Resistant *Enterococcus* Spp. for Native or Prosthetic Valve (or Other Prosthetic Material) Infective Endocarditis (IE) in Patients Unable to Tolerate β-Lactam

REGIMEN	DOSE* AND ROUTE	DURATION (wk)	STRENGTH OF RECOMMENDATION	COMMENTS
Unable to Tolerate β-Lactams				
Vancomycin†	30 mg/kg/24 hr IV in 2 equally divided doses	6	Class IIa, LOE: B	
plus				
Gentamicin‡	3 mg/kg/24 hr IV or IM in 3 equally divided doses	6		
Penicillin Resistance; Intrinsic or β-Lactamase Producer				
Vancomycin	30 mg/kg/24 hr IV in 2 equally divided doses	6	Class IIa, LOE: C	For β-lactamase–producing strain, if able to tolerate a β-lactam antibiotic, ampicillin-sulbactam§ plus aminoglycoside therapy may be used.
plus				
Gentamicin‡	3 mg/kg/24 hr IV or IM in 3 equally divided doses	6		

*Doses recommended are for adults with normal renal function.

†Dose of vancomycin should be adjusted to obtain a serum trough concentration of 10 to 20 µg/mL.

‡Dose of gentamicin should be adjusted to obtain serum peak and trough concentrations of 3 to 4 and <1 µg/mL, respectively.

§Ampicillin-sulbactam dosing is 3 g/6 hr IV.

IM, intramuscular; and IV, intravenous.

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. A scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435-86.

HACEK Organisms.

The primary choice of therapy for IE caused by the HACEK group of organisms is ceftriaxone, given for 4 weeks for native valve infection and 6 weeks for PVE (**eTable 73.4**). Cefotaxime and ampicillin-sulbactam are acceptable alternative therapeutic agents, but their use has been limited because of the ease of dosing (once daily) with ceftriaxone, which is not shared by these other two treatment options. Fluoroquinolones should be efficacious as second-line agents, but clinical experience is limited.

ETABLE 73.4

Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Caused by HACEK Microorganisms

REGIMEN	DOSE AND ROUTE	DURATION (wk)	STRENGTH OF RECOMMENDATION	COMMENTS
Ceftriaxone sodium*	2 g/24 hr IV or IM in 1 dose	4, NVE 6, PVE	Class IIa, LOE: B	Preferred therapy: cefotaxime or another third- or fourth-generation cephalosporin may be substituted.
or				
Ampicillin sodium	2 g IV every 4 hr		Class IIa, LOE: B	Ampicillin sodium may be an option if the growth of the isolate is sufficient to permit in vitro susceptibility results.
or				
Ciprofloxacin†	1000 mg/24 hr orally or 800 mg/24 hr IV in 2 equally divided doses		Class IIb, LOE: C	Fluoroquinolone therapy‡ may be considered for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted; fluoroquinolones generally are not recommended for patients <18 yr old. Treatment for 6 wk is reasonable in patients with PVE. (Class IIa, LOE: C)

*Patients should be informed that intramuscular injection of ceftriaxone is painful.

†Dose recommended for patients with normal renal function.

‡Fluoroquinolones are highly active in vitro against HACEK microorganisms. Published data on the use of fluoroquinolones for endocarditis caused by HACEK are minimal.

HACEK, *Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis, Eikenella corrodens, Kingella* spp.; *IM,* intramuscularly; *IV,* intravenously; *NVE,* native valve infective endocarditis; *PVE,* prosthetic valve infective endocarditis.

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. A scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435-86.

Aerobic Gram-Negative Bacilli and Fungi.

Although they rarely cause IE, coverage of both aerobic gram-negative bacilli and fungi is included here because many experts recommend a combined medical and surgical approach to management of IE caused by these pathogens.[6] Infectious diseases, cardiology, and cardiovascular surgery consultations should be sought in these cases. A lack of clinical trial data, reflecting in part the rarity of these syndromes, makes defining an optimal treatment regimen difficult.

Nevertheless, for IE caused by aerobic gram-negative bacilli, a combination of beta-lactam with an aminoglycoside is recommended, and the selection of these agents should be based on in vitro susceptibility testing results. A fluoroquinolone that is active against the isolated pathogen can be used instead of an aminoglycoside if the infecting isolate is aminoglycoside resistant or if the patient is intolerant of aminoglycosides.

Fungal IE primarily involves prosthetic valves and is characterized by poor outcomes. In some cases the infecting organism does not grow in routine blood cultures, and the infection can manifest as culture-negative endocarditis (discussed next). As noted previously, a majority of cases are caused by *Candida* spp., and many of the infections are health care associated. Because clinical trial data do not exist, defining an optimal treatment regimen is difficult, and drug therapy, which usually includes an amphotericin B–containing product, is associated with both infusion-related (rigors, fever, back pain, hypotension, bronchospasm, tachyarrhythmias) and delayed (nephrotoxicity, anemia, cation-wasting) adverse events that can be severe and limit use of these agents.[6] Moreover, relapse rates are high, even if valve surgery is done. The echinocandins (caspofungin, micafungin, and anidulafungin) have been useful in some patients who cannot tolerate an amphotericin B–containing regimen. Thus, many experts advocate the use of long-term oral suppressive therapy once initial “induction” therapy is completed and an active oral agent is identified. Azole agents, including fluconazole and voriconazole, have been used most often. Unfortunately, none of the echinocandins is available for oral use. The complexity of

antifungal selection warrants consultation with an expert in infectious diseases.

Culture-Negative Endocarditis.

Empiricism begets empiricism. In most cases, when no pathogen is isolated in blood cultures or in other specimens (embolism, valve tissue), empiric antimicrobial therapy is started before specimen collection. Therefore, selecting an optimal treatment regimen for these patients is difficult. Certainly, epidemiologic features of each case should be evaluated to assist in defining a treatment regimen (**Table 73.12**). In addition, the course of illness associated with the endocarditis presentation may offer clues to the cause of the infection and to the specific antibiotics already administered that might have accounted for negative specimen (usually blood) cultures. In addition, an evaluation of blood and tissue should be done to determine if rare causes of endocarditis could account for a culture-negative presentation, particularly in patients who did not receive recent antimicrobial therapy. An evaluation of these rare causes of culture-negative endocarditis is outlined earlier.

TABLE 73.12

Epidemiologic Clues in Etiologic Diagnosis of Culture-Negative Endocarditis

EPIDEMIOLOGIC FEATURE	COMMON MICROORGANISM
Injection drug use (IDU)	*Staphylococcus aureus*, including community-acquired oxacillin-resistant strains Coagulase-negative staphylococci β-Hemolytic streptococci Fungi Aerobic gram-negative bacilli, including *Pseudomonas aeruginosa* Polymicrobial
Indwelling cardiovascular medical devices	*S. aureus* Coagulase-negative staphylococci Fungi Aerobic gram-negative bacilli *Corynebacterium* spp.
Genitourinary disorders, infection, and manipulation, including pregnancy, delivery, and abortion	*Enterococcus* spp. Group B streptococci (*S agalactiae*) *Listeria monocytogenes* Aerobic gram-negative bacilli *Neisseria gonorrhoeae*
Chronic skin disorders, including recurrent infections	*S. aureus* β-Hemolytic streptococci *S. aureus* β-Hemolytic streptococci
Poor dental health, dental procedures	Viridans group streptococci (VGS) Nutritionally variant streptococci *Abiotrophia defectiva* *Granulicatella* spp. *Gemella* spp. HACEK organisms
Alcoholism, cirrhosis	*Bartonella* spp. *Aeromonas* spp. *Listeria* spp. *Streptococcus pneumoniae* β-Hemolytic streptococci
Burns	*S. aureus* Aerobic gram-negative bacilli, including *P. aeruginosa* Fungi
Diabetes mellitus	*S. aureus* β-Hemolytic streptococci *S. pneumoniae*
Early (≤1 yr) prosthetic valve placement	Coagulase-negative staphylococci *S. aureus* Aerobic gram-negative bacilli Fungi *Corynebacterium* spp. *Legionella* spp.
Late (>1 yr) prosthetic valve placement	Coagulase-negative staphylococci *S. aureus* Viridans group streptococci *Enterococcus* spp. Fungi *Corynebacterium* spp.
Dog or cat exposure	*Bartonella* spp. *Pasteurella* spp.

	Capnocytophaga spp.
Contact with contaminated milk or infected farm animals	*Brucella* spp. *Coxiella burnetii* *Erysipelothrix* spp.
Homeless, body lice	*Bartonella* spp.
HIV/AIDS	*Salmonella* spp. *S. pneumoniae* *S. aureus*
Pneumonia, meningitis	*S. pneumoniae*
Solid-organ transplantation	*S. aureus* *Aspergillus fumigatus* *Enterococcus* spp. *Candida* spp.
Gastrointestinal lesions	*Streptococcus gallolyticus (bovis)* *Enterococcus* spp. *Clostridium septicum*

HACEK, *Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* spp; HIV/AIDS, human immunodeficiency virus infection and acquired immunodeficiency syndrome.

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. A scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435-86.

Based on epidemiologic features and the most likely cadre of pathogens, a strategy for selection of antimicrobial therapy can be devised with input from an infectious diseases physician who has expertise in IE management. Considerations include the type of valve—native or prosthetic—and, with prosthetic valves, time since implantation of the valve. These regimens are necessarily broad to cover the most likely pathogens, which include the streptococci, staphylococci, enterococci, and HACEK organisms. Certain epidemiologic features may dictate broader coverage. The most troubling aspects of this approach are that the selected empiric therapy may not be adequate for a specific pathogen, and antimicrobials that would not be administered if the pathogen were identified will be given, with the potential for development of toxicity that may not be fully reversible.

Indications for and Timing of Surgery

The frequency with which surgery is used in the treatment of IE increased on average by 7% per decade between 1969 and 2000, with an attendant decrease in early mortality. In the current era, surgery is the mainstay of therapy for complicated IE. Current practice guidelines (largely based on observational series and expert opinion) advise that surgery should be considered in the presence of (1) heart failure, (2) features suggestive of a high risk of embolism, and (3) uncontrolled infection[22,75] (see **Tables 73G.3** and **73G.4**). A review by Bannay and colleagues[76] demonstrated that early surgery led to significant improvements in survival after treatment for left-sided IE (adjusted HR for mortality, 0.55; 95% CI 0.35 to 0.87; $P = 0.01$). This benefit was further confirmed by a large, prospective, multinational study of the effect of early surgery on in-hospital mortality, accounting for treatment selection, survivorship, and hidden biases.[46] The investigators found that early surgery plus antimicrobial therapy (compared with medical management alone) was associated with a significant reduction in mortality in the overall cohort (12.1% versus 20.7%), as well as after propensity-based matching and adjustment for survivor bias (absolute risk reduction [ARR], −5.9%; $P < 0.001$). The results of these and other studies have led to management algorithms recommending the early consideration of surgical intervention after recognition of native valve IE.

Heart failure is the most frequently encountered reason for consideration of urgent surgical treatment. HF may be caused by severe regurgitation (aortic or mitral), intracardiac fistulas, or less often, vegetation-related valve obstruction. Emergent surgery for HF unresponsive to medical management is crucial, and swift intervention also is recommended, even if temporary stabilization of the patient can be

achieved. Delayed surgery may be considered in the absence of HF after healing of acute endocarditic lesions, which in some circumstances may increase the likelihood of native valve repair.

Uncontrolled infection, the next most likely reason for surgical intervention, can be characterized broadly by increasing vegetation size, abscess formation, false aneurysms, or the creation of fistulas. Persistent fever frequently is associated with these anatomic findings. Early surgery is indicated in the setting of uncontrolled infection associated with persistent fever and positive blood cultures despite an appropriate antibiotic regimen, but surgery ideally should be delayed until after exclusion of extracardiac sources of infection. Perivalvular extension of infection is more common in aortic valve IE (10% to 40% in native valve IE and 56% to 100% in PVE). Some clinicians have noted that perivalvular abscesses most frequently occur in the posterior or lateral portions of the mitral annulus, whereas in aortic IE, extension can occur through the intervalvular fibrosa. The predictors of intervalvular fibrosa invasion include presence of a prosthetic valve (**see Fig. 73.4**), aortic location, and infection with coagulase-negative staphylococci. Pseudoaneurysms and fistula formation occur on average in 1.6% of cases and are more frequently related to *S. aureus* infection (46%). Other, less frequent manifestations of extension include ventricular septal defect, third-degree atrioventricular block (AVB), and acute coronary syndrome. Urgent surgery generally is recommended to treat perivalvular extension of infection (except in rare circumstances) and in cases of IE due to fungi, multidrug-resistant organisms, and gram-negative bacteria. In general, perivalvular extension or infection with aggressive microorganisms warrants early surgery in the absence of severe comorbid disease that would otherwise be prognosis-limiting.

IE-related embolism is common (20% to 50% of cases) and can be fatal. Occult embolism may occur in approximately 20% of patients. A 2007 report indicated that the risk of embolism was highest in the first week after initiation of antibiotic therapy (4.8/1000 patient-days) and decreases thereafter (1.7/1000 patient-days).[60] Some experts therefore suggest that the greatest benefit to patient survival is the prevention of systemic embolization, which can best be realized during the first week of antibiotic therapy.

The exact timing of surgical intervention for embolism prevention should be based on the presence or absence of previous embolic events, other complications of IE, size and mobility of the vegetation, likelihood of conservative surgery (valve repair), and duration of antibiotic therapy.[77] Ultimately, extrapolation of surgical benefits also must consider factors of patient viability, comorbid conditions, potential consequences of conservative management, and patient preferences.

Surgery generally is recommended in the presence of large, mobile vegetations (>10 mm),[57] particularly after an embolic event occurring during treatment with appropriate antibiotics. Even if embolization has not occurred, the presence of HF, severe valvular dysfunction, persistent infection despite appropriate antibiotic therapy, or abscess plus a large vegetation (>10 mm) constitutes an indication for earlier surgery. Only one small, randomized trial has evaluated the role of valve surgery in IE management.[62] Patients underwent valve surgery within 48 hours of randomization. There were several exclusion criteria for enrollment, and patients had to have left-sided IE, severe valvular regurgitation without HF, and vegetations larger than 10 mm to be included in the study. Valve surgery patients had fewer embolic events in follow-up, but other outcome measures, including mortality and infection relapse rates, did not differ between the two groups (each with <40 patients).

Considerable debate surrounds the performance of surgical intervention with a history of recent neurologic embolization. Iung and coauthors[78] systematically performed cerebral and abdominal MRI in early IE and found neurologic lesions in 82% of cases (ischemic lesions in 25, microbleeds in 32, and silent aneurysms in 6), and abdominal lesions in 20 patients (34%). Of importance, these findings led to modifications of classification and/or therapy in 28% of patients. Rossi and colleagues[79] detailed a best-

evidence summary of whether there is an ideal time for surgery in IE with cerebrovascular complications, including intracranial hemorrhage (ICH), ruptured mycotic aneurysm, TIA, meningitis, encephalopathy, and brain abscess. The investigators recommended 1 to 2 weeks of antibiotic treatment before cardiac surgery is indicated. However, earlier surgery is indicated in HF (class I, level of evidence [LOE]: B) and uncontrolled infection (class I, LOE: B) and for prevention of embolic events (class I, LOE: B/C). After stroke, surgery should not be delayed in the absence of coma and once cerebral hemorrhage has been excluded by cranial CT (class IIa LOE: B). After a TIA or a silent cerebral embolism, surgery is recommended without delay (class I, LOE: B). After diagnosis of ICH, surgery should ideally be postponed for at least 1 month (class I, LOE: C). In the case of surgery for PVE, the general principles outlined for native valve IE should be followed. Every patient should have a repeated head CT scan immediately before the operation to rule out preoperative hemorrhagic transformation of a brain infarction. Presence of a hematoma warrants neurosurgical consultation and consideration of cerebral angiography to rule out a mycotic aneurysm.

Medical therapy in the setting of right-sided native valve IE is the mainstay of treatment, and surgical intervention most often can be deferred in the absence of (1) diuretic-resistant right-sided HF associated with severe tricuspid regurgitation, (2) fastidious organisms resistant to antimicrobial treatment (i.e., fungemia or persistent bacteremia for >7 days), or (3) vegetations larger than 20 mm in diameter associated with multiple pulmonary emboli and possible right-sided HF.

Surgical Intervention

Before surgical intervention, several considerations in addition to the confirmation of appropriate antibiotic therapy are important. First, coronary artery assessment using either cardiac catheterization or CT angiography is recommended, to ascertain whether concomitant coronary revascularization is necessary. Before the performance of cardiac surgery, identification of primary or secondary extracardiac sites of infection should be undertaken, and extirpation should be performed if practically possible.

The primary principles guiding surgical management of IE are (1) excision of infected material along with sterilization of remaining tissue and instruments, followed by (2) reconstruction of cardiac or valve structures to permit normal heart function. Valve repair almost always is a favored option in the treatment of valvular IE.[80] If the extent of débridement necessary to eradicate infection precludes valve reconstruction, prosthetic valve replacement may be necessary.

The specific techniques used are tailored to the anatomy encountered at operation. Perforations in a valve cusp or leaflet are reconstructed using pericardial patch or other matrix substances. In general, the use of prosthetic material should be minimized; however, in settings where valve replacement is required, consensus documents do not routinely recommend one particular valve substitute over another (i.e., mechanical versus biologic).[75]

Reports suggest that mitral valve IE can be repaired in up to 80% of patients, particularly by experienced teams at referral centers.[81] A combination of traditional valvuloplasty techniques is utilized,[82] and results are assessed by intraoperative TEE. Although theoretically appealing, mitral valve homografts and pulmonary autografts have failed to gain widespread acceptance.

In the setting of acute IE, mechanical or biologic (xenograft) aortic valve replacement may be required, with few early demonstrated differences between device types.[83,84] Homografts or stentless root xenograft conduits are selectively used to reconstruct severely affected aortic sinuses, repair abscess-related destruction, or correct aortoventricular discontinuity.[85]

Postsurgical outcomes depend on the etiologic microorganism, the extent of tissue destruction, the presence of systolic or diastolic HF, and comorbid conditions. Early operative mortality ranges between

5% and 15%.[86] A 2008 report suggested that surgery within the first week of antibiotic therapy is associated with in-hospital mortality rate of 15%, and the main predictor was periannular extension of disease; risk of recurrent IE was 12%.[87] With isolated infection of leaflets or cusps (particularly in the subacute/chronic phase), early mortality is lower and approaches that seen in normal valve repair and replacement surgery.

Postoperative complications in this high-risk patient population typically include profound intraoperative coagulopathy necessitating mediastinal reexploration, acute renal failure, stroke, low cardiac output, pneumonia, and AVB necessitating pacemaker implantation.[80,86,88]

Outpatient Management and Follow-Up Evaluation

Antimicrobial treatment of IE is done in the outpatient setting once microbiologic control of infection is obtained, and after surgical or other interventions, if required, are completed and clinical recovery is observed.[6] Parenteral therapy is delivered in a variety of settings, related in part to the individual patient's health care coverage; often, therapy is done in a patient's home by a family member who has received instruction regarding (usually) IV infusions. Serial laboratory monitoring for evidence of drug-related toxicity and serum concentrations of drugs, when applicable, is mandatory and can be accomplished in a variety of settings, including home health agencies, primary care offices, and infectious diseases clinics. Monitoring also includes serial visits with an experienced clinician to assess clinical status and evidence of drug tolerance and complications related to an indwelling venous catheter. As outlined earlier, beta-lactam antibiotics frequently are used in the treatment of IE caused by a variety of bacterial infections. These agents are well recognized to have various adverse effects, including diarrhea, which may or may not be caused by *Clostridium difficile* infection, as well as rash, fever, neutropenia, and less often, hepatobiliary or renal toxicities.

Once parenteral antimicrobial therapy is completed (**Table 73.13**), the indwelling venous catheter should be removed, because it can be a nidus of subsequent infection or of other, noninfectious complications, unless there is another need for the device. At completion of therapy, an echocardiogram should be obtained to serve as a baseline (**see Table 73.6**), because patients who have had an initial bout of IE, regardless of whether or not the valve was replaced, are at high risk for subsequent IE relapse or recurrence. Consultation with a cardiologist should determine whether TTE versus TEE is preferred. Daily dental hygiene and dental visits should be done to promote dental health.

TABLE 73.13

Patient Care During and After Completion of Antimicrobial Treatment

Initiation Before or at Completion of Therapy
Echocardiography to establish new baseline
Drug rehabilitation referral for patients who use illicit injection drugs
Education on the signs of endocarditis and need for antibiotic prophylaxis for certain dental/surgical/invasive procedures
Thorough dental evaluation and treatment if not performed earlier in evaluation
Prompt removal of intravenous catheter at completion of antimicrobial therapy
Short-Term Follow-Up
At least 3 sets of blood cultures from separate sites for any febrile illness and before initiation of antibiotic therapy
Physical examination for evidence of heart failure
Evaluation for toxicity resulting from current/previous antimicrobial therapy
Long-Term Follow-Up
At least 3 sets of blood cultures from separate sites for any febrile illness and before initiation of antibiotic therapy
Evaluation of valvular and ventricular function (echocardiography)
Scrupulous oral hygiene and frequent dental professional office visits

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. A scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435-86.

Patients and their family members should be educated about aspects of IE,[6] in particular the importance of obtaining three sets of blood culture specimens if the patient develops fever any time in the future before taking any antibiotic. The critical aspect of securing multiple sets of blood cultures before initiating antibiotic therapy cannot be overemphasized. If a bloodstream infection is confirmed as the cause of the fever, an evaluation for relapsing or recurrent IE is necessary, which generally will include TEE in the evaluation for a source of the infection, in addition to initiating treatment for infection.

Cardiovascular Implantable Electronic Device Infections

The number of patients with CIEDs has dramatically increased over the past two decades, and this trend will continue as the indications for their use expand (**see Chapters 27 and 41**) and the population continues to age. With this expansion of CIED placement, a concomitant increase in infections of these devices has been documented.[89-91] The accompanying morbidity, mortality, and financial burden from CIED infection have been substantial.

Epidemiology

Several database surveys suggest that the rate of CIED infection has increased more than the rate of device implantation.[91-93] Factors associated with increased CIED infection risk include device placement in older patients and those with more comorbidities (particularly renal failure), more leads placed per patient, increased need for device revision or replacement, and complications at the pocket site after device placement or revision, particularly hematoma formation and delayed or poor wound healing. Factors that reduce the likelihood of device infection include the administration of surgical site prophylaxis at the time of device placement or revision and a higher volume of devices implanted by the physician performing the procedure.

Clinical Syndromes

The most common presentation of CIED infections is that of erosion and/or inflammatory changes at the

shoulder generator pocket site, with or without systemic manifestations of infection.[92] For others, systemic manifestations of infection prompt clinical evaluation with or without local findings of infection at the pocket site. Pulmonary manifestations can develop, including pleuritic pain, lung infiltrates, and lung abscess. In addition, cardiac and peripheral stigmata of IE occur in patients with CIED infection, and there may be associated valve infection.

Microbiology

Staphylococcal species predominate as causes of CIED infection, accounting for 60% to 80% of infections in most series.[89-93] Both *S. aureus* and coagulase-negative staphylococci are common pathogens and often are oxacillin resistant. Other gram-positive cocci, including streptococcal and enterococcal species, can cause CIED infection. Aerobic gram-negative bacilli and fungi are identified as pathogens in only a small minority of cases. Rarely, nontuberculous mycobacteria have been identified as causes of CIED infection.

Pathogenesis

Device infection pathogenesis involves the interactions of device, pathogen, and host.[93] Regarding the host, risk factors associated with infection have been outlined previously. For both the device and the pathogen, certain characteristics may not be unique to CIED infection but are considered operative in all types of device infections. Important among the pathogen-related mechanisms is biofilm formation. Bacteria and yeasts can attach and accumulate on the surface of a device, with eventual formation of a layer of organisms and amorphous material that harbors living organisms, able in this setting to evade normal host immune response and antimicrobial therapy. In addition to the mechanical barrier of the biofilm, organisms that accumulate in biofilms in this setting may alter their metabolic activities, protecting them from the static and cidal effects of certain antimicrobials.

On the basis of the proven efficacy of surgical site prophylaxis at CIED implantation, most CIED infections are believed to result from bacterial or fungal contamination of the device at placement. A less frequent mode of device contamination is lead infection occurring as a complication of bloodstream infection from an ectopic nidus such as an infected intravascular catheter.

Ongoing investigations are examining the surface components and physical and chemical aspects of a device and how those features interact with a pathogen's cell surface structures to either enhance or inhibit initial organism adherence to the device. Elucidation of mechanisms of initial pathogen adherence could lead to the development of devices that are more resistant to infection. Moreover, adjunctive therapies that could be administered at device placement or as vaccines before device placement may become available in the future to further reduce infection risks.

Diagnosis

The diagnosis of CIED infection is straightforward in cases where percutaneous device erosion has occurred or purulent drainage is present at a pocket site. Erythema, swelling, and pain at the pocket site also indicate infection. Distinguishing local findings due to early postoperative healing versus those due to infection can sometimes be challenging and may require serial patient examinations to determine the etiology of the local manifestations.

Blood cultures should be obtained in all cases of CIED infection, including those with clinical

manifestations limited to the pocket site. The possibility of CIED infection should be considered in all patients with bloodstream infection. In patients with positive blood cultures, TEE should be performed. The sensitivity of TEE in detecting lead- and valve-related infection is superior to that of TTE.[89,90] A documented limitation of TEE, however, is that lead infection can occur with no abnormalities detected on the TEE image. Moreover, TEE identifies clots on leads in 5% to 10% of patients who have no infection.

Ultimately, intraoperative findings and Gram staining and culture of deep pocket tissue and device samples obtained at complete device removal are useful in confirming CIED infection.

Management

A primary tenet of management of CIED infection includes complete device removal, if infection cure is the goal.[90,94] Despite the well-recognized risks of lead extraction,[94,95] it is essential to reduce the likelihood of relapsing infection. A management algorithm has been developed to assist in the care of patients with CIED infections (**Figs. 73.6** and **73.7**). Duration of antimicrobial therapy is based on the clinical syndrome of CIED infection and the identified pathogen. The recommended duration of antimicrobial therapy for the different infection syndromes is not evidence based. Moreover, no evidence-based data are available to indicate the preferred route of therapy. In cases with complications such as valvular IE, duration of therapy can extend for 6 weeks or longer.

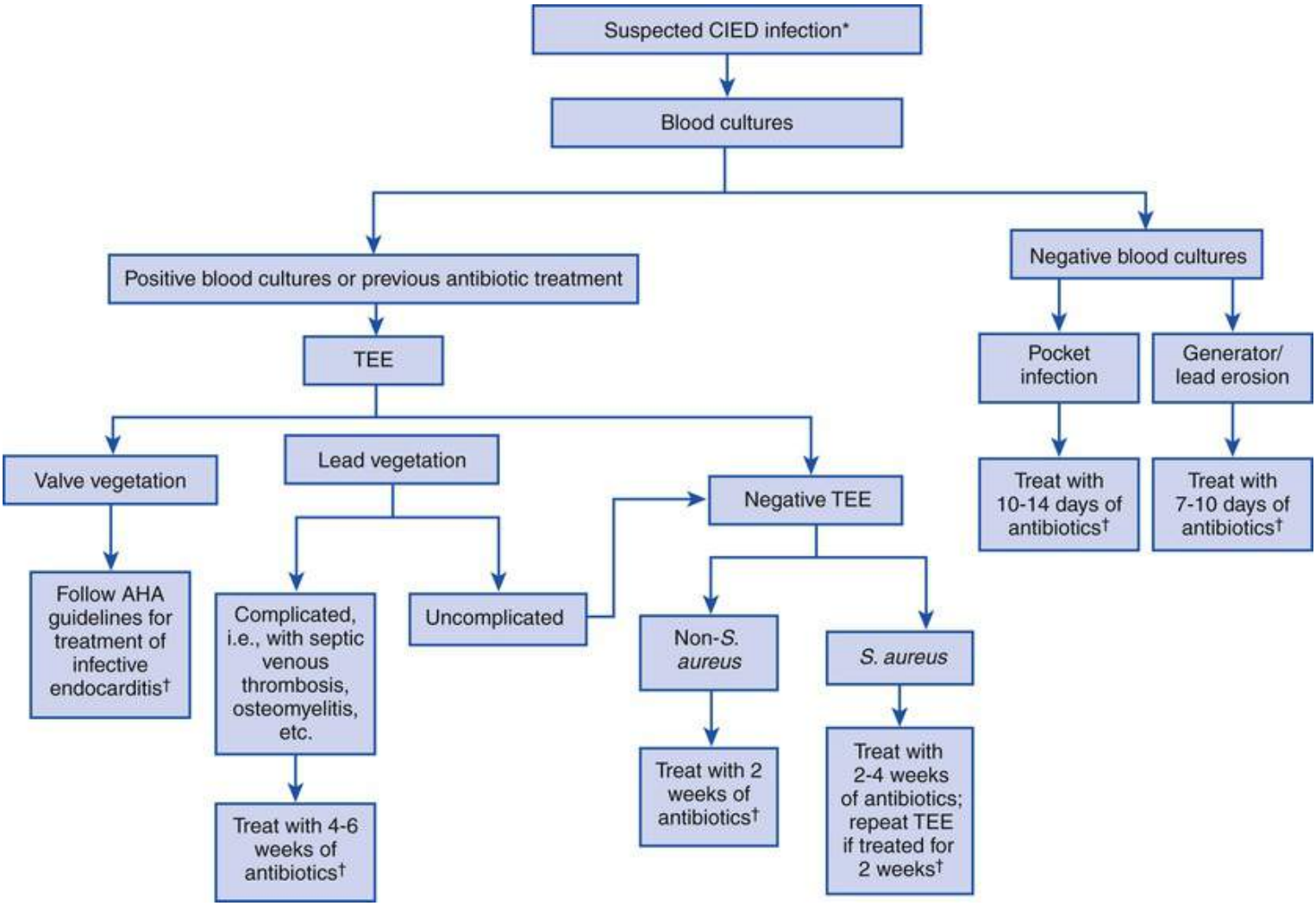

FIGURE 73.6 Approach to management of adults with cardiovascular implantable electronic device (CIED) infection. *A history, physical examination, chest radiograph, electrocardiogram, and echocardiographic device interrogation are standard baseline procedures before CIED removal. †Duration of antibiotics should be counted from the day of device explantation. Treatment can be extended to 4 or more weeks in the setting of metastatic septic complications (i.e., osteomyelitis, organ or deep abscess) or sustained bloodstream infection despite CIED removal. AHA, American Heart Association; TEE, transesophageal echocardiography. (Modified from Sohail MR, Uslan DZ, Khan AH, et al. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. J Am Coll Cardiol 2007;49:1851.)

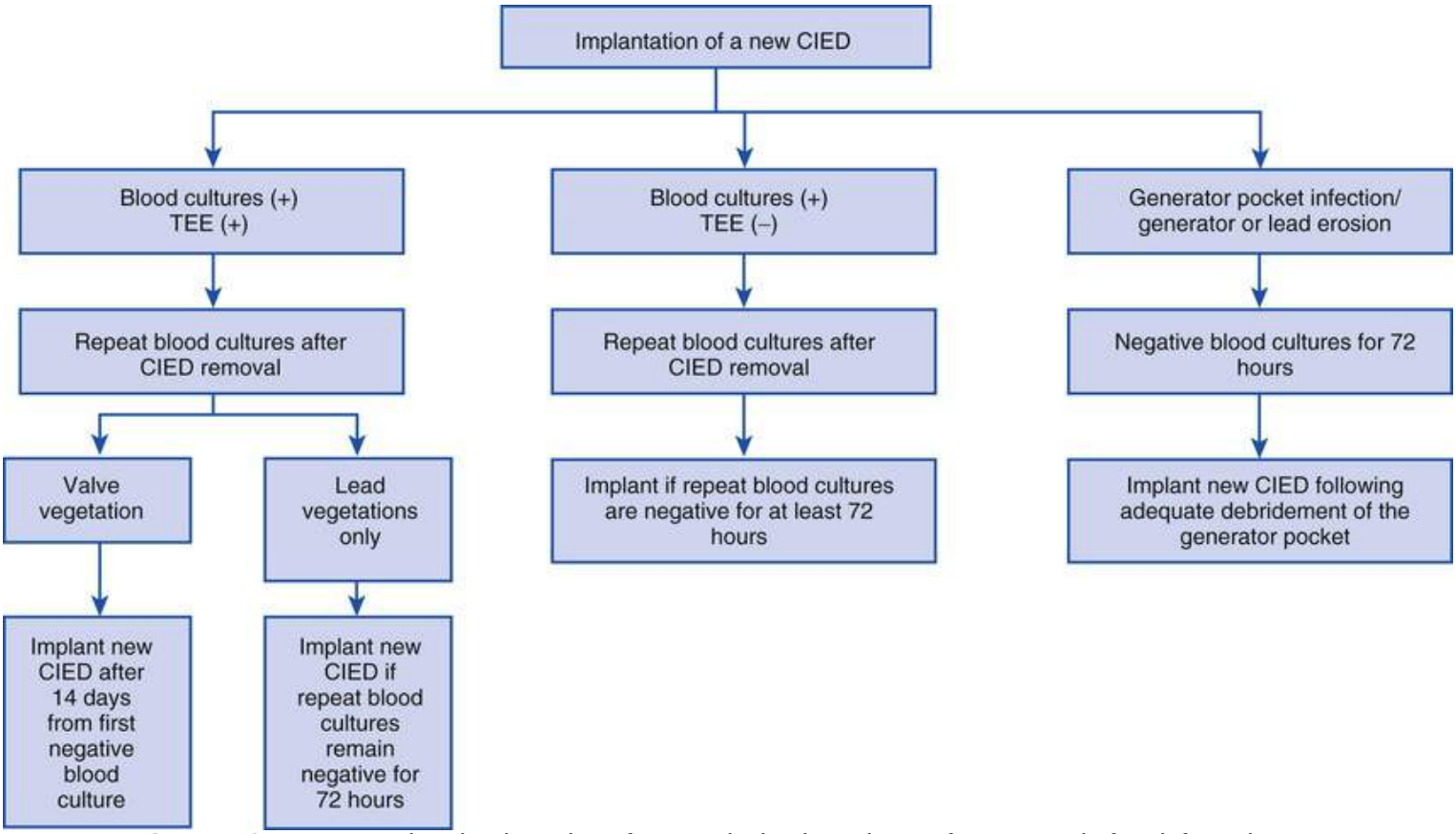

FIGURE 73.7 Approach to implantation of a new device in patients after removal of an infected cardiovascular implantable electronic device (CIED). TEE, Transesophageal echocardiography. (Modified from Sohail MR, Uslan DZ, Khan AH, et al. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. J Am Coll Cardiol 49:1851, 2007.)

The optimal timing of new device placement is undefined. Each patient should undergo individualized assessment to determine the need for a new device. Some experts have advocated that a new device can be implanted 72 hours after removal of the infected device, provided that blood cultures are negative, no valvular IE is present, and control of infection at the pocket site is secured.[90,92]

Management of patients with bloodstream infection as the *sole* manifestation of an infection is more difficult.[90] In such patients a thorough evaluation, including TEE, identifies no nidus responsible for bloodstream infection. The obvious concern is that either the CIED is infected and serves as a source of bloodstream infection, or the bloodstream infection could secondarily infect the CIED. Decisions regarding device removal are complex. If the device is not removed, relapsing bloodstream infection is inevitable once antimicrobial therapy is completed, if the device is the source of bloodstream infection. Conversely, if the CIED is removed but was not infected, the patient was exposed to the risk and complications of device removal without benefit, as well as incurring considerable expense for the procedure.

Prophylaxis

Prospective, placebo-controlled, clinical trials and case-control and meta-analysis studies[96] consistently indicate that the preoperative administration of an antistaphylococcal antibiotic, usually cefazolin, given intravenously 30 to 60 minutes before device placement or revision, is effective in reducing the risk of CIED infection. If vancomycin is deemed a more appropriate choice, the IV administration should begin 2 hours before the procedure. Subsequent postoperative dosing is not recommended with either cefazolin or vancomycin.

Antimicrobial prophylaxis is not recommended for patients with CIEDs who undergo invasive procedures, such as dental, GI, or GU procedures, because evidence-based data indicating that such procedures carry a risk of CIED infection are lacking. The predominance of staphylococci as the agents of CIED infection suggests that these invasive procedures probably are not responsible for device infection, and "secondary" prophylaxis is not warranted.

Left Ventricular Assist Device Infections

Major advances in the technologic aspects of LV assist devices (LVADs) have been pivotal in impacting patient survival,[97,98] and the demand for these devices continues to grow in the United States (**see Chapter 29**). Not surprisingly, device infection occurs in patients with LVADs and will continue to be a major complication of LVAD use as long as it remains a percutaneous device. The most dramatic change in infection risk among cardiac devices may be that associated with LVADs. Infection risks have fallen, largely because of improvements in device design, including reduction in size.

Characterizing the incidence, epidemiology, and risk factors associated with LVAD infections is difficult because of the striking design changes in these devices since their inception.[97,98] The first-generation, pulsatile-flow, volume-displacement devices, including Novacor, Heartmate XVE, and other Thoratec devices, have been associated with higher rates of infection than the more recently reported rates with the second-generation, continuous-flow devices, including Heartmate II, VentrAssist, and MicroMed DeBakey.

Three categories of LVAD infections have been identified based on the portion of the device that is infected. These designations are somewhat arbitrary, however, because infection can involve more than one portion of an LVAD. The most common presentation is that of driveline infection. Erythema and drainage at the driveline site, with or without systemic manifestations of infection, usually are present.

Pump pocket infection is a second infection presentation and can be a complication of driveline infection. Local pain or discomfort with systemic manifestations is present, and abnormal fluid collection is demonstrated on ultrasound examination or CT. Fluid aspiration or surgical drainage procedures yield purulent material.

LVAD-associated IE is the least often diagnosed of the three presentations, but some cases may go undiagnosed (or may be diagnosed only at autopsy) because diagnostic tools such as TEE lack sensitivity. This diagnosis should be considered in all patients with sustained bloodstream infection and no other cardiovascular device that could serve as a nidus for sustained bacteremia or fungemia.

Microbiology

Staphylococcal species are the predominant causes of LVAD infection,[97,98] and oxacillin resistance is common. Less often, a panoply of other bacteria, encompassing enterococci (including VRE) and *Pseudomonas* spp., and fungi (*Candida* spp.) are identified as pathogens. Treatment options, particularly as oral therapy, usually are limited because of the multidrug-resistant profiles of these pathogens.

Management

The medical management of LVAD infections is difficult. Ideally, the device would be completely removed, but this approach requires surgical intervention and is associated with considerable morbidity and mortality. Therefore, antimicrobial therapy is the mainstay of management and often is used for prolonged periods on a recurrent basis. In addition, antimicrobial selection is difficult because of the characteristic multidrug resistance of infecting pathogens and the underlying comorbidities that increase

the likelihood of drug toxicity (e.g., chronic renal failure and colistin or aminoglycoside use for multidrug-resistant *Pseudomonas aeruginosa* infection).

Regardless of site of device infection, blood culture specimens should be obtained in every case of LVAD infection. Positive blood cultures can occur in patients without systemic signs of infection and can indicate the presence of a more complicated infection (e.g., IE rather than only driveline infection) or infection of another cardiovascular device, such as a prosthetic valve or CIED.

A variety of surgical interventions are used in the management of LVAD infection. Such interventions range from local soft tissue débridement for driveline infection to heart transplantation with LVAD removal in an effort to control refractory LVAD endocarditis and its associated complications.

Prevention

Placebo-controlled trials indicating the efficacy of antibiotic prophylaxis at LVAD placement (surgical site prophylaxis) are lacking. Nevertheless, the adoption of this practice is universal,[97,98] and multiple (up to five) antimicrobials often are administered, typically including some combination of vancomycin, rifampin, cefepime, ciprofloxacin, and fluconazole. The duration of antimicrobial prophylaxis after LVAD implantation also has varied widely, with 24 hours as a minimal duration. In some centers, nasal mupirocin also is used for a variable duration both before and after LVAD implantation.

Meticulous daily care at the driveline exit site is advocated. Patient and family education and serial visits with specialized caregivers are critical in infection prevention and in securing an early diagnosis.

Coronary Stent Infections

Although coronary stent infection is exceedingly rare, in view of the millions of coronary stents placed worldwide, questions often arise about the possibility of such infection in patients with bloodstream infection. This section reviews the current knowledge on this cardiac device infection syndrome.

Clinical Presentation

Coronary stent infections are rare. Patients present with fever that begins less than 1 month (often within 7 days) after stent placement.[99] Chest pain is frequent and may be caused by a variety of complications, including myocardial infarction, suppurative pericarditis, and pericardial empyema. The short incubation period between stent placement and onset of fever is consistent with the predominant pathogen, *S. aureus*, which can cause sepsis and its complications. *P. aeruginosa* and coagulase-negative staphylococci also have been documented to cause coronary artery stent infection.

Diagnosis

Diagnostic procedures usually include TEE to rule out myocardial abscess formation and coronary artery aneurysm or pseudoaneurysm. CT or MRI angiography should be done if TEE findings are negative or if surgical intervention is planned.

Management

Because of the extreme rarity of cases, no optimal management strategy has been defined. Moreover, with only approximately 24 cases described in the literature,[99,100] consensus-based recommendations are difficult to provide. With a reported mortality rate approaching 50%, management strategies to date have been unacceptable. *S. aureus* is the predominant pathogen, and device removal appears to be necessary for attempted cure. Therefore, early surgical intervention should be considered, including stent resection, vascular repair, and possibly vascular grafting. Antimicrobial therapy based on pathogen identification and susceptibility results should be administered parenterally for approximately 6 weeks.

Guidelines

Infective Endocarditis

Larry M. Baddour, William K. Freeman, Rakesh M. Suri, Walter R. Wilson, and Robert O. Bonow

The American Heart Association (AHA) guidelines for prevention of infective endocarditis (IE) have been evolving for the past 50 years, with the most recent key updates providing recommendations for antibiotic prophylaxis published in 2007.[1] The updated AHA scientific statement regarding the recommendations for diagnosis and management of this condition were published in 2015.[2] Other guidelines with recommendations relevant to this condition include the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for management of patients with valvular heart disease, revised most recently in 2014,[3] and the European Society of Cardiology (ESC) guidelines on the prevention, diagnosis, and treatment of IE.[4]

Prevention

The 2007 AHA guidelines represented a marked departure from 1997 recommendations and greatly reduced the patient population for whom prophylactic antibiotics are recommended. The 2007 guidelines noted that previous recommendations were based on research showing that antimicrobial prophylaxis is effective for prevention of experimental endocarditis in animal models, but also acknowledge the lack of clinical trial evidence that antimicrobial prophylaxis is effective in humans for prevention of endocarditis after dental, gastrointestinal, or genitourinary procedures. The expert committee also considered the complexity of prior guidelines, which required stratification of patients and procedures on their IE risk.

The 2007 AHA guidelines committee concluded that only an extremely small number of cases of IE might be prevented by antibiotic prophylaxis for dental procedures even if such prophylaxis were 100% effective. Accordingly, the revised guidelines recommend IE prophylaxis for dental procedures only for patients with underlying cardiac conditions associated with the highest risk of adverse outcomes from IE (**Table 73G.1**). These new recommendations were incorporated in the 2014 ACC/AHA guidelines.[3] The guidelines, however, also included the following statement regarding individualization of preventive strategies based on physician and patient preference:

TABLE 73G.1

Cardiac Conditions and Dental Procedures for Which Antibiotic Prophylaxis Is Recommended

Cardiac Conditions Associated With the Highest Risk of Adverse Outcome From Endocarditis for Which Prophylaxis with Dental Procedures Is Recommended (Class I, Level of Evidence: B)
Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous infective endocarditis
Congenital heart disease (CHD)
Unrepaired cyanotic CHD, including those with palliative shunts and conduits
Completely repaired CHD with prosthetic material or device either by surgery or catheter intervention during the first 6 months after the procedure*
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD
Cardiac transplantation recipients who develop cardiac valvulopathy
Dental Procedures for Which Endocarditis Prophylaxis Is Recommended for High-Risk Patients (see above)
All dental procedures and events that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa *except* the following: • Routine anesthetic injections through noninfected tissue • Taking dental radiographs • Placement of removable prosthodontic or orthodontic appliances • Adjustment of orthodontic appliances • Placement of orthodontic brackets • Shedding of deciduous teeth and bleeding from trauma to the lips or oral mucosa

*It is reasonable to stop prophylaxis after 6 months because endothelialization of prosthetic material occurs within 6 months after the procedure.

From Wilson W et al. Prevention of infective endocarditis. Recommendations by the American Heart Association. Circulation 2007;116:1736; and Nishimura RA et al. 2014 AHA/ACCF guideline for the management of patients with valvular heart disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:e521-e643.

The committee recognizes that decades of previous recommendations for patients with most forms of valvular heart disease and other conditions have been abruptly changed by the new AHA guidelines. Because this may cause consternation among patients, clinicians should be available to discuss the rationale for these new changes with their patients, including the lack of scientific evidence to demonstrate a proven benefit for infective endocarditis prophylaxis. In select circumstances, the committee also understands that some clinicians and some patients may still feel more comfortable continuing with prophylaxis for infective endocarditis, particularly for those with bicuspid aortic valve or coarctation of the aorta, severe mitral valve prolapse, or hypertrophic obstructive cardiomyopathy. In those settings, the clinician should determine that the risks associated with antibiotics are low before continuing a prophylaxis regimen. Over time, and with continuing education, the committee anticipates increasing acceptance of the new guidelines among both provider and patient communities.

For patients with conditions in which antibiotic prophylaxis is recommended, the antibiotics are intended for dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa. The guidelines recommend a single oral dose of amoxicillin as the preferred prophylactic agent for patients who do not have a history of type I hypersensitivity reactions to a penicillin. For those who do have a history of such reactions, alternative recommendations include clindamycin, azithromycin, and clarithromycin. For patients who demonstrate a non–type I allergic reaction to a penicillin, a first-generation oral cephalosporin can be used.

Antibiotic administration is not recommended for patients undergoing genitourinary or gastrointestinal tract procedures solely for the purpose of preventing endocarditis. This recommendation is in contrast with previous guidelines that recommended endocarditis antibiotic prophylaxis before selected procedures. Antibiotic prophylaxis for bronchoscopy is not recommended, unless the procedure involves

incision of the respiratory tract mucosa.

Indications for Echocardiography

Echocardiography is strongly supported in virtually all patients with suspected or known IE[2,3] (**Table 73G.2**). The guidelines urge use of transesophageal echocardiography (TEE) when specific questions are not adequately addressed by an initial transthoracic echocardiography (TTE) evaluation, such as when the TTE study is of poor quality or yields negative findings despite a high level of clinical suspicion for endocarditis, if a prosthetic valve is involved, or if the clinical picture is strongly suggestive of IE, such as in a patient with staphylococcal bacteremia or in an elderly patient with valvular abnormalities, making TTE diagnosis difficult.

TABLE 73G.2

ACC/AHA Guidelines for Echocardiography and Computed Tomography in Infective Endocarditis (IE)

INDICATION	CLASS	RECOMMENDATION	LOE
Transthoracic echocardiography (TTE)	I	In patients with suspected IE to identify vegetations, characterize hemodynamic severity of valvular lesions, assess ventricular function and pulmonary pressures, and detect complications.	B
		Reevaluation of patients with IE who have a change in clinical signs or symptoms (e.g., new murmur, embolism, persistent fever, heart failure, abscess, or atrioventricular heart block) and in patients at high risk of complications (e.g., extensive infected tissue/large vegetation on initial echocardiogram or staphylococcal, enterococcal, or fungal infections).	B
Transesophageal echocardiography (TEE)	I	In all patients with known or suspected IE when TTE is nondiagnostic, when complications have developed or are clinically suspected, or when intracardiac device leads are present.	B
		Reevaluation of patients with IE who have a change in clinical signs or symptoms (e.g., new murmur, embolism, persistent fever, heart failure, abscess, or atrioventricular heart block) and in patients at high risk of complications (e.g., extensive infected tissue or large vegetation on initial echocardiogram or staphylococcal, enterococcal, or fungal infections).	B
		Intraoperative TEE for patients undergoing valve surgery for IE.	B
	IIa	Diagnose possible IE in patients with persistent staphylococcal bacteremia without a known source.	B
		Diagnose IE of a prosthetic valve in the presence of persistent fever without bacteremia or a new murmur.	B
	IIb	Detection of concomitant staphylococcal IE in nosocomial *Staphylococcus aureus* bacteremia with a known portal of entry from an extracardiac source.	B
Computed tomography (CT)	IIa	Evaluate morphology and anatomy in the setting of suspected paravalvular infections when the anatomy cannot be clearly delineated by echocardiography.	B

LOE, Level of evidence.

From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACCF guideline for the management of patients with valvular heart disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:e521-e643.

Diagnosis of prosthetic valve endocarditis with TTE is more difficult than diagnosis of endocarditis of native valves. Thus the AHA scientific statement and the ACC/AHA guidelines suggest a lower threshold for performance of TEE in patients with prosthetic valves and suspected endocarditis[2,3] (**Table 73G.2**).

Surgery for Active Endocarditis

The AHA scientific statement, the ACC/AHA guidelines for valvular heart disease, and the ESC guidelines support performance of surgery for patients with life-threatening congestive heart failure or cardiogenic shock related to active endocarditis.[2-4] Indications for surgery for patients with stable endocarditis are considered to be less clear (**Table 73G.3** and **73G.4**).

TABLE 73G.3

ACC/AHA Guidelines for Surgery in Infective Endocarditis (IE)

INDICATION	CLASS	RECOMMENDATION	LOE
Surgery for IE	I	Decisions regarding timing of surgical intervention should be determined by a multispecialty heart valve team of cardiology, cardiothoracic surgery, and infectious disease specialists.	B
		Early surgery (during initial hospitalization before completion of full therapeutic course of antibiotics):	
		In patients with IE who present with valve dysfunction resulting in heart failure symptoms	B
		In patients with left-sided IE caused by *Staphylococcus aureus*, fungal, or other highly drug-resistant organisms	B
		In patients with IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions	B
		In patients with evidence of persistent infection as manifested by persistent bacteremia or fever lasting longer than 5 to 7 days after onset of appropriate antimicrobial therapy	B
		Patients with PVE and relapsing infection (defined as recurrence of bacteremia after a complete course of appropriate antibiotics and subsequently negative blood cultures) without other identifiable source for portal of infection are candidates for surgery.	C
		Complete removal of pacemaker or defibrillator systems, including all leads and the generator, should be part of the early management plan in patients with IE in patients with documented infection of the device or leads	B
	IIa	Complete removal of pacemaker or defibrillator systems, including all leads and the generator, is reasonable in patients with valvular IE caused by *S. aureus* or fungi even without evidence of device or lead infection.	B
		Complete removal of pacemaker or defibrillator systems, including all leads and the generator, is reasonable in patients undergoing valve surgery for valvular IE.	C
		Early surgery (during initial hospitalization before completion of full therapeutic course of antibiotics) is reasonable in patients with IE who present with recurrent emboli and persistent vegetations despite appropriate antibiotic therapy.	B
	IIb	Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) may be considered in patients with NVE who exhibit mobile vegetations >10 mm.	B

LOE, Level of evidence.

From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACCF guideline for the management of patients with valvular heart disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:e521-e643.

TABLE 73.G4

European Society of Cardiology Guidelines for Surgery in Infective Endocarditis

RECOMMENDATIONS: INDICATIONS FOR SURGERY	TIMING	Class	LOE
Heart Failure			
Aortic or mitral NVE or PVE with severe acute regurgitation, obstruction, or fistula causing refractory pulmonary edema or cardiogenic shock.	Emergency	I	B
Aortic or mitral NVE or PVE with severe regurgitation or obstruction causing symptoms of heart failure or echocardiographic signs of poor hemodynamic tolerance.	Urgent	I	B
Uncontrolled Infection			
Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation).	Urgent	I	B
Infection caused by fungi or multiresistant organisms.	Urgent/elective	I	C
Persisting positive blood cultures despite appropriate antibiotic therapy and adequate control of septic metastatic foci.	Urgent	IIa	B
PVE caused by staphylococci or non-HACEK gram-negative bacteria.	Urgent/elective	IIa	C
Prevention of Embolism			
Aortic or mitral NVE or PVE with persistent vegetations >10 mm after one or more embolic episode despite appropriate antibiotic therapy.	Urgent	I	B
Aortic or mitral NVE with vegetations >10 mm, associated with severe valve stenosis or regurgitation, and low operative risk.	Urgent	IIa	B
Aortic or mitral NVE or PVE with isolated, very large vegetations (>30 mm).	Urgent	IIa	B
Aortic or mitral NVE or PVE with isolated large vegetations (>15 mm) and no other indication for surgery.*	Urgent	IIb	C

*Surgery may be preferred if a procedure preserving the native valve is feasible.

LOE, level of evidence; HACEK, *Haemophilus parainfluenzae, H. aphrophilus, H. paraphrophilus, H. influenzae*; *Actinobacillus actinomycetemcomitans*; *Cardiobacterium hominis*; *Eikenella corrodens*; *Kingella, kingae, K. denitrificans*; *NVE,* native valve endocarditis; *PVE,* prosthetic valve endocarditis.

Modified from Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC guidelines for the management of infective endocarditis. The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology. Eur Heart J 2015;36:3075.

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74

Rheumatic Fever

Bongani M. Mayosi

Rheumatic fever is the leading cause of acquired heart disease in children and young adults worldwide. Initiated by a pharyngeal infection with group A beta-hemolytic streptococci (GAS) and following a latent period of approximately 2 to 3 weeks, the illness is characterized by acute inflammation of the heart, joints, skin, subcutaneous tissue, and central nervous system. Pathologically, the inflammatory process causes damage to collagen fibrils and connective tissue ground substance (i.e., fibrinoid degeneration), and thus rheumatic fever is classified as a connective tissue or collagen vascular disease.

The destructive effect on the heart valves leads to the chronic sequelae of the disease—rheumatic heart disease (RHD)—with serious hemodynamic disturbances causing cardiac failure, and other complications such as stoke and infective endocarditis. Referring to the fleeting arthritis and damaging carditis characteristic of rheumatic fever, the French physician Ernst-Charles Lasègue famously said in 1884, “Pathologists have long known that rheumatic fever licks at the joints, but bites at the heart.” Almost all cases of rheumatic fever and RHD and associated deaths are entirely preventable.

Epidemiology

The burden of rheumatic fever and RHD has been characterized by at least four changing patterns over the past 150 years (**Fig. 74.1**). The first pattern represents the preantibiotic fall in incidence of rheumatic fever that is typical of industrialized countries (curve A, **Fig. 74.1**). For example, in the United States the incidence per 100,000 population was 100 at the start of 20th century, 45 to 65 between 1935 and 1960, and is currently estimated to be less than 10 cases per 100,000.[1] The decrease in rheumatic fever incidence preceded the introduction of antibiotics in the 1940s and is almost certainly the result of improved socioeconomic standards, less overcrowded housing, and improved access to medical care.

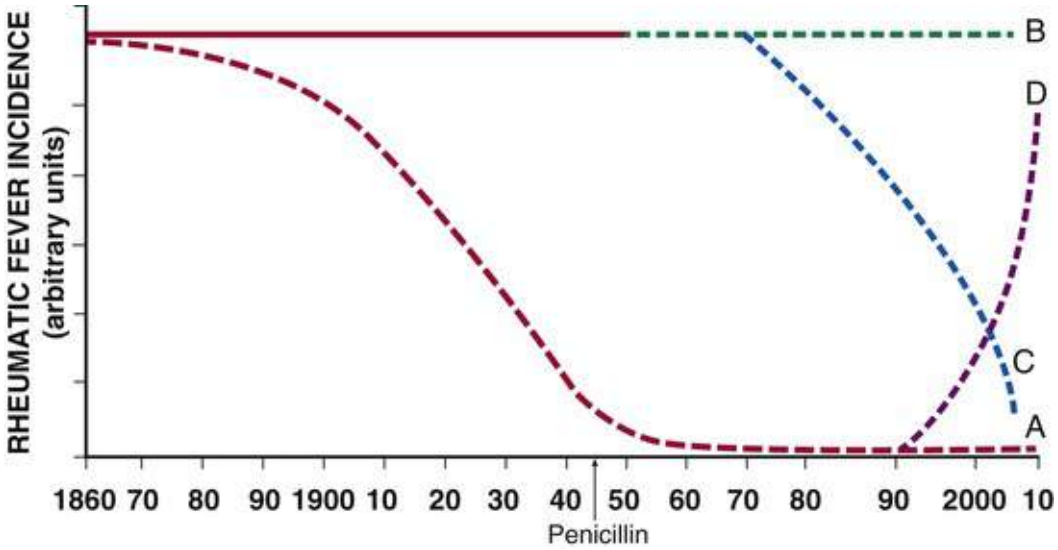

FIGURE 74.1 Incidence of rheumatic fever: four patterns over the past 150 years. Curve A represents the preantibiotic fall in the incidence of rheumatic fever that is typical of industrialized countries. Curve B is typical of the persistent high incidence of rheumatic fever in regions of the world with no comprehensive program for prevention, such as Africa and south Asia. Curve C shows the postantibiotic fall in the incidence of rheumatic fever in countries that instituted comprehensive programs for primary and secondary prevention of rheumatic fever, such as Cuba, Costa Rica, Martinique, and Guadeloupe. Curve D shows the fall and rise in the incidence of rheumatic fever in the formerly Soviet republics of central Asia. (Modified from Parry E, Godfrey R, Mabey D, Gill G, editors. Principles of Medicine in Africa. 3rd ed. Cambridge: Cambridge University Press; 2004, p 861.)

The second pattern is characterized by a persistently high incidence of rheumatic fever in developing regions and among indigenous populations of some developed countries, such as Australia and New Zealand (curve B, **Fig. 74.1**). The incidence of rheumatic fever among 5-to 14-year-old indigenous Australian children is as high as 162 per 100,000 per year in males, and 228 per 100,000 per year in females.[2] This hyperendemic pattern of rheumatic fever affects the majority of the population of the world who live in Africa, Middle East, Asia, eastern Europe, South America, and indigenous communities of Australasia.[3]

Third, some developing countries, such as Cuba, Costa Rica, the French Islands of Martinique and Guadeloupe, and Tunisia, have experienced a falling incidence of rheumatic fever following the implementation of comprehensive public health programs of primary and secondary prevention of rheumatic fever[4] (curve C, **Fig. 74.1**). By contrast, African countries that have not implemented public health programs for prevention of rheumatic fever continue to experience a high incidence of rheumatic fever and RHD.[5]

Outbreaks of rheumatic fever have been reported in affluent communities of the United States and Italy[6] (see Classic References, Veasy). The epidemiologic transition in the former Soviet Union has been associated not only with an increase in mortality rates from atherosclerotic diseases and trauma in Russia, but also in a sustained resurgence of rheumatic fever and RHD in central Asia.[7] The incidence of rheumatic fever fell in central Asia to the same levels as Japan in the middle 1970s, but rose sharply in the post-Soviet period to levels associated with developing countries (curve D, **Fig. 74.1**). Among developing countries, Kyrgyzstan probably has the highest incidence of rheumatic fever and RHD, approximately 543 per 100,000 population per year, thus earning the central Asian republics the dubious distinction of being the rheumatic fever "hot spot" of the world. The resurgence of rheumatic fever in the formerly Soviet republics may reflect the weakening of the primary health care system and the economic crisis of the post-Soviet period (see Classic References, Tulchinsky and Varavikova).

Pathogenesis

Rheumatic fever is a multifactorial disease that follows GAS pharyngitis (the agent) in a susceptible individual (the host) who lives under deprived social conditions (the environment). The theory of *molecular mimicry* holds that GAS pharyngitis triggers an autoimmune response to epitopes in the organism that cross-react with similar epitopes in the heart, brain, joints and skin, and repeated episodes of rheumatic fever lead to RHD[1,8] (**Fig. 74.2**).

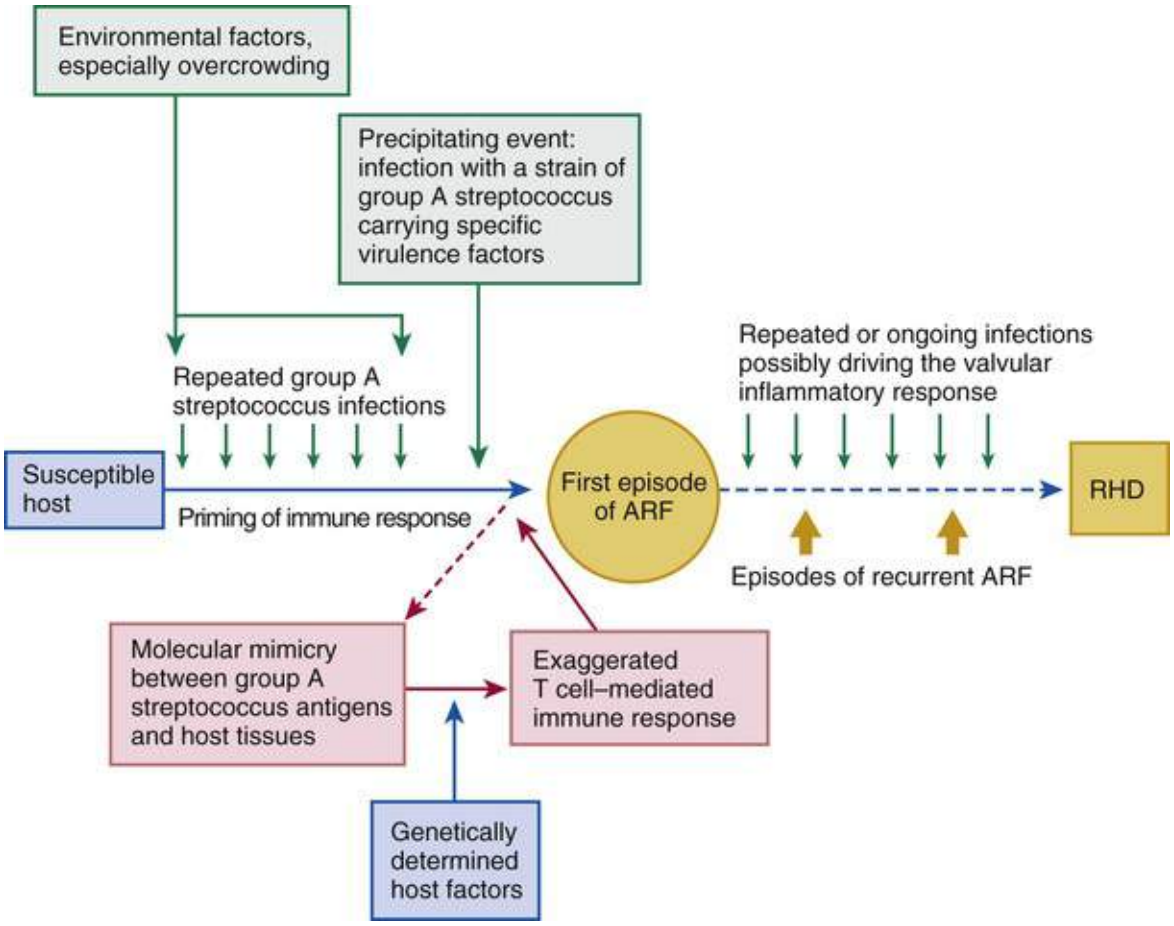

FIGURE 74.2 Pathogenesis of acute rheumatic fever (ARF) and rheumatic heart disease (RHD). (From Carapetis J, McDonald M, Wilson NJ. Acute rheumatic fever. Lancet 2005;366:155.)

The Agent

Epidemiologic and immunologic observations together with the preventive effect of antibiotic treatment for pharyngitis demonstrated in clinical trials strongly support the causative role of untreated GAS pharyngitis in rheumatic fever.[9] Streptococcal skin infection is believed not to cause rheumatic fever. However, a report of rheumatic fever following streptococcal wound infection (see Classic References, Popat and Riding), as well as the high prevalence of pyoderma with relative paucity of streptococcal pharyngitis in aboriginal communities of Australasia with a high incidence of rheumatic fever, raised questions about the link between streptococcal skin infection and rheumatic fever.[10] Although effective antibiotic treatment substantially reduces the risk of rheumatic fever, in situations of untreated epidemic GAS pharyngitis, up to 3% of patients develop the disease.[11]

The hypothesis of molecular mimicry in the pathogenesis of rheumatic fever has been reviewed.[1,9] There is evidence that patients with RHD have cross-reactive autoantibodies that target the dominant GAS epitope of the group A carbohydrate, *N*-acetyl-beta-D-glucosamine (GlcNAc), and laminin and laminar basement membrane in heart valve endothelium. T cells in peripheral blood and heart valves of patients with RHD cross-react with streptococcal M protein and cardiac myosin. Furthermore, autoantibodies against the GAS carbohydrate epitope GlcNAc and cardiac myosin appear during progression of RHD. In addition, autoantibodies against collagen that are not cross-reactive may form because of the release of collagen from damaged valves.

The *two-hit hypothesis* for the initiation of disease proposes that antibody attack of valve endothelium facilitates the extravasation of T cells through activated epithelium into valve tissue, leading to the

formation of granulomatous nodules called Aschoff bodies that are characteristic of rheumatic myocarditis. The area of central necrosis is surrounded by a ring of plump histiocytes called Anitschkow cells (**Fig. 74.3**). These nodules were discovered independently by Ludwig Aschoff and Paul Rudolf Geipel and thus are occasionally called Aschoff-Geipel bodies.

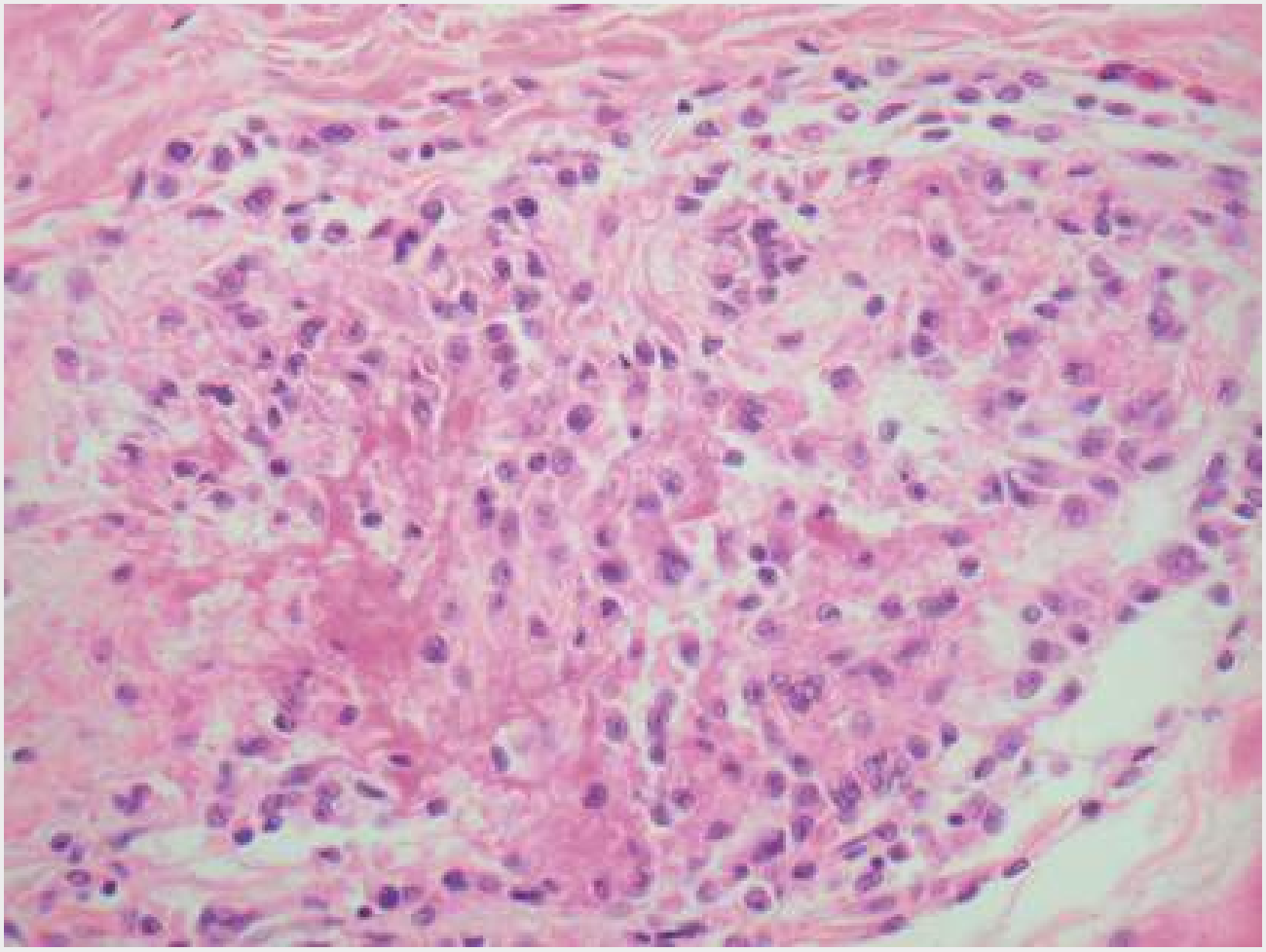

FIGURE 74.3 The Aschoff body of rheumatic fever. Photomicrograph of an Aschoff nodule from the heart in a case of acute rheumatic fever. The nodule is composed of Anitschkow cells; these have clear nuclei with a central bar of chromatin, said to resemble a caterpillar. There is a central area of fibrin. This central necrosis is further surrounded by a mononuclear cell infiltrate. Myocardial fibers adjacent to the Aschoff body are undergoing destruction. (From Sebire NJ, Ashworth M, Malone M, Jacques TS, editors. Diagnostic Pediatric Surgical Pathology. London: Churchill Livingstone; 2010.)

In *Sydenham chorea*, human monoclonal antibodies (mAbs) derived from patients with disease target GlcNAc, gangliosides, and dopamine receptors are found on the surface of neuronal cells in the brain. Human mAbs and autoantibodies in Sydenham chorea activate calcium/calmodulin-dependent protein kinase II (CaMKII) in neuronal cells and recognize the intracellular protein biomarker tubulin. Therefore the theme of molecular mimicry in rheumatic fever is characterized by the recognition of targeted intracellular biomarker antigens (cardiac myosin and brain tubulin), while targeting extracellular membrane antigens (laminin on valve surface endothelium or lysoganglioside and dopamine receptors in the brain).[1,9]

The Host

Several lines of epidemiologic evidence support the role of hereditary factors in susceptibility to rheumatic fever. First, the lifetime cumulative incidence of rheumatic fever in populations exposed to

rheumatogenic GAS infection is constant at 3% to 6% regardless of geography or ethnicity.[12] This suggests that the proportion of susceptible individuals is the same in all continental populations of the world.[13] Second, the familial aggregation of rheumatic fever was reported by Cheadle as far back as 1889.[13] Cheadle reported that the chance of an individual with a family history of rheumatic fever acquiring the disease is "nearly 5 times as great as that of an individual who has no such hereditary taint." The familial aggregation of RHD has been supported by a study of children raised separately from parents with RHD, who had a relative risk of 2.93 for the development of rheumatic fever compared with children whose parents did not have RHD.[13] Also, a study of 435 twin pairs found that the risk of rheumatic fever in a monozygotic twin when the co-twin previously had rheumatic fever is more than six times greater than that in dizygotic twins. The heritability of rheumatic fever is 60%, which highlights the importance of heredity as a major susceptibility factor of the disease.[14]

Numerous studies have been conducted to search for specific genetic susceptibility factors in rheumatic fever.[15] Several genes controlling the adaptive immune response (e.g., HLA class II alleles, cytotoxic T cell lymphocyte antigen 4), the innate immune response (e.g., ficolin 2, mannose-binding lectin 2, receptor for Fc fragments of IgG, Toll-like receptor 2), cytokine genes (e.g., tumor necrosis factor alpha, transforming growth factor beta, interleukin-1 receptor A, interleukin-10), and B cell alloantigens have been implicated in the development of the disease. Although significant associations have been found between genetic factors and rheumatic fever, study results either conflict with each other or are not replicated.[13] Therefore, it is not possible at present to predict the individuals who are at risk of developing rheumatic fever following an episode of untreated streptococcal pharyngitis.

The Environment

It is well known that rheumatic fever is generally associated with low socioeconomic status. The incidence of rheumatic fever has been falling consistently in industrialized countries since the mid-19th century, independently of the advent of penicillin, possibly because of less crowding, improved housing and nutritional conditions, higher levels of parental employment, and better access to health care (curve A, **Fig. 74.1**). In New Zealand, the risk of rheumatic fever is linked to high levels of deprivation based on household income, access to telephone and car, education level, and housing.[16] The impact of the social gradient has also been illustrated in Uganda, where an increased risk of RHD is associated with overcrowding and unemployment. Furthermore, there was interaction between overcrowding and distance from the nearest health center, suggesting that the effect of overcrowding on the risk of acquiring RHD increases with every kilometer increase from the nearest health center.[17] In addition, schoolchildren of lower socioeconomic status have a higher prevalence of disease and more advanced disease in an echocardiographic screening study of RHD in Uganda.[18]

Clinical Features

The typical attack of rheumatic fever follows an episode of streptococcal pharyngitis after a latent period of 2 to 3 weeks. During the latent period there is no clinical or laboratory evidence of active inflammation. However, as many as one third of patients who develop rheumatic fever do so after asymptomatic GAS, and in outbreaks, up 58% of patients have no symptoms of pharyngitis. This is one of the potential barriers to the effectiveness of primary prevention of rheumatic fever solely with antibiotic treatment of GAS pharyngitis and provides the justification for the development of an anti-GAS vaccine as one of the strategies for the control of rheumatic fever and other streptococcal diseases.

Rheumatic fever occurs most frequently in children between ages 4 and 15 years. In developing

countries such as Saudi Arabia and India, juvenile mitral stenosis may occur at age 3 to 5 years.[19] The prevalence of the various clinical features varies in different studies depending on whether the patients are studied prospectively or in retrospect. The illness usually begins with a high fever, but in some patients the fever may be low grade or absent. The most common of the major criteria is *polyarthritis*, which occurs in two thirds to three quarters of the patients, followed by carditis and chorea.

Arthritis

Joint involvement is more common (almost 100%), and more severe in young adults than in teenagers (82%) and children (66%).[20] The joint pain is typically described as "migratory," which refers to the sequential involvement of joints, with inflammation resolving in one joint and then beginning in another joint. In some cases the joint involvement may be additive rather than migratory, with simultaneous involvement of several joints. In untreated patients the number of joints involved may vary from 6 to 16.[20]

The affected joint may be inflamed for only a few days to 1 week before the inflammation subsides. The polyarthritis is severe for approximately 1 week in two thirds of patients and may last another 1 to 2 weeks in the remainder before it resolves completely. If joint swelling persists after 4 weeks, it becomes necessary to consider other conditions, such as juvenile idiopathic arthritis or systemic lupus erythematosus (SLE).[20]

At the onset of the illness the joint involvement is asymmetric and usually affects the lower limbs initially before spreading to the upper limbs. Monoarthritis has been reported in 17% to 25% of patients.[21] The large joints such as the knees, ankles, elbows, and wrists are most frequently involved. The hip, shoulder, and small joints of the hands and feet are less frequently involved. Analysis of the synovial fluid has shown the presence of sterile inflammatory fluid. There may be a reduction in complement components C1q, C3, and C4, suggesting their consumption by immune complexes. Radiographs may show features of a joint effusion, but no other abnormalities are noted.[20]

Jaccoud arthritis or arthropathy (or chronic post–rheumatic fever arthropathy) is a rare manifestation of rheumatic fever characterized by deformities of the fingers and toes (**Fig. 74.4**). The condition may occur after repeated attacks of rheumatic fever and results from recurrent inflammation of the fibrous articular capsule. There is ulnar deviation of the fingers, especially the fourth and fifth fingers, flexion of the metacarpophalangeal joints, and hyperextension of the proximal interphalangeal joints (i.e., swan neck deformity). The hand is usually painless, and there are no signs of inflammation. The deformities are usually correctible but may become fixed in the later stages. There are no true erosions on radiography, and the rheumatoid factor is usually negative. A similar form of arthropathy is seen in patients with SLE.[20]

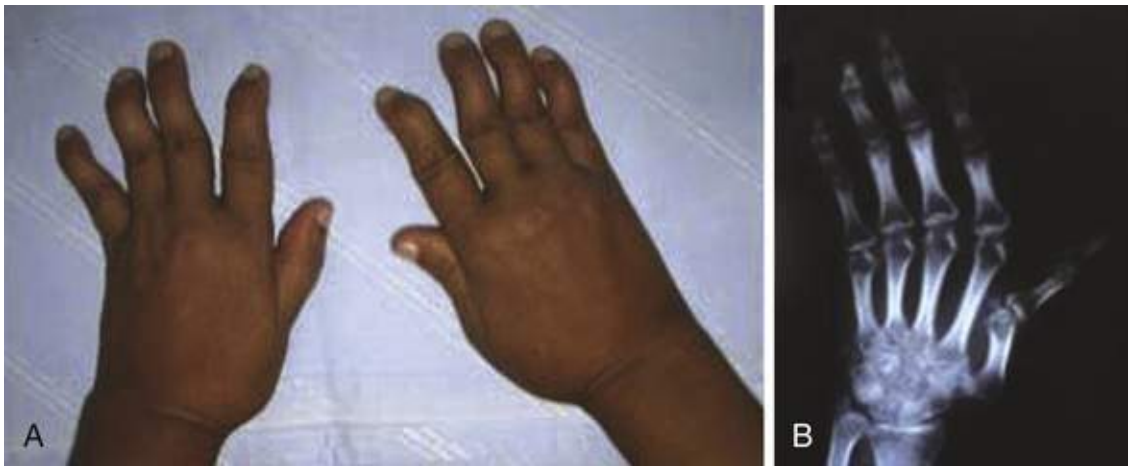

FIGURE 74.4 Post–rheumatic fever Jaccoud arthropathy. **A,** Swan neck deformity in Jaccoud arthropathy, with ulnar deviation and metacarpophalangeal subluxation. **B,** Plain radiograph of left hand showing deformities but not erosions. (From Santiago MB: Jaccoud's arthropathy. Best Prac Res Clin Rheumatol 2011;25:715.)

The arthritis of rheumatic fever responds promptly to nonsteroidal anti-inflammatory drugs, and thus the classic presentation of a migratory polyarthritis may be infrequent where self-medication with NSAIDs, or their prescription without considering the diagnosis, is common. The apparent fall in incidence of rheumatic fever in some developing countries may be related to indiscriminate use of NSAIDs without considering a diagnosis of rheumatic fever.[22] The differential diagnosis of polyarticular arthritis in children and adolescents includes poststreptococcal reactive arthritis, other autoimmune diseases, septic arthritis, infective endocarditis, Lyme disease, lymphoma/leukemia, viral arthropathy and sickle cell disease.

Poststreptococcal reactive arthritis is diagnosed in patients who have an arthritis that is not typical of rheumatic fever but who have evidence of recent streptococcal infection. This condition is said to occur after a shorter latent period than rheumatic fever, is less responsive to NSAIDs, may be associated with renal manifestations, and evidence of carditis is usually not seen. The distinction between poststreptococcal reactive arthritis and rheumatic fever is unclear, and many would recommend that a diagnosis of poststreptococcal reactive arthritis not be made in populations in whom rheumatic fever is common. Even if the diagnosis is considered, it is appropriate to offer a period of secondary penicillin prophylaxis, as for episodes of acute rheumatic fever (ARF), in such populations.[23]

Carditis

Carditis is the most serious manifestation of rheumatic fever because it may lead to chronic RHD with its attendant complications of atrial fibrillation, stroke, heart failure, infective endocarditis, and death. In some patients the carditis may be asymptomatic and is detected during clinical examination of a patient with arthritis or chorea. The incidence of carditis during the initial attack of rheumatic fever varies from 40% to 91% depending on the selection of patients and whether the diagnosis is made on clinical assessment alone or combined with echocardiography.[23]

The incidence of carditis in rheumatic fever varies with the age of the patient. It is reported in 90% to 92% of children under age 3 years, in 50% of children age 3 to 6 years, in 32% of teenagers age 14 to 17 years, and only in 15% of adults with a first attack of rheumatic fever.[20] In a 1951 review of 1000 patients, 65% were diagnosed as having carditis (see Classic References, Bland and Duckett Jones), and in the 1987 report of a Utah outbreak in the United States, 91% had carditis when clinical examination was combined with echocardiography (see Veasy).

The symptoms and signs of carditis depend on whether there is involvement of the pericardium, myocardium, or heart valves. The clinical diagnosis of carditis is based on the detection of an organic murmur that was not previously present (to indicate endocarditis), presence of a pericardial friction rub or signs of pericardial effusion (to indicate pericarditis), or cardiomegaly or congestive heart failure (CHF) (to indicate myocarditis).

Myocarditis in the absence of valvulitis is unlikely to be rheumatic in origin. It should be accompanied by an apical systolic or basal diastolic murmur. Patients with myocarditis may develop cardiomegaly and CHF, which may be severe and life threatening. Myocardial damage may manifest with electrocardiographic changes, which include varying degrees of heart block. Patients with first-degree heart block are usually asymptomatic. Patients with second- and third-degree heart block may be symptomatic and require a pacemaker if they develop CHF.[20] CHF may be caused by myocarditis or severe involvement of one or more heart valves. It occurs in 5% to 10% of the initial episodes and is more frequent during recurrences of rheumatic fever.

Pericarditis is associated with anterior chest pain (**see Chapter 83**), and a pericardial friction rub may be detected on clinical examination. Pericarditis can be detected clinically in about 10% of patients. The pericardial effusion may sometimes be large, but cardiac tamponade is rare, and constrictive pericarditis does not occur.

The most common valvular lesion is mitral regurgitation causing an apical pansystolic murmur. Aortic regurgitation is less common. Stenotic lesions are uncommon in the early stages of the disease, but a transient apical mid-diastolic murmur (Carey-Coombs) may occur in association with the murmur of mitral regurgitation. In patients with a history of previous RHD, a change in the character of the murmurs or the appearance of a new murmur will indicate the presence of acute rheumatic carditis.

Echocardiography is more sensitive and specific than cardiac auscultation for the detection of acute rheumatic carditis, such that it is recommended that all patients with suspected or definite rheumatic fever should undergo echocardiography[24] (see Classic References, Vasan). **Table 74.1** outlines the minimum echocardiographic criteria of the World Heart Federation for the diagnosis of pathologic regurgitation caused by rheumatic valvulitis.[25] The advent of portable echocardiography has increased the availability of cardiac ultrasound to many people in developing countries, resulting in its increasing use in screening for subclinical rheumatic heart valve disease.

TABLE 74.1

World Heart Federation Minimum Echocardiographic Criteria for Diagnosis of Pathologic Valvular Regurgitation Caused by Rheumatic Carditis

Pathologic Mitral Regurgitation*
1. Seen in at least two views.
2. In at least one view, jet length is ≥2 cm.†
3. Peak velocity ≥3 meters/second.
4. Pansystolic jet in at least one envelope.
Pathologic Aortic Regurgitation*
1. Seen in at least two views.
2. In at least one view, jet length is ≥1 cm.†
3. Peak velocity ≥3 meters/second.
4. Pandiastolic jet in at least one envelope.

*All four Doppler criteria must be met.

†A regurgitant jet length should be measured from the vena contracta to the last pixel of regurgitant color (blue or red) on nonmagnified (nonzoomed) images.

From Reményi B, Wilson N, Steer A, et al. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease: an evidence-based guideline. Nat Rev Cardiol 2012;9:297-309.

Sydenham Chorea

Chorea may be the only presenting manifestation of rheumatic fever. It is more common in females, and after puberty there is an even greater female predominance. The latent period between the episode of streptococcal pharyngitis and the development of chorea is considerably longer (6 to 8 weeks) than for arthritis and carditis. Chorea is characterized by the presence of involuntary, purposeless, jerky movements of the hands, arms, shoulders, feet, legs, face, and trunk associated with hypotonia and weakness. The purposeless movements interfere with voluntary activity and disappear during sleep. Initially, chorea may be confined to the face or one arm and sometimes may be unilateral (hemichorea).

Patients also show motor impersistence by intermittently, involuntarily withdrawing the tongue when attempting to protrude it for 30 seconds (jack-in-the-box tongue). Motor impersistence may also be demonstrated by asking the patient to squeeze the examiner's hand. This results in repetitive, irregular squeezes called the “milking sign.” Emotional lability manifests in personality changes, with inappropriate behavior, restlessness, outbursts of anger or crying, and learning difficulties.

Chorea may last for 1 week to 2 years but usually lasts 8 to 15 weeks. When chorea occurs alone, the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and streptococcal antibody titers may be normal because of the long latent period and resolution of the original infection. Chorea does not occur simultaneously with arthritis but may coexist with carditis. Some patients with chorea may have a cardiac murmur, whereas others may only later manifest involvement of the mitral valve.

Sydenham chorea with motor tics may overlap with the involuntary jerks of Tourette syndrome. The term *pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections* (PANDAS) has been used for a subgroup of children with tic or obsessive-compulsive disorders triggered by GAS infection with no associated cardiac valve damage.[26] However, the evidence supporting the existence of PANDAS as a distinct clinical entity has been questioned, leading to the recommendation that, in populations at high risk for rheumatic fever, clinicians should rarely, if ever, make a diagnosis of PANDAS; rather, they should err on the side of diagnosis of rheumatic fever and secondary prophylaxis.[24]

Subcutaneous Nodules

The subcutaneous nodules of rheumatic fever resemble the nodules of rheumatoid arthritis and may be detected over the occiput, elbows, knees, ankles, and Achilles tendons. In rheumatic fever the nodules around the elbow tend to occur over the olecranon, whereas rheumatoid nodules tend to occur more distally along the extensor aspect of the upper forearm. They are usually firm, painless, and freely movable over the subcutaneous tissue. The nodules vary in size from 0.5 to 2 cm and tend to occur in crops (**Fig. 74.5**). They are usually smaller, more discrete, and less persistent than rheumatoid nodules. The nodules were detected in only 1.5% of patients in a series of 786 patients, although a higher prevalence was reported in earlier studies.[20] Nodules are usually seen in children with prolonged active carditis rather than in the early stages of rheumatic fever. They may persist for a few weeks but seldom more than 1 month. Multiple crops of nodules may be related to the severity of the rheumatic carditis.

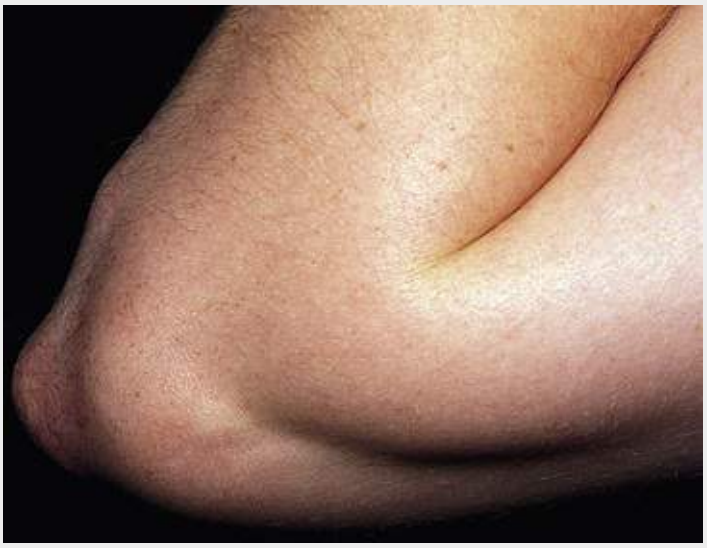

FIGURE 74.5 Subcutaneous nodules of rheumatic fever over the bony prominences of the elbow. (From Beerman, LB, Kreutzer J, Allada V. Cardiology. In Zitelli BJ, McIntire SC, Nowalk AJ, editors. Atlas of Pediatric Physical Diagnosis. 6th ed. Philadelphia: Saunders; 2012.)

Erythema Marginatum

Erythema marginatum is a less common manifestation of rheumatic fever and occurs on the upper arms or trunk but not the face (**Fig. 74.6**). It has a characteristic appearance and is therefore helpful in the diagnosis of rheumatic fever but is not pathognomonic of the disease. The rash is evanescent, pink, and nonpruritic. It extends centrifugally while the skin at the center returns to normal and has an irregular, serpiginous border. The rash may also become more prominent after a hot shower. Erythema marginatum usually occurs in patients with carditis and may occur early or later in the course of the disease.

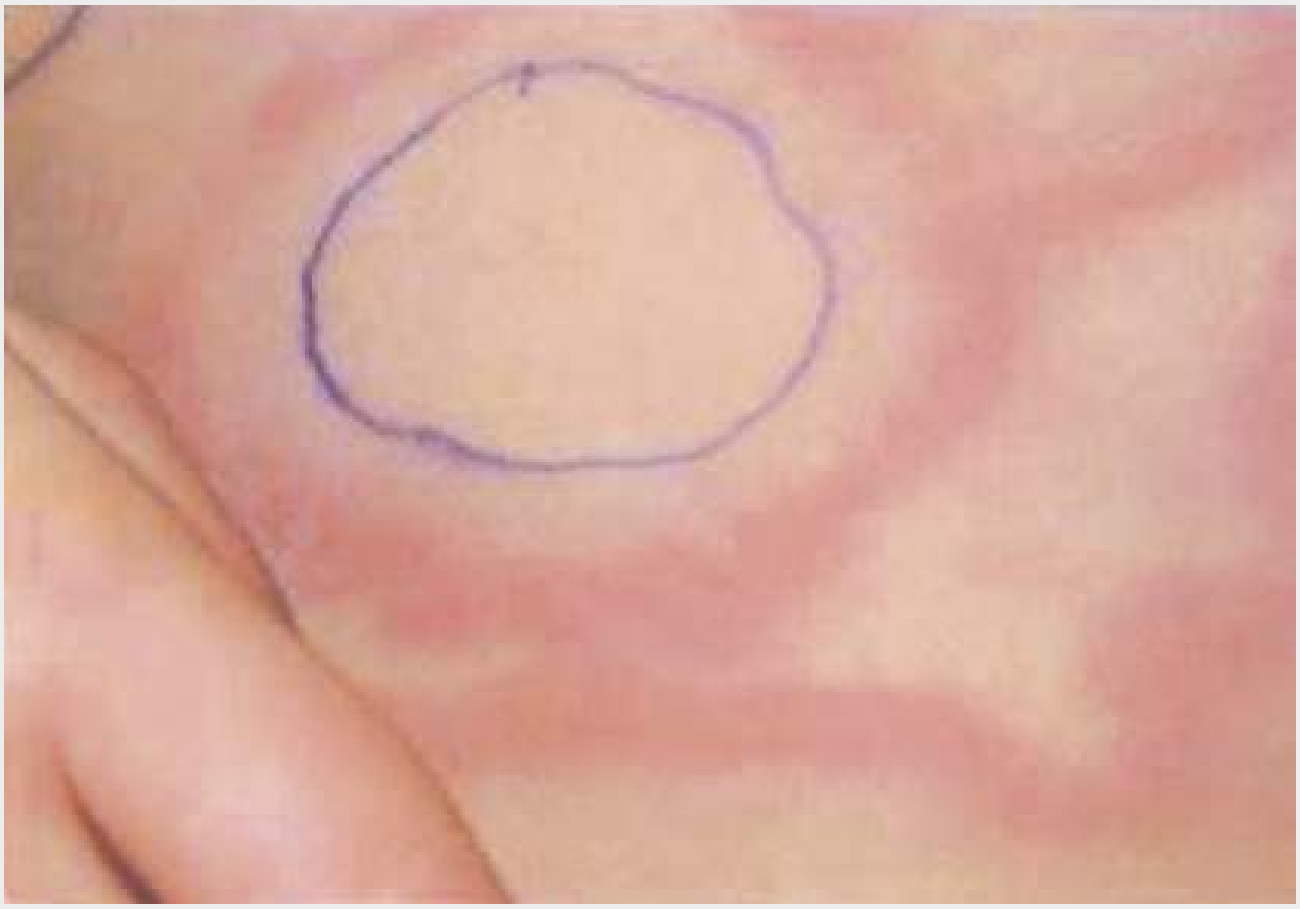

FIGURE 74.6 Erythema marginatum in acute rheumatic fever. The pen mark shows the location of the rash approximately 60 minutes previously. (From Cohen J, Powderly WG. Infectious Diseases. 2nd ed. St Louis: Mosby; 2004.)

Other Manifestations

The temperature is usually raised during attacks of rheumatic fever and ranges from 38.4°C to 40°C. When temperature is used as a minor diagnostic criterion, however, a cutoff value of higher than 37.5°C would allow the diagnosis of fever in 90% of suspected cases of rheumatic fever in endemic communities, such as indigenous Australians. The temperature usually decreases within 1 week and rarely lasts more than 4 weeks.

Abdominal pain may be severe and may mimic acute appendicitis. Epistaxis was reported as a common manifestation in the past but is now uncommon. Rapid sleeping pulse rate, tachycardia out of proportion to fever, malaise, and anemia may be noted in patients with ARF. Rheumatic pneumonia is uncommon and is difficult to distinguish from pulmonary edema and other causes of alveolitis.

Diagnosis

Although no specific clinical, laboratory, or other test exists to confirm conclusively a diagnosis of rheumatic fever, the diagnosis is usually made using the clinical criteria first formulated in 1944 by T. Duckett Jones. Since then the criteria have undergone multiple modifications, with the most recent revision by the American Heart Association (AHA) in 2015[13,27] (**Table 74.2**). The initial diagnosis of ARF is made if, in the presence of preceding GAS infection, two major criteria or one major and two minor criteria are present. The diagnosis of *recurrent* ARF requires two major, one major and two minor, or three minor criteria in the presence of preceding GAS infection. Evidence of preceding GAS infection, essential for the diagnosis, may be obtained from throat swab culture (only positive in approximately 11%

of patients at diagnosis of rheumatic fever) or by demonstrating a rising titer of antistreptococcal antibodies, either antistreptolysin O (ASO) or anti–deoxyribonuclease B (anti-DNase B), or by a positive rapid group A streptococcal carbohydrate antigen test in a child whose clinical presentation suggests a high pretest probability of streptococcal pharyngitis.[13,28]

TABLE 74.2

2015 AHA-Revised Jones Criteria for Diagnosis of Rheumatic Fever*

MAJOR CRITERIA	
Low-Risk Populations	**Moderate- and High-Risk Populations**
Carditis (clinical or subclinical†) Arthritis (polyarthritis only) Chorea Erythema marginatum Subcutaneous nodules	Carditis (clinical or subclinical) Arthritis (including polyarthritis, monoarthritis, or polyarthralgia‡) Chorea Erythema marginatum Subcutaneous nodules
MINOR CRITERIA	
Low-Risk Populations	**Moderate- and High-Risk Populations**
Polyarthralgia Fever (≥38.5°C) ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dL Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)	Monoarthralgia Fever (≥38°C) ESR ≥30 mm in the first hour and/or CRP ≥3.0 mg/dL§ Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

*Annual acute rheumatic fever (ARF) incidence of ≤2 per 100,000 school-aged children or all-age rheumatic heart disease (RHD) prevalence of ≤1 per 1000 people per year.

†Defined as echocardiographic valvulitis, as defined in Table 74.1.

‡Polyarthralgia should only be considered as a major manifestation in moderate- and high-risk populations after exclusion of other causes.

§C-reactive protein (CRP) value must be greater than the normal laboratory upper limit. In addition, because the erythrocyte sedimentation rate (ESR) might evolve during the course of ARF, peak ESR values should be used.

Joint manifestations are only considered in either the major or the minor category, but not in both categories in the same patient.

There are three main changes in the 2015 revised Jones criteria. First, subclinical valvulitis detected by echocardiography (as defined in **Table 74.1**) is accepted as a major criterion for the diagnosis of ARF in all patient populations. Second, there is recognition that the clinical utility of the Jones criteria is determined by the pretest probability and background disease prevalence in a population. To avoid overdiagnosis in low-incidence populations and underdiagnosis in high-risk populations, variability in applying diagnostic criteria in low-risk versus high-risk populations has been introduced in line with the Australian guidelines.[13,24] Low-risk communities are defined as having an ARF incidence of less than 2 per 100,000 school-aged children (usually 5 to 14 years old) per year, or an all-age prevalence of RHD of 1 or more per 1000 population per year. In moderate- to high-risk communities, monoarthritis and polyarthralgia have been added as major criteria to polyarthritis, and a temperature of 38°C and monoarthralgia are the revised minor criteria (**see Table 74.2**).

The addition of monoarthritis or polyarthralgia as a major criterion and the inclusion of a fever higher than 38°C and monoarthralgia as a minor criteria have increased the sensitivity of the modified Jones criteria in communities with hyperendemic levels of ARF.[24]

The 2015 Jones criteria also recognize the clinical entity of “possible” rheumatic fever. It is appropriate for clinical judgment to be applied in parts of the world where rheumatic fever remains common and where it is not possible to fulfill the Jones criteria because of a lack of laboratory facilities to conduct the recommended investigations of a patient with suspected rheumatic fever, as listed in **Table 74.3**.[23,24] When a diagnosis of possible rheumatic fever is made in a high-incidence setting, it is reasonable to consider offering 12 months of secondary prophylaxis, followed by reevaluation based on

history, physical examination, and repeat echocardiogram.

TABLE 74.3
Investigations in Suspected Rheumatic Fever

Recommended for All Cases
White blood cell count
Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
Throat swab before giving antibiotics for GAS culture
Blood culture, if febrile
Antistreptococcal serology: both antistreptolysin O (ASO) and anti-DNase B titers (repeat after 10 to 14 days if first test is not confirmatory)
Electrocardiogram
Chest radiograph
Echocardiogram
Tests for Alternative Diagnoses, Depending on Clinical Features
Repeated blood cultures with temperature spikes if infective endocarditis is suspected
Joint aspirate for possible septic arthritis (microscopy and culture)
Copper, ceruloplasmin, antinuclear antibody, and drug screen for choreiform movements
Serology and autoimmune markers for arboviral, autoimmune, or reactive arthritis
Peripheral blood smear for sickle cell disease

GAS, Group A beta-hemolytic streptococci.

From RHD Australia (ARF/RHD writing group), National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease. 2nd ed. Darwin, Australia: Menzies School of Health Research; 2012.

Treatment

The aim of treatment of a proven attack of rheumatic fever is (1) to suppress the inflammatory response and thus minimize the effects of inflammation on the heart and joints, (2) to eradicate the GAS from the pharynx, (3) to provide symptomatic relief, and (4) to commence secondary prophylaxis.

The longstanding recommendation of bed rest would appear to be appropriate mainly to lessen joint pain. The duration of bed rest should be individually determined, but ambulation can usually be started once the fever has subsided and acute-phase reactants are returning to normal. Strenuous exertion should be avoided, especially for those with carditis.

Even though throat swabs taken during the acute attack of rheumatic fever are rarely positive for GAS, it is advisable for patients to receive an intramuscular (IM) dose of benzathine benzylpenicillin (or erythromycin if allergic to penicillin). Although conventional, this strategy is untested. Thereafter, secondary prophylaxis should be commenced (see Classic References, Manyemba and Mayosi).

The choice of anti-inflammatory agent is among salicylates, NSAIDs, and corticosteroids. A systematic review of randomized controlled trials (RCTs) compared anti-inflammatory agents (e.g., aspirin, corticosteroids, immunoglobulins, pentoxifylline) with placebo or controls, or compared any of the anti-inflammatory agents with one another, in adults and children with rheumatic fever diagnosed according to the Jones or modified Jones criteria.[28] The presence of cardiac disease 1 year after treatment was the major outcome criterion selected. Eight RCTs involving 996 people were included. Several steroidal agents (corticotrophin, cortisone, hydrocortisone, dexamethasone, prednisone) and intravenous (IV) immunoglobulin were compared to aspirin, placebo, or no treatment in the various studies. Six of the trials were conducted between 1950 and 1965, one study in 1990, and the final study in 2001. Overall, there was no significant difference in the risk of cardiac disease at 1 year between the corticosteroid-treated and aspirin-treated groups (six studies, 907 participants; relative risk [RR], 0.87; 95% confidence interval [CI] 0.66 to 1.15). Similarly, use of prednisone (two studies, 212 participants; RR, 1.13; 95% CI 0.52 to 2.45) compared to aspirin did not reduce the risk of developing heart disease after 1 year. The

three studies reporting adverse events all found substantial adverse events. Thus, there is little evidence of benefit from using corticosteroids or IV immunoglobulins to reduce the risk of heart valve lesions in patients with ARF.[28]

These trials may be criticized on at least two grounds. First, the method used to assess cardiac involvement was clinical, with the development or persistence of an apical systolic murmur the usual criterion. It could be argued that observer error and interobserver variability of clinical methodology could invalidate the results, and that the question should be reexamined using modern, noninvasive techniques such as echocardiography. It has been shown, however, that at least during the acute phase of the illness, transthoracic two-dimensional echocardiography with color flow imaging does not add significantly to the clinical evaluation of the degree of cardiac involvement. The second point relates to the duration of follow-up. Lack of clinical evidence of cardiac involvement at 1 or 2 years after the initial attack of ARF is no guarantee that the important sequelae of valvular incompetence or stenosis will not develop in the ensuing decades.

The appropriate dosages of anti-inflammatory agents are aspirin, 100 mg/kg/day in four or five divided doses, and prednisone, 1 to 2 mg/kg/day. The duration of therapy must be gauged from the severity of the attack, presence of carditis, and rate of response to treatment. Milder attacks with little or no carditis may be treated with salicylates for approximately 1 month or until inflammation has subsided, as assessed by clinical and laboratory evidence. More severe cases may require 2 to 3 months of corticosteroid therapy before this can be gradually weaned. Up to 5% of patients may still have rheumatic activity despite treatment at 6 months. Occasionally a “rebound” of inflammatory activity can occur when anti-inflammatory therapy is reduced and may require salicylate treatment.

In patients whose initial attack of rheumatic fever is inadequately treated, there is a high risk that the rheumatic activity will continue and result in valvular incompetence, most often of the mitral valve. The end result of an ongoing rheumatic process with deteriorating valvular function is heart failure. Experience has shown that in such cases, prompt surgical management is the sole option and can result in the survival of up to 90% of patients.[29] It has been suggested that the reduction in cardiac workload following valve surgery results in a settling of the rheumatic process, similar to the beneficial effect observed for bed rest.[30]

Prevention

There are three levels of prevention of rheumatic fever: primordial prevention, based on removal of the social determinants of risk for rheumatic fever; primary prevention of the initial attack; and secondary prevention of recurrent attacks.

Primordial Prevention

Primordial prevention consists of measures to minimize future hazards to health and thus inhibit the establishment factors (environmental, economic, social, behavioral, cultural) known to increase the risk of disease. It addresses broad health determinants rather than preventing personal exposure to risk factors, which is the goal of primary prevention. In the case of rheumatic fever, the improvement of social conditions and increasing access to primary health care have been associated with a dramatic fall in the incidence of the disease even before the discovery of antibiotics (curve A, **Fig. 74.1**). Therefore the prevention of rheumatic fever primarily requires the improvement of socioeconomic status of people at high risk of developing rheumatic fever.

Primary Prevention

Antibiotic treatment of proven or presumed GAS pharyngitis is effective in reducing the attack rate of rheumatic fever by 70%. IM penicillin appears to reduce the attack rate by as much as 80%. There is one fewer case of rheumatic fever for every 50 to 60 patients treated with antibiotics.[11] **Table 74.4** presents the drug regimen of choice.[27]

TABLE 74.4

Drug Regimen of Choice for Primary Prevention of Rheumatic Fever

ANTIBIOTIC	ADMINISTRATION	DOSE
Benzathine benzylpenicillin	Single intramuscular injection	1.2 million units; 50% if <30 kg in weight
Phenoxymethylpenicillin (penicillin VK)	Oral for 10 days	250-500 mg three times daily for 10 days
Erythromycin ethylsuccinate	Oral for 10 days	Varies with the formulation

Data from World Health Organization. Rheumatic fever and rheumatic heart disease: report of a WHO expert panel. WHO Technical Report Series No. 923. Geneva: WHO; 2004.

The treatment of proven or presumed GAS pharyngitis is directed toward eradication of the bacteria from the upper respiratory tract. The infection can usually be eradicated by a single IM injection of benzathine benzylpenicillin or by 10 days' treatment with oral penicillin.[11] Although the use of IM penicillin to prevent rheumatic fever is supported by clinical trials, few trials have been done to test the efficacy of oral penicillin for the primary prevention of rheumatic fever. However, there is resistance to using IM penicillin in some developing countries because of the perceived higher risk of anaphylaxis and the dangers associated with the potential reuse of needles. Concerns over safety of IM penicillin have resulted in government orders prohibiting penicillin injections in hospitals and clinics. Government regulations in response to some of these concerns are warranted, particularly in the area of infection control by preventing needle reuse. However, with respect to the dangers of anaphylaxis, more than 60 years of experience with penicillin has shown that, although toxic reactions to IM penicillin have been reported, severe reactions are exceedingly rare, especially in children. Therefore, when given under sterile conditions with an appropriate injection technique, concern regarding the use of parenteral penicillin is unwarranted.[11]

Three major controversies surround the primary prevention of rheumatic fever. The first concerns the role of active ascertainment of cases of sore throat in school-based primary prevention programs. This strategy has been tested in a cluster randomized trial of 53 schools (approximately 22,000 students) from a high-incidence rheumatic fever setting (approximately 60/100,000/year) in Auckland, New Zealand.[31] The control group received routine general practice care. The intervention was a school-based sore throat clinic program with free nurse-observed oral penicillin treatment of GAS pharyngitis. This study involving 86,874 person-years showed no significant reduction of rheumatic fever in the school-based sore throat clinic programs.

The second controversy relates to the utility of primary prevention as a public health measure for the prevention of rheumatic fever.[4] Although there are no RCTs of this strategy, there are several examples of the successful application of primary prevention in the context of a comprehensive public health program for the prevention of rheumatic fever in Cuba, Costa Rica, and the French islands of Martinique and Guadeloupe (curve C, **Fig. 74.1**).[4,16]

Third, the cost-effectiveness of primary prevention as a public health strategy for the prevention of rheumatic fever has been questioned.[4,8] A study conducted in South Africa shows that a strategy of using a clinical decision rule to diagnose GAS pharyngitis without culturing and providing treatment with a single IM injection of penicillin is a cost-effective strategy for the primary prevention of rheumatic fever

in a high-risk community.[32] A strategy of culturing all children is prohibitively expensive. Taken together with the clinical trial evidence,[11] the evidence suggests that primary prevention by treatment of symptomatic cases of GAS pharyngitis diagnosed on clinical grounds may be a cost-effective public heath strategy for the prevention of rheumatic fever in the context of a comprehensive national program for prevention of the disease.[27]

Secondary Prevention

A systematic review of the effectiveness of antibiotics in the secondary prevention of rheumatic fever shows two principal findings (see Classic References, Manyemba and Mayosi). First, the evidence from clinical trials is strongly in support of the superiority of IM compared to oral penicillin in the prevention of rheumatic fever recurrences. Second, more frequent injections are more effective in preventing rheumatic fever recurrence than injections every 4 weeks. The evidence is strong for injections every 2 weeks, with an almost 50% reduction in the risk of rheumatic fever recurrence compared to injections every 4 weeks. The evidence for injections every 3 weeks is less strong and may be even weaker if the analysis takes into account the systematic error introduced by inadequate randomization and allocation concealment in the studies. Despite this evidence, the World Health Organization (WHO)[27] recommends intervals of 3 to 4 weeks for the secondary prevention of rheumatic fever (**Table 74.5**).

TABLE 74.5

Drug Regimen of Choice for Secondary Prevention of Rheumatic Fever

ANTIBIOTIC	ADMINISTRATION	DOSE
Benzathine benzylpenicillin	Single intramuscular injection every 3-4 weeks	For adults and children ≥30 kg in weight: 1,200,000 units For children <30 kg in weight: 600,000 units
Penicillin V	Oral	250 mg twice daily
Sulfonamide*	Oral	For adults and children ≥30 kg in weight: 1 g daily For children <30 kg in weight: 500 mg daily
Erythromycin	Oral	250 mg twice daily

*Including sulfadiazine, sulfadoxine, and sulfisoxazole.

Data from World Health Organization. Rheumatic fever and rheumatic heart disease: report of a WHO expert panel. WHO Technical Report Series No. 923. Geneva: WHO; 2004.

Recommendations regarding the duration of secondary prophylaxis are largely empiric and based on observational studies. The duration of prophylaxis should be individualized and take into account the socioeconomic conditions and risk of exposure to GAS for that patient. Individuals who have had carditis, with or without valvular involvement, are at higher risk for recurrent attacks and should receive prophylaxis well into adulthood and perhaps for life. If valvular heart disease persists, prophylaxis should be lifelong. Patients who have not had rheumatic carditis may receive prophylaxis until 21 years of age or 5 years after the last attack[27] (**Table 74.6**).

TABLE 74.6

Duration of Secondary Prophylaxis for Rheumatic Fever

CATEGORY OF PATIENT	DURATION OF PROPHYLAXIS
Patient without proven carditis	For 5 years after last attack or until 18 years of age (whichever is longer)
Patient with carditis (mild mitral regurgitation or healed carditis)	For 10 years after last attack or at least until 25 years of age (whichever is longer)
More severe valvular disease	Lifelong
After valve surgery	Lifelong

Data from World Health Organization. Rheumatic fever and rheumatic heart disease: report of a WHO expert panel. WHO Technical Report Series No. 923. Geneva: WHO; 2004.

Future Perspectives

The key challenge to the control of rheumatic fever is related to the identification and removal of barriers to the translation of existing knowledge into policy, programs, and practice. There is good evidence that a comprehensive national program that includes primary and secondary prevention interventions is effective in reducing the incidence of rheumatic fever and rheumatic heart disease in endemic countries.[4] Therefore a need exists for cardiovascular practitioners and other partners in endemic countries to work with their ministries of health to establish national public health programs of prevention, as recommended by WHO in 2001.[27]

The efforts to prevent and control rheumatic fever will be facilitated by improvement of access to and development of better formulations of penicillin, identification of the 3% to 5% of individuals with genetic susceptibility to rheumatic fever, and development of an effective vaccine for GAS infection. Benzathine penicillin is a WHO essential drug, but it is not available to all who need it in affected countries. Furthermore, the current formulations of injectable penicillin require frequent administration and follow-up, which impose a heavy burden on fragile primary health care systems in developing countries. Therefore it is necessary not only to improve access to high-quality benzathine penicillin, but also to develop new, long-acting formulations that will improve adherence and the effectiveness of prevention programs.

An understanding of the molecular genetic mechanisms underlying host susceptibility can provide important insights into the pathogenesis of rheumatic fever, which in turn can inform diagnosis, new treatments, and vaccine development. Currently, the syndromic Jones criteria are not very sensitive or specific in countries with a high incidence, and a test for susceptibility may increase specificity. The identification of all genetic susceptibility factors for rheumatic fever through whole-genome analysis may lead to the development of a useful predictive genetic risk score for the disease and an improvement of the Jones criteria in the future.[14]

A safe, effective, and affordable vaccine designed to prevent GAS infections could have a major impact on the health of millions of people at risk of developing rheumatic fever. Research over several decades has yielded a number of different candidate vaccines in various stages of preclinical and clinical development. Vaccine development efforts have been hampered by several obstacles, which can be overcome through global collaborative efforts to identify key activities and secure financial resources that will accelerate the process, leading to the successful introduction of a safe, effective vaccine for the entire world.[33]

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PART IX
Diseases of the Myocardium, Pericardium, and Pulmonary Vasculature Bed

OUTLINE

75

Congenital Heart Disease in the Adult and Pediatric Patient

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General Considerations

This chapter has been written for the practicing adult cardiologist in the developed world and is compatible with the existing expert management recommendations for the care of adult patients with congenital cardiac defects. (An update on the ACC/AHA guidelines is available online on ExpertConsult.) The discussion will be concentrated on the issues of late adolescence and adulthood; such issues can best be appreciated in the setting of an understanding of the anatomy, physiology, and events during childhood, and these will be discussed in each section when appropriate. Additional information can be found in other sources.[1-3] *Congenital cardiovascular disease* is defined as an abnormality in cardiocirculatory structure or function that is present at birth, even if it is discovered much later. Congenital cardiovascular malformations usually result from altered embryonic development of a normal structure or failure of such a structure to progress beyond an early stage of embryonic or fetal development. The aberrant patterns of flow created by an anatomic defect may, in turn, significantly influence the structural and functional development of the remainder of the circulation. For instance, the presence of mitral atresia in a fetus may prohibit normal development of the left ventricle, aortic valve, and ascending aorta. Similarly, constriction of the fetal ductus arteriosus may result in right ventricular dilation and tricuspid regurgitation in the fetus and newborn.

Postnatal events can markedly influence the clinical presentation of a specific "isolated" malformation. Infants with Ebstein malformation of the tricuspid valve may improve dramatically as the magnitude of tricuspid regurgitation diminishes with the normal fall in pulmonary vascular resistance after birth; and infants with pulmonary atresia or severe stenosis may not become cyanotic until normal spontaneous closure of a patent ductus arteriosus (PDA) occurs. Ductal constriction many days after birth also may be a central factor in some infants in the development of coarctation of the aorta. Still later in life, patients with a ventricular septal defect (VSD) may experience spontaneous closure and develop right ventricular outflow tract obstruction and/or aortic regurgitation with increasing duration of follow-up. These selected examples serve to emphasize that anatomic and physiologic changes in the heart and circulation can continue to evolve from the prenatal period to late adult life.

Incidence in Childhood.

The true incidence of congenital cardiovascular malformations is difficult to determine accurately, partly because of differences in definitions. The incidence in fetal life exceeds that of early childhood, as very complex lesions are associated with early nonviability or later in utero death. Consequently, approximately 0.8% of live births are complicated by a cardiovascular malformation. This figure does not take into account what may be the two most common cardiac anomalies: the congenital, functionally normal bicuspid aortic valve and prolapse of the mitral valve.

Specific defects can show a definite gender preponderance: PDA, Ebstein anomaly of the tricuspid valve, and secundum atrial septal defect (ASD) are more common in females, whereas aortic valve stenosis, coarctation of the aorta, hypoplastic left heart syndrome, pulmonary and tricuspid atresia, and transposition of the great arteries (TGA) are more common in males.

Extracardiac anomalies occur in approximately 25% of infants with significant cardiac disease, and their presence may significantly increase the mortality rate. The extracardiac anomalies are often

multiple. One third of infants with both cardiac and extracardiac anomalies have some established syndrome.

The Adult Patient.

Thanks to the great successes of pediatric cardiac care, the overall number of adult patients with congenital heart disease (CHD) is now greater than the number of pediatric cases. Indeed, more than 90% of patients born in 1990 in Belgium survived to at least age 18 years In the United States, 40,000 babies are born each year with congenital heart defects.[4] More than 35,000 of these will reach age 18 and beyond. There are now approximately 1.3 million American adults with congenital heart defects, more than 50% of which are classified as complex, and in need of lifelong expert surveillance. These moderately complex to very complex patients are at significant risk of premature death, reoperation, or future complications of their conditions and their treatments. Many patients, especially those with moderately complex to very complex conditions, should see a specialist trained in the care of adult CHD. At present, there are not enough such practitioners or facilities to always make this possible. Adult patients should have been taught in adolescence about their condition, their future outlook, and the possibility of further surgery and complications, if appropriate, and they also should have been advised about their responsibilities in ensuring self-care and professional surveillance. Copies of operative reports should accompany patients being transferred for adult care, along with other key documents from the pediatric file.

Table 75.1 lists the types of patients who should be considered as having “simple” CHD and who are suitable for community care. **Tables 75.2 and 75.3** show the diagnoses for moderately complex and very complex patients. Moderately complex and very complex patients should be monitored throughout their lives in a specialized center.

TABLE 75.1

Types of Adult Patients with Simple Congenital Heart Disease*

Native Disease
Isolated congenital aortic valve disease
Isolated congenital mitral valve disease (except parachute valve, cleft leaflet)
Isolated patent foramen ovale or small atrial septal defect
Isolated small ventricular septal defect (no associated lesions)
Mild pulmonic stenosis
Repaired Conditions
Previously ligated or occluded ductus arteriosus
Repaired secundum or sinus venosus atrial septal defect without residua
Repaired ventricular septal defect without residua

*These patients can usually be cared for in the general medical community.

From Webb G, Williams R, Alpert J, et al: 32nd Bethesda Conference: Care of the Adult with Congenital Heart Disease, October 2-3, 2000. J Am Coll Cardiol 37:1161, 2001.

TABLE 75.2

Types of Adult Patients with Congenital Heart Disease of Moderate Severity*

Aorto–left ventricular fistulas
Anomalous pulmonary venous drainage, partial or total
Atrioventricular septal defects (partial or complete)
Coarctation of the aorta
Ebstein anomaly
Infundibular right ventricular outflow obstruction of significance
Ostium primum atrial septal defect
Patent ductus arteriosus (not closed)
Pulmonary valve regurgitation (moderate to severe)
Pulmonic valve stenosis (moderate to severe)
Sinus of Valsalva fistula/aneurysm
Sinus venosus atrial septal defect
Subvalvular or supravalvular aortic stenosis (except hypertrophic obstructive cardiomyopathy)
Tetralogy of Fallot
Ventricular septal defect with the following:
Absent valve or valves
Aortic regurgitation
Coarctation of the aorta
Mitral disease
Right ventricular outflow tract obstruction
Straddling tricuspid/mitral valve
Subaortic stenosis

*These patients should be seen periodically at regional adult congenital heart disease centers.

From Webb G, Williams R, Alpert J, et al: 32nd Bethesda Conference: Care of the Adult with Congenital Heart Disease, October 2-3, 2000. J Am Coll Cardiol 37:1161, 2001.

TABLE 75.3

Types of Adult Patients with Congenital Heart Disease of Great Complexity*

Conduits, valved or nonvalved
Cyanotic congenital heart (all forms)
Double-outlet ventricle
Eisenmenger syndrome
Fontan procedure
Mitral atresia
Pulmonary atresia (all forms)
Pulmonary vascular obstructive diseases
Single ventricle (also called *double-inlet* or *double-outlet, common,* or *primitive ventricle*)
Transposition of the great arteries
Tricuspid atresia
Truncus arteriosus/hemitruncus
Other abnormalities of atrioventricular or ventriculoarterial connection not included above (i.e., crisscross heart, isomerism, heterotaxy syndromes, ventricular inversion)

*These patients should be seen regularly at adult congenital heart disease centers.

From Webb G, Williams R, Alpert J, et al: 32nd Bethesda Conference: Care of the Adult with Congenital Heart Disease, October 2-3, 2000. J Am Coll Cardiol 37:1161, 2001.

CHD in the adult is not simply a continuation of the childhood experience. The patterns of many

lesions change in adult life. Arrhythmias are more frequent and of a different character (**see Chapter 32**). Cardiac chambers often enlarge, and ventricles tend to develop systolic dysfunction. Bioprosthetic valves, prone to early failure in childhood, last longer when implanted at an older patient age. The comorbidities that tend to develop in adult life often become important factors needing attention. As a result, the needs of adult CHD patients are often best met by a physician or a team familiar with both pediatric and adult cardiology issues. For the best results, congenital heart surgery and interventional catheterization procedures should be performed at centers with adequate surgical and institutional volumes of congenital heart cases at any age. Patients undergoing surgery in a nonspecialist environment, even when operated upon by a congenital heart surgeon, suffer a three-fold increased mortality rate compared with those treated in specialized congenital heart centers.[5] In most cases, the specialist environment is a children's hospital; this model will probably not be sustainable for optimal care as the population with CHD expands.

Echocardiographic studies, diagnostic heart catheterizations, electrophysiologic studies, magnetic resonance imaging (MRI), and other imaging modalities of complex cases (**see Chapters 14 to 19**) are best done where qualified staff has relevant training, experience, and equipment. Ideally, patients should be cared for by a multidisciplinary team. Special cardiology and echocardiography skills are essential, but individuals with other special training, experience and interest should also be accessible. These include congenital heart surgeons and their teams, nurses, reproductive health staff, mental health professionals, medical imaging specialists, respiratory consultants, and others.

Etiology

Congenital cardiac malformations can occur with mendelian inheritance directly as a result of a genetic abnormality, be strongly associated with an underlying genetic disorder (e.g., trisomy), be related directly to the effect of an environmental toxin (e.g., maternal diabetes, alcohol), or result from an interaction between multifactorial genetic and environmental influences too complex to allow a single definition of cause (e.g., CHARGE syndrome [see Syndromes in Congenital Heart Disease later]). The latter group is shrinking as genetic research identifies new genetic abnormalities underlying many conditions.

Genetic Considerations.

A single gene mutation can be causative in the familial forms of ASD with prolonged atrioventricular (AV) conduction; mitral valve prolapse; VSD; congenital heart block; situs inversus; pulmonary hypertension; and the syndromes of Noonan, LEOPARD, Ellis–van Creveld, and Kartagener (see Syndromes in Congenital Heart Disease later). The genes responsible for several defects have now been identified (e.g., long-QT syndrome, Holt-Oram syndrome, Marfan syndrome, hypertrophic cardiomyopathy, supravalvular aortic stenosis), and contiguous gene defects on the long arm of chromosome 22 underlie the conotruncal malformations of DiGeorge and velocardiofacial syndromes. However, at present, less than 15% of all cardiac malformations can be accounted for by chromosomal aberrations or genetic mutations or transmission (**see Chapters 7 and 33**).

It is interesting to note, but unexplained, that several different gene defects may lead to the same cardiac malformation (e.g., AV septal defect). Furthermore, the finding that, with some exceptions, only one of a pair of monozygotic twins is affected by CHD indicates that most cardiovascular malformations are not inherited in a simple manner. However, this observation may have led, in the past, to an underestimation of the genetic contribution because most recent twin studies reveal more than double the incidence of heart defects in monozygotic twins but usually in only one of the pair. Family studies indicate a 2-fold to 10-fold increase in the incidence of CHD in siblings of affected patients or in the

offspring of an affected parent. Malformations are often concordant or partially concordant within families. Routine fetal cardiac screening of subsequent pregnancies should be performed in such circumstances.

Environmental Considerations.

Maternal diabetes, maternal rubella infection, ingestion of thalidomide and isotretinoin early during gestation, and chronic maternal alcohol abuse are environmental insults known to interfere with normal cardiogenesis in humans. For example, the incidence of tetralogy of Fallot with pulmonary atresia is increased 10-fold in the offspring of diabetic mothers. Rubella syndrome consists of cataracts; deafness; microcephaly; and, either singly or in combination, PDA, pulmonary valve and/or arterial stenosis, and ASD. Thalidomide exposure is associated with major limb deformities and, occasionally, with cardiac malformations without a predilection for a specific lesion. Tricuspid valve anomalies are associated with ingestion of lithium during pregnancy. Fetal alcohol syndrome consists of microcephaly, micrognathia, microphthalmia, prenatal growth retardation, developmental delay, and cardiac defects (often defects of the ventricular septum) in approximately 45% of affected infants.

Prevention

Physicians who treat pregnant women should be aware of the effects of known teratogens, as well as drugs (e.g., angiotensin-converting enzyme [ACE] inhibitors and fetal renal development), that may have a functional rather than a structural damaging influence on the fetal and newborn heart and circulation. They should also recognize that information about the teratogenic potential of many drugs is inadequate. Appropriate radiologic equipment and techniques for reducing gonadal and fetal radiation exposure should always be used to reduce the hazards of this potential cause of birth defects.

Detection of genetic abnormalities during fetal life is becoming an increasing reality. Fetal cells are obtained from amniotic fluid or chorionic villus biopsy. Many fetuses in whom CHD is detected will undergo genetic testing, and fetal echocardiography is frequently indicated when a chromosomal abnormality is diagnosed due to other reasons. Many social, religious, and legal considerations influence whether termination of pregnancy is performed under these circumstances, but the improved outcomes for even the most complex CHDs frequently argue against the cardiac condition being used as the sole reason. Immunization of children with rubella vaccine has been one of the most effective preventive strategies against fetal rubella syndrome and its associated congenital cardiac abnormalities.

Anatomy

Normal Cardiac Anatomy

The key to understanding CHD is an appreciation of the segmental approach to the diagnosis of both simple and complex lesions.

Cardiac Situs

Cardiac situs refers to the status of the atrial appendages. The normal left atrial appendage is a finger-like structure with a narrow base and pectinate muscles that are confined to the appendage, and a smooth vestibule that is confluent with the smooth-walled body of the left atrium. On the other hand, the right atrial appendage is broad based and the pectinate muscles extend all the way around the vestibule and reach to the cardiac crux. Situs ambiguus refers to hearts with two morphologic left or right atrial appendages. These are dealt with in the section on isomerism and have implications with regard to

associated intracardiac and extracardiac abnormalities.

Atrioventricular Connections

Atrioventricular (AV) connections are the connections between the atria and ventricles. The AV connections are said to be concordant if the morphologic left atrium is connected to the morphologic left ventricle via the mitral valve, and the morphologic right atrium is connected to the morphologic right ventricle via a tricuspid valve. The connections are said to be discordant in other circumstances, such as congenitally corrected TGA (cc-TGA) and univentricular circulations, when both atria are connected predominantly to one of the ventricles.

Ventriculoarterial Connections

Ventriculoarterial connections are the connections between the semilunar valves and the ventricles. Ventriculoarterial concordance occurs when the morphologic left ventricle is connected to the aorta and the morphologic right ventricle is connected to the pulmonary artery. Ventriculoarterial discordance occurs when the morphologic left ventricle is connected to the pulmonary artery, and the aorta is connected to the morphologic right ventricle. A double-outlet right ventricle is present when more than 50% of both great arteries are connected to the morphologic right ventricle. A single-outlet heart has only one great artery connected to the heart.

Atria

Designating an atrium as a morphologic left atrium or right atrium is determined by the morphology of the atrial appendages and not by the status of the systemic or pulmonary venous drainage. The right atrial appendage is broad and triangular, whereas the left is smaller and finger like. The internal architecture is the key feature to an accurate diagnosis, with the right atrium having extensive pectinate muscles that run around the vestibule of the atrium, unlike its left atrial counterpart. Although the pulmonary veins usually drain into a morphologic left atrium and the systemic veins drain into a morphologic right atrium, this is not always the case.

Atrioventricular Valves

The morphologic mitral valve is a bileaflet valve with the anterior or aortic leaflet in fibrous continuity with the noncoronary cusp of the aortic valve. The mitral valve leaflets are supported by two papillary muscle groups located in the anterolateral and posteromedial positions. Each papillary muscle supports the adjacent part of both valve leaflets, with considerable variation in the morphology of the papillary muscles.

The tricuspid valve is a trileaflet valve. It is frequently difficult to identify all three leaflets because of the variability in the anteroposterior commissure. With close inspection, the commissural chordae that arise from the papillary muscles may permit the identification of the three leaflets. The three leaflets occupy a septal anterior, superior, and inferior position. The commissures between the leaflets are the anterior septal, anterior inferior, and inferior commissures. The papillary muscles supporting the valve leaflets arise mostly from the trabeculoseptomarginalis and its apical ramifications.

Morphologic Right Ventricle

The morphologic right ventricle is a triangular-shaped structure with inlet, trabecular, and outlet

components. The inlet component of the right ventricle has attachments from the septal leaflet of the tricuspid valve. Inferior to this is the moderator band, which arises at the base of the trabeculoseptomarginalis, with extensive trabeculations toward the apex of the right ventricle. The outlet component of the right ventricle consists of a fusion of three structures (i.e., the infundibular septum separating the aortic valve from the pulmonary valve, the ventriculoinfundibular fold separating the tricuspid valve from the pulmonary valve, and, finally, the anterior and posterior limbs of the trabeculoseptomarginalis).

Morphologic Left Ventricle

The morphologic left ventricle is an elliptical-shaped structure with a fine trabecular pattern, with absent septal attachments of the mitral valve in the normal heart. It consists of an inlet portion containing the mitral valve and a tension apparatus, with an apical trabecular zone that is characterized by fine trabeculations and an outlet zone that supports the aortic valve.

Semilunar Valves

The aortic valve is a trileaflet valve, with the left and right cusps giving rise to the left and right coronary arteries, respectively, with the noncoronary cusp lacking a coronary artery connection. Of note, the noncoronary cusp is in fibrous continuity with the anterior leaflet of the mitral valve. The aortic valve has a semilunar attachment to the junction of the ventricular outlet and its great arteries. The aortic cusps have a main core of fibrous tissue with endocardial linings on each surface. The cusps are thickened at the midpoint to form a nodule. The characteristics of the pulmonary valve are similar to those of its aortic counterpart, noting the absence of the coronary ostia arising at the superior portion of the sinuses.

Aortic Arch and Pulmonary Arteries

In the normal heart, the aortic arch usually points to the left, with the first branch, the innominate artery, giving rise to the right carotid artery and right subclavian artery. In general, the left carotid and left subclavian arteries arise separately from the aortic arch. By definition the ascending aorta is proximal to the origin of the innominate artery, with the transverse aortic arch extending from the innominate artery to the origin of the left subclavian artery. The aortic isthmus is the area between the left subclavian artery and a PDA or ligamentum arteriosum.

Systemic Venous Connections

In the normal heart, the superior caval vein connects to the roof of the right atrium. The inferior caval vein connects to the inferior portion of the morphologic right atrium, with hepatic veins joining the inferior caval vein before its insertion into the atrium. The coronary veins drain into the flow of the coronary sinus, with the latter running in the posterior AV groove and terminating in the right atrium. The inferior caval vein is guarded by the eustachian valve, which may vary in size among hearts.

Pulmonary Venous Drainage in the Normal Heart

The pulmonary veins drain to the left-sided atrium. Usually three pulmonary veins arise from the trilobed right lung and two pulmonary veins from the bilobed left lung. The pulmonary veins drain into the left atrium in superior and inferior locations. There is a short segment of extraparenchymal pulmonary vein before it disappears into the adjacent hila of the lungs.

Anatomic Variations in the Fetus and Their Implications in Children, Adolescents, and Adults

CHD is being diagnosed with increasing frequency during fetal life. Our ability to modify the evolution of structural (by fetal intervention) and physiologic (by drug therapy) heart disease is increasing. Knowledge of the changes in cardiovascular structure, function, and metabolism that occur during fetal development is perhaps more important today than at any time in the past.

The rapid somatic growth rates of infancy and adolescence are periods of rapid hemodynamic change. Stenotic lesions that may be relatively slowly progressive throughout early childhood need more frequent surveillance during adolescence. Childhood and adolescence is a time to begin educating patients, not just their parents, about their heart disease and the responsibilities that go with it. Issues such as the need for compliance with medications, avoidance of smoking and illicit drug use, and pregnancy and contraception counseling are by no means exclusively issues of the adult with CHD and increasingly require discussion in the pediatric cardiac clinic.

Indeed, the early teenage years should be regarded as part of the transition process before transfer to adult follow-up. The management of the older adolescent and follow-up of adults with newly discovered or previously treated CHD is a burgeoning new subspecialty that will continue to require careful planning to ensure that there are adequate resources for the increasing number of adult “graduates” of pediatric programs. A coordinated approach with specialists in an affiliated adult congenital clinic is clearly desirable.

Adult patients, and often their family members, should understand the cardiac condition both in terms of what has been done so far and what could happen in the future. This is important for a young patient “graduating” into the adult world. Patients need information and should become partners in their own care.

Potential long-term complications in adults with CHD (such as arrhythmias, ventricular failure, conduit obstruction, and endocarditis) should be explained to patients who are at relatively high risk for these issues. The possible need for future therapy, whether medical (antiarrhythmics, anticoagulation, heart failure therapy), catheter based (valve dilation, stents, arrhythmia ablation), or surgical (redo surgery, transplantation), should be discussed if the patient may require any such treatment in the near or intermediate-term future. Day-to-day issues of concern for these young adults need to be addressed, such as exercise prescriptions, driving restrictions, and traveling limitations. Many young people with CHD need advice regarding career choices, entering the work force, insurability, and life expectancy.

Many will want to start a family, and reproductive issues will need to be addressed. Discussion of appropriate contraception methods for any given patient should be offered. Counseling before conception as to the risk to the mother and the fetus for any given pregnancy should be done by specialized physicians. They will take into account the maternal cardiac anatomy, maternal functional status, maternal life expectancy, risk of CHD transmission to the offspring, and risk of premature birth. High-risk patients (e.g., a patient with Marfan syndrome with aortic root dilation; severe pulmonary hypertension; New York Heart Association [NYHA] class III or IV symptoms; and severe aortic stenosis) should be advised against pregnancy. Intermediate-risk patients (e.g., a patient with cyanosis; a patient requiring warfarin because of a mechanical valve or other conditions; or a patient with moderate left ventricular outflow tract obstruction or moderate left ventricular dysfunction) need to know that pregnancy, although possible, may be complicated, and they will require careful follow-up.

Last, but not least, comorbidities such as obesity, smoking, high blood pressure, diabetes, and high

cholesterol measurements add new levels of complexity to these adults as they age, and their consideration must be part of the mandate of the patient's cardiologist.

Pathologic Consequences of Congenital Cardiac Lesions

Congestive Heart Failure

Although the basic mechanisms of cardiac failure are similar for all ages, the common causes, time of onset, and, often, approach to treatment vary with age (**see also Chapters 21 to 31**). Fetal echocardiography now allows the diagnosis of intrauterine cardiac failure. The cardinal findings of *fetal heart failure* are scalp edema, ascites, pericardial effusion, and decreased fetal movements. In *preterm infants*, especially those with a birth weight of less than 1500 g, persistent patency of the ductus arteriosus is the most common cause of cardiac decompensation, and other forms of structural heart disease are uncommon. In *full-term newborns*, the earliest important causes of heart failure are hypoplastic left heart syndrome and aortic coarctation syndrome, sustained tachyarrhythmia, cerebral or hepatic arteriovenous fistula, and myocarditis. Among the lesions commonly producing heart failure *beyond age 1 to 2 weeks*, when diminished pulmonary vascular resistance allows substantial left-to-right shunting, are VSDs and AV septal defects, TGA, truncus arteriosus, and the total anomalous pulmonary venous connection. *Infants younger than 1 year* who have cardiac malformations account for 80% to 90% of pediatric patients who develop congestive failure. In *older children*, heart failure is often due to acquired disease or is a complication of surgical or interventional procedures. In the acquired category are rheumatic and endomyocardial diseases, infective endocarditis, hematologic and nutritional disorders, and severe cardiac arrhythmias.

Congestive heart failure is not common in adult congenital heart practice, although prevention of myocardial dysfunction is a common concern. The adult patient with CHD may develop heart failure in the presence of a substrate (e.g., myocardial dysfunction, valvular regurgitation) and a precipitant (e.g., sustained arrhythmia, pregnancy, or hyperthyroidism). Patients prone to congestive failure include those with long-standing volume loads (e.g., valvular regurgitation and left-to-right shunts) and those with a primary depression of myocardial function (e.g., systemic right ventricles, ventricles damaged during surgery or because of late treatment of ventricular pressure or volume overload). Treatment depends on a clear understanding of the elements contributing to decompensation and on addressing each of the treatable components. Standard adult heart failure regimens are frequently used and may include ACE inhibitors, angiotensin receptor blockers, beta blockers, diuretics, resynchronization pacing, transplantation, and other novel therapies. The evidence for the effectiveness of these strategies is relatively lacking, and many of the proven therapies used for heart failure in acquired heart disease have failed to have a demonstrable benefit in heart failure patients with CHD.

CHD accounts for 40% of pediatric heart transplants, but only 2% of adult heart transplants. Adult CHD heart transplant recipients have a mean survival time of 11 years, similar to that of patients with other forms of heart disease. Patients who have had Fontan surgery tend to have worse outcomes, presumably because they have multiorgan disease. About one third of heart-lung transplants are done for CHD. The 3-year survival rate is about 50%; the rate is even better in patients with Eisenmenger syndrome.

Cyanosis

Central cyanosis refers to arterial oxygen desaturation resulting from the shunting or mixing of systemic venous blood into the arterial circulation. The magnitude of shunting and mixing and the amount of pulmonary blood flow determines the severity of desaturation.

Morphology

Cardiac defects that result in central cyanosis can be divided into two categories: (1) those with increased pulmonary blood flow and (2) those with decreased pulmonary blood flow (**Table 75.4**).

TABLE 75.4

Cardiac Defects Causing Central Cyanosis*

Transposition of the great arteries	Ebstein anomaly
Tetralogy of Fallot	Eisenmenger physiology
Tricuspid atresia	Critical pulmonary stenosis or atresia
Truncus arteriosus	Functionally single ventricle
Total anomalous pulmonary venous return	

*Note 5 Ts and 2 Es.

Pathophysiology

Hypoxemia increases the renal production of erythropoietin, which in turn stimulates bone marrow production of circulating red blood cells, enhancing the oxygen-carrying capacity. Secondary erythrocytosis should be present in all cyanotic patients because it is a physiologic response to tissue hypoxia.[6] The improved tissue oxygenation that results from this adaptation may be sufficient to reach a new equilibrium at a higher hematocrit. However, adaptive failure can occur if the increased whole-blood viscosity rises so much that it impairs oxygen delivery.

Clinical Features

Although erythrocytosis is now rare because of the diminishing prevalence of untreated cyanotic CHD in developed countries, it may cause *hyperviscosity syndrome*. Its symptoms include headaches, faintness, dizziness, fatigue, altered mentation, visual disturbances, paresthesias, tinnitus. and myalgias. Iron deficiency, a common finding in cyanotic adult patients if repeated phlebotomies are done or excessive bleeding occurs, must be treated because it can increase the risk of complications.[8]

Hemostatic abnormalities have been documented in cyanotic patients with erythrocytosis and can occur in up to 20% of patients. A bleeding tendency can be mild and superficial, leading to easy bruising, skin petechiae, and mucosal bleeding, or it can be moderate or life threatening with hemoptysis or intracranial, gastrointestinal, or postoperative bleeding. An elevated prothrombin and partial thromboplastin time; decreased levels of factors V, VII, VIII, and IX; qualitative and quantitative platelet disorders; increased fibrinolysis; and systemic endothelial dysfunction from increased shear stress have all been implicated. Paradoxically, a thrombotic tendency has also been recently described, with 47% of cyanotic patients having an asymptomatic cerebral infarct and 31% having pulmonary thrombosis.[7]

Neurologic complications, including cerebral hemorrhage, can occur secondary to hemostatic defects and can be seen in patients taking anticoagulants. Patients with right-to-left shunts are at risk for paradoxical cerebral emboli, especially if they are iron deficient. A brain abscess should be suspected in a cyanotic patient with a new or different headache or new neurologic symptoms. Air filters should be

used in peripheral and central venous lines in cyanotic patients to avoid paradoxical emboli through a right-to-left shunt.

Renal dysfunction in patients with cyanotic CHD can be manifested as proteinuria, hyperuricemia, or renal failure. Pathologic studies at the level of the glomeruli show evidence of vascular abnormalities, as well as increased cellularity and fibrosis. Hyperuricemia is common and is thought to be due mainly to the decreased reabsorption of uric acid rather than to overproduction associated with erythrocytosis. Urate nephropathy, uric acid nephrolithiasis, and gouty arthritis may occur.

Rheumatologic complications of cyanotic CHD include *gout* and, especially, *hypertrophic osteoarthropathy*, which is thought to be responsible for the arthralgias and bone pain affecting up to one third of cyanotic patients. In patients with right-to-left shunting, megakaryocytes released from the bone marrow can bypass the lung. The entrapment of megakaryocytes in the systemic arterioles and capillaries induces the release of platelet-derived growth factor, promoting local cell proliferation. New osseous formation with periostitis ensues and gives rise to arthralgia and bony pain.

Patients with central cyanosis usually display dilated *coronary arteries*; atherosclerotic narrowing is unusual. Their level of total cholesterol is also lower than that of the general population.

Interventional Options and Outcomes

Complete Repair Procedures

Physiologic or anatomic repair results in total or near-total separation of the pulmonary and systemic circulations in complex cyanotic lesions that leads to relief of cyanosis and shunting. Such procedures should be performed whenever feasible. Complete repairs rarely are without long-term sequelae, despite the inference in the name, and both physicians and patients should be made aware of the need for regular lifelong care in nearly all cases.

Palliative Surgical Interventions

Palliative surgical interventions can be performed in patients with cyanotic lesions to increase pulmonary blood flow while allowing cyanosis to persist. Palliative surgical shunts are summarized in **Table 75.5**. Blalock-Taussig-Thomas, central, and Glenn (also called *cavopulmonary*) shunts are still in use today. Blalock-Taussig-Thomas shunts seldom caused pulmonary hypertension compared with central (Waterston and Potts) shunts and were less prone to causing pulmonary artery distortion. Glenn shunts have the advantage of increasing pulmonary flow without imposing a volume load on the systemic ventricle. Glenn shunts require low pulmonary artery pressures to work, and they may be associated with the development over time of pulmonary arteriovenous fistulas, which can worsen cyanosis.

TABLE 75.5

Palliative Systemic-to-Pulmonary Shunts

Arterial
Blalock-Taussig-Thomas shunt (subclavian artery to PA)
Classic: end-to-side, no or reduced ipsilateral arm pulses
Current: side-to-side tubular grafts, preserved arm pulses
Central shunt (side-to-side tubular graft, aorta to PA)
Potts shunt (descending aorta to LPA)
Waterston shunt (ascending aorta to RPA)
Venous
Glenn shunt (SVC to ipsilateral PA without cardiac or other PA connection)
Bidirectional cavopulmonary (Glenn) shunt (end-to-side SVC to LPA and RPA shunt)

LPA, left PA; *PA*, pulmonary artery; *RPA*, right PA; *SVC*, superior vena cava.

Transplantation

Transplantation of the heart or one or both lungs with surgical cardiac repair, and heart-lung transplantation have been performed in cyanotic patients with or without palliation who were no longer candidates for other forms of intervention (**see Chapter 28**). Pulmonary vascular obstructive disease precludes isolated heart transplantation. An increasing number of CHD patients with previous palliation and ventricular failure are successfully undergoing cardiac transplantation. Timing of transplantation in these patients remains difficult.

Other Management Measures for Cyanosis

The goal of *phlebotomy* is symptom control. When patients have troubling symptoms of hyperviscosity, are iron replete (normal MCV, hematocrit > 65%), and are not dehydrated, removal of 250 to 500 mL of blood over 30 to 45 minutes should be performed with concomitant quantitative volume replacement. The procedure may be repeated every 24 hours if necessary until symptomatic improvement occurs or the hemoglobin level has fallen below 18 to 19 g/dL. Phlebotomy is not indicated for asymptomatic patients.

If iron deficiency anemia is found, *iron supplements* should be prescribed.[8] Cyanotic patients should avoid iron deficiency, which can cause functional deterioration and is associated with an increased risk of stroke and adverse cardiovascular outcomes.

Platelet transfusions, fresh frozen plasma, vitamin K, cryoprecipitate, and desmopressin can be used to treat severe *bleeding*. Given the inherent tendency of cyanotic patients to bleed, aspirin, heparin, and warfarin should be avoided unless the risks of treatment are outweighed by the risks of no treatment. Likewise, nonsteroidal antiinflammatory drugs should be avoided to prevent gastrointestinal bleeding.

Symptomatic hyperuricemia and *gouty arthritis* can be treated as needed with standard therapies.

Reproductive Issues

Pregnancy in a cyanotic CHD patient (excluding a patient with Eisenmenger syndrome) results in a 32% incidence of maternal cardiovascular complications and a 37% incidence of fetal prematurity. Pregnant women with a resting oxygen saturation of more than 85% fare better than women with an oxygen saturation of less than 85% (**see Chapter 90**).

Follow-Up

Although their numbers have dramatically fallen in developed countries, all cyanotic patients should be followed by a CHD cardiologist, and particular attention should be paid to the underlying heart condition; symptoms of hyperviscosity; systemic complications of cyanosis; change in exercise tolerance; change in saturation levels; and prophylaxis against endocarditis, influenza, and pneumococcal infections. The clinician should remember to measure oxygen saturation only after the patient has been resting for at least 5 minutes, and measure blood pressure in the contralateral arm to the side used for an aortopulmonary shunt. In stable cyanotic patients, yearly follow-up is recommended and should include annual flu shots, pneumococcal vaccination, yearly blood work (complete blood count, ferritin, clotting profile, renal function, uric acid), and regular Doppler echocardiographic studies. Home oxygen therapy may occasionally have a role.

Pulmonary Hypertension

Once common because of delayed diagnosis or treatment, severe pulmonary hypertension is a less and less common accompaniment of congenital cardiac lesions in the developed world. When present, the status of the pulmonary vascular bed is often the principal determinant of the clinical manifestations, the course, and whether corrective treatment is feasible (**see Chapter 85**). A recent consensus statement provides important information on this general topic.[9,10] Increases in pulmonary arterial pressure result from elevations of pulmonary blood flow and/or resistance, the latter sometimes caused by an increase in vascular tone but usually the result of underdevelopment and/or obstructive or obliterative structural changes within the pulmonary vascular bed. Although pulmonary hypertension usually affects the entire pulmonary vascular bed, it may occur focally. For example, unilateral pulmonary hypertension may occur in an overshunted lung (the other lung perhaps protected and fed by a cavopulmonary Glenn shunt) or in lung segments supplied by aortopulmonary collateral flow.

Pulmonary vascular resistance normally falls rapidly immediately after birth because of the onset of ventilation and subsequent pulmonary vasodilation. Subsequently, and gradually, the medial smooth muscle of pulmonary arterial resistance vessels thins. This latter process is often delayed by several months in infants with large aortopulmonary or ventricular communications, at which time levels of pulmonary vascular resistance are still somewhat elevated. In patients with high pulmonary arterial pressures from birth, failure of normal growth of the pulmonary circulation may occur, and anatomic changes in the pulmonary vessels in the form of proliferation of intimal cells and intimal and medial thickening often progress, so vascular resistance in an older child or adult ultimately may become relatively fixed by obliterative changes in the pulmonary vascular bed. Quite likely, injury to pulmonary vascular endothelial cells initiates a cascade of events that involve the release or activation of factors that alter the extracellular matrix, induce hypertrophy, cause proliferation of vascular smooth muscle cells, and promote connective tissue protein synthesis. Considered together, these may permanently alter vessel structure and function.

Mechanisms of Development

Intimal damage appears to be related to shear stresses because endothelial cell damage occurs at high shear rates. A reduction in pulmonary arteriolar lumen size due to either thickened medial muscle or vasoconstriction increases the velocity of flow. Shear stress also increases as blood viscosity rises; therefore, infants with hypoxemia and high hematocrit levels, as well as increased pulmonary blood flow,

are at increased risk of developing pulmonary vascular disease. In patients with left-to-right shunts, pulmonary arterial hypertension, if not present in infancy or childhood, may never occur or may not develop until the third or fourth decade or later. Once developed, intimal proliferative changes with hyalinization and fibrosis are not reversible by repair of the underlying cardiac defect. In severe pulmonary vascular obstructive disease, arteriovenous malformations may develop and predispose to sometimes massive hemoptysis.

Most vexing is the variability among patients with the same or similar cardiac lesions in both the time of appearance and the rate of progression of their pulmonary vascular obstructive process. Although genetic influences may be operative (an example is the apparent acceleration of pulmonary vascular disease in patients with CHD and trisomy 21), evidence is now accumulating for important genetic, prenatal, and postnatal modifiers of the pulmonary vascular bed that appear, at least in part, to be lesion dependent. Thus a quantitative variability exists in the pulmonary vascular bed related to the number, not just the size and wall structure, of arterial vessels within the pulmonary circulation, all of which may be modified by coexisting CHD.

Eisenmenger Syndrome

Diminishingly common in the developed world, but still common where early cardiac treatment is unavailable, *Eisenmenger syndrome*, a term coined by Paul Wood, is defined as pulmonary vascular obstructive disease that develops as a consequence of a large preexisting left-to-right shunt such that pulmonary artery pressures approach systemic levels and the direction of the flow becomes bidirectional or predominantly right to left. Congenital heart defects that can result in Eisenmenger syndrome include “simple” defects, such as ASD, VSD, and PDA, as well as more “complex” defects, such as AV septal defect, truncus arteriosus, aortopulmonary window, and univentricular heart. The high pulmonary vascular resistance is usually established in early childhood (often by age 4 years, except in ASD) and is sometimes present from birth.

Natural History of the Unoperated Patient

Patients with defects that allow free communication between the pulmonary and systemic circuits at the aortic or ventricular levels usually have a fairly healthy childhood and gradually become overtly cyanotic during their second or third decade. Exercise intolerance (dyspnea and fatigue) is proportional to the degree of hypoxemia or cyanosis. In the absence of complications, these patients generally have a good functional capacity up to their third decade and thereafter usually experience a slowly progressive decline in their physical abilities. Most patients survive to adulthood, with reported survival rates of 77% at 15 years of age and 42% at 25 years of age.

Congestive heart failure in patients with Eisenmenger syndrome usually occurs after 40 years of age. The most common modes of death are sudden death (≈30%), congestive heart failure (≈25%), and pulmonary hemorrhage (≈15%). Pregnancy, perioperative death at the time of noncardiac surgery, and infectious causes (brain abscesses and endocarditis) account for most of the remainder.

Clinical Manifestations

Patients can present with the following complications: those related to their cyanotic state; palpitations, which occur in nearly half of patients; atrial fibrillation or flutter in ≈35%, ventricular tachycardia in up to ≈10%); hemoptysis, which occurs in approximately 20%; pulmonary thromboembolism, angina,

syncope, and endocarditis, each of which occurs in approximately 10%; and congestive heart failure. Hemoptysis is usually due to bleeding bronchial vessels or pulmonary infarction.

Physical examination reveals central cyanosis and clubbing of the nail beds. Patients with Eisenmenger PDA can have pink nail beds on the right hand (more than the left hand) and cyanosis and clubbing of both feet, or so-called differential cyanosis. This occurs because venous blood shunts through the ductus and enters the aorta distal to the subclavian arteries. The jugular venous pressure in patients with Eisenmenger syndrome can be normal or elevated, especially with prominent *v* waves when tricuspid regurgitation is present. Signs of pulmonary hypertension (a right ventricular heave, palpable and loud P_2, and a right-sided S_4) are typically present. In many patients, a pulmonary ejection click and a soft and scratchy systolic ejection murmur, attributable to dilation of the pulmonary trunk, and (less often) a high-pitched decrescendo diastolic murmur of pulmonary regurgitation (Graham Steell murmur) are audible. Peripheral edema is absent until right-sided heart failure ensues.

Laboratory Investigations

Electrocardiography (ECG).

Peaked P waves consistent with right atrial overload and evidence of right ventricular hypertrophy with right axis deviation are the rule on an ECG. Atrial arrhythmias can be present.

Chest Radiography.

Chest radiography shows dilated central pulmonary arteries with rapid tapering of the peripheral pulmonary vasculature (the radiographic hallmarks of Eisenmenger syndrome). Pulmonary artery calcification may be seen and is diagnostic of long-standing pulmonary hypertension. Eisenmenger syndrome due to VSD or PDA usually has a normal or only slightly increased cardiothoracic ratio. Eisenmenger syndrome due to an ASD typically has a large cardiothoracic ratio because of right atrial and ventricular dilation, along with an inconspicuous aorta, reflecting a low lifelong cardiac output. Calcification of the arterial duct may be seen in Eisenmenger PDA.

Echocardiography.

The intracardiac defect should be seen readily, along with bidirectional shunting. A pulmonary hypertensive PDA is not easily seen. Evidence of pulmonary hypertension is found. Assessment of right ventricular function adds prognostic value.

Cardiac Catheterization.

Cardiac catheterization not only provides direct measurement of the pulmonary artery pressure, documenting the existence of severe pulmonary hypertension, but can also allow assessment of the reactivity of the pulmonary vasculature. Administration of pulmonary arterial vasodilators (O_2, nitric oxide, prostaglandin I_2 [epoprostenol]) can determine which patients have contraindications to surgical repair and which patients have reversible pulmonary hypertension and may benefit from surgical or even catheter repair. Radiographic contrast material may cause hypotension and worsening cyanosis and should be used cautiously.

Open-Lung Biopsy.

Open-lung biopsy is seldom used in the current era, and should be considered only when reversibility of the pulmonary hypertension is uncertain from the hemodynamic data. An expert opinion will be necessary to determine the severity of the changes, often using the Heath-Edwards classification.

Indications for Intervention

Historically, the underlying principle of clinical management in patients with Eisenmenger syndrome was to avoid any factors that may destabilize the delicately balanced physiology. Until the last decade or so, an approach of nonintervention has been recommended. The widespread use of pulmonary vasodilators in Eisenmenger patients began in 2006, after the publication of the BREATHE-5 randomized controlled trial (see below). Since then, a number of trials of agents in various classes have provided evidence of benefit from these "advanced therapies."[11]

In addition to or instead of advanced therapies (which are quite expensive), the therapeutic focus is directed toward preventing complications (e.g., flu shots and pneumococcal vaccine to reduce the morbidity of respiratory infections) or restoring the physiologic balance (e.g., iron replacement for iron deficiency, antiarrhythmic management of atrial arrhythmias, and diuretics for right-sided heart failure). As a general rule, the first episode of hemoptysis should be considered an indication for investigation. Bed rest is usually recommended; although usually self-limiting, each such episode should be regarded as potentially life threatening, and a treatable cause should be sought. When patients are severely incapacitated from severe hypoxemia or congestive heart failure, the main intervention available is lung transplantation (plus repair of the cardiac defect) or, with somewhat better results, heart-lung transplantation. This is generally reserved for individuals without contraindications who are thought to have a 1-year chance of survival of less than 50%. Such assessment is fraught with difficulty because of the unpredictability of the time course of the disease and the risk of sudden death.

Noncardiac surgery should be performed only when absolutely necessary because of its high associated mortality rates. Eisenmenger syndrome patients are particularly vulnerable to alterations in hemodynamics induced by anesthesia or surgery, such as a minor decrease in systemic vascular resistance that can increase right-to-left shunting and possibly potentiate cardiovascular collapse. Local anesthesia should be used whenever possible. Avoidance of prolonged fasting and, especially, dehydration, the use of antibiotic prophylaxis when appropriate, and careful intraoperative monitoring are recommended. The choice of general versus epidural or spinal anesthesia is controversial. An experienced cardiac anesthetist with an understanding of Eisenmenger syndrome physiology should administer anesthesia. Additional risks of surgery include excessive bleeding, postoperative arrhythmias, and deep venous thrombosis with paradoxical emboli. An "air filter" or "bubble trap" should be used for most intravenous lines in cyanotic patients. Early ambulation is recommended. Postoperative care in an intensive care unit setting is optimal.

Interventional Options and Outcomes

Oxygen

Supplemental nocturnal oxygen has been shown to have no impact on exercise capacity or on survival rates in adult patients with Eisenmenger syndrome. Supplemental oxygen during commercial air travel is often recommended, but the scientific basis for this recommendation is lacking.

Transplantation

Lung transplantation may be undertaken in association with repair of existing cardiovascular defect(s). Alternatively, heart-lung transplantation may be required if the intracardiac anatomy is not correctable. The 3-year survival rate after heart-lung transplantation for CHD is approximately 50%. The subgroup of patients with Eisenmenger syndrome may do better, with a 50% 5-year survival rate. These procedures

offer the best hope to individuals with end-stage CHD who are confronting death and have an intolerable quality of life.

Medical Therapy

In 2006, the BREATHE-5 trial was published, demonstrating that bosentan could be safely given to patients with Eisenmenger syndrome. It improved their 6-minute walk distance. Since then, several trials have demonstrated improved outcomes of various types in Eisenmenger patients using the three different drug classes of pulmonary vasodilators: endothelin receptor antagonists; phosphodiesterase inhibitors; and prostacyclins. A recent review article proposed a treatment algorithm for such patients (**Fig. 75.1**).

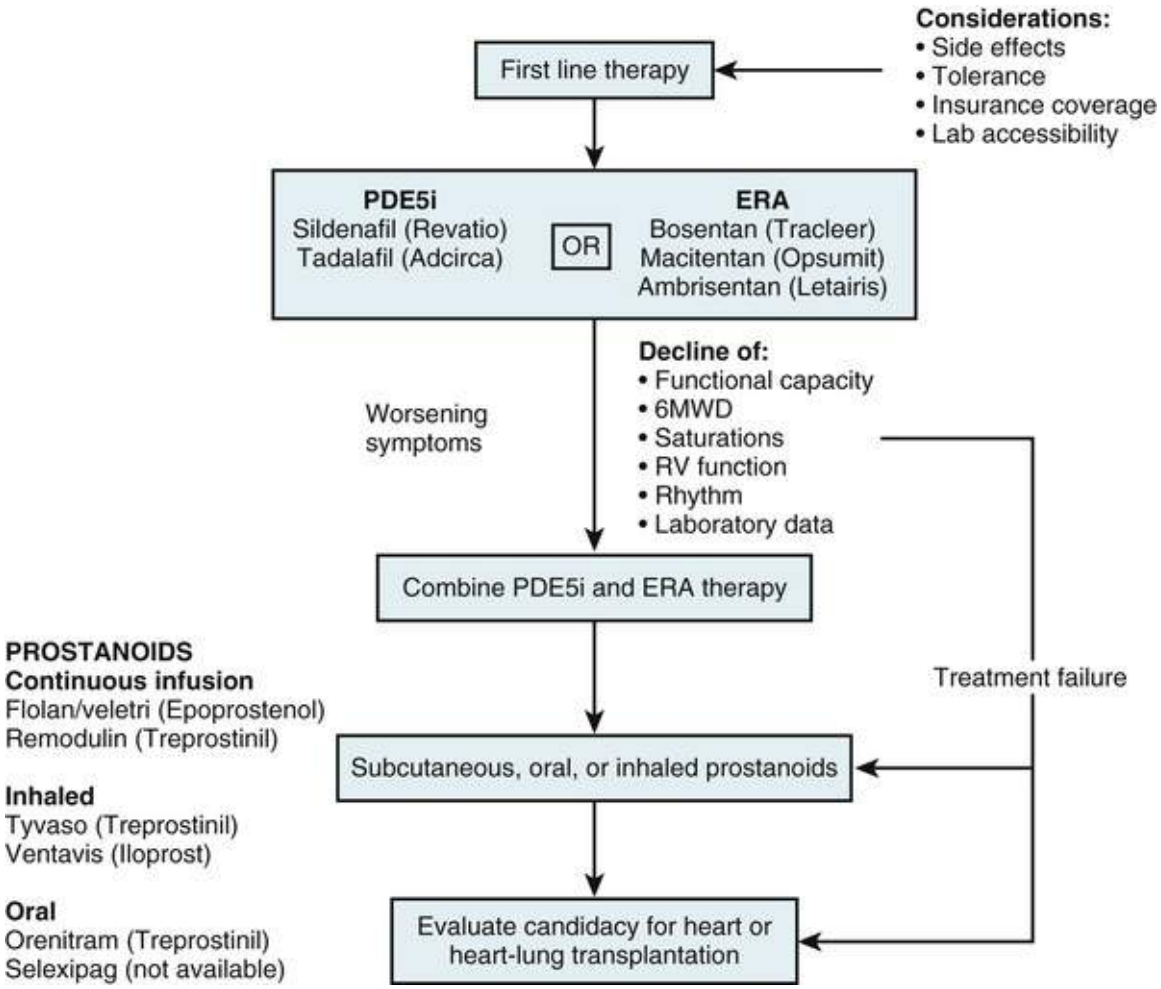


FIGURE 75.1 Suggested treatment algorithm for pulmonary arterial hypertension and Eisenmenger syndrome. *6MWD*, 6-minute walk distance. (From Roth TS, Aboulhosn JA: Pulmonary Hypertension And Congenital Heart Disease. Cardiol Clin 2016;34(3):391-400.)

Follow-Up

Patient education is critical. Avoidance of over-the-counter medications, dehydration, smoking, high-altitude exposure, and excessive physical activity should be stressed. Avoidance of pregnancy with appropriate contraceptive methods is of paramount importance. Annual flu shots, a single dose of pneumococcal vaccine, and use of endocarditis prophylaxis together with proper oral hygiene are recommended. A yearly assessment of the complete blood cell count and uric acid, creatinine, and ferritin levels should be done to monitor treatable causes of deterioration.

Cardiac Arrhythmias

Most arrhythmias encountered in teenagers and young adults are in association with previously operated CHD (**see also Chapters 32 to 38**). Arrhythmias can be a major clinical challenge in adolescent and adult congenital heart patients. They are the most frequent reason for emergency department visits and hospital admissions, and they are usually recurrent and may worsen or become less responsive to treatment with time. Treatment may be challenging.

Atrial Arrhythmias

Atrial flutter and, to a lesser degree, atrial fibrillation are the most common arrhythmias (**see Chapter 38**). Atrial flutter tends to reflect right atrial abnormalities, and atrial fibrillation, left atrial abnormalities. Atrial flutter in such patients is often atypical in appearance and behavior and is better called *intraatrial reentrant tachycardia.* Recognition of atrial flutter can be difficult, and the observer must be vigilant in recognizing 2 : 1 conduction masquerading as sinus rhythm (typically with a resting heart rate of ≈ 100 beats/min). Recurrence is likely and should not necessarily be assumed to represent failure of the management strategy. The conditions in which atrial flutter is most likely are Mustard/Senning repairs of TGA, repaired or unrepaired ASDs, repaired tetralogy of Fallot, and Ebstein anomaly of the tricuspid valve; it is also likely after a Fontan operation. Atrial flutter may reflect hemodynamic deterioration in patients who have had Mustard, Senning, tetralogy of Fallot, or Fontan repairs. Its onset is usually associated with more symptoms and functional limitation.

The pharmaceutical agents most commonly used in therapy are warfarin, beta blockers, amiodarone, sotalol, propafenone, and digoxin. As a rule, patients with good ventricular function can receive sotalol or propafenone, whereas those with depressed ventricular function should receive amiodarone. Other therapies, including pacemakers, ablative procedures, and innovative surgery, are being both applied and refined. Sustained ventricular tachycardia or ventricular fibrillation occurs less often, usually in the setting of ventricular dilation, dysfunction, and scarring. Although sudden death is common in several conditions, the mechanism is poorly understood.

Ventricular Tachycardia

Ventricular tachycardia can be seen as a manifestation of proarrhythmic effects of various agents; in patients with acute myocardial injury or infarction; and in CHD patients with severe ventricular dysfunction. In particular, sustained ventricular tachycardia has occurred in patients with repaired tetralogy of Fallot, where it is seen as a manifestation of hemodynamic problems (usually severe pulmonary regurgitation) requiring repair; as a reflection of right ventricular dilation and dysfunction; and in relation to ventricular scarring.

Sudden Death

Unlike adults, children seldom die suddenly and unexpectedly of cardiovascular disease. Nonetheless, sudden death at any age has been reported with arrhythmias, aortic stenosis, hypertrophic obstructive cardiomyopathy, idiopathic pulmonary arterial hypertension, Eisenmenger syndrome, myocarditis, congenital complete heart block, primary endocardial fibroelastosis, and when there are specific anomalies of the coronary artery origin and course (**see also Chapter 42**).[12]

Atrioventricular Block

First-degree AV block is commonly seen in patients with AV septal defects, Ebstein anomaly, or complete TGA (D-TGA) and in the older ASD patient. Complete heart block may develop in patients with cc-TGA and may develop postoperatively in these and other patients. When pacing is required, epicardial leads are usually placed in cyanotic patients because of the risk of paradoxical embolism. Many adult patients with CHD are prone to problems of vascular access because of prior surgeries, catheter procedures, and pacing leads.

Infective Endocarditis

Infective endocarditis complicating CHD is uncommon before 2 years of age, except in the immediate postoperative period (**see also Chapter 73**). Recent guidelines for endocarditis prophylaxis have substantially altered clinical practice. Maintenance of excellent oral hygiene is encouraged most strongly. Antibiotic prophylaxis prior to dental procedures is recommended for patients with prosthetic heart valves; prosthetic material used for cardiac valve repair; a prior history of infective endocarditis; persistently cyanotic CHD; residual defects that are adjacent to a prosthetic patch or prosthetic device; and for the first 6 months after placement of prosthetic material or a device for CHD and for cardiac transplant recipients who develop cardiac valvulopathy.

Chest Pain

Angina pectoris is an uncommon symptom of congenital cardiac disease, although when there is typical pain a full surveillance for coronary abnormalities (e.g., abnormal origin and course, ostial stenosis, myocardial bridging) is required. Pain caused by pericarditis is commonly of acute onset and associated with fever, and can be identified by specific physical, radiographic, and echocardiographic findings. Most commonly, late postoperative chest pain is musculoskeletal in origin and may be reproduced on upper extremity movement or by palpation. **See also Chapter 56**.

Syndromes in Congenital Heart Disease

The acronym ALCAPA in *ALCAPA syndrome* stands for *a*nomalous *l*eft *c*oronary *a*rtery *a*rising from the *p*ulmonary *a*rtery. It is also called *Bland-White-Garland syndrome* (Videos 75.1 to 75.3).

Alagille syndrome is an autosomal dominant syndrome consisting of intrahepatic cholestasis, characteristic facies, butterfly-like vertebral anomalies, and varying degrees of peripheral pulmonary artery stenoses or diffuse hypoplasia of the pulmonary artery and its branches. It is most commonly caused by point mutations in the *JAG1* gene on chromosome 20p and is less frequently caused by deletions of chromosome 20p (7% of cases) or point mutations in *NOTCH2* (1% of cases).

22q11 deletion syndrome is caused by a microdeletion at chromosome 22q11, resulting in a wide clinical spectrum. It is also known as DiGeorge or velocardiofacial or Takao syndrome. Cardiac defects include conotruncal defects such as interrupted aortic arch, tetralogy of Fallot, truncus arteriosus, and double-outlet right ventricle.

The CHARGE in *CHARGE syndrome* is an acronym for ocular *c*oloboma, congenital *h*eart defects, choanal *a*tresia, *r*etardation of growth and development, *g*enital hypoplasia, and *e*ar anomalies associated with deafness. The phenotype is highly variable. Congenital heart defects seen in the CHARGE association are tetralogy of Fallot with or without other cardiac defects, AV septal defect,

double-outlet right ventricle, double-inlet left ventricle, TGA, interrupted aortic arch, and others. A majority of cases are caused by mutations or deletions of a gene encoding a chromatin remodeling protein, *CHD7*.

Down syndrome is the most common genetic malformation and is caused by trisomy 21. Most of the patients (95%) have complete trisomy of chromosome 21; some have translocation or mosaic forms. The phenotype is diagnostic (short stature, characteristic facial appearance, mental retardation, brachydactyly, atlantoaxial instability, and thyroid and white blood cell disorders). Congenital heart defects are frequent (40%), with AV septal defect, VSD, and PDA being the most common. Patients with Down syndrome are prone to earlier and more severe pulmonary vascular disease than otherwise expected as a result of the lesions identified. Health supervision guidelines for patients with Down syndrome provide management and screening recommendations.[13]

Ellis–van Creveld syndrome is an autosomal recessive skeletal dysplasia syndrome in which common atrium, primum ASD, and partial AV septal defects are the most common cardiac lesions. This syndrome is one of a growing class of "ciliopathies" and is caused by mutations in *EVC1* or *EVC2*.

Holt-Oram syndrome is an autosomal dominant syndrome consisting of radial abnormalities of the forearm and hand associated with secundum ASD (most common); VSD; or, rarely, other cardiac malformations. It is caused by mutations in *TBX5* and is characterized by phenotypic variability within and between families.

LEOPARD syndrome is an autosomal dominant condition. It is a close "cousin" of Noonan syndrome, and it shares a similar genetic substrate (deletion of the *PTPN-11* gene). It includes *l*entigines, *E*CG abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitalia, *r*etardation of growth, and *d*eafness. Rarely, cardiomyopathy or complex CHD may be present.

Noonan syndrome is an autosomal dominant syndrome phenotypically somewhat similar to Turner syndrome but with a normal chromosomal complement. Noonan syndrome is caused by mutations in the *PTPN-11* gene, as well as the *KRAS*, *SOS-1*, *NRAS*, and *RAF-1* genes, leading to the idea that RAS pathway genes contribute to Noonan and related syndromes. Noonan syndrome is associated with congenital cardiac anomalies, especially dysplastic pulmonary valve stenosis, pulmonary artery stenosis, and ASD. Hypertrophic cardiomyopathy is less common. Congenital lymphedema is a commonly associated anomaly.

Rubella syndrome was once a serious condition, but it has largely been eradicated where there are vaccination programs. It is a wide spectrum of malformations caused by rubella infection early in pregnancy, including cataracts, retinopathy, deafness, CHD, bone lesions, and mental retardation. The spectrum of congenital heart lesions is wide and includes pulmonary artery stenosis, PDA, tetralogy of Fallot, and VSD.

Scimitar syndrome (Videos 75.4 and 75.5) is a constellation of anomalies, including a total or partial anomalous pulmonary venous connection (PAPVC) of the right lung to the inferior vena cava, often associated with hypoplasia of the right lung and right pulmonary artery. The lower portion of the right lung (sequestered lobe) tends to receive an additional arterial supply from the abdominal aorta. The name of the syndrome derives from the appearance on a posteroanterior chest radiograph of the shadow formed by the anomalous pulmonary venous connection that resembles a Turkish sword, or scimitar.

SHONE complex (syndrome) is an association of multiple levels of left ventricular inflow and outflow obstruction (subvalvular and valvular left ventricular outflow tract obstruction, coarctation of the aorta, and mitral stenosis [parachute mitral valve and supramitral ring] (Video 75.6). The genetic basis of left-sided lesions, including mitral stenosis, aortic stenosis, left ventricular hypoplasia, and coarctation, is shared, but for the most part causal genes have not been found. *NOTCH-1* mutations are associated

with aortic stenosis.

Turner syndrome is a clinical syndrome resulting from the 45 XO karyotype in about 50% of cases, and from various other X chromosome abnormalities in the remainder. There is a characteristic but variable phenotype, an association with congenital cardiac anomalies, especially postductal coarctation of the aorta and other left-sided obstructive lesions, as well as PAPVC without ASD. The female phenotype varies with the age of presentation and is somewhat similar to that of Noonan syndrome.

Williams syndrome is a contiguous gene syndrome associated with inherited or sporadic deletions at chromosome 7q11.23. The cardiovascular features are caused by the loss of function of ELASTIN, one of the approximately 30 genes in the deletion. Williams syndrome is associated with intellectual deficit, infantile hypercalcemia, characteristic phenotype, and CHD, especially supravalvular aortic stenosis and multiple peripheral pulmonary stenoses. Isolated familial supravalvar aortic stenosis is seen in otherwise phenotypically and intellectually normal families that carry ELASTIN mutations, but not the full deletion.

Evaluation of the Patient With Congenital Heart Disease

Physical Examination

Although the advances in technology have profoundly improved our diagnostic abilities, there is still a role for a detailed clinical examination in the assessment and follow-up of patients with unoperated, palliated, and repaired CHD. The relevant findings pertaining to specific abnormalities are outlined in the appropriate sections that follow, but some general principles bear consideration (**see also Chapter 10**).

Physical Assessment

The presence of characteristic facial or somatic features of an underlying syndrome may be a strong clue to the type of heart disease (e.g., Williams syndrome, Noonan syndrome, Down syndrome) at any age. Central cyanosis can be difficult to diagnose clinically when mild but should be actively excluded by oximetry in any patient with suspected CHD. One should assess both cardiac and visceral situs and not assume the heart will be left sided. Performing careful surveillance of the chest wall for scars is also important in older patients and adults, who do not always know or report the type and sequence of their surgical or catheter interventions.

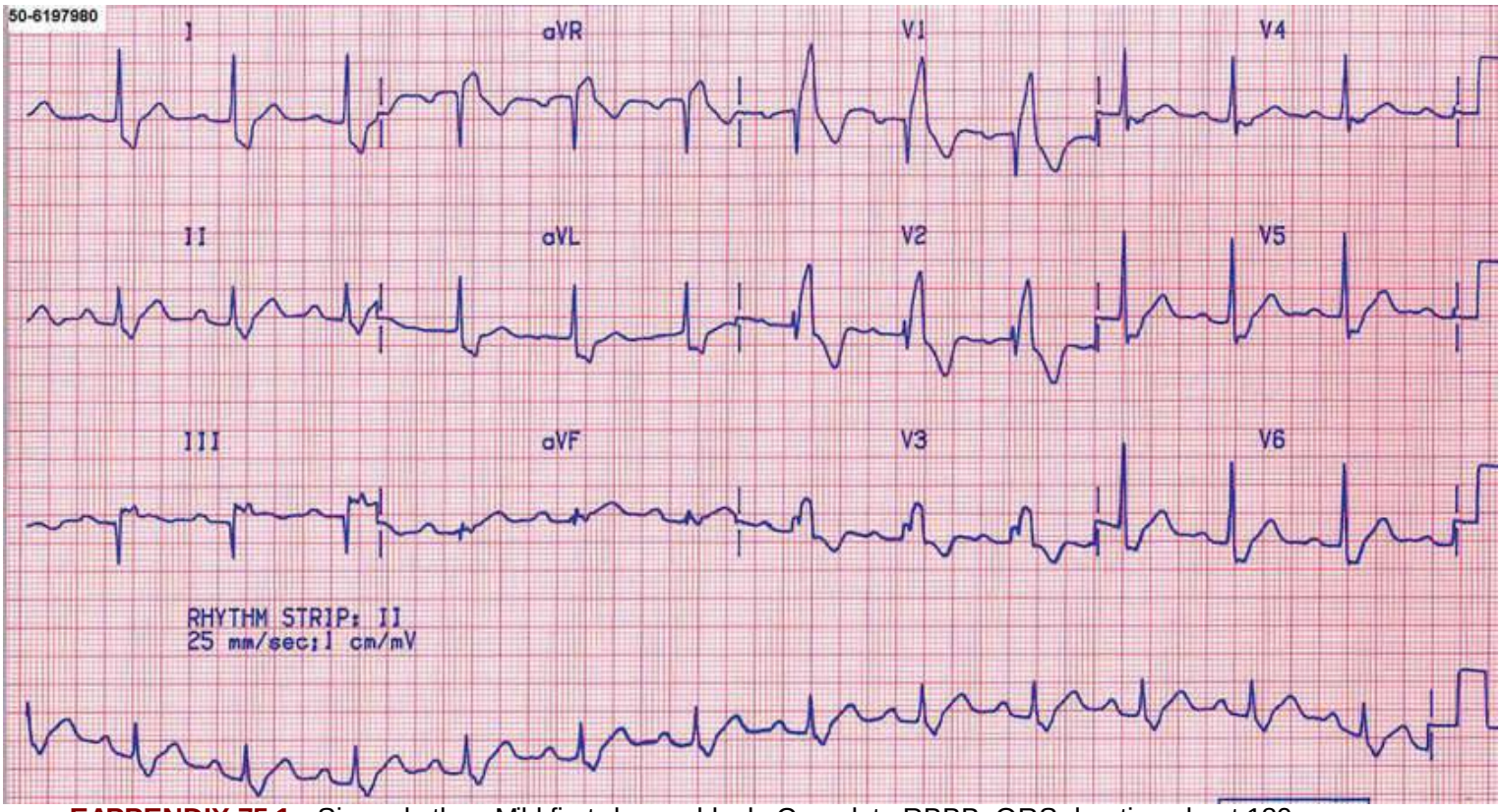
Examination of the upper and lower limb peripheral pulses is important. Delay, absence, or reduction of a pulse is an important clue to the presence of arterial obstruction and its site. The left brachial pulse is often compromised by surgery for coarctation, and blood pressure measurements should not be taken in only the left arm. Similarly, other palliative procedures (Blalock-Taussig-Thomas shunt, interposition grafts) may affect either or both upper limb pulses. Assessing the femoral and carotid pulses in addition to the upper limb pulses is important in such patients. Just as in acquired disease, the pulse volume and character also provide important information regarding the severity of obstructive or regurgitant left heart disease. A low-volume pulse (usually with a narrow pulse pressure) reflects a low cardiac output. Pulsus alternans signifies severe systemic ventricular dysfunction. Pulsus paradoxus points to cardiac tamponade. In adolescents and adults, the jugular venous pressure examination is often important. It may give an indication of cardiac decompensation, cardiac chamber hypertrophy or restriction, valvular regurgitation or stenosis, arrhythmia or conduction disturbance, cardiac tamponade, pericardial constriction, and other phenomena.

Auscultation

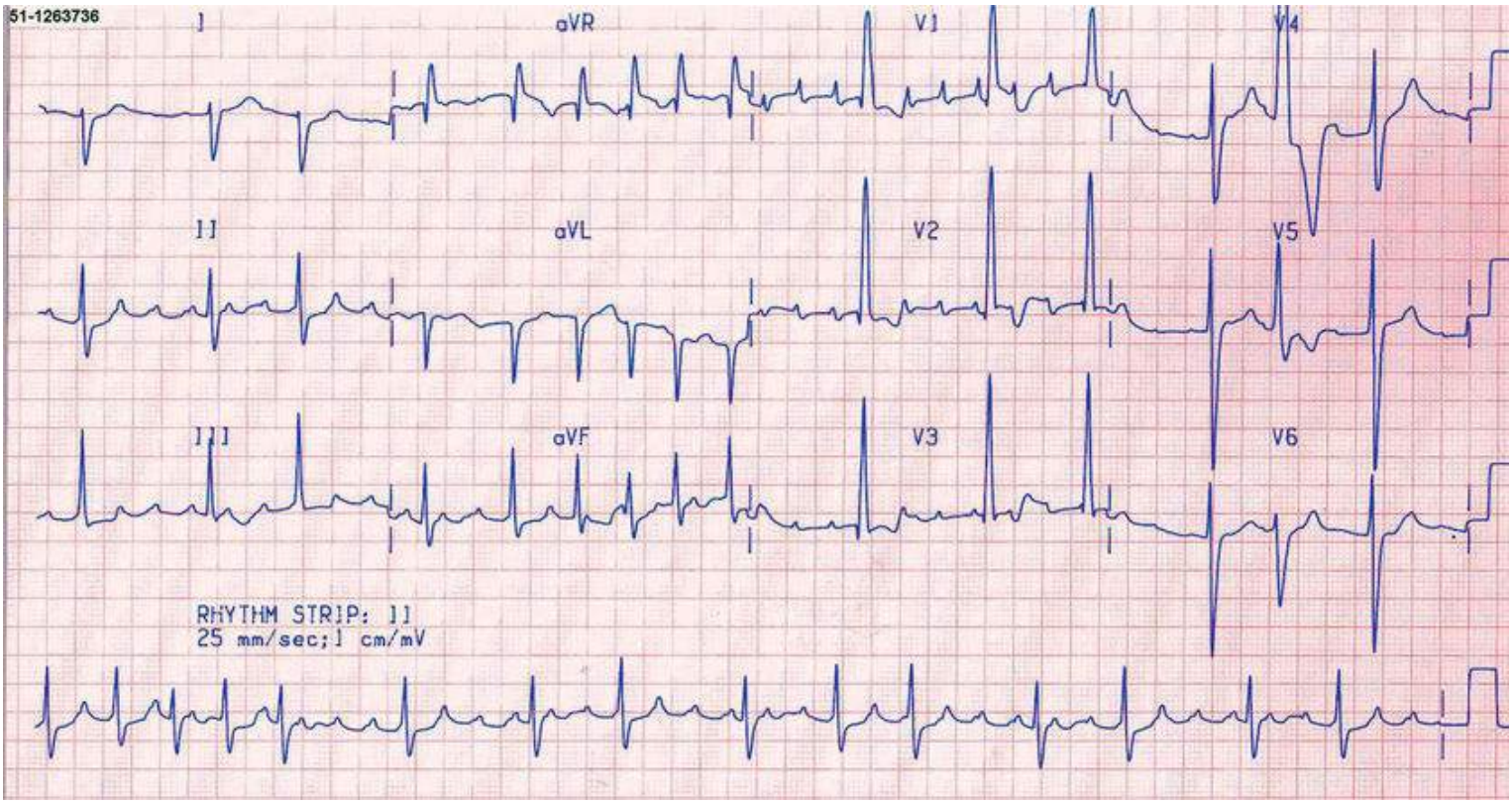
The rules of auscultation follow those developed for acquired heart disease. However, cardiac and vascular malposition may significantly affect the appreciation of heart sounds and murmurs. For example, in TGA treated by an atrial switch procedure, the aorta remains anterior to the pulmonary artery. Consequently, the aortic component of the second sound can be exceptionally loud, and the pulmonary component may be virtually inaudible, making it difficult to estimate the pulmonary artery pressure clinically under such circumstances. Conversely, when there is a valved conduit between the right ventricle and pulmonary artery, the pulmonary closure sound may be extremely loud, even though the pulmonary artery diastolic pressure is low. This is because the conduit is frequently adherent to the chest wall, assisting sound transmission to the stethoscope placed close to it. Calcification of semilunar valves is relatively unusual in childhood and early adult life, making the differentiation of valve stenosis from subvalve or supravalve narrowing, by the presence of an ejection click, more precise in these patients. The differentiation of multiple murmurs is sometimes a challenge. Systolic and/or diastolic murmurs in an individual may have several causes, and supplementary clinical information may be required to establish their significance in some cases. Auscultation over the entire anterior and posterior chest wall is important. The continuous murmurs of aortoaortic collateral arteries in coarctation may be audible only between the shoulder blades posteriorly, for example, and similarly the presence of a localized distal pulmonary artery stenosis or an aortopulmonary collateral artery may be detected only in a localized area of the chest wall.

The Electrocardiogram

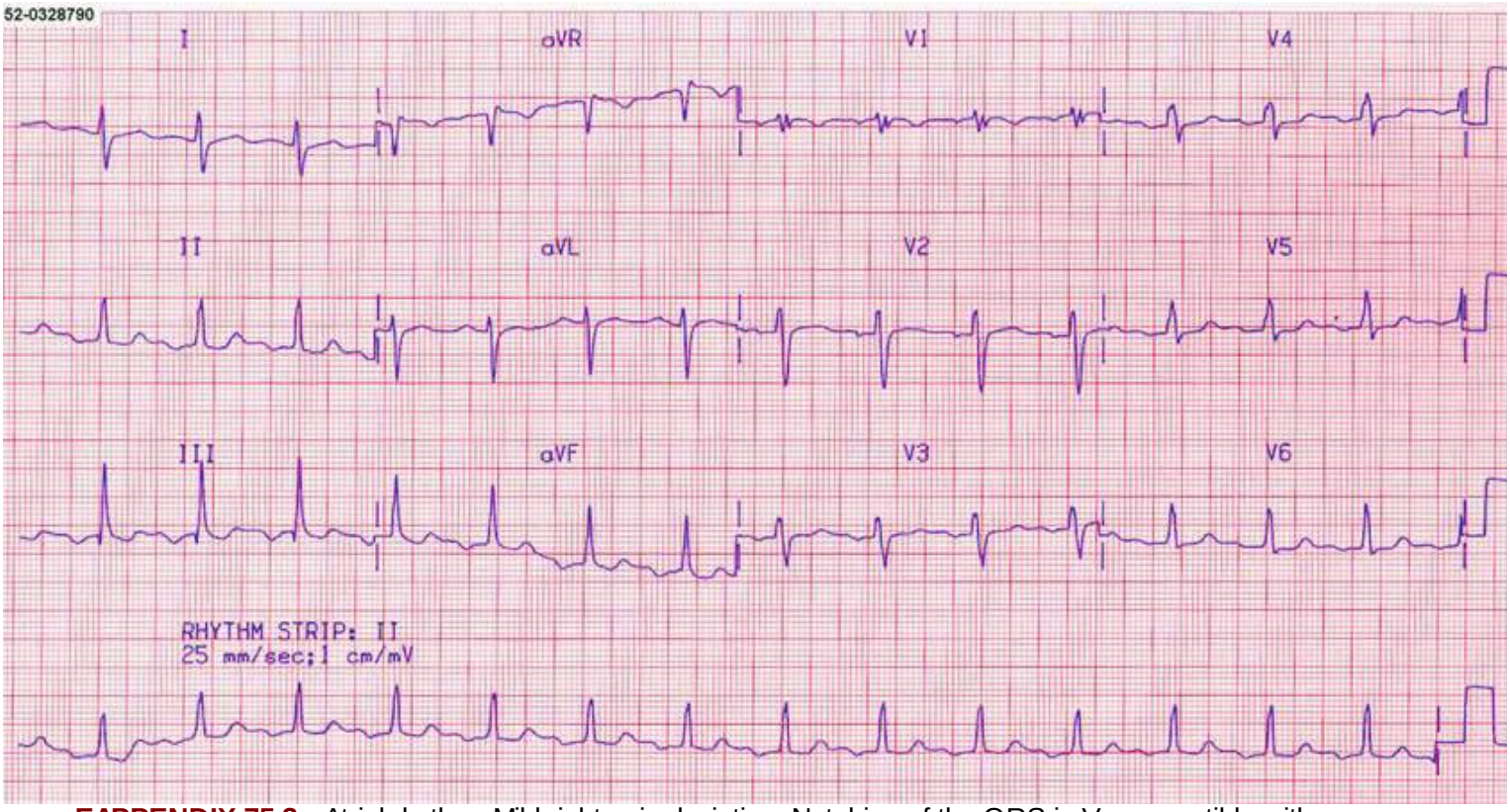
The ECG remains an important tool in the assessment of CHD. The heart rhythm and rate, as well as the AV conduction, can be evaluated (**see Chapter 12** and the ECG figures in the eAppendix). The dominant theme that runs through ECGs in CHD is the prevalence of right heart disease. This often takes the form of right axis deviation along with right atrial and right ventricular hypertrophy. Right ventricular hypertrophy may reflect pulmonary hypertension, right ventricular outflow tract obstruction, or a subaortic right ventricle. Incomplete right bundle branch block often indicates right ventricular hypertrophy due to pressure (e.g., pulmonary hypertension or pulmonary stenosis) or volume (e.g., ASD) overload. Right ventricular volume overload is likely when the r″ in V_1 is less than 7 mm. Very wide QRS complexes should be seen as possible manifestations of dilated and dysfunctional ventricles, most specifically in patients with a combination of repaired tetralogy, complete right bundle branch block, and severe pulmonary regurgitation. The ECG may be uninterpretable in patients with abnormal cardiac or visceral situs unless it is clear where the leads were placed.



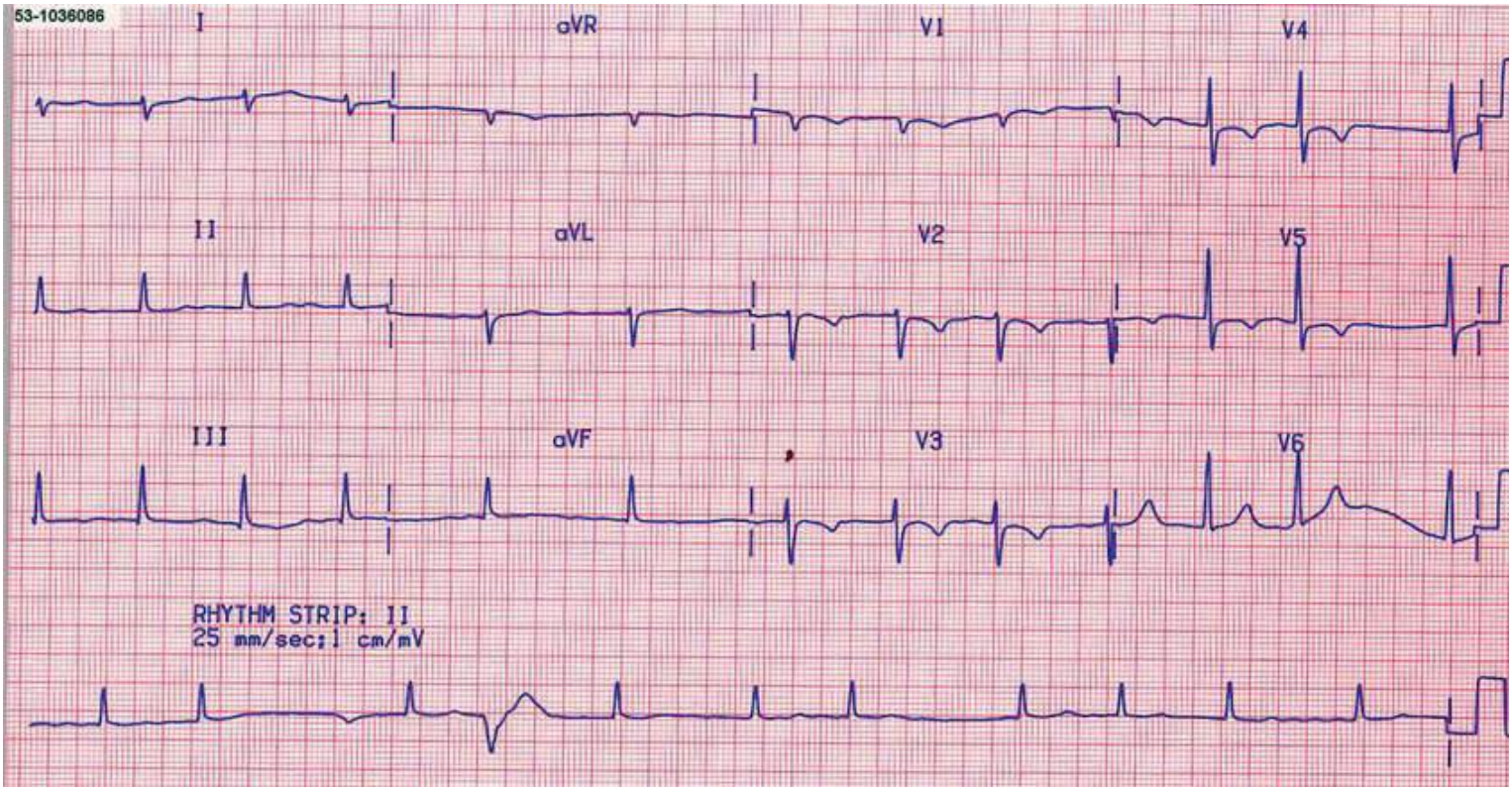
EAPPENDIX 75.1 Sinus rhythm. Mild first-degree block. Complete RBBB. QRS duration about 180 ms. CLINICAL DX: Repaired tetralogy of Fallot. Severe pulmonary regurgitation. Age 50.



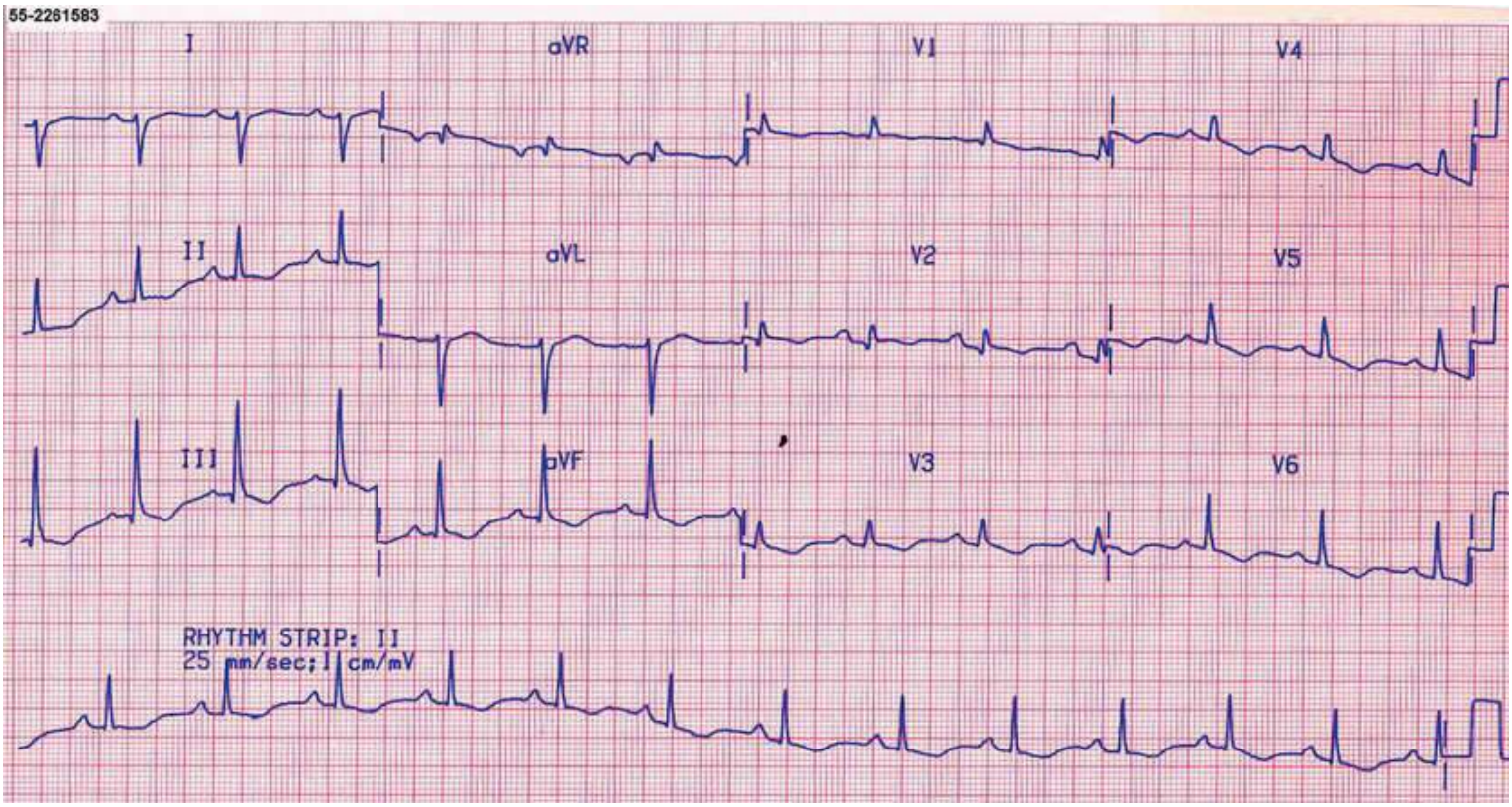
EAPPENDIX 75.2 Atrial flutter at a rate of about 230 bpm. Irregular ventricular response at a rate of about 80 bpm. Marked right-axis deviation and evidence of marked right ventricular hypertrophy in the precordial leads. Nonspecific repolarization changes. CLINICAL DX: Prior Mustard repair of TGA. Paroxysmal “atrial flutter.” Age 24.



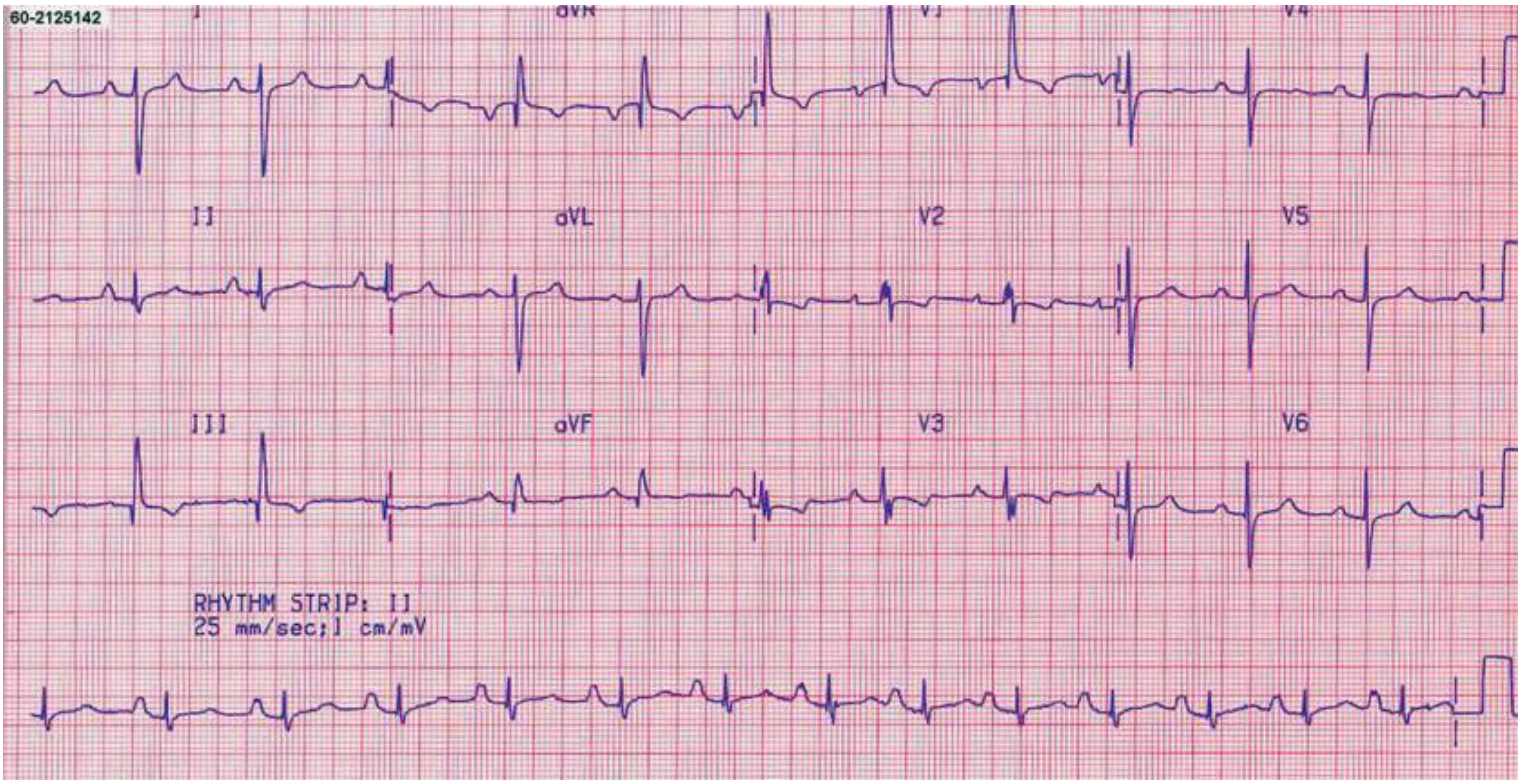
EAPPENDIX 75.3 Atrial rhythm. Mild right-axis deviation. Notching of the QRS in V_1 compatible with an ASD. CLINICAL DX: Prior patch closure of a sinus venosus ASD and partial anomalous pulmonary venous connection. Age 38.



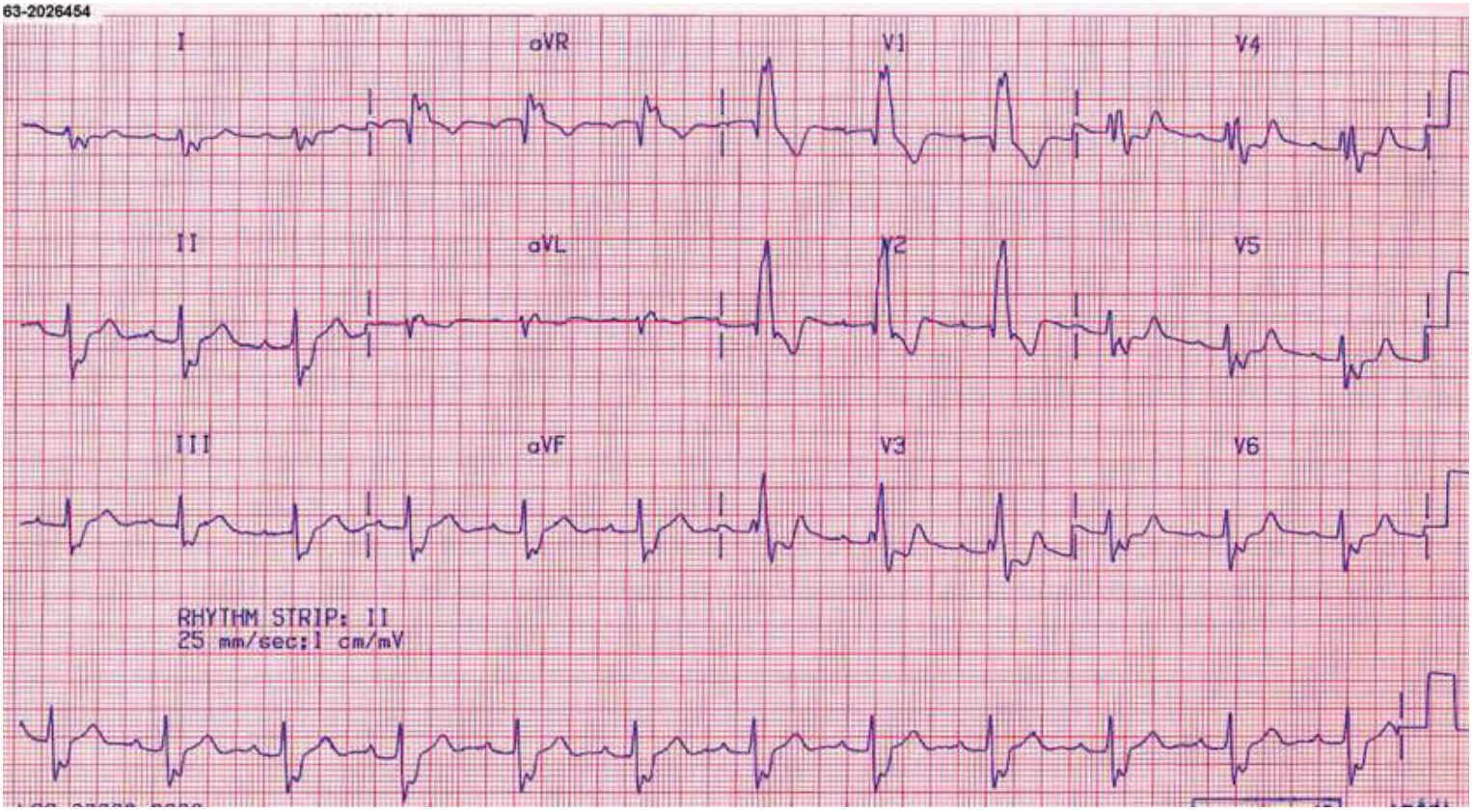
EAPPENDIX 75.4 Atrial fibrillation with an irregular ventricular rate of about 80 bpm. Mild right-axis deviation. Repolarization abnormalities in V_1 to V_5. One ventricular premature beat. CLINICAL DX: Ebstein anomaly. Chronic atrial fibrillation. Age 38.



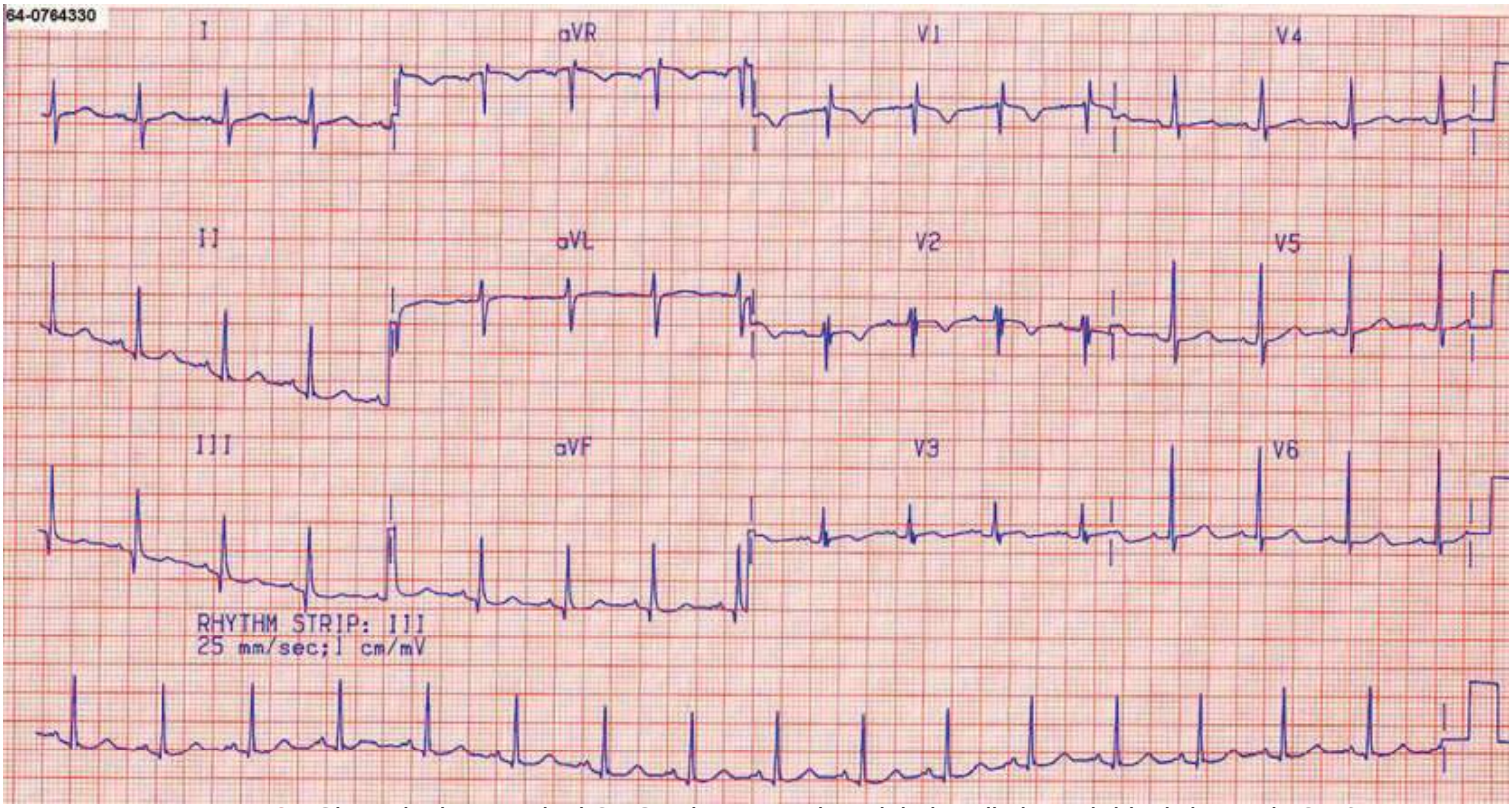
EAPPENDIX 75.5 Sinus rhythm. Marked right-axis deviation. V_1 pattern suggestive of right ventricular volume overload. Widespread nonspecific repolarization abnormalities. CLINICAL DX: Ebstein anomaly. Paroxysmal atrial flutter. Age 20.



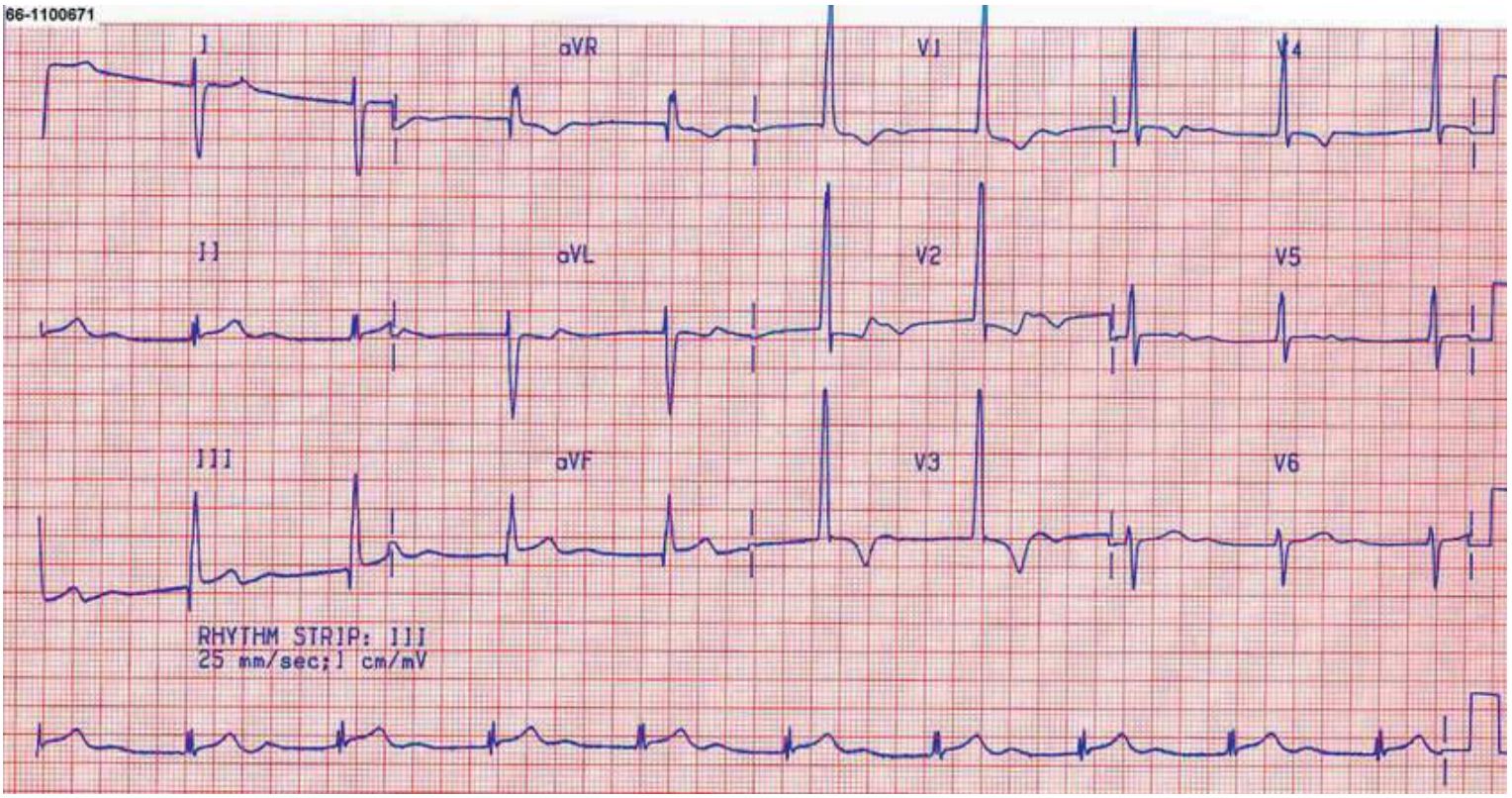
EAPPENDIX 75.6 Sinus rhythm. Possible right atrial overload. Marked right-axis deviation. Marked right ventricular hypertrophy with a strain pattern in V_1 to V_3. CLINICAL DX: Eisenmenger syndrome. Complete unrepaired AV septal defect. Down syndrome. Age 30.



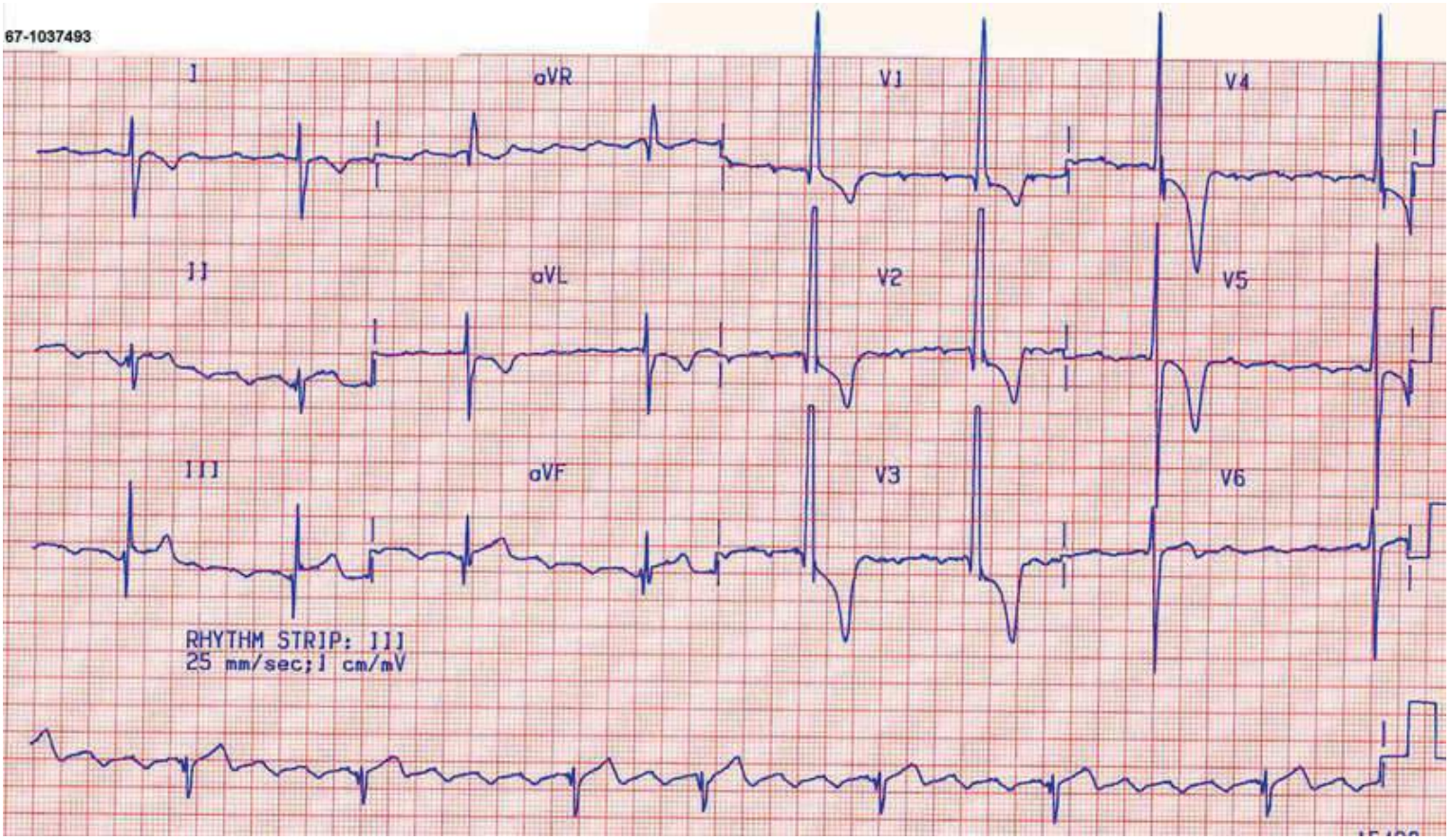
EAPPENDIX 75.7 Sinus rhythm. Borderline first-degree block. Left-axis deviation of initial forces. Complete right bundle branch block (RBBB) with a wide QRS complex approaching 200 ms. CLINICAL DX: Repaired tetralogy with a bioprosthetic pulmonary valve replacement for severe pulmonary regurgitation. Age 32.



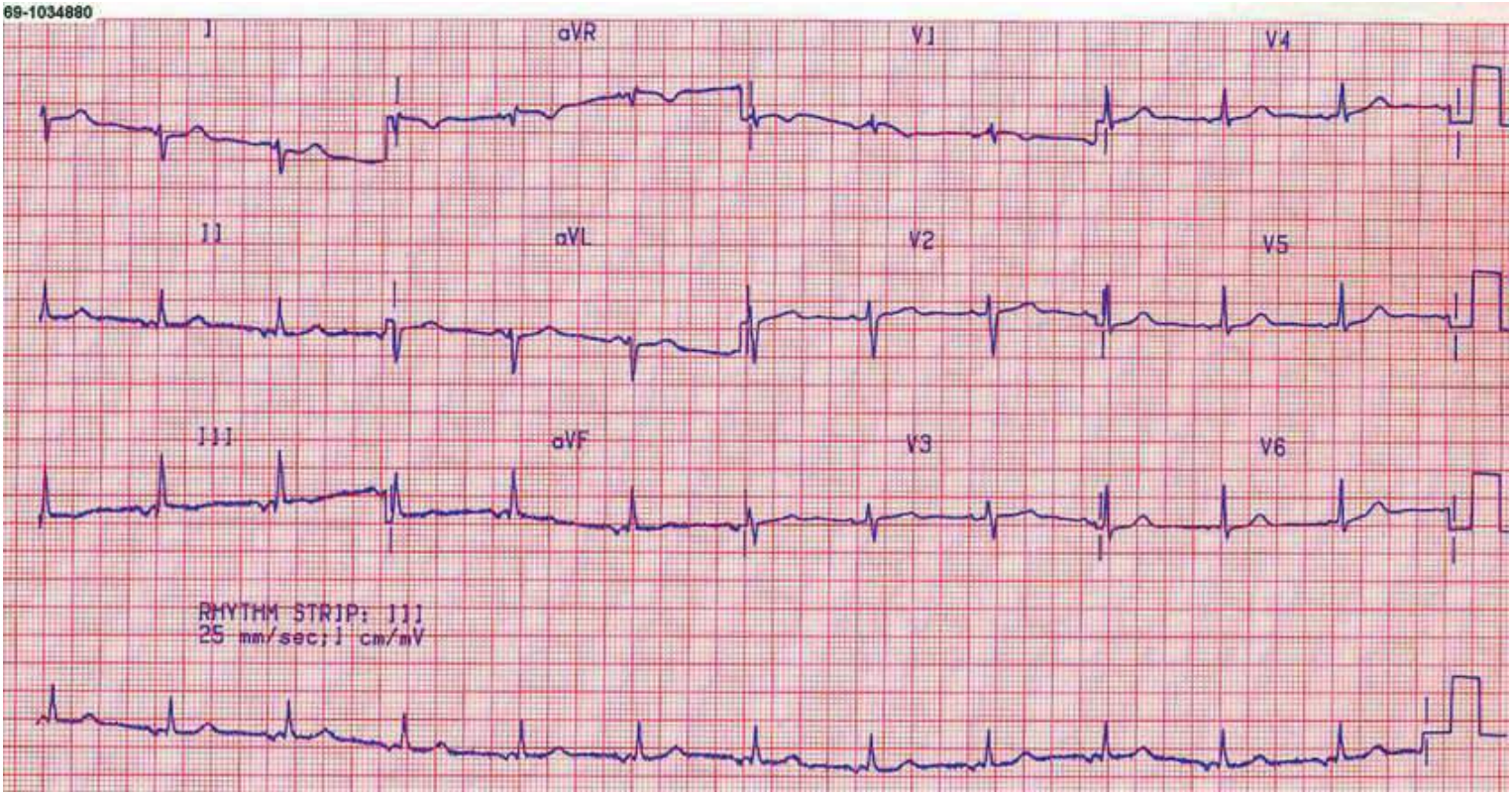
EAPPENDIX 75.8 Sinus rhythm. Vertical QRS axis. Incomplete right bundle branch block (RBBB). QRS notching in V_2. CLINICAL DX: Postoperative secundum ASD repair. Age 21.



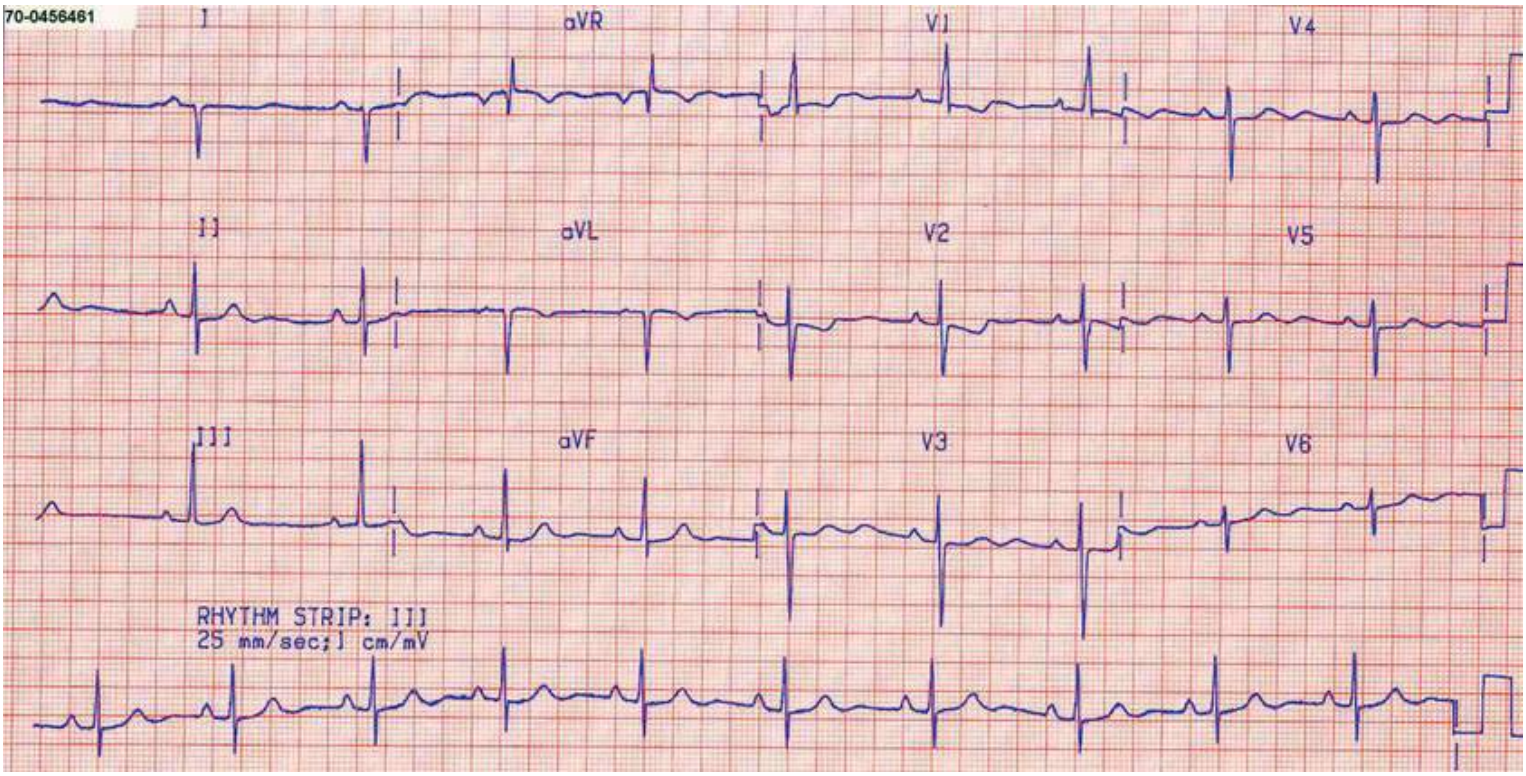
EAPPENDIX 75.9 Junctional rhythm at about 50 bpm. Marked right-axis deviation. Marked right ventricular hypertrophy (RVH) with strain. CLINICAL DX: Mustard repair of TGA. Age 19.



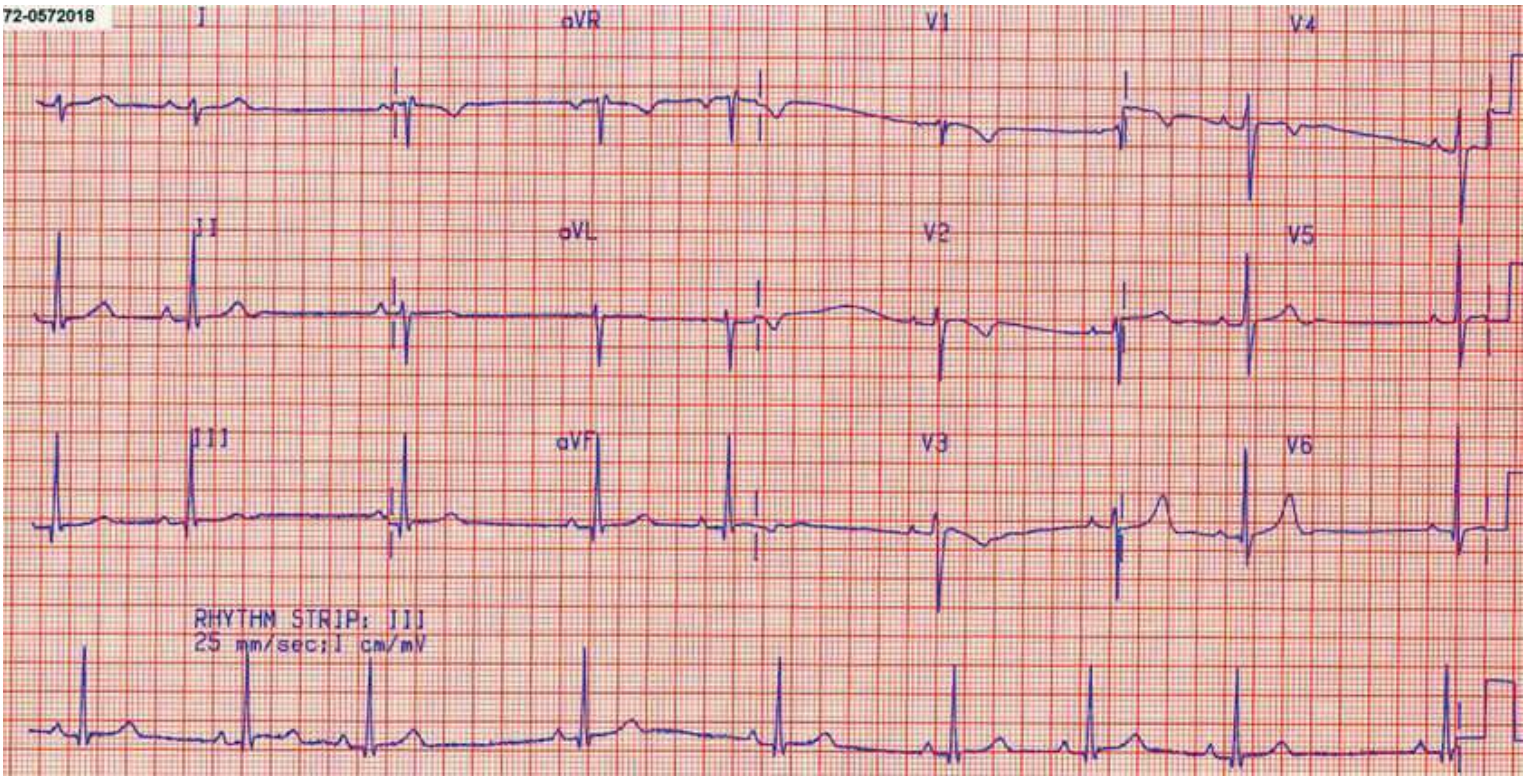
EAPPENDIX 75.10 Atrial flutter with an atrial rate of about 200 bpm and a ventricular rate of about 50 bpm. Marked right-axis deviation. Marked right ventricular hypertrophy (RVH) with strain. CLINICAL DX: Mustard repair of TGA. Age 20.



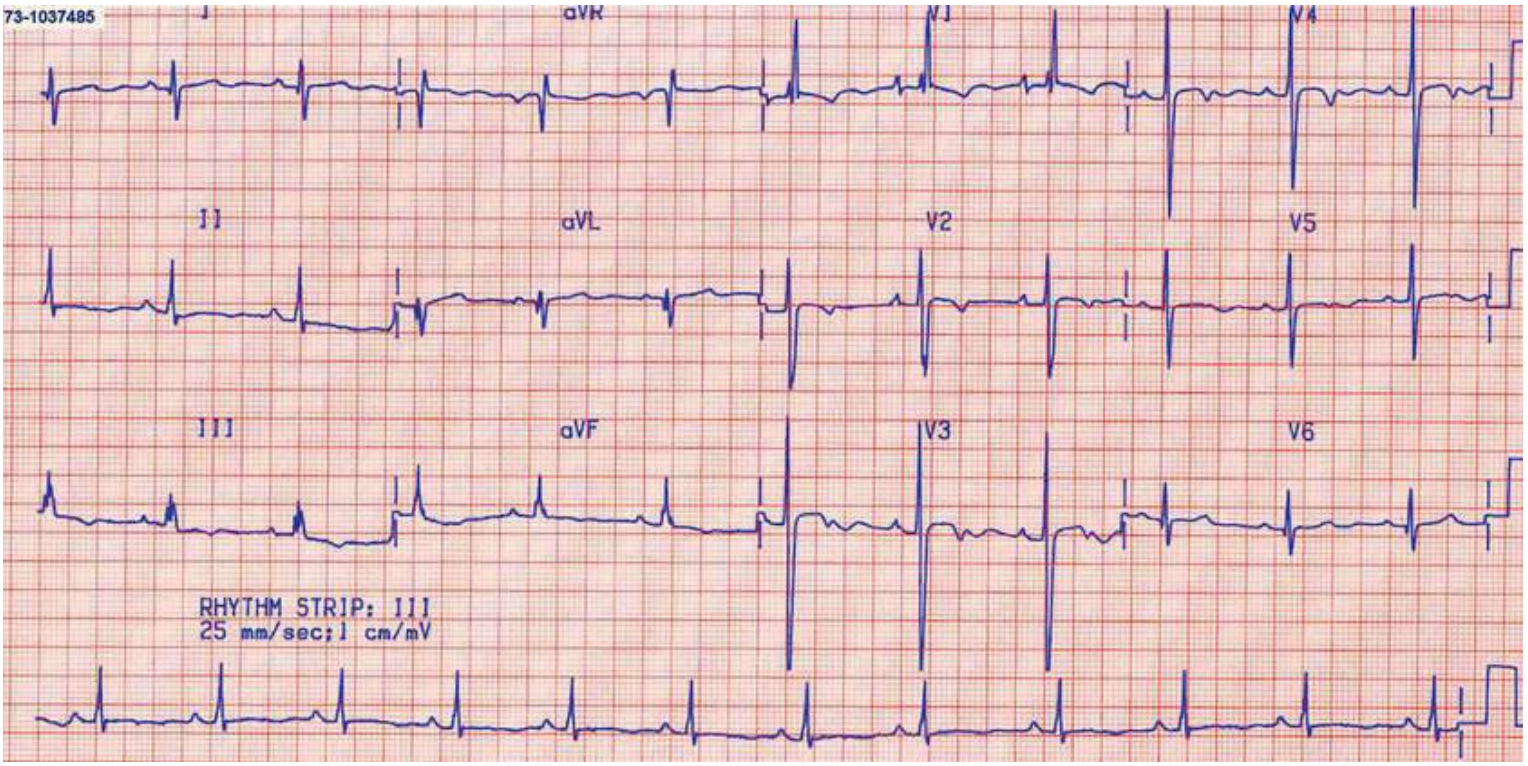
EAPPENDIX 75.11 Atrial rhythm. Moderate right-axis deviation. CLINICAL DX: Repaired sinus venosus ASD and PAPVD. Age 34.



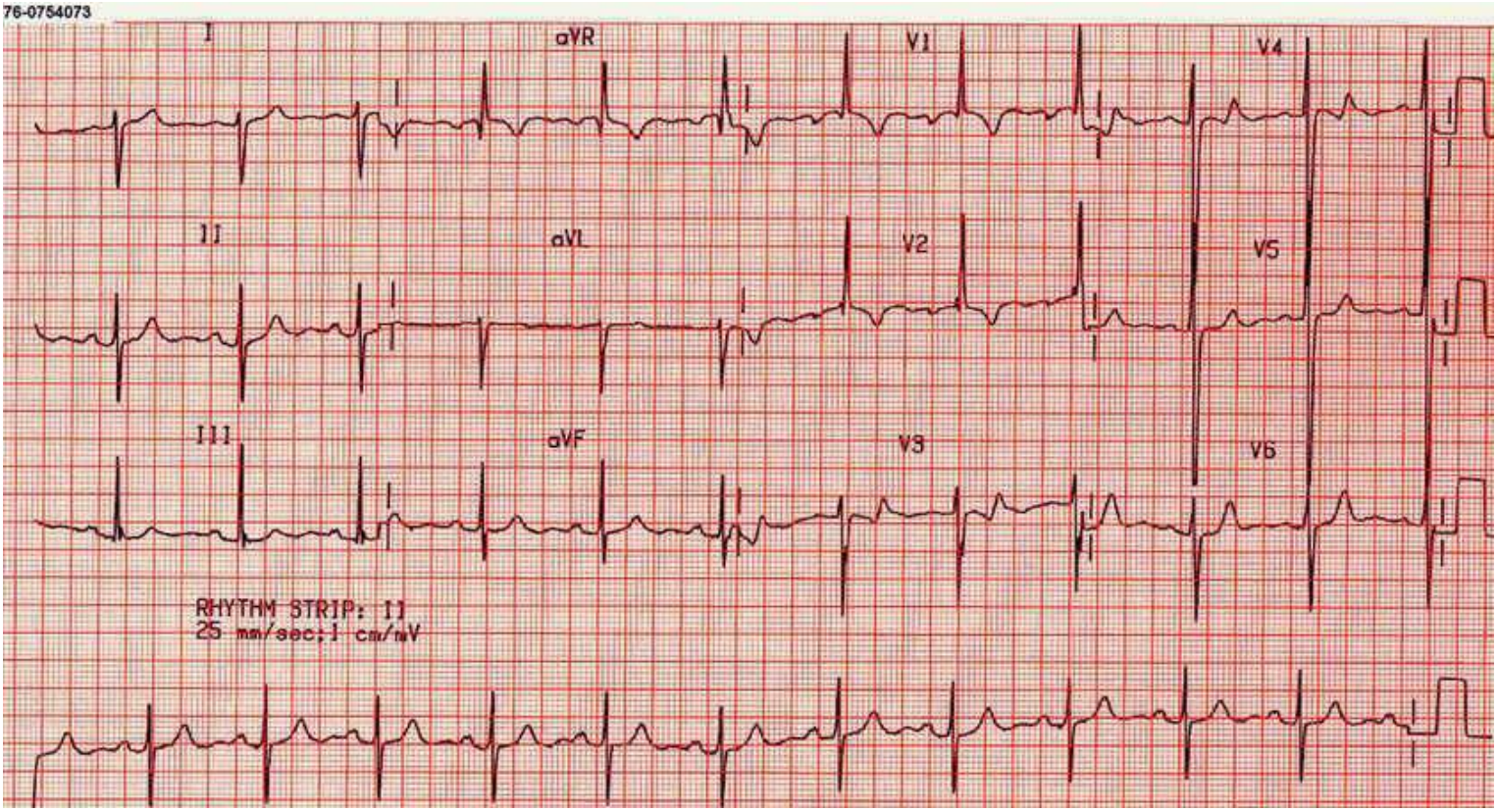
EAPPENDIX 75.12 Sinus bradycardia. Marked right-axis deviation. Voltage evidence of right ventricular hypertrophy (RVH) with strain. CLINICAL DX: Eisenmenger VSD, age 30.



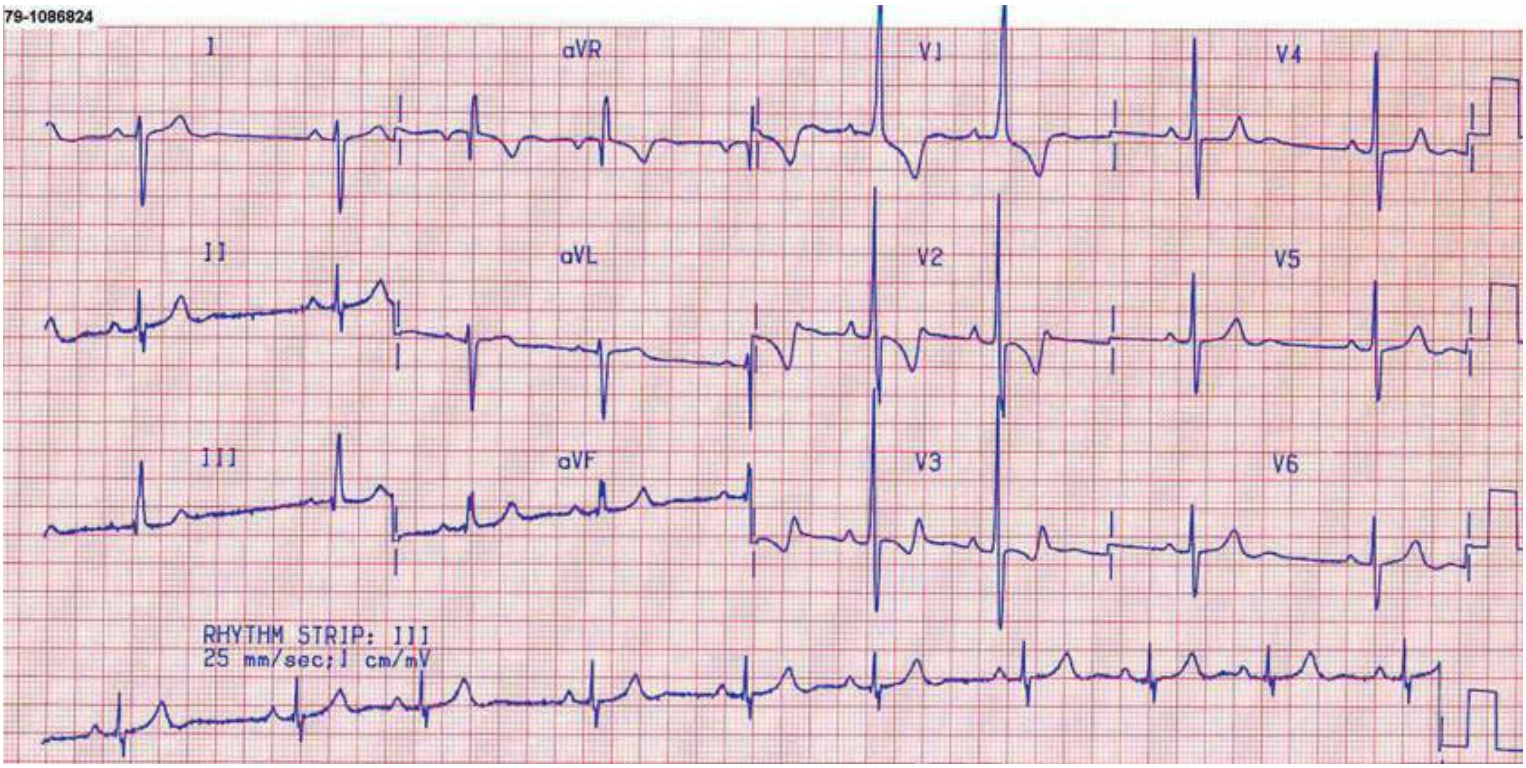
EAPPENDIX 75.13 Sinus rhythm with sinus arrhythmia. Very mild right-axis deviation. QRS notching in V_1. T inversion in V_1 to V_4. CLINICAL DX: Small secundum ASD. Age 22.



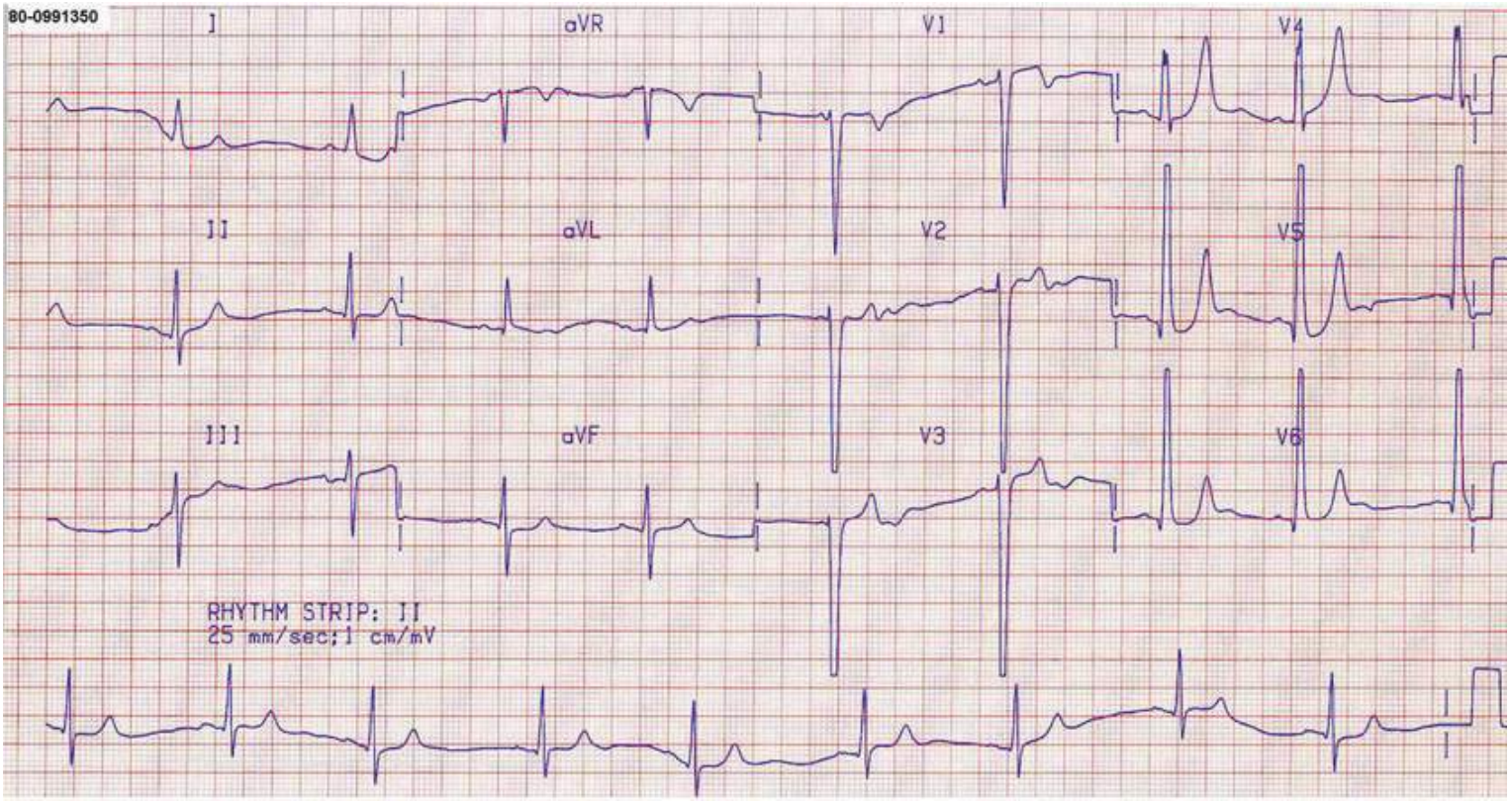
EAPPENDIX 75.14 Sinus rhythm. Mild right-axis deviation. Right atrial overload in V_1. Voltage evidence of right ventricular hypertrophy (RVH) with some strain. CLINICAL DX: Unrepaired tetralogy. Age 22.



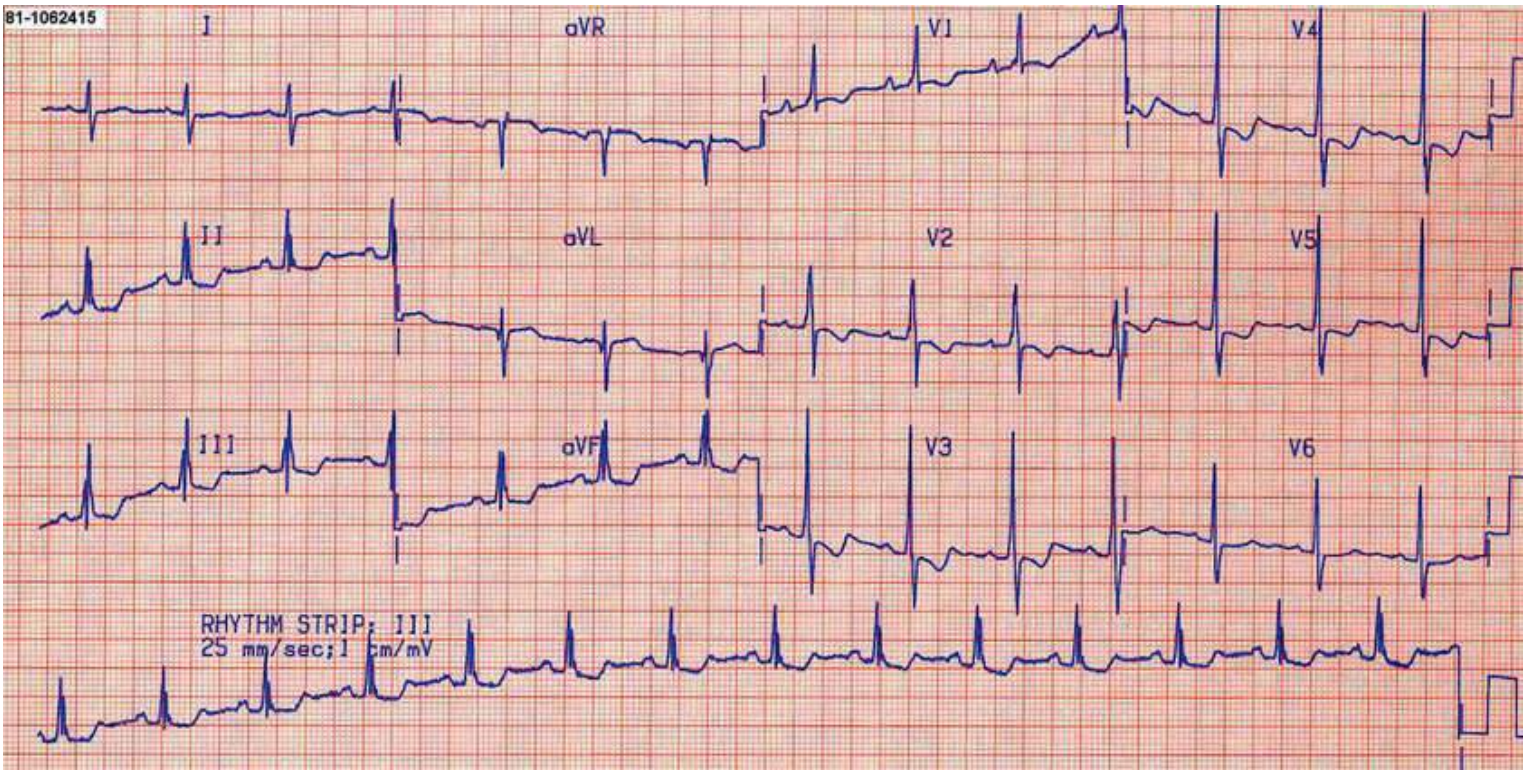
EAPPENDIX 75.15 Sinus rhythm. Indeterminate QRS axis. Marked right ventricular hypertrophy (RVH) with strain. CLINICAL DX: Mustard repair of complete TGA. Age 22.



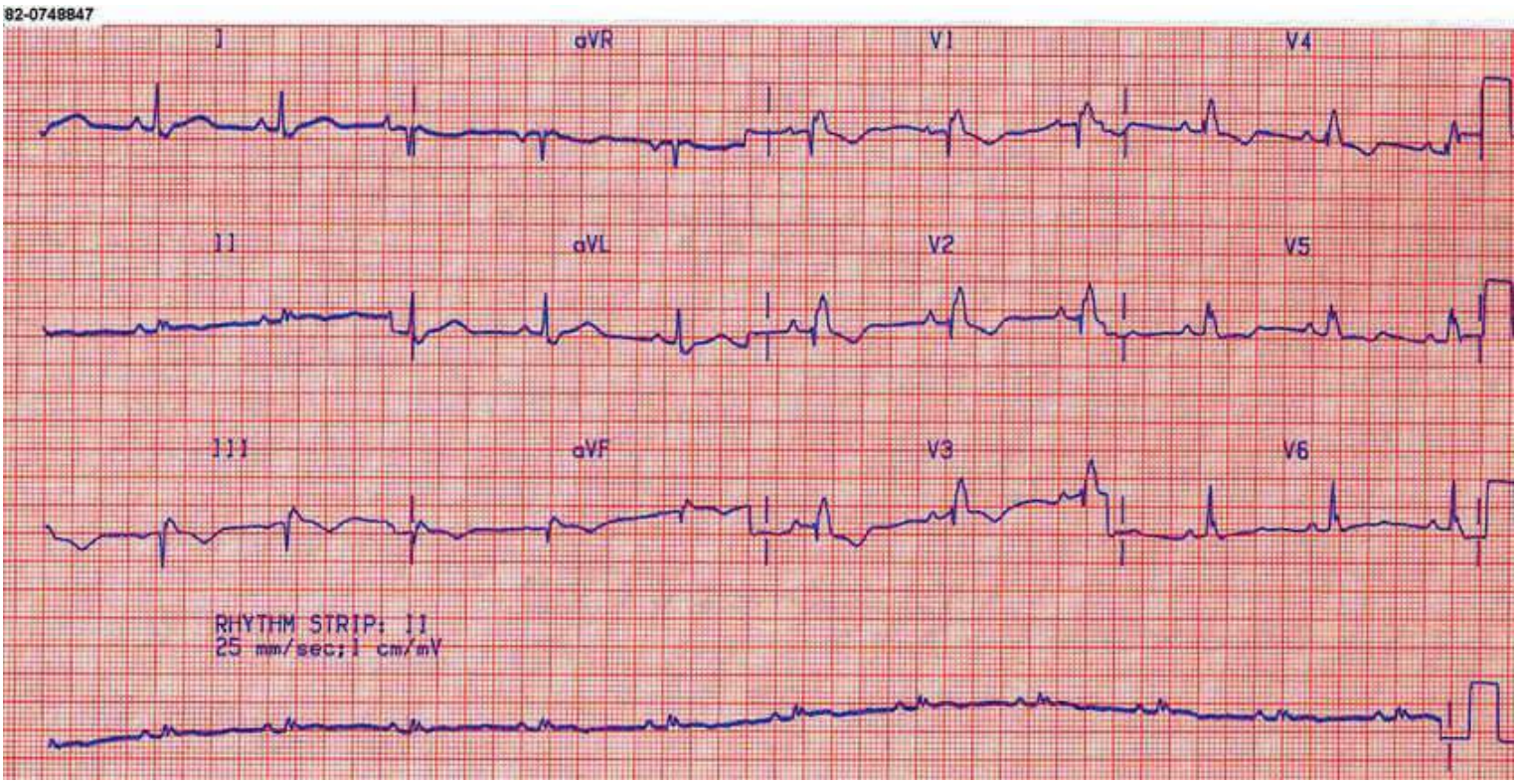
EAPPENDIX 75.16 Sinus rhythm. Marked right-axis deviation. Marked voltage evidence of right ventricular hypertrophy (RVH) with strain. CLINICAL DX: Eisenmenger VSD, age 27.



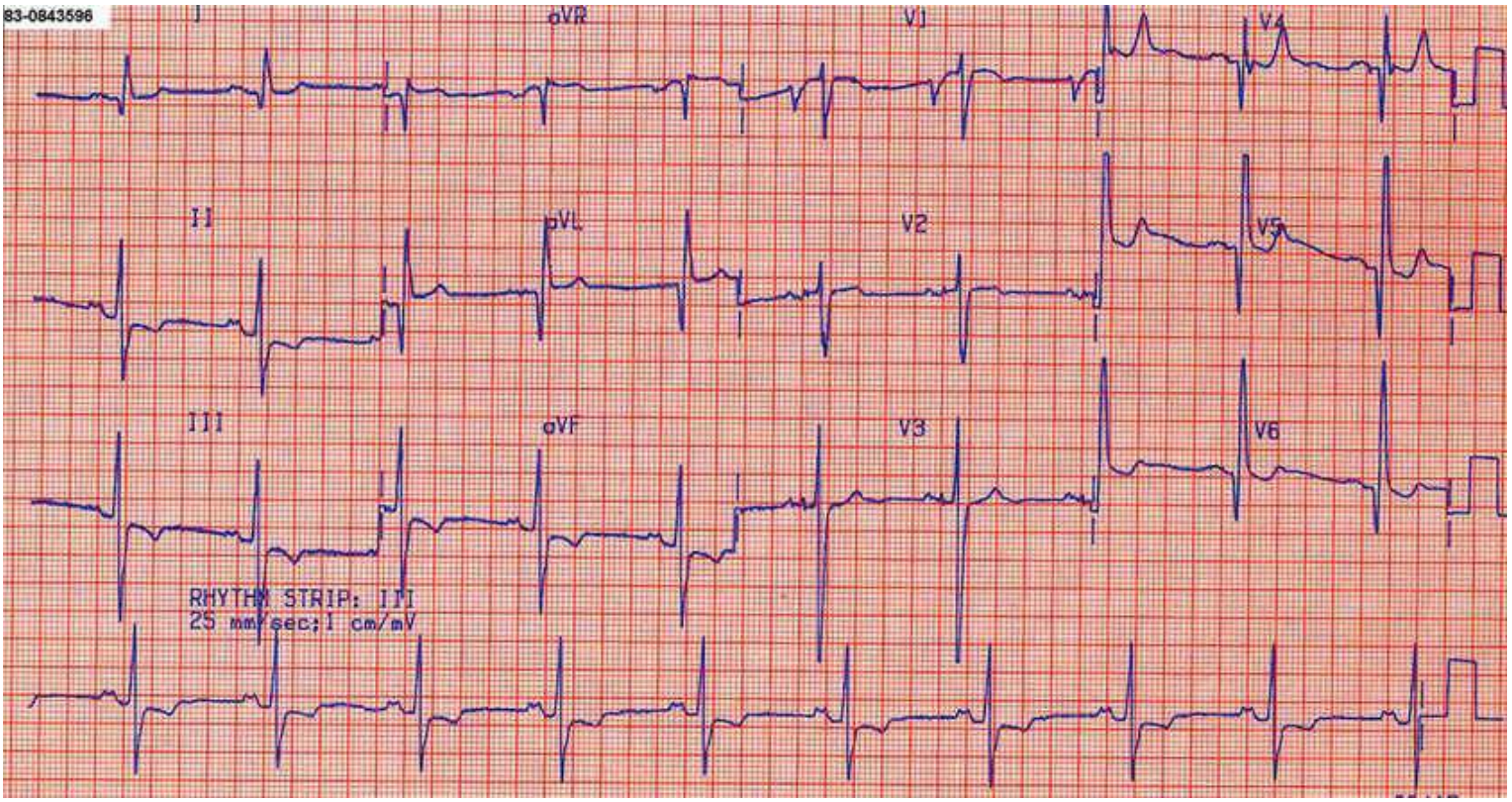
EAPPENDIX 75.17 Sinus rhythm. Voltage evidence of left ventricular hypertrophy (LVH) with QRS prolongation. Somewhat prominent Q waves in V_5 to V_6, with tall T waves in the left chest leads. CLINICAL DX: Severe aortic regurgitation. Age 20.



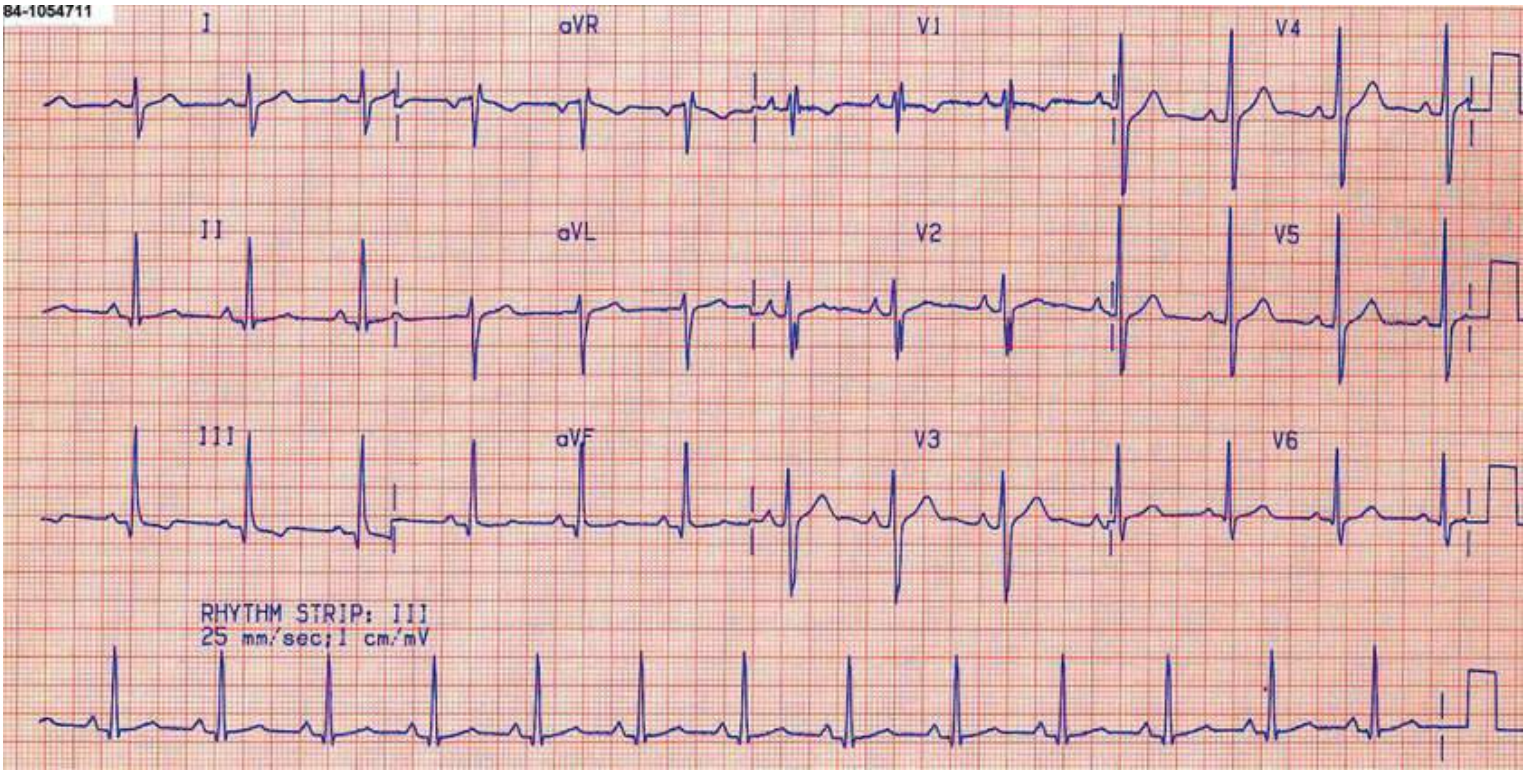
EAPPENDIX 75.18 Sinus rhythm. Slight right-axis deviation. Q wave of 9 mm in V_1 indicative of RVH with an extensive right ventricular strain pattern. Nonspecific repolarization changes in the inferior leads. CLINICAL DX: Unrepaired secundum ASD with modest pulmonary hypertension. Age 58.



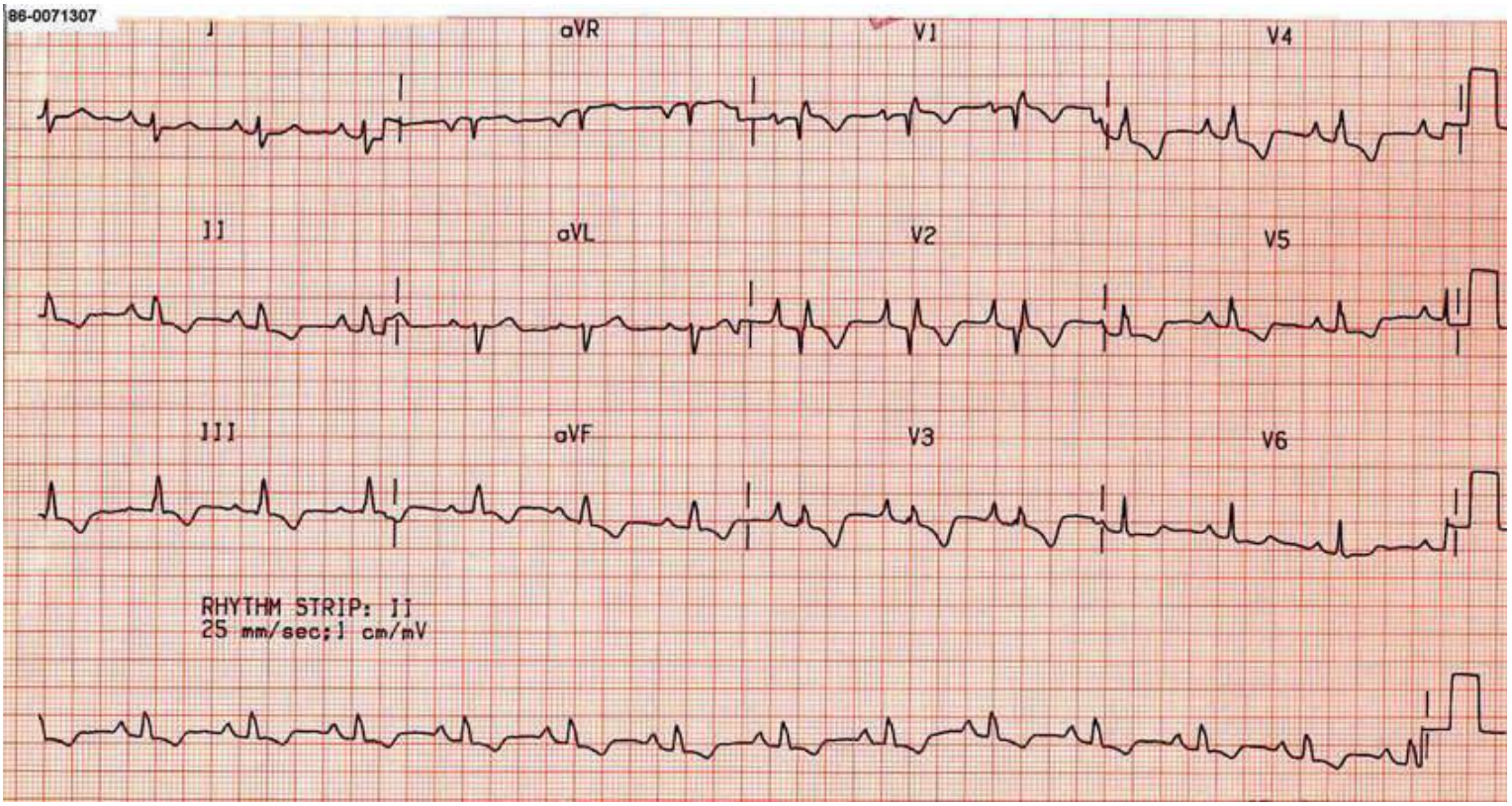
EAPPENDIX 75.19 Sinus rhythm. Leftward axis. Complete RBBB. CLINICAL DX: Repaired Ebstein anomaly. Age 26.



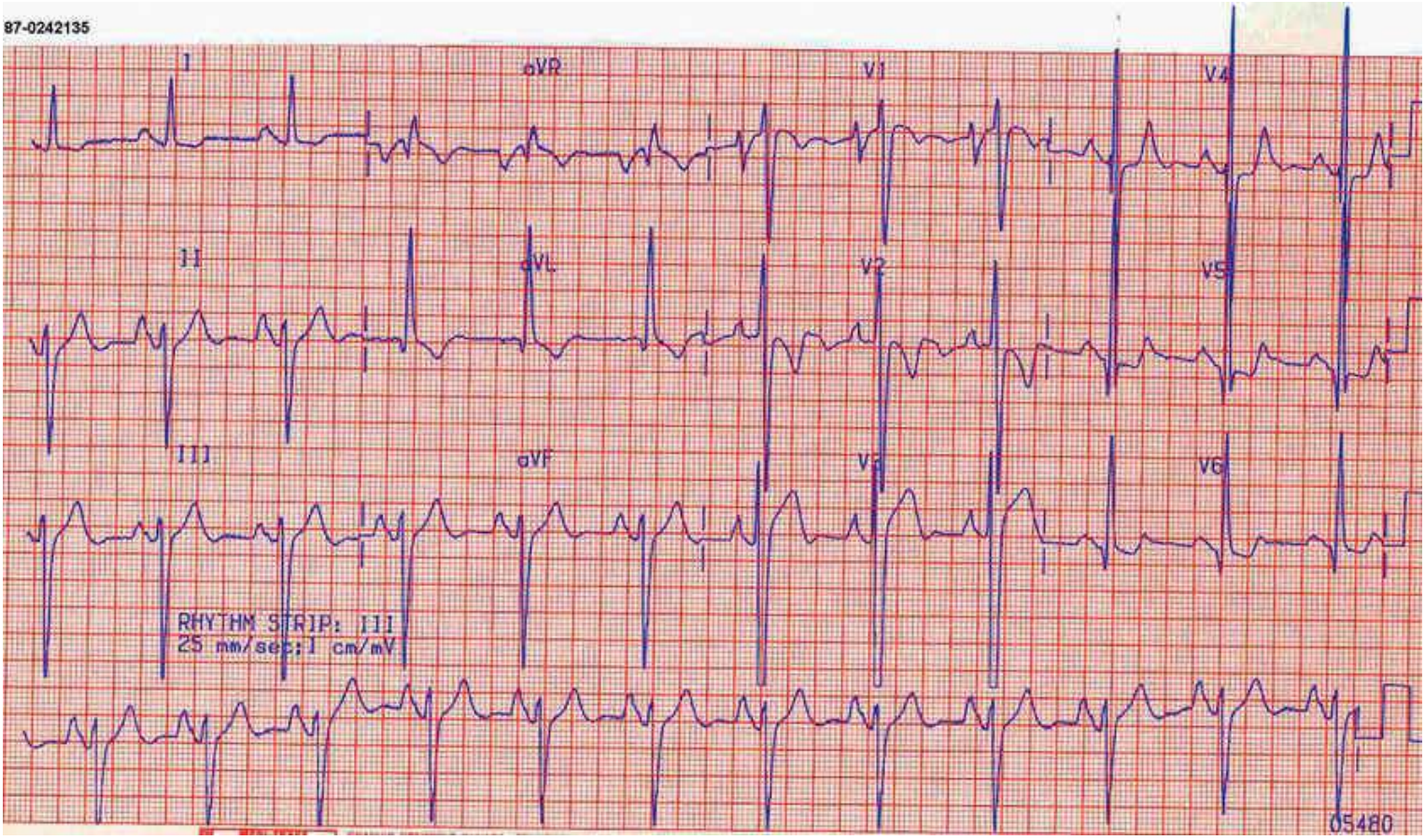
EAPPENDIX 75.20 Sinus rhythm with both right and left atrial overload. Left-axis deviation. Deep Q waves in V_4 to V_6 compatible with left ventricular volume overload in a young person. Repolarization abnormalities. CLINICAL DX: Tricuspid atresia and pulmonary stenosis palliated with a Blalock-Taussig-Thomas shunt. Age 31.



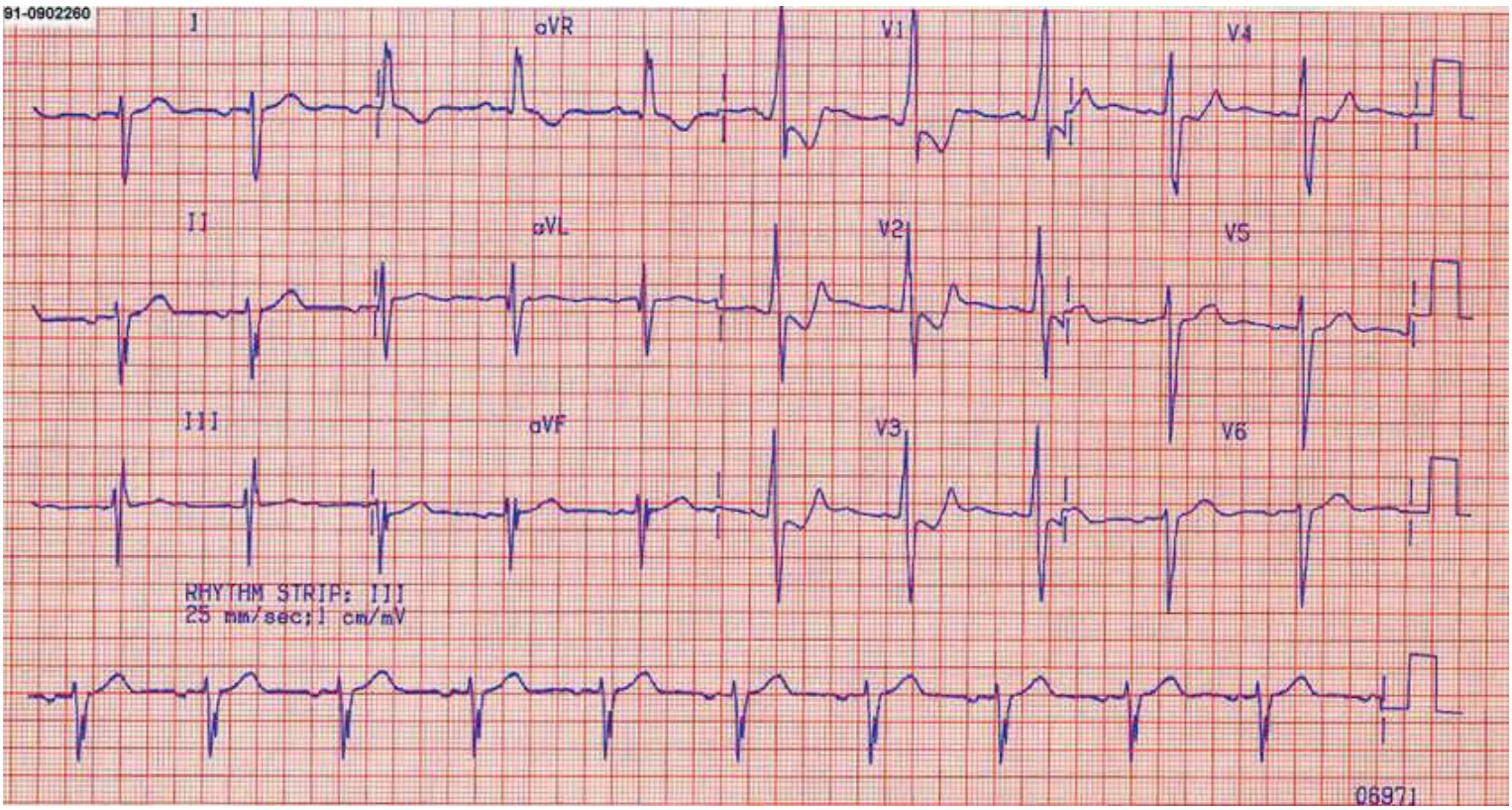
EAPPENDIX 75.21 Sinus rhythm. Mild right-axis deviation. Incomplete RBBB with notching of the QRS complex in leads V_1 and V_2. Mild right atrial overload. CLINICAL DX: Repaired secundum ASD. Age 22.



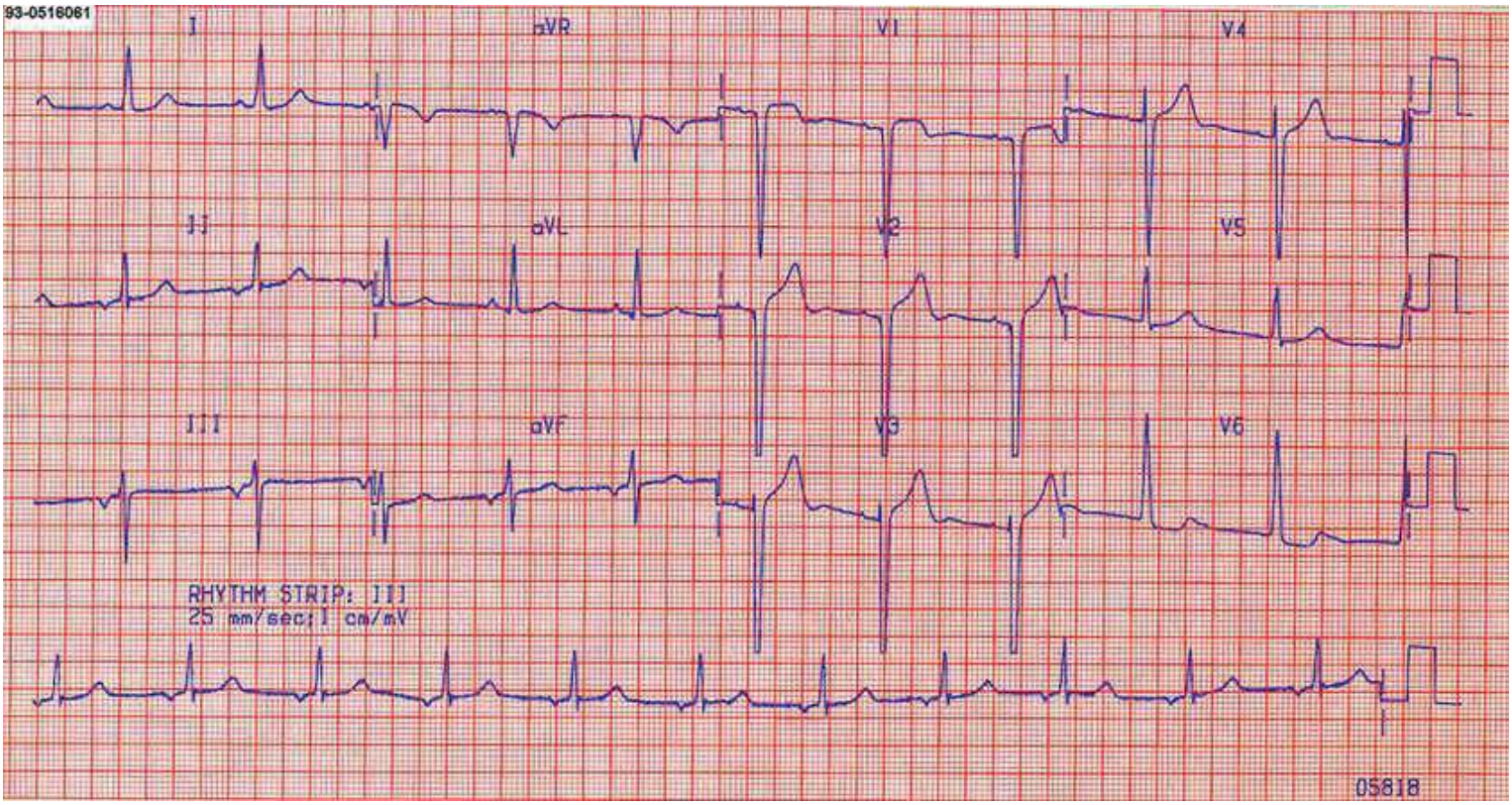
EAPPENDIX 75.22 Sinus rhythm. Right atrial overload most notable in the precordial leads. Low QRS voltage. Incomplete RBBB with a widespread right ventricular strain pattern. CLINICAL DX: Ebstein anomaly. Age 38.



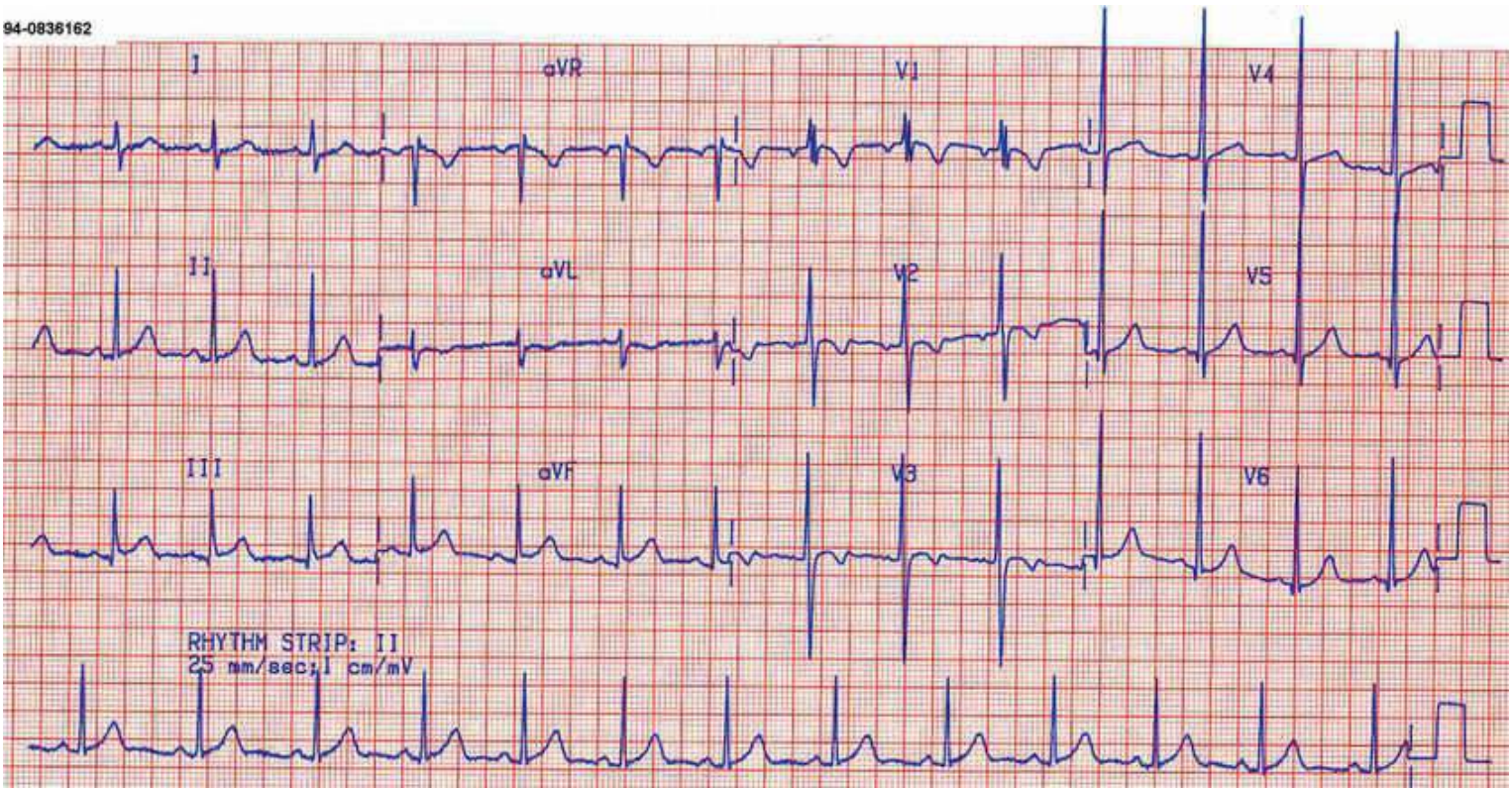
EAPPENDIX 75.23 Sinus rhythm. Left and right atrial overload. Left-axis deviation. Left ventricular hypertrophy. CLINICAL DX: Tricuspid atresia palliated by Blalock-Taussig-Thomas shunts. Age 33.



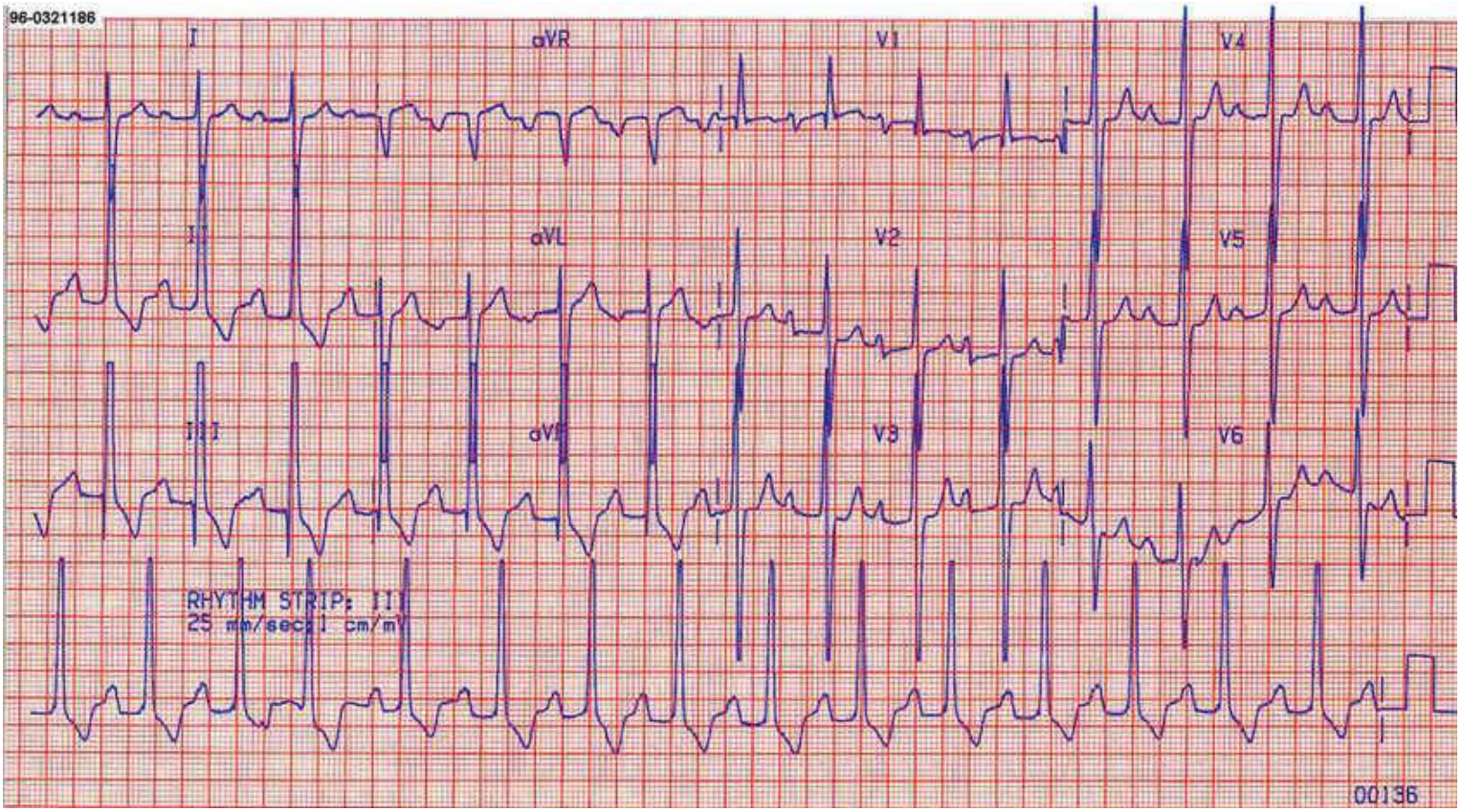
EAPPENDIX 75.24 Atrial rhythm. Left-axis deviation. RVH with strain. CLINICAL DX: Complete AV septal defect with pulmonary stenosis. Still cyanotic, palliated by a cavopulmonary shunt and a Blalock-Taussig-Thomas shunt. Age 19.



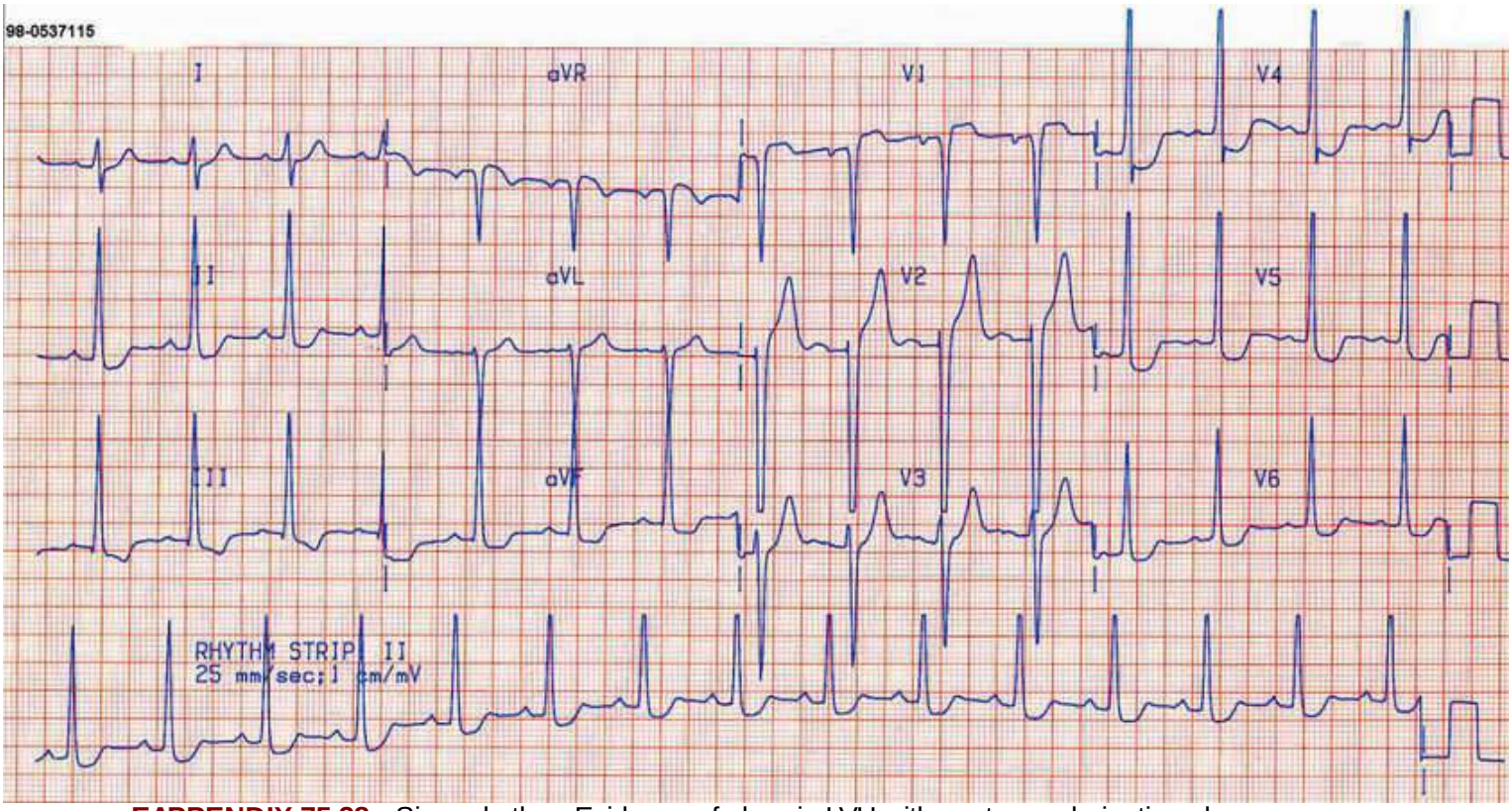
EAPPENDIX 75.25 Atrial rhythm. Incomplete LBBB reflecting LVH with Q waves in V_1 and V_2 and absent Q waves in the left chest leads. CLINICAL DX: Prior repair of coarctation and fibromuscular subaortic stenosis. Age 19.



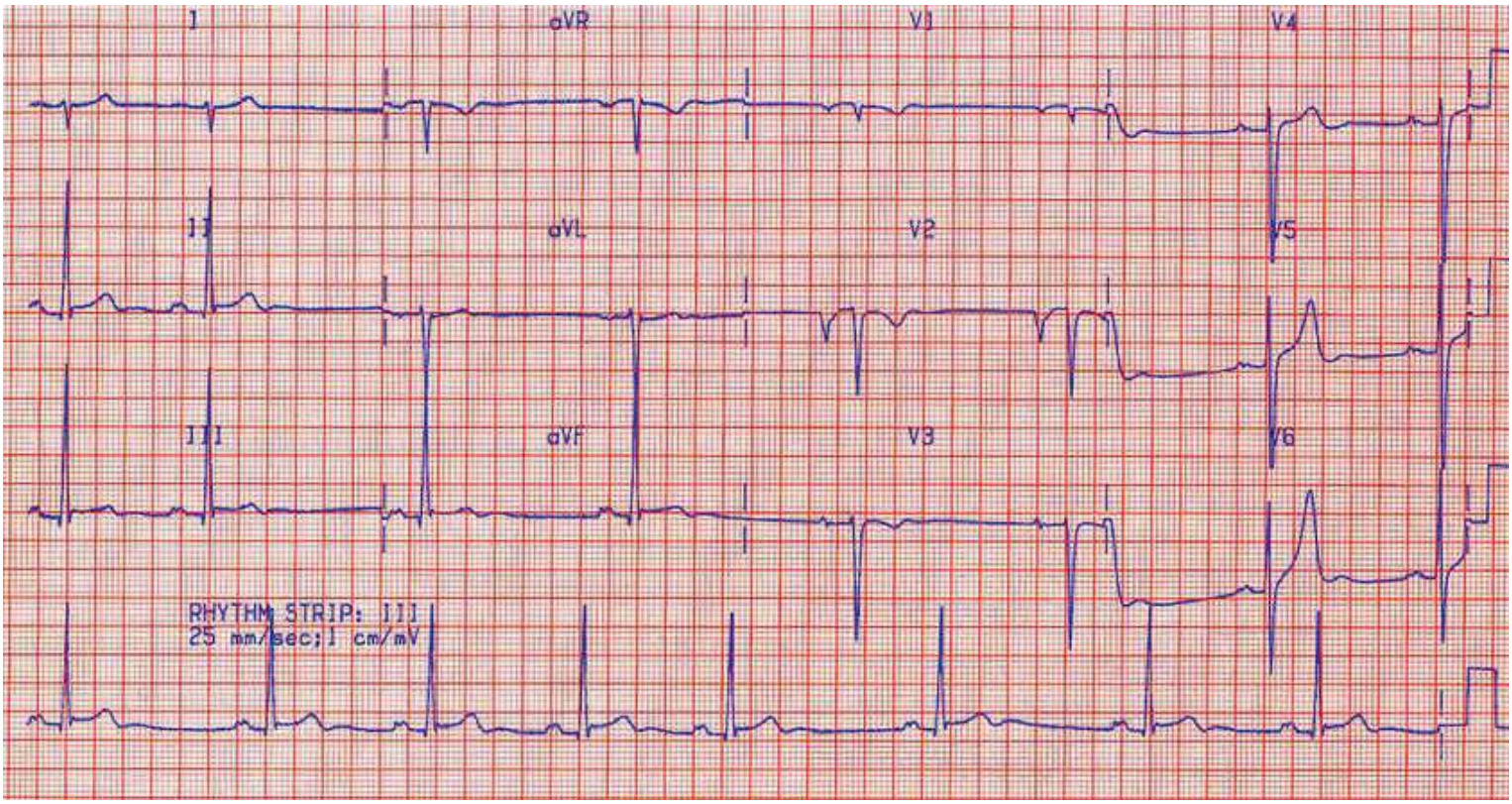
EAPPENDIX 75.26 Sinus rhythm. Normal QRS axis. Prominent R waves in V_1 or with QRS notching. T wave inversion in V_1 to V_3 possibly reflecting "RV strain." CLINICAL DX: Unrepaired secundum ASD, age 19.



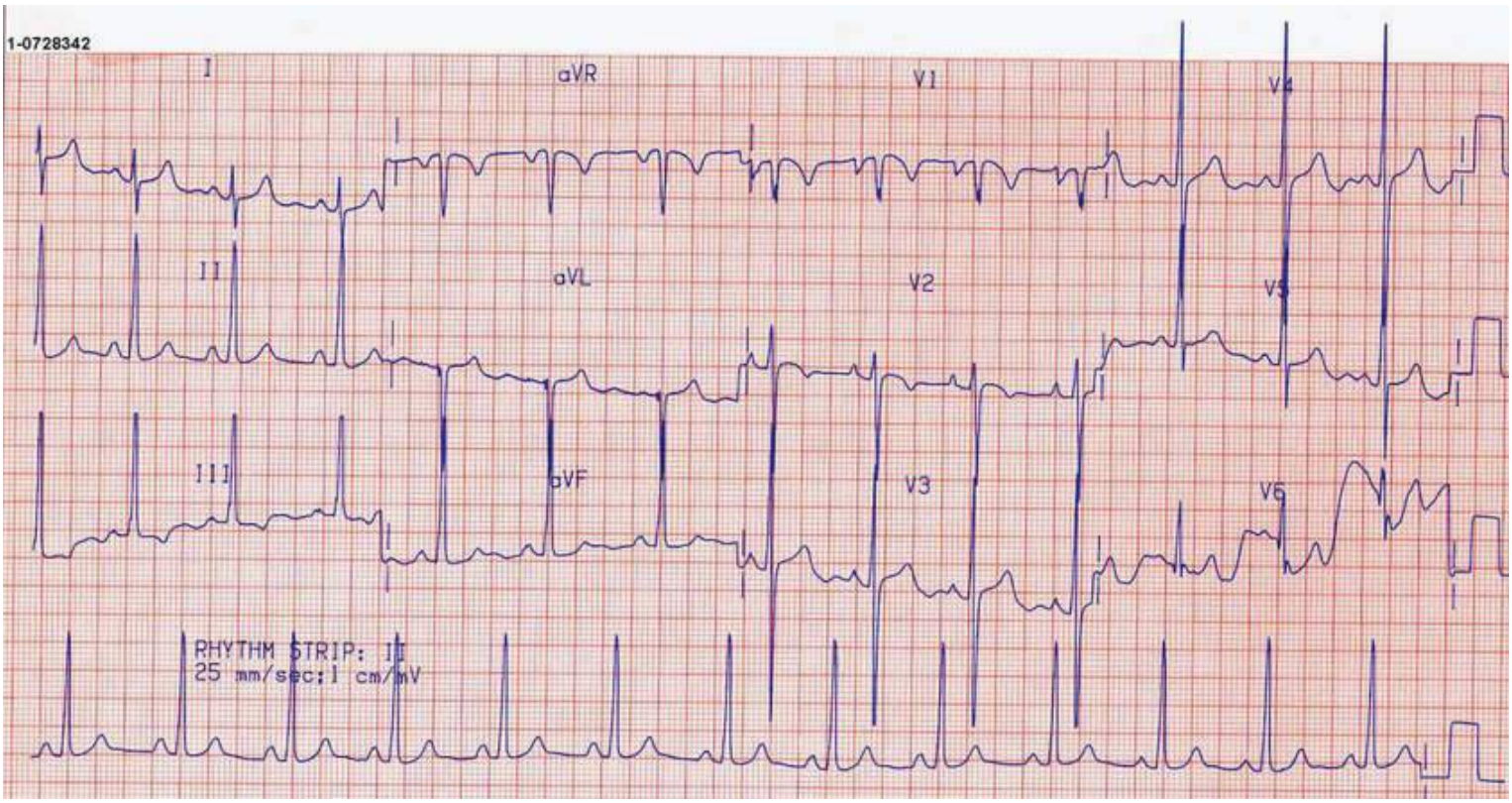
EAPPENDIX 75.27 Sinus rhythm with first-degree block. Probable left and right atrial overload. Right-axis deviation. Prominent R waves in V_1 suggesting elevated subpulmonary pressure. Q wave in V_1 with an absent Q wave in V_5 and V_6. CLINICAL DX: cc-TGA (L-TGA) with single ventricle, pulmonary hypertension, and tricuspid valve stenosis. Age 27.



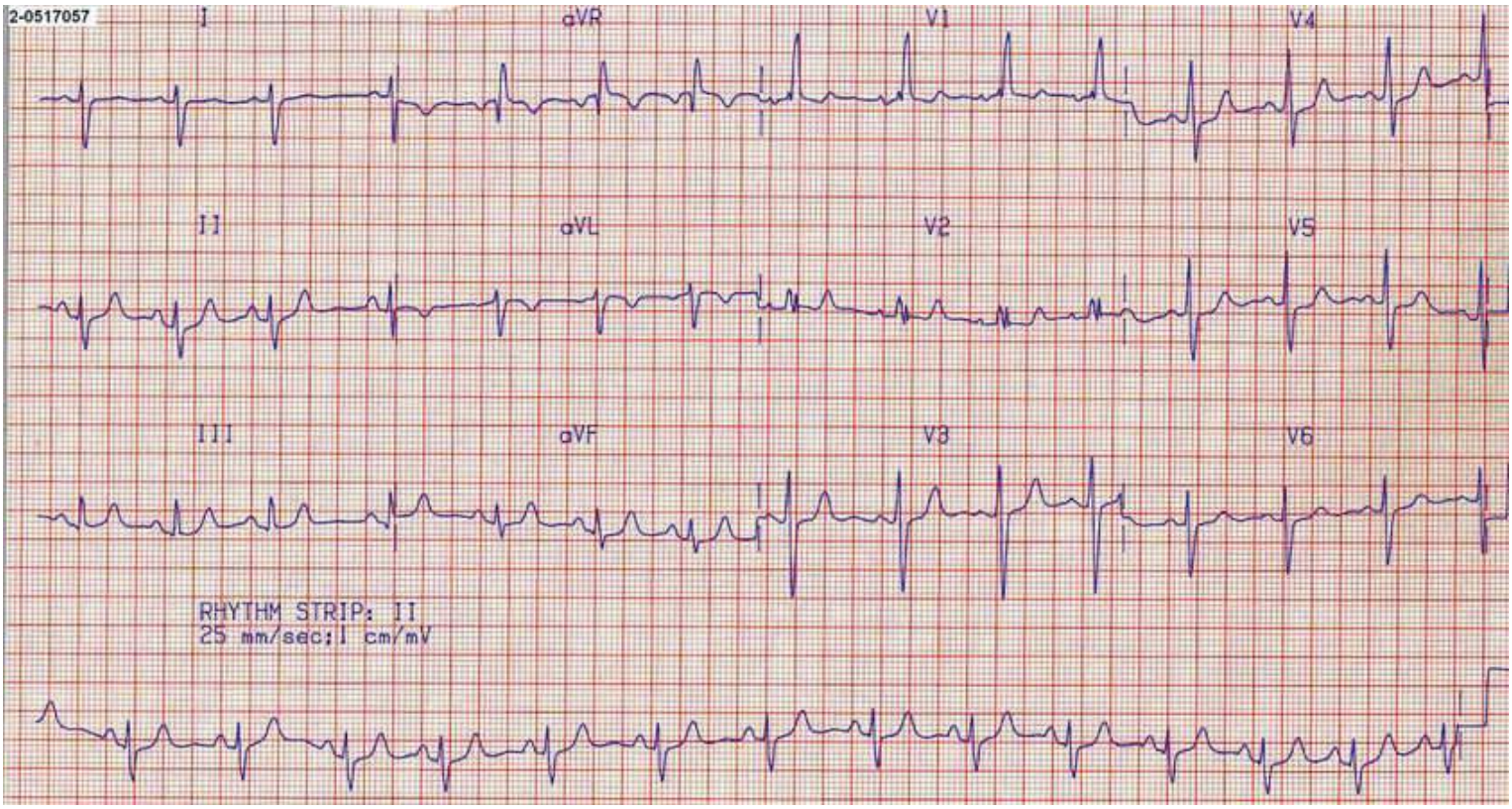
EAPPENDIX 75.28 Sinus rhythm. Evidence of chronic LVH with acute repolarization changes resembling ischemia. CLINICAL DX: Young man with an acutely regurgitant aortic bioprosthesis with mild heart failure and normal coronary arteries. Age 24.



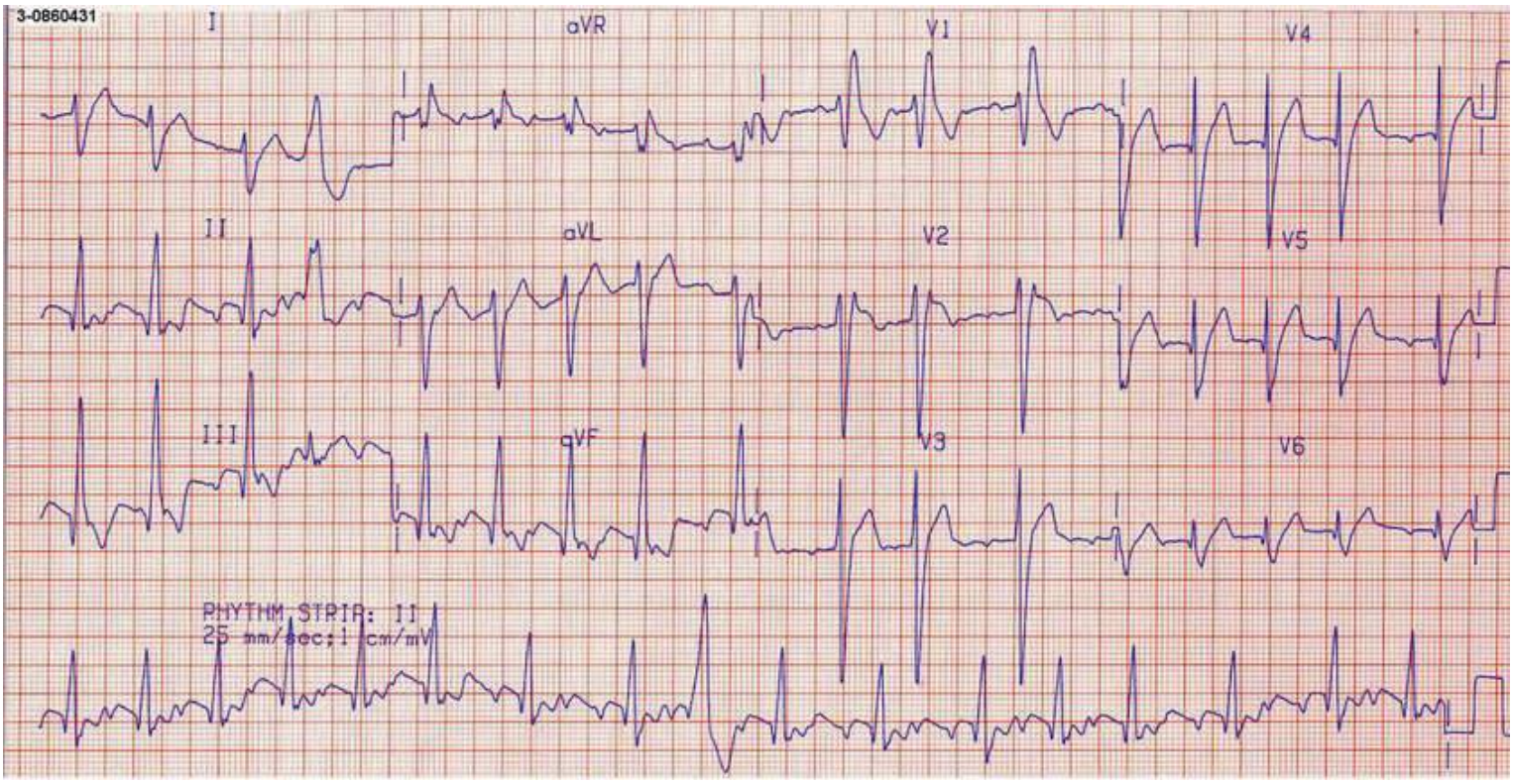
EAPPENDIX 75.29 Sinus rhythm with sinus arrhythmia. Mild right-axis deviation. Markedly prominent and peaked P wave in lead V_2. Mild T wave inversion in the right precordial leads. CLINICAL DX: A 22-year-old person with Marfan syndrome with severe pectus excavatum and moderate mitral regurgitation. The deeply inverted P waves are due to the pectus, and not to right atrial overload.



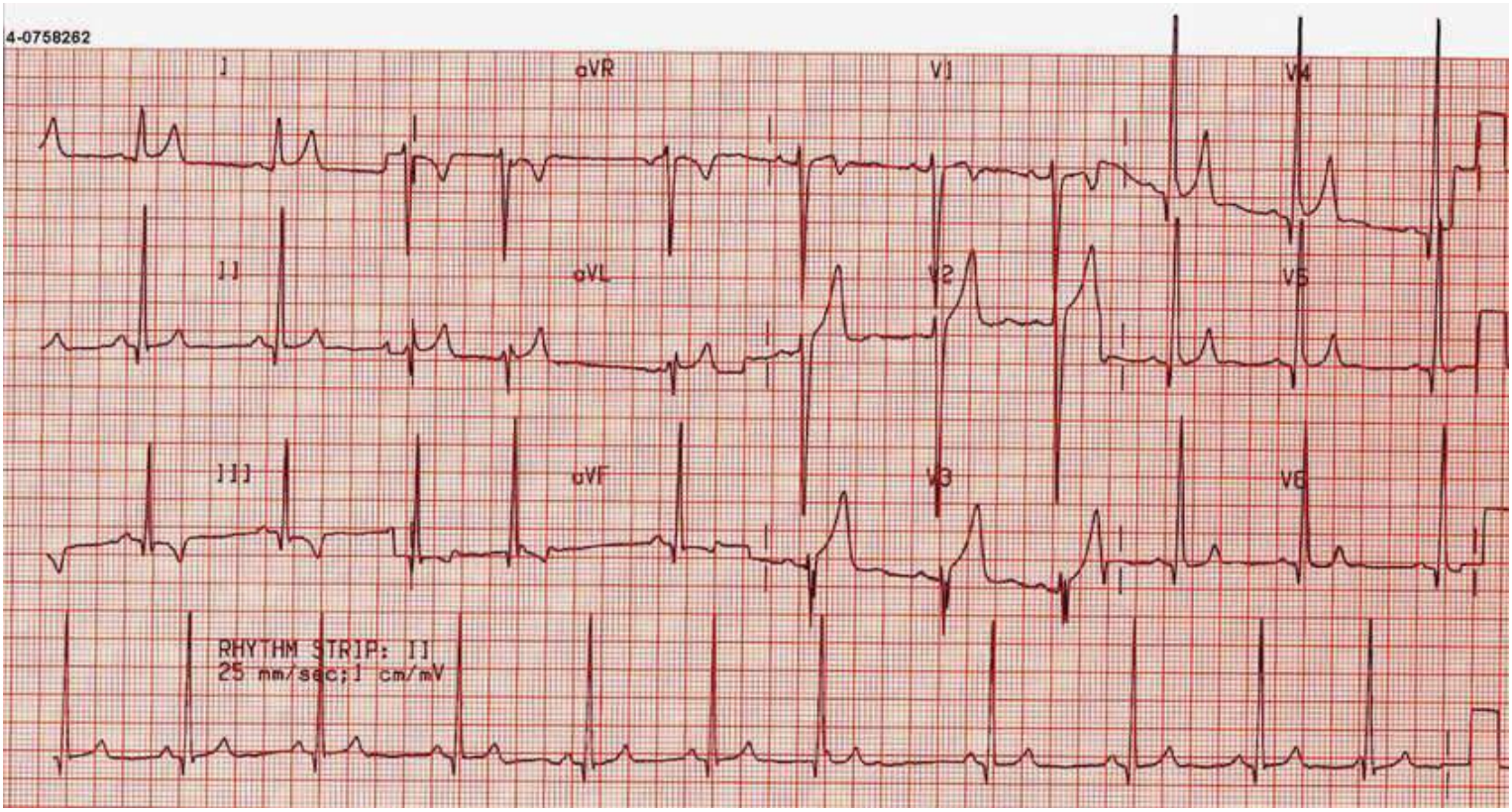
EAPPENDIX 75.30 Sinus rhythm. Vertical axis. Probable right atrial overload (deep P wave inversion in V_1 and peaked P wave in V_2.). CLINICAL DX: Tetralogy of Fallot palliated by a Blalock-Taussig-Thomas shunt. Age 22.



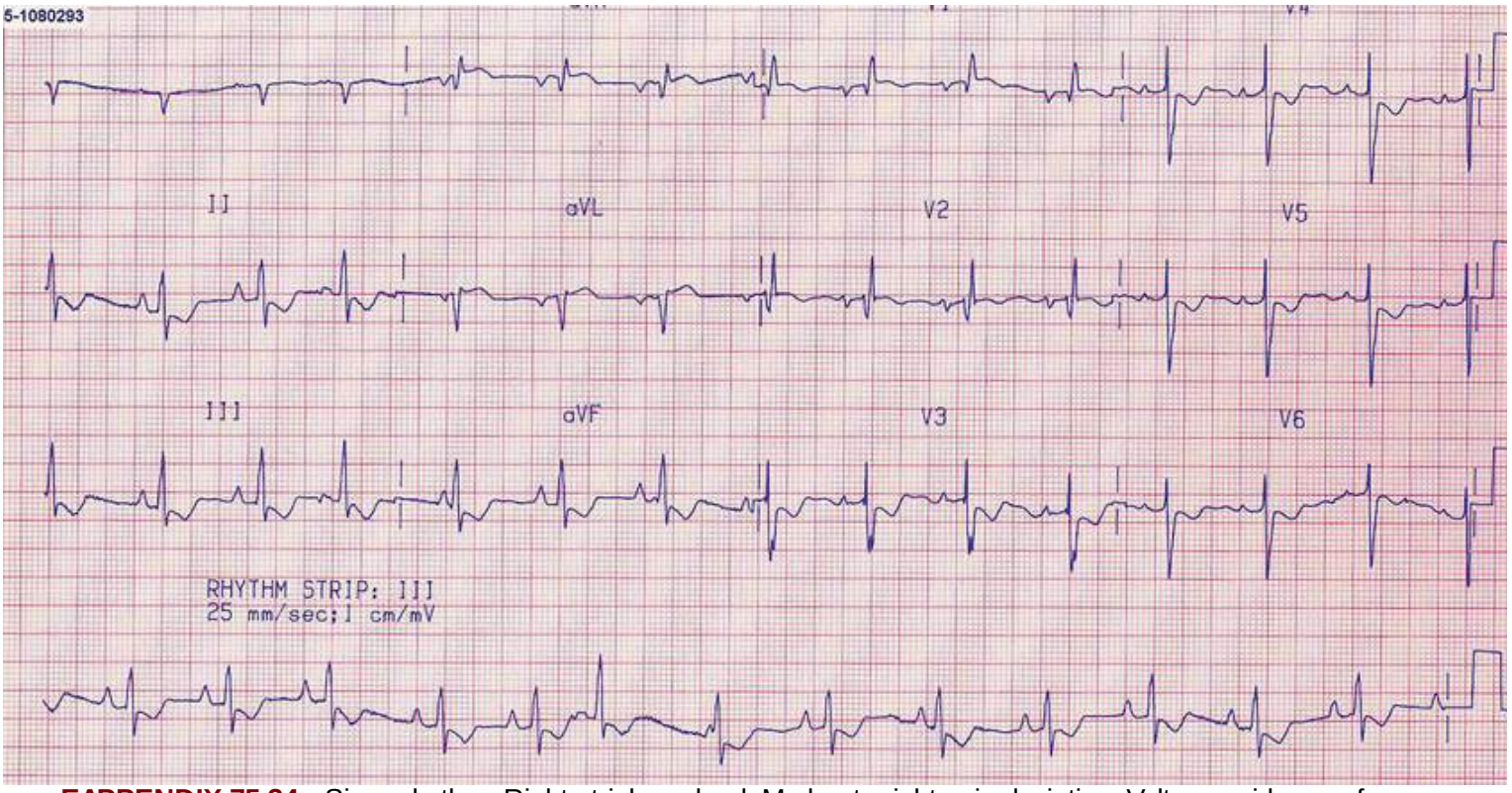
EAPPENDIX 75.31 Sinus rhythm. Marked right-axis deviation. Voltage evidence of RVH. CLINICAL DX: Eisenmenger VSD. Age 27.



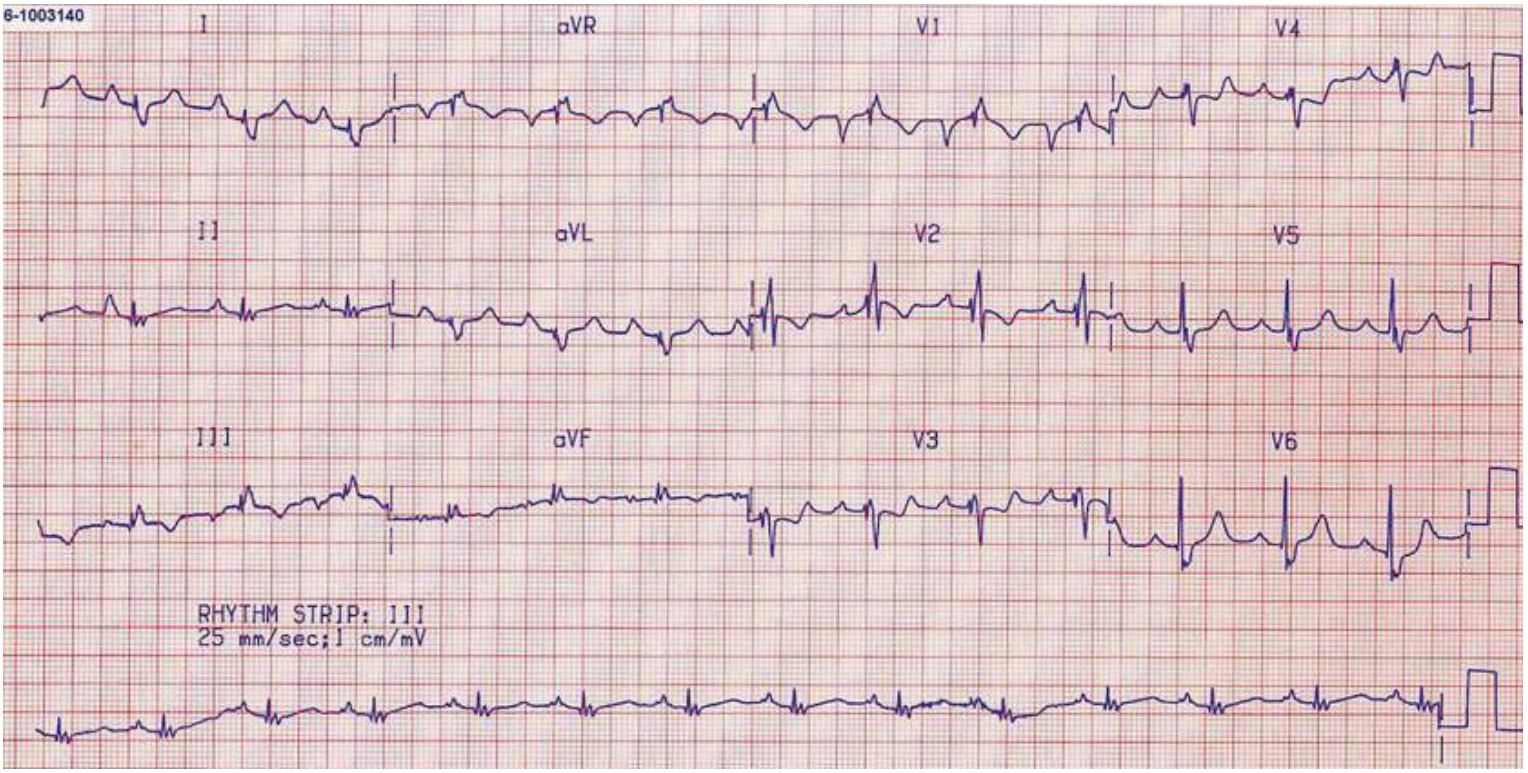
EAPPENDIX 75.32 Atypical atrial flutter with a ventricular rate of about 100 bpm. Right-axis deviation of initial forces. Terminal RBBB. One ventricular premature beat. CLINICAL DX: Repaired tetralogy with residual VSDs and severe tricuspid regurgitation. Age 32.



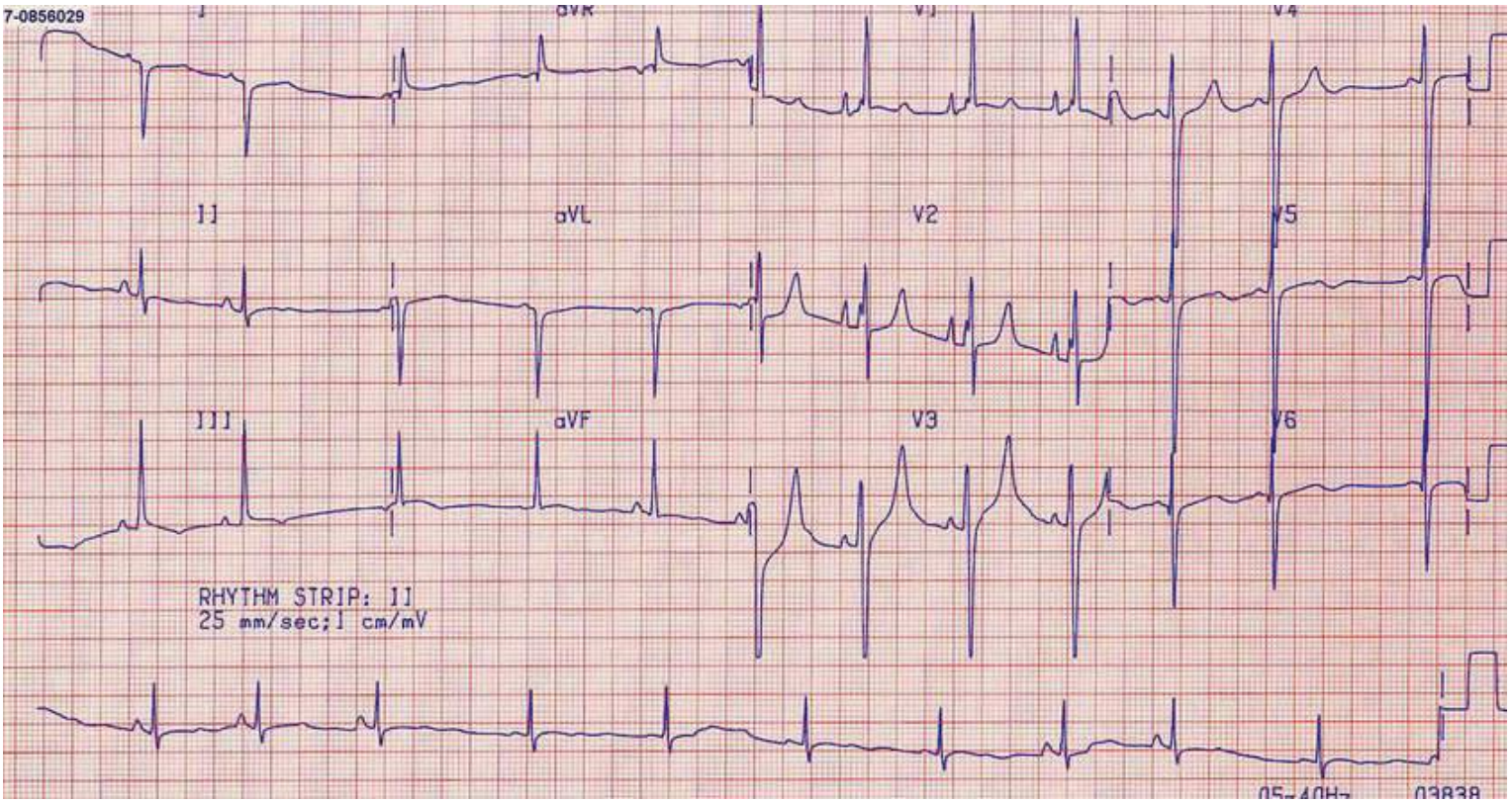
EAPPENDIX 75.33 Sinus rhythm. Possible/probable LVH depending on age. Prominent Q waves in the left chest leads with very tall precordial T waves (the so-called left ventricular volume overload pattern sometimes seen in young people). CLINICAL DX: Severe aortic regurgitation on a bicuspid aortic valve. Age 20.



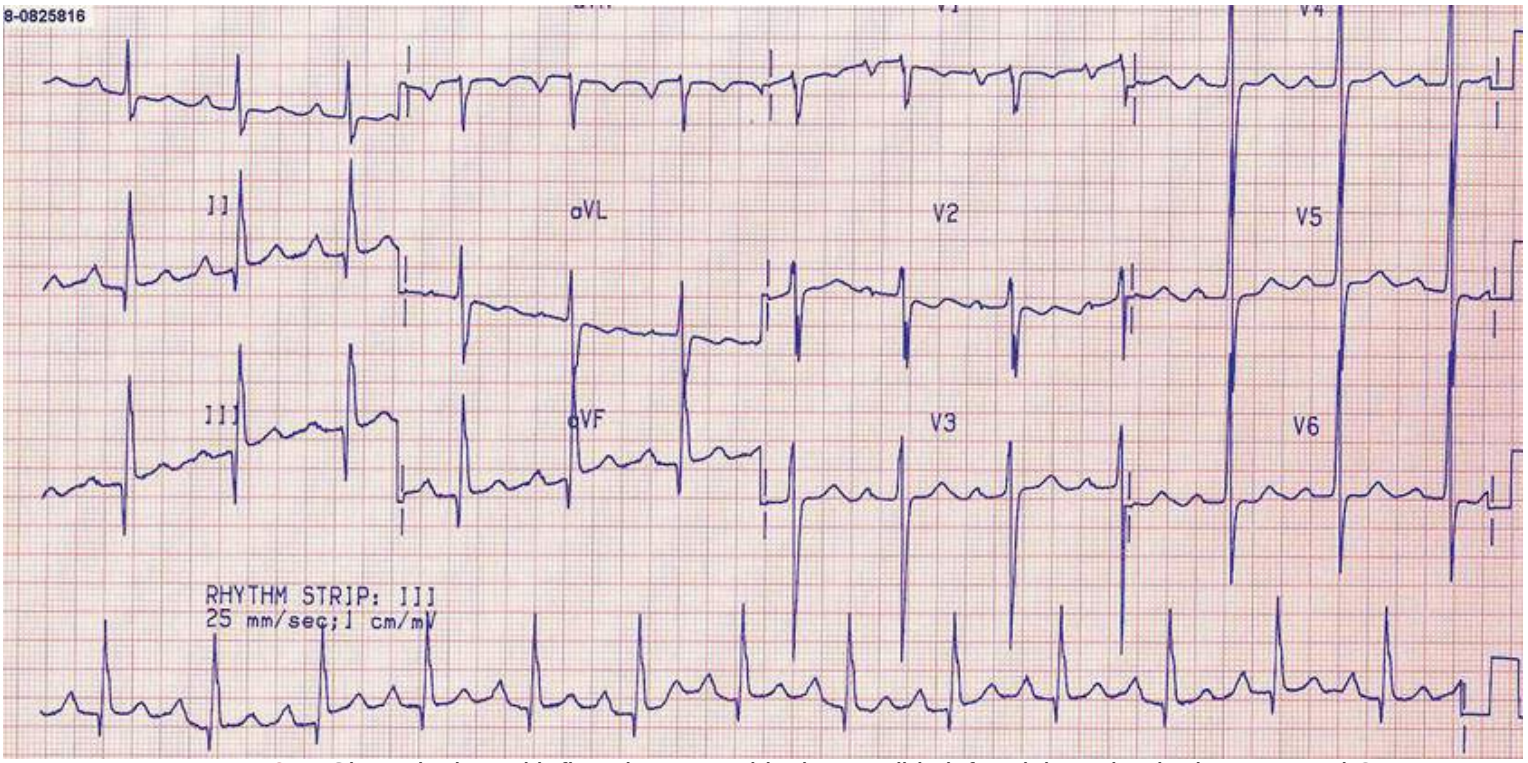
EAPPENDIX 75.34 Sinus rhythm. Right atrial overload. Moderate right-axis deviation. Voltage evidence of RVH with a right ventricular strain pattern. CLINICAL DX: Pulmonary hypertensive ASD. Age 47.



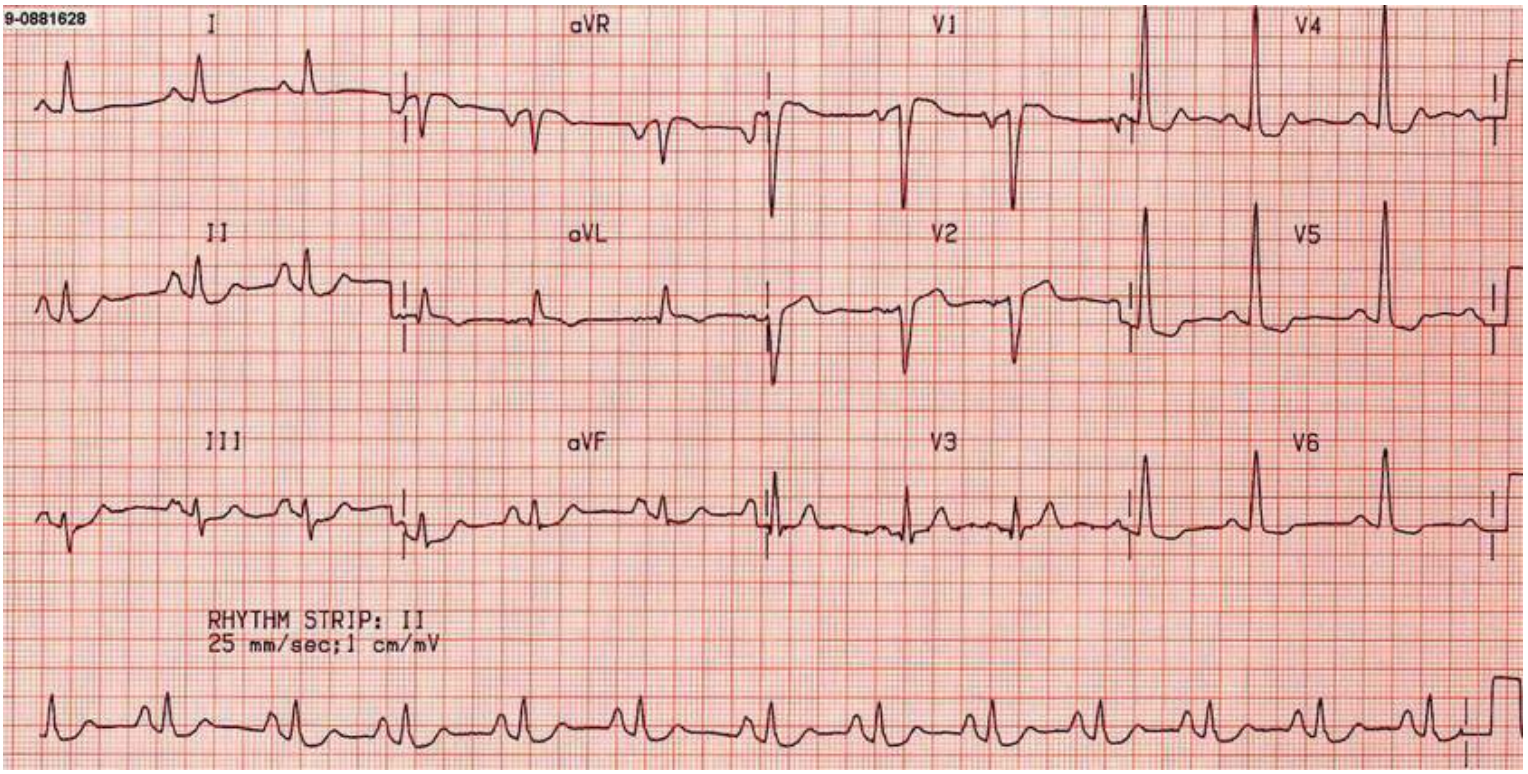
EAPPENDIX 75.35 Sinus rhythm. First-degree AV block. Low-voltage QRS complexes. Right atrial overload (V_1). Abnormal QRS notching in V_2 and V_3. Incomplete RBBB. CLINICAL DX: Ebstein anomaly. Age 19.



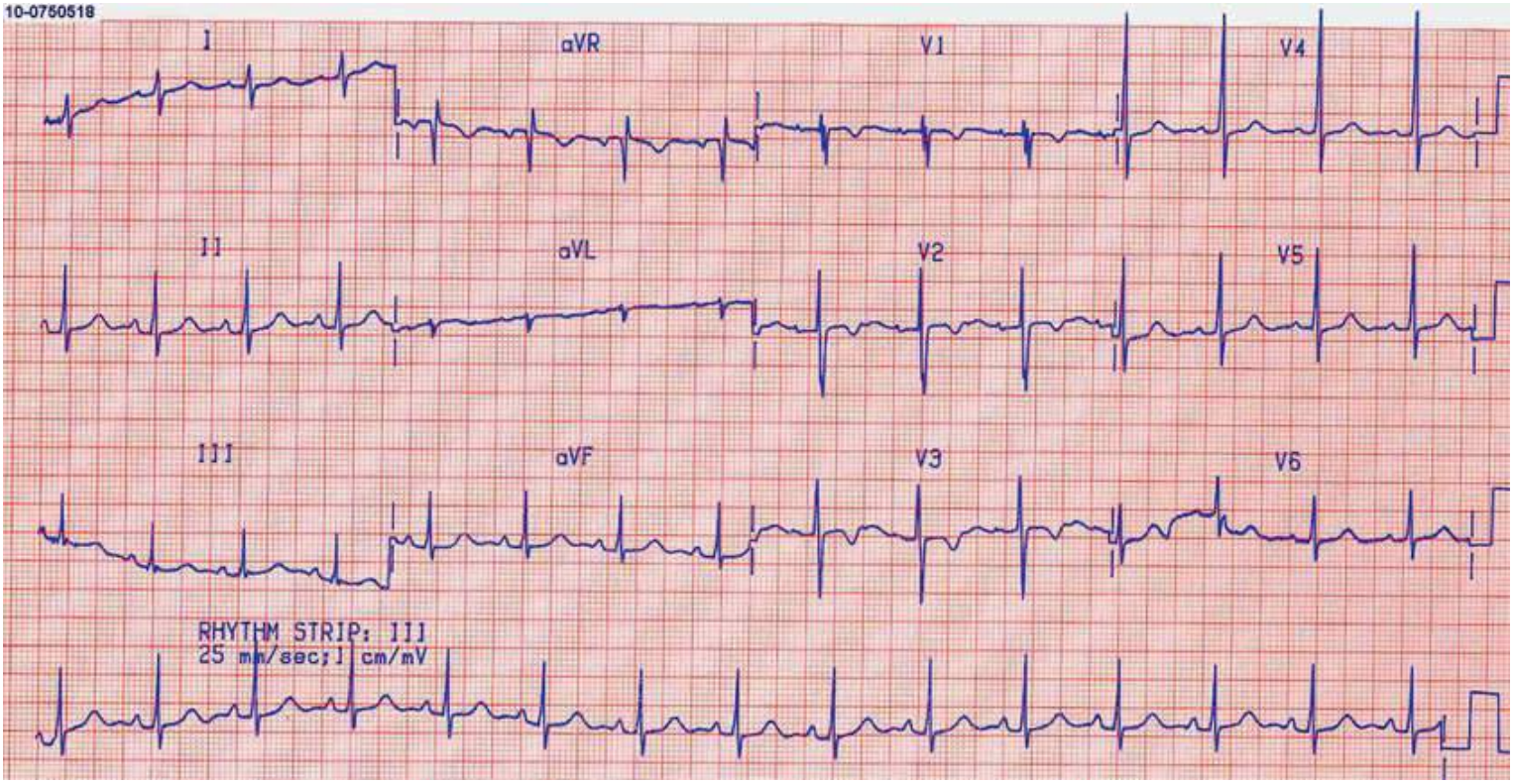
EAPPENDIX 75.36 Sinus rhythm with marked sinus arrhythmia. Marked right atrial overload. Marked right-axis deviation. Marked voltage evidence of RVH. CLINICAL DX: Eisenmenger syndrome due to a large Waterston shunt (ascending aorta to right pulmonary artery) in a patient with tetralogy. Age 21.



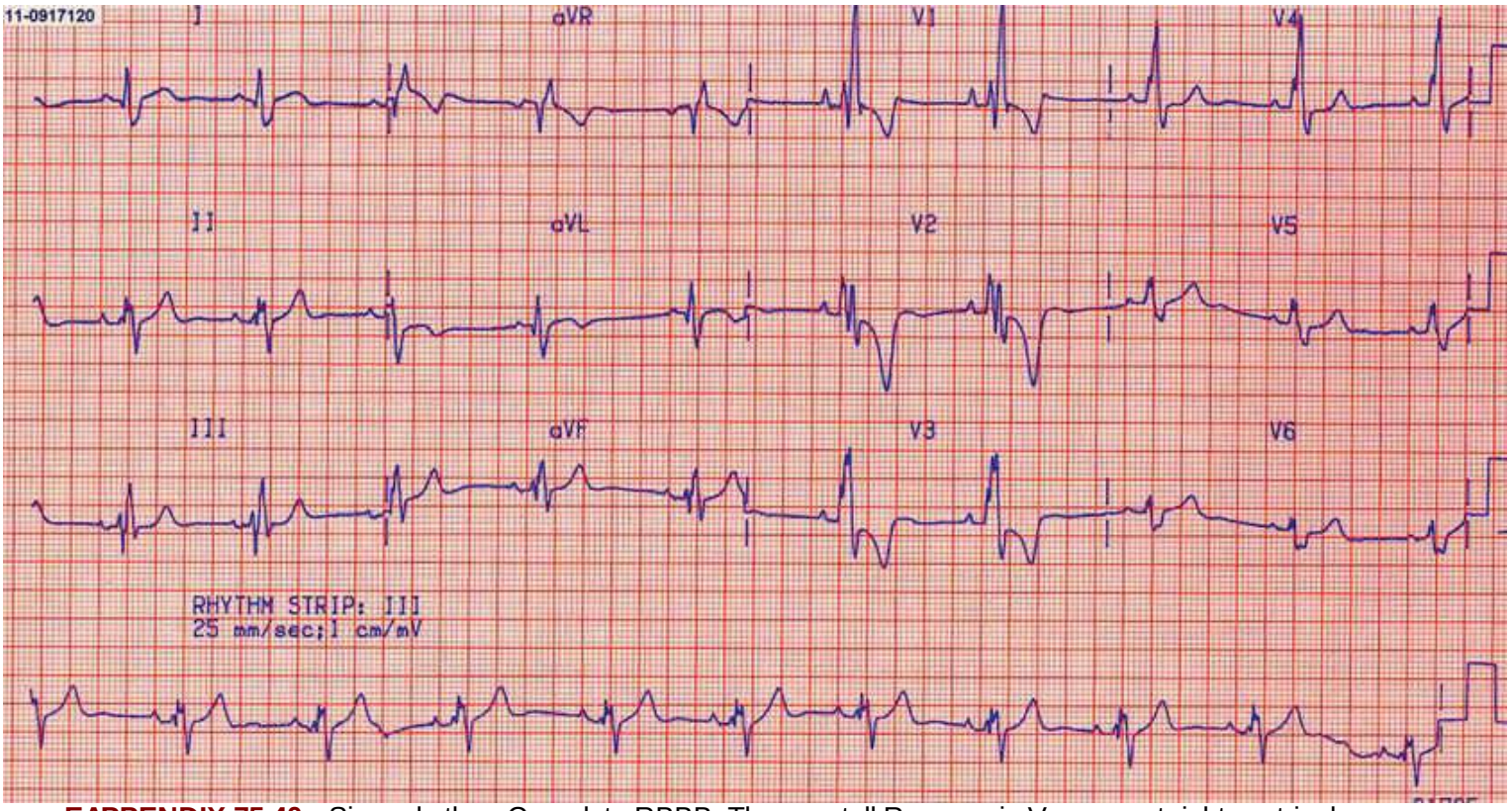
EAPPENDIX 75.37 Sinus rhythm with first-degree AV block. Possible left atrial overload. Absent septal Q waves in leads V_5 and V_6. Prominent inferior Q waves of uncertain significance. CLINICAL DX: Congenitally corrected TGA with severe systemic tricuspid regurgitation. Age 34.



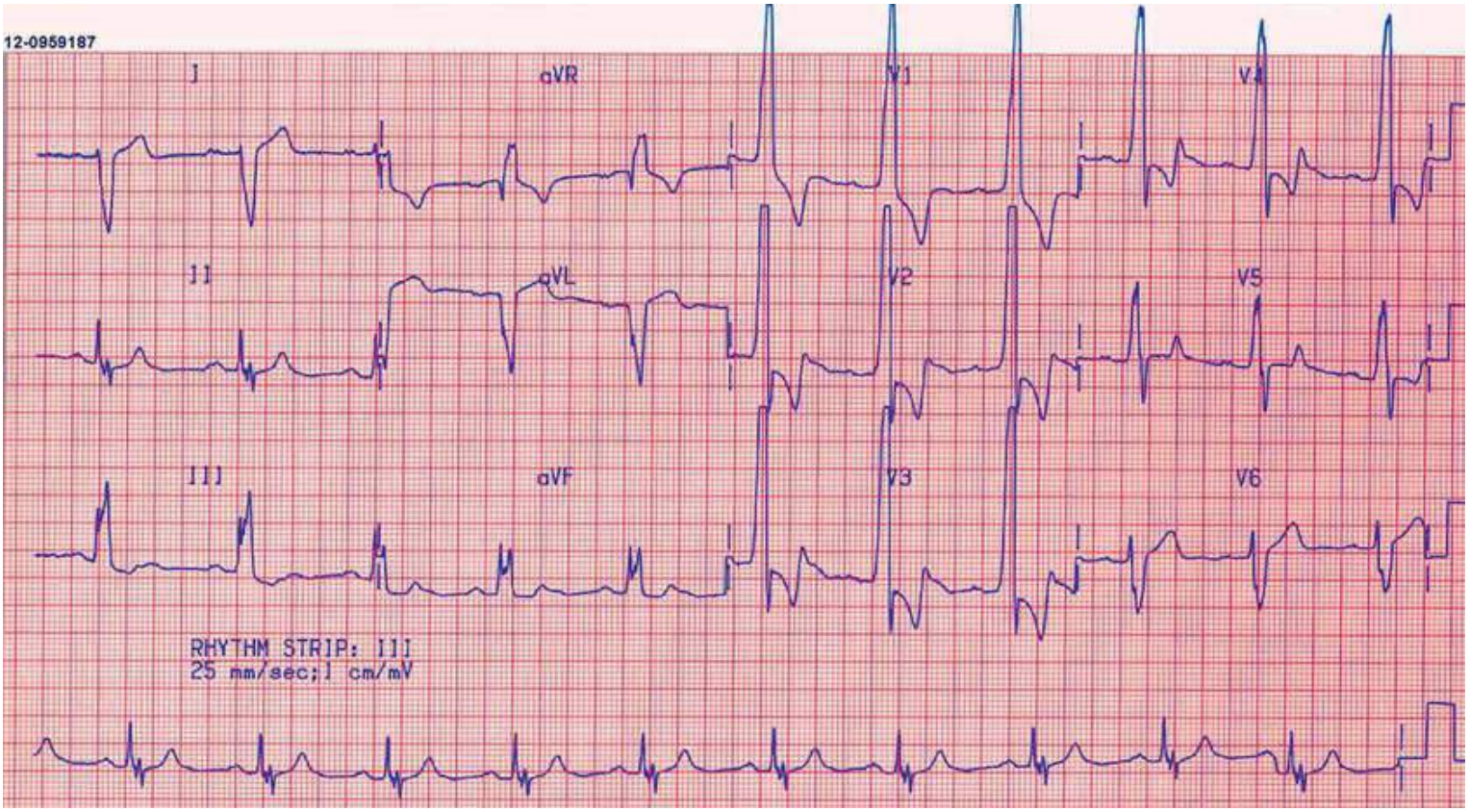
EAPPENDIX 75.38 Sinus rhythm. Right and possibly left atrial overload. Incomplete LBBB with possible left ventricular strain pattern. Possible digoxin effect. CLINICAL DX: Tricuspid atresia with a Blalock-Taussig-Thomas shunt. Age 35.



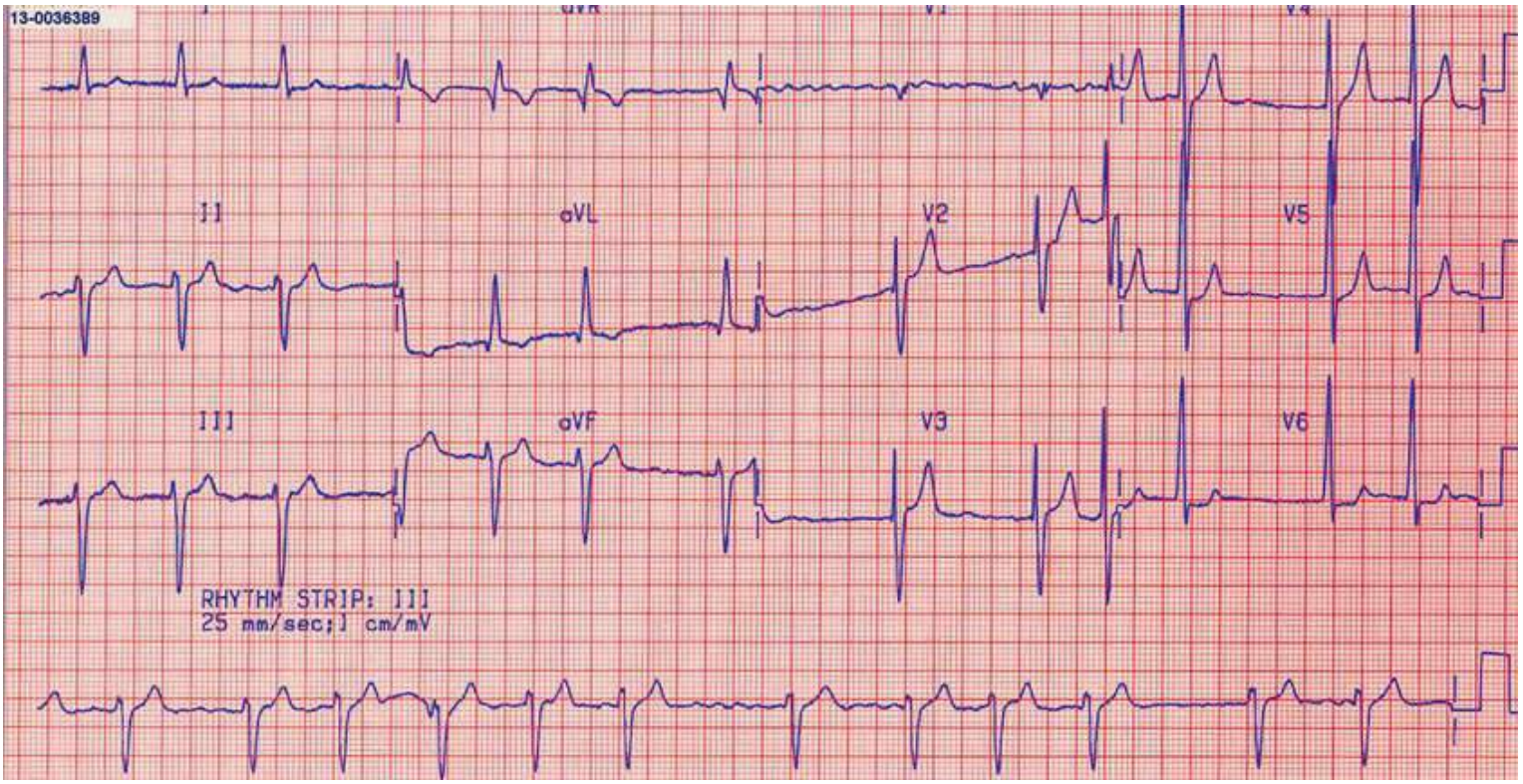
EAPPENDIX 75.39 Sinus rhythm. Vertical axis or mild right-axis deviation. QRS notching in V_1, often seen in secundum ASDs and not changing after repair. T wave inversion in V_1 to V_3 compatible with a right ventricular abnormality. CLINICAL DX: Postoperative secundum ASD repair. Age 29



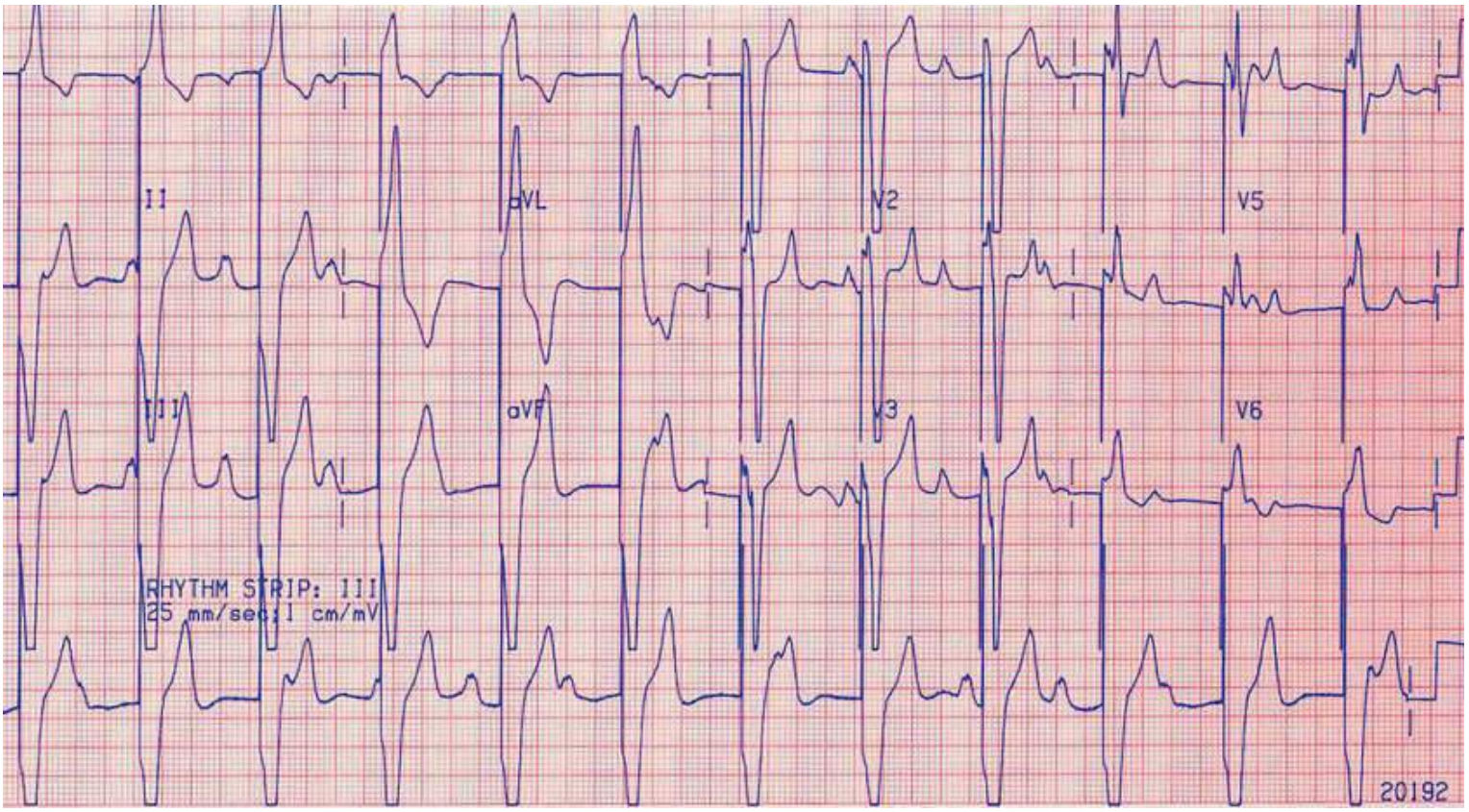
EAPPENDIX 75.40 Sinus rhythm. Complete RBBB. The very tall R waves in V_1 suggest right ventricular hypertension. Right atrial overload in V_1. CLINICAL DX: Complicated repaired tetralogy. Residual pulmonary hypertension following a prior Waterston shunt. VSD patch leak. Age 21.



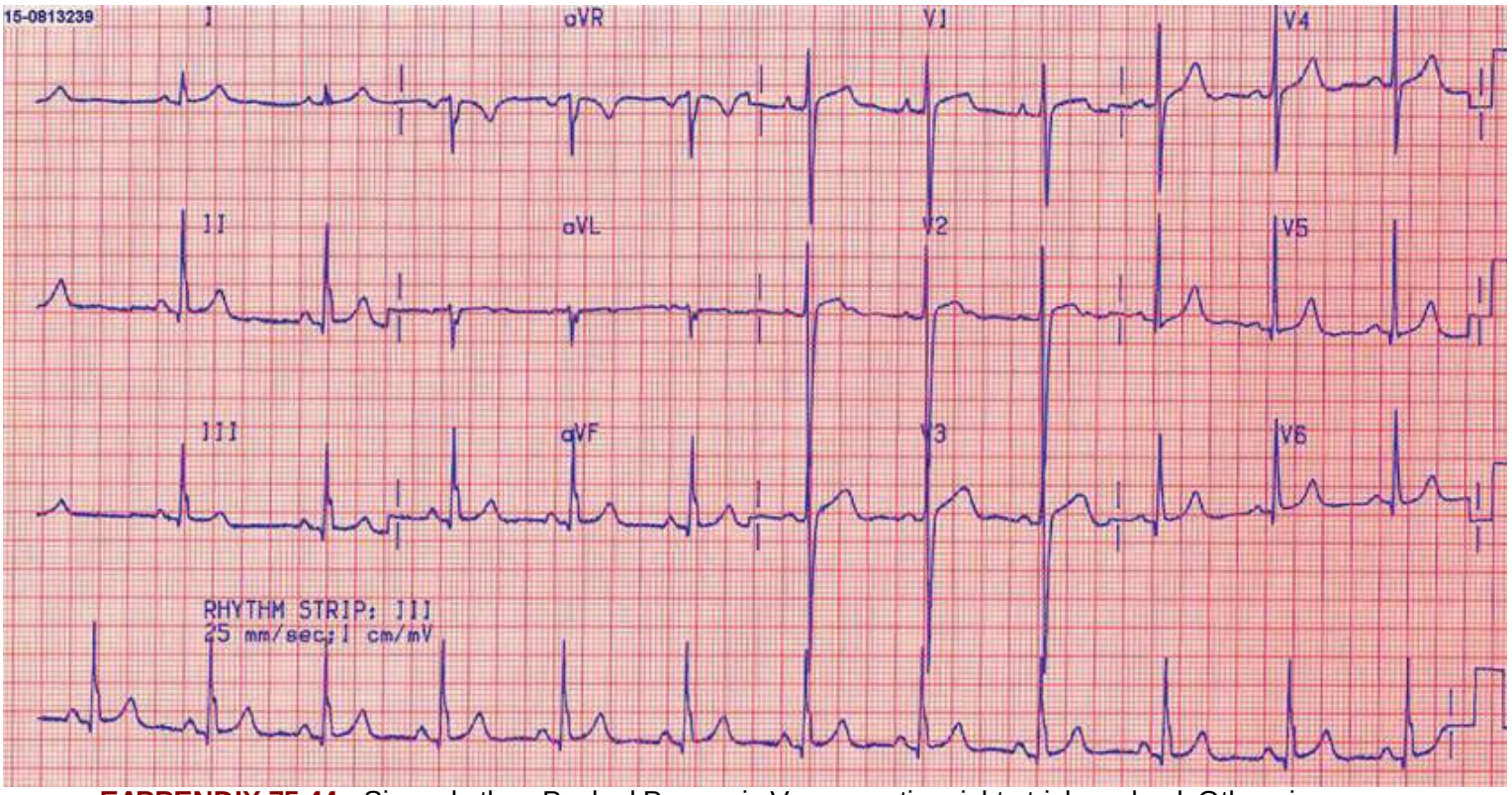
EAPPENDIX 75.41 Sinus rhythm with first-degree AV block. Marked right-axis deviation of initial forces with terminal complete RBBB. No right atrial overload. CLINICAL DX: Mustard repair of TGA, age 17.



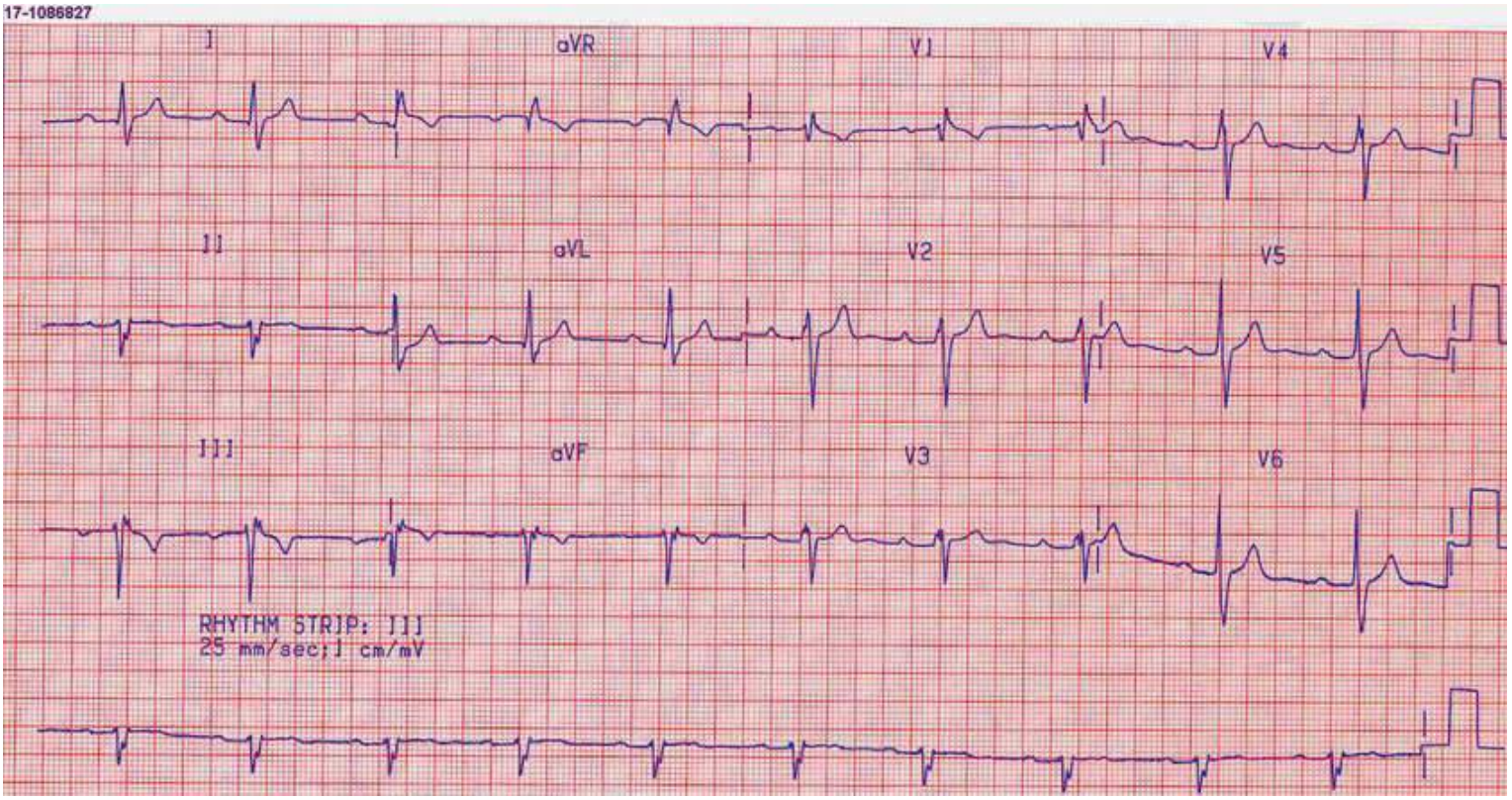
EAPPENDIX 75.42 Atrial fibrillation with a ventricular rate of 80 bpm. Marked left-axis deviation. CLINICAL DX: Repaired ostium primum ASD and mitral repair, still having substantial mitral regurgitation. On digoxin.



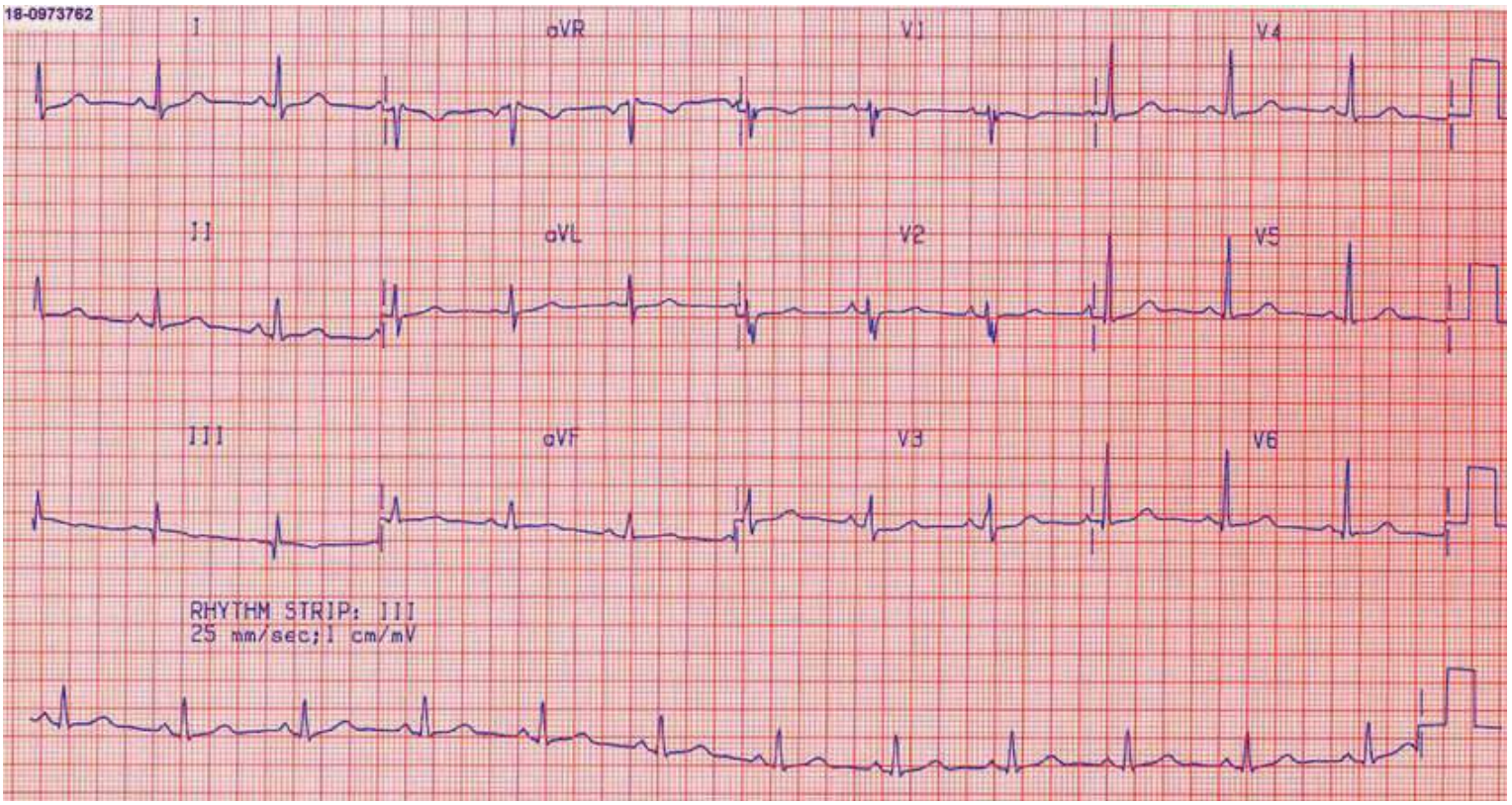
EAPPENDIX 75.43 Sinus rhythm at a rate of about 85 bpm. Complete heart block with ventricular pacing. Marked right atrial overload. CLINICAL DX: Congenitally corrected TGA with a VSD and substantial pulmonary stenosis.



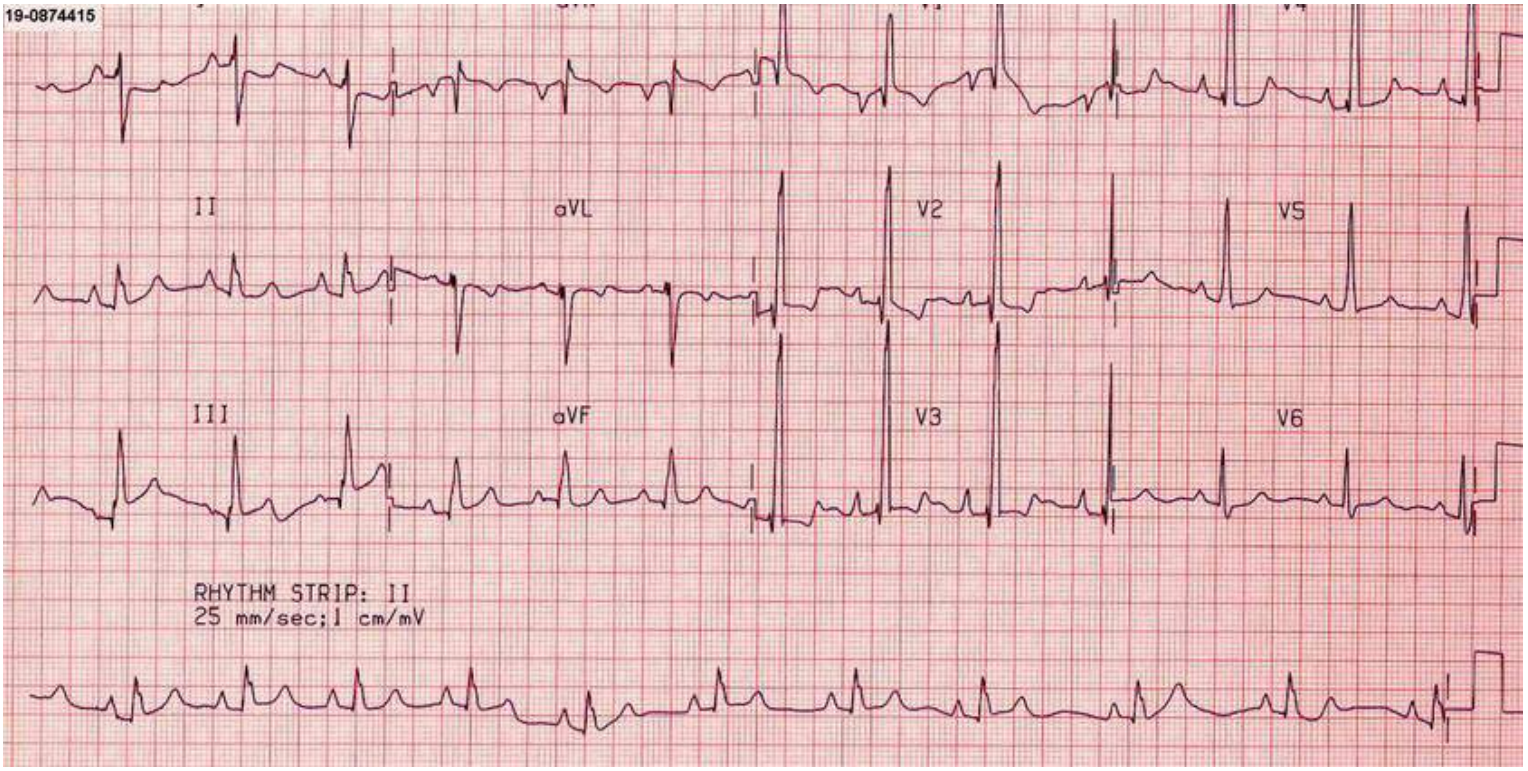
EAPPENDIX 75.44 Sinus rhythm. Peaked P wave in V_1 suggesting right atrial overload. Otherwise normal ECG. CLINICAL DX: Mild pulmonary stenosis. Age 21.



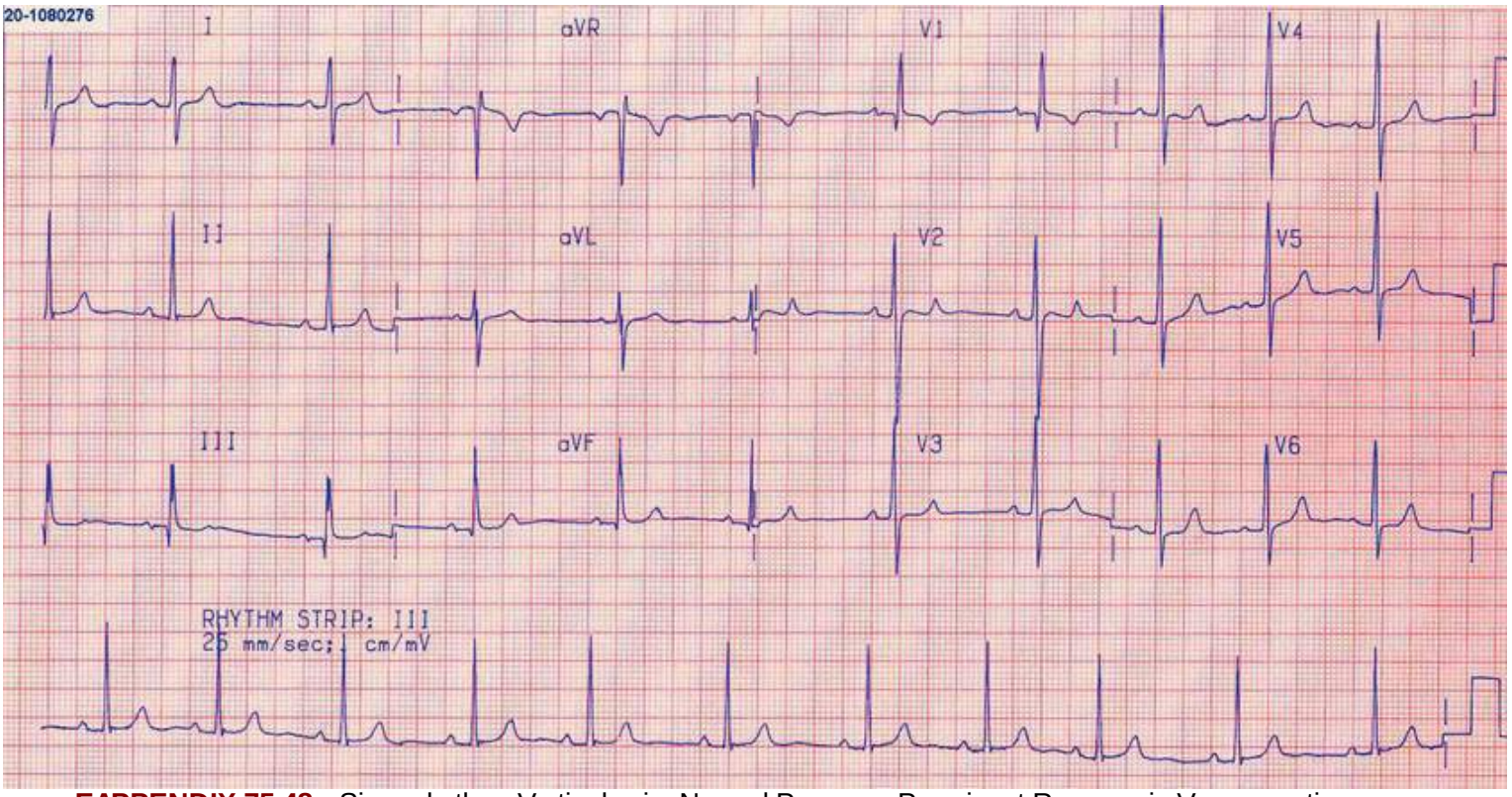
EAPPENDIX 75.45 Sinus rhythm with first-degree AV block. Left-axis deviation. Incomplete RBBB. No left atrial overload pattern. CLINICAL DX: Ostium primum ASD. Age 27.



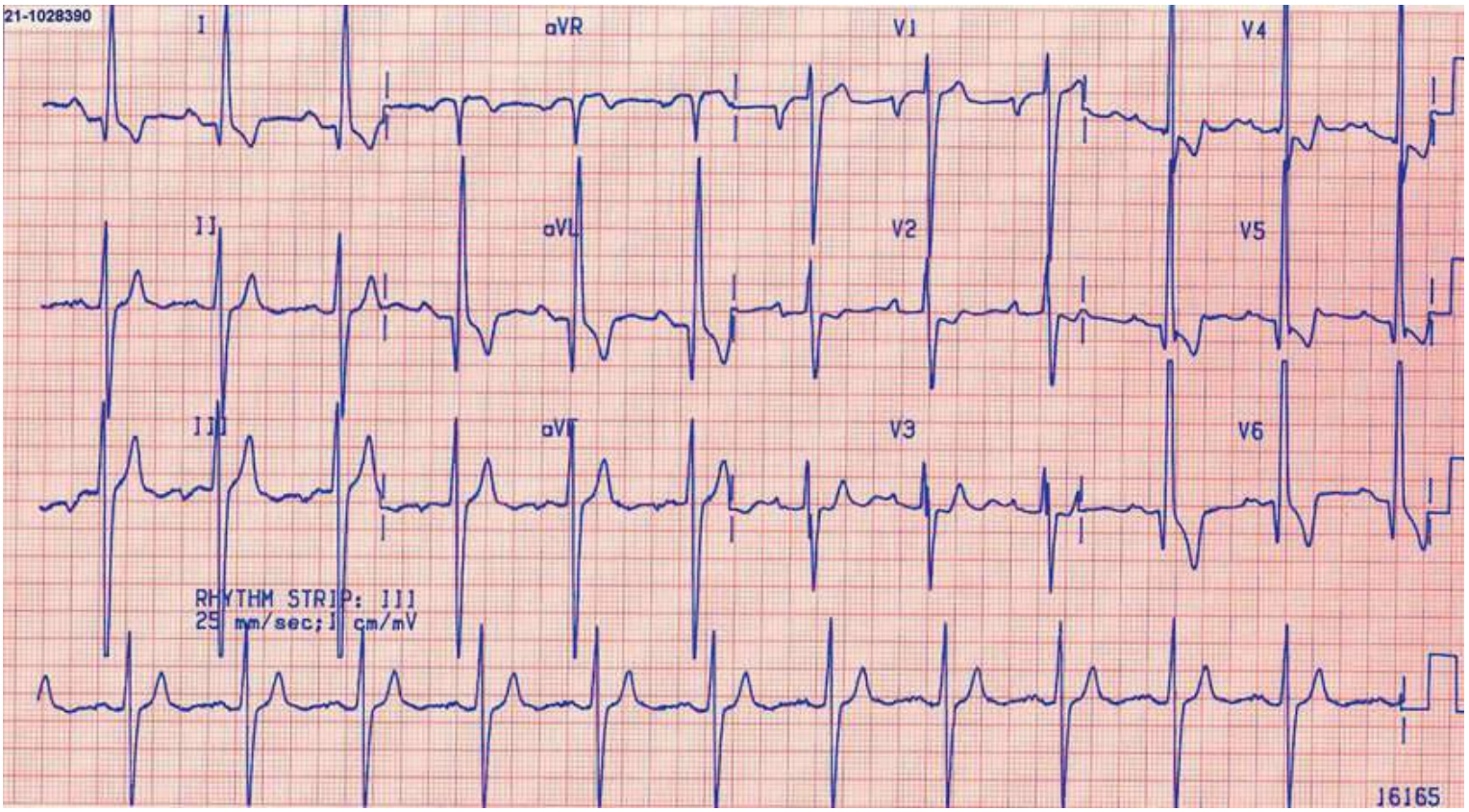
EAPPENDIX 75.46 Sinus rhythm. Peaked P waves in V_2 and V_3 not meeting voltage criteria for right atrial overload. QRS notching in V_1 and V_2 possibly suggestive of an ASD. CLINICAL DX: Ebstein anomaly. Age 46.



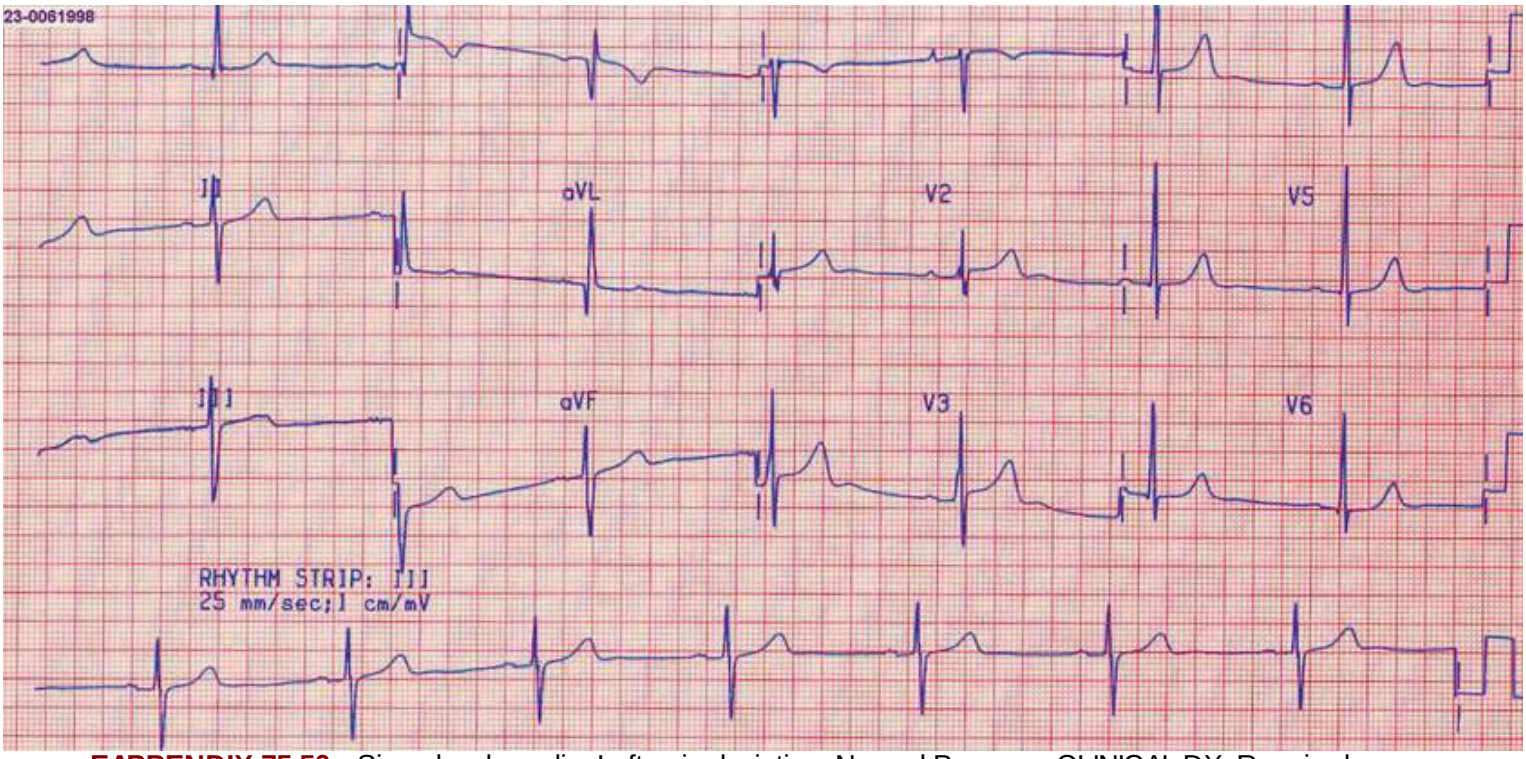
EAPPENDIX 75.47 Sinus rhythm. Right atrial enlargement. Right-axis deviation of initial forces. Voltage evidence of RVH with RV strain. CLINICAL DX: Tetralogy palliated by a Blalock-Taussig-Thomas shunt. Age 21.



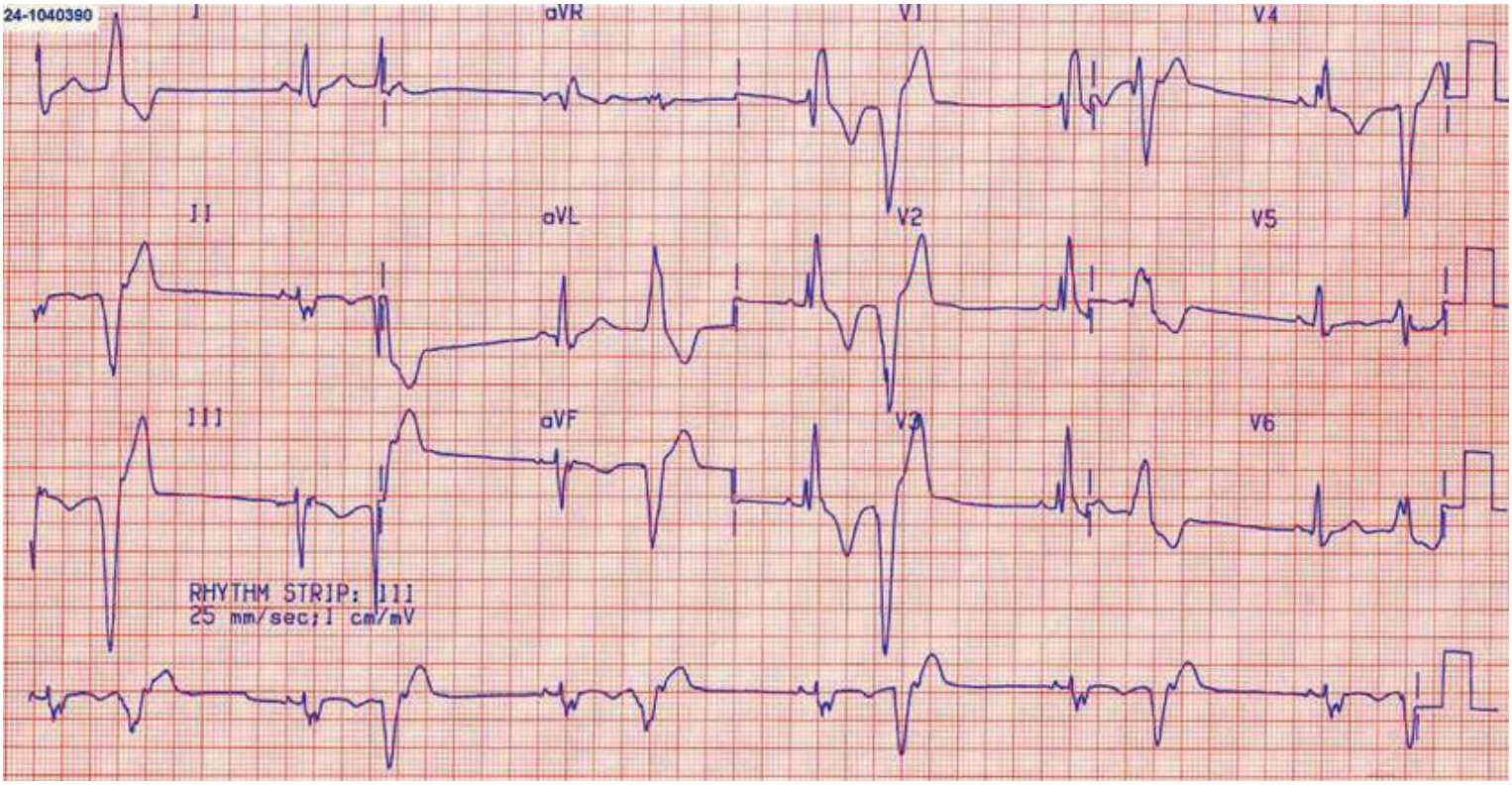
EAPPENDIX 75.48 Sinus rhythm. Vertical axis. Normal P waves. Prominent R waves in V_1 suggesting RV pressure overload. CLINICAL DX: Unrepaired tetralogy. Age 19.



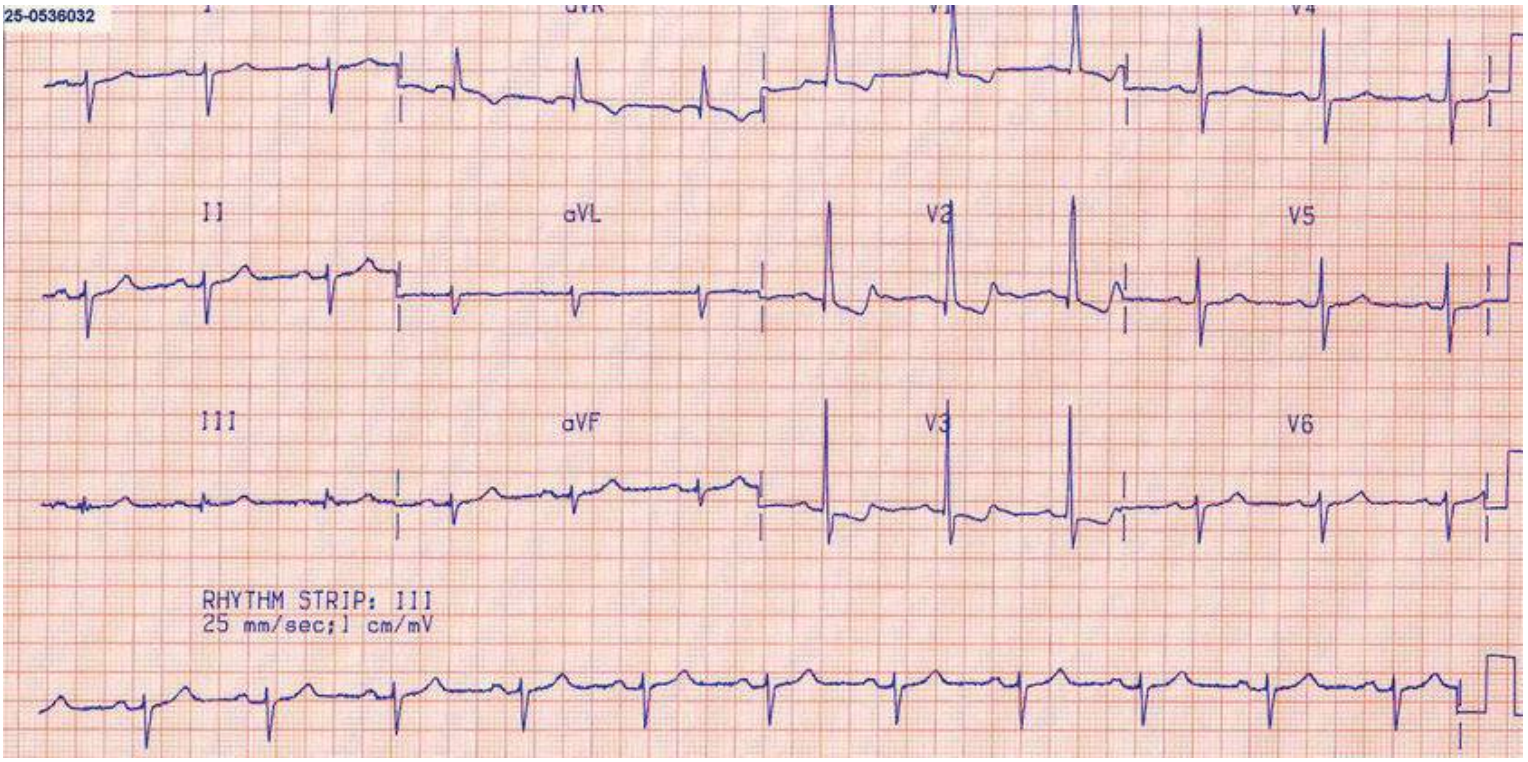
EAPPENDIX 75.49 Sinus rhythm with both left and right atrial overload. Left-axis deviation. Prominent Q waves in the lateral leads. Possible LV strain pattern. Possible digoxin effect. CLINICAL DX: Tricuspid atresia with a VSD and PS palliated with a cavopulmonary (Glenn) shunt and a large Potts shunt. Age 20.



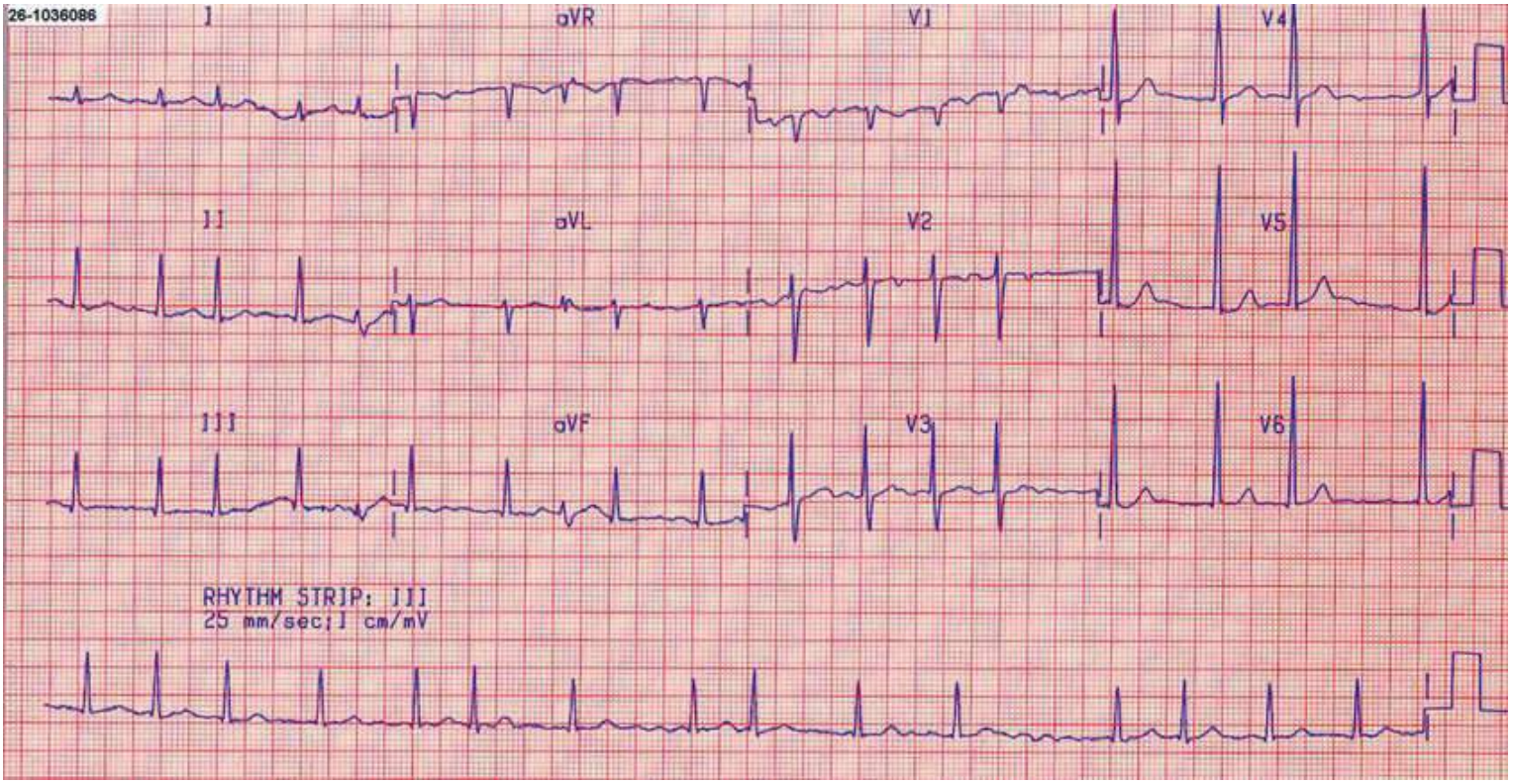
EAPPENDIX 75.50 Sinus bradycardia. Left-axis deviation. Normal P waves. CLINICAL DX: Repaired ostium primum ASD. Cleft mitral leaflet with mild regurgitation. Age 39.



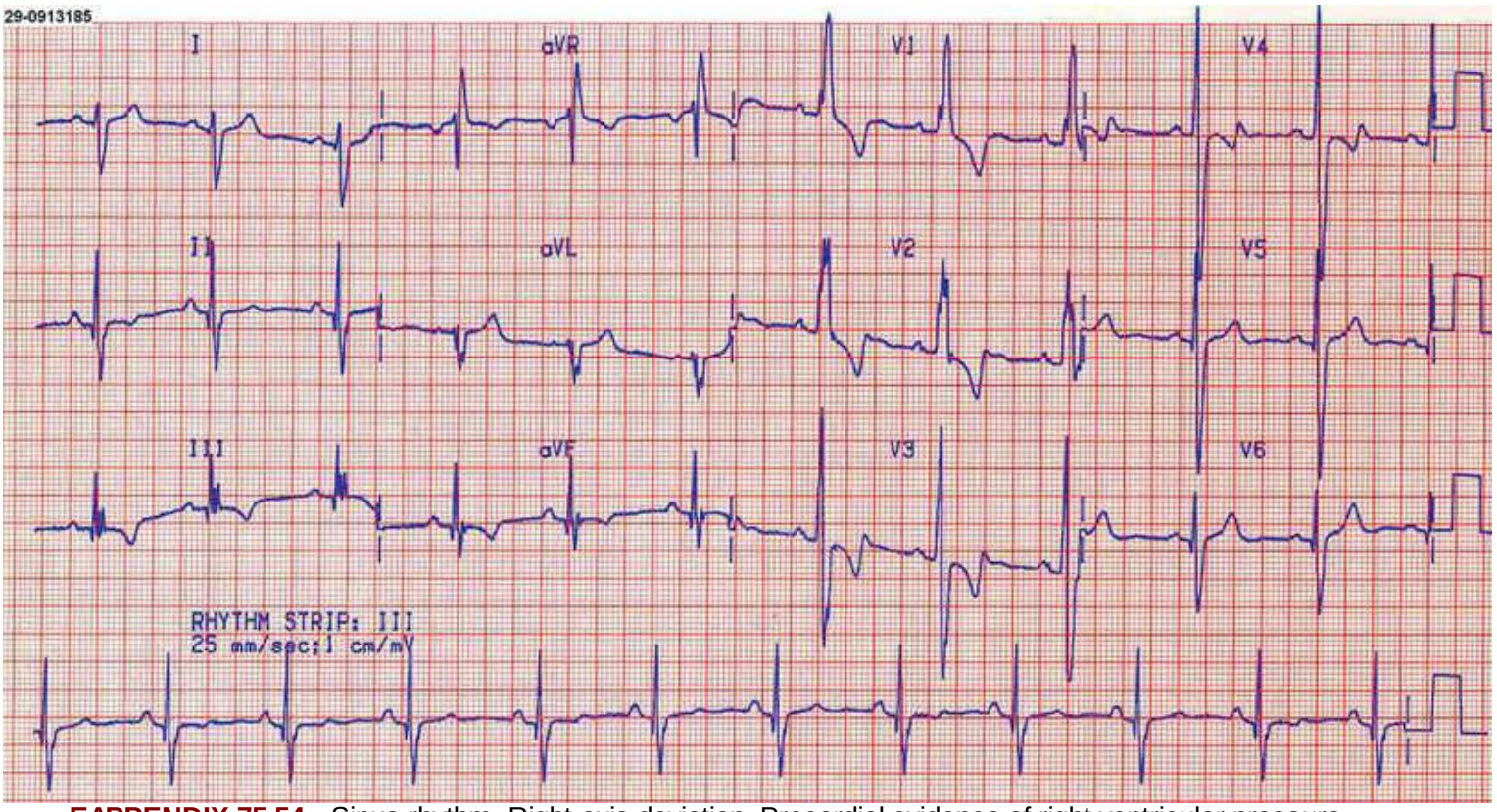
EAPPENDIX 75.51 Sinus rhythm with ventricular bigeminy. VPBs arise in the right ventricle (LBBB pattern). Complete RBBB. CLINICAL DX: Repaired tetralogy. Age 32.



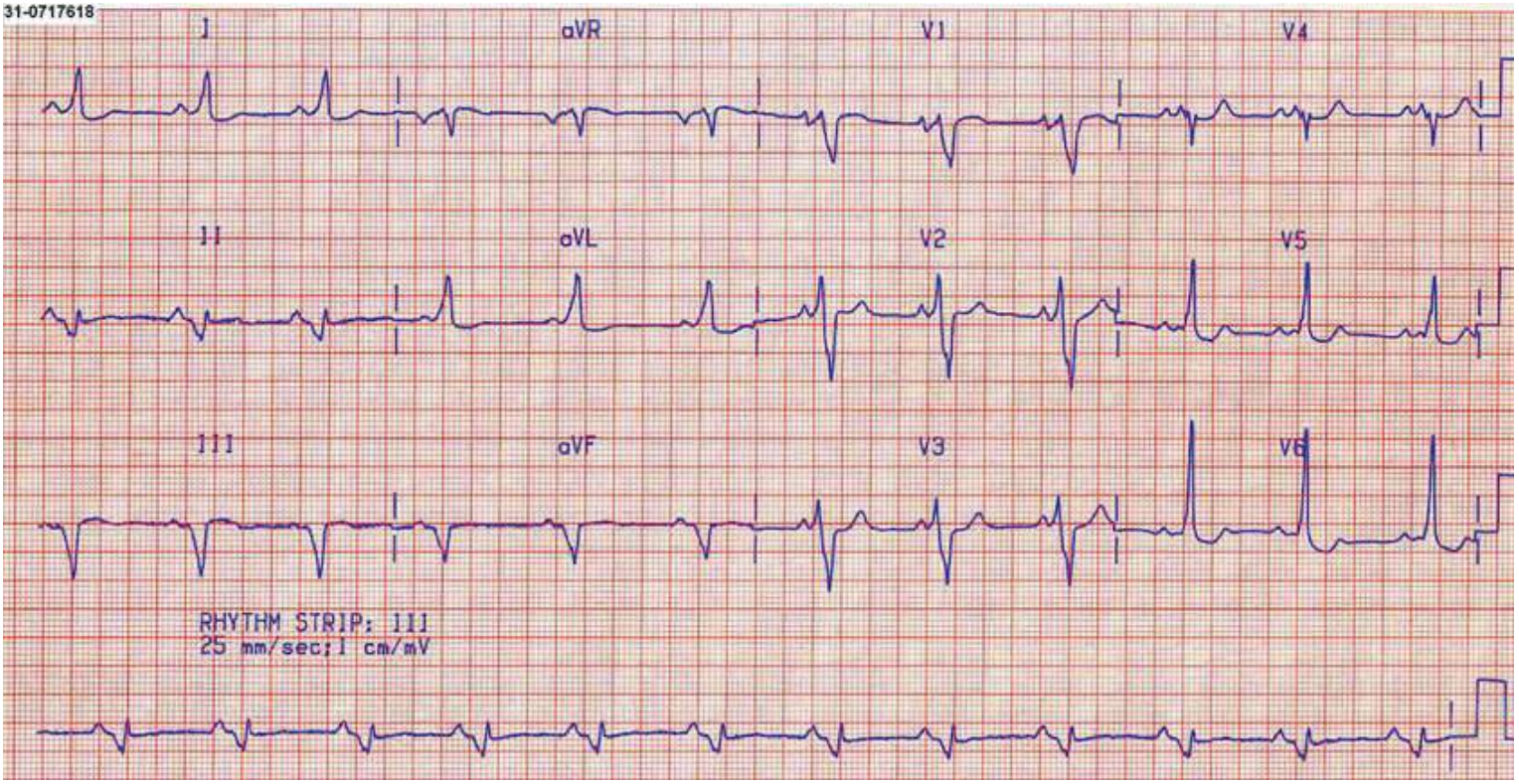
EAPPENDIX 75.52 Sinus rhythm. Marked right-axis deviation. Marked precordial evidence of right ventricular pressure overload. Indeterminate QRS axis. CLINICAL DX: Mustard repair of TGA. Age 32.



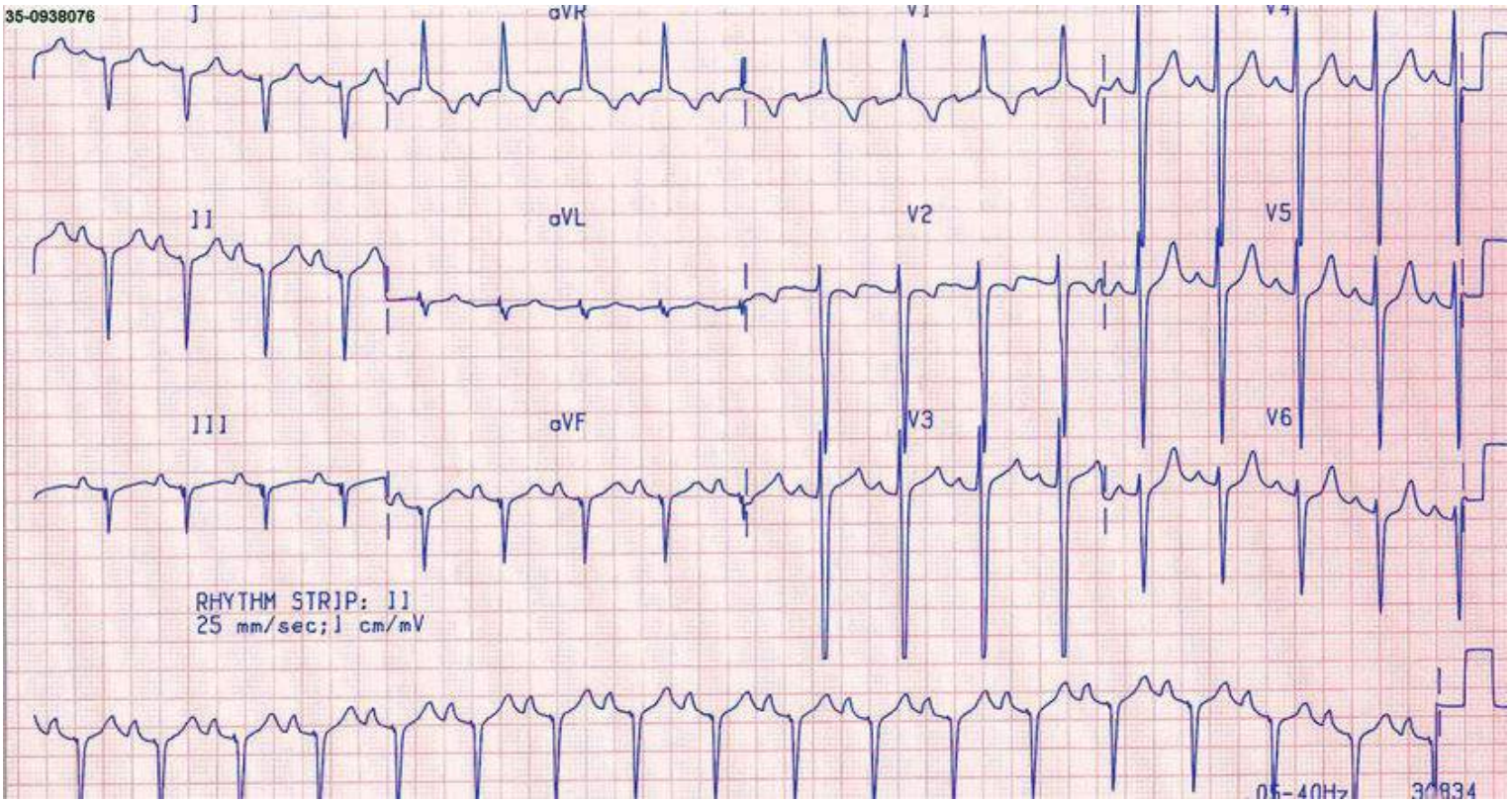
EAPPENDIX 75.53 Atrial fibrillation with ventricular rate of 90 bpm. Normal QRS axis. CLINICAL DX: Ebstein anomaly. Age 33.



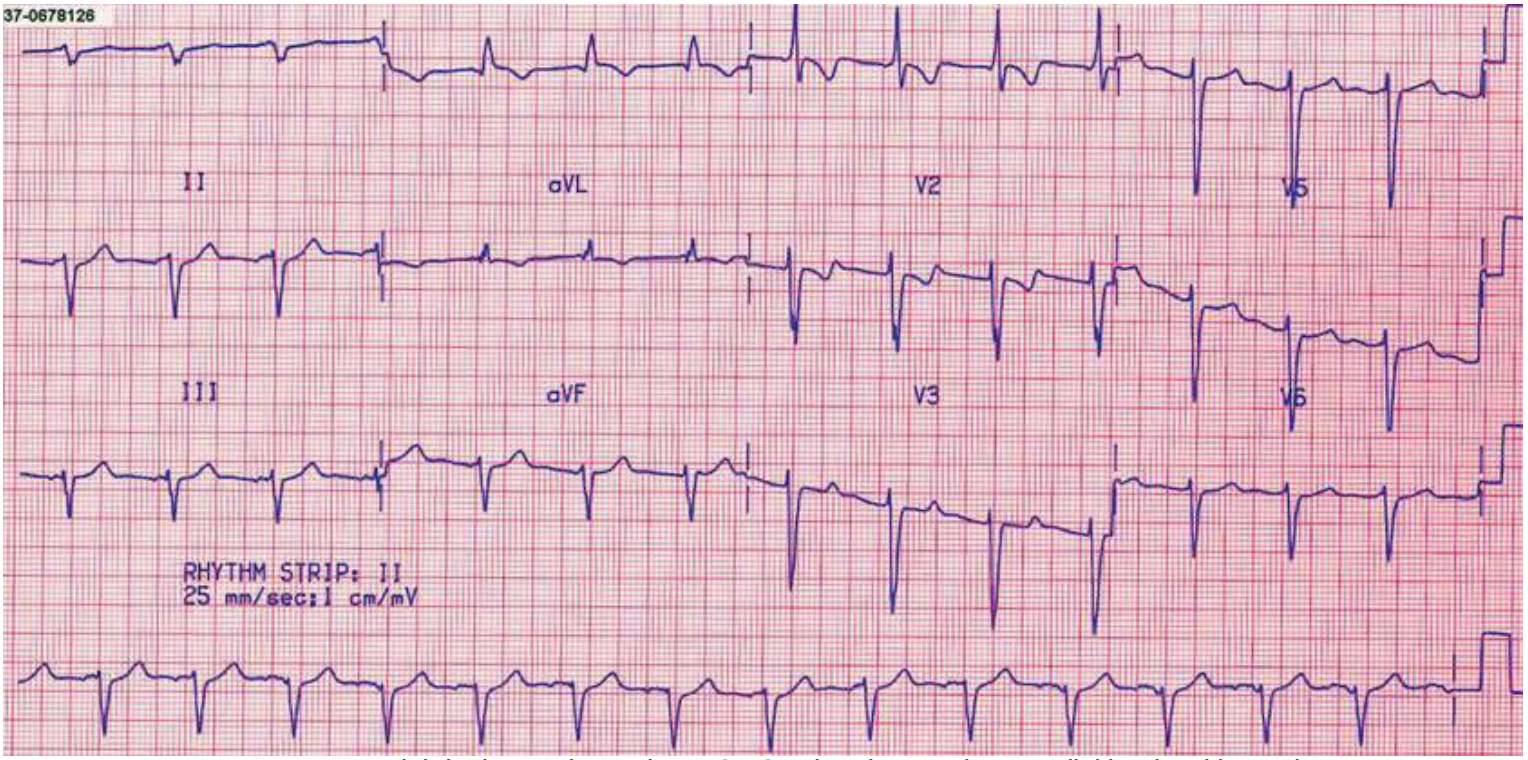
EAPPENDIX 75.54 Sinus rhythm. Right-axis deviation. Precordial evidence of right ventricular pressure overload. RV strain pattern V_1 to V_4. CLINICAL DX: Eisenmenger VSD. Age 20.



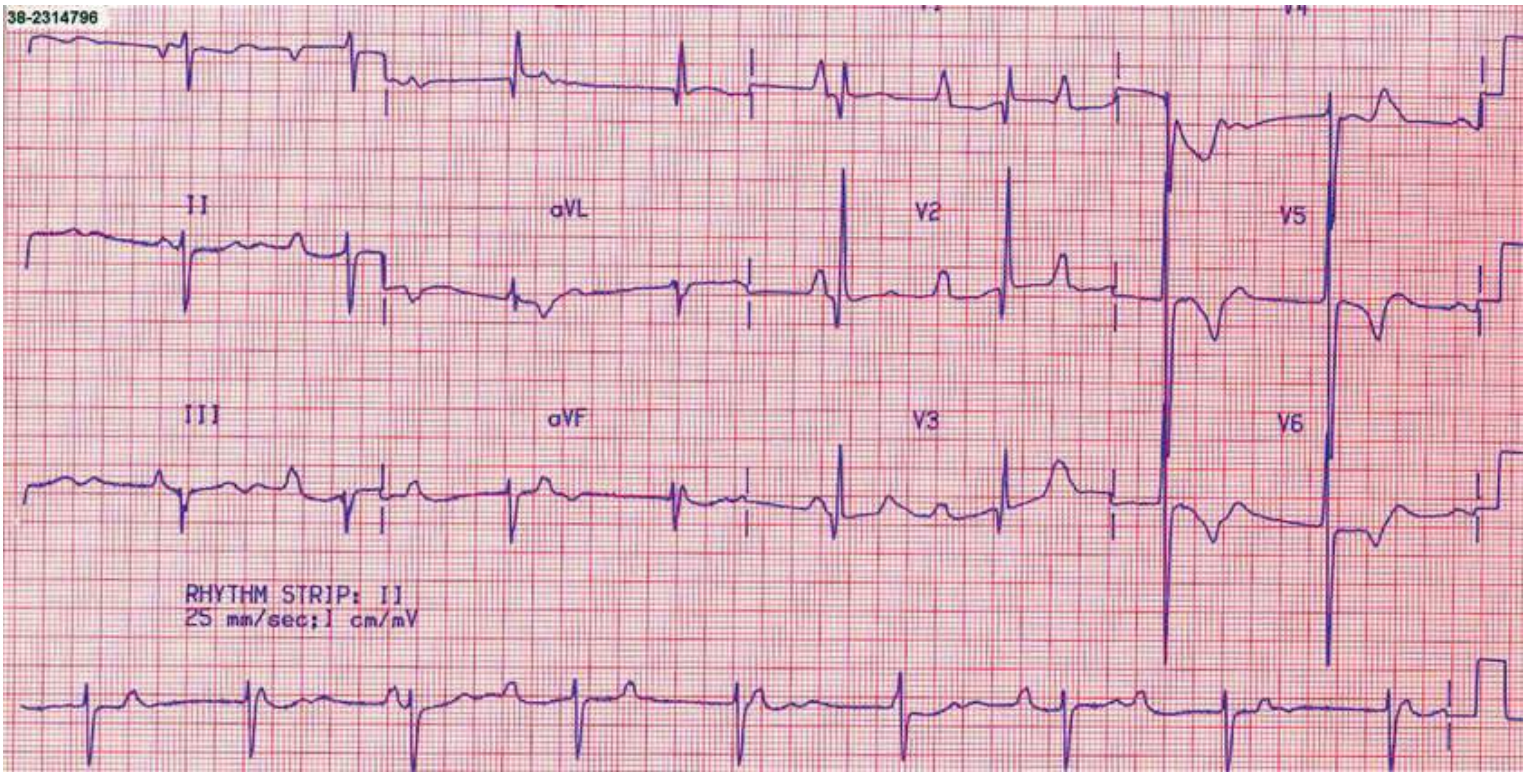
EAPPENDIX 75.55 Sinus rhythm. Short PR interval. Delta waves present. No right atrial overload. CLINICAL DX: Ebstein anomaly. Wolff-Parkinson-White pattern syndrome. Age 25.



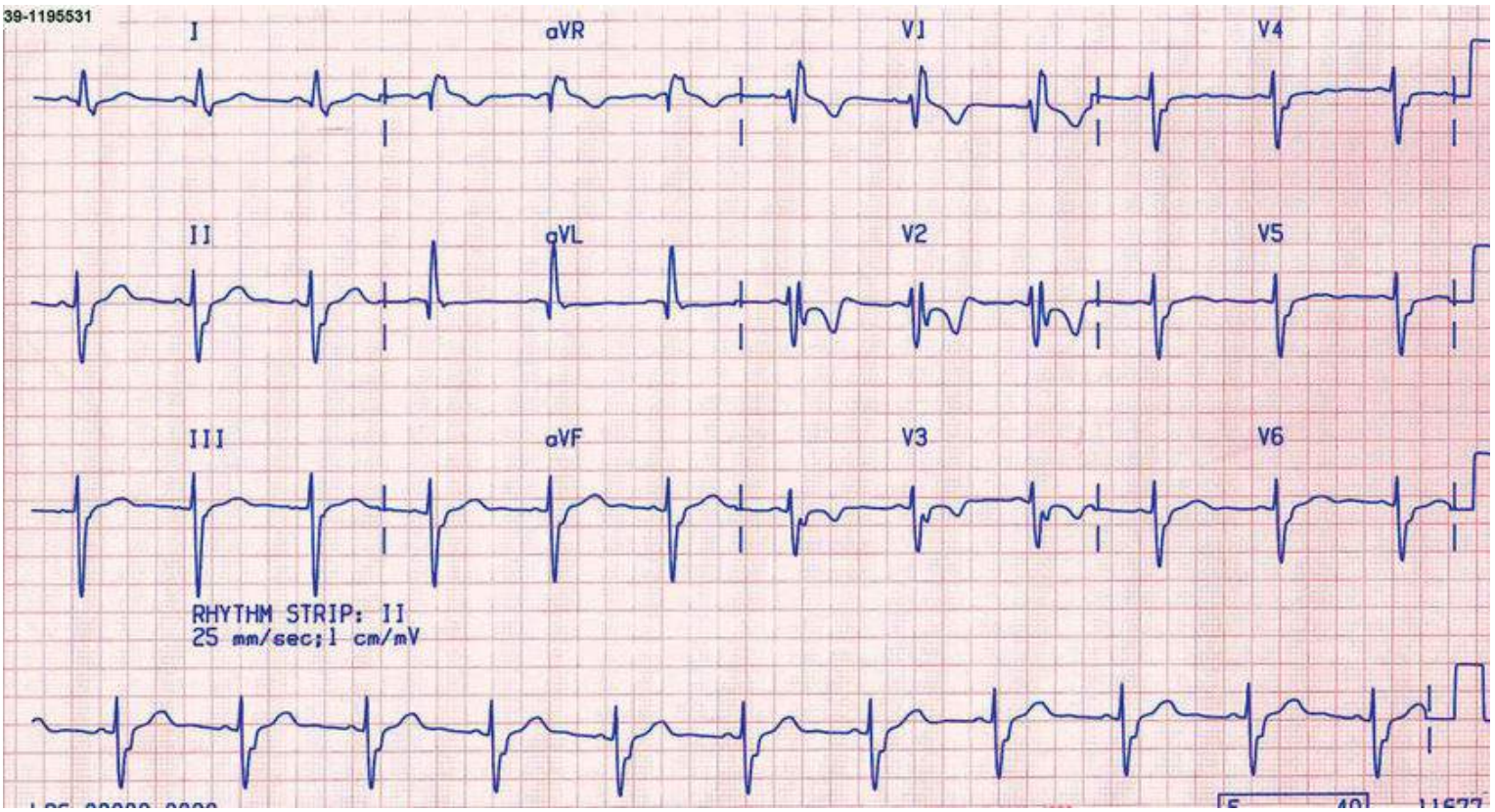
EAPPENDIX 75.56 Sinus tachycardia. Indeterminate QRS axis. Inferior Q waves of uncertain significance. Marked precordial evidence of RVH. Possible right atrial enlargement in lead II. CLINICAL DX: Eisenmenger VSD. Age 34.



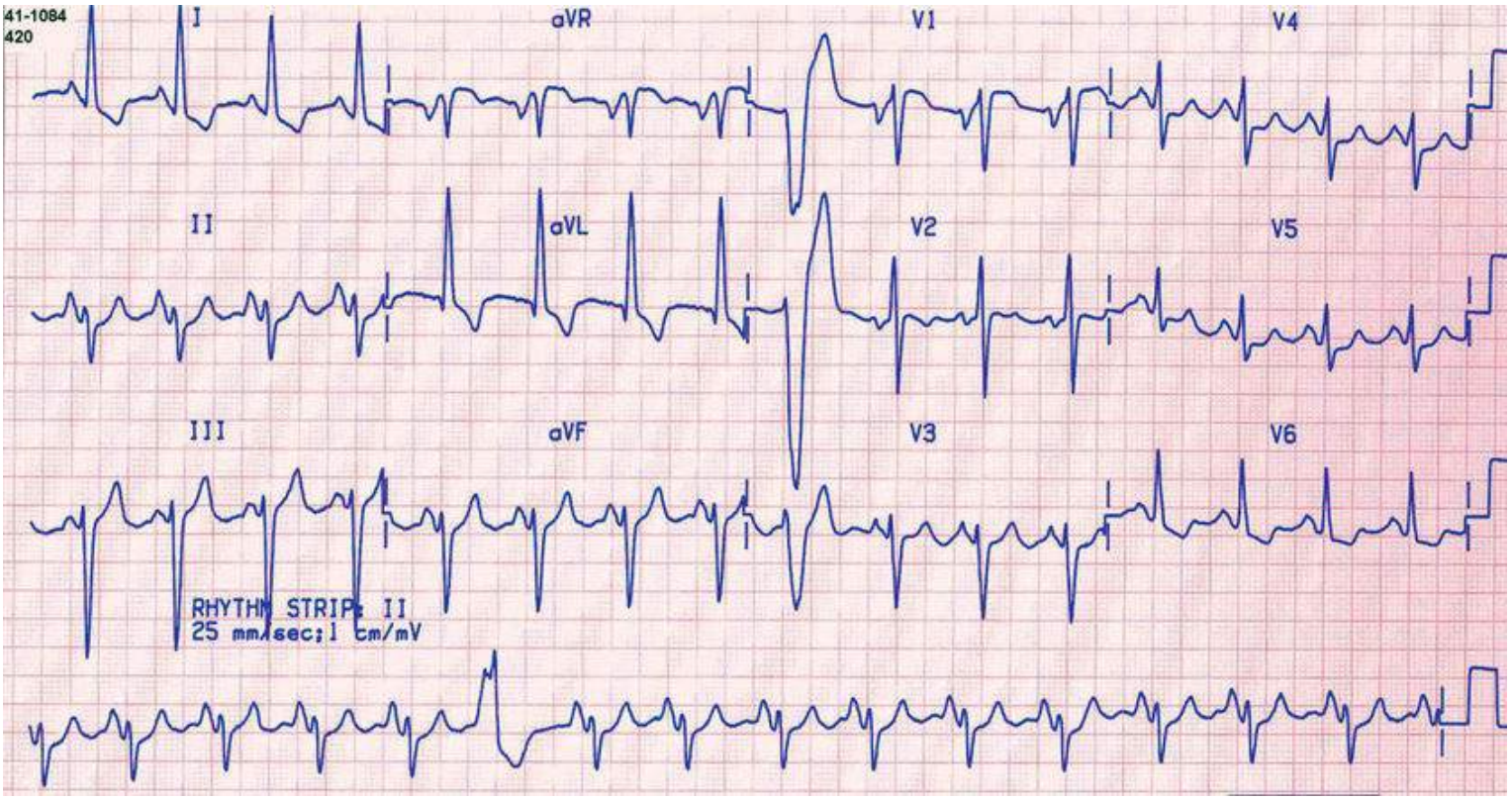
EAPPENDIX 75.57 Atrial rhythm. Indeterminate QRS axis. Abnormal precordial leads without clear significance. CLINICAL DX: Left atrial isomerism with a Fontan procedure. Age 31. Left atrial isomerism means that there is no sinus node in either atrium; thus the abnormal P wave axis.



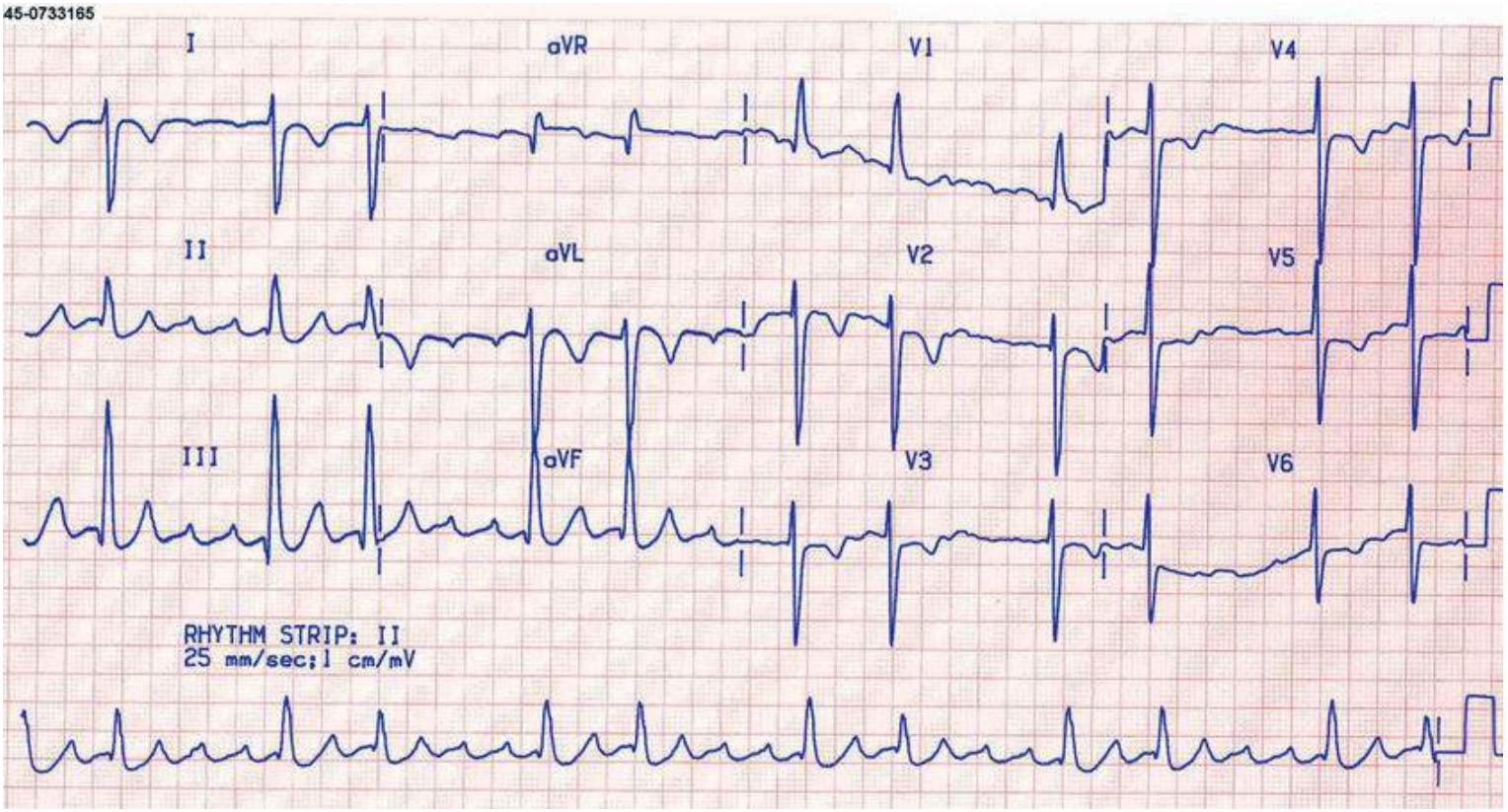
EAPPENDIX 75.58 Atrial rhythm at a rate of about 60 bpm. Complete heart block with a ventricular rate of about 55 bpm. Marked right atrial overload (V_1 and V_2). Q waves in V_1 to V_3 of uncertain significance. Abnormal precordial repolarization pattern. CLINICAL DX: Left atrial isomerism. Complete AV septal defect. Pulmonary hypertension. Age 21.



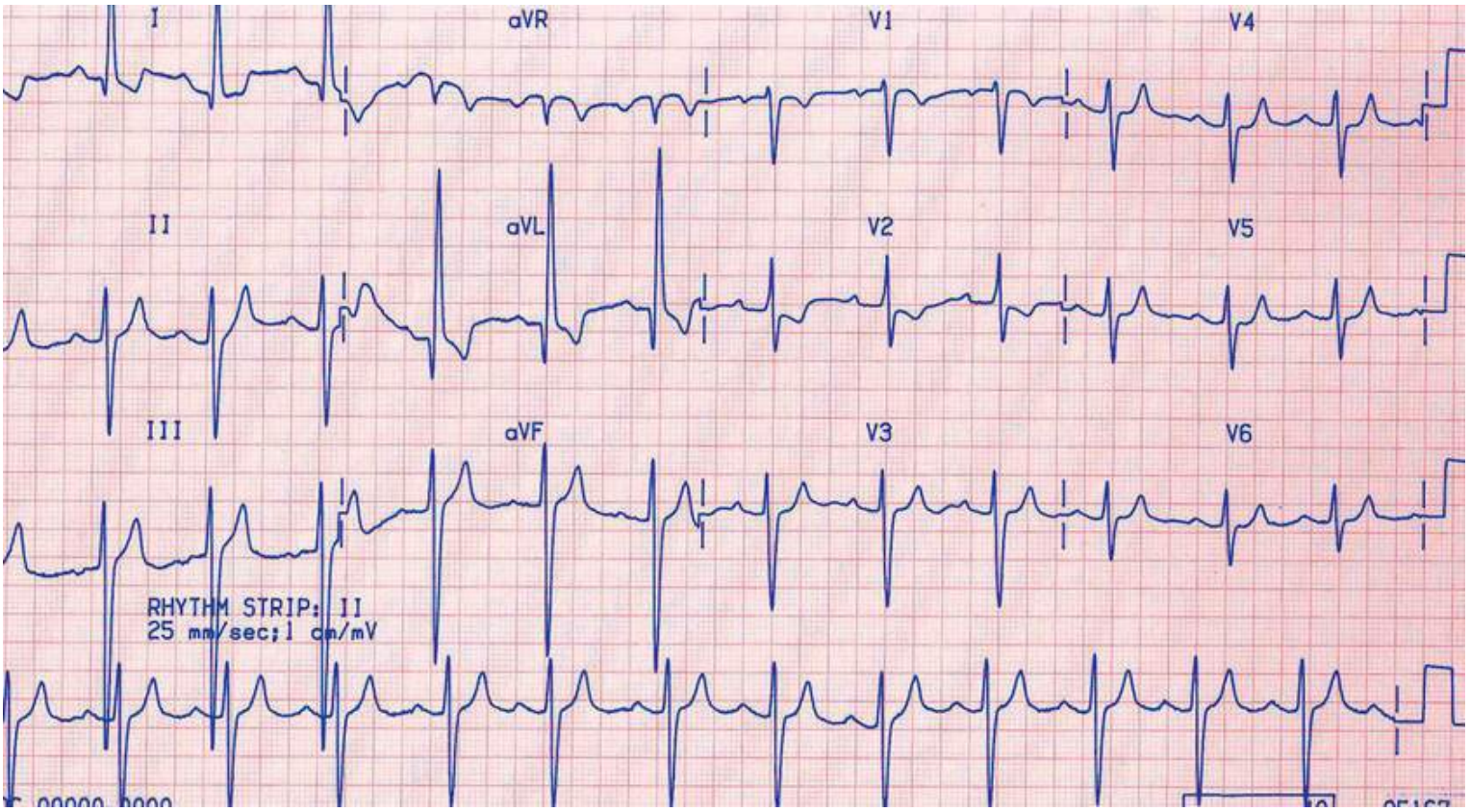
EAPPENDIX 75.59 Sinus rhythm. Left-axis deviation. Complete RBBB. CLINICAL DX: Repaired tetralogy. Age 22.



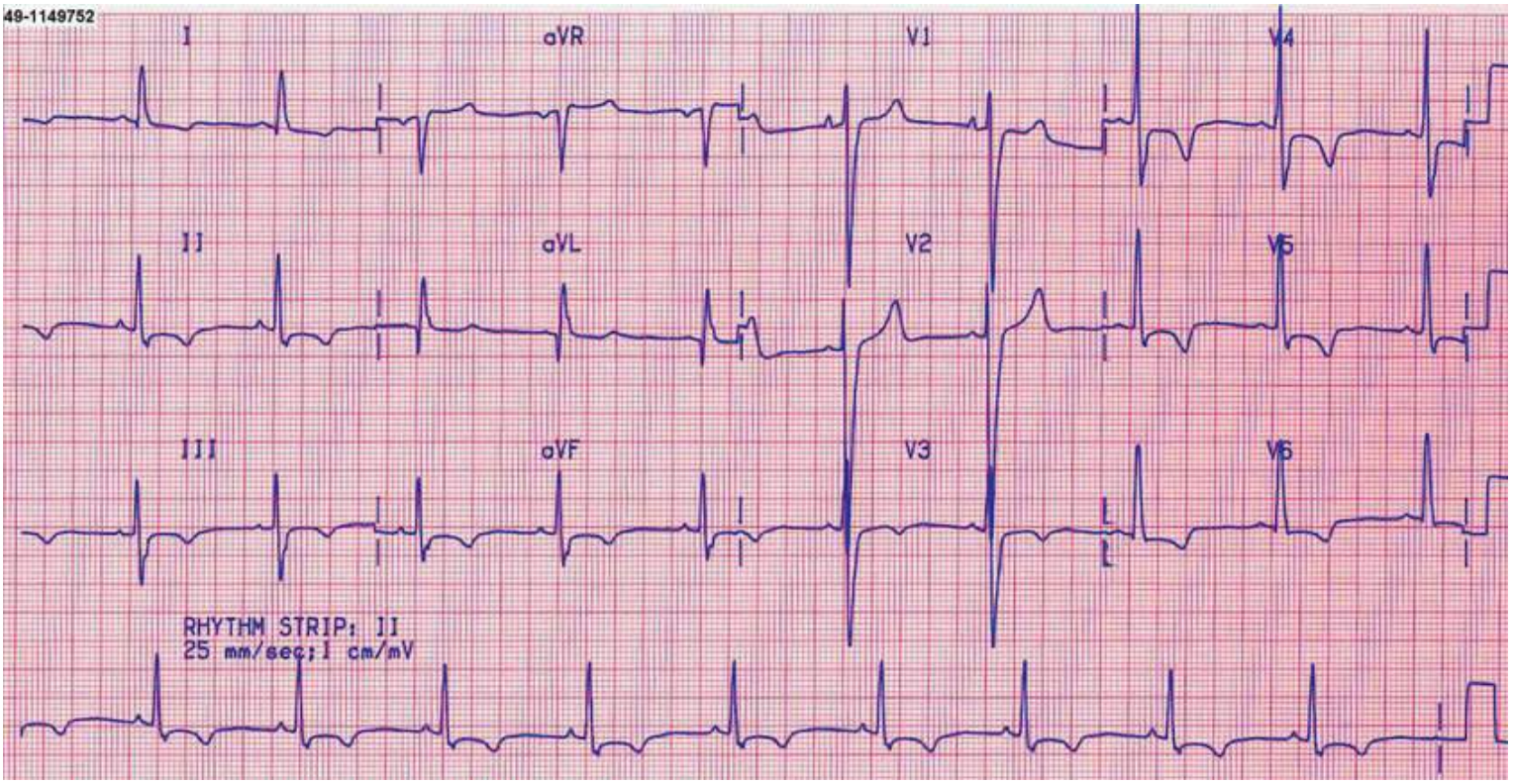
EAPPENDIX 75.60 Sinus rhythm with a ventricular rate of 100 bpm. Left-axis deviation. Possible right atrial overload. Occasional VPBs. Nonspecific repolarization abnormalities. CLINICAL DX: Tricuspid atresia with pulmonary atresia palliated with a Glenn shunt and a Potts shunt. Age 23.



EAPPENDIX 75.61 Atypical atrial flutter with a ventricular rate of about 75 bpm. Marked right-axis deviation. Voltage evidence of RVH with RV strain. CLINICAL DX: Fontan procedure for functionally single ventricle. Age 39.



EAPPENDIX 75.62 Sinus rhythm. Marked left-axis deviation. Possible voltage evidence of LVH in the standard and limb leads. CLINICAL DX: Tricuspid and pulmonary atresia palliated by a Glenn shunt (cavopulmonary shunt to the right lung) and Potts shunt to the left lung. Age 25.



EAPPENDIX 75.63 Sinus rhythm. Normal QRS axis. Probable LVH. T wave inversion in several leads. CLINICAL DX: Fontan procedure. Age 26. Fontan ECGs are difficult to interpret. The important thing is to compare them with the prior ECGs for the same patient.

Atrial flutter (often in an atypical form, or so-called *intraatrial reentrant tachycardia*) is much more

common in young patients than is atrial fibrillation. First-degree block is often seen in AV septal defects, cc-TGA, and Ebstein anomaly. Complete heart block is most often seen in patients with cc-TGA, as well as those with VSD repairs that had been performed in an earlier era.

Left atrial overload may reflect increased pulmonary blood flow, as well as AV valve dysfunction and myocardial failure. Left axis deviation should make one think of an AV septal defect, a univentricular heart, and/or a hypoplastic right ventricle. Deep Q waves in the left chest leads can be caused by left ventricular volume overload in a young person with aortic or mitral regurgitation. Pathologic Q waves can be evidence of the anomalous origin of the left coronary artery from the pulmonary artery.

The Chest Radiograph

The chest radiograph is another valuable tool for the discerning physician caring for patients with congenital heart defects (**see Chapter 15**). Although more recent technologies have rightly attracted much attention, there is value in learning how to interpret the chest radiograph. Some teaching points can be made that may anchor the interpretation of chest radiographs of some CHD patients. The following sections provide a number of clinical and radiographic differential diagnoses.

Criteria for Shunt Vascularity

The criteria for shunt vascularity include (1) uniformly distributed vascular markings with absence of the normal lower lobe vascular predominance; (2) a right descending pulmonary artery diameter that exceeds 17 mm; and (3) a pulmonary artery branch that is larger than its accompanying bronchus (best noted in the right parahilar area). Prominent vascularity is apparent only if the pulmonary-to-systemic flow ratio is greater than 1.5 to 1. As a rule, overt cardiac enlargement implies a shunt greater than 2.5 to 1. Patients with anemia, thyrotoxicosis, or a pulmonary AV fistula and pregnant patients may mimic shunt vascularity.

The group of *cyanotic patients with shunt vascularity* include those with a single ventricle with transposition, persistent truncus arteriosus, tricuspid atresia without significant pulmonary outflow obstruction, total anomalous pulmonary venous connection, double-outlet right ventricle, and a common atrium.

Disorders in *cyanotic patients with a VSD and normal or decreased pulmonary vascularity* include tetralogy of Fallot; tricuspid atresia with pulmonary stenosis; single ventricle and pulmonary stenosis; D-TGA with pulmonary stenosis; cc-TGA with pulmonary stenosis; double-outlet right ventricle with pulmonary stenosis; pulmonary atresia; and asplenia syndrome.

Causes of retrosternal filling on lateral chest radiograph include right ventricular dilation, TGA, ascending aortic aneurysm, and noncardiovascular masses (e.g., lymphoma, thymoma, teratoma, and thyroid masses).

Causes of a straight left heart border include right ventricular dilation, left atrial dilation, cc-TGA, pericardial effusion, Ebstein anomaly, and congenital absence of the left pericardium.

Cardiovascular diseases associated with scoliosis include cyanotic CHD, Eisenmenger syndrome, Marfan syndrome, and occasionally mitral prolapse.

Causes of large central pulmonary arteries include increased pulmonary flow (main pulmonary artery and branches), increased pulmonary pressure (main pulmonary artery and branches), valvular pulmonary stenosis (main and left pulmonary arteries), and idiopathic dilation of the pulmonary artery

(main pulmonary artery).

Situs solitus with cardiac dextroversion is associated with CHD in more than 90% of cases. Up to 80% have a congenitally corrected transposition with a high incidence of associated VSD, pulmonary stenosis, and tricuspid atresia. *Situs inversus with dextrocardia* has a low incidence of CHD, whereas s*itus inversus with levocardia* is virtually always associated with severe CHD.

Cardiovascular Magnetic Resonance Imaging

Cardiac MRI (**see Chapter 17**) in adolescents and adults with CHD has become of ever-increasing importance in the past decade. MRI can circumvent the echocardiographic problem of suboptimal visualization of the heart in adult patients, especially those who have had surgery. This technique can generate information never previously available and do so more easily or more accurately than any other means. New MRI image acquisition methods are faster and provide improved temporal and spatial resolution. Major advances in hardware design, new pulse sequences, and faster image reconstruction techniques now permit rapid high-resolution imaging of the complex cardiovascular anatomy. MRI can produce quantitative measures of the ventricular volumes, mass, and ejection fraction. MRI can quantify blood flow in any vessel.

Cardiac MRI is of particular value when transthoracic echocardiography cannot provide the needed diagnostic information; as an alternative to diagnostic cardiac catheterization; and for MRI's unique capabilities, such as myocardial characterization, deformation imaging by tissue tagging, and vessel-specific flow quantification. The value of MRI compared with echocardiography in the evaluation of the right ventricle has become increasingly appreciated. The capability of MRI to assess the right ventricle is of great importance because the right ventricle is a key component of many of the more complex CHD lesions. In addition, MRI can measure valve regurgitation and delineate postoperative systemic and pulmonary venous pathways, Fontan pathways, and the great vessels. MRI should be considered the best imaging modality in adolescents and adults with repaired tetralogy of Fallot, TGA, a Fontan procedure, and diseases of the aorta. Late gadolinium enhancement can demonstrate myocardial scarring in both preoperative and postoperative CHD, and is increasingly reported to be related to functional and arrhythmic outcomes. In the near future, we will see real-time MRI used to guide interventional procedures, and molecular imaging that will further expand MRI's capabilities.

Echocardiography

Fetal Echocardiography

Fetal echocardiography has “graduated” from being a special area of interest for some pediatric cardiologists to one of standard care. It should be offered to all mothers with increased risk of a fetal cardiac anomaly, including those with, or who have a partner with, CHD, and those with a strong family history. As early as 16 weeks' gestation, excellent images of the fetal cardiac structures can be obtained by the transabdominal route, along with an appreciation of cardiac and placental physiology through the use of Doppler technology. Transvaginal ultrasound is a newer approach that permits the echocardiographer to obtain images at approximately 13 to 14 weeks' gestation. Data are beginning to emerge as to the benefit of this approach, though current opinion would support a follow-up cardiac screening at 18 weeks' gestation. Although it has some application for cases with a higher risk of recurrent CHD (e.g., obstructive left-sided lesions), its accuracy has yet to be determined. This is in part because of the limited number of views that are possible with the relatively fixed position of the

transducer.

Impact of Fetal Echocardiography

Most major structural congenital heart defects are now accurately categorized through fetal echocardiography. Once the abnormalities are identified, families and obstetric caregivers can be counseled as to the impact of the abnormality both on the fetus and the family. Decisions appropriate to the family and fetus can then be made. Although termination of pregnancy is one of the consequences of prenatal diagnosis, it is not the main objective. In fact, data are starting to appear in the literature indicating that prenatal diagnosis of some major cardiac malformations has a direct impact on the outcome, from the vantage points of survival rates, morbidity rates, and costs. This is in part due to the fact that when a prenatal diagnosis is made, subsequent caregivers are prepared for the immediate postnatal effects of the defect. For example, in hypoplastic left heart syndrome and other duct-dependent lesions, prostaglandin E_1 can be started immediately after birth, hopefully in a hospital within or attached to a pediatric cardiology facility.

Fetal echocardiography has also permitted an improved understanding of the evolution of certain congenital cardiac malformations. For example, although the fetal heart is fully formed by the time a prenatal scan is performed, tremendous growth of the cardiac structures still must occur. Therefore, in some circumstances a cardiac chamber that may appear only mildly hypoplastic at 16 weeks' gestation may be profoundly affected at the time of birth. This has a major impact on the management of the newborn as well as the counseling process at 16 weeks' gestation.

Direct Fetal Intervention

The next step is direct intervention for specific cardiac lesions. Intervention has initially involved obstructive lesions, thus far mainly being limited to the left ventricle. The rationale behind this therapy is based on the notion that the relief of obstructive outflow tract lesions will permit growth of the affected ventricle, potentially changing a neonatal pathway from univentricular to biventricular. Cardiac surgery for the fetus is also a future option, and indeed there is already a considerable amount of research on the impact of this in fetal animal models.

Segmental Approach to Echocardiography in Congenital Heart Disease

The following four echocardiographic steps of segmental analysis are crucial in any patient with CHD. Starting from a standard subcostal view, one should determine the position of the apex and the situs of the atria, as well as the AV and ventriculoarterial relationships.

1 Apex

From a standard subcostal view, determine if the apex of the heart is pointing to the right (dextrocardia), to the left (levocardia), or to the middle (mesocardia) (**Fig. 75.2**) (Videos 75.7 to 75.9).

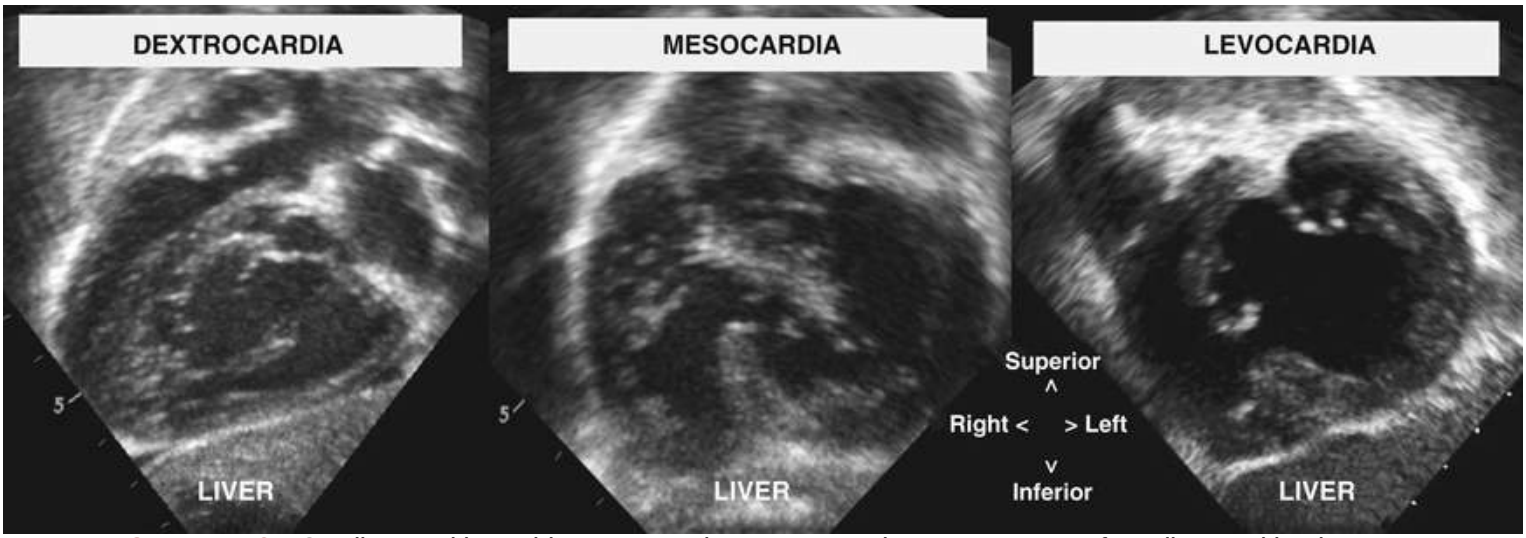


FIGURE 75.2 Cardiac position: This montage demonstrates the assessment of cardiac position in patients with complex congenital heart disease, as obtained from the subcostal position in a coronal plane. This is the optimal plane for determining the position of the apex of the heart.

2 Situs of the Atria *(Fig. 75.3)*

The right and left atria differ morphologically with regard to their appendages. A morphologic right atrium has a broad right atrial appendage, whereas a morphologic left atrium has a narrow left atrial appendage. Right and left atrial appendages, however, are difficult to visualize by transthoracic echocardiography, and one often has to rely on the abdominal situs to determine the atrial situs. The atrial situs follows the abdominal situs in 70% to 80% of cases. From a standard subcostal view with the probe pointing at a right angle to the spine, one can visualize the abdominal aorta, as well as the inferior vena cava and the spine at the back. When the aorta is to the left of the spine and the inferior vena cava to the right of the spine, there is abdominal situs solitus and, in all probability, corresponding atrial situs solitus (meaning the morphologic right atrium is on the right side and the morphologic left atrium is on the left side, the so-called “usual” atrial arrangement). In this setting the usual situation is for the systemic veins to connect to the morphologic right atrium, with the pulmonary veins to the left (**Fig. 75.4**); however, systemic and pulmonary venous drainage does not define the atrial morphology.

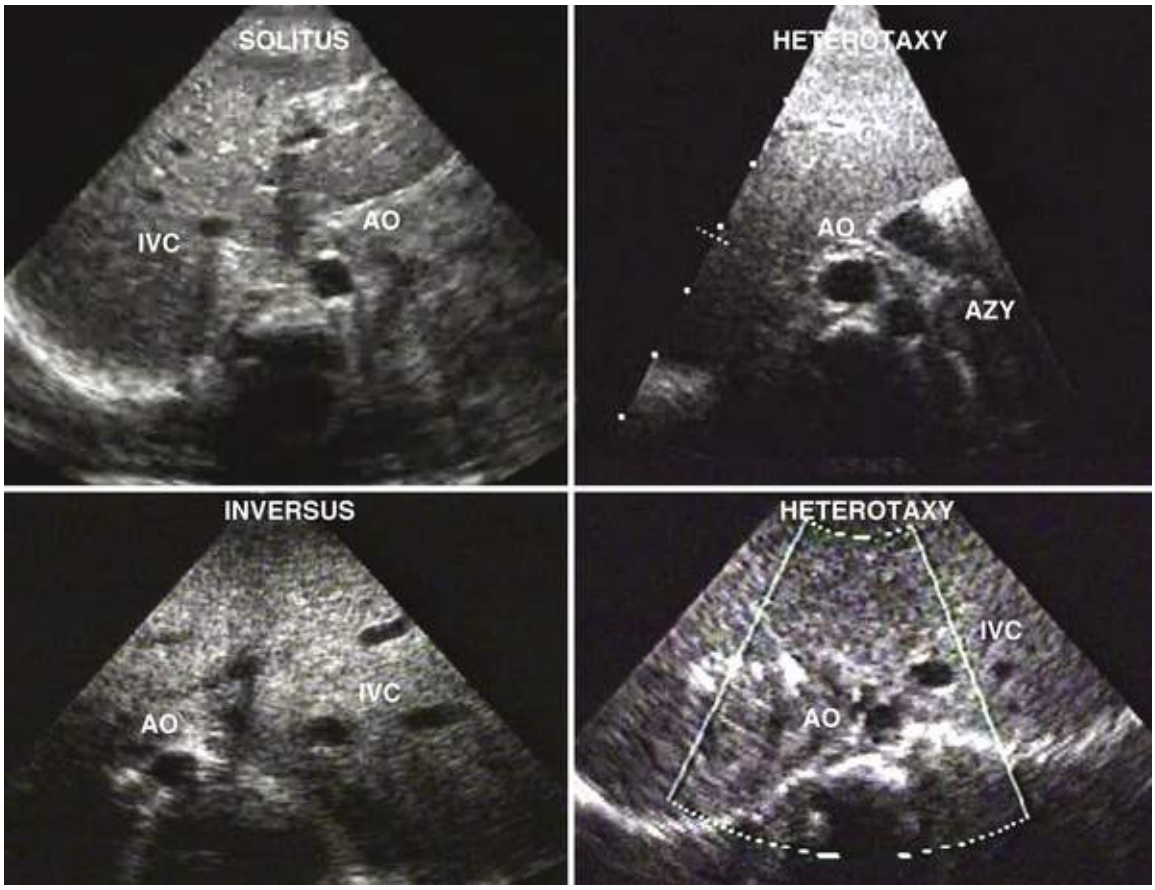


FIGURE 75.3 Montage of the different types of situs as seen by a subcostal echocardiographic scan. Note that situs solitus and inversus are just the mirror images of each other. The upper right picture is in the setting of heterotaxy with an interrupted intrahepatic inferior vena cava, with azygos continuation on the left. This is seen more frequently in left atrial isomerism. The lower right picture is also in the setting of heterotaxy with an intrahepatic inferior vena cava that is positioned closer to the aorta than in solitus or inversus. Note also the midline liver. This pattern is seen more commonly in right atrial isomerism. *AO*, aorta; *AZY*, azygos; *IVC*, inferior vena cava.

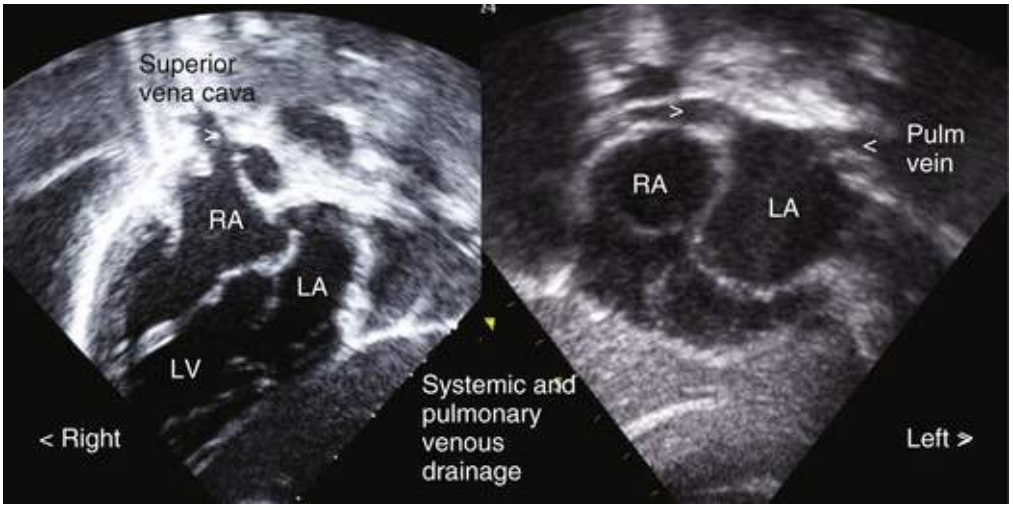


FIGURE 75.4 Systemic and pulmonary venous drainage: This montage demonstrates the systemic and pulmonary venous drainage in a heart with dextrocardia and double-inlet left ventricle. The image on the left shows the superior vena cave connecting to the right-sided atrium. The right-sided panel shows the pulmonary veins draining to the left-sided atrium in the same case. *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium.

When the aorta is to the right of the spine and the inferior vena cava is to the left of the spine, there is abdominal situs inversus and, in all probability, corresponding atrial situs inversus (morphologic right

atrium on the left side and morphologic left atrium on the right side [i.e., mirror-image atrial arrangement]). When both the aorta and inferior vena cava are on the same side of the spine, there is usually abdominal and atrial right isomerism (two morphologic right atria). Left atrial isomerism (two morphologic left atria) is usually suspected when the intrahepatic inferior vena cava is interrupted, with the presence of azygos continuation in the paravertebral gutter, on either the left or right side.

3 Atrioventricular Relationship

Once the situs of the atria is determined, one must assess the position of the ventricles in relation to the atria. The morphologic right ventricle has four characteristic features that distinguish it from the morphologic left ventricle: (1) a trabeculated apex, (2) a moderator band, (3) septal attachment of the tricuspid valve, and (4) lower (apical) insertion of the tricuspid valve. The tricuspid valve is always "attached" to the morphologic right ventricle (**Fig. 75.5**, and see Video 75.8**).** The morphologic left ventricle has the following characteristics: (1) a smooth apex, (2) no moderator band, (3) no septal attachment of the mitral valve, and (4) a higher (basal) insertion of the mitral valve. The mitral valve is always "attached" to the morphologic left ventricle (**see Fig. 75.5**). Once the position of the ventricles is determined, one can establish the AV relationship. When the morphologic right atrium empties into the morphologic right ventricle and the morphologic left atrium empties into the morphologic left ventricle, there is AV concordance. When the morphologic right atrium empties into the morphologic left ventricle, and the morphologic left atrium empties into the morphologic right ventricle, there is AV discordance (**see Fig. 75.5**) (Video 75.10; see Video 75.9).

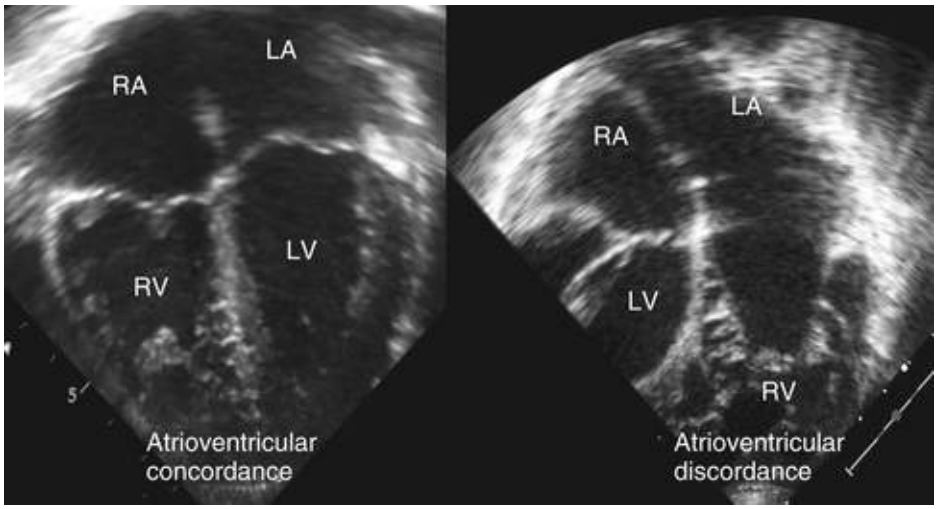


FIGURE 75.5 AV concordance and AV discordance: The image on the left is from a heart with AV concordance. Note that the tricuspid valve is inserted at a lower level than the mitral valve. Also note the heavily trabeculated right ventricle with evidence of the moderator band. The image on the right is from a heart with AV discordance. Note in this image that the left-sided tricuspid valve is inserted at a lower level than its mitral counterpart. Also the right-sided interventricular septum is smooth, with no septal attachments from the right-sided mitral valve. *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle.

The *morphologic right ventricle* is a triangular-shaped structure with an inlet, a trabecular, and an outlet component. The inlet component of the right ventricle has attachments from the septal leaflet of the tricuspid valve. Inferior to this is the moderator band, which arises at the base of the trabeculoseptomarginalis, with extensive trabeculations toward the apex of the right ventricle. The outlet component of the right ventricle consists of a fusion of three structures (i.e., the infundibular septum

separating the aortic from the pulmonary valve, the ventriculoinfundibular fold separating the tricuspid valve from the pulmonary valve, and, finally, the anterior and posterior limbs of the trabeculoseptomarginalis).

The *morphologic left ventricle* is an elliptical-shaped structure with a fine trabecular pattern, with absent septal attachments of the mitral valve in the normal heart. It consists of an inlet portion containing the mitral valve and a tension apparatus, with an apical trabecular zone that is characterized by fine trabeculations and an outlet zone that supports the aortic valve.

What happens when these basic rules do not apply? This is encountered in hearts where both atria are predominantly connected to one ventricle (univentricular AV connection), either by one or two AV valves. There has been recent consensus in the nomenclature, so that a heart such as this is referred to as a *functionally single ventricle*. In general, these are hearts where both ventricular chambers cannot be used to support the systemic and pulmonary venous circulations, such that the only option is a Fontan approach. This approach has been the Rosetta stone of morphology, connecting the European and North American classifications. Of note, in these hearts the apex can be left sided, at the midline, or on the right; none of these placements impacts the classification of a functionally single ventricle. They can also coexist with all types of situs, that is, solitus, inversus, or isomeric. The type of ventriculoarterial connection does not influence this classification. It is possible to have normally related great arteries, discordant arterial connections, or a single outlet, with either aortic or pulmonary atresia. When there are two ventricles, they are usually connected by a VSD, which in the majority of cases is muscular in nature.

In hearts with a *double-inlet ventricle*, both atria are mainly connected to one ventricular chamber, either by two valves or a common AV valve. This is dictated by the 50% rule, whereby more than 50% of the total annular circumference is committed to one ventricular mass, this being independent of the status of the AV valves (**Fig. 75.6**) (Videos 75.11 to 75.17). Of note, the designation of double inlet is not dictated by the morphology or size of the connecting AV valves. They can connect mainly into a ventricle of left or right ventricular morphology, and rarely one ventricle, the morphology of which can be difficult to determine (**Fig. 75.7**) (Video 75.18). The morphology of the ventricles is determined in part by some of the same features described above, but in a ventricular chamber without a connecting AV valve the position of that chamber, relative to the larger one, is an important key to determining its status as a left or right ventricle. For example, a smaller ventricle lying posterior to a larger one is almost always a morphologic left ventricle. A smaller ventricle lying anterior to a larger one is a morphologic right ventricle (**Fig. 75.8**) (Video 75,19).

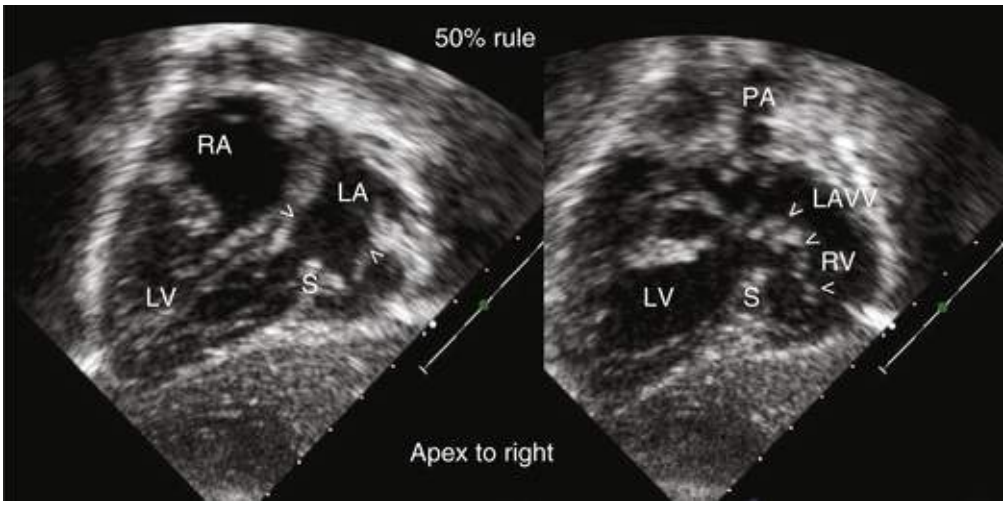


FIGURE 75.6 Fifty percent rule straddling left atrioventricular valve: These two images are from a heart with dextrocardia and a double-inlet left ventricle. Note in the left-hand panel the left-sided AV valve annulus (as indicated by the *white arrows*) overrides the interventricular septum by at least 50%. If the overriding were less than 50%, the designation would be AV discordance. There is straddling of the left-sided AV valve, as indicated by the *white arrows*. The valve has a foot in both ventricles. This demonstrates one of the flaws in the nomenclature; that is, determining in this heart the precise amount of overriding. Of importance, the presence of the straddling valve plays no role in the designation of the AV connection. *LA*, left atrium; *LAVV*, left atrioventricular valve; *LV*, left ventricle; *PA*, pulmonary artery; *RA*, right atrium; *RV*, right ventricle; *S*, interventricular septum.

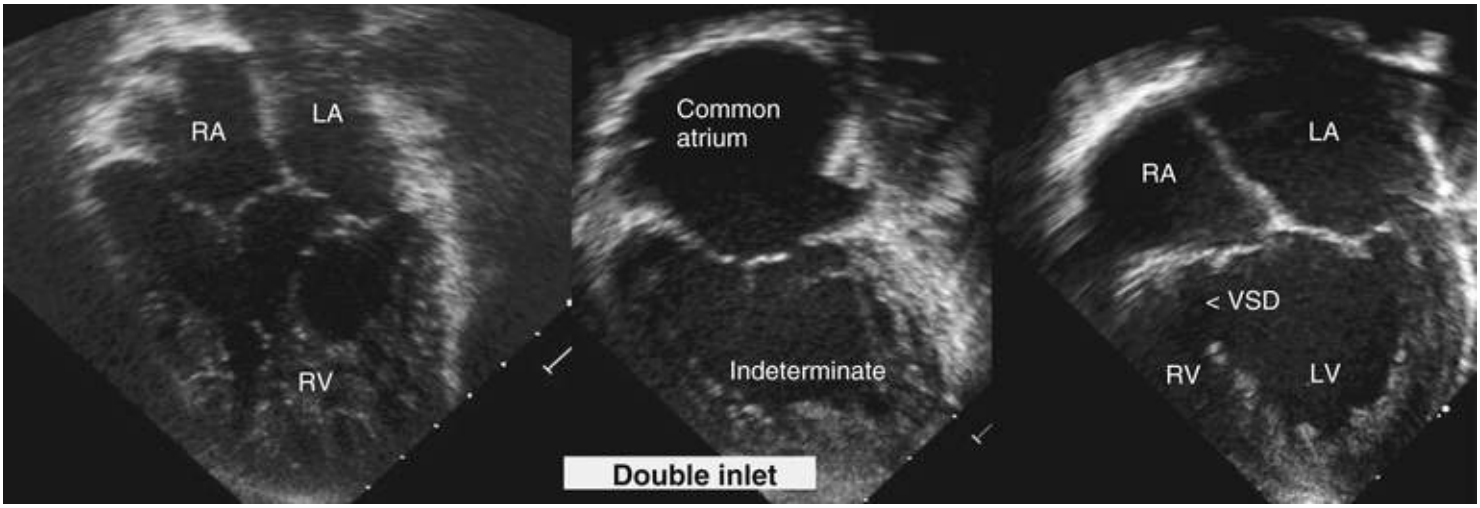


FIGURE 75.7 Double-inlet labels: These three images are from hearts with a double inlet. The one on the left is from a heart with a double-inlet right ventricle (note the coarse trabeculations) with two AV valves that are totally committed to the large right ventricle. The image on the far right is from a heart with a double-inlet left ventricle and two AV valves. Note the hypoplastic right ventricle on the right, and the large VSD. The image in the middle is from a heart with a double inlet and a common AV valve with an associated common atrium (often seen in hearts with isomerism). There was no second chamber in the heart, and the designation of a morphologic left or right ventricle is difficult. *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle; *VSD*, ventricular septal defect.

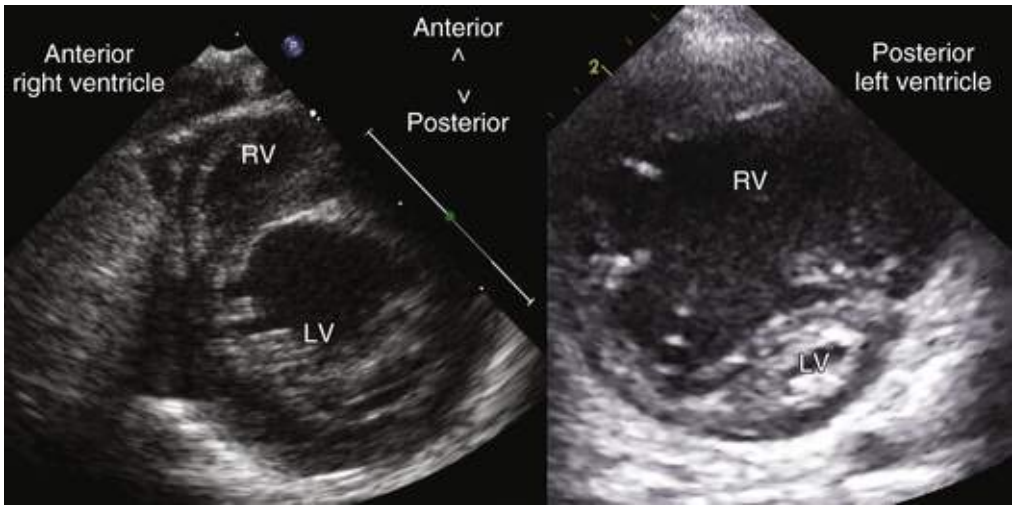


FIGURE 75.8 Chamber position: These two images show how the position of the ventricles can help determine their morphology. On the left-hand side, the larger chamber is posterior and the smaller one anterior; thus the larger chamber is the morphologic left ventricle. The right-hand panel demonstrates the opposite, that is, a dominant right ventricle with a smaller posterior left ventricle. *LV*, left ventricle; *RV*, right ventricle.

Ventricular looping is also an important consideration. For example, in a double-inlet left ventricle, an L loop is more common with the morphologic left ventricle situated on the right of the hypoplastic morphologic right ventricle. In a D loop, the morphologic left ventricle is on the left of the hypoplastic morphologic right ventricle (**Fig. 75.9**) (Videos 75.20 and 75.21).

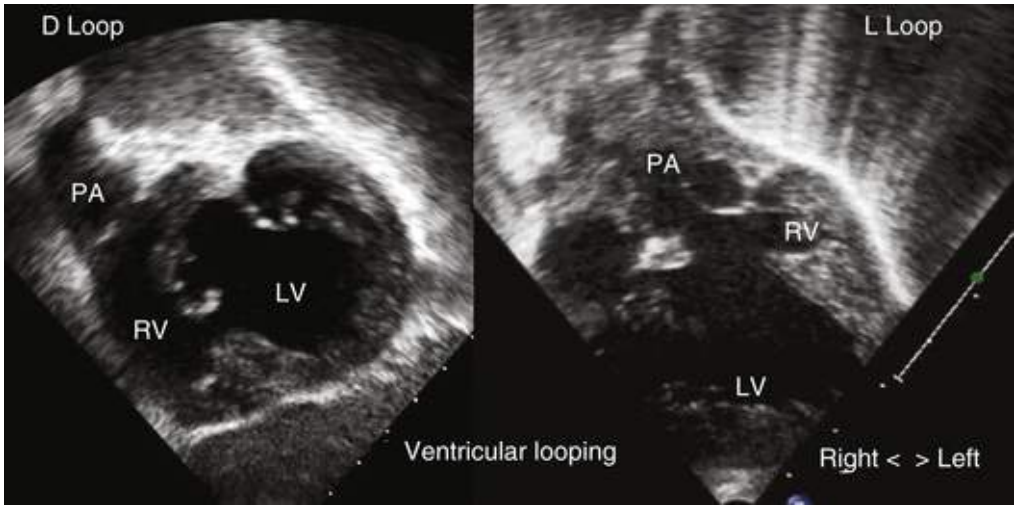


FIGURE 75.9 Ventricular looping: The image on the left taken from the subcostal position shows a heart with levocardia, a D-loop, and a double-inlet left ventricle (i.e., the morphologic left ventricle is on the right and the hypoplastic right ventricle is on the right). The panel on the right, also taken from the subcostal position, is also from a heart with levocardia and a double-inlet left ventricle; however, there is an L-loop, with the morphologic right ventricle being to the left and anterior of the larger morphologic left ventricle. Of note, in the left-hand panel the pulmonary artery arises from the right-sided right ventricle, whereas it arises from the morphologic left ventricle in the right-hand panel. *LV*, left ventricle; *PA*, pulmonary artery; *RV*, right ventricle.

In a *heart with an absent connection*, there is absence of either the left-sided or right-sided AV valve, and a solitary valve connects both atria to the main ventricular mass. This disorder is often referred to as mitral or tricuspid atresia, terms that are still in common use (**Fig. 75.10**) (Videos 75.22 and 75.23; see also Video 75.7). Although the remaining AV valve is often referred to as a mitral or tricuspid valve, this can be misleading, because in some instances the valve morphology does differ from the classic

description in the normal heart. Of importance, the floor of the absent connection consists of sulcus tissue, such that if a pin were to be passed from the right atrium through that tissue, it would end up outside the heart, and not in the hypoplastic left or right ventricle.

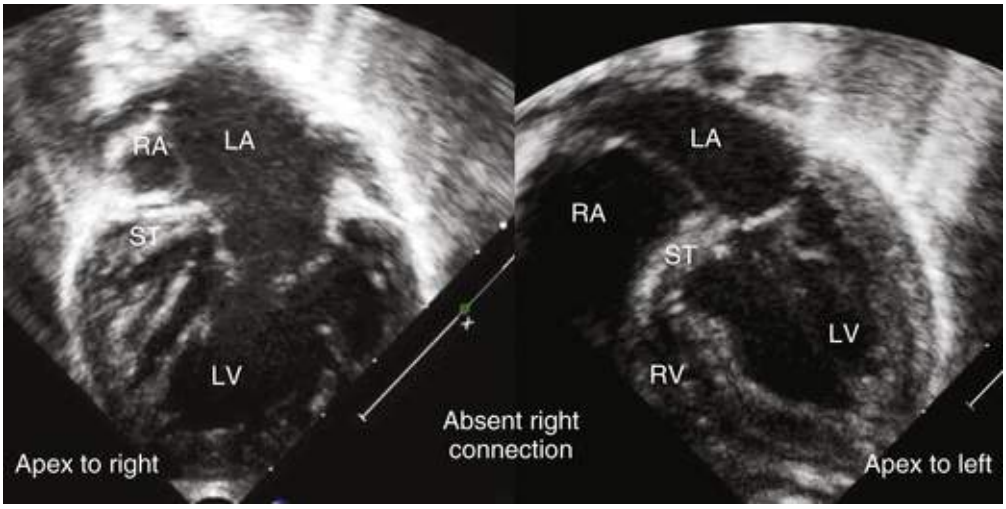


FIGURE 75.10 Absent right connection labels: These two images are from hearts with an absent right connection, the one on the left with associated dextrocardia, and the one on the right with levocardia. Note the pulmonary veins draining into the left atrium and the wedge of sulcus tissue between in the floor of the right atrium as seen in both images. If a pin were passed from the right atrium through the sulcus tissue, it would end up outside the heart in the AV groove, differentiating the condition pictured from an imperforate valve. Also note the hypoplastic right ventricle on the right of the dominant left ventricle in the right-hand panel. *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle; *ST*, sulcus tissue.

If a heart has a *functionally single ventricle in the setting of AV concordance or discordance, but with associated hypoplasia of one ventricle, it requires a Fontan, or single-ventricle, palliation, because the smaller ventricle is incapable of supporting either the systemic or pulmonary venous circulations. This includes hearts with the classic hypoplastic left heart syndrome, pulmonary atresia with an intact ventricular septum (***Fig. 75.11***) (*Videos 75.24 and 75.25*), unbalanced AV septal defects, and corrected transposition with hypoplasia of one or the other ventricle. Again, this classification is not affected by the status of the connecting AV valves, nor of the ventriculoarterial connections.*

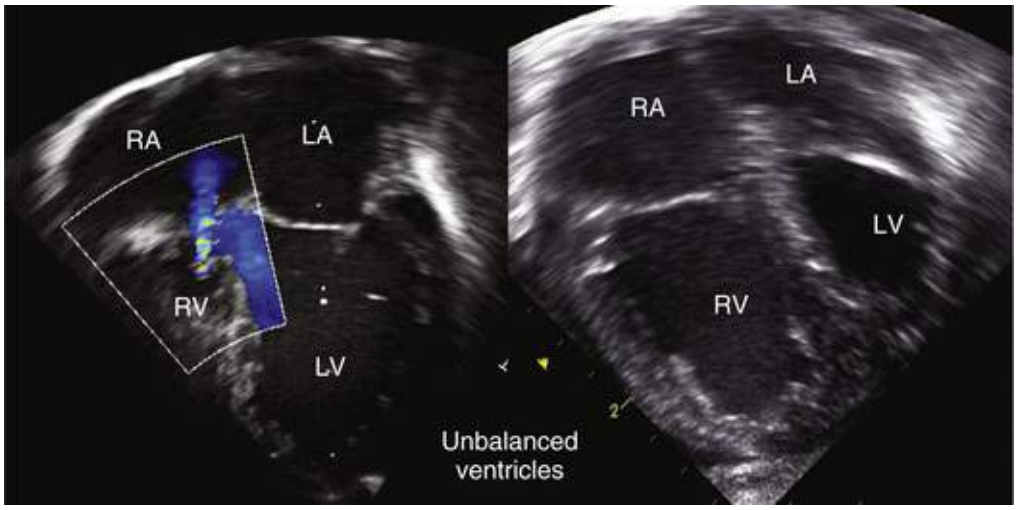


FIGURE 75.11 Unbalanced ventricles: The image on the left is from a heart with AV concordance, but a hypoplastic morphologic right ventricle. Note that the tricuspid valve is perforate because the color Doppler image shows some tricuspid valve regurgitation. This heart is from a case with pulmonary atresia intact ventricular septum. The heart on the right is from a case with hypoplastic left heart syndrome, with a hypoplastic left-sided morphologic left ventricle. The AV connection is concordant. Both cases are referred to as having a "functionally single ventricle" because the small chamber cannot support either the systemic or pulmonary arterial circulation. *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle.

4 Ventriculoarterial Relationship

Once the AV relationship has been determined, one should assess the position of the great artery(s) in relation to the ventricles (**Figs. 75.12 and 75.13**; (see also Videos 75.10, 75.15, 75.16, and 75.20). It is possible to have an aorta and a pulmonary artery, or a solitary outlet from either ventricle, with the other artery being atretic. Also, in some cases, the solitary outlet can be a solitary trunk, which gives rise to the head and neck vessels and the pulmonary and coronary arteries. The pulmonary artery can be distinguished by its early branching pattern into the left and right pulmonary arteries; the pulmonary valve is always "attached" to the pulmonary artery. Similarly, the aorta can be distinguished by its "candy cane" shape and the take-off of its three head and neck vessels (innominate, carotid, and subclavian arteries). The aortic valve is always "attached" to the aorta. Once the position of the great arteries is determined, one can establish the ventriculoarterial relationship. When the morphologic right ventricle ejects into the pulmonary artery and the morphologic left ventricle ejects into the aorta, there is ventriculoarterial concordance. When the morphologic right ventricle ejects into the aorta and the morphologic left ventricle ejects into the pulmonary artery, there is ventriculoarterial discordance. When more than 50% of both great arteries exit from one ventricle (right or left), this is called a *double-outlet* (right or left) *ventricle*.

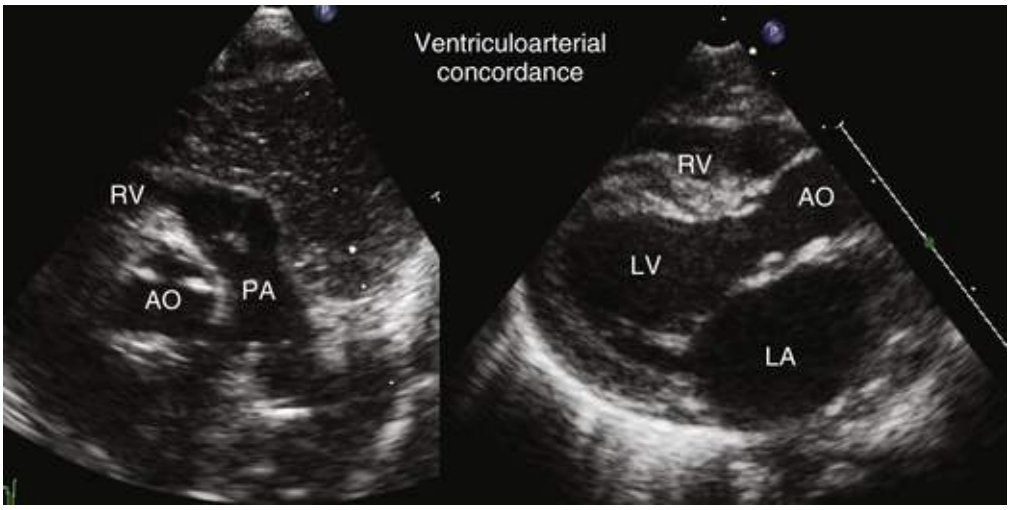


FIGURE 75.12 Ventriculoarterial concordance: These two images are from a heart with an absent right connection (tricuspid atresia) and ventriculoarterial concordance. That is, the aorta arises from the morphologic left ventricle and the pulmonary artery from the more anterior morphologic right ventricle. *AO*, aorta; *LA*, left atrium; *LV*, left ventricle; *PA*, pulmonary artery; *RV*, right ventricle.

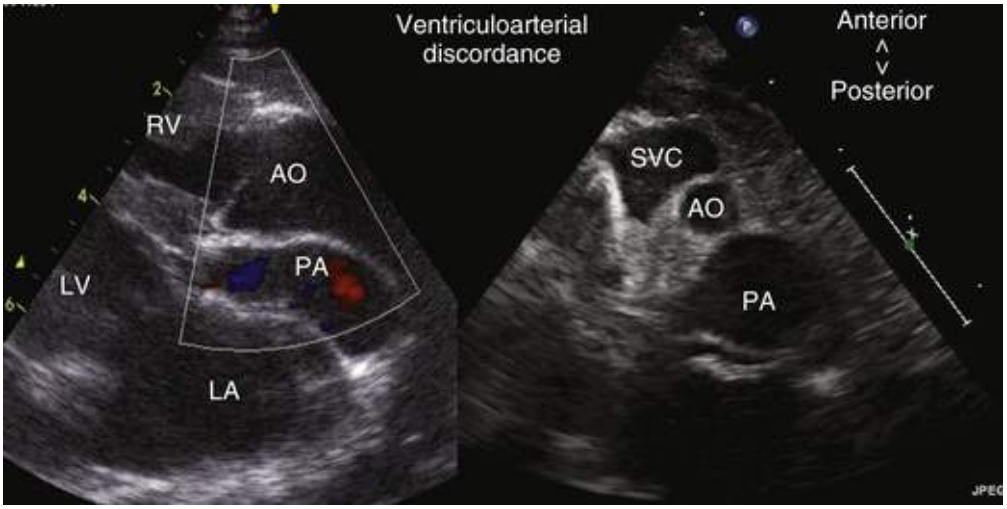


FIGURE 75.13 Ventriculoarterial discordance: These two images are from different hearts, one with a hypoplastic aorta (right-hand panel) and the other with a hypoplastic main pulmonary artery (left-hand panel). Note in both cases the aorta is anterior to the posterior pulmonary artery. The image on the left shows the two great arteries that are parallel to each other, unlike in the image on the right, where the more anterior pulmonary artery crosses the aorta. The image on the right is taken in the short axis plane. *AO*, aorta; *LA*, left atrium; *LV*, left ventricle; *PA*, pulmonary artery; *RV*, right ventricle; *SVC*, superior vena cava.

Once segmental analysis has been completed, one can proceed to the usual echocardiographic windows to determine the nature of the specific lesions, as well as their hemodynamic relevance.

Other Echocardiographic Imaging Modalities

Transesophageal and Three-Dimensional Echocardiography

Transesophageal echocardiography (TEE) offers a better two-dimensional (2D) resolution than transthoracic echocardiography. This is especially important in adult patients who have undergone multiple previous cardiac operations and in whom adequate transthoracic windows are often difficult to obtain.

TEE should be used whenever transthoracic echocardiography or MRI does not provide adequate anatomic or functional information. The addition of real-time three-dimensional (3D) TEE has opened up a new diagnostic window. It can be used in specific cases to (1) depict the spatial relationship of the various structures within the heart, (2) quantify the chamber size, mass, and function, as well as (3) help guide transcatheter procedures.[14] Transthoracic 3D echocardiography has been limited in the adult CHD population because of the size of the patients being imaged and the number of prior operations they may have undergone; its TEE counterpart can play a major role in diagnostic evaluation, however. TEE should be considered in the setting of the conditions discussed in the following sections.

In *secundum atrial septal defect*, use TEE for the assessment of device closure feasibility, measuring ASD size, assessing the adequacy of margins for device anchoring, and ruling out an anomalous pulmonary venous connection. This information can be enhanced by real-time 3D imaging, which provides precise anatomic detail of the ASD (**Fig. 75.14**).

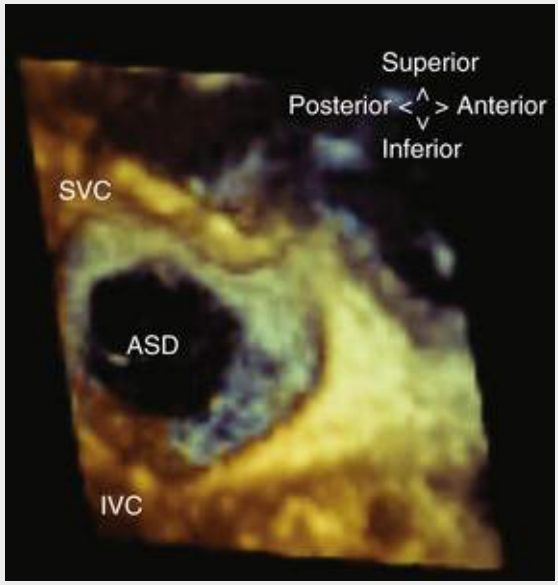


FIGURE 75.14 Three-dimensional secundum ASD: This real-time 3D echocardiographic image obtained by T EE demonstrates the rims of a large secundum atrial septal defect, as seen from the right atrium. ASD, atrial septal defect; IVC, inferior vena cava; SVC, superior vena cava.

In *atrioventricular valve regurgitation*, use TEE for preoperative evaluation of mitral valve leaflet morphology and suitability for mitral valve repair versus replacement. Real-time 3D TEE is rapidly becoming the reference standard for evaluating mitral valve form and function prior to surgical or catheter intervention. As well, this imaging is invaluable in those cases with complex CHD with abnormalities of one or another AV valve. Lesions such as postoperative AV septal defect, corrected transposition (**Fig. 75.15**, and Videos 75.26 and 75.27), or Fontan hearts with a regurgitant systemic AV valve frequently require further intervention. Real-time 3D TEE has been disappointing for tricuspid valve assessment in those with normal connections and no ventricular hypoplasia. This has not been the case in hearts following the Fontan procedure, however, because invariably, the valve being evaluated is more perpendicular to the ultrasound beam (unlike the normal tricuspid valve, the oblique position of which affects the image resolution). Preoperative planning, using imaging plus real-time 3D color Doppler echocardiography, is essential for an optimal repair (**Fig. 75.16** and Video 75.28). Color

Doppler assessment of the site of regurgitation is more sensitive than standard saline testing,[15] and so should be used routinely.

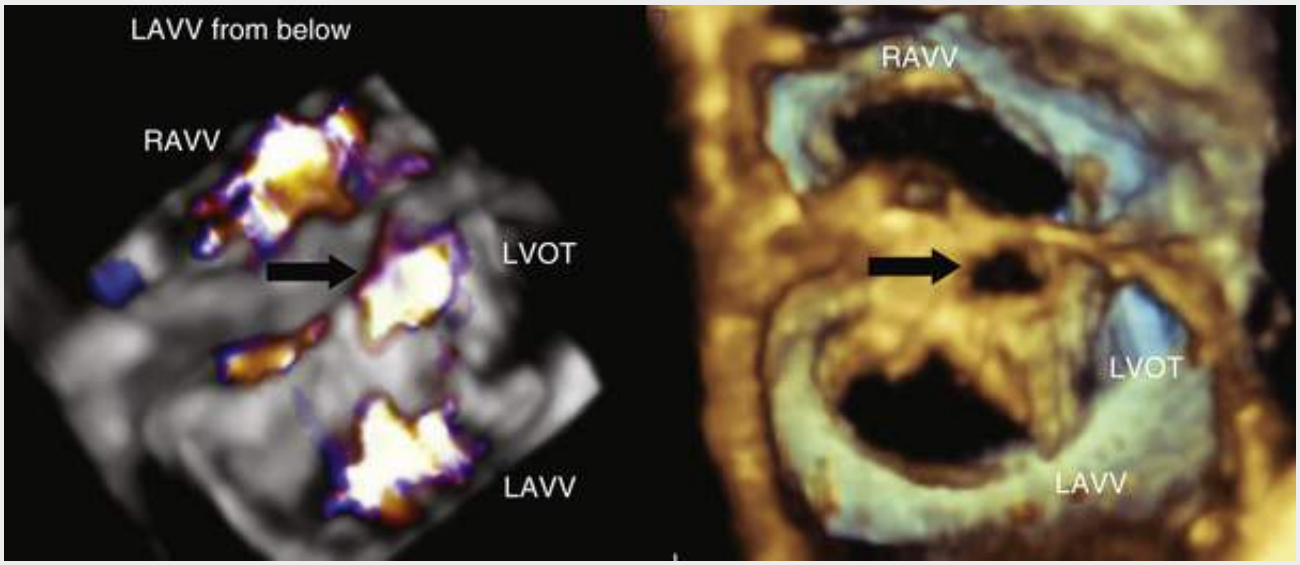


FIGURE 75.15 Three-dimensional postoperative AV septal defect: This TEE real-time 3D image is taken from below in a case following repair of an AV septal defect. It images the left AV valve from below and demonstrates two mechanisms of regurgitation, one from an area of dehiscence of the valve indicated by the *black arrow*, with the second located centrally because of poor coaptation of the leaflets. *LAVV*, left atrioventricular valve; *LVOT*, left ventricular outflow tract; *RAVV*, right atrioventricular valve.

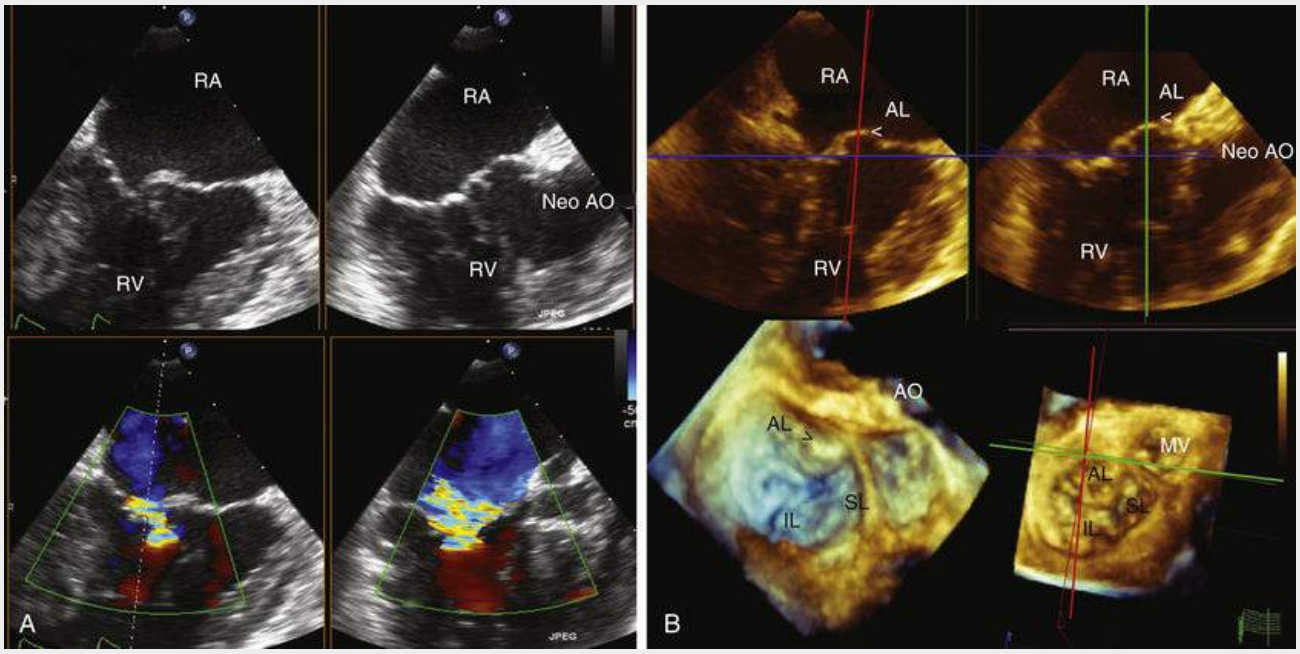


FIGURE 75.16 Three-dimensional tricuspid valve following Fontan procedure. The TEE image labeled A demonstrates moderate tricuspid valve regurgitation following a Fontan procedure in a patient with hypoplastic left heart syndrome and dextrocardia. Although the moderate regurgitation is evident from the color Doppler signal, the precise mechanism and location are unclear. The real-time 3D echocardiography image labeled B displays the tricuspid valve in the MPR mode (multiplane reformatting), as well as a surgical en face view of the tricuspid valve. The *red* and *green lines* are at right angles to each other and show that the main problem is prolapse of the anterior leaflet of the tricuspid valve. The lower right-hand image is taken in the exact same spatial location as the upper two images; the lower left-hand image has been angled to show the prolapse in more detail. Although not seen from the surgical en face view, the position of the aorta has been noted to help with orientation. *AL*, anterior leaflet; *AO*, aorta; *IL*, inferior leaflet; *MV*, mitral valve; *SL*, septal leaflet.

With *Ebstein anomaly*, use TEE for preoperative assessment of the tricuspid valve morphology and the potential for tricuspid valve repair. Thus far, real-time -3D echocardiography has been disappointing for this lesion, because the leaflets are often so thin that there are too many areas of dropout in the images.

In *clot assessment*, use TEE when a right atrial clot is suspected following the Fontan procedure on clinical grounds or by transthoracic echocardiography, or when circuit obstruction is suspected.

Precardioversion.

For any patient who is not adequately anticoagulated, presenting with atrial flutter or fibrillation longer than 24 hours, TEE should be performed before chemical or electrical cardioversion. Patients with a Fontan circuit should undergo TEE irrespective of the duration of atrial tachyarrhythmia to rule out a right or left atrial thrombus.

Guidance of Therapeutic Interventions.

Both standard 2D TEE and, more recently, real-time 3D TEE can be instrumental in helping to guide therapy at the time of transcatheter or surgical procedures. TEE is particularly helpful in the following situations.

Percutaneous Device Closure.

TEE is performed at the time of percutaneous device closure (i.e., transcatheter ASD closure to assist ASD-stretched balloon sizing and device deployment), unless intracardiac echocardiography (ICE) (see later) is available.

Ventricular Volume Assessment.

Real-time 3D echocardiography has already been shown to provide accurate data with regard to left

ventricular volumes and function, and more recently, albeit in younger patients, the same technology has been applied quite successfully to the right ventricle, in particular in persons who have had tetralogy of Fallot.

Intracardiac Echocardiography

Intracardiac echocardiography (ICE) uses lower-frequency transducers that have been miniaturized and mounted into catheters capable of percutaneous insertion into the heart. ICE not only provides high-resolution 2D and hemodynamic data with full Doppler capabilities but also eliminates the need for general anesthesia, which is often required for TEE.

Current applications of ICE include the following:

Percutaneous ASD Device Closure.

ICE supports percutaneous ASD device closure by adequately sizing the defect and assisting device positioning while avoiding the need for general anesthesia. More recently, real-time 3D TEE is being used not only to assess the size and suitability of ASD device closure, but also to monitor the procedure, either in an interventional setting or surgically using robotic procedures.

Electrophysiologic Studies.

ICE assists electrophysiologic procedures by guiding transseptal puncture, enabling endocardial visualization, and ensuring electrode-tissue contact at the time of ablative procedures. Recently, a forward-looking imaging and ablation probe has been developed, which will enable precise localization of energy delivery to an arrhythmogenic focus (**See Chapter 34**).

Cardiac Catheterization

With the development of cross-sectional echocardiography and the subsequent introduction of MRI and fast computed tomographic methods, truly diagnostic cardiac catheterization (**see Chapter 19**) is becoming rare. “Diagnostic” catheterization is reserved for resolving unanswered questions from the less-invasive techniques, and measuring hemodynamics. A good example of this is the assessment of major aortopulmonary collateral arteries in tetralogy of Fallot with pulmonary atresia; the presence and distribution of the arteries may be shown beautifully by MR angiography, but cardiac catheterization may be required to demonstrate the presence of communications with the central pulmonary arteries and measure the pressure within them. There is no adequate substitute for cardiac catheterization to measure ventricular end-diastolic pressures or pulmonary artery pressures and resistance with the precision required to plan for, or assess, the Fontan circulation. Furthermore, diagnostic testing may also be needed to evaluate possible coronary artery disease, especially before heart surgery in adults.

Therapeutic Catheterization

Balloon atrial septostomy was the first catheter intervention that proved useful in treating heart disease, and it remains the standard initial palliation in many infants with D-TGA. Many transcatheter techniques are now used successfully to treat CHD: blade atrial septostomy; device or coil closure of PDA; closure of ASD and patent foramen ovale (PFO); transluminal balloon dilation of pulmonary and aortic valve stenosis; radiofrequency perforation of pulmonary valve atresia; balloon-expandable intravascular stents for right ventricular outflow tract, pulmonary artery, aortic coarctation, and other vascular stenoses; and device occlusion of unwanted collateral vessels and AV fistulas. These have all become treatments of choice in centers with these capabilities. Some are universally accepted as the standard of care (e.g., balloon pulmonary valvuloplasty), whereas debate continues for other interventions (e.g., unoperated

coarctation). One of the most exciting new developments has been that of transcatheter valved stents for the treatment of right ventricular outflow stenosis and regurgitation in patients with congenital defects, a procedure that also has led to an explosion of transcatheter valve techniques for acquired disease. Going along with the extraordinary expansion of interventional techniques for the treatment of structural abnormalities, ablative techniques for the treatment of tachycardias are now performed routinely in centers with congenital heart electrophysiology programs and are crucial to the management of adults with operated and unoperated CHD, in whom arrhythmias are such a burden in terms of their morbidity, as well as a significant cause of late death. The indications, outcomes, and current status of each of these techniques are discussed later in detail in the sections concerning specific lesions.

Specific Cardiac Defects

Left-to-Right Shunts

Atrial Septal Defect and Partial Anomalous Pulmonary Venous Drainage

Morphology

It is important to distinguish between an “atrial septal defect” and an interatrial communication. To understand this problem, a brief review of the embryologic development of the atrial septum is essential. The primary septum grows down from the roof of the developing atria, develops, and breaks down superiorly to form the secondary foramen. The leading edge of the primary septum, or mesenchymal cap, fuses with the superior cushion, with the only communication between the atria being via the secondary foramen. When first formed, the secondary foramen has no upper rim and is flat. At this stage, there is a single orifice that connects the left atrium to the pulmonary veins. Later, after separation into the left and right pulmonary veins and incorporation of their orifices as separate openings, a fold develops superiorly; it had previously been called the septum secundum but at this point it is recognized as the fibrofatty fold. The true atrial septum is a relatively small component of the left and right atria.

Four types of interatrial communications exist: ostium primum, ostium secundum, sinus venosus, and coronary sinus defects (**Fig. 75.17A and D** and Videos 75.29 to 75.31). (Ostium primum is discussed in the section on AV septal defect.) Ostium secundum defects are the only true ASDs; all the others are atrial-level shunts, not being surrounded by true atrial septal tissue. Secundum defects have varying degrees of deficiency of the primary septum during embryologic development. Some are discrete defects, and others represent a series of fenestrations in the primary septum (foramen flap).

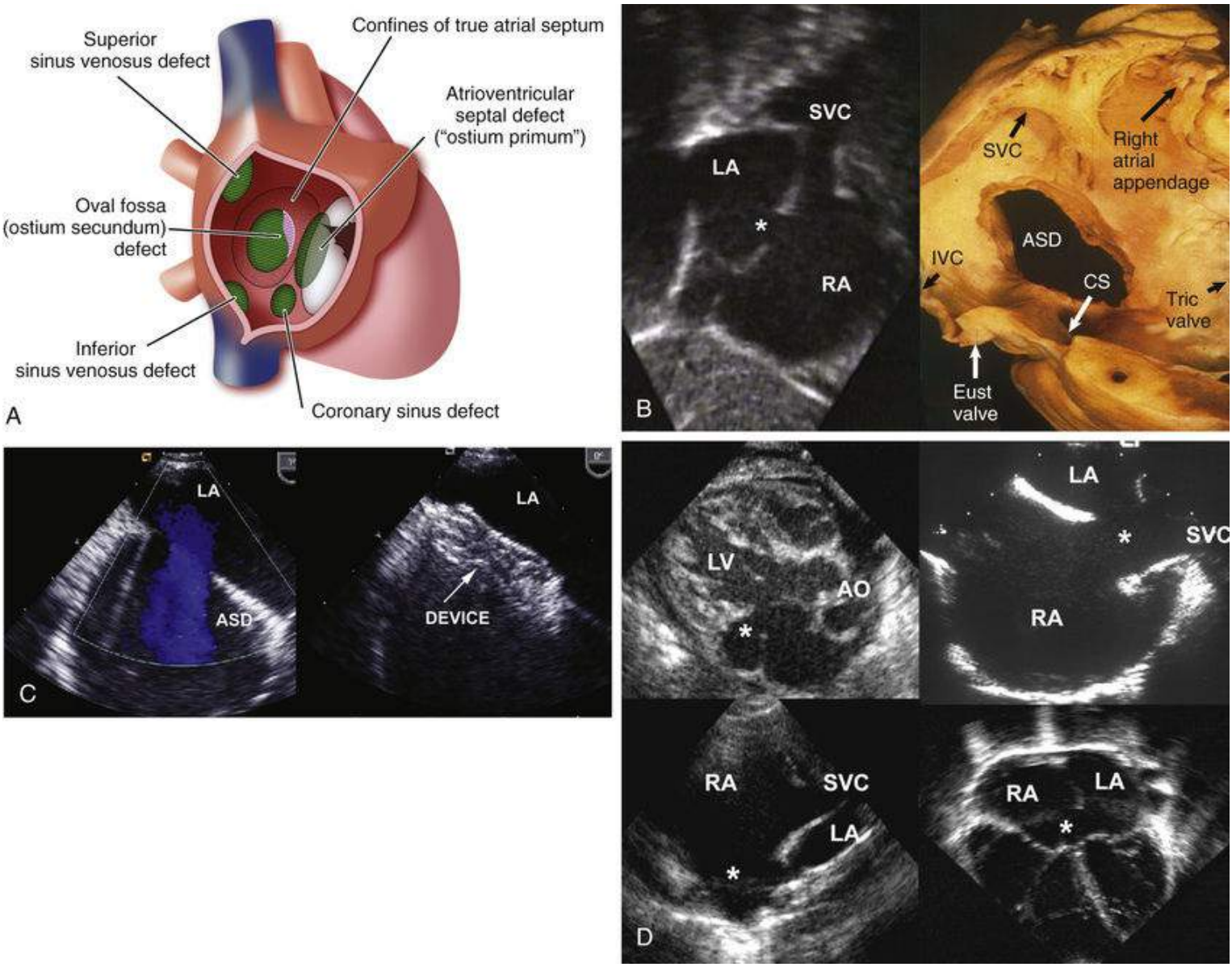


FIGURE 75.17 **A,** Schematic diagram outlining the different types of interatrial shunting that can be encountered. Note that only the central defect is suitable for device closure. **B,** Subcostal right anterior oblique view of a secundum ASD (*asterisk*) that is suitable for device closure. The right panel is a specimen as seen in a similar view, outlining the landmarks of the defect. **C,** The left image is a transesophageal echocardiogram with color flow before device closure, whereas the right side has been taken following release of an Amplatzer device. **D,** Montage of interatrial communications that are not ASDs (*asterisks*) and therefore not suitable for device closure. The upper left image shows a coronary sinus defect due to unroofing; the top right image, a superior sinus venosus defect; the bottom left image, an inferior sinus venosus defect; and the bottom right image, an ASD in the setting of an AV septal defect. *AO*, aorta; *ASD*, atrial septal defect; *CS*, coronary sinus; *Eust*, eustachian; *IVC*, inferior vena cava; *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium; *SVC*, superior vena cava; *Tric*, tricuspid.

Sinus venosus defects of the superior vena caval type are due to a deficiency between the superior vena cava and, usually, the right upper and middle pulmonary veins. In these hearts, there is often partial erosion of the fibrofatty fold, but the true atrial septum is intact, although there can be a separate secundum ASD. These hearts have a superior vena cava–pulmonary vein–left atrial connection, unlike a partial anomalous pulmonary venous connection to the superior vena cava, which connects at a higher point, above the right pulmonary artery, and does not have an atrial connection. Rarely, sinus venosus defects drain to the azygos vein posteriorly. Inferior sinus venosus defects result from a breakdown between the right atrial wall and the inferior right-sided pulmonary veins. Coronary sinus septal defects are rare and occur when there is either a partial or complete deficiency of the roof of the coronary sinus, such that it is possible to have atrial-level shunting at the mouth of the coronary sinus but the true

interatrial septum is intact.

In other situations, there is a partial anomalous pulmonary venous connection; most frequently, the connection is with all of the pulmonary veins or with the left upper lobe pulmonary vein only, draining to the innominate vein; this can coexist with a true ASD. Less frequently, there is a partial anomalous pulmonary venous connection to the coronary sinus or inferior vena cava; the latter is called *scimitar syndrome*. In scimitar syndrome, the primary abnormality is a partial anomalous pulmonary venous connection to the inferior vena caval–atrial junction, but it can occur in association with right lung hypoplasia, sequestration of the right lung, and aortopulmonary collateral circulation. It can be seen in some patients with a secundum ASD, as well as in association with many other forms of CHD.

Pathophysiology

In any type of atrial-level shunt, the degree of left-to-right atrial shunting depends on the size of the defect and the relative diastolic filling properties of the two ventricles. Any condition causing reduced left ventricular compliance (e.g., systemic hypertension, cardiomyopathy, myocardial infarction) or increased left atrial pressure (e.g., mitral stenosis and/or regurgitation) tends to increase the left-to-right shunt. If similar forces are present in the right heart, this will diminish the left-to-right shunt and promote right-to-left shunting.

Natural History

Most large, true secundum ASDs (pulmonary artery blood flow relative to systemic blood flow [Qp/Qs] > 2.0/1.0) are dealt with during childhood by surgical or device closure. An undetected ASD with a significant shunt (Qp/Qs > 1.5/1.0) probably causes symptoms over time in adolescence or adulthood, and symptomatic patients usually become progressively more physically limited as they age. Effort dyspnea is seen in about 30% of patients by the third decade and more than 75% of patients by the fifth decade. Exercise intolerance on cardiopulmonary testing is even more common, reflecting the fact that such patients often do not know what “normal” feels like. Supraventricular arrhythmias (atrial fibrillation or flutter) and right-sided heart failure develop by 40 years of age in about 10% of patients and become more prevalent with aging. Paradoxical embolism resulting in a transient ischemic attack or stroke can call attention to the diagnosis. The development of pulmonary hypertension, although probably not as common as originally thought, can occur at an early age. If pulmonary hypertension is severe, a second causative diagnosis should be sought. The life expectancy is clearly reduced in ASD patients, although not as severely as was quoted in earlier papers because, in them, only statistics on patients with large ASDs were reported.

Clinical Features

The most common presenting symptoms in adults are exercise intolerance (exertional dyspnea and fatigue) and palpitations (typically from atrial flutter, atrial fibrillation, or sick sinus syndrome). Right ventricular failure can be the presenting symptom in older patients. The presence of cyanosis should alert one to the possibility of shunt reversal and Eisenmenger syndrome or, alternatively, to a prominent eustachian valve directing the inferior vena caval flow to the left atrium via a secundum ASD or sinus venosus ASD of the inferior vena caval type. The clinical findings in those with PAPVC/PAPVD are similar to those with an ASD; the primary clinical diagnosis is usually an ASD, with subsequent investigations identifying the precise pathology.

On examination, there is “left atrialization” of the jugular venous pressure (*a* wave = *v* wave). A

hyperdynamic right ventricular impulse may be felt at the left sternal border at the end of expiration or in the subxiphoid area on deep inspiration. A dilated pulmonary artery trunk may be palpated in the second left intercostal space. A wide, fixed split of S_2 is the auscultatory hallmark of ASD, although it is not always present. A systolic ejection murmur, usually grade 2 and often scratchy, is best heard at the second left intercostal space, and a middiastolic rumble, from increased flow through the tricuspid valve, may be present at the left lower sternal border. When right ventricular failure occurs, a pansystolic murmur of tricuspid regurgitation is common.

Laboratory Investigations

ECG.

A sinus rhythm or atrial fibrillation or flutter may be present. The QRS axis is typically rightward in secundum ASD and PAPVD/PAPVC, and there may be crochetage of the QRS complex in the inferior leads. Negative P waves in the inferior leads indicate a low atrial pacemaker often seen in superior sinus venosus defects, which are located in the area of the sinoatrial node and render it deficient. Complete right bundle branch block appears as a function of age. Tall R or R′ waves in V_1 suggest pulmonary hypertension.

Chest Radiography.

The classic radiographic features are of cardiomegaly (from right atrial and right ventricular enlargement), dilated central pulmonary arteries with a pulmonary plethora, indicating increased pulmonary flow, and a small aortic knuckle (reflecting a chronic low cardiac output state). Those with scimitar syndrome often have hypoplasia of the right hemithorax, and some have the classic *scimitar sign*, which represents the course of the right-sided pulmonary veins.

Echocardiography (Videos 75.32 and 75.33).

Transthoracic echocardiography documents the type(s) and size(s) (defect diameter) of the ASD(s), the direction(s) of the shunt(s) (**see Fig. 75.17B**), and sometimes the presence of an anomalous pulmonary venous return. The functional importance of the defect can be estimated by the size of the right ventricle and the presence or absence of right ventricular volume overload (paradoxical septal motion). If the size of the ASD is out of keeping with the size of the right ventricle, suspect an associated abnormality of the pulmonary venous drainage or connection. Indirect measurement of the pulmonary artery pressure can be obtained from the Doppler velocity of the tricuspid regurgitation jet. A dilated coronary sinus is seen in PAPVC to the coronary sinus. In scimitar syndrome, the abnormal pulmonary vein can be seen from the subcostal position during evaluation of the inferior vena cava. Associated stenosis of the pulmonary vein may exist. In adolescents and adults, TEE may also be useful in assessing not only the size of a true ASD, but also any associated PAPVD/PAPVC.

TEE permits better visualization of the interatrial septum and is usually required when device closure is contemplated, partly to ensure that the pulmonary venous drainage or connection is normal. Intracardiac echocardiography (ICE) can be used instead of TEE during device closure to help guide device insertion, reducing the fluoroscopy and procedural time and forgoing the need for general anesthesia.

MRI.

Although TEE can be used with a considerable degree of accuracy in older patients who have poor ultrasound windows, MRI is a less invasive means of obtaining data. MRI provides superb images of the

connecting veins seen more distally and their connections with the hilum of the lung. The pulmonary-to-systemic flow ratio can be calculated for any atrial-level shunt, usually obviating the need for hemodynamic evaluation. The pulmonary-to-systemic flow ratio can also be estimated by radionuclide techniques.

Indications for Intervention

Shunt fractions are now rarely measured and are reserved for "borderline" cases. Hemodynamically insignificant ASDs (Qp/Qs < 1.5) usually do not require closure; a possible exception is when trying to prevent paradoxical emboli in older patients after a stroke. "Significant" ASDs (Qp/Qs > 1.5, or ASDs associated with right ventricular volume overload) should be closed, especially if device closure is available and appropriate. For patients with pulmonary hypertension (pulmonary artery pressure higher than two thirds of the systemic arterial blood pressure, or pulmonary arteriolar resistance higher than two thirds of the systemic arteriolar resistance), closure can be recommended if there is a net left-to-right shunt of at least 1.5 : 1, or evidence of pulmonary artery reactivity when challenged with a pulmonary vasodilator (e.g., oxygen or nitric oxide).

Device Closure.

Device closure of secundum ASDs percutaneously under fluoroscopy and TEE guidance or with intracardiac echocardiographic guidance is the therapy of choice when appropriate (**see Fig. 75.17C** and Video 75.34). Indications for device closure are the same as for surgical closure, but the selection criteria are stricter. Depending on the device, this technique is available only for patients with a secundum ASD with a stretched diameter of less than 36 to 40 mm and with adequate rims (> 5 mm) to enable secure deployment of the device.[16] An anomalous pulmonary venous connection or proximity of the defect to the AV valves or coronary sinus or systemic venous drainage usually precludes the use of this technique. It is a safe and effective procedure in experienced hands; major complications (e.g., device embolization, atrial perforation, thrombus formation) occur in less than 1% of patients, and clinical closure is achieved in more than 80%. Device closure of an ASD improves the functional status in symptomatic patients no matter what their age[17,18] and the exercise capacity in asymptomatic and symptomatic patients. Intermediate follow-up data have proved ASD device closure to be safe and effective,[19] with better preservation of right ventricular function and lower complication rates than surgery. Its cost is also lower than surgery.[20]

Surgery.

Device closure is not an option for those with sinus venosus or ostium primum defects or with secundum defects with unsuitable anatomy. Surgical closure of ASDs can, depending on size and shape, be performed by primary suture closure or by using a pericardial or synthetic patch. The procedure is usually performed via a midline sternotomy, but the availability of a minimally invasive, inframammary, or minithoracotomy approach to a typical secundum ASD should be made known to cosmetically sensitive and other patients. The mortality rate in adult surgical patients without pulmonary hypertension should be less than 1%. Surgical closure of an ASD improves the functional status and exercise capacity in symptomatic patients and improves (but usually does not normalize) survival rates; it also improves or eliminates congestive heart failure, especially when patients are operated on at a young age (e.g., < 25 years). However, surgical closure of ASDs in adult life does not prevent atrial fibrillation or flutter or stroke, especially when patients are operated on after the age of 40 years. The role of a concomitant Cox

maze procedure in patients with a history of atrial flutter or fibrillation should be considered (**see Chapters 34 and 35**). In the setting of preexisting atrial tachyarrhythmias, surgical as well as device closure of an ASD does decrease the incidence of postoperative atrial tachyarrhythmia.[21-23]

Surgery is not necessary when a single anomalously draining vein has not produced right ventricular volume loading. In those with right ventricular volume loading, the surgical technique depends on the nature of the abnormal connection; the goal is to reroute the pulmonary venous blood back to the left atrium. In those with PAPVD to the right atrium, the atrial patch is placed such that the right-sided pulmonary veins drain back to the left atrium. In a superior sinus venosus defect, the deficiency between the superior vena cava and right pulmonary veins is closed.

Reproductive Issues

Pregnancy is well tolerated in patients after ASD closure. Pregnancy is also well tolerated in women with unrepaired ASDs, but the risk of paradoxical embolism is increased (it is still very low) during pregnancy and in the postpartum period. Pregnancy is contraindicated in Eisenmenger syndrome because of the high mortality rates for the mother (≈50%) and fetus (≈60%).

Follow-Up

After device closure, patients require 6 months of aspirin and endocarditis prophylaxis until the device endothelializes, following which, assuming there is no residual shunt, they do not require any special precautions or endocarditis prophylaxis. Patients with sinus venosus defects are at risk of developing caval and/or pulmonary vein stenosis and should be kept under intermittent review. Patients who have had surgical or device repair as adults, patients with atrial arrhythmias preoperatively or postoperatively, and patients with ventricular dysfunction should have long-term cardiology surveillance. Indeed, all patients who have had device closure should probably have an echocardiogram every 5 years or so because of the possibility of late issues, especially erosion. The outcome of patients undergoing PAPVC/PAPVD surgery is invariably excellent, although the precise number of veins that become stenotic after repair is currently unclear. The main issue is that postrepair echocardiography is an unreliable modality for determining the patency of individual veins, and most patients do not undergo MRI follow-up, because they are asymptomatic with a right ventricle that has returned to normal size.

Patent Foramen Ovale

Anatomy

The foramen ovale is a tunnel-like space between the overlying septum secundum and septum primum. It closes in 75% of people at birth. In utero, the foramen ovale is necessary for blood flow across the fetal atrial septum. Oxygenated blood from the placenta returns to the inferior vena cava, crosses the foramen ovale, and enters the systemic circulation. In approximately 25% of people, a patent foramen ovale (PFO) persists into adulthood. PFOs may be associated with atrial septal aneurysms (a redundancy of the interatrial septum), eustachian valves (a remnant of the sinus venosus valve), and Chiari networks (filamentous strands in the right atrium).

Pathophysiology

PFOs have been scrutinized for their implications in the mechanism of cryptogenic stroke. Many of the basic tenets linking PFO and stroke seem plausible but have not been demonstrated. The current views may be summarized as follows. PFOs may serve as either a conduit for paradoxical embolization from the venous side to the systemic circulation or, because of their tunnel-like structure and propensity to stagnant flow, may serve as a nidus for in situ thrombus formation. Variations in PFO size, the status of the right atrial anatomy, varying hemodynamic conditions, and the development of venous thrombi may all contribute to the chances of paradoxical embolization. The risk of a cryptogenic stroke seems increased for larger PFOs. The presence of an interatrial septal aneurysm in combination with a PFO also increases the risk of an adverse event, perhaps because of increased in situ thrombus formation in the aneurysmal tissue or simply because PFOs associated with an interatrial septal aneurysm tend to be larger. Eustachian valves and a Chiari network may direct blood flow from the inferior vena cava toward the atrial septum, encouraging right-to-left shunting in the presence of an interatrial communication. Physiologic (Valsalva maneuvers) and pathologic conditions that increase the right ventricular pressure will raise the right atrial pressure, favoring right-to-left shunting. Finally, pelvic vein thrombi are found more frequently in young patients with cryptogenic stroke than in patients with a known cause of stroke and may provide the source of venous thrombi.

PFOs have also been implicated in the pathophysiology of decompression sickness (arterial gas embolism from the venous side), as well as in the pathogenesis of migraine headaches. *Platypnea-orthodeoxia syndrome* (dyspnea and arterial desaturation when a patient is in the upright position and improvement when the patient is lying down) has also been attributed to the presence of a PFO (Video 75.35).

Clinical Impact

The cause-and-effect relationship between PFO and cryptogenic stroke is still tentative. The recent body of literature would suggest a strong association, if not a causative link, especially in younger patients. Indeed, young patients with cryptogenic stroke have a significantly higher incidence of PFO (36% to 54%) than normal controls (15% to 25%). The association is more controversial in the older patient population. Older patients often have more risk factors for stroke, and the causative role of a PFO in these patients is more difficult to establish.

When a patient presents with a stroke and a PFO is discovered, the usual causes of stroke must first be eliminated. Potential causes of strokes include carotid artery disease, ascending aortic atherosclerosis, atrial fibrillation, neurovascular abnormalities, and/or prothrombotic tendencies. If after an exhaustive investigation (see later) no other cause of the stroke can be found, the PFO may be seen to have possibly had a causative role. The diagnosis of a PFO as a cause of cryptogenic stroke is, at best, a diagnosis of exclusion.

Investigations

A PFO is usually detected by transthoracic echocardiography, TEE, or transcranial Doppler imaging. TEE is the most sensitive test, especially when performed with contrast media injected during a cough or Valsalva maneuver. A PFO is judged to be present if microbubbles are seen in the left-sided cardiac chambers within three cardiac cycles from the maximum right atrial opacification.

Screening for prothrombotic states (e.g., protein C or S deficiency, antithrombin III, or lupus anticoagulant), atrial fibrillation, significant carotid atherosclerosis by carotid Doppler imaging, and neurovascular abnormalities by brain MRA must be undertaken in each patient before a PFO can be

considered a possible culprit.

Therapeutic Options

Once the presumptive diagnosis of a cryptogenic stroke caused by a PFO is determined, treatment modalities to prevent recurrent events include antiplatelet or anticoagulant agents, percutaneous device closure, or surgical PFO closure. Medical therapy for secondary prevention of stroke with warfarin or antiplatelet agents is often used as first-line therapy with similar efficacy (i.e., a yearly stroke recurrence rate of about 2%). Patients with PFO and atrial septal aneurysm who have had strokes seem to be at higher risk of recurrent stroke (≤ 15% per year), and a preventive strategy other than aspirin or warfarin should perhaps be considered. Device closure is safe and seems effective, with a recurrence rate of stroke between nil and 3.8% per year. Surgical closure of PFO is usually performed when cardiac surgery is required for other reasons.

Three recent randomized clinical trials in which device closure was compared with medical treatment (ASA or warfarin) for a patient with a PFO after a stroke, did not show a significant difference between the two treatment arms in the recurrent stroke rate at a mean follow-up time of 2 to 4 years.[24-26]

However, a recent metaanalysis of transcatheter closure versus medical therapy, pooling the data of the three aforementioned studies, suggests that the recurrence rate of a stroke in patient with cryptogenic stroke and PFO is low (1%/year) but that device closure reduces the recurrence risk by half.[27] Further studies will be required to determine the best treatment strategy for patients with PFO and cryptogenic stroke.[28]

Atrioventricular Septal Defect

The terms *atrioventricular septal defect*, *atrioventricular canal defect*, and *endocardial cushion defect* can be used interchangeably to describe this group of defects. The variable components of these lesions are explained in the following sections.

Morphology

The basic morphology of AV septal defect is common to all types and is independent of the presence or absence of an atrial or ventricular communication. These common features (**Figs. 75.18 and 75.19**) are a common AV junction with absence of the membranous and muscular AV septum (resulting in the AV valves being at the same level on echocardiography); inlet and outlet disproportion (resulting in an elongated left ventricular outflow tract); abnormal lateral rotation of the posteromedial papillary muscle; and abnormal configuration of the AV valves. The left AV valve is a trileaflet valve made of superior and inferior bridging leaflets separated by a mural leaflet. The space between the superior and inferior leaflets as they bridge the interventricular septum is called the *cleft* in the left AV valve (Videos 75.36 to 75.39).

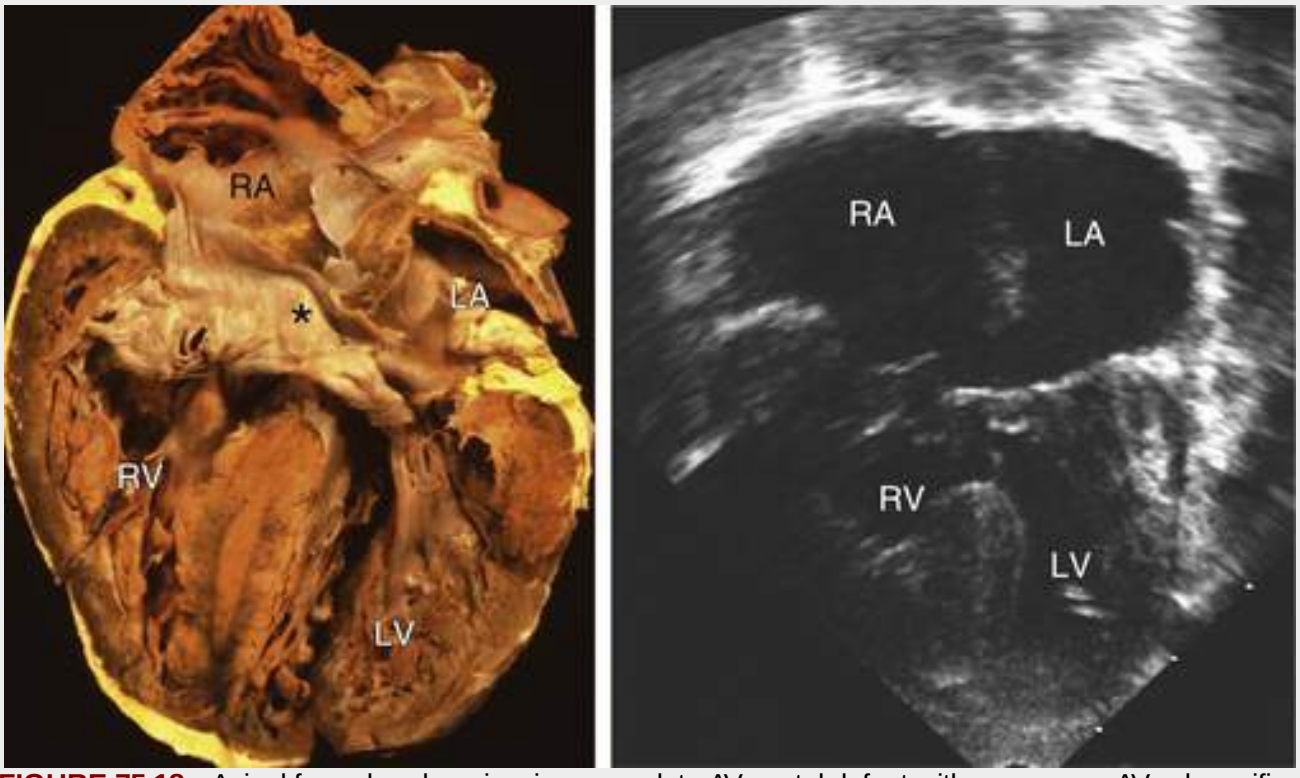


FIGURE 75.18 Apical four-chamber view in a complete AV septal defect with a common AV valve orifice (*). Note the large interatrial and interventricular communications and the large free-floating superior bridging leaflet. *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle.

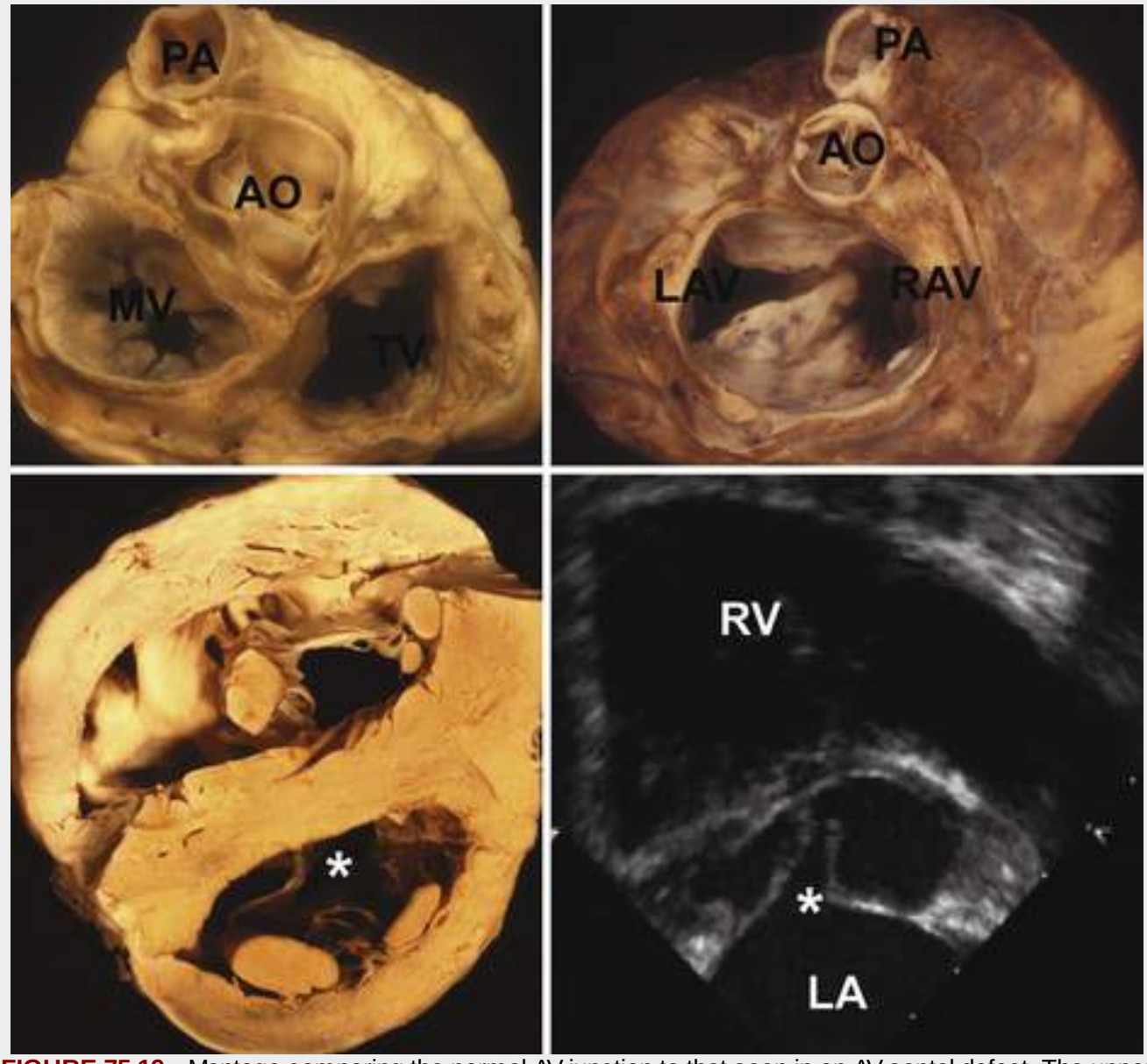


FIGURE 75.19 Montage comparing the normal AV junction to that seen in an AV septal defect. The upper left picture is the normal AV junction as seen from above. Note the normal morphology of the mitral and tricuspid valves, with the aorta wedged between them. The upper right picture is a similar view in an AV septal defect. Note the unwedged aorta, the trileaflet left AV valve, and the cleft between the superior and inferior bridging leaflets. The lower left picture is a specimen of an AV septal defect demonstrating the cleft. The lower right picture is an echocardiogram showing the cleft. *AO*, aorta; *LA*, left atrium; *LAV*, left atrioventricular valve; *MV*, mitral valve; *PA*, pulmonary artery; *RAV*, right atrioventricular valve; *RV*, right ventricle; *TV*, tricuspid valve.

The other feature common to all hearts with an AV septal defect is a "sprung" AV junction (**Fig. 75.20**); this is the cause of the aorta not being wedged between the left and right AV junction, but sitting above it.

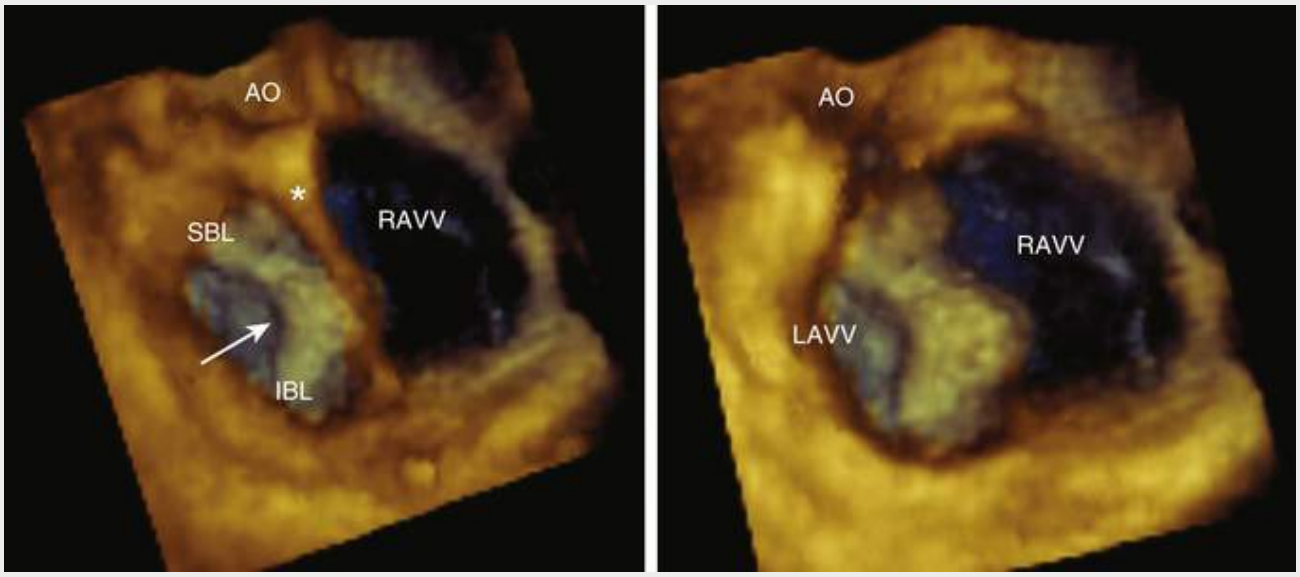


FIGURE 75.20 These images demonstrate the sprung AV junction as seen from above in a heart with an AV septal defect and partitioned orifices. Note the unwedged position of the aorta and the connecting tongue between the superior and inferior bridging leaflets. *AO*, aorta; *LAVV*, left atrioventricular valve; *IBL*, inferior bridging leaflet; *RAVV*, right atrioventricular valve; *SBL*, superior bridging leaflet.

The bridging leaflets may be completely adherent to the crest of the interventricular septum, free floating, or attached by a chordal apparatus. It is possible to have an interventricular communication beneath one, but not the other, bridging leaflet. The degree of chordal attachment beneath the superior and inferior bridging leaflets is also variable.

Partitioned Versus Complete Atrioventricular Septal Defects.

A *partitioned* orifice is one in which the superior and inferior leaflets are joined by a connecting tongue of tissue as they bridge the interventricular septum. This partitions the valve into separate left and right orifices. A *common* AV valve orifice is one in which there is no such connecting tongue, resulting in one large orifice that encompasses the left-sided and right-sided components. Interatrial (ostium primum) and interventricular defects are common in AV septal defect Although most interventricular communications occur in those with a common AV valve orifice, it is possible to have ventricular-level shunting beneath the "connected" bridging leaflets in those with partitioned orifices. The interatrial communication is not a true deficiency of the atrial septum, but is failure of fusion of the leading edge of the primitive primum septum with the AV cushions. As well, a true secundum ASD can coexist with shunting through a primum defect.

By its very nature, the left ventricular outflow tract is elongated in all hearts with an AV septal defect. This exacerbates the multiple potential causes of subaortic stenosis, often with several mechanisms coexisting in the same heart. Potential mechanisms are an isolated fibromuscular shelf, accessory tissue tags, tunnel narrowing due to the inherently elongated outflow tract, abnormal location of the anterolateral papillary muscle, and accessory papillary muscles.

A *double-orifice* left AV valve is a risk factor for repair and subsequent postoperative regurgitation. The second orifice is more often located in the vicinity of the posteromedial papillary muscle. The papillary muscles are closer together than normal, and in some instances there is a single, or parachute, papillary muscle. In others there is dominance of one of the papillary muscles, usually the anterolateral muscle, which is frequently associated with shortened and fused chordae with a blunted superior-mural commissure. This finding can have long-term implications with regard to left AV valve function.[29] The term *unbalanced AV septal defect* refers to cases in which one ventricle is hypoplastic (Videos 75.40 to 75.42). This is seen more commonly in patients with heterotaxy and those with left-sided obstructive

defects.

Pathophysiology

The *native pathophysiology* of those with an isolated shunt at the atrial level (commonly referred to as a *primum defect*) is similar to that of a large secundum ASD, with unrestricted left-to-right shunting through the primum defect, leading to right-sided atrial and ventricular volume overload. Chronic left AV valve regurgitation may produce left-sided ventricular and atrial volume overload. Adults with unrepaired complete AV septal defect usually have irreversible pulmonary vascular disease and are inoperable.

After correction, the medium- and long-term issues regarding pathology are related to left AV valve regurgitation, which increases in frequency with each passing decade, and left ventricular outflow tract obstruction (5% of cases). The latter is more common in those with a primum defect and no interventricular communication, or those with partitioned orifices and an interventricular communication. Also, a single papillary muscle in the left ventricle, or a double-orifice left AV valve, is associated with greater long-term regurgitation. Some develop fibromuscular subaortic stenosis that was not present at the initial repair; in others, it is due to residual anatomic features that were present at the primary repair but were not of sufficient severity at that time to address. Residual significant left AV valve regurgitation may occur and cause significant left atrial, as well as left ventricular, dilation. Left AV valve stenosis from overzealous repair of the valve may also be seen.

Natural History

Patients with an isolated primum ASD have a course similar to that of those with large secundum ASDs, although symptoms may appear sooner when significant left AV valve regurgitation is present. Patients may be asymptomatic until the third or fourth decade, but progressive symptoms related to congestive heart failure, atrial arrhythmias, complete heart block, and variable degrees of pulmonary hypertension develop in virtually all of them by the fifth decade.

Most patients with complete AV septal defect have had surgical repair in infancy. When presenting unrepaired, most adults have established pulmonary vascular disease.

Clinical Issues

In patients with *Down syndrome*, the rate of AV septal defect is 35%. These patients more commonly have a complete AV septal defect with a common AV valve orifice and a large associated VSD. In the current era, most are repaired within the first 6 months of life, so that there is a lower resulting incidence of long-term pulmonary hypertension.

In *patients who do not have Down syndrome*, the clinical presentation depends on the presence and size of the atrial-level and ventricular-level shunts and on the competence of the left AV valve. A large left-to-right shunt gives rise to symptoms of heart failure (exertional dyspnea or fatigue) or pulmonary vascular disease (exertional syncope or cyanosis). In adulthood, palpitations from atrial arrhythmias are common. Cardiac findings on physical examination for patients with an isolated shunt at the atrial level are similar to those of patients with secundum ASD, with the important addition of a prominent left ventricular apex and pansystolic murmur when significant left AV valve regurgitation is present. Cases with a primum defect and a restrictive ventricular-level shunt have similar findings, but with the addition of a pansystolic murmur heard best at the left sternal border. Complete AV septal defects have a single S_1 (common AV valve), a middiastolic murmur from augmented AV valve inflow, and findings of pulmonary

hypertension and/or a right-to-left shunt.

Laboratory Investigations

ECG.

Most patients have left axis deviation. Complete AV block and/or atrial fibrillation or flutter can be present in older patients. Partial or complete right bundle branch block is usually associated with right ventricular dilation or prior surgery.

Chest Radiography.

If the defect has not been repaired, chest radiography demonstrates cardiomegaly with right atrial and right ventricular prominence with increased pulmonary vascular markings. In patients with a small interatrial communication and important left AV valve regurgitation, there is cardiomegaly due to left ventricular enlargement and normal pulmonary vascular markings. Findings of Eisenmenger syndrome are also possible. If the defect has been repaired, the heart and lungs may appear normal.

Echocardiography.

Echocardiography has replaced angiography in assessing virtually all patients with AV septal defect. The cardinal and common features discussed in the morphology section are readily recognized by echocardiography. In the four-chamber view, the AV valve(s) appear at the same level, irrespective of the presence or absence of a ventricular-level shunt beneath the bridging leaflets. The typical inferior primum defect is seen in this view. The degree of associated AV valve regurgitation, the left-to-right shunt, and the estimated right ventricular systolic pressure should be determined. When using the right AV valve to assess right ventricular pressure, care must be taken to ensure that the jet is not contaminated by an obligatory left ventricle–to–right atrial shunt. Three-dimensional echocardiography is very useful in the planning of surgical intervention because it increases our understanding of the complex anatomy, in particular commissural abnormalities, and shows the precise location of the sites of AV valve regurgitation.

Cardiac Catheterization.

Cardiac catheterization has mostly been replaced by echocardiography for the evaluation of patients with an AV septal defect. The one role it still has is in the evaluation of the patient who presents late and may have associated pulmonary vascular or coronary disease.

Indications for Intervention

The patient with an unoperated or newly diagnosed AV septal defect and significant hemodynamic defects requires surgical repair. Equally, patients with persistent left AV valve regurgitation (or stenosis from a previous repair) that is causing symptoms, patients with an atrial arrhythmia or deterioration in ventricular function, and patients with significant subaortic obstruction (a mean gradient > 50 mm Hg at rest) require surgical intervention.

In the presence of severe pulmonary hypertension (pulmonary artery pressure higher than two thirds of the systemic blood pressure or pulmonary arteriolar resistance higher than two thirds of the systemic arteriolar resistance), there must be a net left-to-right shunt of at least 1.5 : 1, or evidence of pulmonary artery reactivity when challenged with a pulmonary vasodilator (e.g., oxygen, nitric oxide, and/or prostaglandins).

Interventional Options and Outcomes

Isolated Shunt at Atrial Level (Primum Atrial Septal Defect).

Pericardial patch closure of the primum ASD with concomitant suture (with or without annuloplasty) of the cleft left AV valve is usually performed. When left AV valve repair is not possible, replacement may be necessary. In the short term, the results of repair of partial AV septal defect are similar to those following closure of secundum ASD, but sequelae of left AV ("mitral") valve regurgitation, subaortic stenosis, and AV block may develop or progress. A subsequent repair of the left AV valve is more challenging in adults because the leaflets are usually less pliable than in children.

Complete Atrioventricular Septal Defect.

The "staged approach" (pulmonary artery banding followed by intracardiac repair) has been supplanted by primary intracardiac repair in infancy. The goals of intracardiac repair are ventricular and atrial septation with adequate left and right AV valve reconstruction. Single-patch, double-patch, and no-patch techniques for closing atrial-level and ventricular-level shunts have been described with comparable results. The "Australian" technique is also used in complete AV septal defects; the common leaflets are sewn directly onto the crest of the interventricular septum, and the primum defect is closed with a patch. Patients with a single papillary muscle or double-orifice left AV valve have a higher frequency of ongoing left AV valve regurgitation. Occasionally, left AV valve replacement is necessary when valve repair is not possible. The intermediate- and long-term results following repair are good in terms of the survival rates; with each decade, however, there is an increasing incidence of patients who require further surgery to address progressive left AV valve regurgitation. Those with a simple primum defect or a small interventricular communication are at greater risk of developing significant left AV valve regurgitation, compared with patients with a common AV valve and a large ventricular component. This is related to more deficient leaflet tissue in those with a pure primum defect or small interventricular communication.

Reproductive Issues

Pregnancy is well tolerated in patients with complete repair and no significant residual lesions. Women in NYHA classes I and II with an unoperated, isolated primum ASD usually tolerate pregnancy well. Pregnancy is contraindicated in Eisenmenger syndrome because of the high mortality rates for the mother (≈50%) and fetus (≈60%).

Follow-Up

All patients who have a repair require periodic follow-up by an expert cardiologist because the 5-year freedom rate from reoperation is only 74%.[30] Long-term complications include patch dehiscence or residual septal defects (1%), development of complete heart block (3%), late atrial fibrillation or flutter, significant left AV valve dysfunction (10%), and subaortic stenosis (5% to 10%). Left AV valve regurgitation requiring left AV valve repair or replacement occurs in least 10% to 20% of patients.[31,32] Subaortic stenosis develops or progresses in 5% to 10% of patients after repair, particularly in patients with primum ASD, especially if the left AV ("mitral") valve has been replaced. Particular attention should be paid to patients who have pulmonary hypertension before operation. Antibiotic prophylaxis is only necessary in the first 6 months following surgery unless there is a residual patch leak or a prosthetic valve has been used.

Isolated Ventricular Septal Defect

Morphology

The ventricular septum can be divided into three major components, the inlet, trabecular, and outlet components, all abutting a small membranous septum lying just underneath the aortic valve. VSDs (**Fig. 75.21**) are classified into three main categories according to their locations and margins (**Fig. 75.22**). *Muscular VSDs* are bordered entirely by myocardium and can have a trabecular, inlet, or outlet location. *Membranous VSDs* often have inlet, outlet, or trabecular extension and are bordered in part by fibrous continuity between the leaflets of an AV valve and an arterial valve. *Doubly committed subarterial VSDs* are more common in Asian and South American patients, are situated in the outlet septum, and are bordered by fibrous continuity of the aortic and pulmonary valves (Videos 75.43 to 75.45). This section deals with VSDs occurring in isolation from major associated cardiac anomalies.

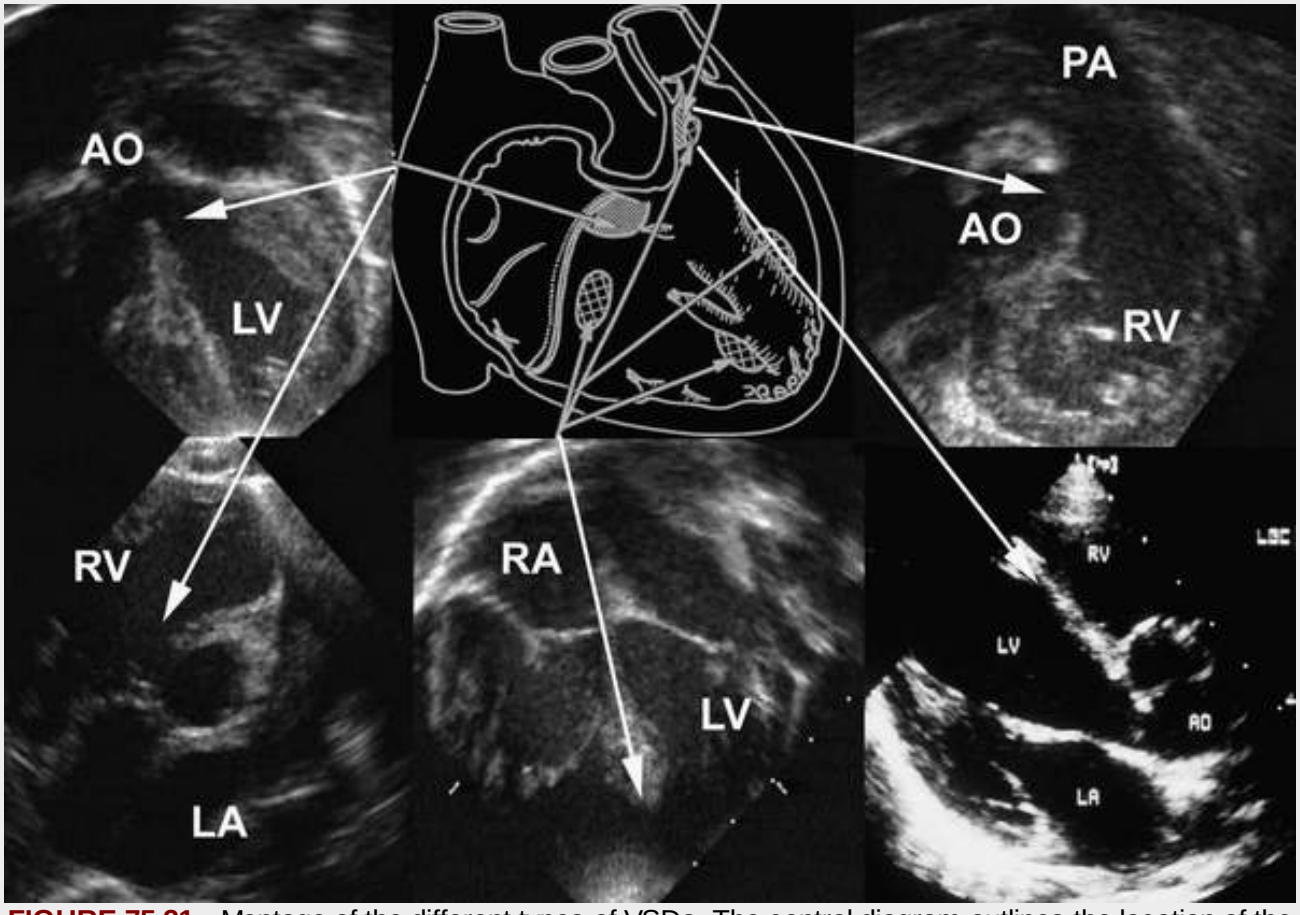


FIGURE 75.21 Montage of the different types of VSDs. The central diagram outlines the location of the various types of defects as seen from the right ventricle. The two left images show a perimembranous VSD as seen in the five-chamber and short axis views. Note the defect is roofed by the aorta and is next to the tricuspid valve. The bottom middle echocardiogram shows a muscular apical defect. The upper right image is a right anterior oblique view in a doubly committed VSD. The lower right image is a short axis view showing an outlet VSD with prolapse of the right coronary cusp. *AO*, aorta; *LV*, left ventricle; *PA*, pulmonary artery; *RA*, right atrium; *RV*, right ventricle; *VSD*, ventricular septal defect.

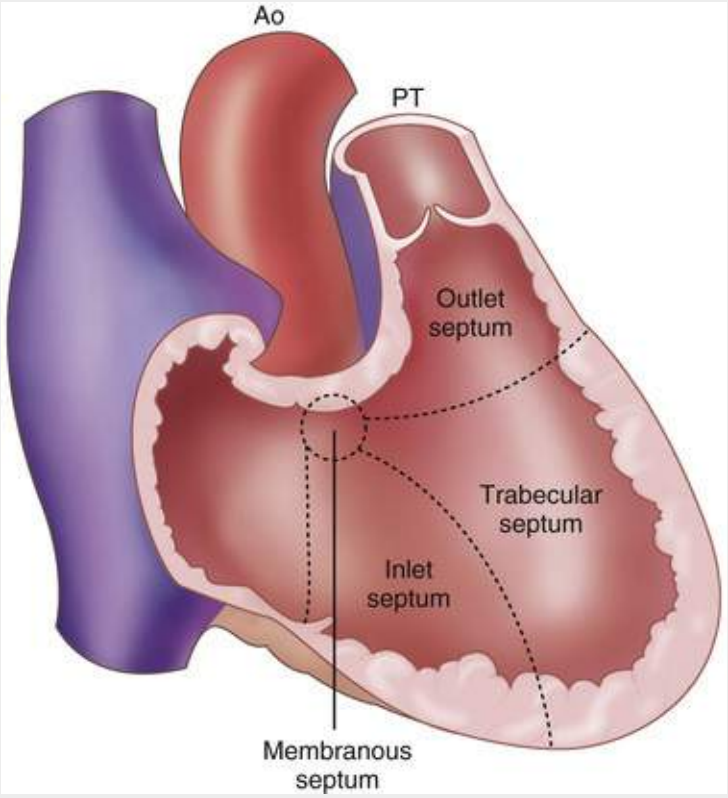


FIGURE 75.22 Four components of the ventricular septum shown here from the right ventricular aspect are now described by Anderson and associates as inlet and outlet components of the right ventricle because these areas do not correspond to septal structures as initially suggested. *Ao*, aorta; *PT*, pulmonary trunk. (Modified from Anderson RH, Becker AE, Lucchese E, et al: Morphology of congenital heart disease. Baltimore, University Park Press, 1983.)

Pathophysiology

A *restrictive VSD* is a defect that produces a significant pressure gradient between the left ventricle and the right ventricle (pulmonary-to-aortic systolic pressure ratio < 0.3) and is accompanied by a small (≤1.4/1) shunt. A *moderately restrictive VSD* is accompanied by a moderate shunt (Qp/Qs of 1.4 to 2.2/1) with a pulmonary-to-aortic systolic pressure ratio of less than 0.66. A large or *nonrestrictive VSD* is accompanied by a large shunt (Qp/Qs > 2.2) and a pulmonary-to-aortic systolic pressure ratio of greater than 0.66. An *Eisenmenger VSD* has a systolic pressure ratio of 1 and a Qp/Qs of less than 1 : 1, or a net right-to-left shunt.

Natural History

A *restrictive VSD* does not cause significant hemodynamic derangement and may close spontaneously during childhood and sometimes even in adult life. A perimembranous defect in an immediately subaortic position, or any doubly committed VSD, may be associated with significant aortic regurgitation. Late development of subaortic and subpulmonary stenosis (see double-chambered right ventricle), as well as the formation of a left ventricular–to–right atrial shunt, is well described and should be excluded at follow-up. A *moderately restrictive VSD* imposes a hemodynamic burden on the left ventricle, which leads to left atrial and ventricular dilation and later dysfunction, as well as a variable increase in pulmonary vascular resistance. A *large or nonrestrictive VSD* in the absence of obstruction to pulmonary blood flow features left ventricular volume overload early in life, with a progressive rise in pulmonary artery pressure and a fall in left-to-right shunting. In turn, this leads to higher pulmonary vascular resistance and eventually to Eisenmenger syndrome.

Clinical Features

Like patients with ASDs and AV septal defect, most patients with significant defects will undergo closure in childhood in developed societies. Large VSDs will usually produce symptoms in early infancy, and closure at 3 to 6 months of age is the norm. The role of "prophylactic" VSD closure in children with a substrate for the development of aortic regurgitation is controversial, with most units waiting for at least mild to moderate aortic regurgitation to develop before advising surgery (which usually reverses or stabilizes its progression). Most adult patients with a small *restrictive VSD* are asymptomatic. Physical examination reveals a harsh or high-frequency pansystolic murmur, usually grade 3 to 4, heard with maximal intensity at the left sternal border in the third or fourth intercostal space. Patients with a *moderately restrictive VSD* often present with dyspnea in adult life, perhaps triggered by atrial fibrillation. Physical examination typically reveals a displaced cardiac apex with a similar pansystolic murmur, and occasionally an apical diastolic rumble and third heart sound at the apex from the increased flow through the mitral valve. Patients with large *nonrestrictive Eisenmenger VSDs* present as adults with central cyanosis and clubbing of the nail beds. Signs of pulmonary hypertension (i.e., a right ventricular heave, palpable and loud P_2, and right-sided S_4) are typically present. A pulmonary ejection click, a soft and scratchy systolic ejection murmur, and a high-pitched decrescendo diastolic murmur of pulmonary regurgitation (Graham Steell murmur) or aortic regurgitation may be audible. Peripheral edema usually reflects right-sided heart failure.

Laboratory Investigations

ECG.

The ECG mirrors the size of the shunt and the degree of pulmonary hypertension. *Small, restrictive VSDs* usually produce a normal tracing. *Moderate-sized VSDs* produce a broad, notched P wave characteristic of left atrial overload, as well as evidence of left ventricular volume overload, namely deep Q waves and tall R waves, with tall T waves in leads V_5 and V_6, and perhaps eventually atrial fibrillation. Following repair of perimembranous defects, there is usually right bundle branch block.

Chest Radiography.

The chest radiograph reflects the magnitude of the shunt, as well as the degree of pulmonary hypertension. A *moderate-sized shunt* causes signs of left ventricular dilation with some pulmonary plethora.

Echocardiography.

Transthoracic echocardiography can identify the location, size, and hemodynamic consequences of the VSD, as well as any associated lesions (aortic regurgitation, right ventricular outflow tract obstruction, or left ventricular outflow tract obstruction) (Videos 75.46 to 75.52).

Cardiac Catheterization.

Cardiac catheterization may be required when the hemodynamic significance of a VSD is questioned or when the assessment of pulmonary artery pressures and resistances is necessary. In some centers or countries, therapeutic catheterization is performed for percutaneous closure (see later).

Indications for Intervention

The presence of a significant VSD (symptoms; significantly increased left ventricular and left atrial size;

or deteriorating left ventricular function) in the absence of irreversible pulmonary hypertension warrants closure. If severe pulmonary hypertension (see ASD section) is present, closure is seldom feasible. Other relative indications for VSD closure include the presence of a perimembranous or outlet VSD with more than mild aortic regurgitation or a history of recurrent endocarditis.

Interventional Options and Outcomes

Surgery.

Surgical closure by direct suture or with a patch has been used for more than 50 years with a low perioperative mortality rate, even in adults, and a high closure rate. Patch leaks are not uncommon but seldom need reoperation.

Device Closure.

Successful transcatheter device closure of trabecular (muscular) and perimembranous VSDs has been reported. Trabecular VSDs have proven more amenable to this technique because of their relatively straightforward anatomy and the presence of a muscular rim to which the device attaches well; therefore, the closure rates are excellent and the procedural mortality rate is low. Immediate- as well as short-term results are good. The closure of perimembranous VSDs is technically more challenging due to their proximity to valve structures; careful patient selection is required. The procedure has not gained widespread acceptance, and should be performed only in centers with appropriate expertise. Short-term follow-up data show complete closure in 96% of patients; aortic and/or tricuspid regurgitation or complete heart block develops in less than 15% of patients.

Reproductive Issues

Pregnancy is well tolerated in women with small or moderate VSDs and in women with repaired VSDs. Pregnancy is contraindicated in Eisenmenger syndrome because of the high mortality rates for the mother (≈50%) and fetus (≈60%).

Follow-Up

For patients with a good to excellent functional class and good left ventricular function before surgical closure, the life expectancy after surgical correction is close to normal. The risk of progressive aortic regurgitation is reduced after surgery, as is the risk of endocarditis, unless a residual VSD persists. Yearly cardiac evaluation is suggested for patients with right ventricular outflow tract obstruction, left ventricular outflow tract obstruction, and aortic regurgitation not undergoing surgical repair; patients with Eisenmenger syndrome; and adults with significant atrial or ventricular arrhythmias. Cardiac surveillance is also recommended for patients who had late repair of moderate or large defects, which are often associated with left ventricular impairment and elevated pulmonary artery pressure at the time of surgery.

Patent Ductus Arteriosus

Morphology

The ductus arteriosus derives from the left sixth primitive aortic arch and connects the proximal left pulmonary artery to the descending aorta, just distal to the left subclavian artery.

Pathophysiology

The ductus is widely patent in the normal fetus, carrying unoxygenated blood from the right ventricle through the descending aorta to the placenta, where the blood is oxygenated. Functional closure of the ductus from vasoconstriction occurs shortly after a term birth, whereas anatomic closure from intimal proliferation and fibrosis takes several weeks to complete. Some patients have a "ductus-dependent" physiology as neonates. This means their circulation depends on the ductus for pulmonary blood flow, as in severe aortic coarctation, hypoplastic left heart syndrome, and, sometimes, D-TGA. If spontaneous closure of the ductus occurs in such neonates, clinical deterioration and death usually follow quickly.

Isolated PDAs, the subject of this section, are often categorized according to the degree of left-to-right shunting, which is determined by both the size and length of the duct and the difference between the systemic and pulmonary vascular resistances, as follows:

- Silent: tiny PDA detected only by nonclinical means (usually echocardiography)
- Small: continuous murmur common; Qp/Qs < 1.5/1
- Moderate: continuous murmur common; Qp/Qs of 1.5 to 2.2/1
- Large: continuous murmur present; Qp/Qs > 2.2/1
- Eisenmenger syndrome: continuous murmur absent; substantial pulmonary hypertension, differential hypoxemia, and differential cyanosis (pink fingers, blue toes)

Clinical Features

A *small* audible duct usually causes no symptoms but may rarely present as an endovascular infection. Physical examination may reveal a grade 1 or 2 continuous murmur peaking in late systole and best heard in the first or second left intercostal space. Patients with a *moderate-sized* duct may present with dyspnea or palpitations from atrial arrhythmias. A louder continuous or "machinery" murmur in the first or second left intercostal space is typically accompanied by a wide systemic pulse pressure from aortic diastolic runoff into the pulmonary trunk and signs of left ventricular volume overload, such as a displaced left ventricular apex and sometimes a left-sided S_3 (meaningful in adults only). With a moderate degree of pulmonary hypertension, the diastolic component of the murmur disappears, leaving a systolic murmur. Adults with a *large* uncorrected PDA eventually present with a short systolic ejection murmur, hypoxemia in the feet more than the hands (differential cyanosis), and Eisenmenger physiology.

Laboratory Investigations

ECG.

The ECG reflects the size and degree of shunting occurring through the duct. A *small* duct produces a normal ECG. A *moderate* duct may show left ventricular volume overload with broad, notched P waves together with deep Q waves, tall R waves, and peaked T waves in V_5 and V_6. A *large* duct with Eisenmenger physiology produces findings of right ventricular hypertrophy.

Chest Radiography.
A *small* duct produces a normal chest radiograph. A *moderate-sized* duct causes moderate cardiomegaly with left-sided heart enlargement, a prominent aortic knuckle, and increased pulmonary perfusion. Ring calcification of the ductus may be seen through the soft tissue density of the aortic arch or pulmonary trunk in older adults. A *large* PDA produces an Eisenmenger appearance with a prominent aortic knuckle.

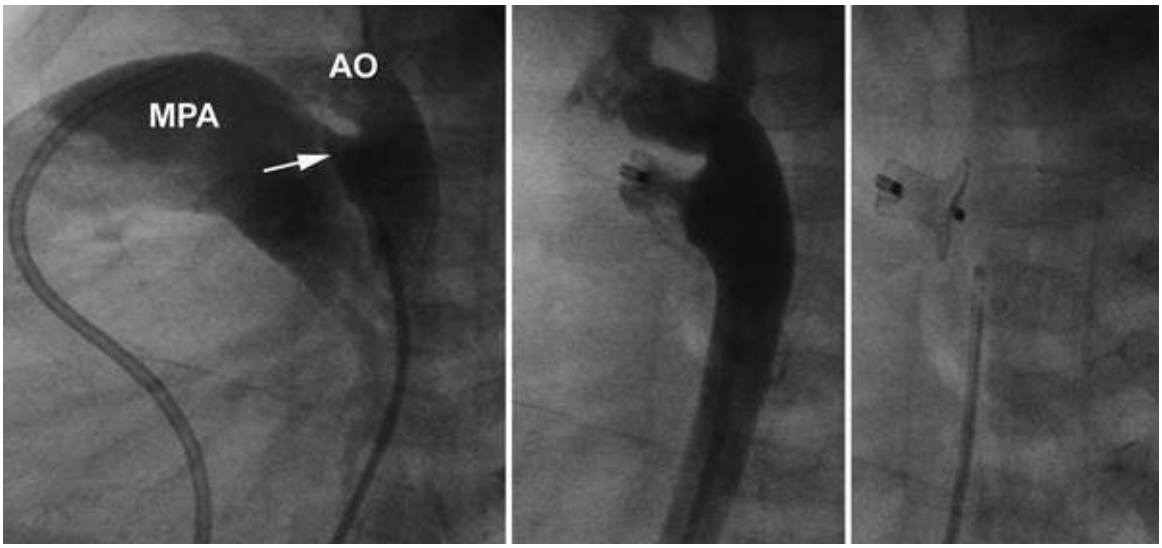
Echocardiography.
Echocardiography allows determination of the presence, size, and degree of shunting and the physiologic consequences of the shunt. The PDA is seen with difficulty in an Eisenmenger context. A bubble study will show the communication.

Indications for Intervention

There is no debate about the desirability of closing a hemodynamically important PDA, with significant left-to-right shunting, at any age. There is ongoing debate about the merits of closing an inaudible or small PDA strictly to reduce the risk of endarteritis, and likely it is not warranted.[33] In the presence of severe pulmonary hypertension (see Atrial Septal Defect earlier), closure is seldom indicated. Contraindications to ductal closure include irreversible pulmonary hypertension or active endarteritis.

Interventional Options and Outcomes

Transcatheter Treatment (eFig. 75.1).



EFIGURE 75.1 Montage of a patent arterial duct (*arrow*), before and after device occlusion. *AO*, aorta; *MPA*, main pulmonary artery.

Over the past 20 years, the efficacy and safety of transcatheter device closure for ducts smaller than 8 mm have been established, with complete ductal closure achieved in more than 85% of patients by 1 year following device placement, at a mortality rate of less than 1%.[34] In centers with appropriate resources and experience, transcatheter device occlusion should be the method of choice for ductal closure.

Surgical Treatment.

Surgical closure, by ductal ligation and/or division, has been performed for more than 50 years with a

marginally greater closure rate than device closure but somewhat higher rates of morbidity and mortality. Immediate clinical closure (no shunt audible on physical examination) is achieved in more than 95% of patients. Surgical closure is a low-risk procedure in children. The surgical mortality rate in adults is 1% to 3.5% and relates to the presence of pulmonary arterial hypertension and difficult ductal morphology (calcified or aneurysmal) often seen in adults. Surgical closure should be reserved for those in whom the PDA is too large for device closure or at centers without access to device closure.

Reproductive Issues

Pregnancy is well tolerated in women with silent and small PDAs and in patients who were asymptomatic before pregnancy. In women with a hemodynamically important PDA, pregnancy may precipitate or worsen heart failure. Pregnancy is contraindicated in Eisenmenger syndrome because of the high mortality rates for the mother (≈50%) and fetus (≈60%).

Follow-Up

Patients with device occlusion or after surgical closure should be examined periodically for possible recanalization. Silent residual shunts may be found by transthoracic echocardiography. Endocarditis prophylaxis is recommended for 6 months following PDA device closure or for life if any residual defect persists following device closure. Patients with a silent or small PDA do not require endocarditis prophylaxis or follow-up.

Persistent Truncus Arteriosus

Morphology

Persistent truncus arteriosus is an anomaly in which a single vessel forms the outlet of both ventricles and gives rise to the systemic, pulmonary, and coronary arteries. It is always accompanied by a VSD and frequently by a right-sided aortic arch. The truncal valve is usually tricuspid but is quadricuspid in about one third of patients. Truncal valve regurgitation and truncal valve stenosis are each seen in 10% to 15% of patients. There can be a single coronary artery.

Truncus arteriosus is classified anatomically according to the mode of origin of pulmonary vessels from the common trunk. In the commonest type (type I), a partially separate pulmonary trunk of variable length exists and gives rise to left and right pulmonary arteries. In type II, each pulmonary artery arises separately but close to the other from the posterior aspect of the truncus. In type III, each pulmonary artery arises separately from the lateral aspect of the truncus. Less commonly, one pulmonary artery branch may be absent, with aortopulmonary collateral arteries supplying the lung that does not receive a pulmonary artery branch from the truncal artery.

Pathophysiology

Pulmonary blood flow is governed by the size of the pulmonary arteries and the pulmonary vascular resistance. In infancy, pulmonary blood flow is usually excessive because pulmonary vascular resistance is not greatly increased. Thus, in the neonate, only minimal cyanosis is present. With time, the pulmonary vascular resistance increases, relieving the left ventricular volume load but at the price of increasing cyanosis. When pulmonary vascular resistance reaches systemic levels, Eisenmenger physiology and bidirectional shunting occur. Significant truncal valve regurgitation produces a volume load on both the

right and left ventricles because of the biventricular origin of the truncal artery.

Natural History

Most deaths from congestive heart failure occur before 1 year of age. Unoperated patients who survive past 1 year will most likely present with established pulmonary hypertension. The prevalence of truncal valve regurgitation increases with age.

Clinical Features

Infants with truncus arteriosus usually present with mild cyanosis coexisting with the cardiac findings of a large left-to-right shunt. This is the result of excessive pulmonary blood flow due to a low pulmonary vascular resistance. Symptoms of heart failure and poor physical development usually appear in the first weeks or months of life. The most frequent physical findings include cardiomegaly, collapsing peripheral pulses, a loud single second heart sound, a harsh systolic murmur preceded by an ejection click, and a low-pitched middiastolic rumbling murmur and bounding pulses. A decrescendo diastolic murmur suggests associated truncal valve regurgitation.

DiGeorge syndrome may be seen with truncus arteriosus. Facial dysmorphism, a high incidence of extracardiac malformations (particularly of the limbs, kidneys, and intestine), atrophy or absence of the thymus gland, T-lymphocyte deficiency, and a predilection to infection also may be features of the clinical presentation.

The physical findings are different if pulmonary blood flow is restricted by a high pulmonary vascular resistance: cyanosis is prominent, and only a short systolic murmur may be heard in association with an ejection click. Pulmonary vascular obstruction usually does not restrict pulmonary blood flow before 1 year of age.

Adults presenting with an unrepaired truncus arteriosus can be expected to have Eisenmenger syndrome and its typical findings.

Laboratory Investigations in Unrepaired Truncus Arteriosus

ECG.

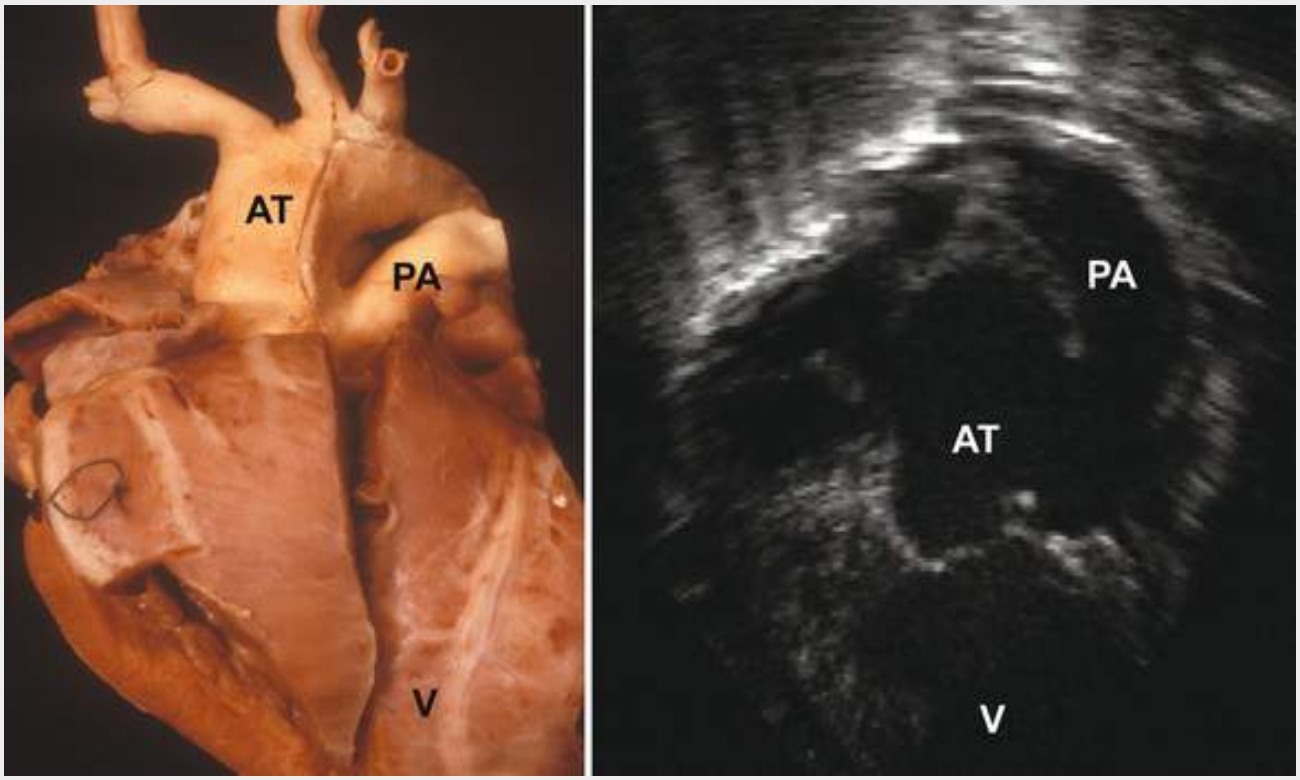
This demonstrates biventricular hypertrophy with strain as the pulmonary resistance rises.

Chest Radiography.

This demonstrates cardiomegaly with prominent pulmonary arterial markings and unusually high hilar areas. A right aortic arch occurs in 50% of cases.

Echocardiography.

In most cases, 2D echocardiography provides a complete diagnosis (**eFig. 75.2**). The study should demonstrate the overriding truncal root, the origin of the pulmonary arteries, the number of truncal cusps, the origin of the coronary arteries, the functional status of the truncal valve, and the VSD size.



EFIGURE 75.2 View of the origin of the pulmonary artery in truncus arteriosus. Note the lateral origin of the pulmonary artery. *AT*, ascending trunk; *PA*, pulmonary artery; *V*, ventricle.

Cardiac Catheterization and Angiography.
Cardiac catheterization and angiography are rarely necessary and in fact carry a risk of both morbidity and death. In general, significant arterial desaturation in the absence of branch pulmonary artery stenosis indicates that the lesion cannot be repaired.

Indications for Intervention

Early surgical intervention, within the first 2 months of life, is indicated in almost all cases. In the presence of severe pulmonary hypertension (see ASD section), surgical intervention is not performed.

Interventional Options and Outcomes

Operation consists of closure of the VSD, leaving the aorta arising from the left ventricle; excision of the pulmonary arteries from their truncal origin; and the placement of a valve-containing prosthetic conduit or aortic homograft valve conduit between the right ventricle and the pulmonary arteries to establish circulatory continuity. Truncal valve regurgitation is a challenging problem and may require valve replacement or repair.

Important risk factors for perioperative death are severe truncal valve regurgitation, an interrupted aortic arch, coronary artery anomalies, and age at initial operation older than 100 days. Patients with only one pulmonary artery are especially prone to early development of severe pulmonary vascular disease.

Reproductive Issues

Patients with a repaired truncus arteriosus and no hemodynamically important residual lesions should tolerate pregnancy well. Patients with significant conduit obstruction and/or important truncal valve regurgitation need prepregnancy counseling, with consideration of correction of the lesions before pregnancy and/or careful follow-up throughout pregnancy. Pregnancy is contraindicated in patients with

Eisenmenger syndrome, given its 50% maternal mortality rate.

Follow-Up

Patients operated on early (< 1 year of age) generally do well. However, conduit change is often indicated within the first few years after repair as the patient outgrows its size.[35] Those patients with significant truncal valve stenosis and/or regurgitation may eventually require truncal valve replacement. Patients operated on late (> 1 year of age) require careful follow-up for any signs of progression of pulmonary hypertension. Endocarditis prophylaxis is required in all patients.

Cyanotic Heart Disease

Tetralogy of Fallot (Including Tetralogy with Pulmonary Atresia)

Morphology

The four components of tetralogy of Fallot are an outlet VSD, obstruction to right ventricular outflow, overriding of the aorta (<5%), and right ventricular hypertrophy (**Figs. 75.23 and 75.24**). The fundamental abnormality contributing to each of these features is anterior and cephalad deviation of the outlet septum, which is malaligned with respect to the trabecular septum. Thus tetralogy may occur in the setting of double-outlet right ventricle (aortic override > 50%) and may coexist with an AV septal defect. Right ventricular outflow tract obstruction is of variable severity. Often a stenotic, bicuspid pulmonary valve with supravalvular hypoplasia exists. The dominant site of obstruction is usually at the subvalve level. In some cases the outflow tract is atretic, and the heart can be diagnosed as having tetralogy of Fallot with pulmonary atresia (also known as *complex pulmonary atresia* when major aortopulmonary collateral arteries are present). The management and outcome for patients with major aortopulmonary collateral arteries differ significantly than in those with less extreme forms of tetralogy and are discussed separately at the end of this section.

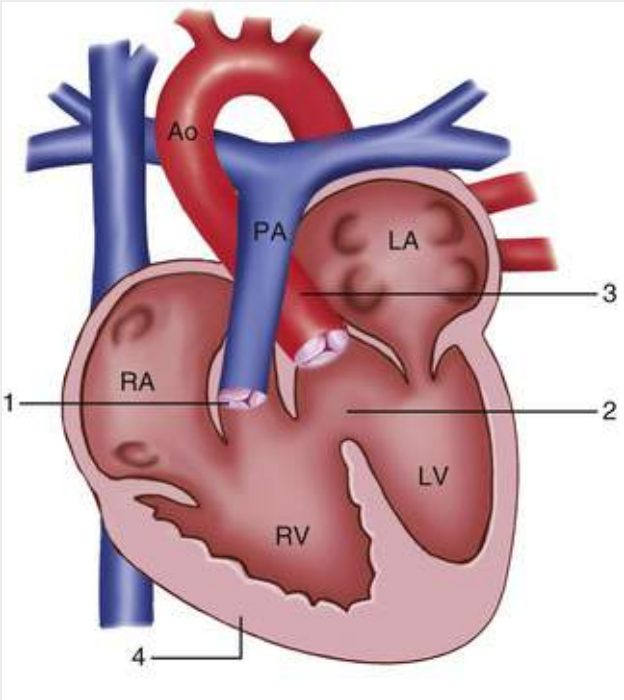


FIGURE 75.23 Diagrammatic representation of tetralogy of Fallot. 1, pulmonary stenosis; 2, ventricular septal defect; 3, overriding aorta; 4, right ventricle hypertrophy. *Ao*, aorta; *LA*, left atrium; *LV*, left ventricle; *PA*, pulmonary artery; *RA*, right atrium; *RV*, right ventricle. (From Mullins CE, Mayer DC: Congenital heart disease: a diagrammatic atlas. New York, Wiley-Liss, 1988.)

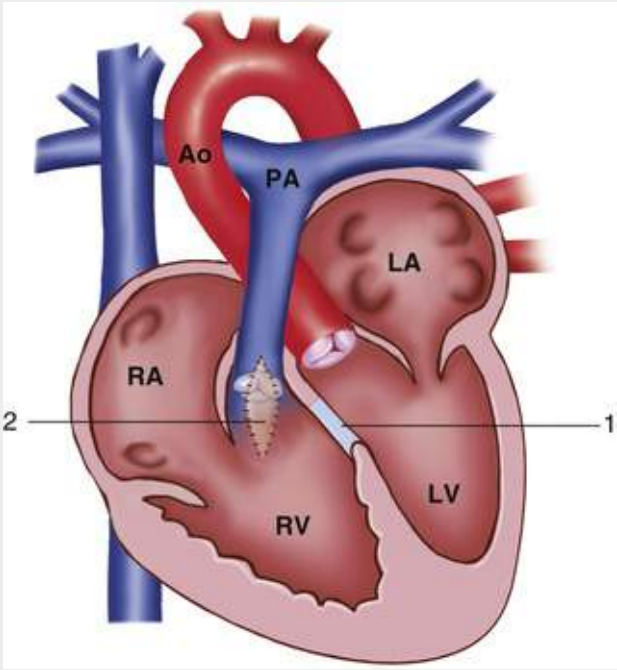


FIGURE 75.24 Diagrammatic representation of the surgical repair of tetralogy of Fallot. 1, patch closure of ventricular septal defect; 2, right ventricular outflow/main pulmonary artery outflow patch (transannular patch). *Ao*, aorta; *LA*, left atrium; *LV*, left ventricle; *PA*, pulmonary artery; *RA*, right atrium; *RV*, right ventricle. (From Mullins CE, Mayer DC: Congenital heart disease: a diagrammatic atlas. New York, Wiley-Liss, 1988.)

Associated Anomalies

A right aortic arch occurs in about 25% of patients, and abnormalities of the course of the coronary arteries occur in approximately 5%. The most common coronary anomaly is when the anterior descending artery originates from the right coronary artery and courses anteriorly to cross the infundibulum of the right ventricle. Furthermore, the origin of the left main stem is often rotated clockwise, increasing the risk of coronary compression during later right ventricular outflow tract stenting or stent-valve placement. *Absent pulmonary valve syndrome* is a rare form of tetralogy in which stenosis and regurgitation of the right ventricular outflow tract are due to a markedly stenotic pulmonary valve ring with poorly formed or absent valve leaflets. The pulmonary arteries are usually markedly dilated or aneurysmal and may produce airway compression at birth, a poor prognostic feature.

Pathophysiology

In the absence of alternative sources of pulmonary blood flow, the degree of cyanosis reflects the severity of right ventricular outflow tract obstruction. There is right-to-left shunting across the VSD. In the unoperated patient, a *tetralogy "spell"* is an acute fall in arterial saturation due to dynamic subpulmonary obstruction, and it may be life threatening. Its treatment is aimed at relieving obstruction and increasing systemic resistance. Relief of hypoxia with oxygen and morphine, intravenous propranolol, and systemic vasoconstriction (e.g., squatting, knee-chest position, vasoconstrictor drugs) usually reverses the cyanosis.

Natural History

Progressive hypoxemia in the first years of life is expected. Survival to adult life is rare without palliation or correction. The presence of additional sources of a blood supply (see later) modifies the rate of progression of cyanosis and its complications.

Clinical Features

Unoperated Patients.

Variable cyanosis exists. A right ventricular impulse and systolic thrill are often palpable along the left sternal border. An early systolic ejection sound that is aortic in origin may be heard at the lower left sternal border and apex; the second heart sound is usually single. The intensity and duration of the systolic ejection murmur vary inversely with the severity of subvalve obstruction—the opposite of the relationship that exists in patients with pulmonary valve stenosis. With extreme outflow tract stenosis or pulmonary atresia and during an attack of paroxysmal hypoxemia, no murmur or only a short, faint murmur may be detected. A continuous murmur faintly audible over the anterior or posterior chest reflects flow through aortopulmonary collateral vessels or a duct.

After Palliative Surgery.

Progressive cyanosis with its complications can result from worsening right ventricular outflow tract obstruction, gradual stenosis and occlusion of palliative aortopulmonary shunts (**see Table 75.5**), or the development of pulmonary hypertension (sometimes seen after Waterston or Potts shunts have been used). Progressive ascending aortic dilation and aortic regurgitation can occur. Central cyanosis and clubbing are invariably present.

After Reparative Surgery.

After intracardiac repair, more than 85% of patients are asymptomatic on follow-up, although objective testing will usually demonstrate a reduction in maximal exercise performance. Palpitations from atrial and ventricular arrhythmias and exertional dyspnea from progressive right ventricular dilation secondary to chronic pulmonary regurgitation or severe residual right ventricular outflow tract obstruction occur in 10% to 15% of patients within 20 years after initial repair. An ascending aortic aneurysm and significant aortic regurgitation from a dilated aortic root may occasionally be present. A parasternal right ventricular lift and a soft and delayed, or absent, P_2 with a low-pitched diastolic murmur from pulmonary regurgitation may exist. A systolic ejection murmur from right ventricular outflow tract obstruction, a high-pitched diastolic murmur from aortic regurgitation, and a pansystolic murmur from a VSD patch leak may also be heard.

Tetralogy of Fallot with Pulmonary Atresia and Major Aortopulmonary Collateral Arteries

This subgroup represents one of the greatest challenges in CHD. The aim of unifocalization surgery is to amalgamate all the sources of pulmonary blood flow and establish unobstructed right ventricular–to–pulmonary artery continuity while achieving a normal pulmonary artery pressure and a closed ventricular septum. When this is not possible, a combined interventional catheterization and surgical approach may be indicated. Balloon dilation and stenting of stenosed arteries and anastomoses can “rehabilitate” the segmental supply and allow subsequent VSD closure; if the VSD has already been closed, it can reduce the right ventricular pressure (Video 75.53).

Laboratory Investigations

ECG.
In adults with repaired tetralogy of Fallot, a complete right bundle branch block following repair has been the rule. The QRS width may reflect the degree of right ventricular dilation and, when extreme (>180 msec) or rapidly progressive, may be a risk factor for sustained ventricular tachycardia and sudden death.

Chest Radiography.
Characteristically, the unrepaired patient has a normal-sized, boot-shaped heart (*coeur en sabot*) with prominence of the right ventricle and a concavity in the region of the underdeveloped right ventricular outflow tract and main pulmonary artery. After repair, the right ventricle is often prominent, and the left heart border tends to be straightened by a dilated right ventricular outflow tract. The aortic arch may be on the right side (25%). The ascending aorta is sometimes prominent.

Echocardiography (Fig. 75.25).
In the *unoperated* patient, the complete diagnosis can usually be established by echocardiography alone. The study should identify the malaligned and nonrestrictive VSD and overriding aorta (< 50% override) and the presence and degree of right ventricular outflow tract obstruction (infundibular, valvular, and/or pulmonary arterial stenosis). Cardiac catheterization is now rarely required before corrective surgery. The exception to this rule is when there are additional sources of pulmonary blood flow.

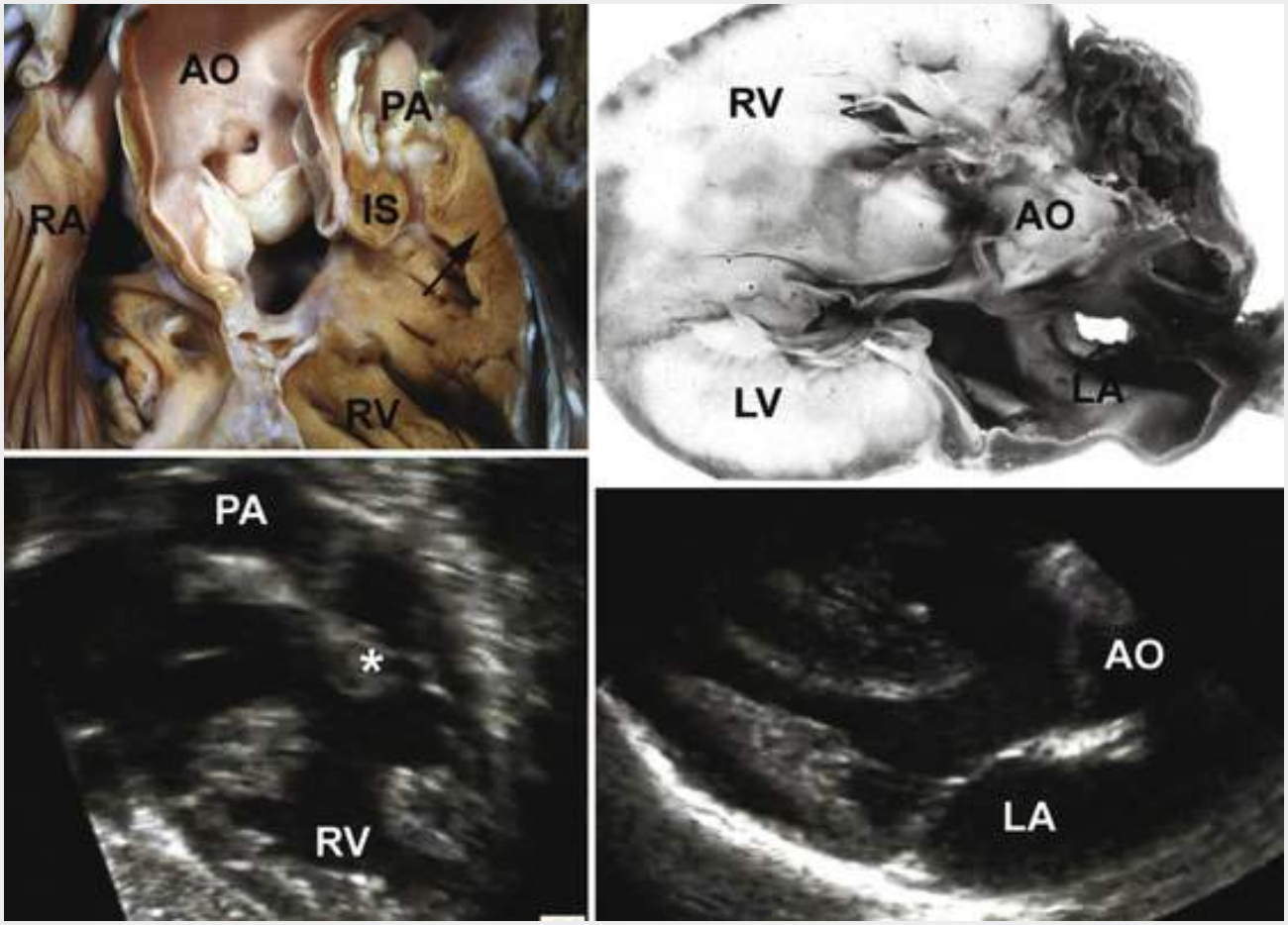


FIGURE 75.25 Montage of tetralogy of Fallot. The two left images are in the right anterior oblique view that demonstrates the anteriorly deviated infundibular septum (*asterisk*) and the VSD. The *arrow* on the specimen points to the hypertrophied septoparietal trabeculations. The right images demonstrate the overriding aorta and the VSD. *AO*, aorta; *IS*, infundibular septum; *LA*, left atrium; *PA*, pulmonary artery; *RA*, right atrium; *RV*, right ventricle.

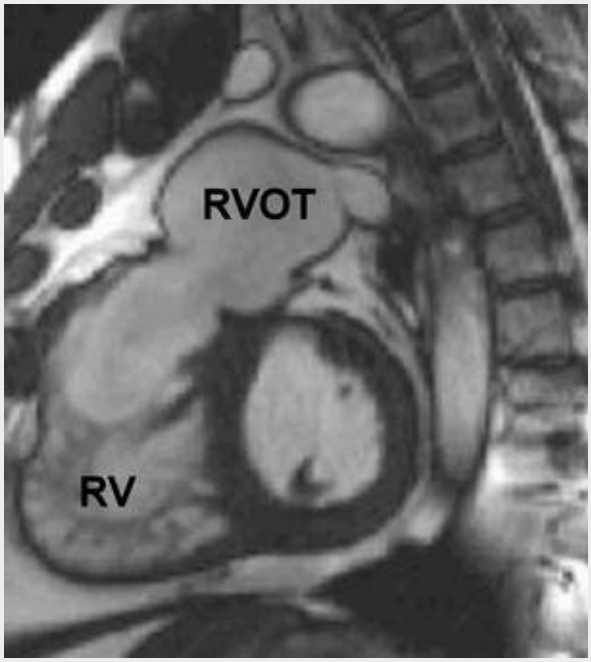
In patients with *repaired* tetralogy of Fallot, the residual pulmonary stenosis and regurgitation, residual VSD, right and left ventricular size and function, aortic root size, and degree of aortic regurgitation should be assessed.

Cardiac Catheterization and Angiocardiography.

Although echocardiography, MRA, and fast computed tomography (CT) may delineate the presence and proximal course of the pulmonary blood vessels, the preoperative assessment of tetralogy with pulmonary atresia with major aortopulmonary collateral arteries usually includes delineation of the arterial supply to both lungs by selective catheterization and angiography to show the course and segmental supply from the collateral arteries and central pulmonary arteries. Major aortopulmonary collateral arteries usually arise from the descending aorta at the level of the tracheal bifurcation.

MRI.

The goals of MRI examination after tetralogy of Fallot repair include the quantitative assessment of the left and, particularly, right ventricular volumes, stroke volumes, and ejection fraction; imaging of the anatomy of the right ventricular outflow tract (**eFig. 75.3**), pulmonary arteries, aorta, and aortopulmonary collaterals; and quantification of pulmonary, aortic, and tricuspid regurgitation.



EFIGURE 75.3 This MRI image after tetralogy repair demonstrates its use in imaging right ventricular outflow tract aneurysms, and in assessing right ventricular volumes. *RV*, right ventricle; *RVOT*, right ventricular outflow tract.

Indications for Intervention

Children.

Symptomatic infants are now repaired at any age, and elective repair in asymptomatic infants during the first 6 months is advocated by many. This is often at the expense of a transannular patch enlargement of the right ventricular outflow tract, which is a risk factor for later reintervention. Marked hypoplasia of the pulmonary arteries, small body size, and prematurity are relative contraindications for early corrective operation; these patients may be successfully palliated by balloon dilation of the right ventricular outflow

tract (with or without stenting) and pulmonary arteries (Video 75.54).

Adults, Unoperated.

For unoperated adults, surgical repair is still recommended because the results are gratifying and the operative risk is comparable to that of pediatric series provided there is no serious coexisting morbidity.

Palliated Patients.

Palliation was seldom intended as a permanent treatment strategy, and most of these patients should undergo surgical repair. In particular, palliated patients with increasing cyanosis and erythrocytosis (from gradual shunt stenosis or development of pulmonary hypertension), left ventricular dilation, or aneurysm formation in the shunt should undergo intracardiac repair with takedown of the shunt unless irreversible pulmonary hypertension has developed.

Repaired Patients.

The following situations *may* warrant intervention after repair: a residual VSD with a shunt greater than 1.5/1; residual pulmonary stenosis (either the native right ventricular outflow or valved conduit if one is present) with right ventricular systolic pressure two thirds or more of systemic pressure; or severe pulmonary regurgitation associated with substantial right ventricular dilation or dysfunction (i.e., right ventricular diastolic volume index > 150 to 170 mL/m^2 or a right ventricular ejection fraction < 45%),[36] exercise intolerance, or sustained arrhythmias. The coexistence of substantial left ventricular dysfunction or a QRS duration of more than 180 msec offers additional support when other indications are present. The development of major cardiac arrhythmias increases over time, and most commonly includes atrial flutter or fibrillation (present in ≤ 20% of patients) or sustained ventricular tachycardia (present in ≤ 14% of patients).[37] The presence of arrhythmias usually reflects hemodynamic deterioration from the right and/or left heart,[37] and should be treated accordingly. Surgery is occasionally necessary for significant aortic regurgitation associated with symptoms or progressive left ventricular dilation and for aortic root enlargement of 55 mm or more. Rapid enlargement of a right ventricular outflow tract aneurysm needs surgical attention.

Interventional Options

Surgery.

Reparative surgery involves closing the VSD with a Dacron patch and relieving the right ventricular outflow tract obstruction. The latter may involve resection of infundibular muscle and insertion of a right ventricular outflow tract or transannular patch (i.e., a patch across the pulmonary valve annulus that disrupts the integrity of the pulmonary valve and causes important pulmonary regurgitation). When an anomalous coronary artery crosses the right ventricular outflow tract and precludes a patch, an extracardiac conduit is placed between the right ventricle and pulmonary artery, bypassing the right ventricular outflow tract obstruction. A PFO or secundum ASD may be closed. Additional treatable lesions such as muscular VSDs, PDAs, and aortopulmonary collaterals may also be addressed at the time of surgery.

Reoperation is necessary in 10% to 15% of patients after reparative surgery over a 20-year follow-up. For persistent right ventricular outflow tract obstruction, resection of a residual infundibular stenosis or placement of a right ventricular outflow or transannular patch, with or without pulmonary arterioplasty, can be performed. Occasionally, an extracardiac valved conduit may be necessary. Pulmonary valve

replacement (either homograft or xenograft) is used to treat severe pulmonary regurgitation. Concomitant tricuspid valve annuloplasty may be performed for moderate or severe tricuspid regurgitation. Concomitant cryoablation may be performed at the time of surgery for patients with preexisting atrial or ventricular arrhythmias.

Transcatheter Valve Replacement.

Percutaneous pulmonary valve replacement (Videos 75.55 and 75.56) can be performed. Compared with surgical pulmonary valve replacement, the mortality rates are similar; the hemodynamic short- and intermediate-term results are favorable; and the morbidity rates are lower. Percutaneous replacement should be done only in CHD centers with expertise in the procedure, however. At present, these therapies are reserved primarily for patients with circumferential right ventricle–pulmonary artery conduits (i.e., homografts, valved conduits) measuring less than 22 mm, although transcatheter pulmonary valve replacements have been performed in patients with native right ventricular outflow tracts.[38] Significant branch pulmonary artery stenosis can be managed with balloon dilation and usually stent insertion.

Implantable Cardioverter-Defibrillator.

When a patient presents with aborted sudden death or sustained ventricular tachycardia, implantable cardioverter-defibrillator (ICD) placement should be considered as a secondary prevention measure,[39] unless there is compelling evidence that a hemodynamic issue could correct the risk for subsequent events. The selection of appropriate candidates for primary prevention ICDs remains controversial. ICDs are probably best reserved for those with a high annual risk of adverse events (≥ 3.5%/year), a group that includes patients with combinations of a prior palliative shunt, QRS higher than 180 msec, inducible ventricular tachycardia, and raised left ventricular end-diastolic pressure.

Interventional Outcomes

The overall survival rate of patients who have had an initial operative repair is excellent, provided the VSD has been closed and the right ventricular outflow tract obstruction has been relieved. A 25-year survival rate of 94% has been reported. Pulmonary valve replacement for chronic pulmonary regurgitation or right ventricular outflow tract obstruction after initial intracardiac repair can be done safely; the mortality rate is 2%. Pulmonary valve replacement, when it is performed for significant pulmonary regurgitation, leads to an improvement in exercise tolerance as well as favorable right ventricular remodeling.[36] Sudden death can occur. Ventricular tachycardia can originate at the site of the right ventriculotomy, from VSD patch sutures, or from the right ventricular outflow tract. Patients at high risk for sudden death include those with right ventricular dilation and a QRS duration of 180 msec or more on the ECG. Moderate-to-severe left ventricular dysfunction is another risk factor for sudden death.[37,39,40] The reported incidence of sudden death is approximately 5%, which accounts for approximately one third of late deaths during the first 20 years of follow-up.

Reproductive Issues

Patients with repaired tetralogy of Fallot can go through pregnancy relatively safely, with an adverse cardiovascular event rate of between 8% and 17%.[23,40] The events are mainly arrhythmias and a worsening NYHA class resulting from right heart failure.[41] The outcome of the offspring relates to the maternal cardiovascular status prior to pregnancy, as well as cardiovascular events during pregnancy. Women with repaired tetralogy of Fallot should be followed diligently during pregnancy. Chromosomal

abnormalities in a parent, such as the CATCH 22 syndrome, have a 50% chance of transmission to the offspring.

Follow-Up

All patients should have expert cardiologic follow-up every 1 to 2 years.

Lesions That Require the Fontan Procedure

The next four sections describe lesions usually or often treated with a Fontan procedure. These include tricuspid atresia, hypoplastic left heart syndrome, double-inlet ventricle, and isomerism. The *Fontan procedure* has become a generic term to describe a palliative surgical procedure that redirects the systemic venous return directly to the pulmonary arteries without passing through a subpulmonary ventricle. It is performed in patients having a functionally single ventricle or in those for whom a biventricular intracardiac repair is not possible, even though there are two good-sized ventricles. Although undoubtedly imperfect, the Fontan circuit restores an in-series pulmonary-to-systemic circulation, removing the chronic volume load of the systemic ventricle previously supporting a parallel circuit of pulmonary and systemic circulations. The earliest iteration of the Fontan procedure was a simple “atriopulmonary” connection, whereby the right atrium or its appendage was anastomosed to the pulmonary arteries. Because of the long-term problems of atrial dilation, arrhythmia, and thrombosis, this procedure has been abandoned in favor of hemodynamically superior versions. In the early 1990s, the total cavopulmonary anastomosis or lateral-tunnel Fontan procedure was introduced. This consisted of a direct, end-to-side superior cavopulmonary anastomosis (bidirectional Glenn operation) in combination with an intraatrial baffle or tube connection of the inferior vena cava to the underside of the confluent pulmonary arteries. More recently, the inferior vena cava has been directed to the pulmonary arteries via an extracardiac conduit, completely excluding the atrium from the circuit. It remains to be seen whether these modifications will have the desired effect of reducing late morbidity, and all patients will require regular and careful review in special centers.

Tricuspid Atresia (Absent Right Atrioventricular Connection)

Morphology

Classic tricuspid atresia is best described as absence of the right AV connection (**Figs. 75.26 and 75.27**, and see Videos 75.22 and 75.23). Consequently, there must be an ASD. There is usually hypoplasia of the morphologic right ventricle, which communicates to the dominant ventricle via a VSD. Patients may be subdivided into those with concordant ventriculoarterial connections and normally related great arteries (70% to 80% of cases) and those with discordant connections, where the aorta arises from the small right ventricle and is fed via the VSD. Associated lesions in the latter group include subaortic stenosis and aortic arch anomalies.

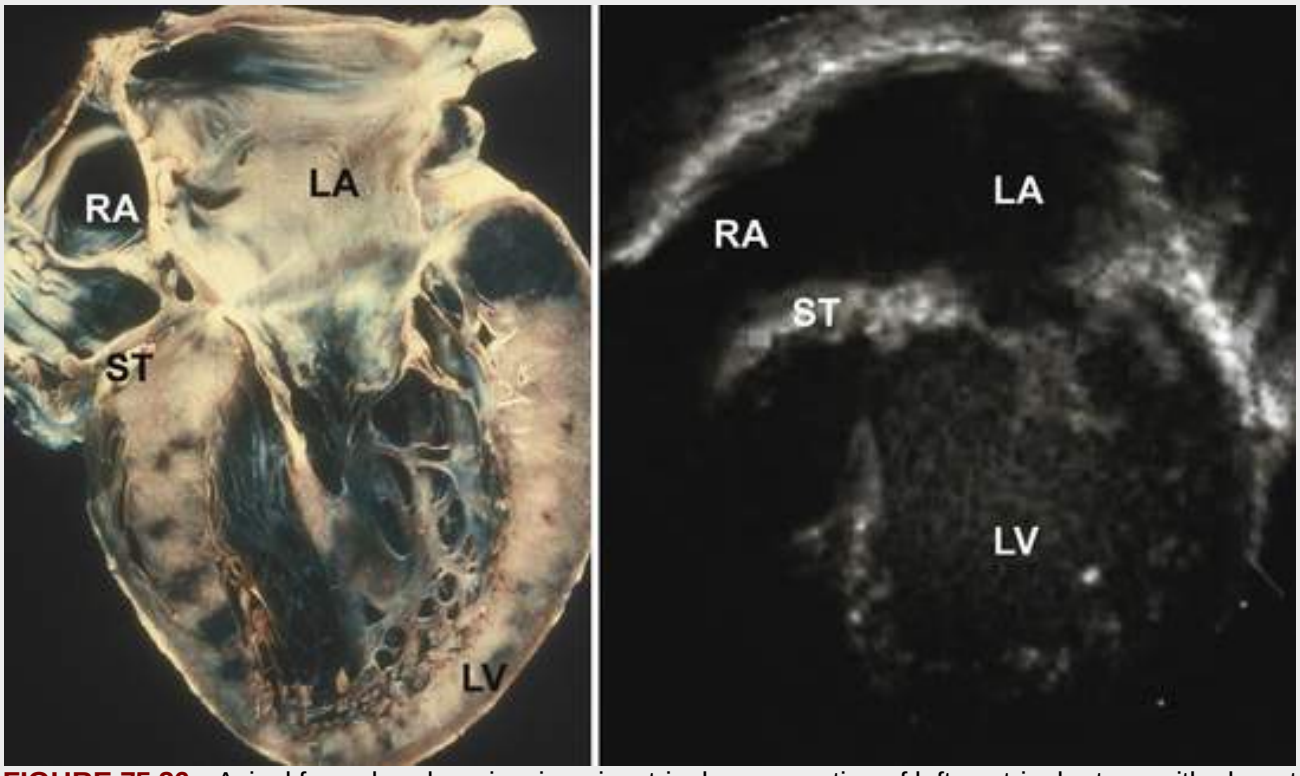


FIGURE 75.26 Apical four-chamber view in univentricular connection of left ventricular type with absent right connection (tricuspid atresia). Note the wedge of sulcus tissue in the floor of the right atrium. *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium; *ST*, sulcus tissue.

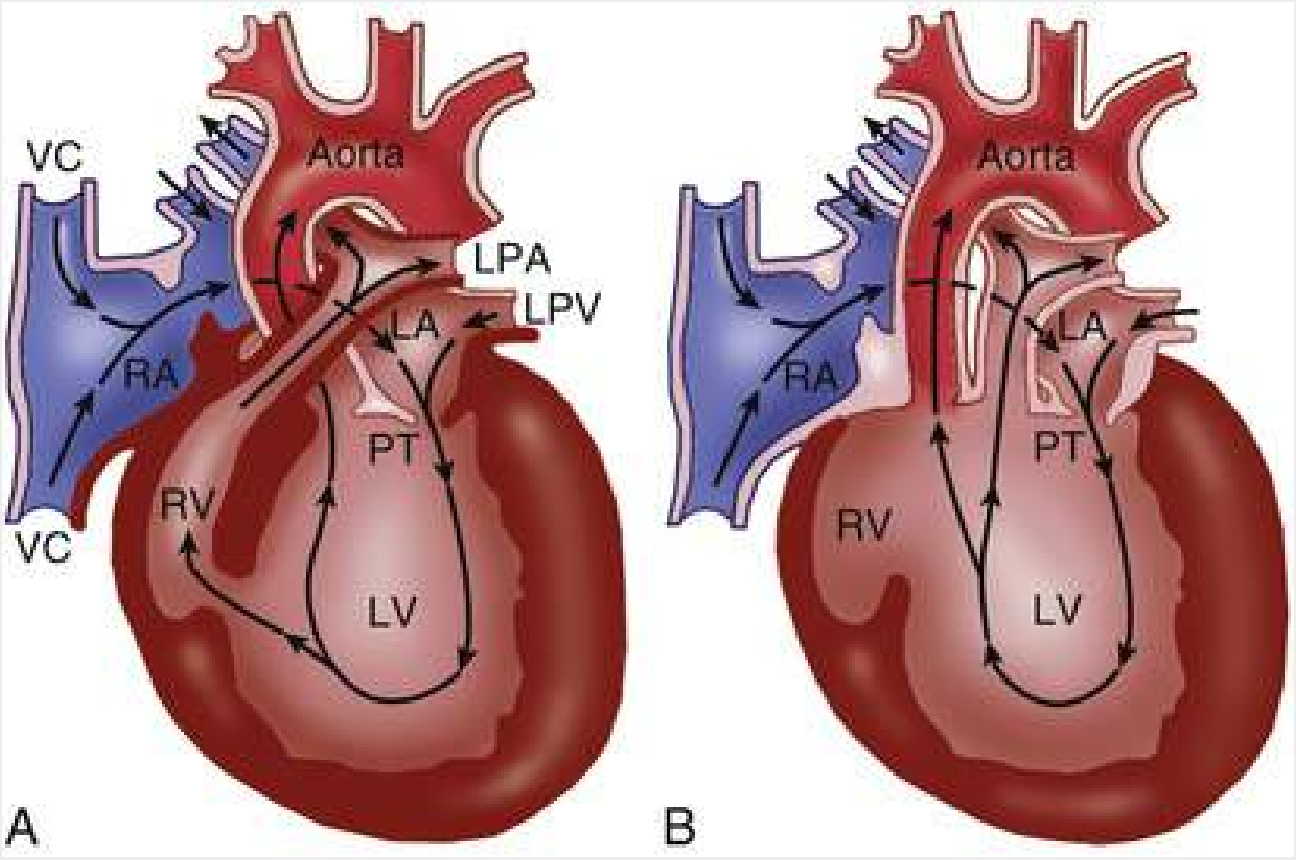


FIGURE 75.27 **A,** Tricuspid atresia with normally related great arteries, a small VSD, diminutive right ventricular chamber, and narrowed outflow tract. **B,** An example of tricuspid atresia and complete transposition of the great arteries in which the left ventricular chamber is essentially a common ventricle, with the aorta arising from an infundibular component (RV) of the common ventricle. *LA*, left atrium; *LPA*, left pulmonary artery; *LPV*, left pulmonary vein; *LV*, left ventricle; *PT*, pulmonary trunk; *RA*, right atrium; *RV*, right ventricle; *VC*, vena cava. (**A** and **B,** Modified from Edwards JE, Burchell HB: Congenital tricuspid atresia: classification. Med Clin North Am 33:1177, 1949.)

Pathophysiology

The clinical picture and management are dominated by issues related to the ventriculoarterial connections. All patients have “mixing” of atrial blood, and thus their degree of cyanosis is governed by the amount of pulmonary blood flow and systemic venous saturations. Patients with concordant ventriculoarterial connections tend to be more cyanosed (depending on the size of the VSD), whereas those with discordant connections are pinker and tend to develop heart failure (because the unobstructed pulmonary circulation arises directly from the left ventricle). Some present with a critical reduction of systemic blood flow because of obstruction at the VSD and/or associated aortic arch anomalies and behave much like patients with hypoplastic left heart syndrome.

Laboratory Investigations

ECG.

Left axis deviation, right atrial enlargement, and left ventricular hypertrophy often occur. Left atrial enlargement may be present if the pulmonary flow is high.

Chest Radiography.

Situs solitus, levocardia, and a left-sided aortic arch usually occur. The heart size and pulmonary vascular markings vary with the amount of pulmonary blood flow. The main pulmonary trunk is inapparent. A right aortic arch exists in 25% of patients.

Echocardiography.

This establishes the full segmental diagnosis. The size of the ASD, VSD, and aortic arch all must be carefully assessed.

Cardiac Catheterization.

This is rarely required for the initial diagnosis or management. It can be useful to assess the degree of subaortic stenosis (by assessing the change in left ventricle–to–aorta pressure gradient while performing an isoprenaline or dobutamine challenge) and is usually performed to measure the pulmonary artery pressure and resistance prior to venopulmonary connections.

Management Options.

In patients with concordant ventriculoarterial connections and severe cyanosis, a systemic-to-pulmonary shunt is performed in the first 6 to 8 weeks of life. In older children, a primary bidirectional Glenn procedure can be considered. In infants with discordant arterial connections, early palliation ranges from pulmonary artery banding to reduce pulmonary blood flow when there is no subaortic narrowing to a full Norwood stage 1 procedure in patients presenting with severe stenosis and a hypoplastic ascending aorta and arch.

The aim of early palliation is to prepare for a Fontan procedure. This should be performed only when there is good ventricular function, unobstructed systemic blood flow, and minimal AV valve regurgitation. Candidates for these corrective procedures must also have a low pulmonary resistance, a mean pulmonary artery pressure of less than 15 mm Hg, and pulmonary arteries of adequate size.

Hypoplastic Left Heart Syndrome

Hypoplastic left heart syndrome is a generic term used to describe a group of closely related cardiac anomalies characterized by underdevelopment of the left cardiac chambers, in association with atresia or stenosis of the aortic and/or the mitral orifices, and hypoplasia of the aorta. The term should be restricted to those with normally connected hearts with concordant AV and ventriculoarterial connections. Hypoplastic left heart syndrome (**Fig. 75.28**) is characterized by duct-dependent systemic blood flow and so tends to present with severe symptoms within the first week of life, as ductal constriction occurs. Untreated, the disease is almost uniformly fatal in infancy. In the past, many infants would present with severe acidemic circulatory collapse, but this is becoming less frequent as fetal ultrasound screening for cardiac anomalies becomes more generally available and successful. Fetal diagnosis allows for a planned delivery and institution of prostaglandin therapy from birth and has now been proven to reduce subsequent preoperative morbidity rates and perioperative mortality rates during the first stage of surgical repair.

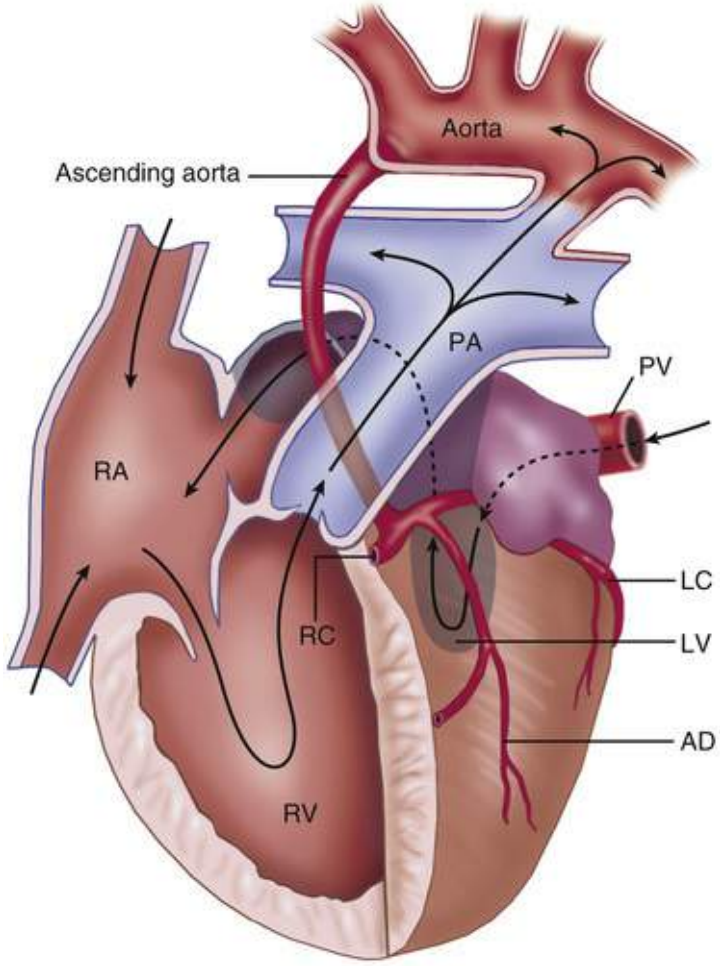


FIGURE 75.28 Hypoplastic left heart with aortic hypoplasia, aortic valve atresia, and a hypoplastic mitral valve and left ventricle. AD, anterior descending; LC, left circumflex; LV, left ventricle; PA, pulmonary artery; PV, pulmonary vein; RA, right atrium; RC, right coronary artery; RV, right ventricle. (From Neufeld HN, Adams P Jr, Edwards JE, et al: Diagnosis of aortic atresia by retrograde aortography. Circulation 25:278, 1962.)

Pathophysiology

It remains uncertain whether hypoplastic left heart syndrome reflects a primary myocardial disease or is a consequence of a structural or hemodynamic abnormality. There is no doubt that in some patients, an apparently isolated dilated cardiomyopathy in early fetal life may evolve (as a result of a subsequent lack of left ventricular growth) into hypoplastic left heart syndrome later in gestation. Congenital structural abnormalities clearly play a significant role as well. This is exemplified by the effect of isolated valvular stenosis to produce a continuum of hypoplastic left heart syndrome to critical aortic stenosis with a normal-sized left ventricle. Therefore, hypoplastic left heart syndrome is likely multifactorial in origin.

Clinical Features.

The diagnosis should be considered in any infant with a sudden onset of circulatory collapse and severe lactic acidosis. As such, it must be distinguished from neonatal sepsis and metabolic disorders. Until excluded, any child presenting in this way should be treated with prostaglandin, which may have a dramatically positive effect if there is an underlying cardiac abnormality and little effect if there is not.

Laboratory Investigations

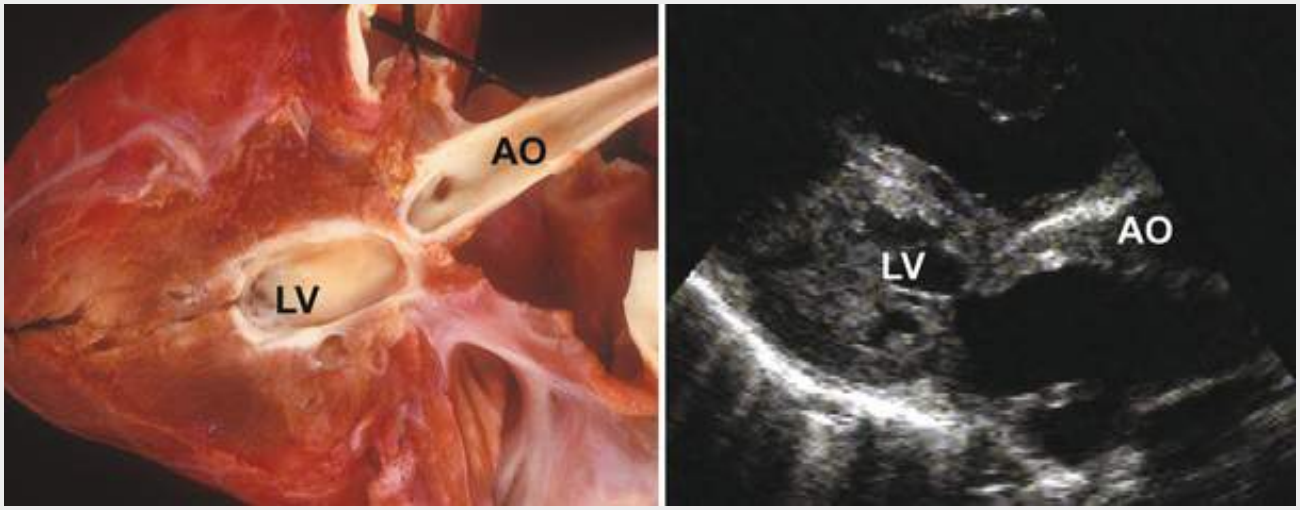
ECG.

This frequently shows right axis deviation, right atrial and ventricular enlargement, and ST and T wave abnormalities in the left precordial leads.

Chest Radiography.

This usually shows some cardiac enlargement shortly after birth, but with clinical deterioration there may be marked cardiomegaly and increased pulmonary venous and arterial vascular markings.

Echocardiography (eFig. 75.4).



EFIGURE 75.4 Long axis view of the left ventricle and aorta in hypoplastic left heart syndrome. Note the associated endocardial fibroelastosis in the specimen. *AO*, aorta; *LV*, left ventricle.

Cross-sectional echocardiography provides a full segmental diagnosis. In its classic form, the left ventricular cavity is small, with a diminutive mitral valve. The myocardium may be thinned or be of normal thickness, but the endocardium is usually thickened, consistent with endocardial fibroelastosis. There may be fistulous communications between the left ventricular cavity and the coronary arteries, a feature much more likely when the mitral valve is patent and the aortic valve atretic. The aortic root is usually diminutive, less than 4 to 5 mm in diameter at the level of the sinuses of Valsalva, and narrowed in its ascending portion. The aortic arch is usually larger, but there is often a juxtaductal coarctation. The duct varies in size according to treatment, and assessment of this and the size of the interatrial communication is crucial to management. There may be profound desaturation and rapid demise (because of a combination of reduced pulmonary blood flow and pulmonary edema) in children with an intact atrial septum or restrictive PFO.

Management Options.

Early treatment with prostaglandin is mandatory. Patients presenting in shock require paralysis, mechanical ventilation, and inotropic support. Crucial to managing these patients is maintenance of a balanced pulmonary and systemic blood flow. The cardiac output is fixed and is distributed according to the relative magnitude of the systemic and pulmonary vascular resistance. Thus measures to elevate the pulmonary resistance (by imposing hypercapnia or by alveolar hypoxia) and reduce the systemic

resistance (using vasodilators) are frequently required.

Staged *surgical management* now provides long-term palliation to most patients with hypoplastic left heart syndrome. The first stage, often referred to as the *Norwood procedure*, now has many versions, but its essence is the creation of an unobstructed communication between the right ventricle and an unobstructed aorta. The right ventricular–to–aortic connection is accomplished by direct connection between the transected proximal pulmonary trunk and ascending aorta, usually with a patch extending around the augmented aortic arch. Pulmonary blood flow is established via a systemic-to-pulmonary shunt or the more recently introduced right ventricle–to–pulmonary artery conduit. The PDA is ligated, and a large interatrial communication is created. Early results of this procedure were poor, but survival rates higher than 85% have recently been published. Institutional variations, the interval mortality rate, and cases in which a patient is unsuitable for progression to stage 2 must be taken into account, however, and in some centers, the preferred operation is cardiac transplantation.

Stage 2 consists of an end-to-side superior vena cava–to–pulmonary artery connection (bidirectional Glenn procedure) or a hemi-Fontan procedure (incorporating the roof of the atrium into the pulmonary artery anastomosis). This is performed at approximately 6 months of age as an intermediate step before stage 3, a Fontan operation. A newer innovation is the so-called hybrid procedure, whereby at the first stage each pulmonary artery is banded separately and then, to maintain ductal patency, a stent is placed by the interventional cardiologist, either directly via the main pulmonary artery in concert with the surgeon or percutaneously. The second stage combines the surgical aortopulmonary anastomosis with the bidirectional Glenn procedure. It remains to be seen whether this approach confers a survival or physiologic advantage.

The *adult survivors* of the early attempts at staged Norwood palliation are now entering adult life. Their issues are likely to be common to all late survivors of Fontan palliation with a systemic right ventricle (see below).

Double-Inlet Ventricle

The double-inlet connection falls under the umbrella of univentricular AV connections. In these hearts, more than 50% of each AV connection is attached to a dominant ventricle. In practice this usually means the whole of one junction and more than 50% of the alternative junction are connected to either a left or right ventricle. When there is a common junction, more than 75% of the junction must be connected to the dominant ventricle.

Morphology

In about 75% of patients, the dominant ventricle is a left ventricle that is separated from the right ventricle by a VSD. In 20%, the dominant ventricle is a right ventricle, and the small, incomplete ventricle is of left ventricular apical morphology. In only 5% of cases is there truly only one ventricle in the ventricular mass. In double-inlet left ventricle, the most common ventriculoarterial connection is discordant. Thus the aorta arises from the small right ventricle and is fed via the VSD, and the generally unobstructed pulmonary artery arises from the left ventricle. Aortic and aortic arch anomalies are frequent in these patients.

Pathophysiology

The basic circulatory physiology of *double-inlet left ventricle* is identical to that of tricuspid atresia.

Common mixing of systemic and pulmonary venous blood occurs, and the blood is then ejected from the left ventricle into the pulmonary artery (with discordant connections) or aorta (with concordant connections). In the former the blood must pass through the VSD to gain egress to the aorta. Subaortic stenosis, aortic hypoplasia, and arch anomalies are therefore common. In *double-inlet right ventricle*, it is those patients with concordant ventriculoarterial connections who are at particular risk of systemic outflow obstruction. One or the other, or both, of the two AV valves (when present) may be stenotic, atretic, or regurgitant. Under these circumstances the integrity of the atrial septum becomes important. If there is left or right atrial outflow obstruction, a septectomy or septostomy will be required.

Clinical Features.

When there is critical reduction of systemic outflow, infants may be duct dependent and present with acidemic shock. Conversely, when pulmonary blood flow is reduced, the presentation may be with severe cyanosis or with duct-dependent pulmonary blood flow. Other patients may not present in the neonatal period and will develop heart failure because of increased pulmonary blood flow. Patients undergo the same surgical algorithms as those with tricuspid atresia and so ultimately will undergo a Fontan operation. Their clinical issues are typical of any patient after this procedure.

Laboratory Investigations

ECG.

This is highly variable. Ventricular hypertrophy appropriate to the dominant ventricle is expected.

Chest Radiography.

This is similarly variable and rarely diagnostic.

Echocardiography (Fig. 75.29 and see Videos 75.11 through 75.13)

A full segmental diagnosis should be possible in all patients. Particular attention should be paid to defining AV valve anomalies and the presence and anatomy of any subaortic obstruction. Obstruction may develop even if it is not present at birth, and surveillance for it should be part of the routine examination of these patients.

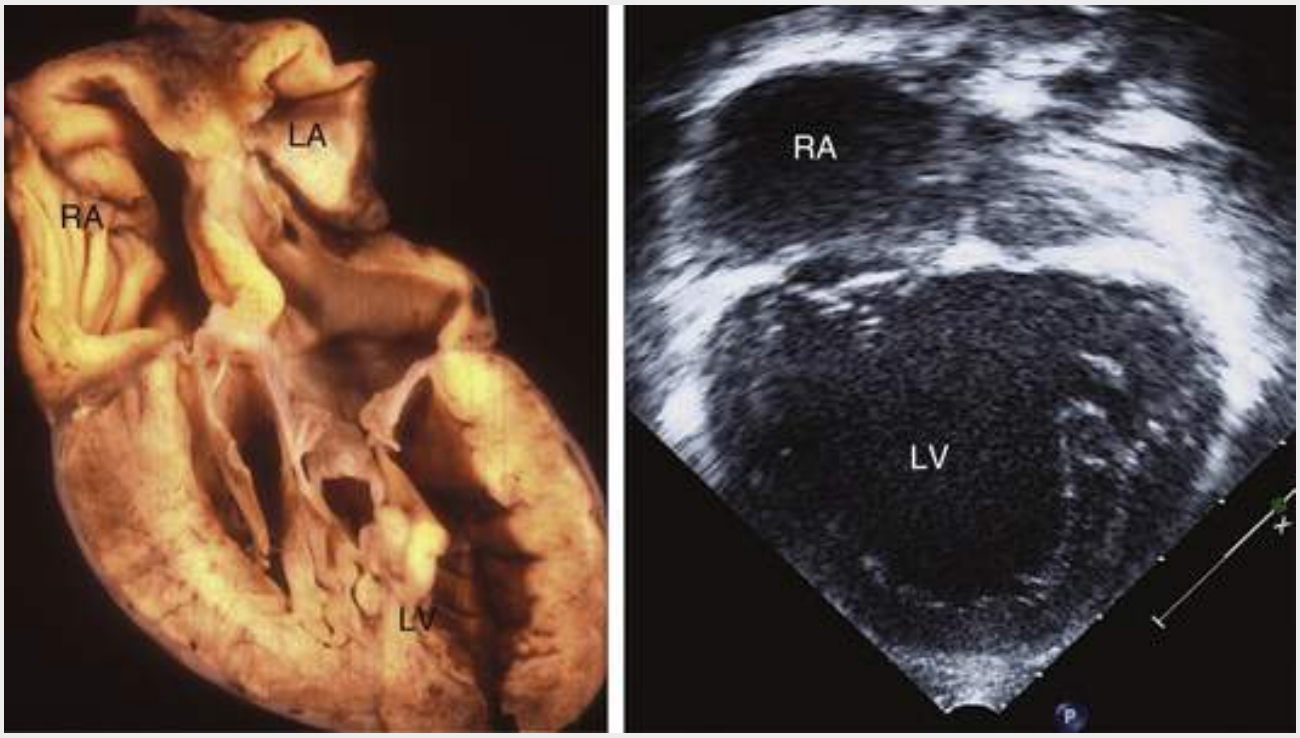


FIGURE 75.29 Apical four-chamber view in a double-inlet univentricular connection of left ventricular type with two AV valves. *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium.

Indications and Options for Intervention.

Survival times without intervention may be prolonged, but at the expense of increasing cyanosis (when there is restriction to pulmonary blood flow) or pulmonary vascular disease (when there is unrestricted pulmonary blood flow). Those born with restricted systemic blood flow require urgent surgical intervention; they usually undergo a Norwood-type repair to establish the pulmonary valve as the unobstructed systemic outflow tract. Pulmonary artery banding is only offered to those infants with pulmonary overcirculation, heart failure, and unobstructed systemic outflow. Subsequently, and sometimes as the primary procedure, a bidirectional Glenn anastomosis is performed as a prelude to a Fontan procedure.

Follow-Up.

These patients should be reviewed frequently and in a center conversant with the issues of the Fontan operation.

Isomerism

For the purposes of illustrating the cardiac manifestations, isomerism describes the situation in which both atrial appendages have either left or right anatomic features (i.e., bilateral right or bilateral left atrial appendages).

Morphology

In left isomerism it is not unusual to have a biventricular AV connection, with separate AV junctions. A common junction (with an AV septal defect) is seen in approximately 30% of cases of left isomerism and more than 90% of hearts with right isomerism. Concordant ventriculoarterial connections predominate in

left isomerism, and a double-outlet right ventricle with an anterior aorta is most frequently seen when there is right isomerism. The venous connections are variable. These variations significantly affect the clinical and interventional management of these patients.

Isomerism of the Right Atrial Appendages

Clinical Features.

Bilateral "right-sidedness" results in a pattern of visceral abnormalities sometimes described as *asplenia syndrome*. The liver is at the midline, both lungs are trilobed with symmetrically short bronchi on the chest radiograph, and the spleen is hypoplastic or absent. The latter mandates immunization against pneumococcal infection and continuous penicillin prophylaxis against gram-positive sepsis. The diagnosis can be inferred from the bronchial pattern on the chest radiograph but most often is established by cross-sectional echocardiography because of early presentation with severe CHD. Abdominal scanning shows an ipsilateral arrangement of the aorta and an anterior inferior vena cava. The intracardiac anatomy is most often that of an AV septal defect with varying degrees of right ventricular dominance, and frequently there is an associated double-outlet right ventricle with an anterior aorta, and subpulmonary stenosis or atresia. Thus cyanosis is the most common presentation. The inferior vena cava may connect to either right atrium, and superior venae cavas are often lateralized and separate. It is the pulmonary venous drainage that is crucial to the presentation and outcome of these children. By definition, the pulmonary veins are draining anomalously to one or the other right atrium, but frequently this is indirect and/or obstructed. Adequate repair of the latter is fundamental to the outcome of these children, who almost uniformly ultimately require a Fontan procedure.

Management Options and Outcomes.

Initial palliation is usually directed toward regulating pulmonary blood flow and dealing with anomalies of pulmonary venous connection. Subsequently these patients (even when there are equal-sized ventricles) are treated along a Fontan algorithm. This is because repair of a complete AV septal defect in the setting of abnormal ventriculoarterial connections is technically difficult or impossible. Thus a unilateral or bilateral superior cavopulmonary anastomosis is performed at approximately 6 months of age, followed when possible by a Fontan procedure at age 2 to 4 years.

The long-term outcome of surgery for right isomerism, however, has been poor, and relatively few patients will be seen in adult CHD clinics. However, improved early palliation and a staged approach toward the Fontan procedure have led to improved results, and more patients with extremely complex underlying disease can be expected to survive into adult life.

Isomerism of the Left Atrial Appendages

Clinical Features.

These patients have bilateral "left-sidedness." Hence they have two left lungs and bronchi, tend to have polysplenia, and frequently have malrotation of the gut. The cardiac abnormalities tend to be less severe than those of right isomerism. These patients are particularly prone to develop atrial arrhythmias because, in them, the normal sinoatrial node is a right atrial structure and is usually absent. The ECG often shows an abnormal P wave axis or wandering pacemaker. Complete heart block may also occur. The anatomic diagnosis is usually established by echocardiography. The abdominal great vessels are both to the right or left of the spine, as with right isomerism, but in left isomerism the vein is a posterior azygos vein that

continues to connect to a left- or right-sided superior vena cava. The intrahepatic inferior vena cava is absent in 90% of patients, and under these circumstances the hepatic veins drain directly to the atria. The pulmonary venous connection needs to be defined precisely before any surgical intervention. Pulmonary arteriovenous malformations are not infrequently seen in patients with left isomerism. These can lead to cyanosis in unoperated or operated patients. The intracardiac anatomy varies from essentially normal to complex. Again, AV septal defect (partial and complete) is overrepresented but with less frequent ventricular imbalance and abnormalities of ventriculoarterial connection.

Management Options.

A biventricular repair is achieved in many more of these patients, albeit with the need for complex atrial baffle surgery to separate the systemic and pulmonary venous returns. The long-term outcome for patients with left isomerism is therefore much better than for those with right isomerism. The issues are much like those related to the type of surgery, but monitoring for arrhythmia needs to be even more intense than usual.

The Fontan Patient (Fig. 75.30)

As stated in the introduction to this section, the uncertain nature of the Fontan circulation and the frequency of its failure require that all patients be followed regularly in a specialized center for CHD, and new symptoms should prompt early reevaluation in such a center.

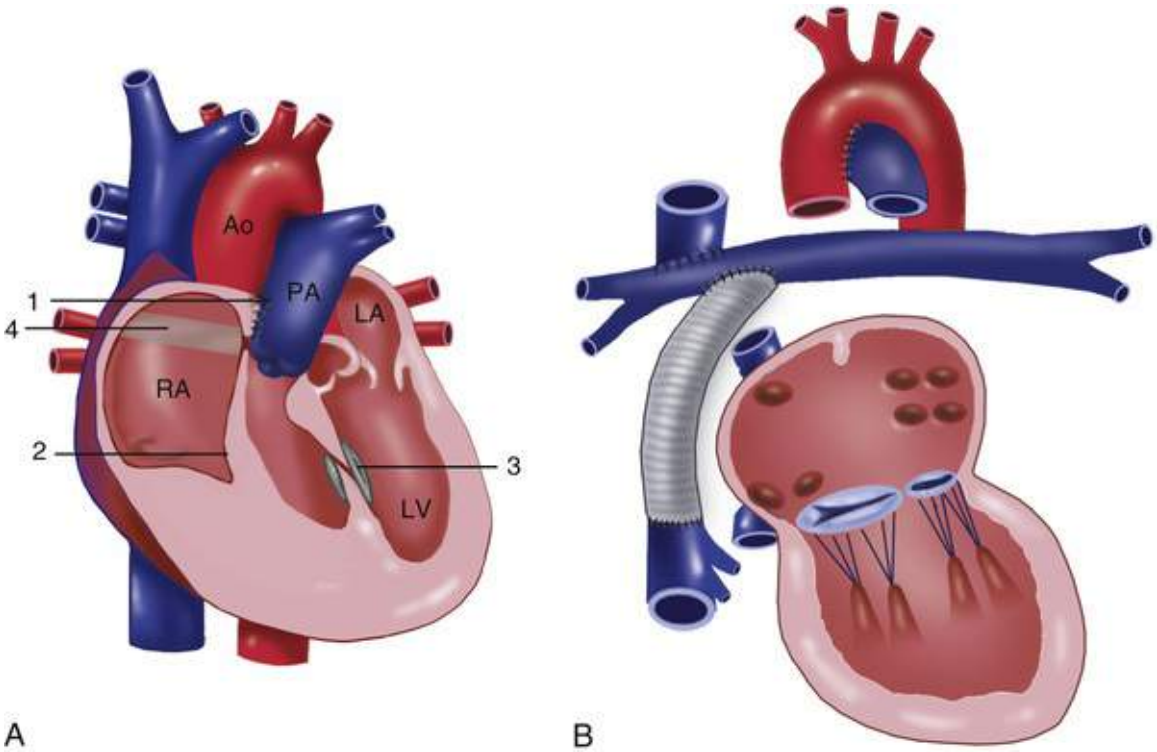


FIGURE 75.30 Modification of the Fontan operation. **A,** Direct atriopulmonary connection (1) for tricuspid valve atresia (2); VSD, oversewn (3); patch closure of ASD (4). **B,** Extracardiac conduit made of a Dacron graft bypassing the right atrium, connecting the inferior vena cava to the inferior aspect of the right pulmonary artery. Superior vena cava is anastomosed to the superior aspect of the right pulmonary artery. *Ao*, aorta; *LA*, left atrium; *LV*, left ventricle; *PA*, pulmonary artery; *RA*, right atrium. (**A,** From Mullins CE, Mayer DC: Congenital heart disease: a diagrammatic atlas. New York, Wiley-Liss, 1988; **B,** from Marcelletti C: Inferior vena cava–pulmonary artery extracardiac conduit: a new form of right heart bypass. J Thorac Cardiovasc Surg 100:228, 1990.)

Since its description for the surgical management of tricuspid atresia in 1971, the Fontan procedure has

become the definitive palliative surgical treatment when a biventricular repair is not possible. The principle is diversion of the systemic venous return directly to the pulmonary arteries without passing through a subpulmonary ventricle. Over the years, many modifications of the original procedure have been described and performed, namely, direct atriopulmonary connection, total cavopulmonary connection, and extracardiac conduit. Fenestration (4 to 5 mm in diameter) of the Fontan circuit into the left atrium is sometimes performed in high-risk patients at the time of surgery, permitting right-to-left shunting and decompression of the Fontan circuit.

Pathophysiology

Elevation of the central venous pressure and a reduced cardiac output (sometimes at rest but always during exercise) are inevitable consequences of the Fontan procedure. Small adverse changes in ventricular function (particularly diastolic); circuit efficiency (elevated pulmonary resistance, obstruction, thrombosis); or the onset of arrhythmia all potentially lead to major symptomatic deterioration.

Although it is reasonable to describe patients after the Fontan procedure as existing in a form of chronic heart failure (because their central venous pressure must be high), this is seldom due to marked systolic dysfunction. Indeed, a small elevation in ventricular diastolic pressure may be much more harmful. Thus it may be incorrect to treat these patients with traditional heart failure medications. *Indeed, in a randomized, blinded placebo-controlled study, ACE inhibition failed to improve ventricular function*[42] *or functional performance, and exercise cardiac output worsened.*

The more "streamlined" Fontan circulations (total cavopulmonary anastomosis, extracardiac conduit) that exclude the right atrium from the circulation have demonstrably better fluid dynamic properties and improved functional performance. Physical obstruction at any or all of the surgical anastomoses, the distal pulmonary arteries, or pulmonary veins (often due to compression by a dilated right atrium) reduces the circulatory efficiency, however. Similarly, elevated pulmonary arteriolar resistances have adverse effects. This is because pulmonary vascular resistance is the single biggest contributor to impairment of venous return and elevation of venous pressure. Relatively little is known about pulmonary vascular resistance late after the procedure, but it has been shown to be elevated in a significant number of patients and to be reactive to inhaled nitric oxide, suggesting pulmonary endothelial dysfunction.

Recently, beneficial effects on exercise performance were shown with bosentan[43] *and sildenafil*[44] *treatment, but this remains to be confirmed in larger studies.*

Clinical Features

The majority of patients (≈90%) present with functional class I to II disease at 5 years' follow-up after a Fontan procedure. Progressive deterioration of functional status with time is the rule. Supraventricular arrhythmias such as atrial tachycardia, flutter, and fibrillation are common. Physical examination in an otherwise uncomplicated patient reveals an elevated, usually nonpulsatile, jugular venous pulse, hepatomegaly early, and a smaller cirrhotic liver later, a quiet apex, a normal S_1, and a single S_2 (the pulmonary artery having been tied off). A heart murmur should not be present, and its identification may suggest the presence of systemic AV valve regurgitation or subaortic obstruction. Generalized edema and ascites may be a sign of protein-losing enteropathy (see later).

Complications and Sequelae

Although often associated with marked symptomatic decline, atrial *arrhythmias* tend to reflect the consequences of the abnormalities of ventricular function and circulatory efficiency described earlier. The massively dilated right atrium after an atriopulmonary connection is commonly associated with atrial flutter and fibrillation (15% to 20% at 5 years' follow-up). Atrial flutter or fibrillation carries a significant rate of morbidity,[45] can be associated with profound hemodynamic deterioration, and needs prompt medical attention. The combination of atrial incisions and multiple suture lines at the time of Fontan surgery along with increased right atrial pressure and size probably explains the high incidence of atrial arrhythmias in such patients. Patients at greater risk for atrial tachyarrhythmias are those who were operated on at an older age, with poor ventricular function, systemic AV valve regurgitation, or increased pulmonary artery pressure. It has been suggested that the exclusion of the right atrium from elevated systemic venous pressure (as in total cavopulmonary connections or extracardiac conduits) leads to a decrease in the incidence of atrial arrhythmias.[46] This apparent benefit may, however, be due exclusively to the shorter length of follow-up in this group of patients. Sinus node dysfunction and complete heart block can occur and require pacemaker insertion.

The reported incidence of *thromboembolic complications, including stroke,* in the Fontan circuit varies from 6% to 25%, depending on the diagnostic method used and the length of follow-up. Thrombus formation may relate to the presence of supraventricular arrhythmias, right atrial dilation, right atrial “smoke,” and the presence of artificial material used to construct the Fontan circuit. Systemic arterial embolism in patients with and without a fenestrated Fontan circuit has also been reported. Protein C deficiency has been reported in these patients and may explain in part their propensity to thromboembolism. There is continuing debate as to the role of anticoagulation or antiplatelet therapy, or both, in the long-term management of these patients,[47] but most receive some form of therapy.

Protein-losing enteropathy, defined as severe loss of serum protein into the intestine, occurs in 4% to 13% of patients after a Fontan procedure. Patients present with generalized edema, ascites, pleural effusion, and/or chronic diarrhea. Protein-losing enteropathy is thought to result principally from chronically elevated systemic venous pressure causing intestinal lymphangiectasia with consequent loss of albumin, protein, lymphocytes, and immunoglobulin into the gastrointestinal tract. The diagnosis is confirmed by finding low serum albumin and protein levels; a low plasma $alpha_1$-antitrypsin level and lymphocyte counts; and, most important, a high $alpha_1$-antitrypsin stool clearance. It carries a dismal prognosis, with a 5-year survival rate of 46% to 59%.

Right pulmonary vein obstruction or compression can occur from the enlarged right atrium or the atrial baffle bulging into the left atrium and can lead to a vicious spiral of increased pulmonary artery pressure with further dilation of the right atrium.

Stenosis or partial obstruction of the Fontan connection leads to exercise intolerance, atrial tachyarrhythmias, and right-sided heart failure. Sudden total obstruction (usually thrombotic) can present as sudden death (Video 75.57).

Progressive deterioration of systemic ventricular function, with or without progressive AV valve regurgitation, is common. Patients with morphologic systemic right ventricles may fare less well than those with morphologic left ventricles.

Mildly raised hepatic transaminase levels from hepatic congestion are frequent but seldom clinically important.[48] *Cirrhosis* due to chronic venous hypertension is increasingly recognized, and monitoring for complications of cirrhosis should be initiated.

Worsening *cyanosis* may relate to worsening ventricular function, the development of venous collateral

channels draining to the left atrium, or the development of pulmonary arteriovenous malformations (especially if a classic Glenn procedure remains as part of the Fontan circulation). In Fontan patients with cirrhosis, the hepatopulmonary syndrome may occur.

Laboratory Investigations

ECG.

Sinus rhythm, atrial flutter, junctional rhythm, or complete heart block may be present on the ECG. The QRS complex reflects the basic underlying cardiac anomaly.

Chest Radiography.

Mild bulging of the right lower heart border from a dilated right atrium is often seen in patients with an atriopulmonary connection.

Echocardiography.

The presence or absence of right atrial stasis, thrombus, patency of a fenestration, and Fontan circuit obstruction should be sought. Superior and inferior vena caval flow is usually phasic with respiration and of low velocity. Assessment of the pulmonary venous flow pattern is important in detecting pulmonary vein obstruction (right pulmonary vein > left pulmonary vein), sometimes caused by an enlarged right atrium. Concomitant assessment of systemic ventricular function and AV valve regurgitation can be readily accomplished. TEE may be required if there is inadequate visualization of the Fontan anastomosis or to exclude thrombus in the right atrium.

MRI.

The objectives of MRI in Fontan patients include assessment of the pathways from the systemic veins to the pulmonary arteries for obstruction and thrombus; detection of Fontan baffle fenestration or leaks; evaluation of the pulmonary veins for compression; assessment of the systemic ventricular volume, mass, and ejection fraction; imaging of the systemic ventricular outflow tract for obstruction; quantitative assessment of the AV and semilunar valve(s) for regurgitation; and quantitative assessment of the aorta for obstruction or an aneurysm and for aortopulmonary, systemic venous, or systemic-to-pulmonary venous collateral vessels.

Diagnostic Catheterization.

Complete heart catheterization is advised if surgical reintervention is planned or if adequate assessment of the hemodynamics is not obtained by noninvasive means.

Management Options and Outcomes

Patient selection for the Fontan procedure is of utmost importance and has a major impact on the clinical outcome. The long-term survival rate in “ideal” candidates is 81% at 10 years, compared with 60% to 71% in “all comers.” Death occurs mostly from congestive heart failure and atrial arrhythmias. The Fontan procedure remains a palliative, not curative, procedure. A more radical approach to the failing atriopulmonary Fontan circulation, including surgical revision of the circuit to an extracardiac conduit, in combination with a Cox maze procedure and, frequently, simultaneous epicardial pacemaker insertion has recently been shown to provide good early and midterm palliation. Ultimately, cardiac transplantation may be required by some of these patients, although their outcomes are less favorable.

Atrial tachyarrhythmias are quite difficult to manage and should quickly raise the thought of long-term anticoagulation. When *atrial flutter* or *fibrillation* is present, an underlying hemodynamic cause should

always be sought, and, in particular, evidence for obstruction of the Fontan circuit needs to be excluded. Prompt attempts should be made to restore the sinus rhythm. Antiarrhythmic medications, alone or combined with an epicardial antitachycardia pacing device, and radiofrequency catheter ablation techniques have had limited success. Surgical conversion from an atriopulmonary Fontan connection to a total cavopulmonary connection with concomitant atrial cryoablation therapy at the time of surgery has been reported with good medium-term success. Epicardial pacemaker insertion for sinus node dysfunction and/or complete heart block may be necessary. Epicardial AV sequential pacing should be employed whenever possible.

The use of *prophylactic long-term anticoagulation* is a contentious issue.[47] Experts recommend that patients with a history of documented arrhythmias, fenestration in the Fontan connection, or spontaneous contrast (smoke) in the right atrium on echocardiography be anticoagulated. For established thrombus, thrombolytic therapy versus surgical removal of the clot and conversion of the Fontan circuit have been described, both with high mortality rates (Video 75.58).

Treatment modalities for *protein-losing enteropathy* include a low-fat, high-protein, medium-chain–triglyceride diet to reduce intestinal lymphatic production; albumin infusions to increase intravascular osmotic pressure; and/or the introduction of diuretics, afterload-reducing agents, and positive inotropic agents to lower the central venous pressure. Most often these therapies are ineffective and should not be continued, if indeed tried at all. Catheter-based interventions such as balloon dilation of pathway obstruction or creation of an atrial fenestration, as well as surgical interventions from conversion or takedown of the Fontan circuit to cardiac transplantation, have also been advocated. Other reportedly effective treatment modalities include subcutaneous heparin, octreotide treatment, and steroid therapy. All therapies have a similar failure rate of about 50%.

When *right pulmonary vein compression or obstruction* is hemodynamically significant, Fontan conversion to a total cavopulmonary connection or extracardiac conduit may be recommended.

Surgical revision of an obstructed Fontan connection (i.e., obstructed right atrium–to–pulmonary artery or superior and inferior venae cava–to–pulmonary artery connection) is recommended, usually with an extracardiac Fontan procedure. Alternatively, balloon angioplasty with or without stenting may be used when appropriate and feasible (Videos 75.59 and 75.60).

For *ventricular failure and valvular regurgitation*, ACE inhibitors are of unproven benefit[42] and do not appear to enhance exercise capacity. Patients with systemic AV valve regurgitation may require AV valve repair or replacement. Cardiac transplantation should also be considered.

If *cyanosis* occurs in the setting of a fenestrated Fontan procedure, surgical or, preferably, transcatheter closure of the fenestration can be attempted. Pulmonary arteriovenous fistulas from a classic A Glenn shunt may be improved by surgical conversion to a bidirectional Glenn connection.

Reproductive Issues

The rather fixed cardiac output and low flow state of a Fontan circuit makes pregnancy rather problematic in these patients. Cardiovascular complications, including arrhythmias and venous congestion, as well as obstetric complications, such as preterm labor and intrauterine growth retardation, mandate that a multidisciplinary high-risk pregnancy team follow these patients once they are pregnant.

Follow-Up

Close and expert follow-up is recommended, with particular attention to ventricular function and systemic AV valve regurgitation. The development of atrial tachyarrhythmia should instigate a search for possible

obstruction at the Fontan anastomosis, right pulmonary vein obstruction, or thrombus within the right atrium. Some institutions have developed multidisciplinary Fontan clinics to advance both clinical research and patient care.

Total Anomalous Pulmonary Venous Connection

A total anomalous pulmonary venous connection is a situation in which all pulmonary veins fail to connect directly to the morphologic left atrium. As a result, all of the systemic and pulmonary venous return usually drains to the right atrium, albeit using varied routes.

Morphology

The anatomic varieties of a total anomalous pulmonary venous connection may be subdivided, depending on the path of the abnormal drainage (**Fig. 75.31**). The anomalous connection is most often supradiaphragmatic, connecting via a vertical vein to the left brachiocephalic vein, directly to the right atrium, to the coronary sinus, or directly to the superior vena cava. In about 10% to 15% the pathway is below the diaphragm. The anomalous trunk then connects to the portal vein or one of its tributaries; to the ductus venosus; or, rarely, to the hepatic or other abdominal veins.

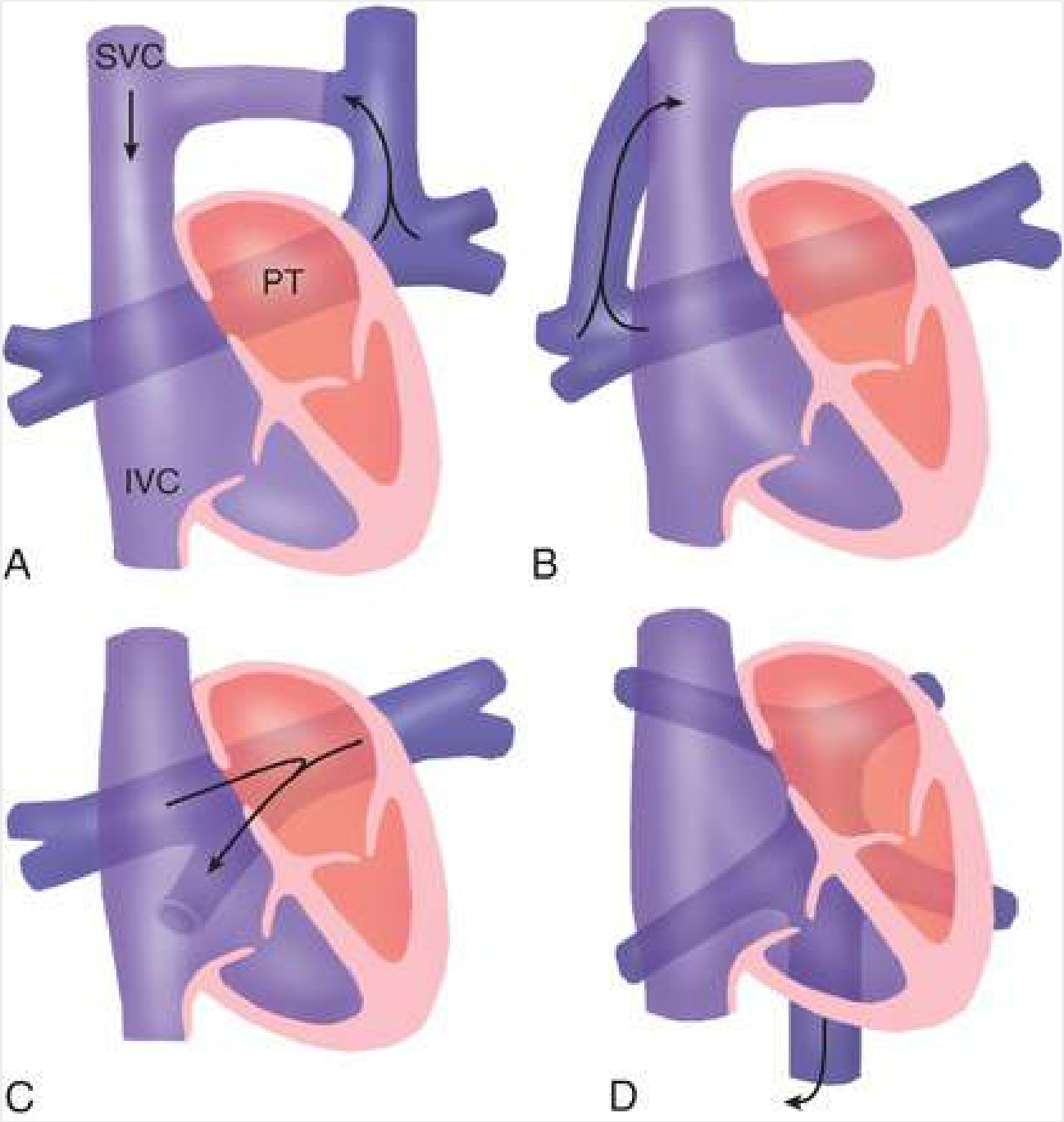


FIGURE 75.31 Anatomic types of total anomalous pulmonary venous return: supracardiac, in which the pulmonary veins drain either via the vertical vein to the anomalous vein **(A)** or directly to the superior vena cava (SVC), with the orifice close to the orifice of the azygos vein **(B)**. **C,** Drainage into the right atrium via the coronary sinus. **D,** Infracardiac drainage via a vertical vein into the portal vein or the inferior vena cava (IVC). *PT*, pulmonary trunk. (**A** to **D,** From Stark J, de Leval M: Surgery for congenital heart defects, 2nd ed. Philadelphia, WB Saunders, 1994, p 330.)

Natural History

Most patients with total anomalous pulmonary venous connection have symptoms during the first year of life and undergo repair, such that this entity is rarely seen in late adolescent and adult patients. If it is the patient has classic signs of an ASD, but with associated cyanosis, because of right-to-left shunting at the atrial level. Older unrepaired patients are also at risk for having elevated pulmonary artery pressure.

Laboratory Investigations

ECG.

This usually shows right axis deviation and right atrial and right ventricular hypertrophy.

Chest Radiography.

In the unrepaired older patient with an abnormal connection to the coronary sinus or a left vertical vein, there is cardiomegaly with increased pulmonary blood flow. The right atrium and ventricle are dilated and hypertrophied, and the pulmonary artery segment is enlarged. The so-called figure-of-8, or snowman, heart is due to enlargement of the heart and the presence of a dilated right superior vena cava, innominate vein, and left vertical vein.

Echocardiography (Fig. 75.32).

This usually shows marked enlargement of the right ventricle and a small left atrium. Demonstrating the entire pathway of pulmonary venous drainage is usually possible in younger patients, and in that group cardiac catheterization (which may be hazardous) is almost never performed. An echo-free space representing the pulmonary venous confluence can usually be seen behind the left atrium. The drainage of all four pulmonary veins and their connections must be identified.

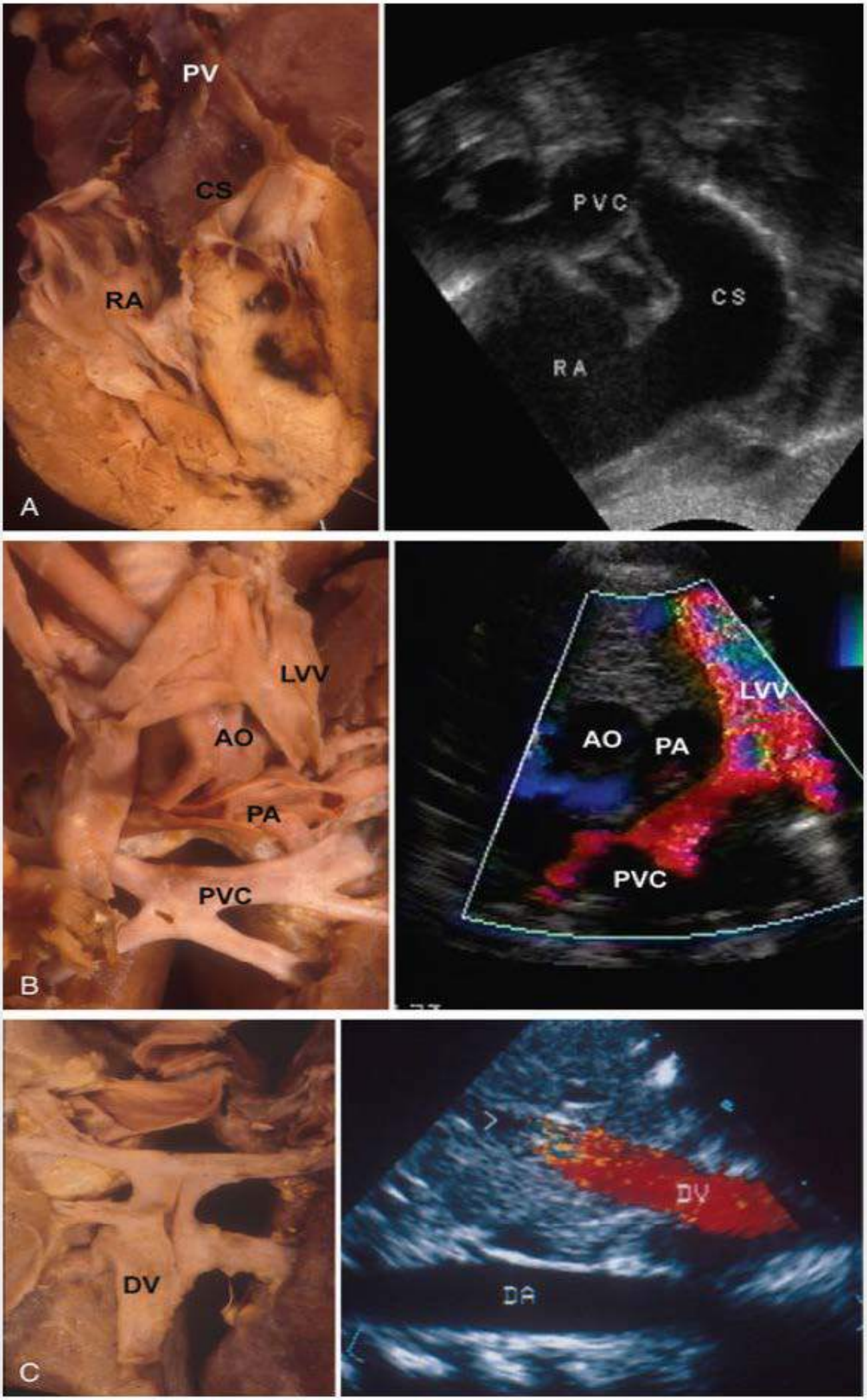

PV
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FIGURE 75.32 **A,** Subcostal view demonstrating total anomalous pulmonary drainage to the coronary sinus. Note the dilated coronary sinus in both images. The echocardiogram also demonstrates an associated confluence that connects to the coronary sinus. **B,** Suprasternal view demonstrating total anomalous pulmonary venous drainage to a left vertical vein. Note the direction of flow in the vertical vein that differentiates it from a left superior vena cava. **C,** Total anomalous pulmonary venous drainage below the diaphragm. The specimen shows the pulmonary veins as they enter the confluence, whereas the echocardiogram demonstrates the descending veins as they enter the liver. Note that the direction of flow is away from the heart. *AO*, aorta; *CS*, coronary sinus; *DA*, descending aorta; *DV*, descending vein; *LVV*, left vertical vein; *PA*, pulmonary artery; *PV*, pulmonary vein; *PVC*, pulmonary venous confluence; *RA*, right atrium.

MRI.

MRI may be helpful in older patients to delineate the site of connections of total anomalous pulmonary venous return when there are multiple mixed sites, and to detect stenosis in postoperative patients.

Intervention and Outcomes

Surgery is usually performed during childhood, most often at presentation. Historically, surgical repair of restenosis was disappointing. However, the sutureless technique, whereby the pulmonary veins are opened widely into the retroatrial space, has markedly improved the results of such surgery. Adult patients have almost always had surgical repair in childhood. As a rule, they function normally and are not too prone to arrhythmias or other problems. They are seen as low-risk adults.

Follow-Up

Early follow-up should be frequent and aimed at early detection of stenosis of the pulmonary veins or the surgical anastomosis. If not present within the first year, stenosis is rare.

Transposition Complexes

The key anatomic feature that characterizes this group of diagnoses is discordant ventriculoarterial connections. This is most commonly seen in the context of AV concordance, also known as *complete transposition* or *dextro-transposition* (*D-TGA)*. The second condition discussed in this section is the combination of ventriculoarterial discordance with AV discordance, commonly referred to as *congenitally corrected TGA* or *levo-transposition* (*L-TGA)*. More complicated arrangements are not considered here.

Complete Transposition of the Great Arteries

Definition and Natural History.

This is a common and potentially lethal form of heart disease in newborns and infants. The malformation consists of the origin of the aorta from the morphologic right ventricle and that of the pulmonary artery from the morphologic left ventricle. Consequently, the pulmonary and systemic circulations are connected in parallel rather than the normal in-series connection. In one circuit, systemic venous blood passes to the right atrium, the right ventricle, and then to the aorta, and back to the systemic veins. In the other, pulmonary venous blood passes through the left atrium and ventricle to the pulmonary artery and then back to the pulmonary veins. This situation is incompatible with life unless mixing of the two circuits occurs.

Approximately two thirds of patients have no major associated abnormalities (*"simple"*

transposition), and one third have associated abnormalities (*"complex" transposition*). The most common associated abnormalities are VSD and pulmonary or subpulmonary stenosis. It is increasingly being diagnosed in utero. Without treatment, about 30% of these infants die within the first week of life, and 90% die within the first year.

Morphology

Some communication between the two circulations must exist after birth to sustain life. Two thirds have a PDA, and about one third have an associated VSD. If there is no significant intracardiac shunt or communication, a balloon atrial septostomy is performed.

Pathophysiology

The degree of tissue hypoxia, the nature of the associated cardiovascular anomalies, and the anatomic and functional status of the pulmonary vascular bed determine the clinical course. Infants with D-TGA are particularly susceptible to the early development of pulmonary vascular obstructive disease even in the absence of a PDA and even with an intact ventricular septum.

Clinical Features.

All adult patients with TGA will have had some type of surgical repair.

Surgical Management Option.

Although neonatal balloon atrial septostomy is often lifesaving, it is palliative and anticipates "corrective" surgery. Atrial redirection procedures were developed in the 1950s and 1960s but were replaced by the arterial switch operation, which became widely adopted in the 1980s.

Atrial Switch Procedure.

The most common surgical procedure in patients who are older adults is the atrial switch operation (**Fig. 75.33**). Patients will have had either a Mustard or a Senning procedure. Blood is redirected at the atrial level using a baffle made of Dacron or pericardium (Mustard operation) or atrial flaps (Senning operation), achieving physiologic correction. Systemic venous return is diverted through the mitral valve into the subpulmonary left ventricle, and the pulmonary venous return is rerouted through the tricuspid valve into the subaortic right ventricle. By virtue of this repair, the morphologic right ventricle supports the systemic circulation.

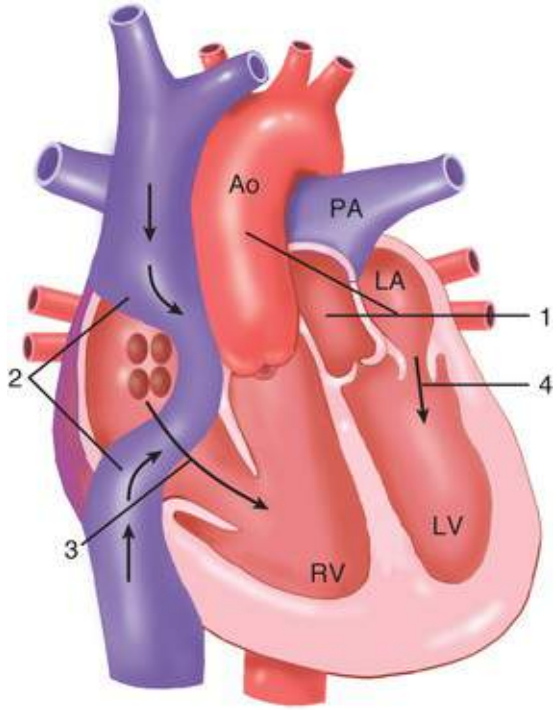


FIGURE 75.33 Diagrammatic representation of atrial switch surgery (Mustard/Senning procedure). Superior vena cava (SVC) and inferior vena cava (IVC) blood is redirected into the morphologic left ventricle (LV), which pumps blood into the pulmonary artery (PA), whereas the pulmonary venous blood flow is rerouted to the morphologic right ventricle (RV), which empties into the aorta (Ao). *LA*, left atrium; *RA*, right atrium; *1*, transposition of the great arteries; *2*, atrial baffles; *3*, pulmonary vein blood flow through tricuspid valve to RV; *4*, IVC and SVC blood flow through mitral valve to LV. (From Mullins CE, Mayer DC: Congenital heart disease: a diagrammatic atlas. New York, Wiley-Liss, 1988.)

Palliative Atrial Switch Procedure *(Videos 75.61 to 75.65)*.

Uncommonly, in patients with a large VSD and established pulmonary vascular disease, a palliative atrial switch operation is done to improve systemic oxygenation. The VSD is left open or enlarged at the time of atrial baffle surgery. These patients resemble patients with Eisenmenger VSDs and should be managed as such.

Arterial Switch Operation.

In the arterial switch operation the arterial trunks are transected and reanastomosed to the contralateral root (**FIg. 75.34**). If present, a VSD is closed. The coronary arteries must be transposed to the neoaorta. This is the most challenging part of the procedure and accounts for most of the deaths. Nonetheless, this rate has fallen to less than 2% in most large centers. The major advantages of the arterial switch procedure, when compared with the atrial switch procedure, are restoration of the left ventricle as the systemic pump and the potential for long-term maintenance of sinus rhythm.

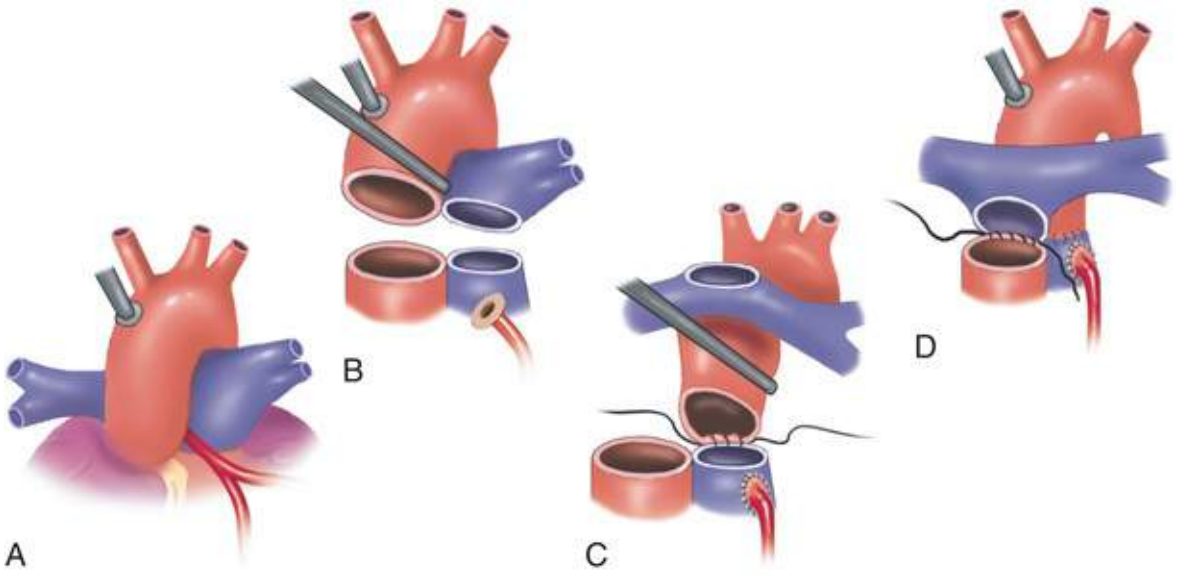


FIGURE 75.34 Complete transposition of the great arteries, corrected by a modified arterial switch operation **(A).** The aorta and pulmonary artery are transected, and the orifices of the coronary arteries are excised with a rim of adjacent aortic wall **(B).** The aorta is brought under the bifurcation of the pulmonary artery, and the pulmonary artery and the aorta are anastomosed without necessitating graft interposition. The coronary arteries are transferred to the pulmonary artery **(C).** The mobilized pulmonary artery is directly anastomosed to the proximal aortic stump **(D).** (**A** to **D,** From Stark J, de Leval M: Surgery for congenital heart defects. New York, Grune & Stratton, 1983, p 379.)

Follow-up studies after the arterial switch operation have demonstrated good left ventricular function and normal exercise capacity. Potential sequelae of the operation include coronary occlusion; supravalvular pulmonary stenosis (which may be treated by either reoperation or balloon angioplasty); supravalvular aortic stenosis; ascending aortic aneurysms; and neoaortic regurgitation, usually mild. Long-term patency and growth of the coronary arteries appear satisfactory, but the very long term results are yet to be defined.

Rastelli Procedure *(Videos 75.66 to 75.68)*.

Infants with TGA plus a VSD and left ventricular outflow tract obstruction may require an early systemic-to-pulmonary artery shunt when a pronounced diminution in pulmonary blood flow exists. A later corrective procedure for these patients bypasses the left ventricular outflow obstruction with an extracardiac conduit between the right ventricle and the distal end of a divided pulmonary artery and uses an intracardiac ventricular baffle to tunnel the left ventricle to the aorta (Rastelli procedure). The late outcomes for the Rastelli procedure are particularly poor (see below), and in recent years another procedure, the Nikaidoh operation, has replaced the Rastelli procedure for some forms of TGA with VSD and pulmonary stenosis. In this operation the pulmonary outflow tract is resected and the aorta translocated posteriorly to sit more “anatomically” above the left ventricle, making subsequent left ventricular outflow tract obstruction less likely. Just as in the Rastelli procedure, the right ventricular outflow tract is reconstructed with a conduit in this operation, but because of the backward translocation of the aorta, there is more space behind the sternum, and the hope is that conduit longevity will be enhanced. The REV (reparation a l'etage ventriculaire) procedure has also been introduced as an alternative treatment for D-TGA with VSD and pulmonary stenosis where the pulmonary outflow tract is repaired without the need for a conduit.

Management Outcomes

Atrial Switch Procedure.

After atrial baffle surgery, most patients who reach adulthood are in NYHA classes I and II, but in many, abnormalities of ventricular filling due to the abnormal atrial pathways may be of more direct importance to the functional capacity than right ventricular performance issues. Some present have symptoms of congestive heart failure (2% to 15%). Echocardiographic evidence of moderate or severe systemic right ventricular dysfunction is present in up to 40% of patients. More than mild systemic tricuspid regurgitation is present in 10% to 40%, both reflecting and exacerbating right ventricular dysfunction. Palpitations and near-syncope or syncope from rhythm disturbances are fairly common. Atrial flutter occurs in 20% of patients by 20 years of age, and sinus node dysfunction is seen in half of the patients by that time. These rhythm disturbances are a consequence of direct and indirect atrial and sinus node damage at the time of atrial baffle surgery.

A shortened life expectancy is the rule, with the survival rate being 70% to 80% at 20 to 30 years' follow-up. Patients with “complex” TGA in general fare worse than those with “simple” TGA. Sudden cardiac death may occur in these patients and may be related to systemic right ventricular dysfunction, the presence of atrial flutter, and/or pulmonary hypertension. The role of primary ICDs in these patients remains fully to be defined.[49] Significant pulmonary vascular disease can develop over time and is related to an older age at the time of the atrial switch operation, particularly in patients with a substantial VSD, as well as in those with long-standing left-to-right shunts through a baffle leak. Superior vena cava or inferior vena cava baffle obstruction often goes undetected because collateral drainage through the azygos vein prevents systemic venous congestion. Pulmonary venous baffle obstruction causes elevated pulmonary artery pressure, and patients can present with dyspnea and pulmonary venous congestive features.[50]

Physical examination of a patient whose condition is otherwise uncomplicated reveals a right ventricular parasternal lift, a normal S_1, a loud single S_2 (P_2 is often not heard because of its posterior location), a pansystolic murmur from tricuspid regurgitation (if present, best heard at the left lower sternal border, but not increasing with inspiration), and a right-sided S_3 when severe systemic ventricular dysfunction is present.

Arterial Switch Procedure.

Data on long-term complications in adults who have undergone the arterial switch procedure are emerging.[51-54] The development of progressive neoaortic valve regurgitation from neoaortic root dilation is the most common long-term sequela. It is time dependent and as such requires periodic follow-up. Supraneopulmonary artery stenosis is a frequent finding[55] but rarely has clinical consequences. The development of ostial coronary artery disease has also been described in some patients. Arrhythmia promises to be less of a problem in this group of patients. Cardiac examination in uncomplicated patients is normal.

Rastelli Procedure.

Compared with either the arterial switch or Mustard procedure, the survival rate after the Rastelli procedure is poor, and the need for repeat intervention is high. Progressive right ventricular–to–pulmonary artery conduit obstruction can cause exercise intolerance or right ventricular angina. Left ventricular tunnel obstruction is frequent, and can present as exertional dyspnea or syncope. Conduit replacement or transcatheter stent or stent-valve implantation is inevitably required in surviving patients.[56] Physical examination in uncomplicated patients reveals, in contrast to those after the atrial

switch procedure, no right ventricular lift, a systolic ejection murmur from the conduit, and two components to the S_2. Long-term comparative outcome studies on the Nikaidoh and REV procedures are lacking.[56]

Laboratory Investigations

ECG.

Sinus bradycardia or junctional rhythm (without a right atrial overload pattern) with evidence of marked right ventricular hypertrophy is characteristically present in patients after the atrial switch procedure. The ECG is typically normal in patients after the arterial switch procedure. The ECG typically shows right bundle branch block after a Rastelli procedure.

Chest Radiography.

On the posteroanterior film, a narrow vascular pedicle with an oblong cardiac silhouette ("egg on side") is typically seen in patients after the atrial switch procedure. On the lateral view, the anterior aorta may be seen to fill the retrosternal space. For the arterial switch, normal mediastinal borders are present. After the Rastelli procedure, the chest radiograph may be normal unless the conduit becomes calcified.

Echocardiography (Videos 75.69 to 75.71).

After the atrial switch procedure, parallel great arteries are the hallmark of TGA (**Fig. 75.35**). They are best visualized from a parasternal long axis view (running side by side) or from a parasternal short axis view (seen en face, with the aorta anterior and rightward). Qualitative assessment of systemic right ventricular function, the degree of systemic tricuspid regurgitation, and the presence or absence of subpulmonary left ventricular obstruction (dynamic or fixed) is important. Assessment of baffle leak or obstruction (**Fig. 75.36**) is best done using color and Doppler flow imaging. Normal baffle flow should be phasic in nature and vary with respiration, with a peak velocity of less than 1 m/sec. After the arterial switch procedure, neoaortic valve regurgitation, supraneopulmonary valve stenosis, and a segmental wall motion abnormality from ischemia due to coronary ostial stenosis should be sought. In patients who have undergone the Rastelli operation, left ventricular–to–aorta tunnel obstruction, as well as right ventricular–to–pulmonary artery conduit degeneration (stenosis or regurgitation), must be assessed.

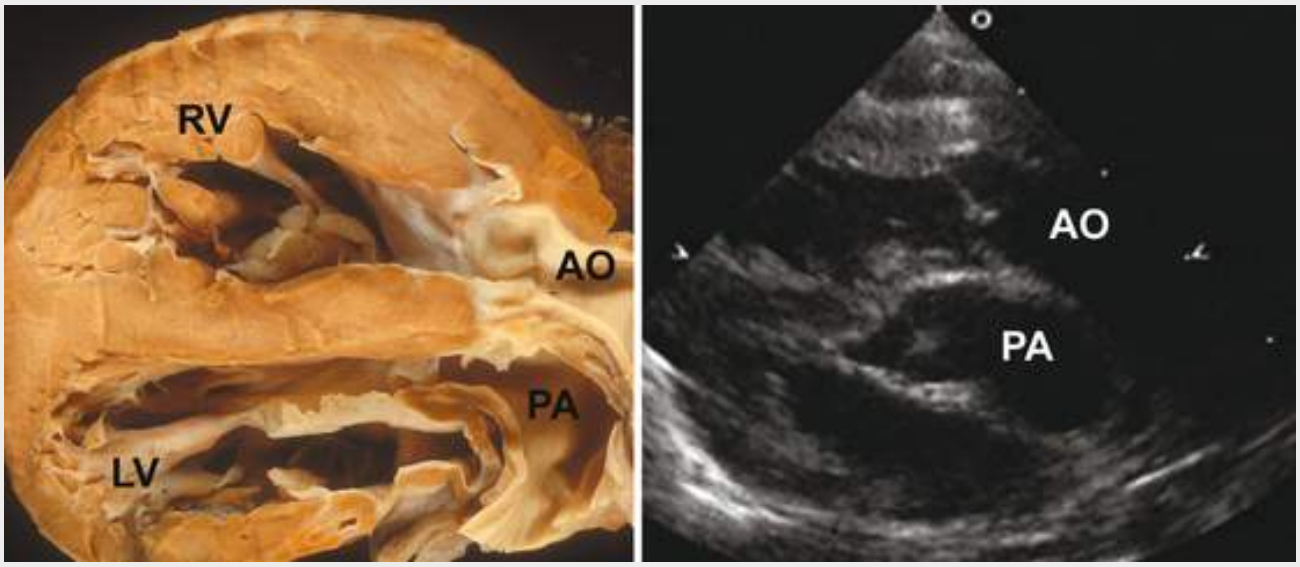


FIGURE 75.35 Parasternal long axis view in transposition of the great arteries. Note the parallel nature of the aorta and pulmonary artery. *AO*, aorta; *LV*, left ventricle; *PA*, pulmonary artery; *RV*, right ventricle.

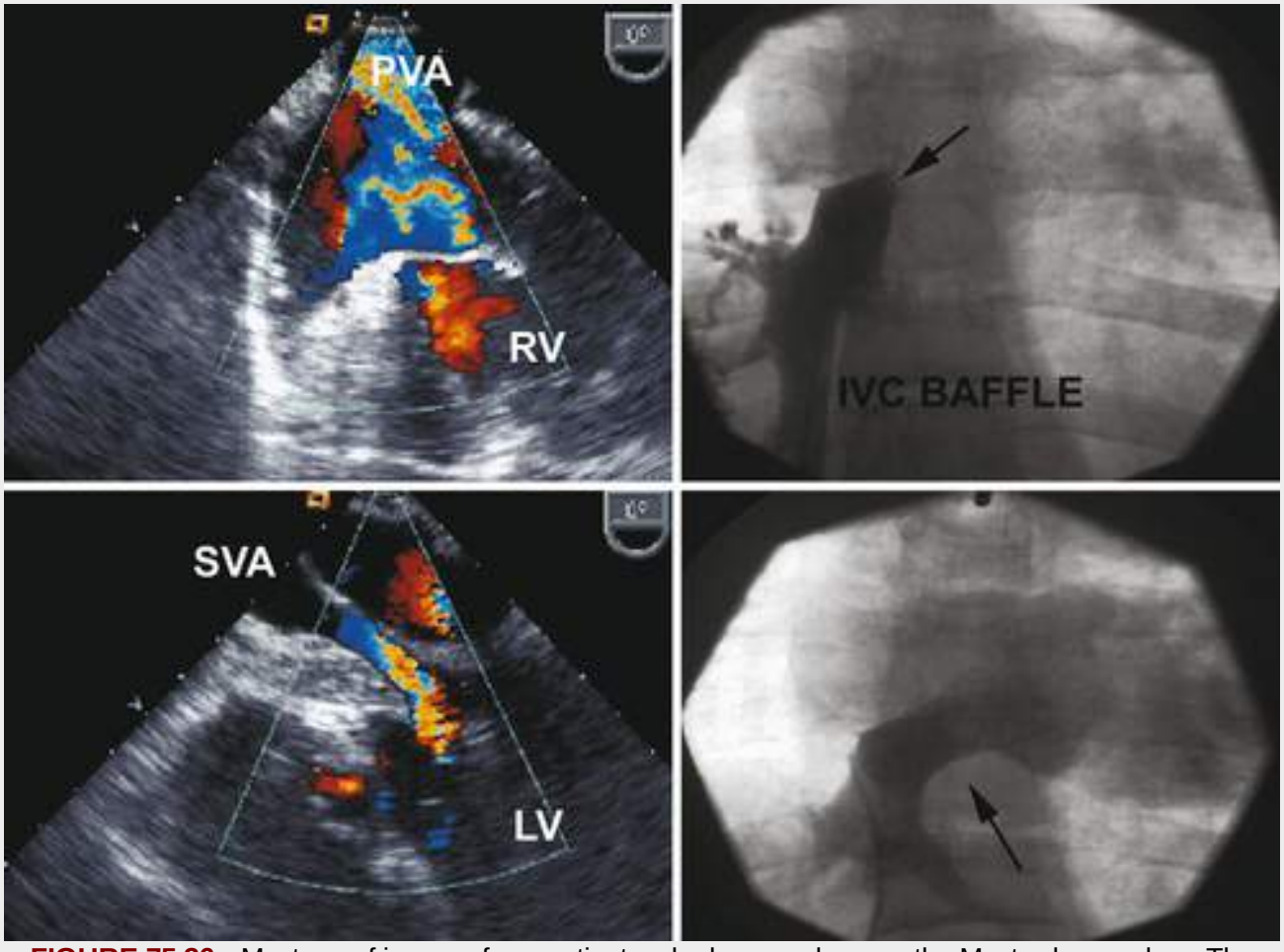


FIGURE 75.36 Montage of images from patients who have undergone the Mustard procedure. The angiogram on the right upper panel shows complete obstruction of the inferior limb of the systemic venous baffle, whereas the lower right panel shows the same case after stenting. The upper left image is a TEE showing the pulmonary venous baffle with some mild flow acceleration in its midpoint. The lower left panel shows the systemic venous baffle at its left ventricular end. *IVC*, inferior vena cava; *LV*, left ventricle; *PVA*, pulmonary venous atrium; *RV*, right ventricle; *SVA*, systemic venous atrium.

MRI.

The major role of MRI in patients who have undergone the atrial switch procedure is to evaluate the

baffles and systemic right ventricular volume and ejection fraction. As a rule, MRI better reports the right ventricular size and function than does echocardiography. For patients who are claustrophobic or have a pacemaker, a CT angiogram may serve as a substitute.

Cardiac Catheterization.

Diagnostic cardiac catheterization may be required for assessing the presence or severity of systemic or pulmonary baffle obstruction, baffle leak, and pulmonary hypertension; coronary ostial stenosis; or tunnel or conduit obstruction when not adequately assessed by noninvasive means.

Indications for Reintervention.

After the *atrial switch procedure,* severe symptomatic right ventricular dysfunction may warrant surgical treatment in the form of a *two-stage arterial switch procedure* or cardiac transplantation. Tricuspid valve repair or replacement is rarely performed for severe systemic (tricuspid) AV valve regurgitation, but may be appropriate if it is due to a flail leaflet or cusp perforation, providing right ventricular function is adequate. A baffle leak resulting in a significant left-to-right shunt (>1.5/1), any right-to-left shunt, or attributable symptoms requires surgical or transcatheter closure. Superior vena cava or inferior vena cava pathway obstruction may require intervention (Video 75.72). Superior vena cava stenosis is usually benign, whereas inferior vena cava stenosis may have greater hemodynamic consequences, depending on the adequacy of alternative routes of venous return, usually via the azygos vein to the superior vena cava. Balloon dilation of superior vena cava or inferior vena cava stenosis is an option in expert hands. Stenting usually relieves the stenosis completely.

Pathway obstruction after the Senning operation is usually more amenable to balloon dilation and stenting (see Video 75.72). Pulmonary venous obstruction, although usually seen early and reoperated on in childhood, may present in adulthood. Symptomatic bradycardia warrants permanent pacemaker implantation, whereas tachyarrhythmias may require catheter ablation, an antitachycardia pacemaker device, or medical therapy. After an atrial switch procedure, transvenous pacing leads must traverse the upper limb of the baffle to enter the morphologic left ventricle. Active fixation is required because of the tightly packed fine apical trabeculations in the morphologic left ventricle. Transvenous pacing should be avoided in patients with residual intracardiac communications because paradoxical emboli can occur.

After an *arterial switch procedure,* significant right ventricular outflow tract obstruction at any level (gradient > 50 mm Hg or right-to-left ventricular pressure ratio > 0.6) may require surgical or catheter augmentation of the right ventricular outflow tract. Myocardial ischemia from coronary artery obstruction may require coronary artery bypass grafting, preferably with arterial conduits. Significant neoaortic valve regurgitation may warrant aortic valve replacement.

In patients who have had the *Rastelli procedure,* significant right ventricle–to–pulmonary artery conduit stenosis (> 50 mm Hg withdrawal gradient or mean echocardiography gradient) or significant regurgitation necessitates intervention. Subaortic obstruction across the left ventricle–to–aorta tunnel necessitates left ventricle–to–aorta baffle reconstruction. A significant residual VSD (shunt > 1.5/1) may require surgical closure.

Reintervention Options.

In patients who have undergone an atrial switch procedure, *medical therapy* is uncertain. The role of afterload reduction with ACE inhibitors, angiotensin receptor blockers,[57] or a beta blockade to preserve the systemic right ventricular function is debatable, and short- to medium-term studies have shown no benefit.[57]

Following an atrial switch procedure, patients with severe, symptomatic, systemic (right) ventricular dysfunction with or without severe systemic (tricuspid) AV valve regurgitation may require consideration of a *heart transplantation*.

Reproductive Issues.

Severe systemic ventricular dysfunction or intractable arrhythmias may be a contraindication to pregnancy, and baffle obstruction should, ideally, be relieved before pregnancy. Women who have undergone an atrial switch procedure usually tolerate pregnancy well, but about 15% will develop worsening right ventricular function or systemic tricuspid regurgitation during the pregnancy.[58] In half of these cases, the problem does not improve after delivery. Pregnancy following an arterial switch procedure is better tolerated, assuming there are no significant hemodynamic lesions prior to pregnancy.[59]

Follow-Up.

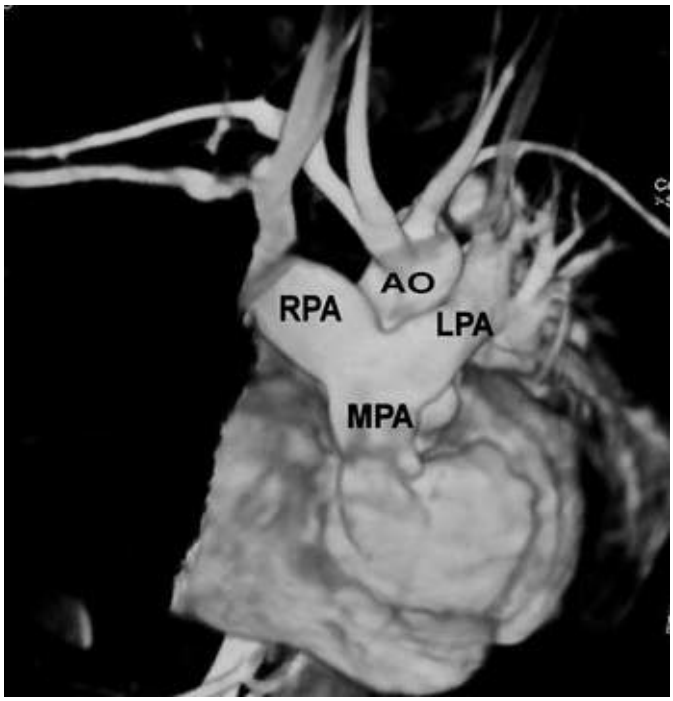
Regular follow-up by physicians with special expertise in CHD is recommended.

Atrial Switch Procedure.

Serial follow-up surveillance of systemic right ventricular function is warranted. Asymptomatic baffle obstructions and leaks should be sought with echocardiography or MRI. Regular Holter monitoring is recommended to diagnose unacceptable bradyarrhythmias or tachyarrhythmias.

Arterial Switch and Rastelli Procedures.

Regular follow-up with echocardiography is recommended. As patients advance in age, the MRI is more suited to assess the branch pulmonary arteries after the LeCompte maneuver (bringing the pulmonary artery anterior to the aorta), because this is a challenging area to see with echocardiography (**eFig. 75.5**).



EFIGURE 75.5 This MRI demonstrates the use of branch pulmonary artery imaging after the LeCompte maneuver as part of the arterial switch procedure. *AO*, aorta; *LPA*, left pulmonary artery; *MPA*, main pulmonary artery; *RPA*, right pulmonary artery.

For the Rastelli procedure, regular follow-up with echocardiography is recommended. Particular attention should be paid to the right ventricular–to–pulmonary artery conduit, as well as the left ventricular–to–aorta tunnel.

Congenitally Corrected Transposition of the Great Arteries

The term *congenitally corrected transposition of the great arteries (cc-TGA)* describes hearts in which there are discordant AV connections in combination with discordant ventriculoarterial connections.

Morphology

cc-TGA is a rare condition, accounting for less than 1% of all CHDs (**Fig. 75.37**). When there is the usual atrial arrangement, systemic venous blood passes from the right atrium through a mitral valve to a left ventricle and then to the posteriorly located pulmonary artery. Pulmonary venous blood passes from the left atrium through a tricuspid valve to a left-sided right ventricle and then to an anterior, left-sided aorta. The circulation is thus "physiologically" corrected, but the morphologic right ventricle supports the systemic circulation. Associated anomalies occur in up to 95% of patients and consist of a VSD (75%), pulmonary or subpulmonary stenosis (75%), and left-sided (tricuspid and often "Ebstein-like") valve anomalies (75%).

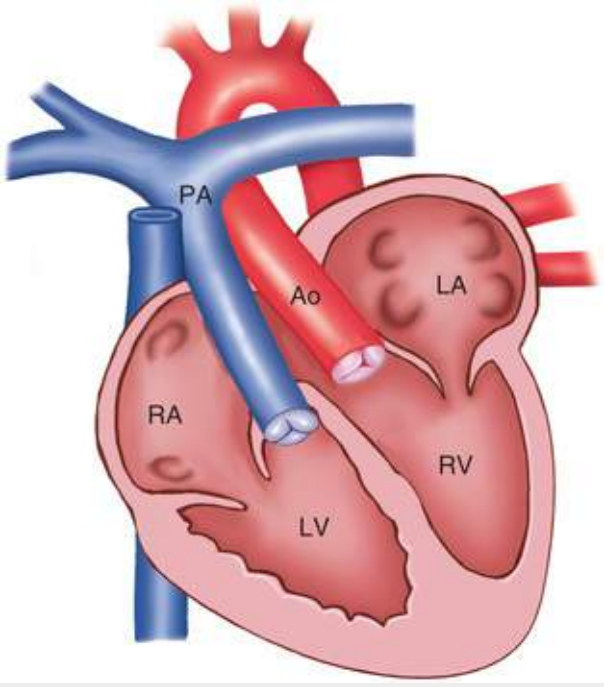


FIGURE 75.37 Diagrammatic representation of congenitally corrected transposition of the great arteries. *Ao*, aorta; *LA*, left atrium; *LV*, left ventricle; *PA*, pulmonary artery; *RA*, right atrium; *RV*, right ventricle. (From Mullins CE, Mayer DC: Congenital heart disease: a diagrammatic atlas. New York, Wiley-Liss, 1988.)

Because of the inherently abnormal conduction system, 5% of patients with cc-TGA are born with a congenital complete heart block and approximately 25% will develop it later in life, spontaneously or as a consequence of surgery.

Pathophysiology

Patients with no associated abnormalities ("isolated" cc-TGA) can exceptionally survive until the

seventh or eighth decade. Progressive systemic (tricuspid) AV valve regurgitation and systemic (right) ventricular dysfunction tend to occur from the fourth decade onward, whereas atrial tachyarrhythmias are more common from the fifth decade onward. In addition to those born with congenital complete heart block, acquired complete AV block continues to develop at a rate of 2% per year, concentrated mainly at the time of cardiac surgery. Patients with associated anomalies (VSD, pulmonary stenosis, left-sided [tricuspid] valve anomaly) often have undergone surgical palliation (systemic-to-pulmonary artery shunt for cyanosis) or repair of the associated anomalies (see Surgical Procedures), but a significant number of patients are naturally balanced by a combination of their VSD and subpulmonary left ventricular outflow tract obstruction. Although cyanosed, they often remain well, with no intervention for many years.

Clinical Features

Unoperated Patients.

Patients with no associated defects can be asymptomatic until late adulthood. Dyspnea, exercise intolerance from developing congestive heart failure, and palpitations from supraventricular arrhythmias most often arise in the fifth decade. Patients with well-balanced VSD and pulmonary stenosis can present with paradoxical emboli or cyanosis, especially if pulmonary stenosis is severe. Physical examination of a patient whose condition is otherwise uncomplicated reveals a somewhat more medial apex due to the side-by-side orientation of the two ventricles. The A_2 is often palpable in the second left intercostal space due to the anterior location of the aorta. A single S_2 (A_2) is heard, with P_2 often being silent due to its posterior location. The murmur of an associated VSD or of left AV valve regurgitation may be heard. The murmur of pulmonary stenosis radiates upward and to the right, given the rightward direction of the main pulmonary artery. If there is complete heart block, cannon "A waves" with an S_1 of variable intensity are present.

VSD Patch and Left Ventricular–to–Pulmonary Artery Conduit Repair.

Most patients are in functional class I at 5 to 10 years after surgery despite the common development of systemic tricuspid regurgitation and systemic right ventricular dysfunction after surgical repair. Dyspnea, exercise intolerance, and palpitations from supraventricular arrhythmia often occur in the fourth decade. Physical examination reflects the basic cardiac malformation with or without residual coexisting anomalies.

Laboratory Investigations

ECG.

An abnormal direction of initial (septal) depolarization from right to left causes reversal of the precordial Q wave pattern (Q waves are often present in the right precordial leads and absent in the left). First-degree AV block occurs in about 50%, and complete AV block occurs in up to 25% of patients. Atrial arrhythmias may be seen.

Chest Radiography.

Chest radiography characteristically reveals absence of the normal pulmonary artery segment in favor of a smooth convexity of the left supracardiac border produced by the left-sided ascending aorta. The main pulmonary trunk is medially displaced and absent from the cardiac silhouette; the right pulmonary hilum

is often prominent and elevated compared with the left, producing a right-sided "waterfall" appearance.

Echocardiography (Fig. 75.38, and Videos 75.73 to 75.75)

Echocardiography permits the identification of the basic malformation, as well as any associated anomalies. The right-sided morphologic left ventricle is characterized by its smooth endocardial surface and is guarded by a bileaflet AV (mitral) valve with no direct septal attachment. The morphologic right ventricle is recognized by its apical trabeculation and moderator band and is guarded by a trileaflet, apically displaced AV valve (tricuspid valve) with direct attachment to the septum. The AV valves therefore show reversed offsetting, a strong clue to the diagnosis. Ebstein-like malformation of the left (tricuspid) AV valve is defined by excessive (> 8 mm/m^2 body surface area) apical displacement of the left (tricuspid) AV valve, with or without dysplasia (Videos 75.76 to 75.80).

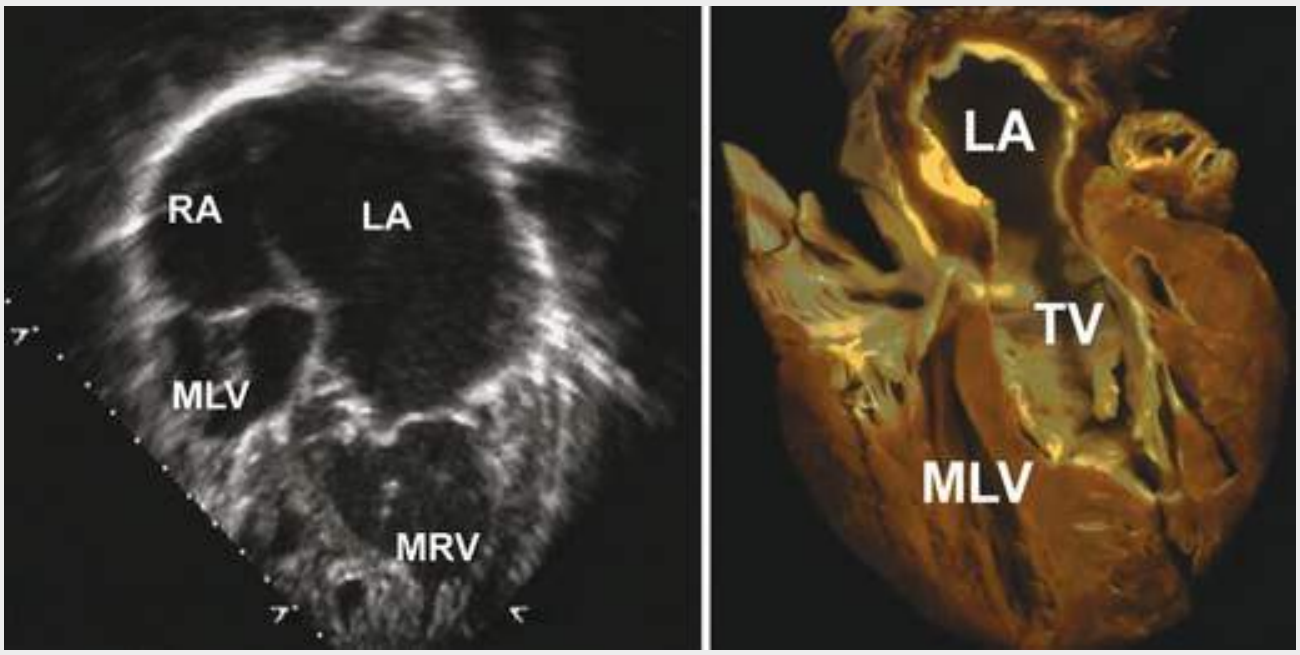


FIGURE 75.38 Four-chamber view in cc-TGA with dysplasia and displacement of the morphologic left-sided tricuspid valve. *LA*, left atrium; *MLV*, morphologic left ventricle; *MRV*, morphologic right ventricle; *RA*, right atrium; *TV*, tricuspid valve.

MRI.

The major role of MRI in cc-TGA patients is to evaluate the systemic right ventricular volume and ejection fraction. It does so better than echocardiography can at present. For claustrophobic patients or those with a pacemaker, a high-quality radionuclide angiogram or a CT angiogram with volume estimates may serve as a substitute. MRI can evaluate other issues, as well, including conduit function and AV valve regurgitation.

Cardiac Catheterization.

This is rarely required for diagnosis but may be indicated before surgical repair to demonstrate the coronary artery anatomy, as well as ventricular end-diastolic and pulmonary artery pressures.

Indications for Intervention and Reintervention.

If moderate or severe systemic (tricuspid, left) AV valve regurgitation develops, valve replacement should be considered. Left AV valve replacement should be performed before systemic right ventricular function deteriorates, namely, at an ejection fraction of 45% or more. When tricuspid regurgitation is

associated with poor systemic (right) ventricular function, the double-switch procedure should perhaps be considered. Patients with end-stage symptomatic heart failure should be referred for cardiac transplantation. The presence of a hemodynamically significant VSD (Qp/Qs > 1.5/1) or residual VSD with significant native or postsurgical (conduit) pulmonary outflow tract stenosis (echocardiography mean or catheter gradient > 50 mm Hg) may require surgical correction, although the latter is sometimes best left alone because it can maintain a neutral septal position and minimize systemic tricuspid regurgitation. Left AV valve replacement at the time of VSD and pulmonary stenosis surgery should be considered if concomitant left AV valve regurgitation is present. Pacemaker implantation is usual when complete AV block is present. The optimal pacing modality is DDD. Active fixation electrodes are required because of the lack of apical trabeculation in the morphologic left ventricle. Transvenous pacing should be avoided if there are intracardiac shunts because paradoxical emboli may occur. Epicardial leads are preferred under these circumstances.

Interventional Options.

Medical therapy with ACE inhibitors, angiotensin receptor blockers, or beta-blocker therapy for patients with systemic ventricular dysfunction may be intuitive, but no benefit has yet been demonstrated[60]

Conduit replacement or repair is inevitably required in survivors of this type of initial surgery. Fortunately, it is now possible in some patients and in many countries to repair a failing conduit with a percutaneously delivered stented valve.

Valve repair is usually unsuccessful because of the abnormal, often Ebstein-like, anatomy of the valve. Consequently, for significant regurgitation, *tricuspid valve replacement* is preferable to repair, but it carries a higher risk if there is significant right ventricular dysfunction (ejection fraction < 45%).

The *double-switch procedure* has been successfully performed in children[61,62] and carefully selected adults. It should be considered for patients with severe tricuspid regurgitation and systemic ventricular dysfunction. Its purpose is to relocate the left ventricle into the systemic circulation and the right ventricle into the pulmonary circulation, achieving physiologic correction. An atrial switch procedure (Mustard or Senning), together with either an arterial switch procedure (when pulmonary stenosis is not present) or a Rastelli-type repair, the so-called *Ilbawi procedure* (left ventricle tunneled to aorta and right ventricle–to–pulmonary artery valved conduit when VSD and pulmonary stenosis are present), can be performed after adequate left ventricular retraining, leaving the regurgitant tricuspid valve and failing right ventricle on the pulmonary side.

Patients with deteriorating systemic (right) ventricular function should be treated aggressively with medical therapy but may need to be considered for *cardiac transplantation*.

Interventional Outcomes.

After conduit repair and VSD patching, the median survival time of patients reaching adulthood is 40 years. The usual causes of death are sudden death (presumed arrhythmic) or, more commonly, progressive systemic right ventricular dysfunction with systemic (tricuspid) AV valve regurgitation. The major predictor of a poor outcome is the presence of left AV (tricuspid) valve regurgitation. Reoperation is common (15% to 25%), with left AV valve replacement usually being the primary reason. Data in adults using the double-switch procedure are lacking, and this procedure should be considered experimental in this patient population.

Reproductive Issues.

Severe systemic ventricular dysfunction or intractable arrhythmias may be a contraindication to

pregnancy, and severe systemic tricuspid regurgitation or conduit problems should, ideally, be relieved before pregnancy. In women with a good functional capacity, pregnancy is usually well tolerated, but worsening tricuspid regurgitation or ventricular dysfunction or arrhythmias may occur and be poorly tolerated.

Follow-Up.

All patients should have at least annual follow-up visits with a cardiologist who has expertise in the care of patients with congenital cardiac defects. Regular assessment of systemic (tricuspid) AV valve regurgitation by serial echocardiographic studies and systemic ventricular function by MRI or radionuclide angiography should be done. Holter recording can be useful if paroxysmal atrial arrhythmias or transient complete AV block is suspected.

Double-Outlet Right Ventricle

The term *double-outlet right ventricle* describes hearts in which more than 50% of each semilunar valve arises from the morphologic right ventricle. It may coexist with any form of atrial arrangement or AV connection and is independent of the infundibular (conal) anatomy.

Morphology (Fig. 75.39)

Few morphologic descriptors have invoked more discussion and controversy than double-outlet right ventricle. The definition given above is flawed but pragmatic. To some extent this anatomic definition is less important than the understanding of the relationship between the great vessels and the VSD and the anatomy of the outlets to the great vessels, both of which are crucial determinants of clinical presentation and management.

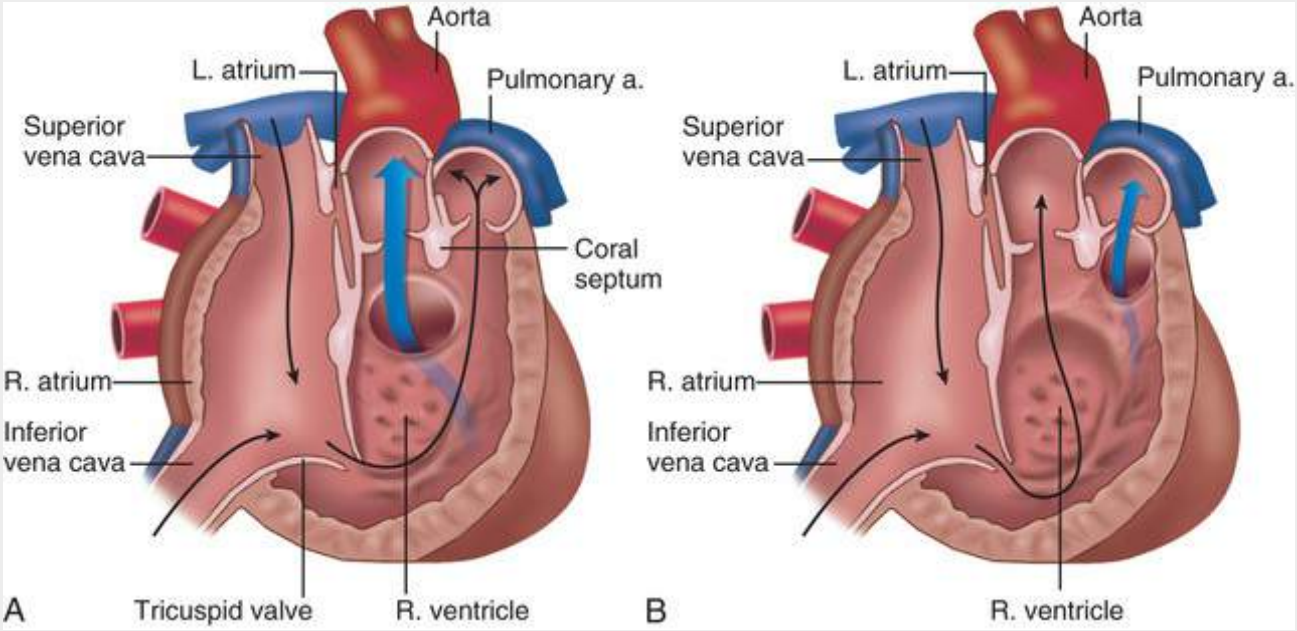


FIGURE 75.39 Double-outlet right ventricle with side-by-side relationship of great arteries is illustrated in both panels. **A,** A subaortic VSD below the crista supraventricularis favors delivery of left ventricular blood to the aorta. **B,** Subpulmonary location of the VSD above the crista favors streaming to the pulmonary trunk. (**A** and **B,** From Castañeda A, Jonas RA, Mayer JE, et al: Cardiac surgery of the neonate and infant. Philadelphia, WB Saunders, 1994, p 446.)

Clinical Features

Three main categories of double-outlet right ventricle exist: (1) double-outlet right ventricle with a subaortic VSD, (2) double-outlet right ventricle with a subpulmonary VSD, and (3) double-outlet right ventricle with a noncommitted VSD.

When present, the anatomy of the infundibular septum further modifies the hemodynamics. Taking double-outlet right ventricle with a *subaortic VSD* as an example, where the aorta and its semilunar valve are closest to, or overriding, the trabecular septum, anterior deviation of the outlet septum causes subpulmonary stenosis, and the clinical scenario and management algorithm are similar or identical to that of tetralogy of Fallot. Conversely, if the outlet septum is deviated posteriorly, there will be subaortic stenosis, often with a coexisting abnormality of the aortic arch. The presentation and management of this variation are therefore entirely different. If there is no deviation of the outlet septum, and no outlet obstruction, the clinical scenario will be that of a simple VSD. Double-outlet right ventricle with a *subpulmonary VSD* (Taussig-Bing anomaly) can be considered along with TGA. This is because the usual position of the pulmonary artery (posterior to and leftward of the aorta) means that the streaming of deoxygenated and oxygenated blood is similar to that of transposition, even though most of the pulmonary valve is connected to the right ventricle. Anterior deviation of the outlet septum causes subaortic stenosis and aortic anomalies, and posterior deviation causes subpulmonary stenosis and limits pulmonary blood flow. It is also important to recognize double-outlet right ventricle with a *noncommitted VSD*. This defines hearts in which the VSD is remote from the outlets, making surgical management particularly difficult.

Associated Lesions

More than half of patients with double-outlet right ventricles have associated anomalies of the AV valves. Mitral valve stenosis or atresia, associated with a hypoplastic left ventricle, is common. Ebstein anomaly of the tricuspid valve, complete AV septal defect, and overriding or straddling of either AV valve may

occur.

Laboratory Investigations

Because of the diversity of the underlying anatomies, discussion of the ECG and radiographic features is not included here.

Echocardiography.

This is the mainstay of diagnosis. The commitment of the semilunar valves to the ventricles is ascertained. When present, deviation of the outlet septum beneath a semilunar valve likely has implications for downstream development of the great vessels. For example, when there is subaortic stenosis, the echocardiographic examination is incomplete until abnormalities of the aortic arch have been excluded. Preoperative evaluation must also take into account potential AV valve anomalies and straddling, in particular.

Indications for Intervention

The goals of operative treatment are to establish continuity between the left ventricle and aorta, create adequate right ventricle–to–pulmonary continuity, and repair associated lesions. Palliative surgery is reserved for those in whom biventricular repair is not possible and in those with markedly reduced pulmonary blood flow. In the latter, an aortopulmonary shunt may be placed to temporize before complete correction. For most of the remainder, complete repair is now performed as a primary procedure. In double-outlet right ventricle with a subaortic VSD, repair is accomplished by creating an intraventricular baffle that conducts left ventricular blood to the aorta. If there is coexisting subpulmonary stenosis, the repair is similar to that of tetralogy of Fallot. When the VSD is subpulmonary, but without subpulmonary stenosis, repair is accomplished by closure of the VSD and the arterial switch procedure. Subpulmonary stenosis is frequently present in a double-outlet right ventricle with a subpulmonary VSD. In these cases the aorta is connected to the left ventricle using an intraventricular baffle, and a right ventricle–to–pulmonary artery conduit is placed to complete the repair (Rastelli procedure). Classic surgical approaches cannot be used when the VSD is remote and uncommitted to either semilunar orifice. Occasionally the VSD can be baffled toward the aorta, but when this is not possible, the right ventricle may be used as the systemic ventricle. This requires a Mustard or Senning atrial redirection procedure, closure of the VSD, and placement of a conduit between the left ventricle and the pulmonary trunk.

Interventional Options and Outcomes

The late follow-up of the surgical procedures described earlier (e.g., tetralogy of Fallot repair, arterial switch procedure, Rastelli procedure) tends to be less satisfactory when there is a double-outlet right ventricle than when more classic indications were present. The development of subaortic stenosis is more likely because of the abnormal geometry of the left ventricular outflow tract that often results after correction. Similarly, right ventricle–to–pulmonary artery conduit obstruction is more likely because of the spatial difficulties imposed on placement of the conduit, with respect to the position on the right ventricle and the sternum. Because of these considerations, the options for catheter interventions are often fairly limited. However, recurrent arch obstruction and distal pulmonary artery obstruction are amenable to balloon dilation with or without stenting.

Follow-Up

All of these patients require at least annual review by a congenital cardiologist.

Left Ventricular Outflow Tract Lesions (Fig. 75.40)

Coarctation of the Aorta

Aortic arch obstruction may be divided into (1) localized coarctation in close proximity to a PDA or ligamentum, (2) tubular hypoplasia of some part of the aortic arch, and (3) aortic arch interruption.

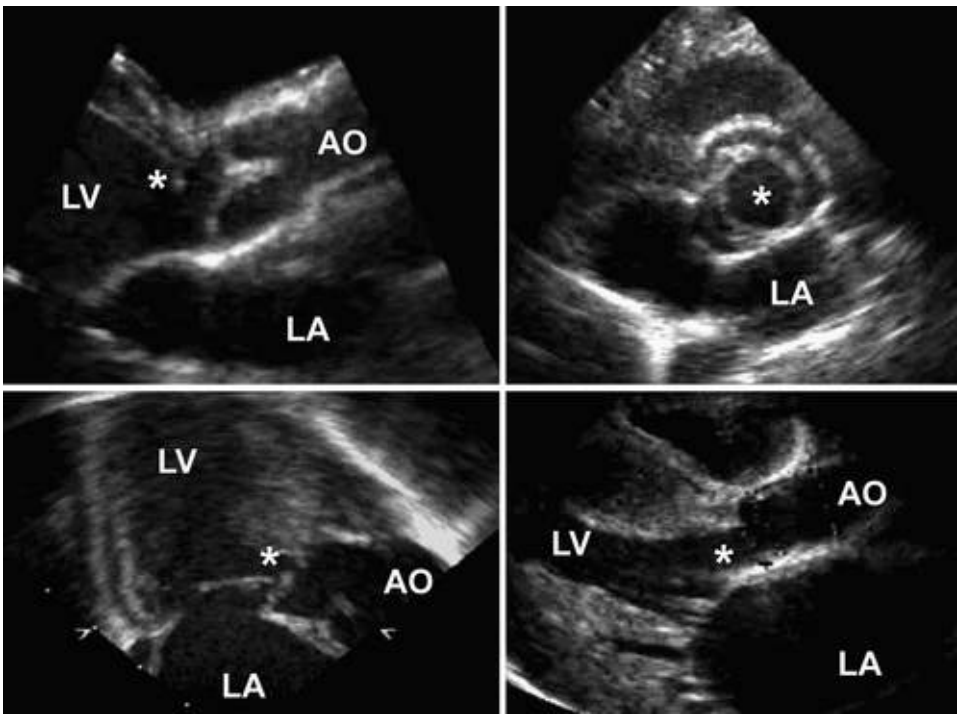


FIGURE 75.40 Montage demonstrating the different types of left ventricular outflow tract obstruction (*asterisks*). The upper left image shows isolated fibromuscular obstruction; the upper right, stenosis due to a bicuspid aortic valve; the lower left, obstruction because of chordal apparatus from the anterior mitral leaflet; and the lower right, obstruction due to tunnel narrowing at the valvular, annular, and subvalvular level. *AO*, aorta; *LA*, left atrium; *LV*, left ventricle.

Localized Aortic Coarctation

Morphology

This lesion consists of a localized shelf in the posterolateral aortic wall opposite the ductus arteriosus. Associated isthmic hypoplasia, which is common in the infant presentation, has important long-term implications, because persistent arch hypoplasia, even in the absence of a discrete obstruction, is one of the mechanisms of ongoing hypertension.

Clinical Features.

Coarctation occurs two to five times more commonly in males, and there is a high degree of association with gonadal dysgenesis (Turner syndrome) and bicuspid aortic valve (≥50%). Other common associated

anomalies include VSD and mitral stenosis or regurgitation. Additional lesions have an impact on the outcome.

Beyond the neonatal period the majority of patients with isolated coarctation are asymptomatic, with the findings of reduced femoral pulses and/or hypertension. Heart failure is uncommon because the left ventricle has a chance to become hypertrophied, thus maintaining a normal wall stress. Complaints of headache, cold extremities, and leg fatigue with exercise may be noted in the older patient.

Presentation in adulthood again may be entirely asymptomatic, and picked up during routine health checks, usually because of the discovery of a murmur or unexplained hypertension. Indeed, coarctation of the aorta should be excluded in all new cases of hypertension, by clinical examination of the pulses and upper and lower limb blood pressure measurements (see below). In some adolescents and adults, presentation is with symptoms of functional decline, in the setting of concentric left ventricular hypertrophy, or in more extreme cases, left ventricular dilation and dysfunction. Associated abnormalities include intracranial aneurysms (most commonly of the circle of Willis) in 2% to 10% and acquired intercostal artery aneurysms. One definition of *significant aortic coarctation* requires a gradient of more than 20 mm Hg across the coarctation site at angiography with or without proximal systemic hypertension. A second definition of significant aortic coarctation requires the presence of proximal hypertension in the company of echocardiographic or angiographic evidence of aortic coarctation. If there is an extensive collateral circulation there may be a minimal pressure gradient or no gradient at all and acquired aortic atresia.

Death in patients who do not undergo repair is most often due to heart failure (usually in patients > 30 years of age), coronary artery disease, aortic rupture or dissection, concomitant aortic valve disease, infective endarteritis or endocarditis, or cerebral hemorrhage. Of Turner syndrome patients, 35% have aortic coarctation.

Leg claudication (pain) is rare unless there is concomitant abdominal aortic coarctation. A thorough clinical examination reveals upper limb systemic hypertension, as well as a differential systolic blood pressure of at least 10 mm Hg (brachial artery > popliteal artery pressure). Radial-femoral pulse delay is evident unless significant aortic regurgitation coexists. Auscultation may reveal an interscapular systolic murmur emanating from the coarctation site and a widespread crescendo-decrescendo systolic murmur throughout the chest wall from the intercostal collateral arteries. Funduscopic examination can reveal “corkscrew” tortuosity of retinal arterioles.

Laboratory Investigations

ECG.

This reveals left ventricular hypertrophy of various degrees, depending on the height of arterial pressure above the obstruction and the patient's age. Coexisting right ventricular hypertrophy usually implies a complicated lesion.

Chest Radiography.

The characteristic posteroanterior film feature is the so-called figure-3 configuration of the proximal descending thoracic aorta due to both prestenotic and poststenotic dilation. Rib notching (unilateral or bilateral, second to ninth ribs) is present in 50% of cases. Rib notching is unilateral if the right or left subclavian arteries arise from the aorta distal to the coarctation. Rib notching is noted as an erosion of the undersurface of a posterior rib, usually at its outer third, with a sclerotic margin.

Echocardiography.

This demonstrates a posterior shelf, a well-expanded isthmus and transverse aortic arch (in most cases), and a high-velocity jet with diastolic persistence through the coarctation site. Interestingly, a slow upstroke is observed on the abdominal aortic velocity profile compared with that seen in the ascending aorta.

MRI.

This provides detailed information in this age-group and may be performed before intervention,[63] particularly if balloon dilation is the treatment of choice. This is the best tool for postintervention imaging surveillance[64] and has become routine in many centers.

Angiocardiography.

This is reserved for delineating the coarctation at the time of balloon dilation or stent placement (Videos 75.81 to 75.83).Primary management in those cases with a well-expanded isthmus and transverse aortic arch invariably involves balloon dilation and/or stent placement (Video 75.84).

Interventional Outcomes.

Surgical repair of simple coarctation usually relieves the obstruction, with a minimal mortality rate (1%). Paraplegia due to spinal cord ischemia is uncommon (0.4% or perhaps less)[65] and may occur in patients who do not have a well-developed collateral circulation. The prevalence of recoarctation reported in the literature varies widely, from 7% to 60%, but is probably about 10% depending on the definition used, the length of follow-up, and the age at surgery. The appropriateness of the surgical repair for a given anatomy is probably the main factor dictating the chance of recoarctation rather than the type of surgical repair itself. True aneurysm formation at the site of coarctation repair is also a well-recognized entity, with a reported incidence of between 2% and 27%. Aneurysms are particularly common after Dacron patch aortoplasty and usually occur in the native aorta opposite the patch. Late dissection at the repair site is rare, but false aneurysms, usually at the suture line, can occur. Long-term follow-up after surgical correction of coarctation of the aorta still reveals an increased incidence of premature cardiovascular disease and death, mainly resulting from prevalent associated risk factors (i.e., male sex, hypertension, and hyperlipidemia).[66] The respective roles of stent therapy and surgery over balloon dilation of aortic coarctation are becoming better defined.[67]

The outcomes of *transcatheter techniques* may involve complications. After balloon dilation (**Fig. 75.41**), aortic dissection, restenosis, and aneurysm formation at the site of coarctation all have been documented. These complications have been reduced with the now increasing if not exclusive use of primary stenting in the adults with native coarctation as well as recoarctation.[68] Medium-term outcomes of stent therapy in children have also been favorable.[69] The significance of aneurysm formation is often unknown, and longer-term data are necessary.

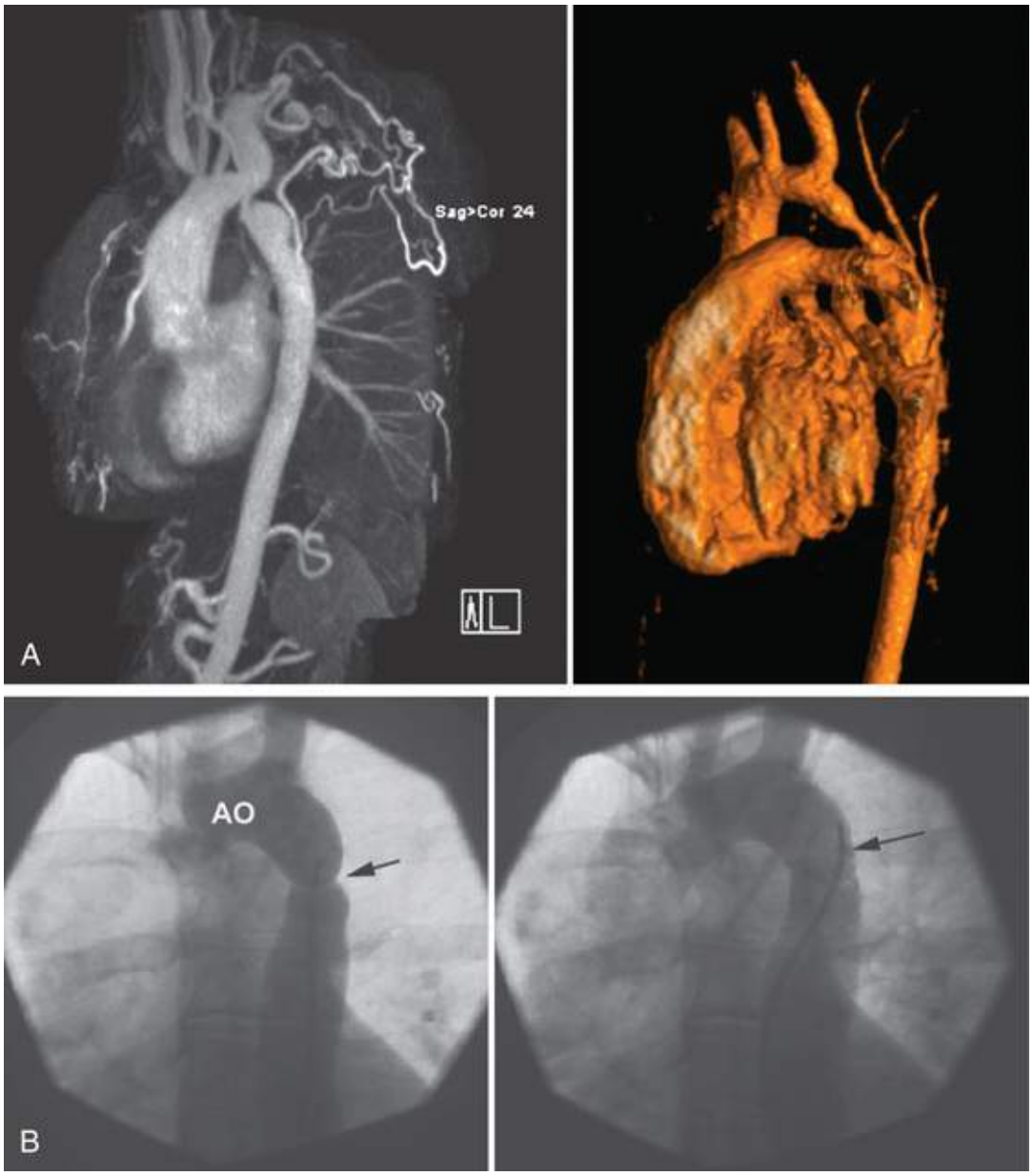


FIGURE 75.41 **A,** Montage of coarctation of the aorta. The left image shows the site of the posterior shelf. The right image is from an MRI and shows the posterior shelf and some associated transverse arch hypoplasia. **B,** Angiogram of coarctation of the aorta, before and after stenting. *AO*, aorta.

Prior hypertension resolves in up to 50% of patients but may recur later in life, especially if the intervention is performed at an older age.[70] In some of these patients, this may be essential hypertension, but a hemodynamic basis should be sought and blood pressure control should be attained. Systolic hypertension is also common with exercise and is not a surrogate marker for recoarctation of the aorta.[70,71] It may be related to residual arch hypoplasia or to increased renin and catecholamine activity from residual functional abnormalities of the precoarctation vessels. The criteria for and significance of exertional systolic hypertension are controversial, but its presence may predict the future development of chronic hypertension.[71] Late cerebrovascular events occur, notably in patients undergoing repair as adults and in those with residual hypertension. Endocarditis or endarteritis can occur at the coarctation site or on intracardiac lesions; if this occurs at the coarctation site, embolic manifestations are restricted to the legs.

Reproductive Issues.

Patients with repaired aortic coarctation usually tolerate pregnancy well unless they have hemodynamically significant residual lesions, such as severe recoarctation or aortic stenosis from a bicuspid aortic valve. A greater propensity to develop hypertension during pregnancy has, however, been

reported.[72]

Follow-Up.

All patients should have a follow-up examination every 1 to 3 years. Particular attention should be directed toward residual hypertension; heart failure; intracardiac disease such as an associated bicuspid aortic valve, which can become stenotic or regurgitant later in life; or an ascending aortopathy sometimes seen in the presence of a bicuspid aortic valve. Complications at the site of repair such as restenosis and aneurysm formation should also be sought using clinical examination, chest radiography, echocardiography, and periodic MRI or CT scanning.[64] Patients with a Dacron patch repair should probably undergo an MRI or a spiral CT examination every 3 to 5 years or so to detect subclinical aneurysm formation. Hemoptysis from a leaking or ruptured aneurysm is a serious complication requiring immediate investigation and surgery. New or unusual headaches raise the possibility of berry aneurysms. It has long been said that coarctation patients are prone to premature coronary artery disease, but a recent study did not confirm this suspicion.[66] There is substantial evidence of a generalized arteriopathy in coarctation patients that is not addressed by relief of the obstruction.[73]

Aortic Arch Interruption.

Aortic arch interruption is a rare lesion, but one where surgical success has resulted in an ever-growing number of older children, adolescents, and, now, adults with a history of surgical intervention. Of importance, it is associated with DiGeorge syndrome with microdeletion of chromosome 22. Interruptions distal to the left subclavian artery (type A) occur almost as frequently as interruptions distal to the left common carotid artery (type B). The right subclavian artery is of variable origin, frequently arising from the descending aortic segment distal to the interruption.

Virtually all patients have associated intracardiac anomalies, typically either a VSD (80% to 90% of cases) or an aorticopulmonary window (10% to 20%). As well, muscular left ventricular outflow tract obstruction is a common association in those with a VSD, this being due to posterior deviation of the outlet septum. Other complex intracardiac malformations such as TGA, aortopulmonary window, and truncus arteriosus are common.

Primary repair at the time of presentation is the main mode of treatment, and includes a direct connection between the interrupted segments in conjunction with closure of the VSD. Surgical resection of the posteriorly deviated outlet septum is dealt with at the time of primary repair in some centers, whereas others address it at a later date.

The medium- and long-term outcomes are reasonable,[74] but there may be a need for reintervention for left ventricular outflow tract obstruction and recurrent arch obstruction.

Congenital Aortic Valve Stenosis

Congenital aortic valve stenosis is a relatively common anomaly. It occurs much more frequently in males, with a gender ratio of 4 : 1. Associated cardiovascular anomalies have been noted in up to 20% of patients. PDA and coarctation of the aorta occur most frequently with aortic valve stenosis; all three of these lesions may coexist. As well, congenital abnormalities of the mitral valve and endocardial fibroelastosis are encountered more frequently in early presentations, but the clinical sequelae may persist into adulthood.

Morphology

The basic malformation consists of thickening of the valve tissue with various degrees of commissural fusion. Despite the fusion of the leaflets, in most cases there are still three sinuses. The valve is most commonly bicuspid; in most cases, this is the result of fusion of two leaflets, rather than an actual absence of one of the leaflets. The fusion usually involves the two coronary sinuses, or the right and noncoronary sinus. In some patients (usually newborns), the stenotic aortic valve is unicuspid and dome shaped, with no attachment or just one lateral attachment to the aorta at the level of the orifice. In infants and young children with severe aortic stenosis, the aortic valve annulus may be relatively underdeveloped. Aortopathy is a common association and results in associated dilation of the ascending aorta and sinuses.

Clinical Presentation

For the adult cardiologist, a history of aortic valve stenosis in a newborn is relevant because it shows that this population invariably does not have isolated aortic valve pathology. It is common for them to have associated endocardial fibroelastosis, as well as abnormalities of their mitral valves. These patients as newborns often present in heart failure, are usually managed with balloon dilation at the time of presentation, and invariably have ongoing aortic valve issues in the form of residual stenosis and/or regurgitation. Many require reintervention in their younger years in the form of further balloon dilation or aortic valve replacement. These patients are surviving into their adolescent and young adult years, and will have more ongoing issues than those who present at a later date. In older children, adolescents, and adults, the diagnosis is usually made following the detection of a murmur. Symptomatic functional decline, presyncope, and syncope are rarely the first presenting features. Natural history studies performed several years ago demonstrated that a more rapid progression of aortic valve stenosis is more likely to happen within the first 2 years of life, following which the rate of progressive obstruction is more uniform.

Clinical Findings

In general most patients beyond the neonatal period are asymptomatic, having normal peripheral pulses if the stenosis is less severe, and low-volume, slow-rising pulses when it progresses. Exercise fatigue and chest pain occur only when the stenosis is severe. With severe stenosis there is a systolic thrill in the same area that can also be felt in the suprasternal notch and carotid arteries. Beyond the newborn period there is usually an ejection click at the apex that precedes the murmur. The second heart sound is usually normal in children, with reversed splitting seen only in older patients with severe stenosis. A systolic ejection murmur is heard along the left sternal border, with radiation into the right infraclavicular area. Associated aortic regurgitation may be heard.

Laboratory Investigations

ECG.

Left ventricular hypertrophy with or without strain is the hallmark feature.

Chest Radiography.

The overall heart size is normal unless left ventricular remodeling is severe or there is important associated valvar regurgitation. Dilation of the ascending aorta can be seen in those with an associated aortopathy.

Echocardiography.

Two-dimensional echocardiography provides detailed information about the morphology of the valve, the left ventricular function, and the presence of associated left-sided lesions. Doppler echocardiography can be used to determine the severity of stenosis and the presence or absence of associated aortic regurgitation. Doppler imaging provides peak instantaneous gradients that are higher than the peak-to-peak gradients determined from cardiac catheterization. Mean gradients as derived from Doppler imaging and catheterization correlate closely and can be used in the decision process for patients outside the pediatric age-group. The aortic valve area (determined by the modified Gorlin equation, which provides accurate information on valve areas) is used in the adult population. Whatever the absolute number chosen to work with, the additional finding of left ventricular hypertrophy on ECG and echocardiography provides supportive data regarding the timing for intervention. The pediatric community generally agrees that a peak-to-peak gradient of 60 mm Hg or more probably warrants intervention even in the absence of symptoms, although clearly the thresholds for intervention are different in adults.[75]

Cardiac Catheterization.

Cardiac catheterization is now rarely used to establish the site and severity of obstruction to the left ventricular outflow. Instead, catheterization is undertaken when therapeutic interventional balloon aortic valvuloplasty is indicated in children and young adults, and to determine if associated coronary artery disease is present in the adult population.

Cardiac MRI.

In older patients, providing an adequate evaluation of the ascending aorta can be difficult with echocardiography; MRI overcomes this limitation, providing data that can help determine if aortic root surgery is necessary, either independently or at the time of aortic valve intervention.

Management Options

In this era, balloon dilation has almost completely replaced primary surgical valvotomy in the pediatric population (Video 75.85). Balloon valvuloplasty retains a place in the management of adolescents and young adults, but with increasing age it becomes a less attractive option; it is rarely successful in those with sclerotic and calcified valves, at any age. A 2012 paper compared the results of surgical versus balloon therapy for congenital aortic stenosis.[76] Another described the midterm outcomes of the Ross procedure in infants.[77]

Genetic Implications

The incidence of bicuspid aortic valve in first-degree relatives is such that when a new index case is diagnosed, family members should be screened. This usually involves the parents and any siblings. This is important because some individuals with a bicuspid aortic valve have neither significant stenosis nor regurgitation, but do have associated aortopathy with progressive dilation of the aortic root that may lead to aortic dissection.

Follow-Up

Follow-up studies indicate that aortic valvotomy in children and adolescents is a safe and effective means of palliative treatment with excellent relief of symptoms. Aortic regurgitation can occasionally be progressive and require valve replacement. Moreover, after commissurotomy, the valve leaflets remain

somewhat deformed, and further degenerative changes including calcification will likely lead to significant stenosis in later years. Thus prosthetic aortic valve replacement is required in approximately 35% of patients within 15 to 20 years of the original operation. For those children and adolescents requiring aortic valve replacement, the surgical options include replacement with a mechanical aortic valve, an aortic homograft, or a pulmonary autograft in the aortic position (Ross procedure). Accumulating evidence shows that the Ross procedure may ultimately be preferable to the aortic homograft. In the pulmonary autograft, the patient's pulmonary valve is removed and used to replace the diseased aortic valve, and the right ventricular outflow tract is reconstructed with a pulmonary valve homograft. This approach appears to confer a survival advantage in the younger age-group, where repeated mechanical valve replacement is associated with an increased mortality rate. Despite this advantage, caution is necessary when the approach is used for patients with a bicuspid aortic valve and aortic regurgitation. This is due to associated aortic root dilation, which is inherent to this lesion and may complicate the long-term durability of the Ross procedure. This surgical approach can be performed in patients of any age, from neonates to adults. Neither homografts nor autografts require anticoagulation.

Subaortic Stenosis

Morphology

Discrete Fibromuscular Lesions.

Such lesions consist of a ridge or fibrous ring encircling the left ventricular outflow tract at varying distances from the aortic valve. The subvalvular fibrous ridge may extend onto the aortic valve cusps and almost always makes contact with the ventricular aspect of the anterior mitral leaflet at its base. In cases with fibrous discontinuity between the mitral and aortic valves, it forms more of a tunnel obstruction.

Focal Muscular Lesions.

Rarely there is a focal muscular obstruction on the crest of the interventricular septum; in some patients, this is a variant of hypertrophic cardiomyopathy, and in others it is not. The way to differentiate the two is through genetic testing, or if that is negative, with echocardiographic follow-up.

Hypoplasia of the Left Ventricular Outflow Tract.

In some cases, valvular and subvalvular aortic stenoses coexist with hypoplasia of the aortic valve annulus and thickened valve leaflets, producing a tunnel-like narrowing of the left ventricular outflow tract. Additional findings often include a small ascending aorta.

Discrete Subaortic Stenosis and VSD.

This combination is frequently encountered in the pediatric age-group, with the fibromuscular component often being absent at the initial echocardiographic evaluation. The association should be suspected in VSDs with some associated anterior malalignment of the aorta and a more acute aortoseptal angle. These hearts will also develop a double-chambered right ventricle from hypertrophied right ventricular muscle bundles. In a different subset of patients with aortic arch interruption and a VSD, there is muscular subaortic stenosis due to posterior deviation of the infundibular septum.

Clinical Features

These types of obstruction are not truly “congenital” because they are rarely present at birth, but are acquired later, in an otherwise normal heart or when there are associated VSDs or aortic arch obstruction.

Most patients have a systolic murmur and consequently are referred for evaluation. It is a systolic ejection murmur best heard along the lower left sternal border with the absence of an ejection click. There is often a carotid thrill, however.

Laboratory Investigations

ECG.

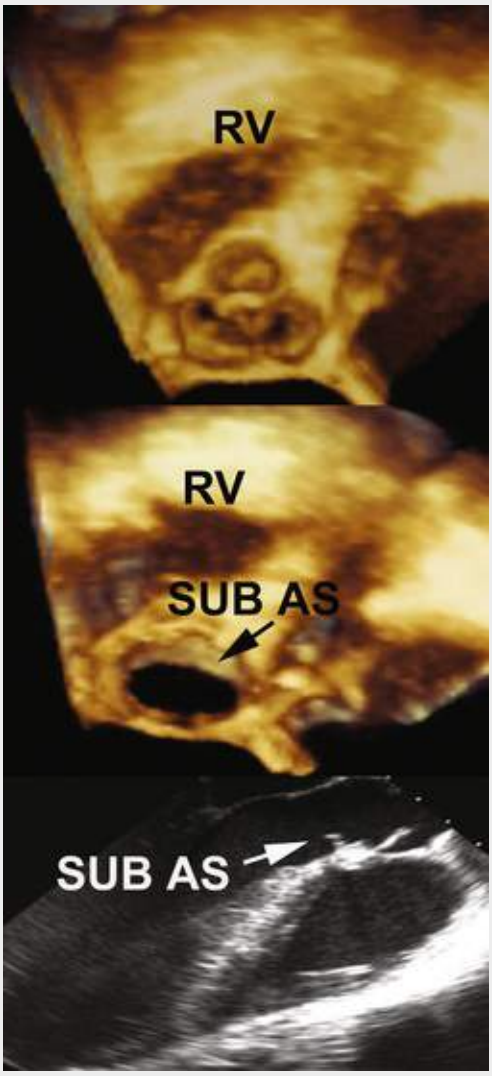
In patients with associated defects, the ECG reflects the major abnormality rather than the associated left ventricular outflow tract obstruction. With isolated forms of left ventricular outflow tract obstruction where the obstruction is significant, there may be left ventricular hypertrophy.

Chest Radiography.

This is usually unhelpful in these patients.

Echocardiography (Videos 75.86 to 75.88).

Echocardiography is the standard diagnostic tool in this lesion. Not only can it permit an accurate delineation of the mechanisms of obstruction, but it provides detailed data regarding associated lesions. In all forms the parasternal long axis view is key to providing an accurate diagnosis. The presence of mitral aortic discontinuity, the relationship of a fibromuscular ridge to the aortic valve, the presence of accessory obstructive tissue, and the dimensions of the aortic annulus and root all are well imaged in this view. In addition, color flow mapping permits the identification of associated aortic valve regurgitation and provides hemodynamic evidence of the site of onset of obstruction. The extension of a fibromuscular ridge onto the anterior mitral leaflet is best appreciated in the apical five-chamber view. This also provides the best site for pulsed or continuous-wave Doppler assessment of the maximum gradient across the left ventricular outflow tract. In the older patient TEE plays an important role in delineating the pathology. Real-time 3D echocardiography provides additional information, particularly in patients with complex mechanisms of left ventricular outflow tract obstruction (**eFig. 75.6**).



EFIGURE 75.6 These images demonstrate fibromuscular subaortic stenosis as seen by 3D echocardiography. The upper two panels show the aortic valve as seen by the surgeon; the middle image is just distal to that and shows the crescent-shaped subaortic membrane. The lower image shows the fibromuscular ridge as seen by transesophageal 2D echocardiography. *RV*, right ventricle; *SUB AS*, subaortic stenosis.

Cardiac Catheterization.

This technique is no longer of importance in evaluating this lesion. Balloon dilation of discrete fibrous ridges has recently been reported from one center to have had favorable long-term outcomes,[78] although it is rarely the treatment of choice.

MRI.

In general, MRI is unnecessary unless there are problems obtaining the needed information by echocardiography.

Interventional Options

Surgical intervention is indicated either at the time of the repair of the underlying primary lesion or in those patients with discrete obstruction when the obstruction is severe enough to raise concerns.

Discrete Subaortic Stenosis (Fibrous and Muscular Stenosis).

The rate of progression is varied and may be slow. In general the approach to the latter group has been to intervene when there is a mean echocardiography gradient across the left ventricular outflow tract of greater than 30 mm Hg to avoid future aortic leaflet damage and minimize recurrence. Surgery involves a

fibromyectomy, with the approach being through the aortic root, with care taken to avoid damage to the aortic valve or to create an iatrogenic VSD. There is a recurrence rate of subaortic stenosis requiring reoperation in up to 20% percent of patients.· In some cases the recurrence is in the form of a fibrous ridge, whereas in others there is acquired pathology of the aortic valve in the form of stenosis and/or regurgitation. Reoperation may just involve repeat resection of a recurrent fibrous ridge or, in patients with significant aortic regurgitation, it may involve surgery on the aortic valve.

Complex Forms of Left Ventricular Outflow Tract Obstruction and an Intact Ventricular Septum.

In patients with an intact ventricular septum, the indications for intervention are similar to those with discrete obstruction. The difference lies in the fact that the surgical approach must be modified according to the underlying pathology, and that reoperation is more frequent. Resection of any fibromuscular component or accessory tissue (provided it is not a primary support mechanism for the mitral valve); a valve-sparing Konno operation; and, in those cases with a hypoplastic aortic annulus, a classic Konno procedure with aortic valve replacement are the potential surgical options.

Left Ventricular Outflow Tract Obstruction and Complex Forms of Chd.

In general, surgery on the left ventricular outflow tract is part of the general repair of the lesion and is not dependent on the precise degree of obstruction across this site.

Outcomes

Immediate complications related to surgery include complete AV block, inadvertent creation of a VSD, or mitral regurgitation from intraoperative damage to the mitral valve apparatus. Long-term complications include recurrence of fibromuscular subvalvular left ventricular outflow tract obstruction (≤20%), clinically important aortic regurgitation, and valvular aortic stenosis (especially in the context of a bicuspid aortic valve or aortic coarctation).[79,80] In some patients with predominant acquired aortic valve stenosis, balloon dilation has been the treatment of choice.

Follow-Up

Particular attention should be paid to patients with residual or recurrent subaortic stenosis or those with an associated bicuspid aortic valve or important aortic regurgitation because they are most likely to require surgery eventually. Reoperation is more likely in patients with complex forms of obstruction, those who are younger at the time of operation, and those who had incomplete relief of obstruction at the initial procedure. Patients with bioprosthetic aortic valves in the aortic position (following the Konno procedure) or the pulmonary position (following the Ross-Konno procedure) need close follow-up. Endocarditis prophylaxis should be used for patients with prosthetic valves.

Supravalvular Aortic Stenosis

Morphology

Three anatomic types of supravalvular aortic stenosis are recognized, although some patients may have findings of more than one type. Most common is the hourglass type, in which marked thickening and

disorganization of the aortic media produce a constricting annular ridge at the superior margin of the sinuses of Valsalva. The membranous type is the result of a fibrous or fibromuscular semicircular diaphragm with a small central opening stretched across the lumen of the aorta. Diffuse hypoplasia of the ascending aorta characterizes the third type.

Because the coronary arteries arise proximal to the site of outflow obstruction in supravalvular aortic stenosis, they are subjected to the elevated pressure that exists within the left ventricle. These vessels are often dilated and tortuous, and premature coronary atherosclerosis has been described. Moreover, if the free edges of some or all of the aortic cusps adhere to the site of the supravalvular stenosis, coronary artery inflow may be compromised. The left ventricle may have a "ballerina foot" configuration, which can result in muscular left ventricular outflow tract obstruction, particularly when associated with significant supravalvular obstruction.

Clinical Features

The clinical picture of supravalvular obstruction differs in major respects from that observed in the other forms of aortic stenosis. Chief among these differences is the association of supravalvular aortic stenosis with Williams syndrome.

Williams Syndrome

The designation *supravalvular aortic stenosis syndrome*, *Williams syndrome*, or *Williams-Beuren syndrome* has been applied to the distinctive picture produced by the coexistence of the cardiac features in the setting of a multisystem disorder. Beyond infancy in these patients, a challenge with vitamin D– or calcium-loading tests unmasks abnormalities in the regulation of circulating 25-hydroxyvitamin D.

The entire spectrum of clinical manifestations includes auditory hyperacusis, inguinal hernia, a hoarse voice, and a typical personality that is outgoing and engaging. Other manifestations of this syndrome include intellectual impairment, "elfin facies," narrowing of peripheral systemic arteries (beware of coexistent renal artery stenosis) and pulmonary arteries, strabismus, and abnormalities of dental development consisting of microdontia, enamel hypoplasia, and malocclusion.

In an older child or adult, progressive joint limitation and hypertonia may become a problem. Adult patients are usually handicapped by their developmental disabilities.

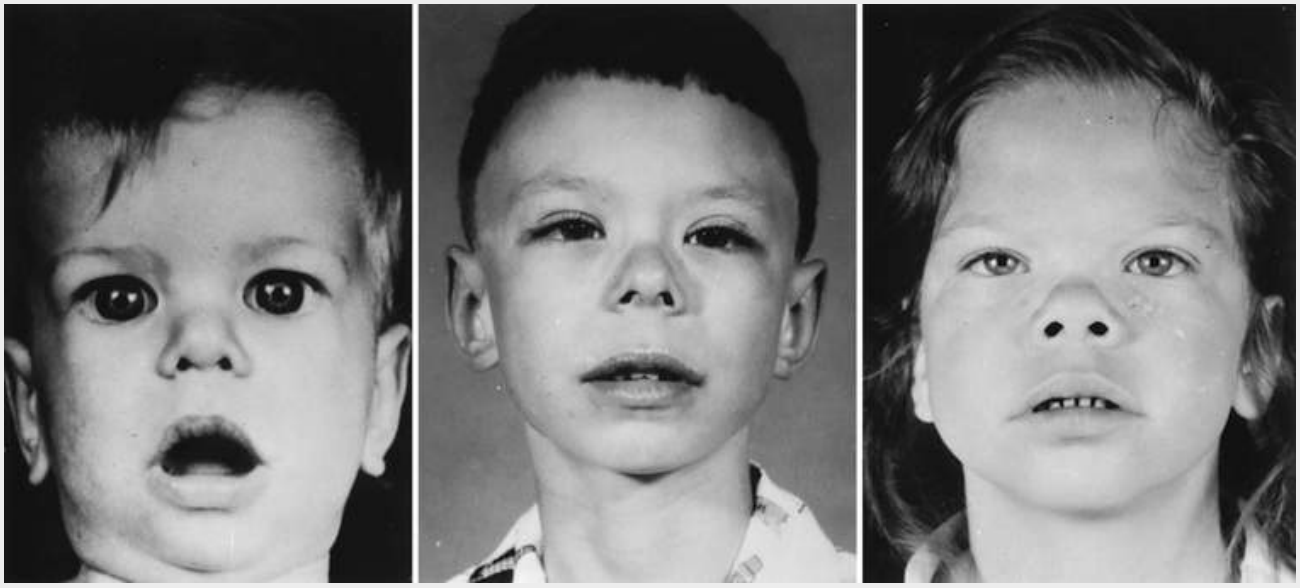
Williams syndrome was previously considered to be nonfamilial; however, most patients have anomalies in the elastin gene on chromosome 7q11.23. Elastin is an important component of the arterial wall, but precisely how mutations in elastin genes cause the phenotypes of supravalvular aortic stenosis is not known.

Familial Autosomal Dominant Presentation

Occasionally the aortic anomaly and peripheral pulmonary arterial stenosis are also found in familial and sporadic forms not associated with the other features of the syndrome. Affected patients have normal intelligence and are normal in facial appearance. Genetic studies suggest that when the anomaly is familial, it is transmitted as autosomal dominant with variable expression. Some family members may have peripheral pulmonary stenosis either as an isolated lesion or in combination with the supravalvular aortic anomaly.

Clinical Features

Patients with Williams syndrome are intellectually challenged (**eFig. 75.7**). The typical appearance is similar to that of the elfin facies observed in the severe form of idiopathic infantile hypercalcemia and is characterized by a high prominent forehead, stellate or lacy iris patterns, epicanthal folds, an underdeveloped bridge of the nose and mandible, an overhanging upper lip, strabismus, and anomalies of dentition.



EFIGURE 75.7 Typical elfin facies in three patients with supravalvular aortic stenosis. (From Friedman WF, Kirkpatrick SE: Congenital aortic stenosis. In Adams FH, Emmanouilides GC, Riemenschneider TA, et al [editors]: Moss' heart disease in infants, children, and adolescents, 4th ed. Baltimore, Williams & Wilkins, 1989.)

Prior studies of the natural history of the principal vascular lesions in these patients—supravalvular aortic stenosis and peripheral pulmonary artery stenosis—indicate that the aortic lesion is usually progressive, with an increase in the intensity of obstruction related often to poor growth of the ascending aorta. This has recently been questioned in a longitudinal single-center study, where those with smaller gradients at presentation appeared to have evidence of regression of their stenosis. Those with pulmonary branch stenosis, whether associated with the aortic lesion or not, tend to show no change in or a reduction in right ventricular pressure with time.

With few exceptions, the major *physical findings* resemble those observed in patients with aortic valve stenosis. Among these exceptions are accentuation of aortic valve closure due to elevated pressure in the aorta proximal to the stenosis, an absent ejection click, and the especially prominent transmission of a thrill and murmur into the jugular notch and along the carotid vessels. The narrowing of the peripheral pulmonary arteries may produce a late systolic or continuous murmur heard best in the lung fields and is usually accentuated by inspiration. Another hallmark of supravalvular aortic stenosis is that the systolic pressure in the right arm is usually higher than in the left arm. This pulse disparity may relate to the tendency of a jet stream to adhere to a vessel wall (*Coanda effect*) and selective streaming of blood into the innominate artery.

Laboratory Investigations

ECG.

There will be left ventricular hypertrophy when the obstruction is severe. Biventricular or even right ventricular hypertrophy may be found if there is significant narrowing of peripheral pulmonary arteries.

Chest Radiography.
In contrast to valvular stenosis, dilation of the ascending aorta or pulmonary artery is absent.

Echocardiography.
This is a valuable technique for localizing the site of obstruction to the supravalvular area. Most often the sinuses of Valsalva are dilated and the ascending aorta and arch appear small or of normal size. The diameter of the aortic annulus is always greater than that of the sinotubular junction. The proximal coronary arteries may become aneurysmal. Doppler examination determines the location of obstruction but usually overestimates the gradient compared with that obtained at cardiac catheterization. This results from the obstruction being lengthy, and the Doppler gradient is overestimated due to the phenomenon of pressure recovery.

Angiocardiography.
This is necessary to define an accurate hemodynamic gradient across the left ventricular outflow tract, as well as to determine the status of the coronary arteries. Echocardiography alone provides inadequate imaging of the coronary arteries, and in some instances there is no clinical evidence of coronary compromise prior to surgery due to the high proximal coronary perfusion pressure, which becomes evident in the immediate or early postoperative period, when the perfusion pressure falls because of the relief of the obstruction.

Usually it also involves an assessment of the branch pulmonary arteries, as well as the brachiocephalic, renal, and mesenteric arteries, all of which can be stenotic. Because of the nature of the anatomic defect, transcatheter balloon angioplasty, with or without stenting, is not an effective treatment option.

Interventional Options and Outcomes

Surgical intervention for supravalvular aortic stenosis has been successful in most cases, with good medium- and long-term results. A variety of surgical procedures may be performed, all of which are tailored to the type of pathology. The use of a Y patch, resection with end-to-end anastomosis, or a Ross procedure are the main techniques employed. Additional procedures including osteoplasty or coronary bypass of ostial stenosis, aortic valvuloplasty, and subaortic resection, may be necessary in some cases.

The cardiac prognosis is good, with some patients requiring further surgery for recurrent supravalvular stenosis.[81] Because peripheral pulmonary artery stenosis tends to improve with time, there is a reluctance to attempt intervention, either surgical or via balloon angioplasty. Long-term behavioral and intellectual problems persist.

Congenital Mitral and Tricuspid Valve Anomalies

Congenital Mitral Stenosis

Morphology
Anatomic types of mitral stenosis include the parachute deformity of the valve, in which shortened chordae tendineae converge and insert into a single large papillary muscle, or into one dominant muscle with a few chordae inserting into a second smaller papillary muscle (see Video 75.6); thickened leaflets with shortening and fusion of the chordae tendineae; an anomalous arcade of obstructing

papillary muscles; accessory mitral valve tissue; and a supravalvar circumferential ridge or “ring” of connective tissue arising at the base of the atrial aspect of the mitral leaflets. Associated cardiac defects are common, including endocardial fibroelastosis, coarctation of the aorta, PDA, and left ventricular outflow tract obstruction (Videos 75.89 and 75.90). An association between persistence of the left superior vena cava and obstructive left-sided lesions also exists.

Clinical Features.

In most cases the findings are incidental at the time of evaluation of another left-sided obstructive lesion, such as coarctation of the aorta or aortic valve stenosis. The classic auscultatory findings seen with rheumatic mitral valve stenosis are often absent in the congenital form. Typical findings include a normal S_1, a middiastolic murmur with or without some presystolic accentuation, and no opening snap.

Laboratory Investigations

ECG.

In milder forms this is usually normal, or there may be left atrial hypertrophy, with or without right ventricular hypertrophy due to associated pulmonary hypertension.

Chest Radiography.

This is normal in milder forms, with evidence of pulmonary edema in those cases with more severe obstruction.

Echocardiography.

Two-dimensional and, more recently, 3D echocardiography, combined with Doppler studies, usually provides a complete analysis of the anatomy and function of congenital mitral stenosis. The status of the papillary muscles is best appreciated in the precordial short axis view. If two papillary muscles are present, they are usually closer together than is seen in the normal heart. The precordial long axis view permits identification of a supravalvular mitral ring, as well as the degree of mobility of the valve leaflets. In some instances, the supravalvar ring starts at the annular level, but extends somewhat distally onto the leaflets. Color-flow Doppler imaging allows identification of the level of the obstruction, as well as the presence of mitral valve regurgitation. Pulsed or continuous-wave Doppler imaging provides an accurate assessment of the mean gradient across the mitral valve. The advantage of the pressure half-time lies in the fact that it is independent of cardiac output, unlike the mean gradient across the mitral valve. An indirect assessment of pulmonary artery pressure is also important and is included in the decision process of whether or not to intervene.

Interventional Options and Outcomes.

In asymptomatic cases clinical and echocardiographic follow-up is all that is necessary. The presence of a single papillary muscle in itself does not predict progressive stenosis. If the patient starts to develop pulmonary hypertension or symptoms, surgical intervention is usually indicated. Mitral valve balloon dilation is usually not as successful as it is in rheumatic mitral valve stenosis. Surgery usually involves removing a supramitral ring when present, and splitting both papillary muscles and the fused chordal apparatus in those patients with more common forms of congenital mitral stenosis.[82,83] In general, surgical intervention provides temporary relief, with many operated cases requiring valve replacement later in life.[84,85]

Congenital Mitral Regurgitation

Morphology

Isolated Congenital Mitral Valve Regurgitation.

This is usually due either to an isolated cleft of the anterior mitral valve leaflet or is the result of leaflet dysplasia. In the latter cases there is evidence of shortened chordae in conjunction with dysplastic valve leaflets. In those with an isolated mitral valve *cleft*, the deficiency in the anterior mitral leaflet points toward the left ventricular outflow tract, unlike those cases with an AV septal defect. In general the larger the cleft in the anterior mitral leaflet, the greater the degree of regurgitation.

In cases with a *dysplastic* mitral valve, the chordal apparatus is shortened, with varying degrees of dysplasia of the leaflets.

Complex Congenital Mitral Valve Regurgitation.

This is seen more frequently in association with abnormalities of the ventriculoarterial connection, such as double-outlet right ventricle, transposition and VSD, and corrected transposition. In the first two there is often a cleft in the anterior mitral valve leaflet, with some chordal support apparatus that renders the valve less regurgitant than in those patients with an isolated cleft. In cc-TGA the morphologic mitral valve may have an associated cleft, be dysplastic, or have multiple papillary muscles, all of which increase the tendency for it to be regurgitant.

Clinical Features.

The presence of symptoms relates to the severity of the regurgitation in patients in whom the pathology is isolated to the valve. Exercise intolerance, combined with a pansystolic murmur at the apex, with or without a middiastolic murmur are the cardinal clinical features.

Laboratory Investigations

ECG.

This is either normal or demonstrates left atrial and left ventricular hypertrophy.

Chest Radiography.

This demonstrates cardiomegaly predominantly involving the left ventricle and atrium.

Echocardiography.

Doppler echocardiography and 2D and 3D echocardiography provide an accurate evaluation of the mechanisms and degree of valvular regurgitation. The cleft in the anterior mitral valve leaflet is best seen in the precordial short axis view, pointing toward the left ventricular outflow tract (Videos 75.91 to 75.96). Three-dimensional echocardiography evaluation helps by determining the extent of the cleft. Patients with a dysplastic mitral valve lack mobility of the valve leaflets and have shortened chordae, resulting in the appearance of tethering and poor coaptation. Color Doppler interrogation helps in locating the site of regurgitation. The severity of regurgitation is assessed in the standard fashion. Three-dimensional echocardiography permits a comprehensive evaluation of the mechanisms of regurgitation, with additional information being obtained regarding commissural length, leaflet area, and

sites of regurgitation from color-flow Doppler imaging.

Angiocardiography and MRI.
These procedures are seldom helpful in management planning.

Interventional Options and Outcomes.

The need for intervention depends on the severity of regurgitation and its impact on left ventricular function. Surgery should not be delayed until patients become symptomatic. Surgery involves suture of an isolated cleft, with or without associated commissuroplasties. In those patients with a dysplastic mitral valve, leaflet extension in conjunction with an annuloplasty and commissuroplasty usually results in effective control of the regurgitation in the short and medium term. Despite this, many of these patients end up with a mitral valve replacement at some stage in the future.

Ebstein Anomaly

Morphology

The common feature in all cases of Ebstein anomaly is apical displacement of the septal tricuspid leaflet in conjunction with leaflet dysplasia (**Fig. 75.42**). Many, but not all, have associated displacement of the posterior mural leaflet, with the anterior leaflet never being displaced. Although the anterior leaflet is never displaced apically, it may be adherent to the free wall of the right ventricle, causing right ventricular outflow tract obstruction. The displacement of the tricuspid valve results in “atrialization” (functioning as an atrial chamber) of the inflow tract of the right ventricle and consequently produces a variably small functional right ventricle. Associated anomalies include PFO or ASD in approximately 50% of patients; accessory conduction pathways in 25% (usually right sided); and, occasionally, varying degrees of right ventricular outflow tract obstruction, VSD, aortic coarctation, PDA, or mitral valve disease. Left ventricular abnormalities resembling noncompaction syndrome have also been described.

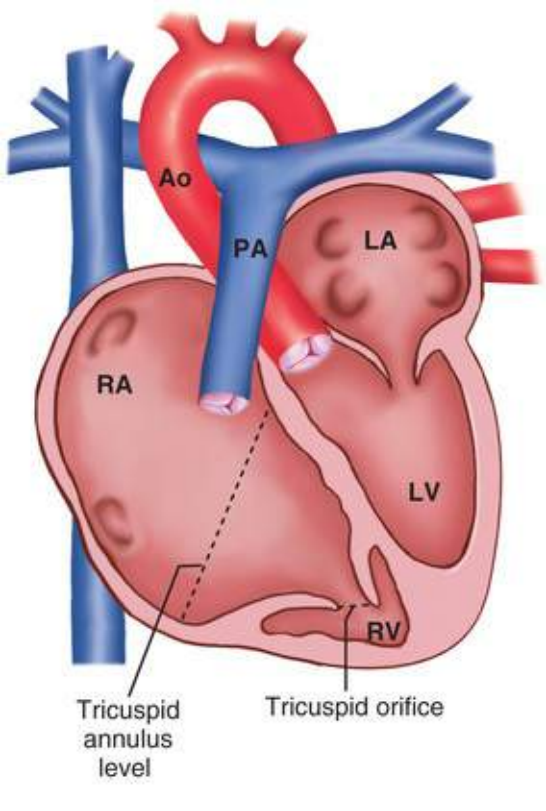


FIGURE 75.42 Diagrammatic representation of Ebstein anomaly. *Ao*, aorta; *LA*, left atrium; *LV*, left ventricle; *PA*, pulmonary artery; *RA*, right atrium; *RV*, right ventricle. (From Mullins CE, Mayer DC: Congenital heart disease: a diagrammatic atlas. New York, Wiley-Liss, 1988.)

Pathophysiology

Varying degrees of tricuspid regurgitation (or exceptionally tricuspid stenosis) result from the abnormal tricuspid leaflet morphology with consequent further right atrial enlargement. Right ventricular volume overload from significant tricuspid regurgitation and infundibular dilation can also be present. Right-to-left shunting through a PFO or ASD occurs if the right atrial pressure exceeds the left atrial pressure (which is often the case when severe tricuspid regurgitation is present).

Natural History.

The natural history of patients with Ebstein anomaly depends on its severity. When the tricuspid valve deformity and dysfunction are extreme, death in utero from hydrops fetalis is the norm. When the tricuspid valve deformity is severe, symptoms usually develop in newborn infants. Patients with moderate tricuspid valve deformity and dysfunction usually develop symptoms during late adolescence or young adult life. Adults with Ebstein anomaly can occasionally remain asymptomatic throughout life if the anomaly is mild; exceptional survival to the ninth decade has been reported.

Clinical Features.

With severe tricuspid valve deformity, newborns and infants present with failure to thrive and right-sided congestive heart failure. In general, children who present after the neonatal period remain asymptomatic until late adolescence or early adult life. Most adult patients present with exercise intolerance (exertional dyspnea and fatigue), palpitations of supraventricular origin, or cyanosis from a right-to-left shunt at the atrial level. Occasionally, a paradoxical embolus resulting in a transient ischemic attack or stroke can call attention to the diagnosis. Right-sided cardiac failure from severe tricuspid regurgitation and right ventricular dysfunction is possible. Sudden death (presumed to be arrhythmic in nature) is described.

Physical examination typically and surprisingly reveals a normal jugular venous pressure because of the large and compliant right atrium and atrialized right ventricle; a widely split S_1 with a loud tricuspid component (the “sail sound”); a widely split S_2 from a right bundle branch block; and a right-sided third heart sound. A pansystolic murmur (typically increasing on inspiration) from tricuspid regurgitation is best heard at the lower left sternal border. Cyanosis from a right-to-left shunt at the atrial level may or may not be present.

Laboratory Investigations

ECG.

The ECG presentation of Ebstein anomaly varies widely. Low voltage is typical. Peaked P waves in leads II and V_1 reflect right atrial enlargement. The PR interval is usually prolonged, but a short PR interval and a delta wave from early activation through an accessory pathway can be present. An rsr′ pattern consistent with right ventricular conduction delay is typically seen in lead V_1, and right bundle branch block is common in adults. Atrial flutter and fibrillation are common. The ECG may be normal.

Chest Radiography.

A rightward convexity from an enlarged right atrium and atrialized right ventricle coupled with a leftward convexity from a dilated infundibulum give the heart a “water bottle” appearance on chest radiography. Cardiomegaly, highly variable in degree, is the rule. The aortic knuckle and the pulmonary trunk are inconspicuous. The pulmonary vasculature is usually normal to reduced.

Echocardiography.

The diagnosis of Ebstein anomaly is usually made by echocardiography (**Fig. 75.43**). Apical displacement of the septal leaflet of the tricuspid valve by 8 mm/m^2 or more, combined with an elongated sail-like appearance of the anterior leaflet, confirms the diagnosis. The size of the atrialized portion of the right ventricle (identified between the tricuspid annulus and the ventricular attachment of the tricuspid valve leaflets) and the systolic performance of the functional right ventricle can be estimated. The degree of tricuspid regurgitation (and rarely stenosis) can be assessed. Associated defects such as ASDs, as well as the presence and direction of shunting, can also be identified (Videos 75.97 to 75.100).

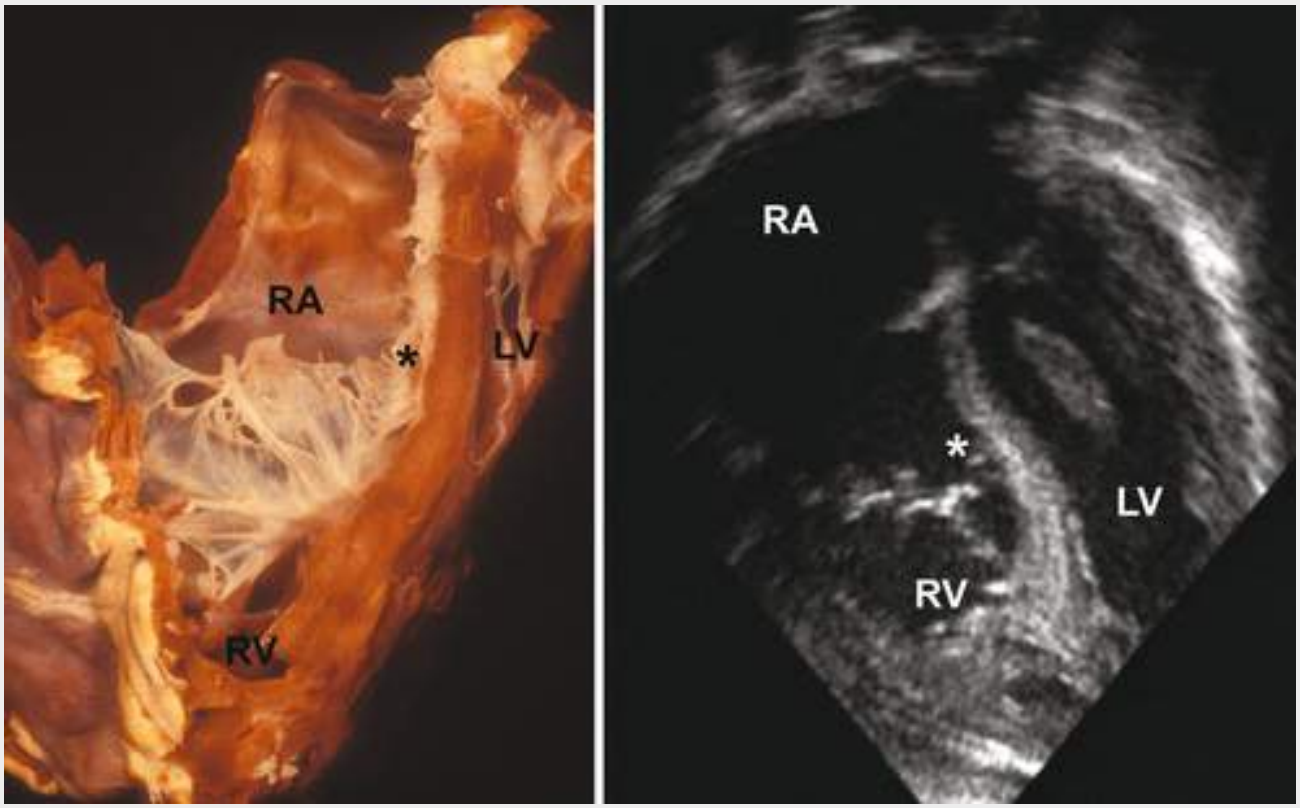


FIGURE 75.43 Apical four-chamber view in Ebstein malformation of the tricuspid valve. Note the significant displacement of the septal tricuspid valve leaflet (*asterisk*), with associated valve dysplasia. *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle.

Angiography.
Cardiac catheterization is required mainly when concomitant coronary artery disease is suspected and to determine if pulmonary artery pressures are elevated. When performed, selective right ventricular angiography shows the extent of tricuspid valve displacement, the size of the functional right ventricle, and the configuration of its outflow tract.

MRI.
This investigation can offer insights into functional right ventricular volume and function.

Indications for Intervention.

Indications for intervention include substantial cyanosis, right-sided heart failure, poor functional capacity, and perhaps the occurrence of paradoxical emboli. Recurrent supraventricular arrhythmias not controlled by medical or ablation therapy and asymptomatic substantial cardiomegaly (cardiothoracic ratio > 60%) are relative indications.[86,87,88]

Interventional Options.

Tricuspid valve repair when feasible is preferable to tricuspid valve replacement. The feasibility of tricuspid valve repair depends primarily on the experience and skill of the surgeon, as well as the adequacy of the anterior leaflet of the tricuspid valve to form a monocusp valve or a cone-like structure.[89] Tricuspid valve repair is possible when the edges of the anterior leaflet of the tricuspid valve are not severely tethered down to the myocardium and when the functional right ventricle is of adequate size (> 35% of the total right ventricle). If the tricuspid valve is irreparable, valve replacement will be necessary, usually with a bioprosthetic tricuspid valve.

For “high-risk” patients (those with severe tricuspid regurgitation, an inadequate functional right

ventricle [because of size or function], and/or chronic supraventricular arrhythmias), a bidirectional cavopulmonary connection can be added to reduce the right ventricular preload if pulmonary artery pressures are low (this procedure in adults is controversial, however, because it may lead to superior vena cava syndrome).[90] Occasionally a Fontan operation may be the best option in patients with tricuspid stenosis and/or a hypoplastic right ventricle. A concomitant right atrial or biatrial maze procedure at the time of surgery should be considered in patients with chronic atrial flutter or fibrillation. If an accessory pathway is present, this should be mapped and obliterated either at the time of surgical repair or preoperatively in the catheter laboratory. Recurrent arrhythmias following ablation do occur because of the multiple pathways and difficult anatomy and may require repeat catheter ablation.[91] An atrial communication, if present, should be closed. In occasional patients with a resting oxygen saturation of more than 90% and exercise intolerance caused by worsening hypoxemia, closure of the PFO/ASD may be indicated without addressing the tricuspid valve itself.

With satisfactory valve repair, the medium- and long-term prognoses are good.[92] Right ventricular remodeling usually occurs[93] and symptomatic improvement is the norm.[94] Late arrhythmias can occur, however. With valve replacement, results are just as satisfactory. Valve re-replacement may be necessary because of a previous failing repair, bioprosthesis, or thrombosed mechanical valve.

Reproductive Issues.

In the absence of maternal cyanosis, right-sided heart failure, or arrhythmias, pregnancy is usually well tolerated.[95]

Follow-Up.

All patients with Ebstein anomaly should have regular follow-up, the frequency being dictated by the severity of their disease. Particular attention should be paid to patients with cyanosis, substantial cardiomegaly, poor right ventricular function, and recurrent atrial arrhythmias. Patients with substantial tricuspid regurgitation following tricuspid valve repair need close follow-up, as do patients with recurrent atrial arrhythmias, degenerating bioprostheses, or dysfunctional mechanical valves.

Valvular and Vascular Conditions (see Chapters 63, 67–70)

Sinus of Valsalva Aneurysm and Fistula

Morphology

The malformation consists of a separation, or lack of fusion, between the media of the aorta and the annulus fibrosus of the aortic valve. The receiving chamber of a right aortic sinus aortocardiac fistula is usually the right ventricle, but occasionally, when the noncoronary cusp is involved, the fistula drains into the right atrium. Approximately 5% to 15% of aneurysms originate in the posterior or noncoronary sinus. The left aortic sinus is seldom involved. Associated anomalies are common and include VSD, bicuspid aortic valve, and aortic coarctation.

Clinical Features

The deficiency in the aortic media appears to be congenital. Reports in infants are exceedingly rare, and they are infrequent in children because progressive aneurysmal dilation of the weakened area develops

but may not be recognized until the third or fourth decade of life, when rupture into a cardiac chamber occurs. A congenital aneurysm of an aortic sinus of Valsalva, particularly the right coronary sinus, is an uncommon anomaly that occurs three times more often in males. An unruptured aneurysm usually does not produce a hemodynamic abnormality. Rarely, myocardial ischemia may be caused by coronary arterial compression. Rupture is often of abrupt onset, causes chest pain, and creates continuous arteriovenous shunting and acute volume loading of both right and left heart chambers, which promptly results in heart failure. An additional complication is infective endocarditis, which may originate either on the edges of the aneurysm or on those areas in the right side of the heart that are traumatized by the jet-like stream of blood flowing through the fistula.

The presence of this anomaly should be suspected in a patient with a combination of chest pain of sudden onset; resting or exertional dyspnea; bounding pulses; and a loud, superficial, continuous murmur accentuated in diastole when the fistula opens into the right ventricle, as well as a thrill along the right or left lower sternal border.

Laboratory Investigations

ECG.

This may show biventricular hypertrophy, or it may be normal.

Chest Radiography.

This may demonstrate generalized cardiomegaly and usually heart failure after the fistula develops.

Echocardiography.

Studies based on 2D and pulsed Doppler echocardiography may detect the walls of the aneurysm and disturbed flow within the aneurysm or at the site of perforation. TEE may provide more precise information than the transthoracic approach.

Cardiac Catheterization.

This reveals a left-to-right shunt at the ventricular or, less commonly, the atrial level; the diagnosis may be established definitively by retrograde thoracic aortography.

Management Options and Outcomes

Preoperative medical management consists of measures to relieve cardiac failure and to treat coexistent arrhythmias or endocarditis, when present. At operation the aneurysm is closed and amputated, and the aortic wall is reunited with the heart, either by direct suture or with a prosthesis. All efforts should be made to preserve the aortic valve in children because patch closure of the defect combined with prosthetic valve replacement greatly increases the risk of operation in small patients. Late results of surgical repair have been excellent.[96] Successful device closure of the ruptured aneurysm has also been reported.

Vascular Rings and Compression

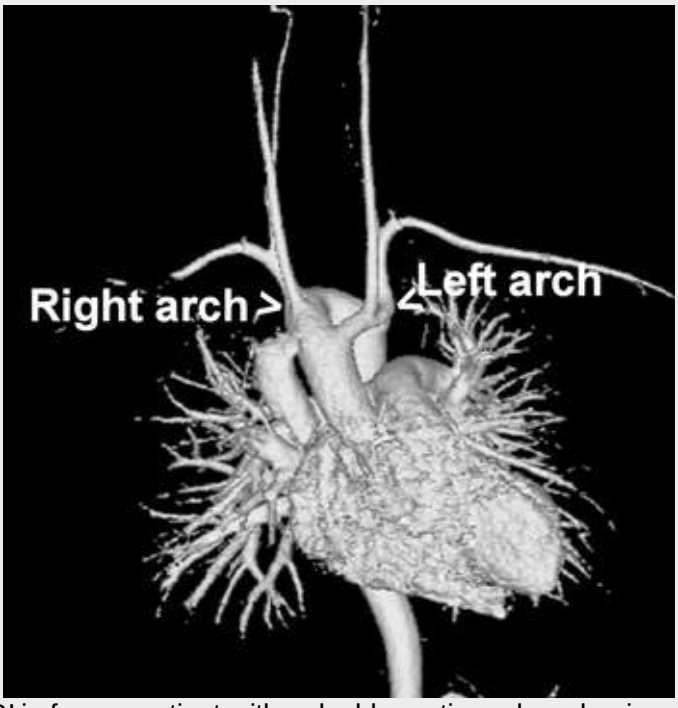
Morphology

The term *vascular ring* is used for those aortic arch or pulmonary artery malformations that exhibit an

abnormal relation with the esophagus and trachea, often causing dysphagia and/or respiratory symptoms.

Double Aortic Arch.

The most common vascular ring is produced by a double aortic arch in which both the right and left fourth embryonic aortic arches persist (**eFig. 75.8**). In the most common type of double aortic arch, there is a left ligamentum arteriosum or occasionally a ductus arteriosus. Although both arches may be patent at the time of diagnosis, invariably the left arch distal to the left subclavian artery is atretic and is connected to the descending aorta by a fibrous remnant that completes the ring. In the setting where both arches are patent, the right arch is typically larger than the left. This usually occurs as an isolated lesion, with the respiratory symptoms being caused by tracheal compression and frequently associated laryngomalacia, usually in the neonate and young infant.



EFIGURE 75.8 This MRI is from a patient with a double aortic arch, a dominant posterior right arch, and a hypoplastic but patent left aortic arch.

Right Aortic Arch.

A right aortic arch with a left ductus or ligamentum arteriosum connecting the left pulmonary artery and the upper part of the descending aorta is the next most frequent vascular ring seen. Although all cases with this lesion have a vascular ring, not all cases are symptomatic. Indeed, those patients who are symptomatic usually have an associated diverticulum of Kommerell. This is a large outpouching at the distal takeoff of the left subclavian artery from the descending aorta. It is the combination of the diverticulum and the ring that causes the airway compression. Other cases without a diverticulum of Kommerell have a loose vascular ring, made up of the aberrant left subclavian artery and a left ligamentum.

Anomalous Origin of a Right Subclavian Artery.

Anomalous origin of a right subclavian artery is one of the most common abnormalities of the aortic arch. Although the aberrant right subclavian artery runs posterior to the esophagus, it does not form a vascular ring unless there is an associated right-sided ductus or ligamentum to complete the ring. During adulthood about 5% of patients with an aberrant right subclavian artery (and a left ductus) develop symptoms

(usually dysphagia rather than respiratory symptoms) owing to rigidity of the aberrant vessel.

Retroesophageal Descending Aorta.

This is a rarer but more problematic type of vascular compression. In this setting there may be either an ascending left and descending right aorta or an ascending right and descending left aorta. The retroesophageal component of the descending aorta causes esophageal, and sometimes tracheal, compression, in conjunction with the left- or right-sided ligamentum.

Pulmonary Artery Sling.

This is usually made up of the left pulmonary artery arising from the right pulmonary artery, which runs posterior to the trachea but anterior to the esophagus. This is usually seen in isolation and can be associated with significant hypoplasia of the tracheobronchial tree, which is the predominant cause of the airway symptoms.

Clinical Features

The symptoms produced by vascular rings depend on the tightness of anatomic compression of the trachea and esophagus and consist principally of respiratory difficulties, including stridor and dysphagia. Not all patients with a vascular ring are symptomatic, and cases with an aberrant left subclavian artery are frequently detected at the time of evaluation for associated CHD such as tetralogy of Fallot. Although most patients with a true ring and some airway compression present early in life, others present later with dysphagia and still others escape diagnosis forever.

Laboratory Investigations

ECG.

This appears normal unless associated cardiovascular anomalies are present.

Chest Radiography.

If there is evidence of a right aortic arch in a symptomatic patient, a vascular ring should be suspected. In some instances, there is evidence of some airway narrowing. The barium esophagogram is a useful screening procedure. Prominent posterior indentation of the esophagus is observed in many of the common vascular ring arrangements, although the pulmonary artery vascular sling produces an anterior indentation.

Echocardiography.

Although echocardiography is a sensitive tool for evaluating the laterality of the aortic arch, including a detailed assessment of the associated brachiocephalic vessels, MRI is rapidly becoming the preferred mode of investigation prior to intervention. This technique has the added advantage of imaging the more posterior structures that run behind the esophagus and trachea. In general, if there is normal branching of the innominate artery, to the right for a left aortic arch and to the left for a right, along with the correct "sidedness" of the descending aorta, then a vascular ring can be excluded. *Most cases with a double aortic arch* have a dominant right arch, with the descending aorta appearing to dip posteriorly as it runs behind the esophagus. A patent ductus or ligamentum can usually be identified by echocardiography. When both arches are patent, a frontal plane sweep from inferior to superior demonstrates both patent arches, as well as their brachiocephalic vessels. *A right aortic arch with an aberrant left subclavian artery* is suspected when it is not possible to identify normal branching of the left-sided innominate artery. *A retroesophageal descending aorta* should be suspected when the ascending aorta and its

brachiocephalic arteries are readily identified but there is difficulty in identifying the descending aorta as it traverses behind the esophagus. *A left pulmonary artery sling* is suspected when the normal branching pattern of pulmonary arteries cannot be identified. In this setting color Doppler imaging permits the identification of the left pulmonary artery as it arises from the right pulmonary artery and runs in a posterior and leftward direction.

MRI and CT.

MRI and CT play a major role in the evaluation of patients with a vascular ring. In fact, MRI has become the gold standard for the evaluation of the aorta and its branches. The only disadvantage for infants is that general anesthesia is often required to achieve a successful examination. On the other hand, spiral CT is a technique that is fast and provides better definition of the affected airways. This latter technique is particularly valuable for patients with a pulmonary artery sling, where the vascular ring often plays a secondary role to the airway abnormalities. The advantages of these techniques are that, unlike echocardiography, they permit a precise assessment of the more posterior vascular structures and their relationships to the esophagus and airways. These techniques are particularly valuable in the more complex forms, such as a retroesophageal descending aorta.

Management Options and Outcomes

The severity of symptoms and the anatomy of the malformation are the most important factors in determining treatment. Patients, particularly infants, with respiratory obstruction require prompt surgical intervention. A left thoracotomy is the surgical approach in most patients with a vascular ring. Operative repair of the double aortic arch requires division of the minor arch (usually the left) and the ligamentum. Patients with a right aortic arch and a left ductus or ligamentum arteriosum require division of the ductus or ligamentum and/or ligation and division of the left subclavian artery, which is the posterior component of the ring. Video-assisted thoracoscopy is an alternative to open thoracotomy for management. In patients with a pulmonary artery vascular sling, surgery consists of detachment of the left pulmonary artery at its origin and anastomosis to the main pulmonary artery directly or by way of a conduit with its proximal end brought anterior to the trachea. The addition of tracheal narrowing that requires surgical intervention adds to the mortality rate in this group of patients, as does the association with intracardiac malformations.

Pulmonary Stenosis with Intact Ventricular Septum

This lesion exists as a continuum, ranging from some patients with an isolated valvular stenosis to others in whom there is complete atresia of the pulmonary outflow tract (**Fig. 75.44 and eFig. 75.9**). The pulmonary valve may vary from a well-formed trileaflet valve with varying degrees of commissural fusion to an imperforate membrane.

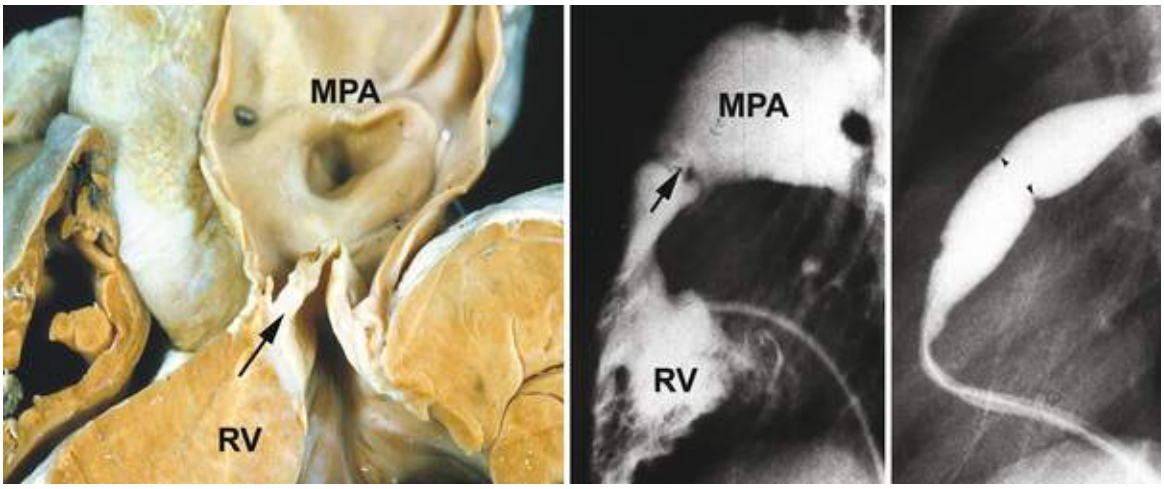
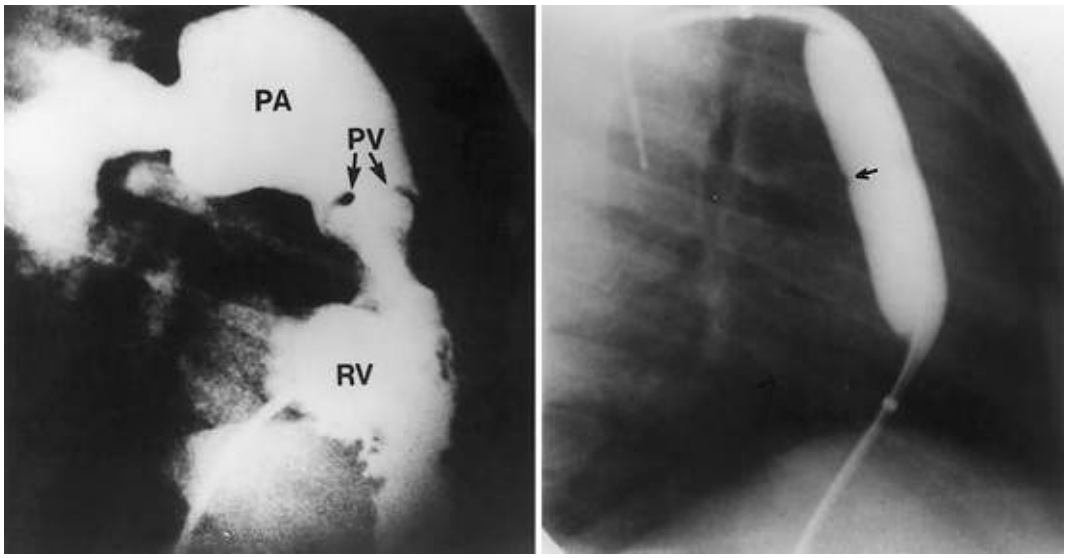


FIGURE 75.44 Montage of pulmonary valve stenosis demonstrating typical pathology (**left,** *arrow*) with a thickened pulmonary valve and obstruction due to commissural fusion. Note the poststenotic dilation. The angiogram demonstrates a case before (**middle,** *arrow*) and during (**right**) balloon dilation. *MPA*, main pulmonary artery; *RV*, right ventricle.



EFIGURE 75.9 Right ventriculogram (RV) in the lateral projection **(left)** from a patient with valvular pulmonic stenosis. The pulmonary valve (PV) is thickened and domes in systole (*arrows*). Poststenotic dilation of the pulmonary artery (PA) is seen. At **right**, successful balloon valvuloplasty shows almost complete disappearance of the stenotic waist (*arrow*). (Courtesy of Dr. Thomas G. DiSessa.)

In pulmonary valve stenosis due to valvular dysplasia, the obstruction is caused not by commissural fusion but by a combination of thickened and dysplastic pulmonary valve leaflets in combination with varying degrees of supravalvular pulmonary stenosis. The supravalvular stenosis is classically at the distal part of the pulmonary valve sinuses, and there is usually no poststenotic pulmonary artery dilation. This entity is associated with Noonan syndrome, which in turn may be associated with hypertrophic cardiomyopathy.

In those with isolated pulmonary valvular stenosis who present beyond the neonatal period, the right ventricle and tricuspid valve are usually normal. However, cases with valvular stenosis presenting in the newborn period very often have abnormalities of the tricuspid valve, in particular some leaflet dysplasia and an associated shortened chordal support apparatus.

The other group, those with pulmonary valve atresia, have varying degrees of right ventricular hypoplasia, varying from a tripartite right ventricle to conditions with associated infundibular atresia,

with intrinsic myocardial abnormalities that persist for life. Those with the smallest right ventricle often have primitive coronary artery–to–right ventricular connections (sometimes termed *sinusoids*), which in some instances are responsible for myocardial perfusion via the suprasystemic right ventricle (so-called *ventricular dependency*). There is frequently associated endocardial fibroelastosis of the right ventricle. The tricuspid valve is invariably abnormal, usually with thickened dysplastic leaflets and varying degrees of leaflet tethering due to a shortened chordal apparatus.

The importance of understanding the right ventricular and tricuspid valve abnormalities is that these persist throughout life and have a significant impact on right ventricular and tricuspid valve function in patients who end up with a biventricular circulation. As well, those with the smallest right ventricle may have persistent coronary artery abnormalities that eventually result in both left and right ventricular myocardial perfusion issues.

Two modes of presentation exist. The first mode is seen in patients who present in the neonatal period, usually with associated pathology of the tricuspid valve, right ventricle, and/or coronary arteries. The second mode is seen beyond the neonatal period, when the valvular stenosis is usually isolated.

Clinical Features

Patients who present beyond the neonatal period with isolated mild to moderate right ventricular outflow tract obstruction of any type usually have no symptoms. Patients with severe right ventricular outflow tract obstruction may present with exertional fatigue, dyspnea, lightheadedness, and chest discomfort (right ventricular angina). Physical examination may reveal a prominent jugular *a* wave, a right ventricular lift, and possibly a thrill in the second left intercostal space. Auscultation reveals a normal S_1, a single or split S_2 with a diminished P_2, and a systolic ejection murmur best heard in the second left intercostal space. When the pulmonary valve is thin and pliable, a systolic ejection click that decreases on inspiration is heard. As the severity of the pulmonary stenosis progresses, the interval between S_1 and the systolic ejection click becomes shorter, S_2 becomes more widely split, P_2 diminishes or disappears, and the systolic ejection murmur lengthens and peaks later in systole, often extending beyond A_2. An ejection click seldom occurs with dysplastic pulmonary stenosis. Cyanosis may be present when a PFO or ASD permits right-to-left shunting.

Adult patients with trivial and mild valvular right ventricular outflow tract obstruction do not become worse with time. Moderate valvular right ventricular outflow tract obstruction can progress in 20% of unoperated patients, especially in adults because of calcification of the valve, and may require intervention. Some of these patients can also become symptomatic, particularly in later life, because of atrial arrhythmias resulting from right ventricular pressure overload and tricuspid regurgitation. Patients with severe valvular right ventricular outflow tract obstruction will have had balloon or surgical valvotomy to survive to adult life. Long-term survival in patients with repaired pulmonary valve stenosis is similar to that of the general population, with excellent to good functional class at long-term follow-up in most patients. A few patients have severe pulmonary regurgitation, and some will require pulmonary valve replacement. Because of the restrictive nature of the right ventricle, most patients do not develop progressive right ventricular dilation, even if they have free pulmonary regurgitation.

Outside the newborn period and early infancy, patients with *Noonan syndrome* have short stature, webbed necks, and broad-shaped chests in a fashion similar to Turner syndrome. Noonan syndrome is inherited as an autosomal dominant disorder, and in 85% to 90% of patients there is a gene mutation (*PTPN11* in 50%, *SOS1* in 10% to 15%, and *RAF1* and *RIT1* in 5% of cases). Noonan syndrome affects both sexes equally. Noonan syndrome is often difficult to diagnose in the neonate, and in some instances

the diagnosis of the dysplastic pulmonary valve is the first clue to the diagnosis.

Laboratory Investigations

ECG.

In the *newborn* period, in patients with significant right ventricular hypoplasia or in patients with Noonan syndrome findings of an associated hypertrophic cardiomyopathy, an ECG may show left-axis deviation and left ventricular dominance. Other patients may have a normal QRS axis. Right atrial overload is present in those with increased right atrial pressure. In the *infant*, *child*, and *adult*, the findings depend on the severity of the stenosis. In milder cases the ECG should be normal. As the stenosis progresses, evidence of right ventricular hypertrophy appears. Right atrial overload is associated with moderate to severe pulmonary stenosis.

Chest Radiography.

In the *infant*, *child*, and *adult* with mild or moderate pulmonary stenosis, chest radiography often shows a heart of normal size and normal pulmonary vascularity. Poststenotic dilation of the main and left pulmonary arteries is often seen, unless there is pulmonary valve dysplasia. Right atrial and right ventricular enlargement is observed in patients with severe obstruction and right ventricular failure. The pulmonary vascularity is usually normal in the absence of a right-to-left atrial shunt but may be reduced in patients with severe stenosis and right ventricular failure.

Echocardiography (Videos 75.101 to 75.103).

Two-dimensional echocardiographic and continuous-wave Doppler examination characterizes the anatomic valve abnormality and its severity and has essentially eliminated the requirement for diagnostic cardiac catheterization. Although traditionally, maximum instantaneous gradients have been used to select patients for balloon valvuloplasty, recent data would suggest the contrary. Mean Doppler gradients appear to correlate better with catheter-derived peak-to-peak gradients, with a value of 50 mm Hg being the cut point for intervention.

The right ventricular size is currently best assessed indirectly from the tricuspid annular dimension. In the absence of a VSD there is an excellent correlation between the two. Right ventricular pressure can be assessed indirectly from the tricuspid regurgitation gradient. Tricuspid valve morphology and function and the status of the interatrial septum all need to be addressed. Three-dimensional echocardiography is helpful in patients for whom surgery is contemplated for associated tricuspid valve regurgitation.

Those with pulmonary valve dysplasia have a thickened fleshy pulmonary valve, lack of poststenotic dilation, and varying degrees of supravalvular pulmonary stenosis (Video 75.103). The associated diagnosis of hypertrophic cardiomyopathy can be confirmed or excluded. If the initial echocardiogram does not demonstrate hypertrophic cardiomyopathy, further studies should be performed throughout childhood and adolescence, particularly in cases with left axis deviation.

Interventional Options and Outcomes

Presentation after the neonatal period usually implies that a well-developed right ventricle and valve are present, and elective balloon dilation of the pulmonary valve is the therapeutic procedure of choice, with excellent short- and medium-term results. The same approach applies to those with a dysplastic pulmonary valve, though in many instances only partial relief of the gradient is possible, with surgery being required when the gradient increases. In those patients, partial pulmonary valvectomy, or patch

insertion, is usually necessary to relieve the obstruction, in some cases in conjunction with relief of supravalvar stenosis. The long-term results are very good in this group, though ongoing issues with hypertrophic cardiomyopathy affect patients with this association.

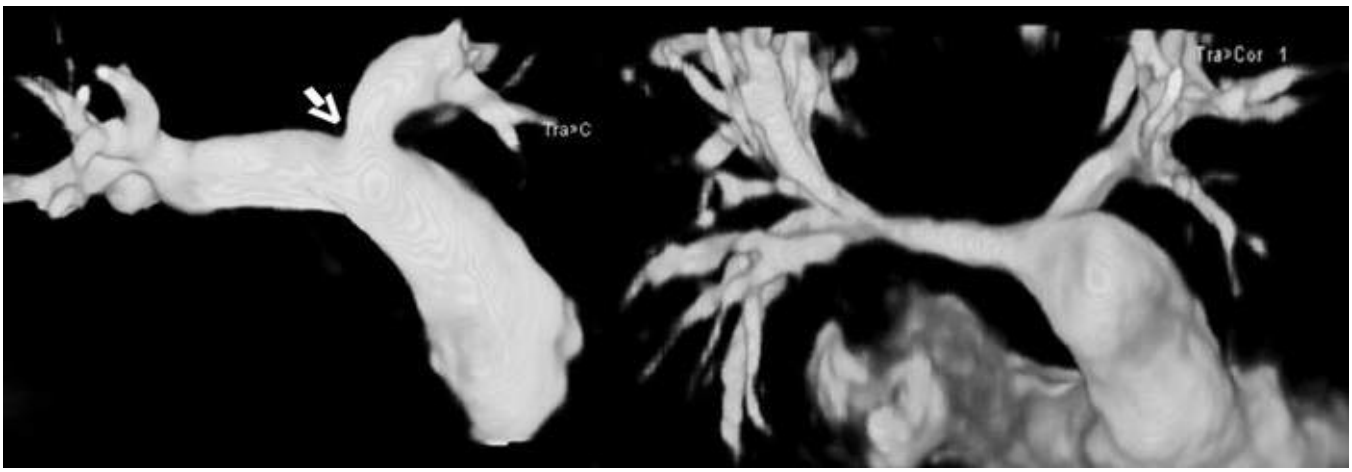
Despite the excellent survival results from the second natural history study (survival rate after surgical valvotomy of 95.7%, compared with sex-matched controls of 96.6%), recent long-term data suggest that this patient population faces ongoing challenges. In one series, after a mean follow-up period of 33 years, 53% of patients had required further intervention and 38% had either atrial or ventricular arrhythmias. In another series after balloon valvotomy, there was a 26% reintervention rate at 20 years, usually for restenosis. A 2012 paper compared outcomes after surgical intervention and balloon pulmonary valvuloplasty.[97] Although the outcomes were very good over the first 20 years, those in the surgical group appeared to have a higher need for surgical reintervention 20 to 40 years after the procedure, compared with those undergoing balloon dilation.

In those with pulmonary atresia and an intact ventricular septum, there is a complex algorithm for determining whether the right ventricle is large enough for an eventual biventricular circulation (sometimes achieved solely by radiofrequency perforation and dilation of the pulmonary valve in the neonatal period) (Video 75.104), or whether a Fontan procedure is the most appropriate approach. In others who had undergone perforation of the pulmonary valve, but who had a persistently small right ventricle, a one-and-a-half ventricle approach is used, which adds a bidirectional cavopulmonary shunt to the circulation.

Although a small percentage of patients follow a late course identical to those with “simple” valve stenosis, many patients with pulmonary atresia and an intact ventricular septum have higher rates of late morbidity and mortality and arrhythmias primarily related to abnormalities of the tricuspid valve, and they also may have consequences of palliative surgery.[98]

Peripheral Pulmonary Artery Stenosis

In patients with peripheral pulmonary artery stenosis, both peripheral pulmonary artery stenosis and an intact ventricular septum are seen (**eFig. 75.10**). It excludes those with an associated VSD, which is dealt with in the sections on tetralogy of Fallot and pulmonary atresia with a VSD. Also excluded is Noonan syndrome.



EFIGURE 75.10 This panel shows two cases with peripheral pulmonary artery stenosis as seen by MRI. The one on the left shows a central proximal left pulmonary artery stenosis, and the right panel shows a case with diffuse stenosis of both branch pulmonary arteries.

Cause

In the past, the most important cause of significant pulmonary artery stenoses producing symptoms in newborns was maternal *rubella infection during pregnancy*.

Peripheral pulmonary artery stenosis is associated with supravalvular aortic stenosis in patients with *Williams syndrome*, which is discussed in the section on supravalvular aortic stenosis.

Peripheral pulmonary artery stenosis is a component of *Alagille syndrome*, with some cases having a *JAG1* mutation.

Isolated branch pulmonary artery stenosis is encountered mainly in the proximal left pulmonary artery and is invariably related to a sling of ductal tissue that causes stenosis when the ductus arteriosus closes after birth. In most cases this is fairly mild, but a significant obstruction resulting in failure of distal growth of the left pulmonary artery may also be seen.

Morphology

Apart from the isolated form mentioned earlier, the stenoses are usually diffuse and bilateral and extend into the mediastinal, hilar, and intraparenchymal pulmonary arteries.

Clinical Features

The degree of obstruction is the principal determinant of clinical severity. The type of obstruction determines the feasibility of intervention. Most patients are asymptomatic. A systolic ejection murmur heard at the upper left sternal border and well transmitted to the axilla and back is most common. No pulmonary ejection click is heard. The pulmonic component of the second heart sound may be accentuated and is loud only if there is proximal pulmonary hypertension. A continuous murmur is often audible in patients with significant branch stenosis. The murmurs in the lung fields are typically increased by inspiration.

Laboratory Investigations

ECG.

Right ventricular hypertrophy is seen when obstruction is severe. Left-axis deviation with counterclockwise orientation of the frontal QRS vector is common in rubella syndrome and when there is also supravalvular aortic stenosis.

Chest Radiography.

Mild or moderate stenosis usually produces normal findings. Detectable differences in vascularity between regions of the lungs or dilated pulmonary artery segments are uncommon. When obstruction is bilateral and severe, right atrial and ventricular enlargement may be seen.

Echocardiography.

Echocardiography is helpful in making the diagnosis and excluding associated lesions; however, it is limited in its ability to image the distal pulmonary arteries beyond the hilum of the lung. Right ventricular pressure assessment may help if there is associated tricuspid valve regurgitation.

MRI and Spiral CT.

These are valuable diagnostic tests because they permit a more distal evaluation of the branch pulmonary

arteries. The advantage of spiral CT in young children is that it can be performed without the need for either heavy sedation or general anesthesia. Although most patients require cardiac catheterization and angiography, these other techniques are excellent for the initial evaluation and for following the progress of the lesions.

Radionuclide Quantitative Lung Perfusion Scan.
This is valuable in cases with unilateral stenosis to determine whether intervention is necessary. Similar flow estimates can now be obtained by MRI.

Cardiac Catheterization and Angiocardiography.
This permits the assessment of right ventricular pressure and the pressures in the pulmonary arterial tree. Angiocardiography is the key to precisely assessing the extent and severity of the stenoses.

Interventional Options and Outcomes

For those cases with isolated left pulmonary artery stenosis where there is less than 30% of flow to the lung, balloon dilation with or without stent insertion is effective in relieving the obstruction. In those cases with more diffuse bilateral stenoses, the indications for intervention depend on the right ventricular pressure. Because the natural history of diffuse peripheral pulmonary artery stenosis in Williams syndrome is one of potential regression over time, intervention is in general reserved for those cases with systemic or suprasystemic right ventricular pressure. Intervention also depends in part on the extent of the stenosis and the dilation capability of the lesions, with or without stenting. In some cases, several attempts at dilation are required to achieve any improvement in vessel caliber. High-pressure balloons are usually necessary, but some lesions cannot be dilated even with such balloons. Recently, improved results have been reported using “cutting” balloons, which may assist dilation in a stenosis that is otherwise not dilatable. As a rule, surgery has little to offer patients with diffuse peripheral pulmonary artery stenoses and can indeed make the situation worse.

Subpulmonary Right Ventricular Outflow Tract Obstruction (Anomalous Muscle Bundles or a Double-Chambered Right Ventricle)

Morphology

A double-chambered right ventricle is formed by right ventricular obstruction due to anomalous muscle bundles. Although this can occur in isolation, it is more frequently part of a combination of lesions that includes right ventricular muscle bundles, a perimembranous-outlet VSD, and subaortic stenosis with or without aortic valve prolapse.

Clinical Features

Most cases are discovered as an incidental finding during the routine follow-up of a VSD. In some cases there may be only a systolic ejection murmur. If the obstruction is isolated, there is a systolic ejection murmur that is heard best in the upper left sternal border. If the VSD is the predominant lesion, the right ventricular outflow tract murmur may not be appreciated. Before the routine use of echocardiography, the diagnosis was often made during follow-up for a VSD when the pansystolic murmur decreased in intensity and a systolic ejection murmur emerged. The patients are usually pink unless there is progression

of the subpulmonary stenosis in the setting of a VSD. The diagnosis may be more problematic in adults.

Laboratory Investigations

ECG.

The ECG is similar to those with isolated pulmonary valve stenosis beyond the newborn period. In cases with a nonrestrictive VSD and mild subpulmonary stenosis, the ECG typically shows biventricular hypertrophy resulting from a left-to-right shunt and associated pulmonary hypertension. If the stenosis is more severe, right ventricular hypertrophy will be seen. Those with a restrictive VSD may have a normal ECG or left ventricular hypertrophy, the latter of which is replaced with right ventricular hypertrophy if the stenosis increases in severity.

Chest Radiography.

This is usually normal in those with isolated subpulmonary stenosis, whereas those with a VSD may have increased or reduced pulmonary blood flow, depending on the severity of the obstruction.

Echocardiography (see Videos 75.48 to 75.52).

Doppler and 2D echocardiography usually provide a complete diagnosis. The level of subpulmonary obstruction is appreciated best in a combination of subcostal right anterior oblique and precordial short axis views. These views permit the identification of the relationship of the VSD to the muscle bundles, as well as the degree of anterior malalignment of the infundibular septum in those with a VSD. The precordial short axis view is best for evaluating the presence of possible subpulmonary stenosis and aortic cusp prolapse. Color and pulsed or continuous-wave Doppler evaluation usually allows differentiation of the VSD flow jet from that originating from the muscle bundles. This permits an accurate assessment of the hemodynamic effect of the subpulmonary obstruction.

Cardiac Catheterization and Angiocardiography.

This technique is rarely necessary. In older patients in whom the echocardiographic images of the subpulmonary region may be suboptimal, a combination of MRI and echocardiography is all that is generally necessary.

Management Options and Outcomes

Management is dictated by the severity of the obstruction and the presence of associated defects. In patients with isolated subpulmonary stenosis, surgery is indicated when the right ventricular pressure is more than 60% of the systemic pressure. This involves resection of the muscle bundles through the right atrium. For those cases with an associated VSD, the decision is based on the size of the VSD, the presence of associated subaortic stenosis, the presence of aortic valve prolapse, and the severity of the right ventricular obstruction. These patients tend to have progressive disease, so many cases that are followed conservatively for several years will eventually require surgery. In general the outcome is excellent, with a low rate of recurrence after surgical resection of obstructive muscle bundles. Infrequently, recurrence of the subaortic obstruction may occur.

Miscellaneous Lesions

Cor Triatriatum

Morphology

In this malformation, failure of resorption of the common pulmonary vein results in a left atrium divided by an abnormal fibromuscular diaphragm into a posterosuperior chamber receiving the pulmonary veins and an anteroinferior chamber giving rise to the left atrial appendage and leading to the mitral orifice. The communication between the divided atrial chambers may be large, small, or absent, depending on the size of the opening(s) in the diaphragm, which determines the degree of obstruction to pulmonary venous return. Elevations of both pulmonary venous pressure and pulmonary vascular resistance may result in severe pulmonary artery hypertension.

Clinical Features

Cor triatriatum is often detected as an incidental finding in a patient who has an echocardiogram for another reason. In general these represent the unobstructed form that requires no early intervention. Patients with more severe obstruction present in a fashion similar to patients with congenital pulmonary vein stenosis.

Laboratory Investigations

ECG.

In unobstructed cases this is normal, whereas in those with significant obstruction there is right ventricular hypertrophy due to the associated pulmonary hypertension.

Chest Radiography.

This may be normal in those with mild obstruction or demonstrate pulmonary edema with significant obstruction.

Echocardiography.

The diagnosis is established by 2D echocardiography or TEE, with further insight from 3D reconstruction. The obstructive diaphragm is visualized in the parasternal long- and short axis and four-chamber views and can be distinguished from a supravalvular mitral ring by its position superior to the left atrial appendage, which forms part of the distal chamber. Also present is diastolic fluttering of the mitral leaflets and high-velocity flow detected by Doppler examination in the distal atrial chamber and at the mitral orifice (Videos 75.105 to 75.107).

Cardiac Catheterization and Angiocardiography.

This technique is usually unnecessary, unless there are concerns regarding the hemodynamic consequences.

Management Options and Outcomes

Surgical resection of the membrane is the treatment of choice for patients with significant obstruction. This results in symptom relief and a reduction of pulmonary artery pressure. In general the outcome following surgery is good. With the advent of more routine use of echocardiography, a subset of cases with typical but nonobstructive forms has been recognized. Thus far these cases appear to remain asymptomatic, with an infrequent need for surgical intervention.

Pulmonary Vein Stenosis

Congenital pulmonary vein stenosis may occur as a focal stenosis at the atrial junction or as generalized hypoplasia of one or more pulmonary veins. The incidence of associated cardiac malformations is extremely high, including VSD, ASD, tetralogy of Fallot, tricuspid and mitral atresia, and AV septal defect. In other cases the pulmonary vein stenosis is acquired after surgical intervention for a total anomalous pulmonary venous connection. Children frequently present with recurrent respiratory infections, whereas adults exhibit exercise intolerance. Pulmonary hypertension is one of the consequences of pulmonary vein stenosis, whether it is congenital or acquired. In cases with unilateral pulmonary vein stenosis, clinical symptoms are frequently absent because there is pulmonary blood flow redistribution away from the affected lung.

Laboratory Investigations

ECG.

The ECG is usually normal unless there is evidence of pulmonary hypertension, in which case right ventricular hypertrophy may be seen.

Chest Radiography.

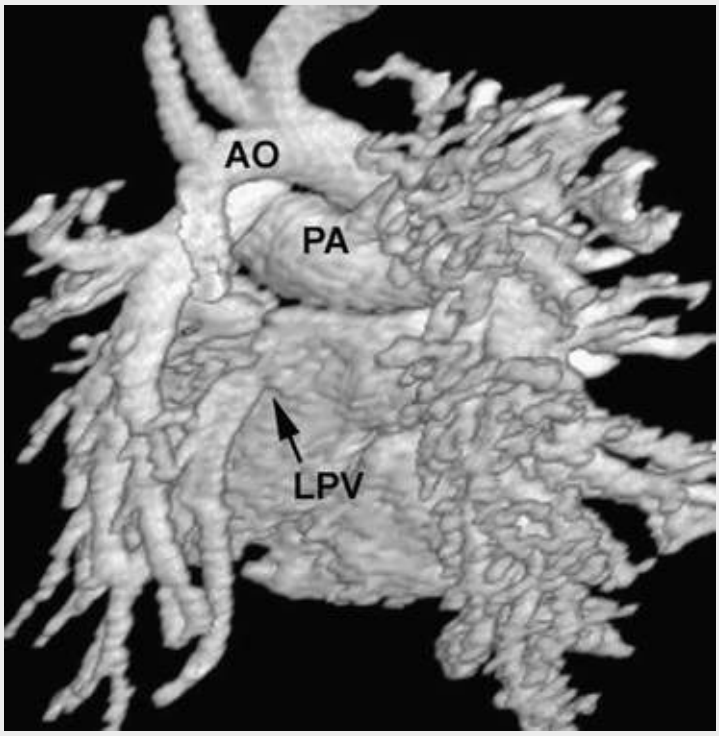
With unilateral pulmonary vein stenosis there is oligemia of the affected lung and increased flow to the contralateral side. If the obstruction is bilateral, pulmonary edema may be seen.

Echocardiography.

This can usually exclude or confirm the diagnosis of pulmonary vein stenosis. Assessment of pulmonary artery pressure from tricuspid or pulmonary valve regurgitation is possible. Doppler color flow assessment of the right- and left-sided pulmonary veins is the best screening tool. If there is evidence of turbulence or aliasing in the color flow pattern, then spectral analysis with pulsed Doppler imaging will help confirm the diagnosis. Usually pulmonary venous flow is of low velocity and phasic. If the pattern is of high velocity and turbulent, there is disturbed pulmonary venous flow. Absolute Doppler gradients may or may not be helpful for two reasons. First, the absolute velocity depends on the amount of pulmonary blood flow to that segment of lung. Second, it is often difficult to obtain a parallel line of interrogation of the pulmonary veins that will affect gradient assessment. The absolute velocity is less important than the diagnosis of pulmonary vein stenosis and its effect on pulmonary artery pressure.

MRI.

MRI has now become the gold standard for the diagnosis of pulmonary vein stenosis (**eFig. 75.11**). It permits a detailed assessment of the pulmonary veins and pulmonary blood flow. Velocity assessment is now possible, though this is in the actual veins themselves rather than at the venoatrial junction, which is the site assessed by Doppler echocardiography.



EFIGURE 75.11 Three-dimensional MRI demonstrating stenosis of the left lower lobe pulmonary vein. *AO*, aorta; *LPV*, left pulmonary vein; *PA*, pulmonary artery.

Cardiac Catheterization and Angiography.
In general a combination of echocardiography and MRI makes invasive procedures unnecessary, unless transcatheter therapy is contemplated.

Management Options and Outcomes

If the patient has unilateral pulmonary vein stenosis and normal pulmonary artery pressure, no treatment may be necessary. Continued follow-up is important because this is often a progressive disease that can subsequently affect both sides. In cases with bilateral stenoses the outlook in the past was believed to be hopeless, with a virtually 100% mortality rate. Stents usually provided only temporary relief. More recently a pericardial reflection procedure (the “sutureless” repair) using native tissue has resulted in some early success for this lesion. This involves using native atrial tissue, pericardium, and pleura to form a pocket around the surgically resected stenotic region.

Pulmonary Arteriovenous Fistula

Abnormal development of the pulmonary arteries and veins in a common vascular complex is responsible for this congenital anomaly. A variable number of pulmonary arteries communicate directly with branches of the pulmonary veins. Most patients have an associated Weber-Osler-Rendu syndrome or complex CHD (e.g., left isomerism); associated problems include bronchiectasis and other malformations of the bronchial tree, as well as absence of the right lower lobe. Pulmonary AV fistulas may also complicate classic Glenn shunts used in the palliation of cyanotic CHD and are believed to be due to the absence of “hepatic factor” in the venous blood feeding the superior vena cava–pulmonary artery connection. Hepatopulmonary syndrome may also be associated with substantial right-to-left intrapulmonary shunting. The amount of right-to-left shunting depends on the extent of the fistulous communications and may result in cyanosis. Paradoxical emboli or a brain abscess may result and cause major neurologic deficits. Patients with hereditary hemorrhagic telangiectasia are often anemic because of repeated blood loss and

may have less obvious cyanosis because of anemia. Systolic and continuous murmurs may be audible over areas of the fistula. Rounded opacities of various sizes in one or both lungs on chest radiography may suggest the presence of the lesion.

Laboratory Investigations

Echocardiography is helpful in the initial diagnostic process with the use of a saline contrast injection into a systemic vein. With pulmonary arteriovenous malformations, there is early pulmonary venous return to the left atrium, but not as quickly as for patients with a PFO or ASD and right-to-left atrial shunting. More recently, CT and MRI techniques have provided valuable diagnostic information. Pulmonary angiography reveals the site and extent of the abnormal communication.

Management Options

Unless the lesions are widespread throughout both lungs, surgical treatment aimed at removing the lesions with preservation of healthy lung tissue is commonly indicated to avoid the complications of massive hemorrhage, bacterial endocarditis, and rupture of arteriovenous aneurysms. Transcatheter balloon or plug or coil occlusion embolotherapy may prove to be the therapeutic procedure of choice in some patients. In patients with underlying CHD, redirecting hepatic venous return to the affected lung can reverse the arteriovenous malformations and improve the hypoxemia.

Coronary Arteriovenous Fistula

Morphology

A coronary arteriovenous fistula is a communication between one of the coronary arteries and a cardiac chamber or vein. The right coronary artery (or its branches) is the site of the fistula in about 55% of patients; the left coronary artery is involved in about 35%; and both coronary arteries are involved in a few. Connections between the coronary system and a cardiac chamber appear to represent persistence of embryonic intertrabecular spaces and sinusoids. Most of these fistulas drain into the right ventricle, right atrium, or coronary sinus. Coronary–to–pulmonary artery fistulas are an occasional and usually incidental finding during coronary angiography.

Clinical Features

The shunt through the fistula is usually small, and myocardial blood flow is not compromised. Potential complications include pulmonary hypertension and congestive heart failure if a large left-to-right shunt exists, bacterial endocarditis, rupture or thrombosis of the fistula or of an associated arterial aneurysm, and myocardial ischemia distal to the fistula due to a “myocardial steal.”

Most pediatric patients are asymptomatic and are referred because of a cardiac murmur that is loud, superficial, and continuous at the lower or midsternal border. The site of maximal intensity of the murmur is related to the site of drainage and is usually away from the second left intercostal space, which is the classic site of the continuous murmur of persistent ductus arteriosus.

Laboratory Investigations

ECG.

This is usually normal unless there is a large left-to-right shunt.

Chest Radiography.

Radiographic findings are often normal and seldom show selective chamber enlargement.

Echocardiography.

Coronary artery fistulas are now recognized with a high degree of accuracy with the advent of routine coronary artery evaluation during most pediatric echocardiography examinations. A significantly enlarged feeding coronary artery can be detected, and the entire course and site of entry of the arteriovenous fistula can be traced by Doppler color-flow mapping. The shunt entry site is characterized by a continuous turbulent systolic and diastolic flow pattern. Multiplane TEE also accurately defines the origin, course, and drainage site of the fistula.

Cardiac Catheterization and Angiocardiography.

If echocardiography demonstrates a significant coronary artery fistula, hemodynamic evaluation and possible intervention are warranted. Standard retrograde thoracic aortography, balloon occlusion angiography of the aortic root with a 45-degree caudal tilt of the frontal camera ("laid back" aortogram), or coronary arteriography can be used reliably to identify the size and anatomic features of the fistulous tract.

Management Options and Outcomes

Small fistulas have an excellent long-term prognosis. Untreated larger fistulas may predispose the individual to premature coronary artery disease in the affected vessel. Coil embolization at the time of cardiac catheterization is rapidly becoming the treatment of choice (Video 75.108). Surgical treatment is still required in some instances.

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76

Catheter-Based Treatment of Congenital Heart Disease in Adults

John M. Lasala, David T. Balzer

The number of adults living with congenital heart disease has been steadily increasing, with recent estimates suggesting that adults now outnumber children with the disease (**see Chapter 75**). As this population continues to grow, the number of adults requiring intervention for the disease increases. Congenital heart disease is extremely variable and involves all aspects of cardiovascular physiology such that specialized training has become a necessity for anyone caring for these patients. Indeed, the most recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines state that interventions for adults must be performed at regional adult congenital heart disease centers of excellence by providers with “expertise in the surgical and transcatheter management of patients with congenital heart disease.”[1] In addition, because of the complexity of disorders in these patients, any site undertaking the care of adults with congenital heart disease must have a well-established multidisciplinary team that includes congenital cardiothoracic surgeons, cardiac anesthesiologists, cardiac intensivists, and congenital cardiologists.[1] Pediatric interventional cardiologists are also key persons on the team, and

partnerships between adult congenital interventionalists and pediatric interventional cardiologists are mandatory. As the capabilities of the congenital catheterization laboratory continue to evolve, the line between surgical and catheter-based interventions will become more and more blurred. Many interventions already take place in highly specialized hybrid operating suites in which interventional cardiologists work alongside their cardiothoracic surgery colleagues. This combined model of intervention will continue to be adapted for adult congenital interventions, and it is this ongoing evolution that makes the field so exciting. Furthermore, as interventional approaches change, the indications for intervention become a "moving target." As a result, national guidelines may become outdated sooner than in decades past; therefore, interventional cardiologists who treat adults must remain knowledgeable about the ever-changing medical literature on this topic. In this chapter we review major areas in which catheter-based interventions have become well established for adults with congenital heart disease. The topic of congenital heart disease in adults is reviewed in **Chapter 75**.

Valvular Interventions

The first static pulmonary balloon valvuloplasty was performed in 1982; successful catheter-based interventions have since been performed on all types of cardiac valves.[2] Although valvuloplasty defined the early era of congenital interventional catheterization, valve replacement is defining the current era.

Pulmonary Valvuloplasty

In "typical" pulmonary valve stenosis, there are normal valve leaflets with limited valve excursion resulting from partial fusion. Static pulmonary valvuloplasty, which aims to separate the fused leaflets, was first performed in the early 1980s and has since replaced surgical valvotomy as the initial intervention in cases of typical isolated valvar pulmonary stenosis.[3] Valvuloplasty for thick and/or dysplastic valves is less successful; moreover, balloon dilation will be unsuccessful in relieving any muscular subvalvar stenosis. Indications for pulmonary valvuloplasty in adults with congenital heart disease has been outlined elsewhere (**see Chapter 75**).[1] Before pulmonary valvuloplasty is performed, a complete right heart catheterization should be performed, followed by right ventricular (RV) angiography, to profile the right ventricular outflow tract (RVOT). Angiographic measurements of the pulmonary annulus allow for selection of the appropriately sized balloon, which is approximately 120% of the measured pulmonary annulus. Successful balloon valvuloplasty can usually be achieved with hand inflation of the selected balloon. After dilation of the pulmonary valve, repeat angiography should be performed to rule out vascular injury and assess the degree of pulmonary regurgitation.

Outcomes and Complications

Case selection is critical for optimizing outcomes. Patients with typical pulmonary valve stenosis will have relatively thin leaflets with partial fusion and will respond well to balloon valvuloplasty.[4] The most common complication for pulmonary valvuloplasty is pulmonary regurgitation (<10% with 2+ or greater pulmonary regurgitation), which is usually well tolerated. Major adverse events or unplanned surgeries were not reported for patients with typical valvar stenosis in the most recent report from the National Cardiovascular Data Registry (NCDR).[4]

Pulmonary Valve Replacement

The pulmonary valve is a semilunar valve separating the right ventricle from the main pulmonary artery. It allows for unobstructed right ventricular ejection while maintaining pulmonary arterial diastolic pressure via competent leaflet coaptation. Unfortunately, many patients with congenital heart disease have pulmonary valve disease involving stenosis or regurgitation, or a combination of both. Furthermore, bioprosthetic valves that are implanted in infants to reconstruct the right ventricular outflow tract will invariably fail. The largest anatomic subcategory of "severe" congenital heart disease in adults is tetralogy of Fallot,[5] in which the surgical repair leaves patients with severe pulmonary regurgitation and variable degrees of RVOT obstruction. Over time, pulmonary valve disease will be manifested by symptoms (e.g., exercise intolerance, congestive heart failure, dysrhythmias) heralding significant RV dysfunction. In an effort to avoid such dysfunction, relief of stenosis and placement of a competent valve are warranted. Determining the optimal timing for pulmonary valve replacement continues to be an issue; there are currently several indications in symptomatic[1] and asymptomatic[6] patients with pulmonary valve disease (**see Chapter 75**).

Pulmonary Valve Systems

There are currently two available valve systems approved by the Food and Drug Administration (FDA) for use in the pulmonary valve: Melody Transcatheter Pulmonary Valve (Medtronic, Inc., Minneapolis) and SAPIEN XT Pulmonic Valve (Edwards Lifesciences, Irvine, CA). Each has its own unique strengths and weaknesses.

Melody Valve

Developed by Dr. Philipp Bonhoeffer in conjunction with Medtronic, the Melody valve (**Fig. 76.1**) has a bovine jugular vein valve sutured to a platinum-iridium stent frame and is deployed by the proprietary Ensemble delivery system. The valve is available in two sizes, approved for use in circumferential right ventricular–pulmonary artery (RV-PA) conduits with original implant diameters of 16 to 22 mm. Numerous reports have described its off-label use in native RVOTs and failed bioprosthetic valves,[7,8] and some authors have demonstrated good valve function at implant diameters of up to 24 mm.[9] With a maximal implant diameter of 24 mm, the Melody valve's most significant limitation is size. In addition, because the valve is harvested and not manufactured, there are natural limitations to its supply. The strength of the valve is primarily in the design of the Ensemble delivery system, which covers the valve until it is positioned in the RV-PA conduit and employs a balloon-in-balloon catheter, making delivery easy to control and predictable.

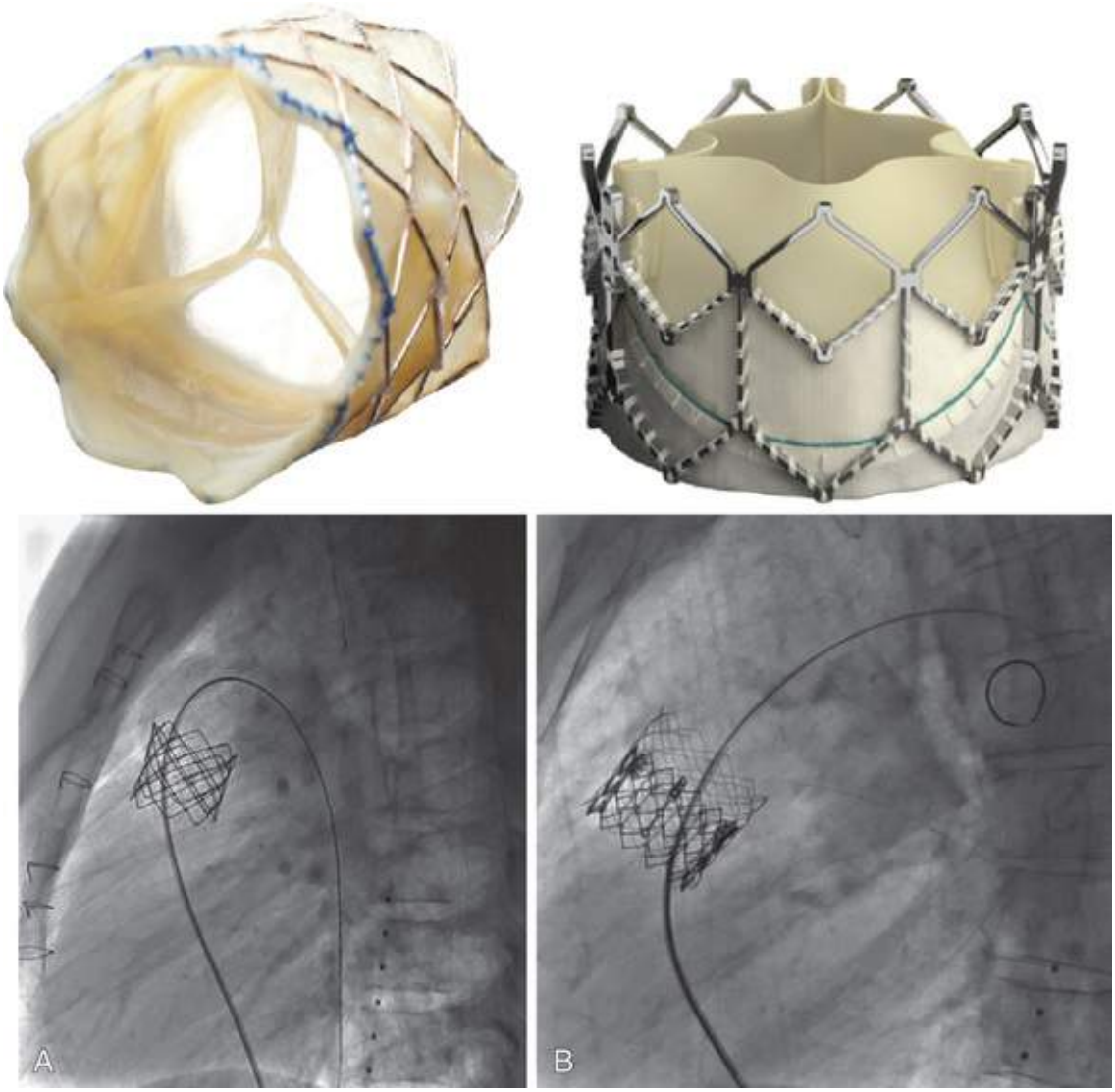

FIGURE 76.1 FDA-approved transcatheter valves and fluoroscopic appearances on lateral projection. **A,** Melody valve (Medtronic, Minneapolis). **B,** Edwards SAPIEN XT valve (Edwards Lifesciences LLC, Irvine, CA).

SAPIEN Valve

Originally designed for the treatment of aortic valve disease and validated in the PARTNER trial,[10] the SAPIEN XT transcatheter balloon expandable prosthesis (**see Fig. 76.1**) has only recently been approved for use in the pulmonary position. Since its introduction in the early 2000s, the valve has undergone modifications to improve its safety profile and procedural outcomes.[11] The SAPIEN 3 valve is the newest iteration; it is characterized by a trileaflet valve created with bovine pericardium and treated with the same patented ThermaFix process as the Carpentier-Edwards surgical valves. In contrast to the Melody system, the Edwards family of valves have demonstrated superior radial strength and a wider range of sizes (approved for use in conduits with a diameter of 18 to 28 mm), but their delivery systems are more difficult to maneuver.

Outcomes and Complications

The Melody valve has been approved by the FDA since 2010. Early[12] and intermediate[13] outcome data have demonstrated excellent procedural success and freedom from RVOT reintervention at rates of 98% at 3 years and 91% at 5 years. SAPIEN valves have had similarly good early outcomes[14] and have had favorable comparisons with the Melody valve.[15] Important procedural complications include vascular

injury, conduit disruption, pulmonary artery perforation, stent or valve embolization, coronary artery compression, ventricular arrhythmias, and tricuspid valve injury.[8] Long-term complications include stent frame fracture, valve dysfunction, and endocarditis.[8,13,16,17]

Arterial Interventions

The pathologic “arterial” conditions encountered most frequently by congenital interventionalists are related to anatomic lesions in the pulmonary arterial tree, followed by coarctations of the aorta. As in other interventional areas, technologic advances have increased the breadth of catheter-based treatments for congenital heart disease, as well as the quality and durability of the outcomes. In adult patients, stenting has become a well-established companion to angioplasty, and has improved acute and long-term outcomes.

Pulmonary Angioplasty

A myriad of congenital heart lesions involve pulmonary artery disorders; moreover, many congenital heart surgeries involve RV-PA conduits, systemic-pulmonary arterial shunts, and pulmonary artery (PA) bands that distort the normal PA anatomy. As a result, many patients are left with fixed obstructions to the pulmonary blood flow. Depending on the location of the obstruction, these lesions can result in elevated RV pressure or significant flow discrepancies between lung segments. Over time, these obstructions can have deleterious effects on RV function and the pulmonary vasculature. Indications for pulmonary arterial intervention have been described elsewhere (**see Chapter 75**).[1] There are currently no stents approved by the FDA for use in pulmonary arteries; however, Palmaz Genesis stents (Cordis, Milpitas, CA) and the EV3 family of stents (Covidien/Medtronic, Minneapolis) have been used and have shown good radial strength, a low profile, and achievable diameters. In children or in small or distal pulmonary arteries in adults, it is reasonable to use premounted stents.

Outcomes and Complications

The heterogeneous nature of pulmonary arterial disease has resulted in a wide spectrum of clinical outcomes following catheter-based interventions. Both the anatomic location of the stenosis and its circumstances of formation as a congenital or postoperative feature have contributed importantly to the differences in clinical outcomes. Complications include vascular tears, stent embolization or malpositioning, pulmonary edema, and the need for unanticipated procedures or surgeries; some patients may not survive. Several reviews from Boston Children's Hospital have described the differences between proximal and distal lesions,[18] as well as the effectiveness of using cutting and/or high-pressure balloons for resistant lesions.[19] A report from the NCDR revealed reasonable safety; in 245 procedures across all age-groups, adverse events were reported in 13.2% of cases and major adverse events in 1.2% of cases, and two patients died.[4]

Stenting for Coarctation of the Aorta

Coarctation of the aorta is a narrowing in the normal dimensions of the aortic arch (**see Chapter 75**). Coarctations usually occur around the isthmus of the aorta, where the ductus arteriosus was once inserted. The increase in afterload imposed by the coarctation can result in left ventricular (LV) dysfunction and

cardiogenic shock, which often develop in early infancy. More frequently, the body develops extensive collaterals through the chest wall, which minimize the increase in afterload and preserve systolic function. Over time, patients with coarctation will develop hypertension to varying degrees and, eventually, coronary artery disease and LV diastolic dysfunction.[20] Treatment of coarctation has traditionally required cardiothoracic surgery; however, catheter-based treatments have been evolving. Coarctation stenting is typically performed in a retrograde approach via the femoral artery. After measuring the baseline gradient, angiography is performed and measurements are taken of the distal aortic arch and thoracic aorta (at the level of the diaphragm). The covered Cheatham pulmonary (CP) stent (NuMED, Inc., Hopkinton, NY) is approved by the FDA for use in coarctation, but other stents have been frequently used off-label. The diameter of the implanted balloon should be no larger than that of the surrounding aorta or 3.5 times the narrowest dimension.[21] Stents are most frequently placed by balloon-in-balloon catheters because of the improved control. Once a stiff guidewire is positioned across the coarctation, a long sheath is positioned above the narrowed area and a mounted stent advanced into position at the site of coarctation. The stent is uncovered and deployed with inflation of the balloon catheter. After successful placement of the stent, additional serial dilations of any residual waist may be considered. Follow-up angiography should be performed to rule out dissection or aneurysm before measuring the final pressure gradient. Indications for coarctation intervention are discussed elsewhere (**see Chapter 75**).[1] Comparisons between balloon angioplasty, aortic stenting, and surgical resection have been done, and catheter-based stenting has emerged as the preferred treatment modality for older children and adults.[20]

Outcomes and Complications

Coarctation stenting is safe and compares favorably with surgery in regard to elimination of the pressure gradient.[4,20-23] The NCDR report noted more frequent stenting in older children and adults, with nearly 84% of stented patients achieving a postprocedural gradient of less than 10 mm Hg.[4] Complications include access injuries, vascular tears or dissections, stent embolization or malpositioning, restenosis, and aneurysm; death may result. For adults in the NCDR, 8.6% experienced an adverse event, but only one major adverse event occurred in 92 patients.[4] Long-term follow-up will continue to reveal the true risk of late aneurysm and restenosis in these patients. For children who are not fully grown, future dilations to keep pace with somatic growth should be anticipated.

Septal Interventions

Techniques for Closure of Atrial Septal Defects

Atrial septal defects (ASDs) are the third most common form of congenital heart disease. They occur in 56 to 100 live births per 100,000 infants.[24] Isolated ASDs will result in left-to-right shunting, with the magnitude of the shunt determined by ventricular compliance and atrioventricular valve stenosis. Significant left-to-right shunts result in RV dilation; if they are left unrepaired, they may ultimately result in pulmonary arterial muscularization and elevations in the pulmonary vascular resistance by the sixth decade of life.[24] In an effort to avoid irreversible changes in pulmonary vascular resistance, early closure of significant ASDs has become standard practice.[24] Transcatheter devices and techniques have evolved substantially since the first case was reported in 1976 by King and colleagues. The currently available devices each have unique strengths and weaknesses (**Fig. 76.2**).[24] Indications for intervention have been previously outlined.[1]

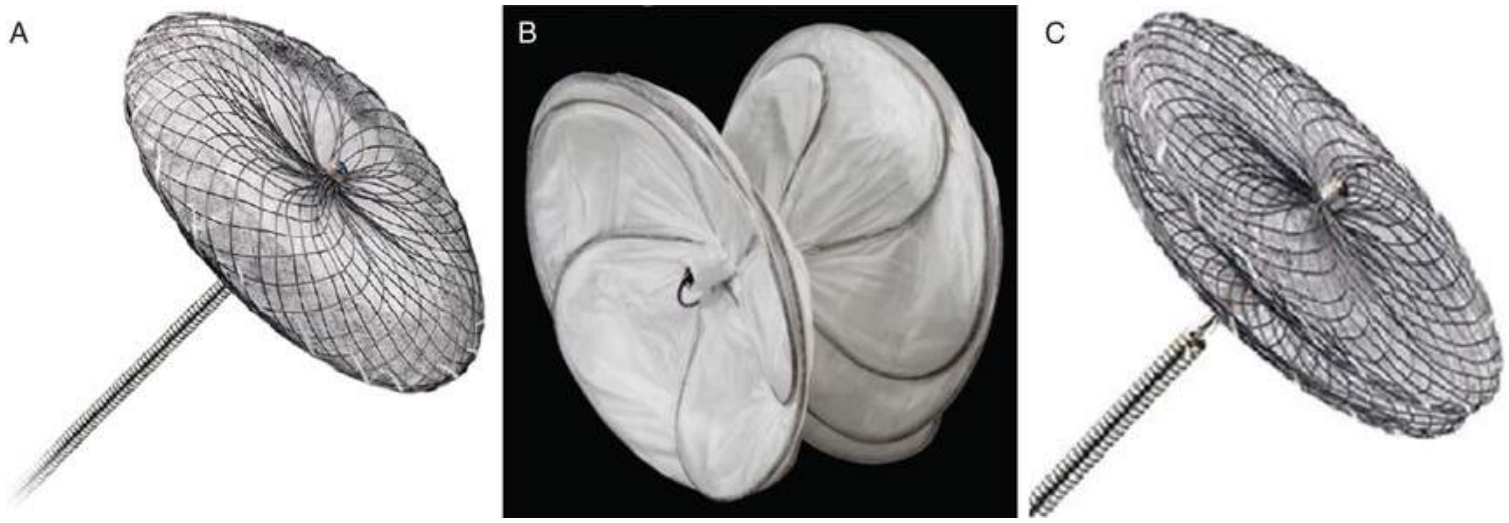

FIGURE 76.2 Various closure devices for atrial septal defects. **A,** Amplatzer Cribriform device (St. Jude Medical, St. Paul). **B,** GORE Cardioform Septal Occluder (W.L. GORE and Associates, Inc., Flagstaff, AZ). **C,** Amplatzer Septal Occluder (St. Jude Medical, St. Paul).

Amplatzer Devices

Originally introduced in the mid-1990s, the Amplatzer Septal Occluder (ASO) (St. Jude Medical, Inc., St. Paul) has been used in thousands of cases across the globe. The ASO is made of woven Nitinol wire that forms a self-centering device, with left and right atrial discs and a central waist. The device is filled with interwoven Dacron polyester fibers to facilitate platelet aggregation and endothelialization. The device is secured to a delivery cable and introduced into the left atrium via the appropriately sized, proprietary TorqVue sheath. ASOs can treat ASDs of many sizes as long as the atrial septal rim is substantial enough that the device can be placed securely. If the septal rim is deficient (<5 mm in contiguous zones), stable positioning will be more difficult to achieve and at times may not be possible. Numerous deployment techniques can be used if the septal rim is deficient, but they are outside the scope of this chapter and are described elsewhere.[25-27] Shortly after the introduction of the ASO, Amplatzer developed the Multi-Fenestrated Septal Occluder, or Cribriform device. In contrast to the ASO, the Cribriform device does not have a waist and is therefore not self-centering. Its primary benefit, therefore, is that it can be placed in a small central defect and also covers numerous satellite defects. Its deployment is identical to that of the ASO, using the same TorqVue sheaths and delivery cables.

Outcomes and Complications

When compared with surgery in the US Pivotal Trial, the ASO demonstrated superior safety and statistically similar closure rates. The postmarket approval study and multicenter community use trial have further solidified the ASO's position as a safe and effective device for transcatheter closure of an ASD or a patent foramen ovale.[28,29] Major adverse events reported include arrhythmias, device embolization, device erosion, device fracture, stroke, and left arterial thrombus. One of the most significant adverse events is device erosion. After the first reported case in 2002, AGA/St. Jude revised the ASO instructions for use, but erosions continued to be reported to the Manufacturer and User Facility Device Experience (MAUDE) database. In response to ongoing erosion reports (<0.05% of worldwide sales, estimated to be ≈ 0.1% of implants), the FDA and AGA/St. Jude made additional changes to the instructions for use in an effort to minimize the erosion risk, and recommended closer follow-up with more frequent echocardiograms. In addition to erosion, several case reports in children and adults have demonstrated delayed endothelialization in the setting of endocarditis, and concerns have been raised

regarding the optimal length of time for subacute bacterial endocarditis prophylaxis following device placement.[30]

GORE Devices

The GORE Helex device (no longer commercially available) was approved in 2006. It was not self-centering and therefore was relatively limited with regard to the sizes of defects it could effectively treat (i.e., the device had to be two times the diameter of the defect). The original Helex delivery system was cumbersome, and the device was arguably too flexible, so GORE redesigned its septal occluder system. It is now marketed as the GORE Cardioform Septal Occluder (GSO) (W.L. Gore and Associates, Flagstaff, AZ). The new device consists of a five-wire Nitinol frame, which adds radial strength and improves structural integrity, and it is covered with the same expanded polytetrafluoroethylene (ePTFE) membrane as the original Helex device. The redesigned delivery system is much more intuitive, and it maintains its novel retention cord mechanism. Because of its non–self-centering design, the GSO can only close defects up to 18 mm in diameter.

Outcomes and Complications

The GSO was approved by the FDA in 2012 and has demonstrated comparable safety and efficacy to the ASO in closure of patent foramen ovale and ASD.[31-33] GORE is currently conducting a prospective, randomized, multicenter, multinational trial (REDUCE Clinical Study [NCT00738894]) comparing the risk of recurrent cryptogenic stroke in patients who undergo patent foramen ovale closure with the GSO and are also given antiplatelet medications versus patients who receive antiplatelet medications only. In contrast to the ASO, there has never been a report of device erosion following implantation of a GORE device. Overall, percutaneous device placement has established itself as the preferred intervention for ASDs because of its excellent outcomes and safety record.[34]

Techniques for Closure of Ventricular Septal Defects

Ventricular septal defects (VSDs) are the most common congenital heart defects and can range in size from tiny pinholes to near absence of the septum (**see also Chapter 75**).[35] VSDs can be an isolated finding or associated with other complex congenital heart diseases, primarily conotruncal defects (e.g., tetralogy of Fallot, double-outlet right ventricle, transposition of the great arteries). The ventricular septum has four primary regions: inlet, outlet, perimembranous area, and muscular area, and defects can occur in any location and extend to adjacent regions. The shunt through a VSD is predicated on ventricular outflow obstruction and downstream vascular resistance. The management of VSD is a complex topic beyond the scope of this chapter, and indications for intervention have been previously described (**see Chapter 75**).[1] Catheter-based device closure of muscular, traumatic, postoperative residual, and postinfarct VSDs has become a reasonable alternative to surgery. Perimembranous VSD remains controversial because of the associated risk of heart block. Inlet VSDs are not amenable to transcatheter techniques, because there is no circumferential tissue on which to securely “land” a device.[35,36]

Outcomes and Complications

Complications specific to transcatheter device closure of VSDs include aortic regurgitation, tricuspid regurgitation, rhythm disturbances, and atrioventricular (AV block); death occurs rarely. In a review of the European registry of transcatheter VSD devices, Carminati and associates[37] found that VSDs in the

perimembranous location were at increased risk for developing complete AV block. When similar devices have been used, others have found similar rates of AV block, ranging from 2% to 6%.[38-40] Interestingly, a lower risk of AV block has been seen in some cases when the first-generation Amplatzer ductal occluders have been used.[41]

Treatment of Patent Ductus Arteriosus

Patent ductus arteriosus is a frequent congenital heart defect that is most commonly detected in infancy because of the associated murmur (**see also Chapter 75**). The ductus arteriosus is a fetal remnant of the sixth arch connecting the pulmonary artery to the lesser curvature of the aortic arch; it directs the RV output preferentially into the descending aorta. After birth, several important physiologic changes (loss of circulating placental prostaglandins and increased oxygen tension) lead to early functional closure of the ductus followed by anatomic closure in the following weeks to months. For patients in whom the ductus remains patent, the elevation in systemic vascular resistance and drop in peripheral vascular resistance promotes a left-to-right shunt with resultant pulmonary overcirculation and left heart dilation. Left untreated, a patent ductus arteriosus (PDA) can lead to significant heart failure, atrial arrhythmias (secondary to atrial hypertension), and pulmonary hypertension. Rarely, the PDA can be a site for infective endarteritis.[42] Prior to catheter-based interventions, significant PDAs were ligated surgically via posterolateral thoracotomy. Indications for intervention have been outlined elsewhere.[1] From the earliest reports of catheter-based closure in 1967, numerous devices have been introduced to treat the various morphologic differences in ductal anatomy. From coils, to vascular plugs, to dedicated occlusion devices, the interventionalist has multiple options for PDA occlusion (**Fig. 76.3**). There is consensus regarding the indication for closure in a large PDAs with associated left heart dilation, but there is current controversy with respect to the need for closing "silent" PDAs.[43]

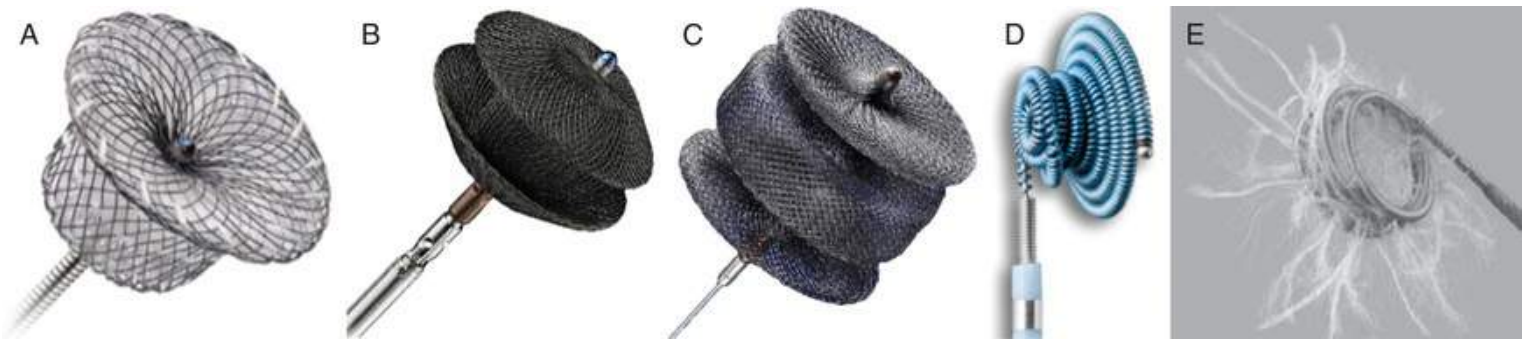

FIGURE 76.3 Various closure devices for patent ductus arteriosus. **A,** Amplatzer Ductal Occluder (St. Jude Medical, St. Paul). **B,** Amplatzer Ductal Occluder II (St. Jude Medical, St. Paul). **C,** Amplatzer Vascular Plug II (St. Jude Medical, St. Paul). **D,** Nit-Occlud PDA Occluder (PFM Medical AG, Köln, Germany).

Amplatzer Duct Occluders (First- and Second-Generation)

The ADO-I device is made of a Nitinol wire mesh packed with Dacron polyester fabric to facilitate platelet aggregation and endothelialization. The second-generation ADO-II has symmetric retention skirts, which allow it to be placed in an antegrade or a retrograde fashion. The ADO-II is not packed with polyester fibers, because the Nitinol wire weave is tighter than in the ADO-I.

Amplatzer Vascular Plugs (Second- and Fourth-Generation)

In patients with long, tubular ducts, a vascular plug may be the optimal occlusion device. The vascular plugs have a conveniently low profile and work well in ducts with sufficient length to ensure that the left pulmonary artery and aorta are not obstructed. The AVP-II has a wide assortment of sizes (3 to 22 mm). The AVP-IV has fewer available sizes (4 to 8 mm) and is slightly longer than AVP-II, but it offers an even lower profile, so that it can navigate tortuous anatomy with ease.

Nit-Occlud Device

The Nit-Occlud device (PFM Medical, Carlsbad, CA) has a single Nitinol wire coil, which can be wound in a funnel shape when it is advanced from the catheter. The Nit-Occlud device can be delivered via a 4 Fr guide catheter with a controlled-release mechanism. The Nit-Occlud comes in multiple sizes with variable levels of wire stiffness.

Standard Coiling

After small ducts have been crossed, they can be reliably occluded with simple coils or detachable coils.

Outcomes and Complications

Transcatheter closure of PDA has become a reliable procedure with excellent technical success and good efficacy.[4] Numerous articles have reviewed the outcomes of detachable coils and the Amplatzer devices and found the overall closure rate to be approximately 94%.[43] Chinese reviews of 1500 patients have reported technical success rates of 99% and occlusion rates of 100% at 6-month follow-up.[44] Serious adverse events are extremely rare.[4] Minor complications, including vascular injuries, device embolization, residual shunts, blood loss requiring transfusion, hemolysis, and aortic or pulmonary artery narrowing not requiring intervention, occur in the youngest patients, but rarely in adults.[4]

Future Perspectives

The transcatheter management of structural congenital heart disease in adults has undergone rapid advances over the past decade. Pulmonary valve implants have become a mainstay of therapy for patients with pulmonic valve stenosis and/or regurgitation. Valve-in-valve implants appear likely to play an important role in managing degenerative bioprosthetic valves.

These therapies can be expected to evolve rapidly, as can other new, unexpected, and sophisticated approaches to the transcatheter management of structural heart disease. Current trials regarding the Edwards valve-in-valve registry for mitral and aortic valves are ongoing. The Medtronic Evolute R has approval for aortic valve-in-valve procedures.

Acknowledgment

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77

The Dilated, Restrictive, and Infiltrative Cardiomyopathies

Rodney H. Falk, Ray E. Hershberger

There is, at present, no universal definition of cardiomyopathy. Even though it is now agreed that myocardial disease secondary to atherosclerotic coronary artery disease, valvular disease, congenital heart disease, and systemic hypertension should not be classified as a cardiomyopathy, opinion differs as to whether the condition should be defined on the basis of morphology and whether molecular disturbances such as the channelopathies should be included. An American Heart Association definition[1] describes cardiomyopathies as "a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilation and are due to a variety of causes and frequently are genetic. Cardiomyopathies either are confined to the heart or are part of a generalized systemic disorder often leading to cardiovascular death or progressive heart failure–related disability." This classification includes patients with predominantly electrical dysfunction of the heart, a group not included in a European Working Group definition.[2] Both U.S. and European experts, however, have recognized the growing importance of genetics in patients with cardiomyopathy since these position papers were released.

The ability to combine genetic information with phenotypic information regarding both left ventricular (LV) and right ventricular (RV) structure and function forms the basis of cardiovascular genetic medicine (**Fig. 77.1**). Clinical genetic testing in patients with cardiomyopathies not only benefits asymptomatic patients and family members through proper cascade risk assessment, but may also enhance the care of symptomatic patients, as it is likely that in the near future, genomic information will both predict the natural history and guide therapy. The expansion of clinical genetic testing that has been made possible by next-generation sequencing also brings new challenges in terms of knowing which tests to order, how to conduct pretest counseling and obtain consent, and how to interpret molecular genetic test results. **Table 77.1**[3,4] presents an overview of the classification of cardiomyopathies based on phenotypic (the "phenome") and genetic information. The phenome includes data on cardiac morphology, physiology, and cellular and molecular pathology, as well as on other aspects of the environment relevant to the specific disease in question.[5] Despite the integration of genetics and genomics, the phenotypic information derived from information about LV and RV chamber size and function remains highly relevant in terms of clinical care despite the absence of universally accepted cardiomyopathy definitions. Numerous genes, having had rare variants reported in association with one or more of the genetic cardiomyopathies, have now been noted, and some genes have been reported to cause more than one phenotype (**Fig. 77.2**) Although this chapter focuses primarily on nonsyndromic cardiomyopathies, there are multiple syndromes in which a cardiomyopathy develops in concert with multiorgan system involvement. Hypertrophic cardiomyopathy (HCM; **see Chapter 78**) is also mentioned briefly herein because of its significant genetic overlap with dilated cardiomyopathy (DCM) and restrictive cardiomyopathy (RCM). It is also important to recognize that although myocardial dysfunction as a result of hypertension and ischemic heart disease must be differentiated from the cardiomyopathies, the diseases often coexist and may aggravate an underlying primary cardiomyopathy.

FIGURE 77.1 Interaction of genome and phenome. The *arrow* depicts the bimodal interaction between genes and the environment, or the genome and phenome. The goal of human genetic studies has always been to understand genomic variation and its impact on phenotypes, and vice versa. Genetic and genomic effects in cardiovascular diseases are now becoming integrated into the practice of cardiovascular medicine.

TABLE 77.1

Classification of the Cardiomyopathies by Phenome and Genome

TYPE	PHENOME			GENOME		
	Morphology	Physiology	Pathology	Systemic Conditions, Clinical Features, Risk Factors	Nonsyndromic, Usually Single Gene	Syndromic
Dilated (DCM)	Dilation of LV and RV with minimal or no wall thickening	Reduced contractility is the primary defect; variable degree of diastolic dysfunction	Myocyte hypertrophy; scattered fibrosis	Hypertension; alcohol; thyrotoxicosis, myxedema; persistent tachycardia; toxins (e.g., chemotherapy, especially anthracyclines); radiation	Diverse gene ontology (**see Fig. 77.2**) with >30 genes implicated (**see also eTable 77.1**)	Diverse array of associated conditions, especially muscular dystrophies: Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy, Duchenne/Becker muscular dystrophy; Laing distal myopathy; Barth syndrome; Kearns-Sayre syndrome; others[3,4]
Restrictive (RCM)	Usually normal chamber sizes; minimal wall thickening	Contractility normal or near-normal with a marked increase in end-diastolic filling pressure	Specific to type, diagnosis: amyloid, iron, glycogen storage disease, others	Endomyocardial fibrosis, amyloid, sarcoid, scleroderma, Churg-Strauss syndrome, cystinosis, lymphoma, pseudoxanthoma elasticum, hypereosinophilic syndrome, carcinoid	If not associated with systemic genetic disease, genetic cause usually from sarcomeric gene mutations (**see eTable 77.1**)	Gaucher disease, hemochromatosis, Fabry disease, familial amyloidosis; mucopolysaccharidoses, Noonan syndrome
Hypertrophic (HCM)	Usually normal or reduced internal chamber dimension; wall thickening pronounced, especially septal hypertrophy	Systolic function increased or normal	Myocyte hypertrophy, classically with disarray	Severe hypertension can confound clinical, morphologic diagnosis	Mutations of genes encoding sarcomeric proteins (**see Chapter 78; also see eTable 77.1**)	Noonan syndrome, LEOPARD syndrome, Danon syndrome, Fabry disease, Wolff-Parkinson-White syndrome, Friedreich ataxia, MERRF, MELAS (**see Chapter 97**)
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	Scattered fibrofatty infiltration, classically of RV but also of LV; dilation of RV or LV, or both, is common but not universal	Ventricular arrhythmias (VT, VF) early or late, reduced contractility with progressive disease; can mimic DCM	Islands of fatty replacement; fibrosis	Palmoplantar keratoderma, wooly hair in Naxos syndrome	Mutations of genes encoding proteins of desmosome (**see Fig. 77.2, eTable 77.1, and eFig. 77.4**)	Naxos syndrome
Left ventricular noncompaction (LVNC)	Ratio of noncompacted to compacted myocardium increased with normal LV or RV or any other phenotype	Normal to reduced systolic function	Myocardium normal and ranging to findings consistent with other coexisting cardiomyopathies	Phenotype observed in setting of other types of cardiomyopathy	Various cardiomyopathy genes associated, but uncertain whether genetic cause or developmental defect during organogenesis; see text	
Infiltrative	Usually thickened walls; occasional dilation	Restrictive physiology; systolic function usually mildly reduced	Specific to type, diagnosis: amyloid, iron, glycogen storage disease, others		See RCM, above	See RCM, above
Inflammatory	Normal or dilated without hypertrophy	Reduced systolic function	Inflammatory infiltrates	Hypereosinophilic syndrome (see text), acute myocarditis (**see Chapter 79**)		
Ischemic	Normal or dilated without hypertrophy	Reduced systolic function	Areas of infarcted myocardium	Hypercholesterolemia, hypertension, diabetes, cigarette smoking, family history	Familial hypercholesterolemia; other heritable lipid disorders	Familial hypercholesterolemia
Infectious	Normal or dilated without hypertrophy	Reduced systolic function	Specific to infection	Viral (especially acute myocarditis); protozoal (e.g., Chagas disease); bacterial, direct infection (e.g., Lyme disease) or from acute cellular toxicity as result of systemic toxins (e.g., *Streptococcus*, gram-negative, others) (**see Chapter 79**)	Genetic predisposition to infection and/or variable response to infective agent	

LV, left ventricle; *MELAS*, mitochondrial encephalopathy, lactic acidosis, and strokelike symptoms; *MERRF*, myoclonic epilepsy associated with ragged-red fibers; *RV*, right ventricle; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia.

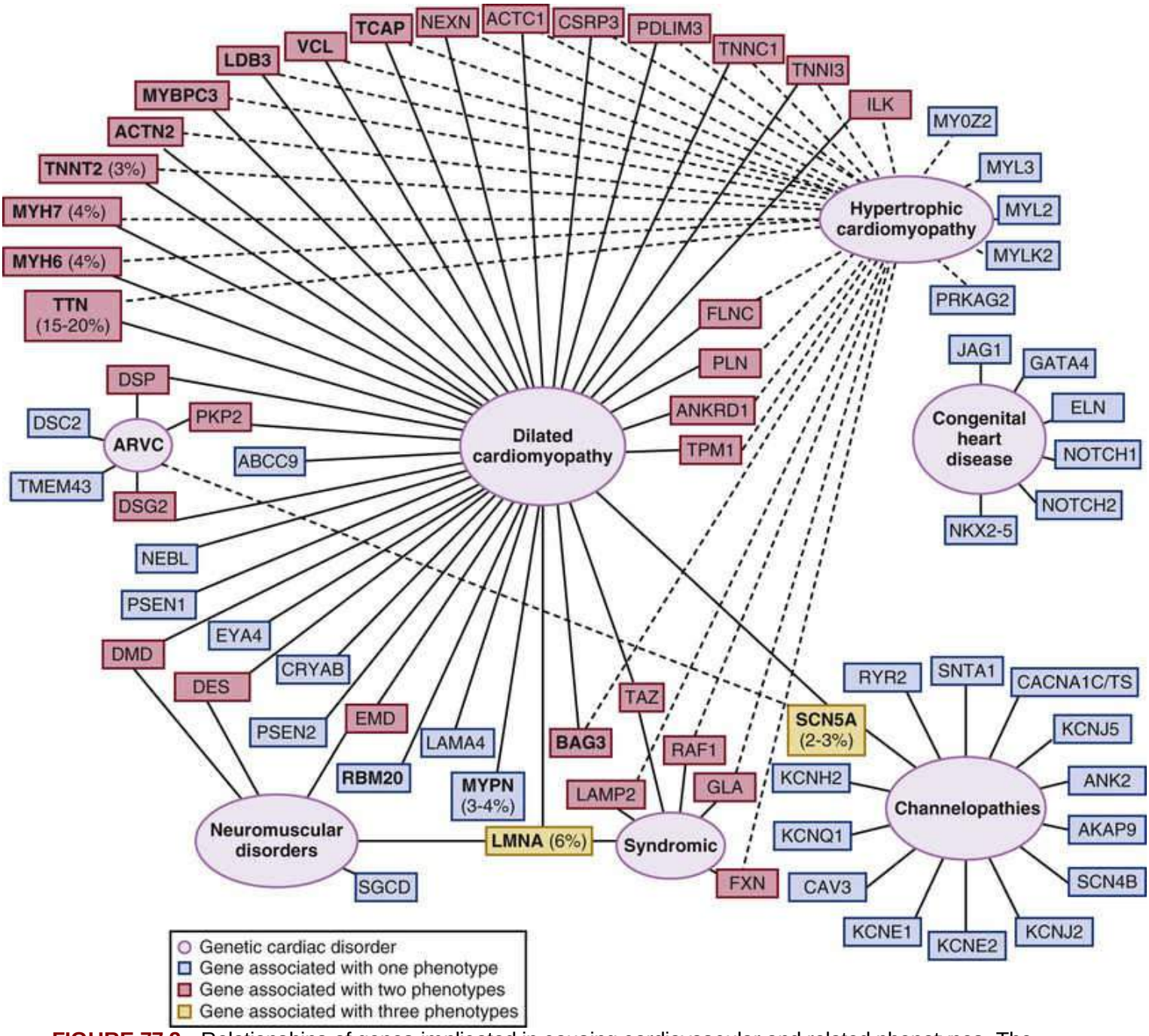


FIGURE 77.2 Relationships of genes implicated in causing cardiovascular and related phenotypes. The gene relationships for several cardiovascular phenotypes are shown, with the principal focus on DCM genetics. Common cardiac phenotypes are shown in the *purple ovals,* and *lines* connect each phenotype to the gene or genes (shown in a box) of which rare variants have been implicated in causing the phenotype. The gene boxes are color-coded according to the number of phenotypes with which they are associated: *blue* indicates one phenotype, *red* indicates two phenotypes, and *orange* indicates three phenotypes (as shown in the lower left corner of the figure). For a gene causing 3% or more of familial DCM cases, the frequency is included with its name. HCM gene associations are indicated by *dotted lines.* Well-established HCM genes include two sarcomere genes (*MYH7* and *MYBPC3*) that together account for 80% of HCM cases for which a genetic cause can be identified. Three other sarcomere genes (*TNNT2*, *TNNI3*, and *TPM1*) account for an additional 15% of such cases. The other numerous genes implicated have caused only one or a few reported cases. The evidence in support of rare variants in the genes shown and their relevance for the specified cardiomyopathy varies considerably.

The Dilated Cardiomyopathies

A dilated cardiomyopathy (DCM) is characterized by a dilated left ventricle with systolic dysfunction that is not caused by ischemic or valvular heart disease. A large number of genetic causes of DCM should be

considered (**see Fig. 77.2 and eTable 77.1**) before labeling the cardiomyopathy as "idiopathic," which is a term that reflects our inability to make a specific diagnosis. A latent period of asymptomatic LV systolic dysfunction often occurs before the development of clinical symptoms in patients with DCM (**Fig. 77.3**). Patients with DCM are also at risk for ventricular arrhythmias and may occasionally initially be seen because of aborted sudden cardiac death (**see also Chapter 42**).

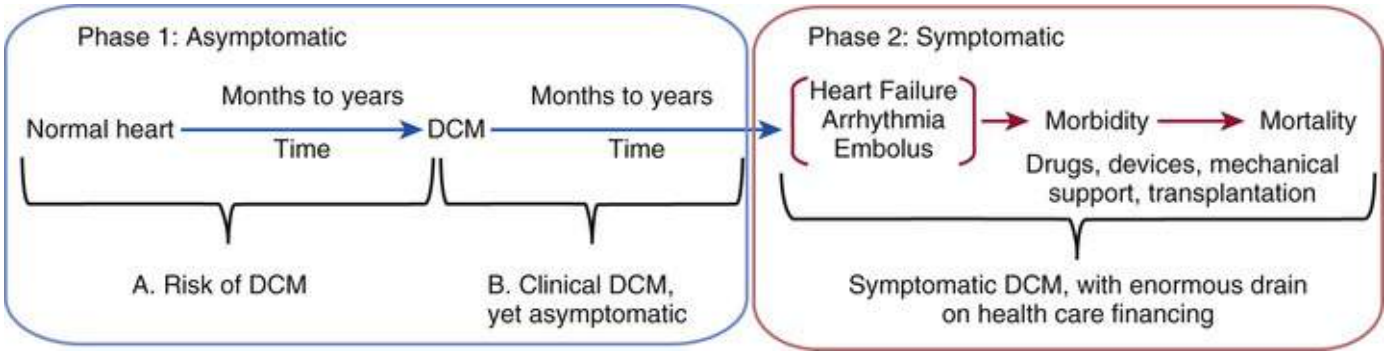


FIGURE 77.3 Asymptomatic and symptomatic phases of DCM. Phase 1 includes two periods, both asymptomatic. In the first period (1A), individuals who harbor one or more rare DCM variants have a risk of developing DCM over time. During this phase, genetic information identifies the individuals who would benefit from periodic clinical screening to detect early clinical disease. In phase 1B, DCM is present but asymptomatic, at times for years, and may evade detection unless periodic clinical cardiovascular imaging efforts detect it. Once disease has been detected, medical therapy can be initiated in an effort to prevent progression to phase 2. In phase 2, late-stage disease becomes symptomatic, with heart failure, arrhythmia, or embolus, the presenting features of DCM. (From Morales A, Hershberger RE: The rationale and timing of molecular genetic testing for dilated cardiomyopathy. Can J Cardiol 2015;31:1309-12.)

ETABLE 77.1

Genes Reported to Harbor Rare Variants in Association with Nonsyndromic Cardiomyopathy

GENE*	PROTEIN	FUNCTION	OMIM	DCM†	RCM†	ARVC†	LVNC†	HCM†
TTN	Titin	Sarcomere structure/extensible scaffold for other proteins	188840	18% to 25%				CR
LMNA	Lamin A/C	Structure/stability of inner nuclear membrane; gene expression	150330	6%			CR	
MYH7	Beta-myosin heavy chain	Sarcomeric protein; muscle contraction	160760	4%	CR		CR	40%
TNNT2	Cardiac troponin T	Sarcomeric protein; muscle contraction	191045	3%	CR		CR	5%
SCN5A	Sodium channel	Controls sodium ion flux	600163	2%				
MYH6	Alpha-myosin heavy chain	Sarcomeric protein; muscle contraction	160710	1% to 2%				CR
MYPN	Myopalladin	Sarcomeric protein, Z-disc	608517	1% to 2%				
MYBPC3	Myosin-binding protein C	Sarcomeric protein; muscle contraction	600958	1%			CR	40%
RBM20	RNA binding protein 20	RNA binding protein of a spliceosome		1% to 2%				
ANKRD1	Ankyrin repeat domain, containing protein 1	Cardiac ankyrin repeat protein (CARP); localized to myopalladin/titin complex	609599	1%				
LAMA4	Laminin a-4	Extracellular matrix protein	600133	<1%				
VCL	Metavinculin	Sarcomere structure; intercalated discs	193065	<1%				
LDB3	Cypher	Cytoskeletal assembly; targeting/clustering of membrane proteins	605906	<1%			CR	
TCAP	Titin-cap or telethonin	Z-disc protein that associates with titin; aids sarcomere assembly	604488	<1%				
PSEN1/2	Presenilin 1/2	Transmembrane proteins, gamma-secretase activity	104311/ 600759	<1%				
ACTN2	Alpha-actinin-2	Sarcomere structure; anchor for myofibrillar actin	102573	<1%				CR
CRYAB	Alpha B crystallin	Cytoskeletal protein	123590	<1%				
TPM1	Alpha-tropomyosin	Sarcomeric protein; muscle contraction	191010	<1%	CR		CR	2%
ABCC9	SUR2A	Kir6.2 regulatory subunit, inwardly rectifying cardiac K_{ATP} channel	601439	<1%				
ACTC1	Cardiac actin	Sarcomeric protein; muscle contraction	102540	<1%	CR		CR	<1%
PDLIM3	LIM domain protein 3	Cytoskeletal protein	605889	<1%				
ILK	Integrin-linked kinase	Intracellular serine-threonine kinase; interacts with integrins	602366	<1%				
TNNC1	Cardiac troponin C	Sarcomeric protein; muscle contraction	191040	<1%			CR	CR
TNNI3	Cardiac troponin I	Sarcomeric protein, muscle contraction; also seen as recessive	191044	<1%	CR			5%
PLN	Phospholamban	Sarcoplasmic reticulum Ca^{2+} regulator; inhibits SERCA2 pump	172405	<1%			CR	CR
DES	Desmin	DAGC; transduces contractile forces	125660	<1%				
SGCD	Delta-sarcoglycan	DAGC; transduces contractile forces	601411	<1%				
NEBL	Nebulette	Binds actin; Z-disc assembly	605491	<1%				
NEXN	Nexilin	Cardiac Z-disc	613122	<1%				
CSRP3	Muscle LIM protein	Sarcomere stretch sensor/Z-discs	600824	<1%				CR
EYA4	Eyes-absent 4	Transcriptional coactivators (Six and Dach)	603550	CR				
DMD‡	Dystrophin	Dystrophin-associated glycoprotein complex, transduces contractile force	300377	?				
TAZ‡	Tafazzin	Unknown	300394	CR			CR	
MYL2	Regulatory myosin light chain	Sarcomeric protein; stabilizes long helical neck of myosin head	160781	CR	CR			<1%
MYL3	Essential myosin light chain	Sarcomeric protein; stabilizes long helical neck of myosin head	160790		CR			1%
PKP2	Plakophilin 2	Desmosomal protein	602861	<1%	CR	10% to 40%		
DSG2	Desmoglein	Desmosomal protein	125671	CR	CR	10% to 40%		
DSP	Desmoplakin	Desmosomal protein	125647	<1%	CR	5% to 15%		
DSC2	Desmocollin	Desmosomal protein	125645	CR	CR	2%		
JUP	Junction plakoglobin	Desmosomal protein	173325		CR	CR		
TMEM43	Transmembrane protein 43	Nuclear envelope protein	612048	CR	CR	CR		
TGFB3	Transforming growth factor-beta-3	Growth factor, differentiation, and proliferation	190230	CR	CR	CR		
RYR2	Ryanodine receptor 2	Calcium handling for myocyte contraction	180902	CR	CR	CR		

*Gene symbol.

†Percentages; the fraction of probands carrying mutations of that gene for the phenotypes shown based on primary and secondary reports.

‡X-linked.

ATP, adenosine triphosphate; *CR*, case reports with insufficient data to estimate the frequency within the phenotype.

When investigating a patient with DCM, a full history, including risk factors for coronary artery disease, should be acquired. Unless the patient is questioned in detail, the duration of symptoms may be significantly underestimated. Angina may occur, even in the absence of epicardial coronary disease, but

symptoms suggestive of angina should raise the possibility of coronary artery disease, either as a coexistent disease or as a major causative factor. Patients should be questioned carefully about alcohol consumption (**see Chapter 80**), both present and past. If a spouse is available, that person's input may be of great value because underreporting of heavy alcohol intake is common. A family history is essential, not only of symptoms suggestive of heart failure but also of sudden cardiac death, which may be referred to by the patient as "death from a massive heart attack." Occasionally, the constellation of symptoms may allow an astute clinician to detect an uncommon cause; for example, the combination of deafness, maternally inherited diabetes, and heart failure in a relatively young patient suggests a mitochondrial cardiomyopathy.

Findings on clinical examination reflect the biventricular dysfunction present in DCM (**see Chapter 21**). Electrocardiography frequently reveals LV hypertrophy, nonspecific ST-T wave changes, or bundle branch block (**see Chapter 21**). Pathologic Q waves may be present, although their presence should raise the possibility of advanced atherosclerotic heart disease rather than primary cardiomyopathy. In advanced cases with extensive fibrosis, low-voltage limb leads may be seen.

Echocardiography (**see also Chapter 14**) reveals biventricular dilation, which can range from mild to severe, as can LV systolic dysfunction (**Fig. 77.4**). LV wall thickness is usually within the normal range, but the LV mass is almost invariably increased. Most commonly, global LV hypokinesis is present, but regional wall motion abnormalities may also be seen, particularly septal dyskinesis in those with left bundle branch block. Disproportionate thinning of a dyskinetic wall should raise the possibility of coronary artery disease rather than primary cardiomyopathy. Mitral and tricuspid regurgitation is frequently present and may be severe, even when the clinical examination does not reveal a loud murmur. Other than impaired leaflet coaptation, the mitral and tricuspid valves appear to be structurally normal, and structural abnormalities suggest primary valvular disease rather than cardiomyopathy. Diastolic function in DCM ranges from normal to restrictive (**see also Chapter 26**). A restrictive pattern is most commonly seen in patients with volume overload in "decompensated" heart failure and often improves with initiation of diuretic or vasodilator therapy.

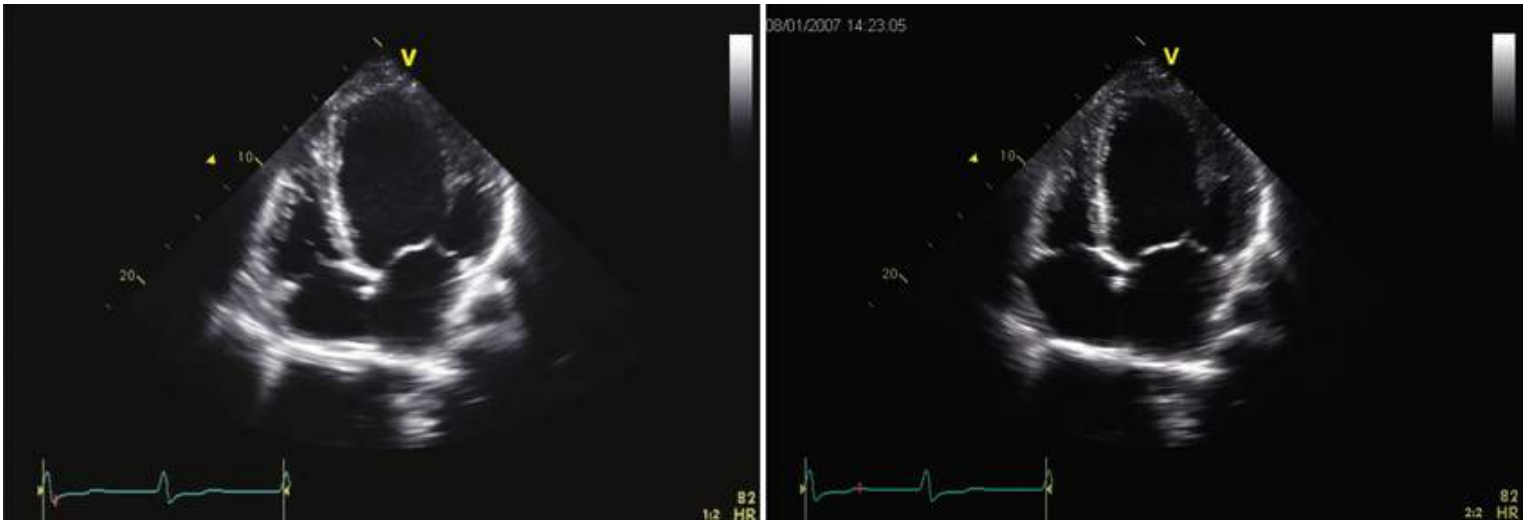


FIGURE 77.4 Echocardiogram in a patient with dilated cardiomyopathy. The end-diastolic frame **(left)** and end-systolic frame **(right)** in a 40-year-old man with severe DCM (ejection fraction < 20%) are shown. Note the globular LV shape, typical of advanced DCM. Despite the severe reduction in LV ejection fraction, he had only mild symptoms, attributable, in part, to preservation of stroke volume because of the marked increase in LV end-diastolic volume.

Coronary angiography (**see Chapter 20**) should be considered in all patients who have risk factors

for coronary artery disease or who are of an age at which this may be a causative factor. Alternatively, computed tomography (CT) coronary angiography (**see Chapter 18**) may be used, although it does not allow hemodynamic study, which may be useful in some patients. Because coronary artery disease is common, the functional significance of any obstructive coronary lesions found should be carefully evaluated insofar as their presence may be coincidental to DCM.

Cardiac magnetic resonance imaging (CMR) (**see also Chapter 17**) can be helpful in evaluating cardiomyopathies. A pattern of nontransmural delayed gadolinium enhancement in a noncoronary distribution in a dilated left ventricle suggests a nonischemic cause. Certain conditions, such as sarcoidosis, may have a rather typical appearance.[6] CMR is able to evaluate the extent of myocardial fibrosis in DCM and may provide information complementary to that obtained with cardiac biopsy. Unless a specific condition is suspected, cardiac biopsy is often unrewarding in the evaluation of DCM, but it may occasionally provide an unexpected diagnosis.[7] The risk for perforation during heart biopsy should be weighed against the small likelihood of finding a treatable cause with it.

Genetics of Dilated Cardiomyopathy

In a significant proportion of patients with DCM, no obvious cause can be found even with a comprehensive evaluation; these patients are assigned a diagnosis of *idiopathic DCM*. Family-based studies have shown that if clinical screening with an electrocardiogram (ECG) and/or echocardiogram is conducted in the first-degree family members of patients with DCM, evidence of DCM will be found in at least 20% to 35% of them, thereby establishing a diagnosis of *familial DCM*.[8] Familial DCM is now thought to have a genetic basis of diverse ontology (**see Fig. 77.2**).[9] Recent studies in families with familial DCM suggest that a genetic cause can be identified in at least 30% of cases and perhaps in as many as 40%, as extrapolated from studies of individual genes or small numbers of genes in gene discovery publications (**see eTable 77.1**). Truncating variants in the giant scaffolding protein titin (*TTN*) have been shown to be the most common, associated with 15% to 20% of cases of DCM (**Fig. 77.5**).[10,11] The proportion of rare variants thought to be causative of DCM attributed to any specific gene is much smaller, usually ranging from less than 1% to 2% to 3% (**see eTable 77.1**). Even though familial DCM is now considered a genetic disease, the issue of whether idiopathic DCM has a genetic basis in cases in which there is no evidence of familial DCM has not been resolved. Patients with DCM typically have an asymptomatic phase for many years before symptomatic heart failure, an arrhythmia, or an embolic event develops later in the course of the disease (**see Fig. 77.3**).[12] Occasionally, asymptomatic but clinically detectable DCM is discovered serendipitously during routine or preprocedural medical screening, usually prompted by subtle abnormalities on an ECG that lead to an echocardiogram. The time span needed for clinical disease to develop illustrates the remarkable ability of the myocardium to maintain normal—or close to normal—cardiac output and filling pressure for years despite clinically detectable asymptomatic DCM. This principle underlies the observation that the family history is much less sensitive than clinical screening via echocardiography in detecting DCM among family members of an individual with a new diagnosis of idiopathic DCM and emphasizes the necessity of clinical screening of all first-degree family members when a new diagnosis of any cardiomyopathy has been made (**Fig. 77.6**).

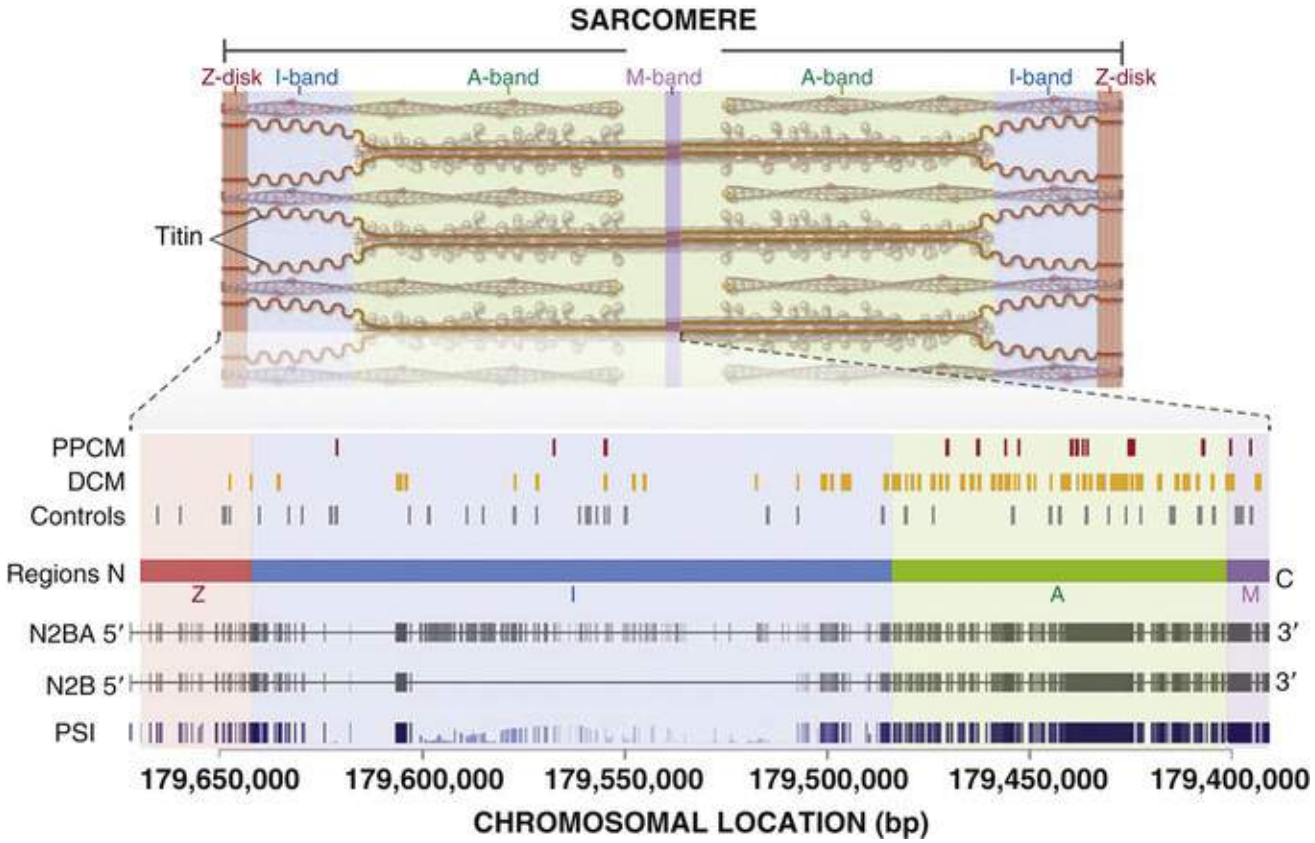


FIGURE 77.5 The giant protein titin and its involvement in DCM. Titin, the largest protein in the body, which is made up of more than 35,000 amino acids, is encoded by *TTN*, which acts as a scaffolding protein for sarcomere assembly. The large size of *TTN* made investigation extremely challenging prior to the development of next-generation sequencing strategies. Recent work has implicated truncating variants of *TTN* in 15% to 25% of familial DCM patients and 10% to 15% of nonfamilial DCM patients. Truncating variants include nonsense, frameshift, splice site, or other variants that cause the protein to be truncated. The upper part of the diagram shows the protein structure, with sarcomeric regions labeled (Z-disk and I, A, and M bands). The lower portion shows the locations of truncating variants in peripartum cardiomyopathy (PPCM), DCM, or controls. The exons of the primary two cardiovascular transcripts expressed (N2BA, N2B) are shown, along with their proportions spliced in (PSI). (From Ware JS, Li J, Mazaika E, et al: Shared genetic predisposition in peripartum and dilated cardiomyopathies. N Engl J Med 2016;374:233-41.)

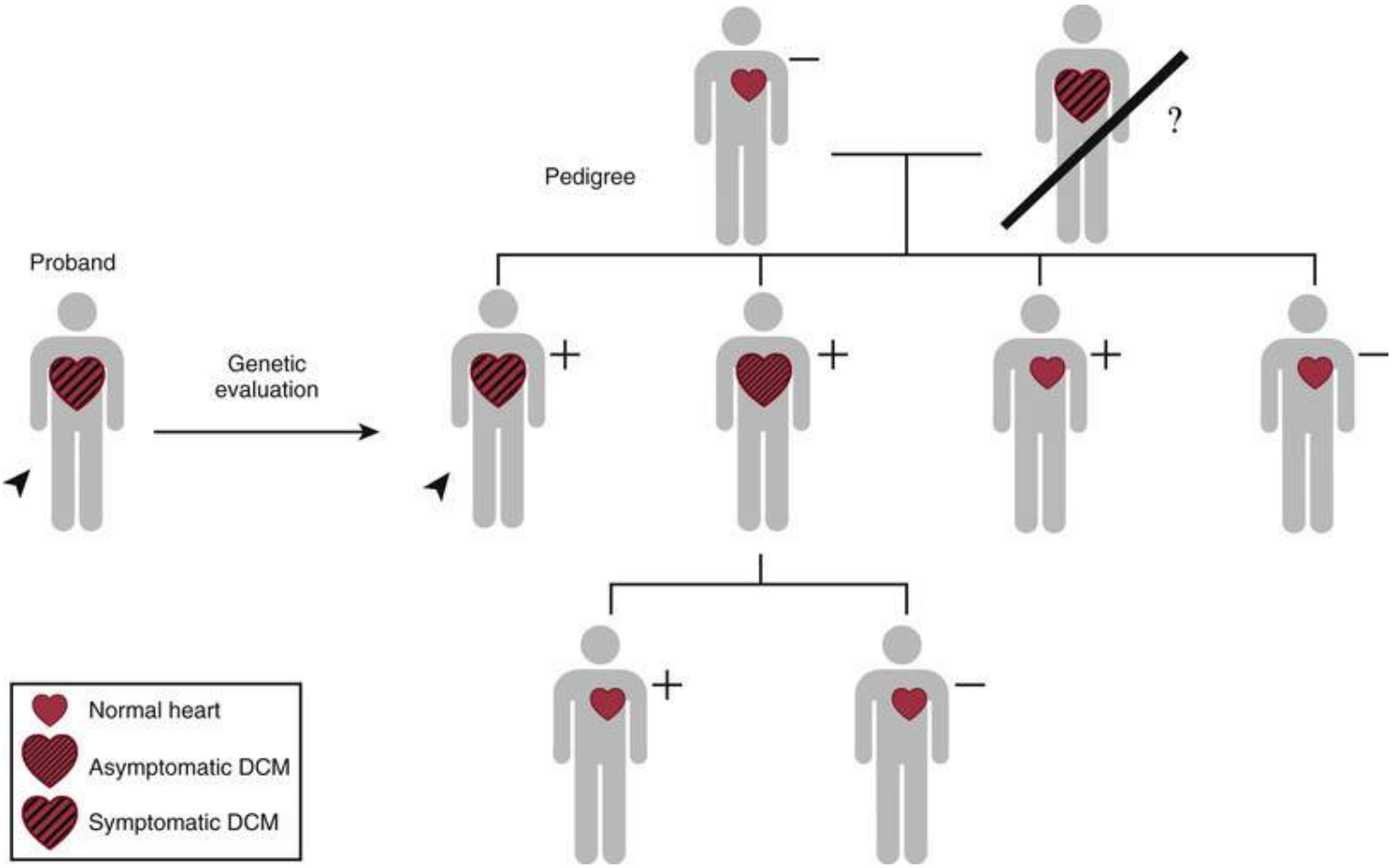
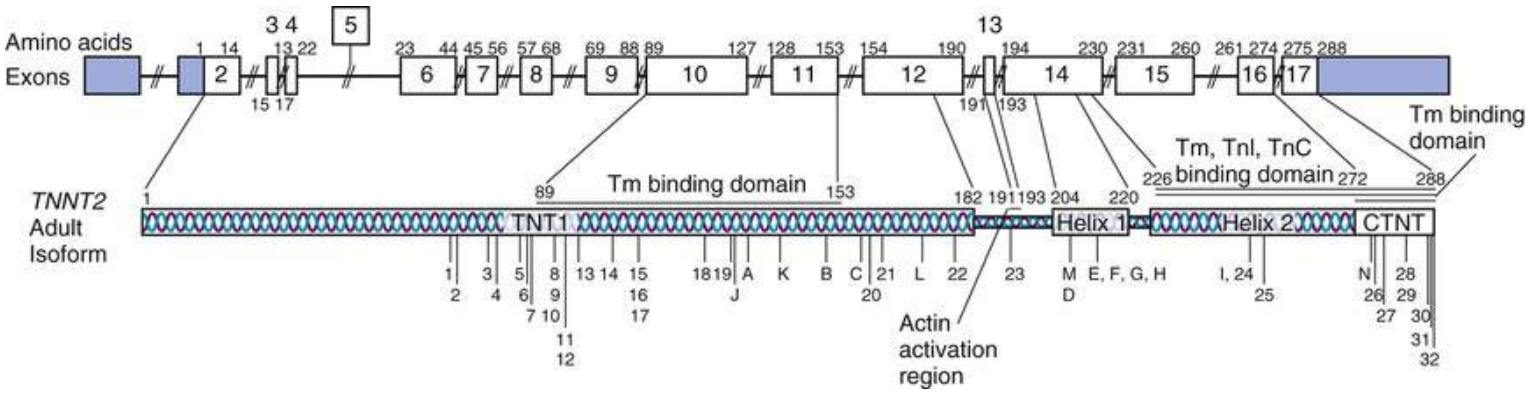


FIGURE 77.6 Genetic evaluation for cardiomyopathy. The goal of a genetic evaluation is to assess genetic risk of the proband and the proband's at-risk family members. The proband is the first patient identified with the trait or disease of interest, here depicted as an individual with DCM and shown as an enlarged heart. The at-risk relatives can be shown by a pedigree, or a graphical depiction of the family relationships. A genetic evaluation includes a comprehensive family history for three generations or more and genetic and family counseling for all patients and families. In this example, the proband's mother died with a known diagnosis of DCM, but neither a genetic evaluation nor family screening was undertaken. With a new diagnosis of cardiomyopathy, clinical screening of first-degree relatives is indicated. In this example, the proband's three siblings are clinically evaluated. One is found to have asymptomatic DCM; the other two do not have clinical evidence of DCM. Because DCM has been found in one sibling, the sibling's children also have undergone clinical cardiovascular screening. A genetic evaluation is also indicated. In most cases, genetic testing should be undertaken for the one clearly affected person in a family to facilitate family screening and management. In this case, the proband is sequenced first, and a pathogenic mutation is identified. This permits sequencing of the at-risk family members. The affected sibling is a mutation carrier, as is one unaffected sibling, who will be advised to have ongoing surveillance with clinical screening for early-onset DCM so that treatment can be initiated prior to the development of symptomatic DCM. One sibling is shown to not carry the mutation, so that individual can be released from clinical surveillance. The affected sibling's offspring can now also undergo genetic testing to assess risk. The one who is a mutation carrier will need clinical surveillance for development of DCM, with early intervention to attempt to prevent symptomatic disease. In this pedigree, the negative genetic testing result of the unaffected individual in the first generation indicates that the mutation, inherited by multiple individuals in the second generation, was transmitted from the affected individual in the first generation. The finding that three affected family members all carried the same mutation builds the evidence that the variant indeed is the pathogenic variant in this family. The *solid diagonal line* in the first generation depicts a deceased individual.

Genetics of Familial Dilated Cardiomyopathy

The genes shown to cause familial DCM are classified by subcellular location (gene ontology). As shown in **Fig. 77.2** and **eTable 77.1**, most of the implicated genes encode sarcomere, Z-disk, or cytoskeleton proteins. The broad representation of other genes encoding a wide variety of proteins demonstrates the

diverse pathways that can lead to a final phenotype of DCM.[9] Presumably, other yet unknown pathways may also be relevant in the pathogenesis of DCM. More than 30 genes have been identified to cause DCM (referred to as locus heterogeneity). The diverse subcellular locations of genes implicated in DCM differentiate this form of cardiomyopathy from HCM (**see also Chapter 78**) and arrhythmogenic right ventricular cardiomyopathy (ARVC), which are caused by variants in genes encoding sarcomeric or desmosomal proteins, respectively (**see Fig. 77.2**). In addition to locus heterogeneity, the molecular genetics of DCM is also characterized by allelic heterogeneity; that is, mutations commonly occur at many locations in a DCM gene, and many mutation sites in genes shown to cause both DCM and HCM are specific to that cardiomyopathy (**see eFig. 77.1**). So-called overlap phenotypes are not uncommon, particularly for sarcomeric genes, wherein mutations that have been shown to cause DCM, HCM, and RCM may be seen in an extended pedigree. Indeed, all three phenotypes (HCM, RCM, DCM) have been reported with the same mutation in an extended family.[13]



EFIGURE 77.1 Molecular genetic allelic heterogeneity**.** An example of molecular genetic allelic heterogeneity is shown for *TNNT2*, which encodes cardiac troponin T, a key sarcomeric protein involved in both DCM and HCM. The mutations known to cause DCM (letters A through N) or HCM (numbers 1 through 32) are shown. The genomic structure of *TNNT2* is presented in the **upper** part of the figure with exons numbered through 17; amino acids are also numbered by exon. The **lower** portion shows the adult troponin T protein isoform and its key domains. (From Hershberger RE, Pinto JR, Parks SB, et al: Clinical and functional characteristics of *TNNT2* mutations identified in patients with dilated cardiomyopathy. Circ Cardiovasc Genet 2009;2:306.)

Clinical Genetics of Familial Dilated Cardiomyopathy

Familial DCM is characterized by a relatively unitary final phenotype[9] of "generic" DCM. That is, for almost all genes implicated in DCM, there are no unique or distinguishing genotypic or phenotypic features that have been associated with specific gene mutations. The only general phenotypic variation that has been noted[8,14] is "DCM with prominent conduction system disease," a phenotype that is observed in lamin A/C (LMNA) DCM and in some cases of sodium channel (SCN5A) and desmin (DES) DCM (**see eTable 77.1**). Occasionally, a clinically mild muscular dystrophy phenotype can be identified in patients with LMNA cardiomyopathy and a new diagnosis of DCM. However, if the muscular dystrophy is prominent, in most cases it will have been identified in a neuromuscular clinic, with DCM being an incidental finding at the time of evaluation. Regardless of the setting, when a new diagnosis of idiopathic DCM is made, vigilance in detecting syndromic disease is essential, with particular attention being directed to neuromuscular phenotypes.

Most cases of familial DCM are transmitted via autosomal dominant inheritance, with the offspring of a mutation carrier having a 50% chance of inheriting the mutation. Autosomal recessive disease has been

reported, particularly in consanguineous families. X-linked DCM resulting from mutations in the gene for Duchenne muscular dystrophy (DMD) in patients without any findings of muscular dystrophy has been reported both in males and in carrier females, although the prevalence of DMD-DCM in cohorts of patients with idiopathic DCM has not been studied systematically. Mitochondrial DCM has also been reported, particularly in the setting of syndromic disease.[3]

Familial DCM is characterized by age-dependent penetrance, which means that an individual harboring a DCM-causing allele will manifest evidence of the DCM phenotype with increasing age.[8,14] Most genetic DCM cases become evident in the fourth to seventh decades, although DCM occurring in adolescence, childhood, or infancy is not uncommon. Variations in the age at onset of DCM are common across families with mutations in the same DCM gene, at times marked, and even in family members of an extended pedigree with the same mutation. Penetrance in familial DCM is commonly incomplete; that is, an individual with a disease-causing allele may not manifest any aspect of the disease phenotype. Also, expression is variable in that the clinical features and the phenotype can vary significantly between individuals in the same family or between families with the same mutation. Both incomplete penetrance and variable expressivity confound the assessment of familial DCM in family pedigrees. This is particularly relevant for a newly discovered or novel candidate mutation in a family because full segregation of the candidate mutation with the disease phenotype in one or more extended families is one of the most helpful approaches for determining the pathogenicity of such variants.[15]

Incomplete penetrance and variable expressivity at times result in marked phenotypic variability within and between families with DCM, even with the same mutation. The explanation for this phenomenon is not clear. Both environmental and genetic factors have been postulated and range from intrinsic (e.g., hypertension) and extrinsic phenomic components (e.g., toxins, viruses, adverse or favorable drug exposure) to a combination of various genomic variants resulting in a different genetic milieu (e.g., a second mutation in a different disease gene, risk alleles in the same or other relevant DCM pathways, variability in epigenetics or gene expression, and others).

Allelic heterogeneity, in which mutations in one gene can give rise to different and distinct phenotypes seemingly unrelated to one another (**see Fig. 77.2 and eFig. 77.1**), is also observed with some DCM genes, and knowledge of these allelic variants can be critical when considering a genetic diagnosis of DCM. One of the most remarkable examples is *LMNA*, which encodes the proteins lamin A and lamin C, key components of the inner nuclear membrane. For example, mutations in *LMNA* cause a distinctive DCM phenotype in which conduction system disease and arrhythmia occur before the onset of DCM. Mutant lamin proteins also cause a variety of syndromic diseases spanning striated muscle, adipose, nerve, and vascular tissues. These phenotypes, collectively termed the *laminopathies*, include skeletal myopathies (autosomal dominant Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy type 1B, and others [**see Chapter 97**]), lipodystrophy syndromes, peripheral neuropathy, and accelerated aging syndromes, most notably Hutchinson-Gilford progeria.

Approach to Clinical Genetic Evaluation, Including Genetic Testing

Guidelines for evaluation and clinical genetic testing for DCM, applicable to all cardiomyopathies with a possible genetic cause (**see Fig. 77.6**), include a comprehensive three- to four-generation search of the family history for any evidence of any type of cardiomyopathy, muscular dystrophy, or other evidence of syndromic disease that may have a cardiomyopathy component.[4,16] However, as noted earlier, even if it is obtained by a skilled professional, the family history might be negative because DCM may be

asymptomatic in family members. Accordingly, cardiovascular clinical screening of all first-degree relatives is essential; history taking, a physical examination, an ECG, and echocardiography should be acquired at a minimum. If evidence of DCM is identified in a relative, screening of that relative's first-degree relatives is indicated (i.e., stepwise or cascade clinical screening). Genetic testing, within the context of genetic counseling, is indicated with any evidence of familial disease because identification of a disease-associated mutation (in one or more clearly affected family members) can permit molecular genetic testing of other at-risk family members with preclinical disease and thereby aid in their risk stratification. Those who test negative for the family mutation should have a significantly reduced risk for the development of DCM; those with a family DCM mutation should undergo enhanced clinical screening to detect early DCM, with the rationale that early intervention, usually with angiotensin-converting enzyme (ACE) inhibitors or beta blockers, may delay or prevent progression of the disease.

Genetic testing is now conducted by next-generation sequencing in panels of DCM genes ranging from 20 to 30 or more and has recently been advocated for individuals with cardiomyopathy regardless of results of family clinical cardiovascular screening results.[12] Pancardiomyopathy panels now also contain more than 50 genes, and their competitive cost structure suggests that large test panels will quickly become the norm. Genetic testing should always be conducted within the context of genetic counseling, the goals of which are to review the genetic inheritance patterns and clinically relevant facts regarding idiopathic and familial DCM and ensure that a comprehensive family history has been completed and properly interpreted, including identification of at-risk relatives. Counseling is also essential to provide information regarding the risks, benefits, and limitations of clinical genetic testing, including the possible consequences of uncertain or inconclusive results or the discovery of heritable disease and its potential psychological implications. These processes are time-consuming and require specialized knowledge; guidelines suggest that referral of patients to individuals or centers with experience should be considered if local resources for completion of the process are not available.[4]

The recommendation for genetic testing recognizes that with the greater number of genes being tested in pancardiomyopathy panels, a greater number of variants of unknown or uncertain significance may be encountered.[12] Clinicians ordering clinical genetic testing must understand this concept and be prepared to deal with this reality as the results become available. The emergence of next-generation sequencing of panels of genes has fueled an extremely active period for reevaluation of testing strategies, including approaches to interpreting large numbers of variants. All of this will require careful, comprehensive translational research to understand the optimal testing strategies, including large databases of disease-associated variants.

Therapy for Dilated Cardiomyopathy

Therapy for DCM is similar to that for all types of heart failure with a reduced ejection fraction, and is discussed in detail in **Chapter 25**. Attention should be paid to treatment of atrial arrhythmias (see Tachycardia-Induced Cardiomyopathy, later). In selected patients, cardiac resynchronization therapy should be considered (**see Chapter 27**), and/or referral for a ventricular assist device or cardiac transplantation may be also needed (**see also Chapters 28 and 29**).

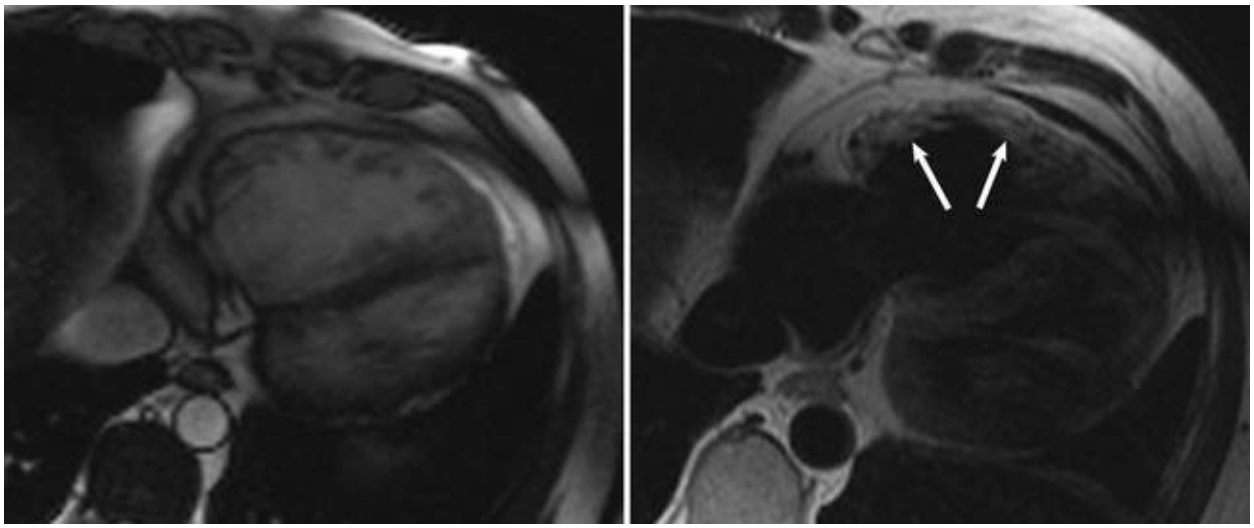
Alcoholic and Diabetic Cardiomyopathies

Excessive alcohol intake is cardiotoxic and may be manifested as DCM, and is discussed in detail in **Chapter 80**.[17] The importance of obtaining as accurate an alcohol history as possible in assessing patients

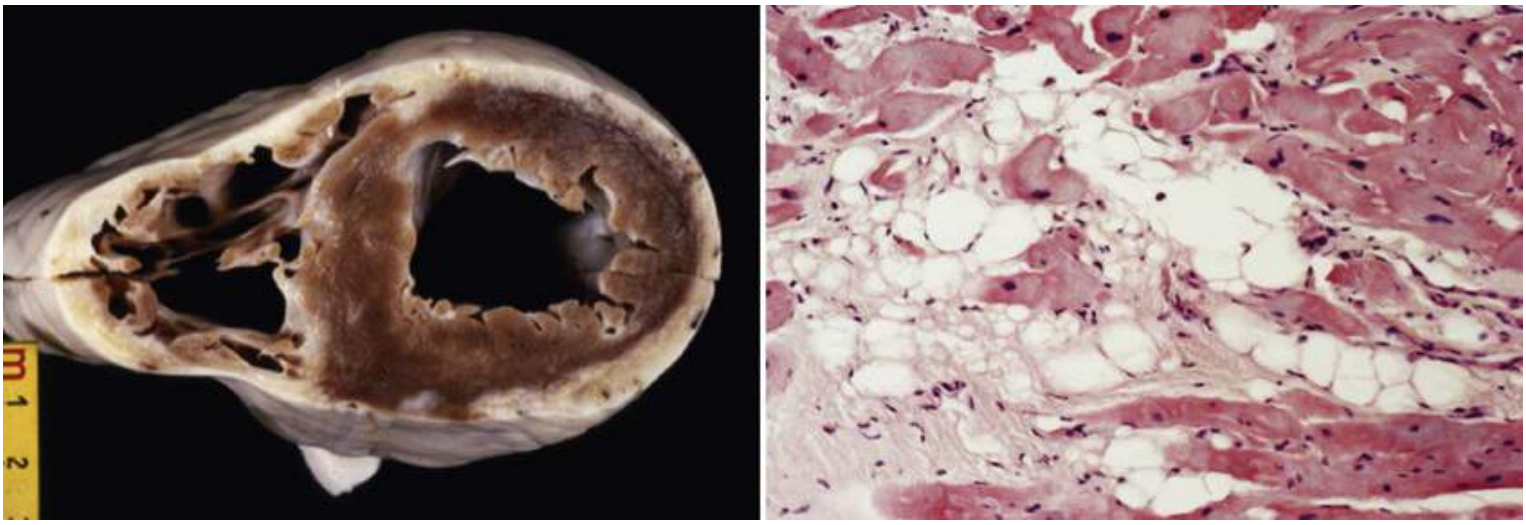
with DCM cannot be overstated. The existence of a specific diabetic cardiomyopathy independent of the effect of diabetes on the vasculature is debated, both in terms of its existence and, among those who believe it to exist, in the form that it takes.[18] Subtle abnormalities in both systolic and diastolic function do seem to be prevalent in diabetic patients, but their clinical relevance to the development of overt disease is unclear. Nevertheless, data do support good glycemic control as a preventative against the development of heart failure[19](**see Chapter 51**).

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined cardiomyopathy characterized by fibrofatty replacement of the myocardium. The right ventricular nomenclature is preserved to reflect the current medical literature, even though biventricular involvement occurs in up to 50% of cases and a small proportion of cases affect predominantly the left ventricle (**eFigs. 77.2 and 77.3**). The disorder is conceptualized as having three stages: an early subclinical phase in which imaging studies are negative but during which sudden cardiac death can still occur; next, a phase in which (usually) RV abnormalities are obvious without any clinical manifestation of RV dysfunction but with the development of a symptomatic ventricular arrhythmia; and, finally, progressive fibrofatty replacement and infiltration of the myocardium leading to severe RV dilation and aneurysm formation and associated right-sided heart failure (**see eFig. 77.2**). LV dilation and failure may also arise at this stage or may occur later (sometimes referred to as phase 4).[20]



EFIGURE 77.2 MRI in a 46-year-old man with arrhythmogenic right ventricular cardiomyopathy and abnormal findings on an ECG. **Left,** Steady-state precision image showing marked dilation of the right ventricle. **Right,** T1-weighted image showing extensive fatty infiltration of the RV wall (*arrows*). These appearances are typical of arrhythmogenic cardiomyopathy. (From Murphy DT, Shine SC, Cradock A, et al: Cardiac MRI in arrhythmogenic right ventricular cardiomyopathy. AJR Am J Roentgenol 2010;194:W299.)



EFIGURE 77.3 Arrhythmogenic right ventricular cardiomyopathy. **Left,** Autopsy specimen from a 39-year-old man with ARVC who died suddenly. The specimen shows fatty replacement of the RV free wall. There is also involvement of the subepicardial region of the LV free wall, which demonstrates the biventricular nature of ARVC in some patients. **Right,** Typical histologic appearance of a patient with advanced ARVC showing fatty replacement of the myocardium. (**Left,** From Rizzo S, Pilichou K, Thiene G, Basso C. The changing spectrum of arrhythmogenic right ventricular cardiomyopathy. Cell Tissue Res 2012;348:319; **right,** from Leone O, Veinot JP, Angelini A, et al: 2011 Consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. Cardiovasc Pathol 2012;21:245.)

The electrical manifestations of ARVC are a reflection of the pathologic disturbance. In the early stage, slow conduction and electrical uncoupling may lead to a fatal arrhythmia. As the disease progresses, fibrofatty infiltration results in inhomogeneous activation and a further delay in conduction. The predominant site of cardiac involvement, known as the triangle of dysplasia, was believed to involve the RV outflow tract, an area below the tricuspid valve, and the RV apex. However, recent data suggest that the RV apex is only involved in advanced disease and that an area involving the basal inferior and anterior right ventricle and the posterolateral left ventricle may be most commonly involved.[21] Patients with ARVC exhibit a typical monomorphic ventricular tachycardia (VT) characterized by left bundle branch block morphology with a superior axis[22] and typical T wave inversions extending to V_3 or beyond. A classic “epsilon wave” in the right precordial leads is a specific but insensitive finding (**Fig. 77.7**).

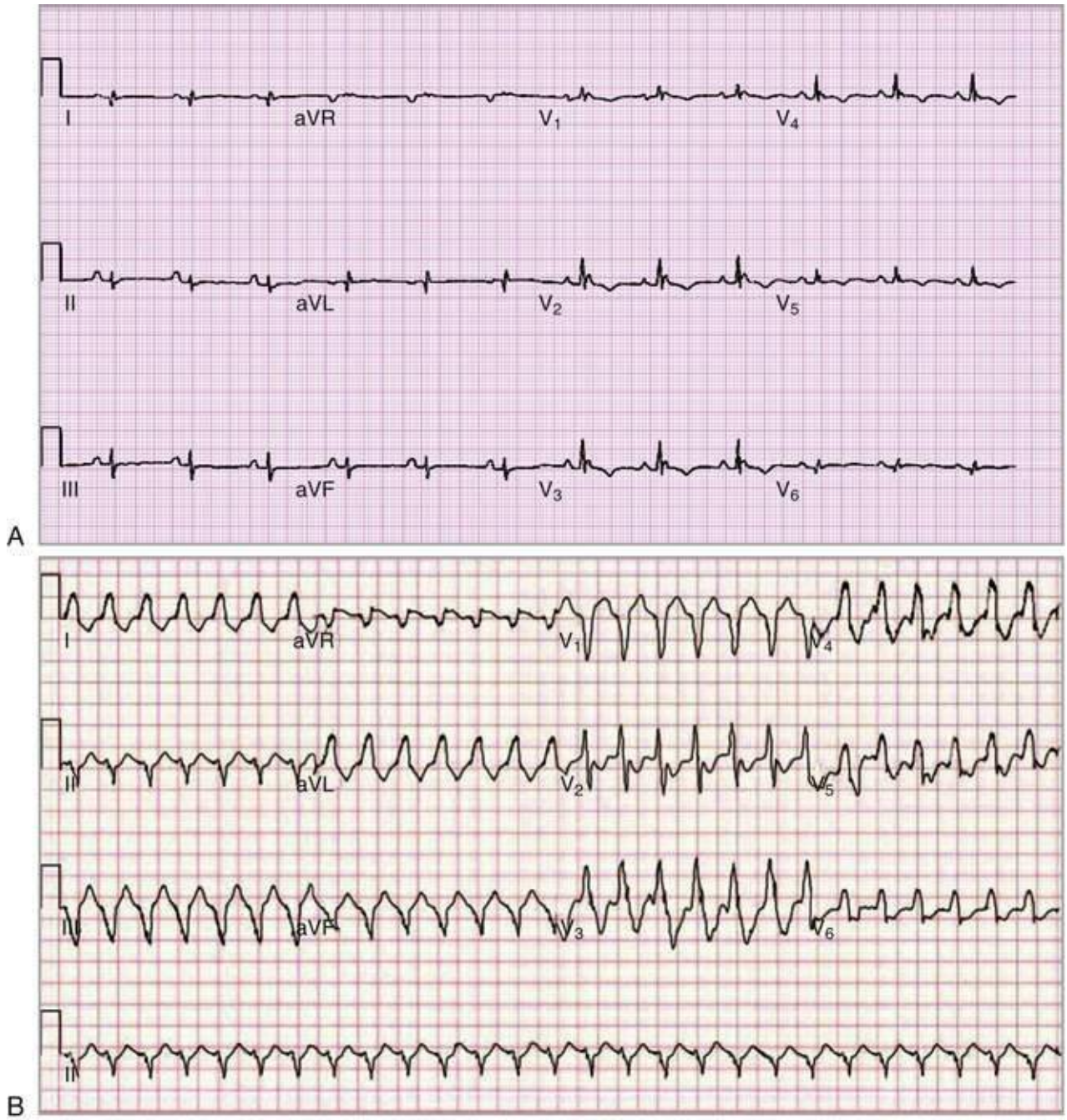
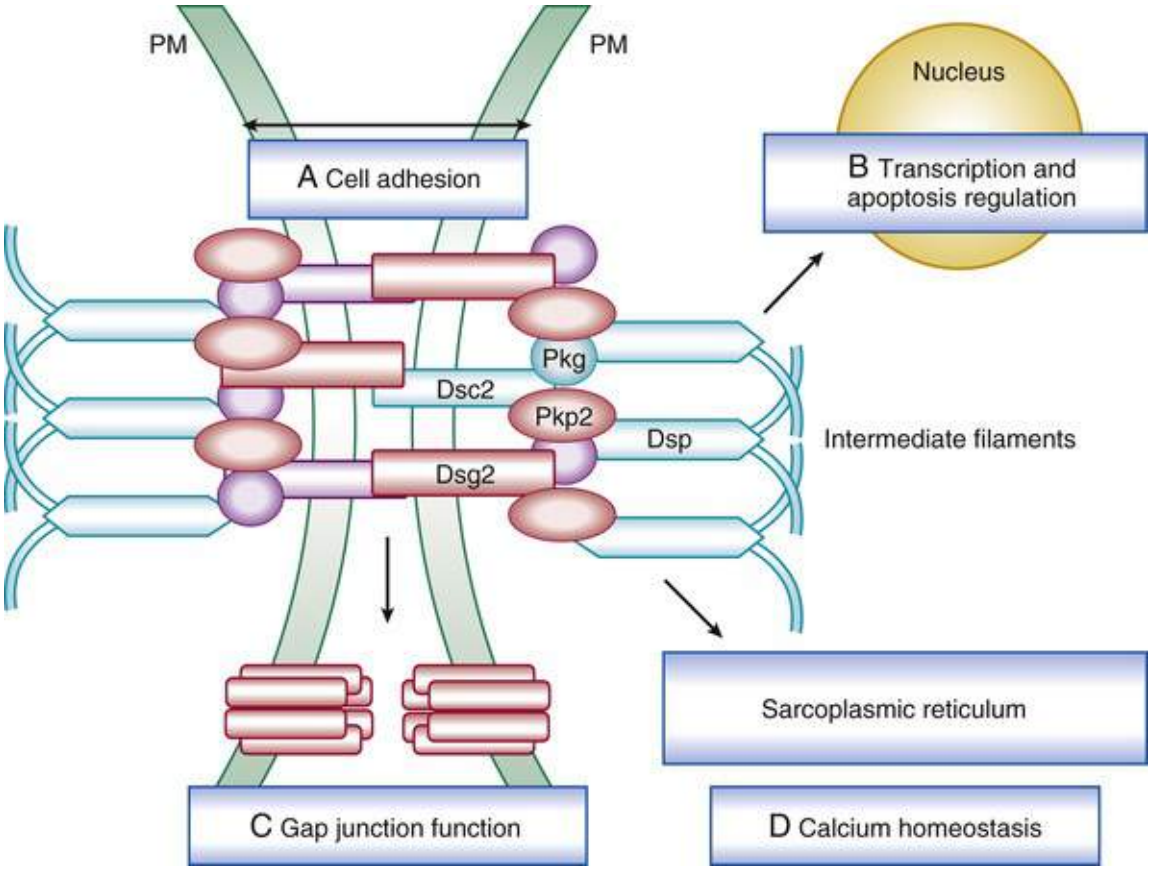


FIGURE 77.7 Arrhythmogenic right ventricular cardiomyopathy. **A,** ECG of a patient with ARVC. A typical ECG shows inverted T waves in the anterior precordial leads and an "epsilon potential" early during ventricular repolarization representing a "late potential" caused by delayed depolarization of an area of the right ventricle. **B,** Ventricular tachycardia in a patient with ARVC. There are left bundle branch block morphologic findings with a leftward axis. (From Hauer RN, Cox MG, Groeneweg JA: Impact of new electrocardiographic criteria in ARVC. Front Physiol 2012;3:352.)

Genomic Cause of Arrhythmogenic Right Ventricular Cardiomyopathy

Unlike genetic DCM, which has a final common phenotype despite its extensive locus heterogeneity, ARVC is driven by molecular alterations in genes encoding proteins that are key for cell-to-cell adhesion (**eFig. 77.4**).[23] Extensive work over the past decade has implicated genes encoding the desmosome, one of three key components of the intercalated disc, the end-to-end connection between ventricular myocytes,[23] in the pathogenesis of ARVC. In addition to desmosomes, the intercalated disc includes gap junctions mediating small-molecule communications. Mechanical coupling is mediated through the desmosome and adherens junctions (**see Chapter 22**), and disruptions of desmosomal proteins have been associated with ARVC. The classic hallmark of ARVC, fibrofatty replacement, is now understood to be related to aberrant

Wnt signaling of desmosomal proteins, as well as direct plakoglobin signaling, which transforms myocytes into adipocytes with disease progression.[23]



EFIGURE 77.4 Desmosomal proteins relevant for arrhythmogenic right ventricular cardiomyopathy. The cardiac desmosome and proposed roles of the desmosome in supporting structural stability through cell-cell adhesion *(A),* regulating transcription of genes involved in adipogenesis and apoptosis *(B),* and maintaining proper electrical conductivity through regulation of gap junctions *(C)* and calcium homeostasis *(D)* are presented. *Dsc2*, desmocollin-2; *Dsg2*, desmoglein-2; *Dsp*, desmoplakin; *Pkg*, plakoglobin; *Pkp2*, plakophilin 2; *PM*, plasma membrane. (From Awad MM, Calkins H, Judge DP: Mechanisms of disease: molecular genetics of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Nat Clin Pract Cardiovasc Med 2008;5:258.)

Molecular Genetics.

When a genetic cause can be identified, mutations in the genes encoding plakophilin 2 (*PKP2*), desmoglein 2 (*DSG2*), and desmoplakin (*DSP*) account for most genetic causes of ARVC (**see eTable 77.1 and Fig. 77.2**). Other genes encoding desmosomal proteins (desmocollin [*DSC2*], junction plakoglobin [*JUP*]) or affecting desmosomal physiology (e.g., transmembrane protein [*TMEM*]) have been implicated (**see eTable 77.1**). The degree of locus heterogeneity is similar for HCM and ARVC, in which five or fewer genes contribute to most of the identifiable genetic causes. However, as for DCM and HCM, the genes implicated in ARVC show extensive allelic heterogeneity.

Clinical Genetics.

The autosomal recessive syndromic *Naxos disease*, so named because it was discovered on the Greek island of Naxos, is manifested as ARVC cosegregating with palmoplantar keratoderma and wooly hair. Molecular genetic analysis has shown a homozygous two–base pair frameshift deletion of *JUP*, which encodes plakoglobin. This observation first implicated the desmosome in ARVC and prompted the

molecular genetic discovery of other desmosomal proteins. Other mutations in *JUP* have also been associated with cutaneous disease or wooly hair phenotypes, although cardiovascular phenotypes have not been identified in most of these allelic variants.[23] A second autosomal recessive syndromic disease, *Carvajal syndrome*, resembles Naxos disease in that individuals have palmoplantar keratoderma and wooly hair, but individuals with Carvajal syndrome manifest DCM, not ARVC. Carvajal syndrome is caused by a frameshift mutation in *DSP*, which encodes desmoplakin.[23] Other mutations in *DSP* have been identified with only ARVC or with only skin or hair manifestations. Even though reduced penetrance and variable expressivity are commonly observed in all genetic cardiomyopathies, these features may be particularly prominent in ARVC, in part because of the difficulty of assessing the phenotype and also because the arrhythmia component may be the only feature of the disease in some individuals long before structural changes can be identified.

Diagnosis

The more advanced the disease, the easier the diagnosis, but recognition of earlier stages, which may be manifested as aborted sudden death without detectable structural abnormalities, can be difficult. In addition, with increasing use of CMR for the diagnosis of cardiac pathology, a trend toward overdiagnosis of ARVC is now being recognized (**see also Chapter 17**). Although, in experienced hands, CMR is a useful tool for both diagnosis and evaluation of the extent of structural abnormalities in ARVC, early disease may not be apparent despite ventricular arrhythmia,[24] and overdiagnosis of the disease by less-experienced CMR readers has been recognized.[25] Endomyocardial biopsy for ARVC is one of the diagnostic criteria but is rarely undertaken nowadays because of the potential for higher major complication rates and for false-negative findings.[26] The diagnosis of ARVC currently rests primarily on the combination of clinical, electrocardiographic, and genetic findings, which are divided into major and minor diagnostic criteria as proposed in a 2010 consensus statement (**eTable 77.2**).

ETABLE 77.2

Revised Task Force Criteria for the Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy

Diagnostic Terminology for Revised Criteria
• Definite diagnosis: 2 major criteria, or 1 major and 2 minor criteria, or 4 minor criteria from different categories • Borderline: 1 major criterion and 1 minor criterion, or 3 minor criteria from different categories • Possible: 1 major criterion, or 2 minor criteria from different categories
I. Global and/or Regional Dysfunction and Structural Alterations
Major Criteria
By two-dimensional echocardiography: Regional RV akinesia, dyskinesia, or aneurysm *and* one of the following (end diastole): Parasternal long-axis view of RVOT (PLAX) ≥32 mm (≥19 mm/m^2) Parasternal short-axis view of RVOT (PSAX) ≥36 mm (≥21 mm/m^2) *or* Fractional area change <33% By MRI: Regional RV akinesia, dyskinesia, or dyssynchronous RV contraction *and* one of the following: Ratio of RVEDV to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female) *or* RVEF ≤40% By RV angiography: Regional RV akinesia, dyskinesia, or aneurysm
Minor Criteria
By two-dimensional echocardiography: Regional RV akinesia or dyskinesia and one of the following (end diastole): PLAX RVOT ≥29 to <32 mm (≥16 to <19 mm/m^2) PSAX RVOT ≥32 to <36 mm (≥18 mm to <21 mm/m^2) *or* Fractional area change >33% to ≤40% By MRI: Regional RV akinesia, dyskinesia, or dyssynchronous RV contraction *and* one of the following: Ratio of RVEDV to BSA ≥100 to <110 mL/m^2 (male) or ≥100 to <110 mL/m^2 (female) *or* RVEF <40% to ≤45%
II. Tissue Characterization of Wall
Major Criteria
Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of RV free wall myocardium in at least one sample, with or without fatty replacement of tissue seen on endomyocardial biopsy
Minor Criteria
Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of RV free wall myocardium in at least one sample, with or without fatty replacement of tissue seen on endomyocardial biopsy
III. Repolarization Abnormalities
Major Criteria
Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals >14 years of age (in absence of complete right bundle branch block QRS ≥120 msec)
Minor Criteria
Inverted T waves in leads V_1 and V_2 in individuals >14 years of age (in absence of complete right bundle branch block) or in V_4, V_5, or V_6
Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years of age in presence of complete right bundle branch block
IV. Depolarization/Conduction Abnormalities
Major Criteria
Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of T wave) in right precordial leads (V_1 to V_3)
Minor Criteria
Late potentials by signal-averaged ECG in at least 1 of 3 parameters in absence of QRS duration ≥110 msec on standard ECG
Filtered QRS duration ≥114 msec
RMS voltage of terminal 40 msec <20 μV
Terminal activation duration of QRS ≥55 msec measured from nadir of S wave to end of QRS complex, including R′ in V_1, V_2, or V_3 in absence of complete right bundle branch block

BSA, body surface area; *PLAX*, parasternal long-axis; *PSAX*, parasternal short-axis; *RVEDV*, RV end-diastolic volume; *RVEF*, RV ejection fraction; *RVOT*, RV outflow tract.

Modified from Marcus FI, McKenna WJ, Sherrill D, et al: Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Eur Heart J 2010;31:806.

Approach to Clinical Genetic Evaluation, Including Clinical Genetic Testing

Current studies estimate that a plausible genetic cause can be identified in approximately half of ARVC cases.[27-29] The impact of multiple mutations in desmosomal genes has been emphasized, as well as the impact of the revised task force clinical criteria, which has increased the sensitivity of molecular genetic testing.[28] A recent study of 439 index patients and their 562 family members showed an earlier onset of

disease in those who were positive for the mutation, although clinical characteristics were similar for both groups with disease onset.[30] For clear-cut cases of ARVC, genetic testing is indicated so that cascade testing of at-risk family members can be accomplished. This is particularly relevant for ARVC insofar as arrhythmias, especially sudden cardiac death, can occur before other phenotypic features become evident. The genes involved in ARVC show significant allelic heterogeneity, thus making it difficult to discern pathogenic variants from uncommon polymorphisms, as is the case for clinical genetic testing for all cardiomyopathies.[29] Pancardiomyopathy testing, especially for a phenotype of prominent VT, ventricular fibrillation, or sudden cardiac death with biventricular dilation and systolic dysfunction of unknown cause otherwise consistent with DCM, may also yield rare variants in the genes associated with ARVC. Even though conventional recommendations currently discourage the use of genetic testing for the diagnosis of ARVC, molecular genetic testing will probably be used more frequently in the near future to assist in making the diagnosis, especially as genetic testing proliferates and is used more commonly for all cardiomyopathies regardless of phenotype.

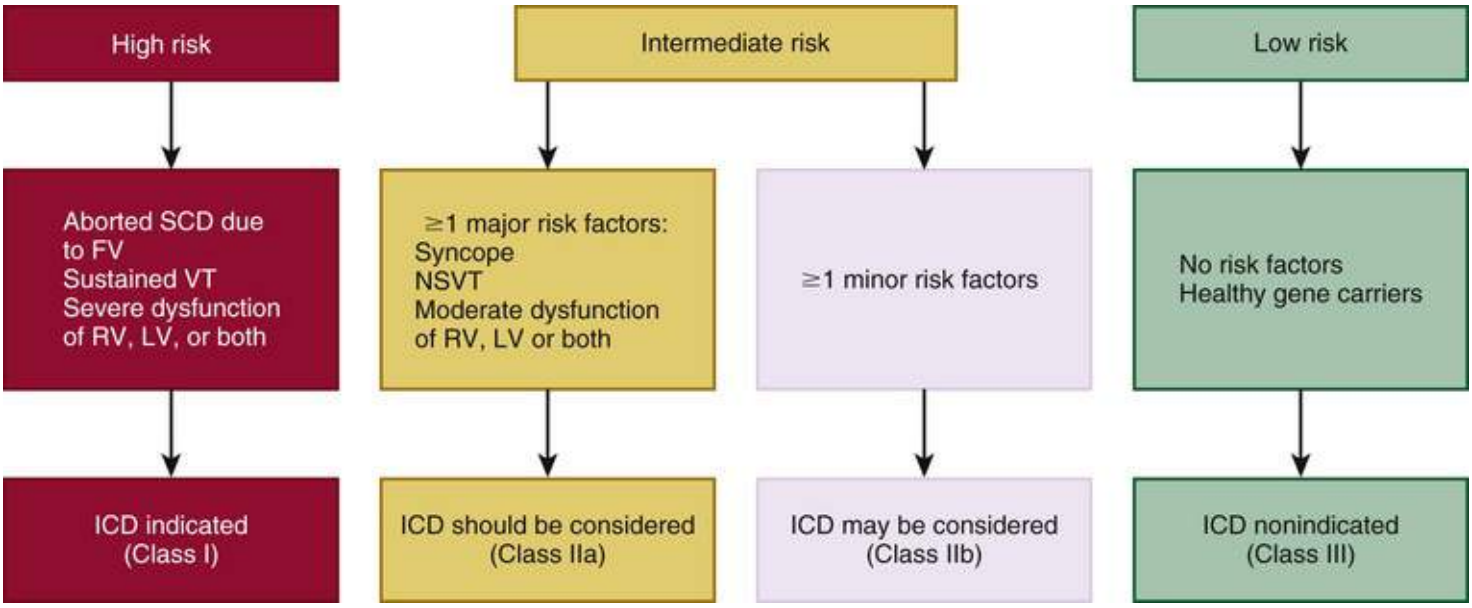
Differential Diagnosis

The differential diagnosis of ARVC in the early stages (before the onset of visible structural abnormalities) includes idiopathic and RV outflow tract VTs. The morphology of the classic ARVC-related VT differs from these entities, and in the presence of precordial T-wave inversion during sinus rhythm, ARVC should be the initial diagnosis. Cardiac sarcoidosis may occasionally mimic ARVC morphologically and be indistinguishable, even with multiple imaging modalities. Cardiac biopsy in patients with sarcoidosis often fails to show the pathognomonic granulomas but may reveal extensive fibrosis, which may also be confused with ARVC.

Treatment

Currently, the mainstay of therapy for ARVC is suppression and prevention of ventricular arrhythmias and the risk for sudden cardiac death, and prevention of disease progression. There is evidence that intense physical exertion is associated with an earlier onset of symptoms and an increased risk of sustained VT, and therefore patients with a definite diagnosis of ARVC are advised not to participate in athletic activity.[31,32] The classic monomorphic VT in ARVC with predominant RV involvement is generally well tolerated, even at a rapid rate, possibly because of preserved LV function in most patients. Nevertheless, VT of a different morphology may occur and sudden death is not uncommon. Antiarrhythmic drugs may suppress a symptomatic arrhythmia but have not been shown to prevent sudden death. Beta-blocking agents may suppress catecholamine-triggered arrhythmia and slow progression of ventricular dysfunction and have been recommended as potentially valuable in all patients with ARVC.[32] An implantable defibrillator (ICD) is recommended in patients with aborted sudden death, syncope, or decreased LV function and may be considered in other patients (**eFig. 77.5**). Catheter ablation has not been shown to reduce sudden death but is valuable in a patient with an ICD and frequent arrhythmias or in occasional patients with very well tolerated single-morphology VT. Ablation appears to be most successful when lesions are made in both the epicardial and endocardial surfaces of the heart; it should be performed only at centers experienced in the technique, either as a combined procedure or with epicardial ablation reserved for recurrence after endocardial ablation.[33] Heart failure may occur in advanced ARVC and is treated with standard drugs. Because a history of vigorous sustained exercise among carriers of a pathogenic ARVC desmosome mutation is associated with an earlier onset of symptoms and a higher prevalence of VT or ventricular fibrillation,[31] there is a task force recommendation that persons with

definite or suspected ARVC should not compete in most competitive sports.[34]



EFIGURE 77.5 Recommendations for implantable defibrillator in ARVC. (Corrado D, Wichter T, Link MS, et al: Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an International Task Force Consensus Statement. Circulation 2015;132:441-53.)

Left Ventricular Noncompaction

Whether LV noncompaction (LVNC) should be classified as a distinct cardiomyopathy has been debated extensively, as LVNC is a morphologic trait that is shared by many cardiomyopathies as well as by other conditions, such as the channelopathies and congenital heart disease. Underlying this debate is the lack of adverse outcomes of the LVNC itself, so that published accounts of adverse events stem from an otherwise defined cardiomyopathy or arrhythmia phenotype. Whether LVNC is a marker of another genetically driven cardiovascular pathologic condition remains uncertain. When combined with the absence of any unique LVNC gene ontology, the question of phenotype versus cardiomyopathy remains unresolved, although mounting evidence has increased to favor the phenotype.[35] In 2006, LVNC was included as a genetic cardiomyopathy in an AHA scientific statement.[1] In 2008, the European Society of Cardiology questioned whether LVNC should be classified as a cardiomyopathy or "merely a congenital or acquired morphologic trait that is shared by many phenotypically distinct cardiomyopathies."[2] LVNC does not have its own gene ontology but intersects with those of DCM, HCM, and ARVC (**see eTable 77.1**). In support of its heritable basis, one recent systematic study of families of probands in whom LVNC was diagnosed showed familial disease in 32 of 50 probands (64%), with the phenotypes of many family members also being limited to LVNC (i.e., without DCM or HCM). Interestingly, in 41% of these (23 of 56) patients, plausible mutations in sarcomeric genes were identified, even though nonpenetrance of LVNC among family members carrying these mutations was common.[36]

Defining the LVNC phenotype has been confounded by various echocardiographic or CMR approaches that have led to an estimate of its frequency in a population-based study of as high as 23%; furthermore, the concordance of three different echocardiographic diagnostic schemata was congruent in only 30% of cases.[37] These diagnostic criteria have been summarized and include four echocardiographic-based and two cardiac CMR–based (**eTable 77.3**). The criteria used to define LVNC use ratios of compacted to

noncompacted myocardium and LV size and function are not components of the diagnosis. Echocardiographic-based approaches differ as to whether measurements are obtained at end-systole or end-diastole, and the ratio of compacted to noncompacted myocardium varies. CMR approaches measure either the ratio of trabeculated to compact myocardium (T/M ratio of > 2.3 is considered LVNC) or the ratio of the mass of noncompacted to compacted myocardium (trabeculations > 20% are considered LVNC). The population-based Multi-Ethnic Study of Atherosclerosis evaluated the range of normal LV wall thicknesses in eight ventricular wall regions in 1000 participants using a T/M ratio of 2.3.[38] In 323 fully evaluable individuals without cardiac disease or hypertension, 140 (43%) had a T/M ratio of greater than 2.3 in at least one LV region, and in 20 (6%) the T/M ratio was greater than 2.3 in more than two regions. No associations were identified with age, sex, ethnicity, height, or weight.

ETABLE 77.3

Echocardiographic and Magnetic Resonance Imaging Diagnostic Criteria for Left Ventricular Noncompaction

Echocardiographic Criteria
Chin, et al. (California criteria)*
LVNC is defined by an X/Y ratio ≤0.5
These criteria evaluate trabeculae at the LV apex on the parasternal short-axis and apical views and by using the LV free wall thickness at end-diastole
Jenni, et al. (Zurich criteria)†
Bilayered myocardium consisting of a thin C layer and a much thicker NC layer with deep endomyocardial recesses: NC/C > 2
Predominant location of the pathology is midlateral, midinferior, and at the apex
Evidence of intertrabecular recesses filled with blood from the LV cavity
Acquisition of image views: short axis with measurement of the NC/C ratio performed at end-systole
Stöllberger and Finsterer (Vienna criteria)‡
Four or more trabeculations protruding from the LV wall, located apical to the papillary muscles and visible in one imaging plane
Trabeculations with the same echogenicity as the myocardium and synchronous movement with ventricular contractions
Perfusion of the intertrabecular recesses from the LV cavity
Acquisition of images in the apical four-chamber view; atypical views to obtain the best-quality image for differentiation between false chords, aberrant bands, and trabeculations
Paterick, et al. (Milwaukee criteria)§
Evaluation of trabeculation sizes (NC myocardium) in relation to C wall thicknesses in multiple imaging windows and at different ventricular levels throughout the cardiac cycle
Identification of the bilayered myocardium (C and NC) in short-axis views at the mid and apical levels and in the apical two- and four-chamber and apical long-axis views
Thicknesses of the C and NC sections of the myocardium are best measured in short-axis views at end-diastole, with an NC/C ratio > 2 being diagnostic of LVNC
Magnetic Resonance Criteria
Petersen, et al.‖
Ratio between NC and C layers > 2.3 at end-diastole
Jacquier, et al.¶
Trabeculated LV mass > 20% of global LV mass (measurements made at end-diastole)

*Chin TK, Perloff JK, Williams RG, et al: Isolated noncompaction of left ventricular myocardium: a study of eight cases. Circulation 1990;82:507.

†Jenni ER, Oechslin J, Schneider C, et al: Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. Heart 2001;86:666.

‡Stöllberger C, Finsterer J: Left ventricular hypertrabeculation/noncompaction. J Am Soc Echocardiogr 17:91, 2004.

§Paterick TE, Umland MM, Jan MF, et al: Left ventricular noncompaction: a 25-year odyssey. J Am Soc Echocardiogr 2012;25:363.

‖Petersen SE, Selvanayagam JB, Wiesmann F, et al: Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. J Am Coll Cardiol 2005;46:101.

¶Jacquier A, Thuny F, Jop B, et al: Measurement of trabeculated left ventricular mass using cardiac magnetic resonance imaging in the diagnosis of left ventricular non-compaction. Eur Heart J 2010;3:1098.

C, compacted; *NC*, noncompacted; *X*, distance from the epicardial surface to the trough of the trabecular recess; *Y*, distance from the epicardial surface to the peak of the trabeculation.

Modified from Paterick TE, Umland MM, Jan MF, et al: Left ventricular noncompaction: a 25-year odyssey. J Am Soc Echocardiogr 2012;25:363.

Molecular and Clinical Genetics of Left Ventricular Noncompaction

LVNC has been observed in all cardiomyopathy phenotypes.[39] Although some studies suggest that LVNC

with normal LV systolic function, physiology, and chamber dimension engenders an increased risk for the later development of systolic dysfunction, as well as an ongoing increased risk for thromboembolism related to the marked increase in noncompacted (trabecular) mass, it has been difficult to estimate the disease-related risk that is specific to LVNC and independent of the underlying cardiomyopathy itself. Mutations in approximately a dozen genes known to cause familial DCM or HCM have also been identified in individuals with familial LVNC,[36] but these variants have no unique characteristics that predict an LVNC phenotype.

Approach to Clinical Genetic Evaluation, Including Clinical Genetic Testing, for Left Ventricular Noncompaction

If LVNC is identified in concert with another cardiomyopathy (DCM, HCM, RCM), the approach to the primary cardiomyopathy will drive the genetic evaluation process, as outlined earlier. This should include appropriate imaging modalities (echocardiography or CMR) as needed to define the phenotype in at-risk family members. For probands in whom LVNC has been identified but who are completely asymptomatic and have a normal cardiovascular phenotype except for the LVNC, family-based screening has not been studied and has not been recommended.

Clinical Management of Left Ventricular Noncompaction

It is not clear that any specific management is indicated for LVNC if it is identified independent of another cardiovascular diagnosis. When LVNC is diagnosed in concert with another cardiomyopathy (e.g., DCM, HCM, RCM, ARVC), the specific cardiomyopathy diagnosis will direct the surveillance and any treatment approaches, as per conventional guidelines. Whether the stroke rate is increased in patients with LVNC and normal cardiac function is uncertain, and no primary prevention recommendations are available. Case reports suggest that thromboembolic disease may occur in cases in which only LVNC has been identified, especially with extensive evidence of noncompaction. In clinical situations with clear evidence suggesting transient ischemic events, reversible neurologic deficits, or stroke without other obvious cause, secondary prevention should be considered and combined with an evaluation for a hypercoagulable condition.

Tachycardia-Induced Cardiomyopathy

Tachycardia for a prolonged period can result in diastolic and systolic ventricular dysfunction, even in the absence of other cardiac diseases. This condition is known as tachycardia-induced cardiomyopathy.[40] It is a diagnosis that can be made only retrospectively when correction of an arrhythmia is associated with improved ventricular function. However, it should be considered in any patient with tachycardia and LV systolic dysfunction who is not in sinus rhythm. The cardiomyopathy may be manifested either as an isolated condition or in association with preexisting cardiac disease. Thus a patient with mild DCM in whom atrial fibrillation develops may have a tendency for the development of decompensated heart failure, not only because of the loss of atrial function but also because the rapid, irregular rate of atrial fibrillation leads to further systolic dysfunction. Hyperthyroidism should be ruled out because it may cause both tachycardia and, rarely, an independent DCM. The “purest” form of tachycardia-induced cardiomyopathy is probably that caused by incessant or extremely frequent atrial tachycardia or permanent reciprocating junctional tachycardia, often in a child or young patient with systolic dysfunction.[41] However, almost any arrhythmia can cause tachycardia-induced cardiomyopathy, including

very frequent premature ventricular contractions (PVCs) or recurrent nonsustained VT.[42] Incessant atrial tachycardia causing tachycardia-induced cardiomyopathy may be mistaken for sinus tachycardia. If a previous ECG is available, comparison may be helpful, with specific attention being paid to subtle differences in P-wave morphology.

The duration of the arrhythmia, more than the heart rate, is probably a critical factor in tachycardia-induced cardiomyopathy. Among 30 patients with incessant atrial tachycardia and tachycardia-induced cardiomyopathy, the mean duration of symptoms was 6 years. The mean ventricular response was just 117 beats/min, and rate control (primarily by ablation) was associated with normalization of the ejection fraction in all but one patient.[41] A decreased ejection fraction in the presence of atrial fibrillation may occasionally improve after the restoration of sinus rhythm. If the ventricular rate is well controlled, improvement of LV systolic function in atrial fibrillation with a reduced ejection fraction is uncommon, but it is important to assess ventricular rate control with 24-hour monitoring to confirm control during both exercise and rest. Most patients with PVC-associated tachycardia-induced cardiomyopathy have more than 20,000 PVCs over a 24-hour period, but the condition has also been described with a lesser frequency of arrhythmia.[33] Catheter ablation of PVCs, if possible, is generally associated with improvement in ventricular function in these patients.

Most cases of tachycardia-induced cardiomyopathy improve within 3 to 6 months after correction of the arrhythmia, but occasional patients have been seen with late improvement, up to 1 year. Because the rapid, irregular ventricular response to atrial fibrillation is associated with marked beat-to-beat variation in the ejection fraction, the most accurate way to determine whether an improvement in systolic function has really occurred is to evaluate the ejection fraction early after restoration of sinus rhythm and then compare it with a reevaluation 3 to 6 months later.

Following restoration of sinus rhythm, subtle abnormalities in LV function may remain, such as mild LV dilation despite normalization of the ejection fraction, and recurrence of arrhythmia can be associated with deterioration of LV function.[43] In an animal model, tachycardia was associated with diastolic dysfunction often before a decrease in systolic function. Tachycardia-induced LV diastolic dysfunction may occur in humans in the presence of a normal ejection fraction. Although poorly studied, it may be responsible for the symptoms of heart failure in some patients with arrhythmia and a preserved LV ejection fraction.[44] Few data on improvement in diastolic dysfunction following correction of arrhythmia are available.

Peripartum Cardiomyopathy

Peripartum cardiomyopathy (PPCM) is a DCM that occurs in a temporal relationship to pregnancy (**see also Chapter 90**). The incidence and clinical features of PPCM may differ among geographic regions, with the U.S. incidence estimated to be between 1 in 1150 and 1 in 3200 live births, as compared with 1 in 1000 live births in South Africa and 1 in 300 live births in Haiti. In the United States, PPCM is disproportionately found in black patients. Older age and multiple-fetus pregnancies appear to be risk factors. A genetic basis for PPCM, has support from two studies, which show that in at least some proportion of cases, a rare variant genetic cause, similar to that of familial DCM (reviewed earlier), is at play.[45,46] From a database of 520 DCM probands, all those or their family members with DCM who met the formal criteria for PPCM were identified, and rare variant mutations in known DCM genes (*MYH7*, *SCN5A*, *PSEN2*, *MYH6*, *TNNT2*, and *MYBPC3*) were present in 6 of 19 women who had sequence information available.[45] In a second earlier study, among 90 families with DCM, 6% were found to have at least one member with PPCM, and genetic screening of relatives of three patients with PPCM who

failed to show complete recovery revealed undiagnosed DCM in all three families.[46] From this study comes the recommendation that if DCM occurs during or following pregnancy, the same guidelines for idiopathic DCM presented earlier should be followed, namely, obtaining a comprehensive family history and performing clinical screening of first-degree relatives, including echocardiography (**see Fig. 77.6**). With evidence of familial disease, clinical genetic testing is indicated as for idiopathic DCM. A more recent study[11] provided more definitive evidence of the rare variant genetic basis of PPCM, where 172 women with PPCM underwent sequencing for DCM genes, with *TTN* truncating variants (TTNtv's) identified in 26 of the 172 (15%), similar to prior studies of TTNtv's in idiopathic DCM. This genetic evidence, combined with that of the prior studies, provides substantial evidence pointing to a rare-variant genetic cause of PPCM similar to other forms of DCM.

Clinical Features

In patients with PPCM, symptoms and signs of heart failure develop during pregnancy or after delivery, similar to those of any patient with heart failure caused by LV systolic dysfunction. Most diagnoses are made in the 4 months following delivery; prepartum diagnoses are most commonly made in the last month of pregnancy. However, the disorder has also been described in early pregnancy (pregnancy-associated cardiomyopathy). Because symptoms similar to those of heart failure (dyspnea, fatigue, and edema) may occur in normal pregnancy, it is possible that a proportion of cases have a delayed diagnosis. Furthermore, because spontaneous resolution of LV dysfunction is known to occur, mild cases in the peripartum period may be overlooked. Given the rarity of the disease, it is not possible to precisely determine the incidence of PPCM in subsequent pregnancies of patients who have had a previous episode. However, recurrence appears to be related to the degree of recovery from the initial episode; PPCM seems less likely to recur in women who enter a second pregnancy with a normal ejection fraction than in those with a persistent reduction in the ejection fraction.[47]

In approximately 50% of patients with PPCM who are given standard medical therapy, the LV ejection fraction returns to normal, although the patients may still be at risk for recurrent PPCM. The remainder are often stabilized with medical therapy; however, a proportion of patients may experience progressive heart failure. Following delivery, treatment of PPCM is the same as for other causes of systolic dysfunction. However, if heart failure occurs during pregnancy, ACE inhibitors or angiotensin-receptor blockers are contraindicated because of the risk for fetotoxic effects. Diuretics should be used with caution, and metoprolol should be used rather than carvedilol. Eplerenone should be avoided, but spironolactone can be used cautiously later in pregnancy.

Elevated prolactin occurs in nursing mothers, and the cleaved 16kDa N-terminal fragment of prolactin has been shown in experimental studies to produce marked endothelial damage and cardiomyocyte dysfunction. In addition, full-length prolactin promotes inflammation in peripartum cardiomyopathy. This has led to the clinical use of bromocriptine in PPCM, with a small pilot study showing a greater rate of LVEF normalization compared to controls.[47a] Although this disorder has a variable prevalence and outcome in different racial groups,[47b] the use of a short course of bromocriptine early in peripartum cardiomyopathy is strongly advocated in Europe.[47c] Despite lack of evidence from larger controlled trials it appears to be safe and should be considered in cases of PPCM. Heart transplantation has been performed in patients with severe PPCM. In the United States, approximately 5% of all women undergoing cardiac transplantation have PPCM as their primary indication; it represents the fourth most common cause in women. Posttransplantation outcomes of PPCM are similar to those for other indications.

Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy (TC) (referred to as Takotsubo syndrome in Europe),[48] or stress-induced cardiomyopathy, is an acute, reversible condition first recognized in the 1990s. A recent European task force proposed a uniform definition (**Table 77.2**). It is estimated that in 2012, about 5500 patients were admitted to U.S. hospitals with TC, with an even greater number developing the condition while they were in the hospital secondary to a comorbid condition or stress. In an International Takotsubo Registry of 1750 patients, 89.8% were women, the vast majority postmenopausal.[49] Chest pain was the predominant symptom in 76%, dyspnea in 47%, and syncope in 7.7%. A preceding physical trigger occurred in 36% and an emotional trigger in 28%, and troponin values were elevated in 87%, with ST elevation shown on the ECG in almost half of the patients.

TABLE 77.2

Definition of Takotsubo Syndrome/Cardiomyopathy According to the Position Statement From the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology

1. Transient regional wall motion abnormalities of LV or RV myocardium occur and are frequently, but not always, preceded by a stressful trigger (emotional or physical).
2. The regional wall motion abnormalities usually[a] extend beyond a single epicardial vascular distribution and often result in circumferential dysfunction of the ventricular segments involved.
3. There is an absence of culprit atherosclerotic coronary artery disease, including acute plaque rupture, thrombus formation, and coronary dissection or other pathologic conditions, to explain the pattern of temporary LV dysfunction observed (e.g., hypertrophic cardiomyopathy, viral myocarditis).
4. New and reversible electrocardiography (ECG) abnormalities (ST segment elevation, ST depression, LBBB,[b] T-wave inversion, and/or QTc prolongation) are seen during the acute phase (first 3 months).
5. Significantly elevated levels of serum natriuretic peptide (BNP or NT-proBNP) are seen during the acute phase.
6. A positive but relatively small elevation in cardiac troponin can be measured with a conventional assay (i.e., disparity between the troponin level and the amount of dysfunctional myocardium present).[c]
7. Recovery of ventricular systolic function is apparent on cardiac imaging at follow-up (3 to 6 months).[d]

[a]Acute, reversible dysfunction of a single coronary territory has been reported.

[b]Left bundle branch block may be permanent after Takotsubo syndrome, but its presence should alert clinicians to exclude other cardiomyopathies. T-wave changes and QTc prolongation may take many weeks to months to normalize after recovery of LV function.

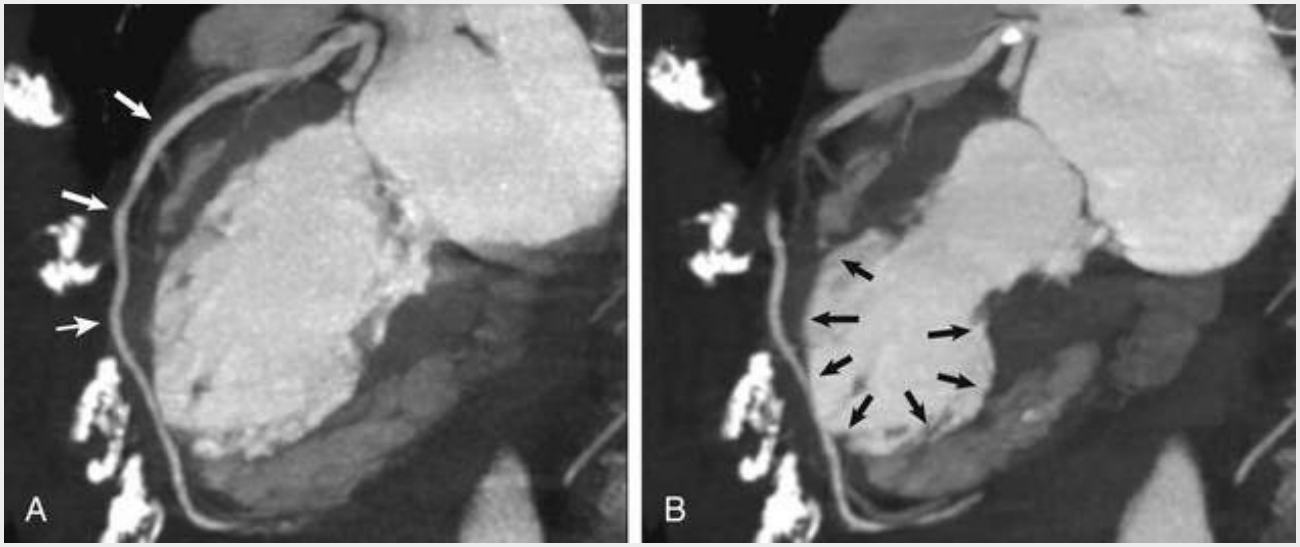
[c]Troponin-negative cases have been reported but are atypical.

[d]Small apical infarcts have been reported. Bystander subendocardial infarcts have also been reported, involving a small proportion of the acutely dysfunctional myocardium. These infarcts are insufficient to explain the acute regional wall motion abnormality observed.

From Lyon AR, Bossone E, Schneider B, et al: Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2016;18:8-27.

LV contractile abnormalities in TC are prominent, and although they involve the LV apex (resulting in the synonym of “apical ballooning syndrome”) in more than 80% of patients, (**eFig. 77.6**), regional wall motion abnormalities may be limited to the midventricular wall or other LV walls in a minority of patients. The wall motion abnormalities are characterized by their lack of a single coronary artery distribution, and coronary angiography reveals no evidence of acute obstructive coronary disease. Compensatory hyperdynamic contraction of the basal LV segments with associated apical LV dyskinesis may result in acute LV outflow tract obstruction because of systolic anterior motion of the mitral valve with an associated outflow tract gradient and hypotension. Although the long-term prognosis is good, an in-hospital mortality rate of 4.1% has been reported, primarily because of irreversible cardiogenic

shock, LV rupture, or embolization of LV thrombi. Malignant ventricular arrhythmia, particularly torsades de pointes associated with Takotsubo-related QT prolongation, may occur, as (rarely) may complete heart block.[50]



EFIGURE 77.6 Cardiac MRI in a patient with Takotsubo cardiomyopathy. **A,** Cardiac MRI (diastolic frame) demonstrating a patent left anterior descending artery (*arrows*). **B,** Classic apical ballooning (*arrows*) of the left ventricle (systolic frame) in the same patient as in **A.** (From Sanz J: Evolving diagnostic and prognostic imaging of the various cardiomyopathies. Ann N Y Acad Sci 2012;1254:123.)

The mechanism of myocardial dysfunction in stress-induced cardiomyopathy has not been fully elucidated, but a leading hypothesis suggests that a catecholamine surge results in regional microvascular dysfunction in susceptible patients, accompanied by cellular calcium overload.[51] Recurrence of Takotsubo cardiomyopathy is uncommon and is estimated to occur in in 1.5% to 2% of cases annually, with some recurrences occurring early after the initial event and others after many years.[52] Recurrence may be associated with dyskinesis in an area of the heart that is different from the area affected in the initial manifestation.

Therapy

Takotsubo cardiomyopathy is a self-limited disorder, usually with rapid resolution of the symptoms and LV dysfunction. The European task force position statement suggests classification into lower-risk and higher-risk categories, with the latter based on an LV ejection fraction of less than 45%, hypotension and an outflow tract gradient of greater than 40 mm Hg, and/or the presence of an arrhythmia.[48] Consideration of an ACE inhibitor and/or a beta blocker is recommended in the higher-risk groups. Because of the occasional association with acute QT prolongation, care should be taken to avoid using QT-prolonging medications, such as macrolide antibiotics or certain antiarrhythmic agents. In patients with hypotension associated with Takotsubo cardiomyopathy, pressors should be used with caution because LV outflow tract obstruction may be precipitated. Occasionally, thrombus formation may occur in the dyskinetic segment. Even though a visualized thrombus mandates anticoagulation, routine anticoagulation for dyskinesis without thrombus is not recommended, because of the rapid resolution of the condition. Although the occurrence of a catecholamine trigger might be a reason to use a beta blockade in all patients to prevent recurrence, the rarity of recurrence plus the description of de novo and recurrent Takotsubo cardiomyopathy in patients receiving beta blockers has reduced enthusiasm for this approach.

Restrictive and Infiltrative Cardiomyopathies

The restrictive cardiomyopathies (RCMs) are a heterogeneous group of diseases characterized by a nondilated left ventricle, often with a well-preserved ejection fraction. The predominant manifestation is diastolic dysfunction as a result of myocardial disease, and although severe hypertensive disease, aortic stenosis, and some cases of HCM may feature restrictive pathophysiology, these conditions are not classified as RCMs. Some infiltrative cardiac diseases such as amyloidosis produce an RCM, whereas others, such as sarcoidosis, have an infiltrative component but are predominantly manifested as DCMs. Thus, just as DCM is a morphologic condition that encompasses several causes of cardiomyopathy, the terms *restrictive cardiomyopathy* and *infiltrative cardiomyopathy* are pathophysiologic and anatomic definitions of cardiomyopathies that have overlaps with several well-defined conditions.

Approach to Identifying a Cause of Restrictive Cardiomyopathy

Because RCM is not always an isolated cardiac disease but may arise secondary to other acquired or genetic diseases, the diagnostic approach is challenging for the cardiovascular specialist (**see Table 77.1**). Endomyocardial biopsy may be much more relevant for the diagnosis of a specific cause in patients with RCM than in those with DCM or HCM insofar as RCM may be caused by an infiltrative cardiac process without systemic involvement or with subclinical involvement of other organs.[53] When a cause cannot be identified, the condition is known as *idiopathic RCM*. Unlike with DCM, *familial RCM* is distinctly uncommon. Regardless of whether a cause can be found, a comprehensive family history should always be obtained and clinical screening of first-degree relatives should be strongly considered.[3,54] If the family history is suggestive or screening of first-degree relatives shows a related myocardial abnormality, a genetic cause can be sought by following the cardiomyopathy guidelines (**see Fig. 77.6**).

Clinical and Molecular Genetics of Restrictive Cardiomyopathy

The clinical genetic features of familial RCM are similar to those of DCM in that reduced penetrance and a variable age at onset are commonly observed. Genes with rare variants implicated in the cause of idiopathic and nonsyndromic RCM are in most cases ones that encode sarcomeric proteins (**see eTable 77.1**).[13,55,56] Although some locus heterogeneity is apparent, it is much less so than with DCM (**see eTable 77.1**). Because cardiac hemodynamic findings commonly exhibit restrictive physiology in HCM, the genetic similarity of HCM and RCM suggests that in these cases the RCM phenotype can be viewed as a minimally hypertrophic HCM phenotype with prominent restrictive physiology. As noted earlier, at times "overlap" or "crossover" phenotypes of RCM and HCM have been observed in families with mutations in sarcomeric genes that demonstrate this principle.[13,55,56]

Clinical Features of Idiopathic Restrictive Cardiomyopathy

Idiopathic RCM has been described in individuals from infancy to late adulthood; it usually carries a poor prognosis, especially in children.[57] The disease is rare, and the largest adult series contains only 91 cases seen over a 17-year period.[58] In one series of 32 unrelated patients with end-stage disease, RCM was considered to be genetically determined either by the identification of pathogenic mutations (60%) or by evidence of familial disease without a known pathogenic mutation (in an additional 5 patients), for a total of 75% of these patients with a genetic cause.[59] Symptoms of idiopathic RCM are nonspecific and

reflect the presence of heart failure. Dyspnea is an initial complaint in most patients, edema occurs in approximately half, and palpitations, fatigue, and orthopnea are reported by 22% to 33%. Physical examination is usually consistent with biventricular heart failure, with jugular venous distention noted in most patients but ascites and significant edema being found in advanced cases. Atrial fibrillation is common, and a third heart sound is heard in one in four patients; murmurs are not a feature. The ECG has normal voltage, with only a minority of patients showing intraventricular conduction delay.

Echocardiography reveals a typical pattern of biatrial enlargement and nondilated ventricles with a normal LV ejection fraction and LV wall thickness (**Fig. 77.8**). At cardiac catheterization, both RV and LV filling pressure is elevated. Endomyocardial biopsy demonstrates nonspecific findings such as myocyte hypertrophy, interstitial fibrosis, and, not uncommonly, endocardial fibrosis. The survival rate is reduced in comparison with that of an age- and sex-matched population; the observed survival rate from the time of diagnosis is 64% at 5 years and 37% at 10 years.[60] Most deaths are associated with cardiac causes, either suddenly or secondary to heart failure, although a third die of noncardiac causes related to progressive age.

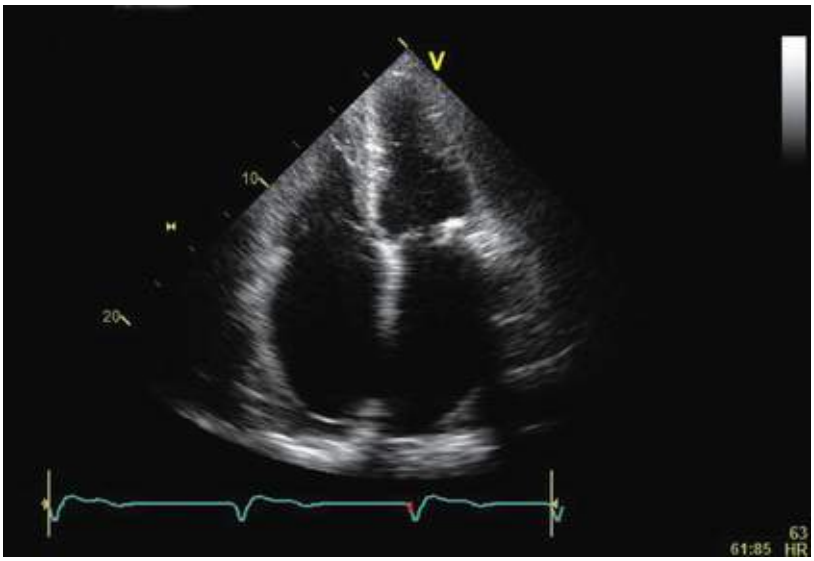


FIGURE 77.8 Echocardiogram showing restrictive cardiomyopathy**.** An apical four-chamber view is shown in an 80-year-old man with long-standing RCM. The LV ejection fraction was normal, with evidence of severe diastolic dysfunction on echocardiography and cardiac catheterization. Note the massive biatrial enlargement and normal LV wall thickness.

The differential diagnosis of idiopathic RCM includes the infiltrative cardiomyopathies, such as amyloidosis, or constrictive pericarditis. Unlike idiopathic RCM, amyloidosis is associated with increased LV wall thickness and subtle abnormalities in LV systolic function, with specific findings on cardiac biopsy. Constrictive pericarditis is more difficult to differentiate from RCM because most of the clinical features overlap between the two disorders. A thickened pericardium noted on echocardiography, CT, or CMR in a patient with heart failure and a preserved ejection fraction without wall thickening suggests constrictive pericarditis; however, it bears emphasis that 18% of patients with constrictive pericarditis have normal pericardial thickness.[61] Advanced echocardiographic techniques may be of help in distinguishing constrictive pericarditis from RCM (**see also Chapter 14**), but endomyocardial biopsy may be required unless an alternative diagnosis is clear. Treatment of idiopathic RCM is generally limited to medical treatment of heart failure, but in selected advanced cases, cardiac transplantation has been performed with similar outcomes as in those with nonrestrictive cardiomyopathy.[58]

Cardiac Amyloidosis

Cardiac amyloidosis is an infiltrative cardiomyopathy that in some forms is associated with a toxic component. The term *amyloid* refers to a proteinaceous material derived from misfolded products of a variety of precursor proteins. On electron microscopy, amyloid fibrils are seen as extracellular, nonbranching fibrils 7 to 10 nm in diameter. Amyloid deposits also contain a serum amyloid P component, as well as several other common constituents such as heparan and dermatan sulfate proteoglycans and glycosaminoglycans, apolipoprotein E, type IV collagen, and laminin.

The type of amyloidosis is defined by the precursor protein. The four most common precursor proteins associated with cardiac amyloidosis are light chains produced by a plasma cell dyscrasia (amyloid light-chain [AL] amyloidosis), amyloid derived from wild-type transthyretin (TTRwt) (previously referred to as senile systemic amyloidosis) or mutant TTR (ATTRm, or familial amyloidosis), and localized atrial amyloid deposits derived from atrial natriuretic peptide. Secondary (AA) amyloidosis, in which the deposits are derived from the inflammatory protein serum amyloid A, rarely involves the heart (**Table 77.3**).

TABLE 77.3

Features of Cardiac Amyloidosis Based on Amyloid Type

TYPE OF AMYLOIDOSIS	PRECURSOR PROTEIN	USUAL AGE AT ONSET	MAIN ORGANS INVOLVED	AVERAGE SURVIVAL TIME IN UNTREATED PATIENTS	SPECIFIC TREATMENT
AL (primary)	Abnormal light chains	50+	All except central nervous system; heart involved in 50% of cases	Noncardiac disease, 24 months; disease with heart failure, < 9 months	Chemotherapy aimed at plasma cells
Familial (ATTR)	Mutant TTR	20-70+ (partially dependent on mutation)	Peripheral and autonomic neuropathy; heart	7 to 10 years for neuropathy	Liver transplantation. Investigational agents to stabilize TTR (tafamidis) or suppress its production
Senile systemic amyloidosis (SSA)	Wild-type TTR	70+	Heart	5 to 7 years	Investigational agents to stabilize TTR (tafamidis) or suppress its production
Isolated atrial amyloidosis (IAA)	Atrial natriuretic peptide	Unknown	Cardiac atria (particularly in already diseased hearts)	No effect on survival	None needed
AA (secondary amyloidosis)	Serum amyloid A (SAA), an inflammatory protein	Teens upward, depending on underlying inflammatory condition	Liver, kidney; heart rarely	10+ years	Treatment of underlying inflammatory condition

The clinical pattern and prognosis of cardiac amyloidosis differ among the different types; AL amyloidosis is often a multiorgan disease; ATTRm amyloidosis affects the heart or the peripheral or autonomic nervous system, or both; and ATTRw predominantly affects the heart. Individual types of cardiac amyloidosis are described in the following sections.

Amyloid Light-Chain Amyloidosis

The precursor protein of AL amyloidosis is an abnormal light chain produced by dysfunctional plasma cells. AL amyloidosis is closely related to multiple myeloma, may overlap with it, and is treated with similar drugs. Of all the amyloidoses, AL amyloidosis affects the most organs, with almost every organ system potentially being involved except for the central nervous system. Approximately 50% of patients with AL amyloidosis have evidence of cardiac involvement at the initial evaluation, which is clinically significant in about 75%.[62] The clinical manifestation of AL cardiac amyloidosis is rapidly progressive heart failure, often associated with evidence of systemic disease elsewhere. Although the heart failure is biventricular, right-sided signs frequently predominate, with prominent peripheral edema and occasional ascites. At times patients may have typical angina because of amyloid infiltration of small vessels.

Postural syncope may be due to autonomic dysfunction, but recurrent exertional syncope or presyncope may indicate severe cardiac disease with a fixed, low cardiac output.

Physical examination usually reveals sinus rhythm or, less commonly, atrial fibrillation with a normal- to low-volume pulse. Jugular venous pressure may be markedly elevated, and a Kussmaul sign is frequently present. The apex beat is often impalpable and heart sounds are generally normal. An unusual feature of cardiac amyloidosis, particularly AL amyloidosis, is the absence of a fourth heart sound despite the small stiff ventricle. This corresponds to atrial systolic dysfunction secondary to atrial infiltration. If a third heart sound is present, it usually indicates RV dysfunction. A pleural effusion is often detected on physical examination and may be large, particularly if pleural amyloid infiltration is also present. Congested hepatomegaly is common and ascites may be detected. Evidence of noncardiac involvement is a useful clue to the presence of a systemic disorder and may include periorbital purpura (virtually pathognomonic of AL amyloidosis), heavy proteinuria, peripheral or autonomic neuropathy, macroglossia, or cachexia.

The *ECG* frequently shows low-voltage limb leads, often with an unusually rightward axis (**Fig. 77.9A**). First-degree AV block is common, and Q waves are frequently seen in leads V_1 to V_3. Left bundle branch block is rare in AL amyloidosis.

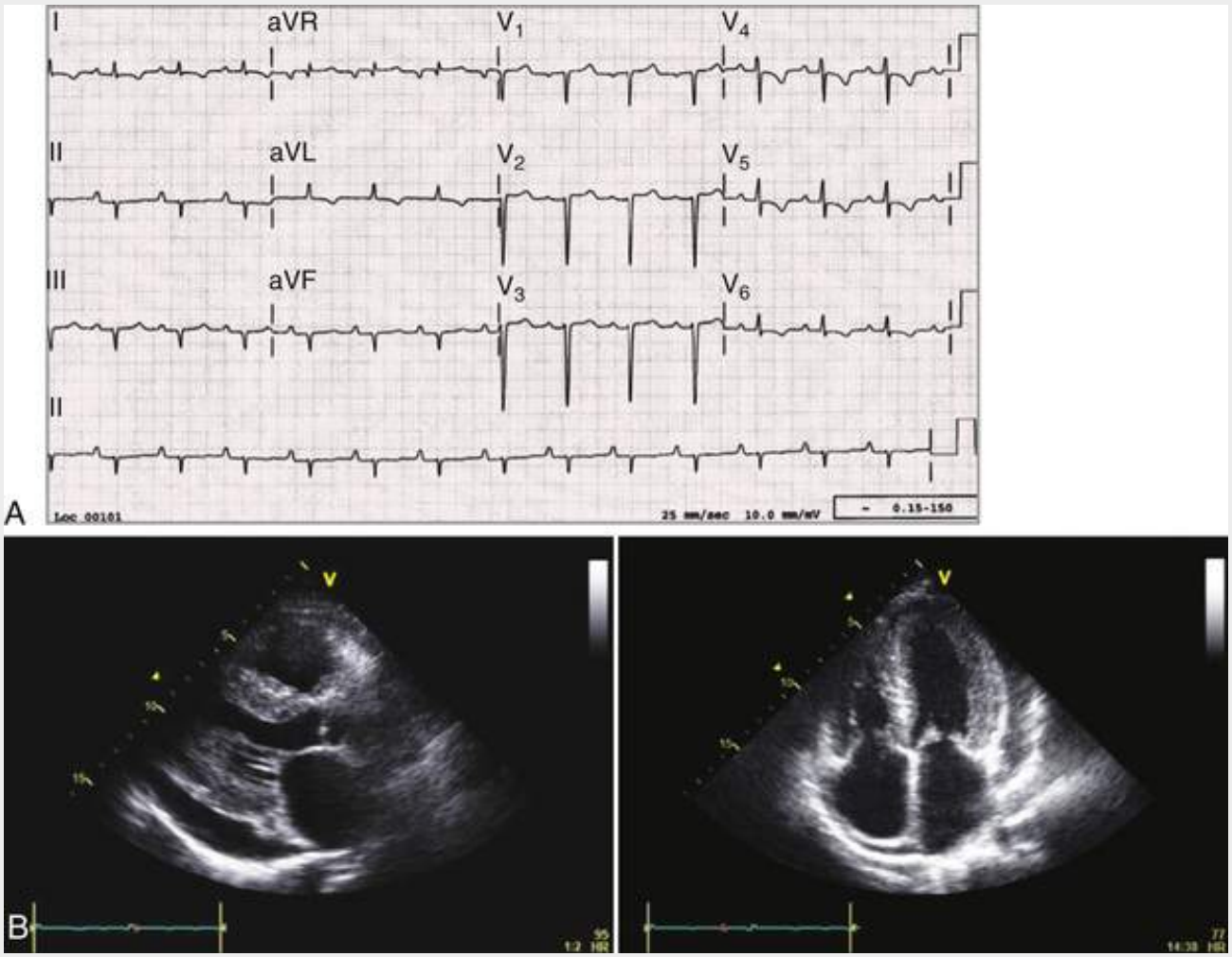
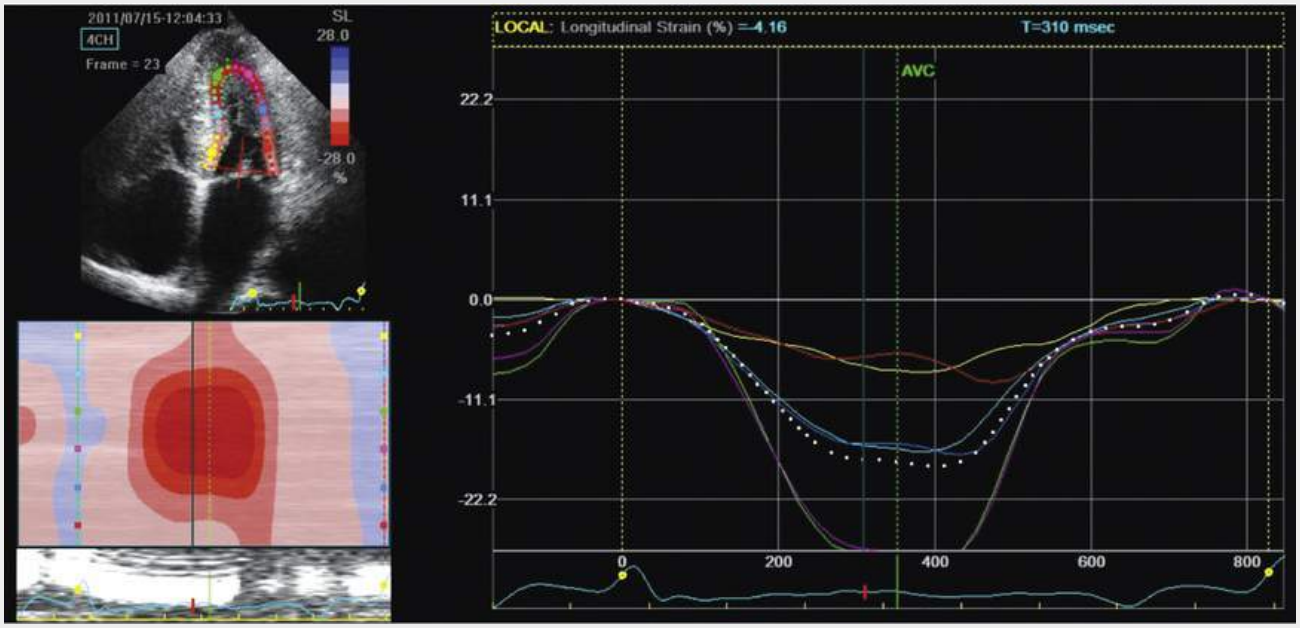
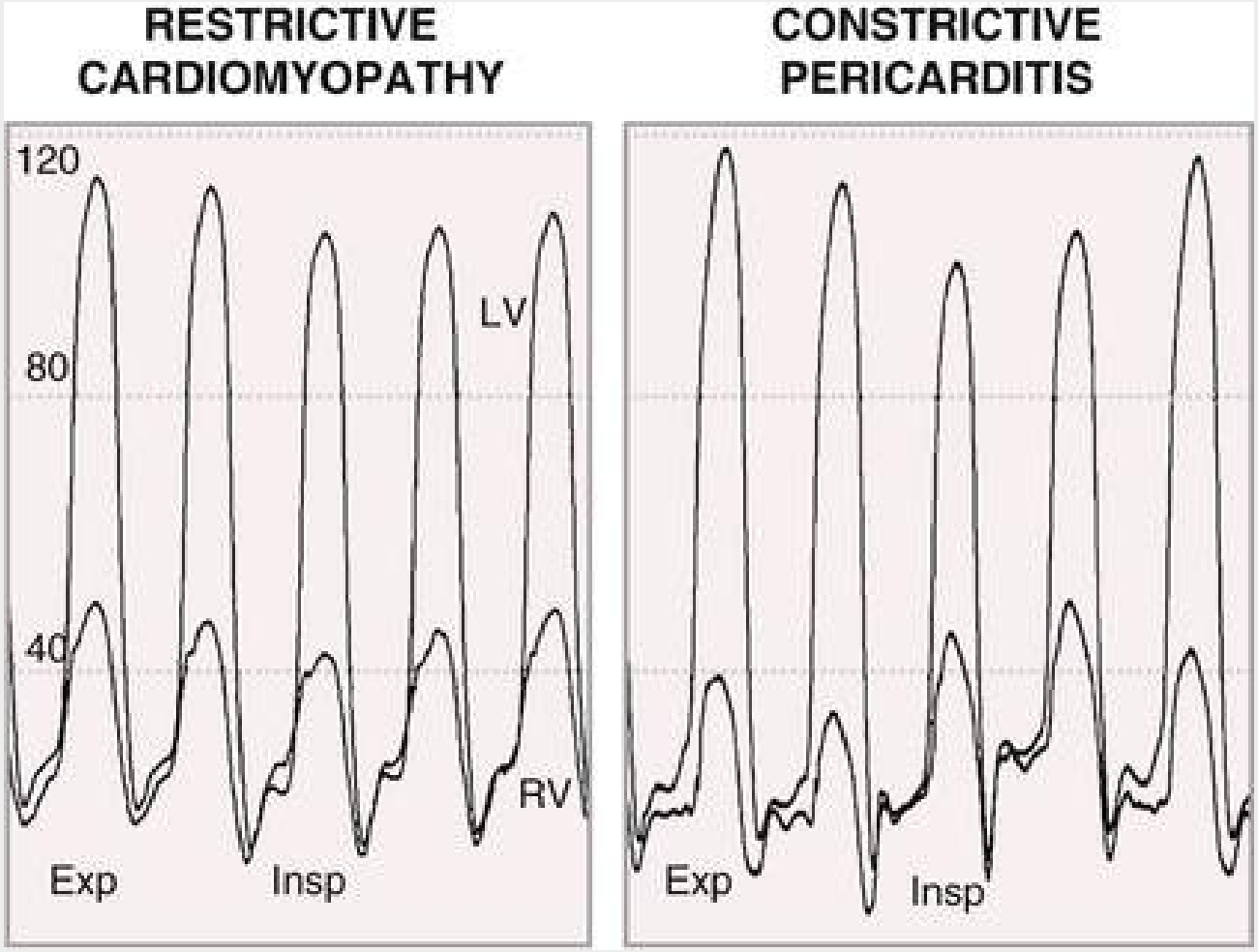


FIGURE 77.9 Cardiac amyloidosis. **A,** ECG in a patient with AL amyloidosis. Note the low-voltage limb leads with an unusual axis, pseudomyocardial infarction pattern in the inferior and septal leads, and T wave inversions. **B,** Echocardiogram in a patient with AL amyloidosis. Parasternal **(left)** and apical four-chamber **(right)** views in the same patient as in **A** are shown. Concentric wall thickening and biatrial enlargement with a pericardial effusion are evident. The patient was in severe heart failure and received a heart transplant followed by chemotherapy and autologous stem cell transplantation.

Echocardiography generally reveals a pattern strongly suggestive of an infiltrative cardiomyopathy, and is similar in all types of cardiac amyloidosis. The LV cavity is normal to small, LV and, often, RV wall thickness is increased, and there may be increased myocardial echogenicity (**Fig. 77.9B**). Mitral regurgitation, if present, is rarely more than moderate, and the aortic valve seldom shows any significant amyloid-related dysfunction. Doppler tissue imaging frequently suggests elevated LV filling pressure and severely impaired longitudinal LV systolic function, even with a near-normal LV ejection fraction. Speckle tracking shows a classic appearance of regional longitudinal dysfunction characterized by relative apical sparing and prolonged diastolic relaxation[63] (**see eFig. 77.7**). Occasionally, asymmetric septal thickening with an LV outflow tract gradient may be present and mimic HCM. Cardiac catheterization shows bilateral elevation of filling pressures, and a dip-and-plateau tracing is often seen; unlike in constrictive pericarditis, however, equalization of diastolic pressures is uncommon. Careful evaluation of simultaneously recorded LV and RV pressures during respiration demonstrates concordant changes in systolic pressures in amyloidosis and other restrictive cardiomyopathies, as opposed to a discordance (inspiratory increase in RV systolic pressure with a simultaneous decrease in LV pressure) seen in constrictive pericarditis (**see eFig. 77.8**).[64]



EFIGURE 77.7 Echocardiographic strain imaging in amyloid cardiomyopathy. The “bulls-eye” appearance of the longitudinal strain pattern from an echocardiographic apical four-chamber view is shown in a patient with familial amyloid cardiomyopathy and a normal ejection fraction. The appearance represents a gradient of longitudinal strain from the apex to the base with relatively well-preserved apical strain and severely impaired basal strain. In contrast, normal subjects have no significant strain gradient from the apex to the base. This appearance, a useful diagnostic finding, is seen in more than 80% of patients with cardiac amyloidosis, regardless of the precursor amyloid protein.



EFIGURE 77.8 Hemodynamics of restrictive cardiomyopathy and constrictive pericarditis. Differentiation of RCM **(left)** and constrictive pericarditis **(right)** can be achieved by examination of simultaneously measured RV and LV systolic pressure responses to respiration. In constrictive pericarditis, inspiration is associated with an increase in RV systolic pressure and a concordant decrease in LV systolic pressure (ventricular interdependence). This is not seen with RCM. *Exp*, expiration; *Insp*, inspiration. (From Nishimura RA, Carabello BA: Hemodynamics in the cardiac catheterization laboratory of the 21st century. Circulation 2012;125:2138.)

CMR is a useful diagnostic tool for all forms of cardiac amyloidosis. The classic features of cardiac amyloidosis (**Fig. 77.10**) include biventricular thickening with normal cavity size, as well as atrial septal thickening. With the use of gadolinium, there is often difficulty in nulling the myocardium, and late gadolinium enhancement typically shows diffuse or patchy subendocardial enhancement, which often involves the atrium. This combination of findings is unusual in other cardiomyopathies and strongly suggests cardiac amyloidosis.

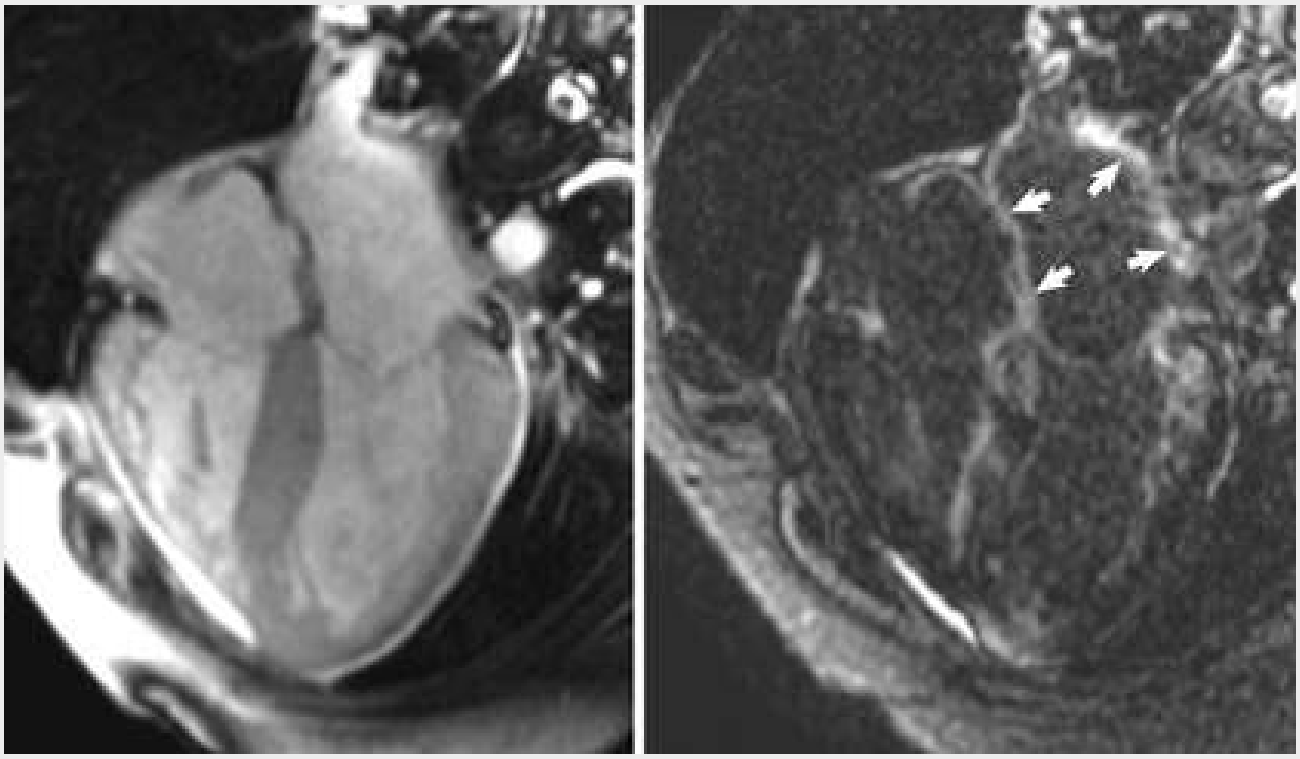


FIGURE 77.10 Cardiac MRI in a patient with amyloid cardiomyopathy. The **left panel** shows a thickened left ventricle with biatrial enlargement and a thickened atrial septum. The **right panel** is from the same patient and shows extensive delayed gadolinium enhancement involving not only the ventricles but also the atria extensively (*arrows*). Atrial amyloid deposition is associated with impaired atrial contraction and intraatrial thrombus formation.

Nuclear imaging using standard isotopes, such as sestamibi, is generally negative for ischemia, even in a patient with angina. Positron emission tomography (PET) with vasodilator stress such as adenosine may show widespread stress-induced subendocardial ischemia related to the small-vessel disease; early studies with the amyloid-avid agent florbetapir, approved for Alzheimer imaging, may show avid myocardial uptake. As discussed in **Chapter 21**, ^{99m}technetium pyrophosphate (^{99m}Tc-PYP) scanning shows promise in diagnosing AL amyloidosis.

Familial and Senile Systemic Amyloidosis

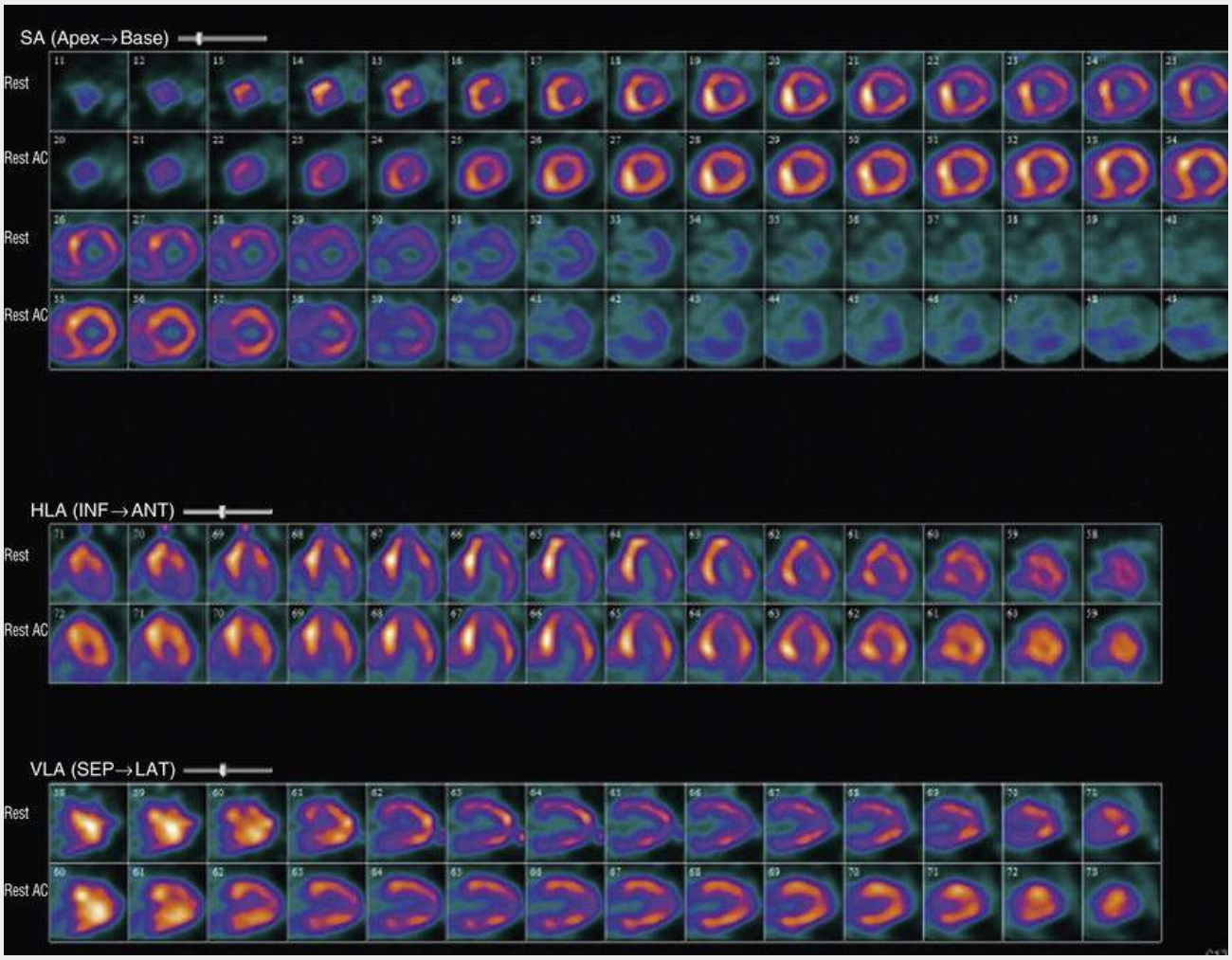
Familial amyloidosis is an autosomal dominant disease with relatively high penetrance. It is usually due to a point mutation in the hepatically expressed protein TTR encoded by the gene *TTR*. TTR is a 55-kDa protein that serves as a carrier of the thyroid hormone thyroxine (T_4) and retinol-binding protein bound to retinol; hence the acronym ***t***ransports ***t***hyroxine and ***r***etinol. Approximately 100 *TTR* point mutations are known, almost all of which produce an unstable protein that causes cardiac and/or peripheral or autonomic nervous system dysfunction. The two most common mutations are Val30Met and Val122Ile. Val30Met has been described worldwide, with several endemic areas in Japan, Brazil, Sweden, and Portugal. In younger patients, the disease is predominantly manifested as a neuropathy, and cardiac involvement, if it occurs, consists of sinus node dysfunction and mild cardiac infiltration. In contrast, when the disease occurs after middle age, cardiomyopathy tends to predominate. Val122Ile is a relatively common cause of amyloid cardiomyopathy. Approximately 3.4% of the U.S. black population and the Afro-Caribbean population in the United Kingdom are heterozygous for the Val122Ile mutation, which can result in amyloid cardiomyopathy in the sixth and seventh decades of life. The mutation is associated with an increased risk of developing heart failure even if an overt amyloid cardiomyopathy is not present.[65] Val122Ile is almost never associated with neuropathy, other than carpal tunnel syndrome.[66]

Wild-type ATTRwt is due to the deposition of amyloid derived from normal TTR. The heart is the only major organ to be clinically involved, but deposits of amyloid are frequently also found at autopsy in the lungs and gastrointestinal tract.[67] ATTRwt tends to occur from the end of the seventh decade onward and is predominantly a disease of men, with a male-to-female ratio of approximately 20 : 1.[67] Although small deposits of amyloid derived from wild-type TTR are commonly seen on pathologic examination of aged hearts, patients with clinically apparent ATTRwt have extensive deposits leading to cardiac dysfunction. The disease is characterized by progressive biventricular failure without neuropathy. Previously considered a rarer disease than ATTRm or AL amyloidosis, it is probably the commonest form of amyloid cardiomyopathy.

Distinctive Clinical Features.

In contrast to the low voltage of AL amyloidosis, the ECG in TTR amyloidosis frequently shows normal voltage with nonspecific conduction disturbance and ST-T wave changes. Left bundle branch block is more common, and particularly in ATTRwt, high-degree AV block may occur as the disease progresses. The echocardiographic appearance of TTR cardiomyopathy, whether caused by a mutant protein or wild-type protein, is similar to that of AL amyloidosis described earlier. Nonetheless, the course is more indolent, and if left untreated, the survival rate is considerably longer in ATTRwt than in untreated AL amyloidosis, with survival in ATTRm being somewhere between the other two.[68] This observation gave rise to a hypothesis that in AL amyloidosis, in addition to damage from infiltration, a toxic component from circulating free light chains may exist. Subsequent observations showing rapid clinical improvement in heart failure after treatment of AL amyloidosis, as well as compelling laboratory data demonstrating light chain toxicity, appear to have confirmed the initial hypothesis.[69]

Technetium pyrophosphate scanning (DPD scanning in Europe) has emerged as an extremely useful diagnostic tool for patients with suspected TTR amyloidosis. The finding of a strongly positive scan is virtually pathognomonic for TTR amyloidosis, with patients with AL amyloidosis having little or no uptake of the isotope in myocardium. A strongly positive scan in a patient with a typical echocardiographic appearance of amyloidosis and no evidence of a plasma cell dyscrasia is considered diagnostic of TTR amyloidosis and may obviate the need for a tissue biopsy (**eFig. 77.9**).[70,71]



EFIGURE 77.9 Technetium pyrophosphate scan in an 81-year-old patient with wild-type amyloidosis (ATTRwt.). Paired sets of images with nonattenuation-corrected images are labeled "rest," and corresponding CT-based attenuation-corrected images are labeled "rest AC." The patient had heart failure and marked wall thickening on his echocardiogram; he did not have any evidence of a plasma cell dyscrasia. The heart avidly took up the isotope (a normal heart exhibits no uptake). This is virtually pathognomonic of TTR amyloidosis. In this case, it was later confirmed by biopsy. Genetic testing for a *TTR* mutation was negative. *AC*, attenuation corrected; *HLA*, horizontal long axis; *SA*, short axis; *VLA*, vertical long axis. (Courtesy Dr. Sharmila Dorbala, Brigham and Women's Hospital, Boston.)

Isolated atrial amyloid cannot be diagnosed other than on a biopsy specimen. Its predominant manifestation is an increased prevalence of atrial fibrillation, and its main significance lies in the recognition that if it is found in an operative biopsy specimen from an excised atrial appendage, it is not associated with ventricular amyloidosis.

Diagnosis

The diagnosis of amyloidosis relies on clinical awareness of and suspicion for the disease, clinical features, blood and tissue analysis, and positive findings on biopsy. In patients with AL amyloidosis, serum and/or urine immunofixation generally reveals a monoclonal gammopathy. Measurement of serum free kappa and lambda light chains demonstrates an excess of either kappa or lambda in more than 90% of cases of AL amyloidosis and is a very useful test for monitoring the response to therapy. Patients with TTR amyloidosis do not have a disease-related monoclonal gammopathy and have a normal serum free light chain ratio. However, an unrelated monoclonal gammopathy of unknown significance is present in more than 5% of patients older than 70 years and may confuse the picture if found in a patient with TTR amyloidosis. Bone marrow biopsy in patients with AL amyloidosis usually reveals an excess of plasma cells, often in the range of 10% to 20% of the total cellularity. Plasma cell cellularity in the marrow in

excess of 30% suggests an overlap syndrome with multiple myeloma.

A definitive diagnosis of the amyloidoses usually requires biopsy. Subcutaneous fat pad aspiration may show amyloid deposits in more than 80% of patients with AL amyloidosis, but experience in staining the small deposits is needed to avoid false-positive or false-negative results. The yield of fat pad biopsy is lower in TTR amyloidoses. Endomyocardial biopsy is almost universally positive in cardiac amyloidosis, unlike many other cardiomyopathies. It also offers the advantage of being able to measure right-sided heart pressures at the time of the biopsy and, in skilled hands, carries a low complication rate.

It is not sufficient simply to make a tissue diagnosis of amyloidosis without precise typing of the amyloid, because treatment differs greatly, depending on the underlying precursor protein. Immunohistochemistry, ideally performed on a fresh tissue specimen, has moderate specificity, but inaccuracies still occur even in skilled hands. Molecular analysis of the amyloid type may be needed in cases in which the clinical pattern is equivocal, and laser microdissection of amyloid deposits with subsequent proteomic analysis is now considered the "gold standard."[72]

Treatment

The aim of treatment is twofold: treatment of the heart failure and management of the underlying amyloidogenic protein. In AL amyloidosis, diuretics are the mainstay of heart failure therapy. Hypotension is frequently present (often because of a combination of autonomic dysfunction and low cardiac output), and ACE inhibitors are poorly tolerated; they can precipitate worsening hypotension even with low doses. There is no evidence that beta blockade (even if tolerated) affects the outcome (although in low doses it may be helpful for control of the ventricular rate in atrial fibrillation), and calcium channel blockers are contraindicated because they frequently worsen heart failure. For severe heart failure, an intravenous infusion of diuretics with renal-dose dopamine may help mobilize fluid, but the role of inotropes is unclear. In TTR amyloidosis without autonomic neuropathy, ACE inhibitors in low doses are better tolerated than in AL. If high-degree AV block develops and necessitates pacing, biventricular pacing should be attempted because RV pacing in the stiff small-cavity ventricle appears to be detrimental.

Treatment of the plasma cell dyscrasia causing AL amyloidosis requires careful coordination between the cardiologist and a hematologist skilled in treating the disease, and consists of chemotherapy directed against plasma cells. High-dose chemotherapy with autologous stem cell transplantation is generally poorly tolerated in patients with cardiac amyloidosis, but bortezomib-based regimens are showing great promise in rapidly controlling the underlying plasma cell dyscrasia and stabilizing the patient.[73] Long-term survival is increasingly common. In many patients, normalization of serum free light chains is associated with significant improvement in heart failure despite the apparently unchanged appearance on echocardiography, most likely because of removal of the cardiotoxic effects of the amyloid precursor.[74]

In ATTRm amyloidosis, removal of the source of the amyloidogenic protein requires liver transplantation. Unfortunately, some patients with cardiac amyloidosis due to ATTRm have progression of the infiltrative cardiomyopathy even after liver transplantation; this is believed to be due to continued amyloid deposition derived from wild-type (as opposed to mutant) TTR. A combined liver-heart transplant needs to be considered in some patients, particularly if neuropathy and cardiomyopathy coexist. Some ATTRm patients, particularly those with Val122Ile, may benefit from isolated heart transplantation, because significant amyloid does not seem to recur in the transplanted heart. Heart transplantation for AL amyloidosis has successfully been performed and requires a carefully selected patient with clinically isolated cardiac amyloidosis who after transplantation is also willing to undergo intensive chemotherapy to abolish the plasma cell dyscrasia. Although many patients with ATTRwt are outside the usual age range

for cardiac transplantation, it has been performed successfully with a good long-term outcome. Because ATTRwt patients do not produce a mutant TTR, there is no role for liver transplantation. Unlike the dilated and ischemic cardiomyopathies, the role of an ICD in amyloidosis is far less clear. Many patients with amyloidosis who have had an ICD implanted still die suddenly with pulseless electrical activity, and use of an ICD should probably be limited to patients with aborted sudden death or syncope clearly caused by a ventricular arrhythmia. The Transthyretin-Associated Amyloidoses Outcome Survey (THAOS; NCT00628745) is a global, multicenter, longitudinal observational survey with a minimum duration of 10 years that is designed to better understand and characterize the natural history of the disease by studying a large and heterogeneous patient population.

Sarcoid Cardiomyopathy

Sarcoidosis is a multisystem disorder of unknown cause characterized histologically by noncaseating granulomas. In the United States the disease is most commonly seen in the black population and is more common in women than in men. Sarcoid has a higher incidence in Scandinavia and Japan. Cardiac involvement takes the form of ventricular dysfunction, heart block, and/or ventricular arrhythmias. Despite frequently being described as an RCM, the most common phenotype of sarcoid heart disease is a DCM, occasionally with aneurysm formation. Although most patients with sarcoid cardiomyopathy also have evidence of noncardiac disease, particularly lung disease, clinically isolated cardiac sarcoidosis is increasingly being recognized as a cause of heart block and ventricular arrhythmias. Sudden death, presumably from a ventricular arrhythmia, may be the first manifestation either of sarcoidosis itself or of heart disease in a patient with known pulmonary or systemic sarcoid. The prevalence of cardiac involvement in patients with pulmonary sarcoidosis was previously thought to be no more than 5%, but autopsy studies indicate a much higher prevalence, and recent cardiac imaging studies have demonstrated abnormalities in at least 25% of patients with pulmonary sarcoidosis.[75] With advanced imaging studies and a high index of suspicion, cardiac sarcoidosis is being diagnosed with increasing frequency in the absence of clinically apparent noncardiac disease.

Pathology

The pathology of sarcoid heart disease raises puzzling questions about the cause of the systolic dysfunction, which can be severe. Noncaseating granulomas, the hallmark of the disease, are patchily distributed even in severe disease and thus cannot alone account for the severe systolic dysfunction. Granulomatous lesions are associated with edema and inflammation, and widespread myocardial fibrosis is seen late in the disease (**Fig. 77.11**). The patchy nature of granulomatous infiltration and the sometimes extensive fibrosis render cardiac biopsy a low-yield procedure for detecting diagnostic histology in cardiac sarcoidosis, and finding granulomas may be difficult even at autopsy, because end-stage disease is characterized predominantly by fibrosis.[76] Occasionally, the right ventricle may be severely and predominantly involved, and several cases of apparent ARVC with a typical appearance on multimodality imaging have been described that are later found to be due to cardiac sarcoidosis.[77] RV function can be impaired in patients with severe pulmonary sarcoidosis and pulmonary hypertension, even in the absence of direct sarcoid involvement of the heart.

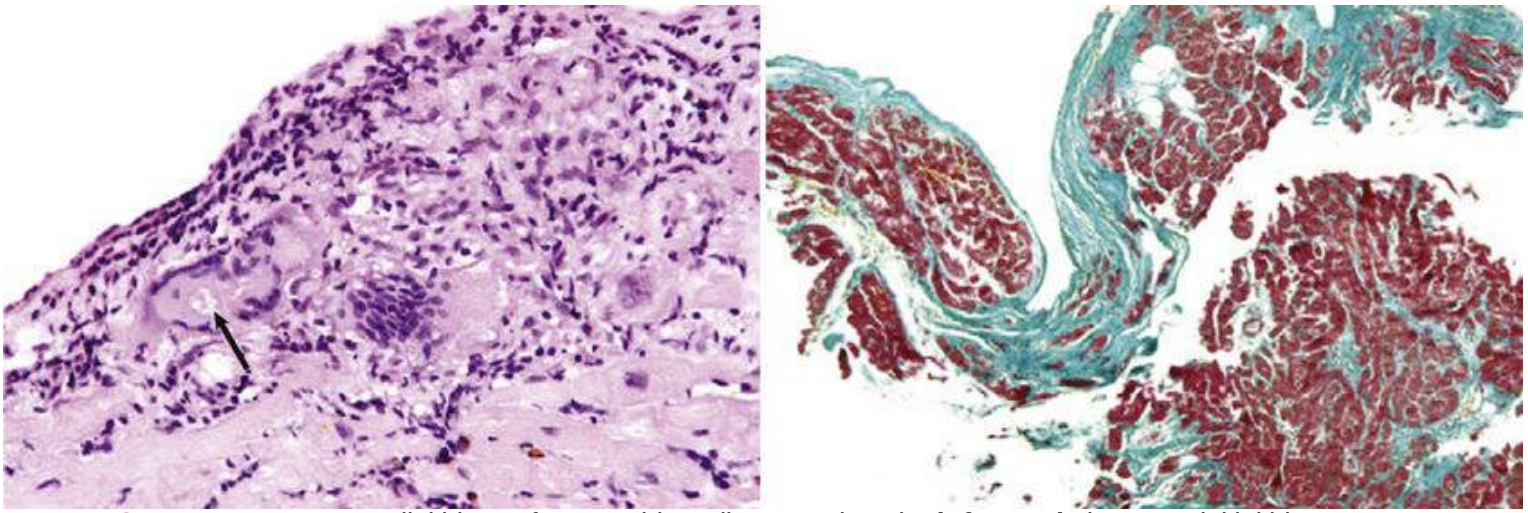


FIGURE 77.11 Myocardial biopsy for sarcoid cardiomyopathy. The **left panel** shows an initial biopsy specimen (hematoxylin-eosin staining) with an inflammatory noncaseating granuloma typical of sarcoid. The *arrow* points to an "asteroid body" in the cytoplasm of the giant cell; this is a common finding in various granulomatous diseases. The **right panel** shows a follow-up biopsy specimen (Masson trichrome stain, initial magnification 100×) in the same patient. No granulomas are present, and there is now extensive interstitial fibrosis (*green-staining area*). This demonstrates how granulomas may be missed on biopsy, particularly in advanced sarcoid cardiomyopathy, when fibrosis is extensive. (From Leone O, Veinot JP, Angelini A, et al: 2011 Consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. Cardiovasc Pathol 2012;21:245.)

Clinical Features

The most common noncardiac site of sarcoid involvement is the lungs, with approximately half of patients having overt parenchymal disease and the remainder having isolated bilateral hilar lymphadenopathy. Other findings, in decreasing order of frequency, are hepatic and gastrointestinal involvement, ocular sarcoidosis, and neurologic sarcoidosis. Skin involvement in sarcoidosis is not uncommon, and lesions appear to have a predilection for scars and tattoos. In patients with established extracardiac sarcoid, LV systolic dysfunction is almost always due to associated cardiac sarcoidosis.

The most common clinical feature of cardiac sarcoidosis is biventricular heart failure. Mitral regurgitation, often caused by papillary muscle involvement in addition to LV dilation, may be severe. Sarcoid granulomas have a predilection for the cardiac conduction system, and high-degree AV block may occur, either as an initial manifestation of cardiac sarcoidosis or later in the disease (**Fig. 77.12**). Both atrial and ventricular arrhythmias are common, the latter arising from either ventricle. Once causes such as Lyme disease have been ruled out, complete heart block in a young patient suggests sarcoidosis, especially if ventricular arrhythmias are present, and imaging should be pursued in all such cases. Sudden cardiac death is almost always associated with grossly visible scarring and fibrosis at autopsy. A rare manifestation of cardiac sarcoidosis is acute sarcoid myocarditis, characterized by high-degree AV block, malignant ventricular arrhythmia, and heart failure. It may be difficult to distinguish this from giant cell myocarditis unless systemic features of sarcoid are also present.

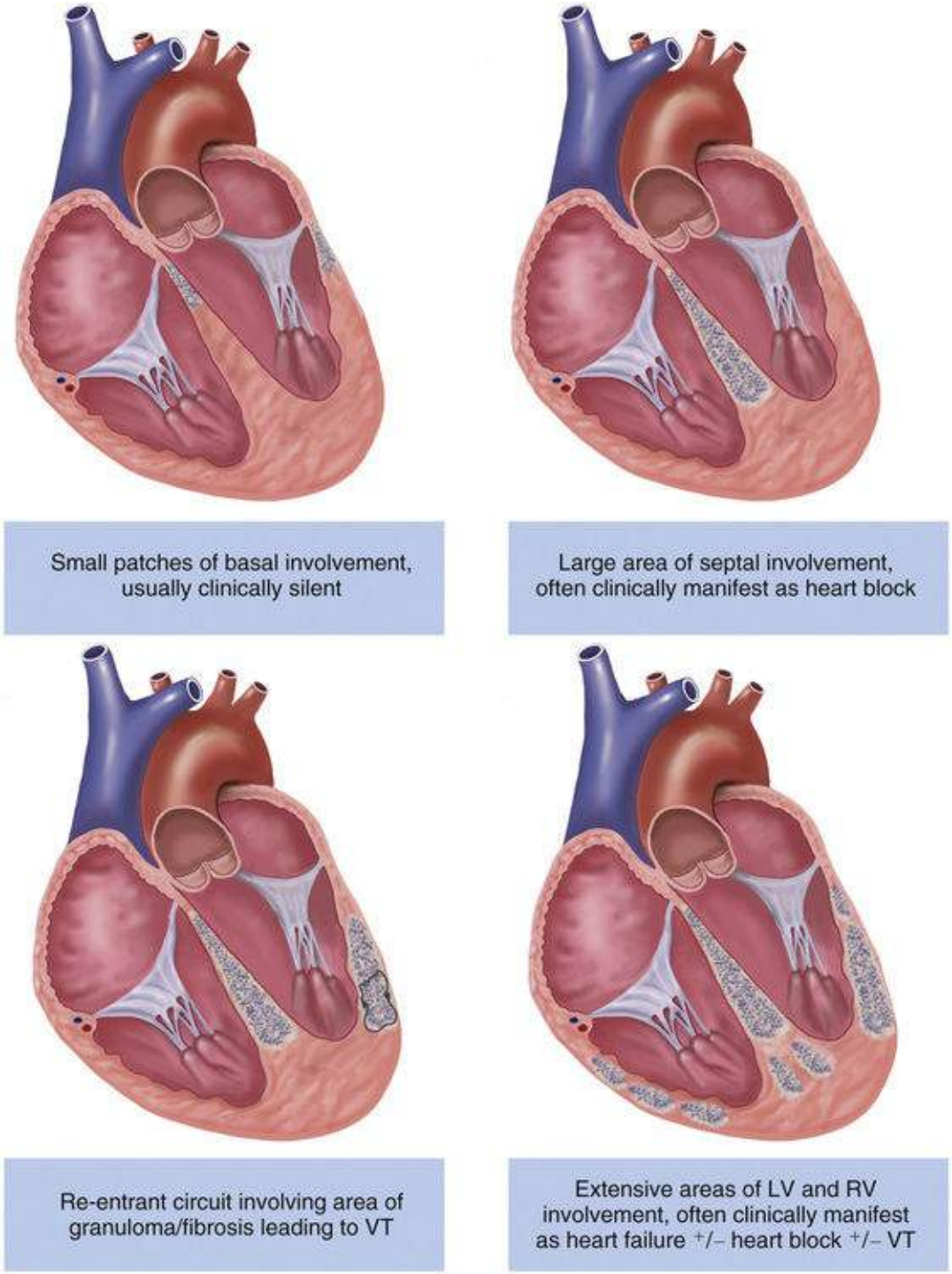


FIGURE 77.12 Illustrative examples of the extent of cardiac sarcoid pathologic changes in relation to clinical manifestations of the disease. (From Birnie DH, Nery PB, Ha AC, Beanlands RS. Cardiac sarcoidosis. *J Am Coll Cardiol.* 2016;68:411-21.)

Diagnosis

Laboratory testing for sarcoidosis is generally unrewarding. An elevated sedimentation rate may be present but is nonspecific, as is a finding of elevated immunoglobulins. Hypercalcemia (believed to be due to activation of vitamin D by macrophages in sarcoid granulomas), although uncommon, is a useful clue. Although elevation of serum ACE may be helpful for diagnosis, there is a wide range in the normal population because of a polymorphism in the *ACE* gene. Normal ACE levels may be seen in patients with untreated sarcoidosis, and serial ACE levels do not appear to correlate with treatment response.

CMR with gadolinium enhancement (**see also Chapter 17**) is a sensitive test for detecting abnormalities in cardiac sarcoidosis (**Fig. 77.13**). Delayed gadolinium enhancement may be found in

either a coronary or noncoronary distribution, is usually nontransmural, and has a predilection for the basal and/or midventricular septum.[75] The finding of myocardial late gadolinium enhancement by CMR in a patient with proven extracardiac sarcoidosis is a marker for subsequent major cardiac events, including sudden death, and the risk of major events is proportional to the amount of late gadolinium enhancement.[78] In the acute stage, T2-weighted imaging may show myocardial edema, which is characterized by focal areas of thickening and increased signal intensity on T2-weighted and early gadolinium-enhanced images.[79]

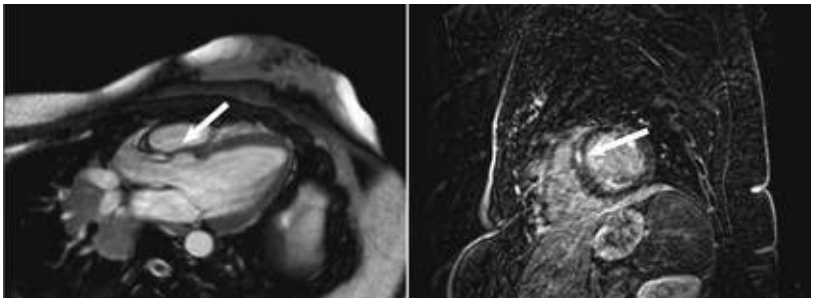


FIGURE 77.13 Cardiac MRI in a patient with sarcoidosis. Heart failure developed late in pregnancy and was initially diagnosed as PPCM. Echocardiography revealed a reduced ejection fraction with the basal septal thinning typical of sarcoidosis. The appearance was confirmed on MRI (**left panel**, *arrow*). Delayed gadolinium uptake showed midmyocardial gadolinium uptake (**right panel**, *arrow*) consistent with sarcoidosis, which was subsequently confirmed on a biopsy specimen.

^{18}F-fluorodeoxyglucose (FDG) PET scanning (**see also Chapter 16**) is complementary to CMR in patients with sarcoidosis; it reveals areas of inflammation in active disease, permits serial evaluation of response to therapy, and is becoming an important tool for the diagnosis and management of cardiac disease.[80] An example of a combined PET-CT scan in a patient with cardiac amyloidosis is shown in **Fig. 77.14**.

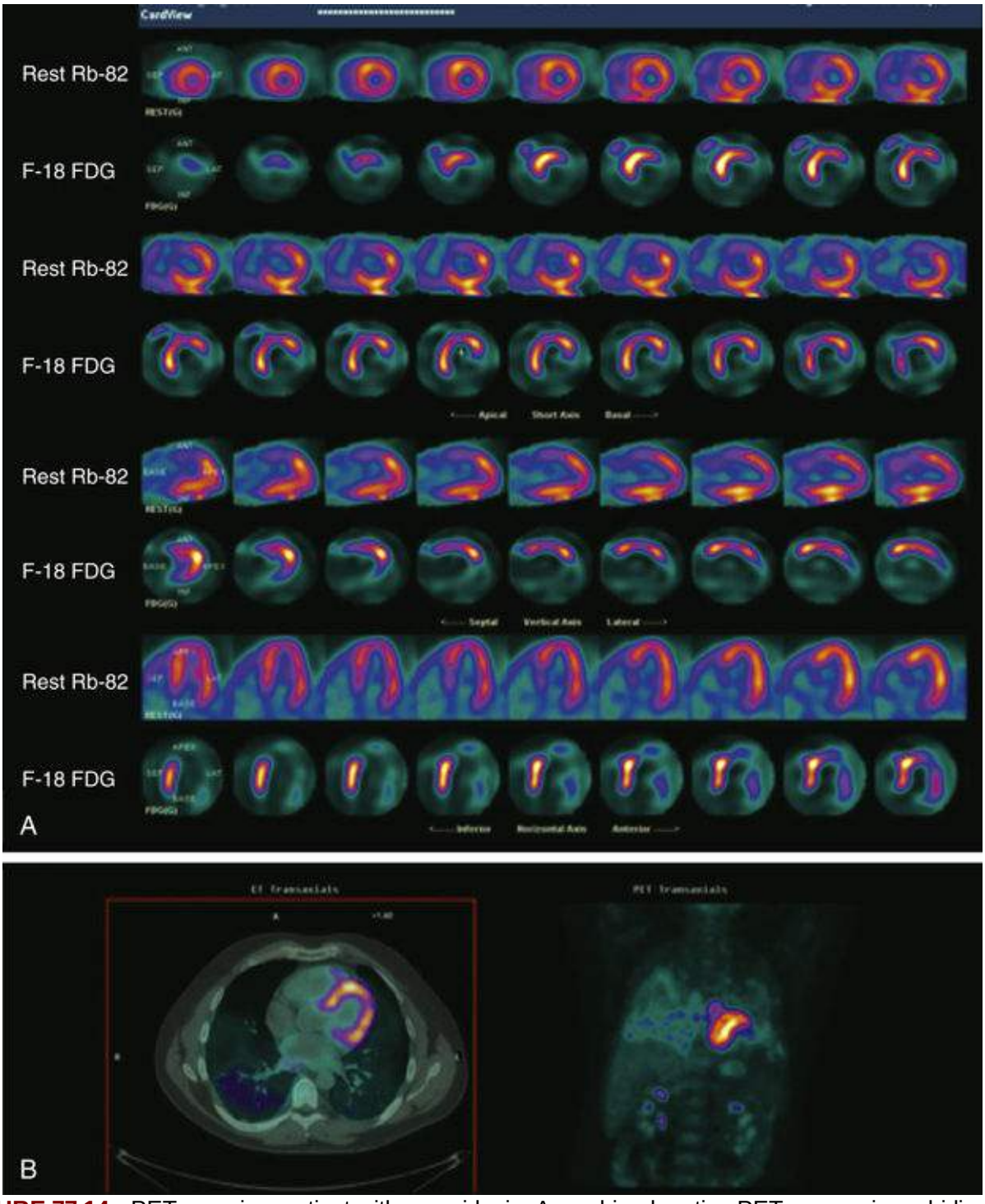
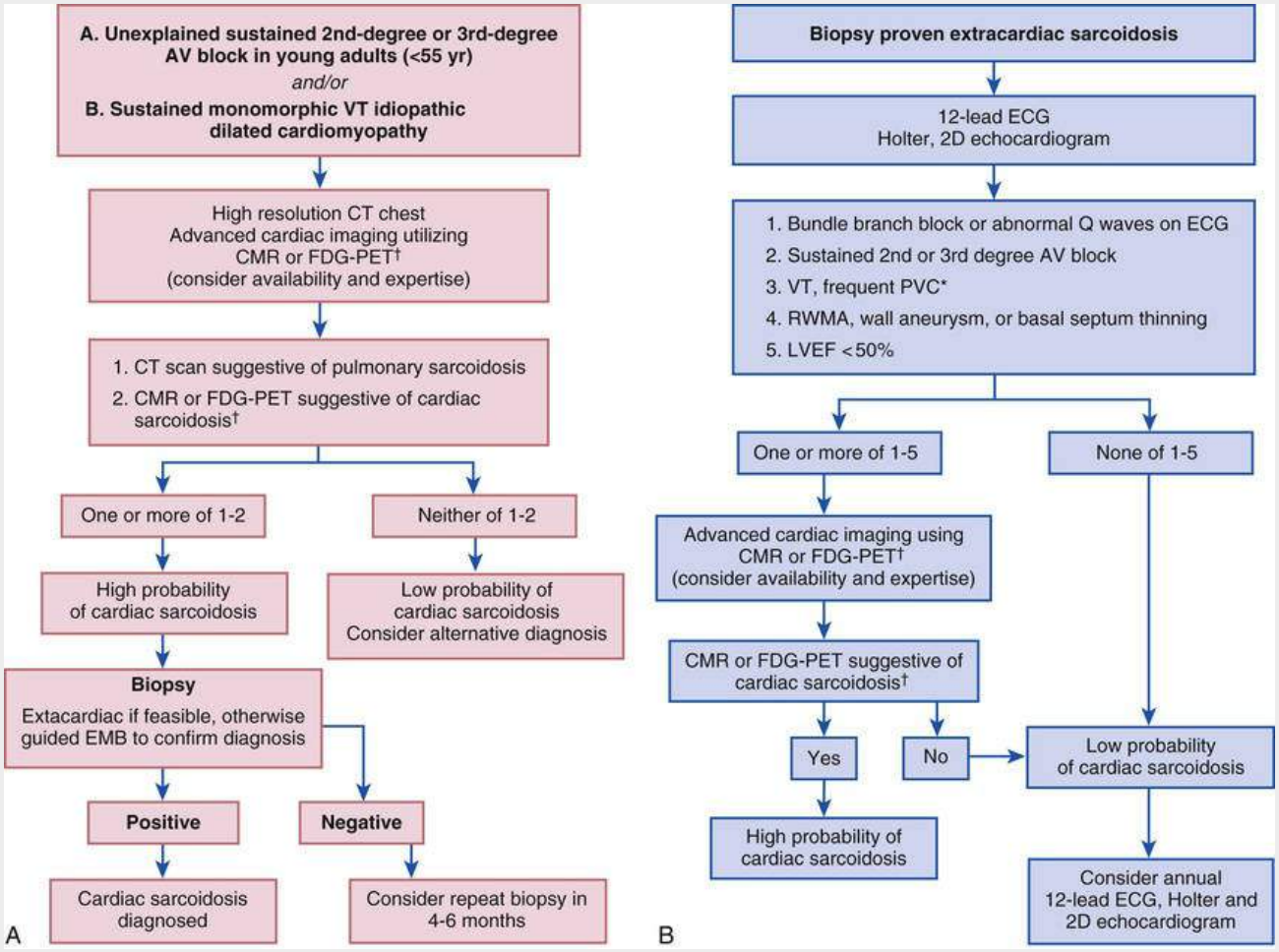


FIGURE 77.14 PET scan in a patient with sarcoidosis. A combined resting PET scan using rubidium-82 and ^{18}F-FDG (a glucose analogue) is shown for a 53-year-old man with a history of pulmonary sarcoidosis who had palpitations and atrial flutter. **A,** From the top, each pair of images represents the rubidium-82 scan and, underneath it, the corresponding ^{18}F-FDG image. The scans show a basal and midanteroseptal perfusion defect with intense FDG uptake in these regions suggestive of myocardial inflammation. Normal myocardium does not exhibit any FDG uptake because it is using free fatty acids. **B,** Combined CT-PET images in the same patient demonstrating the intense cardiac uptake. (Courtesy Dr. Sharmila Dorbala, Brigham and Women's Hospital, Boston. From Dubrey SW, Falk RH: Diagnosis and management of cardiac sarcoidosis. Prog Cardiovasc Dis 2010;52:336.)

Tissue Biopsy.

A positive cardiac biopsy showing noncaseating granulomas is diagnostic of cardiac sarcoidosis if giant cell myocarditis is ruled out. However, the patchy nature of the granulomatous infiltration results in a low

yield of positive biopsies. Targeted biopsy of another organ, such as enlarged hilar lymph nodes, may give a higher yield, or alternatively, biopsy of an area of definite abnormality seen on PET or CMR may be valuable. Although the 2006 recommendations of the Japanese Society of Sarcoidosis and of the Granulomatous Disorders suggest diagnosis by a combination of major and minor criteria, including myocardial biopsy, PET-CT and CMR are more sensitive and are playing an increasing role. An algorithm for the diagnosis of cardiac sarcoidosis is presented in **eFig. 77.10**.



EFIGURE 77.10 Diagnostic algorithm for cardiac sarcoidosis. The diagnostic approach differs according to the clinical findings, including conduction system disease and/or ventricular arrhythmia **(A)** or biopsy-proven extracardiac sarcoidosis **(B).** *In the absence of coronary artery disease, defined as more than 1000 PVCs per 24 hours. †Gallium-67 scintigraphy or technetium-based myocardial perfusion imaging are reasonable alternatives if FDG-PET or CMR is not available. *CMR*, cardiac magnetic resonance; *EMB*, endomyocardial biopsy; *LVEF*, LV ejection fraction; *RWMA*, regional wall motion abnormality. (From Youssef G, Beanlands RS, Birnie DH, Nery PB: Cardiac sarcoidosis: applications of imaging in diagnosis and directing treatment. Heart 2011;97:2078.)

Treatment

No randomized clinical trials of the treatment of cardiac sarcoidosis have been published. Standard heart failure therapy should be instituted if heart failure is present, but in addition, steroid therapy is often given, particularly in patients with newly diagnosed sarcoidosis and systolic dysfunction. Steroids are frequently effective in noncardiac sarcoidosis, and nonrandomized data suggest a benefit in patients with cardiac sarcoid complicated by heart failure, particularly early in the disease when irreversible fibrosis has not yet developed. Prednisone is generally initiated in doses between 1 mg/kg and 40 mg daily and

tapered gradually over a period of several months with careful monitoring.[81] Methotrexate is often used as a second agent if steroid therapy is unsuccessful,[82] and several recent case reports have shown promising responses to anti-TNF monoclonal antibodies.

Management of arrhythmia often requires a pacemaker and/or implantable defibrillator. On the assumption that high-degree AV block in systemic sarcoidosis is a marker of associated myocardial sarcoidosis, use of a pacemaker-ICD has been recommended for any patient with sarcoidosis who requires pacing. Prophylactic use of an ICD based on a reduced ejection fraction, similar to other patients with heart failure with a depressed ejection fraction, is also appropriate (**see also Chapter 27**), but the role of an ICD in a patient with sarcoidosis and mild cardiac disease but no high-degree AV block or frequent ventricular arrhythmia is less clear.[83] The 2014 Heart Rhythm Society Consensus Recommendations for ICD implantation in patients with cardiac sarcoidosis are a useful guide, and suggest incorporation of advanced imaging and possible electrophysiologic study in such patients (**eTable 77.4**).[84] Cardiac transplantation may be undertaken in patients with severe cardiac sarcoidosis after careful evaluation for noncardiac involvement. Less than 0.2% of transplants in the United States are performed for cardiac sarcoidosis; outcomes are at least equivalent to those of other cardiac transplant patients.[85]

ETABLE 77.4

Heart Rhythm Society Recommendations for Management of Arrhythmia in Cardiac Sarcoidosis

Diagnosis and Screening	
It is recommended that patients with biopsy-proven extracardiac sarcoidosis should be asked about unexplained syncope/presyncope/significant palpitations.	I
It is recommended that patients with biopsy-proven extracardiac sarcoidosis should be screened for cardiac involvement with a 12-lead electrocardiogram.	I
Screening for cardiac involvement with an echocardiogram can be useful in patients with biopsy-proven extracardiac sarcoidosis.	IIa
Advanced cardiac imaging, CMR, or FDG-PET at a center with experience in CS imaging protocols can be useful in patients with one or more abnormalities detected on initial screening by symptoms/ECG/echocardiogram.	IIa
Screening for CS in patients age < 60 years with unexplained second-degree (Mobitz II) or third-degree atrioventricular block can be useful.	IIa
Advanced cardiac imaging, CMR, or FDG-PET is not recommended for patients without abnormalities on initial screening by symptoms/ECG/echocardiogram.	III
Management of Conduction Abnormalities	
Device implantation can be useful in CS patients with an indication for pacing, even if the atrioventricular block reverses transiently.	IIa
Immunosuppression can be useful in CS patients with second-degree (Mobitz II) or third-degree atrioventricular block.	IIa
ICD implantation can be useful in patients with CS and an indication for permanent pacemaker implantation.	IIa
Management of Ventricular Arrhythmias	
Assessment of myocardial inflammation with FDG-PET can be useful in CS patients with ventricular arrhythmias.	IIa
Immunosuppression can be useful in CS patients with ventricular arrhythmias and evidence of myocardial inflammation.	IIa
Antiarrhythmic drug therapy can be useful in patients with ventricular arrhythmias refractory to immunosuppressive therapy.	IIa
Catheter ablation can be useful in patients with CS and ventricular arrhythmias refractory to immunosuppressive *and* antiarrhythmic therapy.	IIa
Risk Stratification for Sudden Cardiac Death	
An electrophysiologic study for the purpose of sudden death risk stratification may be considered in patients with LVEF > 35%, despite optimal medical therapy and a period of immunosuppression (if there is active inflammation).	IIb
CMR for the purpose of sudden death risk stratification may be considered	IIb
ICD Implantation	
Spontaneous sustained ventricular arrhythmias, including prior cardiac arrest	I
LVEF ≤ 35% despite optimal medical therapy and a period of immunosuppression (if there is active inflammation)	I
ICD implantation can be useful in patients with CS, independent of ventricular function and one or more of the following: 1. An indication for permanent pacemaker implantation 2. Unexplained syncope or near-syncope, felt to be arrhythmic in etiology 3. Inducible sustained ventricular arrhythmias.	IIa
ICD implantation may be considered in patients with an LVEF 36% to 49% and/or an RV ejection fraction < 40%, despite optimal medical therapy for heart failure and a period of immunosuppression (if there is active inflammation).	IIb

CMR, cardiac magnetic resonance; *CS*, cardiac sarcoidosis; *ECG*, electrocardiogram; *FDG-PET*, fluorodeoxyglucose-positron emission tomography; *ICD*, implantable cardioverter-defibrillator; *LGE*, late gadolinium enhancement; *LVEF*, left ventricular ejection fraction; *RV*, right ventricular.

From Birnie DH, Nery PB, Ha AC, Beanlands RS. Cardiac sarcoidosis. J Am Coll Cardiol 2016;68:411-21. Modified from Birnie DH, Sauer WH, Bogun F, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm 2014;11:1305-23.

Fabry Disease

Fabry disease is caused by progressive lysosomal accumulation of neutral glycosphingolipids, primarily globotriaosylceramide; it results from deficiency of the enzyme alpha-galactosidase A, which is encoded by *GLA* on the X chromosome.[86] As an X-linked condition, most disease occurs in males with transmission by female carriers, although significant disease in later years can also be seen in women.[86-88] The disease phenotype encompasses diverse signs and symptoms with the following major manifestations: angiokeratomas, acroparesthesias, anhidrosis, ocular changes, and eventually cardiovascular, cerebrovascular, and renal disease, all largely related to the central pathophysiology of small-vessel vascular disease from the deposition of glycosphingolipid and consequent vascular insufficiency. The hallmark of the classic early-onset disease in males in childhood is episodic crises of severe pain in the extremities (acroparesthesias), characterized by burning pain in the distal end of the extremities, triggered by a variety of stressors, and resulting in ischemia of peripheral nerves from small-vessel disease. Angiokeratomas, red and purple punctate dermal lesions involving the lower midsection, buttocks, thighs, and upper part of the legs, may be one of the earliest signs of the disease and accumulate progressively with age. Anhidrosis is also an early finding in most cases. A survey of the phenotypic characteristics derived from a Fabry registry[87] showed that the age at onset and phenotypic variability were related to the degree of alpha-galactosidase A deficiency, with less than 1% of the activity associated with the earliest and most aggressive disease (**eTable 77.5**).[86-88]

ETABLE 77.5

Age at Onset of Fabry Disease in Early-Onset Classic Disease and in Renal and Cardiac Variant Cases

MANIFESTATION	CLASSIC	RENAL VARIANT	CARDIAC VARIANT
Age at onset	4 to 8 years	>25 years	>40 years
Average age at death	41 years	>60 years	>60 years
Angiokeratoma	++	–	–
Acroparesthesias	++	–/+	–
Hypohidrosis/anhidrosis	++	–/+	–
Corneal/lenticular opacity	+	–	–
Heart	LVH, ischemia	LVH	LVH, cardiomyopathy
Brain	TIA, stroke	–	–
Kidney	ESRD	ESRD	Proteinuria
Residual alpha-galactosidase A enzyme activity	<1%	>1%	>1%

ESRD, end-stage renal disease; *LVH*, left ventricular hypertrophy; *TIA*, transient ischemic attack.

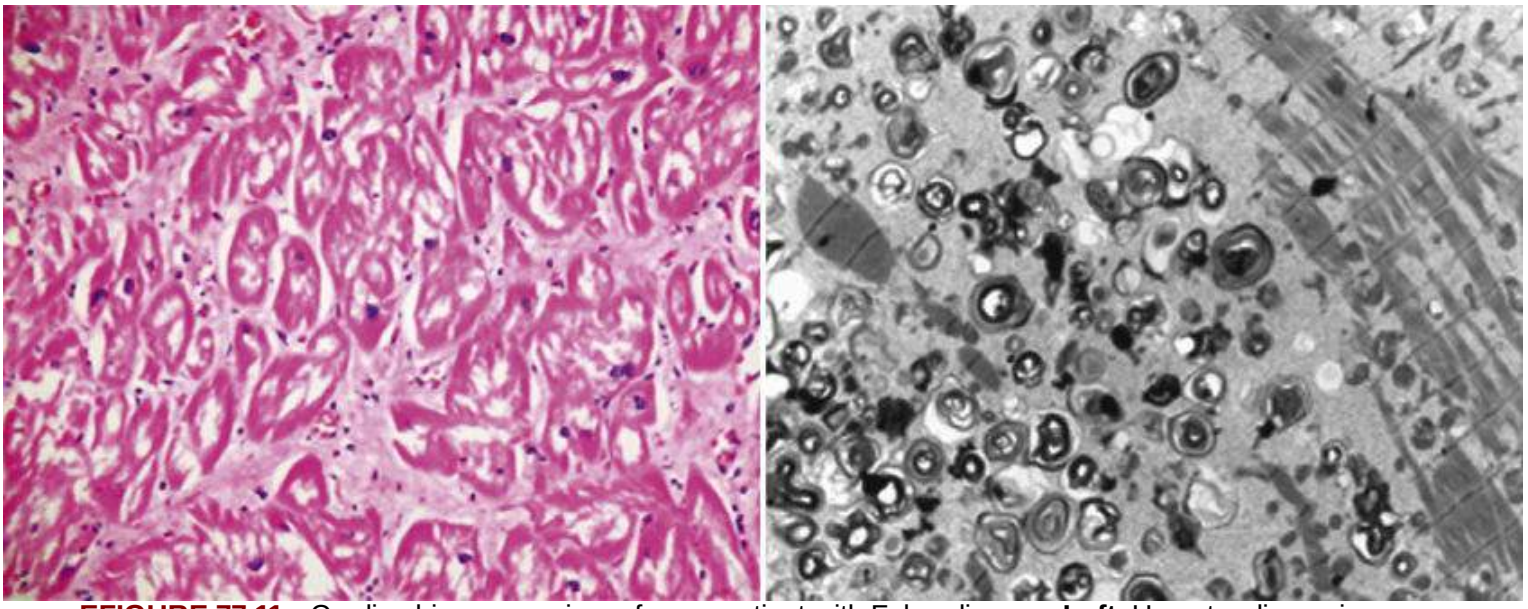
Modified from Mehta A, Hughes DA: Fabry disease. In Pagon RA, Adam MP, Ardinger HH, et al. Gene Reviews. Seattle: University of Washington. Initial posting August 5, 2002; last update January 5, 2017.

Most morbid and mortal manifestations of Fabry disease are related to cardiovascular, cerebrovascular, and renal disease and occur in men in midlife who have had the classic phenotype and onset in early life, although the age at onset of advanced disease is variable and in some cases it may occur in the second and third decades. Cerebrovascular issues related to small-vessel disease include transient ischemic attacks and thrombosis resulting in stroke in up to a quarter of patients in a variety of locations, most commonly the posterior circulation. Cardiovascular involvement is not usually clinically apparent until the third or fourth decade, but eventually some manifestation of cardiovascular disease occurs in most patients. The most common finding is LV hypertrophy on echocardiography, although the degree of hypertrophy is mild in many cases in the third decade but is progressive with age. Worsening LV hypertrophy is associated with angina that occurs consequent to small-vessel disease, and epicardial coronary disease is uncommon. Findings on the ECG initially include a short PR interval and LV

hypertrophy, with later evidence of heart block. Nonspecific intraventricular conduction delays are also seen. Bradycardia is common and a few patients will require pacemakers. Nonspecific ST-T changes are also common. Echocardiographic features range from mild to severe LV hypertrophy, the latter being more common in older patients, and mild to significant diastolic dysfunction. In most cases systolic function is normal, although heart failure has been reported with advanced disease. Palpitations and arrhythmia also occur.

Atypical phenotypes of Fabry disease have been categorized as cardiac or renal variants. Although most classic Fabry disease is syndromic, as noted earlier, and in the vast majority of cases a diagnosis of Fabry disease will be established before referral for cardiovascular or renal consultation, occasionally patients will be referred to cardiovascular or renal specialists for organ-specific disease before the diagnosis of Fabry disease is made. The atypical cardiac variant phenotype has few or none of the classic signs and symptoms but rather may be manifested as unexplained LV hypertrophy in the sixth to eighth decades, at times accompanied by cardiomyopathy, mitral insufficiency, and mild proteinuria but minimal or no renal dysfunction. Because of its protean manifestations, the frequency of Fabry disease in patients who have unexplained LV hypertrophy consistent with a diagnosis of HCM has been investigated. In a study of 1386 patients at 13 European centers that included men and women older than 35 and 40 years, respectively, all with diagnoses of HCM, systematic screening for Fabry disease was performed by searching for *GLA* mutations, and when identified, it was confirmed by alpha-galactosidase A levels.[89] Seven individuals (0.5%) were identified, 4 of the 7 being women 45 to 72 years of age, all with significant LV hypertrophy (ranging from 15 to 22 mm). Only 3 had other signs of Fabry disease, most commonly angiokeratomas. Exclusion of mutations in other genes encoding sarcomeric proteins known to cause HCM was not reported in this study, but comprehensive molecular (panel) testing for HCM would now identify sarcomeric variants, as well as *GLA* variants.

The diagnosis of Fabry disease rests on showing reduced alpha-galactosidase A activity and molecular genetic testing for mutations in *GLA*. An endomyocardial biopsy specimen showing inclusions in vascular endothelial cytoplasm on light or electron microscopy can also lead to the diagnosis (**eFig. 77.11**). Because the cardiovascular findings in adults with Fabry disease almost always include LV hypertrophy and in many cases a diagnosis of HCM is considered, genetic testing with gene panels now includes *GLA* to ensure that atypical cases of Fabry disease will not be missed.



EFIGURE 77.11 Cardiac biopsy specimen from a patient with Fabry disease. **Left,** Hematoxylin-eosin staining (200×) demonstrating hypertrophied vacuolated myocytes. **Right,** Transmission electron microscopy (10,000×) showing intracytoplasmic lamellar bodies within myocytes. (From Leone O, Veinot JP, Angelini A, et al: 2011 Consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. Cardiovasc Pathol 2012;21:245.)

Importantly, treatment of Fabry disease is available as enzyme replacement, which can arrest the deposition of globotriaosylceramide and in some cases reverse the disease phenotype, ameliorate symptoms, and restore organ function. For this reason, the diagnosis of Fabry disease, even though rarely encountered by most physicians, is important.

Gaucher Disease and Glycogen Storage Diseases

Gaucher disease is an autosomal recessive glycogen storage disease that results from deficient beta-glucocerebrosidase enzyme activity caused by homozygous or compound heterozygous mutations in *GBA*.[90] The clinical spectrum of disease varies greatly and ranges from a lethal acute perinatal form and a subacute juvenile form, both of which share major central nervous system disease, to a mostly asymptomatic adult form; all forms share splenomegaly, hepatomegaly, cytopenia, and pulmonary disease because of deposition of glucosylceramide in reticuloendothelial cells, including peripheral blood leukocytes. Cardiac involvement is uncommon to rare but has been reported in patients with allelic variants, with mitral and aortic valve calcification leading to valvular insufficiency and stenosis in the setting of corneal opacification and splenomegaly. Recurrent pericarditis resulting in constriction, as well as DCM with systolic dysfunction, has also been reported. Enzyme replacement therapy is now available and in most cases will stabilize or reverse the disease process, thus accentuating the relevance of identifying Gaucher disease.

Hemochromatosis

Hemochromatosis is a disease caused by iron overload in which iron infiltrates major organs, especially the liver, heart, thyroid, gonads, skin, and pancreatic islet cells, to give the characteristic clinical findings of advanced disease that include cirrhosis, cardiomyopathy, diabetes, and endocrine disease. Hemochromatosis is categorized as hereditary (or primary) when arising from genetic disease or as secondary when caused by increased absorption associated with the thalassemias, sickle cell disease, or

the sideroblastic anemias or when related to excess blood transfusions for myelodysplasia or aplastic anemia. The content and distribution of iron are tightly regulated because of its toxicity and the inability of the body to excrete iron. Recent progress has been made in further understanding the molecular mechanisms of iron adsorption, use, storage, and recycling.[91]

HFE (hemochromatosis gene)-associated hereditary hemochromatosis is an autosomal recessive disease that in almost all cases results from the homozygous mutation Cys282Tyr, although 3% to 8% of cases are compound heterozygotes for Cys282Tyr and His63Asp. The carrier frequency of the Cys282Tyr variant ranges as high as 11% in individuals of European descent, although the disease is twice as likely to develop in women and penetrance varies even with Cys282Tyr homozygotes.[92] The onset of clinical disease from iron overload is insidious, and signs and symptoms are insensitive and nonspecific. Screening tests include serum ferritin and percent transferrin saturation, with the accepted level being 200 ng/mL in women and 300 ng/mL in men or 45% in women and 50% in men. If both tests are negative, iron overload is effectively excluded. With elevated transferrin saturation, molecular genetic testing for *HFE* is indicated. With elevated transferrin saturation and ferritin levels higher than 1000, iron removal, usually by phlebotomy, is indicated, and evaluation of liver and cardiac function is indicated.

The cardiovascular findings of hemochromatosis, regardless of cause, are similar and may bring the patient to medical attention before diagnosis because of other organ system involvement in a minority of cases, so clinicians always need to consider hemochromatosis in the differential diagnosis of a nondilated cardiomyopathy with mild to moderate systolic dysfunction. Cardiovascular dysfunction begins with a restrictive nondilated phenotype that with advancing disease progresses to systolic dysfunction, mild to moderate LV dilation consistent with DCM, and then advanced disease and eventual heart failure.[93] In most cases, arrhythmias and conduction system disease accompany the progressive myocardial dysfunction and include AV and bundle branch blocks and bradyarrhythmias and tachyarrhythmias, some of which may result in syncope and sudden cardiac death. CMR has evolved to become a sensitive noninvasive diagnostic modality. A definitive tissue-based diagnosis of iron overload causing cardiac dysfunction can also be made by endomyocardial biopsy, which may be particularly useful if other testing is inconclusive or the degree of cardiovascular involvement by hemochromatosis is confounded by other cardiovascular disease (e.g., coronary disease). Definitive treatment is centered on iron removal, usually by phlebotomy in *HFE*-associated hereditary hemochromatosis, and as iron stores are depleted, cardiac function will improve in most cases, sometimes to a dramatic degree. Cardiac transplantation can be avoided in most patients with timely diagnosis and phlebotomy.

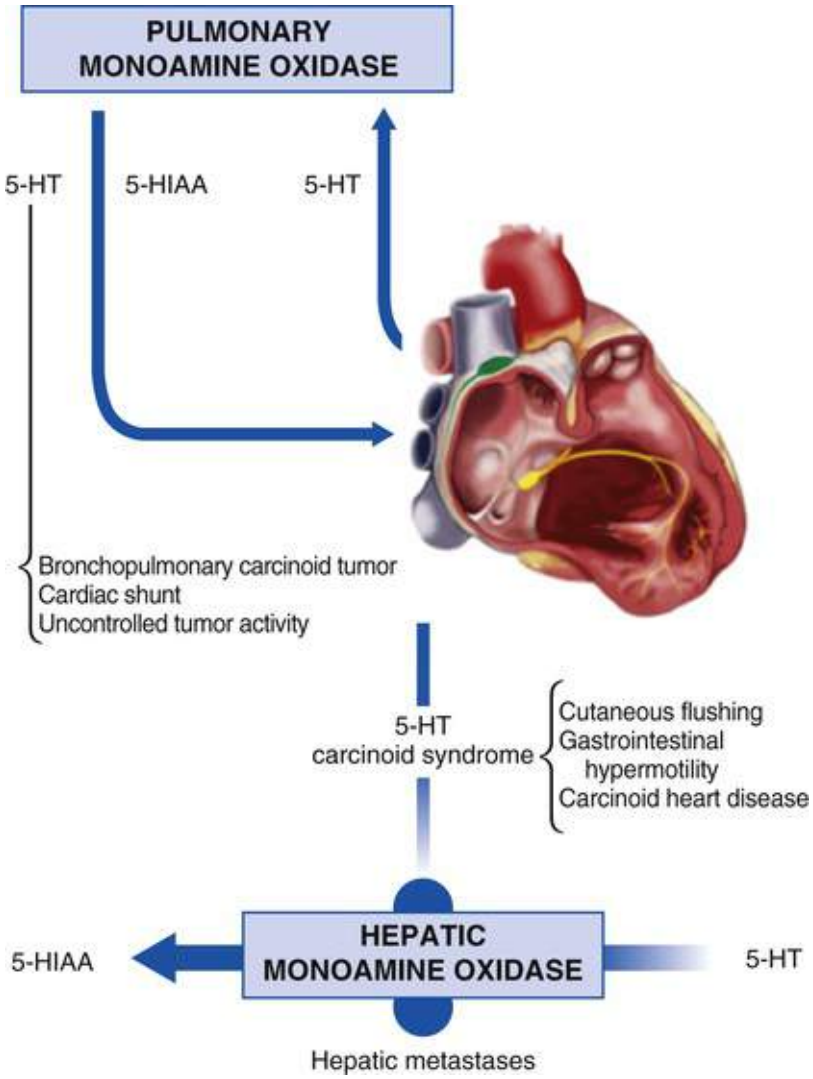
Endomyocardial Disease

The endomyocardial diseases, another cause of RCM, are unified by the finding of endocardial fibrosis. Several conditions share the pathologic end phenotype of fibrosis of the endocardium, but no unifying hypothesis for this pathology has emerged, and each condition may have its own distinctive cause. *Endomyocardial fibrosis* (EMF), a disease first described in Uganda in 1948 (initially termed tropical endocardial disease or endocardial fibroelastosis), may well be the most common cause of RCM worldwide. Although only rarely observed in North America, related conditions that pathologically resemble EMF include Löffler endocarditis, usually observed in adults, or the distinctly different onset of *neonatal endocardial fibroelastosis* (EFE) associated with hypoplastic left-heart syndrome and other congenital heart disease or in utero mumps infection. EFE, recently recapitulated in a model system,[94] can be differentiated from EMF by its epidemiology and more diffuse involvement of the left ventricle, whereas endocardial fibrosis more involves the RV and LV apices and subvalvular apparatus. Neonatal

EFE has been observed in a few families, and a genetic cause has been considered (see Online Mendelian Inheritance in Man [OMIM] 226000), and the X-linked *Barth syndrome* (see OMIM 302060) is categorized as a DCM with associated EFE, a proximal skeletal myopathy, and growth retardation. At times, noncompaction has also been observed in Barth syndrome.

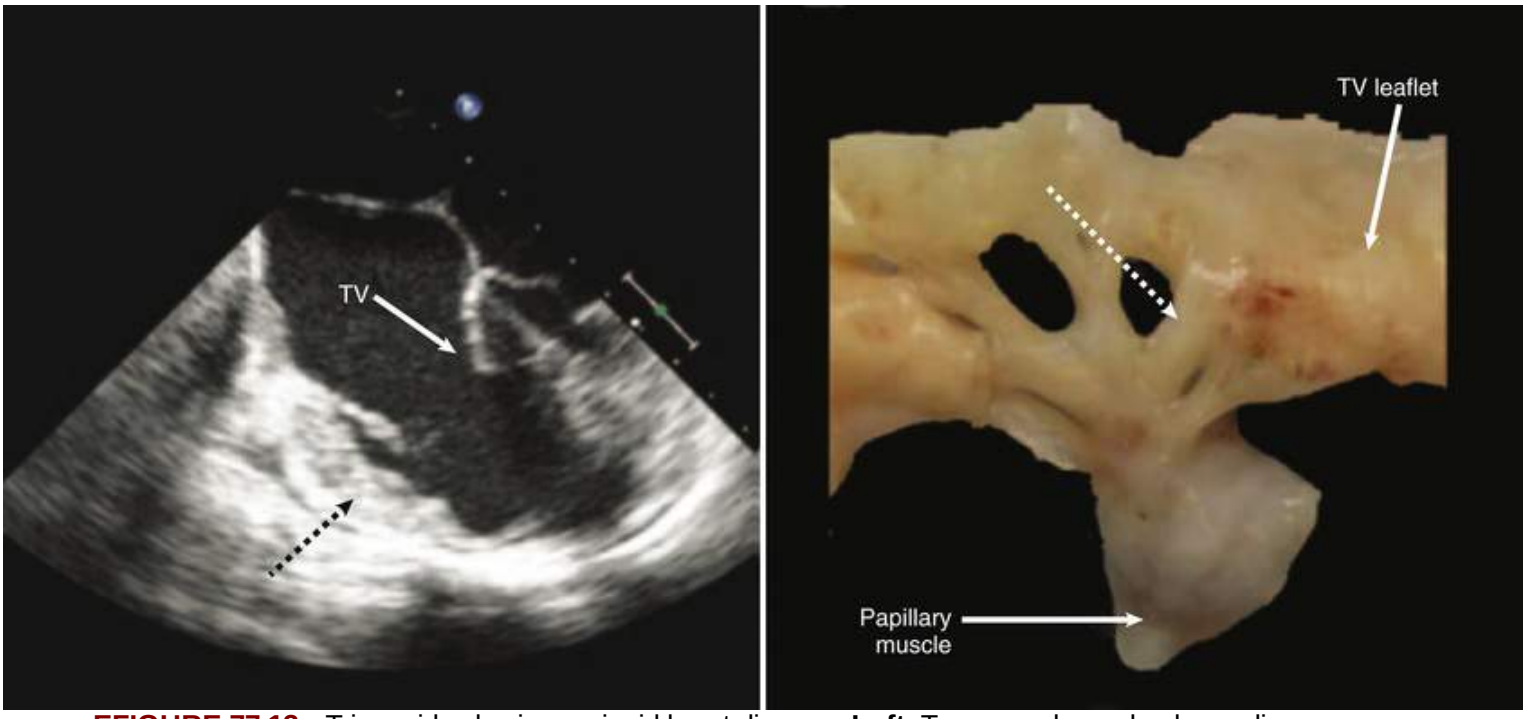
Carcinoid Heart Disease

Carcinoid heart disease is a rare condition that occurs as part of carcinoid syndrome, a systemic disorder mediated by elevated circulating levels of vasoactive substances, including serotonin (5-hydroxytryptamine [5-HT]), 5-hydroxytryptophan, histamine, bradykinin, tachykinins, and prostaglandins produced by a rare metastatic neuroendocrine malignancy, carcinoid.[95] *Carcinoid syndrome* is characterized by a triad of symptoms—flushing, diarrhea, and bronchospasm—that occur in association with hepatic metastases. The metastases produce high levels of these vasoactive substances, particularly 5-HT, which reaches the systemic circulation via the hepatic vein. High levels in the right side of the heart cause progressive fibrotic endocardial plaque[96] (**eFig. 77.12**). Inactivation in the lung to hydroxyindoleacetic acid (5-HIAA) generally protects the left-sided heart structures, but these structures may become involved if levels are very high or if a patent foramen ovale allows right-to-left shunting.[97] Carcinoid heart disease has very rarely also been described in association with nonmetastatic ovarian cancer.



EFIGURE 77.12 Mechanism of carcinoid syndrome. Serotonin (5-HT) is usually metabolized in the liver to 5-HIAA, but in the presence of carcinoid metastases the amount of 5-HT produced exceeds the degradation capacity of the liver, enters the hepatic vein, and passes through the right side of the heart. 5-HT is metabolized in the lung and does not cause left-sided heart damage unless there is a large amount, a patent foramen ovale, or, rarely, additional production by a bronchopulmonary carcinoid. (From Castillo JG, Silvay G, Solis J: Current concepts in diagnosis and perioperative management of carcinoid heart disease. Semin Cardiothorac Vasc Anesth 2013;17:212.)

The characteristic pathologic features of carcinoid heart disease are right-sided valve thickening and retraction resulting from myofibroblast proliferation along with deposition of collagen and smooth muscle cells. Tricuspid annular and subvalvar involvement and pulmonary root constriction also occur, thereby adding to the valvular dysfunction. Very rarely the heart is involved directly by carcinoid metastases.[95,96] Physical examination reveals evidence of RV volume and pressure overload with murmurs of tricuspid and pulmonary regurgitation and stenosis. In the late stage of the disease, peripheral edema and ascites with low cardiac output occur, although the valvular disease may be hemodynamically severe before significant clinical deterioration takes place. Symptoms of right-sided heart failure in the setting of known carcinoid syndrome are highly suggestive of carcinoid heart disease, but cardiac involvement may occasionally be the initial feature of carcinoid syndrome. Chest radiography and electrocardiography are generally unrevealing in carcinoid heart disease. Elevation of urinary 5-HIAA levels is highly specific and moderately sensitive for the diagnosis of carcinoid syndrome, and the echocardiographic and CMR features of thickened immobile tricuspid and pulmonary valves with combined stenosis and regurgitant lesions are highly suggestive of carcinoid heart disease[98] (**eFig. 77.13**).



EFIGURE 77.13 Tricuspid valve in carcinoid heart disease. **Left,** Transesophageal echocardiogram showing thickened tricuspid valve (TV) leaflets and endocardial thickening as a result of carcinoid plaque (*dashed arrow*). **Right,** Surgical specimen of the TV showing thickened, retracted papillary muscle as a result of carcinoid plaque and thickened chordae (*dashed arrow*). (From Bhattacharyya S, Toumpanakis C, Burke M, et al: Features of carcinoid heart disease identified by 2- and 3-dimensional echocardiography and cardiac MRI. Circ Cardiovasc Imaging 2010;3:103.)

Untreated patients with carcinoid syndrome have a median survival time of 3 to 4 years, and the presence of carcinoid heart disease shortens this to less than 1 year.[95] Therapy is not generally curative and includes debulking the hepatic metastases by embolization or partial hepatic resection and by the use of octreotide, a somatostatin analogue that binds to somatostatin receptors on the surface of carcinoid tumor cells and inhibits the secretion of vasoactive substances. Although the development and progression of carcinoid heart disease are associated with increasing 5-HIAA levels,[99] a decrease in 5-HIAA levels afterward does not appear to cause a change in the cardiac valvular lesions, and they may even progress.[95] Valve replacement in carcinoid heart disease can be performed successfully[100] but carries unique challenges, such as the development of an *acute carcinoid crisis* characterized by profound hypotension, severe flushing bronchoconstriction, and arrhythmias. Thus a surgical and anesthetic team knowledgeable about the condition and working with an endocrinologist, both intraoperatively and perioperatively, is of critical importance. Once advanced carcinoid valve disease is recognized on echocardiography, surgery is recommended even in the absence of significant right-sided heart dysfunction; patients who have undergone surgery are believed to be likely to have a more favorable outcome.[95]

Löffler (Eosinophilic) Endocarditis

Löffler endocarditis occurs within the spectrum of the hypereosinophilic conditions in which increased numbers of eosinophils invade and damage tissues in a variety of organs, including the endocardium and myocardium, by releasing highly active biologic substances. The cause of the eosinophilia in Löffler endocarditis includes known and idiopathic causes, such as a broad spectrum of helminthic or other parasitic infections, malignancy including carcinoma or eosinophilic leukemia, and allergy including drug reactions, all of which may have associated hypereosinophilia, as well as idiopathic hypereosinophilia

syndrome. Hypereosinophilia has been defined as either a chronic absolute eosinophil count higher than 1500 cells/mL for at least 1 month, although hypereosinophilia persisting for 6 months or longer is common, or pathologic evidence of hypereosinophilic tissue invasion. One family has been reported with autosomal dominant transmission linked to 5q31-q33, and more recently, hypereosinophilia syndrome in the setting of myeloproliferative disease has responded to tyrosine kinase inhibitors, but a unifying genetic or environmental hypothesis is not yet available.

Hypereosinophilic syndromes affecting the heart, although rare, when present cause considerable morbidity and mortality. Some cases of myocardial hypereosinophilic disease may be identified at endomyocardial biopsy during evaluation for idiopathic RCM, and in such situations a thorough evaluation for an underlying cause should be completed. Regardless of cause, eosinophilic-mediated cardiac disease has been categorized into three stages: acute, intermediate, and fibrotic. In the acute phase, usually characterized by few or no signs or symptoms, eosinophils invade the myocardium, degranulate, and aided by lymphocytes, cause intense myocardial inflammation and eventually myocardial necrosis. Even though findings on echocardiography may be normal during this phase, contrast-enhanced CMR can detect disease,[101,102] and myocardial biomarkers may be elevated to variable degrees. In the second stage, thrombus favoring the apices covers the affected endocardium. Symptoms include chest pain or dyspnea. Other evidence of disease includes mitral or tricuspid valvular regurgitation, cardiomegaly, and heart failure. Embolism of endocardial thrombus to the brain or other organs is common and may be the initial feature of the disease. The ECG may show T wave inversions, and imaging studies will reveal mural thrombus in affected areas, at times so extensive that large portions of the myocardial chamber are obliterated with clot. The third fibrotic phase progresses with diffuse scarring that results in endocardial fibrosis and RCM. The scar process commonly involves the mitral and tricuspid subvalvular structures; it impairs their mobility and leads to valvular regurgitation. Valve leaflet scarring can also occur. If disease can be identified in the first stage, therapy is focused on treatment of the underlying condition. Corticosteroids and cytolytic therapies have been used with some response. The fibrotic stage needs to be addressed surgically by valve release, repair, or replacement and by resection of the endocardial scar to mitigate the restrictive nature of the endocardial fibrosis.

Endomyocardial Fibrosis

Endomyocardial fibrosis (EMF), an unusual disease in North America but common in Africa, is characterized by fibrosis of the LV and RV apical endocardium causing an RCM. First reported in Uganda, it has been found in tropical regions of Africa, the south Asian subcontinent, and Brazil, although it is also found in subtropical Africa and some cases occur rarely in moderate climates, including North America. A population prevalence of approximately 20% in rural Mozambique has been reported,[103] with more males affected than females (23% versus 17%). In addition, family clustering was identified in this study, although whether this was related to environmental exposure common to the family units selected for study, to a genetic predisposition, or to both was not addressed. A bimodal peak in age has been noted in several studies, with onset in the first decade and a second peak occurring in the second to fourth decades of life.

The cause of EMF remains unknown, but its pathology resembles that of other conditions in North America that are more commonly encountered, such as eosinophilic cardiomyopathy or hypereosinophilic syndrome, discussed earlier. However, elevated eosinophil counts in peripheral blood or cardiac tissue from endomyocardial biopsy have seldom been observed in EMF. Although one or more infectious agents could be causal, no consistent unifying infectious cause has been established. Environmental exposure to

cerium, a rare element present in affected areas, has also been considered. Family-based disease has been observed in several reports, but whether familial predisposition is related to environmental or genetic causes, or to both, remains unknown.

In most cases heart failure symptoms from left or right restrictive physiology predominate the clinical findings and include dyspnea on exertion, paroxysmal nocturnal dyspnea, and edema. Ascites, at times a prominent feature, is common to all the endomyocardial diseases. Cardiovascular imaging shows restrictive filling with apical fibrosis that commonly involves the mitral and tricuspid subvalvular apparatus, accompanied by atrial enlargement. As noted earlier, successful surgical resection of the endocardial fibrosis with valve repair or replacement can have a dramatic effect on symptoms and survival, although the operation itself is associated with a significant risk for morbidity and mortality.

Future Perspectives

Enormous progress has recently been made in understanding the genetic basis of cardiomyopathy, accelerated in large part by next-generation sequencing strategies. Sequencing of the exome, defined as the 1% to 2% of the human genome that encodes the approximately 19,000 genes, has greatly facilitated progress in understanding the genomic basis of the cardiomyopathies. The genomic information reviewed herein, limited in most cases by mutation surveys of one or a few candidate genes, will give way to comprehensive genome-wide strategies to identify and understand rare and common variants relevant to disease susceptibility and cause, including structural and other nonprotein coding genomic variants, in much larger populations of patients with cardiomyopathy. This will enable a more comprehensive and insightful understanding of the genomic basis of human disease, including that affecting the myocardium. Our present rudimentary understandings of “mendelian genetics,” an oversimplified concept of “single-gene” genetics, is rapidly evolving into much greater complexity.

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78

Hypertrophic Cardiomyopathy

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Hypertrophic cardiomyopathy (HCM), the most common of the genetic cardiovascular diseases, is characterized by heterogeneous clinical expression, distinctive pathophysiologic features, and a diverse natural history.[1-5] It is caused by a multitude of mutations in genes encoding proteins of the cardiac sarcomere.[6-10] Although many patients with HCM have a normal life span, HCM has been regarded as the most common cause of sudden death (SD) in the young, including competitive athletes.[11-13] It also constitutes a risk for atrial fibrillation (AF), and it is responsible for heart failure–related disability at virtually any age.[9,14-16] Since the modern description of HCM was developed more than 50 years ago, our understanding of the clinical complexity and spectrum of this disease has evolved dramatically.[17] Most importantly, contemporary cardiovascular treatments have now reduced HCM-related mortality rates significantly.[18-22] This chapter offers an updated summary of HCM with respect to its diagnosis, natural history, and management.

Definition, Prevalence, and Nomenclature

HCM is characterized by a thickened but nondilated left ventricle in the absence of another cardiac or systemic condition (e.g., aortic valve stenosis, systemic hypertension, and some expressions of physiologic athlete's heart) capable of producing the magnitude of left ventricular (LV) hypertrophy evident (**Figs. 78.1 and 78.2**).[1,3,23,24] Several epidemiologic studies report the prevalence of the HCM phenotype in the general population at 1 : 500, equivalent to approximately 700,000 affected people in the United States. More recent estimates, which take into account genetic and imaging diagnostic modalities, place the prevalence closer to 1 : 200.[25] This frequency in the general population exceeds the number of diagnosed patients in cardiovascular practice (estimated at 100,000),[26] suggesting that most affected individuals remain unrecognized during their lifetime and usually do not have symptoms or suffer cardiovascular events.

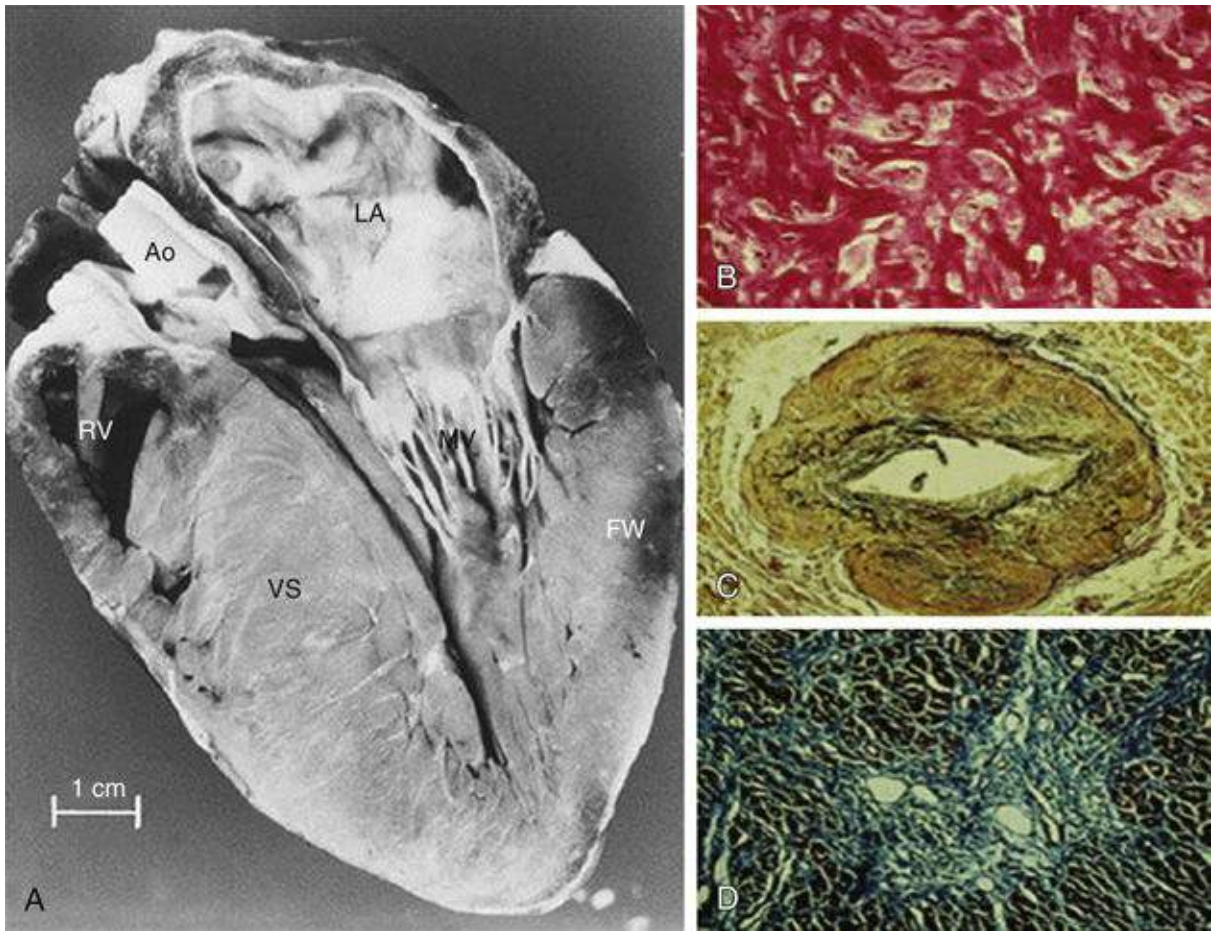


FIGURE 78.1 Gross morphology and histopathology of HCM. **A,** Gross heart specimen shown in a cross-sectional plane similar to that of the echocardiographic (parasternal) long axis; pattern of LV hypertrophy is asymmetric, disproportionately involving the ventricular septum (VS), which typically bulges into the LV outflow tract. *Ao*, aorta; *FW*, free wall of left ventricle; *LA*, left atrium; *RV*, right ventricle. **B,** Histopathology characteristic of left ventricle in HCM, with septal myocardium showing markedly disordered architecture with adjacent hypertrophied cardiac muscle cells arranged at perpendicular and oblique angles. **C,** Intramural coronary artery with narrowed lumen and thickened wall, due primarily to medial (M) hypertrophy. **D,** Scar in VS, representing repair process following clinically silent ischemia and myocyte death. (From Maron BJ: Sudden death in hypertrophic cardiomyopathy. J Cardiovasc Transl Res 2009;2:368-80.)

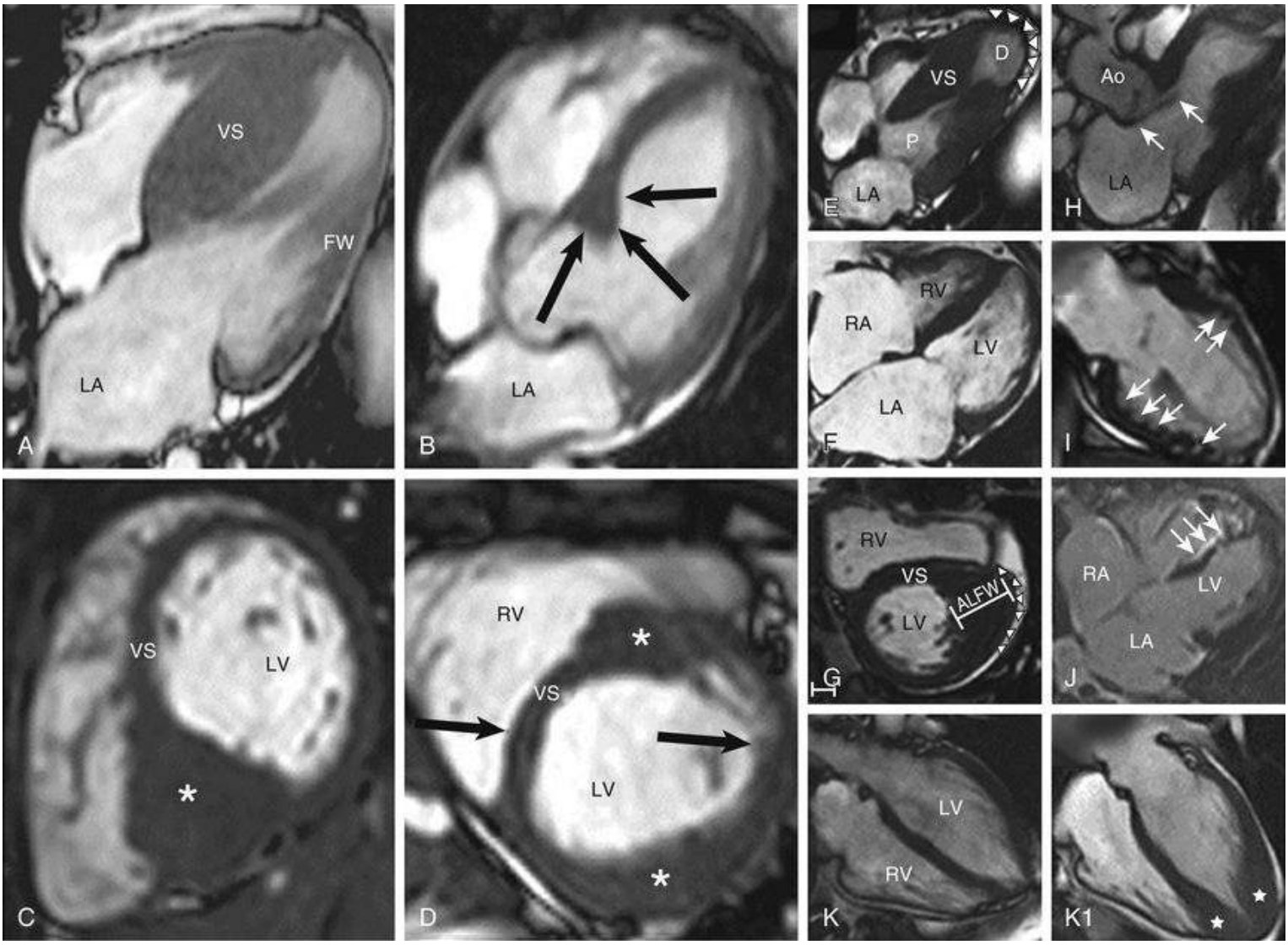


FIGURE 78.2 CMR in HCM. Spectrum of the phenotype. **A,** Hypertrophy involving the ventricular septum (VS) and sparing LV free wall (FW). **B,** Focal area of hypertrophy sharply confined to basal anterior septum (*arrows*), **C,** Extreme thickness of 33 mm in the posterior ventricular septum (*asterisk*). **D,** Noncontiguous segmental areas of hypertrophy involving the basal anterior septum and posterior free wall (*asterisks*) separated by regions of normal LV thickness (*arrows*). **E,** LV apical aneurysm (*arrowheads*) with midcavity muscular obstruction. **F,** "End-stage" remodeling with enlargement of LV cavity (and atria) and wall thinning, associated with systolic dysfunction (ejection fraction < 50%). **G,** Massive hypertrophy (wall thickness 34 mm) confined to anterolateral LV free wall (ALFW). **H, I, J,** Morphologic abnormalities in the absence of LV hypertrophy in genetically affected patients. **H,** Primary elongation of anterior mitral leaflet (*arrows*). **I,** Multiple LV myocardial crypts (*arrows*). **J,** LGE indicative of replacement myocardial fibrosis (*arrows*). **K and K1,** De novo phenotypic conversion at advanced age. **K,** Absent LV hypertrophy at age 46 years. **K1,** At age 51 years, apical HCM (*stars*) is now evident. (**A** to **D** from Maron BJ, Maron MS: Hypertrophic cardiomyopathy. Lancet 2013;381:242. **E** to **K1** from Maron BJ, Haas TS, Kitner C, et al: Onset of apical hypertrophic cardiomyopathy in adulthood. Am J Cardiol 2011;108:1783.)

HCM is a global disease, reported in more than 50 countries from all continents.[1,2] The first contemporary reports of HCM in 1958 were from Brock (in the cardiac catheterization laboratory) and from Teare (at autopsy), describing "asymmetrical hypertrophy of the heart" as being responsible for SD in a small group of young people. This disease rapidly acquired a confusing array of names, with most emphasizing the highly visible feature of LV outflow obstruction.[27] However, because obstruction to LV outflow is not always present and about one third of patients have the nonobstructive form of HCM, the preferred and generally accepted name for this condition is hypertrophic cardiomyopathy (HCM), with or without outflow obstruction.[1-4,19,23]

Gender and Race.

As an autosomal dominant disease, HCM is expected to occur with equal frequency in men and women.[4,23] The predominance of men with HCM reported in the literature probably reflects an underdiagnosis in women, who achieve clinical recognition less frequently and at older ages than men. Women may be at greater risk than men for progression to advanced heart failure (usually associated with outflow obstruction), although there is no relationship between gender and SD risk or overall HCM-related mortality rates. HCM has been reported in many races; it appears to be underrecognized in African- Americans, and most competitive athletes who die suddenly of HCM are previously undiagnosed black men.[11-13] The clinical expression, presentation, and course of HCM, as well as the phenotypic expression, are similar throughout the world, although the morphologic form characterized by hypertrophy confined to the LV apex may be more common in Japan.[1,2]

Genetic Basis and Testing.

HCM is transmitted as a mendelian trait with an autosomal dominant pattern of inheritance (**see also Chapter 7**); every offspring of an affected relative has a 50% chance of inheriting the disease.[1-3,23] Molecular studies, conducted intensively over two decades, have provided access to a laboratory-based diagnosis by identifying disease-causing (pathogenic) mutations, and providing in the process important insights into the broad clinical expression of HCM, including identification of individuals with pathogenic mutations but without evidence of the disease phenotype (LV hypertrophy).

HCM is known to be caused by mutations in 11 or more genes encoding proteins of the thick and thin contractile myofilament components of the cardiac sarcomere or the adjacent Z-disc (**Figs. 78.3 and 78.4**). Two sarcomere genes, β-myosin heavy chain (*MYH7*) and myosin-binding protein C (*MYBPC3*) are by far the most common, accounting for 70% of patients for whom genotyping has been successful. Troponin T *(TNNT2*), troponin I (*TNNI3*), and several other genes are each responsible for 5% or fewer cases. Underscoring the vast genetic heterogeneity of HCM is the recognition of over 1500 individual mutations (largely missense), most of which are unique to individual families.[6,28-32]

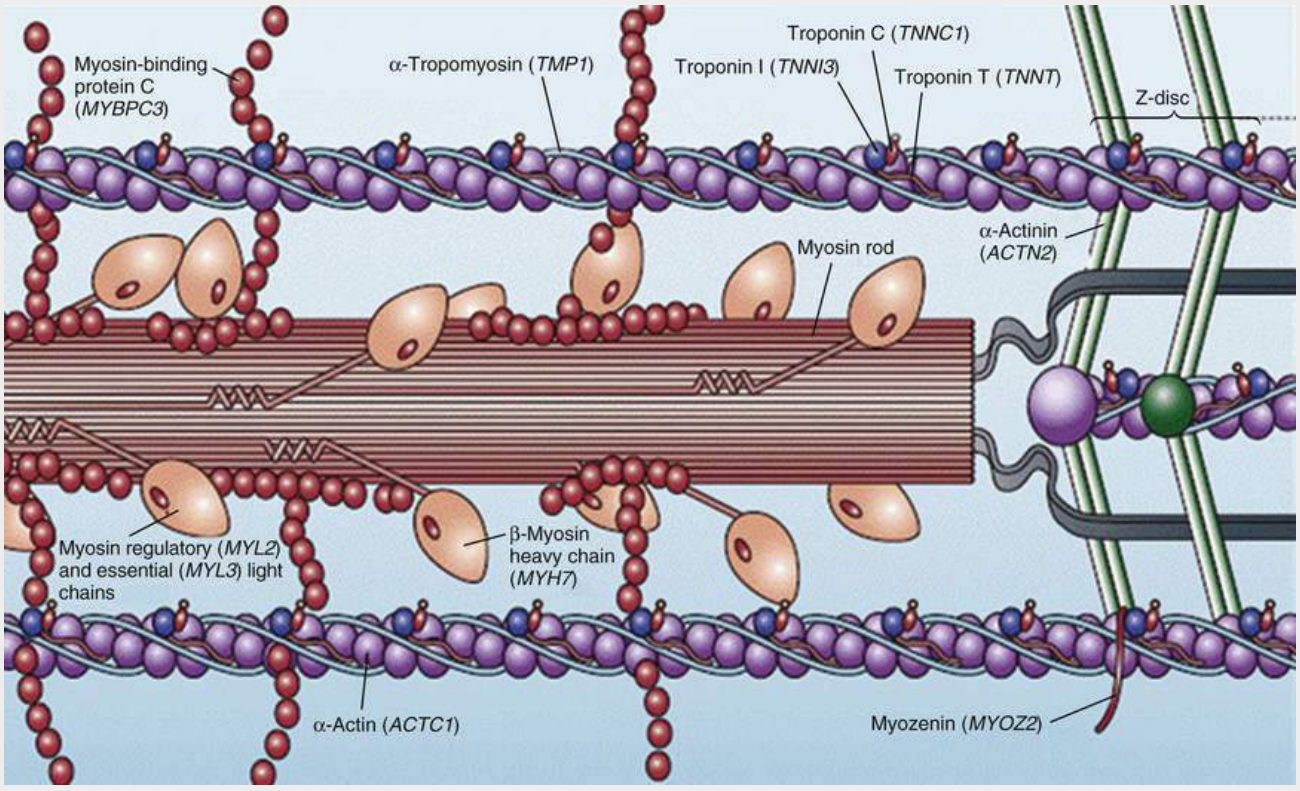


FIGURE 78.3 Locations of genes within the cardiac sarcomere known to cause HCM. (From Maron BJ, Maron MS: Hypertrophic cardiomyopathy. Lancet 2013;381:242.)

Molecular Substrate of HCM	
Strongest evidence for pathogenicity	
Thick filament	
1. β-myosin heavy chain	MYH7
2. Regulatory myosin light chain	MYL2
3. Essential myosin light chain	MYL3
Thin filament	
4. Cardiac troponin T	TNNT2
5. Cardiac troponin I	TNNI3
6. Cardiac troponin C	TNNC1
7. α-tropomyosin	TPM1
8. α-cardiac actin	ACTC
Intermediate filament	
9. Cardiac myosin-binding protein C	MYBPC3
Z-disc	
10. α-actinin2	ACTN2
11. Myozenin2	MYOZ2
Lesser evidence of pathogenicity	
Thick filament	
12. α-myosin heavy chain	MYH6
13. Titin	TTN
Z-disc	
14. Muscle LIM protein	CSRP3
15. Telethonin	TCAP
16. Vinculin/metavinculin	VCL
Calcium handling	
17. Calsequestrin	CASQ2
18. Junctophilin 2	JPH2

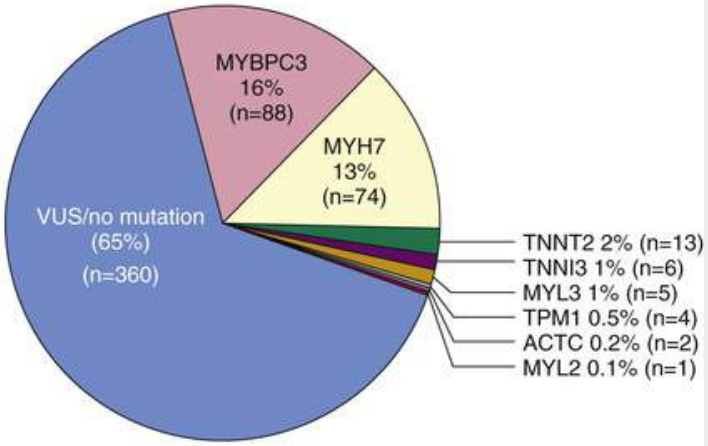


FIGURE 78.4 Genetic substrate in HCM. **Left,** Genes known to be associated with HCM. **Right,** Distribution of genes encoding proteins of the cardiac sarcomere identified in unrelated HCM probands undergoing clinical genetic testing. A variety of laboratories report a wide range in mutational yield (24% to 63%), leaving a significant proportion of the HCM population genotype-negative. However, based on current commercial genetic testing, only about 35% of families are genotyped to a pathogenic mutation. *VUS,* Variant of uncertain significance. (From Maron BJ, Maron MS, Semsarian C: Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. J Am Coll Cardiol 2012;60:705.)

In clinical practice, the greatest advantage of commercially available genetic testing (**Fig. 78.5**) is the opportunity to identify or exclude an affected status in family members without LV hypertrophy.[6,29] This strategy first requires identification of a pathogenic mutation in a relative (proband) with clinically expressed HCM. With current commercial genetic testing, however, a genotype for a disease-causing mutation can be identified in only about 35% of families; this is a major obstacle to performing cascade screening of family members. Genetic testing not infrequently identifies novel but ambiguous sequence variants for which the pathogenicity is unresolved (variants of unknown significance; VUSs) and which have no application to clinical family screening. This issue and the not uncommon phenomenon of reclassification, in which pathogenic mutations can be down-graded to VUSs (or vice versa) with time, underscore the challenges remaining in translating complex molecular science to patient care. The possibilities offered by next-generation techniques, including whole-exome and whole-genome analysis, may be considerable because they may provide enhanced screening capabilities and reduced costs, but they will also increase the frequency with which VUSs are recognized.[32]

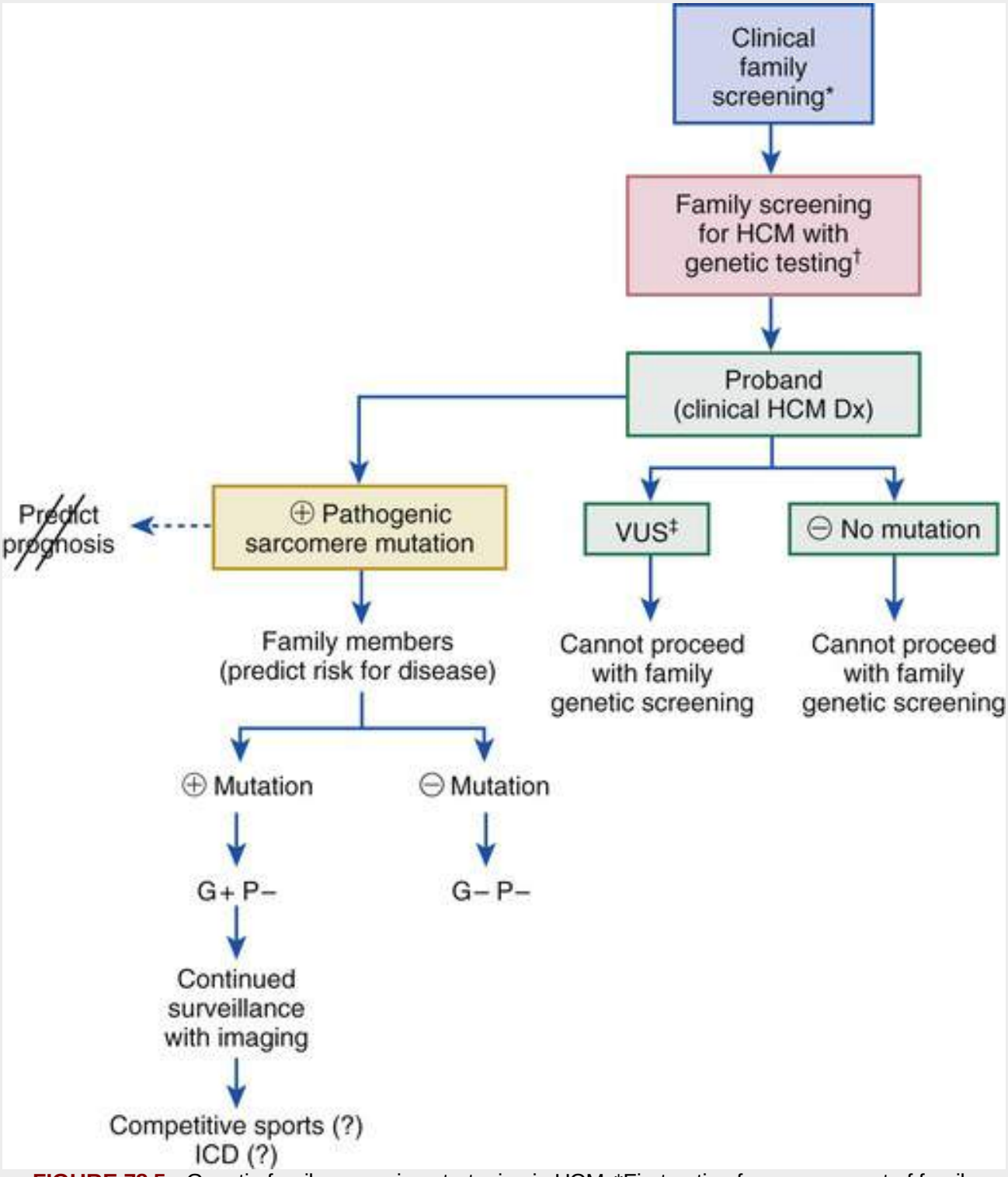


FIGURE 78.5 Genetic family screening strategies in HCM. *First option for assessment of family members would be a clinical screening evaluation with imaging tests and ECG; †the option of genetic testing is triggered largely for those relatives without LV hypertrophy, with indeterminate clinical testing and imaging. *Dx*, diagnosis; *ICD*, implantable cardioverter-defibrillator; *VUS,* variant of uncertain significance. (From Maron BJ, Maron MS, Semsarian C: Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. J Am Coll Cardiol 2012;60:705.)

Notably, despite early aspirations, predicting the prognosis and risk for SD in individual HCM patients based on specific sarcomere mutations has proved unreliable, and therefore patient management decisions are not determined by genetic testing results.[2,4,30] Population-based association studies have demonstrated a more severe course in gene-positive patients than gene-negative patients, as well as in patients with thick-filament mutations (*MYBPC3* and *MYH7*) compared with those with thin-filament mutations (*TNNT2* and *TNNI3*).[8,10,31] In HCM, there is inconsistent evidence for whether multiple pathogenic sarcomere mutations coexisting in the same patient lead to early disease onset and/or a more

severe clinical profile.[6]

Genetic testing is crucial for clarifying the diagnosis in patients with metabolic and storage disorders for which the clinical presentation and pattern of LV hypertrophy can mimic sarcomeric HCM but for which the pathophysiology, natural history, and management are dissimilar.[24] For example, *LAMP2* cardiomyopathy is associated with a lethal natural history refractory to defibrillation therapy (with survival uncommon beyond 25 years) and requires early recognition and likely heart transplant,[33] and Fabry disease requires enzyme replacement therapy.[34]

Morphologic Findings and the Role of Cardiac Imaging

Phenotype and Left Ventricular Hypertrophy

The clinical diagnosis of HCM has conventionally been made with two-dimensional echocardiography. However, cardiovascular magnetic resonance (CMR) imaging has emerged with an expanded role in the diagnosis (and management) of HCM patients by virtue of its high-resolution tomographic imaging capability (**see Fig. 78.2**). CMR also allows for quantification of late gadolinium enhancement (LGE), a marker for myocardial fibrosis. CMR is complementary to echocardiography by resolving technically ambiguous LV wall thicknesses or visualizing relevant areas of hypertrophy blind to echocardiography (e.g., in the anterolateral free wall, posterior (inferior) septum, or apical left ventricle).[35-40]

Cardiac imaging in clinically identified adults and children with HCM typically documents an absolute increase in LV wall thickness of 15 mm or more (21 to 22 mm on average, and up to > 50 mm), although any LV wall thicknesses (including those within normal range) are consistent with a genetically affected status.[40] Borderline LV wall thicknesses of 13 to 14 mm can create diagnostic ambiguity, particularly in the differential diagnosis of physiologic athlete's heart (**eTable 78.1**).

Diverse and myriad patterns of asymmetric LV hypertrophy are characteristic of HCM (**see Fig. 78.2**), even in related patients (although identical twins share the same morphology). Typically, one or more regions of the LV chamber are of greater thickness than other areas, often with a sharp demarcation at the point of transition in thickness, or there are noncontiguous patterns of segmental hypertrophy (**see Fig. 78.2**), as well as extension into the right ventricular (RV) wall, in some patients. No single morphologic form of HCM is considered “classic” or typical.

ETABLE 78.1

Distinguishing Hypertrophic Cardiomyopathy from Athlete's Heart When Left Ventricular Hypertrophy Is Within the "Gray Zone" of Overlap*

	PATHOLOGIC LV HYPERTROPHY (HCM)	PHYSIOLOGIC LV HYPERTROPHY (ATHLETE'S HEART)
Focal pattern of LV hypertrophy	+	0
LV cavity < 45 mm	+	0
LV cavity > 55 mm	0	+
Left atrium enlargement	+	0
Bizarre ECG patterns	+	+
Abnormal LV filling pattern	+	0
Family history of HCM	+	0
Decreased LV thickness with deconditioning	0	+
VO_2 increase > 110%	0	+
Late gadolinium enhancement	+	0
Pathogenic sarcomere mutation	+	0

*Wall thickness 13 to 15 mm in males and 11 to 12 mm in females.

ECG, electrocardiogram; *HCM*, hypertrophic cardiomyopathy; *LV*, left ventricular; *VO_2* peak oxygen consumption; +, present; 0, absent.

From Maron BJ, Maron MS. Hypertrophic cardiomyopathy. Lancet 2013;381, 242-255.

Hypertrophy is frequently extensive, involving the ventricular septum and LV free wall. In a sizeable minority, wall thickening is limited to segmental areas, including the most distal portion of the LV chamber (i.e., apical HCM); this is a distinctive morphologic form associated with marked T-wave negativity on ECG,[1,33,40] which is part of the HCM clinical spectrum caused by sarcomere mutations.[9] Indeed, in 20% of patients, the LV mass calculated by CMR may be normal or near-normal because of hypertrophy localized to small areas of the left ventricle.[38]

Usually, the HCM phenotype remains incomplete until adolescence, when accelerated growth and maturation are accompanied by spontaneous (often striking) increases in LV wall thickness and a more extensive distribution of hypertrophy. Occasionally, these structural changes may not occur until midlife or even later (late-onset adult LV hypertrophy) (**see Fig. 78.2**), although not usually associated with the development of symptoms or arrhythmic events.[1] In genetically affected family members without LV hypertrophy (i.e., those who are gene positive but phenotype negative), a variety of clinical and imaging findings have been reported, including subclinical diastolic dysfunction, blood-filled myocardial crypts, mitral valve leaflet elongation, collagen precursor biomarkers and myocardial scarring, or 12-lead ECG abnormalities (**see Fig. 78.2**).[28,36,41] A minority of athletes with marked repolarization abnormalities on ECG (but normal LV wall thickness) may progress to clinical and phenotypic evidence of HCM.

Mitral Valve Apparatus

Primary structural abnormalities of the mitral apparatus responsible for LV outflow obstruction are part of the phenotypic expression of HCM (**see Fig. 78.2**). The mitral valve may be more than twofold the normal size due to elongation of both leaflets, or there may be segmental enlargement of only the anterior or posterior leaflet, more frequently observed in younger patients.[41] In older patients, outflow obstruction often occurs in the presence of a particularly small LV outflow tract, mitral leaflets of normal length, and mitral-septal contact created by a modest anterior excursion of the valve combined with posterior motion of the septum.

Histopathology

In HCM, hypertrophied cardiac muscle cells (myocytes) in both the ventricular septum and LV free wall have bizarre shapes and are often arranged in a chaotic and disorganized architectural pattern (**see Fig. 78.1**).[1] At autopsy, areas of cellular disarray are evident in 95% of HCM patients; they usually occupy substantial portions of both hypertrophied and nonhypertrophied LV myocardium.

The vast majority of HCM patients also exhibit structurally abnormal intramural coronary arterioles with thickened vessel walls caused by media smooth muscle hyperplasia. These microvascular changes cause narrowing of the vessel lumen, which is likely responsible for an impaired vasodilator response and blunting of the coronary flow reserve (**see Fig. 78.1**). These abnormalities are believed to cause "small-vessel" ischemia, which, over extended periods of time, results in myocyte death and a repair process characterized by replacement myocardial fibrosis (**see Fig. 78.1**).[1,2,37] The volume of the interstitial (matrix) collagen compartment, constituting the structural framework of the LV myocardium, is greatly expanded.

The combination of disorganized cellular architecture, microvascular ischemia, and replacement fibrosis predisposes to disordered patterns and increased dispersion of electrical depolarization and repolarization, in turn serving as an unstable electrophysiologic substrate predisposing to reentry ventricular tachyarrhythmias and a likely mechanism for SD.

Pathophysiology

Left Ventricular Outflow Tract Obstruction

HCM is predominantly a disease of mechanical obstruction, in which the majority of patients (70%) have the propensity to develop impedance to LV outflow with dynamic gradients of 30 mm Hg or more, either at rest or with physiologic exercise.[1-4,27,42] Long-standing outflow obstruction is the most relevant clinical determinant of HCM-related progressive heart failure symptoms (**Figs. 78.6 and 78.7**).[18,19] Alternatively, only a weak relationship has been demonstrated between outflow obstruction and SD risk.

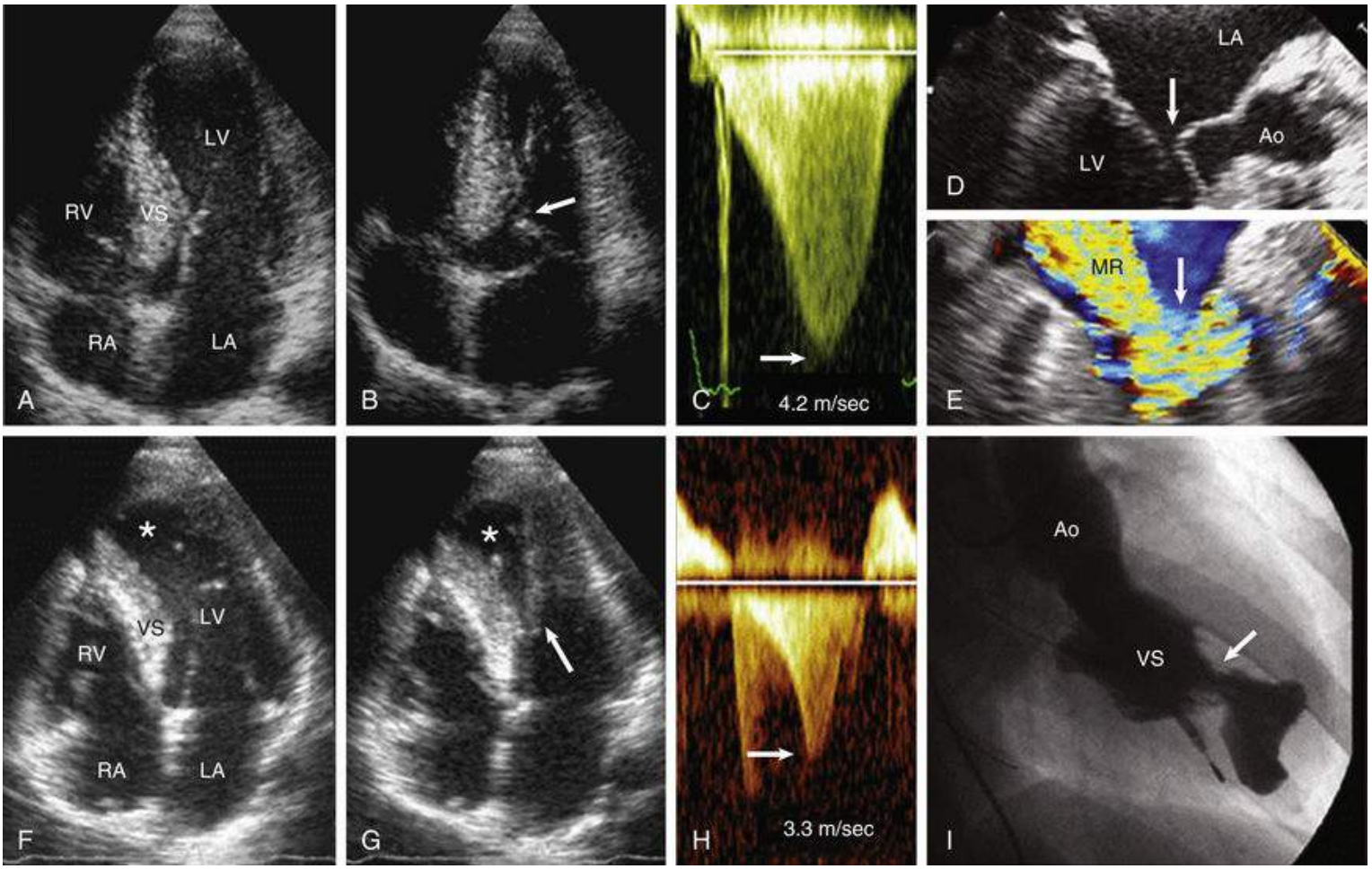


FIGURE 78.6 Dynamic LV outflow obstruction. **A** to **E,** Subaortic obstruction due to systolic anterior motion (SAM) of the mitral valve. Echocardiographic apical four-chamber view at **(A)** end-diastole and at **(B)** end-systole as the anterior mitral leaflet bends acutely with septal contact (*arrow*). **C,** Continuous-wave (CW) Doppler interrogation of the LV outflow tract showing the typical late-peaking waveform, with velocity of 4.2 m/s in midsystole, estimating a gradient of 70 mm Hg (*arrow*). **D** and **E,** transesophageal echo plane showing incomplete mitral leaflet coaptation during SAM (*arrow*), producing posteriorly directed mitral regurgitation (MR) jet. **F** to **I,** Midventricular obstruction. Echocardiographic apical four-chamber view at end-diastole **(F)** and end-systole, showing hypertrophied anterolateral papillary muscle appearing to insert directly into anterior mitral leaflet, creating midventricular muscular obstruction **(G)** (*arrow*). **H,** CW Doppler interrogation of LV outflow tract showing late-peaking waveform with peak velocity of 3.3 m/s, estimating a gradient of 45 mm Hg (*arrow*). **I,** LV ventriculogram showing hourglass contour of chamber associated with midventricular obstruction (*arrow*). *Ao*, aorta; *LA*, left atrium; *LV*, left ventricular; *MR*, mitral regurgitation; *RA*, right atrium; *RV*, right ventricle; *VS*, ventricular septum. (From Yacoub MH, El-Hamamy I, Said K, et al. The left ventricular outflow in hypertrophic cardiomyopathy: from structure to function. J Cardiovasc Transl Res 2009;2:510-517; Olivotto I, Girolami F, Nistri S, et al. The many faces of hypertrophic cardiomyopathy: from developmental biology to clinical practice. J Cardiovasc Transl Res 2009;2:349-67.)

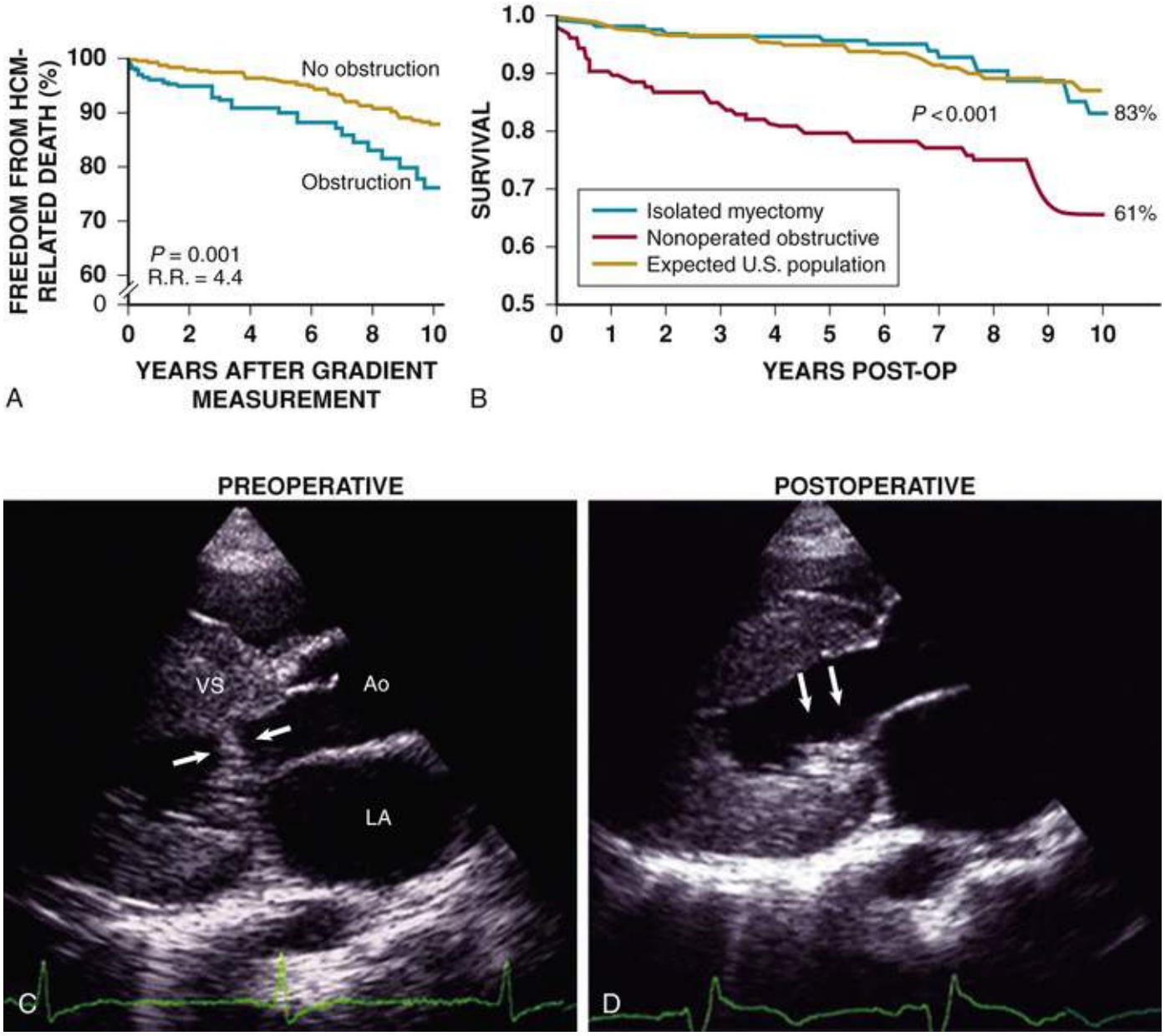


FIGURE 78.7 Clinical significance of LV outflow tract obstruction in HCM. **A,** Probability of severe progressive heart failure (NYHA class III or IV), or stroke in patients with LV outflow obstruction significantly exceeds that in patients without obstruction (relative risk, 4.4; $P < 0.001$). **B,** After myectomy, with relief of LV outflow obstruction and normalization of intraventricular pressures, showing survival free from all-cause mortality compared with age- and gender-matched U.S. population, and also nonoperated patients with obstruction ($P < 0.001$). Before surgical myectomy **(C)** echocardiographic parasternal long-axis end-systolic frames from 26-year-old woman with HCM and dynamic LV obstruction due to SAM and septal contact (*arrows*). After myectomy **(D)** with both SAM and obstruction obliterated (*arrows*). (**A** from Maron MS, Olivotto I, Betocchi S, et al: Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003;348:295. **B** from Ommen SR, Maron BJ, Olivotto I, et al: Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2005;46:470.)

Dynamic subaortic obstruction in HCM is usually produced by systolic anterior motion (SAM) of the mitral valve in which elongated leaflets bend sharply, contacting the ventricular septum in midsystole by means of a drag effect, i.e., pushing force of flow directly on the leaflets, producing markedly increased intraventricular systolic pressures that over time increase the myocardial wall stress and oxygen demand (**see Fig. 78.6**).[43] The magnitude of the outflow gradient, which is reliably estimated noninvasively with continuous-wave Doppler imaging, is directly related to the duration of mitral valve–septal contact, with posteriorly directed mitral regurgitation a secondary consequence (**see Fig. 78.6**). A central or anteriorly directed mitral regurgitation jet usually suggests an intrinsic mitral valve abnormality (e.g., with myxomatous degeneration). A congenital anomaly of the anterolateral papillary muscle insertion directly

into the anterior leaflet (without interposition of chordae tendineae) can produce midcavity muscular obstruction and is identifiable by both echocardiography and CMR.[35,36]

Subaortic gradients (and associated systolic ejection murmurs) can be spontaneously variable, reduced, or abolished by interventions, which decrease myocardial contractility (e.g., beta-adrenergic blocking drugs) or increase ventricular volume or arterial pressure (e.g., squatting, isometric handgrip, phenylephrine). Alternatively, gradients can be augmented by circumstances in which the arterial pressure or ventricular volume is reduced (e.g., Valsalva maneuver, administration of nitroglycerin or amyl nitrite, blood loss, dehydration) or when LV contractility is increased (as with premature ventricular contractions, infusion of isoproterenol or dobutamine, or physiologic exercise).[3,4] Consumption of a heavy meal or small amounts of alcohol can also transiently increase subaortic gradients.

Provocable physiologic gradients are associated with severe heart failure symptoms in some patients who become candidates for septal reduction therapy.[2,42] In asymptomatic or mildly symptomatic HCM patients, such latent gradients can be predictive of progression in heart failure symptoms over time. Provocable gradients can be blunted by inhibition of sympathetic stimulation with beta blockers.

Nonobstructive Hypertrophic Cardiomyopathy; Diastolic Dysfunction

Uncommonly (in ≈ 10%), patients with the nonobstructive form of HCM (gradient < 30 mm Hg at rest and with physiologic exercise) experience progressive heart failure to New York Heart Association (NYHA) class III or IV, at which point they may become candidates for heart transplant, with (or without) systolic dysfunction. Nonobstructive HCM patients are almost five times less likely to develop NYHA class III or IV disease than are patients with obstruction.[19] Therefore, asymptomatic and mildly symptomatic nonobstructive HCM patients make up a substantial proportion of the overall HCM clinical spectrum (at least one third), a subgroup previously underrecognized in the natural history of this disease (**Fig. 78.8**).

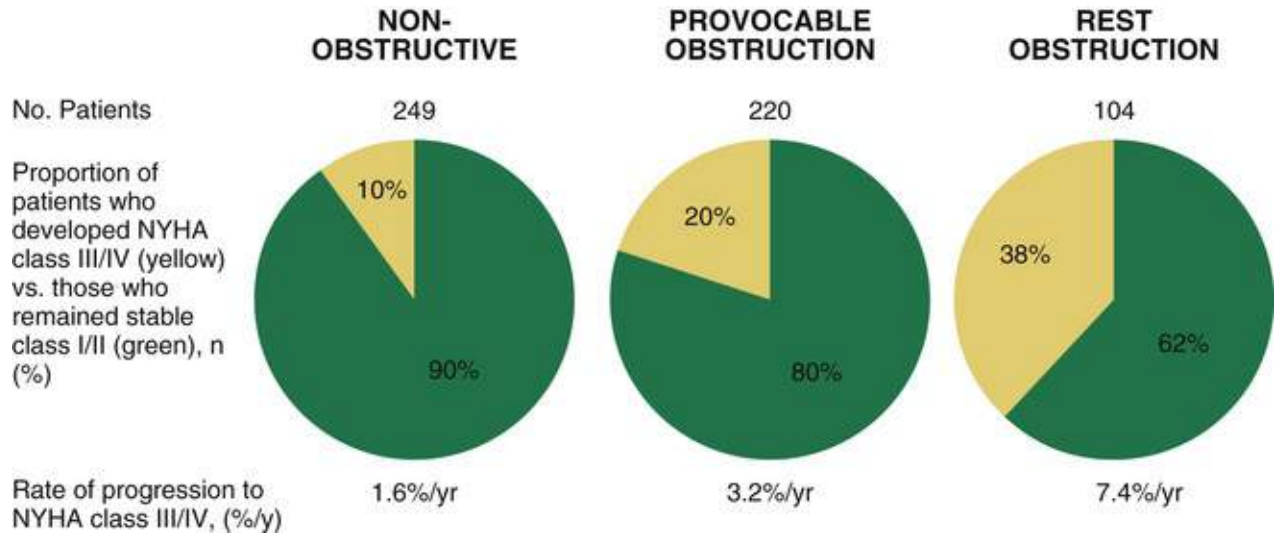


FIGURE 78.8 Comparative frequency of advanced and progressive heart failure (to NYHA classes III and IV) among the three hemodynamic subgroups. The proportion of patients who develop severe heart failure (and the rate of progression) is much less among nonobstructive patients than in patients with provocable or rest obstruction. (From Maron MS, Rowin EJ, Olivotto I, et al: Contemporary natural history and management of nonobstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2016;67:1399.)

Evidence of impaired LV relaxation and filling, by pulsed and tissue Doppler imaging or strain

techniques, is present in most HCM patients, probably contributing to symptoms of exertional dyspnea, although unrelated to the severity of LV hypertrophy.[1-3,44] In particular, diastolic dysfunction (**see also Chapter 26**) is the likely cause of limiting symptoms in patients with nonobstructive disease; it represents the mechanism by which progressive heart failure develops in the presence of preserved LV systolic function, which is occasionally refractory to medical management and ultimately requires heart transplant.[19,45] The most commonly observed pattern is delayed relaxation, characterized by a prolonged rapid filling phase associated with a decreased rate and volume of LV filling and (in sinus rhythm) a compensatory increase in the contribution of atrial systole to overall filling.

Reduced ventricular compliance in HCM probably results largely from those factors determining the passive elastic properties of the LV chamber, such as hypertrophy, replacement scarring, interstitial fibrosis, abnormal microvascular blood flow, and disorganized cellular architecture. Furthermore, abnormal energetic handling and diastolic calcium overload, occurring possibly as a result of abnormalities in the late sodium current, have been shown to contribute to diastolic dysfunction,[8] Unfortunately, few echocardiographic measurements of diastolic dysfunction available in clinical practice reliably predict the prognosis, symptoms, or filling pressures in the individual HCM patient, with the possible exceptions of reduced mitral annulus E′ velocity on tissue Doppler imaging[44] and restrictive filling patterns.[46]

Microvascular Dysfunction

Myocardial ischemia due to microvascular dysfunction appears to be an important pathophysiologic component of the HCM disease process, promoting adverse LV remodeling and ultimately affecting the clinical course.[47] Positron emission tomography (PET) is the technique most useful in the assessment of microvascular function, although it has not penetrated into routine clinical cardiovascular practice. A marked reduction in coronary reserve demonstrated with PET early in the clinical course has been reported to be a determinant of the prognosis.

Clinical Features

Physical Examination

In HCM, findings on physical examination (**see also Chapter 10**) vary related largely to the hemodynamic state. Patients with LV outflow obstruction characteristically have a medium-pitch systolic ejection murmur at the lower left sternal border and apex that varies in intensity with the magnitude of the subaortic gradient; it increases with the Valsalva maneuver, during or immediately after exercise, or on standing. Such variability, together with the characteristic lack of radiation of the murmur to the neck, aids in differentiating dynamic subaortic obstruction from fixed aortic stenosis. Most HCM patients with loud murmurs of at least grade 3/6 are likely to have LV outflow gradients of more than 30 mm Hg; arterial pulses may rise rapidly with the bisferiens pulse contour.

Initial clinical suspicion of HCM may occur with recognition of a heart murmur on routine or preparticipation sports examinations, although most patients are identified by virtue of symptom onset or cardiac events. Physical findings in patients without subaortic gradients are more subtle, with only a soft systolic murmur or no murmur at all, although a forceful apical systolic thrust may raise the suspicion of HCM.

Symptoms

Symptoms of heart failure may develop at any age, with functional limitation predominantly resulting from exertional dyspnea and fatigue; orthopnea or paroxysmal nocturnal dyspnea occasionally occurs in advanced stages. Such disability can be exacerbated by large meals or ingestion of alcohol and is frequently accompanied by chest pain, either typical or atypical of angina, possibly related to structural microvasculature abnormalities. Patients may also experience impaired consciousness with syncope or near-syncope and light-headedness explained by arrhythmias or outflow obstruction. Palpitations are common and may be linked to a variety of tachyarrhythmias, most frequently supraventricular, including AF and, less commonly, ventricular ectopy. The nature of symptoms in HCM is usually similar in patients with or without outflow obstruction.[1-4,19]

Electrocardiographic Findings

In HCM, the 12-lead ECG pattern (**see also Chapter 12**) is abnormal in about 90% of probands and in about 75% of asymptomatic relatives.[1-4] ECGs show a wide variety of abnormal patterns, some of which are distinctly abnormal or even bizarre, but none are pathognomonic of the disease or can be used alone to predict the outcome. The most common abnormalities include increased voltages consistent with LV hypertrophy, ST-T changes (including marked T-wave inversion in the lateral precordial leads), left atrial enlargement, deep and narrow Q waves, and diminished R waves in the lateral precordial leads.

Normal ECG patterns are more commonly associated with mild LV hypertrophy and a favorable clinical course, but do not exclude the possibility of future SD events. Increased voltages (tall R waves or deep S waves) are only weakly correlated with the magnitude of LV hypertrophy and do not reliably distinguish obstructive from nonobstructive HCM.

Cardiac Imaging

Cardiac imaging of HCM by two-dimensional echocardiography is discussed in **Chapter 14** and cardiac magnetic resonance imaging in **Chapter 17**.

Family Screening Strategies.
Clinical screening of relatives in HCM families is performed with two-dimensional echocardiography, CMR, and 12-lead electrocardiography, in addition to history taking and physical examination (**Table 78.1**). Clinical screening evaluations are usually performed on a 12- to 18-month basis, beginning at the age of about 12 years. If these studies do not show the HCM phenotype by the time full growth is achieved (18 to 21 years), it is more likely that a mutation that might cause HCM is absent. Morphologic conversion to LV hypertrophy can be delayed well into adulthood, however, and therefore it is not possible to provide reassurance that a normal echocardiogram at maturity unequivocally defines an unaffected genetic status. In such clinical circumstances, it may be prudent to selectively extend echocardiographic surveillance into adulthood at 5-year intervals or, alternatively, pursue genetic testing.[1-4]

TABLE 78.1

Proposed Clinical Family Screening Strategies With Echocardiography or Cardiovascular Magnetic Resonance (and 12-Lead Electrocardiography) for Detection of HCM with Left Ventricular Hypertrophy*

Age < 12 years
Optional unless:
Malignant family history of premature death from HCM, or other adverse complications
Competitive athlete in an intense training program
Onset of symptoms
Other clinical suspicion of early left ventricular hypertrophy
Age 12 to 21 years†
Every 12 to 18 months
Age > 21 years
Imaging at onset of symptoms, or possibly at 5-year intervals at least through midlife; more frequent intervals for imaging are appropriate in families with malignant clinical course or history of late-onset HCM

*In family members who had not undergone genetic testing, or in whom testing was unresolved or indeterminant.

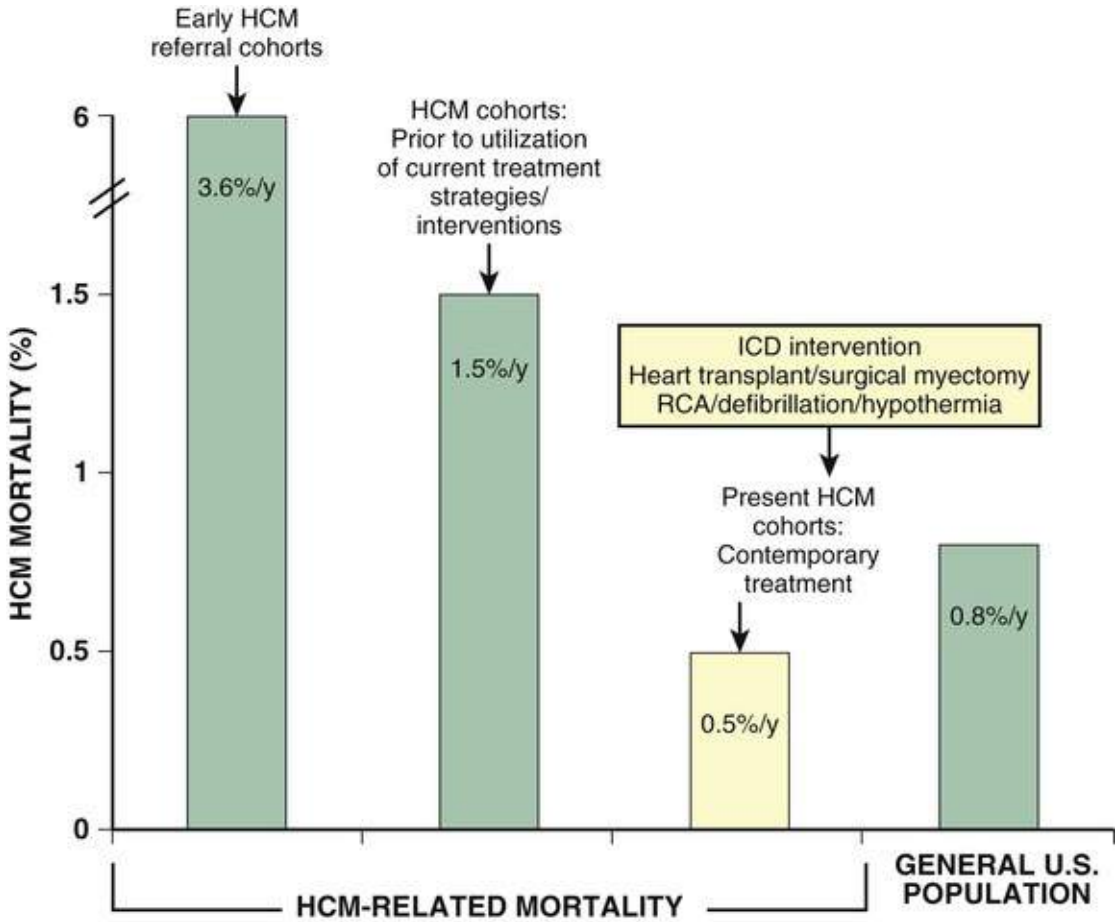
†Age range takes into consideration individual variability in achieving physical maturity, and in some patients screening may be justified at an earlier age; initial evaluation should be performed no later than early pubescence.

From Maron BJ, Maron MS, Semsarian C: Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. J Am Coll Cardiol 60:705, 2012.

Clinical Course

Natural History

HCM is perhaps unique among cardiovascular diseases in having the potential for clinical presentation during all phases of life, from infancy to old age.[1-4,17-22] Affected patients at either extreme of this age range appear to have the same basic disease process, although not necessarily the same clinical course. During the last decade, greater clarity has emerged regarding the natural history and clinical course of HCM. For example, cohort studies now report overall HCM-related mortality rates of less than 1% per year with the use of contemporary treatment options (**eFig. 78.1**), contrasting sharply with the older HCM literature. The now obsolete annual mortality rates of 4% to 6% were derived from highly selected cohorts at tertiary centers incorporating substantial patient referral bias skewed toward high-risk patients, and were reported in the era before implanted cardioverter-defibrillators (ICDs), surgical myectomy, and transplants for HCM were available to many patients.



EFIGURE 78.1 Historical 50-year reduction in HCM-related mortality rates. With contemporary management strategies, a mortality rate of 0.5% per year now is achievable, in contrast to data from older eras. *ICD*, implantable cardioverter-defibrillator; *OHCA*, out-of-hospital cardiac arrest. (From Maron BJ, Rowin EJ, Casey SA, et al: Hypertrophic cardiomyopathy associated with low cardiovascular mortality with contemporary management strategies. J Am Coll Cardiol 65:1915, 2015.)

In most patients, HCM is compatible with a normal life expectancy and a good quality of life with little or no disability; major therapeutic interventions are not necessary to achieve that outcome.* Indeed, not uncommonly, adults with HCM survive into their 70s, 80s, and even 90s, often with no or mild symptoms,[48-50] achieving longevity rates statistically similar to those of an age- and sex-matched general U.S. population. This recognition underscores the important principle that most HCM patients deserve a large measure of reassurance regarding their prognosis.[1,2,4,19-22]

Specific subgroups also exist within the expansive HCM population who are at higher risk for important disease complications and premature death. Such patients may proceed along specific adverse pathways (**Figs. 78.9 and 78.10**), punctuated by clinical events that alter their natural history and ultimately dictate targeted treatment strategies: (1) sudden and unexpected death; (2) progressive heart failure with exertional dyspnea and functional limitation (with or without obstruction); and (3) repetitive, persistent, permanent AF, with the risk for embolic stroke. Among these major disease end-points, which are treatable with contemporary interventions (e.g., ICDs, septal myectomy, heart transplant, and defibrillation), progressive heart failure now predominates; arrhythmic SD events are the least common. Approximately 40% of patients referred to tertiary HCM centers will experience one of these end-points, although the risk of incurring two of these complications in any single patient is uncommon (<10%).

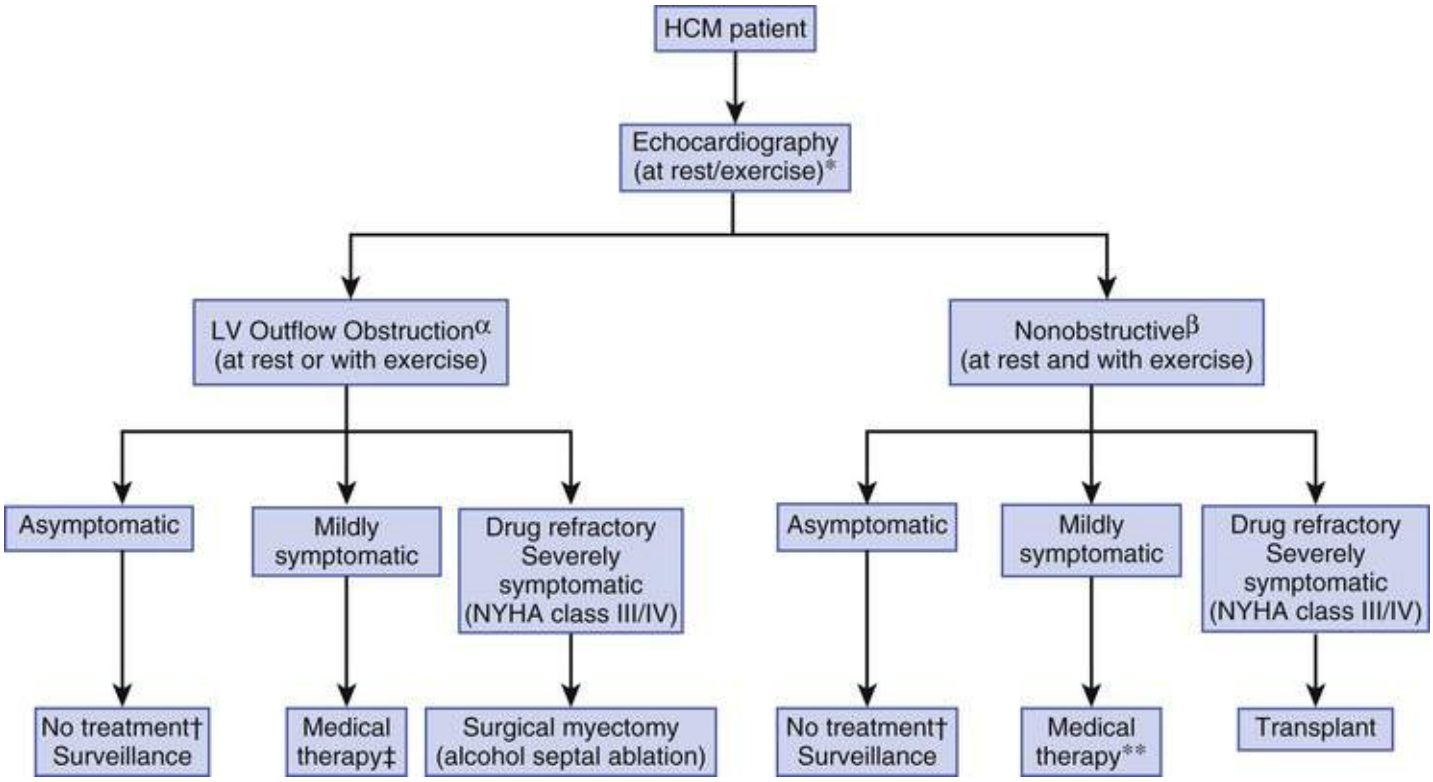


FIGURE 78.9 Heart failure management strategies starting with echocardiography. *Patients without LV outflow tract gradient (<30 mm Hg) at rest should undergo stress (exercise) echocardiography. †No data on benefit of pharmacologic therapy, although beta blockers are often administered prophylactically in clinical practice. **Beta blockers, calcium channel antagonists, and possibly diuretics administered judiciously. ‡Usually, beta blockers or calcium channel antagonists (verapamil), or disopyramide. α, generally regarded, by definition, as ≥ 30 mm Hg outflow gradient, but ≥ 50 mm Hg when septal reduction intervention is considered (i.e., septal myectomy; alcohol ablation), β, no or trivial (< 30 mm Hg) outflow gradient at rest and with exercise. (From Maron BJ, Ommen SR, Semsarian C, et al: State-of the Art Review: hypertrophic cardiomyopathy: present and future, with translation into contemporary cardiovascular medicine. J Am Coll Cardiol 2014;64:83.)

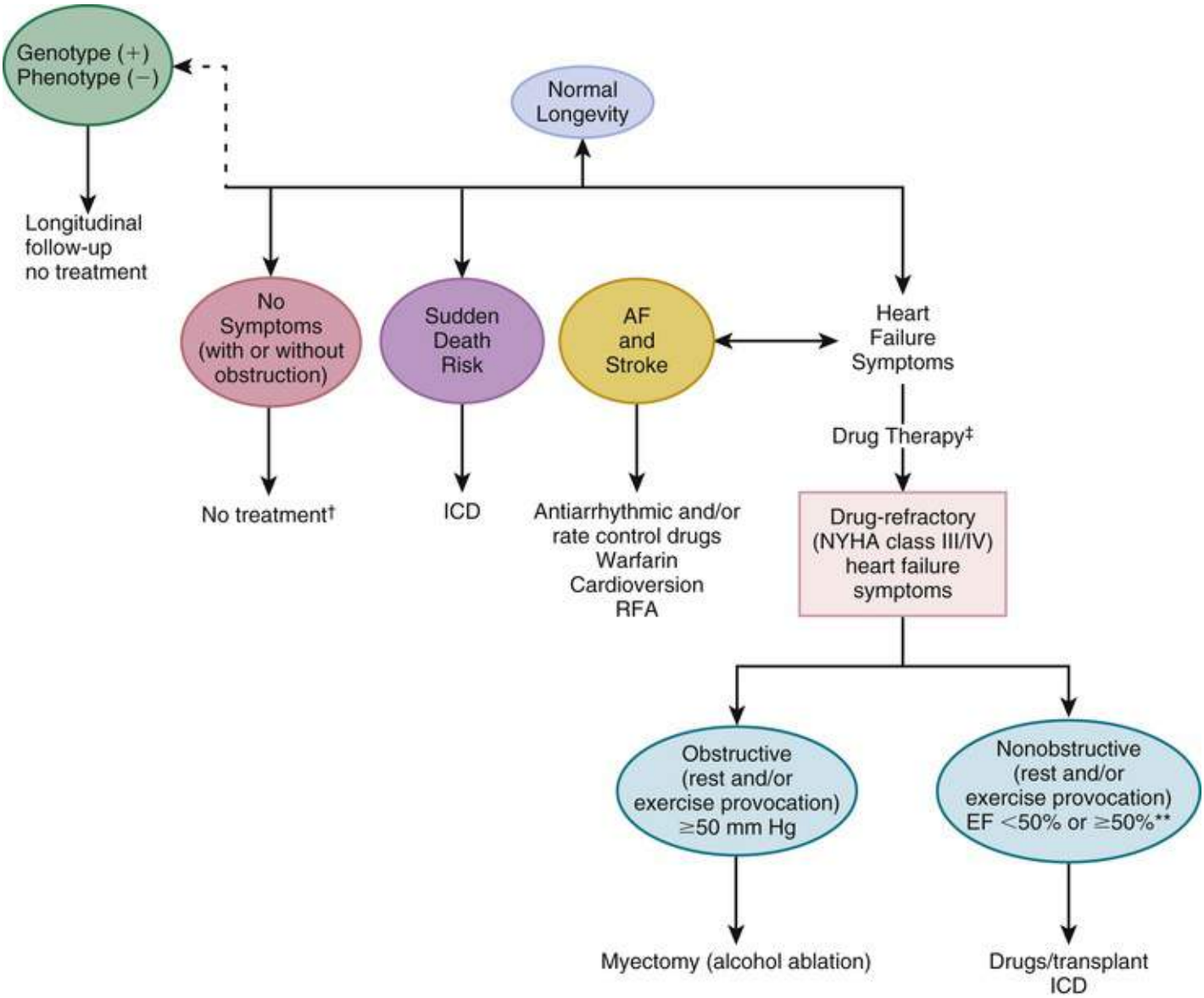


FIGURE 78.10 Prognostic pathways and treatment strategies for HCM. The majority of HCM patients probably experience a benign and stable clinical course without the need for major treatment interventions. Adverse pathways (i.e., sudden death, heart failure, and atrial fibrillation) are not necessarily mutually exclusive, because patients may progress along more than one. NYHA, New York Heart Association. Patients identified as genotype-positive, phenotype-negative may or may not develop morphologic conversion to LV hypertrophy during adolescence. †No data are available on benefit of drug treatment for asymptomatic patients, although in clinical practice, β-blockers or calcium channel blockers are sometimes administered prophylactically. ‡Usually, β-blockers and calcium channel blockers, occasionally disopyramide, and possibly diuretics (administered judiciously). **Patients in this subgroup are eligible for heart transplant with ejection fraction of < 50% or ≥ 50%. (From Maron BJ, Maron MS: Hypertrophic cardiomyopathy. Lancet 2013;381:242.)

Heart Failure

Some element of heart failure (**see also Chapters 25 and 26**) with exertional dyspnea is common in HCM, with the principal determinants of progressive heart failure attributable to LV outflow obstruction; diastolic dysfunction in the absence of obstruction is less often the primary mechanism (**see Fig. 78.9**).[1-3,18,19,21,22]

About 2% to 3% of HCM patients at referral centers develop advanced (end-stage) heart failure, usually associated with systolic LV dysfunction (ejection fraction < 50%), a consequence of small-vessel–mediated myocardial ischemia and diffuse transmural scarring (**eFig. 78.2 and see Fig. 78.2**).[2,4,54-

[57] The most reliable risk marker for evolution to end-stage disease appears to be a family history of HCM with systolic dysfunction. This profound expression of heart failure is associated with adverse LV remodeling, often resulting in LV wall thinning or chamber enlargement, or both. It usually leads to progressive heart failure over several years and requires heart transplant at a relatively young age (43 ± 13 years), and earlier than in other non-HCM patients. A potential premonitory end-stage phase has been identified in some patients with nonobstructive HCM and a low to normal ejection fraction (i.e., 50% to 60%) associated with substantial LGE (**Figs. 78.10 and 78.11 and eFig. 78.2**).[39] HCM end-stage disease has a variable genetic substrate not consistently related to any specific disease-causing gene or mutation; it is indistinguishable from end-stage disease with a preserved ejection fraction except for a higher frequency of multiple sarcomere mutations.[45]

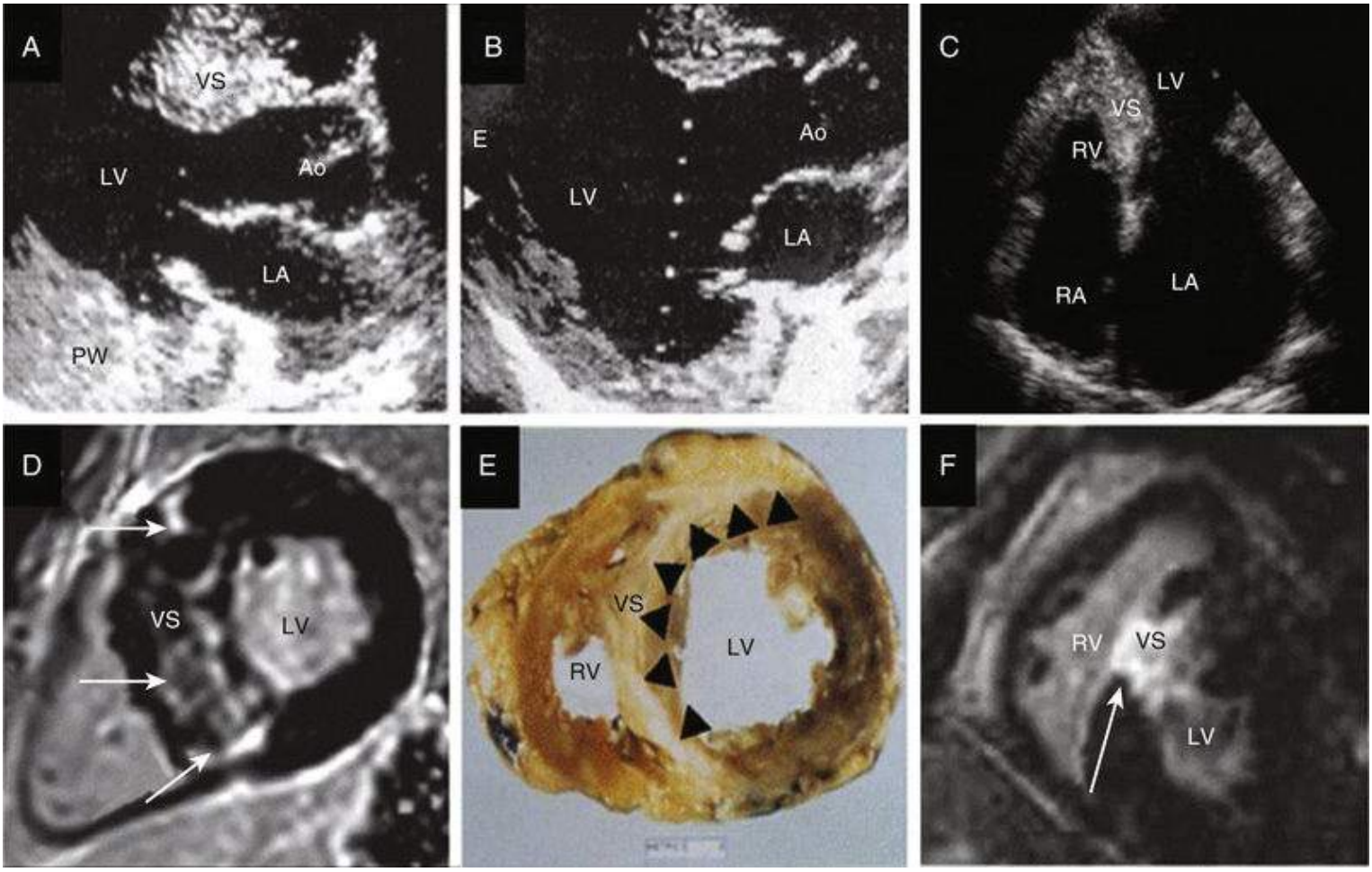
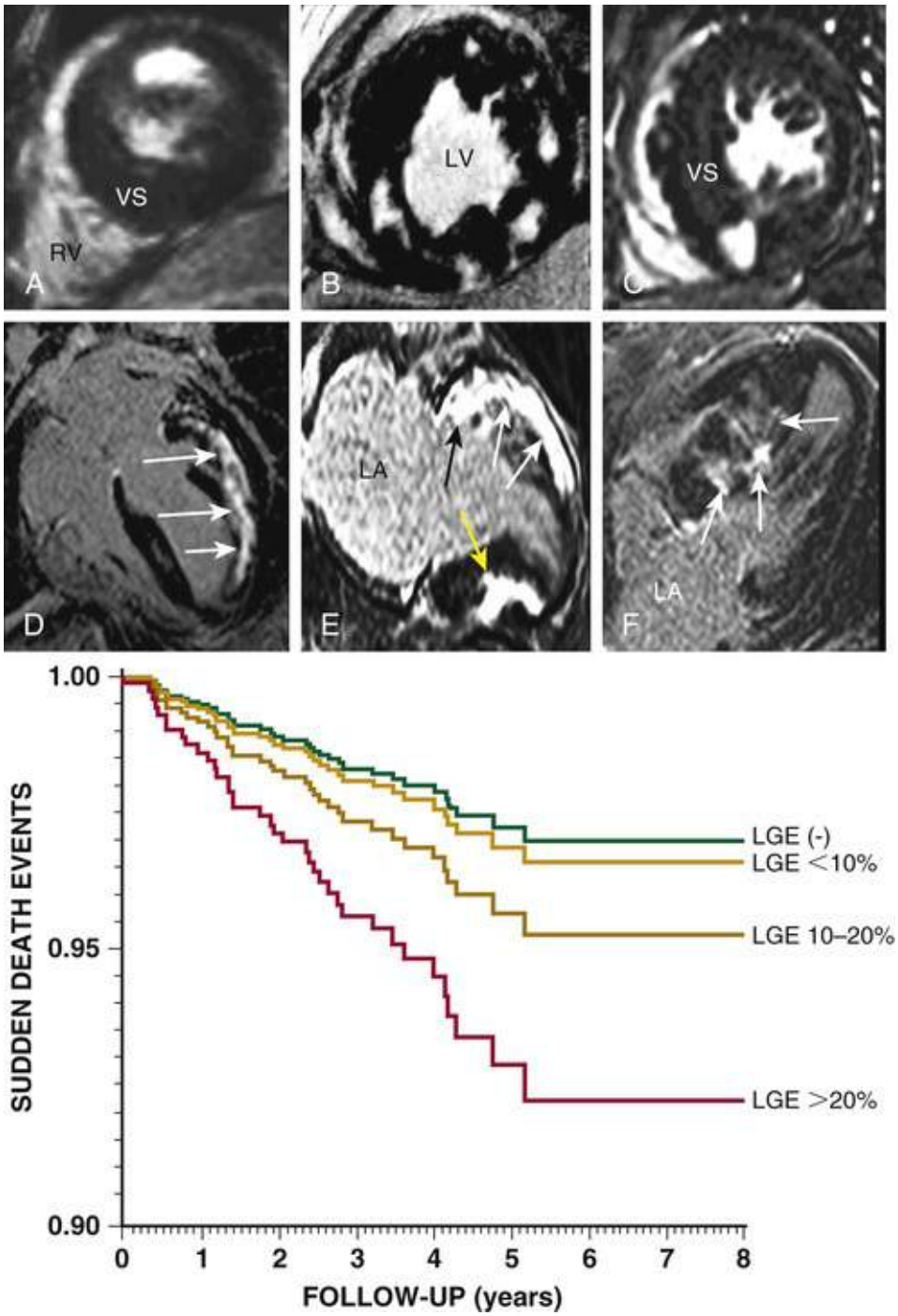


FIGURE 78.11 Myocardial scarring and outcome in HCM. **A** to **C,** End-stage HCM. **A,** Parasternal long-axis echocardiographic image in 37-year-old man showing hypertrophied ventricular septum and left ventricular posterior wall, reduced cavity size, and normal ejection fraction. **B,** Same patient shown with later conversion to end-stage disease and systolic dysfunction with remodeling in the form of septal and free wall thinning, and left ventricular cavity enlargement. **C,** Restrictive form with biatrial enlargement, small ventricular cavities, and normal ejection fraction, often associated with myocardial scarring. **D,** Contrast-enhanced MRI in a high-risk 32-year-old man, showing transmural ventricular septal LGE occupying more than 15% of LV mass (*arrows*) associated with multiple bursts of nonsustained ventricular tachycardia on ambulatory (Holter) ECG. **E,** "End-stage" heart showing extensive, transmural scarring involving septum and extending into anterior wall (*arrowheads*). **F,** Large transmural ventricular septal scar (*arrowheads*) produced by alcohol septal ablation procedure. *Ao*, aorta; *LA*, left atrium; *LV*, left ventricle; *PW*, posterior wall; *RV*, right ventricle; *VS*, ventricular septum. (**A, B,** and **D** from Maron BJ, Maron MS: Hypertrophic cardiomyopathy. Lancet 2013;381:242. **F** from Valeti US, Nishimura RA, Holmes DR et al: Comparison of surgical septal myectomy and alcohol septal ablation with cardiac magnetic resonance imaging in patients with hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol 2007;49:350.)



EFIGURE 78.2 **Top panel:** Pattern of late gadolinium enhancement (LGE) with contrast CMR showing in *white areas* diverse distribution from focal **(A** and **C)** to diffuse **(B, D, E, F)**. **Bottom panel:** Relation of magnitude of LGE (percentage of LV mass) to survival with HCM. More extensive LGE is associated with higher sudden death event rates. (From Chan RH, Maron BJ, Olivotto I, et al: Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation 130:484, 2014.)

Epidemiology of Sudden Death; Risk Stratification Strategies

Sudden death (**see also Chapter 42**) events in HCM may occur at a wide range of ages, most commonly in adolescents and adults younger than 30 years of age, but also not infrequently in midlife (**see Figs. 78.10 and 78.11 and eFig. 78.2**).[20,22] The underlying electrical substrate is unpredictably unstable, and SD may be the initial clinical manifestation of the disease unidentified in asymptomatic (or mildly symptomatic) patients.[1-4] Although the risk for SD can extend into midlife, it is significantly less common in patients 60 years of age or older, suggesting that in a genetic disease such as HCM, the potential for

lethal ventricular tachyarrhythmias is mitigated at the more advanced ages (even in the presence of conventional risk markers), as if at some point the disease declares itself to be largely free of adverse clinical events (**Fig. 78.12**).[50] Indeed, about 75% of deaths in HCM patients are unrelated to HCM, particularly in older patients.[49]

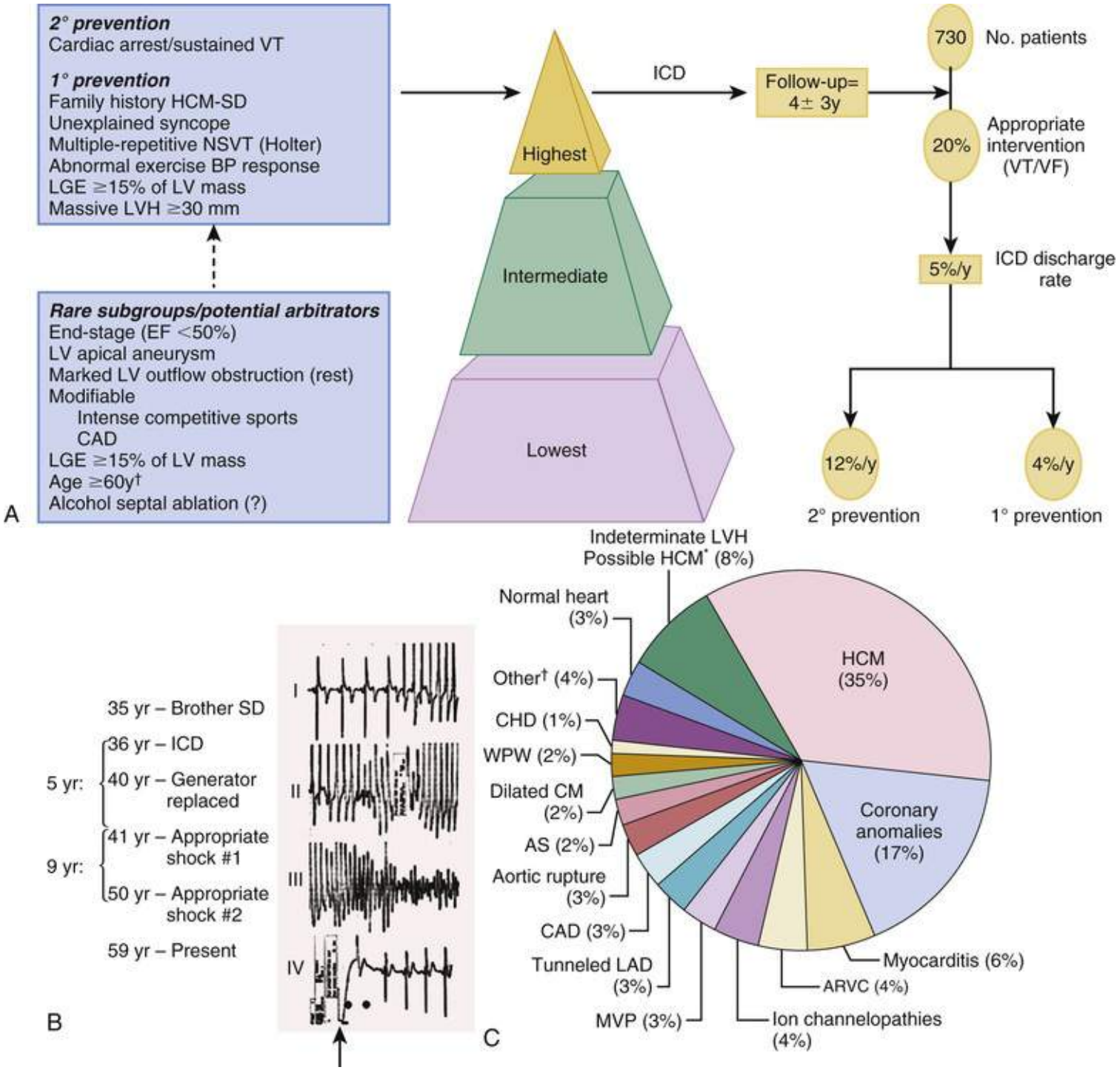


FIGURE 78.12 Prevention of sudden death. **A,** Flow-diagram summarizing HCM risk markers (to left) and ICD-related outcome in 730 high-risk children and adults from the HCM international and multicenter ICD registry studies (to right). **B,** Intracardiac electrogram obtained at 1 : 20 AM (while asleep) 5 years after implant from a 35-year-old man with HCM who received a prophylactic ICD because of a family history of SD and marked ventricular septal thickness (31 mm). Tracing I: Ventricular tachycardia (VT) at 200 bpm begins abruptly; II: Defibrillator senses VT and charges; III: VT deteriorates to ventricular fibrillation (VF); IV: Defibrillator issues a 20-J shock (*arrow*), restoring sinus rhythm. A virtually identical sequence occurred 9 years later during sleep; this patient is now 56 years old and asymptomatic. **C,** HCM is the single most common cause of sudden death in young competitive athletes in the United States, although several other largely genetic heart diseases also account for many of these events. ARVC, arrhythmogenic right ventricular cardiomyopathy; AS, aortic valve stenosis; CAD, coronary artery disease; CHD, congenital heart disease; CM, cardiomyopathy; LAD, left anterior descending; LVH, left ventricular hypertrophy; MVP, mitral valve prolapse; WPW, Wolff-Parkinson-White syndrome. *Regarded as possible (but not definitive) evidence for HCM at autopsy with mildly increased LV wall thicknesses (18 ± 4 mm) and heart weight (447 ± 76 g). (**B** from Maron BJ, Spirito P, Shen W-K, et al: Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA 298:405, 2007. **C** from Maron BJ. Historical perspectives on sudden death in young athletes with evolution over 35 years. Am J Cardiol 116:1461, 2015.)

Whereas most SDs occur during sedentary or modest physical activities, such events are not uncommonly associated with vigorous exertion; this is consistent with the long-standing observation that HCM is the most common cardiovascular cause of SD in competitive athletes, including high school, college, and postgraduate participants (**see Fig. 78.12**).[12,13] This association of HCM with exercise-related SD is the basis for the prudent recommendations by the 36th Bethesda Conference (and subsequently by AHA/ACC guidelines) to disqualify young athletes with HCM from intense competitive sports to reduce risk.[11]

Among the broad HCM population, the greatest SD risk is associated with specific clinical markers (**see Fig. 78.12**):

Secondary Prevention: Patients who have had a prior cardiac arrest and have sustained ventricular tachycardia (VT) must have an ICD implanted for secondary prevention.

Primary Prevention: Patients with one or more of the following markers are candidates for primary prevention (the markers assume greater weight in patients younger than 50 years of age) for whom an ICD can be considered):* (1) a family history of one or more premature HCM-related deaths, particularly if the death was sudden or occurred in close relatives; (2) unexplained syncope, especially if it was recent and in a young patient; (3) a hypotensive or attenuated blood pressure response to exercise; (4) multiple, repetitive (or prolonged), nonsustained bursts of VT on serial ambulatory ECGs; (5) massive LV hypertrophy (wall thickness ≥ 30 mm Hg) (**see Fig. 78.2**), as well as LV apical aneurysms (**Table 78.2**). The risk for SD is unrelated to the pattern or location of the LV hypertrophy. In contrast to the risk for SD, greater LV wall thickness is not associated with an increased likelihood of progressive heart failure symptoms.

TABLE 78.2

Risk Factors for Sudden Death in Hypertrophic Cardiomyopathy

Secondary Prevention
Cardiac arrest or sustained VT
Conventional Primary Prevention Risk Markers
Family history of sudden death due to HCM
Unexplained recent syncope
Multiple or repetitive nonsustained VT (on ambulatory ECG)
Hypotensive or attenuated blood pressure response to exercise
Massive LV hypertrophy (wall thickness ≥ 30 mm*)
Extensive or diffuse late gadolinium enhancement (contrast-enhanced CMR)
Potential High-Risk Subsets for Primary Prevention
End-stage phase (ejection fraction < 50%)
LV apical aneurysm with scarring
Potential Arbitrators for Primary Prevention†
Substantial LV outflow gradient at rest
Extensive or diffuse late gadolinium enhancement
Transmural scar associated with alcohol septal ablation
Multiple sarcomere mutations
Modifiable
Intense competitive sports
Atherosclerotic coronary artery disease

*Or the equivalent in children according to body size.

†To arbitrate decision making regarding prophylactic implantable defibrillators in patients for whom risk level remains ambiguous after assessment by the conventional risk factor algorithm.

CMR, cardiovascular magnetic resonance; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; LV, left ventricular; VT, ventricular tachycardia.

From Maron BJ, Maron MS: Hypertrophic cardiomyopathy. Lancet 381:242, 2013.

The presence of one or more major risk factors in the individual patient's clinical profile justifies consideration for primary prevention with an ICD, particularly when a family history of SD, unexplained syncope, or massive LV hypertrophy is present (these are also the most reliable markers for assessing the risk in children with HCM). This current risk stratification strategy for HCM, based on United States/Canada (ACC/AHA) guidelines, expert consensus panels and other data and experience, reliably identifies most high-risk patients and has been shown to be largely responsible for a reduction in HCM-related mortality rates to 0.5% per year (**see eFig. 78.1**).[18-22] Resolving complex risk assessment dilemmas involving primary SD prevention therapy may require a shared decision-making strategy that takes into account the desires of a fully informed patient and the experience and judgment of the individual clinician.

This risk algorithm is incomplete, however, and a minority of patients without any of the conventional primary prevention risk factors remain susceptible to SD.[58] In this regard, extensive LGE on contrast-enhanced CMR (particularly when it is present in 15% or more of the LV mass) has been shown to be associated with an increased SD risk; it is a new marker and independent predictor of SD, even in the absence of conventional risk factors, and its presence would lead to consideration of a prophylactic ICD (**see Table 78.2 and Fig. 78.12**).[37] Therefore, extensive LGE expands the risk stratification algorithm to incorporate patients not otherwise considered at an unacceptably high risk, and also is a marker for progression to the end-stage phase with systolic dysfunction (**see Figs. 78.2 and 78.11**). Absent or focal LGE denotes a lower risk, as does LGE localized to the junctional areas of RV attachment to the septum.

In 2014, the European Society of Cardiology proposed a novel mathematical/statistical risk score model[3] to identify patients who may benefit from ICD therapy or who do not require primary prevention implants.[59] Determination of the precise role for this scoring strategy in the clinical arena is ongoing.[60]

A number of other disease features can be regarded as potential arbitrators for prophylactic ICD decisions in individual patients when the level of risk is judged to be ambiguous based on conventional markers (**see Table 78.2**). These include subgroups within the heterogeneous HCM disease spectrum (i.e., thin-walled akinetic LV apical aneurysms with regional myocardial scarring often associated with midcavity muscular obstruction (**see Fig. 78.2**),[61] extensive LGE of 15% or more of the LV mass on CMR, coexistent obstructive atherosclerotic coronary artery disease, marked LV outflow obstruction at rest, evolution to systolic dysfunction (**see Figs. 78.2 and 78.11**), and transmural infarction from percutaneous alcohol septal ablation (**see Fig. 78.11**).[62-67]

There is no compelling evidence that particular ECG patterns, T-wave alternans, or myocardial bridging of the left anterior descending coronary artery (although more frequent in HCM than the general population) predict SD risk in HCM.[68] Furthermore, the prognosis appears benign in gene carriers without LV hypertrophy, and there is little evidence to justify disqualification of such individuals from most competitive sports or employment opportunities.[11]

Management

Prevention of Sudden Death

The ICD has altered the natural history of HCM for many patients by virtue of effectively and reliably aborting potentially lethal ventricular tachyarrhythmias, both for secondary prevention after cardiac arrest (12% per year) and primary prevention (4% per year), based on risk factor analysis (**see Fig. 78.12**).* Defibrillator intervention rates are similar in children, adolescents, and adults with HCM. Appropriate ICD interventions in high-risk patients occur with similar frequency in those implanted for one, two, three, or more risk factors (patients with one risk factor account for 35% of ICD interventions).[18,20,21,69] The timing of these ICD events shows a measure of unpredictability, as evidenced by the absence of a distinctive circadian pattern, the extended periods of time that can elapse between the clinical decision to implant an ICD and the time at which the device is required to intervene and terminate ventricular tachyarrhythmias, and the infrequency of recurrence following cardiac arrest. Notably, after an appropriate ICD intervention, progression of heart failure symptoms rarely occurs, different from the clinical circumstances in ischemic heart disease after ICD shocks. Older patients (≥ 60 years) are less often considered for primary prevention devices, given that HCM-related SD is uncommon in this age-group (**see Fig. 78.12**).[50] Decisions regarding prophylactic implantable defibrillators must also take into account the not inconsequential risk of transvenous ICD-related complications (5% per year)[70,71] and psychosocial consequences of long-term device therapy, particularly in children and adolescents. Subcutaneous ICDs could be an attractive alternative for young HCM patients to avoid the potentially deleterious impact of chronically implanted transvenous leads on the vascular system.[72] However, uncertainty persists with regard to SD prevention, given the limited experience with spontaneous VT termination outside the laboratory setting and the absence of antitachycardia pacing capability with these devices.

Pharmacologic treatment with amiodarone or other antiarrhythmic drugs for primary prevention of SD in high-risk patients is an obsolete strategy; it lacks the proven efficacy of the ICD, and there is a likelihood of important side effects occurring during the long risk period typically experienced by young

HCM patients.[20] Recurrent ventricular tachyarrhythmias triggering the ICD are uncommon in HCM; radiofrequency ablation is an unproven treatment strategy due to a diffusely abnormal substrate, with the exception of patients with LV apical aneurysms in whom an arrhythmic focus can be abolished.[61]

Treatment of Heart Failure

Drugs

Limiting symptoms of heart failure (i.e., exertional dyspnea with or without chest pain) is attributable to diastolic dysfunction, outflow tract obstruction, mitral regurgitation, microvascular ischemia, or any combination of these pathophysiologic variables (**see Fig. 78.9**).[1,2] Symptom relief with medical treatment can be highly variable, and drug administration is often empirically tailored to requirements of individual patients. Since the mid-1960s, beta-adrenergic receptor blocking drugs have been used extensively to relieve symptoms of heart failure in HCM by slowing the heart rate, thereby decreasing myocardial oxygen consumption and augmenting ventricular filling, as well as mitigating exercise-induced outflow gradients by reducing the force of the LV contraction.

Verapamil has the potential to improve symptoms and exercise capacity, largely in patients without obstruction to LV outflow. This is likely because it can provide heart rate control and improved ventricular relaxation and filling, and it serves as a potential treatment for chest pain by increasing the myocardial blood flow.[1,2] Although beta blockers are usually the first drug option, there is no evidence that combining beta blockers and verapamil is advantageous; also, together these drugs may lower the heart rate and/or blood pressure excessively.

Disopyramide is a third option (in combination with an AV nodal blocking agent) to ameliorate gradient and symptoms in patients with outflow obstruction when other drugs fail to control symptoms, although its use can be limited by parasympathetic side effects.[73] Diuretic agents, administered judiciously and used predominantly in patients with nonobstructive disease, can relieve pulmonary congestion and LV filling pressures. Novel agents currently under investigation to mitigate symptoms in HCM include small-molecule, allosteric myosin inhibitors.[5]

Medical therapeutic strategies for patients with systolic dysfunction and advanced heart failure are similar to those for congestive heart failure in non-HCM cardiac diseases, including the administration of beta blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), and diuretics, or spironolactone (**see Fig. 78.9**). The role of biventricular pacing for treatment of heart failure in end-stage HCM remains uncertain. HCM patients may also have severe refractory heart failure with preserved systolic function, an absence of extensive scarring, residual marked LV hypertrophy, and nondilated ventricular chambers.

End-stage HCM, with or without systolic dysfunction, and with severely limiting heart failure symptoms is virtually the sole indication for heart transplant in HCM.[1-4] Survival rates after transplant in HCM are similar to (or possibly more favorable) than those in other cardiac diseases (75% at 5 years; 60% at 10 years).[56]

Surgical Myectomy

Heart failure caused by LV outflow obstruction is reversible by septal reduction (i.e., myectomy or selective alcohol septal ablation). On the basis of extensive worldwide experience spanning over 50 years, and substantiated in guidelines and expert consensus panel recommendations from all major international cardiovascular societies, septal myectomy has been judged the preferred and primary

management option for disabled patients with severe drug-refractory symptoms (i.e., NYHA functional class III or IV disease [or the equivalent in children] due to obstruction to LV outflow under basal conditions or with physiologic exercise [i.e., gradient ≥ 50 mm Hg]) (**see Fig. 78.9**).[1-4,23,74-80]

Transaortic ventricular septal myectomy (Morrow procedure) involves resecting a small portion of muscle (usually 3 to 10 g) from the basal septum. Many surgeons now perform a more aggressive myectomy with muscular resection extending more distally within the septum to the base of the papillary muscles, and reorienting abnormally displaced papillary muscles judged as contributing to obstruction. Cutting of mitral valve chordae (in association with a shallow septal resection) has been advanced for patients with mild septal hypertrophy to effectively achieve gradient relief.[77] Of note, the expected operative mortality rate has decreased steadily and is now less than 1% at experienced HCM centers, making myectomy potentially the safest open heart procedure.[75,78]

The primary objective of surgical myectomy is reduction in heart failure symptoms and improvement in the quality of life, by virtue of relieving the outflow obstruction (and SAM) and associated mitral regurgitation, resulting in normalization of the LV pressures (**see Fig. 78.7**). Indeed, long-term follow-up studies report that 90% to 95% of patients undergoing myectomy experience both permanent abolition of the basal outflow gradient, without compromise in global LV function, and relief of symptoms over periods of up to 25 years, substantiating the likelihood of reversing heart failure due to outflow obstruction in HCM.[2,74,76,78]

In addition to substantial improvement in the quality of life, there is evidence from nonrandomized studies that myectomy is associated with extended survival rates equivalent to those expected in the age- and sex-matched general population and superior to those of nonoperated patients with outflow obstruction, including also a possible reduction in SD rate.[74] Surgical myectomy is not recommended for asymptomatic (or mildly symptomatic) patients, because conclusive evidence is lacking that prophylactic relief of obstruction is advantageous or necessary, while even the very low operative mortality rate could exceed the risk of the disease for some patients.

Alcohol Septal Ablation

Percutaneous alcohol septal ablation, an alternative to myectomy in selected patients, involves injection of 1 to 3 mL of 95% alcohol into a major septal perforator coronary artery to create necrosis and a permanent transmural myocardial infarction in the proximal ventricular septum.[62-67] The scar, which occupies approximately 10% of the LV wall (≤ 30% of the septum), causes progressive thinning and restricted basal septal excursion, outflow tract enlargement, and, in most patients, a reduced LV outflow tract gradient and mitral regurgitation.[20]

Alcohol ablation substantially improves heart failure symptoms in many patients, although long-term prognostic and efficacy data comparable to surgery are not yet available.[62-67] Nonrandomized data show that gradient and symptom relief after alcohol ablation are similar to myectomy, although less consistent; in patients over 65 years of age, symptom improvement with myectomy may be superior to that with ablation. Approximately 10% to 20% of patients incur high-degree AV block after alcohol ablation requiring permanent pacing or multiple procedures to obtain a satisfactory clinical result. Even in experienced centers, alcohol ablation may be associated with procedural mortality and complication rates similar to those of myectomy.

Remaining incompletely resolved is the important issue of the clinical consequences of the alcohol-induced transmural scar, which represents a potentially unstable electrical substrate and a nidus for lethal ventricular tachyarrhythmias that could raise the risk for SD in susceptible patients. There is evidence to support an increased level of arrhythmogenicity directly attributable to the alcohol-induced transmural

myocardial infarct (**see Fig. 78.11**), exceeding that expected following myectomy. The long-term risk associated with alcohol ablation remains unresolved, because a randomized trial of myectomy versus ablation is not feasible. Decisions regarding prophylactic ICD implants after alcohol ablation are individualized.[20,63-67,75]

All consensus and guideline panels regard alcohol ablation as an alternative treatment strategy for patients with obstructive HCM who are not considered optimal myectomy candidates (e.g., those of particularly advanced age, with significant comorbidities and potentially increased operative risk, or with a strong personal aversion to surgery) (**see Fig. 78.9**). Furthermore, alcohol septal ablation should not be performed in HCM patients with concomitant conditions, including intrinsic mitral valve disease or coronary artery disease necessitating bypass grafting, and should be discouraged in patients with extreme hypertrophy and/or complex abnormalities of the submitral valve apparatus.[4]

Dual-Chamber Pacing

Approximately 25 years ago, permanent dual-chamber pacing was promoted as an alternative to surgical myectomy for obstructive HCM patients with heart failure symptoms.[4] However, the role for pacing in HCM has become exceedingly limited, as several randomized studies demonstrated that the subjectively perceived symptomatic benefit associated with pacing appeared to be largely a placebo effect.

Treatment of Atrial Fibrillation

Symptomatic AF is the most common sustained arrhythmia in HCM, frequently accounting for unexpected hospital admissions, lost productivity, and impaired quality of life.[1-4,14,15,81-91] AF is not associated with increased HCM-related mortality or a promoter of progressive heart failure symptoms. Paroxysmal, persistent, or permanent AF occurs in 20% to 25% of HCM patients, increasing in incidence with age and related to left atrial enlargement and dysfunction. Symptomatic paroxysmal AF can adversely impact the quality of life, with frequent visits to the emergency room for cardioversion. However, the mortality rate specifically attributable to AF with HCM is low (<1% per year) and primarily due to embolic stroke in the absence of anticoagulation. No HCM gene has been linked to AF.[85]

Because of the potential for clot formation and embolization, patients with AF require anticoagulant therapy (**see Fig. 78.10**).[2-4,81,82] Although the vitamin K antagonist warfarin remains widely employed, novel oral anticoagulants are reasonable alternatives in HCM patients. Anticoagulation decisions are tailored to individual patients after consideration of lifestyle modifications, hemorrhagic risk, and expectations for compliance. The CHA_2DS_2-VASc score is neither validated nor relevant to HCM, and the number of episodes necessary to initiate treatment is unresolved, although a low threshold is prudent. Although data specifically in HCM are limited, amiodarone is regarded as the most effective drug in reducing AF recurrences; beta blockers and verapamil are usually administered to control the heart rate in patients with persistent or permanent AF.

In relatively small studies, only partial and short-term success has been achieved in controlling drug-refractory recurrent paroxysmal AF with radiofrequency catheter ablation (pulmonary vein isolation).[83,84,87] Short-term outcome in HCM is 40% of patients experiencing freedom from AF for 1 year. The long-term outcome is largely unresolved, with not inconsequential rates of repeat procedures and arrhythmic recurrences. Patients with a history of AF, undergoing surgical myectomy, should be considered for an adjunctive MAZE procedure.

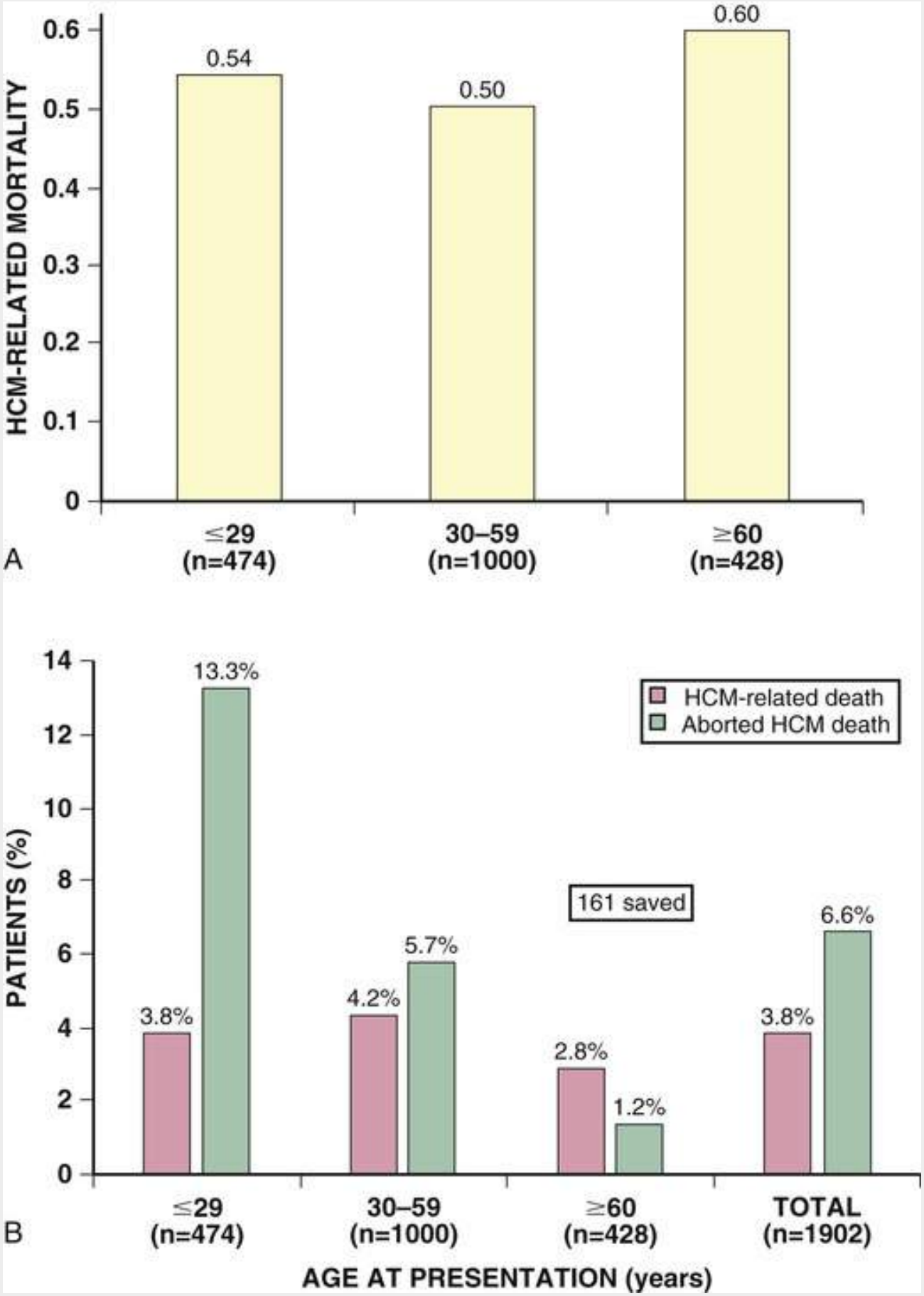
Other Management Issues

There is no evidence that HCM patients are generally at increased risk during pregnancy and delivery. Maternal morbidity and mortality rates appear to be confined to an extremely small subset of symptomatic women with high-risk clinical profiles (e.g., severe heart failure, ventricular tachyarrhythmias, or LV outflow obstruction), who deserve specialized and preventive obstetric care. Otherwise, most women with HCM undergo normal (vaginal) delivery, without a necessity to consider cesarean section.

Bacterial endocarditis is an uncommon but potentially profound complication of HCM (prevalence < 1%), with vegetations most commonly involving the anterior mitral leaflet or septal endocardium at the site of mitral valve contact. Preventive antimicrobial prophylaxis remains a prudent strategy before dental or surgical procedures, particularly for HCM patients with outflow obstruction.[88]

Outcomes; Hypertrophic Cardiomyopathy–Related Mortality Rates.

Over the last 15 years, with the emergence of dedicated HCM centers of excellence,[89] comprehensive HCM-related diagnostic and management strategies have evolved substantially in accordance with the U.S./Canada (ACC/AHA) guidelines.[4] They include an expanded risk stratification algorithm with greater appreciation for at-risk patients. The emergence of contemporary treatment advances has changed the clinical course of the disease for many patients and resulted in a significant reduction in deaths related to HCM in tertiary center cohort analyses.[17-22,90] By virtue of employing contemporary treatment strategies (e.g., ICDs for primary prevention of SD, transplant for refractory heart failure in nonobstructive disease, surgical myectomy to reverse severe heart failure due to LV outflow obstruction, modern defibrillation techniques associated with therapeutic hypothermia), the mortality rates for HCM can be reduced to as low as 0.5% per year, independent of patient age at presentation (**eFig. 78.3 and see eFig. 78.1**). These data redefine the mortality risk and alter the historical perception of HCM as a grim, relentless, progressive disease.[90]



EFIGURE 78.3 **A,** HCM-related mortality rates with contemporary treatment interventions are similar (about 0.5% per year) at all ages of presentation. **B,** Deaths averted by such treatments with a total of 161 lives saved. (From Maron BJ, Rowin EJ, Casey SA, et al: How hypertrophic cardiomyopathy became a contemporary treatable genetic disease with low mortality: shaped by 50-years of clinical research and practice. JAMA Cardiol 1:98, 2016.)

Athlete's Heart

Additional content on athlete's heart and HCM is presented in an online supplement for this chapter entitled Athlete's Heart and Hypertrophic Cardiomyopathy.

Future Perspectives

The last decade has witnessed a greatly increased understanding of the diagnosis, clinical profile, and natural history of HCM, and most notably has produced crucial advances in management. Indeed, HCM has been transformed from a disease with a seemingly unfavorable prognosis to one compatible with normal life expectancy, in which all major complications are associated with a potentially effective treatment option. A list of classic references in the field is presented in the online supplement for this chapter entitled Classic Hypertrophic Cardiomyopathy References.

Nevertheless, future investigative efforts are necessary, including development of even more precise risk stratification strategies to reliably identify all patients at unacceptably high risk for SD deserving of consideration for ICD therapy, but also limiting the number of unnecessary device implants. There will also be continuing efforts to define the proper role of alcohol ablation relative to surgical myectomy in the management of symptomatic patients with outflow obstruction, as well as a more complete understanding regarding the use of commercial genetic testing, the impact of next-generation sequencing, and further clarification of genotype-phenotype relationships.

Finally, as advanced heart failure continues to emerge as an increasingly common complication of HCM, a major unmet need will be more reliable prospective identification of at-risk patients and the development of novel, targeted, disease-specific pharmacologic options to relieve heart failure symptoms, particularly in the absence of outflow obstruction. Active research and clinical trials are ongoing to identify disease-specific drugs targeting HCM pathophysiology.

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Athlete's Heart and Hypertrophic Cardiomyopathy

Intensive and long-term athletic training can increase the LV diastolic cavity dimension, wall thickness, and calculated mass, creating a physiologic entity known as athlete's heart.[1] Such absolute increases in LV wall thickness are usually modest and evident in only some athletes, but can be more common and substantial in elite and highly trained individuals, particularly those participating in rowing and cycling. They are not associated with participation in purely isometric sports such as weightlifting. Diagnostic dilemmas may arise in distinguishing clinically benign and physiologic LV hypertrophy (as a consequence of athletic training) from pathologic conditions such as HCM (**eTable 78.1**).[1] Clinical parameters that favor the diagnosis of HCM in trained athletes in the ambiguous “gray zone” of overlap between the two conditions (when the maximum LV wall thicknesses is 13 to 15 mm) include identification of a disease-causing sarcomeric mutation or recognition of HCM in a relative; finding of a transmitral Doppler waveform consistent with altered LV relaxation and filling; an LV end-diastolic cavity dimension of less than 45 mm, and LGE by CMR. Parameters favoring physiologic athlete's heart include regression of LV wall thickness on serial CMR studies after a short (4- to 6-week) period of deconditioning and an enlarged LV cavity size (> 55 mm).

Preparticipation Screening

Detection of cardiovascular abnormalities with the potential for unexpected and unpredictable SD associated with intense physical training and competition is a major objective of preparticipation screening for high school and college-aged sports participants. In the United States, the customary screening practice dictates a personal and family history and physical examination.[2] Although HCM can

be suspected and identified by this process, it may remain unrecognized given that many affected individuals do not have a heart murmur or historical clues (e.g., syncope or a family history of HCM). Mandatory incorporation of the ECG into a national screening program for competitive athletes is not feasible or recommended within the current U.S. health care system for several reasons: the unfavorable cost-efficacy with insufficient resources, the substantial possibility of borderline and false-positive test results (and the uncertainty that accompanies these circumstances), the variability in ECG patterns with respect to race, and the possibility of false-negative testing in about 10% of those with clinically expressed HCM,[3] On the other hand, a national ECG screening program for detection of cardiovascular disease in competitive athletes has achieved some success in Italy.[4] Broad-based screening of athlete populations with echocardiography appears to be an even less practical strategy.

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*See references 1, 2, 4, 20, 22, 34, 52, 53, 59-61.

*See references 1-4, 8, 20, 22, 52, 59.

79

Myocarditis

Leslie T. Cooper Jr, Kirk U. Knowlton

Overview and Definition

In its broadest sense, *myocarditis* refers to any inflammation of the myocardium. Inflammation can be

found after any form of injury to the heart, including ischemic damage, mechanical trauma, and genetic cardiomyopathies. More specifically, however, *classic myocarditis* refers to inflammation of the heart muscle occurring as a result of exposure to either discrete external antigens, such as viruses, bacteria, parasites, toxins, or drugs, or internal triggers, such as autoimmune activation against self-antigens. Although viral infection remains the most commonly identified cause of myocarditis, drug hypersensitivity and toxic drug reactions, other infections, and peripartum cardiomyopathy also can lead to myocarditis.

The pathogenesis of myocarditis is a classic paradigm of cardiac injury followed by immunologic response from the host as cardiac inflammation. The relative incidence of viral causes is continually evolving as new diagnostic tools based on molecular epidemiology become available. Indeed, more than 20 viruses have been associated with myocarditis, and the most frequent are currently parvovirus B19 (B19V) and human herpesvirus 6.[1] Historically, enteroviruses such as coxsackievirus B were the most commonly identified pathogens, and strains of enterovirus remain widely used in rodent models of the disease.[2] If the host immune response is overwhelming or inappropriate, the inflammation may destroy the heart tissue acutely or may linger, producing cardiac remodeling that leads to dilated cardiomyopathy (DCM), heart failure, or death. Fortunately for most patients, clinical myocarditis often is self-limited if proper support and follow-up care are available. In many cases the virus is cleared successfully, and the immune response is down-modulated. In some patients, however, an autoimmune reaction to endogenous antigens lingers beyond this phase and can cause persistent cardiac dysfunction. Sometimes viral genomes persist in the heart with or without acute inflammation.[3] Viral genomes commonly are detected in endomyocardial biopsy (EMB) specimens from patients with DCM and may signal a disease-related infection. As discussed in this chapter, with new insights into the understanding of the pathophysiology of myocarditis and new therapies for this condition, the outlook for affected patients is continuing to improve.

Epidemiology

Globally, the number of cases of myocarditis in 2015 was approximately 2.2 million, an increase from approximately 1.48 million cases in the 2013 world population.[4] In 2015 there were approximately 200,000 deaths in men and 150,000 deaths in women from both myocarditis and cardiomyopathy, with a death rate of between 5 and 6 per 100,000 in males and between 4 and 5 per 100,000 in females (**Fig. 79.1**). The burden of myocarditis as a percentage of prevalent heart failure varies by age and region from approximately 0.5% to 4.0%.[5]

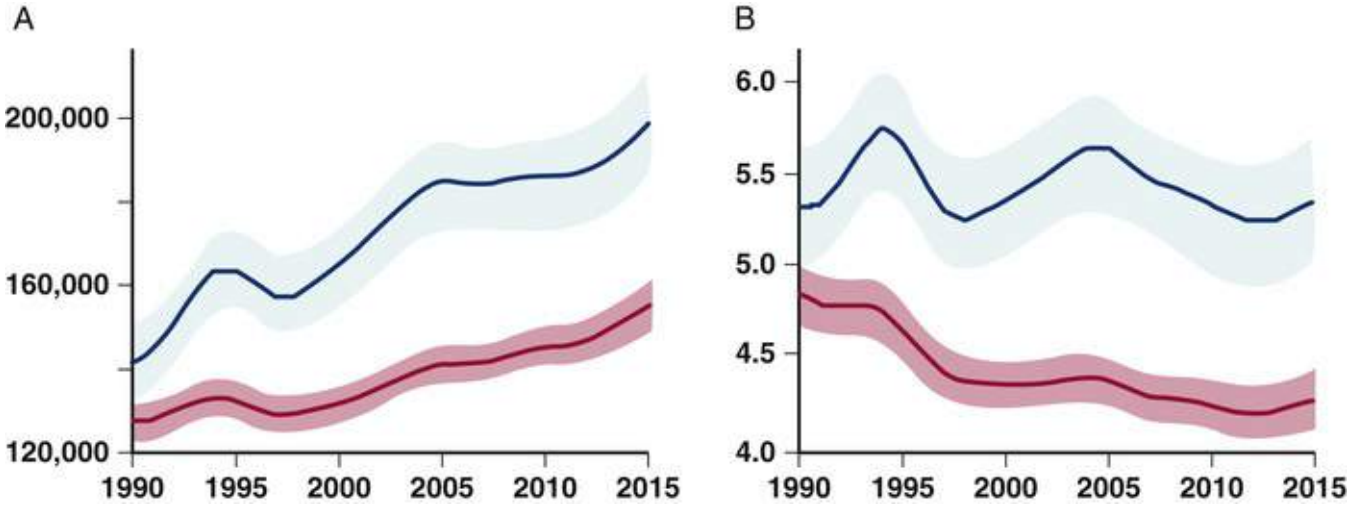

FIGURE 79.1 **A,** Number of global deaths with 95% uncertainty interval for women (*red*) and men (*blue*) due to cardiomyopathy and myocarditis from 1990 to 2015. **B,** The global death rate per 100,000 people with 95% uncertainty interval for women (*red*) and men (*blue*) due to cardiomyopathy and myocarditis from 1990 to 2015. (From the Global Burden of Disease Project, Institute for Health Metrics and Evaluation database. Image provided by Greg A. Roth, MD, MPH, and Catherine O. Johnson, Division of Cardiology, University of Washington, Institute for Health Metrics and Evaluation. Heymans S, Eriksson U, Lehtonen J, Cooper LT Jr: The quest for new approaches in myocarditis and inflammatory cardiomyopathy. J Am Coll Cardiol 2016;68:2348-64.)

In clinical case series of sudden death, myocarditis often is the third leading cause after hypertrophic cardiomyopathy and congenital and atherosclerotic coronary artery disease. Myocarditis is responsible for sudden cardiovascular death in approximately 2% of infants, 5% of children, and 5% to 14% of young athletes.[6,7] The overall rate of myocarditis was 3% (6 of 200) in autopsies of patients experiencing sudden death in Japan.[8] This rate should be seen in the context of the unselected diagnosis rate of myocarditis, 0.11% of 377,841, in autopsies registered in Japan from 1958 to 1977.

Myocarditis is responsible for a substantial minority of DCM cases (**see also Chapters 21 and 77**). In a review of DCM case series from 1978 to 1995 in which EMB was performed, the incidence of biopsy-proven myocarditis varied widely, ranging from 0.5% to 67%, with an average of 10.3%. Data from the U.S. Pediatric Cardiomyopathy Registry, in which 46% (222/485) of children with an identified cause of DCM had myocarditis, are illustrative of recent reports. As in most DCM case series, only a minority of children in this series, 34% of 1426, had a specific cause of DCM identified.[9]

Most case series show a male predominance, which may be mediated by sex hormones. The prevalence of myocarditis as a cause of cardiomyopathy is relatively high in the first year of life, declines from age 2 to 11 years, and rises again from puberty to about age 40 years. The population-based prevalence of myocarditis is likely higher, because the diagnostic test, EMB, is infrequently performed outside of referral medical centers.

The differing histologic criteria used to define myocarditis are responsible for some of the variation in the reported prevalence of myocarditis. The standard Dallas criteria define idiopathic myocarditis as an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease (**Fig. 79.2A** and **Table 79.1**).[10] These criteria have been criticized because of interreader variability in interpretation, lack of prognostic value, and low sensitivity due in part to sampling error. Specific immunohistochemical stains that detect cellular antigens, such as anti-CD3 (T lymphocytes), anti-CD68 (macrophages), and class I and II human leukocyte antigens (**Fig. 79.2B**), may have greater sensitivity for small infiltrates than that of hematoxylin-eosin stain. Markers of complement activity such as C4d also are commonly found in native cardiomyopathic hearts. Newer immunohistochemical stains have a greater predictive value for cardiovascular events than the Dallas criteria.[11]

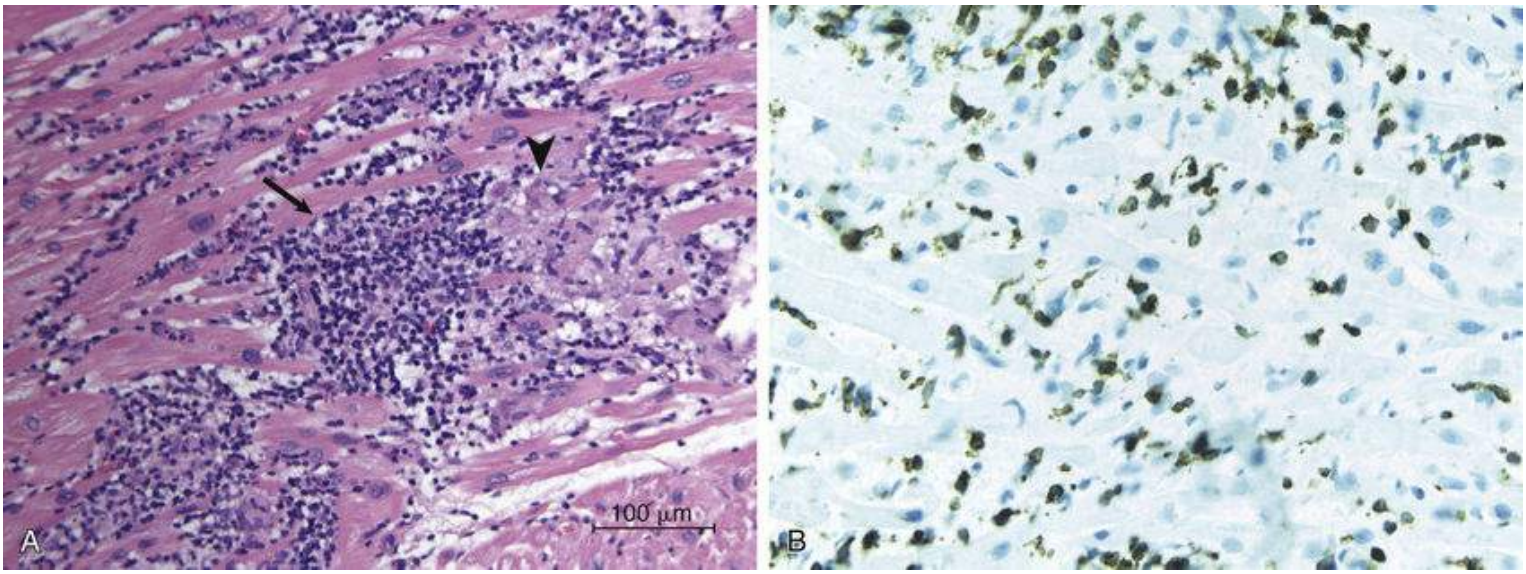

FIGURE 79.2 **A,** Acute myocarditis with widespread lymphocytic and histiocytic infiltrate (*arrow*) and associated myocyte damage (*arrowhead*). **B,** CD3 immunostaining of T lymphocytes in a patient with acute myocarditis. (Courtesy Dylan Miller, MD. From Cooper LT: Myocarditis. N Engl J Med 2009;360:1526.)

TABLE 79.1

Endomyocardial Biopsy Diagnosis of Myocarditis: the Dallas Criteria

DEFINITION		
Idiopathic *myocarditis*: "an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease"		
CLASSIFICATION		
First biopsy • Myocarditis with or without fibrosis • Borderline myocarditis (repeat biopsy may be indicated) • No myocarditis Subsequent biopsy • Ongoing (persistent) myocarditis with or without fibrosis • Resolving (healing) myocarditis with or without fibrosis • Resolved (healed) myocarditis with or without fibrosis		
DESCRIPTORS		
	INFLAMMATORY INFILTRATE	**FIBROSIS**
Distribution	Focal, confluent, diffuse	Endocardial, interstitial
Extent	Mild, moderate, severe	Mild, moderate, severe
Type	Lymphocytic, eosinophilic, granulomatous, giant cell, neutrophilic, mixed	Perivascular, replacement

Modified from Leone O, Veinot JP, Angelini A, et al: 2011 Consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. Cardiovasc Pathol 2012;21:245.

The presence of viral genomes in heart tissue may indicate an active infectious myocarditis. In the posttransplantation setting, the presence of viral genomes in myocardial biopsy material predicts future rejection episodes and graft loss in children.[12] Viruses for which testing is commonly done in the setting of suspected myocarditis are B19V, adenovirus, cytomegalovirus, enterovirus, Epstein- Barr virus, hepatitis C virus, herpes simplex viruses 1, 2, and 6, and influenza viruses A and B. New diagnostic criteria that rely on higher B19V copy numbers or evidence of active viral replication have been proposed.[2] For epidemiologic studies in which universal EMB is not feasible, diagnostic classifications that rely on clinical syndromes, biomarkers, and/or imaging abnormalities have been used[13] (**Table 79.2**).

TABLE 79.2

Three-Tiered Clinical Classification for Diagnosis of Myocarditis by Level of Diagnostic Certainty

DIAGNOSTIC CATEGORY	CRITERIA	HISTOLOGIC CONFIRMATION	BIOMARKER, ECG, OR IMAGING ABNORMALITIES CONSISTENT WITH MYOCARDITIS	TREATMENT NEEDED
Possible subclinical acute myocarditis	In the clinical context of possible myocardial injury *without* cardiovascular symptoms but with at least one of the following: Biomarkers of cardiac injury raised ECG findings suggestive of cardiac injury Abnormal cardiac function on echocardiogram or CMR	Absent	Required	Not known
Probable acute myocarditis	In clinical context of possible myocardial injury *with* cardiovascular symptoms and at least one of the following: Biomarkers of cardiac injury raised ECG findings suggestive of cardiac injury Abnormal cardiac function on echocardiogram or CMR	Absent	Required	Per clinical syndrome
Definite myocarditis	Histologic or immunohistologic evidence of myocarditis	Present	Not required	Tailored to specific cause

CMR, cardiac magnetic resonance imaging.

Modified from Sagar S, Liu PP, Cooper LT, Jr: Myocarditis. Lancet 2012;379:738.

Specific Etiologic Agents

In most cases, myocarditis is triggered by an inciting event, such as infection or exposure to a drug or toxin that activates the immune response. A subset of cases is due to primary immunologic abnormalities in the affected patient. Advanced techniques in virology, immunology, and molecular biology have demonstrated that there are many potential causes of myocarditis. Almost any infectious agent has been associated with myocarditis. In clinical practice, however, it is often difficult to identify a specific etiologic agent.

Viruses

Viral infection has been implicated as one of the most common infectious causes of myocarditis (**Table 79.3**). The earliest evidence of virus infection and its association with myocarditis and pericarditis was acquired during outbreaks of influenza, poliomyelitis, measles, and mumps, and in cases of pleurodynia associated with enterovirus infection.[14] Modern virologic and molecular techniques have demonstrated that adenoviruses, enteroviruses, and parvovirus are among the most commonly identified infectious agents in myocarditis. The precise incidence caused by these agents varies geographically and temporally. Nevertheless, in metaanalyses, polymerase chain reaction (PCR) studies in patients with clinically suspected myocarditis or cardiomyopathy who subsequently underwent heart biopsy demonstrated that virus could be identified 3.8 times more frequently in patients with myocarditis than in control subjects. Additional evidence indicates that persistence of the viral genome in patients with cardiomyopathy is associated with increased ventricular dysfunction and worse outcome during follow-up.

TABLE 79.3

Causes of Myocarditis

VIRUSES AND VIRAL DISORDERS	BACTERIA AND BACTERIAL DISORDERS	CARDIOTOXINS	HYPERSENSITIVITY MEDIATORS AND FACTORS
Adenovirus*	*Chlamydia*	Anthracycline drugs*	Cephalosporins
B19V	Cholera	Arsenic	Clozapine
CVB*	Leptospirosis	Carbon monoxide	Diuretics
Cytomegalovirus*	Lyme disease	Catecholamines	Hypereosinophilia
Epstein-Barr virus	*Mycoplasma*	Chagas disease	Insect bites
Hepatitis C virus	*Neisseria*	Cocaine*	Kawasaki disease
Herpes simplex virus	Relapsing fever	Copper	Lithium
HIV*	*Salmonella*	Ethanol*	Sarcoidosis
Influenza virus	Spirochete	Heavy metals	Snake bites
Mumps	*Staphylococcus*	Lead	Sulfonamides
Poliovirus	*Streptococcus*	Leishmaniasis	Systemic disorders
Rabies	Syphilis	Malaria	Tetanus toxoid
Rubella	Tetanus	Mercury	Tetracycline
Varicella-zoster virus	Tuberculosis	Protozoa	Wegener granulomatosis
Yellow fever			

*Frequent cause of myocarditis.

Modified from Elamm C, Fairweather D, Cooper LT: Pathogenesis and diagnosis of myocarditis. Heart J 2012;98:835.

Enteroviruses, Including Coxsackieviruses.

Coxsackievirus is a member of the Enterovirus genus, Picornaviridae family. It is a nonenveloped lytic virus. Its capsid proteins harbor a single, positive-strand RNA genome of 7.4 Kb. Throughout the history of studies that address the causes of myocarditis, enteroviruses such as coxsackievirus B3 or echovirus are commonly identified in a subset of patients at a higher frequency than in control subjects. Using molecular techniques such as PCR and in situ hybridization, the enterovirus genome has been identified in the heart of 15% to 30% of patients with myocarditis and 7% to 30% of specimens with DCM, although the incidence in different studies varies considerably. Coxsackievirus infection meets the criteria of Koch's postulates as a cause of myocarditis in humans: It can be regularly found in the lesions of the disease; it has been isolated in pure culture from patients with myocarditis; and when inoculated into a mouse it can recapitulate the disease, after which the virus can be recovered from the heart of the infected mouse.

Coxsackievirus is a close relative of the poliovirus and rhinovirus, viruses that have been studied extensively. Although the disease phenotypes are different, the many similarities in viral replication cycles have facilitated an understanding of the mechanisms by which coxsackievirus can cause disease. Coxsackievirus typically enters the host through the gastrointestinal or respiratory system. It uses the coxsackievirus-adenovirus receptor (CAR), a transmembrane adhesion protein, as its primary receptor for cell entry. It can cause a broad range of clinical syndromes, including meningitis, skin rashes, acute respiratory illness, skeletal myositis, and myocarditis.

Most recently, evaluation of patients with myocarditis has demonstrated a decrease in the prevalence of enteroviruses in the myocardium. This is particularly evident in Western Europe. The reason for this decrease is not clear, but it may be related to a herd immunity that occurs after a period of prolonged exposure to the virus. The lower incidence also may be confounded by seasonal outbreaks of enterovirus infections, thereby making the exact incidence dependent on the outbreaks.

Adenovirus.

Adenoviruses are nonenveloped DNA viruses that also use CAR (adenovirus types 2 and 5), as well as

integrins, as receptors for entry into the target cell. The adenovirus capsid harbors a double-stranded DNA genome. Adenoviruses commonly infect mucosal surfaces. The adenovirus genome is consistently identified in a subset of patients with myocarditis. The incidence in myocarditis patients has been recorded to be as high as 23% and as low as less than 2%.[15] Although mechanisms of adenoviral infection have been studied in considerable detail in cell culture and other diseases, it has been challenging to study adenovirus-mediated myocarditis, in the face of difficulties identifying an appropriate mouse model using the same adenoviruses that affect humans.

Parvovirus.

Considerable attention during the last decade has focused on the role of parvovirus B19 (B19V) of the genus Erythrovirus in the pathogenesis of myocarditis because of the high prevalence of B19V DNA in hearts of patients with myocarditis. Parvovirus is a nonenveloped, nonlytic virus with a single-strand, positive-strand DNA genome of approximately 5.6 Kb. Humans are the only known host for B19V, making it challenging to study in animal models, but examples of myocarditis in mice stimulated with the capsid protein VP1 or antibodies against VP1 have been reported.[15] Its primary receptor is globoside, also known as group P antigen. This antigen is found primarily on erythroid progenitors, erythroblasts, and megakaryocytes. It also has been shown to be expressed on endothelial cells. This finding may be important for its role in the pathogenesis of myocarditis. The infection is thought generally to be spread by the respiratory route. The incidence of infection in the general population is high, with evidence of B19V infection demonstrated in approximately 50% of children at age 15 years, and detectable IgG directed against B19V found in as many as 80% of elderly patients.[16] With PCR studies, the PVB genome has been identified in 11% to 56% of patients with myocarditis and in 10% to 51% of patients with DCM.

In keeping with the high prevalence of B19V in the general population, the pathogenic role of B19V continues to be clarified. In one study, B19V was assessed by immunohistochemistry and PCR assay. The investigators found that B19V was detectable by immunohistologic analysis in 65% of patients with myocarditis, 35% of patients with DCM, and 8% of noninflamed control hearts. The viral load was assessed by genome copy numbers in the samples that were positive for B19V on immunohistologic analysis. The viral load was significantly higher in patients with acute myocarditis, followed by those with DCM, and it was lowest in the patients with normal hearts without inflammation.[17] In addition, viral RNA replicative intermediates were detected only in patients with inflamed hearts. It has also been determined that evidence of viral transcription is associated with an anomalous host myocardial transcriptome.[18] These findings indicate that the amount of B19V viral DNA is associated with the disease phenotype. Of importance, the virus was found in endothelial cells and not myocardial cells. Other studies have suggested a bystander role for B19V in adult myocarditis,[16] with persistence of low-level B19V titers a frequent finding, but unrelated to ongoing myocardial injury. Additional experimentation is needed to determine mechanisms by which B19V could contribute to myocarditis and cardiomyopathy.

Human Immunodeficiency Virus.

The improved survival rate of patients with human immunodeficiency virus (HIV) infection (**see also Chapter 82**) has affected the incidence of heart disease in this population, There has been a shift from myocardial and pericardial disease to a higher incidence of coronary artery disease. In retrospective series and autopsy studies in patients infected with HIV, the incidence of cardiac involvement ranged from 25% to 75%. Clinical cardiovascular presentations associated with HIV infection include myocarditis, pericarditis, DCM, arrhythmias, and vascular diseases. Myocarditis with lymphocytic

infiltration has been reported in 40% to 52% of patients who die of acquired immunodeficiency syndrome (AIDS). The incidence of myocardial disease, however, appears to have decreased with increased antiretroviral therapy. This is especially true as it relates to DCM, pericardial disease, and arrhythmias. The incidence of cardiomyopathy, myocarditis, and pericardial diseases correlates with the severity of the HIV infection as measured by a low $CD4^+$ count or high viral titers. Owing to ongoing changes in therapy for HIV infection, the exact incidence of myocardial diseases is not clear, but it continues to be a problem. In addition, many patients in developing regions of the world do not receive highly active antiretroviral therapy and may present with cardiac disease. Although HIV infection can be associated with ventricular dysfunction, the mechanisms by which this occurs have not been fully elucidated; however, activation of cytokines and alteration of immune cells that affect cardiac function are likely to be involved. Convincing evidence that HIV directly infects the myocardium is lacking. The pathogenesis of HIV-associated cardiomyopathy is complicated by infection with pathogens that are associated with immunosuppression, malnutrition, and other confounding effects. In the post–antiretroviral therapy era, acute coronary syndromes and coronary artery disease are the major cardiovascular diseases that occur in HIV-infected patients in the United States.[19]

Hepatitis C Virus.

Hepatitis C virus infection appears to be mainly associated with cardiomyopathy in Asian countries such as Japan. A low incidence of hepatitis C virus antibodies (4.4%) was identified in patients who were studied in the Myocarditis Treatment Trial. This occurrence rate was nevertheless higher than that (1.8%) in the general U.S. population. Perhaps the higher incidence of hepatitis C virus infection in DCM is related to the overall higher incidence of this infection in Asia. Myocardial biopsy samples from patients with cardiomyopathy have demonstrated the presence of the hepatitis C viral genome, and a rise in serum antibody titers has been documented in patients so affected. The phenotype associated with hepatitis C virus also has been reported to include hypertrophic cardiomyopathy, suggesting that hepatitis C may have a direct effect on growth and hypertrophy of the myocardial cells. Symptomatic myocarditis generally is observed in the first to third weeks of illness. It has been reported that heart function can return to normal with clearance of the virus.

Influenza Virus.

Influenza A virus infection is a well-recognized cause of myocarditis, and this association should be kept in mind during periodic outbreaks of influenza A. The exact incidence of myocarditis with influenza A outbreaks is not known, but it generally is considered to be in the 5% range. During pandemics such as the 2009 H1N1 pandemic, myocarditis was reported in 5% to 15% of cases as diagnosed by changes on the electrocardiogram (ECG) and the presence of cardiac symptoms. Some cases manifested with fulminant myocarditis. Histopathologic examination usually demonstrates the presence of the inflammatory infiltrate that is typical of myocarditis.[20]

Bacteria

Nonviral pathogens such as bacteria and parasites can affect the heart and, in some cases, activate an immune reaction in the heart. Virtually any bacterial agent can cause myocardial dysfunction, but it does not necessarily mean that the bacterium has infected the myocardium. In the case of sepsis or other severe bacterial infections, the myocardial dysfunction generally is attributed to activation of inflammatory mediators (**see Chapter 23**). Of note, however, bloodstream infection by virtually any bacterial infection can result in metastatic foci in the myocardium. This finding is most commonly associated with bacterial endocarditis. Some bacterial infections are well known to have specific effects on the heart that can be

mediated by direct infection or activation of inflammatory mechanisms. The most common of these include diphtheria, rheumatic heart disease, and streptococcal infections.

Corynebacterium Infection.

Myocardial involvement with *Corynebacterium diphtheriae* is a serious complication and is the most common cause of death in diphtheria. In up to one half of fatal cases, evidence of cardiac involvement can be found. Studies from the last decade indicate that there is evidence of myocardial involvement in 22% to 28% of patients. The overall incidence has decreased in developed countries because of vaccination, but recently, there have been a growing number of unprotected individuals in developed countries as well. This may be related to vaccine avoidance. *C. diphtheriae* produces an exotoxin that severely damages the myocardium and the cardiac conduction system. Cardiac damage is due to the liberation of this exotoxin, which inhibits protein synthesis by interfering with host translational mechanisms. The toxin appears to have an affinity for the cardiac conduction system. Both antitoxin therapy and antibiotics are important in the treatment of diphtheria.

Streptococcal Infection.

The most commonly detected cardiac complication after beta-hemolytic streptococcal infection is acute rheumatic fever, which is followed by rheumatic valve disease in approximately 60% of patients. Rarely, involvement of the heart by the streptococcus may produce a nonrheumatic myocarditis distinct from acute rheumatic carditis. This clinical entity is characterized by the presence of an interstitial infiltrate composed of mononuclear cells with occasional polymorphonuclear leukocytes, which may be focal or diffuse. In contrast with rheumatic heart disease, streptococcal myocarditis usually occurs coincident with the acute infection or within a few days of the pharyngitis. Electrocardiographic abnormalities, including ST elevation and prolongation of the PR and QT intervals, are common. Rare sequelae may include sudden death, conduction disturbances, and arrhythmias.

Tuberculosis.

Involvement of the myocardium by Mycobacterium tuberculosis (not tuberculous pericarditis) is rare. Tuberculous involvement of the myocardium occurs by means of hematogenous or lymphatic spread or may arise directly from contiguous structures and may cause nodular, miliary, or diffuse infiltrative disease. On occasion, it may lead to arrhythmias, including atrial fibrillation and ventricular tachycardia, complete atrioventricular block, heart failure, left ventricular aneurysms, and sudden death.

Whipple Disease.

Although overt involvement is rare, intestinal lipodystrophy, or Whipple disease, is not uncommonly associated with cardiac involvement. Periodic acid–Schiff–positive macrophages can be found in the myocardium, pericardium, coronary arteries, and heart valves of patients with this disorder. Electron microscopy has demonstrated rod-shaped structures in the myocardium similar to those found in the small intestine, representing the causative agent of the disease, *Tropheryma whipplei*, a gram-negative bacillus related to the actinomycetes. An inflammatory infiltrate and foci of fibrosis also may be present. The valvular fibrosis may be severe enough to result in aortic regurgitation and mitral stenosis. Although it usually is asymptomatic, nonspecific electrocardiographic changes are most common; systolic murmurs, pericarditis, complete heart block, and even overt congestive heart failure may occur. Antibiotic therapy appears to be effective in treatment of the basic disease, but relapses can occur, often more than 2 years after the initial diagnosis.

Lyme Carditis.

Lyme disease is caused by a tick-borne spirochete (*Borrelia burgdorferi*). It usually begins during the summer months with a characteristic rash (erythema chronicum migrans), followed by acute neurologic, joint, or cardiac involvement, usually with few long-term sequelae. Early studies indicated that up to 10% of untreated patients with Lyme disease demonstrated evidence of transient cardiac involvement, the most common manifestation being atrioventricular block of variable degree. With the early use of antibiotics, however, Lyme carditis is now considered to be a rare manifestation.[21] Of patients with Lyme disease reported to the Centers for Disease Control (CDC), only 1.1% were identified as having Lyme carditis.[22] Syncope due to complete heart block is frequent with cardiac involvement because of the commonly associated depression of ventricular escape rhythms. Diffuse ST-segment and T-wave abnormalities are transient and usually asymptomatic. An abnormal gallium scan is compatible with cardiac involvement, and the demonstration of spirochetes in myocardial biopsy specimens of patients with Lyme carditis suggests a direct cardiac effect. Patients with second-degree or complete heart block should be hospitalized and undergo continuous electrocardiographic monitoring. Temporary transvenous pacing may be required for a week or longer in patients with a high-grade block. It is thought that antibiotics can prevent subsequent complications and may shorten the duration of the disease; therefore, they are used routinely in patients with Lyme carditis. Intravenous antibiotics are suggested, although oral antibiotics can be used when only mild cardiac involvement is present. Corticosteroids may reduce myocardial inflammation and edema, which in turn can shorten the duration of the heart block. It is thought that treatment of the early manifestations of the disease will prevent development of late complications.

Protozoa

Chagas disease is one of the major causes of nonischemic cardiomyopathy throughout the world, although the incidence is changing. In a remarkable tale of discovery at the beginning of the 20th century, Carlos Chagas almost single-handedly identified the parasite, *Trypanosoma cruzi*, which causes the entity now known as Chagas disease. He also elucidated the relatively complex life cycle of the parasite in poor, rural areas of Brazil.[23] The parasite resides in and replicates in an infected host such as an armadillo or a domestic cat. The parasite then infects triatomine insects, including the hematophagous reduviid bug that feeds on the blood of infected vertebrate carriers. The triatomine acts as the vector of infection when it bites a human, depositing the parasite in its feces in the area of the bite wound, conjunctiva, or other mucous membranes. Once within the now-infected individual, the parasite replicates and infects target organs such as the heart. Parasitic infection of cardiac myocytes and activation of the associated immune function damage the heart and other organs and lead to the clinical manifestations of Chagas disease; **Fig. 79.3** shows the life cycle.[24]

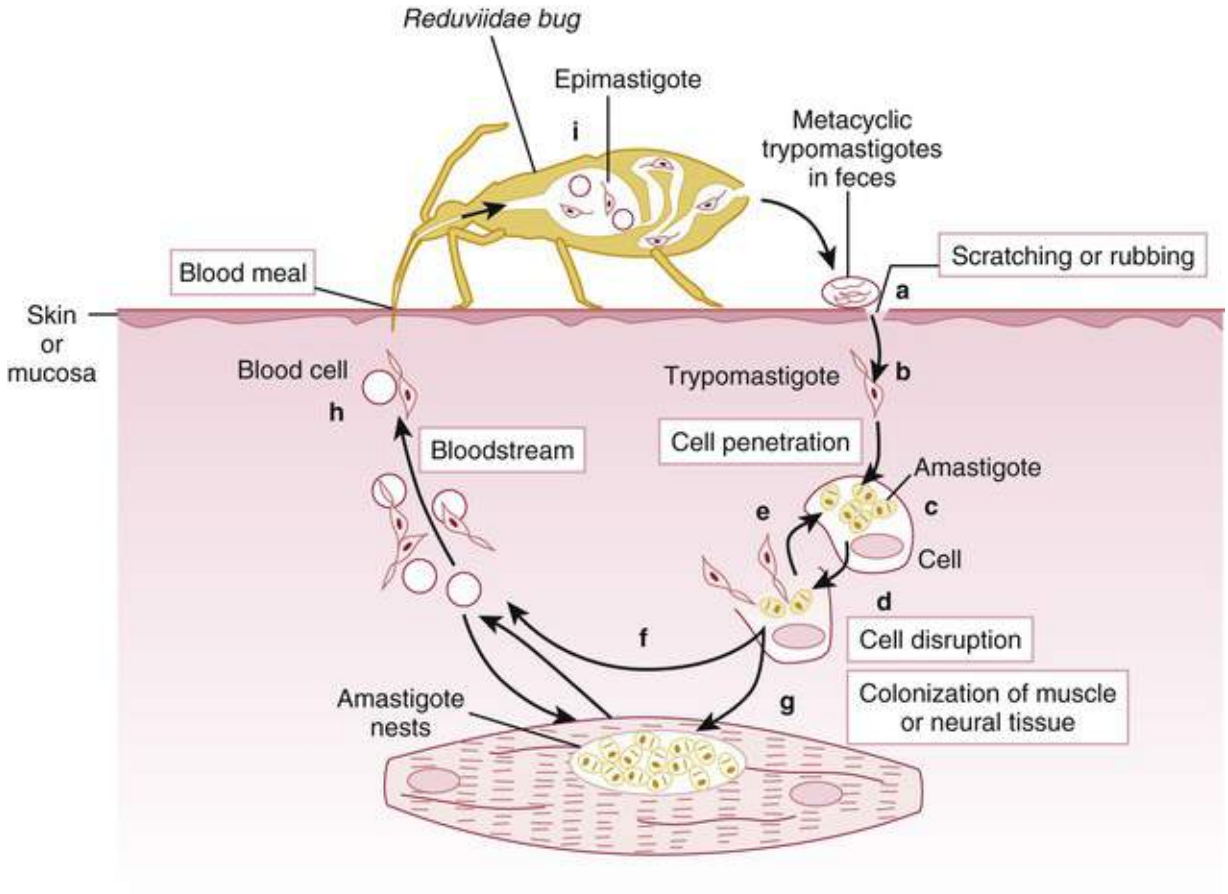

FIGURE 79.3 The life cycle of *Trypanosoma cruzi.* Reduviid bugs transmit *T. cruzi.* While partaking of a blood meal **(A),** the insect defecates on the host's skin, releasing the infective trypomastigote form of the parasite. The trypomastigotes penetrate the host's skin or mucous membrane through abrasions caused by scratching or rubbing the bitten area **(B)**. Trypomastigotes can infect host cardiac, skeletal, smooth muscle, or neural cells, subsequently giving rise to the round amastigote form that can replicate intracellularly **(C)**. Amastigotes can give rise to trypomastigotes that can lyse cells **(D)**. Amastigotes and trypomastigotes released from dying cells can propagate the infection or reenter the circulation (**E** to **G**). Insects can pick up the parasite when consuming a blood meal **(H)**; it develops into the epimastigote form that replicates in the insect gut **(I)**. (From Macedo AM, Oliveira RP, Pena SD: Chagas' disease: role of parasite genetic variation in pathogenesis. Expert Rev Mol Med 2002;4:1.)

Chagas disease is endemic in poor, rural areas of Central and South America (**see eFig. 79.1**). The distribution of Chagas disease is changing to include more urban and traditionally nonendemic areas because of migration of infected individuals from the rural to urban areas. Vector control initiatives in the endemic areas and aggressive screening of the blood supply has reduced the overall incidence of Chagas disease. In the 1980s, 17.4 million people were infected in 18 endemic countries.[25] By 2010, it was estimated that the number of infected persons had dropped to nearly 5.7 million. In 1990, it was estimated that 700,000 new cases were diagnosed each year. In 2010, that number had decreased to 29,925. Similarly, the number of annual deaths from Chagas disease has decreased, from 50,000 per year in 1990 to approximately 12,500 per year.[24,26] However, at the same time that Chagas disease is decreasing worldwide, the incidence in the developed world is increasing because of immigration from endemic areas. It is currently estimated that approximately 238,000 people in the United States are infected with *T. cruzi*.[27] This has important implications in relation to blood transfusion and organ donation, because the infectious agent can be transferred from donor to recipient; this is a particularly important consideration in the immunocompromised transplant recipient.

EFIGURE 79.1 Distribution of Chagas disease in the Americas. (Modified from Acquatella H: Chagas' disease. *In* Abelmann WH, Braunwald E [editors]: Atlas of Heart Disease: Cardiomyopathies, Myocarditis, and Pericardial Disease. Philadelphia, Current Medicine, 1995, pp 8.1-8.18; and Liu PP, Schultheiss HP: Myocarditis. *In* Libby P, Bonow RO, Mann DL, Zipes DP [editors]: Braunwald's Heart Disease. Philadelphia, Saunders, 2008.)

Symptoms from *T. cruzi* infection typically begin 1 to 2 weeks after a bite from an infected triatomine or can occur up to a few months after transfusion of infected blood. The parasite load can affect the severity of clinical presentation. The acute phase is accompanied by the presence of parasites in the blood smear. The acute phase of *T. cruzi* infection lasts for 4 to 8 weeks. During the acute phase of parasite infection, most affected patients are either asymptomatic or have a mild, subacute febrile illness. Other potential manifestations include adenopathy, hepatomegaly, myocarditis, and meningoencephalitis. Cardiovascular abnormalities during the acute phase might include nonspecific ECG changes, first-degree atrioventricular block, and cardiomegaly on chest x-ray examination. Death occurs from myocarditis or meningoencephalitis in less than 5% to 10% of symptomatic patients. In up to 90% of patients, the symptoms of disease resolve spontaneously. Of these, approximately 60% to 70% never develop chronic Chagas disease manifestations even in the absence of treatment with trypanocidal drugs, but these patients will remain seropositive throughout life. Aside from seropositivity for *T. cruzi,* the patients without manifestations of disease exhibit no signs or laboratory findings of Chagas disease, as described further on. The other 30% to 40% of patients ultimately develop more typical manifestations of the chronic form of Chagas disease. Treatment with antiparasite drugs such as benznidazole usually can cure the patient during the acute illness.[23,24] The chronic phase of *T. cruzi* infection continues throughout the infected host's life. The 30% to 40% of patients with acute illness that go on to develop chronic Chagas disease usually manifest the disease within 5 to 15 years after the initial infection. However, less than 1% of patients with chronic Chagas disease report a history of symptoms of acute Chagas disease. The

chronic form is characterized by myocardial fibrosis, destruction of the conduction system, ventricular dilation, thinning of the apex of the heart, and formation of a thrombus in the apex of the heart. These changes lead to heart failure, arrhythmia, atrioventricular and bundle branch block, and possible thromboembolism. Gastrointestinal disturbances also can be a prominent part of the presentation. It is reported that 50% to 90% of patients with chronic Chagas disease remain asymptomatic despite ongoing pathologic processes.[23,24]

Congenital transmission of the parasite to a fetus from the mother is another important mechanism of transmission of the parasite. Conversely, the parasite can be passed from the mother to the infant at the time of birth. *T. cruzi* also has been shown to infect the placenta and subsequently infect the fetus in utero. Congenital transmission occurs in 1% to 5% of pregnancies when the mother has chronic Chagas disease. Congenital transmission of this disease results in spontaneous abortion, premature birth, or infection of organs in the fetus.[23,24]

The goal of treatment in all forms of Chagas disease is to eradicate the parasite. Antitrypanosomal treatment is strongly recommended for all patients with acute, congenital, and reactivated infections. It also is recommended for all children who have chronic *T. cruzi* infection who are 18 years of age or younger. Therapy should be offered to patients 19 to 50 years of age without advanced heart disease. Strong consideration should be given for treatment of persons who have not previously been treated but have acquired HIV infection or are being considered for organ transplantation. Chagas disease is associated with both active persistent parasite infection and an immune response that may be directed against the parasite or may be a response of autoimmune origin.[28] Antiparasite treatment generally is not indicated in patients with advanced heart failure from Chagas disease.

Helminths

Echinococcosis (Hydatid Cyst)

Echinococcosis is endemic in many sheep-raising areas of the world, particularly Argentina, New Zealand, Greece, North Africa, and Iceland; however, cardiac involvement in patients with hydatid disease is uncommon (<2%). The usual host of *Echinococcus granulosus* is the dog, but humans may serve as intermediate hosts if they accidentally ingest ova from contaminated dog feces. When cardiac involvement is present, the cysts usually are intramyocardial, located in the interventricular septum or left ventricular free wall.

A myocardial cyst can degenerate and calcify, develop daughter cysts, or rupture. Rupture of the cyst is the most dreaded complication; rupture into the pericardium can result in acute pericarditis, which may progress to chronic constrictive pericarditis. Rupture into the cardiac chambers can result in systemic or pulmonary emboli. Rapidly progressive pulmonary hypertension can occur with rupture of right-sided cysts, with subsequent embolization of hundreds of scolices, fragments of the tapeworm, into the pulmonary circulation. The liberation of hydatid fluid into the circulation can produce profound, fatal circulatory collapse as a result of an anaphylactic reaction to the protein constituents of the fluid. It is estimated that only approximately 10% of patients with cardiac hydatid cysts experience clinical symptoms. The ECG may reflect the location of the cyst. Chest pain usually is due to rupture of the cyst into the pericardial space with resultant pericarditis. Large cystic masses sometimes produce right-sided obstruction. The chest radiograph may show an abnormal cardiac silhouette or a calcified lobular mass adjacent to the left ventricle. Two-dimensional echocardiography, computed tomography, or cardiac

magnetic resonance (CMR) imaging may aid in the detection and localization of heart cysts. Eosinophilia, when present, is a useful adjunctive finding. The Casoni skin test or serologic evaluation for echinococcus has a limited role in cardiac diagnosis. In terms of therapy, despite the availability of effective drugs such as mebendazole and albendazole, surgical excision generally is recommended, even for asymptomatic patients. This is because of the significant risk of rupture of the cyst and its attendant serious and sometimes fatal consequences.

Trichinosis

Infection with *Trichinella spiralis* is common after ingestion of infected meat, usually pork. The parasite typically infects skeletal muscle. Reports of the incidence of clinically detectable cardiac involvement average around 25% of infected patients worldwide. Cardiomyopathy and arrhythmias may develop in some patients and constitute the most common cause of death in this infection. Less frequently, death is due to pulmonary embolism secondary to venous thrombosis or neurologic complications. Although the parasite can invade the heart, it does not usually encyst there, and a finding of larvae or larval fragments in the myocardium is rare. The heart may be dilated and flabby, and a pericardial effusion may be present. A prominent focal infiltrate composed primarily of eosinophils can be found, with occasional microthrombi in the intramural arterioles. Areas of muscle degeneration and necrosis are present.

The clinical myocarditis in trichinosis may be mild and go unnoticed, but in a subset of cases it is manifested by heart failure and chest pain, usually appearing around the third week of the disease. Electrocardiographic abnormalities are detected in approximately 20% of patients with trichinosis and parallel the time course of clinical cardiac involvement, initially appearing in the second or third week and usually resolving by the seventh week. The most common electrocardiographic abnormalities are repolarization abnormalities and ventricular premature complexes. The diagnosis usually is based on the demonstration of indirect immunofluorescent antibody in a patient with the clinical features of trichinosis. Eosinophilia, when present, is a supportive finding. The skin test result is usually but not invariably positive. Treatment is with anthelminthics and corticosteroids; dramatic improvement in cardiac function has been reported after completion of an appropriate regimen of these agents.

Physical Agents, Including Adverse Drug Effects

A wide variety of substances other than infectious agents can act on the heart and damage the myocardium. In some cases, the damage is acute, transient, and associated with evidence of an inflammatory myocardial infiltrate with myocyte necrosis (e.g., with the arsenicals and lithium). Other agents that damage the myocardium can lead to chronic changes with resulting histologic evidence of fibrosis and a clinical picture of a dilated or restrictive cardiomyopathy. Numerous chemicals and drugs (both industrial and therapeutic) can lead to cardiac damage and dysfunction. Several other physical agents (e.g., radiation, excessive heat) also can contribute directly to myocardial damage. Additional content on this this topic is discussed in an online supplement for this chapter titled Additional Physical Agents That Cause Myocarditis.

Additional Physical Agents That Cause Myocarditis

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Radiation

The cardiac effects of radiation therapy are discussed in **Chapter 81**. Briefly, radiation therapy can lead to a variety of cardiac complications that arise long after the completion of the therapy, including pericarditis with effusion, tamponade, or constriction; coronary artery fibrosis and myocardial infarction; valvular abnormalities; myocardial fibrosis; and conduction disturbances. Although irradiation probably results in some degree of tissue damage in all patients, clinically significant cardiac involvement occurs in the minority of patients, usually long after the treatment has ended. Radiation-induced cardiac damage is related to the cumulative dose of the radiation and the mass of heart irradiated. The late cardiac damage that may follow irradiation appears to result from a long-lasting injury of the capillary endothelial cells, which leads to cell death, capillary rupture, and microthrombi. Because of this damage to the microvasculature, ischemia results and is followed by myocardial fibrosis. In addition to microvascular damage, the major epicardial coronary arteries can become narrowed, especially at the ostia.

Occasionally a patient will develop acute cardiac complications after radiation therapy. This typically manifests as acute pericarditis. A mild, transient, asymptomatic depression of left ventricular function is sometimes seen early after radiation therapy. The more common clinical expressions of heart disease occur months or years after the exposure. The pericardium is the most common site of clinical involvement, with findings of chronic pericardial effusion or pericardial constriction (**see Chapter 83**). Myocardial damage occurs less frequently and is characterized by myocardial fibrosis with or without endocardial fibrosis or fibroelastosis. Left and/or right ventricular dysfunction at rest or with exercise appears to be a common, albeit usually asymptomatic, finding 5 to 20 years after radiation therapy. Often there is a latent period of a decade or more between the radiation exposure and the development of ventricular dysfunction or valvular deformity. ECG abnormalities, heart block, accelerated atherosclerosis, and a variety of arrhythmias may be seen months or years after therapeutic radiation, although the ultimate clinical significance is unclear.

Heat Stroke

Heat stroke results from failure of the thermoregulatory center following exposure to a high ambient temperature. It is manifested principally by hyperpyrexia, renal insufficiency, disseminated intravascular coagulation, and central nervous system dysfunction. However, ECG abnormalities appear to be common in heat stroke; pulmonary edema and transient right and/or left ventricular dysfunction may occur, along with hypotension and circulatory collapse. Pathologic changes include dilation of the right side of the heart, particularly the right atrium. Hemorrhages of the subendocardium and the subepicardium are frequently seen at necropsy and often involve the interventricular septum and posterior wall of the left ventricle. Histologic findings include degeneration and necrosis of muscle fibers, as well as interstitial edema. Sinus tachycardia is invariably present, whereas atrial and ventricular arrhythmias usually are absent. Transient prolongation of the QT interval may be seen, along with ST-segment and T wave

abnormalities. It can take up to several months for these repolarization abnormalities to resolve. Serum enzyme levels can be elevated and may reflect myocardial damage, at least in part, although concomitant rhabdomyolysis often is present.

Hypothermia

Low temperatures also can result in myocardial damage. Cardiac dilation can occur, with epicardial petechiae and subendocardial hemorrhages. Microinfarcts are found in the ventricular myocardium, presumably related to abnormalities in the microcirculation. The lesions are not caused by the low temperature per se but appear to be the result of the circulatory collapse, hemoconcentration, capillary slugging, and depressed cellular metabolism that accompany hypothermia. Clinical manifestations of hypothermia include sinus bradycardia, conduction disturbances, atrial (and occasionally ventricular) fibrillation, hypotension, a fall in cardiac output, reversible myocardial depression, and a characteristic deflection of the terminal portion of the QRS pattern (Osborn wave). Treatment includes core warming (often using extracorporeal blood warming), cardiopulmonary resuscitation, and management of pulmonary, hematologic, and renal complications. Notwithstanding its potential cardiac risks, mild therapeutic hypothermia appears to improve the neurologic outcome after cardiac arrest and is a currently accepted practice.

Drugs

Drug-induced hypersensitivity syndrome may involve the heart and be associated with myocarditis. The syndrome usually emerges within 8 weeks of the initiation of a new drug but can occur at any time after drug consumption. Common agents include antiepileptics, antimicrobials, allopurinol, and sulfa-based drugs. Dobutamine, often used for hemodynamic support in patients with failing hearts, may be associated with eosinophilic myocarditis, and the drug should be stopped when eosinophilia appears or when an unexpected decline in left ventricular function is noted. Presenting characteristics may include a rash (unless the patient is immunologically compromised), fever, and multiorgan dysfunction (including hepatitis, nephritis, and myocarditis). Diffuse myocardial involvement may result in systemic hypotension and thromboembolic events. CMR imaging and measurement of cardiac biomarkers may help identify patients with cardiac involvement. EMB may demonstrate eosinophils, histiocytes, lymphocytes, myocardial necrosis, and occasionally granuloma and vasculitis. Myocardial involvement is patchy, so a definitive diagnosis is made only when the biopsy findings are positive. Corticosteroids and drug withdrawal usually resolve this syndrome; however, some patients may display a prolonged and relapsing course.

Clozapine is an effective antipsychotic medication that is used to treat severe, refractory schizophrenia. Myocarditis is a rarely reported side effect of clozapine therapy, with the initial incidence reported at between 0.01% and 0.001%. More recent observations, however, have found an incidence of myocarditis in 1% to 10% of patients. Perhaps the increased incidence is related to an increased awareness of the risk. Myocarditis can develop at any time during treatment but occurs most frequently within the first 4 days to 22 weeks after initiation of clozapine. The peak incidence is at around 19 to 21 days. Clozapine-related myocarditis probably is the result of a hypersensitivity reaction. It may be accompanied by eosinophilia, with eosinophilic infiltration seen in myocardial biopsy material. Clozapine also is a potent anticholinergic compound, and high levels associated with altered metabolism from CYP450 enzymes also could contribute to the cardiac effects. With clear evidence of myocarditis in a patient taking this drug, immediate discontinuation is indicated.[29]

Vaccination for smallpox among uniformed service members has been demonstrated to be associated with myopericarditis. In a prospective assessment of myocarditis following smallpox vaccination, clinical myopericarditis and subclinical myocarditis were noted at an incidence of 463 and 2868 per 100,000 subjects, respectively (in a healthy cohort the incidence was 2.2 clinical myopericarditis patients per 100,000). There were no cases of clinical myopericarditis or subclinical myocarditis in a control group that received trivalent influenza vaccination.[30]

As new chemotherapeutic agents are developed to target specific pathways in the heart, it is becoming increasingly apparent that cancer chemotherapy can induce cardiomyopathy (**see also Chapter 81**).[31] Fulminant myocarditis has been described in two patients that were receiving combination immune checkpoint blockade using ipilimumab and nivolumab.[32] Future attention to the mechanisms by which chemotherapeutic agents induce cardiomyopathy may give additional insight into mechanisms of myocarditis.

Pathogenesis

Much of the current understanding of the pathogenesis of myocarditis is derived from mouse models of enteroviral infection, particularly coxsackievirus B3, and rodent models of autoimmune myocarditis.[33] The principles derived from these models have been applied to human myocarditis of different causes.[2] The description of the pathogenesis draws from cellular animal and human data. The pathogenesis of viral myocarditis can be divided into three major components: viral infection and replication, immunologic response (innate and adaptive immune response), and, ultimately, a phase of chronic cardiac remodeling (**Fig. 79.4**). MicroRNAs have also been shown to have a role in myocarditis (see online supplement for details on MicroRNAs in Myocarditis).

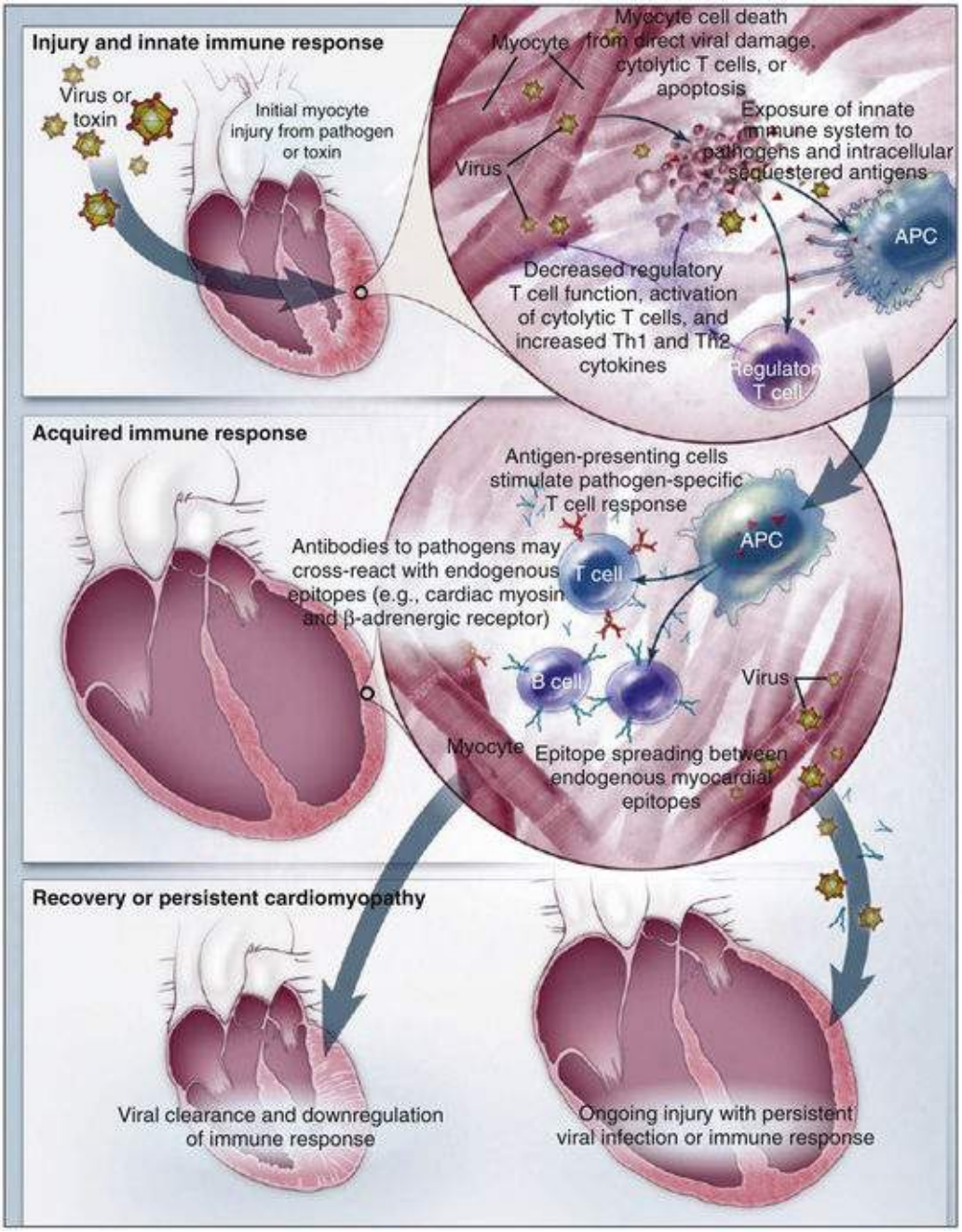

FIGURE 79.4 Pathogenesis of myocarditis. The current understanding of the cellular and molecular pathogenesis of postviral and autoimmune myocarditis is based solely on animal models. In these models, the progression from acute injury to chronic DCM may be simplified into a three-stage process. Acute injury leads to cardiac damage, exposure of intracellular antigens such as cardiac myosin, and activation of the innate immune system. Over weeks, specific immunity that is mediated by T lymphocytes and antibodies directed against pathogens and similar endogenous heart epitopes causes robust inflammation. In most patients, the pathogen is cleared and the immune reaction is down-regulated, with few sequelae. In other patients, however, the virus is not cleared, and it causes continued myocyte damage; heart-specific inflammation may persist because of mistaken recognition of endogenous heart antigens as pathogenic entities. *APC*, antigen-presenting cell. (Reprinted from Cooper LT: Myocarditis. N Engl J Med 2009;360:1526.)

Micro RNAs in Myocarditis

Microribonucleic acids (miRNAs) have been shown to have a role in myocarditis and in limiting viral replication.[1,2] miR-208b and miR-499 can be detected in the plasma of myocarditis patients. Interestingly, plasma miRNA levels reflect myocardial damage but not inflammation in acute viral myocarditis.[3] miR-21 and miR-146b have been shown to be involved in murine myocarditis through regulation of Th-17

differentiation. Inhibition of miR-21 and miR-146b decreased the severity of myocarditis.[4] miR-203 increases in murine myocarditis and increases cell viability, thus enhancing coxsackievirus B3 replication.[5] miR-141 can inhibit host protein synthesis by targeting the RNA cap binding protein eukaryotic initiation factor 4E.[6] miR-126 is up-regulated with coxsackievirus infection and activates the protein kinase C/transcription factor AP-1 pathway that is an important signaling molecule for coxsackievirus replication.[7] miR-10a* targets the three-dimensional RNA sequence of CVB3 and increases its synthesis.[8] miR-221 and miR-222 are significantly elevated in myocarditis, but act in a defensive manner by affecting proteins that are needed for efficient viral replication.[9]

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Viral Infection

Viruses enter the host through a variety of locations, including the gastrointestinal system and respiratory system. The virus may undergo initial replication in the host in organs such as the liver, spleen, and pancreas. Ultimately, the virus reaches the heart via dissemination through the blood or lymphatic vessels. The steps include attachment of the virus to its receptor, entry of the virus into the cell, replication of the virus within the affected cell in the heart, and for lytic viruses, exit of the virus from the cell to allow infection of other cardiac cells. In the case of coxsackievirus, the virus infects the cardiac myocyte. In addition, however, viruses such as B19V may infect other cells in the heart; B19V has been demonstrated to infect the cardiac endothelial cell and is not found in the cardiac myocyte.[18]

Initially, the virus binds to a viral receptor, ultimately resulting in internalization of the virus (**Fig. 79.5**). This process includes entry of the viral capsid proteins and the viral genome. In the case of coxsackieviruses and adenoviruses, the receptor is a transmembrane molecule, CAR, named for these two viruses, which are known to use it as a receptor.[34] Genetic deletion of CAR in the cardiac myocyte

markedly inhibits infection of the heart and development of myocarditis.[35] In addition to CAR, coxsackievirus infection can be facilitated by interaction with the decay-accelerating factor (DAF), or CD55. CAR acts as a receptor in both human and mouse cells. CAR is a tight junction protein in noncardiac cells and is expressed at high levels in the intercalated disc of myocardial cells. Entry of the virus through the receptor activates a signaling complex that includes $p56^{lck}$, Abl, and Fyn kinase.[34]

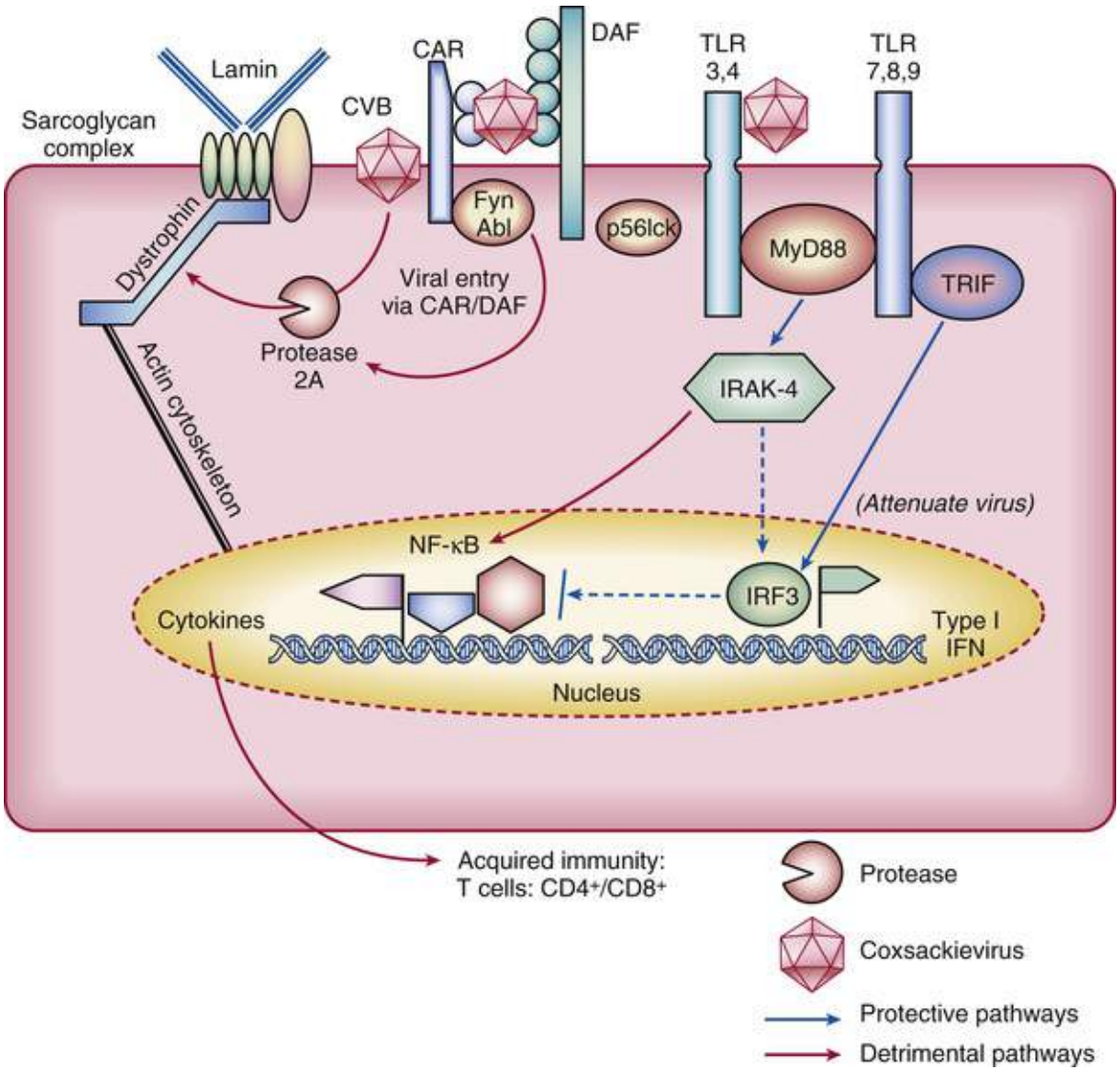

FIGURE 79.5 The pathogenesis of viral myocarditis, such as that caused by coxsackievirus. The virus enters the cell membrane through internalization receptors of the coxsackievirus-adenovirus receptor (CAR), which in turn can trigger receptor-associated kinases such as p56lck, Fyn, and Abl to alter host myocyte cytoskeleton to facilitate viral entry. Viruses such as coxsackievirus B (CVB) can directly produce enzymes such as protease 2A that can disassemble the important cytoskeletal components such as dystrophin-sarcoglycan complex, leading to myocyte remodeling and destruction. Engagement of the receptor also activates tyrosine kinases, which are important for T-cell clonal expansion and linking between the innate and acquired immune systems. The virus also activates innate immunity by engaging Toll-like receptors (TLRs) through adaptors such as MyD88 and TRIF (Toll/interleukin-1 [IL-1] receptor domain–containing adaptor-inducing interferon-β). Activation and translocation of NF-κB, on the one hand, will produce cytokines and trigger acquired immunity such as $CD4^+/CD8^+$ T-cell mobilization. On the other hand, this can be attenuated by the activation of IRF3 and type I interferon (IFN) production. The latter may be protective through multiple mechanisms, including attenuation of the virus. *DAF*, decay-accelerating factor (CVB coreceptor); *IRAK*, interleukin receptor–associated kinase (a signaling protein in innate immune pathway); *IRF*, interferon regulatory factor.

On entry of the enterovirus into the cell, the positive, single-strand RNA is released from the

icosahedral capsid and translated using host translational mechanisms. The viral RNA is translated as a single, monocistronic polyprotein, which is cleaved into its separate peptides by the viral proteases 2A and 3C; through an autocatalytic cleavage process, VP0 is cleaved into VP2 and VP4. This results in generation of capsid and nonstructural proteins, including an RNA-dependent RNA polymerase that is required for replication of the viral genome. The other nonstructural proteins also are required for replication of the positive-strand RNA through a negative-strand intermediate. Once the numbers of viral capsid proteins have been amplified and the positive-strand RNA has replicated, the positive-strand RNA is encapsidated into the newly formed viral capsid proteins VP1, VP2, VP3, and VP4. The encapsidated coxsackievirus RNA is released from the myocardial cell through a process of cell lysis and disruption of the sarcolemmal membrane.

Several mechanisms are recognized to affect membrane integrity, thus affecting in turn release of the replicated virus. Muscle cells rely on the subsarcolemmal protein dystrophin and the associated proteins in the dystrophin-glycoprotein complex to maintain the integrity of the sarcolemmal membrane. Hereditary absence of dystrophin in Duchenne muscular dystrophy, for example, causes cardiac and skeletal muscle dysfunction. In enterovirus-induced murine myocarditis, it has been demonstrated that one of the nonstructural proteins, protease 2A, is able to directly cleave dystrophin, thus disrupting the dystrophin-glycoprotein complex. This decreases the sarcolemmal membrane integrity and facilitates the release of the virus from the myocardial cell. When dystrophin is not present in the mouse heart, as occurs in Duchenne muscular dystrophy, coxsackievirus is released more efficiently from the myocyte to infect adjacent cells.[36] However, when a dystrophin protein is expressed that cannot be cleaved by protease 2A, viral replication and the extent of myocardial damage is decreased.[37] Proteases 2A and 3C can cleave other host proteins that are involved in the maintenance of membrane integrity, initiation of translation of host proteins, regulation of apoptosis, innate immune response, and serum response fator.[38] Other lytic viruses use similar mechanisms. For example, adenovirus expresses a proteinase that cleaves the cytoskeletal protein cytokeratin 18.

Generally, the activation of the innate and adaptive, antigen-specific immune response eliminates or greatly reduces the replication of the virus within the host cell. In some instances, however, the virus can persist within the myocardium. In keeping with the presence of the enteroviral genome in a subset of patients with DCM, it is thought that persistence of the enteroviral genome could contribute to the ongoing remodeling that occurs with DCM. The feasibility of this concept has been shown in a mouse model, in which low-level, cardiac-specific expression of a replication-defective enteroviral genome can cause cardiomyopathy. However, the proportion of patients in whom the enteroviral genome can be identified with reverse transcriptase PCR (rtPCR) or in situ hybridization techniques generally is less than 10%. The early phases of enteroviral infection and intramyocardial innate immunity can now be studied in human induced pluripotent stem cells that are differentiated to cardiac myocytes.

Other types of viruses also have been detected in cardiac biopsy specimens from patients with DCM. These viruses include B19V, herpesvirus, cytomegalovirus, hepatitis C virus, and others.[15] Distinguishing whether the presence of a viral genome in each patient is causative or an incidental finding in cardiomyopathy has not been trivial. For example, the B19V viral genome can be detected in a high percentage of patients independent of whether they have cardiomyopathy. It has been demonstrated that only 15.9% of patients that have evidence of B19V DNA on EMB have evidence of B19V mRNA. Interestingly, there is a significant difference in expression profiling in the biopsies that show transcriptionally active B19V, suggesting that transcriptional activity of the B19V may have a role in the pathogenesis.[18]

Innate Immunity

Innate immunity is effective during the earliest stages of virus infection. It is an antigen-independent defense mechanism that protects the host from a broad range of microbial pathogens. Innate immunity is initiated in the first days of enteroviral infection and is the major immune mechanism responsible for inhibiting viral infection and replication during the first 4 to 5 days after infection. In addition to innate immune mechanisms in noncardiac organs, important innate immune responses also are activated in the cardiac myocyte.[36] One of the classic and best-characterized examples of innate immunity is the activation of interferon signaling that occurs with viral infection. The two broad classes of interferons use different receptors: Type I interferons bind to the IFN-α receptor and include interferon-α and interferon-β, whereas IFN-γ is the sole type II interferon member. Both types of interferons are effective at limiting viral replication when added to infected cells or when administered to a coxsackievirus-infected mouse.[36] The absence of type I interferon receptors or interferon-β in mice is associated with a marked increase in mortality rates but has less effect on early viral replication in the heart. In a phase II clinical trial, it has been demonstrated that administration of interferon-β to virus-positive patients with symptoms of heart failure caused significant clearance or reduction of the virus load and improvement in the New York Heart Association (NYHA) functional class and quality of life. In enterovirus-positive patients, interferon-β may improve survival rates.[39] Additional content on this this topic is discussed in an online supplement for this chapter titled The Role of Innate Immunity in Myocarditis.

The Role of Innate Immunity in Myocarditis

Toll-Like Receptors

Toll-like receptor (TLR) activation is among the most common and earliest innate immune mechanisms. Multiple TLRs (TLR2, TLR3, TLR4, TLR7, and TLR9) have been implicated in inflammatory heart disease and myocarditis.[1] The receptors recognize pathogen-associated molecular patterns activating a defense against the invading pathogens. TLRs do not have the high specificity conferred by the antigen-specific B and T cells and thus react more quickly. Stimulation of the TLRs by foreign ribonucleic acids, DNA, or proteins leads to activation of signaling and transcriptional mechanisms, which result in increases in cytokines and interferon regulatory factors that increase expression of interferons and other antiviral signaling pathways. TLR signaling uses adaptor molecules and kinases such as MyD88 and interleukin receptor–associated kinases (IRAKs). Both TLR3 and TLR4 are abundant in the myocardium. TLR3 recognizes double-stranded RNA, whereas TLR7 and TLR8 can be activated by single-stranded RNA. Both single- and double-stranded RNA are generated as part of the coxsackievirus replication cycle. TLR4 recognizes bacterial lipopolysaccharides. Disruption of TLR3 was shown to augment encephalomyocarditis virus–induced heart disease in the mouse. A similar effect is observed with CVB3 infection. Also, TLR4 disruption increases the pathogenesis of coxsackievirus B3–induced myocarditis.

The downstream molecules of TLR signaling have been shown to have a significant effect on coxsackievirus B3 infection. One of the better-studied of these molecules is MyD88, which binds to TLR4, and the endosomal molecules TLR7 to TLR9. When mice with a global knockout of MyD88 are infected, a marked reduction is seen in the susceptibility to viral infection, indicating that the absence of MyD88 confers host protection, potentially through direct activation of IRF-3 and interferon-β. The absence of MyD88 also controls the induction of α-myosin heavy chain–stimulated autoimmune myocarditis through defective induction of dendritic cell–mediated TNF-α.[2]

Other Innate Immune Mechanisms

Other innate immune responses are important in the control of the initial phases of viral infection. For example, inhibition of glycoprotein 130 (gp130) signaling by transgenic expression of the suppressor of cytokine signaling (SOCS)-1 or -3 results in a marked increase in the susceptibility to viral infection in the mouse. In addition, the relevance of RNA helicases in the activation of innate immunity against viral infection has been demonstrated. dsRNA can be recognized by the RNA helicases, retinoic acid–induced protein (RIG-I), and melanoma differentiation–associated gene 5 (MDA-5). These RNA helicases can interact with mitochondrial antiviral signaling (MAVS), activating signaling cascades that ultimately increase type I interferons.[3,4] The importance of MAVS after infection with RNA viruses was confirmed in MAVS-knockout mice.[3,4]

Activation of inflammasomes has been demonstrated to occur in patients with acute viral myocarditis within the first 4 weeks of the onset of the disease. The inflammasome is a macromolecular complex that is activated during myocardial injury. It stimulates processing of IL-1β and IL-18, which are important in the innate immune response against viral infection. It is thought that inflammasome activation can limit viral replication, though it could also damage the cell. Evasion of the inflammasome process might decrease myocardial cell damage, but might also contribute to viral persistence.[5,6]

Macrophages have been shown to have an important role in the early innate immune response. They act as scavengers, microbicidal effector cells, and regulatory cells in the onset of cardiac inflammation. Early recruitment of inflammatory macrophages ($Ly6C^{hi}$) occurs following cardiac injury. Chemokine (C-C motif) receptor 2 (CCR2) has been implicated in having a role in macrophage infiltration in the heart of CVB3 infected mice. Although macrophages are involved in the early response to injury, they are also responsive to T cells. CD4+ T (type 1 T helper [Th1]) cells influence the differentiation of monocytes toward proinflammatory M1 macrophages. The interferon-γ secreted by Th1 cells potentiates microbicidal activity of macrophages. $Ly6C^{low}$ M2 macrophages blunt the inflammatory response and predominate during myocardial healing.[7]

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Acquired Immunity

Acquired immunity becomes a prominent manifestation of viral myocarditis beginning approximately 4 to 5 days after the viral infection, although the peak and pattern of activation are variable. The acquired immune response is an antigen-specific response that is directed to a single antigen and is mediated by T and B cells. T cells are targeted to infected cells and attempt to limit infection by destroying the host cell through secretion of cytokines or perforins. These can contribute to the death of the infected cell through necrotic and/or apoptotic mechanisms. Thus, although T cell–mediated immune mechanisms are important for controlling and limiting viral replication, they also can have detrimental effects on the infected organ by stimulating cell death mechanisms in the infected host. Appropriately limiting the T-cell and B-cell immune mechanisms could limit damage to the heart, but such inhibition needs to be balanced by the need to inhibit viral replication.[40]

The acquired immune process is initiated when the variable region of the T-cell receptor binds to peptides with specific amino acid sequences that are recognized as foreign to the host. When $CD4^+$ T cells interact with antigen-presenting cells such as dendritic cells, the $CD4^+$ cells can differentiate into different effector cell subsets, such as the classic Th1 and Th2 cell subtypes: Th17 and T regulatory (Treg) cells. Cytokines in the cellular microenvironment can control how the cells differentiate. The precise cellular signaling cascades and pattern of cytokine production that are associated with differentiation of these distinct T-cell subtypes has been reviewed elsewhere.[40,41] Appropriate regulation of effector T cells is needed to control infections and at the same time avoid inappropriate immunologic destruction of host tissue such as myocardial cells. Activation of T cells also leads to B-cell activation, which results in secretion of antigen-specific antibodies directed against the invading pathogen. After initial activation, the immune cells undergo clonal expansion to attack the source of antigen, which could include a viral coat protein or, in some cases, proteins in the cardiac myocyte such as myosin. There is evidence that cross reaction with the host may occur because of “molecular mimicry” between the virus and the host. Treg cells have important functions for the suppression of Th1-cell and Th2-cell immune responses and were previously identified as T helper cells. They are characterized by the expression of the forkhead transcription factor, Foxp3, and are defined as $CD4^+CD25^+Foxp3^+$. The classic model held that commitment of $CD4^+$ cells to the different effector lineages involved stable programs of gene expression and that once differentiated, they maintained that effector phenotype even as changes in the microenvironment occurred. This model, however, has evolved, because of evidence that $CD4^+$ T cells have an element of plasticity in that they can alter their functional programs and in this way change the balance between Treg cells and cytokine-producing T cells and the type of cytokines that they produce.[40] This plasticity may be important as new therapeutic strategies are developed. The activation of T cells is highly dependent on an interaction with the innate immune-signaling cascade. For example, the T cell receptor downstream signaling uses p56lck. It is interesting that p56lck also has been shown to bind to the CAR-DAF receptor complex and that it is involved in viral entry. When p56lck is genetically deleted from the mouse, typical myocarditis is almost eliminated, with no significant mortality rates after infection.[42]

Alterations in any of the pathogenic mechanisms just described could, theoretically, affect the susceptibility to viral infection. For example, alterations in the mechanism of viral entry and replication, innate or acquired immune-signaling mechanisms, or the integrity of the sarcolemmal membrane could affect the susceptibility to develop myocarditis on exposure to a given virus. Nutrition is also likely to have an effect on the susceptibility to viral infection. It is thought that a deficiency of selenium can increase the risk of myocarditis, as has been described in the Keshan province in China. When selenium deficiency was prevented, the incidence of myocarditis and DCM decreased. Furthermore, selenium deficiency in mice also increased the susceptibility to enteroviral myocarditis. The number of

mechanisms known to affect the susceptibility to myocarditis in humans is far from complete.

Cardiac Remodeling

Remodeling of the heart after cardiac injury (**see also Chapter 23**) can significantly affect cardiac structure and function, and the degree of such remodeling may mean the difference between appropriate healing and the development of DCM. The virus can directly enter the endothelial cells and myocytes and effect changes that lead to direct cell death or hypertrophy. The virus also can modify the myocyte cytoskeleton, as mentioned earlier, leading to DCM. The inflammatory process outlined earlier for both innate and acquired immunity can lead to cytokine release and activation of matrix metalloproteinases that digest the interstitial collagen and elastin framework of the heart (**see Chapter 23**).

Clinical Syndromes

Myocarditis has a wide-ranging array of potential clinical presentations, a feature that contributes to the difficulties in diagnosis and classification. The clinical picture may be one of asymptomatic electrocardiographic or echocardiographic abnormalities or may include signs and symptoms of chest pain, cardiac dysfunction, arrhythmias or heart failure, and/or hemodynamic collapse. Transient electrocardiographic or echocardiographic abnormalities have been observed frequently during community viral outbreaks or influenza epidemics, but most patients remain asymptomatic from a cardiac standpoint and have few long-term sequelae. Chest pain from myocarditis may resemble typical angina and be accompanied by ECG changes, including ST-segment elevation. Coronary vasospasm, demonstrated using intracoronary acetylcholine infusion, is one cause for chest pain in patients with clinical signs of myocarditis in the absence of significant coronary atherosclerosis.[43] Chest pain also may mimic that in pericarditis, suggesting epicardial inflammation with adjacent pericardial involvement. The outcome of myopericarditis generally is good, with only two sudden deaths reported from four published case series (N = 128) (**Table 79.4**). Additional content on clinical syndromes is presented in an online supplement for this chapter entitled Specific Clinical Presentations of Myocarditis.

TABLE 79.4

Outcome of Myopericarditis and Perimyocarditis in Recent Clinical Series

STUDY	SETTING	TROPONIN (PEAK)	FOLLOW-UP	MORTALITY RATES
Imazio et al, 2008	Myopericarditis/adult (40 patients)	TnI: 7.7 ± 6.7 μg/L (1.5-22.5)	12 months	0%; normalization of parameters in 97.5%
Machado et al, 2010	Myopericarditis/adult (14 patients)	TnI: 7.3 μg/L (4.4-10.2)	20 months	21.4%
Kobayashi et al, 2012	Myopericarditis/pediatric (12 patients)	TnI: 4.75 μg/L (1.35-9.72)	2 months (2 weeks to 3 years)	0%; normal LVEF and function
Buiatti et al, 2012	Perimyocarditis/adult (62 patients)	TnI: 10.5 ± 17.0 μg/L	4.5 ± 0.8 years	0%; normalization of echo features in 100%

LVEF, left ventricular ejection fraction; *TnI,* troponin I.

Modified from Imazio M, Cooper LT: Management of myopericarditis. Expert Rev Cardiovasc Ther 2013;11:193.

Myocarditis typically has a bimodal distribution in terms of age in the population, with the acute or fulminant presentation more commonly seen in young children and teenagers. By contrast, the presenting symptoms are more subtle and insidious, often with DCM and heart failure, in the older adult population. The difference in presentation probably is related to the maturity of the immune system, whereby the young tend to mount an exuberant response to the initial exposure of a provocative antigen. By contrast, older persons would have developed a greater degree of tolerance and show a chronic inflammatory

response only to the chronic presence of a foreign antigen or with a dysregulated immune system that predisposes to autoimmunity. Myocarditis probably is responsible for 10% to 50% of new-onset cases of idiopathic DCM, a rate that varies depending on the criteria used for diagnosis. Viral myocarditis has been associated with heart failure from both systolic and isolated diastolic dysfunction.[44]

The presentation of myocarditis varies by cause. For example, B19V frequently causes chest pain from endothelial dysfunction, whereas ventricular arrhythmias and heart block are more common in giant cell myocarditis (GCM).[44] Associated physical examination findings point to specific causes for myocarditis. Enlarged lymph nodes with hilar adenopathy on the chest radiograph may suggest systemic sarcoidosis. A pruritic, maculopapular rash with an elevated eosinophil count suggests a hypersensitivity reaction to a drug or toxin. Patients who present with DCM complicated by sustained or symptomatic ventricular tachycardia or high-grade heart block are at high risk for having GCM or cardiac sarcoidosis. A study of 72 young Finnish patients with initially unexplained atrioventricular block revealed that 25% had either cardiac sarcoidosis (19%) or GCM (6%). Of these 18 patients, 7 (39%) experienced sustained ventricular tachycardia or cardiac death or required transplantation over an average follow-up period of 48 months (**Fig. 79.6**).[45] A prospective study of 12 patients with biopsy-proven GCM revealed that 25% of patients with a cardiomyopathy of less than 6 months' duration that failed to respond to usual care or was complicated by ventricular tachycardia or high-grade heart block had GCM.[46] In patients who fail to recover from an acute episode of myocarditis, the persistence of left ventricular dysfunction can sometimes be due to ongoing immune activation or chronic myocarditis.[1] Failure to clear virus from the heart has been postulated to underlie some cases of persistent heart failure. Recognition of endogenous proteins, such as cardiac myosin, as “foreign” may contribute to ongoing inflammation even after successful viral clearance.[47,48] In clinical practice, the distinction between a noninflammatory DCM and a chronic inflammatory DCM with or without viral infection requires EMB. As discussed further on, the lack of positive large-scale trial data supporting either immunosuppression or antiviral therapy currently limits the application of EMB in this setting.

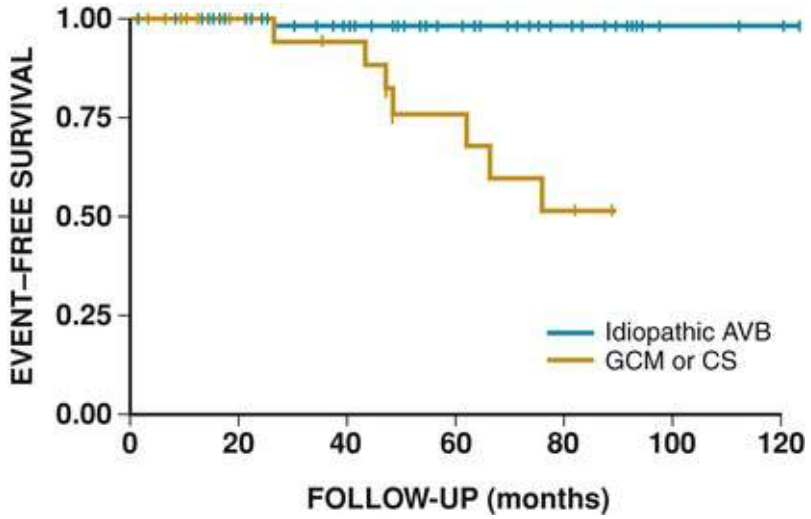

FIGURE 79.6 Kaplan-Meier curves for survival free of major adverse cardiac events (cardiac death, cardiac transplantation, ventricular fibrillation, or treated sustained ventricular tachycardia) in patients with pacemaker implantation for atrioventricular block that remained idiopathic or atrioventricular block due to cardiac sarcoidosis (CS) or GCM. (From Kandolin R, Lehtonen J, Kupari M: Cardiac sarcoidosis and giant cell myocarditis as causes of atrioventricular block in young and middle-aged adults. Circ Arrhythm Electrophysiol 2011;4:303.)

Specific Clinical Presentations of Myocarditis

Acute Myocarditis

Classically, patients with myocarditis present with nonspecific symptoms related to the heart. In a recent series of 245 patients with clinically suspected myocarditis, the most common symptoms included fatigue (82%), dyspnea on exertion (81%), arrhythmias (55%, both supraventricular and ventricular), palpitations (49%), and chest pain at rest (26%).[1] These can be difficult to distinguish from acute ischemic syndromes because they result in release of troponin, ST-segment elevation on electrocardiography, and segmental wall motion abnormalities on echocardiography. Therefore, the symptoms can be quite nonspecific, although some symptoms indicate cardiac involvement. The viral prodrome of fever, chills, myalgias, and constitutional symptoms occurs in 20% to 80% of the cases and can be readily missed by the patient; thus, they cannot be relied on for a diagnosis.

Many cases of myocarditis present with de novo onset of heart failure, particularly when the patient is middle aged or older. When the health care team fails to identify other causes of heart failure, viral myocarditis, along with idiopathic dilated cardiomyopathy (DCM), becomes the diagnosis of exclusion. To distinguish myocarditis from idiopathic DCM, almost one third of the cases of viral myocarditis will recover to normal cardiac function with appropriate supportive therapy, which is less frequent in genetic DCM.

Fulminant Myocarditis

Approximately 10% of patients with biopsy-proven myocarditis display fulminant myocarditis. This entity is characterized by an abrupt onset, usually within 2 weeks of a viral illness. Patients have hemodynamic compromise and hypotension, often requiring pressors or mechanical support. The echocardiogram reveals diffuse global hypofunction, rarely, cardiac dilation, and typically, thickening of the ventricular wall, probably due to myocardial edema from myocardial inflammation and cytokine release. Endomyocardial biopsy (EMB) reveals typical and diffuse myocarditis in virtually each histologic section, making it a reliable source of confirmation. On follow-up, 93% of the original cohort were alive and transplant free 11 years after the initial biopsy, compared with only 45% of those with chronic myocarditis.[2] This underscores the importance of supporting patients with fulminant myocarditis as aggressively as needed to maximize the time for recovery.

Giant Cell Myocarditis

Another distinctive clinicopathologic form of myocarditis is giant cell myocarditis (GCM). This disorder is more subtle in onset than fulminant myocarditis and may not be distinguishable from other forms of myocarditis initially. Patients may present with heart failure, arrhythmia, or heart block, which despite standard medical therapy fails to improve. The survival time for this population is less than 6 months; it is improved with the use of immunosuppressive therapy.[3] Preliminary data suggest that high-dose multiagent immunosuppression may improve the prognosis; however, there are no prospective randomized trials to confirm this approach. Early discontinuation of immunosuppression may lead to recurrence. EMB reveals a distinctive pattern of giant cells with active inflammation and scar tissue. Currently, cardiac transplantation, often preceded by mechanical circulatory support, remains the only alternative for most patients with this disorder. Early recognition and immunosuppressive therapy may alter this approach.

Patients with GCM often have other autoimmune disorders, including thymoma and Crohn disease. The pathophysiologic mechanism remains unknown but is suspected to be autoimmune in nature.

Chronic Active Myocarditis

Patients in this group are mostly older adults with myocarditis, and the onset is often insidious and difficult to pinpoint. The patient presents with symptoms compatible with moderate ventricular dysfunction, such as fatigue and dyspnea. Pathologic examination of a myocardial biopsy specimen may show active myocarditis, but more frequently it is only borderline or generalized chronic myopathic changes with fibrosis and myocyte dropout. Some may progress to diastolic dysfunction with predominantly fibrosis; this condition ultimately resembles a restrictive cardiomyopathy.

This category encompasses 60% to 70% of patients with active or borderline myocarditis who present with DCM of unknown cause. Use of newer imaging approaches, such as magnetic resonance imaging with gadolinium enhancement and positron emission tomography–computed tomography (PET-CT), molecular diagnosis by immunohistopathologic analysis, assessment of up-regulation of immune markers, and molecular testing, including PCR and in situ hybridization, may expand this population significantly.

Eosinophilic Myocarditis

The eosinophil may be associated with myocardial inflammation in three distinct forms. *Allergic eosinophilic myocarditis* is caused by a hypersensitivity reaction to a foreign antigen, almost always a drug. This form of myocarditis requires a high degree of suspicion (related to the initiation of new agents) and subtle declines in left ventricular function. Withdrawal of the offending agent and administration of corticosteroids usually result in resolution. The heart may be inflamed in association with systemic eosinophilic disorders, resulting in myocardial, endocardial, and valvular involvement (*Löffler endocarditis*). The outcome is dependent on control of the underlying condition. Finally, *fulminant necrotic myocarditis* presents in a fashion similar to fulminant myocarditis, has no clear cause, and requires aggressive medical immunosuppression and occasional mechanical support.

Peripartum Cardiomyopathy

Peripartum cardiomyopathy is characterized by the onset of left ventricular dysfunction in the last month of pregnancy or within 5 months of delivery, with no preexisting cardiac dysfunction and no recognized cause of the cardiomyopathy. There is evidence that patients submitted to EMB early after presentation have a high frequency of myocarditis.[4] Because most patients with this disorder recover with standard therapy, biopsy is recommended only for those with persistent left ventricular dysfunction and symptoms despite heart failure management.

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Diagnostic Approaches

The diagnosis of myocarditis traditionally has required a histologic diagnosis according to the classic Dallas criteria. However, because of low sensitivity due to the patchy nature of the inflammatory infiltrates in the myocardium and the reluctance of clinicians to perform an invasive diagnostic procedure, myocarditis is severely underdiagnosed. Because the incidence of the disease is likely to be much higher than is appreciated, a high level of clinical suspicion, together with hybrid clinical and laboratory criteria and new imaging modalities, may help secure the diagnosis without necessarily resorting to biopsy in all cases (**see Table 79.2**).[2] Although clinical and imaging criteria have been used to estimate the myocarditis prevalence in various cohorts without EMB confirmation, such criteria probably sacrifice diagnostic specificity.

Laboratory Testing

The role of cardiac injury biomarkers in screening for myocarditis in patients with acute viral illness has been investigated in accordance with the hypothesis that a diagnosis of heart damage in this setting may indicate a greater risk of arrhythmias or cardiomyopathy. In this regard, elevated cardiac troponin values help to confirm cases of suspected myocarditis. Whereas older studies suggested that the sensitivity of troponins for myocarditis was low, more recent studies using more sensitive assays in less chronic disease support the value of troponin. For example, troponin levels predicted the severity of myocarditis and short-term prognosis in a case series of 65 children with recent-onset myocarditis. Fulminant myocarditis was associated with higher levels of cardiac troponins I and T (cTnI and cTnT) than acute myocarditis, and a higher cardiac troponin level was associated with a lower left ventricular ejection fraction.[49] In a case series of adults hospitalized with acute or fulminant myocarditis, creatine kinase–MB concentrations of greater than 29.5 ng/mL predicted in-hospital death with a sensitivity of 83% and a specificity of 73%. A growing literature also supports a role for TnI as an autoantigen as well as a biomarker for diagnosis.[50]

During the influenza A epidemic (H3N2) in Japan from 1998 to 1999, the myosin light-chain concentration was raised in 11.4% of patients without cardiac symptoms.[51] Recently, Renko and associates prospectively measured cTnI levels in 1009 children to determine the incidence of myocarditis in children hospitalized for an acute infection. TnI levels exceeded the screening limit (0.06 µg/L) in only six children, none of whom had electrocardiographic or echocardiographic abnormalities. Thus the incidence of acute myocarditis during childhood viral infections appears to be low, so routine TnI screening for asymptomatic myocarditis in unselected children without cardiac symptoms probably is not indicated.[52] The rate of asymptomatic increases in troponin after smallpox vaccination is as high as 28.7 per 1000.[30] The risk of acute cardiomyopathy appears low in the first year after smallpox vaccination, but the longer-term significance of a troponin rise in this setting is not known.[53]

A variety of other biomarkers have demonstrated prognostic value in acute myocarditis. In children with fulminant myocarditis, higher serum creatinine, lactate, and aspartate transaminase (AST) levels are associated with increased in-hospital mortality rates.[54] N-terminal pro–B type (brain) natriuretic peptide (NT-pro-BNP) is predictably elevated in children with acute DCM due to myocarditis and generally

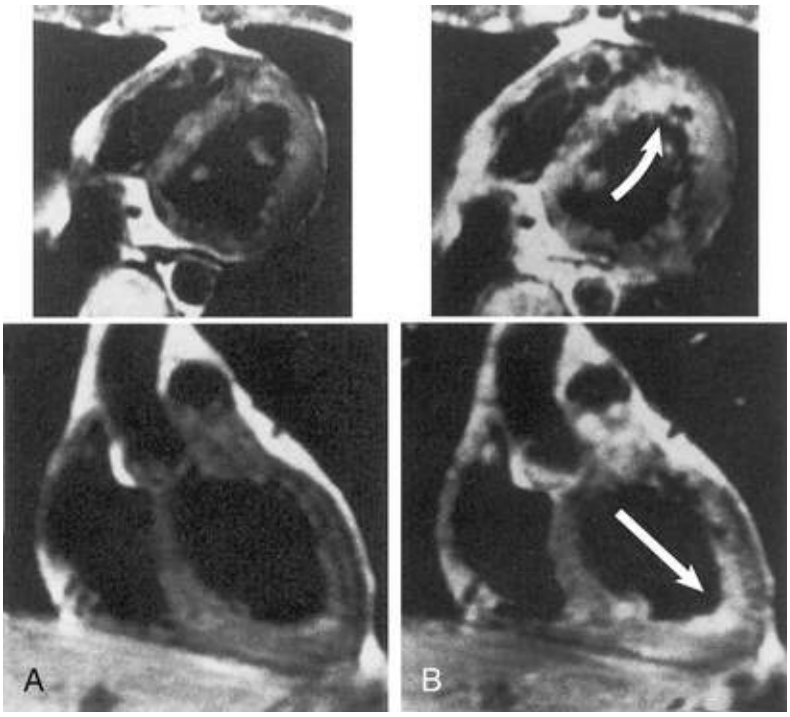
declines rapidly in children who recover left ventricular function.[55] In adults, higher interleukin-10 and soluble Fas concentrations are associated with an increased risk of death. Anti–heart antibodies have been reported to predict an increased risk of death or need for transplantation.[56] However, few anti–heart antibody tests are standardized or available in clinical laboratories. Nonspecific biomarkers of inflammation, such as the leukocyte count, C-reactive protein, erythrocyte sedimentation rate, and leukocyte count have low specificity. Circulating viral antibody titers do not correlate with tissue viral genomes and are rarely of diagnostic use in clinical practice.[57]

Pathognomonic ECG findings are lacking in acute myocarditis, but nonspecific repolarization changes and sinus tachycardia are common (**see also Chapter 12**). PR-segment depression and diffuse ST-segment elevation may accompany a clinical presentation of myopericarditis.[58] The presence of a QRS width greater than 120 milliseconds in duration and Q waves is associated with a great risk of cardiac death or need for heart transplantation.[59]

Cardiac Imaging

An assessment of left ventricular function is essential in all cases of suspected myocarditis, accomplished by means of cardiac imaging (**see also Chapters 14 to 17**). Echocardiography is an excellent choice for imaging, although there are no specific echocardiographic features of myocarditis. In patients who have an acute cardiomyopathy, the most common pattern is a dilated, spherical ventricle with reduced systolic function. Patients with heart failure due to fulminant myocarditis typically present with small cardiac chambers and mild and reversible ventricular hypertrophy from inflammation. Right ventricular dysfunction is less common and heralds a poor prognosis. Of interest, segmental wall motion abnormalities often are present early and may mimic the regional changes seen in a myocardial infarction. A pericardial effusion usually signifies myopericarditis.

CMR can distinguish most cases of ischemic from nonischemic cardiomyopathy, and certain patterns of signal abnormality strongly suggest acute myocarditis (**eFig. 79.2**).[60] Furthermore, the T1-weighted, myocardial delayed enhancement technique can quantitate regions of damage and possibly predict the risk of cardiovascular death and ventricular arrhythmias after myocarditis.[61] Abnormalities on delayed enhancement imaging also correlate with myocarditis in patients who present with chest pain and normal coronary arteries. However, the T2-weighted, short tau inversion recovery (STIR) and T1-weighted delayed postcontrast signal abnormalities seen in acute myocarditis usually decrease with time. In a recent study the sensitivity and specificity of CMR in suspected myocarditis more than 14 days after symptom onset were poor (sensitivity, 63%; specificity, 40%).[62] Thus, CMR performs best in the setting of acute cardiomyopathy or chest pain with elevated troponin. Both T1- and T2-weighted sequences should be used, to optimize the sensitivity and specificity.[63] T2 mapping has been used recently to decrease artifacts that are common with T2-weighted sequences.



EFIGURE 79.2 **A,** Precontrast T1-weighted transaxial (*upper*) and coronal (*lower*) magnetic resonance images through the left ventricle in a patient with myocarditis. **B,** Postcontrast magnetic resonance images at the same levels after injection of contrast material. Note enhancement of the myocardial signal in the septum and apical region (*arrows*). (From Matsouka H, Hamada M, Honda T, et al: Evaluation of acute myocarditis and pericarditis by Gd-DTPA enhanced magnetic resonance imaging. Eur Heart J 1994;15:283.)

Although most nuclear imaging techniques are ancillary in the evaluation of suspected myocarditis, positron emission tomography (PET) imaging remains useful for diagnosing cardiac sarcoidosis.[64] Isiguzo and colleagues recently showed a significant association of metabolism-perfusion mismatch by rubidium-FDG PET with clinically active disease in cardiac sarcoidosis patients.[65] Case control series suggest that patients with cardiomyopathy or ventricular arrhythmias due to cardiac sarcoidosis may benefit from steroid therapy.

Endomyocardial Biopsy

EMB remains essential for the diagnosis of specific forms of myocarditis.[66] The rate of major complications with EMB is less than 1 in 1000 when the procedure is done by experienced operators.[67] In children with suspected myocarditis, EMB demonstrating myocarditis can identify responders to medical treatment. Because myocarditis may only involve regions of one ventricle, several large-volume cardiac centers are routinely performing left as well as right ventricular biopsy. In these centers, the safety of left ventricular biopsy is equivalent to that of right ventricular biopsy, and the diagnostic yield is greater.[68,69]

The clinical scenarios in which EMB is most useful are suspected GCM and fulminant lymphocytic myocarditis (**Fig. 79.7**).[70,71] GCM should be considered in acute DCM that fails to respond to usual care or is complicated by high-grade heart block or sustained ventricular tachycardia. The use of immunosuppressive therapy that includes cyclosporine probably increases the transplant-free survival rate in patients with GCM whose symptoms are of less than 6 months' duration.[46,72] Histologically, GCM is defined by a diffuse or multifocal inflammatory infiltrate of lymphocytes and multinucleated giant cells in the absence of granuloma. In contrast with cardiac sarcoidosis, in which the giant cells are located within the granuloma, the giant cells often are located at the edges of the inflammation, where myocyte damage is present. Eosinophils are significantly more common in GCM, whereas fibrosis is significantly more common in cardiac sarcoidosis. Immunohistochemistry may be beneficial in differentiating GCM

from cardiac sarcoidosis.

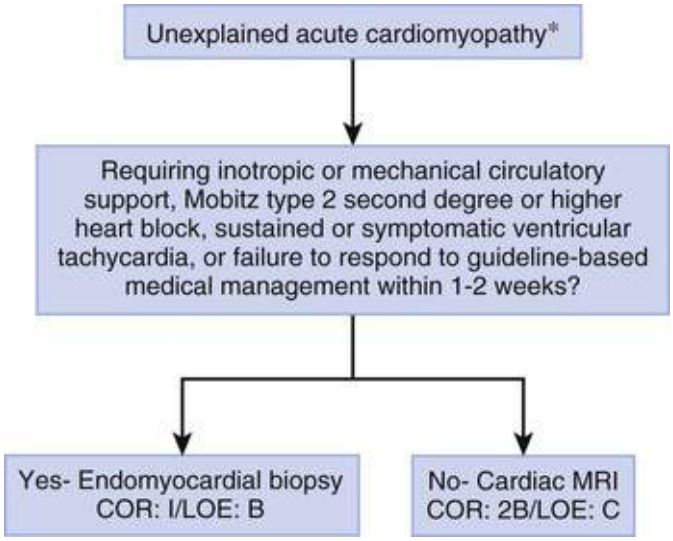


FIGURE 79.7 Algorithm for the evaluation of suspected myocarditis in the setting of unexplained acute cardiomyopathy. *COR,* class of recommendation; *LOE,* level of evidence; *MRI,* magnetic resonance imaging. *Usually a DCM. Fulminant myocarditis may have normal end-diastolic diameter with mildly thickened walls. Exclude ischemic, hemodynamic (valvular, hypertensive), metabolic, and toxic causes of cardiomyopathy as indicated clinically. (From Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2016;134:e282-93.)

Prognosis

The prognosis for patients with acute myocarditis varies in relation to the clinical scenario and degree of left ventricular dysfunction at presentation.[73] Patients who present with myopericarditis or chest pain suggestive of an acute coronary syndrome usually do well if their left ventricular function is normal or near normal.[74] However, approximately 15% of patients with myopericarditis may develop recurrent myopericarditis. In acute DCM, the risk of death or need for cardiac transplantation is increased in those myocarditis patients with lower left ventricular function, lower right ventricular function, and higher pulmonary artery pressures. In children, the time course of left ventricular functional recovery extends to at least 8 years, and the overall risk of death or requirement for transplantation approaches 30% (**Fig. 79.8**).[75,76] In patients with a recent onset of DCM who were bridged to recovery with a left ventricular assist device, myocardial inflammation was present but fibrosis was less evident.[77] There is a risk of late heart failure due to diastolic dysfunction years after the apparent resolution of acute myocarditis.[44]

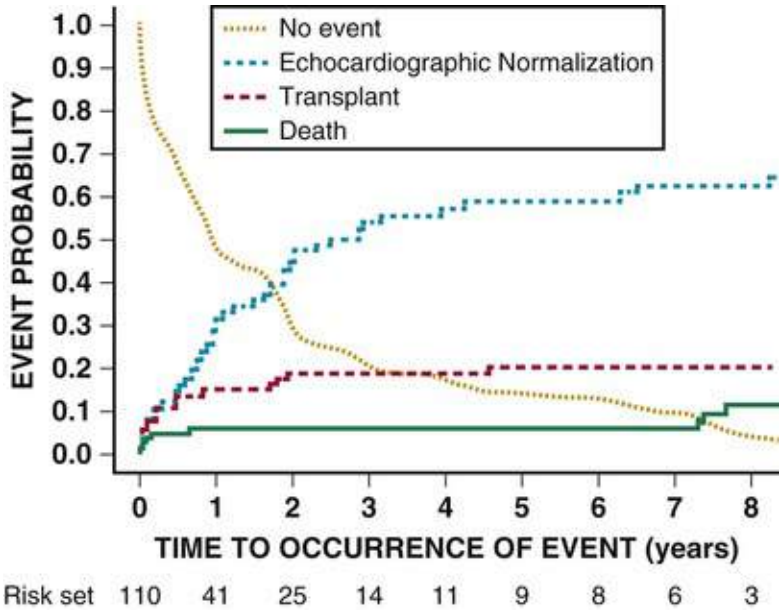


FIGURE 79.8 Crude cumulative incidence rates of echocardiographic normalization, cardiac transplantation, and death among children with biopsy-confirmed myocarditis. (From Foerster SR, Canter CE, Cinar A, et al: Ventricular remodeling and survival are more favorable for myocarditis than for idiopathic dilated cardiomyopathy in childhood: an outcomes study from the Pediatric Cardiomyopathy Registry. Circ Heart Fail 2010;3:689.)

In chronic DCM, the presence of inflammatory cells on EMB may define a subset of patients who will improve with a short course of immunosuppression. Some investigators have demonstrated that the presence of active myocarditis defined by immunohistology, but not conventional Dallas criteria, predicts the risk of death or need for transplantation. The presence of viral genomes on EMB may portend a poor outcome. Older clinical data for enteroviruses in acute cardiomyopathy were mostly consistent with this conclusion, but in recent years, the impact of viral genomes on the outcome has been questioned. Possibly the variable findings with respect to viral genomes may be due to a changing spectrum of viruses, from enteroviruses to B19V and human herpesvirus 6. In addition, genetic background differences in study populations, and possibly unmeasured environmental toxins or nutritional deficiencies, may account for differences in study outcomes. Recently, studies that have evaluated the impact of CMR imaging–associated delayed gadolinium enhancement on the cardiovascular risk following acute myocarditis generally support an association between delayed gadolinium enhancement and subsequent arrhythmic events.[63]

Treatment

The first-line therapy for all patients with myocarditis and heart failure is supportive care (**see Chapter 25**). A small proportion of patients will require hemodynamic support that ranges from vasopressors (**see Chapter 24**) to intraaortic balloon pump and ventricular assist devices (**see Chapter 29**) (**Fig. 79.9**). Guidelines for myocarditis management have been published by the American Heart Association,[78] Japanese Circulatory Society, and European Society of Cardiology (ESC) working group on myocarditis and pericarditis.[66] In patients who present with an acute DCM and a syndrome of heart failure, the current American College of Cardiology/American Heart Association (ACC/AHA) guidelines for heart failure care should be followed (**see Chapter 25**, Guidelines: Management of Heart Failure with a Reduced Ejection Fraction).[79] Clinical experience suggests that standard pharmacotherapy is effective in myocarditis, although trials of heart failure management in myocarditis have not been done.

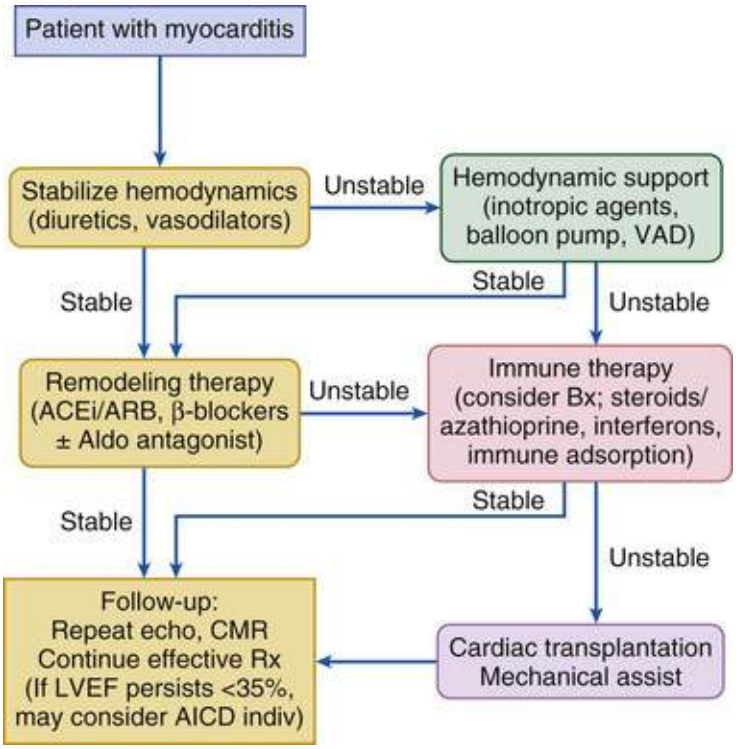


FIGURE 79.9 Treatment algorithms for patients with myocarditis, depending on hemodynamic stability and response to general supportive and remodeling treatment regimen at each step. All patients require aggressive support and appropriate follow-up. Immune therapy at present is still indicated mainly to support those who have failed to improve spontaneously. *ACEi,* angiotensin-converting enzyme inhibitor; *AICD,* automatic implantable cardioverter-defibrillator; *Aldo,* aldosterone; *ARB,* angiotensin receptor blocker; *Bx,* biopsy; *CMR,* cardiac magnetic resonance; *echo,* echocardiography; *indiv,* based on individual assessment of risk versus benefit; *LVEF,* left ventricular ejection fraction; *VAD,* ventricular assist device.

Routine treatment of mild to moderately severe acute myocarditis with immunosuppressive drugs is not recommended for adults. These data are based on the U.S. Myocarditis Treatment Trial, in which immunosuppression with prednisone and either azathioprine or cyclosporine effected similar changes in the left ventricular ejection fraction and transplant-free survival rates compared with placebo. Significant exceptions are recognized, including those of patients with GCM, cardiac sarcoidosis, eosinophilic myocarditis, and myocarditis associated with inflammatory connective tissue disorders. Also, the data from case-controlled series regarding the use of intravenous immunoglobulin (IVIG) and immunosuppressive drugs are neutral to favorable in the pediatric literature. Treatment of viral infection may be helpful in the management of posttransplantation viral heart disease in children.[12] However, in adult patients with chronic DCM and viral genomes detected by PCR assay on heart biopsy tissue, only one trial series suggests that 6 mIU of interferon-β three times per week can improve enteroviral or adenoviral heart infection.[39] There may be a role for a short course of immunosuppression in patients with chronic DCM who fail to respond to guideline-based heart failure management. In the Tailored Immunosuppression in Inflammatory Cardiomyopathy trial, 85 patients with chronic inflammatory cardiomyopathy without persistent viral infection were randomly assigned to receive either prednisone and azathioprine or placebo.[80] Immunosuppressive treatment was associated with an increase in the left ventricular ejection fraction from 26% to 46% and an improved quality of life. Larger, multicenter trials are needed to assess whether immunosuppression will affect clinically meaningful end points such as the risk of death or admission to hospital in this population.

Patients with ventricular arrhythmias or heart block due to acute myocarditis should be hospitalized for electrocardiographic monitoring. Arrhythmias usually resolve after several weeks. The ACC/AHA/ESC guidelines for the management of arrhythmias recommended that acute arrhythmia emergencies be

managed conventionally in the setting of myocarditis. Generally, the indications for an implantable cardiac-defibrillator (ICD) are the same as with nonischemic DCM. In the setting of GCM or cardiac sarcoidosis, the high rate of ventricular arrhythmias may warrant early consideration for an ICD. In patients with suspected lymphocytic myocarditis and nonsustained ventricular tachycardia, a temporary external defibrillator vest may be used while it is determined whether the arrhythmias will persist after the acute inflammatory phase.

Mechanical circulatory support (**see also Chapter 29**) or extracorporeal membrane oxygenation may allow a bridge to transplantation or recovery in patients with cardiogenic shock despite optimal medical care. In those patients who recover, the time to recovery in acute myocarditis varies, ranging from a few weeks to a few months. Transplantation also is an effective therapy for patients with myocarditis who have refractory heart failure despite optimal medical therapy and mechanical circulatory support. Survival rates after transplantation for myocarditis are similar to survival rates for other causes of cardiac transplantation. However, the risk of graft loss may be greater in children who undergo transplantation.

Future Perspectives

One of the major gaps in the management of myocarditis is the lack of a sensitive and specific noninvasive test. In this regard, diagnostic techniques are evolving to identify novel blood-based biomarkers reflecting cardiac inflammation through microarray and proteomic analysis of tissues from both laboratory models and patient samples.[38] Moreover, with improved understanding of pathophysiologic mechanisms, new therapies also are being developed and evaluated in clinical trials. These new treatments, including cell-based therapies that selectively inhibit T cell responses, induce apoptosis of activated T cells, and increase Treg cells, will be evaluated in planned clinical trials. Such prospective investigations should be designed specifically to establish efficacy in women. Translational studies focused on genomic markers in biopsy samples and peripheral blood should help refine risk assessments and target therapies to the populations at highest need.

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80

Cardiomyopathies Induced by Drugs or Toxins

Richard A. Lange, L. David Hillis

Many toxins, some used by a substantial fraction of the population, may affect the heart adversely, so it is important to understand the myriad ways in which these substances may influence the cardiovascular system. This chapter focuses on environmental exposures and commonly prescribed pharmacologic agents, as well as frequently used illicit drugs, including cocaine and amphetamines. **Chapter 81** discusses the toxicities of various chemotherapeutic agents in greater detail.

Ethanol

An estimated two thirds of Americans occasionally consume ethanol, and approximately 10% are considered heavy consumers. Although ingestion of a moderate amount of ethanol (usually defined as three to nine drinks per week) is associated with a reduced risk for cardiovascular disease (**Fig. 80.1**),[1] binge drinking and the consumption of excessive amounts have the opposite effect. When ingested in substantial amounts, ethanol may cause ventricular systolic and/or diastolic dysfunction, systemic arterial hypertension, angina pectoris, coronary vasospasm, arrhythmias, stroke, and even sudden cardiac death.

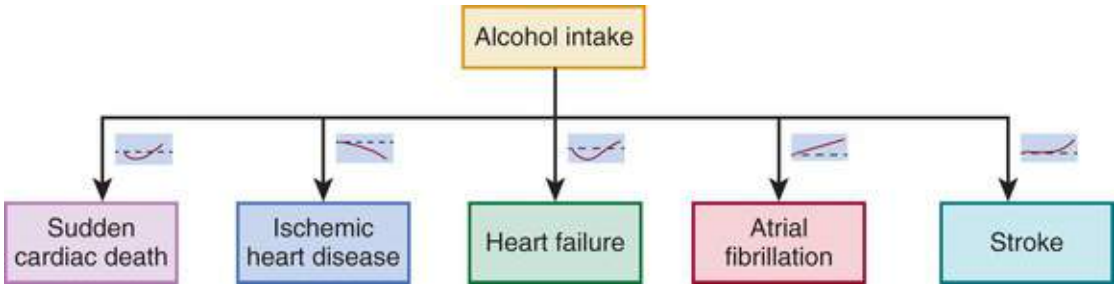

FIGURE 80.1 Schematic illustration of the relationships between alcohol intake and several major cardiovascular disease outcomes. The *small boxes* represent the approximate relationship between alcohol intake and the corresponding cardiovascular end point; the *dashed line* indicates the risk among nondrinkers as the reference group. (From Conen D. Alcohol consumption and incident cardiovascular disease; not just one unifying hypothesis. Eur Heart J 2015;36:897.)

Effects of Ethanol on Cardiac Myocyte Structure and Function

Ethanol may cause myocardial damage via several mechanisms (**Table 80.1**).[2,3] First, ethanol and its metabolites acetaldehyde and acetate may exert a direct toxic effect on the myocytes. Second, deficiencies of certain vitamins (e.g., thiamine), minerals (e.g., selenium), or electrolytes (e.g., magnesium, phosphorus, or potassium), which sometimes occur in heavy ethanol consumers, may adversely affect myocardial function. Third, certain substances that sometimes contaminate alcoholic beverages, such as lead (often found in “moonshine” alcohol) or cobalt, may damage the myocardium.

TABLE 80.1

Mechanisms of Ethanol-Induced Myocardial Injury

Direct Toxic Effects
Uncoupling of the excitation/contraction system
Reduced calcium sequestration in the sarcoplasmic reticulum
Inhibition of the sarcolemmal adenosine triphosphate–dependent Na^+/K^+ pump
Reduction in the mitochondrial respiratory ratio
Altered substrate uptake
Increased interstitial/extracellular protein synthesis
Myocyte apoptosis
Toxic Effect of Metabolites
Acetaldehyde
Ethyl esters
Nutritional or Trace Metal Deficiencies
Thiamine
Selenium
Electrolyte Disturbances
Hypomagnesemia
Hypokalemia
Hypophosphatemia
Toxic Additives
Cobalt
Lead
Arsenic

Ethanol impairs excitation-contraction coupling, calcium handling and sensitivity, mitochondrial oxidative phosphorylation, and cardiac contractility by adversely affecting the function of the sarcolemmal membrane, sarcoplasmic reticulum, mitochondria, and contractile proteins. Electron microscopic studies of the hearts of experimental animals in close temporal proximity to heavy ethanol ingestion demonstrate dilated sarcoplasmic reticula and swollen mitochondria, along with fragmented cristae and glycogen-filled vacuoles. With sustained exposure to ethanol, myofibrillar degeneration and replacement fibrosis appear. In addition to the effects of ethanol on the myocardial contractile apparatus, acute or chronic consumption may adversely influence myofibrillar protein synthesis and apoptosis. Microscopically, the hearts of chronic heavy consumers of ethanol manifest an increased accumulation of collagen in the extracellular matrix, as well as increased intermolecular cross-links.

Ethanol and Heart Failure

Chronic heavy ethanol ingestion may induce left ventricular diastolic and/or systolic dysfunction.[3] Diastolic dysfunction, which is caused, at least in part, by interstitial fibrosis of the myocardium, is often demonstrable in heavy consumers of ethanol even in the absence of symptoms or obvious signs. About half of asymptomatic chronic alcoholics have echocardiographic evidence of left ventricular hypertrophy with preserved systolic performance. By Doppler echocardiography (**see also Chapter 14**), the left ventricular relaxation time is often prolonged, the peak early diastolic velocity is reduced, and the acceleration of early diastolic flow is slowed—all manifestations of left ventricular diastolic dysfunction. Even small amounts of alcohol are associated with an acute worsening of diastolic function, as assessed by early diastolic velocity (E′), its ratio to late diastolic velocity (E′/A′), and the ratio of mitral to myocardial early diastolic velocity (E/E′).[4] Abnormal increases in left ventricular filling pressure during volume or pressure loading may be observed.

Ethanol may induce asymptomatic left ventricular systolic dysfunction even when it is ingested by healthy individuals in relatively small quantities, as occurs in subjects who are considered “social” drinkers. As many as 30% of asymptomatic chronic alcoholics have echocardiographic evidence of left

ventricular systolic dysfunction. With continued heavy ethanol ingestion, symptoms and signs of heart failure often develop (**see also Chapter 21**) as a result of dilated cardiomyopathy. In fact, ethanol abuse is the leading cause of nonischemic dilated cardiomyopathy in industrialized countries; it accounts for approximately half of those with this diagnosis. The likelihood of ethanol-induced dilated cardiomyopathy developing correlates with the amount of ethanol that is consumed in a lifetime: most men in whom it develops have consumed more than 80 g of ethanol (i.e., 1 liter of wine, eight standard-sized beers, or one-half pint of hard liquor) per day for at least 5 years. Women appear to be even more susceptible than their male counterparts to ethanol's cardiotoxic effects in that dilated cardiomyopathy may develop in women following the consumption of a smaller amount of ethanol per day and per lifetime.

Although heavy intake of ethanol is associated with nonischemic dilated cardiomyopathy, individuals with light to moderate ethanol consumption (5 to 25 g/day) actually have a lower incidence of congestive heart failure than do those who do not drink at all.[5,6] In patients with left ventricular dysfunction, light to moderate ethanol ingestion does not exacerbate heart failure.[7] In subjects with ischemic cardiomyopathy, light to moderate ethanol consumption may reduce mortality rates.[8,9]

Subjects with markedly symptomatic ethanol-induced dilated cardiomyopathy may manifest a substantial improvement in left ventricular systolic function and symptoms of heart failure with complete abstinence or a dramatic reduction in ethanol consumption (i.e., to less than 60 g of ethanol per day or the equivalent of four standard drinks). Although most of this improvement occurs in the first 6 months of abstinence, it often continues for as long as 2 years of observation.

Ethanol and Systemic Arterial Hypertension

Experts estimate that ethanol has causal importance in up to 11% of men with hypertension (**see Chapter 46**). Individuals who consume more than two drinks daily are 1.5 to 2 times more likely to have hypertension than are age- and sex-matched nondrinkers. This effect is dose related and most prominent when daily ethanol intake exceeds two drinks (i.e., 30 g of ethanol).[10] “Social” ethanol consumption is associated with a modest rise in systolic arterial pressure, whereas heavy consumption and binge drinking may lead to a substantial increase. Although the mechanism by which ethanol induces a rise in systemic arterial pressure is not completely understood, studies have demonstrated that ethanol consumption increases plasma levels of catecholamines, renin, cortisol, and aldosterone, each of which may cause systemic arterial vasoconstriction. In individuals with ethanol-induced hypertension, abstinence often normalizes systemic arterial pressure.

Ethanol and Lipid Metabolism

Ethanol consumption inhibits the oxidation of free fatty acids by the liver, which stimulates hepatic triglyceride synthesis and the secretion of very low density lipoprotein cholesterol. Most commonly, therefore, ethanol consumption causes hypertriglyceridemia. In addition, heavy ingestion may cause an increase in the serum concentrations of total cholesterol and low-density lipoprotein (LDL) cholesterol. Regular ethanol consumption increases the serum concentration of high-density lipoprotein (HDL) cholesterol.[11] Subjects with hyperlipidemia should be encouraged to limit their ethanol intake.

Coronary Artery Disease

Heavy ethanol use is associated with an increased incidence of atherosclerotic coronary artery disease and resultant cardiovascular morbidity and mortality (**see also Chapter 61**). This rise may result, at least in part, from the increased likelihood that heavy ethanol consumers (versus nondrinkers) have systemic arterial hypertension, increased left ventricular muscle mass (with concomitant diastolic and/or systolic dysfunction), and hypertriglyceridemia (**Table 80.2**). Conversely, light to moderate ethanol intake (two to seven drinks per week) is associated with a decreased risk for myocardial infarction and cardiovascular morbidity and mortality in both men and women.[12–15] Even in men already at low risk for cardiovascular disease on the basis of body mass index, physical activity, smoking, and diet, moderate alcohol intake is associated with a reduced risk for myocardial infarction (MI) (**Fig. 80.2**).[16] This lower risk for cardiovascular morbidity and mortality in consumers of moderate amounts of ethanol than in nondrinkers or heavy consumers is supported by numerous retrospectively and prospectively conducted studies. The French were noted to have a reduced incidence of coronary artery disease when compared with inhabitants of other countries despite high smoking rates and a diet high in fat (the so-called *French paradox*). Although this diminished incidence was initially attributed to the antioxidant and hemostatic properties of red wine, similar findings were subsequently reported in mild to moderate consumers of other alcoholic beverages and in other study populations. Several prospectively performed cohort studies have demonstrated that drinkers of moderate amounts of ethanol are 30% to 70% less likely than nondrinkers or heavy consumers to manifest coronary artery disease or ischemic stroke.[17] Some studies have suggested that the consumption of all alcoholic beverages exerts such an effect, whereas others have reported that this so-called *cardioprotection* is strongest with the consumption of wine.[18] The mechanism or mechanisms by which the consumption of moderate amounts of ethanol reduces cardiovascular risk appear to be multifactorial in that moderate consumption exerts several beneficial effects, including (1) an increase in the serum concentrations of HDL cholesterol, apolipoprotein A-I, and adiponectin; (2) inhibition of platelet aggregation; (3) decreased serum fibrinogen concentration; (4) increased antioxidant activity (from the phenolic compounds and flavonoids contained in red wine); (5) antiinflammatory effects (with lower concentrations of white blood cells and C-reactive protein); (6) improved fibrinolysis (resulting from increased concentrations of endogenous tissue plasminogen activator and a concomitant decrease in endogenous plasminogen activator inhibitor activity); and (7) improved insulin sensitivity (**Fig. 80.3**).[2,19]

TABLE 80.2

Qualitative Effects of Light to Moderate and Heavier Alcohol Intake on Cardiovascular Risk Factors and Outcomes

CARDIOVASCULAR RISK FACTORS AND OUTCOMES	LIGHT TO MODERATE ALCOHOL INTAKE (<2 DRINKS PER DAY)	HEAVIER ALCOHOL INTAKE (>2 DRINKS PER DAY)
Blood pressure	↔	↑↑
HDL cholesterol	↑↑	↑↑↑
Triglycerides	↑	↑↑
LDL cholesterol	↔ or ↓	↑
Platelet aggregability/coagulability	↓	↓↓
Systemic inflammation	↓	↑
Congestive heart failure	↓	↑↑
Coronary artery disease (angina, nonfatal MI)	↓↓	↔ or ↑
Atrial fibrillation	↔	↑↑
Stroke	↓	↑↑
Sudden cardiac death	↓↓	↑

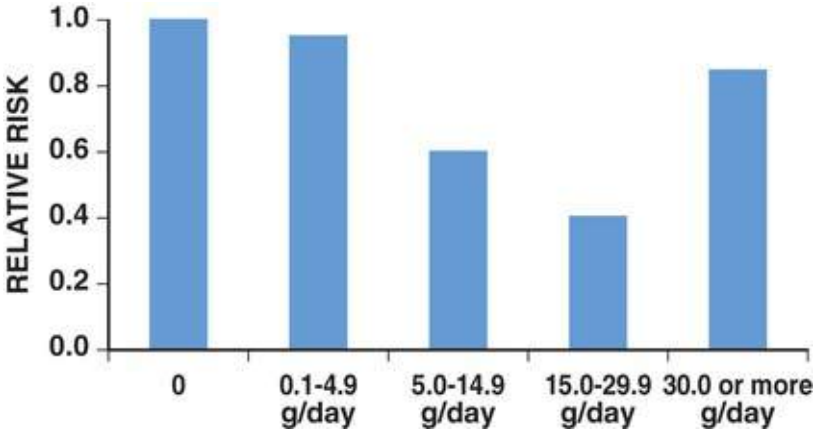

FIGURE 80.2 Relative risk for myocardial infarction (MI) according to daily alcohol intake in men already at low risk for cardiovascular disease on the basis of body mass index, physical activity, smoking, and diet. Moderate alcohol intake is associated with a lower risk for MI.

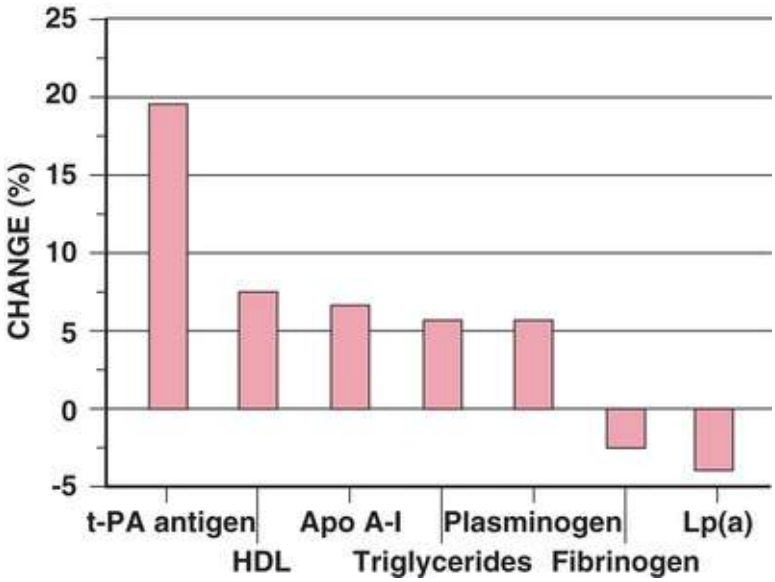

FIGURE 80.3 Percentage of change in various serologic variables caused by ethanol ingestion. Ingestion of ethanol, 30 g daily for 1 to 9 weeks, was associated with increased serum concentrations of tissue plasminogen activator (t-PA) antigen, HDL cholesterol, apolipoprotein A-I (Apo A-I), serum triglycerides, and serum plasminogen, as well as decreased concentrations of serum fibrinogen and lipoprotein(a) [Lp(a)]. The reduced risk for cardiovascular events seen in subjects who consume moderate amounts of ethanol may be caused, at least in part, by these beneficial changes in serologic variables.

Men and women manifest a difference in the cardioprotective effect of alcohol (**Fig. 80.4**). The maximal beneficial effect of ethanol occurs at lower doses for women than for men, and the range of alcohol consumption at which it is protective is wider for men than for women. In addition, the relative cardioprotective effect of ethanol is greater for middle-aged and elderly individuals than for young adults.[20] Light to moderate ethanol consumption is associated with similar reductions in risk for coronary artery disease in diabetic and nondiabetic men and women.[21] In survivors of MI, moderate ethanol consumption appears to reduce the risk of subsequent mortality.[8,22,23] In patients suffering an acute MI, those with light or moderate alcohol use have a better prognosis than do heavy drinkers or abstainers, even though recent ingestion of ethanol does not appear to reduce infarct size or the propensity for the subsequent appearance of arrhythmia or heart failure.

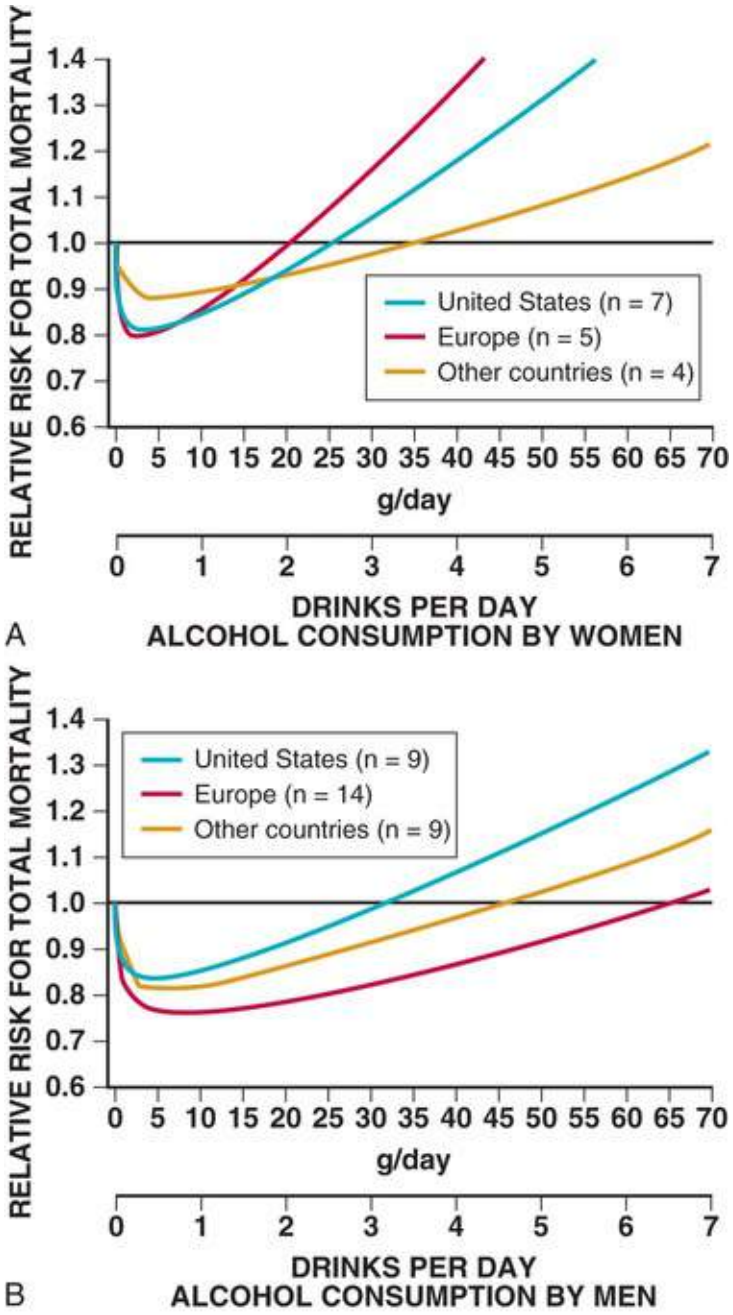

FIGURE 80.4 Relative risk for total mortality and alcohol intake in women **(A)** and men **(B)** in the United States, Europe, and other countries (Australia, Japan, and/or China). A J-shaped relationship between alcohol consumption and total mortality is observed in both men and women. Consumption of alcohol, up to four drinks per day in men and two drinks per day in women, is inversely associated with total mortality. Higher doses of alcohol were associated with increased mortality. The inverse association in women disappears at doses lower than in men.

Arrhythmias

Ethanol consumption is associated with a variety of atrial and ventricular arrhythmias, most commonly (1) atrial or ventricular premature beats, (2) supraventricular tachycardia, (3) atrial flutter, (4) atrial fibrillation, (5) ventricular tachycardia, or (6) ventricular fibrillation (**see also Chapters 35, 38, 39**). The most common ethanol-induced arrhythmia is atrial fibrillation. Ethanol is of causal importance in about a third of subjects with new-onset atrial fibrillation; in those younger than 65 years it may be responsible in as many as two thirds. Most episodes occur after binge drinking, usually on weekends or holidays—hence the term “holiday heart.” Electrophysiologic testing in humans without cardiac disease has shown that ethanol enhances vulnerability to the induction of atrial flutter and fibrillation. Treatment

of these ethanol-induced arrhythmias is abstinence.

Ethanol may be arrhythmogenic via several mechanisms. In many ethanol consumers, concomitant factors may predispose to arrhythmias, including cigarette smoking, electrolyte disturbances, metabolic abnormalities, hypertension, and sleep apnea. Acute ethanol ingestion induces diuresis, which is accompanied by the concomitant urinary loss of sodium, potassium, and magnesium. The presence of myocardial interstitial fibrosis, ventricular hypertrophy, cardiomyopathy, or autonomic dysfunction may also enhance the likelihood of dysrhythmias. Prolongation of the QT interval, decreased heart rate variability, diminished vagal modulation, and reduced baroreflex sensitivity have also been noted in patients with alcohol use or withdrawal.[24]

Sudden Death

In subjects without known cardiac disease, the decrease in cardiovascular mortality rates that is associated with moderate ethanol intake results largely from a reduction in the incidence of sudden death (**Fig. 80.5**) (**see also Chapter 42**). Of the more than 21,000 men in the Physicians Health Study,[25] those who consumed two to four or five to six drinks per week had a significantly reduced risk for sudden death (relative risks, 0.40 and 0.21, respectively) when compared with those who rarely or never drank. In contrast, heavy ethanol consumption (i.e., six or more drinks per day) or binge drinking was associated with an increased risk for sudden death. Heavy ethanol consumption is associated with an increased incidence of sudden death independent of the presence of coronary artery disease. The incidence of ethanol-induced sudden death increases with age and the amount of ethanol that is ingested. For example, daily ingestion of more than 80 g of ethanol is associated with a threefold increased incidence of mortality when compared with daily consumption of a lesser amount.

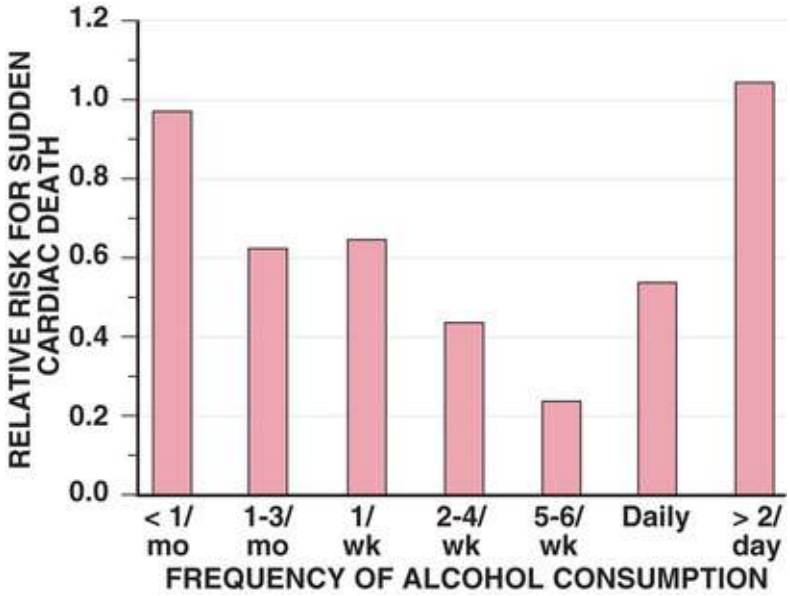

FIGURE 80.5 Ethanol consumption and risk for sudden cardiac death in U.S. male physicians. In comparison to those who had less than one drink per month (*far left bar*), those who consumed small or moderate amounts of ethanol (*middle bars*) had a reduced risk for sudden cardiac death. In contrast, those who consumed at least two drinks per day (*far right bar*) had an increased risk.

Cocaine

Cocaine is currently the most commonly used illicit drug in subjects seeking care in hospital emergency departments, and it is the most frequent cause of drug-related deaths reported by medical examiners in the United States. Its use is associated with a number of cocaine-related cardiovascular complications, including angina pectoris, MI, cardiomyopathy, aortic dissection, and sudden death (**Table 80.3**).

TABLE 80.3

Cardiovascular Complications of Cocaine Use

Myocardial ischemia
Angina pectoris
Myocardial infarction
Sudden death
Arrhythmias
Pulmonary edema
Myocarditis
Endocarditis
Aortic dissection

Pharmacology and Mechanisms of Action

Cocaine (benzoylmethylecgonine) is an alkaloid extracted from the leaf of the *Erythroxylon coca* bush, which grows primarily in South America. It is available in two forms: the hydrochloride salt and the "freebase." Cocaine *hydrochloride* is prepared by dissolving the alkaloid in hydrochloric acid to form a water-soluble powder or granule, which can be taken orally, intravenously, or intranasally (so-called chewing, mainlining, or snorting, respectively). The *freebase* form is manufactured by processing the cocaine with ammonia or sodium bicarbonate (baking soda). Unlike the hydrochloride form, "freebase" cocaine is heat stable, so it can be smoked. It is known as "crack" because of the popping sound that it makes when heated.

Cocaine hydrochloride is well absorbed through all mucous membranes; therefore users may achieve a high blood concentration with intranasal, sublingual, vaginal, or rectal administration. The route of administration determines the rapidity of onset and duration of action. The euphoria associated with smoking crack cocaine occurs within seconds and is short-lived. Crack cocaine is considered the most potent and addictive form of the drug. Cocaine is metabolized by serum and liver cholinesterases to water-soluble metabolites (primarily benzoylecgonine and ecgonine methyl ester), which are excreted in urine. Because cocaine's serum half-life is just 45 to 90 minutes, it is detectable in blood or urine only for several hours after use. However, its metabolites persist in blood or urine for 24 to 36 hours after administration.

When applied locally, cocaine acts as an anesthetic by virtue of its inhibition of membrane permeability to sodium during depolarization, thereby blocking the initiation and transmission of electrical signals. When given systemically, it blocks the presynaptic reuptake of norepinephrine and dopamine, thereby producing an excess of these neurotransmitters at the site of the postsynaptic receptor (**Fig. 80.6**). In short, cocaine acts as a powerful sympathomimetic agent.

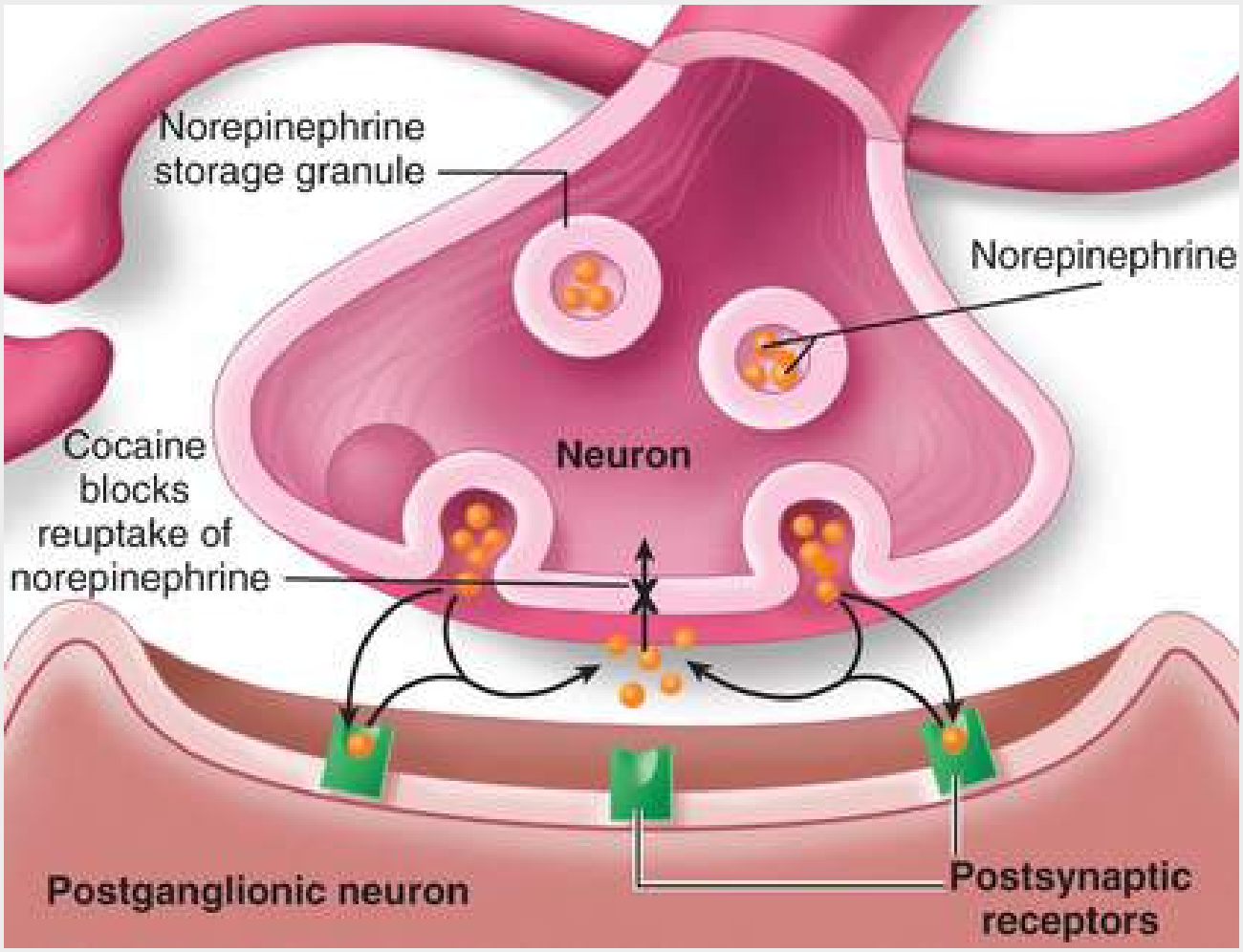

FIGURE 80.6 Mechanism by which cocaine alters sympathetic tone. Cocaine blocks the reuptake of norepinephrine by the preganglionic neuron (X), thereby resulting in excess amounts of this neurotransmitter at postganglionic receptor sites.

Cocaine-Related Myocardial Ischemia and Infarction

Since 1982, numerous reports have associated cocaine use with myocardial ischemia and infarction (**see also Chapters 57, 59, and 60**).[26] Cocaine-related myocardial ischemia or infarction may result from (1) increased myocardial oxygen demand in the setting of a limited or fixed oxygen supply, (2) marked coronary arterial vasoconstriction, and (3) enhanced platelet aggregation and thrombus formation (**Fig. 80.7**).

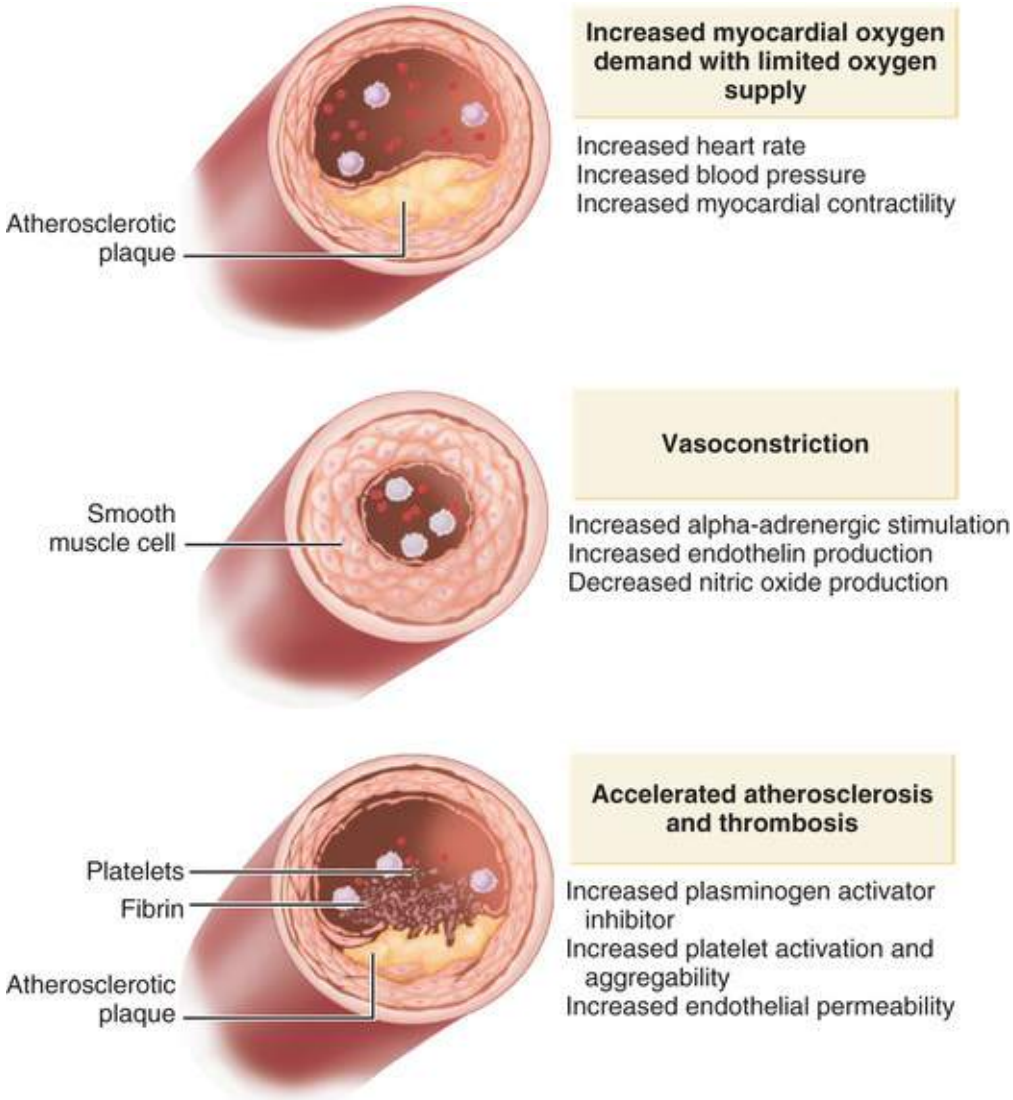

FIGURE 80.7 Mechanisms by which cocaine may induce myocardial ischemia or infarction. Cocaine may induce myocardial ischemia or infarction by increasing the determinants of myocardial oxygen demand in the setting of limited oxygen supply (*top*), thereby causing intense coronary arterial vasoconstriction (*middle*) or inducing accelerated atherosclerosis and thrombosis (*bottom*).

By virtue of its sympathomimetic effects, cocaine increases the three major determinants of myocardial oxygen demand: heart rate, left ventricular wall tension, and left ventricular contractility. At the same time, ingestion of even small amounts of the drug causes vasoconstriction of the epicardial coronary arteries (so-called *inappropriate vasoconstriction*) in that the myocardial oxygen supply decreases as the demand increases. Cocaine induces vasoconstriction in normal coronary arteries but exerts a particularly marked vasoconstrictive effect in diseased segments. As a result, cocaine users with atherosclerotic coronary artery disease probably have an especially high risk for an ischemic event after cocaine use. Cocaine-induced coronary arterial vasoconstriction results primarily from the stimulation of coronary arterial alpha-adrenergic receptors because it is reversed by phentolamine (an alpha-adrenergic antagonist) and exacerbated by propranolol (a beta-adrenergic antagonist). In addition, cocaine causes increased endothelial production of endothelin (a potent vasoconstrictor) and decreased production of nitric oxide (a potent vasodilator), which may also promote vasoconstriction.

Cocaine use may enhance platelet activation and aggregability, as well as increase concentrations of plasminogen activator inhibitor and von Willebrand factor released from endothelial cells, which may promote thrombus accumulation. The presence of premature atherosclerotic coronary artery disease, as observed in postmortem studies of long-term cocaine users, may provide a nidus for thrombosis. In vitro studies have shown that cocaine causes structural abnormalities in the endothelial cell barrier—it

increases its permeability to LDL and enhances the expression of endothelial adhesion molecules (thereby favoring leukocyte migration), all of which are associated with atherogenesis.

Chest pain is the most common cardiovascular complaint of patients seeking medical assistance following cocaine use. Approximately 6% of those who come to the emergency department with cocaine-associated chest pain have enzymatic evidence of myocardial necrosis. Most subjects with cocaine-related MI are young, nonwhite, male cigarette smokers without other risk factors for atherosclerosis who have a history of repeated cocaine use (**Table 80.4**). The deleterious effects of cocaine on the myocardial oxygen supply and demand are substantially exacerbated by concomitant cigarette smoking, which by itself induces coronary arterial vasoconstriction through an alpha-adrenergic mechanism. Following concomitant cocaine use and smoking, the heart rate and systemic arterial pressure increase markedly, and coronary arterial vasoconstriction is more intense than with either alone.

TABLE 80.4

Characteristics of Patients with Cocaine-Induced Myocardial Infarction

Dose of Cocaine
5-6 lines (150 mg) to as much as 2 g Serum concentration, 0.01-1.02 mg/L
Frequency of Use
Reported in chronic, recreational, and first-time users
Route of Administration
Occurs with all routes of administration 75% of reported MIs occurred after intranasal use
Age
Mean, 34 years (range, 17-71 years) 20% younger than 25 years
Sex
80%-90% male
Timing
Often within minutes of cocaine use Reported as late as 5-15 hours after use

In subjects who are otherwise considered to be at low risk for MI, the risk for infarction increases 24-fold during the 60 minutes after cocaine use. The occurrence of MI after cocaine use appears to be unrelated to the amount ingested, its route of administration, and the frequency of its use: cocaine-related infarction has been reported with doses ranging from 200 to 2000 mg, after ingestion by all routes, and in habitual and first-time users. About half the patients with cocaine-related MI have no angiographic evidence of atherosclerotic coronary artery disease. Therefore, when subjects with no or few risk factors for atherosclerosis, particularly those who are young or have a history of substance abuse, are seen with acute MI, urine and blood samples should be analyzed for cocaine and its metabolites.

Cardiovascular complications resulting from cocaine-related MI are relatively uncommon, with ventricular arrhythmias occurring in 4% to 17%, congestive heart failure in 5% to 7%, and death in less than 2%. This low incidence of complications is caused, at least in part, by the young age and absence of extensive multivessel coronary artery disease in most patients with cocaine-related infarction. If complications develop, most occur within 12 hours of hospitalization. Following hospital discharge, continued cocaine use and recurrent chest pain are common. Occasionally, a patient has recurrent nonfatal or fatal MI.

Cocaethylene

In individuals who use cocaine in temporal proximity to the ingestion of ethanol, hepatic transesterification leads to the production of a unique metabolite, cocaethylene. Cocaethylene is often detected postmortem in subjects who are presumed to have died of cocaine and ethanol toxicity. Similar to cocaine, cocaethylene blocks the reuptake of dopamine at the synaptic cleft, thereby possibly potentiating the systemic toxic effects of cocaine. In experimental animals, in fact, cocaethylene is more lethal than cocaine. In humans, the combination of cocaine and ethanol causes a substantial increase in myocardial oxygen demand. The concomitant use of cocaine and ethanol is associated with a higher incidence of disability and death than use of either agent alone. Individuals presumably dying of a combined cocaine-ethanol overdose have much lower blood cocaine concentrations than do those presumably dying of a cocaine overdose alone, thus suggesting an additive or synergistic effect of ethanol on the catastrophic cardiovascular events that are induced by cocaine.

Cocaine-Induced Myocardial Dysfunction

Long-term cocaine abuse has been associated with left ventricular hypertrophy, as well as with left ventricular diastolic and/or systolic dysfunction. In a recent study,[26] cardiac magnetic resonance imaging detected cardiac abnormalities in 71% of asymptomatic consecutive cocaine abusers. The main findings were a decrease in systolic function of left and right ventricles, an increase of left ventricular mass, and the presence of focal fibrosis (late gadolinium enhancement). There was a significant association between years of cocaine use and probability of left ventricular systolic dysfunction. Aside from the effects of long-term cocaine use on myocardial performance, it may cause an acute deterioration in left ventricular systolic and/or diastolic function or transient apical ballooning (also called Takotsubo cardiomyopathy or “broken heart syndrome”) (**see also Chapter 25**). Cocaine may adversely affect left ventricular systolic function by several mechanisms. First, as noted previously, cocaine may induce myocardial ischemia or infarction. Second, the profound repetitive sympathetic stimulation induced by cocaine is similar to that observed in patients with pheochromocytoma; either may result in cardiomyopathy and characteristic microscopic changes of subendocardial contraction band necrosis. Third, the concomitant administration of adulterants or infectious agents may cause myocarditis, which has been seen on occasion in intravenous cocaine users studied after death. Fourth, studies in experimental animals have shown that cocaine increases the production of reactive oxygen species, alters cytokine production in the endothelium and in circulating leukocytes, stimulates the transcription of genes responsible for changes in the composition of myocardial collagen and myosin, and induces myocyte apoptosis.

Arrhythmias

Although cardiac dysrhythmias may occur with cocaine (**Table 80.5**), its precise arrhythmogenic potential is poorly defined. In many cases the dysrhythmias ascribed to cocaine occur in the setting of profound hemodynamic or metabolic derangements, such as hypotension, hypoxemia, seizures, or MI. Nonetheless, because of cocaine's sodium and potassium channel–blocking properties and its ability to enhance sympathetic activation, it is considered a probable cause of cardiac arrhythmias.[28] The development of lethal arrhythmias with cocaine use may require an underlying substrate of abnormal myocardium. Life-threatening arrhythmias and sudden death in association with cocaine use occur most often in individuals with myocardial ischemia or infarction or in those with nonischemic myocellular damage. Long-term cocaine use is associated with increased left ventricular mass and wall thickness, which are known risk

factors for ventricular dysrhythmias.

TABLE 80.5

Cardiac Dysrhythmias and Conduction Disturbances Reported with Cocaine Use

Sinus tachycardia
Sinus bradycardia
Supraventricular tachycardia
Bundle branch block
Complete heart block
Accelerated idioventricular rhythm
Ventricular tachycardia
Ventricular fibrillation
Asystole
Torsades de pointes
Brugada pattern (right bundle branch block with ST-segment elevation in leads V1, V2, and V3)

Cocaine may affect the generation and conduction of cardiac impulses by several mechanisms. First, its sympathomimetic properties may increase ventricular irritability and lower the threshold for fibrillation. Second, it inhibits action potential generation and conduction (i.e., it prolongs the QRS and QT intervals) as a result of its sodium channel–blocking effects. In so doing, it acts in a manner similar to that of a class I antiarrhythmic agent. Accordingly, Brugada-type electrocardiographic features and torsades de pointes have been observed following cocaine use. Third, cocaine increases the intracellular calcium concentration, which may result in afterdepolarizations and triggered ventricular arrhythmias. Fourth, it reduces vagal activity, thereby potentiating its sympathomimetic effects.

Aortic Dissection

Because aortic dissection or rupture has been temporally related to cocaine use, it should be considered a possible cause of chest pain in cocaine users (**see also Chapter 63**). Cocaine has been implicated as a causative factor in 0.5% to 37% of cases of aortic dissection, with an average interval from cocaine use to the onset of symptoms of 12 hours (range, 0 to 24).[29] Dissection probably results from a cocaine-induced increase in systemic arterial pressure. In addition to aortic rupture, cocaine-related rupture of mycotic and intracerebral aneurysms has been reported.

Amphetamines

Amphetamines were previously prescribed for the treatment of obesity, attention deficit disorder, and narcolepsy; at present, their use is strictly limited. The most frequently abused amphetamines are dextroamphetamine, methcathinone, methamphetamine, methylphenidate, ethylphenidate, ephedrine, propylhexedrine, phenmetrazine, and 3,4-methylene-dioxymethamphetamine (MDMA, also known as *Ecstasy*). Recently, many deaths have been reported from exposure to paramethoxymethamphetamine (PMMA, also known as *Death* and *Dr. Death*), an amphetamine similar in structure MDMA but substantially more toxic.[30] *Ice* is a freebase form of methamphetamine that can be inhaled, smoked, or injected. Because amphetamines are sympathomimetic agents, their use has been associated with systemic arterial hypertension, premature coronary artery disease, acute coronary syndromes, MI, myocardial damage consistent with catecholamine excess, aortic dissection, and lethal arrhythmias.[31] Similar to cocaine, amphetamines may induce intense coronary arterial vasoconstriction with or without thrombus formation. Finally, dilated cardiomyopathy can develop following repetitive amphetamine use, with recovery of cardiovascular function occurring after drug discontinuation. Although initial case reports

suggested that stimulants prescribed for the treatment of attention-deficit/hyperactivity disorder (ADHD) were linked to adverse cardiovascular events (which prompted the Food and Drug Administration to issue a black box warning in 2006), subsequent studies have shown that the use of ADHD medications is not associated with an increased risk for serious cardiovascular events in children[32] (**Fig. 80.8**) or young and middle-aged adults.[33]

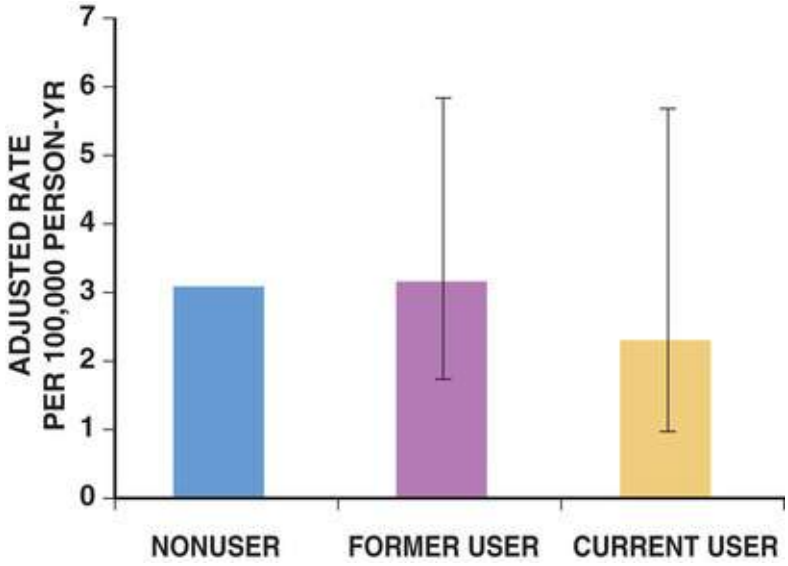

FIGURE 80.8 Adjusted rates of serious cardiovascular events according to use of ADHD drugs. Use of ADHD medications is not associated with an increased risk for serious cardiovascular events. (From Cooper WO, Habel LA, Sox CM, et al: ADHD drugs and serious cardiovascular events in children and young adults. N Engl J Med 2011;365:1896.)

Cathinones

Cathinones bind to monoamine transporters for dopamine, serotonin, and norepinephrine, which accounts for their sympathomimetic properties. Like cocaine and amphetamines, these substances produce stimulant effects and are therefore sometimes used as substitutes for the traditional illicit drugs.

The leaves of khat (*Catha edulis*) are chewed for the central stimulant action of their cathinone content. Khat use is highly prevalent in East African and Middle Eastern countries, in particular, Somalia and Yemen, and it is an emerging problem in Australia and Europe. Khat chewing has been linked to MI, dilated cardiomyopathy, vascular disease (such as hypertension and stroke), and thromboembolism.[34] Khat chewing is an independent risk factor for acute MI: moderate khat chewers were shown to be at high risk (odds ratio, 7.6), and heavy khat chewers were at even higher risk (odds ratio, 22.3).[35]

Many synthetic cathinones (mephedrone, methylenedioxypyrovalerone [MDPV], and methylone), colloquially known on the street as *meow*, have gained renewed popularity as designer drugs of abuse, particularly among young people.[36] These compounds are marketed as “bath salts” or “plant food” and labeled “not for human consumption” to circumvent regulatory restrictions on drugs of abuse. They are used by the oral route, nasal insufflation (“snorting”), intramuscular or intravenous injection, and rectal insertion, with most ingestion occurring by nasal insufflation or oral ingestion (or both). Synthetic cathinones have been associated with myocarditis and sudden death.

Synthetic Cannabinoids

These drugs consist of psychoactively inert dry plant material sprayed with synthetic cannabinoid receptor agonists. Marketed as incense and best known by the street names “spice” and “K2,” when smoked they provide a marijuana-like effect; their use has been associated with MI in adolescents.[37,38]

Ma Huang (Ephedra)

The dietary supplement ephedra, also known as ma huang, contains ephedrine and its enantiomer pseudoephedrine. Ma huang increases catecholamines at synaptic areas in the brain and heart and directly stimulates alpha- and beta-adrenergic receptors. As a result, it typically induces an increase in heart rate, blood pressure, cardiac output, and peripheral resistance. Its use has been associated with stroke, MI, sudden death, and cardiomyopathy.

Catecholamines and Beta-Adrenergic Receptor Agonists

Catecholamines, administered exogenously or secreted by a neuroendocrine tumor (e.g., pheochromocytoma or neuroblastoma), may produce acute myocarditis (with focal myocardial necrosis and inflammation), cardiomyopathy, tachycardia, and arrhythmias. Similar abnormalities have been described with the excessive use of beta-adrenergic agonist inhalants and methylxanthines in patients with severe pulmonary disease. The administration of beta-adrenergic receptor agonists or catecholamines (i.e., dobutamine or epinephrine, respectively) has been associated with the appearance of transient left ventricular apical dyskinesis and anterior electrocardiographic T-wave inversions; this entity is known as *takotsubo* or *stress cardiomyopathy* (**see also Chapter 25**). Several mechanisms may be responsible for the acute and chronic myocardial damage associated with catecholamines. They may exert a direct toxic effect on the myocardium through changes in autonomic tone, enhanced lipid mobility, calcium overload, free radical production, or increased sarcolemmal permeability. Alternatively, myocardial damage may be secondary to a sustained increase in myocardial oxygen demand and/or a decrease in myocardial oxygen supply (the latter caused by catecholamine-induced coronary arterial vasoconstriction or platelet aggregation).

Energy Drinks

Emergency department visits related to energy drinks have more than doubled to more than 20,000 visits annually. Cardiovascular complications reported after energy drink ingestion include arrhythmias (i.e., atrial fibrillation, supraventricular tachycardia, ventricular fibrillation, torsades de pointes), MI, and cardiac arrest, often in young persons.[39] Adverse effects and toxicities associated with energy drinks have been attributed to (1) the high caffeine content and the fact that the drinks are often consumed in an excessive or rapid manner; (2) consumption by young individuals who may be caffeine naïve and prone to consume large quantities; (3) mixture with alcohol and other substances; and (4) other ingredients in the drinks that may increase the cardiovascular risks.

Inhalants

The inhalants may be classified as organic solvents, organic nitrites (such as amyl nitrite or amyl butyl), and nitrous oxide. Organic solvents include toluene (airplane glue, rubber cement, and paint thinner), Freon, kerosene, gasoline, carbon tetrachloride, acrylic paint sprays, shoe polish, degreasers (trichloroethylene), nail polish remover, typewriter correction fluid, adhesives, permanent markers, room fresheners, deodorants, dry-cleaning agents, and lighter fluid. These solvents are most often inhaled by children or young adolescents (so-called huffing, sniffing, or dusting). Acute or chronic inhalant use has occasionally been reported to induce cardiac abnormalities, most commonly dysrhythmias; rarely, inhalant use has been associated with myocarditis, MI, and sudden death. The inhalation of Freon, for example, can sensitize the myocardium to catecholamines; in such individuals, fatal arrhythmias have been reported to occur when the user is startled during inhalation.

Antiretroviral Agents

Subjects treated with highly active antiretroviral therapy (HAART) have been observed to have severe hypertriglyceridemia (serum triglycerides >1000 mg/dL), marked elevations in lipoprotein(a) and hypercholesterolemia, increased LDL and decreased HDL cholesterol levels, and insulin resistance. Not surprisingly, therefore, patients treated with these agents have an increased risk for atherosclerosis (**see also Chapter 82**). Epidemiologic studies have linked certain antiretroviral medications (some nucleoside reverse transcriptase inhibitors [i.e., abacavir or didanosine-containing regimens] and protease inhibitors [i.e., indinavir and lopinavir-ritonavir]) with a higher risk for coronary heart disease. Conversely, nonnucleoside reverse transcriptase inhibitors, entry inhibitors, and integrase inhibitors do not appear to increase the risk for coronary heart disease.[40]

Serotonin Agonists

The medicinal use of serotonin agonists, such as ergotamine and methysergide (migraine therapy), bromocriptine, cabergoline, and pergolide (Parkinson disease therapy), and fenfluramine and dexfenfluramine (appetite suppressants) has been associated with left- and right-sided valvular disease (**Table 80.6**). Recreational and regular use of MDMA (*Ecstasy*) has also been associated with valvular disease.[41] The echocardiographic and histopathologic findings resemble those described in patients with carcinoid syndrome. Grossly, the valve leaflets and chordae tendineae are thickened and have a glistening white appearance. Histologically, the leaflet architecture is intact, but a plaquelike encasement of the leaflets and chordal structures occurs, and proliferative myofibroblasts surrounding an abundant extracellular matrix are observed.

TABLE 80.6

Serotonin Agonists Associated with Valvular Disease

DRUGS	AFFECTED VALVES	DOSE DEPENDENCY
Ergotamine	AV, MV, and TV	Not reported
Methysergide	AV and MV	Not reported
(Dex)Fenfluramine	AV, MV, and TV	Yes
Pergolide	AV, MV, and TV	Yes
Cabergoline	AV, MV, and TV	Yes
Bromocriptine	AV, MV, and TV	Yes
MDMA *(Ecstasy)*	AV and MV	Not reported
Benfluorex	AV, MV, and TV	Yes

AV, aortic valve; *MV*, mitral valve; *TV*, tricuspid valve.

Two medications used to treat subjects with migraine headaches, ergotamine and triptans, have been associated with acute MI.[42] Ergotamine causes vasoconstriction of the intracerebral and extracranial arteries; rarely, its use has been associated with coronary arterial vasospasm and acute MI. Its vasoconstrictor effects are exaggerated by concomitant caffeine ingestion or use of beta-adrenergic blockers. Triptans, selective 5-hydroxytryptamine agonists, also exert their therapeutic effects by inducing cerebral arterial vasoconstriction. Several reports have appeared of patients in whom coronary vasospasm and acute MI occurred following the administration of therapeutic doses of sumatriptan or zolmitriptan; some of these MIs were complicated by ventricular tachycardia/fibrillation and sudden cardiac death. Following oral sumatriptan, electrocardiographic changes consistent with cardiac ischemia (in the absence of atherosclerotic CAD), QT prolongation, and torsades de pointes have been observed.

Chemotherapeutic Agents

Several chemotherapeutic agents may adversely affect cardiac function, and some have been reported to induce hypertension, acute cardiomyopathy, myocardial ischemia or infarction, pericarditis, dysrhythmias, QT interval prolongation, and/or sudden death (**see Chapter 81**).

Environmental Exposures

Exposure to environmental pollutants and/or toxins can occur by three different routes: inhalation, ingestion, or dermal absorption. The physiologic response to a given exposure to an environmental pollutant may vary between individuals because of differences in their underlying health status or polymorphisms in the genes encoding detoxifying enzymes, as well as other factors. In the section that follows we will review the cardiovascular effects of metal pollutants and other environmental toxins. The effects of air pollution on cardiovascular disease are discussed in **Chapter 52**.

Metal Pollutants

Epidemiologic and experimental studies both suggest that metals (e.g., cadmium and lead) and metalloids (e.g., arsenic) are associated with the development of cardiovascular disease.

Cobalt

In the mid-1960s, an acute and fulminant form of dilated cardiomyopathy was described in heavy beer drinkers. It was suggested that the cobalt chloride that was added to beer as a foam stabilizer was the

causative agent; therefore, its addition was discontinued. Subsequently, this acute and severe form of cardiomyopathy disappeared. More recently, several reports of dilated cardiomyopathy after occupational exposure to cobalt have appeared; in these individuals, high concentrations of cobalt were demonstrated in endomyocardial biopsy specimens.

Lead

Environmental exposure to lead can occur from air and dust, and sometimes from drinking water and food. Although public health interventions that banned the use of lead in gasoline, paint, and solder have reduced the overall lead exposure, both children and adults have continued lead exposure because of its use in batteries and toys and its release through industrial sources, as well as the persistence of lead in house paint, plumbing fixtures, and soil. Prospective and cross-sectional studies have demonstrated an association between the current levels of lead exposure and the risk of adverse cardiovascular outcomes. The relative risks of death from MI and stroke for individuals with the highest tertile of blood lead levels were approximately 2- to 2.5-fold greater, respectively, than in patients with the lowest tertile of blood lead levels. Moreover, in cross-sectional studies, blood lead levels were associated with peripheral arterial disease. Moderate to high levels of lead exposure are nephrotoxic, whereas low levels of lead exposure can lead to the development and progression of chronic kidney disease. Patients with lead poisoning typically have complaints that are referable to the gastrointestinal and central nervous systems. On occasion, subjects with lead poisoning have electrocardiographic abnormalities, atrioventricular conduction defects, and overt congestive heart failure; rarely, myocardial involvement may contribute to or be the principal cause of death.[43]

Cadmium

Cadmium is a by-product of the mining and refining of zinc, lead, and copper ores. The use of cadmium has increased dramatically through applications such as nickel-cadmium batteries and metal coatings. Cadmium from industrial sources and phosphate fertilizers containing cadmium fertilizers contaminate the soil. Leafy green and root vegetables concentrate cadmium bound to organic matter in soil, leading to a major cadmium exposure pathway through diet and tobacco smoking. Other dietary sources include shellfish and organ meats (liver and kidney). Epidemiologic studies suggest there is an association between exposure to cadmium and cardiovascular and kidney disease. Increased levels of cadmium in blood or urine are associated with a higher incidence of death from coronary heart disease, heart failure, and stroke.

Mercury

Occupational exposure to metallic mercuric vapor may cause systemic arterial hypertension and myocardial failure. Although some studies have suggested that high mercury content in fish may counteract the beneficial effects of its omega-3 fatty acids, thereby increasing the risk for atherosclerotic cardiovascular disease, more recent assessments have not supported an association between total mercury exposure and the risk for coronary artery disease.

Antimony

Various antimony compounds have previously been used for the treatment of patients with schistosomiasis. Their use is often associated with electrocardiographic abnormalities, including prolongation of the QT interval and T-wave flattening or inversion. Rarely, chest pain, bradycardia,

hypotension, ventricular arrhythmias, and sudden death have been reported.

Arsenic

The main sources of inorganic arsenic exposure are drinking water obtained in regions where ground water is contaminated by industrial sources or naturally occurring arsenic, as well as in food (rice, grains, and some juices). The intake of arsenic associated with the consumption of fish does not have the level of toxicity attributed to inorganic arsenic or its metabolites. Although occupational exposure to sources of arsenic has decreased over the past several decades, exposure to arsenic in drinking water still remains a global environmental health problem. Approximately 10 million individuals in the United States live in areas where arsenic levels in drinking water exceed the World Health Organization and Environmental Protection Agency recommended limit of 10 µg/L. Prospective studies evaluating arsenic exposure have reported an association between low to moderate arsenic levels and the occurrence of cardiovascular disease, especially coronary artery disease. Arsenic exposure is associated with ECG abnormalities, pericardial effusion, and myocarditis, as well as established cardiovascular risk factors such as hypertension, diabetes, and abnormal renal function (estimated glomerular filtration rate or albuminuria), supporting a causal role for arsenic in the development of cardiovascular disease.[43]

Other Environmental Toxins

Aluminum Phosphide.

Aluminum phosphide (AP) is an inorganic phosphide that is commonly used as an insecticide and rodenticide in grain storage and grain-processing facilities. Inhalation or ingestion of AP results in the generation of phosphine gas, which produces widespread organ toxicity and mortality in 37% to 100% of subjects. Cardiac toxicity from AP poisoning is characterized by myocarditis, refractory heart failure, and cardiac arrhythmias, including ventricular tachycardia.[44]

Thallium.

Thallium salts are toxic when inhaled, ingested, or absorbed through the skin. Gastrointestinal and neurologic symptoms of poisoning occur within 12 to 24 hours of a single toxic dose (>1 g in adults). Several weeks after acute exposure, individuals are predisposed to cardiac arrhythmias and sudden death.

Cardenolides.

Cardenolides are naturally occurring plant toxins that act primarily on the heart and cause serious dysrhythmias—including second- or third-degree heart block—and cardiac arrest. Poisoning with the digitalis cardenolides (digoxin and digitoxin) is reported worldwide. Cardiotoxicity from other cardenolides—such as the yellow, pink, or white oleander; sea mango tree; and coconut crabs—is a major problem in southern Asia. In India and Sri Lanka, yellow oleander has become a popular means of self-harm, with tens of thousands of ingestions annually and a case fatality ratio of 5% to 10%. Prolonged hospitalization and observation are recommended because the occurrence of dangerous dysrhythmias may be delayed for up to 72 hours after ingestion.

“Mad Honey.”

Honey produced from the nectar of rhododendrons growing on mountains of the eastern Black Sea region of Turkey may contain grayanotoxins, which bind to voltage-dependent sodium channels in the heart and thereby lead to bradycardia and atrioventricular block. Poisoning may present with ST elevation and

symptoms mimicking acute MI. Symptoms of “mad honey” poisoning (i.e., nausea, vomiting, hypotension, and syncope) occur a few minutes to several hours after ingestion of the honey, with the severity of the poisoning being dependent on the amount ingested. Grayanotoxins are metabolized and excreted rapidly, so the toxic effects of honey poisoning are rarely fatal and typically resolve in 2 to 9 hours.

Aconitine (Monkshood).

Aconite roots, most commonly from the monkshood plant, are commonly used in Chinese and Japanese herbal medications for treating subjects with musculoskeletal pain. Aconitine blocks the conduction of voltage-sensitive sodium channels in cardiac and nerve tissue, which results in the rapid onset of various gastrointestinal, neurologic, and cardiac symptoms, including paresthesias, muscle weakness, vomiting, hypotension, ventricular dysrhythmias, and refractory cardiovascular collapse. Enhancement of the transmembrane inward sodium current during the plateau phase of the action potentially prolongs repolarization in cardiac myocytes and results in afterdepolarizations with triggered automaticity, which underlies the ventricular dysrhythmias. Although ventricular arrhythmia is the most common electrocardiographic finding in acute aconitine poisoning, frequent ventricular ectopic beats, bundle branch block, sinus tachycardia, and sinus bradycardia have also been reported.

Scombroid.

Acute severe myocardial dysfunction secondary to histamine poisoning has been reported within 1 hour of the ingestion of spoiled scombroid fish, such as tuna or bonito. The flesh of these fish is rich in histidine, which is metabolized by gastrointestinal flora to histamine. The diagnosis is based mainly on clinical findings, but it can be documented by determination of histamine concentrations in the ingested fish or increased plasma histamine levels in the patient within 4 hours of fish ingestion.

Envenomations.

Black widow spider, bee, wasp, jellyfish, cobra, and scorpion envenomations have been associated with cardiac complications, including MI, acute cardiac failure, myocarditis, bradyarrhythmias, heart block, ventricular tachyarrhythmias, and sudden death. The mechanism or mechanisms by which these adverse outcomes occur include systemic release of catecholamines, cardiac ion channel modulation, coronary arterial vasoconstriction, and direct myotoxic effects.

Future Directions

Although adverse cardiovascular events have been associated with various medications, recreational drugs, and toxins, the precise mechanism of their effects is often unknown, and as a result, effective treatment is not established. This information is essential to avoid agents that interfere with specific molecular pathways that regulate cardiac function and to develop therapy that limits cardiotoxicity. When new medications are approved for use, postmarketing studies should be required to identify any cardiotoxic effects that may occur infrequently—and hence are not evident when the drug is studied in limited numbers of subjects—or only in the presence of concomitant conditions. For specific agents, such as chemotherapeutic compounds and antiretroviral agents, effective approaches to the identification of early (i.e., days to weeks) and late (months to years) cardiotoxic effects should be defined.

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81

Cardio-Oncology

Bonnie Ky

Cardiovascular (CV) disease and cancer are two disease states that are associated with a substantial public health burden. There are an estimated 15 million people with CV disease and 14 million with a history of cancer, and there are risk factors and common biologic mechanisms shared by both of these disease states. The intersection of CV disease and cancer has led to the burgeoning discipline of cardio-oncology. This multidisciplinary field encompasses the care of patients with CV disease who develop cancer; cancer patients and survivors who are at risk for the development of CV disease secondary to cancer therapy; and cancer patients and survivors who develop overt CV disease. CV disease related to cancer therapy is often termed *cardiotoxicity*. The diseases encompassed by the term are not only heart failure (HF) and left ventricular (LV) dysfunction (the latter sometimes referred to as cancer therapeutics

cardiac dysfunction, or CTRCD),[1] but also a myriad of others, including hypertension (HTN) (**see Chapter 47**), myocardial ischemia (**see Chapter 61**), arrhythmia (**see Chapter 32**), pulmonary HTN (**see Chapter 85**), pericardial disease (**see Chapter 83**), valvular disease (**see Chapter 67**), peripheral vascular disease (**see Chapter 64**), and venous and arterial thrombosis.

The incidence and, thus, significance of cardiotoxicity with cancer therapy are believed to be growing. There are several reasons for this increase. First, cancer patients are living longer because they are receiving improved treatment regimens, so the observed "late effects" of cancer therapies are increasing. Second, cancer therapies are rapidly evolving, and new drug development has led to the increasing use of "targeted" strategies, many of which also affect fundamental signaling pathways that are necessary for cardiomyocyte and endothelial cell function and homeostasis. **Chapter 81** reviews the epidemiology, clinical manifestations, and pathophysiology of CV disease with commonly used chemotherapeutic agents, targeted therapies, hormonal therapy, and radiation therapy (RT) (**Table 81.1**). Care of the CV patient prior to, during, and after therapy and strategies to mitigate cardiotoxicity are also discussed.

TABLE 81.1

Cardiotoxic Effects of Cancer Therapies

AGENT	REPORTED CARDIOTOXIC EFFECTS	COMMENTS
Anthracyclines		
Doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone	Cardiac arrhythmias, CM, HF	Risk factors include cumulative dose, although genetic variation may confer increased risk at lower dosages; conventional CV risk factors and disease; additional cardiotoxic therapies, including RT or trastuzumab
Taxanes		
Paclitaxel	Arrhythmia, myocardial ischemia	May exacerbate risk of anthracycline cardiotoxicity secondary to pharmacokinetic effects
Alkylating and Alkylating-Like Agents		
Cyclophosphamide	Myopericarditis, arrhythmias	Rare; CV complications reported only at high dosages
Cisplatin, carboplatin, oxaliplatin	Endothelial dysfunction, arterial vasospasm, HTN	
Antimetabolites		
5-Fluorouracil, capecitabine	Coronary vasospasm, myocardial ischemia, infarction, arrhythmias, ECG changes, sudden death	May be related to endothelial injury, vasoconstriction, and vasospasm; typically managed with nitrates and calcium channel blockers
Monoclonal Antibody Tyrosine Kinase Inhibitors		
Bevacizumab	HTN, CM, HF, thrombosis	Low risk of CM or HF
Trastuzumab	CM, HF	Increased risk of CM and HF with anthracyclines; HTN, obesity, and borderline normal baseline LVEF are also established risk factors; many LVEF declines are reversible, but in approximately 20% of patients, reversibility is not seen
Pertuzumab	CM, HF	Risk of CM and HF remains incompletely defined, but thus far, it has been modest
Proteasome Inhibitors		
Bortezomib	CM, HF, edema	Reversible proteasome inhibitor
Carfilzomib	CM, HF, edema	Irreversible proteasome inhibitor; cardiotoxicity rates greater
Small-Molecule Tyrosine Kinase Inhibitors		
Sunitinib	HTN, CM, HF, thrombosis	Risk of HTN that tends to occur early; relationship between afterload and CM risk remains to be determined
Sorafenib	HTN, CM, ischemia, thrombosis	Risk of HTN; also associated with ischemia
Imatinib	CM, edema, pericardial effusion	Risk of CM very low
Nilotinib	Peripheral vascular disease, ischemic heart disease	
Ponatinib	Peripheral vascular disease, ischemic heart disease	
Dasatinib	Pulmonary HTN, pericardial effusion	
Immune-Modulating Agents		
Thalidomide	Edema, thrombosis, arrhythmia	
Lenalidomide	Edema, thrombosis, arrhythmia	
Immune check-point inhibitors	Myocarditis	
Androgen-Deprivation Therapy		
Leuprolide, goserelin, triptorelin, flutamide, bicalutamide	Metabolic syndrome, ischemia, coronary artery disease	
Estrogen-Receptor Modulators		
Tamoxifen	Thrombosis	Favorable effects on lipids
Aromatase inhibitors (anastrozole, letrozole, exemestane)	Hypercholesterolemia, HTN, combined end point of dysrhythmia, valvular disease, and pericarditis	
Radiation Therapy	Valvular disease, pericardial disease, vascular disease, ischemia, coronary artery disease, CM, HF	Major CV events tend to occur late, although early abnormalities in cardiac function and perfusion are observed

CM, cardiomyopathy; *CV*, cardiovascular; *ECG*, electrocardiogram; *HF*, heart failure; *HTN*, hypertension; *RT*, radiation therapy.

Epidemiology, Clinical Manifestations, and Pathophysiology of Cancer Therapy Cardiotoxicity

Traditional Chemotherapeutic Agents

Anthracyclines

Anthracyclines have been in use since the 1950s, are used widely in both adults and children, and are clearly associated with an increased risk of cardiotoxicity, primarily manifested as HF and LV

dysfunction. The American College of Cardiology and American Heart Association Heart Failure Guidelines have classified exposure to cardiotoxic therapies, such as anthracyclines, as stage A HF.[2] Reports of the incidence of anthracycline-associated cardiotoxicity have varied widely in the literature; in part, this may be because of variability in the definition of CV outcomes across retrospective analyses and the lack of systematic and rigorously ascertained longitudinal follow-up data, particularly in adults. Historically, cardiotoxicity has been classified as acute, subacute, or chronic,[3] although more recent studies have challenged this paradigm. Acute cardiotoxicity tends to occur early, during therapy, and is typically rare (≈1%), manifesting as arrhythmias, electrocardiogram changes, pericarditis, or possibly even myocarditis and HF. Estimates for subacute cardiotoxicity, which typically occurs within 1 year of therapy, and chronic (or late-onset) cardiotoxicity suggest a more frequent occurrence, with a reported incidence in the literature that varies widely, from 1.6% to 23%. Late-onset cardiotoxicity may occur 10 to 20 years after therapy, possibly in the setting of an additional stressor (i.e., a “second hit”). On an individual patient level, implicating cardiotoxic cancer therapy exposure as the cause of late-onset cardiomyopathy (CM) and HF often remains a diagnosis of exclusion.

More recent data have suggested an alternative paradigm regarding late cardiotoxicity.[4] A study of 2625 patients treated with anthracyclines followed over a median of 5.2 years (interquartile range [IQR] 2.6 to 8.0) with serial echocardiography monitoring (baseline, every 3 months during chemotherapy and the first year after chemotherapy, every 6 months for the following 4 years, and yearly afterward) noted the following. The overall incidence of cardiotoxicity, defined as a decrease in the LV ejection fraction (LVEF) of more than 10% from baseline to less than 50%, was 9%. In 98% of cases, cardiotoxicity was detected within the first year after chemotherapy had been completed, with a median time between the last dose of anthracyclines and the development of cardiotoxicity of 3.5 months (IQR, 3 to 6). In five patients, cardiotoxicity was detected after 5.5 years. The LVEF at the completion of chemotherapy and the cumulative anthracycline dose were independently associated with a risk of cardiotoxicity. A very small number of patients were hospitalized; the majority were managed as outpatients. HF therapy was initiated in all patients who developed cardiotoxicity, and 82% of the patients recovered their LVEF, either fully or partially. Overall, these findings might suggest a need for increased screening after completion of chemotherapy, and they challenge the notion of irreversible LVEF declines with early pharmacologic intervention.

Risk factors for cardiotoxicity include the dosage of the anthracycline. Retrospective analyses suggest an incidence of HF, as defined by clinical signs and symptoms, of 1.7% at a cumulative dose of 300 mg/m^2, 4.7% at 400 mg/m^2, 15.7% at 500 mg/m^2, and 48% at 650 mg/m^2.[3] It is notable that standard errors for many of these estimates are large, given the small sample sizes. More recent data from childhood cancer survivors also indicate that genetic variations in single-nucleotide polymorphisms modify the association between the anthracycline dose and CM risk.[5] In adults, additional clinical risk factors for anthracycline-induced cardiotoxicity include age (**Fig. 81.1**), traditional CV risk factors (HTN, diabetes, obesity, and hyperlipidemia), the presence of coronary artery disease or CM, prior chest RT, or additional cardiotoxic therapy.[5]

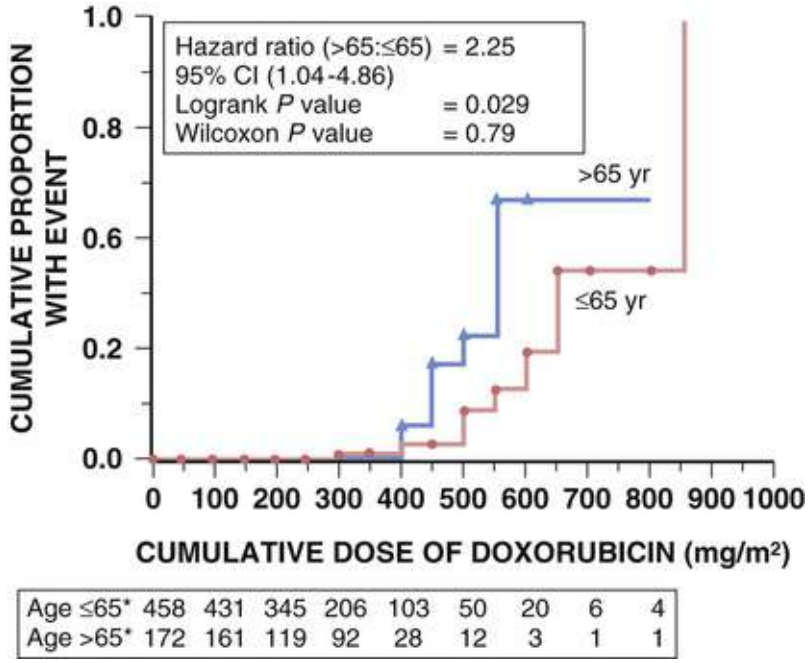

FIGURE 81.1 Risk of doxorubicin-associated heart failure by patient age and cumulative dose. The figure graphically depicts the cumulative doxorubicin dose at the onset of doxorubicin-associated heart failure in 630 patients according to patient age older or younger than 65 years. (From Swain SM, Whaley FS, Ewer MS: Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003;97:2869.)

Several basic mechanisms have been proposed to explain anthracycline-induced cardiotoxicity. The first is formation of reactive oxygen species (ROS) and increased oxidative stress via redox cycling of the quinone moiety of doxorubicin, formation of anthracycline-iron complexes, and topoisomerase-2β (Top2β) inhibition (**Fig. 81.2**).[6] Furthermore, anthracyclines have been shown to cause impaired calcium signaling and intracellular sequestration affecting myocardial relaxation; a decrease in cardiac progenitor cells; and alterations in neuregulin (NRG)/ErbB signaling.[6,7] Of these potential mechanisms, the most widely cited and accepted mechanism is the formation of ROS, leading to oxidative stress and subsequent injury to cardiac myocytes and endothelial cells.[6,7] The quinone moiety of the anthracycline enters cells and undergoes redox cycling, generating free radicals via both an enzymatic pathway involving the mitochondrial respiratory chain and also via a nonenzymatic pathway involving direct interactions between anthracyclines and intracellular iron. Toxic hydroxyl radicals from anthracycline-iron complexes act as cytotoxic messengers. This results in impaired mitochondrial function, cellular membrane damage, and cytotoxicity. Nitric oxide synthase (NOS) also contributes to the generation of anthracycline-mediated reactive nitrogen species, worsening nitrosative stress.

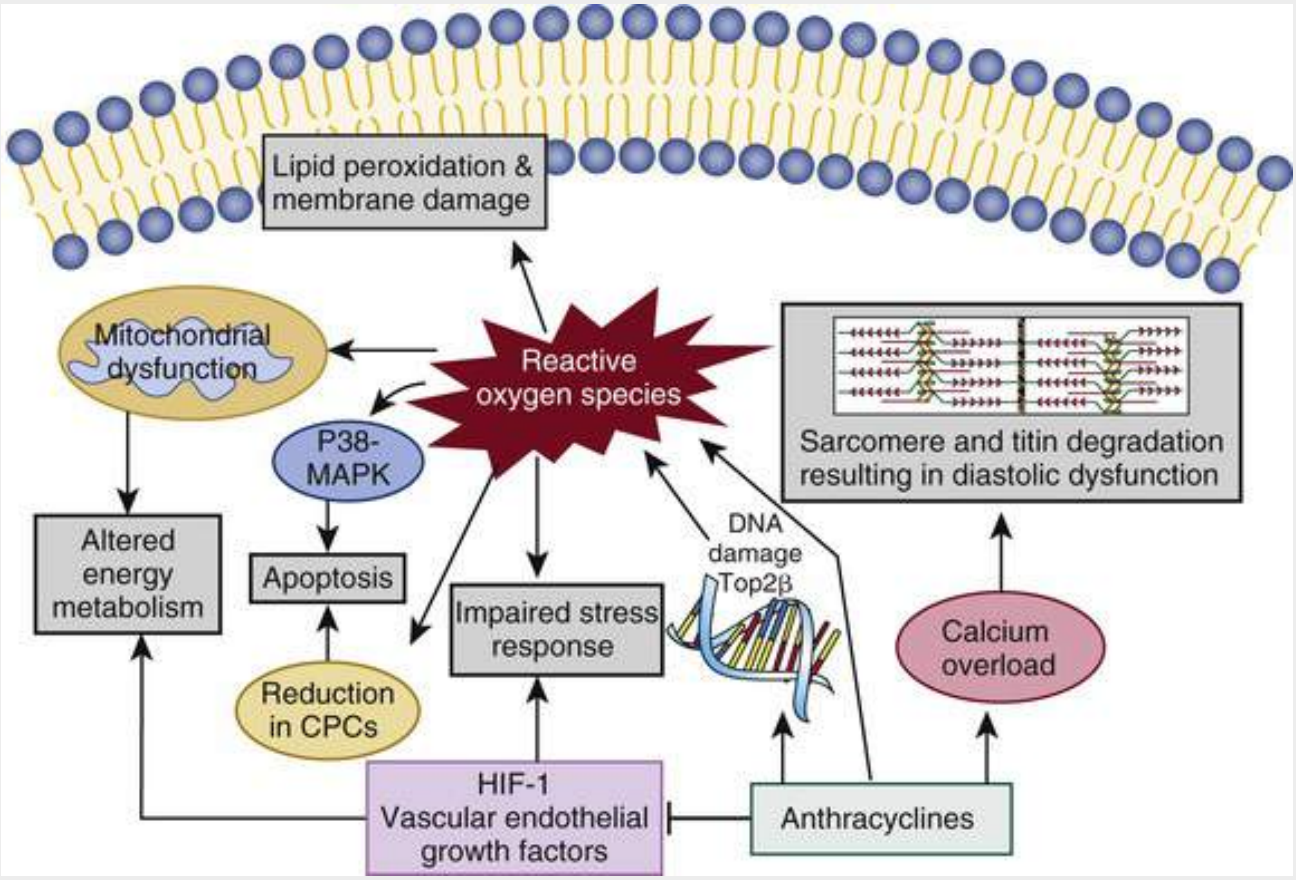

FIGURE 81.2 Proposed mechanisms of anthracycline cardiotoxicity. Using anthracyclines results in the generation of reactive oxygen species (ROS), potentially via topoisomerase 2β inhibition, as well as calcium overload, reduction in cardiac progenitor cells (CPCs), and hypoxia-inducible factor (HIF) inhibition.

More recent data suggest that the formation of ROS also occurs via the isozyme Top2, and, more specifically, Top2β, in cardiomyocytes.[6] Mice lacking Top2β are protected from anthracycline-induced DNA damage, cardiomyocyte death, and declines in cardiac function. These findings need to be further validated, but even now they suggest that this pathway may be a mechanism for engineering therapies that are less cardiotoxic and may be a tool for better stratifying the risk for individual patients. Interestingly, as discussed below, dexrazoxane, an iron chelator and cardioprotectant, binds to Top2β and results in Top2β degradation.

Data derived from in vitro and in vivo animal models support the hypothesis that anthracyclines also affect the population of cardiac progenitor cells, resulting in an impaired response to pathologic stress and injury repair. Anthracycline chemotherapy may also render cardiomyocytes more susceptible to alterations in NRG-1 and ErbB signaling and downstream prosurvival pathways.[6,7] NRG-1 administration is cardioprotective in the setting of anthracycline-induced cardiotoxicity, and conversely, NRG-1 heterozygotes have decreased survival rates and cardiac function with doxorubicin exposure as compared with wild types. A recent investigation using a modified bivalent NRG-1β demonstrated the potential for engineering NRG-1β to exploit its cardioprotective effects in the setting of doxorubicin cardiotoxicity, while reducing its possible proneoplastic effects.[7] In vitro studies have demonstrated an inhibitory effect of doxorubicin on hypoxia-inducible factor (HIF) and downstream pathways. Anthracyclines have been shown to result in impaired diastolic relaxation via calpain-dependent titin proteolysis.

Taxanes

The taxanes, paclitaxel (Taxol) and its semisynthetic analogue docetaxel (Taxotere), disrupt microtubular networks as their mechanism of antitumor activity. Used alone, these drugs have relatively little cardiotoxicity; there may be predominantly asymptomatic bradycardia and atrioventricular block.[8] However, when paclitaxel was given in close combination with high-dose doxorubicin, high rates of HF were observed (21%). This is believed to be secondary to alterations in doxorubicin metabolism when they are given with taxanes. Subsequent studies have demonstrated that limiting the doxorubicin dosages and separating the paclitaxel infusion time from the doxorubicin infusion time substantially decreased the risk of HF. Docetaxel given with anthracyclines is also reported to only mildly increase the risk of HF, again related to alterations in the pharmacokinetics and pharmacodynamics of anthracyclines.

Alkylating and Alkylating-Like Agents

Cyclophosphamide, used in the treatment of breast cancer and hematologic malignancies, is typically well tolerated. At higher dosages, greater than 100 mg/kg, there have been case reports of hemorrhagic myocarditis, tachyarrhythmias, HF, and pericardial disease.

Platinum-based agents, often considered alkylating-like agents, are commonly used in germ-cell testicular cancer, as well as ovarian, lung, and breast cancers and other solid tumors. Platinum cardiotoxicity has been perhaps most well studied in the testicular cancer population. Testicular cancer has high cure rates, and survivors often live 30 to 50 years after treatment, but they suffer from an increased long-term risk of CV events believed to be related to platinum therapy exposure. One epidemiologic study with a median observation time of 19 years reported a 5.7-fold increased risk of coronary artery disease and 2.3-fold increased risk of atherosclerotic disease as defined by coronary disease, cerebrovascular disease, and peripheral arterial disease in patients receiving platinum-based chemotherapy regimens compared with patients receiving no chemotherapy.[9] These effects were worsened in patients who received concomitant RT, and patients also had abnormal androgen levels. Some studies have also suggested that platinum is associated with endothelial damage, because plasma platinum levels remain detectable in patients up to 20 years after therapeutic exposure.

Antimetabolites

5-Fluorouracil (5FU) is used in the treatment of many solid tumors, including gastrointestinal, breast, head and neck, and pancreatic cancers. Specific CV effects include myocardial ischemia, which is the most common, as well as cardiac arrhythmias, HTN, hypotension, CM, and cardiac arrest. In vitro and in vivo studies suggest that 5FU is associated with endothelial injury, vasospasm and vasoconstriction, and interstitial fibrosis.

In one prospective study of 106 patients treated with 5FU, 9% (8.5%) had symptoms of cardiotoxicity, presenting primarily as angina and electrocardiographic changes.[10] Elevations in cardiac biomarkers such as N-terminal probrain natriuretic peptide (NT-proBNP) were also observed. These symptoms, often treatable with nitrates and calcium channel blockers, have historically been attributed to vasospasm, although the mechanism and pathophysiology remain poorly defined. The oral agent capecitabine (Xeloda), which is metabolized to fluorouracil, has also been associated with a 6.5% incidence of cardiac events, defined by angina in 4.6%, myocardial infarction, ventricular tachycardia, and sudden death.[8]

Additional Cancer Therapies

Proteasome Inhibitors

Proteasome inhibitors, such as bortezomib and carfilzomib, are used in the treatment of relapsed or refractory and newly diagnosed cases of multiple myeloma, a disorder characterized by an excess of bone marrow cells and monoclonal protein. Strategies to treat myeloma include the use of ubiquitin proteasome inhibitors; proteasome complexes are responsible for the degradation of the majority of regulatory proteins, including those that control cell-cycle progression, apoptosis, and DNA repair.[5] Cancer cells generally have higher levels of proteasome activity compared with normal cells, and are thus believed to be particularly susceptible to the proapoptotic effects of proteasome inhibitors. Protein homeostasis, however, is also hypothesized to play a role in the maintenance of cardiac function.[11] In patients with dilated CM, for example, oligomeric protein deposits are found in cardiomyocytes and are associated with increased cardiac stress. Both bortezomib, which results in reversible inhibition, and carfilzomib, an irreversible inhibitor, are associated with an incidence of HF of 4% and 7%, respectively; the incidence of cardiotoxicity is greater with carfilzomib.[5] Additional cardiotoxicities, such as HTN, diastolic dysfunction, increases in pulmonary pressures, elevations in natriuretic peptides, and worsened dyspnea, have also been observed with these therapies.

Immune-Modulating Agents

Immune modulatory agents such as thalidomide and lenalidomide are used in the treatment of multiple myeloma.[12] These agents are primarily associated with an increased risk of venous thromboembolic events, on the order of 2% to 4%, secondary to antiangiogenic effects and alterations in factors including thrombomodulin, von Willebrand factor antigen, and factor VIII. Reportedly, this incidence increases significantly when the agents are used in combination with other agents such as dexamethasone or anthracyclines. To mitigate the risk of thromboembolism, the International Myeloma Working Group recommends the use of aspirin, low-molecular-weight heparin, or warfarin with combination therapy, with the exact agent dependent upon the risk factor profile and the individual patient.

Immune check-point inhibitors are a newer class of agents used in a variety of solid tumors. These agents have been associated with a very low, but clinically significant, risk of myocarditis. Case reports of patients treated with both anti-CTLA-4 and anti-PD1 antibodies have described case fatalities secondary to marked cardiac compromise.

Targeted Therapies

The treatment of a number of malignant neoplasms has changed radically during the past few years with the advent of so-called targeted therapies. As opposed to traditional chemotherapeutics, which target basic cellular processes present in most cells, these therapies target factors that are specifically dysregulated in cancerous cells. It was hoped that this approach would reduce toxicities typical of standard chemotherapeutics (e.g., alopecia, gastrointestinal toxicity, myelotoxicity) and at the same time be more effective at treating the cancer. In some situations, this has been the case, but concerns about cardiotoxicity have surfaced for several agents.

ErbB Antagonists (Trastuzumab, Pertuzumab, T-DM1)

Trastuzumab is a humanized monoclonal antibody that binds subdomain IV of human epidermal growth factor receptor 2 (HER2)/neu, also known as ErbB2. Trastuzumab exerts its antitumor effects by blocking

HER2 cleavage, resulting in antibody-dependent, cell-mediated cytotoxicity and inhibition of ligand-independent, HER2-mediated signaling affecting the following downstream pathways: phosphoinositide 3-kinase (PI3K), serine/threonine-specific protein kinase Akt, mitogen-activated protein kinase (MAPK), and extracellular-signal–regulated kinase 1/2 (ERK1/2), and the mechanistic target of rapamycin (mTOR).[6] Trastuzumab also exerts antiangiogenic effects. First approved by the Food and Drug Administration (FDA) in 1998 for advanced metastatic cancer, it received expanded indications for early-stage HER2+ breast cancer in 2007.[13]

Phase III clinical trials with trastuzumab suggest that the risk of severe HF is low, on the order of 1.7% to 4.1%, but the risk of declines in LVEF are greater, on the order of 7.1% to 18.6%.[3,14,15] As a result, the FDA recommends cardiac monitoring every 3 months during trastuzumab therapy. Studies suggest that adherence to cardiac monitoring may be low, and some clinicians favor the notion that monitoring be performed only in high-risk individuals.[16] However, retrospective analyses from various large data sources, including the Surveillance, Epidemiology, and End Results (SEER) Program, the Cancer Research Network, and the Canadian health care system databases, indicate that the incidence of HF and CM development may be higher.[3] For example, analyses of SEER patients reported an incidence of HF of 41.9% at 3 years following combination therapy with anthracyclines and trastuzumab.[17] In the Cancer Research Network, there was a 20.1% incidence of HF and/or CM with combination therapy.[3] Data from the Ontario Cancer Registry suggest a 3- to 5-year risk of major cardiac events (HF hospitalization, urgent visit, outpatient diagnosis, or CV death) on the order of 4.8% to 5.2%.[18] As with anthracycline cardiotoxicity, hospital-based HF events occur less frequently, but patients treated with sequential anthracyclines and trastuzumab therapy are observed to have an increased risk (hazard ratio [HR], 3.96; 95% confidence interval [CI], 3.01 to 5.22), as do patients treated with trastuzumab alone (HR, 1.76; 95% CI, 1.19 to 2.60). The risk of HF and CM is greatest in the setting of sequential anthracycline and trastuzumab exposure, and additional risk factors for trastuzumab cardiotoxicity include the presence of obesity, a lower baseline LVEF, HTN, or diabetes; antihypertensive therapy; and increased patient age.

Importantly, LVEF declines with trastuzumab are largely reversible and occur during therapy. As a consequence, trastuzumab-associated cardiotoxicity was initially termed type II dysfunction by many, to distinguish it from anthracycline-associated cardiotoxicity, which was termed type I dysfunction.[3] This classification has largely fallen out of favor because of its oversimplification of the situation and because of the lack of strong evidence that the biologic underpinnings and clinical manifestations of anthracycline and trastuzumab cardiotoxicity are fundamentally distinct and do not overlap. Moreover, the reversibility of LVEF declines with trastuzumab is not universally observed. In the HERceptin Adjuvant (HERA) Trial, a phase III randomized trial of trastuzumab, approximately 20% to 30% of patients did not demonstrate LVEF recovery, and some patients suffered a subsequent decline in LVEF even after an initial recovery was noted.[14] Conversely, as noted above, LVEF recovery is observed with anthracyclines.[4]

Dose delays and interruptions have also been shown to be associated with worse overall survival rates, emphasizing the importance of the delivery of cancer therapy. The clinical determinants of LV recovery, as defined by an improvement in LVEF, have not been rigorously defined with trastuzumab, but observations suggest that temporary cessation of therapy and/or institution of cardiac medications (e.g., angiotensin-converting enzyme [ACE] inhibitors and beta blockers) are associated with recovery. Longitudinal data defining the changes in cardiac size and function over time suggest that measures of LV size, primarily end-systolic volumes; contractility (longitudinal and circumferential strain); and ventricular-arterial coupling (afterload) are independently associated with LVEF decline and recovery.

It is widely speculated that the cardiac dysfunction observed with trastuzumab is a direct consequence of ErbB2 inhibition in cardiomyocytes, but this remains to be definitively proven (**Fig. 81.3**).[6,7] Basic studies have been limited, in part, by the lack of robust systems to study the in vitro and in vivo effects of trastuzumab, a humanized antibody. The NRG/ErbB system functions as a paracrine and juxtacrine system between microvascular endothelial cells and cardiomyocytes. NRG-1 is expressed in vascular endothelial cells, and ErbB2 and ErbB4 are expressed in cardiomyocytes and endothelial cells. Recombinant NRG-1β activates ErbB2 and ErbB4 receptor phosphorylation in cardiomyocytes in vitro. Important downstream mediators, as noted above, include PI3K/Akt, MAPK/ERK, steroid receptor activator (Src)/focal adhesion kinase, and NOS. All of these pathways are fundamental for cardiac homeostasis, cell survival, mitochondrial function, cell growth, and focal adhesion formation. Mice with a cardiac-specific deletion of ErbB2 develop dilated CM and demonstrate exaggerated systolic dysfunction after pressure overload compared with wild-type mice. ErbB2 and ErbB4 expression is preserved during compensated hypertrophy, but it declines in the early stages of systolic dysfunction in mice subjected to pressure overload. Overall, these findings suggest that perturbations in ErbB receptor signaling are important in the maintenance of cardiac function. More recent data suggest that disruption of ErbB2 signaling results in endothelial dysfunction and an altered vascular phenotype, potentially contributing to the cardiomyopathic phenotype.

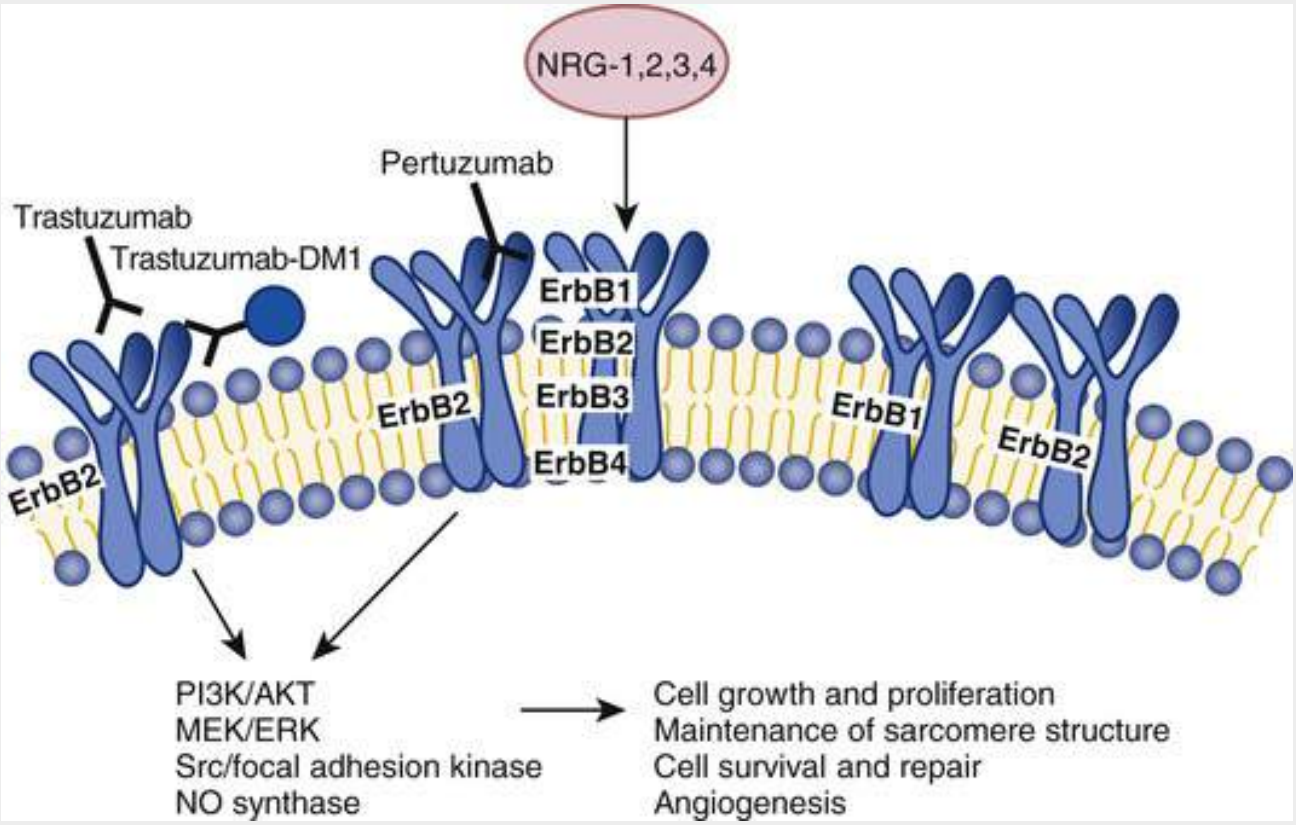

FIGURE 81.3 Proposed mechanisms of trastuzumab cardiotoxicity. Trastuzumab is hypothesized to result in perturbations of the neuregulin (NRG)/ErbB signaling pathway; this results in inhibition of fundamental cardiovascular signaling pathways, which are responsible for cell growth, maintenance of cardiomyocyte structure, cell survival, and angiogenesis.

There are a number of newer ErbB antagonists, including pertuzumab and ado-trastuzumab emtansine.

Pertuzumab is a humanized monoclonal antibody that binds HER2 at subdomain II of the HER2 extracellular domain[3]; it is administered in conjunction with trastuzumab. Pertuzumab also stimulates antibody-dependent, cell-mediated cytotoxicity, and prevents dimerization to other ligand-activated HER receptors, especially HER3. As with trastuzumab, clinical guidelines for pertuzumab suggest monitoring of cardiac function every 3 months. Although the CV effects are still being elucidated, clinical data to date have not demonstrated a substantial cardiotoxic signal. In the CLEOPATRA study of patients with HER2-positive metastatic breast cancer, the rate of LV dysfunction according to the Common Terminology Criteria for Adverse Events (CTCAE) was 6.6% in the pertuzumab group, compared with 8.6% in the control group. In the pertuzumab group, there was one event of symptomatic LV dysfunction that occurred at 40 months and resolved after 3 months with discontinuation of trastuzumab and pertuzumab. In the remainder of patients who suffered from declines in LVEF, the condition was largely reversible in most, but not all.

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate used in the treatment of metastatic breast cancer. The maytansine-derived cytotoxic agent, which is able to inhibit cell division and induce tumor cell death, is attached to trastuzumab by a stable thioether linker. The design facilitates the intracellular delivery of the drug to HER2 tumor cells. To date, no major signal for dose-limiting cardiotoxicity has been observed, although long-term data with larger numbers of patients are needed to define the risk of cardiotoxicity with greater certainty.

Tyrosine Kinase Inhibitors and Monoclonal Antibodies

Many of the targeted cancer therapeutics inhibit the activity of tyrosine kinases. Tyrosine kinases (TKs) attach phosphate groups to tyrosine residues of other proteins, thereby changing the activity, subcellular localization, and rate of degradation of the proteins. In the normal cell, these wild-type (i.e., normal) TKs play many roles in regulating basic cellular functions. However, in leukemias and cancers, the gene encoding the causal (or contributory) TK is amplified (leading to overexpression) or mutated, leading to a constitutively activated state that drives proliferation of the cancerous clonal cells or blocks their normal death.

Vascular Endothelial Growth Factor Receptor Inhibitors

Vascular endothelial growth factor receptor (VEGFR) signaling pathway inhibitors are used in the treatment of metastatic renal cell cancers; gastrointestinal stromal tumors; and thyroid, hepatocellular, and colon cancers; they are under active investigation for many additional indications. Bevacizumab is a humanized recombinant anti-VEGF antibody. The CV risks associated with bevacizumab include HTN; a low incidence of HF (on the order of 1.6%, but with a relative risk of 4.7 compared with placebo); and an increased incidence of arterial thromboembolic events (7.1% with bevacizumab versus 2.5% with chemotherapy alone). Sorafenib is a small-molecule TK inhibitor that blocks VEGFR, platelet-derived growth factor (PDGFR), and rapidly accelerated fibrosarcoma (Raf); it is used in the treatment of metastatic renal cell, thyroid, and hepatocellular cancers and other solid tumors. Sorafenib is associated with cardiac ischemia and HTN. Both bevacizumab and sorafenib have less pronounced cardiotoxic effects than sunitinib.

Sunitinib is a multitargeted oral TK inhibitor used in the treatment of metastatic renal cell carcinoma, gastrointestinal stromal tumors, and neuroendocrine tumors.[19,20] Recent studies have suggested its potential effectiveness in the adjuvant renal cell carcinoma setting. Axitinib and pazopanib are other small-molecule TK inhibitors that also affect the VEGFR signaling pathway. These antiangiogenic TK

inhibitors have been associated with HTN, CM and HF, cardiac ischemia, and arterial thrombotic events. Of these agents, we focus on describing the epidemiology and basic mechanisms of sunitinib, because it is the most well studied agent to date and is used widely in clinical practice. This discussion is also relevant to other TK inhibitors that have off-target effects on the VEGFR and PDGFR.

Sunitinib results in HTN, as well as declines in LVEF. In phase III trials and subsequent clinical experience, the incidence of HTN ranges from 5% to 47% and the incidence of significant LVEF declines is estimated to be on the order of 10%.[7] HTN secondary to sunitinib tends to occur early, with the median time to HTN (defined as a systolic blood pressure of ≥ 140 mm Hg or diastolic blood pressure of ≥ 90 mm Hg) occurring within 1 to 20 days of the first two cycles of sunitinib therapy. The incidence of systolic HTN in one pooled analysis was 58%, and of diastolic HTN was 48% by the end of cycle 1.[21] By the end of cycle 2, 80% had systolic HTN and 68% had diastolic HTN. The median (range) blood pressures were 160 (140 to 220) mm Hg over 98 (90 to 129) mm Hg in those with a history of HTN and 130 (100 to 139) mm Hg over 82 (59 to 89) mm Hg without a history of HTN. Prospective observational data suggest that the rate of LV dysfunction in the metastatic renal cell cancer population, as defined by declines in LVEF, is on the order of 10%. The majority of these events occur early after the initiation of therapy, primarily within the first 3 months, with a low risk of late cardiotoxicity. LVEF declines have also been observed to be reversible, although predictors of LVEF recovery remain to be defined. As sunitinib and other TK inhibitors gain more widespread use, maximizing tolerability and minimizing toxicity has become increasingly critical. The mechanisms of sunitinib cardiotoxicity are believed to be secondary to the inhibition of key signaling pathways critical to CV homeostasis, energy compromise, and increased afterload,[7] although the relative importance of each of these mechanisms remains unknown. Additional content on the mechanisms of sunitinib toxicity are presented in the online supplement titled Sunitinib Cardiotoxicity.

Bcr-Abl Targeted Therapies

Imatinib, the first targeted small-molecule TK inhibitor of the fusion protein Bcr-Abl, which arises from the chromosomal translocation that creates the Philadelphia chromosome, revolutionized the treatment of chronic myeloid leukemia. In vitro and in vivo murine studies first suggested a relationship between imatinib and CM.[22] Clinically, imatinib is associated with a low incidence of HF. Newer Bcr-Abl TK inhibitors have raised more substantive concerns. Dasatinib, with more potent activity than imatinib against Bcr-Abl, has been associated with significant pulmonary HTN that is observed to be largely reversible with cessation of the drug.[22] This finding prompted the FDA to recommend that patients be evaluated for cardiopulmonary disease prior to and during dasatinib treatment. Nilotinib and ponatinib have both been associated with peripheral vascular disease and ischemic heart disease. Moreover, nilotinib has been associated with cardiometabolic effects, including hyperglycemia and hyperlipidemia, and ponatinib with HTN likely related to VEGFR1-3 inhibition. Retrospective studies suggest the incidence of peripheral arterial disease is on the order of 1.3% to 6.2%, and the incidence of combined CV events, including ischemic heart disease, ischemic cerebrovascular disease, and peripheral arterial disease, may be on the order of 10% to 15.9%. The biologic mechanisms of cardiotoxicity remain unknown. Comprehensively deciphering the mechanisms of these kinase inhibitors remains challenging given their nonselectivity; they typically affect more than 30 different kinases.

Hormonal Therapy

Androgen Deprivation Therapy

In prostate cancer, androgen deprivation therapy (ADT) is used to reduce levels of androgens in the circulation and decrease prostate cell growth. Potential agents include gonadotropin-releasing hormone (GnRH) agonists, such as leuprolide, goserelin, and triptorelin, and antiandrogens, such as flutamide and bicalutamide. These therapies have adverse metabolic effects, and observational studies suggest that they result in increased body weight, decreased insulin sensitivity, and dyslipidemia. Changes in body composition occur early, within the first few months of therapy. Multiple cohort studies indicate an increased risk of CV events in men, including coronary disease, myocardial infarction, sudden cardiac death, or death due to CV disease.[23] Not all studies corroborate this effect, however, and this has resulted in the consensus amongst experts that it is "reasonable to state that there may be a relationship between ADT and CV events."[23] Recent literature suggests that the CV risk in patients treated with ADT may vary according to the comorbidity status, with ADT having a greater and worse impact on CV survival rates in patients who have greater CV and overall comorbidities.

Selective Estrogen Receptor Modulators and Aromatase Inhibitors

Tamoxifen is a selective estrogen receptor modulator widely used in adjuvant therapy for estrogen receptor–positive breast cancer. Data regarding the cardioprotective effect of tamoxifen have been conflicting. Tamoxifen does exert a favorable effect on lipids, with a reduction in total cholesterol and LDL levels. Some studies demonstrate a potential effect on decreasing the ischemic heart disease incidence, with a relative risk of 0.76 (95% CI, 0.60 to 0.95; $P = 0.02$),[24] although other studies demonstrate no significant effect. An increased risk of thromboembolic events, however, is well established; they occur largely during the first 2 years of exposure and in older women. A metaanalysis from the Early Breast Cancer Trialists' Collaborative Group confirmed a significant, but small, increased risk in venous thromboembolism with tamoxifen.

Aromatase inhibitors (e.g., anastrozole, letrozole, exemestane) block the conversion of androgens to estrogen. The two major classes that are currently in use differ according to their ability to bind reversibly versus irreversibly to aromatase. Data regarding the potential CV effects of aromatase inhibitors have been conflicting, but it is hypothesized that these agents inhibit the beneficial effects of estrogen related to the regulation of lipids, coagulation, antioxidant systems, and nitric oxide production. Aromatase inhibitors are associated with worse hypercholesterolemia and HTN, and a longer duration of exposure is associated with an increased risk of CV disease. Pooled data analyses from multiple large cohort studies suggest that there is a modestly increased risk of CV disease, as defined by myocardial infarction, angina, or HF, with aromatase inhibitors compared with tamoxifen (odds ratio [OR], 1.26; 95% CI, 1.10 to 1.43; $P < 0.001$).[25] A recent retrospective analysis of 13,273 postmenopausal women with hormone receptor–positive breast cancer without prior CV disease with a maximum follow-up of 21 years determined that compared with tamoxifen, aromatase inhibitors were not associated with an increased risk of cardiac ischemia or stroke. However, there was a nonsignificant association with HF and CM and a significant association with a combined outcome of dysrhythmia, valvular dysfunction, and pericarditis.[26]

Radiation Therapy

In the United States, where nearly 3 million women live with breast cancer, radiation therapy (RT) has been critical for improved cancer control and survival rates.[27] Despite these gains, incidental irradiation

to cardiac structures results in an increased risk of CV morbidity and mortality. The clinical manifestations of RT cardiotoxicity include coronary disease, CM and HF, valvular disease, arrhythmia, and pericardial disease. Increasing data suggest that early subclinical changes, including cardiac perfusion defects and cardiac strain abnormalities, occur earlier, within 6 months of RT, even with the use of modern techniques.

In a metaanalysis of over 23,000 women with breast cancer, there was an excess of deaths not resulting from breast cancer as early as 5 years following RT, principally due to CV disease and lung cancer.[28] Subsequent epidemiologic studies support these results. Retrospective analyses of 4456 women treated between 1954 and 1984 who had survived at least 5 years after breast cancer treatment were evaluated an average of 28 years after cancer therapy. A total of 3075 of these women had received RT, and 6% had chemotherapy exposure as well. Cardiac and vascular diseases were defined by ICD codes, and included pericarditis, myocarditis, valvular disease, ischemic heart disease, conduction disorders, HF, hypertensive disease, pulmonary heart disease, vasculocerebral disease, diseases of the arteries, and diseases of the circulatory system. In this study, RT was associated with a 1.76-fold increased risk of cardiac mortality and a 1.33-fold increased risk of vascular mortality. Patients with left-sided disease had a 1.56-fold increased risk of cardiac mortality compared with those with right-sided disease. SEER cancer registry analyses of 308,861 U.S. women with early breast cancer and RT also confirmed an increased risk of death in patients with left-sided versus right-sided disease.[28] A breast cancer study from 2013 suggests that the rate of major CV events increased linearly by 7.4% for each Gray (Gy) increase in mean RT dose to the heart.[29]

Similar studies in Hodgkin lymphoma survivors corroborate an association between the RT dose to the heart and the risk of CV disease that is progressive over time, increasing the risk of CV complications 3- to 5-fold compared with the general population. In a single-center, retrospective analysis of 1279 Hodgkin lymphoma survivors treated with mediastinal radiation, the cumulative incidence of cardiac disease increased from 2.2% at 5 years to 16% at 20 years.[30] Relative to healthy age-matched controls, the standard incidence ratio was 3.19 for coronary artery bypass surgery, 1.55 for percutaneous revascularization, 9.19 for valve surgery, 12.91 for pericardial stripping or pericardiocentesis, and 1.9 for defibrillator or pacemaker placement.

In addition to the cumulative RT dose, which represents a critical determinant of the development of cardiac disease, additional risk factors include the radiation field, younger age, higher number of fractions, concomitant chemotherapy (anthracyclines), CV risk factors (diabetes, tobacco use, obesity, HTN, and hypercholesterolemia), and preexisting CV disease.

Irradiation results in valvular disease with leaflet thickening, fibrosis, and calcification.[31] Left-sided valves are more commonly affected, particularly the aortic valve, followed by the mitral and tricuspid valves. Fibrosis and calcification of the aortic root, aortic valve annulus, aortic valve leaflets, aortic-mitral intervalvular fibrosa, mitral valve annulus, and the base and mid portions of the mitral valve leaflets typically occur. Sparing of the mitral valve tips and commissures has been noted, and used as a feature to distinguish radiation-induced valvular disease from other disease states, such as rheumatic heart disease. Regurgitation is more commonly encountered than stenosis, with the exception of the aortic valve, where stenotic lesions are reported to be more common. The reported incidence of significant valve disease is 1% at 10 years, 5% at 15 years, and 6% at 20 years, with the incidence increasing significantly at more than 20 years after radiation exposure. This risk is related to the RT dose. The pathophysiology of radiation-induced heart disease is believed to be associated with an increase in TGF-β and osteogenic factors, including bone morphogenetic protein 2, osteopontin, and alkaline phosphatase.

RT is also associated with the development of HF and CM. Diffuse myocardial fibrosis and

microvascular and macrovascular injury result in systolic and diastolic dysfunction, and can manifest as a restrictive CM phenotype. Regional wall motion abnormalities have also been noted. However, most imaging-based studies evaluating the longitudinal changes over time with RT remain small; the way in which microvascular disease and macrovascular disease impact the development of overt CM and the type of CM occurring remain unknown. On a microvascular level, irradiation results in endothelial cell loss and dysfunction, increased inflammation, and decreased capillary density. On a macrovascular level, there is proximal (ostial) involvement of coronary arteries, and lesions are fibrous, fibrocalcific, fibrofatty, and laden with cholesterol and lipid. A higher prevalence of perfusion abnormalities has been observed in left-sided compared with right-sided breast cancer patients, with an increase in disease in the left anterior descending artery territory. Irradiation also results in autonomic dysfunction, defined by an elevated resting heart rate and abnormal heart rate recovery. These abnormalities can lead to impaired exercise tolerance and an increased risk of death, independent of ischemic heart disease or LV dysfunction. Radiation-induced pericardial disease can occur acutely, as pericarditis and pericardial effusions. Pericardial thickening and constrictive pericarditis have also been noted, and can be delayed several weeks to years after radiotherapy.

Cardiovascular Care of the Cancer Patient

The approach to the CV care of an oncology patient is often classified as a continuum across three stages: prior to cancer therapy, during cancer therapy, and after completion of cancer therapy.[32] At each of these stages, priorities in cardio-oncology include the safe and effective delivery of oncologic therapy through the identification of patients at high risk for CV disease, the optimization of CV risk factors, and the careful management of CV disease (**Fig. 81.4**). Guidelines set forth by the American Society of Clinical Oncology (ASCO) recommend that prior to the initiation of therapies that can result in HF, clinicians should perform a comprehensive assessment that includes history taking and a physical examination, screening for and optimization of CV disease risk factors (HTN, diabetes, dyslipidemia, obesity, and smoking), and evaluation of cardiac function by echocardiography (**eTable 81.1**).

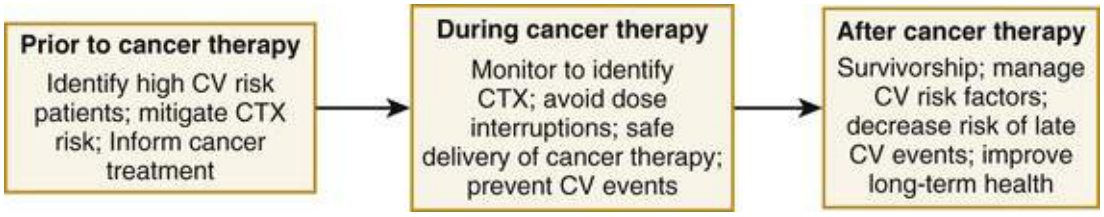

FIGURE 81.4 Approach to the cardiovascular care of the cancer patient. Care occurs along a continuum prior to, during, and after cancer therapy. At each of these stages, the goals are to minimize cardiovascular toxicity and maximize the effectiveness of oncologic therapy. *CTX*, cardiotoxicity; *CV*, cardiovascular.

eTABLE 81.1

Recommendations for Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: ASCO Clinical Practice Guideline

RECOMMENDATION	EVALUATION OF EVIDENCE
Guideline Question 1: Which cancer patients are at increased risk for developing cardiac dysfunction?	

Recommendation 1.1
It is recommended that cancer patients who meet any of the following criteria should be considered at increased risk for developing cardiac dysfunction.
Treatment that includes any of the following:
• High-dose anthracycline (e.g., ≥ 250 mg/m^2 doxorubicin, ≥ 600 mg/m^2 epirubicin)
• High-dose (≥30 Gy) radiotherapy where the heart is in the treatment field
• Lower-dose anthracycline (e.g., < 250 mg/m^2 doxorubicin, < 600 mg/m^2 epirubicin) in combination with lower-dose radiotherapy (<30 Gy) where the heart is in the treatment field
• Treatment with lower-dose anthracycline (e.g., < 250 mg/m^2 doxorubicin, < 600 mg/m^2 epirubicin) or trastuzumab alone, and the presence of any of the following risk factors:
  • Multiple (≥2) cardiovascular risk factors, including smoking, HTN, diabetes, dyslipidemia, obesity during or after completion of therapy
  • Older (≥ 60 years) age at cancer treatment
  • Compromised cardiac function (e.g.. borderline low LVEF [50% to 55%], history of myocardial infarction, moderate or more severe valvular heart disease) at any time prior to or during treatment
• Treatment with lower-dose anthracycline (e.g., < 250 mg/m^2 doxorubicin, < 600 mg/m^2 epirubicin) followed by trastuzumab (sequential therapy)
	Evidence-based; benefits outweigh harms;
	evidence quality: intermediate;
	strength of recommendation: moderate

Recommendation 1.2 No recommendation can be made on the risk of cardiac dysfunction in cancer patients with any of the following treatment exposures: • Lower-dose anthracycline (e.g., < 250 mg/m^2 doxorubicin, < 600 mg/m^2 epirubicin) *or* trastuzumab alone, and no additional risk factors (as defined in 1.1) • Lower-dose radiotherapy (<30 Gy) where the heart is in the treatment field, and no additional cardiotoxic therapeutic exposures or risk factors (as defined in 1.1) • Kinase inhibitors	Evidence-based; evidence quality: low
Guideline Question 2: Which preventive strategies minimize the risk prior to initiation of therapy?	
Recommendation 2.1 Avoid or minimize the use of potentially cardiotoxic therapies if established alternatives exist that would not compromise cancer-specific outcomes.	Consensus-based; benefits outweigh harms; strength of recommendation: strong
Recommendation 2.2 Clinicians should perform a comprehensive assessment in cancer patients that includes a history and physical examination, screening for cardiovascular disease risk factors (HTN, diabetes, dyslipidemia, obesity, smoking), and an echocardiogram prior to initiation of potentially cardiotoxic therapies.	Evidence- and consensus-based; benefits outweigh harms; evidence quality: high; strength of recommendation: strong
Guideline Question 3: Which preventive strategies are effective in minimizing the risk during the administration of potentially cardiotoxic cancer therapy?	
Recommendation 3.1 Clinicians should screen for and actively manage modifiable cardiovascular risk factors (smoking, HTN, diabetes, dyslipidemia, obesity) in all patients receiving potentially cardiotoxic treatments.	Informal consensus– and evidence-based; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate
Recommendation 3.2 Clinicians may incorporate a number of strategies, including use of the cardioprotectant dexrazoxane, or continuous infusion, or liposomal formulation of doxorubicin for prevention of cardiotoxicity in patients planning to receive high-dose (e.g., ≥ 250 mg/m^2 doxorubicin, ≥ 600 mg/m^2 epirubicin) anthracyclines.	Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate
Recommendation 3.3 For patients who require mediastinal radiation therapy that might impact cardiac function, clinicians should select lower radiation doses when clinically appropriate, and use more precise or tailored radiation fields, with exclusion of as much of the heart as possible. These goals can be accomplished through use of advanced techniques, including: • Deep inspiration breath holding for patients with mediastinal tumors or breast cancer in which the heart might be exposed. • Intensity-modulated radiation therapy that varies the radiation energy while treatment is delivered in order to precisely contour the desired radiation distribution and avoid normal tissues.	Evidence- and informal consensus–based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: strong
Guideline Question 4: What are the preferred surveillance or monitoring approaches during treatment in patients at risk for cardiac dysfunction?	
Recommendation 4.1 Clinicians should complete a careful history and physical examination in patients who are receiving potentially cardiotoxic treatments.	Informal consensus–based; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: strong
Recommendation 4.2 In individuals with clinical signs or symptoms concerning for cardiac dysfunction during routine clinical assessment, the following strategy is recommended: • Echocardiogram for diagnostic workup	Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: strong
• Cardiac magnetic resonance imaging (MRI) or multigated acquisition (MUGA) scan if echocardiogram is not available or technically feasible (e.g., poor image quality), with preference given to cardiac MRI	• Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate
• Serum cardiac biomarkers (troponins, natriuretic peptides) or echocardiography-derived strain imaging, in conjunction with routine diagnostic imaging	• Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate
• Referral to a cardiologist based on findings	Informal consensus–based; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: strong
Recommendation 4.3 Routine surveillance imaging may be offered during treatment in asymptomatic patients considered to be at increased risk (Recommendation 1.1) of developing cardiac dysfunction. In these individuals, echocardiography is the surveillance imaging modality of choice that should be offered. Frequency of surveillance should be determined by health care providers based upon clinical judgment and patient circumstances.	Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate
Recommendation 4.4 No recommendations can be made regarding continuation or discontinuation of cancer therapy in individuals with evidence of cardiac dysfunction. This decision, made by the oncologist, should be informed by close collaboration with a cardiologist, fully evaluating the clinical circumstances, and considering the risks and benefits of the continuation of therapy responsible for the cardiac dysfunction.	Informal consensus–based; benefits outweigh harms; evidence quality: insufficient
Recommendation 4.5 Clinicians may use routine echocardiographic surveillance in patients with metastatic breast cancer continuing to receiving trastuzumab indefinitely. The frequency of cardiac imaging for each patient should be determined by health care providers, based	Evidence- and informal consensus–based; benefits outweigh harms; evidence quality: low; strength of recommendation:

upon clinical judgment and patient circumstances.	moderate
Guideline Question 5: What are the preferred surveillance and monitoring approaches after treatment in patients at risk for cardiac dysfunction?	
Recommendation 5.1 Clinicians should complete a careful history and physical examination in cancer survivors previously treated with potentially cardiotoxic therapies.	Informal consensus–based; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: strong
Recommendation 5.1.1 In individuals with clinical signs or symptoms concerning for cardiac dysfunction, the following approaches should be offered as part of recommended care:	Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: strong
• Echocardiogram for diagnostic workup	
• Cardiac MRI or MUGA if echocardiogram is not available or technically feasible (e.g., poor image quality), with preference given to cardiac MRI	• Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate
• Serum cardiac biomarkers (troponins, natriuretic peptides)	• Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate
• Referral to a cardiologist based on findings	Informal consensus–based; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: strong
Recommendation 5.2 An echocardiogram may be performed between 6 and 12 months after completion of cancer-directed therapy in asymptomatic patients considered to be at increased risk (Recommendation 1.1) of cardiac dysfunction.	Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate
Recommendation 5.2.1 Cardiac MRI or MUGA may be offered for surveillance in asymptomatic individuals if an echocardiogram is not available or technically feasible (e.g., poor image quality), with preference given to cardiac MRI.	Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate
Recommendation 5.3 Patients identified to have asymptomatic cardiac dysfunction during routine surveillance should be referred to a cardiologist or a health care provider with cardio-oncology expertise for further assessment and management.	Informal consensus–based; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: strong
Recommendation 5.4 No recommendations can be made regarding the frequency and duration of surveillance in patients at increased risk (Recommendation 1.1) who are asymptomatic and have no evidence of cardiac dysfunction on their 6- to 12-month posttreatment echocardiograms.	Informal consensus–based; relative balance of benefits and harms; evidence quality: insufficient
Recommendation 5.5 Clinicians should regularly evaluate and manage cardiovascular risk factors such as smoking, HTN, diabetes, dyslipidemia, and obesity in patients previously treated with cardiotoxic cancer therapies. A heart-healthy lifestyle, including the role of diet and exercise, should be discussed as part of long-term follow-up care.	Evidence- and consensus-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate

From Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2017;35(8):893-911.

Identifying Cancer Patients at Risk for Cardiovascular Disease

A growing body of research is focused on developing prediction tools to identify patients at increased risk of cardiotoxicity prior to overt disease.[33] It is widely accepted that exposure to potentially cardiotoxic therapies represents stage A HF, and as such, many of the clinical and research efforts have focused on mitigating the risk of development of overt HF and CM, and more specifically, early risk stratification.[2] In the following section, we will elaborate on the current data related to clinical and treatment risk factors, that is, the use of genetics, circulating biomarkers, and imaging indices prior to therapy. Clinical and treatment factors associated with a risk of CM and HF in cancer patients have been noted above (**see also Chapter 25**). Briefly, these include high-dose anthracyclines; high-dose chest RT; a combination of lower doses of anthracyclines and chest RT; CV risk factors, including tobacco use, HTN, diabetes, dyslipidemia, older age, and a history of CV disease; a borderline low LVEF (50% to 55%); and greater-than-moderate valvular disease.[3,14,34] Although this is an area of active investigation, there are no validated clinical risk prediction algorithms currently used to identify high-risk patients prior to the initiation of cancer therapy.

An additional tool that holds promise for identifying high-risk patients and can aid in our understanding of disease mechanisms is the use of genetic markers. Much of our current understanding of the genetics of anthracycline-induced cardiotoxicity has come from the study of childhood survivors; these studies implicate that polymorphisms in carbonyl reductase (CBR) and hyaluronan synthase 3 (*HAS3*) are independent modifiers of the anthracycline-related CM risk.[35] CBRs catalyze the reduction of anthracyclines to cardiotoxic alcohol metabolites, whereas the *HAS3* gene encodes for hyaluronan (HA),

a ubiquitous component of the extracellular matrix that plays a role in the tissue response to injury. Additional studies in childhood cancer survivors have identified polymorphisms in genes that regulate intracellular transport (*SLC28A3*, *SLC28A1*) of anthracyclines as independent predictors of CM risk.[36] A study of adult hematopoietic cell transplantation patients treated with anthracyclines identified an association between a polymorphism in the doxorubicin efflux transporter (*ABCC2*) and cardiotoxicity, suggesting an important role for alterations in anthracycline metabolism in the development of cardiotoxicity.[37] This study also identified *RAC2*, involved in free radical generation, and *HFE*, a regulator of iron metabolism, as risk modifiers. The causal role of genes implicated in familial dilated CM remains an area of active investigation, as does the use of patient-specific, human-induced, pluripotent stem cell–derived cardiomyocytes to characterize the genetic basis of anthracycline-induced cardiotoxicity.

Biomarkers, including established CV biomarkers such as troponin (Tn) and NT-proBNP, and more novel biomarkers, both individually and in combination, hold promise as aids for risk stratification (**see also Chapter 21**), but they are not yet recommended routinely or standardly evaluated prior to cancer therapy.[5] Imaging tools, such as echocardiography and multigated acquisition (MUGA) scanning, are used widely to screen for abnormalities in LVEF prior to cardiotoxic cancer therapies, because the baseline LVEF is associated with subsequent cardiotoxicity in studies of patients with breast cancer who are receiving anthracyclines and trastuzumab. Newer measures of cardiac mechanics, including strain imaging, with a large focus on longitudinal strain, and three-dimensionally derived measures of cardiac structure and function, have also been recommended by expert consensus groups as monitoring strategies prior to therapy, with a focus on evaluating the change over time as discussed below (**see also Chapter 14**).[1] Although baseline abnormalities in measures of longitudinal strain, prior to any cancer therapy, have not been demonstrated to be associated with a subsequent decline in LVEF, there are data to suggest that baseline abnormalities in circumferential strain and ventricular-arterial coupling are associated with subsequent cardiac dysfunction.[38] Studies in populations who do not have cancer have suggested that abnormalities in circumferential strain reflect an inherent vulnerability to cardiac dysfunction. These modalities are further described in the following section.

Cardiovascular Care of the Cancer Patient During Therapy

Multiple strategies, including cardiac biomarkers and imaging modalities, are used during cancer therapy to monitor patients. Cardiac troponins are sensitive and specific markers of myocardial injury and play an important role in the diagnosis of acute coronary syndromes. In cardio-oncology, troponin has been the most widely studied biomarker. The largest study to date has been of 703 patients treated with high-dose chemotherapy.[5] Here, patients underwent frequent TnI monitoring at multiple time points with each cycle of treatment (immediately after each cycle and 12, 24, 36, and 72 hours after each cycle) and 1 month after chemotherapy. The pattern of TnI elevation identified patients at various levels of risk for cardiotoxicity. Specifically, the highest cardiotoxicity event rate was observed among patients with early (within 72 hours) TnI elevation (≥ 0.08 ng/mL) that persisted at 1 month after treatment. A similar study performed in patients treated with trastuzumab demonstrated that elevated TnI was associated with a lack of LVEF recovery despite HF therapy. There have also been multiple reports on the use of TnI as a marker of cardiotoxicity with other treatment exposures (e.g., sunitinib, sorafenib, lapatinib). Validation of these findings in additional cohorts is an area of active investigation, and will be of absolute necessity prior to the widespread use of Tn as a standardized monitoring strategy in cancer patients undergoing cardiotoxic therapies. High-sensitivity Tn assays that provide superior diagnostic accuracy for acute coronary

syndromes are also under investigation for the early detection of cardiotoxicity. The natriuretic peptides brain-type natriuretic peptide (BNP) and NT-proBNP are standard biomarkers used in clinical practice for the diagnosis and management of HF.[2] However, conclusions regarding the role of natriuretic peptides for the prediction and diagnosis of cancer therapy cardiotoxicity remain conflicting. Some studies have demonstrated a significant association with cardiotoxicity, but others have not.

The 2016 European Society of Cardiology position statement suggests that biomarkers during cardiotoxic chemotherapy may be considered, although it also identified challenges in understanding the timing of laboratory assessment, use of different assays, definition of upper limit of normal, and interpretation and management strategies of abnormal values.[5] Moreover, the group noted that data are still needed to validate the use of biomarkers as a robust strategy for preventing or improving longer-term toxicity events. The ASCO guidelines has suggested that cardiac biomarkers (troponins, natriuretic peptides) be used in conjunction with routine diagnostic imaging in the evaluation of patients at risk for LV dysfunction during cancer therapy, noting that the benefits outweigh the harms and the quality of the evidence was intermediate (**see eTable 81.1**).[32] There is an ongoing body of work that evaluates the role of newer biomarkers in risk prediction. These include markers of oxidative and nitrosative stress, such as myeloperoxidase (MPO)[39] and asymmetric dimethylarginine (ADMA), and immunoglobulin E (IgE) in the study of anthracycline and trastuzumab cardiotoxicity.

As it pertains to the application of imaging tools for understanding the changes in cardiac function that occur with cancer therapy, there have been many small studies. Some have evaluated changes in conventional measures of diastolic function, which have not been shown to be strongly predictive of subsequent systolic dysfunction, although these studies are not definitive given the marked limitations in sample size.[1] Additional research has focused on imaging tools such as speckle tracking–derived longitudinal strain. Longitudinal strain has demonstrated promise as a measure of subclinical cardiotoxicity, and multiple small studies have reported that a decline in longitudinal strain is associated with a subsequent decline in LVEF.[1] Changes in circumferential strain are also associated with subsequent LVEF decline, with moderate discriminative ability.[38] The American Society of Echocardiography (ASE) expert consensus group has recommended the use of global longitudinal strain (GLS) for the early detection of cardiac dysfunction in patients with cancer undergoing cardiotoxic therapy, with a particular focus on change over time (**see also Chapter 14**).[1] There remains concern about variability in data, lack of robust cut points, limitations in technique (e.g., through plane motion), and lack of adequate expertise across clinical centers.[5] However, this is an area of active research, with ongoing studies aimed at understanding its prognostic and predictive value.

Cardiac magnetic resonance (CMR) imaging is another imaging modality used in the clinical and research evaluation of patients with cancer (**see also Chapter 17**).[1] CMR provides accurate and reproducible LV size and function assessment without ionizing electromagnetic radiation. CMR can also be used in the detection of myocardial masses and pericardial disease. An active body of research is evaluating the use of relaxation times (T1, T2, and T2*) to gain insight into changes in the myocardium in cancer patients exposed to cardiotoxic therapy.

Cardioprotective Strategies Before and During Therapy

There have been a number of studies evaluating the use of cardioprotective pharmacologic therapies prior to, during, and immediately after cancer therapy, in children and in adults, primarily anthracycline and/or trastuzumab therapy. An agent specific to the mechanisms of anthracycline cardiotoxicity (i.e., dexrazoxane, a derivative of the chelating agent ethylenediaminetetraacetic acid [EDTA]), is used as a

prophylactic strategy, largely in pediatric populations, although it is not currently approved by the FDA for this indication. Dexrazoxane may exert cardioprotective effects via a number of mechanisms. One long-standing hypothesis has been that dexrazoxane prevents ROS generation by binding and removing free and bound iron from the doxorubicin-iron complex. More recently, it has also been postulated that dexrazoxane inhibits Top2β, which, as described above, has been recently implicated as a mediator of anthracycline cardiotoxicity. Multiple clinical trials in children as well as adults have evaluated the use of dexrazoxane, with data overall suggesting a decrease in the incidence of HF and LVEF or a fractional shortening decline. However, its use has been limited by concerns over an increased risk of subsequent hematologic malignancies, including acute myeloid leukemia and myelodysplastic syndromes.

There are numerous ongoing studies evaluating the potential cardioprotective, prophylactic effects of conventional HF and CV pharmacologic therapies, including beta blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), aldosterone antagonists, and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors.[34] These therapies have been administered prior to, during, or after anthracyclines or trastuzumab in adults and children. Again, most of the data related to these therapies are derived from small studies. Carvedilol and nebivolol have been studied in small, placebo-controlled randomized control trials of patients treated with anthracyclines.[40] Here, treatment with beta blockers was associated with an attenuation of the LVEF decline that was observed in the placebo group exposed to anthracyclines. Metoprolol individually has not been shown to have an effect in small studies, but in combination with ACE inhibitors, there was a modest beneficial effect on mitigating LVEF declines in patients with malignant hemopathies. Enalapril did not prevent LVEF declines when administered during chemotherapy but did decrease the risk of cardiac events when administered 1 month after high-dose chemotherapy in patients with TnI positivity. Two randomized, placebo-controlled studies of ARBs in breast cancer patients receiving anthracyclines with or without trastuzumab were recently published. One smaller, single-center study of 130 participants receiving anthracycline chemotherapy suggested that candesartan attenuated a very modest decline in LVEF (≈2% absolute percentage points) that had been observed in the group not receiving candesartan.[40] Another study of 206 breast cancer patients receiving anthracyclines and trastuzumab did not demonstrate any significant difference in cardiac events or LVEF in patients treated with candesartan as compared with patients given placebo.[41] Spironolactone was associated with a beneficial effect on LVEF and diastolic function measures in a small study of patients treated with anthracycline. HMG-CoA reductase inhibitors are associated with an attenuation of LVEF declines in patients with hematologic malignancies, and a trial in cancer patients treated with anthracycline is ongoing.

Limitations of these studies largely include a small sample size; lack of a consensus on the definition of a clinically relevant cardiotoxicity outcome; lack of generalizability; and questions about optimal timing of pharmacologic administration. As such, no expert consensus group currently recommends the use of prophylactic therapy without another CV indication (e.g., ACE inhibitor in a diabetic patient with HTN).[5] The potential cardioprotective effect of nonpharmacologic therapies, such as exercise and dietary modification, are also under active investigation. Although no specific exercise or diet-based guidelines exist in cardio-oncology, there is a biologic basis for the protective effects of exercise. One retrospective analysis suggested that a higher metabolic equivalent tasks-hour per week in cancer patients was associated with a lower risk of CV events.[42]

Cardiovascular Care of Cancer Survivors

Epidemiologic data from large cohort studies suggest that there are still an excess number of deaths

secondary to CV or circulatory causes in cancer survivors, although this risk is decreasing over time. Additional content on the epidemiology of cancer survivors is presented in the online supplement titled Care of Cancer Survivors. The Children's Oncology Group currently recommends CM and HF screening guidelines for survivors of childhood cancer based upon age, anthracycline dosage, and RT exposure.[43] They recommend screening by echocardiography or MUGA annually, biannually, or every 5 years, depending upon exposure (**Table 81.2**). Although the appropriateness of screening in survivors is widely accepted, the population and frequency of screening has recently been called into question given concerns about overutilization and cost-effectiveness. As a result, there have been efforts to harmonize recommendations for cardiomyopathy surveillance for survivors of childhood cancer.[44] The ASCO Guidelines on Survivorship Care recommend that clinicians regularly evaluate and manage CV risk factors such as smoking, HTN, diabetes, dyslipidemia, and obesity in patients previously treated with cardiotoxic cancer therapies (**see eTable 81.1**).[32] A heart-healthy lifestyle, including the role of diet and exercise, should be discussed as part of long-term follow-up care. The guidelines recommend that an echocardiogram be performed at 6 to 12 months after completion of cancer therapy in asymptomatic patients at increased risk for CV disease, but make no recommendations regarding continued surveillance. This recommendation is based largely on data described above, suggesting that most episodes of cardiotoxicity occur within the first year after anthracycline completion.[4]

TABLE 81.2

Children's Oncology Group Recommendations for Cardiac Monitoring

AGE AT TREATMENT	IRRADIATION WITH POTENTIAL IMPACT TO HEART	ANTHRACYCLINE DOSAGE (BASED UPON DOXORUBICIN)	RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM OR MUGA SCAN
< 1 year old	Yes	Any	Every year
	No	< 200 mg/m^2	Every 2 years
		≥ 200 mg/m^2	Every year
1-4 years old	Yes	Any	Every year
	No	< 100 mg/m^2	Every 5 years
		≥ 100 to < 300 mg/m^2	Every 2 years
		≥ 300 mg/m^2	Every year
≥ 5 years old	Yes	< 300 mg/m^2	Every 2 years
		≥ 300 mg/m^2	Every year
	No	< 200 mg/m^2	Every 5 years
		≥ 200 to < 300 mg/m^2	Every 2 years
		≥ 300 mg/m^2	Every year
Any age with decrease in serial function			Every year

MUGA, multigated acquisition scanning.

Children's Oncology Group: Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers. Version 4.0., 2013. http://www.survivorshipguidelines.org/pdf/LTFUGuidelines_40.pdf.

Recent data from the St. Jude Lifetime Cohort Study of 1820 adult survivors of childhood cancer exposed to anthracycline chemotherapy or chest-directed RT, or both, suggest a high prevalence of subclinical dysfunction, with abnormal GLS (8%) and diastolic dysfunction (9.7%) despite a normal LVEF.[45] Abnormalities in GLS were associated with treatment exposure, including chest RT (dose response on the order of an increased RR of 1.38 to 2.39 with increasing dose), anthracycline dosages of more than 300 mg/m^2 (RR, 1.72), metabolic syndrome (RR, 1.94), and diastolic dysfunction (RR, 1.68). Another St. Jude study of 1853 survivors of childhood cancers with a median age of 31 years suggested that CM, as defined by an LVEF of less than 50%, was identified in 7.4%, coronary artery disease in 3.8%, and

arrhythmia in 4.6%.[46] Male sex, anthracycline dosages of 250 mg/m^2 or higher, cardiac radiation exposure or more than 1500 cGy, and HTN were associated with an increased risk of CM.

Management of HF or CM once it ensues largely follows established CV guidelines, including the use of various diagnostic and therapeutic strategies, such as pharmacologic and device therapies (**see guidelines for Chapter 25**).[2] Randomized clinical trials examining therapies specifically in cancer patients with CM have not yet been performed, and as such, the effectiveness of certain CV medications over others in this patient population remains largely unknown, as does the optimal duration of therapy. Of note, in one retrospective analysis of 201 cancer patients treated with anthracyclines who developed CM with a subsequent LVEF of 45% or less, institution of ACE inhibitors and beta blockers in combination was associated with a greater likelihood of recovery of the LVEF, as was institution of cardiac medications within 6 months of the detection of LV dysfunction.[47] Guidelines for the management of CV risk factors largely follow established CV guidelines, with no specific recommendations in cancer survivors. However, these are needed, because the observational data described above suggest that CV risk factors pose a markedly additive risk of CV disease in cancer patients as compared with controls.[2,48]

Future Perspectives

The field of cardio-oncology continues to evolve. The need for the dedicated CV care of cancer patients will continue to grow as both cancer and CV disease remain highly prevalent; as there is a growing population of survivors; and as newer cancer therapies affect fundamental CV signaling pathways, resulting in both subclinical and overt cardiotoxic effects. With this growth comes a call to (1) advance our understanding of the basic pathophysiologic mechanisms; (2) translate these findings to improve upon cancer therapeutics and cardioprotective strategies; (3) understand the epidemiology and natural history of cardiotoxicity and CV remodeling with cancer therapies; (4) develop robust mechanisms to identify high-risk CV patients; and (5) personalize the delivery of therapy to maximize its oncologic effectiveness and minimize its cardiotoxic potential. There is a great need for continued clinical and research education and expertise and collaborative efforts among cardiologists, oncologists, industry partners, patient advocates, and officials of the National Institutes of Health and FDA[33] so that a framework can be built to address gaps in knowledge and personalize the delivery of therapy by means of robust, evidence-based medicine.

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Sunitinib Cardiotoxicity

Sunitinib blocks signaling pathways that play a crucial role in the maintenance of vascular and cardiac energy homeostasis, such as VEGFR 1-3, PDGFR α/β, c-Kit, and fms-like tyrosine kinase-3 (Flt3) pathways. The direct effects of vascular toxicity and increased afterload on cardiac function in the setting of sunitinib remain speculative to date. VEGF, a downstream target of HIF-1α, is a critical stress-induced cardioprotective mechanism.[1] The blockade of VEGF-VEGFR signaling in mice subjected to pressure overload results in a reduction in capillary density, impaired compensatory hypertrophy, LV dilation, and contractile dysfunction. In animal models of nonischemic CM, overexpression of VEGF led to attenuation of apoptosis and proapoptotic signaling pathways and delayed progression to HF after tachypacing. Exposure to sunitinib in animal models results in increased expression of genes involved in the hypoxia response, including cardiac prolyl hydroxylase domain–containing protein 3 (PHD3), which is important in the regulation of HIF-1α.

Sunitinib also inhibits PDGFR, which plays a critical role in cell survival and cardioprotection in the setting of pathologic stress.[2-4] In animal models, PDGFR-β is up-regulated in the setting of pressure overload stress, and mice with cardiac-specific deletion of PDGFR-β exposed to marked increases in afterload after transaortic constriction, suffered from greater LV dilation, worsened cardiac function, and pulmonary congestion compared with controls. The PDGFR-β knockout mice also show impaired activation of prosurvival signaling pathways and increased apoptosis after pressure overload, and decreased expression of proangiogenic genes. In vivo, sunitinib treatment led to coronary microvascular dysfunction, postulated to be secondary to a loss of pericytes. PDGFR inhibition impairs the growth and survival of pericytes, a type of cell that is closely associated with the microvasculature.

Sunitinib has also been shown to inhibit the stem cell growth factor receptor known as c-Kit or CD117, which is expressed by precursors for hematopoietic stem cells and endothelial progenitor cells, and is important for mobilization of these cells to sites of injury.[4,5] Reduced c-Kit kinase activity impairs injury repair after myocardial infarction.

In vitro and in vivo animal studies suggest that sunitinib therapy results in compromised myocyte energy homeostasis and inhibits the compensatory up-regulation of adenosine monophosphate–activated protein kinase (AMPK), which is critical in maintaining favorable myocardial energetics.[1] Sunitinib inhibits AMPK activity in mice; in cardiomyocyte culture, restoration of AMPK activity reduced cell death. Whether these findings translate to mechanisms in humans remain to be elucidated.

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Care of Cancer Survivors

The British Childhood Cancer Survivor Study included 34,489 5-year survivors of childhood cancer diagnosed from 1940 to 2006, who were followed until 2014. These data suggest that there were 64.2 excess deaths per 100,000 person-years due to circulatory causes, a standardized mortality ratio of 3.8 (95% CI, 3.4 to 4.3), and an absolute excess risk of 3.6 (95% CI, 3.0 to 4.1).[1] In childhood cancer survivors age 60 years or older, circulatory causes exceeded secondary neoplasms as the cause for excess deaths (37% vs 31%).

Data from the Childhood Cancer Survivor Study (CCSS) indicate that the cumulative incidence of all-cause deaths in patients with cancer was 10.7% for those diagnosed in the 1970s, 7.9% for those diagnosed in the 1980s, and 5.8% for those diagnosed in the 1990s.[2] The cumulative incidence of death from a cardiac cause at 15 years decreased from 0.5% in patients treated from 1970 to 1974 to 0.1% in patients treated from 1990 to 1994. Although it is unknown if these reductions are attributable to safer delivery of cancer therapy and reduced exposure to cardiotoxic therapies or delayed presentation of CV disease, a reduction in treatment exposure was associated with a reduction in overall mortality rates in the CCSS data. Greater follow-up time is necessary to better understand the validity of this observation.[1]

The impact of CV risk factors in cancer survivors has been well studied. Traditional CV risk factors have been shown to have a more significant effect in survivors on the subsequent development of overt CV disease, as compared with controls who do not have cancer. Data from the CCSS suggested that in 10,724 5-year cancer survivors, the incidence of National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) for grade 3 to 5 CV events, including coronary artery disease, HF, valvular disease, and arrhythmia, by 45 years of age was 5.3%, 4.8%, 1.5%, and 1.3%, respectively.[3] Siblings, in contrast, had a very low risk of any events, each less than 1%. The prevalence of CV risk factors such as HTN and dyslipidemia was also higher in survivors, as compared with siblings. HTN alone increased the risk of all CV events, and the combinations of risk factors that included HTN resulted in the highest rate ratios (e.g., HTN and diabetes rate ratio of 23.5 for coronary disease; 35.3 for HF). The excess risk secondary to cardiotoxic therapeutic exposure (anthracyclines, chest RT) was also most marked in survivors who developed HTN. The relative excess risk due to an interaction between HTN and chest radiotherapy was 27.9 for coronary disease and 18.3 for HF, and was also increased for valvular disease and arrhythmia. There was also a significant interaction between HTN and anthracyclines and the risk of HF. Additional studies in adult cancer survivors corroborate that there is a significant interaction between the association of CV risk factors and subsequent CV disease and death in cancer survivors compared with controls.[4]

Risk prediction algorithms, primarily based upon demographic variables and treatment characteristics, have been derived and validated by CCSS investigators.[5] Similar proof-of-principle risk scores have been developed in breast cancer patients with the use of SEER Medicare data to predict the 3-year risk of HF or CM by integrating clinical factors (including age; treatment regimen [anthracyclines, trastuzumab]; and the presence of HTN, diabetes, coronary artery disease, atrial fibrillation, and renal disease) for the prediction of subsequent HF and CM.[6] Other cardiac risk scores, incorporating only age and LVEF, have also been developed in breast cancer patients treated with adjuvant anthracyclines and trastuzumab to predict the 5-year risk of cardiac events (definite or probable cardiac death or HF associated with an absolute decrease in LVEF of > 10% from baseline to < 55% or a decrease of > 5% to a value < lower limit of normal).[7] Many of these risk scores relevant to the breast cancer population, in particular, have not yet been externally validated and are not in routine clinical use.

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Cardiovascular Abnormalities in HIV-Infected Individuals

Priscilla Y. Hsue, David D. Waters

More than 37,000,000 people, including 2,400,000 in Europe and North America, were living with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) in 2015.[1] The introduction of highly active antiretroviral therapy (ART) beginning in 1996 dramatically decreased the HIV-related mortality rates, and the trend toward decreasing mortality rates has persisted since then.[2] As a consequence, by 2015 half of all HIV/AIDS patients in the United States were age 50 years or older. Projections from European cohorts such as the Dutch ATHENA Cohort predict that by the year 2030, 73% of individuals living with AIDS will be age 50 years and older and 84% of HIV-infected individuals will have an age-related noncommunicable comorbidity, such as cardiovascular (CV) disease, diabetes, kidney disease, osteoporosis, or cancers not related to AIDS. With improving longevity, non-AIDS conditions are now accounting for the majority of deaths among individuals receiving ART, and CV disease has become an increasingly significant problem in the HIV population. Deaths due to CV disease among individuals living with HIV have ranged from 6.5% to 15% of total deaths, depending on the cohort studied.[3,4]

The mechanisms underlying CV disease in HIV patients are largely poorly understood but are known to be multifactorial. They include many traditional risk factors and also factors related to HIV, such as the side effects of antiretroviral medication. These effects are significant and include metabolic issues, immune activation, chronic inflammation, microbial translocation, and coinfection with other viral pathogens such as cytomegalovirus.[5] Such mechanisms are ongoing even when HIV infection has been treated; the CD4 count and HIV viral load may be controlled, but the infection has not been cured. Viral replication continues within HIV reservoirs, leading to a continued need for ART and continued abnormal immune function and chronic inflammation; all of these factors underlie CV disease as well as other comorbidities observed in HIV infection.[6]

This review will focus on CV manifestations of HIV infection, with particular emphasis on CV risk factors and coronary heart disease (CHD). In developed countries, ART has transformed HIV infection into a chronic disease state; cardiologists should be aware of HIV-associated CV diseases, along with the unique issues they pose in this clinical setting.

Cardiovascular Risk Factors in HIV Patients

Traditional coronary risk factors are more common in HIV patients, particularly those receiving ART, than in noninfected persons (**see Chapter 10**). Dyslipidemia, metabolic syndrome, hypertension, and cigarette smoking are all more prevalent in HIV patients, leading to higher calculated 10-year Framingham Risk Scores in this group than in noninfected controls. In a Danish cohort, age-associated comorbidities, including hypertension, angina pectoris, myocardial infarction (MI), peripheral arterial disease, and CV disease, were all significantly more common among HIV-infected individuals than controls.[7]

Lipid Abnormalities

The early stages of untreated HIV infection are characterized by lipid abnormalities (**see Chapter 48**), such as low- levels of high-density lipoprotein (HDL) cholesterol, hypertriglyceridemia, and low- levels of low-density lipoprotein (LDL) cholesterol with predominantly small, dense LDL cholesterol particles.[8] After initiation of ART, LDL and total cholesterol levels increase but HDL cholesterol levels remain low, particularly if protease inhibitors are used.[9] In the Swiss HIV Cohort Study, hypercholesterolemia and hypertriglyceridemia were 1.7 to 2.3 times more common among patients taking protease inhibitors than

in patients not taking them. Thus, the overall effect on lipids of HIV infection is an atherogenic lipid profile with a reduction in HDL cholesterol and an increase in triglycerides, oxidized LDL cholesterol, and small, dense LDL cholesterol. The prevalence of hyperlipidemia in HIV patients is 28% to 80% in different studies, with the commonest abnormality being hypertriglyceridemia.

Most HIV drugs have the potential to increase LDL cholesterol levels, but important differences exist among drug classes and among drugs within classes.[10] Protease inhibitors increase triglyceride levels, with ritonavir being the worst culprit; in some cases it may cause extreme hypertriglyceridemia exceeding 1000 mg/dL. The lower doses of ritonavir used nowadays result in less hypertriglyceridemia, but increased triglyceride levels are also seen with ritonavir-saquinavir and ritonavir-lopinavir combinations. Atazanavir has less effect on triglyceride levels. Second-generation protease inhibitors, the integrase inhibitor raltegravir and the entry inhibitor maraviroc, have favorable effects on lipid profiles, particularly in comparison with older forms of ART.[10] Tenofovir alafenamide (TAF), a newer formulation of tenofovir disoproxil fumarate (TDF) that was approved by the Food and Drug Administration (FDA) in November of 2015, has been associated with higher levels of total cholesterol, LDL cholesterol, and HDL cholesterol than those in individuals treated with TDF; total cholesterol/HDL ratios remain unchanged.[11]

Lipodystrophy and the Metabolic Syndrome

Lipodystrophy is a syndrome characterized by fat accumulation in the dorsocervical region and an increase in or preservation of visceral fat, with subcutaneous and peripheral fat loss, resulting in relative central adiposity (**see Chapter 49**). Lipodystrophy develops in 20% to 35% of patients after initiation of ART, particularly in those who have taken protease inhibitors and the nucleoside reverse-transcriptase inhibitors stavudine and didanosine. Newer protease inhibitors such as atazanavir do not appear to induce lipodystrophy.

Lipodystrophy in HIV patients is commonly associated with features of the metabolic syndrome (**see Chapter 49**). Specifically, these features are insulin resistance, impaired glucose tolerance, elevated triglycerides, low HDL cholesterol levels, and hypertension. The reported prevalence of the metabolic syndrome in HIV patients has varied from 8.5% to 52%, with rates at the higher end of this range reported in Latin American countries and rates at the lower end in multicenter studies where patients had less exposure to ART.[12] Progression to metabolic syndrome is common in the first 3 years after initiation of an ART regimen that includes stavudine or lopinavir/ritonavir, but is less common with newer drugs. Most studies indicate that the presence of metabolic syndrome is a predictor for CV disease and death in HIV patients.[12]

Diabetes

Whether HIV infection is associated with an increased incidence of diabetes has been controversial (**see Chapter 51**). The protease inhibitors indinavir and lopinavir/ritonavir can cause insulin resistance, as do the thymidine analogs, particularly stavudine.[12] However, these drugs are no longer recommended for initial treatment of HIV because of their toxicities. In a recent large cohort study from Denmark, the risk of diabetes irrespective of ART use reported from 1996 to 1999 was nearly three times that of the general population; this increased risk was no longer seen from 1999 to 2010, however.[13] The study found that indinavir, saquinavir, stavudine, and didanosine were associated with an increased risk of diabetes, a finding that could partly explain the difference in risk in the two periods. These drugs are rarely part of modern ART.

Another recent study, from the South Carolina Medicaid system, found little difference in the incidence of diabetes in 6816 patients infected with HIV and an equal number of uninfected adults matched for age, sex, and race between 1994 and 2003; from 2004 to 2011, however, HIV patients had a lower incidence of diabetes than uninfected controls.[14] Exposure to protease inhibitors was associated with a higher risk of diabetes (adjusted relative risk, 1.35; 95% confidence interval [CI], 1.03 to 1.78). Other factors may play a role in the development of diabetes, including chronic inflammation, worsened control of HIV disease, hepatitis C virus coinfection, and autoimmune destruction, along with demographic factors such as older age and male gender.

Smoking

Smoking is common among HIV patients. In a recent large cohort study from Denmark, nearly half of HIV patients were current smokers, compared with one fifth of noninfected individuals.[15] Rates of death from all causes, including factors not related to AIDS, were substantially increased among smoking HIV patients compared with nonsmoking HIV patients. A 35-year-old HIV patient had a median life expectancy of 62.6 years (95% CI, 59.9 to 64.6) if a smoker and 78.4 years (95% CI, 70.8 to 84.0) if a nonsmoker. More life-years were lost in association with smoking than with HIV (12.3 life-years [95% CI, 8.1 to 16.4] compared with 5.1 life-years [95% CI, 1.6 to 8.5]). The population-attributable risk of death associated with smoking was 61.5% among HIV patients and 34.2% among controls. Studies modeling the impact of risk factor modification among individuals with HIV have demonstrated that smoking cessation, plus reduced lipid levels and reduced blood pressure, decrease the relative risk of CV disease; there is also an increase in risk associated with age.[16]

Smoking cessation strategies appear to have the same modest success rates in HIV patients as in noninfected individuals. A metaanalysis of eight trials in 1822 HIV smokers showed that behavioral interventions increased abstinence with a moderate effect size (relative risk [RR],1.51; 95% CI, 1.17 to 1.95).[17] Potential drug-drug interactions of ART with pharmacotherapies for smoking cessation have not been completely evaluated in HIV-infected individuals. An alternate approach is to train HIV care physicians to provide smoking cessation counseling and treatment. In one center in the Swiss HIV Cohort Study, all medical staff competed a structured half-day workshop on treatment for nicotine dependence.[18] Subsequently, rates of smoking cessation were significantly increased and rates of smoking relapse reduced relative to comparison institutions, with cessation rates higher among individuals with CV risk factors.

Hypertension and Chronic Kidney Disease

The prevalence rates of hypertension (**see Chapter 47**) and chronic kidney disease (**see Chapter 98**) have been reported to be higher in HIV patients than in the general population; this finding is not consistent, however, and may be influenced by a variety of factors, including the type of ART a patient is taking. Both hypertension and prehypertension have been shown to increase the risk of MI in HIV patients, just as they do in uninfected persons.[19] A prospective cohort study demonstrated that among individuals with normal renal function,[20] the incidence of chronic kidney disease increased among individuals exposed to TDF or one of two protease inhibitor regimens, atazanavir/ritonavir or lopinavir/ritonavir.[21] Similarly, chronic kidney disease expressed as either albuminuria or a depressed glomerular filtration rate (GFR) has been associated with an increased risk of CV events in HIV-infected individuals.[22] As in individuals without HIV, the baseline impaired eGFR is strongly related to CV disease, as demonstrated

in a cohort of more than 35,000 HIV-infected individuals.[20] A risk score model for development of chronic kidney disease among HIV-infected individuals has been proposed; it includes both HIV-related and traditional components.[23]

Atherosclerosis in HIV Patients

The underlying mechanism whereby HIV infection accelerates atherogenesis is incompletely understood, but it appears to be a combination of direct viral effects, effects of ART and associated metabolic changes, immune activation and chronic inflammation, and coinfection with other viral pathogens, along with traditional risk factors (**Fig. 82.1**). Regarding direct viral effects, low-level transcription of HIV genes may continue even after years of ART.[24] The HIV-encoded proteins transactivator of transcription (tat) and negative factor (nef) induce inflammation and endothelial dysfunction. Additionally, the HIV envelope protein gp-120 has been linked to higher endothelin-1 levels. Thus, the HIV virus itself may promote atherogenesis by releasing low levels of proteins. Only one controversial report has demonstrated the presence of HIV in the endothelium; in contrast, most studies show that the impact of HIV on the endothelium is likely due to downstream effects of the virus, such as chronic inflammation.

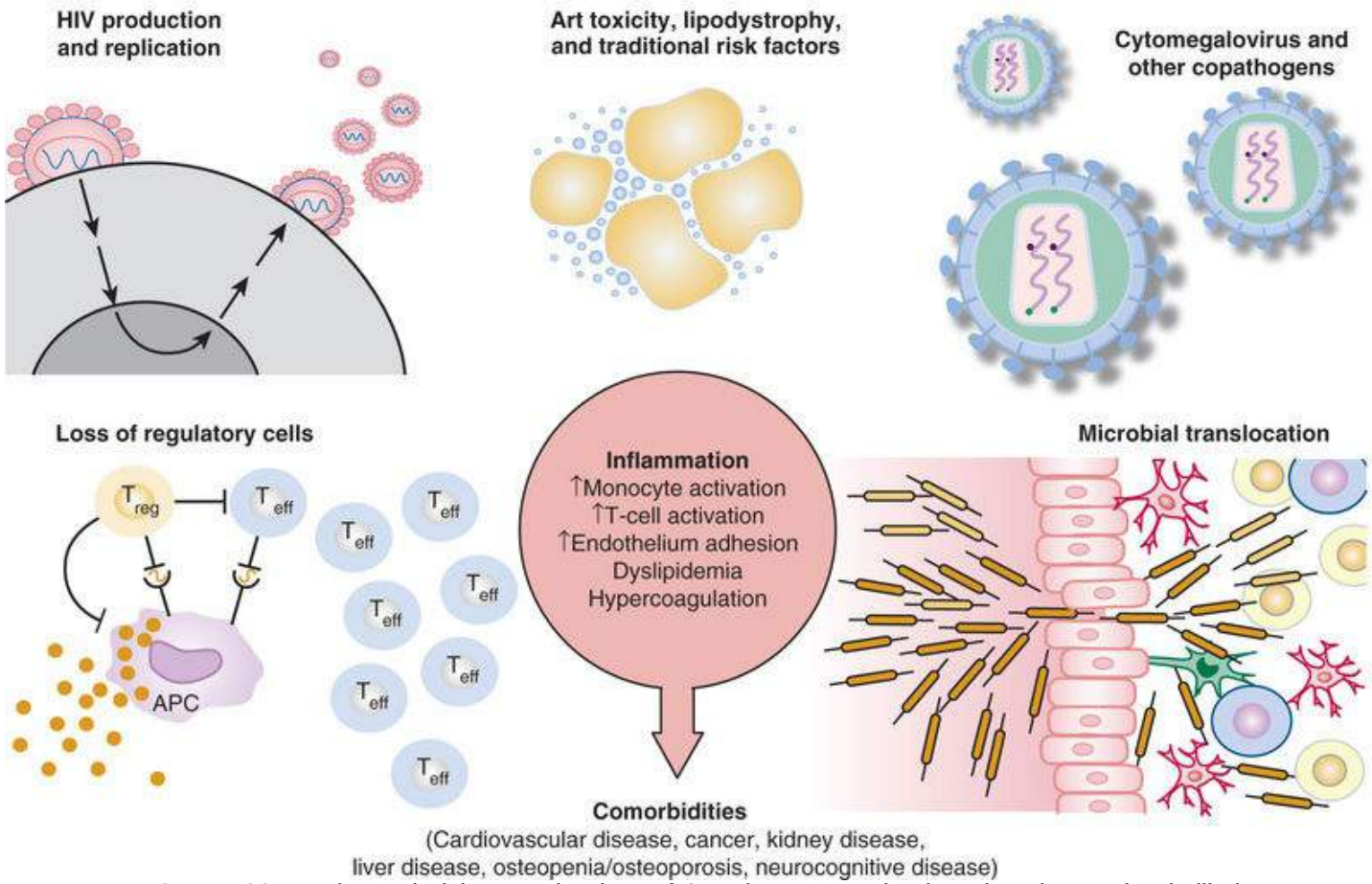

FIGURE 82.1 The underlying mechanism of CVD in HIV remains largely unknown but is likely multifactorial, as shown in the figure. It includes ongoing viral replication, side effects from ART, traditional risk factors, coinfection with other viral pathogens, immune activation, and microbial translocation in the gut. All of these factors may increase inflammation in the setting of treated and suppressed HIV disease, resulting in monocyte activation, dyslipidemia, hypercoagulability, vascular disease function, and end-organ disease, not only in the heart but in other systems, as shown above. (From Deeks SG, Lewin SR, Havlir DV:. The end of AIDS: HIV infection as a chronic disease. Lancet 2013;382(9903):1525-33.)

ART drugs, particularly the older drugs, may promote atherosclerosis by mechanisms in addition to dyslipidemia. Protease inhibitors induce reactive oxygen species and endothelial cell apoptosis.[24] Nucleoside reverse-transcriptase inhibitors increase platelet reactivity, and non-nucleoside reverse-transcriptase inhibitors cause monocytes to adhere to the vascular endothelium.

Chronic inflammation and T-cell activation play a central role in the development of atherosclerosis.[5,25] Untreated HIV-infected individuals have very high levels of T cells, and even after successful treatment with ART, higher-than-normal T-cell levels persist. T-cell activation leads to higher levels of inflammatory markers, such as interleukin-6, D-dimer, and high-sensitivity C-reactive protein. As established by the Strategies for Management of Antiretroviral Therapy (SMART) Study (a study of continuous vs. intermittent ART), these higher levels of inflammatory and coagulation markers are independent predictors of CV events[26] and fatal CV disease in the setting of treated HIV infection.[27]

Monocytes and macrophages are critical to the pathogenesis of HIV disease,[28] as well as atherosclerosis; for this reason, they may also play a unique role in HIV-associated CV disease. Activated monocytes have been shown to accelerate the progression of carotid atherosclerosis, and their presence predicts the progression of coronary artery calcium (CAC) in HIV.[29] In a study where aortic inflammation was assessed by ^{18}fluorine-2-deoxy-D-glucose positron emission tomography (18F-FDG-PET), HIV patients had higher levels of aortic inflammation than controls and the degree of aortic inflammation

correlated with a circulating marker of monocyte and macrophage activation, sCD163.[30] Monocytes from HIV patients and from patients without HIV infection but with an acute coronary syndrome have been shown to share a procoagulant phenotype; this suggests another mechanism whereby monocytes in HIV patients might drive atherosclerosis.[31]

The CD4 count and viral load also influence the CV risk. The CD4 count nadir predicts subclinical carotid atherosclerosis, and a low CD4 count with ART has been associated with an increased risk of CV disease. A low CD4 count was independently associated with an increased prevalence of carotid plaques in one study, and in another, the CD4 nadir of 350 cells/mm^3 or less was correlated with arterial stiffness. Such data suggest that earlier initiation of ART may be beneficial (see Strategic Timing of AntiRetroviral Treatment [START] Study below). Other studies have shown that initiation of HIV medication improves endothelial function but does not restore it to normal and that higher viral loads correlate with worsened endothelial dysfunction as measured by brachial artery flow–mediated dilation.

In the current era of HIV management, the link between immune depression and CV events may be attenuated. For example, no association was found between immune depression, a lower CD4 count, and CV events in a recent report from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study.[32]

Many biomarkers predictive of CV events in uninfected cohorts are elevated in HIV patients, reflecting endothelial dysfunction, procoagulant changes, fibrinolytic effects, increased activation of platelets, and inflammation. Levels of endothelial cell–derived markers such as von Willebrand factor antigen are elevated, particularly in patients with a high viral burden or advanced disease. Circulating levels of intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) are elevated in HIV patients compared with uninfected controls; levels were directly related to the degree of inflammation as assessed by soluble receptor type 2 for TNF-alpha (s-TNFR2). Increased inflammation as assessed by cytomegalovirus-specific T-cell responses is associated with higher levels of carotid intima–media thickness (IMT).

HIV infection is associated with high levels of interleukin-6, D-dimer, and high-sensitivity C-reactive protein; levels remain elevated in treated and suppressed HIV disease,[33] a finding demonstrated in multiple studies of different cohorts. These biomarkers are strong predictors of non-AIDS events,[34] including increased rates of CV events,[26] increased risk of CV disease[35] and deaths due to CV disease,[27] and increased rates of all other causes of mortality, in HIV patients.[36] Markers of myocardial stress, such as ST2, growth differentiation factor (GDF)-15, and N-terminal pro–B-type natriuretic peptide (NT-proBNP), also are predictors of mortality in HIV patients.[37]

Chronic activation of the immune system in HIV infection may also be due to microbial translocation in the gastrointestinal tract, leading to elevated levels of circulating microbial products such as lipopolysaccharide. Residual microbial translocation during suppressive ART is associated with the degree of immune reconstitution, as reflected by CD4 T-cell count recovery. A marker of the monocyte response, sCD14, has been linked to increased mortality rates in HIV patients.[38] Therapies that reduce the impact of microbial gut translocation, specifically rifaximin and sevelamer, have failed to show a significant effect on microbial translocation in HIV patients.[39,40]

Because HIV and CV disease have such a multifactorial impact on a patient, it has been difficult to determine, and is still unclear, which biomarker may be best for predicting the CV risk in HIV infection.

Features of Coronary and Carotid Atherosclerosis That May Be Unique to HIV Patients

Atherosclerosis in HIV patients may be a distinctive pathologic entity from the atherosclerosis seen in the general population (**see Chapter 48**). Autopsy studies have reported that coronary atherosclerosis in young HIV patients resembles transplant vasculopathy (**see Chapter 28**), or that it is characterized by diffuse, circumferential vessel involvement with proliferation of smooth muscle cells mixed with abundant elastic fibers. In addition, calcification of the internal elastic media has been described in HIV patients.

Cardiac computed tomography (**see Chapter 18**) has provided insight into the features of coronary disease in HIV patients.[41] The prevalence of coronary artery calcification by cardiac computed tomography was not higher in HIV patients than in controls across seven studies. However, CT angiographic studies reveal that noncalcified plaques are much more common in HIV patients.[42] In a metaanalysis of nine studies that included 1229 HIV patients and 1029 controls, the prevalence of coronary stenosis (> 30% or > 50%) or calcified plaques did not differ between the two groups.[43] However, noncalcified plaques were more than three times more likely to be present in HIV patients (58% compared with 17%). Noncalcified plaques are more likely to be lipid laden, inflammatory, and prone to rupture. High-risk features of plaque have also been reported in the setting of HIV.[44]

In non-HIV cohorts, carotid IMT is associated with prevalent CV disease and risk factors, as well as an increased risk of future stroke and MI. Many observational studies have measured carotid IMT in individuals with HIV and in controls. As shown in **Fig. 82.2**, the carotid IMT of individuals with HIV was, on average, 0.04 mm thicker (95% CI, 0.02 to 0.06 mm; $P < 0.001$) than that of uninfected controls in a metaanalysis.[41] This conclusion should be viewed with caution because of differences among the studies in population characteristics, study designs, sample sizes, length of follow-up, and ultrasound techniques used. Carotid plaque has also been found to be more common in HIV patients compared with uninfected controls across six studies.[41] Interestingly, carotid IMT has been shown to be an independent predictor of mortality in HIV.[45]

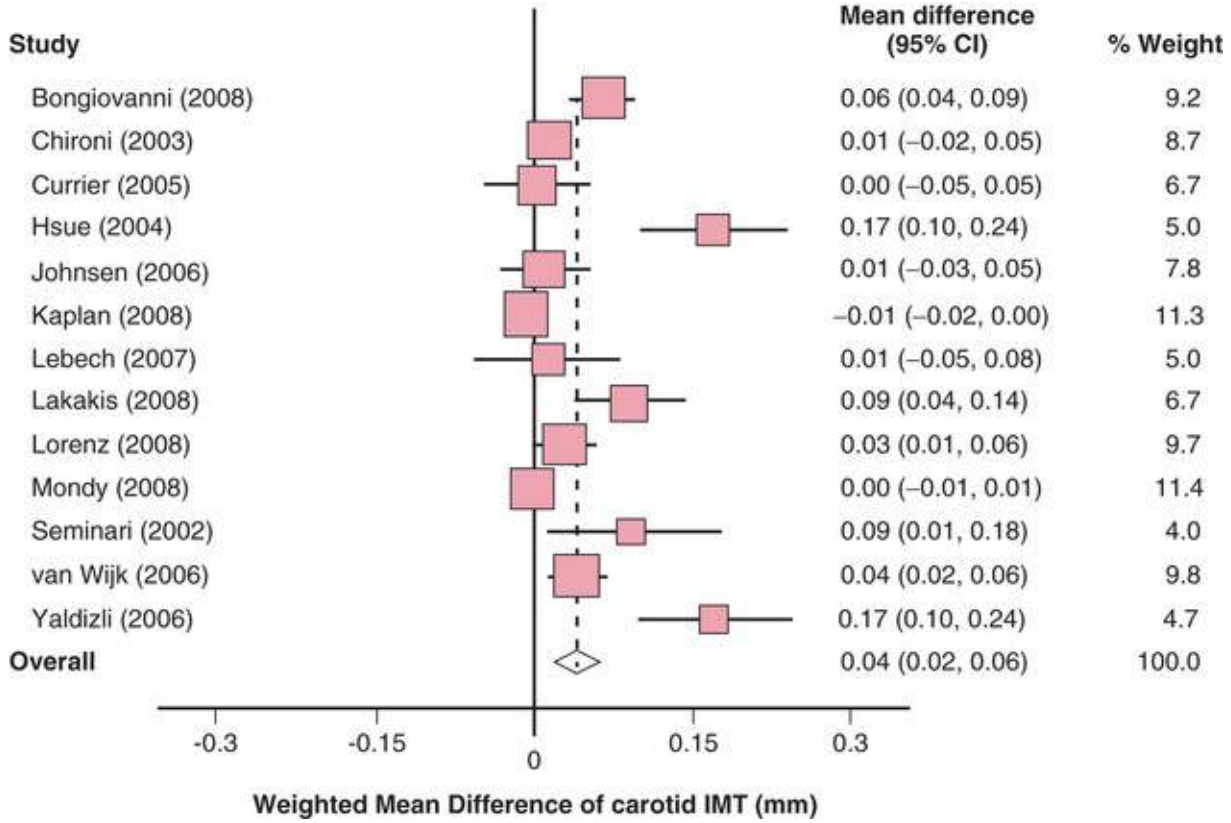

FIGURE 82.2 Differences in carotid IMT by HIV status. Metaanalysis of 13 studies evaluating the associations between HIV status and carotid intima–media thickness (IMT). The carotid IMT of individuals with HIV infection was, on average, 0.04 mm thicker (95% CI, 0.02 to 0.06 mm; $P < 0.001$) than that of individuals without HIV infection. *WMD*, weighted mean difference. (From Stein JH, Currier JS, Hsue PY: Arterial disease in patients with human immunodeficiency virus infection: what has imaging taught us? JACC Cardiovasc Imaging 2014;7:515-25.)

Coronary Disease in HIV Patients

Epidemiology

The first case reports of MI in HIV-infected patients taking ART began to appear in 1998 (**see Chapter 58**). Since these initial reports, many observational studies have reported higher rates of CHD among HIV-infected individuals. For example, the Veterans Aging Cohort Study followed 55,109 uninfected and 27,350 HIV-infected persons for 5.9 years.[46] The risk of MI was increased in HIV-infected patients for each decade of age from the 30s to the 70s. After adjusting for Framingham risk factors, comorbidities, and substance use, HIV-positive veterans had an increased risk of MI compared with uninfected veterans (hazard ratio [HR], 1.48; 95% CI, 1.27 to 1.72). An excess risk remained among virally suppressed patients compared with uninfected veterans (HR, 1.39; 95% CI, 1.17 to 1.66). The impact of HIV on risk was comparable to traditional risk factors, including hypertension, diabetes, and hyperlipidemia. Many other observational studies confirm an increased risk of CHD in HIV-infected individuals of about 1.5- to 2-fold when compared with uninfected controls.

The risk of ischemic stroke (**see Chapter 65**) was also increased in HIV-infected men compared with uninfected persons in the Veterans Aging Cohort Study (incidence rate ratio [IRR] 1.25; 95% CI, 1.09 to 1.43; $P < 0.01$).[47] After adjusting for demographic factors, ischemic stroke risk factors, comorbid diseases, and substance use, the risk of ischemic stroke was attenuated but still higher among HIV-infected men (HR, 1.17; 95% CI, 1.01 to 1.36; $P = 0.04$).

The relative contributions of HIV infection itself and the adverse effects of ART to CHD risk have been

a topic of controversy. There is general agreement that the risk of CV events increases with increasing duration of ART. On the other hand, a randomized trial clearly demonstrated that continuous ART was associated with fewer CV events than intermittent ART. Initiation of ART in treatment-naïve patients improves markers of atherosclerosis such as endothelial function. The increased risk of CV events with intermittent ART and the improvement in markers of risk with initiation of therapy strongly suggest that HIV itself increases the risk for CV disease. However, the risk remains elevated in virally suppressed individuals, either because of the consequences of infection or of ART, or both.

Individual antiretroviral drugs have been linked to an increased risk of CV events, specifically, indinavir, lopinavir-ritonavir, didanosine, and abacavir.[48] The nucleoside reverse-transcriptase inhibitor abacavir has been particularly controversial in this regard. In 2008 the D:A:D Study reported a 90% increase in MI risk in HIV-positive individuals receiving ART regimens that included abacavir. This risk was particularly evident among current or recent abacavir users. In more than a dozen studies published since then, most, but not all, have confirmed an association. In a recent report of 49,717 D:A:D participants, abacavir use was still associated with an increase in MI rate (RR, 1.98; 95% CI, 1.72 to 2.29).[49] This effect has been attributed to the propensity of the drug to induce platelet hyperreactivity. Other mechanisms have been postulated, which include endothelial dysfunction and leukocyte and endothelial cell interactions. Atazanavir, which causes hyperbilirubinemia, was associated with lower IMT progression compared with other HIV regimens.[50]

Clinical Presentation

The clinical presentation of acute coronary syndrome differs in HIV patients compared with uninfected individuals (**see Chapters 59 and 60**). HIV patients are on average more than a decade younger than uninfected persons and are more likely to be men, to be current smokers, and to have low HDL cholesterol levels. Their risk scores tend to be lower and they are more likely to have single-vessel than multiple-vessel coronary artery disease. In general, HIV patients hospitalized with acute coronary syndrome have excellent immediate outcomes.

In earlier studies, HIV patients had substantially higher rates of restenosis after percutaneous coronary interventions with bare metal stents, compared with uninfected patients. Restenosis in HIV patients has been associated with higher C-reactive protein levels and higher levels of CD8+ T cells.[51] More recent studies, in which most patients received drug-eluting stents, show similar medium-term outcomes between HIV patients and matched controls.[52] A report from the Nationwide Inpatient Sample detected no increase in in-hospital mortality rates among 9771 HIV-infected patients undergoing cardiac surgery, including coronary bypass, compared with matched uninfected controls.[53] Long-term outcome studies after coronary bypass surgery have not been reported in large cohorts of HIV patients. Using a U.S. inpatient discharge database, the Nationwide Inpatient Sample, the percentage of HIV-infected individuals undergoing CV surgeries increased from 0.09% to 0.23%, and individuals with HIV were not at increased risk for death while inpatients, although they were more likely to require blood transfusion and have postoperative complications.[53]

Some data indicate that HIV patients with acute coronary syndromes have been less likely than uninfected patients to receive investigations and treatments that have been shown in uninfected patients to reduce mortality rates and recurrent events. For example, in a U.S. Nationwide Inpatient Sample from 1997 to 2006, comparing nearly 6000 HIV MI patients with more than 2.5 million uninfected MI patients, only 48% of HIV patients underwent coronary arteriography, compared with 63% of noninfected patients.[54] This discrepancy occurred despite a younger age and more comorbidity in the HIV group. It is

likely that HIV patients with acute coronary syndromes likely now receive more aggressive treatment; indeed, in the large D:A:D database, mortality rates from CHD declined between 1999 and 2000 and 2009 and 2011.[2] In addition, the type of MI may be distinct in HIV. Using type I (atherothrombotic) and type II (demand-related) classifications for MI, more than 40% of MIs in a North American cohort of HIV-infected individuals were classified as type II,[55] a finding that may underlie some of the conflicting data regarding patient characteristics, outcomes, and predictors in the setting of HIV that have been reported in the literature.

As with acute coronary syndromes, the clinical features of ischemic stroke differ in HIV patients compared with uninfected individuals. HIV stroke patients tend to be younger and to be male. The risk factors for ischemic stroke in the general population (i.e., hypertension, diabetes, smoking, and dyslipidemia) are also risk factors for stroke in HIV patients.

Treatment

The treatment of CHD in HIV-infected individuals should largely be guided by existing recommendations for uninfected patients because clinical trial data for treatment in HIV patients is insufficient. However, two aspects specific to HIV-infected patients deserve mention: (1) the potential contribution of ART to CV disease and (2) the treatment of hyperlipidemia in HIV disease, for which separate recommendations have been devised.

Antiretroviral Therapy and Cardiovascular Disease

Since ART first became available in the 1990s, the indications for treatment and specific drug regimens have evolved rapidly. In earlier years, when the benefits of ART were more limited and treatment-related adverse effects were more common, it was recommended that the drugs not be used until patients were at increased risk of immunosuppression. More recent studies suggest that the chronic immune stimulation and inflammation that accompany early asymptomatic HIV infection can result in long-term morbidity. Thus, whereas treatment was initially restricted to patients with low CD4 counts, it is now widely accepted that treatment should be started in all individuals with HIV infection with detectable viremia irrespective of the CD4 cell count.[56] Initiation of ART is recommended as soon as possible in the setting of acute HIV infection because initiation prior to the development of HIV antibody positivity reduces the size of the latent HIV reservoir, reduces immune activation, and may protect against infection of central memory T cells. Early initiation of ART as compared with deferred initiation has been beneficial with respect to AIDS-related and non-AIDS–related events; this benefit did not reach significance for CV outcomes, however.[57] The impact of early ART on CV disease and CV risk in HIV remains unknown.

Planned discontinuation of early ART after a specific treatment duration is not recommended, because the benefits do not persist and the subsequent viral rebound is associated with increased clinical events and the potential for transmission.[56] Initiation of ART in “elite controllers” (defined as patients with confirmed HIV infection and persistent undetectable HIV RNA without ART) remains controversial.

What combinations of drugs are recommended for initial therapy? The integrase strand transfer inhibitor agents (InSTIs) have taken a key role as first-line therapy because they are highly effective, with higher, more rapid rates of virologic suppression compared with protease inhibitors and non-nucleoside reverse-transcriptase inhibitors, the previous mainstays of ART. InSTIs have the additional advantage of being extremely well tolerated. The relative advantages and disadvantages of the three available InSTIs are listed in **Table 82.1**.

TABLE 82.1

Integrase Strand Transfer Inhibitors

	DOLUTEGRAVIR	ELVITEGRAVIR	RALTEGRAVIR
FDA Approval	2013	2012	2007
Advantages	Superior to efavirenz and ritonavir-boosted darunavir Once-daily dosing Pill size is small Lowest risk of resistance with virologic failure Relatively few drug interactions Can be taken with or without food Superior to raltegravir in treatment-experienced patients	Superior to ritonavir-boosted atazanavir in HIV-infected women Once-daily dosing	Superior to ritonavir-boosted atazanavir and ritonavir-boosted darunavir Longest safety record Fewest drug interactions Can be taken with or without food
Disadvantages	Raises serum creatinine due to inhibition of tubular secretion of creatinine Higher rates of insomnia and headache than comparators in some studies	Requires pharmacokinetic boosting with cobicistat or ritonavir for once-daily dosing Most drug interactions Cobicistat raises serum creatinine due to inhibition of tubular secretion of creatinine Should be taken with food	Must be taken twice daily Not coformulated as part of a complete regimen

Adapted from Nordell AD, McKenna M, Borges ÁH, et al: Severity of cardiovascular disease outcomes among patients with HIV is related to markers of inflammation and coagulation. J Am Heart Assoc 2014;3(3):e000844.

Recommended initial ART regimens for most patients are dolutegravir/abacavir/ lamivudine, dolutegravir plus TAF/emtricitabine, elvitegravir/

cobicistat/TAF/emtricitabine, and raltegravir plus TAF/emtricitabine (a slash separating components indicates that the components are available as coformulations.).[56] Up to 96% of patients who remain in care and receive ART have undetectable plasma HIV RNA levels.

Abacavir is a component of the recommended regimen of dolutegravir/ abacavir/lamivudine. Approximately half of individuals who are positive for the HLA-B*5701 allele experience a hypersensitivity reaction to abacavir that may be life threatening. In one large prospective study, PREDICT-1, 5.6% of patients tested positive. It is recommended that HLA-B*5701 testing be performed prior to abacavir use and those who test positive should not be given abacavir.[56]

An association between abacavir and an increased risk of MI is supported by several, but not all, studies.[49] Thus, current guidelines recommend that abacavir be used with caution in patients who have or are at high risk for CV disease.[56]

Several non–InSTI-containing regimens suppress HIV RNA in most patients who adhere to therapy. These regimens may be optimal for a given patient based on individual clinical features, preferences, or financial considerations or where InSTIs are not available. These regimens are recommended therapeutic options: (1) darunavir (boosted with cobicistat or ritonavir) plus TAF/emtricitabine, TDF/emtricitabine, or abacavir/lamivudine, (2) efavirenz/TDF/emtricitabine, or (3) rilpivirine/TAF (or TDF)/emtricitabine. Each of these combinations has advantages and disadvantages. Option 1 has a low risk of resistance with virologic failure, even with poor adherence; option 2 exhibits high efficacy in patients with a baseline HIV RNA measurement of higher than 100,000 copies/mL; and option 3 has the lowest risk of metabolic adverse effects.[56]

Modifications to ART are needed in pregnant patients and in those with hepatitis B and C coinfection or opportunistic infections.[56] Osteoporosis and fractures are increased with HIV infection. During the first year or two after initiation of ART, patients may lose 2% to 6% of their bone mineral density. Regimens containing TDF are associated with a greater initial decline in bone mineral density than regimens containing TAF or abacavir; thus, TDF is not recommended for patients with osteopenia or osteoporosis.[56]

Monitoring of kidney function with eGFR, urinalysis, and testing for glycosuria and albuminuria or

proteinuria is recommended when ART is initiated or changed and every 6 months (along with HIV RNA) once HIV RNA is stable. TDF, especially with a boosted protease inhibitor, increased the risk of chronic kidney disease in cohort studies and thus is not recommended for patients with an eGFR of less than 60 mL/min. Long-term data on TAF in patients with preexisting renal disease are limited. TDF or TAF should be discontinued if renal function worsens, particularly if there is evidence of proximal tubular dysfunction.[56]

With improvements in ART, there has been less need for patients taking it to switch drugs because of virologic failure and drug resistance. Some patients who have virologic suppression but are taking older regimens that are less convenient or have more adverse effects may benefit from switching to the improved ART drugs, however. Reasons for considering switching therapy in such patients include the development of adverse effects, the benefits of reducing dosages or the number of pills to be taken, or the occurrence of drug-drug interactions. Switching therapy may also be considered for pregnant patients. Some patients may benefit from switching even if they are doing well on their current treatment. For instance, switching is reasonable for patients taking regimens containing stavudine, didanosine, or zidovudine because of long-term toxic effects or regimens of older protease inhibitors that have higher pill burdens and greater metabolic toxicities than darunavir or atazanavir. Some drugs that are no longer recommended for initial use may be safely continued for patients who are tolerating them. For example, although nevirapine and efavirenz have substantial early toxic effects, they are safe and tolerable over the long term.[56]

Recommendations for laboratory monitoring can be summarized as follows. As close to the time of HIV diagnosis as possible and before ART is begun, the following factors should be measured: CD4 cell count; plasma HIV RNA level; serologic studies for hepatitis A, B, and C; serum chemistries; estimated creatinine clearance; complete blood cell count; and urine glucose and protein. Genotypic resistance assays for reverse-transcriptase and protease should be ordered for all patients. Routine pretreatment screening for integrase resistance is not currently routinely recommended. Screening for syphilis and mucosal nucleic acid amplification testing for chlamydial infection and gonorrhea should also be done at the time of HIV diagnosis, and a lipid profile should be obtained. Other laboratory assessments should be individualized, in keeping with current guidelines. If ART is initiated on the first visit, all laboratory specimens should be drawn before the first dose is started.

Worldwide, the number of HIV patients receiving ART has increased from 7,500,000 in 2010 to 17,000,000 in 2015.[1] Even so, only 46% of HIV-infected individuals are receiving ART, and 20,000,000 patients are untreated. Improving ART coverage is a United Nations priority.

Initiation of ART in the very early stages of HIV infection preserves immunologic function and reduces inflammation; it might also be expected to curtail the potential of HIV infection to induce atherosclerosis, although this has not been proven in the setting of randomized clinical trials. In addition, newer ART drugs do not carry the adverse metabolic consequences of older therapies. These considerations provide hope that current HIV patients may experience a lower risk of CV events compared with patients from 10 to 15 years ago.

Treatment of Hyperlipidemia in HIV Patients

The Infectious Diseases Society of America and Adult AIDS Clinical Trials Group published specific guidelines in 2003 for the evaluation and management of ART-related hyperlipidemia (**see Chapter 48**). These recommendations were largely based on National Cholesterol Education Program Adult Treatment Panel III guidelines (ATP III), and advocated LDL cholesterol targets according to the level of CV risk based on the Framingham Risk Score predictions for 10 years. In 2013 the American College of

Cardiology (ACC) and the American Heart Association (AHA) produced new guidelines on the treatment of cholesterol for reducing the atherosclerotic CV risk in adults, which replaced the outdated ATP III guidelines.[58] The ACC/AHA guidelines recommend treatment with moderate- or high-intensity statins for patients with established atherosclerotic CV disease, patients with an LDL cholesterol level of 190 mg/dL or higher, patients with diabetes who are 40 to 75 years of age and have an LDL cholesterol level of 70 to 189 mg/dL, and patients with a 10-year CV risk of 7.5% or more who are 40 to 75 years of age and have an LDL cholesterol level of 70 to 189 mg/dL.[58]

Some evidence suggests that the guidelines are not accurate in detecting HIV patients who should be treated with statins. For example, in a recent study, high-risk coronary plaque morphology was shown by CT angiography in 36% of 108 HIV-infected patients, but statins would be recommended for only 19% of them by the 2013 guidelines and 7% by the ATP III guidelines.[59] Furthermore, compliance with guidelines appears to be suboptimal. In the HIV Outpatient Study of 2005 patients, one fifth had a 10-year CV risk of more than 20%, and yet a large percentage of at-risk patients who were eligible for pharmacologic treatment did not receive recommended interventions and did not reach recommended treatment goals.[60]

Specific drug-drug interactions are important to consider when initiating lipid-lowering therapy in HIV patients. Both protease inhibitors and non-nucleoside reverse-transcriptase inhibitors can affect cytochrome P450 isoforms. In general, all protease inhibitors inhibit CYP3A4, with the highest level of inhibition with ritonavir, followed by indinavir, nelfinavir, amprenavir, and saquinavir. Delavirdine, a non-nucleoside reverse-transcriptase inhibitor, is also an inhibitor of CYP3A4, whereas nevirapine and efavirenz result in induction of the enzyme.

Both simvastatin and lovastatin blood levels increase dramatically with protease inhibitor use, and thus these statins are contraindicated with protease inhibitors because of the risk of rhabdomyolysis. Atorvastatin blood levels increase to a lesser extent, so that it may be used at lower doses. Pravastatin and fluvastatin are safe because they are not metabolized by CYP3A4, but their capacity to reduce LDL cholesterol levels is limited. Rosuvastatin has minimal P450 metabolism, although levels appear to be increased when it is used in combination with atazanavir/ritonavir and lopinavir/ritonavir, so limiting doses to 10 mg with those drugs is advised. A metaanalysis of 18 studies of antiretrovirally treated HIV-infected individuals receiving statin therapy reported that statin therapy significantly lowered the total cholesterol, LDL cholesterol, and triglyceride levels, with limited efficacy for HDL levels.[61] Statin therapy, when dose adjusted for drug-drug interactions, was associated with low rates of adverse events.

The 2003 HIV guidelines for the treatment of hyperlipidemia recommended diet and exercise interventions, which have been shown to decrease total cholesterol levels by 11% to 25% in HIV populations. Pravastatin 20 to 40 mg/day or atorvastatin 10 mg/day was recommended as starting therapy for elevated LDL cholesterol levels in patients taking any protease inhibitor or delavirdine. Fluvastatin 20 to 40 mg/day was considered an alternative second-line agent.

The 2003 guidelines are somewhat antiquated because contemporary ART interferes much less often with statin metabolism compared with older forms of ART. Additionally, trials done in non-HIV populations since 2003 have demonstrated that more potent statins at higher doses provide more CV event reduction than lower doses of weaker statins. This evidence is reflected in the treatment recommendations of the 2013 ACC/AHA guidelines. In light of these considerations, it seems reasonable to treat HIV patients who are not taking ART metabolized by the hepatic CYP3A4 enzyme system more aggressively, perhaps in line with the current ACC/AHA recommendations. Of note, the European Society of Cardiology Guidelines recommend that individuals with HIV and dyslipidemia be treated to achieve the LDL goal as it is defined for high-risk individuals.[62]

Hypertriglyceridemia is common in HIV patients and can be treated with fibrates (gemfibrozil 600 mg

twice a day or micronized fenofibrate 54 to 160 mg daily) when triglyceride levels exceed 500 mg/dL. Fibrates and statins have a drug-drug interaction and should be used only at low doses when combined. Niacin and bile acid sequestrants are not recommended for use in HIV patients. Ezetimibe appears safe and effective when added to maximally tolerated doses of a statin; it lowers LDL cholesterol levels modestly when used alone in HIV patients. PCSK9 inhibitors profoundly lower LDL cholesterol levels and are being investigated in large clinical trials to determine whether they also reduce CV events. PCSK9 inhibitors might be advantageous for certain HIV patients, but they have not yet been investigated in this population. Elevated PCSK9 levels have been reported in the setting of coinfection with HIV and hepatitis C virus; of note, PCSK9 levels increased in a stepwise fashion, along with IL-6 levels.[63]

Whether statins reduce CV events in HIV-infected patients to the same extent as in noninfected subjects is uncertain. It has been suggested in some studies that statins reduce LDL cholesterol levels less in HIV patients than in uninfected patients. Although HIV infection is characterized by high levels of inflammatory markers, statins may reduce these markers less in HIV-infected than in noninfected subjects.[64] As previously noted, coronary plaques in HIV patients are more likely to be of the soft, noncalcified variety. In a recent placebo-controlled trial, atorvastatin decreased the volume of such noncalcified plaques and also decreased their high-risk features, but no impact on vascular inflammation or inflammatory markers was demonstrated.[64]

Screening for Coronary Risk Factors in HIV Patients

The traditional CV risk factors appear to cluster in the HIV population.

The increase in CV risk with increasing numbers of risk factors is more logarithmic than linear, such that a large proportion of HIV patients are at high risk. Thus, smoking cessation, diet and exercise recommendations, and guideline-based treatment of diabetes and hypertension should all be aggressively pursued in HIV patients. As previously noted, a young HIV-infected smoker loses more life-years to continued smoking than to HIV disease.[15] Addressing CV risk factors in HIV patients is often difficult because of the burden of concomitant medical conditions, including HIV, and a correspondingly large pill burden.

Risk Assessment Models

None of the multivariate models for calculating the CV risk in the general population have been validated in HIV-infected cohorts. The most widely used screening tool is the Framingham Risk Score, which appears to underestimate the risk in HIV patients who are smokers, are receiving ART, or have an intermediate or higher 10-year predicted risk. It seems important to use a risk assessment tool that that has been validated in the population to which the patient belongs, particularly one that takes into account HIV-specific features that may alter the CV risk.

A new prediction model for CV events was recently published, based upon 1010 events occurring in 32,663 HIV-positive persons from Australia and 20 countries in Europe.[65] The model included age, gender, systolic blood pressure, smoking status, family history of CV disease, diabetes, total cholesterol, HDL cholesterol, CD4 lymphocyte count, cumulative exposure to protease and nucleoside reverse-transcriptase inhibitors, and current use of abacavir. A reduced model omitted ART. The model performed better than the Framingham Risk Score, even after the Framingham score had been recalibrated to the HIV population.

Other risk prediction models have been developed for HIV populations. Studies comparing different

models have yielded quite different results with less overlap than would be expected. For practical purposes, until a generally accepted, easy-to-use, well-validated risk assessment tool for HIV populations becomes available, it seems reasonable to use risk assessment tools such as the Framingham Risk Score and to accept the results with the expectation that they are underestimates of the true risk.

Biomarkers and Signs of Coronary Disease in HIV Patients

Clinicians should be aware that symptoms of coronary disease may develop in relatively young HIV-infected patients and may be atypical (**see Chapter 10**). The sensitivity and specificity of exercise or pharmacologic stress testing have not been established in HIV disease, so that use of these tests currently follows guidelines for the general population.

Several biomarkers have been reported to be higher in HIV-infected patients who develop coronary disease compared with those who do not, including soluble CD163, soluble CD14, monocyte chemoattractant protein 1 (markers of monocyte activation), D-dimer, interleukin-6, intercellular adhesion molecule-1, soluble-tumor necrosis factor-α receptor I and II, C-reactive protein, and osteoprotegerin.[26,27,33,66] Other biomarkers have been reported to be lower in HIV-infected patients who develop coronary disease compared with those who do not, including adiponectin, soluble receptor activator of nuclear factor-κB ligand, and vitamin D. None of these markers have been developed to the point where they are used clinically to aid in the diagnosis of coronary disease. The biomarker profile predictive of CV disease in HIV is likely distinct from that in the noninfected population; this suggests that HIV infection has a role in the disease process.

Screening for CAC may have diagnostic value in the assessment of HIV patients. Middle-aged patients with HIV infection are more likely to have CAC than are noninfected controls of a similar age; in at least one study, long-term ART increased the probability of CAC. CAC scores tend to be higher in HIV-infected patients compared with uninfected controls. During a 5-year follow-up in the Multicenter AIDS Cohort Study, 21% of HIV-infected men developed CAC compared with 16% of uninfected men, an association that persisted after adjustment for traditional and HIV-associated risk factors (HR, 1.64; 95% CI, 1.13 to 3.14).[67] The presence of coronary calcium in HIV patients is predictive of future CV events, just as it is in the general population.[68]

Chest CT imaging (**see Chapter 18**) allows for the measurement of epicardial adipose tissue (EAT) thickness. HIV-infected individuals have thicker EAT than noninfected persons; increased EAT is predictive of CV events in HIV patients, as it is in noninfected individuals.[68] EAT overlies the coronary arteries and has been postulated to accelerate coronary atherosclerosis by secreting proinflammatory substances. Thicker EAT is associated with a longer duration of ART, thicker carotid IMT, and the presence of coronary plaque.[69]

A limitation of screening for CAC in HIV patients is that noncalcified plaques are much more common in this population than in uninfected patients.[43] The CAC score may thus underestimate the severity of coronary disease. In addition, if all plaques are noncalcified, the diagnosis of coronary disease would be missed. In the Multicenter AIDS Cohort Study, noncalcified plaques were more prevalent in HIV patients compared with controls (prevalence ratio, 1.28; 95% CI, 1.13 to 1.45), a difference that remained statistically significant even after adjustment for coronary risk factors.[42] In addition, more than a third of HIV-infected individuals had a significantly elevated carotid IMT of 1 mm or more despite having no CAC, suggesting that a negative CAC scan does not rule out CV risk in HIV.[70]

Coronary CT angiography (**see Chapter 20**) detects noncalcified coronary plaques and thus is often a useful diagnostic test in HIV-infected patients, depending upon the clinical circumstances. In the

Multicenter AIDS Cohort Study, coronary artery stenosis of more than 50% was more frequently found in HIV patients than in uninfected controls.[42] The detection of coronary plaques in an HIV-infected patient should lead to initiation or intensification of treatment for CV risk factors. Statin therapy, smoking cessation, and aggressive control of hypertension and diabetes become mandatory in this setting. Coronary lesions have been shown to improve with statin therapy in HIV-infected patients.[64]

Carotid ultrasound (**see Chapter 14**), performed for measuring the carotid IMT and determining whether coronary plaques are present and, if so, their severity, has been useful in research about atherosclerosis related to HIV infection.[71] Changes in the carotid IMT over time can be challenging to assess because of measurement variations. The presence of carotid plaques or an abnormally thickened carotid IMT should lead to more aggressive control of risk factors. Brachial artery flow–mediated dilation is useful for assessing the role of the endothelium in HIV-associated CV disease and for evaluating responses to interventions, but it may be challenging to perform in the clinical setting. Increased fibrosis has been shown in HIV-infected individuals by means of cardiac MRI.[72]

Although few studies have addressed the topic, cardiac screening has been shown to be cost-effective in HIV patients at intermediate risk for coronary disease.[73] Depending on the clinical features of a patient, screening for CAC and IMT or stress testing could be considered an appropriate first step. An ECG should be obtained in all HIV-infected adults, and an echocardiogram is reasonable because of the high prevalence of left ventricular hypertrophy and left ventricular dysfunction present in HIV patients (discussed below).

Chronic Inflammation and Cardiovascular Disease

Chronic inflammation and immune activation are thought to be important contributors to HIV-associated CV disease.[5] Although the mechanisms underlying CV disease in HIV are multifactorial, as shown in **Fig. 82.1**, chronic inflammation is thought to underlie CV disease in HIV, as well as in other non-AIDS conditions, including renal disease, neurologic disease, and cancers. Many different therapies are being evaluated as proof-of-concept interventions for reducing inflammation; they include therapies used in cardiology, such as statins, aspirin, ACE inhibitors, and aldosterone-receptor antagonists. Additionally, trials evaluating agents used in other inflammatory states such as rheumatoid arthritis are being studied, including low-dose methotrexate, TNF-alpha inhibitors, IL-6 inhibitors, and IL-1β inhibitors. The impact of these differing interventions on relieving inflammation and lowering the risk for CV diseases is unknown, and their safety for use in HIV patients and effects on CV end points are also unknown at this time.

Other Cardiovascular Conditions in HIV Patients

Pulmonary Hypertension

The prevalence of idiopathic pulmonary hypertension (PH) in the general population is estimated to be one to two persons per million, but in HIV-infected patients a prevalence of 0.5%, several thousand times higher, has been consistently reported (**see Chapter 85**). This prevalence has remained constant with the advent of ART; for example, a survey from France published in 2008 reported a prevalence of 0.46%. An evaluation of the prevalence of pulmonary arterial hypertension in HIV patients at hospital discharge or following death was lower than the previous and consistently reported prevalence, suggesting that this diagnosis may be underrecognized.[74] Studies of HIV patients screened with Doppler echocardiography

suggest that many more have mild, asymptomatic PH and that the true prevalence is considerably higher than 0.5%. For example, in our study of 106 HIV-infected patients, 87 had a pulmonary artery systolic pressure of 30 mm Hg or higher on echocardiographic studies; PH was confirmed by right heart catheterization in 16 of the 65 who underwent this procedure.[75] In another recent study, PH was detected by echocardiography in 23 of 374 HIV-infected patients (6.1%), of whom only 3 had symptoms of PH.[76]

The pathology of PH associated with HIV infection is similar to that in PH patients without HIV. It includes intimal thickening of small pulmonary arteries with plexogenic lesions in the media, leading ultimately to obstruction of small pulmonary arteries. Severe PH leads to worsening dyspnea, curtailed exercise capacity, right heart failure, and sudden cardiac death. PH may occur at any stage of HIV infection and does not appear to be related to the CD4 count, type of ART used, or other HIV-related factors.

PH is a harbinger of early death in HIV-infected patients. In older studies, the mean survival time of HIV patients with PH was 6 months. The survival time is likely much better if asymptomatic patients are included and may also be improved in patients who are given contemporary therapy for PH. In a series of 77 HIV-infected PH patients treated at a specialized French center between 2000 and 2008, the overall survival rate was 88% at 1 year and 72% at 3 years.[77] Predictors of the survival rate were a cardiac index of more than 2.8 L/min/m^2 and a CD4 lymphocyte count of more than 200 cells/µL. In HIV patients with symptomatic PH, death is almost always caused by the PH rather than other complications of HIV.

As with idiopathic PH, no single cause of HIV-associated PH has been identified, but many potential contributing factors have been implicated. Increased levels of inflammatory markers such as vascular endothelial growth factor-A, platelet-derived growth factor, and interleukin 1 and 6 have been demonstrated in HIV-associated pulmonary arterial hypertension. Certain HIV proteins have been shown to activate endothelial cells indirectly, such as the envelope glycoprotein-120, which is associated with higher levels of endothelin-1. Levels of endothelin-1 have been correlated with pulmonary artery systolic pressure among HIV-infected patients with PH,[76] suggesting that this potent vasoconstrictor plays a central role in the pathogenesis of HIV PH. Another potential mechanism is asymmetric dimethylarginine (ADMA)–induced endothelial dysfunction; elevated ADMA levels have been reported in HIV-associated PH.[78] Finally, a genetic predisposition to HIV-associated PH has been suggested, and some evidence indicates that autoimmunity may contribute.

Optimal treatment for HIV-associated PH remains unclear. ART does not appear to be beneficial. Pulmonary vasodilator testing reveals that a small minority of HIV-infected PH patients respond to calcium channel blockers.[79] The drug-drug interaction between calcium channel blockers and protease inhibitors means that the dose of the calcium channel blocker should be limited. The dual endothelin-receptor antagonist bosentan has been shown to improve pulmonary vascular resistance and exercise tolerance over 1 year of treatment, similar to the response expected in uninfected PH patients. Of note, the recommended dose of bosentan for individuals taking protease inhibitors is 62.5 mg/day or every other day instead of the usual dose of 125 mg twice daily. Studies of the selective endothelin-receptor antagonists ambrisentan and sitaxsentan have not been reported in the setting of HIV.

The phosphodiesterase type-5 inhibitors sildenafil, tadalafil, and vardenafil have been shown in clinical trials to improve hemodynamics and exercise tolerance in PH patients without HIV infection. No such trials have been reported in HIV-associated PH; however, isolated case reports suggest similar improvements should be expected in HIV PH patients.[79] Sildenafil is metabolized by the 3A4 isoform of the cytochrome P450 system, and interactions have been described with the protease inhibitors saquinavir, ritonavir, and indinavir. Because of these drug-drug interactions, the dose of sildenafil in HIV-infected individuals who are concurrently taking protease inhibitors should be carefully monitored. The

other phosphodiesterase type-5 inhibitors share this problem.

Several small series demonstrate that prostacyclin analogues induce hemodynamic benefit in HIV patients with PH.[79] Subcutaneous treprostinil and inhaled iloprost have improved functional capacity in the very small numbers of HIV-infected PH patients that have been reported. In general, the treatment of PH in HIV-infected patients does not appear to differ much from treatment in uninfected patients, except that specific clinical trial data are lacking for HIV patients, and concomitant protease inhibitor therapy introduces the problem of drug-drug interactions. Case reports have described cures of HIV-associated pulmonary arterial hypertension.

Cardiomyopathy and Left Ventricular Abnormalities

The incidence of HIV-associated cardiomyopathy has decreased dramatically from the pre-ART era, from 25.6 cases per 1000 person-years to 3.9 cases, according to one review (**see Chapter 79**).[80] Additionally, in the pre-ART era, HIV-associated cardiomyopathy was defined as symptomatic, systolic dysfunction with left ventricular dilation, and was seen almost exclusively in patients with advanced HIV disease and AIDS; in the post-ART era, the diagnosis often refers to systolic or diastolic dysfunction detected by echocardiography in asymptomatic HIV patients.

The pathophysiology of HIV-associated cardiomyopathy is likely multifactorial, with proposed causes including direct HIV infection of the myocardium with or without myocarditis, coinfection with other viruses such as coxsackievirus B3 and cytomegalovirus, toxicity from ART, autoimmune factors, opportunistic infections, and nutritional disorders. When HIV-associated cardiomyopathy consisted of severe, dilated cardiomyopathy, the cause was believed to be opportunistic infections or myocarditis. Now that the disease has changed to more nuanced myocardial dysfunction, the understanding of mechanisms has become more nuanced as well.

Infection of the heart with the HIV virus is thought to cause impaired systolic function. HIV gene products, such as tat (transactivator of transcription, can also contribute. Proinflammatory cytokines such as interleukin-1β and tumor necrosis factor have also been shown to depress systolic function.[80] Some types of ART cause mitochondrial toxicity, which may impair ventricular function. In sub-Saharan Africa and other poor areas, nutritional deficiencies may contribute to HIV-associated cardiomyopathy. HIV-associated heart failure has been reported in low- and middle-income countries.[81] Most studies of HIV patients have been performed in developed countries with readily available access to ART, so a different spectrum of CV diseases may be observed in developing countries.

Left ventricular hypertrophy is more common in HIV-infected patients than in controls). In one study, HIV-infected participants had a left ventricular mass index that was 8 g/m^2 (the mean) larger than the mass index in controls ($P = 0.001$).[82] The higher left ventricular mass index was independently associated with a lower nadir CD4 T-cell count, suggesting that immunodeficiency may play a role in this process. After adjustment for age and traditional risk factors, HIV patients were 2.4 times more likely to have diastolic dysfunction than controls. Another study compared left ventricular mass in patients with and without HIV infection and with and without hypertension.[83] In both hypertensive and normotensive persons, HIV patients had a greater left ventricular mass and more diastolic dysfunction than uninfected controls.

Treatment recommendations for HIV-related cardiomyopathy are based on trials done in uninfected cardiomyopathy patients, and on guidelines based on these trials.[80] Thus, ACE inhibitors, beta blockers, and aldosterone antagonists should be used, even though trials of these drugs have not been done in HIV-infected patients with cardiomyopathy.

ART is not a therapy specifically used for cardiomyopathy; however, the incidence of cardiomyopathy

has declined dramatically since the introduction of ART. Whether ART can reverse established cardiomyopathy is not known. On the other hand, ART drugs such as zidovudine have direct myocardial toxicity, and ART may accelerate coronary atherosclerosis, ultimately leading to left ventricular dysfunction. The role of inflammation and the immune response in HIV-associated cardiomyopathy is highlighted by a study in HIV-infected children with left ventricular dilation; better left ventricular contractility was seen in those with higher endogenous IgG levels and those treated with intravenous immunoglobulin. Of note, among individuals perinatally infected with HIV, ART appears to have a protective effect on cardiac structure, as well as a deterrent effect on the development of heart failure, suggesting that ART has a protective effect.[84]

Heart transplantation with excellent long-term survival rates has been reported in small numbers of HIV-infected patients. The fear that immunosuppression in such patients might lead to AIDS has proved unfounded, and the notion that HIV infection should be a contraindication to cardiac transplantation is no longer tenable.

HIV-associated cardiomyopathy in the pre-ART era carried a grim prognosis. In one study, the median survival time in patients with AIDS and cardiomyopathy was 101 days, compared with 472 days in patients with AIDS alone. In another study, the adjusted hazard ratio for death for patients with cardiomyopathy associated with AIDS was 5.86, compared with that for idiopathic cardiomyopathy.

Since the advent of ART, the epidemiology and prognosis of HIV-associated cardiomyopathy have improved dramatically. Symptoms of heart failure or echocardiographic evidence of cardiomyopathy greatly increase the risk of death.[80] Sudden cardiac death in HIV patients occurs at 4.5 times the expected rate, and systolic and diastolic dysfunction are known to be present in more than half of such cases.[85] The presence of contractile reserve as assessed by dobutamine stress echocardiography has been reported to be a marker for improved survival rates in HIV patients with cardiomyopathy. Patients with a contractile reserve were also more likely to experience an improvement in the ejection fraction.

Arrhythmias and Sudden Cardiac Death

Cardiac arrhythmias are more common in HIV patients compared with uninfected controls (**see Chapter 32**). In the Veterans Affairs HIV Clinical Case Registry of 30,533 HIV-infected veterans, the prevalence of atrial fibrillation (**see Chapter 38**) was increased and was associated with lower CD4 counts and higher viral loads, as well as the usual clinical factors related to atrial fibrillation.[86] Whether atrial fibrillation should be treated differently in an HIV patient is unknown, because the risks for complications of atrial fibrillation, such as embolic stroke, have not been defined in these patients. Thus the thromboembolic predictive value of calculators such as CHADS2 and CHADS2Vasc remain unknown in the setting of HIV.

HIV patients appear to be more susceptible to sudden cardiac death than uninfected persons (**see Chapter 42**). In a consecutive series of 2860 HIV patients followed for a mean of 3.7 years, the mean sudden cardiac death rate was 2.6 per 1000 person-years (95% CI, 1.8 to 3.8), or 4.5-fold higher than expected.[85] Patients who succumbed to sudden cardiac death had a higher prevalence of previous MI, cardiomyopathy, heart failure, and arrhythmias. Left ventricular systolic dysfunction and diastolic dysfunction, especially in the setting of detectable HIV RNA levels, were predictive of sudden cardiac death in HIV.[87] Additional studies are needed to determine the role of the implantable cardioverter defibrillator (ICD) in prevention of sudden cardiac death in HIV.

Cerebrovascular Disease

In the Veterans Aging Cohort Study the risk of ischemic stroke was increased in HIV-infected men compared with uninfected persons (IRR, 1.25; 95% CI, 1.09 to 1.43; $P < 0.01$) (**see Chapter 65**).[47] After adjusting for demographic factors, ischemic stroke risk factors, comorbid diseases, and substance abuse, the risk of ischemic stroke was attenuated but still higher among HIV-infected men (HR, 1.17; 95% CI, 1.01 to 1.36; $P = 0.04$). In a large series from the U.S. Nationwide Inpatient Sample, the in-hospital mortality rate was higher in HIV-infected than uninfected stroke patients (7.6% vs. 5.2%).[88] Some evidence suggests that the rate of stroke may be higher in women infected with HIV than in men with infection.[89]

The risk of hemorrhagic stroke also appears to be elevated in HIV-infected patients. In a database study covering all residents in Quebec from 1985 to 2007, the incidence of intracerebral and subarachnoid hemorrhage was higher in HIV-infected individuals than uninfected age-matched controls (HR, 3.28; 95% CI, 1.75 to 6.12). The risk among HIV-infected individuals with an AIDS-defining condition was particularly high (HR, 7.64; 95% CI, 3.78 to 15.43). Among those without an AIDS-defining condition, the hazard ratio was nearly doubled but was not statistically significant.[89] Other studies have also demonstrated increased rates of intracerebral hemorrhage in the setting of HIV.[90]

The mechanisms accounting for the increase in stroke risk in HIV patients are in general similar to the mechanisms accounting for the increased risk of MI: HIV-associated immune activation and inflammation, adverse effects of long-standing ART use, and the usual stroke risk factors, including hypertension and smoking. In a case control study, achievement of viral suppression was associated with a reduced risk of ischemic stroke, suggesting that treated and suppressed HIV disease reduced the risk for stroke.[91] Carotid IMT is a strong independent marker of stroke risk; the age-adjusted carotid IMT is increased in HIV patients compared with controls. Impaired fibrinolysis resulting in a hypercoagulable state has been described in HIV patients with hyperinsulinemia and fat redistribution who are receiving protease inhibitors.

In the pre-ART era, severely immunocompromised HIV-infected individuals with and without strokes often exhibited an intracranial vasculopathy with aneurysmal arteriopathy and, at times, concomitant infections, including varicella zoster virus and cytomegalovirus infections.[89] Pathologic examination of affected vessels revealed subintimal fibrosis, disruption of the internal elastic lamina, and thinning of the media layer. All abnormalities improved with initiation of ART; this finding suggests that this entity is unlikely to be clinically relevant in virally suppressed contemporary patients.

The data linking ART to an increased risk of stroke are less compelling than the data for MI, possibly because of the lower incidence of stroke. A high viral load and a low CD4 count increase the risk of stroke. Yet even treated individuals with well-controlled infection show evidence of inflammation and immune activation, and probably are at increased risk for stroke.

Scant data are available comparing the prognosis of stroke in HIV patients with their uninfected counterparts. Similarly, the acute and long-term treatment of stroke in HIV patients has not been differentiated from stroke treatment in uninfected individuals. Primary and secondary prevention of stroke in HIV patients is of great importance because of the increased risk in these patients, and because of their high prevalence of modifiable risk factors, specifically smoking, dyslipidemia, and hypertension. Several studies have reported that aspirin and statins are underused in HIV patients. The benefit of aspirin may extend beyond its antithrombotic properties because it reduces markers of T-cell and monocyte activation in virologically suppressed HIV-infected patients.

Future Perspectives

ART has transformed HIV infection into a chronic disease. CV disease is therefore a growing health concern in the aging HIV population. Coronary artery disease, along with other emerging CV conditions, including heart failure, diastolic dysfunction, PH, stroke, and arrhythmias, is more common in HIV-infected individuals even once the HIV disease has been treated and suppressed. The underlying mechanism for the increased risk in HIV patients, as well as the optimal methods for treating CV disease in HIV-infected individuals, remains largely unknown. How to best identify and treat individuals at risk is also undefined. Treatment and risk prediction will likely be combined in some manner, with both targeting traditional risk factors along with HIV-specific issues. HIV infection and ART may lead to CV disease resulting from chronic persistent inflammation, because of the fact that although medication controls HIV disease, it does not cure it. By the year 2030, more than 70% of people living with HIV are projected to be age 50 years or older. Thus, because CV disease is prevalent among older individuals (**see Chapter 88**), it will likely continue to be a significant health concern among individuals living with HIV, both now and in the future. Cardiologists and caregivers of people living with HIV should be aware of HIV-related CV issues and their treatment.

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83

Pericardial Diseases

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The pericardium is the site of a wide variety of diseases that result in some of the classic physical, imaging, and hemodynamic findings in cardiology, including acute pericarditis, pericardial effusion and tamponade, constrictive and subacute effusive-constrictive pericarditis, and selected specific pericardial disease etiologies. For more detailed treatments of pericardial anatomy, physiology, and disease, see the classic monograph by Shabetai,[1] the 2015 European Society of Cardiology (ESC) guidelines for diagnosis and management,[2] and two recent consensus statements on multimodality imaging in pericardial disease.[3,4]

Anatomy and Physiology of the Pericardium

The pericardium is composed of two layers, the *visceral pericardium*, a monolayer of mesothelial cells and collagen and elastin fibers adherent to the epicardial surface of the heart, and the fibrous *parietal layer*, which is normally about 2 mm thick and surrounds most of the heart (**Fig. 83.1**).[1] The parietal pericardium is largely acellular and contains collagen and elastin fibers. The visceral pericardium reflects back near the origins of the great vessels and is continuous with and forms the inner layer of the parietal pericardium. The pericardial space or sac is contained within these two layers, and normally contains up to 50 mL of serous fluid. The reflection is a few centimeters proximal to the junctions of the caval vessels with the right atrium; thus, portions of the caval vessels lie within the pericardial sac. Posterior to the left atrium, the reflection occurs at the oblique sinus of the pericardium. The left atrium is largely extrapericardial. The parietal pericardium has ligamentous attachments to the diaphragm, sternum, and other structures.

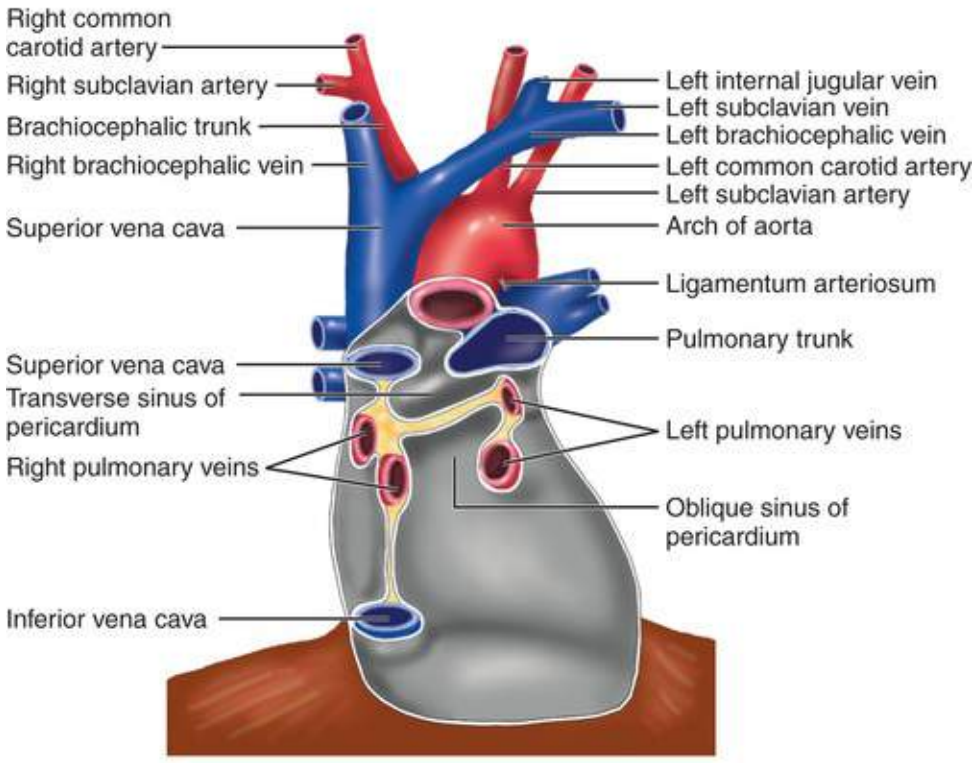
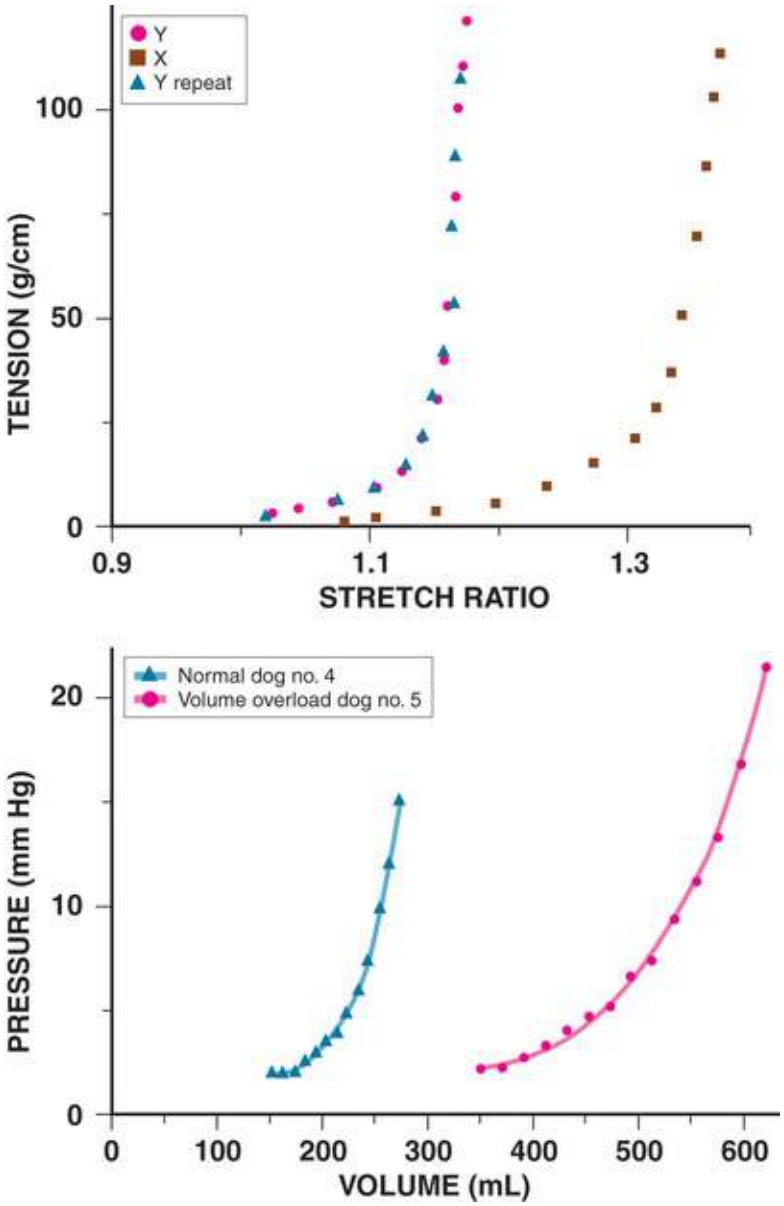


FIGURE 83.1 The pericardial reflections near the origins of the great vessels shown after removal of the heart. Note that portions of the caval vessels are within the pericardial space. (From Johnson D: The pericardium. In Standring S [editor]: Gray's anatomy. St. Louis, Mosby, 2005, pp 995-6.)

Although its removal has no obvious negative consequences, the pericardium does have functions.[1] Its attachments maintain the heart at a relatively constant position within the thorax, and it provides a barrier to infection. The pericardium is well innervated with mechanoreceptors, chemoreceptors, and phrenic afferent receptors that participate in reflexes arising from the pericardium and/or epicardium (e.g., the Bezold-Jarisch reflex) and transmission of pericardial pain. The pericardium also secretes prostaglandins and related substances that may modulate neural traffic and coronary tone.

The best-characterized mechanical function of the pericardium is its *restraining* effect on cardiac volume.[1] This reflects the mechanical properties of the parietal pericardial tissue. At low stresses, the tissue is very elastic (**eFig. 83.1, top**). With further stretch, it abruptly becomes stiff and resistant to even more stretch. The point on the stress-strain relation (**see eFig. 83.1, top**) where this transition occurs is near the upper range of physiologic cardiac volumes. The *pressure-volume relation* (PVR) of the pericardial sac reflects the properties of the tissue (**see eFig. 83.1, bottom**, left curve) (i.e., a flat, compliant segment transitioning relatively abruptly to a noncompliant segment around the upper limit of normal total cardiac volume).[1] Thus, the sac has a relatively small reserve volume. When exceeded, the pressure within the sac operating on the surface of the heart increases rapidly and is transmitted into the cardiac chambers. The shape of the pericardial PVR dictates that once a critical level of effusion is reached, relatively small amounts of additional fluid will cause large increases in intrapericardial pressure and have marked effects on cardiac function. Conversely, removal of small amounts of fluid can result in striking benefit. The shape of the pericardial PVR also suggests that it *normally* restrains the cardiac volume (i.e., the force it exerts on the surface of the heart limits filling, with a component of *intracavitary pressure* reflecting the surface pressure). Studies with specially designed balloons demonstrate a substantial surface pressure, especially when the upper limit of normal cardiac volume is

exceeded.[1]



EFIGURE 83.1 **Top,** relationship between stretch and tension in vitro in normal human pericardial tissue. The tissue has been stretched in two, mutually orthogonal directions (X, Y). Note relatively abrupt transition from relatively flat to steep, inelastic relationship. In addition, the tissue is anisotropic (i.e., the relation between tension and stretch depends on the direction of stretch). **Bottom,** pressure-volume relationship of the normal canine pericardium (left) and after 4 weeks of cardiac dilation because of volume overload (right). Note relatively abrupt transition to a steep relationship in normal pericardium and marked shift to the right and flattening after chronic volume overload. (**Top,** from Lee MC, Fung YC, Shabetai R, LeWinter MM: Biaxial mechanical properties of the human pericardium and canine comparisons. Am J Physiol 1987;22:H75. **Bottom,** from Freeman G, LeWinter M: Pericardial adaptations during chronic cardiac dilation in dogs. Circ Res 1984;54:294.)

Pericardial contact pressure has also been estimated by quantifying the shift in the right and left heart diastolic PVR before and after pericardiectomy.[1] A decrease in pressure at a given volume is the *effective* pericardial pressure at that volume. Studies in normal canine hearts indicate negligible pressure at low normal filling volumes, with pressures in the range of 2 to 4 mm Hg at the upper range of normal. At filling volumes above normal the pressure rapidly increases. Thus, at a left-sided filling pressure of approximately 25 mm Hg, the contact pressure is approximately 10 mm Hg. Patients undergoing pericardiotomy during heart surgery develop mild postoperative increases in cardiac volume, consistent with relief of the underlying, normal pericardial restraint to filling.

The normal pericardium also contributes to diastolic interaction, defined here as transmission of intracavitary filling pressure to adjoining chambers.[1] Thus, for example, a portion of the right ventricular (RV) diastolic pressure is transmitted to the left ventricle across the interventricular septum and contributes to the left ventricular (LV) diastolic pressure. Because its presence increases the RV intracavitary pressure, the pericardium amplifies diastolic interaction. As cardiac volume increases, the pericardium contributes increasingly to intracavitary filling pressures owing both to external contact pressure and increased diastolic interaction. When the cardiac chambers dilate rapidly, the restraining effect of the pericardium and its contribution to diastolic interaction are augmented, resulting in a hemodynamic picture with features of both cardiac tamponade and constrictive pericarditis. An example is RV myocardial infarction (MI).[1] Here, the right heart dilates rapidly such that the total heart volume exceeds the pericardial reserve volume. As a result, left- and right-sided filling pressures equilibrate at elevated levels and a paradoxic pulse and inspiratory increase in systemic venous pressure (Kussmaul sign) may occur. Other conditions with similar effects include acute pulmonary embolus and subacute mitral regurgitation.[1]

Chronic cardiac dilatation (e.g., in dilated cardiomyopathy or regurgitant valvular disease) can result in cardiac volumes well in excess of the pericardial reserve volume, yet exaggerated restraining effects are not observed. Thus, the pericardium adapts to accommodate chronic increases in cardiac volume. In experimental chronic volume overload, the pericardial PVR shifts to the right and its slope decreases (**see eFig. 83.1, bottom**, right curve) (i.e., it becomes more compliant, along with an increase in area and mass and a decreased effect on the diastolic PVR).[1] Presumably, a similar effect occurs with large, slowly accumulating effusions.

Acute Pericarditis

Definition, Causes, Epidemiology, and Pathophysiology

Acute pericarditis is an inflammatory syndrome with or without pericardial effusion with a wide variety of causes (**Table 83.1**).[1,2,5-7] The background prevalence of tuberculosis (TB) is a key element in the assessment of a suspected case of pericarditis. In developing regions where TB is endemic, it is the most common cause of pericarditis and effusion. TB is infrequent in developing countries and therefore a much less important consideration.[2,6,7]

TABLE 83.1

Categories of Diseases That Can Involve the Pericardium and Selected Specific Etiologies

Idiopathic*
Infectious
Viral* (echovirus, coxsackievirus, adenovirus, cytomegalovirus, hepatitis B virus, infectious mononucleosis, HIV/AIDS
Bacterial* (*M. tuberculosis*, *M. avium-intracellulare*, pneumococcus, staphylococcus, streptococcus, *Mycoplasma*, Lyme disease, *H. influenzae*, *Neisseria meningitides*, and many others)
HIV-associated*
Fungal (histoplasmosis, coccidioidomycosis)
Protozoal
Inflammatory
Connective tissue disease* (systemic lupus erythematosus, rheumatoid arthritis, scleroderma, dermatomyositis, Sjögren syndrome, mixed)
Drug-induced* (e.g., procainamide, hydralazine, isoniazid, cyclosporine)
Arteritis (polyarteritis nodosa, temporal arteritis)
Inflammatory bowel disease
Postcardiotomy, postthoracotomy,* post–cardiac injury syndrome*
Genetic immune system diseases* (tumor necrosis factor receptor-1–associated periodic syndrome [TRAPS], familial Mediterranean fever)
Miscellaneous: sarcoidosis, Erdheim-Chester disease, Churg-Strauss disease, immunoglobulin G4–related disease
Post–Myocardial Infarction
Early
Late (Dressler syndrome)*
Cancer
Primary: mesothelioma, fibrosarcoma, lipoma, and others
Secondary*: breast and lung carcinomas, lymphomas, Kaposi sarcoma
Radiation-Induced Disorders*
Early Post–Cardiac Surgery and Post–Orthotopic Heart Transplantation
Hemopericardium
Trauma
Post–myocardial infarction free wall rupture
Endomyocardial biopsy
Dissecting aortic aneurysm
Device- and procedure-related: percutaneous coronary procedures, implantable defibrillators, pacemakers, post–arrhythmia ablation, post–atrial septal defect closure, post–left atrial appendage isolation, post–percutaneous valve repair/replacement, laparoscopic hiatal hernia repair
Oral anticoagulants
Congenital
Cysts, congenital absence
Miscellaneous
Stress cardiomyopathy
Cholesterol (“gold paint” pericarditis)
Chronic renal failure, dialysis-associated*
Chylopericardium
Hypothyroidism and hyperthyroidism
Amyloidosis
Pneumopericardium
Polycystic kidney disease
Pulmonary arterial hypertension

*Etiologies that can present as the syndrome of acute pericarditis.

There are limited epidemiologic data documenting the incidence and prevalence of acute pericarditis. The incidence is difficult to quantify because many cases are likely undiagnosed. At autopsy, the frequency is approximately 1%.[2,7] Pericarditis is commonly seen in the emergency department, where it accounts for up to 5% of patients with nonischemic chest pain.[5,7] A review of causes in published series is presented in **Table 83.2**.[2,5-7] Presumed viral and idiopathic forms are most common in developed countries. We use *idiopathic* to denote acute pericarditis for which no specific cause is found with routine

diagnostic testing as outlined below. Most idiopathic cases are presumed to be viral. Testing for specific viruses is costly and has a low yield and little impact on management.[8] Such a term, although an admission of ignorance, is clinically meaningful if nonviral causes of pericarditis have been excluded, because treatment with antiinflammatory therapy is similar for all cases and the prognosis is good.[2,5-7]

TABLE 83.2

Etiology of Pericarditis in Major Series

ETIOLOGY	REPORTED FREQUENCY (%)
Idiopathic	15% (Africa) to 80% to 90% (Europe)
Infectious pericarditis	
Viral	Largely unknown
Bacterial	
Tuberculosis	1% to 4% in developed countries; up to 70% in Africa
Purulent	<1% in developed countries; 2% to 3% in Africa
Other infectious causes	Rare, largely unknown
Noninfectious pericarditis	
Neoplastic	5% to 9% to 35% (in tertiary referral centers)
Autoimmune	2% to 24%
Other noninfectious causes	Rare (largely unknown)

In a contemporary series of acute pericardial syndromes from Northern Italy, the incidence of acute pericarditis was 27.7 cases/100,000 population/year with concomitant myocarditis in about 15%.[9] In a series of hospitalized patients with acute pericarditis from Finland, the standardized incidence rate of hospitalization was 3.32/100,000 population/year.[10] Men age 16 to 65 years were at higher risk (relative risk [RR], 2.02), with the highest risk difference among young adults compared with the overall population. Acute pericarditis was the cause of 0.20% of all cardiovascular admissions. The proportion of admissions declined in younger patients. The in-hospital mortality rate was 1.1%; it increased with age and in persons with severe infections such as pneumonia or septicemia.

Most of the various causes of pericardial inflammation result in a response characterized by edema, thickening of the parietal layer, production of exudative pericardial fluid, and increased friction between the layers.[1] Acute pericarditis and myocarditis share common causes, and, as noted, as many as 15% of pericarditis cases are associated with myocarditis.[2,7,9,11] Coexistent myocarditis is usually manifested by a modest release of biomarkers such as troponin I (**see Chapter 79**). LV dysfunction is rare, and the long-term prognosis of pericarditis complicated by myocarditis is excellent.[11] When ventricular function is normal, the term *myopericarditis* is used. Cases with impaired function are labeled *perimyocarditis*.

History and Differential Diagnosis

In more than 90% of cases, the main symptom of acute pericarditis is chest pain, often quite severe.[2,5-7] It is usually retrosternal but may be localized to the left anterior chest and radiate to the neck, shoulders, and arms. The trapezius ridge is a classic radiation. Pericardial pain is pleuritic and worsened by lying down. Associated symptoms include dyspnea, cough, and occasionally hiccups. An antecedent history suggesting a viral illness is common. The history may provide clues to specific causative diagnoses. Thus, for example, a known cancer or autoimmune disorder, high fevers with shaking chills, or weight loss suggests a specific (i.e., nonidiopathic) cause.

The differential diagnosis of chest pain is lengthy (**see Chapters 10 and 56**). Diagnoses most easily confused with pericarditis include myocardial ischemia/infarction, pneumonia with pleurisy, pulmonary embolism/infarction, costochondritis, and gastroesophageal reflux. Acute pericarditis is usually easily distinguished from myocardial ischemia, but further testing may be required to resolve the issue. Other

considerations include aortic dissection, intraabdominal processes, pneumothorax, and herpes zoster pain before skin lesions appear. Rarely, pericarditis can signal a preceding, silent MI.

Physical Examination

Patients with *uncomplicated* acute pericarditis often appear uncomfortable and anxious, with low-grade fever (<38°C) and sinus tachycardia. Arrhythmias are rare. Thus, atrial fibrillation or flutter is reported in less than 5% of cases.[12] The pathognomonic physical sign of acute pericarditis is the friction rub. A rub is reported in about one third of cases at presentation. Rubs are typically evanescent and may require repeated auscultation for detection.[5-7] The rub is ascribed to friction between the pericardial layers. The classic rub consists of three components corresponding to ventricular systole, early diastole, and atrial contraction, and can be likened to the sound made when walking on crunchy snow. The rub is usually loudest at the lower left sternal border and best heard with the patient leaning forward. It is important to perform a thorough physical examination to look for clues to specific causative diagnoses as well as findings suggesting significant pericardial effusion.

Laboratory Testing

The electrocardiogram (ECG) is a key test for diagnosing acute pericarditis (**see Chapter 12**). The classic finding is "diffuse" ST-segment elevation (**Fig. 83.2**).[2,5-7] The ST-segment vector points leftward, anteriorly, and inferiorly, with ST-segment elevation in all leads except aVR and often V_1. Usually, the ST segment is coved upward and resembles the current of injury of transmural ischemia. The distinction between acute pericarditis and transmural ischemia is usually not difficult because of more extensive lead involvement and lack of evolution to pathologic Q waves in pericarditis, and more prominent reciprocal ST depression in ischemia. However, ST elevation in pericarditis can at times involve a smaller number of leads and in some cases the ST segment more closely resembles early repolarization. As with the rub, ECG changes can be dynamic. Frequent recordings can yield a diagnosis in patients who initially have neither rub nor ST elevation. PR-segment depression is also common and considered the earliest ECG sign of acute pericarditis, reflecting pericardial involvement overlying the atria (**see Fig. 83.2**). PR depression can occur without ST elevation and be the initial or sole ECG manifestation. The typical ECG evolution follows four stages: (1) PR depression and/or diffuse ST-segment elevation, (2) normalization of the ST segment, (3) T-wave inversion with or without ST-segment depression, and (4) normalization. The ECG often evolves without all four stages.

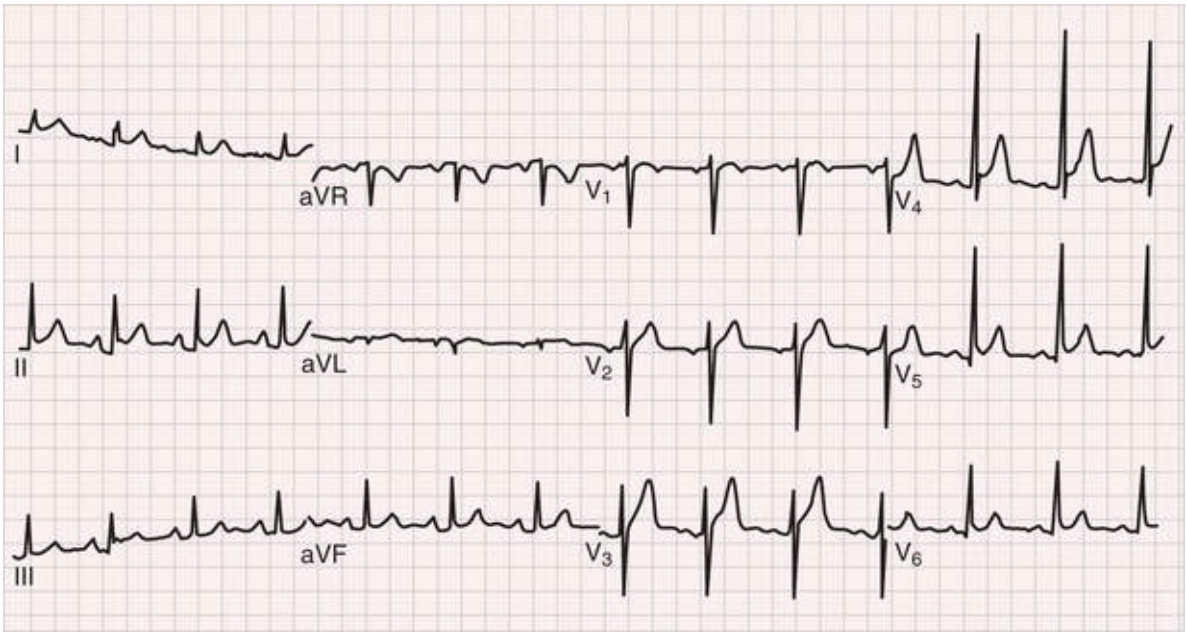


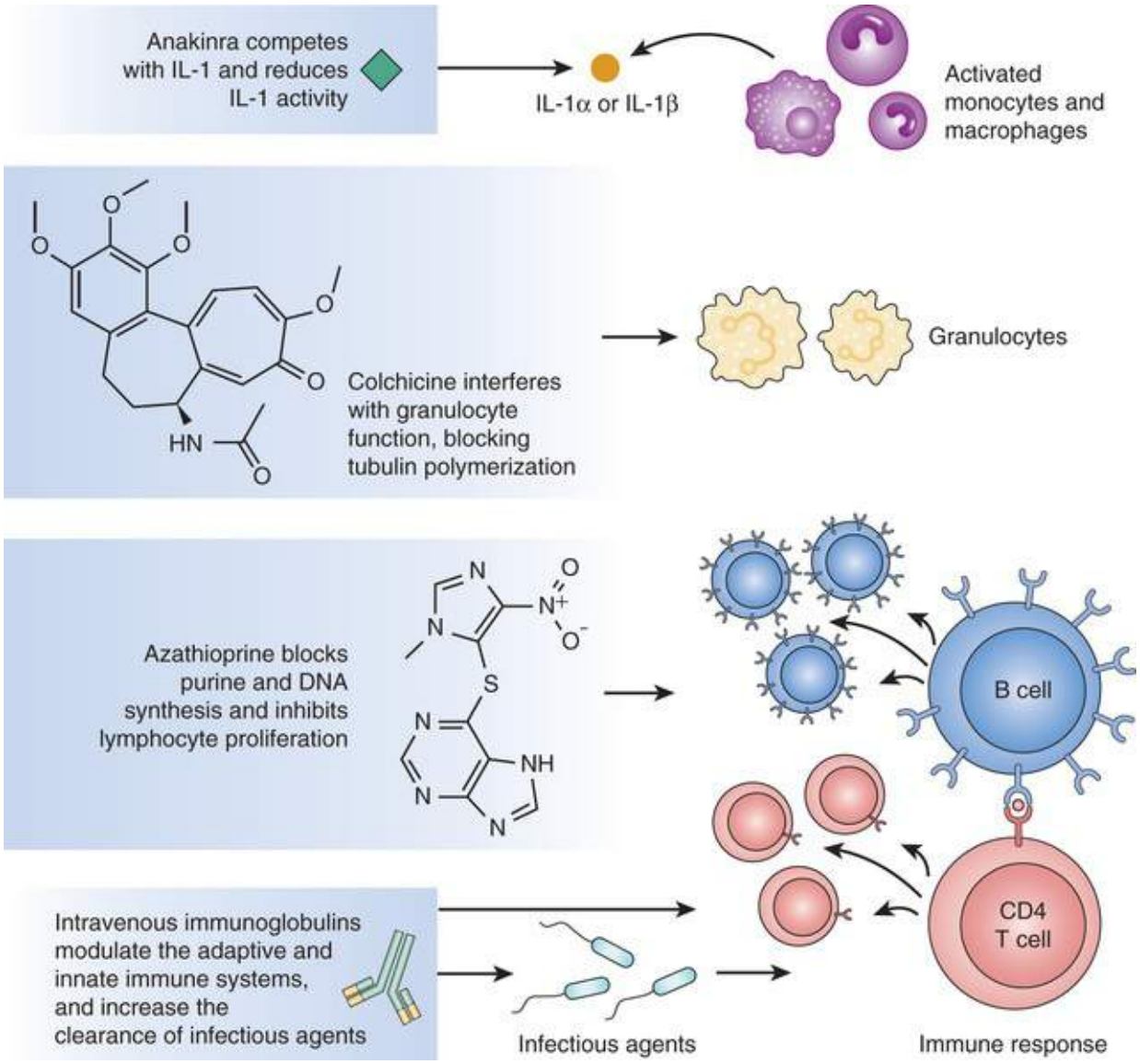
FIGURE 83.2 The electrocardiogram in acute pericarditis. Note the presence of both diffuse ST-segment elevation and PR-segment depression.

Although usually considered a hallmark of pericarditis, typical ECG changes reflect concomitant involvement of the myocardium, because the pericardium is electrically silent. For that reason, ECG changes are reported in no more than 60% of cases and are more common (>90%) with concomitant myocarditis.[9,11] Additional ECG changes that may constitute clues to the cause of pericarditis or associated findings include atrioventricular block in Lyme disease, pathologic Q waves signifying a previous, silent MI, and low-voltage or electrical alternans pointing toward significant effusion.

Many patients with acute pericarditis have a modestly elevated white blood cell (WBC) count.[2,5-7] WBCs in excess of 13,000 to 14,000/mm^3 suggest a specific etiology. As noted earlier, as many as 15% of patients with acute pericarditis have coexistent myocarditis based on elevations in biomarkers such as troponin I (**see Chapter 67**). Patients with myocarditis almost always have ST-segment elevation.[9,11] In almost all cases the LV ejection fraction (EF) is normal. Another concern in patients with elevated injury biomarkers is a prior silent MI followed by subsequent pericarditis. The latter usually occurs after large MIs with transmural ECG changes.[13]

Serum high-sensitivity C-reactive protein (hsCRP) is elevated in approximately three fourths of patients with acute pericarditis.[14] Normal values generally occur in patients seen early or who have previously received antiinflammatory therapy. hsCRP usually normalizes within 1 week and in almost all cases by 4 weeks after the initial evaluation. Increased hsCRP is independently associated with recurrent symptoms. It has been suggested that serial hsCRPs be used to help confirm the diagnosis of pericarditis and monitor disease activity in order to individualize the duration of therapy.[2,14] Although the utility of hsCRP for this purpose has not been prospectively shown, the association of elevated values with recurrences provides a rationale for measurement at the initial encounter and when it is uncertain how long treatment should be maintained.

Chest radiograms are normal in uncomplicated acute pericarditis.[1,5,7] Occasionally, small pulmonary infiltrates or pleural effusions are present, presumably caused by the underlying causative infection. Mass lesions and enlarged lymph nodes suggestive of neoplastic disease have great significance. Because small to moderate effusions may not cause an abnormal cardiac silhouette, even modest cardiac enlargement is of concern and generally associated with an effusion of more than 300 mL (**eFig. 83.2**).



EFIGURE 83.2 Mechanisms of action of newer antiinflammatory drugs used to treat pericarditis. (From Imazio M, Lazaros G, Brucato A, Gaita F: Recurrent pericarditis: new and emerging therapeutic options. Nat Rev Cardiol 2016;13:99.)

The echocardiographic-Doppler examination (**see Chapter 14**) is completely normal in approximately 40% of patients with acute pericarditis.[5-7] It is performed mainly to determine if an effusion is present and recommended in all patients with suspected pericarditis.[2] Pericardial effusion is reported in about 60% of cases of acute pericarditis and is usually mild (< 10 mm on semiquantitative echocardiographic assessment). Moderate or larger effusions (> 20 mm) are unusual and may signal a diagnosis other than *idiopathic* pericarditis. An effusion in a patient with a history consistent with acute pericarditis can be considered confirmatory of the diagnosis.

Echocardiography is also useful in unusual cases where associated myocarditis is severe enough to alter ventricular function and to detect a previously silent MI. It is rarely necessary to use imaging modalities other than echocardiography in uncomplicated acute pericarditis. However, as discussed below, in difficult cases computed tomography (CT) and/or cardiac magnetic resonance imaging (MRI) can help to detect pericardial thickening and/or active inflammation.[2]

Diagnosis, Natural History, and Management

ESC guidelines include the results of the first randomized clinical trials in pericarditis as well as more recent observational studies. However, objective data to support recommendations for management of

acute pericarditis as well as other pericardial diseases remain limited. Most are based on expert opinion and consensus. According to the guidelines, the clinical diagnosis of acute pericarditis can be made based on two of the following criteria: (1) chest pain, (2) pericardial friction rub, (3) ECG changes consisting of typical ST elevation and/or PR depression, and (4) pericardial effusion.[2]

In cases with atypical presentations, imaging to detect pericardial thickening and inflammation can be helpful in establishing the diagnosis. This may be provided by CT based on thickening and enhanced imaging after contrast injection, and/or MRI based on edema on T2-weighted dark blood images and late pericardial enhancement indicating active inflammation and/or fibrosis after injection of gadolinium (**see Chapters 17 and 18**).[2,7] Elevation of biomarkers of inflammation (e.g., hsCRP) is supportive of the diagnosis but not definitive.

Initial management is focused on confirming the diagnosis, screening for specific causes that would alter management, detection of effusion and other echocardiographic abnormalities, alleviation of symptoms, and appropriate treatment if a specific cause is discovered (**Table 83.3**). Certain features are associated with both an increased risk of complications and nonviral etiologies that may warrant targeted therapies (**Fig. 83.3**). On this basis, triage of patients is possible after initial evaluation (**see Fig. 83.3**).[2,5,7,15] We recommend the following routine laboratory evaluation: ECG, complete blood count, serum creatinine, hsCRP and troponin I, chest radiograph, and echocardiogram. Additional testing should be guided by suspicion of a specific cause. Thus, for example, in young women, obtaining antinuclear antibody (ANA) titers to test for systemic lupus erythematosus is reasonable because acute pericarditis can occasionally be its initial presentation. However, low ANA titers are common in patients with *recurrent* idiopathic pericarditis without other systemic lupus erythematosus criteria.[16] Thus, in this setting, low ANA titers appear to be nonspecific, possibly reflecting an immune-mediated pathogenesis. **Fig. 83.3 and Table 83.3** summarize our recommendations for triage and initial management of patients with definite or suspected acute pericarditis.

TABLE 83.3

Initial Approach to the Patient with Definite or Suspected Acute Pericarditis

1. If the diagnosis is suspected but not certain, listen often for pericardial rub and obtain ECGs frequently to check for diagnostic findings.
2. If the diagnosis is suspected or certain, obtain the following tests to help confirm the diagnosis (if necessary) and determine whether a specific causative diagnosis and/or significant associated conditions and/or complications are present: Hemogram hsCRP Troponin I Chest radiograph Echocardiogram Consider additional testing on the basis of clinical suspicion of a specific etiology
3. If the diagnosis is likely or certain, initiate therapy with an NSAID plus colchicine

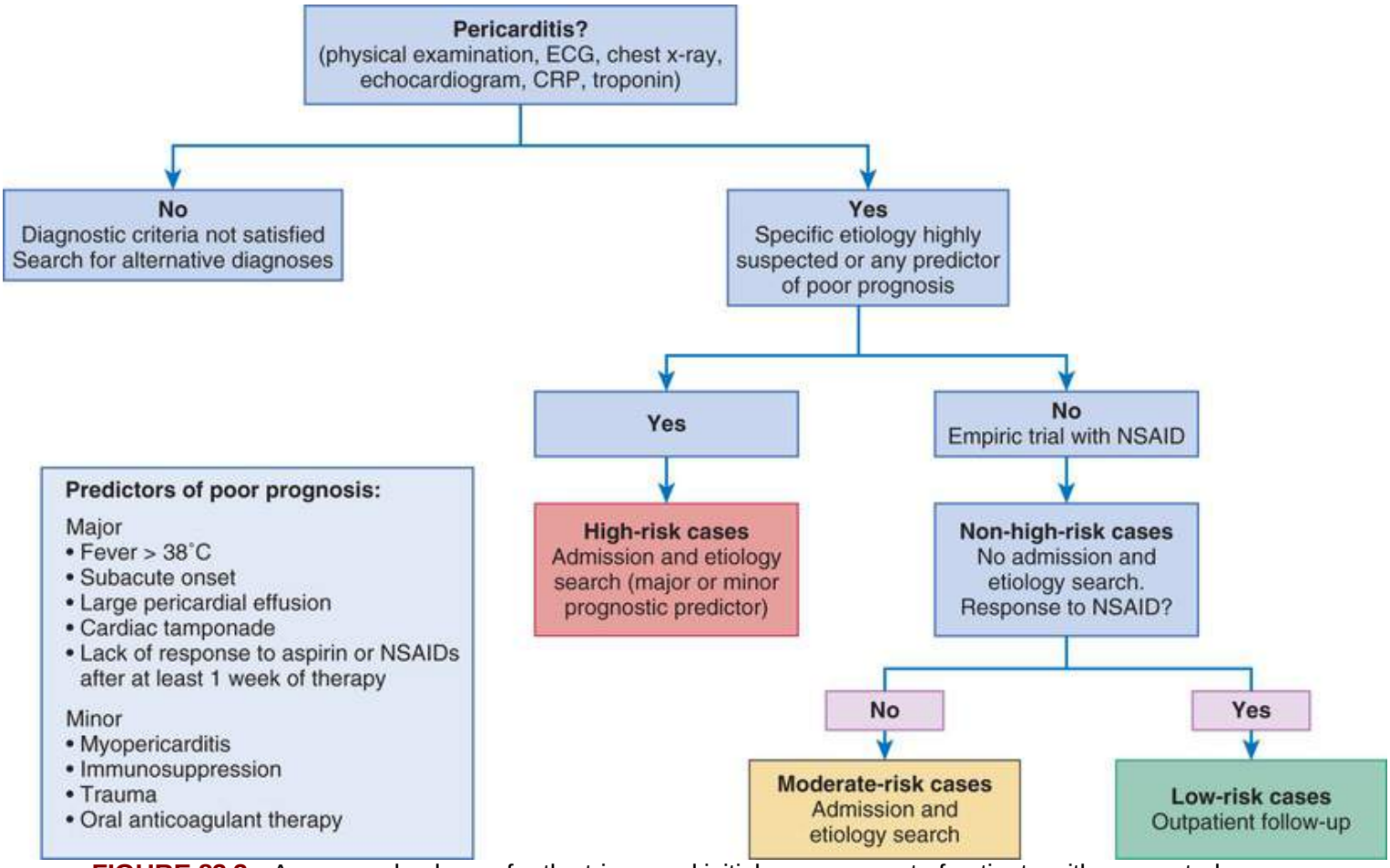


FIGURE 83.3 A proposed scheme for the triage and initial management of patients with suspected pericarditis, including markers of elevated risk (*inset*). *CRP*, C-reactive protein; *ECG*, electrocardiogram. See also references 2, 5, 7, and 15. (From Adler Y, Charron P, Imazio M, et al: 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: the task force for the diagnosis and management of pericardial diseases of the European Society of Cardiology (ESC). Eur Heart J 2015;36:2921.)

Acute idiopathic pericarditis is a self-limited disease without significant complications or recurrence in 70% to 90% of patients.[5-7,17] If laboratory data do not contradict the diagnosis of *idiopathic* pericarditis, symptomatic treatment with nonsteroidal antiinflammatory drugs (NSAIDs) is recommended.[2,5-7,18-20] Other recommendations include restriction of physical activity beyond a sedentary level until resolution of symptoms and normalization of hsCRP for patients not involved in competitive sports. For athletes, a return to sports is recommended after an arbitrary term of 3 months and only after symptoms have fully resolved and hsCRP levels, ECG findings, and echocardiographic findings have normalized.[2]

The choice of a specific antiinflammatory regimen is based on concomitant therapies (e.g., favoring aspirin [ASA] if antiplatelet therapy is required), patient preferences, and the medical history (allergies, intolerances, proven efficacy).[2,5-7,21] Two alternative regimens with an excellent safety profile are recommended (**Table 83.4**): ibuprofen 600 to 800 mg orally three times daily, or ASA 750 to 1000 mg orally three times daily.[2] Gastric protection in the form of a proton pump inhibitor should be provided. Many patients have gratifying responses to the first few doses of an NSAID. Most respond fully after 10 to 14 days and need no additional treatment. As noted, using normalization of hsCRP to guide the duration of therapy is a reasonable alternative to a predetermined time course.[2,14] Once the patient is asymptomatic and the hsCRP has normalized, tapering rather than abrupt cessation of antiinflammatory drugs should be considered in an attempt to reduce recurrences (**see Table 83.4**).[2]

TABLE 83.4

Empirical Antiinflammatory Therapy for Acute Idiopathic Pericarditis

DRUG	USUAL DOSAGES	INITIAL DURATION	TAPERING*
Aspirin	750-1000 mg every 8h	1-2 weeks	Decrease doses every week for 2-3 weeks, then discontinue
Ibuprofen	600-800 mg every 8h	1-2 weeks	Decrease doses every week for 2-3 weeks, then discontinue
Colchicine	0.5-0.6 mg once (<70 kg) or 0.5-0.6 mg BID (≥70 kg)	3 months	Optional, over 2-3 weeks

*Therapy duration is individualized and guided by symptoms and hsCRP. Maintain initial dose and taper only if patient is asymptomatic and hsCRP is normalized.

Colchicine is recommended for 3 months as an adjunct to NSAIDs. Colchicine added to standard antiinflammatory therapy improves the response and reduces recurrences by approximately half during follow-up.[2,22-24] The drug is thought to exert an antiinflammatory effect by blocking microtubule assembly in WBCs. Weight-adjusted doses (0.5 to 0.6 mg orally every 12 hours or 0.5 to 0.6 mg once daily for patients < 70 kg) are recommended.[2,22]

Reliable patients with no more than small effusions who respond well to initial therapy need not be admitted to the hospital. Those who do not respond well initially, who have larger effusions, in whom a cause other than idiopathic pericarditis is suspected, or who meet any high-risk criteria (**see Fig. 83.3**) should be hospitalized for observation, diagnostic testing, and treatment.[2,5-7] In those who respond slowly to an NSAID and colchicine, analgesics may allow time for a more complete response. Initial use of the intravenous (IV) route of administration for NSAIDs can be considered to more quickly alleviate symptoms.[2,21]

Corticosteroid use should be minimized in patients with acute pericarditis because it may impair the clearance of infectious agents.[2,5-7] However, there are selected indications for corticosteroid use: (1) contraindications to or failure of an NSAID and colchicine, (2) underlying conditions (e.g., autoimmune diseases) whose primary treatment is corticosteroids, (3) concomitant diseases (e.g., renal failure), (4) pregnancy, and (5) concomitant therapies constituting relative contraindications to NSAIDs and/or colchicine (e.g., oral anticoagulants). Relatively low doses of corticosteroids are recommended (e.g., prednisone 0.2 to 0.5 mg/kg daily) to minimize complications.[2] Recent data on recurrence show that high doses of corticosteroids (e.g., prednisone 1.0 to 1.5 mg/kg/day) are associated with major side effects in about one quarter of patients, leading to drug withdrawal, more hospitalizations, and more recurrences.[2,25] Tapering should be gradual, typically over 6 to 12 weeks, and guided by the symptomatic response and hsCRP levels.[2,25] High-dose corticosteroids, especially with rapid tapering, appear to particularly increase recurrences. Concurrent colchicine should be administrated during corticosteroid therapy.

Complications of acute pericarditis include effusion, tamponade, and constriction. As noted earlier, small effusions are common. Relatively little is known about the incidence of more significant complications. In the largest modern report, a specific cause was identified in 17% of patients.[26] Over an average 31-month follow-up, tamponade developed in 3.1% and constriction in 1.5%. Most complications occurred in patients with identified specific causes. Constrictive pericarditis was addressed in more detail in a recent analysis of 500 patients.[17] Overall, constriction developed in 1.8% over a median 72-month follow-up. In the 83% of patients with idiopathic pericarditis, constriction developed in only 0.48%.[17] Thus, patients with idiopathic pericarditis can be reassured that the chance of developing constriction is exceedingly low.

Recurrent Pericarditis

Recurrences occur in 15% to 30% of patients with idiopathic acute pericarditis,[5-7,27,28] Recurrences are

the most common complication and may seriously affect the quality of life. They have never been associated with evolution to constrictive pericarditis. The risk of constriction is associated with the etiology, not the number of recurrences.[17] A diagnosis of recurrent pericarditis requires new symptoms and signs of disease activity (friction rub, ECG changes, new or worsening pericardial effusion, elevation of hsCRP) after a symptom-free interval of at least 4 to 6 weeks to allow completion of antiinflammatory therapy for a previous episode.[2,5-7] It is not unusual for patients to have recurrent pain without objective evidence of disease activity. These patients may respond to repeated treatment, but should not be classified as having a definite recurrence.

For recurrences we recommend therapy with an NSAID plus colchicine and a proton pump inhibitor at the same doses outlined for an initial episode. Therapy should be continued until complete resolution of symptoms, signs, and laboratory findings, including hsCRP if elevated. At this point the NSAID should be gradually tapered. If this therapy fails, corticosteroids may replace the NSAID or may be added as "triple therapy." As for an initial episode, doses of 0.2 to 0.5 mg/kg/day of prednisone or its equivalent are recommended for at least 2 to 4 weeks until symptoms and signs resolve and hsCRP normalizes, followed by gradual tapering every 2 to 4 weeks.[2] Colchicine in doses discussed earlier should always be included for at least 6 months. The duration of therapy may be prolonged to 12 months in more difficult cases.[2] For recurrence during corticosteroid tapering, we recommend maintaining the same dose if possible and controlling the recurrence by adding an NSAID, increasing the dosage of the NSAID, and/or starting colchicine if this has not been done. Some patients have recurrences that are mild and easily managed with reinstitution of an NSAID for a brief period of time. In our experience, these patients often do not have objective evidence of inflammation. There is no need to employ more intensive antiinflammatory regimens in these patients.

For patients with recurrences who are resistant to colchicine and corticosteroids (i.e., who cannot withdraw from corticosteroids and still have recurrences while taking colchicine), additional therapies are available.[2] All are off-label indications and supported by case reports and/or small series. These patients are relatively rare, representing no more than 5% to 10% of recurrent pericarditis cases.[29,30] Therapies include azathioprine (2 mg/kg/day orally for several months with gradual dose increases and monitoring of WBCs, transaminases, and amylases), which may allow discontinuation or reduction of corticosteroid doses,[2] human intravenous immunoglobulin (400 to 500 mg/kg/day for 5 days with a possible repeat course after 1 month),[31] or anakinra, an interleukin 1 antagonist (1 to 2 mg/kg/day up to 100 mg daily subcutaneously for several months).[32] The optimal duration of therapy for these treatments is not established. Their mechanisms of action (including colchicine) in recurrent pericarditis are summarized in **eFig. 83.2**. For physicians who do not ordinarily prescribe these drugs it is prudent to enlist the help of colleagues experienced in their use. As a last resort for cases refractory to all medical therapies, pericardiectomy may be considered.[2,29,33]

Pericardial Effusion and Cardiac Tamponade

Etiology

Virtually any disease that can cause pericarditis can cause an effusion (**see Table 83.1**).[1,2,8,34] Effusions are common early after cardiac surgery and orthotopic heart transplantation, but tamponade is unusual.[2] They usually resolve within several weeks to a few months. Various miscellaneous, noninflammatory diseases can cause effusion (**see Table 83.1**). Patients with severe circulatory congestion may have small to moderate transudative effusions. Bleeding into the pericardial sac occurs after blunt and penetrating

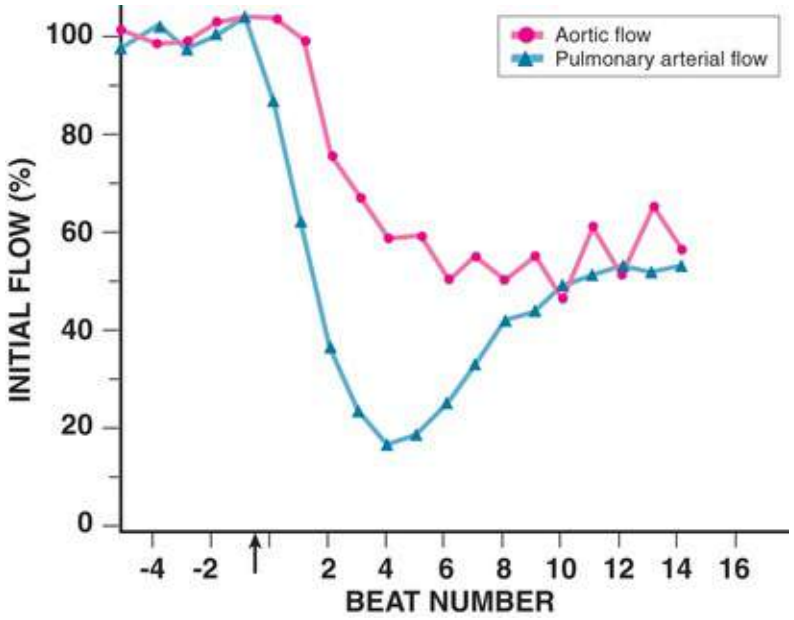
trauma, following post-MI rupture of the LV free wall, and, increasingly, as a complication of cardiac procedures. Retrograde bleeding is a major cause of death due to aortic dissection (**see Chapter 63**). Pericardial effusions are also common in patients with pulmonary hypertension.[35] Asymptomatic pericardial effusions are often discovered when a chest x-ray or echocardiogram is performed for unrelated indications. Last, otherwise healthy patients are occasionally encountered with large, asymptomatic pericardial effusions with no clear etiology.[2]

Those causes of effusion with a high incidence of progression to tamponade include bacterial, fungal, and HIV-associated infections (**see Chapter 82**); bleeding; and neoplastic involvement. Although large effusions due to acute idiopathic pericarditis are unusual, because this type of pericarditis is so common it accounts for a significant percentage of tamponade cases. About 20% of large, symptomatic effusions without an obvious etiology following routine evaluation constitute the initial presentation of a cancer.[2,8] Details of pericardial effusion pertinent to selected, specific disease entities are discussed in the sections at the end of this chapter.

Pathophysiology and Hemodynamics

Formation of an effusion is a generic response to inflammatory, infectious, or neoplastic diseases involving the pericardium. Lymphomas occasionally cause effusion in association with enlarged mediastinal lymph nodes by obstructing lymph drainage.[1] The pathophysiology of effusions when there is no obvious inflammation or bleeding (e.g., with uremia or idiopathic disease) is very poorly understood.

When an effusion accumulates, the pressure in the pericardial sac depends on the amount of fluid and the pericardial PVR.[1] The mechanical consequences of high pressure acting on the surface of the heart mainly result from compression and collapse of the right heart and caval vessels. Underfilling of the left heart then ensues from reduced right heart output. **eFig. 83.3** depicts an experiment illustrating these principles. Clinically, cardiac tamponade has a continuum from an effusion causing minimal effects to full-blown circulatory collapse. The most critical point occurs when an effusion reduces the diastolic volume of the cardiac chambers such that cardiac output declines. As discussed earlier, the limited pericardial reserve volume dictates that modest amounts of rapidly accumulating fluid (as little as 150 to 200 mL) can impair cardiac function. In contrast, large, slowly accumulating effusions are often well tolerated. The compensatory response to a hemodynamically significant effusion includes increased adrenergic tone and parasympathetic withdrawal. The resultant tachycardia and increased contractility maintain the cardiac output and blood pressure for a period of time.[1] Eventually, however, both decline. Patients who cannot mount a normal adrenergic response (e.g., those receiving beta blockers) are more susceptible to the effects of an effusion. In terminal tamponade, a depressor reflex with paradoxic bradycardia may supervene.



EFIGURE 83.3 Non–steady state responses to an abrupt increase in pericardial pressure provide insights into the pathophysiology of cardiac tamponade. The figure shows an experiment in a dog in which aortic and pulmonary arterial stroke volumes (SVs) were measured beat to beat before and after fluid was abruptly introduced into the pericardial sac (arrow). This causes an immediate decrease in pulmonary SV but no change in aortic SV. Two beats later aortic SV decreases and a new steady state is then achieved with equivalent decreases in aortic and pulmonary SV. During the time required to reach a new steady state, pulmonary SV is less than aortic SV. This transient inequality results in transfer of blood from the pulmonary into the systemic circulation and may explain the decrease in pulmonary vascularity on chest radiograph in tamponade. Thus, the primary, direct effect of increased pericardial pressure is to impede right heart filling, with effects on the left heart largely secondary to underfilling. (From Ditchey R, Engler R, LeWinter M, et al: The role of the right heart in acute cardiac tamponade in dogs. Circ Res 1981;48:701.)

As fluid accumulates, left- and right-sided atrial and ventricular diastolic pressures rise, and in severe tamponade they equalize at a pressure similar to that in the pericardial sac, typically 20 to 25 mm Hg (**Fig. 83.4**). Equalization is closest during inspiration. Thus, the pericardial pressure dictates intracavitary pressure and *transmural* filling pressures of the cardiac chambers are near zero. Correspondingly, cardiac volumes progressively decline. The small end-diastolic ventricular volume (decreased preload) mainly accounts for the reduced stroke volume (SV). Because of compensatory increases in contractility, the end-systolic volume also decreases, but not enough to maintain the SV. Because the right heart filling pressure is normally lower than the left heart filling pressure, as fluid accumulates pressures increase more rapidly in the right heart than the left heart.

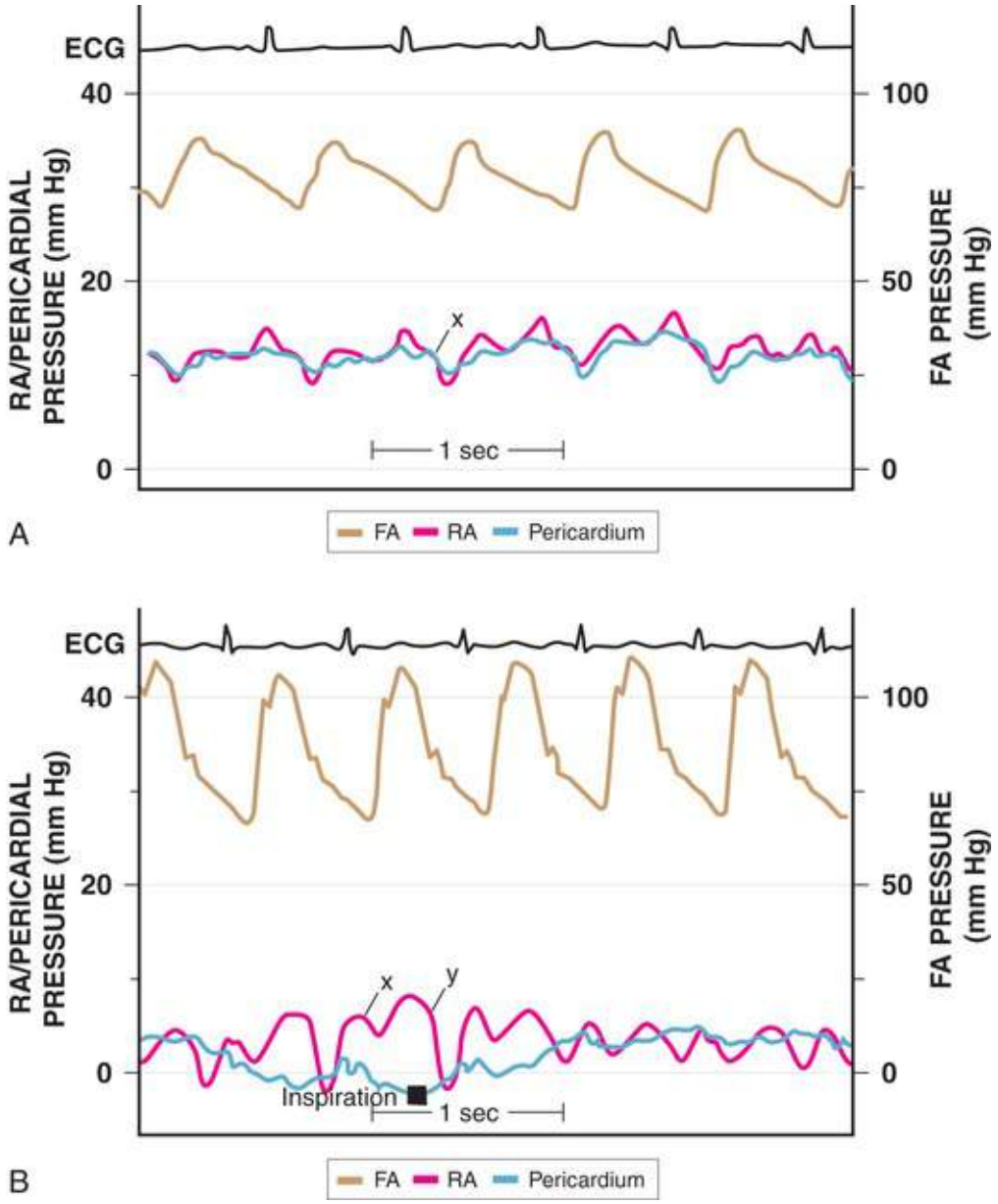


FIGURE 83.4 Femoral arterial (FA), right atrial (RA), and pericardial pressure before **(top)** and after **(bottom)** pericardiocentesis in a patient with cardiac tamponade. Both RA and pericardial pressure are about 15 mm Hg before pericardiocentesis. In this case there was a negligible paradoxic pulse. Note presence of x descent but absence of y descent before pericardiocentesis. Pericardiocentesis results in marked increase in FA pressure and marked decrease in RA pressure. During inspiration, pericardial pressure becomes negative, there is clear separation between RA and pericardial pressure, and y descent is now evident and prominent, suggesting the possibility of an effusive-constrictive picture.
(Modified from Lorell BH, Grossman W: Profiles in constrictive pericarditis, restrictive cardiomyopathy and cardiac tamponade. In Baim DS, Grossman W [editors]: Grossman's cardiac catheterization, angiography, and intervention. Philadelphia, Lippincott Williams & Wilkins, 2000, p 840.)

In addition to elevated and equal intracavitary filling pressures, low transmural filling pressures, and small cardiac volumes, two other hemodynamic abnormalities are characteristic of tamponade. One is loss of the y descent of the RA or systemic venous pressure wave (**see Fig. 83.4**). The x and y *descents* correspond to periods when venous inflow is increasing. Loss of the y descent has been explained based on the concept that the total heart volume is fixed in severe tamponade.[1] Thus, blood can enter the heart only when blood is simultaneously leaving. The normal y descent begins when the tricuspid valve opens (i.e., when blood is not leaving). In tamponade, inflow cannot increase and the descent is lost. The x descent occurs during ventricular ejection. Because blood is leaving the heart, inflow can increase and the x descent is retained. Loss of the y descent is appreciated in systemic venous or RA pressure recordings and is a useful clue to the presence of tamponade. Although absence of the y descent and loss

of diastolic venous inflow have been considered classic signs, in many cases of tamponade in the modern era pulsed-wave Doppler recordings do reveal venous inflow into the right heart during ventricular diastole.[1,3,4,36] These patients can have effusive-constrictive pericarditis, with a mixed hemodynamic picture.

The second characteristic finding is the paradoxic pulse (**Fig. 83.5**), an abnormally large decline in systemic arterial pressure during inspiration (defined as a drop of > 10 mm Hg in systolic pressure). Other causes of *pulsus paradoxus* include constrictive pericarditis, pulmonary embolus, and pulmonary disease with large variations in intrathoracic pressure. In severe tamponade, the arterial pulse may be impalpable during inspiration. The mechanism of the paradoxic pulse is multifactorial, but respiratory changes in systemic venous return are certainly important.[1] In tamponade, in contrast to constriction, the normal inspiratory *increase* in systemic venous return is present and the normal inspiratory *decline* in systemic venous pressure is retained (Kussmaul sign is *absent*). The increase in right heart filling occurs, once again, under conditions where total heart volume is fixed and left heart volume markedly reduced. The interventricular septum shifts to the left in exaggerated fashion on inspiration, encroaching on the left ventricle such that the SV and pressure generation are further reduced (**see Fig. 83.5**). This is termed *exaggerated ventricular interaction* (in distinction from the previous definition of ventricular interaction).[3,4] Although the inspiratory increase in right heart volume (preload) increases the RV SV, a few cardiac cycles are required to increase the LV filling and SV and counteract the septal shift. Other factors that may contribute include increased afterload caused by transmission of negative intrathoracic pressure to the aorta and traction on the pericardium caused by descent of the diaphragm. Associated with these mechanisms, left and right heart pressure and stroke volume variations are exaggerated and 180 degrees out of phase (**see Fig. 83.5**). **Table 83.5** lists the hemodynamic findings in tamponade compared with constrictive pericarditis. When there are preexisting elevations in diastolic pressures and/or volume, tamponade can occur without a paradoxic pulse.[1] Examples include chronic LV dysfunction, aortic regurgitation, and atrial septal defect. In patients with retrograde bleeding into the pericardial sac due to aortic dissection, tamponade may occur without a paradoxic pulse because of aortic valve disruption and regurgitation.

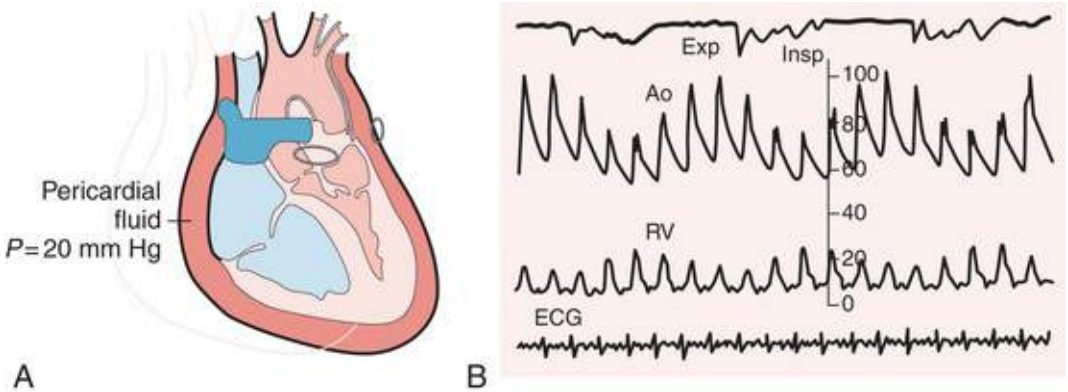


FIGURE 83.5 **Left,** schematic illustration of leftward septal shift with encroachment of left ventricular volume during inspiration in cardiac tamponade. **Right,** respiration marker and aortic and right ventricular pressure tracings in cardiac tamponade. Note paradoxic pulse and marked respiratory variation that is out of phase by 180 degrees in right- and left-sided pressures. (From Shabetai R: The pericardium. New York, Grune & Stratton, 1981, p 266.)

TABLE 83.5

Hemodynamics in Cardiac Tamponade and Constrictive Pericarditis

	TAMPONADE	CONSTRICTION
Paradoxic pulse	Usually present	Present in ~1/3
Equal left/right filling pressures	Present	Present
Systemic venous wave morphology	Absent y descent	Prominent y descent (M or W shape)
Inspiratory change in systemic venous pressure	Decrease (normal)	Increase or no change (Kussmaul sign)
Square root sign in ventricular pressure	Absent	Present

Although mean left- and right-sided filling pressures are typically 20 to 25 mm Hg, tamponade can occur at lower filling pressures, termed *low-pressure tamponade*.[1,2,37] Low-pressure tamponade often occurs when there is a decrease in blood volume in the setting of a preexisting effusion that would not otherwise cause hemodynamic consequences. A modestly elevated pericardial pressure can then lower the transmural filling pressure to levels where the SV is compromised. Because venous pressure is only modestly elevated or even normal, the diagnosis may be missed. Low-pressure tamponade may be observed during hemodialysis, in patients with blood loss and volume depletion, and when diuretics are administered to patients with effusions. In the only sizeable report, about 20% of patients undergoing closed pericardiocentesis met the criteria for low-pressure tamponade.[37] Compared with high-pressure tamponade, low-pressure patients were less often critically ill and signs of tamponade were less prominent. Echocardiographic findings were similar and benefit was derived from pericardiocentesis.

Pericardial effusions can be loculated or localized, resulting in regional tamponade, most commonly after cardiac surgery.[1,2] Although reports are scarce, regional tamponade can cause atypical hemodynamic findings (e.g., reduced cardiac output with unilateral filling pressure elevation). Regional tamponade should be considered whenever there is hypotension in a setting where a loculated effusion is present or suspected. Rarely, large pleural effusions and pneumopericardium can compress the heart and cause tamponade.[1,2,38]

Clinical Presentation

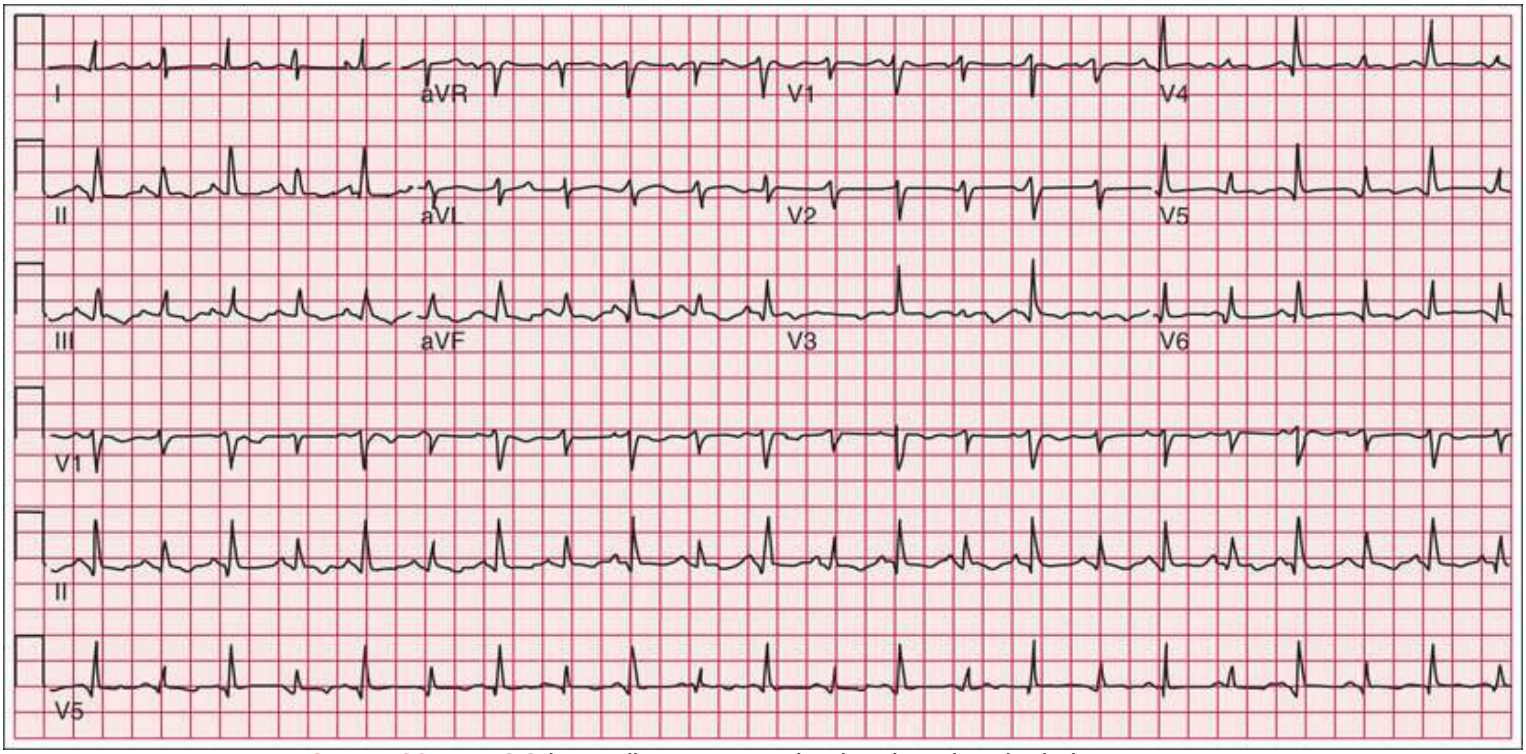
A history pertinent to a specific pericardial disease etiology may be elicited. As noted earlier, asymptomatic effusions may be discovered in otherwise healthy patients when chest imaging is performed for an unrelated reason.[2] Specific etiologies are rarely found in these cases. Effusions do not cause symptoms in and of themselves without tamponade, although patients may have pain due to pericarditis. Patients with tamponade may complain of dyspnea, the mechanism of which is uncertain because there is no pulmonary congestion, and they are more comfortable sitting forward. Other symptoms reflect the severity of cardiac output and blood pressure reduction.

A complete physical examination in patients with pericardial effusion can provide clues to a specific cause. In pericardial effusion without tamponade, the cardiovascular examination is normal unless the effusion is large, the cardiac impulse is difficult to palpate, and the heart sounds are muffled. A friction rub may of course be present. Tubular breath sounds may be heard in the left axilla or base due to bronchial compression. The presence of *Beck's triad* of hypotension, muffled heart sounds, and elevated jugular venous pressure suggests severe tamponade. Patients with tamponade appear uncomfortable and display varying signs of reduced cardiac output and shock, including tachypnea, diaphoresis, cool extremities, peripheral cyanosis, depressed sensorium, and, rarely, yawning.[1,2] Hypotension is usually present, although in early stages compensatory mechanisms maintain the blood pressure. Some patients with subacute tamponade are *hypertensive* on presentation, with a decline in blood pressure following

pericardial drainage.[39] A paradoxic pulse is the rule, but it is important to be alert to situations where it may be absent. The paradox is quantified by cuff sphygmomanometry as the difference between the pressure at which Korotkoff sounds first appear and that at which they are present with each contraction. Tachycardia is also the rule unless heart rate–lowering drugs have been administered, conduction system disease coexists, or a preterminal bradycardic reflex has supervened. The jugular venous pressure is markedly elevated except in low-pressure tamponade, and the y descent is usually absent (**see Fig. 83.4**). The normal decrease in venous pressure on inspiration is retained. Examination of the heart itself is consistent with an effusion, as outlined above. Tamponade can be confused with anything that causes hypotension, shock, and elevated jugular venous pressure, including decompensated heart failure, pulmonary embolus or other causes of pulmonary hypertension, and RV MI.

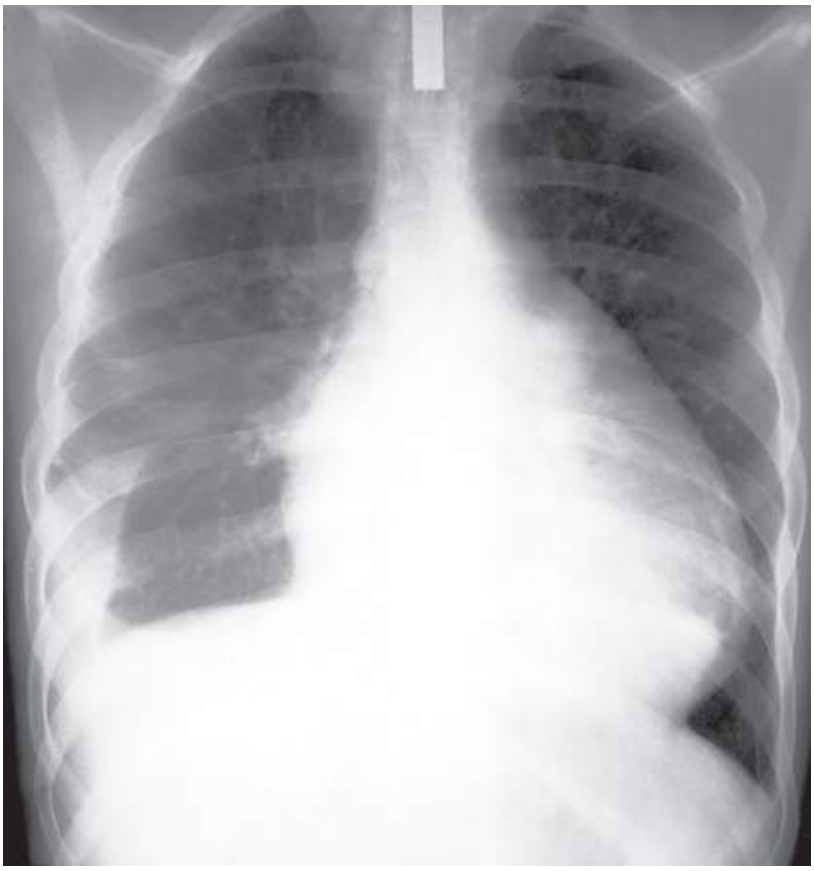
Laboratory Testing

ECG abnormalities include reduced voltage and electrical alternans (**eFig. 83.4**).[1,2] Reduced voltage is nonspecific and can be caused by conditions such as emphysema, infiltrative myocardial disease, and pneumothorax. Electrical alternans is specific but relatively insensitive and caused by anteroposterior swinging of the heart with each contraction. When pericarditis coexists, the usual ECG findings may be present.



EFIGURE 83.4 ECG in cardiac tamponade showing electrical alternans.

The chest radiograph reveals a normal cardiac silhouette until effusions are at least moderate in size. With larger effusions the anteroposterior cardiac silhouette assumes a rounded, flask-like appearance (**eFig. 83.5**). Lateral views may reveal the fat pad sign, a linear lucency between the chest wall and anterior surface of the heart resulting from separation of parietal pericardial fat from epicardium. The lungs are oligemic.



EFIGURE 83.5 Anteroposterior chest radiograph in a patient with a large pericardial effusion (see text). (From Kabbani SS, LeWinter M: Cardiac constriction and restriction. In Crawford MH, DiMarco JP [editors]: Cardiology. St. Louis, Mosby, 2001, p 5,15.5.)

M-mode and two-dimensional Doppler echocardiography are the standard noninvasive methods for detection of pericardial effusion and tamponade.[3,4] A significant effusion appears as a lucent separation between the parietal and visceral pericardium for the entire cardiac cycle (**Fig. 83.6** and Video 83.1). Small effusions are usually first evident over the posterobasal left ventricle. Fluid then spreads anteriorly, laterally, and behind the left atrium, where it is limited by the visceral pericardial reflection. Ultimately, the separation becomes circumferential. Circumferential effusions are graded as small (echo-free space in diastole < 10 mm), moderate (10 to 20 mm), or large (> 20 mm).[3,4] Because the rapidity of accumulation is critical, the hemodynamic significance of an effusion may not be closely correlated with its size. However, it is unusual for tamponade to occur without a circumferential effusion. Frond-like or shaggy-appearing structures in the pericardial space detected by echocardiography suggest clots, chronic inflammation, or neoplastic pericardial processes. As discussed below, CT and MRI are more precise than transthoracic echocardiography for estimating pericardial thickness. *Transesophageal echocardiography* (TEE), however, is comparable to CT and MRI for this purpose.[3,4]

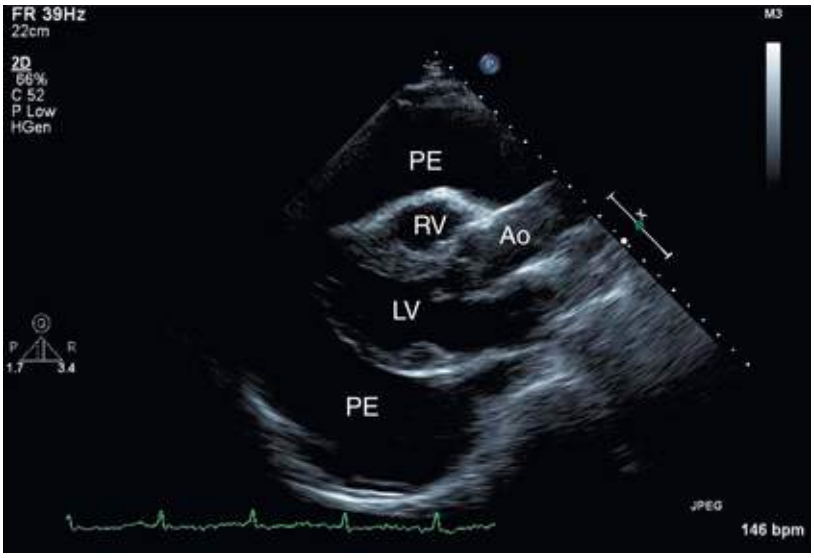


FIGURE 83.6 Two-dimensional echocardiogram of a large, circumferential pericardial effusion (PE). *Ao*, aorta; *LV*, left ventricle; *RV*, right ventricle. (From Kabbani SS, LeWinter M: Cardiac constriction and restriction. In Crawford MH, DiMarco JP [editors]: Cardiology. St. Louis, Mosby, 2001.)

Several echocardiographic findings indicate that tamponade is severe enough to cause hemodynamic compromise.[3,4,36] These include early diastolic collapse of the right ventricle, late diastolic indentation or collapse of the right atrium, and exaggerated respiratory variation in RV and LV size and interventricular septal shifting during inspiration causing a bulge or "bounce." Early diastolic RV collapse (**Fig. 83.7** and see Video 83.1) and late diastolic RA collapse (**eFig. 83.6** and see Video 83.1) are signs that usually first appear relatively early during tamponade, when pericardial pressure transiently exceeds intracavitary pressure.[3,4,36] Rarely, a large *pleural* effusion can cause right-sided chamber collapse, and isolated LV and LA chamber collapse can occur with pericardial hematomas after cardiac surgery.[3,4] The cardiac chambers are small in tamponade and, as noted, the heart may swing anteroposteriorly (see Video 83.1). Distention of the inferior vena cava that does not diminish with inspiration is an important confirmatory finding. Doppler velocity recordings demonstrate exaggerated respiratory variation in right- and left-sided venous and valvular flow, with inspiratory increases on the right and decreases on the left.[3,4,36] Caval inflow occurs largely during ventricular systole. These flow patterns are at least as sensitive for tamponade as M-mode and two-dimensional echocardiographic features.

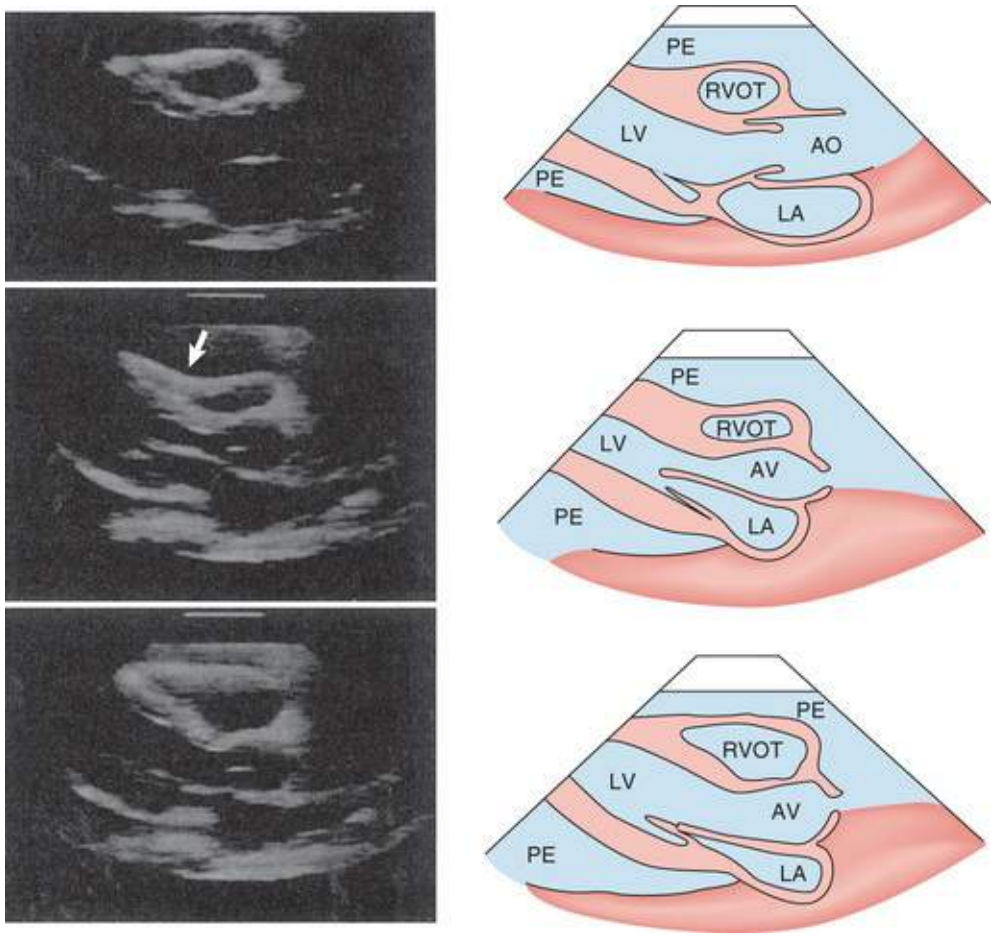
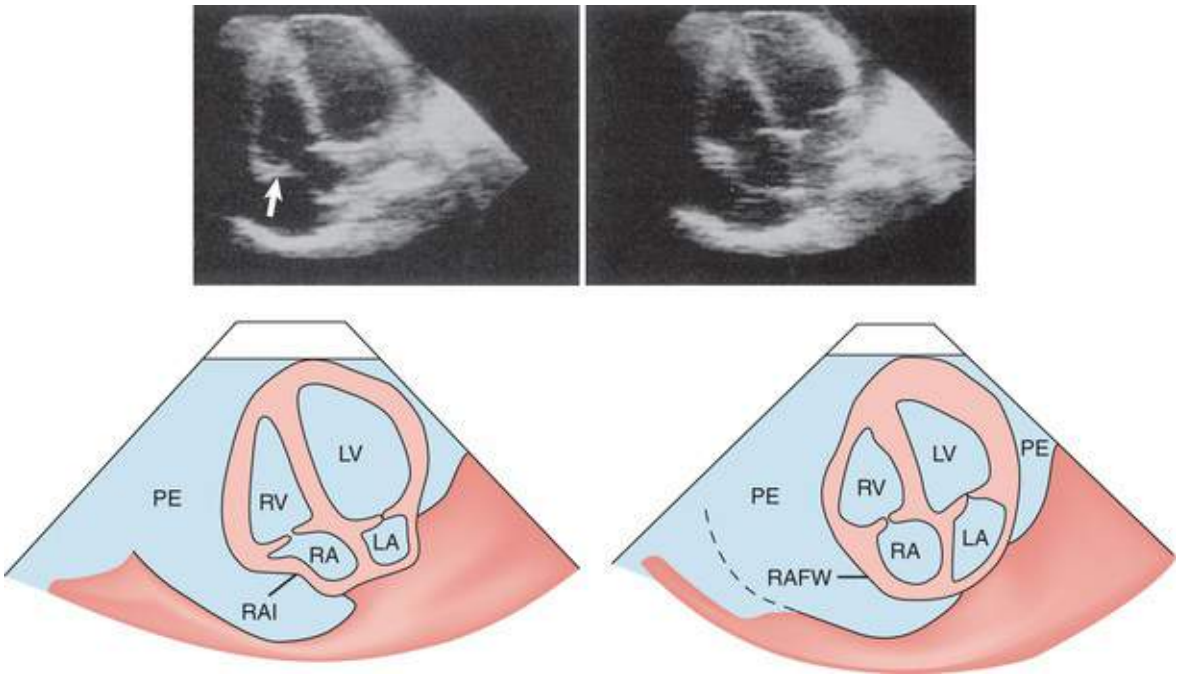


FIGURE 83.7 Two-dimensional echocardiogram illustrating diastolic collapse or indentation of the right ventricle in cardiac tamponade. **Top,** systole; **middle,** early diastole with indentation indicated by *arrow*; **bottom,** late diastole with return of normal configuration. *AV*, aortic valve; *LA*, left atrium; *LV*, left ventricle; *PE*, pericardial effusion; *RVOT*, right ventricular outflow tract. (From Weyman AE: Principles and practice of echocardiography. Philadelphia, Lea & Febiger, 1994, p 1119.)



EFIGURE 83.6 Two-dimensional echocardiogram illustrating right atrial collapse or indentation in cardiac tamponade. (From Gilliam LD: Hemodynamic compression of the right atrium: a new echocardiographic sign of cardiac tamponade. Circulation 1983;68:294.)

With most effusions, transthoracic echocardiography provides sufficient diagnostic information to make management decisions. TEE studies provide better-quality images, but are usually impractical in sick patients unless they are intubated. Fluoroscopy is useful in the cardiac catheterization laboratory for detection of procedure-related effusions when they cause damping or abolition of cardiac pulsation. CT (**see Chapter 18**) and MRI (**see Chapter 17**) are useful adjuncts to echocardiography in the characterization of effusion and tamponade, but neither is ordinarily required and/or advisable in sick patients who require urgent management and treatment decisions.[40,41] They have a role when hemodynamics are atypical, other conditions complicate interpretation, the severity of tamponade is uncertain, or echocardiography is technically inadequate. Video 83.2 is a magnetic resonance cine image of a large, circumferential effusion and a small, underfilled left ventricle. The right ventricle is not compressed because of long-standing pulmonary hypertension, evidenced by RV enlargement. Here, coexistent pulmonary hypertension reduces the accuracy of echocardiographic signs of tamponade.

CT and MRI provide more detailed quantitation and regional localization of effusions than echocardiography and are useful with loculated effusions and coexistent pleural effusions. In Video 83.3 , the wide field of view afforded by MRI demonstrates both a large pericardial effusion and a pleural effusion in a patient with polyserositis. Pericardial thickness can be measured with both methods, allowing indirect assessment of the severity and chronicity of inflammation; as discussed earlier, MRI with gadolinium directly identifies inflammation. Clues to the nature of pericardial fluid can be gained from CT attenuation coefficients.[3,4] Attenuation similar to water suggests a transudative effusion; attenuation denser than water, a malignant effusion or bloody or purulent fluid; and attenuation less dense than water, a chylous effusion. Malignant effusions are associated with a thicker pericardium than benign effusions.[40] A thickness of more than 4.1 mm on CT points to metastatic involvement. Finally, cine CT or MRI provides information similar to echocardiography for the assessment of tamponade (e.g., septal shifting, chamber collapse).

Management

Management is dictated first and foremost by whether tamponade is already present or has a high chance of developing (**Table 83.6**).[1,2,41] Situations where tamponade is a near term threat include suspected bacterial (including tuberculous) pericarditis, hemopericardium, and any moderate to large effusion that is not thought to be chronic and/or is increasing in size. When tamponade is present or threatened, decision making requires urgency and a low threshold for pericardiocentesis (**see Table 83.6**). *In the absence of actual or threatened tamponade,* management can be more deliberative. This includes several categories of patients. Some have acute pericarditis with a small to moderate effusion detected as part of routine evaluation. Others do not have symptoms or signs of pericarditis or effusion but undergo echocardiography because of the presence of diseases known to involve the pericardium. The rest are asymptomatic and have effusions detected when tests are performed for reasons other than suspected pericardial disease (e.g., evaluation of an enlarged cardiac silhouette or investigation of thoracic pathology).

TABLE 83.6

Initial Approach to the Patient with Pericardial Effusion

1. Determine if tamponade is present or threatened based on history, physical examination, echocardiogram.
2. If tamponade is not present or threatened: If etiology is not apparent, consider diagnostic tests as for acute pericarditis. If effusion is large, consider a course of an NSAID plus colchicine or corticosteroid; if no response, consider closed pericardiocentesis.
3. If tamponade is present or threatened: Urgent or emergent closed pericardiocentesis or careful monitoring if trial of medical treatment to reduce effusion is considered appropriate.

In many cases of effusion where tamponade is neither present nor threatened, a cause will be evident or suggested based on the history and/or previous diagnostic tests. When a diagnosis is not clear, an assessment of specific causes should be undertaken, including the diagnostic tests recommended for acute pericarditis and anything else dictated by the clinical picture (e.g., screening for neoplastic or autoimmune diseases, infections, and hypothyroidism). Careful judgement should be exercised in testing. Thus, a patient with severe heart failure and circulatory congestion with a small effusion does not need such testing, but patients with evidence of a systemic disease deserve very careful attention.

In patients without actual or imminent tamponade, pericardiocentesis (closed or open with biopsy) can be undertaken for diagnostic purposes but is not always required. As discussed above, in many cases a diagnosis will either be obvious when the effusion is first noted or become evident as part of the initial investigations. Moreover, in this setting routine analysis of pericardial fluid has a low diagnostic yield.[2,8,41] In situations where pericardiocentesis is felt to be necessary for diagnostic purposes, consideration should be given to open drainage with biopsy.

Otherwise healthy patients with large, asymptomatic effusions and no evidence of tamponade or a specific cause are a special category.[2,41] The effusions are by definition chronic and in general stable, but a minority (perhaps 20% to 30%) develop tamponade unpredictably. Moreover, after closed pericardiocentesis the effusions may not reaccumulate.[2,41] Thus, there is a rationale for pericardiocentesis following routine evaluation for specific etiologies as outlined above. Before undertaking pericardiocentesis, a course of an NSAID or corticosteroids combined with colchicine may be considered, because this has a low risk. In the absence of evidence of inflammation (e.g., increased CRP, gadolinium uptake on MRI), however, antiinflammatory regimens are not likely to be efficacious. Recurrence of this type of effusion after closed pericardiocentesis is considered an indication for pericardiectomy or a pericardial window.[2,41]

Patients with actual or threatened tamponade constitute a medical emergency. With the exception of those who do not wish prolongation of life (mainly those with metastatic cancer), hospital admission and careful hemodynamic and echocardiographic monitoring are mandatory. The great majority of patients require pericardiocentesis to treat or prevent tamponade, but there are some exceptions. Patients with acute, apparently idiopathic pericarditis with no more than mild tamponade can be treated for a brief period of time under careful monitoring with an NSAID and/or prednisone combined with colchicine in an attempt to rapidly shrink the effusion. Patients with known inflammatory/autoimmune diseases can be treated similarly (there is no evidence that corticosteroids increase recurrence in these patients). Patients with *suspected* bacterial infections or hemopericardium *with small effusions (< 10 mm)* should be considered to have threatened tamponade because of the cause. These patients may be suitable for initial conservative management and careful monitoring because the risk of closed pericardiocentesis is increased with smaller effusions.

Hemodynamic monitoring with a central venous or pulmonary artery catheter is often useful, especially in patients with threatened or mild tamponade in whom a decision is made to defer pericardiocentesis.

Monitoring is also helpful *after* pericardiocentesis to assess reaccumulation and the presence of underlying constriction (**see Fig. 83.4**), as discussed subsequently. Insertion of a catheter in the central circulation should not be allowed to delay definitive therapy in critically ill patients.

For the majority of patients in this category, urgent or emergent pericardiocentesis is indicated. Once actual or threatened tamponade is diagnosed, IV hydration with normal saline should be instituted.[2,41,42] Positive inotropes are of little value. Volume expansion and positive inotropes are temporizing measures and should not be allowed to substitute for or delay pericardiocentesis. In the vast majority of cases, *closed pericardiocentesis* is the treatment of choice. Before proceeding, it is important to be sure that there is indeed an effusion large enough to cause tamponade that is amenable to a closed approach, especially if the hemodynamic findings are atypical. Loculated effusions or effusions containing clots or fibrinous material increase the risk and difficulty of closed pericardiocentesis. An open approach should be considered for safety and to obtain pericardial tissue and create a window.

Whether to perform closed versus open pericardiocentesis in patients with hemopericardium can be a difficult decision.[2,41] The danger of a closed approach is that lowering intrapericardial pressure will allow more bleeding without affording an opportunity to correct its source. In cases of trauma or post-MI LV rupture, closed pericardiocentesis should usually be avoided. If bleeding is slower (e.g., due to a procedural coronary perforation or puncture of a cardiac chamber), closed pericardiocentesis is often indicated because bleeding may stop spontaneously and/or the procedure can provide temporary relief before definitive repair. Closed pericardiocentesis in patients with hemopericardium due to type A aortic dissection has been considered relatively contraindicated. However, in a small series of patients, preoperative pericardiocentesis using intermittent cycles of drainage dictated by systolic blood pressure levels appeared to be safe and effective for stabilization.[43]

The most common approach to closed pericardiocentesis is subxiphoid needle insertion with echocardiographic guidance to minimize the risk of myocardial puncture and assess the completeness of fluid removal.[2] Once the needle has entered the pericardial space, a modest amount of fluid is immediately removed (perhaps 50 to 100 mL) in an effort to produce rapid improvement. A guidewire is then inserted and the needle replaced with a pigtail catheter. The catheter is manipulated to maximize fluid removal. When possible, the procedure should be performed in the cardiac catheterization laboratory with experienced personnel in attendance. If echocardiographic guidance is unavailable, the needle should be directed toward the left shoulder. Echocardiographically guided pericardiocentesis has a success rate of more than 95% and a rate of serious complications of less than 2%.[44,45] Rarely, patients suffer *pericardial decompression syndrome* following either closed or open drainage.[46] This is a poorly understood but life-threatening syndrome characterized by combinations of cardiogenic pulmonary edema and shock.

If a pulmonary artery catheter has been inserted, the RA and pulmonary capillary wedge pressure and cardiac output should be monitored before, during, and after the procedure. Ideally, the pericardial fluid pressure should also be measured. Hemodynamic monitoring is useful for several reasons. Initial measurements confirm and document the severity of tamponade. Measurements after completion establish a baseline to assess reaccumulation. As discussed below, some patients with tamponade have coexisting constriction (i.e., effusive-constrictive pericarditis), which is difficult to detect when an effusion dominates but becomes apparent after pericardiocentesis.[47] Following pericardiocentesis, repeat echocardiography and in many cases continued hemodynamic monitoring should be employed to assess reaccumulation. Intrapericardial catheters should be left in place for several days to allow continued drainage. This minimizes recurrence and facilitates the delivery of intrapericardial drugs if appropriate.[2,48,49]

Open pericardiocentesis is occasionally preferred for the initial removal of fluid. Bleeding due to trauma and rupture of the LV free wall have been mentioned previously in this regard. Loculated effusions and/or effusions that are borderline in size are drained more safely in the operating room. Recurring effusions, especially those causing tamponade, can initially be drained using a closed approach because of logistical considerations. However, open pericardiocentesis with biopsy and creation of a pericardial window are preferred for recurrences severe enough to cause tamponade.[2]

Percutaneous balloon pericardiotomy and pericardioscopy have been employed to drain fluid, create pericardial windows, and perform pericardial biopsy.[50,51] Balloon pericardiotomy may be particularly useful for malignant effusions and other situations where recurrence is common and a definitive approach without a surgical procedure is desirable. These methods appear safe and effective, but experience is limited and confined to centers with a special interest in pericardial disease.

Analysis of Pericardial Fluid

Normal pericardial fluid has the features of a plasma ultrafiltrate.[1] Lymphocytes are the predominant cell type. Although routine analysis of fluid does not have a very high yield for disease etiology, analysis is rewarding with bacterial infections and malignant effusions. Measurements should include WBCs and differential, hematocrit, and protein content.[2] Although most effusions are exudates, detection of a transudate reduces diagnostic possibilities. Sanguineous fluid is nonspecific and does not necessarily indicate active bleeding. Chylous effusions can occur after traumatic or surgical injury to the thoracic duct or obstruction by neoplasms. Cholesterol-rich (“gold paint”) effusions occur in hypothyroidism. Pericardial fluid should routinely be stained and cultured for bacteria, including *Mycobacterium tuberculosis*, and fungi and as much fluid as possible submitted for detection of malignant cells.

In suspected tuberculous pericardial disease, several other tests are useful. including unstimulated interferon-gamma (uIFN-γ), adenosine deaminase (ADA), lysozyme levels, and the polymerase chain reaction (PCR).[1,2,8,18] If there is a suspicion of tuberculous pericarditis, at least one of these tests should be routine because of the difficulty in diagnosing this disorder and delays in making a diagnosis by culture.

New and novel approaches for the analysis of pericardial fluid have been the subject of active investigation. As discussed below, there may be a role for measurement of tumor markers as a screen for malignant effusion.[2,52] Selected cytokine and related biomarkers measured in both pericardial fluid and serum have shown promise in distinguishing various types of inflammatory effusions, but their precise roles have not been elucidated.[53,54] Identification of genomic material by PCR may be helpful in identifying a viral etiology in patients with effusions of uncertain etiology.[55]

Pericardioscopy and Percutaneous Biopsy

Pericardioscopic-guided drainage of pericardial effusions was discussed earlier. When standard noninvasive methods of evaluating the cause of pericardial effusions are unsuccessful, extended pericardioscopically guided biopsies combined with a battery of immunologic and molecular methods applied to both fluid and tissue (e.g., PCR) have been advocated to improve the diagnostic yield and management.[50] This is a promising approach that appears safe in experienced hands. However, experience is limited and it is not known whether such an approach will in fact improve long-term outcomes.

Constrictive Pericarditis

Etiology

Constrictive pericarditis is the end stage of an inflammatory process involving the pericardium. Most diseases listed in **Table 83.1** can cause constriction. In the developed world the disorder is most commonly idiopathic or due to surgical complications or radiation injury.[1,2,56,57] TB was a very common cause before the advent of effective drug therapy and remains important in developing countries.[58] Constriction can follow an initial insult by as little as several months and occasionally less, but typically takes years to develop. The end result is fibrosis, often calcification, and adhesions of the parietal and visceral pericardium. Scarring is usually more or less symmetric and impedes filling of all heart chambers. Most patients have a thickened pericardium, but 18% are reported to have normal thickness on direct histopathologic examination and 28% on CT scanning.[2-4] In a subset of patients, constriction is transient and/or reversible by antiinflammatory drugs. This is observed early after cardiac surgery and in other patients with intense pericardial inflammation (discussed below).[1,59-62]

Pathophysiology

The consequence of pericardial scarring is markedly restricted filling of the heart.[1,2] This results in elevated and equal filling pressures in all chambers and systemic and pulmonary veins. In early diastole the ventricles fill rapidly because of markedly elevated atrial pressures and accentuated early diastolic ventricular suction related to small end-systolic volumes. During early to mid-diastole, ventricular filling abruptly ceases when the cardiac volume reaches the limit set by the pericardium. Thus, almost all filling occurs early in diastole. Systemic venous congestion results in hepatic congestion, peripheral edema, ascites, anasarca, and cardiac cirrhosis. Reduced cardiac output also results from impaired filling and causes fatigue, muscle wasting, and weight loss. In “pure” constriction, ventricular contractile function is preserved, although the EF can be reduced because of a small end-diastolic volume. The myocardium is occasionally involved in inflammation and fibrosis, leading to contractile dysfunction, which predicts a poor result after pericardiectomy.[63]

Failure of transmission of intrathoracic respiratory pressure changes to the cardiac chambers through the thickened pericardium is an important contributor to the pathophysiology of constrictive pericarditis (**Fig. 83.8**). On inspiration, the drop in intrathoracic pressure is transmitted to the pulmonary veins but not the left heart.[1] Consequently, the small pulmonary venous to LA pressure gradient that normally drives left heart filling is reduced, resulting in decreased transmitral inflow. The inspiratory decrease in LV filling allows an increase in RV filling and a leftward interventricular septal shift. The opposite occurs with expiration. As in tamponade, these changes result in exaggerated respiratory variation in mitral and tricuspid inflow and LV and RV systolic and diastolic pressure and volumes. High systemic venous pressure and reduced cardiac output induce retention of sodium and water by the kidneys. Inhibition of natriuretic peptides may exacerbate increased filling pressures.[64]

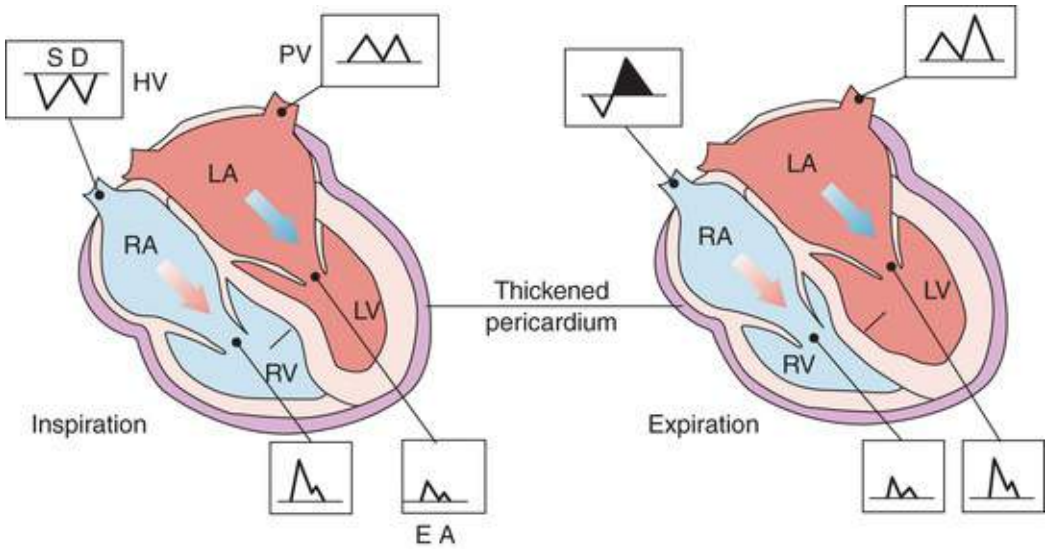


FIGURE 83.8 Schematic representation of transvalvular and central venous flow velocities in constrictive pericarditis. During inspiration the decrease in left ventricular filling results in a leftward septal shift, allowing augmented flow into the right ventricle. The opposite occurs during expiration. *D*, diastole; *EA*, mitral inflow; *HV*, hepatic vein; *LA*, left atrium; *LV*, left ventricle; *PV*, pulmonary venous flow; *RA*, right atrium; *RV*, right ventricle; *S*, systole.

Clinical Presentation

The usual presentation consists of signs and symptoms of right heart failure, including lower extremity edema, vague abdominal complaints, and passive hepatic congestion. With progression, hepatic congestion worsens and can progress to ascites, anasarca, and jaundice due to cardiac cirrhosis. Signs and symptoms of left heart failure, dyspnea, cough, and orthopnea may also appear. Atrial fibrillation and tricuspid regurgitation, which further exacerbate venous pressure elevation, are common at this stage. At the end stage, effects of a chronically low cardiac output are prominent, including fatigue, muscle wasting, and cachexia. Other findings include recurrent pleural effusions and syncope. Constrictive pericarditis can be mistaken for any cause of right heart failure, as well as end-stage liver disease.

Physical Examination

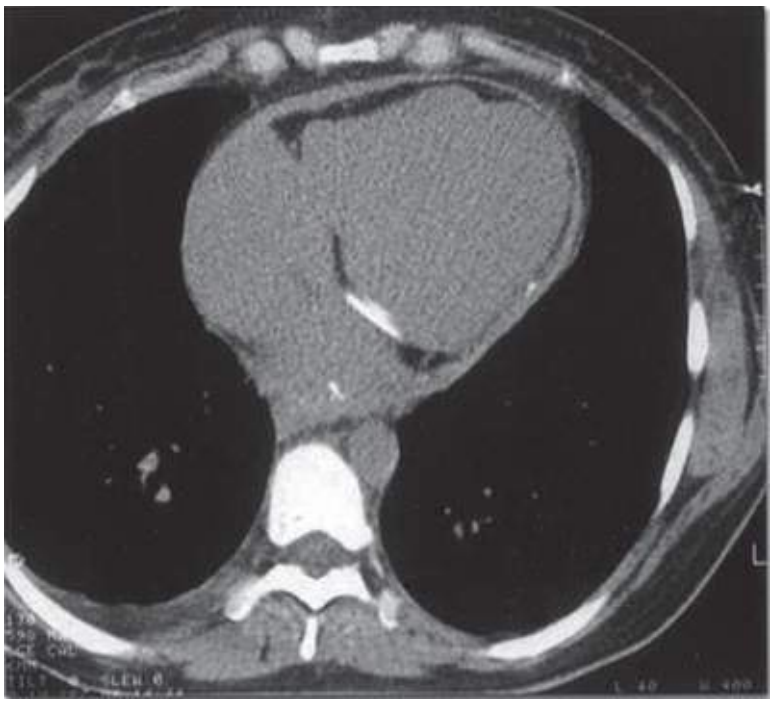
Physical findings include markedly elevated jugular venous pressure with a prominent, rapidly collapsing y descent. This, combined with a normal x descent, results in an M- or W-shaped venous pressure contour. In patients with atrial fibrillation, the x descent is lost, leaving only the prominent y descent. The latter can be difficult to distinguish from tricuspid regurgitation, which, as noted above, may also be present. The *Kussmaul sign*, an inspiratory increase in mean venous pressure, is usually present,[1] or the pressure may simply fail to decrease on inspiration. The Kussmaul sign reflects loss of the normal increase in right heart venous return on inspiration, even though tricuspid flow increases. These venous pressure abnormalities contrast with tamponade, where the y descent is lost. A paradoxic pulse occurs in perhaps one third of patients, especially with an effusive-constrictive picture. It is probably best explained by the aforementioned lack of transmission of decreased intrathoracic pressure to the left heart. **Table 83.5** reviews hemodynamic findings in tamponade versus constriction.

The most notable cardiac physical finding is the pericardial knock, an early diastolic sound best heard at the left sternal border and/or the cardiac apex. It occurs slightly earlier and has a higher frequency content than a third heart sound and corresponds to early, abrupt cessation of ventricular filling. Widening of second sound splitting may also be present, as well as a tricuspid regurgitant murmur. Abdominal

examination reveals hepatomegaly, often with palpable venous pulsations, with or without ascites. Other signs of hepatic congestion/cirrhosis include jaundice, spider angiomas, and palmar erythema. Lower extremity edema is the rule. Muscle wasting, cachexia, and massive ascites and anasarca occur with end-stage constriction.

Laboratory Testing

There are no specific ECG findings. Nonspecific T-wave abnormalities, reduced voltage, and LA enlargement may be present. Atrial fibrillation is very common. On chest radiography, the cardiac silhouette can be enlarged due to a coexisting pericardial effusion. Pericardial calcification is seen in a minority of patients and suggests TB (**eFig. 83.7**), but is not diagnostic of constrictive physiology. Pleural effusions are common and can be a presenting sign. If left heart filling pressures are markedly elevated, pulmonary vascular congestion and redistribution may be present.



EFIGURE 83.7 CT scan showing increased pericardial thickness and mild calcification in a patient with constrictive pericarditis.

Echocardiography and Doppler Echocardiography Examination

M-mode and two-dimensional transthoracic and Doppler echocardiography are primary imaging modalities in the evaluation of constrictive pericarditis (**see Chapter 14**). Major findings include pericardial thickening and calcification (best appreciated with transesophageal echocardiography), abrupt displacement of the interventricular septum during early diastole (septal bounce), and signs of systemic venous congestion (dilation of hepatic veins, inferior vena caval distention with blunted respiratory variation).[3,4,36] Premature pulmonic valve opening resulting from elevated RV early diastolic pressure and exaggerated septal shifting during respiration are common. As discussed above, the LV EF is usually normal. Mild to moderate (but not severe) biatrial enlargement is common.

Lack of transmission of intrathoracic pressure to the cardiac chambers and the resulting mitral/tricuspid inflow patterns have been discussed earlier. In accordance with these patterns, Doppler measurements usually reveal exaggerated respiratory variation in both mitral and tricuspid inflow velocity and tricuspid-mitral inflow velocity differences, with the latter 180 degrees out of phase (**see Fig. 83.8**). Although there is some overlap with tamponade, these inflow patterns have good sensitivity and specificity for diagnosing constriction and also help in differentiation from restrictive cardiomyopathy.[3,4,36] Typically, patients with constriction demonstrate an increase of 25% or more in mitral E velocity during expiration compared with inspiration and increased diastolic flow reversal with expiration in the hepatic veins. The mitral E-wave deceleration time is usually less than 160 ms. However, up to 20% of patients with constriction do not exhibit typical respiratory changes, most likely because of markedly increased LA pressure or possibly a mixed constrictive-restrictive pattern due to myocardial involvement. In patients without typical respiratory mitral-tricuspid flow findings, examination after maneuvers that decrease the preload (head-up tilt, sitting) can unmask characteristic respiratory variations.

Respiratory variations in mitral inflow velocity similar to those observed in constrictive pericarditis can be observed in chronic obstructive pulmonary disease (COPD), RV MI, pulmonary embolism, and pleural effusion.[3,4,36] These conditions have clinical and echocardiographic features that differentiate them from constrictive pericarditis. Superior vena caval flow velocities are particularly helpful in distinguishing constriction from COPD. Patients with COPD display a marked increase in inspiratory superior vena cava systolic forward flow velocity not seen in constriction. As discussed earlier, TEE is superior to transthoracic echocardiography for estimating the pericardial thickness and correlates well with CT.[3,4,36] When mitral inflow velocities by transthoracic echocardiography are technically inadequate or equivocal, measurement of the transesophageal pulmonary venous Doppler velocity demonstrates pronounced respiratory variation, larger than that observed across the mitral valve.

Tissue Doppler and strain (deformation) imaging are useful adjuncts for diagnosing constriction and distinguishing it from restrictive cardiomyopathy (see below).[3,4,36] Tissue Doppler reveals increased e′ velocity of the medial mitral annulus and septal abnormalities corresponding to the “bounce.” The lateral mitral annular e′ is lower than the medial annular e′, an abnormality termed *annulus reversus*. In restrictive cardiomyopathy, the characteristic tall and narrow transmitral E is present, but the e′ is reduced. Regional variations in deformation and strain include reduced LV circumferential strain, torsion, and early diastolic untwisting with preserved longitudinal strain and deformation. In contrast, in restriction, circumferential strain and untwisting are preserved but these parameters are reduced in the longitudinal direction.

Cardiac Catheterization and Angiography

Cardiac catheterization in patients with suspected constriction provides documentation of hemodynamics and assists in discriminating between constriction and restrictive cardiomyopathy (**see Chapter 19**).[1,2] Coronary angiography should ordinarily be performed in patients being considered for pericardiectomy. Rarely, external pinching or compression of a coronary artery by the constricting pericardium is detected.

The RA and RV diastolic pressure, pulmonary capillary wedge pressure, and pre–a wave LV diastolic pressure are elevated and equal, or nearly so, at around 20 mm Hg. Differences of more than 3 to 5 mm Hg between the left and right heart filling pressures are rare. The RA pressure tracing shows a preserved x descent, a prominent y descent, and roughly equal a-wave and v-wave heights, with a resultant M or W configuration. RV and LV pressures reveal an early, marked diastolic dip followed by a plateau (dip-and

plateau, or square root sign) (**Fig. 83.9**). Respiratory variation in the LV and RV systolic and diastolic pressures is increased. This has been quantified using the *systolic area index*, or the ratio of RV to LV systolic pressures × time area in inspiration versus expiration.[2,65] A ratio higher than 1.1 strongly suggests constriction. Pulmonary artery and RV systolic pressures are often modestly elevated to 35 to 45 mm Hg. Greater elevation is not a feature of constriction and casts doubt on the diagnosis. Hypovolemia (e.g., due to diuretic therapy) can mask hemodynamic findings. Rapid infusion of 1 L of normal saline over 6 to 8 minutes may reveal typical features. The SV is reduced, but cardiac output can be preserved because of tachycardia.

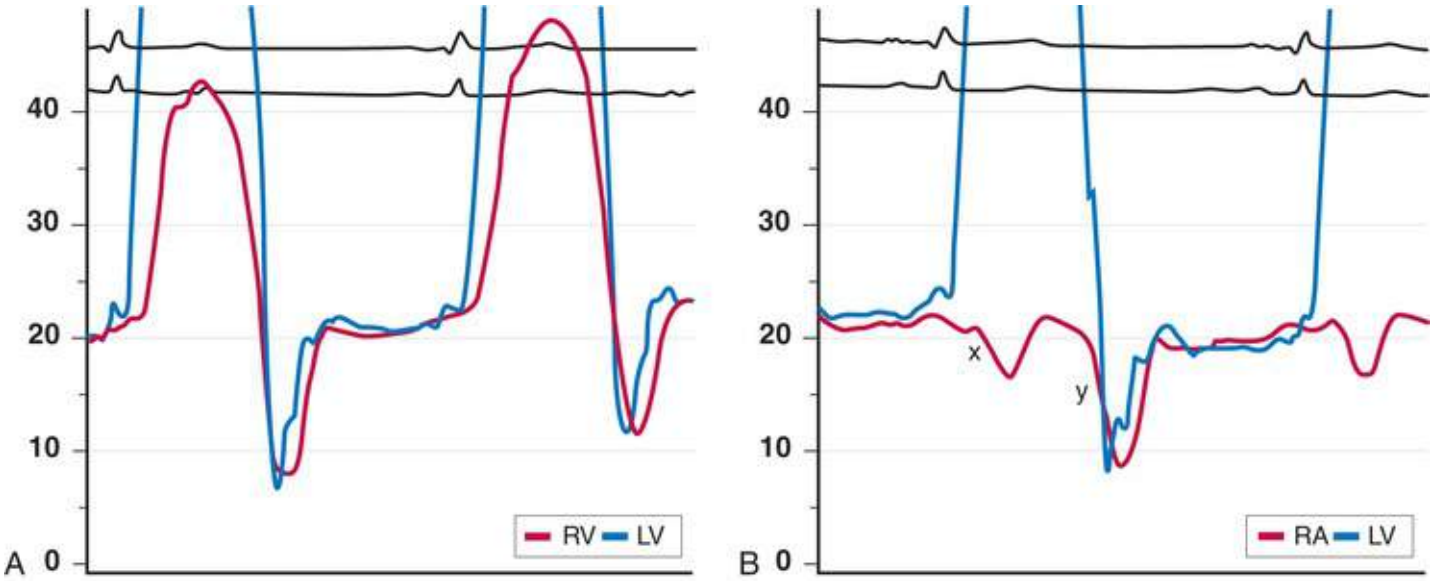


FIGURE 83.9 Pressure recordings in a patient with constrictive pericarditis. **A,** Simultaneous right ventricular (RV) and left ventricular (LV) pressure tracings with equalization of diastolic pressure as well as "dip-and-plateau" morphology; **B,** Simultaneous right atrial (RA) and LV pressure with equalization of RA and LV diastolic pressure. Note the prominent *y* descent. (From Vaitkus PT, Cooper KA, Shuman WP, Hardin NJ: Images in cardiovascular medicine: constrictive pericarditis. Circulation 1996;93:834.)

Computed Tomography and Magnetic Resonance Imaging

ECG-synchronized CT (**see Chapter 18**) and MRI (**see Chapter 17**) are important adjuncts to echocardiography-Doppler examinations in evaluating suspected constrictive pericarditis. CT is helpful in detecting even minute amounts of pericardial calcification and is the most accurate method for measuring thickness (normal < 2 mm) (**see eFig. 83.3**).[3,4,66,67] These features make CT particularly well suited for preoperative planning. CT can also obviate the need for invasive coronary angiography in some patients with normal-appearing vessels. Its major disadvantage is the frequent need for iodinated contrast medium to best display pericardial pathology. MRI provides a detailed examination of the pericardium without the need for contrast or ionizing radiation. It is less sensitive for detecting calcification than CT and less accurate for measuring thickness. The "normal" pericardium visualized by MRI is up to 3 to 4 mm in thickness. This most likely reflects the entire pericardial "complex," with physiologic fluid representing a component of the measured thickness. Cine acquisition MRI or CT is useful for detecting common findings of constriction (septal bounce, ventricular interaction) when echocardiography is technically inadequate (Video 83.4). Additional CT/MRI findings include distorted ventricular contours, hepatic venous congestion, ascites, and pleural effusions.

A thickened pericardium indicates acute and/or chronic pericarditis. Late gadolinium enhancement on MRI is more specific for active inflammation and may be useful in identifying patients who are candidates for medical management with antiinflammatory drugs (**Fig. 83.10** and see below).[59-62] If there is evidence of impaired diastolic filling, pericardial thickening, especially with calcification, is virtually diagnostic of constriction. Absence of thickening argues against the diagnosis but, as noted earlier, does not exclude it. Most patients with constriction and normal thickness have calcification and distorted ventricular contours, providing clues to the diagnosis. Localized constriction caused by focal thickening is reported. In patients being considered for pericardiectomy, delineation of the location and severity of thickening and calcification by CT or MRI aids in risk stratification and surgical planning.

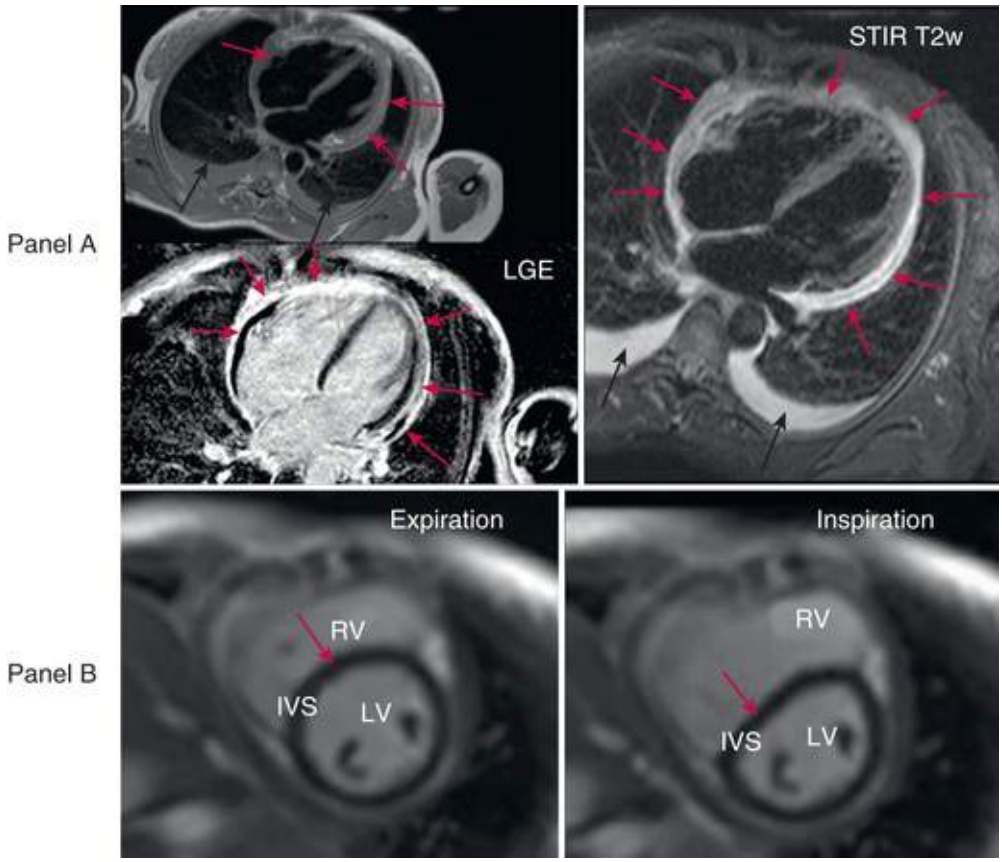


FIGURE 83.10 MRI of a patient with active pericarditis and constrictive physiology at presentation. In panel **A,** pericardial thickening and inflammation are present (*red arrows* indicate late gadolinium enhancement on the left and edema on STIR T2w image on the right). In panel **B,** real-time MRI reveals septal flattening or a "bounce" (*red arrows*) on inspiration owing to exaggerated ventricular interdependence. *IVS*, interventricular septum; *LGE*, late gadolinium enhancement; *LV*, left ventricle; *RV*, right ventricle. (Modified from Imazio M, Gaita F, LeWinter M: Evaluation and treatment of pericarditis: a systematic review. JAMA 2016;314:1498.)

Differentiating Constrictive Pericarditis from Restrictive Cardiomyopathy

Because of their treatment differences, distinguishing constrictive pericarditis from restrictive cardiomyopathy is important (**Table 83.7**). Restrictive cardiomyopathy used to be unusual and most commonly caused by amyloidosis, but it has become more prevalent because of its occurrence in a subgroup of patients with heart failure with a preserved EF who are obese and have features of the

metabolic syndrome.[69] The presentation and course of constriction and restriction overlap in many respects. A pericardial knock points to constriction, but third heart sounds in restrictive disease can be confusing. ECG and chest radiographic findings are mostly nonspecific. However, a calcified pericardium indicates constriction, while a low QRS voltage suggests amyloidosis. Echocardiographic distinctions are very helpful. Patients with restriction usually have thick-walled ventricles resulting from infiltrative processes or hypertrophy, but this is not invariably present.[68] Marked biatrial enlargement is typical of restriction but not constriction. In constriction, the most distinctive finding is the septal bounce. As discussed above, the pericardium is usually but not invariably thickened in constriction.

TABLE 83.7

Hemodynamic and Echocardiographic Features of Constrictive Pericarditis Compared with Restrictive Cardiomyopathy

	CONSTRICTION	RESTRICTION
Prominent y descent in venous pressure	Present	Variable
Paradoxic pulse	~1/3 cases	Absent
Pericardial knock	Present	Absent
Equal right- and left-sided filling pressures	Present	Left at least 3-5 mm Hg higher than right
Filling pressures > 25 mm Hg	Rare	Common
Pulmonary artery systolic pressure > 60 mm Hg	No	Common
Square root sign	Present	Variable
Respiratory variation in left-sided and-right-sided pressures/flows	Exaggerated	Normal
Ventricular wall thickness	Normal	Usually increased
Pericardial thickness	Increased	Normal
Atrial size	Possible LA enlargement	Biatrial enlargement
Septal bounce	Present	Absent
Tissue Doppler E′ velocity	Increased	Reduced
Speckle tracking	Normal longitudinal, decreased circumferential restoration	Decreased longitudinal, normal circumferential restoration

Doppler flow measurements are also useful in differentiating constrictive from restrictive physiology.[3,4,36] Enhanced respiratory variation in mitral inflow velocity (>25%) is seen in constriction, but varies by less than 10% in restriction (**see Fig. 83.8**). In restriction, pulmonary venous systolic flow is blunted and diastolic flow is increased; this is not observed in constriction. Hepatic veins demonstrate enhanced expiratory flow reversal with constriction, in contrast to increased inspiratory flow reversal in restriction. As discussed above, tissue Doppler and strain imaging can aid in differentiation.[3,4,36]

Hemodynamic differentiation between constrictive pericarditis and restrictive cardiomyopathy can be difficult. However, careful attention to the hemodynamic profile usually allows for their distinction (**see Table 83.7**). In both conditions, RV and LV diastolic pressures are markedly elevated. In restriction, diastolic pressure in the left ventricle is usually higher than in the right ventricle by at least 3 to 5 mm Hg, whereas in constriction, LV and RV diastolic pressures track closely and rarely differ by more than 3 to 5 mm Hg. Severe pulmonary hypertension is observed in restriction but virtually never in constriction. Extremely high diastolic pressure elevations (> 25 mm Hg) are much more common in restriction.[1,2,36,68] Finally, the *systolic area index* is greater in constriction than restriction and reported to have high sensitivity and specificity for distinguishing between them.[65]

CT or MRI is very useful in differentiating constriction from restriction because each has the ability to assess pericardial thickness and calcification, although once again, some patients with constriction have normal thickness.[3,4,66,67] Endomyocardial or abdominal fat pad biopsy is used to diagnose amyloidosis. Brain natriuretic peptide (BNP) levels are elevated in restrictive cardiomyopathy but not in constriction.[64]

Management

Constrictive pericarditis has a progressive but variable course. For most patients, surgical pericardiectomy is the definitive treatment. Pericardiectomy for constriction has a relatively high perioperative mortality rate, ranging from 2% to nearly 20% in modern series.[56-58,69-72] Risk factors for poor outcomes include radiation-induced disease; comorbidities, especially COPD and renal insufficiency; coronary artery disease and prior cardiac surgery; reduced LV EF; cardiopulmonary bypass; and New York Heart Association (NYHA) stage IV symptoms. Severely debilitated patients with stage IV symptoms in general have a prohibitively high risk. Radiation-induced disease is also considered a relative contraindication**.** Relatively healthy older patients with mild constriction can be managed nonsurgically, with pericardiectomy held in reserve until the disease progresses. Otherwise, surgery should not be delayed once the diagnosis is made. Diuretics and salt restriction are used to relieve the volume overload, but patients ultimately become refractory. Because sinus tachycardia is compensatory, beta-adrenergic blockers and calcium antagonists that slow the heart rate should be avoided. In patients with atrial fibrillation and a rapid ventricular response, digoxin is recommended for rate control.

Pericardiectomy can be performed through a median sternotomy or a left fifth interspace thoracotomy and involves radical excision of as much parietal pericardium as possible.[1,2,73] The visceral pericardium is inspected and resection considered if it is involved. Most surgeons attempt pericardiectomy without cardiopulmonary bypass. The latter is available as a backup measure and is frequently required to facilitate access to the lateral and diaphragmatic surfaces of the heart and allow removal of a maximal amount of tissue. Ultrasonic or laser debridement is an adjunct to conventional debridement or as the sole technique in patients with extensive, calcified adhesions.[2] The “waffle” procedure, in which multiple transverse and longitudinal incisions are made in the epicardial layer, is an alternative in patients with extensive epicardial involvement; it can be performed without cardiopulmonary bypass.[74]

Hemodynamic and symptomatic improvement following pericardiectomy is achieved in some patients very soon after surgery. In others improvement may be delayed for weeks to months. Videos 83.5 and 83.6 are cine MR images before and after successful pericardial stripping demonstrating relief of exaggerated respiratory variation in the right and left heart volume. There have been a number of reports of long-term results of pericardiectomy for constriction.[56,69-71,75] One-year survival rates range from 81% to 91%; 5-year rates from 64% to 85%; and 10-year rates from 49% to 81%. Most survivors are largely free of adverse cardiovascular outcomes. Long-term results are worst in patients with radiation-induced disease, impaired renal function, a reduced LV EF, moderate or severe tricuspid regurgitation, low serum sodium levels, and advanced age. LV diastolic function returns to normal in about 40% of patients early and about 60% late after surgery.[75] Persistence of abnormal filling is correlated with symptoms. Poor responses to pericardiectomy have been attributed to myocardial atrophy or fibrosis, incomplete resection, and development of recurrent cardiac compression by mediastinal inflammation and fibrosis. Tricuspid regurgitation usually does not improve and can cause hemodynamic deterioration.

There have been several reports of transient or reversible constrictive pericarditis.[2,61,62] Patients presenting early after cardiac surgery appear to be most common. Many patients have coexistent effusions and can be classified as having effusive-constrictive pericarditis (see below). Because reported patients have been treated with various antiinflammatory regimens, it is unknown if the disease would have improved spontaneously. Reversible constriction typically resolves in 2 to 3 months. MRI late gadolinium enhancement has been correlated with severity of fibrosis and inflammation in operative specimens from patients with constriction.[60] Intensity of enhancement as well as a pericardial thickness of 3 mm or more on late enhancement images is predictive of resolution of constriction with antiinflammatory drug treatment (**see Fig. 83.10**).[1,61,62] Responders also have higher hsCRP levels. Although it is attractive to identify patients with constriction in whom surgery can be avoided, it is not clear how common they are,

because reported series are small and highly selected.[59,60,62,63] Nonetheless, patients with intense late gadolinium enhancement on MRI, especially those with a pericardial thickness of more than 3 mm, should be considered for a trial of antiinflammatory therapy, especially if they have had recent cardiac surgery, symptoms have appeared relatively rapidly, the hsCRP is elevated, and there is not extensive calcification. NSAIDs, colchicine, and corticosteroids have been used in various combinations; there is no obvious preferred agent or combination. Thus, it is impossible to make informed recommendations in regard to treatment strategies. As a practical matter, an antiinflammatory regimen should be administered for perhaps 2 to 3 months to allow time for it to work, but surgery should not be excessively delayed if the benefit is not apparent. Although there is no specific evidence to support it, we suggest combined corticosteroids and colchicine in dosages similar to those recommended for recurrent pericarditis.

Effusive-Constrictive Pericarditis

Effusive-constrictive pericarditis combines elements of effusion/tamponade and constriction. Constrictive features usually are detected after pericardiocentesis.[2,47] A proposed definition of underlying constriction is the failure of RA pressure to decline by at least 50% to a level below 10 mm Hg when pericardial pressure is reduced to almost 0 mm Hg by pericardiocentesis and/or all detectable fluid is removed. Many cases of “transient” or medically treatable constrictive pericarditis may represent effusive-constrictive pericarditis. The course can be quite variable, but is usually subacute, ranging from 1 to 2 to several months. An inflammatory effusion typically dominates early, with constriction becoming more prominent later, but there are many variations. The visceral pericardium is usually prominently involved. The reported incidence of effusive-constrictive pericarditis in patients with pericardial effusion varies from 1% to 15% in different series and may be especially high in patients with TB.[47]

The most common causes of effusive-constrictive pericarditis are cancer, irradiation, TB, complications following pericardiotomy, and connective tissue diseases; the condition may be idiopathic, as well. TB is by far the leading cause in sub-Saharan Africa.[2,47] Physical, hemodynamic, and echocardiographic findings are mixtures of those associated with effusion and constriction and may vary with time as the syndrome progresses. The diagnosis may require acquisition of pericardial fluid and biopsy specimens if the cause is not obvious and tamponade does not mandate pericardiocentesis. Management is tailored to the specific cause, if known. In idiopathic and postpericardiotomy cases, antiinflammatory treatment as described above for noneffusive constrictive pericarditis may be used in an attempt to avoid pericardiectomy, but no guidance is available in regard to a preferred approach. MRI with gadolinium uptake and measurement of hsCRP may be useful to identify patients with active inflammation who are more likely to respond to an antiinflammatory regimen. Pericardiectomy is ultimately required in many patients.

Specific Etiologies of Pericardial Disease

The pericardium is involved in a wide variety of diseases (**see Table 83.1**). The following sections discuss the most significant specific diseases affecting the pericardium.

Infectious Diseases

Viral Pericarditis

Viral pericarditis is presumed to be the most common pericardial infection in countries with a low prevalence of TB.[1,2] Numerous viruses have been implicated (**see Table 83.1**). The definitive diagnosis requires identification of viral particles or genomic material in pericardial fluid or tissue or a rise in serum antibodies. This is impractical and/or unnecessary in the vast majority of cases of acute pericarditis because management of immunocompetent patients is not affected by a specific viral diagnosis.

Bacterial Pericarditis

In sub-Saharan Africa the most common bacterial cause of pericardial disease is TB. In the developed world, TB and other forms of bacterial (purulent) pericarditis are unusual in immunocompetent patients. We first discuss TB and then other forms of bacterial pericarditis.

Tuberculous Pericarditis

Tuberculous pericarditis represents a secondary localization with a primary infection in a different organ (most commonly, pleural-pulmonary infection).[2,76] The primary infection site may not be obvious. The clinical presentation may be acute pericarditis with effusion, apparent isolated effusion, effusive-constrictive pericarditis, or constrictive pericarditis. Acute pericarditis without an effusion is very uncommon. Making the correct diagnosis is critical because the death rate is high (20% to 40% within 6 months of diagnosis) in the absence of effective anti-TB treatment.

A *definitive* diagnosis requires demonstration of tubercle bacilli in pericardial fluid or tissue.[2,76] A *probable* diagnosis is achieved with evidence of the disease elsewhere and/or a lymphocytic pericardial exudate with elevated uIFN-γ, ADA, or lysozyme levels. A presumptive diagnosis without evidence as outlined above is appropriate only in countries with a high prevalence of TB followed by a positive response to empirical anti-TB therapy.[2,76]

Rifampicin, isoniazid, pyrazinamide, and ethambutol for at least 2 months, followed by isoniazid and rifampicin for a total of 6 months, is recommended. Treatment for 9 months or longer gives no better results, and has disadvantages of increased cost and risk of poor compliance.[2,76,77]

In addition to its high mortality rate if untreated, tuberculous pericarditis has a high risk (20% to 40%) of evolving to constriction, often within 6 months.[2,76,77] Prompt antibiotic therapy is essential to prevent this. Additional treatments that may be useful to prevent constriction include intrapericardial urokinase and adjunctive prednisolone for 6 weeks.[2,78] The latter may halve the frequency of this complication but should be avoided in HIV patients. Pericardiectomy is recommended if the patient's condition is not improving or is deteriorating after 4 to 8 weeks of therapy.[2]

Nontuberculous Bacterial Pericarditis

In developed countries, nontuberculous bacterial pericarditis is rare, amounting to less than 1% of pericarditis cases, and generally manifests as part of a serious febrile illness (fever > 38°C) with a moderate to large pericardial effusion.[2,18] If bacterial pericarditis is suspected, urgent pericardiocentesis is mandatory for the diagnosis, providing effusions are of sufficient size. Blood cultures should be obtained in any patient with pericarditis and fever higher than 38°C.[2,18]

The pericardial fluid is usually purulent, with a low glucose concentration and high WBC count with a large proportion of neutrophils. The diagnosis is made by microscopic detection of bacteria and/or positive cultures of fluid.[2]

Intravenous antimicrobial therapy should be started empirically until microbiologic results are

available. Prolonged drainage is crucial. Purulent effusions are often heavily loculated and likely to reaccumulate. Intrapericardial thrombolysis may help to achieve adequate drainage before one must resort to surgery. Subxiphoid pericardiostomy and rinsing of the pericardial sac should be considered.[2,18]

Bacterial pericarditis has a very high mortality rate if untreated. Purulent pericarditis has a high risk of evolving to constrictive pericarditis.[17]

Pericardial Disease and Human Immunodeficiency Virus

Various pericardial diseases have been reported in HIV patients (**see Chapter 82**). The epidemiology has been greatly altered by highly active antiretroviral therapy (HAART), which has markedly reduced the incidence of all forms of cardiac involvement.[76,79] In a recent large cohort of HIV patients,[79] 85% of whom received HAART, a pericardial effusion was detected in less than 1%. In general, patients receiving HAART have pericardial disease etiologies and prognoses similar to those of patients without HIV. In contrast, pericardial diseases are more complex and have a negative prognostic significance in the setting of untreated HIV and AIDS.[80] Small, asymptomatic pericardial effusions of uncertain etiology are common in untreated HIV and are associated with a poor prognosis.[76] TB is the most common cause of pericardial effusion in African HIV patients.[76,79] Other, less common forms of pericardial disease include involvement by various neoplasms, typical acute pericarditis, and myopericarditis. Constriction is rare.

Pericarditis in Patients with Renal Disease

Pericardial disease in patients with renal failure is now uncommon, but should always be considered in patients with appropriate signs and symptoms. There are three main presentations: (1) uremic pericarditis, often with moderate to large effusions, occurring before dialysis or within 8 weeks from its initiation and related to retention of toxic metabolites; (2) “dialysis pericarditis,” occurring 8 weeks or more after initiation of dialysis; and (3) constrictive pericarditis, which is rare.[2,80] Some features of pericardial disease in patients with renal disease are distinctive. Chest pain is relatively infrequent (one third of patients are asymptomatic), ECG changes are usually absent because the myocardium is not involved, and pericardial effusions are often bloody because of uremic coagulopathy. Tamponade is uncommon because effusions usually develop gradually.

Intensive dialysis is effective in uremic pericarditis naïve to dialysis; when patients already receiving dialysis develop pericarditis, intensifying dialysis may be effective. Pericardiocentesis should be considered in patients not responding to dialysis and of course in those with tamponade. The role of antiinflammatory regimens is unknown, but there does not appear to be a major component of inflammation in these patients.

Pericardial Involvement in Systemic Autoimmune and Autoinflammatory Diseases

Systemic inflammatory diseases (systemic lupus erythematosus, rheumatoid arthritis, scleroderma, systemic vasculitides, sarcoidosis, inflammatory bowel disease) are common causes of pericarditis and/or pericardial effusion.[2,81] As many as 10% of patients with pericarditis (often recurrent) have a known systemic inflammatory disease. Rarely, pericardial disease is the first manifestation. The degree of pericardial involvement is usually related to the activity of the underlying disease. Concomitant myocarditis may be present, because these diseases also cause myocardial inflammation. Constrictive

pericarditis rarely occurs, especially in rheumatoid arthritis patients.[2,81]

A subgroup of these patients, especially children, may be affected by rare, autoinflammatory periodic fevers.[2,77] Periodic fevers are genetic disorders characterized by mutations of genes involved in the regulation of the inflammatory response, without involvement of specific T cells or autoantibodies. The most common are *familial Mediterranean fever* (FMF), in which serositis episodes last 1 to 3 days, and *tumor necrosis factor receptor–associated periodic syndrome* (TRAPS), in which episodes last weeks. Mutations associated with these disorders are encountered rarely in patients presenting with recurrent pericarditis. A positive family history for pericarditis or periodic fevers and the need for immunosuppressive agents are clues to the presence of these diseases. Genetic testing is required for diagnosis.

Various antiinflammatory regimens have been employed. They are dictated by the specific disease and may include corticosteroids and/or combinations of additional drugs. For periodic fevers, anti-IL1 (e.g., anakinra) or anti-TNF agents should be considered.[4] Colchicine is highly effective in FMF, especially for prophylaxis, but not for TRAPS. Management requires a multidisciplinary approach, including cardiologists, rheumatologists/clinical immunologists, and other specialists as needed.

Post–Cardiac Injury Syndromes

The term post–cardiac injury syndrome (PCIS) is applied to a group of inflammatory pleuropericardial syndromes, including post-MI pericarditis, postpericardiotomy syndrome (PPS), and posttraumatic pericarditis.[2,82] With the exception of *early* post-MI pericarditis, all are presumed to have an autoimmune pathogenesis triggered by initial damage to pericardial tissue associated with myocardial necrosis (late post-MI pericarditis), surgical trauma (PPS), accidental thoracic trauma (traumatic pericarditis), or iatrogenic trauma (pericarditis after cardiac procedures, including perforation during percutaneous coronary intervention [PCI] and valve procedures, various arrhythmia ablation procedures, device implantations, and LA isolation procedures).

An immune-mediated pathogenesis is supported by a latent period, generally a few weeks, before the appearance of the first manifestations, a response to antiinflammatory drugs, and possible recurrences. PCIS is an emerging cause of pericarditis in developed countries because of an aging population and expansion of cardiac procedures.

According to proposed criteria, the diagnosis of PCIS after a cardiac injury requires at least two of the following: (1) fever without an alternative cause, (2) pleuritic chest pain, (3) pericardial or pleural rubs, (4) pericardial and/or pleural effusion, and (5) elevated hsCRP.[2,82]

Specific definitions and considerations apply to post-MI pericarditis (**see also Chapter 5**). Two forms are recognized.[83] *Early post-MI pericarditis* occurs soon after the MI. It is rare in the primary PCI era and occurs in association with large, transmural MIs because of absent or late/failed reperfusion. *Late post-MI pericarditis (Dressler syndrome)* is also rare (< 1% of MIs in the primary PCI era) and most common after large MIs.

Early post-MI pericarditis is usually asymptomatic and diagnosed by auscultation of a rub generally 1 to 3 days after the index event. It rarely causes an effusion large enough to produce tamponade. However, tamponade does occur with LV free wall rupture. Because of its association with large MIs, early post-MI pericarditis should alert the clinician to this possibility, especially if an effusion is present. In the occasional symptomatic patient, pleuritic chest pain appears within the above time frame. It is important to distinguish pericardial pain from recurrent ischemic discomfort. Ordinarily, this is not difficult on clinical grounds. Typical ECG changes of acute pericarditis are uncommon. Pericardial inflammation is

localized to the infarcted area; hence, ECG changes usually involve subtle reelevation of the ST segment in the originally involved leads. An atypical T-wave evolution consisting of persistent upright T waves or early normalization of inverted T waves appears to be highly sensitive for early post-MI pericarditis.[2,83] Late post-MI pericarditis occurs from 1 week to a few months after MI. Symptoms include fever and pleuritic chest pain. Physical examination may reveal pleural and/or pericardial rubs. The chest radiograph may show a pleural effusion and/or enlargement of the cardiac silhouette. The ECG often demonstrates changes typical of acute pericarditis. Effusions are common, but tamponade is unusual.

Treatment of PCIS is based on empirical antiinflammatory therapy plus colchicine as outlined for viral/idiopathic pericarditis.[2,82,83] Asymptomatic early post-MI pericarditis does not require treatment. Acetaminophen or aspirin as needed is preferred for occasional symptomatic patients.

The prognosis of PCIS is generally good. Long-term follow-up is warranted because constrictive pericarditis has been reported in about 3% of cases.[17]

Metastatic Pericardial Disease

Metastatic pericardial disease may present as acute pericarditis, effusion, effusive-constrictive pericarditis, or constriction.[2,19,77,84] Effusions are often moderate to large and frequently cause tamponade. They are usually caused by direct pericardial implants resulting from hematogenous spread and less commonly by metastatic lymphatic involvement. Virtually any metastatic tumor can involve the pericardium. Lung and breast cancers are most common, with lymphomas, leukemias, melanomas, and cancers of contiguous organs (e.g., the esophagus) making up most of the rest.

The definitive diagnosis is based on confirmation of malignant infiltration of the pericardium by pericardial fluid cytology or biopsy.[2,19,77,84] A probable diagnosis may be achieved by detection of tumor markers in pericardial fluid (CEA, GATA3, VEGF, and various others), although none has proven accurate enough to definitively distinguish malignant from benign effusions.[2,52] Evidence of malignant disease elsewhere with concomitant pericarditis or pericardial effusion is very suggestive. In almost two thirds of patients with documented malignancy, pericardial effusion is due to nonmalignant causes (e.g., radiation, other therapies, or opportunistic infections).[77,84]

Management of these patients requires a multidisciplinary approach, including oncologists, radiotherapists, and other subspecialists as needed.[2,19,77,84]

General principles include (1) using appropriate systemic antineoplastic treatment;(2) performing therapeutic and diagnostic pericardiocentesis for cardiac tamponade and as a diagnostic tool for moderate to large pericardial effusions that are suspected to be neoplastic (prolonged drainage is recommended to reduce the high recurrence rate [> 40% to 50%]; additional interventions for recurrent effusions include surgical pericardial window creation and percutaneous balloon pericardiotomy);(3) performing intrapericardial instillation of cytostatic/sclerosing agents is an option to prevent recurrences, and can be surprisingly effective (the agent used should be tailored to the type of cancer [e.g., cisplatin in lung cancer, thiotepa in breast cancer]); and (4) irradiation for controlling malignant effusions in patients with radiosensitive tumors such as lymphomas and leukemias.

In practice, management is usually palliative in patients with advanced disease, and aimed at relief of symptoms rather than treatment of the underlying disease, taking into account the prognosis and the overall quality of life of the patient.

Radiation-Induced Pericarditis

Chest radiation is an important cause of pericardial disease.[2,85] Radiation therapy can also affect the myocardium, valves, coronary arteries, and all mediastinal structures, inducing fibrosis. Most cases are secondary to therapy for Hodgkin lymphoma or breast or lung cancer. Modern treatment with lower doses and better shielding and dose calculation has reduced this complication, with a drop in incidence from 20% to about 2.5%.[2,85]

Radiation can induce an early, transient, often subclinical acute or subacute pericarditis with or without effusion. Constrictive pericarditis may appear 2 to 20 years later and is not *necessarily* preceded by clinically diagnosed early pericarditis. Late constriction affects a very variable number of patients and appears to be dose dependent and often related to a late effusion in the acute phase. The latter may be serous or hemorrhagic and has a high probability of leading to fibrous adhesions. Therapy for symptomatic pericarditis with or without effusion during the acute phase is similar to that for idiopathic pericarditis.[2,77] Concomitant myocardial damage contributes to poor outcomes after pericardiectomy for constriction.[2]

Thyroid-Associated Pericardial Disease

Pericardial effusions develop in 25% to 35% of patients with severe hypothyroidism (**see Chapter 92**).[2] These effusions can be large but rarely if ever cause tamponade. Hypothyroid effusions often have high concentrations of cholesterol. They gradually resolve with thyroid replacement. Rarely, effusion can occur in hyperthyroidism.

Pericardial Diseases in Pregnancy and During Lactation

Small, insignificant pericardial effusions are observed in approximately 40% of healthy pregnant women (**see Chapter 90**).[2,86] Pregnancy per se does not influence the incidence, cause, or course of pericardial disease but it does impact its management. Pericarditis is usually viral or idiopathic and has a good prognosis, with outcomes similar to those in the general population. For medical therapy, NSAIDs may be prescribed during the first trimester and early second trimester. After gestational week 20, all NSAIDs (except aspirin ≤100 mg/day) can cause constriction of the ductus arteriosus and impair fetal renal function and should either not be started or should be withdrawn. Low-dose corticosteroids (e.g., prednisone 0.2 to 0.5 mg/kg/day) are a viable option that can be adopted for the entire duration of pregnancy if necessary. Absent a specific indication (e.g., FMF), colchicine is contraindicated during pregnancy.[2,86] Paracetamol is allowed throughout pregnancy and breastfeeding, as are proton pump inhibitors. Normal vaginal delivery should be encouraged in the absence of contraindications. During lactation, ibuprofen, indomethacin, naproxen, and prednisone are allowable. Colchicine is considered contraindicated, although in women with FMF no adverse events affecting fertility, pregnancy, or fetal or child development have been reported, even after prolonged exposure.[2,77]

Pericardial Diseases in Children

Pericarditis is an important cause of chest pain in children, accounting for about 5% of patients in pediatric emergency departments. The etiologic spectrum differs from adults, with specific causes more common, including bacterial infections, autoimmune diseases, and PCIS following surgical repair of congenital defects.[2,77] Children often have a more marked systemic inflammatory response compared with adults. Fever and pleuropulmonary involvement and elevation of inflammatory markers are more common

than in adults.

At present, there are no randomized clinical trials in pediatric settings, and thus the management of pericardial syndromes in children follows the general scheme for adults, with appropriate dose adjustments.[2] Aspirin should generally be avoided because of the risk of Reye syndrome. Colchicine can be used, but corticosteroids should be restricted even more than in adults given the possibility of side effects that are particularly deleterious in children (e.g., striae rubra, growth impairment). Corticosteroid dependence is particularly difficult and biologic agents such as anakinra have been used as an alternative to allow corticosteroid withdrawal.[32] Exercise restriction can be particularly bothersome for children, especially in recurrent cases. The long-term prognosis is generally good, albeit related to the etiology of pericardial syndromes.[4,77]

Stress Cardiomyopathy

Stress cardiomyopathy (takotsubo syndrome) has become increasingly recognized over the past decade. Reversible ballooning of the apical portion of the left ventricle was originally described, but variants are common. Pericarditis and pericardial effusion are detected in an uncertain but significant percentage of patients, and there is at least one report of cardiac tamponade.[87] The mechanism of pericardial involvement is likely epicardial inflammation, but there is no definite proof of this.[87]

Hemopericardium

Any form of chest trauma can cause hemopericardium.[1,2] Post-MI free wall rupture occurs within several days of transmural MI (**see Chapter 5**). Hemopericardium due to retrograde bleeding into the pericardial sac is an important complication of type I dissecting aortic aneurysm (**see Chapter 57**). These patients can have combined aortic regurgitation due to disruption of the aortic valve and tamponade without a paradoxic pulse. The role of pericardiocentesis has been discussed above.

A variety of invasive cardiology procedures can be complicated by hemopericardium.[2] Puncture of atrial or ventricular walls can occur during mitral valvuloplasty and newer percutaneous mitral procedures.[2,88] Tamponade can occur rapidly or with a delayed course and can usually be managed with percutaneous drainage. Small pericardial effusions are occasionally observed after device closure of atrial septal defects, but tamponade is rare.[2] Insertion of the Watchman LA appendage device and other LA isolation procedures is complicated by a significant incidence of perforation and effusions. which not infrequently cause tamponade.[89,90] Transcutaneous aortic valve implantation is complicated by about a 1% incidence of tamponade.[91]

Pericardial effusion and tamponade due to coronary perforation is a rare complication of PCI (**see Chapter 62**), with an incidence of 0.1% to 0.6%.[2,92] The clinical presentation is usually rapidly progressive cardiac decompensation, although occasionally it can be more delayed. The diagnosis is usually made by extravasation of dye from a coronary vessel. Loss of cardiac pulsation on fluoroscopy indicates a significant effusion. Management requires sealing the perforation, pericardiocentesis, and reversal of anticoagulation.[2,92] If a perforation cannot be managed, percutaneous emergency surgery is indicated. Endomyocardial biopsy is occasionally complicated by perforation, but tamponade is unusual.[2,93]

Pericardial effusion and tamponade can occur as complications of various catheter-based arrhythmia procedures, including atrial fibrillation ablations. The incidence of effusion following atrial fibrillation ablation has been under 1%.[94,95] Many patients can be managed conservatively, and closed drainage is

usually sufficient. Epicardial ventricular tachycardia ablations can also cause hemopericardium.[96] RV perforation occasionally complicates pacemaker and implantable defibrillator lead insertion, as well as acute lead dislodgement, but rarely causes tamponade.[97] Finally, cardiac tamponade is a rare complication of laparoscopic gastroesophageal surgery.[98]

Congenital Anomalies of the Pericardium

Pericardial cysts are rare, benign congenital malformations typically located at the right or left cardiophrenic angle and rarely in other mediastinal locations.[2,8,99] Cysts are typically round or elliptical, with a size from a few centimeters to more than 20 cm. They do not communicate with the pericardial sac. Histologically, cysts are lined with a single layer of mesothelial cells, with the remainder of the wall composed of collagen and elastic fibers. Cysts are usually discovered as an incidental finding on imaging studies, but may occasionally become symptomatic due to hemorrhage or infection, increasing in size and causing symptoms due to compression of adjacent structures.[99] On CT imaging, cysts appear as round or elliptical masses with the same density as water. Absent complications, pericardial cysts do not show contrast enhancement or delayed gadolinium uptake.[100]

Surgery is not ordinarily recommended for pericardial cysts unless they become symptomatic. However, approximately 10% of apparent cysts actually represent a pericardial diverticulum with a persistent connection to the pericardial sac. This may not be apparent on imaging studies and only identified at surgery.[101] These lesions may cause atypical symptoms that are relieved only after surgery. Minimally invasive thoracoscopic resection or percutaneous aspiration is a less invasive alternative.[101]

Congenital absence of the pericardium is also very rare (**see Chapter 75**). Usually, part or all of the left parietal pericardium is absent, but partial absence of the right side has also been reported.[2] Partial absence of the left pericardium is associated with other anomalies, including atrial septal defect, bicuspid aortic valve, and pulmonary malformations. Although often asymptomatic, herniation of portions of the heart through the defect and/or torsion of the great vessels can occur, with life-threatening consequences. Patients can have chest pain or syncope, or may succumb to sudden death. The ECG typically reveals an incomplete right bundle branch block. Absence of all or most of the left pericardium results in a chest radiograph with a leftward shift of the cardiac silhouette and an elongated left heart border. Echocardiography reveals paradoxic septal motion and RV enlargement. CT or MRI establishes a definitive diagnosis. Pericardiectomy ameliorates symptoms and prevents herniation.

Primary Pericardial Tumors

Various, rare primary pericardial neoplasms have been reported, including mesotheliomas, fibrosarcomas, lymphangiomas, hemangiomas, teratomas, neurofibromas, and lipomas.[1,2] It is difficult to generalize about presentation and course. Many are locally invasive and/or compress cardiac structures or are detected because of an abnormal cardiac silhouette on chest radiograph. Mesotheliomas and fibrosarcomas are lethal. Others such as lipomas are benign. CT and MRI are helpful in delineating the anatomy of these tumors, but surgery is required for diagnosis and treatment.

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Pulmonary Embolism

Samuel Z. Goldhaber

State-of-the-Art Findings in Pulmonary Embolism

Pulmonary embolism (PE) and deep vein thrombosis (DVT) together constitute one of the “big three” cardiovascular diseases, the other two being myocardial infarction (MI) and stroke. *Venous thromboembolism* (VTE) encompasses PE and DVT. Estimates of the global incidence of VTE range from 1.2 to 2.7 per 1000 per year.[1] There is seasonality in hospitalizations for PE. The highest number of admissions is in the winter, and the lowest number is in the summer.[2]

In the United States, PE causes more than 100,000 deaths annually. Most deaths in hospitalized patients with PE result from right heart failure due to the initial PE or from recurrent PE despite anticoagulation. PE has an approximately 4% in-hospital case fatality rate in adults 65 years of age or older in the United

States. However, the 30-day readmission rate is 15%, and the 6-month mortality rate jumps to 20% in this population.[3] Patients residing in zip (postal) codes with lower socioeconomic status have increased in-hospital mortality rates and less frequently receive thrombolysis compared with patients residing in zip codes with higher socioeconomic status.[4]

Major long-term complications of VTE include recurrent VTE, chronic thromboembolic pulmonary hypertension (CTEPH),[5] and postthrombotic syndrome (also called chronic venous insufficiency) of the legs.[6] Postthrombotic syndrome patients report worse long-term physical health, mental health, and quality of life than controls.[7] Newly diagnosed VTE patients cost the U.S. health care system $7 to $10 billion annually.[8] The estimated cost of VTE for the European Union ranges from 1.5 billion to 13.2 billion Euros annually.[9]

In a European Registry of PE, the 30-day case fatality rate was 5%.[10] Over a 13-year period in Europe, thrombolytic therapy use increased from 0.7% to 1.0%, and surgical embolectomy procedures doubled from 0.3% to 0.6%. The United States and Europe share common trends over the past decade: (1) an increase in the incidence of PE, (2) a decrease in the hospital length of stay, and (3) a decrease in the case fatality rate.[11] Increased age[12] and concomitant DVT[13] are associated with a higher 30-day mortality rate.

Cancer patients have a fourfold increased risk of VTE compared with the general population.[14] When unprovoked VTE occurs, there is an increased likelihood that occult cancer will subsequently be detected, especially during the first 6 months after the diagnosis of VTE.[15] Age, prior provoked VTE, and cigarette smoking may help predict the presence of occult cancer in patients with a first unprovoked episode of VTE.[16] Nevertheless, it remains controversial whether to order abdominopelvic CT scans to try to diagnose occult cancer in patients with a first unprovoked episode of VTE.[17] VTE is also a women's health disease. PE is the leading cause of maternal death in the United States. Overall, pregnancy increases the risk of VTE fivefold,[18] and this risk persists for at least 12 weeks into the postpartum period.[19]

There is increasing recognition that VTE and atherothrombosis have similarities in epidemiology and pathophysiology. Inflammation, with its underlying prothrombotic state, is a pivotal factor in the pathophysiology of PE and links VTE and arterial thrombosis.[20] This realization has uncovered a wide range of unconventional risk factors for PE related to inflammation. For example, patients with the inflammatory state of severe sepsis and septic shock have a high incidence of VTE despite the use of thromboprophylaxis. In a multicenter prospective study of these intensive care unit (ICU) patients, the rate of VTE was 37% and associated with an increased length of stay and a trend toward higher death rates due to PE.[21] Chronic kidney disease is also associated with VTE,[22] probably because impaired kidney function heightens oxidative stress and inflammation. Other inflammation-based risk factors for VTE include inflammatory bowel disease, rheumatoid arthritis, psoriasis, pneumonia, urinary tract infections, influenza, diabetes mellitus, or other potential triggers such as transfused blood or erythropoietin-stimulating factors.

The risk of subsequent arterial cardiovascular events doubles in VTE patients compared with controls.[23] Among 1023 Australian patients initially hospitalized with PE, the cumulative mortality rate was 32% over 5 years, with 40% of the deaths attributed to cardiovascular causes. The mortality rate following discharge was 2.5 times higher than in an age-matched and sex-matched population.[24] In a Danish observational study with a median follow-up of 16 years, 1853 participants suffered MI, and 699 were diagnosed with VTE. MI was associated with a 72% increased risk of PE.[25] Heart failure and chronic obstructive pulmonary disease (COPD) also potently increase the risk for in-hospital death among patients with VTE.

PE impairs the quality of life.[7] Young adults diagnosed with VTE have a doubling of prescriptions of

psychotropic drugs compared with age- and gender-matched controls. Antidepressants were most frequently prescribed (53%), followed by sedatives (22%), anxiolytics (20%), and antipsychotics (5%).[26] PE and DVT increase in frequency with age but also afflict infants, children, and teenagers.[27] Recurrence after completion of a time-limited course of anticoagulation occurs often, especially when surgery, trauma, or estrogens do not precipitate the initial event. VTE exacts a psychological toll on patients, who wonder whether they will suffer a recurrent event and worry about the potential burden on their families, diminished quality of life, and shortened life span.

Advances in diagnostic, therapeutic, and preventive strategies, coupled with novel perspectives on VTE pathophysiology, have emerged at an unprecedented pace. Clinical and electronic decision tools facilitate early VTE detection and improve prevention strategies. Novel oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban allow the management of PE and DVT with fewer bleeding complications than with warfarin. Fixed dosing, the absence of drug-food interactions, the minimal number of drug-drug interactions, and no need for testing blood coagulation levels simplify NOAC therapy and enhance the safety of anticoagulation.[28]

With recognition of the critical role of the activated platelet in VTE pathogenesis, low-dose aspirin provides additional prophylactic and therapeutic options. For patients requiring advanced therapy beyond anticoagulation alone, invasive tools such as ultrasound-facilitated and catheter-assisted thrombolysis with low-dose tissue plasminogen activator therapy promise a lower rate of hemorrhagic complications than that associated with traditional, systemically administered high-dose thrombolysis. Reduced-dose systemic thrombolysis with tissue plasminogen activator is also gaining a foothold in the advanced therapy armamentarium because of its low rate of major bleeding.[29]

Our knowledge of the genetics of VTE is expanding rapidly.[30] To date, at least 17 genes have been demonstrated to harbor genetic variation associated with VTE risk. Common polymorphisms account for only about 5% of VTE heritability. The translational application of our advances in genetics remains elusive (**see also Chapter 6**).

Molecular Pathophysiology

VTE and atherothrombosis have intertwining risk factors and pathophysiology. Dichotomizing PE as a “red clot” disease and atherothrombosis as a “white clot” disease is no longer tenable. VTE is part of a pan–cardiovascular syndrome that includes coronary artery disease, peripheral artery disease, and cerebrovascular disease. The Virchow triad of stasis, hypercoagulability, and endothelial injury often activates the pathophysiologic cascade leading to VTE. Inflammation is not included in the Virchow triad, but it is a key precipitant. Infection and its associated inflammation lead to the recruitment of platelets—one of the first steps necessary for thrombus initiation. Activated platelets release polyphosphates, procoagulant microparticles, and proinflammatory mediators. These activated platelets bind neutrophils and stimulate them to release their nuclear material and to form weblike extracellular networks containing DNA, histones, and neutrophil granule constituents. These networks are called *neutrophil extracellular traps* (NETs) and consist of DNA extruded from leukocytes. NETs are prothrombotic and procoagulant. Histones stimulate platelet aggregation and promote platelet-dependent thrombin generation. As venous thrombi start to organize, neutrophils infiltrate the NETs. As thrombi mature, NETs provide the scaffold that binds red blood cells and promotes further platelet aggregation.[31]

Venous thrombi contain fibrin, red blood cells, platelets, and neutrophils (**Fig. 84.1**). These thrombi flourish in an environment of stasis, low oxygen tension, oxidative stress, increased expression of

proinflammatory gene products, and impaired endothelial cell regulatory capacity. Inflammation resulting from infection, transfusion, or erythropoiesis-stimulating factor[32] activates a cascade of biochemical reactions in the vein endothelium that promotes thrombosis.[33]

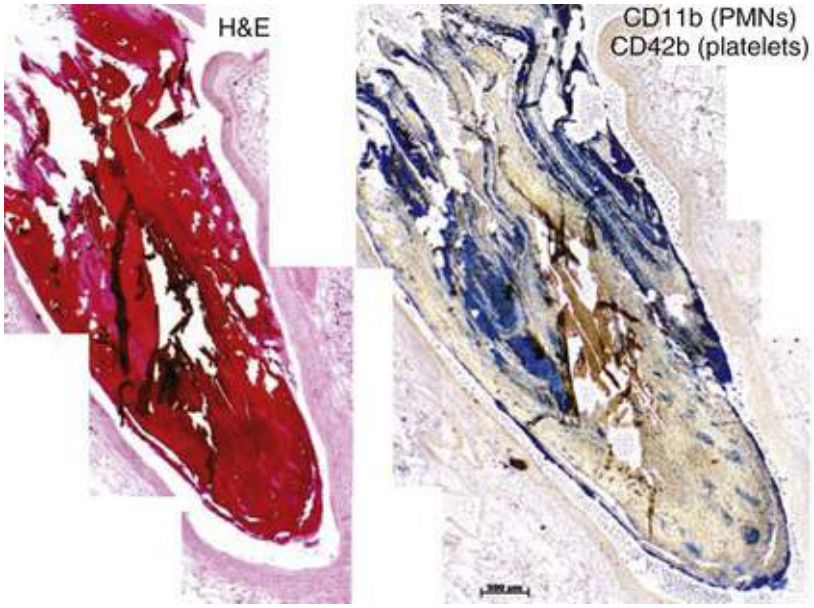

FIGURE 84.1 Micrographs of a fatal PE examined at autopsy. **Left,** Conventional hematoxylin-eosin (H&E)–stained preparation. **Right,** Two special stains were used for this preparation: a CD11b stain for polymorphonuclear leukocytes (*PMNs*, polymorphonuclear monocytes) (*light brown*) and a CD42b stain for platelets (*blue*). The special staining shows that this fatal thromboembolus is composed mostly of platelets (*blue*). (Courtesy Alexander S. Savchenko, PhD, and Denisa D. Wagner, PhD.)

The high recurrence rate of VTE in the absence of anticoagulation supports the hypothesis that venous thrombosis can persist as a subclinical, perhaps chronic, inflammatory state that becomes clinically apparent intermittently, when activated platelets degranulate and release preformed proinflammatory mediators. The JUPITER (Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin) study found a 43% reduction in symptomatic VTE among an initially healthy cohort of 17,802 subjects with asymptomatic elevation of baseline hsCRP levels who were treated with rosuvastatin 20 mg daily.[34] The principal postulated mechanism of action was rosuvastatin's antiinflammatory effect, evidenced by its reduction of hsCRP levels.

Cardiopulmonary Dynamics

PE can elicit a complex cardiopulmonary response that includes increased pulmonary vascular resistance due to vascular obstruction, neurohumoral agents, or pulmonary artery baroreceptors; impaired gas exchange caused by increased alveolar dead space from vascular obstruction and hypoxemia from alveolar hypoventilation and right-to-left shunting, as well as impaired carbon monoxide transfer caused by loss of gas exchange surface; alveolar hyperventilation caused by reflex stimulation of irritant receptors; increased airway resistance due to bronchoconstriction; and decreased pulmonary compliance due to lung edema, lung hemorrhage, and loss of surfactant.

The extent of pulmonary vascular obstruction, the presence of underlying cardiopulmonary disease, and the neurohumoral response determine whether right ventricular dysfunction ensues. As obstruction increases, pulmonary artery pressure rises. Further increases in pulmonary vascular resistance and

pulmonary hypertension result from secretion of vasoconstricting compounds such as serotonin, reflex pulmonary artery vasoconstriction, and hypoxemia. The overloaded right ventricle releases cardiac biomarkers such as pro–B type natriuretic peptide (pro-BNP), brain natriuretic peptide (BNP), and troponin, all of which portend an increased likelihood of adverse clinical outcomes.

The sudden rise in pulmonary artery pressure abruptly increases right ventricular afterload, with consequent elevation of right ventricular wall tension followed by right ventricular dilation and dysfunction (**Fig. 84.2**). As the right ventricle dilates, the interventricular septum shifts toward the left, leading to underfilling and decreased left ventricular diastolic distensibility. With hampered filling of the left ventricle, systemic cardiac output and systolic arterial pressure both decline, impairing coronary perfusion and causing myocardial ischemia. Elevated right ventricular wall tension after massive PE reduces right coronary artery flow and increases right ventricular myocardial oxygen demand, causing ischemia. Perpetuation of this cycle can lead to right ventricular infarction, circulatory collapse, and death.

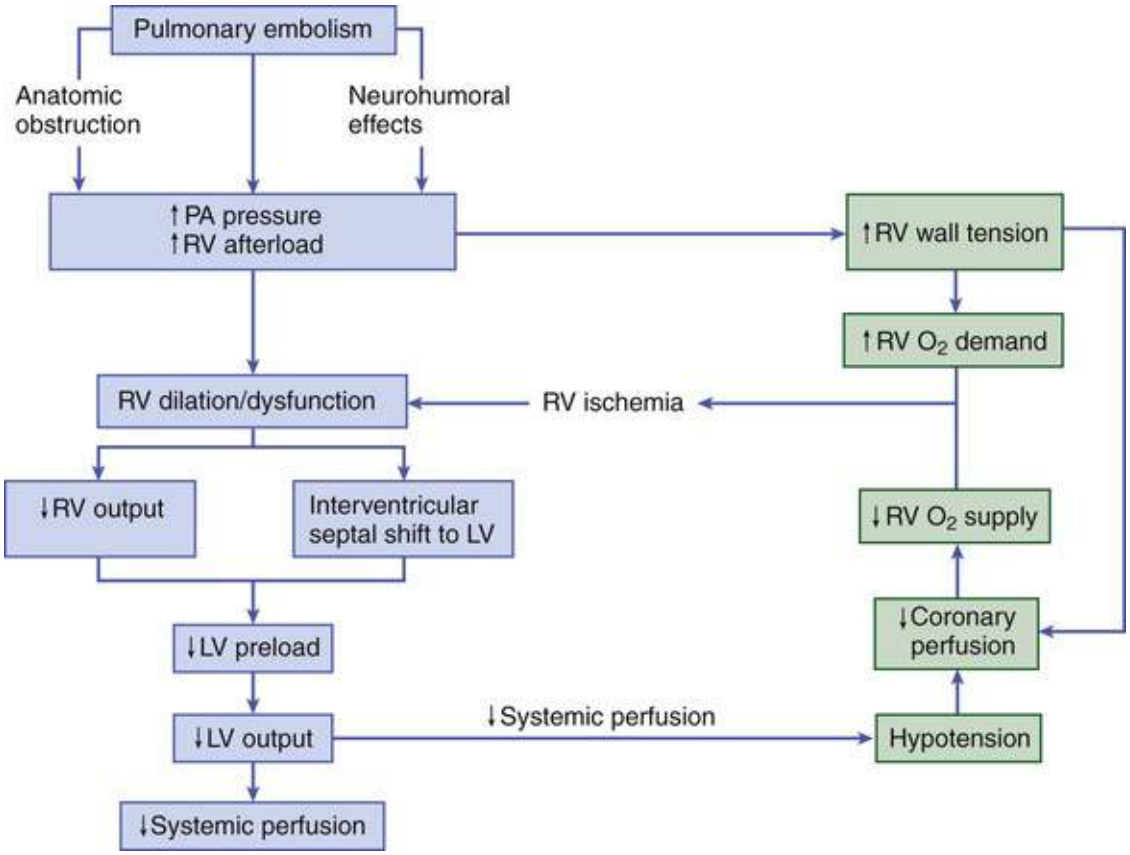

FIGURE 84.2 Pathophysiology of right ventricular dysfunction and its deleterious effects of causing decreased systemic arterial pressure, decreased coronary perfusion, and deteriorating ventricular function. *LV*, left ventricle/ventricular; *PA*, pulmonary artery; *RV*, right ventricle/ventricular.

Classification of Pulmonary Embolism

Classification of acute PE (**Table 84.1**) can assist with prognostication and clinical management. Massive PE accounts for 5% to 10% of cases. Submassive PE is more common, occurring in approximately 20% to 25% of patients. Low-risk PE constitutes the majority of PE cases, approximately 65% to 70%.

TABLE 84.1

Classification of Acute Pulmonary Embolism

CATEGORY (FREQUENCY)	PRESENTATION	THERAPY
Massive PE (5% to 10%)	Systolic blood pressure < 90 mm Hg or poor tissue perfusion or multisystem organ failure plus extensive thrombosis, such as "saddle" PE or right or left main pulmonary artery thrombus	Anticoagulation (usually with high-dose intravenous UFH), plus advanced therapy: systemic thrombolysis, pharmacomechanical catheter–directed therapy, surgical embolectomy, and/or inferior vena cava (IVC) filter
Submassive PE, high risk (15%)	Hemodynamically stable but moderate or severe RV dysfunction or enlargement, coupled with biomarker elevation indicative of RV microinfarction and/or RV pressure overload	Anticoagulation until decision made regarding implementation of advanced therapy; controversy centers on this group. For systemic thrombolysis, reducing the rate of cardiovascular collapse and death must be balanced against the increased rate of hemorrhagic stroke.
Submassive PE, low risk (5% to 10%)	Hemodynamically stable with RV dysfunction or biomarker elevation, but not both	Anticoagulation followed by "watch and wait." Implement advanced therapy if there is clinical deterioration.
Small to moderate PE (70%)	Normal hemodynamics and normal RV size and function	Anticoagulation and consider brief hospital stay or entirely home therapy.

RV, right ventricular; *UFH*, unfractionated heparin.

Massive Pulmonary Embolism

Patients with massive PE can develop cardiogenic shock and multisystem organ failure. Renal insufficiency, hepatic dysfunction, and altered mentation occur commonly. Massive PE has a high mortality rate. Thrombosis is widespread, affecting at least half of the pulmonary arterial vasculature. Clot typically is present bilaterally, sometimes as a "saddle" PE in the main pulmonary artery. Dyspnea usually is the most prominent symptom; chest pain is unusual; transient cyanosis is common; and systemic arterial hypotension requiring pressor support occurs frequently. Excessive fluid boluses may worsen right-sided heart failure, rendering therapy more difficult. These patients may require heroic efforts to enable survival, such as extracorporeal membrane oxygenation.[35]

Submassive Pulmonary Embolism

Submassive PE patients present with normal systemic arterial pressure. The European Society of Cardiology PE Guidelines now subdivide submassive PE into high-risk and low-risk entities.[36] Patients with submassive PE, high risk, present with both right ventricular hypokinesis and elevated cardiac biomarkers such as troponin, pro-BNP, or BNP. Those with submassive PE, low risk, present either with right ventricular dysfunction or elevated cardiac biomarkers, but not both. Usually, one third or more of the pulmonary artery vasculature is obstructed in submassive PE patients. Sudden onset of moderate pulmonary arterial hypertension (**Fig. 84.3**) and right ventricular enlargement occur commonly. If patients have no previous history of cardiopulmonary disease, they may appear clinically well, but this initial impression may be misleading. They are at risk for recurrent PE, even with adequate anticoagulation. Most survive, but some will deteriorate clinically and require escalation of therapy with pressor support or thrombolysis.[37]

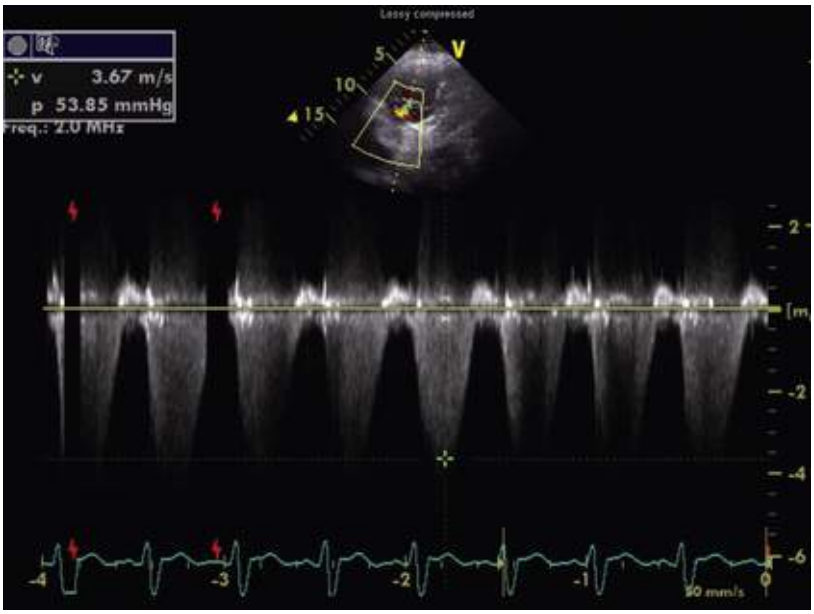

FIGURE 84.3 Doppler echocardiographic tracing obtained in a patient with submassive PE. The estimated pulmonary artery systolic pressure is 54 mm Hg, with an additional contribution of right atrial pressure, resulting in moderately severe acute pulmonary hypertension.

Low-Risk Pulmonary Embolism

Patients with low-risk PE exhibit no markers of an adverse prognosis. They present with normal systemic arterial pressure, no cardiac biomarker release, and normal right ventricular function. They often prove to have an anatomically small PE and appear clinically stable. Adequate anticoagulation usually leads to an excellent clinical outcome. They may be good candidates for home therapy.[38]

Pulmonary Infarction

Pulmonary infarction is characterized by pleuritic chest pain that may be unremitting or may wax and wane. Hemoptysis occasionally accompanies the pleurisy. The embolus typically lodges in the peripheral pulmonary arterial tree, near the pleura (**Fig. 84.4**). Tissue infarction usually occurs 3 to 7 days after embolism. Signs and symptoms often include fever, leukocytosis, elevated erythrocyte sedimentation rate, and radiologic evidence of infarction.

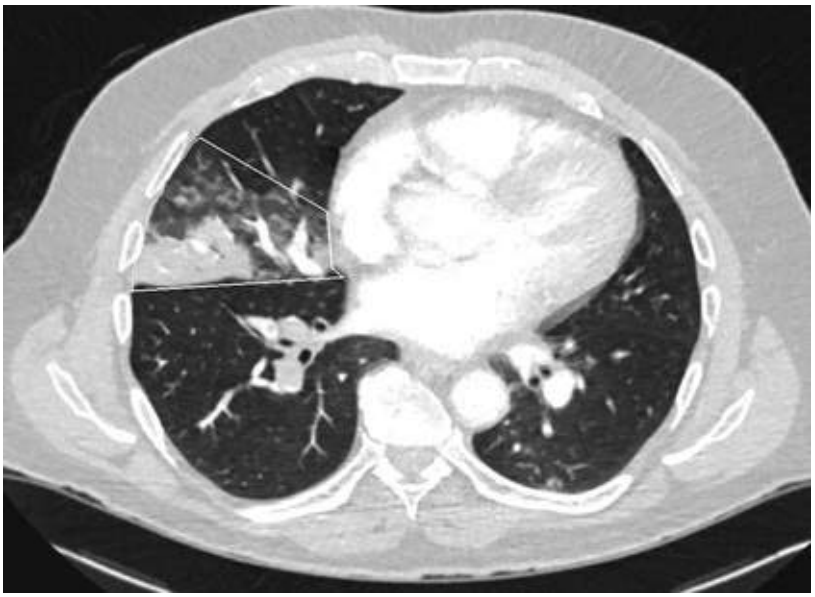

FIGURE 84.4 Chest computed tomography (CT) image showing a large, wedge-shaped (*outline*), right-sided pulmonary infarction.

Paradoxical Embolism

Paradoxical embolism may manifest with a sudden stroke, which may be misdiagnosed as "cryptogenic." The cause is a DVT that embolizes to the arterial system, usually through a patent foramen ovale. The DVT can be small and break away completely from a tiny leg vein, leaving no residual evidence of thrombosis that can be imaged on venous ultrasound examination.[39]

Nonthrombotic Pulmonary Embolism

Sources of embolism other than thrombus are uncommon. They include fat, tumor, air, and amniotic fluid. Fat embolism most often occurs after blunt trauma complicated by long bone fractures.[40] Air embolus can occur during placement or removal of a central venous catheter. Amniotic fluid embolism may be catastrophic and is characterized by respiratory failure, cardiogenic shock, and disseminated intravascular coagulation. Intravenous drug abusers sometimes self-inject hair, talc, and cotton as contaminants of the drug of abuse; these patients also are susceptible to septic PE, which can cause endocarditis of the tricuspid or pulmonic valve.

Classification of Deep Vein Thrombosis

Lower Extremity Deep Vein Thrombosis and the Relationship Between Deep Vein Thrombosis and Pulmonary Embolism

Patients present with DVT symptoms about twice as frequently as with symptoms of PE. Leg DVT occurs approximately 10 times more often than upper extremity DVT. The more proximal the thrombus is within the deep leg veins, the more likely it is to embolize and cause acute PE. When venous thrombi detach from their sites of formation, they travel through the venous system toward the vena cava. They pass through the right atrium and right ventricle and then enter the pulmonary arterial circulation. An extremely

large embolus may lodge at the bifurcation of the pulmonary artery, forming a saddle embolus (**Fig. 84.5**). Many patients with large PEs lack ultrasonographic evidence of DVT, probably because the clot has already embolized to the lungs.

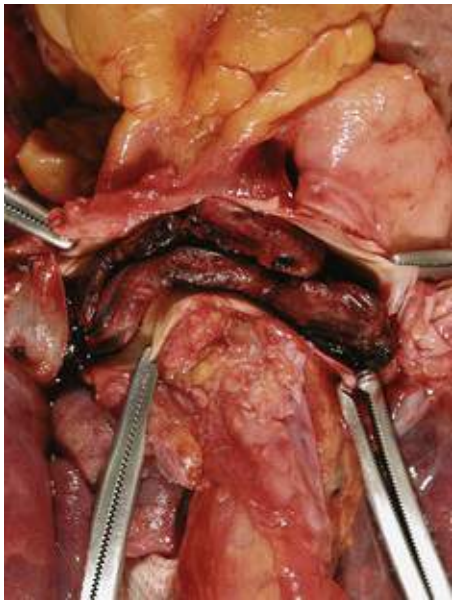

FIGURE 84.5 Surgical specimen from a 41-year-old woman with poorly controlled hypertension who suffered an intracerebral hemorrhage, complicated 6 days later by acute PE. Emergency catheter embolectomy was unsuccessful, and she suffered cardiac arrest. At autopsy, a large saddle embolus extended from the root of the pulmonary artery into the left and right lungs.

Upper Extremity Deep Vein Thrombosis

Upper extremity DVT is an increasingly important clinical entity because of the more frequent placement of pacemakers and implantable cardioverter-defibrillators, as well as more frequent use of chronic indwelling catheters for chemotherapy and nutrition. The likelihood of upper extremity DVT increases as the size of a peripherally inserted central catheter increases.[41]

A hospital initiative to use smaller-diameter catheters and to minimize the number of lumens can markedly reduce the frequency of catheter-associated DVT.[42] Patients with upper extremity DVT are at risk for PE, superior vena cava syndrome, and loss of vascular access. In a study of 3790 patients receiving peripherally inserted central catheters during hospitalization, central catheter use tripled the likelihood of upper-extremity DVT and increased by about 50% the likelihood of leg DVT.[43]

Postthrombotic Syndrome and Chronic Venous Insufficiency

Dysfunction of the valves of the deep venous system often results from damage due to DVT. Obstruction of the deep veins may limit the outflow of blood, causing increased venous pressure with leg muscle contraction. Abnormal hemodynamics in the large veins of the leg are transmitted to the microcirculation, causing venous microangiopathy.[6] Patients with DVT who develop postthrombotic syndrome have higher levels of inflammatory markers compared with those who do not.[44] Physical findings may include varicose veins, abnormal pigmentation of the medial malleolus, and skin ulceration (**Fig. 84.6**). Postthrombotic syndrome has high economic impact[45] because of time lost from work and the expense of medical diagnosis and treatment. Chronic venous disease is associated with a reduced quality of life as a

consequence of pain, decreased physical function, and decreased mobility. Vascular compression stockings (below-knee, 30 to 40 mm Hg) do not prevent the development of postthrombotic syndrome after an acute proximal DVT.[46] However, for patients with venous insufficiency, vascular compression stockings are a mainstay of therapy, improving venous hemodynamics, reducing edema, alleviating calf discomfort, and minimizing skin discoloration.

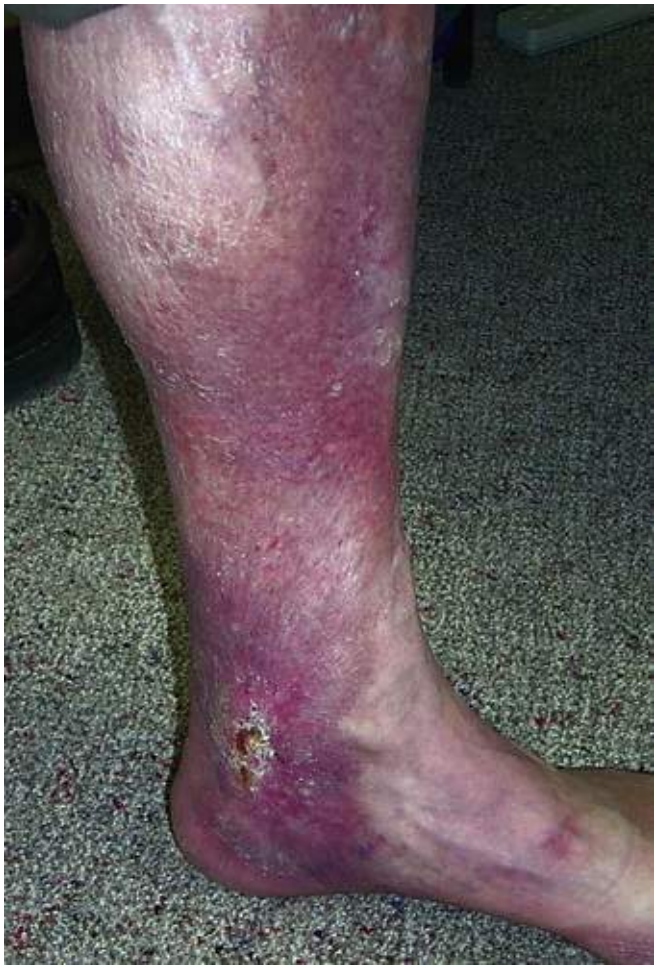

FIGURE 84.6 Left medial malleolus venous ulcer due to postthrombotic syndrome in a 57-year-old man with a history of left iliofemoral DVT and extensive tobacco use. Note the erythema and thickening of the skin of the left lower calf. (Courtesy Suresh Vedantham, MD.)

Superficial Venous Thrombosis

In a large Danish population-based case-control study, the risk of VTE was 3.4% in the 3 months following diagnosis of superficial venous thrombosis. The risk of VTE remained elevated fivefold for more than 5 years after the initial superficial venous thrombosis.[47] Short-term use of fondaparinux (2.5 mg once daily for 45 days) is the best validated anticoagulant therapy.[48]

Epidemiology

General Considerations

The incidence of VTE in North America and Europe is approximately 1.5 cases per 1000 person-years.

About two thirds of cases are DVT, and the rest are PE with or without DVT. The incidence increases with age in both men and women. Approximately half of VTE cases occur without antecedent trauma, surgery, immobilization, or cancer. Cardiovascular risk factors are associated with VTE. A metaanalysis of data for 63,552 patients with VTE and control subjects found that the relative risk for VTE was 2.3 for obesity, 1.5 for hypertension, 1.4 for diabetes mellitus, 1.2 for cigarette smoking, and 1.2 for hypercholesterolemia.[49] The overlap between venous and arterial thrombosis risk factors means that clinicians can counsel patients on steps to reduce VTE and coronary heart disease risk simultaneously.

Clinical Risk Factors

Risk factors for VTE in the community include advancing age, frailty, and immobility; the presence of cancer or venous insufficiency; previous VTE; or traumatic injury. Pregnant women also are at risk. Of those suffering VTE in the Worcester Venous Thromboembolism Study, 23% had undergone surgery and 36% had been hospitalized within the preceding 3 months. Among those patients, fewer than half had received anticoagulant prophylaxis.[50]

Obesity increases the risk of VTE. In a study of more than 1 million women with a mean age of 56 years in the United Kingdom, VTE risk increased with increasing body mass index (BMI). Women with a BMI 35 kg/m^2 or greater, for example, were three to four times more likely to develop VTE than women with a BMI between 22 and 25 kg/m^2.[51] A Spanish VTE registry called RIETE (Registro Informatizado de Enfermedad TromboEmbólica) included 18,023 patients with PE. Immobilized patients had a more than twofold increased risk of fatal PE. Of RIETE patients dying from PE, 43% had a history of recent immobilization for 4 days or longer.[52]

Some risk factors for VTE are not readily modifiable (**Table 84.2**). As VTE patients with cancer survive longer due to advances in oncologic therapy, the frequency of VTE is increasing, because cancer patients have a marked increased incidence of VTE (**see Chapter 81**). Cancer chemotherapy–associated VTE is common. Increased VTE risk is associated with solid tumors, especially adenocarcinomas of the pancreas, stomach, lung, esophagus, prostate, and colon. Less well known is that VTE risk also increases with “liquid tumors,” such as myeloproliferative disorders, lymphoma, and leukemia.

TABLE 84.2

Major Risk Factors for Venous Thromboembolism That Are Not Readily Modifiable

Advanced age
Arterial disease, including carotid and coronary disease
Personal or family history of venous thromboembolism
Recent surgery, trauma, or immobility, including stroke
Congestive heart failure
Chronic obstructive pulmonary disease
Acute infection
Blood transfusion
Erythropoietin-stimulating factor
Chronic inflammation (e.g., inflammatory bowel disease)
Chronic kidney disease
Air pollution
Long-haul air travel
Pregnancy, oral contraceptive pills, or postmenopausal hormone replacement therapy
Pacemaker, implantable cardioverter-defibrillator leads, or indwelling central venous catheter
Hypercoagulable states
Factor V Leiden resulting in activated protein C resistance
Prothrombin gene mutation 20210
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Antiphospholipid antibody syndrome (acquired, not inherited)

Pregnancy, hormonal contraception, and postmenopausal hormonal therapy each contribute to increased risk. Use of progesterone-only birth control pills is not associated with increased VTE risk. Long-haul air travel is among the most frequently discussed acquired risk factors, although the associated risk of fatal PE is less than one in one million. When death occurs, however, it is dramatic and especially tragic because the victim is often an otherwise healthy young person.

Hypercoagulable States

The two most common identified genetic causes of thrombophilia are factor V Leiden and the prothrombin gene mutation (**see Chapter 93**). Normally, a specified amount of activated protein C (aPC) can be added to plasma to prolong the activated partial thromboplastin time (aPTT). Patients with “aPC resistance” exhibit blunted aPTT prolongation and are predisposed to the development of PE and DVT. A single-point mutation, designated factor V Leiden, in the factor V gene causes aPC resistance. Factor V Leiden triples the risk of VTE and is associated with recurrent pregnancy loss, probably as a consequence of placental vein thrombosis. Use of oral estrogen-containing contraceptives by patients with factor V Leiden increases the VTE risk by at least 10-fold. A single-point mutation in the 3′ untranslated region of the prothrombin gene (G-to-A transition at nucleotide position 20210) increases levels of prothrombin. The prothrombin gene mutation doubles the risk of VTE.

The antiphospholipid syndrome, the most common acquired thrombophilia, can cause venous or arterial thrombosis, thrombocytopenia, recurrent fetal loss, or acute ischemic encephalopathy. The presence of specific autoantibodies is an essential component of the diagnosis. The persistence for at least 12 weeks of one of the following antiphospholipid antibodies is required: IgG or IgM anticardiolipin antibodies, anti-beta2-glycoprotein I, antiprothrombin, or lupus anticoagulant. Presence of the antiphospholipid syndrome means heightened susceptibility to recurrent venous or arterial thrombosis if anticoagulation is

discontinued.[53]

Obtaining a family history remains the fastest and most cost-effective method of identifying a predisposition to venous thrombosis. Investigation with blood tests to detect known causes of hypercoagulability can be misleading. Consumption coagulopathy caused by venous thrombosis, for example, may be misdiagnosed as deficiency of antithrombin, protein C, or protein S. Heparin administration can depress antithrombin levels. Use of warfarin ordinarily causes a mild deficiency of protein C or protein S. Oral contraceptives and pregnancy also depress protein S levels.

Diagnosis

PE notoriously masquerades as other illnesses, such as asthma, pneumonia, pleurisy, acute coronary syndrome, and congestive heart failure. PE often occurs concomitantly with other illnesses, especially pneumonia and heart failure, thereby confounding the diagnostic workup. The most useful approach is a clinical assessment of likelihood, based on presenting symptoms and signs, in conjunction with judicious diagnostic testing. When PE is not among the most likely diagnoses, a normal plasma D-dimer enzyme-linked immunosorbent assay (ELISA) usually can rule out this condition. When PE is strongly suspected, a D-dimer ELISA need not be obtained, and one can proceed directly to chest computed tomography (CT) imaging.[54] Although the traditional upper limit of normal for a D-dimer screening test is 500 ng/mL, the upper limit of normal should be increased for patients older than 50 years. For these older patients, the age-adjusted D-dimer cutoff level is defined as age multiplied by 10.[55]

Clinical Presentation

PE causes nonspecific symptoms and signs. Hence, clinical suspicion for PE is of paramount importance in guiding diagnostic testing. Dyspnea is the most frequent symptom, and tachypnea is the most frequent sign (**Table 84.3**). Severe dyspnea, syncope, or cyanosis portends a major life-threatening PE, in which the patient often lacks chest pain. Paradoxically, severe pleuritic pain often signifies that the embolism is small, not life-threatening, and located in the distal pulmonary arterial system, near the pleural lining.

TABLE 84.3

Most Common Symptoms and Signs of Pulmonary Embolism

Symptoms
Unexplained dyspnea
Chest pain, especially pleuritic or “positional”
Anxiety
Cough
Signs
Tachypnea
Tachycardia
Low-grade fever
Left parasternal lift
Jugular venous distention
Tricuspid regurgitant murmur
Accentuated P_2
Hemoptysis
Leg edema, erythema, tenderness

PE should be suspected in hypotensive patients who have evidence of (1) venous thrombosis or predisposing VTE risk factors, (2) acute cor pulmonale (acute right ventricular failure), with features such as distended neck veins, right-sided S_3 gallop, right ventricular heave, tachycardia, or tachypnea, especially if (3) there are echocardiographic findings of right ventricular dilation and hypokinesis or electrocardiographic evidence of acute cor pulmonale manifested by a new $S_1Q_3T_3$ pattern (**Fig. 84.7**), new right bundle branch block, or right ventricular ischemia with inferior T wave inversion, or T wave inversion in leads V_1 through V_4. Clinical decision rules can stratify patients into groups with a high clinical likelihood of PE or without a high clinical likelihood of PE, using a set of seven bedside assessment questions known as the Wells criteria (**Table 84.4**).

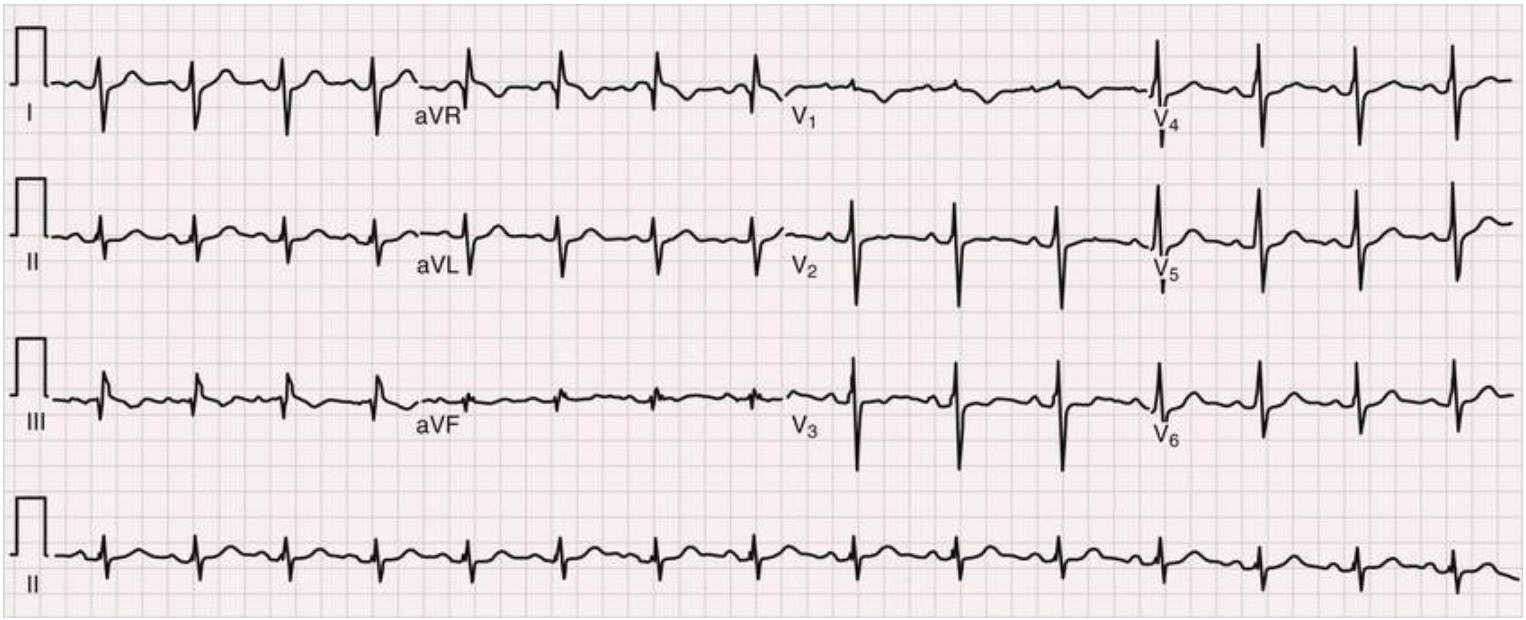

FIGURE 84.7 Electrocardiogram (ECG) from a 33-year-old man who presented with a left main pulmonary artery embolism on chest CT scan. He was hemodynamically stable, with normal right ventricular function on echocardiography. His troponin and BNP levels were normal. He was managed with anticoagulation alone. The initial ECG tracing shows $S_1Q_3T_3$ (leads I and III) with an S wave in lead I, Q wave in lead III, and inverted T wave in lead III, and incomplete right bundle branch block, with inverted or low amplitude T waves in leads V_1 through V_4.

TABLE 84.4

Classic Wells Criteria for Assessing Clinical Likelihood of Pulmonary Embolism

CRITERION	SCORING*
DVT symptoms or signs	3
An alternative diagnosis is less likely than PE	3
Heart rate > 100 beats/min	1.5
Immobilization or surgery within 4 weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1
Cancer treated within 6 months or metastatic	1

*More than 4 score points indicates high probability; 4 score points or fewer indicates probability that is not high.

Differential Diagnosis

PE has a broad differential diagnosis, covering a wide spectrum from life-threatening conditions such as

acute MI to anxiety states (**Table 84.5**). Concomitant illnesses should be taken into account. For example, if pneumonia or heart failure does not respond to appropriate therapy, the possibility of coexisting PE should be considered. Idiopathic pulmonary hypertension may manifest with sudden exacerbations that mimic acute PE.

TABLE 84.5

Differential Diagnosis of Pulmonary Embolism

Anxiety, pleurisy, costochondritis
Pneumonia, bronchitis
Acute coronary syndrome
Pericarditis
Congestive heart failure
Aortic dissection
Idiopathic pulmonary hypertension

Diagnostic Methods Other Than Imaging

Plasma D-Dimer Assay

The plasma D-dimer assay, a blood screening test, relies on the following principle: Most patients with PE have ongoing endogenous fibrinolysis that is not effective enough to prevent PE but breaks down some of the fibrin clot to D-dimers. Although elevated plasma concentrations of D-dimers are sensitive for the diagnosis of PE, they are not specific. Even in the absence of PE, levels are elevated for at least 1 week postoperatively and also are abnormally high in patients with MI, sepsis, cancer, or almost any other systemic illness. The plasma D-dimer assay therefore is ideally suited for screening outpatients or emergency department patients who have suspected PE but no coexisting acute systemic illness. This test generally is not useful for screening acutely ill hospitalized inpatients, because they usually have elevated D-dimer levels. In addition to being a screening test for PE, an elevated D-dimer independently correlates with increased rates of mortality and subsequent VTE across a broad variety of disease states.[56]

Electrocardiogram

The electrocardiogram (ECG) helps exclude acute MI and acute pericarditis. This test may lead the clinician toward the diagnosis of PE among patients with electrocardiographic manifestations of right-sided heart strain. The most famous sign of right heart strain is $S_1Q_3T_3$, but I have found that the most common sign is T wave inversion in leads V_1 to V_4. Keep in mind that right-sided heart strain is not specific for PE and may be observed in patients with asthma, COPD, or idiopathic pulmonary hypertension. In patients with massive PE, the ECG may not be especially remarkable and may exhibit sinus tachycardia or slight ST-segment and T-wave abnormalities, or may even have an entirely normal appearance.

Imaging Methods

Chest Radiography

A near-normal radiographic appearance in the setting of severe respiratory compromise is highly suggestive of massive PE. Major chest radiographic abnormalities are uncommon. Focal oligemia

(Westermark sign) indicates massive central embolic occlusion. A peripheral wedge-shaped density above the diaphragm (Hampton hump) usually indicates pulmonary infarction (**see Fig. 84.4**). A subtle abnormality suggestive of PE is enlargement of the descending right pulmonary artery. The chest radiograph also can help identify patients with diseases that mimic PE, such as lobar pneumonia and pneumothorax, but patients with these illnesses also can have concomitant PE.

Lung Scanning

Pulmonary radionuclide perfusion scintigraphy (lung scanning) uses radiolabeled aggregates of albumin or microspheres that lodge in the pulmonary microvasculature. Patients with large PE often have multiple perfusion defects. If ventilation scanning is performed on a patient with PE but no intrinsic lung disease, a normal ventilation study result is expected, yielding ventilation-perfusion mismatch interpreted as a high probability of PE. However, many patients with low-probability scans but with clinical findings strongly suggestive of PE do, in fact, have PE proven by invasive pulmonary angiography. Thus, a clinical probability assessment helps in correct interpretation of the scan results.

Most lung scans are nondiagnostic. An unequivocal normal or high-probability scan is the exception, not the rule. Interobserver variability is common, even among experts. Three principal indications for obtaining a lung scan are renal insufficiency, anaphylaxis occurring in reaction to an intravenous contrast agent that cannot be suppressed with high-dose corticosteroids, and pregnancy (lower radiation exposure to the fetus than CT scanning).

Chest Computed Tomography

Chest CT has supplanted pulmonary radionuclide perfusion scintigraphy as the initial imaging test in most patients with suspected PE.[57] Multidetector-row CT scanners can rapidly image the entire chest with submillimeter resolution. Three-dimensional images can be reconstructed, and color can be added electronically to enhance details of thrombus localization. The CT scan helps determine surgical or catheter accessibility to the thrombus. One cautionary note is that the CT scan may lead to overdiagnosis of PE due to breathing motion artifact or beam-hardening artifact.[58]

The latest generation of scanners can image thrombus in sixth-order vessels. These thrombi are so tiny that their clinical significance is uncertain (**Fig. 84.8**). The chest CT scan also can detect other pulmonary diseases that manifest in conjunction with PE or explain a clinical presentation that mimics PE. These diseases include pneumonia, atelectasis, pneumothorax, and pleural effusion, which may not be well visualized on the chest radiograph. A chest CT scan sometimes detects an incidental but critical finding, such as a small lung carcinoma.

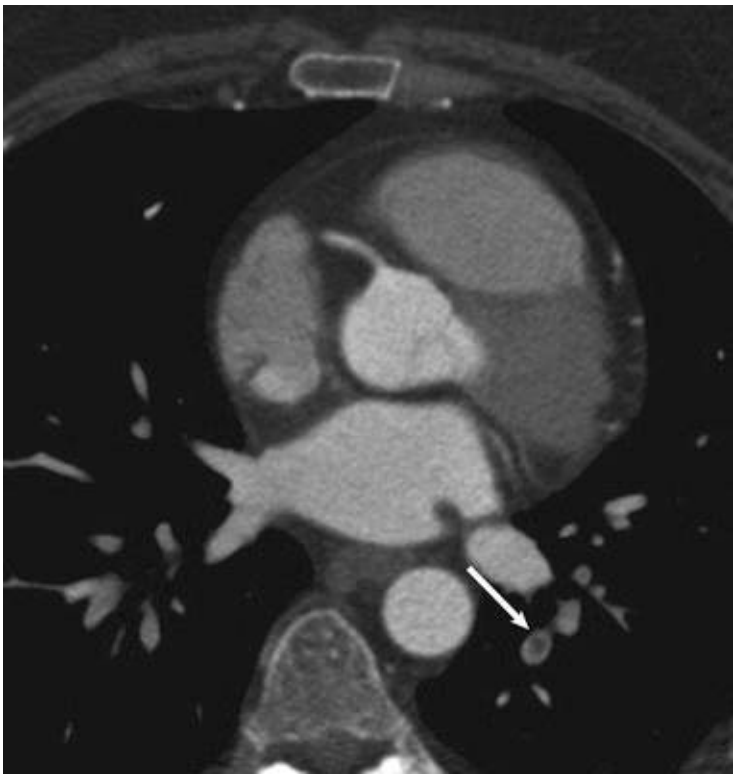

FIGURE 84.8 Small peripheral pulmonary embolism in the left lower lobe (*arrow*). (Courtesy U. Joseph Schoepf, MD.)

For patients with PE, the CT scan serves as a prognostic and diagnostic test. It shows a four-chamber view of the heart and images the pulmonary arteries. Careful evaluation of the CT scan can detect signs of right ventricular dysfunction by analyzing (1) the right ventricular–to–left ventricular diameter ratio (**Fig. 84.9**), (2) right ventricular–to–left ventricular volume ratio, (3) interventricular septal bowing, and (4) reflux of contrast medium into the inferior vena cava.[59] Right ventricular enlargement on CT correlates with right ventricular dysfunction and portends a complicated hospital course often marked by clinical deterioration. A right-to-left ventricular dimensional ratio of 0.9 or greater on a chest CT scan is abnormal, indicates right ventricular enlargement, and correlates with right ventricular dysfunction on echocardiography.

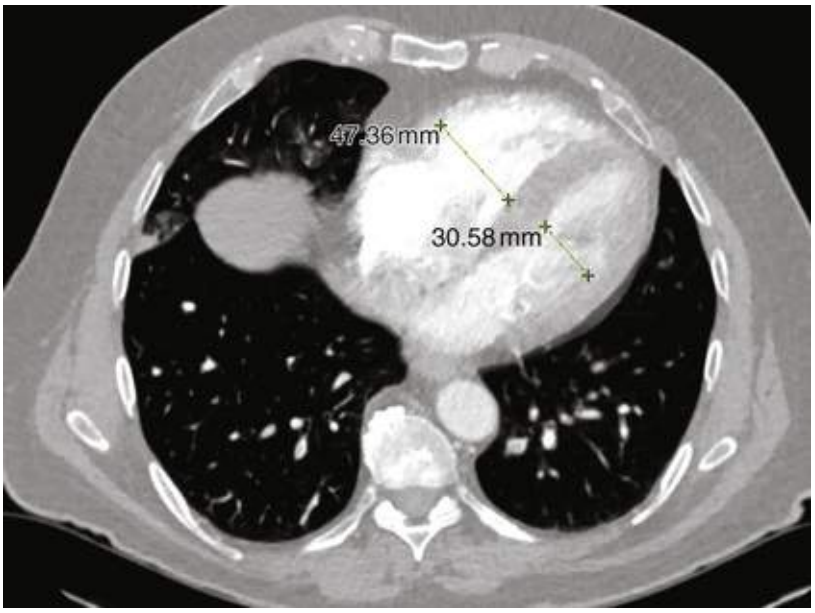

FIGURE 84.9 Enlarged right ventricle on chest CT in a patient with PE. Normally, the ratio of the diameters of the right ventricle and the left ventricle is less than 0.9. This patient has an RV diameter of 47 mm and an LV diameter of 31 mm. The RV/LV diameter ratio of 1.5 is abnormally high. *LV*, left ventricular; *RV*, right ventricular.

Echocardiography

About one half of unselected patients with acute PE have normal echocardiographic findings, so this modality is not recommended as a routine diagnostic test for PE. Echocardiography is, however, a rapid, practical, and sensitive technique for detection of right ventricular overload among patients with established PE. Moderate or severe right ventricular hypokinesis, persistent pulmonary hypertension, patent foramen ovale, and free-floating thrombus in the right atrium or right ventricle are associated with a high risk of death or recurrent thromboembolism.[60] Echocardiography also can help identify illnesses that may mimic PE, such as MI and pericardial disease.

Venous Ultrasonography

The primary diagnostic criterion for DVT on ultrasound imaging is loss of vein compressibility (**Fig. 84.10**). Normally, the vein collapses completely when gentle pressure is applied to the skin overlying it. Upper extremity DVT can be more difficult to diagnose than leg DVT because the clavicle can hinder attempts to compress the subclavian vein. At least one half of the patients with PE have no imaging evidence of DVT, probably because the entire DVT embolized to the pulmonary arteries. Therefore, if the level of clinical suspicion of PE is moderate or high, patients without evidence of DVT should undergo further investigation for PE.

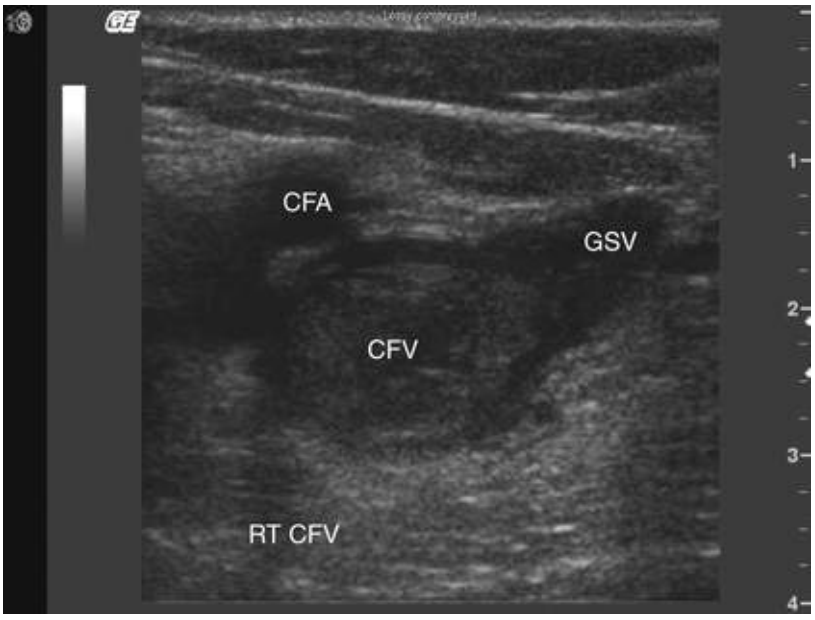

FIGURE 84.10 DVT involving the right common femoral vein (*RT CFV*) seen on venous ultrasound examination. The common femoral vein (*CFV*) does not compress and is dilated. Thrombotic material can be visualized within the vein. *CFA*, common femoral artery; *GSV*, greater saphenous vein. (Courtesy Samuel Z. Goldhaber, MD, and Gregory Piazza, MD, MS.)

Magnetic Resonance Imaging

Gadolinium-enhanced magnetic resonance angiography (MRA) is far less sensitive than CT for the detection of PE, but unlike chest CT or catheter-based pulmonary angiography, MRA does not require ionizing radiation or injection of an iodinated contrast agent. Pulmonary MRA also can assess right ventricular size and function. Three-dimensional MRA can be performed during a single breath-hold and may provide high resolution from the main pulmonary artery through the segmental pulmonary artery branches. MRA has limited sensitivity for detection of distal PE and cannot be used as a stand-alone test to exclude PE.[61]

Pulmonary Angiography

Invasive pulmonary angiography formerly was the reference standard for the diagnosis of PE, but it is now rarely performed as a diagnostic test. Use of this modality is routine, however, to plan interventions such as pharmacomechanical catheter–assisted therapy. New thrombus usually has a concave edge. Chronic thrombus leads to bandlike defects called webs, in addition to intimal irregularities and abrupt narrowing or occlusion of lobar vessels.

Contrast Phlebography

Although contrast phlebography was once the reference standard for DVT diagnosis, this study is now rarely obtained for diagnostic purposes. Venography is the first step, however, for evaluation of patients with large femoral or iliofemoral DVT who will undergo invasive pharmacomechanical catheter–directed therapy.

Overall Strategy: An Integrated Diagnostic Approach

A wide array of diagnostic tests can investigate suspected PE. The first step in an integrated diagnostic strategy (**Fig. 84.11**) is a directed history and physical examination to assess the clinical likelihood of

acute PE. The finding of a clinical probability that is not high is followed by D-dimer testing; a normal D-dimer assay usually rules out PE. If the D-dimer is elevated, chest CT usually provides the definitive diagnosis or exclusion of PE.

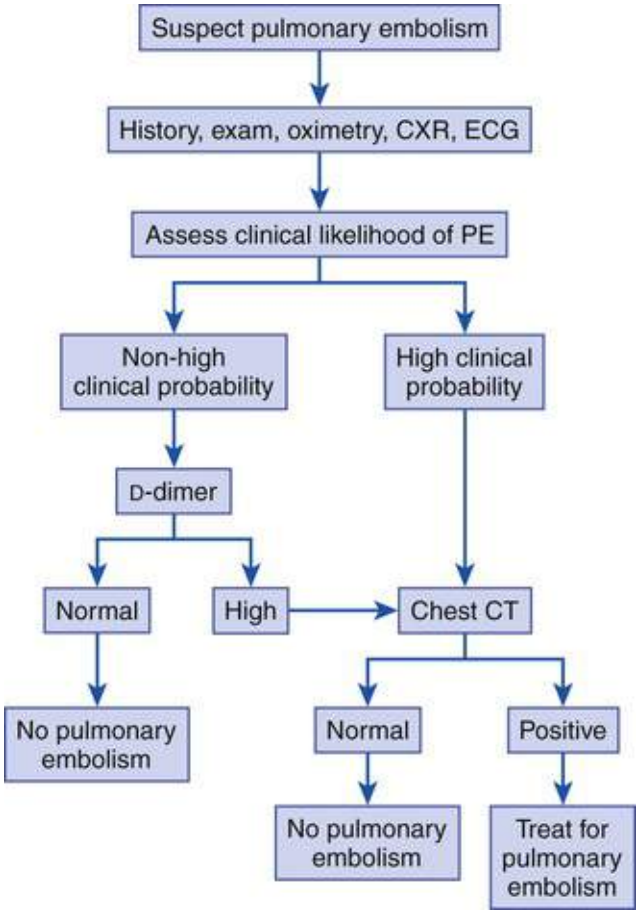

FIGURE 84.11 Integrated diagnostic approach. *CXR*, chest x-ray [examination].

Diagnostic Electronic Decision Support

It is essential to bring runaway technology under control and to slow down the overuse of CT scanning. Too little attention is paid to history taking, physical examination, clinical likelihood scoring systems, and D-dimer screening. Undue reliance on advanced imaging technology has adverse consequences aside from the increased cost, including unnecessary exposure to radiation and intravenous contrast agents, with potential complications of renal dysfunction or anaphylaxis. Electronic decision support at the time of ordering chest CT scans can reduce unwarranted imaging and increase the proportion of test results that are positive for PE.[62]

Anticoagulation Therapy for Acute Pulmonary Embolism

Risk Stratification

PE manifests with a wide spectrum of acuity, ranging from mild to severe. Therefore, rapid and accurate

risk stratification assumes paramount importance. Low-risk patients have an excellent prognosis with anticoagulation alone (**see also Chapter 93**). High-risk patients may require intensive hemodynamic and respiratory support with pressors, mechanical ventilation, or extracorporeal membrane oxygenation.[63] In addition to anticoagulation, advanced management[64] options include systemic thrombolysis, pharmacomechanical catheter–assisted therapy, vena cava filter placement, or surgical embolectomy[65] (**Fig. 84.12**). The three key components for risk stratification are (1) clinical evaluation, (2) assessment of right ventricular size and function, and (3) analysis of cardiac biomarkers to determine whether there is right ventricular microinfarction.

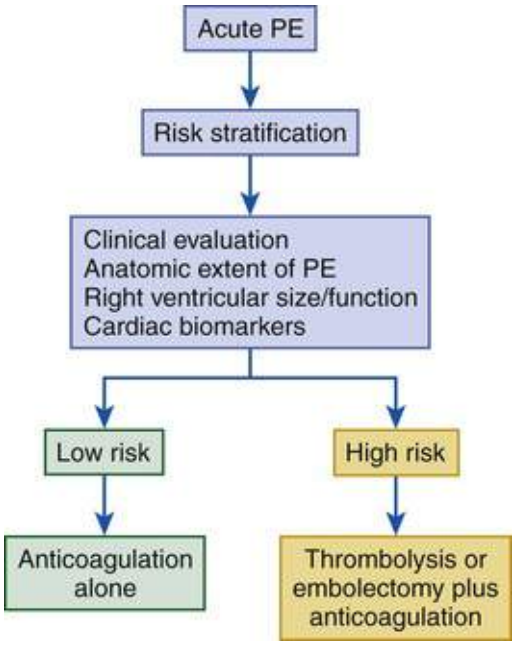

FIGURE 84.12 Management strategy for acute PE, based on risk stratification.

Clinical evaluation is straightforward if the patient looks and feels well and has no evidence of right ventricular dysfunction. The Pulmonary Embolism Severity Index (PESI) identifies 11 features from demographics, history, and clinical findings that can be weighted and scored to identify low-risk and high-risk patients[66] (**Table 84.6**).

TABLE 84.6

Pulmonary Embolism Severity Index (PESI) and Simplified PESI: Predictors of Prognostic Risk

PESI Criteria*	
Age > 80 years	Age in years
Male sex	+10
History of cancer	+30
History of heart failure	+10
History of chronic lung disease	+10
Heart rate ≥ 110 beats/min	+20
Systolic blood pressure < 100 mm Hg	+30
Respiratory rate ≥ 30 breaths/min	+20
Temperature <36°C	+20
Altered mental status	+60
Arterial oxygen saturation <90%	+20
Simplified PESI† Criteria	
Age > 80 years	+1
History of cancer	+1
History of heart failure or chronic lung disease	+1
Heart rate ≥ 110 beats/min	+1
Systolic blood pressure < 100 mm Hg	+1
Arterial oxygen saturation <90%	+1

*Class 1, ≤65; class 2, 66 to 85; class 3, 86 to 105; class 4, 106 to 125; class 5, 126 or more. In the PESI score, classes 1 and 2 are considered low risk, and classes 3 to 5 are considered high risk.

†Patients with a score of 0 are considered to be at low risk for PE; those with scores of 1 or higher are considered at high risk.

Clinicians should try to detect right ventricular dysfunction on physical examination by looking for distended jugular veins, a systolic murmur of tricuspid regurgitation, or an accentuated P_2. Clinical evaluation should integrate the results of electrocardiography that might show a right ventricular strain pattern (right bundle branch block, $S_1Q_3T_3$, negative T waves in leads V_1 through V_4), chest CT, echocardiography, and cardiac biomarkers of right ventricular injury.

Parenteral Anticoagulation

Unfractionated Heparin

Anticoagulation is the cornerstone of treatment for acute PE. Unfractionated heparin (UFH) is a highly sulfated glycosaminoglycan that is partially purified, most often from pig intestinal mucosa. The short half-life of UFH is advantageous for patients who may require subsequent insertion of an inferior vena cava filter, systemic thrombolysis, catheter-directed pharmacomechanical therapy, or surgical embolectomy.

Heparin acts primarily by binding to antithrombin, a protein that inhibits the coagulation factors thrombin (factor IIa) and factors Xa, IXa, XIa, and XIIa. Heparin subsequently promotes a conformational change in antithrombin that accelerates its activity approximately 100- to 1000-fold. This action prevents additional thrombus formation and permits endogenous fibrinolytic mechanisms to lyse at least some of the clot that has already formed. Heparin does *not* directly dissolve thrombus. Beyond its anticoagulant activity, heparin also exerts pleiotropic effects, including antiinflammatory[67] and vasodilatory properties.[68]

For patients with average bleeding risk, UFH should be started with an intravenous bolus of 80 units/kg, followed by a continuous infusion at 18 units/kg/hr. The aPTT should be targeted between 1.5 and 2.5 times the control value. The therapeutic range commonly is 60 to 80 seconds. Monitoring continuous intravenous UFH infusions using anti-Xa assays (instead of aPTT) is gaining popularity,

because this approach measures heparin's effect directly. This assay has special utility for patients with a baseline elevation in aPTT, such as those with lupus anticoagulant. The target level for therapeutic dosing is 0.3 to 0.7 units/mL.

Low-Molecular-Weight Heparin

Low-molecular-weight heparin (LMWH) consists of fragments of UFH that exhibit less binding to plasma proteins and endothelial cells. It therefore has greater bioavailability, with a more predictable dose response, and a longer half-life compared with UFH. These features permit weight-based LMWH dosing without laboratory tests, because no dose adjustment is needed in most instances. The kidneys metabolize LMWH, and patients with renal impairment require downward adjustment of LMWH dosing. If a quantitative assay is desired, an anti-Xa level can be obtained. Whether use of anti-Xa levels improves efficacy and safety remains controversial.

LMWH is recommended as monotherapy without anticoagulation for cancer patients with VTE. In one randomized trial, dalteparin monotherapy reduced by about half the recurrent VTE rate compared with warfarin.[69] In a subsequent trial of tinzaparin monotherapy versus warfarin in cancer patients, patients treated with tinzaparin had a rate of bleeding about 40% lower than those treated with warfarin.[70] A randomized trial of edoxaban versus LMWH for treatment of VTE in cancer patients is ongoing.[71]

Fondaparinux

Fondaparinux is an anticoagulant pentasaccharide that specifically inhibits activated factor X. It can be thought of as an ultra–low-molecular-weight heparin. Fondaparinux's predictable and sustained pharmacokinetic properties allow a fixed-dose, once-daily subcutaneous injection, without the need for coagulation laboratory monitoring or dose adjustment. Fondaparinux has a 17-hour half-life, and its elimination is prolonged in patients with renal impairment. Fondaparinux is licensed for the initial treatment of acute PE and acute DVT. It is often used off label for the management of suspected or proven heparin-induced thrombocytopenia, because it does not cross-react with heparin-induced antibodies.[72]

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a serious immune-mediated complication of heparin.[73,84] It occurs approximately 10 times more often with UFH than with LMWH. Immunoglobulin G antibodies bind to a heparin–platelet factor 4 complex to activate platelets, causing the release of prothrombotic microparticles. The microparticles promote excessive thrombin generation, which can result in paradoxical thrombosis despite thrombocytopenia. The thrombosis usually manifests as extensive and often bilateral DVT (sometimes affecting one upper extremity and one lower extremity) or PE, but presentations of MI, stroke, and unusual types of arterial thrombosis (such as mesenteric arterial thrombosis) also have been described.

The 4T point score is a semiquantitative clinical screening test for HIT.[74] The four components are (1) *t*hrombocytopenia, (2) *t*iming of decrease in platelet count, (3) *t*hrombosis or other sequelae such as skin necrosis, and (4) absence of o*t*her explanation. Heparin-induced thrombocytopenia should be suspected when the platelet count decreases to less than 100,000 or to less than 50% of baseline. The thrombocytopenia is usually mild, in the range of 40,000 to 70,000. Typically, heparin-induced thrombocytopenia occurs after 5 to 10 days of heparin exposure, most often in cardiac surgical ICUs.

ELISA testing quantifies anti–platelet factor 4 (PF4)/heparin antibody levels, which are measured in

optical density (OD) units. The higher the OD value, the more likely the diagnosis of HIT with thrombosis and of acute PE.[75] The serotonin release assay is the reference standard laboratory test for HIT. When HIT is diagnosed, UFH or LMWH should be discontinued immediately, and patients should not receive platelet transfusions. For HIT with thrombosis, a parenteral direct thrombin inhibitor such as argatroban or bivalirudin should be used. In a single-hospital initiative to substitute LMWH for UFH, HIT cases decreased by 79% and hospital HIT-related expenditures decreased by more than $250,000 annually.[76]

Warfarin Anticoagulation

Warfarin is a vitamin K antagonist, first approved for clinical use in 1954. It prevents gamma-carboxylation activation of coagulation factors II, VII, IX, and X. The full anticoagulant effect of warfarin becomes evident after 5 to 7 days, even if the prothrombin time, used to monitor warfarin's effect, becomes elevated more rapidly. For patients with VTE, the usual target international normalized ratio (INR) range is between 2.0 and 3.0. Self-monitoring of INRs improves patient satisfaction and quality of life and may reduce the rate of thromboembolic events.

Warfarin Overlap with Heparin

Initiation of warfarin as monotherapy to treat acute VTE without UFH, LMWH, or fondaparinux may paradoxically exacerbate hypercoagulability, increasing the likelihood of recurrent thrombosis. Warfarin monotherapy decreases the levels of two endogenous anticoagulants, proteins C and S—thus increasing thrombogenic potential. Overlapping warfarin for at least 5 days with an immediately effective parenteral anticoagulant counteracts the procoagulant effect of unopposed warfarin.

Dosing and Monitoring of Warfarin

Dosing warfarin is both an art and a science. Warfarin traditionally is dosed using an “educated guess” coupled with trial and error. Most practitioners begin with 5 mg daily. Debilitated or elderly patients require a reduced dose. Monitoring warfarin requires walking a tightrope—high INRs predispose to bleeding complications and constitute the most common reason for emergency hospitalization for adverse drug events in older Americans. In contrast, subtherapeutic dosing makes patients vulnerable to recurrent VTE. All patients taking warfarin should wear a medical alert bracelet or necklace in case they require rapid reversal of warfarin. Warfarin can have side effects other than hemorrhage, such as hair loss and increased levels of arterial calcification.[77] Some patients complain of “feeling cold” and fatigue.

Warfarin use is plagued by multiple drug-drug and drug-food interactions. Most antibiotics increase the INR, but some, like rifampin, lower the INR. Even seemingly benign drugs such as acetaminophen increase the INR in a dose-dependent manner. On the other hand, green leafy vegetables contain vitamin K, which lowers the INR. Concomitant medications with antiplatelet effects may increase the bleeding risk without increasing the INR. These include fish oil supplements, vitamin E, and alcohol. Centralized anticoagulation clinics, staffed by nurses or pharmacists, have eased the administrative burden of prescribing warfarin and have facilitated safer and more effective anticoagulation.

Warfarin Pharmacogenomics

Genetic determinants of warfarin dose response include CYP2C9-variant alleles—which impair the hydroxylation of S-warfarin, resulting in extremely low warfarin dose requirements—and variants in the gene encoding vitamin K epoxide reductase complex 1 (VKORC1). Pharmacogenetic testing has marginal

usefulness at best, however, and is not used in routine clinical practice.

Warfarin "Bridging"

When patients undergo elective surgery or procedures such as colonoscopy, warfarin is temporarily discontinued. To ensure continued anticoagulation perioperatively, "bridging" with LMWH used to be prescribed preoperatively while the warfarin activity washed out. Yet, the BRIDGE Trial of atrial fibrillation patients showed that forgoing bridging anticoagulation was noninferior to bridging with LMWH. The group that was not bridged had a 59% reduction in major bleeding complications.[78] Subsequently, the practice of routine bridging for VTE patients has fallen out of favor. Now, with only a few exceptions, such as patients with extreme thrombophilia or patients who have mechanical heart valves, we forgo bridging and simply hold warfarin preoperatively (usually for 4 days) and on the day of surgery.

Novel Oral Anticoagulants

Non–vitamin K antagonist oral anticoagulants (NOACs) (**see also Chapter 93**) have a rapid onset of action and provide full anticoagulation within several hours of ingestion. They are prescribed in fixed doses without laboratory coagulation monitoring and have minimal drug-drug or drug-food interactions. These agents have a short half-life, so do not require bridging when they are stopped for an invasive diagnostic or surgical procedure. For VTE treatment, they are noninferior to warfarin for efficacy and are superior to warfarin for safety.[79]

Evolution of Oral Anticoagulants for Pulmonary Embolism and Deep Vein Thrombosis Treatment

The limitations of warfarin prompted the development of NOACs. Four NOACs are licensed for VTE treatment: dabigatran (an oral thrombin inhibitor),[80,81] and three factor Xa inhibitors[82]: rivaroxaban,[83,84] apixaban,[85] and edoxaban[86] (**Table 84.7**). For extended therapy after an initial 6-month course of anticoagulation, dabigatran was compared with warfarin and with placebo.[87] Extended therapy studies against placebo were also carried out with rivaroxaban[83] and with apixaban.[88]

TABLE 84.7

Novel Oral Anticoagulants (NOACs) for Venous Thromboembolism—Acute and Extended Therapy

DRUG AND STUDY NAME	NOAC	WARFARIN
Acute Therapy		
Dabigatran/ RE-COVER	(*N* = 1274)	(*N* = 1265)
	2.4% recurrence	2.1% recurrence
Dabigatran/ RE-MEDY	(*N* = 1430)	(*N* = 1426)
	1.8% recurrence	1.3% recurrence
Dabigatran/ RE-COVER II	(*N* = 1279)	(*N* = 1289)
	2.3% recurrence	2.2% recurrence
Rivaroxaban/ EINSTEIN Acute DVT	(*N* = 1841)	(*N* = 1718)
	2.1% recurrence	3.0% recurrence
Rivaroxaban/ EINSTEIN-PE	(*N* = 2420)	(*N* = 2413)
	2.1% recurrence	1.8% recurrence
	1.1% major bleeding	2.2% major bleeding
Apixaban AMPLIFY	(*N* = 2691)	(*N* = 2704)
	2.3% recurrence	2.7% recurrence
	0.6% major bleeding	1.8% major bleeding
Edoxaban/HOKUSAI—VTE	(*N* = 4143)	(*N* = 4149)
	3.2% recurrence	3.5% recurrence
	8.5% clinically relevant bleeding	10.3% clinically relevant bleeding
Extended Therapy		
Dabigatran/RE-SONATE	(*N* = 681)	(*N* = 662)
	0.4% recurrence	5.6% recurrence
Rivaroxaban/EINSTEIN DVT Continued Treatment	(*N* = 602)	(*N* = 594)
	1.3% recurrence	7.1% recurrence
Apixaban Extension VTE	(*N* = 829)	(*N* = 840)
	1.7% recurrence	8.8% recurrence

2016 American College of Chest Physicians Guidelines

The American College of Chest Physicians (ACCP) 2016 Guidelines recommend NOACs rather than warfarin to treat acute VTE patients (without cancer), regardless of whether short-term (3 to 6 months) anticoagulation is planned or extended anticoagulation without a stop date is planned. The 2016 Guidelines are based upon the pivotal trials used to obtain Food and Drug Administration (FDA) approval for dabigatran, rivaroxaban, apixaban, and edoxaban and characterize the evidence favoring NOACs over warfarin as “moderate or high quality.” The Guidelines add: “Based on less bleeding with NOACs and greater convenience for patients and health-care providers, we now suggest that a NOAC is used in preference to vitamin K antagonists for the initial and long-term treatment of VTE in patients without cancer.”[89]

Managing Bleeding Complications from Anticoagulants

Protamine sulfate can be given for life-threatening bleeding caused by UFH or LMWH. Life-threatening bleeding caused by warfarin can be managed with prothrombin complex concentrates to achieve immediate hemostasis.[90] For acute management of bleeding in patients taking NOACs, the initial assessment should focus on ensuring hemodynamic stability, detecting the source of bleeding, estimating the time that has elapsed since the last dose of NOAC, and determining renal function. Patients can then be risk stratified. Those with minor bleeding will respond to local hemostatic measures. Those with moderate bleeding may require aggressive volume replacement and definitive surgical intervention. With severe or life-threatening bleeding, hemodynamic support in an intensive care setting plus replacement agents such as prothrombin complex concentrate may be warranted.[91] Prothrombin complex concentrate is licensed to manage bleeding from warfarin. For major bleeding due to NOACs, consider using antidotes

such as idarucizumab to reverse dabigatran[92] or andexanet to reverse rivaroxaban; apixaban, or edoxaban[93] (available in ongoing clinical trials). The International Society of Thrombosis and Haemostasis has issued guidelines on when and how to use antidotes for NOACs.[94] The principal indications are life-threatening bleeding or required emergency surgery or procedural intervention in patients at high risk for bleeding.

Optimal Duration of Anticoagulation Therapy and Selection of an Optimal Anticoagulant

Risk of Recurrent Venous Thromboembolism After Discontinuation of Anticoagulation

There is a high risk of recurrence of VTE after the discontinuation of anticoagulation. Cardiovascular inflammation may explain the recurrent nature of VTE.[95] In a 10-year cohort study of 1626 Italian patients with VTE who received full anticoagulation for a minimum of 3 months, the overall cumulative incidence of recurrence was 11% at 1 year, 20% at 3 years, 29% at 5 years, and 40% at 10 years. Patients with idiopathic or unprovoked VTE have even higher recurrence rates: 15% at 1 year, 26% at 3 years, 41% at 5 years, and 53% at 10 years.[96]

Men suffer recurrent VTE more often than women. In a patient-level metaanalysis of multiple cohort studies, recurrence rates for those with unprovoked VTE after discontinuation of anticoagulation were as follows: 10% for men versus 5% for women at 1 year; 16% for men versus 8% for women at 2 years; 22% for men versus 9% for women at 3 years; and 43% for men versus 11% for women at 5 years.[97] The Vienna Prediction Model uses a nomogram to predict the likelihood of recurrence. Key components that increase the likelihood are male sex, PE (rather than DVT) symptoms at initial presentation, and the magnitude of quantitative D-dimer elevation.[98] Persistent thrombus imaged on chest CT does not predict recurrent PE. Approximately one half of patients with PE will have persistent thrombus on chest CT 6 months after the initial event.

Abnormally elevated D-dimer levels after withdrawal of anticoagulation may signify ongoing hypercoagulability. Yet, the risk for recurrence in patients with a first unprovoked episode of VTE who have a subsequent negative D-dimer result is not low enough to justify stopping anticoagulant therapy. In 319 patients with a negative D-dimer after completing 3 to 7 months of anticoagulation, the rate of recurrent VTE was 6.7% per patient-year.[99]

How to Determine the Optimal Duration of Anticoagulation

Classifying a patient's VTE as provoked or unprovoked helps determine the optimal duration of anticoagulation. Those patients with unprovoked VTE have a higher rate of recurrence than those with provoked VTE after anticoagulation is discontinued. Whether a VTE event is provoked or unprovoked is sometimes uncertain. These circumstances require an individualized duration of therapy. Decisions about continuing or stopping anticoagulation should take patient and family preferences into account. Overall, long-term treatment with warfarin reduces the risk of recurrent VTE but increases the risk of major bleeding.[100] In a double-blind randomized trial of 24 months versus 6 months of warfarin anticoagulation in 371 patients with idiopathic PE, the additional 18 months of anticoagulation reduced the composite outcome of recurrent VTE and major bleeding by 78%. The benefit, however, was not maintained after

discontinuation of anticoagulation.[101]

The EINSTEIN CHOICE study is investigating the optimal medication regimen for extended-duration therapy in patients who have completed 6 to 12 months of anticoagulation for the index acute VTE event. Patients enrolled in this trial are randomized to one of three groups: rivaroxaban 20 mg daily versus rivaroxaban 10 mg daily versus aspirin 100 mg daily. Both doses of rivaroxaban were superior to aspirin for preventing recurrent VTE. The three groups were equivalent with respect to major bleeding complications.[102]

For patients with cancer who require treatment for VTE, an extended duration of anticoagulation is recommended until the cancer is considered cured. LMWH as monotherapy is the standard anticoagulant used under these circumstances.

Aspirin for Extended-Duration Anticoagulation

Two pivotal studies tested low-dose aspirin versus placebo in patients with unprovoked VTE who had completed 6 to 12 months of standard anticoagulation. The studies were similar in patient inclusion and exclusion criteria, and the dose of aspirin was the same (100 mg) in both trials. In a metaanalysis of the results, data for 1224 patients were analyzed, showing a 32% reduction in the rate of recurrence of VTE and a 34% reduction in the rate of major vascular events.[103] Thus, aspirin confers an evidence-based therapeutic benefit for patients who do not wish to restrict the lifestyle with the burdens of indefinite-duration anticoagulation.

Selection of an Optimal Oral Anticoagulant for Extended-Duration Anticoagulation

Standard-intensity extended-duration anticoagulation with warfarin has been the conventional approach, with a target INR range of 2.0 to 3.0. Low-intensity warfarin, with a target INR range of 1.5 to 2.0, is also well validated in the PREVENT (Prevention of Recurrent Venous Thromboembolism) trial.[104] Rivaroxaban, dabigatran, and apixaban are markedly superior to placebo for the prevention of recurrent VTE after a standard 6- to 12-month initial course of anticoagulation (**see Table 84.7**). Dabigatran is noninferior to warfarin for extended-duration anticoagulation.[80]

Advanced Therapy (in Addition to Anticoagulation) for Acute Pulmonary Embolism

Patients with massive PE or high-risk submassive PE (with both right ventricular dysfunction and troponin elevation due to right ventricular injury) generally warrant advanced therapy. Options include full-dose systemic thrombolysis, half-dose systemic thrombolysis, pharmacomechanical catheter–directed therapy (usually with low-dose thrombolysis), surgical embolectomy, and inferior vena cava filter placement.

Massive Pulmonary Embolism

Multidisciplinary Pulmonary Embolism Response Teams (PERTs) are being set up throughout the United States to evaluate immediately those patients who present with massive or high-risk submassive PE. Team

members have subspecialized cognitive and technical skills in PE, and the team approach promotes consensus and a unified, reasoned plan for the individual patient.[105] PERTs are becoming especially important as our emphasis on advanced management is shifting toward an interventional approach.[106]

Systemic Thrombolysis Administered Through a Peripheral Vein

Thrombolysis reverses right-sided heart failure by physical dissolution of anatomically obstructing pulmonary arterial thrombus. The hallmarks of successful therapy are reduction of right ventricular pressure overload and prevention of continued release of serotonin and other neurohumoral factors that exacerbate pulmonary hypertension. Dissolution of thrombus in the pelvic or deep leg veins theoretically decreases the likelihood of recurrent PE. Thrombolysis may also improve pulmonary capillary blood flow and reduce the likelihood of developing CTEPH.

When prescribing thrombolysis, there are three intensities of dosing: (1) full-dose systemic thrombolysis (licensed), (2) half-dose systemic thrombolysis (prescribed off label), or (3) low-dose thrombolysis as part of a strategy of using catheter-directed pharmacomechanical therapy in the cardiac catheterization or Interventional Radiology laboratory.[64] The FDA has approved alteplase for massive PE, in a dose of 100 mg delivered through a peripheral vein as a continuous infusion over 2 hours, without concomitant heparin. Patients who receive thrombolysis up to 14 days after onset of new symptoms or signs can derive benefit, probably because of the effects on the bronchial collateral circulation. Intracranial hemorrhage is the most feared and severe complication.

A metaanalysis examined patients randomized to thrombolytic therapy versus anticoagulation alone, with most patients classified as submassive PE (1775 out of a total of 2115) because they had hemodynamic stability despite right ventricular dysfunction. Thrombolysis resulted in a 47% reduction in the all-cause mortality rate, a 60% decrease in recurrent PE, a 2.7-fold increased risk of major bleeding, and a 4.6-fold increased risk of intracranial hemorrhage.[107]

Advances in Pharmacomechanical Catheter–Directed Therapy, Including Thrombolysis

The 1% to 3% rate of intracranial hemorrhage in patients with PE receiving full-dose systemic thrombolysis has dampened enthusiasm for this potentially life-saving therapy. Pharmacomechanical catheter–directed reperfusion, however, holds the promise of good efficacy, with lower rates of major bleeding owing to lower doses of thrombolytic agent. The typical dose of tissue plasminogen activator in a pharmacomechanical catheter–based procedure, for example, is 24 mg or less—compared with 100 mg for systemic administration.

Interventional mechanical techniques usually performed in conjunction with low-dose thrombolysis include mechanical fragmentation and aspiration of thrombus through a standard pulmonary artery catheter, clot pulverization with a rotating basket catheter, rheolytic thrombectomy, and pigtail rotational catheter embolectomy. After reduction of thrombus burden, pulmonary artery balloon dilation and stenting can be undertaken to treat residual vessel stenoses. Successful catheter embolectomy rapidly restores normal blood pressure and decreases hypoxemia.

Low-intensity ultrasound–facilitated fibrinolysis (**Fig. 84.13**) is a novel approach. Ultrasound disaggregates fibrin strands, increases clot permeability, and disperses infused fibrinolytic drug into the clot through acoustic microstreaming effects. The SEATTLE II Trial studied 150 patients with massive or submassive PE to evaluate the safety and efficacy of ultrasound-facilitated, catheter-directed fibrinolysis using 24 mg of tissue plasminogen activator. No patient suffered intracranial hemorrhage. This procedure

decreased right ventricular dilation, reduced pulmonary hypertension, and decreased the anatomic thrombus burden.[108]

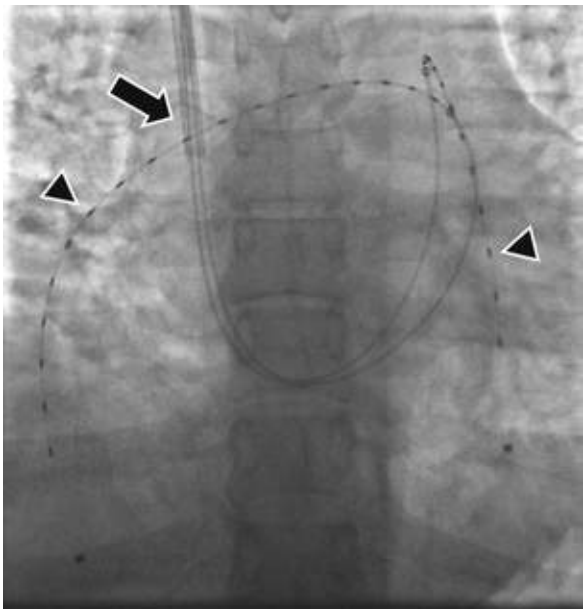

FIGURE 84.13 Bilateral low-power ultrasound–facilitated catheter-directed thrombolysis in a 20-year-old woman with massive PE. In the dual-catheter (*arrow*) system shown, the outer catheter has side holes to permit administration of fluids and medications such as alteplase. The inner sheath contains catheters with ultrasound transducers (*arrowheads*).

Surgical Embolectomy

Emergency surgical embolectomy has reemerged for the management of patients with massive PE and systemic arterial hypotension or submassive PE with severe right ventricular dysfunction, in whom contraindications preclude thrombolysis (**Fig. 84.14**). This procedure also is suitable for patients with acute PE who require surgical excision of a right atrial thrombus or closure of a patent foramen ovale. Surgical embolectomy also can be used as rescue therapy for patients in whom PE is refractory to thrombolysis. Results are best when patients undergo surgery before they become pressor-dependent and before the onset of cardiogenic shock and multisystem organ failure.[109] Avoidance of blind instrumentation of the fragile pulmonary arteries is imperative. Extraction is limited to directly visible clots. In the largest single-center case series, 115 patients underwent surgical pulmonary embolectomy. The overall 30-day mortality rate was 6.6%. In the subgroup of 56 patients with submassive PE, the operative mortality rate was 3.6%.[110]

FIGURE 84.14 Surgical pulmonary embolectomy specimen in a 72-year-old woman who presented with presyncope, hypotension, and hypoxia. She was diagnosed with massive PE by chest CT scan and underwent emergency pulmonary embolectomy. This patient survived despite the marked extent of the lesion.

Inferior Vena Cava Filters

Appropriate use of inferior vena cava (IVC) filters is a hot topic. On the plus side, filters hold the promise of reducing PE rates by trapping DVTs that have detached from pelvic and leg veins and are hurtling toward the heart. The negative side is that filters can cause complications, can add expense, and have not been rigorously studied in critically ill patients.[111,112]

Use of IVC filters in the United States has increased about 25-fold in the past 20 years. Among Medicare patients with acute PE, about 17% undergo IVC filter placement. In these patients with IVC filters, the in-hospital mortality rate has fallen in the past decade from about 8% to 4%. These patients with filters had a greater frequency of comorbidities such as cancer, heart failure, atherosclerosis, and vascular disease. Filter use appears especially high in blacks, men, and octogenarians. Overall use in the United States varies markedly by region, with highest insertion rates in the South Atlantic states and lowest rates in the mountain states.[113]

Patients with massive PE benefit most from IVC filter insertion. In the International Cooperative PE Registry (ICOPER), 108 of 2392 patients presented with massive PE. Their mortality rate was 52% at 90 days. However, 10 of the 11 patients who received IVC filters survived for 90 days.[114] Among massive PE patients in the Nationwide Inpatient Sample, those receiving filters had a lower mortality rate compared with other massive PE patients, regardless of whether thrombolytic therapy was used in the patients without filters (**Fig. 84.15**).[115] In a nested case-control study within a large European VTE registry, VTE patients with a high risk of bleeding who received filters showed a trend toward lower rates of all-cause deaths compared with patients with high-risk bleeding who did not have filters.[116] In a registry of California hospitals, IVC filter insertion reduced the short-term risk of death only among patients with acute VTE who had a contraindication to anticoagulation because of active bleeding.[117] Filters are rarely advisable in VTE patients who are good candidates for long-term full-intensity anticoagulation. In the PREPIC2 trial of filter insertion plus anticoagulation versus anticoagulation alone, IVC filter insertion did not reduce the risk of symptomatic recurrent PE at 3 months.[118]

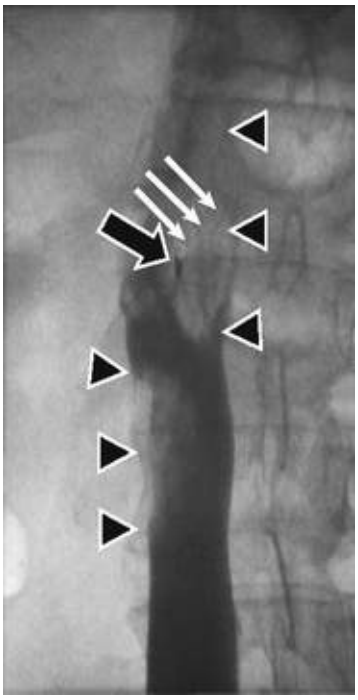

FIGURE 84.15 Large PE-in-transit, with thrombus (*arrowheads*) trapped below and visualized above the Bard Eclipse inferior vena cava filter. The force of the embolizing DVT displaced one of the filter struts (*white arrows*). The "hook" to retrieve the filter is marked with the *black arrow*.

Generally accepted consensus recommendations for IVC filter insertion include (1) major bleeding even with full-dose anticoagulation, (2) major contraindications to full-dose anticoagulation, and (3) recurrent PE despite well-documented full-dose anticoagulation for an existing VTE. There remain outside these consensus recommendations special populations in whom benefits of IVC filter insertion may outweigh risks: (1) patients with massive PE or high-risk submassive PE, (2) patients undergoing surgical pulmonary embolectomy, and (3) surgical patients during preoperative evaluation who are at high risk of VTE with a concomitant high risk of bleeding if anticoagulated.[112]

The Angel catheter is a temporary device that combines the function of an IVC filter with that of a triple-lumen central venous catheter. It is intended for bedside placement without fluoroscopy, using standard venous access techniques. This device is designed to prevent clinically significant PE in patients with recognized contraindications to standard pharmacologic thromboprophylaxis. In a European Angel Catheter Registry that had enrolled 60 patients, only one developed a PE.[119]

Chronic Thromboembolic Pulmonary Hypertension

Chronic thromboembolic pulmonary hypertension (**see also Chapter 85**) occurs in 2% to 4% of patients with acute PE.[120] CTEPH results from persistent obstruction of pulmonary arteries and progressive vascular remodeling. Not all patients presenting with CTEPH have a history of clinically overt PE. The diagnostic workup should include ventilation-perfusion scintigraphy, which has high sensitivity for detecting CTEPH and a negative predictive value of nearly 100%. CT angiography usually reveals mosaic perfusion, part or complete occlusion of pulmonary arteries, and intraluminal bands and webs. Patients with suspected CTEPH should be referred to a specialized center for right-heart catheterization and pulmonary angiography.[121]

Primary therapy for CTEPH is surgical pulmonary thromboendarterectomy, which confers mostly excellent long-term results that are often curative. The operation entails a median sternotomy, cardiopulmonary bypass, and deep hypothermia with circulatory arrest periods. Some patients are not surgical candidates or have residual pulmonary arterial vasoconstriction that may respond to sildenafil or

bosentan. Percutaneous pulmonary artery balloon dilation shows promise in patients who are not deemed eligible candidates for surgery. Riociguat, which stimulates soluble guanylate activity, is approved for patients with inoperable CTEPH or those who have not had resolution of pulmonary hypertension despite pulmonary thromboendarterectomy.

Deep Vein Thrombosis Interventions

Indications for catheter-directed DVT thrombolysis remain uncertain but usually include extensive iliofemoral and upper extremity venous thrombosis. In Norway, the CaVenT Study Group randomly assigned 209 patients with iliofemoral DVT to receive catheter-directed thrombolysis versus conventional therapy with LMWH bridging to warfarin. At 24 months, the frequency of postthrombotic syndrome was 56% in the conventionally treated group, compared with 41% in the intervention group ($P = 0.047$). Iliofemoral patency was present in 66% of the intervention group, compared with 47% of the group receiving conventional anticoagulation.[122] The U.S. National Heart, Lung, and Blood Institute (NHLBI) sponsored the ATTRACT study, a randomized trial of pharmacomechanical catheter–directed thrombolysis versus conventional anticoagulation in 692 patients with iliac or femoral vein DVT. The primary endpoint is the incidence of postthrombotic syndrome. ATTRACT will provide high-quality data regarding the routine use of pharmacomechanical catheter–directed thrombolysis to prevent postthrombotic syndrome in patients with symptomatic proximal DVT.[123]

Emotional Support

Patients find PE to be emotionally draining. They and their families seek reassurance that most patients have good outcomes once the diagnosis has been established. They must confront PE-related issues such as genetic predisposition, potential long-term disability, changes in lifestyle related to anticoagulation, and the possibility of suffering a recurrent event. Clinicians can help allay this emotional burden by discussing the implications of PE with patients and their families. I find that a good way to introduce this topic is to ask: “How are you coping with your PE emotionally and psychologically?” My nurse and I started a PE support group 25 years ago to facilitate these discussions. We usually meet once a month in the evening. The conversation focuses on patient and family anxiety, coupled with the day-to-day difficulties that arise in the aftermath of PE.

Prevention

Rationale for In-Hospital Prophylaxis

PE is the most preventable cause of in-hospital death, but once PE occurs, it is difficult to diagnose, expensive to treat, and potentially lethal despite therapy. VTE prevention is of paramount importance because it is preferable to diagnosis and treatment. Fortunately, low fixed-dose anticoagulant prophylaxis is effective and safe during hospitalization (**Table 84.8**). Commonly used regimens include minidose unfractionated heparin 5000 units twice or three times daily, enoxaparin 40 mg daily, and dalteparin 5000 units daily. A multifaceted approach of electronic alerts, sharing comparative practitioner metrics, and continuing medical education can increase the frequency of appropriate VTE prophylaxis and reduce the incidence of 90-day symptomatic VTEs.[124]

TABLE 84.8

Common Regimens for Venous Thromboembolism Prevention

CONDITION	PROPHYLAXIS
Hospitalization with medical illness	Unfractionated heparin 5000 units SC bid or tid *or* Enoxaparin 40 mg SC qd *or* Dalteparin 2500 units or 5000 units SC qd *or* Fondaparinux 2.5 mg SC qd with normal renal function (in patients with a heparin allergy such as heparin-induced thrombocytopenia) *or* Graduated compression stockings or intermittent pneumatic compression for patients with contraindications to anticoagulation Consider combination pharmacologic and mechanical prophylaxis for high-risk patients
General surgery	Unfractionated heparin 5000 units SC bid or tid *or* Enoxaparin 40 mg SC qd *or* Dalteparin 2500 or 5000 units SC qd
Major orthopedic surgery	Warfarin (target INR 2 to 3) *or* Enoxaparin 30 mg SC bid *or* Enoxaparin 40 mg SC qd *or* Dalteparin 2500 or 5000 units SC qd *or* Fondaparinux 2.5 mg SC qd *or* Rivaroxaban 10 mg qd *or* Aspirin 81 mg qd *or* Dabigatran 220 mg qd *or* Apixaban 2.5 mg twice daily *or* Intermittent pneumatic compression (with or without pharmacologic prophylaxis)

SC, subcutaneous.

In the United States, about 7 million acutely ill medical patients at increased risk for VTE are hospitalized annually with conditions such as pneumonia, heart failure, and COPD. They have a high risk for development of VTE and account for more than 20% of the attributable risks for VTE. Thromboprophylaxis can halve the rate of VTE while patients are hospitalized. The stasis and immobilization associated with postoperative venous thrombosis may actually increase paradoxically after hospital discharge, because following short hospital stays, patients are often too weak and debilitated to walk at home. After hospital discharge, prophylactic anticoagulation is not routinely prescribed. The peak incidence of VTE occurs within the first month after hospital discharge.[125]

To determine whether extended-duration administration of anticoagulation is superior to a standard short course of prophylaxis with enoxaparin, the APEX Trial compared the anti-Xa NOAC, betrixaban, administered for 35 to 42 days, with enoxaparin, administered for 6 to 14 days, in 7513 hospitalized medically ill patients at risk for VTE. Betrixaban has a longer half-life (23 hours) and undergoes less renal clearance than other NOACs. There was a 24% reduction in VTEs among the extended-duration betrixaban patients compared with those assigned to enoxaparin. There was no difference in major bleeding episodes between the two groups.[126] The ongoing MARINER trial is also examining postdischarge medical patients at risk for VTE who will randomly receive rivaroxaban versus placebo.[127]

In-Hospital Risk Factors for Venous Thromboembolism and Bleeding

The most widely used risk assessment tool to decide whether to administer VTE prophylaxis to hospitalized medical patients is the Padua Prediction Score, which has a point scoring system based on 11 variables (**Table 84.9**). A score of 4 or more points indicates a high risk for developing VTE. A simpler validated model to identify VTE risk in hospitalized medical patients, developed at the Intermountain Medical Center in Utah, may help facilitate risk assessment. The model predicts a high risk if a patient has at least one of the following four risk factors: (1) previous VTE, (2) a medical indication for bed rest, (3) a peripherally inserted central venous catheter, or (4) cancer.[128] Pharmacologic thromboprophylaxis is generally withheld if the bleeding risk is excessively high due to threatened, active, or recent major

bleeding or thrombocytopenia.

TABLE 84.9

Padua Prediction Score for Identification of Hospitalized Patients at Risk for Venous Thromboembolism*

RISK FACTOR	SCORING
Cancer	3
Previous VTE	3
Immobility	3
Thrombophilia	3
Trauma/surgery	2
Age ≥ 70 years	1
Heart/respiratory failure	1
Acute MI or stroke	1
Infection/rheumatologic disorder	1
Obesity	1
Hormonal treatment	1

*High risk for developing PE is defined as 4 score points or greater.

Mechanical Prophylaxis in Medically Ill Patients

Mechanical measures consist of intermittent pneumatic compression devices, which enhance endogenous fibrinolysis and increase venous blood flow, and graduated compression stockings. Pharmacologic thromboprophylaxis is more effective than mechanical prophylaxis. Therefore, mechanical measures are prescribed primarily when there is a contraindication to anticoagulation.

Advances in Venous Thromboembolism Prophylaxis in Major Orthopedic Surgery

Extended prophylaxis after hospital discharge decreases the risk of PE and DVT among patients undergoing major orthopedic surgery, particularly total hip or knee replacement, without increasing the frequency of major bleeding events. There is evidence to support the use of virtually any prophylactic measure in patients undergoing major orthopedic surgery. Approved approaches include LMWH, warfarin, NOACs, aspirin, and mechanical measures. The PEPPER Trial [NCT02810704], which is just getting under way, will randomize about 25,000 patients undergoing total knee or hip replacement to warfarin (target INR 1.7 to 2.2) versus rivaroxaban 10 mg daily versus low-dose aspirin 81 mg daily.

Future Perspectives

Breakthroughs in understanding PE are advancing at a rapid pace. Inflammation activates platelets, which play a central role in releasing microparticles that accelerate the thrombotic process. VTE and atherothrombosis have overlapping risk factors and pathophysiologic findings. Risk stratification is more critical than ever before. Not only must we decide which patients are too unstable for anticoagulation alone, but we also need to identify those low-risk patients with PE who can be managed as outpatients.

For patients who have massive or submassive PE, data suggest that thrombolysis reduces mortality rates among patients who initially are hemodynamically unstable or who have stable blood pressure with right ventricular dysfunction and elevated cardiac markers. Pharmacomechanical catheter–directed therapy is an innovative technology that may reduce the thrombus burden by means of a lower dose of

thrombolysis than with peripheral intravenous administration. Registry data also suggest that vena cava filter placement may reduce mortality rates in hemodynamically unstable patients with PE. Inpatient pharmacologic prophylaxis is effective, safe, and standard practice for VTE prevention in patients at moderate or high risk. We continue to investigate which drugs, dosages, and criteria are optimal for extended out-of-hospital VTE prophylaxis among high-risk medical patients. Consortia of clinicians, patients, and the public are working together to improve VTE awareness and to advocate for implementing the cutting-edge technologies, drugs, and best practices that we have discovered.

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85

Pulmonary Hypertension

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Definition

Pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure (mPAP) of 25 mm Hg or greater at rest, as assessed by right heart catheterization (RHC). PH was previously known as an orphan disease, that is, a condition that affects few individuals and is overlooked by the medical profession, health care systems, and pharmaceutical companies. Although PH is indeed rare, one can no longer say that it is being overlooked. Indeed, a number of recent important discoveries have improved our understanding of the disease, helped guide patient management, and laid foundations for future research. Since the mid-20th century, major achievements have been made in the field, from the development of RHC techniques to the first description of so-called primary PH and the progress achieved thanks to the National Institutes of Health (NIH) Primary Pulmonary Hypertension Registry and the World Pulmonary Hypertension conferences that have taken place five times in 40 years: 1973

(Geneva, Switzerland), 1998 (Evian, France), 2003 (Venice, Italy), 2008 (Dana Point, California, United States), and 2013 (Nice, France). The most recent guidelines provide a clear classification of the major clinical subcategories of PH (**Table 85.1**), among which pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) have been subject to the most rapid advancements in terms of knowledge and treatment options in past decades.[1]

TABLE 85.1

Comprehensive Clinical Classification of Pulmonary Hypertension

1. Pulmonary arterial hypertension
1.1. Idiopathic
1.2. Heritable
1.2.1. *BMPR2* mutation
1.2.2. Other mutations
1.3. Drug- and toxin-induced
1.4. Associated with:
A.4.1. Connective tissue disease
1.4.2. Human immunodeficiency virus (HIV) infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Schistosomiasis
1′. Pulmonary venoocclusive disease and/or pulmonary capillary hemangiomatosis
1′.1. Idiopathic
1′.2. Heritable
1′.2.1. *EIF2AK4* mutation
1′.2.2. Other mutations
1′.3. Drug-, toxin-, and radiation-induced
1′.4. Associated with:
1′.4.1. Connective tissue disease
1′.4.2. HIV infection
1″. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left heart disease
2.1. Left ventricular systolic dysfunction
2.2. Left ventricular diastolic dysfunction
2.3. Valvular disease
2.4. Congenital or acquired left heart inflow or outflow tract obstruction and congenital cardiomyopathies
2.5. Congenital or acquired pulmonary vein stenosis
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
4.1. Chronic thromboembolic pulmonary hypertension
4.2. Other pulmonary artery obstructions
4.2.1. Angiosarcoma
4.2.2. Other intravascular tumors
4.2.3. Arteritis
4.2.4. Congenital pulmonary artery stenosis
4.2.5. Parasites (hydatidosis)
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1. Hematologic disorders: chronic hemolytic anemias, myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with or without dialysis), segmental pulmonary hypertension

BMPR2, bone morphogenetic protein receptor type 2; *EIF2AK4*, eukaryotic translation initiation factor 2 alpha kinase 4.

From Galie N, Humbert M, Vachiery J-L, et al: 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2016;37:67.

PH is a complex, multidisciplinary disorder. The term *pulmonary hypertension* refers to the presence of high pulmonary vascular pressure, which can be the end result of a variety of different underlying disorders. By definition, PH is an mPAP of 25 mm Hg or greater.[1] The definition of normal versus abnormal is based on several factors: (1) the population resting mPAP is approximately 14 mm Hg, and a value of 20 mm Hg encompasses two standard deviations above the mean; (2) a value of 25 mm Hg is therefore definitively above the normal distribution of values; and (3) the value of 25 mm Hg has, by

consensus, been used to identify candidates for participation in clinical trials and registries. *Precapillary PH* is defined as an mPAP of 25 mm Hg or more; a pulmonary capillary wedge pressure (PCWP) of 15 mm Hg or less; and a pulmonary vascular resistance (PVR) of more than 3 Wood units. Precapillary PH may be group 1 (pulmonary arterial hypertension [PAH]), group 3 (PH due to lung disease), group 4 (CTEPH), or group 5 (PH due to unclear or multifactorial mechanisms) in origin. *Postcapillary PH* is present when the mPAP is 25 mm Hg or more and the PCWP is 15 mm Hg or more. Postcapillary PH is most common in group 2 patients, or those with PH due to left heart disease; it can also occur in group 5 patients, or those with PH with unclear or multifactorial mechanisms. Recent guidelines have updated the characterization of postcapillary PH and now rely on the DPG (diastolic PAP–mean PCWP) gradient to determine the presence of pulmonary vascular disease as opposed to passive congestion. A DPG of less than 7 mm Hg and/or a PVR of less than 3 Wood units reflects isolated postcapillary PH, whereas a DPG of more than 7 mm Hg and /or a PVR of more than 3 Wood units is considered *combined postcapillary and precapillary PH.*[1]

Anatomy

The lung has a unique double arterial blood supply from the pulmonary and bronchial arteries, as well as double venous drainage into the pulmonary and azygos veins. Each pulmonary artery accompanies the appropriate generation of bronchus and divides with it down to the level of the respiratory bronchiole. Pulmonary arteries are classified as elastic or muscular. Elastic arteries are conducting vessels that are highly distensible at a low transmural pressure. As the arteries decrease in size, the number of elastic laminae decreases and the amount of smooth muscle increases. Eventually, in vessels between 100 and 500 µm, elastic tissue is lost from the media and the arteries become muscular. The intima of the pulmonary arteries consists of a single layer of endothelial cells and their basement membrane. The adventitia is composed of dense connective tissue in direct continuity with the peribronchial connective tissue sheath. The muscular arteries are 500 µm or smaller in diameter and are characterized by a muscular media bounded by internal and external elastic laminae. Arterioles are precapillary arteries smaller than 100 µm in outer diameter and composed solely of a thin intima and single elastic lamina. The alveolar capillaries are lined with a continuous layer of endothelium resting on a continuous basement membrane and focally connected to scattered pericytes located beneath the basement membrane. Within the respiratory units, the pulmonary arteries and arterioles are centrally located and give rise to precapillary arterioles, from which a network of capillaries radiates into the alveolar walls. The alveolar capillaries collect at the periphery of the acini and then drain into venules located in the interlobular and interlobar septa.

The bronchial circulation provides nutrition to the airways. The bronchial arteries ramify into a capillary network drained by bronchial veins; some empty into the pulmonary veins and the remainder into the systemic venous bed. The bronchial circulation therefore constitutes a physiologic right-to-left shunt. Normally, blood flow through this system amounts to approximately 1% of the cardiac output (CO), and the resulting desaturation of left atrial blood is usually trivial.

Pathology

Different pathologic features characterize the diverse clinical PH groups. In PAH the pathologic lesions involve mainly the distal pulmonary arteries (< 500 µm in diameter) and are characterized by medial hypertrophy, intimal proliferative and fibrotic changes (concentric, eccentric), adventitial thickening with

moderate perivascular inflammatory infiltrates, complex lesions (plexiform, dilated lesions), and thrombotic lesions (**Fig. 85.1**). PAH patients may show significant bronchial arterial remodeling. Such changes in the systemic vasculature may cause episodes of hemoptysis and are more often observed in PAH patients harboring a *BMPR2* mutation.[2]

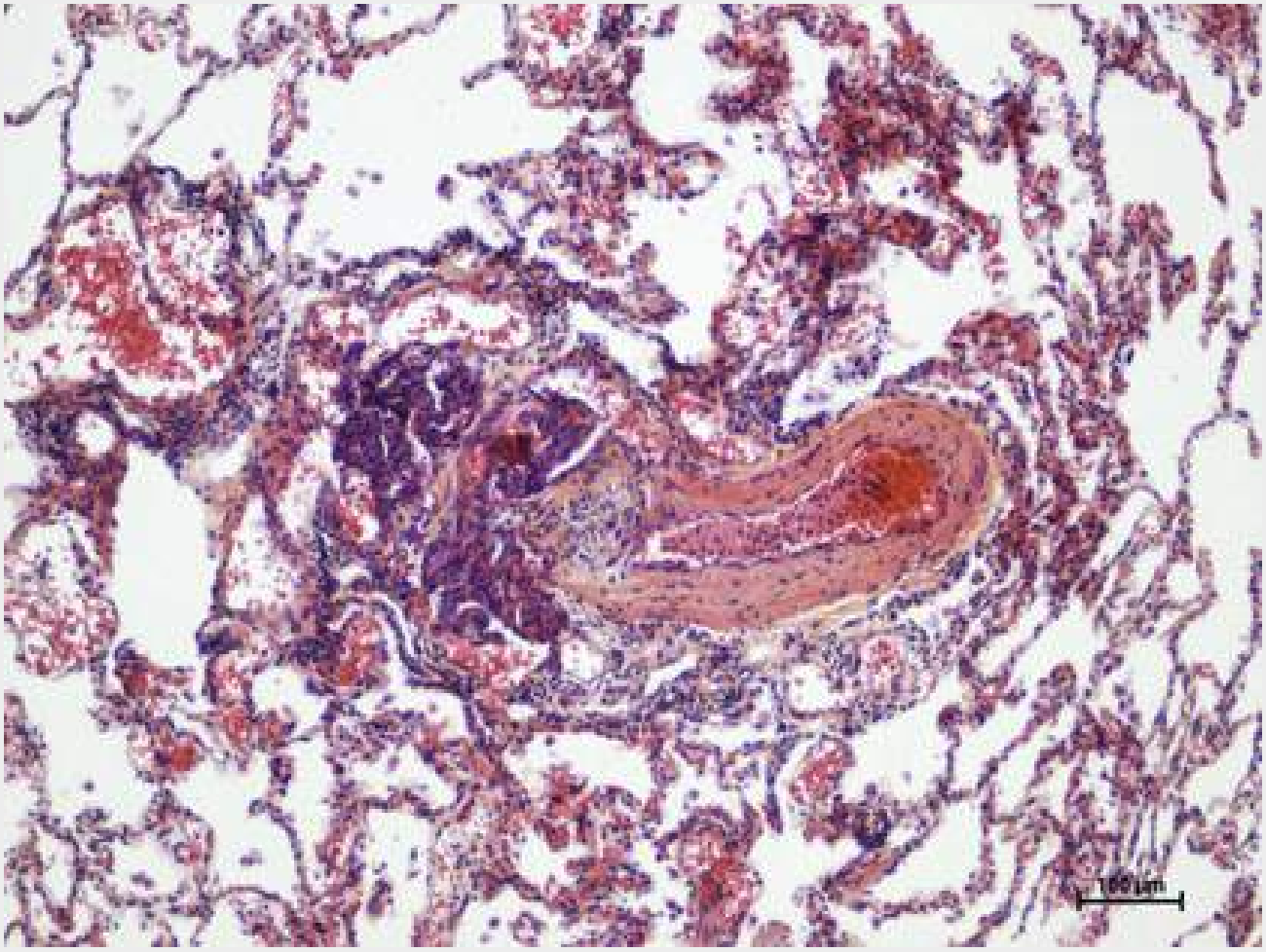


FIGURE 85.1 Plexiform lesion in a patient with PAH.

The pulmonary veins are classically unaffected in PAH, whereas in pulmonary veno-occlusive disease (PVOD), the septal veins and preseptal venules are involved and exhibit occlusive fibrotic lesions, venous muscularization, patchy capillary proliferation, pulmonary edema, occult alveolar hemorrhage, lymphatic dilation with lymph node enlargement (vascular transformation of the sinus), and inflammatory infiltrates. In PVOD the distal pulmonary arteries are affected by medial hypertrophy, intimal fibrosis, and uncommon complex lesions**.** Alveolar capillaries in PVOD are typically dilated and engorged due to downstream obstruction, and frank angioproliferation may even occur to produce lesions of pulmonary capillary hemangiomatosis (PCH). Previously regarded as different entities, current data support the concept that PVOD and PCH are in fact varied expressions of the same disorder. Indeed, clinicopathologic studies indicate marked overlap in the histologic findings of PVOD and PCH, and their clinical and radiographic findings are virtually indistinguishable. The notion of a common disorder is further emphasized by the recent discovery that mutations in the *EIF2AK4* gene are responsible for heritable cases of both PVOD and PCH.[3]

In PH caused by left-sided heart disease, the pathologic changes are characterized by enlarged and thickened pulmonary veins, pulmonary capillary dilation, interstitial edema, alveolar hemorrhage, and lymphatic vessel and lymph node enlargement. The distal pulmonary arteries may be affected by medial

hypertrophy and intimal fibrosis. In PH caused by lung diseases and/or hypoxia, pathologic changes include medial hypertrophy and intimal obstructive proliferation of the distal pulmonary arteries. A variable degree of destruction of the vascular bed in emphysematous or fibrotic areas may also be present.

In CTEPH, organized thrombi are tightly attached to the pulmonary arterial medial layer in the elastic pulmonary arteries and replace the normal intima. These thrombi may completely occlude the lumen or form different grades of stenosis, webs, and bands. In nonoccluded areas, a pulmonary arteriopathy indistinguishable from that of PAH (including plexiform lesions) may develop. Collateral vessels from the systemic circulation (from bronchial, costal, diaphragmatic, and coronary arteries) can grow and at least partially perfuse the areas distal to complete obstructions.[4] In group 5 PH (**see Table 85.1**), one can identify heterogeneous conditions with different pathologic bases for which the cause is unclear or multifactorial.

Pathobiology

PH has a multifactorial pathobiology in which an imbalance in vasoconstriction and vasodilation, thrombosis, and cell proliferation and remodeling of the walls of the pulmonary arteries contribute to increased PVR.[5] As discussed earlier, pulmonary vascular remodeling involves the intima, media, and adventitia of small pulmonary arteries (diameter < 500 μm); all cell types (endothelial, smooth muscle, and fibroblastic), as well as inflammatory cells and platelets, may play a significant role in the condition. Pulmonary vasoconstriction has been regarded as an early component of the PH process, and excessive vasoconstriction has been related to abnormal function or expression of potassium channels and to endothelial dysfunction. Endothelial dysfunction is characterized by impaired production of vasodilators such as nitric oxide (NO) and prostacyclin, along with overexpression of vasoconstrictors such as endothelin-1.[6] Many of these abnormalities both elevate vascular tone and promote vascular remodeling and therefore represent logical pharmacologic targets. Recent genetic and pathophysiologic studies of PH have emphasized the relevance of several other mediators, such as angiopoietins, serotonin, bone morphogenetic proteins (BMPs), and growth factors (platelet-derived growth factor [PDGF], fibroblast growth factor [FGF], epidermal growth factor [EGF], and the transforming growth factor-beta [TGF-β] superfamily). Abnormal proteolysis of the extracellular matrix, autoimmunity, and inflammation are also likely to contribute to the pathobiology of PH, and there is a growing body of literature on the role of cytokines and chemokines in pulmonary vascular remodeling.[7]

Genetics

Idiopathic pulmonary arterial hypertension (IPAH) corresponds to sporadic disease without any family history of PAH or known triggering factor. In 1954, Dresdale and colleagues described the first case of familial PAH and demonstrated the existence of a heritable form of the disease. Since then, many cases of familial PAH have been described, and it was recognized that heritable/familial PAH is inherited as an autosomal dominant trait with incomplete penetrance (the disease will in turn develop in ≈ 20% of mutation carriers). A possible genetic anticipation phenomenon, characterized by the age at onset of the disease being significantly lower in each succeeding generation, has been refuted for heritable/familial PAH.[8] In 2000, *BMPR2* (BMP receptor type 2) was identified as the first PAH-predisposing gene. This gene is located on the long arm of chromosome 2 (2q31-32) and encodes a type II receptor (BMPRII) belonging to the TGF-β receptor superfamily. The BMPRII receptor is involved in the regulation of growth, differentiation, and apoptosis of pulmonary artery endothelial and smooth muscle cells. When

PAH occurs in a familial context, germline mutations in the *BMPR2* gene are detected in more than 75% of cases.[9] *BMPR2* mutations can also be detected in approximately 15% to 20% of apparently sporadic cases. The observation of a personal or familial history of hereditary hemorrhagic telangiectasia in patients with PAH allowed identification of other genes involved in the development of PAH, namely, activin A receptor type II–like kinase 1 (*ACVRL1* or *ALK1*) and endoglin (*ENG*). Furthermore, mutations in other genes (i.e., *BMPR1B*, *CAV1*, and *SMAD9*) have been identified but are considerably less common. Of note, ALK1, ENG, and Smads proteins are all involved in the TGF-β signaling pathway. A channelopathy caused by a mutation in the *KCNK3* gene has been identified in familial and idiopathic cases of PAH, thus indicating for the first time that heritable disease may involve factors apparently independent of the TGF-β signaling pathway.[10,11] Like IPAH, heritable/familial PAH affects twice as many females as males. It must be emphasized that *BMPR2* mutation carriers are younger at the time of diagnosis of PAH and have a more severe hemodynamic compromise (a higher mPAP, lower CO, lower PVR, and lower likelihood of having an acute vasodilator component). Therefore, *BMPR2* mutation carriers are likely to die sooner than their IPAH counterparts and are also more likely to undergo transplantation.[12] It is currently recommended that genetic counseling be offered to family members of patients with heritable/familial PAH.[13] These family members can be tested for the causal mutation (if any); current research is attempting to identify the best PAH screening tool for asymptomatic mutation carriers.[14] Individuals who test positive for PAH-causing mutations and first-degree relatives of heritable PAH patients may be considered for an annual echocardiogram.[1]

Other heritable forms of PH with a recessive mode of transmission have been described in patients with PVOD/ PCH. By using whole-exome sequencing it was found that recessive mutations in *EIF2AK4* (also called *GCN2*) were cosegregated with PVOD/PCH in all families studied in the French National Registry. Bi-allelic *EIF2AK4* mutations were also detected in 5 of 20 histologically confirmed sporadic cases of PVOD/PCH. All mutations, either in a homozygous or compound-heterozygous state, disrupted function of the gene.[15] *EIF2AK4* encodes a serine-threonine kinase present in all eukaryotes that can induce changes in gene expression in response to amino acid deprivation. The pathophysiologic link between bi-allelic *EIF2AK4* loss-of-function mutations and vascular cell proliferation and remodeling of lung vessels remains elusive.[3]

Hemodynamics

The pulmonary circulation is characterized by high flow, low pressure, and low resistance. The normal mPAP at rest is 14.0 ± 3.3 mm Hg, and this value is independent of sex and ethnicity. The resting mPAP is just slightly influenced by age (< 30 years, 12.8 ± 3.1 mm Hg; between 30 and 50 years, 12.9 ± 3.0 mm Hg; > 50 years, 14.7 ± 4.0 mm Hg). Thus, the normal mPAP at rest is virtually independent of age and rarely exceeds 20 mm Hg. According to current guidelines, PH is defined as an mPAP of 25 mm Hg or higher at rest, but more work is needed to better describe the natural history of patients with an mPAP ranging from 21 to 24 mm Hg. PH can be classified as precapillary if the pulmonary arterial wedge pressure (PAWP) is 15 mm Hg or lower; as postcapillary if the PAWP is higher than 15 mm Hg; or as combined precapillary and postcapillary as described earlier.

During exercise, the mPAP is dependent on the exercise level and age. With mild exercise, the mPAP is 19.4 ± 4.8 mm Hg in persons younger than 50 years versus 29.4 ± 8.4 mm Hg in persons 50 years or older. The exercise mPAP is related to age and frequently exceeds 30 mm Hg, especially in elderly individuals; this makes it difficult to define normal mPAP values during exercise. Given these

circumstances, the diagnosis of exercise-induced PH was abandoned in 2008 because of insufficient evidence. Data have since shown that the upper limit of normal of mPAP flow relationships is 3 mm Hg/liter/min with a resistive vessel distensibility on the order of 1% to 2% change in diameter per mm Hg pressure and that higher pressure is associated with decreased exercise capacity. Exercise-induced PH is thus reemerging as a possible clinical entity with a physiologic substrate but remains a research topic until more is known about the natural history of this condition.

The normal pulmonary vascular bed offers less than 10% of the resistance to flow than does the systemic bed and can be approximated as the ratio of the drop in pressure (in mm Hg) to mean flow (in liter/min). The PVR can be calculated as the ratio (mPAP − PAWP)/CO, whereas the total pulmonary resistance (TPR) corresponds to the ratio mPAP/CO. The ratio can be multiplied by 80 to express the results in dyne-sec • cm^{-5} or be expressed in mm Hg/liter/min, which is referred to as a Wood unit. The calculated PVR in normal adults is 67 ± 23 dyne-sec • cm^{-5} (or 1 Wood unit). The physiologic range of the PVR and TPR and the impact of exercise, age, and posture have been a matter of debate for many years. The supine resting PVR in persons younger than 24, 24 to 50, 51 to 69, and 70 years or older is 61 ± 23, 69 ± 28, 86 ± 15, and 90 ± 39 dyne-sec • cm^{-5}, respectively. The corresponding TPR is 165 ± 50, 164 ± 46, 226 ± 64, and 223 ± 45 dyne-sec • cm^{-5}, respectively. During moderate exercise in persons 50 years or younger, an 85% increase in CO is associated with a 25% decrease in TPR and a 12% decrease in PVR. At 51 to 69 years of age, there is no significant decrease in TPR and PVR during exercise. In individuals 70 years or older, the TPR may even increase by 17%, whereas the PVR does not change significantly. At higher exercise levels, the TPR decreases in all age-groups.

Classification of Pulmonary Hypertension

The clinical classification of PH was most recently revised by the 2015 ESC/ERS Guidelines and is depicted in **Table 85.1**.[1]

Group 1 Pulmonary Arterial Hypertension

Changes in classification have been made to reflect the evolving understanding of the clinical and pathologic manifestations of PAH. PAH should not be considered a disease itself but as one measurable sign (elevated pulmonary arterial blood pressure) of an underlying pulmonary vasculopathy for which the clinical context must be appropriately diagnosed. Clinical experience and formal disease registry databases make it increasingly clear that the diseases in group 1 PAH, such as congenital heart disease (CHD) and connective tissue disease, have very different demographics, manifestations, and outcomes. The prevalence of group 1 PAH is in the range of 15 to 50 cases per million.

Causes

Idiopathic Pulmonary Arterial Hypertension

Formerly referred to as primary pulmonary hypertension (PPH), IPAH is a rare disease of unknown cause and is the most common type of group 1 PAH in current-day registries. IPAH is a sporadic disease for which there is neither a family history of PAH nor an identified risk factor. It has a female preponderance (2 : 1 in the NIH registry, 4 : 1 in the current-day REVEAL registry). Even though the mean age at diagnosis was 37 years in the NIH registry and approximately 50 years in the more recent registries,

IPAH can affect children and adults into their 70s.

Heritable Pulmonary Arterial Hypertension

Hereditary transmission of PAH has been reported in approximately 6% to 10% of patients with PAH. The genetic details of heritable PAH are discussed earlier.

Drug- and Toxin-Induced Pulmonary Arterial Hypertension

An association between anorexigens (appetite-suppressant drugs that increase, release, and block the reuptake of serotonin) and PAH was initially observed in the 1960s, when an epidemic of IPAH (then termed PPH) was noted in Europe after the introduction of aminorex fumarate. Structurally related compounds such as fenfluramine, dexfenfluramine, and benfluorex were also demonstrated to be associated with the development of PAH in the 1980s, 1990s, and 2000s, and have since been withdrawn from the market.[16] Epidemiologic studies have also linked the development of PAH to rapeseed oil, L-tryptophan, interferon alpha and beta, and illicit drugs such as methamphetamines. More recently, the tyrosine kinase inhibitor dasatinib has been associated with the development of PAH.[17] From the approval of dasatinib in November 2006 to September 30, 2010, nine incident cases of PAH in patients treated with dasatinib were identified in the French National Registry, which corresponds to an estimated incidence of 0.45% in patients exposed to dasatinib in France. Improvement is usually observed after cessation of the use of dasatinib. Recent experimental data have shown that dasatinib induces lung vascular toxicity and predisposes a person to PH.[18]

Pulmonary Arterial Hypertension Associated With Connective Tissue Diseases.
The prevalence of PAH is greatest in those with the scleroderma spectrum of diseases, although PAH can occur in the setting of any of the connective tissue diseases. Two prospective studies using echocardiography as a screening tool but requiring hemodynamic confirmation with RHC found the prevalence of PAH in the scleroderma population to be 8% to 12%. Because PAH has a high prevalence in patients with scleroderma, scleroderma patients constitute a high-risk group in whom screening can be done; early therapy can be instituted if a diagnosis of PAH is then made in a patient. A reduction in the diffusion capacity of carbon monoxide may precede the clinical or echocardiographic abnormalities. Currently, echocardiography is the most common screening tool (**see Chapter 14**), although studies to refine the screening process in this high-risk group are under way. Recently, a novel screening approach that involves a two-step algorithm, including clinical, pulmonary function test, and echocardiographic variables, was developed.[19] Six simple screening tests in step 1 of the algorithm are used to determine whether referral for echocardiography is appropriate. In step 2, the step 1 prediction score and two echocardiographic variables are used to determine whether referral for RHC is appropriate. The sensitivity of this algorithm is 96%, with a specificity of 48% and positive and negative predictive values of 35% and 98%, respectively.

Unfortunately, the prognosis for patients with scleroderma-associated PAH is poor, even in the current treatment era. In the PAH Quality Enhancement Research Initiative, the 3-year survival rate of patients with scleroderma-associated PAH was 60% as compared with 77% in patients with IPAH; the 3-year survival rate of patients with scleroderma-associated PAH in the French National Registry was only 56%.[20,21] Patients with the scleroderma spectrum of disease may also be at higher risk for other types of PH, including diastolic dysfunction and hypoxemic lung disease.

Pulmonary Arterial Hypertension Associated With Human Immunodeficiency Virus Infection.

PAH is a rare, but well-established, complication of human immunodeficiency virus (HIV) infection. Population studies of individuals infected with HIV suggest that the incidence of PAH is approximately 0.5% and is independent of the $CD4^+$ cell count or previous opportunistic infections. The prevalence of HIV-associated PAH has not changed with the widespread use of highly active antiretroviral therapy. The mechanism is unknown, but the hemodynamics and clinical course are similar to those of IPAH. The prognosis of HIV-associated PAH has improved in recent years. In a recent single-center observation, the survival rate was 88% at 1 year and 72% at 3 years, with a cardiac index higher than 2.8 liters/min/m^2 and a $CD4^+$ lymphocyte count greater than 200 cells/μL, both having been demonstrated to be independent predictors of survival.[22] Routine screening for PAH in HIV-infected patients is not recommended, because of the relatively low prevalence of the disorder in these patients, although PAH should be considered in HIV-infected patients with symptoms of dyspnea in whom another cause cannot be found.

Pulmonary Arterial Hypertension Associated With Portal Hypertension.

The development of PAH in association with elevated pressure in the portal circulation is known as portopulmonary hypertension. Portal hypertension, as opposed to the underlying liver disease, is the risk factor. Neither the severity of the liver disease nor the degree of portal hypertension predicts the presence or severity of portopulmonary hypertension. Epidemiologic studies have estimated the prevalence of PAH in these individuals to be 2% to 6%, but it may be higher in those referred for liver transplantation. Although echocardiography serves as a good screening tool in this population, hemodynamic confirmation is required. The high-flow state of the underlying disease or the high-output cardiac failure with elevated left-sided cardiac filling pressure must be differentiated from true portopulmonary hypertension.

The presence of PAH increases the risk associated with liver transplantation. The recent International Liver Transplant Society Practice Guidelines make recommendations for screening, diagnosis, treatment, and implications for liver transplantation in the setting of portopulmonary hypertension.[23] Based on observational cohorts, a pre–liver transplantation mPAP of 35 mm Hg or greater and an increased PVR are associated with increased morbidity and mortality rates; an mPAP of 45 to 50 mm Hg or greater should be considered an absolute contraindication to liver transplantation.

Pulmonary Arterial Hypertension Associated With Congenital Heart Disease.

PAH is a well-recognized complication of uncorrected increased pulmonary blood flow associated with congenital systemic-to-pulmonary shunts (**see Chapter 75**). PAH associated with CHD represents a very heterogeneous patient population. **Table 85.2** summarizes the clinical classification of PAH associated with CHD. Eisenmenger syndrome is defined as CHD with an initial large systemic-to-pulmonary shunt that induces progressive pulmonary vasculopathy with PAH and subsequent reversal of the shunt and central cyanosis. Eisenmenger syndrome occurs more frequently when blood flow is extremely high and the shunt exposes the pulmonary vasculature to systemic-level pressure, as occurs with a ventricular septal defect, patent ductus arteriosus, or truncus arteriosus. At this point, surgical correction of the defect is contraindicated. PAH may also be present when the shunt is predominantly systemic to pulmonary. It is important to determine in such cases if the shunt is correctable or not. Occasionally a marked elevation of PVR may be present with small cardiac defects, and these patients are considered to have PAH with small or coincidental defects. It is unlikely that these small defects account for the high PVR. Patients have a clinical picture similar to that of IPAH, and closing the defect is contraindicated. Lastly, patients may have PAH after the correction of an intracardiac shunt, particularly if closure took

place late.

TABLE 85.2

Clinical Classification of Pulmonary Arterial Hypertension Associated With Congenital Heart Disease

1. Eisenmenger syndrome Includes all large intracardiac and extracardiac defects that begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present
2. PAH associated with prevalent systemic-to-pulmonary shunts Correctable* Noncorrectable Includes moderate to large defects; PVR is mildly to moderately increased; systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature
3. PAH with small or coincidental defects† Marked elevation in PVR in the presence of small cardiac defects (usually ventricular septal defects < 1 cm and atrial septal defects < 2 cm of effective diameter as assessed by echocardiography), which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH; closing the defects is contraindicated
4. PAH after defect correction Congenital heart disease is repaired but PAH either persists immediately after correction or recurs or develops months or years after correction in the absence of significant postoperative haemodynamic lesions

*With surgery or intravascular percutaneous procedure.

†The size applies to adult patients. In adults the simple diameter may not be sufficient for defining the hemodynamic relevance of the defect, and also the pressure gradient, shunt size and direction, and pulmonary-to-systemic flow ratio should be considered.

PAH, pulmonary arterial hypertension; *PVR*, pulmonary vascular resistance.

From Galie N, Humbert M, Vachiery J-L, et al: 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2016;37:67.

An important feature of PAH in patients with CHD is the right ventricular adaptive response to elevated PAH. With onset early in life, marked hypertrophy and preservation of a fetal-like phenotype occur. As a result, these patients can sustain an increased afterload with better right ventricular function for many years or decades than can those in whom PAH develops later in life. Survival times for patients with Eisenmenger syndrome is better than for those with IPAH. Currently approved PAH-specific therapies have demonstrated benefit in patients with Eisenmenger syndrome.

Pulmonary Arterial Hypertension Associated With Schistosomiasis.

Diagnosed most commonly in endemic areas of South America and sub-Saharan Africa, recent publications suggest that PH associated with schistosomiasis has clinical and histologic features similar to those of IPAH. PAH develops in approximately 5% of patients with hepatosplenic schistosomiasis, making it one of the most prevalent causes of PAH worldwide.[24]

Pulmonary Veno-Occlusive Disease and/or Pulmonary Capillary Hemangiomatosis

PVOD and/or pulmonary capillary hemangiomatosis (PCH) is a rare pulmonary microvasculopathy affecting primarily the septal veins and preseptal venules, characterized by occlusive fibrotic lesions, venous muscularization, and patchy capillary proliferation. PVOD/PCH also exhibits the findings of pulmonary venous hypertension, including pulmonary hemosiderosis, interstitial edema, and lymphatic dilation with lymph node enlargement (vascular transformation of the sinus). In theory, histologic proof would be required for definitive diagnosis of PVOD/PCH, but surgical lung biopsy is a high-risk procedure in these patients and is therefore contraindicated. Although the risk factors and clinical features may be indistinguishable from those of PAH, patients with PVOD/PCH may have a familial history of consanguinity, or a personal history of exposure to alkylating agents (mitomycin-C, cyclophosphamide), occupational exposure to organic solvents, or a connective tissue disease such as systemic sclerosis.[25,26] These patients usually present with a markedly reduced diffusing capacity of carbon monoxide and oxygen saturation at rest.[27] High-resolution computed tomography (CT) of the chest

in patients with PVOD/PCH is characterized by a higher frequency of centrilobular ground-glass opacities, septal lines, and mediastinal lymph node enlargement than in those with PAH. The rapid development of pulmonary edema after the administration of PAH therapy is sometimes the first clue to the appropriate diagnosis and can be life-threatening. Familial cases of PVOD/PCH have been described, often in consanguineous families. Recessive mutations in *EIF2AK4* (also called *GCN2*) cosegregated with PVOD/PCH are found in 100% of familial cases and 25% of sporadic cases of histologically confirmed PVOD/PCH. These findings point to *EIF2AK4* as the major gene linked to the development of PVOD/PCH and may be considered a diagnostic tool in this rare condition.[15] Heritable PVOD/PCH due to bi-allelic *EIF2AK4* mutations is characterized by a younger age at diagnosis, but the severity of disease is similar to that in noncarriers of *EIF2AK4* mutations. Survival rates of patients with PVOD are poor, and lung transplantation is the treatment of choice for eligible patients.

Clinical Diagnosis

Given the multiple potential causes and factors contributing to the presence of PH, a methodical and extensive evaluation is warranted in most patients with common symptoms in whom the diagnosis is being considered (**Fig. 85.2**).

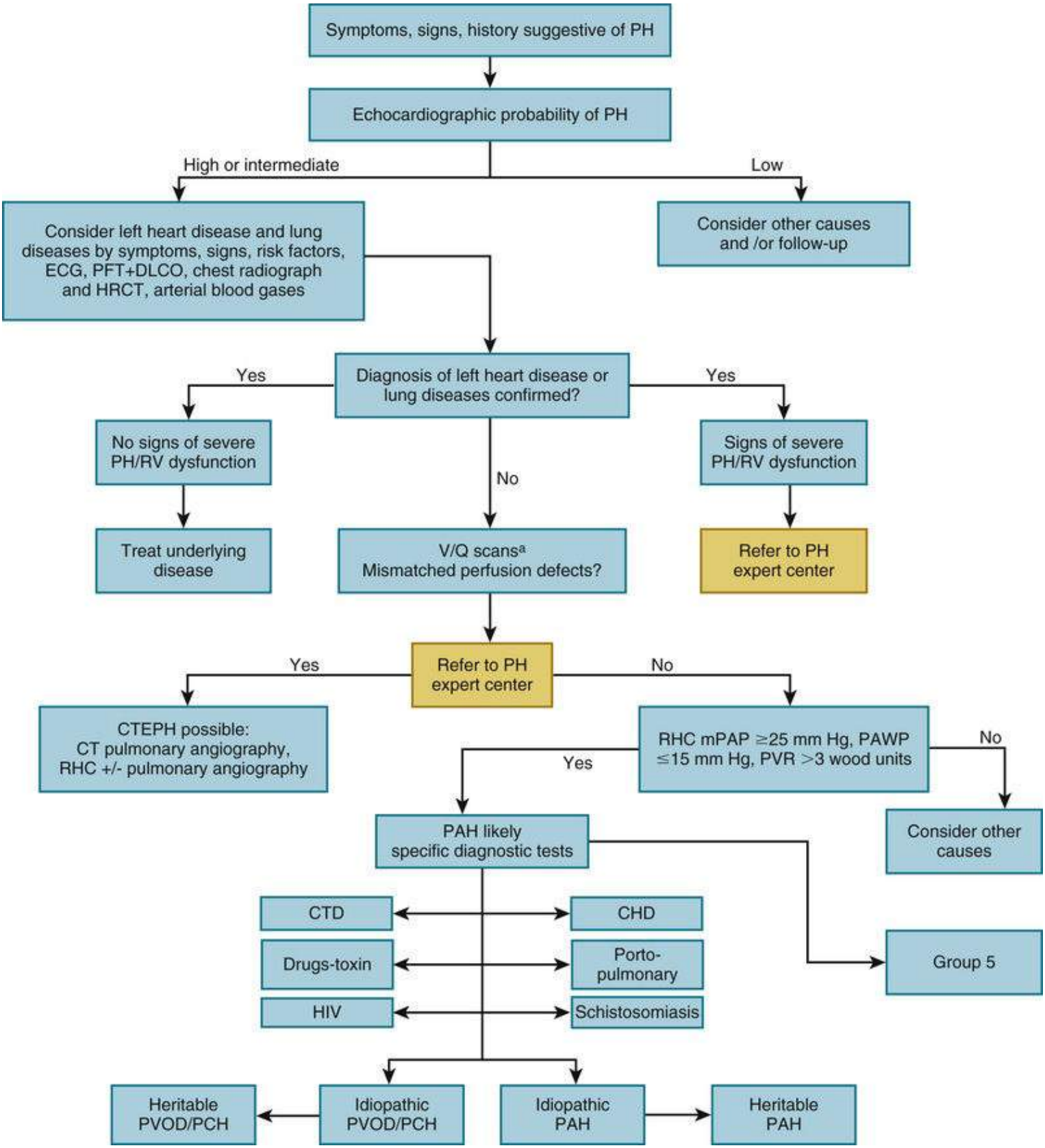


FIGURE 85.2 Evidence-based diagnostic algorithm for PAH patients (group 1 patients only). (Modified from Galie N, Humbert M, Vachiery J-L, et al: 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2016;37:67.)

Symptoms

The most common initial symptoms of PH include exertional dyspnea or reduced exercise tolerance, chest pain, fatigue, and light-headedness. Manifestations of more advanced disease include syncope, abdominal distention, and lower extremity edema attributable to right ventricular failure. Of course, the presence of

risk factors for the development of PAH (e.g., connective tissue disease, family history, CHD, use of appetite suppressants) should heighten awareness of the disorder. In the NIH registry, the average time from the onset of symptoms to diagnosis was 2 years (see Classic References). Sadly, current-day registries suggest that a delay in diagnosis persists. In the REVEAL registry, 21.1% of patients experienced symptoms for more than 2 years before PAH was recognized.[28] A delay in diagnosis was most frequently observed in patients whose symptoms occurred at a younger age (< 36 years) and in those with chronic obstructive pulmonary disease (COPD) or obstructive sleep apnea. It appears that young people in whom cardiopulmonary disease is considered less likely to be present or patients thought to have an alternative explanation for the symptoms are most at risk for a delayed diagnosis.

Physical Examination

The physical examination can be subtle or nonspecific, but certain findings should raise suspicion for PAH (**see also Chapter 10**). Features of the physical examination pertinent to the evaluation of PH are listed in **Table 85.3**.

TABLE 85.3

Features of the Physical Examination Pertinent to the Evaluation of Pulmonary Hypertension

Sign	Implication
PHYSICAL SIGNS THAT REFLECT THE SEVERITY OF PULMONARY HYPERTENSION	
Accentuated pulmonary component of S_2 (audible at the apex in > 90%)	High pulmonary pressure that increases force of pulmonic valve closure
Early systolic click	Sudden interruption of opening of the pulmonary valve into a high-pressure artery
Midsystolic ejection murmur	Turbulent transvalvular pulmonary outflow
Left parasternal lift	High right ventricular pressure and hypertrophy present
Right ventricular S_4 (in 38%)	High right ventricular pressure and hypertrophy present
Increased jugular A wave	Poor right ventricular compliance
PHYSICAL SIGNS THAT SUGGEST MODERATE TO SEVERE PULMONARY HYPERTENSION	
Moderate to severe pulmonary hypertension	
Holosystolic murmur that increases with inspiration	Tricuspid regurgitation
Increased jugular V waves	
Pulsatile liver	
Diastolic murmur	Pulmonary regurgitation
Hepatojugular reflux	High central venous pressure
Advanced pulmonary hypertension with right ventricular failure	
Right ventricular S_3 (in 23%)	Right ventricular dysfunction
Distention of jugular veins	Right ventricular dysfunction or tricuspid regurgitation, or both
Hepatomegaly	Right ventricular dysfunction or tricuspid regurgitation, or both
Peripheral edema (in 32%)	
Ascites	
Low blood pressure, diminished pulse pressure, cool extremities	Reduced cardiac output, peripheral vasoconstriction
PHYSICAL SIGNS THAT SUGGEST A POSSIBLE UNDERLYING CAUSE FOR OR ASSOCIATIONS WITH PULMONARY HYPERTENSION	
Central cyanosis	Abnormal ventilation-perfusion ratio, intrapulmonary shunt, hypoxemia, pulmonary-to-systemic shunt
Clubbing	Congenital heart disease, pulmonary venopathy
Cardiac auscultatory findings, including systolic murmurs, diastolic murmurs, opening snap, and gallop	Congenital or acquired heart or valvular disease
Rales, dullness, or decreased breath sounds	Pulmonary congestion or effusion, or both
Fine rales, accessory muscle use, wheezing, protracted expiration, productive cough	Pulmonary parenchymal disease
Obesity, kyphoscoliosis, enlarged tonsils	Possible substrate for disordered ventilation
Sclerodactyly, arthritis, telangiectasia, Raynaud phenomenon, rash	Connective tissue disorder
Peripheral venous insufficiency or obstruction	Possible venous thrombosis
Venous stasis ulcers	Possible sickle cell disease
Pulmonary vascular bruits	Chronic thromboembolic pulmonary hypertension
Splenomegaly, spider angiomas, palmar erythema, icterus, caput medusae, ascites	Portal hypertension

From McLaughlin VV, Archer SL, Badesch DB, et al: ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc., and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53:1573.

An accentuated pulmonic component of the second heart sound is present in most patients with PAH because of the high pulmonary pressure, which results in more forceful closure of the pulmonic valve. If a split S_2 is audible at the apex, P_2 may be accentuated and the possibility of PAH should be further investigated. The findings on physical examination are helpful to gauge the severity of PAH and to detect associated disorders as summarized in **Table 85.3**.

Electrocardiogram

Although the electrocardiogram is neither sensitive nor specific for PAH, it is an inexpensive, noninvasive test that can provide valuable information (**see also Chapter 12**). Common electrocardiographic findings include right atrial enlargement, right axis deviation, and right ventricular enlargement, often with a strain pattern (**Fig. 85.3A**).

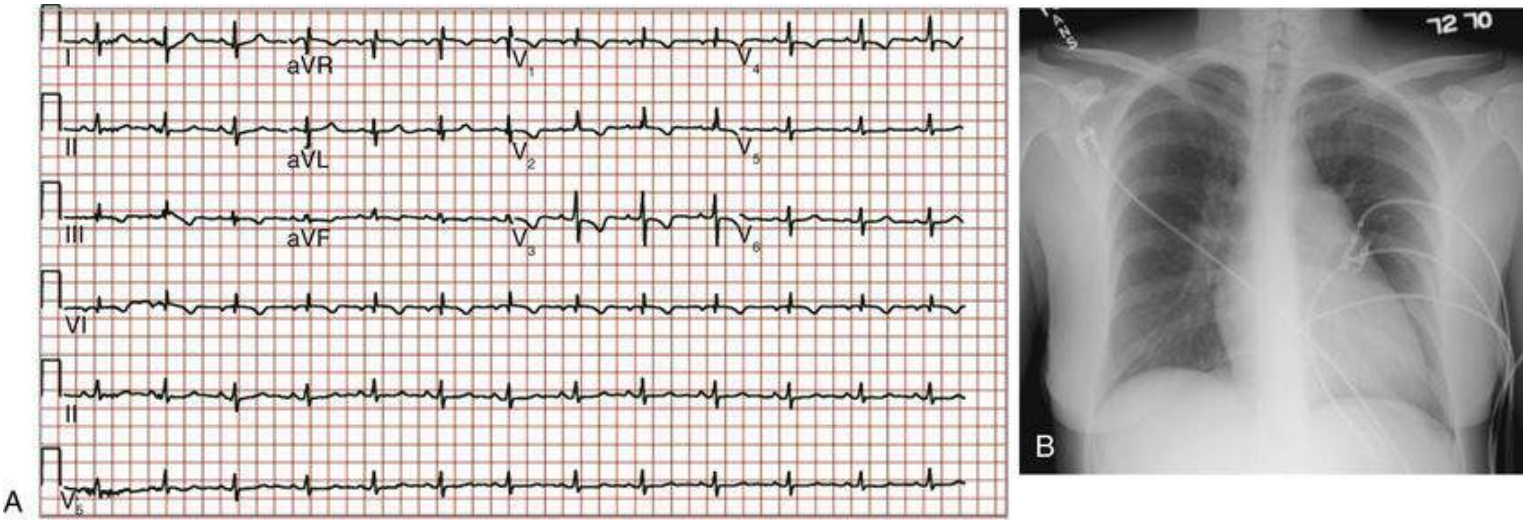


FIGURE 85.3 Clinical assessment of PAH. **A,** Electrocardiogram of a patient with PAH. **B,** Chest radiograph of a patient with PAH.

Chest Radiograph

Findings on the chest radiograph that suggest the presence of PH includes enlarged main and hilar pulmonary artery shadows with "pruning" or attenuation of the peripheral vasculature (**see Fig. 85.3B**) and right ventricular enlargement, which is best appreciated on the lateral view. Other findings on the chest radiograph may point to an associated diagnosis, such as hyperinflation with flat diaphragms (COPD) or pulmonary venous congestion (left-sided heart disease) (**see also Chapter 15**).

Echocardiogram

If PH is suspected from the history, assessment of risk factors, and physical examination, an echocardiogram is the next appropriate study (**see also Chapter 14**). Echocardiography also serves as a useful noninvasive screening test for PH in at-risk populations (e.g., scleroderma or CHD patients). Doppler echocardiography can simultaneously provide an estimate of the right ventricular systolic pressure and functional and morphologic sequelae of PH and give clues to other potential cardiac causes of PH. Common echocardiographic features of PAH include right atrial enlargement, right ventricular enlargement and dysfunction, small underfilled left-sided heart chambers, interventricular septal flattening, tricuspid regurgitation with elevated velocity, and reduced tricuspid annular plane systolic

excursion (TAPSE). A saline contrast injection can be used to detect an intracardiac shunt. One must acknowledge the limitations of the estimated right ventricular systolic pressure because of multiple potential sources of error in this measurement. In any given patient, the estimated right ventricular systolic pressure must be put into context with the patient's symptoms, previous medical history, and other findings on the two-dimensional echocardiogram. In the absence of other potential causes of PH, such as left-sided heart disease or hypoxemic lung disease, an estimated right ventricular systolic pressure greater than 40 mm Hg generally warrants further evaluation in a patient with unexplained dyspnea. Other echocardiographic findings that warrant further evaluation include right atrial and right ventricular enlargement and abnormal interventricular septal motion. Guidelines for echocardiographic assessment of the right heart in adults have recently been published.[29] A checklist for the echocardiographic evaluation of PH is reviewed in **eTable 85.1**.[30]

ETABLE 85.1

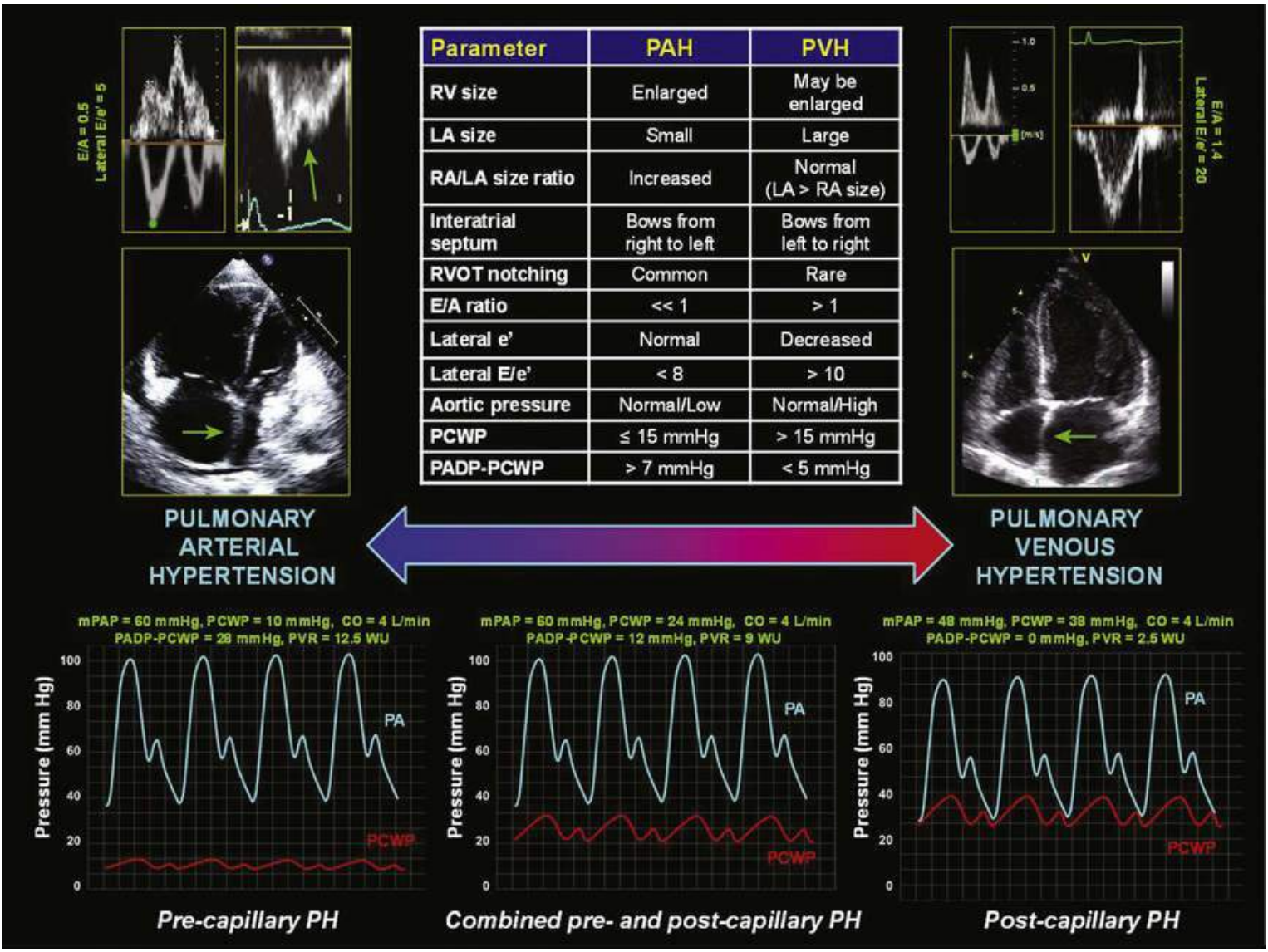
Checklist for the Echocardiographic Evaluation of Pulmonary Hypertension

COMPLETED?	ACTION ITEM	NOTES
☐	Record estimated PASP	Underestimated when Doppler beam alignment is poor or when TR jet is minimal Overestimated in patients with significant anemia or in some cases of agitated saline-enhanced TR jet on continuous-wave Doppler (due to feathering) Assumes absence of pulmonic stenosis Echocardiographic PASP does not equal mean PA pressure (definition of PH per guidelines is based on invasive hemodynamics = mean PA pressure ≥ 25 mm Hg)
☐	Evaluate RV size and function	Signs of RV enlargement (apical 4-chamber view): RV shares apex with LV; RV bigger than LV; RV basal diameter > 4.2 cm RV hypertrophy (subcostal view): RV end-diastolic wall thickness > 5 mm RV systolic dysfunction: RV fractional area change < 35%; TAPSE < 1.6 cm; RV tissue Doppler s′ velocity < 10 cm/s at base of RV free wall (tricuspid annulus) Septal flattening: in systole = RV pressure overload and in diastole = RV volume overload
☐	Evaluate for signs of elevated PVR	RVOT notching on pulse-wave Doppler profile is sign of elevated PVR Peak TR velocity (units = m/s)/RVOT VTI (units = cm) < 0.18: unlikely PVR is elevated
☐	Estimate volume status	Use size and collapsibility of inferior vena cava (during sniff maneuver) to determine RA pressure Hepatic vein flow: systolic flow reversal can be sign of severe TR, RV overload, and/or increased RV stiffness Signs of RA overload/enlargement: RA area > 18 cm^2; interatrial septum bows from right to left
☐	Evaluate severity of tricuspid regurgitation	Features suggestive of severe TR include dense TR jet on continuous-wave Doppler, V-wave cut-off sign; and systolic flow reversal on hepatic vein pulse-wave Doppler imaging
☐	Evaluate for pericardial effusion	In patients with PAH, the presence of pericardial effusion is poor prognostic sign
☐	Evaluate for causes of PH (left heart disease, shunt lesions)	Left heart disease: look for overt LV systolic dysfunction, grade 2 or worse diastolic dysfunction, severe aortic or mitral valve disease, and less common abnormalities of left heart (e.g., hypertrophic cardiomyopathy, cor triatriatum) Shunt lesions: perform agitated saline bubble study
☐	Differentiate PAH from pulmonary venous hypertension	Signs that favor pulmonary venous hypertension: LA enlargement (LA size > RA size); interatrial septum bows from left to right; E/A ratio > 1.2; E/e′ (lateral) > 11; lateral e′ < 8 cm/s In patients with significantly elevated PASP at rest: grade 1 diastolic dysfunction pattern (E/A ratio < 0.8) favors PAH diagnosis because of underfilled LA and decreased LV compliance due to RV/LV interaction (extrinsic compression of LV by RV) See also Fig. 1

LV, left ventricular; *PA*, pulmonary artery; *PAH*, pulmonary arterial hypertension; *PASP*, pulmonary artery systolic pressure; *PH*, pulmonary hypertension; *PVR*, pulmonary vascular resistance; RA, right atrial; *RV*, right ventricular; *RVOT*, right ventricular outflow tract; *TAPSE*, tricuspid annular plane systolic excursion; *TR*, tricuspid regurgitation; *VTI*, velocity-time integral.

From McLaughlin VV, Shah SJ, Souza R, et al.: Management of pulmonary arterial hypertension. J Am Coll Cardiol. 2015;183:1976.

The echocardiogram often provides information on the possibility of group 2 PH, or PH caused by left-sided heart disease. Left ventricular systolic or diastolic dysfunction and aortic and mitral valvular heart disease are easily assessed on an echocardiogram. The presence of left atrial enlargement suggests a chronically elevated left-sided filling pressure. The spectrum of echocardiographic and hemodynamic findings in PH is summarized in **eFig. 85.1**. In some instances, particularly in the assessment of CHD, a transesophageal echocardiogram provides additional information. The role of exercise echocardiography is controversial at this time.



Parameter	PAH	PVH
RV size	Enlarged	May be enlarged
LA size	Small	Large
RA/LA size ratio	Increased	Normal (LA > RA size)
Interatrial septum	Bows from right to left	Bows from left to right
RVOT notching	Common	Rare
E/A ratio	<< 1	> 1
Lateral e'	Normal	Decreased
Lateral E/e'	< 8	> 10
Aortic pressure	Normal/Low	Normal/High
PCWP	≤ 15 mmHg	> 15 mmHg
PADP-PCWP	> 7 mmHg	< 5 mmHg

EFIGURE 85.1 Pulmonary arterial hypertension versus pulmonary venous hypertension: echocardiographic and invasive hemodynamic differentiation. The **left panel** demonstrates prototypical echocardiographic and invasive hemodynamic findings from a patient with PAH. The right atrium and right ventricle are severely enlarged, and the left ventricle and left atrium are small and underfilled. The interatrial septum bows from right to left. On mitral inflow, the E/A ratio is less than 1 because of underfilling of the left atrium and decreased compliance of the left ventricle due to extrinsic compression from the enlarged right ventricle. The lateral e′ velocity and lateral E/e′ ratio are normal (<8), suggesting normal left ventricular relaxation and filling pressures. There is notching in the right ventricular outflow tract profile on pulse-wave Doppler imaging due to increased PA stiffness. PCWP is normal and the PADP-PCWP gradient is severely increased. The **right panel** demonstrates prototypical echocardiographic and invasive hemodynamic findings from a patient with pulmonary venous hypertension. The left atrium is enlarged and the interatrial septum bows from left to right. On mitral inflow, the E/A ratio is more than 1, lateral e′ velocity is reduced, and lateral E/e′ ratio is increased, suggestive of grade 2 diastolic dysfunction with impaired left ventricular relaxation and elevated left ventricular filling pressures. There is no notching in the right ventricular outflow tract profile. PCWP is elevated and there is no gradient between the PADP and PCWP. Note that although the right ventricle in the right panel is not enlarged, right ventricular enlargement and dysfunction can be present in patients with isolated pulmonary venous hypertension. The **middle panel** includes a table listing parameters for echocardiography and invasive hemodynamic testing that are helpful for differentiating PAH from pulmonary venous hypertension. The **lower middle panel** demonstrates invasive hemodynamic findings in a patient with combined precapillary and postcapillary PH (elevated PCWP and PADP-PCWP gradient). It should be noted that the most challenging patients are in this middle zone (combined precapillary and postcapillary PH), with echocardiographic findings that lie in the middle of the prototypical examples of PAH and pulmonary venous hypertension shown here. In these patients, careful evaluation of the echocardiogram and invasive hemodynamics will be necessary for an accurate diagnosis. CO, cardiac output; E/A, ratio of early to late (atrial) mitral inflow velocities; E/e′, ratio of early mitral inflow velocity to early diastolic mitral annular tissue velocity; LA, left atrial; mPAP, mean pulmonary arterial pressure; PADP, pulmonary artery diastolic pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVH, pulmonary

venous hypertension; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; RVOT, right ventricular outflow tract.

The most important echocardiographic prognostic indicators for PAH include the presence of pericardial effusion and the severity of right ventricular dysfunction. The estimated right ventricular systolic pressure is less meaningful prognostically, and in fact this value may fall as the disease progresses and the right ventricle becomes more dysfunctional.

Ventilation-Perfusion Lung Scintigraphy.

Patients with unexplained dyspnea and PH should be evaluated for CTEPH. Ventilation-perfusion lung scintigraphy is considered the most sensitive study for this purpose.[31] If one has a normal- or very low–probability ventilation-perfusion scan, CTEPH can be excluded. Many patients with PAH have a slightly heterogeneous perfusion picture, but not segmental or larger defects. Although spiral CT is an excellent means of evaluating a patient for acute pulmonary embolism, it may miss surgically accessible CTEPH. If CTEPH is still a concern after noninvasive imaging, one should proceed to pulmonary angiography. Pulmonary angiography must be done with caution in patients with advanced hemodynamics. The use of nonionic and low-osmotic contrast material at the slowest flow rate and smallest volume possible is essential. Findings of CTEPH on pulmonary angiography include irregular outlines of contrast-filled arterial contours, pouches, webs, bands, and complete vascular occlusion.

Pulmonary Function Tests.

Pulmonary function tests are useful to assess for obstructive or restrictive lung disease. If these disorders need further evaluation, an arterial blood gas or high-resolution CT study may be appropriate. Patients with group 1 PAH may have modest restriction of and a mildly reduced diffusion capacity of carbon monoxide. A declining diffusion capacity of carbon monoxide in a patient with scleroderma may precede the development of PAH.

Cardiac Magnetic Resonance Imaging.

Although not required for the diagnosis of PAH, cardiac magnetic resonance (CMR) provides an excellent assessment of right ventricular function and may be helpful in assessing for CHD. In response to chronic PH, the right ventricle dilates and there is a reduction in systolic function and stroke volume. The interventricular septum bows into the left ventricle in diastole and systole. Commensurate with this, a right ventricular end-diastolic volume index lower than 84 mL/m^2, a left ventricular end-diastolic volume index higher than 40 mL/m^2, and a stroke volume index higher than 25 mL/m^2 are associated with better survival rates in patients with IPAH. A right ventricular ejection fraction lower than 35% noted on CMR is predictive of death.[32]

Overnight Oximetry.

In addition to the history, overnight oximetry may help identify patients with obstructive sleep apnea. Formal polysomnography may be indicated in patients with significant nocturnal desaturation. Obstructive sleep apnea may cause modest PH, mediated in part by hypoxic vasoconstriction.

Significant PAH (mPAP ≥ 35 mm Hg) can rarely be attributable to sleep-related disordered breathing; however, untreated obstructive sleep apnea will limit the effectiveness of other treatment approaches and should therefore be conscientiously evaluated and managed in all patients with PAH.

Laboratory Studies.

Given the epidemiologic associations, laboratory studies to screen for connective tissue diseases, HIV

disease, and liver disease are included in the diagnostic evaluation. Natriuretic peptides may also be measured to assess the prognosis and response to treatment.

Functional Assessment.

The 6-minute hall walk (6MW) is an important functional test for quantifying exercise ability. Despite its technical inelegance and limitations, the 6MW (when performed appropriately in a standardized fashion) has proved to be a useful prognostic predictor and an important parameter to include in the clinical assessment of disease progression and treatment effect.

The 6MW has been the primary endpoint of almost every clinical trial involving PAH to date. A recent analysis of patients enrolled in a 16-week clinical trial of tadalafil versus placebo attempted to delineate the minimal important difference of the 6MW.[33] Using a distributional and anchor-based methodology, the authors assessed the correlation between change in 6MW distance and change in the physical component summary score of the 36-item Short-Form Health Survey (SF-36). They found the minimal important difference of the 6MW to be approximately 33 meters. Two other metaanalyses have assessed the correlation of change in 6MW distance with clinical events over short-term clinical trials and found either a modest correlation or no correlation.[34,35] Although still useful in longitudinally assessing an individual patient, the role of 6MW distance as a primary endpoint in future clinical trials is a topic of ongoing debate.

Cardiopulmonary exercise testing offers a more sophisticated means of assessing exercise capacity and gas exchange. Poor prognostic indicators during cardiopulmonary exercise testing include a peak systolic blood pressure lower than 120 mm Hg and a peak oxygen uptake of less than 10.4 mL/kg/min.

Right Heart Catheterization

Invasive hemodynamic assessment by RHC is pivotal in the evaluation of any patient with suspected PAH. RHC is typically performed after the noninvasive testing for PH described earlier. Some patients initially suspected of having PAH will not require RHC because they have had an alternative diagnosis established by noninvasive testing. However, all patients who are still suspected of having PAH after noninvasive evaluation should undergo RHC before the initiation of therapy. The usefulness of RHC is dependent on the accuracy and completeness of the data obtained. Essential measurements during RHC include the following:

- Oxygen saturation (superior and inferior vena cavas, pulmonary and systemic arteries)
- Right atrial pressure
- Right ventricular pressure
- Pulmonary artery pressure
- Left-sided filling pressure (PAWP, left atrial pressure, or left ventricular end-diastolic pressure [LVEDP])
- CO/cardiac index
- PVR
- Systemic blood pressure

- Heart rate
- Response to acute vasodilators

Misinterpretation of PAWP is a common pitfall in the invasive diagnosis of PH. PAWP should be measured at end-expiration and in several different segments of the pulmonary vasculature. LVEDP should be determined if there is any doubt about the accuracy of the PAWP tracing or if the results are unexpected in a given patient. A fluid challenge may be necessary to elicit the presence of diastolic dysfunction.

Acute vasodilator testing should be performed in most patients with IPAH, HPAH, and drug-induced PAH. Exceptions include patients who would not be candidates for long-term therapy with a calcium channel–blocking agent, such as those with hemodynamic instability or overt right-sided heart failure. Responders are rare among patients with associated PAH. The most common agents used for acute vasodilator testing are inhaled NO, intravenous epoprostenol, and intravenous adenosine. An acute response is defined as a decrease in mPAP by at least 10 mm Hg to an absolute mPAP value lower than 40 mm Hg in the setting of unchanged or increased CO.[36]

Compliance With Guidelines

Despite publication of the diagnostic algorithmic recommendations in multiple sources, many patients are treated with PAH-specific therapies without having completed the required diagnostic studies. A recent initiative studied compliance with the American College of Chest Physicians diagnostic algorithm.[37] This initiative demonstrated that compliance with the guidelines was poor and that the studies that were *not* performed most frequently included the ventilation-perfusion scan (57%), HIV serology (29%), and connective tissue disease serology (50%). Ten percent of patients were assigned the diagnosis of PAH without RHC. Only 7% of patients being treated with calcium channel–blocking agents fulfilled the criteria for an acute responder. Tools to improve compliance with the guidelines may improve care and outcomes in patients with PAH. Establishing a correct diagnosis is critical before the commencement of PAH-specific therapy.

Treatment

Treatment of PAH has evolved considerably over the past decade, in part because of advances in knowledge of the disease and the availability of agents that target known derangements in the pathobiologic process. Multiple treatment algorithms have been published over recent years. The algorithm from the 2015 ESC/ERS Guidelines[1] is reproduced in **Fig. 85.4.** Treatment decisions are often made with the severity of illness in mind. **Table 85.4** reviews factors that are known to influence the prognosis of patients with PAH. Current treatment goals include palliating the symptoms and improving the exercise tolerance, right ventricular function, and hemodynamics. Even though we strive to improve survival rates, clinical trials of PAH are often of insufficient size and duration to demonstrate a survival benefit, but a recent metaanalysis of currently approved therapies has suggested durable effects on outcomes.[38]

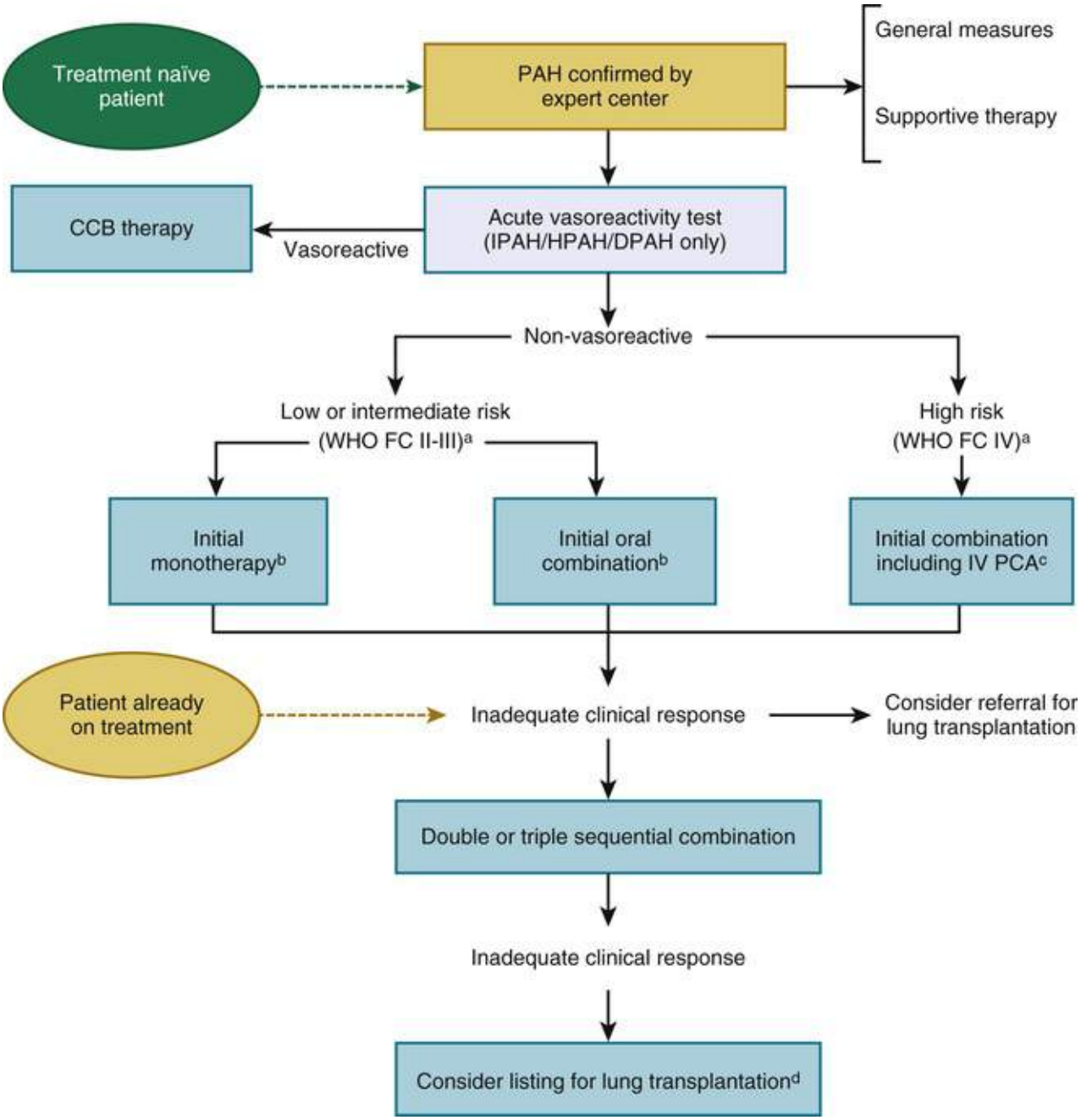


FIGURE 85.4 Evidence-based treatment algorithm for pulmonary arterial hypertension patients (group 1 patients only). (Modified from Galie N, Humbert M, Vachiery J-L, et al: 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2016;37:67.)

TABLE 85.4

Risk Assessment in Pulmonary Arterial Hypertension

DETERMINANTS OF PROGNOSIS* (estimated 1-year mortality rate)	LOW RISK (<5%)	INTERMEDIATE RISK (5% to 10%)	HIGH RISK (>10%)
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope†	Repeated syncope‡
WHO functional class	I, II	III	IV
6MWD	> 440 m	164-440 m	< 165 m
Cardiopulmonary exercise testing	Peak V_{O2} > 15 mL/min/kg	Peak V_{O2}	Peak V_{O2} < 11 mL/min/kg
	(> 65% pred.)	11-15 mL/min/kg (35% to 65% pred.)	(<35% pred.)
	VE/V_{CO2} slope < 36	VE/V_{CO2} slope 36-44.9	VE/V_{CO2} slope ≥ 45
NT-proBNP plasma levels	BNP < 50 ng/L	BPN 50-300 ng/L	BNP > 300 ng/L
	NT-proBNP < 300 ng/L	NT-proBNP 300-1400 ng/L	NT-proBNP > 1400 ng/L
Imaging (echocardiography, CMR imaging)	RA area < 18 cm^2	RA area 18-26 cm^2	RA area > 26 cm^2
	No pericardial effusion	No, or minimal, pericardial effusion	Pericardial effusion
Hemodynamics	RAP < 8 mm Hg	RAP 8-14 mm Hg	RAP > 14 mm Hg
	CI ≥ 2.5 L/min/m^2	CI 2.0-2.4 L/min/m^2	CI <2.0 L/min/m^2
	Sv_{O2} > 65%	Sv_{O2} 60% to 65%	Sv_{O2} < 60%

*Most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for IPAH and the cut-off levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.

†Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.

‡Repeated episodes of syncope, even with little or regular physical activity.

6MWD, 6-minute walking distance; *BNP*, brain natriuretic peptide; *CI*, cardiac index; *CMR*, cardiac magnetic resonance; *NT-proBNP*, N-terminal pro–brain natriuretic peptide; *pred.*, predicted; *RA*, right atrium; *RAP*, right atrial pressure; Sv_{02},mixed venous oxygen saturation; V_{O2}, oxygen consumption; VE/V_{CO2}, ventilator equivalents for carbon dioxide; *WHO*, World Health Organization.

From Galie N, Humbert M, Vachiery J-L, et al: 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2016;37:67.

General Measures.

Basic counseling and education about the disease state are important components in the care of patients with PAH. Low-level graded aerobic exercise such as walking is recommended. The benefits of intensive pulmonary rehabilitation have been demonstrated. Patients are advised against heavy physical exertion and isometric exercise because this may evoke exertional syncope. Oxygen supplementation to keep the saturation higher than 92% at rest and with exertion, sleep, or altitude is advisable. This may not be possible in patients with intracardiac shunting (including a patent foramen ovale). A sodium-restricted diet (<2400 mg/day) is advised and is particularly important for management of the volume status in those with right ventricular failure. Routine immunizations, such as those against influenza and pneumococcal pneumonia, are advised.

The hemodynamic fluctuations of pregnancy, labor, delivery, and the postpartum period are potentially life-threatening in patients with PAH, with a maternal mortality rate of 30% to 50%. Current guidelines recommend that pregnancy be avoided or be terminated early in women with PAH.[1] A contemporary account of pregnancies in patients with PAH described 26 pregnancies at 13 PAH centers.[39] Three deaths (12%) occurred, and refractory right-sided heart failure developed in one patient, who underwent heart-lung transplantation following delivery. There were two spontaneous and six induced abortions. Overall,

62% of the pregnancies resulted in a healthy baby without maternal complications. These women had well-controlled PAH (mean PVR of 500 ± 352 dyne-sec · cm^{-5}). Half of them were long-term responders to calcium channel–blocking agents. A retrospective five-center observation of 18 pregnancies from 1999 to 2009 resulted in 3 deaths (17% mortality rate).[40] It is important to discuss effective methods of birth control with women of childbearing potential in whom PAH is diagnosed.

Background Therapy.

Although there is a pathobiologic rationale for the use of anticoagulants in PAH, current observational registry data are heterogeneous and inconclusive. In a European registry, a survival benefit was noted in IPAH patients treated with anticoagulation; however, a survival benefit was not noted in the U.S. REVEAL Registry.[41,42] Neither registry demonstrated a benefit in associated PAH patients. Diuretics are indicated to manage right ventricular volume overload. Occasionally, intravenous diuretics are required. Serum electrolytes and renal function should be monitored closely. There are few data pertaining to digoxin, although it is sometimes used in patients with right-sided heart failure and a low CO and in those with atrial arrhythmias.

Calcium Channel–Blocking Agents

Calcium channel–blocking agents can be effective therapies for the few patients with a very robust response to acute vasodilator testing, as discussed previously. The current consensus definition of a positive response is defined as a fall in mPAP of at least 10 mm Hg to an mPAP of 40 mm Hg or less with unchanged or increased CO. Patients who meet these criteria may be treated with a calcium channel–blocking agent and should be monitored closely for both the safety and efficacy of therapy. If patients who meet the definition of an acute response do not improve to functional class I or II while taking calcium channel–blocking agents, they should not be considered chronic responders, and an alternative PAH-specific therapy should be prescribed. Very few patients (<7%) with IPAH do well over the long term with calcium channel–blocking drugs (see Classic References). Long-acting nifedipine, diltiazem, and amlodipine are the most commonly used agents. Because of its potential for negative inotropic effects, verapamil should be avoided.

Prostanoids

The reduced prostacyclin synthase level in patients with PAH results in inadequate production of prostacyclin I_2, a vasodilator with antiproliferative effects. Administration of prostanoids has been a mainstay of PAH therapy for almost two decades. Currently, multiple prostanoids are commercially available: epoprostenol (continuous intravenous), treprostinil (continuous subcutaneous, continuous intravenous, intermittent inhaled and oral), and iloprost (intermittent inhaled). Prostanoids are complex therapies that are best administered at centers with expertise in the complicated delivery systems and chronic management of their side effects and dosage regimens.

Epoprostenol was the first therapy approved by the U.S. Food and Drug Administration (FDA) for the indication of what was then called PPH in 1995. Randomized controlled clinical trials in patients with PPH (now called IPAH) demonstrated improvements in exercise tolerance as measured by 6MW distance, hemodynamics, quality of life, and survival over a 12-week period (see Classic References). Long-term observational series have also suggested improved survival rates with intravenous epoprostenol. In addition, intravenous epoprostenol has been evaluated for PAH related to the scleroderma spectrum of diseases. A 12-week randomized controlled clinical trial in this population demonstrated improvements in 6MW distance and hemodynamics. Observational series have also

reported favorable effects of intravenous epoprostenol in patients with numerous forms of associated PAH.

Epoprostenol must be delivered by continuous intravenous infusion. Each patient must learn the techniques of sterile preparation of the medication, operation of the ambulatory infusion pump, and care of the central venous catheter. A thermostable formulation of epoprostenol that does not require ice packs and can be mixed less frequently has more recently been approved. Intravenous epoprostenol is commonly started in the hospital at a dosage of 2 ng/kg/min and titrated upward, depending on the symptoms of PAH and the adverse effects of the therapy. Even though the dosage regimens are highly individualized, the optimal dosage for most adult patients tends to be in the range of 25 to 40 ng/kg/min. A high-CO state has been reported in a series of patients with IPAH treated with chronic epoprostenol therapy and is consistent with the drug having positive inotropic effects. The development of a chronic high-output state could have long-term detrimental effects on underlying cardiac function and should be avoided. Common side effects include jaw pain, flushing, nausea, diarrhea, rash, and musculoskeletal pain. Infections and interruptions in infusion can be life-threatening.

Treprostinil is a stable prostacyclin analogue that has pharmacologic actions similar to those of epoprostenol, but it differs in that it is chemically stable at room temperature and has a longer half-life (4 hours). Treprostinil is currently approved to be administered as a continuous subcutaneous infusion, a continuous intravenous infusion, an intermittent inhaled treatment, and orally. It was first studied as a subcutaneous infusion in a placebo-controlled, multicenter randomized trial of 470 patients over a 12-week period. The 6MW distance improved by 16 meters, although this improvement was noted to be dose related. The optimal dose of treprostinil has not been determined, but dosages of 75 to 150 ng/kg/min are typical. Adverse effects have included pain and erythema at the site of the subcutaneous infusion (85% of patients). Other common side effects included headache, diarrhea, rash, and nausea. Based on bioequivalence data, treprostinil has also been approved by the FDA to be delivered on a continuous intravenous basis. It has been reported that intravenous treprostinil is associated with a higher incidence of gram-negative sepsis than is intravenous epoprostenol. Recently a 60-patient study demonstrated the feasibility of delivering treprostinil via a fully implantable, programmable intravascular delivery system.[43] Patients were followed for approximately 1 year, and no catheter infections or occlusions were reported. This system is currently under FDA review.

A key element of the long-term efficacy of the parenteral prostacyclins appears to be related to the strategy of upward dosage titration of the drug over time. It is important to increase the dosage to the point that the side effects can be tolerated in patients who remain symptomatic because of a direct relationship between the dosage of drug and improvement in exercise testing and hemodynamics. Once an optimal dosage has been achieved, the dosage is kept constant thereafter. Patients who deteriorate after a long period of stability do not usually respond to further increases in the dosage.

Treprostinil is also approved for intermittent inhaled use. In a multicenter, randomized, placebo-controlled study of 235 patients with PAH who were still symptomatic despite therapy with either oral bosentan or sildenafil, the addition of inhaled treprostinil resulted in an improvement in the primary endpoint of 6MW distance.[44] Common side effects included cough, headache, nausea, dizziness, and flushing. Treprostinil diethanolamine is a salt form of treprostinil designed to release the drug in a sustained-release osmotic tablet for twice-daily dosing. Oral treprostinil has been studied as monotherapy in 349 patients with PAH over a 12-week period. An improvement of 23 meters ($P = 0.0125$) in the primary endpoint of 6MW distance was observed.[45] No improvements in the secondary endpoints of time to clinical worsening or functional class were observed. The most common adverse events were headache, nausea, diarrhea, and jaw pain. Oral treprostinil has also been studied in 350 patients with

PAH as add-on therapy to endothelin receptor antagonists and/or phosphodiesterase (PDE) inhibitors.[46] In this 16-week study, the placebo-corrected median difference in 6MW distance was 11 meters ($P = 0.07$). No improvements were observed in the secondary endpoints of time to clinical worsening or functional class, and the adverse event profile was similar to that in the monotherapy trial. Oral treprostinil was FDA approved in December of 2013.

Iloprost is an inhaled prostanoid that was studied in a 12-week multicenter, randomized, placebo-controlled trial of 207 patients. This study demonstrated improvement in a novel composite endpoint, which included improvement by at least one level of functional class, improvement in 6MW distance by at least 10%, and absence of clinical deterioration. Inhaled iloprost has also been studied in combination with bosentan in a multicenter, randomized, placebo-controlled trial. After 12 weeks, improvements were seen in functional class and time to clinical worsening. The combination appeared to be safe. Common side effects of inhaled iloprost included cough, headache, flushing, and jaw pain.

Selexipag is an oral, selective prostacyclin receptor agonist that is chemically distinct from prostacyclin analogs. A phase 2 study demonstrated a statistically significant reduction in PVR in patients with PAH.[47] A placebo-controlled, event-driven, study of selexipag in 1156 patients with PAH demonstrated a 40% reduction ($P < 0.001$) in the composite endpoint of death, hospitalization for PAH, worsening of PAH resulting in the need for lung transplantation or atrial septostomy, initiation of parenteral prostanoids or chronic oxygen for worsening of PAH, and disease progression.[48] Notably, the effect of selexipag was consistent across subgroups, including types of treatment (no background therapy vs monotherapy or dual oral background therapy), disease cause, sex, age, and functional status. The most common adverse effects in the selexipag group were consistent with the known side effects of prostacyclin, including headache, diarrhea, nausea, and jaw pain.

Endothelin Receptor Antagonists

Endothelin-1 is a potent vasoconstrictor and smooth muscle mitogen that contributes to the pathogenesis of PAH. Three endothelin receptor antagonists, bosentan, ambrisentan, and macitentan, are currently commercially available for the treatment of PAH.

Bosentan has been studied in multiple placebo-controlled trials of PAH. The initial multicenter, randomized, placebo-controlled trial involving 32 patients with functional class III or IV PAH demonstrated improvements in 6MW distance and hemodynamics over a 12-week period. The BREATHE-1 study, a multicenter, randomized, placebo-controlled trial of 213 functional class III and IV patients with PAH demonstrated an improvement in 6MW distance and the composite endpoint of time to clinical worsening over a period of 16 weeks (see Classic References). Bosentan has also been evaluated in functional class II patients in a 6-month multicenter, randomized, placebo-controlled trial. This study demonstrated an improvement in PVR and time to clinical worsening. The improvement in 6MW distance was not statistically significant. Bosentan has been studied specifically in patients with congenital systemic-to-pulmonary shunts and Eisenmenger physiology. In this population, improvements in PVR, mPAP, and 6MW distance were noted and bosentan did not worsen oxygen saturation. Bosentan is currently used widely in patients with PAH. Close follow-up of both efficacy and safety is encouraged. The FDA requires that liver function tests be done on a monthly basis, and an algorithm for managing elevated liver function test results is available on the package insert. Other side effects include headache, anemia, and edema.

Ambrisentan has been studied in two phase III multicenter, randomized, 12-week placebo-controlled trials in 394 patients with PAH and demonstrated an improvement in 6MW distance and time to clinical worsening. The FDA no longer requires monthly liver function test monitoring in patients taking

ambrisentan, although many experts continue to perform liver function tests periodically. Other side effects of ambrisentan include headache and lower extremity edema, which is more common in the population older than 65 years.

Macitentan has been studied in a phase III long-term morbidity and mortality trial in which the primary endpoint was time from initiation of treatment to first occurrence of a composite endpoint of death, atrial septostomy, lung transplantation, initiation of treatment with parenteral prostanoids, or worsening PAH.[49] Seven hundred forty-two patients were randomly assigned to either placebo; macitentan, 3 mg; or macitentan, 10 mg daily. There was a 30% and 45% risk reduction in the primary endpoint with the 3-mg and 10-mg doses, respectively. The most frequent adverse events were headache, nasopharyngitis, and anemia. The incidence of edema and elevated liver function test results was similar in the placebo and macitentan groups.

Phosphodiesterase Inhibitors

The reduction in NO synthase in patients with PAH results in derangements of the cyclic guanosine monophosphate (GMP) pathway. PDE5 inhibition has the potential to inhibit the hydrolysis of cyclic GMP and has proved to be an effective therapy for PAH.

Sildenafil was studied in a 12-week multicenter, randomized, placebo-controlled trial and was found to improve 6MW distance and hemodynamics, but not the secondary endpoint of time to clinical worsening. The improvement in 6MW distance was not dose related, and sildenafil is currently approved at a dosage of 20 mg three times daily. More impressive hemodynamic improvements were achieved with higher dosages, and some patients were treated with dosages of up to 80 mg three times daily. Tadalafil was studied in a 16-week multicenter, randomized, placebo-controlled trial and demonstrated an improvement in the primary endpoint of 6MW distance. The highest dosage studied (40 mg) also resulted in an improvement in the secondary endpoint of time to clinical worsening. Tadalafil is approved at a dosage of 40 mg once daily. The most common side effects of the PDE5 inhibitors include headache, flushing, dyspepsia, myalgia, and epistaxis. Rare episodes of sudden vision or hearing loss have been reported.

Soluble Guanylate Cyclase Stimulators

Riociguat is a first-in-class agent that directly stimulates soluble guanylate cyclase independent of NO and increases the sensitivity of soluble guanylate cyclase to NO. In a 12-week, multicenter, open-label, uncontrolled phase II trial in patients with PAH and CTEPH, riociguat improved the 6MW distance and hemodynamics.[50] More recently, a randomized controlled trial of 261 patients with either inoperable CTEPH or persistent PH after pulmonary endarterectomy demonstrated an improvement in the primary endpoint of 6MW distance and the secondary endpoints of PVR, NT-pro-brain natriuretic peptide (BNP), and functional class with riociguat.[51] A randomized controlled trial of 443 patients with PAH (some previously treated with endothelin receptor antagonists or nonparenteral prostanoids) also demonstrated an improvement in the primary endpoint of 6MW distance, as well as multiple secondary endpoints, including PVR, NT-pro-BNP, functional class, and time to clinical worsening with riociguat.[52] The most common adverse events included headache, dyspepsia, peripheral edema, and hypotension. Riociguat should not be used concurrently with PDE5 inhibitors.

Up-Front Combination Therapy

Using multiple agents to target distinct pathobiologic pathways has been successful in other

cardiovascular diseases, including systemic hypertension (**see Chapter 46**) and heart failure (**see Chapter 25**). Given the multiple agents that target distinct pathways in PAH, the use of combination therapy has been explored. Sequential combination therapy has been used in practice and in some clinical trials. More recently, up-front combination therapy has been studied in both a randomized control trial and an observational series. The AMBITION study evaluated 500 treatment-naïve, functional class II or III PAH patients who were randomized to first-line monotherapy with tadalafil or monotherapy with ambrisentan versus up-front combination therapy with tadalafil and ambrisentan.[53] The primary endpoint was a composite of clinical failure events (including death, hospitalization, PAH progression, and an unsatisfactory clinical status). The study was positive, with a 50% reduction in events in the combination group. In addition, improvements were observed in exercise capacity, rate of satisfactory clinical response, and NT-proBNP plasma levels. A single-center observational pilot study on an initial triple combination in 19 World Health Organization functional class (WHO-FC) III and IV patients has provided preliminary evidence of the benefits of up-front triple-combination therapy in patients with severe PAH.[54] Given the high mortality rate of the disease and these encouraging results, the treatment paradigm in PAH is shifting to earlier and more aggressive combination therapy.

Investigational Therapies.

Although three pathways are currently targeted, outcomes are still suboptimal in patients with PAH, and active research on potential therapies for this disease continues. After initial enthusiasm, clinical trial results with kinase inhibitors, including imatinib and nilotinib, and the apoptosis-signal–regulating kinase 1 selonsertib have failed to demonstrate efficacy. Ubenimex is a small-molecule, dual-inhibitor of aminopeptidase and leukotriene A4 hydrolase (LTA4H) currently being evaluated in a phase II trial in PAH patients receiving background therapy. Bardoxolone methyl is a once-daily Nrf2 activator and NF-kB suppressor that promotes mitochondrial respiration and reduces reactive oxidative stress and inflammation. It is currently being studied in phase 2 and 3 trials in PAH. FK506 (tacrolimus) is an activator of BMP signaling that has been recently tested in PAH patients. Targeting the serotonin pathway is another novel approach in development. Last, components of the immune system involved in the development of PAH also offer a potential new area of treatment. Targeting of the IL-6 pathway (tocilizumab) or B cells (rituximab) is currently being studied in phase II PAH trials.

Interventional Therapies.

Atrial septostomy creates a right-to-left interatrial shunt, decreases the right-sided heart filling pressure, improves right ventricular function, and improves left-sided heart filling. Several case series have reported hemodynamic and clinical improvements following this procedure. Although the shunt created decreases systemic arterial oxygen saturation, the goal is an improvement in systemic oxygen delivery based on the improved CO. However, the procedural mortality rate is high, in the range of 9% to 22%, and it is driven by the severity of PAH and right-sided heart failure in patients undergoing this procedure. The recommended technique is graded balloon dilation of the fossa ovalis, which can be achieved in stages over a period of several weeks in unstable patients. It should not be performed in patients with impending death and severe right ventricular failure. Predictors of procedure-related failure or death include a mean right atrial pressure higher than 20 mm Hg, a PVR index higher than 55 units/m^2, or a predicted 1-year survival rate of less than 40%. Currently, atrial septostomy is recommended for patients with severe PAH and intractable right-sided heart failure despite maximal medical therapy. The goals of this procedure are palliation and restoration and maintenance of clinical stability until transplantation can

be performed. Atrial septostomy should be performed only by experienced operators in centers with the resources to care for such critically ill patients. Expert-based consensus guidelines define the following as contraindications to atrial septostomy: mean right atrial pressure higher than 20 mm Hg, resting arterial oxygen saturation lower than 90% on room air, or LVEDP higher than 18 mm Hg.

The advent of disease-targeted therapy for severe PAH has reduced and delayed patient referral for lung transplant programs. The long-term outcomes of medically treated patients remains uncertain, and transplantation should continue to be an important option for those who fail on such therapy and remain in WHO-FC III or IV. Delayed referral in combination with the length of the waiting time, due to the shortage of organ donors, may increase the chances of death for patients on the waiting list and the severity of their clinical status at the time of transplantation.

The overall survival rate following transplantation for PAH has increased to 52% to 75% at 5 years and to 45% to 66% at 10 years. Considering all of the above information, it seems reasonable to consider eligibility for lung transplantation after an inadequate clinical response to the initial monotherapy, and to refer the patient soon after an inadequate clinical response is confirmed with maximal combination therapy. Both heart-lung and double-lung transplantation have been performed for PAH, although the threshold for unrecoverable right ventricular systolic dysfunction and/or left ventricular diastolic dysfunction is unknown. Currently, the vast majority of patients worldwide receive bilateral lungs. Patients with Eisenmenger syndrome due to simple shunts have been treated by isolated lung transplantation and repair of the cardiac defect or by heart-lung transplantation. Recent reports indicate that venoarterial extracorporeal membrane oxygenation (ECMO) may be employed in awake end-stage PH patients for bridging to lung transplantation.

Prognosis

Recently, two large registries have shed light on the prognosis of patients with PAH in the era of PAH-specific therapies. The French registry demonstrated that the survival rate of patients with PAH has improved over the predicted survival rate based on the NIH registry, although it still remains suboptimal, with 1-, 2-, and 3-year survival rates of 85.7%, 69.5%, and 54.9%, respectively, for incident cases.[55] Important predictors of survival times included sex (males fare worse), functional class, exercise tolerance as measured by 6MW distance, and hemodynamics, specifically right atrial pressure and CO. Similarly, in the large U.S.-based REVEAL registry, important prognostic variables were described.[56] Key predictors of outcome in this study included the cause of PAH, functional class, sex, exercise tolerance, and hemodynamics that reflect right ventricular function.

Longitudinal Assessment

Several investigators have proposed scores and parameters indicative of future risk in patients with PAH.[1,57] They were mostly based on the meticulous analysis of data derived from randomized controlled trials and large registries. Although several approaches aiming at predicting the future risk are still based mostly on expert opinion and require independent validation, consensus recommendations on reassessment have been made. The 2009 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) expert consensus document on PH relies on routine assessment of several prognostic indicators, such as WHO functional class, 6MW distance, and echocardiographic and hemodynamic parameters (**Table 85.5**).[36] Patients who achieve WHO-FC I or II with a 6MW distance greater than 400 meters and have normal right ventricular function on echocardiography and normal

hemodynamic measurements of right ventricular function (right atrial pressure and cardiac index) can be assessed on a 3- to 6-month basis by either the referring physician or a PH specialty center. High-risk patients (i.e., those who remain in WHO-FC III or IV with a 6MW distance < 300 meters and have imaging evidence of right ventricular dysfunction and abnormal hemodynamics) should be evaluated at 1- to 3-month intervals. Every assessment should include reevaluation of the WHO functional class and 6MW distance, with echocardiography performed approximately every 12 months or every 6 to 12 months depending on the clinical course. In stable patients, RHC should be performed to assess the response to therapy and signs of clinical worsening; in unstable patients, hemodynamic data should be obtained more frequently. Following the same approach, the 2015 ESC/ERS PH guidelines state that the overall treatment goal in patients with PAH is achieving a “low-risk” status (**see Table 85.5**), which is usually associated with good exercise capacity, good quality of life, good right ventricular function, and a low mortality risk.[1] Specifically, this means bringing and/or keeping the patient in WHO-FC II whenever possible. In most patients, this will be accompanied by a near-normal or normal 6MW distance of more than 440 meters because this number has been derived from the largest cohort investigated so far. Nevertheless, individual factors must be considered, and lower values may be acceptable in elderly patients or patients with comorbidities; values of more than 440 meters may not be sufficient in younger, otherwise healthy patients. Especially in those patients, cardiopulmonary exercise testing should be regularly used because it provides more objective information on exercise capacity and right ventricular performance. It should be noted that these treatment goals are not always realistic and may not be achievable in patients with advanced disease, patients with severe comorbidities, or very old patients.

TABLE 85.5

Longitudinal Evaluation of Patients With Pulmonary Arterial Hypertension*

	LOW RISK	HIGH RISK
Clinical course	Stable; no increase in symptoms and/or decompensation	Unstable; increase in symptoms and/or decompensation
Physical examination	No evidence of right-sided heart failure	Signs of right-sided heart failure
Functional class†	I/II	IV
6MW distance†	> 400 meters	< 300 meters
Echocardiogram	Right ventricular size and function normal	Right ventricular enlargement or dysfunction
Hemodynamics	Right atrial pressure normal	Right atrial pressure high
	Cardiac index normal	Cardiac index low
Brain natriuretic peptide	Nearly normal or remaining stable or decreasing	Elevated or increasing
Treatment	Oral therapy	Intravenous prostacyclin and/or combination treatment
Frequency of evaluation	Every 3-6 months‡	Every 1-3 months
Functional class assessment	Every clinic visit	Every clinic visit
6MW distance	Every clinic visit	Every clinic visit
Echocardiogram§	Yearly or center dependent	Every 6-12 months or center dependent
Brain natriuretic peptide¶	Center dependent	Center dependent
Right heart catheterization	Clinical deterioration and center dependent	Every 6-12 months or clinical deterioration

*For patients in the high-risk category, consider referral to a pulmonary hypertension specialty center for contemplation of advanced therapies, clinical trials, and/or lung transplantation.

†The frequency of follow-up evaluation for patients in functional class III and/or having a 6MW distance of between 300 and 400 meters would depend on a composite of detailed assessments of the other clinical and objective characteristics listed.

‡For patients who remain stable with established therapy, follow-up assessments can be performed by referring physicians or pulmonary hypertension specialty centers.

§Echocardiographic measurement of pulmonary artery systolic pressure is an estimation only, and it is strongly advised that its evaluation not be relied on as the sole parameter for making therapeutic decisions.

¶The usefulness of serial brain natriuretic peptide levels to guide management in individual patients has not been established.

6MW, 6-minute walk.

From McLaughlin VV, Archer SL, Badesch DB, et al: ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc., and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53:1573.

Goal-Oriented Strategy.

This recommended approach relies on improving clinical markers that have prognostic significance and systematically escalating treatment until a specific goal is attained. This requires that certain parameters be identified early and followed over time and that a threshold value for each parameter be defined before starting therapy.

Although the primarily observational studies mentioned earlier do not allow definitive conclusions, reasonable goals of therapy include the following[30]:

- WHO-FC: I or II
- Echocardiography/CMR: normal or near-normal right ventricular size and function
- Hemodynamics: normal right ventricular function (right atrial pressure < 8 mm Hg and cardiac index > 2.5 to 3.0 liters/min/m^2
- 6MW distance: more than 380 to 440 meters (may not be aggressive enough)
- Cardiopulmonary exercise testing: peak V_{O_2} higher than 15 mL/min/kg and V_E/V_{CO_2} (minute ventilation–carbon dioxide production slope; Eq_{CO_2}) lower than 45 liters/min

• BNP level: “normal”

Patients who achieve these parameters, no matter which specific therapy or approach is used, seem to have a better prognosis than do those who do not achieve these goals. A more aggressive approach to goal-oriented therapy may help us improve survival rates. Despite the many observations that support attainment of such goals, many patients today fall far short of them. For example, approximately 60% of functional class III patients and 50% of functional class IV patients in the REVEAL registry are not being treated with a prostacyclin despite not being at the goal functional class of I or II.[58] Both patient unwillingness and physician reluctance to proceed to the most aggressive therapy are contributing factors.

Consensus recommendations on reassessment are provided in the 2009 ACCF/AHA expert consensus document on PH and in the 2015 ESC/ERS PH guidelines. They rely on routine evaluation of important prognostic indicators such as WHO functional class, 6MW distance, and echocardiographic and hemodynamic parameters (**see Tables 85.4 and 85.5**). In most cases, goals of therapy include improvement to functional class I or II status, 6MW distance greater than 400 meters (considering demographic factors), and normal or near-normal right ventricular function as assessed by echocardiography or invasive hemodynamics.

Perioperative and Intensive Care Unit Management.

Patients with significant PAH are at high risk for general anesthesia. The perioperative risk was studied in an international, prospective 3-year questionnaire–based survey among 11 PH centers.[59] Major complications occurred in about 6% of their patients, and the overall perioperative mortality rate was about 3.5%. The factor that increased complications and mortality rates was more advanced disease as manifested by a higher right atrial pressure and a lower 6MWD. The need for emergency surgery and the use of perioperative vasopressors also increased the risk.

PAH can be considered a fixed obstructive cardiopulmonary lesion with an intraoperative physiology similar to that of severe aortic or mitral stenosis. During induction of anesthesia, systemic vasodilation is common and the systemic blood pressure can decrease. Systemic hypotension can exacerbate right ventricular ischemia by decreasing the right coronary artery perfusion pressure during systole, resulting in decreased CO due to worsening right ventricular function. The reduction in pulmonary blood flow results in more underfilling of the left atrium and left ventricle, worsening the systemic hypotension. Furthermore, as underfilling of the left ventricle becomes more pronounced and overloading of the right ventricle increases, increased interventricular septal flattening ensues, thereby further decreasing the ability of the left ventricle to fill. These abnormalities can quickly result in acute decompensation and potential death in a patient with PAH.

Given the risk of general anesthesia in a patient with PAH, the following strategies can help to ensure the best outcome perioperatively: (1) try to avoid general anesthesia if possible (e.g., use a nerve block); (2) evaluate and treat for decompensated right heart failure; (3) in patients with severe PAH (such as those with functional class III or IV symptoms, or those who are receiving intravenous or subcutaneous prostacyclins), perform preoperative RHC and optimize the hemodynamics prior to elective surgery; and (4) in the operating room, have available PA catheter monitoring, transesophageal echocardiography, and inhaled NO. All PAH patients should continue vasodilator medications perioperatively. A PAH specialist should be involved in perioperative management, especially in the management of high-risk PAH patients who are taking advanced prostanoid therapies.

With advances in pharmacologic therapy for PAH, many patients can now survive with a good

functional status. However, despite these improvements in treatment, the right ventricle remains vulnerable, and patients can quickly spiral downward in the setting of stressors such as infection and/or medication and/or dietary noncompliance, becoming critically ill. Unfortunately, there is scant evidence for the appropriate management of PAH patients in the intensive care unit, and treatment guidelines are based primarily on expert consensus.[60]

Management of the right ventricle is central to successfully treating PAH patients who are critically ill. Often, clinicians give fluids to patients with sepsis or hypotension, a management strategy that can have dire consequences in the setting of PAH. For example, in a patient with PAH who is septic or has a severe infection, systemic vasodilation occurs. As outlined earlier when describing the hemodynamic reaction to general anesthesia, the right ventricle can become more ischemic because of decreased right ventricular perfusion, resulting in further exacerbation of systemic hypotension due to decreased CO. The right ventricle enlarges and compresses the left ventricle further, decreasing left ventricular filling. In this setting, administration of intravenous fluids will only compound the problem as the right ventricular diastolic pressure rises (further impeding the right coronary blood flow) and interventricular septal flattening will worsen.

It is also important to note that acute-on-chronic right ventricular failure in PAH is physiologically different than acute right ventricular failure (e.g., right ventricular myocardial infarction). Most PAH patients are not preload dependent in the setting of right ventricular failure, and even small boluses of intravenous fluid can be harmful. Finally, renal venous congestion often occurs in patients with PAH who are critically ill with right ventricular failure. The right atrial pressure (and therefore central venous pressure) is high in decompensated PAH, resulting in increased renal venous pressure, and systemic hypotension decreases renal perfusion. These hemodynamic changes decrease the renal blood flow and result in increased fluid retention.

Because of these hemodynamic abnormalities, we advocate the following steps for the management of critically ill PAH patients: (1) consider invasive hemodynamic monitoring (e.g., pulmonary artery catheter) for diagnostic purposes to determine the hemodynamic abnormality and filling pressures present; (2) increase the systemic blood pressure with drugs such as dobutamine and/or phenylephrine to achieve a systolic blood pressure of more than 90 mm Hg; (3) optimize the central venous pressure to 8 to 10 mm Hg (use intravenous diuretics or ultrafiltration or continuous venovenous hemofiltration if necessary); (4) transfuse packed red blood cells to maintain the hemoglobin at more than 10 g/dL; (5) continue pulmonary vasodilator drugs that the patient was taking previously as an outpatient; and (6) consider prescribing inhaled NO (typical dosage, 20 ppm), especially if the patient is on a ventilator, remembering to wean off slowly to avoid rebound elevations in PA pressure. If these measures fail to work, adding an inotropic agent to increase the right ventricular contractility can be considered. In addition, the use of short-term, percutaneous, partial ventricular support devices, such as a Tandem Heart (inflow cannula in the right atrium and outflow cannula in the pulmonary artery) or a right ventricular Impella catheter has been described in the setting of right ventricular failure.[61,62] In severe cases, where there is a clearly reversible cause of right ventricular decompensation, extracorporeal life support (e.g., VA-ECMO) can be administered and can be life-saving; bilateral lung transplantation should also be considered in these cases.

Collaborative Care of the Pulmonary Arterial Hypertension Patient.

The management of the PAH patient requires a multidisciplinary approach and collaboration between local care and the PH specialty center. Additional content on this topic is presented in an online supplement entitled Collaborative Care of the Pulmonary Arterial Hypertension Patient.

Group 2 Pulmonary Hypertension Caused by Left-Sided Heart Disease

Definition

Left-sided heart disease is probably the most frequent cause of PH. The key hemodynamic factor that differentiates group 2 PH from others is the elevation in the left-sided heart filling pressure, PAWP. Left-sided ventricular or valvular dysfunction may result in chronic left atrial hypertension, with passive backward transmission of this pressure to the pulmonary vasculature leading to PH. Most commonly, the transpulmonary gradient is normal (< 12 mm Hg) and the PVR is normal or nearly normal (< 3 Wood units). Pulmonary venous hypertension can be a consequence of left ventricular dysfunction, mitral or aortic valve disease, cardiomyopathy, cor triatriatum, or pericardial disease. Although mitral stenosis was a common cause of pulmonary venous hypertension decades ago, heart failure with a preserved ejection fraction (HFpEF) is a common cause of pulmonary venous hypertension currently (**see Chapter 26**). It is presumed that the mechanism of both is similar. Specifically, a chronic elevation in left-sided diastolic filling pressure causes backward transmission of the pressure to the pulmonary venous system. In most cases this results in a passive increase in pulmonary artery pressure. In a subset of patients, a reactive vasoconstriction in the pulmonary arterial bed increases the pulmonary arterial pressure beyond what is expected from the elevated left atrial pressure alone; criteria for combined precapillary and postcapillary PH are reviewed earlier. The presence of PH in the setting of both left ventricular systolic dysfunction and HFpEF portends a poor prognosis.

Pathobiology and Pathophysiology.

Primary or pathognomonic vascular changes in the arterial wall may be absent in group 2 PH. Capillary and arterial remodeling develop as a result of backward transmission of increased pulmonary venous pressure. The pathologic changes are characterized by enlarged and thickened pulmonary veins, pulmonary capillary dilation, interstitial edema, alveolar hemorrhage, and lymphatic vessel and lymph node enlargement. The distal pulmonary arteries may be affected by medial hypertrophy and intimal fibrosis.

The severity of the PH depends, in part, on the contractility of the right ventricle. In the presence of a normal right ventricle, an increase in left atrial pressure initially results in a decrease in the PVR and the pressure gradient across the lungs because of distention of compliant small vessels or recruitment of additional vascular channels, or both. With further increases in left atrial pressure, the pulmonary arterial pressure rises along with the pulmonary venous pressure such that at a constant pulmonary blood flow, the pressure gradient between the pulmonary artery and veins and PVR remain constant. When the pulmonary venous pressure approaches or exceeds 25 mm Hg on a chronic basis, a disproportionate elevation in pulmonary artery pressure may occur, with the pressure gradient between the pulmonary artery and veins rising while the pulmonary blood flow remains constant or falls. This is indicative of an elevation in PVR caused in part by pulmonary arterial vasoconstriction. Some patients may have a genetic predisposition in which the chronically elevated pulmonary venous pressure serves as a trigger for the development of structural changes similar to those found in IPAH. Marked reactive PH with a pulmonary artery systolic pressure in excess of 80 mm Hg occurs in less than a third of patients whose pulmonary venous pressure is elevated more than 25 mm Hg; this finding suggests a broad spectrum of pulmonary vascular reactivity to chronic increases in pulmonary venous pressure. The molecular

mechanisms involved in elevating the PVR are unclear.

Although the right ventricle may initially adapt to the elevated afterload with hypertrophy, it might ultimately progress to chamber dilation, functional tricuspid incompetence, and right ventricular dysfunction. The right ventricle is the ultimate victim of these pulmonary vascular changes, and a common phenotype of end-stage pulmonary venous hypertension is right ventricular failure with systemic venous congestion, renal dysfunction, and ascites. Eventually, reductions in right ventricular output may lead to underfilling of the left ventricle and, at times, a paradoxical decrease in PAWP.

Diagnosis.

PH as a consequence of left ventricular systolic dysfunction, aortic and mitral valve disease, and cor triatriatum is often recognized because of the distinct clinical and echocardiographic patterns of these phenotypes. Recognition of PH resulting from HFpEF is more challenging, and HFpEF is commonly mistaken for IPAH. **Table 85.6** highlights some of the features that can help distinguish PH caused by HFpEF from group 1 PAH. Patients with PH caused by HFpEF tend to be older than group 1 PAH patients and often have more comorbid conditions, such as systemic hypertension, diabetes, coronary artery disease, and obesity. Although exertional dyspnea is often the chief complaint in both groups, orthopnea and paroxysmal nocturnal dyspnea are more specific for HFpEF. Chest imaging may provide evidence of an elevated left-sided heart filling pressure. Pulmonary vascular congestion or interstitial edema may be present on radiography. Chest CT will often reveal a mosaic perfusion pattern and ground-glass opacities consistent with chronic interstitial edema. Electrocardiographic clues favoring HFpEF include left ventricular enlargement, left atrial enlargement, and atrial fibrillation. Frequently, electrocardiographic findings of right ventricular enlargement are absent. Echocardiographic findings suggestive of HFpEF include left atrial enlargement, left ventricular hypertrophy, and Doppler indices of diastolic dysfunction, although grade 1 diastolic dysfunction is common in group 1 PAH. In general, right atrial and right ventricular dilation and intraventricular septal motion consistent with right ventricular pressure and volume overload are much more impressive in group 1 PAH.

TABLE 85.6

Distinguishing Pulmonary Arterial Hypertension From Heart Failure With Preserved Ejection Fraction

CHARACTERISTIC	PULMONARY ARTERIAL HYPERTENSION MORE LIKELY	HFPEF MORE LIKELY
Age	Younger	Older
Comorbid conditions: diabetes mellitus, hypertension, coronary artery disease, obesity (metabolic syndrome)	Often absent	Often present and multiple
Symptoms: paroxysmal nocturnal dyspnea, orthopnea	Often absent	Often present
Cardiac examination	Right ventricular heave, loud P_2, tricuspid regurgitation murmur	Sustained left ventricular impulse, S_4
Chest x-ray	Clear lung fields	Pulmonary vascular congestion, pleural effusions, pulmonary edema
Chest CT	Often clear lungs	Mosaic perfusion pattern, ground-glass opacities consistent with chronic interstitial edema
ECG	Right axis deviation, right ventricular enlargement	Left atrial enlargement, left ventricular enlargement atrial fibrillation, no right axis deviation
Natriuretic peptides	Often elevated	Often elevated
Echocardiography showing left atrial enlargement, left ventricular hypertrophy	Absent	Often present
Echocardiography showing diastolic dysfunction	Grade 1 common	Grade 2, 3 common
Echocardiography of right ventricle	Often enlarged, may share the apex	Often normal, mildly enlarged
Echocardiography showing pericardial effusion	Sometimes	Rare

HFpEF, heart failure with a preserved ejection fraction.

Even though the clinical factors listed earlier provide useful information for differentiating PH in the setting of HFpEF from group 1 PAH, invasive hemodynamic testing is required for a definitive diagnosis.

To make the diagnosis of PAH, the PAWP or LVEDP must be less than 16 mm Hg. If an ideal PAWP tracing cannot be obtained, the LVEDP should be measured directly. If a patient with many characteristics of HFpEF has a PAWP or LVEDP lower than 16 mm Hg, provocative maneuvers should be considered. Exercise is commonly used. Patients often report symptoms of dyspnea with exercise, during which an increase in the heart rate and a reduction in the diastolic filling time may increase the left-sided filling pressure and, as a result, pulmonary artery pressure. Saline loading is frequently used in laboratories without the ability to perform exercise studies. An increase in PAWP in a patient undergoing vasodilator testing with the typical agents used in group 1 PAH should raise suspicion for HFpEF.

Treatment

Treatment of group 2 patients, or those with pulmonary venous hypertension, should always be targeted at the underlying cause. In many patients, a reduction in the left-sided filling pressure will result in a reduction in pulmonary artery pressure. Emphasis should be placed on blood pressure control, volume management, and sodium restriction. Comorbid diseases such as obesity, diabetes, and obstructive sleep apnea must be addressed. Atrial fibrillation is not well tolerated in these patients, and every attempt to maintain the sinus rhythm should be made. No PAH-specific therapy is currently approved for the treatment of pulmonary venous hypertension. In the setting of left ventricular systolic dysfunction, both prostanoids and endothelin receptor antagonists have been studied and have failed to demonstrate a treatment benefit and may even be harmful.

There has been enthusiasm for the use of PDE5 inhibitors for HFpEF. A single-center, randomized controlled study of sildenafil in 54 patients with HFpEF and PH (pulmonary artery systolic pressure > 40 mm Hg) demonstrated that chronic (1 year) treatment was associated with a reduction in right ventricular dilation, enhanced right ventricular contractile function, and improvements in measures of alveolar-capillary gas exchange.[63] However, a multicenter randomized controlled trial of 216 stable patients with HFpEF found no difference in the primary endpoint of change in peak oxygen consumption in those treated with sildenafil versus placebo.[64] There were also no differences in the secondary clinical endpoints. This study did not enrich for patients with HFpEF and more severe PH, and further study in this subgroup may be warranted. More recently a phase II trial of macitentan in patients with combined precapillary and postcapillary pulmonary hypertension has been completed.

Group 3 Pulmonary Hypertension Caused by Chronic Respiratory Diseases

PH is a frequent complication of chronic respiratory diseases such as COPD[65] and interstitial pulmonary fibrosis (IPF).[66] Even though frequently moderate, PH has an impact on the functional capacity and survival rate in these patients. PH should be suspected when patients have signs of right-sided heart failure and when dyspnea and/or severe hypoxemia cannot be explained by the severity of the impairment in lung function. Patients with PH who are hypoxemic should be treated according to guidelines for the management of these respiratory diseases, including long-term oxygen therapy and lung transplantation when appropriate. The impact of PH on exercise capacity and outcomes is more significant in the minority of patients with mPAP higher than 40 mm Hg. Such patients with severe PH have the worst survival rates and should be referred to an expert PH center for complete evaluation and management.

Epidemiology and Natural History of Pulmonary Hypertension in Chronic

Obstructive Pulmonary Disease

A better understanding of the consequences of chronic lung diseases on the pulmonary circulation has been possible since the late 1940s with the demonstration of hypoxic pulmonary vasoconstriction and the first hemodynamic measurements in diseased humans. Severe chronic respiratory diseases cause alveolar hypoxia, which in turn causes PH as a result of ongoing pulmonary vasoconstriction and remodeling. PH increases the work of the right ventricle, thereby leading to right ventricular enlargement (hypertrophy and dilation) and possibly resulting in right-sided heart dysfunction and failure. Because alveolar hypoxia is a prominent cause of PH in patients with severe chronic hypoxemia (Pa_{O_2} < 55 to 60 mm Hg), long-term oxygen therapy is recommended for these patients.

A study of the natural history of PH in patients with COPD shows that its progression is slow and the mPAP may remain stable over long periods. In a study in which 93 patients were observed for 5 to 12 years, the changes in mPAP were rather small (+0.5 mm Hg/yr, with similar evolution of mPAP in patients with or without initial PH). In another study on the natural history of PH in 131 patients with stable COPD, the evolution of pulmonary hemodynamics was evaluated by performing two RHCs at a mean time interval of 6.8 ± 2.9 years. At inclusion all patients had an mPAP at rest lower than 20 mm Hg. At the second RHC, 33 patients had a resting mPAP higher than 20 mm Hg, but this elevation was generally mild. Patients in whom an mPAP higher than 20 mm Hg developed at the second RHC had a higher resting mPAP and a significantly lower resting Pa_{O_2} at inclusion. Logistic regression analysis showed that the resting mPAP was an independent predictor at inclusion for the subsequent development of mPAP higher than 20 mm Hg. In addition, patients with COPD in whom an elevated mPAP (> 20 mm Hg) developed had significant worsening of Pa_{O_2}, whereas the mean Pa_{O_2} was stable in the remainder. Thus, progression of the mPAP over time in patients with COPD and mild to moderate hypoxemia is usually slow.

Robust data on the prevalence of PH in large populations of patients with COPD of all levels of severity have been difficult to produce because of the poor sensitivity of echocardiographic screening in COPD, the lack of systematic RHC analysis in large cohorts of patients, and the usual focus on particular subsets of patients. However, it is clear that severe PH (defined as mPAP > 40 mm Hg) is rare in patients with COPD. Conversely, moderate elevations in mPAP in patients with COPD are more common. In the modern management era (when long-term oxygen therapy was widely available), the National Emphysema Treatment Trial reported an mPAP of 26.3 ± 5.2 mm Hg in a series of 120 patients with severe emphysema. Another analysis of patients with severe COPD who were candidates for lung volume reduction surgery or lung transplantation showed that 36.7%, 9.8%, and 3.7% of patients had an mPAP of 26 to 35 mm Hg, 36 to 45 mm Hg, and more than 45 mm Hg, respectively. In this study, the mPAP was inversely correlated with the Pa_{O_2}. Cluster analysis suggested the existence of four groups of patients: (1) patients with a moderately lowered forced expiratory volume in 1 second (FEV_1) and Pa_{O_2} and a normal mPAP level; (2) patients with severe airflow obstruction, moderate hypoxemia, and PH; (3) patients with severe airflow obstruction, severe hypoxemia, and a high mPAP; and (4) patients with moderate airflow obstruction contrasting with moderate to severe PH and severe hypoxemia. When compared with the other groups, the last group of patients was characterized by a higher FEV_1, a lower Pa_{O_2}, and a higher level of mPAP. Moreover, the Pa_{CO_2} was significantly lower than in the other groups, suggesting a more pronounced pulmonary vascular component. Consistent with these data, only 27 of a series of 998 patients with COPD had severe PH as defined by an mPAP of more than 40 mm Hg.

Interestingly, 16 of these 27 patients had another cause of PH. Indeed, patients with COPD may have severe comorbid conditions that may favor precapillary or postcapillary PH, including systolic and diastolic left-sided heart diseases, CTEPH, portal hypertension, sleep-related disordered breathing, and exposure to drugs that may induce PAH. The remaining 11 patients (1.1%) had COPD as the only cause of PH, with a median mPAP of 48 mm Hg. These patients with severe PH had an unusual pattern of cardiopulmonary abnormalities consisting of mild to moderate airway obstruction, severe hypoxemia, hypocapnia, and a decreased diffusion capacity for carbon monoxide (D_{LCO}). In these patients, exertional dyspnea was more severe and survival times were shorter than in control COPD patients.

In some situations, such as during exercise, during sleep, and with exacerbations, the PH may be more troublesome. First, the mPAP may increase with exercise in patients with advanced COPD. Indeed, the PVR does not decrease with exercise in patients with severe COPD (as opposed to healthy individuals). Thus an increase in CO with exercise will induce increases in the mPAP and may contribute to the limitation of exercise. Second, some data show episodes of alveolar hypoventilation and subsequent hypoxia in patients with COPD; such events may contribute to the pathophysiology of PH. Third, exacerbations of COPD may be the cause of marked increases in mPAP during episodes of acute respiratory failure. These acute changes in mPAP are reversible and correlate with the Pa_{O_2}. However, the exact link between exacerbations and PH in COPD is currently unknown, although patients with COPD and PH have more severe COPD exacerbations than do those without PH. Altogether, PH is a strong prognostic factor in patients with COPD who are being treated with long-term oxygen therapy, even in the modern management era.

Pathology and Pathophysiology of Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease.

Chronic inflammation and alveolar hypoxia, loss of pulmonary capillaries because of emphysema, and possibly mechanical injury as a result of hyperinflation are likely to contribute to PH secondary to COPD. Pathologic studies support the concept that pulmonary arterial remodeling, reduction of the number of pulmonary vessels because of emphysema-related loss of such vessels, and pulmonary thrombosis contribute to chronic PH in patients with COPD. Postmortem studies have shown muscularization of the small resistance pulmonary arteries, which can extend to the periphery in normally nonmuscularized vessels. Thickened media and intimal changes are common in COPD, but no complex plexiform lesions described in PAH have been found in these studies. In addition, inflammatory processes have been detected in the pulmonary arteries and distal airways of these patients, as well as in smokers without PH. Pulmonary vascular inflammation is currently considered a key player in other pulmonary vascular diseases such as PAH and CTEPH and could also play a role in PH complicating the course of COPD.

Diagnosis of Pulmonary Hypertension in Patients With Chronic Obstructive Pulmonary Disease.

Diagnosis of PH in patients with COPD is difficult because it is challenging to differentiate signs of PH from the comorbid lung disease and possibly other cardiovascular complications such as systolic or diastolic left-sided heart disease. Symptoms such as shortness of breath and fatigue are nonspecific. In the era of long-term oxygen therapy, signs of right-sided heart failure are rare in COPD except during severe acute exacerbations or in the most severe cases. Peripheral edema may also have other causes than right-sided heart failure. Simple tests such as chest radiography, electrocardiography, spirometry,

plethysmography, D_{LCO}, and arterial blood gases are important to perform but do not allow an accurate prediction of PH. However, they are useful in raising suspicion for PH. Indeed, when severe dyspnea on exertion and/or severe hypoxemia is not explained by the severity of COPD, it is of major importance to investigate whether the symptoms could be due to a comorbid condition such as PH. Along the same line, an unexpectedly low 6MW distance and severe desaturation should raise suspicion for PH. In patients with COPD and severe PH, the incremental maximal cardiopulmonary exercise test displays a pattern, also observed in chronic heart failure, characterized by very low maximal work, larger ventilatory reserve at peak exercise, and lower end-tidal Pa_{CO_2} than in patients with COPD and no or mild to moderate PH. Biomarkers such as BNP, when elevated, do not distinguish left-sided from right-sided heart failure and can be normal in patients with mild to moderate PH. Doppler echocardiography is an interesting noninvasive tool for screening for PH and evaluating left-sided heart function. However, its sensitivity and specificity are suboptimal in patients with COPD. Thus normal findings on Doppler echocardiography may not be sufficient to exclude PH if it is clinically suspected. Importantly, PH cannot be diagnosed on the basis of Doppler echocardiography. Indeed, the “gold standard” diagnostic procedure for diagnosis of PH is RHC. As discussed previously, RHC will not only allow the diagnosis of precapillary PH but will also evaluate its hemodynamic severity and exclude a postcapillary component. At this stage it is essential to emphasize the importance of screening for comorbid conditions such as left-sided heart disease, sleep-related disordered breathing, pulmonary embolism, and interstitial lung disease, which may contribute to the clinical findings.

Treatment of Pulmonary Hypertension in Patients With Chronic Obstructive Pulmonary Disease

Optimizing COPD care, including of course smoking cessation, is the first step in management. Besides this, long-term oxygen therapy is the cornerstone for prevention and management of PH in COPD, and it should be prescribed for patients with COPD and a Pa_{O_2} lower than 60 mm Hg. Long-term oxygen therapy resulted in a slight decrease in mPAP in patients treated for more than 18 hr/day in the NOTT study, but nocturnal oxygen therapy (10 to 12 hr/day) did not improve the mPAP. Thus long-term oxygen therapy may stabilize, attenuate, and sometimes reverse PH in patients with COPD.

Attempts to treat patients with COPD and comorbid PH with vasodilators such as calcium channel–blocking agents have proved disappointing inasmuch as inhibition of hypoxic vasoconstriction leads to deleterious effects on gas exchange. The efficacy of sildenafil in improving exercise tolerance in a group of patients with COPD and moderately increased PAP has been tested.[67] This was a double-blind, randomized controlled trial of 60 patients receiving 20 mg sildenafil (29 patients) or placebo (31 patients) three times daily and undergoing pulmonary rehabilitation for 3 months. The primary endpoint was the gain in cycle endurance time at a constant work-rate. Secondary endpoints included performance in the incremental exercise test, 6MW distance, and quality of life. None of the endpoints was reached; therefore the authors concluded that in patients with severe COPD and moderately increased PAP, concomitant treatment with sildenafil does not improve the results of pulmonary rehabilitation in exercise tolerance. Similar disappointing results were obtained in a study of 120 patients with COPD and mild PH randomized to tadalafil (10 mg daily) or placebo for 12 weeks, the primary endpoints being exercise tolerance and stress test within a respiratory rehabilitation program.[68] Based on consistent observations that pulmonary vasodilators offer no clinical benefit to patients with COPD and PH, guidelines do not recommend such therapies and emphasize the need for more randomized controlled studies in this area.

If patients with COPD and PH are eligible, lung transplantation should be considered. In a

retrospective analysis of 409 patients with end-stage COPD (mean FEV_1 of 23 ± 7%) who underwent evaluation for lung transplantation, Andersen and colleagues[69] showed that precapillary PH was present in 36% of the patients (13% had postcapillary PH). As reported by many other groups, precapillary PH was mild to moderate in most patients, and only 1.5% had an mPAP higher than 40 mm Hg. Interestingly PH was associated with worse survival rates in patients with COPD, but it did not influence survival rates after lung transplantation, thus highlighting the fact that PH should be considered an important parameter in patients with COPD who are candidates for lung transplantation.

Pulmonary Hypertension in Other Chronic Respiratory Diseases

PH is a frequent and severe complication of interstitial lung diseases such as IPF and the syndrome of combined pulmonary fibrosis and emphysema.[70] Of note, PH occurring in other respiratory conditions such as sarcoidosis,[71] pulmonary Langerhans cell histiocytosis,[72] and lymphangioleiomyomatosis[73] are classified in the group of PH with multiple or unknown causes. When present, PH has a dramatic impact on the morbidity and survival rates of patients with IPF. Despite recent therapeutic progress (including pirfenidone and nintedanib, which reduce the rate of decline in lung function in patients with mild to moderate disease), management of IPF remains largely supportive because of a relentless progression to respiratory failure and death after a median of only 3 years from the time of diagnosis. Precapillary PH is common in patients with advanced IPF, with a prevalence of 32% to 46% at RHC during evaluation for lung transplantation. The hemodynamic severity of PH in this context is usually mild (mPAP < 35 mm Hg), although 2% to 10% of patients have mPAP values higher than 35 mm Hg. In these patients PH is associated with marked dyspnea, decreased exercise capacity (as measured by 6MW distance and peak oxygen uptake during cardiopulmonary exercise testing), lower D_{LCO}, greater oxygen requirements, and reduced survival rates. In patients with moderate functional impairment, the prevalence of PH is lower. In a recent series of patients who underwent systematic RHC at the initial evaluation of IPF, PH was present in 14.9%, and an mPAP higher than 35 mm Hg was found in 5%, thus demonstrating that PH may develop earlier in some patients. As in COPD, the frequency of PH increases in the presence of comorbid conditions, including obstructive sleep apnea, venous thromboembolic disease, and left ventricular dysfunction, or in the setting of the syndrome of combined pulmonary fibrosis and emphysema. The primary treatment approach is to correct the hypoxemia with supplemental oxygen whenever appropriate and to consider lung transplantation when not contraindicated by age or comorbid conditions.

As in COPD, the pathogenesis of PH in patients with IPF is not limited to hypoxic pulmonary vasoconstriction. Indeed, pulmonary hemodynamics do not correlate with impairment in pulmonary function in this setting, and oxygen supplementation rarely reverses PH in patients with interstitial lung diseases and especially IPF. Together with hypoxia, parenchymal lung destruction, intrinsic pulmonary vascular abnormalities, alteration in cytokines and other mediators, microvascular injuries, and possibly autoimmunity may collectively contribute to the pulmonary vascular remodeling in IPF.

Overall, it has become clear that conventional management of underlying IPF, including supplemental oxygen, does not address the issue of associated PH. PAH therapies have been tested to improve clinical outcomes and hemodynamics in PH secondary to IPF. Currently available studies have been rather disappointing because of the low number of patients studied, the poor clinical and hemodynamic characterization of the patients, and the concern that vasodilators may contribute to worsening gas exchange via inhibition of hypoxic pulmonary vasoconstriction. The NIH IPF network study of sildenafil has evaluated patients with IPF and D_{LCO} lower than 35% of predicted (and therefore included some patients with associated PH, although there was no confirmation by RHC). This study was negative for the

primary endpoint of a 20% change in 6MW distance. In an exploratory post hoc analysis, the small group of patients with echocardiographic evidence of right ventricular dysfunction had a stronger trend toward a treatment benefit consisting of greater improvement in exercise capacity and quality of life. However, post hoc analysis of a negative trial cannot be considered convincing evidence. In addition, hypoxemia observed has confirmed that vasodilator therapy can have deleterious effects on gas exchange in IPF. Studies of oral endothelin receptor antagonists in IPF with PH have been negative.[74-76] Raghu and colleagues have reported negative results of a trial on the treatment of IPF with ambrisentan and issued a detailed analysis of patients with PH randomized in this trial. Of the initial 488 patients randomized in the global trial, PH was found in 68 individuals (defined as having an mPAP > 22 mm Hg and a PAWP ≤ 15 mm Hg), but the follow-up hemodynamic data were available in only 19 of them (12 in the ambrisentan-treated arm and 7 in the placebo-treated arm) and did not reveal any major differences. A lack of efficacy in the entire study group and the higher incidence of IPF progression events in the ambrisentan-treated arm argue against the use of ambrisentan in patients with IPF.

A small nonrandomized pilot study that evaluated 12 weeks of treatment with riociguat in 15 patients with different forms of interstitial disorders showed that the drug might improve the cardiac index, PVR, and 6MW distance, but no changes were recorded in the mPAP.[77] Of note, the arterial oxygen saturation decreased in treated patients. To what extent these data actually translate into clinical improvement was unclear, and the authors concluded that further studies were necessary to evaluate the safety and efficacy of riociguat in these patients. Therefore, riociguat was tested in a randomized controlled trial versus placebo in patients with PH due to idiopathic interstitial pneumonia. This trial was prematurely terminated because of an increased risk of death and other serious adverse events in the active treatment arm.[78]

Group 4 Chronic Thromboembolic Pulmonary Hypertension

CTEPH is a common subset of PH that is curable by surgery.[79] The definition of CTEPH is based on findings described after at least 3 months of effective anticoagulation (to discriminate chronic from acute disease). Such findings include precapillary PH and at least one segmental perfusion defect detected by lung scanning, multidetector CT angiography, and/or pulmonary angiography. CTEPH is caused by chronic obstruction of major pulmonary arteries following pulmonary embolism. CTEPH occurs in 3 to 30 individuals per million general population per year and has been shown to be a long-term complication of pulmonary embolism with a cumulative incidence of 0.1% to 9.1% within 2 years after a symptomatic event. These large margins of error result from referral bias, the paucity of early symptoms, and the difficulty in properly distinguishing an acute pulmonary embolism revealing preexisting CTEPH from a truly causal initial venous thromboembolic event. In the international CTEPH registry, a clinical history of acute venous thromboembolism was observed in three quarters of patients with CTEPH and was an independent risk factor for CTEPH when compared with IPAH. However, a number of cases may still originate from asymptomatic venous thromboembolism. CTEPH appears to be caused primarily by venous pulmonary thromboembolism, as opposed to primary pulmonary vascular in situ thrombosis. Prothrombotic factors such as inadequate anticoagulation, a large thrombus mass and residual thrombus, and recurrences may contribute to development of the disease. However, CTEPH does not show the classic risk profile of venous thromboembolism, and only some specific thrombophilic factors such as lupus anticoagulant/antiphospholipid antibodies and the coagulation factor VIII have been found to be associated with it. Thus a purely mechanistic view of CTEPH as a disease caused by obliteration of central pulmonary arteries by pulmonary emboli is too simplistic, and it has been proposed that the

pulmonary embolism may be followed by a pulmonary vascular remodeling process modified by infection, immune phenomena, inflammation, circulating and vascular-resident progenitor cells, thyroid hormone replacement, and malignancy. Hypercoagulation, “sticky” red blood cells, high platelet counts, and uncleavable fibrinogens contribute to major vessel obliteration in CTEPH. Nonplasmatic risk factors include splenectomy, ventriculoatrial shunt for hydrocephalus therapy, and inflammatory bowel disease. Associated with major pulmonary vascular obstruction, CTEPH consists of small pulmonary vessel disease (pulmonary arteriopathy),[4] which may originate from a high-flow or high-pressure state in previously unaffected vessels or be driven by hypoxia, infection, and inflammation from associated conditions.

CTEPH occurs equally in both sexes, and all age-groups can be affected, yet the median age of patients is 63 years. Physical signs in early CTEPH are generally absent. Only in later disease stages are nonspecific signs of right-sided heart dysfunction detected. Clinical symptoms of CTEPH resemble those of IPAH, with edema and hemoptysis occurring more often in CTEPH and syncope being more common in IPAH. Clinical suspicion is based on risk factors and symptoms. Although CT is the tool for diagnosis of acute pulmonary embolism, the ventilation-perfusion lung scan is the main imaging modality for CTEPH detection. Criteria for diagnosing CTEPH on a ventilation-perfusion scan are at least one defect encompassing at least half a segment. Potential pitfalls are small matched defects or nonsegmental perfusion abnormalities as occur in PAH and PVOD. In patients with large central thrombi and PAH associated with CHD or in those with pulmonary arterial aneurysms, the perfusion defects typically remain nonsegmental. RHC will demonstrate precapillary PH. PVR is a predictor of prognosis for surgical candidates. Concomitant small pulmonary vascular disease is a predictor of an adverse surgical outcome in CTEPH. Contrast-enhanced CT angiography, including three-dimensional rendering techniques, depicts pulmonary artery webs and bands, wall irregularities, stenoses, and complete vascular obstructions, as well as bronchial collaterals. High-resolution CT of the chest screens for comorbid parenchymal disease (such as emphysema, bronchitis, or interstitial lung disease), as well as pulmonary infarcts. Perfusion inequalities manifested as a mosaic parenchymal pattern can be detected. The final step in the diagnostic pathway is the classic side-selective pulmonary angiography in the anteroposterior and lateral projections for the purpose of confirming the diagnosis, assessing the most proximal involvement, and evaluating for surgical complexity and accessibility.

Surgery is the treatment of choice for CTEPH. In contrast to embolectomy, pulmonary endarterectomy creates a surgical plane through the medial layer of the pulmonary artery with the patient under deep hypothermia and circulatory arrest. According to the surgical specimen, four anatomic types of CTEPH are distinguished: type 1 disease (≈ 25% of cases) involving the main and lobar pulmonary arteries with fresh red thrombus superimposed on white obstructions; type 2 disease (≈ 40% of cases) consisting of intimal thickening and fibrosis proximal to segmental arteries; type 3 disease (≈ 30% of cases) with fibrosis, intimal webbing, and thickening confined to distal segmental and subsegmental arteries; and type 4 disease (< 5% of cases) defined by microscopic distal arteriolar vasculopathy without visible thrombus. Type 4 is not operable. General operability criteria include NYHA functional class II, III, or IV; surgical accessibility of thrombi in the main, lobar, or segmental pulmonary arteries, with a reasonable relationship to hemodynamic severity; absence of severe comorbid diseases; and patient consent. Advanced age per se is not a contraindication to surgery. A difficult issue in the preoperative assessment of patients with CTEPH is definition of the extent of small-vessel disease. Patients with CTEPH and defects in the main, lobar, or proximal segmental level have proximal disease and are best suited for surgery. In contrast, patients with significant PH but little or no obstruction are considered poor candidates for surgery. This latter group is believed to display significant pulmonary arteriopathy. The

contemporary in-hospital mortality rate due to perioperative complications is as low as 4.7% or less. After surgery, most patients exhibit hemodynamics that are almost normal and experience substantial relief from their symptoms. The International CTEPH registry has reported survival data in a cohort of 679 patients newly diagnosed with CTEPH who were prospectively included over a 24-month period. The estimated survival rates at 1, 2, and 3 years were 93%, 91%, and 89%, respectively, in the 404 operated patients, and only 88%, 79%, and 70%, respectively, in the 205 patients who did not undergo operation.[80] Thus patients who do not undergo surgery or who suffer from persistent or residual PH after surgery face a poor prognosis.

Optimal medical treatment for CTEPH consists of anticoagulants and diuretics, and oxygen in cases of heart failure or hypoxemia. Lifelong anticoagulation is recommended, even after pulmonary endarterectomy; no data exist on the efficacy and safety of new oral anticoagulants. Although there is no consensus, routine cava filter placement is not justified by the available evidence. Pulmonary microvascular disease in CTEPH has provided the rationale for the off-label use of drugs approved for PAH. Some nonrandomized studies have provided evidence for an improvement in exercise capacity and hemodynamics. Medical treatment of CTEPH with targeted therapy may be justified in technically nonoperable patients or in the presence of an unacceptable surgical risk-benefit ratio (**Fig. 85.5**).

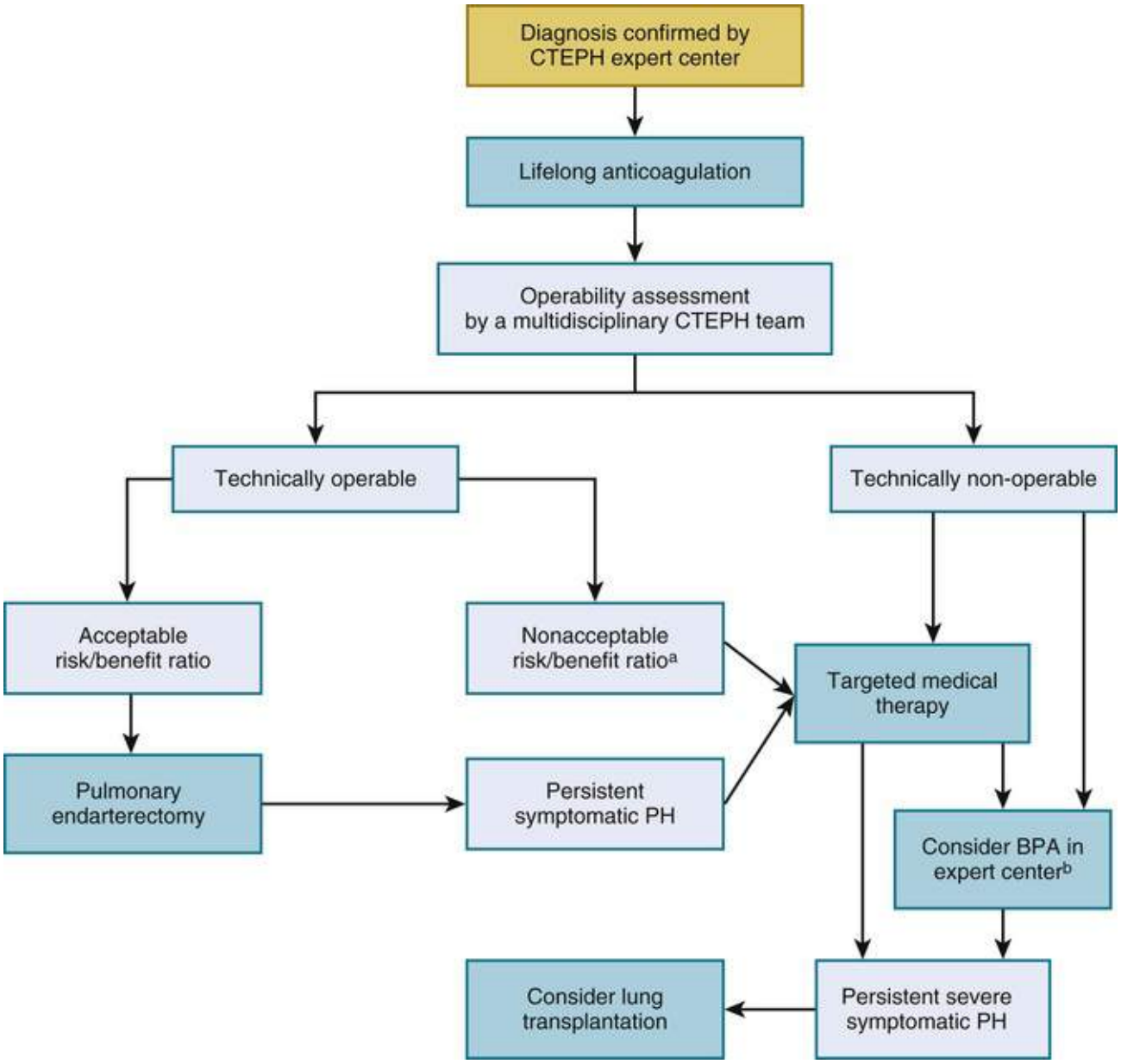


FIGURE 85.5 Treatment algorithm for chronic thromboembolic pulmonary hypertension. (Modified from Galie N, Humbert M, Vachiery J-L, et al: 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2016;37:67.)

Patients with persistent or recurrent PH after pulmonary endarterectomy may also be candidates for targeted medical therapy. Additional content on this topic is presented in an online supplement entitled Targeted Medical Therapy After Pulmonary Endarterectomy.

Other pulmonary artery obstructions may be due to angiosarcoma (and other intravascular tumors), pulmonary arteritis (such as Takayasu arteritis), congenital pulmonary artery stenoses, or parasitic infection (hydatidosis). The most common differential diagnosis of CTEPH in expert centers remains progressive tumoral occlusion of proximal pulmonary arteries (with additional thrombosis). Such cases are due principally to pulmonary artery sarcomas. Differentiation from CTEPH can be difficult, and findings on CT or magnetic resonance angiography, as well as ^{18}F-fluorodeoxyglucose positron emission tomography, may be useful in distinguishing an obstruction by tumor from thrombotic material.

Pulmonary Hypertension With Unclear or Multifactorial Causes

Hematologic Disorders.

PH can complicate the course of chronic myeloproliferative disorders, including polycythemia vera, essential thrombocythemia, and chronic myelogenous leukemia. Several mechanisms may contribute to the development of PH, including congestive heart failure secondary to a high CO and fluid overload, CTEPH, direct obstruction of pulmonary arteries because of intrapulmonary hematopoiesis, portopulmonary PH, drug-induced PAH (as from dasatinib or interferon), and splenectomy.

Splenectomy as a result of trauma or as a consequence of hematologic disorders may increase the risk for development of IPAH or CTEPH, which is more likely to be distal.

Chronic hemolytic anemia, including sickle cell disease (SCD) and beta-thalassemia, may cause PH through multiple mechanisms ranging from postcapillary PH because of high-output heart failure to precapillary PH caused by pulmonary vascular remodeling and thrombosis, proximal and distal CTEPH, and portopulmonary hypertension. Of the chronic hemolytic anemias, PH has been described most frequently in association with SCD. In a prospective study of 398 patients with SCD, a tricuspid regurgitant velocity higher than 2.5 meters/sec was measured in 27%, who then underwent RHC. The prevalence of PH was 6%, with approximately half meeting the criteria for group 1 PAH and the other half being categorized as having postcapillary PH.[81] The positive predictive value of echocardiography for the detection of PH was 25%. The role of PAH-specific therapy for PAH associated with SCD is unclear because no PAH-specific therapy has been adequately studied in patients with SCD. A double-blind placebo-controlled trial of sildenafil in patients with SCD and a tricuspid regurgitant velocity of 2.7 meters/sec or higher was stopped early because of a higher percentage of patients experiencing adverse events, particularly hospitalization for a pain crisis, in the sildenafil arm.[82]

Systemic Disorders.

Sarcoidosis is a common systemic granulomatous disease of unknown origin. PH is an increasingly recognized complication of sarcoidosis, with a reported prevalence of 1% to 28%. PH is most often due to destruction of the capillary bed by the pulmonary fibrotic process in type IV disease and/or to the resultant chronic hypoxia. However, the severity of PH may be more severe than expected when considering the degree of parenchymal lung disease, which can be modest or even absent, and to the blood gas abnormalities, thus suggesting that other mechanisms could contribute to the development of PH. Among these mechanisms, one can consider extrinsic compression of large pulmonary vessels by lymph node enlargement or mediastinal fibrosis; granulomatous infiltration of the pulmonary vasculature, especially that affecting the pulmonary veins; cardiac sarcoidosis, which may cause heart failure and postcapillary PH; and hepatic sarcoidosis, which may cause portopulmonary PH. Management, including corticosteroid therapy, lung or heart-lung transplantation, and off-label use of PAH drugs, will depend on the dominant pathomechanism at play.

Pulmonary Langerhans cell histiocytosis (also known as *pulmonary histiocytosis X*) is a rare lung disease that predominantly affects young adults and develops almost exclusively in those with a history of current or previous cigarette smoking. Precapillary PH is frequently detected in patients with advanced lung destruction, although no clear relationship exists between PH and the extent of parenchymal lung disease and/or hypoxia, thus suggesting that alternative or additional pathomechanisms might contribute to an intrinsic pulmonary vasculopathy that involves both the precapillary arterioles and postcapillary venous compartment (with frequent PVOD-like lesions). Patients with pulmonary Langerhans cell histiocytosis in whom PH develops have a particularly poor prognosis, and early referral for lung transplantation assessment is recommended. Encouraging recent data suggest that agents licensed for use in patients with PAH confer improvements in pulmonary hemodynamics and are generally well tolerated. Further investigation of the use of PAH medical therapy in this population is warranted. Additional content on the causes of type 5 PAH, including lymphangioleiomyomatosis,

metabolic causes, and tumor metastasis, is presented in an online supplement entitled Systemic Disorders Causing Type 5 Pulmonary Arterial Hypertension.

Fibrosing mediastinitis may be associated with severe PH secondary to compression of the large pulmonary arteries and veins. Ventilation-perfusion lung scan, CT of the chest, and pulmonary angiography are useful for accurate diagnosis. However, the findings can mimic those of proximal thrombotic obstruction. The major causes are histoplasmosis, tuberculosis, and sarcoidosis.

PH has been reported in patients with *end-stage renal disease maintained on long-term hemodialysis*. There are several potential explanations for the development of PH in these patients: the mPAP may be increased by a high CO (resulting from the arteriovenous access and anemia), as well as by fluid overload. In addition, diastolic and systolic left-sided heart dysfunction is also common and leads to postcapillary PH. Furthermore, the hormonal and metabolic derangement associated with end-stage renal disease might promote dysfunction of the pulmonary vascular tone.

Pulmonary Hypertension Registries

Guidelines recommend that the management of PAH and CTEPH be performed in specialized centers with multidisciplinary teams working in a shared care approach. Such centers should be part of larger national or international networks, which should be able to capture valuable information in registries and patient cohorts to better understand the epidemiologic trends of these severe and uncommon conditions. The first registry to evaluate the characteristics and survival statistics of patients with PH and later develop a prognostic model was the NIH primary PH registry in the 1980s. A prognostic equation was developed from data collected before the availability of PAH-targeted therapies. This equation describes the natural history of IPAH but cannot be used to predict survival rates for treated patients in the modern management era. In the modern management era, several registries of PAH and CTEPH have been developed that compensate for the NIH equation's shortcomings. Among others, these include the French National Registry,[55] the United Kingdom and Ireland registry,[83] the U.S. registry to evaluate early and long-term PAH disease management (REVEAL),[56,58] the COMPERA Registry,[84] and the international CTEPH registry.[79] Although similar in many respects, PAH registries vary in patient populations, including the number of patients with newly and previously diagnosed PAH, as well as the era of observation, period of survival, and timing of assessment of potential predictive factors. Nonetheless, the predictive factors identified in each registry share an important homology in that the cause of the disease, patient sex, and markers of right-sided heart dysfunction are integral in depicting survival possibilities. Interestingly, the PAH risk score and equations have been generated from these registries and have been validated in independent contemporary cohorts. In the most recent period of PAH registries, changes in patients' phenotypes have been demonstrated, with a higher proportion of patients being older than 60 years and having an increased frequency of cardiovascular risk factors such as obesity and diabetes.

In recent registries, approximately half the patients with PAH display idiopathic, heritable, and drug-induced disease, whereas the remaining patients have PAH associated with connective tissue diseases, CHD, portal hypertension, and HIV infection. In the Western world, scleroderma is the most common associated condition, but CHD still predominates in developing countries. In endemic regions of Brazil, PAH caused by hepatosplenic schistosomiasis is an ongoing problem. At diagnosis, approximately three quarters of patients with PAH are in NYHA functional class III or IV, thus emphasizing that the diagnosis still occurs late in the course of the disease in patients with marked exercise limitation and hemodynamic compromise. The delay between the symptom onset (mainly dyspnea on exercise) and the diagnosis of

PAH is still 2 years or more in most modern management registries, similar to that observed in the NIH registry, which emphasizes the need for better awareness of PAH and diagnostic strategy. The low estimates of the prevalence and incidence of PAH in Western countries are 15 and 2 cases per million adult inhabitants per year, respectively (6 cases and 1 case per million of adult inhabitants per year, respectively, for IPAH). Survival rates of patients with PAH remain poor—and even more so in patients with scleroderma or familial PAH. In IPAH, 1-, 2-, and 3-year survival rate estimates are in the range of 85% to 90%, 75% to 85%, and 55% to 75%, respectively, thus indicating that PAH remains a dramatic condition in the modern management era. Multivariate analysis indicates that being female, having a better 6MW distance/NYHA functional class, and exhibiting better right ventricular hemodynamic function are jointly associated with better survival prognoses.[55] Refining prognostic factors is currently the main focus of the REVEAL study group, which has produced and validated a PAH risk score calculator that may be useful in predicting outcomes of patients with PAH.

Future Perspectives

Even though our understanding of the pathogenesis and treatment of PAH has advanced substantially over recent decades, we still have a long way to go. A basic understanding of the pathobiology of PAH often relies on animal models, which do not accurately reflect human disease.[85] In the hope of advancing translational science, the Pulmonary Hypertension Breakthrough Initiative is a project that harvests explanted lungs from patients with PAH at the time of lung transplantation. Similarly, national and international consortia have been launched in recent years allowing major international partnerships in the field of pulmonary vascular medicine.[12] Making human tissue available for study has the potential to accelerate advances in the basic and translational sciences.[85] Patients with PAH currently have a better quality of life and survival than they did a decade or two ago, but their survival is still suboptimal, and more advances in medical therapies are needed.[86] Fortunately, numerous therapies, including some with novel mechanisms of action, are currently being investigated.[87] Data from important current-day registries continue to shed light on important prognostic variables and may help guide us in appropriate treatment strategies.[86] The importance of the right ventricle cannot be overstated. Imaging modalities for the right ventricle are being refined, and it is likely that CMR will play a crucial role. Patients do not die of high pulmonary artery pressure. They die of right ventricular failure. A better grasp on treating the failing right ventricle is a priority for the future.

Although we have made considerable inroads in the treatment of group 1 PAH, clinical trial data for the more common disorders of group 2 and 3 PH are lacking. Off-label use of PAH-specific therapy in these populations is common, but there is little in the way of efficacy and safety data. Trials of populations disproportionately enriched in patients with PH in the setting of left-sided heart disease or parenchymal lung disease may be a good starting point.

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Collaborative Care of the Pulmonary Arterial Hypertension Patient

Because of the delay from the onset of symptoms to the diagnosis of pulmonary arterial hypertension (PAH), greater awareness in the community is required to achieve an earlier diagnosis. Some community settings may be equipped to perform a thorough diagnostic evaluation, including right heart catheterization with vasodilator testing, but others may not. An open dialogue with a pulmonary hypertension (PH) center will help facilitate a correct and timely diagnosis in instances where local expertise is not available.

Given the complexities of the diagnosis, and the cost and side effect profile of the therapies, referral to a PH center for confirmation of the diagnosis and comanagement of the patient should be considered. A series describing new referrals to three PH specialty centers demonstrated that patients are referred late and have functional class 3 and 4 symptoms more than half of the time; the diagnosis is often incorrect (nearly half of patients receive a different diagnosis after evaluation at the referral center); and PAH-specific therapy is commonly started inappropriately.[1] In fact, 30% of patients received PAH-specific therapies before referral, and 57% of the time the use of PAH-specific therapy was not in accordance with PH guidelines.

The PH center often can provide specialized care that is not available in the community. PH nurse clinicians are critical in the management of PAH patients. They provide vital education regarding the disease and its therapies, and maintain an active role in case management to titrate medications, monitor side effects, and recognize complications. Access to clinical research trials and advanced treatment options, such as parenteral prostacyclins and lung or heart-lung transplantation, is an important aspect of the level of care available at PH centers.

Collaboration is key, and it is incumbent upon the PH center to maintain an open dialogue with the local health care providers. The primary care physician, local cardiologist, or pulmonologist must be kept up to date on the patient's status and their therapies because he or she may be the first physician to encounter a complication of PAH therapy (e.g., a line infection), recognize disease progression (e.g., fluid retention and right heart failure), or diagnose a new problem (e.g., pneumonia). Because many patients live far from a PH center, comanagement of such issues is in the best interests of the patient.

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Targeted Medical Therapy After Pulmonary Endarterectomy

The use of targeted therapy in operable patients with severe hemodynamic compromise as a bridge to pulmonary endarterectomy has not yet been supported by scientific evidence. The dual endothelin antagonist bosentan was evaluated in 157 patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or persistent/recurrent PH after pulmonary endarterectomy, over 16 weeks. This study demonstrated a positive treatment effect of bosentan on hemodynamics, but no improvement was observed in exercise capacity in CTEPH.[1] Thus it was decided to propose further clinical trials to better define the role of medical therapy in patients with CTEPH. In the CHEST-1 study, riociguat was administered to 261 of 446 screened patients with inoperable CTEPH, or persistent/recurrent PH after pulmonary endarterectomy, for 16 weeks, and its use led to a mean increase of 39 meters in the 6MW distance ($P < 0.001$; primary endpoint) and to a least-squares mean difference of 246 dynes.cm.s^{-5} in the pulmonary vascular resistance (PVR; $P < 0.001$, secondary endpoint); the time to clinical worsening remained unchanged.[2] Eligible patients (n = 237) from the CHEST-1 study entered the CHEST-2 open-label extension study, in which all patients received riociguat individually adjusted to a maximum dosage of 2·5 mg three times per day. At 2 years, the overall survival rate was 93%.[3] Preoperative medical treatment is uncertain because the magnitude of effects was small in one RCT.[4] Prospective randomized controlled trials are needed in patients with potential treatment benefit, for example, patients with a high PVR and technically challenging anatomy.

In 2001 Feinstein and Landzberg published a report of 18 patients with nonoperable CTEPH who they subjected to balloon dilation of the pulmonary arteries. Despite a significant decrease of mPAP, 11 patients developed reperfusion pulmonary edema and 3 required mechanical ventilation. Recently, Japanese investigators have refined balloon pulmonary angioplasty (BPA) by using smaller balloons, by cautiously limiting the number of balloon inflations per session to one or two pulmonary vascular segments, and by the use of intravascular imaging.[5] An average number of 4.8 sessions is needed per patient to improve parameters of right ventricular function. Several complications, such as hemoptysis, hemorrhage, and reperfusion edema, have been reported after BPA. A high mPAP, a first BPA session, and severe hemodynamics are the main risk factors for pulmonary edema. Prevention and management of complications are important, including a careful stepwise approach to reduce the risk of reperfusion edema. Limiting the blood flow by using undersized balloons for pulmonary artery dilation may reduce the reperfusion vascular insults at initial sessions. At subsequent sessions, when the hemodynamic conditions are less severe, a balloon of the proper size can be used for dilation of the vessels. Such a careful approach, with targeting of only one lobe during each session and cautious balloon sizing, has reduced the incidence of complications such as hemoptysis and reperfusion pulmonary edema to 2% in individual centers. Further studies should evaluate the benefits of medical treatment before BPA. Nasal continuous positive airway pressure or nasal high-flow oxygen therapy is used to treat mild to moderate hypoxemia in reperfusion edema. A critical complication in BPA is pulmonary artery perforation, which may lead to severe lung hemorrhage and death. Proper wire positioning and knuckle wire techniques may be helpful to reduce pulmonary perforation. Using a balloon of disproportionate size to the vessel could be a risk for pulmonary artery rupture. Stent implantation to prevent restenosis in BPA for CTEPH is not necessary, and no obvious restenosis or recurrence has been reported after BPA to date.[6]

BPA is not currently extensively used, but it is rapidly gaining attention worldwide. This investigational procedure should be performed only by experienced persons in centers that treat many

CTEPH patients. Independent evaluations are needed to define its short- and long-term efficacy and safety.

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Systemic Disorders Causing Type 5 Pulmonary Arterial Hypertension

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis is a rare multisystem disorder affecting women that is characterized by cystic lung destruction, lymphatic abnormalities, and abdominal tumors (angiomyolipoma). Pulmonary hypertension (PH) of mild hemodynamic severity may occur in these patients, even with mild impairment in pulmonary function. *Neurofibromatosis type 1* (also known as *von Recklinghausen disease*) is an autosomal dominant disease that can be recognized by characteristic café au lait skin lesions and cutaneous fibromas. Cases of PH have been reported that may be due to *chronic thromboembolic pulmonary hypertension* (CTEPH), as well as to *comorbid lung disease*. In rare cases, histologic examination has found pulmonary vascular disease involving arteries and veins. Very rare cases of PH have been observed in patients with *antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis*, with the clinical features being similar to those of PAH.

Metabolic Disorders

PH may occur in *type Ia glycogen storage disease*, a rare autosomal recessive disorder caused by a deficiency of glucose-6-phosphatase. The mechanisms of PH are uncertain; portacaval shunts, atrial septal defects, severe restrictive pulmonary disease, and thromboembolic disease are thought to play a role. Plexiform lesions have been reported in a postmortem study of a single patient.

Gaucher disease, a rare disorder attributable to a deficiency of lysosomal B glucosidase, causes an accumulation of glucocerebroside in reticuloendothelial cells. PH has been reported in these patients; several potential mechanisms are thought to be involved (interstitial lung disease, chronic hypoxia, capillary plugging by Gaucher cells, and splenectomy).

The association of *thyroid diseases* and PH has been reported in a number of studies. The high prevalence of autoimmune hypothyroidism and hyperthyroidism suggest that these conditions may share a common (auto)immune susceptibility.

Metastatic Tumor Emboli

Occlusion of the microvasculature by metastatic tumor emboli represents another cause of rapidly progressive PH. Severe hypoxemia is often observed in such cases. High-resolution CT of the chest frequently shows thickening of septa. In contrast, a ventilation-perfusion lung scan may show multiple subsegmental perfusion defects. Pulmonary microvascular cytologic sampling through a pulmonary artery catheter in the wedge position is an important diagnostic tool. Most reported cases occur in association with breast, lung, or gastric cancer.

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Chronic Lung Diseases and Cardiovascular Disease

Surya P. Bhatt, Mark T. Dransfield

Chronic lung diseases (CLDs) encompass the spectrum of obstructive and restrictive lung disorders. Both major categories are highly prevalent in the population and are associated with substantial rates of morbidity and mortality. Although each pulmonary disease has a specific etiopathogenic pathway, there is substantial overlap in these pathways, as well as increasing recognition that the inflammatory state associated with these disorders is not confined to the lungs but extends to the systemic circulation, with effects on extrapulmonary organs, especially the cardiovascular system. The natural history of these CLDs is punctuated by acute exacerbations during which the inflammatory state is heightened. Although the mortality rate of cardiovascular disease is declining, that is not the case for CLD; CLD is now the third leading cause of death in the United States and the only chronic disease category for which the mortality rate continues to rise.[1,2] The most important risk factors for CLD are cigarette smoking, age, and environmental exposure to pollutants (**see also Chapter 52**). Although these risk factors are also the most common ones for cardiovascular disease, multiple recent studies have shown that cardiovascular disease

is more frequent in CLD independent of these shared risk factors.[3,4] There is also an overlap in disease presentation, symptoms, clinical examination findings, and diagnostic test results as well as a number of important medication interactions, adding significant complexity to the care of these patients. In addition, cardiovascular disease frequently contributes to exacerbations and hospitalizations in patients with CLD. Approximately half the patients with CLD remain undiagnosed, and it is probable that greater awareness of the overlapping manifestations of CLD and cardiovascular disease can help identify both disorders earlier and perhaps reduce the associated morbidity. Most of the current published evidence regarding the prevalence, impact, diagnosis, and treatment of cardiovascular disease in patients with CLD is for chronic obstructive pulmonary disease (COPD), though recent reports suggest that cardiac disease is an important comorbidity in patients with other CLDs as well.

Chronic Obstructive Pulmonary Disease

Epidemiology of COPD and Associated Cardiovascular Disease

COPD is a chronic inflammatory disease of the lungs characterized by partially reversible airflow obstruction. Approximately 8% of people in the United States have COPD.[2] The age-adjusted prevalence of coronary artery disease (CAD) in the United States is 6%, and about 1.7% of the population has congestive heart failure (CHF). Given the aging population and greater longevity, it is expected that many of these chronic diseases coexist; however, a number of cardiovascular diseases occur at a greater frequency in patients with COPD than in the general population.[1]

Coronary Artery Disease (see Chapters 59 to 61)

COPD and CAD share multiple risk factors, including older age and cigarette smoking; however, these do not fully account for the increased risk of CAD in COPD. There is a dose-response relationship between a low forced expiratory volume in the first second (FEV_1) and cardiovascular mortality rates. Results from the Lung Health Study showed that the adjusted cardiovascular mortality rate increases by 28% for every 10% reduction in FEV_1. Although FEV_1 is not part of the traditional Framingham Study risk factors for CAD, the Renfrew and Paisley prospective population study reported that approximately one fourth of the attributable risk for death due to CAD is due to a low FEV_1, placing reduced lung function very high on the list of cardiovascular risk factors. Epidemiologic studies have shown that CAD occurs 2 to 5 times more frequently in COPD patients than in controls, and this relationship holds even after adjusting for shared risk factors. As is the case in the general population, COPD is underrecognized in patients with CAD, with approximately half of the patients remaining undiagnosed. There are no population-level data for the prevalence of COPD in patients with CAD, but data from clinical studies suggest that this ranges from 7% to 34%.[1]

Congestive Heart Failure (see Chapter 24)

Poor lung function is also a risk factor for CHF; a low FEV_1 is associated with incident heart failure and an increased risk of hospitalization due to heart failure. Cross-sectional studies have shown that up to one fifth of COPD patients have undiagnosed heart failure. Heart failure with preserved left ventricular ejection fraction (HFpEF) occurs in approximately 5% of COPD patients, with a higher prevalence in

older patients, and subclinical diastolic dysfunction has been reported in up to 75% of COPD patients. The prevalence of COPD in patients with heart failure is also high, with estimates ranging from 11% to 55%.[5]

Cerebrovascular and Peripheral Arterial Disease (see also Chapters 64 and 65)

Multiple epidemiologic studies have demonstrated an inverse relationship between FEV_1 and ischemic stroke. Data from the Copenhagen City Heart Study show that the risk of ischemic stroke increases by 5% for every 10% decrease in FEV_1, after adjustment for cardiovascular risk factors. The relationship between COPD with demonstrated airflow obstruction and ischemic stroke is weaker, though current evidence suggests there is a higher risk than in the general population. Peripheral arterial disease and aortic aneurysms are also common in COPD, with small studies demonstrating that up to one third of patients with COPD have peripheral arterial disease.[1]

Cardiac Arrhythmias (see also Chapters 37 to 39)

Supraventricular and ventricular arrhythmias are common in COPD and are more frequent than in matched controls.[6] Multifocal atrial tachycardia is almost exclusively seen in patients with COPD. Twenty-four-hour monitoring of stable but hypoxemic COPD patients shows a high frequency of various electrocardiographic abnormalities, including supraventricular tachycardia (69%), ventricular premature beats (83%), ventricular bigeminy (68%), and nonsustained ventricular tachycardia (22%). Low FEV_1 is also associated with incident atrial fibrillation.[6]

Pathophysiology of Cardiovascular Disease in COPD

Although COPD and cardiovascular disease share multiple risk factors, these do not fully account for the increased occurrence of CAD in COPD. Multiple overlapping pathobiologic pathways are likely involved in the development of both COPD and CAD (**Table 86.1**). These same mechanisms are important in the pathogenesis of other cardiovascular morbidities seen in COPD, including cerebrovascular and peripheral arterial disease.

TABLE 86.1

Cardiovascular Risk Factors in Chronic Lung Disease

TRADITIONAL OR SHARED RISK FACTORS	OVERLAPPING PATHWAYS
Cigarette smoking	Systemic inflammation
Aging and senescence	Oxidative stress
Environmental pollutants	Prothrombotic state
Sex	Activated renin-angiotensin system
Diet	Genetics
	Sedentarism

Coronary Artery Disease

The major pathogenetic mechanism for CAD is atherosclerosis. Multiple studies have shown an inverse relationship between the age-adjusted FEV_1 and carotid intima-media thickness. Carotid plaques, especially vulnerable lipid-rich ones, are more frequently seen in COPD patients than in smokers without

airflow obstruction and nonsmokers.[7] Patients with COPD have greater arterial stiffness as measured by aortic pulse wave velocity, after adjustment for age and smoking. The degree of emphysema seen on computed tomography is independently associated with thoracic aortic as well as coronary artery calcification. Indeed, COPD can be considered a proatherosclerotic condition, much like some autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, with a magnitude of risk equivalent to or greater than other proinflammatory conditions such as diabetes mellitus and chronic kidney disease.[8] Although the mechanistic pathways for accelerated atherosclerosis in COPD remain unclear, a number of overlapping mechanisms have been implicated (**Fig. 86.1 and see Table 86.1**).

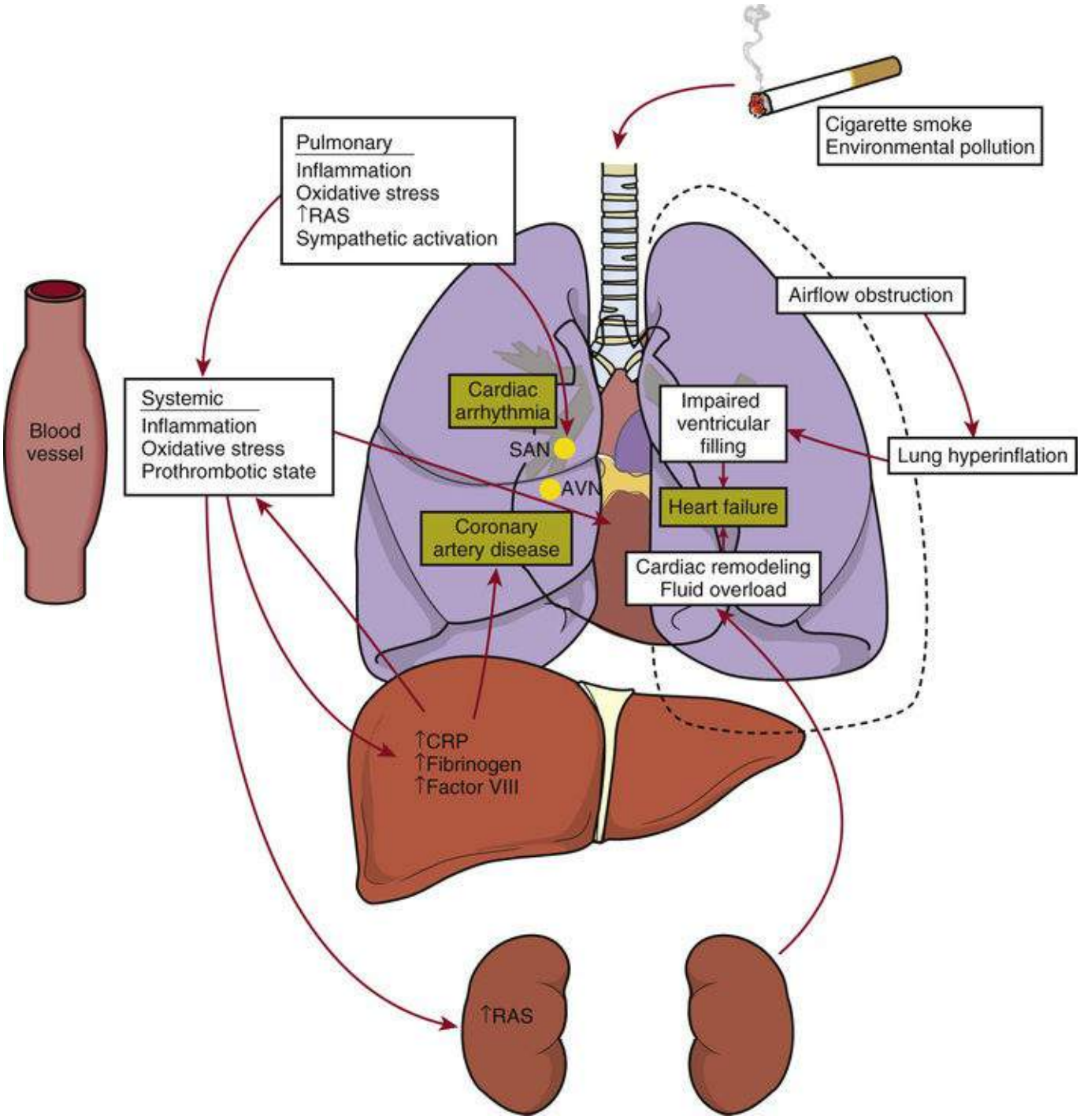

FIGURE 86.1 Possible overlapping pathways of cardiovascular disease in chronic lung disease. *Coronary artery disease*: Cigarette smoke and environmental agents induce inflammation as well as oxidative stress in the lungs, which translocates into the systemic circulation. Cytokines such as interleukins, tumor necrosis factor, and granulocyte macrophage colony–stimulating factor, as well as reactive oxygen species, can stimulate the liver to produce acute-phase reactants such as C-reactive protein and procoagulants such as fibrinogen and factor VIII. They can also induce the bone marrow to release inflammatory cells such as leukocytes and monocytes, as well as platelets. In addition, chronic hypoxia induces activation of the renin-angiotensin system and upregulation of the sympathetic nervous system, both of which can contribute to endothelial dysfunction. These multiple factors can result in increased expression of adhesion molecules on the vascular endothelium (intercellular adhesion molecule [ICAM] and vascular cell adhesion molecule [VCAM]), which in turn stimulate chemotaxis of monocytes and macrophages into the vascular intima, platelet aggregation and greater uptake of oxidized low-density lipoprotein (ox-LDL) and formation of lipid-rich plaques. *Heart failure*: Air trapping and lung hyperinflation can cause diastolic dysfunction and impaired ventricular filling. Coronary artery disease and activation of the renin-angiotensin system can result in cardiac remodeling and congestive heart failure. *Cardiac arrhythmias*: Sympathetic activation, either resulting from chronic hypoxemia or due to medication effects, can result in supraventricular and ventricular arrhythmias.

Shared Risk Factors

Aging and Senescence.

The prevalence of both COPD and CAD increases with age. COPD is about 6 times more frequent in persons older than 70 years as in those age 40 to 49 years; CAD is seen 17 times more frequently in those older than 65 years than in those age 18 to 44 years. Advancing age is associated with chronic inflammation, oxidative stress, progressive telomeric shortening, and impaired capacity of tissues to repair damage, factors associated with cellular senescence and implicated in vascular aging as well as emphysema. This process is accelerated by environmental agents, including cigarette smoking.[1]

Cigarette Smoking.

The strongest risk factor for COPD is cigarette smoking, which is also a major risk factor for CAD. Cigarette smokers have a 15% to 50% lifetime risk of developing COPD, and the population-attributable risk is 50% to 70%. It should be noted that approximately a third to half of the COPD cases worldwide occur in lifetime never smokers.[9] Second-hand smoke exposure also increases the risk of developing airflow obstruction 1.5 fold. In developing countries, biomass fuel exposure is associated with a 2.5 times greater risk of COPD than in matched controls. Both these types of non–active smoking–related exposures are also risk factors for CAD.

Environmental Pollutants.

Exposure to particulate matter (PM) and gaseous pollutants increases the risk of developing COPD,[10] and the population-attributable risk for COPD from occupational exposure to dusts is approximately 19%, and up to 30% in never smokers. These exposures are also associated with an increase in acute coronary events, as well as progressive atherosclerotic heart disease. Chronic residence in areas with high levels of PM is associated with a higher mortality rate resulting from COPD (hazard ratio, 1.22 per 10 $\mu g/m^3$ increase in PM10); a similar increase in mortality rates has also been observed for CAD.

Sex.

Although COPD is generally considered to be a disease of older men, recent data suggest there may be greater susceptibility to cigarette smoke in women. For an equivalent smoking exposure burden, more women develop COPD than men; this difference could also be the result of the smaller airways in women. Similarly, although men have a higher incidence of CAD than women, recent data suggest that women may be more susceptible to the harmful vascular effects of cigarette smoking than men.[11]

Diet.

Multiple studies have suggested a weak link between the intake of various dietary factors and the loss of lung function. In population-based studies, a higher intake of vitamins C, D, and E, carotenoids, flavonoids, and fruits rich in antioxidants have all been reported to slow the rate of age-related lung function decline; however, supplementation of these dietary factors has not been demonstrated to improve lung function.[12] Similarly, antioxidant supplementation, vitamins C and E, beta carotene, and omega-3 fatty acids have all been reported to decrease the occurrence of CAD in nonrandomized trials.

Overlapping Pathobiologic Pathways (see Fig. 86.1)

Atherosclerosis and Inflammation

Multiple studies have documented heightened systemic inflammation in COPD, and systemic inflammation is well established as a major factor in the development and progression of atherosclerosis. COPD is associated with chronic low-grade systemic inflammation that likely stems from ongoing pulmonary inflammation. In vivo experiments in rabbits exposed to particulate matter have shown that there is a marked increase in vulnerable plaques even in the absence of dyslipidemia, and this is associated with pulmonary and systemic inflammation. These effects are mediated by airway epithelial cells and macrophages that release proinflammatory mediators, such as interleukin-1, interleukin-6, tumor necrosis factor-α, interleukin-8, and granulocyte macrophage–colony stimulating factor. The resultant pulmonary inflammation translocates into the systemic circulation, stimulating the liver to produce acute phase reactants such as C-reactive protein and procoagulants, including factor VIII and fibrinogen, and leading to a chronic, low-grade systemic inflammatory state. The lungs are constantly exposed to environmental agents, including cigarette smoke, air pollutants, and infectious agents, all of which can cause a chronic inflammatory condition.[13] The data for direct associations between markers of systemic inflammation and measures of atherosclerosis in COPD are, however, sparse and with weak correlations.

Oxidative Stress

A close relationship exists between inflammation and oxidative stress. Inflammation in the lungs is associated with a disturbance in the oxidant-antioxidant balance, with a rise in oxidative stress.[13] Reactive oxygen species cause oxidative injury to cells, resulting in up-regulation of proinflammatory mediators both in the lungs and systemically. Oxidative stress also causes lipid peroxidation, and the resulting oxidized low-density lipoprotein is an important mediator of atherosclerosis.

Prothrombotic State

The low-grade systemic inflammation seen in COPD can also result in a prothrombotic state. COPD patients have decreased platelet volume and higher platelet counts compared with matched controls, and these are associated with a lower response to antiplatelet agents. COPD is also associated with increased levels of prothrombin and coagulation factors II, V, VII, VIII and IX, and with lower levels of tissue factor pathway inhibitor. These changes are associated with a greater predisposition to thrombin generation.[14]

Genetics

Multiple genetic associations exist for pathways of inflammation and oxidative stress common to COPD and CVD.[15] Both conditions are characterized by accelerated aging, the result of accumulated DNA damage and telomere shortening. A number of other mechanisms are likely involved with shared genetic associations. For instance, glutathione-S-transferase, an important mediator of oxidative stress in COPD, has also been implicated in atherosclerosis; matrix metalloproteinases cause proteolysis and damage to the alveolar wall, and are also involved in early atherosclerosis and plaque rupture.

Renin-Angiotensin System

The lungs have high concentrations of angiotensin-converting enzyme, and chronic hypoxia can activate the renin-angiotensin system, which has potent proinflammatory and profibrotic effects.[1] Up-regulation of the renin-angiotensin system also causes endothelial dysfunction and may lead to vasoconstriction and thrombosis. Renin-angiotensin system activation has also been implicated in atherosclerosis.

Sedentarism

Physical activity is a modifiable behavior associated with COPD outcomes. Physical activity progressively declines with worsening disease severity and is a strong predictor of all-cause mortality rates in COPD, as well as in patients with CAD. Sedentary habits are strongly associated with CAD, and it remains to be investigated if low physical activity is just a consequence of disease severity in COPD or if physical activity alters disease progression.[16]

Heart Failure

CAD is the most important risk factor for systolic heart failure; with the accelerated atherosclerosis frequently observed in COPD, coronary ischemia is the most likely pathogenetic mechanism for the greater frequency of heart failure reported in COPD. Coronary ischemia also likely results in diastolic dysfunction, and activation of the renin angiotensin system also has a role in cardiac dysfunction and remodeling. A substantial proportion of patients with COPD have static and dynamic hyperinflation. Static hyperinflation is characterized by a reduced inspiratory capacity to total lung capacity at rest, and is associated with a reduced cardiac chamber size and impaired left ventricular diastolic filling.[17] Dynamic hyperinflation is reflective of air trapping during exertion, and this has a strong inverse correlation with the oxygen pulse, an estimate of stroke volume, on cardiopulmonary exercise testing, suggesting a lower stroke volume as the thoracic lung volume increases. The mechanisms underlying the effects of lung hyperinflation on cardiac performance are likely related to the effect on ventricular filling, reduced venous return, or associated dyspnea, resulting in activation of the renin-angiotensin system, salt and fluid retention by the kidneys, and relative volume overload. Severe COPD is also associated with right heart dysfunction, which when severe can result in a septal bulge toward the left ventricle and impair left ventricular filling. Pulmonary hypertension is frequently seen (**see Chapter 85**) but is rarely severe, and can cause impaired left ventricular filling even in patients with only mildly elevated pulmonary arterial pressures.[18]

Cardiac Arrhythmias

Patients with COPD frequently have acid-base abnormalities as well as hypoxemia and hypercapnia, all risk factors for supraventricular and ventricular arrhythmias. These abnormalities are more commonly seen in either late stages of the disease or during acute exacerbations. A substantial number of COPD patients, even with milder disease, have autonomic neuropathy; this is associated with a prolonged QTc interval and a greater risk of ventricular arrhythmias. COPD is characterized by an increased sympathetic tone, with a higher resting heart rate compared with age-matched controls. A number of medications, including β-agonists, anticholinergics, and theophylline, may also be proarrhythmogenic. These are discussed further in the section on Medication Interactions.

Clinical Manifestations: Overlap and Diagnosis

COPD is characterized by one or more of the following: chronic cough, sputum production, wheezing, and dyspnea on exertion or at rest. Patients with severe disease can also have paroxysmal nocturnal dyspnea. These symptoms are nonspecific and the diagnosis should always be confirmed by spirometry. Spirometry involves a forced exhalation maneuver from maximal inhalation (total lung capacity) to maximal exhalation (residual volume), with the volume of gas expired defined as the forced vital capacity (FVC). The volume of air exhaled in the first 1 second of this maneuver, or forced expiratory volume (FEV_1),

falls with increasing disease severity and airflow obstruction. The diagnostic hallmark of COPD is the demonstration of a reduced ratio of FEV_1 to FVC of less than 0.70, or less than the lower limit of normal as defined by normative population reference values, in the presence of symptoms.

Patients with COPD and cardiovascular disease are often seen by both cardiologists and pulmonologists, who frequently miss the diagnosis that does not belong to their specialty. This is both due to a lack of awareness as well as the substantial overlap in symptoms. COPD, CAD, and heart failure can all present with exertional dyspnea. In addition to dyspnea, COPD and heart failure share other common symptoms, such as cough and wheezing, and sometimes nocturnal cough and paroxysmal nocturnal dyspnea. These are symptoms common to both systolic heart failure and HFpEF. Peripheral edema is also commonly seen in both heart failure and COPD, particularly when the latter is severe and associated with cor pulmonale. In patients with an established diagnosis of one condition, the symptoms of the other are commonly overlooked and ascribed to the primary condition. In patients with symptoms that are disproportionate to the severity of the underlying disease, coexisting lung and cardiovascular disease should be suspected and investigated.

In the majority of patients, COPD can be differentiated from cardiovascular disease with a thorough history and physical examination, supported by appropriate laboratory and radiographic studies, including chest radiographs, spirometry, two-dimensional (2D) echocardiography, blood biomarkers such as troponins and brain natriuretic protein, and resting and stress electrocardiography. Although the lungs are poor conductors of ultrasound, recent studies have demonstrated that lung ultrasound artifacts can be used to detect pulmonary edema and differentiate CHF from COPD in acute settings.[19] Spirometric confirmation of airflow obstruction is necessary for a definitive diagnosis of COPD, which should not be made on the basis of the smoking history and symptoms alone. Although differentiation of these conditions is frequently possible, physiologic changes associated with heart failure can confound the detection and severity grading of airflow obstruction. Interstitial edema can manifest as a reduction in FVC and thus an artificially elevated FEV_1/FVC ratio (pseudorestrictive pattern). Peribronchial edema can cause bronchial hyperreactivity and bronchoconstriction, resulting in airflow obstruction (cardiac asthma). For these reasons, it is recommended that spirometric evaluation of lung disease be done when the patient is as euvolemic as possible. Lung volumes are often elevated in COPD and reduced with heart failure, and plethysmography estimation of total lung capacity may be useful in differentiating the two conditions, although significant overlap of lung volumes in these conditions reduces specificity. The diffusing capacity of carbon monoxide (DLCO) is a surrogate for oxygen transfer through the blood-alveolar barrier and is more likely to be low in patients with emphysema than in heart failure patients, in whom the DLCO is frequently normal or elevated due to increased intrapulmonary blood volume. In some patients with coexisting severe disease, cardiopulmonary exercise testing may become necessary to understand the relative contributions of each disease to exercise limitation.

Treatment and Medication Interactions

Most guideline documents now agree that the treatment of COPD and cardiovascular disease should follow standard recommendations for each disease. Nonpharmacologic therapy with pulmonary rehabilitation is associated with significant improvement in dyspnea, respiratory quality of life, and exercise capacity, independent of severity of lung disease, and the presence of cardiac comorbidity should not be considered a contraindication for exercise training (**see Chapter 53**); rehabilitation exercises have clear benefits in cardiovascular disease as well. The mainstays of pharmacologic therapy for COPD are inhaled bronchodilators, including β-agonist and anticholinergic medications, and inhaled

corticosteroids in those with more advanced disease and frequent exacerbations. Although these medications alleviate dyspnea and improve exercise capacity and respiratory quality of life, there remains debate about whether some of these medications increase the risk of cardiovascular events.[20] Large population studies, albeit retrospective, have found a 1.5 to 4.5 times increased incidence of arrhythmias with the use of the short-acting β-agonist medications. A similarly increased risk of arrhythmias has also been reported for long-acting β-agonists. The data for the short-acting anticholinergic drug ipratropium are mixed, with some but not all studies showing a slightly greater risk of arrhythmias. Although metaanalyses of safety data for long-acting antimuscarinics such as tiotropium suggested a greater risk of arrhythmias in those with significant underlying cardiac disease, a recent large randomized controlled study to address safety issues found that there is no increased risk of arrhythmias with the use of tiotropium, even in those with established cardiac disease.[21] Post hoc safety studies have also suggested that the risk of cardiac events and mortality is not increased by tiotropium, although clinical studies excluded those with recent cardiac events or with unstable cardiac disease, in whom caution should be exercised.[22]

There are also reports of increased hospitalizations in CHF patients treated with inhaled β-agonist medications. Use of theophylline and oral steroids is also associated with atrial fibrillation (**see also Chapter 38**). Pooled analyses suggest that roflumilast, a selective phosphodiesterase-4 inhibitor, has a safe cardiac profile, but post-approval phase 4 data are not yet available.[23] Azithromycin is used to prevent frequent exacerbations and can cause prolongation of the QT interval (**see also Chapters 32 and 33**). Retrospective data suggesting there might be an increased risk of arrhythmias with the use of azithromycin provoked the issuance of a black box warning from the U.S. Food and Drug Administration. However, multiple large randomized studies did not report adverse cardiac effects; these studies excluded patients with a prolonged QTc interval, and this safety precaution is now recommended in clinical practice.

Multiple cardiac medications are also frequently used in patients with COPD. There is notable concern for worsening airflow obstruction with the use of beta blockers, although clinical trials suggest this is clinically not significant, especially for cardioselective medications. Indeed, the use of cardioselective beta blockers in COPD is associated with improved survival rates, both over the long term and when continued during acute exacerbations. Retrospective data also suggest that their use is associated with a reduction in exacerbation frequency, likely due to their cardioprotective effects, although this remains to be confirmed in randomized trials. Retrospective studies also suggest a beneficial effect on exacerbation frequency with the use of statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers; however, a large randomized study failed to show any benefits of statins on exacerbation rates.[1]

Acute Exacerbations

The natural history of COPD is punctuated by episodes of acute exacerbation of symptoms, which often result in hospitalization, significantly affect the quality of life and accelerate the decline of lung function, and are associated with substantial short- and long-term risks of mortality. These exacerbations are associated with heightened pulmonary and systemic inflammation, increased oxidative stress, increased sympathetic tone, lung hyperinflation, and cardiac arrhythmias. Exaggerated signals along these pathways confer a greater risk of coronary ischemia, rupture of vulnerable plaques, ventricular cardiac arrhythmias, and heart failure. The risk of an acute myocardial infraction 1 to 5 days after an exacerbation is doubled, and subclinical ischemia is likely more common.[24] Indeed, levels of troponin and N-terminal brain natriuretic protein are elevated during exacerbations and are both associated with higher mortality rates.

Diastolic dysfunction is common in stable COPD and can decompensate in the setting of subclinical or clinically detected cardiac arrhythmias. Congestion along the peribronchovascular bundle can increase airway reactivity and cause a decompensation in respiratory status that can be clinically difficult to distinguish from usual acute exacerbations.

Prognosis

The coexistence of cardiac disease and COPD frequently results in poorer outcomes. Approximately half the patients with COPD die of cardiovascular disease. The presence of heart failure approximately doubles the 4-year mortality risk in COPD. Patients with diastolic dysfunction have a greater frequency of COPD exacerbations, and severe exacerbations are associated with diastolic dysfunction in about a third of patients. COPD also has an adverse impact on cardiovascular outcomes, and is associated with a two-fold increased frequency of hospitalizations due to angina and myocardial infarction. COPD is also associated with a considerably greater risk of rehospitalization and death after myocardial infarction.

Interstitial Lung Disease

Interstitial lung diseases (ILDs) are a heterogeneous group of diffuse parenchymal lung disorders that are linked by genetic susceptibility, environmental exposures including cigarette smoking, and aging, and characterized by varying degrees of inflammation and fibrosis of the lung parenchyma, resulting in progressive loss of lung function and death. The major categories of ILD are idiopathic pulmonary fibrosis (IPF) and nonspecific interstitial pneumonitis (NSIP), which is now recognized as a distinct entity. Other rarer ILDs include smoking-related interstitial pneumonitis and acute and subacute interstitial pneumonitis. NSIPs are either idiopathic or seen in association with collagen vascular diseases, hypersensitivity pneumonitis, and drug toxicity. Cardiovascular disease associated with connective tissue diseases is described elsewhere (**see Chapter 94**). This section focuses on IPF, the major type of ILD and that with the worst long-term prognosis.

IPF has a prevalence of 13 to 42 cases per 100,000 in the United States, and although prevalence data are scarce for non-IPF ILDs, these in combination are likely more prevalent.[25] Indeed, in populations at risk for ILD, such as smokers, the rate of interstitial lung abnormalities visualized on computed tomography (CT) scans can be as high as 10%.[26] IPF is associated with the same type of cardiac comorbidities as COPD. Arrhythmias are reported in about one fifth, CHF in 4% to 26%, and CAD in 3% to 68%, depending on the disease severity.[4] Similar to COPD, IPF has been identified as an independent risk factor for developing CAD, and the risk might be greater for IPF for similar levels of smoking exposure. The mechanisms for this association are similar to those reported for COPD, with upregulation of inflammatory and oxidative pathways. Cardiovascular disease is second only to respiratory failure as a cause of death in IPF patients, with 25% dying of cardiac causes, and a diagnosis of ILD prompt a careful evaluation for cardiac disease.[27]

ILDs usually present with symptoms of chronic dry cough and exertional dyspnea. Clinical examination usually reveals Velcro-like crackles at lung bases, which can be mistaken for the basilar crackles heard in heart failure. Pulmonary function tests show a restrictive defect on spirometry ($FEV_1/FVC > 0.70$ and FVC < 80% predicted); restrictive defects should be confirmed with lung volume measurements. CT can usually differentiate IPF from heart failure based on the predominant pleural-based basal interstitial opacities without pleural effusion, although this may not be straightforward when the two diseases

coexist. The definitive diagnostic test for IPF is lung biopsy. There is no known cure for IPF, although two recently approved oral drugs, pirfenidone and nintedanib, can slow disease progression. Nintedanib is a tyrosine kinase inhibitor, and there are reports of QT prolongation, left ventricular dysfunction, hypertension, and arterial thrombosis associated with the use of tyrosine kinase inhibitors, although most of the data were derived from their use in cancer patients.

Bronchial Asthma

Bronchial asthma is a chronic inflammatory disease of the airways characterized by reversible airflow obstruction. Although bronchodilator reversibility is useful to support a diagnosis of asthma, this is not sufficiently specific to differentiate asthma from COPD, which can still be associated with bronchodilator reversibility in approximately 40% of patients. The prevalence of asthma is approximately 8% in the United States. Although asthma is also associated with chronic inflammation and data to support a relationship between chronic asthma and cardiovascular disease are scarce, the CAD risk appears to be slightly greater than in the general population after adjustment for other cardiac risk factors.[28]

Lung function findings in bronchial asthma usually include airflow obstruction that is reversible on administering bronchodilators. Patients with mild asthma may have normal spirometry, and those with severe uncontrolled asthma may have airflow obstruction that does not fully reverse with bronchodilators, similar to COPD. Bronchial asthma is often readily diagnosed by the history, physical examination, and spirometry when it occurs early in life. However, older patients presenting with cough, wheezing, and nocturnal dyspnea should be additionally evaluated for cardiac causes. Congestion along the bronchovascular bundle in patients with left ventricular failure may result in cardiac asthma. Cardiac asthma is diagnosed clinically, although mild or negative bronchoprovocation test results with methacholine support the diagnosis. Although the data to support the use of bronchodilators for cardiac asthma are scant, a trial of bronchodilators is often recommended to determine if bronchial asthma coexists. Treatment of cardiac asthma is primarily directed at improving cardiac function.

Given the high prevalence of asthma, it is important to consider the potential cardiac side effects of inhaled medications, especially long-acting β-agonists such as salmeterol and formoterol. When used alone, these medications are associated with a 1.5 to 4.5 times increased risk of asthma-related mortality, and in some cases cardiac mortality likely due to arrhythmias, prompting the FDA to issue a black box warning against monotherapy with these medications. A combination of long-acting β-agonists with inhaled corticosteroids appears to ameliorate this risk.[29,30]

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disorder of mucus and sweat glands and primarily manifests as obstructive airway disease and pancreatic insufficiency. There are approximately 30,000 patients with CF in the United States and about 70,000 worldwide. With advances in diagnosis, therapy, and care, the median survival time has steadily increased from 10 years in the early 1960s to 40 years currently. With increasing longevity, there is growing awareness of the cardiovascular complications of this chronic inflammatory lung disease. The mechanisms for accelerated atherosclerosis are likely similar to those seen in other CLDs; endothelial dysfunction as evidenced by impaired brachial artery flow–mediated dilation has been documented in CF patients as young as 7 to 18 years old.[31] In addition to CLD, these patients are usually deficient in fat-soluble antioxidant vitamins despite supplementation, resulting

from pancreatic insufficiency. Nutritional recommendations are usually to ingest a high-fat diet that provides up to 40% of total calories to compensate for maldigestion, as well as the increased energy expenditure observed in CF. Consistent alterations in levels of polyunsaturated fatty acids have been observed in CF patients; they are likely proatherosclerotic. CF-related diabetes also is a strong risk factor for early CAD.

Lung Transplantation

Approximately 2100 lung transplants were performed in the United States in 2016, most commonly for COPD, IPF, and CF. Within 3 years of lung transplantation, 90% of recipients without preexisting cardiovascular risk factors develop one or more incident cardiac risk factors and 40% develop two or more risk factors.[32] These risks are accentuated by the use of immunosuppressive medications such as cyclosporine and glucocorticosteroids, which are associated with accelerated vasculopathy. Compared with other solid-organ transplants, such as the heart, kidney, and liver, which have 10-year survival rates that approximate 50% to 60%, the 10-year survival rate for lung transplants is only 22%. The main cause of death within 5 years of lung transplantation is bronchiolitis obliterans syndrome, and cardiovascular causes account for 5% of deaths. However, with increasing longevity of these patients, cardiovascular disease is expected to increase, and cardiac assessment should be part of the evaluation of all patients following transplantation.

Future Perspectives

CLDs are associated with a high prevalence of cardiovascular disease compared with matched controls. Many CLDs such as COPD and IPF should be regarded as proatherosclerotic conditions and these patients should be screened accordingly for cardiovascular disease. Accelerated atherosclerosis is likely due to a combination of traditional cardiovascular risk factors as well as systemic inflammation and oxidative stress. In patients with symptoms disproportionate to the severity of their underlying disease, additional causes, including CAD and heart failure, should be actively investigated. Drugs used for COPD and IPF can increase the risk of arrhythmias, and caution should be exercised, with close attention paid to risk-benefit analyses as well as consideration of additional drug interactions. Pulmonary rehabilitation is associated with significant improvement in the functional status of all patients with CLD, and the presence of cardiac comorbidity should not be considered a contraindication. A low index of suspicion for cardiac disease is recommended in all patients with CLD, irrespective of the severity of disease.

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87

Sleep-Disordered Breathing and Cardiac Disease

Susan Redline

Sleep-disordered breathing (SDB) is prevalent in patients with cardiac diseases, contributing to a reduced quality of life, a reduced functional capacity, and poor outcomes. SDB causes acute and chronic physiologic stressors that can exacerbate cardiac ischemia, reduce systolic and diastolic function, cause cardiac structural and electrical remodeling, and increase the risk of cardiac arrhythmias and sudden death. Despite strong evidence linking SDB to cardiovascular disease (CVD), and the vulnerability of the cardiac patient to SDB-related stressors, SDB often goes unrecognized in cardiology practice, so there is potential for improved recognition and initiation of interventions. This chapter reviews aspects of SDB recognition, pathophysiology, and health outcomes relevant to cardiac disease.

Definitions

SDB refers to a spectrum of sleep-related breathing disorders that includes obstructive sleep apnea (OSA), central sleep apnea (CSA), Cheyne-Stokes respiration, and sleep-related hypoventilation. The

mechanisms and risk factors for these disorders have overlapping as well as unique characteristics. Each is associated with impaired ventilation during sleep and sleep disruption, although they differ in regard to their roles and the severity of altered neuromuscular respiratory drive and airway collapsibility that they cause. The constellation of symptoms and diagnostic criteria and their associations with CVD are summarized in **Table 87.1**.

TABLE 87.1

Key Features of Obstructive Sleep Apnea and Central Sleep Apnea

	OBSTRUCTIVE SLEEP APNEA	CENTRAL SLEEP APNEA
Common presenting symptoms	Snoring, observed apneas, gasping or snorting during sleep, daytime sleepiness	Observed apneas, gasping or snorting during sleep, frequent awakenings, unrefreshed sleep, fatigue
Diagnosis	Home sleep apnea test or polysomnography showing AHI > 5 with a predominance of obstructive apneas or hypopneas (>50%)	Polysomnography showing a predominance of central apneas or hypopneas (>50%) with a central apnea hypopnea index > 5 Cheyne-Stokes respiration: ≥ 3 consecutive central apneas/central hypopneas separated by crescendo and decrescendo change in breathing amplitude with a cycle length ≥ 40 sec associated with a central AHI > 5
Associated risk factors	Obesity, male, middle to older age	Male, older age
Associated cardiovascular disease*	Resistant hypertension, stroke, heart failure (preserved and reduced ejection fraction), atrial fibrillation, coronary artery disease	Atrial fibrillation, heart failure (reduced and preserved ejection fraction), stroke, pulmonary hypertension, coronary artery disease

*Order shown indicating approximate relative strength of association.

Obstructive sleep apnea (OSA), characterized by recurrent episodes of complete (apnea) or partial (hypopnea) upper airway occlusion, affects 34% of middle-aged males and 17% of middle-aged females.[1] OSA and CVD are commonly aggregated because of their shared risk factors (e.g., central obesity) and causal relationships; therefore, the prevalence of OSA is as high as 40% to 80% in patients with hypertension, heart failure (HF), coronary heart disease (CHD), and cerebrovascular disease.[2] Patients with OSA typically report loud or disruptive snoring, poor sleep quality, and unrefreshed sleep. Excessive daytime sleepiness is a cardinal symptom, and its presence marks severe disease that is associated with an increased risk of adverse CVD outcomes, as well as better adherence with OSA treatment.[3] People with OSA commonly have an impaired quality of life and a depressed mood; in patients with concomitant CVD, these important patient-centered outcomes can improve with OSA treatment.[4]

The diagnosis of OSA is based on (1) symptoms of breathing disturbances during sleep (snoring, snorting, gasping, or breathing pauses) *or* daytime sleepiness or fatigue, despite sufficient opportunities to sleep and unexplained by other medical problems; *and* (2) five or more obstructive apneas or hypopneas per hour of sleep (Apnea-Hypopnea Index [AHI]) documented in a sleep study. OSA may be diagnosed in the absence of symptoms if the AHI is greater than 15.[5] Each apnea or hypopnea represents a reduction in breathing for at least 10 seconds, associated with a drop in oxygen saturation and/or a brain cortical arousal (**Fig. 87.1**).[6] Apneas indicate a near absence of airflow during the period of obstruction, but hypopneas are recorded when the airflow is reduced by 30% to 50%. OSA severity is judged based on the frequency of breathing disturbances (AHI level), degree of hypoxemia and sleep disruption, and level of daytime impairment, such as sleepiness and cognitive impairment.

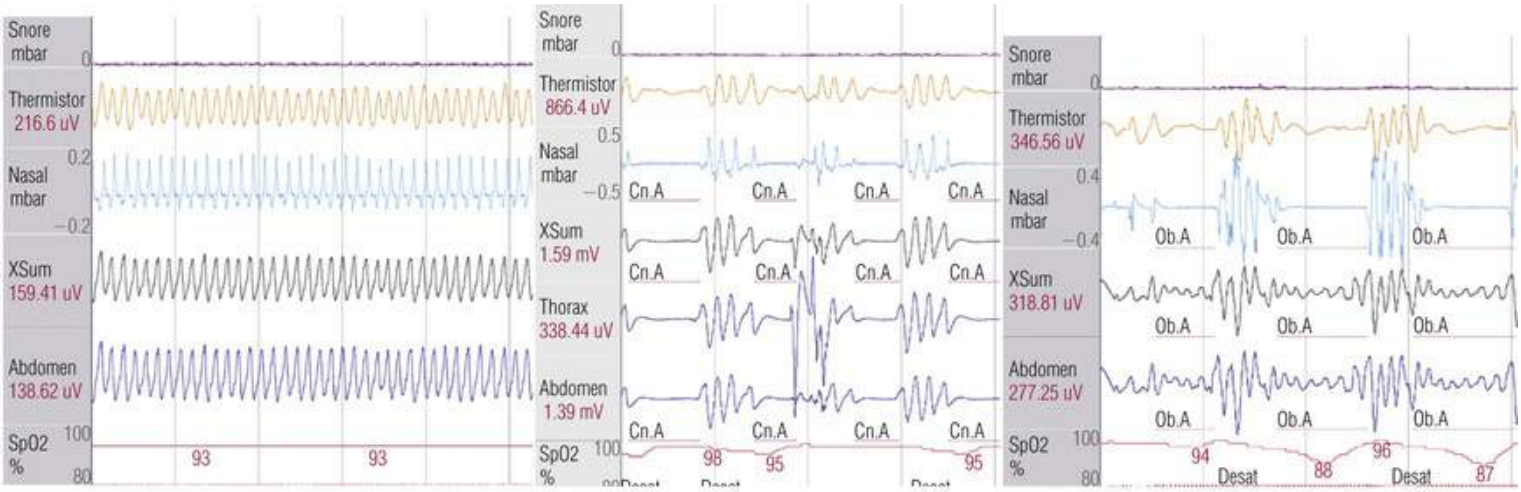


FIGURE 87.1 Examples from an overnight sleep study, displaying respiratory channels. The first panel shows normal breathing with stable oxygen saturation values. The second panel shows repetitive central apneas, characterized by 15- to 40-second periods of absent airflow (shown on the nasal and thermistor channels), with no associated respiratory effort of snoring, and oxyhemoglobin desaturation of 3% with each event. The third panel shows obstructive apneas, characterized by absent airflow with persistent effort on the thorax and abdominal channels, with deep desaturations (each panel is ≈ 3 minutes long).

The AHI and other indices of sleep are measured with multichannel overnight recordings that minimally quantify changes in airflow, breathing effort, and oxygen saturation. Home-based sleep apnea tests typically collect these core features, needed for diagnosing SDB, but not additional information required to characterize the sleep quality. In contrast, polysomnography performed in the sleep laboratory records respiratory data as well as data from the electroencephalogram, electrocardiogram, and leg muscles, providing the ability to specifically stage sleep, quantify sleep fragmentation, and identify other sleep-related phenomena such as periodic leg movements. Although home sleep apnea tests are increasingly used due to their lower cost, in-laboratory polysomnography still serves to evaluate patients with complex comorbidities, such as HF. When interpreting the results of home sleep apnea tests, it is important to note that they can underestimate the AHI by approximately 12%,[7] and larger misclassifications are likely in patients with poor sleep quality, such as those with HF.

Pathophysiology

Pathophysiology of Obstructive Sleep Apnea

The pharyngeal airway has no bony or cartilaginous support, and its size and shape dynamically change with each expiration and inspiration (when negative intraluminal pressure causes the airway to be “sucked' inward). Its patency therefore depends on the activation of pharyngeal dilator muscles, which decreases with sleep onset. Whether an apnea occurs depends on whether the level of neuromuscular activation of the upper airway muscles is adequate to overcome forces that promote airway collapse during sleep.[8]

The presence of an anatomically small airway (e.g., micrognathia, fat deposition in the lateral pharyngeal walls) and lying in the supine position (when gravitational and positional factors alter the position of the tongue and other soft tissues) increase the level of neuromuscular drive needed to maintain airway patency. Therefore, patients with small oropharyngeal airways due to craniofacial factors or excessive airway soft tissue have an increased risk for OSA. When a person is in the recumbent position, there can be a rostral redistribution of peripheral fluid from the lower extremities to the neck area, contributing to airway narrowing during sleep, and this factor can predispose patients with HF and even

mild peripheral edema or venous stasis to OSA.[9] The lung volume influences the pharyngeal wall stiffness through tractional forces; therefore, reduced lung volumes, as may occur in obesity or with pulmonary congestion, can exacerbate the propensity for OSA.[10] Conversely, high lung volumes, as in chronic obstructive lung disease, may modestly protect against OSA.[11] Increased nasal resistance (e.g., due to nasal septal deviation, polyps) promotes airway collapse by increasing the negative intraluminal suction pressure, and is a risk factor for OSA in conditions such as pregnancy or allergy associated with nasal swelling.[12]

Pharyngeal muscle activation depends both on the sensitivity of central and peripheral respiratory chemoreceptors and on neuromuscular responsiveness to CO_2 (**Fig. 87.2**).[10] During sleep, the blood CO_2 typically mildly increases, and this helps to activate respiratory muscles and stiffen airway dilators, protecting the upper airway. Depressed chemosensitivity and arousal response may prevent appropriate termination of apneas, prolonging the duration of the apnea and the severity of oxyhemoglobin desaturation. This ventilatory control problem can cause pathologic CO_2 retention and acidosis during sleep, a phenomenon common in obesity-hypoventilation and sleep-hypoventilation syndromes.[13] Conversely, an overly sensitive response to CO_2 can cause wide fluctuations in the ventilatory drive, resulting in central nervous system arousal and sleep fragmentation. Episodic hyperventilation can drive CO_2 levels to below the apneic threshold, precipitating cycles of apneas. This mechanism also occurs in CSA, and in its most extreme form, is manifested as Cheyne-Stokes respiration.[2]

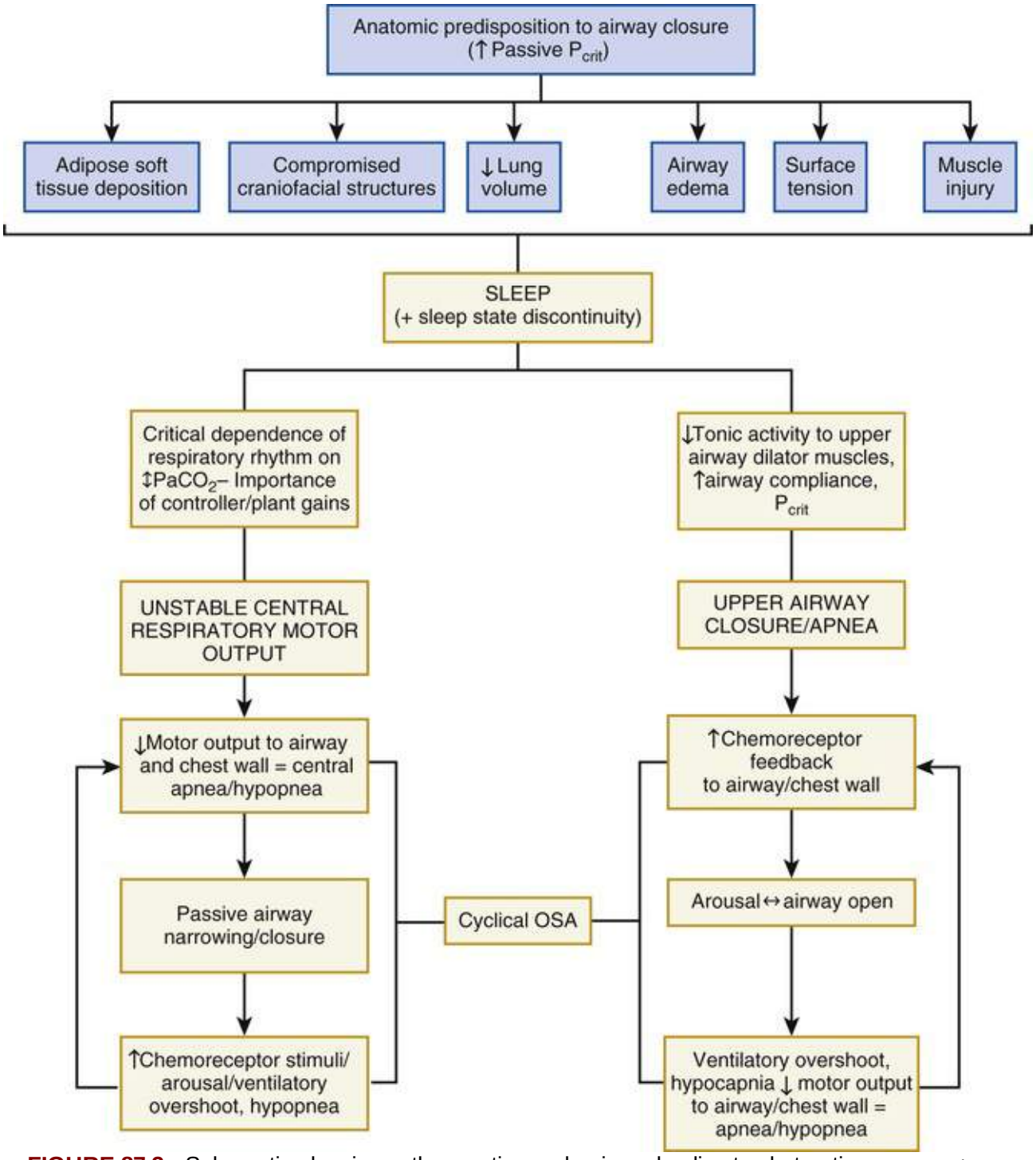


FIGURE 87.2 Schematic showing pathogenetic mechanisms leading to obstructive apneas. (From Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP: Pathophysiology of sleep apnea. Physiol Rev 2010;90:47-112.)

The severity of OSA can vary by sleep stage and position. During REM (rapid eye movement) sleep, the neuromuscular drive is low and fluctuating; it is the stage when OSA is commonly most severe. Women appear predisposed to "REM-dependent" OSA, referring to a predominance of apneas in REM sleep.[14] OSA also can worsen following acute ingestion of alcohol, which reduces neuromuscular activation, and when a person is in the supine position.[15]

Pathophysiology of Central Sleep Apnea

Variants of CSA occur secondary to genetic syndromes, neuromuscular disease, and opioid use, reflecting abnormalities of the central and peripheral ventilatory control systems.[16] In adults, CSA often occurs in association with cardiac or cerebrovascular disease. Its pathogenesis relates to a heightened sensitivity to

CO_2 and a prolonged circulation delay between the pulmonary capillaries and carotid chemoreceptors, causing instability in breathing.[17] Periods of hyperventilation cause CO_2 levels to fall below the apneic threshold, precipitating apneas and hypopneas. The occurrence of cycles of crescendo-decrescendo breathing is recognized as Cheyne-Stokes respiration.

Risk Factors for and Recognition of Sleep-Disordered Breathing

Male sex, older age, and obesity are well-recognized OSA risk factors.[18] OSA is 2- to 4-fold more prevalent in men than in women.[19] Factors that predispose men to OSA include android patterns of adiposity (associated with upper airway fat deposition) and relatively long pharyngeal length, which predisposes to collapsibility.[20] The OSA prevalence increases in women following menopause, and hormone replacement therapy is associated with reduced AHI levels, consistent with a role for sex hormones in modulating risk.[21] Although the precise role of sex hormones on OSA is not well understood, estrogens and progesterone influence ventilation, including responses to hypoxia and CO_2.[22] However, OSA severity increases not only in older women but also in older men, reflecting age-related comorbidities (e.g., cardiac diseases, neurologic diseases) and other age-related effects on airway stiffness and ventilation.[18] OSA in elderly persons may differ from that in middle-aged individuals, with less prominent associations with snoring, obesity, autonomic system dysregulation, and CVD reported.[23] It is not known whether differences in studies of middle-aged populations compared with older populations result from study biases or are true differences in OSA effects across the population.

Being overweight or obese accounts for approximately 40% to 60% of cases of OSA. Obese middle-aged individuals are 4-fold or more likely to have OSA as compared with normal-weight individuals.[1] Obesity contributes to OSA through effects on airway narrowing caused by fat deposition in the tongue and parapharyngeal tissues and by reducing chest wall compliance and lung volumes. Obesity-associated cytokine levels also may influence ventilatory control and promote daytime sleepiness. Even a modest weight loss or weight gain can have an impact on the severity of OSA. For example, a 1% increase in the body mass index (BMI, kg/m^2) is estimated to increase the AHI by 3%; this finding emphasizes the importance of weight management in OSA.[1] Approximately 20% of OSA patients are *not* obese, however, and the absence of obesity should not preclude an appropriate evaluation of patients with OSA symptoms. Other risk factors for OSA are craniofacial features that narrow the oropharyngeal airway, upper airway dilator muscle dysfunction, heightened ventilatory chemosensitivity, and a low respiratory arousal threshold.[18]

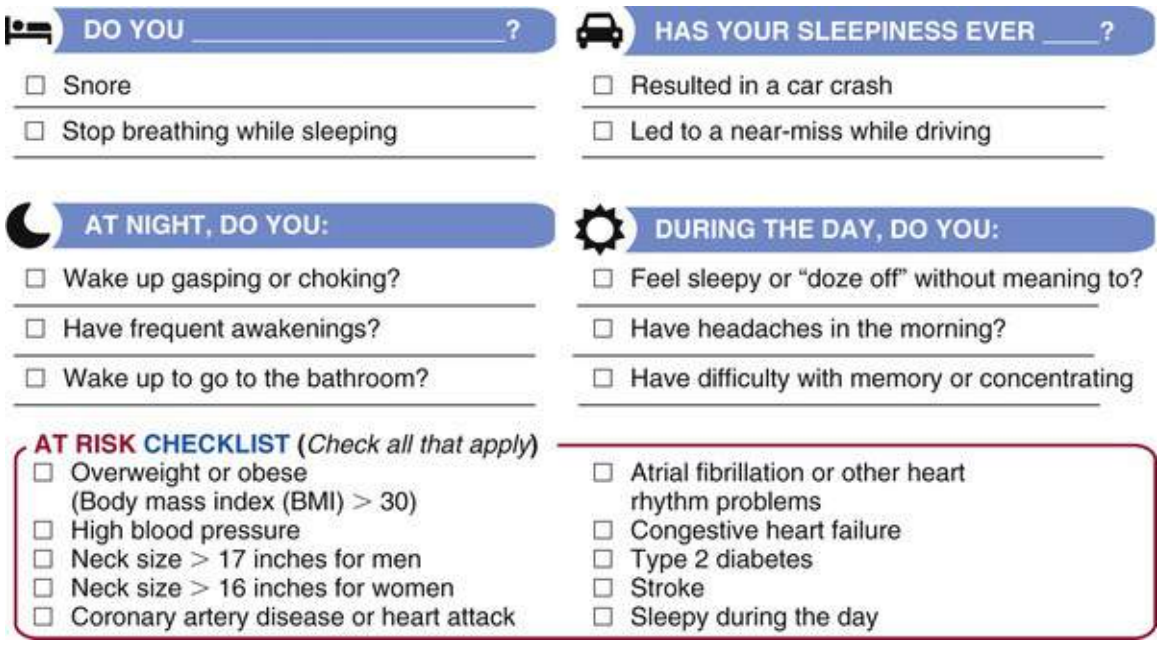
A first-degree relative of a patient with OSA has an approximately 2-fold increased risk of OSA compared with someone without an affected relative.[24] Over 60% of the genetic variance explaining OSA is not associated with obesity, indicating the importance of multiple etiologic factors.[25] Several genetic variants associated with OSA may also be associated with cardiac disease and abnormal lipid and glucose levels, suggesting overlapping genetic mechanisms (“pleiotropy”) for OSA and cardiac disease.[26,27] Sexual dimorphisms in genetic variants for OSA have been identified, similar to reports of sex-based differences in genetic variants for adiposity and cardiac disease.[26]

Population studies have demonstrated that clinically significant OSA often goes unrecognized and untreated.[28] Despite improved public awareness of OSA, it is estimated that more than 80% of individuals with moderate or severe OSA are undiagnosed.[28,29] Even among those diagnosed, more than 30% of patients report that the period between onset of symptoms and diagnosis exceeded 10 years.[30]

Underrecognition is high among ethnic and minority groups and elderly individuals, particularly African Americans and older Chinese Americans,[29] groups also at risk for cardiometabolic diseases. Underrecognition in women may result from the preferential reporting of symptoms of fatigue rather than sleepiness, and the frequency of comorbid insomnia that can confound the diagnosis and reduce the sensitivity of screening questionnaires.[21] Women often display REM-predominant OSA and may experience apneas that result in arousal without desaturation, findings that home sleep tests may miss.

Risk factors for CSA are male sex, hypocapnia during wakefulness, and older age, as well as HF, CVD, and atrial fibrillation.[17] Due to elevations in sympathetic drive, patients with CSA may not report sleepiness, and rather report symptoms of insomnia, such as difficulty falling asleep and frequent awakenings.

The role of routine screening for sleep apnea is not established. In 2017, The U.S. Preventive Services Task Force concluded that there was insufficient evidence to recommend routine screening for sleep apnea in primary care settings.[31] However, patients with diagnosed sleep apnea frequently report prolonged delays between the onset of symptoms and diagnosis and treatment, indicating a need to improve recognition.[30] Screening questions (**eFig. 87.1**) or web-based algorithms that combine information on snoring frequency, age, BMI, and sex for calculating OSA risk,[32] should be considered in cardiology practices,[33] settings where sleep apnea prevalence is high, to improve identification and expedite treatment of this disorder.



EFIGURE 87.1 Screening questions for sleep apnea. (From American Academy of Sleep Medicine: Are You at Risk for Obstructive Sleep Apnea? www.sleepeducation.org/docs/default-document-library/sleep-apnea-risk-assessment.pdf.)

Pathophysiologic Mechanisms That Link Sleep-Disordered Breathing to Cardiovascular Diseases

During healthy sleep, individuals experience a decrease in sympathetic nervous system activity and an increase in parasympathetic activity, with associated decreased levels of blood pressure (BP) and heart rate. Repetitive collapse of the upper airway that disrupts sleep continuity and causes arousal disturbs

these patterns, resulting in surges in sympathetic activity and acute BP elevations.[17,34] Impaired gas exchange with intermittent hypoxia further affects the autonomic nervous system, as well as triggers release of acute-phase proteins and reactive oxygen species. The release of these mediators may favor an augmented inflammatory and hypercoagulable state, exacerbating insulin resistance and lipolysis.[35] Hypoxia and autonomic nervous system alterations can contribute to electrical remodeling of the heart and myocyte injury. Oxyhemoglobin desaturation resulting from apneas and hypopneas further compromises oxygenation of myocardial tissue. Inspiratory efforts against a closed glottis (with OSA) additionally cause wide swings in intrathoracic pressure, negatively affecting preload and afterload and left ventricular (LV) transmural pressure, increasing myocardial oxygen consumption and impeding stroke volume. The pathophysiologic consequences of OSA are shown schematically in **Fig. 87.3** and further summarized later in this chapter.

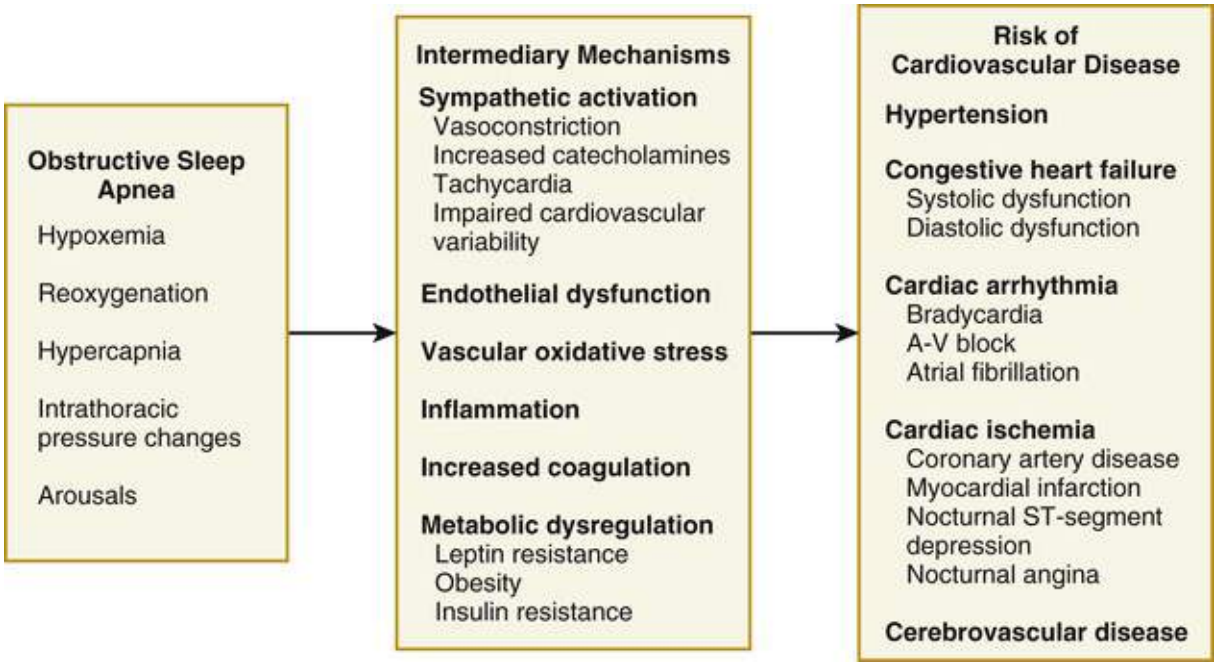


FIGURE 87.3 Schematic showing links among apnea-related physiologic stressors, intermediate mechanisms, and cardiovascular outcomes. (From Shamsuzzaman ASM, Gersh BJ, Somers VK, et al: Obstructive sleep apnea: implications for cardiac and vascular disease. JAMA 2003;290(14):1906-14.)

Sleep-Disordered Breathing and Hypertension

Approximately 30% of patients with essential hypertension (**see also Chapter 46**) and 80% of patients with resistant hypertension have OSA.[36] Conversely, more than 50% of patients with OSA have hypertension.[37] Patients with severe untreated OSA who are prescribed intensive antihypertensive therapy are at a 4-fold increased risk of elevated BP compared with patients with less severe OSA.[38] Although the aggregation of hypertension and OSA partially reflects common risk factors, experimental animal and human data indicate that OSA is causally associated with hypertension. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) identified OSA as a treatable cause of hypertension.[39]

OSA has both acute and chronic effects on BP.[40] Acutely, the BP and heart rate increase within 10 seconds of the termination of an apnea or hypopnea, corresponding to peak times of the arousal,

ventilation, and oxygen saturation nadir.[41] Frequent arousals trigger chemoreflexes and sympathetic output to the peripheral blood vessels, with consequent vasoconstriction, and altered renin-angiotensin-aldosterone system activity. Transient increases in BP can persist into the daytime. Chronic intermittent surges in BP also cause vascular remodeling.

OSA is associated with a nondipping overnight BP pattern, increases in daytime BP to prehypertensive and hypertensive ranges, and an increased risk of resistant hypertension.[42] "Dose-response" associations are reported. Specifically, a 1-unit increase in the AHI is estimated to increase the odds of nondipping systolic BP by 4%.[38] The Wisconsin Cohort Study, a prospective study of state employees, reported that the odds ratio, adjusted for obesity and other confounders, for the presence of hypertension after 4 years of follow-up was 2.9 for moderate or severe OSA.[43] Recent data indicate that it is the apneas and hypopneas occurring in REM sleep, rather than the AHI occurring across all sleep stages, that is associated most strongly with hypertension incidence.[44] During REM sleep, the sympathetic drive is highest, the muscular tone is lowest, and the respiratory events tend to last the longest and be associated with the most severe hypoxemia.

Over 30 randomized controlled trials have examined BP responses to continuous positive airway pressure (CPAP), the mainstay therapy for OSA.[45] Metaanalyses estimate that CPAP treatment reduces the systolic and diastolic BP by an average of 2 to 3 mm Hg and 1.5 to 2 mm Hg, respectively. Generally, studies reported larger effects for nocturnal BP than daytime BP, and in individuals who have high CPAP adherence or more severe OSA, or are younger, sleepier, or have resistant hypertension (with average BP improvements of 4 to 9 mm Hg). CPAP also can improve nondipping patterns, a well-established risk factor for all-cause mortality rates. The Heart Biomarker Evaluation in Apnea Treatment (HeartBEAT) study compared CPAP with supplemental oxygen therapy and usual care in patients with OSA at increased CVD risk, most of whom were under care by cardiologists and were using an average of 2.4 antihypertensive medications.[46] Relative to the usual care group, which included guideline-based management of CVD, the CPAP group experienced significant lowering of the 24-hour BP (by 2.4 mm Hg), with larger changes for the nocturnal BP (by 3.5 mm Hg). A metaanalysis of six studies that evaluated the influence of CPAP on resistant hypertension estimated that CPAP reduced the ambulatory 24-hour systolic and diastolic BP by 7.2 mm Hg and 5.0 mm Hg, respectively.[47] CPAP use in resistant hypertension also improved the nocturnal BP and nondipping patterns. To address the role of CPAP in reducing the incidence of hypertension, a multicenter trial conducted in Spain randomized 723 patients with moderate OSA but without significant sleepiness to CPAP or usual care.[48] Over a median of 4 years of follow-up, an intention-to-treat analysis showed no reduction in the incidence of hypertension or CVD events with CPAP. However, in an analysis of patients who used CPAP for 4 hours or more per night, a significant 31% reduction in incident hypertension or CVD was observed and the magnitude of the 24-hour BP improvement was related directly to the hours of CPAP use (each additional hour of CPAP use resulted in a decrease in the average systolic BP of 1.3 mm Hg).

The existing clinical trials highlight the importance of treatment adherence in achieving BP improvement. Other sources of variability in responses to OSA treatment include differences in residual apneic activity with treatment, severity of OSA, age, and cause of hypertension. The level of CPAP adherence needed to obtain a significant BP reduction is unknown. Although a minimum threshold of 4 hours of CPAP use per night is commonly targeted, more than 6 hours of CPAP use per night, including use during the late-night hours in REM sleep, is likely more effective. A variety of pathophysiologic processes contribute to hypertension, including insulin resistance, obesity, autonomic nervous system dysfunction, and variations in salt and fluid balance. OSA likely affects these mechanisms differently, and is likely to be more effective in certain subgroups. Different treatment responses also may reflect

variations in the duration of OSA prior to the initiation of treatment. Individuals who have had untreated OSA for years may undergo chronic remodeling of the vascular bed and changes in BP regulatory mechanisms that are not readily reversed with CPAP. Earlier treatment or a longer duration of treatment interventions than is commonly evaluated in clinical trials may be needed to observe larger BP improvements. A recent study showed that three microribonucleic acids predicted BP responses in patients with OSA and resistant hypertension, suggesting the potential usefulness of biomarkers for predicting responsive subgroups.[49]

Combining CPAP with other modalities, such as medications or weight loss, may have greater effects than single-modality therapy and also may be considered as a form of adjunctive therapy. Patients with hypertension and OSA have less improvement in the 24-hour BP than hypertensive patients without OSA. The addition of CPAP, when used for 4 hours or more per night, enhances the effects of pharmacotherapy in improving the BP.[50] Among obese patients with moderate OSA and elevations of C-reactive protein (CRP), a combination of weight loss plus CPAP proved more effective in lowering the BP than CPAP alone, suggesting the importance of concomitant lifestyle interventions in high-risk groups.[51]

Based on the existing evidence, hypertension guidelines identify OSA as a prevalent and modifiable cause of systemic hypertension.[39] Although average treatment effects are modest, long-term improvements of systolic BP by 2 to 3 mm Hg may reduce the risk of stroke and CHD by as much as 10%. Therefore, OSA treatment, especially when high levels of adherence are achieved and efficacy is greater, should have a beneficial population-level effect on adverse cardiovascular outcomes.

Sleep-Disordered Breathing and Coronary Heart Disease

SDB exacerbates atherosclerosis by triggering sympathetic nervous system activity, augmenting the release of proinflammatory proteins and contributing to dyslipidemia, insulin resistance, and endothelial dysfunction.[52-56] SDB-related episodes of recurrent hypoxemia activate leukocytes and endothelial cells, increase the expression of adhesion molecules, and lead to the release of oxygen free radicals.[57] Patients with SDB have elevations of proinflammatory mediators that are also implicated in atherogenesis, including transcription factor nuclear factor-kappa B, leukotriene B4, intercellular adhesion molecules, tumor necrosis factor-alpha (TNF-α), CRP, and interleukin-6 (IL-6). Prothrombotic markers (including fibrinogen, plasminogen-activating inhibitor-1, activated coagulation factors XIIa and VIIa, thrombin/antithrombin III complexes, and soluble P selectin) and markers of oxidative stress (overnight urinary 8-isoprostane levels, oxidized DNA, and neutrophil superoxide generation) also rise.[57] Many of these biomarkers vary in direct proportion to the severity of SDB-related hypoxemia. Although the extent to which biomarker elevations are independent of obesity or other confounders is not clear, several studies have demonstrated that SDB treatment with CPAP, even for as short a time as 2 weeks, reduces sympathetic activation, inflammation, oxidative stress, and endothelial dysfunction.[58]

Cardiac imaging provides insights into the association between OSA and subclinical CVD. The Multi-Ethnic Study of Atherosclerosis showed that after adjusting for multiple confounders, the coronary artery calcium burden (CAC > 400) was 40% more common in individuals with a physician diagnosis of sleep apnea than in controls. Furthermore, over 8 years, the CAC was more likely to progress in those with OSA than in those without SDB.[59] Polysomnography can characterize patterns of association between sleep-related stressors and the CAC. Higher CAC scores are associated with increases in the overnight arousal frequency and decreased time in state N3 sleep (slow-wave sleep, when sympathetic activity is

lowest and parasympathetic tone is lowest).[60]

In addition to contributing to the chronic atherosclerotic burden, OSA may cause acute ischemia because of both decreased oxygen delivery (secondary to obstructed breathing and hypoxemia) and increased oxygen consumption (associated with elevated diastolic and transmural pressures and cardiac hypertrophy).[61,62] Ischemic stressors may be most notable during the rebreathing phase of obstructive apneas, when large hemodynamic changes occur.[2] The fractional flow reserve, a quantitative measurement of coronary artery stenosis, can dynamically vary with obstructive apneas because of fluctuations in the intrathoracic pressure that affect the venous and aortic pressures and coronary perfusion.[63] Patients with intermediate coronary lesions may experience intermittent myocardial ischemia as a result of cyclical changes in the coronary blood flow. Endothelial damage and compromised coronary vascular conductance may ensue due to surges in the BP and heart rate associated with sympathetic activation and reduced endothelial production of nitric oxide.[64] Subclinical ischemia can be manifested on overnight electrocardiograms of patients with OSA, showing ST segment depression, which indicates nocturnal myocardial ischemia, and changes in QT dispersion, as well as paroxysms of ventricular tachycardia or atrial fibrillation that are associated temporally with the occurrence of apneas.[65-67] Women with OSA have elevated levels of high-sensitivity troponin, a marker of subclinical myocardial injury; the level of troponin is one factor in the risk for HF or death in untreated OSA.[68] In a prospective analysis of more than 10,000 individuals, patients with significant nocturnal hypoxemia had a nearly 2-fold increase in the risk of sudden cardiac death after potential confounders had been considered.[69] Individuals with OSA compared with those without OSA were more likely to experience a morning-peak onset of myocardial infarction[70] and die suddenly between midnight and 6:00 AM, the hours when apneas and hypopneas occur.[71]

More than 75% of patients presenting with acute coronary artery syndrome reportedly have SDB.[72] The contribution of SDB to ischemia in this setting is uncertain. Some research findings suggest that patients with SDB may develop a collateral coronary blood flow from periods of intermittent hypoxemia, with resultant angiogenesis,[73] which may reduce the extent of myocardial injury immediately following an ischemic event. In contrast, infarct sizes are reportedly higher 3 months after myocardial infarction salvage procedures in patients with OSA than in patients without OSA.[61]

Recent epidemiologic studies from across the world provide evidence that SDB is an independent risk factor for CHD. In the prospective Sleep Heart Health Study cohort, moderate to severe SDB was associated with a 35% increased incidence of CHD over 8 years; among men younger than age 70 years, this risk was 70%.[74] In over 5000 participants in the Multi-Ethnic Study of Atherosclerosis who were free of known CVD at baseline and followed for 7.5 years, a physician-diagnosis of sleep apnea was associated with a 1.9 increased adjusted hazard ratio for incident cardiovascular events and a 2.4-fold higher mortality rate.[75] Several studies from Spain followed patients referred to sleep laboratories for periods of 5 to 10 years. Among men, untreated severe OSA was associated with a 2.9-fold increased risk of fatal cardiovascular events and a 3.2-fold increased risk of nonfatal cardiovascular events compared with a control group. A prospective study of over 1000 women followed for a median time of 72 months showed that women with untreated mild to moderate or severe OSA also had significantly increased CVD mortality rates over those of controls; after adjusting for confounders, the mortality rate was 3.5-fold higher in women with severe OSA than in controls.[76] Patients with CHD who have OSA experience higher rates of major acute cardiovascular events than patients without OSA.[77,78] Untreated OSA is also associated with an increased need for a revascularization procedure as compared with rates in patients without OSA.[79,80]

Several large observational studies demonstrate that patients with severe OSA treated with CPAP have

significantly reduced rates of fatal and nonfatal CVD compared with untreated patients.[2] Patients with CHD treated with CPAP reportedly have lower rates of nocturnal ischemia, acute coronary syndrome, need for coronary revascularization, and death from CVD compared with untreated patients with OSA. Only three large randomized controlled trials have examined the role of CPAP in secondary prevention of CVD in patients with moderate to severe OSA. All studies excluded patients with significant sleepiness, and one also excluded those with severe overnight hypoxemia. Interventions were CPAP (or autotitrating PAP) or conservative therapy. Modest CPAP adherence limited all studies, and two were underpowered to detect moderate improvements. The first study, following 725 patients without CVD for a median of 4 years, did not find a benefit for the CPAP group. However, patients who used CPAP for 4 hours or more per night experienced a significant improvement in the composite study outcome (incidence density ratio, 0.72; 95% confidence interval [CI], 0.52 to 0.98) compared with controls and nonadherent patients.[81] The Randomized Intervention with Continuous Positive Airway Pressure in Coronary Artery Disease and OSA (RICCADSA), randomized 244 nonsleepy patients with established CHD and moderate or severe OSA to CPAP or usual care in a single European center.[82] At a median follow-up time of 57 months, the CPAP group compared with the usual-care group had a 20% nonstatistically significant reduction in the primary composite endpoint. When restricted to patients using CPAP for 4 hours or more per night, a significant 80% decrease in event rates was observed (HR, 0.29; 0.10 to 0.86). The multicenter international Sleep Apnea Cardiovascular Endpoints (SAvE) trial followed 2717 patients with a history of coronary artery or cerebrovascular disease for a mean of 3.7 years.[4] This study did not observe a difference in the primary composite endpoint. A subanalysis showed that individuals adherent to CPAP had a 40% significant reduction in cerebrovascular events compared with a propensity-matched subgroup from the usual-care group. The better effect for cerebrovascular disease than for the composite endpoint or CHD is in agreement with observational data showing stronger associations between OSA and cerebrovascular disease compared with CHD.[83]

The existing data suggest that CPAP is unlikely to improve CVD outcomes unless it is used for at least 4 hours per night. However, even if CPAP were used for shorter times, the SAvE study demonstrated that CPAP significantly improved the patient's quality of life and mood and resulted in fewer days of missed work, indicating that the effects of CPAP are beneficial in patients with CVD.[4] The results of these studies also emphasize the need to provide adherence support for patients prescribed CPAP. In patients with CVD, adjunctive behavioral therapies (e.g., motivational education) have demonstrated improvements of CPAP use by an average of 90 minutes per night.[84] The existing trials also indicate a need to further develop and evaluate alternatives to CPAP.

Sleep-Disordered Breathing, Cardiac Function, and Heart Failure

Both CSA and OSA are common in HF, present in up to 60% of HF patients.[17,85] CSA is the most common SDB variant associated with HF with a reduced ejection fraction (HFrEF), but OSA is predominant in HF with a preserved ejection fraction (HFpEF). Both conditions commonly occur in the same individual. Patients with a reduced ejection fraction without clinically significant HF also have a higher prevalence of SDB than age-matched individuals with normal cardiac function.[86]

There is a bidirectional relationship between HF and SDB (**Fig. 87.4**). In patients with HF, pulmonary vascular congestion, elevated peripheral and central chemosensitivities, and a prolonged circulation time can cause hyperventilation, with instability in ventilation leading to apneas.[9,17,87] Conversely, SDB may

adversely affect cardiac function by contributing to systemic and pulmonary hypertension, nondipping BP, atherosclerosis and ischemic injury, hypoxemia- and catecholamine-related myocyte injury, and cardiac remodeling. Hypoxia can trigger pulmonary vasoconstriction, which may increase the right ventricular afterload, cause right ventricular distention and leftward shift of the ventricular septum during diastole, impair left ventricular (LV) filling, and reduce the stroke volume and cardiac output.[88] SDB is increasingly recognized as a common cause of diastolic dysfunction, with effects attributable to chronic pressure overload, impaired coronary flow reserve, and inflammation leading to cardiac interstitial fibrosis.[89] Population studies show that the LV mass and LV mass volume ratio (concentric remodeling) increase in proportion to the severity of SDB, with associations stronger in adults younger than 65 years of age.[90] Indices of diastolic dysfunction, including an increased E/A ratio, reduced mitral deceleration, and isovolumic relaxation, are higher in patients with SDB compared with controls.[91-93]

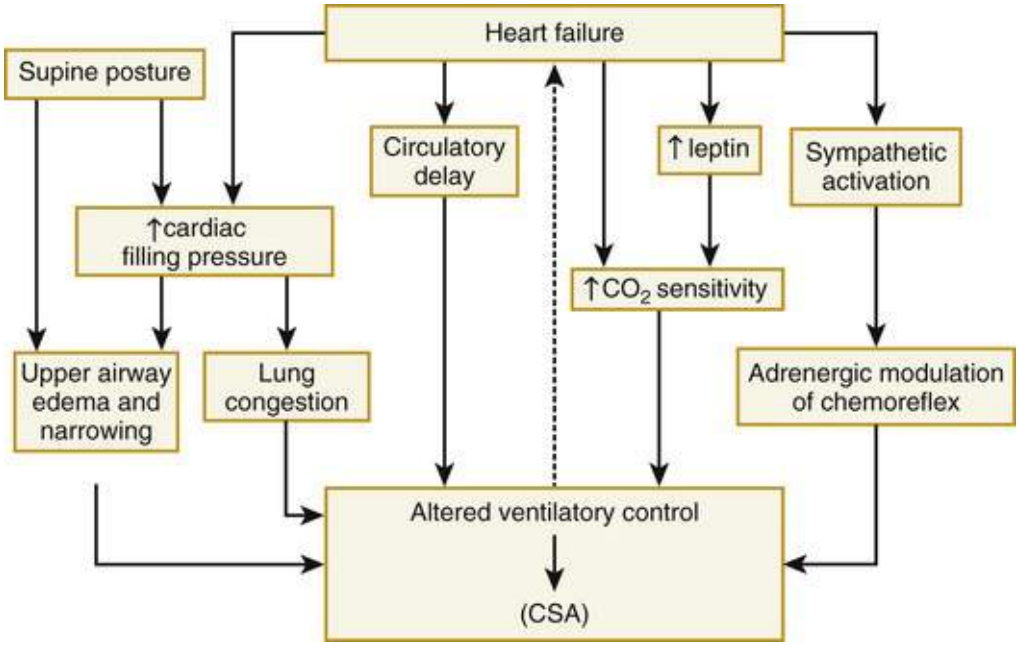


FIGURE 87.4 Schematic outlining possible mechanisms underlying development of central sleep apnea and the possible feedback from central sleep apnea resulting in exacerbation of heart failure. (From Somers VK, White DP, Amin R, et al: Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research [National Institutes of Health].Circulation 2008;118(10):1080-111.)

Prospective studies have shown that SDB independently predicts new-onset HF. Middle-aged men with severe SDB (predominantly OSA) have an estimated 60% increased 8-year incidence of HF compared with men without SDB. A 14-year prospective analysis of data from the Atherosclerosis Risk in Communities Study (ARIC) demonstrated that women with SDB have an approximately 30% increased incidence of HF or death compared with women without SDB, and also have an increased risk for developing LV hypertrophy. In older men, the Outcomes of Sleep Disorders in Older Men Study (MrOS) demonstrated that the presence of SDB predicted a nearly 2-fold increased incidence of HF.[94] However, in this study, the risk was related to the presence of CSA or Cheyne-Stokes respiration rather than OSA.

In patients with HF, SDB predicts HF exacerbations and progression, including an impaired quality of life, increased fatigue, a reduced functional status, more frequent hospitalizations, arrhythmias, and death.[95,96] CPAP treatment, by reducing the BP and improving oxygenation, subendocardial ischemia, the

preload and afterload, sympathetic activation, and inflammatory and oxidative stress, could improve cardiac function. Short-term studies demonstrate that PAP can reduce HF symptoms and improve the quality of life and functional status. A retrospective analysis of approximately 30,000 Medicare beneficiaries with newly diagnosed HF showed that treatment of SDB decreased rates of readmission, costs of health care, rates of mortality.[97] Small randomized controlled studies in HF also demonstrated that CPAP improved the vascular and myocardial sympathetic nerve function, myocardial energetics, and diastolic dysfunction.[2] A metaanalysis estimated that CPAP treatment in OSA and HF was associated with a 5.2% improvement in the LV ejection fraction.[98]

Given this evidence and the strong observational data and known physiologic effects of SDB on cardiac function, the American Heart Association published an HF guideline in 2013 that recommended screening patients with HF for SDB and treating those who test positive. Current treatment strategies include optimization of cardiac function, with a particular focus on minimizing the fluid overload, and weight loss as appropriate. Exercise and elastic stockings can help prevent rostral redistribution of fluid. Although PAP is indicated for OSA, there is uncertainty on how to treat CSA/Cheyne-Stokes respiration in patients with HFrEF. The CSA may improve after intensive HF treatment with pharmacotherapy and cardiac resynchronization therapy.[99] The Canadian Positive Airway Pressure (CANPAP) study demonstrated that CPAP improved several intermediate endpoints in patients with CSA and HFrEF (ejection fraction, catecholamines), but did not improve mortality rates. A post hoc analysis suggested improved heart transplant-free survival in patients in whom CSA was suppressed.[100] Based on this observation, two multinational studies evaluated the role of adaptive servoventilation (ASV), a pressure device that delivers autoadjusting pressure support on a breath-by-breath basis and can suppress both obstructive and central apneas (which are more difficult to suppress with CPAP).[101] The first trial (SERVE-HF trial), conducted in 1345 patients with symptomatic HF, an LV ejection fraction of less than 45%, and moderate or severe CSA, unexpectedly showed a 34% increase in CVD mortality rates.[102] In 2015, an advisory was issued against the use of PAP for treatment of patients in whom CSA predominates in the setting of HFrEF with an ejection fraction of less than 35%. A second ongoing trial, Effect of ASV on Survival and Hospitalizations (ADVENT-HF), is testing an alternative ASV device in patients with OSA or CSA. Other therapies under investigation are transvenous phrenic nerve stimulation (PNS) and nocturnal oxygen supplementation (NOS). The results of a 6-month efficacy study of PNS are promising, with improved indices of SDB.[103] NOS therapy can stabilize breathing in patients with CSA and improve intermediate markers of cardiac function and quality of life[104]; ongoing larger trials are being planned.

Sleep-Disordered Breathing and Cardiac Arrhythmias

Patients with SDB are predisposed to ventricular and atrial arrhythmias because of underlying cardiac risk factors and cardiac disease, as well as to the specific SDB-related stressors of intermittent hypoxemia, acidosis, surges of sympathetic nervous system activation, and swings in intrathoracic pressures.[105-107] Susceptibility to atrial arrhythmias also reflects the vulnerability of the atrial walls to swings in intrathoracic pressure and mechanoreceptor activation, as well as sensitivity of the pulmonary vein ganglia to autonomic stimulation.[106] Bradycardia and atrioventricular block may occur secondary to vagal stimulation accompanying apneas and hypoxemia.

Abnormalities of P wave morphology and QT dispersion, indicative of underlying electrical conduction problems, have been observed in the overnight recordings of patients with SDB.[108,109] Moreover, apneas and hypopneas appear to be direct triggers of paroxysms of ventricular tachycardia and

atrial fibrillation. Analysis of the temporal patterns of overnight arrhythmias demonstrated a 17-fold increased rate of arrhythmias occurring after an episode of apnea compared with a period of normal breathing.[67] Based on this analysis, a patient with moderate OSA (AHI 25) is estimated to experience one episode of a significant arrhythmia every 6 months attributable to apneic activity. In community studies, moderate or severe OSA was associated with a 2- to 4-fold increased risk of nocturnal arrhythmias; this finding suggested a basis for the observed increase in nocturnal sudden cardiac death in SDB.[105] The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) showed that 18% of 10,132 patients in the registry with atrial fibrillation had an OSA diagnosis.[110] Patients with OSA had a higher rate of severe or disabling symptoms, a history of more aggressive atrial fibrillation therapies, and higher hospitalization rates. Among patients referred to cardiology clinics for atrial fibrillation, patients with SDB experience increased rates of recurrent atrial fibrillation; with CPAP treatment, rates decrease to the levels observed in patients without SDB.[111] Patients with SDB compared with those without SDB have an increased occurrence of atrial fibrillation following pulmonary vein ablation procedures or coronary artery bypass graft surgery, suggesting that untreated SDB is an important prognostic factor.[106,112-117] The degree of hypoxemia appears to be a potent stimulus for ventricular arrhythmias,[118] sudden cardiac death,[69] and recurrence of atrial fibrillation following cardioversion.[111]

A metaanalysis estimated that CPAP use in patients with OSA reduces the atrial fibrillation risk by 44%.[117] Uncontrolled studies indicate that CPAP treatment is associated with a significantly decreased recurrence rate of AF after electrical cardioversion or ablative therapies and reduces the likelihood of progression to more permanent forms of atrial fibrillation. A high frequency of central apneas predicts nocturnal atrial fibrillation and incident atrial fibrillation in individuals without clinically apparent cardiac disease.[119] These findings have influenced a consensus panel to identify OSA as an atrial fibrillation risk factor,[120] and they support the growing interest in screening patients undergoing evaluation for pulmonary vein isolation for SDB. The high rate of atrial fibrillation recurrence in untreated patients has discouraged the use of ablation procedures until OSA is treated with CPAP.

Future Perspectives

SDB is highly prevalent in patients with hypertension, coronary artery disease, HF (with or without a reduced ejection fraction), atrial and ventricular arrhythmias, and stroke. The profound nightly disturbances that occur with SDB cause a range of physiologic disturbances that adversely affect the cardiac structure and function, and likely exacerbate the incidence and progression of these diseases. Treatment of OSA can improve the BP, ejection fraction, ventricular ectopy, and recurrence rate of atrial fibrillation and can also improve the quality of life and mood in patients with CVD. The existing data indicate that patients with OSA who successfully use CPAP have reduced rates of resistant hypertension and experience improved outcomes, including fewer cardiac and cerebrovascular events and lower mortality rates. Although the impact of directly treating CSA on cardiovascular outcomes remains uncertain, the presence of CSA potently predicts increased mortality rates, and patients with CSA and HF may benefit from intensive HF therapy. Cardiologists may be increasingly involved in recognizing SDB and can use information on its pathophysiologic effects to tailor interventions and inform chronic disease management strategies.

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PART X
Cardiovascular Disease in Special Populations

OUTLINE

88

Cardiovascular Disease in the Elderly

*Daniel E. Forman, Jerome L. Fleg *, Nanette Kass Wenger*

Aging predisposes people to cardiovascular disease (CVD), as well as to multiple comorbidities that intertwine and fundamentally alter the management of CVD.[1] Geriatric cardiology is a subdiscipline of cardiology that is oriented to the distinctive complexities and needs of older cardiovascular (CV) patients.[2] On average, patients with CVD are living longer than in previous eras, and the principles of geriatric cardiology are therefore increasingly relevant for all CV providers (**see also Chapter 45**).

Successes in medical care as well as advances in prevention and public health have contributed to sizable increases in longevity. In 1900 in various countries, the usual lifespan was 25 to 50 years,[3] but it has now increased throughout the world.[4] In the United States, the number of people 65 years of age or older was barely 3 million in 1900, but it is now about 46 million, and it is expected to be almost 84 million by the year 2050.[5] The subgroup of persons who are 85 years of age or older is the most rapidly increasing demographic group in the world. In the United States, this very old subgroup was only about 0.2% of the total population in 1900, but it is anticipated to reach 5% to 6% by 2050.

Older adults, even those with no prior CVD or CVD risk factors, are likely to develop CVD as a progression of the physiologic and pathologic changes in old age.[6] The prevalence of coronary heart disease (CHD), heart failure (HF), atrial fibrillation (AF), peripheral arterial disease (PAD), and most other types of CVD escalates in relation to age, reflecting distinctive physiologic vulnerabilities. Some types of CVD (e.g., aortic stenosis and sick sinus syndrome) arise almost exclusively in old age. Age-related vulnerability to CVD is compounded by cumulative CVD risk factors over a lifetime.[7]

Approximately 70% of those age 65 years or older in the United States have CVD, including 85% of those 80 years of age or older.[8] This means that there are a disproportionate number of hospitalizations, procedures, and costs, as well as more use of health care resources, among the elderly.[9] The mortality rates associated with CVD also escalate; adults 75 years of age or older make up only about 6% of the current U.S. population but account for over 50% of CVD deaths. Even when treatments go well, detrimental consequences are more likely to occur. CVD is a common precursor to functional decline, frailty, diminished independence, and disability[10]; many older patients who are ostensibly “successfully treated” by standard metrics still end up living in long-term care facilities for the rest of their lives. Subclinical CVD manifestations may also occur that predispose elderly people to an insidious decline in physical and cognitive function, frailty, and other detrimental clinical sequelae.[11]

What Is Aging?

Aging is customarily measured in chronological years, but the broad concept of aging is significantly more complex than years alone would indicate.[1] Fundamental aspects of aging are determined by the mounting toll of biologic stresses over time (e.g., oxidative stress, inflammation) in juxtaposition to diminishing homeostatic capacities (contingent on telomere length, gene expression, and other biologic factors). The progression of aging is moderated by each person's lifelong health habits (e.g., nutrition, physical activity, sleep, alcohol), CVD risk factors (e.g., blood pressure, cholesterol, tobacco, weight), comorbidities (e.g., infections, metabolic diseases, chronic kidney disease [CKD], chronic obstructive pulmonary disease [COPD]), psychological status (e.g., depression, anxiety), social structure (e.g., spouse, children), and functional capacity (e.g., physical, cognitive). Although chronological years are immutable, other aspects of aging can often be modified. Habitual exercise, for example, fundamentally reduces the trajectory of aging[12] and the susceptibility to age-related CVD.

Age-Associated Changes in Cardiovascular Structure and Function

To better understand the distinctions of CVD in old age, it is important to clarify basic physiologic principles that modify the baseline health and affect disease. Although age-associated changes in CV structure and function are commonly characterized as “normal,” there are intrinsic changes that resemble early disease (e.g., stage 1 hypertension and early atherosclerosis). Essentially, CV aging and CVD interconnect as parts of a continuum, with underlying molecular links.[6] Lakatta describes a progression of abnormal molecular signaling within the DNA environment of aging vascular cells to a compensatory physiology that progressively morphs toward disease. The abnormal molecular signals, sensing, and responses result in abnormal transcription, cell renewal, and proteostasis. Renin-angiotensin-aldosterone signaling and proinflammatory cytokines are homeostatic responses that help to limit molecular abnormalities, but they also increase the allostatic load on the CV system and gradually predispose a person to CVD (**Fig. 88.1**).[6]

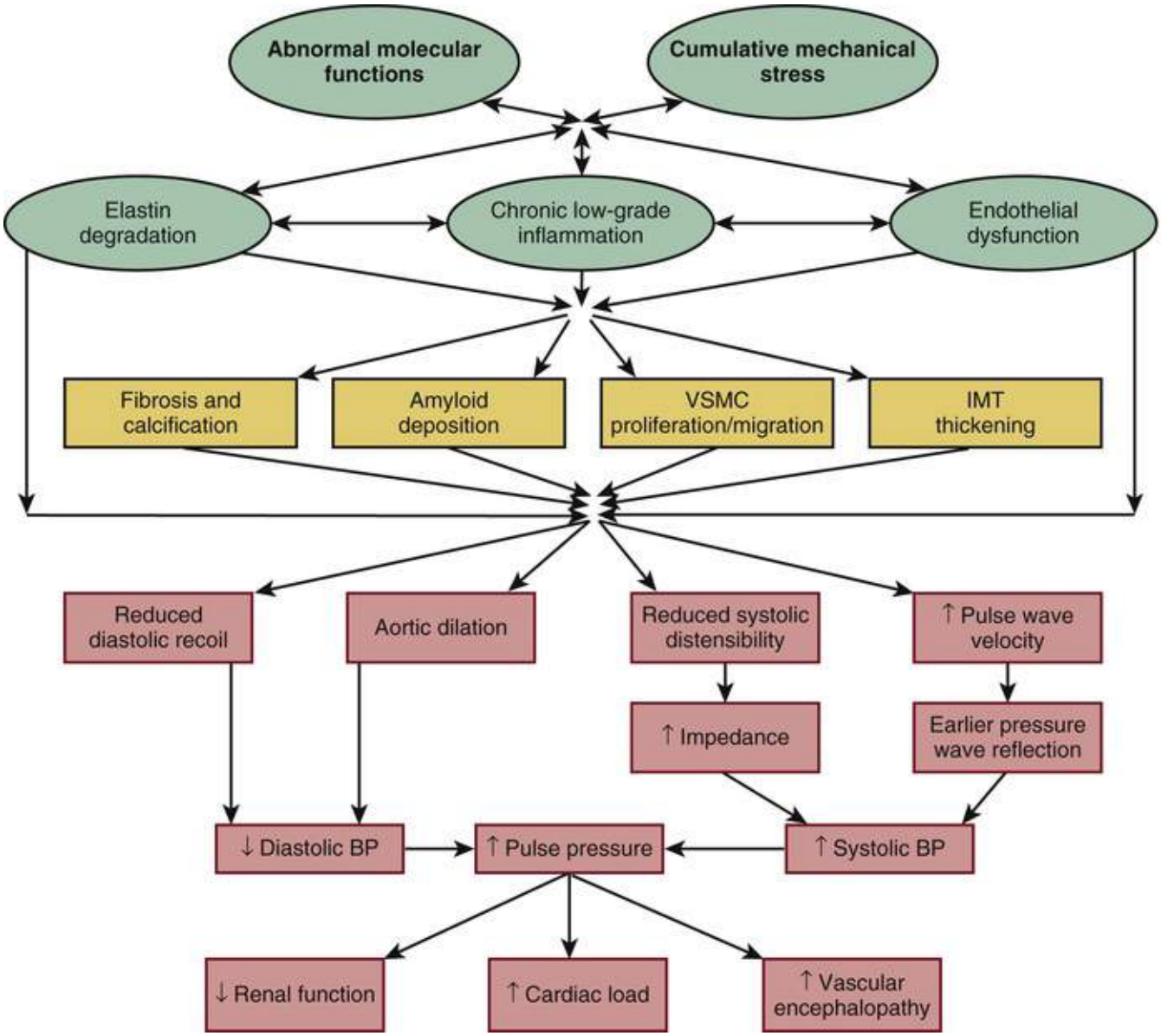

FIGURE 88.1 Conceptual model of arterial aging and arterial decline. Age-associated molecular disorders and cumulative mechanical stress lead to a state of chronic inflammation, elastin degradation, and endothelial and VSMC dysfunction. Downstream effects result in arterial wall calcification, fibrosis, amyloid deposition, VSMC proliferation, and intimal-medial thickening. These structural changes lead to functional alterations that result in widened pulse pressure. The increase in pulsatility leads to increased left ventricular load, chronic kidney disease, and vascular dementia. (Modified from Lakatta EG. So! What's aging? Is cardiovascular aging a disease? J Mol Cell Cardiol 2015;83:1-13.)

Vasculature

Prominent structural and functional changes affect the arterial system in older adults, even those with no apparent CVD. The arterial wall media thickens because of smooth muscle cell hypertrophy, extracellular matrix accumulation, and calcium deposition. Intimal-medial thickness (IMT) increases nearly 3-fold between the ages of 20 and 90 years in normotensive individuals.[13] The range of IMT also increases with age, suggesting a variable response to aging, likely due to different genetic and lifestyle factors.

Along with increased IMT, advancing age leads to fraying of elastic fibers, as well as increases in collagen content and enzymatic cross-linking in the media that reduces arterial distensibility and increases stiffness.[14] Irreversible nonenzymatic glycation-based cross-linking of collagen forms advanced glycation end products (AGEs) that exacerbate the stiffening.

Changes in both vasodilating nitric oxide (NO) and vasoconstricting angiotensin II also contribute to

vascular aging. Age-dependent reductions in endothelium-dependent vasodilation have been attributed to reduced NO production.[14] Animal studies show both lower NO levels and reduced NO, consistent with reduced endothelial NO synthesis. Conversely, angiotensin II in the vessel wall increases 1000-fold with substantially increased angiotensin II signaling.

Both oxidative stress and chronic low-grade inflammation are key mediators of the structural and functional changes in the arterial wall with aging (**see also Chapter 44**). Oxidative stress results from excessive generation of reactive oxygen species by enzymes such as NADPH oxidase, uncoupled NO synthase, and xanthine oxidase by the mitochondrial transport chain and from reduced antioxidant capacity.[15] Increased reactive oxygen species and dysfunctional endothelial NO synthase contribute to age-associated decrements in endothelium-mediated vasodilation. Elevated oxidative stress also leads to enhanced protein oxidation, activation of inflammatory and endoplasmic reticulum stress responses, and apoptosis.

As a result of structural and functional changes in the arterial walls, stiffening of large and medium-sized arteries occurs with aging, independent of disease. Even when pressures are within the normotensive range, the systolic blood pressure (SBP) generally rises. However, in the majority of older adults, the SBP progresses into the hypertensive range (**see also Chapter 46**). In contrast, the diastolic blood pressure (DBP) tends to rise until the sixth decade and declines thereafter because of the reduced elastic recoil from the stiffer large arteries (**Fig. 88.2**).[14] High blood pressure in older adults is therefore typically manifested as isolated or predominant SBP elevation. The pulse pressure, the difference between SBP and DBP, also increases, augmenting the pulsatile load on the heart and vasculature. Several studies suggest that pulse pressure is a more potent predictor of CV events in middle-aged and older adults than either SBP or DBP.[13]

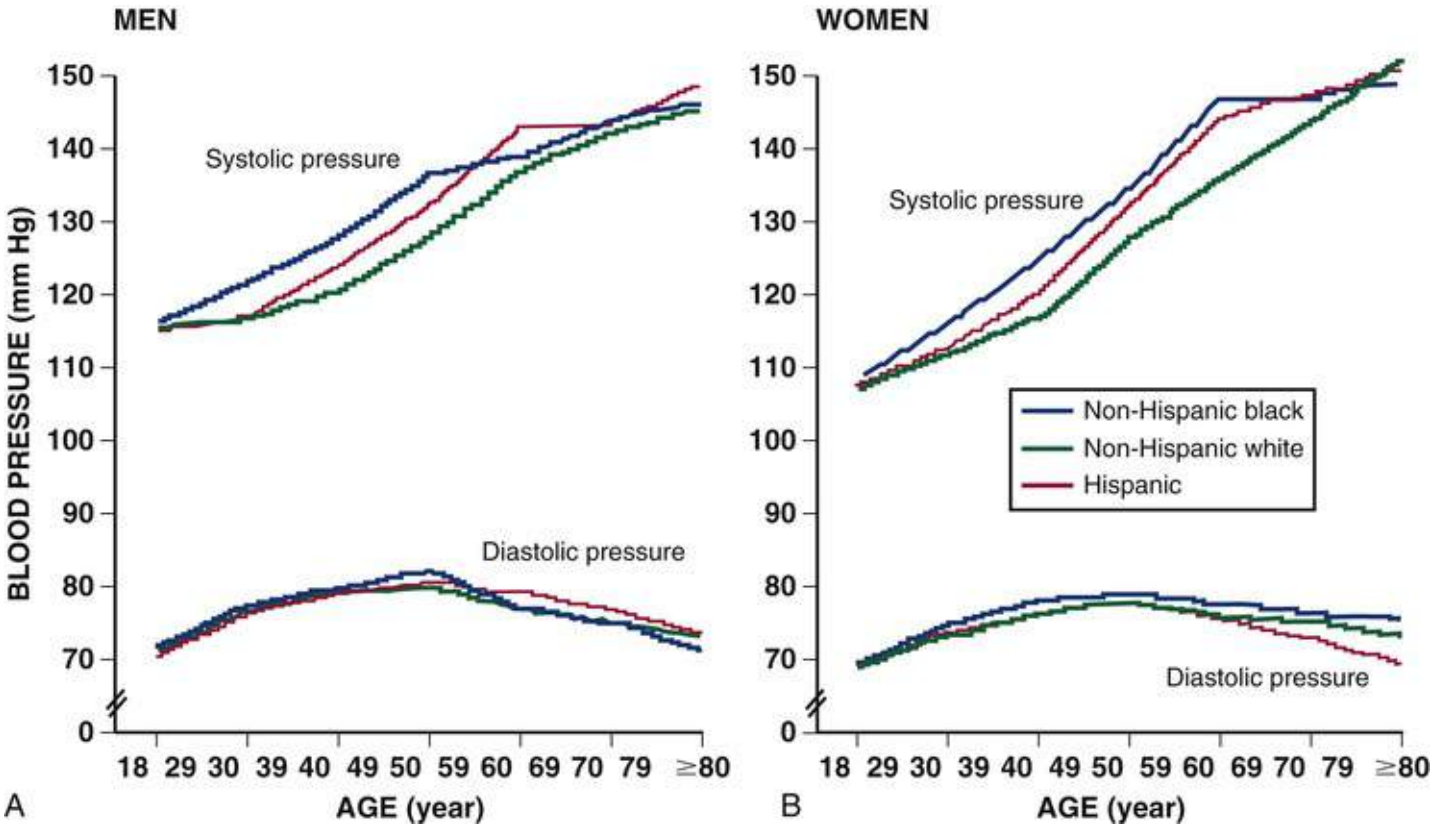

FIGURE 88.2 Age-associated changes in blood pressure in men and women by race and ethnicity. (From Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Circulation 2011;123(21):2434-2506.)

The pulse wave velocity (PWV), the speed with which an arterial pulse wave traverses the arterial tree, is another index of arterial stiffness that provides insights regarding aging changes in the arterial system; PWV is typically measured between the carotid and femoral arteries. Aortofemoral PWV increases 2- to 3-fold across the adult lifespan in normotensive populations. Studies in both healthy cohorts and those with CVD have shown that a higher PWV predicts future CV events, independent of the blood pressure.[14]

Left Ventricular Composition and Mass

In younger adults, the heart is composed of approximately 25% cardiomyocytes and a complex structure of connective tissue. With aging there is a decrease in the total number of cardiomyocytes, likely due to apoptosis, as well as an increase in their individual sizes (i.e., hypertrophy).[13] In both animal and human studies, apoptotic myocytes were more prevalent in the hearts of older males compared with females, paralleling an age-related decline of left ventricular (LV) mass in men but not in women. Within the connective tissue, the collagen content, fibrosis, and deposition of cardiac amyloid and lipofuscin all increase. The heart therefore becomes more fibrotic and stiffer with age (i.e., greater passive and active tension).[13]

Left Ventricular Wall Thickness, Cavity Size, and Shape

Despite the absence of an increase in cardiac mass with aging, there is a significant increase in myocardial thickness,[13] particularly due to increased cardiomyocyte size. Although concentric LV hypertrophy occurs, the interventricular septum increases in thickness more than the free wall, and there is

a change in LV shape. A magnetic resonance imaging (MRI) study in healthy volunteers demonstrated shortening of the left ventricle along its long axis and a shift from an elongated prolate ellipsoid geometry to a more spherical left ventricle with age.[13] Because a more spherical ventricle is exposed to higher wall stress, the age-associated change in cardiac shape has important implications for contractile efficiency. Greater LV sphericity is associated with a higher incidence of LV dysfunction and HF (**see also Chapter 23**) A large cardiac MRI study shows age-related declines in both LV diastolic and systolic volumes and an increased LV mass/volume ratio in both sexes.[13]

Resting Cardiac Function

In healthy normotensive adults, the resting echocardiographic LV shortening fraction and radionuclide LV ejection fraction (LVEF), the two most commonly used measures of global LV systolic performance, are not age related.[13] Prolonged contractile activation of the thickened LV wall maintains a normal ejection time, and compensates for the late systolic augmentation of the blood pressure, preserving the systolic LV pump function despite increased arterial stiffness. In contrast, LV diastolic performance is prominently altered by aging. Whereas LV diastolic filling occurs primarily in early diastole in younger adults, the transmitral early diastolic peak-filling rate declines by 30% to 50% between ages 20 and 80 years.[13] Conversely, there is an age-associated increase in peak A-wave velocity, which represents late LV filling facilitated by atrial contraction. The increase in late LV filling is mediated via a modest age-associated increase in left atrial size.[13]

Although age-related delays in the early diastolic filling rate do not usually compromise the end-diastolic volume and stroke volume at rest, stress-induced tachycardia (e.g., with exercise, fever, or other physiologic stress) is likely to exacerbate diastolic filling abnormalities. Tachycardia not only disproportionately shortens the time available for diastolic filling, but also exacerbates the impaired energy-dependent uptake of calcium into the sarcoplasmic reticulum. Therefore, fast heart rates are commonly associated with diastolic filling abnormalities, and the higher LV diastolic pressure is transmitted into the lungs despite a normal resting LV systolic function. These findings are commonly manifested as HF with a preserved ejection fraction (HFpEF), especially when superimposed on other common age-associated comorbidities such as hypertension, diabetes, CHD, and AF (**see also Chapter 26**).

The enlargement of the left atrium that occurs as a function of age and diastolic dysfunction occurs primarily after age 70 years[13] and increases the susceptibility of older adults to AF. Whereas AF is often well tolerated in many younger adults, it is more likely to provoke symptoms and clinical events among the elderly. Not only is AF commonly associated with poorly tolerated fast ventricular rates, but the AF-induced loss of the atrial boost to diastolic filling aggravates age-related diastolic filling impairment. Thus, older patients with AF are more likely to have a reduced cardiac output and resultant dyspnea and fatigue than younger individuals (**see also Chapter 38**).

Age-associated myocardial changes also predispose some older adults to myocardial ischemia and HF. A thicker left ventricle predisposes to subendocardial ischemia by increasing the distance between the epicardial coronary arteries and the subendocardial myocytes. In addition, capillary growth and flow regulation in older hearts may not match the oxygen demands of the hypertrophied myocytes (in contrast to cardiac hypertrophy in young athletes). These intramyocardial changes in capillarity and flow dynamics are compounded by peripheral arterial stiffening and an accelerated PWV (i.e., faster reflected pressure waves now arriving in systole, such that subendocardial perfusion is no longer bolstered by augmented pressures in diastole).[14]

Amidst aforementioned age-associated changes in the vasculature and heart, especially when compounded by prolonged exposure to other CVD risk factors, the occurrence of CVD increases dramatically in older adults (**Table 88.1**).[13] Intrinsic vulnerability to atherosclerosis in the vasculature predisposes to myocardial ischemia, myocardial infarction (MI), stroke, and PAD. Heart failure with a reduced ejection fraction (HFrEF) may develop as the result of ischemic coronary events or prolonged hypertension, either of which can impair LV systolic function. However, HFpEF is more likely to develop in the setting of ventricular stiffening, especially in association with hypertension, AF, and diabetes, all of which increase in frequency with age. Furthermore, CV aging occurs in a context of other age-related changes that compound the effects of CVD (**Table 88.2**)[13] (**see also Chapter 26**). Risks of myocardial ischemia and HF are, for example, considerably worsened in the presence of concomitant renal, metabolic, hematologic, pulmonary, and other noncardiac physiologic changes.

TABLE 88.1

Relationship of Cardiovascular Aging in Healthy Humans to Cardiovascular Disease

AGE-ASSOCIATED CHANGES	PLAUSIBLE MECHANISMS	POSSIBLE RELATIONSHIP TO DISEASE
CV Structural Remodeling		
↑ Intimal-medial thickness	↑ VSMC migration and matrix production	Early stages of atherosclerosis
↑ Vascular stiffness	Elastin fragmentation ↑ Elastase activity	Systolic hypertension
	↑ Collagen production and cross-linking	
	Altered growth factor regulation and tissue repair	Atherosclerosis
↑ LV wall thickness	↑ LV myocyte size	↓ Early LV diastolic filling
	↓ Myocyte number Focal collagen deposition	↑ LV filling pressure/dyspnea
↑ Left atrial size	↑ Left atrial volume/pressure	↑ Risk of atrial fibrillation
Calcium deposits in valves and conduction system	Mechanical stress	Aortic stenosis Atrioventricular block
CV Functional Changes		
Altered vascular tone	↓ NO production/effects	Vascular stiffening/hypertension
	↓ βAR responses	
↓ CV reserve	↑ Vascular load	Lower threshold for heart failure

βAR, beta-adrenergic receptor; CV, cardiovascular; LV, left ventricular; VSMC, vascular smooth muscle cell.

TABLE 88.2

Common Age-Related Changes That Compound Cardiovascular Disease Risks

Kidneys	↓ Glomerular filtration rate ↓ Renal metabolism
Lungs	↓ Ventilatory capacity ↑ Ventilation/perfusion mismatching
Musculoskeletal	↓ Skeletal muscle mass and function (sarcopenia) ↓ Protein reserves ↓ Bone mass
Immune function	↑ Susceptibility to infections
Hematopoietic	↑ Levels of coagulation factors ↑ Platelet aggregability ↑ Inhibitors of fibrinolysis ↑ Anemia
Neurohormonal	↓ Cerebral autoregulatory
Liver	↓ Hepatic metabolism
Mood	↑ Depression ↑ Anxiety
Sleep	↑ Obstructive sleep apnea

Cardiovascular Response to Exercise

The ability to perform physical exercise is highly relevant in clinical evaluation, especially in older

adults. The CV response to exercise is a well-established metric for diagnosis, prognostication, and monitoring of patients with CVD. It is also strongly predictive of the ability of older individuals to withstand major procedures or aggressive therapies (**see also Chapter 13**).

Aerobic Exercise Capacity

Numerous studies have demonstrated that cardiorespiratory fitness (oxygen consumption [VO_2] max per kg weight at peak exercise) declines markedly with age. In cross-sectional studies, the decline is approximately 50% from the third to ninth decade. In longitudinal studies, a more pronounced age-associated VO_2max decline is evident, regardless of habitual physical activity levels (**Fig. 88.3**).[13] The decline is only partially explained by changes in maximal heart rate and other CV parameters. Sarcopenia, the age-related atrophy and weakening of skeletal muscle, contributes significantly to the age-associated decrease in VO_2max. Age-related sarcopenia involves a reduced number, size, and function of muscle fibers. By age 75 years, muscle mass typically represents approximately 15% of body weight compared with 30% in young adults. Fast-twitch fibers atrophy to a greater extent than slow-twitch fibers, which likely contributes to decrements in strength that are proportionally greater than the loss of muscle mass. Increased intramuscular fat and decreased mitochondrial bioenergetics contribute to reduced muscle function.[16] Effects of CVD (most notably HF) on skeletal muscle compound the effects of sarcopenia.[17]

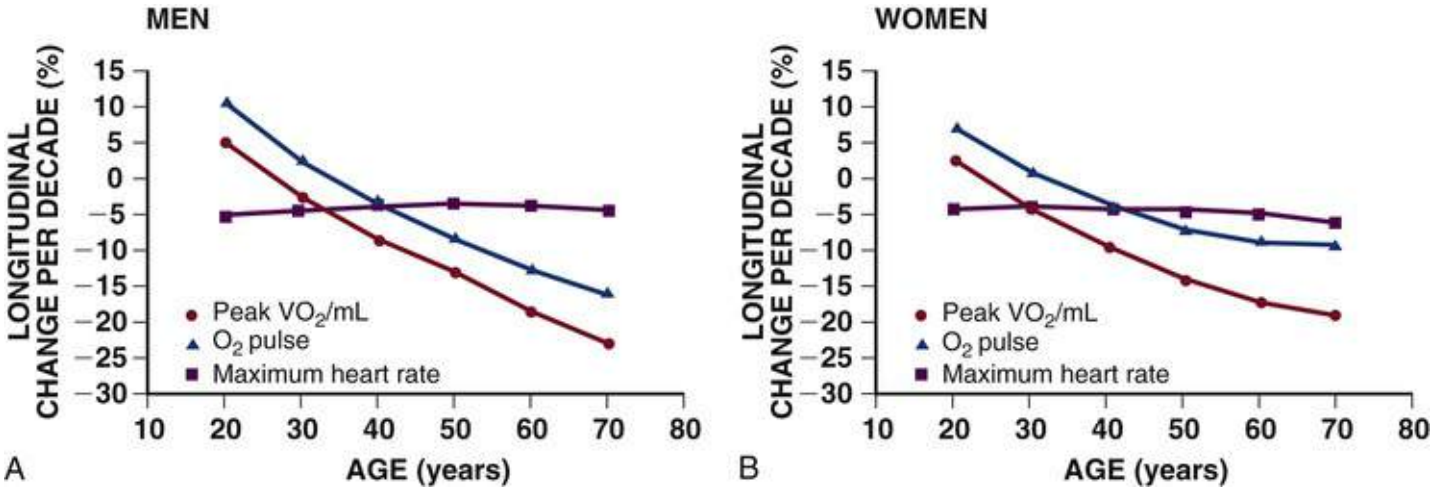

FIGURE 88.3 Longitudinal changes in peak oxygen consumption and its components, maximal heart rate, and oxygen pulse in healthy volunteers. Although the decrease in heart rate remained relatively constant over time, at approximately 5% per decade, an accelerated age-associated decline occurred in oxygen pulse that parallels that seen for peak oxygen consumption. (From Fleg JL, Strait J. Age-associated changes in cardiovascular structure and function: a fertile milieu for future disease. Heart Fail Rev. 2012;17(4-5):545-54.)

The accelerated decline of aerobic capacity with age has important implications regarding functional independence and quality of life (QOL). Because many of the activities of daily living require fixed aerobic expenditures, they require a significantly larger percent of VO_2max in older than younger adults. When the energy required for an activity approaches or exceeds the aerobic capacity of an elderly individual, he or she will be less likely to perform it.

Cardiac Function During Exercise

A decline of approximately 50% in the peak VO_2 between the ages of 20 and 80 years was accompanied

by a decline of approximately 30% in cardiac output and approximately 20% in arteriovenous uptake. The decrease in cardiac index with age at maximal effort was due primarily to a reduced heart rate because the LV stroke volume is preserved in men and women.[13] Although older individuals have a blunted capacity to reduce LV end-systolic volume and to increase LVEF with exercise, this deficit is offset by a larger end-diastolic volume[13] (i.e., a slower heart rate allows more time for LV filling, and thus a greater amount of blood remains in the heart at end diastole). Although slower LV diastolic filling is a normal aspect of aging, inability to increase the LV end-diastolic volume during exercise is suggestive of cardiac pathology. Mechanisms for the age-associated reduction in maximal LVEF include reduced intrinsic myocardial contractility, increased arterial afterload, arterial-ventricular load mismatching, and blunted sympathetic modulation of LV contractility and arterial afterload.[13,14] These changes contribute to susceptibility to CVD, and adversely affect its prognosis.

Geriatric Domains Pertinent to Cardiovascular CARE

Just as physiologic changes that occur with age determine distinctive CVD vulnerabilities and complexities, geriatric syndromes can play a determinative role that affects disease physiology, presentation, and management. Multimorbidity, polypharmacy, frailty, disability, delirium, and the presence of other geriatric syndromes fundamentally affect CVD, cause differences in CVD in older adults and younger adults, and even cause differences from one older CVD patient to another. Precepts of evidence-based CVD therapeutic strategies often lose applicability as geriatric syndromes transform prototypical CVD concerns (**Table 88.3**).

TABLE 88.3

Geriatric Syndromes and Clinical Implications

GERIATRIC SYNDROME	DIAGNOSIS	PROGNOSIS	DISEASE MANAGEMENT	PROCESS OF CARE
Multimorbidity: Chronic diseases (diabetes mellitus, arthritis, COPD), as well as geriatric syndromes (falls, incontinence, sarcopenia)	Affects or complicates disease presentation	Confounds CVD risk assessment ↓ Short- and long-term disease prognosis	Primary management of CVD may exacerbate comorbid conditions Coexisting diseases may preclude guideline-directed therapies	Multiple providers Conflicting medical priorities Care for CVD may exacerbate another problem Requires working across specialties
Polypharmacy: ≥4 chronic medications	Drug-drug or drug-disease interactions	↑ Adverse events, hospitalizations, deaths	Overtreatment and poor adherence are likely Impacted by age-related changes in pharmacodynamics and/or pharmacokinetics	Drug complexities Across transitions Between providers Over different systems and types of care
Frailty	Multiple frailty metrics with different rationales: Fried frailty phenotype: ↓ Weight, ↓ energy, ↓ physical activity, ↓ speed, ↓ strength Parsimonious measures that incorporate Fried precepts: gait speed, short physical performance battery Frailty Index based on cumulative deficits	Increased vulnerability to adverse outcomes (from disease or therapy) ↑ Risk of procedural and therapeutic complications ↑ Risk of disability, falls, hospitalization, death	Crucial to recognize as part of shared decision making Potentially modifiable with exercise and diet	Frailty affects all aspects of CVD care Decision making Risk assessment Recovery ↑ Value of rehabilitation
Disability	Inability to care for oneself or to manage one's own home Diagnostic tools: Katz Index of Independence in Activities of Daily Living (ADL); Bristol ADL Scale Lawton Instrumental Activities of Daily Living (IADL) Scale; Barthel IADL Index	↑ Risk of adverse outcomes, complications, death	↓ Functional status leads to reduced capacity for self-care (e.g., difficulties with medication administration and/or self-monitoring)	Acute CVD event may precipitate worsening in functional status Poor health care transitions
Delirium	Disturbed attention Predisposing risks include cognitive deficit, sensory limitations, disorienting medications Confusion Assessment Method (CAM)	↑ Length of stay ↑ Death ↓ Shared decision making	Optimize environment to increase orientation, avoid sedation, reduce medications, reduce pain Optimize safety	Can manifest as agitated state or quiet and withdrawn state

COPD, chronic obstructive pulmonary disease; *CVD*, cardiovascular disease.

Multimorbidity

Multimorbidity, or the presence of “multiple chronic conditions,” implies a situation in which two or more chronic conditions are active. For therapies to achieve outcomes that are perceived by a patient with multimorbidity as having value, they must usually address all of the many conditions.[18] Thus, multimorbidity fundamentally transforms the CVD therapeutic paradigm, which would be oriented primarily to CVD-specific care and which may fail to address comorbid conditions or even make them worse.

Multimorbidity increases with age and is prevalent in more than 70% of adults age 75 years or older[19]; in up to 90% of older HF patients,[20] it challenges the basic principles underlying conventional CV management. “Evidence-based” CVD guidelines often rely on investigations that in the past chose study populations with few, if any, comorbidities. Such rigorous selection of study populations allowed delineation of therapies for specific diseases free from the confounding effects of comorbid states. Such evidence-based therapy guidelines are less meaningful when they are applied to clinical circumstances in which multiple diseases and medications are present in older patients (as is commonly the case). In these

groups, they are likely to engender interactions and complexities that were never studied originally. In a study of Medicare patients,[21] the dyad of hypertension and hyperlipidemia was present in 53%; among patients with HF, stroke, or AF, 50% had five or more comorbidities (**Fig. 88.4**).[18,21]

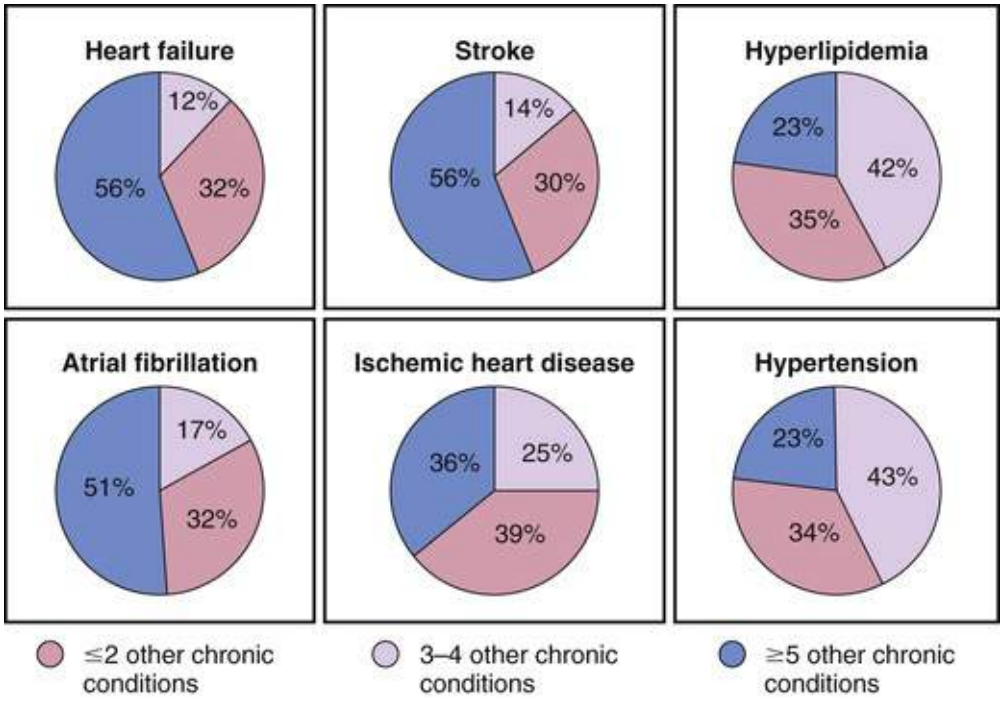

FIGURE 88.4 Number of coexisting chronic conditions among Medicare fee-for-service beneficiaries with common cardiovascular diagnoses. (From Fleg JL, Aronow WS, Frishman WH. Cardiovascular drug therapy in the elderly: benefits and challenges. Nat Rev Cardiol. 2011;8(1):13-28; Arnett DK, Goodman RA, Halperin JL, et al. AHA/ACC/HHS strategies to enhance application of clinical practice guidelines in patients with cardiovascular disease and comorbid conditions: from the American Heart Association, American College of Cardiology, and U.S. Department of Health and Human Services. J Am Coll Cardiol. 2014;64(17):1851-56.)

Management of CVD must be considered with added precautions because conventional therapies more often induce untoward outcomes when multiple comorbidities are present (e.g., angiotensin-converting enzyme [ACE] inhibitors are more likely to provoke a fall in an older patient with sarcopenia and Parkinson disease). Furthermore, outcomes of older patients with CVD are often more likely to be determined by noncardiac comorbidities. For example, short-term rehospitalization for HF is frequently determined by comorbidities other than CVD. Despite contributing to only 14% of the Medicare population, patients with six or more chronic conditions account for 25% of readmissions.[19] Such patients usually see on average two primary care providers and five specialists a year, each prioritizing his or her own disease orientation and thereby contributing to fragmented care and increased risk.[22]

Polypharmacy

Polypharmacy is common among older adults with multimorbidity because clinicians prescribe a group of evidence-based medications oriented to each disease; this often results in a risky accumulation. Each guideline is supported by evidence, but there is no guideline that addresses medication regimens for multiple concurrent diseases and their aggregated effects.[23] “Quality indicators,” which are frequently used to assess the quality of care, are often based on clinical guidelines; they may implicitly reinforce incentives for clinicians to prescribe guideline-based medications irrespective of the total number of medications the patient is taking. Although most CVD guidelines acknowledge that clinical judgment is

needed to integrate evidence-based standards with each patient's idiosyncrasies and complexities, they do not provide a refined strategy to achieve or access such tailored care.[1] Consequently, the concept of individualizing guideline-based CVD care is often more theoretical than real, especially because a divergence from guideline recommendations may be (mis)interpreted (e.g., by insurers) as substandard care (and potentially vulnerable to punitive repercussions, such as nonremuneration or insinuations of negligence) rather than appropriate care. Similarly, CV adherence initiatives such as “get with the guidelines”[24] implicitly encourage cardiologists to prioritize full regimens of CV medications without explicit modifications that adjust for comorbidities and patient complexity.

The Sloan survey shows that 44% of older men and 57% of older women received five or more prescription medications,[25] a finding typical among those with CVD. Consequences are often dangerous. Common scenarios include patients who might receive multiple medications for hypertension despite a context of poor gait, poor nutrition, sarcopenia, and falls. Similarly, many patients with CHD and AF may be prescribed aspirin, P2Y12 inhibitors, and warfarin despite a history of epistaxis or other bleeding pathologies. Most CVD patients are also taking medications to control cholesterol levels or diabetes, enhance memory, relieve the pain of arthritis, help prostate disorders, provide bladder control, relieve anxiety or insomnia, and benefit many other typical comorbidities, compounding the risks for adverse drug reactions, poor adherence, and exorbitant costs.[25]

The safety risks associated with mounting numbers of medications in old age are compounded by age-related changes in pharmacokinetics and pharmacokinetics (**see also Chapter 8**). Pharmacokinetics refers to the processing of a drug by the body, which encompasses absorption, distribution, metabolism, and excretion.[25] Pharmacodynamics relates to the actions of drugs on the body.[25] Both are significantly affected by aging effects on body composition, metabolism, and vulnerability to adverse sequelae. Because most cardiac medications are absorbed by passive diffusion, gastrointestinal aging has only minor effects on absorption. Distribution is more affected by age. Medications that are distributed predominantly in skeletal muscle (e.g., digoxin) must be adjusted for age-related lean tissue atrophy, particularly among women, in whom lean mass is usually less than men. Weight is also usually lower in older adults, and weight-based dosage adjustments are indicated for many medications (e.g., low-molecular weight heparin (LMWH]). The most significant age changes of pharmacokinetics are related to metabolism and excretion. Changes in renal metabolism are especially significant. In general, the glomerular filtration rate (GFR) is lower in older women than men, and decreases about 10% per decade in both sexes.[26] By age 80 years, the GFR is typically one half to two thirds of that in younger adults. This reduction can be masked by overestimation of the GFR using the Modified Diet in Renal Disease formula and the Chronic Kidney Disease Epidemiology Collaboration. The Cockroft-Gault is the preferred GFR equation; it accounts for age, sex, and weight, and characterizes a linear decrease of renal function. The dosage of many medications cleared by the kidney must be reduced in old age, such as digoxin, LMWH, glycoprotein IIb or IIIa inhibitors, and direct oral anticoagulants (DOACs) (**see also Chapter 98**).

Hepatic metabolism is affected by multiple processes pertaining to drug delivery, enzymatic transport into liver cells, and enzymatic transformation and/or excretion via efflux transporter enzymes into bile. These processes can be influenced by heterogeneous factors such that there is no validated algorithm to estimate age-related changes in hepatic and extrahepatic drug clearance. The most notable age-related changes are evident in oxidative biotransformation by membrane-bound cytochrome P (CYP)-450. Clearance of beta blockers (e.g., metoprolol), calcium channel blockers (e.g., verapamil, diltiazem, and dihydropyridines), and many statins (e.g., atorvastatin and fluvastatin) depends on this pathway and usually diminishes with age.

Pharmacodynamic alterations are especially common amidst age-related constitutional changes.

Changes in thirst, temperature regulation, autonomic reflexes, sympathetic and cholinergic receptors, and cell signaling all have an impact on the effects of medications, with greater susceptibility to orthostasis, syncope, and other clinical sequelae. Changes in vascular stiffness and endothelial responses are also coupled to neurohormonal changes and cognitive declines, with greater susceptibilities to hemodynamic instability, delirium, and other consequences.

The context of multimorbidity, polypharmacy, altered pharmacokinetics and pharmacodynamics, and other age-related factors contributes to higher risks of adverse drug events. Studies show rates as high as 10.7%, and CV drugs account for about half of the reported events.[27] Budnitz and colleagues demonstrated four leading "culprit" medications: warfarin (33.3%), insulin (13.9%), oral antiplatelet medications (13.3%), and oral hypoglycemics (10.7%).[27] Although the Beers criteria[28] includes medications typically problematic for older adults (and which should generally be avoided), this study highlights the fact that standard cardiac medications may also become harmful as patients grow older. Because the number of medications prescribed is the most significant risk factor for adverse drug interactions, this risk increases markedly with age. Advancing age also increases the risks of medication errors, with many detrimental consequences, including causation of approximately 20% of hospital readmissions.

Drug-drug interactions are typical in patients taking several medications, particularly when medications are metabolized by the same pathway (**Table 88.4**).[29] Amiodarone, for example, inhibits CYP oxidative enzymes and increases drug levels of those medications that would normally be metabolized (**see also Chapter 36**). Effects may also occur if clinical actions of medications are additive (e.g., administering aspirin, clopidogrel, and apixaban together will exacerbate bleeding risks) or competing (e.g., administering liraglutide and steroids together will decrease glucose control).

TABLE 88.4

Common Iatrogenic Effects of Secondary Prevention Medications in Older Patients with Cardiovascular Disease

MEDICATION CLASS	MEDICATION	GENERAL SIDE EFFECTS	DRUG-DRUG INTERACTIONS	DRUG–COMORBID DISEASE INTERACTIONS
Antiischemics and antihypertensives	Beta blockers	Confusion, fatigue, dizziness, bronchospasm, conduction block, chronotropic incompetence, claudication, depression, cold sensitivity, incontinence Hypoglycemia Increased system absorption in body fat, with delayed metabolism	Calcium channel blockers: conduction disease and chronotropic incompetence Sulfonylureas: hypoglycemia	COPD: ↑ bronchospasm Depression or anxiety: ↑ fatigue and depression PAD: ↑ claudication Raynaud syndrome: ↑ symptoms HF: ↑ decompensation Conduction disease: bradycardia, heart block
	ACE inhibitors	Falls, dizziness, hypotension (orthostatic, postprandial), hyperkalemia, fatigue, azotemia, cough	Diuretics (and other antihypertensives): hypotension NSAIDs: renal failure	CKD : hyperkalemia and renal failure
	Nitrates	Dizziness, hypotension, syncope, headache	Diuretics: hypotension and ↓ cardiac output) Phosphodiesterase inhibitors: severe hypotension Alcohol: hypotension	Aortic stenosis: hypotension
	Diuretics	Urinary frequency and incontinence, electrolyte abnormalities (e.g., hypokalemia, hyponatremia, hypomagnesemia), hyperglycemia, hyperuricemia, dehydration, muscle cramps	ACE inhibitors and other diuretics: hypotension	CKD: worsened renal failure Diabetes: ↑ hyperglycemia Incontinence: ↑ incontinence
	Calcium channel blockers	Dizziness, flushing, peripheral edema (dihydropyridines), constipation (verapamil)	Beta blockers: conduction disease and chronotropic incompetence	HF: decompensation Conduction disease: bradycardia, heart block GI: ↑ constipation
Antiplatelet	Aspirin	GI bleeding, dyspepsia, tinnitus, skin reactions	Warfarin, DOACs, or thienopyridine: ↑ bleeding	History of GI bleeding: ↑ bleeding risks
	Thienopyridines	GI bleeding, bruising, rash	Warfarin, DOACs, and/or aspirin: ↑ bleeding.	History of GI bleeding: ↑ bleeding risks
Cholesterol reduction	Statins	Myalgias, confusion, renal insufficiency, liver toxicity	Medications metabolized by cytochrome P450 system (fibrates, amiodarone, erythromycin, diltiazem, azole antifungals): ↑ statin levels and ↑ levels of the other medications Fibric acids: myopathy (gemfibrozil > fenofibrate) Grapefruit juice: ↑ statin levels (via cytochrome P450 mechanism)	Hypothyroidism, CKD, diabetes: ↑ susceptibility to statin-induced myopathy

ACE, angiotensin-converting enzyme; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *DOAC*, direct oral anticoagulant; *GI*, gastrointestinal; *HF*, heart failure; *NSAID*, nonsteroidal antiinflammatory drug; *PAD*, peripheral artery disease.

Drug-disease interactions occur as medications that benefit one chronic disease adversely exacerbate another disease or syndrome. Beta blockers for cardiac ischemia may, for example, trigger bronchospasm or claudication in patients with concomitant COPD or PAD. Calcium channel blockers can exacerbate chronic constipation, which is usually further compounded by sedentariness. Diuretics can aggravate incontinence and related social isolation and depression. In general, almost every medication brings risks of unintended consequences, reinforcing the geriatric precept to consider removing therapies if their value is not clear. A related principle of “deprescribing” medications is a growing focus in clinical care and research.[30]

Nonadherence is another concern for older CVD patients. Given the high risk associated with CVD

among older adults, the same population that is vulnerable to ill effects from over prescription is also highly susceptible to poor outcomes if certain medications are omitted. Thus, in a context of pervasive polypharmacy it is still critical to emphasize adherence to CV medications.[23,31] The challenge is to prescribe medications that are predominantly beneficial. Adding pharmacists to transcatheter aortic valve replacement (TAVR), HF, and other CVD care teams can often help achieve this goal.

Frailty

Frailty generally implies a state of vulnerability to stressors and limited reserves to stabilize declines across multiple physiologic systems.[32] Adults who are frail are prone to developing disease, and have worse disease outcomes and greater risks for harmful sequelae from standard therapies. With the advent of TAVR, the interest in frailty became accelerated among cardiology proceduralists because frailty serves as a key selection criterion when TAVR is being considered.[33] However, the interest in frailty quickly expanded to also better conceptualize personalized management with respect to acute coronary syndromes (ACSs), CHD, and many other types of CV care.[34] The prevalence of frailty ranges from 20% to 70% in different populations of CVD patients.

A single frailty assessment tool has not become dominant, and two prevailing approaches to identify frailty have evolved[35]: frailty conceptualized as an observable phenotype versus frailty conceptualized as a numerical index. The “eyeball test” is one of the earliest examples of frailty as a phenotype, but it is inherently inexact. Fried et al.[32] advanced the premise of a “frailty phenotype” by identifying five specific physical characteristics by which it could be standardized: weakness, low energy, slowed walking speed, decreased physical activity, and weight loss. Those with one or two domains are classified as prefrail, and those with three to five domains are considered frail.

Fried et al.[32] also explained frailty as a biologic manifestation of inflammation; circulating inflammatory biomarkers (high-sensitivity C-reactive protein and interleukin-6), as well as inflammatory cells (neutrophils and monocytes), are increased in frailty.[32] Thus, frailty interacts with CVD, such that adults who are frail by Fried criteria are more likely to have CVD, and older adults with CVD are more likely to be frail. Fried's conceptualization of frailty as a biologic phenomenon also explicitly differentiates frailty from multimorbidity and disability.[32]

In contrast, Mitnitski and Rockwood[36] describe frailty as an index of deficits of candidate variables (i.e., a ratio of physical deficits as well as morbidities, disability, and other clinical variables that accumulate and progressively burden an individual). The magnitude and speed at which deficits accumulate can be used to gauge vulnerability and risk. Although, Mitnitski and Rockwood originally identified 92 candidate domains for the frailty index, in subsequent studies as few as 30 were determined to be effective for assessment.

Despite their methodologic and conceptual differences, the Fried index, Mitnitski and Rockwood index and many other frailty indices are concordant in defining frailty as a state of increased vulnerability that predicts greater clinical risk. Moreover, the different frailty tools all tend to regard frailty as a dynamic state such that measurements can be repeated to distinguish changes in clinical status. Still, the inconsistencies regarding frailty assessments have contributed to confusion, inconsistency, and controversy in this field.[35]

In general, a “frailty phenotype” is easier to recognize in a clinical setting as part of a physical examination. Alternatively, the “frailty index” is more easily determined using criteria coded in electronic clinical and administrative datasets. Variations on the Mitnitski and Rockwood index have been used to track trajectories of frailty across health systems.[37] Many groups are now studying variations in CVD

therapy relative to the degree of frailty.

Alternatives to Fried's composite of physical phenotypic features include single-measure performance assessments,[38] including gait speed, handgrip strength, balance, or chair rise as demonstrated by Afilalo in a video tutorial.[39] Any one of these parsimonious assessments provides relatively efficient screening and assessment by a clinician as part of a routine evaluation and/or before an anticipated procedure. The prognostic utility of gait speed in community populations provides compelling validation as a single assessment of physical frailty.[40] The continuous nature of gait speed also enables detection of small changes (0.1 m/sec) where ordinal scales might not be as sensitive. The Timed Up and Go (TUG) and Short Physical Performance Battery (SPPB)[38] are also easy to implement and expand upon gait speed to better quantify strength, balance, and other pertinent clinical perspectives.

Disability

Disability refers to a physical or mental condition that limits a person's movements, senses, or activities. Whereas younger adults with CVD are usually able to rebound after a successful CVD hospitalization or therapy, recovery is less certain among older adults with similar disease. Disability is greater among women than men. Multimorbidity, frailty, polypharmacy, and other geriatric syndromes predispose to disability in the hospitalized elderly person, especially in the context of acute illness, deconditioning, cognitive impairment, poor sleep quality, and other burdens that tend to occur in older adults. Frailty is particularly conducive to disability, with disability often arising when physiologic reserve and compensation are depleted. The impact of hospital-related disability[41] is common and in some respects paradoxical because older adults are vulnerable to morbid effects from the hospitalizations that are used to deliver care. Thus, even patients who receive optimal care are less likely to recover to their prehospital capacity.[42] Recurrent hospitalizations tend to contribute to a cycle of progressive disability, with inability to recover from illness that progresses and induces a worsening QOL and an escalation of mortality risks (**Fig. 88.5**).[43] Sarcopenia, increased fat mass, poor nutrition, cognitive decline, and inflammation all contribute to disability risk.

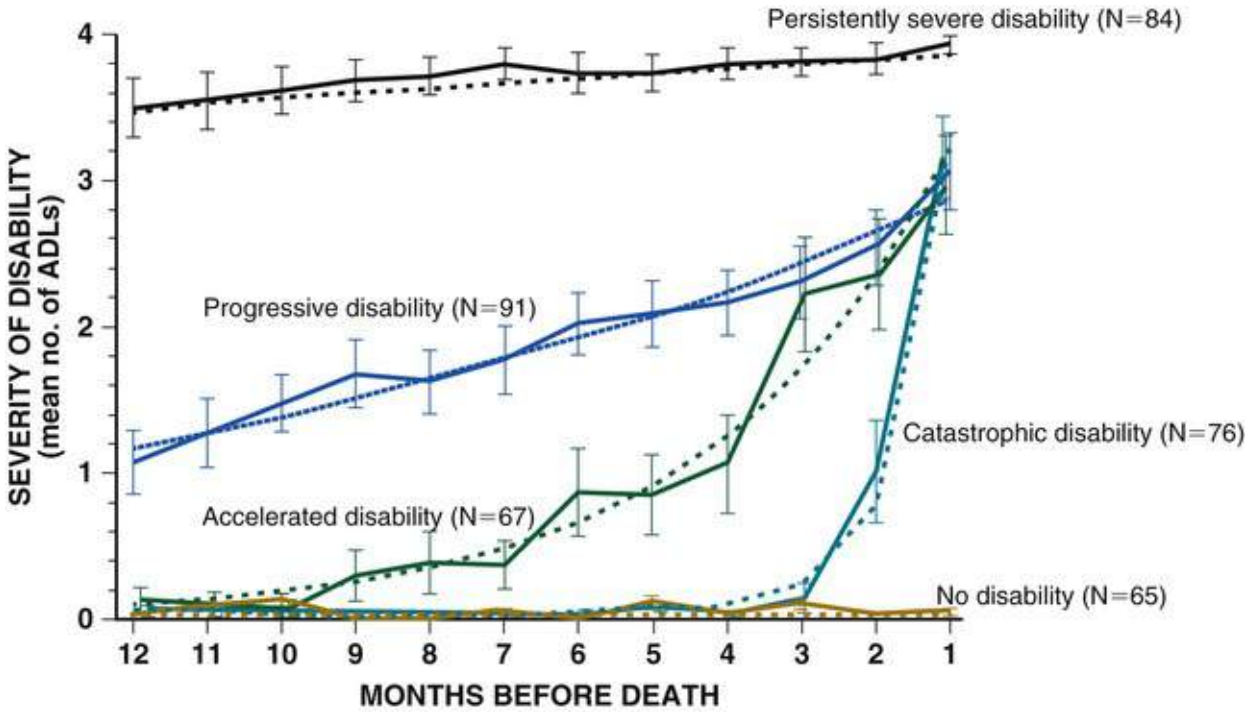

FIGURE 88.5 Trajectories of disability in the last year of life. Most decedents had high levels of disability in the last month of life, yet more than half were not disabled 12 months before death. The severity of disability is indicated by the mean number of activities of daily living (ADLs) in which the subjects had disability. The *solid lines* indicate the observed trajectories, and the *dashed lines* indicate the predicted trajectories. The *I bars* indicate 95% confidence intervals for the observed severity of disability. (From Gill TM, Gahbauer EA, Han L, Allore HG. Trajectories of disability in the last year of life. *N Engl J Med.* 2010;362(13):1173-80.)

The utility of CVD therapy to mitigate age-related disability has not been a primary focus of most research initiatives. Therapies prioritized to treat CVD may inadvertently also increase vulnerabilities to disability (e.g., myalgias with statins and/or fatigue with beta blockers). However, endpoints in some recent CV trials reflect recognition of this possibility: Instead of focusing on thromboembolic events, bleeding, and such customary disease metrics in an aspirin trial, the ASPirin in Reducing Events in the Elderly (ASPREE)[44] trial is focused on “disability-free life,” including freedom from dementia.

Delirium

Delirium is a disorder of disturbed attention that can be manifested as agitated disruptive behavior or as quiet and withdrawn behavior that is less likely to elicit attention and a corrective response. Although delirium is not directly related to CVD pathophysiology, it has a direct bearing on CVD management and outcomes. Among hospitalized elderly persons, 15% to 55% are affected, predisposing to high mortality rates as well as to frailty and disability. Presentation usually entails a rapid decline in consciousness with difficulty focusing or sustaining attention.

The strongest risk factor for delirium is baseline cognitive dysfunction. Dementia affects 14% of adults age 70 years or older in the United States, increasing to 37% in those over 90 years.[45] Moreover, dementia rates are higher in those with CVD, including reports of 35% of those undergoing coronary artery bypass graft (CABG)[46] surgery and 47% of those hospitalized with HF.[47]

Multiple factors of hospitalization are likely to trigger delirium, including the stress of a new environment, poor sleep, new medications, withdrawal from home medications, pain, dehydration, hypoxia, and metabolic shifts. Anticipatory screening by the Confusion Assessment Method (CAM) is a validated tool for screening in a hospital setting[48] and can prompt modification of precipitating factors (e.g., environmental modifications, medication adjustments, electrolyte and nutritional enhancements).

Relevance of Geriatric Syndromes to Cardiovascular Disease

An overriding principle of geriatrics is that the presence of CVD and its management often have the inadvertent effects of destabilizing a tenuous equilibrium in older adults. Incontinence, for example, may not seem to be a CV problem, but it can be induced or aggravated by diuresis or CV medications that affect sphincter or bladder control and may profoundly affect a patient's fundamental confidence, self-efficacy, and lifestyle. Likewise, falls may be provoked by routine CV medications, especially in the common contexts of frailty, polypharmacy, poor hydration, delirium, and other geriatric risks. In general, geriatric syndromes are usually relevant to CVD management because they confound therapy, transitions, health literacy, decision making, adherence, and resiliency to recover (**Fig. 88.6**). Although greater morbidity and mortality risks of CVD usually imply greater absolute risk-lowering benefits of therapy, there is also the potential for greater complications. Iatrogenesis, delirium, and disability are all more likely. Clinical guidelines are relevant, but their application to older adults requires added attention to the broader clinical context.

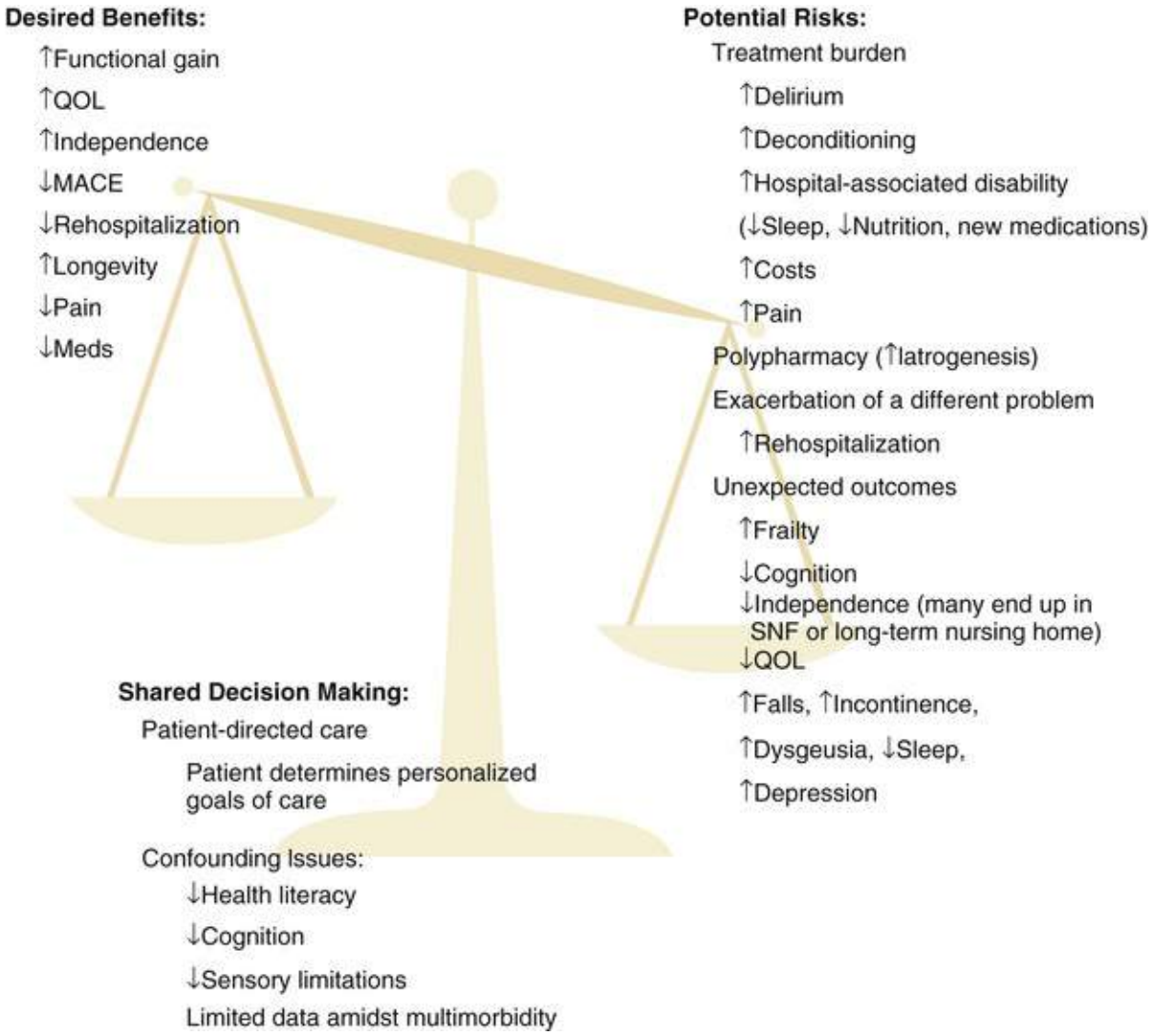

FIGURE 88.6 Shared decision making. Among older adults with CVD, clinical goals are more typically oriented to functional gains, independence, and quality of life (QOL), often with less priority ascribed to traditional CVD endpoints of major adverse cardiovascular events (MACE) and survival that are emphasized in most major trials. Therapeutic risks are also relatively greater for older adults, particularly as geriatric syndromes compound the potential for harm. Shared decision making is an important goal, but it is fundamentally challenged by common limitations of health literacy, cognition, elucidating data, and other vital elements. SNF, Skilled nursing facilities.

Aging and Specific Cardiovascular Conditions

Ischemic Heart Disease

Age is a strong and independent risk factor for the development of coronary atherosclerosis, and older adults constitute the majority of U.S. patients with new-onset angina pectoris. The AHA reports that 20% of men and 10% of women age 60 to 79 years have ischemic heart disease (IHD), with the prevalence increasing to 32% and 19% in men and women over 80 years of age (**see also Chapter 58**).[8] Atherosclerosis is more severe and diffuse in older adults, with a higher prevalence of left main stenosis, multivessel disease, and impaired LV function. Although obstructive epicardial atherosclerotic plaque is the dominant cause of myocardial ischemia in older adults, other pathophysiologic mechanisms include microvascular dysfunction, endothelial dysfunction, vascular spasm, and microembolism; LV hypertrophy with associated microvascular deficiency or other factors may lead to supply-demand imbalance.[49]

Presentation

Only a minority of older adults describe typical angina, with ischemic presentations more often characterized by exertional fatigue and dyspnea, lack of energy, and epigastric or back discomfort (**see also Chapter 56**). Postprandial or emotional stress symptoms are common. Many of these symptoms are difficult to differentiate from comorbidities. The history may be further challenged by a declining activity level, comorbid conditions, and cognitive impairment. Silent myocardial ischemia is also common. Baseline electrocardiogram (ECG) abnormalities are more prevalent than at a younger age and further confound assessments.

Risk Stratification

Most risk assessment models pertain to younger populations, with uncertain specificity and sensitivity for older adults, who often have differing social demographics, symptoms and signs, risk factors, comorbidities, and laboratory and ECG features.[50] Ischemic evaluation, as in younger age-groups, is based on the pretest likelihood of IHD, such that a low-risk patient may not warrant additional testing and a high-risk older adult is a candidate for invasive angiography; those with an intermediate pretest probability benefit most from risk stratification (**see also Chapter 3**). Exercise tolerance testing (ETT) is less feasible in older adults due to the lower exercise capacity associated with aging and comorbidities, as well as baseline ECG abnormalities that limit ischemic assessments (**see also Chapter 13**). However, ETT with modified exercise protocols (e.g., beginning at lower intensities of exercise and smaller workload increments) often enables adequate exercise stress provocation in older patients. Imaging (i.e., myocardial perfusion imaging or echocardiography) increases the sensitivity and specificity for the diagnosis of ischemia. In a metaanalysis of the optimal noninvasive strategy for risk assessment for patients over 65 years of age with known or suspected IHD, stress imaging with nuclear myocardial perfusion or echocardiography effectively stratified the risk, whereas ETT alone did not.[50] For older patients unable to exercise, pharmacologic stress testing can facilitate risk stratification, but the added utility of exercise to delineate physical function, hemodynamics, arrhythmia, and other pertinent clinical parameters remains an important consideration.

Although older adults have a high prevalence of coronary artery calcium, the value of the coronary artery calcium score in elderly patients is limited. Coronary CT angiography is less accurate in assessing

lesion severity in older patients due to their high prevalence of coronary artery calcium.[51] Invasive coronary angiography, a prerequisite for ascertaining the feasibility and selection of revascularization procedures, is recommended for older adults whose clinical characteristics and results of noninvasive testing indicate a high likelihood of significant CHD. It is also recommended with a moderate clinical risk profile with decreased LV systolic function. Despite risks of bleeding, stroke, contrast-induced kidney injury, arterial tortuosity, CKD, and reduced tolerance for sedatives and narcotics, older adults still benefit from coronary angiography and subsequent revascularization, due to the high prevalence of multivessel and left main disease.

Management (see also Chapter 62)

The 2012 ACCF/AHA/ACC/AATS/PCNA/SCAI/STS Guideline for the Management of Patients with stable (S) IHD[52] includes a specific focus on older adults. More than one third of patients with SIHD are over age 75 years. Pharmacologic agents to control angina symptoms are comparable to those prescribed at a younger age, but with added attention to adverse effects (e.g., aspirin increases the risk of bleeding; beta blockers may exacerbate adrenergic dysfunction, bradycardia, and hypotension; calcium channel blockers may also induce bradycardia and hypotension, as well as pedal edema, constipation, and incontinence; ACE inhibitor and angiotensin receptor blocker (ARB) therapy may impair renal function due to the high prevalence of renal artery stenosis; and nitrates can exacerbate postural hypotension).

Invasive coronary angiography and optimal revascularization are recommended for older adults with refractory symptoms, particularly those with significant ischemia shown on noninvasive diagnostic tests.[53] In the 4-year follow-up of the Trial of Invasive versus Medical Therapy in Elderly patients (TIME) study, better symptom relief and exercise capacity were achieved by revascularization than by an optimized medical strategy in elderly SIHD patients.[54]

In decisions for revascularization therapy, physiologic status has greater bearing than chronological age. The Euro SCORE and the Society of Thoracic Surgery risk scores not only integrate surgical parameters and comorbidities, but also now include metrics of mobility and frailty (gait speed), respectively, as added perspectives to help gauge the short-term procedural outcomes and the longer-term QOL and ability to live independently.[55]

In older adults, percutaneous coronary intervention (PCI) has a greater rate of procedural complications than in younger adults, including bleeding, stroke, contrast-induced kidney injury, and postprocedural MI. Dual antiplatelet therapy, a requisite concomitant for optimal performance of drug-eluting stents, is associated with increased bleeding and transfusion risk in elderly adults. Bleeding risks can be minimized by using weight and renal dose-adjustments of anticoagulant and antiplatelet agents.

The choice of PCI over CABG involves consideration of the anatomy, comorbidities, functional capacity, and patient preferences. In U.S. patients over 65 years of age but without acute MI, there is no difference in the mortality rates with CABG or PCI at 1 year following the procedure, but the mortality rate is lower with CABG than with PCI at 4 years. The higher rate of complete revascularization with CABG decreases the recurrence of symptoms and the need for repeat revascularization and improves the mortality rate.[56] However, CABG requires a longer recovery time, has a higher risk of stroke, and carries procedure-related neurologic complications. Notably, some reports show that more than 50% of post-CABG patients experience short-term cognitive impairment and approximately 20% experience long-term cognitive impairment, although reviews suggest that postoperative cognitive changes may correspond primarily to baseline cognitive deficiencies.[46,57]

Acute Coronary Syndromes

In the United States, the average age of the first episode of an acute coronary syndrome (ACS) is 65 years in men and 72 years in women (**see also Chapters 59 and 60**). Age is the strongest risk factor for poor outcomes following an ACS. The importance of age as a prognostic marker is reflected in the majority of ACS risk scores, including the Evaluation of the Methods and Management of Acute Coronary Events (EMMACE) and the Global Registry of Acute Coronary Events (GRACE).[58] About 60% of hospitalizations for ACS are for patients over 65 years of age, with approximately 85% of deaths due to ACS occurring in this age-group; 32% to 43% of non–ST elevation (NSTE)–ACS admissions and 24% to 28% of ST-elevation MI (STEMI) hospital admissions were for patients older than 75 years.[59]

Presentation

Although ACS involves predominantly men in their middle years, the numbers and proportion of women with ACS increase in old age. Among adults 75 to 84 years old, the numbers of men and women with ACS are similar, and in the population over 80 years of age, the majority of ACSs occur in women. Mortality rates are generally higher in older women than men with ACS. NSTE-ACS is far more prevalent than STEMI in the older population.

Elderly ACS patients are less likely to present with typical ischemic chest pain, but rather to develop autonomic symptoms, including dyspnea, diaphoresis, nausea and vomiting, presyncope or syncope, weakness, altered mental status, or confusion,[58] even when chest discomfort is present. Chest pain is reported in only approximately 40% of those older than 85 years compared with nearly 80% in those younger than 65 years; consequently, there is a reduced probability of the prompt and correct diagnosis of ACS in the elderly, leading to delays in therapy.

Because of a lower activity level, symptoms in older adults are less likely to be induced by physical exertion, but rather to be precipitated by hemodynamic stresses with comorbidities, particularly infection or dehydration. Heart failure classified as Killip class 2 or higher is 45% more likely at presentation at age 85 years or older. Type 2 MI is also more common in older adults due to other comorbid conditions such as tachycardia, hypoxemia from pneumonia, chronic lung disease, and bleeding episodes. A high index of suspicion is important in elderly patients to achieve a timely diagnosis.

Diagnosis

Because elderly patients are more likely to present with NSTE-ACS than STEMI, dynamic ST segment–T wave changes are important for detecting ischemia, although interpretation for ischemia is also commonly confounded by baseline ECG abnormalities. Initial and serial assessments of cardiac biomarkers are important, with the caveat that elderly individuals have higher baseline levels of troponin (cTn); 20% of community-dwelling adults over 70 years of age have levels above the 99th percentile at baseline. A key priority is to differentiate ACS from a multiplicity of acute and chronic conditions that also lead to low-level myocardial necrosis (type 2 MI). Further, a larger portion of elderly patients with ACS have elevated BNP, which predicts a worse outcome.

Management

ACS guidelines stress that older patients present complex challenges because of atypical symptoms, confounded by a high prevalence of cardiac and noncardiac comorbidities, age-related alterations in CV anatomy and physiology, and an increased risk for adverse drug events and interactions caused by

polypharmacy. Although the pharmacologic standards of care for ACS do not differ with age, medication side effects are more common in elderly ACS patients. Antianginal agents, oxygen for hypoxemic patients, and antiplatelet and/or anticoagulant therapy are indicated; bivalirudin may reduce bleeding compared with unfractionated heparin plus GPIIb/IIIa inhibitors.

Revascularization for STEMI

Timely reperfusion is the cornerstone of care of older patients with STEMI, who have reasonable post-MI outcomes when treated aggressively. Elderly STEMI patients have more contraindications to reperfusion, but even if eligible, they are less likely to receive it. Primary PCI with stent placement is preferred over thrombolysis in older adults because it results in greater survival benefit, reduced reinfarction and need for repeat revascularization, and less intracranial hemorrhage. Although, compared with placebo, fibrinolytic therapy reduced STEMI mortality rates in elders, few older adults were studied in seminal trials. Moreover, compared with PCI, fibrinolytic therapy has been associated with a significantly increased risk of myocardial rupture after age 75.[60] In most cases, fibrinolytics are used in STEMI presenting 12 hours or sooner after symptom onset and expected to have a system delay (≥ 120 min) before a possible PCI.

Revascularization for NSTE-ACS

Because older adults with NSTE-ACS are at generally greater risk than their younger counterparts, an early invasive strategy has more benefit in elderly than in younger patients in the absence of prohibitive comorbidities. PCI is safe even for NSTE-ACS patients who are 90 years of age or older, with high success rates and a low major bleeding risk, especially with the radial artery approach. In older adults with NSTE-ACS and diabetes, there is a greater survival advantage with CABG as a revascularization strategy. However, the operative mortality rates and risks of major complications are substantial, up to 8% at 80 years of age or older.[59] Both prolonged hospitalization and postsurgery recovery are also significant. In the After Eighty study, an invasive strategy was superior to a conservative strategy in the reduction of composite events (i.e., MI, need for urgent revascularization, stroke, and death) for patients 80 years of age or older.[61] The small number of nonagenarians had no significant benefit. The two strategies did not differ in bleeding complications, likely related to the predominant use of a radial access approach.[61]

Care Following an Acute Coronary Syndrome; Discharge Planning

Patients over 80 years of age have longer lengths of stay following ACS (8 days for those older than 80 years vs. 5 days for those younger than 65 years); frail individuals have longer hospital stays and increased rates of discharge to institutional care. Elderly patients have a high risk of rehospitalization and death, with a 50% increased mortality risk per 10 years of increasing age starting at age 65. Commonly encountered complications of ACS in older adults relate to cardiac vulnerabilities (e.g., HF, pericarditis, atrial and ventricular arrhythmias, and conduction system abnormalities) but also to the added vulnerabilities associated with physiologic aging in the heart, lungs, kidneys, neuroautonomic system, and metabolic system. Heart failure is a particularly common manifestation in ACS in older patients. Similarly, bleeding, procedural complications, medication side effects, delirium, and other age-related vulnerabilities are common.

In-hospital mortality and complication rates increase with advancing age, but lower mortality rates have been reported in patients receiving more recommended therapies. Beta blockers have greater benefit

in elderly patients in preventing subsequent MI and death than in younger groups. ACE inhibitors and ARB therapies are beneficial in the elderly, particularly those with HF or reduced LV systolic function. Benefits of statins are established in older adults through their early 80s.[59] Dual antiplatelet therapy after PCI/stenting presents a challenge in older adults who also require antithrombotic therapy (e.g., warfarin or DOACs) for AF, deep vein thrombosis (DVT), a mechanical heart valve, or other reasons. Recent trials suggest that therapy with a P2Y12 inhibitor plus an oral anticoagulant, and omitting of aspirin, may be as effective as triple therapy in preventing MI, CV death, and ischemic stroke, with decreased bleeding.[62]

Comprehensive discharge planning includes the patient and family, and must address comorbidity, polypharmacy, frailty, and often impaired communication and cognition. Failure to understand and comply with the plan of care contributes to the high rate of ACS readmission and poor outcomes. The incidence of death among elderly patients in the first year after NSTEMI increased markedly with age, from 13.3% at 65 to 79 years to 45.5% at age 90 years or more. Rehospitalizations are due to nearly as many non–CV-related conditions as CV-related conditions. At 1 year, nonagenarians had substantially higher rates of death with or without a preceding rehospitalization and twice the adjusted mortality rate as the 65- to 79-year age group.[63]

Cardiac Rehabilitation

Comprehensive cardiac rehabilitation (see Prevention of Cardiovascular Disease in Older Persons, later) has great value for older ACS and SIHD patients.[64] It can help achieve reduced mortality rates, decreased hospitalization rates, and an improved QOL. Despite a class IA recommendation in all clinical practice guidelines, referrals decrease in relation to age, especially for older women.

Heart Failure

Heart failure epitomizes a convergence of CVD and geriatrics (**see also Chapter 21**). (1) The incidence and prevalence of HF rise exponentially with age, and entail the predisposing aspects of CV physiologic aging, mounting CVD risk factors over a lifetime, and geriatric syndromes. (2) The HF pathophysiology affects multiple systems (i.e., encompassing the heart as well as the vasculature, lungs, kidneys, and skeletal muscle).

Epidemiology

In the United States, the number of HF patients is projected to increase from about 5.7 million persons currently to nearly 8 million persons by 2030.[65] In the 2011 to 2014 National Health and Nutrition Survey (NHANES), the HF prevalence rose from 1.4% in men and 1.9% in women 40 to 59 years to 14.1% and 13.4% in men and women, respectively, 80 years of age or older.[8] The incidence of HF also increases markedly with age, rising from approximately 0.1% in persons 45 to 54 years old to approximately 3% in those 85 years of age or older.[66] The incidence of HFpEF increases particularly rapidly among the very old; underlying diastolic LV filling changes as well as a high prevalence of hypertension, diabetes, AF, and other predisposing comorbid risks are all pervasive in the older adult demographic, intensifying the susceptibility to HFpEF.[67] Hospital discharges for HF approximate 1.1 million per year in the United States, the majority in older adults. National Center for Health Statistics data show HF hospitalizations were 85.7 per 10,000 in adults age 65 to 74; 214.6 per 10,000 in adults age 75 to 84; and 430.7 per 10,000 in adults age 85 and older (**Table 88.5**).[8]

TABLE 88.5

Heart Failure in Older Adults Versus Middle-Aged Adults

CHARACTERISTIC	OLDER ADULTS	MIDDLE-AGED ADULTS
Prevalence	6% to 18%	<1%
Gender	Predominantly women	Predominantly men
Cause	Hypertension	Coronary heart disease
Left ventricular systolic function	Normal	Impaired
Left ventricular diastolic function	Impaired	Normal or mildly impaired
Comorbidities	Multiple	Few

Mortality rates from HF also increase exponentially with aging; annual mortality rates are less than 10 per 100,000 in adults age 45 to 49 years, rising to 150 per 100,000 in octogenarians.[66] The median survival time was only 20 months for 825 patients 85 years or older versus 50 months for those younger than 85 years in a Danish study of 8507 hospitalized HF patients.[68] Atrial fibrillation, a lower LVEF, and renal insufficiency were associated with greater long-term mortality rates. Comorbid risks for HF overlap in older and younger adults, but the higher prevalence of comorbidities in older adults results in a higher attributable risk (defined by the prevalence times the relative risk) for developing HF despite a lower relative risk. Cardiovascular comorbidities were greater in those younger than 85 years than in those older than 85 years, reflecting differences in the risk factors predisposing to HFrEF or HFpEF, and the somewhat accelerating incidence of HFpEF in very old age.

In the Cardiovascular Health Study (CHS), a community-based sample of individuals age 65 years or older at baseline, hypertension and CHD were the most common HF antecedents, each accounting for approximately 13% of incident HF cases. Other common risk factors for HF in CHS were diabetes, PAD, valvular disease, AF, and reduced renal function. The relationship between multimorbidity and HF is explained in part by the stresses induced by conditions superimposed upon age-related reductions in CV reserve.[69] Inflammation associated with mounting comorbidity also exacerbates HF risks, particularly HFpEF.[67] Lifestyle factors (e.g., smoking, obesity, and low physical activity) increase HF risk in older and younger populations.

Pathophysiology

Numerous population-based observational studies have demonstrated important age-related differences in the clinical profile and pathophysiology of HF (**Table 88.5** and see also **Chapter 23**).[70] Whereas HF is more frequent in men than women at younger ages and through the 70s, women predominate by age 80 and beyond. More than half of older HF patients have a normal or near normal LVEF (i.e., HFpEF); in contrast, HFrEF is the dominant form of HF in younger patients. Although mortality rates from HFpEF are somewhat lower than for HFrEF, hospitalization rates are similar.[71]

Diagnosis

Because HF affects multiple organ systems, no single test or procedure can definitively diagnose HF or exclude it (**see also Chapter 24**). The specificity of the major Framingham diagnostic criteria for HF, orthopnea, and paroxysmal nocturnal dyspnea in older adults is low because these classic manifestations of HF can also be found in non-HF disorders such as pulmonary disease, deconditioning, and depression. The low physical activity levels of many older adults may mask the development of dyspnea or fatigue.

Among 5771 community-dwelling adults 65 years old or older in CHS, 7% had both orthopnea and paroxysmal nocturnal dyspnea (PND), but only 20% of these had centrally adjudicated HF.[72] Elevated jugular venous pressure is the most specific sign of fluid retention in HF and is useful for the diagnosis of

HFrEF or HFpEF. Nonetheless, many patients with chronic HF may be euvolemic and may not have classic HF symptoms and signs. Peripheral edema is also common but is not specific because it also may occur secondary to venous insufficiency, obesity, or low serum albumin. Similarly, symptoms of fatigue at rest may prompt concerns regarding depression rather than HF. Many older adults may attribute their HF symptoms to aging, thus delaying presentation until symptoms are more severe. Cognitive or sensory impairments may delay the diagnosis of HF in older adults.

When symptoms and signs of HF are insufficient or equivocal, objective laboratory criteria are helpful in establishing the diagnosis. A chest x-ray showing pulmonary venous hypertension and/or interstitial pulmonary edema is diagnostic. Both B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro-BNP) are neurohormones secreted by the failing ventricle in HF in response to increased myocardial wall stress. Because modest increases of these hormones occur with advanced age, higher cutpoints to diagnose HF are needed in older patients.[73] BNP levels are generally lower in HFpEF than HFrEF, making them less reliable as a diagnostic index for a population in which HFpEF predominates. BNP has never been demonstrated to improve the accuracy of diagnosing HF or the efficacy of its treatment in real-world settings.[74]

After establishing a clinical diagnosis of HF, the next step is to determine its cause. In older adults, the cause may be multifactorial, with hypertension, IHD, valvular disease, and diabetes the most common antecedents. Treatable conditions such as hypertension, AF, myocardial ischemia, and significant aortic or mitral valvular lesions are important priorities. Age itself is not a cause of HF; LVEF is well maintained through the mid-80s, although early diastolic performance declines gradually as adults age.

Cardiac imaging remains an important part of the HF workup in older as in younger adults, both in establishing the cause and in guiding therapy. Given its wide availability, modest cost, noninvasiveness, and ability to measure both cardiac anatomy and function, echocardiography is the most attractive initial imaging test. Findings of AS, pericardial effusion, or LV wall motion abnormalities suggestive of CHD are all common among older adults, and have important diagnostic and therapeutic implications, as does the determination of LVEF. Reduced LVEF occurs in less than half of octogenarians with HF.

For older adults not adequately imaged by transthoracic echocardiography, cardiac magnetic resonance (CMR) imaging provides an alternate method to determine both cardiac structure and function. If renal function is adequate, the intravenous contrast agent gadolinium may be useful as part of the CMR examination to determine the presence and severity of myocardial scarring. Computed coronary tomographic angiography may be useful if CHD is strongly suspected from clinical or echocardiographic data, although its accuracy in older adults may be diminished by coronary artery calcifications. Invasive coronary angiography is generally reserved for individuals in whom CHD is suspected and who are candidates for coronary revascularization. Technetium pyrophosphate imaging is highly sensitive and specific for diagnosing transthyretin amyloidosis, an infiltrative cardiomyopathy that predominantly affects the elderly.[75] This disorder typically presents as HFpEF and has an especially adverse prognosis.

Lifestyle Management in Heart Failure

Although major advances have occurred in drug and device treatment of chronic HF in recent decades, lifestyle factors such as diet, physical activity, and patient/caregiver education retain an important role. Recent studies suggest that strict sodium and fluid restriction may not be necessary or optimal in HF patients, especially older adults. Rigid sodium and fluid restriction in elders may reduce an already low caloric intake and exacerbate malnutrition and sarcopenia, both common in older HF patients and associated with adverse outcomes. In one trial, a sodium intake of 2.7 g/day reduced the rate of death or hospitalization by 25% compared with an intake of 1.8 g/day.[76]

Numerous trials have shown that exercise training in older patients with HFrEF improves the functional capacity to a similar relative degree as in younger patients without increased safety concerns. Although earlier exercise training studies were too small to reliably examine the effect of exercise training on rates of mortality or hospital admissions in HFrEF patients, the HF: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial studied 2331 patients. It reported a similar modest improvement in a combined endpoint of all-cause mortality and hospitalizations, as well as in combined CV deaths and HF hospitalizations, in the 435 patients age 70 years or older compared with younger patients in a program of 36 supervised exercise sessions followed by home training for up to 4 years.[77] Based on the HF-ACTION results, Medicare approved outpatient-supervised CR for stable HFrEF patients. Incorporating resistance exercises as well as flexibility and balance training is especially useful to counter age- and disease-associated deficits in these domains. In the absence of a formal training program, regular walking or other moderate-intensity exercise is encouraged. Although an equivalent CV event–driven rationale for exercise training in HFpEF is not available, many smaller trials suggest benefits, which may relate principally to improvements in peripheral mechanisms of disease (e.g., skeletal muscle and peripheral perfusion). Studies of exercise training for more frail HF patients (HFrEF and HFpEF) are ongoing.[64,78]

Education of older HF patients and their caregivers regarding HF manifestations and treatment helps ensure optimal adherence, improve the QOL, and reduce hospitalizations. Because HF exacerbations are usually preceded by fluid retention, it is helpful if patients weigh themselves daily, preferably in the early morning after urinating. If weight gain of 5 or more pounds or signs of decompensation (e.g., increased edema, paroxysmal nocturnal dyspnea, orthopnea, exertional dyspnea, and/or fatigue) occur, patients or their caregivers should be instructed to increase the diuretic dose temporarily and/or to contact their health care provider. In older patients with NYHA class III HF, an implanted pulmonary artery pressure sensor resulted in more medication changes, a 58% decrease in 30-day all-cause readmissions, and a 49% decrease in HF hospitalizations over 515 days of mean follow-up.[79]

Because of the high hospitalization rates and their associated costs in older HF patients, much attention has been directed toward developing disease management programs to optimize HF patient care and improve outcomes. Although not all HF disease management trials have shown benefit, a metaanalysis of 25 trials including 5942 patients recently hospitalized for HF found that interventions, typically involving home visits and/or telephone follow-up, reduced HF readmissions at both 6 and 12 months postbaseline.[80] Multiple trials have also confirmed an improved QOL from such programs. However, the inclusion of more HF patients who are 80 years of age or older is needed to determine the utility of such programs in this high-risk subset.

Pharmacotherapy for Chronic HFrEF

Although ACE inhibitors, ARBs, and beta blockers reduce CV events and improve survival rates in patients with HFrEF, this evidence base is derived from randomized clinical trials (RCTs) that enrolled only modest numbers of patients over age 65 years, and very few age 80 years of age or older (**see also Chapter 25**). Thus, clinicians must exercise caution in implementing these guideline-based recommendations in aged HF patients with multiple comorbidities. For example, in the Studies of Left Ventricular Dysfunction (SOLVD) Treatment trial, the largest trial of ACE inhibitors, although 36% of patients were age 65 years or older, none were 81 years or older. The proportion of patients over 80 years old in RCTs of beta blockers is similarly very small. In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), a subgroup analysis showed that metoprolol had similar efficacy for reducing CV events in HFrEF patients 65 years of age or older as in younger

patients, but none were 81 years old or more. The Randomized Aldactone Evaluation Study (RALES) showed a 30% reduction in all-cause mortality rates with the aldosterone blocker spironolactone in patients with NYHA class III to IV HFrEF, including 9% who were 80 to 90 years old, though none were over 90 years. Despite this high proportion of older patients in RALES, the selection was limited to relatively healthy elderly persons, and only about 20% of real-world very old HFrEF patients would have been eligible to enroll.[70] Finally, although nearly half of the Digoxin Investigative Group (DIG) participants were 65 years of age or older, only about 5% were 80 years or older.[66] Regardless of the drug regimen in older HFrEF patients, frequent follow-up for adverse effects and need for medication adjustment is essential.

Diuretics

Diuretics remain the cornerstone for treatment of congestive signs and symptoms in chronic HFrEF despite the absence of RCT data that they reduce CV mortality rates. Observational studies suggest that chronic use may be associated with adverse outcomes, likely mediated by activation of neurohormones and electrolyte imbalances. Any of the three commonly used loop diuretics, furosemide, torsemide, and bumetanide, may be considered for older adults. Each should be started at a low dosage and slowly up-titrated to achieve euvolemia; after euvolemia is achieved, lower doses can be tried. Serum electrolytes and renal function require more careful monitoring in the elderly to reduce the risk for hypokalemia, hyponatremia, and prerenal azotemia. Concerns regarding incontinence and/or disproportionate concerns regarding voiding are also pertinent because such concerns may ultimately overwhelm an older patient's treatment experience.

ACE Inhibitors or ARBs

Based on strong clinical trial evidence, older HFrEF patients who have no history of allergy or intolerance to ACE inhibitors should be prescribed these drugs, starting at low doses. ARBs should be considered for patients who cannot tolerate an ACE inhibitor. Close monitoring is required to avoid hypotension, hyperkalemia, or azotemia, especially in the first few weeks after initiating or up-titrating therapy. In RCTs, the average daily dose of an ACE inhibitor or ARB was lower in older than younger patients.

Sacubitril-Valsartan Combination

The 2014 PARADIGM-HF study showed that the combination of the neprilysin inhibitor sacubitril and the ARB valsartan reduced total mortality rates by 16%, CV death rates by 20%, and HF hospitalization risks by 21% compared with the ACE inhibitor enalapril in 8442 patients with NYHA class II to IV HFrEF. These benefits were similar in the 1563 patients over 75 years of age and in younger groups.[81] Although hypotension, renal impairment, and hyperkalemia increased with age in both treatment arms, findings of more hypotension but less renal impairment or hyperkalemia with sacubitril-candesartan were consistent across age-groups. The high current cost of this novel therapy has limited its use.

Beta Blockers

Unlike ACE inhibitors and ARBs, a class effect is not evident for beta blockers in HFrEF. Clinical trial data support only carvedilol, metoprolol succinate extended release, bisoprolol, nebivolol, and bucindolol, but the latter two drugs are not approved for use in the United States. Although major RCTs of beta blockers included few patients older than 80 years, benefits appear similar across ages. In

hypertensive older patients with HFrEF, carvedilol may be a better beta blocker choice than metoprolol succinate or bisoprolol because of its vasodilating properties and tendency to lower blood pressure more effectively. In registry data analyses, only about one third of older HFrEF patients reached target doses used in prior RCTs (carvedilol 25 mg twice/day or bisoprolol 10 mg/day).[82] Side effects such as fatigue and/or chronotropic insufficiency are more common in older patients, limiting maximal tolerated doses.

Aldosterone Antagonists

Despite powerful RCT evidence for the efficacy of aldosterone antagonists in HFrEF, their effectiveness and tolerability in real-world patients has been questioned.[83] These drugs should be used with caution in older adults, with careful monitoring of renal function and serum potassium. Generally, patients should be started and maintained on spironolactone 12.5 mg daily or eplerenone 25 mg daily (or every other day if renal insufficiency is evident). Because aldosterone antagonists are administered for their neurohormonal benefits rather than modest diuretic effects, the dose should not be titrated up based on the volume status. Although hyperkalemia has been a major limiting factor in older adults, the recent approval of the oral potassium-binding drug patiromer may enable more such individuals to benefit from aldosterone antagonists.

Digoxin

Even after over two centuries, use of digitalis in HF patients remains controversial. The drug has a narrow therapeutic window and lack of life-prolonging benefits; nonetheless, the large DIG trial showed that digoxin reduced HF hospitalizations in HFrEF patients in sinus rhythm, including those up to 80 years. This trial antedated the widespread use of beta blockers and aldosterone antagonists, so its benefit in the current era is unclear. Recommended digoxin doses in older HFrEF patients are 0.125 mg a day or lower. Digoxin in these doses generally achieves a serum digoxin concentration of 0.5 to 0.9 ng/mL, which is likely to provide maximum clinical benefit with low risk of toxicity.[84] Routine checking of the serum digoxin concentration is not necessary but should be considered when symptoms or signs of digoxin toxicity are suspected.

Other Pharmacologic Therapies

Although an RCT demonstrated a reduction of CV events with the combination of hydralazine and isosorbide dinitrate in younger (mean age 57 years) African Americans with HFrEF, adequate data in older patients are lacking. However, the combination might be considered in patients unable to tolerate ACE inhibitors, ARBs, and/or beta blockers. There is no evidence of a long-term survival benefit from oral phosphodiesterase inhibitors, such as amrinone, milrinone, and vesnarinone or a calcium-sensitizing phosphodiesterase inhibitor such as levosimendan in HFrEF. Conversely, these drugs have been associated with increased mortality rates in RCTs. Although not usually considered for older HFrEF patients, in such individuals with refractory symptoms despite optimal evidence-based therapy, they may provide greater improvement in function and QOL than traditional therapies. The recently approved drug ivabradine acts by lowering the heart rate via inhibition of the I_f current without affecting the contractility. In the Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial (SHIFT), ivabradine reduced HF hospitalization rates but not mortality rates in HFrEF patients with a resting heart rate of more than 70 beats/min despite maximally tolerated doses of beta blockers.[85] Although significant benefit was seen across age-groups, the risk reduction was greater in patients younger than 53 years (hazard ratio [HR], 0.62) than over 69 years (HR, 0.84).

Nonmedical Options for Chronic HFrEF

The high rates of mortality and morbidity in patients with HFrEF despite guideline-based medical therapy have led to development of nonmedical options, including devices and surgical procedures. Device therapy is discussed in the section on Aging and Cardiac Rhythm Abnormalities in this chapter. Given the chronic shortage of donor hearts for transplantation, patients in their eighth decade and beyond are not likely to be cardiac transplant recipients. Fortunately, the development of long-term or permanent LV assist devices (LVADs) has been shown to improve survival rates and the QOL in such patients with end-stage HF. Risks of bleeding, infection, and thrombosis have been reduced with the advent of continuous-flow LVADs. An analysis of 1149 continuous-flow LVAD recipients showed similar 1-year mortality rates in the 163 patients 70 years of age or older compared with younger patients, although the risk of gastrointestinal bleeding was higher in the older group.[86] The health-related QOL improved to a similar extent in 493 LVAD recipients age 70 years or older as in 977 younger recipients. However, appropriate patient selection in experienced centers is critical for favorable outcomes.

Functionally active older HFrEF patients may benefit from cardiac surgical procedures. Although CABG surgery has not been shown to improve overall survival rates in persons with a reduced LVEF,[87] it is generally considered for functionally independent older HFrEF patients with multivessel CHD and evidence of ongoing myocardial ischemia and symptoms despite optimal medical therapy. Similarly, surgery or TAVR in elders with severe AS is accompanied by a markedly improved survival rate and functional status, although with a higher risk for bleeding and stroke and a greater need for pacemaker implantation. Cardiac transplantation has been employed successfully in highly selected patients in their 60s and early 70s, although with slightly higher rates of surgical complications and mortality but fewer rejection episodes than in younger patients.

Pharmacotherapy for Chronic HFpEF

Symptoms are similar in patients with HFrEF and HFpEF, and symptomatic management of HFpEF is also similar to that described above for HFrEF (**see also Chapters 25 and 26**). Diuretics play a major role in controlling fluid retention and dyspnea. However, unlike HFrEF, there is no evidence of symptomatic benefit or reduction of CV events from ACE inhibitors, ARBs, or beta blockers.[88] Still, beta blockers, rate-slowing calcium channel blockers, and digoxin may reduce symptoms by controlling the heart rate in patients with concomitant AF. Although digoxin tended to reduce HF hospitalizations in HFpEF patients with a normal sinus rhythm in the ancillary DIG trial, this benefit was offset by higher hospitalization rates due to angina pectoris.[66] Spironolactone failed to significantly reduce the composite endpoint of CV death, aborted cardiac arrest, or HF hospitalization in the 3445 HFpEF patients in the TOPCAT trial, but reduced HF hospitalization rates by a significant 17%.[89] Marked geographic heterogeneity in patient characteristics was noted, with patients in the placebo group from Russia and Soviet Georgia having mortality rates approximately 80% lower than in the Americas. In the latter subset, spironolactone reduced the primary outcome by a significant 18%. Thus, spironolactone remains a consideration for older HFpEF patients who are symptomatic despite diuretics and after control of blood pressure and/or ischemia.

Pulmonary Hypertension

Pulmonary hypertension (PH) is increasingly recognized among older adults and is usually secondary to LV dysfunction (**see also Chapter 85**). Differentiation of PH from HF or pulmonary disease is a key challenge, and specialized centers have evolved that focus on this differential effort.[90] HFpEF

accompanied by pulmonary venous hypertension is associated with increased mortality rates, as well as worse symptoms and a diminished QOL.[91]

Pulmonary arterial hypertension was once considered a disease that primarily affected young women, but it is increasingly recognized in the geriatric population. Recent registry data show an increase in the proportion of elderly patients with pulmonary arterial hypertension, particularly elderly males.[92] Because fewer than 20% of elderly patients were enrolled in the clinical trials of the newer oral and parenteral therapies, extrapolation of these data to older adults is uncertain. Rather than subcutaneous or intravenous treprostinil or epoprostenol, the oral medications bosentan, ambrisentan, and sildenafil or inhaled iloprost may be more appropriate for initial therapy.[93]

Valvular Heart Disease (see also Chapter 67)

Just as other age-associated changes in CV structure may predispose a person to developing overt CVD, the cardiac valves undergo myxomatous degeneration and collagen infiltration, especially in the left heart. In the aortic valve, these processes are manifested as valvular sclerosis, detected on physical examination by a short ejection murmur, and confirmed on echocardiography by leaflet thickening without calcification or orifice narrowing. Echocardiographic aortic sclerosis was observed in about half of individuals 85 years of age or older in the CHS and was associated with atherosclerotic risk factors, including hypertension, hyperlipidemia, smoking, and diabetes. In approximately 2% of older adults, progressive calcification of the aortic leaflets results in valvular narrowing (i.e., aortic stenosis). Aortic valvular regurgitation, found in over a quarter of octogenarians, is usually due to annular dilation caused by chronic hypertension or leaflet calcification.

In the mitral valve, myxomatous degeneration usually is manifested as mitral regurgitation (MR) and is the primary mechanism for MR in older persons. Calcific deposits may also occur in the mitral valve leaflets, but more often are found in the mitral annulus, particularly in older women. Functional (i.e., secondary) MR is also common in seniors, usually due to ischemia-related papillary muscle dysfunction or to mitral annular dilation resulting from LV enlargement. Less common causes of mitral or aortic valvular regurgitation are endocarditis, rheumatic heart disease, mitral chordal rupture, aortic dissection, and trauma.

Aortic Stenosis

Aortic stenosis is the prototypical valvular lesion in older adults, present in approximately 15% of those 65 years or older, and is severe, as defined by a valve area of less than 1 cm^2 or 0.6 cm^2/m^2 body surface area, in approximately 2% (**see also Chapter 68**). In the majority, aortic stenosis is secondary to calcification of a trileaflet aortic valve; patients with congenital bicuspid valves generally present 1 to 2 decades earlier. Patients are generally asymptomatic on initial presentation, with a harsh late-peaking systolic ejection murmur. In older sedentary individuals, the cardinal symptoms of angina, exercise intolerance, or syncope may not be reported because exertion sufficient to precipitate them occurs infrequently. The second heart sound is usually diminished and may be absent if calcification is extensive. In contrast to younger adults, the carotid artery upstroke is often not delayed because of large artery stiffening. The diagnosis is confirmed by Doppler echocardiography, which demonstrates the stenotic, calcified aortic valve with a high transvalvular Doppler flow velocity, and a calculated aortic valve area of less than 1.0 cm^2. LV hypertrophy is generally present, as well as a reduced early diastolic LV filling rate; however, these findings are nonspecific because they are often present in older adults due to aging changes and hypertension; the LVEF is usually preserved until late in the disease course.

The classic findings of severe aortic stenosis on Doppler echocardiography are a stenotic, heavily calcified valve with restricted leaflet motion. A mean gradient across the aortic valve of 40 mm Hg or more and a peak flow velocity of more than 4 m/sec with an LV stroke volume index of 35 mL/m^2 or more signifies the most common hemodynamic pattern (high flow, high gradient). However, more than 40% of older patients have lower mean transvalvular gradients and/or peak velocities (i.e., low-gradient aortic stenosis). About half of this latter group also have LV stroke volume indices of less than 35 mL/m^2, or so-called low-flow, low-gradient aortic stenosis. This hemodynamic pattern is more common in women with small LV cavities and in patients with AF.[94] All-cause mortality rates over long-term follow-up are similar in medically treated patients with low-flow, low-gradient aortic stenosis to rates in patients with the more typical high-flow, high-gradient pattern; both groups experience a significant mortality rate reduction from aortic valve replacement (AVR). However, the subset with the high-flow, low-gradient pattern did not generally have a mortality benefit from AVR.[94]

More robust older adults can generally undergo surgical AVR with acceptable morbidity and mortality rates. A tissue valve is generally preferred over a mechanical valve in older individuals to avoid the need for anticoagulation, unless AF is present. Deterioration of bioprosthetic valves generally occurs more slowly in older than younger patients, increasing the likelihood that the prosthetic valve will not need to be replaced during the patient's limited lifespan. In the large Society of Thoracic Surgery national database, patients 65 to 80 years old who underwent surgical AVR experienced similar long-term survival rates with mechanical and bioprosthetic valves but had higher rates of bleeding and stroke with lesser rates of reoperation and endocarditis with mechanical valves.[95]

Until the last several years, the only option for AVR was open heart surgery. In patients with a relatively low risk who were over 80 years of age, typical of those undergoing surgical AVR, the 30-day mortality rate averages approximately 5% and the 1-year mortality rate is approximately 10%. Mortality and morbidity rates from surgical AVR are substantially increased in seniors with major comorbidities and with concomitant CABG. A large proportion of such high-risk patients who are 80 years or older are not referred or accepted for surgical AVR because of their excessive risk.

Transcatheter AVR (TAVR) has been transformative as an alternative for this sizeable high-risk older patient subset with severe aortic stenosis. In the initial PARTNER trial, the 1-year mortality rate in otherwise inoperable patients with severe aortic stenosis randomized to TAVR was 30% compared with 50% in the medically treated group. Subsequent trials in patients at high surgical risk showed similar 30-day and 1-year survival rates in patients randomized to TAVR versus surgical AVR. The risks of stroke, vascular complications, permanent pacemaker implantation, and paravalvular leakage are generally higher with TAVR, although rates of stroke and vascular complications decreased in more recent trials. In the very large Transcatheter Valve Therapy Registry, the 30-day mortality rate after TAVR declined from 4% to 3% between 2013 and 2015 and the 1-year mortality rate declined from 26% to 22% during that time.[96] After TAVR, substantial improvement is seen in functional capacity, NYHA class, and QOL, as in surgical AVR. Excellent durability of TAVR, as defined by stability of the aortic valve gradient and valve area, has been demonstrated to 5 years. TAVR should be considered in high-risk older patients whose life expectancy exceeds 1 to 2 years. As experience with TAVR increases, it may become an attractive alternative to surgical AVR in intermediate-risk and even low-risk older patients with severe aortic stenosis. As with other bioprosthetic valves, daily aspirin 75 to 100 mg is recommended as antithrombotic therapy.

Aortic Regurgitation

The prevalence of aortic regurgitation (AR) increases with age. Common causes of AR in older adults are

valvular disease (degenerative or infectious) or aortic root dilation due to hypertension, connective tissue disease, aortic dissection, or trauma. Severe AR may be asymptomatic for many years; however, the life expectancy without surgery is about 2 years in older individuals once HF develops. Left ventricular dilation, a reduced ejection fraction (EF), and moderate or greater pulmonary hypertension predict higher mortality rates. In one large series, the 15-year mortality rate was 74% in unoperated patients.[97]

The classic diastolic high-pitched blowing murmur of AR is generally heard best at the lower left sternal border if due to valvular disease and at the upper right sternal border if due to aortic root disease. The presence of a widened pulse pressure is not as helpful an ancillary sign of AR in older adults because they often have a widened pulse pressure due to arterial stiffening. Definitive diagnosis of AR is made by quantifying the regurgitant jet on Doppler echocardiography. Severe AR accompanied by a systolic LV dimension of more than 4.5 cm or an LVEF of less than 50% is an indication for AVR even in the absence of symptoms.[98] Older patients are more likely to develop HF symptoms and LV dysfunction earlier in the disease course and have higher postoperative mortality rates than younger individuals. Operative mortality rates in older patients vary with LV function, increasing from less than 5% with normal function to 14% for LVEF of less than 35%. Although moderate or severe AR has been a contraindication for TAVR to date, recent small series have shown successful treatment of AR by TAVR.[99] TAVR may become a reliable alternative to surgical AVR in high-risk older individuals with severe AR.

Mitral Stenosis

With the dramatic reduction in rheumatic heart disease in developed countries over the past half century, mitral stenosis, the hallmark lesion of this disease, has become uncommon (**see also Chapter 69**). At present, mitral stenosis is most commonly seen in foreign-born older adults, typically women, often with a prior mitral commissurotomy. Congestive symptoms generally indicate significant transmitral obstruction and a valve area of less than 1.0 cm^2. Associated AF is more common in older patients with mitral stenosis due to superimposed age-related left atrial enlargement and electrophysiologic changes. The resultant stasis of blood in the left atrium, especially the appendage, increases the risk for systemic thromboembolism, including stroke.

The pathognomonic low-pitched diastolic murmur of mitral stenosis may be absent or of low intensity in older adults due to an increased anteroposterior chest diameter or low stroke volume. In addition, the first heart sound may not be loud and the opening snap may be absent due to a fibrotic calcified mitral valve. Echocardiography is essential to confirm the diagnosis of MS, determine its severity, and characterize the extent of leaflet calcification and presence of associated MR.

In symptomatic elders with severe mitral stenosis, an intervention to increase the mitral valve area is usually indicated. If the valve leaflets are not heavily calcified and their motion not severely restricted, percutaneous balloon valvulotomy may be attempted. However, success rates are below 50% in older patients, and the rates of procedural complications and mortality are increased; cardiac tamponade occurs in approximately 5% and thromboembolism in approximately 3%; approximately 3% of patients die. Risks from mitral valve replacement are also increased in older adults, with perioperative mortality rates of 10% or more. Thus, the decision to perform balloon valvulotomy rather than surgical mitral valve replacement is individualized, with considerations of valvular anatomy, operative risk, life expectancy, and patient preference.

Mitral Annular Calcification

Mitral annular calcification (MAC) is an age-associated degenerative process that is more common in

older women than men.[100] It has been reported in about approximately 10% of community-dwelling adults age 45 to 84 years and in much higher percentages in those 85 years of age or older. The process parallels that in the aortic valve, including the association with common atherosclerotic risk factors. Older patients with severe CKD have a particularly high rate of MAC. When MAC is extensive, it compromises the sphincter function of the mitral annulus, and may stretch the mitral leaflets during systole, causing MR. Although mitral stenosis may result from severe MAC that protrudes into the valve orifice, the mitral stenosis is rarely severe. Calcific deposits from MAC may extend into the membranous ventricular septum, causing conduction disturbances. MAC increases the risk for endocarditis, especially perivalvular abscesses, because of the avascularity of the annular tissue. Several studies have shown an increased risk of stroke or silent brain infarction in older patients with MAC. Although the net benefit of anticoagulation in patients with MAC is unclear, individuals with associated AF, mitral stenosis, or severe MR are usually considered for such therapy.

Mitral Regurgitation

Mitral regurgitation (MR) is a common valvular lesion in older adults, with more than 10% of individuals age 75 years or older having at least moderate MR. Myxomatous degeneration is the most frequent structural cause, with endocarditis, rheumatic heart disease, and papillary muscle rupture after MI less frequent causes. Functional MR is most often due to chronic LV and annular dilation or to ischemic papillary muscle dysfunction. Whereas myxomatous degeneration in younger populations typically presents as chest pain and mitral valve prolapse and is typically seen in women, in later life MR and congestive symptoms are seen in the most common presentation, with a similar prevalence in men and women. Chronic MR is often asymptomatic in older adults until it becomes severe. Presenting symptoms are initially exercise intolerance and fatigue, progressing to congestive symptoms as systolic LV function declines. Secondary pulmonary hypertension is common in severe MR, and may result in right-sided HF.

Physical findings with significant MR are not generally altered by age; Doppler echocardiography quantifies the size of the regurgitant jet and provides insights regarding the cause of MR based on leaflet and annular morphology and LV size and function.

The prognosis of older patients with MR depends on its severity and cause. Patients with acute MR secondary to papillary muscle rupture after an acute MI are an especially high-risk group due to the underlying myocardial insult and hemodynamic instability. Emergent surgical resection of the damaged papillary muscle and infarct zone is the treatment of choice. Patients with severe chronic MR and LV systolic dysfunction and/or dilation are also at high risk of adverse outcomes. Medical therapy for such patients should include ACE inhibitors or ARBs and beta blockers, diuretics to relieve congestive symptoms, and rate or rhythm control of AF.

The 2014 ACC/AHA Guidelines for Valvular Heart Disease recommend mitral valve repair or replacement for severe MR and an LV end-systolic dimension of 45 mm or larger and/or LVEF of less than 60%, or pulmonary artery systolic pressure higher than 50 mm Hg at rest or higher than 60 mm Hg after acute exercise.[98] Major therapeutic decisions after older patients with severe MR have been stabilized with optimal medical therapy include if and when to repair or replace the mitral valve. Most older patients fulfilling the criteria for mitral valve intervention are candidates for valve repair. Exceptions are those whose mitral valve leaflets are fused, extensively fibrotic, or calcified, and those with chordal shortening or fusion. Several sizeable studies have shown that patients in their 70s and 80s have reasonably low mortality rates (≈5% or less) from mitral valve repair, with 70% to 80% 5-year survival rates; these results are similar to or better than those with mitral valve replacement. Functional status and QOL are also improved to a similar degree after mitral valve repair or replacement.

In parallel to the development of TAVR for treatment of severe aortic stenosis, percutaneous mitral valve repair using the MitraClip now provides a less invasive approach for severe MR. This device reduces the mitral annular size similar to surgical annuloplasty. In the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II, 351 older patients (mean, 76 years) with a calculated surgical mortality risk of 12% or more underwent MitraClip insertion. At 30 days, cardiac death occurred in 5%, MI in 1%, and stroke in 2.6%. At 12 months following the procedure, the NYHA class and QOL had improved substantially, LV volumes were reduced, and the MR severity was less than 2+ in 84% of patients.[101] A more recent study of 564 patients of mean age 83 years reported a 30-day mortality rate of 6%, strokes in 2%, and bleeding in 3%, with reduction of MR to a grade less than 2 in 93%.[102] Thus, percutaneous repair is an attractive option for a large proportion of high-risk older patients with severe MR.

Endocarditis

Endocarditis in older adults typically occurs as a result of indwelling vascular catheters, genitourinary or gastrointestinal instrumentation, pacemaker or ICD leads, prosthetic implants, or MAC (**see also Chapter 73**). Diabetes and genitourinary and gastrointestinal cancer are major predisposing conditions. The most common pathogens in this age-group are *Staphylococcus aureus*, often methicillin resistant, *Streptococcus bovis*, and enterococci. Morbidity and mortality rates from endocarditis are higher in older persons, due in part to comorbidities such as HF. Fewer vegetations and emboli but more abscesses are found in older adults.[103] Indications for endocarditis prophylaxis are similar regardless of age and include prosthetic valve implants, prior endocarditis, and cardiac transplantation.

Cardiac Rhythm Abnormalities (see Chapter 32)

Cardiac rhythm disorders increase in frequency with aging and become increasingly important contributors to morbidity and mortality. Both age-related changes in the heart and cardiac conduction system and the high prevalence of CVD are the substrates for arrhythmias. Fibrous, fatty, and calcific infiltration of the conduction system, calcification of the cardiac fibrous skeleton, reduction in the number of functioning sinus node pacemaker cells, impaired intracellular calcium handling, and blunted adrenergic responsiveness all increase the susceptibility to arrhythmias.[104] Medications may also increase the incidence of arrhythmias, because sinus node automaticity and conduction disorders may be exacerbated by drugs. Both right and left bundle branch block increase with age. Management of cardiac rhythm disorders at an elderly age is complicated by a reduced life expectancy, multimorbidity, geriatric syndromes such as frailty, cognitive impairment, and polypharmacy, and the increased vulnerability to the adverse effects of therapies.

Though the resting heart rate does not change with aging, the maximal heart rate decreases as a result of sinus node responsivity to beta-adrenergic sympathetic stimulation[104]; comparably, beat-to-beat variability also decreases with age. Atrial ectopy occurs in about 10% of elderly individuals in the absence of known cardiac disease, with ventricular ectopy in 6% to 11% on resting ECG.

Bradyarrhythmias

Bradyarrhythmias are primarily due to sinus node dysfunction and atrioventricular (AV) block and increase with age (**see also Chapter 40**). The number of sinus node pacemaker cells decreases with age, with less than 10% functional by age 75.[104] Medications for comorbidities (e.g., beta blockers for IHD) may also increase the incidence of bradyarrhythmias. Similarly, bradyarrhythmia may be provoked as a

secondary effect of treatment for sick sinus (or tachy-brady) syndrome when pharmacologic management of the tachyarrhythmia provokes bradycardia, even to the point where a pacemaker becomes required. Hemodynamic effects may develop from decreased cardiac output, with dizziness, light-headedness, and syncope common sequelae, although symptoms may also include dyspnea, exercise intolerance, fatigue, or rarely chest pain. The ECG is the first diagnostic study, with a Holter monitor, event monitor, or implantable loop recorder also useful for detecting bradyarrhythmias. Assessing for chronotropic incompetence by exercise testing may be of benefit for patients with activity-related symptoms.

The initial management involves discontinuation of relevant medications (e.g., beta blockers, calcium channel blockers, digoxin, clonidine, and amiodarone). The presence of hypothyroidism and Lyme disease should also be considered. Temporary cardiac pacing may be warranted. For persistent symptomatic bradycardia, permanent cardiac pacing is usually indicated (**see also Chapter 41**). More than 75% of pacemakers are implanted in patients age 65 years or older, with half over 75 years.[105] There is a class I indication for pacemaker implantation for sinus node dysfunction with documented symptomatic bradycardia or chronotropic incompetence, and a class II indication for symptoms at a heart rate of less than 40 beats/min.[106] Pacemaker implantation carries a class I indication for third-degree or advanced second-degree AV block with symptomatic bradycardia; an escape rhythm originating below the AV node; a rate of less than 40 beats/min; pauses of 5 seconds or longer; or after cardiac surgery without expectation for resolution. In the elderly, pacemakers can help mitigate falls and syncope, and increase the exercise capacity and QOL.

Dual-chamber pacing improves the QOL in elderly patents, likely because programmable pacing of both the atrial and ventricular rates improves diastolic flow and cardiac output, which are more dependent on the atrial contribution to ventricular filling in this population. Dual-chamber pacing also reduces the incidence of recurrent AF and decreases the rate of hospitalizations. Cardiac resynchronization therapy (CRT) has benefit for selected patients with symptomatic systolic HF (EF ≤ 35%) and a prolonged QRS (> 150 ms), as well as those with mild systolic dysfunction with an anticipated high pacing frequency (<40%).[107] Class I indications for CRT are similar in older and younger patients.[106] In CRT trials, few patients older than age 75 years were enrolled; subgroup analyses from the Cardiac Resynchronization–Heart Failure (CARE-HF) group, age younger than 66 years versus older than 66 years, and Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) group, age 65 years or younger versus older than 65 years, suggest that older patients derive similar benefit. The U.S. Food and Drug Administration has recently approved the first leadless pacemaker; studies assessing its safety and efficacy are ongoing.[105] Older, frailer patients may derive particular benefit because lead and generator pocket complications can likely be averted.

The 2012 Guideline update supports remote monitoring after the initial 2-week period,[106] which is particularly important for older adults who may have physical limitations that make frequent in-person visits for pacemaker surveillance more challenging. Nevertheless, patients with cognitive impairment may have difficulty performing home-based transmissions, and detailed patient/caregiver education is essential. Remote monitoring may allow earlier detection of clinical deterioration, which may reduce hospital readmission rates.

Supraventricular Arrhythmias

Supraventricular Tachycardia

Episodes of supraventricular tachycardia (SVT; **see also Chapter 37**), in which atrial tachycardia, AV

nodal reentrant tachycardia (AVNRT), and AV reciprocating tachycardia (AVRT) are present, have been observed in up to 50% of the normal elderly population in studies using 24-hour monitoring.[104] Management is similar to younger adults. Multifocal atrial tachycardia (MAT) is especially common in the setting of decompensated pulmonary disease; patients are often quite ill and symptomatic. Management of MAT is often constrained by poor tolerance of beta blockers and amiodarone, and limitation of use of non–dihydropyridine calcium channel blockers when there is LV dysfunction. The best outcome is achieved by control of the underlying pulmonary disease.

Atrial Fibrillation

Atrial fibrillation (AF) occurs in about 12% of patients age 75 years or older and 18% of patients age 85 years or older (**see also Chapter 38**). The high prevalence of AF relates to age-related changes in the atrial tissues, including fibrosis and conduction abnormalities that provide the substrate for electrical disarray. Hypertension and structural heart disease, common at an elderly age, lead to additional maladaptive atrial changes and further predispose a person to AF.

The 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation estimates that approximately one third of patients with AF are 80 years of age or older.[108] Because changes in the cardiac structure and function that accompany aging differ from those in younger adults, AF may occur in elderly patients in the absence of underlying heart disease. Nonetheless, elderly patients with AF are a heterogeneous group with multiple comorbidities,[108] which must be considered in management decisions; the most common comorbid chronic conditions are hypertension, IHD, obesity, hyperlipidemia, and HF. Because most AF studies involve cohorts 5 to 10 years younger than the average age of AF patients in the general population, it is uncertain whether findings of these studies can be generalized to patients 75 years of age and older and, especially, those 85 years of age and older.

Common symptoms of AF are palpitations, light-headedness, chest discomfort, shortness of breath, fatigue, and decreased activity tolerance. Acute pulmonary edema may arise with an abrupt loss of the atrial contribution to ventricular filling in a stiff left ventricle. Palpitations are less common than in younger patients, and symptoms are frequently minimal or atypical. Less commonly, AF may be initially manifested as syncope or a fall.

Nonvalvular AF is associated with a 5-fold increase in stroke. Strokes are often severe, and adverse outcomes are likely even after controlling for age and comorbidities. Increasing age is a potent risk factor for stroke, as highlighted in the CHA_2DS_2-VASc score, which assigns 1 point for age 65 to 74 years, 2 points for age 75 years or older, and 1 point for female sex. Thus, all women age 65 years or older and all men age 75 years or older have a CHA_2DS_2-VASc score of 2 or more and are candidates for anticoagulation. In patients with nonvalvular AF, the selection of antithrombotic therapy should be based on the risk of thromboembolism, irrespective of whether the AF is paroxysmal, persistent, or permanent.

Advanced age increases the risk of bleeding. The HAS-BLED[109] score reflects the bleeding risk associated with age. “Old age” within the HAS-BLED score is defined as 65 years or older. Concomitant CHD may contribute to an increased bleeding risk when dual antiplatelet agents are combined with anticoagulation. In the ISAR-Triple study, with a mean patient age of 74 years, 6 weeks of triple therapy (clopidogrel, aspirin, and warfarin) versus 6 months of clopidogrel and warfarin resulted in less bleeding with similar major adverse cardiac events (MACEs).[110] Fall risks are also pertinent when considering anticoagulation in older adults, although anticoagulant benefits generally far outweigh even a high risk of falling.[111] The decision to initiate anticoagulation must incorporate the risks for stroke and for bleeding, because both increase with advanced age, especially in association with comorbidities common to older

adults.

Warfarin has been the traditional anticoagulant, with a target international normalized ratio (INR) of between 2 and 2.5 recommended at an elderly age. The estimated maintenance dose of warfarin is lower in seniors, typically 2 to 5 mg daily, often initiated without a loading dose or with a loading dose of 5 mg. The requirements for regular INR surveillance as well as dietary limitations constitute significant challenges for many older patients. Multiple drug interactions with warfarin pose added problems, as does the increased risk of osteoporosis, particularly in women. Direct-acting oral anticoagulants (DOACs) constitute alternatives to warfarin without the need for dietary restriction or INR monitoring. Among patients 75 years of age or older, DOACs demonstrated similar or better stroke prevention efficacy with similar or less bleeding compared with warfarin. Dose adjustment may be required based on age, body weight, and/or renal function. For patients who are not candidates for anticoagulation, an alternative may be percutaneous left atrial appendage closure with the WATCHMAN device, approved for use in the United States[112] but with sparse data for older patients.

Symptoms of AF may be managed by rate or rhythm control. Because a rate control strategy is safer and usually as effective as rhythm control, it is the recommended first-line treatment in asymptomatic or mildly symptomatic patients of all ages. Class I options for achieving rate control include beta blockers and nondihydropyridine calcium channel blockers. Digoxin can aid in rate control in relatively sedentary individuals. Dronedarone is also useful. However, both nondihydropyridine calcium channel blockers and dronedarone are contraindicated in systolic HF. Given the vulnerability of older adults to medication-induced heart block, particularly with amiodarone and digitalis, the Rate Control Efficacy in Permanent Atrial Fibrillation (RACE) II trial[113] assessed a more lenient rate control strategy. Therapy targeting a heart rate of less than 110 beats/min in elderly adults (class IIb) without significant symptoms, CHD, or HF was comparable to strict rate control (< 80 beats/min), which may help obviate the need for cardiac pacing secondary to bradycardia.

Antiarrhythmic drugs have a higher incidence of adverse events in older adults because of the potential for drug interactions, unpredictable pharmacokinetics and pharmacodynamics, and variable renal function.[114] A rhythm control strategy was associated with increased mortality rates in older adults in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial. Because a rhythm control strategy does not obviate the need for anticoagulation, a rate control strategy is preferable in older adults. Nonetheless, maintenance of the sinus rhythm has also been associated with a better QOL,[115] and many clinicians still try to restore the sinus rhythm in older adults at least once.

Atrioventricular node ablation to create a complete heart block with pacemaker implantation has a class IIa recommendation to achieve a regular rhythm in symptomatic patients in whom pharmacologic therapy has failed. Catheter or surgical AF ablation are also compelling considerations, but older patients are not well represented in the ablation literature, and in particular, data are lacking in the older population following ablation.[108,116] Older adults commonly have large atria and chamber fibrosis that may reduce the likelihood of restoring and maintaining the sinus rhythm.

Ventricular Arrhythmias

Although the incidence of ventricular arrhythmias increases with age, the incidence of sudden cardiac death (SCD) appears to decline after age 80 years, mostly because rates of other causes of death rise (**see also Chapters 39 and 42**). The ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of SCD addresses older adults.[117] Overall, medical therapy for ventricular arrhythmias does not differ by age. In older post-MI patients, beta-blocker therapy of ventricular arrhythmias is associated with reduced rates of SCD.

Although the prevalence of ventricular premature complexes increases with age, no specific treatment is required in the absence of bothersome symptoms. Symptomatic ventricular premature complexes often respond to a low-dose beta blockade. The potentially life-threatening ventricular arrhythmias, sustained ventricular tachycardia and ventricular fibrillation, virtually always occur with structural heart diseases such as ischemic or hypertensive cardiomyopathy.

Implantable Cardioverter-Defibrillators

Both the ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of SCD and the ACC/AHA/HRS 2008 guidelines for device therapy of cardiac rhythm abnormalities address older adults.[106,117] The relevance of comorbidities, the limited life expectancy, and QOL issues are emphasized when considering implantable cardioverter-defibrillators (ICDs) for elderly patients (**see also Chapter 41**). The ICD guidelines do not have age-based indications, and acknowledge that few clinical trials of device-based therapy have enrolled enough older patients to reliably estimate the benefits in this age-group.[117] In the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II, patients with an LVEF of 30% or less and prior MI, ICD therapy improved survival rates in those older than 70 years of age by more than 30% compared with conventional therapy. Nonetheless, the potential durability of the ICD benefit is shorter and the risk of procedural complications higher in older patients.[118] The benefit is limited because causes of death other than SCD are a factor and because ventricular tachycardia or ventricular fibrillation is less often a cause of SCD than asystole or pulseless electrical activity in elderly patients. In a metaanalysis of the three major ICD trials (CASH, CIDS, AVID), patients 75 years or older were more likely to die from causes other than arrhythmia.[118]

The guidelines address end-of-life issues, stipulating that ICDs should not be placed in patients with a life expectancy of less than 1 year.[106,119] Implanting physicians are also encouraged to discuss end-of-life issues before implantation, and to encourage patients to complete advance directives and specifically address device management and deactivation if the patient becomes terminally ill. Device deactivation in hospice care prevents multiple potential painful shocks in terminally ill patients and may enable painless sudden death in the highly symptomatic patient with end-stage HF.

Venous Thromboembolic Disease

Epidemiology and Diagnosis

Deep vein thrombosis (DVT) and pulmonary embolism (PE) increase exponentially in occurrence with advancing age; increased blood thrombotic factors, limited mobility, and laxity of the large venous valves contribute to risks. More than half of cases of venous thromboembolism (VTE) follow surgery injury, serious medical illness, or prolonged bed rest (**see also Chapter 84**). Malignancy is also a significant contributor. A sharp increase in risk occurs after age 65 years, with a hazard ratio of 1.7 for every decade after age 65. VTE occurs in 30/100,000 persons at age 40 years versus 260/100,000 at age 80 years or older. Half of all patients with acute VTE are older than 70 years, and one fourth are 80 years of age or older.[120] PE is more common than DVT in elderly patients. There is an increased hospital mortality rate with acute PE in older adults, a 10% to 30% excess compared with younger individuals and a 1-year mortality rate of 39%.

In older adults, DVT has less typical symptoms, such as lower extremity discomfort or difficulty with ambulation, than in younger adults, likely because of the more frequent occurrence of proximal DVT without calf involvement. PE requires a high index of suspicion in any older patient admitted for shortness

of breath. Pleuritic chest pain and hemoptysis are less likely with PE than cough or syncope. Older adults with PEs are more likely to have ECG abnormalities, including $S_1Q_3T_3$, right bundle branch block (RBBB), AF, and anterior T wave abnormalities.

Color-flow imaging, in addition to duplex Doppler ultrasound, is highly accurate for the diagnosis of DVT. D-dimer tests are highly sensitive for thrombus formation and can be used to exclude VTE in patients with a low clinical probability. The application of age-adjusted cutoff values substantially increases the specificity without modifying the sensitivity and seems particularly useful in patients over 50 years of age.[121,122] In the Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism (ADJUST-PE) study, compared with a fixed D-dimer cutoff of 500 µg/L, the combination of a pretest probability assessment with an age-adjusted D-dimer cutoff was associated with a larger number of patients in whom PE could be ruled out with a low likelihood of subsequent clinical VTE.[123]

Management

Aggressive prophylaxis for VTE prevention is the most important intervention, particularly early mobilization for hospitalized patients. The routine use of compression stockings to prevent postthrombotic syndrome in acute VTE is not recommended in the 2016 guidelines (in contrast to prior editions).[124] Thromboprophylaxis with LMWH or low-dose unfractionated heparin is recommended, with extensive studies validating its use in elderly patients. Fondaparinux is also effective. Compression stockings are recommended when the anticoagulant bleeding risk is excessive.

The number of patients 75 years of age or older who require anticoagulation is rising steadily. Managing these patients is challenging because of their high risk of both thrombosis and bleeding. Frailty; chronic comorbid conditions, including renal impairment; polypharmacy; and frequent acute illnesses are all common; anticoagulant drugs must be used carefully. Initial heparin therapy is a requisite factor when warfarin is started. LMWH is preferable to unfractionated heparin because of the simplicity of administration, lower risk of major bleeding events, and lower rate of mortality; LMWH facilitates early hospital discharge and home management. Dose adjustment to body weight and renal function in older adults is essential. Conventional anticoagulation for DVT lasts 3 months, but bleeding risks, particularly in patients older than 75 years and/or with concomitant cognitive impairments, falls, or other complexities often affect the treatment duration. Unprovoked VTE is reasonably treated for a longer duration when the bleeding risk is acceptable.

In an international prospective VTE registry of patients older than 80 years,[125] anticoagulation was associated with an incidence of major bleeding of 3.4%, which exceeded the 2.1% incidence of recurrent VTE. In the same population, a 3.7% incidence of fatal PE exceeded the 0.8% incidence of fatal bleeding. Thus in this vulnerable high-risk population, anticoagulation is favored, but individualization is requisite for those at higher risk of bleeding. VTE has a 30% 10-year recurrence rate in patients not receiving long-term anticoagulation. VTE recurrence and bleeding risks are also greatest in the initial 3 to 6 weeks of therapy; careful surveillance is therefore necessary, particularly in the early phases of therapy.

In acutely ill PE patients with hypotension and hemodynamic instability, systemic thrombolysis is the preferred form of management. Catheter-assisted thrombus removal or catheter-based thrombolysis is also recommended in centers where this specialized care is available. For subsegmental PE and no proximal DVT, clinical surveillance is recommended rather than anticoagulation, with a low risk of recurrent VTE. Anticoagulation is advised over clinical surveillance in patients with a high VTE risk.[124]

Long-term anticoagulation with DOACs or warfarin is appropriate when there is no malignancy, but LMWH is preferable to warfarin in the presence of cancer.[124] In a metaanalysis of randomized trials of

DOACs in elderly adults, DOACs were associated with equal or greater efficacy than warfarin with reduced bleeding. DOACs also had a significantly lower risk of VTE or VTE-related deaths than conventional anticoagulation in elderly adults.[126,127] The DOACs overcome several drawbacks of warfarin therapy, including fewer drug-drug interactions and no requirement for anticoagulation monitoring. DOACs have a rapid onset and offset of action. Dosing must be adjusted for renal function.

Syncope

The prevalence of syncope increases with age, rising to over 20% among adults age 75 years or older (**see also Chapter 43**). More than 80% of patients hospitalized for syncope are 65 years of age or older. The incidence may be underestimated in older adults because syncope is often misclassified as an unexplained fall, collision, or traumatic episode.[128] Amnestic features associated with falls or trauma in older adults add to imprecision because histories are often ambiguous with falls or accidents, and often lead to workups in which syncope is never considered.[129]

Prognosis and Management Complexity

The prognosis of syncope worsens with age, with 2-year mortality rates reported to exceed 25%. Cardiac syncope has the worst mortality prognosis because of the hazards associated with cardiac disease. However, other causes of syncope can be similarly detrimental among older adults because the noncardiac predisposing factors can also be hazardous (e.g., Parkinson disease, DM, amyloid disease, and dementia).[130] Syncope in older adults is often associated with falls, collisions, or traumatic events that compound the prognostic risks. Syncope in older adults often becomes a life-changing event because it catalyzes the progression to institutionalization, depression, and a worsening QOL.[1]

Whereas syncope guidelines are based on a robust literature oriented to CV physiology and technologic advances, syncope in older adults is also fundamentally linked to geriatric domains.[1] Age-related physiologic changes predispose to syncope because they erode homeostasis[128] and fluid conservation.[131] Attenuated baroreceptor and autonomic reflexes, changes in adrenergic responsiveness, and impaired maintenance of intravascular volume are destabilizing when concomitant morbidities and/or pharmacologic stresses overwhelm the weakened equilibrium. Contributing factors include CVDs (e.g., valvular heart disease, AF, pulmonary hypertension, amyloidosis), non–CV diseases (e.g., diabetes, Parkinson disease, dementia, dehydration), and polypharmacy (e.g., alpha blockers; beta blockers; calcium channel blockers; ACE inhibitors, diuretics, and cholinergic medications). Older adults with syncope have an average of 3.5 chronic medical illnesses and are taking three times as many medications as the general population.[132] Frailty exacerbates risks and management challenges.

Orthostatic syncope is particularly common when impaired baroreceptors are compounded by poor hydration and excessive vasodilating medications.[133] Postprandial hypotension and diminished thirst with aging commonly exacerbate these susceptibilities.[132] Age-related orthostatic hypotension can be contributory; although many older adults have asymptomatic orthostatic hypotension, their vulnerability to syncope is increased.[134]

Reflex-mediated causes of syncope are also common, including both vasovagal syncope and carotid sinus syndrome. Vasovagal syncope typically occurs from either unopposed vagal tone (cardioinhibitory) or from peripheral and splanchnic pooling (vasodepressor). Vasodepressor syncope is common with reduced vagal activity, and often occurs without prodromal nausea, pallor, or diaphoresis. Cardioinhibitory vasovagal syncope is often linked to carotid sinus syndrome and underlying carotid sinus hypersensitivity. Age-related stiffening of the carotid vasculature impedes transduction of pressure

to the baroreceptors, and often leads to increased baroreceptor sensitivity. Pressure on the neck can trigger the carotid sinus and provoke decreased sympathetic tone, leading to excessive vasodilation, bradycardia, and diminished cardiac output. Whereas the estimated prevalence of carotid sinus syndrome is as high as 30% among older adults, carotid sinus hypersensitivity can also be asymptomatic.[135]

Bradyarrhythmias and tachyarrhythmias commonly predispose to cardiac syncope.[104] Bradycardias in older adults often result from medications, sick sinus syndrome, and/or AV block, and predispose to syncope through impaired cardiac output. Atrial and ventricular tachycardias are also highly prevalent, and predispose to impaired cardiac output, particularly in combination with ventricular diastolic filling abnormalities.

Structural CV abnormalities with aging that impair cardiac output also predispose to syncope. The most common cause is aortic stenosis, which is associated with effort syncope when cardiac output cannot increase to meet demands. Pulmonary hypertension, atrial myxoma, hypertrophic cardiomyopathy, aortic dissection, PE, and subclavian steal syndrome are less common structural CV abnormalities associated with syncope in older adults.

Diagnosis and Treatment

As in younger adults, a careful history and physical examination and a systematic approach to diagnosis are essential. Postural vital signs are more likely to yield a definitive diagnosis compared with electroencephalograms, head and neck imaging, cardiac enzyme measurements, and telemetry. The diagnostic yield of an echocardiogram varies with the probability of finding significant structural heart disease, which may be determined from a careful history, physical examination, and ECG.

Orthostatic and vasovagal syncope are often delineated by the history and physical examination, with treatment relying on modification of contributing factors. Preventive strategies may include medication adjustments, instructions to rise slowly from supine positions, increasing salt and water intake, and modification of dietary habits for postprandial hypotension.[136] Compression stockings may help mitigate venous pooling. Caffeine intake may reduce splanchnic blood flow and moderate postprandial hypotension. Pharmacologic therapies such as fludrocortisone, salt tablets, and midodrine may also be useful, but iatrogenic risks must also be considered.

Carotid sinus massage has been applied in multiple studies of unexplained syncope in older adults. If a positive result is not obtained, the procedure is repeated on the opposite side. If a cardioinhibitory response is elicited, atropine is usually administered and carotid sinus massage repeated to clarify the relative degree of vasodepression. Transient neurologic complications have been reported (i.e., abnormal sensations or visual symptoms, paresthesia, paresis, or cognitive dysfunction). In most instances these symptoms resolve within a short time.

Tilt-table (TT) testing can enhance diagnostic evaluations. The addition of nitroglycerin (NTG) to TT testing increases its sensitivity. Whereas isoproterenol was originally used to increase the sensitivity of TT, it is associated with significant side effects in older adults (e.g., ischemia, hypertension, and arrhythmia). Isoproterenol during TT can also obscure bradyarrhythmias that may underlie a predisposition to syncope. Compared with isoproterenol, NTG during TT is more easily administered, better tolerated (although associated with significant hypotension and/or headaches), and more effective clinically.

Diagnostic modalities for detecting arrhythmias range from ECGs and in-hospital telemetry to event monitors and implanted loop recorders. The utility of a given diagnostic modality for detecting arrhythmia is highly dependent on the frequency of the arrhythmia, and duration of monitoring is directly related to diagnostic yield. The capacities of older patients are also relevant because event monitors require the

patient to engage with the monitoring device in a manner that can be difficult for many seniors. Implantable loop recorders have the highest diagnostic yield, more commonly revealing bradyarrhythmias than tachyarrhythmias.[137]

Peripheral Arterial Disease, Abdominal Aortic Aneurysm, and Aortic Dissection

Peripheral artery disease (PAD) is atherosclerosis of the noncardiac arteries (**see also Chapter 64**). Lower extremity (LE) and carotid PAD, abdominal aortic aneurysm (AAA), and aortic dissection are all types of PAD. The incidence and prevalence of PAD in all three regions rise steeply with age; about 25% of both men and women over 80 years and over 30% of nonagenarians have PAD.[138] Although LE-PAD is slightly more prevalent in women over 90 years, carotid artery stenosis and AAA are more prevalent in comparably aged men.

Lower Extremity Peripheral Arterial Disease

Epidemiology

In the 2016 AHA/ACC Guideline on the Management of Patients with LE-PAD, patients identified at increased risk included those 65 years of age and older and those 50 to 64 years of age with other risk factors for atherosclerosis, a family history of PAD, or known atherosclerosis in another vascular bed.[139] The prevalence of LE-PAD and its earlier occurrence of symptoms are influenced by several modifiable risk factors, including cigarette smoking, diabetes, hypertension, hypercholesterolemia, and decreased renal function, although the association between age and PAD persisted even after adjustment for baseline demographics and clinical risk factors. The natural history of patients with asymptomatic PAD or with mild or moderate claudication is relatively benign, in contrast to the rapid progression characteristic of patients with ischemic rest pain or limb-threatening ischemia. Elderly PAD patients frequently have concomitant IHD and cerebrovascular disease, contributing to the significant rates of CV morbidity, disability, and mortality.

Diagnosis

The clinical presentation depends on the severity and location of the arterial stenosis and varies from claudication to limb-threatening ischemia. Only 10% of elderly individuals have classic claudication, 40% are asymptomatic, and 50% have atypical leg symptoms. Claudication is characterized by reproducible pain with ambulation relieved with rest. Its typically entails slow symptom progression, with critical limb ischemia occurring in only 1% to 2% over 5 years. By contrast, nonfatal MI or stroke may occur in 20%.

Claudication adversely affects the QOL and is associated with high rates of depression. Patients may describe exertional non–joint-related limb symptoms, rest pain, perceived walking impairment, or a decline in activity over time. Nonhealing lower extremity wounds may be evidence of critical limb ischemia. In the Rotterdam Study, 19% of persons over 55 years and 48% to 55% of those over 80 years had PAD, yet only 6% of older adults had claudication.[140] This likely reflects multiple comorbidities, such as neuropathy, arthritis, spinal stenosis, HF, and COPD, which result in indistinguishable symptoms or limit mobility. At 10-year follow-up, there was a 40% mortality rate, increasing to 70% in high-risk categories.

The presence of PAD increases the risk for CV events and substantially increases the risk for limb-related morbidity. Identification of PAD by screening is important because it detects patients at increased risk of atherosclerosis at other sites: asymptomatic patients identified at screening often benefit from medical therapy such as aspirin and reduction of atherosclerotic risk factors.

Physical examination includes inspection of the skin of the extremities, palpation of all peripheral pulses, auscultation for bruits, examination of the abdomen, and extremity neurologic examination. Patients with significant PAD have pallor of the feet on elevation; ulcerations of the extremities are typically between the digits or at the tips of the toes. Noninvasive vascular testing both confirms the diagnosis of PAD and ascertains the level and extent of disease. An ankle brachial index (ABI) is the initial recommended diagnostic and prognostic test and is indicated in all patients with new PAD with exertional leg symptoms[139,141] and in those over 65 years with nonhealing leg wounds.[142] Guidelines[143] also suggest ABI screening for patients with a family history of AAA and current smokers or those over 50 years who ever smoked, as well as individuals with diabetes. An ABI of less than 0.9 triples the risk for death from CVD. Definitions for normal and abnormal ABI were modified in 2011 based on results of the ABI Collaboration. A normal ABI is 1.00 to 1.40, an abnormal ABI is 0.90 or less, and a borderline ABI is 0.91 to 0.99. However, the ABI may be misleading in older adults with stiff, noncompressible calcified arteries that cause a high ABI; therefore, most consider an ABI of more than 1.30 consistent with PAD in older adults. An alternative measure is the toe brachial index, with values of less than 0.70 considered diagnostic of PAD.[139,144] An exercise ABI may be helpful in patients with borderline resting ABI values and symptoms suggestive of claudication.[139,141] With exercise, patients with claudication typically have ABIs between 0.4 and 0.9, those with rest pain have ABIs between 0.2 and 0.4, and those with critical limb ischemia, defined as ischemic pain at rest or tissue loss including skin alteration or gangrene, have ABIs of 0 to 0.4. Because many older adults are unable to perform a treadmill exercise test, hall walks are also commonly used to assess the functional response to therapy and to provide prognostic information. Duplex ultrasound, computed tomography angiography, or magnetic resonance angiography may be valuable for diagnosing the location of the arterial obstruction, assessing the severity of stenosis, and planning for intervention. Invasive angiography is useful when revascularization is being considered.

Management

The goals of management of LE-PAD are amelioration of symptoms and a decrease in the risk of atherosclerotic CVD progression and PAD complications.[143] Multiple measures are requisite to improve symptoms and prevent limb loss. Lifestyle interventions such as a structured exercise regimen can significantly benefit elderly PAD patients.[141,143,145] Although smoking is the greatest risk factor for PAD in older adults, they are less likely than younger patients to receive a recommendation for smoking cessation or referral for intensive smoking cessation therapy.[146]

Precepts of therapy are consistent with guidelines applied to younger adults with PAD, including blood pressure control and statin therapy, with the latter potentially improving symptoms. Simvastatin therapy significantly increases the walking capacity.[29] High-intensity statins are recommended, with consideration of moderate-intensity statins at age over 75 years. Statins, antiplatelet therapy, and beta blockers decreased the 10-year mortality rate in the Rotterdam Study.[140] There is no evidence that beta blockers used to manage hypertension adversely affect claudication. Decisions to use aspirin plus clopidogrel should be individualized in high-risk patients not at increased bleeding risk.[142] There is no benefit of oral anticoagulation over aspirin in reducing mortality rates, but oral anticoagulation increases major bleeding events. The recent Effects of Ticagrelor and Clopidogrel in Patients with Peripheral Artery Disease

(EUCLID) trial failed to show that ticagrelor was superior to clopidogrel in patients with PAD, at a mean age of 66 years, 28% of whom were women.[147] Cilostazol, a phosphodiesterase inhibitor, is advised to improve claudication symptoms and walking distance but is contraindicated in patients with HF[148]; a comparable response to cilostazol was documented at ages younger and older than 65 years. A metaanalysis showed that 100 mg cilostazol twice daily improved the maximal walking distance by 50% and the pain-free walking distance by 67%. The protease-activated receptor (PAR-1) antagonist vorapaxar has been suggested to reduce the risk of acute limb ischemia due to bypass graft thrombosis and native vessel in-situ thrombosis in patients with symptomatic PAD, but further studies are requisite.[149]

Endovascular therapy (atherectomy, angioplasty, stenting) or surgical bypass is recommended for critical limb ischemia and for lifestyle-limiting claudication in patients with an inadequate response to guideline-directed medical therapy. Patient preferences and goals of care are important considerations in the evaluation for revascularization. Considerations include the extent of the disability as assessed by the patient, the inadequacy of response to medical and structured exercise therapy, the location and extent of disease, the status of comorbid conditions, and the risk-to-benefit ratio. In the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) trial, both supervised exercise and stent revascularization were superior to optimal medical care alone.[150] Recently there has been an increase in endovascular revascularization, which is associated with lesser hospital mortality rates and decreased major amputations, with results comparable to standard surgical intervention. In the Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial,[151] patients who had undergone bypass surgery and those who had undergone balloon angioplasty had comparable overall survival and amputation-free survival. However, for those patients who survived for at least 2 years after randomization, a surgical-first revascularization strategy was associated with a significant increase in subsequent overall survival and a trend toward improved amputation-free survival.[139]

Amputation is recommended for tissue loss beyond salvage, with recognition that older adults are less likely to adapt to prosthetic devices; amputation often results in decreased independence and long-term care placement. More than half of all patients who undergo amputation for critical limb ischemia are over age 80 years. The increase in amputation in older adults is likely related in part to the late recognition of PAD.

Abdominal Aortic Aneurysm

Epidemiology

The occurrence of abdominal aortic aneurysm (AAA) increases with aging and is 5 times more common in men than in women, but the gender difference diminishes with age (**see also Chapter 63**). The prevalence rises from 1.3% in men and 0% in women age 45 to 54 years to 12.5% in men and 5.2% in women age 75 to 84 years.[140] Typically, AAA involves the aortic segment between the renal and inferior mesenteric arteries.

Diagnosis and Management

AAAs are typically asymptomatic. Inflammatory changes, abnormal collagen remodeling and cross-linking, and loss of elastin and smooth muscle cells interrupt the integrity of the aortic wall. The diagnosis is made by an abdominal aortic diameter of more than 3 cm. Growth of more than 1.5 cm in diameter per year is a key concern. Aneurysm diameter is the strongest predictor of rupture, with both a larger aneurysm diameter and more rapid increase in aneurysm expansion associated with symptoms and

complications.[152]

Although typically asymptomatic, there may be mesenteric ischemia or acute renal failure, either due to atherosclerotic or atherothrombotic disease. The dreaded complication is aortic rupture, which carries a mortality rate of up to 90%. Rupture occurrence is low for an aortic diameter of less than 4 cm, 20% for a diameter of more than 5 cm, 40% for a diameter of more than 6 cm, and >50% for an AAA diameter of 7 cm or greater. Aortic rupture is characterized by severe acute pain, pulsatile abdominal mass, and hypotension. In general, decisions regarding AAA repair in an older patient are individualized, with considerations of age, risk factors for perioperative morbidity and mortality, anatomic factors, and the experience of the medical center; older patients may benefit more from endovascular repair, provided their anatomy is appropriate.

AAA screening has led to significantly reduced mortality rates in men age 65 to 79 years who undergo duplex ultrasound screening, but similar screening benefits for women are not clear. The U.S. Preventive Services Task Force (USPSTF)[153] recommends one-time screening with abdominal duplex ultrasonography for men age 65 to 75 years who have ever smoked and also recommends consideration of screening if there is a first-degree relative with AAA or a history of CVD, hyperlipidemia, obesity, or hypertension.

A very large AAA, even if it is asymptomatic, warrants rapid evaluation and prompt referral for vascular surgery. No pharmacotherapy has been shown to delay or decrease AAA expansion. No further screening is recommended for an AAA of less than 3 cm. With an AAA diameter of 3 to 4 cm, guidelines recommend annual ultrasound imaging; with an AAA diameter of 4 to 5.4 cm, imaging every 6 months; and with an AAA diameter of more than 5.5 cm or a growth rate of more than 1 cm per year, CT or MRI for confirmation and evaluation for repair. Conservative management is recommended for asymptomatic patients with an AAA of less than 5.5 cm.

The medical therapy of AAA includes tobacco cessation, blood pressure control, and statin therapy. For AAAs of 5.5 cm or more or an increase in the growth rate, endovascular or open surgical repair is recommended.[142] There is no evidence that moderate-intensity physical activity precipitates AAA rupture. The United Kingdom Endovascular Aneurysm Repair (EVAR) trial compared endovascular repair with open repair for AAAs of 5.5 cm or more in patients age 60 years or older (mean age, 74 years).[154] Patients were 90.7% male and had a mean age of 74 years. The perioperative mortality rate with endovascular repair was 1.8%, compared with 4.3 % for open repair; patients included nonagenarians. However, the initial benefit was not sustained over time. Reintervention was required in 5.1% with endografts versus 1.7% who had had open surgery; this finding underscores the need to carefully evaluate stent grafts over time.[142,154]

Aortic Dissection

Pathophysiology and Epidemiology

The pathophysiology of aortic dissection relates to medial degeneration characterized by disruption and loss of the elastic fibers, decreased proteoglycan deposition, and loss of smooth muscle cells. The typical cause in elderly adults is atherosclerotic or iatrogenic in contrast to younger individuals, in whom dissection is more likely to be caused by Marfan syndrome or other genetic diseases. In the International Registry of Acute Aortic Dissection (IRAD), 65% of the patients were men with a mean age of 63 years; women were generally older, with a mean age 67 years; 32% of patients were over age 70 years and were more likely to have atherosclerosis, prior aortic aneurysm, iatrogenic dissection, or intramural

hematoma.[155] Hypertension remains the most important predisposing factor for acute aortic dissection.

Clinical Presentation

Aortic dissection typically presents as an acute catastrophic illness with severe chest pain and acute hemodynamic compromise. The classic presentation is of chest pain (80%), which is far more likely to be anterior (71%) than posterior (32%). Older adults appear less likely to have chest pain and may present with syncope, cerebrovascular accident, or HF. Hypotension is more common at presentation than in younger patients and carries an ominous prognosis. A pulse deficit, although less common in older adults, is associated with increased mortality rates. Based on an IRAD review, the murmur of aortic regurgitation, indicating propagation retrograde to involve the aortic valve, is less common in patients over age 70 years. Computed tomographic angiography is the initial diagnostic procedure of choice due to its widespread availability. The typical finding of a widened mediastinum on chest x-ray in type A dissection has decreased in recent years.[155]

Management

Type A dissection occurs in about 32% of aortic dissections. In octogenarians managed medically, there was a 45% to 62% hospital mortality rate with type A dissection. In a comparable population, surgery was associated with a 63% 1-year survival rate (with an uncomplicated dissection), favoring surgical management. Surgical operative mortality rates have declined over time. In contrast, for complicated type A aortic dissection (i.e., with neurologic defect, mesenteric ischemia, or cardiopulmonary resuscitation), medical management is often preferable. Type B aortic dissection is also usually managed medically; parenteral beta blockade may obtain a heart rate of less than 60 beats/min and an SBP in the range of 100 to 120 mm Hg. There has been increasing use of endovascular repair for type B dissection in the IRAD Registry.[155]

Cerebrovascular Disease and Stroke

Stroke is the second most common cause of death in the United States and the third most common cause of disability (**see also Chapter 65**). Men have a greater occurrence of stroke at a younger age, but stroke is more prominent in women than men over 75 years of age.[156] More women die annually from stroke in the United States (58% of total), primarily because of the larger numbers of elderly women. Approximately 15% of all strokes are heralded by a transient ischemic attack (TIA).

Stroke is a leading cause of long-term disability (in women more than men); among U.S. Medicare stroke patients discharged from the hospital, approximately 45% return home, 24% are discharged to inpatient rehabilitation facilities, and 31% are discharged to skilled nursing facilities (SNFs). Of patients who return home, one third use home health care services. Adults over 85 years comprise 17% of patients and have higher risk-adjusted mortality rates, greater disability rates, longer hospitalizations, and less evidence-based care. Recent ASA/AHA guidelines on cerebrovascular disease and stroke[157] clarify that older patients have increased mortality and morbidity rates and more adverse events, including hemorrhagic transformation and reduced neurologic recovery, plus a high susceptibility to iatrogenic effects of pharmacologic, percutaneous, and surgical stroke therapies.

Primary and Secondary Prevention of Stroke

Stroke risk factors require both primary and secondary preventive interventions, as in a younger

population.[157,158] The AHA/ASA Guideline for Primary Prevention of Stroke[157] emphasizes primary prevention because 76% of strokes are first events. Aspirin 160 to 325 mg is indicated, but an added benefit of clopidogrel is uncertain.

Hypertension is a powerful risk factor for both ischemic stroke and intracranial hemorrhage. Antihypertensive therapy with a reduction of SBP of 10 mm Hg was associated with an average 41% reduction in stroke risk. Although the benefit of hypertension treatment in preventing stroke is clear,[159] optimal blood pressure goals for elderly patients remain controversial.

Diabetes mellitus increases the incidence of ischemic stroke at all ages, but more prominently in the nonelderly population. The reduced survival rate of diabetic stroke patients is more common for women. In the ACCORD study, targeting the SBP to lower than 120 mm Hg in patients with type 2 diabetes did not reduce CV events compared with a target SBP of lower than 140 mm Hg, except for the endpoint of stroke, in which intensive blood pressure reduction was better.[159]

Atrial fibrillation is a powerful risk factor for stroke, independently increasing the risk about 5-fold at all ages, but with the percentage of stroke attributable to AF increasing from 1.5% at age 50 to 59 years to 23.5% at 80 to 89 years. Screening for AF in patients with cryptogenic stroke or TIA is recommended, and anticoagulation with warfarin or a DOAC is a requisite for reducing the stroke risk. Aggressive management of blood pressure plus antithrombotic prophylaxis is recommended for AF patients.[159] Screening women over age 75 years by pulse followed by an ECG when indicated, is recommended.

Carotid ultrasound screening to ascertain stroke risk is reasonable for patients over age 65 years prior to elective CABG surgery and in those with PAD, a history of cigarette smoking, a history of stroke or TIA, or carotid bruits. Because patients over 80 years of age were excluded from the Asymptomatic Carotid Atherosclerosis Study, the benefits of endarterectomy cannot be extrapolated to those patients, however. In patients over age 70 years, carotid endarterectomy may provide an improved outcome compared with carotid artery stenting; the two techniques have equivalent benefits in younger patients.[158]

Ischemic Brain Injury

Brain ischemia results from an inadequate blood supply bringing needed oxygen to the brain. Ischemia from thrombosis or embolism is common.

Thrombosis

Ischemic stroke is the most common type of stroke in the United States, but many uncertainties remain regarding acute therapies at an elderly age. The role of acute intravenous treatment with recombinant tissue plasminogen activator (TPA) is uncertain for patients with one of the following exclusion criteria: age over 80 years, taking oral anticoagulants despite an INR of 1.7 or less, a baseline NIH Stroke Scale score of more than 25 or a history of both stroke and diabetes mellitus.[160] The Third International Stroke Trial (IST-3) suggested a TPA benefit at least as great in patients 80 years of age or older.[161] A time window of 3 to 4.5 hours is critical for intravenous TPA. The risk-to-benefit ratio of acute angiography and thrombus extraction with intraarterial thrombectomy in specialized stroke centers has not been established for an elderly population.

Decompressive surgery for malignant cerebral edema, although potentially lifesaving for stroke patients, must be individualized[162]; the value of decompressive craniectomy is uncertain in patients over age 65 years. In the Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY) II trial,[163] patients with a median age of 70 years derived a survival benefit from decompressive hemicraniectomy for a large MCA ischemic stroke. However, most were still left

disabled and required assistance with most activities of daily living.

Embolism

Although AF is the dominant cardiac cause of cerebral embolism (see above), valve disorders, cardiac chamber thrombi, and aortic and carotid atherosclerosis are other high-risk sources, identifiable by imaging studies.

Hemorrhage

Brain hemorrhage involves excess blood in the closed cranial cavity; the hemorrhage may be intracerebral or subarachnoid. Intracerebral hemorrhage (ICH) is the most lethal form of stroke, particularly in the elderly.[164] The Surgical Trial in Lobar Intracerebral Hemorrhage II (STICH), with about half of patients over age 70 years, suggested a potential benefit of early surgical intervention specifically for superficial ICHs.[165] The recommendation is for aggressive care for 2 full days following ICH and postponement of a new do-not-resuscitate order to permit appropriate family discussion and decision making.[164,166] Resumption of antithrombotic therapy following ICH related to antithrombotic therapy must be individualized, considering the risk of subsequent thromboembolism or recurrent ICH and the overall patient status. The most common cause of subarachnoid hemorrhage is rupture of an intracranial aneurysm,[167] for which microsurgical clipping and/or endovascular coiling may be beneficial.

Other Stroke-Related Issues

Vascular cognitive impairment[168] is the second most common cause of dementia, with modest evidence that blood pressure control in middle-aged and young-elderly individuals may help prevent late-life dementia; the usefulness of blood pressure lowering for adults over age 80 years is not well established for this purpose.

Prompt and continued comprehensive stroke rehabilitation is requisite for restoring function and maximizing independence. Older adults with chronic pain following a stroke require precise ascertainment of such pain and pharmacologic management with amitriptyline, nortriptyline, or lamotrigine. Patients benefit from a collaborative approach that addresses end-of-life decision making and palliative care, and that includes the patient and family.[169]

Prevention of Cardiovascular Disease in Older Persons

Efforts to prevent new or recurrent CV events in older adults center on control of modifiable factors known to facilitate development or progression of CVD. It is often less clear that controlling these “risk factors” among older adults similarly reduces the risk of CV events. Most landmark clinical trials that established the treatment benefit included few if any individuals older than 70 to 75 years, or only those without the comorbidities typically found in this age-group. Risks for mortality from disorders other than CVD may reduce the likelihood of demonstrating a survival benefit in older adults. Finally, older adults represent selective survivors of their birth cohorts and may be less susceptible than the decedents to the adverse effects of certain risk factors. The following sections review the available evidence regarding common CV risk factors in older individuals.

Hypertension

Prior to the 1980s, the age-associated elevation of SBP in older adults was generally considered a normal finding that did not warrant treatment (**see also Chapter 46**). Numerous observational studies have since documented increased CV morbidity and mortality rates in such individuals.[14] After age 70 years, isolated systolic hypertension (ISH) accounts for more than 90% of all patients with hypertension.[14] Hypertension is the most common CV risk factor among older men and women, with prevalence rates of approximately 70% in those age 75 years and older.[14,170] Hypertension has the greatest population-attributable risk for CHD, cerebrovascular disease, and PAD among older adults. Over 70% of older adults with incident MI, stroke, acute aortic syndromes, or HF have preexisting hypertension. Hypertension is the most prevalent antecedent of HF, especially with a preserved EF, and of CKD.[8] Multiple clinical trials in older cohorts have shown benefits of hypertension treatment.[25] Although only two trials showed significant reductions in total mortality rates, several showed substantial reductions in rates of stroke and HF. The reduction in CV events appeared similar in subgroups older versus younger than the median age in all eight trials reporting this comparison. The landmark HYpertension in the Very Elderly Trial (HYVET) demonstrated a 39% significant decrease in rates of fatal stroke, 21% significant decrease in all-cause mortality rates, and 64% significant decrease in rates of HF over 1.8 years of mean follow-up in 3845 patients 80 years of age or older with SBP of 160 mm Hg or higher treated with the thiazide-like diuretic indapamide to a target blood pressure of 150/80 mm Hg versus placebo.[171] More recently, the Systolic Blood Pressure Intervention Trial (SPRINT) showed a 34% reduction in the rate of CV events and a 33% reduction in mortality rates in 2636 patients age 75 years or older with SBP over 130 mm Hg randomized to a target of 120 mm Hg versus 140 mm Hg.[172]

The Eighth Joint National Committee on Prevention, Evaluation, and Treatment of Hypertension (JNC 8) revised the goal blood pressure from the prior target of less than 140/90 mm Hg to less than 150/90 mm Hg in adults age 60 years or more, which sparked considerable controversy.[173] This target, which antedated the SPRINT findings, will likely be lowered based on the SPRINT results. In older patients with CHD, excessive lowering of the DBP should be avoided to avoid deleterious reductions in coronary blood flow. Some studies have found higher CHD rates when the DBP is reduced below 70 to 75 mm Hg.[14]

Hypertension Management

Nonpharmacologic interventions are recommended as initial therapy to manage mild hypertension (**see also Chapter 47**). Such an approach is especially useful in older adults to avoid or reduce the number and doses of antihypertensive drugs and their potential for adverse effects, biochemical changes, and high costs. For milder hypertension, lifestyle modifications may be the only treatment needed. These include aerobic exercise; reductions in excess body weight, mental stress, and intake of sodium and alcohol; smoking cessation; and adoption of the Dietary Approaches to Stop Hypertension (DASH) eating plan.[14] The declines in blood pressure with both weight reduction and sodium restriction are usually larger in older than in younger adults.[14] However, data are scanty in patients over age 75 years.

Five major classes of antihypertensive drugs, diuretics, beta-adrenergic blockers, ACE inhibitors, ARBs, and calcium channel blockers, have been shown in clinical trials to reduce CV events in older adults.[14] Two or more drugs will be required to achieve target blood pressure levels in approximately two thirds of seniors with hypertension. Combination therapy often allows lower individual drug dosages, minimizing dose-dependent side effects and achieving a longer duration of action and additive target organ protection,[14] although it also contributes to polypharmacy. Initiation of antihypertensive drugs in

older adults should be at the lowest doses, with gradual increments as tolerated, given the age-related changes in absorption, distribution, metabolism, and excretion of pharmacologic agents. The choice of specific agents is dictated by efficacy, tolerability, specific comorbidities, and cost.

Dyslipidemia

Dyslipidemia remains an important CV risk factor in older adults, although the relative risk imparted by lipid disorders may be attenuated compared to younger populations (**see also Chapter 48**). Multiple cohort studies have shown that both the total cholesterol and low-density lipoprotein cholesterol (LDL-C) correlated significantly with fatal CHD in both sexes across a broad age range, including patients older than 65 years.[29] Despite the voluminous literature demonstrating a reduction in CV events in both primary and secondary prevention populations receiving medications, primarily statins, to lower LDL-C, the majority of patients in these trials were younger than age 65 years, and very few were 80 years or older (**Table 88.6**).[174] The benefits of statin therapy to reduce LDL-C were similar or greater in older versus younger patients. In the Study Assessing Goals in Elderly (SAGE) trial, limited to patients 65 to 85 years old with 3 minutes or more of ischemia during 48-hour ambulatory ECG monitoring, 80 mg of atorvastatin reduced all-cause mortality rates by 67% compared with pravastatin 40 mg, although major CV events were reduced to a lesser extent. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, atorvastatin 80 mg reduced major CV events by 16% compared with pravastatin 40 mg in patients hospitalized with ACS; the risk was reduced similarly in the subset age-group over 65 years. In a recent study of over 500,000 veterans of mean age 68.5 years (98% men) with known atherosclerotic CVD, a graded association was observed between the intensity of statin therapy and all-cause mortality rates.[175] Similar benefits of statins were seen in patients 76 to 84 years, in whom the mortality rate was 9% lower with high-intensity versus moderate-intensity statins.

TABLE 88.6

Statin Trials Supporting Secondary Prevention in Older Adults

TRIAL NAME	MEDICATION	N	AGE RANGE (yrs)	PERCENTAGE OF OLDER PATIENTS	FOLLOW-UP (yrs)	OUTCOMES
4S	Simvastatin	4,444	35-70	≥ 65 yrs (23%)	5.4	34% RRR in all-cause mortality 34% RRR in MACE
HPS	Simvastatin	20,536	40-80	≥ 70 yrs (29%)	5	25% RRR in death or MI
CARE	Pravastatin	4,159	21-75	≥ 65 yrs (31%)	5	24% RRR in death or MI
LIPID	Pravastatin	9,014	31-75	≥ 65 yrs (36%)	6.1	24% RRR in all-cause mortality and cardiac mortality 29% RRR in nonfatal MI 20% RRR in coronary revascularization
MIRACL	Atorvastatin	3,086	18-80	Not reported	16 wks	16% RRR in death, nonfatal MI, recurrence of myocardial ischemia, and resuscitated cardiac arrest
TNT	Atorvastatin	10,001	35-75	≥ 65 yrs (38%)	4.9	19% RRR in composite endpoint of MACE, CHD-related death, nonfatal MI, or stroke
SAGE	Pravastatin vs. Atorvastatin	893	65-85	≥ 65 yrs (100%)	1	29% RRR in MACE and 67% RRR in death in atorvastatin group
PROSPER	Pravastatin	2,565	70-82	≥ 70 yrs(100%)	3.2	20% RRR in CHD, nonfatal MI, and stroke

CHD, coronary heart disease; *MACE*, major adverse cardiovascular events; *MI*, myocardial infarction; *RRR*, relative risk reduction.

Although secondary analyses of several primary prevention trials have also shown a risk reduction in older subsets, the benefits of statins for primary prevention in this age-group are less clear than for secondary prevention. In the PROspective Study of Pravastatin in the Elderly at risk (PROSPER) trial, a reduction in CV endpoints was seen only in the subset with known CV disease and only in men. The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin

(JUPITER) showed that rosuvastatin decreased CV endpoints by 44% in 17,802 clinically healthy persons 60 to 71 years old with elevated serum C-reactive protein levels and LDL-C levels of less than 130 mg/dL. Based on the available data, the 2013 ACC-AHA Prevention Guidelines recommend moderate-intensity statin therapy, designed to lower LDL-C by 30% to 49%, in patients older than 75 years with known CV disease and LDL-C of 70-189 mg/dL.[176] This differs from the recommendation of high-intensity statin therapy (i.e., lowering LDL-C at least 50%, in those 40 to 75 years old). For older adults already receiving high- dose statins and tolerating them well, the guidelines do not recommend lowering the dose. High-intensity statin therapy is recommended for individuals with LDL-C of 190 mg/dL or more regardless of age. Cholesterol-lowering drugs are not recommended in persons over 75 years of age without clinical atherosclerotic CVD unless LDL-C is 190 mg/dL or more. In older individuals with LDL-C of 70 to 189 mg/dL, the potential but unproven benefit of long-term statin therapy must be weighed against the cost, inconvenience, and possible side effects.

The safety of statins in older patients has been amply demonstrated in a metaanalysis of 26 RCTs, including data from 170,000 patients.[177] No dose adjustment is generally needed in elders; the statin dose was titrated to achieve the desired LDL-C goal. The most common side effect observed with statins is myalgia, which occurs in about 5% of patients.[178] Myopathy documented by elevated muscle enzyme levels is much less common, occurring in 0.01% to 0.05%. The most severe adverse effect, rhabdomyolysis, has an incidence of 3.4 per 100,000 person-year. Age is not an independent risk factor for these complications.

In older patients intolerant of statins or who cannot achieve their LDL-C goal while receiving maximal statin doses, ezetimibe may be a useful adjunct. Ezetimibe reduces cholesterol absorption from the gut, generally reducing LDL-C by 15% to 20%. Ezetimibe is generally well tolerated in the elderly, though it reduced CV events by a modest 6% in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT).[179] Fibrates are sometimes used to raise low HDL-C or reduce elevated triglycerides, but evidence supporting their benefit in reducing CVD events is relatively sparse.[180] The combination of gemfibrozil and statins is associated with an increased risk of rhabdomyolysis (0.12%) and should usually be avoided, especially in older adults. Niacin (nicotinic acid) is the most effective drug available to raise low HDL-C; it also reduces elevated triglycerides and modestly lowers LDL-C. Recent trials in patients treated with statins showed no benefit of high-dose niacin in reducing CV events.[181]

Diabetes

Advancing age is accompanied by reduced insulin sensitivity and secretion, contributing to greater glucose intolerance and higher rates of type 2 diabetes mellitus in older adults (**see also Chapter 51**). Approximately 15% of adults 65 years of age or older have diagnosed diabetes, and in another 7% diabetes is undiagnosed.[29] In older adults, diabetes is often underdiagnosed due to the absence of classic symptoms. An estimated 30% of older adults with diabetes have clinical CHD, double the prevalence in age-matched patients who do not have diabetes. Older adults with diabetes and CVD are at high risk for adverse macrovascular and microvascular outcomes as well as functional disability and geriatric syndromes (e.g., frailty and falls).

The primary treatment goals for older adults with diabetes include managing hyperglycemia and reducing the risk of adverse clinical outcomes. Lifestyle modification is principal. Weight loss can reduce insulin resistance and improve glycemic control. Dietary interventions that optimize macronutrient content as well as calorie count help improve glycemic control, independent of weight change. Regular aerobic and resistance exercise lower HbA1c by 0.5% to 1.0% in older adults, even without changes in body

weight or fat mass.

Despite the benefits of lifestyle interventions, most older diabetic patients require medications to achieve glycemic control. Because several large clinical trials have found either no effect or even increased mortality rates in older patients receiving intensive glycemic therapy, a less-intensive target HbA1c of 7% to 7.9% is recommended for most older adults, especially those with long-standing diabetes and chronic comorbidities, including CVD. Even higher targets may be considered for older patients with frailty or a short life expectancy.[182]

Metformin is favored as a first-line therapy due to its low risk for hypoglycemia and other adverse effects. Additional options include the short-acting sulfonylurea glipizide and the short-acting insulin secretagogue repaglinide.[29] Two new agents worthy of consideration are the sodium-glucose cotransporter 2 inhibitor empagliflozin and the glucagon-like peptide-1 analogue liraglutide, both of which reduced CV events in large RCTs. The reduced CV risk with empagliflozin was especially prominent in patients 65 years old or older.[183] If insulin therapy is needed, ultra–long-acting basal and very short-acting prandial insulins are strongly preferred over intermediate-acting insulin formulations. Although tighter glycemic control in diabetes may help to avoid microvascular complications, a greater reduction in CV risk may be achieved with control of concurrent risk factors, such as hypertension and dyslipidemia.[29]

Tobacco

Although only 9.8% of men and 8.5% of women 65 years old or older in the United States were current smokers in a 2008 survey, 54.3% of men and 28.9% of women over 65 years of age were former smokers.[8] Numerous studies have demonstrated that continued smoking increases the rate for recurrent coronary and vascular events in both younger and older patients; reduced CV event rates are seen among those who quit smoking. Data from the Coronary Artery Surgery Study registry showed a reduction in MI and death in former smokers age 70 years or older, similar to that in younger patients with CHD. A metaanalysis of 17 general population studies in over 1.2 million persons age 60 years or older from seven countries showed a dose-dependent increase in all-cause mortality rates in current smokers, with a mean relative mortality of 1.83 versus never smokers. Among former smokers, the mortality risk was attenuated to 1.34. Risk reduction from smoking cessation was seen even in persons age 80 years or over.[184] In a registry of patients with CHD, the mortality rate was markedly lower in recent quitters than in persistent smokers. Smoking cessation also reduces the risk of new or recurrent stroke and improves claudication symptoms.

Physical Inactivity

Physical inactivity is a well-established risk factor for multiple chronic diseases, including hypertension, type 2 diabetes, CHD, stroke, PAD, depression, osteoporosis, and certain cancers (**see also Chapter 53**). Physical inactivity is also associated with increased CV mortality rates.[29] Because the biologic and clinical repercussions of a sedentary lifestyle exacerbate age-related pathophysiologic changes, the health consequences and societal costs of physical inactivity are especially relevant to older adults. Physical inactivity results in decreased functional capacity, increased risk of falling, worsened psychological status, and reduced cognitive function. In older adults, decreased physical activity constitutes the most common modifiable CV risk factor after hypertension. Only 18% of persons 75 years or older reported regular moderate or vigorous physical activity, and only 14% of men and 8% of women 65 years or older reported aerobic and muscle-strengthening activities that met the 2008 federal physical activity

guidelines. Patel and colleagues reported increased total mortality rates, especially CV mortality rates, over a 14-year follow-up in men and women 50 to 74 years old who sat more than 6 hours per day compared with those who sat only 3 hours per day[185]; similar findings have been reported in other studies.[29]

An extensive literature shows that reducing physical inactivity (i.e., increasing activity) improves the health status regardless of age, gender, race, or ethnicity. Regular physical activity improves CHD risk factors, including body weight, blood pressure, serum lipids, and insulin sensitivity, as well as bone density, muscular strength, functional capacity, and cognitive and psychological functioning, all key elements of health and well-being in older adults.[29] Numerous observational studies and RCTs demonstrate that older adults benefit from initiating an exercise program; benefits include greater functional capacity, less mobility disability, better QOL, reduced recurrent CV events, and an increase in active life expectancy.[29] A lower CV risk has been associated with even modest physical activity in older adults. In the Honolulu Heart Program, relatively healthy men 71 to 93 years old who walked more than 1.5 miles/day experienced half the risk for new CHD than men who walked less than 0.25 miles/day over 2 to 4 years of follow-up; the risk of incident dementia was also reduced.[29]

Physical Activity Prescription

The most important consideration when counseling regarding physical activity is to help shape a program that is pleasurable and achievable, and that avoids injury or exacerbation of comorbid problems. Aerobic activity, strength activity, balance, and flexibility are all vital components. For adults willing to enter a formal exercise program, specific exercises can help improve tolerance of the physical demands of daily living and recreational activities. Generally, work intensities start lower than in younger patients, with smaller increments over time, especially in those with significant comorbidities that limit mobility (e.g., arthritis, pulmonary disease, and PAD). Increasing the frequency and duration of exercise sessions should supersede increases in intensity to reduce the potential for overuse injuries. For adults who are disinclined to exercise in a program, increasing activity as part of daily living is also beneficial. Regular leisure activities such as housekeeping, walking, and gardening are all healthful.

Accumulating evidence suggests that activity benefits may increase in proportion to intensity. Reports in patients with established heart disease, including one study of patients with a mean age of 75 years, suggest that high-intensity aerobic interval training can elicit greater improvement in exercise capacity than continuous exercise at a lower intensity.[29] Despite these encouraging data, such training is more complex than traditional training, necessitating more supervision for implementation and safety. Larger studies are needed to establish the efficacy and safety of high-intensity interval training in older patients.

Cardiac Rehabilitation

Cardiac rehabilitation consists of structured exercise training combined with secondary prevention reinforcement, including an individualized exercise prescription as well as close supervision and support (**see also Chapter 54**).[29] It can be particularly helpful in catalyzing physical activity and wellness in adults who are sedentary amidst illness, deconditioning, and entrenched behavior patterns. Older adults with CHD who participated in supervised cardiac rehabilitation had mortality rates that were 21% to 34% lower than nonparticipants over the subsequent 5 years, independent of other risk factors.[186] Patients also benefit in terms of increased physical capacity, independence, and self-efficacy after a hospitalization and/or CVD exacerbation, mitigating the risks of posthospitalization disability.[64] Unfortunately, the vast majority of older patients do not participate in cardiac rehabilitation due to

multiple factors, including lack of referral, logistical barriers, or socioeconomic barriers. Failure to refer, particular for women, is a major contributor to the low participation of older adults. Participation in cardiac rehabilitation by Medicare-eligible recipients is only approximately 12%.[29]

Obesity

An estimated two thirds of seniors are overweight or obese (i.e., body mass index [BMI] ≥ 30 kg/m^2), closely paralleling rates in the general population. Data from NHANES suggest that 35% of noninstitutionalized women and 40% of men 65 to 74 years old are obese, as well as 27% of women and 26% of men 75 years of age or older.[8] Between 1988 and 1994 and 2007 and 2008, obesity rates increased 30% to 40% in older women and 67% to 100% in older men.

Being overweight or obese is associated with mildly increased mortality rates,[8] but the risk ratio decreases as age advances. Given the higher mortality rates in old age, the mortality risk attributable to obesity is higher in older adults. In obese patients with established CVD, multiple studies have demonstrated an obesity paradox; overweight and obese patients have higher survival rates than patients of normal weight. Similar findings have been observed in older populations with CVD, but most of these studies have not differentiated between fat and lean mass, which likely plays an important role in health effects in old age.

Diet

Undernutrition is more common in older than younger individuals due to a combination of medical and socioeconomic factors: 5% to 10% of community-dwelling persons age 70 years or older are undernourished, and the prevalence increases to 30% to 65% in institutionalized elders. It is useful for cardiologists and primary care providers to assess the dietary intake of older patients, provide general dietary advice, and refer to a nutritionist if a major dietary deficiency or malnutrition is suspected. Vitamin and mineral deficiencies are common in seniors due to inadequate intake, decreased absorption, and the effects of disease and medications. Vitamin D deficiency is particularly common in older adults due to low sunlight exposure and reduced synthesis by the skin, and has been associated with increased CV mortality rates.[29] Trials of vitamin D supplementation have not shown consistent benefit.

The Mediterranean diet (i.e., fruits, vegetables, whole grains, and nuts plus low intake of saturated fat) has been associated with beneficial effects on CV risk factors and outcomes in both older and younger adults. Some of these benefits may emanate from flavonoids, which are abundant in fruits, vegetables, nuts, tea, and wine, and have antiinflammatory and antioxidant effects. Higher flavanoid intake was associated with a lower risk of CV death in a population of 98,000 adults of an initial mean age of 70 years.[187]

Noncardiac Surgery and Perioperative Management Considerations in Older Adults

The number of individuals over 70 years of age undergoing surgical interventions has increased dramatically and continues to expand. Perioperative management in older adults poses distinctive age-related challenges. Advance directives are important and patients should identify a health care proxy. Suspending a do-not-resuscitate designation is common during procedures, but it is important to clarify management plans should an adverse outcome ensue.

The 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery[188] highlights that 25% to 30% of perioperative deaths are CV related and recommends stratifying by MACE risks. The Revised Cardiac Risk Index (RCRI) determines risk using six criteria: (1) IHD; (2) HF; (3) cerebrovascular disease; (4) diabetes requiring preoperative insulin use; (5) CKD (creatinine > 2 mg/dL); and (6) undergoing suprainguinal vascular, intraperitoneal, or intrathoracic surgery. The risk for cardiac death, MI, HF, cardiac arrest, or heart block with no predictors is 0.4%, with one predictor 0.9%, two predictors 6.6%, and three or more predictors 11% or more. The risk is compounded by geriatric domains (e.g., multimorbidity, frailty, polypharmacy, disability, impaired cognition, and mood). The functional status is often more relevant than the RCRI criteria because it entails issues of sarcopenia, frailty, inflammation, and nutrition and their bearing on the metabolic demands of surgery, as well as risks associated with immobilization. Gait speed, a marker of frailty, has been recognized as an important predictor of adverse outcomes even beyond standard assessments by the Society of Thoracic Surgery scoring system; a slow gait speed (≥0.8 m/sec) adds significantly to risks based on the Society of Thoracic Surgery score.[189]

Age-related changes alter drug pharmacodynamics and pharmacokinetics, rendering older patients more vulnerable to anesthetic and analgesic complications. Although regional (epidural) anesthesia does not generally decrease the mortality risk or risk of postoperative delirium or cognitive dysfunction, it is associated with better peripheral vascular circulation, less blood loss, improved pain control, reduced ileus, attenuation of thromboembolic complications, fewer respiratory complications, reduced postoperative narcotic requirements, and a reduced surgery stress response.

Specific Complications and Their Management

Table 88.7 lists some of the basic management principles that pertain to older adults.[188] Geriatric domains compound risks.[190] Delirium is a frequent complication in older adults, with an incidence of 40% to 52%.[191] Postoperative delirium is associated with persistent cognitive deficits and contributes to short- and long-term mortality risks, as well as increased hospital costs, functional decline, and disability. Delirium is highest following cardiac and aortic surgery and substantially less with hip surgery or minor procedures. Avoidance of restraints, provision of hearing and vision aids, presence of family, early mobilization, a normal sleep/wake cycle, adequate pain management, and hydration are key preventive strategies. Postoperative cognitive dysfunction entails deterioration in memory and executive functions in the days to weeks after surgery, but because patients are not confused, conventional screening tools for delirium are insensitive. The incidence following major surgery has been reported to be more than 50%, and is associated with a protracted hospital stay and diminished QOL. Recent studies suggest that postoperative cognitive dysfunction may correspond primarily to baseline cognitive deficiencies[46,57]; this highlights the strong need for thorough preoperative assessments.

TABLE 88.7

Perioperative Medications and Cardiovascular Management Considerations

MEDICATIONS	CARDIOVASCULAR MANAGEMENT CONSIDERATIONS
Discontinue before surgery • ASA, NSAIDs 5-7 days before surgery to ↓ bleeding • Anticoagulants 1-4 days before surgery; consider bridging when indicated • Anticholinergics to ↓ delirium • Diuretics: hold for 24 hr • Benzodiazepine: taper to ↓ withdrawal • Hypoglycemics typically held **Continue or start before surgery** • Antiepileptics • Cardiovascular and antihypertensive medications • Insulin usually at half normal dose and steroids at stress dose • Beta blockers (if high risk based on ≥ 3 revised cardiac risk index factors) should be started several days before surgery and continued for at least 1 month following surgery (heart rate goal, 55-60 beats/min) **Avoid entirely** • Prophylactic nitroglycerin	**Hypertension:** treat very high blood pressure (>180/110 mm Hg) but avoid overly aggressive therapy that may increase risks of intraoperative hypotension **Myocardial infarction:** pain may be masked by narcotics; ST segments are an independent marker of risk and warrant biomarker evaluation • Postoperative myocardial infarction has similar pathology and management to nonsurgical patient, but needs to be differentiated from demand ischemia **Arrhythmias:** often related to noncardiac causes such as infection, hypotension, hypothermia, hypokalemia or hypomagnesemia, pulmonary embolism, ischemia, volume overload, pain, and hypoxemia • Supraventricular tachycardia; ↑ perioperative stroke; ↑ length of stay; ↑ cost • Postoperative atrial fibrillation occurs in about 4% of patients < age 50 but in up to 25% of patients > age 70; ventricular ectopic activity occurs in as many as one third of high-risk patients • Atrial fibrillation occurs in 3% to 5% of major nonthoracic, noncardiac surgical procedures, and 10% to 15% of intrathoracic procedures. Stable patients should be treated with heart rate control and anticoagulation with unfractionated or low-molecular-weight heparin. **Heart failure (volume overload):** common amidst volume overload of surgery (particularly due to reduced cardiovascular reserves that occur with aging) **Deep vein thrombosis:** The risk range is 4% to 8% in older patients not receiving prophylaxis, and doubles in high-risk settings. Predisposing factors include older age, venous stasis, hypercoagulable state. Preventive strategies include early ambulation, mechanical prophylactic measures such as graded pneumatic compression boots or compression stockings, and anticoagulation.

Decubitus ulcers are also common in older surgical patients. Risks include loss of subcutaneous tissue and decreased elasticity of the aged skin, which predisposes to damaged superficial tissues when the skin is compressed for prolonged periods. There may be secondary infection, delayed recovery, and prolonged hospitalization, typically with discharge to a transitional care facility. Preventive measures include routine postoperative skin examination, frequent repositioning, use of support surfaces that redistribute pressure, pressure-relieving overlays in the operating room, and use of foam alternatives and heel protectors.

Older adults are also susceptible to hypothermia due to impaired central and peripheral thermoregulatory function and the effects of anesthesia. It is particularly common among underweight or frail older adults, and may contribute to electrolyte abnormalities, platelet dysfunction, an increased risk for wound infection, and impaired drug metabolism. Warming to a core temperature of about 36°C is recommended, with correction of electrolyte abnormalities.

Respiratory complications are more common with age and include pneumonia, prolonged ventilation, and the requirement for intubation. Postoperative aspiration pneumonia is also common, with risks compounded by cognitive decline, delirium, and sedation. Urinary tract infections and acute or progressive renal failure are also common. Minimizing nephrotoxins and urinary catheters and maintaining hydration are important considerations.

Postoperative Priorities

Early mobilization is vital to perioperative care; it can minimize DVT, deconditioning, frailty, and sarcopenia. Early mobilization has also been associated with improved cardiac output and hemodynamics, and it may reduce bone loss, hypocalcemia, joint contractures, constipation, incontinence, pressure ulcers, sensory deprivation, atelectasis, hypoxemia, pneumonia, depression, delirium, anxiety, and insomnia. To mitigate delirium and cognitive perturbations, it is important to minimize sedation and opiates, provide early extubation, and place an emphasis on recovery. Risk assessment at discharge must include consideration of hospitalization-associated disability, frailty, sarcopenia, deconditioning, and malnutrition, as well as altered cognition; all may provoke dependency and loss of independence, as well as rehospitalization. The use of rehabilitation is critical whether delivered by a home health worker or physical therapist or in an SNF or rehabilitation facility.

Distinctive Precepts of Patient-Centered CARE in Relation to Old Age

In younger adults, CVD typically entails an identifiable pathophysiologic perturbation that disrupts a baseline of health that is generally similar from one patient to another. However, in older adults, CVD pathophysiology more likely occurs in a more heterogeneous baseline physiology. Each senior has idiosyncratic physiology, metabolism, body composition, comorbidity, and lifestyle contexts such that CVD affects the person in ways that are relatively distinctive. Thus, while guidelines-based care provides an important therapeutic standard among younger CVD patients, in older adults, individualized management becomes relatively more imperative.[192] Whereas standard CVD therapeutics are oriented primarily to prolonging survival rates and/or preventing MACE, each older adult is more likely to have distinctive goals. Many place greater value on enhancing their functional capacity, independence, QOL, and/or other dimensions of health and well-being, factors that are jeopardized by CVD[2] in old age.

Diagnosis

Prototypical CV symptoms of pain, dyspnea, dizziness, exercise intolerance, and other complaints are less sensitive and specific in the context of age-related clinical and physiologic changes. Clinical signs (e.g., rales, edema) have many similar limitations. Diagnostic delays often result in CVD being recognized only after it has progressed to an advanced stage and often too late to implement time-sensitive revascularization or other therapeutic options.[193] Ironically, at other times, CVD is more likely to be overdiagnosed in many older adults, particularly in relation to diagnostic imaging techniques (e.g., perfusion imaging or CT scanning for CHD) or biomarkers (e.g., BNP for HF)[194] that can be more reflective of age-related physiologic changes than disease.

Risk Assessment

Prognostic risks in older adults are commonly compounded by risks associated with aging physiology (e.g., more aggressive CHD) or comorbid disease (e.g., multiple types of concurrent CVD as well as COPD, CKD, cancer, and other noncardiac diseases), as well as geriatric domains (e.g., multimorbidity, polypharmacy, delirium, falls, and even lack of family support for someone frail and disabled). In almost every risk prediction model, age stands out as the highest predictor of poor outcome.[6] Yet the basic application of prognosis is also blurred by the way prognosis is conceptualized and measured. Prognosis connotes “disease outcomes,” and in younger populations refers primarily to death and morbidity. In older CVD patients, prognosis is usually applied more broadly, with reference to functional capacity, QOL, and other concerns that are more pertinent with age but are usually less well delineated and measured. Therefore, related risk-to-benefit concepts often become ambiguous for elderly CVD patients struggling with multiple personal issues.

Disease Management and Care Coordination

The fact that there are high risks associated with CVD in old age implies that the potential for risk reduction is increased with effective therapies. However, risks for harm from therapies are also increased. Older adults not only have a reduced capacity to tolerate medications, devices, and procedures, but the therapeutic effects of these interventions are usually more variable**.** Even when acute

therapy seems to go well, progression to frailty and disability may occur. Therefore, guidelines and precepts cannot be immediately applied to typical geriatric patients, but must be weighted in terms of risks and benefits relative to each patient's circumstances and the continuum of aging changes. Caregiving becomes as much an art as a science. CVD therapies elemental for younger adults require greater individualization in older patients.[195] Although this has value in its potential to engender personalized care, it also raises the countervailing tension that less standardized care may lead to variable quality and outcomes.

Shared decision making seems a relatively logical way to facilitate CVD management that meets the personal needs and circumstances of each patient, but it assumes that older adults understand their diseases and aggregate health circumstances, as well as the value and limitations of each therapy.[22] Limitations in health literacy are common in any age, but are especially relevant for older adults with CVD. Vascular and myocardial disease, frailty, multimorbidity, dementia, and depression are among the age-sensitive dynamics that detract from cognitive capacities that enable health literacy. Improved decision-making tools for patients and caregivers remain an important aspect of care.

Each older patient's values are also pertinent. Some may experience aggressive therapies as burdensome and eschew options that seem likely to yield important benefits (e.g., treating hypertension in an asymptomatic senior). Others may feel devalued or even maltreated unless a full medical armamentarium is employed, even if no meaningful benefits are likely (e.g., insisting on a TAVR despite advanced Parkinson disease). Complicated family dynamics are also common, ranging from a spouse or child demanding a therapy with uncertain utility, to those who fail to provide any support or help.

Most older patients also have multiple providers, including multiple physicians as well as advanced practice nurses, physician assistants, pharmacists, nutritionists, speech pathologists, physical and occupational therapists, and social workers, as well as possible palliative care and hospice consultants. Having multiple providers provides complementary expertise but it also may predispose the patient to fragmented care. The potential for mixed messaging, counterproductive therapeutic plans, confusion, and nonadherence is high. The conceptual value of having a medical “quarterback” to integrate care of older adults across multiple providers has been emphasized. Although this is often assumed to be the domain of the primary care provider, decisions regarding medications, devices, procedures, and ongoing monitoring increasingly require CV expertise. Thus, CV clinicians must increasingly be skilled to work within such complex team relationships. Effective interpersonal skills and organization are increasingly requisite for successful CV care.

The impact of transitions is also greater in older than younger CVD patients. Transitions between floors and services within hospitals, from hospital to home, and from hospitals to SNFs to home all entail complex management issues, multiple systems of care, and a high potential for confusion. At each point of transition the older adult is vulnerable to adverse events. A critical part of CVD care is reconciliation of medications and management at each stage of treatment and emphasis on the broader priorities of physical and cognitive function that help to mitigate susceptibility to frailty, disability, delirium, and decline.

Adherence

Adherence is a significant challenge among older adults. Reasons include poor coordination of recommendations from multiple clinicians, limited health literacy (typically exacerbated by cognitive declines), and/or limited financial and social resources. Poor adherence also can evolve when recommendations are not aligned with a patient's goals and preferences.[196] Multiple tools for improving adherence, including medication lists, electronic reminders, pill organizers and dispensers, and remote

monitoring devices, have been promoted, but suboptimal medication management often persists. Taking steps to ensure that treatment recommendations are consistent with patients' goals and capacities remains an important part of enhanced solutions. Costs are also relevant. Despite introduction of a Medicare prescription program in 2006, 8% of older adults did not fill one or more prescriptions because of costs[25,197] and proportions of those who did not fill prescriptions have continued to rise in older adults with low incomes.

Life Expectancy

Anticipated life expectancy is sometimes used to gauge the utility of care for older patients. Convenient tools to approximate the length of life have been developed and validated.[198] CVD therapies may then be considered in relation to the predicted longevity, with the intention of only using therapies when there is sufficient longevity for a meaningful effect. These decisions must be informed by awareness of each therapy's anticipated lag time to benefit as well as any potential lag time to harm. It is important to clarify which therapies are likely to relieve symptoms and which may extend life. Therapies providing symptom improvement can be useful even if longevity is limited (e.g., balloon aortic valvuloplasty), whereas those that primarily prolong survival times (e.g., statin therapy) might only have value for those with significant life expectancy. This approach is also limited by the fact that many therapies have multiple effects. Whereas statins take about 2 years to yield likely survival benefits for CHD, they can reduce claudication more rapidly.[29]

Opportunities for Telehealth

The burgeoning field of telehealth has generated much excitement about potential applications in older adults with CVD, particularly in response to the logistic limitations of many infirm elderly. The utility of telehealth in diabetes management is often shown as a model of potential benefit for broader applications,[199] including monitoring (e.g., blood pressure, pulse), adherence, and physical activity. However, the utility of telehealth has been most successful in younger populations of tech-savvy adults. Its application to older, frailer, and cognitively impaired elderly remains challenged by the skills required to manipulate smart phone applications and/or other telehealth devices, as well as concerns regarding adherence, safety, and value.[200]

Postacute Care: Skilled Nursing Facilities and Long-Term Care

The role of postacute care for CVD patients is changing. Older and sicker patients were once routinely hospitalized for long lengths of stay and were more stable upon discharge to postacute care. As contemporary incentives encourage more rapid discharges from acute hospitalizations, increased numbers of older CVD patients are being discharged to SNFs. Of the more than one million hospital discharges for HF each year in the United States, approximately 20% are discharged to SNFs.[201] Patients are more likely to be unstable, and left to the care of a staff that often lacks advanced CVD sophistication and/or systematized communication with CVD clinicians. Medicare is increasingly demanding that SNFs improve quality metrics and reduce hospital readmissions.[202] SNFs that achieve high performance measures by October 1, 2018, will receive incentive payments; SNFs that lag behind will be subject to penalties.

Palliative Care and End-of-Life Decisions

Palliative care is a holistic approach for patients facing a life-threatening illness (**see also Chapter 31**).

It focuses on symptoms as well as psychosocial and spiritual needs. It provides an extra layer of support, often in association with standard care. Palliative care has been demonstrated to improve the quality of care and even overall survival times,[203] and it is distinct from hospice care, which is oriented to patients with a prognosis of less than 6 months of expected survival, and who have agreed to forgo more aggressive treatment.

In some respects, geriatric cardiology and palliative care overlap. Many palliative care patients are older, and struggle with frailty, disability, and other complexities of care that prompt tailored approaches to CV management. Geriatric cardiology and palliative care are also quite distinct, however.[2] Cardiologists are oriented to the crossroads of management, and must determine which older, frail patients with complex medical needs may still benefit from prevention and intervention strategies that may forestall or reverse a decline (e.g., TAVR may mitigate disease that had initially seemed at the end stage), whereas palliative care is more oriented to management in a context of predominant decline.

Collectively, both cardiologists and palliative care experts have a formidable potential to work synergistically. Cardiologists have particular skills to optimize function, QOL, and other symptomatic improvements for older CVD patients with limited life expectancy, and to provide illuminating insights amidst predictable complexity (e.g., multimorbidity, comorbidity, delirium). Similarly, cardiology care of older adults entails skills to inform end-of-life decision making, including decisions about resuscitation, thresholds of futility, and critical insights to help families and surrogate caregivers if patients lose the capacity to make their own decisions.

Geroscience: Stopping the Aging Clock

Geroscience is an interdisciplinary field that aims to understand the relationship between aging and age-related diseases. Whereas research on CVD and aging has focused primarily on elements of disease and/or the complexity of applying CVD precepts to older adults with multimorbidity and complexity, geroscience is oriented to mechanisms determinant of aging. If constitutive mechanisms of aging can be eliminated or sufficiently forestalled, many age-related diseases may no longer develop. Candidate mechanisms include macromolecular damage, mitochondrial oxidative stress, malformed proteostasis, deficient autophagy and ubiquitin-mediated proteolysis, stem cell dysfunction, diminished bioavailability of nitric oxide, up-regulated renin-angiotensin-aldosterone physiology, and low-grade inflammation.[204]

Caloric restriction and low-molecular-weight pharmaceutical compounds (e.g., rapamycin, resveratrol, and metformin) have received increasing attention as innovative approaches to retard aging. Although caloric restriction may seem counterintuitive for older adults often coping with sarcopenia, frailty, depression, and other aspects of health for which diet is critical, nutritionally balanced modest caloric restriction induces many favorable physiologic benefits. Caloric restriction down-regulates mTor signaling. mTor becomes relatively dysregulated with age, and in animals, mTor inhibition has been demonstrated to preserve CV function and induce other CV benefits.[205] Rapamycin provides similar mTor down-regulating effects. Caloric restriction research has catalyzed a robust area of human investigation wherein drugs triggering similar mechanical benefits are being investigated. Many other signaling pathways and related pharmaceuticals remain in consideration as potential aging modifiers. Metformin increases AMP-kinase, has antiinflammatory benefits, and is easily studied for antiaging effects in humans because it is already approved for treatment of diabetes. The ongoing Targeting Aging with Metformin (TAME) trial is specifically studying the effect of metformin to prevent or delay the onset of age-related diseases and conditions, including CVD.[206]

Although geroscience is an emerging field to prevent age-related diseases, it is important to emphasize the prominence that geriatric perspectives have attained in prevention and treatment of established CVD. Studies of revascularization, HF, arrhythmia, imaging, valvular heart disease, and other foundations of CV care are increasingly inclusive of age-related perspectives regarding pathophysiology, diagnosis, and management. Future studies focusing on the oldest old will provide requisite data for the care of a rapidly growing subset, especially women, with CVD and the need to guide beneficial interventions.

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Cardiovascular Disease in Women

Martha Gulati, C. Noel Bairey Merz

Cardiovascular disease (CVD) remains the leading cause of death in women. Coronary heart disease (CHD) accounted for 399,028 deaths in women in 2014 and accounts for 1 in every 4 female deaths in the United States.[1] Approximately 47.8 million women are living with some form of CVD. The lifetime risk of developing CVD for a 40-year-old woman is estimated to be 1 in 2, with 1 in 3 at risk of developing CHD, 1 in 5 of developing heart failure (HF), and 1 in 5 having a stroke in their lifetime.[1] Since 2001, there has been a continuous decline in mortality rates from heart disease in women,[1] but in younger women (< 55 years of age) in the last 2 decades, there has been no significant improvement in the mortality rate from heart disease.[2]

There are both sex (biologic) and gender (sociocultural) differences in CVD and its outcomes. A number of variables are found to differ in women and men, including several specific CVD risk factors, treatment and management strategies for both primary and secondary prevention of CVD, and pathophysiologic mechanisms of CVD.

Prevention of CVD in women is influenced by an awareness of sex and gender differences. Although more women had been dying from CVD than men in the United States, it was not until 1991 that the National Institutes of Health (NIH) established a policy that all NIH-funded trials studying conditions that

affect both sexes must include both women and men. In 2016, the NIH made it mandatory to include both sexes in cell and animal studies.[3] Although awareness of CVD as the leading cause of death in women increased from 1997 to 2012 (30% vs. 56%; $P < 0.001$), it remains suboptimal and relatively unchanged since 2006, particularly in racial and ethnic minorities.[4] A nationally representative survey done by the Women's Health Alliance showed that even though 74% of women had one or more CVD risk factor, only 16% of women had been informed that they were at risk for heart disease.[5] Physician awareness, education, and assessment of a woman's CVD risk are also far from expected. In a 2014 survey of physicians, only 22% of primary care physicians and 42% of cardiologists felt well equipped to assess the CVD risk in women, and less than 50% of physicians were using the recommended Atherosclerotic Cardiovascular Disease (ASCVD) risk assessment calculator for their women patients.[6]

Sex, Gender, and Genetic Differences in Cardiovascular Disease

The Institute of Medicine has defined *sex* as "the classification of living things, generally as male or female according to their reproductive organs and functions assigned by the chromosomal complement."[7] Sex differences result from true biologic differences in the structure and function of the cardiovascular systems of men and women, in contrast to gender differences, which stem from a person's self-representation and result in psychosocial roles and behaviors imposed by society. Certainly gender differences play a role in the treatment of CVD and, hence, the impact outcomes, but they are very different from sex differences, which arise from the genetic differences between men and women. Sex differences arise from the chromosomal differences between men (XY) and women (XX).

Genetic markers predictive of CVD remain undefined to date in women. The Women's Health Genome Study followed 19,313 white women prospectively for a median of 12.3 years to assess whether a genetic risk score could improve the predictive risk assessment of women beyond traditional risk factors.[8] The prediction of CVD risk in women by means of the comprehensive literature-based genetic risk score has not improved; thus, no genetic marker is known that can be used to improve the risk assessment in women, beyond traditional methods.

Risk Factors for Cardiovascular Disease in Women (See also Chapter 45)

Established Risk Factors

Age

Age powerfully predicts the risk for CVD, and specifically CHD. The prevalence of CVD increases with age in both men and women, but CHD events lag at least 10 years in women compared with men.[1] CHD increases in women after the age of 60 years, with 1 in 3 women having evidence of CHD after the age of 65 years, in contrast with 1 in 8 in women age 45 to 64 years. The ASCVD risk score increases with increasing age.[9] The largest sex difference in CHD mortality rates occurs in relatively young and middle-aged women, with relative stagnation in rates, in contrast with continued declines seen in men and elderly women.[2]

Family History

A history of CHD in a first-degree relative imparts a risk for an individual. The ASCVD risk assessment tool and the AHA Guidelines for the Prevention of Cardiovascular Disease in Women define a family history of premature CHD as a first-degree relative with CHD before the age of 65 years for women and age 55 years for men.[9,10] Premature CHD in first-degree female relatives is a relatively more potent family history risk factor than in male relatives.[11] In addition, women classified as low risk for CHD (using the Framingham Risk Score) but with a sister with premature CHD more likely have evidence of subclinical CHD as shown by the amount of coronary artery calcium, based on a study of 102 asymptomatic women.[12] The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults recommends consideration of a premature family history of CVD when assessing risk in asymptomatic adults.[9]

Hypertension (See also Chapters 46 and 47)

Women have a higher overall prevalence of hypertension compared with men, depending on age. Based on the National Health and Nutrition Examination Survey (NHANES), before the age of 60, more men than women have hypertension, but after age 60, the prevalence of hypertension is higher in women.[13] Hypertension rises twofold to threefold in women taking oral contraceptives, which raise the blood pressure by 7 to 8 mm Hg on average.[14]

The NHANES from 2011 to 2014 demonstrated that hypertensive women more likely received treatment than men (56.3% vs. 50.6%).[13] Younger women (≤ 59 years) were more likely to have controlled blood pressure compared with men. Women over the age of 60 not only had a higher prevalence of hypertension but had poorer blood pressure control than men.[13]

Hypertension is associated with an increased risk of the development of congestive heart failure, and this risk appears to be greater in women.[15] Women who present with strokes more likely have a history of hypertension than men.[16] Indeed, the lifetime risk of stroke is greater in women compared with men, related to their greater life expectancy and the rise in stroke rates with age.

Diabetes (See also Chapter 51)

Diabetes increased the risk of CHD and confers a greater risk for CHD in women than men, increasing a woman's risk of CHD by threefold to sevenfold, with only a twofold to threefold increase in diabetic men. In addition, the risk of fatal CHD in a diabetic woman is 3.5 times that in a nondiabetic woman, and is higher than in diabetic men (relative risk [RR] of fatal CHD is 2.0 that of a nondiabetic man).[17] In addition, women with type 1 diabetes have twice the risk of fatal and nonfatal cardiovascular events, and a 40% greater risk of all-cause deaths compared with men.[18]

The American Diabetes Association suggests consideration of diabetes screening for women and men over the age of 45 years, and then every 3 years if the results are normal. For women with a history of gestational diabetes, screening for diabetes should occur 6 to 12 weeks postpartum and every 1 to 2 years thereafter.[19]

Dyslipidemia (See also Chapter 48)

Dyslipidemia is common in women; more than half of American women have a total cholesterol level greater than 200 mg/dL and 36% have a low-density lipoprotein cholesterol (LDL-C) level greater than 130 mg/dL. Notably in women, adverse changes in the lipid profile accompany menopause and include increased levels of total cholesterol, LDL-C, and triglycerides and decreased levels of high-density lipoprotein cholesterol (HDL-C), although it remains unclear how much risk factor worsening is related to aging as opposed to menopause-related hormonal changes.[20]

The ASCVD risk assessment focuses on LDL-C as the primary target of lipid-lowering therapy to reduce the risk of CVD.[9] The use of nuclear magnetic resonance spectroscopy for lipoprofiles, apolipoproteins, particle size, and density has not demonstrated superiority over a standard fasting lipid profile for cardiovascular risk assessment in asymptomatic women.[21]

HDL-C levels in women average around 10 mg/dL higher than in men throughout their lives. HDL is inversely associated with ASCVR events.[22] Nonetheless, HDL as a target of therapy has, to date, never improved outcomes and is not the target of the ASCVD risk assessment.

Smoking

In 2014, 18.8% of men and 14.8% of women reported tobacco use, putting them at increased risk of CVD.[23] Although women smoke less than men, smoking may be more detrimental in women than men. Female smokers die 14.5 years earlier than female nonsmokers, and male smokers die 13.2 years earlier than male nonsmokers.[24] Cessation of smoking substantially reduces the risk in women; the mortality risk among former smokers decreases nearly to that of never smokers.[25]

The use of oral contraceptives and smoking imparts an even greater risk of myocardial infarction (MI) than smoking alone, likely related to prothrombotic effects. Smoking 25 or more cigarettes a day increases a women's risk by 12-fold, but smoking 25 or more cigarettes a day and taking oral contraception increases one's risk by 32-fold.[26] Third-generation hormonal contraceptives appear to pose less risk than prior- and fourth-generation formulations.[14]

Physical Activity and Physical Fitness (See also Chapter 53)

Sedentary behavior is more common in women than in men (31.7% vs. 29.9%), and inactivity increases with age,[1] although gender bias in physical activity measurement instruments, which do not consider domestic activities such as cooking, cleaning, and childcare, may account for these observed differences. Using the 2008 U.S. federal physical activity guidelines, in every age-group adult women studied in the 2014 National Health Interview Survey reported performing less leisure time physical activity than men.[27]

Physical inactivity is associated with higher blood pressure, worse cholesterol levels, poorer glucose metabolism, poorer mental health, and obesity. Physical inactivity, quantified by a prolonged sitting time, has been shown to be an independent risk factor for CVD in women beyond leisure-time physical activity.[28]

Exercise capacity, also known as physical fitness, strongly and independently predicts all-cause mortality rates in asymptomatic women and can be quantified. In the Women Take Heart Project, asymptomatic women who did not achieve 5 metabolic equivalents (METs) on the Bruce protocol had a threefold increased risk of death compared with women who achieved more than 8 METs.[29] Furthermore, the risk of death among asymptomatic and symptomatic women whose exercise capacity was less than 85% of the predicted value for age was at least twice that of women whose exercise capacity was at least 85% of their age-predicted value.[30] Age-predicted fitness can be estimated using the validated nomogram (**Fig. 89.1**). In the Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women 2011 Update, physical inactivity or poor physical fitness is a criterion for placing a woman in the "at-risk" group.[10]

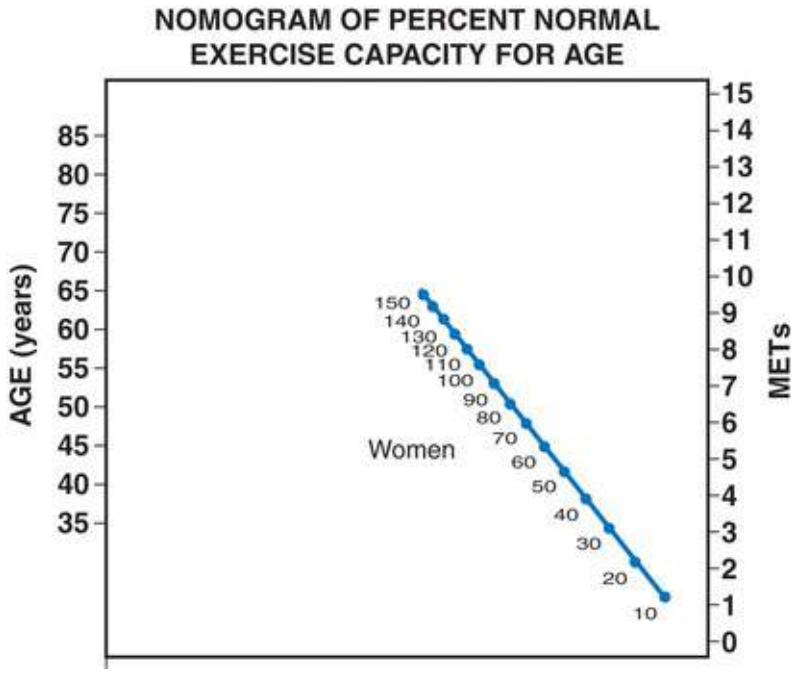

FIGURE 89.1 Nomogram of the percentage or predicated exercise capacity for age in asymptomatic women. A *line* drawn from the patient's age on the left-hand scale to the MET value on the right-hand scale will cross the percentage line corresponding to the patient's percentage of predicted exercise capacity for age. (From Gulati M, Black HR, Shaw LJ, et al: The prognostic value of a nomogram for exercise capacity in women. N Engl J Med 2005;353:468.)

Emerging Risk Factors

Metabolic Syndrome (See also Chapters 45 and 50)

NHANES data from 2003 to 2012 indicate that 35.6% of women met the criteria for having the metabolic syndrome, with higher rates than seen in men (33.3%; $P < 0.01$).[31] In addition, those with the metabolic syndrome have an increased risk of developing CVD, and this association is strongest in women, with a relative risk of CHD of 2.63, compared with a relative risk of 1.98 in men, when compared with their same gender counterparts without the metabolic syndrome.[32]

Obesity (See also Chapter 50)

Obesity, defined as a body mass index (BMI) of more than 30 kg/m^2, is epidemic in the United States, with the 2011 to 2014 NHANES estimation of obesity in women at 38%, higher than the prevalence in men (34.3%).[33] The rising incidence of diabetes is associated closely with obesity. In the Nurses' Health Study, obesity was the most powerful predictor of diabetes, with women with a BMI of 35 kg/m^2 or higher having a relative risk for diabetes almost 40-fold greater than women with a BMI of less than 23 kg/m^2. The pattern of obesity appears to be related to CVD, whereby a waist circumference larger than 35 inches, indicative of visceral obesity, is related to an elevated CVD risk, whereas an elevated BMI alone is not.[34]

Although obesity has also been associated with an increased mortality rate from CVD and shortened life expectancy from CVD,[35] obesity is not an independent risk factor for CVD given that obesity is strongly associated with many of the traditional CHD risk factors. Notably, overweight, defined as a BMI of more than 25 kg/m^2 but less than 30 kg/m^2, is associated with lower mortality rates and CVD death rates compared with a leaner measurement.[36] Obesity may simply be a marker for low physical activity and fitness levels. Prior work in women where both obesity and physical fitness were measured suggests that physically fit obese women are not at an elevated risk, and conversely lean women who are not physically fit have an elevated risk.[37]

High-Sensitivity C-Reactive Protein (See also Chapter 50)

Although high-sensitivity C-reactive protein (hsCRP) is not a causal risk factor for CVD, it may improve risk detection in women.[38] The Women's Health Study demonstrated that a model that included hsCRP improved the cardiovascular risk prediction in women.[38] For women with the metabolic syndrome, hsCRP may add prognostic information regarding the future cardiac risk. In one study of apparently healthy women, women with the metabolic syndrome and hsCRP levels greater than 3.0 mg/L had almost twice the risk of future cardiovascular events as those with the metabolic syndrome and an hsCRP level of less than 3.0 mg/L.[39] Measuring hsCRP is not recommended in the routine risk assessment of women, but rather it is an option in those persons in the intermediate risk range based on the Framingham Risk Score.[40]

Autoimmune Disease (See also Chapter 94)

Systemic inflammation in autoimmune disease may accelerate atherosclerosis and ischemic heart disease, and these diseases occur more frequently in women.[41] Rheumatoid arthritis and systemic lupus erythematosus (SLE) are associated with a significantly increased risk for CVD.[42,43] Cardiovascular events often occur in younger women with SLE, with a risk for acute MI 9-fold to 50-fold greater than in the general population.[44] Traditional risk factors such as smoking, family history of premature CHD, hypertension, and elevated cholesterol levels do not completely account for the increased risk of CHD in patients with SLE. In the Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women 2011 Update, systemic autoimmune collagen-vascular disease was listed as a criterion for an “at-risk” status.[10]

Polycystic Ovary Syndrome (See also Chapter 92)

Unique to women, polycystic ovary syndrome (PCOS) is associated with the development of many of the features of metabolic syndrome, as well as insulin resistance, although first-degree male relatives also appear to have more insulin resistance.[45] Women with PCOS have an increased prevalence of impaired

glucose tolerance, the metabolic syndrome, and diabetes compared with women without PCOS.[46] PCOS may confer an elevated risk for CVD independent of established risk factors in older postmenopausal women.[47] Furthermore, in the National Heart, Lung, and Blood Institute (NHLBI)–sponsored Women's Ischemia Syndrome Evaluation (WISE) study of postmenopausal women with PCOS, the cumulative 5-year CVD event-free survival rate was 79% for women with PCOS compared with 89% for women without PCOS.[47]

Functional Hypothalamic Amenorrhea (See also Chapter 92)

Up to 10% of premenopausal women have documented ovarian dysfunction, with a larger proportion having subclinical hormonal dysfunction that may increase CVD risk. Functional hypothalamic amenorrhea (FHA) is a cause of a premenopausal ovarian dysfunction and occurs when gonadotropin-releasing hormone increases, thereby increasing luteinizing hormone in a pulse frequency, causing amenorrhea and hypoestrogenemia. Psychological stressors or metabolic insults such as caloric restriction or excessive exercise can induce FHA. In a large cohort study, women with menstrual irregularities had a 50% increased risk of nonfatal and fatal CHD compared with women with regular menstrual cycling. Additional data indicate that FHA is associated with premature coronary atherosclerosis in women undergoing coronary angiography, and that use of oral contraceptive therapy may offer protection.[48] Thus amenorrhea and cycling irregularity may augment CVD risk in women, a topic that requires further work.

Eclampsia, Preeclampsia, and Pregnancy-Associated Hypertension (See also Chapter 90)

Gestational hypertension of any sort is associated with an increased risk of hypertension, chronic kidney disease, diabetes, stroke, and CVD (including HF and MI).[49-51] Women with a history of preeclampsia have approximately double the risk for subsequent ischemic heart disease (IHD), stroke, and venous thromboembolic events over the 5 to 10 years following the pregnancy.[52] The median age for a stroke in these women is 50 years or younger; this indicates that the risk for CVD is accelerated even though these women have a premenopausal status and would be presumed to have a lower risk because they are being screened for and treated for CVD risk factors.[53] Despite the association with elevated CVD events and labeling of pregnancy as a “stress test” for future cardiovascular events, some research suggests that the risk of CVD results from shared prepregnancy risk factors rather than any direct influence of the hypertensive disorder that occurred during pregnancy.[54] The Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women 2011 Update listed a history of preeclampsia or pregnancy-induced hypertension as a criterion for an “at-risk” status. Additionally, hypertensive disorders of pregnancy are noted in the 2014 Guidelines for Stroke Prevention in Women to be associated with an increased risk of stroke during pregnancy, immediately after pregnancy, and even years after the associated pregnancy.[16]

Gestational Diabetes (See also Chapter 90)

A history of gestational diabetes doubles the risk of diabetes in the 4 months postpartum and remains a lifelong risk factor for diabetes and CVD.[55] Fasting glucose levels of 121 mg/dL or higher during pregnancy increase the risk for diabetes in the early puerperium by 21-fold.[56] The Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women 2011 Update incorporated a history of gestational diabetes as an “at-risk” criterion, which means that attention to cardiovascular risk factors and

implementation of therapeutic lifestyle changes is required in these women throughout life.

Breast Cancer Therapy (See also Chapter 81)

Recent advancements in breast cancer treatment have led to improved survival rates from that disease but an elevated risk of CVD.[57] Breast cancer therapies are associated with varying degrees of direct cardiovascular injury in conjunction with significant indirect lifestyle changes that also reduce cardiovascular reserves.[58] Although it is uncertain whether breast cancer overall, or specific therapies for breast cancer per se, will emerge as risk factors for CVD, this issue assumes increasing importance in the management of women surviving breast cancer, given that recent work demonstrates an increased risk of CVD just 7 years after the breast cancer diagnosis.[57]

Reproductive Hormones

Oral Contraceptive Therapy

The AHA and the American College of Obstetricians and Gynecologists (ACOG) have published guidelines on medical eligibility for contraceptive use.[16,59] For most women, who are healthy and free of CVD and cardiovascular risk factors, the use of combination estrogen-progestin oral contraceptives is associated with low relative and absolute risks of CVD.[60] Women who are smokers over the age of 35 years and women with uncontrolled hypertension, a history of thromboembolic disease, or a history of IHD have an unacceptable level of CVD risk associated with oral contraceptives.[14,16]

Postmenopausal Hormone Therapy

Most cases of CVD occur after menopause in older women, in association with an increased burden of established CVD risk factors.[61] It is for this reason that postmenopausal hormone therapy is thought to reduce the CVD risk, a theory supported by observational data. Nonetheless, randomized trials, such as the Heart and Estrogen/Progestin Replacement Study (HERS) I, HERS II, Women's Health Initiative (WHI), and Raloxifene Use for The Heart (RUTH), found that neither hormone therapy nor selective estrogen receptor modulators (SERMs) prevent primary or secondary CVD events. The AHA Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women 2011 Update and the AHA Guidelines for the Prevention of Stroke both state that hormone replacement therapy and SERMS should not be used for the primary or secondary prevention of CVD and are a class III, level of evidence A, intervention.[10,16]

Assessment of Risks for Cardiovascular Disease in Women (See also Chapter 45)

The INTERHEART study examined the association of multiple risk factors with the risk of an MI and compared the relative risks of their association by gender.[62] This study found that nine factors accounted for 94% of the population-attributable risk for acute MI in women and 90% of the risk in men. These risk factors included the apolipoprotein B/apolipoprotein A-1 ratio, cigarette smoking, hypertension, diabetes, abdominal obesity, psychosocial factors (index score based on depression, stress at home or work, financial stress, life events, and a control score), fruit and vegetable intake, exercise, and alcohol intake. For most of the risk factors, the strength of the association was similar amongst both sexes, but diabetes and psychosocial factors had a greater association with the risk of acute MI in women. Lifestyle choices, including exercise, fruit and vegetable consumption, and modest alcohol consumption were associated with a greater level of prevention of acute MI in women compared with men (**Fig. 89.2**).[62]

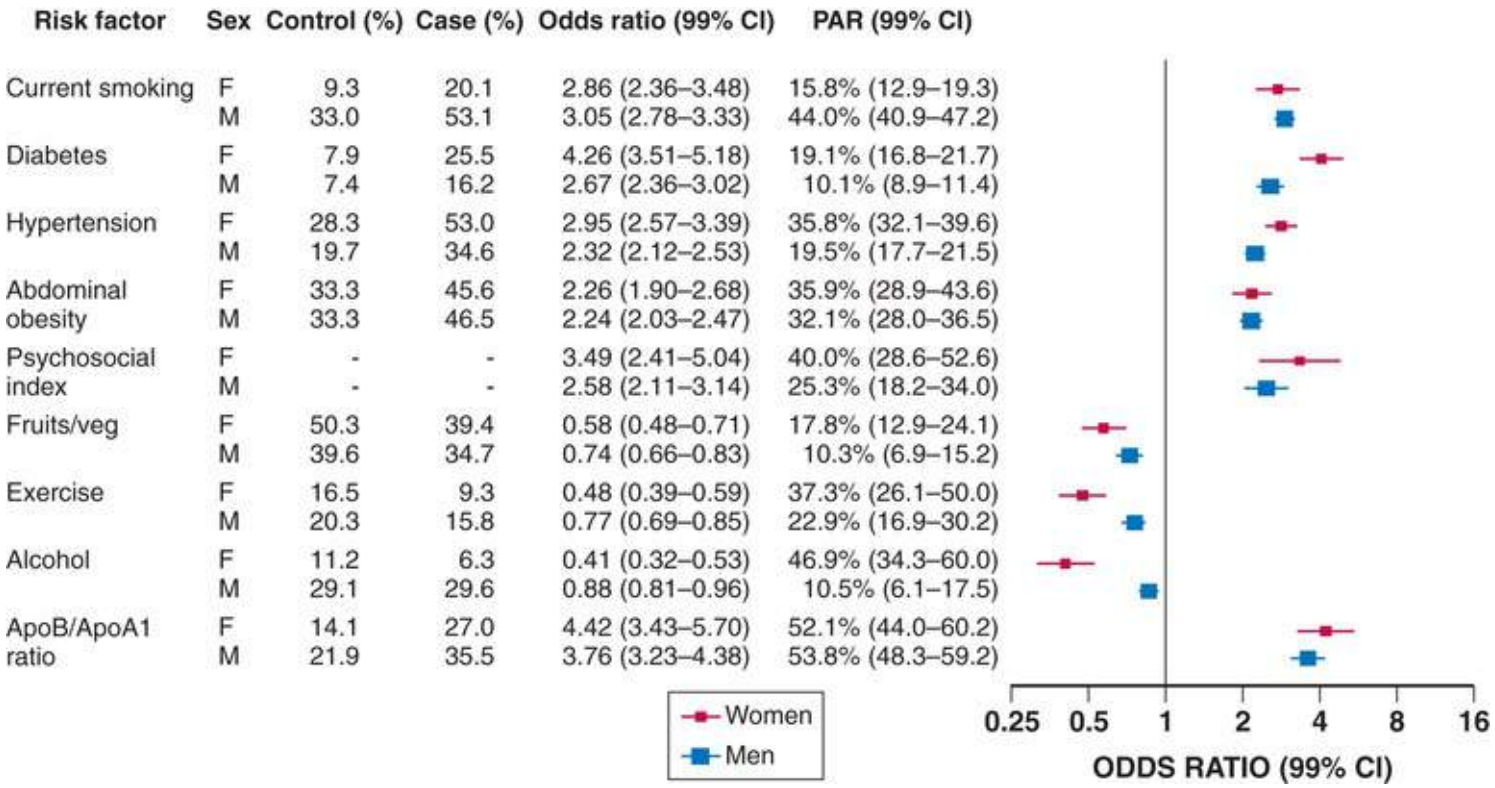

FIGURE 89.2 Relative risk of cardiac risk factors among women and men from the INTERHEART Study. A case-control comparison of the relative risk for a myocardial infarction based on gender. (From Yusuf S, Hawken S, Ounpuu SD, et al: Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries [the INTERHEART study]: case-control study. Lancet 2004;364:937.)

The Framingham Risk Score has limitations, particularly in nonwhite and female populations.[63] Nonetheless, it was the basis of the 2011 AHA Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women, which used the Framingham Risk Score to stratify women into three categories: high risk, at risk, and optimal risk, and placed emphasis on the lifetime risk of CVD in women.[10] The Reynolds risk score calculates the risk in women and men. It includes the hsCRP and family history as risk factors and considers cerebrovascular events as an outcome. The European "SCORE" (Systematic Coronary Risk Evaluation) includes geographic variability within European countries as a calibration metric. The 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce the

atherosclerotic cardiovascular (ASCVD) risk in adults offer a new risk score that was derived in population studies that included white and black men and women.[9]

Specific Cardiovascular Diseases in WOMEN

Ischemic Heart Disease in Women

Both sexes can experience the typical symptoms of myocardial ischemia, particularly MI (**see also Chapter 56**). Yet there may be a difference in symptom perception based on sex, with more women reporting symptoms that have been labeled as "atypical."[64] In an analysis of 69 studies of symptoms in those presenting with an acute coronary syndrome (ACS), the absence of chest pain or chest discomfort was noted more often in women than in men (37% vs. 27%).[65] Data from the National Registry of Myocardial Infarction show that women were more likely than men to present with an MI without any chest pain at all (42 % vs. 31%' $P < 0.001$), particularly younger women, who have the highest hospital mortality rates.[66] The absence of chest pain and the hospital mortality differences became attenuated with age. For many women, the symptoms may often be more nonspecific or less severe and can include shortness of breath; pain or discomfort in other body locations, such as that localized to the arm(s), shoulder, middle back, jaw, or epigastrium; indigestion; nausea or vomiting; diaphoresis; faintness or dizziness or syncope; fatigue; generalized weakness; or palpitations.[64]

The NIH-NHBLI–sponsored Women's Ischemia Syndrome Evaluation (WISE) collected detailed information on symptoms of women, including ischemic symptoms.[67] This study confirmed more atypical symptoms, with symptoms often occurring at rest, in addition to symptoms that were stress related.[67] This nonspecific clinical presentation makes it difficult to evaluate symptoms and make a precise estimation of the likelihood of CAD in women. Evidence regarding the "typical" presentation of chest pain symptoms and its relationship to the likelihood of IHD and/or obstructive CAD was derived largely from male populations.

Diagnosis of Ischemic Heart Disease

The more atypical presentation of women makes the diagnostic evaluation of symptomatic women challenging and results in more frequent referral for diagnostic testing to improve the precision of the IHD likelihood estimate. The classification of IHD risk in women refers solely to women who present for evaluation of suspected CAD who have chest discomfort or some ischemic equivalent, including excessive dyspnea.[68] Broadly characterized, premenopausal women with symptoms should be considered at low risk. Symptomatic women in the fifth decade of life should be considered at low to intermediate IHD risk, if they are capable of performing routine activities of daily living (ADLs). If performance of routine ADLs is compromised, a woman in her 50s should be elevated to the intermediate IHD risk category. Women in their 60s are also generally considered at intermediate IHD risk, and women 70 years of age and older are considered at high risk for CAD. Based on the 2014 Consensus Statement for Noninvasive Testing in the Clinical Evaluation of Women with Suspected Ischemic Heart Disease, women at low IHD risk are not candidates for a diagnostic evaluation; in the exceptional case, a routine exercise electrocardiogram (ECG) is the recommended test.[68] The woman with a low-intermediate or intermediate risk is a candidate for an exercise ECG if she has a functional capacity estimate of 5 METs or higher. Women at intermediate-high IHD risk with an abnormal 12-lead resting ECG should be referred for CAD noninvasive imaging, including pharmacologic stress myocardial perfusion imaging (MPI), echocardiography, cardiovascular magnetic resonance (CMR) imaging, or coronary computed tomography

angiography (CCTA). Women with a high IHD risk with stable symptoms may be referred for a stress imaging modality for functional assessment of the ischemic burden and guidance of posttest antiischemic therapies (**Fig. 89.3**).[68]

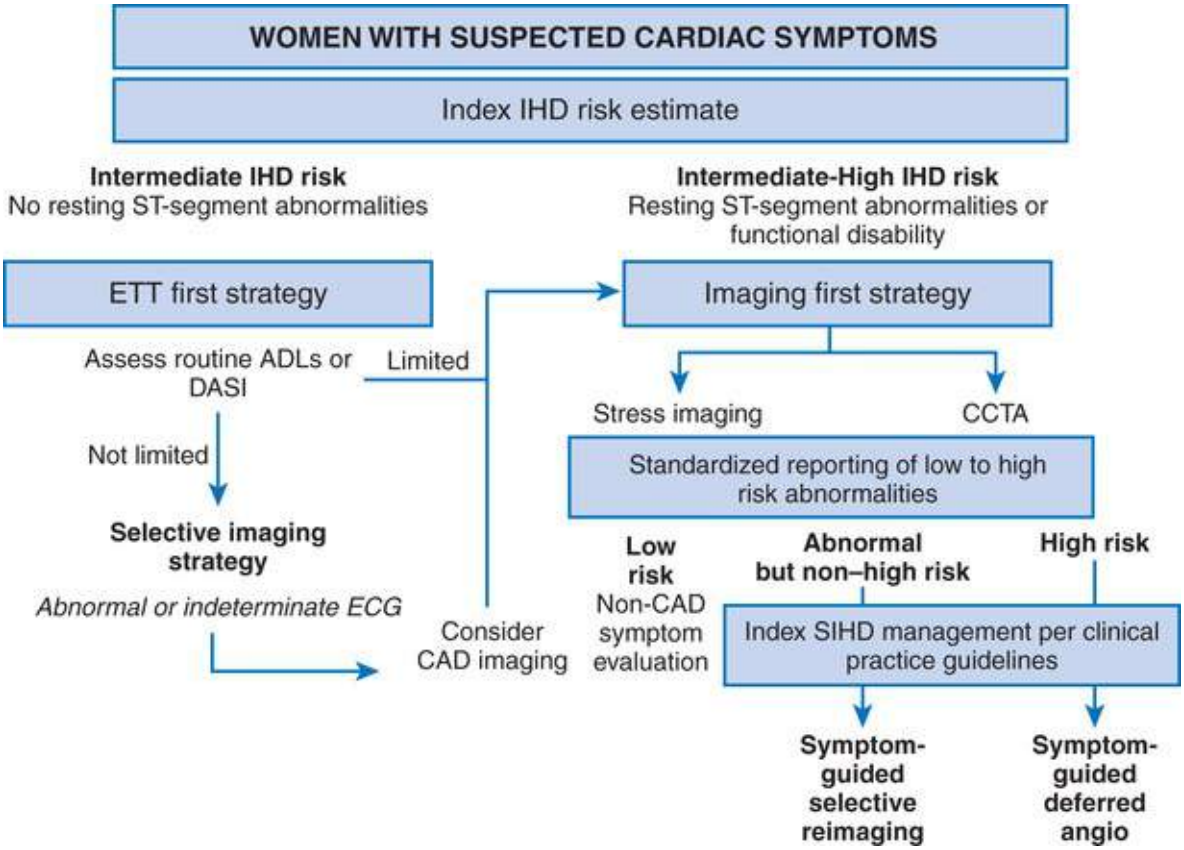

FIGURE 89.3 Diagnostic evaluation of women with suspected ischemic heart disease (IHD) and intermediate-risk and intermediate-high IHD risk. *ADL*, activities of daily living; *angio*, angiography; *CCTA*, coronary computed tomography angiography; *DASI*, Duke Activity Status Index, *ETT*, exercise treadmill testing; *SIHD*, stable ischemic heart disease. (From Mieres J, Gulati M, Bairey Merz N, et al. Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association. Circulation 2014;130(4):350-79.)

These guidelines emphasize the usefulness of the traditional exercise stress test without imaging as the initial test of choice for women with a normal ECG who are able to exercise. The exercise ECG has often been considered less useful in women because of a higher false-positive rate. This diminished accuracy of the ECG response to exercise in women has been attributed to more frequent resting ST-T wave changes, lower ECG voltage, and hormonal factors such as endogenous estrogen in premenopausal women and hormone replacement therapy in postmenopausal women.[69] The sensitivity and specificity for the diagnosis of obstructive CAD in women ranges from 31% to 71% and 66% to 86%, respectively.[70] Although the ST segment depression with exercise may be less diagnostic of obstructive CAD in women given the lower sensitivity of the test, a negative exercise ECG stress test has significant diagnostic value. Although the positive predictive value of ST segment depression with exercise testing in women is significantly lower than in men (47% vs. 77%; $P < 0.05$), the negative predictive value of ST segment depression in symptomatic women was similar to that in men (78% vs. 81%).[71] In addition, a markedly abnormal exercise ECG demonstrating 2 mm or more of ST segment changes, in particular when occurring at low workloads (< 5 METs) or persisting for more than 5 minutes into recovery, is associated with a high likelihood of obstructive CAD for both women and men. A woman with a negative exercise ECG and normal exercise abilities has an excellent event-free survival rate and a low risk of obstructive

CAD.[70] In addition, the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial showed that the prognostic value of an exercise ECG is no different than an exercise MPI test. This study randomized 824 symptomatic women with an estimated functional capacity of 5 METs or more with suspected CAD to either an exercise ECG or exercise MPI stress test, and measured major adverse CAD outcomes over the following 2 years.[72] The results revealed that functionally capable women presenting for evaluation of chest pain symptoms had similar 2-year outcomes whether randomized to exercise ECG or MPI ($P = 0.59$). This trial showed that an exercise ECG prompted a follow-up evaluation with a stress MPI test in nearly 1 in 5 women; this supported an ECG-first strategy, limiting follow-up stress imaging to women with indeterminate or abnormal ECG findings.

With any imaging modality used in women, considerations must be made regarding the amount of radiation exposure. Many cardiac diagnostic procedures, including stress MPI, CCTA, and coronary angiography, expose women to ionizing radiation. In women for whom the benefit of IHD risk detection far exceeds the small projected cancer risk following exposure, radiation exposure should not be a consideration as a physician makes a decision.[73] For all other women, in particular low-risk premenopausal women, alternative tests without radiation exposure (i.e., exercise ECG) or a no-testing strategy should be applied. The Council for Radiation Protection and Measurement has emphasized several key principles to guide the referral of women to MPI, CCTA, and coronary angiography, including justification of use, dose reduction optimization, and an adequate knowledge base to guide use.[74] Following the guidelines and meeting the ACC's appropriate use criteria can limit radiation exposure in women, lowering cancer risks from imaging in the population.[75,76]

Beyond Obstructive Coronary Artery Disease: The Paradox of Ischemic Heart Disease in Women

Patients with signs and symptoms of IHD have paradoxical sex differences. Women have less anatomic obstructive CAD and relatively more preserved left ventricular function despite higher rates of myocardial ischemia and mortality compared with men, even when controlling for age.[67,77] Data from the WISE and other studies implicate adverse coronary reactivity,[78] microvascular dysfunction,[79] and plaque erosion/distal microembolization[80] as contributory to a female-slanted myocardial ischemia pathophysiology. Thus, knowledge beyond an anatomic description of obstructive CAD may provide important clues to myocardial ischemia detection and treatment for women. For these reasons, the term *ischemic heart disease* is more useful than CAD when discussing women and their forms of CHD.

Treatment of Ischemic Heart Disease

Acute Coronary Syndrome and Angina

Optimal medical therapy for women with IHD does not differ from that for men according to the non–gender-based, ACC/AHA guidelines for ST and non-ST elevation MI and chronic angina.[81,82] Nonetheless, women often receive less intensive medical therapy or lifestyle counseling, which ultimately influences outcomes.[83,84] In addition to the differences in medical therapy, there are sex differences in the use of cardiac catheterization and revascularization and the timing of these procedures, which are associated with poorer outcomes in women after an ACS or MI.[83] Based on the most recent assessment of adhering to guidelines for the treatment of ST-elevation MI, there remains a significant sex difference in the aggressiveness of care, which has an impact on mortality rates in women. In the “Get With the Guidelines” data on 31,555 men and women with ST-elevation MI, younger women (≤ 45 years) and

older women (> 45 years) were less likely to receive angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) at discharge, to receive lipid-lowering therapy, to have a blood pressure of less than 140/90 mm Hg at discharge, or to receive stents, and fewer women received a door-to-balloon time of 90 minutes or less/door-to-thrombolytic time of 30 minutes or less. There were no differences in the use of the intraaortic balloon pump ($P = 0.99$) or left ventricular assist device ($P = 0.36$) between younger women and younger men. All women had significantly increased in-hospital mortality rates and lengths of stay, but older women were less likely to receive ACE inhibitors at discharge, to have LDL levels recorded during hospitalization, to be advised on rehabilitation or weight management, to be treated with beta blockers within 24 hours of presentation, or to be discharged with clopidogrel, aspirin, or beta blockers. There was a significant interaction between age and gender ($P = 0.03$) for in-hospital deaths such that the gender disparity was greater in the younger cohort than the older cohort. A similar interaction was seen for the door-to-thrombolytic time such that the gender delay was greatest in the youngest women (odds ratio [OR] of delay > 30 minutes in women versus men, 1.73; 95% confidence interval [CI] in younger patients, 1.21 to 2.45 versus 1.08; 95% CI in older patients, 1.00 to 1.18; P interaction = 0.003), with significantly fewer women 45 years of age or younger achieving the door-to-thrombolytic goal of 30 minutes or less.[85]

There are also sex differences regarding invasive strategies with ACS based on the presence or absence of biomarkers. In a metaanalysis of eight ACS trials, an invasive strategy resulted in a reduction of the composite endpoint of death, MI, or repeat ACS in both sexes, but it was more beneficial in women with positive biomarkers (33% risk reduction) in contrast with women with negative biomarkers, where an invasive strategy was not associated with a significant reduction in the composite endpoint.[86] Men had no such difference based on biomarkers. Women also have a higher mortality rate than men with percutaneous coronary intervention (PCI) after an ST or a non-ST elevation MI.[87] In contrast, the use of fibrinolysis has demonstrated a lower incidence of mortality or nonfatal MI at 30 days in women, compared with men who received enoxaparin compared with unfractionated heparin, suggesting that specific therapies may beneficially affect outcomes in women.[88]

Studies document an increased bleeding risk in women undergoing PCI who receive glycoprotein IIb/IIIa inhibitors.[89] In a metaanalysis of ACS populations, men benefited from glycoprotein IIb/IIIa inhibitors but women experienced more harm.[90] Nonetheless, high-risk women with troponin elevations did demonstrate a benefit. Prior studies have suggested that the elevated bleeding risk in women is due to body size and renal function, and studies have shown that the sex difference in bleeding resolves when doses are adjusted for age and renal function.[89]

A persistent pattern of higher mortality rates and poorer cardiovascular outcomes in women compared with men with IHD remains.[83] This is mostly attributable to the suboptimal use of guideline therapy in at-risk women, despite evidence that application of guideline therapy following an ACS reduces the mortality disparity in women and that management of ACS and chronic angina with intensive medical therapy benefits both sexes equally.[91,92]

In addition, women with ACS are more likely than men to have “normal” angiograms or demonstrate no obstructive CAD. “Female-pattern” IHD characterized by a relatively lower obstructive CAD burden and preserved left ventricular ejection fraction (LVEF) represents a yentl syndrome, whereby women receive less recognition and treatment than men with IHD.[93] The National Cardiovascular Data Registry showed that the odds of obstructive CAD are 50% lower for women undergoing coronary angiography compared with men.[77] Other ACS registries have demonstrated more frequent nonobstructive CAD in women compared with men (10% to 25% of women compared with 6% to 10% of men).[94] In the setting of an ACS, “normal” coronary arteries do not have a benign prognosis.[94] Given the 1.4 million ACS events per

year, 600,000 of which are in women, this translates to 60,000 to 150,000 women with ACS and nonobstructive CAD. Despite less obstructive CAD, women have a poorer prognosis after an ACS, particularly younger women.[95] Although the worse prognosis in women has been attributed to advanced age and an increase in comorbidities,[67] in addition to an underutilization of life-saving medication and therapies,[96] sex differences persist despite controlling for such variables.[97] Because women have been underrepresented in the randomized controlled trials of ACS and acute MI, we have limited sex-specific treatment knowledge in this cluster of conditions. Nonetheless, the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study showed that 1 in 8 young women (< 55 years) presenting with an acute MI fell in an unclassified category when using the current established classification system for acute MI (**Table 89.1A**), and as a result the researchers proposed a new classification system for acute MI (**Table 89.1B**).[98]

TABLE 89.1A

Taxonomy Development: Classification by the Third Global Definition of Myocardial Infarction

THIRD UNIVERSAL DEFINITION OF MYOCARDIAL INFARCTION	DEFINITION	CLASSIFICATION OF VIRGO PATIENTS (n)
Type I	Plaque rupture, ulceration, fissuring, erosion, dissection with resulting thrombus*	504
Type 2	Condition other than CAD contributes to imbalance between myocardial oxygen supply or demand*	40
Type 3	Cardiac death with symptoms suggesting ischemia	Excluded
Type 4a	Related to percutaneous coronary intervention	Excluded
Type 4b	Stent thrombosis	2
Type 5	Related to coronary artery bypass graft	Excluded
Unclassified		54*

*Of the 54 unclassified patients, 51 were women.

VIRGO, Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients.

From Spatz ES, Curry LA, Masoudi FA, et al: The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) Classification System: A Taxonomy for Young Women with Acute Myocardial Infarction. Circulation 2015;132:1710-18.

TABLE 89.1B

VIRGO Classification System in Myocardial Infarction Patients

Class I: Plaque-Mediated Culprit Lesion

Culprit lesions refer to the obstruction (or near obstruction) of a major epicardial vessel, most likely the result of a plaque rupture, fissure, or ulceration. Culprit lesions are usually treated with PCI or CABG, plus or minus thrombectomy, unless there is evidence of spontaneous resolution (e.g., residual haziness, contrast staining). Additionally, some culprit lesions may not be amenable to revascularization due to the size of the vessel or the location of the lesion.

Class IIa: Obstructive CAD With Evidence for Supply-Demand Mismatch*

Maximum stenosis of any one major epicardial vessel is > 50%, though no culprit lesion is identified. An additional "insult" is implicated as causing a mismatch between myocardial oxygen supply and/or demand.

Class IIb: Obstructive CAD *Without* Evidence for Supply-Demand Mismatch*

Maximum stenosis of any one major epicardial vessel is > 50%, though no culprit lesion is identified; no clinical evidence for myocardial oxygen supply-demand mismatch.

Class IIIa: Nonobstructive CAD With Evidence for Supply-Demand Mismatch*

Maximum stenosis of any one major epicardial vessel is < 50%, though no culprit lesion is identified; an additional "insult" is implicated as causing a mismatch between myocardial oxygen supply and/or demand.

Class IIIb: Nonobstructive CAD *Without* Evidence for Supply-Demand Mismatch

Maximum stenosis of any one major epicardial vessel is < 50%, though no culprit lesion is identified; no clinical evidence for myocardial oxygen supply-demand mismatch.

Class IV: Other, Nonatherosclerotic Pathophysiologic Mechanism

Distinct pathophysiologic mechanism identified with probable or definite certainty, including vasospasm, dissection, embolism.

Class V: Indeterminate

Presentation fits into 2 or more of the above classes (e.g., prior angioplasty without obstructive coronary artery disease on presentation); distal pruning of vessels without description of degree of stenosis or certainty regarding whether there is an acute occlusion.

*Clinical evidence supporting a scenario of myocardial oxygen supply-demand mismatch included systolic blood pressure > 180 mm Hg or < 90 mm Hg; diastolic blood pressure > 100 mm Hg; heart rate > 120 beats/min; atrial fibrillation/flutter; ventricular tachycardia/fibrillation; severe illness (pneumonia, exacerbation of chronic obstructive pulmonary disease, trauma, acute renal failure, stroke, severe gastrointestinal bleed, anemia, sepsis, surgical complication, any fracture, hyperosmolar hyperglycemic state, diabetic ketoacidosis); other (surgery, hypoglycemia, seizure, acute liver failure, *Clostridium difficile* colitis, pyelonephritis). *CABG*, coronary artery bypass graft; *CAD*, coronary artery disease; *PCI*, percutaneous coronary intervention; *VIRGO*, Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients.

From Spatz ES, Curry LA, Masoudi FA, et al: The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) Classification System: A Taxonomy for Young Women With Acute Myocardial Infarction. Circulation 2015;132:1710-18.

The increasing recognition of MI in those without obstructive CAD is now commonly referred to as myocardial infarction with nonobstructive coronary arteries (MINOCA).[99] MINOCA occurs more frequently in women, particularly younger women. Although hyperlipidemia may be less common, other traditional CVD risk factors are frequently present. All-cause mortality rates appear to be lower in MINOCA compared with MI with obstructive CAD, but they are still substantial (in-hospital mortality rate, 1.1 vs. 3.2%, $P = 0.001$; 12-month mortality rate, 6.7% vs. 3.5%; $P = 0.003$).[99] There are multiple potential causes for MINOCA, including but not limited to subendocardial ischemia (coronary microvascular disease), myocarditis, coronary vasospasm, takotsubo cardiomyopathy, hypertrophic cardiomyopathy, and spontaneous coronary artery dissection. At this time, diagnosis requires additional testing and imaging to determine the cause. The current guidelines that exist for ST and non-ST elevation MI do not differ by sex, and no studies to date support the value of specific therapies for MINOCA; hence efforts to improve the application of guidelines in practice could improve MI and IHD outcomes in women.[81,82,100,101]

Nonobstructive Ischemic Heart Disease

Women with any symptoms suggestive of myocardial ischemia have a probability of obstructive CAD that is lower than that for men. The WISE study demonstrated that 57% of women with symptoms and signs of ischemia had no obstructive CAD by coronary angiography.[102] In women without obstructive CAD, more than half will continue to have signs and symptoms of myocardial ischemia, undergo repeated

hospitalizations, and be studied with coronary angiography.[103] From the WISE data, such women with chest pain and no obstructive CAD have a higher rate of mortality and adverse cardiovascular events when compared with asymptomatic women, underscoring that the prognosis in women with symptoms and signs of ischemia is not benign, even when no obstructive CAD is present and the coronary arteries are "normal" (**Fig. 89.4**).[104]

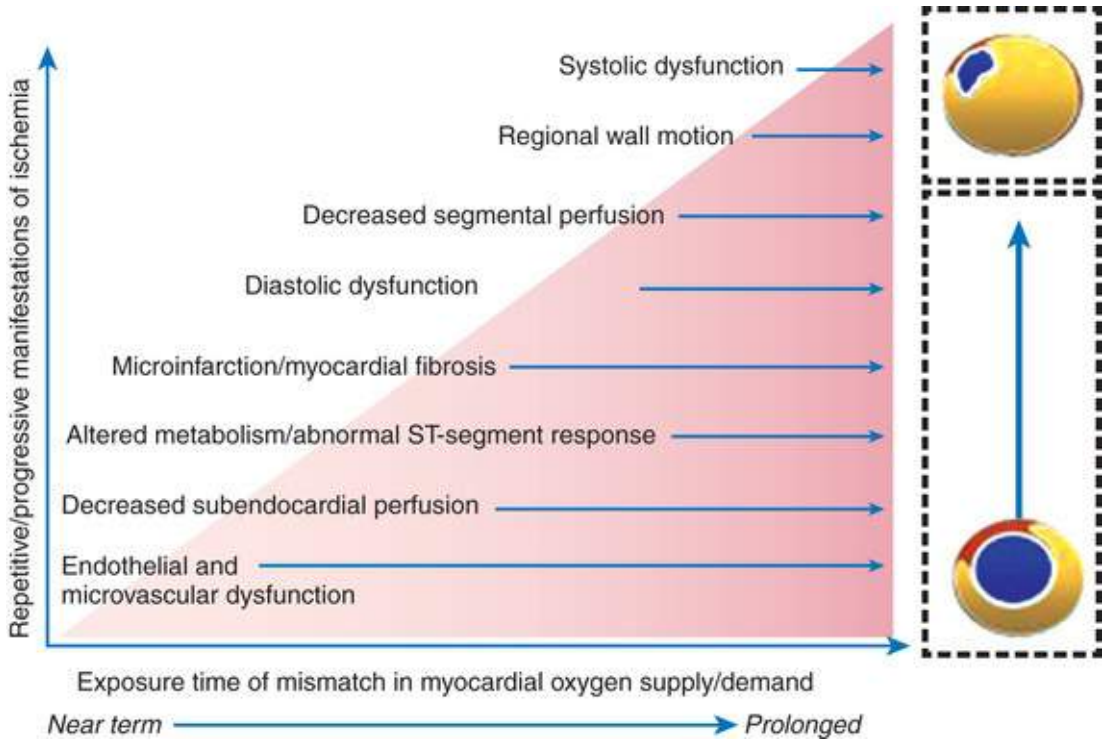

FIGURE 89.4 Cascade of mechanisms and manifestations of ischemia that affect IHD risk in women.

Microvascular Angina (See also Chapter 57)

Microvascular coronary dysfunction may cause IHD with no obstructive CAD. It appears to be more prevalent in women than men, possibly because of risk factor clustering and hormonal alterations, and likely contributes to the observed paradoxical frequent (atypical) symptoms, evidence of ischemia, and adverse outcomes in women (**Fig. 89.5**). Formerly referred to as "cardiac syndrome X," characterized by signs and symptoms of ischemia with no obstructive CAD, it has long been considered more prevalent in women. The WISE study has documented that at least half of the cardiac syndrome X women have microvascular coronary dysfunction, which results in IHD adverse outcomes.[105] A hypothetical model of microvascular angina in women is depicted in **Fig. 89.5**. This model provides a rationale for why current approaches for detection of focal obstructive coronary lesions are less effective in women with a greater prevalence of nonobstructive CAD. Abnormal coronary reactivity occurs in the setting of underlying atheroma vulnerable to clinical instability and more progressive disease states. For this reason, identifying nonobstructive atheroma may provide greater risk information in women. An overarching working model incorporates this proposed female-specific IHD pathophysiology (**see Fig. 89.5**). Although the relationship between microvascular coronary dysfunction and epicardial atherosclerosis is not fully understood, a leading hypothesis is that it is a single disease process, where the response to intimal injury may vary related to sex differences in vascular remodeling and vascular reactivity.

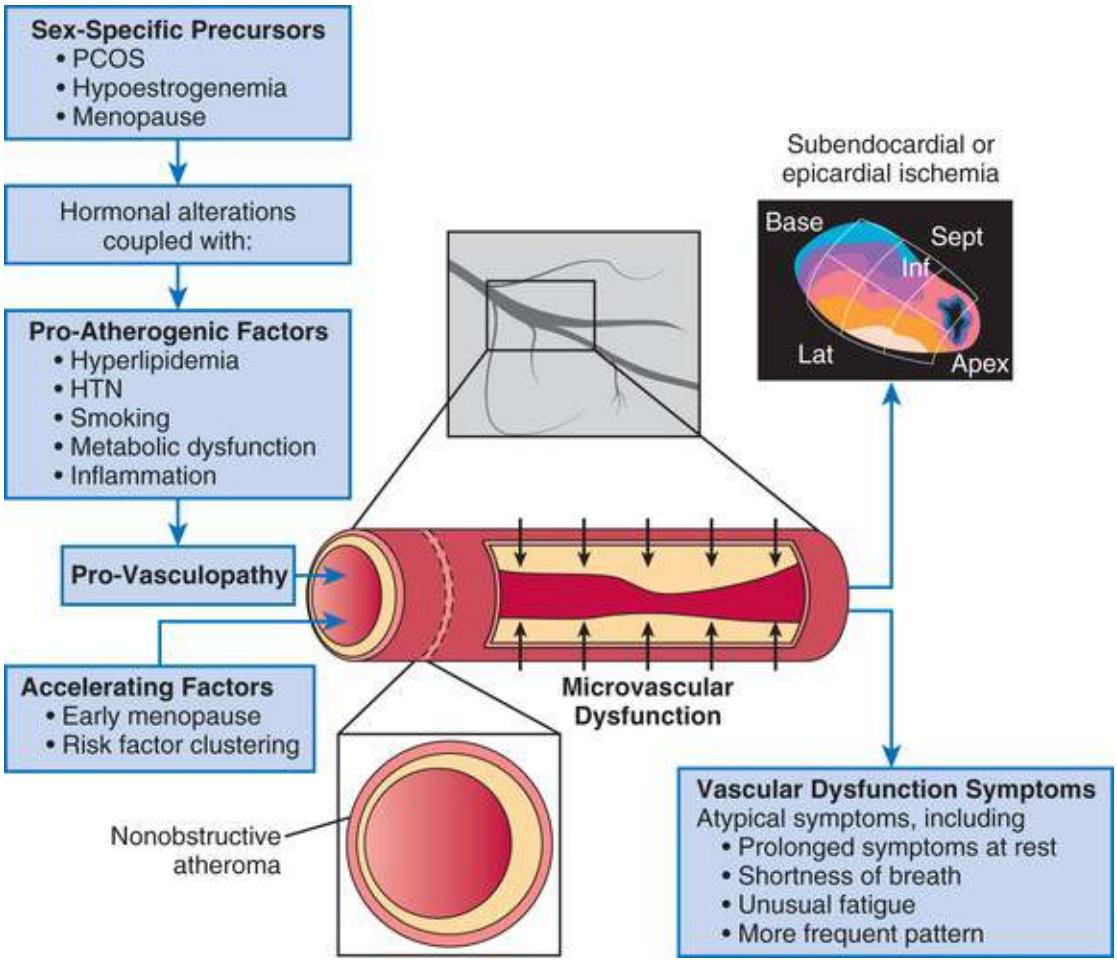

FIGURE 89.5 Model of microvascular angina in women. *HTN*, hypertension; *PCOS*, polycystic ovary syndrome.

Takotsubo Cardiomyopathy (See also Chapters 58 and 59)

Takotsubo cardiomyopathy should be considered in women as part of the differential diagnosis of ACS.[106] Other names for this syndrome include transient ventricular ballooning syndrome, left ventricular apical ballooning syndrome, stress-induced cardiomyopathy, ampulla cardiomyopathy, and broken heart syndrome. Takotsubo cardiomyopathy occurs in an estimated 1% to 2% of ACS patients, with women (particularly postmenopausal women) accounting for over 90% of the cases.[106]

Coronary Artery Bypass Grafting and Valve Surgery

Coronary artery bypass graft (CABG) surgery is a common procedure for the treatment of obstructive CAD for both men and women in the United States. Women undergo approximately 25% of CABG procedures annually.[1] Women have higher perioperative morbidity and mortality rates after CABG than men; this is typically explained by baseline differences in age, risk factors, comorbidities, and left ventricular dysfunction.[107] Women have more postoperative depression and may have a poorer quality of life 1 year after CABG,[108] although this is perhaps attributable to gender-related reporting bias. When off-pump CABG is performed, outcomes are more favorable for women. In a large study of 12,812 consecutive isolated CABG patients from 1997 to 2006, women who underwent off-pump CABG had a lower operative mortality rate than women who underwent traditional CABG (OR, 2.07; $P = 0.005$).[109]

There are no sex-specific guidelines for valvular heart disease and valve surgery, although there are sex-specific outcome data after valve surgery. In a large series of 2255 patients from Canada who underwent surgical aortic valve replacement (AVR), the mean age of women was older than that for men

(68.3 ± 12.3 years vs. 64.3 ± 14.1 years).[110] Women were equally as likely to get a mechanical valve as a bioprosthetic valve in this series. Although women had more late post-AVR strokes, they had fewer reoperations and had better overall long-term survival rates compared with men.[110] Results in the Massachusetts Cardiac Surgery Database from 2000 to 2008 demonstrate that among women and men undergoing AVR (in isolation or with CABG), there were no sex differences in mortality rates at 30 days or 1 year.[111] Postoperative stroke was again more frequent in women (3.0% for women vs. 2.2% for men; P = 0.31); postoperative MI and septicemia occurred more frequently in men (MI, 10.9% in women vs. 13.6% in men; *P* = 0.001; septicemia, 1.2% in women vs. 2.0% in men; *P* = 0.009). In a study of 641 patients from two large centers in Canada, female sex was associated with better short- and long-term survival rates after transcatheter aortic valve intervention (TAVI), although women had more iliac complications (9% in women vs. 2.5% in men; *P* = 0.030).[112] In the PARTNER trial of high-risk and inoperable patients with severe aortic stenosis (1220 women and 1339 men), women had lower rates of renal disease, smoking, hyperlipidemia, and diabetes, yet a higher STS mortality risk compared with men. Despite again noting increased vascular and major bleeding complications in women, women had lower 1-year mortality rates with TAVI compared with men (19.0% vs. 25.6%; *P* < 0.001).[113] For mitral valve replacement surgery, regardless of the type of valve replacement (mechanical or bioprosthetic), women have better long-term survival rates than men.[110] Recent data regarding transcatheter mitral valve repair (TMVR) with the MitraClip have shown no difference by sex in terms of rehospitalization for heart failure but superior long-term survival rates in women compared with men.[114]

Peripheral Arterial Disease in Women

Peripheral arterial disease (PAD) has a high prevalence in women in the United States (**see also Chapter 64**). It increases with age and ranges from 2% at age 40 years to as high as 25% at 80 years or older.[115] The incidence of PAD in patients with chronic kidney disease has been shown to have significant sex differences, with women having a 1.53-fold greater adjusted PAD risk compared with men followed in the Chronic Renal Insufficiency Cohort (*P* < 0.001).[116] Despite the prevalence of PAD, awareness of this issue is the lowest of awareness of CVD risk factors and other forms of CVD, with 3 out of every 4 Americans having no awareness of PAD.[117] Lower extremity PAD is associated with equal morbidity and mortality rates and comparable health costs as IHD and ischemic stroke.[118] PAD can be assessed using the ankle-brachial index (ABI); PAD is diagnosed when the ABI is lower than 0.90.

PAD symptoms show sex differences. Women with PAD can lack the classic symptom of intermittent claudication and may even be asymptomatic. As with other CVDs, there appears to be a long “latent phase” that can progress over time. This was demonstrated in the Women's Health and Aging Study (WHAS) of 933 disabled women 65 years of age or older, where 328 (35%) had an ABI of less than 0.90, and 63% of those with PAD had no exertional leg symptoms.[119] Asymptomatic PAD appears about twice as common in women as in men.[120]

Despite displaying fewer symptoms with PAD, once a diagnosis of PAD is made, women appear to have more functional impairment from PAD than men. In a cohort of 560 people with PAD and intermittent claudication, the treadmill distance to the onset of intermittent claudication symptoms was 33% shorter and the treadmill walking distance was 23% shorter in women than in men.[121]

Although women have more functional capacity impairment, men with critical limb ischemia were twice as likely as women to undergo revascularization, based on one analysis.[122] Nonetheless, the same institution has more recently demonstrated no sex differences in revascularization rates in PAD patients,[123] in contrast with other contemporary registries.[124] Multiple studies have reported similar amputation-free

survival rates after lower extremity revascularization for PAD in men and women, but with diabetic patients with PAD, amputation rates actually appear lower in women compared with men.[125] Sex differences in survival rates after lower extremity PAD revascularization have been inconsistent, but issues of gender are often confounded by morbidity, age, and procedural factors that affect perioperative mortality rates. The 2012 A Call to Action: Women and Peripheral Artery Disease: A Scientific Statement from the American Heart Association addresses the epidemiology, diagnosis, and management of PAD in women.[115]

Other forms of PAD also demonstrate sex differences. Mesenteric arterial disease is far more frequent in women, with 70% of chronic intestinal ischemia events occurring in women and two thirds of acute presentations occurring in elderly women.[115] Renal artery stenosis and abdominal aortic aneurysms are more common in men than women. Because abdominal aortic aneurysms are less frequently associated with deaths in women, screening in asymptomatic women is not recommended, in contrast with men.[126]

Heart Failure in Women (See also Part IV)

Heart failure (HF) affects 6.5 million Americans, including 3.6 million women.[1] In 2014, there were 37,287 deaths in women due to HF and more deaths in women than in men (55.8% vs. 44.2%).[1] The lifetime risk for developing HF (without a prior MI) in a 40-year-old is 1 in 6 for a woman compared with 1 in 9 for a man. The prevalence of HF increases with age, with more women than men having HF after the age of 79 years (**Fig. 89.6**).

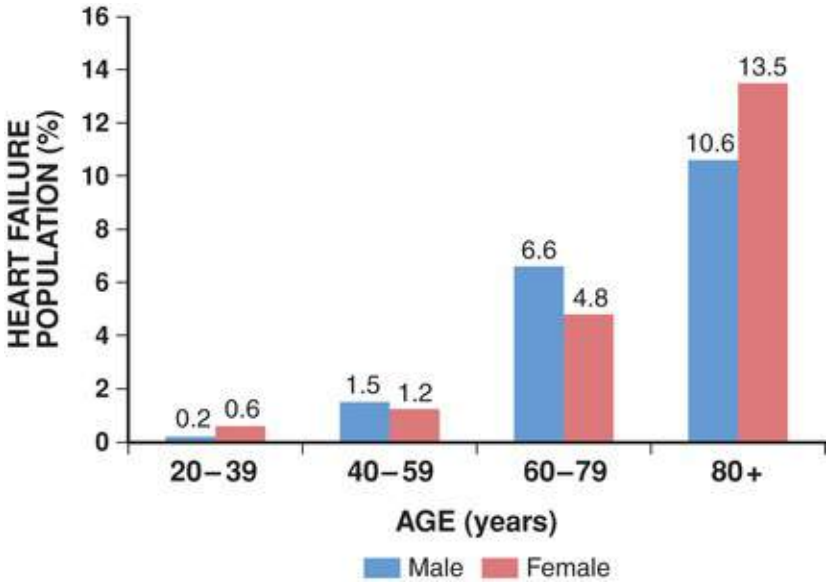

FIGURE 89.6 Prevalence of heart failure by sex and age (National Health and Nutrition Examination Survey: 2009 to 2012). (From Mozaffarian D, Benjamin EJ, Go AS et al: Heart Disease and Stroke Statistics 2016 Update: AReport from the American Heart Association. Circulation 133(4):e38-e60.)

The risk factors associated with HF and its underlying pathophysiology differ by gender. Women with HF have more hypertension, valvular heart disease, and thyroid disorders than men but are less likely to have obstructive CAD. Even though obstructive CAD is less frequent in women, when it is present it is a stronger risk factor for the development of HF than hypertension. Risk factors selective for women include cardiac toxicity from chemotherapeutic drugs used for treatment of breast cancer and peripartum cardiomyopathy. Women who present with acute decompensated HF are twice as likely as men to have preserved left ventricular function or HF with preserved ejection fraction (HFpEF),[127] with obesity being

a significant risk factor for women with HFpEF, particularly African American women.[128] Even those women with an impaired LVEF will have a higher LVEF when compared with men. Notably, women with HF have a lower quality of life, lower functional capacity, more hospitalizations for HF, and more frequent episodes of depression. Nonetheless, the overall survival rate is better for women compared with men with HF. This is not just a result of women having more HFpEF events, because mortality rates from HF do not relate to a preserved or impaired ejection fraction in either sex, although those with ischemic cardiomyopathy have a worse prognosis.[129]

Peripartum Cardiomyopathy (See also Chapter 90)

Peripartum cardiomyopathy causes an impaired LVEF that occurs in the last month of pregnancy or within 5 months postpartum with no preexisting cardiac disease and no identifiable cause. Its incidence is estimated to be 1 in 4000 pregnancies, and is associated with risk factors including advanced maternal age, African descent, high parity, twin pregnancy, usage of tocolytics, and poverty.[130] After the diagnosis, about half recover their LVEF within 6 months; however, 20% deteriorate and either die or require heart transplantation. Recovery appears to be related to a less severe decline in LVEF.[131] The risk during a subsequent pregnancy is not entirely clear, but in a retrospective analysis of 44 patients with peripartum cardiomyopathy in a pregnancy, the LVEF declined in the next pregnancy in both those who had recovered left ventricular dysfunction (from 56 ± 7% to 49 ± 10%; $P = 0.002$) and in those with persistent impairment of LVEF (from 36 ± 9% to 32 ± 11%; $P = 0.08$).[132]

Diagnosis of Heart Failure

In term of diagnosing acute HF, the Studies Of Left Ventricular Dysfunction (SOLVD) study demonstrated that women with an impaired systolic LVEF were more likely than men to have edema, elevated jugular venous pulsation, and an S_3 gallop.[133] In contrast, the Acute Decompensated Heart Failure National Registry (ADHERE) showed no sex differences in presenting signs and symptoms of acute HF, and this study included 54,674 women, accounting for more than half the number in the registry.[134] The difference in this study compared with others may relate to the fact that the ADHERE registry specifically looked for patients with acute decompensated HF rather than those with chronic symptoms. There may be sex differences in the biomarker brain natriuretic peptide (BNP) used to diagnose HF. Women have higher baseline BNP values than men, but BNP values higher than 500 pg/mL predict death more strongly in women with HF than men.[135] Nonetheless, a recent study from Japan showed that in patients with acute decompensated HF, no sex differences were found in the mean BNP levels; an elevated BNP level predicted future cardiovascular events in men but not women.[136] Further studies are needed to delineate and understand the sex differences in these biomarkers.

Treatment of Heart Failure

Treatment for HF may benefit both sexes equally; however, the underrepresentation of women in HF trials and the fact that HFpEF is more prevalent in women contribute to our lack of evidence regarding treatment of HF in women.[127] The CHARM trials, along with others, showed women were more likely to have preserved left ventricular function (50%) than men (35%).[62] Overall evidence-based HF therapies are underused in both sexes, but more so in women. Women less likely receive vasoactive agents, but men and women have equal hospital lengths of stay and age-adjusted in-hospital morality HF rates. At this time, the HF guidelines are not sex specific because sex-specific pathophysiologic mechanisms are not well understood and there is a lack of randomized trials.

Implantable cardioverter-defibrillator (ICD) devices are underused in both sexes with HF, but particularly in women. The Get With the Guidelines–Heart Failure database from 2005 to 2009 examined all potential eligible patients from the Medicare database. Eligible women were less likely than men to get an ICD (42.4% vs. 26.5%; $P < 0.0001$), particularly black women. There was an increase in ICD utilization over time, and the racial disparities disappeared by 2009, but the sex disparities persisted.[137] None of the randomized trials for ICDs enrolled sufficient numbers of women to permit conclusions regarding sex differences. Although studies to date are underpowered for the detection of sex differences, they do indicate that ICDs do not demonstrate a mortality benefit in women. The Sudden Cardiac Death in Heart Failure Trial (SCDHeFT) included 588 women in NYHA functional class II to III with an LVEF of 35% or less (ischemic and nonischemic cardiomyopathy) and did not show a benefit of an ICD in women. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) II included patients with ischemic cardiomyopathy with an LVEF of 30% or less; there was a nonsignificant trend toward lower mortality rates in women with an ICD.[137] This study, like those preceding it, enrolled too few women to draw a strong conclusion, however. In a prospective study from Canada of 6021 patients (20% women) referred for an ICD, 5450 patients underwent ICD placement. Women had similar implantation rates but greater complication rates both at 45 days and at 1 year (OR, 1.78; 95% CI, 1.24 to 2.58; $P = 0.002$ at 45 days; HR, 1.91; 95% CI, 1.48 to 2.47; $P < 0.001$ at 1 year); there was no sex difference in the mortality rate.[138] The early complications were lead repositioning for men and lead replacement for women, and the late complications for both genders included pocket infection and electrical storm often related to a lead. In addition, women were less likely to receive appropriate shocks or appropriate therapy via shock or antitachycardia pacing compared with men (HR, 0.69; 95% CI, 0.51 to 0.93; $P = 0.015$ at 45 days; and HR, 0.73; 95% CI, 0.59 to 0.90; $P = 0.003$ at 1 year). These differences may result in part from sex differences in body size and a delayed presentation in women.

Cardiac resynchronization therapy (CRT) also shows benefit in both women and men with HF and a wide QRS complex, but observational data from the National Cardiovascular Data Registry demonstrated that the mortality benefit is more pronounced in women, confirming earlier randomized trials that compared CRT with medical therapy alone.[139]

Cardiac Transplantation

Heart transplantation occurs far less frequently in women compared with men, with only 29% of heart transplants in the United States in 2015 occurring in women.[1] This disparity may reflect the older age of women with HF and differences in choices related to transplantation. There does appear to be a sex difference in survival rates while awaiting heart transplantation, with more women dying than men (risk of death in women with UNOS status 1A was HR, 1.20; 95% CI, 1.05 to 1.37; $P = 0.01$), a disparity that is not accounted for based on the current UNOS transplant criteria.[140] This finding does suggest a transplant allocation bias, favoring men over women awaiting heart transplantation. Survival data after transplantation also may result from bias in women compared with men, with the survival gap increasing slightly with time (survival rate for women vs. men at 1 year, 86% vs. 88%; at 3 years, 76% vs. 79%; at 5 years, 68% vs. 72%).[131]

Arrhythmias and Sudden Cardiac Death in Women (See also Part V)

Important sex differences in cardiac electrophysiology can affect arrhythmias and sudden cardiac death.[141]

Starting at puberty, women have higher resting heart rates compared with men. Women also have longer QT intervals and a greater risk for drug-induced torsades de pointes. There are sex differences in characteristics of supraventricular tachycardias (SVTs). Atrioventricular (AV) nodal reentrant tachycardia (AVNRT) is twice as common in women as in men, and AV reentrant tachycardia as seen in Wolff-Parkinson-White syndrome is more common in men. Atrial and ventricular fibrillations also occur more frequently in men with Wolff-Parkinson-White syndrome. Compared with men, women with atrial fibrillation tend to be more symptomatic, have higher risks of stroke and death, and are less likely to receive anticoagulation and ablation procedures than men, and yet they fare worse when treated with antiarrhythmic medications.[142] Although women have an overall lower risk of sudden cardiac death, women with cardiac arrest who receive therapeutic hypothermia have significantly better outcomes than men.[143] Other data show that women are less likely than men to get recommended treatment after an out-of-hospital cardiac arrest.[144]

Prevention of Cardiovascular Disease in Women (See also Part VI)

Guidelines for CVD prevention in women were largely based on the Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women 2011 Update but have been replaced by the 2013 ACC/AHA evidence-based guidelines on the treatment of blood cholesterol to reduce ASCVD in adults.[145] These guidelines apply to both women and men and lack sex-specific recommendations.

An important component of secondary CVD prevention includes cardiac rehabilitation (**see also Chapter 54**).[146] Cardiac rehabilitation improves functional capacity, decreases anginal symptoms, facilitates CVD risk reduction, and improves psychosocial well-being in both sexes. It also improves the quality of life and medication compliance and reduces rates of morbidity and mortality. Both sexes should be referred for cardiac rehabilitation after experiencing angina or any type of MI, undergoing coronary revascularization (either CABG or PCI) or valvular heart surgery, or receiving a diagnosis of chronic HF.[147] Cardiac rehabilitation is remarkably underused in the United States, however, with an estimated participation rate of only 10% to 20% of eligible patients. Women are particularly underreferred and are less likely to complete cardiac rehabilitation even if they enroll.[148]

Acknowledgments

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90

Pregnancy and Heart Disease

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Pregnancy is associated with hemodynamic stress on the cardiovascular system, and this can be

associated with increased risks for both mother and baby, particularly in women with preexisting cardiovascular disease. In the current era, the number of pregnancies in women with cardiovascular disease is increasing, in part due to the growing population of women with congenital heart disease, the older age at conception, and the larger number of pregnant women with comorbidities such as obesity, hypertension, and diabetes. Thus, there is an increasing need for the cardiologist to understand pregnancy and its impact on women with heart disease.

Even in otherwise healthy women, pregnancy outcomes are important for the cardiologist to consider. Maternal complications that develop during pregnancy can be predictors of long-term cardiovascular health. For instance, women with placental disorders, hypertensive disorders of pregnancy, or pregnancy-related diabetes mellitus have high rates of cardiovascular disease later in life.[1,2] When encountered in clinical practice, therefore, pregnancy complications may provide an opportunity for early identification of women at increased risk for development of cardiovascular disease later in life,[3] and perhaps such women should be referred to their primary care physician or a cardiologist to monitor cardiovascular risk factors.

Most women with cardiovascular disease are aware of their cardiac condition prior to pregnancy. Less commonly, cardiovascular disease may come to attention for the first time during pregnancy either because it was previously unrecognized or because it developed de novo. Although women with cardiac disease should have preconception counseling, many have not been adequately informed about the risks of pregnancy. For physicians counseling such women with cardiac disease, a comprehensive knowledge of the underlying defect as well as of the hemodynamic changes that pregnancy will impose is imperative. Fortunately, most women with cardiovascular disease can go through pregnancy successfully with proper care, but a careful prepregnancy evaluation is mandatory. For women with low-risk cardiac conditions, preconception assessment provides reassurance and may help to prevent unnecessary therapies during pregnancy. For women with moderate- and high-risk cardiac conditions, preconception counseling regarding pregnancy risks and contraception options is necessary for women to make informed, safe decisions.

Detecting cardiac decompensation during pregnancy can be difficult because the symptoms and signs of a normal pregnancy can mimic those of cardiac disease. Light-headedness, shortness of breath, peripheral edema, and even syncope often occur during a normal pregnancy, leading the less experienced physician to suspect cardiac disease when none is present. An understanding of the normal findings on cardiac examination in a pregnant patient is therefore important. Women with heart disease are at increased risk for maternal cardiac and perinatal complications.[4] Most cardiac complications can be safely treated during pregnancy, but in some women, the hemodynamic stress of pregnancy leads to irreversible cardiac deterioration. Maternal deaths are now rare in Western countries, but cardiac causes of death have increased and are now the most common indirect cause of maternal deaths in many countries[5] (**Fig. 90.1**). Although the most prevalent cardiac diagnosis among pregnant women is congenital heart disease, maternal deaths are often secondary to acquired diseases, such as myocardial infarction, aortic dissection, and cardiomyopathies.

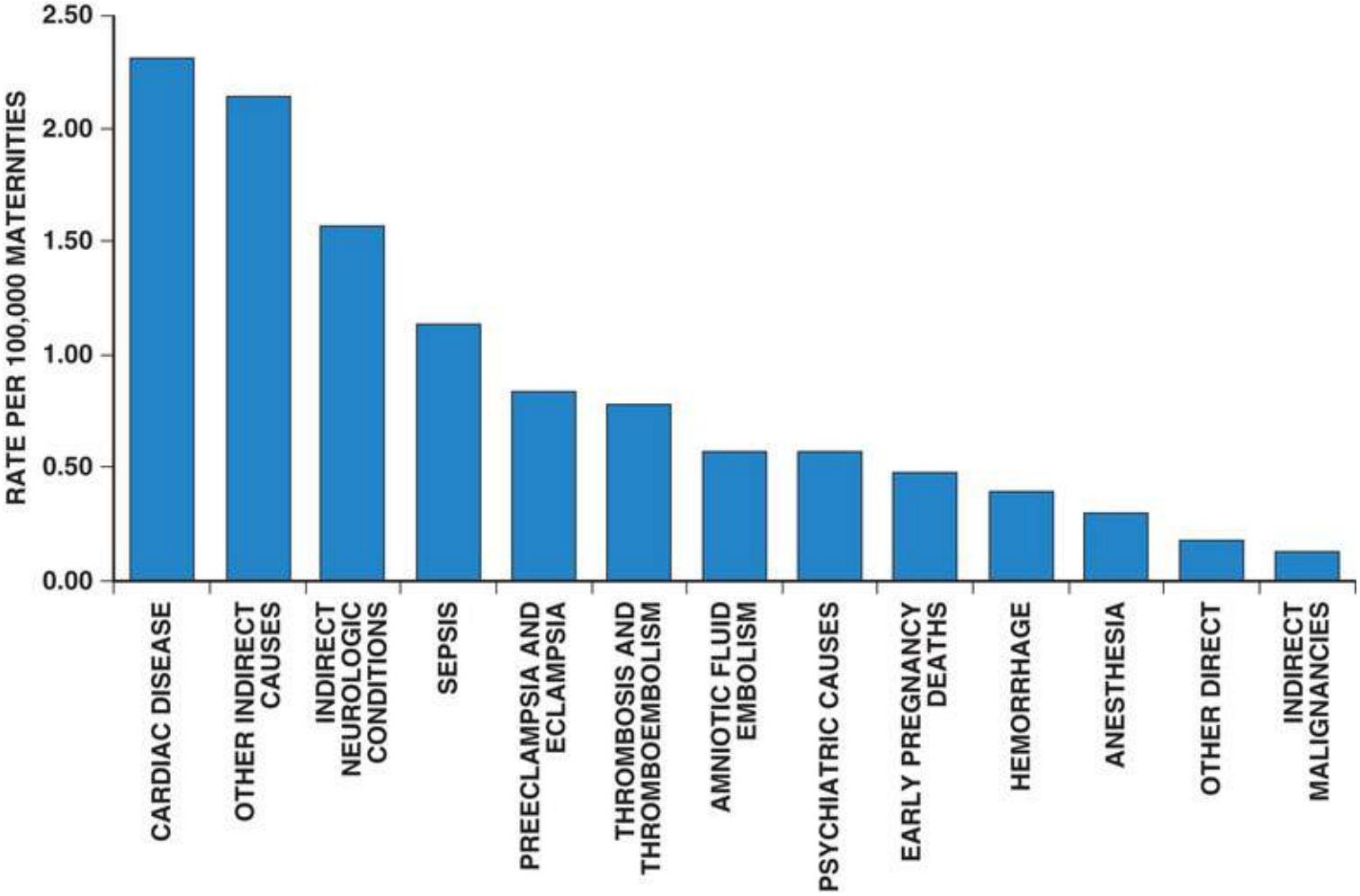

FIGURE 90.1 Leading causes of maternal death in the United Kingdom. Deaths per 100,000 maternities. (From Cantwell R, Clutton-Brock T, Cooper G, et al. Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG*. 2011;118[Suppl 1]:1-203.)

Hemodynamic Changes of Pregnancy

The hemodynamic changes of pregnancy begin early in the first trimester (**Fig. 90.2**). The plasma volume begins to increase in the sixth week of pregnancy and by the second trimester approaches 50% above baseline. The plasma volume then tends to plateau until delivery. This increased plasma volume is followed by a slightly lesser rise in red cell mass, which results in the relative anemia of pregnancy. The heart rate begins to increase to approximately 20% above baseline to facilitate the increase in cardiac output. Uterine blood flow increases with placental growth, and an accompanying fall in peripheral resistance may result in a slight fall in blood pressure, which also begins in the first trimester. The venous pressure in the lower extremities rises, causing pedal edema in approximately 80% of healthy pregnant women. The adaptive changes of a normal pregnancy result in an increase in cardiac output, which by the end of the second trimester approaches 30% to 50% above baseline. These hemodynamic changes may be problematic for the mother with cardiac disease. Maternal hemodynamics and perinatal outcomes are interrelated; abnormal uteroplacental flow or an inappropriate drop in the maternal cardiac output during pregnancy is associated with adverse perinatal outcomes.[6,7]

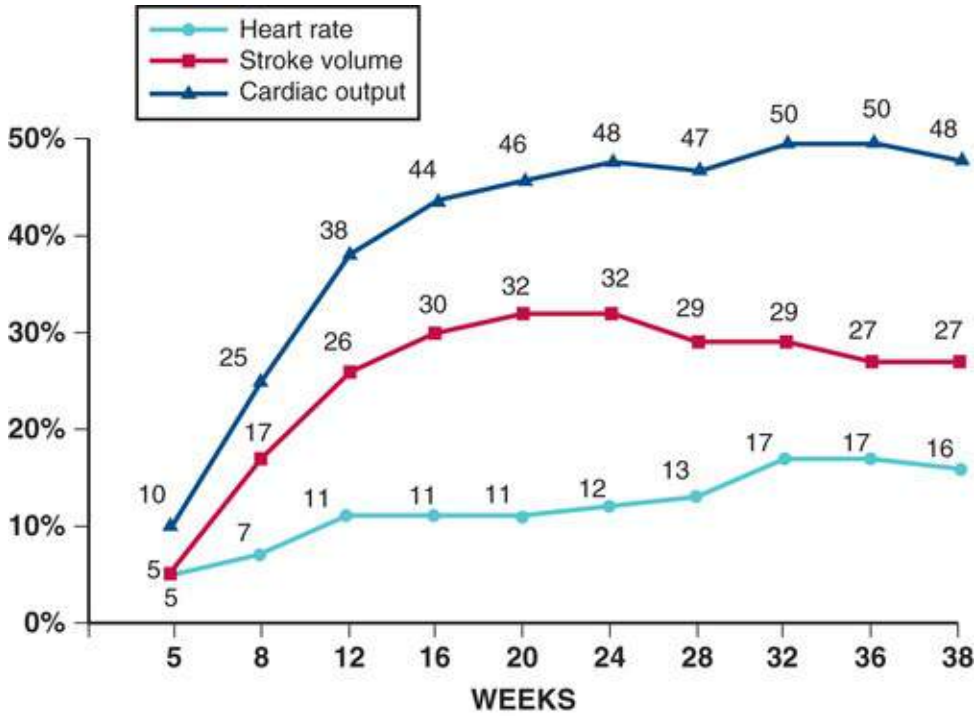

FIGURE 90.2 Hemodynamic changes in pregnancy. Percentage of changes in heart rate, stroke volume, and cardiac output measured in the lateral position throughout pregnancy compared with prepregnancy values. (From Elkayam U, Goland S, Pieper PG, Silverside CK. High-risk cardiac disease in pregnancy: part I. J Am Coll Cardiol 2016;68:396-410.)

The hemodynamic changes during labor and delivery are abrupt. With each uterine contraction, up to 500 mL of blood is released into the circulation, prompting a rapid increase in cardiac output and blood pressure. The cardiac output often is 50% above baseline during the second stage of labor and may be even higher at the time of delivery. During a normal vaginal delivery, approximately 500 mL of blood is lost. By contrast, with a cesarean delivery, approximately 1000 mL of blood often is lost, which may pose a more significant hemodynamic burden to the parturient. After delivery of the baby, an abrupt increase in venous return occurs, in part because of autotransfusion from the uterus but also because the baby no longer compresses the inferior vena cava. In addition, autotransfusion of blood continues in the 24 to 72 hours after delivery, and this is when pulmonary edema may occur.

Preconception Counseling

Risk Stratification

Prepregnancy counseling is important because it gives prospective mothers appropriate information about the advisability of pregnancy and is an opportunity for discussions about the risks to her and the baby. Patients with risks for heart disease should be seen by a physician with experience in pregnancy and heart disease. The initial cardiac evaluation should include a clinical examination, 12-lead electrocardiogram, and transthoracic echocardiogram. In patients with congenital heart disease, the perception of normal activity may be skewed because of long-standing altered exercise expectations, and an exercise test is helpful in delineating the true functional aerobic capacity. Pregnancy outcomes have been associated with an impaired chronotropic response to exercise in women with congenital heart disease.[8] A careful family history is important to assess whether there is any congenital heart disease in the patient's family or that of her partner. Genetic counseling should be offered to women with inherited cardiac conditions. Occasionally, women may consider preimplantation genetic screening, and this requires input from

genetics and fertility specialists.

A careful discussion of the maternal and fetal risks, and of whether or not these risks might change with time or treatment, is indicated. The possibility that pregnancy might cause irreversible hemodynamic deterioration should be considered; this is specifically relevant to women with ventricular dysfunction. The long-term outlook for the mother is a difficult, but important, aspect of counseling. If the woman is going to pursue a pregnancy, a strategy should be outlined regarding the frequency of follow-up evaluation by the cardiologist, and a plan should be put in place for obstetric and cardiovascular management during the pregnancy.

An assessment of maternal cardiac risk incorporates general risk predictors, lesion-specific risks, and individual factors. General predictors of adverse maternal cardiac events in women with heart disease include (1) a prior cardiac event (e.g., heart failure, transient ischemic attack, or stroke before pregnancy) or arrhythmia; (2) a baseline New York Heart Association (NYHA) class higher than class II or cyanosis; (3) a left-sided heart obstruction (mitral valve area < 2 cm^2, aortic valve area < 1.5 cm^2, or peak left ventricular outflow tract gradient > 30 mm Hg as assessed by echocardiography); (4) reduced systemic ventricular systolic function (ejection fraction < 40%); (5) pulmonary regurgitation; (6) mechanical valve prosthesis; or (7) significant atrioventricular valve regurgitation. Risk scores based on these predictors have been developed and can be used as a starting point in risk stratification.[9-11] The use of any of these risk scores carries limitations. The risk indexes are highly population dependent. Some series, for example, include only patients with congenital heart disease; others include patients with acquired heart disease. In all series there are high-risk patient populations, such as those with clinically significant pulmonary hypertension or dilated aortas, who are underrepresented.[9-11] A British working group created a risk stratification tool using a World Health Organization classification that incorporates general and lesion-specific diagnoses.[12,13] All of these risk prediction tools should be used as a guide, along with known lesion-specific risks, other clinical information, and, of course, clinical judgment.

There is a growing population of women conceiving with fertility therapy, including women with heart disease.[14] When fertility therapy is being considered in the cardiac patient, in addition to the cardiac-related risks described earlier, it is important to consider the risks associated with the underlying cause of infertility (i.e., women with infertility or subfertility have higher rates of hypertensive disorders of pregnancy), the risk of fertility medications and therapies (i.e., ovarian hyperstimulation syndrome), and the consequences of multifetal pregnancies (i.e., higher rates of prematurity).

Contraindications to Pregnancy

In some situations, the maternal risk from pregnancy is prohibitively high, and women should be counseled to avoid pregnancy and sometimes even to consider termination of pregnancy if it occurs (**Table 90.1**). No data exist regarding the precise level of pulmonary hypertension that poses a major threat to the mother, but systolic pulmonary artery pressures higher than 60% to 70% of the systemic pressure are likely to be associated with maternal compromise; in these circumstances, pregnancy is best avoided. Women who have a left ventricular ejection fraction of less than 30% from any cause are not likely to withstand the volume load that pregnancy imposes and should be advised not to become pregnant. Patients with Marfan syndrome and a dilated aortic root more than 45 mm in diameter are vulnerable to progressive aortic dilation, dissection, and rupture during pregnancy. A number of other high-risk cardiac conditions, such as complex congenital heart disease, mechanical valves, and severe asymptomatic aortic stenosis, require careful preconception risk stratification.[14a,14b]

TABLE 90.1

High-Risk Cardiac Conditions During Pregnancy

Pregnancy Is Contraindicated
Pulmonary hypertension from any cause
Eisenmenger syndrome
Dilated cardiomyopathy with severe left ventricular systolic dysfunction (subaortic ventricular ejection fraction < 30%)
Peripartum cardiomyopathy with residual left ventricular systolic dysfunction
Symptomatic severe aortic stenosis
Severe mitral stenosis
Marfan syndrome with an aortic root dimension > 45 mm
Inherited aortopathies: Vascular-type (type IV) Ehlers-Danlos syndrome, Loeys-Dietz syndrome with any aortic dilation, Turner syndrome with aortic dilation ≥ 2.7 cm^2
Chronic aortic dissection
Pregnancy Is High Risk
Mechanical prosthetic valves
Dilated cardiomyopathy with moderate left ventricular systolic dysfunction
Severe asymptomatic aortic stenosis
Unrepaired coarctation of the aorta
Cyanotic cardiac heart disease (non–Eisenmenger syndrome)
Fontan circulation
Complete transposition of the great arteries with Mustard or Senning operation
Other complex congenital heart diseases

Evaluation and Testing During Pregnancy

Physical Examination

Evaluation of the pregnant patient begins with a thorough physical examination, including cardiac examination. Because of the altered hemodynamics during pregnancy, the physical examination findings in a healthy pregnant woman reflect such changes and may mimic those in cardiac disease. The heart rate increases and the pulse volume is often bounding. By the middle of the second trimester, the jugular venous pressure may be slightly elevated, with brisk descents, because of the volume overload and reduced peripheral resistance. The apical impulse is more prominent. On auscultation, the first sound may appear loud. The second sound also may appear accentuated, and these combined auscultatory features may suggest an atrial septal defect or pulmonary hypertension. A third sound is very common. An ejection systolic murmur is commonly heard at the left sternal edge, never more than grade 3/6 in intensity, which relates to increased flow through the left or right ventricular outflow tract. Continuous murmurs also may be heard, as either a cervical venous hum or a mammary souffle, and are caused by the hyperdynamic circulation. The venous hum is best heard over the right supraclavicular fossa. The mammary souffle (continuous or systolic) is due to increased flow in the mammary arteries and is heard over the breast late in pregnancy or during lactation. There should be no diastolic murmur. Peripheral edema is common as pregnancy advances.

Laboratory Evaluation

Despite the hemodynamic volume load of pregnancy, most healthy pregnant women have low levels of B-type natriuretic peptide throughout pregnancy and after delivery. By comparison, women with heart disease have higher B-type natriuretic peptide levels throughout pregnancy compared with nonpregnant women, and normal B-type natriuretic peptide levels have a good negative predictive value for predicting adverse cardiac events.[15]

Imaging

Chest Radiography

A chest radiograph is not obtained routinely in any pregnant patient because of concern about radiation exposure to the fetus, but it should not be withheld when the history and clinical findings raise concerns about maternal cardiac status. The chest radiograph in a normal healthy patient may show slight prominence of the pulmonary artery, and as pregnancy advances, elevation of the diaphragm may suggest an increase in the cardiothoracic ratio.

Echocardiography

Transthoracic echocardiography is the cornerstone of cardiac evaluation in pregnancy. In a normal pregnancy, the left ventricular end-diastolic measurement is slightly increased, and there may be similar increases in right ventricular size and the volumes of both atria. There can also be a small increase in the left ventricular wall thickness during pregnancy. Measurement of ejection fraction is determined by changes in preload and afterload, and with the patient in the supine position, preload may be reduced because the fetus may compress the inferior vena cava. The increased cardiac output leads to increases in the velocities across the left and right ventricular outflow tracts. Careful comparison of the two-dimensional anatomic appearances will help differentiate this from a true valvar abnormality. The valve area calculation may be more helpful than a simple measurement of valve gradient; the latter may appear to be increased as pregnancy advances because the circulation becomes more hyperkinetic and cardiac output increases. Transesophageal echocardiography is seldom performed during pregnancy; however, when necessary, it can be performed safely, although careful monitoring of maternal oxygen saturation is necessary if midazolam is used for sedation.

Magnetic Resonance Imaging and Computed Tomography

When necessary, magnetic resonance imaging (MRI), without gadolinium, can be done in pregnancy.[16] Gadolinium is associated with neonatal risk and is usually avoided. MRI may be required in women with high-risk aortopathies who do not have baseline aortic imaging prior to pregnancy or to exclude aortic dissection in women presenting with chest pain. Dural ectasia is diagnosed with MRI; it is an important diagnosis for women with Marfan syndrome who require epidural analgesia. Computed tomography (CT) is not recommended unless necessary because of the risks of radiation exposure to the fetus.

General Management Principles During Pregnancy

During pregnancy, a multidisciplinary team approach is recommended, with close collaboration with the obstetrician, so that the mode, timing, and location of delivery can be planned. The management should be tailored to the specific needs of the patient. There is also a close relationship between maternal health and fetal well-being. The frequency of clinical visits is based on the underlying cardiac condition, with high-risk women being followed more often. Serial echocardiograms during pregnancy are useful in women with mechanical valves who are vulnerable to development of thrombosis during pregnancy, women with ventricular dysfunction, and women at risk for aortic root dilation. Fetal growth should be monitored by the obstetric team, and for the woman with congenital heart disease, a fetal cardiac echocardiogram is offered at approximately 18 to 22 weeks' gestation to determine whether a congenital cardiac anomaly is present.

Medical Therapy

Medical therapy should not be withheld when women develop cardiovascular complications during pregnancy; however, when administration of cardiovascular drugs is being contemplated, the potential fetal adverse effects of the drugs require consideration. For many cardiovascular medications, there are limited data on medication safety during pregnancy, and clinical decisions must be made based on the benefit for the patient versus the potential fetal and neonatal risks. The U.S. Food and Drug Administration (FDA) classification of these drugs has been used for many years, but this categorical system is being replaced by a more narrative structure for pregnancy labeling. The potential side effects of cardiovascular medications are shown in **Table 90.2**. A medication should be given only if the benefits are felt to outweigh the potential risk to the fetus. Principles to be considered include the use of drugs with the longest safety record, the use of the lowest dose and shortest duration necessary, and avoidance of a multidrug regimen, if possible. These issues need to be reviewed carefully with the prospective mother.

TABLE 90.2

Effects of Cardiovascular Drugs on Fetus During Pregnancy and on Infant During Breastfeeding

DRUG	POTENTIAL FETAL SIDE EFFECTS	USE DURING BREASTFEEDING
Adenosine	Likely safe; no known teratogenic effect	Not known if there is transfer to breast milk; likely safe because half-life is short
Amiodarone	Contraindicated; goiter, hypothyroidism and hyperthyroidism, bradycardia, intrauterine growth restriction	Transfer to breast milk; use during breastfeeding not recommended
Aldosterone antagonists	Contraindicated; antiandrogenic effects; oral clefts	Transfer to breast milk; safety of breastfeeding unknown
Angiotensin-converting enzyme inhibitors	Contraindicated; IUGR, oligohydramnios, renal failure, abnormal bone ossification	Transfer to breast milk; use of captopril and enalapril during breastfeeding have been reported
Angiotensin II receptor blockers	Contraindicated; renal malformations, oligohydramnios, abnormal bone ossification	Not known if there is transfer to breast milk; use during breastfeeding not recommended
Aspirin	Safe; low-dose aspirin not harmful; high-dose aspirin associated with premature fetal duct closure	Use with caution during breastfeeding
Antiplatelet drugs: Clopidogrel	Safe	Unknown if there is transfer to breast milk; use during breastfeeding not recommended
Beta blockers	Relatively safe; IUGR, neonatal bradycardia, neonatal hypoglycemia Labetalol frequently used to treat hypertension Atenolol may be associated with lower-birth-weight babies when compared with other beta blockers	Transfer to breast milk; compatible with breastfeeding
Calcium channel blockers	Relatively safe; few data; concern regarding uterine tone at time of delivery Nifedipine frequently used to treat hypertension Diltiazem has been reported to have possible teratogenic effects	Transfer to breast milk; compatible with breastfeeding
Digoxin	Safe; no adverse effects	Transfer to breast milk; compatible with breast feeding
Flecainide	Relatively safe; limited data; used to treat fetal arrhythmias	Transfer to breast milk
Heparin	Safe; does not cross placenta, increased risk of subplacental bleeding	No transfer to breast milk; compatible with breastfeeding
Hydralazine	Safe; no major adverse effects, maternal lupus-like syndrome reported	Transfer to breast milk; compatible with breastfeeding
Furosemide	Safe; caution regarding maternal hypovolemia and reduced placental blood flow	Compatible with breastfeeding
Lidocaine	Safe; high doses may cause neonatal central nervous system depression	Transfer to breast milk; compatible with breastfeeding
Methyldopa	Safe; often used to treat hypertension in pregnancy	Transfer to breast milk; compatible with breastfeeding
Procainamide	Relatively safe; limited data; has been used to treat fetal arrhythmias, no major fetal side effects	Transfer to breast milk; compatible with breastfeeding, but long-term effects are not known
Propafenone	Limited data	Unknown
Sotalol	Safe; often used to treat fetal arrhythmias	Transfer to breast milk; not recommended
Statins	Contraindicated; congenital anomalies	Not known if there is transfer to breast milk; use during breastfeeding not recommended
Warfarin	Warfarin embryopathy when used between 6 and 12 weeks' gestation, placental and fetal hemorrhage, central nervous system abnormalities	Transfer to breast milk; compatible with breastfeeding

Interventions and Surgery

Cardiac catheterization should be performed in women presenting with an acute coronary syndrome. Radiation exposure to the fetus can be minimized by lead screening of the mother's abdomen and pelvis. Balloon valvuloplasty is performed during pregnancy in women with severe mitral, pulmonary, or aortic

stenosis who have symptoms refractory to medical therapy, provided the valve anatomy is favorable. Most valvuloplasties are successful in improving valve gradients, but worsening regurgitation, arrhythmias, tamponade, maternal death, precipitous labor, and fetal death have been reported. The procedure should be performed in centers with extensive experience and surgical back-up; if it is undertaken after 26 weeks of pregnancy, obstetric standby should be available in case of premature labor. Transcatheter aortic valve implantation is not routinely performed in pregnant women, but may be considered in select situations.

Cardiac surgery during pregnancy is seldom necessary and should be avoided whenever possible. A higher risk of fetal malformation and loss has been documented when cardiopulmonary bypass is performed in the first trimester; if it is performed in the last trimester, the likelihood of precipitating premature labor is greater. Later in the third trimester, delivery can be performed prior to cardiac surgery if there is adequate fetal maturity. From a fetal outcome perspective, the optimal time for maternal cardiac surgery during pregnancy is likely between 20 and 28 weeks of gestation. Fetal outcomes may also be improved by use of normothermic rather than hypothermic extracorporeal circulation, higher pump flows, higher pressures, and as short a bypass time as possible. Obstetric monitoring of the fetus during the procedure is recommended so that fetal bradycardia may be dealt with promptly and uterine contractions may be controlled. In the current era, with the interventions outlined above, cardiothoracic surgery of the mother can be performed with relative safety during pregnancy, with a maternal mortality rate similar to that in a nonpregnant woman unless the surgery is emergent. However, fetal complications (prematurity and death) are increased in association with urgent high-risk surgery, maternal comorbidity, and early gestational age.[17] A multidisciplinary approach is important to optimize the outcome for both mother and baby.

Labor and Delivery

The hemodynamic changes that occur at the time of labor and delivery mandate that for the high-risk patient with cardiac disease, a multidisciplinary approach during labor and delivery be used. The cardiologist and the obstetrician should work with the anesthesiologist to determine the safest mode of delivery. For most patients with cardiac disease, a vaginal delivery is feasible and preferable because it is associated with fewer complications.[18] A cesarean delivery is usually reserved for obstetric reasons. An important exception to this rule is that of the patient who is anticoagulated with warfarin, because the baby also is anticoagulated and thus at increased risk for intracranial hemorrhage from the stress of vaginal delivery. Cesarean delivery also may be considered in patients who have a dilated aorta, severe pulmonary hypertension, severe heart failure, or a severe obstructive lesion such as aortic stenosis.[18] For women with high-risk conditions, delivery should take place in a center where expertise is available to monitor the hemodynamic changes of labor and delivery and to intervene when necessary. If vaginal delivery is elected, delivery can be accomplished with the mother in the left lateral position so that the fetus does not compress the inferior vena cava, thereby maintaining venous return. Some women with high-risk cardiac lesions may benefit from an assisted second stage (i.e., with forceps or vacuum extraction) to avoid a long labor. For those women with tenuous hemodynamics, Swan-Ganz catheterization before the onset of active labor facilitates optimization of the hemodynamics and should be continued for at least 24 hours after delivery, when pulmonary edema commonly occurs. No universal consensus has yet emerged regarding the administration of antibiotic prophylaxis at the time of delivery for patients with lesions vulnerable to infective endocarditis. Because bacteremia may occur even during an uncomplicated delivery, antibiotic prophylaxis remains optional for patients most vulnerable to the

deleterious effects of endocarditis—that is, those with prior endocarditis, cyanotic heart disease, and prosthetic valves.[19]

Specific Cardiac Conditions in Pregnancy

Congenital Heart Disease (see also Chapter 75)

Few operations for congenital heart disease are considered curative, and many women have residua and sequelae that must be carefully evaluated at the time of prepregnancy counseling. Maternal cardiac, obstetric, and perinatal adverse outcomes are increased in women with congenital heart disease, although outcomes vary widely depending on the cardiac lesion (**Fig. 90.3**).[20] Perinatal risk includes transmission of heart disease to offspring; the type of maternal cardiac lesion present will affect the propensity of the baby to inherit congenital cardiac disease.

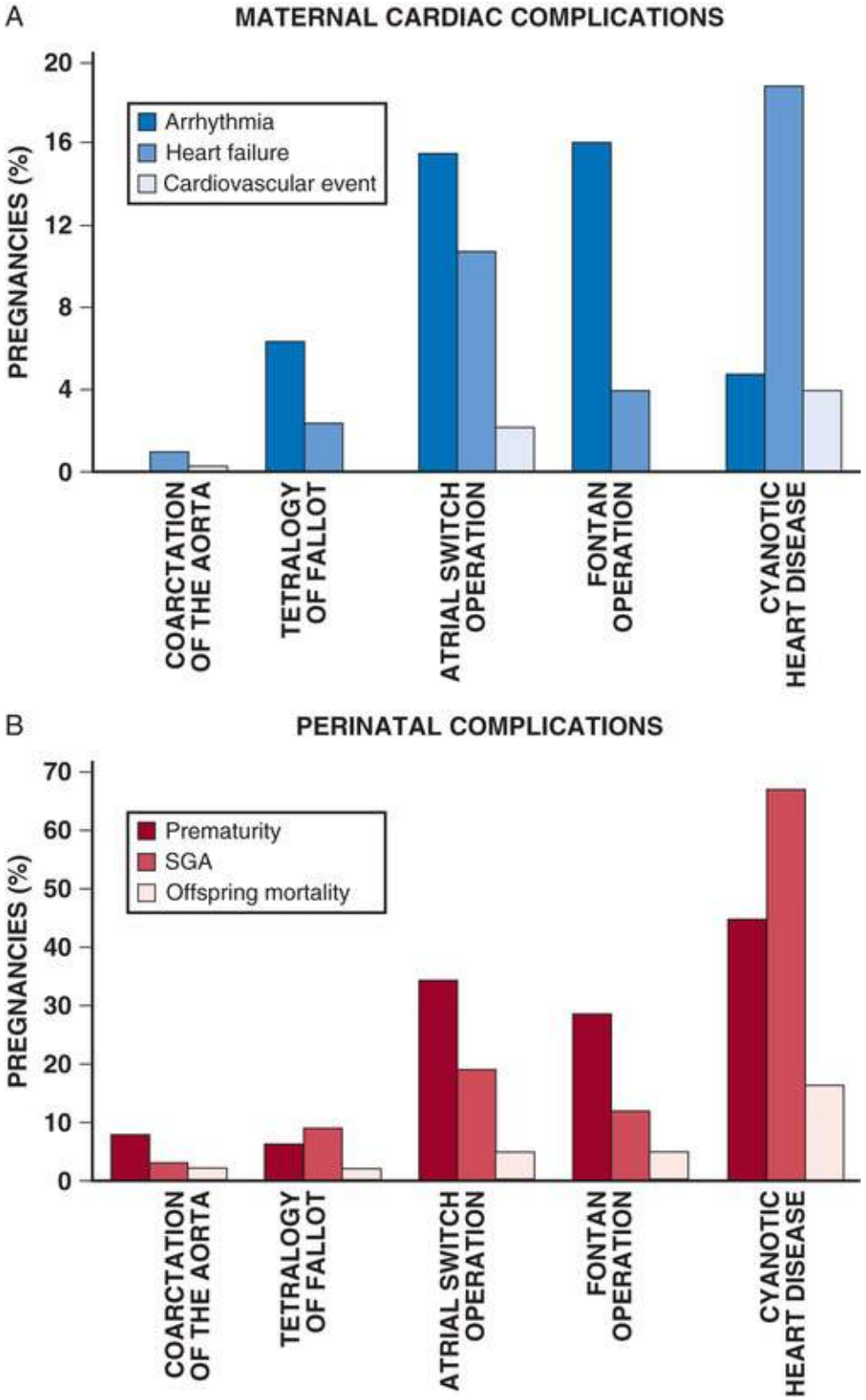

FIGURE 90.3 **A,** Cardiac complications in women with congenital heart disease. *Dark blue bars*, arrhythmias; *light blue bars*, heart failure; *white bars*, other cardiovascular complications (cardiovascular mortality, myocardial infarction, and/or cerebrovascular accidents). **B,** Perinatal complications in women with congenital heart disease. *Dark red bars*, prematurity; *light red bars,* small-for-gestational-age babies; *white bars*, fetal and neonatal mortality. (Data from Drenthen W, Pieper PG, Roos-Hesselink JW, et al. Outcome of pregnancy in women with congenital heart disease: a literature review. J Am Coll Cardiol. 2007;49:2303-11.)

Shunt Lesions

Women with simple shunts often do well during pregnancy. Secundum atrial septal defect is one of the most common congenital heart defects. The volume load on the right ventricle usually is well tolerated, and even women with large unrepaired secundum atrial septal defects usually do not develop cardiac

complications during pregnancy unless concomitant pulmonary hypertension or atrial fibrillation is present. Meticulous attention should be paid to the maternal leg veins, particularly during and after delivery, because deep vein thrombosis could result in a paradoxical embolus and stroke. Women with small ventricular septal defects or patent ductus arteriosus with small ducts with normal or near-normal pressures usually tolerate pregnancy without difficulty. With a large shunt, the added volume load of pregnancy may rarely potentially precipitate left ventricular failure. Women with ventricular septal defects or patent ductus arteriosus and pulmonary hypertension should be counseled that pregnancy is contraindicated.

Coarctation of the Aorta

Most women with coarctation of the aorta will have had a repair prior to pregnancy. When the presence of a coarctation is known, the entire aorta should be imaged at the time of prepregnancy counseling because some women may have residual or recurrent coarctation or aneurysm. Most women will have a successful pregnancy with proper care. The most common maternal complication is systemic hypertension, which may require therapy.[21] A significant coarctation can impair flow to both the uterus and fetus, which may result in small-for-dates babies or even fetal loss. Aggressive antihypertensive therapy should be avoided because of the chance of placental hypoperfusion. Because of the associated aortopathy, the entire aorta is vulnerable to dilation, aneurysm, and dissection.

Tetralogy of Fallot

Most women with tetralogy of Fallot will have had previous surgical repair and should be free of cyanosis. An occasional adult will be seen who has not had previous surgery or in whom palliation was achieved with a surgically created shunt (e.g., Blalock-Taussig shunt). In such cases, pregnancy may pose a risk, depending on the degree of cyanosis, as noted below. For those patients with previous intracardiac repair, a careful assessment of any hemodynamic residua and sequelae should be undertaken before advice is given about the safety of a pregnancy. For those women with an effective surgical repair, good exercise capacity, and minimal residua, pregnancy is well tolerated if they are properly managed. The volume load of pregnancy may not be well tolerated when women have significant right ventricular dilation and dysfunction.[22] Additionally, these women may be at risk for atrial and even ventricular arrhythmias.

Pulmonary Stenosis

Women with isolated valvar pulmonary stenosis almost always tolerate pregnancy well. Some women will have had a pulmonary valvuloplasty and may have residual pulmonary regurgitation. These women also do well if they have good exercise capacity and preserved right ventricular systolic function.

Ebstein Anomaly

The safety of a pregnancy in patients with Ebstein anomaly depends on right ventricular size and function, degree of tricuspid regurgitation, and presence or absence of an atrial communication. The latter is present in approximately 50% of patients, and if the patient is cyanotic at rest, the risk of pregnancy increases considerably. An atrial communication poses the added potential risk of a stroke from a paradoxical embolus, and meticulous attention should be paid to the possibility of maternal deep vein thrombosis. Atrial arrhythmias may not be well tolerated in the pregnant woman with this anomaly, and women are at risk for both atrial fibrillation and atrioventricular reentry tachycardia (**see also Chapter**

37). Accessory bypass tracts causing preexcitation can precipitate rapid tachycardia. Pregnancy risks may be less after successful surgical repair or replacement of the tricuspid valve if there is no other residual disease.

Complete Transposition of the Great Arteries

Women with complete transposition of the great arteries will have had surgery in childhood. Atrial switch operations (Mustard or Senning operation) leave the morphologic right ventricle as the systemic pump, and, over time, the subaortic right ventricle can dilate or weaken. The function of the subaortic ventricle and the degree of systemic atrioventricular valve regurgitation are important determinants of the pregnancy outcome. In a study of 49 completed pregnancies, the most common maternal cardiac complication was arrhythmias, occurring in 22% of the pregnancies.[23] Heart failure and maternal death have been reported. Prematurity is common, and small-for-gestational-age babies are common. Some women have irreversible subaortic ventricular dysfunction or worsening systemic atrioventricular valve regurgitation.[24] Careful preconception evaluation by an expert is important for women with this condition. Dysfunction of the subaortic right ventricle can be a contraindication to pregnancy. Women with atrial switch operations are at risk for arrhythmias and heart failure immediately postpartum and should have monitoring in a cardiac intensive care unit after delivery.

The more contemporary repair for complete transposition is the arterial switch operation (Jatene operation), and these women are now reaching child-bearing age. Women who have undergone this operation may have neoaortic root dilation, aortic regurgitation, pulmonary stenosis, or coronary artery stenosis, and these lesions will affect the pregnancy risk. Preconception assessment by an expert in congenital heart disease is important. Women who have undergone the arterial switch operation who do not have major residual lesions tend to do well.[25] All women with repaired transposition should deliver at a high-risk pregnancy unit.

Fontan Operation

Women who have undergone a Fontan operation will have single-ventricle physiology, typically without a subpulmonic ventricle. Blood flow through the lungs is from passive flow. These women are at increased risk for maternal complications during pregnancy, particularly atrial arrhythmias, which may cause profound hemodynamic deterioration and heart failure.[26,27] They are vulnerable to development of thrombosis in the Fontan circuit because of the low flow through the circuit and prothrombotic state of pregnancy. Function of the single ventricle may deteriorate because of the volume load of pregnancy. Fetal and neonatal complications such as prematurity and low birth weight are major problems in this population.[27,28] This is a complex condition, and preconception counseling by an expert in adult congenital heart disease is crucial. The Fontan circulation is preload dependent, and minimizing pushing at the time of delivery is important to prevent complications. Immediately postpartum, women should have careful monitoring of their rhythm and volume status in a cardiac intensive care unit.

Cyanotic Heart Disease

There are a number of cardiac conditions, such as unrepaired tetralogy of Fallot, where women of child-bearing age may present with cyanosis. Cyanosis poses risks for both mother and fetus.[29] The decrease in peripheral resistance that accompanies pregnancy augments the right-to-left shunt and may exaggerate the maternal cyanosis. Because of the erythrocytosis that accompanies cyanosis and the propensity to thrombosis, women in whom venous thrombosis develops are at risk of paradoxical embolus and stroke.

In addition to the degree of maternal cyanosis, right ventricular function must be assessed before pregnancy by echocardiography or MRI. As for patients with other complex congenital heart diseases, preconception counseling by an expert in adult congenital heart disease is crucial.

Maternal hypoxia imposes a pronounced handicap to fetal growth and survival. In a study of 44 women with 96 pregnancies (excluding women with Eisenmenger syndrome), maternal oxygen saturations of less than 85% were associated with a poor fetal outcome; only 2 of 17 pregnancies (12%) resulted in live-born infants.[29] Conversely, when the maternal oxygen saturation was 90% or higher, 92% of the pregnancies resulted in a live birth. Maternal cardiovascular complications occurred in 14 patients (32%). Eight patients had heart failure, and bacterial endocarditis occurred in two patients, both with surgically palliated tetralogy of Fallot. Two patients had thrombotic complications, one pulmonary and one cerebral.

Pulmonary Hypertension (see also Chapter 85)

In women of childbearing age, pulmonary arterial hypertension may be idiopathic or it may be secondary to congenital cardiac shunts or connective tissue disorders. Pulmonary arterial hypertension, regardless of the cause, carries a high mortality rate when it is associated with pregnancy. The volume load of pregnancy can compromise the poorly functioning right ventricle, precipitating heart failure. The fall in peripheral resistance augments right-to-left shunting, thereby contributing to development of cyanosis. Labor and delivery are particularly dangerous, and the highest incidence of maternal death is during parturition and the puerperium. An abrupt decrease in afterload may occur as the baby is delivered, and hypovolemia from blood loss can cause hypoxia, syncope, and sudden death. Vagal responses to pain also may be life-threatening. A systematic review of pregnancy in 73 women with pulmonary arterial hypertension reported a maternal mortality rate of 25%.[30] Maternal morbidity and mortality are due to right ventricular heart failure, pulmonary hypertensive crises, pulmonary embolism, arrhythmias, and bleeding. Neonatal and fetal deaths are also increased, and premature deliveries occur in many pregnancies. Some recent series have suggested that more successful maternal and neonatal outcomes may be possible.[31,32] Advanced therapies for pulmonary arterial hypertension are being increasingly used in the pregnant population and may, in part, be responsible for improved outcomes. Intravenous and inhaled prostacyclins and phosphodiesterase type 5 inhibitors are the most commonly used pulmonary arterial hypertension medications used during pregnancy. Bosentan is not used during pregnancy because of the potential for teratogenicity.

Termination of pregnancy is the safer option, although in patients with pulmonary hypertension, this too may be a more complex procedure, and cardiac anesthesia is helpful in this regard. For women who continue pregnancy, the mode of delivery needs to be determined after careful consideration by the treating physicians. Cesarean delivery with cardiac anesthesia is an option. If the vaginal route is selected, it should take place in an intensive care unit. Epidural analgesia must be administered with due caution to minimize peripheral vasodilation. A prolonged second stage should be avoided. The use of an anti–deep vein thrombosis device (i.e., Thromboguard) or a compression pump may help prevent peripheral venous thrombosis. In-hospital monitoring should be continued for at least 2 weeks after delivery. Appropriate advice about contraception should be given to all patients.

Marfan Syndrome (see also Chapter 75)

The most common connective tissue disorder is Marfan syndrome, caused by a mutation in the *FBN-1* gene encoding the glycoprotein fibrillin. Marfan syndrome is inherited in an autosomal dominant pattern.

Preconception counseling, including genetic evaluation, is essential and should include advice about the risks of cardiovascular complications for the mother and the risk of transmission to offspring. A careful clinical and cardiovascular imaging evaluation should be performed. Cardiac investigations include a transthoracic echocardiogram and a cardiac MRI or CT to assess the entire aorta for aortic dilation or dissection. It has been suggested that pregnancy usually is contraindicated if the ascending aorta is larger than 4.4 cm in diameter,[33] although the exact dimension is a matter of debate. The European Society of Cardiology guidelines on cardiovascular diseases during pregnancy suggest that women with Marfan syndrome undergo aortic replacement if the aorta is greater than 4.5 cm.[18] It should be emphasized to all women with Marfan syndrome and those with previous aortic dissection that pregnancy is not uniformly safe and the risks are unpredictable. Pregnancy increases the risk of aortic complications in the long term.[33] Aortic complications during pregnancy carry a high maternal mortality rate of up to 11%. Associated cardiovascular problems also need to be evaluated, including the possibility of aortic regurgitation and mitral valve prolapse with associated regurgitation.

Many women are already receiving treatment with beta-adrenergic blockers or angiotensin II receptor antagonists to prevent aortic dilation and dissection. Beta blockers should be continued during pregnancy because they may prevent progressive aortic dilation and dissection. Angiotensin II receptor antagonists should be stopped during pregnancy because of the fetal risk. Periodic echocardiographic surveillance every 6 to 8 weeks is recommended to monitor the mother's aortic root size, with the interval dependent on the initial echocardiographic findings. Any chest pain should be promptly evaluated to rule out dissection. During labor and delivery, pushing should be avoided, with an assisted second stage if necessary. In women with a dilated aorta, delivery should occur in a tertiary care center where experienced cardiothoracic surgical expertise is available.

Valvular Heart Disease (see also Chapter 67)

Aortic Stenosis (see also Chapter 68)

Aortic stenosis in women of childbearing age is usually secondary to a bicuspid aortic valve. In low-income countries, aortic stenosis may be secondary to rheumatic heart disease. A detailed echocardiographic assessment of the valve function should be performed before pregnancy is contemplated. A stress test can be useful to assess functional capacity and blood pressure response to exercise. Women with severe aortic stenosis (a valve area < 1 cm^2 or a mean gradient > 40 mm Hg) need careful preconception risk stratification by a cardiologist with expertise in pregnancy and heart disease. Some women with severe aortic stenosis who have an excellent functional capacity and a normal blood pressure response to exercise will be able to tolerate pregnancy. Others may require valve surgery prior to pregnancy. In addition, a careful examination of the entire thoracic aorta is indicated to look for bicuspid valve associated aortopathy; even with a functionally normal valve, an aortic dilation or ascending aortic aneurysm may be present. Surgical repair prior to pregnancy should be considered if the aorta is larger than 5 cm.

Mild and moderate aortic stenosis is usually well tolerated if the patient has a normal exercise capacity and no symptoms. Pregnancy in women with severe aortic stenosis is characterized by an increased incidence of heart failure, arrhythmias, premature labor, and shorter pregnancy duration. In one study of 96 pregnancies in women with at least moderate aortic stenosis, 21% of women were hospitalized for cardiac reasons during pregnancy.[34] Although maternal mortality rates are very low in contemporary series, death has been reported in this group of women.

Labor and delivery can be particularly problematic in such patients because of the abrupt hemodynamic

changes, including immediately postpartum when there is an abrupt fall in afterload as the baby is delivered. Blood loss at the time of parturition also can precipitate maternal collapse. Epidural analgesia needs to be carefully and slowly administered, and spinal block should be avoided because of the potential for hypotension. Delivery may be facilitated by arterial lines or central venous pressure monitoring, which should be continued for at least 24 hours after delivery. Over the long term, women with moderate or severe aortic stenosis who have been pregnant are more likely to require cardiac interventions when compared with women who have not been pregnant.[35]

Mitral Stenosis (see also Chapter 69)

Mitral stenosis is almost always due to rheumatic heart disease, and cardiac complications during pregnancy are common. Symptoms tend to worsen during pregnancy because of the increased plasma volume coupled with the increase in heart rate, which shortens the diastolic filling time and increases the left atrial pressure. Any decrease in stroke volume causes a further reflex tachycardia, which contributes further to the elevated left atrial pressure. Atrial arrhythmias and pulmonary edema are the most common cardiac complications.[36] The onset of atrial fibrillation may precipitate acute pulmonary edema. Maternal death can occur, particularly in low-income countries where access to pregnancy care is difficult. Perinatal morbidity and mortality rates are also increased.

Women should undergo careful echocardiographic evaluation of the mitral valve and pulmonary pressures before proceeding with pregnancy. Exercise echocardiography also may be helpful in delineating the hemodynamic response to effort in terms of mitral gradient and the presence or absence of pulmonary hypertension. Women with severe mitral stenosis should have a valve intervention prior to pregnancy. During pregnancy, the cornerstone of medical therapy for the symptomatic patient is beta blockade. This pharmacologic mode slows the heart rate, prolongs the diastolic filling time, and can result in marked clinical improvement with control of symptoms. Bed rest also may be helpful to slow the heart rate and to minimize cardiac demands. The use of diuretics is appropriate if pulmonary edema is present. Anticoagulants should be administered in the setting of atrial fibrillation. When the mother fails to respond adequately to medical management, balloon valvuloplasty may be performed if the valve anatomy is favorable and there is no concomitant mitral regurgitation.[37] Surgical valvotomy may be performed but should be reserved for patients with symptoms refractory to medical therapy in whom balloon valvotomy is not feasible.

Mitral and Aortic Regurgitation

Mitral and aortic regurgitation may be tolerated in pregnancy, provided that the regurgitation is of no more than moderate, the mother is asymptomatic before pregnancy, and ventricular function is preserved. Closer monitoring during pregnancy usually is warranted, however, particularly for those with mitral regurgitation, because the left ventricle tends to dilate as pregnancy progresses, and this may exacerbate the degree of mitral regurgitation.

Prosthetic Valves (see also Chapter 71)

Pregnancy for the woman with a prosthetic valve poses risks for mother and baby. The choice of a prosthetic valve for the woman of childbearing age involves a detailed discussion of the relative risks so that she can make an informed decision about whether to select a tissue or mechanical prosthesis. Tissue valves are less thrombogenic than mechanical valves and therefore are less problematic in pregnancy because they do not routinely involve the use of warfarin. The disadvantage is their tendency to

degenerate after an average of 10 to 15 years, necessitating a reoperation, with its attendant risks and potential for death. Mechanical prostheses, by contrast, have a greater longevity but require anticoagulation, and whichever anticoagulant strategy is chosen during pregnancy, there is a higher chance of fetal loss, placental hemorrhage, and prosthetic valve thrombosis.

Tissue Prostheses

The most common types of tissue valves used currently are porcine and pericardial valves. For patients in sinus rhythm, they confer the advantage that warfarin is not required, although most patients take low-dose (81-mg) aspirin. These valves are vulnerable to structural degeneration and calcification, which occurs more rapidly in younger patients. In addition, mitral prostheses tend to degenerate faster than those in the aortic position. Some evidence suggests that pregnancy may accelerate valve degeneration; this potential disadvantage is not universally accepted, however, and other large series have shown no difference in structural valve degeneration in young women who had a pregnancy and those who did not. Nonetheless, all tissue valves will degenerate, necessitating a second operation, with an operative risk that usually is higher than for the first. In some series, the mortality rate for a second valve replacement may be as high as 6%, and it must be recognized that if death occurs after a successful pregnancy, the young child is left without a mother. Thus, at the time of counseling women of childbearing age about valve choice, the surgical results from the individual physician's institution should be reviewed. These findings may vary considerably on the basis of both surgical volume and expertise. Use of homografts poses similar problems of structural deterioration and reoperation. The Ross operation, in which an autograft pulmonary valve is placed in the aortic position and a tissue prosthesis (usually porcine) is implanted in the pulmonary position, is associated with good outcomes during pregnancy when the hemodynamic indices are good. Nonetheless, the Ross procedure eventually requires reintervention.

Mechanical Prostheses

During pregnancy, the maternal blood is highly thrombogenic because of increased concentration of clotting factors, increased platelet adhesiveness, and decreased fibrinolysis. These changes contribute to a significant risk of maternal valve thrombosis and thromboembolism. Although the maternal risk of valve thrombosis is primarily dependent on the anticoagulation regimen chosen and the quality of anticoagulation control, the type of valve, position of the valve (mitral more than aortic), and function of the valve are also determinants of outcome. Women are also at risk of bleeding complications, cerebrovascular events, heart failure, arrhythmias, and endocarditis. Fetal and neonatal complications are increased in this group of women and include fetal loss, stillbirths, intracranial hemorrhage, prematurity, and low-birth-weight babies.

The management of anticoagulation during pregnancy in women with a mechanical valve prosthesis is controversial, and no universal consensus has emerged. Potential anticoagulation options include vitamin K antagonists, low-molecular-weight heparin, unfractionated heparin, or a combination or vitamin K antagonists and heparin. There is no perfect anticoagulation strategy, and each regime is associated with some hazard for the mother or the fetus. In general, the maternal risk is lowest with vitamin K antagonists and the fetal risk is lowest with heparin. A systematic review of pregnancy outcomes in women with mechanical valves (n = 2468 pregnancies), stratified according to the type of anticoagulant used during pregnancy, is shown in **Table 90.3**.[38] All anticoagulant regimens, however carefully managed, carry an increased risk of fetal loss and spontaneous abortion and the potential for hemorrhagic complications, including placental bleeding, miscarriage, and fetal death. Before any approach is adopted, it is

imperative to explain the risks to the patient. With all anticoagulant regimens, the addition of low-dose aspirin, 75 to 162 mg/day, may confer additional maternal benefit. As yet, no data support the use of anti-Xa and direct thrombin inhibitors in patients with prosthetic valves. Mothers with mechanical prostheses are best managed by a multidisciplinary team in a center that provides training and expertise in the management of complex heart disease and pregnancy.

TABLE 90.3

Primary Outcomes of Mothers with Mechanical Valves Taking Anticoagulants During Pregnancy and Their Infants*

ANTICOAGULATION REGIME	MATERNAL MORTALITY RATES ESTIMATED % (95% CI)	MATERNAL THROMBOEMBOLISM RATES ESTIMATED % (95% CI)	LIVE BIRTHS ESTIMATED % (95% CI)	WARFARIN EMBRYOPATHY AND FETOPATHY ESTIMATED % (95% CI)
Vitamin K antagonists (INR target 2.5 to 3.5)	0.9 (0.1, 1.6)	2.7 (1.4, 4.0)	64.5 (48.8, 80.2)†	2.0 (0.3, 3.7)†
Sequential treatment	2.0 (0.8, 3.1)	5.8 (3.8, 7.7)	79.9 (74.3, 85.6)	1.4 (0.3, 2.5)‡
LMWH alone	2.9 (0.2, 5.7)	8.7 (3.9, 13.4)	92.0 (86.1, 98.0)	NA
UFH alone	3.4 (0, 7.7)	11.2 (2.8, 19.6)	69.5 (37.8, 100)	NA§

*Estimates are presented as proportions per 100 affected pregnancies with 95% confidence intervals.

†Of these, 7/407 [0.8% (0.0, 1.7)] represent embryopathy and 5/197 [2.1% (0.1, 4.1)] represent fetopathy.

‡All cases represent fetopathy.

§There were four cases of intracranial bleeding in women using UFH; bleeding was secondary to prematurity and not the anticoagulant effect because UFH does not cross the placenta.

CI, confidence interval; *INR*, International Normalized Ratio; *LMWH*, low-molecular-weight heparin; *NA*, not applicable; *UFH*, unfractionated heparin.

Modified from D'Souza R, Ostro J, Shah PS, et al. Anticoagulation for pregnant women with mechanical heart valves: a systemic review and meta-analysis. *Eur Heart J*. 2017;38(19):1509-16.

Effects of Pharmacologic Therapy in Valvular Disease

Warfarin.

Fetal exposure to warfarin between 6 and 9 weeks' gestation is associated with *warfarin embryopathy* (stippled epiphyses, nasal hypoplasia). *Warfarin fetopathy* (optic atrophy and central nervous system abnormalities) occurs with exposure later in gestation.[39] The reported risk of embryopathy varies widely but probably averages 2% to 4%. This risk is reduced by initiation of heparin before 6 weeks of gestation. The disadvantage of stopping warfarin is an increased risk of maternal valve thrombosis. The risk of warfarin-related perinatal complications is dose related, but whether warfarin embryopathy, specifically, is dose related continues to be debated.[39] One study suggested that the risk is very low if the maternal warfarin dose is 5 mg/day or less.[40] Warfarin is associated with fewer live births when compared with heparin.[41] Because warfarin carries the lowest risk of maternal valve thrombosis and death, the American College of Cardiology/American Heart Association (ACC/AHA)[42] and the European Society of Cardiology (ESC)[18] have recommended the use of oral anticoagulants in the second and third trimesters until approximately the 36th week of pregnancy with strict control of international normalized ratio values (**Fig. 90.4**). The transition period, when warfarin is discontinued and heparin started, may need to be earlier in women at high risk of preterm birth. Because the fetal risk in the first trimester appears to be dose related, guidelines recommend consideration of continuation of oral anticoagulants in

the first trimester in women whose warfarin dose is less than 5 mg/day. These options must be fully discussed with the patient before she becomes pregnant, not only for the medicolegal implications but to ensure she has complete understanding of all the risks and benefits to mother and baby.

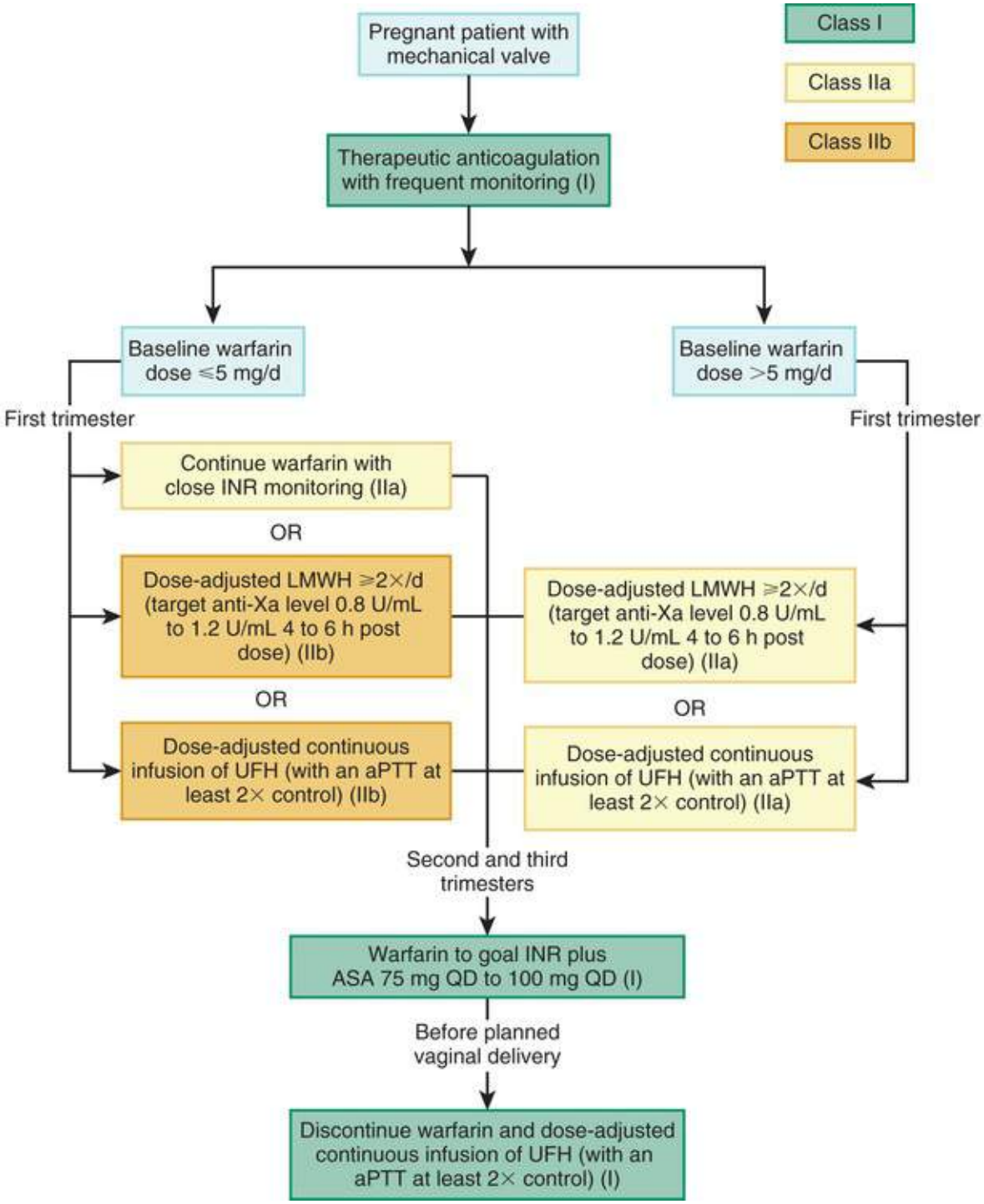

FIGURE 90.4 Anticoagulation of pregnant women with mechanical valves: recommendations from the American College of Cardiology/American Heart Association. *aPTT,* activated partial thromboplastin time; *ASA,* acetylsalicylic acid; *INR,* international normalized ratio; *LMWH,* low molecular weight heparin. (From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2438-88.)

Low-Molecular-Weight Heparin.

Although the use of heparin eliminates the risk of warfarin embryopathy, there is a significant increase in

the risk of maternal thromboembolic complications, including valve thrombosis. Low-molecular-weight heparin is an attractive alternative to unfractionated heparin because of its ease of use and superior bioavailability. It does not cross the placenta, so embryopathy does not occur.

However, no large prospective trials have been conducted to confirm the usefulness of low-molecular-weight heparin in this setting, and reported studies are confined to small series.

Live birth rates are highest with the use of low-molecular-weight heparin, but rates of maternal thromboembolic complications and maternal mortality are increased when compared with warfarin. Thromboembolic complications are usually, but not always, associated with fixed-dose regimes or subtherapeutic anti-Xa levels. The low-molecular-weight heparin dose requirements can change dramatically throughout pregnancy owing to changes in renal clearance and plasma volume. Furthermore, preinjection anti-Xa levels may still be subtherapeutic when the postinjection level is therapeutic. Data remain limited regarding optimal anti-Xa levels, timing of measurement (peak levels versus trough levels, or both), and the frequency of testing. Despite these limitations, the ACC/AHA[42] (**see Fig. 90.4**) and the ESC[18] suggest that low-molecular-weight heparin can be used as an alternative to warfarin for women requiring more than 5 mg/day of warfarin. The American College of Chest Physicians suggests that low-molecular-weight heparin can be used as an alternative to warfarin in any woman, regardless of the warfarin dose.[43] If low-molecular-weight heparin is used, it should be administered subcutaneously every 12 hours and the dose adjusted so that a 4-hour postinjection anti-Xa level is maintained at approximately 1.0 to 1.2 units/mL. Low-molecular-weight heparin should be discontinued at least 36 hours before delivery; at this time a switch to an infusion of unfractionated heparin should be made because it can be started and stopped abruptly. This precaution is especially important if epidural analgesia is to be used, because its prolonged effect increases the risk of spinal hematoma. Unfractionated heparin should be resumed as soon as possible after delivery in the absence of bleeding complications.

Unfractionated Heparin.

Unfractionated heparin is a large molecule that does not cross the placenta and does not cause developmental abnormalities in the fetus. Laboratory control of the activated partial thromboplastin time (aPTT) is difficult, in part because of the variation in response to standard doses and the wide variation in the reagents used to monitor doses. If used during pregnancy, heparin should be given as an infusion and the activated partial thromboplastin time ratio at least 2 control. Subcutaneous unfractionated heparin has been used throughout pregnancy to avoid any fetal exposure to warfarin, but it has been shown to be a poor anticoagulant in pregnancy. The ACC/AHA valve guidelines do not recommend subcutaneous heparin in pregnant women with mechanical valves. [42]

Cardiomyopathies (see also Chapter 77)

Dilated Cardiomyopathy

In young women, dilated cardiomyopathy is often idiopathic, but it may be secondary to the effects of drugs or toxins or to infection. Occasionally, a genetic cause of dilated cardiomyopathy is present, in which case, transmission to offspring should be addressed. Women with dilated cardiomyopathy usually are counseled not to have a pregnancy if the ejection fraction is lower than 30% or if they are in NYHA functional class III or IV.[18] Careful echocardiographic evaluation should be performed before pregnancy. Exercise stress testing may also be helpful, because women with cardiomyopathy may not tolerate pregnancy well if they have a poor aerobic capacity.

Women with dilated cardiomyopathy are at risk for deterioration in left ventricular systolic function,

pulmonary edema, and arrhythmias. Maternal death is rare but has been described. In one study of 36 pregnancies in 32 women with dilated cardiomyopathy, 14 of 36 pregnancies (39%) were complicated by at least one adverse maternal cardiac event.[44] A poor functional class and moderate or severe left ventricular dysfunction were the main determinants of adverse maternal cardiac outcomes. Conversely, women with dilated cardiomyopathy who have only mild left ventricular systolic function, have a good functional class, and have no prior heart failure or arrhythmia often do well in pregnancy.

Women with cardiomyopathies should continue beta-blocker therapy when indicated. Because angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists are contraindicated in pregnancy, the ventricular function must be assessed without the medications before pregnancy. Symptomatic patients who proceed with a pregnancy may need hydralazine for afterload reduction. Heart failure typically occurs in the third trimester or early postpartum period. Women who develop pulmonary edema should be treated with diuretics and may require hospital admission and bed rest. Early delivery may be necessary in women who decompensate during pregnancy or in those with severe left ventricular systolic dysfunction.

Hypertrophic Cardiomyopathy (see also Chapter 78)

A wide spectrum of anatomic and hemodynamic abnormalities has been documented in hypertrophic cardiomyopathy, including left ventricular outflow tract obstruction, mitral regurgitation, arrhythmias, and diastolic dysfunction. Some patients are asymptomatic, with minimal hemodynamic disturbance; others exhibit profound functional limitation, with marked hemodynamic perturbations. A careful personal history, review of family history, an electrocardiogram, exercise testing, and transthoracic echocardiography should precede counseling about the advisability of a pregnancy. The prospective parents should be informed about the autosomal dominant inheritance pattern, which has variable penetrance. In many patients, a genetic cause can be identified, and genetic counseling and family screening are appropriate before pregnancy is contemplated.

Most studies suggest that women with hypertrophic cardiomyopathy tolerate pregnancy well.[45] The decrease in afterload that might exacerbate the outflow gradient is largely offset by the maternal increase in plasma volume. Patients with significant symptoms before pregnancy (usually related to severe left ventricular outflow tract obstruction) may develop complications. Sudden death in pregnancy is rare but has been reported, and this fact highlights the need for careful preconception evaluation.[45] Heart failure and arrhythmias, both atrial and ventricular, can occur during pregnancy. The reported frequency of arrhythmias and heart failure during pregnancy varies between studies, likely due to differences in patient selection, small numbers, and variable study methods. Maternal cardiac complications at the time of delivery have been reported to occur in as many as 23% of pregnancies.[46] Medications such as beta blockers should be continued throughout pregnancy, but the dose may need to be increased as the pregnancy progresses. Diuretics may be used to treat heart failure in pregnancy, but care must be taken to avoid volume depletion, which exacerbates the left ventricular outflow gradient. Meticulous attention should be paid to hemodynamics at the time of delivery. Hypotension with epidural anesthesia and spinal block should be avoided, specifically in women with obstructive hypertrophic cardiomyopathy. Blood losses should be promptly replaced. Cesarean delivery is indicated for obstetric reasons only. Avoidance of the Valsalva maneuver and a facilitated second stage of labor are advised in women with obstructive hypertrophic cardiomyopathy.

Peripartum Cardiomyopathy

Peripartum cardiomyopathy (PPCM) is a life-threatening condition associated with left ventricular dysfunction occurring during the last months of pregnancy or in the months following delivery in previously healthy women. The incidence of PPCM varies among populations; it is approximately 1 in 3000 in the United States compared with 1 in 300 in Haiti. Known risk factors include black race, older maternal age, multiparity, and preeclampsia. The majority of women present in the first month postpartum. Women may present with heart failure, cardiogenic shock, arrhythmias, or stroke secondary to left ventricular thrombus. Mortality rates in the United States have been reported at between nil and 19%.[47] Uncertainty can exist about whether the cardiomyopathy developed during pregnancy or was a preexisting cardiomyopathy that became apparent during pregnancy.

The cause and pathophysiology are poorly understood, but an angiogenic imbalance is thought to be important, with excess antiangiogenic factors occurring in combination with host susceptibility.[48] Inflammation may play a role, because serum markers of inflammation are elevated in many patients. An unbalanced peripartum oxidative stress may also be important because it leads to the proteolytic cleavage of the nursing hormone prolactin, with the resultant formation of a 16-kDa subform. This subform of prolactin is a potent antiangiogenic, proapoptotic, and proinflammatory agent that affects the endothelium, cardiac vasculature, and cardiac myocyte function. This hypothesis has led to a potential therapeutic strategy with blockade of prolactin by bromocriptine, a dopamine D_2 receptor agonist. This treatment has been shown to prevent the disease in experimental animal models and appeared to be successful in small pilot studies with respect to prevention and treatment in patients.[49] Because prolactin acts as a scavenger for thrombin, its elimination by bromocriptine may increase the risks of thromboembolism, and concomitant heparin anticoagulation has been advised. Randomized trials are necessary to determine safe and effective treatment strategies.

In other respects, the treatment of PPCM is similar to that for other forms of congestive heart failure, except that angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists should not be used in women who present antenatally.[50] Hydralazine and nitrates can be used for afterload reduction. Beta blockers and digoxin can be used during pregnancy. Diuretics should be used to treat pulmonary edema, and inotropes may be necessary in more severe cases. Aldosterone antagonists may have antiandrogenic effects on the fetus and should be avoided. Left ventricular thrombi are common, and consideration should be given to anticoagulation with heparin in patients with an ejection fraction lower than 35%. Women with severe PPCM should be transferred to a center that can offer mechanical support and transplant services. Temporary circulatory support, with either an intraaortic balloon pump or a left ventricular assist device, or extracorporeal membrane oxygenation may be necessary in those with cardiogenic shock. Cardiac transplantation may be considered in patients refractory to mechanical circulatory support. Early fetal delivery may be necessary in women with refractory heart failure, but the timing and mode of delivery depend on the maternal clinical status. Cesarean delivery is the preferred mode of delivery in hemodynamically unstable patients.

In a study of 100 women with PPCM, normalization of ventricular systolic function occurred in 72%, but recovery was unlikely if the left ventricular ejection fraction was less than 30% or if the left ventricular end-diastolic dimension was greater than 6 cm at the time of diagnosis[51] (**Fig. 90.5**). Left ventricular systolic function usually improves within the first 6 to 12 months postpartum. All women with PPCM are at risk for recurrence in subsequent pregnancies, and this may result in significant clinical deterioration and death. Women who do not have full recovery of left ventricular systolic function are at highest risk and should be advised that pregnancy is contraindicated because of the 20% maternal mortality rate with subsequent pregnancies.

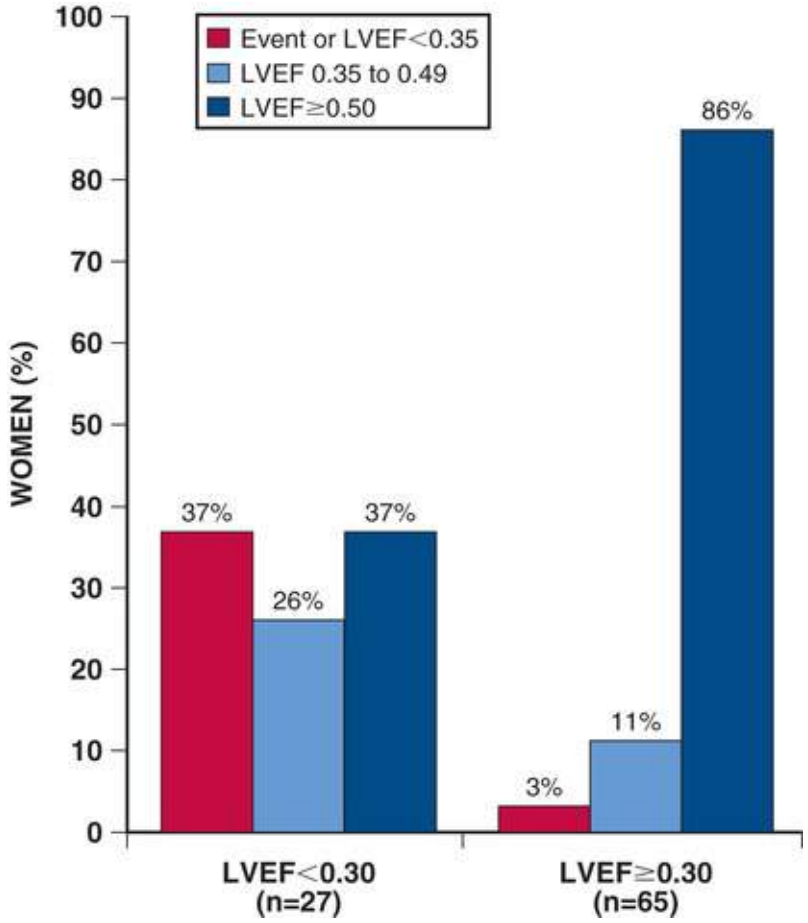

FIGURE 90.5 Recovery of left ventricular systolic function in women with peripartum cardiomyopathy. Comparison of left ventricular systolic function at 1 year postpresentation based on the initial left ventricular ejection fraction. *Red column*, percentage of women with no recovery (event of final ejection fraction < 0.35); *blue column*, percentage of women with partial recovery (final ejection fraction 0.35 to 0.49); *purple column*, percentage of women with complete recovery (final ejection fraction 0.50 to 0.49). (From McNamara DM, Elkayam U, Alharethi R, et al. Clinical outcomes for peripartum cardiomyopathy in North America: results of the IPAC study (Investigations of Pregnancy-Associated Cardiomyopathy). J Am Coll Cardiol 2015;66:905-14.)

Coronary Artery Disease and Pregnancy-Associated Myocardial Infarction (see also Chapter 58)

Coronary disease, of any type, is uncommon in women of childbearing age. Atherosclerotic coronary artery disease may occur with older maternal age, the presence of diabetes, or tobacco abuse. Other coronary lesions such as coronary dissection, coronary thrombus, and coronary artery spasm occur in this young cohort. One study of 50 pregnancies in women with preexisting coronary disease reported a 10% risk of maternal death, acute coronary syndrome, myocardial infarction, or heart failure during pregnancy.[52] This included one maternal death secondary to cardiac arrest. New or progressive angina occurred in 18% of the pregnancies. Ischemic complications were more common in women with coronary atherosclerosis as an underlying diagnosis. High rates of adverse fetal and neonatal complications were also seen.

Pregnancy-associated acute myocardial infarction is rare, but with the rise in maternal age and increasing number of high-risk women who become pregnant, the incidence is increasing. When it occurs, pregnancy increases the maternal mortality rate to an estimated 5% to 10%. The most common cause of pregnancy-associated acute myocardial infarction is coronary artery dissection (**Fig. 90.6**), and the most commonly involved artery is the left anterior descending artery. This tends to occur more commonly in the third trimester or early postpartum period. In a review of 150 cases of pregnancy-associated acute

myocardial infarction, heart failure or cardiogenic shock occurred in 38% of pregnancies, ventricular arrhythmias in 12%, and recurrent angina or infarction in 20%.[53] The most common cause of pregnancy-associated acute myocardial infarction was coronary dissection, found in more than 40% of the women.

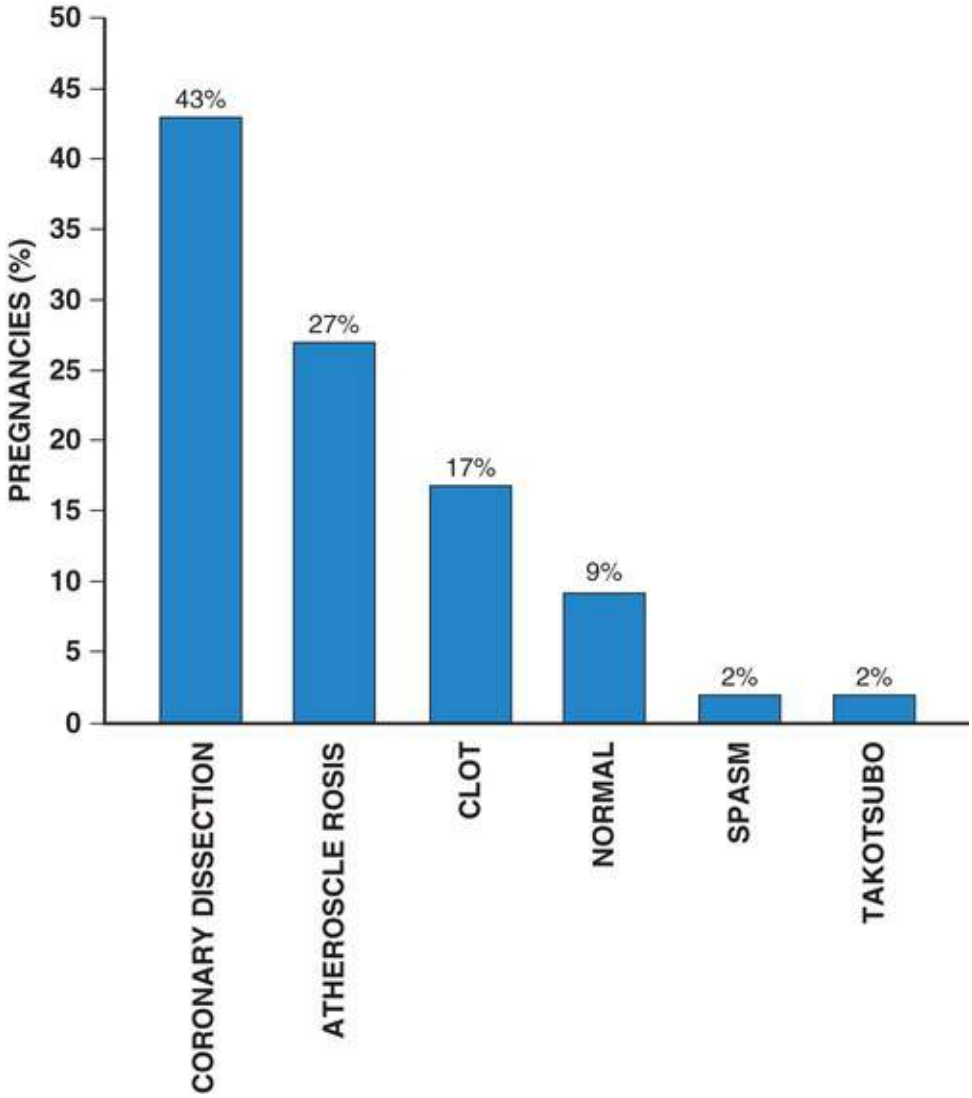

FIGURE 90.6 Causes of acute myocardial infarction in pregnancy. (Data from Elkayam U, Jalnapurkar S, Barakkat MN, et al. Pregnancy-associated acute myocardial infarction: a review of contemporary experience in 150 cases between 2006 and 2011. Circulation 2014;129:1695-1702.)

When an acute coronary syndrome occurs, women should be immediately referred to a skilled intervention center for diagnostic angiography. This management strategy is preferable to thrombolysis, because of the increased likelihood of coronary dissection during pregnancy. Tissue plasminogen activator does not cross the placenta but may cause placental bleeding and should be avoided unless the situation is life-threatening. Many of the standard drug therapies used to treat myocardial infarction, such as morphine, nitroglycerin, aspirin, beta blockers, heparin, and clopidogrel, can be used during pregnancy. Angiotensin-converting enzyme inhibitors and statins are usually avoided because of potential fetal risks. There is limited information on the use of the glycoprotein IIb/IIIa receptor inhibitors prasugrel and ticagrelor in pregnancy. Because of the potential for iatrogenic coronary dissection–related coronary interventions, stenting is reserved for patients with persistent or recurrent ischemia or those who are unstable. Coronary bypass may be considered in women with left main disease or significant proximal coronary artery stenosis.

Hypertension (see also Chapter 46)

Hypertension is the most common medical problem in pregnancy and is a well-recognized contributor to maternal morbidity and mortality rates. The different types of hypertension seen in pregnancy are shown in **Table 90.4**. Gestational hypertension is distinguished from preeclampsia by the lack of proteinuria, maternal organ dysfunction, or uteroplacental abnormalities. Approximately 25% of patients will develop preeclampsia, so close monitoring is warranted. Preeclampsia also develops in approximately 25% of patients with chronic hypertension. The cause of preeclampsia is not entirely clear, but endothelial dysfunction that causes abnormal remodeling of the placental spiral arteries is likely a contributory factor. Hypertension is just one feature of the diffuse endothelial dysfunction, which is associated with vasospasm, reduced end-organ perfusion, and activation of the coagulation cascade. Preeclampsia tends to occur more commonly in nulliparous women; in women with a body mass index of more than 30 kg/m^2; age older than 40 years; preexisting medical conditions (renal disease or pregestational diabetes mellitus, systemic lupus erythematosus, or antiphospholipid antibody syndrome); or a history of preeclampsia, fetal growth restriction, or placental abruption; and in those conceiving after assisted reproductive techniques, with multifetal pregnancies. Hypertension usually does not develop until the second half of gestation, sometimes accompanied by new-onset significant proteinuria (excretion of 3 g of protein over 24 hours) and maternal organ dysfunction or uteroplacental dysfunction.

TABLE 90.4

Classification of Hypertension in Pregnancy*

HYPERTENSION TYPE	DEFINITION AND/OR DESCRIPTION
Chronic hypertension	Hypertension (blood pressure ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) predating pregnancy or diagnosed before 20 weeks of gestation May have associated family history of hypertension or overweight or obesity Secondary causes of hypertension need to be excluded
Gestational hypertension	New hypertension (blood pressure ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) arising after the 20th week of pregnancy and without any of the abnormalities that define preeclampsia (see below) Progresses to preeclampsia in about 25% of cases Blood pressure often normalizes by 12 weeks' postpartum
Preeclampsia (de novo or superimposed on chronic hypertension)	Hypertension developing after 20 weeks' gestation plus one of more of the following variables: Proteinuria Other maternal organ dysfunction: Renal insufficiency Liver involvement (elevated transaminases and/or severe right upper quadrant or epigastric pain) Neurologic complications (eclampsia, altered mental status, blindness, stroke, or more commonly hyperreflexia when accompanied by clonus, severe headaches when accompanied by hyperreflexia, persistent visual scotomata) Hematologic complications (thrombocytopenia, disseminated intravascular coagulation, hemolysis) Uteroplacental dysfunction Fetal growth restriction
White coat hypertension	Diagnosis confirmed by demonstrating normal blood pressure using 24 h ambulatory blood pressure monitoring Occurs in approximately one in four clinic patients

*Based on Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. *Pregnancy Hypertens*. 2014;4:97-104.

Various professional societies have guidelines on the diagnosis and management of hypertensive disorders in pregnancy, including the American Society of Obstetrics and Gynecology,[54] the Society of Obstetrics and Gynecology of Canada,[55] the Society of Obstetric Medicine of Australia and New Zealand,[56] and the International Committee of the International Society for the Study of Hypertension in Pregnancy.[57] Although antihypertensive medications are effective in treating chronic hypertension that has worsened during pregnancy, they are not effective in preventing the progression of preeclampsia. To reduce the likelihood of preeclampsia, women considered to be at increased risk should be given low-dose aspirin (starting > 16 weeks' gestation), and calcium supplements should be given to calcium-depleted individuals. When preeclampsia develops, women should be admitted to the hospital, with close

monitoring by maternal fetal medicine or obstetric medicine specialists. Hypertension is usually treated with oral antihypertensive agents; commonly used drugs are labetalol, nifedipine, hydralazine, and methyldopa. A blood pressure above 160 to 170 mm Hg systolic and 110 mm Hg diastolic requires urgent treatment. Intravenous labetalol or hydralazine can be used in this setting. Magnesium sulfate often is administered to prevent eclamptic seizures and for fetal neuroprotection if the fetus is premature. Women presenting with preeclampsia after 37 weeks' gestation are delivered. Women with severe forms of preeclampsia and/or HELLP syndrome (*h*emolysis, *e*levated *l*iver enzymes and *l*ow *p*latelet count), regardless of gestational age, are delivered as soon as the mother is stabilized. Women presenting with milder forms of preeclampsia before 37 weeks are often managed conservatively unless the blood pressure cannot be controlled or there is pulmonary edema; new-onset neurologic symptoms; progressive liver, renal, or platelet abnormalities; placental abruption; or nonreassuring cardiotocography and/or ultrasound findings. The blood pressure usually normalizes rapidly after delivery, but it can increase between days 3 and 10 after pregnancy, warranting close monitoring in the postpartum period.

Arrhythmias (see also Chapters 32 and 36)

Because of the physiologic changes of pregnancy, the heart may be more vulnerable to arrhythmias during this time. Potential contributing factors include the increase in preload, causing more myocardial irritability; increased heart rate, which may affect the refractory period; fluid and electrolyte shifts; and changes in catecholamine levels. Worsening of arrhythmias is not a consistent feature, however, and many women with a history of tachycardia may not notice any change in the frequency of symptoms. The presenting symptom complex may be difficult to separate from the normal symptoms of pregnancy, including a sensation of fast heartbeat and skipped beats, which most commonly are supraventricular ectopic complexes. The general approach should include taking a careful history, looking for any precipitating causes, and ruling out any concomitant medical problems (i.e., thyroid disease) by performing appropriate laboratory tests, such as a complete blood count, electrolyte level measurement, and thyroid function determination. A transthoracic echocardiogram will help define whether the arrhythmia occurs in the setting of structural heart disease. In the absence of underlying cardiac disease, pharmacologic treatment should be administered if the patient is symptomatic or if the arrhythmia poses a risk to mother or baby.

Supraventricular Arrhythmias (see also Chapter 37)

Supraventricular arrhythmias are common arrhythmias encountered during pregnancy. They occur in women with structurally normal hearts and in women with preexisting cardiac disease. In general, treatment is the same as for nonpregnant women, but with added concern about medication effects on the fetus (**see Table 90.2**). Maintenance of the sinus rhythm is the preferred strategy for most pregnant women with supraventricular tachycardia. For drug therapy in general, the lowest dose necessary to treat the arrhythmia should be administered, with periodic evaluation of whether it is necessary to continue treatment. Intravenous adenosine usually is the drug of choice for supraventricular reentry tachycardias if vagal maneuvers fail. Atrial fibrillation (**see Chapter 38**) may be an indication of an underlying structural heart disease such as mitral stenosis. In women with structural heart disease and atrial fibrillation, treatment of

the atrial arrhythmia and anticoagulation are both necessary. Oral beta blockers and digoxin have been used in many pregnant women and can be safely used to prevent recurrences. There is less experience with other antiarrhythmic agents (**see Chapter 36**) during pregnancy. If a woman is unstable or if the

arrhythmia is unresponsive to medical therapy, electrical cardioversion can be performed during pregnancy. Some experts recommended use of fetal monitoring at the time of elective cardioversion, in case transient fetal bradycardia occurs. Catheter ablation is almost never necessary, but when it is, catheter ablation without fluoroscopic guidance should be considered if possible.

Ventricular Tachycardia (see also Chapter 39)

Ventricular tachycardia is relatively uncommon during pregnancy. Women with idiopathic or outflow tract ventricular tachycardia may come to attention when they present with symptoms during pregnancy. These women have a structurally normal heart and their outcome is usually good with medical therapy. Ventricular tachycardia, syncope, and sudden death can occur in women with a long QT syndrome, specifically in the postpartum period (**see Chapter 33**). A study of 391 women with a long QT syndrome demonstrated that cardiac events (syncope, aborted cardiac arrest, or sudden cardiac death) were 2.7 times more common in the 9-month postpartum period compared with the pregnancy period.[58] Women with a long QT2 are at higher risk for cardiac complications than women with a long QT1 or QT3. Beta-blocker therapy significantly decreases the risk of serious cardiac events. All women with a long QT syndrome should receive beta blockers during pregnancy and in the postpartum period. Ventricular tachycardia may also occur in women with cardiomyopathies, ischemic heart disease, valvular heart disease, or congenital heart disease.

The treatment of ventricular tachycardia depends on the underlying cardiac condition and the hemodynamic status of the mother. Electrical cardioversion should be performed in women with hemodynamic compromise. Women with idiopathic ventricular tachycardia often respond to beta blockers or calcium channel blockers. Treatment of ventricular tachycardia in pregnant women with structural heart disease should be decided upon in consultation with an electrophysiologist.

Contraception

Addressing contraception options is an important aspect of the care of female patients with cardiac disease. Contraceptive advice should be given before women become sexually active. This is particularly important for adolescents with congenital heart disease or other inherited cardiac conditions, who, like others in this age group, often become sexually active. For some women, pregnancy may carry a high risk of morbidity and even death and detailed advice about various contraceptive methods and their effectiveness is very important. Selecting an optimal form of contraception should be individualized, with consideration of the likelihood of compliance and contraception safety and effectiveness. Emergency oral contraception (the “morning-after” pill) is safe for women with heart disease.

Condoms help protect and are safe for women with heart disease; however, the recognized failure rate is approximately 15 pregnancies/100 woman-years of use. The decision to use a barrier method, therefore, depends on how critical it is for the woman to avoid pregnancy. Intrauterine devices are safe for most women with heart disease and are an effective form of contraception, with low failure rates. A vasovagal response occurring in a patient with pulmonary arterial hypertension, such as Eisenmenger syndrome, could be life-threatening, and many physicians therefore avoid use of IUDs in such patients. Combination estrogen-progesterone oral preparations may not be safe for all women with heart disease. Combined oral contraceptive pills have an extremely low failure rate, and for this reason, as well as their ease of use, these agents are widely taken. For the woman with heart disease, however, an important concern is the associated increased risk of venous thromboembolism, atherosclerosis, hyperlipidemia,

hypertension, and ischemic heart disease, particularly in women who are older than 40 years and those who smoke. In addition, women with congenital heart disease who have cyanosis, atrial fibrillation or flutter, mechanical prosthetic heart valves, or a Fontan circulation probably should avoid estrogen-containing preparations. Patients with significantly impaired ventricular function from any cause or with a history of any previous thromboembolic event should avoid estrogen. Progesterone-only contraceptives are likely safe for most women with heart disease but are less reliable than combined preparations. Other contraceptive modalities include transdermal patches containing estrogen and progesterone and injectable preparations, both of which have similar efficacy rates. Injectable progesterone, given once every 3 months, is a reasonable option for women with heart disease. Subdermal implants, which are inserted into the arm, also are available. Fluid retention and irregular menstruation may be problematic, but cardiovascular contraindications are otherwise the same as those for progesterone. Tubal sterilization can be performed laparoscopically or through a laparotomy approach. For patients with tenuous cardiac hemodynamics, some risk of cardiac instability is likely, and cardiac anesthesia may be preferable. For patients with pulmonary hypertension or Fontan physiology, general anesthesia may be hazardous, and insufflation of the abdomen may elevate the diaphragm, thereby contributing to unstable cardiorespiratory function. Tubal sterilization can be safely accomplished with the use of an intrafallopian plug, which is inserted endoscopically.[59]

Future Perspectives

There have been significant advances in our understanding of pregnancy outcomes and risk stratification over the past two decades. Although pregnancy outcomes remain unknown for some rare cardiac conditions, in newly discovered genetic diseases and in women with new congenital cardiac phenotypes (i.e., those with hypoplastic left heart syndrome), the current assembly of large multicenter cohorts will likely help to define outcomes in these populations in the future. Despite our improved understanding of pregnancy risks, this information continues to be poorly conveyed to women, and tools to improve patient education still need to be developed. Except in the field of hypertensive disorders, randomized trials addressing treatment of heart disease in the pregnant patient are lacking. Although challenging, randomized trials will eventually be needed to define optimal treatment strategies for some conditions in the pregnant population. Finally, maternal mortality rates from cardiac causes have increased worldwide, and many of these deaths can be prevented.[5] In some parts of the world, access to care or to trained medical professionals is not yet available. Developing systems to improve maternal cardiac care on a global scale must be a focus for the future.

Guidelines

Pregnancy and Heart Disease

Candice K. Silversides and Carole A. Warnes

General Management Principles

The European Society of Cardiology (ESC) guidelines on the management of cardiovascular diseases

during pregnancy are a comprehensive set of recommendations pertaining to the care of pregnant women with cardiovascular disease.[1] General recommendation for preconception counseling, antenatal care, and delivery in pregnant women with heart disease are shown in **Table 90.G1**.

TABLE 90.G1

European Society of Cardiology Guidelines on the Management of Cardiovascular Diseases During Pregnancy: General Recommendations for the Care of the Pregnant Women with Heart Disease

CLASS	LEVEL OF EVIDENCE	RECOMMENDATION
Preconception Counseling		
I	C	Prepregnancy risk assessment and counseling is indicated in all women with known or suspected congenital or acquired cardiovascular or aortic disease.
I	C	Genetic counseling should be offered to women with congenital heart disease or congenital arrhythmia, cardiomyopathies, aortic disease, or genetic malformation associated with cardiovascular disease.
Pregnancy Care		
I	C	High-risk patients should be treated in specialized centers by a multidisciplinary team.
I	C	Echocardiography should be performed in any pregnant patient with unexplained or new cardiovascular signs or symptoms.
IIa	C	Magnetic resonance imaging (without gadolinium) should be considered if echocardiography is insufficient for diagnosis.
IIb	C	A chest radiograph with shielding of the fetus may be considered if other methods are not successful in clarifying the cause of dyspnea.
IIb	C	Cardiac catheterization may be considered with very strict indications, timing, and shielding of the fetus.
Labor and Delivery		
I	C	For the prevention of infective endocarditis in pregnancy, the same measures should be used as in the nonpregnant patient.
I	C	Vaginal delivery is recommended as the first choice in most patients.
IIa	C	In patients with severe hypertension, vaginal delivery with epidural analgesia and elective instrumental delivery should be considered.
IIa	C	Cesarean delivery should be considered for obstetric indications or for patients with dilation of the ascending aorta of more than 45 mm, severe aortic stenosis, preterm labor while taking oral anticoagulants, Eisenmenger syndrome, or severe heart failure.
IIb	C	Cesarean delivery may be considered in Marfan patients with an aortic diameter of 40 to 45 mm.
III	C	Prophylactic antibiotic therapy during delivery is not recommended.

Modified from Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J 2011;32:3147-97.

Specific Cardiovascular Conditions

Adult Congenital Heart Disease

Recommendations for the care of pregnant women with congenital heart disease are available in the American College of Cardiologists/American Heart Association (ACC/AHA) guidelines for the management of adults with congenital heart disease,[2] an AHA scientific statement on the management of pregnancy in patients with complex congenital heart disease,[3] the ESC guidelines on the management of cardiovascular diseases during pregnancy,[1] and the Canadian Cardiovascular Society consensus conference on the management of adults with congenital heart disease.[4-6] These guidelines address pregnancy recommendations for women with simple shunt lesions, congenital valve disease, and other complex congenital heart conditions, including Eisenmenger syndrome.

Marfan Syndrome

The ACC/AHA/American Association for Thoracic Surgery (AATS) guidelines for the diagnosis and management of patients with thoracic disease and the ESC guidelines on the management of cardiovascular diseases during pregnancy[1] provide recommendations for the care of pregnant women with Marfan syndrome. In order to determine pregnancy risk, imaging of the entire aorta (CT/MRI) should be performed before pregnancy in patients with Marfan syndrome or any other known aortic disease. Women

with Marfan syndrome and aortic dilatation should deliver in a center where cardiothoracic surgery is available.

Differing thresholds for prophylactic aortic replacement in women with Marfan syndrome have been suggested. The ESC suggests that prophylactic surgery be performed in women with an aortic diameter of 4.5 cm or more.[1] The ACC/AHA/AATS guidelines for the diagnosis and management of patients with thoracic aortic disease suggest that it is reasonable to prophylactically replace the aortic root and ascending aorta if the diameter is more than 4 cm.

Valvular Heart Disease

The ACC/AHA guidelines for the management of patients with valvular heart disease provide recommendations for the care of the pregnant women with native valve disease.[7] Recommendations for pregnant women with stenotic valve lesions are shown in **Table 90.G2,** and indications for valve interventions during pregnancy are shown in **Table 90.G3**. Similar guidelines are available from the ESC.[1]

TABLE 90.G2

ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease: Pregnancy in Women with Native Valve Stenosis

CLASS OF RECOMMENDATION	LEVEL OF EVIDENCE	RECOMMENDATIONS
I	C	All patients with suspected valve stenosis should undergo a clinical evaluation and transthoracic echocardiography before pregnancy.
I	C	All patients with severe valve stenosis (stages C and D) should undergo prepregnancy counseling by a cardiologist with expertise in managing patients with valvular heart disease during pregnancy.
I	C	All patients referred for a valve operation before pregnancy should receive prepregnancy counseling by a cardiologist with expertise in managing patients with valvular heart disease during pregnancy about the risks and benefits of all options for operative interventions, including a mechanical prosthesis, a bioprosthesis, and valve repair.
I	C	Pregnant patients with severe valve stenosis (stages C and D) should be monitored in a tertiary care center with a dedicated heart valve team of cardiologists, surgeons, anesthesiologists, and obstetricians with expertise in the management of high-risk cardiac patients during pregnancy.
IIa	C	Exercise testing is reasonable in asymptomatic patients with severe aortic stenosis (aortic velocity ≥ 4 m/sec or mean pressure gradient ≥ 40 mm Hg, stage C) before pregnancy.
I	C	Anticoagulation should be given to pregnant patients with mitral stenosis and atrial fibrillation unless contraindicated.
IIa	C	Use of beta blockers as required for rate control is reasonable for pregnant patients with mitral stenosis in the absence of contraindication if tolerated.
IIb	C	Use of diuretics may be reasonable for pregnant patients with mitral stenosis and heart failure symptoms (stage D).
III	B	Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should not be given to pregnant patients with valve stenosis.

From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guidelines for the Management of Patients with Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:2440-92.

TABLE 90.G3

ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease: Valve Interventions in Pregnant Women

CLASS OF RECOMMENDATION	LEVEL OF EVIDENCE	RECOMMENDATIONS
I	C	Valve intervention is recommended before pregnancy for symptomatic patients with severe aortic stenosis (aortic velocity ≥ 4.0 m/sec or mean pressure gradient ≥ 40 mm Hg, stage D).
I	C	Valve intervention is recommended before pregnancy for symptomatic patients with severe mitral stenosis (mitral valve area ≤ 1.5 cm^2, stage D).
I	C	Percutaneous mitral balloon commissurotomy is recommended before pregnancy for asymptomatic patients with severe mitral stenosis (mitral valve area ≤ 1.5 cm^2, stage C) who have valve morphology favorable for percutaneous mitral balloon commissurotomy.
IIa	C	Valve intervention is reasonable before pregnancy for asymptomatic patients with severe aortic stenosis (aortic velocity ≥ 4.0/sec or mean pressure gradient ≥ 40 mm Hg, stage C).
IIa	B	Percutaneous mitral balloon commissurotomy is reasonable for pregnant patients with severe mitral stenosis (mitral valve area ≤ 1.5 cm^2, stage D) with valve morphology favorable for percutaneous mitral balloon commissurotomy who remain symptomatic with NYHA class III to IV heart failure symptoms despite medical therapy.
IIa	C	Valve intervention is reasonable for pregnant patients with severe mitral stenosis (mitral valve area ≤ 1.5 cm^2, stage D) and valve morphology not favorable for percutaneous mitral balloon commissurotomy only if there are refractory NYHA class IV heart failure symptoms.
IIa	B	Valve intervention is reasonable for pregnant patients with severe aortic stenosis (mean pressure gradient ≥ 40 mm Hg, stage D) only if there is hemodynamic deterioration or NYHA class III to IV heart failure symptoms.
III	C	Valve operation should not be performed in pregnant patients with valve stenosis in the absence of severe heart failure symptoms.

From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:2440-92.

Women with mechanical heart valves are at high risk for complications during pregnancy. An important aspect of care for pregnant women with mechanical valves concerns anticoagulation therapy. There is no universal consensus on the management of anticoagulation for these women; all are associated with a potential risk. Possible anticoagulation options include vitamin K antagonists, low-molecular-weight heparin, unfractionated heparin, or a combination of vitamin K antagonists and heparin. In general, the maternal risk is lowest with vitamin K antagonists and the fetal risk is lowest with heparin. The ACC/AHA guidelines for the management of patients with valvular heart disease,[7] ESC guidelines on the management of cardiovascular diseases during pregnancy,[1] and American College of Chest Physicians guidelines on antithrombotic therapy and prevention of thrombosis[8] all provide recommendations for the management of anticoagulation in women with mechanical valves during pregnancy. The specific recommendations from the ACC/AHA are shown in **Table 90.G4**. All women with mechanical prosthetic heart valves should be cared for at tertiary care centers by a multidisciplinary team with expertise in pregnancy and heart disease.

TABLE 90.G4

ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease: Anticoagulation in Pregnant Women with Mechanical Valves

CLASS OF RECOMMENDATION	LEVEL OF EVIDENCE	RECOMMENDATIONS
I	B	Therapeutic anticoagulation with frequent monitoring is recommended for all pregnant patients with a mechanical prosthesis.
I	B	Warfarin is recommended in pregnant patients with a mechanical prosthesis to achieve a therapeutic international normalized ratio (INR) in the second and third trimesters.
I	C	Discontinuation of warfarin with initiation of intravenous unfractionated heparin (with an activated partial thromboplastin time [aPTT] > 2 times control) is recommended before planned vaginal delivery in pregnant patients with a mechanical prosthesis.
I	C	Low-dose aspirin (75 to 100 mg) once per day is recommended for pregnant patients in the second and third trimesters with either a mechanical prosthesis or bioprosthesis.
IIa	B	Continuation of warfarin during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin to achieve a therapeutic INR is 5 mg/day or less after full discussion with the patient about risks and benefits.
IIa	B	Dose-adjusted low-molecular-weight heparin at least 2 times per day (with a target anti-Xa level of 0.8 U/mL to 1.2 U/mL, 4 to 6 hours postdose) during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is greater than 5 mg/day to achieve a therapeutic INR.
IIa	B	Dose-adjusted continuous intravenous unfractionated heparin (with an aPTT at least 2 times control) during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is greater than 5 mg/day to achieve a therapeutic INR.
IIb	B	Dose-adjusted low-molecular-weight heparin at least 2 times per day (with a target anti-Xa level of 0.8 U/mL, 4 to 6 hours postdose) during the first trimester may be reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is 5 mg/day or less to achieve a therapeutic INR.
IIb	B	Dose-adjusted continuous infusion of unfractionated heparin (with an aPTT of at least 2 times control) during the first trimester may be reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is 5 mg/day or less to achieve a therapeutic INR.
III	B	Low-molecular-weight heparin should not be administered to pregnant patients with mechanical prostheses unless anti-Xa levels are monitored 4 to 6 hours after administration.

From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:2440-92.

Cardiomyopathies

Guidelines for the management of pregnant women with cardiomyopathies, including peripartum cardiomyopathy, are available in the ESC guidelines on the management of cardiovascular diseases during pregnancy.[1] Careful preconception assessment is required for all women with cardiomyopathies. Women with severe left ventricular systolic dysfunction are at high risk for complications during pregnancy and should be counseled to avoid pregnancy. Women with clinical heart failure should be treated similarly to standards for nonpregnant patients, with the caveat that some heart failure drugs are contraindicated during pregnancy. Peripartum cardiomyopathy represents a unique condition with potential for full recovery of ventricular function after presentation. The risk of complications in subsequent pregnancies is based on the degree to which the left ventricular systolic function recovers. Pregnancy is not recommended if the left ventricular ejection fraction does not normalize.[1]

Hypertension

Guidelines on the diagnosis and management of hypertensive disorders in pregnancy have been published by a number of professional societies, including the American Society of Obstetrics and Gynecology,[9] Society of Obstetrics and Gynecology of Canada,[10] Society of Obstetric Medicine of Australia and New Zealand,[11] International Committee of the International Society for the Study of Hypertension in Pregnancy,[12] and ESC.[1]

Arrhythmias

In pregnant women who are unstable due to a tachyarrhythmia, direct-current cardioversion or defibrillation is recommended. Antiarrhythmic therapy is typically reserved for symptomatic patients or

those in whom tachycardia causes hemodynamic compromise. The ACC/AHA/Heart Rhythm Society (HRS) guidelines for the management of adult patients with supraventricular tachycardia[13] and the ESC guidelines on the management of cardiovascular diseases during pregnancy[1] provide recommendations for the management of supraventricular tachycardia in pregnant women. Recommendations for management of supraventricular tachycardia in pregnancy are shown in **Table 90.G5.** The 2006 AHA/ACC/ESC guidelines address atrial fibrillation in the pregnant patient.[14] For women who are stable, quinidine or procainamide may be used for pharmacologic cardioversion. Protection against thromboembolism is recommended throughout pregnancy and should be chosen with regard to the stage of pregnancy.

TABLE 90.G5

ACC/AHA Guideline for the Management of Adult Patients with Supraventricular Tachycardia: Recommendations for Treatment in Pregnant Patients

CLASS OF RECOMMENDATION	LEVEL OF EVIDENCE	RECOMMENDATIONS
Recommendations for Acute Treatment of Supraventricular Tachycardia (SVT) in Pregnant Patients		
I	C-LD	Vagal maneuvers are recommended for acute treatment in pregnant patients with SVT.
I	C-LD	Adenosine is recommended for acute treatment in pregnant patients with SVT.
I	C-LD	Synchronized cardioversion is recommended for acute treatment in pregnant patients with hemodynamically unstable SVT when pharmacologic therapy is ineffective or contraindicated.
IIa	C-LD	Intravenous metoprolol or propranolol is reasonable for acute treatment in pregnant patients with SVT when adenosine is ineffective or contraindicated.
IIb	C-LD	Intravenous verapamil may be reasonable for acute treatment in pregnant patients with SVT when adenosine and beta blockers are ineffective or contraindicated.
IIb	C-LD	Intravenous procainamide may be reasonable for acute treatment in pregnant patients with SVT.
IIb	C-LD	Intravenous amiodarone may be considered for acute treatment in pregnant patients with potentially life-threatening SVT when other therapies are ineffective or contraindicated.
Recommendations for Ongoing Management of SVT in Pregnant PatientsPatients		
IIa	C-LD	The following drugs, alone or in combination, can be effective for ongoing management in pregnant patients with highly symptomatic SVT: Digoxin Flecainide Metoprolol Propafenone Propranolol Sotalol Verapamil
IIb	C-LD	Catheter ablation may be reasonable in pregnant patients with highly symptomatic, recurrent, drug-refractory SVT with efforts toward minimizing radiation exposure.
IIb	C-LD	Oral amiodarone may be considered for ongoing management in pregnant patients when treatment of highly symptomatic, recurrent SVT is required and other therapies are ineffective or contraindicated.

Modified from Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients with Supraventricular Tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2016;67:e27-e115.

The AHA/ACC/ESC guidelines for the management of patients with ventricular arrhythmias and prevention of sudden death[15] and the ESC guidelines on the management of cardiovascular diseases during pregnancy[1] provide recommendations for the management of ventricular tachycardia during pregnancy. Pregnant women with ventricular tachycardia or ventricular fibrillation should undergo electrical cardioversion or defibrillation. The AHA guidelines for cardiopulmonary resuscitation and emergency cardiovascular care in special situations[16] address cardiac arrest in pregnancy. There are both maternal and obstetric modifications to consider; however, in general, women should be treated according to the standard basic life support and advanced cardiac life support algorithms. Defibrillation should not be delayed, and typical advanced cardiac life support drugs and dosages should be used. Obstetric and neonatal teams should immediately prepare for possible emergency cesarean delivery. If there is no return of spontaneous circulation after 4 minutes of resuscitative efforts, resuscitation teams must consider performing an immediate emergency cesarean delivery to improve neonatal outcomes.

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91

Cardiovascular Disease in Heterogeneous Populations

Michelle A. Albert, Mercedes R. Carnethon

In an era of unprecedented advances in the detection and management of cardiovascular diseases, disparities in risk and outcome persist, largely defined by race, ethnicity, and socioeconomic status.[1] This chapter provides an overview of the burden of cardiovascular disease, with a focus on hypertension and type 2 diabetes; disease management issues in hypertension, coronary heart disease, and heart failure; and ongoing needs for emerging scientific research to address cardiovascular disparities.

Epidemiology of Cardiovascular Disease in Heterogeneous Populations

Cardiovascular Disease in Racial and Ethnic Groups

According to the 2014 National Health Interview Survey (NHIS), the burden of coronary heart diseases (CHDs) varies only slightly by racial or ethnic group (**Fig. 91.1A**). Rates of CHD incidence are declining twice as quickly in white men (<6.5%/year) as in black men (<3.2%/year); similar patterns are apparent for white women (<5.2%/year) and black women (<4.0%/year).[1] The disparities are most pronounced in

mortality rates; black men were twice as likely to experience fatal CHD as white men (hazard ratio [HR], 2.18; 95% confidence interval [CI], 1.24 to 2.56), and black women were 63% more likely to experience fatal CHD than white women (HR, 1.63; 95% CI, 1.0 to 2.62).[2] Disparities in stroke prevalence and incidence are even more significant (**see Fig. 91.1B**).

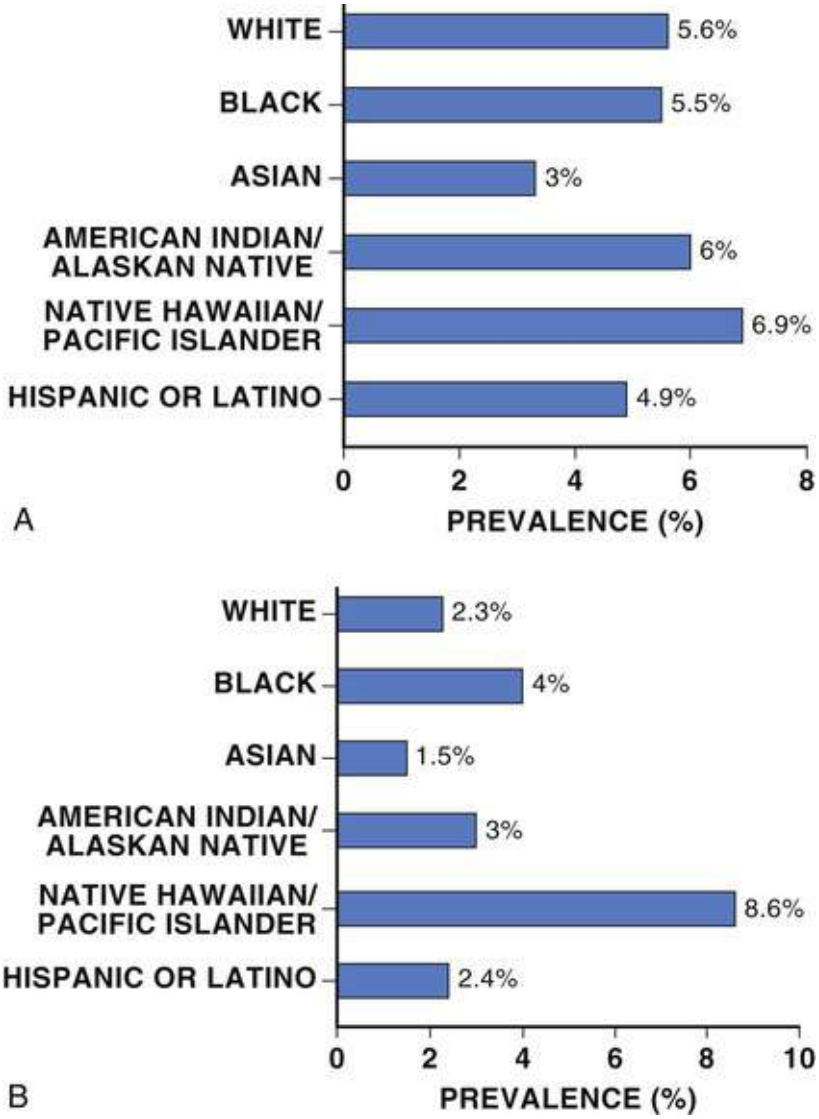


FIGURE 91.1 **A,** Prevalence of coronary heart disease in the United States, 2014. **B,** Prevalence of stroke in the United States, 2014. (From http://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2014_SHS_Table_A-1.pdf.)

Hypertension (see also Chapters 46 and 47)

Blacks have higher rates of hypertension than other racial or ethnic groups.[3] Several proposed mechanisms may contribute to an increased incidence in blacks (**Table 91.1**). **Fig. 91.2** presents the epidemiology of hypertension prevalence, awareness, treatment, and control (**see Fig. 91.2A to D**) in the United States and globally. Although rates of awareness in blacks are higher (**see Fig. 91.2C**) than in other groups and blacks use more medications to treat hypertension, blacks have a lower rate of control than other racial or ethnic groups (**see Fig. 91.2D**).[4] American Indian/Alaska Natives (26.4%) also have higher rates of hypertension than Hispanic or Latino adults (22.9%) or Asian adults (19.5%).[5]

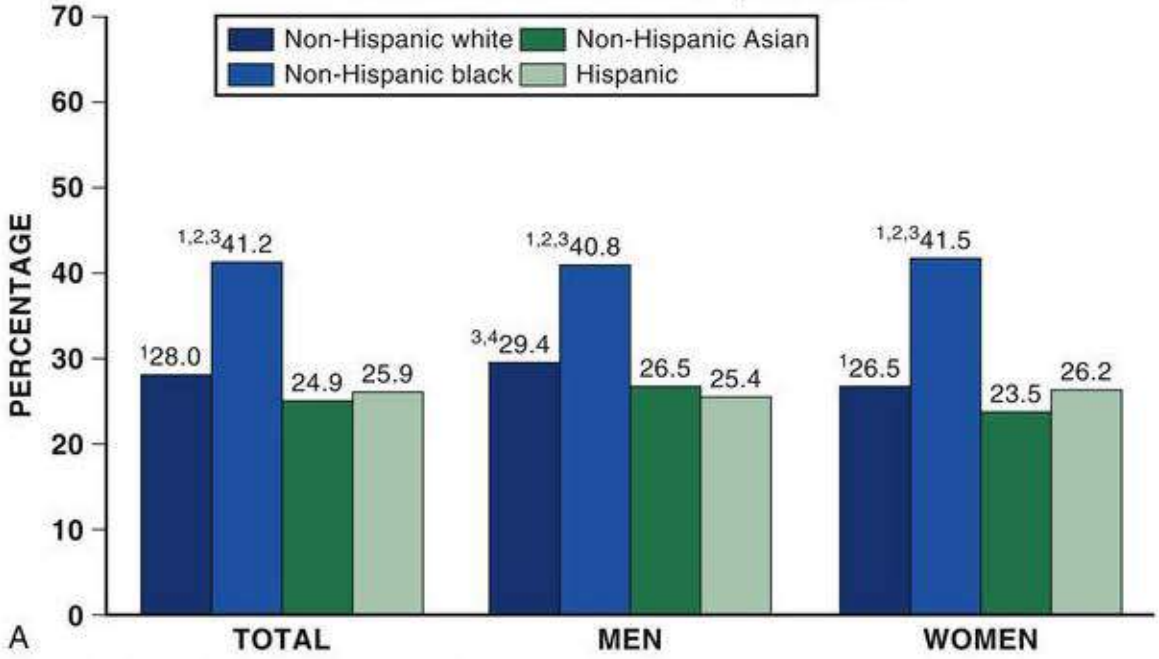
TABLE 91.1

Proposed Mechanisms for the Increased Incidence of Hypertension in Blacks

Genetic susceptibility
Socioeconomic status
Renal and cellular salt handling
Dietary Na/K
Alterations in renin-angiotensin-aldosterone system
Vasodilator deficiency
Increased sleep apnea
Low birth weight

From Taylor AL, Wright JT, Piña IL. Heart disease in varied populations. In Mann DL Zipes DP, Libby P, et al (editors): Braunwald's heart disease, 10th edition. Philadelphia, Elsevier, 2015.

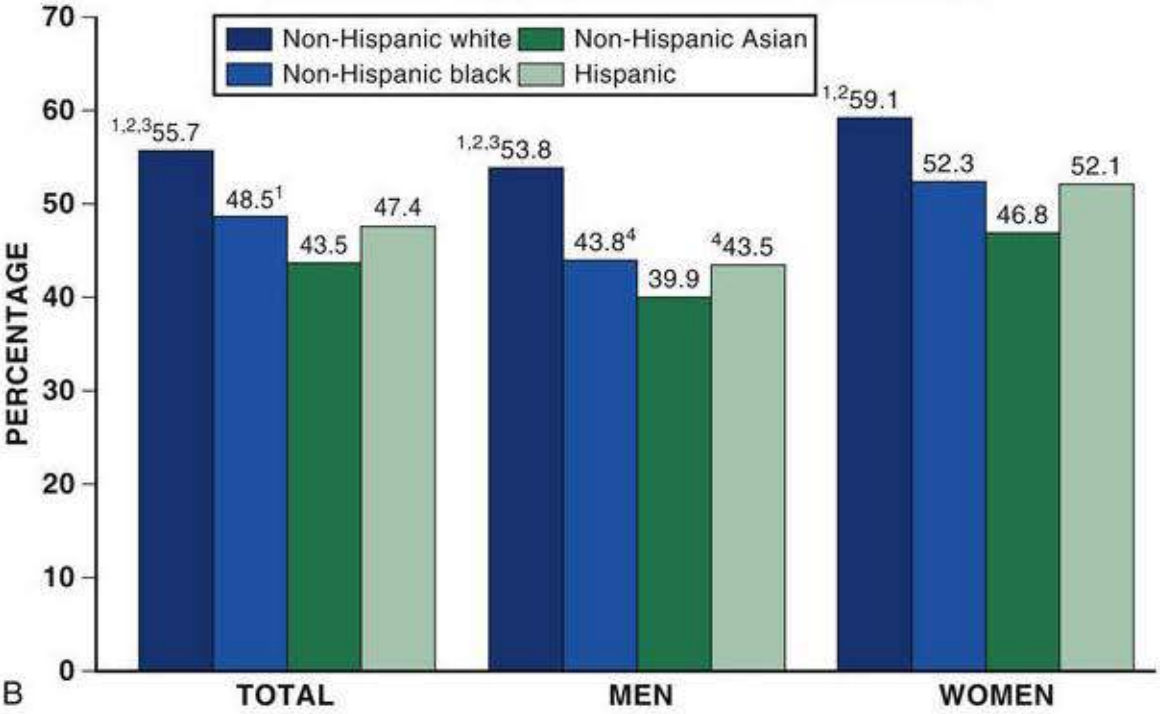
PREVALENCE OF HYPERTENSION AMONG ADULTS AGED 18 AND OVER, BY SEX AND RACE AND HISPANIC ORIGIN: US, 2011-2014.



A

[1]Significant difference from non-Hispanic Asian.
[2]Significant difference from non-Hispanic white.
[3]Significant difference from Hispanic.
[4]Significant difference from women in the same race and Hispanic origin group.
Note: Estimates are age-adjusted by the direct method to the 2000 U.S. census population using age group 18–39, 40–59, and 60 and over, see reference 9.

PREVALENCE OF CONTROLLED HYPERTENSION AMONG ADULTS WITH HYPERTENSION AGED 18 AND OVER, BY SEX AND RACE AND HISPANIC ORIGIN: US, 2011-2014.



B

[1]Significant difference from non-Hispanic Asian.
[2]Significant difference from non-Hispanic black.
[3]Significant difference from Hispanic.
[4]Significant difference from women in the same race and Hispanic origin group.
Note: Estimates are age-adjusted by the direct method using computed weights based on the subpopulation of persons with hypertension in the 2011–2012. National Health and Nutrition Examination Survey; see reference 7.

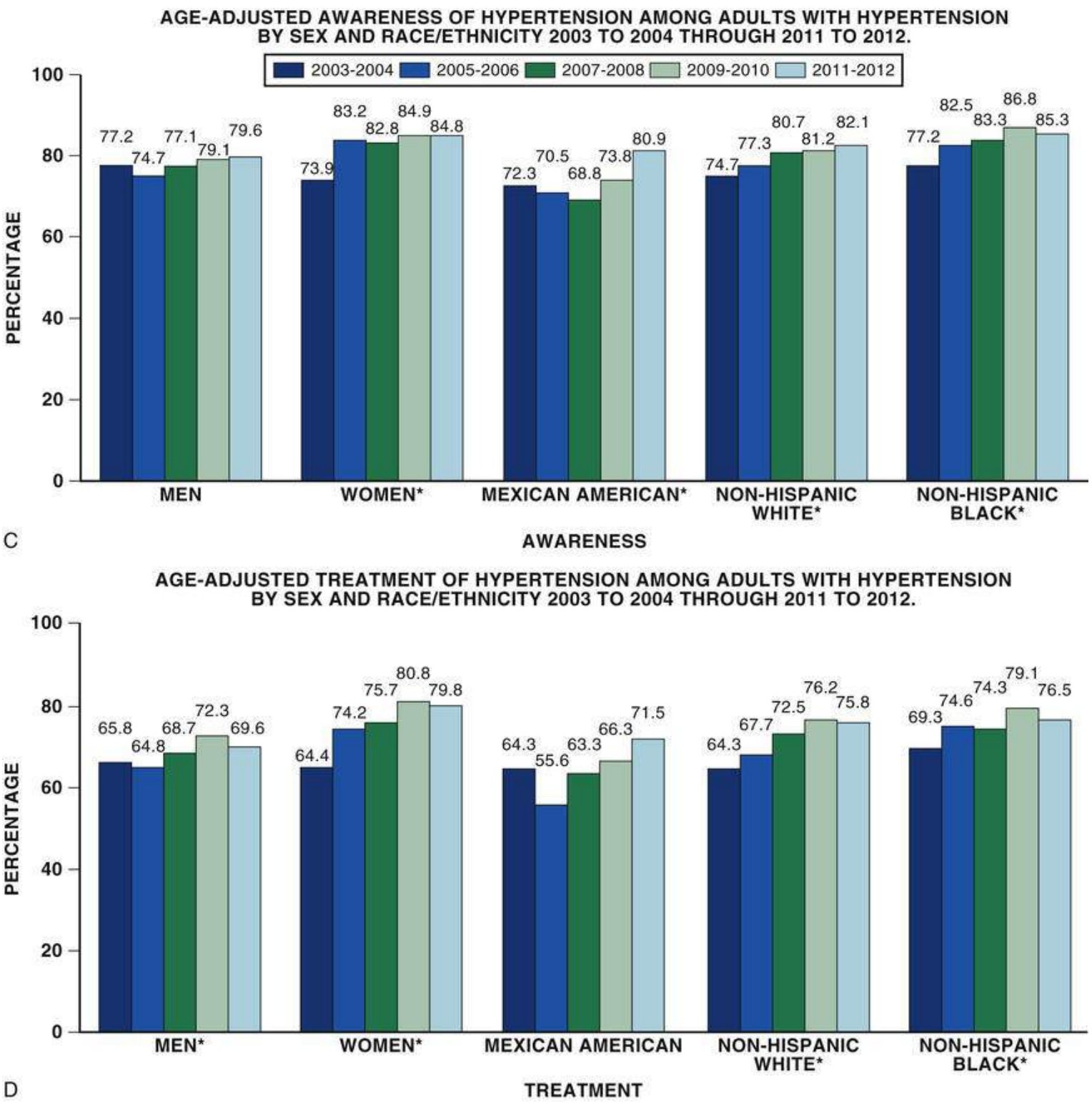


FIGURE 91.2 Epidemiology of adults with hypertension by race/ethnicity, United States. (**A** and **B** adapted from Yoon SS, Carroll MD, Fryar CD. Hypertension prevalence and control among adults, United States, 2011-2014, NCHS Data Brief 2015;220:1-8. **C** and **D** From American Heart Association; adapted from Yoon SS, Gu Q, Nwankwo T, et al. Trends in blood pressure among adults with hypertension: United States, 2003 to 2012, Hypertension 2015;65(1):54-61; and Crim MT, Yoon SS, Ortiz E, et al. National surveillance definitions for hypertension prevalence and control among adults. Circ Cardiovasc Qual Outcomes 2012;5(3):343-51.)

Among Hispanics/Latinos, the hypertension prevalence varies considerably by subgroup. In the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), which measured blood pressure in 16,415 Hispanics/Latinos (but does not include a comparison population of nonHispanics), rates were highest among participants from Cuban, Puerto Rican, and Dominican ethnic backgrounds.[6] Hispanics/Latinos in the HCHS/SOL study were less likely to be aware of their hypertension and less likely to be treated than non-Hispanic whites.[4]

National estimates of hypertension prevalence based on measured blood pressure in Asian Americans are lacking. Amongst the six largest Asian American populations (Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese), Filipinos have particularly high rates of hypertension (53.2% to 59.9%), with poor awareness and control rates.[3,7] Filipino patients of older age, those with comorbid medical conditions, and those who did not smoke had improved hypertension treatment, and patients with health insurance had better blood pressure control. These findings suggest that better access to health care and an approach targeted toward multiple risk factors are needed to decrease the hypertension prevalence and risk among Filipinos.[8]

Type 2 Diabetes (see also Chapters 50 and 51)

The overall age-standardized prevalence of diabetes in the U.S. population is 14.3%, but Hispanics/Latinos, blacks, Asians, and American Indian/Alaskan Natives (17.5%) have a higher prevalence than non-Hispanic whites.[9,10]

The diabetes prevalence largely parallels the obesity "epidemic," with evidence of disparities emerging even in childhood.[11] In the Hispanic/Latino community, Dominicans, Puerto Ricans, and Mexicans (17% to 18%) seem to have a higher prevalence than South Americans and Cubans (10% to 13%).[12] This observed variation agrees with genetic research that describes a higher prevalence of diabetes among Hispanics/Latinos with greater African and Native American ancestry.[13] However, emerging research comparing the relative contributions of socioeconomic, environmental, and psychosocial factors, plus ancestry, to diabetes disparities has indicated that socioeconomic factors make up the largest group of mediating factors.[14]

Although the prevalence of diabetes generally parallels the obesity epidemic,[15] that is not the case for Asian Americans. Asian Americans have on average a lower body mass index than other racial or ethnic groups, but, even so, they have evidence of insulin resistance.[15,16,17] Pacific Islanders, South/East Asians, and Filipinos have rates of diabetes at least twofold to threefold higher than whites, and the magnitude of difference is even greater in Chinese, Japanese, Korean, and Vietnamese adults, who had a lower prevalence of diabetes in aggregate than non-Hispanic whites.[7,17] Filipinos and South/East Asians have higher rates of treatment than non-Hispanic whites.[7]

Cardiovascular Disease in Other Population Groups

Persons with psychological conditions and sexual minorities warrant increased attention because of their elevated risks of cardiovascular disease and its effects on health disparities. Psychological conditions including but not limited to anxiety, major depressive disorder, and bipolar disorder affect at least 43.8 million adults, with numerous others who are suffering but are undiagnosed and untreated.[18] This epidemic includes especially vulnerable populations, such as persons of lower socioeconomic status, the homeless, and military veterans.[19] An elevated cardiovascular risk is associated with adverse risk behaviors, isolation, limited contact with the health care system, and downward socioeconomic mobility; medications used to control some forms of mental illness can lead to weight gain and/or sedation, factors that contribute to decreases in motivation for physical activity.[20,21]

Persons whose sexual orientation is lesbian, gay, bisexual, or transgender (LGBT) have not historically been considered "minorities," but they have emerged as a sizeable, distinctive social community. Attention to the unique health needs in the LGBT population have traditionally focused on sexual health and less commonly on cardiovascular disease prevention and management. One exception that reflects the intersection between sexual and cardiovascular health relates to the shift of acquired immunodeficiency

syndrome (AIDS) from an acute illness to a chronic illness, and its associated cardiovascular risks (**see also Chapter 82**). Although the burden of HIV/AIDS is not restricted to sexual minorities, the largest proportion of affected individuals are practicing male homosexuals and nonwhite minority women.[22] Medications used to manage HIV/AIDS have performed well in sparing associated wasting syndromes, but as a result have yielded a higher burden of overweight and obesity and consequent metabolic disorders, including hypertension and diabetes.[23] HIV^+ status (versus HIV− status) is associated with a reduced systolic heart function and an increased prevalence of left ventricular hypertrophy, even after adjustments have been made for metabolic factors. These cardiac changes may predispose individuals with HIV/AIDS to heart failure.[24]

Cardiovascular Disease Management

Hypertension

Lifestyle modification through behavioral intervention that focuses on weight loss, reduced sodium intake, increased physical activity, and reduced alcohol consumption remains the cornerstone of hypertension management. The Systolic Blood Pressure Intervention Trial (SPRINT) studied antihypertensive drug therapy that focused on lowering the systolic blood pressure (SBP) to less than 120 mm Hg rather than to less than 140 mm Hg in 9361 nondiabetic/stroke-free individuals whose SBP was 130 to 180 mm Hg and who had an increased cardiovascular disease risk (≈2%/year). The results showed that there was a 25% lower rate of combined outcomes for myocardial infarction (MI), acute coronary syndrome without MI, stroke, acute decompensated heart failure, or cardiovascular disease death, and a 27% reduced rate of all-cause mortality.[25] Stratified analyses revealed similar results in blacks and nonblacks, with a CI that included 1.0 among blacks. Generalizability of the SPRINT population to the U.S. adult population 50 years old or older using National Health and Nutrition Examination Survey (NHANES) data showed that 4% to 5% of Hispanics and blacks compared with 9% of whites meet eligibility criteria for the study.[26] Nonetheless, approximately 8.5% of blacks and 14.2% of Hispanics with treated hypertension met the blood pressure targets identified in the SPRINT study, a finding that suggests there is substantial room for a hypertension-related cardiovascular disease risk reduction in these groups.

Pharmacotherapy informed by race or ethnicity for black patients favors thiazide diuretics and calcium channel blocker drugs as first-line therapy in a majority of older blacks without contraindications (**Table 91.2**). Yet, data for Hispanics and Asians are limited.[27,28] Ongoing barriers to successful hypertension management in black patients include menthol cigarette smoking, lack of regular health care visits, and insurance issues.[27,28]

TABLE 91.2

Hypertension Guidelines and Recommendations: Initial Drug Selection

GUIDELINE	EVIDENCE REVIEW METHODOLOGY	GENERAL ADULT POPULATION	GENERAL AFRICAN AMERICAN ADULT POPULATION	DIABETES MELLITUS	CHRONIC KIDNEY DISEASE
JAMA 2014 Hypertension Guideline	Systematic review	ACE-I, ARB, CCB, thiazide	Thiazide, CCB	ACE-I, ARB, BB CCB, thiazide	ACE-I, ARB
International Society on Hypertension in Blacks (2010)	Consensus	NA	Diuretic or CCB, RAS inhibitor plus CCB preferred over RAS inhibitor plus thiazide unless edema or high volume	ACE-I, ARB	ACE-I, ARB
American College of Cardiology Foundation and American Heart Association (2011)	Consensus	ACE-I ARB, CCB, thiazide	Thiazide, CCB	ACE-I, ARB, BB, CCB, thiazide	ACE-I, ARB
National Institute for Health and Care Excellence (2011)	Systematic review	≥55: CCB, thiazide <55: ACE-I, ARB, BB	Thiazide, CCB	ACE-I, ARB	ACE-I, ARB
National Kidney Foundation Kidney Disease Outcomes Quality Initiative (2012)	Consensus (graded)	NR	NR	NR	ACE-I or ARB with albuminuria >30 mg/d
European Society of Hypertension and European Society of Cardiology (2013)	Consensus (graded)	ACE-I, ARB, BB CCB, thiazide,	Thiazide, CCB	ACE-I/ARB	ACE-I, ARB
American Society of Hypertension and International Society of Hypertension (2014)	Consensus	<60: ACE-I, ARB ≥60: CCB, thiazide	Thiazide, CCB	Non-African Americans: ACE-I, ARB African Americans: CCB, thiazide	ACE-I, ARB
Canadian Hypertension Education Program	Consensus	ACE-I, ARB, BB (<60), CCB, thiazide	ACE-I, ARB, BB (<60), CCB thiazide	ACE-I, ARB, BB (<60), CCB, thiazide	—

JAMA, Journal of the American Medical Association; *ACE-I*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin-receptor blocker; *BB,* beta blocker; *CCB*, calcium channel blocker; *RAS,* renin-angiotensin system.

Adapted from Still CH, Ferdinand KC, Ogedegbe G, Wright JT Jr. Recognition and management of hypertension in older persons: focus on African Americans. J Am Geriatr Soc 2015;63(10):2130-8.

One of the largest studies to include Hispanic patients (N=8045), the International Verapamil SR/Trandolapril (INVEST; N=8045) trial, demonstrated the effectiveness of both sustained-release verapamil and atenolol in this ethnic group.[29] However, atenolol was associated with increased incident diabetes. Therefore, some argue that because diabetes disproportionately affects the Hispanic population, use of a therapy targeted at the renin-angiotensin-aldosterone system may be more appropriate in Hispanics/Latinos.[30]

The general features of hypertension across the heterogeneous Asian diaspora appear similar. High salt intake, increased salt sensitivity, and more sustained 24-hour blood pressure elevations likely contribute to elevated risks of stroke compared with CHD amongst Asians.[31] The Japanese Society of Hypertension recommends the use of calcium channel blockers, angiotensin-converting enzyme inhibitors, and diuretics as first-line therapy for patients without other compelling indications.[32] Diuretics are recommended for salt-sensitive elderly Japanese patients. Like blacks, South Asian patients develop hypertension at an earlier age and have accelerated end-organ damage compared with whites. Because morbidity and mortality data in South Asians are lacking, management principles resemble those of the general population, including early screening and use of combination therapy.[33]

Coronary Heart Disease

More than 1 million percutaneous coronary interventions (PCIs) are performed annually in the United States for CHD. Blacks and Hispanics have longer wait times and are less likely to undergo PCI than whites, regardless of their insurance status.[34] Data from a large national improvement quality registry,

ACTION Registry-GWTG of STEMI and NSTEMI patients, showed that rates of catheterization were lower for NSTEMI and similar for STEMI in blacks compared with whites.[35] Black patients were also less likely to have coronary artery bypass grafting (CABG). In general, blacks and Hispanics have poorer revascularization outcomes, related to multidimensional influences, including individual, provider, hospital, and societal factors. For example, poorer CABG outcomes among blacks and Hispanics relate in part to hospital quality and socioeconomic factors because poor and racial or ethnic minority patients receive care at lower-performing hospitals, according to standardized quality measures.[36,37] Notably, although little is known about the impact of the United States health care reform on cardiovascular care, racial and ethnic disparities in those who received cardiovascular interventional care persisted after enactment of the Massachusetts health care reform act in 2006.[38]

Use of secondary prevention medications also varies by race and ethnicity: Blacks have 36% lower odds of medication adherence after an acute coronary syndrome.[39] Black and Hispanic women seem to adhere least to medication regimens 1 year following MI, suggesting that there is substantial room for improvement in post-MI care and understanding of treatment barriers in these patients.[40,41] Medication discontinuation is associated with side effects and physician discontinuation advice; higher rates of adherence are related to having private insurance, having assistance with paying for prescriptions, and having an outpatient follow-up appointment scheduled before hospital discharge.

In the context of dual antiplatelet therapy use after drug-eluting stent placement for acute coronary syndrome, there is limited specific data about racial and ethnic groups showing the effectiveness of the drugs and the adverse events that may occur, such as major bleeding. Although genetic and clinical data are sparse, the data that exist show that blacks may have a greater thrombogenic propensity than other groups, as well as a higher prevalence of both arterial and venous thrombosis.[42]

Heart Failure

Blacks have a higher prevalence of heart failure and an earlier onset and presentation than other racial and ethnic groups. Emerging work suggests that there are complex relationships between heart failure with preserved systolic function and race and ethnicity; a study of 13,437 patients (≈86% white, 8% black, and 6% Asian) from four large health systems in the United States demonstrated that although blacks and Asians had a lower risk of death than whites, blacks had more rehospitalizations than other racial and ethnic groups.[43] Data from the Atherosclerosis Risk in Communities (ARIC) study demonstrated that heart failure with systolic dysfunction might be more common in middle-aged blacks, who represented 73% of the heart failure patients in this observational cohort. In contrast with some other databases, in this African American subgroup of ARIC, heart failure with preserved systolic function had an overall better prognosis than heart failure with reduced systolic function. Deaths over a median follow-up period of almost 14 years were 21% for those without heart failure, 31% for those with preserved systolic function heart failure, and 61% for those with reduced systolic dysfunction heart failure.[44]

Impaired vascular function caused by reduced endothelial nitric oxide synthesis and resultant endothelial dysfunction appears to play a key role in the heart failure pathophysiology in blacks.[45] The landmark African-American Heart Failure Trial (A-HeFT) study in 1052 black patients with New York Heart Association class III or IV heart failure showed a 43% reduction in deaths with fixed-dose isosorbide dinitrate and hydralazine treatment compared with placebo against a background of standard heart failure therapy.[45] In a subsequent Genetic Risk Assessment of Heart Failure (GRAHF) substudy of A-HeFT (n=352 patients), the NOS3 Glu298Glu genotype was associated with improvement in the event-

free composite score of survival, hospitalization, and quality of life, in patients treated with isosorbide dinitrate and hydralazine.[46]

Data regarding the prevalence of heart failure and effectiveness of therapeutic options are lacking for Hispanics despite their high prevalence of risk factors and structural heart disease. Among persons of Hispanic/Latino background in the Echocardiographic Study of Latinos (ECHO-SOL), left ventricular systolic and diastolic dysfunction were 3.6% and 50.3%, respectively, with more than 90% of the cardiac dysfunction categorized as subclinical or unrecognized.[47] Central Americans and Cuban Americans had a greater prevalence of diastolic dysfunction than Mexican-Americans. Current American Heart Association/American College of Cardiology (AHA/ACC) guidelines do not propose specific therapy for heart failure based on Hispanic ethnicity.

Information about heart failure in Asians is sparse. **Fig. 91.3** illustrates the potential features of heart failure in Asia. In the United States, data from the GWTG-HF registry showed that Asians with heart failure were more likely to be younger males; to have hypertension, diabetes, and renal disease; and to be uninsured compared with whites.[48]

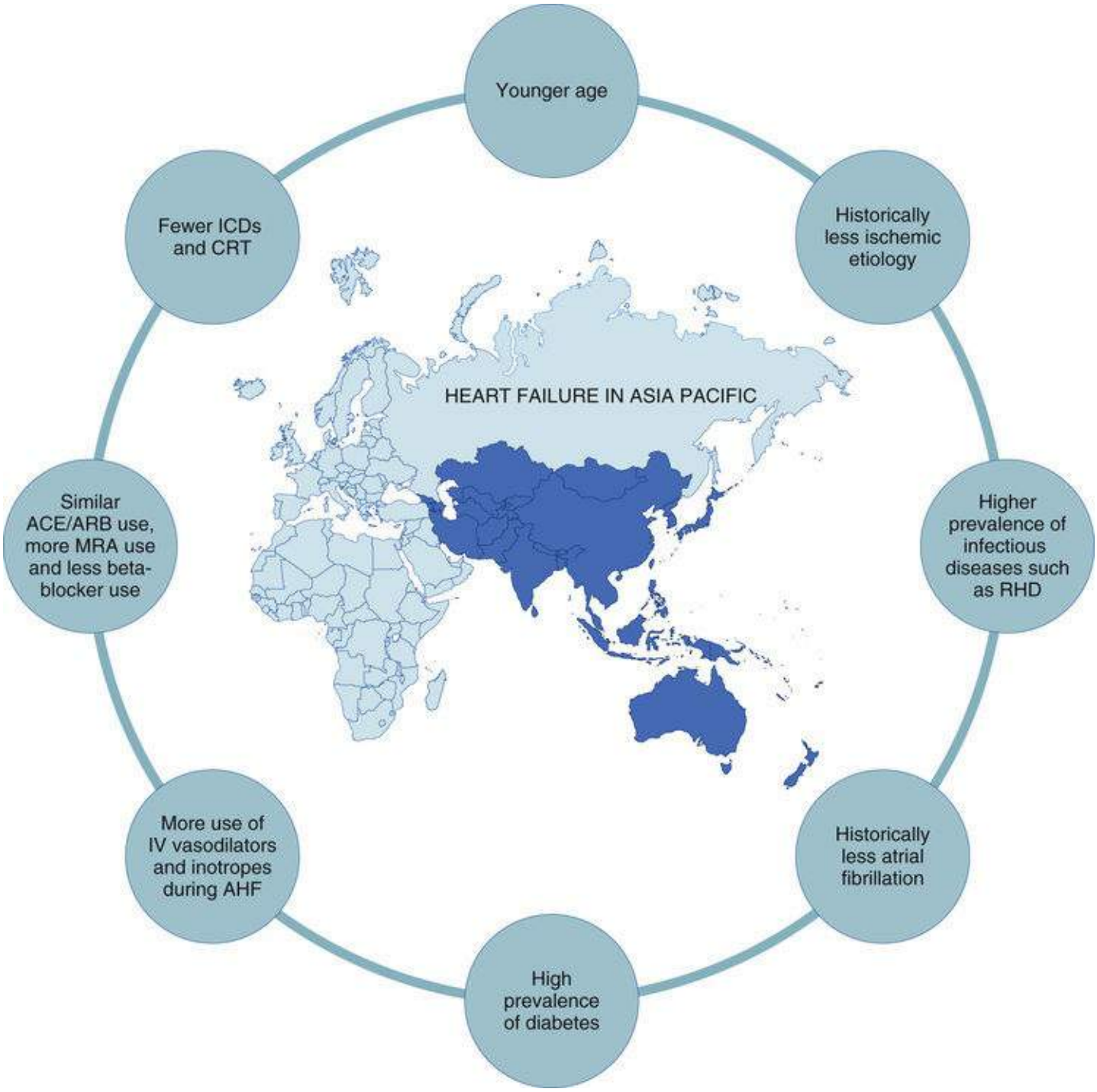


FIGURE 91.3 Heart failure phenotype in the Asian diaspora. (Adapted from Mentz RJ, Roessig L, Greenberg BH, et al. Heart failure clinical trials in East and Southeast Asia: understanding the importance and defining the next steps. JACC Heart Fail 2016;4(6):419-27.)

Potential for Emerging Scientific Research to Address Group Disparities in Cardiovascular Disease

Despite what we have learned about the origin of disparities over the past few decades, disparities appear to be growing rather than shrinking. For areas with available clinical trial data for therapies that effectively treat cardiovascular disease in different racial and ethnic groups, comprehensive delivery and adherence present important challenges. Moreover, efforts to realize the potential of “precision” and “personalized” medicine should also target populations that experience the greatest burden of health disparities, lest unmet needs become more pronounced. Additionally, longitudinal information is needed

on recent immigrant populations, including those from Asia, where the cardiovascular risk varies markedly by country of origin, and those from Africa, where there is a burgeoning epidemic of cardiovascular disease associated with urbanization (**see also Chapter 1**).[49] Specific issues in the near future include scaling, dissemination, and implementation of known effective strategies for prevention and treatment of cardiovascular disease in high-risk heterogeneous populations.

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PART XI
Cardiovascular Disease and Disorders of other Organs

OUTLINE

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Endocrine Disorders and Cardiovascular Disease

Irwin Klein, Bernadette Biondi

The endocrine system is linked closely with many important cardiovascular diseases. As our understanding of the cellular and molecular effects of various hormones has evolved, we understand better the clinical manifestations that arise from excessive secretion of hormones and from glandular failure and subsequent hormone deficiency states. Recognition of the cardiovascular abnormalities associated with pathologic changes in endocrine glands preceded identification of the specific hormones produced by these glands.

This chapter reviews the spectrum of cardiac disease states that arise from changes in specific endocrine functions. This approach allows us to explore the cellular mechanisms whereby various hormones can alter the cardiovascular system through changes in lipid metabolism and actions on cardiac myocytes, vascular smooth muscle cells, and other target cells and tissues. In addition, this chapter discusses epidemiologic studies and metaanalyses on cardiovascular morbidity and mortality associated with endocrine dysfunction to guide clinicians on the appropriate treatment of affected patients.

Pituitary Hormones and Cardiovascular Disease

The pituitary gland consists of two distinct anatomic portions. The anterior pituitary, or adenohypophysis, contains six different cell types; five of them produce polypeptide or glycoprotein hormones, and one, the sixth, consists of nonsecretory chromophobic cells. Of these cell types, the somatotropic cells, which secrete human growth hormone (hGH), and the corticotropic cells, which produce adrenocorticotropic hormone (ACTH), can contribute to cardiac disease. The posterior pituitary, or neurohypophysis, is the anatomic location of the nerve terminals that secrete vasopressin (antidiuretic hormone), which helps control water balance, and oxytocin, the milk letdown polypeptide.

Growth Hormone

Excessive secretion of hGH and insulin-like growth factor type 1 (IGF-1) by benign pituitary adenomas leads to the clinical syndrome of gigantism in youth, before fusion of the bony epiphysis, and to acromegaly in adults, after maturation of the long bones. hGH exerts its cellular effects through two major pathways. The first is by binding of the hormone to specific hGH receptors on target cells. Such receptors exist in the heart, skeletal muscle, fat, liver, and kidneys, as well as in many additional cell types throughout fetal development.[1] The second growth-promoting effect of hGH results from stimulation of the synthesis of IGF-1. The liver produces most of the IGF-1, but other cell types can produce IGF-1 under the influence of hGH.

Shortly after identification of the IGF family, this second messenger was thought to mediate most actions of hGH. The ability to promote glucose uptake and cellular protein synthesis gave rise to the term “insulin-like.” IGF-1 binds to its cognate IGF-1 receptor, which is localized on almost all cell types. Genetic experiments have demonstrated that the presence of IGF-1 receptors on cell types is linked closely to the ability of these cells to divide. Studies in which the IGF-1 receptor was overexpressed in cardiac myocytes showed that this condition produced an increase in myocyte number and mitotic rate and enhanced the replication of myocytes after differentiation.

Infusion of hGH or IGF-1 acutely changes cardiac function and hemodynamics. The acute increases in cardiac contractility and cardiac output may result, at least in part, from a decrease in systemic vascular

resistance and left ventricular afterload.[2]

Cardiovascular Manifestations of Acromegaly

Acromegaly is a relatively uncommon condition with an annual incidence of 3 to 4 cases per million. Despite its rarity, acromegaly is associated with markedly increased rates of morbidity and mortality; the standardized mortality ratio ranges from 1.3 to 3.[3] About 60% of acromegalic patients develop cardiovascular disease.[4] Hypertension, insulin resistance, diabetes mellitus, and hyperlipidemia are the cardiovascular risk factors associated most frequently with acromegaly.[4-6] Death in acromegalic patients occurs primarily from cardiovascular disease and diabetes, especially in undiagnosed and untreated patients. Only 20% of patients with acromegaly and diabetes will survive 20 years.[7-8] Multiple studies have implicated that increased rates of neoplasia of the gastrointestinal tract, colon polyps, colon cancer, and pulmonary disease are factors in this increased mortality rate[5]; cardiovascular and cerebrovascular events are more frequent contributors to death, however.[7-8] The recently published Endocrine Society Clinical Practice Guidelines recommend that acromegalic patients undergo evaluation for associated comorbidities (hypertension, diabetes mellitus, cardiovascular disease, and sleep apnea).[9]

The cardiovascular and hemodynamic effects of acromegaly vary considerably depending on the patient's age and the disease's severity and duration. A specific acromegalic cardiomyopathy develops in patients with persistently increased secretion of hGH and IGF-1. It can occur even in the absence of cardiovascular risk factors and is manifested as biventricular concentric hypertrophy.[10] As many as two thirds of patients with acromegaly meet echocardiographic criteria for left ventricular hypertrophy (LVH); the right ventricular mass also increases in acromegaly, a finding indicating a more generalized process than systemic hypertension.[10,11] The natural history of this specific cardiomyopathy has three phases.[2] The first phase typically develops in young patients with new-onset acromegaly and involves a hyperkinetic syndrome with increased myocardial contractility and enhanced cardiac output. More evident hypertrophy usually develops during the second phase of cardiomyopathy and is associated with impaired diastolic filling, which reduces the cardiac performance during exercise. Impaired systolic function and low cardiac output progressively develop in the late phase of the disease in patients in whom acromegaly is undiagnosed or undertreated. Heart failure can complicate this late phase of the disease and portends a poor prognosis.[12] Hypertension, type 2 diabetes, and hyperlipidemia may further contribute to impaired contractile function.[13]

The clinical disease activity of patients with an excess of hGH is correlated better with serum levels of IGF-1 than with hGH concentrations. Secondary hypertension accompanies acromegaly and occurs with a mean prevalence of 33% to 46%.[13] The mechanism underlying hypertension in acromegaly remains poorly understood. Administration of hGH promotes sodium retention and volume expansion, and IGF-1 has a potent antinatriuretic effect independent of any effect on aldosterone. Studies of the renin-angiotensin-aldosterone system have shown failure to inhibit release of renin optimally by volume expansion. Both angiotensin-converting enzyme inhibitors and angiotensin receptor blockers can cause a paradoxical increase in blood pressure in patients with acromegaly. Impaired glucose tolerance and diabetes mellitus occur in 15% to 38% of acromegalic patients.[14] The role of hyperinsulinemia in the hypertension associated with acromegaly has been questioned.[14] Although initial reports suggested that accelerated atherosclerosis impairs cardiac function in patients with long-standing acromegaly, a postmortem study revealed significant coronary artery disease in only 11% of patients dying of disease-related causes. Angiography shows normal or dilated coronary arteries in most cases. Fewer than 25% of patients have positive nuclear stress tests, indicating that atherosclerosis and ischemic heart disease do not likely

account for the marked degree of biventricular cardiac hypertrophy, cardiac failure, and cardiovascular death.

Acromegaly increases the prevalence of aortic and mitral valve disease, which persists despite cure of the acromegaly. Progressive mitral regurgitation and increased left ventricular preload and afterload occur in patients with uncontrolled acromegaly. Patients with acromegaly may exhibit dilation of the aortic root.

Abnormalities on the electrocardiogram (ECG), including left axis deviation, septal Q waves, ST-T wave depression, abnormal QT dispersion, and conduction system defects, develop in up to 50% of patients with acromegaly. A variety of dysrhythmias can occur, including atrial and ventricular ectopic beats, sick sinus syndrome, and supraventricular and ventricular tachycardia.[15,16] Monitoring shows a fourfold increase in complex ventricular arrhythmias. Signal-averaged ECGs reveal a parallel rise in late potentials, a finding related to ventricular arrhythmia. Patients with active acromegaly more commonly show these electrophysiologic abnormalities than do treated patients.[16] Patients with newly diagnosed, untreated acromegaly also manifest derangements in cardiac autonomic function, as measured by heart rate recovery and variability.

Diagnosis

In 99% of cases, acromegaly arises from benign adenomas of the anterior pituitary gland. At diagnosis most of these neoplasms are classified as macroadenomas (> 10 mm), and patients have clinical evidence of having had the disease for longer than 10 years. The biochemical diagnosis of acromegaly depends on demonstrating elevated serum IGF-1 levels and the lack of suppression of hGH to less than 1 µg/L following an oral glucose load.[9] Localization of the tumor uses magnetic resonance imaging (MRI) of the pituitary gland or computed tomographic (CT) scanning when MRI is contraindicated or unavailable.

Treatment

Treatment aims to control tumor growth and normalize serum hGH and IGF-1 levels to reduce the risk of premature death and improve the quality of life.[9] Transsphenoidal surgery with resection of the adenoma cures 50% to 70% of patients. Preoperative medical therapy with somatostatin receptor ligands is recommended to reduce the surgical risk in patients with heart failure or severe comorbidities.[9] The cardiovascular complications of acromegaly usually improve with treatment, and survival rates improve significantly in patients achieving disease remission as defined by the normalization of serum IGF-1 and serum hGH levels to less than 1 µg/L.[9] hGH and/or IGF-1 levels that remain elevated after surgery mandate medical therapy.[9] A residual tumor mass following surgery may require radiotherapy if medical therapy is unavailable, unsuccessful, or not tolerated.[9]

Cardiovascular Manifestations of Growth Hormone Deficiency

hGH has an important role in the development of the normal heart and the maintenance of its normal structure and function in adult life.[2] Untreated adult hGH-deficient patients can have cardiac and endothelial dysfunction, insulin resistance, a deranged lipid profile, increased carotid intima-media thickness, elevated inflammatory markers, increased body fat with abdominal obesity, hypercoagulability, and decreased skeletal muscle mass and strength.[17] Patients with hypopituitarism not treated with hGH have a doubled overall mortality rate, principally because of increased cardiovascular mortality rates.[18,19] Early premature atherosclerosis can develop in hypopituitary patients not receiving hGH therapy;

therefore, growth hormone therapy should be continued after a patient with persistent growth hormone deficiency has reached adult height. Growth hormone may have beneficial effects in patients with congestive heart failure due to either ischemic or idiopathic dilated cardiomyopathy.[17-19]

Prolactin Disease

The most common disorder of the anterior pituitary gland is the development of small (< 1 cm), prolactin-producing pituitary adenomas causing amenorrhea and galactorrhea. Prolactin plays an increasingly recognized stimulatory role in inflammation, and prolactin receptors may become localized in human coronary artery plaques, a finding that suggests that prolactin might influence atherogenesis. Because hypothalamic dopamine normally inhibits prolactin secretion, dopamine agonists such as cabergoline and bromocriptine are first-line treatments. Such treatment in prolactin disease has fortunately not been linked with cardiac valvular disease as it has in Parkinson disease.[20] Patients with prolactinoma can have an unfavorable cardiovascular and metabolic risk profile.

Adrenal Hormones and Cardiovascular Disease

Adrenocorticotropic Hormone and Cortisol

The adrenocorticotropic cells in the anterior pituitary synthesize a large protein (proopiomelanocortin), which is processed in the corticotropic cell into a family of smaller proteins that include adrenocorticotropic hormone (ACTH). The adrenal cortex zona glomerulosa produces aldosterone, and the zona fasciculata produces primarily cortisol and some androgenic steroids. The zona reticularis also produces cortisol and androgens. ACTH regulates the synthesis of cortisol in the zona fasciculata and zona reticularis.

Cushing Disease and Cushing Syndrome

Cushing syndrome results from prolonged and inappropriately high exposure of tissues to glucocorticoids.[21] Excessive cortisol secretion and its attendant clinical disease states can arise from excessive release of ACTH by the pituitary (Cushing disease) or through the adenomatous or rarely malignant neoplastic process arising in the adrenal gland itself (Cushing syndrome).[21] Well-characterized conditions of adrenal glucocorticoid and mineralocorticoid excess appear to result from the excessively high levels of (ectopic) ACTH produced by small cell carcinoma of the lung, carcinoid tumors, pancreatic islet cell tumors, medullary thyroid cancer, and other adenocarcinomas and hematologic malignancies.[21] Clinical signs and symptoms of Cushing syndrome often develop in patients treated with exogenous steroids at doses equivalent to 20 mg of prednisone daily for more than 1 month.

Cortisol, a member of the glucocorticoid family of steroid hormones, binds to receptors located within the cytoplasm of many cell types (**Fig. 92.1**). After binding cortisol, these receptors are translocated to the nucleus and function as transcription factors. Several cardiac genes contain glucocorticoid response elements in their promoter regions that confer transcriptional-level glucocorticoid responsiveness. Such genes include those that encode voltage-gated potassium channels, as well as protein kinases, which serve to phosphorylate and regulate the voltage-gated sodium channels. In addition, there are more rapidly acting, nontranscriptional pathways by which cortisol may regulate the activity of voltage-gated potassium channels.

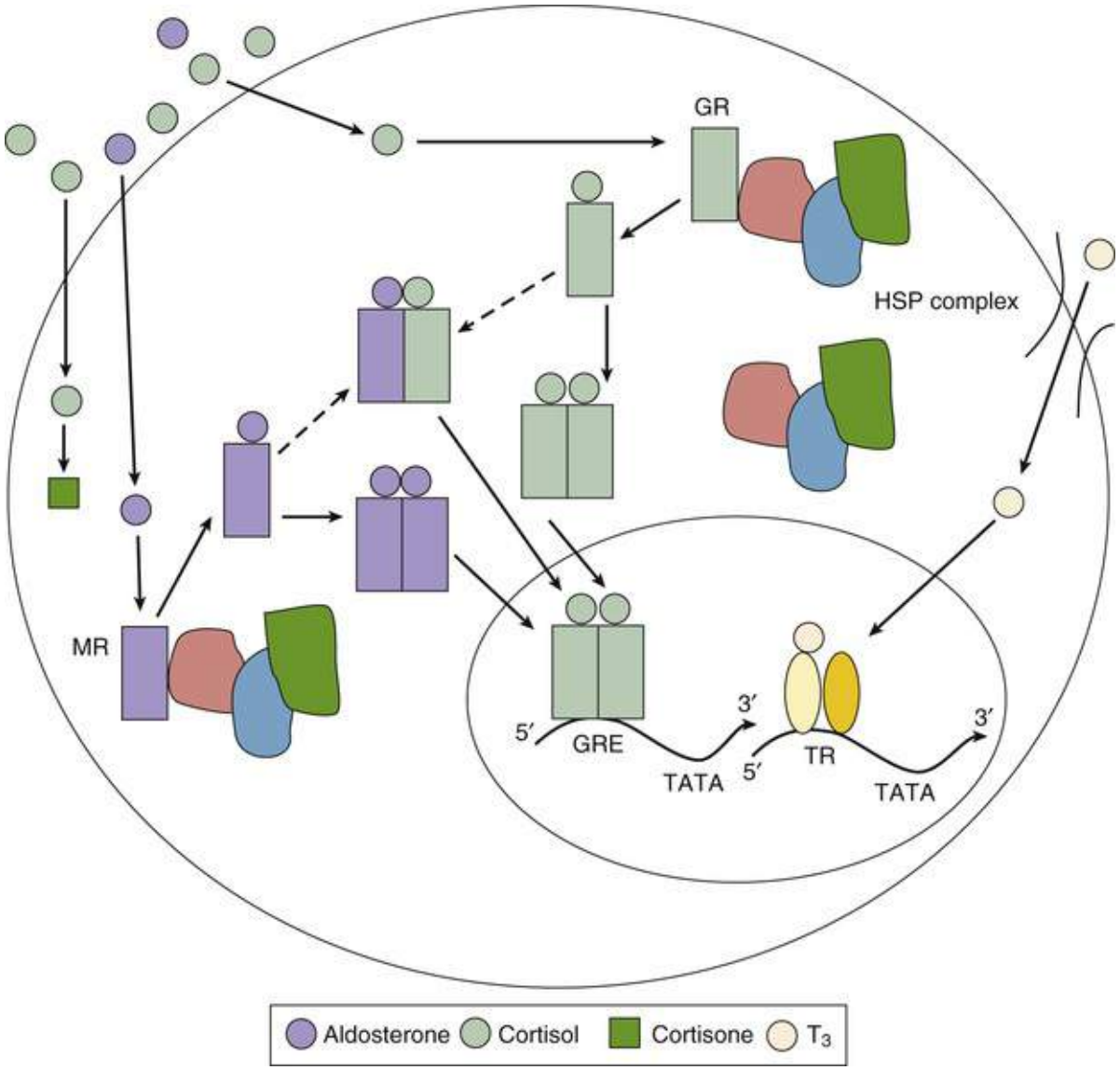

FIGURE 92.1 Schematic representation of a generalized mechanism of action of the nuclear hormone receptor. The mineralocorticoid receptor (MR) has similar affinities for aldosterone and cortisol. Circulating levels of cortisol are 100 to 1000 times greater than those of aldosterone. In MR-responsive cells, the enzyme 11-beta-hydroxysteroid dehydrogenase metabolizes cortisol to cortisone, thereby allowing aldosterone to bind to the MR. The MR and glucocorticoid receptor (GR) are cytoplasmic receptors that after binding ligand, translocate to the nucleus and bind to glucocorticoid response elements (GREs) in the promoter regions of responsive genes. Triiodothyronine (T_3) is transported into the cell via specific membrane proteins and binds to thyroid hormone receptors (TRs), which are bound to thyroid hormone response elements in the promoter regions of T_3-responsive genes. *HSP*, heat shock protein; *TATA*, TATA box promoter region. (Courtesy Dr. S. Danzi.)

The cardiac effects of Cushing syndrome arise from the effects of glucocorticoids on the heart, liver, skeletal muscle, and fat tissue.[22-24] LVH and concentric remodeling can result. Glucocorticoid excess is also associated with left ventricular dysfunction, myocardial fibrosis, and dilated cardiomyopathy.[25] The increased cardiovascular morbidity and mortality rates of Cushing syndrome are largely due to cerebrovascular, peripheral vascular, and coronary artery disease and to chronic congestive heart failure.[22-28] Compared with matched controls, patients with active disease have a hazard ratio (HR) of 6.0 (2.1 to 17.1) for heart failure, 2.1 (0.5 to 8.6) for acute myocardial infarction, and 4.5 (1.8 to 11.1) for stroke.[26-28] Chronic cortisol hypersecretion causes central obesity, hypertension, insulin resistance, dyslipidemia, a prothrombotic state, and the metabolic syndrome. Cortisol-mediated hypertension has multiple mechanisms. The centripetal obesity characteristic of glucocorticoid excess resembles that seen in insulin resistance syndromes. In addition, the marked muscle weakness resulting from corticosteroid-

induced skeletal myopathy contributes to impaired exercise tolerance.

Patients with Cushing disease can exhibit a variety of electrocardiographic changes. The duration of the PR interval appears to be correlated inversely with adrenal cortisol production rates. The mechanism underlying this correlation may be related to expression or regulation of the voltage-gated sodium channel (SCN5A). Changes on the ECG, specifically in the PR and QT intervals, may also arise from the direct (nongenomic) effects of glucocorticoids on the voltage-gated potassium channel (Kv1.5) in excitable tissues.

A particular complex of cardiac and adrenal lesions, referred to as the *Carney complex*, is a combination of Cushing syndrome, cardiac myxoma, and a variety of pigmented dermal lesions (not café au lait spots). This monogenic autosomal dominant trait has been mapped to the q2 region of chromosome 17.[29] Myxomas most commonly occur in the left atrium but can arise throughout the heart, can develop at young ages, and can be multicentric.

Diagnosis

The diagnosis of Cushing disease and Cushing syndrome requires the demonstration of increased cortisol production as reflected by an elevated 24-hour urinary free cortisol level or nocturnal salivary cortisol level.[21] ACTH measurement assesses whether the disease is pituitary, adrenal, or ectopically based; anatomic localization of the suspected lesions with MRI confirms the laboratory findings.

Treatment

Treatment of excessive cortisol production depends on the underlying mechanisms.[30] Initial resection of primary lesion(s) is recommended for underlying Cushing disease (based in the pituitary) and also for Cushing disease related to ectopic and adrenal causes. Transsphenoidal selective adenomectomy with or without postoperative radiation therapy can partially or completely reverse the increased ACTH production by the anterior pituitary. Cushing syndrome requires surgical removal of one adrenal gland (adrenal adenoma, adrenal carcinoma) or both adrenal glands (multiple nodular disease). Immediately after surgery, cortisol and mineralocorticoid (fludrocortisone) need to be replaced to prevent adrenal insufficiency.

Drug therapy before or after surgery can help control persistent cortisol production. Pasireotide can decrease ACTH production from a pituitary tumor. The adrenal enzyme inhibitor ketoconazole may be used alone or in combination with metyrapone to enhance control of severe hypercortisolemia. Mitotane is used primarily to treat adrenal carcinoma. Mifepristone is approved in the United States for people with Cushing syndrome who have type 2 diabetes or glucose intolerance. Mifepristone blocks the direct effect of cortisol on tissues and leads to an improvement in hypertension and/or diabetes in 40% to 60% of patients. Etomidate is useful where immediate parenteral action is required and in seriously ill patients who cannot take oral medications. The goal of therapy is the clinical normalization of cortisol levels.

Primary Hyperaldosteronism (see also Chapter 46)

Aldosterone production by the zona glomerulosa is responsive to the renin-angiotensin system.[30] Renin secretion responds primarily to changes in intravascular volume. Aldosterone synthesis and secretion depend primarily on regulation by angiotensin II, which binds to the angiotensin II type I receptor on cells of the zona glomerulosa.[31] Primary hyperaldosteronism (PA) refers to a group of disorders in which aldosterone production is inappropriately high; production is relatively independent from the major

regulators of secretion (angiotensin II and plasma potassium concentration) and is not suppressible with sodium loading.[32] Common causes of PA include an adrenal adenoma, unilateral or bilateral adrenal hyperplasia, or, in rare cases, an adrenal carcinoma or an inherited condition known as glucocorticoid-remediable aldosteronism.[32]

The mechanism of action of aldosterone on target tissues resembles that reported for glucocorticoids (**see Fig. 92.1**). Aldosterone enters cells and binds to the mineralocorticoid receptor, which then is translocated to the nucleus and promotes the expression of aldosterone-responsive genes. In addition to kidney cells, in which mineralocorticoid receptors control sodium transport, in vitro studies have demonstrated these receptors in rat cardiac myocytes.

In humans, primary aldosteronism causes cardiovascular damage; it can induce development of cardiac hypertrophy, myocardial fibrosis, and diastolic dysfunction.[31-33] Recent prospective studies have reported that more than 10% of hypertensive patients have primary aldosteronism, and that normokalemic hypertension constitutes the most common presentation of the disease.[32] Severe hypokalemia occurs in only a minority of patients (9% to 37%).[32] Primary aldosteronism is associated with higher rates of cardiovascular morbidity and mortality than age- and sex-matched patients with essential hypertension.[32] Primary aldosteronism should be investigated in patients with (1) severe hypertension, (2) treatment-resistant hypertension, (3) hypertension with spontaneous or diuretic-induced hypokalemia, (4) hypertension with adrenal incidentaloma, (5) hypertension and sleep apnea, or (6) a family history of early-onset hypertension or cerebrovascular accident at a young age (< 40 years of age).[32,34,35]

The plasma aldosterone/renin ratio detects possible PA. Patients should have unrestricted dietary salt intake before testing and should be potassium replete.[32-35] Mineralocorticoid receptor antagonists should be withdrawn for at least 4 weeks before testing, especially in patients with mild hypertension. Patients with an abnormal aldosterone/renin ratio undergo one or more confirmatory tests to definitively confirm or exclude the diagnosis.[32,35] After sodium loading, plasma aldosterone levels lower than 5 ng/dL make the diagnosis of PA unlikely. Levels above 10 ng/dL indicate very probable PA.[32] Caution should be used when performing confirmatory tests; patients with spontaneous hypokalemia, plasma renin levels below detection levels, and plasma aldosterone concentrations of more than 20 ng/dL do not require further testing.[32] All patients with suspected disease should undergo adrenal CT to seek adrenocortical carcinoma.[32]

Treatment (see also Chapters 25, 26, 46, and 47)

Patients with primary hyperaldosteronism and hypokalemia should receive slow-release potassium chloride supplementation to maintain plasma potassium. The aldosterone antagonist spironolactone or eplerenone (as a second choice) should be used to control hypertension, hypokalemia, and the deleterious cardiovascular effects of aldosterone hypersecretion.[32] Surgical treatment is practicable in young patients (< age 35 years) with spontaneous hypokalemia, marked aldosterone excess, and unilateral adrenal lesions with evidence of a cortical adenoma on adrenal CT.[32] Adrenal venous sampling before surgery can help to distinguish between unilateral and bilateral adrenal disease. Unilateral laparoscopic adrenalectomy can cure hypokalemia and improve or cure hypertension in such patients.

Patients with bilateral disease and those reluctant to undergo surgery should receive medical treatment with mineralocorticoid receptor antagonists.[32] Genetic testing for familial hyperaldosteronism should be performed in patients with a family history of hypertension and stroke at a young age (< 40 years).[32] Very young patients should be tested for germline mutations in KCNJ5 causing familial hyperaldosteronism type 3.[32]

Addison Disease

Thomas Addison was the first to describe the association of atrophy and loss of function of the adrenal glands with marked changes in the cardiovascular system. Primary adrenal insufficiency occurs when the adrenal cortex cannot produce sufficient glucocorticoids and/or mineralocorticoids.[36] Acute addisonian crisis, one of the most severe endocrine emergencies, is characterized by hypovolemia, hypotension, and acute cardiovascular collapse resulting from renal sodium wasting, hyperkalemia, and loss of vascular tone. Primary adrenal insufficiency arises most commonly from bilateral loss of adrenal function on an autoimmune basis; as a result of infection, hemorrhage, or metastatic malignancy; or in selected cases, from inborn errors of steroid hormone metabolism.[36] Addison disease can occur at any age; it may be associated with other autoimmune disorders (e.g., Hashimoto thyroiditis, type 1 diabetes mellitus, autoimmune gastritis/pernicious anemia, and vitiligo).[36] In contrast, secondary adrenal insufficiency, which results from pituitary-dependent loss of ACTH secretion, leads to a fall in glucocorticoid production; mineralocorticoid production, including aldosterone, remains at relatively normal levels.[36] Studies have addressed the issue of relative hypothalamic-pituitary-adrenal insufficiency in acutely ill patients. Although the actual existence of such an entity and diagnostic criteria for establishing this condition remain to be validated, its possible existence has reopened the question of the need for stress-dose cortisol treatment in the management of patients with critical illness.

The noncardiac symptoms, including increased pigmentation, abdominal pain with nausea and vomiting, hypoglycemia, and weight loss, can be chronic; tachycardia, hypotension, hyponatremia, hyperkalemia, loss of autonomic tone, and cardiovascular collapse and crisis may develop, especially in acutely ill or untreated patients with Addison disease.[36] Delayed treatment of more severe symptoms will increase rates of morbidity and mortality.[37] Blood pressure measurements uniformly show a low diastolic pressure (< 60 mm Hg) along with orthostatic changes that reflect loss of volume and acquired autonomic dysfunction. Laboratory findings (hyponatremia and hyperkalemia) indicate loss of aldosterone production (renin levels are high). Hyperkalemia can alter findings on the ECG by producing low-amplitude P waves and peaked T waves. Patients with newly diagnosed, untreated Addison disease have reduced left ventricular end-systolic and end-diastolic dimensions in comparison with controls. Cardiac atrophy is an unusual condition; it is seen with malnutrition caused by anorexia, in astronauts after prolonged space flight, in populations with sodium-deficient diets, and characteristically with Addison disease (teardrop heart; **Fig. 92.2**). This atrophy reflects a response to decreases in the cardiac workload because restoration of normal plasma volume with mineralocorticoid and glucocorticoid replacement increases ventricular mass.

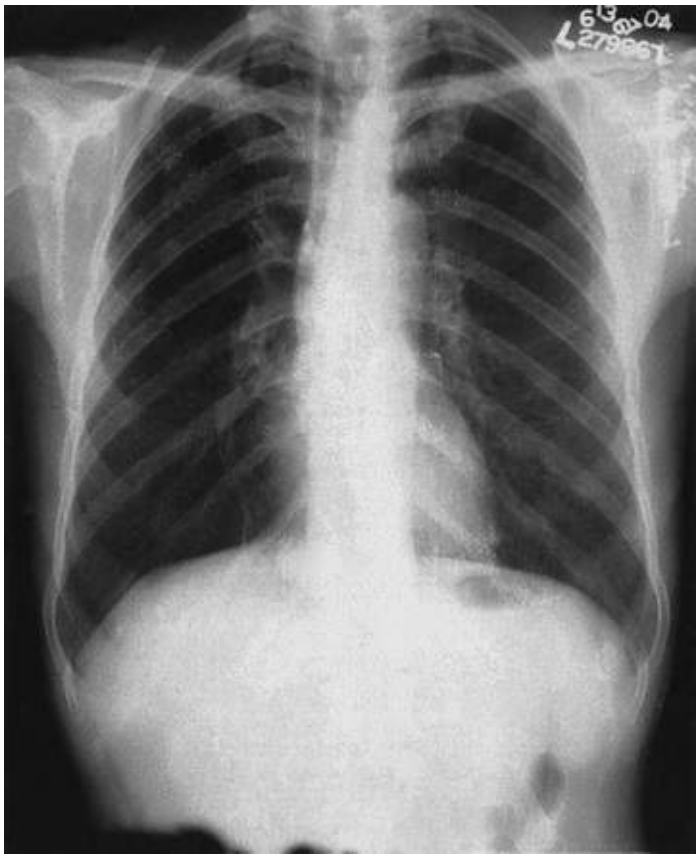

FIGURE 92.2 Routine chest radiograph of a patient with Addison disease related to tuberculosis. In addition to the small cardiac silhouette, calcified lymph nodes are present in the hilum of the right lung. (Courtesy Dr. J.B. Naidich.)

Diagnosis

Acute adrenal insufficiency characteristically occurs in the setting of acute stress, infection, or trauma in a patient with chronic autoimmune adrenal insufficiency or in children with congenital abnormalities in cortisol metabolism. It can also develop as a result of bilateral adrenal hemorrhage in patients with severe systemic infection or diffuse intravascular coagulation.[38] Secondary adrenal insufficiency can occur in the setting of hypopituitarism and is usually chronic, but acute changes caused by pituitary hemorrhage (apoplexy) or pituitary inflammation (lymphocytic hypophysitis) can also occur. Acute adrenal insufficiency can develop in patients treated over a long term with suppressive doses of corticosteroids (> 10 mg of prednisone for > 1 month) if treatment is stopped precipitously or if an acute, severe, non–endocrine-related illness arises.

The diagnostic criteria include low cortisol levels (morning cortisol < 140 nmol/L [< 5 µg/dL]) or cortisol levels that fail to rise above 500 nmol/L (20 µg/dL) 30 or 60 minutes after an intravenous injection of 250 µg of corticotropin.[38] The simultaneous measurement of plasma renin and aldosterone can help to determine whether a mineralocorticoid deficiency is present.

Treatment

Addison disease is a potentially lethal condition.[37,38] Management of acute addisonian crisis requires adequate hydrocortisone replacement therapy (100 mg given as an initial intravenous bolus; then 100 mg every 8 to 12 hours for the first 24 hours, and tapering of the dose over the next 72 to 96 hours).[38] Large volumes of normal saline with 5% dextrose can address the intravascular fluid deficit.[38] Potential underlying precipitating causes (including infection, acute cardiac or cerebral ischemia, or

intraabdominal emergency) require identification and treatment. Long-term treatment of adrenal insufficiency consists of oral corticosteroid therapy (hydrocortisone ≈20 mg in two divided oral doses per day, or prednisone 5 mg administered orally once or twice daily).[38] Patients with confirmed aldosterone deficiency should receive mineralocorticoid replacement with fluorohydrocortisone (starting dose, 50 to 100 µg in adults).[38] Diuretics and aldosterone antagonists, such as spironolactone or eplerenone, should be avoided.[38,39]

Pheochromocytoma

Pheochromocytomas (**see also Chapters 46 and 47**) are primarily benign tumors arising from neuroectodermal chromaffin cells; they usually arise in the adrenal medulla and abdomen, but they may arise anywhere in the plexus of sympathetic adrenergic nerves.[40] Autopsy studies have shown that in 75% of patients the diagnosis was not clinically suspected and that in more than 50% of patients it contributed to death. Most pheochromocytomas are sporadic, but recent data suggest that about 20% are familial.[40,41] Six different familial autosomal dominant diseases can be suspected clinically: neurofibromatosis type 1, multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau syndrome, renal cell carcinoma with *SDHB* mutation, *Carney triad* (paragangliomas, gastric stromal tumors, pulmonary chondromas), and *Carney-Stratakis syndrome* (paragangliomas and gastric stromal sarcomas). When pheochromocytoma coexists with medullary thyroid carcinoma or occasionally with hyperparathyroidism, it is designated multiple endocrine neoplasia syndrome type 2A (MEN2A). In patients with MEN2B, pheochromocytomas coexist with medullary thyroid cancer and with mucosal neuromas frequently seen on the lips and tongue.

Clinical manifestations of pheochromocytoma include headache, palpitations, excessive sweating, tremulousness, chest pain, weight loss, and a variety of other constitutional complaints. Hypertension may be episodic but is usually constant and is paradoxically associated with orthostatic hypotension on arising in the morning. The paroxysmal attacks and classic symptoms result from episodic excessive catecholamine secretion.[42,43]

Hypertension caused by pheochromocytoma can first present at the time of elective surgical intervention for an unrelated condition. As a result of release of norepinephrine with an increase in systemic vascular resistance, cardiac output is minimally (if at all) increased despite increases in the heart rate. The ECG can show LVH, as well as repolarization abnormalities, findings suggesting left ventricular strain. Although ventricular and atrial ectopy and episodes of supraventricular tachycardia can occur, little distinguishes the LVH from that of essential hypertension.

Impaired left ventricular function and cardiomyopathy have occurred in patients with pheochromocytoma.[42,43] The mechanism underlying this condition is complex and includes an increased left ventricular work and LVH from associated hypertension; potential adverse effects of excess catecholamines on myocyte structure and contractility; and changes in coronary arteries, including thickening of the media, which presumably impairs blood flow to the myocardium. Postmortem examination of patients with previously diagnosed or undiagnosed disease can show histologic evidence of myocarditis. The possibility of catecholamine-stimulated tachycardia in turn mediating left ventricular dysfunction should be addressed because treatments designed to slow the heart rate may improve left ventricular function. Life-threatening cardiovascular manifestations of pheochromocytoma primarily result from hypertensive emergencies (abnormalities of cardiac rhythm and serious ventricular arrhythmias or conduction disturbances).[42,43] Reversible dilated hypertrophic cardiomyopathy and takotsubo cardiomyopathy are well-established cardiac manifestations of pheochromocytoma.

The primary catecholamine released from adrenal pheochromocytomas is norepinephrine, but

epinephrine can also increase. Demonstration of elevated serum dopamine levels implies malignant transformation, which in turn suggests that the tumor may have arisen in an extraadrenal site and have distinct gene expression profiles. Rarely, pheochromocytoma can arise within the heart, presumably from chromaffin cells, which are part of the adrenergic autonomic paraganglia.

Diagnosis

An increase in norepinephrine, epinephrine, or their metabolites in serum or blood is essential to establish the diagnosis. Quantitative 24-hour urinary fractionated metanephrine levels are the most reliable screening procedures; they provide a sensitivity of 97% and a specificity of 91%.[40] CT is the first-choice imaging modality because of its excellent spatial resolution for the thorax, abdomen, and pelvis.[40] MRI is recommended in patients with metastatic disease and for detection of skull base and neck paragangliomas.[40] ^{131}I-metaiodobenzylguanidine can localize catecholamine-producing lesions, and ^{18}F-fluorodeoxyglucose positron emission tomography scanning can visualize metastatic disease.[40] Genetic testing can aid counseling of patients with established disease and their families.[40]

Treatment

Definitive treatment of pheochromocytoma requires removal of the lesion.[40] Accurate preoperative localization reduces the operative mortality rate and eliminates the need for exploratory laparotomy. Endoscopic procedures are now standard for small tumors, and open resection is indicated for large tumors (e.g., > 6 cm) or invasive pheochromocytomas.[40]

Preoperative pharmacologic treatment should be provided to prevent perioperative cardiovascular complications.[40] It includes 7 to 14 days of alpha-adrenergic blockade (usually with doxazosin, prazosin, or phenoxybenzamine) to normalize the blood pressure. Beta-blocking drugs can normalize the heart rate but should follow the establishment of a sufficient alpha blockade. Before surgical treatment, a high-sodium diet and fluid intake should be started to improve the blood volume contraction and prevent severe hypotension after tumor removal. Operative intervention requires constant blood pressure monitoring, and intravenous phentolamine or sodium nitroprusside may be required to treat episodic hypertension intraoperatively.[40] Gauges of the success of surgery include effective blood pressure and symptom improvement, as well as measurement of urinary catecholamines 4 weeks after the procedure. Lifelong annual biochemical testing to assess for recurrent or metastatic disease is necessary.

Parathyroid Hormones and Cardiovascular Disease

Diseases of the parathyroid glands can produce cardiovascular disease and alter cardiac function through two mechanisms. Parathyroid hormone (PTH) is a protein hormone that can affect the heart, vascular smooth muscle cells, and endothelial cells. PTH-induced changes in serum calcium levels also affect the cardiovascular system.[44]

PTH can bind to its receptor and alter the spontaneous beating rate of neonatal cardiac myocytes through an increase in intracellular cyclic adenosine monophosphate (cAMP). PTH can also alter the calcium influx and cardiac contractility in adult cardiac myocytes and the relaxation of vascular smooth muscle cells. Moreover, a variety of tissues, including cardiac myocytes, produce the structurally related PTH-related peptide (PTHrP). PTHrP can bind to the PTH receptor on cardiac cells and stimulate accumulation of cAMP and contractile activity, as well as regulate L-type calcium currents. Long-term treatment with recombinant human PTH may require monitoring for adverse cardiac effects.

Hyperparathyroidism

In primary hyperparathyroidism, hypercalcemia (or high-normal serum calcium levels) occurs in the presence of inappropriately normal or elevated PTH concentrations because of an overproduction of PTH. Primary hyperparathyroidism producing hypercalcemia most often results from adenomatous enlargement of one of the four parathyroid glands. Cardiovascular actions of hypercalcemia include increased cardiac contractility; shortening of the ventricular action potential duration, primarily through changes in phase 2; and blunting of the T wave and changes in the ST segment, occasionally suggesting cardiac ischemia.[44] The QT interval shortens and occasionally the PR interval decreases. Treatment with digitalis glycosides appears to increase sensitivity of the heart to hypercalcemia.

Hypercalcemia may lead to pathologic changes in the heart, including the myocardial interstitium and conducting system, as well as calcific deposits in the valve cusps, annuli, and possibly coronary arteries. Although initially observed in fairly long-standing and severe hypercalcemia, so-called metastatic calcifications can also occur in secondary parathyroid disease arising from chronic renal failure, in which the serum calcium-phosphorus product constant is exceeded. Patients with primary hyperparathyroidism generally maintain normal left ventricular systolic function, but severe or chronic disease may impair diastolic function. Changes in left ventricular structure and function do not appear to improve by 1 to 2 years after successful parathyroid surgery.[45]

Diagnosis

A simultaneous increase in serum immunoreactive PTH (best represented by the intact PTH assay) with elevation of the serum calcium level establishes the diagnosis of primary hyperparathyroidism. Other causes of hypercalcemia include malignancy with an increased level of PTHrP or hypercalcemia arising directly from bony metastases or neoplastic (lymphoma) or nonneoplastic disease (e.g., sarcoidosis), leading to an increase in the synthesis and release of 1,25-dihydroxyvitamin D_3.

Treatment

Treatment of hyperparathyroidism is with surgical removal of the parathyroid adenoma.[46] Calcimimetic medications (cinacalcet) can lower PTH concentrations and normalize serum calcium levels.[46] Asymptomatic primary hyperparathyroidism, routinely encountered in clinical endocrinology practice, may not require definitive treatment.

Hypocalcemia

Low serum levels of total and ionized calcium directly alter myocyte function. Hypocalcemia prolongs phase 2 of the action potential duration and the QT interval. Severe hypocalcemia can impair cardiac contractility and give rise to a diffuse musculoskeletal syndrome consisting of tetany and rhabdomyolysis. Primary hypoparathyroidism is rare and can develop after surgical removal of the parathyroid glands, as may occur after treatment of thyroid cancer; in the setting of polyglandular dysfunction syndromes, as a result of glandular agenesis (DiGeorge) syndrome; and in the rare heritable disorder pseudohypoparathyroidism. Recombinant human PTH offers a treatment option.

Chronic renal failure is the most common cause of low serum calcium and high PTH levels. In such patients the effects of chronically high levels of PTH (secondary hyperparathyroidism) on the heart and cardiovascular system may be both causative and serve as a biomarker in assessing heart failure treatment strategies.[47,48] In elderly patients with progression of aortic stenosis, a rise in serum PTH and bone

remodeling occurs.[49] The ability of PTH to stimulate G protein–coupled receptors may impair myocyte contractility and contribute to LVH. Cinacalcet can treat the secondary hyperparathyroidism associated with chronic renal failure. A trial to assess its effectiveness on cardiovascular events, however, showed no significant benefit.

Vitamin D Deficiency

Most body tissues and cells express the vitamin D receptor. The active form of vitamin D, 1,25(OH)2D, has a wide range of biologic actions, including inhibiting cellular proliferation and inducing terminal differentiation, inhibiting angiogenesis, stimulating insulin production, and inhibiting renin production.[50] Approximately 30% to 50% of people in the general population have vitamin D deficiency.[50] Observational evidence suggests that lower levels of vitamin D are associated with increased all-cause and cardiovascular morbidity rates.[51,52] Vitamin D deficiency can contribute to coronary risk factors and cardiovascular disease; it predisposes to hypertension, diabetes mellitus and the metabolic syndrome, LVH, congestive heart failure, stroke, peripheral arterial disease, and chronic vascular inflammation. Epidemiologic studies have also recently linked vitamin D deficiency with an increased risk of major adverse cardiovascular events and a twofold risk of myocardial infarction. A recent metaanalysis of 18 randomized controlled trials in which 57,000 individuals were studied showed that a vitamin D intake of more than 500 IU/day improves all-cause mortality rates, in part by decreasing cardiovascular deaths.[53]

Thyroid Hormones and Cardiovascular Disease

The thyroid gland and the heart share a close relationship that arises during embryologic life. During ontogenesis, the thyroid and heart migrate together. Changes in cardiovascular function in all types of thyroid disease illustrate the close physiologic relationship between the heart and the thyroid.[54-56] Cardiovascular complications commonly occur in both subclinical and overt thyroid dysfunction.[54-56]

Cellular Mechanisms of Thyroid Hormone Action on the Heart

Diagnosis and management of thyroid hormone–mediated cardiac disease states require understanding of the cellular mechanisms of thyroid hormone on the heart and vascular smooth muscle cells.[54-56] Under the regulation of thyroid-stimulating hormone (thyrotropin, TSH), the thyroid gland concentrates iodide and, through a series of enzymatic steps, synthesizes predominantly tetraiodothyronine (T_4 ≈ 80%) and a smaller percentage of triiodothyronine (T_3 ≈ 20%) (**Fig. 92.3**). The active thyroid hormone, triiodothyronine, accounts for the vast majority of biologic effects, including stimulation of tissue thermogenesis, alterations in the expression of various cellular proteins, and actions on the heart and vascular smooth muscle cells.[54-57]

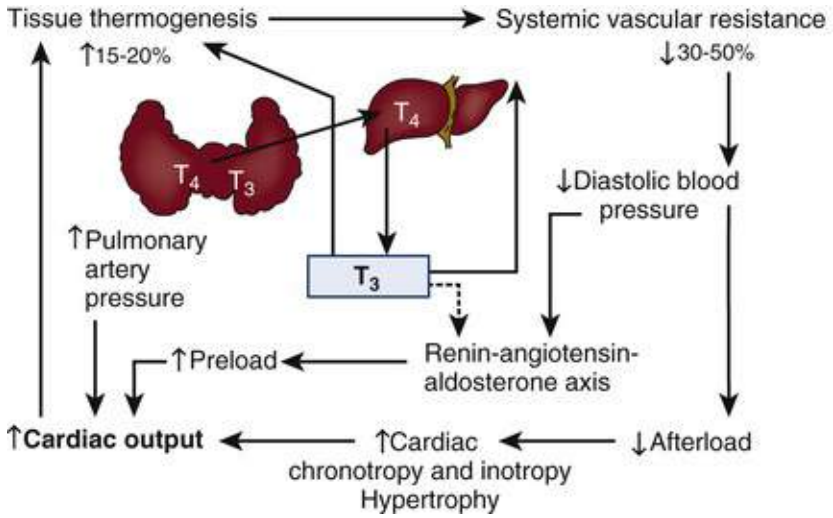

FIGURE 92.3 Changes in cardiovascular hemodynamics associated with thyroid dysfunction. The individual changes for hyperthyroidism are noted for each parameter. The effects of hypothyroidism are diametrically opposite.

Approximately 80% to 90% of the extrathyroidal T_3 is produced by deiodination of T_4 by the type I (D1) and type II (D2) deiodinases.[58] D1 is expressed in the liver and kidney, and D2 is expressed in the central nervous system, bone, skin, pituitary gland, brown adipose tissue, skeletal muscle, and heart. Type 3 deiodinase (D3) can inactivate both T_4 and T_3 and acts primarily during embryonic life; in healthy adults, its expression persists in the heart and can arise in ischemic tissue.[59] Free T_3 enters cells via transport proteins (**Fig. 92.4**) of the monocarboxylate transporter (MCT8, MCT10) and organic anion-transporting polypeptide 1C1 (OATP) family of cell surface transporters.[60] As reported for the steroid and retinoic acid families of receptor proteins, the thyroid hormone receptors bind as homodimers or heterodimers to the thyroid hormone response elements in a promoter region of specific genes. Binding to the promoter regions can activate or repress gene expression.

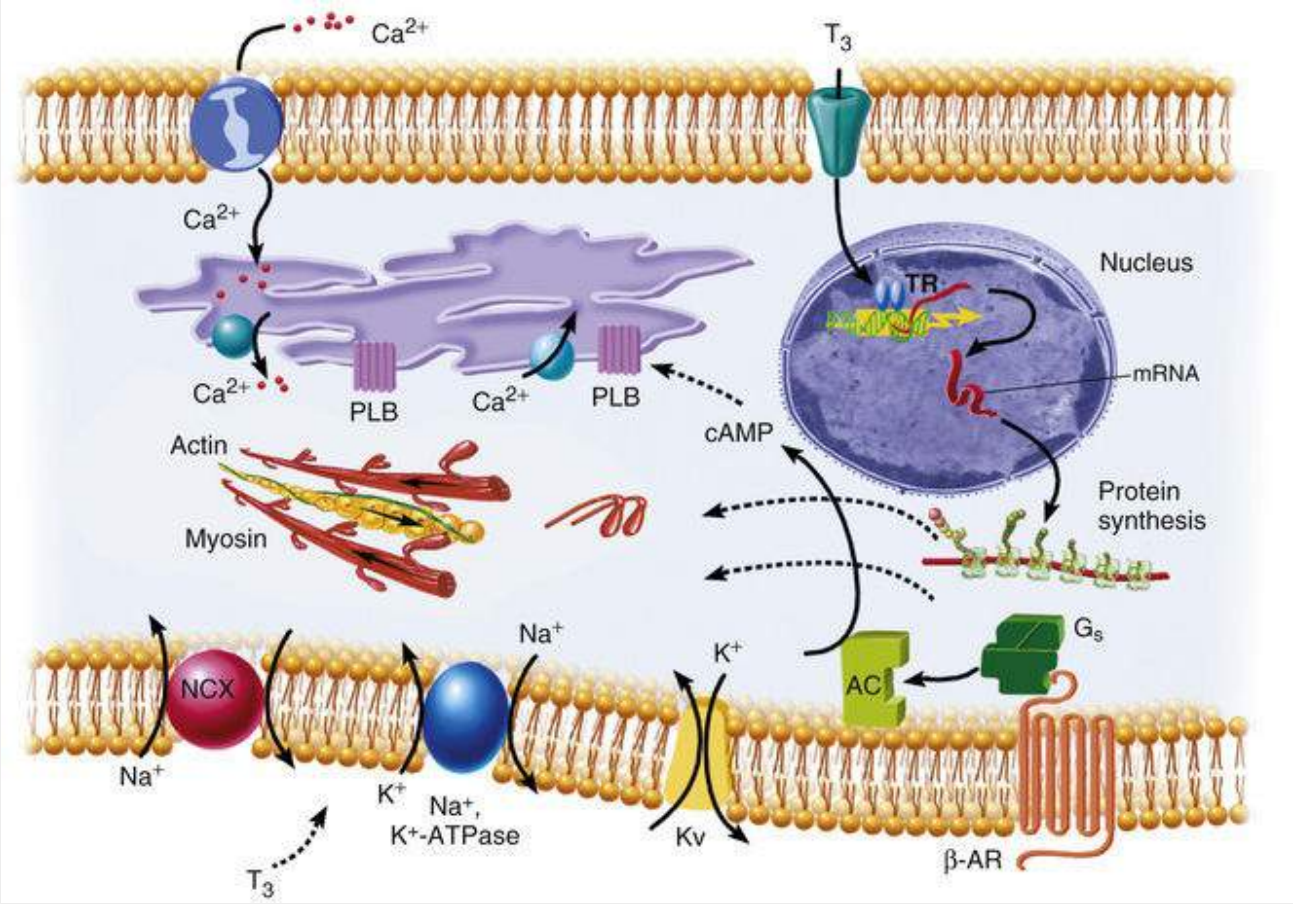

FIGURE 92.4 T_3 enters the cell via specific membrane transporters and binds to nuclear T_3 receptors. The complex binds to thyroid hormone response elements and regulates the transcription of specific genes. Nonnuclear T_3 actions on channels for Na^+, K^+, and Ca^{2+} ions are indicated. *AC*, adenylyl cyclase; *β-AR*, beta-adrenergic receptor; *Gs*, guanine nucleotide–binding protein subunit; *Kv*, voltage-gated potassium channel; *mRNA*, messenger RNA; *NCX*, sodium calcium exchanger; *PLB*, phospholamban; *TR*, T_3 receptor protein.

Thyroid hormone transcriptionally regulates many cardiac proteins (**Table 92.1**), including structural and regulatory proteins, cardiac membrane ion channels, and cell surface receptors, thus providing a molecular mechanism to explain many of the effects of thyroid hormone on the cardiovascular system.[54-56] Major T_3 targets include myosin heavy chain isoforms (alpha and beta). The human ventricle expresses primarily beta-myosin, and limited alterations in isoform expression accompany thyroid disease states. Changes in myosin heavy chain isoform expression occur in the human atria in various diseases, including congestive heart failure and severe hypothyroidism.[54-56,59,61,62]

TABLE 92.1

Thyroid Hormone Regulation of Cardiac Gene Expression

Positively Regulated
Alpha-myosin heavy chain
Sarcoplasmic reticulum Ca^{2+}-ATPase
Na^{+},K^{+}-ATPase
Voltage-gated potassium channels (Kv1.5, Kv4.2, Kv4.3)
Atrial and brain natriuretic peptide
Malic enzyme
Beta-adrenergic receptor
Guanine nucleotide–binding protein Gs
Adenine nucleotide transporter 1
Negatively Regulated
Beta-myosin heavy chain
Phospholamban
Na^{+}-Ca^{2+} exchanger
Thyroid hormone receptor alpha1
Adenylyl cyclase types V, VI
Guanine nucleotide–binding protein Gi
Monocarboxylate transporters 8 and 10

Sarcoplasmic reticulum Ca^{2+}-adenosine triphosphatase (ATPase) (SERCA) is an important ion pump that determines the magnitude of myocyte calcium cycling (**see Chapter 22**). Reuptake of calcium into the sarcoendoplasmic reticulum early in diastole in part determines the rate at which the left ventricle relaxes (isovolumic relaxation time). The polymeric protein phospholamban regulates the activity of SERCA2, and inotropic agents that enhance cardiac contractility through increases in myocyte cAMP act by stimulating the phosphorylation of phospholamban. Thyroid hormone inhibits the expression of phospholamban and increases phospholamban phosphorylation.[54-56] This molecular mechanism can explain why diastolic function varies inversely across the entire spectrum of thyroid disease states, including even mild subclinical hypothyroidism (**Fig. 92.5**),[63-65] and why even mild degrees of hypothyroidism can contribute to heart failure.[66,67] In addition, beta-adrenergic blockade of the heart in hyperthyroidism does not decrease the rapid diastolic relaxation, thus further dissociating thyroid hormone from the adrenergic effects of thyrotoxicosis.[54-56]

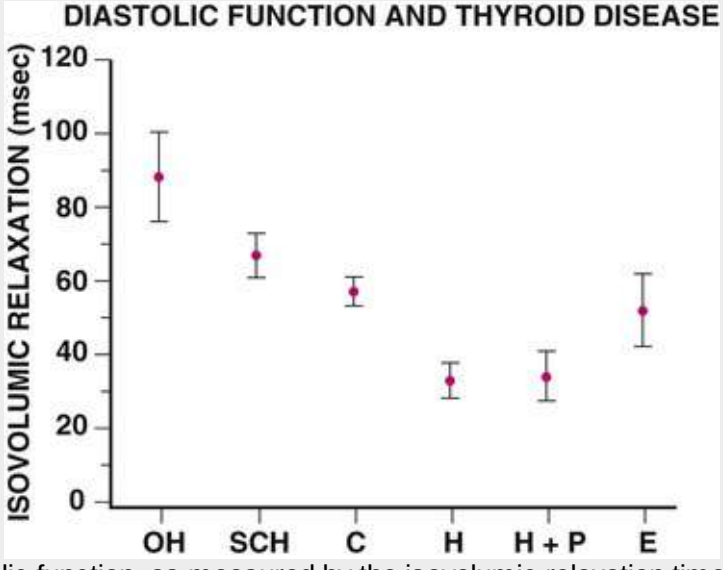

FIGURE 92.5 Diastolic function, as measured by the isovolumic relaxation time, varies over the entire range of thyroid disease, including overt hypothyroidism (OH), subclinical hypothyroidism (SCH), control (C), hyperthyroidism (H), hyperthyroidism after beta-adrenergic blockade (H + P), and hyperthyroidism after treatment to restore normal thyroid function (E).

Changes in other myocyte genes, including Na^+,K^+-ATPase, account for the increase in basal oxygen consumption of the experimental hyperthyroid heart and explain the decrease in digitalis sensitivity of hyperthyroid patients. Thyroid hormone can also regulate the expression of genes that encode its own nuclear receptors and plasma membrane transport proteins (MCT8 and MCT10) within cardiac myocytes (**see Table 92.1**).

In addition to the well-characterized nuclear effects of thyroid hormone, some cardiac responses to thyroid hormone appear to result from nontranscriptional mechanisms,[68,69] as suggested by their relatively rapid onset of action—faster than attributable to changes in gene expression and protein synthesis—and failure to be affected by inhibitors of gene transcription.

Thyroid Hormone–Catecholamine Interaction

Early observations of the heart in hyperthyroidism emphasized that it was functioning similar to the way it might in hyperadrenergic states, and this finding led to the proposal that sensitivity to catecholamines might be enhanced in this setting. This postulate formed the basis for the test described by Emil Goetsch in 1918, in which hyperthyroidism could be diagnosed by demonstrating a marked cardioacceleration and blood pressure response to small subcutaneous doses of epinephrine. The increased $beta_1$-adrenergic receptors on cardiac myocytes observed in experimental hyperthyroidism provide a mechanism for the enhanced catecholamine sensitivity.[70,71] A carefully controlled study of nonhuman primates, however, found no increase in sensitivity of the heart or cardiovascular system to catecholamines in experimental hyperthyroidism.[71] Accompanying the increased levels of $beta_1$-adrenergic receptors and guanosine triphosphate–binding proteins, thyroid hormone decreases the expression of cardiac-specific adenylyl cyclase catalytic subunit isoforms (V, VI) and thereby maintains the cellular response to beta-adrenergic agonists and cAMP generation within normal limits.[71] Cardiac tissue contains both β_1- and β_2-adrenergic receptor subtypes. T_3 causes a rapid fourfold induction of cardiac β_1-receptor mRNA and a threefold increase in the number of cardiac β_1-receptors, which persists for 48 hours. T_3 administration influences β_2-receptor expression only minimally.[71]

Diagnosis of Thyroid Function Disorders

There is a battery of sensitive and specific laboratory tests that can establish a diagnosis of thyroid disease with a high degree of precision. The serum TSH level is the most widely used and sensitive measure for the diagnosis of thyroid dysfunction.[72] Serum TSH levels uniformly increase in patients with primary hypothyroidism (> 4.5 mU/L), and they are low (< 0.1 mU/L) in hyperthyroidism due to the feedback of excessive T_4 and T_3 serum levels on thyrotropin pituitary synthesis and secretion. In the presence of abnormal TSH levels, measurement of free thyroxine (FT_4) and total T_3 (TT_3) or free T_3 (FT_3) can distinguish subclinical from overt thyroid dysfunction.[55,72] Overt and subclinical hyperthyroidism result most commonly from increased thyroid hormone synthesis related to Graves' disease, toxic adenoma, or toxic multinodular goiter.[55,71] Hashimoto disease, prior thyroid surgery, and, in some parts of the world, iodine deficiency are the most common causes of hypothyroidism.[55]

Hemodynamic Alterations in Thyroid Disease

Changes in myocardial contractility and hemodynamics occur across the entire spectrum of thyroid disease (**Table 92.2 and see Fig. 92.5**). Multiple studies, including those in experimental animals, as well

as invasive and noninvasive measurements in humans, indicate that T_3 regulates cardiac inotropy and chronotropy through direct and indirect mechanisms.[54-56,62-65,71] T_3 acts on tissues throughout the body to increase myocardial oxygen consumption and tissue thermogenesis (**see Fig. 92.3**). Echocardiographic data indicate that, in humans, newly diagnosed thyrotoxicosis induces an improvement in left ventricular systolic function and an enhancement in left ventricular relaxation, diastolic flow velocities, and isovolumic relaxation time. T_3 decreases the systemic vascular resistance in arterioles of the peripheral circulation through direct effects on vascular smooth muscle cells. Moreover, thyrotoxicosis may augment the vascular endothelial generation of nitric oxide.[73-75] The drop in systemic vascular resistance results in a smaller left ventricular end-systolic volume. A decrease in mean arterial pressure and activation of the renin-angiotensin-aldosterone system with increased serum angiotensin-converting enzyme activity occurs, as does an increase in renal sodium reabsorption. The increase in plasma volume, coupled with an increase in erythropoietin, increases the blood volume. The combination of expanded blood volume and improvement in diastolic relaxation of the heart contributes to an increased left ventricular end-diastolic volume.[56] Despite the marked reduction in systemic vascular resistance, the pulsatile arterial load undergoes a compensatory change, and increased aortic input sustains the systolic arterial pressure.[56] The systolic arterial pressure almost invariably increases and diastolic arterial pressure decreases in patients with overt hyperthyroidism, so that the pulse pressure characteristically widens and the mean arterial pressure only marginally decreases.[56] Systolic hypertension may develop in up to 30% of hyperthyroid patients and is more pronounced in older patients.[54]

TABLE 92.2

Cardiovascular Changes with Thyroid Disease

PARAMETER	NORMAL	HYPERTHYROID	HYPOTHYROID
Systemic vascular resistance (dyne-cm · sec−5)	1500-1700	700-1200	2100-2700
Heart rate (beats/min)	72-84	88-130	60-80
Cardiac output (liters/min)	5.8	>7.0	<4.5
Blood volume (% of normal)	100	105.5	84.5

The net effect of an increased preload and a decreased afterload yields an increased left ventricular stroke volume in hyperthyroidism.[54-56] In turn, the rise in heart rate and the increased stroke volume combine to cause a twofold to threefold increase in cardiac output. Cardiac output may more than double in hyperthyroidism. Measurements of acetate metabolism by positron emission tomography have demonstrated that the marked increase in cardiac output in hyperthyroidism causes no change in energy efficiency.[54-56] In fact, the hyperthyroid heart increases its performance through the modulation of hemodynamic loads; this positive effect on energy metabolism and oxygen consumption improves the left ventricular mechanical efficiency, optimizing its cardiac mechanical-energetic consumption.[54-56]

Diametrically opposed hemodynamic changes occur in hypothyroidism (**see Table 92.2**). Left ventricular function falls reversibly in hypothyroidism. The cardiac preload decreases because of the impaired diastolic function and the decreased blood volume; the left ventricular ejection fraction at rest, during exercise, and during cardiopulmonary exercise testing declines and tends to improve with restoration of euthyroidism.[54-56] The afterload increases in patients with hypothyroidism as a result of increased systemic vascular resistance, arterial stiffness, and endothelial dysfunction. Systemic vascular resistance may increase as much as 30%, and the mean arterial pressure may rise in up to 20% of patients with diastolic hypertension.[54-56] Even mild hypothyroidism may decrease the endothelial-derived relaxing factors.[73-75] The diastolic hypertension in patients with hypothyroidism is associated with a low renin

level and a decrease in the hepatic synthesis of renin substrate. The cardiac output may decrease by as much as 30% to 40% in hypothyroidism.[54] Despite the decrease in cardiac output and contractility of the hypothyroid myocardium, studies of myocardial metabolism by positron emission tomography have shown that the hypothyroid myocardium is energy-inefficient despite the low level of overall oxygen consumption.[56,75] Indeed, an increased afterload is one of the major factors determining myocardial oxygen consumption.[75]

Hyperthyroidism

Cardiovascular symptoms are an integral clinical feature, and often one of the predominant clinical features, of patients with hyperthyroidism. Most patients experience palpitations resulting from increases in the rate and force of cardiac contractility. The increase in heart rate results from a decrease in parasympathetic stimulation and an increase in sympathetic tone. Heart rates higher than 90 beats/min at rest and during sleep occur commonly, the normal diurnal variation in heart rate is blunted, and the increase during exercise is exaggerated. Many hyperthyroid patients experience exercise intolerance and exertional dyspnea, caused in part by skeletal and respiratory muscle weakness.[71] The low vascular resistance and increased preload compromise the cardiac functional reserve, which cannot rise further to accommodate the demands imposed by submaximal or maximal exercise.[71,75]

A subset of thyrotoxic patients can experience angina-like chest pain. In older hyperthyroid patients with known or suspected coronary artery disease, the increase in cardiac work associated with the increase in cardiac output and cardiac contractility can produce myocardial ischemia, which can respond to beta-adrenergic–blocking agents (beta blockers) or restoration of a euthyroid state. Rare patients, usually younger women, experience a syndrome of chest pain at rest associated with ischemic electrocardiographic changes. Cardiac catheterization has demonstrated that most of these patients have angiographically normal coronary arteries, but coronary vasospasm similar to that found in variant angina can occur (**see also Chapters 61 and 89**). Myocardial infarction develops very rarely, and these patients appear to respond to calcium channel–blocking agents or nitroglycerin.

Hyperthyroidism is associated with a substantial degree of pulmonary hypertension (mean pulmonary artery systolic pressure > 50 mm Hg).[71,76,77] Pulmonary hypertension in turn places a significant degree of stress and afterload on the right ventricle, thus implying that although systemic vascular resistance decreases with thyrotoxicosis, pulmonary vascular resistance does not. Correction of hyperthyroidism usually reduces the pulmonary arterial pressure.[71,77] Severe pulmonary hypertension may also reverse completely after successful treatment of hyperthyroidism. In addition to the reduction in pulmonary blood flow, a specific vasoactive effect of methimazole may explain the improvement in the pulmonary vasculature hemodynamics after treatment of hyperthyroidism.[71,77]

Autoimmune Involvement of the Cardiovascular System in Patients with Graves' Disease and Hashimoto Disease

Hyperthyroidism and hypothyroidism occasionally are linked to autoimmune cardiovascular involvement. Pulmonary arterial hypertension, myxomatous cardiac valve disease, and irreversible dilated cardiomyopathy have been reported in patients with Graves' disease.[71,77] Pulmonary hypertension may result from immune-mediated endothelial damage.[71,77] Takotsubo cardiomyopathy is linked to severe thyrotoxicosis and may be a presenting manifestation of thyroid storm.[77]

Peripartum cardiomyopathy can occur in thyrotoxic African American women.[71,77] Patients with autoimmune thyroid disease may have anticardiolipin antibodies and antiphospholipid syndrome. Recent

reports have documented cerebrovascular ischemic symptoms in young, primarily Asian women with Graves' disease. This syndrome, *moyamoya disease*, is characterized by anatomic occlusion of the terminal portions of the internal carotid arteries and appears to improve both anatomically and symptomatically following treatment.

Atrial Fibrillation in Overt Hyperthyroidism (see also Chapter 38)

The most common rhythm disturbance in patients with hyperthyroidism is sinus tachycardia, but atrial fibrillation causes the most clinical concern. The prevalence of atrial fibrillation in patients with hyperthyroidism ranges from 2% to 20%, in contrast to 2.3% of cases of atrial fibrillation in the control population with normal thyroid function. The ability to restore thyrotoxic patients to a euthyroid state and sinus rhythm justifies TSH testing in most patients with a recent onset of otherwise unexplained atrial fibrillation or other supraventricular arrhythmias. Atrial fibrillation may be the first symptom of thyroid hormone excess in the elderly. Approximately 7% to 8% of middle-aged hyperthyroid patients may develop atrial fibrillation; this prevalence increases stepwise in each decade, with a peak at approximately 15% in patients older than 70 years and a prevalence of 20% to 40% in patients with underlying heart disease, coexistent ischemic heart disease, or heart valve disease.[78] Treatment of atrial fibrillation in the setting of hyperthyroidism includes beta-adrenergic blockade with a $beta_1$-selective or nonselective agent to control the ventricular response (**Table 92.3**).[79-82] Symptomatic relief can occur rapidly. According to the American College of Cardiology/American Heart Association, the first-line treatment of atrial fibrillation and heart failure in patients with thyroid dysfunction should aim primarily to restore a euthyroid state because cardiovascular drugs generally have a reduced efficacy in the face of thyroid hormone excess.[79] Therefore, treatment of hyperthyroidism with beta-adrenergic blockade followed by antithyroid drugs or radioiodine should be the first-line therapy in patients with overt hyperthyroidism and atrial fibrillation to obtain conversion to sinus rhythm and to improve hemodynamics.[81,82] Successful treatment of hyperthyroidism and restoration of normal serum levels of T_4 and T_3 results in reversion to sinus rhythm in two thirds of patients within 2 to 3 months.

TABLE 92.3

Beta-Adrenergic Receptor Blockade for the Treatment of Hyperthyroidism*

DRUG	DOSAGE	FREQUENCY	CONSIDERATIONS
Propranolol	10-40 mg	tid or qid	Nonselective β-AR blockade; longest experience
Atenolol	25-100 mg	bid	Relative beta1 selectivity; increased patient compliance
Metoprolol	25-50 mg	qid	Relative beta1 selectivity
Nadolol	40-160 mg	qd	Nonselective β-AR blockade; once daily; least experience to date
Esmolol	Intravenous pump, 50-100 μg/kg/min		In the ICU setting of severe hyperthyroidism or storm

*Each of these drugs has been approved for the treatment of cardiovascular diseases, but to date none has been approved for the treatment of hyperthyroidism.

β-AR, beta-adrenergic receptor; *ICU*, intensive care unit.

Digitalis may help to control the ventricular response in hyperthyroidism-associated atrial fibrillation, but because of the increased rate of digitalis clearance, the decreased sensitivity of drug action resulting from the high cellular levels of Na^+,K^+-ATPase, and the decreased parasympathetic tone, patients usually require higher doses. Anticoagulation, especially with the new non–vitamin K–dependent agents, in patients with hyperthyroidism and atrial fibrillation is controversial. The potential for systemic or cerebral embolization must be weighed against the risk for bleeding and complications.[80-82] Whether hyperthyroid patients have an increased risk for systemic embolization per se remains uncertain. Thus in

younger patients with hyperthyroidism and atrial fibrillation in the absence of other heart diseases, hypertension, or other independent risk factors for embolization (CHADS VASC score = 0), the benefits of anticoagulation have not been proved and might be outweighed by the risk.

Older patients or those with atrial fibrillation of longer duration have a lower rate of reversion to sinus rhythm.[71,82] In hyperthyroid patients who do not regain normal rhythm spontaneously within 4 months of normalization of thyroid function, pharmacologic or electrical cardioversion should be considered after evaluation of the age of the patient and the underlying cardiac status.[71,81-83] Many such patients will warrant anticoagulant therapy. In patients undergoing ablation to treat atrial fibrillation, the preprocedure reversal of abnormal thyroid function testing increases the short-term and long-term success rates.[81,82]

Heart Failure in Overt Hyperthyroidism

The cardiovascular alterations in hyperthyroidism include increased resting cardiac output and enhanced cardiac contractility (**see Table 92.2**). Nevertheless, a minority of patients have symptoms, including dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea, as well as signs demonstrating peripheral edema, elevated jugular venous pressure, or an S_3. This complex of findings, coupled with failure to increase the left ventricular ejection fraction with exercise, suggests a hyperthyroid cardiomyopathy.[75] The term often used in this setting, *high-output failure*, is not appropriate, because although the resting cardiac output is as much as two to three times normal, the exercise intolerance does not appear to result from cardiac failure but rather from skeletal muscle weakness and perhaps associated pulmonary hypertension.[54-56,66,75,77] High-output states, however, can increase the renal sodium reabsorption and expand the plasma volume. Although the systemic vascular resistance falls with hyperthyroidism, the pulmonary vascular resistance does not, and because of the greater output to the pulmonary circulation, the pulmonary artery pressure increases. This leads to a rise in mean venous pressure, hepatic congestion, and peripheral edema of the type associated with primary pulmonary hypertension or right-sided heart failure.

In patients with long-standing hyperthyroidism and marked sinus tachycardia or atrial fibrillation, a low cardiac output, impaired cardiac contractility with a low ejection fraction, an S_3, and pulmonary congestion can develop; all are consistent with heart failure.[54,56,75] Review of such cases suggests that the impairment in left ventricular function results from the prolonged high heart rate and the development of rate-related heart failure. When the left ventricle becomes dilated, mitral regurgitation may also develop (**see Chapter 69**). Recognition of this phenomenon has importance because treatment aimed at slowing the heart rate or controlling the ventricular response in atrial fibrillation appears to improve left ventricular function, even before initiation of antithyroid therapy. These patients are critically ill and should be managed in an intensive care unit setting. Some patients with hyperthyroidism, similar to the overall congestive heart failure population, do not tolerate initiation of beta blockers in full doses.[54,75]

Treatment of Overt Hyperthyroidism

Treatment of patients with thyrotoxic cardiac disease should include a beta-adrenergic antagonist to lower the heart rate to 10% or 15% above normal. Beta blockers improve the tachycardia-mediated component of ventricular dysfunction, but the direct inotropic effects of thyroid hormone will persist (**see Table 92.3 and see Fig. 92.4**). The rapid onset of action and improvement in many of the signs and symptoms of hyperthyroidism indicate that most patients with overt symptoms should receive beta blockers. Definitive therapy can then be accomplished safely with iodine-131 alone or in combination with an antithyroid drug.[80-82] A recent study affirmed the importance of definitive treatment with iodine-131 by showing that

such treatment is associated with lower cardiovascular mortality rates.[84] Pretreatment with methimazole may be considered before definitive treatment of hyperthyroidism with radioactive iodine or surgery in elderly patients.[80-82]

Thyroid storm, the most severe form of hyperthyroidism, can present with an altered mental status; fever; gastrointestinal symptoms, including pain, nausea, and rarely jaundice; and cardiovascular findings of exaggerated tachycardia, new-onset supraventricular arrhythmias such as atrial fibrillation, or hypotension and cardiovascular collapse. Untreated, the mortality rate from this condition may be as high as 50%, and outcomes vary based on management of the cardiovascular manifestations. These patients require intensive care unit monitoring in addition to the use of antithyroid drugs, potassium iodide, attention to other coexistent medical problems such as infection or trauma, and awareness of drugs they may be taking, such as amiodarone. These patients may tolerate intravenous administration of beta-adrenergic blocking drugs or calcium channel blockers poorly. The development of hypotensive cardiac arrest or worsening heart failure represents the untoward effects of such agents in patients with thyrotoxic heart disease. As noted above, intensive monitoring, judicious use of esmolol, and standard fluid and volume management with simultaneous treatment to lower T_4 and T_3 levels can optimize the therapeutic response (**see Table 92.3**).

Hypothyroidism

The prevalence of hypothyroidism is estimated to be 2% to 4% and increases with advancing age. In contrast to the dramatic clinical signs and symptoms of hyperthyroidism, the cardiovascular findings of hypothyroidism are more subtle.[54,55,63] Mild degrees of bradycardia, diastolic hypertension, a narrow pulse pressure and relatively quiet precordium, and decreased intensity of the apical impulse are all characteristic. Treatment of hypothyroid patients with restoration of a euthyroid state resolves these changes in parallel with the return of systemic vascular resistance to lower levels (**see Table 92.2**).

Hypothyroidism also increases total and low-density lipoprotein (LDL) cholesterol in proportion to the rise in serum TSH levels.[85] Although thyroid hormone can alter cholesterol metabolism through multiple mechanisms, including a decrease in biliary excretion, the primary mechanism involves changes in LDL metabolism caused by decreases in the hepatic LDL receptor number and reduced activity of cholesterol 7α-hydroxylase, an enzyme that lowers cholesterol levels.[85] One study reported that the liver-selective thyroid hormone agonist eprotirome can lower cholesterol levels in statin-treated patients, in support of this concept.[86]

The serum creatine kinase (CK) level rises from 50% to 10-fold in up to 30% of patients with hypothyroidism. Analysis of isoform specificity indicates that more than 96% is CK-MM, consistent with a skeletal muscle origin of the increased enzyme release.[87] The serum level of CK in patients with hypothyroidism after initiation of standard oral thyroid hormone replacement declines slowly with a half-life of approximately 14 days. An interesting issue is whether some patients with statin-induced myopathy have underlying thyroid disease as a contributing factor.[87] Both conditions have similar myopathy or myalgia symptoms (**Table 92.4**), and evaluation of these patients should include thyroid function testing with TSH.

TABLE 92.4

Clinical Characterization of Muscle Disease Syndromes

Hypothyroid Related
Myalgia: nonspecific muscle symptoms, cramping, especially nocturnal; variable creatine kinase (CK) level
Myopathy: impaired endurance, usually with elevation of the CK level; pseudomyotonia
Hoffmann syndrome: impaired function; pseudohypertrophy; often marked elevations in CK level
Statin Induced
Myopathy: any associated disease
Myalgia: muscle aches, weakness without elevation in CK level
Myositis: symptoms plus elevated CK level
Rhabdomyolysis: symptoms plus markedly elevated CK levels

Pericardial effusions can occur, and occasionally, they are large and cause the appearance of cardiomegaly on chest radiographs. Although rare, tamponade with hemodynamic compromise may occur. Echocardiography demonstrates small to moderate effusions in up to 30% of overtly hypothyroid patients; the effusions resolve over a period of weeks to months after initiation of thyroid hormone replacement.

As a result of changes in ion channel expression and parasympathetic tone the ECG in hypothyroidism may show sinus bradycardia, low voltage, and prolongation of the action potential duration and QT interval. The QT prolongation predisposes patients to ventricular arrhythmias, and in some patients with acquired torsades de pointes, the disorder has improved or completely resolved with thyroid hormone replacement.[54]

Increases in risk factors for atherosclerosis, including hypercholesterolemia, hypertension, endothelial dysfunction, and elevated levels of homocysteine, may elevate the risk for atherosclerosis and coronary and systemic vascular disease in patients with hypothyroidism (**see Chapters 45, 46, and 48**).[55,63] Myocardial perfusion scans have demonstrated abnormalities suggestive of myocardial ischemia, but these defects appear to resolve with thyroid hormone treatment. TSH screening can be advised for all adults, particularly patients with hypertension, hypercholesterolemia, hypertriglyceridemia, coronary or peripheral vascular disease, and unexplained pericardial or pleural effusions, as well as for various musculoskeletal syndromes or statin-associated myopathy.[88]

Treatment of Overt Hypothyroidism

Replacement doses of purified preparations of levo-thyroxine sodium (L-T_4) are the treatment of choice in hypothyroid patients.[89,90] The optimal replacement dose of levo-thyroxine should take into account both the age of the patient and the cause of hypothyroidism.[89] Indeed, the levo-thyroxine dosage should be lower in the elderly and higher in patients with more severe disease, particularly those who have undergone thyroidectomy or prior iodine treatment for Graves' disease.[89] In all patients, thyroid hormone replacement should suffice to restore the serum TSH level to normal so that patients are clinically and chemically euthyroid. The known effects of thyroid hormone on the heart and cardiovascular system do not support the concept that these patients benefit from maintenance of mild hypothyroidism.[89-91]

Treatment of hypothyroidism yields predictable responses, especially from a cardiovascular perspective. Stepwise thyroid hormone replacement with levo-thyroxine sodium incrementally decreases the serum TSH, serum cholesterol, and serum CK levels and improves left ventricular performance (**Fig. 92.6**). Patients younger than 50 years with no history of heart disease generally tolerate full replacement doses of levo-thyroxine (1.5 µg/kg/day) without concern for untoward cardiac effects. Patients older than 50 years with known or suspected coronary artery disease have more complicated issues.[89,90] Three major issues arise. The first is whether to perform coronary artery revascularization before initiating thyroid hormone replacement. If patients are not candidates for percutaneous intervention and have unstable

angina, left main coronary artery disease, or three-vessel disease with impaired left ventricular function, even in the setting of overt hypothyroidism, coronary artery bypass grafting can be performed. Rarely, a patient has sufficiently profound hypothyroidism to prolong bleeding times and partial thromboplastin times, a situation that requires preoperative supplementation of clotting factors. Thyroid hormone replacement can be delayed until the postoperative period, when it can be administered in full doses parenterally or orally.[89,90]

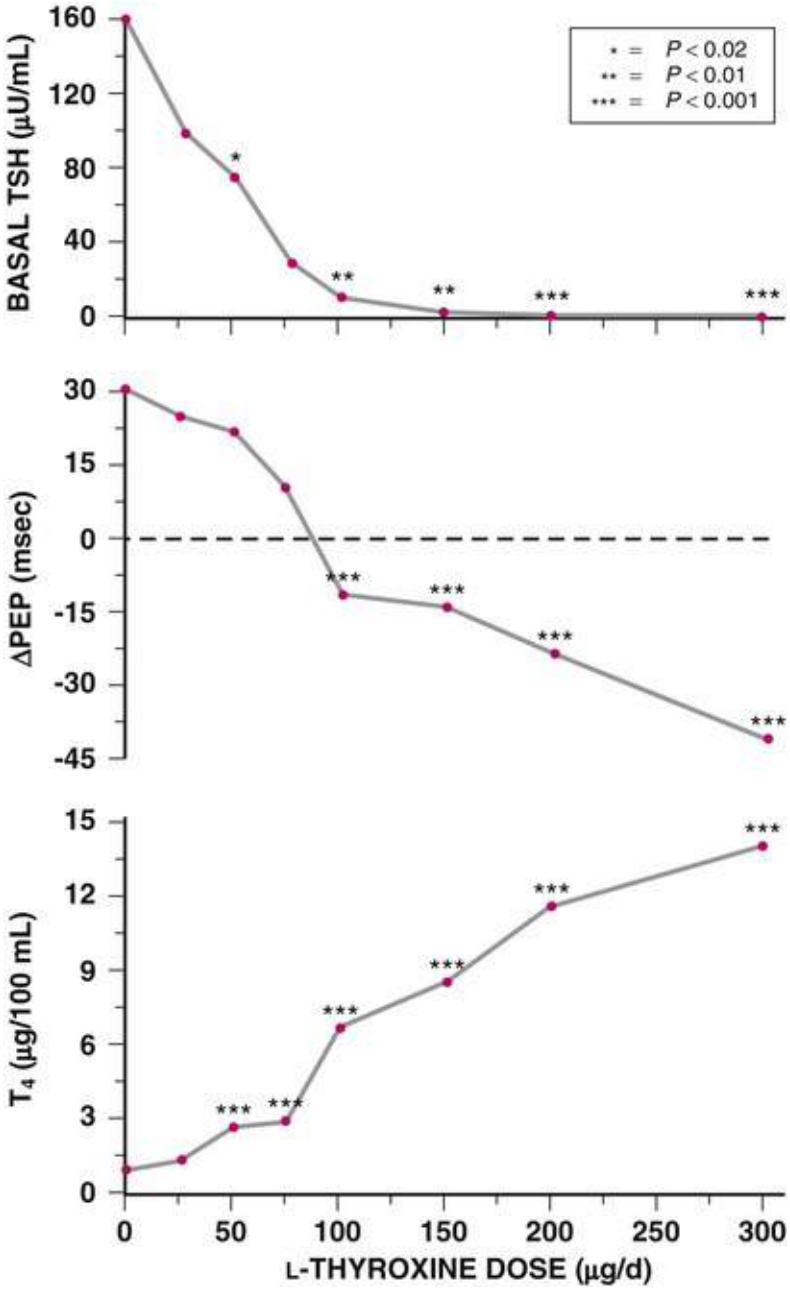

FIGURE 92.6 Response to stepwise levothyroxine sodium treatment of hypothyroid patients as assessed by serum TSH and T_4 levels and by improvement in left ventricular contractility as measured noninvasively by the change in the preejection period (ΔPEP). (From Crowley WF Jr, Ridgway EC, Bough EW, et al: Noninvasive evaluation of cardiac function in hypothyroidism: response to gradual thyroxine replacement. N Engl J Med 296:1, 1977.)

The second issue involves patients with known stable cardiac disease in whom cardiac revascularization is not clinically indicated. Treatment of such patients should begin with low doses (12.5 μg) of levo-thyroxine and then stepwise increases (12.5 to 25 μg) every 6 to 8 weeks until the serum TSH level normalizes.[89,90] Thyroid hormone replacement in this setting and its ability to lower systemic

vascular resistance and decrease afterload, as well as improve myocardial efficiency, can actually decrease clinical signs of myocardial ischemia. Beta blockers are an ideal concomitant therapy to control the heart rate.

The third important issue involves patients who although potentially at risk for coronary artery disease, exhibit no clinical signs or symptoms. In this group, thyroid hormone replacement can start at low doses, generally in the range of 25 to 50 µg/day, and then increase by 25 µg every 6 to 8 weeks until the serum TSH level is normal. If signs or symptoms of ischemic heart disease develop, the same recommendations apply as for patients with known underlying heart disease.[89,90] In the rare condition of *myxedema coma* characterized by the development of hypothermia, altered mental status, hypotension, bradycardia, and hypoventilation in patients with severe and long-standing hypothyroidism, the need for thyroid hormone replacement is more of an emergency.[89] Treatment can be accomplished by intravenous administration of 200 µg of L-T_4 followed by 100 µg of L-T_4 per day to restore vital functions in patients with severe coma. L-T_3 may also be started simultaneously with L-T_4 in a dosage of 10 to 20 µg, followed by 10 µg every 6 hours for 1 or 2 days until the patient's cerebral function improves.[89] Patients with myxedema coma require intensive care unit monitoring with volume repletion, gentle warming, and ventilatory support in the presence of CO_2 retention. Administration of hydrocortisone (50 to 100 mg three times daily) should be undertaken until the results of serum cortisol testing are obtained. When treated in this manner, the hemodynamics, including systemic vascular resistance, cardiac output, and heart rate, will improve within 24 to 48 hours. Severe hyponatremia should be corrected with the judicious administration of hypertonic saline solution (50 to 100 mL of 3% sodium chloride) followed by an intravenous bolus of 40 to 120 mg furosemide.

Subclinical Thyroid Disease

In contrast to overt symptomatic thyroid disease, subclinical thyroid disease implies the absence of classic hyperthyroid- or hypothyroid-related symptoms in patients with thyroid dysfunction. The definition now includes the demonstration of an abnormal TSH level in patients with normal serum levels of total T_4, free T_4, total T_3, and free T_3.[55] With the advent of widespread TSH screening, the magnitude of subclinical thyroid disease may exceed that of overt disease by threefold to fourfold.

Subclinical Hyperthyroidism

Subclinical hyperthyroidism is diagnosed when the serum TSH level is persistently subnormal or undetectable (TSH < 0.1 mU/L) and free thyroid hormone levels are in the mid-to-high range of their reference intervals. The prevalence of endogenous subclinical hyperthyroidism varies greatly depending on the diagnostic criteria, age, sex, and iodine intake of the population.[55] Subclinical hyperthyroidism may increase the left heart rate, ventricular mass, arterial stiffness, and left atrial size and may induce diastolic dysfunction, thereby impairing left ventricular performance.[55] Sinus tachycardia and atrial premature beats frequently occur in young patients, and in older patients (> 60 years), subclinical hyperthyroidism is not associated with symptoms of adrenergic overactivity; there may be associated weight loss, muscle weakness, and most importantly atrial fibrillation.[91-93] Data from all the available metaanalyses demonstrate that subclinical hyperthyroidism is associated with an increased risk of total mortality, coronary heart mortality, incident atrial fibrillation, and heart failure.[67,93] Based on these results, treatment of subclinical hyperthyroidism using methimazole can normalize the serum TSH. In the face of clinical improvement, radioiodine or surgery may be considered as definitive therapy in elderly patients with

persistently undetectable serum TSH levels. Some studies suggest that cardioselective β-blocker treatment may improve the heart rate, left ventricular mass, and diastolic dysfunction in young symptomatic patients.[81,82]

Subclinical hyperthyroidism may develop during L-T_4 therapy in doses that suppress the serum TSH. In some patients receiving thyroid hormone replacement for hypothyroidism, the low TSH level may be the result of unintentional excessive medication, requiring reduction of the L-T_4 dose. Intentional TSH–suppressive doses of levo-thyroxine are only indicated in patients with a previous diagnosis of thyroid cancer with a high risk of recurrences; the risks and -benefits of TSH suppression should be considered in older patients.[94]

Subclinical Hypothyroidism

Subclinical hypothyroidism is diagnosed when the serum TSH is above the upper limit of the normal reference range and free thyroid hormones are within their respective reference range.[55,89] It occurs in up to 4% to 20% of the adult population, and its prevalence increases with advancing age. Although a strong female predilection exists in younger patients, this difference diminishes in older populations. Patients may have mild disease (TSH 4.5 to 9.9 mU/L) or more severe dysfunction (TSH ≥ 10 mU/L). Hashimoto thyroiditis represents the most common cause of acquired subclinical hypothyroidism in the adult. Subclinical hypothyroidism can impair left ventricular diastolic function (**see Fig. 92.5**) and left ventricular systolic and diastolic dysfunction on effort. It can also alter the lipid metabolism, thereby altering the endothelial function and leading to an increased risk of heart failure, atherosclerosis, and coronary heart disease.[55,89]

Two recent metaanalyses assessed individual participant data from the available prospective cohort studies and demonstrated a significant trend of increased risk of heart failure and coronary heart disease events and mortality at higher serum TSH concentrations, particularly in participants with a TSH level of 10 mU/L or greater.[67,95] Therefore, despite the lack of definitive long-term studies on the outcome of mild-to-moderate hypothyroidism with and without replacement therapy, recommendations for treatment of patients with a serum TSH level of 10 mIU/L or higher have fallen on the side of replacement treatment with levo-thyroxine.[90,96] A recent study from the United Kingdom's General Practitioners database showed that treatment of TSH levels between 5 and 10 mIU/mL lowered the incidence of ischemic heart disease events and cardiovascular mortality in patients younger than 70 years.[97] These findings suggest the consideration of treatment of mild disease, particularly in young patients with evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors for these diseases.[55]

Amiodarone and Thyroid Function (see also Chapter 36)

Amiodarone is an iodine-rich antiarrhythmic agent used for the treatment of ventricular and atrial tachyarrhythmias. Its 30% iodine content by weight and its structural similarity to levo-thyroxine cause abnormalities in thyroid function test results in as many as 60% of patients treated for short or long periods.[98] The finding that dronedarone, a noniodinated benzofuran antiarrhythmic, does not alter thyroid function reinforces this concept. Similar to other iodinated drugs, amiodarone inhibits the 5′-monodeiodination of T_4 in the liver and pituitary. Inhibition of T_4 metabolism in the liver decreases serum T_3 levels and increases serum T_4 levels, whereas serum TSH levels initially remain normal. With more chronic treatment and as the total iodide content in the body rises, T_4 synthesis and release from the thyroid gland can be inhibited, thereby producing a rise in TSH levels. Patients with underlying goiter,

autoimmune thyroid disease, or enzymatic defects in thyroid hormone biosynthesis and even some patients without any risk factors can progress to overt chemical and clinical hypothyroidism with a marked rise in serum TSH levels. The overall prevalence of hypothyroidism in amiodarone-treated patients is between 15% and 30%. Symptoms of hypothyroidism in this setting can be subtle, and significant hypothyroidism can occur even in their absence.

Thyroid function should be measured every 3 months in all patients receiving amiodarone (**Fig. 92.7**). The effect on thyroid function does not depend on the dose and can occur at any time after initiating treatment; furthermore, because of the high lipid solubility and long half-life of amiodarone, this effect can persist up to 1 year after discontinuing therapy.

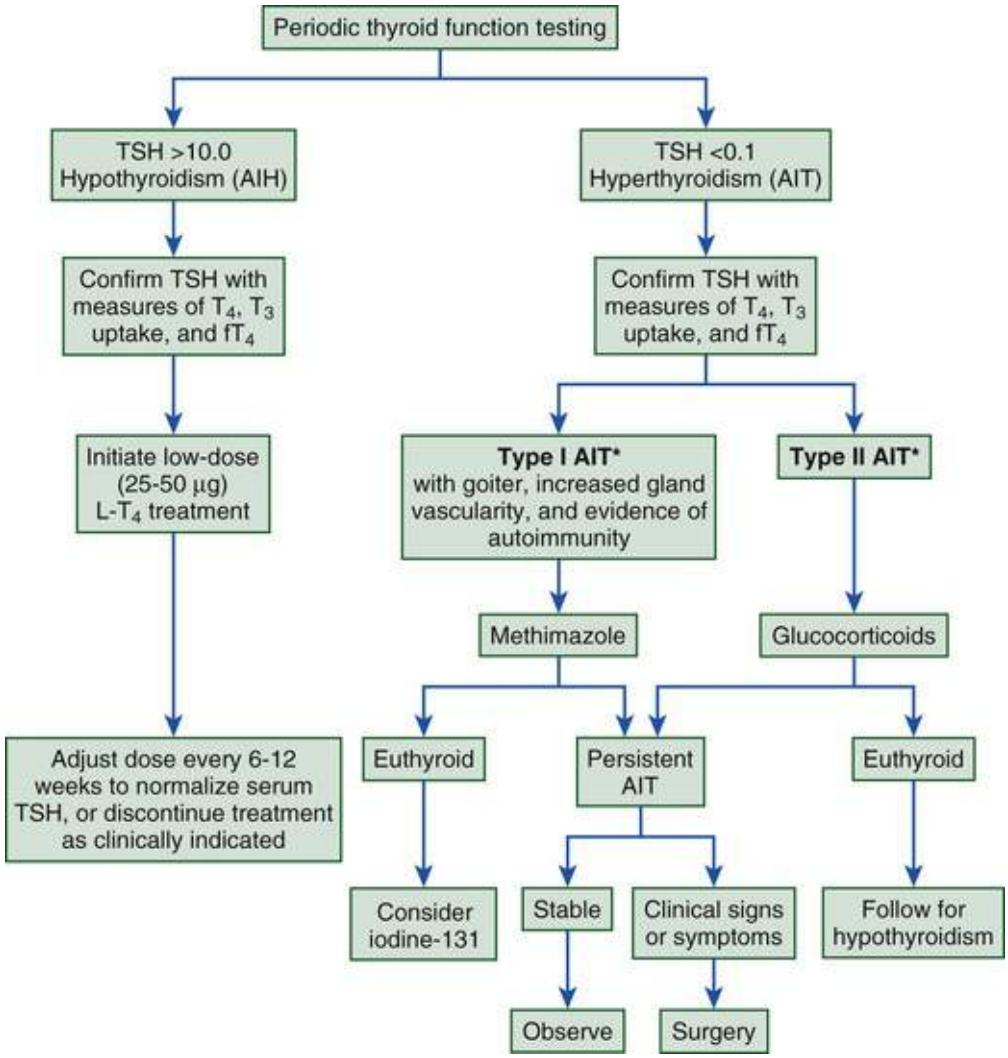

FIGURE 92.7 Amiodarone-induced thyrotoxicosis (AIT) can be diagnosed on the basis of classic signs and symptoms of hypothyroidism or hyperthyroidism or, more commonly, by routine (every 3 to 6 months) thyroid function testing. Any single abnormal TSH level should be confirmed. Clinical hypothyroidism with a TSH level higher than 10 mIU/mL should be treated. AIT management is described and depends on the severity and duration of clinical findings. *Mixed types I and II of AIT may require combination therapy with thionamides and corticosteroids. AIH, amiodarone-induced hypothyroidism; fT_4, free T_4.

Less common but perhaps more challenging is the development of *amiodarone-induced thyrotoxicosis*.[99] Although not initially observed in the iodine-replete American population, the experience from more iodine-deficient populations (as in Italy) suggested that it occurs with a prevalence as high as 10%. The onset was often sudden and could occur shortly after initiation of amiodarone therapy, during chronic treatment, or up to 1 year after stopping therapy. Clinical clues to the development

of this condition include a new onset or recurrence of ventricular irritability (increased firing of an implantable cardioverter-defibrillator), decreased warfarin dose requirements, or return or worsening of the obstructive physiology of hypertrophic cardiomyopathy (**see also Chapter 78**).

Although the pathogenesis is multifactorial, early studies distinguished two forms of amiodarone-induced thyrotoxicosis.[99] Type I occurs primarily in patients with preexisting thyroid disease and most commonly in iodine-deficient areas. These patients may rarely have an increase in 24-hour radioiodine uptake and frequently some measures of thyroid autoimmunity, including antithyroid antibodies. In contrast, a variety of proinflammatory cytokines, including IL-6, presumably mediate type II thyroiditis. It is primarily a destructive process causing release of preformed thyroid hormone, which may continue for weeks or months and most often is associated with low-to-absent radioiodine uptake. Further experience has shown that these two types have substantial overlap in many of the distinguishing features. Amiodarone-induced thyrotoxicosis is associated with a threefold increased risk for major adverse cardiovascular events, underscoring its clinical importance.[100] **Fig. 92.7** proposes a scheme for following thyroid function testing for patients treated with amiodarone.

Because of the increased thyroidal and total-body iodine content, use of iodine-131 is almost always ineffective. Similarly, treatment with antithyroid drugs has marginal effectiveness. Corticosteroids (prednisone 20 to 40 mg/day) provide benefit, perhaps with increased usefulness in patients with type II disease who have high serum levels of IL-6. However, corticosteroids can be instituted in all patients because when effective, the response usually occurs within 2 to 4 weeks of initiating treatment. In patients unresponsive to glucocorticoids with evidence of hyperthyroidism—including weight loss, tachycardia, palpitations, worsening angina, ventricular tachycardia, or other untoward cardiac effects—treatment with antithyroid therapy (methimazole 10 to 30 mg/day) is variably effective and can cause considerable side effects. Total thyroidectomy can be performed safely and can rapidly reverse the hyperthyroidism.[101] Preoperative treatment with beta blockers is indicated, and there have been no reported cases of resulting thyroid storm. Whether amiodarone-mediated thyroid dysfunction should mandate discontinuation of therapy with the drug is an important issue. There is no evidence that stopping treatment with amiodarone hastens the resolution of chemical hyperthyroidism.

Changes in Thyroid Hormone Metabolism That Accompany Cardiac Disease

In addition to the changes in thyroid function that can result from classic thyroid disease, primary alterations in levels of serum total and free T_3 and occasionally in serum T_4 can accompany a variety of acute and chronic illnesses, including sepsis, starvation, and cardiac disease. In the absence of thyroid gland abnormalities, changes in serum T_3 levels result from alterations in thyroid hormone metabolism. Some refer to such cases as nonthyroidal illness. The mechanism for this decrease in serum T_3 levels is multifactorial and in part related to a decrease in 5′-monodeiodination in the liver. Up to 30% of patients with heart failure have a low serum T_3 level, a finding in patients treated with or without amiodarone. In patients with congestive heart failure, the fall in serum T_3 levels is correlated with the severity of heart failure as assessed by the New York Heart Association classification.[102-105] In addition, in patients with heart failure and preserved ejection fraction, the serum level of T_3 was inversely proportional to the level of pro-brain natriuretic peptide. In view of the deleterious effects of hypothyroidism on the myocardium, T_3 replacement may provide benefit. A population-based study of patients with cardiac disease showed that a low serum T_3 level strongly predicts all-cause and cardiovascular mortality rates. These

observations led to studies examining the administration of L-T_4, L-T_3, or thyroid hormone analogs in patients with heart failure to potentially improve their prognosis. L-T_3 infusion in patients with chronic and stable dilated cardiomyopathy and low-T_3 syndrome improved cardiac performance and the neurohumoral milieu without a significant increase in myocardial O_2 consumption.[103,105]

Following uncomplicated acute myocardial infarction, serum T_3 levels fall by about 20% and reach a nadir after approximately 96 hours. Experimental myocardial infarction in animals produces a similar decrease in serum T_3 levels, and replacement of T_3 levels to normal may increase left ventricular contractile function. Children and adults undergoing cardiac surgery with cardiopulmonary bypass demonstrate a predictable fall in serum T_3 levels in the perioperative period.[106] Although treatment strategies involving acute intravenous administration of T_3 to adults after coronary bypass graft surgery have shown improvement in cardiac output and a decrease in systemic vascular resistance, overall mortality rates did not change. In this group of patients, atrial fibrillation decreased by as much as 50% when compared with age-matched controls.[106] Pediatric cardiac patients, especially those undergoing surgery in the neonatal period, demonstrate an even greater decline in serum T_3 levels that can last longer. A low postoperative T_3 level identifies patients at increased risk for morbidity and mortality. A prospective, randomized study has shown that especially in neonates, administration of T_3 in doses sufficient to restore serum T_3 levels to normal decreases the degree of therapeutic intervention and the need for postoperative inotropic agents.[107]

Future Perspectives

The knowledge that a variety of naturally occurring hormones have such profound effects on the heart and cardiovascular system suggests that these actions can be harnessed to treat a variety of cardiovascular diseases. The ability of thyroid hormone to lower cholesterol levels and enhance cardiac contractility (especially diastolic function) via novel transcription-based mechanisms, and at the same time lower the systemic vascular resistance, provides a platform for developing novel therapies. In addition, the recognition that growth hormone and serum T_3 levels are altered in the setting of various forms of cardiac disease and heart failure can provide new biomarkers for assessing novel treatment strategies.

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Pituitary Function and Cardiovascular Disease

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*For references to the older literature, please consult the tenth edition of *Braunwald's Heart Disease*, **Chapter 81**.

93

Hemostasis, Thrombosis, Fibrinolysis, and Cardiovascular Disease

Jeffrey I. Weitz

Hemostasis preserves vascular integrity by balancing the physiologic processes that maintain blood fluidity under normal circumstances and prevent excessive bleeding after vascular injury. Preservation of blood fluidity depends on an intact vascular endothelium and a complex series of regulatory pathways that maintain platelets in a quiescent state and keep the coagulation system in check. In contrast, arrest of bleeding requires rapid formation of hemostatic plugs at sites of vascular injury to prevent exsanguination. Perturbation of hemostasis can lead to thrombosis, which can occur in arteries or veins and causes considerable morbidity and mortality. Arterial thrombosis is the most common cause of acute coronary syndrome, ischemic stroke, and limb gangrene, whereas thrombosis in the deep veins of the leg leads to postthrombotic syndrome and pulmonary embolism (**see also Chapter 84**).

Most arterial thrombi form on top of disrupted atherosclerotic plaques because plaque rupture exposes thrombogenic material in the core to blood (**see also Chapter 44**). This material then triggers platelet aggregation and fibrin formation, which results in the generation of a platelet-rich thrombus that temporarily or permanently occludes blood flow.[1] The consequent reduction in blood flow can cause acute coronary syndrome, transient ischemic attack, or ischemic stroke.

In contrast to arterial thrombi, venous thrombi rarely form at sites of obvious vascular disruption.[2] Although venous thrombi can develop after surgical trauma to veins or arise due to indwelling venous catheters, they usually originate in valve cusps of the deep veins of the calf or in muscular sinuses, which can cause stasis. Sluggish blood flow in these veins reduces oxygen supply to the avascular valve cusps. Hypoxemia induces endothelial cells lining the valve cusps to express adhesion molecules, which tether tissue factor–bearing leukocytes and microparticles onto their surface. Tissue factor–bearing leukocytes and microparticles adhere to these activated cells and induce coagulation.[3] In addition, webs of DNA released from activated neutrophils, called neutrophil extracellular traps (NETs), also contribute to thrombosis by providing a scaffold that binds platelets and promotes their activation and aggregation.[4] Impaired blood flow exacerbates local thrombus formation by reducing clearance of activated clotting factors. Thrombi that extend into the proximal veins of the leg can dislodge and travel to the lungs to produce pulmonary embolism.

Arterial and venous thrombi contain platelets and fibrin, but the proportions differ. Arterial thrombi are rich in platelets because of high shear in the injured arteries.[1] In contrast, venous thrombi, which form under low-shear conditions, contain relatively few platelets and consist mostly of fibrin and trapped red cells.[3] Because of the predominance of platelets, arterial thrombi appear white, whereas venous thrombi appear red because of the trapped red cells.

The antithrombotic drugs used for prevention and treatment of thrombosis target components of thrombi and include antiplatelet drugs, which inhibit platelets; anticoagulants, which attenuate coagulation; and fibrinolytic agents, which induce fibrin degradation (**Fig. 93.1**). With the predominance of platelets in arterial thrombi, strategies to inhibit or treat arterial thrombosis focus mainly on antiplatelet agents, although in the acute setting, anticoagulants and fibrinolytic agents may also be used. For occlusive arterial thrombi that require rapid restoration of blood flow, mechanical and/or pharmacologic methods enable thrombus extraction, compression, or degradation. Although rarely used for this indication, warfarin prevents recurrent ischemic events after acute myocardial infarction. The recent observations that the addition of low-dose rivaroxaban, an oral factor Xa inhibitor, to dual-antiplatelet therapy reduces recurrent ischemic events and stent thrombosis in patients with acute coronary syndrome, whereas its addition to aspirin reduces the risk of major adverse coronary and limb events in patients with stable coronary or peripheral artery disease, highlight the potential usefulness of anticoagulants on top of antiplatelet agents for secondary prevention (**see also Chapters 59 and 60**).

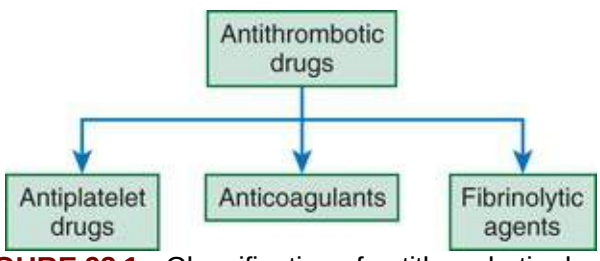

FIGURE 93.1 Classification of antithrombotic drugs.

Anticoagulants are the mainstay for prevention and treatment of venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism.[3] Antiplatelet drugs are less effective than anticoagulants for prevention of venous thrombosis because of the limited platelet content of venous thrombi. Nonetheless, when given for secondary prevention, aspirin produces about a 30% reduction in risk for recurrent VTE,[5,6] a finding that highlights the overlap between venous and arterial thrombosis. Selected patients with VTE benefit from fibrinolytic therapy[6]; for example, patients with massive pulmonary embolism achieve more rapid restoration of pulmonary blood flow with systemic or catheter-directed fibrinolytic therapy than with anticoagulant therapy alone (**see Chapter 84**). Similarly, some patients with extensive iliac and/or femoral vein thrombosis may have a better outcome with catheter-directed fibrinolytic therapy and/or mechanical thrombus extraction in addition to anticoagulants.

This chapter reviews hemostasis and thrombosis and highlights the processes involved in platelet activation and aggregation, blood coagulation, and fibrinolysis. It reviews the major components of the hemostatic system: the vascular endothelium, platelets, and coagulation and fibrinolytic systems. The chapter then focuses on antiplatelet, anticoagulant, and fibrinolytic drugs in common use. It also provides a brief overview of new antithrombotic drugs in advanced stages of development.

Hemostatic System

Vascular Endothelium (see also Chapter 44)

A monolayer of endothelial cells lines the intimal surface of the circulatory tree and separates blood from the prothrombotic subendothelial components of the vessel wall. Accordingly, the vascular endothelium encompasses about 10^{13} cells and covers a vast surface area. Rather than serving as a static barrier, healthy vascular endothelium dynamically regulates hemostasis by inhibiting platelets, suppressing coagulation, and promoting fibrinolysis.

Platelet Inhibition

Endothelial cells synthesize prostacyclin and nitric oxide and release them into blood. These mediators not only serve to potently vasodilate but also inhibit platelet activation and subsequent aggregation by stimulating adenylate cyclase and increasing intracellular levels of cyclic adenosine monophosphate (cAMP). In addition, endothelial cells express the ecto-adenosine diphosphatase (ecto-ADPase) CD39 on their surface. This membrane-associated enzyme attenuates platelet activation by degrading ADP.[7]

Anticoagulant Activity

Intact endothelial cells actively regulate thrombin generation. Endothelial cells express heparan sulfate proteoglycans on their surface. Like medicinal heparin, heparan sulfate binds circulating antithrombin and enhances its activity. Heparan sulfate proteoglycans also bind tissue factor pathway inhibitor (TFPI), a naturally occurring inhibitor of coagulation.[8] Additional TFPI becomes tethered to the endothelial cell surface via glycosylphosphatidylinositol anchors. Administration of heparin or low-molecular-weight heparin (LMWH) displaces glycosaminoglycan-bound TFPI from the vascular endothelium, and the released TFPI may contribute to the antithrombotic activity of these drugs by inhibiting tissue factor–bound factor VIIa in a factor Xa–dependent fashion.

Endothelial cells are central to the protein C anticoagulant pathway because they express thrombomodulin and endothelial cell protein C receptor (EPCR) on their surfaces.[9] The protein C

pathway is initiated when thrombin binds to thrombomodulin. Once bound, the substrate specificity of thrombin is altered such that it no longer acts as a procoagulant but becomes a potent activator of protein C (**Fig. 93.2**). Activated protein C serves as an anticoagulant by degrading and inactivating activated factor V and factor VIII (factors Va and VIIIa, respectively), key cofactors involved in thrombin generation, a reaction enhanced by protein S. EPCR on the endothelial cell surface promotes this pathway by binding protein C and presenting it to the thrombin-thrombomodulin complex for activation.[9]

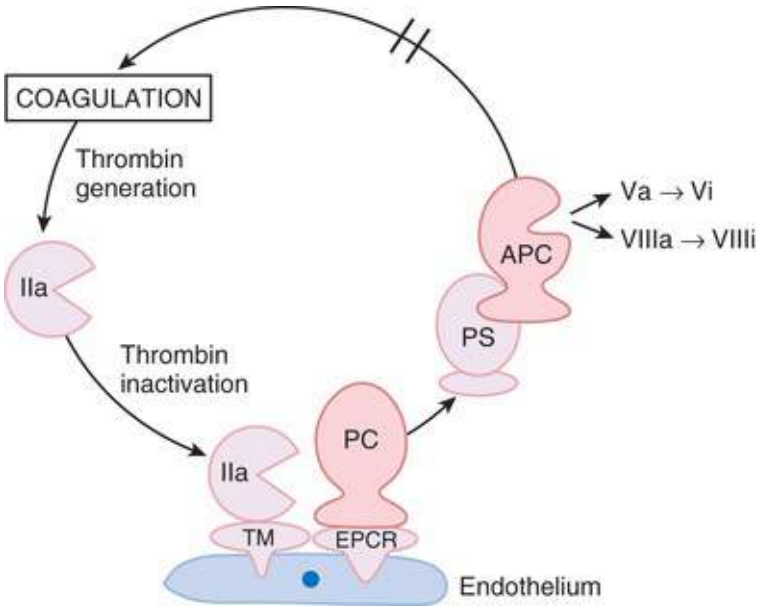

FIGURE 93.2 Protein C pathway. Activation of coagulation triggers thrombin (IIa) generation. Excess thrombin binds to thrombomodulin (TM) on the endothelial cell surface. Once bound, the substrate specificity of thrombin is altered such that it no longer acts as a procoagulant but becomes a potent activator of protein C (PC). The endothelial cell protein C receptor (EPCR) binds protein C and presents it to thrombomodulin-bound thrombin for activation. Activated protein C (APC), together with its cofactor protein S (PS), binds to the activated platelet surface and proteolytically degrades factors Va and VIIIa into inactive fragments (Vi and VIIIi). Degradation of these activated cofactors inhibits thrombin generation *(double bar).*

Fibrinolytic Activity

The vascular endothelium modulates fibrinolysis by synthesizing and releasing tissue and urokinase plasminogen activators (t-PA and u-PA, respectively), which initiate fibrinolysis by converting plasminogen to plasmin.[10] Whereas endothelial cells constitutively express t-PA, they produce u-PA in the settings of inflammation and wound repair. Endothelial cells also produce type 1 plasminogen activator inhibitor (PAI-1), the major regulator of both t-PA and u-PA. Therefore, net fibrinolytic activity depends on the dynamic balance between the release of plasminogen activators and PAI-1. Fibrinolysis localizes to the endothelial cell surface because these cells express annexin II, a coreceptor for plasminogen and t-PA that promotes their interaction. Hence, healthy vessels actively resist thrombosis and help maintain platelets in a quiescent state.[10]

Platelets

Platelets enter the circulation after the fragmentation of bone marrow megakaryocytes. Because they are lack nuclei, platelets have a limited capacity to synthesize proteins. Thrombopoietin, a glycoprotein

synthesized in the liver and kidneys, regulates megakaryocytic proliferation and maturation, as well as platelet production.[11] Once they enter the circulation, platelets have a life span of 7 to 10 days.

Damage to the intimal lining of the vessel exposes the underlying subendothelial matrix. Platelets home to sites of vascular disruption and adhere to the exposed matrix proteins. Adherent platelets undergo activation and not only release substances that recruit additional platelets to the site of injury, but also promote thrombin generation and subsequent fibrin formation (**Fig. 93.3**). A potent platelet agonist, thrombin amplifies platelet recruitment and activation. Activated platelets then aggregate to form a plug that seals the leak in the vasculature. An understanding of the steps in these highly integrated processes helps pinpoint the sites of action of antiplatelet drugs and rationalizes the usefulness of anticoagulants for the treatment of arterial and venous thrombosis.

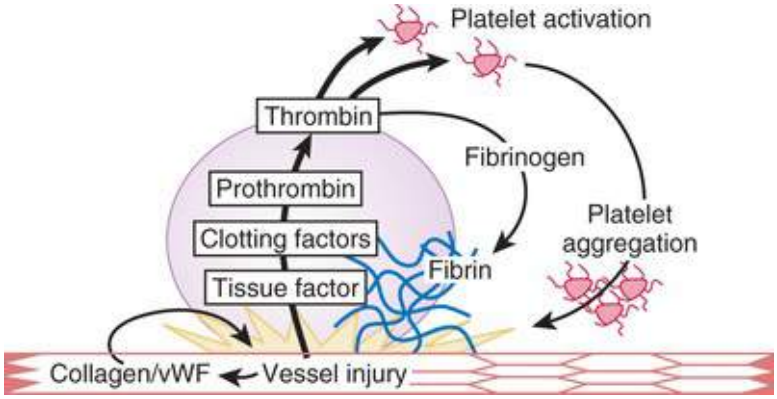

FIGURE 93.3 Central role of thrombin in thrombogenesis. Vascular injury simultaneously triggers platelet adhesion and activation, as well as activation of the coagulation system. Platelet activation is initiated by exposure of subendothelial collagen and von Willebrand factor (vWF), onto which platelets adhere. Adherent platelets become activated and release ADP and thromboxane A_2, platelet agonists that activate ambient platelets and recruit them to the site of injury. Coagulation, which is triggered by tissue factor exposed at the site of injury and enhanced by assembly of clotting factor complexes on the activated platelet surface, results in thrombin generation. Thrombin not only converts fibrinogen to fibrin but also serves as a potent platelet agonist. When platelets are activated, glycoprotein (GP) IIb/IIIa on their surfaces undergoes a conformational change that endows it with the capacity to ligate fibrinogen and mediate platelet aggregation. Fibrin strands then weave the platelet aggregates together to form a platelet/fibrin thrombus.

Adhesion

Platelets adhere to exposed collagen and von Willebrand factor (vWF) and form a monolayer that supports and promotes thrombin generation and subsequent fibrin formation.[12] These events depend on constitutively expressed receptors on the platelet surface, $\alpha_{2\beta1}$ and glycoprotein VI (GP VI), which bind collagen, and GP Ibα and GP IIb/IIIa ($\alpha_{IIb\beta3}$), which bind vWF. Receptors crowd the platelet surface, but those involved in adhesion are the most abundant; every platelet has approximately 80,000 copies of GP IIb/IIIa and 25,000 copies of GP Ibα. Receptors cluster in cholesterol-enriched subdomains, which render them more mobile, thereby increasing the efficiency of platelet adhesion and subsequent activation.[13]

Under low-shear conditions, collagen can capture and activate platelets on its own. The captured platelets undergo cytoskeletal reorganization, which causes them to flatten out and adhere more closely to the damaged vessel wall. Under high-shear conditions, however, collagen and vWF must act in concert to support optimal platelet adhesion and activation. The vWF synthesized by endothelial cells and megakaryocytes assembles into multimers that range in size from 550 kDa to greater than 10,000 kDa.[14]

When released from storage in the Weibel-Palade bodies of endothelial cells or the alpha-granules of platelets, most of the vWF enters the circulation, but the vWF released from the abluminal surface of endothelial cells accumulates in the subendothelial matrix, where it binds collagen via its A3 domain. This surface-immobilized vWF can simultaneously bind platelets via its A1 domain. In contrast, circulating vWF does not react with unstimulated platelets. This difference in reactivity reflects the conformation of vWF; circulating vWF is in a coiled conformation, which prevents access of its platelet-binding domain to vWF receptors on the platelet surface, whereas immobilized vWF assumes an elongated shape, which exposes the platelet-binding A1 domain. In their extended conformation, large vWF multimers act as the molecular glue that tethers platelets to the damaged vessel wall with sufficient strength to withstand a higher shear force. Large vWF multimers provide additional binding sites for collagen and heighten platelet adhesion because platelets have more vWF receptors than collagen receptors.[14,15] Adhesion to collagen or vWF results in platelet activation, the next step in platelet plug formation.

Activation

Adhesion to collagen and vWF initiates signaling pathways that result in platelet activation. These pathways induce cyclooxygenase-1 (COX-1)-dependent synthesis and release of thromboxane A_2 and trigger the release of ADP from storage granules. Thromboxane A_2 is a potent vasoconstrictor and, like ADP, locally activates ambient platelets and recruits them to the site of injury, thereby expanding the platelet plug. To activate platelets, thromboxane A_2 and ADP must bind to their respective receptors on the platelet membrane. The thromboxane receptor (TP) is a G protein–coupled receptor that is found on platelets and the endothelium, which explains why thromboxane A_2 induces vasoconstriction as well as platelet activation.[16] ADP interacts with a family of G protein–coupled receptors on the platelet membrane.[17,18] The most important of these is $P2Y_{12}$, which is the target of the thienopyridines (clopidogrel and prasugrel) and ticagrelor. $P2Y_1$ also contributes to ADP-induced platelet activation such that maximal ADP-induced platelet activation requires activation of both receptors. A third ADP receptor, $P2X_1$, is an adenosine triphosphate (ATP)-gated calcium channel. Platelet storage granules contain ATP, as well as ADP; the ATP released during the platelet activation process may contribute to the platelet recruitment process in a $P2X_1$-dependent fashion.

Although TP and the various ADP receptors signal through different pathways, they all trigger an increase in the intracellular concentration of calcium in platelets. The increase in calcium induces changes in platelet shape via cytoskeletal rearrangement, granule mobilization and release, and subsequent platelet aggregation. Activated platelets promote coagulation by expressing phosphatidylserine on their surface, an anionic phospholipid that supports the assembly of coagulation factor complexes. Once assembled, these clotting factor complexes trigger a burst of thrombin generation and subsequent fibrin formation. In addition to converting fibrinogen to fibrin, thrombin amplifies platelet recruitment and activation and promotes expansion of the platelet plug. Thrombin binds to protease-activated receptor types 1 and 4 (PAR-1 and PAR-4, respectively) on the platelet surface and cleaves their extended amino-terminal tail (**Fig. 93.4**), thereby generating new amino-termini that serve as tethered ligands that bind and activate the receptors.[19] Low concentrations of thrombin cleave PAR-1, whereas PAR-4 cleavage requires higher thrombin concentrations. Cleavage of either receptor triggers platelet activation.

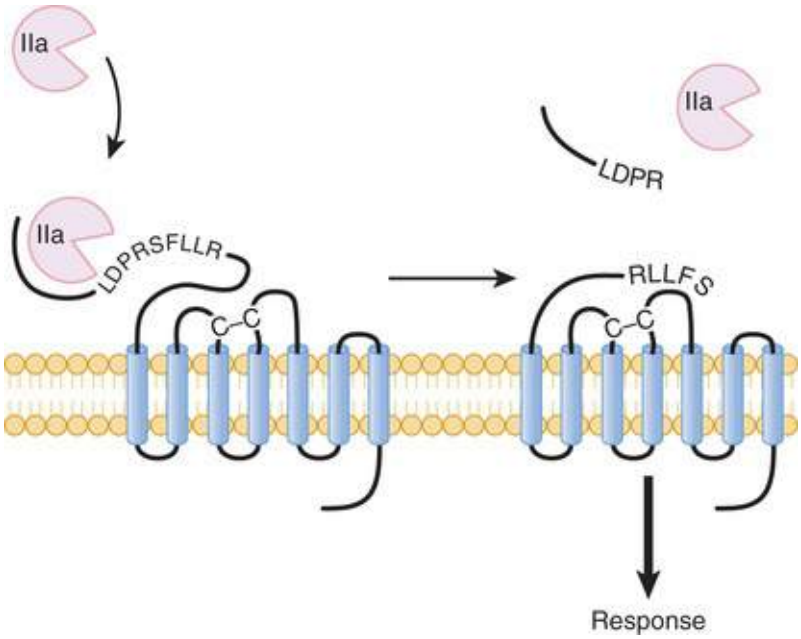

FIGURE 93.4 Activation of PAR-1 by thrombin. Thrombin (IIa) binds to the amino-terminal of the extracellular domain of PAR-1, where it cleaves a specific peptide bond. Cleavage of this bond generates a new amino-terminal sequence that acts as a tethered ligand and binds to the body of the receptor, thereby activating it. Thrombin then dissociates from the receptor. Analogues of the first five or six amino acids of the tethered ligand sequences, known as thrombin receptor agonist peptides, can independently activate PAR-1. *LDPRSFLLR*, Leu-Asp-Pro-Arg-Ser-Phe-Leu-Leu-Arg; *RLLFS*, Arg-Leu-Leu-Phe-Ser.

In addition to providing a surface on which clotting factors assemble, activated platelets also promote fibrin formation and subsequent stabilization by enhancing the factor V, factor VIII, factor XI and factor XIII. Thus, a coordinated activation of platelets and coagulation, and the fibrin network that results from the action of thrombin, help anchor the platelet aggregates at the site of injury. Activated platelets also release adhesive proteins, such as vWF, thrombospondin, and fibronectin, which may augment platelet adhesion at sites of injury, as well as growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β), which promote wound healing.

Platelet Aggregation

Aggregation is the final step in formation of the platelet plug by linking platelets to each other to form clumps. GP IIb/IIIa mediates these platelet-to-platelet linkages. On nonactivated platelets, GP IIb/IIIa exhibits minimal affinity for its ligands. Upon platelet activation, GP IIb/IIIa undergoes a conformational change that reflects transmission of inside-out signals from its cytoplasmic domain to its extracellular domain.[18] This transformation enhances the affinity of GP IIb/IIIa for its ligands, fibrinogen, and, under high-shear conditions, vWF. Arg-Gly-Asp (RGD) sequences located on fibrinogen and vWF, as well as a platelet-binding Lys-Gly-Asp (KGD) sequence on fibrinogen, mediate their interactions with GP IIb/IIIa. When subjected to high shear, circulating vWF elongates and exposes its platelet-binding domain, which enables its interaction with the conformationally activated GP IIb/IIIa.[15] Divalent fibrinogen and multivalent vWF molecules serve as bridges and bind adjacent platelets together. Once bound to GP IIb/IIIa, fibrinogen and vWF induce outside-inside signals that augment platelet activation and result in the activation of additional GP IIb/IIIa receptors, thus creating a positive feedback loop. Because GP IIb/IIIa serves as the final effector in platelet aggregation, it is a logical target for potent antiplatelet drugs. Fibrin, the ultimate product of the coagulation system, tethers the platelet aggregates together and anchors them to the site of injury.

Coagulation

Coagulation results in the generation of thrombin, which converts soluble fibrinogen to fibrin.[20] Coagulation occurs through the action of discrete enzyme complexes composed of a vitamin K–dependent enzyme and a nonenzyme cofactor that assemble on anionic phospholipid membranes in a calcium-dependent fashion. Each enzyme complex activates a vitamin K–dependent substrate that becomes the enzyme component of the subsequent complex (**Fig. 93.5**). Together, these complexes generate a small amount of thrombin that feeds back to amplify its own generation by activating the nonenzyme cofactors and platelets.[20] The phosphatidylserine expressed on the surface of activated platelets provides an anionic surface on which the complexes assemble. The three enzyme complexes involved in thrombin generation are extrinsic tenase, intrinsic tenase, and prothrombinase. Although extrinsic tenase initiates the system under most circumstances, the contact system also plays a role in some situations.

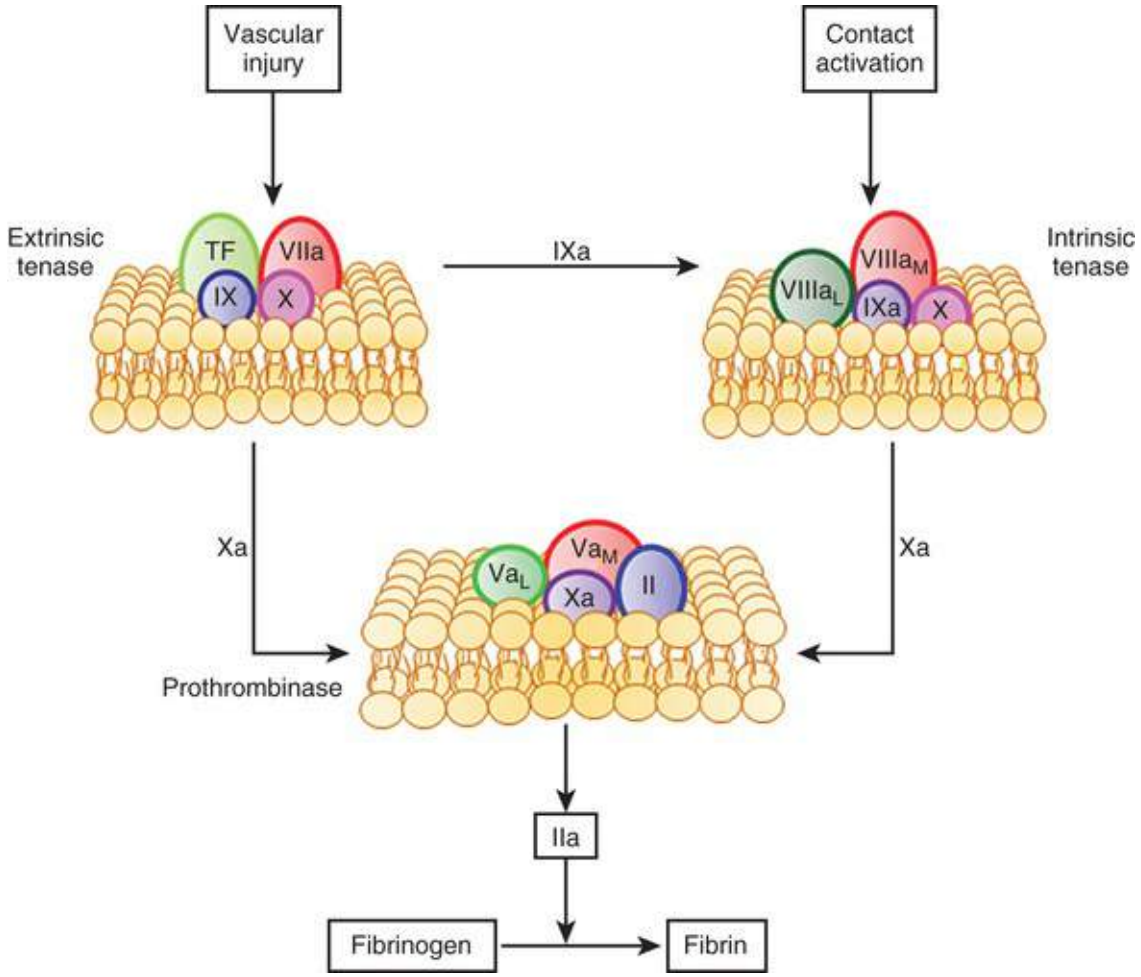

FIGURE 93.5 Coagulation system. Coagulation occurs through the action of discrete enzyme complexes composed of a vitamin K–dependent enzyme and a nonenzyme cofactor. These complexes assemble on anionic phospholipid membranes, such as the surface of activated platelets, in a calcium-dependent fashion. Vascular injury exposes tissue factor (TF), which binds factor VIIa to form extrinsic tenase. Extrinsic tenase activates factors IX and X. Factor IXa binds to factor VIIIa to form intrinsic tenase, which activates factor X. Factor Xa binds to factor Va to form prothrombinase, which converts prothrombin (II) to thrombin (IIa). Thrombin then converts soluble fibrinogen to insoluble fibrin.

Extrinsic Tenase

This complex forms on exposure of tissue factor–expressing cells to blood. Tissue factor exposure occurs

after atherosclerotic plaque rupture because the core of the plaque is rich in cells that express tissue factor. Denuding injury to the vessel wall also exposes the tissue factor constitutively expressed by subendothelial smooth muscle cells. In addition to cells in the vessel wall, circulating monocytes and monocyte-derived microparticles (small membrane vesicles) also provide a source of tissue factor.[21] When tissue factor–bearing monocytes or microparticles bind to platelets or other leukocytes and their plasma membranes fuse, transfer of tissue factor takes place. By binding to the adhesion molecules expressed on activated endothelial cells or to P-selectin on activated platelets, these tissue factor–bearing cells or microparticles can initiate or augment coagulation.[21] This phenomenon probably explains how venous thrombi develop in the absence of obvious vessel wall injury.[2]

An integral membrane protein, tissue factor serves as a receptor for factor VII. Once bound, factor VII undergoes autoactivation,[22] thereby forming the extrinsic tenase complex, which is a potent activator of factors IX and X. Upon activation, factors IXa and Xa serve as the enzyme components of intrinsic tenase and prothrombinase, respectively.

Intrinsic Tenase

Factor IXa binds to factor VIIIa on anionic cell surfaces to form the intrinsic tenase complex. Factor VIII circulates in blood in a complex with vWF. Thrombin cleaves factor VIII and releases it from vWF, thereby converting it to its activated form. Activated platelets express binding sites for factor VIIIa. Once bound, factor VIIIa binds factor IXa in a calcium-dependent fashion to form the intrinsic tenase complex, which then activates factor X. The change in catalytic efficiency of factor IXa–mediated activation of factor X that occurs with deletion of individual components of the intrinsic tenase complex highlights their importance. Absence of the membrane or factor VIIIa almost completely abolishes enzymatic activity, and the catalytic efficiency of the complete complex is 10^9-fold greater than that of factor IXa alone. Because intrinsic tenase activates factor X at a rate 50- to 100-fold faster than extrinsic tenase does, intrinsic tenase plays a critical role in the amplification of factor Xa and thrombin generation. The bleeding that occurs in patients with hemophilia, which is a congenital deficiency of factor VIII or factor IX, highlights the importance of intrinsic tenase in hemostasis.

Prothrombinase

Factor Xa binds to factor Va, its activated cofactor, on anionic phospholipid membrane surfaces to form the prothrombinase complex. Activated platelets release factor V from their alpha granules, and this platelet-derived factor V may play a more important role in hemostasis than its plasma counterpart does. Although plasma factor V requires thrombin activation to exert its cofactor activity, the partially activated factor V released from platelets already exhibits substantial cofactor activity. Activated platelets express specific factor Va binding sites on their surface, and bound factor Va serves as a receptor for factor Xa. The catalytic efficiency of activation of prothrombin by factor Xa increases by 10^9-fold when factor Xa is incorporated into the prothrombinase complex. Prothrombin binds to the prothrombinase complex, where it undergoes conversion to thrombin in a reaction that releases prothrombin fragment 1.2 (F1.2). Plasma levels of F1.2 therefore provide a marker of prothrombin activation.

Fibrin Formation

Thrombin, the final effector in coagulation, converts soluble fibrinogen to insoluble fibrin. Fibrinogen is a dimeric molecule, each half of which is composed of three polypeptide chains. the Aα, Bβ, and γ chains. Numerous disulfide bonds covalently link the chains together and join the two halves of the fibrinogen

molecule (**Fig. 93.6**). Electron micrographic studies of fibrinogen reveal a trinodular structure with a central E domain flanked by two D domains. Crystal structures show symmetry of design with the central E domain, which contains the amino-termini of the fibrinogen chains joined to the lateral D domains by coiled-coil regions.

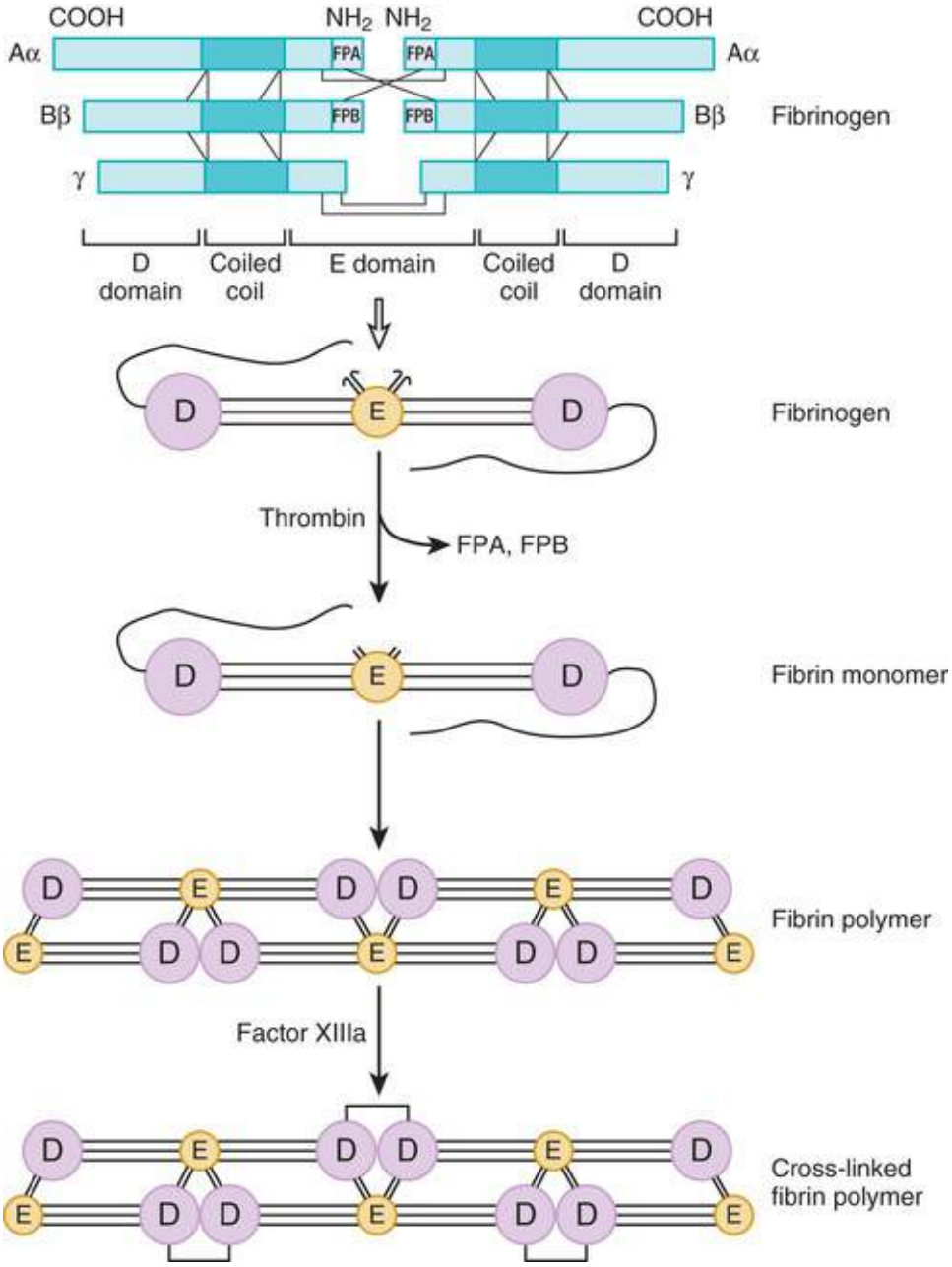

FIGURE 93.6 Fibrinogen structure and conversion of fibrinogen to fibrin. A dimer, each half of the fibrinogen molecule is composed of three polypeptide chains, the Aα, Bβ, and γ chains. Numerous disulfide bonds *(lines)* covalently link the chains together and join the two halves of the fibrinogen molecule to yield a trinodular structure with a central E domain linked via the coiled-coil regions to two lateral D domains. To convert fibrinogen to fibrin, thrombin cleaves specific peptide bonds at the amino (NH_2) terminals of the Aα and Bβ chains of fibrinogen to release fibrinopeptide A (FPA) and fibrinopeptide B (FPB), thereby generating fibrin monomer. Fibrin monomers polymerize to generate protofibrils arranged in a half-staggered overlapping manner. By covalently cross-linking the α and γ chains of adjacent fibrin monomers, factor XIIIa stabilizes the fibrin network and renders it resistant to degradation.

Fibrinogen, the most abundant plasma protein involved in coagulation, circulates in an inactive form. Thrombin binds to the amino-terminals of the Aα and Bβ chains of fibrinogen, where it cleaves specific peptide bonds to release fibrinopeptide A and fibrinopeptide B and generates fibrin monomers (**see Fig.**

93.6). Because they are products of the action of thrombin on fibrinogen, fibrinopeptide plasma levels provide an index of thrombin activity. Release of the fibrinopeptides creates new amino-termini that extend as knobs from the E domain of one fibrin monomer and insert into preformed holes in the D domains of other fibrin monomers. This creates long strands known as protofibrils that consist of fibrin monomers noncovalently linked together in a half-staggered, overlapping fashion.

Noncovalently linked fibrin protofibrils are unstable. By covalently cross-linking α- and γ-chains of adjacent fibrin monomers, factor XIIIa stabilizes the fibrin network in a calcium-dependent fashion and renders it relatively resistant to degradation. Factor XIII circulates in blood as a heterodimer consisting of two A and two B subunits. The active site and calcium binding sites of factor XIII are localized to the A subunit. Platelets contain large amounts of factor XIII in their cytoplasm, but platelet-derived factor XIII consists only of A subunits. Both plasma and platelet factor XIII are activated by thrombin.

Contact Pathway

Current thinking views exposure of tissue factor as the sole pathway for activation of coagulation and regards the contact system—which includes factor XII, prekallikrein, and high-molecular-weight kininogen—as unimportant for hemostasis because patients deficient in these factors do not have bleeding problems. The physiologic role of factor XI is more difficult to assess because the plasma level of factor XI in patients with congenital deficiency of factor XI, so-called hemophilia C, does not predict the propensity for bleeding. Although the capacity of thrombin to feed back upon and activate platelet-bound factor XI may explain this phenomenon, platelet-derived factor XI may be more important than circulating factor XI for hemostasis.

We cannot ignore the contact pathway, however, because coronary catheters and other blood-contacting medical devices, such as stents or mechanical heart valves, probably trigger clotting through this mechanism.[23] Factor XII binds to the surface of catheters or devices, where it undergoes a conformational change that results in its activation. Factor XIIa converts prekallikrein to kallikrein in a reaction accelerated by high-molecular-weight kininogen, and factor XIIa and kallikrein then feed back to activate additional factor XII. Factor XIIa propagates coagulation by activating factor XI (**Fig. 93.7**).

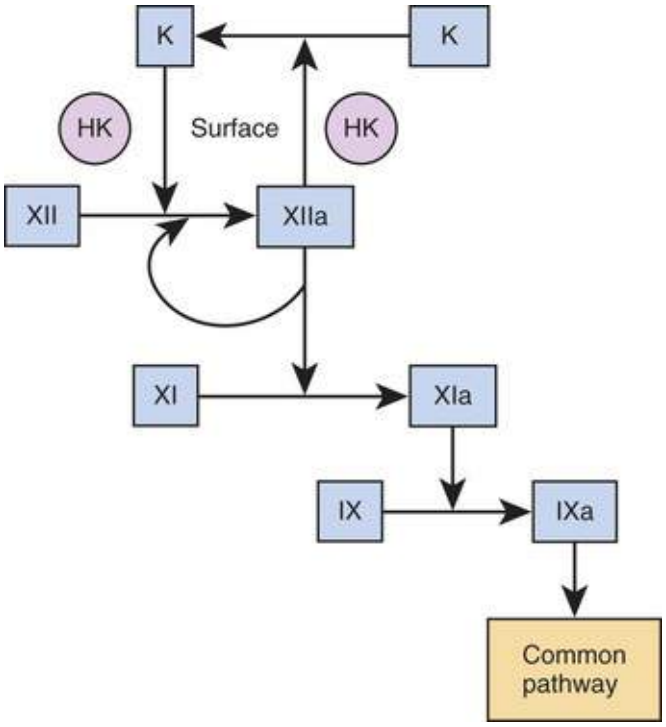

FIGURE 93.7 Contact system. Factor XII is activated by contact with negatively charged surfaces. Factor XIIa converts prekallikrein (PK) to kallikrein (K) and can feed back to activate more factor XII. Similarly, factor XIIa also can feed back to amplify its own generation. Approximately 75% of circulating PK is bound to high-molecular-weight kininogen (HK), which localizes it to anionic surfaces and promotes activation of PK. Factor XIIa propagates clotting by activating factor XI, which then activates factor IX. The resultant factor IXa assembles into the intrinsic tenase complex, which activates factor X to initiate the common pathway of coagulation.

In addition to its role in device-related thrombosis, the contact pathway may also contribute to the stabilization of arterial and venous thrombi. Thus mice deficient in factor XII or factor XI form small unstable thrombi at sites of arterial or venous damage, suggesting that these factors contribute to thrombus stabilization.[24] Potential physiologic activators of the contact pathway include polyphosphates released from activated platelets, DNA or RNA released from damaged or apoptotic cells in atherosclerotic plaque, and the DNA and histone network of NETs extruded from activated neutrophils, which not only promotes platelet adhesion and activation but also triggers activation of factor XII.[24] Support for the role of these activators in thrombosis comes from observations in mice that phosphatases and DNA- or RNA-degrading enzymes attenuate thrombosis at sites of injury. These activators of thrombosis have uncertain roles in humans. Although patients with unstable angina have increased plasma levels of factor XIa,[25] it is unknown whether this reflects activation by factor XIIa or by thrombin. A recent study showed that lowering of factor XI with an antisense oligonucleotide in patients undergoing knee arthroplasty reduced the risk of postoperative VTE to a greater extent than enoxaparin. These findings identify factor XI and factor XII as potential targets for new anticoagulants. Regardless of the extent to which the contact pathway contributes to thrombin generation, the final product of coagulation is fibrin. Hemostasis depends on a dynamic balance between the formation of fibrin and its degradation; the fibrinolytic system mediates fibrin breakdown.

Fibrinolytic System

Fibrinolysis begins when plasminogen activators convert plasminogen to plasmin, which then degrades fibrin into soluble fragments (**Fig. 93.8**). Blood contains two immunologically and functionally distinct plasminogen activators, t-PA and u-PA. t-PA mediates intravascular fibrin degradation, whereas u-PA

binds to a specific u-PA receptor (u-PAR) on the surface of cells, where it activates cell-bound plasminogen.[10] Consequently, pericellular proteolysis during cell migration and tissue remodeling and repair are the major functions of u-PA.

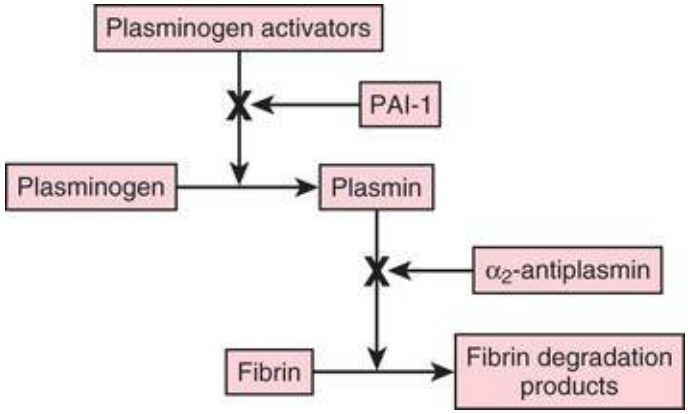

FIGURE 93.8 Fibrinolytic system and its regulation. Plasminogen activators convert plasminogen to plasmin. Plasmin then degrades fibrin into soluble fibrin degradation products. The system is regulated at two levels. Type 1 plasminogen activator inhibitor (PAI-1) inhibits the plasminogen activators, whereas alpha$_2$-antiplasmin serves as the major inhibitor of plasmin.

Regulation of fibrinolysis occurs at two levels. PAI-1 and, to a lesser extent, PAI-2 inhibit the plasminogen activators, whereas alpha$_2$-antiplasmin inhibits plasmin.[10] Endothelial cells synthesize PAI-1, which inhibits both t-PA and u-PA, whereas monocytes and the placenta synthesize PAI-2, which specifically inhibits u-PA. Thrombin-activated fibrinolysis inhibitor (TAFI) also attenuates fibrinolysis and provides a link between fibrinolysis and coagulation.[26] Impaired fibrinolysis promotes thrombus accumulation, whereas its excessive activation leads to bleeding.

Mechanism of Action of Tissue Plasminogen Activator

t-PA, a serine protease, contains five discrete domains: a fibronectin-like finger domain, an epidermal growth factor domain, two kringle domains, and a protease domain. Synthesized as a single-chain polypeptide, plasmin converts single-chain t-PA into a two-chain form. Both forms of t-PA convert plasminogen to plasmin. Native Glu-plasminogen is a single-chain polypeptide with a Glu residue at its amino-terminal. Plasmin cleavage near the amino-terminal generates Lys-plasminogen, a truncated form with a Lys residue at its new amino-terminus. t-PA cleaves a single peptide bond to convert single-chain Glu- or Lys-plasminogen into two-chain plasmin, which is composed of a heavy chain containing five kringle domains and a light chain containing the catalytic domain. Because its open conformation exposes the t-PA cleavage site, Lys-plasminogen is a better substrate for t-PA than Glu-plasminogen is, which assumes a circular conformation that renders this bond less accessible.

t-PA has little enzymatic activity in the absence of fibrin, but its activity increases by at least three orders of magnitude when fibrin is present.[10] This increase in activity reflects the capacity of fibrin to serve as a template that binds t-PA and plasminogen and promotes their interaction. t-PA binds fibrin via its finger and second kringle domains, whereas plasminogen binds fibrin via its kringle domains. Kringle domains are loop-like structures that bind Lys residues on fibrin. Degradation of fibrin exposes more Lys residues, which provides additional binding sites for t-PA and plasminogen. Consequently, degrading fibrin stimulates activation of plasminogen by t-PA more than intact fibrin does.

Alpha$_2$-antiplasmin rapidly inhibits circulating plasmin by docking to its first kringle domain and then

inhibiting the active site.[10] Because plasmin binds to fibrin via its kringle domains, plasmin generated on the fibrin surface resists inhibition by alpha$_2$-antiplasmin. This phenomenon endows fibrin-bound plasmin with the capacity to degrade fibrin. Factor XIIIa cross-links small amounts of alpha$_2$-antiplasmin onto fibrin, which prevents premature fibrinolysis.

Like fibrin, annexin II on endothelial cells binds t-PA and plasminogen and promotes the interaction of these proteins. Cell surface gangliosides and alpha-enolase may also bind plasminogen and promote its activation by altering its conformation into the more readily activated open form. Plasminogen binds to endothelial cells via its kringle domains. Lipoprotein(a), which also possesses kringle domains, impairs cell-based fibrinolysis by competing with plasminogen for cell surface binding (**see also Chapter 48**). This phenomenon may explain the association between elevated levels of lipoprotein(a) and atherosclerosis (**see also Chapters 45 and 48**).[27]

Mechanism of Action of Urokinase Plasminogen Activator

Synthesized as a single-chain polypeptide, single-chain u-PA (scu-PA) has minimal enzymatic activity. Plasmin readily converts scu-PA into an active two-chain form that can bind u-PAR on cell surfaces. Further cleavage at the amino-termini of two-chain u-PA yields a truncated, lower-molecular-weight form that lacks the u-PAR binding domain.[10]

Two-chain forms of u-PA readily convert plasminogen to plasmin in the absence or presence of fibrin. In contrast, scu-PA does not activate plasminogen in the absence of fibrin, but can activate fibrin-bound plasminogen because plasminogen adopts a more open and readily activatable conformation when immobilized on fibrin. Like the higher-molecular-weight form of two-chain u-PA, scu-PA binds cell surface u-PAR, where plasmin can activate it. Many tumor cells elaborate u-PA and express u-PAR on their surface. Plasmin generated on these cells promotes their ability to metastasize.[28]

Mechanism of Action of Thrombin-Activatable Fibrinolysis Inhibitor

Thrombin activatable fibrinolysis inhibitor (TAFI) originates in the liver and circulates in blood in a latent form, where thrombin bound to thrombomodulin can activate it. Unless bound to thrombomodulin, thrombin activates TAFI inefficiently.[26] Activated TAFI (TAFIa) attenuates fibrinolysis by cleaving Lys residues from the carboxy-termini of chains of degrading fibrin, thereby removing binding sites for plasminogen, plasmin, and t-PA. TAFI links fibrinolysis to coagulation in that the thrombin-thrombomodulin complex not only activates TAFI, which attenuates fibrinolysis, but also activates protein C, which mutes thrombin generation (**Fig. 93.2**). TAFIa has a short half-life in plasma because the enzyme is unstable.[26] Genetic polymorphisms can result in the synthesis of more stable forms of TAFIa. Persistent attenuation of fibrinolysis by these variant forms of TAFIa may render patients susceptible to thrombosis.[26]

Thrombosis

A physiologic host defense mechanism, hemostasis focuses on arrest of bleeding by forming hemostatic plugs composed of platelets and fibrin at sites of vessel injury. In contrast, thrombosis reflects a pathologic process associated with intravascular thrombi that fill and occlude the lumens of arteries or veins.

Arterial Thrombosis (see also Chapter 44)

Most arterial thrombi occur on top of disrupted atherosclerotic plaques. Coronary plaques with a thin fibrous cap and a lipid-rich core are most prone to disruption.[1] Rupture of the fibrous cap exposes thrombogenic material in the lipid-rich core to blood and triggers platelet activation and thrombin generation. The extent of plaque disruption and the content of thrombogenic material in the plaque determine the consequences of the event, but host factors also contribute. Breakdown of the regulatory mechanisms that limit platelet activation and inhibit coagulation can augment thrombosis at sites of plaque disruption. Decreased production of nitric oxide and prostacyclin by diseased endothelial cells can trigger vasoconstriction and platelet activation.[29] Proinflammatory cytokines lower expression of thrombomodulin by endothelial cells, which promotes thrombin generation, and stimulate expression of PAI-1, which inhibits fibrinolysis.[30]

Products of blood coagulation contribute to atherogenesis, as well as to its complications. Microscopic erosions in the vessel wall trigger the formation of tiny platelet-rich thrombi. Activated platelets release PDGF and TGF-β, which promote a fibrotic response.[31] Thrombin generated at the site of injury not only activates platelets and converts fibrinogen to fibrin but also activates the thrombin receptor PAR-1 on smooth muscle cells and induces their proliferation, migration, and elaboration of extracellular matrix. Incorporation of microthrombi into plaque promotes their growth, and decreased endothelial cell production of heparan sulfate—which normally limits smooth muscle proliferation—contributes to plaque expansion. The multiple links between atherosclerosis and thrombosis have prompted the term *atherothrombosis*.

Venous Thrombosis (see also Chapter 84)

Venous thrombosis may be caused by genetic or acquired hypercoagulable states or by such factors as advanced age, obesity, or cancer, which are usually acquired and are associated with immobility (**Table 93.1**). Inherited hypercoagulable states and these acquired risk factors combine to establish the intrinsic risk for thrombosis in each individual. Superimposed triggering factors, such as surgery, smoking, pregnancy, or hormonal therapy, modify this risk, and thrombosis occurs when the combination of genetic, acquired, and triggering forces exceeds a critical threshold (**Fig. 93.9**).

TABLE 93.1

Classification of Hypercoagulable States

HEREDITARY	MIXED	ACQUIRED
Loss of Function		
Antithrombin deficiency	Hyperhomocysteinemia	Advanced age
Protein C deficiency		Previous venous thromboembolism
Protein S deficiency		Surgery
Gain of Function		Immobilization
Factor V Leiden		Obesity
Prothrombin gene mutation		Cancer
Elevated factor VIII, IX, or XI levels		Pregnancy, puerperium
		Drug-induced: L-asparaginase, hormonal therapy

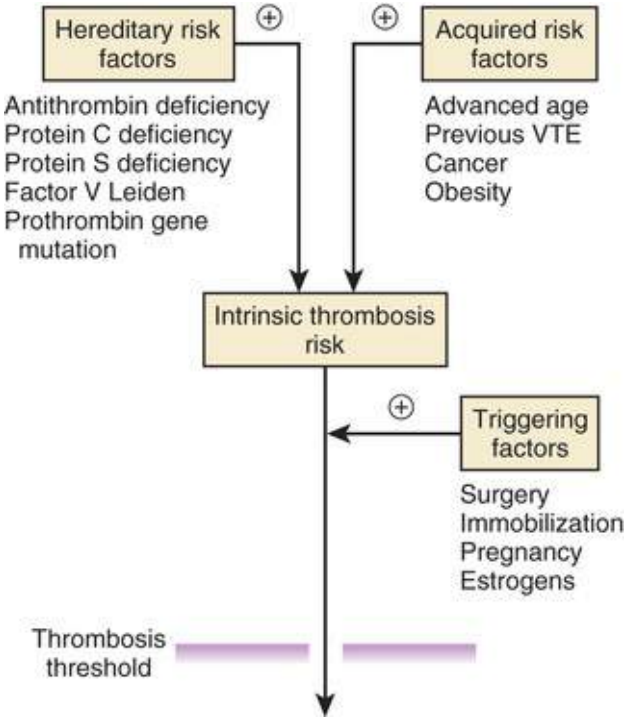

FIGURE 93.9 Thrombosis threshold. Hereditary and acquired risk factors combine to create an intrinsic risk for thrombosis in each individual. This risk is increased by extrinsic triggering factors. If the intrinsic and extrinsic forces exceed a critical threshold at which thrombin generation overwhelms protective mechanisms, thrombosis occurs. VTE, venous thromboembolisn.

Some acquired or triggering factors entail a higher risk than do others. For example, major orthopedic surgery, neurosurgery, multiple traumas, and metastatic cancer (particularly adenocarcinoma) entail the highest risk, whereas prolonged bed rest, the presence of antiphospholipid antibodies, and the puerperium are associated with intermediate risk; pregnancy, obesity, long-distance travel, and the use of oral contraceptives or hormonal replacement therapy are mild risk factors. Up to half of patients with VTE before the age of 45 years have inherited hypercoagulable disorders (so-called thrombophilia), particularly those whose event occurred in the absence of risk factors or with minimal provocation, such as after minor trauma or a long-haul flight or with estrogen use. The following sections describe the inherited and acquired hypercoagulable states.

Inherited Hypercoagulable States

Inherited hypercoagulable states fall into two categories. Some are associated with gain-of-function mutations in procoagulant pathways, such as factor V Leiden, the prothrombin gene mutation, and increased levels of procoagulant proteins; others are associated with loss-of-function mutations of endogenous anticoagulant proteins, such as deficiencies of antithrombin, protein C, and protein S. Although all of these inherited hypercoagulable disorders increase the risk for VTE, only increased levels of procoagulant proteins are clearly associated with an increased risk for arterial thrombosis.

Factor V Leiden

The factor V Leiden mutation, present in about 5% of white individuals, is the most common inherited thrombophilia. Because of a founder effect, the mutation is less common in Hispanics and blacks and rare in Asians. Caused by a point mutation in the factor V gene, the defect results in the synthesis of a factor V molecule with a Gln residue in place of an Arg residue at position 506, one of three sites where activated protein C cleaves factor Va to inactivate it. Consequently, activated factor V Leiden resists rapid

proteolysis and persists 10-fold longer in the presence of activated protein C than its wild-type counterpart does. The mutation is inherited in an autosomal dominant fashion. Individuals heterozygous for the factor V Leiden mutation have a fivefold increased risk for VTE; those homozygous for the mutation have a higher risk. However, the absolute risk for venous thrombosis is low with factor V Leiden, and with a yearly risk of 0.1% to 0.3%, patients with this disorder have a lifetime risk for thrombosis of only 5% to 10%.

An activated protein C resistance assay establishes the diagnosis of factor V Leiden in most cases. This assay involves calculation of the ratio of the activated partial thromboplastin time (APTT) measured after the addition of activated protein C divided by that determined before its addition. Use of factor V–deficient plasma increases the specificity of the test. When the clotting assay results are equivocal, genetic testing using a polymerase chain reaction (PCR)–based assay confirms the diagnosis.

Prothrombin Gene Mutation

The second most common thrombophilic disorder, the prothrombin gene mutation, reflects a G-to-A nucleotide transition at position 20210 in the 3′-untranslated region of the prothrombin gene. This mutation causes elevated levels of prothrombin, which enhance thrombin generation. The prevalence of the prothrombin gene mutation is about 3% in white persons and is lower in Asians and blacks. The mutation increases the risk for venous thrombosis to a similar extent as factor V Leiden does. Laboratory diagnosis depends on genetic screening after PCR amplification of the 3′-untranslated region of the prothrombin gene. Although persons heterozygous for this mutation have 30% higher levels of prothrombin than noncarriers do, the wide range of prothrombin levels in healthy individuals precludes the use of this phenotype for carrier identification.

Elevated Levels of Procoagulant Proteins

Elevated levels of factor VIII and other coagulation factors, including fibrinogen and factors IX and XI, appear to be independent risk factors for venous thrombosis. Increased levels of factor VIII are also associated with an up to threefold increase in the risk for myocardial infarction.[32] Although the molecular bases for the high levels of these coagulation factors have yet to be identified, genetic mechanisms probably contribute because these quantitative abnormalities have high heritability.

Antithrombin Deficiency

Synthesized in the liver, antithrombin regulates coagulation by forming a 1 : 1 covalent complex with thrombin, factor Xa, and other activated clotting factors. Heparan sulfate or heparin accelerates the rate of antithrombin interaction with its target proteases. Inherited antithrombin deficiency is rare; it occurs in approximately 1 in 2000 people and can be due to decreased synthesis of a normal protein or production of a dysfunctional protein. A parallel reduction in the levels of antithrombin antigen and activity identifies deficiencies caused by decreased synthesis, whereas decreased antithrombin activity in the presence of normal antigen levels identifies dysfunctional forms of antithrombin. Comparison of antithrombin activity with or without added heparin identifies variants with impaired heparin-binding capacity.

Acquired antithrombin deficiency results from decreased synthesis, increased consumption, or enhanced clearance. Decreased synthesis can occur in patients with severe hepatic disease, particularly cirrhosis, or in those given L-asparaginase. Increased activation of coagulation can result in antithrombin consumption in disorders such as extensive thrombosis, disseminated intravascular coagulation, severe sepsis, disseminated malignancy, or prolonged extracorporeal circulation. Heparin treatment can also

reduce antithrombin levels up to 20% by enhancing the clearance of antithrombin. Severe antithrombin deficiency can develop in some patients with nephrotic syndrome because of loss of protein in urine.

Protein C Deficiency

Thrombin initiates the protein C pathway when it binds thrombomodulin on the endothelial cell surface (**see Fig. 93.2**). Thrombin bound to thrombomodulin activates protein C approximately 1000-fold more efficiently than free thrombin does.[9] EPCR augments this process 20-fold by binding protein C and presenting it to the thrombin-thrombomodulin complex for activation.[9] Activated protein C then becomes dissociated from the activation complex and decreases thrombin generation by inactivating factors Va and VIIIa on the activated platelet surface. For efficient inactivation of these factors, activated protein C must bind to protein S, its cofactor.

Protein C deficiency can be inherited or acquired. Approximately 1 in 200 adults has heterozygous protein C deficiency inherited in an autosomal dominant fashion, but most have no history of thrombosis. The variable phenotypic expression of hereditary protein C deficiency suggests the existence of other, yet unrecognized, modifying factors. In contrast to antithrombin deficiency, in which the homozygous state is associated with embryonic lethality, homozygous or doubly heterozygous protein C deficiency can occur. Newborns with these disorders often develop purpura fulminans characterized by widespread thrombosis.

Inherited protein C deficiency can result from decreased synthesis of normal protein or from synthesis of dysfunctional forms of protein C. Identification of the type of deficiency requires simultaneous measurement of protein C antigen and activity; reduced synthesis of a normal protein results in a parallel reduction in protein C antigen and activity, whereas synthesis of a dysfunctional protein results in normal antigen with reduced activity.

Acquired protein C deficiency can be due to decreased synthesis or increased consumption. Decreased synthesis can occur in patients with severe liver disease or in those given warfarin. Protein C consumption can occur with severe sepsis, with disseminated intravascular coagulation, and after surgery. Although antithrombin levels can be low in patients with nephrotic syndrome, protein C levels are normal or elevated in such patients.

Protein S Deficiency

Protein S serves as a cofactor for activated protein C (**see Fig. 93.2**). In addition, protein S may directly inhibit prothrombin activation because of its capacity to bind factors Va and Xa, components of the prothrombinase complex, in the presence of zinc. The importance of the direct anticoagulant activity of protein S is uncertain.

In the circulation, approximately 60% of total protein S is bound to C4b-binding protein, a complement component; only the remaining free 40% is functionally active. Diagnosis of protein S deficiency requires measurement of both the free and bound forms of protein S. Inherited protein S deficiency can result from reduced synthesis of the protein or synthesis of a dysfunctional protein. Acquired protein S deficiency can be due to decreased synthesis, increased consumption, loss, or shift of free protein S to the bound form. Decreased synthesis can occur in patients with severe liver disease or in those given warfarin or L-asparaginase. Increased consumption of protein S occurs in patients with acute thrombosis or disseminated intravascular coagulation. Patients with nephrotic syndrome can excrete free protein S in their urine, which causes decreased protein S activity. Total protein S levels in these patients are often normal because the levels of C4b-binding protein increase, thus shifting more protein S to the bound form.

C4b-binding protein levels also increase in pregnancy and with the use of oral contraceptives. This shifts more protein S to the bound form and lowers the levels of free protein S and protein S activity. The consequences of this phenomenon are uncertain.

Other Hereditary Disorders

A polymorphism in the gene that encodes the EPCR has been linked to venous thrombosis. Associated with EPCR shedding and high levels of soluble EPCR, this polymorphism reduces endothelial EPCR, and soluble EPCR competes with its endothelial cell counterpart for protein C binding.

A polymorphism in factor XIII that results in more rapid activation by thrombin is associated with a small reduction in the risk for VTE, myocardial infarction, and ischemic stroke in some but not all case-control studies.[33] The frequency of this polymorphism varies among different ethnic populations, and certain environmental factors, such as obesity and estrogen therapy, may augment its protective effect. More work is needed to determine the extent to which this polymorphism modulates the risk for thrombosis.

Acquired Hypercoagulable States (see also Chapter 84)

Acquired hypercoagulable states may develop during surgery and the period of immobilization following it; in persons of advanced age; in those who are obese, have cancer, are pregnant, or are taking estrogen therapy (oral contraceptive or hormone replacement therapy); or in those with a history of VTE, antiphospholipid syndrome, or hyperhomocysteinemia (**see Table 93.1**). These conditions can occur in isolation or in conjunction with hereditary hypercoagulable states.

Surgery and Immobilization

Surgery can directly damage veins, and immobilization after surgery leads to stasis in the deep veins of the leg. The risk for VTE in surgical patients depends on the patient's age, the type of surgery, and the presence of active cancer. Patients older than 65 years have a greater risk, and high-risk types of surgery include major orthopedic procedures, neurosurgery, and extensive abdominal or pelvic surgery, especially for cancer. Because the risk for VTE increases up to 20-fold in these patients, they require thromboprophylaxis until they gain full mobility. Hospitalization and nursing home confinement account for approximately 60% of cases of VTE, again reflecting the impact of immobilization. Hospitalization for medical illness accounts for a similar proportion of cases as hospitalization for surgery, thus highlighting the need for thromboprophylaxis in medical patients as well as in surgical patients.

Advanced Age

Predominantly a disease of older age, VTE in those younger than 50 years has an incidence of 1 per 10,000 and increases approximately 10-fold per decade thereafter. Men have an overall age-adjusted incidence rate approximately 1.2-fold higher than women. Although incidence rates are higher in women during the reproductive years, after 45 years of age, men have higher incidence rates. Many potential mechanisms may increase the incidence of VTE with advanced age, including decreased mobility, associated diseases, and vascular endothelium that is less resistant to thrombosis. Levels of procoagulant proteins also increase with age.

Obesity

The risk for VTE increases approximately 1.2-fold for every 10-kg/m^2 increase in body mass index, but the basis for the association between obesity and VTE is unclear. Obesity leads to immobility; in addition, adipose tissue, particularly visceral fat, expresses proinflammatory cytokines and adipokines, which may promote coagulation by increasing levels of procoagulant proteins or impair fibrinolysis by elevating levels of PAI-1.

Cancer

Approximately 20% of patients with VTE have cancer.[34] Cancer patients with VTE have reduced survival times compared with those without VTE. Patients with brain tumors, pancreatic cancer, or advanced ovarian or prostate cancer have particularly high rates of VTE.[34] Treatment with chemotherapy, hormonal therapy, and biologic agents (such as erythropoietin and antiangiogenic drugs) further increases the risk, as do central venous catheters or surgery for cancer. The pathogenesis of thrombosis in cancer patients is multifactorial and involves a complex interplay between the tumor, patient characteristics, and the hemostatic system. Many types of tumor cells express tissue factor or other procoagulants that can initiate coagulation. In addition to its role in coagulation, tissue factor also acts as a signaling molecule that promotes tumor proliferation and spread.[35] Patient characteristics that contribute to VTE include immobility and venous stasis secondary to extrinsic compression of major veins by tumor. Surgical procedures, central venous catheters, and chemotherapy can injure vessel walls. In addition, tamoxifen and selective estrogen receptor modulators (SERMs) induce an acquired hypercoagulable state by reducing levels of natural anticoagulant proteins.

A proportion of patients with unprovoked VTE have occult cancer. This observation has prompted some experts to recommend extensive screening for cancer in such patients, but the potential harm—including procedure-related morbidity, the psychological impact of false-positive test results, and the cost of screening—offsets any benefits of this approach. Studies comparing extensive cancer screening with little or no screening in patients with unprovoked VTE have not demonstrated a reduction in cancer-related mortality rates with screening. Therefore unless symptoms suggestive of underlying cancer are present, only age-appropriate screening for breast, cervical, colon, and possibly prostate cancer is indicated because screening for these cancers may reduce mortality rates.

Pregnancy

Pregnant women have a fivefold to sixfold higher risk for VTE than do age-matched nonpregnant women. VTE occurs in approximately 1 in 1000 pregnancies, and in approximately 1 in 1000 women VTE develops in the postpartum period. VTE is the leading cause of maternal morbidity and mortality. Patient-related factors influence the risk for VTE in pregnancy and the puerperium, including age older than 35 years, body mass index higher than 29, cesarean delivery, thrombophilia, or a personal or family history of VTE. Ovarian hyperstimulation and multiparity also increase risk for thrombosis.

More than 90% of deep vein thrombi in pregnancy occur in the left leg, probably because the enlarged uterus compresses the left iliac vein. Hypercoagulability occurs in pregnancy because of the combination of venous stasis and changes in blood. Uterine enlargement reduces venous blood flow from the lower extremities. This is not the only contributor to venous stasis, however, because blood flow from the lower extremities begins to decrease by the end of the first trimester. Systemic factors also contribute to hypercoagulability. Thus levels of procoagulant proteins, such as factor VIII, fibrinogen, and vWF, increase in the third trimester of pregnancy. Coincidentally, suppression of the natural anticoagulant pathways takes place. These changes enhance thrombin generation, as evidenced by elevated levels of

F1.2 and thrombin-antithrombin complexes.

About half the episodes of VTE in pregnancy occur in women with thrombophilia. The risk for VTE in women with thrombophilic defects depends on the type of abnormality and the presence of other risk factors. Risk appears highest in women with antithrombin, protein C, or protein S deficiency and lower in those with factor V Leiden or the prothrombin gene mutation. In general, these women have a higher daily risk for VTE in the postpartum period than during pregnancy. The risk during pregnancy is similar in all three trimesters. Therefore, women needing thromboprophylaxis require treatment throughout pregnancy and for at least 6 weeks postpartum.

Sex Hormone Therapy (see also Chapter 92)

Oral contraceptives, estrogen replacement therapy, and SERMs are all associated with an increased risk for VTE. The relatively high risk for VTE associated with first-generation oral contraceptives prompted the development of low-dose formulations. Currently available low-estrogen combination oral contraceptives contain 20 to 50 µg of ethinyl estradiol and one of several different progestins. Even these low-dose combination contraceptives are associated with a threefold to fourfold increased risk for VTE in comparison with nonusers. In absolute terms this translates to an incidence of 3 to 4 per 10,000 as compared with 5 to 10 per 100,000 in nonusers of reproductive age.

Even though smoking increases the risk for myocardial infarction and stroke in women taking oral contraceptives, it is unclear whether smoking affects the risk for VTE. Obesity, however, increases the risk of both arterial and venous thrombosis. The risk for VTE is highest during the first year of oral contraceptive use and persists only for the duration of use. Case-control studies suggest a 20- to 30-fold higher risk for VTE in women with inherited thrombophilia who use oral contraceptives than in nonusers with thrombophilia or users without these defects. Despite the increased risk, routine screening for thrombophilia in young women considering oral contraceptive use is not recommended. Based on the incidence and case fatality rate of thrombotic events, estimates suggest that screening 400,000 women would detect 20,000 factor V Leiden carriers and that prevention of a single death would necessitate withholding oral contraceptives in all these women. Even larger numbers of women with less prevalent thrombophilic defects would require screening.

Hormonal replacement therapy with conjugated equine estrogen, with or without a progestin, is associated with a small increase in the risk for myocardial infarction, ischemic stroke, and VTE. SERMs, such as tamoxifen, are estrogen-like compounds that serve as an estrogen antagonist in the breast but as estrogen agonists in other tissues, such as bone and the uterus. Like estrogens, tamoxifen increases the risk for VTE by threefold to fourfold. The risk is higher in postmenopausal women, particularly those receiving systemic combination chemotherapy. Because of this risk, aromatase inhibitors, which antagonize estrogens by blocking their synthesis from androgens, are sometimes used in place of tamoxifen for the treatment of estrogen receptor–positive breast cancer. Aromatase inhibitors are associated with a lower risk for VTE than tamoxifen. Raloxifene, a SERM used to prevent osteoporosis, increases the risk for VTE threefold when compared with placebo, which contraindicates the use of raloxifene for prevention of osteoporosis in women with a history of VTE.

History of Previous Venous Thromboembolism

A history of previous VTE places patients at risk for recurrence. When anticoagulation treatment stops, patients with unprovoked VTE have a risk for recurrence of approximately 10% at 1 year and 30% at 5 years. This risk appears independent of whether an underlying thrombophilic defect is present, such as

factor V Leiden or the prothrombin gene mutation. The risk for recurrent VTE is lower in patients whose incident event occurred in association with a transient risk factor, such as major surgery or prolonged immobilization. These patients have a risk for recurrence of approximately 1% at 1 year and 5% at 5 years. Patients whose VTE occurred on the background of minor risk factors, such as a long-haul flight have an intermediate risk for recurrence. Patients at highest risk for recurrence are those with inherited deficiencies of antithrombin, protein C, or protein S; those with antiphospholipid antibody syndrome; patients with advanced malignancy; or those homozygous for factor V Leiden or the prothrombin gene mutation. Their risk for recurrence likely ranges from 15% at 1 year to up to 50% at 5 years.

Antiphospholipid Syndrome

A heterogeneous group of autoantibodies directed against proteins that bind phospholipid; some antiphospholipid antibodies, known as lupus anticoagulants (LA), prolong phospholipid-dependent coagulation assays. Others, anticardiolipin (ACL) antibodies, target cardiolipin, and a subset of ACL antibodies recognizes other phospholipid-bound proteins, particularly $beta_2$-glycoprotein I. Patients with thrombosis in association with a persistent LA and/or ACL antibody have antiphospholipid syndrome. Primary antiphospholipid syndrome occurs in isolation, whereas secondary forms are associated with autoimmune disorders, such as systemic lupus erythematosus or other connective tissue diseases. Patients with antiphospholipid syndrome can have arterial, venous, or placental thrombosis. Arterial thrombosis can cause a transient ischemic attack, stroke, or myocardial infarction. Cerebral vein thrombosis can occur in addition to deep vein thrombosis and pulmonary embolism. Placental thrombosis probably causes pregnancy-related complications that characterize antiphospholipid syndrome. Such complications include fetal loss before 10 weeks' gestation and unexplained fetal death after 10 weeks' gestation, intrauterine growth restriction, preeclampsia, and eclampsia. Treatment with aspirin and/or LMWH during pregnancy may reduce the risk for these complications in women with antiphospholipid syndrome but not in those with other documented thrombophilic defects.

Laboratory diagnosis of antiphospholipid syndrome requires the presence of an LA or ACL antibody on tests taken at least 6 weeks apart. Diagnosis of an LA requires a battery of phospholipid-dependent clotting tests, whereas immunoassays detect ACL antibodies. Only ACL antibodies of medium to high titer and of the IgG or IgM subclass are associated with thrombosis. Approximately 3% to 10% of healthy individuals have ACL antibodies. Such antibodies also occur with certain infections, such as mycobacterial pneumonia, malaria, or parasitic disorders, and after exposure to some medications. Frequently, these antibodies are transient and of low titer. Approximately 30% to 50% of patients with systemic lupus erythematosus or other connective tissue disorders have ACL antibodies, and 10% to 20% have an LA.

The mechanism by which antiphospholipid antibodies trigger thrombosis is unclear. These antibodies directly activate endothelial cells in culture and induce the expression of adhesion molecules that can tether tissue factor–bearing leukocytes or microparticles onto their surface. ACL antibodies also interfere with the protein C pathway, inhibit catalysis of antithrombin by endothelial heparan sulfate, and impair fibrinolysis. The relative importance of these mechanisms in humans remains unclear.

Hyperhomocysteinemia (see also Chapter 45)

Homocysteine serves as a methyl group donor during the metabolism of methionine, an essential amino acid derived from the diet. The interconversion of methionine and homocysteine depends on the

availability of 5-methyltetrahydrofolate, a methyl group donor; vitamin B_{12} and folate, cofactors in the interconversion; and the enzyme methionine synthase. Increased levels of homocysteine can result from increased production or reduced metabolism. Severe hyperhomocysteinemia and cystinuria, which are rare, usually result from deficiency of cystathionine beta-synthetase. The more common mild to moderate hyperhomocysteinemia often results from genetic mutations in methyltetrahydrofolate reductase (MTHFR) in association with nutritional deficiency of folate, vitamin B_{12}, or vitamin B_6. The common C677T and A1298C polymorphisms in MTHFR are associated with reduced enzymatic activity and increased thermolability, respectively, thereby increasing the requirement for nutritional cofactors. Hyperhomocysteinemia can also be associated with certain drugs, such as methotrexate, theophylline, cyclosporine, and most anticonvulsants, as well as with some chronic diseases, such as advanced renal disease, severe hepatic dysfunction, or hypothyroidism.

Although elevated levels of fasting serum homocysteine (> 15 mmol/L) were once common, routine fortification of flour in North America with folic acid has lowered homocysteine levels in the general population. Elevated serum homocysteine may be associated with an increased risk for myocardial infarction, stroke, and peripheral artery disease, as well as VTE. Administration of folate along with vitamin B_{12} and vitamin B_6 reduces levels of homocysteine. Nonetheless, randomized trials have shown that such therapy does not lower the risk for recurrent cardiovascular events in patients with coronary artery disease or stroke, nor does it lower the risk for recurrent VTE. Based on these negative trials and the declining incidence of hyperhomocysteinemia, enthusiasm for screening for hyperhomocysteinemia has declined.

Treatment of Thrombosis

Antiplatelet Drugs

The commonly used antiplatelet drugs include aspirin, thienopyridines (ticlopidine, clopidogrel, and prasugrel), ticagrelor, cangrelor, dipyridamole, GPIIb/IIIa antagonists, and vorapaxar. Each agent has a distinct site of action (**see Fig. 93.10**).

Aspirin

Aspirin is the most widely used antiplatelet agent worldwide. Because it is an inexpensive and effective drug, aspirin serves as the foundation of most antiplatelet strategies.

Mechanism of Action

Aspirin produces its antithrombotic effect by irreversibly acetylating and inhibiting platelet COX-1 (**Fig. 93.10**), a critical enzyme in the biosynthesis of thromboxane A_2. At high doses (≈ 1 g/day), aspirin also inhibits COX-2, an inducible COX isoform found in endothelial cells and inflammatory cells.[36] In endothelial cells, COX-2 initiates the synthesis of prostacyclin, a potent vasodilator and inhibitor of platelet activation that antagonizes the effects of thromboxane A_2.

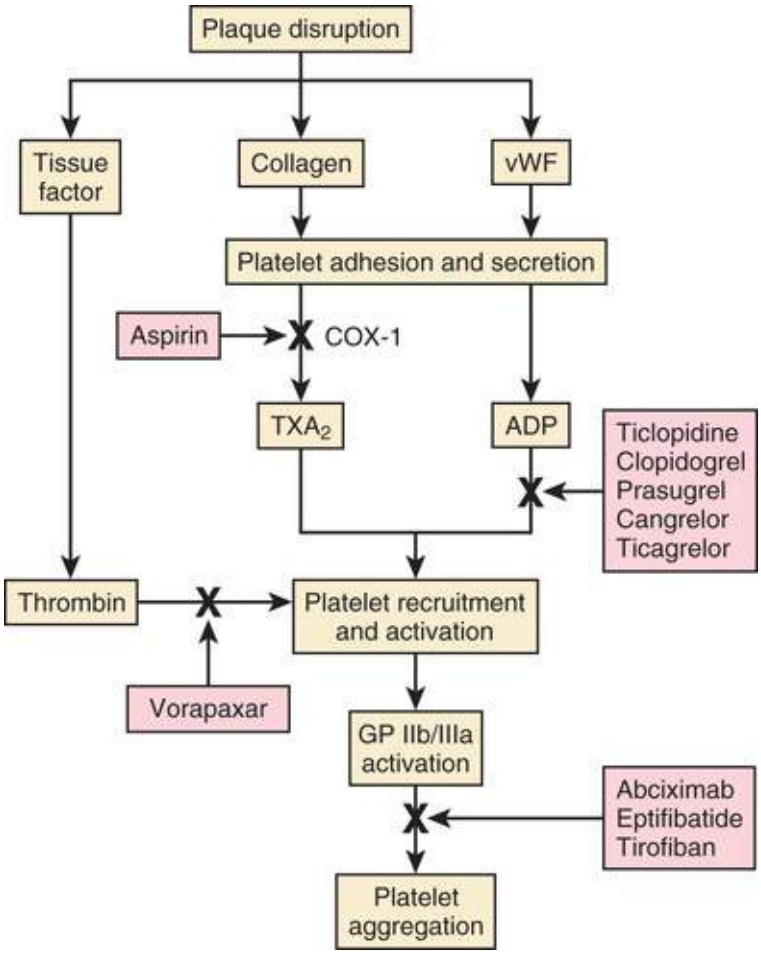

FIGURE 93.10 Sites of action of antiplatelet drugs. Aspirin inhibits the synthesis of thromboxane A_2 (TXA_2) by irreversibly acetylating cyclo-oxygenase 1 (COX-1). The reduced release of TXA_2 attenuates platelet activation and recruitment to the site of vascular injury. Ticlopidine, clopidogrel, and prasugrel irreversibly block $P2Y_{12}$, a key ADP receptor on the platelet surface; cangrelor and ticagrelor are reversible inhibitors of $P2Y_{12}$. Abciximab, eptifibatide, and tirofiban inhibit the final common pathway of platelet aggregation by blocking binding of fibrinogen and vWF to activated GP IIb/IIIa. Vorapaxar inhibits thrombin-mediated platelet activation by targeting protease-activated receptor-1 (PAR-1), the major thrombin receptor on platelets.

Indications

Aspirin is widely used for secondary prevention in patients with established coronary, cerebrovascular, or peripheral artery disease. In such patients, aspirin produces about a 20% reduction in the risk for cardiovascular death, myocardial infarction, or stroke.[36] Use of aspirin for primary prevention is more controversial. Metaanalyses suggest that daily aspirin use produces a 20% to 25% reduction in the risk for a first cardiovascular event in patients at moderate to high risk for cardiovascular disease. Recent studies, however, have questioned whether the benefits of daily aspirin for primary cardiac protection outweigh its associated risks for gastrointestinal and intracerebral hemorrhage.[37] Consequently, aspirin is no longer recommended for primary cardiac prevention unless the baseline cardiovascular risk is at least 1% per year and 10% at 10 years (**see also Chapters 45 and 89**).[38]

Dosages

Usually administered at dosages of 75 to 325 mg once daily, there is no evidence that higher-dose aspirin is more effective than lower doses, and some metaanalyses suggest reduced efficacy with higher doses.[36] Because the side effects of aspirin, particularly gastrointestinal bleeding, depend on the dosage, daily

aspirin dosages of 75 to 150 mg suffice for most indications. Rapid platelet inhibition requires an initial dose of non–enteric-coated aspirin of at least 160 mg.[36]

Side Effects

The most common side effects are gastrointestinal, and they range from dyspepsia to erosive gastritis or peptic ulcers with bleeding and perforation.[36] Use of enteric-coated or buffered aspirin in place of plain aspirin does not eliminate the risk for gastrointestinal side effects. The risk for major bleeding with aspirin is 1% to 3% per year. The concomitant use of aspirin and anticoagulants such as warfarin increases the risk for bleeding. When combined with warfarin, use of low-dose aspirin (75 to 100 mg daily) is best. Eradication of *Helicobacter pylori* infection and administration of proton pump inhibitors may reduce the risk for aspirin-induced upper gastrointestinal bleeding in patients with peptic ulcer disease.

Patients with a history of aspirin allergy characterized by bronchospasm should not receive aspirin. This problem occurs in approximately 0.3% of the general population but is more common in patients with chronic urticaria or asthma, particularly those with coexisting nasal polyps or chronic rhinitis.[39] Clopidogrel can be used in place of aspirin in such patients. Aspirin overdose is associated with hepatic and renal toxicity.

Aspirin Resistance

The term *aspirin resistance* is used to describe both clinical and laboratory phenomena.[40] A diagnosis of clinical aspirin resistance, defined as failure of aspirin to protect patients from ischemic vascular events, can be made only after such an event occurs. This retrospective diagnosis provides no opportunity to modify therapy. Furthermore, it is unrealistic to expect aspirin, which selectively blocks thromboxane A_2–induced platelet activation, to prevent all vascular events. The biochemical definition of aspirin resistance involves failure of the drug to inhibit thromboxane A_2 synthesis and/or arachidonic acid–induced platelet aggregation. Potential mechanisms for aspirin resistance include poor adherence, reduced or delayed absorption of aspirin due to its enteric coating,[41] thromboxane A_2 generation via pathways distinct from COX-1, increased activity of thromboxane A_2–independent pathways of platelet activation, use of concomitant medications that interfere with the action of aspirin, and pharmacogenetic factors. Tests used for the diagnosis of biochemical aspirin resistance include measurements of thromboxane B_2, the stable metabolite of thromboxane A_2, in serum or in urine, and assessment of arachidonic acid–induced platelet aggregation. These tests have not been standardized, however, and there is no evidence that they identify patients at risk for recurrent vascular events or that resistance can be reversed either by giving higher doses of aspirin or by adding other antiplatelet drugs. Until such information is available, testing for aspirin resistance remains a research tool.

Thienopyridines (see also Chapters 59 to 61)

The thienopyridines include ticlopidine, clopidogrel, and prasugrel, drugs that target $P2Y_{12}$, a key ADP receptor on platelet.

Mechanism of Action

The thienopyridines selectively inhibit ADP-induced platelet aggregation by irreversibly blocking $P2Y_{12}$ (**see Fig. 93.10**). These prodrugs require metabolic activation by the hepatic cytochrome P-450 (CYP)

enzyme system. Therefore, when given in usual doses, ticlopidine and clopidogrel have a delayed onset of action. The metabolic activation of prasugrel is more efficient than that of clopidogrel. Consequently, prasugrel acts more rapidly and produces greater and more predictable inhibition of ADP-induced platelet aggregation than clopidogrel.[42] The active metabolites of the thienopyridines bind irreversibly to $P2Y_{12}$. Consequently, these drugs have prolonged action, which can present problems if patients require urgent surgery. To reduce the risk for bleeding, thienopyridine therapy must be stopped approximately 5 days before surgery.

Indications

When compared with aspirin in patients with recent ischemic stroke, myocardial infarction, or peripheral arterial disease, clopidogrel reduced the risk for cardiovascular death, myocardial infarction, and stroke by 8.7%. Therefore, clopidogrel is marginally more effective than aspirin, but it is more expensive, although the cost of clopidogrel has decreased now that generic forms are available. The combination of clopidogrel and aspirin capitalizes on the capacity of each drug to block complementary pathways of platelet activation. For example, this combination is recommended after stent implantation in coronary arteries. **Chapter 62** discusses the use of antiplatelet agents after intervention.

The combination of clopidogrel and aspirin is also effective in patients with unstable angina (**see also Chapter 60**). In 12,562 such patients, the risk for cardiovascular death, myocardial infarction, or stroke was 9.3% in those randomly assigned to the combination of clopidogrel and aspirin and 11.4% in those given aspirin alone. This 20% relative risk reduction with combination therapy was highly statistically significant. However, combining clopidogrel with aspirin increases the risk for major bleeding to approximately 2% per year, a risk that persists even with a daily aspirin dose of 100 mg or less. Therefore use of clopidogrel plus aspirin should be restricted to situations in which there is clear evidence of benefit. For example, this combination has not proved to be superior to clopidogrel alone in patients with acute ischemic stroke or to aspirin alone for primary prevention in those at risk for cardiovascular events.

Prasugrel was compared with clopidogrel in 13,608 patients with acute coronary syndromes scheduled to undergo percutaneous coronary intervention (PCI).[42] The incidence of the primary efficacy endpoint—a composite of cardiovascular death, myocardial infarction, and stroke—was significantly lower with prasugrel than with clopidogrel (9.9% and 12.1%, respectively), mainly because of a reduction in the incidence of nonfatal myocardial infarction. The incidence of stent thrombosis was also significantly lower with prasugrel than with clopidogrel (1.1% and 2.4%, respectively). These advantages, however, were at the expense of significantly higher rates of fatal bleeding (0.4% and 0.1%, respectively) and life-threatening bleeding (1.4% and 0.9%, respectively) with prasugrel. Because patients older than 75 years and those with a history of previous stroke or transient ischemic attack have a particularly high risk for bleeding, prasugrel should be avoided in older patients, and the drug is contraindicated in those with a history of cerebrovascular disease. Caution is required if prasugrel is used in patients weighing less than 60 kg or in those with renal impairment.

Dosages

Clopidogrel is given once daily at a dose of 75 mg.[36] Because its onset of action is delayed for several days, 300- to 600-mg loading doses of clopidogrel are given when rapid ADP receptor blockade is desired (**see also Chapter 62**). After a loading dose of 60 mg, prasugrel is given once daily at a dose of 10 mg.[36] Patients older than 75 years or weighing less than 60 kg should receive a daily prasugrel dose of

5 mg.

Clopidogrel Resistance.
The capacity of clopidogrel to inhibit ADP-induced platelet aggregation varies among subjects.[43] This variability reflects, at least in part, genetic polymorphisms in the CYP isoenzymes involved in the metabolic activation of clopidogrel (**see also Chapters 8, 59, and 60**). The most important of these enzymes is CYP2C19. Clopidogrel-treated patients with the loss-of-function *CYP2C19*2* allele exhibit reduced platelet inhibition in comparison with those with the wild-type *CYP2C19*1* allele and experience a higher rate of cardiovascular events.[44] This is important because estimates suggest that up to 25% of whites, 30% of blacks, and 50% of Asians carry the loss-of-function allele, which may render them resistant to clopidogrel. Even patients with reduced-function *CYP2C19*3*, *CYP2C19*4*, or *CYP2C19*5* alleles may derive less benefit from clopidogrel than do those with the full-function *CYP2C19*1* allele. Patients with polymorphisms in *ABCB1* may exhibit impaired clopidogrel absorption, and polymorphisms in *CYP3A4* can contribute to reduced metabolic activation of clopidogrel. Polymorphisms in both these enzymes have been linked to adverse clinical outcomes. In contrast to their effect on the metabolic activation of clopidogrel, polymorphisms in *CYP2C19* and *CYP3A4* do not appear to influence activation of prasugrel, nor do they affect the response to ticagrelor.

Although concomitant administration of clopidogrel with proton pump inhibitors, which inhibit CYP2C19, reduces the effect of clopidogrel on ADP-induced platelet aggregation, this interaction has questionable clinical significance. Atorvastatin, a competitive inhibitor of CYP3A4, reduced the inhibitory effect of clopidogrel on ADP-induced platelet aggregation in one study, a finding unconfirmed in subsequent investigations.[45]

The influence of genetic polymorphisms on clinical outcomes with clopidogrel has raised the possibility that pharmacogenetic profiling and/or point-of-care platelet function testing could be used to identify clopidogrel-resistant patients so that they could be targeted for more intensive antiplatelet therapy.[46] Although up to 30% of clopidogrel-treated patients have evidence of reduced responsiveness to the drug, randomized clinical trials have failed to show that more intensive antiplatelet therapy improves the outcome in such patients.[47] Consequently, there is no indication for routine clopidogrel resistance testing at this time. Because their antiplatelet effects are more predictable, guidelines recommend prasugrel or ticagrelor instead of clopidogrel for high-risk patients.

Ticagrelor

As an orally active inhibitor of $P2Y_{12}$, ticagrelor differs from the thienopyridines in that it does not require metabolic activation and it produces reversible inhibition of the ADP receptor.

Mechanism of Action

Like the thienopyridines, ticagrelor inhibits $P2Y_{12}$. Because it does not require metabolic activation, ticagrelor has a more rapid onset and offset of action than clopidogrel does and it produces greater and more predictable inhibition of ADP-induced platelet aggregation.

Dosages

Ticagrelor is initiated with an oral loading dose of 180 mg followed by 90 mg twice daily. The dose does

not need adjustment in patients with renal impairment, but caution is needed in patients with hepatic impairment or in those receiving potent inhibitors or inducers of CYP3A4 because ticagrelor is metabolized in the liver via CYP3A4. Ticagrelor is usually administered in conjunction with aspirin; the daily aspirin dose should not exceed 100 mg.

Side Effects

In addition to bleeding, as with all $P2Y_{12}$ inhibitors, the most common side effects of ticagrelor are dyspnea, which can develop in up to 15% of patients, and bradyarrhythmias. The dyspnea, which tends to occur soon after initiating ticagrelor, is usually self-limited and mild in intensity but can be persistent and may necessitate drug discontinuation in some patients. Although the exact mechanism responsible for these side effects is unknown, they may be adenosine-mediated because ticagrelor inhibits its reuptake.

Indications (see also Chapters 59 and 60)

When compared with clopidogrel in patients with acute coronary syndromes,[44] ticagrelor produced a greater reduction in the primary efficacy endpoint—a composite of cardiovascular death, myocardial infarction, and stroke at 1 year—than did clopidogrel (9.8% and 11.7%, respectively; $P = .001$). This difference reflected a significant reduction in both cardiovascular death (4.0% and 5.1%, respectively; $P = .001$) and myocardial infarction (5.8% and 6.9%, respectively; $P = .005$) with ticagrelor relative to clopidogrel. Rates of stroke were similar with ticagrelor and clopidogrel (1.5% and 1.3%, respectively), and there was no difference in rates of major bleeding. When minor bleeding was added to the major bleeding results, however, ticagrelor showed an increase relative to clopidogrel (16.1% and 14.6%, respectively; $P = .008$). Ticagrelor was also superior to clopidogrel in patients with acute coronary syndrome who underwent PCI or cardiac surgery. Based on these observations, guidelines give preference to ticagrelor over clopidogrel, particularly in higher-risk patients.

Cangrelor

Cangrelor is a rapidly acting reversible inhibitor of P2Y12 that is administered intravenously. It has an immediate onset of action, a half-life of 3 to 5 minutes, and an offset of action within an hour. Cangrelor is licensed for use in patients undergoing PCI and produces rapid ADP receptor blockade in those who have not received pretreatment with clopidogrel, prasugrel, or ticagrelor.[48]

Dipyridamole

A relatively weak antiplatelet agent on its own,[36] an extended-release formulation of dipyridamole combined with low-dose aspirin, a preparation marketed as Aggrenox, is used for prevention of stroke in patients with transient ischemic attacks.

Mechanism of Action

By inhibiting phosphodiesterase, dipyridamole blocks the breakdown of cAMP. Increased levels of cAMP reduce intracellular calcium and inhibit platelet activation. Dipyridamole also blocks the uptake of adenosine by platelets and other cells. With more extracellular adenosine, there is a further increase in local cAMP levels because the platelet adenosine A_2 receptor and adenylate cyclase are coupled (**Fig. 93.11**).

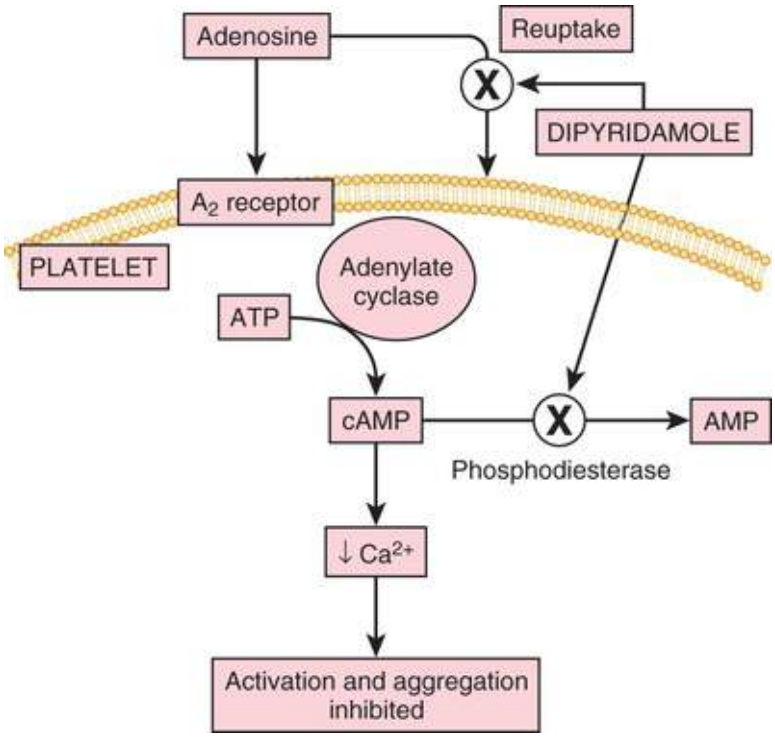

FIGURE 93.11 Mechanism of action of dipyridamole. Dipyridamole increases levels of cAMP in platelets by (1) blocking the reuptake of adenosine, thereby increasing the concentration of adenosine available to bind to the A_2 receptor, and (2) inhibiting phosphodiesterase-mediated cAMP degradation. By promoting calcium uptake, cAMP reduces intracellular levels of calcium. This, in turn, inhibits platelet activation and aggregation.

Dosages

This fixed combination is given twice daily. Each capsule contains 200 mg of extended-release dipyridamole and 25 mg of aspirin.

Side Effects

Because dipyridamole has vasodilatory effects, caution is necessary in patients with coronary artery disease. Gastrointestinal complaints, headache, facial flushing, dizziness, and hypotension can also occur. These symptoms often subside with continued use of the drug.

Indications

Dipyridamole plus aspirin was compared with aspirin or dipyridamole alone and with placebo in patients with an ischemic stroke or a transient ischemic attack. The combination reduced the risk for stroke by 22.1% in comparison with aspirin and by 24.4% in comparison to dipyridamole.[49] A second trial compared dipyridamole plus aspirin with aspirin alone for secondary prevention in patients with ischemic stroke. Vascular death, stroke, or myocardial infarction occurred in 13% of patients given combination therapy and in 16% of those treated with aspirin alone. Although the combination of dipyridamole plus aspirin compares favorably with aspirin, the combination is not superior to clopidogrel. In a large randomized trial that compared dipyridamole plus aspirin with clopidogrel for secondary prevention in patients with ischemic stroke, recurrent stroke event rates were similar (9.0% and 8.8%, respectively), as were rates of vascular death, stroke, and myocardial infarction (13.1% in both treatment arms). However, there was a trend toward more hemorrhagic strokes with dipyridamole plus aspirin than with clopidogrel (0.8% and 0.4%, respectively) and more major bleeding (4.1% and

3.8%, respectively).

Although dipyridamole/aspirin can replace aspirin for stroke prevention, because of the vasodilatory effects of dipyridamole and the paucity of data supporting the usefulness of this drug in patients with symptomatic coronary artery disease, dipyridamole/aspirin is contraindicated in such patients; clopidogrel is a better choice in patients with coronary artery disease.

Glycoprotein IIb/IIIa Receptor Antagonists (see also Chapters 59, 60, and 62)

As a class, parenteral GPIIb/IIIa receptor antagonists have a niche in patients with acute coronary syndromes. The three agents in this class are abciximab, eptifibatide, and tirofiban.

Mechanism of Action

A member of the integrin family of adhesion receptors, GPIIb/IIIa is expressed on the surface of platelets and megakaryocytes. With approximately 80,000 copies per platelet, GPIIb/IIIa is the most abundant receptor. GPIIb/IIIa is inactive on resting platelets. With platelet activation, however, inside-outside signal transduction pathways trigger conformational activation of the receptor. Once activated, GPIIb/IIIa binds fibrinogen and, under high-shear conditions, vWF. Once bound, fibrinogen and vWF bridge adjacent platelets together to induce platelet aggregation.

Although abciximab, eptifibatide, and tirofiban all target the GPIIb/IIIa receptor, they are structurally and pharmacologically distinct (**Table 93.2**).[43] Abciximab is a Fab fragment of a humanized murine monoclonal antibody directed against the activated form of GPIIb/IIIa. Abciximab binds to the activated receptor with high affinity and blocks the binding of adhesive molecules. In contrast to abciximab, eptifibatide and tirofiban are synthetic molecules. Eptifibatide is a cyclical heptapeptide that binds GPIIb/IIIa because it incorporates the KGD motif, whereas tirofiban is a nonpeptidic tyrosine derivative that acts as an RGD mimetic. With its long half-life, abciximab persists on the surface of platelets for up to 2 weeks. Eptifibatide and tirofiban have shorter half-lives.

TABLE 93.2

Features of Glycoprotein IIb/IIIa Antagonists

FEATURE	ABCIXIMAB	EPTIFIBATIDE	TIROFIBAN
Description	Fab fragment of humanized mouse monoclonal antibody	Cyclical KGD-containing heptapeptide	Nonpeptidic RGD mimetic
Specific for GP IIb/IIIa	No	Yes	Yes
Plasma half-life	Short (min)	Long (2.5 hr)	Long (2.0 hr)
Platelet-bound half-life	Long (days)	Short (sec)	Short (sec)
Renal clearance	No	Yes	Yes

KGD, Lys-Gly-Asp sequence; *RGD*, Arg-Gly-Asp sequence.

In addition to targeting the GPIIb/IIIa receptor, abciximab (but not eptifibatide or tirofiban) also inhibits the closely related $\alpha_{v\beta3}$ receptor, which binds vitronectin, and $\alpha_{M\beta2}$, a leukocyte integrin. Inhibition of $\alpha_{v\beta3}$ and $\alpha_{M\beta2}$ may endow abciximab with antiinflammatory and/or antiproliferative properties that extend beyond platelet inhibition.

Dosages

All of the GPIIb/IIIa antagonists are given as an intravenous bolus followed by an infusion. Because of their renal clearance, eptifibatide and tirofiban doses require reduction in patients with renal insufficiency.

Side Effects

In addition to bleeding, thrombocytopenia is the most serious complication. Antibodies directed against neoantigens on GPIIb/IIIa that are exposed on antagonist binding cause thrombocytopenia, which is immune mediated. With abciximab, thrombocytopenia occurs in up to 5% of patients and is severe in approximately 1% of these individuals. Thrombocytopenia is less common with the other two agents and occurs in approximately 1% of patients.

Indications (see also Chapter 62)

Abciximab eptifibatide and tirofiban are used occasionally in patients undergoing PCI, particularly those with acute myocardial infarction, whereas tirofiban and eptifibatide are used in high-risk patients with unstable angina.

Vorapaxar

Unlike the other antiplatelet drugs, vorapaxar inhibits PAR-1, the major thrombin receptor on human platelets. Vorapaxar was compared with placebo for secondary prevention in 26,449 patients with previous myocardial infarction, ischemic stroke, or peripheral artery disease.[50] Overall, vorapaxar reduced the risk for cardiovascular death, myocardial infarction, or stroke by 13% but doubled the risk for intracranial bleeding. In the prespecified subgroup of 17,779 patients with previous myocardial infarction, however, vorapaxar reduced the risk for cardiovascular death, myocardial infarction, or stroke by 20% (from 9.7% to 8.1%). The rate of intracranial hemorrhage was higher with vorapaxar than with placebo (0.6% and 0.4%, respectively; $P = .076$), as was the rate of moderate or severe bleeding (3.4% and 2.1%, respectively; $P < .001$). Based on these data, the drug is now licensed for patients younger than 75 years with myocardial infarction who have no history of stroke, transient ischemic attack, or intracranial bleeding and who weigh more than 60 kg.

Anticoagulants

There are parenteral and oral anticoagulants. Currently available parenteral anticoagulants include heparin, LMWH, fondaparinux, a synthetic pentasaccharide, and bivalirudin. Currently available oral anticoagulants include warfarin; dabigatran etexilate, an oral thrombin inhibitor; and rivaroxaban, apixaban, and edoxaban, oral factor Xa inhibitors.[51]

Parenteral Anticoagulants

Heparin

A sulfated polysaccharide, heparin is isolated from mammalian tissues rich in mast cells (**Table 93.3**). Most commercial heparin is derived from porcine intestinal mucosa and is a polymer of alternating D-glucuronic acid and *N*-acetyl-D-glucosamine residues.[52]

TABLE 93.3

Comparison of Features of Heparin, Low-Molecular-Weight Heparin, and Fondaparinux

FEATURES	HEPARIN	LMWH	FONDAPARINUX
Source	Biologic	Biologic	Synthetic
Molecular weight	15,000	5,000	1,500
Target	Xa and IIa	Xa and IIa	Xa
Bioavailability (%)	30	90	100
Half-life (hr)	1	4	17
Renal excretion	No	Yes	Yes
Antidote	Complete	Partial	No
Heparin-induced thrombocytopenia	<5%	<1%	Rare

Mechanism of Action.

Heparin acts as an anticoagulant by activating antithrombin (previously known as antithrombin III) and accelerating the rate at which it inhibits clotting enzymes, particularly thrombin and factor Xa. Antithrombin, the obligatory plasma cofactor for heparin, belongs to the serine protease inhibitor (serpin) superfamily. Synthesized in the liver and circulating in plasma at a concentration of 2.6 ± 0.4 μM, antithrombin acts as a suicide substrate for its target enzymes.

To activate antithrombin, heparin binds to the serpin via a unique pentasaccharide sequence found on a third of the chains of commercial heparin (**Fig. 93.12**). Heparin chains lacking this pentasaccharide sequence have little or no anticoagulant activity.[53] Once bound to antithrombin, heparin induces a conformational change in the reactive center loop of antithrombin that renders it more readily accessible to its target proteases. This conformational change enhances the rate at which antithrombin inhibits factor Xa by at least two orders of magnitude, but has little effect on the rate of thrombin inhibition by antithrombin. To promote thrombin inhibition, heparin serves as a template that binds antithrombin and thrombin simultaneously. Formation of this ternary complex brings the enzyme in close apposition to the inhibitor, thereby promoting the formation of a stable covalent thrombin-antithrombin complex.

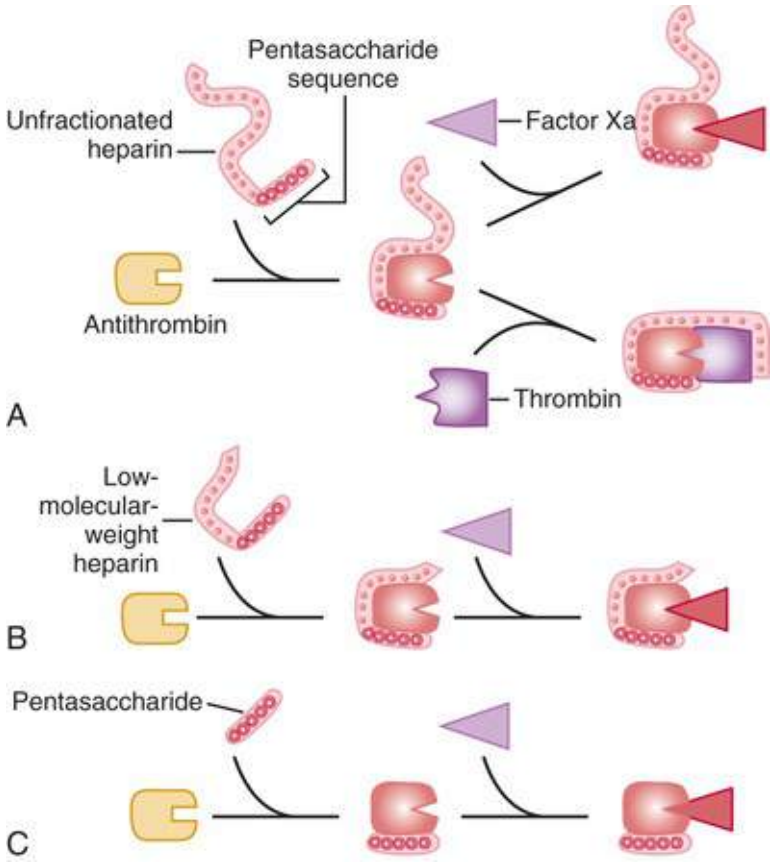

FIGURE 93.12 Mechanism of action of heparin, LMWH, and fondaparinux, a synthetic pentasaccharide. **A,** Heparin binds to antithrombin via its pentasaccharide sequence. This induces a conformational change in the reactive center loop of antithrombin that accelerates its interaction with factor Xa. To potentiate thrombin inhibition, heparin must simultaneously bind to antithrombin and thrombin. Only heparin chains composed of at least 18 saccharide units, which corresponds to a molecular weight of 5400, are of sufficient length to perform this bridging function. With a mean molecular weight of 15,000, all the heparin chains are long enough to do this. **B,** LMWH has greater capacity to potentiate factor Xa inhibition by antithrombin than thrombin does because with a mean molecular weight of 4500 to 6000, at least half of the LMWH chains are too short to bridge antithrombin to thrombin. **C,** Fondaparinux, a synthetic pentasaccharide, only accelerates inhibition of factor Xa by antithrombin because it is too short to bridge antithrombin to thrombin.

Only pentasaccharide-containing heparin chains composed of at least 18 saccharide units (which corresponds to a molecular weight of 5400) have sufficient length to bridge thrombin and antithrombin together.[53] With a mean molecular weight of 15,000 and a range of 5,000 to 30,000, almost all the chains of unfractionated heparin are long enough to provide this bridging function. Consequently, by definition, heparin has equal capacity to promote inhibition of thrombin and factor Xa by antithrombin and has an anti–factor Xa–to–anti–factor IIa (thrombin) ratio of 1 : 1. Heparin causes the release of TFPI from the endothelium. A factor Xa–dependent inhibitor of tissue factor–bound factor VIIa,[8] TFPI may contribute to the antithrombotic activity of heparin. Longer heparin chains induce the release of more TFPI than shorter chains do.

Pharmacology of Heparin.

Heparin requires parenteral administration and is usually administered subcutaneously or by continuous intravenous infusion. If administered subcutaneously for the treatment of thrombosis, the dose must be high enough to overcome the limited bioavailability associated with this method of delivery. In the circulation, heparin binds to the endothelium and to plasma proteins other than antithrombin. Binding of heparin to endothelial cells explains its dose-dependent clearance. At low intravenous doses, the half-life of heparin is short because it rapidly binds to the endothelium. With higher intravenous doses of heparin, the half-life

is longer because heparin clearance is slower once the endothelium is saturated. Clearance is mainly extrarenal; heparin binds to macrophages, which internalize and depolymerize the long heparin chains and secrete shorter chains back into the circulation. Because of its dose-dependent clearance mechanism, the plasma half-life of heparin ranges from 30 to 60 minutes with bolus intravenous doses of 25 and 100 units/kg, respectively.

Once heparin enters the circulation, it binds to plasma proteins other than antithrombin, a phenomenon that reduces the anticoagulant activity of heparin. Some of the heparin-binding proteins found in plasma are acute-phase reactants whose levels are elevated in ill patients. Activated platelets or endothelial cells release other proteins that can bind heparin, such as large multimers of vWF. Activated platelets also release platelet factor 4 (PF4), a highly cationic protein that binds heparin with high affinity. The large amounts of PF4 associated with platelet-rich arterial thrombi can neutralize the anticoagulant activity of heparin. This phenomenon may attenuate heparin's capacity to suppress thrombus growth.

Because levels of heparin binding–proteins in plasma vary from person to person, the anticoagulant response to fixed or weight-adjusted doses of heparin is unpredictable. Consequently, monitoring of coagulation is essential to ensure a therapeutic response, particularly when heparin is administered for the treatment of established thrombosis, because a subtherapeutic anticoagulant response may render patients at risk for recurrent thrombosis, whereas excessive anticoagulation increases the risk for bleeding.

Monitoring the Anticoagulant Effect of Heparin.

The APTT or anti–factor Xa level is used to monitor heparin.[53] Although the APTT is the test most often used for this purpose, there are problems with the assay: APTT reagents vary in their sensitivity to heparin, and the type of coagulometer used for testing can influence the results. Consequently, laboratories must establish a therapeutic APTT range with each reagent-coagulometer combination by measuring both the APTT and anti–factor Xa levels in plasma samples collected from heparin-treated patients. With most APTT reagents and coagulometers in current use, heparin levels are therapeutic with a twofold to threefold prolongation of the APTT. Anti–factor Xa levels can also be used to monitor heparin therapy. With this test, therapeutic heparin levels range from 0.3 to 0.7 units/mL. Although this test is gaining in popularity, anti–factor Xa assays have yet to be standardized, and results can vary widely between laboratories.

Up to 25% of patients with VTE are heparin resistant; they require more than 35,000 units/day to achieve a therapeutic APTT. It is useful to measure anti–factor Xa levels in heparin-resistant patients because many will have a therapeutic anti–factor Xa level despite a subtherapeutic APTT. This dissociation in test results occurs because elevated plasma levels of fibrinogen and factor VIII, both acute-phase proteins, shorten the APTT but have no effect on anti–factor Xa levels.[53] Anti–factor Xa levels are better than the APTT for monitoring heparin in patients who exhibit this phenomenon. Patients with congenital or acquired antithrombin deficiency and those with elevated levels of heparin-binding proteins may also need high doses of heparin to achieve a therapeutic APTT or anti–factor Xa level. If there is good correlation between the APTT and the anti–factor Xa level, either test can be used for monitoring heparin therapy.

Dosages.

For prophylaxis, heparin is usually given in fixed doses of 5000 units subcutaneously two or three times daily. With these low doses, monitoring of coagulation is unnecessary. In contrast, monitoring is essential when the drug is given in higher doses. Fixed-dose or weight-based heparin nomograms are used to standardize heparin regimens and to shorten the time required to achieve a therapeutic anticoagulant

response. At least two heparin nomograms have been validated in patients with VTE, and both reduce the time required to achieve a therapeutic APTT. Weight-adjusted heparin nomograms have also been evaluated in patients with acute coronary syndromes. After an intravenous heparin bolus of 5000 units or 70 units/kg, a heparin infusion rate of 12 to 15 units/kg/hr is usually administered.[53] In contrast, weight-adjusted heparin nomograms for patients with VTE use an initial bolus of 5000 units or 80 units/kg, followed by an infusion of 18 units/kg/hr. Thus achievement of a therapeutic APTT requires higher doses of heparin in patients with VTE than in those with acute coronary syndromes. This difference may reflect differences in thrombus burden. Heparin binds to fibrin, and the fibrin content of extensive deep vein thrombi is greater than that of coronary thrombi.

Traditionally, heparin manufacturers in North America measured heparin potency in USP units, with a unit defined as the concentration of heparin that prevents 1 mL of citrated sheep plasma from clotting for 1 hour after the addition of calcium. In contrast, manufacturers in Europe measured heparin potency with anti-Xa assays that use an international heparin standard for comparison. Because of problems with heparin contamination by oversulfated chondroitin sulfate,[52] which the USP assay system does not detect, North American heparin manufacturers now use the anti-Xa assay to measure heparin potency. Use of international units in place of USP units results in a 10% to 15% reduction in the heparin dose. This change is unlikely to affect patient care because dosing of heparin has been done this way in Europe for many years. Furthermore, heparin monitoring ensures a therapeutic anticoagulant response in high-risk situations, such as cardiopulmonary bypass surgery or PCI.

Limitations of Heparin.

Heparin has pharmacokinetic and biophysical limitations (**Table 93.4**). The pharmacokinetic limitations reflect heparin's propensity to bind in a pentasaccharide-independent fashion to cells and plasma proteins. Binding of heparin to endothelial cells explains its dose-dependent clearance, whereas binding to plasma proteins results in a variable anticoagulant response and can lead to heparin resistance.

TABLE 93.4

Pharmacokinetic and Biophysical Limitations of Heparin

LIMITATIONS	MECHANISM
Poor bioavailability	Limited absorption of long heparin chains
Dose-dependent clearance	Binds to endothelial cells
Variable anticoagulant response	Binds to plasma proteins; levels vary from patient to patient
Reduced activity in the vicinity of platelet-rich thrombi	Neutralized by platelet factor 4 released from activated platelets
Limited activity against factor Xa incorporated into the prothrombinase complex and thrombin bound to fibrin	Reduced capacity of heparin-antithrombin complex to inhibit factor Xa bound to activated platelets and thrombin

The biophysical limitations of heparin reflect the inability of the heparin-antithrombin complex to inhibit factor Xa when it is incorporated into the prothrombinase complex, the complex that converts prothrombin to thrombin, and to inhibit thrombin bound to fibrin. Consequently, factor Xa bound to activated platelets within platelet-rich thrombi can generate thrombin, even in the presence of heparin. Thrombin bound to fibrin protects it from inhibition by the heparin-antithrombin complex. Clot-associated thrombin can then trigger growth of thrombi by locally activating platelets and amplifying its own generation through feedback activation of factors V, VIII, and XI. Neutralization of heparin by the high concentrations of PF4 released from activated platelets within the platelet-rich thrombus further compounds this problem.

Side Effects.

The most common side effect of heparin is bleeding. Other complications include thrombocytopenia, osteoporosis, and elevated levels of transaminases.

Bleeding.

The risk for heparin-induced bleeding increases with higher heparin doses. Concomitant administration of drugs that affect hemostasis, such as antiplatelet or fibrinolytic agents, increases the risk for bleeding, as does recent surgery or trauma.[54] Protamine sulfate will neutralize heparin in patients with serious bleeding. A mixture of basic polypeptides isolated from salmon sperm, protamine sulfate binds heparin with high affinity to form protamine-heparin complexes that undergo renal clearance. Typically, 1 mg of intravenous protamine sulfate neutralizes 100 units of heparin. Anaphylactoid reactions to protamine sulfate can occur, but administration by slow intravenous infusion reduces the risk for this problem.[53]

Thrombocytopenia.

Heparin-induced thrombocytopenia (HIT) is an antibody-mediated process triggered by antibodies against neoantigens on PF4 that are exposed when heparin binds to this protein.[55] These antibodies, which are usually of the IgG subtype, bind simultaneously to the heparin-PF4 complex and to platelet Fc receptors. Such binding activates the platelets and generates platelet microparticles. Circulating microparticles are procoagulant because they express anionic phospholipids on their surface and can bind clotting factors, thereby promoting thrombin generation.

Typically, HIT occurs 5 to 14 days after the initiation of heparin therapy, but it may be manifested earlier if the patient has received heparin within the past 3 months (**Table 93.5**). Even a 50% decrease in the platelet count from the pretreatment value should raise suspicion of HIT in those receiving heparin. HIT is more common in surgical patients than in medical patients and, like many autoimmune disorders, occurs more frequently in females than in males.[55]

TABLE 93.5

Features of Heparin-Induced Thrombocytopenia

FEATURE	DETAILS
Thrombocytopenia	Platelet count of ≤ 100,000/μL or a decrease in platelet count of ≥ 50% from baseline
Timing	Platelet count falls 5-14 days after starting heparin
Type of heparin	More common with unfractionated heparin than with LMWH
Type of patient	More common in surgical patients than in medical patients; more common in women than in men
Thrombosis	Venous thrombosis more common than arterial thrombosis

HIT is associated with either arterial or venous thrombosis. Venous thrombosis, which is manifested as deep vein thrombosis and/or pulmonary embolism, is more common than arterial thrombosis. Arterial thrombosis manifests as ischemic stroke or acute myocardial infarction. Rarely, platelet-rich thrombi in the distal aorta or iliac arteries can cause critical limb ischemia.

The diagnosis of HIT is established via enzyme-linked assays to detect antibodies against heparin-PF4 complexes or via platelet activation assays. Enzyme-linked assays are sensitive but are not specific and can be positive even in the absence of any clinical evidence of HIT.[56] The most specific diagnostic test is the serotonin release assay. This test involves quantification of serotonin release after exposure of washed platelets loaded with labeled serotonin to patient serum in the absence or presence of various concentrations of heparin. If the patient's serum contains HIT antibody, the addition of heparin induces platelet activation and subsequent serotonin release.

To manage HIT, heparin therapy should be stopped in patients with suspected or documented HIT, and

an alternative anticoagulant should be administered to prevent or treat thrombosis (**Table 93.6**).[55] The agents most often used for this indication are parenteral direct thrombin inhibitors, such as lepirudin, argatroban, or bivalirudin, or factor Xa inhibitors, such as fondaparinux or rivaroxaban. Patients with HIT, particularly those with associated thrombosis, often have evidence of increased thrombin generation, which can lead to consumption of protein C. If these patients receive warfarin without a concomitant parenteral anticoagulant, the further decrease in protein C levels induced by the vitamin K antagonist can trigger skin necrosis. To avoid this problem, patients with HIT require treatment with a direct thrombin inhibitor or fondaparinux or rivaroxaban until the platelet count returns to normal levels. At this point, low-dose warfarin therapy can be introduced, and the thrombin inhibitor or fondaparinux can be discontinued when the anticoagulant response to warfarin has been therapeutic for at least 2 days.

TABLE 93.6

Management of Heparin-Induced Thrombocytopenia

Stop all heparin.
Give an alternative anticoagulant, such as lepirudin, argatroban, bivalirudin, fondaparinux, or rivaroxaban.
Do not give platelet transfusions.
Do not give warfarin until the platelet count returns to baseline levels; if warfarin was administered, give vitamin K to restore the INR to normal.
Evaluate for thrombosis, particularly deep vein thrombosis.

Osteoporosis.

Treatment with therapeutic doses of heparin for more than a month can cause a reduction in bone density. This occurs in up to 30% of patients treated over the long term with heparin,[53] and symptomatic vertebral fractures occur in 2% to 3% of these individuals. Studies in vitro and in laboratory animals have provided insight into the pathogenesis of heparin-induced osteoporosis. These investigations suggest that heparin causes bone resorption by decreasing bone formation and enhancing bone resorption. Thus heparin affects the activity of both osteoclasts and osteoblasts.

Elevated Levels of Transaminases.

Therapeutic doses of heparin frequently cause a modest elevation in serum levels of hepatic transaminases without a concomitant increase in the level of bilirubin. Levels of transaminases rapidly return to normal when use of the drug is stopped. The mechanism responsible for this phenomenon is unknown.

Low-Molecular-Weight Heparin

Consisting of smaller fragments of heparin, LMWH is prepared from unfractionated heparin by controlled enzymatic or chemical depolymerization. The mean molecular weight of LMWH is around 5000, one third the mean molecular weight of unfractionated heparin.[53] Because of its advantages over heparin (**Table 93.7**), LMWH has replaced heparin for many indications.

TABLE 93.7

Advantages of Low-Molecular-Weight Heparin and Fondaparinux over Heparin

ADVANTAGE	CONSEQUENCE
Better bioavailability and longer half-life after subcutaneous injection	Can be given subcutaneously once or twice daily for both prophylaxis and treatment
Dose-independent clearance	Simplified dosing
Predictable anticoagulant response	Monitoring of coagulation is unnecessary in most patients
Lower risk for heparin-induced thrombocytopenia	Safer than heparin for short- or long-term administration
Lower risk for osteoporosis	Safer than heparin for long-term administration

Mechanism of Action.

Like heparin, LMWH exerts its anticoagulant activity by activating antithrombin. With a mean molecular weight of 5000, which corresponds to approximately 17 saccharide units, at least half of the pentasaccharide-containing chains of LMWH are too short to bridge thrombin to antithrombin (**see Fig. 93.12**). These chains retain the capacity to accelerate inhibition of factor Xa by antithrombin because this activity results largely from the conformational changes in antithrombin evoked by pentasaccharide binding. Consequently, LMWH catalyzes inhibition of factor Xa by antithrombin more than inhibition of thrombin.[53] Depending on their unique molecular weight distributions, LMWH preparations have anti–factor Xa to anti–factor IIa ratios ranging from 2 : 1 to 4 : 1 (**see Table 93.3**).

Pharmacology of Low-Molecular-Weight Heparin.

Although usually given subcutaneously, LMWH can be administered intravenously if a rapid anticoagulant response is needed. LMWH has pharmacokinetic advantages over heparin. These advantages arise because the shorter heparin chains bind less avidly to endothelial cells, macrophages, and heparin-binding plasma proteins. Reduced binding to endothelial cells and macrophages eliminates the rapid, dose-dependent, and saturable mechanism of clearance that is a characteristic of unfractionated heparin. Instead, clearance of LMWH is not dose dependent and its plasma half-life is longer. Based on measurement of anti–factor Xa levels, LMWH has a plasma half-life of approximately 4 hours. Because of its renal clearance, LMWH can accumulate in patients with renal insufficiency.

LMWH exhibits approximately 90% bioavailability after subcutaneous injection.[53] Because LMWH binds less avidly to heparin-binding proteins in plasma than heparin does, LMWH produces a more predictable dose response, and resistance to LMWH is rare. With a longer half-life and more predictable anticoagulant response, LMWH can be given subcutaneously once or twice daily without monitoring coagulation, even when the drug is administered in treatment doses. These properties render LMWH more convenient than unfractionated heparin. Capitalizing on this feature, studies in patients with VTE have shown that home treatment with LMWH is as effective and safe as in-hospital treatment with continuous intravenous infusions of heparin.[53] Outpatient treatment with LMWH streamlines care, reduces health care costs, and increases patient satisfaction.

Monitoring of Low-Molecular-Weight Heparin.

In most patients, LMWH does not require monitoring of coagulation. If monitoring is necessary, the anti–factor Xa level is measured because most LMWH preparations have little effect on the APTT. Therapeutic anti–factor Xa levels with LMWH range from 0.5 to 1.2 units/mL when measured 3 to 4 hours after drug administration. With prophylactic doses of LMWH, peak anti–factor Xa levels of 0.2 to 0.5 units/mL are desirable.[53]

Situations that may require LMWH monitoring include renal insufficiency and obesity. Monitoring of

LMWH in patients with a creatinine clearance of 50 mL/min or less is advisable to ensure that no drug accumulation takes place. Although weight-adjusted LMWH dosages appear to produce therapeutic anti–factor Xa levels in overweight patients, this approach has not been well studied in those with morbid obesity. It may also be advisable to monitor the anticoagulant activity of LMWH during pregnancy because dose requirements can change, particularly in the third trimester. Monitoring should also be considered in high-risk settings, such as when patients with mechanical heart valves are given LMWH for prevention of valve thrombosis.

Dosages.

The doses of LMWH recommended for prophylaxis or treatment vary depending on the preparation. For prophylaxis, once-daily subcutaneous doses of 4000 to 5000 units are often used, whereas doses of 2500 to 3000 units are given when the drug is administered twice daily. For treatment of VTE, a dose of 150 to 200 units/kg is given if the drug is administered once daily. If a twice-daily regimen is used, a dose of 100 units/kg is given. In patients with unstable angina, LMWH is administered subcutaneously twice daily at a dose of 100 to 120 units/kg. The dose is reduced in patients with renal impairment.

Side Effects.

The major complication of LMWH is bleeding. Metaanalyses suggest that the risk for major bleeding may be lower with LMWH than with unfractionated heparin. HIT and osteoporosis also are less common with LMWH than with unfractionated heparin.

Bleeding.

The risk for bleeding with LMWH increases when antiplatelet or fibrinolytic drugs are given concomitantly.[54] Recent surgery, trauma, or underlying hemostatic defects also increase the risk for bleeding with LMWH. Although protamine sulfate serves as an antidote for LMWH, it incompletely neutralizes the anticoagulant activity of LMWH because it binds only the longer chains.[53] Because longer chains contribute to thrombin inhibition by antithrombin, protamine sulfate completely reverses the anti–factor IIa activity of LMWH. In contrast, protamine sulfate only partially reverses the anti–factor Xa activity of LMWH because the shorter pentasaccharide-containing chains of LMWH do not bind protamine sulfate. Consequently, continuous intravenous unfractionated heparin may be safer than subcutaneous LMWH for patients at high risk for bleeding.

Thrombocytopenia.

The risk for HIT is about fivefold lower with LMWH than with heparin.[55] LMWH binds less avidly to platelets and causes less release of PF4. Furthermore, with lower affinity for PF4 than for heparin, LMWH is less likely to induce the conformational changes in PF4 that trigger the formation of HIT antibodies. LMWH should not be used to treat patients with HIT, because most HIT antibodies exhibit cross-reactivity with LMWH.[55] This in vitro cross-reactivity is not simply a laboratory phenomenon; thrombosis can occur in HIT patients treated with LMWH.

Osteoporosis.

The risk for osteoporosis is lower with long-term LMWH than with heparin.[53] For extended treatment, therefore, LMWH is a better choice than heparin because of the lower risk for osteoporosis and HIT.

Fondaparinux

A synthetic analogue of the antithrombin-binding pentasaccharide sequence, fondaparinux differs from LMWH in several ways (**see Table 93.3**). Fondaparinux is licensed for thromboprophylaxis in medical, general surgical, and high-risk orthopedic patients and as an alternative to heparin or LMWH for the initial treatment of patients with established VTE. Although fondaparinux is licensed as an alternative to heparin or LMWH in patients with acute coronary syndrome in Europe and Canada, it is not approved for this indication in the United States.

Mechanism of Action.

As a synthetic analogue of the antithrombin-binding pentasaccharide sequence found in heparin and LMWH, fondaparinux has a molecular weight of 1728. Fondaparinux binds only to antithrombin (**see Fig. 93.12**) and is too short to bridge thrombin to antithrombin. Consequently, fondaparinux catalyzes inhibition of factor Xa by antithrombin and does not enhance the rate of thrombin inhibition.[53]

Pharmacology of Fondaparinux. (see also Chapter 62).

Fondaparinux exhibits complete bioavailability after subcutaneous injection. With no binding to endothelial cells or plasma proteins, clearance of fondaparinux does not depend on the dosage, and its plasma half-life is 17 hours. The drug is administered subcutaneously once daily. Because of its renal clearance, fondaparinux is contraindicated in patients with creatinine clearance lower than 30 mL/min, and it should be used with caution in those with a creatinine clearance lower than 50 mL/min.[53]

Fondaparinux produces a predictable anticoagulant response after administration in fixed doses because it does not bind to plasma proteins. The drug is given at a dosage of 2.5 mg once daily for prevention of VTE. For initial treatment of established VTE, fondaparinux is given at a dosage of 7.5 mg once daily. The dosage can be reduced to 5 mg once daily for those weighing less than 50 kg and increased to 10 mg for those heavier than 100 kg. When given in these doses, fondaparinux is as effective as heparin or LMWH for the initial treatment of patients with deep vein thrombosis or pulmonary embolism and produces similar rates of bleeding.[52]

Fondaparinux is used at a dosage of 2.5 mg once daily in patients with acute coronary syndromes. When this prophylactic dose of fondaparinux was compared with treatment doses of enoxaparin in patients with non–ST-segment elevation acute coronary syndrome, no difference in the rate of cardiovascular death, myocardial infarction, or stroke was seen at 9 days. The rate of major bleeding, however, was 50% lower with fondaparinux than with enoxaparin, which resulted in a 17% reduction in mortality rates at 1 month with fondaparinux. In patients with acute coronary syndromes who require PCI, there is a risk for catheter thrombosis with fondaparinux unless adjunctive heparin is given.

Side Effects.

Although fondaparinux can induce the formation of HIT antibodies, HIT does not occur.[56] This apparent paradox reflects the fact that induction of HIT requires heparin chains of sufficient length to bind multiple PF4 molecules. Fondaparinux is too short to do so. In contrast to LMWH, there is no cross-reactivity of fondaparinux with HIT antibodies. Consequently, fondaparinux appears to be effective for the treatment of HIT, although large clinical trials supporting its use are lacking.

The major side effect of fondaparinux is bleeding, and it has no antidote. Protamine sulfate has no effect on the anticoagulant activity of fondaparinux because it fails to bind to the drug. Recombinant activated factor VII has reversed the anticoagulant effects of fondaparinux in volunteers, but it is unknown whether this agent controls fondaparinux-induced bleeding.

Parenteral Direct Thrombin Inhibitors

Heparin and LMWH indirectly inhibit thrombin because they require antithrombin to exert their anticoagulant activity. In contrast, direct thrombin inhibitors do not require a plasma cofactor; instead, they bind directly to thrombin and block its interaction with its substrates. Approved parenteral direct thrombin inhibitors include lepirudin, argatroban, and bivalirudin (**Table 93.8**). Lepirudin and argatroban are licensed for the treatment of HIT, whereas bivalirudin is approved as an alternative to heparin in patients undergoing PCI, including those with HIT.

TABLE 93.8

Comparison of the Properties of Hirudin, Bivalirudin, and Argatroban

PROPERTY	HIRUDIN	BIVALIRUDIN	ARGATROBAN
Molecular mass	7000	1980	527
Site or sites of interaction with thrombin	Active site and exosite 1	Active site and exosite 1	Active site
Renal clearance	Yes	No	No
Hepatic metabolism	No	No	Yes
Plasma half-life (minutes)	60	25	45

Lepirudin

A recombinant form of hirudin, lepirudin is a bivalent direct thrombin inhibitor that interacts with the active site of thrombin and with exosite 1, the substrate binding site.[55] For rapid anticoagulation, lepirudin is given by continuous intravenous infusion, but the drug can be administered subcutaneously for thromboprophylaxis. Lepirudin has a plasma half-life of 60 minutes after intravenous infusion and is cleared by the kidneys. Consequently, lepirudin accumulates in patients with renal insufficiency. Antibodies against the drug develop in a high proportion of lepirudin-treated patients. Although these antibodies rarely cause problems, in a small subset of patients they can delay lepirudin clearance and enhance its anticoagulant activity; some of these patients experience serious bleeding.

Lepirudin is usually monitored with the APTT, and the dose is adjusted to maintain an APTT 1.5 to 2.5 times control. The APTT is not an ideal test for monitoring lepirudin therapy because the clotting time plateaus with higher drug concentrations. Although the ecarin clotting time provides a better index of the lepirudin dose than the APTT does, the ecarin clotting time has yet to be standardized, and the test is not available in all coagulation laboratories.

Argatroban

Argatroban, a univalent inhibitor that targets the active site of thrombin, is metabolized in the liver.[55] Consequently, it must be used with caution in patients with hepatic insufficiency. Because it is not cleared by the kidneys, argatroban is safer than lepirudin for patients with HIT and renal impairment. Argatroban is administered by continuous intravenous infusion and has a plasma half-life of approximately 45 minutes. The APTT is used to monitor its anticoagulant effect, and the dosage is adjusted to achieve an APTT 1.5 to 3 times the baseline value, but not to exceed 100 seconds. Argatroban also prolongs the international normalized ratio (INR), a feature that can complicate transitioning of patients to warfarin. This problem can be circumvented by using levels of factor X in place of the INR to monitor warfarin. Alternatively, the argatroban infusion can be stopped for 2 to 3 hours before determination of the INR.

Bivalirudin (see also Chapter 62)

A synthetic 20–amino acid analogue of hirudin, bivalirudin is a divalent thrombin inhibitor.[55] Thus the NH_2-terminal portion of bivalirudin interacts with the active site of thrombin, whereas its COOH-terminal tail binds to exosite 1, the substrate-binding domain on thrombin. Bivalirudin has a plasma half-life of 25 minutes, the shortest half-life of all the parenteral direct thrombin inhibitors. It is degraded by peptidases and is partially excreted via the kidneys. When given in high doses in the cardiac catheterization laboratory, the anticoagulant activity of bivalirudin is monitored with the activated clotting time. With lower doses, its activity can be assessed via the APTT.

Studies comparing bivalirudin with heparin plus a GPIIb/IIIa antagonist suggest that bivalirudin produces less bleeding. This feature, plus its short half-life, renders bivalirudin an attractive alternative to heparin in patients undergoing PCI. Bivalirudin has also been used successfully in patients with HIT who require PCI.[55]

Oral Anticoagulants

For over 60 years, the vitamin K antagonists, such as warfarin, were the only available oral anticoagulants. This situation changed with the introduction of the direct oral anticoagulants, which include dabigatran, rivaroxaban, apixaban, and edoxaban.

Warfarin

A water-soluble vitamin K antagonist initially developed as a rodenticide, warfarin is the coumarin derivative most often prescribed in North America. Like other vitamin K antagonists, warfarin interferes with the synthesis of vitamin K–dependent clotting proteins, which include prothrombin (factor II) and factors VII, IX, and X. Warfarin also impairs synthesis of the vitamin K–dependent anticoagulant proteins C and S.[57]

Mechanism of Action.

All the vitamin K–dependent clotting factors possess glutamic acid residues at their N-terminals. A posttranslational modification adds a carboxyl group to the gamma carbon of these residues to generate gamma-carboxyglutamic acid. This modification is essential for expression of the activity of these clotting factors because it permits calcium-dependent binding of them to anionic phospholipid surfaces. A vitamin K–dependent carboxylase catalyzes the gamma-carboxylation. Thus, vitamin K from the diet undergoes reduction to vitamin K hydroquinone by vitamin K reductase (**Fig. 93.13**). Vitamin K hydroquinone serves as a cofactor for the carboxylase enzyme, which in the presence of carbon dioxide, replaces the hydrogen on the gamma carbon of glutamic acid residues with a carboxyl group. During this process, vitamin K hydroquinone is oxidized to vitamin K epoxide, which then undergoes reduction to vitamin K in a reaction catalyzed by vitamin K epoxide reductase.

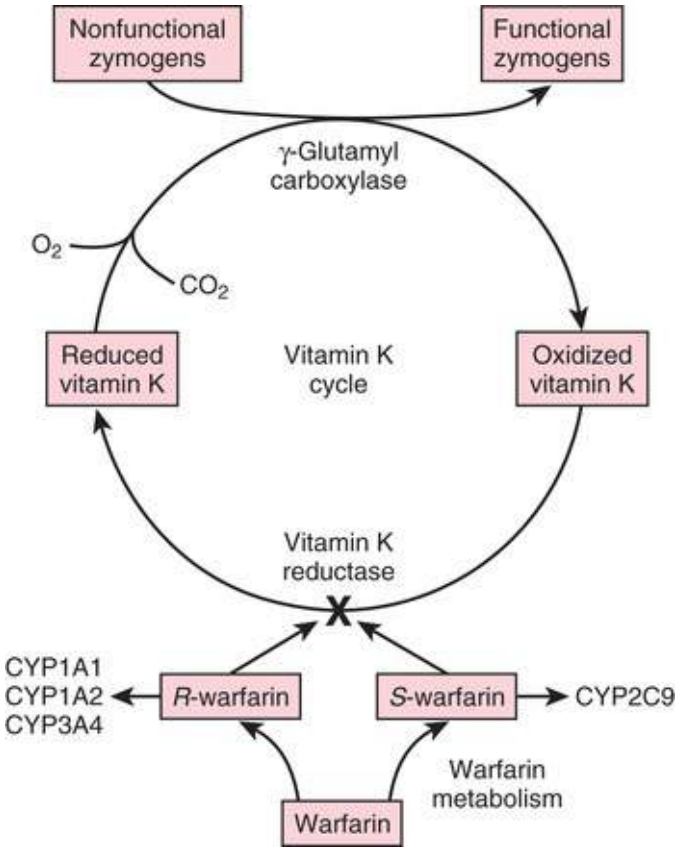

FIGURE 93.13 Mechanism of action of warfarin. A racemic mixture of *S*- and *R*-enantiomers, *S*-warfarin is most active. By blocking vitamin K epoxide reductase, warfarin inhibits the conversion of oxidized vitamin K into its reduced form. This inhibits vitamin K–dependent gamma-carboxylation of factors II, VII, IX, and X because reduced vitamin K serves as a cofactor for a gamma-glutamylcarboxylase, which catalyzes the gamma-carboxylation process, thereby converting prozymogens to zymogens capable of binding calcium and interacting with anionic phospholipid surfaces. *S*-warfarin is metabolized by CYP2C9. Common genetic polymorphisms in this enzyme can influence the metabolism of warfarin. Polymorphisms in the C1 subunit of vitamin K reductase (*VKORC1*) can also affect susceptibility of the enzyme to warfarin-induced inhibition, thereby influencing warfarin dosage requirements.

Warfarin inhibits vitamin K epoxide reductase, thereby blocking the gamma-carboxylation process. This results in the synthesis of partially gamma-carboxylated clotting proteins with little or no biologic activity. Warfarin exerts its anticoagulant activity when the newly synthesized clotting factors with reduced activity gradually replace their fully active counterparts. The antithrombotic effect of warfarin requires a reduction in the functional levels of factor X and prothrombin, clotting factors with half-lives of 24 and 72 hours, respectively.[57] Because the antithrombotic effect of warfarin is delayed, patients with established thrombosis or at high risk for thrombosis require concomitant treatment with a rapidly acting parenteral anticoagulant, such as heparin, LMWH, or fondaparinux.[53]

Pharmacology.

Warfarin is a racemic mixture of *R*- and *S*-isomers. It is rapidly and almost completely absorbed from the gastrointestinal tract. Levels of warfarin in blood peak approximately 90 minutes after administration. Racemic warfarin has a plasma half-life of 36 to 42 hours, and more than 97% of circulating warfarin is bound to albumin. Only the small fraction of unbound warfarin is biologically active.[57]

Warfarin accumulates in the liver, where the two isomers are metabolized via distinct pathways. The more active *S*-enantiomer of warfarin is primarily metabolized by CYP2C9 (**see Fig. 93.12**). Two

relatively common variants, *CYP2C9*2* and *CYP2C9*3*, encode an enzyme with reduced activity. Approximately 25% of whites have at least one variant allele of *CYP2C9*2* or *CYP2C9*3*; these variant alleles are less common in blacks and Asians (**Table 93.9**). Patients with one variant allele require 20% to 30% lower maintenance doses of warfarin, whereas those homozygous for these alleles require 50% to 70% lower doses than do those with the wild-type *CYP2C9*1* alleles. Consistent with the decreased warfarin dose requirement, patients with at least one *CYP2C9* variant allele are at increased risk for bleeding. Thus when compared with individuals with no variant alleles, the relative risk for warfarin-associated bleeding in *CYP2C9*2* or *CYP2C9*3* carriers is 1.9 and 1.8, respectively.[57]

TABLE 93.9

Frequencies of *CYP2C9* Genotypes and *VKORC1* Haplotypes in Different Populations and Their Effect on Warfarin Dose Requirements

GENOTYPE/HAPLOTYPE	FREQUENCY (%)			DOSE REDUCTION COMPARED WITH WILD-TYPE (%)
	Whites	Blacks	Asians	
CYP2C9				
*1/*1	70	90	95	—
*1/*2	17	2	0	22
*1/*3	9	3	4	34
*2/*2	2	0	0	43
*2/*3	1	0	0	53
*3/*3	0	0	1	76
VKORC1				
Non-A/non-A	37	82	7	—
Non-A/A	45	12	30	26
A/A	18	6	63	50

Warfarin interferes with the vitamin K cycle by inhibiting the C1 subunit of vitamin K epoxide reductase (VKORCI).[57] Polymorphisms in *VKORC1* can influence the anticoagulant response to warfarin. Several genetic variations of *VKORC1* are in strong linkage disequilibrium and have been designated as non-A haplotypes. *VKORC1* variants are more prevalent than variants of *CYP2C9*. Asians have the highest prevalence of *VKORC1* variants, followed by whites and blacks. Warfarin dose requirements for patients heterozygous or homozygous for the A haplotype are 25% and 50% lower, respectively, than the dose needed for patients with the non-A/non-A haplotype. Polymorphisms in *CYP2C9* and *VKORC1* explain up to 25% of the variability in warfarin dose requirements.[58-60] These findings prompted the U.S. Food and Drug Administration to amend the prescribing information for warfarin to recommend lower starting doses for patients with the *CYP2C9* and *VKORC1* genetic variants. In addition to genetic factors, fluctuations in the dietary intake of vitamin K, drugs, and various disease states influence the anticoagulant effect of warfarin. Consequently, computerized genotype-based warfarin-dosing algorithms also include pertinent patient characteristics, such as age, body weight, and concomitant medications.[58] Although these algorithms streamline warfarin dosing, randomized trials following time in therapeutic range with genotype-based warfarin dosing have yielded mixed results. It remains unclear whether better dose identification improves patient outcomes in terms of reducing hemorrhagic complications or recurrent thrombotic events.[59,60]

Monitoring.

Warfarin therapy is most often monitored with the prothrombin time, a test sensitive to reductions in the levels of prothrombin, factor VII, and factor X.[57] The test involves the addition of thromboplastin, a reagent that contains tissue factor, phospholipid, and calcium, to citrated plasma and determination of the time until clot formation. Thromboplastins vary in their sensitivity to reductions in the levels of vitamin

K–dependent clotting factors. Consequently, less sensitive thromboplastins will trigger the administration of higher doses of warfarin to achieve a target prothrombin time. This issue can cause problems because higher doses of warfarin increase the risk for bleeding.

The INR was developed to circumvent many of the problems associated with the prothrombin time. To calculate the INR, the patient's prothrombin time is divided by the mean normal prothrombin time, and this ratio is then multiplied by the international sensitivity index (ISI), an index of the sensitivity of the thromboplastin used for determination of the prothrombin time to reductions in levels of the vitamin K–dependent clotting factors. Highly sensitive thromboplastins have an ISI of 1.0. Most current thromboplastins have ISI values that range from 1.0 to 1.4.[57]

Although the INR has helped standardize anticoagulant practice, problems persist. The precision of INR determination varies depending on reagent-coagulometer combinations, which has led to variability in INR results. Unreliable reporting of the ISI by thromboplastin manufacturers also complicates determination of the INR. Furthermore, every laboratory must establish the mean normal prothrombin time with each new batch of thromboplastin reagent. To accomplish this, the prothrombin time must be measured in fresh plasma samples from at least 20 healthy volunteers via the same coagulometer that is used for patient samples.

For most indications, warfarin is administered at doses that produce a target INR of 2.0 to 3.0. An exception is patients with mechanical heart valves in the mitral position or in patients with a mechanical heart valve in other positions who have additional risk factors for stroke, such as atrial fibrillation, in whom a target INR of 2.5 to 3.5 is recommended. Studies in patients with atrial fibrillation demonstrate an increased risk for ischemic stroke when the INR falls below 1.7 and an increase in bleeding with INR values higher than 4.5. These findings highlight the narrow therapeutic window of vitamin K antagonists. In support of this concept, a study in patients receiving long-term warfarin therapy for unprovoked VTE demonstrated a higher rate of recurrent VTE with a target INR of 1.5 to 1.9 than with a target INR of 2.0 to 3.0.

Dosages.

Warfarin is usually started at a dose of 5 to 10 mg. Lower doses are used for patients with *CYP2C9* or *VKORC1* polymorphisms that affect the pharmacodynamics or pharmacokinetics of warfarin and render patients more sensitive to the drug. The dose is then titrated to achieve the desired target INR. Because of its delayed onset of action, patients with established thrombosis or those at high risk for thrombosis are given concomitant treatment with a rapidly acting parenteral anticoagulant, such as heparin, LMWH, or fondaparinux. Initial prolongation of the INR reflects a reduction in the functional levels of factor VII. Consequently, concomitant treatment with the parenteral anticoagulant should be continued until the INR has been therapeutic for at least 2 consecutive days. A minimum 5-day course of parenteral anticoagulation is recommended to ensure that the levels of prothrombin have fallen into the therapeutic range with warfarin.

The narrow therapeutic window of warfarin renders frequent monitoring of coagulation necessary to ensure a therapeutic anticoagulant response. Even patients with stable warfarin dose requirements should have their INR determined every 3 to 4 weeks. Although a recent study has raised the possibility that testing every 12 weeks may suffice in such patients, these results require confirmation in a large number of patients.[61] More frequent INR monitoring is necessary with the introduction of new concomitant medications because many drugs enhance or reduce the anticoagulant effects of warfarin.

Side Effects.

Like all anticoagulants, the major side effect of warfarin is bleeding; a rare complication is skin necrosis. Warfarin crosses the placenta and can cause fetal abnormalities, so it should not be used during pregnancy.

Bleeding.

At least half of the bleeding complications with warfarin occur when the INR exceeds the therapeutic range. Bleeding complications may be mild, such as epistaxis or hematuria, or more severe, such as retroperitoneal or gastrointestinal bleeding. Life-threatening intracranial bleeding can also occur. To minimize the risk for bleeding, the INR should be maintained in the therapeutic range. In asymptomatic patients whose INR is between 3.5 and 9, warfarin should be withheld until the INR returns to the therapeutic range. If the patient is at high risk for bleeding, sublingual or oral vitamin K can be administered. A vitamin K dose of 1 to 2.5 mg is usually adequate for patients with an INR between 4.9 and 9, whereas 2.5 to 5 mg can be used for those with an INR higher than 9. Higher doses of oral vitamin K (5 to 10 mg) produce more rapid reversal of the INR and may be helpful if the INR is excessively high.

Patients with serious bleeding need additional treatment. These patients require 10 mg of vitamin K by slow intravenous infusion with additional doses of vitamin K until the INR is in the normal range and four factor prothrombin complex concentrate to replace the vitamin K–dependent clotting proteins. Prothrombin complex concentrate is preferred over fresh frozen plasma for warfarin reversal because it normalizes the INR more rapidly and because the volume of administration is much smaller.[57]

Warfarin-treated patients who experience bleeding when their INR is in the therapeutic range require investigation of the cause of the bleeding. Those with gastrointestinal bleeding often have underlying peptic ulcer disease or a tumor. Similarly, investigation of hematuria or uterine bleeding in patients with a therapeutic INR may unmask a tumor of the genitourinary tract.

Skin Necrosis.

A rare complication of warfarin, skin necrosis usually occurs 2 to 5 days after initiation of therapy. Well-demarcated erythematous lesions form on the thighs, buttocks, breasts, or toes. Typically, the center of the lesion becomes progressively necrotic. Examination of skin biopsy specimens taken from the borders of these lesions reveals thrombi in the microvasculature.

Warfarin-induced skin necrosis occurs in patients with congenital or acquired deficiencies of protein C or protein S or in patients with HIT who are not receiving an alternate parenteral anticoagulant.[57] Initiation of warfarin therapy in these patients produces a precipitous fall in plasma levels of proteins C or S, thereby eliminating this important anticoagulant pathway before warfarin exerts an antithrombotic effect through lowering the functional levels of factor X and prothrombin. The resultant procoagulant state triggers thrombosis that is localized to the microvasculature of fatty tissues for unknown reasons.

Treatment involves discontinuation of warfarin and reversal with vitamin K, if needed. An alternative anticoagulant, such as heparin or LMWH, or fondaparinux or rivaroxaban in patients with HIT, should be given to patients with thrombosis. Protein C concentrates may accelerate healing of the skin lesions in protein C–deficient patients; fresh frozen plasma may be of value for those with protein S deficiency. Occasionally, skin grafting is necessary in those with extensive skin loss. Because of the potential for skin necrosis, patients with known protein C or protein S deficiency require overlapping treatment with a parenteral anticoagulant when initiating warfarin therapy. Warfarin should be started at low doses in these patients, and the parenteral anticoagulant should be continued until the INR is therapeutic for at least 2 to 3 consecutive days.

Pregnancy.

Warfarin crosses the placenta and can cause fetal abnormalities or bleeding. The fetal abnormalities include a characteristic embryopathy, which consists of nasal hypoplasia and stippled epiphyses. The risk for embryopathy is highest with warfarin administration in the first trimester of pregnancy. Central nervous system abnormalities can also occur with exposure to warfarin at any time during pregnancy. Finally, maternal administration of warfarin produces an anticoagulant effect in the fetus that can cause bleeding. This is of particular concern at delivery, when trauma to the head during passage through the birth canal can lead to intracranial bleeding. Because of these potential problems, warfarin is contraindicated in pregnancy, particularly in the first and third trimesters. Instead, heparin, LMWH, or fondaparinux can be given during pregnancy for prevention or treatment of thrombosis. Warfarin does not pass into breast milk and thus is safe for nursing mothers.

Special Problems.

Patients with a LA or those who need urgent or elective surgery present special challenges. Observational studies have suggested that patients with thrombosis complicating antiphospholipid syndrome require higher-intensity warfarin regimens to prevent recurrent thromboembolic events, an approach that increases the risk for bleeding. Recent randomized trials, however, indicated that usual-intensity warfarin treatment (INR of 2.0 to 3.0) is as effective as higher-intensity therapy and produces less bleeding.[62] Monitoring of warfarin can be problematic in patients with antiphospholipid syndrome if the LA prolongs the baseline INR; factor X levels can be used instead of the INR in such patients.

There is no need to stop warfarin treatment before procedures associated with a low risk for bleeding, including dental cleaning, simple dental extraction, cataract surgery, or skin biopsy.[57] In contrast, warfarin must be stopped 5 days before elective invasive procedures associated with a moderate or high risk for bleeding to allow the INR to return to normal levels. Only patients at high risk for thrombosis while not taking warfarin (such as those with mechanical heart valves or atrial fibrillation patients with a prior history of stroke) require bridging with once- or twice-daily subcutaneous injections of LMWH when the INR falls below 2.0. The last dose of LMWH should be given 12 to 24 hours before the procedure, depending on whether LMWH is administered twice or once daily, respectively. Once hemostasis is secure after the procedure, warfarin can be restarted. Thromboprophylaxis with LMWH can be given starting the day after major surgery and should be continued until the INR is therapeutic.

Direct Oral Anticoagulants (see also Chapters 38, 59, 60, and 84)

Direct oral anticoagulants that target thrombin or factor Xa are now available as alternatives to warfarin. These drugs have a rapid onset of action and half-lives that permit once- or twice-daily administration. Designed to produce a predictable level of anticoagulation, the new oral agents are more convenient to administer than warfarin because they are given in fixed doses without the need for routine monitoring of coagulation. As a class, the direct oral anticoagulants are at least as effective as warfarin and produce less serious bleeding, in particular, they cause less intracranial hemorrhage.

Mechanism of Action.

The new oral anticoagulants are small molecules that bind reversibly to the active site of their target enzyme. **Table 93.10** summarizes the pharmacologic features of these agents.

TABLE 93.10

Comparison of the Features of the New Oral Anticoagulants

FEATURES	RIVAROXABAN	APIXABAN	EDOXABAN	DABIGATRAN
Target	Xa	Xa	Xa	IIa
Molecular weight	436	460	548	628
Prodrug	No	No	No	Yes
Bioavailability (%)	80	60	50	6
Time to peak (hr)	3	3	2	2
Half-life (hr)	7-11	12	9-14	12-17
Renal excretion (%)	33	25	50	80

Dosages.

For prevention of stroke in patients with nonvalvular atrial fibrillation, rivaroxaban is given at a dosage of 20 mg once daily, with a reduction to 15 mg once daily in patients with a creatinine clearance of 15 to 49 mL/min; dabigatran is given at a dosage of 150 mg twice daily, with a reduction to 75 mg twice daily in those with a creatinine clearance of 15 to 30 mL/min; apixaban is given at a dosage of 5 mg twice daily, with a reduction to 2.5 mg twice daily for patients with at least two of the "ABC" criteria (i.e., *a*ge over 80 years, *b*ody weight under 60 kg, and *c*reatinine over 1.5 g/dL); and edoxaban is given at a dosage of 60 mg once daily for patients with a creatinine clearance of 50 to 95 mL/min and with a reduction to 30 mg once daily for patients with any one of the following criteria: creatinine clearance 15 to 50 mL/min, body weight of 60 kg or less, or use of potent P-glycoprotein inhibitors, such as verapamil or quinidine.

Dabigatran, rivaroxaban, apixaban, and edoxaban are also licensed for treatment of patients with VTE. Dabigatran and edoxaban are started after patients have received at least a 5-day course of treatment with a parenteral anticoagulant such as LMWH; dabigatran is given at a dose of 150 mg twice daily provided the creatinine clearance is over 30 mL/min, and the dosage regimen for edoxaban is identical to that used in patients with atrial fibrillation. In contrast, rivaroxaban and apixaban can be given in all-oral regimens; rivaroxaban is started at a dose of 15 mg twice daily for 21 days and is then reduced to 20 mg once daily thereafter, whereas apixaban is started at a dose of 10 mg twice daily for 7 days and is then reduced to 5 mg twice daily thereafter.[63] For long-term secondary prevention, the dosage of apixaban can be lowered to 2.5 mg twice daily and the dose of rivaroxaban can be lowered to 10 mg once daily, doses that have safety profiles similar to those of placebo and aspirin, respectively.[64]

Dabigatran, rivaroxaban, and apixaban are licensed for thromboprophylaxis after elective hip or knee replacement surgery; edoxaban is not licensed for this indication except in Japan. Thromboprophylaxis is started after surgery and is continued for at least 30 days in patients undergoing hip replacement and for 10 to 14 days in patients undergoing knee replacement. Dabigatran is given at a dose of 220 mg once daily, whereas rivaroxaban and apixaban are given at doses of 10 mg once daily and 2.5 mg twice daily, respectively.

Monitoring.

Although administered without routine monitoring, in some situations determination of the anticoagulant activity of the direct oral anticoagulants can be helpful,[65] including assessment of adherence, detection of accumulation or overdose, identification of bleeding mechanisms, and determination of activity before surgery or intervention. For qualitative assessment of anticoagulant activity, the prothrombin time can be used for factor Xa inhibitors and the APTT for dabigatran. Rivaroxaban and edoxaban prolong the prothrombin time more than apixaban does. In fact, because apixaban has such a limited effect on the prothrombin time, anti–factor Xa assays are needed to assess its activity.[65] The effect of the drugs on tests

of coagulation varies depending on the reagents used to perform the tests, and variability increases with conversion of the prothrombin time to an INR. Chromogenic anti–factor Xa assays and the diluted thrombin clotting time or ecarin clotting or chromogenic assays with appropriate calibrators provide quantitative assays to measure plasma levels of the factor Xa inhibitors and dabigatran, respectively.[65]

Side Effects.

As with any anticoagulant, bleeding is the most common side effect of the direct oral anticoagulants. Although the direct oral anticoagulants are associated with less intracranial bleeding than warfarin is, the risk for gastrointestinal bleeding is higher with dabigatran (at the 150-mg, twice-daily dose), rivaroxaban, and edoxaban (at the 60-mg, once-daily dose) than with warfarin. Dyspepsia occurs in up to 10% of patients treated with dabigatran; this problem improves with time and can be minimized by taking the drug with food.

Periprocedural Management.

Like warfarin, the direct oral anticoagulants must be stopped before surgical procedures associated with a moderate or high risk for bleeding.[65] The drugs should be withheld for 1 to 2 days or longer if renal function is impaired. Assessment of residual anticoagulant activity before high-risk procedures is prudent if such assays are available. After surgery, patients should receive thromboprophylaxis with LMWH until hemostasis is restored, at which point the direct oral anticoagulants can be restarted.

Cardiac procedures such as atrial fibrillation ablation or pacemaker implantation can safely be performed without interruption of the direct oral anticoagulants. However, it may be prudent to hold the dose in the morning of the day of the procedure to avoid intervention at peak drug levels.

Management of Bleeding.

With minor bleeding, withholding one or two doses of drug is usually sufficient.[66] With more serious bleeding, the approach is similar to that with warfarin, except that vitamin K administration is of no benefit; the anticoagulant and any antiplatelet drugs should be withheld, the patient should be resuscitated with fluids and blood products as necessary, and the bleeding site should be identified and managed. Coagulation testing will determine the extent of anticoagulation, and renal function should be assessed so that the half-life of the drug can be calculated.[66] Timing of the last dose of anticoagulant is important, and oral activated charcoal may help prevent absorption of drug administered in the past 4 hours particularly in cases of overdose. If bleeding continues or is life-threatening or if it occurs in a critical organ (e.g., the eye) or in a closed space (e.g., the pericardium or retroperitoneum), reversal of the anticoagulant should be considered.

Idarucizumab is licensed for dabigatran reversal in patients with serious bleeding or in those requiring urgent surgery or intervention.[67] A humanized antibody fragment, idarucizumab binds dabigatran with 350-fold higher affinity than that of dabigatran for thrombin to form an essentially irreversible complex that is cleared by the kidneys. (**Table 93.11**) Idarucizumab is given intravenously as a 5-g bolus and is supplied in a box containing two 50-mL vials, each containing 2.5 g of idarucizumab.[67] Idarucizumab rapidly reverses the anticoagulant effects of dabigatran and normalizes the aPTT, diluted thrombin time, or ecarin clot time.[68]

TABLE 93.11

Reversal Agents for Direct Oral Anticoagulants

FEATURE	IDARUCIZUMAB	ANDEXANET ALFA	CIRAPARANTAG
Structure	Humanized antibody fragment	Recombinant human factor Xa variant	Synthetic, small cationic molecule
Mass (Da)	47,776	39,000	573
Mechanism of action	Binds dabigatran with high affinity	Competes with factors Xa (and IIa) for binding	Binds via hydrogen bonding
Target	Dabigatran	Rivaroxaban, apixaban, edoxaban and heparins	Dabigatran, rivaroxaban, apixaban, edoxaban and heparins
Administration	Intravenous bolus	Intravenous bolus followed by a 2 hour infusion	Intravenous bolus
Measurement of Reversal	Activated partial thromboplastin time, diluted thrombin time, or ecarin clotting time or chromogenic assay	Calibrated anti-factor Xa assays	Whole-blood clotting time
Elimination	Renal (catabolism)	Not reported	Not reported
Cost	$3,500 per dose in the United States	Unknown; likely to be at least as much as idarucizumab	Likely to be low

Andexanet alfa and ciraparantag are under development for reversal of rivaroxaban, apixaban, and edoxaban, but neither is licensed (**see Table 93.11**). Until these agents are available, 4-factor prothrombin complex concentrate (25 to 50 units/kg) should be given to reverse them.[66] If there is continued bleeding, activated prothrombin complex concentrate (50 units/kg) or recombinant factor VIIa (90 µg/kg) can be administered.[66]

Andexanet alfa and ciraparantag are specific reversal agents. Andexanet alfa is a recombinant variant of factor Xa. Its active-site serine residue has been replaced with an alanine residue to eliminate catalytic activity, and its membrane-binding domain has been removed to circumvent its incorporation into the prothrombinase complex.[69] Andexanet serves as a decoy and binds rivaroxaban, apixaban, and edoxaban and sequesters them until they can be cleared. It also reverses heparin, LMWH, and fondaparinux by competing with factor Xa and thrombin for the antithrombin-heparin complex. It is administered as an intravenous bolus of 400 mg, followed by a 2-hour infusion of 480 mg, to reverse apixaban or rivaroxaban if the last dose was taken more than 7 hours previously. It is administered as an intravenous bolus of 800 mg, followed by a 2-hour infusion of 960 mg, to reverse edoxaban or rivaroxaban if the last dose was taken within the past 7 hours.[70,71] When given in this manner to patients taking these drugs who presented with serious bleeding, andexanet reversed the anti–factor Xa activity while it was administered and appeared to restore hemostasis.[70,71] Additional efficacy and safety information is needed prior to its approval.

At an earlier stage of development than andexanet, ciraparantag is a synthetic, cationic small molecule that binds rivaroxaban, apixaban, and edoxaban, as well as dabigatran, heparin, LMWH, and fondaparinux. When given as an intravenous bolus to volunteers who took 60 mg of edoxaban, ciraparantag reduced the whole-blood clotting time in a concentration-dependent manner.[72] Because it binds citrate and other calcium chelators, routine tests of coagulation, such as the INR, APTT or anti–factor Xa activity cannot be used to monitor ciraparantag reversal. Although the whole-blood clotting time may be useful for this purpose, the test is not widely available. Therefore, additional studies are needed before ciraparantag will be approved.

Pregnancy.

As small molecules, the direct oral anticoagulants can all pass through the placenta. Consequently, these agents are contraindicated in pregnancy, and when used by women of childbearing potential, appropriate contraception is important. Small amounts of rivaroxaban pass into breast milk, and it is unknown whether the other direct oral anticoagulants also do so. Therefore, direct oral anticoagulants should not be used in nursing mothers.

Novel Anticoagulants in Development

Although the direct oral anticoagulants represent a major advance in oral anticoagulation therapy, the search for more effective and safer anticoagulants continues. Evidence showing that factor XII and factor XI, components on the contact system, are important for thrombus stabilization and growth has caused these factors to emerge as promising targets for novel anticoagulants. Supporting this concept, a phase II, proof-of-concept study revealed that lowering factor XI levels with an antisense oligonucleotide prior to elective knee replacement surgery was more effective than enoxaparin in preventing postoperative VTE without increasing the risk of bleeding.[73] More studies with this and other inhibitors of factor XI or factor XII are needed to identify the better target and to assess efficacy and safety.

Fibrinolytic Drugs (see also Chapter 59)

Used to degrade thrombi, fibrinolytic drugs are administered systemically or are delivered via catheters directly into the substance of the thrombus. Currently approved fibrinolytic agents include streptokinase; acylated plasminogen streptokinase activator complex (anistreplase); urokinase; recombinant t-PA (rt-PA), also known as alteplase or activase; and two recombinant derivatives of rt-PA, tenecteplase and reteplase. Each of these agents acts by converting the proenzyme, plasminogen, to plasmin, the active enzyme.[10] There are two pools of plasminogen—circulating plasminogen and fibrin-bound plasminogen (**Fig. 93.14**). Plasminogen activators that preferentially activate fibrin-bound plasminogen are fibrin specific. In contrast, nonspecific plasminogen activators do not discriminate between fibrin-bound and circulating plasminogen.[74] Activation of circulating plasminogen results in the generation of unopposed plasmin, which can trigger the systemic lytic state. Alteplase and its derivatives are fibrin-specific plasminogen activators, whereas streptokinase, anistreplase, and urokinase are nonspecific agents.

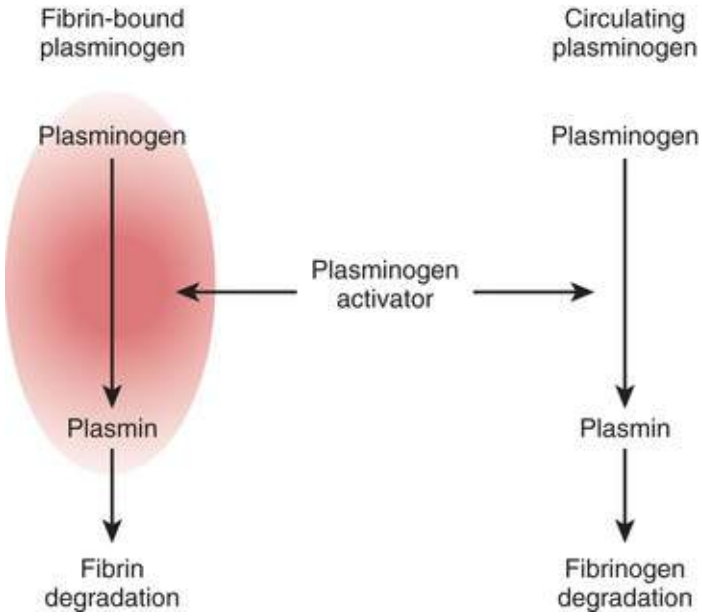

FIGURE 93.14 Consequences of activation of fibrin-bound or circulating plasminogen. The fibrin specificity of plasminogen activators reflects their capacity to distinguish between fibrin-bound and circulating plasminogen, which depends on their affinity for fibrin. Plasminogen activators with high affinity for fibrin preferentially activate fibrin-bound plasminogen. This results in the generation of plasmin on the fibrin surface. Fibrin-bound plasmin, which is protected from inactivation by alpha$_2$-antiplasmin, degrades fibrin to yield soluble fibrin degradation products. In contrast, plasminogen activators with little or no affinity for fibrin do not distinguish between fibrin-bound and circulating plasminogen. Activation of circulating plasminogen results in systemic plasminemia and subsequent degradation of fibrinogen and other clotting factors.

Streptokinase

Unlike other plasminogen activators, streptokinase is not an enzyme and does not directly convert plasminogen to plasmin. Instead, it forms a 1 : 1 stoichiometric complex with plasminogen, thereby inducing a conformational change in plasminogen that exposes its active site (**Fig. 93.15**). This conformationally altered plasminogen then converts additional plasminogen molecules to plasmin.[75] Streptokinase has no affinity for fibrin, and the streptokinase-plasminogen complex activates both free and fibrin-bound plasminogen. Activation of circulating plasminogen generates sufficient amounts of plasmin to overwhelm alpha$_2$-antiplasmin. Unopposed plasmin not only degrades fibrin in the occlusive thrombus but also induces a systemic lytic state.[74]

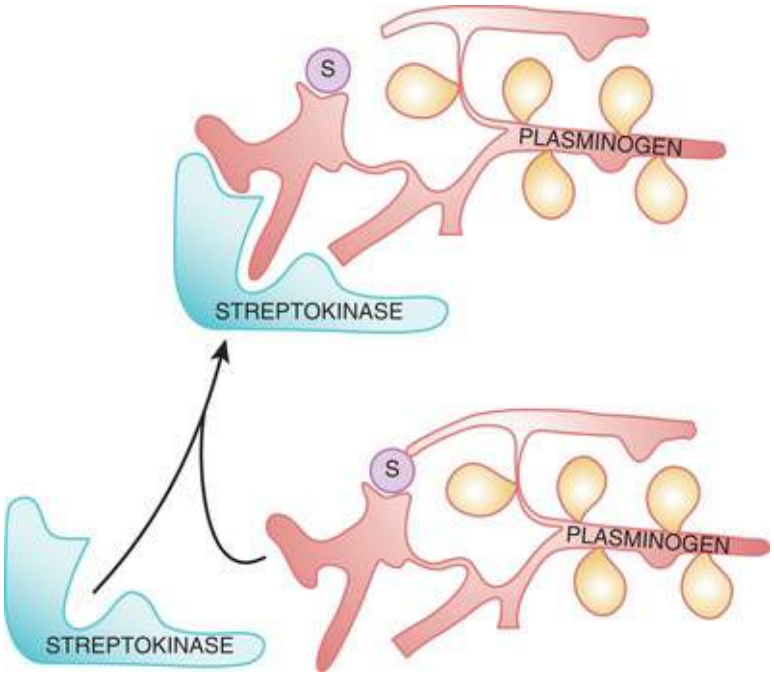

FIGURE 93.15 Mechanism of action of streptokinase. Streptokinase binds to plasminogen and induces a conformational change in plasminogen that exposes its active site. The streptokinase/plasmin(ogen) complex then serves as the activator of additional plasminogen molecules.

When given systemically to patients with acute myocardial infarction, streptokinase reduces mortality rates. For this indication the drug is usually administered as an intravenous infusion of 1.5 million units over a period of 30 to 60 minutes. Patients who receive streptokinase can form antibodies against it, as can patients with previous streptococcal infection. These antibodies can reduce the effectiveness of streptokinase. Allergic reactions occur in approximately 5% of patients treated with streptokinase. They may be manifested as a rash, fever, chills, and rigors; rarely, anaphylactic reactions can occur. Transient hypotension is common with streptokinase and probably reflects plasmin-mediated release of bradykinin. The hypotension usually responds to leg elevation and administration of intravenous fluids and low doses of vasopressors, such as dopamine or norepinephrine.

Anistreplase

To generate anistreplase, streptokinase is mixed with equimolar amounts of Lys-plasminogen, a plasmin-cleaved form of plasminogen with a Lys residue at its N-terminal. The active site of Lys-plasminogen exposed on combination with streptokinase is then blocked with an anisoyl group. After intravenous infusion, the anisoyl group is slowly removed by natural deacylation, which yields a half-life of approximately 100 minutes for the complex.[76] This allows drug administration via a single bolus infusion. Although it is more convenient to administer, anistreplase offers few mechanistic advantages over streptokinase. Like streptokinase, anistreplase does not distinguish between fibrin-bound and circulating plasminogen. Consequently, anistreplase produces a systemic lytic state. Similarly, allergic reactions and hypotension are just as frequent with anistreplase as they are with streptokinase. When anistreplase was compared with alteplase in patients with acute myocardial infarction, reperfusion was achieved more rapidly with alteplase than with anistreplase. Improved reperfusion was associated with a trend toward better clinical outcomes and reduced mortality rates with alteplase. The modest improvement in outcomes and the high cost of anistreplase dampened enthusiasm for its use.

Urokinase

Originally isolated from cultured fetal kidney cells and later synthesized using recombinant DNA technology, urokinase is a two-chain serine protease with a molecular weight of 34,000.[74] Urokinase directly converts plasminogen to plasmin. Unlike streptokinase, urokinase is not immunogenic, and allergic reactions are rare. Urokinase produces a systemic lytic state because it does not discriminate between fibrin-bound and circulating plasminogen. Despite many years of use, systemic urokinase has never been evaluated for coronary fibrinolysis; instead, urokinase was mostly used for catheter-directed lysis of thrombi in the deep veins or in peripheral arteries. Because of production problems, the availability of urokinase is limited and it is rarely used.

Alteplase

A recombinant form of single-chain t-PA, alteplase has a molecular weight of 68,000. Plasmin rapidly converts alteplase into its two-chain form. The interaction of alteplase with fibrin is mediated by the finger domain and, to a lesser extent, by the second kringle domain (**Fig. 93.16**).[10] Alteplase has a considerably higher affinity for fibrin than for fibrinogen. Consequently, the catalytic efficiency of plasminogen activation by alteplase is two to three orders of magnitude higher in the presence of fibrin than in the presence of fibrinogen.[74] Although alteplase preferentially activates plasminogen in the presence of fibrin, it is not as fibrin selective as first thought. Its fibrin specificity is limited because like fibrin, (DD)E, the major soluble degradation product of cross-linked fibrin, binds alteplase and plasminogen with high affinity. As a result, (DD)E is as potent as fibrin as a stimulator of plasminogen activation by alteplase. Plasmin generated on the fibrin surface results in thrombolysis, whereas plasmin generated on the surface of circulating (DD)E degrades fibrinogen. Fibrinogenolysis results in the accumulation of fragment X, a high-molecular-weight clottable fibrinogen degradation product. Incorporation of fragment X into hemostatic plugs formed at sites of vascular injury renders them susceptible to lysis.[77] This phenomenon may contribute to alteplase-induced bleeding.

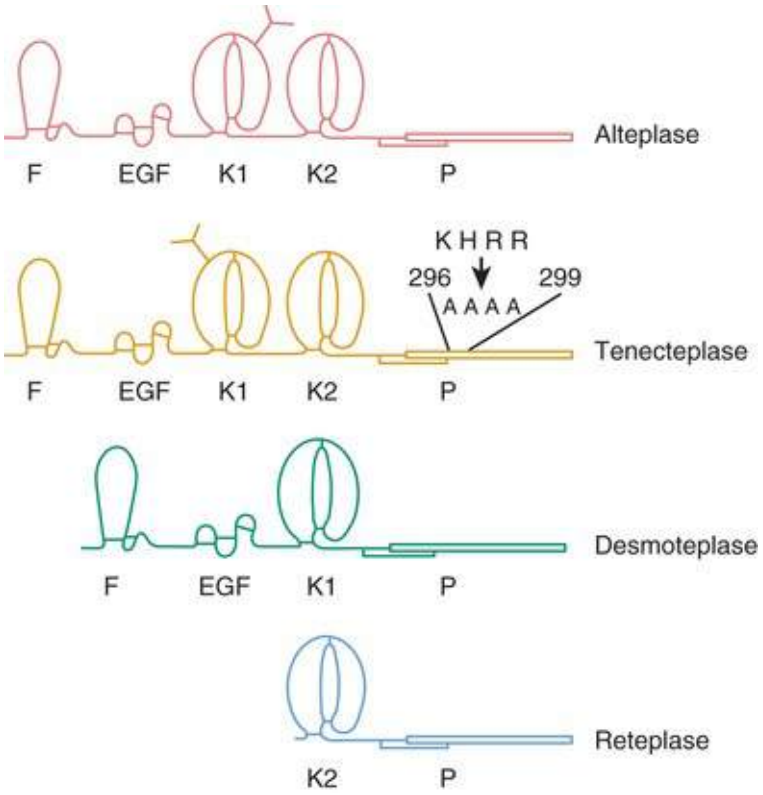

FIGURE 93.16 Domain structures of alteplase, tenecteplase, desmoteplase, and reteplase. The finger (F), epidermal growth factor (EGF), first and second kringles (K1 and K2, respectively), and protease (P) domains are illustrated. The glycosylation site (Y) on K1 has been repositioned in tenecteplase to endow it with a longer half-life. In addition, a tetra-alanine substitution in the protease domain renders tenecteplase resistant to PAI-1 inhibition. Desmoteplase differs from alteplase and tenecteplase in that it lacks a K2 domain. Reteplase is a truncated variant that lacks the F, EGF, and K1 domains.

A trial comparing alteplase with streptokinase for the treatment of patients with acute myocardial infarction demonstrated significantly lower mortality rates with alteplase than with streptokinase, although the absolute difference was small. Patients older than 75 years with anterior myocardial infarction presenting less than 6 hours after the onset of symptoms derived the greatest benefit from alteplase. Acute myocardial infarction or acute ischemic stroke is treated with an intravenous infusion of alteplase over a 60- to 90-minute period. The total dose of alteplase usually ranges from 90 to 100 mg. Allergic reactions and hypotension are rare, and alteplase is not immunogenic.

Tenecteplase

A genetically engineered variant of t-PA, tenecteplase was designed to have a longer half-life than t-PA and to be resistant to inactivation by PAI-1.[78] To prolong its half-life, a new glycosylation site was added to the first kringle domain (**see Fig. 93.16**). Because addition of this extra carbohydrate side chain reduced fibrin affinity, the existing glycosylation site on the first kringle domain was removed. To render the molecule resistant to inhibition by PAI-1, a tetra-alanine substitution was introduced at residues 296 to 299 in the protease domain, the region responsible for the interaction of t-PA with PAI-1.

Tenecteplase is more fibrin specific than t-PA. Although both agents bind to fibrin with similar affinity, the affinity of tenecteplase for (DD)E is significantly lower than that of t-PA. Consequently, (DD)E does not stimulate systemic plasminogen activation by tenecteplase to the same extent as t-PA does. As a result, tenecteplase produces less fibrinogenolysis than t-PA does.

For coronary fibrinolysis, tenecteplase is administered as a single intravenous bolus. In a large phase III trial that enrolled more than 16,000 patients, the 30-day mortality rate with single-bolus tenecteplase was similar to that with accelerated-dose t-PA. Although rates of intracranial hemorrhage were also

similar with both treatments, patients given tenecteplase had less noncerebral bleeding and a reduced need for blood transfusions in comparison with those treated with t-PA. The improved safety profile of tenecteplase probably reflects its enhanced fibrin specificity.

Reteplase

A recombinant t-PA derivative, reteplase is a single-chain variant that lacks the finger, epidermal growth factor, and first kringle domains (**see Fig. 93.16**). This truncated derivative has a molecular weight of 39,000.[76] Reteplase binds fibrin more weakly than t-PA does because it lacks the finger domain. Because it is produced in *Escherichia coli*, reteplase is not glycosylated; this feature endows it with a plasma half-life longer than that of t-PA. Consequently, reteplase is given as two intravenous boluses separated by 30 minutes. Clinical trials in patients with acute myocardial infarction showed improved 30-day survival rates when reteplase was compared with streptokinase, but its noninferiority compared with alteplase.

Other Fibrinolytic Agents.
Other fibrinolytic agents include desmoteplase (**see Fig. 93.16**), a recombinant form of the full-length plasminogen activator isolated from the saliva of the vampire bat, and alfimeprase, a truncated form of fibrolase, an enzyme isolated from the venom of the southern copperhead snake. Clinical studies with these agents have been disappointing. Desmoteplase, which is more fibrin specific than t-PA, was investigated for the treatment of acute ischemic stroke. Patients initially seen 3 to 9 hours after the onset of symptoms were randomly assigned to one or two doses of desmoteplase or to placebo. Overall response rates were low, and no differences from placebo were noted. Mortality rates were higher in the desmoteplase arm.

Alfimeprase is a metalloproteinase that degrades fibrin and fibrinogen in a plasmin-independent fashion. In the circulation, alpha$_2$-macroglobulin inhibits alfimeprase, so alfimeprase must be delivered via a catheter directly into the thrombus. Despite promising phase II results, studies of alfimeprase for the treatment of peripheral arterial occlusion or for restoration of flow in blocked central venous catheters were stopped because of lack of efficacy. The disappointing results with desmoteplase and alfimeprase highlight the challenges of introducing new fibrinolytic drugs.

Future Perspectives

Thrombosis in arteries or veins involves interplay among the vessel wall, platelets, the coagulation system, and fibrinolytic pathways. Activation of coagulation also triggers inflammatory pathways that may contribute to thrombosis. A better understanding of the biochemistry of platelet aggregation and blood coagulation and advances in structure-based drug design have identified new targets and prompted the development of novel antithrombotic drugs. Despite these advances, however, arterial and venous thromboembolic disorders remain a major cause of morbidity and death. The search for better targets and more potent, safer, or more convenient antiplatelet, anticoagulant, and fibrinolytic drugs continues.

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94

Rheumatic Diseases and the Cardiovascular System

Justin C. Mason

Inflammatory rheumatic diseases have a long-recognized relationship with the cardiovascular system. Because the treatment of these diseases has improved considerably over the last 20 years and increased survival rates, the importance and complexity of this interrelationship have achieved prominence. Patients with multisystem rheumatic diseases may on occasion initially be evaluated by a cardiovascular specialist, a cardiologist, or a vascular or cardiothoracic surgeon, and early recognition of the immune-mediated basis of the cardiovascular disease reduces morbidity and mortality rates. The vasculature may represent a primary target organ of the underlying rheumatic disease and can be affected at numerous sites and at all levels. Thus large-vessel vasculitides may affect the entire aortic wall. Systemic sclerosis (SSc) commonly results in pulmonary arterial vasculopathy and pulmonary artery hypertension (PAH). Antineutrophil cytoplasmic antibody (ANCA)–associated systemic vasculitides (AASVs) affect arterioles preferentially. Antiphospholipid syndrome (APS) causes both venous and arterial thromboses. Cardiac complications of systemic lupus erythematosus (SLE) include coronary arteritis, pericarditis, myocarditis, and valvular heart disease. Renal artery stenosis leading to uncontrolled hypertension is a feature of Takayasu arteritis (TA), and occlusive lesions in the subclavian, axillary, or iliac arteries may lead to limb claudication in patients with TA and giant cell arteritis (GCA). Rheumatic diseases have equally important secondary effects on the cardiovascular system. Chronic systemic inflammation predisposes to endothelial dysfunction and increased arterial stiffness, thereby escalating the risk for the development of atherosclerosis. Cardiovascular specialists are increasingly recognizing the significantly increased prevalence of premature myocardial infarction and stroke in patients suffering from rheumatoid arthritis (RA) and SLE. Many outstanding clinical challenges remain, and predominant among them are early recognition, diagnosis, and treatment of patients with rheumatic disease who have the highest risk for cardiovascular complications, alongside improved understanding of the underlying molecular mechanisms and the development of preventive strategies.

Atherosclerosis

Premature Atherosclerosis

Recognition of the role of inflammation in atherosclerosis has highlighted and stimulated study of the potential relationship between systemic inflammatory diseases and premature atherogenesis. This effort has substantially advanced our understanding of both the underlying pathogenic mechanisms and the epidemiology. Current priorities include identification of patients most at risk and the development of preventive therapeutic strategies.[1] Evidence supporting an association between inflammatory diseases and accelerated atherogenesis is best developed for RA and SLE. In addition, ankylosing spondylitis, psoriatic arthritis, AASV, TA, and APS may all be associated with premature atherosclerosis. Cardiovascular specialists should consider an underlying inflammatory disease in young patients with otherwise unexplained angina, myocardial infarction, or stroke. Patients with a rheumatic disease who suffer a myocardial infarction have worse outcomes in terms of both heart failure and mortality than does the age-matched general population.[2]

Endothelial Dysfunction and Vascular Injury

Homeostatic mechanisms promote a quiescent, antithrombotic, antiadhesive vascular endothelium and control vasodilation and permeability (**see Chapters 44 and 57**). Prolonged systemic inflammation such as that seen in RA and SLE may promote endothelial injury, increased endothelial apoptosis, and endothelial vasodilator dysfunction.

Traditional risk factors alone do not explain the increased burden of atherosclerosis, but inflammation may exacerbate the effects of classic risk factors.[3] When compared with the general population, patients with systemic inflammatory diseases more commonly exhibit endothelial dysfunction and increased aortic stiffness. Although the results of individual studies vary, effective treatment of the underlying inflammation may not always reverse the endothelial dysfunction or improve the aortic stiffness.[4,5] This observation and the fact that the plaque burden may not be increased have led to the hypothesis that the systemic inflammatory environment may predispose to increased plaque instability and rupture, a conjecture supported by autopsy studies. Thus, both accelerated atherogenesis and higher-risk plaque may contribute to the observed increased incidence of premature cardiovascular events.[6,7]

Various molecular mechanisms mediate the increased risk for atherosclerotic disease and cardiovascular events. In addition to the traditional cardiovascular risk factors, disease-related factors may include effects of the proinflammatory cytokines tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and IL-6 on endothelial activation, leukocyte adhesion, endothelial injury, and permeability. Increased endothelial cell apoptosis and a diminished capacity for repair may contribute. Autoantibodies (e.g., antiphospholipid antibodies), $CD4^{+}CD28^{-}$ cytotoxic T cells, $Th17/T_{REG}$ imbalance, complement deficiency or excessive activation, genetic polymorphisms, and the deleterious effects of drugs, including corticosteroids and cyclosporine, may also contribute.[2,3]

Rheumatoid Arthritis

RA, an autoimmune, symmetric inflammatory polyarthritis with a female-to-male ratio of 3 : 1, affects up to 1% of the population in the Western world, with the onset of symptoms most commonly occurring between 30 and 50 years of age. Up to 80% of patients have a positive serum rheumatoid factor and/or anti–cyclic citrullinated peptide (CCP) antibodies. A systemic inflammatory response is evident, with

low-grade fever, weight loss, raised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), hypoalbuminemia, normochromic normocytic anemia, and thrombocytosis.

A variety of studies have shown subclinical arterial disease with increased carotid intimal-medial thickness (IMT) and early plaque development. Although RA independently raises the risk for atherosclerosis, the precise mechanistic relationship between RA and atherogenesis remains unknown. Similarly, the mechanisms and long-term outcomes of abnormalities in myocardial perfusion and coronary flow reserve that have been reported in patients with RA and normal epicardial arteries remain to be established.[8] The initial abnormalities in vascular function may occur at or before the onset of RA symptoms.[9] The direct effect of chronic inflammation on vascular endothelium may itself promote atherogenesis, in addition to exacerbating the actions of traditional cardiovascular risk factors.[6,10] Moreover, the systemic inflammatory environment might contribute to the features of plaque and blood that promote cardiovascular events in patients with RA.[11]

Patients with RA have increased classic risk factors for atherosclerosis. Tobacco smoking is associated with both cardiovascular risk and the development of RA. Similarly, insulin resistance and the metabolic syndrome are more common in RA. Patients with RA may have a dyslipidemic pattern that includes high triglyceride levels and low levels of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol.[12] The risk for myocardial infarction in patients with RA is considered similar to that in those with diabetes mellitus, and women with RA are twice as likely as age-matched controls in the general population to suffer myocardial infarction. Although death rates from both heart attack and stroke are comparable to those in the general population, events occur at an earlier age, with 50% of premature deaths in patients with RA being a direct consequence of cardiovascular disease. The excess mortality rate becomes apparent 7 to 10 years after diagnosis and has been associated with persistent disease activity and the presence of rheumatoid factor and anti-CCP antibodies. Current evidence suggests that patients with RA who suffer a myocardial infarction are less likely to receive acute reperfusion therapy and secondary preventive measures and thus have worse outcomes.[6,13]

Treatment

Drug therapy for RA has undergone a remarkable evolution over the past 20 years, with the focus on biologic therapies and aggressive management of early disease. Clinical trials have demonstrated that this approach reduces symptoms and structural damage to joints. Increasing evidence suggests treatment to target to control synovitis also confers vascular protection.[14]

Methotrexate is now the most widely used disease-modifying antirheumatic drug (DMARD), and since its introduction, mortality rates from myocardial infarction in patients with RA have improved. Similar observations have been made for sulfasalazine and hydroxychloroquine. Patients who do not respond adequately to DMARD therapy should switch to biologic therapies. Such agents now include those targeting TNF-α (infliximab, adalimumab, etanercept, certolizumab, and golimumab), the IL-6 receptor (tocilizumab), CTLA4Ig (abatacept), and the B cell–depleting monoclonal antibody rituximab. An aggressive disease-modifying approach also minimizes the use of nonsteroidal antiinflammatory drugs (NSAIDs) and the requirement for corticosteroid therapy. Glucocorticoids may adversely affect traditional risk factors such as insulin resistance, hypertension, and lipid profiles and may hasten carotid plaque formation in RA.[10] Because NSAIDs and cyclooxygenase-2 (COX-2)-selective NSAIDs (coxibs), although effective, may elevate the blood pressure and increase the frequency of thrombotic cardiovascular events, caution is required regarding their use in patients with cardiovascular complications of inflammatory disease.[15] However, evidence suggests that NSAID use in patients with RA does not confer an increased risk for cardiovascular events, thus indicating that their antiinflammatory

effects predominate.

Definitive demonstration of the potential cardiovascular benefits of the biologic therapies will require the results of long-term prospective studies (see later). TNF-α promotes vascular endothelial activation and dysfunction and may lead to plaque destabilization, and hence blockade would appear to be an attractive therapeutic option. Infliximab therapy may improve endothelial function as measured by flow-mediated dilation 4 to 12 weeks after infusion, whereas etanercept has been reported to reduce aortic stiffness. Analysis of carotid IMT suggests that TNF-α antagonists reduce systemic inflammation and retard progression of IMT.[10] Tight therapeutic control of RA disease activity per se appears to have a beneficial effect on the risk for myocardial infarction.[14] Treatment of the arthritis must be combined with a careful review of classic risk factors and appropriate steps taken to modify them. Although precise guidelines are awaited, most rheumatologists have a low threshold for addition of a statin. Meanwhile, debate continues concerning the pros and cons of disease-specific cardiovascular risk calculators,[16] and new scores are under investigation.[17]

Atherosclerosis and Systemic Lupus Erythematosus

SLE, a systemic autoimmune disease, is found usually in women, at a ratio of 9 : 1, and affects all racial groups but more commonly those of Afro-Caribbean, Asian, and Chinese extraction. Constitutional symptoms at initial evaluation include night sweats, lethargy, malaise, and weight loss. Frequent mucocutaneous features include the classic butterfly facial rash, oral ulcers, and alopecia. Serositis, myalgia, arthralgia, and Jaccoud nonerosive arthropathy also occur. Potentially life-threatening complications include glomerulonephritis leading to renal failure, central nervous system (CNS) involvement with cerebral vasculitis, pneumonitis, shrinking lung syndrome, and PAH. Hematologic involvement includes lymphopenia in most and frequently hemolytic anemia, neutropenia, and thrombocytopenia. Cardiac manifestations of SLE are relatively rare but include pericarditis, myocarditis, endocarditis, aortitis, and coronary arteritis. Understanding of the pathogenesis of SLE continues to improve. A defect in apoptotic cell clearance results in the exposure of nuclear antigens to an immune system with hyperreactive B cells. Loss of immune tolerance results in the generation of autoantibodies and immune complexes. Deposition of immune complexes in target organs leads to activation of complement and tissue injury.[18]

Most patients have high-titer antinuclear antibodies and antibodies against double-stranded DNA (dsDNA). The latter are more specific for the diagnosis of SLE; the presence of antibodies against one or more nuclear antigens, including Sm, Ro, La, and ribonucleoprotein (RNP), reinforces the diagnosis. Complement activation and consumption of C3 and C4 leading to reduced plasma levels characterize active disease. The ESR also rises in active disease, but CRP levels typically remain normal except in those with serositis or secondary infection.

A variety of studies have suggested an increased risk for myocardial infarction and stroke in patients with SLE that is between 2-fold and 10-fold and up to 50-fold greater than that in the general population. The young age of patients with SLE and cardiovascular disease (67% of female patients with SLE and a first cardiac event typically occur before 55 years of age) suggests that SLE accelerates arterial disease.[19] A study of 1874 cases (9485 person-years follow-up) revealed a 2.66-fold increase in the risk of myocardial infarction, stroke, and coronary intervention when compared with the general population.[20] Although the pattern and extent of coronary artery disease in SLE does not appear to differ (**Fig. 94.1**), the plaque may be more vulnerable to rupture. Patients with SLE have worse outcomes following myocardial infarction than the age-matched general population does, with a higher risk for the development of cardiac failure and increased mortality rates.[2,6] This difference may result from the late diagnosis of ischemic

heart disease and a reluctance to treat aggressively.

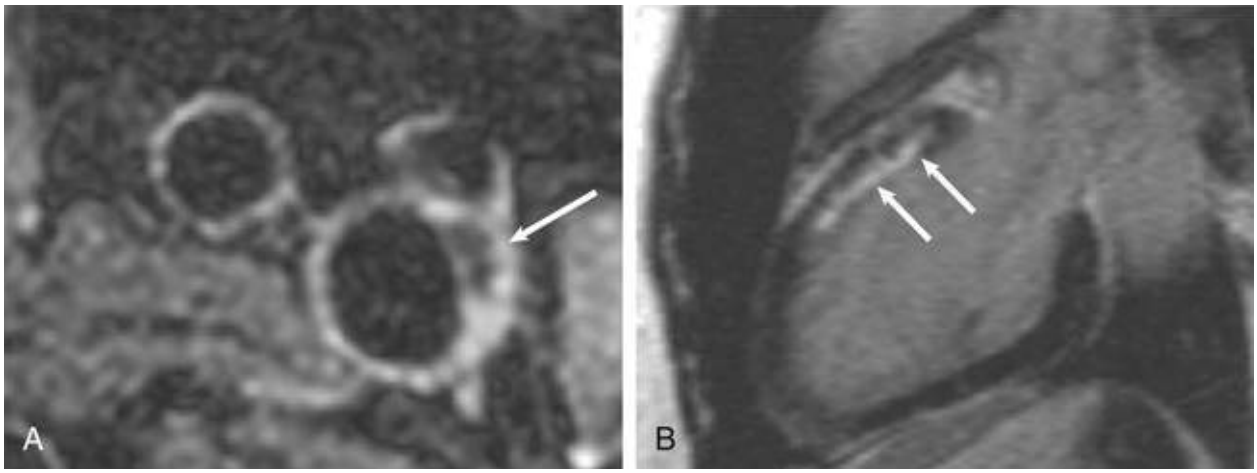

FIGURE 94.1 Atherosclerosis in systemic lupus erythematosus. **A,** Transaxial T2-weighted CMR of the carotid bifurcation showing atherosclerotic plaque *(arrow).* The lipid-filled core and fibrous cap can be seen along with evidence of calcification. **B,** CMR showing a two-chamber view in the late phase after gadolinium injection. Subendocardial late gadolinium enhancement is present in the anteroseptal left ventricle (*arrows*) and extends from the base of the heart to the midventricular region, consistent with a previous subendocardial myocardial infarction.

Hypertension is common in SLE because of renal disease and the use of glucocorticoids in many patients. Similarly, patients with SLE commonly have metabolic syndrome, which is associated with renal impairment, higher corticosteroid doses, and Korean or Hispanic ethnicity.[21] Patients with SLE also have lipid abnormalities, including high levels of very low-density lipoprotein (VLDL) and triglycerides, elevated or normal LDL cholesterol, and reduced HDL cholesterol. Moreover, proinflammatory HDL leading to increased oxidatively-modified LDL cholesterol was seen in 45% of patients with SLE as compared with 20% of those with RA and 4% of the general population.[12] Antibodies against oxidized LDL also occur in SLE and may promote atherogenesis.

Treatment

Mild SLE with rash and arthralgia can be treated with simple analgesics and NSAIDs, with the addition of hydroxychloroquine if required. Organ involvement, including mild renal impairment, hematologic abnormalities, myositis, arthritis, and cutaneous lesions, requires the addition of prednisone and typically an immunosuppressant such as azathioprine, mycophenolate mofetil (MMF), or methotrexate to aid in controlling the disease and to facilitate steroid sparing. Cyclophosphamide and high-dose corticosteroids remain the first-line treatment of life-threatening complications, including myocarditis, cerebritis, severe hematologic involvement, and glomerulonephritis. MMF may replace cyclophosphamide for lupus nephritis because of its equivalent efficacy and concerns regarding the risk for permanent infertility seen in up to 50% of patients treated with cyclophosphamide. Most rheumatologists consider rituximab an effective treatment of severe SLE, although clinical trials to date have proved disappointing and further data are awaited. A variety of regimens have been used, including combinations of rituximab, prednisone, and cyclophosphamide.[22] Belimumab, a monoclonal antibody that binds to the soluble B lymphocyte stimulator and prevents its interaction with B cell surface receptors, has a modest disease-modifying effect in patients with moderate non–renal-related SLE.

Defining effective strategies for prevention of cardiovascular disease in patients with SLE will require long-term prospective trials with adjudicated cardiovascular endpoints. Undertreated and/or persistently

active disease is associated with accelerated atherogenesis. Therefore adequate individualized immunosuppressive therapy should minimize cardiovascular complications. Hydroxychloroquine reduces LDL cholesterol and lowers mortality rates from cardiovascular disease in patients with SLE. Aggressive management of traditional risk factors is also advocated, including diligent monitoring and tight blood pressure control. Statins are widely used, particularly in patients with renal impairment. Caution and careful monitoring should be exercised in patients with active myositis, because statin therapy can exacerbate this complication. The clinical data available do not support significant protection against atherosclerosis by statins 2 to 3 years after initiation, although longer-term analysis is awaited.[18,23]

Atherosclerosis in Association With Other Rheumatic Diseases

The relationship between chronic inflammation and atherogenesis implies that many rheumatic diseases may be associated with a premature and increased cardiovascular risk (**Table 94.1**). Because data in support of this hypothesis are derived from relatively small studies, important current clinical challenges include the need to determine (1) which rheumatic diseases pose the greatest cardiovascular threat, (2) a means of identifying subsets of patients most at risk, and (3) strategies to minimize cardiovascular events.

TABLE 94.1

Coronary Artery Involvement and the Rheumatic Diseases

Premature Atherosclerosis
Systemic lupus erythematosus
Rheumatoid arthritis
Ankylosing spondylitis
Psoriatic arthritis
Gout
Takayasu arteritis
Giant cell arteritis
Coronary Arteritis
Systemic lupus erythematosus
Takayasu arteritis
Kawasaki disease
Churg-Strauss syndrome
Polyarteritis nodosa
Granulomatous polyangiitis
Rheumatoid arthritis

Ankylosing spondylitis, psoriatic arthritis, and gout may also be associated with atherosclerotic disease. Hyperuricemia independently predicts cardiovascular disease, and patients with gout often have hypertension, hyperlipidemia, obesity, and diabetes mellitus. Many drugs used for the treatment of cardiac disease, including diuretics, beta blockers, and low-dose aspirin, can increase serum uric acid levels. In contrast, losartan, angiotensin-converting enzyme (ACE) inhibitors, atorvastatin, and fenofibrate may reduce urate levels.[24] Allopurinol may reduce the risk for congestive cardiac failure and cardiovascular-associated death. In addition to achieving a serum uric acid level lower than 0.36 mmol/L, patients with gout should receive dietary advice and aggressive management of cardiovascular risk factors.

A systematic review of articles on cardiovascular disease in patients with psoriatic arthritis has revealed increased traditional risk factors, endothelial dysfunction, aortic stiffness, and subclinical atherosclerosis. The limited data available also suggest that adequate suppression of inflammatory disease activity leads to improvement in endothelial dysfunction and carotid IMT.[25] Patients with ankylosing spondylitis have demonstrated impaired endothelial function and increased carotid IMT and pulse wave velocity, all of which indicate an increased risk for atherosclerosis.[26] The impact of the increasing use of anti-TNF-α therapies on the incidence of cardiovascular events in these patients should

emerge from international biologic registries.

Vasculitides

The vasculitides, a heterogeneous group of diseases, represent a significant clinical challenge, both diagnostically and therapeutically. The primary systemic vasculitides are classified as large-, medium-, or small-vessel disease. This leaves a small group of unclassified conditions, including Behçet disease, relapsing polychondritis, primary CNS vasculitis, and Cogan syndrome.[27]

The histologic features of vasculitis include perivascular inflammatory infiltrates that may invade the arterial wall, fibrinoid necrosis, thrombosis, fibrosis, and scar formation. Fibrinoid necrosis, a specific feature of the medium- and small-vessel vasculitides, typically affects the tunica media. Complications include stenosis and occlusions resulting in organ ischemia, thrombosis, aneurysm formation, and hemorrhage. Although biopsy is optimal for making the diagnosis, suitable tissue may not always be accessible, or arterial biopsy may present hazards, as in patients with TA. Thus the diagnosis often depends on clinical findings, laboratory indices, and imaging studies.

The vasculitides have a complex, multifactorial, and poorly understood immunopathogenesis. The endothelium may be subject to complement-mediated injury as a consequence of immune complex deposition in polyarteritis nodosa (PAN) or rheumatoid vasculitis. In the medium- and small-vessel vasculitides, ANCAs may activate neutrophils and subsequently damage the endothelium. The proinflammatory cytokines TNF-α, IL-1, IL-6, and interferon-gamma (IFN-γ) may activate the endothelium and induce the expression of adhesion molecules, including E-selectin, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1), thereby facilitating leukocyte adhesion and recruitment into the vessel wall and surrounding tissue.

Cardiovascular disease in patients with vasculitis, although relatively rare, can be life-threatening. Aortitis, hypertension, coronary arteritis, valvular heart disease, pericarditis, myocarditis, conduction abnormalities, accelerated atherosclerosis, and cardiac failure can all occur. This section focuses on the vasculitides most likely to be encountered by cardiovascular disease specialists.

Large-Vessel Vasculitis

Giant Cell Arteritis

GCA affects large- and medium-sized arteries. The disease affects those older than 50 years, with the incidence increasing with age. GCA occurs most commonly in northern Europe, Scandinavia, and the United States in people of northern European ancestry. GCA typically affects extracranial branches of the aorta and, in addition to the temporal arteries, may involve the subclavian and axillary arteries, the thoracic aorta, and on occasion the femoral and iliac arteries. Clinical features include fever, weight loss, malaise, headache, temporal artery thickening with loss of pulsation, scalp tenderness, and jaw claudication. The most feared complication, anterior ischemic optic neuropathy (AION), may be manifested as amaurosis fugax or sudden permanent visual loss. Up to 25% of patients are initially found to have systemic features without the classic sign of tenderness and temporal artery involvement. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) has confirmed earlier autopsy findings and shown widespread arteritis with increased FDG uptake throughout the aorta and subclavian and iliac arteries in more than 50% of patients.

Pathogenesis

Histopathologic examination reveals localized fragmentation of the internal elastic lamina closely associated with an inflammatory infiltrate consisting predominantly of IFN-γ–producing $CD4^+$ T lymphocytes, monocytes/macrophages, and occasional characteristic multinucleated giant cells. Recent studies have revealed that activated $CD83^+$ dendritic cells initiate the arterial wall inflammation and colocalize with activated T cells. Local synthesis of growth factors such as platelet-derived growth factor leads to proliferation of smooth muscle cells and concentric stenosis of the arterial lumen (**Fig. 94.2**). Release of matrix metalloproteinases and generation of reactive oxygen species can result in arterial wall injury and aneurysm formation.

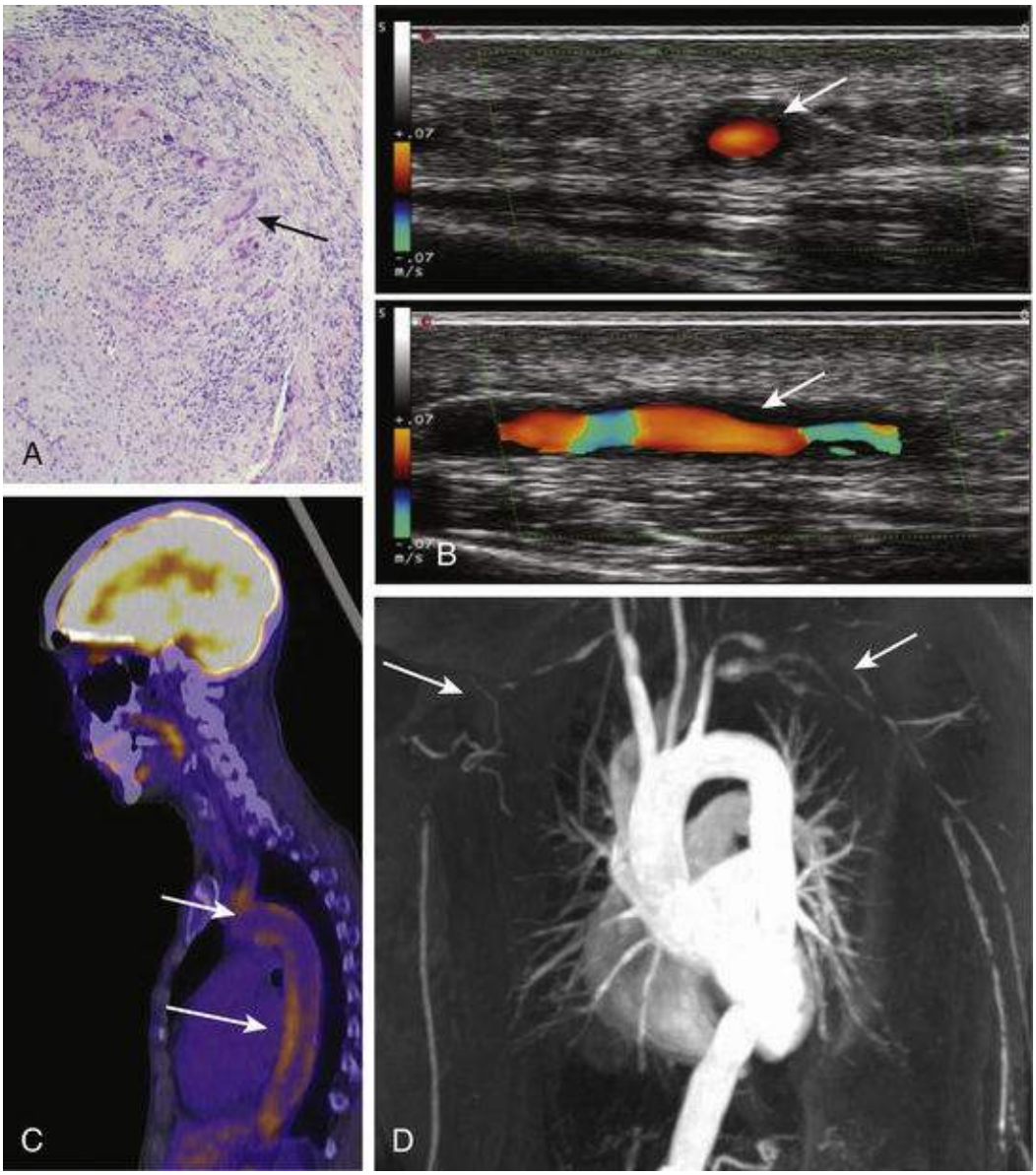

FIGURE 94.2 Giant cell arteritis. **A,** A temporal artery biopsy specimen stained with hematoxylin-eosin shows evidence of myofibroblast proliferation and vessel occlusion, a focal mononuclear cell inflammatory infiltrate, and the presence of multinucleated giant cells *(arrow).* **B,** Dark hypoechoic, circumferential wall thickening (halo sign) *(arrows)* is seen around the temporal artery lumen in active GCA in both the transverse and longitudinal views. **C,** ^{18}FDG-PET-CT scan demonstrating uptake in the thoracic aorta, consistent with active arteritis. **D,** Magnetic resonance angiogram demonstrating bilateral stenosis of the left subclavian and axillary arteries *(arrows)* in a 65-year-old woman with upper limb ischemic symptoms. (**B,** Courtesy Dr. Wolfgang Schmidt, Medical Centre for Rheumatology Berlin-Buch, Berlin, Germany.)

Diagnosis

Biopsy is the definitive means of diagnosis and should be considered for all patients. However, the need for biopsy should not delay treatment. Temporal artery biopsy is positive in up to 80% of patients. Recent interest has focused on temporal artery ultrasound, which can reveal a characteristic halo sign with concentric homogeneous thickening of the arterial wall and evidence of flow disturbance and stenosis (**see Fig. 94.2**).

Cardiovascular Complications

Although rare, severe cardiovascular complications can occur and include dissecting thoracic aortic aneurysms (**Table 94.2**). Imaging and autopsy studies suggest that aortitis and aortic wall thickening are frequent in GCA, although their relationship with the development of aortic aneurysm remains unclear. Increased FDG uptake in the thoracic aorta can be associated with an increased risk for aortic dilation. Overall, patients with GCA have a 17-fold increased risk for thoracic aortic aneurysms. Those with conventional cardiovascular risk factors, poorly controlled disease, and aortic regurgitation have a higher risk. In the absence of guidelines, we recommend annual thoracic aortic screening for those with FDG-PET–positive thoracic aortic uptake or with evidence on magnetic resonance angiography (MRA) or computed tomography angiography (CTA) of aortic wall thickening, and screening every 2 to 3 years for the remainder of patients. CTA and MRA are the optimal imaging techniques. Pericarditis, coronary arteritis, limb ischemia, accelerated atherosclerosis, myocardial infarction, and cerebrovascular accidents are all associated with GCA. Yet most outcome studies do not report increased mortality rates, so the impact of severe cardiovascular disease seems to be small.[28]

TABLE 94.2

Cardiovascular Disease in the Systemic Vasculitides

Vasculitides	Cardiovascular Complications
Large-Vessel Vasculitis	
Giant cell arteritis	Thoracic/abdominal artery aneurysm, limb ischemia, pericarditis, coronary arteritis, IHD, MI
Takayasu arteritis	Aortic regurgitation, limb ischemia, aortic stenosis, aortic aneurysm, stroke, hypertension, coronary arteritis and aneurysm, IHD, MI, myocarditis, cardiac failure
Kawasaki disease	Coronary artery aneurysm, MI, myocarditis, pericarditis, valvular dysfunction, cardiac failure
Medium-Vessel Vasculitis	
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Myocarditis, pericarditis, coronary arteritis, cardiomyopathy, cardiac fibrosis, valvular dysfunction, MI
Polyarteritis nodosa	Myocarditis, pericarditis, coronary arteritis, coronary aneurysm, hypertension, cardiac failure
Wegener granulomatosis (granulomatous polyangiitis)	Myocarditis, pericarditis, coronary arteritis, valvular heart disease, cardiac failure
Microscopic polyangiitis	Pericarditis, coronary microaneurysm, MI

IHD, ischemic heart disease; *MI*, myocardial infarction.

Takayasu Arteritis

TA, a granulomatous panarteritis, affects the aorta and its major branches, typically before the age of 40 years. The disease predominates in women, with a female-to-male ratio of up to 10 : 1. Because the diagnosis is often delayed, substantial arterial injury accrues. The current diagnostic criteria depend on detection of established stenotic disease and do not yet reflect the increasing sensitivity of noninvasive imaging.[29]

The presentation is typically nonspecific and associated with fever, night sweats, arthralgia, malaise, profound tiredness, and lethargy. TA may be accompanied by symptoms of upper limb claudication, and carotidynia occurs in up to 25% of patients. The aorta may be involved throughout its length, and even

though any branches can be diseased, the most commonly affected are the subclavian and common carotid arteries. More than 90% of patients have stenotic/occlusive arterial lesions, whereas approximately 25% have aneurysms. The pulmonary arteries are involved in up to 50% of patients, and aortic valve regurgitation and coronary arteritis may occur (**Fig. 94.3**).

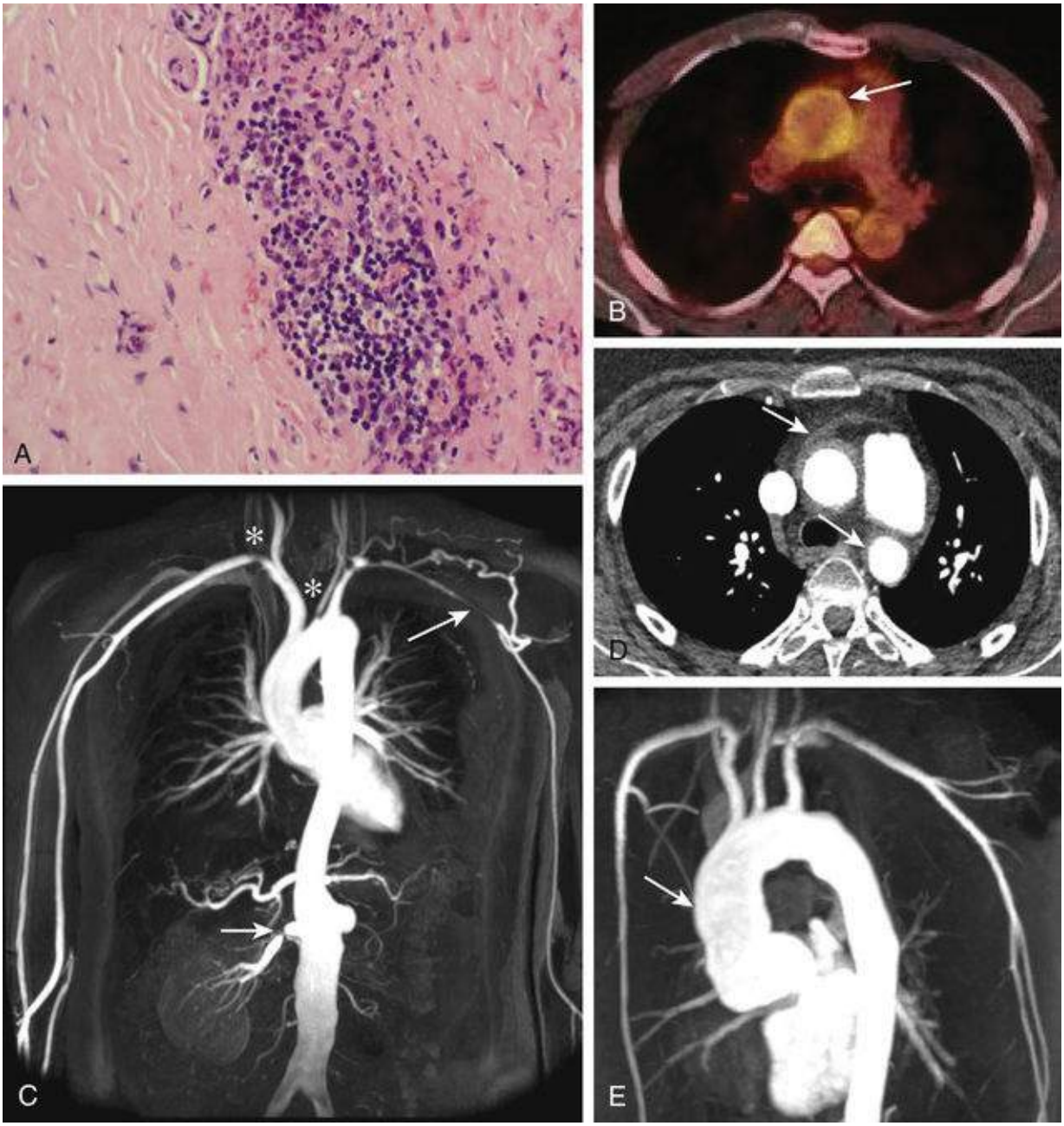

FIGURE 94.3 Takayasu arteritis **A,** Hematoxylin-eosin staining of a common carotid artery biopsy specimen obtained at surgery shows a focal mixed mononuclear cell inflammatory infiltrate with a multinucleated giant cell. **B,** ^{18}FDG-PET-CT scan demonstrating uptake in the aortic arch *(arrow)*, consistent with active arteritis. **C,** MRA demonstrating stenosis of the left subclavian artery with collateral formation *(long arrow)*, proximal stenoses in the right subclavian and left common carotid arteries *(stars)*, proximal stenosis in the right renal artery *(short arrow)*, and an atrophic left kidney. **D,** CT angiogram demonstrating thickening of the wall of the ascending and descending aorta *(arrows).* **E,** MRA revealing severe dilatation of the ascending aorta *(arrow)* requiring aortic valve replacement.

TA has severe consequences, with 74% reporting compromised daily activities and 23% unable to work. In our cohort, survival at 10 years is higher than 95%; similarly, in the United States, survival rates of 94% to 96% are reported, whereas in Korea the survival rate was 87% at 10 years. In Japan, 15-year

survival rates have improved to 96.5%. However, the survival rate fell to 67% in a subset of patients with serious complications and/or a progressive disease course.

Pathogenesis

Arteritic lesions demonstrate adventitial thickening and focal leukocytic accumulation of the media with intimal hyperplasia. The leukocytes include activated dendritic cells, T and B lymphocytes, macrophages, and multinucleated giant cells (**see Fig. 94.3**). Growth factor–driven mesenchymal cell proliferation leads to intimal hyperplasia and fibrosis and subsequent arterial stenosis or occlusion. Local matrix metalloproteinase synthesis may predispose to aneurysmal dilation.

Diagnosis

Diagnosis of TA depends principally on the physician including the disease in the differential diagnosis. The variable nature of the features of TA and the lack of constitutional symptoms in 30% to 50% of patients initially present a challenge to a prompt diagnosis. In addition to improved physician awareness, a list of “red flags” that raise the possibility of TA is helpful (**Table 94.3**).[30] One's index of suspicion must be high in young patients with an unexplained acute-phase response or hypertension. Similarly, common initial signs, including diminished or absent pulsation or arterial bruits, can suggest the diagnosis.

TABLE 94.3

“Red Flags” for Takayasu Arteritis

In patients younger than 40 years the following may be indicative of TA:
Unexplained acute-phase response (raised ESR and/or CRP)
Carotidynia
Hypertension
Discrepant blood pressure between the arms (> 10 mm Hg)
Absent or weak peripheral pulse or pulses
Limb claudication
Arterial bruit
Angina

Laboratory abnormalities during active disease include raised ESR and CRP (in 75% of patients), often accompanied by normochromic normocytic anemia, thrombocytosis, hypergammaglobulinemia, and hypoalbuminemia. No specific autoantibodies or other serologic abnormalities exist, however. Noninvasive imaging is now the optimal means of diagnosis because tissue biopsy is rarely available. High-resolution ultrasound, cardiac magnetic resonance (CMR), MRA, CTA, and PET have all been studied. Although the potential of these techniques is not in doubt, their specificity and sensitivity in the management of TA remain undetermined. ^{18}F-FDG-PET-CT may reveal evidence of active arteritis and lead to early detection of prestenotic disease. A current consensus review has suggested that this technique is particularly useful for the detection of active arteritis in patients not receiving immunosuppressive therapy. Demonstration of arterial wall enhancement, edema, or thickening on MRA and CTA may facilitate the diagnosis of prestenotic disease, and stenoses and aneurysms can be readily identified and monitored (**see Fig. 94.3**). Color duplex ultrasound has particular use in assessing the common carotid and proximal subclavian arteries in TA. Homogeneous, bright concentric arterial wall thickening is a typical finding in affected common carotid arteries.

Cardiovascular Complications

In addition to the sequelae associated with cerebral, internal organ, and limb ischemia, aneurysms, PAH,

or aortic rupture may develop. Cardiac complications include aortic valve insufficiency, accelerated atherosclerosis, cardiac ischemia, myocarditis, myocardial infarction, and heart failure. Coronary disease is often asymptomatic, as illustrated by the identification of silent myocardial injury in 27% of a cohort that we studied.[31] Patients with TA can also have secondary accelerated atherosclerosis. Thallium stress scintigraphy revealed myocardial perfusion defects in 53%, whereas intraarterial angiography has shown that up to 30% have coronary artery lesions typically affecting the ostia and proximal segments, with the left main coronary artery being most commonly affected. Neither MRA nor ^{18}F-FDG-PET-CT reliably identifies coronary arteritis, which is best identified by coronary CTA.[32] Inflammation of the ascending aorta predisposes to coronary artery involvement, as well as to dilation of the aortic root with subsequent aortic valve regurgitation and the need for aortic valve replacement.[33] Left ventricular dysfunction may affect up to 20% and may reflect myocarditis, ischemic heart disease, and hypertension. High blood pressure occurs commonly with renal artery stenosis often in association in TA.

Kawasaki Disease

Kawasaki disease (KD) predominantly affects children younger than 5 years with a peak incidence at 6 to 24 months of age. The vasculitis affects medium and small arteries, notably the coronary arteries. All racial groups may be affected, with the highest incidence recorded in Asia (20 to 100 per 100,000 children < 5 years of age). KD is an acute self-limited illness that typically resolves within 1 to 2 months, although the mortality rate still remains 1% to 2%. Characteristic initial features include fever of 5 days' duration or longer, bilateral conjunctivitis, and mucocutaneous lesions, including red fissured lips and a strawberry tongue. Cervical lymphadenopathy may be prominent, with erythema affecting the palms and soles and a polymorphous exanthema.

Pathogenesis

The cause of KD is unknown, although occasional seasonal epidemics and an increased incidence in siblings suggests infection may trigger the disease and lead to an uncontrolled immunologic response in a genetically susceptible host. A variety of organisms have been implicated, including streptococci, staphylococci, and *Propionibacterium acnes*. Despite this interest, no definitive evidence supports an infectious cause. Tissue specimens show endothelial injury, perhaps caused by proinflammatory cytokines and activated neutrophils. Infiltration of the arterial wall by neutrophils, T cells, and macrophages is associated with the development of arterial stenosis or, more commonly, aneurysms. Coronary artery aneurysms develop in up to 20% of patients during the first month of the illness, and 50% will regress in the following years.

Diagnosis

Neutrophilia, thrombocytosis, and a raised acute-phase response occur acutely. Echocardiography can detect coronary involvement from the second week of illness and can be used to monitor progress. Coronary angiography is not performed acutely because of the risk of precipitating myocardial infarction, but it can be used after 6 months to establish the degree of coronary artery involvement. The electrocardiogram (ECG) demonstrates abnormalities in up to 50% of patients, including tachycardia, T wave inversion, ST depression, atrioventricular block, and rarely, ventricular arrhythmia.

Cardiovascular Complications

Coronary artery aneurysms develop in up to 25% of untreated patients with KD. Sudden death can occur

as a consequence of myocardial infarction following acute coronary thrombosis or rupture of a coronary artery aneurysm. Pericarditis, pericardial effusion, myocarditis, valvular dysfunction, and cardiac failure may all occur, whereas peripheral arterial involvement is less common but may affect the limb, renal, and visceral arteries.

Treatment

Aspirin (80 to 100 mg/kg/day) in four divided doses is recommended, along with intravenous immunoglobulin (IVIG). This treatment combination reduces development of coronary artery aneurysm to 5%, with a significant impact on mortality rates. Twenty percent of patients are resistant to IVIG, however, and these patients can receive corticosteroids, although the results reported are variable.

Most patients with KD have a good outcome. Yet in up to 20% of those with coronary artery aneurysms, coronary stenoses eventually develop, and these patients require follow-up by an experienced cardiologist. Although the risk for long-term complications, including myocardial infarction and sudden death, is greater in those with giant aneurysms,[34] the risk for thrombosis and myocardial infarction still remains increased in those in whom aneurysms have regressed and throughout adult life.

Idiopathic Aortitis

Aortitis can complicate SLE, Cogan syndrome, Behçet disease, human leukocyte antigen (HLA) B27–positive spondyloarthropathy, KD, and GCA. Aortitis may also be idiopathic, although a number of such cases are now recognized to fall within the IgG4-related disease spectrum.[35] The clinical features are nonspecific and include malaise, lethargy, chest pain, fever, and weight loss, and the diagnosis is often made only at the time of surgery. The ESR and CRP are typically raised, and the extent of the disease can be demonstrated by ^{18}F-FDG-CT-PET scanning and aortic MRA or CTA (**Fig. 94.4**). Dilation of the aortic root may require aortic valve and root replacement, whenever possible preceded by immunosuppressive therapy to control aortic wall inflammation. Treatment involves corticosteroids and a steroid-sparing immunosuppressant drug such as azathioprine, methotrexate, or MMF. The B-cell–depleting antibody has proven particularly effective for IgG4-related disease.

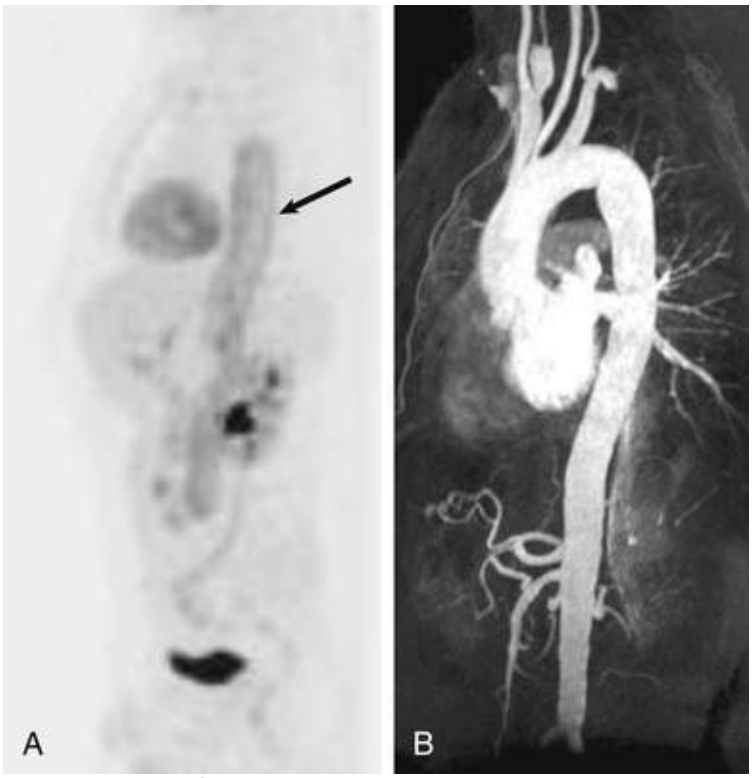

FIGURE 94.4 Idiopathic aortitis. **A,** ^{18}F-FDG-PET scan demonstrating high-grade tracer uptake *(arrow)* in the aorta from below the level of the arch to just above the level of the aortic bifurcation, in keeping with aortitis. The activity is largely concentric around the aortic lumen. **B,** MRA showing aortic ectasia.

Treatment of Large-Vessel Vasculitis

The evidence base for the treatment of large-vessel vasculitis is remarkably small.[36] Although GCA and TA typically respond to steroids, gaining remission requires high doses and a considerable side effect burden. In GCA, the dependence on prednisone and conflicting evidence concerning the efficacy of steroid-sparing drugs, combined with concerns about AION, often result in overtreatment and considerable side effects. Indeed, 86% of patients experience glucocorticoid-related adverse events at 10-year follow-up. Both of these diseases have a high relapse rate when the dose of corticosteroid is tapered, suggesting persistent vasculitis. Potential mechanistic insight into this observation comes from a recent report of two pathogenic pathways in GCA. Raised plasma IL-17 and Th17 cells in the arterial wall were rapidly normalized by prednisone therapy and remained suppressed as the dose was reduced. In contrast, the Th1-promoting cytokine IL-12 and IFN-γ-producing Th1 cells demonstrated corticosteroid resistance, which may account for the reemergence of disease.[37] Corticosteroid treatment of GCA should be tapered carefully to maintain remission and minimize side effects. Although the literature is somewhat conflicting, methotrexate and azathioprine represent suitable corticosteroid-sparing agents for those unable to reduce the dose of prednisone sufficiently. Most patients with active TA require steroid-sparing immunosuppressive drugs. Methotrexate and azathioprine are the most widely prescribed, and small open-label studies support their use. In patients failing to respond or in those with life-threatening disease such as coronary arteritis or myocarditis, aggressive treatment with intravenous pulsed cyclophosphamide is recommended.

Case reports suggest that anti-TNF-α therapy can treat refractory GCA effectively. However, a randomized placebo-controlled trial of the use of infliximab in 44 patients with GCA in remission with corticosteroids ended prematurely when it failed to demonstrate a benefit, either in terms of preventing relapse or as a steroid-sparing agent, and a second trial using etanercept only showed a modest steroid-

sparing effect. Recent reports suggest that the anti–IL-6 receptor monoclonal antibody tocilizumab can treat GCA effectively and results of the first clinical trial are awaited.[38] Open-label studies suggest that TNF-α blockade can treat patients with TA who fail to respond adequately to combination therapy with prednisone and steroid-sparing immunosuppressant drugs, including cyclophosphamide. A recent review of all published cases of TA treated with TNF-α antagonists found complete remission in 37%, partial remission in 53.5%, and no response in 9.5%. Only a small number of patients with TA have received tocilizumab. These patients have generally responded well, at least in the short term, and further data are awaited with interest.[39,40] The suppression of both constitutional symptoms and CRP synthesis by tocilizumab complicates disease monitoring and may be falsely reassuring. Follow-up of patients with TA should therefore include angiographic monitoring, preferably with CMR because it avoids radiation exposure.

Critical analysis of the published results suggests that percutaneous angioplasty or bypass surgery requires caution in patients with TA or GCA. Indications for surgical intervention include aneurysmal enlargement with risk for rupture, severe aortic regurgitation or coarctation, stenotic or occlusive lesions resulting in severe symptomatic coronary artery or cerebrovascular disease, uncontrolled hypertension as a consequence of renal artery stenosis, and stenoses leading to critical limb ischemia. Whenever possible, surgery should be delayed until immunosuppression has achieved clinical remission.[33]

Medium-Vessel Vasculitis

The medium-vessel vasculitides include Churg-Strauss syndrome (CSS, eosinophilic granulomatosis with polyangiitis, EGPA), granulomatosis with polyangiitis (GPA; Wegener granulomatosis), and microscopic polyangiitis (MPA). Although these diseases have overlapping features, they represent distinct clinical entities. GPA is most frequently associated with a cytoplasmic ANCA (cANCA) staining pattern that recognizes the antigen proteinase-3, whereas MPA is most commonly associated with a perinuclear ANCA (pANCA) directed against myeloperoxidase.

Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss Syndrome)

EGPA, a systemic small-vessel necrotizing vasculitis with a prevalence of 10 to 14 per million population, has three disease phases. An initial prodrome characterized by allergic rhinitis, sinusitis, and asthma precedes peripheral blood eosinophilia and eosinophilic infiltrative lesions in the lung and myocardium. Some years later, a systemic phase follows with necrotizing vasculitis affecting the skin, peripheral nerves, gastrointestinal tract, and kidney (in 30%). Up to 40% of patients with EGPA are ANCA positive and typically have pANCA. ANCA-negative patients are more likely to suffer cardiopulmonary complications, whereas pANCA-positive patients seem to be more at risk for renal and peripheral nerve involvement. The diagnosis depends on the clinical features, imaging studies, ANCA, and whenever possible, biopsy results. Patients have a markedly raised peripheral eosinophil count and evidence of necrotizing vasculitis, including eosinophilic infiltration (**Fig. 94.5**).

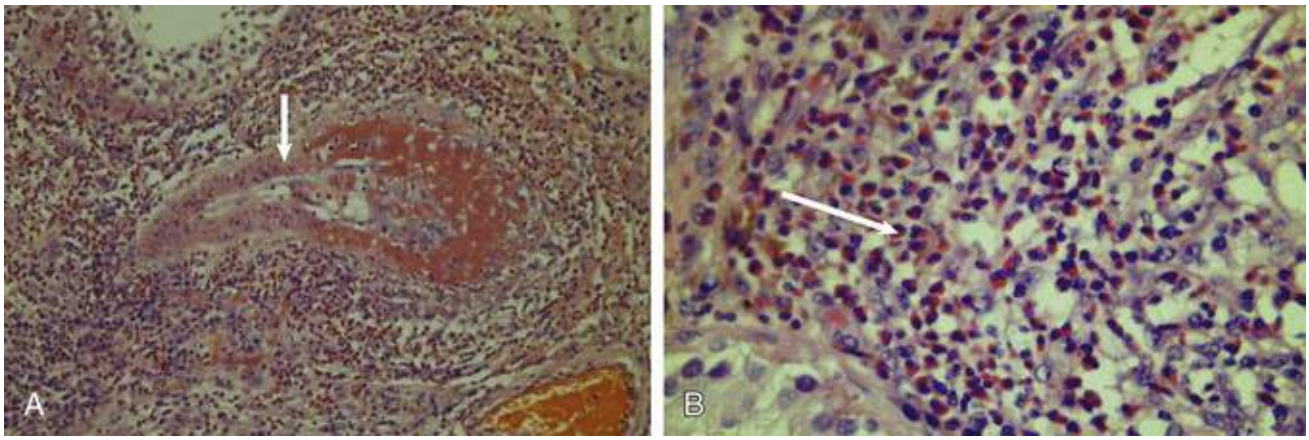

FIGURE 94.5 Churg-Strauss syndrome. **A,** Hematoxylin-eosin staining of a small artery *(arrow)* demonstrates fibrinoid necrosis and a dense perivascular mononuclear cell infiltrate. **B,** At higher magnification the inflammatory cells can be identified as predominantly eosinophils (*long arrow*) with scattered macrophages.

The diagnosis of EGPA requires consideration of a number of alternatives, including GPA and MPA. A history of asthma, the presence of marked peripheral eosinophilia, and a dense eosinophilic infiltrate highly suggest CSS. Viral infections, including cytomegalovirus and hepatitis B and C, must be excluded. In light of the eosinophilia, parasitic infestation, particularly by helminths, should be sought and excluded. Eosinophilia in the absence of demonstrable vasculitis may represent idiopathic hypereosinophilic syndrome or an underlying leukoproliferative disorder.

Cardiovascular Complications

Of all the vasculitides, EGPA is the most likely to be associated with severe and potentially fatal cardiac disease (**see Table 94.2**). Cardiac involvement complicates up to 60% of cases, and the disease spectrum includes pericarditis, myocarditis, coronary arteritis, myocardial infarction, cardiac fibrosis, arterial thrombosis, and valvular dysfunction. Cardiac disease is a prominent cause of death. Cardiomyopathy occurs as a result of ischemia secondary to arteritis affecting the intramyocardial arteries or, less frequently, the epicardial coronary arteries. Myocarditis is associated with eosinophilic infiltration, fibrosis, and occasionally, granuloma formation. Release of major basic protein and eosinophil-derived neurotoxin by infiltrating eosinophils can lead to direct tissue injury. Myocarditis may result in the development of restrictive, congestive, or dilated cardiomyopathy, or death.

Investigation

Cardiac involvement in EGPA requires urgent investigation, aggressive treatment, and initially, a 12-lead ECG and transthoracic echocardiography (**see Fig. 94.5**). Common findings include evidence of left ventricular dilation in 30% of patients, a reduced shortening fraction, and increased cardiac wall echogenicity. Contrast-enhanced CMR provides the most sensitive means of detecting myocardial involvement.[41] If the diagnosis remains in doubt, endomyocardial biopsy may reveal eosinophilic infiltration with or without fibrosis, although vasculitis is rarely seen and the patchy nature of the disease results in a low diagnostic yield.

Treatment

High-dose corticosteroid treatment typically results in a good response and is associated with a 90% remission of disease. Relapses occur frequently on tapering steroid therapy, and prednisone-related side effects are common. In the presence of severe disease, including cardiac, gastrointestinal, CNS, and renal

involvement, an immunosuppressant drug should be prescribed concomitantly. Although further clinical trials are required, the first choice of drug is pulsed intravenous cyclophosphamide. Once remission is achieved, generally by 3 to 6 months, cyclophosphamide can be replaced by azathioprine or methotrexate. In some patients with milder disease and evidence of steroid side effects, azathioprine or methotrexate should be added to aid in steroid tapering. In refractory disease, anecdotal case reports have suggested the effectiveness of IVIG or TNF-α blockade. We await further results from the study of B cell depletion and anti-interleukin-5 inhibition.[42]

Polyarteritis Nodosa

PAN is an increasingly rare disease characterized by a systemic necrotizing vasculitis of medium-sized arteries complicated by aneurysmal nodules. Viral infections, particularly with cytomegalovirus, human immunodeficiency virus, and hepatitis B and C viruses, should be specifically sought and excluded. The classic type of PAN is an ANCA-negative vasculitis with the predominant clinical features including fever, malaise, arthralgia, weight loss, livedo reticularis, cutaneous nodules, and a vasculitic rash. Abdominal, cardiac, and testicular pain may occur, and some patients manifest mononeuritis multiplex. Hematuria, proteinuria, and/or hypertension indicates renal involvement.

The pathogenesis of PAN remains poorly understood. The initial vascular endothelial injury is followed by local release of IL-1 and TNF-α, which predispose to chronic inflammation and up-regulation of cellular adhesion molecules. Recruitment of neutrophils is followed by monocyte infiltration, local endothelial disruption, thrombosis, and fibrinoid necrosis (**Fig. 94.6**). The associated arterial wall injury predisposes to aneurysm formation. The diagnosis of PAN is not straightforward. Although a biopsy can be definitive, the yield is variable and dependent on an accessible lesion. A deep skin biopsy specimen from an involved nodular site is optimal. Combined sural nerve and muscle biopsy may also be helpful. Occasionally, nodules are detected on a medium-sized peripheral artery that can safely undergo biopsy. Renal biopsy should be approached with caution because of the risk for hemorrhage from microaneurysms. Despite increasing use of noninvasive imaging with CTA or MRA, mesenteric arteriography remains the most accurate way of identifying renal or hepatic microaneurysms.

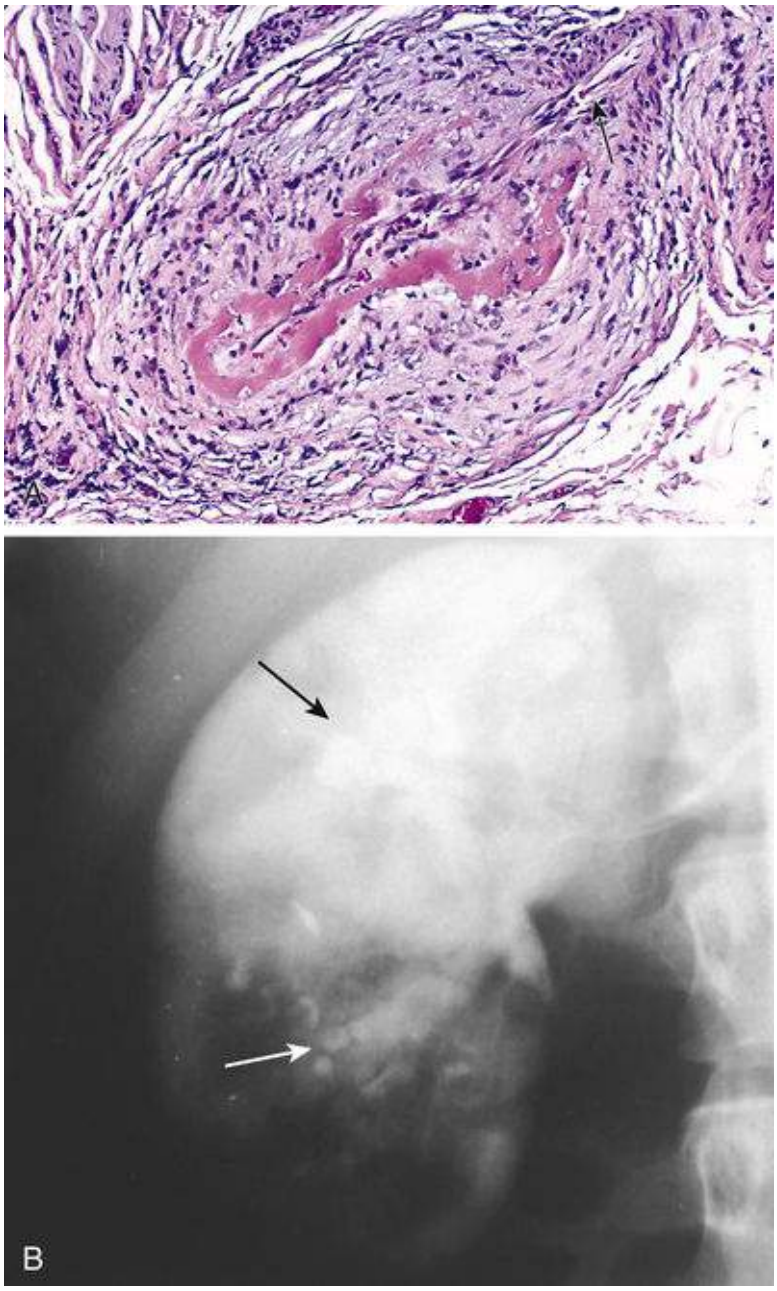

FIGURE 94.6 Polyarteritis nodosa. **A,** Photomicrograph of a hematoxylin-eosin–stained section of an artery biopsy specimen from a patient with PAN showing segmental fibrinoid necrosis, thrombotic occlusion of the lumen, and a small uninvolved remnant *(arrow).* **B,** Right renal angiogram showing multiple small aneurysms *(white arrow)* and a normal calyceal system *(black arrow).* (From Mitchell RN, Schoen FJ: Blood vessels. In Kumar V, Abbas A, Aster JC (editors): Robbins and Cotran pathologic basis of disease, 9th ed. Philadelphia, Elsevier Saunders, 2014.)

Cardiovascular Complications

Cardiac involvement in PAN is often subclinical and clinically apparent in only 10% of patients. Congestive cardiac failure is most commonly seen and may result from a specific myocarditis or coronary arteritis. Alternatively, the underlying cause may be PAN-related renal disease complicated by hypertension. Five percent of patients develop pericarditis, as well as supraventricular tachycardia and valvular disease. Coronary angiography may reveal coronary artery microaneurysms, coronary arteritis, or coronary spasm. Coronary CTA may demonstrate coronary artery aneurysms.

Treatment

Glucocorticoids form the basis of treatment of PAN. In those with cardiac disease, significant proteinuria

with or without renal impairment, CNS involvement, gastrointestinal disease, or mononeuritis multiplex, intravenous cyclophosphamide therapy is used initially. Some physicians prefer oral cyclophosphamide, and although side effects are more common, time until relapse may be longer. Six months of cyclophosphamide is usually sufficient to achieve disease remission, and treatment can be switched to oral azathioprine. In those with refractory disease, infliximab given in combination with methotrexate or azathioprine may provide benefit.

Granulomatosis With Polyangiitis (Wegener Granulomatosis)

GPA is a granulomatous necrotizing vasculitis that commonly affects the sinuses, upper airways, lungs, skin, joints, and kidneys. Diagnosis is based on clinical features, biopsy evidence, and typically a positive cANCA with antibodies against proteinase-3. The disease may be confined to the upper airways or be more generalized and include ocular inflammation, cutaneous vasculitis, arthralgia, cavitating lung lesions (**Fig. 94.7**), pulmonary hemorrhage, and acute renal failure. Clinical cardiac involvement is rare, although it has been reported in up to 30% of autopsy cases. The most frequently encountered problem is pericarditis, which can lead to hemodynamic compromise and tamponade. The presence of congestive cardiac failure is a poor prognostic sign and associated with a 25% mortality rate in the first year. Underlying causes include coronary arteritis, myocarditis, and occasionally valvular heart disease.

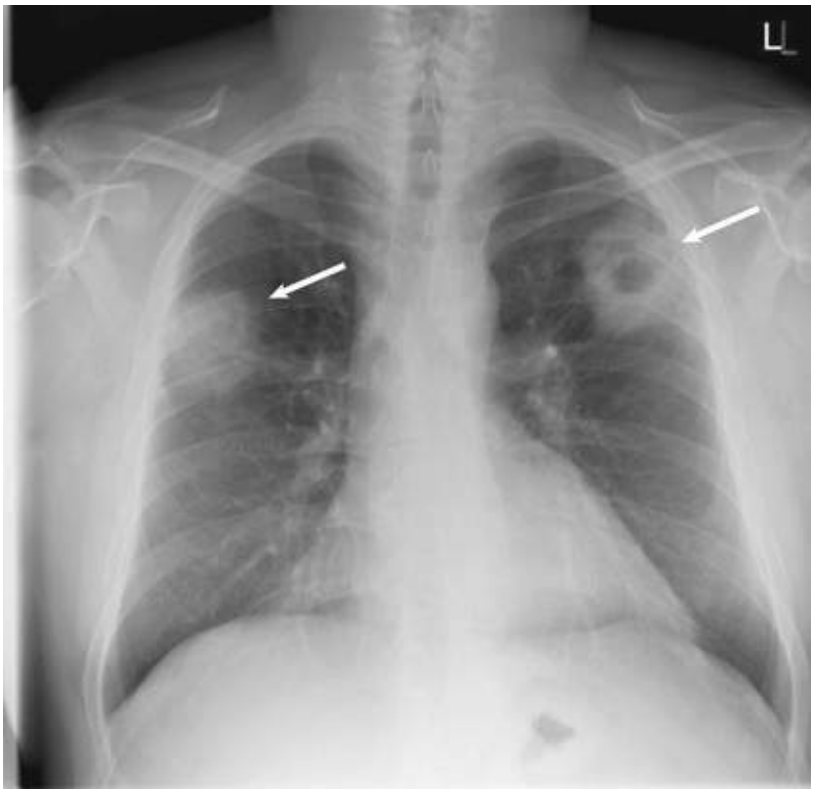

FIGURE 94.7 Granulomatosis with polyangiitis. Chest radiograph of a 36-year-old man showing pulmonary involvement with evidence of opacification and cavitation in the left upper lobe lesion *(arrows).*

Microscopic Polyangiitis

MPA is most commonly associated with glomerulonephritis, renal impairment, and pulmonary hemorrhage. Cardiac disease is rarely clinically significant, but pericarditis occurs in 10% of patients, and congestive cardiac failure develops in up to 18%. Subclinical and occasionally symptomatic acute

myocardial infarction can occur. Evidence from case reports and small series shows that this disease also features symptomatic aortitis and coronary artery microaneurysms.

Investigation

Cardiac involvement should initially be investigated noninvasively with modalities that include rest or stress echocardiography. Contrast-enhanced CMR can sensitively detect the myocardial pathology, and coronary CTA can demonstrate coronary arteritis and microaneurysms. Echocardiography suggests valvular thickening as a common and typically asymptomatic finding in GPA. Aortic valve regurgitation may occur because of distortion and thickening of valve cusps or from aortic root dilation. On occasion, coronary artery catheterization may be required, and as for other vasculitides, it should be used cautiously in those suspected of having active coronary arteritis. When possible, steps should be taken to suppress disease activity with immunosuppressive therapy before angiography. Coronary arteritis can cause multiple small areas of myocardial infarction, which often remain clinically silent until the development of congestive cardiac failure. Occasionally, granulomas in conduction tissue can cause cardiac dysrhythmia.

Treatment

For both GPA and MPA, high-dose prednisone (1 mg/kg/day) is recommended and may be preceded by pulsed intravenous methylprednisolone if indicated. Patients with the most severe disease, including pulmonary hemorrhage, severe cardiac disease, or significant renal impairment, receive pulsed intravenous cyclophosphamide to induce remission over the first 3 to 6 months. Cyclophosphamide can then be replaced with azathioprine, methotrexate, or MMF. In less severe limited disease, remission can be achieved reliably with prednisolone in combination with azathioprine or methotrexate.[43] Increasing evidence suggests that B cell depletion therapy is effective for AASV and achieves remission at a rate comparable to that of cyclophosphamide.[44,45]

Pericarditis and Myocarditis

Pericarditis

Pericarditis commonly complicates the autoimmune connective tissue diseases, particularly SLE, SSc, and RA. Nonetheless, clinically significant pericarditis develops in fewer than 30% of patients. The reported prevalence ranges from 11% to 85%, depending on the type of study used to detect disease. Thus in necropsy studies, prevalence is high, with pericardial involvement reported in 40% of individuals with RA, 40% to 80% of those with SLE, and up to 70% of those with SSc. Pericarditis is diagnosed by echocardiography, which detects pericardial thickening or small effusions in up to 50% of these patients. CMR can also provide accurate definition of the extent of pericardial involvement.

Systemic Lupus Erythematosus

In SLE, pericarditis is usually associated with disease flare and often with polyserositis. The symptoms are typically mild and consist of chest pain, which is worse on lying flat, and dyspnea, which may have a pleuritic component. Complicated pericarditis is rare, and in only 1% to 2% is the effusion sufficiently large to cause cardiac tamponade. Constrictive pericarditis or infective pericarditis occur infrequently.

Rheumatoid Arthritis

Clinically significant pericarditis affects only 1% to 2% of patients with RA, more commonly male, seropositive patients. Constrictive pericarditis can develop over a period of months. Hemodynamically significant pericarditis, although reported, is extremely rare in patients being treated with antirheumatic therapy. Indeed, the more aggressive approach to management of RA and the increasing use of biologic therapies appear to have reduced the incidence of symptomatic pericarditis.

Systemic Sclerosis

The two most commonly encountered forms of scleroderma are diffuse cutaneous SSc (dSSc) and limited cutaneous SSc (lSSc). Following an initial vascular inflammatory phase, the predominant lesion is fibrosis, which affects multiple organs.[46] In addition to the severe cutaneous manifestations, common clinical features include arthralgia, telangiectasia, pulmonary fibrosis, PAH, and esophageal dysmotility. Renal crises are common and complicated by hypertension. Aggressive intervention is essential and includes the use of ACE inhibitors and calcium channel antagonists. This approach has transformed the prognosis. Pericardial disease is common and more frequent in those with dSSc and a history of renal crisis. Echocardiography typically demonstrates small pericardial effusions, which are rarely hemodynamically significant. Rapidly accumulating large effusions may occur occasionally.

Pericardial Fluid Analysis

Analysis of pericardial fluid is rarely useful diagnostically unless infective pericarditis is suspected. Immune complexes, antinuclear and anti-dsDNA antibodies, complement consumption, and normal glucose levels have been reported in pericardial exudates from patients with SLE. In RA the pericardial fluid glucose concentration may be lower than that in plasma, and although rheumatoid factor activity is often detected, it is not considered diagnostic.

Treatment

In most cases a small pericardial effusion appears on a routine chest radiograph or echocardiogram and requires no specific treatment. Those with troublesome symptoms of pericarditis can receive a short course of an NSAID unless contraindicated. Low-dose oral prednisone may be required or used as an alternative. Recurrent cases, in particular, require further optimization of the regular immunosuppressive therapy. Pericardial fluid accumulation may be sufficient to cause hemodynamic compromise and even cardiac tamponade requiring pericardiocentesis or, in recurrent cases, a pericardial window. For immunosuppressed patients, pericardial fluid should be analyzed for an infective cause. Advice should be sought from a microbiologist to ensure that the correct specimens are sent, including those required to exclude tuberculosis.

Myocarditis

Myocarditis is a rare but recognized cause of mortality in patients with autoimmune rheumatic diseases and is most commonly seen in patients with SLE, SSc, and polymyositis or dermatomyositis. Although most commonly present in those with an established rheumatic disease, myocarditis may be an initial feature requiring consideration of these conditions in the differential diagnosis of those with unexplained heart failure. The most common symptom of myocarditis is recent-onset exertional dyspnea with evidence of hypoxia.[47] A patient rarely presents with severe heart failure at the initial evaluation, and

echocardiography usually reveals relatively modest changes in ventricular size and function. PAH must be excluded. In addition to standard blood tests, investigations should include ESR, antinuclear antibody, antibodies against dsDNA and extractable nuclear antigens, rheumatoid factor, a myositis immunoblot screen, and complement factor C3 and C4 levels.

Systemic Lupus Erythematosus

Although the widespread use of more effective immunosuppressive regimens has reduced the prevalence of myocarditis in patients with SLE to fewer than 10%, most of whom have subclinical myocarditis, it remains an important and potentially life-threatening complication. Other potential causes of heart failure include hypertension, ischemic heart disease, valvular heart disease, and complications associated with renal failure.

The initial symptoms of myocarditis vary from low-grade fever, dyspnea, and palpitations to signs of severe heart failure. In addition to complement consumption, a raised ESR, and an increased titer of anti-dsDNA antibodies, the troponin I level may increase markedly. The ECG typically shows nonspecific findings such as sinus tachycardia or ST or T wave changes. Supraventricular or ventricular tachycardias may also occur. Echocardiography aids in assessment (**Fig. 94.8**). Functional abnormalities may include segmental, regional, or global wall motion abnormalities; chamber dilation; and a reduced ejection fraction. In contrast, left ventricular hypertrophy in SLE is more commonly associated with poorly controlled hypertension, whereas systolic and diastolic abnormalities in left ventricular function have been associated with both hypertension and ischemic heart disease. CMR can detect myocarditis and myocardial fibrosis, and gadolinium or adenosine stress first-pass perfusion may demonstrate coronary microvascular dysfunction. Indeed, CMR and PET identifies coronary myocardial dysfunction and reduced coronary flow reserve in patients with SLE.[48]

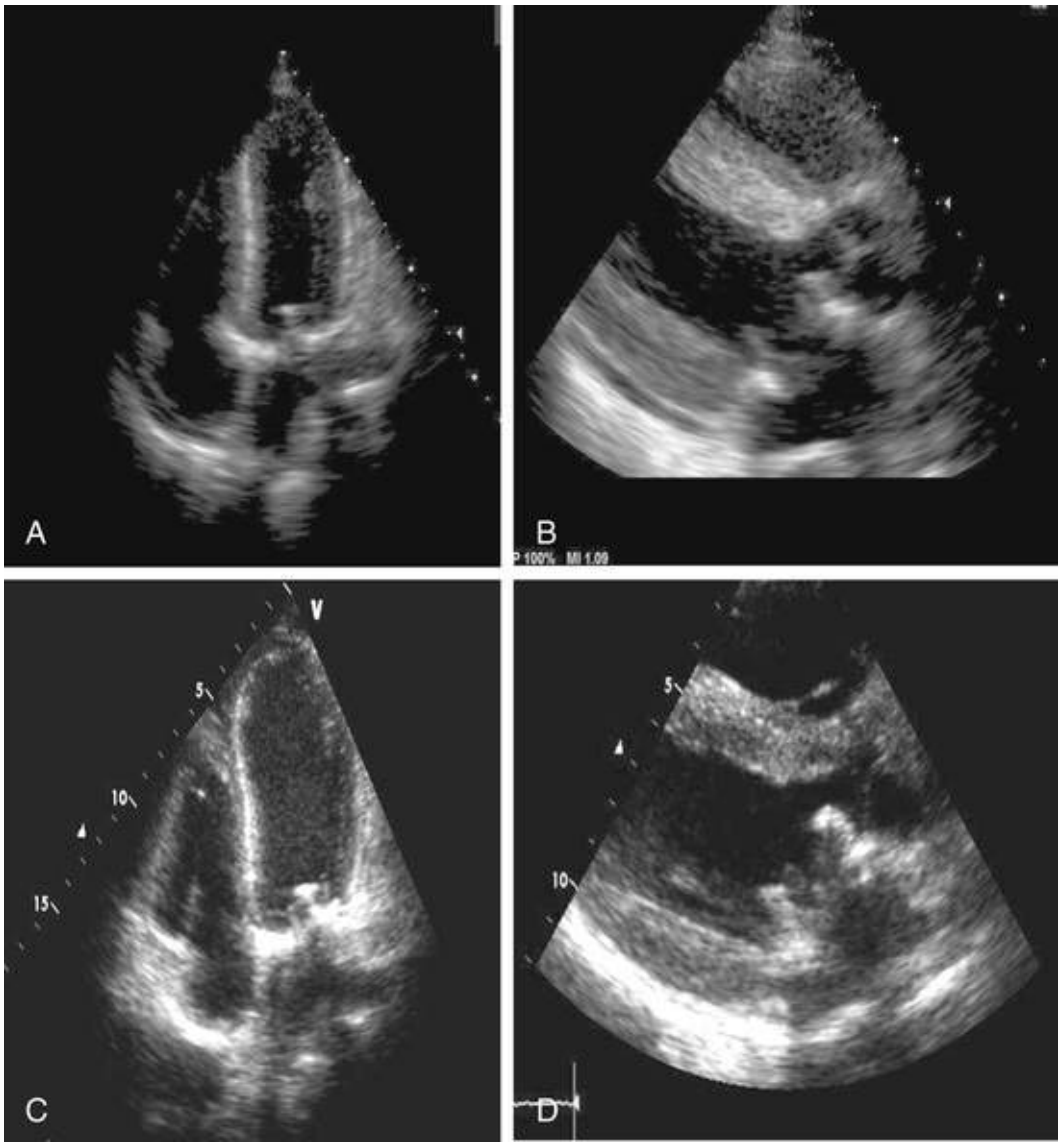

FIGURE 94.8 Myocarditis in systemic lupus erythematosus. **A** and **C,** Four-chamber view, **B** and **D,** Left ventricular view. In a 20-year-old patient with dyspnea and active SLE, the initial echocardiogram (**A** and **B**) showed mild impairment of ventricular function. Following symptomatic deterioration, the echocardiogram was repeated 6 days later and demonstrated markedly increased thickening of the left ventricular wall with a bright signal suggestive of inflammatory infiltration (**C** and **D**). These findings were associated with substantial deterioration in left ventricular function.

Opinion is divided on the use of endomyocardial biopsy. It will not permit a specific diagnosis of SLE per se. Biopsy may, however, demonstrate an underlying inflammatory cause and features suggestive of SLE. Histopathologic analysis typically reveals small focal areas of fibrinoid necrosis with infiltration of lymphocytes and plasma cells, along with evidence of the deposition of immune complexes closely associated with myocyte bundles. Immunofluorescent studies may reveal granular staining and deposition of complement in and around myocardial blood vessels. Biopsy may also help exclude other potential causes of cardiomyopathy.

Systemic Sclerosis

Inflammatory myocarditis rarely results in symptomatic cardiomyopathy in patients with SSc; it affects mostly those with prominent skeletal muscle myositis. Echocardiography may demonstrate impaired diastolic and systolic function and a reduced ejection fraction, occasionally severe enough to cause cardiac failure. Endomyocardial biopsy most commonly reveals myocardial fibrosis. The fibrosis occurs focally and affects both ventricles. As with other lesions in SSc, microvascular disease is considered an

important pathogenic factor. Reduced coronary flow reserve occurs commonly,[49] and subclinical myocardial ischemia probably contributes importantly to the ventricular dysfunction.

Myositis

Polymyositis and dermatomyositis affect the proximal skeletal muscles and can cause severe weakness. In dermatomyositis, additional characteristic cutaneous manifestations include a violaceous heliotrope rash, Gottron papules, and periungual erythema. In pediatric cases, subcutaneous calcification is common and vasculitis may lead to severe gut ischemia and hemorrhage. In adults, particularly those older than 60 years, dermatomyositis may be paraneoplastic in origin. In severe cases, myositis involves the myocardium and pharyngeal or respiratory muscles and can be life-threatening. Creatine kinase levels rise markedly, and electromyography demonstrates fibrillation and polyphasic action potentials. Magnetic resonance imaging of the proximal limb muscles helps identify the muscles involved and most amenable to biopsy. Histopathologic findings include muscle fiber necrosis and regeneration, a predominantly $CD8^+$ T lymphocyte infiltrate, and HLA class I expression. Clinically significant myocarditis affects only 3%. Echocardiography may reveal ventricular dysfunction, whereas endomyocardial biopsy specimens demonstrate interstitial and perivascular lymphocytic infiltrates, contraction band necrosis, variable cardiomyocyte size, and degeneration and patchy fibrosis. Overt cardiac failure is rare; more common are rhythm and conduction abnormalities, including left anterior hemiblock and right bundle branch block.

Other Causes of Myocarditis

Even though postmortem studies have revealed evidence of myocarditis in patients with RA, it is seldom manifested clinically or causes heart failure. Although heart failure affects patients with RA more than it does age- and sex-matched controls, it predominantly reflects atherosclerotic coronary artery disease.[2] Myocarditis is also rarely associated with other rheumatic diseases, including ankylosing spondylitis, adult Still disease, GCA, and TA.

Treatment

Cardiac failure following myocarditis associated with autoimmune disease is treated with standard protocols and supportive interventions (**see Chapter 25**). SLE-related myocarditis requires urgent corticosteroid treatment and, when severe, intravenous methylprednisolone, 1 g/day for 3 days, followed by oral prednisone, 1 mg/kg/day. These patients typically receive pulsed intravenous cyclophosphamide. For more modest disease, treatment can include the addition of or increased dosages of azathioprine or MMF. Some evidence suggests benefit of IVIG in resistant cases. Management of myocarditis complicating dermatomyositis or polymyositis uses a similar approach. Myocarditis in patients with SSc rarely requires aggressive treatment. Because high-dose corticosteroids increase the risk for a renal crisis, early use of intravenous cyclophosphamide is favored.

Valvular Heart Disease

Clinically significant valvular disease can complicate many rheumatic diseases. Mechanisms may include direct damage to cardiac valve leaflets or aortic valve regurgitation as a consequence of aortitis affecting the ascending aorta (**see also Section 8**).

Systemic Lupus Erythematosus

Valvular abnormalities occur commonly in patients with SLE, and necropsy studies have reported lesions in up to 75%. Verrucous endocarditis (Libman-Sacks endocarditis) and nonspecific valvular thickening occur most commonly. Valvulitis with rapid valvular dysfunction may also happen rarely. Transthoracic echocardiography detects verrucae in 2.5% to 12% and thickening in 4% to 38%, which increases to 30% and 43%, respectively, in those undergoing transesophageal echocardiography. Libman-Sacks lesions typically affect both valve surfaces, most commonly the mitral valve. Active valve lesions contain immunoglobulins, fibrin clumps, areas of focal necrosis, and a leukocytic infiltrate, whereas older healed lesions exhibit vascular fibrous tissue predisposing to scarring and valve leaflet deformity. These abnormalities may cause valvular regurgitation. Libman-Sacks endocarditis occurs more commonly in SLE complicated by antiphospholipid antibodies and can accompany primary antiphospholipid syndrome.

Libman-Sacks endocarditis is generally asymptomatic and may not cause a murmur. Assessment of SLE patients with a murmur may not be straightforward, and requires exclusion of bacterial endocarditis. Echocardiography can help distinguish Libman-Sacks endocarditis from infectious endocarditis, an important consideration in immunosuppressed patients. In contrast to the typically nonmobile vegetations of Libman-Sacks lesions, bacterial vegetations usually localize at the valve leaflet closure line and demonstrate mobility that is independent of valve leaflet motion. The presence of Libman-Sacks lesions increases the risk for secondary infective endocarditis, and prophylactic antibiotic prophylaxis should be considered to cover high-risk procedures such as invasive dental treatment (**see Chapter 73**). Complications of SLE-related valvular disease are rare, with hemodynamic effects seen in fewer than 5%. Valve replacement may be required for symptomatic regurgitation and occasionally for stenosis. The verrucous lesions may also embolize or rupture and lead to a cerebrovascular accident or peripheral embolism. Chordae tendineae rupture may also occur.

Treatment

Most patients require no specific treatment, although annual echocardiography can be used to monitor valve function. The introduction of corticosteroid therapy may have reduced the prevalence of Libman-Sacks endocarditis, and thus prednisone treatment may be considered in those with early active lesions. Patients with uncomplicated Libman-Sacks endocarditis with valve thickening on the echocardiogram are not routinely anticoagulated. Those with definitive vegetations or evidence of embolic phenomena should be considered for lifelong anticoagulation therapy.[50]

Seronegative Spondyloarthropathies

The seronegative spondyloarthropathies include ankylosing spondylitis, postinfectious reactive arthritis, inflammatory bowel disease–related arthritis, and psoriatic arthritis. HLA-B27 is associated with ankylosing spondylitis and reactive arthritis. The spondyloarthropathies share overlapping clinical features, including asymmetric, predominantly large-joint oligoarthritis, ocular inflammation, sacroiliitis, spinal disease, and enthesopathy. Ankylosing spondylitis and reactive arthritis commonly involve the aortic root and valve. Aortic valvulitis leads to aortic cusp thickening and retraction and subsequently to symptomatic aortic regurgitation, which may cause heart failure. Proximal aortitis affecting the ascending aorta leads to aortic root thickening and subsequently to dilation and aortic regurgitation, the prevalence of which relates to disease duration.

Treatment

Management of the spondyloarthropathies has traditionally consisted of NSAIDs and, in more severe cases, the addition of DMARDs such as methotrexate, sulfasalazine, and leflunomide. Although these agents have some efficacy in the treatment of peripheral inflammatory arthritis, they have little effect on spinal inflammation. The use of TNF-α antagonists for ankylosing spondylitis and psoriatic arthropathy has markedly improved control of the disease, with beneficial effects on peripheral arthritis, spinal disease, and extraarticular complications, including uveitis.[51] Although evidence is currently limited, initiation of biologic therapy in those with early signs and symptoms of aortitis may reduce the risk for cardiovascular complications, including aortic regurgitation.[52]

Rheumatoid Arthritis

Valvular thickening is commonly associated with RA in echocardiographic studies and at autopsy, but seldom causes clinical problems. Patients with seropositive RA and with prominent extraarticular nodular disease more frequently have valvular lesions. Echocardiography typically reveals mitral valve involvement, with valve thickening, asymptomatic mitral regurgitation, and prolapse being the predominant findings. Histopathologic examination of the valves demonstrates granulomatous nodular lesions. No specific treatment is indicated, although on occasion hemodynamically significant disease develops and requires mitral or aortic valve replacement.

Takayasu Arteritis

Cardiac valve dysfunction commonly complicates TA. In a recent series of 204 Korean patients, 23% had an abnormality in at least one valve, with regurgitation at the aortic valve found in 18% and at the mitral valve in 7.5%.[53] Inflammation of the ascending aorta predisposes to dilation of the aortic root and aortic valve regurgitation. Approximately 15% of patients require aortic valve replacement with or without aortic root replacement with a graft. If possible, surgery should follow control of disease activity with immunosuppressive therapy.[33]

Cardiac Conduction Disturbances

A variety of rheumatic diseases cause conduction abnormalities and cardiac rhythm disturbances.

Systemic Lupus Erythematosus and Sjögren Syndrome

Adult SLE seldom causes primary conduction abnormalities or a rhythm disturbance, which may instead result from underlying ischemic heart disease or myocarditis. Female patients with SLE or Sjögren syndrome who test positive for antibodies against the Ro and/or La antigens carry the risk of bearing a child with a congenital heart block, which may be complicated by myocarditis. These antibodies can cross the placenta and induce myocardial inflammation and can target the conduction system and lead to fibrosis. The precise incidence is not established, but the usual figures quoted are 1 case in 20,000 live births with a range of 11,000 to 25,000. Patients with SLE, the overlap syndromes, and Sjögren syndrome should be screened for anti-Ro and anti-La before pregnancy and be counseled appropriately. The fetus of a mother known to be antibody positive should be screened in utero by echocardiography every 2 weeks from 16 weeks of gestation onward. Incomplete atrioventricular block can reverse, and myocarditis may

respond to dexamethasone therapy. Complete atrioventricular block is irreversible and associated with mortality rates of up to 20%, with 65% requiring insertion of a pacemaker.

Systemic Sclerosis

Conduction system disease affects up to 50% of SSc patients. The patchy myocardial fibrosis characteristically associated with SSc may account for the abnormalities seen with disruption of the conduction pathways. Supraventricular arrhythmias are usually benign and amenable to treatment. Ventricular conduction abnormalities also frequently occur in SSc. In these patients ventricular ectopy is common and closely associated with sudden death.

Spondyloarthropathies

Conduction abnormalities frequently complicate the HLA-B27–related spondyloarthropathies. In ankylosing spondylitis, up to 30% of patients experience conduction system disease, predominantly caused by subaortic fibrosis extending into the septum and affecting the atrioventricular node. Atrioventricular conduction block occurs commonly and may become complete.

Polymyositis and Dermatomyositis

Conduction abnormalities are the most common cardiac manifestation of the myositis syndromes. Left anterior hemiblock and right bundle branch block occur most frequently and occasionally progress to complete heart block. The inflammation and fibrosis associated with polymyositis and dermatomyositis affect the conduction pathways, as demonstrated in 25% of autopsy cases.

Rheumatoid Arthritis

ECG screening studies in patients with RA have revealed arrhythmias or conducting system abnormalities in up to 50%, although they are usually clinically inapparent. Rheumatoid myocarditis and amyloid deposition in the heart can cause atrioventricular node conduction block. Similarly, rheumatoid nodules may disrupt the conduction system and cause all types of conduction abnormality.

Pulmonary Arterial Hypertension

PAH (**see Chapter 85**) can result from the connective tissue diseases and is of concern to rheumatologists as a significant cause of premature death (**Table 94.4**). PAH often manifests late in disease evolution or remains undiagnosed. Furthermore, PAH frequently proves resistant to optimized treatment of the underlying connective tissue diseases. Notwithstanding, increased awareness, recognition of high-risk groups, improved screening, and novel therapies point toward a better outlook.

TABLE 94.4

Pulmonary Arterial Hypertension in Rheumatic Diseases

RHEUMATIC DISEASE	FEATURES OF PULMONARY ARTERIAL HYPERTENSION
Systemic sclerosis	Prevalence of 5% to 12%; more common in limited cutaneous SSc
Polymyositis/scleroderma overlap	Annual screening recommended; survival rate at 3 years of 47% to 56%
Systemic lupus erythematosus	Prevalence of 0.5% to 17.5%; survival rate at 3 years of 74%; thrombotic arteriopathy is most common underlying cause; 83% of patients have anticardiolipin antibodies; patients with severe Raynaud phenomenon, anticardiolipin antibodies, and anti-U1RNP require screening
Rheumatoid arthritis	Prevalence data limited; reported to be up to 20%; clinically significant disease rare, often secondary to chronic obstructive pulmonary disease, chronic thromboembolic disease, or interstitial lung disease; improved rheumatoid arthritis treatment may result in reduced incidence
Sjögren syndrome	Pulmonary arterial hypertension a very rare complication of Sjögren syndrome; usually occurs late in course of disease; prevalence unknown
Takayasu arteritis	Pulmonary arteritis present in up to 50% of patients; pulmonary arterial hypertension prevalence of 12%

RNP, ribonucleoprotein.

Systemic Sclerosis

SSc is the most resistant of the connective tissue diseases to treatment and has the highest mortality rates. PAH has very serious prognostic implications and is the most common single cause of SSc-related death.[54,55] Novel therapeutic options offer renewed hope, and early data suggest improved survival rates.[56]

Pathogenesis

Arterial remodeling is a central component in the pathogenesis of PAH and follows uncontrolled smooth muscle cell proliferation, deposition of extracellular matrix and subsequent fibrosis, vasoconstriction, and in situ thrombosis that together lead to increased pulmonary vascular resistance. Right ventricular dilation, dysfunction, and failure follow the development of PAH. Because PAH may develop very rapidly, effective screening strategies for patients with SSc are essential to detect PAH and allow early therapeutic intervention.

Screening

The prevalence of PAH in patients with SSc is between 5% and 12%. Although more common with lSSc, PAH also frequently occurs in patients with dSSc. Debate continues regarding the frequency of screening and whether to include both symptomatic and asymptomatic patients. Screening of asymptomatic patients may improve survival rates.[57] PAH may occur as an early or a late complication, and there is a lack of reliable predictive risk factors. Annual screening should include echocardiography and pulmonary function testing.[54] In the latter, the carbon monoxide diffusing capacity may predict the development of PAH and the prognosis. Pulmonary fibrosis can also complicate SSc and may exacerbate PAH (**Fig. 94.9**). Echocardiographically assessed pulmonary artery pressure may miss early asymptomatic disease. Positive results from screening should be followed by diagnostic right-heart catheterization.[58] The level of NT-pro-brain natriuretic protein (BNP) relates to the degree of right ventricular dysfunction and the severity of PAH.

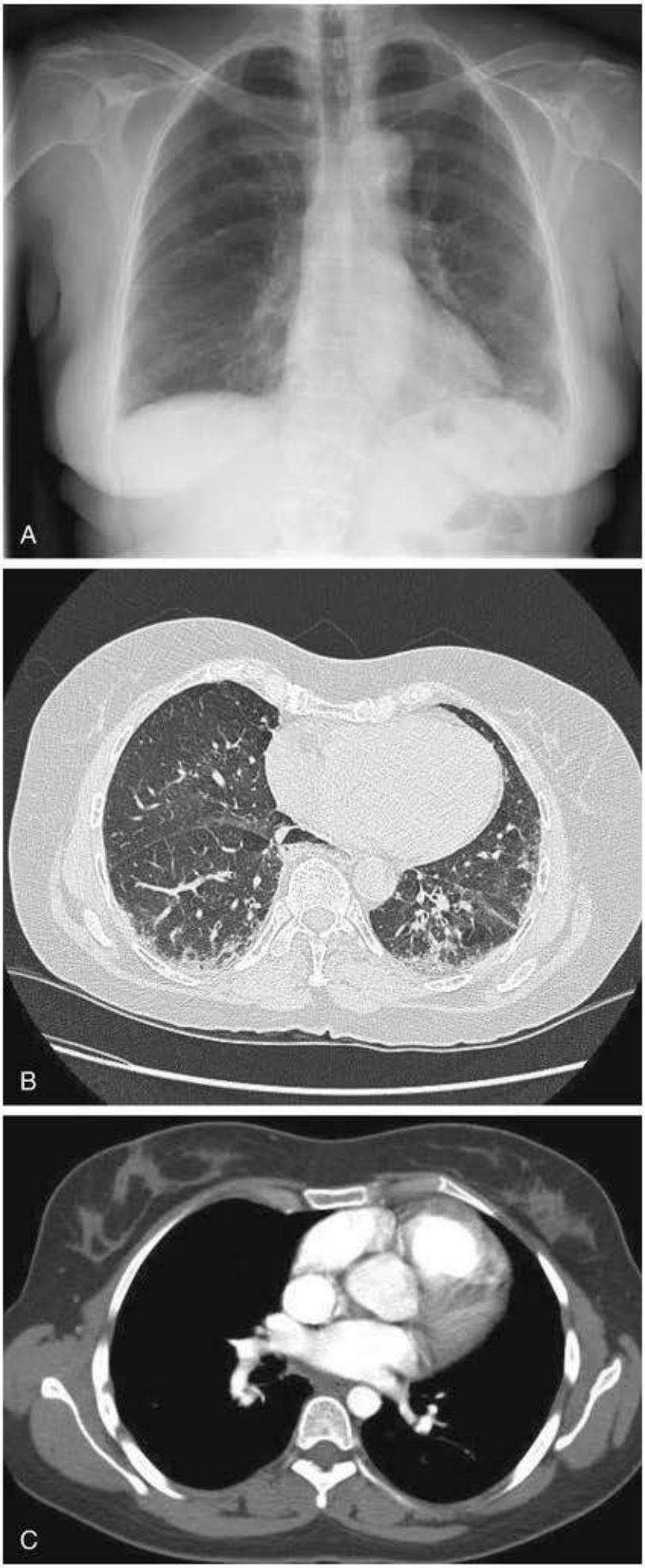

FIGURE 94.9 Systemic sclerosis. **A,** Chest radiograph of a patient with dSSc showing interstitial shadowing, mainly in the lung bases, along with associated loss of volume, consistent with early pulmonary fibrosis. **B,** CT of the thorax demonstrating ground-glass opacity, subpleural honeycombing

with thickening of the interlobular septa, and linear fibrotic bands, in keeping with pulmonary fibrosis. There is also evidence of associated mild traction bronchiectasis. **C,** Pulmonary CTA in a patient with limited cutaneous scleroderma and pulmonary hypertension. The right atrium and right ventricle are enlarged, and there is dilation of the pulmonary trunk.

Treatment and Outcome

The typical initial symptom of PAH is dyspnea, and the diagnosis is often delayed until clinical evidence of hemodynamic impairment is apparent, not the least because of the multiple potential causes of dyspnea in patients with SSc. Delayed diagnosis is also reflected in the very poor 3-year survival rate of 47% to 56%, thus emphasizing the need for early diagnosis and treatment, which may improve the outcome.[58] The aims of treatment have been summarized as improvement in New York Heart Association (NYHA) functional class and quality of life, delay in clinical deterioration, and improved long-term outcome. Although standard PAH outcome measures can assess the response to treatment (**Chapter 85**), not all of them have been validated in patients with SSc and they may be complicated by coexistent conditions, including pulmonary fibrosis and musculoskeletal pain. Supported by clinical trials, treatment targets three main pathways with agents used alone and increasingly in combination.[59] Endothelin-1 receptor antagonists include the original bosentan, sitaxsentan, ambrisentan, and most recently macitentan. Epoprostenol, iloprost, or treprostinil target the prostacyclin pathway, and open-label studies have shown improvements in symptoms and the 6-minute walking distance. Similarly, the phosphodiesterase type 5 antagonist sildenafil improved exercise capacity in a placebo-controlled trial.

Systemic Lupus Erythematosus

The prevalence of PAH in patients with SLE varies between studies and was recently estimated to be between 0.5% and 17.5%. These patients are typically females of reproductive age, in whom PAH during pregnancy markedly increases the risk for death.

Pathogenesis

In situ pulmonary thrombosis or chronic thromboembolic disease leading to thrombotic arteriopathy is the most common cause of PAH in patients with SLE, and 83% of such patients have anticardiolipin antibodies. Additional causes include pulmonary arteritis, underlying interstitial lung disease, and left-sided heart disease secondary to myocarditis, hypertension, or ischemic heart disease.

Clinical Findings and Diagnosis

Dyspnea, which may be associated with fatigue, cough, and chest pain, is the typical initial symptom. The development of PAH does not necessarily reflect the duration of SLE or its severity. Limited data concerning predictive features indicate that patients with severe Raynaud phenomenon, anticardiolipin antibodies, and anti-U1RNP antibodies have more susceptibility to develop PAH. These patients should be screened annually with echocardiography to estimate the pulmonary artery pressure. Raised pressure should be investigated further by right-heart catheterization.

Treatment and Outcome

Management of PAH in patients with SLE uses a dual approach that combines optimized immunosuppression and vasodilator therapy,[60] although protocols vary between centers.[56] Limited

evidence supports therapeutic decisions in PAH associated with SLE; many centers reserve combination therapy for those with NYHA class III or IV disease. In contrast to SSc-related PAH, the response to increased corticosteroids and pulsed intravenous cyclophosphamide can be good, and once response is achieved, switching from cyclophosphamide to azathioprine or MMF can reduce toxicity. Stronger trial evidence is available for the use of vasodilator therapies, which include dual endothelin-1 receptor antagonists such as bosentan, prostacyclin therapy, and sildenafil. In those with anticardiolipin antibodies, life-long anticoagulation with warfarin is indicated. The 3-year survival rate of 74% is higher than that in patients with SSc-related PAH.[60]

Rheumatoid Arthritis

Pulmonary complications in RA include pleural effusions, pulmonary nodules, interstitial lung disease, bronchiolitis obliterans, and occasionally PAH.[61] PAH in patients with RA most commonly results from other underlying diseases, including chronic obstructive pulmonary disease, chronic pulmonary thromboembolism, hyperviscosity syndromes, lung surgery, or left-sided heart disease. PAH, however, may be related to extraarticular manifestations of RA, pulmonary fibrosis, or isolated pulmonary arteritis. Dyspnea is the most common initial symptom. The diagnosis is often delayed, first because dyspnea is frequently attributed to other potential causes and, second, because of a limited exercise capacity in patients with severe arthritis. Diagnosis of PAH by the measures outlined above should be followed by specific investigations such as high-resolution pulmonary CT, CTA, pulmonary function tests, and a ventilation-perfusion scan to determine the underlying cause. No specific guidelines inform the treatment of PAH arising as a primary complication of RA. Any evidence of active RA should be treated aggressively and preferably with biologic agents such as TNF-α or IL-6 receptor antagonists. Specific treatment of PAH should also be considered, including the use of endothelin-1 antagonists or phosphodiesterase type 5 inhibitors.

Sjögren Syndrome

Clinically significant PAH very rarely complicates Sjögren syndrome and usually occurs late, most typically in patients with NYHA functional class III or IV; the diagnosis is established as described for RA above. Little evidence guides therapeutic decisions, and regimens vary considerably.[62] Therapy with corticosteroids and immunosuppressive drugs, including azathioprine and cyclophosphamide, should be optimized to gain control of the underlying Sjögren syndrome activity. These measures may provide at least transient benefit in PAH, particularly in patients with evidence of active interstitial lung disease. Anecdotal evidence suggests beneficial effects of B cell depletion therapy with rituximab in patients with severe disease and may offer a future approach for those with PAH. In the majority, enhanced immunosuppression is combined with standard PAH treatment, including the use of prostanoids, endothelin-1 antagonists, and phosphodiesterase type V inhibitors.[62]

Takayasu Arteritis

Pulmonary artery involvement in TA is often overlooked. Yet 50% of patients with TA have evidence of pulmonary arteritis in autopsy studies, and PAH develops in 12%. Even though pulmonary arteritis typically coexists with disease of the aorta, it can be isolated. Systemic hypertension and left ventricular dysfunction may cause secondary PAH. The pulmonary arterial lesions seen include stenoses, occlusions,

and aneurysms. PAH may develop acutely early in the disease course or later and more insidiously following progressive pulmonary artery narrowing. When present, symptoms may include dyspnea, chest pain, and peripheral edema. These symptoms are often ascribed to other causes, including left ventricular dysfunction, and the diagnosis is typically delayed. Unless specifically sought, pulmonary artery involvement can be missed on initial radiologic studies. Dedicated CMR and contrast-enhanced CTA are the most sensitive detection modalities. Abnormalities should be pursued with echocardiography and other studies as described above.

No available clinical trials guide therapeutic decisions. Aggressive treatment of the underlying arteritis with high-dose corticosteroids and a steroid-sparing drug such as methotrexate is recommended. Pulsed intravenous cyclophosphamide is typically reserved for nonresponders, and the emerging efficacy of biologic therapies for TA, including TNF-α and IL-6 receptor antagonists, suggests that they should be considered early in refractory disease. Warfarin is often used, particularly in those with evidence of thrombosis or pulmonary infarction. Endothelin-1 antagonists or sildenafil may help in patients with more severe or resistant PAH.[63] Open reconstructive surgery or percutaneous angioplasty may prove successful.

Thrombosis in Rheumatic Diseases

Thrombosis is an important pathologic process in many rheumatic diseases and a cause of significant morbidity and mortality (**see also Chapter 93**). Large-vessel thrombosis, both venous and arterial, can occur in Behçet disease and APS. Thrombosis in situ also occurs in small vessels, principally as the end result of chronic vessel wall hyperplasia or inflammation in diseases such as SSc, the vasculitides, and PAH. Chronic thromboembolic PAH can complicate SLE and SSc.

Activation of the coagulation cascade leading to thrombosis may be caused by abnormalities in the vessel wall, blood constituents, or blood flow (**see Chapters 44 and 93**). Abnormalities in endothelial function have particular relevance to rheumatic diseases. The prolonged systemic inflammation in patients with SLE, Behçet disease, and the vasculitides can cause endothelial apoptosis, a local inflammatory response, and endothelial activation. Cytokine-mediated endothelial activation disturbs anticoagulant and fibrinolytic mechanisms. Treatment of prothrombotic risk in these diseases requires consideration of approaches that include immunosuppression to control disease activity and minimize endothelial dysfunction, antiplatelet agents, anticoagulation, and the use of statins.

Antiphospholipid Syndrome (see also Chapter 93)

APS is associated with thrombosis (both arterial and venous) and with first-trimester fetal loss. Laboratory tests demonstrate antiphospholipid antibodies, most commonly anticardiolipin antibodies, and/or a positive lupus anticoagulant test. Anticardiolipin antibodies, typically of the IgG or IgM isotype and present in medium to high titer, or the lupus anticoagulant should be demonstrated on at least two occasions 6 or more weeks apart. Antiphospholipid antibodies directed against $beta_2$-glycoprotein-1 may activate the endothelium, monocytes, and platelets. This leads to surface expression of cellular adhesion molecules and generation of tissue factor by both monocytes and the vascular endothelium. The increased tissue factor and thromboxane A_2 synthesis by platelets results in a procoagulant state. Thrombosis requires a second hit, such as that provided by activation of the complement cascade. Antiphospholipid antibodies may also interact with other proteins in the coagulation cascade such as prothrombin, factor X, protein C, and plasmin and can adversely affect fibrinolysis. Laboratory studies have demonstrated that

antiphospholipid antibodies enhance leukocyte–endothelial cell interactions and induce thrombosis through inhibition of endothelial nitric oxide (eNOS) activation and nitric oxide biosynthesis. The mechanism involves binding of antibody to domain I of beta$_2$-glycoprotein-1 and impaired eNOS phosphorylation.[64]

Cardiovascular Disease

Valvular abnormalities are the most frequently reported cardiac abnormality in patients with APS. The most commonly detected lesions are verrucous endocarditis (Libman-Sacks endocarditis) and nonspecific valvular thickening (see earlier) (**Fig. 94.10**). Although lesions are commonly found, clinically significant features are rare. Symptomatic disease is more frequent in those with high antibody titers. Congestive cardiac failure develops in up to 5% of patients, and 13% require cardiac valve replacement. Histologic analysis of the valves reveals deposition of antiphospholipid antibodies with complement activation. Occasionally, amaurosis fugax, a transient ischemic attack, or a stroke is seen as a consequence of arterial thromboembolism. Coronary thrombosis and myocardial infarction can complicate primary APS in 0.5% to 6% of patients, and intracardiac thrombi can also occur. APS in patients with SLE may enhance their risk for myocardial infarction and stroke.

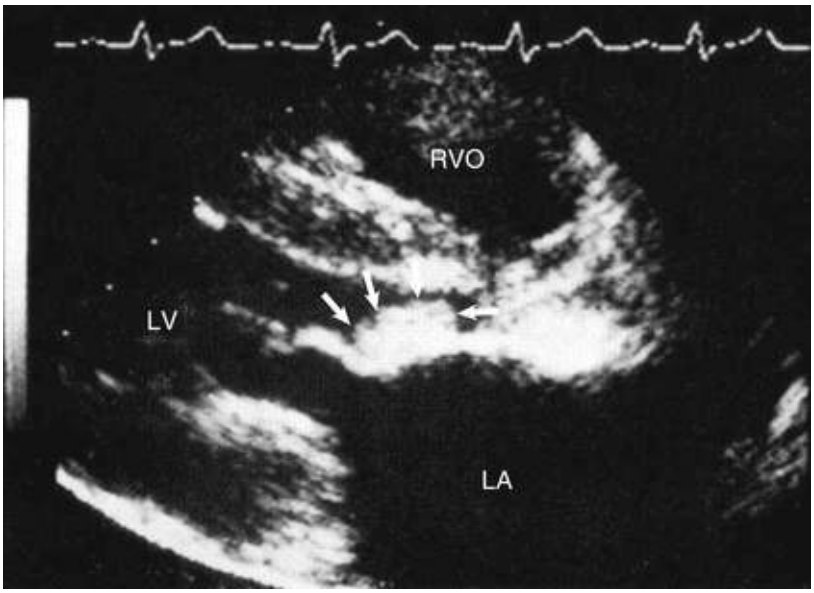

FIGURE 94.10 Parasternal long-axis view of the heart from a patient with SLE and high-titer antiphospholipid antibodies. A massive vegetation is seen on the ventricular surface of the anterior mitral leaflet *(arrows),* but it is not interfering with valve mobility. *LA*, left atrium; *LV*, left ventricle; *RVO*, right ventricular outflow. (Courtesy Professor Petros Nihoyannopoulos, National Heart and Lung Institute, Imperial College, London.)

Treatment

Confirmed thrombosis in patients with APS requires anticoagulation. Most centers target an international normalized ratio (INR) of 2.5 to 3.5. Some evidence supports the use of low-dose aspirin in patients with SLE complicated by antiphospholipid antibodies. In contrast, low-dose aspirin did not protect against deep venous thrombosis or pulmonary embolic disease in a study of men with primary APS.

Behçet Disease

Behçet disease occurs throughout the world but most commonly in Turkey, Iran, Japan, and Korea at 80 cases per 100,000 individuals, which falls to 4 to 8 per 100,000 in the United States, France, Germany, and the United Kingdom. This multisystem disorder includes orogenital ulceration, acneiform skin lesions, and arthralgia. It may cause uveitis and can cause blindness in the young. Arthralgia is common, and less frequently, patients suffer from meningoencephalitis, gastrointestinal ulceration, or vascular complications.

The vasculitis associated with Behçet disease predominantly affects the pulmonary arteries and veins, with thrombosis being a prominent clinical feature. Most thrombi are venous and cause superficial thrombophlebitis and deep venous thrombosis, including superior vena cava obstruction, cerebral vein thrombosis, and Budd-Chiari syndrome. In a small number of cases, pulmonary arterial vasculitis leads to in situ pulmonary arterial thrombosis. Although small studies have suggested that thrombosis is linked to the concurrent presence of a prothrombotic condition such as factor V Leiden or prothrombin mutations, this is not thought to be the cause in most. Indirect evidence suggests that the procoagulant state arises from an activated, adhesive, and prothrombotic endothelium due to chronic vascular inflammation. A clinical trial comparing treatment of thrombosis in Behçet disease with anticoagulation, immunosuppression, or a combination of both therapies supports this hypothesis. A higher proportion of patients treated with anticoagulation alone had recurrent thrombosis than did those prescribed immunosuppression. Pulmonary arterial aneurysms are a rare life-threatening complication in Behçet disease (**Fig. 94.11**), and aneurysms may also occur in other arterial beds. Other cardiovascular complications occur in less than 10% and include pericarditis, myocarditis, intracardiac thrombosis, myocardial infarction, and myocardial aneurysm.[65]

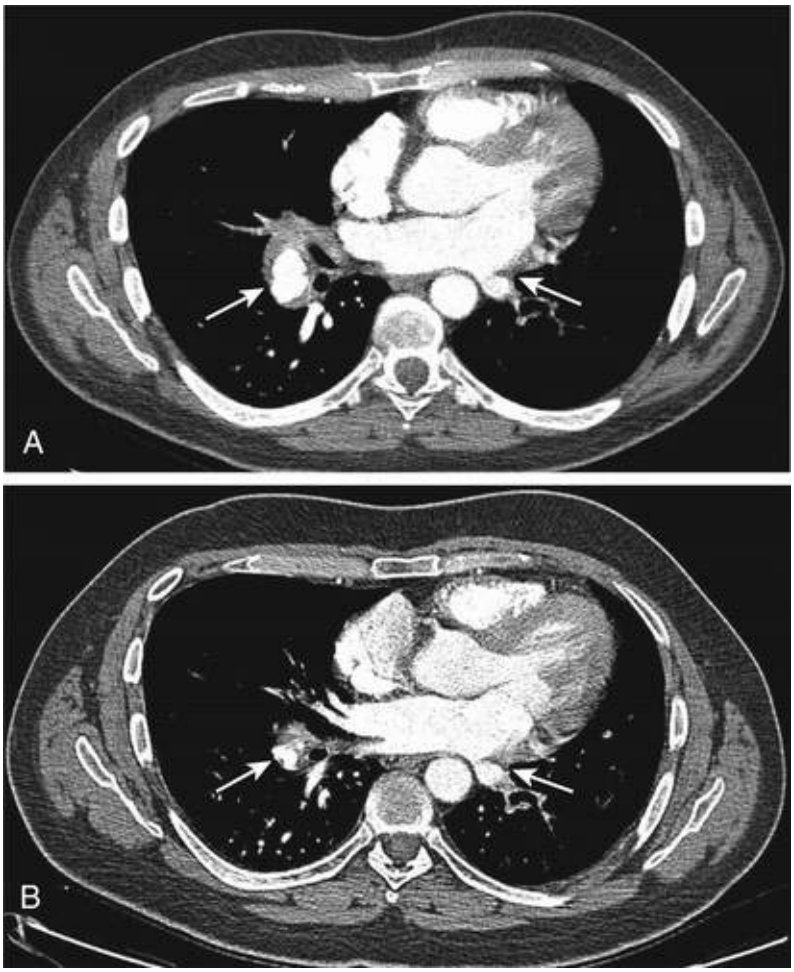

FIGURE 94.11 **A,** CT angiogram of a patient with Behçet disease showing bilateral pulmonary artery aneurysms *(arrows).* **B,** Following 4 months of treatment with the TNF-α antagonist infliximab, some reduction in the size of the pulmonary aneurysm on the right is seen. (Courtesy Professor Dorian Haskard, National Heart and Lung Institute, Imperial College, London.)

Treatment

Scant clinical trial data are available to guide therapeutic decisions for the cardiovascular manifestations of Behçet disease. The European League Against Rheumatism (EULAR) guidelines recommend immunosuppression for the treatment of thrombosis,[66] an approach common in endemic areas.[65] First-line treatment of these patients in emergency units in nonendemic areas is usually anticoagulation. This approach is appropriate because the cause of the thrombosis may not be immediately apparent, although patients with aneurysms have a substantial risk for bleeding. Patients should be seen in a specialist clinic for assessment of the need for long-term anticoagulation, immunosuppressive therapy, and noninvasive angiographic screening for aneurysms. Arterial aneurysms are treated aggressively with cyclophosphamide and high-dose prednisone to reduce inflammatory disease activity before surgical intervention, which may involve stenting via a percutaneous route or open surgical repair. Because the lesions often recur, patients require regular screening. Anecdotal evidence suggests the effectiveness of anti-TNF-α therapy in those with recurrent aneurysms or those who fail to respond to cyclophosphamide (**see Fig. 94.11**).

Antirheumatic Drugs and Cardiovascular Disease

Drug therapy for many rheumatic diseases has advanced dramatically over the past 20 years. Contributory

factors include more accurate diagnostic tests and imaging data, improved understanding of the mechanistic actions of drugs, and the development of novel targeted therapies. This section emphasizes the beneficial and deleterious effects of antirheumatic drugs on the cardiovascular system.

Relationship Between Drug Treatment and Cardiovascular Disease

Although inflammation contributes to atherogenesis and patients with systemic inflammatory rheumatic diseases have a heightened risk for premature myocardial infarction and stroke, causality remains unproven.[6] The impact of antiinflammatory drugs on atherogenesis and the incidence of cardiovascular events might provide insight in this regard.[1] To date, no clinical trial has convincingly demonstrated a beneficial effect of antiinflammatory drugs on cardiovascular outcomes. Indeed, the traditional NSAIDs or coxibs actually lead to a small but measurable increased risk for thrombosis. NSAID use in patients with inflammatory arthritis does not appear to confer increased cardiovascular risk, thus suggesting that their antiinflammatory role predominates. Similarly, statins reduce serum CRP levels, and large clinical trials suggest that in part, statins provide vascular protection independent of their actions on LDL cholesterol, including immunomodulatory and antiinflammatory effects.

Tumor Necrosis Factor-Alpha Antagonists

TNF-α blockade is an effective therapy for patients suffering from active RA. TNF-α can be targeted by monoclonal antibodies given intravenously or subcutaneously or by subcutaneous injection of etanercept, a soluble TNF receptor fusion protein. The use of these agents is contraindicated in patients with established cardiovascular disease and evidence of NYHA class III and IV cardiac failure, and they should be used with caution in those with mild congestive cardiac failure.[67] In RA the combination of systemic inflammation and traditional risk factors is associated with rapid progression of carotid IMT. Treatment with methotrexate and TNF-α antagonists can reduce this progress,[10] with some evidence for a reduction in cardiovascular events.[68] ^{18}F-FDG-PET scanning revealed subclinical arteritis in patients with RA when compared with those with stable cardiovascular disease, and initiation of anti-TNF-α therapy suppressed the arteritis, illustrating a potential underlying mechanism for this effect.[69] The next question is whether the extent of this subclinical arteritis can predict future cardiovascular events and direct targeted therapies.

Interleukin-6 Inhibition

Tocilizumab, an inhibitor of IL-6 signaling, might be expected to have vasculoprotective effects and, at least in the short term, may improve both endothelial function and aortic stiffness. However, tocilizumab has an adverse effect on lipid profiles and may increase LDL cholesterol, thereby requiring the addition of a statin. Thus long-term prospective studies are now required to determine whether effective suppression of IL-6–driven chronic inflammation can reduce the risk for cardiovascular events, in addition to its established efficacy in the control of RA disease activity.

Drugs Causing B Cell Depletion

Rituximab targets CD20 and depletes B lymphocytes. Initially established as a treatment of B cell

lymphoma, rituximab can control RA disease activity and reduce erosions. Similarly, rituximab demonstrated efficacy equivalent to that of cyclophosphamide for the treatment of ANCA-associated vasculitis and may exert disease-modulating effects in SLE. Short-term studies (4 to 6 months) have suggested that rituximab improves lipid profiles, carotid IMT, and endothelial function.[67] A recent study of 33 patients with active RA, however, found no change in arterial stiffness after 6 or 12 months of therapy. Furthermore, rather than improving lipid profiles, LDL cholesterol was significantly increased.[70] Long-term, adequately powered clinical trials with primary cardiovascular endpoints are required. Severe cardiovascular complications have occurred following rituximab infusions. Regulatory agency advice is that this treatment should be used with caution and the infusion rate reduced in those with preexisting cardiorespiratory disease.

Methotrexate

Methotrexate in dosages up to 25 mg/wk has proven to be remarkably effective in treatment of RA and is frequently used as a steroid-sparing drug in patients with the large-vessel vasculitides. Clinical evidence suggests that methotrexate has a cardiovascular protective effect, with those responding to methotrexate therapy demonstrating improvement in endothelial function. A recent metaanalysis confirmed early reports of a relative risk reduction in cardiovascular mortality of up to 70% in patients with RA prescribed methotrexate versus other DMARDs, although with a somewhat lower extent of protection.[71] Novel additional mechanisms potentially underlying vascular protection have been recently reported, including activation of an AMP-activated, kinase and cyclic AMP, response element–binding protein–dependent pathway[72] and beneficial effects on macrophage cholesterol handling.[73]

Other Disease-Modifying Antirheumatic Drugs

The potential cardiovascular benefits of hydroxychloroquine, an antimalarial drug frequently used for the treatment of RA, SLE, and Sjögren syndrome, have become more widely recognized in recent years. Hydroxychloroquine lowers cholesterol and may improve both endothelial function and aortic stiffness. Clinical studies have demonstrated that hydroxychloroquine reduces the risk for cardiovascular events in patients with both RA and SLE. In contrast, high cumulative doses occasionally are associated with restrictive cardiomyopathy and with retinal damage.

Cyclosporine continues to be used for the treatment of rheumatic disease, including polymyositis, SLE, and RA, as well as in many patients following organ transplantation. Clinical studies suggest that cyclosporine impairs flow-mediated vasodilation. At least in part, this effect reflects reduced eNOS activity and nitric oxide bioavailability. The adverse cardiovascular effects seen with cyclosporine may also reflect its propensity to induce hypertension and renal impairment. Alternative immunosuppressive drugs, used predominantly in the transplantation scenario, include tacrolimus and rapamycin (sirolimus), which appear to have a more favorable vascular profile.

Glucocorticoids

Glucocorticoids have undisputed efficacy in the treatment of systemic inflammatory diseases, including RA, SLE, and the vasculitides. Yet the substantial side effect burden concerns patients and physicians alike. The influence of corticosteroid therapy on the progression of atherosclerosis is complex and dependent on the context. The impact of corticosteroids on blood pressure and glucose and lipid

metabolism may have a deleterious effect. In contrast, in SLE, evidence suggests that insufficient use of glucocorticoids risks persistently active and/or relapsing disease, thereby leading to an increased risk for accelerated atherogenesis. Thus combination therapy with a steroid-sparing drug such as azathioprine, MMF, or methotrexate, which allows prednisone to be tapered to 7.5 mg/day or less, may be optimal, with no proatherogenic effect and potentially a vasculoprotective action.

Statins (see also Chapters 45 and 48)

Large primary prevention trials indicate that statins can reduce cardiovascular morbidity and mortality rates, in part independently of changes in LDL cholesterol.[74] These actions have led to interest in statins as adjunctive therapy for rheumatic diseases, including RA and SLE, for which they have the potential to both reduce the disease activity and lower the cardiovascular risk.[75] Clinical trial evidence supporting the routine use of statins in all patients with RA and SLE is lacking. Although no guidelines exist, most rheumatologists currently consider the cardiovascular risk in patients with RA and SLE as equivalent to that in patients with diabetes mellitus. EULAR has suggested adding a 1.5× multiplier to standard cardiovascular risk calculations.[76] Indications for a statin include an LDL cholesterol level of 190 mg/dL or higher, a long history of RA, a family history of hyperlipidemia, a higher age at disease onset, and the presence of any other cardiovascular risk factors.[77] Moreover, recent reports have recommended further expansion of the cardiovascular risk prediction score for RA.[17]

Nonsteroidal Antiinflammatory Drugs

NSAIDs and coxibs are important and effective drugs for the treatment of pain and inflammation. Concerns regarding atherothrombotic complications have, however, raised reservations regarding their use. As a consequence, patients with rheumatic disease are often denied these medications inappropriately. Although current evidence suggests that both classes have a small, manageable, and dose-dependent risk for cardiovascular complications, establishing the degree of risk and the relative safety profiles between individual drugs is difficult because of clinical trial heterogeneity and a lack of randomized controlled trial data for older NSAIDs. Data overall suggest that no traditional NSAID or COX-2 inhibitor is entirely safe and that naproxen has the best cardiovascular profile as a result of its antiplatelet effects.[78] Despite these reservations, the absolute risk for a cardiovascular event is very low, and gastrointestinal bleeding and perforation represent the major long-term risks associated with NSAIDs (**Table 94.5**). Although coxibs are less likely to cause gastrointestinal problems, many guidelines recommend concomitant prescription of a proton pump inhibitor for patients taking either NSAIDs or coxibs for more than 10 to 14 days.

TABLE 94.5

Cardiovascular Versus Gastrointestinal Risk in Prescribing Nonsteroidal Antiinflammatory Drugs

Patients with CV risk who are taking aspirin should avoid tNSAIDs or coxibs if possible
If essential, consider naproxen plus a PPI if GI risk is low or a coxib in those with significant GI risk
CV risk varies between individual tNSAIDs and coxibs
Patients with cardiac failure or hypertension should avoid tNSAIDs and coxibs
Risk for a CV event with a tNSAID or coxib is < 1% in those with < 2 classic risk factors
Risk for a CV event may increase in older adults, men, and those with preexisting CV disease
Aspirin use increases the risk for GI events associated with tNSAIDs and coxibs
Coprescription of a PPI reduces the risk for GI events with tNSAIDs and coxibs
PPIs are more effective than H_2 antagonists or misoprostol for gastroprotection
GI risk varies between individual tNSAIDs
Use the lowest effective dose for the shortest period

Coxibs, COX-2–selective antiinflammatory drugs; *CV*, cardiovascular; *GI*, gastrointestinal; *PPI*, proton pump inhibitor; *tNSAIDs*, traditional NSAIDs.

Concerns regarding a class effect of the coxibs arose from the APPROVE trial, which demonstrated increased thrombotic cardiovascular events with rofecoxib. Other clinical trials and nonrandomized epidemiology studies in primary care reinforced these concerns. Many of these studies, however, compared coxibs with placebo and not with an NSAID. According to the hypothesis proposed to explain the findings, selective blockade of COX-2 leads to an imbalance between COX-1 and COX-2 enzymatic products such that the effects of thromboxane A_2 exceed those of prostacyclin, thereby predisposing to vasoconstriction, platelet aggregation, and thrombosis. This hypothesis depends on endothelial COX-2 being the predominant source of prostacyclin, and data are conflicted on this, with an important role for COX-1 emerging.[79] Furthermore, data from studies comparing NSAIDs and coxibs in patients with arthritis do not support a class effect based on COX-2 selectivity.[80] Thus, COX-2 inhibition per se confers a cardiovascular risk regardless of the compound's COX isoform specificity. Additional findings from large population-based studies suggest that the NSAID diclofenac and the coxib rofecoxib have a particularly poor cardiovascular profile not shared by naproxen or celecoxib.[81] The study population is important, and few studies have looked in detail at patients with inflammatory arthritis. An inception cohort of 923 patients with early inflammatory arthritis was assessed for NSAID use and cardiovascular outcomes. The investigators demonstrated that exposure to NSAIDs was not associated with an increased risk for death and in fact led to a 2.5-fold reduction in cardiovascular mortality rates. The recently reported Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial enrolled 24,081 RA or osteoarthritis patients with an established or significant risk of cardiovascular disease.[15] Following prescription of esomeprazole and randomization to moderate dosages of celecoxib, naproxen, or ibuprofen, the occurrence of cardiovascular death, nonfatal stroke, and myocardial infarction was recorded. Although drug discontinuation rates were high, the trial revealed celecoxib to be noninferior to naproxen and ibuprofen with respect to cardiovascular safety, and it was significantly safer than either comparator in regard to gastrointestinal risk. These data provide important reassurance concerning the safety of moderate doses of celecoxib.

Wherever possible, NSAIDs and coxibs should be avoided in patients with known ischemic heart disease, previous thrombosis, poorly controlled hypertension, and cardiac failure. In patients in whom antiinflammatory drugs are being considered, an individualized assessment of both gastrointestinal and cardiovascular risk should be made.[80] The patient should be encouraged to use these drugs when required and at the minimally effective dose rather than as a standing dose (**see Table 94.5**).

Future Perspectives

The current challenge is to design and perform adequately powered randomized clinical trials to investigate the efficacy of individual antiinflammatory drugs in preventing atherosclerosis-related cardiovascular events. The data from available studies of antirheumatic therapies, although far from conclusive, do provide the impetus for further trials with large numbers of patients because of the relatively low incidence of cardiovascular events.[6] The ultimate challenge is to test the hypothesis that a relatively aggressive antiinflammatory approach, alongside conventional therapy, will confer additional benefit in those with known atherosclerotic coronary artery disease in the absence of an underlying rheumatic problem. A placebo-controlled trial of the potent antiinflammatory drug colchicine given within 12 hours of an acute myocardial infarction has revealed a potential benefit.[82] Two further large trials are under way: first, the Cardiovascular Inflammation Reduction Trial (CIRT), in which methotrexate (10 to 15 mg/wk) will be compared with placebo,[83] and second, the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) is investigating the ability of an anti–IL-1β approach to reduce the rate of recurrent myocardial infarction, stroke, or cardiovascular death.[84]

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95

Tumors Affecting the Cardiovascular System

Daniel J. Lenihan, Syed Wamique Yusuf, Ashish Shah

Cardiac masses frequently present significant diagnostic and therapeutic clinical challenges. In many

cases, a cardiac mass is detected as an incidental finding and the resultant evaluation may culminate in the confirmation of a cardiac tumor. The finding of a tumor is generally an uncommon event, however; other masses, such as thrombi or vegetations, are much more common. This chapter will begin by describing the initial symptoms and signs that may indicate a cardiac tumor, followed by an explanation of a typical evaluation process, which depends heavily on current sophisticated imaging techniques. Once a cardiac tumor is suspected, the ultimate diagnosis is usually confirmed by a biopsy or surgical procedure because the histologic diagnosis has a direct bearing on further treatment planning. The remainder of the chapter will focus on the delineation and potential management of cardiac tumors and the overall anticipated outcomes. It should be pointed out that this is an inexact science due to the relatively rare occurrence of cardiac tumors. Furthermore, the final pathologic diagnosis is typically confirmed after most of the decisions regarding treatment have been made.

Clinical Manifestations of Cardiac Tumors

Initial Clinical Decision Making Regarding Cardiac Masses

It is interesting to note that patients who have cardiac tumors may present initially with no symptoms or physical findings but have abnormalities on imaging. Alternatively, there may be a host of nonspecific symptoms or physical examination findings, and, of course, there may be specific and detailed symptoms or signs that should alert practitioners to the possibility of a tumor (**Table 95.1**). The most important considerations in confirming the presence of a cardiac tumor are a high index of suspicion and the integration of symptoms, physical findings, and imaging characteristics in a logical way. This process will help to establish a clinically reasonable plan of action.

TABLE 95.1

Range of Clinical Findings That May Indicate a Cardiac Tumor

Completely asymptomatic patient with incidental abnormality on imaging
Low-grade fevers
Transient ischemic attack or cerebral vascular event
Positional dyspnea
Weight loss
Peripheral embolic events
Chest discomfort
Congestive heart failure
Upper extremity and/or neck swelling
Lower extremity venous thrombosis
Palpitations
Arrhythmias
Pericardial effusion or tamponade

The initial evaluation is typically an imaging test, such as two-dimensional (2D) echocardiography[1] or magnetic resonance imaging (MRI),[2] during which a mass is seen. Depending on the characteristics of this mass and the known comorbidities of the patient, additional imaging may be undertaken. These studies might include three-dimensional (3D) echocardiography with contrast,[3] MRI with gadolinium enhancement,[4] coronary angiography (to define the presence of coronary artery disease),[5] position

emission tomography (PET) studies to provide staging for cancer,[5] or computed tomography (CT) imaging to clarify the status of intrathoracic structures.[6,7] Transesophageal echocardiography (TEE) can also provide specific anatomic information that is critical for treatment planning[5] (**Table 95.2**).

TABLE 95.2

Common Testing to Detect Cardiac Tumors

2D or 3D echocardiography
Chest x-ray
Computed tomography
Magnetic resonance imaging
Transesophageal echocardiography
Position emission tomography
Nuclear scintigraphy
Coronary angiography

When one is initially assessing a cardiac mass to determine whether it may be a tumor, the clinical context in which the image is obtained is critical. A differential diagnosis of a cardiac mass is broad and includes tumors, thrombi, infection, and artifacts[8] (**Table 95.3**). For instance, in a patient with new-onset heart failure in whom a 2D echocardiogram shows an apical mass, a cardiac tumor is less likely. The presence of a severe wall motion abnormality plus a mass that appears to be distinct from the myocardial wall, as well as lobulated (**Fig. 95.1**), strongly suggests that the mass is a thrombus as opposed to a tumor. Another scenario might involve routine cardiac imaging in a patient with a history of melanoma that is metastatic to other organs, which reveals a solid mass in an unusual location. Because there is no wall motion abnormality and no significant valvular disease or clinical signs suggestive of infective endocarditis, this is likely to be a metastatic lesion to the heart (**Fig. 95.2**). Motion imaging may be helpful in diagnosing a cardiac tumor. If a tumor is infiltrating the myocardium, it is unlikely to contract in a normal fashion. A left ventricular myocardial apical mass that contracts in a manner similar to the surrounding tissue is likely to be either focal hypertrophy (**Fig. 95.3**) or a left ventricular noncompaction[9,10] (**Fig. 95.4**) as opposed to a cardiac tumor (**Fig. 95.5**). Progression of an image over time may indicate the pathologic process. If a cardiac mass changes in size from one image to the next, suspicion of a cardiac tumor is much higher. However, if an apical mass is stable for months or years, it is unlikely to be a cardiac tumor. Of course, the exact nature and location of a mass is critical in determining whether it is a tumor. A classic example of this principle is lipomatous hypertrophy of the intraatrial septum (**Fig. 95.6**). One might initially suspect a myxoma or other tumor, but a TEE will clearly reveal specific characteristics that are a hallmark for lipomatous hypertrophy, and that will confirm the diagnosis.[11]

TABLE 95.3

Differential Diagnosis of Cardiac Masses

Intracardiac thrombus
Focal myocardial hypertrophy
Left ventricular noncompaction
Infectious disease (abscess)
Primary cardiac tumor
Secondary cardiac tumor (metastasis)
Lipomatous hypertrophy of septum
Cyst
Imaging artifact

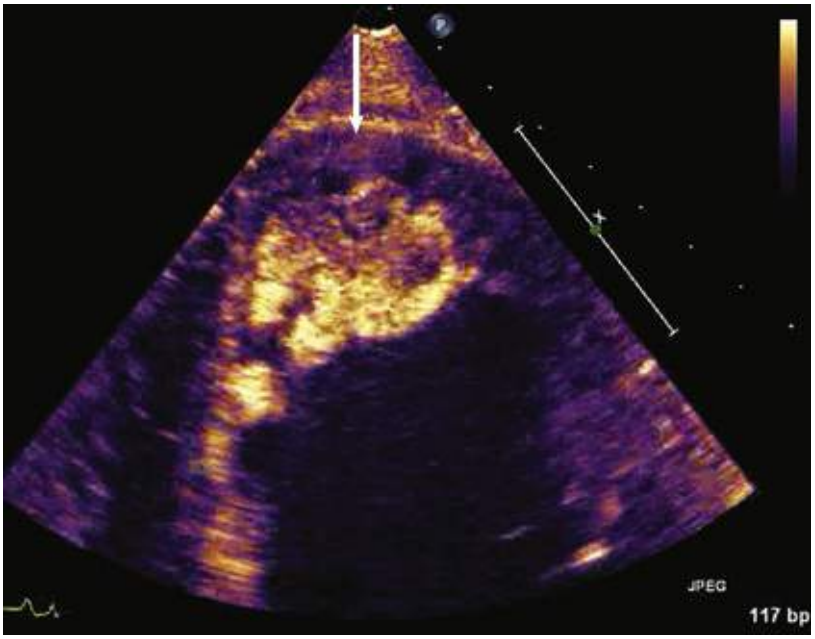

FIGURE 95.1 A large irregular mass noted in the left ventricular apex *(arrow)* in a patient with severe left ventricular dysfunction. The edges are distinct from the myocardium, which is a classic sign for a thrombus.

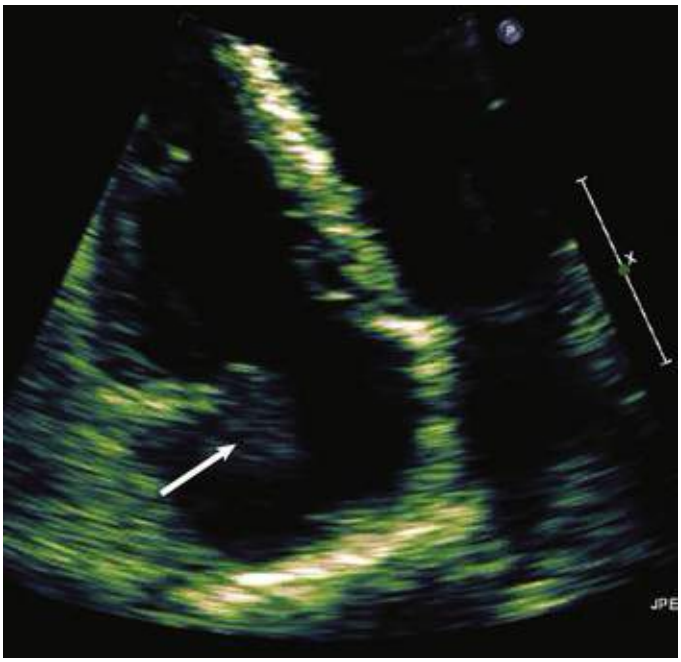

FIGURE 95.2 An irregular mass is noted on the atrial side of the tricuspid valve in a patient with metastatic melanoma.

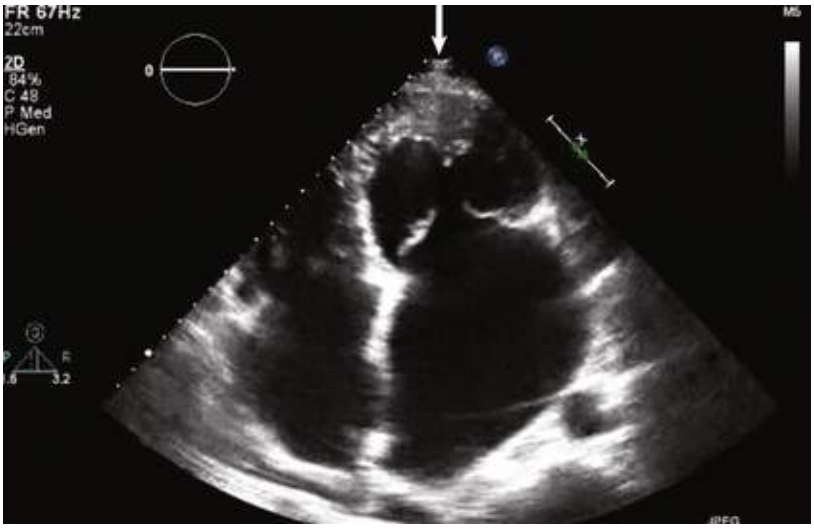

FIGURE 95.3 A four-chamber echocardiographic image showing focal apical hypertrophy *(arrow)* that resulted in severe diastolic heart failure. The apical mass contracted and was stable for years.

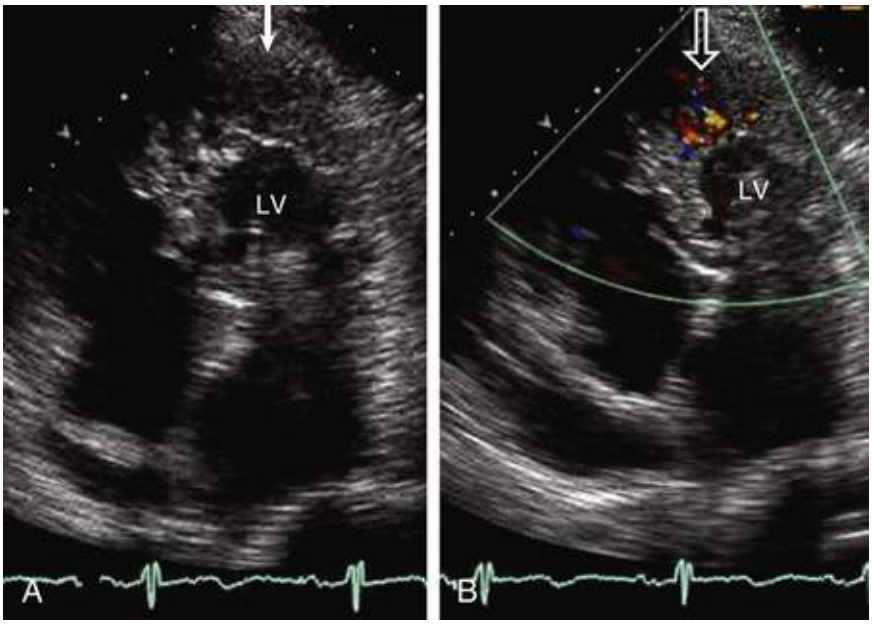

FIGURE 95.4 An apical mass is not solid (*arrow* in **A**), and color flow is detected in "lakes" within the apical mass (*open arrow* in **B**). This is typical of noncompaction cardiomyopathy, and this area does appear to contract.

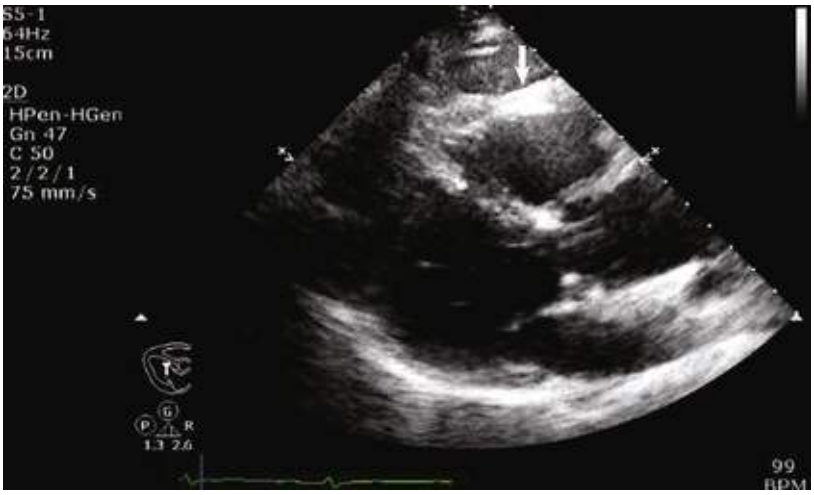

FIGURE 95.5 An echodense area *(arrow)* did not contract and was correlated with intense uptake on PET imaging in a patient with mediastinal T cell lymphoma. This resolved with treatment of the cancer.

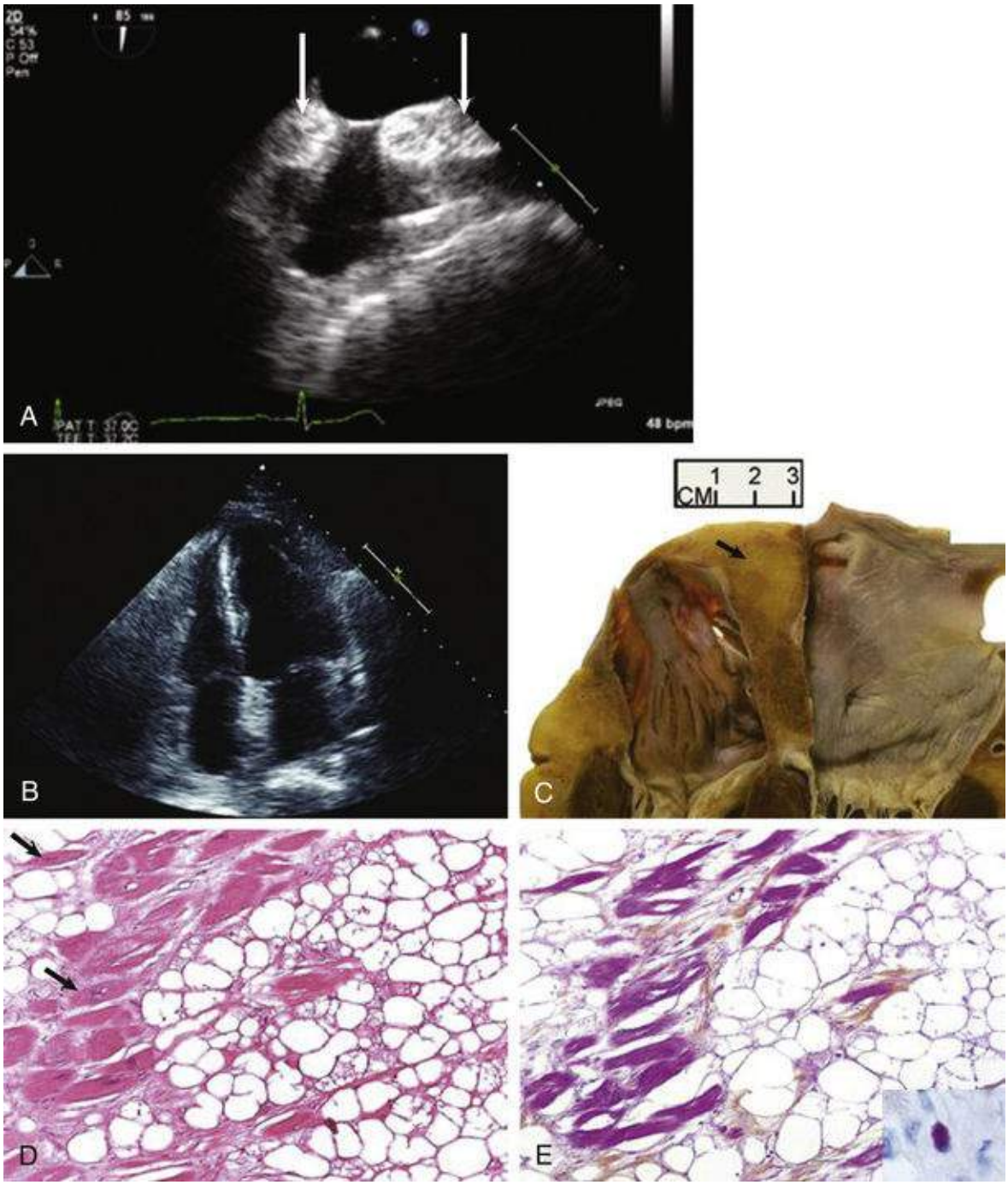

FIGURE 95.6 Lipomatous hypertrophy. **A,** Classic TEE image of lipomatous septal hypertrophy. Note the dumbbell appearance and the thin area of the fossa ovalis *(arrows).* **B,** Four-chamber echocardiogram demonstrating lipomatous hypertrophy of the atrial septum in a 72-year-old woman. **C,** Lipomatous hypertrophy of the atrial septum in a heart from a 62-year-old man. The atrial septum superior to the fossa ovalis was found to have a thickness greater than 3 cm *(arrow).* **D,** Hematoxylin-eosin staining depicts variably hypertrophied and atrophied cardiac myocytes *(arrows)* with associated fibrous tissue and an admixture of mature (larger) and immature (smaller and granular) adipocytes (magnification: 200×). **E,** Movat pentachrome staining highlights the myocytes *(purple)* and associated excess collagen *(tan),* as well as the unusual adipose tissue (magnification: 200×). **E, inset,** Chloracetate esterase staining shows the presence of mast cells (magnification: 400×). (**A, B,** Courtesy Dr. Kenneth Gin, Division of Cardiology, University of British Columbia, Vancouver, British Columbia, Canada.)

Classification of Cardiac Tumors

Cardiac tumors are divided into primary and secondary tumors. Primary cardiac tumors are very rare, with an autopsy incidence of 0.001% to 0.03%.[12] They include benign or malignant neoplasms that may arise from any tissue of the heart. Secondary or metastatic cardiac tumors are 30 times more common than

primary neoplasms, with an autopsy incidence of 1.7% to 14%.[13] **Table 95.4** summarizes some of the pathologic descriptions of cardiac tumors that have been reported, but it is not an exhaustive list. Many specific pathologic descriptions have been reported, and it can be difficult to adequately categorize them. Thus, general categories will be discussed in the remainder of this chapter.

TABLE 95.4

Pathologic Description of Cardiac Tumors

Benign Tumors
Myxoma
Rhabdomyoma
Fibroma
Lipoma
Hemangioma
Papillary fibroelastoma
Cystic tumor of the AV node
Paraganglioma
Malignant Tumors
Sarcoma
Lymphoma
Metastatic Tumors
Renal cell carcinoma
Melanoma
Breast cancer
Lung cancer
Sarcoma
Lymphoma
Leukemia

Benign Primary Cardiac Tumors

The majority (>80%) of primary cardiac tumors are benign, and myxoma is by far the most common type.[12,14] Myxomas constitute approximately 50% of all benign cardiac tumors in adults but only a small percentage of such tumors in children.[15] Rhabdomyoma is the most common benign tumor in children, accounting for 40% to 60% of the cases.[14] Other benign cardiac tumors that have been described include fibromas, lipomas, hemangiomas, papillary fibroelastomas, cystic tumors of the atrioventricular (AV) node, and paragangliomas. The remaining 20% of primary cardiac tumors are malignant and usually are pathologically described as sarcomas.[16-18]

Myxomas

Most myxomas (>80%) are found in the left atrium. They are also found in decreasing frequencies in the right atrium, right ventricle, and left ventricle.[17] The incidence of cardiac myxoma peaks at 40 to 60 years of age, with a female to male ratio of approximately 3 : 1.[17] Most myxomas occur sporadically, but they may be familial; occasionally these have been described in relation to a particular syndrome called the *Carney complex*, an autosomal dominant condition associated with cardiac myxomas, myxomas in other regions (cutaneous or mammary), hyperpigmented skin lesions, hyperactivity of the adrenal or testicular glands, and pituitary tumors. The Carney complex occurs at a younger age, and should be considered

when cardiac myxomas are discovered in atypical locations in the heart.[16]

Etiology and Pathophysiology

The exact origin of myxoma cells remains uncertain, but they are thought to arise from remnants of subendocardial cells or multipotential mesenchymal cells in the region of the fossa ovalis, which can differentiate along a variety of cell lines. The hypothesis is that cardiac myxoma originates from a pluripotential stem cell, and myxoma cells express a variety of antigens and other endothelial markers. Myxomas typically form a pedunculated mass with a short, broad base (85% of myxomas), but sessile forms can also occur.[12] Classically, myxomas appear yellowish, white, or brownish and are frequently covered with thrombus (**Fig. 95.7**). The tumor size can range from 1 cm to more than 10 cm, and the surface is smooth in the majority of cases (**Figs. 95.8 and 95.9**). A villous or papillary form of myxoma has been reported and has a surface that consists of multiple fine or very fine villous, gelatinous, and fragile extensions that have a tendency to fragment spontaneously and are associated with embolic phenomena.[19] Histologically, myxomas are composed of spindle- and stellate-shaped cells with a myxoid stroma that may also contain endothelial cells, smooth muscle cells, and other elements surrounded with an acidic mucopolysaccharide substance. Calcifications may also be seen in some cases.[12]

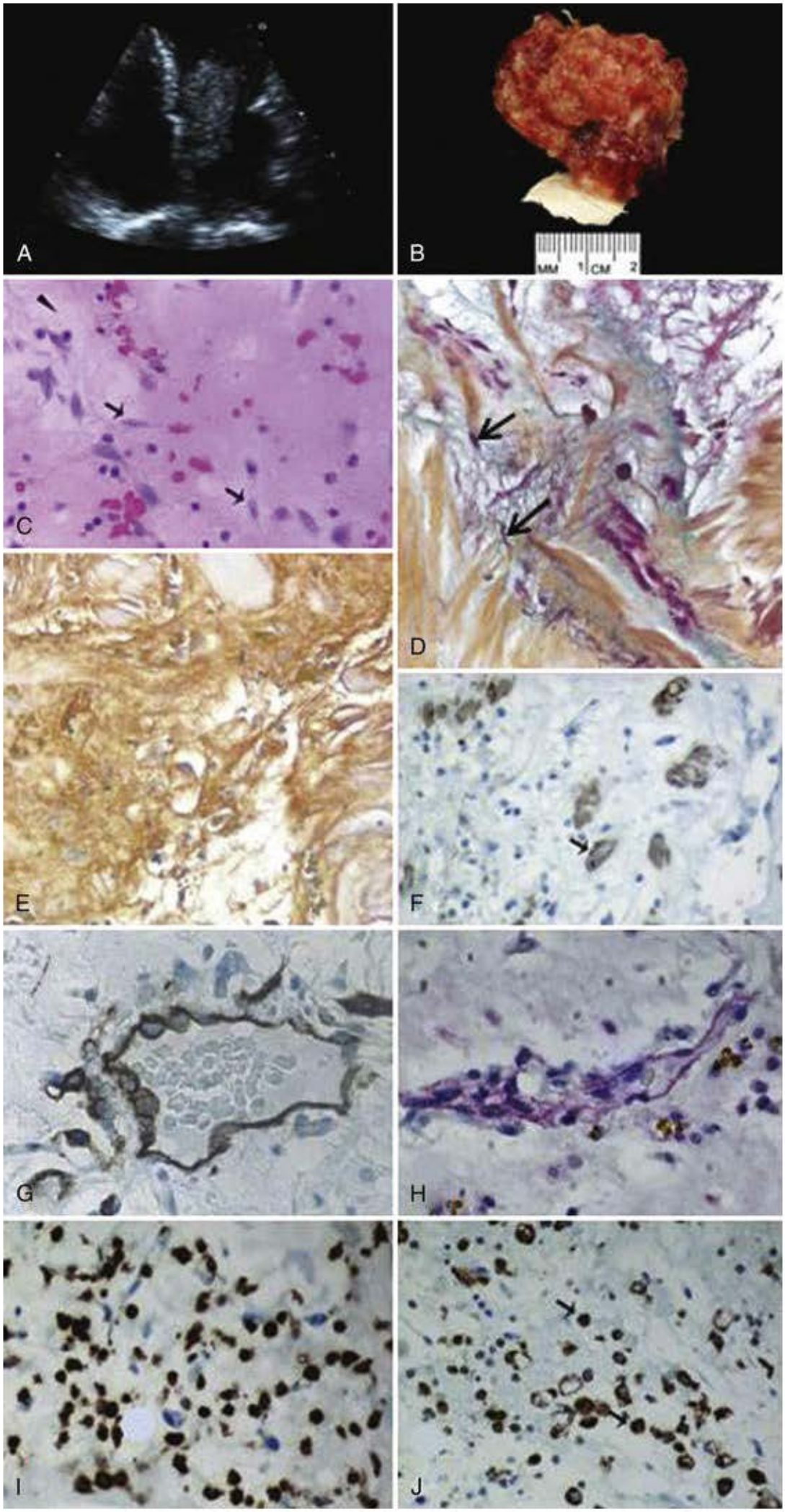
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FIGURE 95.7 Atrial myxoma. **A,** Four-chamber echocardiogram of a left atrial myxoma in a 71-year-old woman showing a mass on the left side of the heart projecting from the atrial septum through the mitral valve into the left ventricle. **B,** Gross photograph of the left atrial myxoma that was surgically excised from the same woman. The tumor is a pedunculated, variegated mass with a friable, gelatinous texture. **C,** Hematoxylin-eosin staining of the loose, proteoglycan-rich tumor (magnification: 200×). The tumor is highly vascular, with vessels containing red blood cells admixed with lipidic cells present in a network throughout the tumor matrix *(arrows).* **D,** Movat pentachrome staining aids in defining the composition of a myxoma (magnification: 400×). A variably loose *(bubbly turquoise appearance)* glycosaminoglycan-rich connective tissue is interspersed with collagen *(yellow),* rare mononuclear cells, and lipidic mesenchymal cells *(arrows, magenta).* **E,** Immunohistochemical staining indicates prominent expression of versican *(golden brown),* a major proteoglycan in myxomas (magnification: 400×). **F** to **H,** Immunohistochemical staining for vessels was positive for alpha smooth muscle actin *(arrow),* CD34, and CD31, respectively (magnification: 400×). **I,** Staining for leukocyte common antigen is positive for mononuclear cells (magnification: 400×). **J,** Staining for CD68 shows several macrophages *(arrows),* some of which are laden with hemosiderin as a result of previous hemorrhage, a common occurrence in myxomas (magnification: 400×).

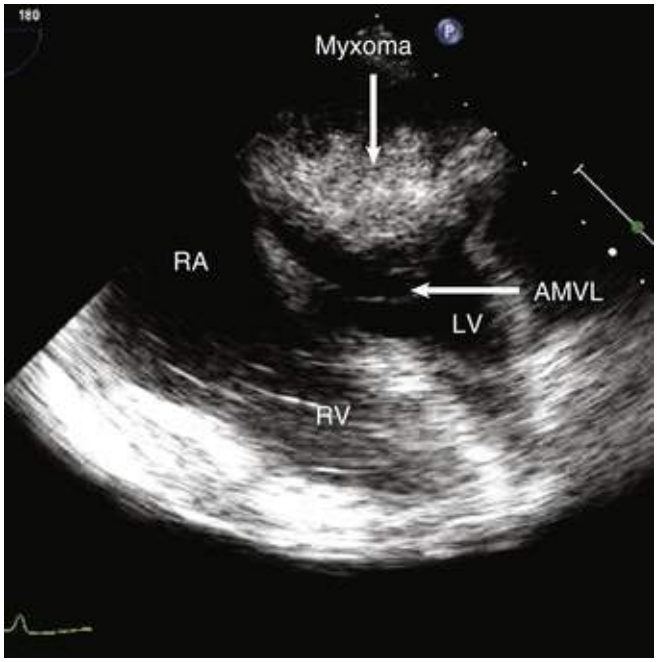


FIGURE 95.8 A large left atrial myxoma prolapsing across the mitral valve, resulting in heart failure symptoms. *AMVL*, anterior mitral valve leaflet; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle.

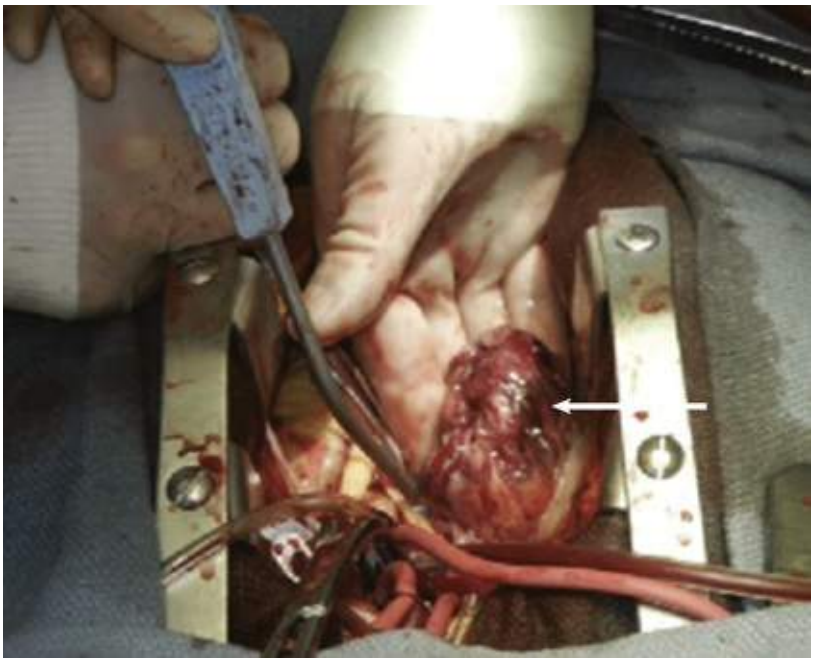


FIGURE 95.9 Gross appearance of a left atrial myxoma. Note the thrombus-appearing material on the surface *(arrow),* which is likely a mechanism for embolic events associated with cardiac myxomas.

Clinical Manifestations

Patients commonly are asymptomatic, and the tumor is seen as an incidental finding on 2D echocardiography. When symptoms are present, dyspnea, especially dyspnea that is worse while lying on the left side, should alert the astute clinician to the possibility of a myxoma. Most clinical presentations related to myxoma result from mitral valve obstruction (syncope, dyspnea, and pulmonary edema) followed by embolic manifestations.[17,19] Patients may present with nonspecific symptoms such as fatigue, cough, low-grade fever, arthralgia, myalgia, weight loss, erythematous rash, and laboratory findings of anemia, an increased erythrocyte sedimentation rate (ESR), and increased levels of C-reactive protein and gamma globulin. Less commonly they may have thrombocytopenia, clubbing, cyanosis, or Raynaud phenomenon. Physical examination findings can reveal a systolic or diastolic murmur suggestive of mitral stenosis. A tumor “plop” may also be heard (a low-pitched diastolic sound heard as the tumor prolapses into the left ventricle).[17,19]

In one study, a cardiac auscultation abnormality was detected in 64% of patients.[20] The most common auscultation findings are a systolic murmur (in 50% of cases) followed by a loud first heart sound (32%), an opening snap (26%), and a diastolic murmur (15%).[19] The reason for the systolic murmur may be damage to the valves, failure of the leaflets to coapt, or narrowing of the outflow tract by the tumor. A diastolic murmur is present due to obstruction of the mitral valve by the myxoma. Tumor plop may be confused with a mitral opening snap or a third heart sound; it can be detected in up to 15% of cases.[20] Chest examination may reveal fine crepitations consistent with pulmonary edema. Extremity examination may also reveal signs of embolic phenomena. The signs vary depending on the vascular territory involved. Involvement of cerebral vessels results in neurologic signs; involvement of coronary arteries may result in an acute coronary syndrome; intestinal arterial obstruction may result in an ischemic bowel; and peripheral arterial obstruction can result in limb-threatening ischemia.

Laboratory Testing

Laboratory test abnormalities may include anemia, elevated serum gamma globulin levels, an elevated

ESR, and elevated levels of serum C-reactive protein, which is present in approximately 75% of patients.[19] There are no specific electrocardiogram (ECG) findings in myxoma. Chest x-ray findings are also nonspecific and include signs of congestive heart failure, cardiomegaly, and left atrial enlargement. In some cases the tumor itself may be visible due to calcification.[20] A 2D echocardiogram usually should demonstrate a mass in the atrium, with the stalk attached to the interatrial septum (**see Fig. 95.8**). A TEE provides specific delineation of the tumor, including the size and origin. CT and MRI scans provide better delineation of the intracardiac mass and the extent of tumor in relation to extracardiac structures, and they provide anatomic definition for preoperative planning.

Treatment

The only definitive treatment of cardiac myxoma is surgical removal. Generally, after median sternotomy, the myxoma is surgically excised using cardiopulmonary bypass and cardioplegic arrest. The tumor is removed by either right or left atriotomy or combined atriotomy, depending on the site and extent of the tumor. Atrial myxomas can also be approached via sternal sparing or minimal access approaches. Using a right limited thoracotomy and peripheral cannulation, patients are placed on cardiopulmonary bypass; cold fibrillatory arrest or cardioplegic arrest may then be used, the atria may be explored, and complete removal of the mass and reconstruction of any defects may be performed. This approach is limited in that only mitral and tricuspid valvulopathy can be corrected. The choice of technique also depends on associated conditions that need surgical intervention, such as valve repair or replacement, and coronary disease if present. Lifelong follow-up is needed because myxomas have some tendency to recur, at rates from 5% to 14%. The time to recurrence in different series varied from 0.5 to 6.5 years.[19,20]

Rhabdomyomas

Rhabdomyomas are usually found in the ventricle and are the most common benign cardiac tumor found in children.[14,15] The majority of these patients have signs of or a family history of tuberous sclerosis.[14] In one study of patients with tuberous sclerosis complex, a cardiac tumor was found in 48% of the patients, with an incidence of 66% in patients less than 2 years old.[21] Frequently, these patients are asymptomatic, although some patients with rhabdomyoma may present clinically with arrhythmias and heart failure.[14,21] These tumors may regress with age; they can sometimes grow or appear during puberty.[21] As a result of these uncertain outcomes, long-term clinical and echocardiographic follow-up is needed in patients with tuberous sclerosis. Most often, surgery can be avoided, although if arrhythmias become a symptomatic problem, antiarrhythmics and ultimately surgery may have to be considered.[14]

Fibromas

Fibromas are histologically composed primarily of fibroblasts or collagen. Typically they occur in children, although they can also occur in adults.[12,17,22] Most often a fibroma is located in the ventricle and interventricular septum, and patients may present with chest pain, pericardial effusion, heart failure, or arrhythmias; the first manifestation may also be sudden death. Cardiomegaly is frequently seen on chest x-ray, which may also show the calcification within the tumor mass.[22] Typically, these tumors are associated with arrhythmias and might require multimodality treatment with medications, electrophysiologic procedures, and/or surgery. If surgical resection is performed, fibromas tend not to recur. A distinguishing feature of fibromas, contrasted to rhabdomyomas, is that there is frequently calcification.[12]

Lipomas

A lipoma is a rare benign cardiac tumor; it makes up only 3% of all benign tumors.[23] Lipomas tend to occur in the left ventricle or the right atrium but may be found anywhere in the heart, as well as the pericardium (**Fig. 95.10**). Although frequently asymptomatic, they may grow large enough to cause obstructive symptoms.

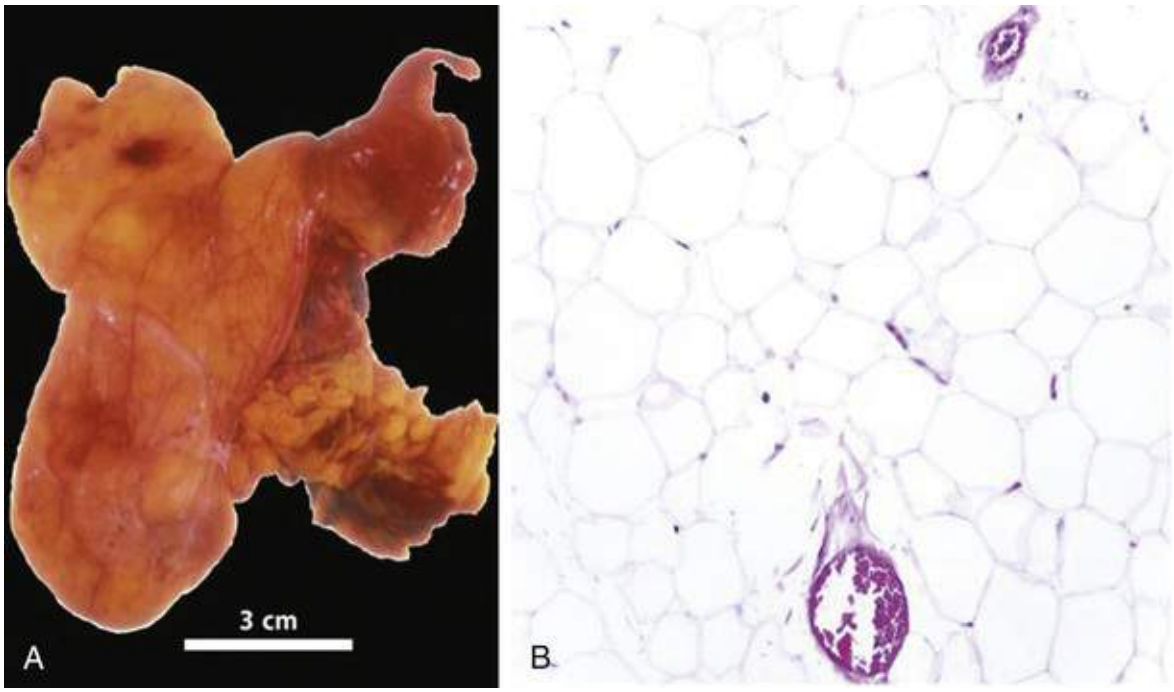


FIGURE 95.10 Pericardial lipoma. **A,** Gross appearance of a pericardial lipoma from a 71-year-old man. **B,** Hematoxylin-and-eosin staining depicts mature adipocytes in the tumor with an associated vascular supply (×200).

Papillary Fibroelastomas

Valvular structures may have a papillary fibroelastoma, which is often found incidentally. They are small in size, typically less than 2 cm, and most commonly occur on the aortic valve, followed by the mitral valve. Rarely they may be found anywhere in the endocardial surface. Most fibroelastomas that have been reported are solitary; multiple ones have been reported rarely.[24] Fibroelastomas may result in embolic phenomena, and when situated on the aortic valve, can cause coronary ostial occlusion. Grossly, a papillary fibroelastoma has a characteristically frondlike appearance, resembling a sea anemone, and histologically it has an inner central core of collagen surrounded by a layer of acid mucopolysaccharides and covered by endothelial cells.[24] For the most part, complete surgical resection is recommended, mainly due to the high likelihood of a systemic embolism (i.e., stroke, myocardial infarction, peripheral embolism, or even sudden death). A recent report with clinical outcomes of a large population of patients with papillary fibroelastomas indicated that rates of cerebrovascular accident or death were increased if surgical removal was not performed.[25] On imaging, especially echocardiographic imaging, there is a characteristic small, mobile, pedunculated, and very echocardiographically dense core that enables the tumor to be differentiated from a vegetation or thrombus. Once the tumor has been completely removed, the chance at recurrence appears low, and there are no compelling data for continuing anticoagulation over the long term unless there are other indications to do so.[24]

Cystic Tumors of the Atrioventricular Node

Because of a location near the AV node, these cystic tumors can present with varying degrees of heart block; sudden death may be the first indication, as well.[26] Cardiac MRI is particularly useful in the diagnosis of this tumor.[27] Cystic tumors of the AV node were previously called mesotheliomas.

Paragangliomas

Paragangliomas are highly vascular tumors and may present with hypertension and chest pain.[28,29] The tumor may be located in the pericardial space with no intracardiac extension.[29] Paragangliomas are often located around the roof of the left atrium and aortic root and may involve the cardiac structures (**eFig. 95.1**).[30] The tumors originating from the roof of the left atrium are often large and require extensive surgery, including cardiac autotransplantation.[30] A coronary angiogram in these patients shows a characteristic “tumor blush” (**Fig. 95.11**).[28,29] Paragangliomas are also known as extraadrenal pheochromocytomas.

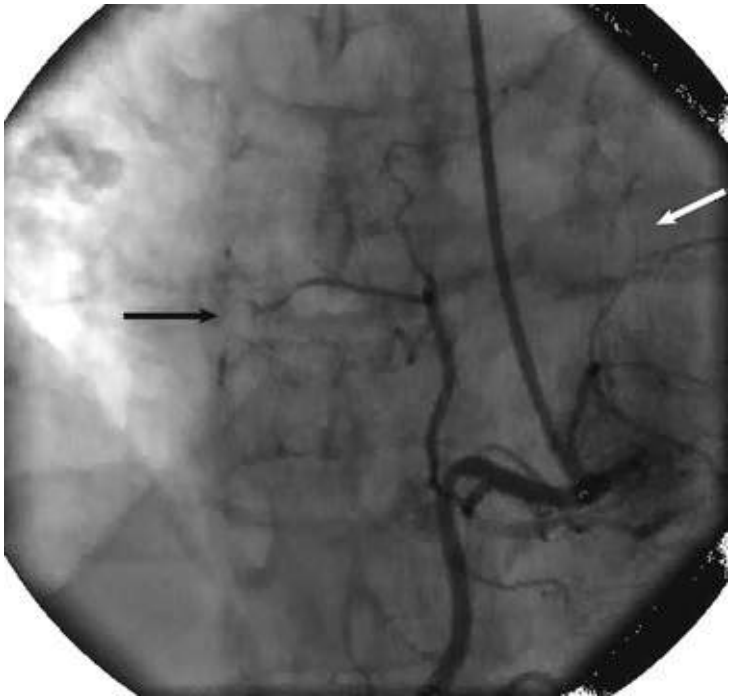
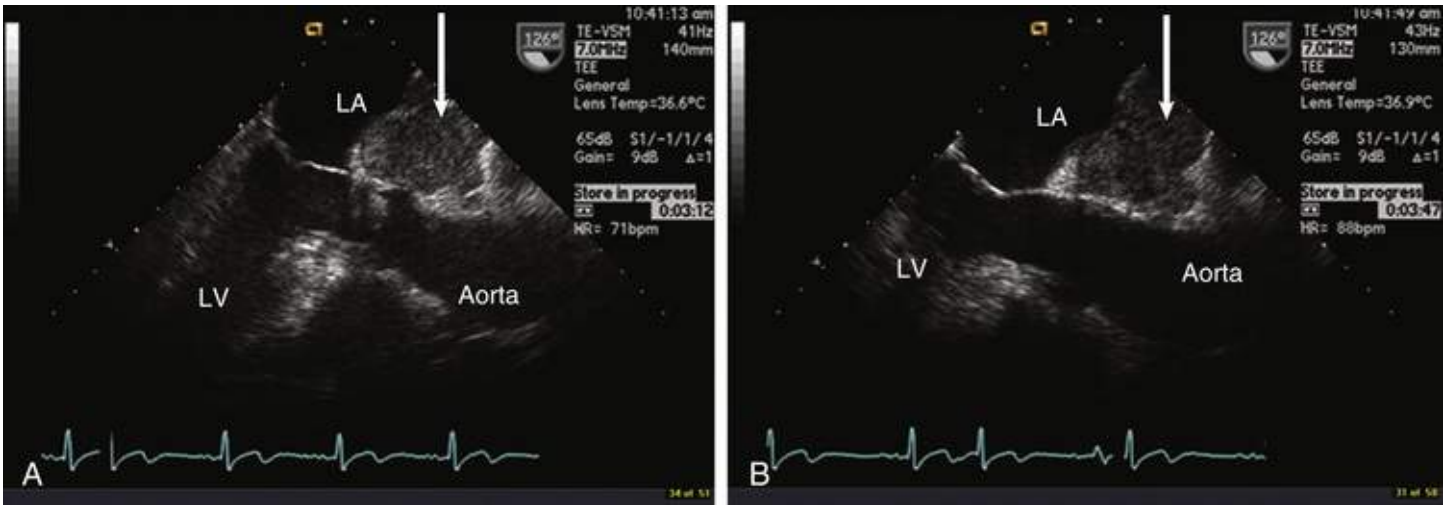


FIGURE 95.11 A tumor blush is noted on angiography *(arrows)* in a patient with a large mediastinal mass.



EFIGURE 95.1 A large mass *(arrow)* in **A** and **B** on the roof of the atrium abutting the aorta that is confirmed to be a paraganglioma. *LA*, left atrium; *LV*, left ventricle.

Other Rare Benign Cardiac Tumors

There are a few, but very rare, reports of hemangioma,[31,32] neurofibroma, teratoma,[33] leiomyoma, and lymphangioma, but there are not enough data to summarize expected findings; typically these will be diagnosed after resection. Complete resection is possible for most of the benign primary tumors, compared with malignant tumors; the perioperative death rate is 1.4%.[34] Hemangiomas are characteristically vascular and may be endocardial or epicardial (**Fig. 95.12**).

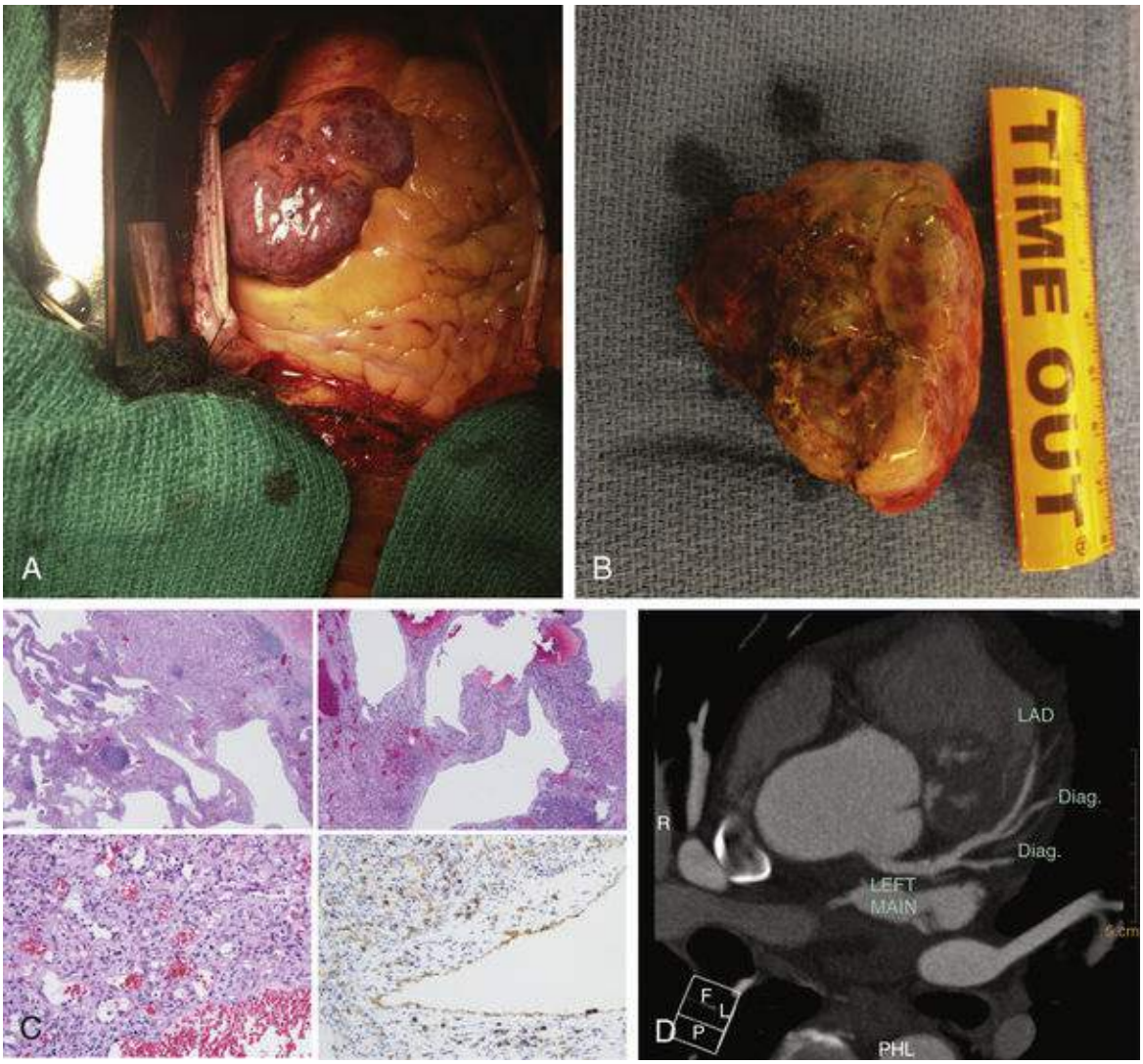


FIGURE 95.12 Primary cardiac hemangioma arising from the right coronary artery at the base of the aorta and right atrium. **A,** Complete resection was possible, with an uneventful postoperative course. **B,** The resected specimen was easily dissected free from adjacent structures and was supplied by the right coronary artery. **C,** Histologic and immunohistochemical features of the tumor. Top left: Low-power view showing large vascular spaces and more solid areas with small capillaries. There is a portion of residual cardiac muscle in the upper right corner (2× magnification). Top right: Medium-power view showing that the vascular spaces are lined by an attenuated endothelial lining with cells with small nuclei. Many of the spaces contain blood and fibrin, and the intervening areas of capillary proliferation have blood and scattered chronic inflammatory cells (4× magnification). Bottom left: High-power view of the capillary-rich area showing plump cells lining the vascular spaces (20× magnification). Bottom right: CD31 immunohistochemistry showing strong brown staining of the lining cells of the large spaces and also of the plump cells in the capillary-rich areas (20× magnification). **D,** CT angiography showing the mass adjacent to the right coronary artery.

Radical Surgical Excision

Most tumors, particularly benign masses, are relatively limited in their size and adjacent cardiac involvement. The surgical approach, whether via median sternotomy or right thoracotomy, allows complete removal and repair of most resulting defects. However, there are a small group of tumors with a complex cardiac involvement. These tumors may invade and obstruct the pulmonary veins or the mitral annulus, rendering complete removal impossible with conventional approaches. Especially in children, an individualized approach is necessary for the best overall resection and outcomes.[35] Pioneered by Reardon and colleagues in Houston, the complete removal of the heart with back-table resection and reconstruction of the pulmonary veins and atria offers a potential cure or palliation for select patients. The approach is

similar to heart transplant cardiectomy, allowing for exposure of the pulmonary veins and complete resection of atrial and even ventricular masses. In their select series, the survival rate was 100% at 1 year among patients with benign tumors and 50% in patients with malignant tumors (primary sarcoma).[36]

Malignant Primary Cardiac Tumors

Sarcomas

Primary cardiac sarcomas constitute approximately 1% of all soft tissue sarcomas and are the most common malignant primary cardiac tumor.[37,38] The age of presentation for cardiac sarcomas ranges from 1 to 76 years, with a mean age of around 40 years.[18,37] Angiosarcomas and unclassified sarcomas account for approximately 76% of all cardiac sarcomas, of which angiosarcomas are the most common.[39] Rhabdomyosarcoma is the most common form of cardiac sarcoma in children. Leiomyosarcoma, synovial sarcoma, osteosarcoma, fibrosarcoma, myxoidsarcoma, liposarcoma, mesenchymal sarcoma, neurofibrosarcoma, and malignant fibrous histiocytoma are other cardiac sarcomas observed.[16,18,39] Angiosarcomas are predominantly found on the right side of the heart, whereas osteosarcomas and unclassified sarcomas are predominantly found on the left side of the heart.[39] Pericardial angiosarcomas are extremely rare.[40]

Clinical Manifestations

Cardiac tumors commonly cause symptoms by three separate mechanisms, obstruction, embolization, and arrhythmias. Rarely pericardial invasion and tamponade may be the first manifestations of the disease. Both atrial and ventricular tumors, when large enough, may result in obstructive symptoms and cause syncope, chest pain, dyspnea, or heart failure. The most common presenting symptoms include dyspnea, followed by chest pain, cough, syncope, hemoptysis, fever, embolic events, and cardiac arrhythmias; sudden death may also be the first manifestation.[18] Large tumors on the right side, besides causing venous congestion, may also limit cardiac filling, with sudden decreases in intravascular volume, potentially precipitating syncope in these patients. Left-sided cardiac tumors, if large enough, can also impair ventricular filling, leading to syncope or heart failure (**Fig. 95.13**). Unfortunately, approximately 29% of cardiac sarcomas are associated with metastatic disease at the time of presentation, typically in the lung.[18,40] Sarcomas, especially left-sided sarcomas, are commonly associated with cardiac embolic events,[16] and arrhythmia can be an important problem as well. A finding of a cardiac mass with pericardial effusion should raise the suspicion of a malignant cardiac tumor.[40] Commonly, pericardial effusion is due to associated pericardial involvement; however, a malignant effusion is not always proven.

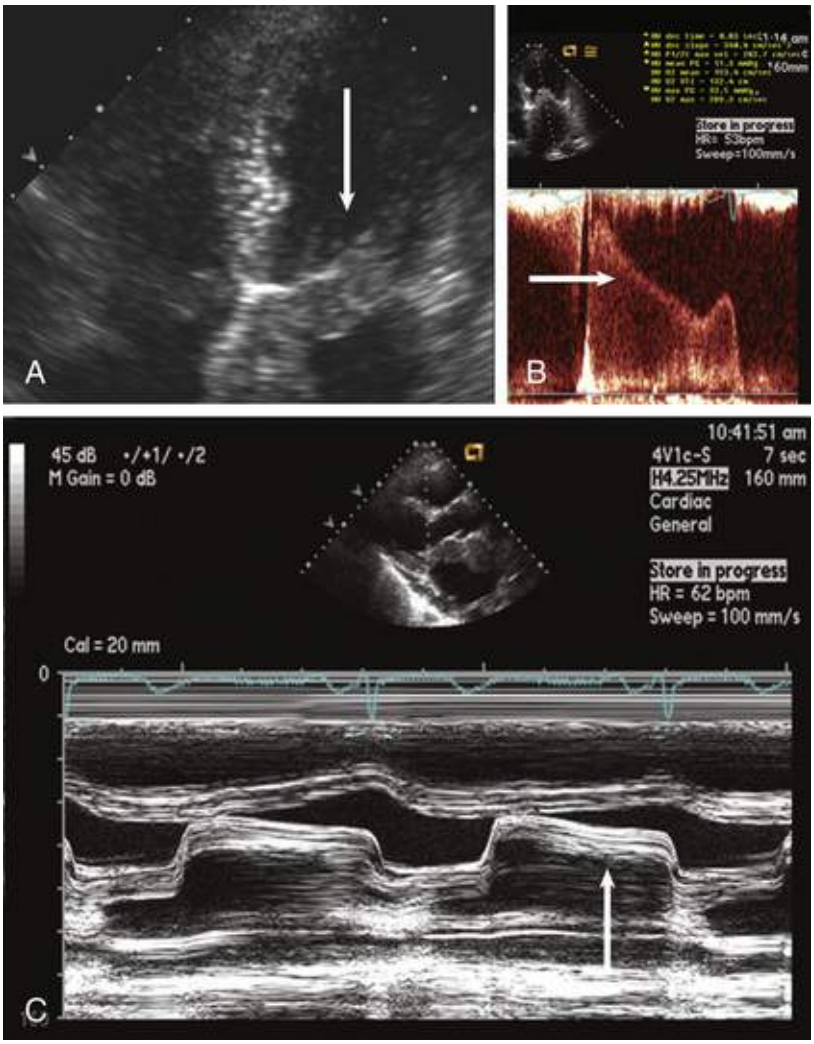


FIGURE 95.13 Echocardiographic Doppler images from a patient with sarcoma who presented with heart failure and mitral stenosis. **A,** Four-chamber image with mitral valve thickening *(arrow).* **B,** Increased velocity across the mitral valve showing stenosis *(arrow).* **C,** M mode showing a classic mitral stenosis pattern.

Laboratory Investigations

Due to the increasing use of CT scanning and better modalities of cardiac imaging, the primary cardiac tumors may be identified at an earlier stage. ECG changes are usually nonspecific; however, heart block, ventricular hypertrophy, bundle branch blocks, atrial flutter, or atrial tachycardia may be present in some cases. Cardiomegaly is a common but nonspecific radiologic finding of cardiac sarcomas.[16] Echocardiography is commonly used in the initial diagnosis of primary cardiac tumors, with transthoracic 2D, 3D, and contrast imaging being appropriate techniques.[41,42] However, transthoracic echocardiography has several well-known limitations: the operator's level of experience is crucial; pulmonary disease may cause the lungs to interfere with the image; or the patient may have narrow rib spaces or an unfavorable body habitus for imaging. TEE can provide more specific and detailed imaging than 2D echocardiography, especially if structures that are more posterior, such as the left atrium, are involved. Cross-sectional imaging methods, such as CT and MRI, have an important role in the evaluation and further assessment of malignant cardiac tumors, especially in the evaluation of myocardial invasion (**Fig. 95.14**), involvement of mediastinal structures, tissue characterization (**Fig. 95.15**), and vascularity.[43,44]

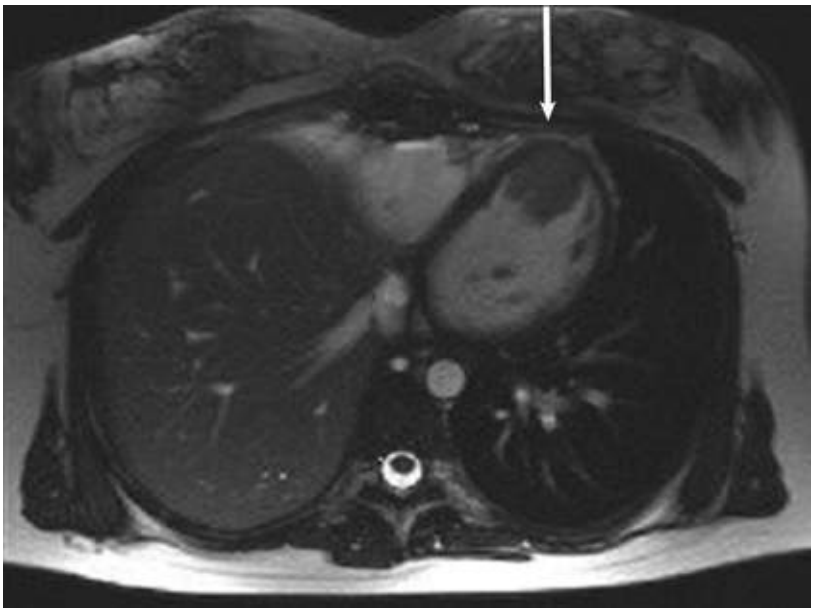


FIGURE 95.14 T_1-weighted cardiac MRI of a left ventricular apical tumor of metastatic alveolar cell sarcoma. Note the indistinct nature of the tumor infiltrating the myocardium *(arrow).* This is in contrast to the distinct line that classically separates thrombus from myocardium.

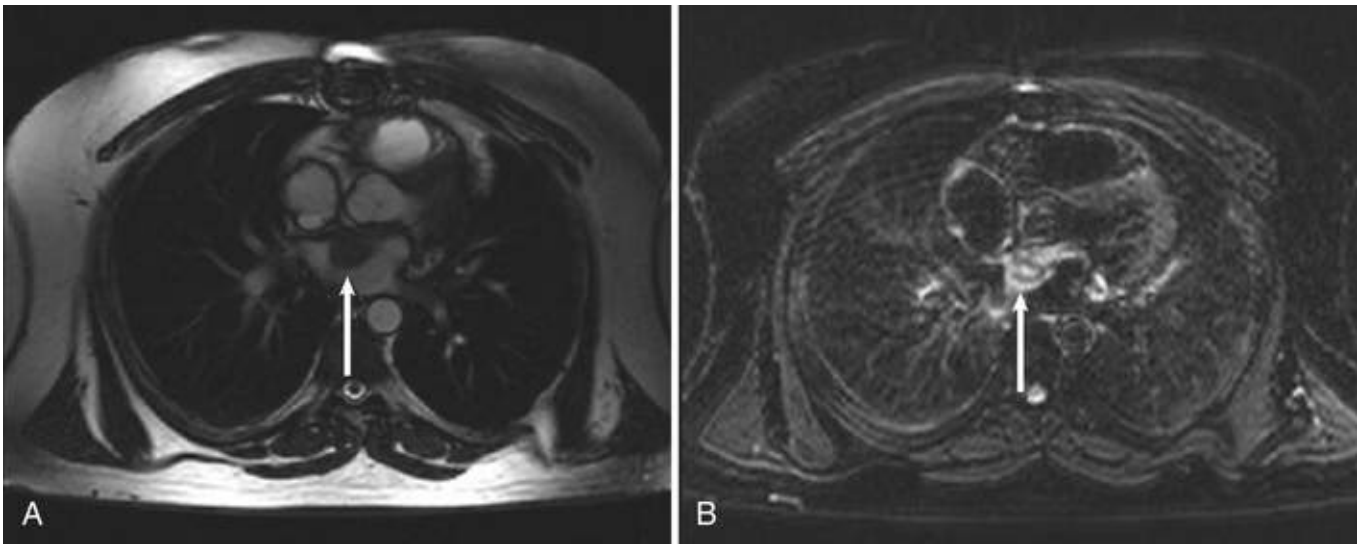


FIGURE 95.15 MRI imaging of a left atrial sarcoma. **A,** T_2-weighted cardiac MRI demonstrating a large left atrial mass near the anterior leaflet of the mitral valve. **B,** Brisk enhancement during first-pass perfusion of the mass confirms a high degree of blood flow, strongly suggesting an angiosarcoma.

Treatment

Complete resection is the optimal goal of surgical treatment.[16,18,45] Once surgical treatment is completed, adjuvant chemotherapy seems prudent, although it has not been widely studied.[45] It is possible that neoadjuvant therapy may be useful, but this is speculative.[46] The most common chemotherapeutic regimen used for cardiac sarcomas is combined doxorubicin and ifosfamide.[40] A combination of docetaxel and gemcitabine also showed some response in various sarcomas and can be used as an alternative chemotherapeutic regimen.[40] Other treatment options include ifosfamide-epirubicin (doxorubicin) and cyclophosphamide, vincristine, doxorubicin, and dacarbazine (CyVADIC).[37] Unlike other sarcomas, cardiac sarcomas overall have a poor prognosis, with a median survival rate of 6 to 25 months after

diagnosis.[12,17,39] The presence of tumor necrosis and metastases is associated with a poor prognosis,[39] as is the presence of a right-sided cardiac sarcoma.[47] Sarcomas other than angiosarcomas, sarcomas on the left side of the heart, and completely resected sarcomas seem to have a better prognosis.[18] At the time of surgical resection patients with negative surgical margins have a better survival rate.[47] Cardiac sarcomas with low-grade histologic findings may appear to have a better survival rate, although in one study there was no significant correlation between the histologic grade and the survival rate.[18,39,48]

Secondary Cardiac Tumors

The autopsy incidence of secondary cardiac tumors ranges from 1.7% to 14% (average, 7.1%) in cancer patients and 0.7% to 3.5% (average, 2.3%) in the general population.[13] In comparison with older series, there is a significant increase in the incidence of cardiac metastases in cancer patients after 1970, predominantly due to improvement in imaging modalities. Cardiac metastases can occur by direct extension, via the circulatory system or lymphatic system, or by intracavitary diffusion through the inferior vena cava (IVC) (**Fig. 95.16**). Pericardial metastasis (69%) is most common, followed by epicardial (34%), myocardial (32%), and endocardial metastases (5%).[49] The pericardium is most often involved due to direct invasion by thoracic cancers, including breast and lung cancers, as well as thoracic lymphomas. Abdominal and pelvic tumors may reach the right atrium through the IVC. The most common tumor exhibiting this tendency is renal cell carcinoma.[40] A recent review suggests that lung cancer is the most common cause of cardiac metastasis, followed by esophageal cancer and hematologic malignancies.[17] The symptoms of cardiac metastases are extremely variable, depending on the location of the tumor. Dyspnea, palpitations, syncope, chest pain, and peripheral edema are common clinical presentations.[40,49] Heart failure, cardiac arrhythmias, heart blocks, acute myocardial infarction, myocardial rupture, systemic embolization, and superior vena cava syndrome (**eFig. 95.2**) are other manifestations of cardiac metastases. A new heart murmur or any new ECG finding without clear symptoms in a cancer patient should raise the suspicion of cardiac metastases. Typical ECG findings encountered in patients with cardiac metastases are ST-T wave changes (mimicking myocardial ischemia or injury), new atrial fibrillation or flutter, and low voltages with electrical alternans indicating a significant pericardial effusion. The ECG findings of myocardial injury may indicate an invasion of the coronary vessels by tumor.[50]

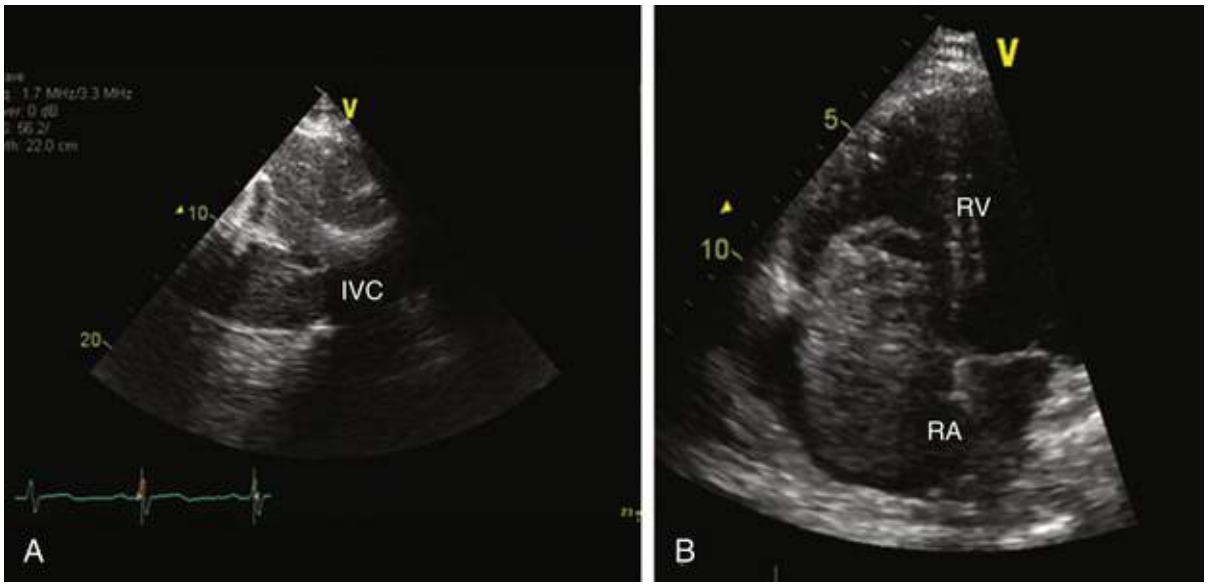
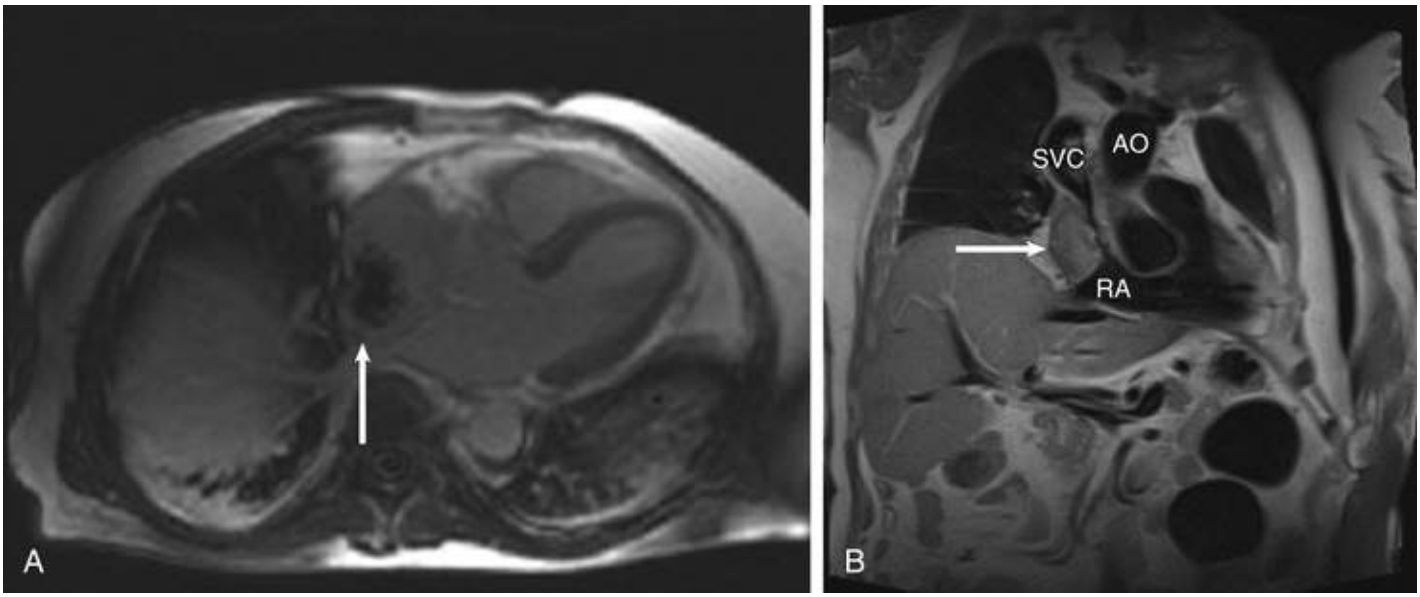


FIGURE 95.16 Renal cell carcinoma. **A,** Renal cell carcinoma invading the inferior vena cava (IVC), **B,** Renal cell carcinoma invading the right atrium (RA) and prolapsing into the right ventricle (RV). A right radical nephrectomy was done, along with removal of the right atrial and IVC tumor.



EFIGURE 95.2 Superior vena cava obstruction. **A,** T_2 using a weighted image. A large irregular right atrial mass extending into the superior vena cava is evident *(arrow).* **B,** A T_2-weighted image showing nearly complete obstruction of the superior vena cava from a right atrial mass in a patient who has a mediastinal mass with neck and facial swelling *(arrow). AO*, aorta; *RA*, right atrium; *SVC*, superior vena cava.

Treatment

Treatment of metastatic cardiac tumors is usually palliative, because the overall prognosis is poor, with more than 50% of patients dying within 1 year.[40] Palliative radiotherapy and chemotherapy in chemosensitive tumors is recommended.[13] In these patients end-of-life care should be discussed and all efforts should be made to improve the quality of life. In highly selected cases, extraordinary surgical approaches can be attempted, such as autotransplantation, but this is an unusual option. The management of a malignant pericardial effusion is typically individualized to a local center's experience, and close

collaboration between oncologists and cardiologists is necessary to ensure an optimal treatment plan.[51] Recent data strongly indicate that infusion of selected chemotherapy may be useful in patients who have a malignant effusion.[52]

Direct and Indirect Complications of Neoplasia

Pericardial Effusion

The differential diagnosis of a pericardial effusion in a patient with a known malignancy includes malignant effusion, radiation-induced or drug-induced pericarditis, idiopathic pericarditis, infectious effusion (including tubercular, fungal, or bacterial), or iatrogenic effusion, secondary to procedures. It is estimated that approximately 40% of patients with cancer and a pericardial effusion were found to have either a radiation-induced effusion (**see also Chapter 80**) or an idiopathic effusion, and only a minority actually have a malignant effusion.[53] Drug-induced pericarditis is typically seen after high-dose anthracycline or cyclophosphamide therapy (**see also Chapter 81**).

Cardiac Tamponade

Approximately one third of patients with pericardial involvement will present with impaired cardiac function, and cardiac compression can progress to tamponade, demanding immediate drainage (**see also Chapter 83**). Patients' symptoms include chest pain, fever, dyspnea, cough, and peripheral edema. Tamponade without two or more signs of an inflammatory process (typical pain, friction rub, fever, diffuse ST segment elevation) is more likely to be malignant (2.9-fold increase in risk).[53] Physical findings and findings on ECG or chest x-ray are typically similar to findings of pericardial effusion due to any cause. Echocardiography demonstrates the effusion, which is usually large, although it does not have to be if the fluid has accumulated quickly. However, tamponade can occur with loculated effusions, and, in these cases, typical echocardiographic signs may be absent. The acute treatment of tamponade includes careful fluid replacement as a temporizing measure if the patient is believed to be volume depleted and hemodynamics are compromised.[53] Echocardiography-guided pericardiocentesis is required. Fluid should be sent for a full battery of diagnostic tests because, as noted, the cause is commonly noncancerous, even in patients with known cancer. In approximately 85% of patients with a malignant effusion, cytologic examination of the pericardial fluid is positive.

Although no randomized clinical trials of various strategies have been done, the risk of recurrence of the effusion appears to be reduced by extended catheter drainage (3 ± 2 days; 11.5% recurrence) as opposed to simple pericardiocentesis.[54] Recurrence of pericardial effusion can often be treated with repeat pericardiocentesis with extended catheter drainage. Some have used intrapericardial instillation of chemotherapeutic agents or sclerosing agents, but it is not clear that this approach is more effective than extended catheter drainage. Occasionally, percutaneous balloon pericardiotomy or pericardiectomy may be required, but patients with malignant effusions have such a poor prognosis (median survival of 135 days in one series of 275 patients) that invasive procedures should be avoided, if possible. Therapy is directed at the underlying tumor.

Constrictive Pericarditis

Constrictive or effusive-constrictive pericarditis is a late complication of chest irradiation that may be

becoming more common because of the longer survival times of patients with breast cancer and Hodgkin disease, who typically receive chest irradiation. This is covered in detail in **Chapter 83**.

Superior Vena Cava Syndrome

In the mid third of the mediastinum, left and right brachiocephalic veins join to form the superior vena cava (SVC). The SVC extends caudally, coursing anterior to the right main stem bronchus, and terminates in the superior right atrium. The SVC is joined posteriorly by the azygos vein and runs posterior to and to the right of the ascending aorta. During its course, the SVC is adjacent to the right paratracheal, azygos, right hilar, and subcarinal lymph node groups. The blood flow in the venous system is under low pressure and the vessel itself is thin walled. Any inflammatory process in the mediastinum or enlargement of the lymph nodes or ascending aorta can cause the SVC to be compressed, resulting in reduced blood flow and eventually complete occlusion (**Fig. 95.17**).

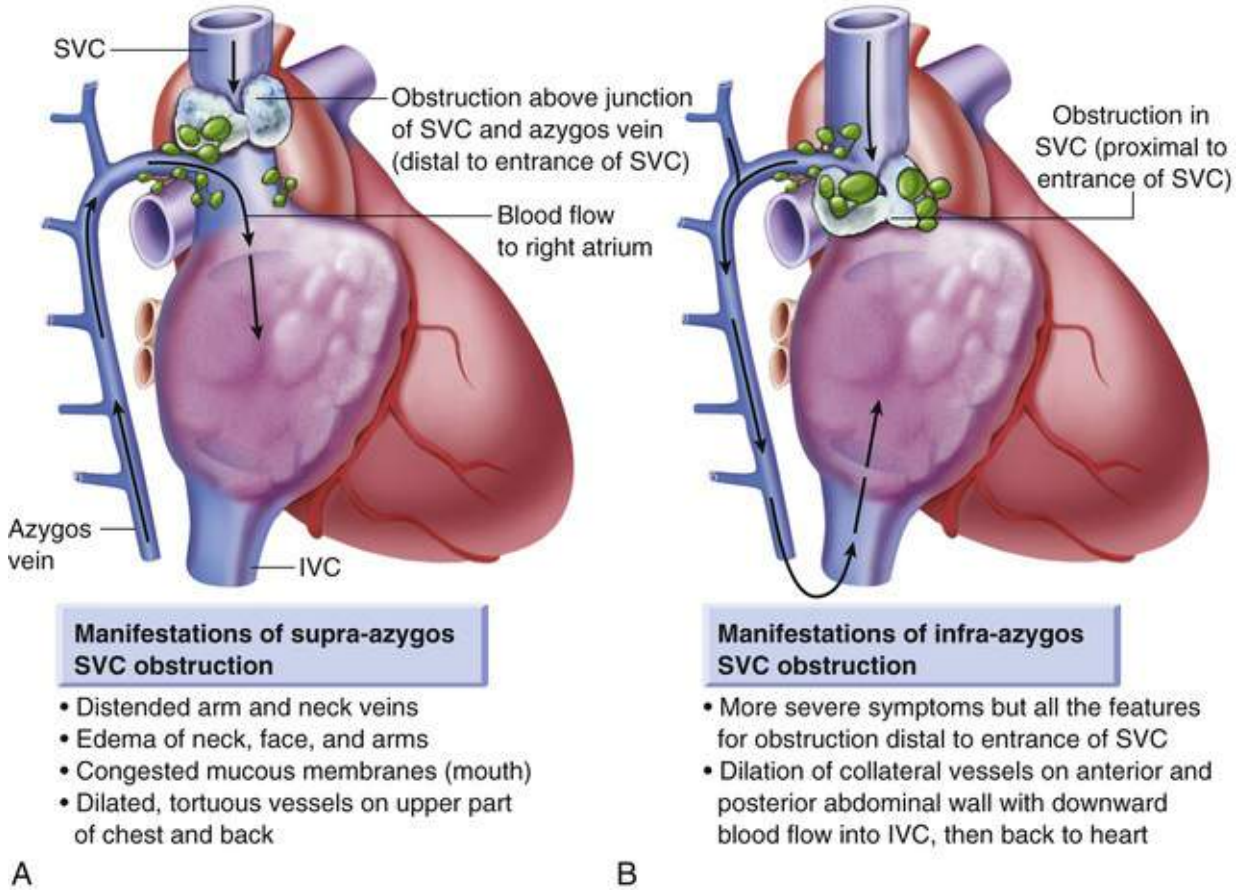


FIGURE 95.17 Anatomy of superior vena cava (SVC) syndrome. **A,** Lymph nodes may obstruct blood return above the entrance of the azygos vein, resulting in edema of the face, neck, and arms and distended veins in the neck and arms and over the upper chest. **B,** Obstruction below the return of the azygos vein results in retrograde flow through the azygos via collateral veins to the inferior vena cava (IVC), causing all the symptoms and signs in **A** plus dilation of the veins over the abdomen. (Modified from Skatin AT (editor): Atlas of diagnostic oncology, 3rd ed. Philadelphia, Elsevier Science, 2003.)

Etiology and Physiology

The SVC syndrome was first described by William Hunter in 1757, in a patient with syphilitic aneurysm of the ascending aorta. Over a period of time, vascular causes have declined, and now the most common

cause of SVC syndrome is malignancy, of which lung carcinoma is the most common, followed by lymphoma and metastatic cancer.[55] Malignancy accounts for more than 85% of causes of SVC syndrome.[56] Other causes of SVC syndrome, which are somewhat benign, account for 3% to 15% of cases and include nonmalignant causes such as thrombosis due to the use of intravascular devices such as catheters or pacemakers, infection, thymoma, substernal thyroid goiter, and aortic aneurysm.[56] Other possibilities include diseases causing systemic vasculitis (e.g., Behçet's disease) and radiation-induced fibrosis.

Clinical Diagnosis

The clinical diagnosis is usually made on the basis of a constellation of symptoms and signs, and a classification system has been proposed.[57] The development of SVC syndrome is usually insidious but occasionally it may develop rapidly. The severity of the syndrome depends on the rapidity of onset of the obstruction and its location. The more rapid the onset, the more severe the symptoms because collateral veins do not have time to distend to accommodate an increased blood flow. A usual patient presentation involves facial edema, dyspnea, and cough.[55,58] Facial edema is most frequently seen; it is worse in the morning and gets better during the day as the patient ambulates. Other less frequent symptoms include stridor, headache, syncope, dizziness, hoarseness, and confusion.[55,58] Common findings on examination include facial edema, distended neck and chest veins, arm edema, and facial plethora.[55]

Laboratory Investigation

Investigations primarily depend on whether the underlying cause is known or not. In the case of a presentation with no prior diagnosis, a chest x-ray, CT image of the chest, and potentially a bronchoscopic examination may reveal lung cancer as the most common cause. CT imaging is usually helpful because it provides a detailed evaluation of the venous system and also helps to identify the principal causes, such as a neoplasm, thrombosis due to central catheters, or infection resulting in sclerosing mediastinitis.[59] Magnetic resonance venography can be used as an alternative to CT scan in patients who are allergic to contrast dyes or in whom a CT scan cannot be obtained for some other reason. Intravenous venography is another option in patients who may not be able to undergo CT scan.

Treatment

The treatment is directly related to the underlying cause. In cases of known malignancy, systemic chemotherapy and radiation therapy are typically carried out. If the main cause of SVC obstruction is thrombosis, stent deployment is an attractive option.[60,61] Surgical bypass of an obstructed SVC is another option, especially if sufficient diagnostic tissue cannot be obtained by other measures.

Valvular Disease

It is certainly common for cardiac tumors to directly affect valvular structures; the type of tumor, its location, its size, and any associated infectious or thrombotic conditions are all factors. An additional tumor that classically has an impact on cardiac valvular structures is the carcinoid tumor. Patients with carcinoid are at substantial risk of developing severe tricuspid regurgitation, which may require surgical repair or replacement. The valvular abnormality includes tethering of the leaflets, resulting in poor coaptation. This can become a difficult condition to manage medically and may require surgical intervention (**Fig. 95.18**).[62]

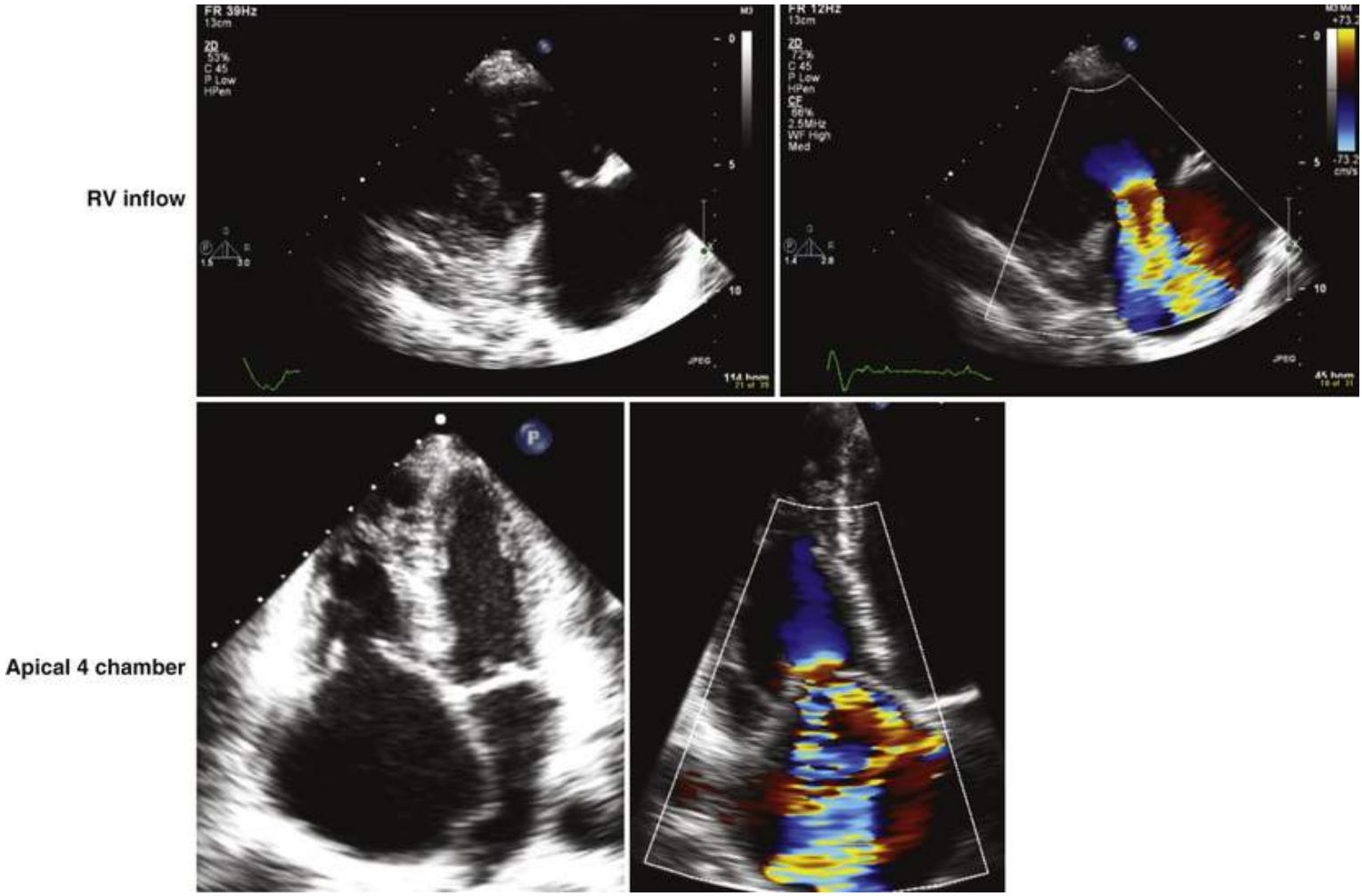


FIGURE 95.18 A typical 2D echocardiographic image of severe tricuspid regurgitation that is commonly encountered in a carcinoid tumor. There is poor coaptation of the tricuspid valve leaflets with tethering, which is seen in many instances.

Future Perspectives

The clinical outcome of patients who have a primary cardiac tumor heavily depend on early detection and prompt, appropriate treatment. Frequently, cardiac tumors are only discovered after a patient experiences a period of a confusing constellation of symptoms, which are ultimately connected to an abnormal image that suggests a cardiac tumor. As a result, the stage of disease is commonly advanced at the time of diagnosis. Once a primary cardiac tumor has been diagnosed, the patient should be managed by a multidisciplinary team, including medical oncologists, radiation oncologists, cardiologists, and cardiac surgeons. Over the last few years, increasing use of imaging modalities (e.g., echocardiography, MRI, and CT) has led to an increasing number of incidental findings of a primary cardiac tumor. Current imaging techniques accurately differentiate tumors from other masses only slightly more than 50% of the time. With improvements in echocardiographic, CT, and MRI imaging techniques, identification of all cardiac tumors will be done with a higher degree of certainty. There is no noninvasive technique that can identify whether the tumor is benign or malignant, and a pathologic sample is needed in all cases for that purpose. Improvement in surgical technique has led to minimally invasive approaches, but surgery still entails general anesthesia and a surgical incision and is a major stress for a patient. Continued refinement in surgical tools and approaches will lead to lower rates of morbidity and mortality. Transvenous biopsy of the cardiac mass for pathologic confirmation (under echocardiographic guidance) is done in some centers. Refinement in this technique will enable better sampling in the future. In some centers, PET scanning is

routinely used to evaluate for metastatic disease. Currently, there are no blood tests available that would point to metastasis, and this represents a large unmet clinical need.

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Psychiatric and Behavioral Aspects of Cardiovascular Disease

Viola Vaccarino, J. Douglas Bremner

The cardiovascular system has long been considered vulnerable to the effects of psychological factors, and popular wisdom holds stress and emotions as important risk factors for cardiovascular disease (CVD). Physiologic and experimental data as a whole substantiate this belief and support the notion that psychosocial adversities, stressful exposures, and a person's mental health status contribute to cardiovascular risk. These factors may influence the development of CVD across the life course beginning in early life, and may affect the entire spectrum of pathophysiologic factors, from CVD risk factors, to lifestyle behaviors, to the progression of coronary atherosclerosis, to the triggering of acute coronary events.[1]

The *stress response*, an adaptive physiologic mechanism that allows an organism to counteract potentially damaging stimuli, results in stimulation of the sympathoadrenal system and the hypothalamus-pituitary-adrenal (HPA) axis with release of cortisol and catecholamines (**see also Chapter 99**). Activation of the stress system is physiologically useful to counteract the stressor. However, according to the “reactivity hypothesis,” cardiovascular responses to psychological stressors, if prolonged or exaggerated, can promote the development of CVD.[2] Heightened cardiovascular reactivity is posited to increase the cardiovascular risk through a multitude of mechanisms, including, among others, a repeated or sustained increase in blood pressure and heart rate, insulin resistance and other metabolic abnormalities, systemic vascular resistance, autonomic dysregulation, ventricular arrhythmias, and dysregulation of the inflammatory and immune systems (**Fig. 96.1**). A blunted physiologic response to stress, however, is also considered maladaptive and may have adverse health consequences.[3] Chronic, cumulative effects of stress have also been implicated in cardiometabolic risk secondary to increased circulating levels of stress hormones and disruption of the normal neuroendocrine homeostasis and circadian rhythm of the stress system.[4]

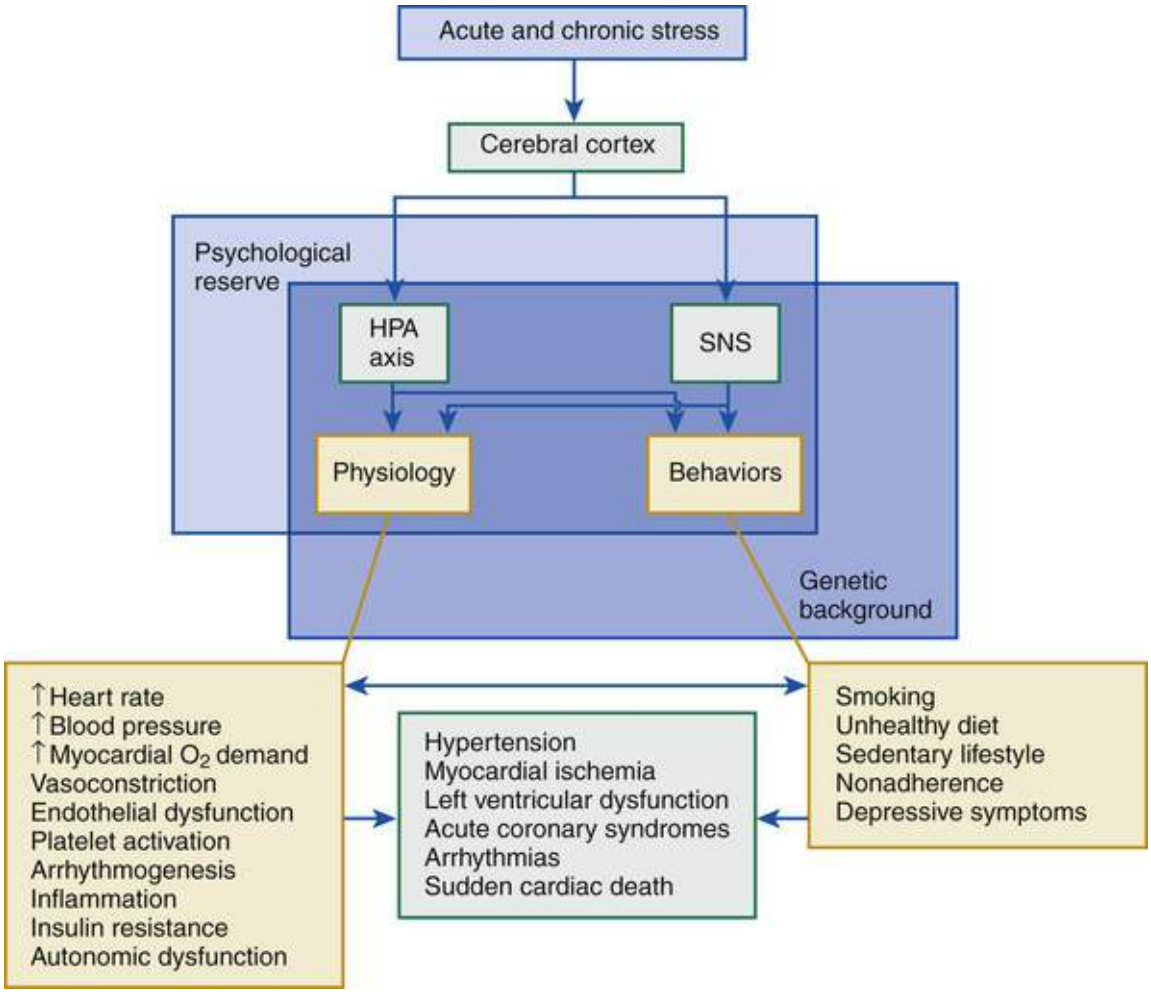

FIGURE 96.1 Potential mechanisms underlying the link between psychological factors and cardiovascular disease. *HPA*, hypothalamic-pituitary-adrenal axis; *SNS*, sympathetic nervous system.

Research in nonhuman primates has provided strong experimental evidence of the adverse cardiovascular effects of chronic stress. Spanning many decades, these studies have demonstrated that chronic psychosocial stress causes endothelial damage and accelerated atherosclerosis.[5] In humans, the adverse effects of experimentally induced stress on the cardiovascular system are well documented (described below under “Mental Stress”). Yet, the effects of naturally occurring stressors on cardiovascular function and CVD risk have been more difficult to demonstrate. One problem is the definition of exposure. Under the general term of “psychosocial stress” investigators have included interrelated but different elements, encompassing a variety of environmental exposures, from traumatic events to job or family difficulties to minor everyday hassles, as well as individuals' responses or emotional states such as perceived distress, depression, and anxiety. Another problem is the lack of standardized measures to consistently define and quantify the type and severity of psychological stress. As discussed in this chapter, to date the most robust evidence implicates a low socioeconomic status, early life adversity, work stress, and depression as risk factors for CVD. In addition to manifest disease, many of these factors have been associated with subclinical markers of CVD. More recently, posttraumatic stress disorder (PTSD) has also been linked to cardiovascular risk. Findings related to other psychosocial/psychiatric factors, such as other forms of self-reported chronic stress/distress, anxiety, and anger/hostility, have been less consistent.

Recognition of psychological and psychiatric factors is important in the management of the cardiac patient, not only because many of these conditions are prevalent and have been linked to adverse cardiovascular outcomes, but also because they are related to health behaviors and lifestyle risk factors that have prognostic significance. These include factors such as lower adherence to treatment

recommendations, lower levels of physical activity, an unhealthy diet, and tobacco smoking. Yet, psychological and psychiatric conditions are less likely to be recognized and managed in current cardiology practice than traditional CVD risk factors. This is because of complexities in definition and assessment, as mentioned above, but also because many symptoms of psychological distress are easily confused with physical disease, for example, fatigue, weight loss, poor appetite, or trouble sleeping.

Current recommendations recognize the need for cardiologists to be more proactive in addressing this important domain of patient care.[6] The goal of this chapter, therefore, is to review key epidemiologic and pathophysiologic evidence linking psychological factors to CVD and discuss their management in the current practice of cardiology. For clarity, we will classify psychiatric and behavioral aspects into general categories of acute stressful events; chronic stressors (including, among others, work stress, low socioeconomic status, and marital and caregiving stress), mental health and psychiatric diagnoses (including depression, anxiety, and posttraumatic stress disorder), and personality traits.

Acute Stress

Stressful and Emotional Triggers of Acute Cardiovascular Events (See Also Chapter 51)

Many studies, albeit not all, have demonstrated an increase in hospital admissions for acute coronary syndromes after emotionally stressful events such as natural and industrial disasters and terroristic attacks.[1] When causes of death were examined, there was no increase in noncoronary deaths. A notable exception to these statistics is the World Trade Center terrorist attack in New York City on September 11, 2001. This event was not linked to a sudden increase in cardiac death or acute coronary care admissions immediately following the attack. It is possible that this event, which was observed by most New Yorkers through news reports on television, did not cause acute stress to the same extent as an incident might that poses a direct threat to personal safety. However, the incidence of cardiovascular ailments diagnosed by physicians increased by more than 50% in the next 3 years. Furthermore, ventricular arrhythmias more than doubled among patients with implantable cardioverter-defibrillators (**see also Chapter 39**), but this increase did not occur until 3 days after the event and persisted in the next 30 days. These data suggest a subacute or chronic impact of the attack rather than an acute triggering effect.

Studies were also conducted during major sporting events such as the Football World Cup, with some evidence of increased cardiac event rates in the cities or regions of the teams involved, especially when the team lost, although not all studies have been consistent.[1] A limitation of these population-level studies is the lack of information on the circumstances surrounding cardiac events for the individuals affected. Apart from emotional stress, cardiac events could be triggered by concomitant factors, for example, vigorous physical exertion (such as running away), heavy eating and drinking, environmental tobacco usage, or outdoor temperature. It is often difficult to rule out these alternative explanations completely. In this respect, studies of emotional triggers at the individual level, where patients are asked about their experiences prior to symptom onset, should provide useful information. On the other hand, patient self-reporting may be affected by recall bias. A study design that attempts to reduce this bias is the case-crossover design, which uses subjects as their own controls by comparing the frequency of a specific exposure in the hours immediately preceding symptom onset with its frequency in a control period, for example, a few days earlier.

Several studies have used this design to examine emotional triggers of acute cardiovascular events.

Among these, acute anger has been studied most extensively. In the Determinants of Myocardial Infarction Onset Study (Onset Study), 2.4% of patients reported being very angry or furious in the 2 hours before acute myocardial infarction[7] (**see also Chapter 58**). In comparison with other times in the previous year, the risk of a myocardial infarction was 2.4 times higher in the 2 hours after self-reported outbursts of moderate or extreme anger, with a greater risk for each increment in anger intensity. The results were not materially different when adjusted for physical activity or consumption of coffee and alcohol. In a systematic review including nine independent case-crossover studies of anger outbursts and acute cardiovascular events, all studies found that there was a higher rate of cardiovascular events in the 2 hours following outbursts of anger compared with other times, although the effect estimate varied across studies.[8] The pooled estimate of risk for acute coronary events was greater than fourfold. Despite this high relative risk, an individual's absolute risk of a cardiovascular event following an anger episode is small. It is higher for individuals with an elevated baseline cardiovascular risk and for those who have frequent outbursts of anger.

In addition to anger, acute negative emotions such as grief and sadness can act as triggers of cardiovascular events.[1] In the Onset Study, using the case-crossover approach, researchers found that the incidence of acute myocardial infarction increased 21-fold in the 24 hours following the death of a significant person.[9] Taking advantage of a large primary care database in the United Kingdom, a recent study reported a prospective relationship between bereavement and increased risk of cardiovascular events. Within 30 days of their partner's death, bereaved people experienced a doubling of the risk of cardiovascular disease, which attenuated after the first 30 days. Other acute stressors that have been linked to increased risk of cardiac events include work-related stress, such as a high-pressure deadline, and exposure to heavy traffic. Again, the absolute risk from these potential triggers is small, but it goes up with an increasing individual cardiovascular risk status.[9] Using population-attributable fractions, it has been estimated that negative emotions play a role in 4% and anger in 3% of acute cardiac events.

Stressful life events have been linked to acute myocardial stunning in susceptible individuals with severe, reversible left ventricular dysfunction, a condition known as takotsubo cardiomyopathy.[10] These patients, almost all women, also show exaggerated sympathetic nervous system stimulation as indicated by markedly elevated plasma catecholamine levels.

Mental Stress

A useful method of assessing the effects of stress and emotion on cardiac function is to measure transient ischemic responses to a standardized psychological stress challenge in the laboratory, or “mental stress test,” using mental arithmetic, color naming, public speeches, and similar tasks (**see also Chapter 57**). This methodology has the advantage of direct experimental manipulation where potential confounding factors can be controlled or eliminated and causal factors and their mechanisms directly investigated. However, this approach is necessarily limited to short-term responses to acute stress artificially induced in the laboratory, and thus may lack practical significance. To address this issue, longitudinal studies have investigated the link between mental stress–induced cardiovascular responses and future CVD events. Greater cardiovascular reactivity to mental stress (mostly defined as acute changes in blood pressure and heart rate) and poor recovery from stress (defined as sustained cardiovascular activation above baseline levels during the posttask period) have been associated longitudinally with cardiovascular outcomes, including elevations in blood pressure and CVD events, whereas evidence of an association with atherosclerosis endpoints such as carotid intima-media thickness and coronary artery calcifications is more limited.[2] Cortisol and catecholamine responses to mental stress have also been related to future

hypertension and other CVD endpoints.

In addition to cardiovascular reactivity, an important phenomenon that has been studied in conjunction with mental stress in cardiac patients is mental stress–induced myocardial ischemia. This condition is analogous to exercise stress ischemia, except that the stimulus is psychological rather than physical.[11]

Mental stress ischemia has been studied with a variety of imaging techniques and a range of stressful stimuli.[12,13] The literature indicates that mental stress ischemia can be induced in one third to two thirds of coronary heart disease patients; younger women with coronary heart disease appear especially susceptible.[14] It is typically painless, and occurs at lower levels of oxygen demand than ischemia due to physical exertion. In addition, mental stress–induced ischemia is generally not related to the severity of coronary artery disease, suggesting that it is not simply a reflection of coronary disease severity. Patients may develop ischemia with mental stress but not with exercise or pharmacologic stress, although results vary. Ischemic responses are induced not only by severe emotional stress, but also by milder challenges similar to those that might be encountered in everyday life. In fact, mental stress–induced (but not exercise-induced) myocardial ischemia is correlated with ischemia measured in daily life ambulatory monitoring. Thus, mental stress testing could potentially provide a means for the identification of patients vulnerable to myocardial ischemia in everyday life.

All the results published to date have indicated that mental stress–induced ischemia is a predictor of a poor prognosis. Five longitudinal studies with a follow-up of 1 to 5 years have found a consistent doubling of the risk of death or subsequent cardiac events. In these studies, coronary heart disease patients with mental stress ischemia were compared with those without mental stress ischemia, independent of coronary disease severity and CVD risk factors.[15] Although the samples of patients followed longitudinally to date are small, current evidence indicates that myocardial ischemic responses to standardized mental stress are prognostically important at least as much as responses to exercise-induced ischemia.

Potential Mechanisms of Acute Stress as a Trigger of Cardiac Events

A key pathophysiologic event underlying an acute coronary event is the progression from a stable plaque to a “vulnerable” plaque. No direct evidence exists to show that acute psychological stress causes atherosclerotic plaque rupture or erosion. However, acute episodes of stress or intense emotions may trigger acute coronary events in susceptible individuals by affecting plaque stability and disruption. This occurs through hemodynamic activation (increases in blood pressure and heart rate), increases in systemic vascular resistance, coronary vasoconstriction, inflammation, and prothrombotic effects, among others. Triggering usually takes place against a background of advanced atherosclerosis; thus it is considered rare in people without underlying coronary artery disease.[16]

The mechanisms behind emotional triggering of acute myocardial ischemia, such as ischemia induced by mental stress, are likely multiple and may include hemodynamic changes, such as increases in blood pressure, heart rate, systemic vascular resistance, and coronary artery vasoconstriction. It is clear, however, that different hemodynamic responses underlie ischemia triggered by acute psychological stress as compared with exercise stress.[11,17] Myocardial ischemic responses to mental stress occur at a lower rate-pressure product than responses to exercise-induced ischemia in the same patients, although the hemodynamic response tends to be larger than in patients who do not become ischemic. Both people with and without preexisting coronary heart disease who develop mental stress ischemia show an increase in systemic vascular resistance, suggesting that a rise in afterload caused by peripheral vasoconstriction may

play a role in ischemia induced by psychological stress.[13] By contrast, systemic vascular resistance is generally decreased by exercise.

Mental stress may also cause abnormal coronary artery vasomotor responses. Patients with atherosclerosis may undergo a paradoxical constriction during mental stress, particularly at points of stenosis, which may reduce myocardial blood flow and thus result in ischemia. Both coronary endothelial dysfunction and vasomotor abnormalities in the coronary microvasculature appear to play a role in myocardial ischemia triggered by psychological stress.

Acute mental stress can also induce cardiac electrical instability, including an increase in T-wave alternans and other measures of abnormal cardiac repolarization that have been related to arrhythmogenesis and sudden cardiac death[18] (**see also Chapter 34**). Autonomic dysfunction and its effects on cardiac electrophysiology form another likely process underlying acute adverse effects of stress on the heart (**see also Chapter 99**). Both sympathetic activation and parasympathetic withdrawal can stimulate arrhythmias and lower the threshold for ventricular fibrillation. Heart rate variability, a measure of the beat-to-beat changes in heart rate as the heart responds to internal and external stimuli, is an accepted noninvasive measure of overall cardiac autonomic function (**see also Chapter 12**). Reduced heart rate variability predicts coronary heart disease in population studies, as well as death, particularly sudden cardiac death, in patients following acute myocardial infarction.[19] Heart rate variability is reduced during acute mental stress in the laboratory, and was found to be reduced during major disasters, such as earthquakes or terroristic attacks, in studies of patients who were undergoing ambulatory electrocardiographic monitoring at the time of the event.[1] These mechanisms may underlie the described connection of acute stress with life-threatening cardiac arrhythmias and sudden cardiac death.

Inflammation and immunity are increasingly recognized as key factors in mediating cellular responses to acute psychological stress. Noradrenaline-dependent adrenergic stimulation due to stress activates the transcription factor nuclear factor κB in circulating monocytes, resulting in initiation of the inflammation cascade. Thus psychosocial stress stimulates mononuclear cell activation and subsequent immune and inflammatory responses, which may result in myocardial ischemia.[20] At the same time, stress-induced neuroimmune circuits involving microglia activation in the brain and sympathetic outflow to the peripheral immune system further reinforce stress-related behaviors and the inflammatory phenotype.[21]

Thus, there are multiple physiologic responses secondary to emotional stress that could trigger cardiac ischemia or sudden death. However, presently little prospective information is available to link these mechanisms of acute stress to cardiovascular endpoints.

Acute Stress and Cardiovascular Disease: Clinical Implications

The clinical significance of acute emotional triggers of cardiac events has not been clearly established. Although the relative risk associated with acute stress is substantial, the absolute risk is smaller, given that these events are relatively uncommon. Accordingly, the population-attributable risk (i.e., the reduction in disease that would be observed if the risk factor were entirely eliminated) is not large (≈4%), but it is fairly similar to that of other acute triggers of coronary events, such as physical exertion, heavy traffic, or excessive alcohol consumption. Furthermore, it is likely that this risk only affects a subset of vulnerable individuals. Some patients may be particularly susceptible to physiologic responses to emotional stimuli and therefore be at higher risk of unfavorable cardiovascular consequences due to stress. If such patients could be identified in advance, specific procedures could be put in place to minimize their exposure to an emotional trigger as well as reduce the risks associated with such exposure.

Although it has been argued that programs that would increase awareness of psychological triggers among clinicians and the public would be beneficial, such programs in general lack evaluation. Whether therapies for CVD prevention, such as aspirin, β-blockers, statins, and angiotensin-converting enzyme inhibitors, also protect against harmful effects of emotional triggers, is similarly not known.

Chronic Stress

Work Stress

Work stress has been extensively studied for its potential adverse cardiovascular effects. A dominant model of work stress includes the "job strain" model developed by Karasek and Theorell.[22] The job strain model postulates that high work demands in combination with low control produce stress, because workers in low-control jobs cannot moderate work pressure by organizing their time or by other means. A third dimension of social support at work was later added, such that the adverse health effects of job stress are greatest in workers who lacked support from colleagues. An alternative model is the effort-reward imbalance model, which proposes that stress occurs when there is a mismatch between high workload and low payback in terms of money, job security, or other forms of recognition. Both these models have been linked to adverse cardiovascular events.[23] In a large metaanalysis including 1.5 million person-years at risk, and 2358 new coronary cases, job strain was associated with a 23% higher rate of coronary heart disease. The association remained after adjustments for socioeconomic status and lifestyle and conventional risk factors, and was noted across sexes, age-groups, socioeconomic strata, and regions.[24] There is less knowledge about whether similar risks apply to patients with established coronary disease; however, studies of patients returning to work after a myocardial infarction reported a 70% or more increase in risk of recurrent events or cardiac death in patients with high job strain or effort-reward imbalance at work.[25] Some studies have suggested gender interactions showing stronger or weaker effects among women than men, but data specific for women are limited, because most studies have included predominantly male working populations.

Low Socioeconomic Status

Socioeconomic status (SES) is generally defined by interrelated factors such as occupational status, economic resources, education, and social class. The existence of a social gradient in health and disease has long been recognized.[22] Beginning many decades ago, the Whitehall Study of British Civil Servants reported that, even among people who are not poor, there is a social gradient in mortality and morbidity, including CVD, from the bottom to the top of society. Such results have been confirmed in many other contexts, including in the United States. Low SES is accompanied by poorer health habits and higher frequencies of standard CVD risk factors, such as hypertension, obesity, smoking, and unhealthy diet, which, however, partially account for the CVD gradient due to social class. In the Whitehall Study, four health behaviors (smoking, alcohol use, diet, and physical activity), and their variation over the follow-up period, explained 45% of the social gradient for the CVD mortality risk.

Psychosocial and material resources play a critical mediating role in the SES and health connection, and the origins of such effects are apparent as early as in childhood. These include financial hardship, poorer housing, neighborhood status, social discrimination and isolation, depression, and adverse working conditions. Employment instability, unemployment, and job loss are additional correlates of SES that have been related to cardiovascular risk.[26]

At least part of the SES effects on health is related to the neighborhood built environment. Degradation of the neighborhood environment, residential turnover, a decline in property values due to foreclosures, safety concerns, lack of access to healthy foods or opportunities to be physically active may contribute to stress, weight gain, increase in blood pressure, and CVD risk.[27,28] Thus, low SES can be viewed as a composite of chronic stressors that may result in adverse behavioral and physiologic consequences.

HPA axis and autonomic dysfunction is observed as SES levels decline, and may increase the risk for central obesity and metabolic risk factors. The Whitehall II study, for example, described a close relationship between lower social position and increased prevalence of metabolic syndrome and its individual components,[22] an association that was minimally affected by differences in health behaviors. Disturbances in neuroendocrine and cardiac autonomic activity, compatible with activation of the neuroendocrine stress axes, were also noted in subjects with metabolic syndrome and subjects of lower SES status. Notably, psychosocial factors (socioeconomic status and job-related stress) explained a large portion of the association between adrenal/autonomic disturbances and metabolic syndrome.

Social Isolation, Lack of Support, and Marital and Caregiving Stress

Both the number and the quality of a person's social contacts have been related to CVD and total mortality rates. Social relationships may improve health in a variety of ways, such as providing instrumental and emotional support and encouraging a person to follow a healthy lifestyle and seek health care if necessary. Emotional support may also buffer the adverse effects of psychological stressors. Reverse causation is possible in individuals who are ill or otherwise at risk for disease, because they may become less engaged with others.

Although a number of population studies have shown an elevated risk of CVD associated with social isolation or lack of support in initially healthy populations, results are not consistent, perhaps because they may reflect variations in measurements and definitions. The effects appear more robust in prognostic studies of patients with coronary heart disease. Both instrumental and emotional aspects of social contacts have been linked to recurrent events and increased mortality rates in cardiac populations, and in general the association persisted after adjusting for lifestyle behaviors and disease severity. In contrast, structural aspects of support, defined as the size of the network of people surrounding an individual, and his or her interactions with this network, have shown a less consistent association with cardiovascular outcomes; social isolation has been associated with increased mortality rates in population studies, however.[29,30]

Marital status is one aspect of a person's social support that has been studied in some detail. Being married has been related to a lower risk for death from ischemic heart disease in both women and men.[31] Conversely, divorce and marital and caregiving stress have been related to an excess CVD risk.[32] The link between marital stress or marital quality and cardiovascular risk is more established among women, although there is little evidence for a true gender difference.[33,34] Caregiving for an ill family member can be quite stressful, and has also been associated with a risk for CVD and death.[35,36] In the Caregiver Health Effects Study, caregiving was associated with a 63% higher adjusted mortality risk. Caregiving may not affect all caregivers adversely, but it seems especially to be a problem for those who report feeling strain.

Adverse Childhood Experiences

Childhood adversity, such as physical, emotional, or sexual abuse, childhood neglect, or household dysfunction, is an emerging risk factor for CVD. Sixty percent of the U.S. population reports at least one

type of such an adverse experience, and 24% report three or more.

Over the years, several studies have documented a link between childhood maltreatment and a number of medical outcomes in adulthood, including CVD and several CVD risk factors such as obesity, diabetes, and hypertension. Most studies, however, have used a retrospective design. More recently, studies using a prospective assessment of outcome events have confirmed that reporting such early exposures predicts the future cardiometabolic health.[37] Exposure to adversity in childhood has also been linked to a faster rise in blood pressure measured longitudinally from childhood to young adulthood.[38] Many potential behavioral, emotional, and biologic explanations may underlie this relationship.[39] In terms of biologic effects, adverse childhood experiences have been related to enduring changes in multiple organ systems, including the nervous, endocrine, and immune systems, changes that have often been observable since childhood.[40] A repeated or chronic activation of the stress systems in exposed youth, especially the HPA axis, is suspected to play a role, and to exert long-term effects on biologic aging and cardiovascular health. Childhood adversity is also a common antecedent of depression and PTSD, which have both been linked to cardiovascular risk through multiple mechanisms.

Chronic Stress and Cardiovascular Disease: Clinical Implications

There are few data on the potential clinical utility of incorporating measures of chronic stress for CVD risk prediction, for prognostic assessment, or for the clinical management of cardiac patients. Some studies, however, suggest that consideration of factors such as work-related stress, long working hours, or measures of SES in addition to standard risk factors may improve the CVD risk prediction. In a nationally representative population in the United Kingdom, incorporating an index of social deprivation based on census data with other risk factors into a clinical algorithm for CVD risk prediction (the QRISK2) improved the accuracy for identification of people at high risk. Accordingly, current European guidelines on CVD prevention recommend assessment of psychosocial stressors by using standardized instruments or even a brief questionnaire, and recommend tailored clinical management of these factors in individual patients (class of recommendation IIa, level of evidence B).[41] In the United States, no established algorithm currently exists that incorporates SES or other measures of chronic stress for CVD risk assessment, and no such indicators are included in prevention guidelines.

Mental Health and Psychiatric Disorders

Depression, anxiety, and PTSD differ from other psychological factors considered in this chapter because they are psychiatric disorders and as such are amenable to clinical diagnosis and management. Most of the evidence linking these factors to CVD risk, however, has involved the measurement of symptom scales rather than psychiatric diagnoses. Depression has received particular attention and has shown the most robust results for a relationship with CVD.

Depression

Depression is a highly prevalent condition and growing global problem. It is three times more common among cardiac patients than controls, and 15% to 30% of cardiac patients have significant depression.[6] This prevalence is higher in women than men, and is especially elevated in young women with heart

disease.[42]

Depression as a risk factor varies from mild (subclinical) depressive symptoms to a clinical diagnosis of major depression. As defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, major depression is characterized by a depressed mood or anhedonia (loss of interest or pleasure) for at least 2 weeks accompanied by significant functional impairment and additional somatic or cognitive symptoms.

Many metaanalyses of observational studies have been conducted and all have provided evidence for an association between clinical depression (or depressive symptoms) and CVD risk, both among individuals initially free of heart disease, and in a variety of heart disease patient populations, including patients with acute coronary syndromes, congestive heart failure, or stable coronary heart disease and those who have undergone coronary bypass surgery. However, individual studies have produced significantly varied risk estimates and have also varied in their ability to adjust for potential confounding factors such as smoking, physical inactivity, and severity of coronary heart disease. In the most recent metaanalyses of 30 prospective cohort studies conducted among individuals initially free of heart disease, depression was associated with a 30% increased risk of future coronary events.[43] The association remained significant in the group of studies that adjusted for potential confounders, such as lifestyle behaviors and sociodemographic factors. Among patients with coronary heart disease (such as a myocardial infarction) with comorbid depression, the risk for recurrent events or death is also generally elevated compared with nondepressed patients, and the risk is especially high for cardiac death, with a pooled odds ratio of 2.7.[6]

Recent literature has also suggested that depression is a heterogeneous condition in its relationship with CVD, and that specific subtypes may be more important, such as new-onset depression after acute coronary syndromes, treatment-resistant depression, or somatic depressive symptoms as opposed to cognitive symptoms. However, there is no clear consensus on whether these different phenotypes carry variations in risk.

Many potential mechanisms have been postulated for the relationship between depression and CVD.[44] Depression is associated with other cardiovascular risk factors, including smoking, sedentary lifestyle, obesity, diabetes, and hypertension. Although many studies have shown an independent effect of depression on cardiac outcomes after adjusting for these factors, most found that these factors account for a significant portion of the risk for cardiac events associated with depression. In coronary heart disease patients, depression is also associated with a severity of functional impairment. If functional limitations become translated into a decrement in physical activity or self-care, this could accelerate the progression of coronary heart disease. In addition, depressed patients show a lower adherence to medication regimens, lifestyle risk factor modification, and cardiac rehabilitation than nondepressed patients. Thus depression may affect cardiac outcomes via behavioral mechanisms involving a healthy lifestyle, a delay in seeking treatment, and nonadherence to secondary prevention. However, whether, and the extent to which, these factors mediate the effect of depression on cardiac outcomes is not clear.

Depression is characterized by dysregulation of the HPA axis and the sympathoadrenal system, with increased, or prolonged, release of cortisol and norepinephrine and disruption of normal circadian patterns. For example, the awakening cortisol response, as well as the nighttime cortisol levels, tends to be increased in depression. In addition, HPA axis hyperactivity has been observed in remitted depression and in nonaffected offspring, suggesting that it may represent a vulnerability factor, possibly a genetic one, rather than a state indicator.[44,45] Although longitudinal data are limited, higher morning cortisol levels and a flatter slope in cortisol across the day have been associated with an increased risk of subsequent cardiovascular death; a higher cortisol response to an acute stressor has also been linked to incident

hypertension.[46]

Several studies have also shown that depressed individuals have reduced parasympathetic flow and lower heart rate variability, a noninvasive measure of cardiac autonomic function, although data are not entirely consistent and antidepressant treatment may also be involved in these effects.[44] Additional indications of autonomic dysfunction that have been described in depressed cardiac patients include an increased heart rate response to orthostatic challenge, an abnormal heart rate response to premature ventricular contractions, and abnormal ventricular repolarization. All these factors are predictors of death in cardiac patients.

Neurobiologic and autonomic abnormalities in depression, as described above, may lead to repeated or sustained elevations in blood pressure, heart rate, and plasma glucose; insulin resistance; and dyslipidemia, as well as systemic inflammation and endothelial dysfunction. In particular, metabolic and immune dysregulation have consistently been reported as frequent correlates of depression. Depression may also facilitate weight gain as a result of inactivity and an unhealthy diet, which in turn promotes metabolic alterations and inflammation. Recent metaanalyses reported significantly higher levels of inflammatory markers, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, in depressed subjects compared with controls.[47] However, effect sizes were modest, with slightly stronger effects for studies using clinical diagnoses of depression rather than symptom scales.[48] Furthermore, results in CVD patients are inconsistent, and to date there is no strong evidence that inflammation is a mechanism in the link between depression and cardiovascular outcomes. Rather, it is likely that there is a bidirectional link between inflammation and depression. For example, immunotherapy with interferon-α can precipitate depression. Cytokines produced peripherally can access the brain, and can induce behavioral responses analogous to a depressive episode.[49] Some evidence also suggests that marked inflammation during an acute coronary syndrome predicts depression onset.[50]

Finally, growing evidence suggests that depression and CVD may be different phenotypic expressions of the same genetic substrate.[51] Such genetic pleiotropy may also underlie the relationship between depression and biologic pathways of risk that are implicated in CVD, such as inflammation or autonomic nervous system and metabolic dysregulation.[44,51] Genes involved in these pathways could be precursors of both depression and CVD, leading to a noncausal association between these two phenotypes.

Anxiety

Anxiety, like depression, includes a large spectrum of conditions, from psychiatric diagnoses amenable to clinical treatment, to subthreshold symptoms that are common in the general population. These are prevalent conditions; as many as 18% of Americans may be affected by one or more anxiety disorders. In general, the various anxiety disorders (generalized anxiety disorder, panic disorder, phobic anxiety, and obsessive-compulsive disorder, among others) are distinct, but they also share a broad range of common features and frequently occur together. Most studies examining the relationship between anxiety and coronary heart disease have considered anxiety symptom scales rather than a clinical diagnosis of anxiety disorder. Study results for an association between anxiety and risk of CVD overall point toward a small increased risk.[2] Studies have differed in their measurement of anxiety, and very few examined clinically diagnosed anxiety disorders, which may differ in their biologic substrate and therefore their relationship with CVD. Anxiety often coexists with depression, and few studies have attempted to tease apart these two conditions; this separation may hardly be feasible given the high correlation between them. Alternatively, this high comorbidity may argue for anxiety and depression as linked constructs and their impact on CVD risk may be reflective of shared components of depression and anxiety, such as more

general distress.[52]

One cognitive aspect of anxiety that might be particularly relevant to CVD risk is rumination, a form of uncontrollable intrusive thinking about something distressing. Rumination has not only been implicated in chronic distress and depression, but also in the development of CVD.[52] Phobic anxiety and panic attacks have also been associated with CVD risk and sudden death in population studies.

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is caused by exposure to a psychologically traumatic event, defined as a threat to life to self or someone close. Traumas can include events such as military combat, childhood abuse, sexual assault, or a motor vehicle accident. Most people think of PTSD as a disorder of veterans; however, in absolute numbers, there are more civilians with PTSD from noncombat events than there are veterans with combat-related PTSD. The lifetime prevalence of PTSD in civilians has been estimated at 1.3% to 7.8%.[53] Although trauma is required for the development of PTSD, only a minority of individuals exposed to trauma will develop the disorder. PTSD is a highly disabling condition; its symptoms are classified in main clusters of reexperiencing (e.g., recurrent memories of the traumatic event that the patient cannot control), avoidance (avoiding things that would remind the person of the trauma), and hyperarousal (e.g., trouble falling or staying asleep, irritability, outbursts of anger, and difficulty concentrating).

In the neurobiologic aspects of PTSD, brain areas involved in both fear and memory are affected, including the hippocampus, prefrontal cortex, and amygdala,[54] as well as stress-responsive neuroendocrine systems including the HPA axis and the sympathetic nervous system that may affect cardiovascular risk.[53]

Growing evidence links PTSD to an increased risk of CVD; across studies, PTSD has been associated with an approximately 50% increased risk for coronary heart disease.[55] Emerging data also suggest that PTSD may be a consequence of, in addition to a cause of, acute, life-threatening cardiovascular events. Among patients with acute coronary syndromes or acute stroke, PTSD is prevalent (10% to 20%) and leads to approximately a doubling of subsequent events.[56,57]

As for other psychiatric disorders, individuals with PTSD are more likely to engage in adverse lifestyle behaviors, such as inactivity and low adherence, which may predispose to cardiovascular risk factors such as obesity, diabetes, and hypertension. The avoidance symptoms of PTSD can lead to social isolation and a lack of emotional and material resources. PTSD is also frequently comorbid with other psychiatric conditions that may affect cardiovascular risk, such as depression and substance abuse. However, direct biologic mechanisms are also plausible. An emerging model postulates that intrusive memories and other symptoms of reexperiencing in PTSD, as well as hyperarousal symptoms, may lead to repeated, heightened physiologic activation, which, in turn, may cause cumulative long-term damaging effects on the cardiovascular system. These effects may occur through vascular and immune mechanisms.[58]

Mental Health and Psychiatric Disorders: Clinical Implications

Despite the important comorbidity between depression and physical illness, less than half of depressed medical patients are recognized by their physicians, and during an admission for acute myocardial infarction, less than 15% of patients with depression are identified.[59] One reason for this may be uncertainty about whether depression treatment will improve outcomes and thus whether systematic depression screening is warranted in cardiac patients. Indeed, studies to date have not proved that treating

depression can improve cardiovascular outcomes. Investigation in this area has been limited, however. Furthermore, depression remains an important illness in and of itself, which deserves proper evaluation and treatment. In addition to affecting the prognosis, depression substantially affects the quality of life of cardiac patients, and is one of the strongest predictors of nonadherence with medical treatment regimens, which may improve if depression improves.[60] By recognizing and treating depression, we can improve patients' overall well-being and their adherence to medical treatments and healthy lifestyle behaviors. Because the literature overall points to depression as a risk factor and a prognostic factor for CVD, it is reasonable for clinicians to evaluate depression as they would any other risk factor, such as smoking and diabetes.[6]

According to the American Heart Association/American College of Cardiology current guidelines for secondary prevention in patients with CVD, screening for depression is reasonable if patients have access to case management in collaboration with their primary care physician and mental health specialist (class IIa, level of evidence B). Treatment of depression is reasonable for its clinical benefits other than improving CVD outcomes (class IIb, level of evidence C). Patients with severe depressive symptoms or a clinical diagnosis of depression should be evaluated in concert with a mental health specialist as needed.

Anxiety disorders are highly prevalent, and regardless of their possible association with CVD risk, they can cause considerable disability and an impaired quality of life. Anxiety often coexists with depression; in this case, the corresponding impact on quality of life is even higher. Thus, these conditions warrant attention from the cardiologist.

PTSD is emerging as a risk factor for CVD and could also be a consequence of an acute cardiovascular event. Given that almost 1½ million patients are discharged from U.S. hospitals each year with a diagnosis of acute coronary syndrome, over 150,000 patients could develop clinically significant PTSD symptoms as a result (**see also Chapter 58**).[56] Thus, PTSD could contribute substantially to repeat hospitalizations, mortality rates, and health care costs for cardiac patients. Nonetheless, as for depression, the utility of routinely screening for PTSD symptoms in cardiac patients is unknown, particularly in the nonveteran population at large (see also next section). Pharmacologic and psychotherapeutic approaches for the treatment of PTSD and other anxiety disorders are available,[61] and thus recognition and treatment of these disorders could have at least theoretical benefits for symptomatic and functional improvement. The benefit in reducing CVD risk, however, is untested.

Personality Traits

Anger and Hostility

The potentially harmful effects of chronic feelings of anger on health have been suspected since ancient times. Not surprisingly then, anger, hostility, and related constructs have received considerable attention as potential risk factors for CVD. Despite being different constructs, anger and hostility are often used interchangeably, and their interconnection is poorly defined. Hostility is a personality or cognitive trait characterized by a negative attitude toward others. It is one of the dimensions of the type A personality that was believed, in early research, to be a risk factor for CVD, a relationship not supported by later investigation. Anger is an emotional state or trait, characterized by feelings ranging from mild irritation to intense fury or rage toward others. An outburst of anger is a fairly well established trigger of acute coronary events and is discussed earlier in this chapter, in the section on acute stress. Anger as a personality trait, however, is a less established risk factor for CVD. Studies have reported heterogeneous results, with about half of the studies failing to find a significant association between anger or hostility

and coronary heart disease. Although evidence is inconsistent, chronic feelings of anger, cynical distrust, and hostility are at least modestly associated with a risk of both the initiation and progression of CVD.[62] The summary combined estimate for anger and hostility from metaanalyses indicated a modest (<20%), but significant, increase in coronary heart disease incidence in initially healthy populations and a 24% increase in recurrent coronary heart disease events in patients with preexisting coronary heart disease. However, studies of higher quality tended to show smaller and nonsignificant effects. The risk associated with anger and hostility appears to be more marked in men, and is in large part explained by behavioral factors such as smoking and physical activity. Anger and hostility have also been linked to stress reactivity, exaggerated autonomic function, reduced heart rate variability, inflammation, and platelet aggregation.[62]

Type D Personality

The type D (or “distressed”) personality, first introduced in 1995 by Denollet and colleagues, is a personality type that combines negative affectivity and social inhibition.[63] It describes individuals who tend to experience negative emotions (dysphoria, tension, worry) and at the same time are inhibited in their expression of emotions, thoughts, and behaviors in a social context. These investigators were able to link this construct to adverse cardiovascular outcomes and total death in a number of studies of CVD patients. Because type D personality is related to other psychosocial characteristics (hostility, anger, depression, and social isolation), its interconnection with these other factors needs more evaluation. However, this personality type appears to be a predictor independent of depression and other psychosocial stressors. These authors propose that it is the combination of these two traits (negative affect and social inhibition) that is damaging, rather than either one alone.

Personality Traits and Cardiovascular Disease: Clinical Implications

Although literature on personality traits and CVD dates back many decades, consistency of results has been an issue. Particularly for anger and hostility, the effect size appears small; whether personality traits provide predictive and prognostic information above and beyond other better-established psychosocial factors and traditional CVD risk factors needs more evaluation. Finally, it is unclear as to what extent these personality traits may be modifiable by interventions. Because of these issues, the clinical significance of these observations is not well established.

Evaluation and Management of Mental Health in the Cardiac Patient (See Also Chapter 58)

General Considerations

Recognition of psychological and psychiatric factors should be considered in the management of the cardiac patient. Psychological factors are important, not only because these conditions are highly prevalent and affect patients' well-being and quality of life, but also because they act as barriers to treatment adherence, obtaining follow-up care, and enacting lifestyle changes. Yet, psychological and psychiatric conditions are less likely to be recognized and managed in current cardiology practice than traditional CVD risk factors. This is because of complexities in definition and assessment, as mentioned above, but also because many symptoms of psychological distress are easily confused with physical disease, for example, fatigue, weight loss, poor appetite, or trouble sleeping.

There is no consensus on whether screening for and treatment of emotional problems, such as depression, anxiety, and PTSD, should be systematically carried out in cardiac patients. That is because it is uncertain whether screening for and treating these problems will translate into a better quality of life or an improved prognosis. Additionally, clinical trials of psychological or psychiatric interventions have thus far only yielded modest improvements in psychological well-being, with null or uncertain effects on cardiac outcomes. Despite this controversy, psychological interventions, such as individual or group counseling, stress management, support for self-care, and pharmacotherapy, are likely to add benefit for the control of standard risk factors, for the promotion of a healthy lifestyle, and for the management of psychological distress when added to standard cardiac rehabilitation or as part of a coordinated care management approach. Such programs require substantial resources and commitment from both patients and staff. However, their potential benefits in improving psychological well-being should not be discounted.

Current clinical guidelines in the United States only mention depression as a psychosocial factor that is reasonable for the non–mental health clinician to recognize if patients have access to adequate care support systems (class of recommendation IIa, level of evidence B). These guidelines further state that treatment of depression may be reasonable for its clinical benefits other than improving CVD outcomes (class IIb, level of evidence C).[64] In contrast, the European guidelines, while noting limitations for depression screening, recognize the importance of a comprehensive approach for the detection of psychosocial risk factors, using at least a preliminary assessment with a short series of yes-and-no questions, and recommend a multimodal behavioral intervention approach integrating health education, physical activity, and psychological therapy (class Ia, level of evidence A).[41] In the case of clinically significant symptoms of depression or other psychosocial factors, the European guidelines recommend consideration of interventions such as psychotherapy, medication, or collaborative care (class IIa, level of evidence A).

Psychotherapy

Psychotherapy helps people with depression understand the behaviors, emotions, and ideas that contribute to depression, regain a sense of control and pleasure in life, and learn coping skills.[65] Psychodynamic therapy is based on the assumption that a person is depressed because of unresolved, generally unconscious conflicts, often stemming from childhood. Interpersonal therapy focuses on the behaviors and interactions with family and friends. The primary goal of this therapy is to improve communication skills

and increase self-esteem during a short period of time. Cognitive behavioral therapy (CBT) involves examining thought patterns that can be negative and self-defeating, and going over the basis of such thoughts and how they contribute to emotions and poor outcomes. Psychotherapy has been shown to be as effective as medications for depression, and some people, especially with early life stress issues, may not respond to medication without psychotherapy.

Because of the increased risk of death in cardiac patients with depression, it was assumed that successful treatment of depression would reduce this risk. The ENRICHD (Enhanced Recovery in Coronary Heart Disease Patients) trial, however, did not find such a beneficial effect of a psychological intervention involving CBT and social learning for cardiac outcomes (patients with severe depression also received psychopharmacologic intervention). The average improvement in depression in comparison with placebo, however, was modest. In post hoc analyses, patients who responded to treatment did have a better outcome than those who did not respond.[66]

Other types of therapy have been shown to be useful for depression and anxiety. These include interpersonal therapy, stress management and stress reduction techniques such as deep breathing, progressive muscle relaxation, yoga, meditation, and mindfulness-based stress reduction.

Antidepressant Medications

Antidepressant medications are another proven method for the treatment of depression and other mental disorders associated with an increased risk for cardiovascular disease, such as PTSD.[67] Antidepressants appear to be more effective in patients with moderate or severe depression than patients with mild depression. Antidepressants act on the serotonin and norepinephrine systems, as well as other neurotransmitter systems, in the brain. Drugs that increase brain levels of serotonin and norepinephrine have been shown to be effective treatments for both depression and anxiety. Many antidepressants bind to proteins called transporters that are responsible for taking the neurotransmitter back up into the neuron after it has been released into the synapse, therefore causing an increase in neurotransmitter at the synapsis level. Many of the antidepressant drugs block the serotonin transporter or the norepinephrine transporter, or a combination of the two. Other antidepressants exert their actions by binding to various receptors that control neurotransmitter function in the brain. The original drugs, the tricyclics, had a more general effect on neurotransmitter function.

Tricyclic Antidepressants

Tricyclics represent the first class of medications found to work for the treatment of depression. They include imipramine (Tofranil), doxepin (Sinequan), amoxapine (Asendin), nortriptyline (Aventyl, Pamelor), and amitriptyline (Elavil). Tricyclics increase norepinephrine and serotonin levels in the synapse. The most common side effects of the tricyclics are the anticholinergic side effects, which include dry mouth, constipation, memory problems, confusion, blurred vision, sexual dysfunction, and decreased urination. Tricyclics have properties like quinidine, leading to an increase in the PR interval, a prolongation of the QRS duration and QT interval, and a flattening of the T wave on the electrocardiogram (**see also Chapter 12**) . These effects are usually not of clinical significance. However, tricyclics should be avoided in patients with preexisting cardiac conduction defects, a prolonged QT interval, congestive heart failure, or a recent myocardial infarction. Prolongation of the QT interval beyond 0.44 seconds is associated with an increased risk of malignant ventricular arrhythmias (torsade de pointes). Indeed, tricyclic medications have been associated with an increased risk of malignant ventricular arrhythmias and sudden cardiac death (**see also Chapters 8, 34, and 42**). For

patients who suffer a cardiac event while being treated with a tricyclic, abrupt withdrawal from the tricyclic medication can be associated with an increased risk of arrhythmias. Therefore, these medications should be tapered slowly over a period of time, assuming the cardiac arrhythmia is manageable. If prolongation of the QT interval or development of hypotension in patients treated with a tricyclic becomes a problem, patients should be slowly tapered off of tricyclics and treated with a selective serotonin reuptake inhibitor (SSRI), venlafaxine, or bupropion (see below). These latter medications are preferred in patients who develop a new onset of depression after an acute myocardial infarction.

The anticholinergic side effects of the tricyclics are especially troublesome for elderly persons, because these patients are more susceptible to the memory impairment and orthostatic hypotension associated with these medications. For this reason, it is recommended that tricyclics not be prescribed for elderly persons.

Selective Serotonin Reuptake Inhibitors

The selective serotonin reuptake inhibitors (SSRIs) include fluoxetine (Prozac, Sarafem), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), escitalopram (Lexapro), and sertraline (Zoloft). They act by blocking the transporter that brings the serotonin back from the synapse into the neuron, and thus have a different side effect profile than tricyclics, specifically fewer to no anticholinergic and cardiac effects, which make them the antidepressant medications of choice in the cardiac patient population.

SSRI medications have not been shown to have greater efficacy in the treatment of depression than the older tricyclics, although a larger number of patients drop out of treatment while taking tricyclics because of side effects. In general, SSRIs, like the older tricyclics, have only modest efficacy over placebo. About 80% of the improvement with antidepressants comes from the placebo response. Patients with mild or moderate depression do not have clinically meaningful responses to antidepressants, whereas those with severe depression have more substantial responses.

The primary advantage of SSRIs in the cardiac patient is less risk of cardiovascular and anticholinergic side effects. Side effects of SSRIs include nausea, diarrhea, headache, insomnia, and agitation. One of the most troubling side effects of the SSRIs is sexual dysfunction, which includes loss of libido, delayed ejaculation, and erectile dysfunction. Antidepressants without sexual dysfunction side effects can be given instead of an SSRI in these cases, including bupropion (Wellbutrin), mirtazapine (Remeron), and trazodone (Desyrel), all drugs not in the SSRI class.

SSRI treatment, especially with fluoxetine, is associated with an increase in risk of bleeding. For the cardiac patient taking aspirin or other antiplatelet or anticoagulation treatment, this can be an important issue. SSRIs stopped suddenly can also result in a potent withdrawal syndrome, including agitation, nervousness, and sometimes suicidal thoughts. SSRIs can cause akathisia and other extrapyramidal side effects, as can the antipsychotics. Akathisia includes feelings of restlessness, pacing, and internal stiffness, which subjectively are very uncomfortable. However, these symptoms are not common, and are treatable with benzodiazepines or low doses of propranolol. A more troubling problem is the potential for suicidality associated with SSRIs. *All* antidepressant medications may carry an increased risk of suicide.

Short-term trials of SSRIs have found them to be safe and effective for cardiac patients. Although treatment of depression has not been demonstrated to improve cardiac outcomes, in a number of trials treatment responders appeared to have better cardiac outcomes than nonresponders, suggesting that the response to treatment may be a key factor.[66] Several observational studies, however, have shown an increased cardiac risk with longer-term use of SSRIs, especially cardiac death. A recent Danish nationwide study, for example, found a significant association between SSRI (as well as tricyclic

antidepressant) use and out-of-hospital cardiac arrest, especially for citalopram and nortriptyline, whereas no association was found for other classes, such as the norepinephrine reuptake inhibitors and the serotonin-norepinephrine dual reuptake inhibitors.[68] An earlier analysis of the Nurses' Health Study in the United States also found that antidepressant use was associated with a threefold higher risk of sudden cardiac death, even after adjusting for the severity of depression and risk factors for coronary heart disease.[69] There was an equal risk for SSRIs as for other antidepressants outside of the SSRI class. However, it should be kept in mind that sudden cardiac death in presumably healthy people is fairly rare, and thus potential risks need to be weighed against potential benefits.

Norepinephrine Reuptake Inhibitors

Antidepressant medications designed to specifically block reuptake of norepinephrine into the synapse are called norepinephrine reuptake inhibitors, or NRIs. Medications in this group include desipramine (Norpramin) and reboxetine (Edronax, Vestra). They have a more favorable profile in terms of anticholinergic side effects and effects on the heart and blood pressure than the tricyclics.

Serotonin and Norepinephrine Dual Reuptake Inhibitors

The latest group of antidepressants has dual reuptake inhibition for serotonin and norepinephrine (SNRIs), and includes venlafaxine (Effexor) and duloxetine (Cymbalta). In general, these drugs have shown a better treatment response for depression than SSRIs and tricyclics. When multiple studies were combined, with the treatment response defined as at least a 50% reduction in symptoms of depression, venlafaxine had a success rate of 74%; this rate was significantly better than SSRIs, with a 61% success rate, and tricyclics, with a 58% success rate.

SNRIs, however, can cause a number of side effects. Both venlafaxine and duloxetine can cause dizziness, constipation, dry mouth, headache, changes in sleep, or more rarely a serotonin syndrome, with restlessness, shivering, and sweating. Venlafaxine has been associated with a dose-dependent increase in blood pressure, which is of particular concern for cardiac patients, especially those with preexisting hypertension. Although not well studied, there is a good possibility that duloxetine has similar effects. Venlafaxine seems to carry the greatest risk of suicidality amongst all of the antidepressants, with a threefold increased risk of attempted or completed suicides.

Monoamine Oxidase Inhibitors

Drugs that block the monoamine oxidase inhibitor enzyme (MAOI drugs), and therefore boost the monoamines (serotonin, norepinephrine), include phenelzine (Nardil) and tranylcypromine (Parnate). They have a more favorable cardiovascular profile than the tricyclics, with little or no effect on cardiac conduction, although they can be associated with orthostatic hypotension and weight gain. They can cause a “wine and cheese reaction” of potentially life-threatening elevations of blood pressure if taken with foods that are high in tyramine content, including wine, cheese, chocolate, and beer. Medications that can precipitate hypertensive reactions if a patient is also taking an MAOI include those with sympathomimetic effects (e.g., amphetamines, ephedrine, cocaine). MAOIs should also not be taken together with meperidine (Demerol). Due to the risk of hypertensive crises, the MAOIs are not recommended for use in cardiac patients, and indeed they are no longer commonly prescribed in general.

Antidepressants with Novel Mechanisms of Action

Some drugs act on various neurotransmitter systems or in general are poorly understood in terms of their

mechanism of action. Bupropion (Wellbutrin) primarily acts on dopamine systems, and is used for both depression and smoking cessation under the brand name Zyban. Side effects include weight loss and restlessness, as well as possible increases in blood pressure; high doses can rarely cause seizures. Mirtazapine (Remeron) is a quatrocyclic antidepressant that has actions on a number of different receptor systems. It blocks presynaptic noradrenergic alpha-2 receptors with associated enhancement of norepinephrine release. Mirtazapine also increases serotonin release. Side effects include sweating and shivering, tiredness, strange dreams, dyslipidemia, weight gain, anxiety, and agitation. It can be associated with mild orthostatic hypotension and anticholinergic side effects. Short-term randomized trials in cardiac patients have not shown an increase in mortality or cardiovascular events associated with these medications.

Other drugs with mixed actions include trazodone (Desyrel) and maprotiline (Ludiomil). The profile of these medications appears safe in terms of anticholinergic side effects and effects on the heart and blood pressure. Trazodone can rarely cause priapism, however (extended painful erection that requires emergency treatment). It is a safe and often effective medication for induction of sleep that does not carry the potential risk of tolerance, as do zolpidem (Ambien) and related insomnia medications.

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is used as a last resort for the treatment of depression in patients who have had multiple failed trials of psychotherapy and medication. ECT has an 80% response rate, which is a better response rate than for medications, and contrary to popular belief, is a safe procedure. ECT causes profound hemodynamic changes, including bradycardia (up to frank asystole, which may last for a few seconds), followed by tachycardia and hypertension. These effects, however, are transient and typically resolve within 20 minutes. Possible complications include persistent hypertension, arrhythmias, asystole lasting more than 5 seconds, ischemia, and heart failure. Older age and preexisting CVD, including hypertension, coronary artery disease, congestive heart failure, aortic stenosis, implanted cardiac devices, and atrial fibrillation, have been associated with increased complication rates. However, most complications remain minor and transient, and the vast majority of patients can safely complete treatment.

There are no absolute contraindications to ECT. However, the procedure should be delayed in patients who are hemodynamically unstable, or have new-onset or uncontrolled arrhythmias or hypertension. In patients with stable coronary heart disease and controlled hypertension, medications can be continued through the morning of the procedure. In patients with an implanted pacemaker, the pacemaker should be tested before and after ECT; the magnet should be placed at the patient bedside in the event that electrical interference leads to pacemaker inhibition and bradycardia. ECT appears safe in patients with an implantable cardioverter-defibrillator (ICD). The detection mode of the ICD should be turned off during ECT, and continuous electrocardiographic monitoring should be performed, with resuscitative equipment by the patient bedside in the event that external defibrillation is necessary.

Anxiolytic Medications

Benzodiazepine Medications

In the 1960s benzodiazepines displaced barbiturates as the most commonly used treatment for insomnia, and became commonly used in patients with anxiety and depression. They were originally marketed as having less potential for dependence and abuse, although this did not bear out over time. Benzodiazepines

act on a receptor in the brain called the GABA-benzodiazepine receptor complex. This is the same complex that alcohol and the inhibitory transmitter GABA bind to, although benzodiazepines have their own binding site. The benzodiazepines most commonly prescribed today include alprazolam (Xanax), which is mainly used for anxiety attacks and panic disorder; clonazepam (Klonopin), which is used for epilepsy; and temazepam (Restoril). Other benzodiazepine medications that are longer acting and that are still sometimes used in the treatment of insomnia include oxazepam (Serax), lorazepam (Ativan), chlordiazepoxide (Librium), clorazepate (Tranxene), and diazepam (Valium), among others. Differences in the individual benzodiazepines are related to the time of onset of action and duration of effect. On average, benzodiazepines increase the user's sleep time by about 1 hour per night.

The side effects from benzodiazepines during the day can cause serious problems. These include daytime drowsiness, dizziness, light-headedness, and memory problems, as well as increased motor vehicle accidents. Use of benzodiazepine medications is associated with a 60% increase in road traffic accidents. The risk is increased further with concurrent alcohol usage and in older age. All medications for insomnia are not recommended for long-term use.

The primary concern in the cardiac patient using benzodiazepines is a potential risk of respiratory suppression. For this reason, benzodiazepines with a shorter half-life should be preferred to those with a longer half-life in cardiac patients. In patients with cardiac disease and associated pulmonary impairment, these medications should be used with caution.

Nonbenzodiazepine “Z-Drug” Medications

The newer generation of insomnia mediations, zaleplon (Sonata), zolpidem (Ambien), eszopiclone (Lunesta), and zopiclone (Imovane), or Z drugs, act on specific subsets of the GABA receptor. They are commonly called “nonbenzodiazepine” medications, but the name is misleading, because they bind to the same GABA-benzodiazepine receptor complex in the brain to which benzodiazepines and alcohol bind. The difference is that they bind to a different part of the same receptor complex. They have been marketed as having less dependency and fewer side effects than the older generation of benzodiazepine medications, and some argue that these drugs have less potential for abuse than the benzodiazepines. However, studies have not shown them to be more effective or safe than the benzodiazepines, and no difference between the different Z drugs for safety or efficacy has been established. As for benzodiazepines, general side effects for all of these medications include memory impairment, drowsiness, and dizziness. An increased risk of road traffic accidents was also seen with zopiclone. Zaleplon has a much shorter half-life (1 hour) than zolpidem (2.5 hours) or eszopiclone (6 hours), and is therefore promoted as being associated with less drowsiness the next day.

Medications with Other Mechanisms of Action

Rozerem (Ramelteon) is a melatonin receptor agonist that is used for insomnia. Side effects include headache, drowsiness, fatigue, nausea, dizziness, and more rarely diarrhea and depression. Advantages of this medication are the absence of abuse potential and the lack of withdrawal symptoms.

Buspirone (Buspar) is an agonist of the serotonin 1A receptor and relatively free of next-day drowsiness and memory impairment, or the potential for dependence or abuse. Buspirone is efficacious in the treatment of anxiety and is preferable to the benzodiazepines for the treatment of the cardiac patient because it lacks respiratory suppressive effects. Side effects are minimal, and include nausea, headache, and light-headedness. A rare side effect is the perception that someone is standing beside the bed when a patient is asleep. There are no known adverse cardiac effects.

Alternative Medicines and Supplements

There are some natural remedies that have been recommended for depression and anxiety. Few large controlled studies have evaluated these approaches, however, and the quality of the research has been highly variable.

St. John's Wort

St. John's wort *(Hypericum perforatum)* is a popular medication for the over-the-counter treatment of mild depression; 12% of Americans report using it at least once a year. St. John's wort has action similar to antidepressants, including monoamine oxidase inhibition, serotonin reuptake inhibition, and actions on sigma receptors. Overall, studies have found that St. John's wort monotherapy for mild and moderate depression is superior to placebo in improving depressive symptoms, with possibly fewer side effects. However, evidence of heterogeneity and a lack of research on severe depression limit the quality of the evidence.[70] St. John's wort can interact with a number of medications, including digoxin, theophylline, protease inhibitors, and cyclosporine.

Omega-3 Fatty Acids

Low dietary intake and low serum or red blood cell levels of omega-3 fatty acids are associated with depression in patients with and without coronary heart disease, and with an increased risk for cardiac death. Two omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid, are found in high concentrations at neuronal synapses in the human brain and are essential for neuronal functioning. In depressed psychiatric patients who were otherwise medically healthy, several studies have indicated that supplementation with omega-3 fatty acids improves the efficacy of antidepressants; among patients with CVD, however, results have been mostly null.[71]

Exercise

A number of studies, dating from the mid-1990s to more recently, have shown that various forms of exercise improve depression (**see also Chapter 53**). Metaanalyses have consistently reported moderate to large effects of exercise on depression, denoting a clinically significant improvement of the same magnitude as psychological or drug treatment.[72]

It has also been shown that a half-hour a day of exercise 6 days a week is an effective exercise “dose” to improve the mood of people who have mild to moderate depression. Therefore, aerobic exercise at a dose consistent with public health recommendations for CVD prevention is also an effective treatment for mild to moderate depression. Exercise may also complement the effects of antidepressant medication in depressed patients who do not have a complete response to medication.

Summary of Management Considerations

Even though treatment of depression or anxiety has not been shown to improve cardiovascular outcomes in the cardiac patient, it is still necessary to recognize and manage these problems if they are severe or persistent, in order to promote patient wellness and quality of life, as well as improve patients' ability to adhere to treatments and lifestyle recommendations.

In many cases the cardiologist can address the problem without the need for an immediate referral to a psychiatrist. Many patients complaining of “anxiety” may actually be worried about their cardiac

condition. In this situation, educating the patient about the cardiac condition, listening to the patient's concerns, and allowing the patient to talk about the worries may go a long way toward relieving distress. The next step is to determine if the patient is having thoughts of taking his or her own life or is having severe impairment in functioning that would necessitate referral to a psychiatrist, psychologist, or social worker; this depends on the severity of the condition and the type of treatment that might be appropriate (medications versus psychotherapy or counseling).

The cardiologist may also start a trial of medication. Benzodiazepines can be used in the short term to manage anxiety but should be limited to less than 2 weeks in order to reduce the risk of developing dependence. They can be useful, however, in the time period before antidepressants start working. An alternative for the treatment of anxiety that does not have the risk of dependence or respiratory suppression is buspirone. Antidepressants useful in the cardiac patient include SSRIs (paroxetine, fluoxetine, sertraline, and others), mirtazapine, and bupropion. Patients who fail to respond to these medications may respond to venlafaxine or duloxetine, with careful monitoring of blood pressure. A healthy lifestyle, especially with physical activity, should always be recommended, tailored to patients' functional capabilities, to decrease depression and improve well-being. There are many self-help books that patients can buy to teach themselves stress reduction techniques, in addition to resources in the community such as counselors and social workers that can teach these skills either individually or in classes.

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97

Neurologic Disorders and Cardiovascular Disease

William J. Groh, Gordon F. Tomaselli, Douglas P. Zipes

Cardiologists are increasingly being asked to play an integral part in the medical team evaluating and treating patients with a primary neurologic disorder because of the potential for associated cardiac morbidity and mortality. In several disorders, the cardiovascular manifestations are responsible for a greater risk than that attributable to the neurologic manifestations. This chapter reviews those neurologic disorders associated with important cardiovascular manifestations or sequelae.

The Muscular Dystrophies

The muscular dystrophies are a group of inherited skeletal muscle diseases. Most also have direct effects on cardiac muscle, with manifestations including heart failure, conduction disease and heart block, atrial and ventricular arrhythmias, and sudden death. With improved multidisciplinary care, patients are living longer and an increasing proportion manifest cardiac disease. The following muscular dystrophies are associated with cardiovascular involvement:

- Duchenne and Becker muscular dystrophies
- Myotonic dystrophies
- Emery-Dreifuss muscular dystrophies and associated disorders
- Limb-girdle muscular dystrophies
- Facioscapulohumeral muscular dystrophy

Duchenne and Becker Muscular Dystrophies

Genetics

Both Duchenne muscular dystrophy and Becker muscular dystrophy are X-linked recessive disorders caused by mutations in the large dystrophin gene (**see also Chapters 7 and 33**). The dystrophin protein and dystrophin-associated glycoproteins provide a structural link between the myocyte cytoskeleton and extracellular matrix functioning to link contractile proteins to the cell membrane. Dystrophin messenger RNA is expressed predominantly in skeletal, cardiac, and smooth muscle, with lower levels in the brain. Absence of dystrophin leads to membrane fragility resulting in myofibril necrosis and eventual loss of muscle fibers with fibrotic replacement. Abnormalities in dystrophin and in dystrophin-associated glycoproteins underlie the degeneration of cardiac and skeletal muscle in several inherited myopathies, including X-linked dilated cardiomyopathy. Cardiac myocytes lacking dystrophin are susceptible to mechanical damage.[1] Beyond the inherited disorders, the loss of dystrophin plays a role in myocyte failure in other cardiomyopathies, including sporadic idiopathic cardiomyopathy, viral myocarditis, and cardiomyopathies associated with coronary artery disease. In Duchenne muscular dystrophy, dystrophin is nearly absent, whereas in Becker muscular dystrophy, dystrophin is present but reduced in size or amount. This leads to the characteristic rapidly progressive skeletal muscle disease in Duchenne and the more benign course in Becker muscular dystrophy. Cardiac involvement is seen in both disorders, and the severity is not correlated with the severity of skeletal muscle involvement. Mutations in specific domains of the dystrophin gene are associated with a higher risk for cardiomyopathy.[2]

Clinical Presentation

Duchenne muscular dystrophy is the most common inherited neuromuscular disease, with an incidence of 1 case in 3600 to 6000 live male births.[3] Patients typically present with skeletal muscle weakness before the age of 5 years, which progresses if untreated such that boys become wheelchair-bound by their early teens (**Fig. 97.1**). Historically, death occurs by age 25 years, primarily from respiratory dysfunction and less often from heart failure. A multidisciplinary treatment approach, including steroids, scoliosis surgery, ventilatory support, and cardiac therapy, has improved survival rates.[4] Becker muscular dystrophy is less

common than Duchenne muscular dystrophy, is associated with a more variable presentation of skeletal muscle weakness (**see Fig. 97.1**), and carries a better prognosis, with most patients surviving to the age of 40 to 50 years.

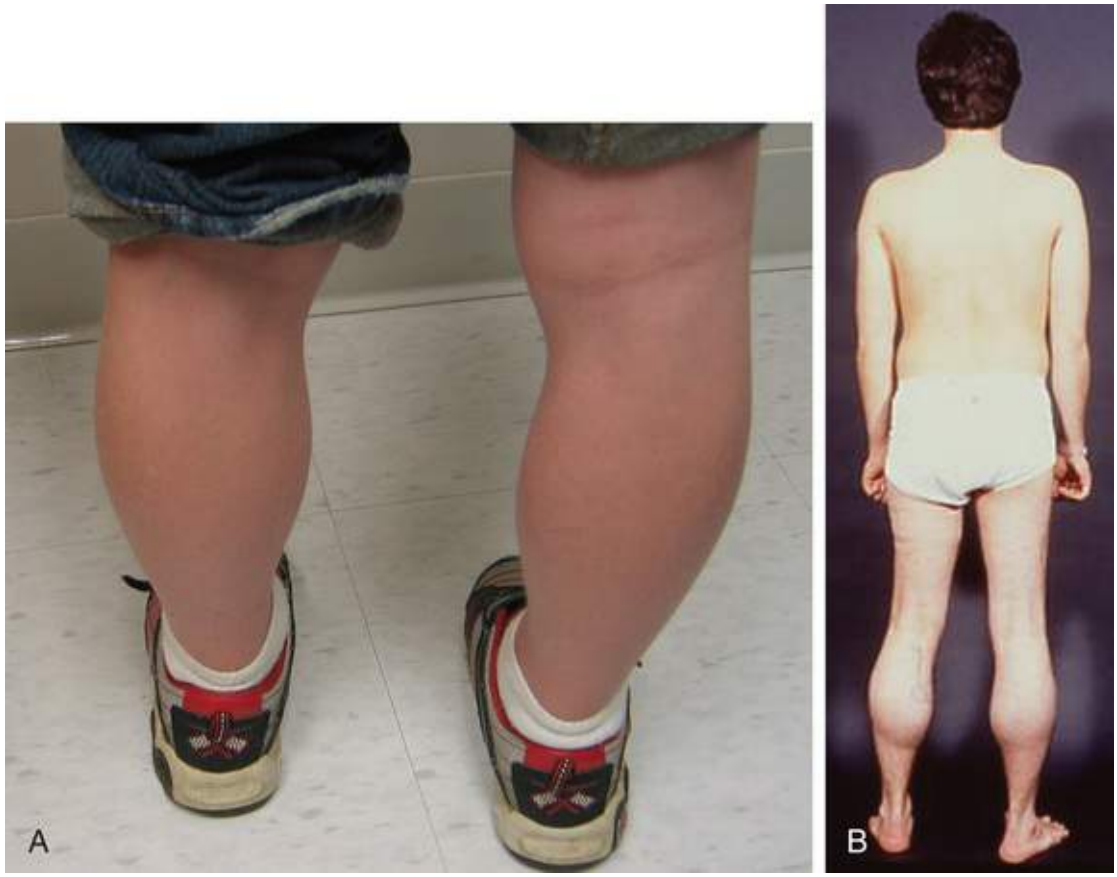


FIGURE 97.1 **A,** Calf pseudohypertrophy in an 8-year-old boy with Duchenne muscular dystrophy. **B,** Becker muscular dystrophy in a 24-year-old man. Dystrophy of the shoulder girdle and calf pseudohypertrophy are evident. (**A,** Courtesy Dr. Laurence E. Walsh; **B,** courtesy Dr. Robert M. Pascuzzi.)

In both Duchenne and Becker muscular dystrophies, elevated serum creatine kinase activity is observed, at levels more than 10 and 5 times normal values, respectively.

Cardiovascular Manifestations

Most patients with Duchenne muscular dystrophy develop a cardiomyopathy, but symptoms can be masked by severe skeletal muscle weakness. Preclinical cardiac involvement is present in one fourth by age 6, with the onset of clinically apparent cardiomyopathy after age 10 common. Cardiac involvement can be diagnosed earlier by cardiac magnetic resonance imaging.[5,6] The majority of patients with Duchenne muscular dystrophy 18 years of age or older develop a dilated cardiomyopathy. Early involvement is observed in the inferobasal and lateral left ventricle (**Fig. 97.2**). As with the skeletal muscle weakness, cardiac involvement in Becker muscular dystrophy is more variable than in Duchenne muscular dystrophy, ranging from none or subclinical disease to severe cardiomyopathy requiring transplant. Cardiac involvement in Becker muscular dystrophy is independent of the severity of skeletal muscle involvement, with some but not all investigators observing an increased likelihood of cardiovascular disease in older patients. More than one half of patients with subclinical or benign skeletal muscle disease were noted to have cardiac involvement if carefully evaluated. Progression in the severity of cardiac involvement is common. Cardiomyopathy can initially solely involve the right ventricle.

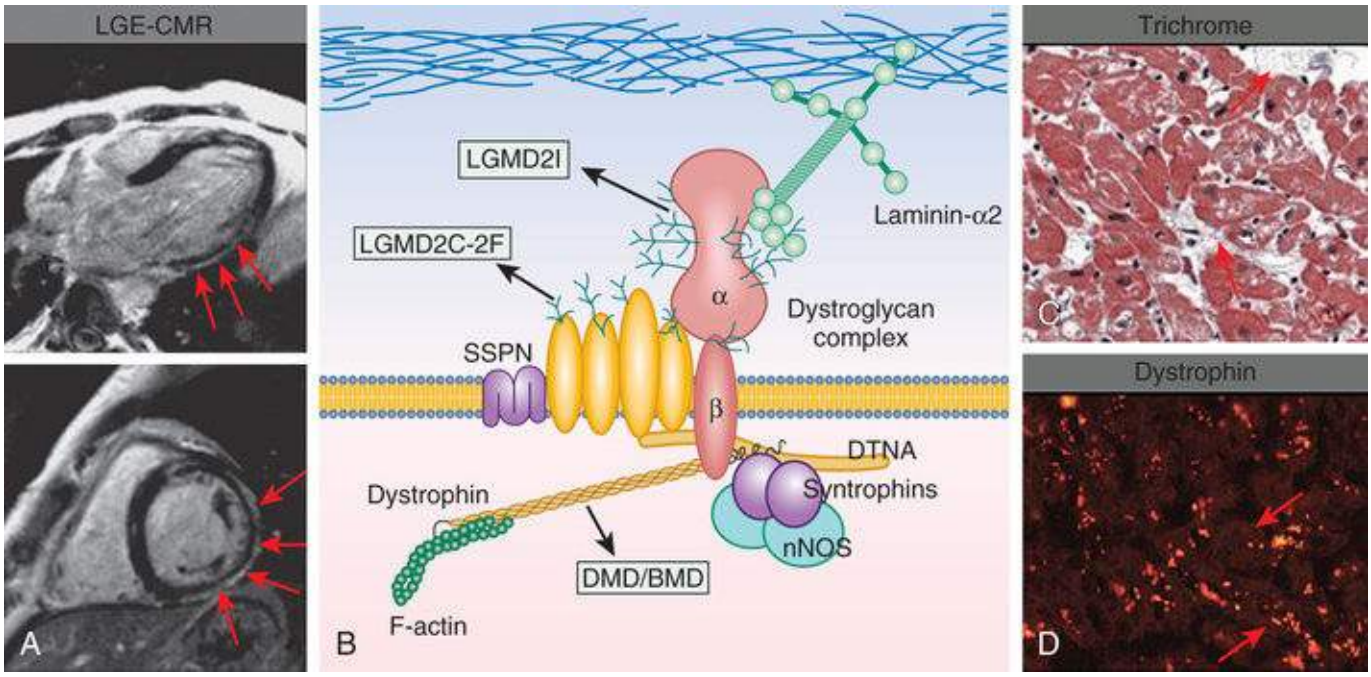


FIGURE 97.2 Cardiac involvement in Duchenne muscular dystrophy. **A**, Late gadolinium enhancement (LGE) images of a patient with Duchenne muscular dystrophy (*red arrows* indicate areas of positive LGE, primarily in the inferior-lateral left ventricle). **B**, Schematic illustration of the constitution of a cardiomyocyte cell membrane, demonstrating connection between intramembranous sarcoglycan complex *(yellow ellipses),* dystroglycan complex (α and β), and dystrophin, which is linked to the intracellular actin cytoskeleton. The dystroglycan complex connects to the basal lamina on the extracellular side via laminin and to syntrophins and nitric oxide synthase (nNOS) via dystrobrevin (encoded by the *DTNA* gene). **C**, Trichrome staining of an endomyocardial biopsy sample taken from the patient shown in (**A**), showing irregular-sized cardiomyocytes in the presence of diffuse interstitial fibrosis *(red arrows).* **D**, Dystrophin staining: A few cardiomyocytes show discontinuous expression of dystrophin in the cell membrane *(red arrows),* whereas most cardiomyocytes have no dystrophin at all in their membranes. *BMD*, Becker muscular dystrophy; *DMD*, Duchenne muscular dystrophy; *LGMD*, limb-girdle muscular dystrophy. (**A, C, D** from American Heart Association; Yilmaz A, Gdynia H-J, Ludolph AC, et al: Images in cardiovascular medicine: cardiomyopathy in a Duchenne muscular dystrophy carrier and her diseased son: similar pattern revealed by cardiovascular MRI. Circulation 2010;121:e237. **B** from Kobayashi YM, Campbell, KP: Skeletal muscle dystrophin-glycoprotein complex and muscular dystrophy. In Hill JA, Olson EN (editors): Muscle fundamental biology and mechanisms of disease. Cambridge, MA, Academic Press, 2012, pp 935-942.)

Thoracic deformities and a high diaphragm can alter the cardiovascular examination in patients with Duchenne muscular dystrophy. A reduction in the anterior-posterior chest dimension is commonly responsible for a systolic impulse displaced to the left sternal border, a grade 1 to 3/6 short midsystolic murmur in the second left interspace, and a loud pulmonary component of the second heart sound. In both Duchenne and Becker types of muscular dystrophy, mitral regurgitation is observed. The presence of mitral regurgitation is related to posterior papillary muscle dysfunction in Duchenne muscular dystrophy and to mitral annular dilation in Becker muscular dystrophy.

Female carriers of Duchenne and Becker muscular dystrophy are at increased risk for dilated cardiomyopathy.

Electrocardiography

In a majority of patients with Duchenne muscular dystrophy, the electrocardiographic tracing is abnormal (**see also Chapter 12**). The classically described electrocardiographic pattern shows distinctive tall R waves and increased R/S amplitude in V_1 and deep narrow Q waves in the left precordial leads possibly related to the posterolateral left ventricular involvement (**Fig. 97.3**). Other common findings include a short PR interval and right ventricular hypertrophy. No association between the presence of a dilated cardiomyopathy and electrocardiographic abnormalities has been established.[7] In Becker muscular

dystrophy, electrocardiographic abnormalities are present in up to 75% of the patients. The electrocardiographic abnormalities observed include tall R waves and an increased R/S amplitude in V_1, akin to that seen in Duchenne muscular dystrophy. Incomplete right bundle branch block also is a frequent finding that may be related to early involvement of the right ventricle. In patients with dilated cardiomyopathy, a left bundle branch block is common.

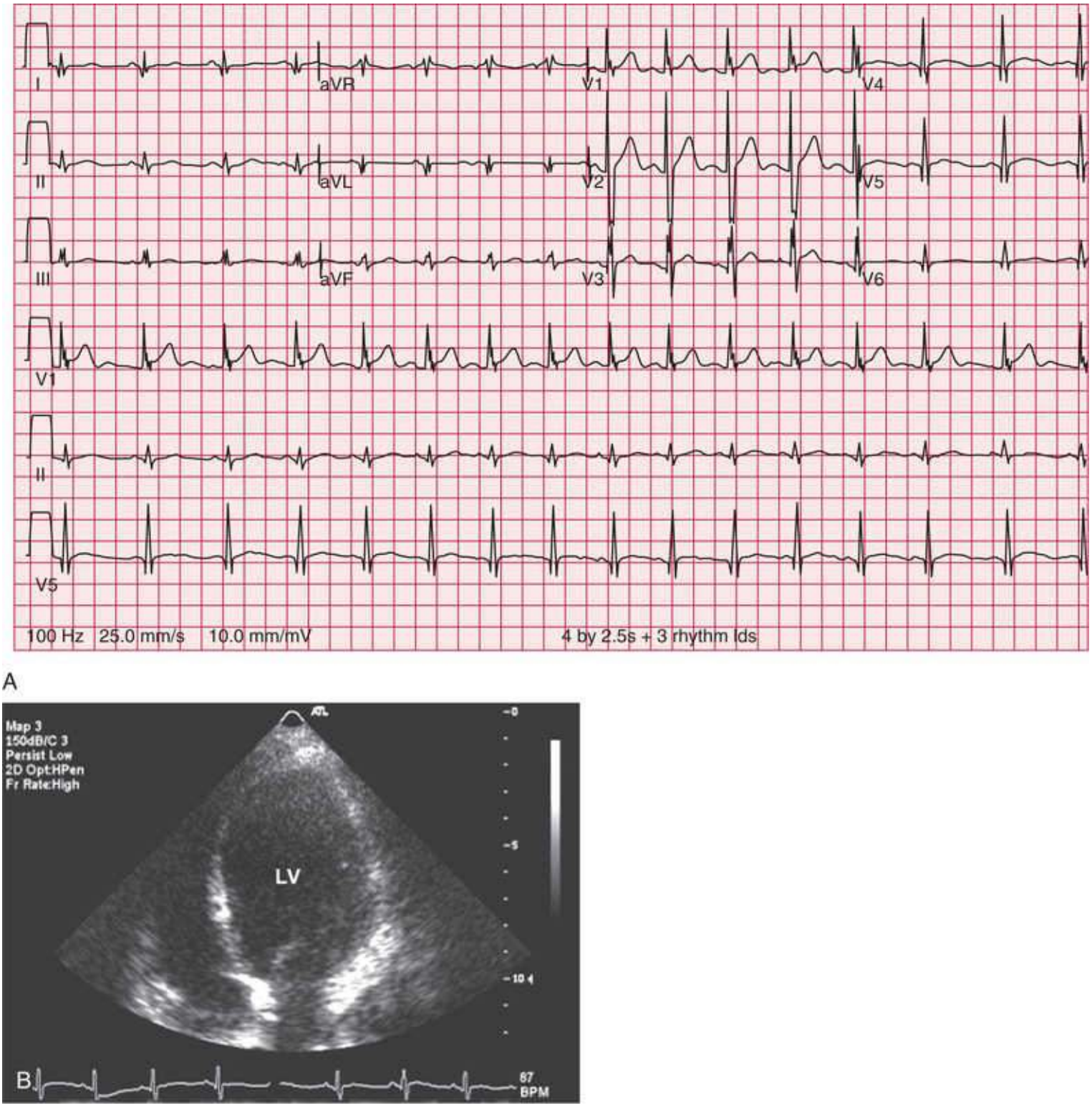


FIGURE 97.3 Dilated cardiomyopathy in a 19-year-old man with Duchenne muscular dystrophy. **A,** ECG showing a QRS complex that is typical of Duchenne muscular dystrophy, with tall R waves in lead V_1 and deep narrow Q waves in leads I and aVL. **B,** Two-dimensional echocardiogram showing a dilated, thinned left ventricle (LV).

Imaging

Clinical care guidelines recommend using screening echocardiography at diagnosis or by the age of 6 years; subsequently every 2 years until the age of 10; and annually thereafter in boys with Duchenne muscular dystrophy (this and other cardiac imaging modalities are described more fully in **Chapters 14 to 18**).[3] Cardiac magnetic resonance imaging, especially with gadolinium contrast, is more sensitive in detecting subclinical ventricular involvement and fibrosis.[2] The presence of fibrosis as indicated by late gadolinium enhancement on MRI predicted a subsequent decrement in left ventricular function.[8] Regional abnormalities in the posterobasal and lateral wall typically occur earlier than in other areas (**see Fig. 97.2**). A process akin to left ventricular noncompaction can be observed, possibly resulting from compensatory mechanisms in response to the failing dystrophic myocardium. Mitral regurgitation can result from dystrophic changes in the posterior leaflet papillary muscles.

Arrhythmias

In Duchenne muscular dystrophy, persistent or labile sinus tachycardia is the most common arrhythmia recognized (**see also Chapter 37**). Atrial arrhythmias, including atrial fibrillation and atrial flutter (**see also Chapter 38**), occur in the setting of respiratory dysfunction and cor pulmonale or are associated with a dilated cardiomyopathy. Abnormalities in atrioventricular conduction have been observed, with both short and prolonged PR intervals recognized. Ventricular arrhythmias occur on monitoring in 30% of patients, primarily ventricular premature beats. Complex ventricular arrhythmias have been reported, more commonly in patients with severe skeletal muscle disease. Sudden death occurs in Duchenne muscular dystrophy, typically in patients with end-stage muscular disease. Whether the sudden death is caused by arrhythmias is unclear. Several follow-up studies have shown a correlation between sudden death and the presence of complex ventricular arrhythmias. The presence of ventricular arrhythmias was not a predictor for all-cause mortality.

Arrhythmia manifestations in Becker muscular dystrophy typically are related to the severity of the associated structural cardiomyopathy. Distal conduction system disease with complete heart block and bundle branch reentry ventricular tachycardia has been observed.

Treatment and Prognosis

Duchenne muscular dystrophy is a progressive skeletal and cardiac muscle disorder. Steroids and steroid derivatives are effective in delaying skeletal muscle disease progression and appear to decrease the progression to a dilated cardiomyopathy.[9] Antisense oligonucleotides facilitate exon skipping of nonsense mutations in the dystrophin gene and have shown promise in early clinical evaluation in appropriate candidates. Gene replacement therapy using novel delivery of functional mini-dystrophin holds future promise. A primary cardiac cause of death is recognized as playing an increasingly significant role because death due to other causes has been with improved respiratory support. There is an equal distribution of cardiac death from heart failure and from sudden death. Angiotensin-converting enzyme (ACE) inhibitors and beta blockers can improve left ventricular function in patients treated early. Angiotensin receptor blockers can be used if the patient cannot tolerate angiotensin-converting enzyme inhibitors. The aldosterone antagonist eplerenone showed benefit in maintaining cardiac magnetic resonance left ventricular circumferential strain in boys already receiving ACE inhibitors or angiotensin receptor blockers.[10] Dosing, age, or clinical status at which pharmacotherapy should be initiated is unclear (**see also Chapters 24 and 25**). Other advanced types of therapy such as implantable cardioverter-defibrillators play an uncertain role but should be considered individually based on clinical

presentation, patient status, and wishes (**see also Chapter 41**). The use of left ventricular mechanical assist devices has been described. Whether heart failure therapies improve long-term outcomes is unclear. However, the age at death has increased, with the majority of patients surviving into their 30s, and recognition and treatment of the associated cardiomyopathy likely plays a role in that success.

In patients with Becker muscular dystrophy, an improvement in left ventricular function also is observed after treatment with ACE inhibitors and beta blockers. Screening left ventricular imaging is recommended as in Duchenne muscular dystrophy. Advanced heart failure therapy, including primary prevention implantable cardioverter-defibrillators, is appropriate in patients with cardiomyopathy. Patients with Becker muscular dystrophy with advanced heart failure can undergo cardiac transplantation, with expected outcomes similar to those for non–muscular dystrophy cohorts of age-matched patients with dilated cardiomyopathy.[11] Female carriers of Duchenne and Becker muscular dystrophies do not develop a cardiomyopathy during childhood, and screening can be delayed until later in adolescence. Whether carriers benefit from heart failure pharmacotherapy is unknown, but such treatment would seem reasonable based on shared mechanisms. Once heart failure is established, conventional therapy is indicated. Cardiac transplantation also has been reported in carriers.

Myotonic Dystrophies

Genetics

The myotonic dystrophies are autosomal dominant disorders characterized by myotonia, which is a delayed muscle relaxation after contraction, weakness and atrophy of skeletal muscles, and systemic manifestations, including endocrine abnormalities, cataracts, cognitive impairment, and cardiac involvement (**Fig. 97.4**). Two distinct mutations are responsible for the myotonic dystrophies. In myotonic dystrophy type 1, the mutation is an amplified trinucleotide cytosine-thymine-guanine (CTG) repeat found on chromosome 19. Whereas unaffected patients have 5 to 37 copies of the repeat, patients with myotonic dystrophy have 50 to several thousand repeats. A direct correlation exists between an increasing number of CTG repeats and earlier age at onset and increasing severity of neuromuscular involvement. Cardiac involvement including conduction disease, arrhythmias, and age at cardiovascular death also correlate with the length of repeat expansion (**Fig. 97.5**). It is typical for the CTG repeat to expand as it is passed from parents to offspring, resulting in the characteristic worsening clinical manifestations in subsequent generations, termed *anticipation*.

FIGURE 97.4 The patient is a 54-year-old man with myotonic dystrophy type 1. Typical characteristics of balding, thin face, and distal muscle atrophy are evident.

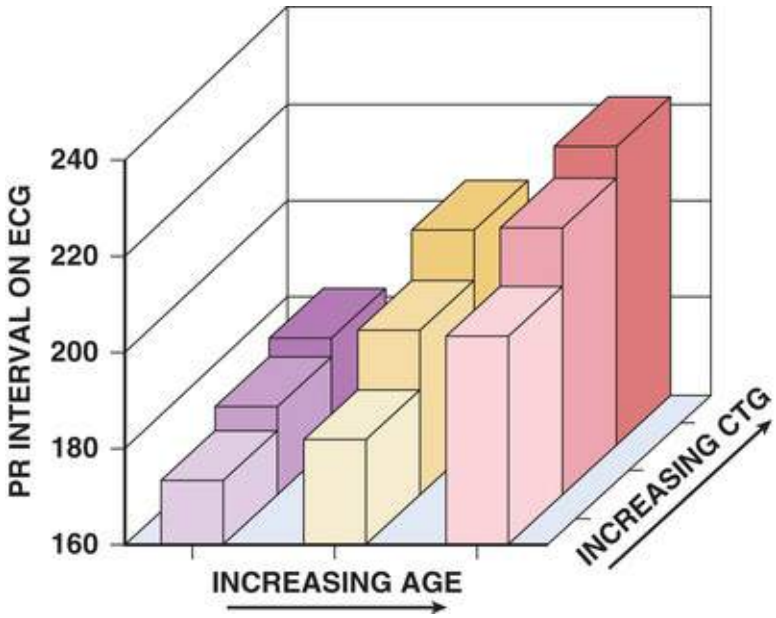


FIGURE 97.5 Relationship between the PR interval on the ECG and age and CTG repeat sequence expansion in 342 patients with myotonic dystrophy type 1. There is a direct relationship between age and CTG repeat sequence expansion and the severity of cardiac conduction disease, as quantified by the PR interval. The relationship suggests that cardiac involvement in myotonic dystrophy type 1 is a time-dependent degenerative process, with the rate of progression modulated by the extent of CTG repeat expansion. (From Groh WJ, Lowe MR, Zipes DP: Severity of cardiac conduction involvement and arrhythmias in myotonic dystrophy type 1 correlates with age and CTG repeat length. J Cardiovasc Electrophysiol 2002;13:444.)

Myotonic dystrophy type 2, also called proximal myotonic myopathy, has generally less severe skeletal muscle and cardiac involvement than type 1. Both congenital presentation and cognitive impairment are

lacking in myotonic dystrophy type 2—typically the most severely involved subsets of the type 1 patients. The genetic mutation responsible for myotonic dystrophy type 2 is a tetranucleotide repeat expansion, cytosine-cytosine-thymine-guanine (CCTG), found on chromosome 3. Intergenerational contraction of the repeat expansion has been reported, and there is no apparent relationship between the degree of expansion and clinical severity.

The molecular mechanism by which both myotonic dystrophies exert their similar phenotypic presentations is by the toxic effects of the large mutant RNA expansion on nuclear RNA–binding proteins. Cardiac involvement is related to the resultant dysregulation of multiple cardiac systems, including sarcomeric proteins, calcium handling, and connexins[12] (**Fig. 97.6**).

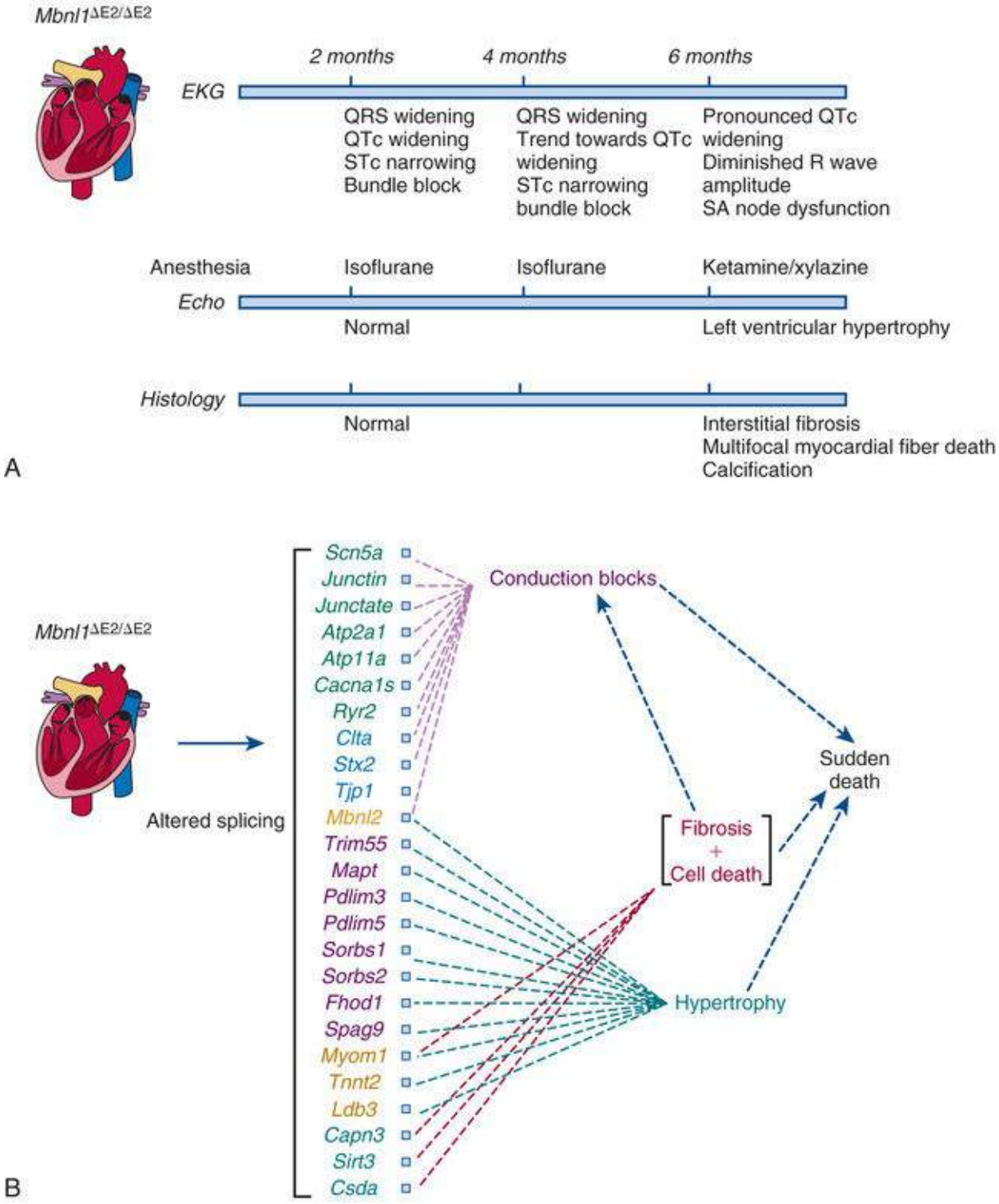


FIGURE 97.6 A mechanism of cardiac pathogenesis in myotonic dystrophy type 1. **A,** Cardiac pathophysiologic findings in a muscleblind-like protein 1 (MBNL1) mouse deletion model. MBNL1 is an RNA splice regulator. It is sequestered and disabled when it binds to the multiple copies of CUG RNA transcribed from the expanded CTG DNA in myotonic dystrophy type 1. Loss of MBNL1 leads to persistence of embryonic splice isoforms in multiple downstream cardiac proteins (**B**). (From Dixon DM, Choi J, El-Ghazali A, et al: Loss of muscleblind-like 1 results in cardiac pathology and persistence of embryonic splice isoforms. Sci Rep 2015;5:9042.)

Clinical Presentation

The myotonic dystrophies are the most common inherited neuromuscular disorders in patients presenting as adults. Until recently, studies have not genetically differentiated myotonic dystrophy types 1 and 2, so the clinical characteristics described probably are for a mixed group of such disorders. Type 1 is significantly more common than type 2, except possibly in certain areas of northern Europe. The global

incidence of myotonic dystrophy type 1 has been estimated to be 1 in 8000, although it is higher in certain populations, such as French Canadians, and lower to nonexistent in other populations, such as African blacks. The age at onset of symptoms and diagnosis averages 20 to 25 years. A congenital presentation is seen in severely affected patients with myotonic dystrophy type 1. Common early manifestations are related to weakness in the muscles of the face, neck, and distal extremities. On examination, myotonia can be demonstrated in the grip, thenar muscle group, and tongue (**Fig. 97.7**). The diagnosis when the patient is asymptomatic is possible using electromyography and genetic testing. Muscle weakness is progressive. Subcapsular cataracts are commonly observed. In general, cardiac symptoms appear after the onset of skeletal muscle weakness but can be the initial manifestation of the disease.

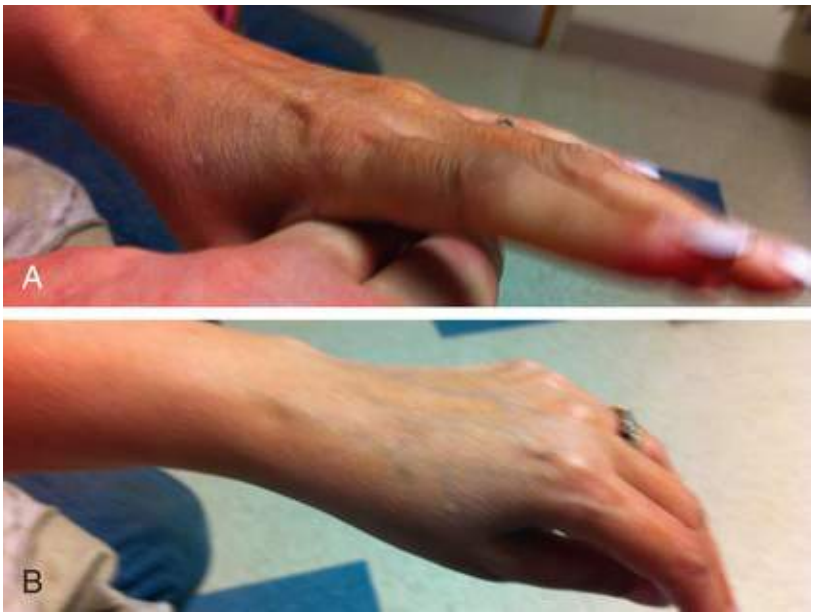


FIGURE 97.7 Grip myotonia in myotonic dystrophy. The patient is unable to fully open the hand **(A)** after exerting a grip **(B).**

Myotonic dystrophy type 2 also manifests with myotonia, muscle weakness, cataracts, and endocrine abnormalities, as in type 1. Age at symptom onset typically is older in myotonic dystrophy type 2.

Cardiovascular Manifestations

Cardiac pathology in the myotonic dystrophies involves degeneration, fibrosis, and fatty infiltration preferentially targeting the specialized conduction tissue, including the sinus node, atrioventricular node, and His-Purkinje system (**Fig. 97.8**). Degenerative changes are observed in working atrial and ventricular tissue but only rarely progress to a symptomatic dilated cardiomyopathy. It is not clear if there are differences in the cardiac pathology observed between myotonic dystrophy type 1 and 2. Patients with type 2 typically demonstrate cardiac involvement later in life or not at all. The primary cardiac manifestations of the myotonic dystrophies are arrhythmias.

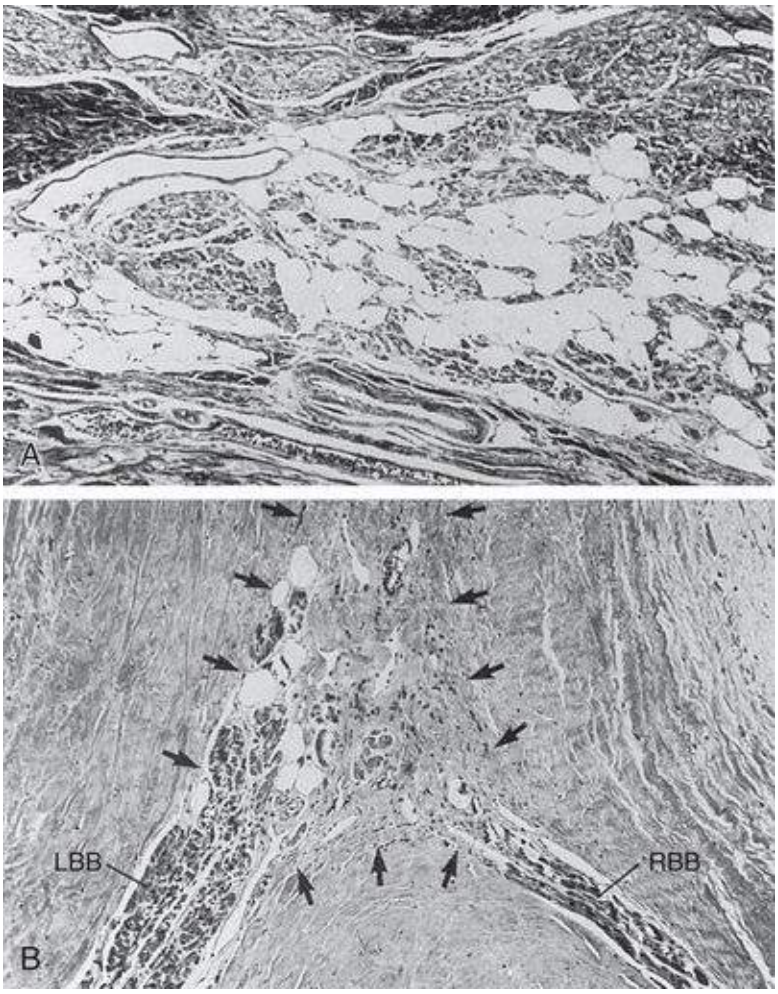


FIGURE 97.8 Histopathologic features of the atrioventricular bundle in myotonic dystrophy. **A,** Fatty infiltration in a specimen from a 57-year-old man (Masson trichrome stain, ×90). **B,** Focal replacement fibrosis and atrophy in a specimen from a 48-year-old woman. *Arrows* demarcate expected size and shape of the branching atrioventricular bundle (hematoxylin-eosin stain, ×90.) *LBB*, left bundle branch; *RBB*, right bundle branch. (From Nguyen HH, Wolfe JT 3rd, Holmes DR Jr, Edwards WD: Pathology of the cardiac conduction system in myotonic dystrophy: a study of 12 cases. J Am Coll Cardiol 1988;11:662.)

Electrocardiography

A majority of adult patients with myotonic dystrophy type 1 exhibit electrocardiographic abnormalities. In a large, unselected, middle-aged U.S. myotonic population, abnormal electrocardiographic patterns were seen in 65% of the patients.[13] Abnormalities included first-degree atrioventricular block in 42%, right bundle branch block in 3%, left bundle branch block in 4%, and nonspecific intraventricular conduction delay in 12%. Q waves not associated with a known myocardial infarction are common. Electrocardiographic abnormalities are less common in younger patients. Conduction disease worsens with advancing age (**Fig. 97.9**).

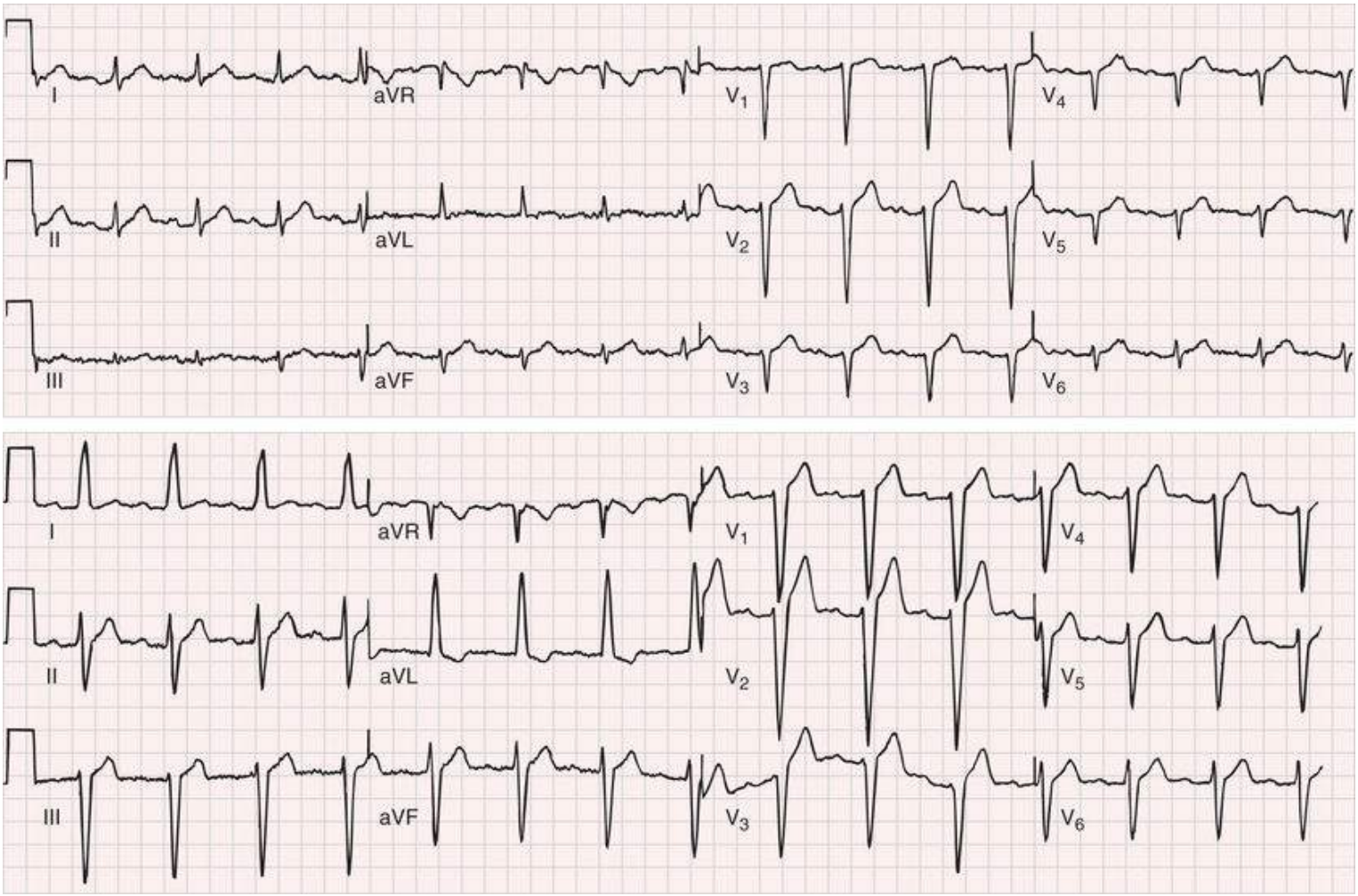


FIGURE 97.9 ECGs obtained 1 year apart in a 36-year-old man with myotonic dystrophy (the *top tracings* are older). Note the abnormal Q waves in the precordial leads. An increasing PR interval and QRS duration are observed, consistent with increasing severity of conduction disease.

Electrocardiographic abnormalities are less common in myotonic dystrophy type 2, occurring in approximately 20% of middle-aged patients.

Imaging and Heart Failure

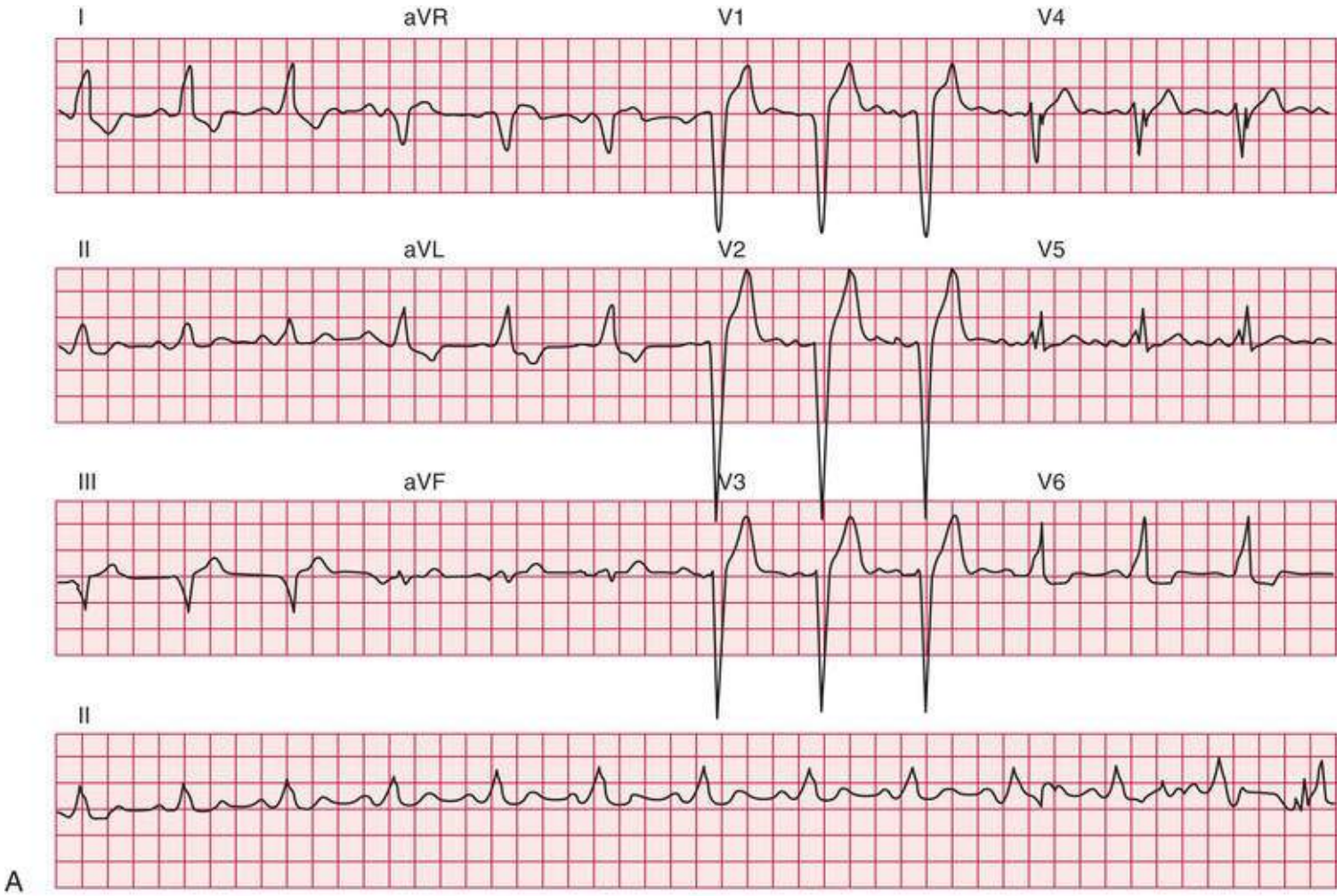
Left ventricular systolic and diastolic dysfunction, left ventricular hypertrophy, mitral valve prolapse, regional wall motion abnormalities, and left atrial dilatation have been reported in patients with myotonic dystrophy type 1 at moderate prevalence rates.[14] Clinical heart failure is observed but is less common than are arrhythmias. Left ventricular hypertrophy and ventricular dilation have been reported in myotonic dystrophy type 2. Cardiac magnetic resonance imaging is more sensitive than echocardiography for detection of early cardiac involvement.[15]

Arrhythmias

Patients with myotonic dystrophy type 1 demonstrate a wide range of arrhythmias. At cardiac electrophysiologic study, the most common abnormality found is a prolonged His-ventricular (H-V) interval (**see also Chapter 34**). Conduction system disease can progress to symptomatic atrioventricular block and necessitate pacemaker implantation. The prevalence of permanent cardiac pacing in patients with myotonic dystrophy type 1 varies widely between studies based on referral patterns and the indications used for implant. Updated practice guidelines have recognized that asymptomatic conduction abnormalities in neuromuscular diseases such as myotonic dystrophy may warrant special consideration

for pacing[16] (**see also Chapter 41**).

Atrial arrhythmias, primarily atrial fibrillation and atrial flutter (**see also Chapter 37**), are the most common arrhythmias observed.[13] Ventricular tachycardia can occur. Patients with myotonic dystrophy type 1 are at risk for ventricular tachycardia occurring as a consequence of reentry in the diseased distal conduction system, as characterized by bundle branch reentry and interfascicular reentry tachycardia (**Fig. 97.10**). Therapy with right bundle branch or fascicular radiofrequency ablation can be curative (**see also Chapter 39**).



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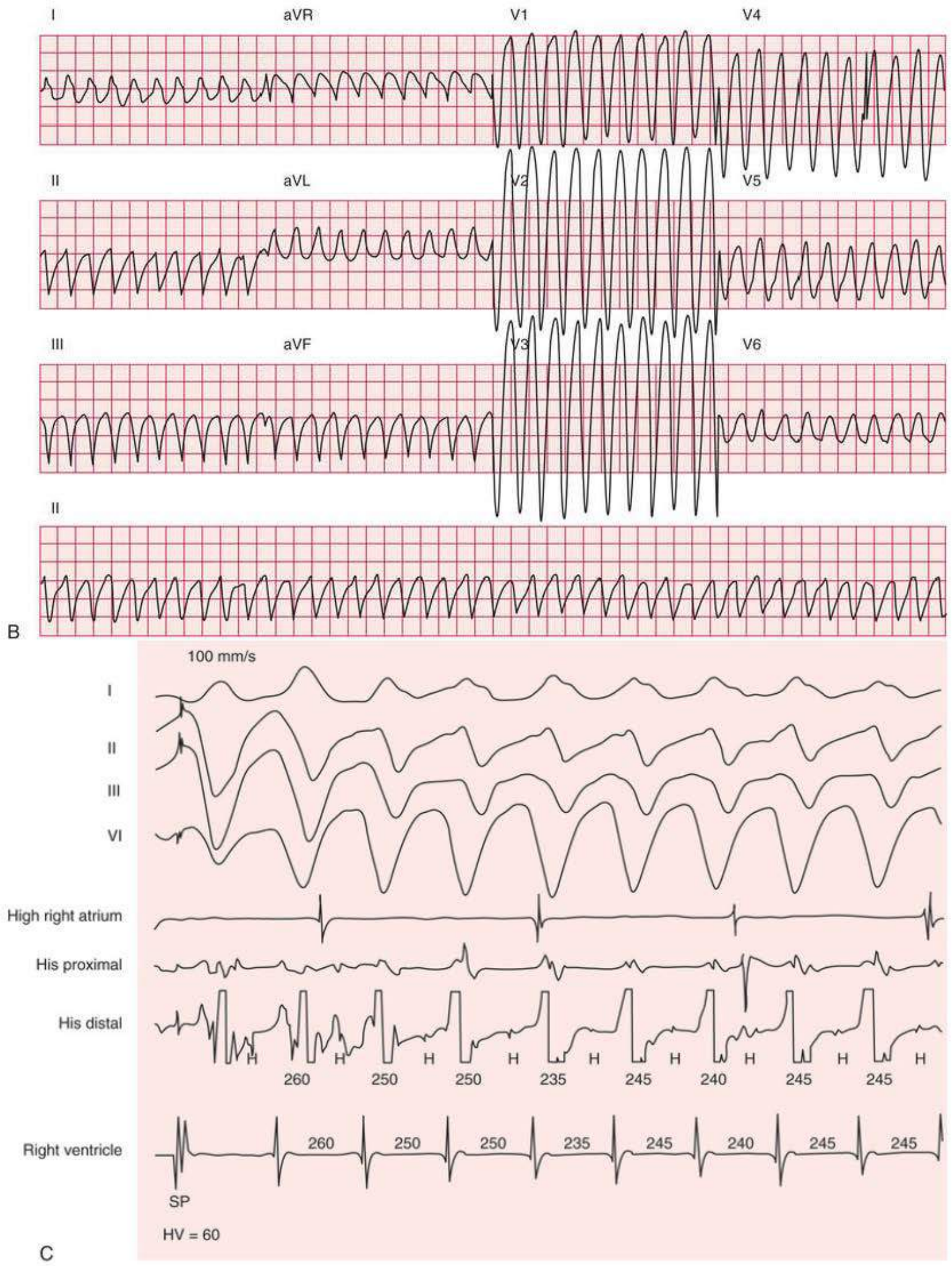


FIGURE 97.10 Bundle branch reentry tachycardia in a 34-year-old woman with myotonic dystrophy type

1 presenting with a symptomatic (recurrent syncope) wide-complex tachycardia. **A,** ECG showing sinus rhythm and a QRS complex with left bundle branch block. **B,** ECG showing a rapid monomorphic tachycardia easily inducible on electrophysiologic study, with left bundle morphology. **C,** Recordings during electrophysiologic study, including the surface ECG (leads I, II, III, V_1) and intracardiac ECGs (high right atrium, His proximal, His distal, and right ventricle). A monomorphic ventricular tachycardia is induced with atrial-ventricular (A-V) dissociation and His association, consistent with bundle branch reentry tachycardia. Note, the H-H interval drives the subsequent V-V interval.

Sudden death is responsible for 18% to 33% of deaths in myotonic dystrophy type 1; presumably, most are due to arrhythmias. Annual rates of sudden death in population studies vary between 0.25% and 2%. The entity of sudden death is second only to respiratory failure as a cause of death. The mechanisms leading to sudden death are not clear. Distal conduction disease producing atrioventricular block can result in the lack of an appropriate escape rhythm and asystole or bradycardia-mediated ventricular fibrillation. Sudden death can occur in myotonic dystrophy type 1 despite pacing, implicating ventricular arrhythmias. Nonarrhythmic causes of sudden death, probably acute respiratory issues, play some role (**see also Chapter 42**).

Arrhythmias and sudden death have been reported in myotonic dystrophy type 2 but seem to be rarer than in type 1.

Treatment and Prognosis

Neurologists recognize the risk for cardiac issues in the myotonic dystrophies and will refer the patient to a cardiologist. Cardiac manifestations occur in both myotonic dystrophy types 1 and 2, and therefore diagnostic evaluation and therapy should be done in both. Cardiac disease is observed at a younger age in myotonic dystrophy type 1 compared with type 2. Echocardiography or other imaging modalities can determine if structural abnormalities are present. Cardiac imaging in adults should be done at diagnosis or with new symptoms. If no significant abnormalities are observed, repeat evaluation every 3 to 5 years is appropriate. In the patient with a dilated cardiomyopathy, standard therapy including ACE inhibitors and beta blockers has improved symptoms. There are no data on the role of ACE inhibitors or beta blockers in preventing the development of a cardiomyopathy in myotonic dystrophy. Patients presenting with symptoms indicative of arrhythmias such as syncope and palpitations should undergo an evaluation, often including a cardiac electrophysiologic study, to determine an underlying causative disorder. Annual electrocardiograms (ECGs) are recommended in asymptomatic patients. The role and interval for ambulatory ECG (Holter) monitoring are not clear (**see also Chapter 35**). The presence of significant or progressive electrocardiographic abnormalities despite a lack of symptoms is an indication for consideration of prophylactic pacing.[16] The presence of severe electrocardiographic conduction abnormalities and atrial arrhythmias were independent risk factors for sudden death.[13] The strategy of pacing when the H-V interval is 70 milliseconds or more decreased sudden death in a large observational trial using propensity analysis for group risk stratification.[17] Implantable cardioverter-defibrillators may be more appropriate prophylactic therapy than pacemakers.[18] The use of cardiac resynchronization therapy may be appropriate in patients requiring ventricular pacing. Anesthesia in patients with myotonic dystrophy increases the risks of both respiratory failure and arrhythmias. Careful monitoring during the perioperative period is mandatory. Monitored anesthesia during cardiac device implants should be done under an anesthesiologist's care.

In patients presenting with wide complex tachycardia, cardiac electrophysiologic study with particular evaluation for bundle branch reentry tachycardia should be done (**see also Chapter 39**).

The course of neuromuscular abnormalities in the myotonic dystrophies is variable. Respiratory failure

from progressive muscle dysfunction is the most common cause of death. Some patients, however, are only minimally limited by weakness up to the age of 60 to 70 years. Sudden death can reduce survival rates in patients with the myotonic dystrophies, including those minimally symptomatic from a neuromuscular status. Decisions regarding prophylactic cardiac devices need to be made with full consideration of all aspects for the care of the myotonic patient.

Emery-Dreifuss Muscular Dystrophy and Associated Disorders

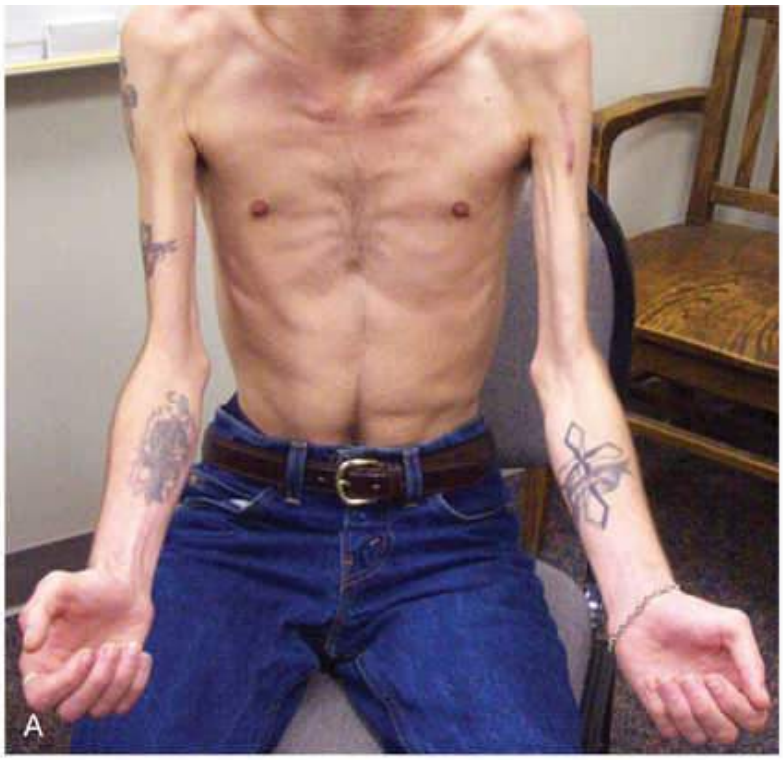
Genetics and Cardiac Pathology

Emery-Dreifuss muscular dystrophy is a rare inherited disorder in which skeletal muscle symptoms are often mild; cardiac involvement is both common and serious. The disease is classically inherited in an X-linked recessive fashion but there is heterogeneity with families that fit an X-linked dominant, autosomal dominant, and autosomal recessive inheritance pattern. The gene responsible for the X-linked Emery-Dreifuss muscular dystrophy, *STA*, encodes a nuclear membrane protein termed emerin. Mutations in genes found on chromosome 1 encoding two other nuclear membrane proteins, lamins A and C, have been identified as responsible for a variety of other disorders with a phenotypic expression similar to X-linked Emery-Dreifuss muscular dystrophy. The disorders include autosomal dominant and recessive Emery-Dreifuss muscular dystrophy, autosomal dominant dilated cardiomyopathy with conduction disease, autosomal dominant limb-girdle muscular dystrophy with conduction disease, and lipodystrophy with associated cardiac abnormalities.[19]

Nuclear membrane proteins such as emerin and lamins A and C provide structural support for the nucleus and interact with the cell's cytoskeletal proteins. Mutations in the tail regions of lamins A and C are responsible for the majority of cases of autosomal dominant Emery-Dreifuss muscular dystrophy with a phenotype of both cardiac and skeletal muscle involvement. Mutations in the rod domain of the lamin A/C gene primarily cause isolated cardiac disease, including dilated cardiomyopathy, conduction system degeneration, and atrial and ventricular arrhythmias.

Clinical Presentation

Emery-Dreifuss muscular dystrophy is characterized by a triad of early contractures of the elbow, Achilles tendon, and posterior cervical muscles; slowly progressing muscle weakness and atrophy, primarily in humeroperoneal muscles; and cardiac involvement (**Fig. 97.11**). The disorder has been labeled “benign X-linked muscular dystrophy” to differentiate the slowly progressive muscular weakness from that of Duchenne muscular dystrophy. In the autosomal dominant and recessive inheritance of Emery-Dreifuss muscular dystrophy, a more variable phenotypic expression and penetrance typically are observed. A mutation in the lamin A/C gene also is responsible for an autosomal dominantly–inherited familial partial lipodystrophy characterized by marked loss of subcutaneous fat, diabetes, hypertriglyceridemia, and cardiac abnormalities.



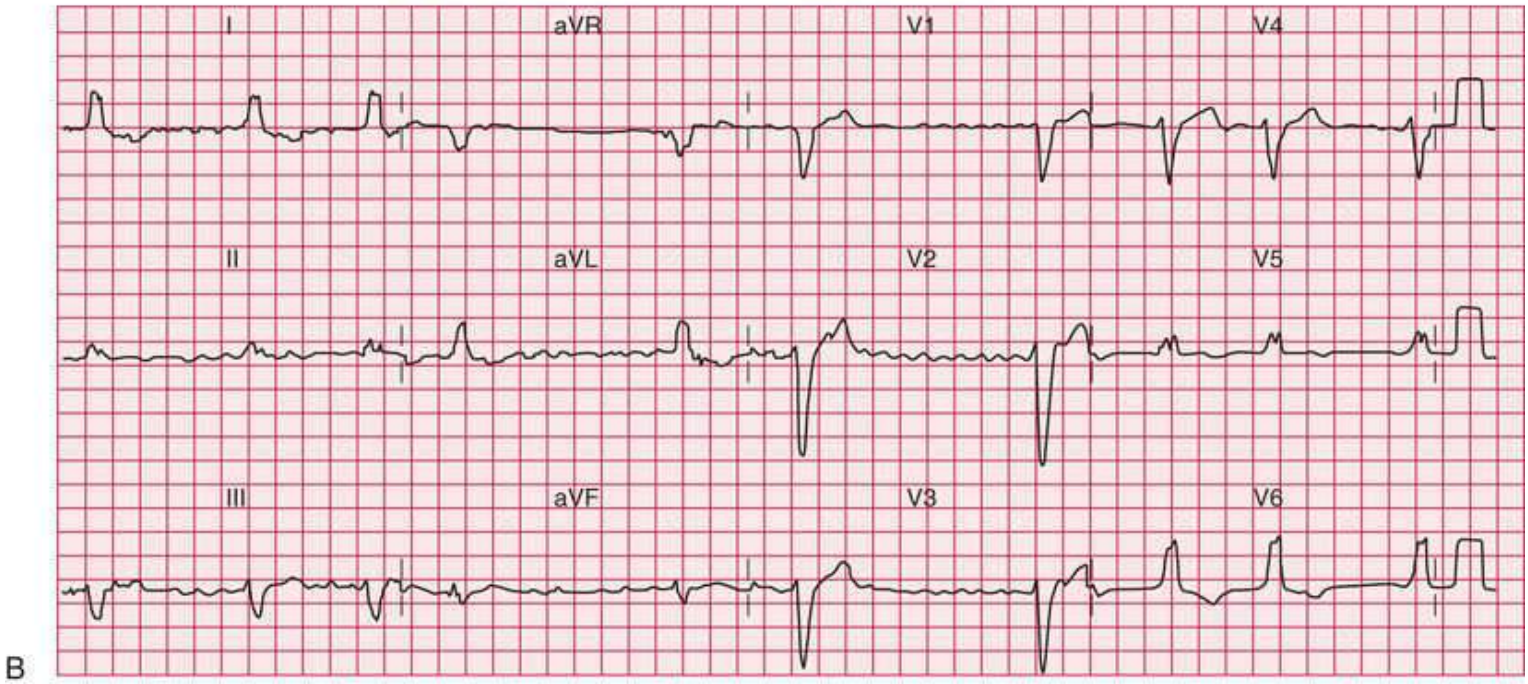


FIGURE 97.11 Emery-Dreifuss muscular dystrophy in a 28-year-old man presenting with syncope. **A,** Contractures of the elbow and atrophy in the humeroperoneal muscles. **B,** ECG obtained at initial presentation showed atrial fibrillation with slow ventricular rate and a QRS complex with left bundle branch block. (Courtesy Dr. Robert M. Pascuzzi.)

Cardiovascular Manifestations

Arrhythmias and dilated cardiomyopathy are the major manifestations of cardiac disease in Emery-Dreifuss muscular dystrophy and its associated disorders. In X-linked recessive Emery-Dreifuss muscular dystrophy, abnormalities in impulse generation and conduction are common. ECGs are abnormal by age 20 to 30 years, commonly showing first-degree atrioventricular block. The atria appear to be involved earlier than the ventricles, with atrial fibrillation and atrial flutter, or more classically, permanent atrial standstill and junctional bradycardia. Abnormalities in impulse generation or conduction are present in virtually all patients by age 35 to 40 years, and requirement for pacing is typical. Ventricular arrhythmias,

including sustained ventricular tachycardia and ventricular fibrillation, occur. Sudden death, presumably due to cardiac disorders, before age 50 is observed. Prophylactic implantable cardioverter-defibrillators are used.[20] Female carriers of X-linked recessive Emery-Dreifuss muscular dystrophy do not exhibit skeletal muscle disease but acquire late cardiac disease, including conduction abnormalities, and sudden death can occur. Although arrhythmias are the most common presentation of cardiac involvement in X-linked recessive Emery-Dreifuss muscular dystrophy, a dilated cardiomyopathy can rarely develop. The dilated cardiomyopathy is more common in patients in whom the survival time has been improved with cardiac device implantation. Both autopsy and endomyocardial biopsy specimens have shown cardiac fibrosis.

Patients with disorders caused by lamin A and C mutations typically present at 20 to 40 years of age with cardiac conduction disease, atrial fibrillation, and dilated cardiomyopathy. Skeletal muscle disease typically is subclinical or absent. Progression of a cardiomyopathy to the extent that heart transplantation is required has been described. Sudden death in those patients with a dilated cardiomyopathy occurs. Pacing often is required for symptomatic heart block. Implantable cardioverter-defibrillators are the appropriate cardiac device for a majority of patients.

Treatment and Prognosis

Patients should be monitored for development of electrocardiographic conduction abnormalities and arrhythmias. Annual evaluation is appropriate. Atrioventricular block can occur with anesthesia. Sudden death even in patients with pacemakers has been observed. Prophylactic placement of an implantable cardioverter-defibrillator is advocated in patients with Emery-Dreifuss muscular dystrophy and its associated disorders if significant electrocardiographic conduction disease is present and pacing is being considered.[20] The use of biventricular pacing should be considered in patients that require ventricular pacing. Whether implantable cardioverter-defibrillators should be considered only in certain subgroups of patients or in all patients with significant conduction disease or cardiomyopathy is not clear. In a large observational European series, risk factors for sudden death and appropriate implantable cardioverter-defibrillator therapy included nonsustained ventricular tachycardia, left ventricular ejection fraction less than 45% at presentation, male sex, and lamin A or C non–missense mutations.[20] Routine imaging for evaluation of left ventricular function is appropriate in all patients with Emery-Dreifuss muscular dystrophy and the associated disorders. Patients with left ventricular dysfunction should benefit from pharmacologic therapy, but data on this issue are limited. Successful heart transplantation has been reported. Female carriers of X-linked recessive Emery-Dreifuss muscular dystrophy develop conduction disease, and electrocardiographic monitoring on a routine basis is appropriate.

Limb-Girdle Muscular Dystrophies

Genetics

The limb-girdle muscular dystrophies are a group of disorders with a limb-shoulder and pelvic girdle distribution of weakness, but with otherwise heterogeneous inheritance and genetic cause.[21] Autosomal recessive (subtypes 2A to 2W), dominant (subtypes 1A to 1H), and sporadic patterns of inheritance have been observed. Genes involved include those encoding dystrophin-associated glycoproteins, sarcomeric proteins, sarcolemma proteins, nuclear membrane proteins, and cellular enzymes. An autosomal dominant limb-girdle muscular dystrophy (subtype 1B) with a high prevalence of arrhythmias and a late dilated cardiomyopathy is caused by mutations encoding lamin A/C, as in Emery-Dreifuss muscular dystrophy.

An autosomal recessive or sporadic limb-girdle muscular dystrophy associated with a progressive dilated cardiomyopathy is caused by mutations affecting the function of the dystrophin-glycoprotein complex, including sarcoglycan and fukutin-related proteins (subtypes 2C to 2F and 2I, respectively). The sarcoglycans complex with dystrophin-associated glycoproteins to counteract mechanical stress associated with contraction. Fukutin-related proteins affect glycosylation of a dystrophin-associated glycoprotein. An autosomal recessive limb-girdle muscular dystrophy associated with a variable onset of a dilated cardiomyopathy is caused by a mutation in a sarcolemmal repair protein termed dysferlin (subtype 2B). Other more recently discovered and rarer subtypes of limb-girdle muscular dystrophy are variably associated with cardiac or arrhythmia abnormalities in limited reports.

Clinical Presentation

The onset of muscle weakness is variable but usually occurs before age 30. The recessive disorders tend to cause earlier and more severe weakness than the dominant disorders. Creatine kinase levels are moderately elevated. Patients commonly present with complaints of difficulty with walking or running secondary to pelvic girdle involvement. As the disease progresses, involvement of the shoulder muscles and then more distal muscles occurs, with sparing of facial involvement. Slow progression to disability and death can occur.

Cardiovascular Manifestations

As with many of the features of the limb-girdle muscular dystrophies, heterogeneity in the presence and degree of cardiac involvement is usual.

The limb-girdle muscular dystrophies types 2C to 2F, termed *sarcoglycanopathies*, manifest with a dilated cardiomyopathy. Cardiac abnormalities are detected in a majority of patients typically a decade after skeletal muscle symptoms occur. Cardiomyopathy is most common in the subtype 2E and least common in the subtype 2D. ECGs show similar abnormalities as in Duchenne and Becker muscular dystrophy, including an increased R wave in V_1 and lateral Q waves. Imaging can show a progressive dilated cardiomyopathy. A severe cardiomyopathy, including presentation with heart failure in childhood, can occur. Sudden death associated with the cardiomyopathy has been reported. Limb-girdle muscular dystrophy type 2I, caused by mutations in fukutin-related proteins, is associated with a dilated cardiomyopathy. The mutation is also responsible for a form of congenital muscular dystrophy. The age at disease onset and severity of skeletal muscle involvement are variable, with symptoms emerging in some patients during childhood but more typically developing after the age of 20 years. Approximately one half of patients with limb-girdle muscular dystrophy type 2I exhibit cardiac involvement (**Fig. 97.12**). Cardiac involvement has been reported as more common in males. Cardiac findings include regional wall motion abnormalities or a dilated cardiomyopathy and heart failure. Advanced heart failure can occur. Conduction disease does not occur separate from the structural cardiac involvement. Limb-girdle muscular dystrophy type 2B, termed a *dysferlinopathy*, has been associated with increased myocardial fibrosis on cardiac magnetic resonance imaging and variably with a dilated cardiomyopathy.

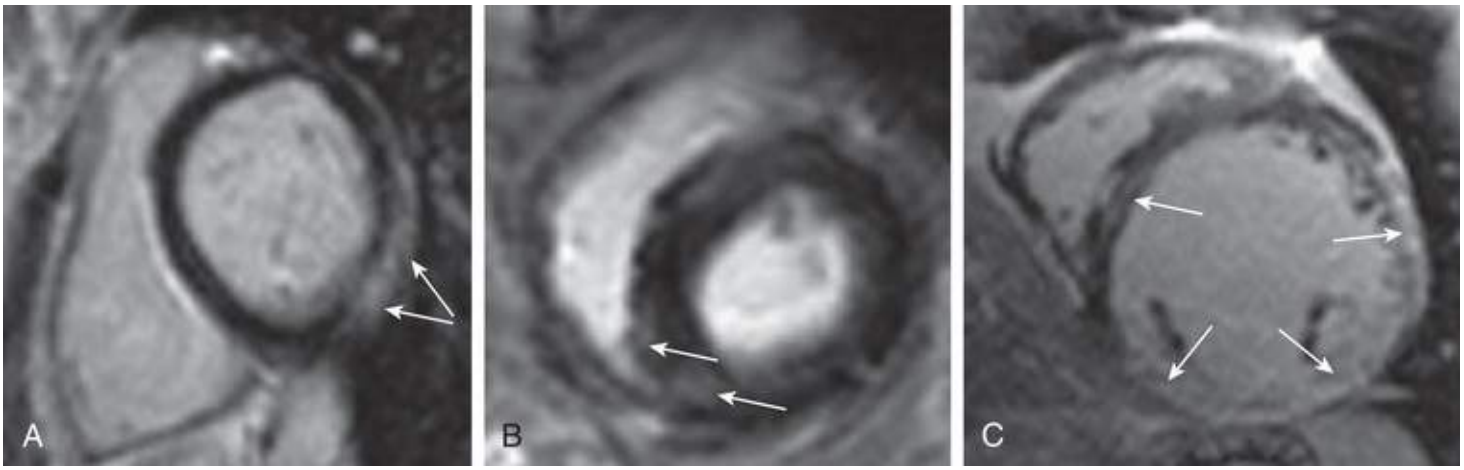


FIGURE 97.12 Cardiac magnetic resonance findings in limb-girdle muscular dystrophy. Late postgadolinium enhancement imaging in limb-girdle muscular dystrophy patients demonstrating **A,** focal epicardial or **B**, midwall enhancement. **C,** a patient with limb-girdle muscular dystrophy 2I and advanced dilated cardiomyopathy had extensive myocardial injury/fibrosis. (From Rosales XQ, Moser SJ, Tran T, et al: Cardiovascular magnetic resonance of cardiomyopathy in limb girdle muscular dystrophy 2B and 2I. J Cardiovasc Magn Reson 2011;13:39.)

The autosomal dominant limb-girdle muscular dystrophy type 1B is caused by mutations in the gene encoding lamins A and C with a clinical phenotype similar to Emery-Dreifuss muscular dystrophy. Skeletal muscle involvement is mild, with cardiac involvement both common and severe. Atrioventricular block develops by early middle age, often necessitating pacing. Sudden death is observed even in patients with pacemakers. A progressive dilated cardiomyopathy can occur, typically after the development of conduction disease.

Treatment and Prognosis

Because of the heterogeneous nature of limb-girdle muscular dystrophy, specific recommendations for routine cardiac evaluation and therapy are based upon the disease type. In patients and families with limb-girdle types that manifest with cardiac involvement, evaluation for ventricular dysfunction, conduction disease, and arrhythmias is indicated. Patients with dilated cardiomyopathies respond to standard heart failure therapy. Heart transplantation has been reported. Prophylactic placement of an implantable cardioverter-defibrillator instead of a pacemaker has been recommended in patients with lamin A and C mutation after conduction disease is observed. In a large observational European series, risk factors for sudden death and appropriate implantable cardioverter-defibrillator therapy included nonsustained ventricular tachycardia, left ventricular ejection fraction less than 45% at presentation, male sex, and lamin A or C non–missense mutations.[20]

Facioscapulohumeral Muscular Dystrophy

Genetics

Facioscapulohumeral muscular dystrophy is the third most common muscular dystrophy after the Duchenne and myotonic types.[22] Underreporting of disease prevalence is likely due to mild subclinical forms. It is a disorder of autosomal dominant inheritance in which the primary genetic mutation occurs at chromosomal locus 4q35, with a contraction of a D4Z4 repeat sequence. The repeat sequence is required to suppress transcription of adjacent genes, and its contraction results in inappropriate protein expression. Genetic heterogeneity with a second mutation has been reported.

Clinical Presentation

Muscle weakness tends to follow a slowly progressive but variable course. The patient initially presents with facial and/or shoulder girdle muscle weakness, which progresses to involve the pelvic musculature.

Cardiovascular Manifestations

Cardiac involvement in facioscapulohumeral muscular dystrophy is reported but does not constitute as significant a problem in prevalence or severity as in other muscular dystrophies. In some series, no evidence of cardiac abnormalities was found. Other series have reported a propensity toward arrhythmias primarily of atrial origin, with atrioventricular conduction abnormalities less common.

Treatment and Prognosis

Because significant clinical cardiac involvement is rare in facioscapulohumeral muscular dystrophy, specific monitoring or treatment recommendations are not well defined. Yearly ECGs have been recommended.

Friedreich Ataxia

Genetics

Friedreich ataxia is a spinocerebellar degenerative disease of autosomal recessive inheritance, characterized clinically by ataxia of the limbs and trunk, dysarthria, loss of deep tendon reflexes, sensory abnormalities, skeletal deformities, diabetes mellitus, and cardiac involvement.[23] The primary genetic abnormality is an expansion of a trinucleotide repeat, guanine-adenine-adenine (GAA), in an intron of a gene that encodes a 210–amino acid mitochondrial protein called frataxin. Loss of frataxin affects mitochondrial iron homeostasis, making the cell susceptible to oxidative stress (**Fig. 97.13**). Messenger RNA for frataxin is highly expressed in the heart. Endomyocardial biopsy samples have shown deficient function in mitochondrial respiratory complex subunits and in aconitase, an iron-sulfur protein involved in iron homeostasis. Impaired mitochondrial lipid metabolism also may play a role in the cardiomyopathy in Friedreich ataxia. Histopathologic examination has revealed myocyte hypertrophy due to proliferation of mitochondria, myocyte degeneration, interstitial fibrosis, active muscle necrosis, bizarre pleomorphic nuclei, and periodic acid–Schiff–(PAS) positive deposition in both large and small coronary arteries. Degeneration and fibrosis in cardiac nerves and ganglia and the conduction system also have been observed. Deposition of calcium salts and iron has been reported.

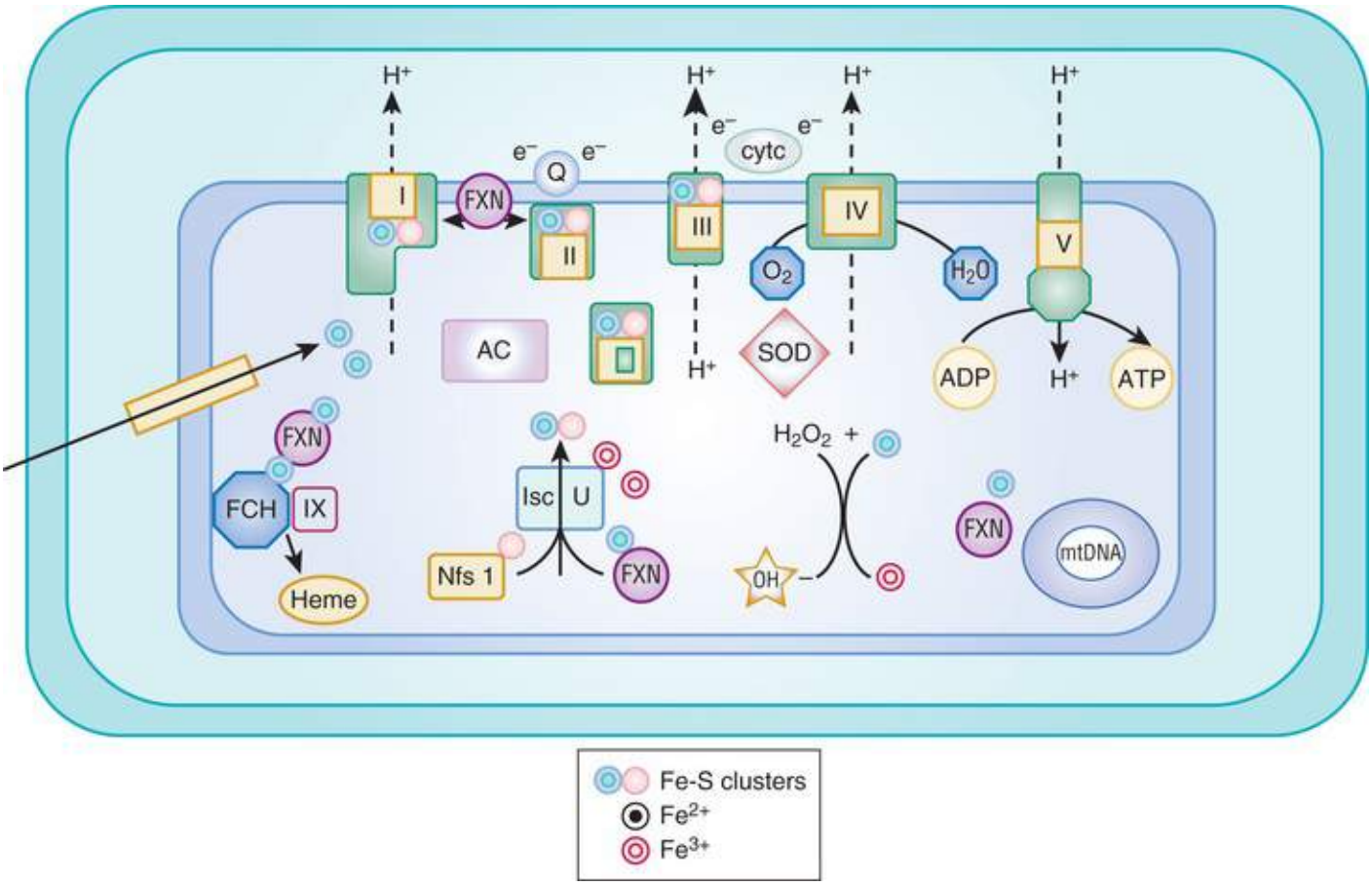


FIGURE 97.13 Postulated functions of frataxin (FXN). 1. Frataxin is a general iron chaperone, providing Fe^{2+} to ferrochelatase (FCH) for heme biosynthesis, mitochondrial iron-sulfur (Fe-S) clusters biogenesis, and maintenance of the mitochondrial aconitase (AC) Fe-S cluster. 2. Frataxin may have a direct interaction with respiratory chain complexes (I-V). 3. Frataxin prevents oxidative stress and protects mitochondrial proteins and mitochondrial DNA (mtDNA) from free Fe^{2+}. It prevents the Fenton reaction by converting Fe^{2+} to Fe^{3+}, and thereby prevents hydroxyl radical formation protecting highly metabolic tissue, including the heart, from oxidative stress. *ADP*, adenosine diphosphate; *ATP*, adenosine triphosphate; *cytc*, cytochrome *c*; e^-, electron; *Isc U*, iron-sulfur cluster scaffold protein; *Nfs*, nitrogen fixation homologue; *Q*, coenzyme Q (ubiquinone); *SOD*, superoxide dismutase. (From Pandolfo M: Friedreich ataxia. Arch Neurol 2008;65:1296.)

An earlier age at symptom onset, increasing severity of neurologic symptoms, and worsening left ventricular hypertrophy are observed in patients in whom genetic testing shows a greater expansion of the GAA repeat.

Clinical Presentation

Friedreich ataxia is the most common inherited spinocerebellar degenerative disease. Neurologic symptoms usually are manifested around puberty and almost always before age 25. Progressive loss of neuromuscular function, with the patient wheelchair-bound 10 to 20 years after symptom onset, is the usual course. Neurologic symptoms precede cardiac symptoms in most but not all cases.

Cardiovascular Manifestations

Friedreich ataxia is associated with a concentric hypertrophic cardiomyopathy (**Fig. 97.14**). Asymmetric septal hypertrophy is rare but has been reported. A left ventricular outflow gradient is atypical but has been observed. The prevalence of hypertrophy increases, particularly with a younger age at diagnosis and also with increasing GAA trinucleotide expansion. Approximately 70% of patients have abnormalities on

imaging studies. Left ventricular hypertrophy is not always present on ECGs despite echocardiographic evidence. Widespread T wave inversions are common (**Fig. 97.15**). Patients with left ventricular hypertrophy without systolic dysfunction typically have no cardiac symptoms. About 10% of patients develop left ventricular systolic dysfunction with an ejection fraction of less than 50%.[24] Presentation with a dilated cardiomyopathy has been reported (**Fig. 97.16**). The dilated cardiomyopathy occurs as a transition from the hypertrophic cardiomyopathy. A severe dilated cardiomyopathy with progressive heart failure can be present.[25]

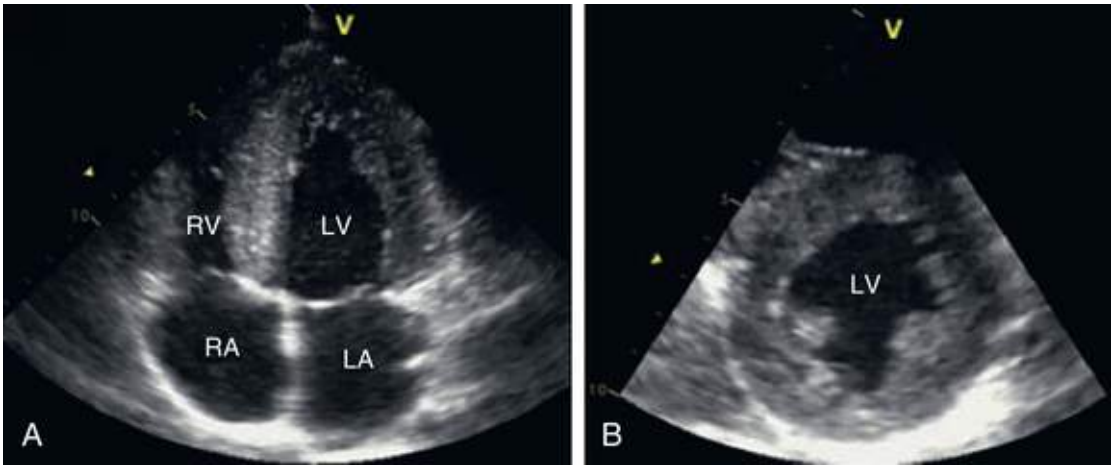


FIGURE 97.14 Hypertrophic cardiomyopathy in Friedreich ataxia. **A**, Echocardiographic apical 4-chamber and **B**, short-axis views from a Friedreich ataxia patient with left ventricular hypertrophy (LV wall thickness 15 mm). *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle. (From Weidemann F, Stork S, Liu D, et al: Cardiomyopathy of Friedreich ataxia. J Neurochem 2013;126[Suppl 1]:88.)

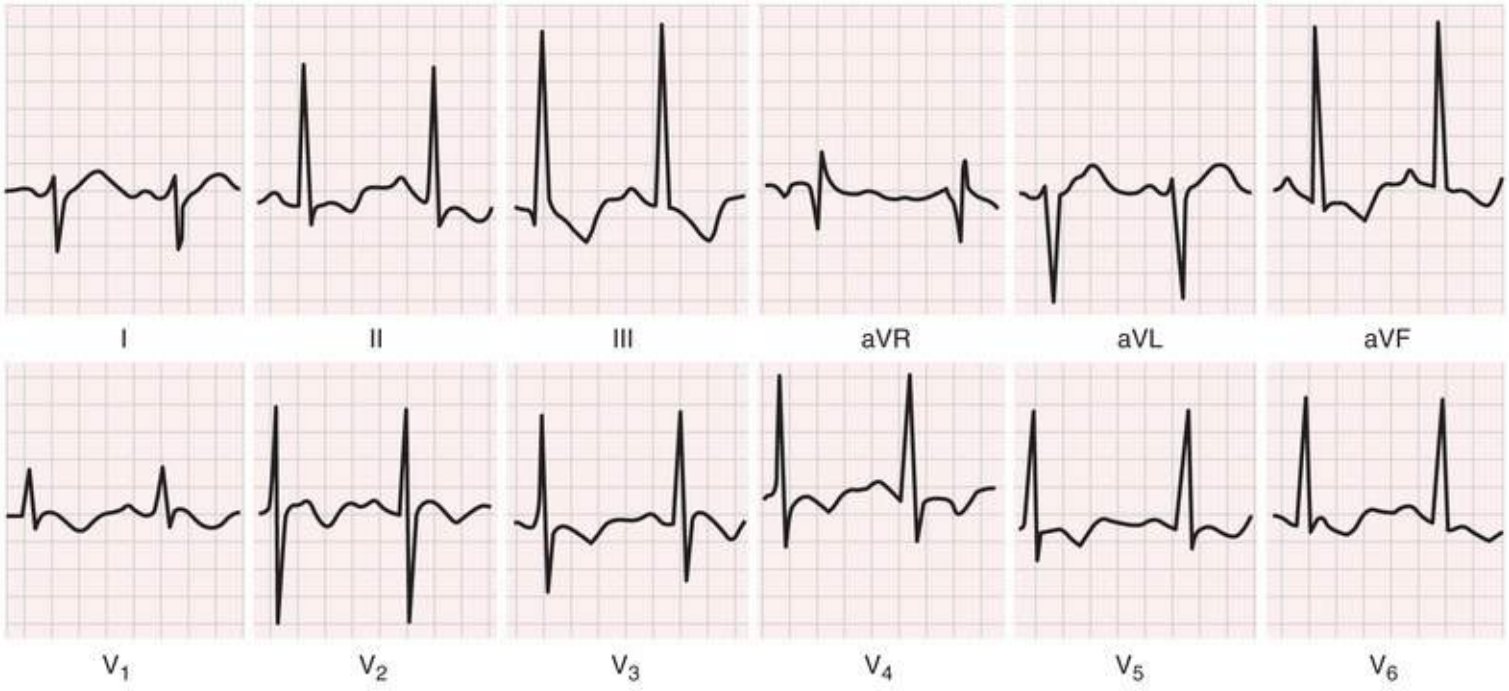


FIGURE 97.15 ECG from a 34-year-old man with Friedreich ataxia. Widespread ST and T changes are evident. (Courtesy Dr. Charles Fisch, Indiana University School of Medicine, Indianapolis.)

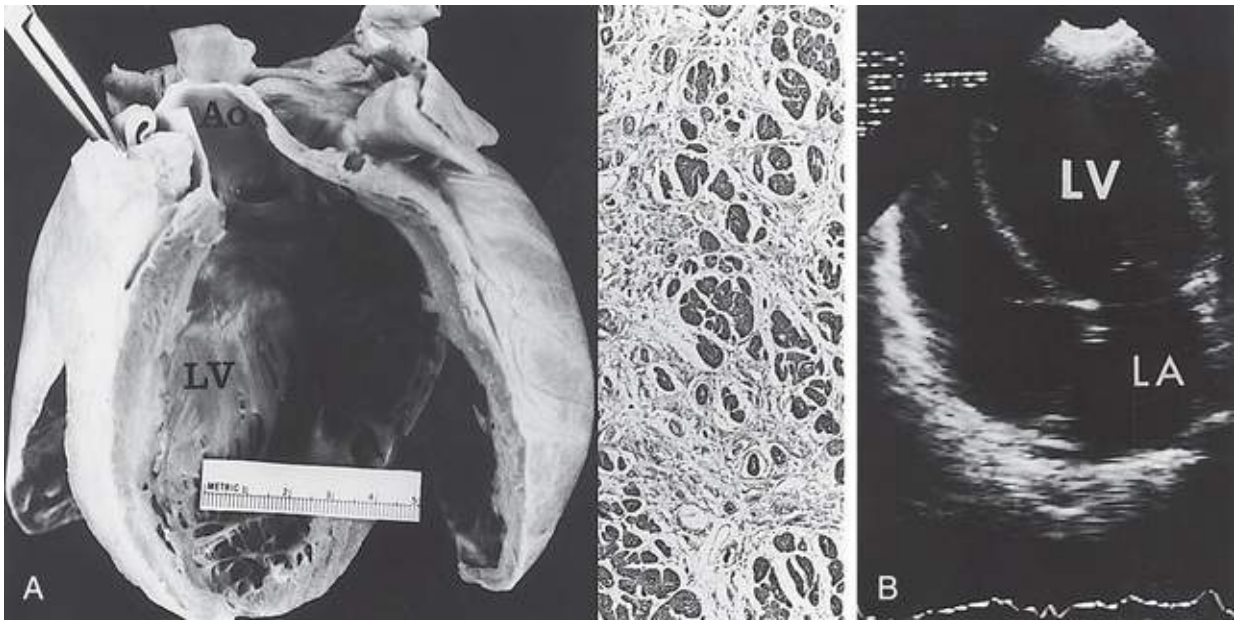


FIGURE 97.16 **A,** Gross and histologic specimens from a 17-year-old boy with Friedreich ataxia whose ECG progressed from a normal appearance at age 13 years to a minimally dilated, hypocontractile left ventricle (LV) 3 to 4 years later. The gross specimen *(left)* shows a mildly dilated LV with normal wall thickness; the walls were flabby. The microscopic section from the left ventricular free wall *(right)* shows marked connective tissue replacement. Although specifically sought, small-vessel coronary artery disease was not identified. **B,** Two-dimensional echocardiogram (apical window) showing the mildly dilated, thin-walled LV. *Ao*, aorta; *LA*, left atrium. (**A, B,** From Child JS, Perloff JK, Bach PM, et al: Cardiac involvement in Friedreich ataxia. J Am Coll Cardiol 1986;7:1370.)

Atrial arrhythmias including atrial fibrillation and flutter are associated with the progression to a dilated cardiomyopathy. Ventricular tachycardia, again in the setting of a dilated cardiomyopathy, has been observed. The hypertrophic cardiomyopathy of Friedreich ataxia is not associated with serious ventricular arrhythmias, as observed in the other types of heritable hypertrophic cardiomyopathies. Myocardial fiber disarray is not commonly observed in the hypertrophic cardiomyopathy of Friedreich ataxia. Sudden death likely due to ventricular arrhythmias has been reported, but a mechanism has not been well characterized.[25]

Treatment and Prognosis

Idebenone, a free radical scavenger, has modest but variable effectiveness for decreasing left ventricular hypertrophy in Friedreich ataxia. Idebenone does not improve left ventricular systolic function. It is unclear whether the modest improvement in cardiac imaging parameters leads to an alteration in the clinical cardiovascular course. Idebenone does not improve neurologic outcomes.

In a majority of patients with Friedreich ataxia, neurologic dysfunction is progressive. Cardiac death occurs in those with a dilated cardiomyopathy. Heart failure is the most common cause of death.[25] Arrhythmias complicate heart failure deaths in one third of patients. Respiratory dysfunction is the second most common cause of death. Death from heart failure occurs earlier than respiratory death, typically before the age of 30 years. The role of pharmacologic or defibrillator therapy in Friedreich ataxia and dilated cardiomyopathy has not been evaluated, but such conventional therapy should be considered until a disease-modifying treatment is available.

Less Common Neuromuscular Diseases Associated With Cardiac Manifestations

The Periodic Paralyses

Genetics and Clinical Presentation

The primary periodic paralyses are rare, nondystrophic disorders of autosomal dominant inheritance resulting from abnormalities in ion channel genes.[26] They can be classified into hypokalemic and hyperkalemic periodic paralyses and Andersen-Tawil Syndrome (**see also Chapter 33**). In addition, acquired hypokalemic periodic paralysis may complicate thyrotoxicosis, especially in men of Asian descent. All patients present with episodic attacks of flaccid paralysis precipitated by variable environmental stimuli including cold and exercise, or with rest after exercise. A late-onset fixed myopathy can occur in hypokalemic and hyperkalemic periodic paralyses.

Hypokalemic periodic paralysis is characterized by episodic attacks of weakness exacerbated by carbohydrate load or occurring during rest after exercise and is associated with decreased serum potassium levels at onset. Penetrance is nearly complete in male patients and 50% in female patients. It is caused by point mutations in the alpha-1 subunit of the dihydropyridine-sensitive calcium channel (CACNA1S) or in the alpha subunit of the skeletal muscle sodium channel (SCN4A). Approximately 20% of cases are of uncertain genetic cause. One third of the cases of thyrotoxic hypokalemic periodic paralysis are caused by mutations in an inward rectifier potassium channel, Kir2.6, which is regulated by thyroid hormone.

Hyperkalemic periodic paralysis also manifests with episodic weakness but with symptoms worsening with potassium supplementation and decreasing with carbohydrate load. Complete penetrance is observed. Potassium levels usually are high but may be normal during an attack. Hyperkalemic periodic paralysis is due primarily to mutations in the alpha subunit of the skeletal muscle sodium channel, *SCN4A*. Multiple different mutations in this gene have been reported that result in a potassium-sensitive failure of inactivation (gain of function) in the sodium channel. Hyperkalemic periodic paralysis is genetically heterogeneous; an *SCN4A* mutation is found in a majority of affected persons, but other loci also have been identified.

Andersen-Tawil syndrome is a distinct periodic paralysis associated with dysmorphic physical features of short stature, low-set ears, micrognathia, hypertelorism, and clinodactyly; abnormalities on the ECG include an abnormal QT-U wave pattern and ventricular arrhythmias[27] (**Fig. 97.17**). Weakness can be triggered by low, normal, or high potassium levels. It can be inherited in an autosomal dominant fashion or can be sporadic. Phenotypic variability and incomplete penetrance can complicate the diagnosis for a given family. Mutations in the *KCNJ2* gene encoding the inward rectifier potassium protein, Kir2.1, that underlie the background current, I_{K1}, are responsible for 60% of cases (type 1 Andersen-Tawil syndrome). The genetic cause(s) in the other 40% of patients (type 2 Andersen-Tawil syndrome) is unknown but seemingly involve other proteins contributing to I_{K1} because the phenotype is indistinguishable from type 1. The loss-of-function of I_{K1} is responsible for the large and prolonged U wave.[28] Andersen-Tawil syndrome has been designated long QT syndrome 7.

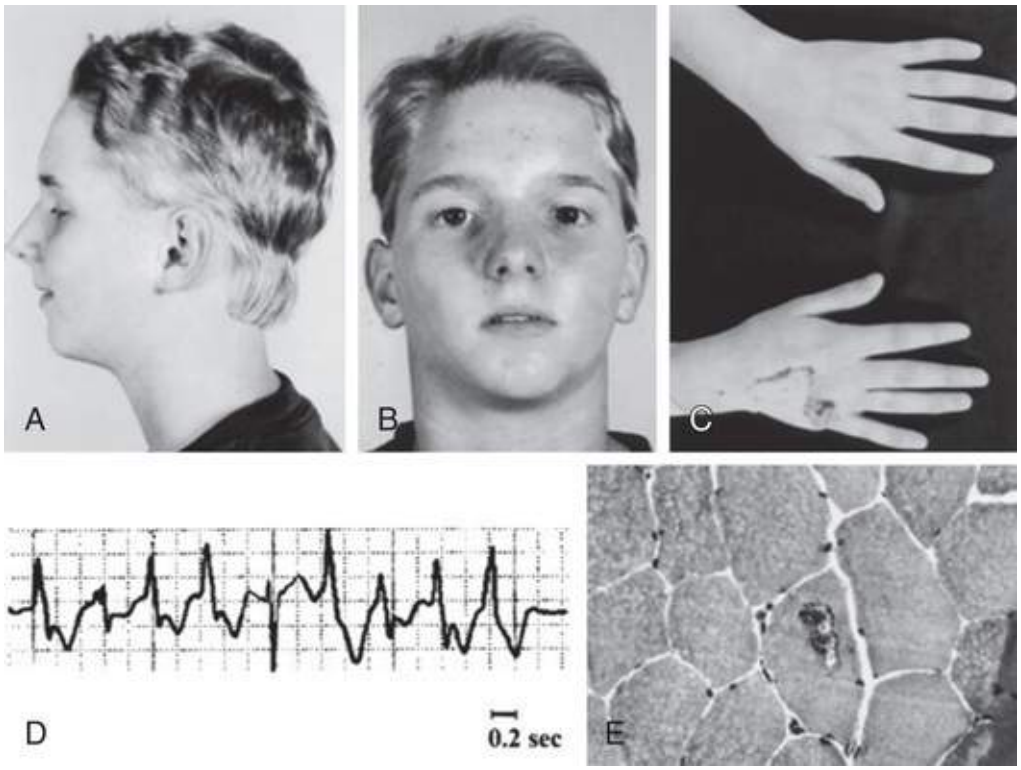


FIGURE 97.17 Andersen-Tawil syndrome. **A, B,** An affected patient exhibits characteristic low-set ears, hypertelorism, micrognathia, and clinodactyly of the fifth digits **(C). D,** ECG rhythm strip demonstrating short runs of polymorphic ventricular tachycardia. **E,** Skeletal muscle biopsy specimen exhibiting tubular aggregates commonly observed in patients with periodic paralysis. (From Plaster NM, Tawil R, Tristani-Firouzi M, et al: Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. Cell 2001;105:511.)

Cardiovascular Manifestations

The periodic paralyses are associated with ventricular arrhythmias. Most arrhythmias occur in hyperkalemic periodic paralysis and Andersen-Tawil syndrome. Bidirectional ventricular tachycardia has been observed without digitalis intoxication (**see also Chapters 12 and 34**). The episodes of bidirectional ventricular tachycardia are independent of attacks of muscle weakness, do not correlate with serum potassium levels, and can convert to sinus rhythm with exercise. The tachycardia typically is less than 150 beats/min and well tolerated. Ventricular ectopy is common.

A prolonged QT interval can be observed. It can be episodic, prolonging associated with weakness or hypokalemia, or occurring as a consequence of antiarrhythmia therapy, or it may be constant. Andersen-Tawil syndrome is associated with a modest prolongation in the QT interval but more specifically a prolonged and prominent U wave. Ventricular arrhythmias, including premature ventricular complexes, ventricular bigeminy, and nonsustained polymorphic ventricular tachycardia, primarily bidirectional tachycardia, are observed in Andersen-Tawil syndrome. Cardiac conduction abnormalities, atypical of long QT syndromes, have been observed in Andersen-Tawil syndrome. Torsades de pointes is observed in Andersen-Tawil syndrome but is less common than in the other long QT syndromes. Syncope, cardiac arrest, and sudden death have been reported in the periodic paralyses, most prominently in the Andersen-Tawil syndrome. The factors that portend an increased risk of life-threatening arrhythmias are not clear. The frequency of ventricular ectopy or nonsustained ventricular tachycardia on ambulatory monitoring did not differentiate Andersen-Tawil syndrome patients with and without syncope.[29]

Treatment and Prognosis

The episodes of weakness typically respond to measures that normalize potassium levels. Weakness in hyperkalemic periodic paralysis can respond to mexiletine. Weakness in hypokalemic periodic paralysis can respond to acetazolamide. Treatment targeting electrolyte abnormalities usually does not ameliorate arrhythmias or, if it does, affords only transient benefit. Improvement in symptomatic nonsustained ventricular tachycardia associated with a prolonged QT interval has been reported with beta-blocker therapy. Class 1A antiarrhythmia agents can worsen muscle weakness and exacerbate arrhythmias associated with a prolonged QT interval. Bidirectional ventricular tachycardia, not associated with a prolonged QT interval, may not respond to beta-blocker therapy. Flecainide decreases the frequency of ventricular arrhythmias assessed by ambulatory monitoring and is associated with a good clinical outcome over 2 years in Andersen-Tawil syndrome.[30] Amiodarone and imipramine have also been shown to have efficacy in small series and case reports. The use of implantable cardioverter-defibrillators has been reported in the Andersen-Tawil syndrome, primarily in those with symptomatic and drug-refractory sustained ventricular arrhythmias.[29] Programming of defibrillators to avoid inappropriate discharges is problematic because ventricular tachycardia is often self-terminating. Prognosis in the Andersen-Tawil syndrome is good despite frequent episodes of ventricular ectopy.

Mitochondrial Disorders

Genetics and Clinical Presentation

The mitochondrial disorders, also termed mitochondrial myopathies, encephalomyopathies, or respiratory chain disorders, are a heterogeneous group of diseases resulting from abnormalities in mitochondrial DNA and respiratory chain function.[31] The list of distinct disorders is extensive. Mitochondrial DNA is inherited maternally, and some of these disorders are thus transmitted from mother to children of both sexes. Many other disorders result from abnormalities in nuclear DNA involved in mitochondrial form and function and are inherited in an autosomal or X-linked fashion. Sporadic cases can occur. Disease severity can vary among family members because both mutant and normal mitochondrial DNA can be present in tissue in variable proportions. a phenomenon termed *heteroplasmy*. It is not surprising, in view of the metabolic function of mitochondria, that these disorders manifest with systemic pathology. Tissue with a high respiratory workload such as brain and skeletal muscle, especially extraocular, retinal, and cardiac muscle, are primarily affected.

Mitochondrial disorders that have cardiac manifestations may appear as part of several clinical phenotypes. *Chronic progressive external ophthalmoplegia* is characterized by involvement of the extraocular muscles and can also involve oropharyngeal muscles. It is primarily a sporadic disease. *Kearns-Sayre syndrome*, a subtype of chronic progressive external ophthalmoplegia, is characterized by ocular myopathy, pigmentary retinopathy, and age at onset before 20 years. Diabetes, deafness, and ataxia can also be associated. *Myoclonus epilepsy with red ragged fibers* (MERRF) is characterized by myoclonus, seizures, ataxia, dementia, and skeletal muscle weakness. *Mitochondrial myopathy with encephalopathy, lactic acidosis, and strokelike episodes* (MELAS) is the most common of the maternally inherited mitochondrial disorders and is characterized by encephalopathy, subacute strokelike events, migraine-like headaches, recurrent emesis, extremity weakness, and short stature. *Leber hereditary optic neuropathy* causes subacute blindness, primarily in young men. Other, mitochondrial point mutation disorders, including *NARP* (neuropathy, ataxia, and retinitis pigmentosa) and *Leigh syndrome* (subacute necrotizing encephalomyelopathy) cause neurodegenerative disorders primarily in children. *Barth syndrome* is an X-linked mitochondrial disease manifested by hypotonia, growth retardation, cyclic neutropenia, and 3-methylglutaconic aciduria in children. It is caused by mutations in exons of the nuclear

gene encoding the tafazzin protein.

Cardiovascular Manifestations

Patients with mitochondrial myopathy can present with chest pain or, more typically, dyspnea with exertion.[32] In chronic progressive external ophthalmoplegia, most commonly in the Kearns-Sayre syndrome variant, cardiac involvement manifests primarily as conduction abnormalities. In the Kearns-Sayre syndrome, atrioventricular block is observed, usually manifesting after eye involvement. The H-V interval is prolonged, consistent with distal conduction disease. Permanent pacing often is seen by early- to mid-adulthood. An increased prevalence of electrocardiographic preexcitation has also been reported. Cardiac magnetic resonance imaging demonstrates nonischemic, late gadolinium enhancement in approximately one third of patients.[32] A dilated cardiomyopathy may occur.

In MERRF and MELAS, a hypertrophic (symmetric or asymmetric) or dilated cardiomyopathy can occur. Other disorders caused by mitochondrial point mutations can manifest with a similar cardiac phenotype of hypertrophic or dilated cardiomyopathy, often in children. Whether the dilated cardiomyopathy represents a progression from the hypertrophic cardiomyopathy or a separate syndrome is not clear. The dilated cardiomyopathy can result in heart failure and death. More than one half of patients with MELAS had nonischemic, late gadolinium enhancement on cardiac magnetic resonance imaging.[32] Leber hereditary optic neuropathy can be associated with a hypertrophic cardiomyopathy and a short PR interval or preexcitation syndromes (**see also Chapter 37**). Barth syndrome is associated with left ventricular noncompaction and endocardial fibroelastosis or a hypertrophic or dilated cardiomyopathy. Heart failure and ventricular arrhythmias occur, often in young children. Cardiac transplantation has been reported.

Treatment and Prognosis

In Kearns-Sayre syndrome, the implantation of a pacemaker has been advocated when significant or progressive conduction disease is evident, even for those cases in asymptomatic patients. The degree of conduction disease that warrants prophylactic pacing is not clear. Implantable cardioverter-defibrillators are recommended in patients with both conduction disease and a dilated cardiomyopathy. In the other mitochondrial disorders, an understanding of the potential and specific presentations for cardiac involvement is necessary. Cardiac evaluation, electrocardiography, echocardiography, and other imaging modalities are recommended. Prophylactic or symptomatic heart failure pharmacotherapy, although not studied in these rare diseases, would seem warranted. Improved survival rates in children with Barth syndrome receiving aggressive treatment for cardiomyopathy and neutropenia has been observed.[33]

Spinal Muscular Atrophy

Genetics and Clinical Presentation

Spinal muscular atrophy is a lower motor neuron disorder manifesting as progressive, symmetric proximal muscular weakness.[34] It is the leading inherited cause of infant death. Spinal muscular atrophy is classified clinically by the age at symptom onset and disease severity into type I (Werdnig-Hoffman disease), type II (intermediate form), type III (Kugelberg-Welander disease), and type IV (adult-onset spinal muscular atrophy).

Spinal muscular atrophy is inherited in autosomal recessive fashion or is sporadic. Mutations or deletions in the telomeric *SMN* (survival of motor neuron) gene are observed in most patients. The loss of

functional SMN protein results in premature neuronal cell death. The SMN protein has a role in cardiac development.

Cardiovascular Manifestations

Cardiac abnormalities reported with spinal muscular atrophy include congenital heart disease, cardiomyopathy, and arrhythmias. Congenital heart disease can be seen with types I and III spinal muscular atrophy (**see also Chapter 75**). The most common abnormality is atrial septal defect; other reports have found ventricular septal defects and hypoplastic left heart syndrome. In spinal muscular atrophy type III, a dilated cardiomyopathy can occur, with endomyocardial biopsy demonstrating fibrosis. Arrhythmias reported include atrial standstill, atrial fibrillation, atrial flutter, and atrioventricular block. Permanent pacing for atrial standstill and atrioventricular block has been reported. Recent reports have questioned whether the noncongenital cardiac abnormalities observed in spinal muscular atrophy are primary or are secondary to progressive pulmonary failure.[35]

Treatment and Prognosis

In spinal muscular atrophy type I, severe skeletal muscle involvement with respiratory failure can limit the lifespan, and treatment of cardiac abnormalities is often not done. In spinal muscular atrophy type III, awareness of the potential for associated cardiac abnormalities is necessary. Directed gene therapy to improve the functional SMN protein holds future promise.

Desmin-Related Myopathies

Genetics and Clinical Presentation

Desmin myopathy is a rare inherited dystrophic disorder affecting skeletal and cardiac muscle.[36,37] The disorder is inherited primarily in autosomal dominant fashion, but autosomal recessive inheritance and sporadic disease have been reported. Typically, symptomatic skeletal muscle abnormalities will be recognized before cardiac involvement. Variability in the phenotype is recognized, however, and in members of affected families, a cardiomyopathy can develop without obvious skeletal muscle abnormalities. Desmin is a cytoskeletal protein that functions as the chief intermediate filament providing support to contracting skeletal and cardiac muscle. Mutations in the desmin gene lead to a disruption in forming functioning intermediate filaments.

Patients typically present in their late 20s with distal weakness that progresses proximally. Difficulty with ambulation and, in severe cases, with respiration can occur. Creatine kinase is mildly elevated in some patients. Muscle biopsy is diagnostic, showing desmin and other myofibrillar protein aggregation with immunostaining. Genetic testing is available.

Cardiovascular Manifestations

The cardiomyopathy associated with the desmin-related myopathies can occur prior to or after the diagnosis of a skeletal myopathy. The cardiac involvement observed typically consists of conduction system disease and, more rarely, ventricular arrhythmias, before the onset of a dilated or restrictive cardiomyopathy.[38] An arrhythmogenic right ventricular cardiomyopathy–like phenotype has been reported. Both sudden death and heart failure–related deaths can occur. Sudden death can occur despite pacemaker implantation.

Treatment and Prognosis

The desmin-related myopathies should be considered in the differential diagnosis in individual patients or families presenting with a skeletal or cardiac myopathy, including those with an arrhythmogenic right ventricular cardiomyopathy. Monitoring for the development of cardiac conduction and structural disease is necessary in affected families. Asymptomatic conduction disease on the ECG predicts future adverse cardiac events.[38] Prophylactic pacemakers or implantable cardioverter-defibrillators should be considered in those patients with significant conduction disease. Heart failure pharmacotherapy is indicated.

Guillain-Barré Syndrome

Clinical Presentation

The Guillain-Barré syndrome is an acute inflammatory demyelinating neuropathy characterized by peripheral, cranial, and autonomic nerve dysfunction (**see also Chapter 99**).[39] It is the most common acquired demyelinating neuropathy. Men are more commonly affected than women. In two thirds of affected patients, an acute viral or bacterial illness, typically respiratory or gastrointestinal, precedes the onset of neurologic symptoms within 6 weeks. The disorder typically manifests with pain, paresthesias, and symmetric limb weakness that progresses proximally and can involve cranial and respiratory muscles. One fourth of affected patients require assisted ventilation.

Cardiovascular Manifestations

Nonambulant patients are at increased risk for deep vein thrombosis and pulmonary emboli. Cardiac involvement related to accompanying autonomic nervous system dysfunction is seen in one half of the patients. Cardiac manifestations include hypertension, orthostatic hypotension, resting sinus tachycardia, loss of heart rate variability, electrocardiographic ST abnormalities, and both bradycardia and tachycardias. Pediatric patients typically have hypertension and tachycardia but rarely bradycardia.[40] Microneurographic recordings have shown increased sympathetic outflow during the acute illness, which normalizes with recovery.

Life-threatening arrhythmias occur in Guillain-Barré syndrome, primarily in patients requiring assisted ventilation. Arrhythmias observed include asystole, symptomatic bradycardia, rapid atrial fibrillation, and ventricular tachycardia or fibrillation. Asystole commonly was associated with tracheal suctioning. Death may occur as a consequence of an arrhythmia.

Treatment and Prognosis

Supportive care should include deep vein thrombosis prophylaxis in nonambulant patients. Early plasmapheresis or intravenous immunoglobulin can improve recovery. In severely affected patients, especially those requiring assisted ventilation, cardiac rhythm monitoring is mandatory. It is reasonable to monitor the rhythm via telemetry in all those admitted with Guillain-Barré syndrome. If serious bradycardia or asystole is observed, temporary or permanent pacing can improve survival. Atropine or isoproterenol during tracheal suctioning can be of benefit. The mortality rate in patients hospitalized with Guillain-Barré syndrome is as high as 15%. In patients who recover from Guillain-Barré syndrome, autonomic function also normalizes, and long-term arrhythmia risk has not been observed.

Myasthenia Gravis

Clinical Presentation

Myasthenia gravis is a disorder of neuromuscular transmission resulting from production of antibody targeted to the nicotinic acetylcholine receptor or muscle-specific receptor tyrosine kinase.[41] The primary symptom, fluctuating weakness, usually begins with the eye and facial muscles and later can involve the large muscles of the limbs. Patients can present at any age, typically at a younger age in women and at an older age in men. Myasthenia gravis is commonly associated with hyperplasia or a benign or malignant tumor (thymoma) of the thymus gland. Multiple autoimmune diseases can complicate myasthenia gravis.

Cardiovascular Manifestations

A myocarditis can occur in patients with myasthenia gravis, especially in those with a thymoma (**see also Chapters 79 and 92**). The etiologic mechanism in myocarditis is a humoral immune response against striational proteins, including titin, the ryanodine receptor, and a potassium-channel protein.[42] Up to 16% of patients with myasthenia gravis have cardiac manifestations not explained by another etiologic disorder. Presentation with arrhythmias, which can include atrial fibrillation, atrioventricular block, asystole, ventricular tachycardia, sudden death, or heart failure, is typical. Autopsy findings are consistent with myocarditis, often giant cell myocarditis. A polymyositis affecting both skeletal and cardiac muscle is seen.[43]

Treatment and Prognosis

Myasthenia gravis is treated with anticholinesterases and immunosuppressive agents. Thymectomy is often indicated. Anticholinesterase agents may slow the sinus rate and cause heart block and hypotension. Pacing can be necessary. Whether immunosuppressive agents or thymectomy might improve associated cardiac disease is unknown. Case reports have described the development of rapidly progressive and fatal heart failure within weeks after thymoma resection in patients in whom histologic examination showed giant cell myocarditis.

Epilepsy

Cardiovascular Manifestations

Epilepsy is a complex brain disorder characterized by chronic unprovoked seizures.[44] Patients with epilepsy are at increased risk for sudden death of unknown cause, which has been termed *sudden unexpected death in epilepsy* (SUDEP) (**see also Chapter 42**). It is the leading cause of premature death in patients with epilepsy, with an incidence ranging from 0.1 to 9.3 per 1000 patient-years, depending on the population studied.[45] The mechanisms leading to sudden death in epilepsy are not clear and probably vary. Central or obstructive postictal apnea, mechanical suffocation possibly exacerbated by prone positioning, excessive respiratory secretions, acute pulmonary edema, and arrhythmias all may be involved (**Fig. 97.18**). A number of drugs affecting the brain prolong the QT interval (**see also Chapters 8 and 36**). A majority of witnessed sudden deaths occur at or in proximity to the time of a seizure. Severe bradycardia with sinus arrest has been documented in monitored patients during seizures, including studies with an implantable loop recorder. Periictal bradycardia is more common in patients with temporal lobe seizures. Whether bradycardia has a role in epileptic patients who experience sudden death

is not clear. Primary ventricular arrhythmia disorders such as long-QT syndrome or right ventricular dysplasia can manifest with symptoms suggestive of epilepsy and could be responsible for a small proportion of sudden deaths. Patients can have concomitant epilepsy and heart disease, leading to ventricular arrhythmias and cardiac arrest.[46]

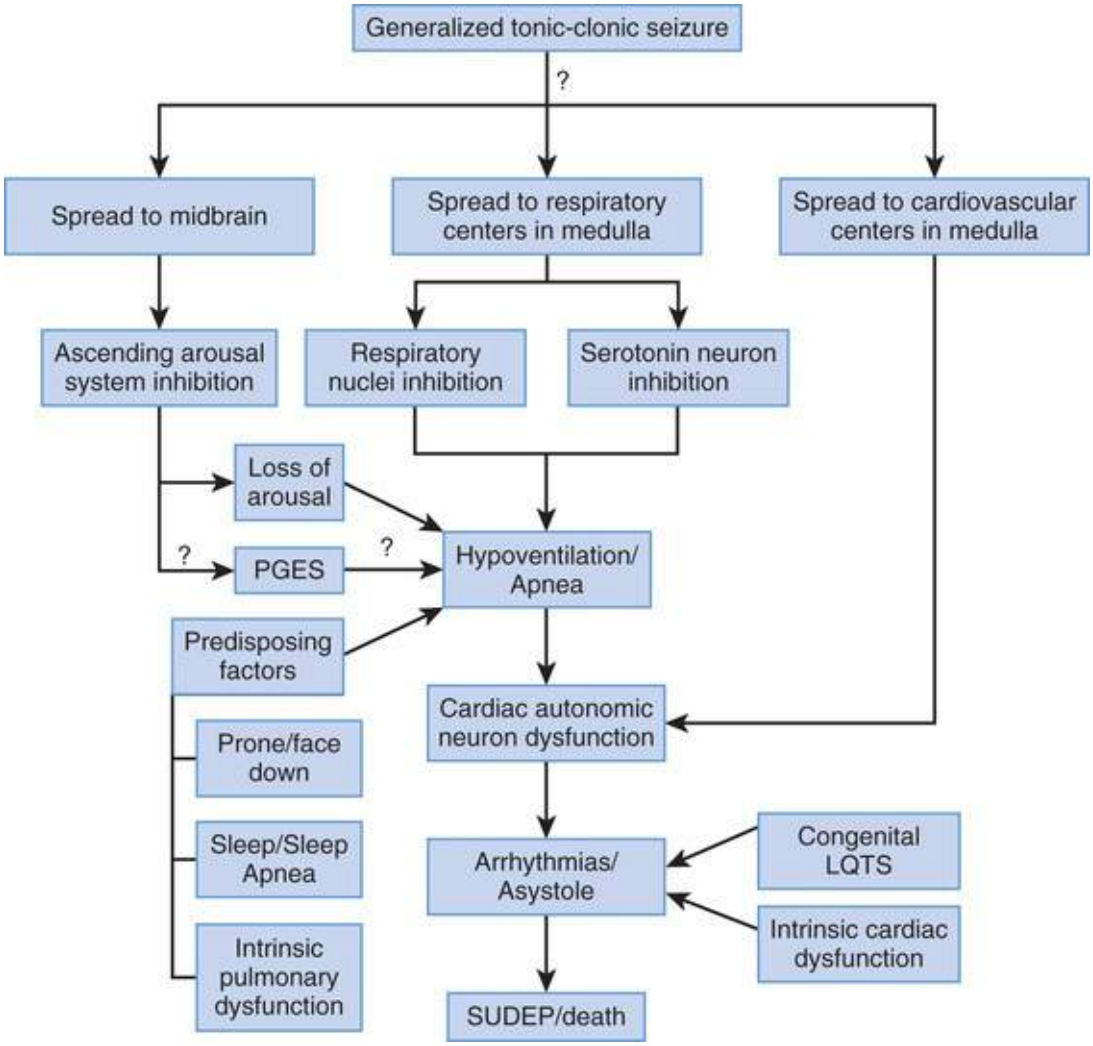


FIGURE 97.18 Pathophysiologic mechanisms underlying sudden unexpected death in epilepsy (SUDEP). SUDEP often results from a generalized tonic-clonic seizure, which leads to inhibition of specific midbrain- and medulla-mediated effects via an unknown pathway. Other factors shown may predispose these patients to SUDEP. *LQTS*, long QT syndrome; *PGES*, postictal generalized EEG suppression. (From Dlouhy BJ, Gehlbach BK, Richerson GB: Sudden unexpected death in epilepsy: basic mechanisms and clinical implications for prevention. J Neurol Neurosurg Psychiatry 2016;87:402.)

Observational studies have assessed risk factors for SUDEP. These include male sex, onset of epilepsy at a young age, a long duration of epilepsy, high seizure frequency especially of generalized tonic-clonic seizures, and the need for polytherapy to control seizures.[45]

Treatment and Prognosis

A primary arrhythmia disorder needs to be considered in the differential diagnosis of epilepsy. Patients with poorly controlled epilepsy should be aggressively evaluated and treated at tertiary epilepsy centers. Epilepsy surgery should be strongly considered. Patients with ictal bradycardia can require pacemaker implantation. Nighttime supervision of the epileptic patient and supine sleeping positions should be considered.

Acute Cerebrovascular Disease

Cardiovascular Manifestations

Acute cerebrovascular diseases, including subarachnoid hemorrhage, other stroke syndromes, and head injury, can be associated with severe cardiac manifestations (**see also Chapter 65**).[47,48] The mechanism by which cardiac abnormalities occur with brain injury is related to autonomic nervous system dysfunction, with both increased sympathetic and parasympathetic output (**see also Chapter 99**). Excessive myocardial catecholamine release is primarily responsible for the observed cardiac pathology. Hypothalamic stimulation can reproduce the electrocardiographic changes observed in acute cerebrovascular disease. Electrocardiographic changes associated with hypothalamic stimulation or blood in the subarachnoid space can be diminished with spinal cord transection, stellate ganglion blockade, vagolytics, and adrenergic blockers.

Electrocardiographic abnormalities are observed in approximately 70% of patients with subarachnoid hemorrhage. Abnormalities including ST elevation and depression, T wave inversion, and pathologic Q waves are observed. Peaked inverted T waves and a prolonged QT interval can occur in a significant proportion of patients with electrocardiographic abnormalities associated with cerebrovascular disease (**Fig. 97.19**). Hypokalemia often seen in patients with subarachnoid hemorrhage can increase the likelihood of QT interval prolongation. Other stroke syndromes often are associated with abnormalities on the ECG, but whether these are related to the stroke syndrome or to underlying intrinsic cardiac disease often is difficult to discern. A prolonged QT interval is more common in subarachnoid hemorrhage than in other stroke syndromes. Closed head trauma can cause electrocardiographic abnormalities similar to those in subarachnoid hemorrhage, including a prolonged QT interval.

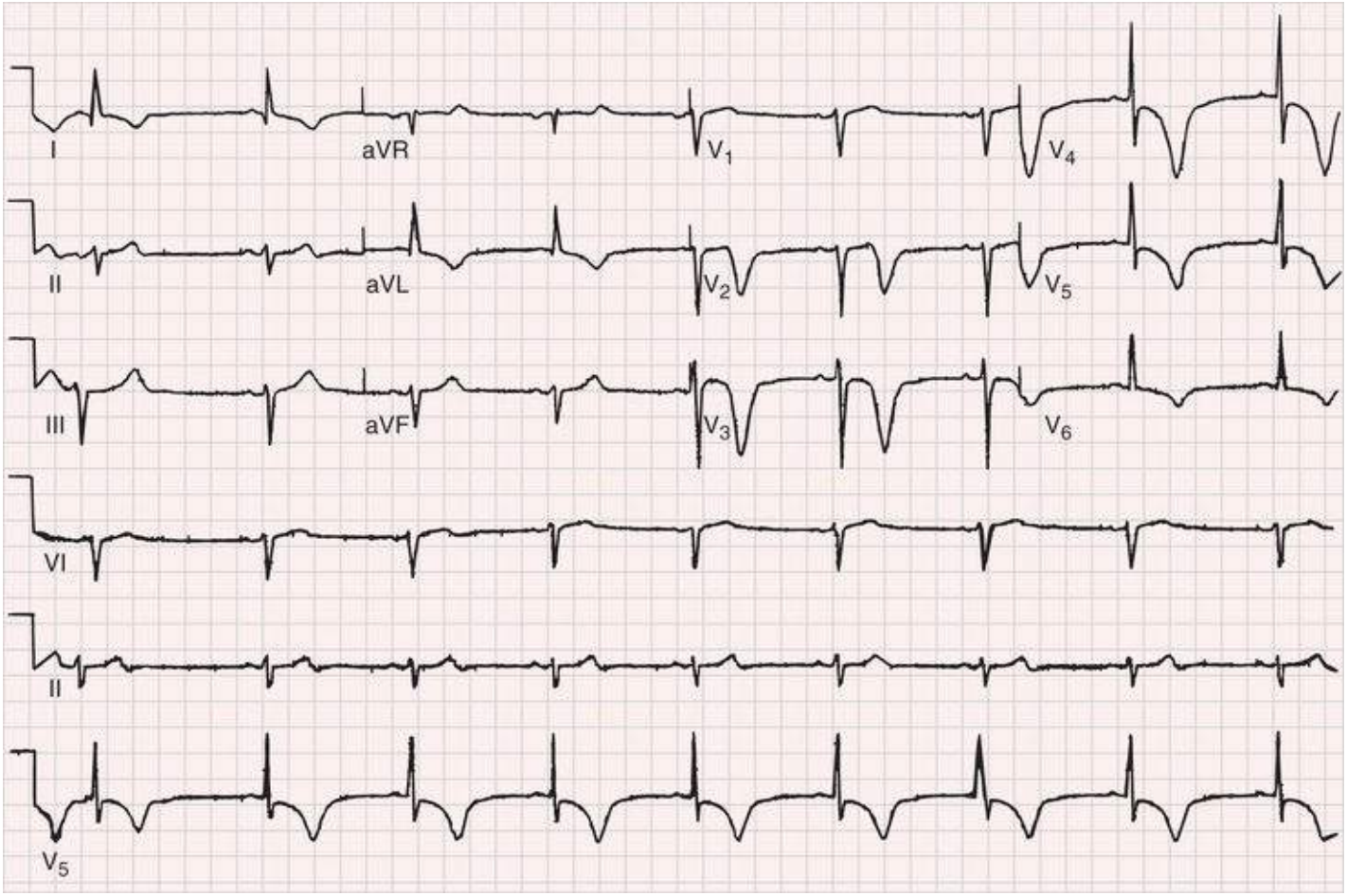
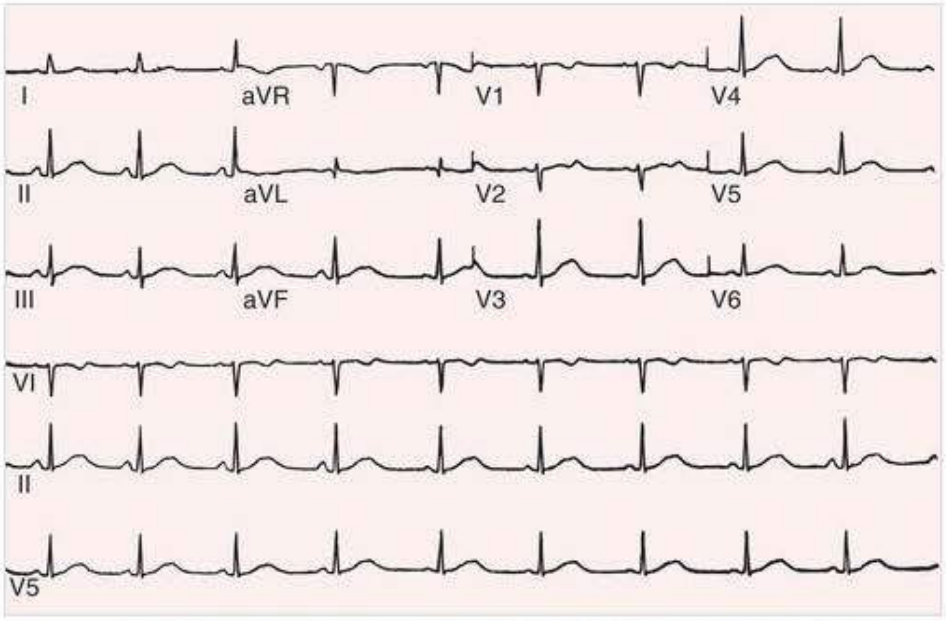


FIGURE 97.19 ECG from a patient with cerebral hemorrhage. Deep and symmetric T wave inversions are evident. (Courtesy Dr. Charles Fisch, Indiana University School of Medicine, Indianapolis.)

Myocardial damage with liberation of enzymes and subendocardial hemorrhage or fibrosis at autopsy can occur in the setting of acute cerebral disease. The term *neurogenic stunned myocardium* is used to describe the reversible syndrome. The process can manifest with selective apical involvement, a takotsubo cardiomyopathy. Cardiac troponin elevation and echocardiographic evidence of left ventricular dysfunction are present in a significant proportion of patients with subarachnoid hemorrhage. Patients with a poorer neurologic status at admission are more likely to have an increased peak troponin level. Women are at higher risk for myocardial necrosis.

Pulmonary edema can accompany the acute neurologic insult. The edema can have both a cardiogenic component, related to systemic hypertension and left ventricular dysfunction, and a neurogenic (pulmonary capillary leak) component.

Life-threatening arrhythmias can occur in the setting of acute cerebrovascular disease. Ventricular tachycardia or fibrillation has been observed in patients with subarachnoid hemorrhage and head trauma. Torsades de pointes–type ventricular tachycardia can occur (**Fig. 97.20**) (**see also Chapter 39**). Often this is observed in the setting of a prolonged QT interval and hypokalemia. Stroke syndromes other than subarachnoid hemorrhage appear to be only rarely associated with serious ventricular tachycardias. Atrial arrhythmias, including atrial fibrillation and regular supraventricular tachycardia, have been observed. Atrial fibrillation is most common in patients presenting with acute thromboembolic stroke. Separating an effect from the cause can be difficult. Bradycardias, including sinoatrial block, sinus arrest, and atrioventricular block, occur in up to 10% of patients with subarachnoid hemorrhage.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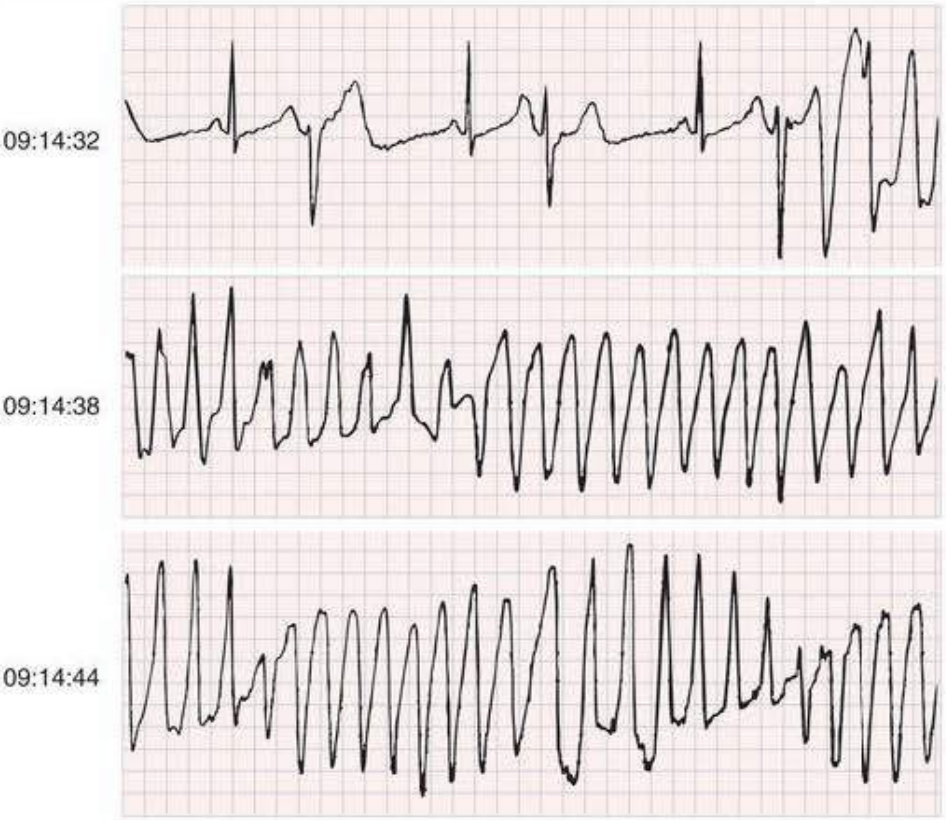
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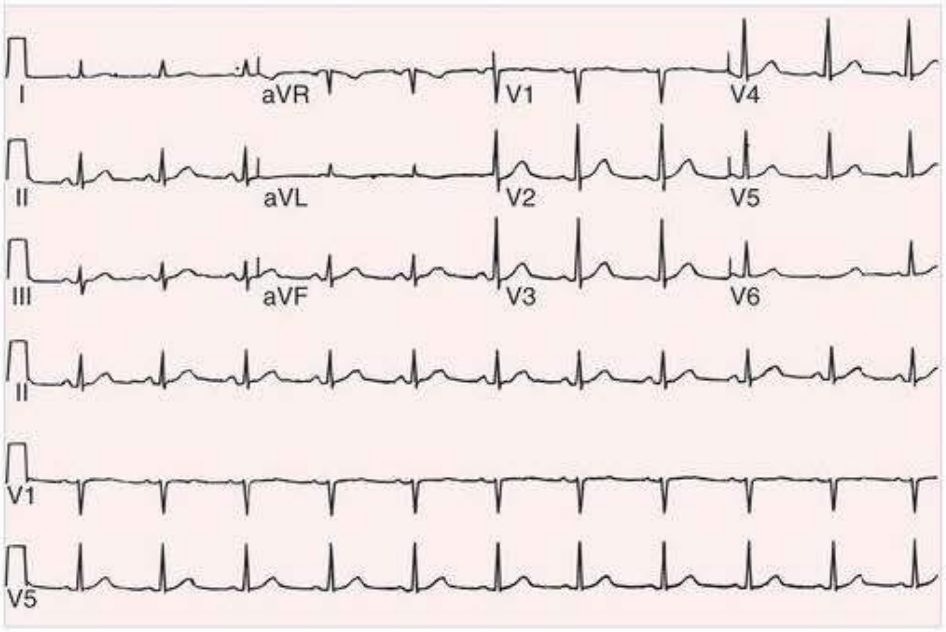
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FIGURE 97.20 Cardiac manifestations with cerebral hemorrhage in a 49-year-old patient. **A,** ECG recorded within 3 hours of admission and 4 hours after onset of symptoms. QT interval prolongation is evident. **B,** Electrocardiographic monitoring 6 hours after admission. Ventricular bigeminy precedes the onset of polymorphic ventricular tachycardia. Cardioversion was required. The patient subsequently was treated with a beta-adrenergic blocker without further ventricular tachycardia. **C,** On an ECG obtained 2 weeks after hospital admission, the QT interval has normalized.

Treatment and Prognosis

Beta blockers appear to be effective in decreasing myocardial damage and in controlling both supraventricular and ventricular arrhythmias associated with subarachnoid hemorrhage and head trauma. Beta blockers increase the likelihood of bradycardia and cannot be used in patients with hypotension requiring vasopressors. Life-threatening arrhythmias occur primarily in the first day after a neurologic event. Continuous electrocardiographic monitoring during this period is indicated. Careful monitoring of potassium levels, especially in patients with subarachnoid hemorrhage, is warranted. Refractory ventricular arrhythmias have been controlled effectively with stellate ganglion blockade. Electrocardiographic abnormalities reflect unfavorable intracranial factors but do not appear to portend a poor cardiovascular outcome. The magnitude of peak troponin elevation is predictive for adverse patient outcomes, including severe disability at hospital discharge and death.[47]

Head injury (blunt trauma or gunshot wound) and cerebrovascular accidents are the leading causes of brain death in patients being considered as heart donors. These donors can manifest electrocardiographic abnormalities, hemodynamic instability, and myocardial dysfunction related primarily to adrenergic storm and not to intrinsic cardiac disease. Experimental studies on whether contractile performance recovers with transplantation are still controversial. Optimization of volume status and inotropic support with careful echocardiographic evaluation and possibly left-heart catheterization can allow the use of some donor hearts that would have otherwise been rejected.

Future Perspectives

Adult cardiologists and electrophysiologists are increasingly participating in the multidisciplinary management of patients with neurologic disorders that manifest cardiac issues. For many of these complex patients, management in tertiary centers is appropriate. Decisions on the use of pharmacotherapy and device therapy to manage cardiac manifestations will need to extrapolate indications from other patient groups because randomized controlled trial data will not be available for a majority of these rare diseases. Gene-based or molecular-targeted therapy is under current evaluation in many of the neurologic diseases and holds future promise.

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98

Interface Between Renal Disease and Cardiovascular Illness

Peter A. Mccullough

The Cardiorenal Intersection

The heart and kidney are inextricably linked in terms of hemodynamic and regulatory functions. In a

normal 70-kg human, each kidney weighs about 130 to 170 g and receives blood flow of 400 mL/min per 100 g; this is approximately 20% to 25% of the cardiac output, and it allows the needed flow to maintain glomerular filtration by approximately 1 million nephrons (**Fig. 98.1**). This flow is several times greater per unit of weight than in most other organs. Although their oxygen extraction is low, the kidneys account for about 8% of the total oxygen consumption of the body. The kidney has a central role in electrolyte balance, protein production and catabolism, and blood pressure regulation. Communication between the kidney and the heart occurs at multiple levels, including via the sympathetic nervous system (SNS), via the renin-angiotensin-aldosterone system (RAAS), and by means of the substances vasopressin, endothelin, and the natriuretic peptides.

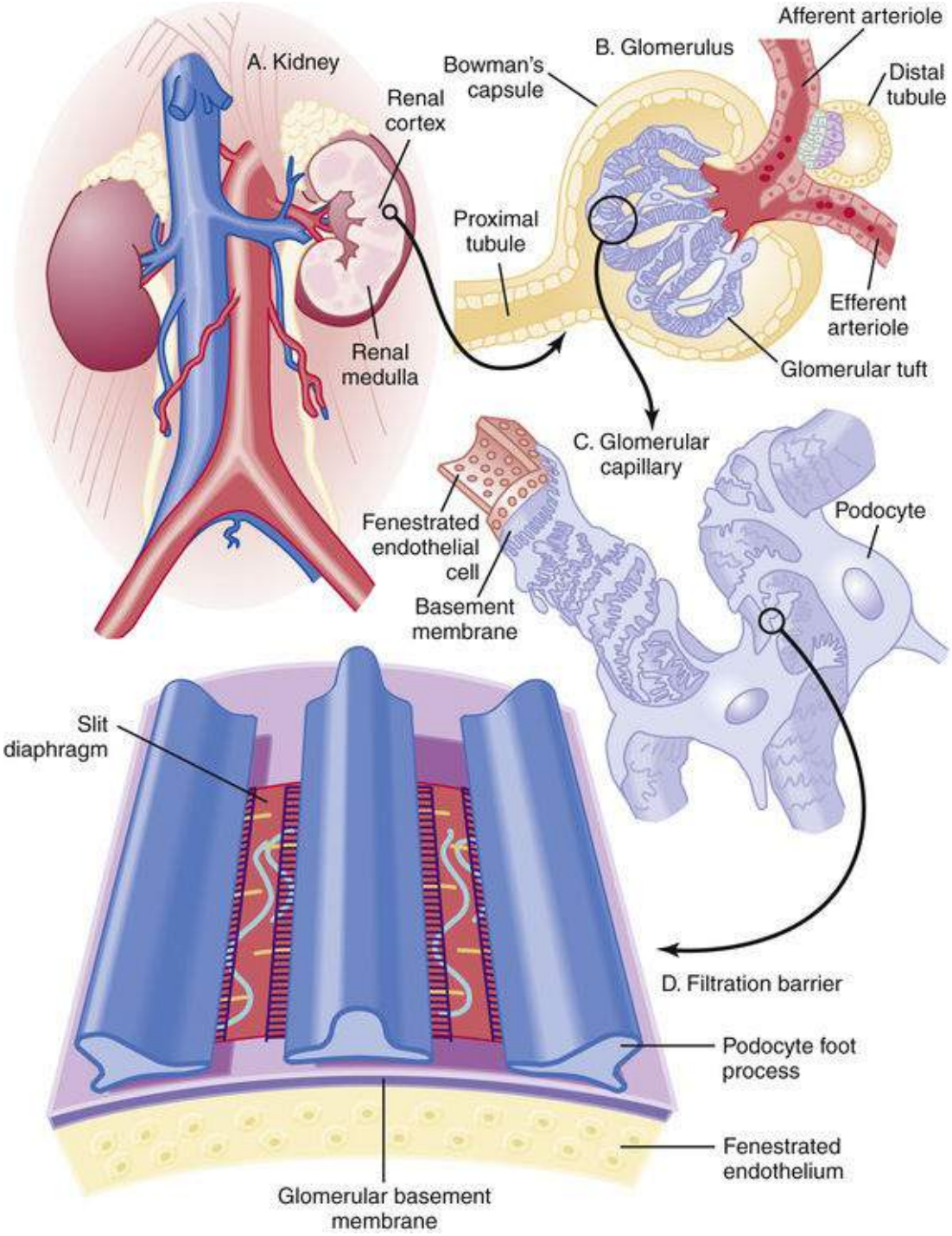

FIGURE 98.1 Normal structure of the glomerular vasculature. Each kidney contains about 1 million glomeruli in the renal cortex (Panel A). Panel B shows an afferent arteriole entering Bowman's capsule and branching into several capillaries that form the glomerular tuft; the walls of the capillaries constitute the actual filter. The plasma filtrate (primary urine) is directed to the proximal tubule, whereas the unfiltered blood returns to the circulation through the efferent arteriole. The filtration barrier of the capillary wall contains an innermost fenestrated endothelium, the glomerular basement membrane, and a layer of interdigitating podocyte foot processes (Panel C). In Panel D, a cross section through the glomerular capillary depicts the fenestrated endothelial layer and the glomerular basement membrane with overlying podocyte foot processes. An ultrathin slit diaphragm spans the filtration slit between the foot processes, slightly above the basement membrane. In order to show the slit diaphragm, the foot processes are drawn smaller than actual scale. (Adapted from Tryggvason K, Patrakka J, Wartiovaara J: Hereditary proteinuria syndromes and mechanisms of proteinuria. N Engl J Med 2006;354(13):1387-401.)

The obesity “pandemic” is spawning secondary epidemics of type 2 diabetes (DM) and hypertension (HTN), disorders that often lead to chronic kidney disease (CKD) and cardiovascular disease (CVD) that is underrecognized in primary care.[1] Among those who have had type 1 or type 2 DM for 25 years or more, the prevalence of diabetic nephropathy as a result of microvascular disease is about 50%.[2]

Approximately half of all cases of end-stage renal disease (ESRD) result from diabetic nephropathy. With the aging of the general population and the shift in cardiovascular care toward the elderly, decreasing levels of renal function, which occur as part of senescence, act as a major adverse prognostic factor after CVD events. CKD accelerates the progression of atherosclerosis, myocardial disease, and valvular disease, and promotes an array of cardiac arrhythmias leading to sudden death.[3]

Chronic Kidney Disease and Cardiovascular Risk

A range of estimated glomerular filtration rate (eGFR) values derived from equations defines CKD.[4] A common definition for CKD stipulates an eGFR of less than 60 mL/min/1.73 m^2 or the presence of kidney damage (**Fig. 98.2**). With aging (age 20 to 80 years) the eGFR declines from about 130 mL/min/1.73 m^2 to 60 mL/min/1.73 m^2. A variety of pathobiologic processes appear to begin when the eGFR drops below 60 mL/min/1.73 m^2 or stage 3 CKD (a serum creatinine [Cr] level of ≈ 1.2 mg/dL in a woman and ≈ 1.5 mg/dL in a man). Because Cr is a crude indicator of renal function and often underestimates renal dysfunction in women and the elderly, calculation of the eGFR or the creatinine clearance (CrCl) by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) and Cockcroft-Gault equation, respectively, is a superior method for the assessment of renal function. The CrCl measurement is used most often for determining drug dosages because it incorporates body weight. For classification of disease, and prognosis, the CKD-EPI equation is preferred because it does not rely on body weight and has the most accurate association with adverse outcomes, including death. The equation is

- **CKD defined as abnormalities of kidney structure or function, present for >3 months, with implications for health.**
- **CKD classified as CGA based on Cause (C), GFR (G) category, and Albuminuria (A) category.**
- **CKD prognosis determined by GFR and Albuminuria Categories.**

GFR categories (mL min/1.73m) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60-89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45-59	1	2	3
	G3b	Moderately to severely decreased	30-44	2	3	3
	G4	Severely decreased	15-29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

GFR (G) and albuminuria (A) grid to reflect the risk of progression by intensity of coloring (green – low risk if no other markers of CKD, yellow – moderately increased risk, orange – high risk, red – very high risk). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year.)

FIGURE 98.2 Diagnostic criteria for chronic kidney disease and kidney damage. *eGFR*, estimated glomerular filtration rate. (Adapted from KDIGO 2012 Clinical Practice Guideline. Kidney Int Suppl 2013;3:63-72.)

$$\mathrm{eGFR} = 141 \times \min(\mathrm{Cr}/\kappa, 1)^{\alpha} \times \max(\mathrm{Cr}/\kappa, 1)^{-1.209} \times 0.993^{\mathrm{Age\ (yrs)}} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$$

where Cr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Cr/κ or 1, and max indicates the maximum of Cr/κ or 1.

Another approved blood test reflecting renal filtration function and used in eGFR equations is cystatin-C.[5] Cystatin-C is a 13-kDa protein produced by all nucleated cells. Its low molecular mass and its high isoelectric point allow it to be freely filtered by the glomerulus and 100% reabsorbed by the proximal tubule. The serum concentration of cystatin-C correlates with the eGFR and, in combination with a stable production rate, provides a sensitive marker of renal filtration function. Serum levels of cystatin-C do not depend on weight and height, muscle mass, age, or sex, so that it is a less variable measure than Cr. Furthermore, measurements can be made and interpreted from a single random sample with reference intervals in women and men being 0.54 to 1.21 mg/L (median, 0.85 mg/L; range, 0.42 to 1.39 mg/L).

In addition, microalbuminuria at any level of the eGFR indicates CKD and occurs as the result of endothelial dysfunction or damage in glomerular capillaries secondary to the metabolic syndrome, DM, and HTN. The most widely accepted definition of microalbuminuria is a random urine albumin/Cr ratio (ACR) of 30 to 300 mg/g. An ACR greater than 300 mg/g is considered gross proteinuria. The random, spot ACR is the office test for microalbuminuria recommended as part of the cardiovascular and renal risk assessment done by cardiologists and other specialists. Microalbuminuria independently predicts the CVD risk for those with and without DM. The amount of albumin and protein in the urine is the most important prognostic factor for the rapid progression of CKD to ESRD.[6] In addition, both the eGFR and degree of albuminuria contribute independently to the risks of future AKI, myocardial infarction (MI), stroke, heart failure (HF), and death (**Fig. 98.3**).[7]

ALL-CAUSE MORTALITY

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR >105	1.1	1.5	2.2	5.0
eGFR 90-105	Ref	1.4	1.5	3.1
eGFR 75-90	1.0	1.3	1.7	2.3
eGFR 60-75	1.0	1.4	1.8	2.7
eGFR 45-60	1.3	1.7	2.2	3.6
eGFR 30-45	1.9	2.3	3.3	4.9
eGFR 15-30	5.3	3.6	4.7	6.6

CARDIOVASCULAR MORTALITY

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR >105	0.9	1.3	2.3	2.1
eGFR 90-105	Ref	1.5	1.7	3.7
eGFR 75-90	1.0	1.3	1.6	3.7
eGFR 60-75	1.0	1.4	2.0	4.1
eGFR 45-60	1.5	2.2	2.8	4.3
eGFR 30-45	2.2	2.7	3.4	5.2
eGFR 15-30	14	7.9	4.8	8.1

KIDNEY FAILURE (ESRD)

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR >105	Ref	Ref	7.8	18
eGFR 90-105	Ref	Ref	11	20
eGFR 75-90	Ref	Ref	3.8	48
eGFR 60-75	Ref	Ref	7.4	67
eGFR 45-60	5.2	22	40	147
eGFR 30-45	56	74	294	763
eGFR 15-30	433	1044	1056	2286

AKI

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR >105	Ref	Ref	2.7	8.4
eGFR 90-105	Ref	Ref	2.4	5.8
eGFR 75-90	Ref	Ref	2.5	4.1
eGFR 60-75	Ref	Ref	3.3	6.4
eGFR 45-60	2.2	4.9	6.4	5.9
eGFR 30-45	7.3	10	12	20
eGFR 15-30	17	17	21	29

PROGRESSIVE CKD

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR >105	Ref	Ref	0.4	3.0
eGFR 90-105	Ref	Ref	0.9	3.3
eGFR 75-90	Ref	Ref	1.9	5.0
eGFR 60-75	Ref	Ref	3.2	8.1
eGFR 45-60	3.1	4.0	9.4	57
eGFR 30-45	3.0	19	15	22
eGFR 15-30	4.0	12	21	7.7

FIGURE 98.3 Relative risks of heart and kidney outcomes in cohorts where eGFR and ACR were measured. *AKI*, acute kidney injury; *CKD*, chronic kidney disease; *ESRD*, end-stage renal disease.
(Adapted from Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, et al: Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010;375(9731):2073-81.)

Implications of Anemia Due to Chronic Kidney Disease

Blood hemoglobin (Hb) levels are associated with CKD and with CVD. The World Health Organization defines anemia as an Hb level of less than 13 g/dL in men and less than 12 g/dL in women; approximately 9% of the general adult population meets this definition. Some 20% of patients with stable coronary disease and 30% to 60% of patients with HF have anemia due to CKD. Hence, anemia is a common and easily identifiable potential cause of constitutional symptoms, as well as a potential diagnostic and therapeutic target, particularly in the setting of iron deficiency or reduced availability of vitamin B_{12} or folic acid.

Anemia contributes to multiple adverse outcomes, in part because of decreased tissue oxygen delivery and utilization.[16] The cause of anemia in patients with CKD can be multifactorial because of impairment in iron transport and a relative deficiency of erythropoietin-α (EPO), an erythrocyte-stimulating protein, which is normally produced by renal parenchymal cells in response to the blood partial pressure of oxygen under the control of the gene regulator hypoxia-inducible factor. Patients with CKD and HF resist the effects of EPO. In addition, increased circulating levels of hepcidin-25, an inhibitor of the ferroportin receptor, impair iron absorption and utilization throughout the body, including in the bone marrow. As the Hb drops over the course of CKD, there is an associated increase in HF hospitalizations and deaths.

Conversely, those patients who have had a spontaneous rise in Hb, whether it be a result of improved nutrition, reduced neurohormonal factors, or other unknown factors, enjoy a significant reduction in endpoints over the next several years. This improvement has been associated with a significant reduction in the left ventricular mass index, suggesting a favorable change in left ventricular remodeling.

Treatment of anemia with exogenous erythrocyte-stimulating proteins (EPO and darbepoetin-α), increasing the Hb level from below 10 g/dL to 12 g/dL, has been linked to favorable changes in left ventricular remodeling, an improved ejection fraction, an improved functional classification, and higher levels of peak oxygen consumption with exercise testing. However, treatment with EPO and supplemental iron, which is needed in approximately 70% of cases of ESRD, is associated with three problems: (1) increased platelet activity and thrombin generation and a resultant increased risk of thrombosis; (2) elevated endothelin and asymmetric dimethylarginine, which theoretically reduces nitric oxide availability, and results in HTN; and (3) worsened measures of oxidative stress. Randomized trials of erythrocyte-stimulating agents (ESAs) as they target higher levels of Hb in CKD have shown higher rates of CVD events and no improvement in rates of mortality, progression of CKD, or health-related quality of life.[8-10] The Reduction of Events with Darbepoetin Alfa in Heart Failure Trial (RED-HF) randomized 2278 patients with systolic HF and mild-to-moderate anemia (Hb = 9 to 12 g/dL) to receive darbepoetin alfa approximately 60 to 600 µg subcutaneously every 2 to 4 weeks (target, Hb 13 g/dL) or placebo and found no reductions in HF hospitalizations or deaths, but a 35% excess risk of thromboembolic complications with the ESA.[11] When the dose exposure of ESA is taken into account, it appears that cardiovascular drug toxicity and not the Hb is responsible for the adverse outcomes reported in ESA trials.[12] As a result of these trials, the current strategy is to use ESA sparingly to maintain an Hb concentration to avoid symptoms and the need for transfusion.

High-dose oral or intravenous iron may overcome the iron-reutilization defect in CKD anemia. In a metaanalysis of 64 trials (including five studies of HF patients) comprising 9004 patients, iron was associated with elevations in Hb and reductions in the need for transfusion.[13] Analysis of the five trials of HF patients with iron deficiency (509 patients received iron therapy and there were 342 controls) showed that intravenous iron was associated with reductions in HF hospitalizations and cardiovascular deaths (odds ratio [OR], 0.39; 95% confidence interval [CI], 0.24 to 0.63; $P = 0.0001$) and improvements in multiple measures of functional status.[14] These results will need confirmation in large-scale clinical trials, but they support consideration of iron repletion in patients with CKD, anemia, and HF when there is evidence of iron deficiency (iron saturation < 20% and ferritin < 200 ng/mL).

Hypoxia-inducible factor has a very short half-life because of a prolyl hydroxylase that breaks down this genetic regulator of EPO as well as vascular endothelial–derived growth factor. There are oral hypoxia-inducible factor, prolyl hydroxylase inhibitors in development that stabilize the hypoxia-inducible factor and allow greater endogenous production of EPO and improved iron transport and elevate Hb concentrations.[15] Phase 3 trials of these agents will assess their efficacy for treating anemia in CKD and allowing for cardiovascular safety.

Contrast-Induced Acute Kidney Injury

Iodinated contrast-induced acute kidney injury (CI-AKI) is most commonly defined by the Kidney Disease International Global Outcomes criteria of a rise in serum Cr of 0.3 mg/dL or more from baseline within 48 hours of intravascular administration or a 50% or more elevation from baseline over the course of hospitalization.[16] The National Cardiovascular Data Registry Cath-PCI (n = 985,737, which studied

patients who underwent elective and urgent percutaneous coronary intervention [PCI]), reported 69,658 (7.1%) cases of CI-AKI (Cr rise ≥ 0.3 mg/dL) and 3,005 (0.3%) cases of AKI requiring dialysis.[17] Transient rises in Cr are associated with longer hospital ward and intensive care unit stays, MI, stroke, HF, rehospitalization, and death after coronary angiography, PCI, and angiography followed by cardiac surgery (**Fig. 98.4**).[18]

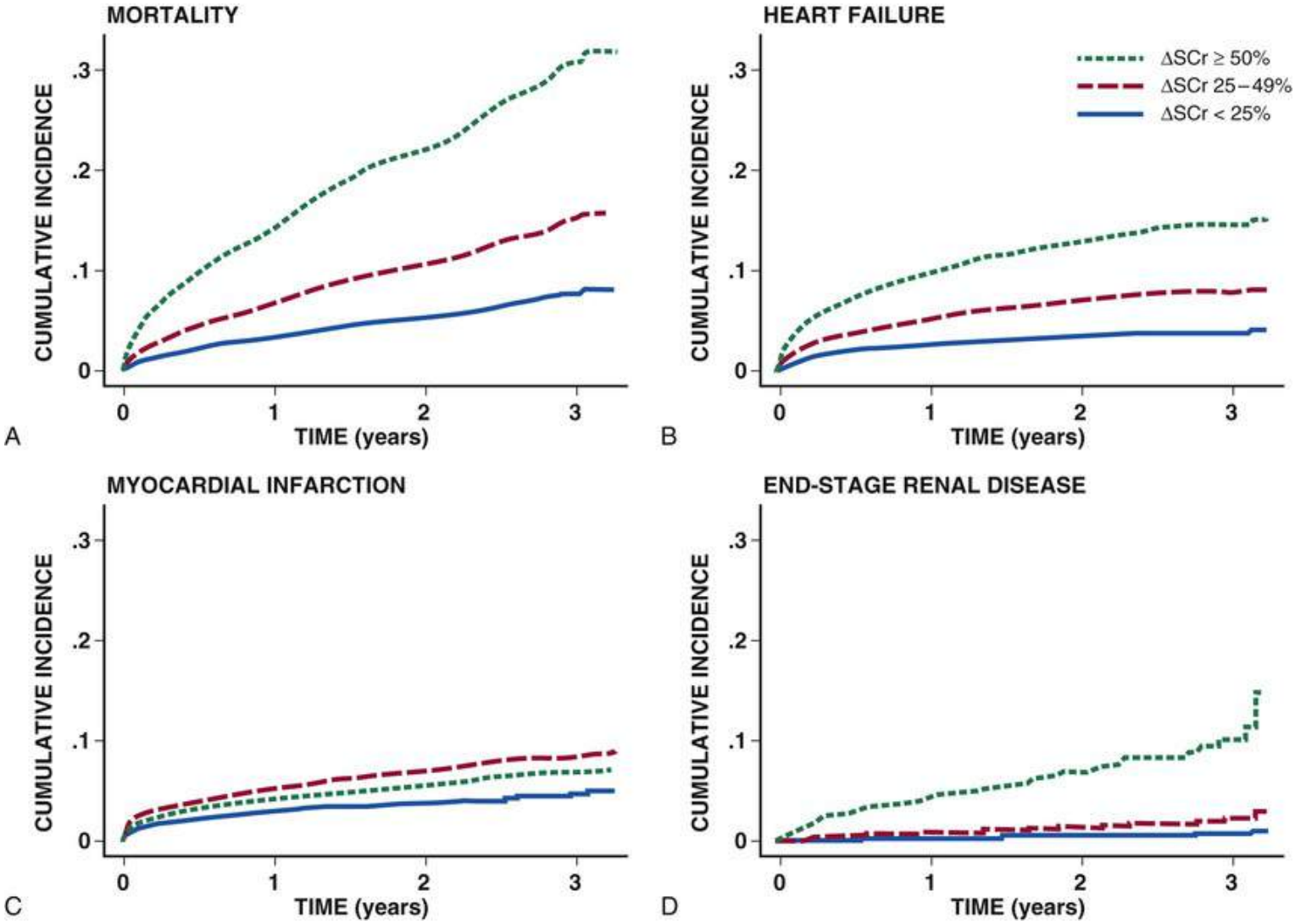

FIGURE 98.4 Cumulative incidence of **(A)** all-cause mortality, **(B)** hospitalization for heart failure, **(C)** hospitalization for myocardial infarction, and **(D)** end-stage renal disease following coronary angiography, according to severity of acute kidney injury as reflected by magnitude of change in serum creatinine (ΔScr) concentration after coronary angiography. Coronary angiography alone = 4219, with PCI = 8205, with cardiac surgery = 2412. (Adapted from James MT, Ghali WA, Knudtson ML, et al: Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators: Associations between acute kidney injury and cardiovascular and renal outcomes after coronary angiography. Circulation 2011;123(4):409-16.)

CI-AKI has three potential pathophysiologic mechanisms: (1) direct toxicity of nephrons by iodinated contrast material, (2) microshowers of atheroemboli to the kidneys (due to catheter and wire exchanges above the renal arteries), and (3) intrarenal vasoconstriction induced by contrast material or atheroemboli. Direct toxicity of nephrons by iodinated contrast media appears related to the ionicity and osmolality of the contrast media given in the milieu of CKD.[18] Microshowers of cholesterol emboli may occur in about 50% of percutaneous interventions using an aortic approach; most episodes are clinically silent.[19] However, in approximately 1% of high-risk cases, an acute cholesterol emboli syndrome can develop, manifested by acute renal failure, mesenteric ischemia, decreased microcirculation to the

extremities, and, in some cases, embolic stroke. Because there is less transaortic movement of wires and catheters, transradial coronary intervention is associated with rates of CI-AKI that are 22% to 50% lower.[20,21] Intrarenal vasoconstriction as a pathologic vascular response to contrast media in CKD and perhaps as an organ reaction to superimposed cholesterol microemboli also injure the kidney. Hypoxia triggers activation of the renal SNS and further reduces renal blood flow (**Fig. 98.5**). The most important predictor of CI-AKI is underlying renal dysfunction. When the eGFR falls to less than 60 mL/min/1.73 m^2, the remaining nephrons must assume the residual filtration load with increased oxygen demands in the face of reduced delivery, and hence there is a greater susceptibility to cytotoxic, ischemic, and oxidative injury.[18]

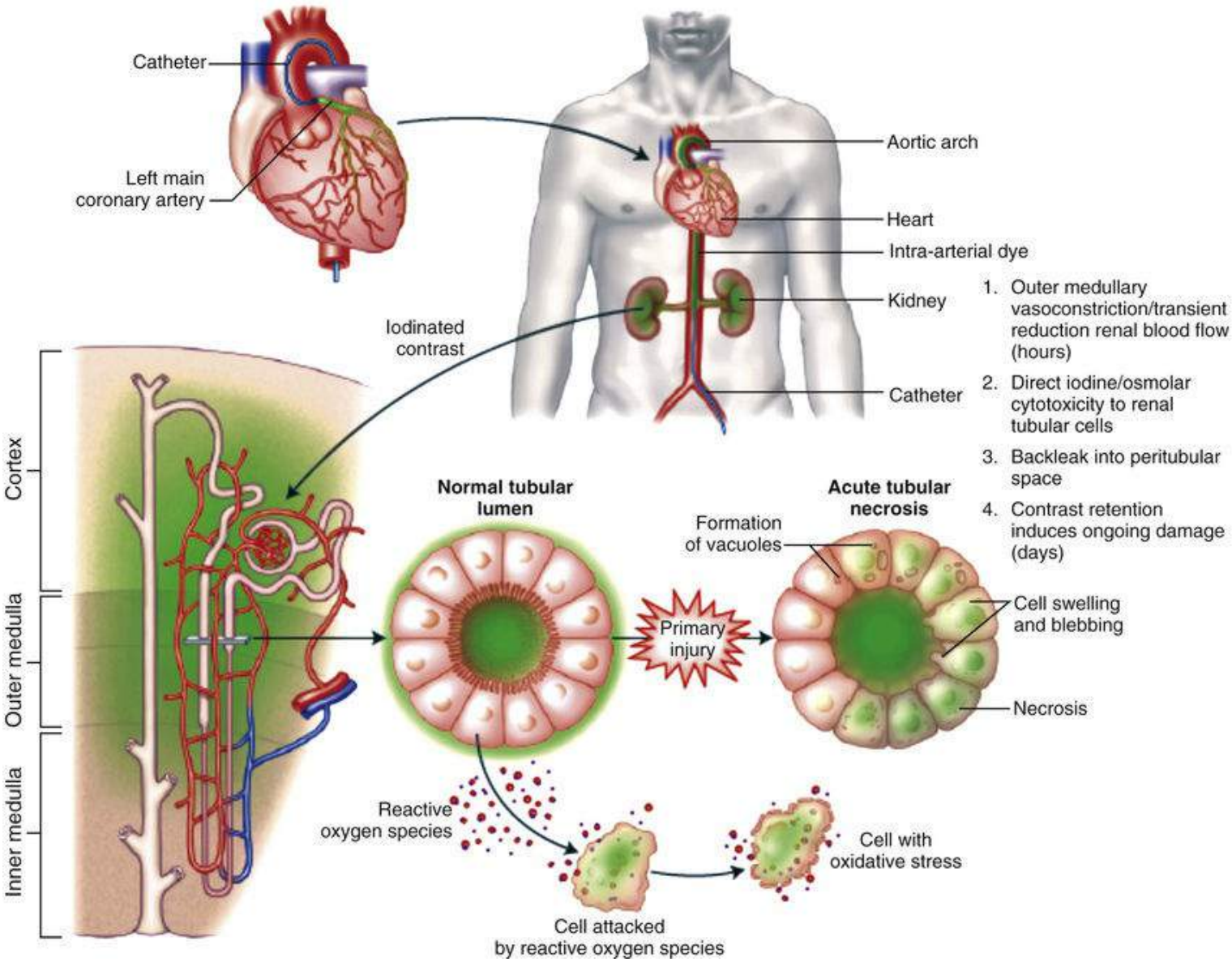

FIGURE 98.5 Pathogenesis of contrast-induced acute kidney injury. (Adapted from Brown JR, McCullough PA: Contrast nephropathy and kidney injury textbook of cardiovascular intervention. New York, Springer, 2011.)

Prevention of Contrast-Induced Acute Kidney Injury

Patients with preexisting CKD (baseline eGFR, < 60 mL/min/1.73 m^2) and, in particular, those with CKD and DM, merit a prevention strategy for CI-AKI. The presence of CKD, DM, and other risk factors,

including hemodynamic instability, use of intraaortic balloon counterpulsation, HF, older age, and anemia, in the same patient entails a risk of CI-AKI of over 50%.[22] The informed-consent process of a high-risk patient before use of intravascular iodinated contrast should include discussion of CI-AKI. CI-AKI prevention involves consideration of four issues: (1) intravascular volume expansion, (2) choice and quantity of contrast material, (3) transradial or femoral approach, and (4) postprocedural monitoring and expectant care.

Because iodinated contrast is water soluble, it is amenable to prevention strategies that expand the intravascular volume and increase the renal filtration and tubular flow of urine into collecting ducts, and then into the ureters and bladder. CI-AKI responds to intravascular administration of isotonic crystalloid solutions to enhance renal elimination of contrast via the urine. Numerous randomized trials have compared isotonic bicarbonate solutions with intravenous saline. The largest and highest-quality trials have shown no differences in the rates of renal outcomes.[23,24] Patient factors should guide the use of either isotonic crystalloid solution. The POSEIDON (Prevention of Contrast Renal Injury with Different Hydration Strategies) trial randomized 396 patients with eGFR of less than 60 mL/min/1.73 m^2 and one additional risk factor to a strategy of measurement of left ventricular end-diastolic pressure and expanding plasma volume versus usual care. Each group had standard of care of normal saline 3 mL/kg for 1 hour before cardiac catheterization. The left ventricular end-diastolic pressure–guided approach was associated with more intensive fluid administration during and after the procedure and with a greater reduction in CI-AKI (6.7%) than in the control group (16.3%); the relative risk (RR) was 0.41; the 95% CI was 0.22 to 0.79; and the *P* 0.000 to 0.005. Thus, it is reasonable to consider intravenous administration of 250 mL of normal saline before the procedure and achieve a urine output of approximately 150 mL/hr throughout and after the procedure.

Randomized trials of iodinated contrast agents have demonstrated the lowest rates of CI-AKI with nonionic, isoosmolar iodixanol. A metaanalysis restricted to 25 head-to-head, prospective, double-blind, randomized, controlled trials compared iodixanol with low-osmolar contrast media (LOCM) in adult patients undergoing angiographic examinations with serum Cr values at baseline and following CM administration.[25] The relative risk of CI-AKI (Cr rise ≥ 0.5 mg/dL) occurring for iodixanol was 0.46 and *P* 0.004, compared with LOCM as summarized in **Fig. 98.6**. These data are consistent with the hypothesis that iodixanol (290 mOsm/kg) is less nephrotoxic than LOCM agents with osmolalities ranging from 600 to 800 mOsm/kg when given intraarterially. However, there appears to be no significant difference in rates of CI-AKI between iodixanol and LOCM when contrast is administered in lower-risk patients or intravenously.[25]

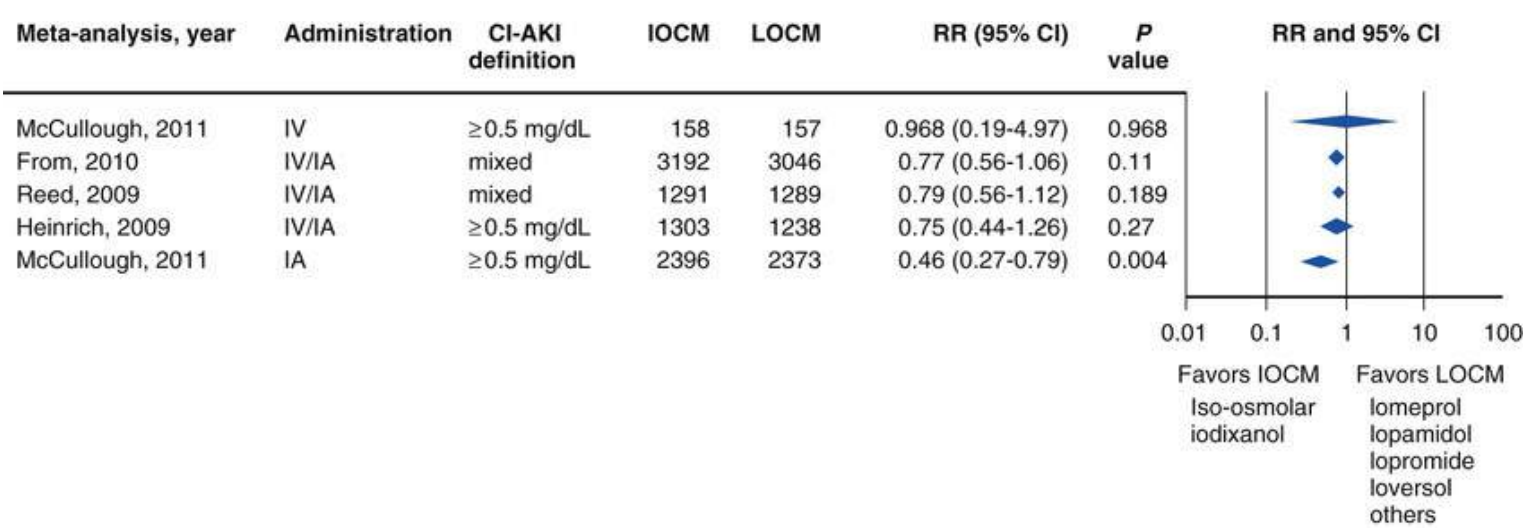

FIGURE 98.6 Compilation of pooled odds ratios from head-to-head trials for IA, IV, and mixed IA and IV metaanalyses of the incidence of CI-AKI (defined as ≥ 0.5 mg/dL increase in sCr from baseline) demonstrating a leftward shift in pooled estimates IV, IV/IA, and IA trials favoring the use of iodixanol. (Adapted from McCullough PA, Brown JR: Effects of intra-arterial and intravenous iso-osmolar contrast medium (iodixanol) on the risk of contrast-induced acute kidney injury: a meta-analysis. Cardiorenal Med 2011;1(4):220-34.)

Although it is desirable to limit contrast to the smallest volume possible in any setting, there is disagreement about a "safe" contrast limit. The lower the eGFR, the less contrast material may cause CI-AKI. In general, it is desirable to limit the contrast medium to less than 30 mL for a diagnostic procedure and less than 100 mL for an interventional procedure. If staged procedures are planned and CI-AKI has occurred with the first procedure, it is advantageous to have more than 10 days between the first and second contrast exposures. As mentioned above, the transradial approach is associated with a significantly lower risk of CI-AKI when controlling for all other factors.

Most trials of preventive strategies for CI-AKI have been small and underpowered and did not find the preventive strategy under investigation superior to placebo. After many small, suggestive studies, a large (n=2308) randomized trial of N-acetylcysteine 1200 mg orally twice a day on the day before and after the procedure showed no differences in the rates of CI-AKI (12.7% for both groups), ESRD, or other outcomes.[26] As a result, neither N-acetylcysteine nor any other drug is approved for the prevention of CI-AKI.

A suggested algorithm for risk stratification and prevention of CI-AKI is shown in **Fig. 98.7**. An eGFR of less than 60 mL/min/1.73 m^2 mandates preprocedural volume expansion, use of transradial access if possible, use of iodixanol or LOCM as the contrast agent, and minimization of contrast volume. Postprocedural monitoring is critical in the current era of short stays and outpatient procedures. In general, high-risk patients in the hospital should have hydration started 1 to 3 hours before the procedure and continued for at least 3 hours afterward. Serum Cr should be measured 24 hours after the procedure. Outpatients, particularly those with an eGFR of less than 60 mL/min/1.73 m^2, should either stay overnight or be discharged to go home with 48-hour follow-up and serum Cr measurement. If severe CI-AKI is going to develop, patients usually have a rise of Cr greater than 0.5 mg/dL in the first 24 hours after the procedure. Thus, for those who do not have this degree of serum Cr elevation and are otherwise uncomplicated, discharge to home may be considered. If a patient has an eGFR of less than 30 mL/min/1.73 m^2, the physician should discuss with the patient the possibility of dialysis and a nephrology consultation for possible preprocedure and postprocedure hemofiltration and dialysis management.

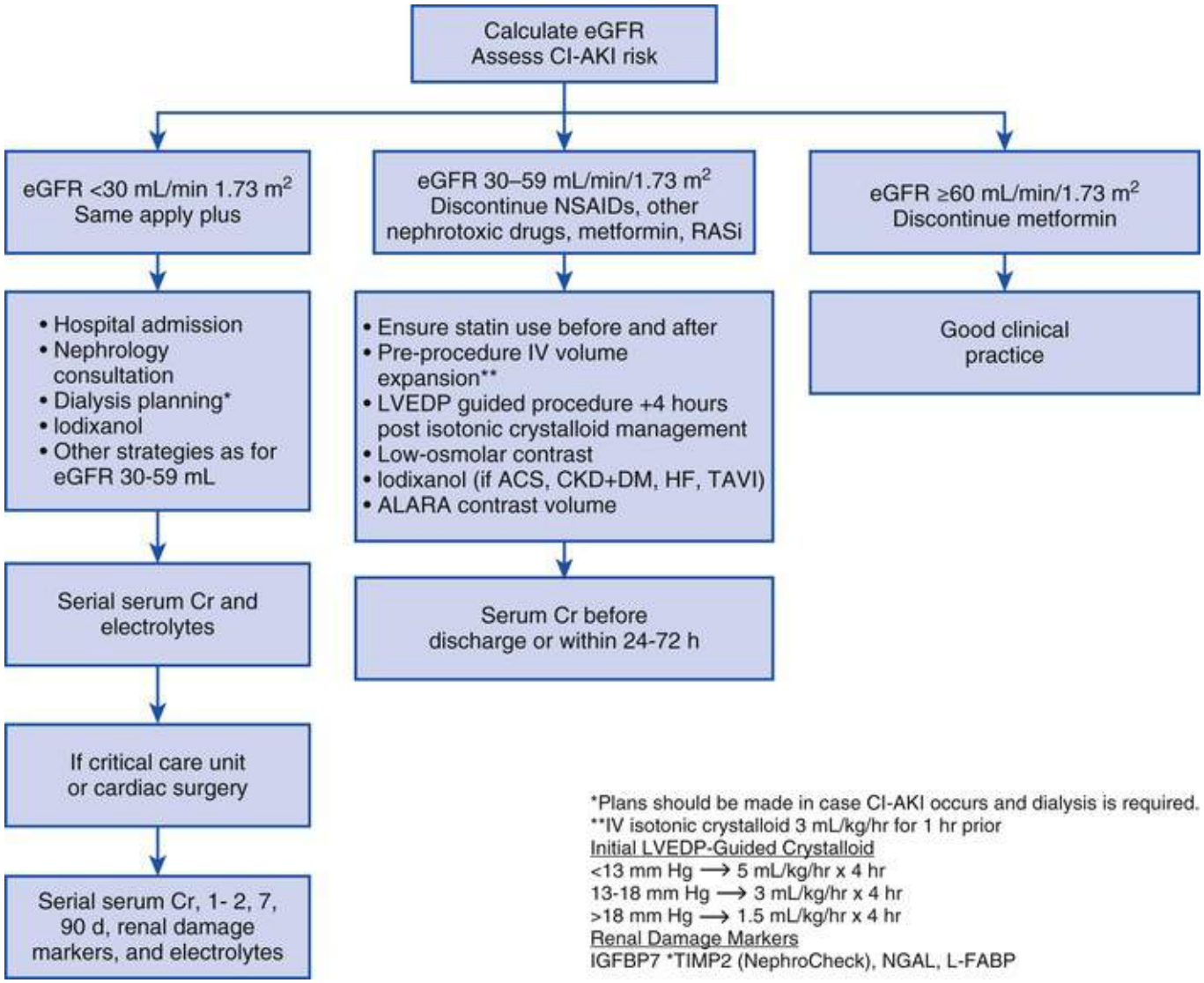

FIGURE 98.7 Algorithm for management of patients receiving iodinated contrast media. *ALARA*, as low as reasonably achievable; *CI-AKI*, contrast-induced acute kidney injury; *CKD*, chronic kidney disease; *Cr*, creatinine; *eGFR*, estimated glomerular filtration rate; *IGFBP7,* insulin-like growth factor binding protein 7; *LVEDP,* left ventricular end-diastolic pressure; *NSAIDs*, nonsteroidal antiinflammatory agents; *RASI,* renin-angiotensin system inhibitors; *TAVI,* transcatheter aortic valve insertion; *TIMP2,* tissue inhibitor of metalloproteinase 2. (Adapted from McCullough PA, Choi JP, Feghall GA, et al: Contrast-induced acute kidney injury. J Am Coll Cardiol 2016;68:1465-73.)

Cardiac Surgery and Acute Kidney Injury

AKI occurs in approximately 15% of patents after some cardiac surgical procedures with or without the use of cardiopulmonary bypass. Rates of AKI are higher when coronary angiography is done on the same day or with relatively few days between the angiogram and the surgery.[27] Cardiac surgery exposes patients to many factors, including endogenous/exogenous toxins (free heme, catalytic iron), metabolic factors, ischemia and reperfusion, neurohormonal activation, inflammation, and oxidative stress, which all may contribute to renal tubular injury heralded by reduced urine output and a rise in serum Cr after cardiac surgery.[28] KDIGO (Kidney Disease Global Outcomes) criteria can be used to identify AKI in this patient group (**Fig. 98.8**).[16] Various markers may predict postoperative AKI.[28] Off-pump cardiac surgery does not seem to lower rates of AKI. Trials of natriuretic peptides, corticosteroids, alpha melanocytic–stimulating hormone agonists, complement inhibitors, and remote ischemic preconditioning have failed to prevent AKI. Thus, at this time, there are no accepted forms of prophylaxis or treatment for AKI

associated with cardiac surgery.

Stage	Serum creatinine	Urine output
1	1.5–1.9 × baseline or ≥0.3 mg/dl (≥26.5 mmol/L) increase	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 × baseline	<0.5 mL/kg/h for >12 h
3	3.0 × baseline, or increase in serum creatinine ≥4.0 mg/dl (≥353.6 mmol/L), or initiation of RRT, or decrease in eGFR <35 mL/min/1.73 m^2 for patients <18 years	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

FIGURE 98.8 Stages of acute kidney injury according to the KDIGO classification. *eGFR*, estimated glomerular filtration rate; *KDIGO*, Kidney Disease: Improving Global Outcomes; *RRT*, renal replacement therapy. (Adapted from KDIGO AKI Work Group: KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;17:1-138.)

Acceleration of Vascular Calcification

When the eGFR falls below 60 mL/min/1.73 m^2, the filtration and elimination of phosphorus fall. In addition, a lower production of 1,25 dihydroxyvitamin D leads to a relative hypocalcemia. Thus, subtle degrees of hyperphosphatemia and hypocalcemia trigger increased release of parathyroid hormone, causing liberation of calcium and phosphorus from bone. The bone, in turn, produces greater amounts of fibroblast growth factor-23, which directs the kidneys to increase the clearance of phosphorus but also promotes left ventricular hypertrophy (LVH). As a result of this abnormal bone and mineral metabolism, patients with ESRD have markedly increased absolute values and rates of accumulation of arterial calcification as well as LVH. A variety of in vitro stimuli can induce vascular smooth muscle cells to assume osteoblast-like functions in vitro, including handling of phosphorus, oxidized low-density lipoprotein cholesterol (LDL-C), vascular calcification factor, parathyroid hormone, and parathyroid hormone–related peptide.

No specific strategy to manipulate the calcium-phosphorus balance or treat secondary hyperparathyroidism evaluated so far changes the annual rate of increase in the coronary artery calcium score or cardiovascular events.[29,30,31]

Renal Disease and Hypertension

The kidney is a central regulator of blood pressure and controls intraglomerular pressure through autoregulation. Sodium retention stimulates increases in systemic and renal arteriolar pressure in an attempt to force greater degrees of filtration in the glomerulus. Glomerular injury activates a variety of pathways that further increase the systemic blood pressure (**see also Chapters 46 and 47**). This effect sets up a vicious circle of more glomerular and tubulointerstitial injury and worsened HTN. A cornerstone of management of combined CKD and CVD is strict blood pressure control. In most patients with CKD and proteinuria, three or more antihypertensive agents are needed to achieve a goal blood pressure of less than 130/80 mm Hg.[32] The Systolic Blood Pressure Intervention Trial (SPRINT) randomized 9361 patients without DM having a mean eGFR of 71 mL/min/1.72 m^2 and found that a

systolic blood pressure target of 120 mm Hg was associated with reduced rates of a first occurrence of MI, acute coronary syndrome (ACS), stroke, HF, or death from cardiovascular causes; however, there were no differences in the rates of progression to CKD, ESRD, or any other renal outcome. The key lifestyle issues for management of CKD and HTN include dietary changes with sodium restriction, weight reduction of 15% or more to a target body mass index of less than 25 kg/m^2, and exercise for 60 minutes per day most days of the week. Pharmacologic therapy aims for strict blood pressure control with an agent that antagonizes the RAAS, often in combined action with a thiazide-type diuretic. Dihydropyridine calcium channel blockers alone, because of relative afferent arteriolar dilation, increase intraglomerular pressure and worsen glomerular injury, and thus should be avoided as singular agents for blood pressure control. Combinations of multiple RAAS-blocking drugs (angiotensin-converting enzyme inhibitors [ACEIs], angiotensin II receptor blockers [ARBs], a direct renin inhibitor) provide no additional benefit but cause more complications. Clinical clues such as poorly controlled blood pressure when the patient is taking more than three agents, abdominal bruits, smoking history, peripheral arterial disease, and a marked change in serum Cr with administration of an ACEI or ARB should raise the possibility of bilateral renal artery stenosis.[33] Although renal artery stenosis accounts for less than 3% of ESRD cases, it represents a potentially treatable condition (**see also Chapter 66**). Attempts to reduce SNS activity to the kidneys have not improved the blood pressure or clinical outcomes in properly controlled trials.[34]

Diagnosis of Acute Coronary Syndromes in Patients With Chronic Kidney Disease

Patients with CKD have higher rates of silent ischemia; the disorder clusters with serious arrhythmias, HF, and other cardiac events (**see also Chapters 56 and 58**). About half of stable outpatients with CKD will have a high-sensitivity cardiac troponin I (cTnI) or cTnT level above the 99th percentile of normal.[35] The degree of elevation of cTn is associated with a left ventricular mass, coronary disease, severity of renal disease, and all-cause mortality.[36] Thus with the use of high-sensitivity assays, in general, cTnI is more advantageous in the diagnostic evaluation of CKD or ESRD patients with acute chest discomfort, whereas chronic elevations of cTnT are more common and more prognostic in stable patients. The diagnosis of MI in patients with CKD or ESRD requires serial troponin measurements because so many are above the 99th percentile of normal at baseline. The skeletal myopathy of CKD can elevate the creatine kinase, myoglobin, and some older-generation cTnI/cTnT assays, making these tests less desirable.

Renal Dysfunction as a Prognostic Factor in Acute Coronary Syndromes

Advances in the diagnosis and treatment of acute ACS include early paramedic response and defibrillation, coronary care units, and pharmacotherapy including antiplatelet agents, antithrombotics, beta receptor–blocking agents, RAAS blockade, lipid-lowering therapy, intravenous thrombolytic agents, and percutaneous intervention (**Tables 98.1 to 98.3**). CKD patients represent 30.5% of patients with ST-segment elevation MI (STEMI) and 42.9% of patients with NSTEMI (**Fig. 98.9**), and they have higher rates of in-hospital death in a graded fashion with worsened renal function (**Fig. 98.10**).[37] There is an independent association between the degree of CKD and the 30-day and 1-year mortality rates after ACS. A reduced baseline eGFR also predicts higher rates of AKI, bleeding, the development of HF, recurrent

MI, rehospitalization, and stroke in the setting of ACS. Patients with ESRD have the highest mortality rate after MI of any large population with chronic disease.

TABLE 98.1

Acute and Chronic Treatments for Coronary Artery Disease in Patients With Chronic Kidney Disease

MEDICATION	NORMAL DOSE	CHRONIC KIDNEY DISEASE POPULATION	PHARMACOLOGY
Antiplatelet Agents			
Aspirin	Acute MI: 160–325 mg by mouth as soon as possible MI prophylaxis: 81–162 mg by mouth once daily PCI: 325 mg by mouth 2 h before surgery, then 160–325 mg by mouth maintenance UA: 75–162 mg by mouth once daily	No specific dosing adjustments in patients with CKD Metaanalysis involving patients undergoing dialysis demonstrated a benefit of aspirin therapy on cardiovascular outcomes	Metabolism: liver, microsomal enzyme system Renal clearance: 80% to 100% 24–72 h Excretion: principally in urine (80% to 100%), sweat, saliva, feces
Clopidogrel	UA/NSTEMI: 300–600 mg initial loading dose, followed by 75 mg by mouth once daily with aspirin STEMI: 75 mg by mouth once daily with aspirin 75–162 mg per day Recent MI: 75 mg by mouth once daily	No specific dosing adjustments in patients with CKD	Metabolism: CYP3A4, CYP2C19 (predominantly), and others to generate active metabolite; also by esterase to an inactive metabolite Excretion: urine and feces
Prasugrel	ACS: Loading dose: 60 mg by mouth once Maintenance dose: 10 mg by mouth once daily with aspirin 81–325 mg per day; bleeding risk may increase if weight < 60 kg, consider 5 mg by mouth once daily (efficacy/safety not established)	No specific dose adjustments in patients with CKD	Metabolism: liver; CYP450, CYP2B6, CYP2C9/CYP2C19 (minor), CYP3A4 substrate; CYP2B6 (weak) inhibitor Excretion: urine (68%) and feces (27%)
Ticagrelor	ACS with PCI and stent: Starting dose: 180 mg by mouth once Maintenance dose: 90 mg by mouth twice daily To be given for 1 year with aspirin as an alternative option for dual antiplatelet therapy	No specific dose adjustments in patients with CKD	Metabolism: hepatic CYP450 Excretion: bile primarily, urine < 1%
Angiotensin-Converting Enzyme Inhibitors			
Examples are captopril, zofenopril, enalapril, ramipril, quinapril, perindopril, lisinopril, benazepril, imidapril, trandolapril, fosinopril	Indicated for treatment of hypertension, prevention of cardiovascular events including HF in those at risk, reduction in progression of type 1 diabetic nephropathy, and reduction in cardiovascular events in patients following MI with left ventricular dysfunction or HF Also indicated for treatment of HF	Dosing schedules may need to be individualized for each dialysis session in order to avoid intradialytic hypotension In general, reduce dose by 50% to 75% in ESRD	Elimination: mainly renal, with elimination half-life of 12.6 h in healthy individuals In patients with impaired renal function (CrCl ≤ 30 mL/min), longer half-life and accumulation have been observed without clinical consequences
Angiotensin II Receptor Antagonists			
Examples are losartan, irbesartan, olmesartan, candesartan, valsartan, telmisartan	Indicated for treatment of hypertension, to reduce progression of type 2 diabetic nephropathy, and to reduce cardiovascular events in patients following MI with left ventricular dysfunction or HF Indicated for HF in those intolerant to ACE inhibitors	As first-line treatment in majority of patients with CKD, recommend use of ACE inhibitors or ARBs; both have been shown to reduce LVH in patients undergoing hemodialysis Levels of ARBs do not change significantly during hemodialysis	Losartan has 88% hepatic and 12% renal clearance
Calcium Channel Blockers			
Dihydropyridines, e.g., amlodipine, felodipine, nicardipine, nifedipine, nimodipine, nitrendipine Nondihydropyridines, e.g., diltiazem, verapamil	In UA/NSTEMI, if β–blockers are contraindicated, a nondihydropyridine CCB should be chosen in absence of clinically significant left ventricular dysfunction or other contraindications*	No specific dose adjustments for patients with CKD Management of chronic CAD in patients undergoing dialysis should follow guidelines for general population and use of CCBs as indicated Hemodynamic and electrophysiologic effects of CCBs are markedly different from each other and should be evaluated when selecting suitable therapy	Amlodipine has renal elimination as major route of excretion, with about 60% cleared in urine Diltiazem undergoes primary liver metabolism
Nitrates			
Nitroglycerin	2% ointment Angina: 0.5–2 inches applied in morning and 6 h later to truncal skin HF: 1.5 inches, increase by 0.5–1 inch up to 4 inches, every 4 h Sublingual: 0.4 mg for relief of chest pain in ACS Sublingual: 0.3–0.6 mg every 5 min Maximum: 3 doses within 15 min	No specific dose adjustments for patients with CKD Care must be used to avoid hypotension in low-volume states such as dialysis sessions	Metabolism: mainly in liver, extrahepatic sites such as vascular wall, red blood cells Excretion: urine
Antianginal Medications			

Ranolazine	500–1000 mg by mouth twice daily Max: 2000 mg per day	No specific dose adjustments for patients with CKD Prolongs QTc interval Recommend close monitoring	Excretion: urine 73% to 75%, feces 25%

*See also Roberts WC, Taylor MA, Shirani J: Cardiac findings at necropsy in patients with chronic kidney disease maintained on chronic hemodialysis. Medicine (Baltimore) 2012;91(3):165-78.

ACE, angiotensin-converting enzyme; *ACS*, acute coronary syndrome; *ARB*, angiotensin-receptor blocker; *CAD*, coronary artery disease; *CCB*, calcium channel blocker; *CKD*, chronic kidney disease; *CrCl*, creatinine clearance; *HF*, heart failure; *LVH*, left ventricular hypertrophy; *MI*, myocardial infarction; *NSTEMI*, non–ST-elevation myocardial infarction; *PCI*, percutaneous coronary intervention; *STEMI*, ST–elevation myocardial infarction; *UA*, unstable angina.

TABLE 98.2

Beta-Adrenergic Receptor Blockers in Patients With Chronic Kidney Disease*

MEDICATION	NORMAL DOSE	CHRONIC KIDNEY DISEASE POPULATION	PHARMACOLOGY
Metoprolol	Acute MI Metoprolol tartrate: 2.5–5 mg rapid IV every 2–5 min, up to 15 mg over 10–15 min, then 15 min after last IV dosage and receiving 15 mg IV or 50 mg by mouth every 6 h for 48 h, then 50–100 mg by mouth twice daily Angina Metoprolol tartrate: initially 50 mg by mouth twice daily, then titrated to 200 mg by mouth twice daily Metoprolol succinate: 100 mg by mouth once daily; no more than 400 mg per day	No specific dose adjustments for patients with CKD Recommend close monitoring for adverse effects	Dialysable: Yes Metabolism: hepatic CYP2D6 Metabolites: inactive Excretion: urine 95%
Esmolol	Immediate control For intraoperative treatment give 80 mg (≈ 1 mg/kg) as bolus dose over 30 seconds, followed by a 150 µg/kg per min infusion, if needed Maximum infusion rate: 300 µg/kg per min Gradual control For postoperative treatment, give loading dosage infusion of 500 µg/kg per min over 1 min, followed by a 4-min infusion of 50 µg/kg per min If no effect within 5 min, repeat loading dose and follow with infusion increased to 100 µg/kg per min	No specific dose adjustments for patients with CKD	Metabolism: extensively metabolized by esterase in cytosol of red blood cells Metabolites: major acid metabolite (ASL–8123), methanol (inactive) Excretion: urine < 1% to 2%
Carvedilol	Hypertension and post-MI protection: 6.25–25 mg by mouth twice daily Start at 6.25 mg by mouth twice daily, then increase every 3–14 days to 12.5 mg by mouth twice daily, then 25 mg by mouth twice daily	No specific dose adjustments for patients with CKD In a small study of patients undergoing dialysis with dilated cardiomyopathies, carvedilol improved left ventricular function and decreased rates of hospitalization, cardiovascular deaths, and total mortality	Elimination: mainly biliary Excretion: primarily via feces

*Hemodialysis reduces blood levels of atenolol, acebutolol, and nadolol; by contrast, levels of carvedilol and labetalol do not change significantly.

CKD, chronic kidney disease; *IV*, intravenous; *MI*, myocardial infarction.

TABLE 98.3

Lipid-Lowering Therapy for Primary and Secondary Prevention in Patients With Chronic Kidney Disease

MEDICATION	NORMAL DOSE	CHRONIC KIDNEY DISEASE POPULATION	PHARMACOLOGY
Rosuvastatin	Cardiovascular event protection 10-40 mg by mouth once daily	Efficacy in LDL-C reduction in CKD demonstrated at doses as low as 2.5 mg daily	Metabolism: liver, CYP450 CYP2C9 Excretion: bile primarily, urine < 2%
Simvastatin	Cardiovascular event protection: 20-40 mg by mouth once daily combined with ezetimibe 10 mg by mouth once daily Maximum dose: 40 mg by mouth given at hour of sleep	Consider starting dose at 5 mg in evening in patients with CKD In SHARP, lipid lowering with statin + ezetimibe was beneficial in patients with CKD In HPS, simvastatin reduced renal decline in patients with CKD	Metabolism: liver, CYP450 CYP3A4 Excretion: bile primarily, urine < 2%
Atorvastatin	Cardiovascular event protection: 10-80 mg by mouth once daily	No specific dose adjustments for patients with CKD Atorvastatin 10 mg in patients with CKD revealed a significantly lower risk of primary end point (nonfatal MI or cardiac death) when compared with placebo With TNT and GREACE studies, atorvastatin showed improvement in renal function in patients with CKD	Metabolism: liver, CYP450 CYP3A4 Excretion: bile primarily, urine < 2%
Fluvastatin	Cardiovascular event protection: 40 mg by mouth twice daily Extended release: 80 mg by mouth once daily	No specific dose adjustments for patients with CKD Caution for increased risk of rhabdomyolysis A multicenter, randomized, double-blind, placebo-controlled trial of fluvastatin was conducted in kidney transplant recipients Fluvastatin reduced LDL-C levels by 32%. Although primary end point did not achieve statistical significance, secondary analysis showed that fluvastatin group experienced fewer cardiac deaths and nonfatal MIs than did placebo group. Coronary intervention procedures were not significantly different between the two groups.	Metabolism: liver, CYP450 CYP2C9 isozyme system (75%), and to a lesser extent by CYP3A4 (≈20%) and CYP2C8 (≈5%) Excretion: bile primarily 90%, urine 5%
Pravastatin	Cardiovascular event protection: Start: 40 mg by mouth once daily, may adjust dose every 4 weeks Maximum dose: 80 mg by mouth once daily	Start at 10 mg by mouth once daily in patients with CKD A randomized trial of pravastatin versus placebo in patients with previous MI and CKD in a secondary analysis showed rate of coronary death or nonfatal MI was lower in patients receiving pravastatin, suggesting that pravastatin is effective for secondary prevention of cardiovascular events in patients with CKD	Metabolism: glucuronidation Excretion: bile primarily 70%, urine 20%
Pitavastatin	Lowering LDL-C and total cholesterol: Start: 1 mg by mouth once daily, may adjust every 4 weeks Maximum dose: 4 mg by mouth once daily	Start at 1 mg by mouth once daily in patients with CKD	Metabolism: glucuronidation Excretion: bile primarily 79%, urine 15%

CKD, chronic kidney disease; *GREACE*, Greek Atorvastatin and Coronary Heart Disease Evaluation; *HPS*, Heart Protection Study; *LDL-C*, low-density lipoprotein cholesterol; *MI*, myocardial infarction; *SHARP*, Study of Heart and Renal Protection; *TNT*, Treating to New Targets.

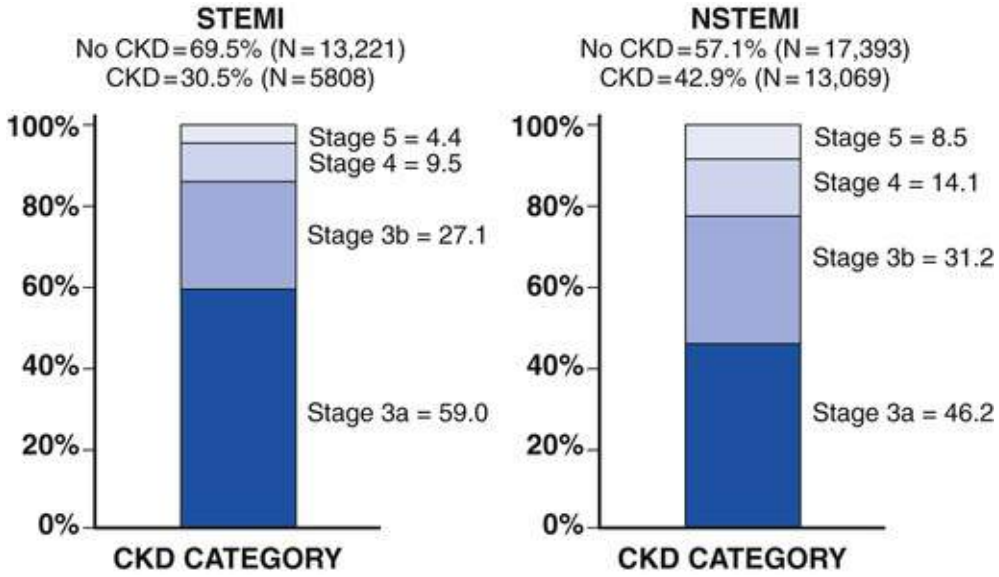

FIGURE 98.9 Prevalence of CKD and stages 3a, 3b, 4, and 5 (no dialysis) and dialysis presenting with STEMI and NSTEMI. Stage 3b as an eGFR 30 to 44 mL/min/1.73 m^2; stage 4 CKD as an eGFR between 15 and 29 mL/min/1.73 $m^{2;}$ and stage 5 CKD as an eGFR of less than 15 mL/min/1.73 m^2 or dialysis therapy. (Adapted from Fox CS, Muntner P, Chen AY, et al; Acute Coronary Treatment and Intervention Outcomes Network registry: Use of evidence-based therapies in short-term outcomes of ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction in patients with chronic kidney disease: a report from the National Cardiovascular Data Acute Coronary Treatment and Intervention Outcomes Network registry. Circulation 2010;121(3):357-65.)

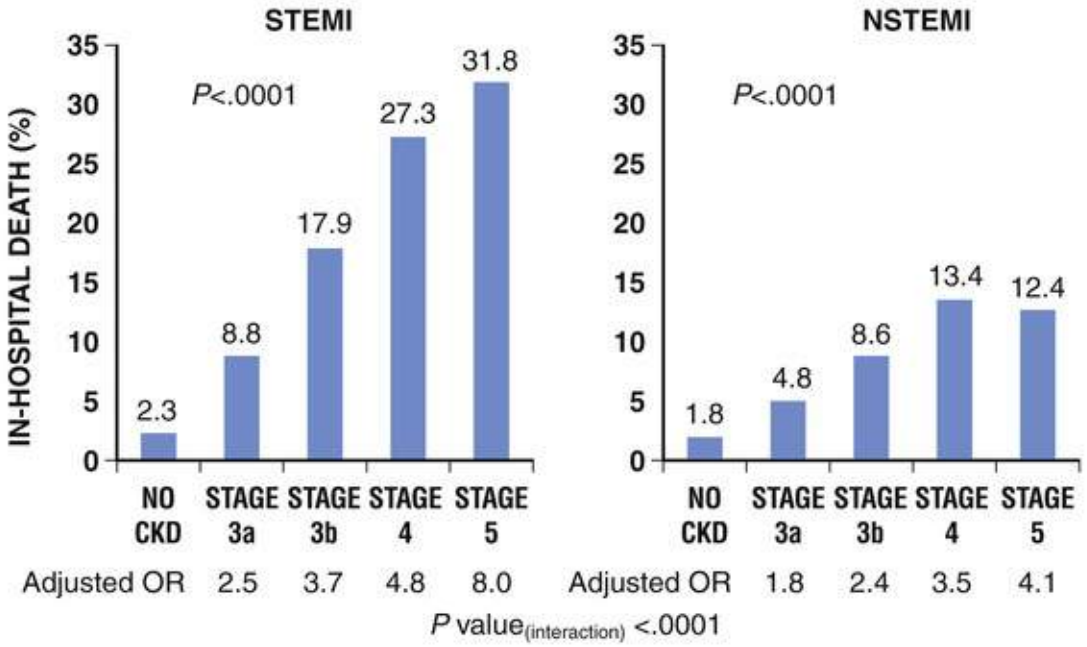

FIGURE 98.10 Crude rates and adjusted odds ratios for death by CKD stages among those presenting with STEMI and NSTEMI, with *Ptrend and Pinteraction for* STEMI vs NSTEMI by CKD stages. Stage 3a CKD was defined as an eGFR between 45 and 59 mL/min/1.73 m^2; stage 3b as an eGFR of 30 to 44 mL/min/1.73 m^2; stage 4 CKD as an eGFR between 15 and 29 mL/min/1.73 m^2; and stage 5 CKD as an eGFR of less than 15 mL/min/1.73 m^2 or dialysis therapy. (Adapted from Fox CS, Muntner P, Chen AY, et al; Acute Coronary Treatment and Intervention Outcomes Network registry: Use of evidence-based therapies in short-term outcomes of ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction in patients with chronic kidney disease: a report from the National Cardiovascular Data Acute Coronary Treatment and Intervention Outcomes Network registry. Circulation 2010;121(3):357-65.)

Reasons for Poor Outcomes After Acute Coronary Syndromes in Patients with Renal Dysfunction

Patients with renal dysfunction may have poor cardiovascular outcomes after ACS for four reasons: (1) excess comorbidities associated with CKD and ESRD, in particular DM and left ventricular dysfunction; (2) therapeutic nihilism; (3) toxicity of therapies; and (4) special biologic and pathophysiologic factors in renal dysfunction that cause worsened outcomes.[38]

The primary defects in thrombosis attributable to uremia are cytokine elevation, excess thrombin generation, and decreased platelet aggregation. Hence, patients with CKD and ESRD can have increased rates of coronary thrombotic events and increased bleeding risks at the same time. In patients with renal dysfunction the risks of bleeding increase with aspirin, unfractionated heparin, low-molecular-weight heparin, thrombolytics, glycoprotein IIb/IIIa antagonists, and thienopyridine antiplatelet agents (**Tables 98.4 and 98.5**). Uremia causes platelet dysfunction by independent mechanisms that add to pharmacologic antiplatelet agents.[39]

TABLE 98.4

Intravenous Glycoprotein IIb/IIIa Inhibitors for Unstable Angina/NSTEMI, STEMI, PCI

AGENT	NORMAL DOSE	CHRONIC KIDNEY DISEASE POPULATION*	PHARMACOLOGY
Abciximab	Adjunct to PCI: 0.25 mg/kg IV bolus over at least 1 min, 10–60 min before start of PCI, then 0.125 µg/kg per min (not to exceed 10 µg per min) continuous IV infusion for 12 h Unstable angina with PCI planned within 24 h: 0.25 mg/kg IV bolus over at least 1 min, then 0.125 µg/kg per min (not to exceed 10 µg per min) IV infusion for 18–24 h concluding 1 h after PCI	No specific dose adjustments for patients with CKD Abciximab should also be considered as adjunctive therapy in patients with ACS who are undergoing dialysis In CKD, safety of abciximab has been shown for Cr levels > 152.5 µmol/L Although increased bleeding with abciximab in patients with CKD has been reported, other studies have shown no increase in bleeding for CKD versus no CKD for abciximab in PCI	Metabolism: unknown, but likely by the reticuloendothelial system CYP450: unknown involvement Excretion: urine
Eptifibatide	ACS: 180 µg/kg IV bolus, then 2 µg/kg per min IV for up to 72 h PCI: 180 µg/kg IV, then a continuous infusion at 2 µg/kg per min, with another 180 µg/kg IV bolus 10 min after first bolus Continue infusion for at least 12 h	CrCl < 50 mL/min and ACS: 180 µg/kg IV, then continuous infusion 1 µg/kg per min Safety and use during hemodialysis are not established	Metabolism: other, minimal CYP450: unknown involvement Excretion: urine 50%
Tirofiban	In patients undergoing PCI, tirofiban is not recommended as an alternative to abciximab† ACS: 0.4 µg/kg per min IV for 30 min, then 0.1 µg/kg per min IV for 48–108 h PCI: Continue 0.1 µg/kg per min IV through procedure and for 12–24 h after	CrCl < 30 mL/min and ACS: reduce dose to 50% of normal rate Safety and use during hemodialysis not established	Excretion: urine 65% (primarily unchanged), feces 25% (primarily unchanged)

*When a glycoprotein IIb/IIIa antagonist is used, abciximab and tirofiban should be considered preferred agents, because no dosing changes are required for abciximab, and dialysis-specific dosing recommendations are available for tirofiban. Increased bleeding but reduced in-hospital mortality rates in CKD patients with ACS treated with glycoprotein IIb/IIIa antagonists has also been shown. (See also Opelami O, Sakhuja A, Liu X, et al. Outcomes of infected cardiovascular implantable devices in dialysis patients. Am J Nephrol. 2014;40(3):280-7.)

†See also Weinhandl ED, Gilbertson DT, Collins AJ: Mortality, hospitalization, and technique failure in daily home hemodialysis and matched peritoneal dialysis patients: a matched cohort study. Am J Kidney Dis 2016;67(1):98-110.

ACS, acute coronary syndrome; *CKD*, chronic kidney disease; *Cr*, creatinine; *CrCl*, creatinine clearance; *IV*, intravenous; *NSTEMI*, non–ST-elevation myocardial infarction; *PCI*, percutaneous coronary intervention; *STEMI*, ST–elevation myocardial infarction.

TABLE 98.5

Antithrombotic Agents for Acute Coronary Syndrome and Other Thrombotic Indications in Patients With Chronic Kidney Disease

AGENT	NORMAL DOSE	CHRONIC KIDNEY DISEASE POPULATION	PHARMACOLOGY
Indirect Factor Xa Inhibitors			
Unfractionated heparin	Recommended dosage and desired aPTT values as per institutional protocol PCI: 60–100 units/kg IV given once Target ACT 250–350 sec In patients receiving glycoprotein IIb/IIIa inhibitor, give 50–70 units/kg IV to target ACT 200 sec STEMI, adjunct treatment, streptokinase use: 800 units/h when < 80 kg body weight or 1000 units per h when > 80 kg body weight Start: 5000 units IV, adjust dose to target aPTT 50–75 sec NSTEMI: 12–15 units/kg per h IV Start: 60–70 units/kg IV; Max 5000 units bolus, max rate 1000 units per h Adjust dose to target aPTT 50–75 sec	In patients with CKD, suggested starting dose of heparin is 50 IU/kg bolus, then 18 IU/kg per h Monitor aPTT level and adjust accordingly as per institutional protocol	Metabolism: liver (partial) Metabolites: none Excretion: urine
Low-molecular-weight heparin (e.g., enoxaparin)	Unstable angina, non–Q-wave myocardial infarction: 1 mg/kg subcutaneously twice daily STEMI, age < 75 years: 30 mg IV bolus plus 1 mg/kg subcutaneously, then 1 mg/kg subcutaneously every 12 h PCI: additional 0.3 mg/kg IV bolus if last subcutaneous administration given > 8 h before balloon inflation STEMI, age > 75 years: 0.75 mg/kg subcutaneously every 12 h (no IV bolus)	CrCl < 30 mL/min STEMI, age < 75 years: 30 mg IV bolus plus 1 mg/kg subcutaneously, then 1 mg/kg subcutaneously once a day STEMI, age > 75 years: 1 mg/kg subcutaneously once a day	Excretion: urine 40%
Direct Factor Xa Inhibitor			
Fondaparinux	Unstable angina/NSTEMI Conservative strategy: 2.5 mg subcutaneously once daily During PCI: add unfractionated heparin 50–60 units/kg IV bolus for prophylaxis of catheter thrombosis[52]	CrCl 30–50 mL/min: use with caution CrCl < 30 mL/min: not indicated	Excretion: urine (primarily unchanged)
Direct Thrombin Inhibitors			
Bivalirudin	Intended for use with aspirin 300–325 mg per day 0.75 mg/kg IV bolus initially, followed by continuous infusion at rate of 1.75 mg/kg per h for duration of procedure Perform ACT 5 min after bolus dose Administer additional 0.3 mg/kg bolus if necessary May continue infusion following PCI beyond 4 h (optional post-PCI, at discretion of treating health care provider) initiated at rate of 0.2 mg/kg per h for up to 20 h as needed	CrCl 10–29 mL/min: usual bolus dose, then initial infusion of 1 mg/kg per h IV up to 4 h Hemodialysis: usual bolus dose, then initial infusion of 0.25 mg/kg per h IV up to 4 h Bivalirudin is a direct thrombin inhibitor with specific dosing adjustments for patients undergoing dialysis and should be preferentially considered	Dialysable: with 25% reduction in levels Excretion: urine
Dabigatran	Indicated for prevention of stroke and thromboembolism associated with nonvalvular atrial fibrillation CrCl > 30 mL/min: 150 mg by mouth twice daily	CrCl 15–30 mL/min: 75 mg by mouth twice daily CrCl <15 mL/min or hemodialysis: not indicated For patients currently taking dabigatran, wait 12 h (CrCl ≥30 mL/min) or 24 h (CrCl < 30 mL/min) after last dose of dabigatran before initiating treatment with parenteral anticoagulant If possible, discontinue dabigatran 1–2 days (CrCl ≥ 50 mL/min) or 3–5 days (CrCl < 50 mL/min) before invasive or surgical procedures because of increased risk of bleeding	Metabolism liver esterases and microsomal carboxylesterases Excretion: feces 7%, urine 86%
Rivaroxaban	Indicated for prevention of stroke and thromboembolism associated with nonvalvular atrial fibrillation, VTE CrCl > 50 mL/min: 15 mg by mouth bid for 3 weeks (acute anticoagulation for VTE) CrCl > 50 mL/min: 20 mg by mouth at hour of sleep (chronic anticoagulation)	CrCl 15–50 mL/min: 15 mg by mouth at hour of sleep CrCl < 15 mL/min: not indicated	Metabolism: liver CYP450 Excretion: feces 28%, urine 66% Half-life: 5–9 h or 11–13 h in elderly
Apixaban	Indicated for prevention of stroke and thromboembolism associated with nonvalvular atrial fibrillation, VTE 2.5 mg by mouth twice daily (VTE prophylaxis) 5 mg by mouth twice daily (chronic anticoagulation)	Age ≥ 80 years, body weight ≤ 60 kg, or serum Cr ≥ 1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily	Metabolism: liver CYP450 CYP3A4/5 while CYP1A2, 2C8, 2C9, 2C19, and 2J2 are minor Excretion: feces 83%, urine 27%
Edoxaban	Indicated for prevention of stroke and thromboembolism associated with nonvalvular atrial fibrillation, VTE 60 mg by mouth once daily (VTE prophylaxis) 60 mg by mouth once daily (chronic anticoagulation)	CrCl > 95 mL/min: Do not use; increased ischemic stroke compared with warfarin CrCl > 50 to 95 mL/min: 60 mg orally once daily CrCl 15-50 mL/min or < 60 kg: 30 mg orally once daily	Metabolism: minimal Excretion: urine

ACT, activated clotting time; *aPTT*, activated partial thromboplastin time; *CKD*, chronic kidney disease; *Cr*, creatinine; *CrCl*, creatinine clearance; *IV*, intravenous; *NSTEMI*, non–ST-elevation myocardial infarction; *PCI*, percutaneous coronary intervention; *STEMI*, ST–elevation myocardial infarction; *VTE*, venous thromboembolism.

Renal dysfunction is a highly inflammatory state, associated with higher rates of plaque rupture and

incident thrombotic CVD events. Patients with CKD have more proximal and extensive CAD than the general population; thus, they have larger areas of myocardium at risk for ischemia and dysfunction. Finally, patients with acute-on-chronic hyperactivation of neurohormonal systems, including the RAAS, the SNS, or systems using endothelin or vasopressin, who do not have adequate counterregulation by natriuretic peptides, nitric oxide, and other systems, may promote worsened ischemia, myocardial dysfunction, and end-organ injury.

Treatment of Myocardial Infarction in Patients With Renal Dysfunction (see also Chapters 59 and 60)

Therapies that benefit the general population and often yield enhanced benefit in patients with CKD and ESRD include aspirin, beta blockers, ACEIs, ARBs, and aldosterone receptor antagonists.[40] Therapies that require dose adjustments on the basis of CrCl include low-molecular-weight heparins, bivalirudin, and glycoprotein IIb/IIIa antagonists. Given that the major inputs for bleeding risks include older age, low body weight, and renal dysfunction, **Tables 98.4 and 98.5** also list agents that are approved in a weight-adjusted dose form and give the currently recommended dose adjustments for commonly used antiplatelet and antithrombotic agents.[39] Greater utilization of such therapies, despite the heightened risk for complications, might attenuate the excess mortality rate reported in CKD and ESRD populations. There have been no randomized trials of PCI in patients with CKD or ESRD. However, the large Swedish Web-system for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) has observed an apparent benefit of revascularization in ACS in CKD groups with an eGFR of 15 mL/min/1.73 m^2 or more (**Fig. 98.11**).[41] Patients with more severe degrees of renal impairment and those undergoing dialysis, although infrequently offered PCI, appeared to have no improvement in survival rates with interventional management.

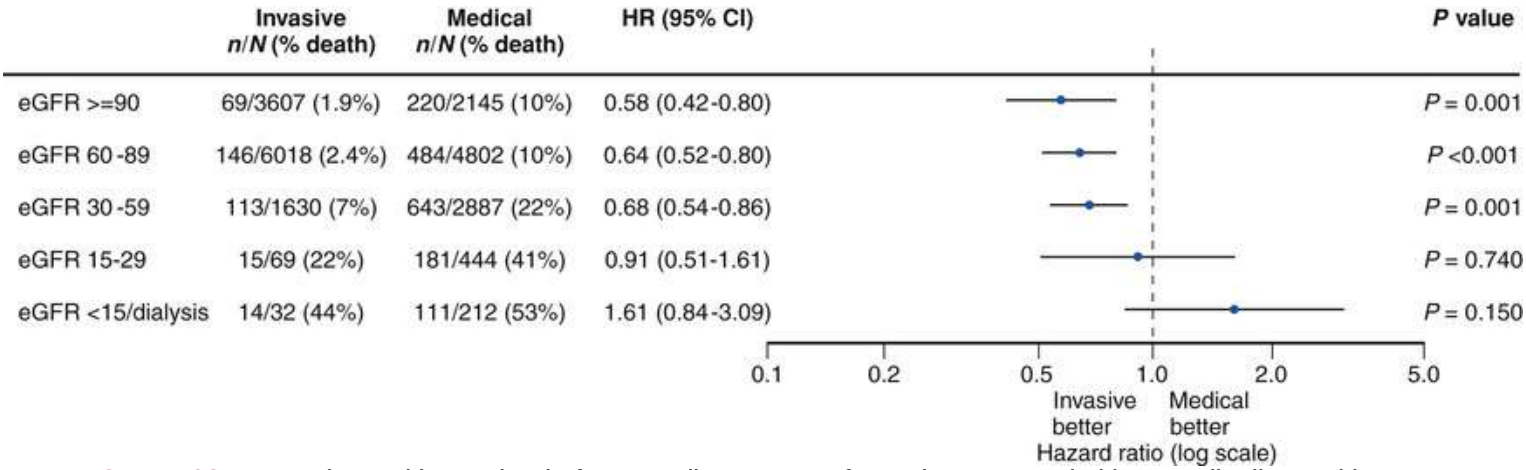

FIGURE 98.11 Estimated hazard ratio for mortality at 1 year for patients treated either medically or with early revascularization. (Adapted from Szummer K, Lundman P, Jacobson SH, et al; SWEDEHEART: Influence of renal function on the effects of early revascularization in non-ST-elevation myocardial infarction: data from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). Circulation 2009;120(10):851-8.)

Cardiorenal Syndromes

The term *cardiorenal syndrome* (CRS) refers to disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other (see also Part IV). Five distinct syndromes have been described according to the clinical scenario and time sequence of organ failure (**Fig. 98.12**). Patients with CKD, and in particular ESRD, have three key mechanical contributors to HF: pressure overload (related to HTN), volume overload, and cardiomyopathy (**Fig. 98.13**). Approximately 20% of patients approaching hemodialysis have a diagnosis of preexisting HF. It is unclear how much of this diagnosis can be attributed purely to chronic volume overload from renal failure and how much is due to impaired systolic or diastolic function. CKD influences the blood levels of B-type natriuretic peptide (BNP) and NT-proBNP. In general, when the eGFR is less than 60 mL/min/1.73 m^2, higher cut points of 200 pg/mL and 1200 pg/mL should be used in the diagnosis of HF with BNP and NT-proBNP, respectively.

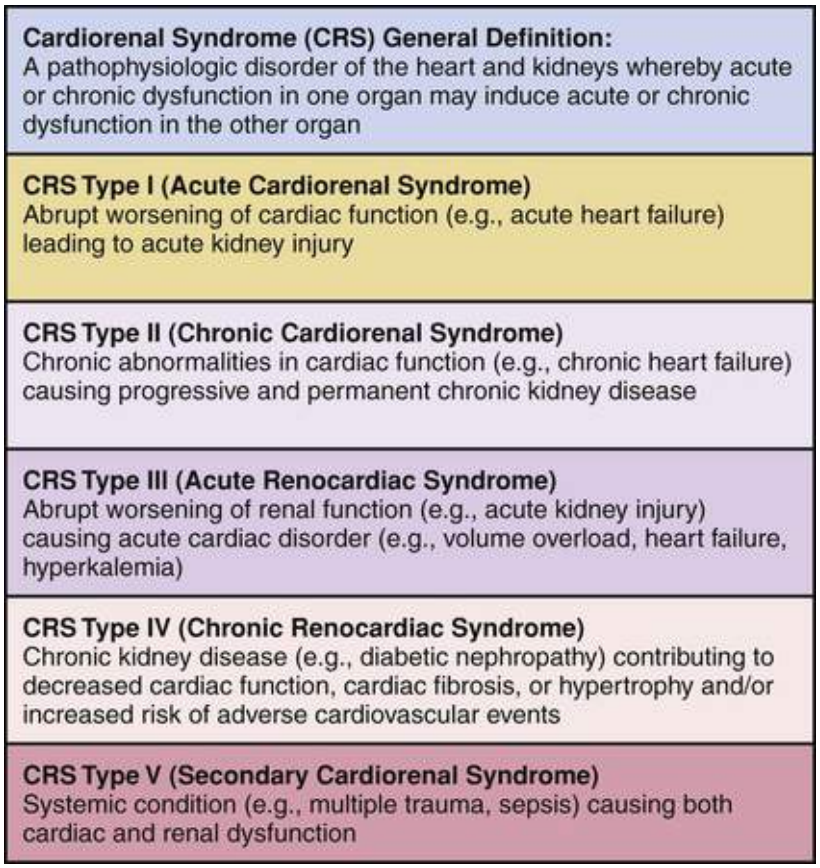

FIGURE 98.12 Definitions of cardiorenal syndromes. (Adapted from Ronco C, Haapio M, House AA, et al: Cardiorenal syndrome. J Am Coll Cardiol 2008;52(19):1527-39.)

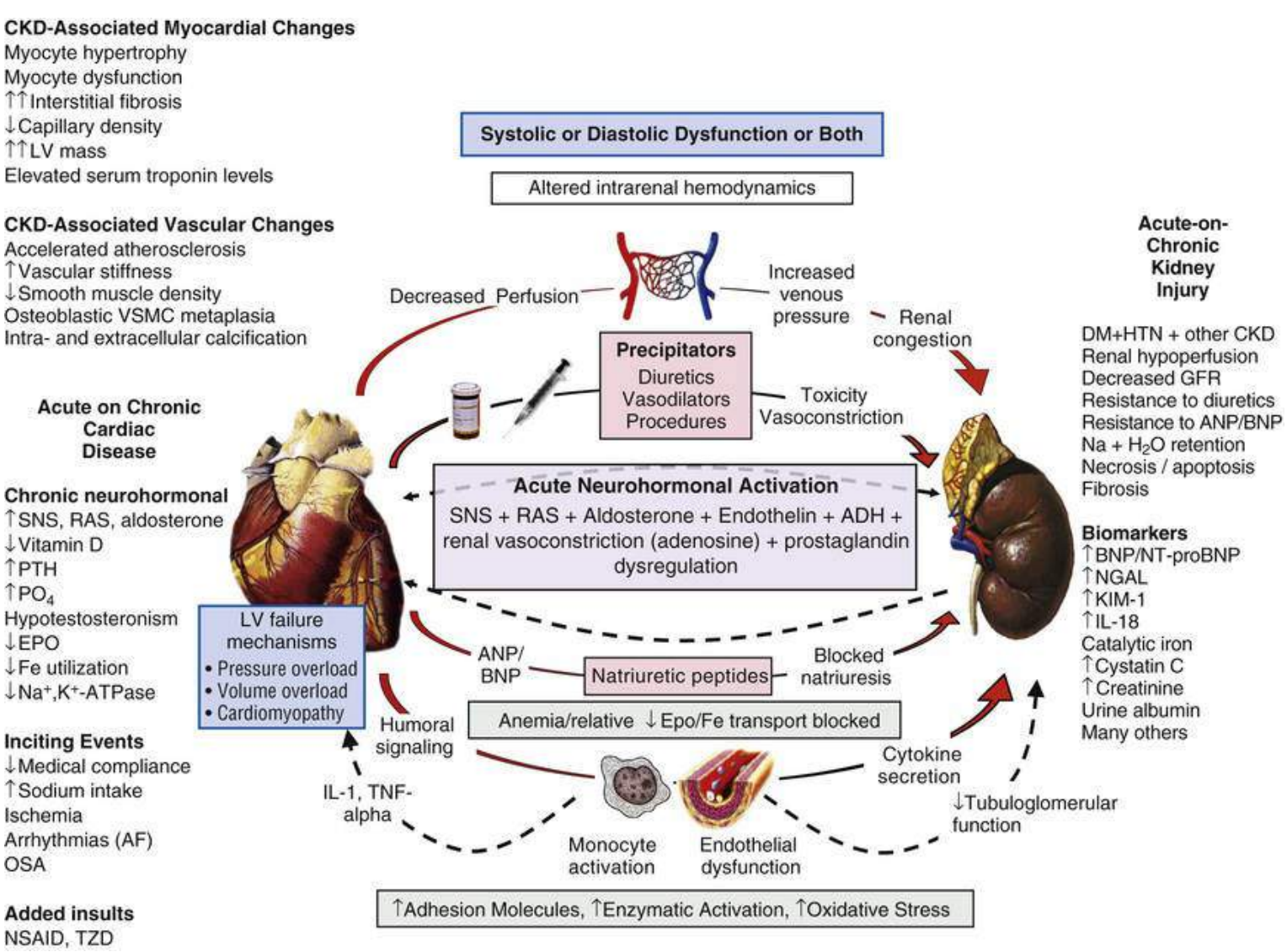

FIGURE 98.13 Pathophysiology of type 1 cardiorenal syndrome or worsening renal function after hospitalization for acutely decompensated heart failure; *KIM-1,* kidney injury molecule-1; *OSA,* obstructive sleep apnea; *TZD,* thiazolidinedione; *VSMC,* vascular smooth muscle cell. (Adapted from Herzog CA, Asinger RW, Berger AK, et al: Cardiovascular disease in chronic kidney disease: a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2011;80(6):572-86.)

Once acute HF is recognized on clinical grounds, approximately 25% of patients will develop a CRS during hospitalization; it will be characterized by a rise in serum Cr of 0.3 mg/dL or more and a reduction in urine output. Of those, approximately one third will return to baseline, one third are left with a worsened eGFR, and the final third have progressive cardiorenal disease resulting in either death or the need for renal replacement therapy.[42] Multiple studies have shown that the predictors of CRS (type 1) include the baseline eGFR, older age, female sex, increased baseline blood pressure, higher initial natriuretic peptide levels, and increased central venous pressure. Because CRS type 1 in patients with HF rarely occurs in the prehospital phase and more commonly develops after treatment is started in the hospital, iatrogenic factors have been implicated. The use of loop diuretics can contribute to CRS type 1, probably by further activating the RAAS and possibly worsening intrarenal hemodynamics.

There are no proven therapeutic strategies for CRS type 1. Failed approaches include continuous furosemide infusions, low-dose dopamine, nesiritide, and programmatic use of inotropic agents. In the setting of poor arterial perfusion, dobutamine or milrinone is commonly used during hospitalizations. Neither agent reduces mortality rates, but both increase the risk of arrhythmias, and milrinone must be dose adjusted when the eGFR is below 45 mL/min/1.73 m^2 (**Table 98.6**) Patients with advanced HF have a reduced renal blood flow, a decreased glomerular filtration rate, enhanced proximal reabsorption of

water, increased absorption of sodium along the loop of Henle, and an overall reduced capacity of the nephron to excrete water. Furthermore, a reduced effective arterial blood volume stimulates vasopressin release, which plays a dominant role in worsening water retention. Hyponatremia and excess body water can be improved with the use of oral tolvaptan or intravenous conivaptan; however, neither therapy reduces rehospitalization or mortality rates in this scenario.

TABLE 98.6

Selected Therapies for Heart Failure in Patients With Chronic Kidney Disease

MEDICATION	NORMAL DOSE	CHRONIC KIDNEY DISEASE POPULATION	PHARMACOLOGY
Dobutamine	Acutely decompensated HF with low cardiac output: continuous infusion of 5-15 µg/kg/min IV Initial rate 5.0 µg/kg/min IV titrate 5-20 µg/kg/min; no more than 40 µg/kg/min	No specific dose adjustments for patients with CKD Recommend close monitoring for adverse effects, including arrhythmias Doses < 5 µg/kg/min may produce hypotension	Principal routes of metabolism are methylation of the catechol and hepatic conjugation May increase renal clearance of other drugs in low cardiac output states.
Milrinone	Acutely decompensated HF with low cardiac output: loading dose of 50 µg/kg IV over 10 minutes, then start maintenance: 0.375 to 0.75 µg/kg/min	Recommended infusion rates (µg/kg/min) CrCl mL/min/1.73 m^2 [CrCl > 50]: No change [50]: 0.43 µg/kg/min [40]: 0.38 µg/kg/min [30]: 0.33 µg/kg/min [20]: 0.28 µg/kg/min [10]: 0.23 µg/kg/min [5]: 0.2 µg/kg/min	Excreted unchanged in urine
Nesiritide	Acutely decompensated HF with pulmonary congestion: 2 µg/kg IV bolus over 1 minute, then 0.01 µg/kg/min IV infusion. If hypotension, discontinue until stabilized, then restart at 30% lower dose	No specific dose adjustments for patients with CKD Recommend close monitoring for adverse effects, including hypotension	Cleared by (1) binding to cell surface clearance receptors with subsequent cellular internalization and lysosomal proteolysis; (2) proteolytic cleavage of peptide by endopeptidases, such as neutral endopeptidase, which are present on vascular luminal surface; and (3) renal filtration
Nitroprusside	Acutely decompensated HF with vasoconstriction: 0.25–0.8 mg/kg/min IV	No specific dose adjustments for patients with CKD Recommend close monitoring for adverse effects, including hypotension and thiocyanate accumulation	Intraerythrocytic reaction but hepatic and renal function impacts thiocyanate accumulation
Valsartan/Sacubitril	Chronic HF with reduced LVEF: sacubitril/valsartan 24/26, 49/51, 97/103 mg orally twice daily	No specific dose adjustments for patients with CKD Monitor Cr, blood urea nitrogen, K+	Metabolism: Sacubitril converted to LBQ657 by esterases; urine 52% to 68%, feces 37% to 48% Valsartan urine ≈ 13%, feces 86%
Ivabradine	Chronic HF with LVEF < 35% and heart rate > 70: start 5 mg orally twice daily and may reduce to 2.5 mg or increase to 7.5 mg twice daily depending on heart rate and tolerability	No specific dose adjustments for patients with CKD	Metabolism: liver CYP450 CYP3A4 Excretion: feces 96%, urine 4%
Hydralazine	Acute and chronic HF, intolerant to RAAS blockers, 25–50 mg by mouth tid or qid	Dose q 8–16 h with CrCl < 10 mL/min	Hepatic clearance, 25% to 40% removed with dialysis
Digoxin	Chronic systolic and diastolic HF, atrial fibrillation with rapid ventricular rate 0.25 mg by mouth qd	0.125 mg po qd or qod	50% to 70% excreted unchanged in urine. Half-life in anuric patients is prolonged to 3.5 to 5 days. Digoxin is not effectively removed from body by dialysis

CKD, chronic kidney disease; *Cr*, creatinine; *CrCl*, creatinine clearance; *HF*, heart failure; *IV*, intravenous; *LVEF*, left ventricular ejection fraction; *RAAS*, renin-angiotensin-aldosterone system.

Treatment efforts should be aimed at reducing congestion within a narrow management window (**see Chapter 25**) and improving left ventricular systolic function, often in the hospitalized setting; the oral and intravenous therapies are used, including diuretics mentioned previously and discussed in detail elsewhere in this text. Observational studies and small trials utilizing continuous venovenous

ultrafiltration have been associated with short-term improvements in symptoms, reductions in fluid weight, shorter hospital stays, and reductions in rehospitalization. However, the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) in patients with persistent congestion and CRS type 1 found no clinical benefits of ultrafiltration over diuretic therapy, and more patients in the ultrafiltration group than in the pharmacologic therapy group incurred serious adverse events (72% vs. 57%; $P = 0.03$).[66] Until larger trials help define the indicated population and optimal timing and mode of ultrafiltration, and until they demonstrate longer-term reductions in hospitalization and mortality rates, ultrafiltration can be considered a last-line approach for the patient with refractory CRS.

The management of the patient who is already receiving dialysis and in HF requires particular care. In general, proven HF therapies, provided they are tolerated, should be employed, along with regular and ad hoc dialysis as needed to control volume overload. Clinicians should keep in mind that ACEIs are dialyzed but ARBs are not. Both agents are associated with reductions in mortality rates in ESRD patients in observational studies. Studies of frequent dialysis performed in the home at lower rates of ultrafiltration have consistently demonstrated lower rates of hospitalization and death in HF patients.[43]

In summary, CKD and HF present a particularly challenging scenario for clinicians and patients. Frequent outpatient monitoring and avoidance of overly aggressive diuresis are advised. Dialysis patients, despite having volume reduction with mechanical fluid removal, should have medical therapy with ACEIs or ARBs, beta blockers, and additional agents for blood pressure control if needed. Ideally, ESRD patients with HF would undergo frequent (daily) hemodialysis treatments at home provided self-care and partner care can be delivered without difficulties.

Chronic Kidney Disease and Valvular Heart Disease

Impaired renal function is linked to mitral annular calcification and to aortic valve sclerosis (see also Section 8). Progressive thickening of the cardiac valves and calcification occur in patients with ESRD.[44] Approximately 80% of patients with ESRD have the murmur of aortic sclerosis. Patients with CKD and ESRD have rates of progressive calcification and valve failure greater than in the general population.[45]

Bacterial endocarditis may develop in patients with ESRD who have temporary access catheters for dialysis (**see also Chapter 73**).[46] Endocarditis with common pathogens, including *Staphylococcus*, *Streptococcus*, and *Enterococcus*, in the mitral, aortic, or tricuspid valves, is associated with a risk of cerebral embolism of 40% and a mortality rate of 50% in ESRD.[46] It becomes very difficult to treat given the continued need for dialysis access and the delay in surgical placement of permanent arteriovenous shunts or fistulas. Unfortunately, surgical mortality rates associated with valve replacement in ESRD related to endocarditis are very high. In the setting of ESRD, when valve surgery is carried out for endocarditis or other causes of valve failure, there has been no difference in survival rates among those who received tissue valves or mechanical valve prostheses. Thus, tissue valves are a reasonable choice given the complicating issue of chronic anticoagulation and bleeding with repeated dialysis vascular access.[47]

Renal Function and Arrhythmias

Uremia, hyperkalemia, acidosis, and disorders of calcium-phosphorous balance are all linked to higher rates of atrial and ventricular arrhythmias (see also Section 5). Given a concurrent substrate of LVH, left ventricular dilation, HF, and valvular disease, it is not surprising that higher rates of virtually all the

arrhythmias have been reported in CKD, including bradyarrhythmias and heart block. Hypokalemia after hemodialysis can be observed for 6 to 8 hours as the plasma potassium concentration equilibrates from approximately 2.0 mEq/L to the normal range of 3.5 to 5.5 mEq/L. During this time, multiple studies indicate an increased risk of sudden cardiac death.[48] There is a general trend to increase the potassium concentration of the dialysis fluid to reduce the large shifts in potassium in ESRD patients. Caveats for practical management include dose adjustment for many antiarrhythmic medications, including dofetilide and sotalol (**Table 98.7**). Observational studies suggest that ESRD patients who survive a sudden death event have a favorable benefit-to-risk ratio for implantable cardioverter-defibrillator (ICD) placement; however, rates of infection are higher and when infection occurs, it is associated with in-hospital mortality rates of approximately 14%.[49] Of concern, CKD, and ESRD in particular, may cause elevated defibrillation thresholds and failure of ICDs and is associated with high rates of shock and antitachycardia pacing therapy (**Fig. 98.14**).[50] Until this association is better understood, patients receiving ICDs should have frequent surveillance and consideration for noninvasive programmed stimulation for appropriate antitachycardia and defibrillation therapy.

TABLE 98.7

Selected Antiarrhythmics in Patients With Chronic Kidney Disease

MEDICATION	NORMAL DOSE	CHRONIC KIDNEY DISEASE POPULATION	PHARMACOLOGY
Amiodarone	Acute ventricular and acute and chronic atrial arrhythmias: First rapid: 150 mg over 10 minutes (15 mg/min) Followed by slow: 360 mg over 6 hours (1 mg/min) Maintenance infusion: 540 mg over the remaining 18 hours (0.5 mg/min) Oral 800 to 1600 mg per day in divided doses until a total of 10 g has been given; then 200 to 400 mg per day	No specific dose adjustments for patients with CKD	Eliminated primarily by hepatic metabolism and biliary excretion; negligible renal excretion
Dronedarone	Atrial fibrillation/atrial flutter: 400 mg orally twice a day with morning and evening meals	No specific dose adjustments for patients with CKD	Dronedarone is extensively metabolized by the liver
Dofetilide	Atrial fibrillation/atrial flutter; 500 µg po bid initially. QTc interval should be measured 2-3 hours after initial dose. If QTc > 15% of baseline, or if QTc is > 500 msec (550 msec in patients with ventricular conduction abnormalities), dofetilide should be adjusted. Continued monitoring for doses 2-5: QTc interval must be determined 2-3 hours after each subsequent dose of dofetilide for in-hospital doses 2-5. If the measured QTc is > 500 msec (550 msec in patients with ventricular conduction abnormalities), dofetilide should be stopped	[CrCl > 60 mL/min]: 500 µg bid [40-60 mL/min]: 250 µg twice daily [20-39 mL/min]: 125 µg twice daily [< 20 mL/min]: contraindicated	Hepatic metabolism accounts for 20% to 30%, 70% to 80% renal elimination
Sotalol	Atrial fibrillation/atrial flutter: 80-160 mg orally twice a day	CrCl 30 to 59 mL/min: Dosage interval should be increased to 24 hours CrCl 10 to 29 mL/min: Dosage interval should be increased to 36 to 48 hours CrCl < 10 mL/min: Dose should be individualized	Excreted unchanged in kidney. Removed with dialysis

CKD, chronic kidney disease; *CrCl*, creatinine clearance; *IV*, intravenous.

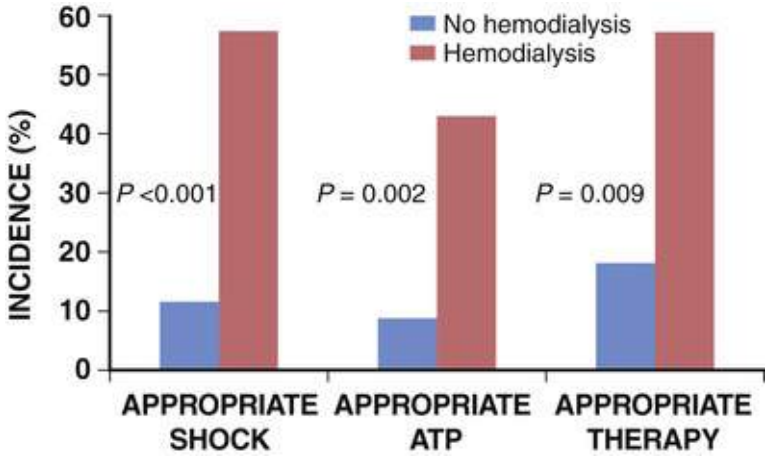

FIGURE 98.14 Incidence of events in patients with implantable cardiodefibrillators with end-stage renal disease and those without. *ATP*, antitachycardia pacing. (Adapted from Hreybe H, Ezzeddine R, Bedi M, et al: Renal insufficiency predicts the time to first appropriate defibrillator shock. Am Heart J 2006;151(4):852-6.)

Consultative Approach to Severe Kidney Disease and Hemodialysis Patients

The prevalence of angiographically significant coronary artery disease (CAD) ranges from 25% in young, nondiabetic hemodialysis patients to 85% in older ESRD patients with long-standing DM.[51] Of those initiating dialysis, 87% have some structural abnormality on echocardiography, including LVH, reduced LVEF, right ventricular hypertrophy or dysfunction, pulmonary HTN, or valvular disease.[52] Thus, many years of CKD must be associated with these progressive changes, and we cannot attribute them to the dialysis procedure itself in most patients who are in the first few months of treatment. Cardiac death in dialysis patients younger than age 45 may be 100 times greater than that in the general population. The prevalence and severity of CAD among patients with ESRD is daunting in terms of both occurrence and extent of poor outcomes. Medicare beneficiaries with CKD prior to initiation of dialysis are 60% more likely to have a billing claim submitted for the diagnosis of CVD and 70% more likely to have a claim submitted for "atherosclerotic heart disease." Of those claims incident to dialysis, a substantial proportion of patients, perhaps the majority, have established CAD. In diabetic renal transplant candidates, 30% will have one or more lesions with greater than 75% stenosis.[53] When comparing patients who undergo evaluation for CAD, those with ESRD have substantially more numerous, proximal, and severe coronary artery lesions, as well as more severe left ventricular dysfunction. The patient with incipient ESRD on dialysis can be considered the highest cardiovascular risk patient in medicine, with expected rates of CHD death that are many-fold those expected for a non-ESRD patient, even those with a burden of several cardiovascular risk factors.

Despite the use of multiple medications, most published series of ESRD patients from either clinical trials or registries indicate the mean systolic blood pressure is approximately 155 mm Hg. Indeed 80% of ESRD patients have HTN, but it is adequately controlled in only 30% of these patients. Peritoneal dialysis, more frequent in-center, and home hemodialysis are associated with much better blood pressure control than thrice-weekly hemodialysis.[54] Arteriovenous fistulas used for dialysis access cause recirculation of blood in one of the extremities (usually the upper arm), and depending on their size and proximity, can account for as much as 25% shunting. This volume loads the right ventricle and can predispose to the development of HF and right ventricular dysfunction after the onset of ESRD and use of the shunt or fistula.[55] Long-term cardiorenal protection involves two important concepts: (1) blood

pressure control and (2) use of an agent that blocks the RAAS, such as an ACEI or ARB, as the base of therapy. The RAAS appears to have considerable redundancy and is able to maintain its function, if not increase its overall level of activity, without participation by the kidneys. Hence, this hyperactivation of the RAAS is a target for therapy even in anephric patients because the ACEI or ARB can reduce the LVH and possibly improve survival rates. A small trial demonstrated that ramipril can preserve the residual urine output in those receiving peritoneal dialysis, which is a consistently favorable finding in ESRD.[56] A case-matched study of ESRD patients found that those who were taking an ACEI or ARB had improved survival rates, and this benefit appeared to get larger for longer durations of use.[57] ACEI or ARB therapy may worsen hyperkalemia in patients with ESRD. As tolerated, the clinician should consider adjusting the dialysis regimen to improve potassium removal. Patiromer calcium, a gastrointestinal potassium-binding polymer, was approved in starting doses of 8.4 g orally per day for acute and extended treatment of hyperkalemia.[58]

With an ACEI or ARB as a base of therapy, the antihypertensive regimen can be further modified according to the drug's efficacy in lowering the blood pressure and reducing the CAD events. Beta blockers can be used as both antihypertensive and antiischemic agents. In those with HF, beta blockers improve the left ventricular ejection fraction and reduce rates of hospitalization, sudden death, and all-cause mortality. Patients with ESRD who receive beta blockers after CAD events may have large relative risk reductions in all-cause mortality.

Decisions regarding an additional antihypertensive or cardioprotective agent should be based on ease of management, likelihood of patient compliance, and lack of adverse effects. Guidelines for non-ESRD patients state that the optimal office systolic blood pressure should be less than 130 mm Hg. The difficult task in the ESRD patient is to achieve these goals without having hypotension during dialysis sessions. Given the high rates of severe CAD in ESRD, hypotension during dialysis can worsen clinical and subclinical ischemia, which is recognized as chest discomfort, shortness of breath, ST-segment depression on electrocardiography, and elevations of cTn on blood testing.

The goal of LDL-C reduction, in most cases with a statin and ezetimibe, in patients with ESRD is supported by a 17% reduction in major atherosclerotic events shown in the Study of Heart and Renal Protection in patients with predialysis CKD and ESRD.[59] Use of nonstatin lipid-lowering agents can be stylized to treat statin-intolerant patients and those with hypertriglyceridemia at risk for pancreatitis. Among those with CKD and ESRD, there are no clear sources of evidence that these drugs reduce cardiovascular events. Colesevelam, a bile-acid sequestrant, also can aid in lowering serum phosphorus.

In ESRD with DM, blood glucose control to a target glycohemoglobin level of less than 7% can be expected to reduce rates of microvascular complications (retinopathy) and, to a lesser extent, clinically important atherosclerotic disease (MI, stroke, CVD death). Patients with ESRD should stop smoking. The specific use of antiplatelet or antithrombotic agents for the prevention of CVD risk in ESRD requires caution.

In the setting of stable symptomatic CAD, an analysis from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial suggested that PCI had no benefit over optimal medical therapy in patients with predialysis CKD.[60] There are no similar trial data available in patients with ESRD. After treatment with optimal medical therapy in a patient with ESRD and symptomatic CAD, the next step is coronary angiography and consideration of revascularization. In the common scenario of multivessel disease, multiple studies have shown that the coronary artery bypass graft (CABG) is associated with superior outcomes over PCI with drug-eluting stents, probably due to more complete revascularization and protection from recurrent MI.[61] Patients with ESRD undergoing coronary revascularization procedures have an increased risk for adverse events, including death.

Dialysis-dependent patients undergoing CABG face a 4.4-fold increased risk of in-hospital death, a 3.1 times greater risk of mediastinitis, and a 2.6-fold increased risk of stroke compared with patients undergoing CABG who are not on dialysis.[40]

In summary, patients with ESRD have a greater coronary heart disease risk than would be calculated from standard risk scores. An aggressive approach with medical management for CAD is warranted, even in the case of subclinical CAD. A low threshold for diagnostic testing should be held in ESRD patients. When significant multivessel CAD is found, ESRD patients appear to benefit from revascularization with CABG compared with PCI. If it is clinically reasonable, patients should be given that opportunity for improved survival times and a reduction in future cardiac events.

Evaluation and Management of the Renal Transplant Recipient

Cardiovascular screening is recommended in high-risk CKD patients prior to renal transplantation.[62] These include persons with DM; men over age 45 years and women over age 55 years; and patients with a history of ischemic heart disease, an abnormal electrocardiogram, left ventricular dysfunction, history of smoking, or duration of dialysis more than 2 years. Controversies exist regarding the ideal screening test for CAD in ESRD patients. The choice of exercise versus pharmacologic stress and echocardiography versus nuclear scintigraphic imaging must be individualized. One suggested algorithm uses dobutamine stress echocardiography (**Fig. 98.15**). Coronary cardiac computed tomographic angiography may be considered as another screening tool with the understanding that it can exclude significant coronary disease and identify very low risk patients who may move on to renal transplantation.[63] Coronary angiography and revascularization can be performed with little loss in renal function in very low eGFR groups if it is done carefully with staged intervals between the diagnostic procedure and PCI or CABG (**Fig. 98.16**).[64] After renal transplantation, treatment with lipid-lowering therapy (i.e., low-potency statins such as fluvastatin or pravastatin) is generally associated with a favorable benefit-to-risk ratio.[65] A metaanalysis of 22 studies (with 3465 participants) has supported the use of statins in renal transplant recipients for the reduction of cardiovascular events.[66]

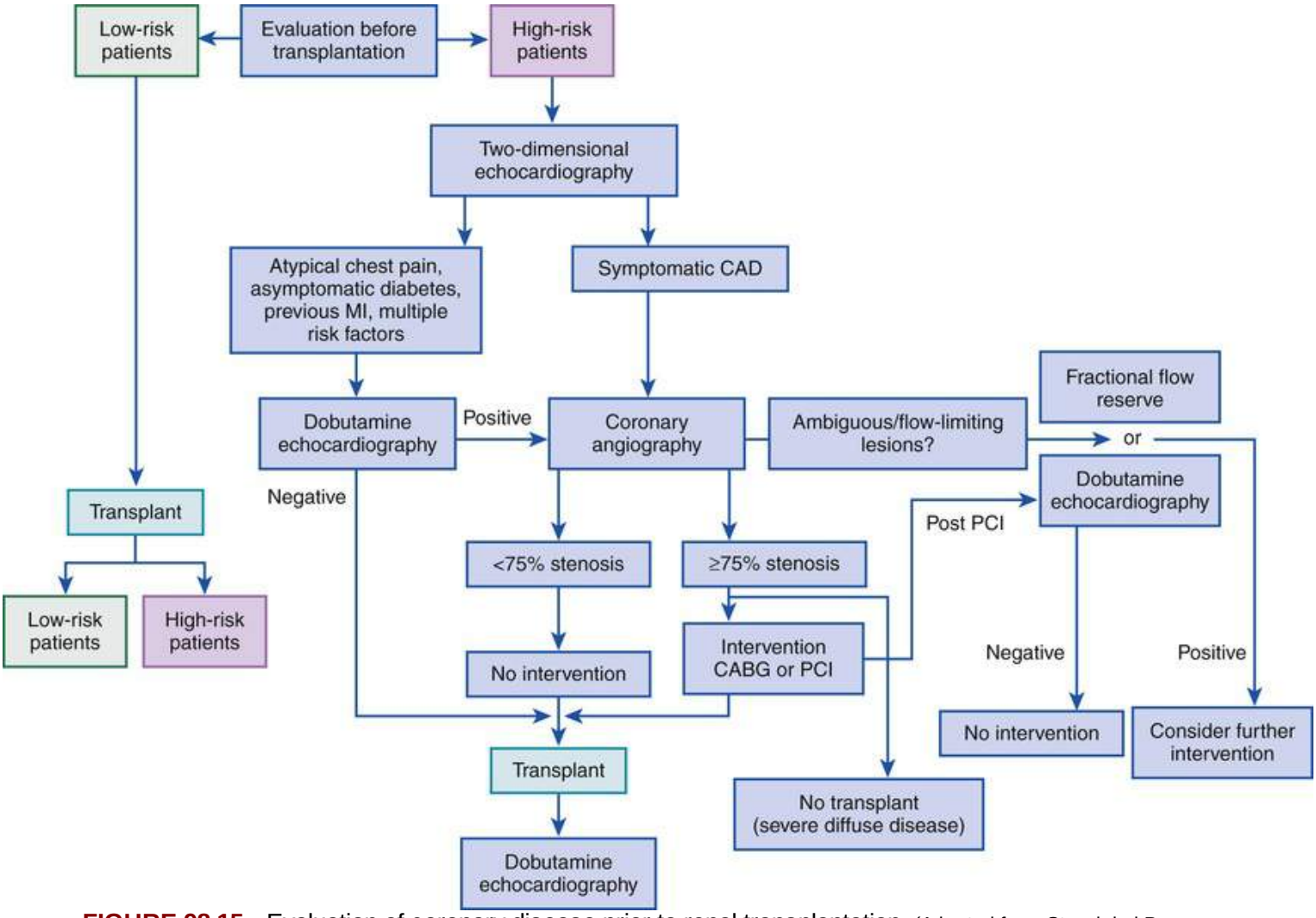

FIGURE 98.15 Evaluation of coronary disease prior to renal transplantation. (Adapted from Stenvinkel P, Herzog C: Cardiovascular disease in chronic kidney disease. In Floege J, Johnson R, Feehally J (editors): Comprehensive clinical nephrology, 4th ed. St. Louis, Elsevier, 2010.)

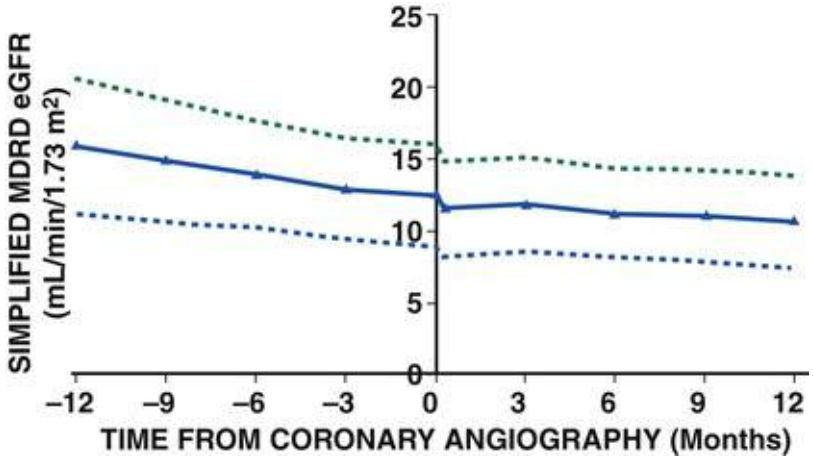

FIGURE 98.16 Renal filtration function (eGFR) before and after coronary angiography in pre-renal transplant candidates undergoing coronary angiography. (Adapted from Kumar N, Dahri L, Brown W, et al: Effect of elective coronary angiography on glomerular filtration rate in patients with advanced chronic kidney disease. Clin J Am Soc Nephrol 2009;4(12):1907-13.)

Future Perspectives

Recognition has increased over the last several decades for the fact that patients with CKD have a high risk for CVD. Frequent clinical scenarios in which renal function influences patient care include patients who have undergone PCI or cardiac surgery and patients who have ACS, HF, valvular disease, or arrhythmias. Results from retrospective studies and clinical trial subgroups form the basis of current recommendations, given the lack of prospective randomized trials in CKD and ESRD. Further study of the adverse metabolic milieu of CKD is likely to lead to generalizable diagnostic and therapeutic targets for the future management of renal patients with cardiovascular illness.

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99

Cardiovascular Manifestations of Autonomic Disorders

David Robertson, Rose Marie Robertson

Autonomic disorders in humans commonly present with abnormalities of blood pressure and/or heart rate, with reduced stability of these vital signs, and/or with alterations in their usual responses to external and internal stimuli. Because most of these disorders are uncommon, many clinicians are not familiar with them or with the principles involved in their management. In both acute and chronic clinical situations, consultation with a cardiologist is often appropriately sought, and is expected to provide diagnostic and therapeutic assistance. To facilitate effective consultation, in this chapter we will briefly review the current understanding of normal autonomic cardiovascular control and the normal responses to autonomic function testing, and then review the autonomic disorders that the consulting cardiologist is likely to encounter. We will describe the current understanding of these disorders, address how to arrive at a

diagnosis, and review effective initial approaches to management. Even though many autonomic disorders are rare, it is worth the effort to try to understand them, because understanding provides opportunities to improve or even extend lives and educates us about normal physiology.[2] We will also briefly touch on specific autonomic aspects of several cardiovascular disorders that are primarily covered in other chapters.

Overview of Autonomic Circulatory Control

The autonomic nervous system (ANS) plays an essential moment-to-moment role in adjusting the circulation to meet the needs of the body as its environment changes. The central nervous system receives information about that environment (both internal and external) via a broad range of inputs as diverse as visual sensors, postural sensors, volume and pressure sensors, and others, and integrates this information, primarily in the medulla. The major components of the autonomic response system are the sympathetic, parasympathetic, and enteric components, with the first two providing the major integrated vasomotor response. The effects of autonomic input to the cardiac conduction system, the myocardium itself, and the coronary vasculature are discussed in **Chapters 22, 34, and 46**. Because the integrated control of the BP and its modifications in autonomic disorders are less familiar, we will delineate the relevant physiology here, prior to discussing how it is used in testing the function of the various components of the autonomic nervous system, and how it can be helpful in reaching a diagnosis.

The Baroreflex

In humans, the chronic maintenance of the BP is provided by endocrine, renal, capillary shift, and autonomic mechanisms, but the exquisite control needed to reduce the lability of BP with shifts in posture and other changes is achieved primarily and most rapidly by the baroreflex system. This system is made up of an integrated complex of neurons supporting a group of reflexes (**Fig. 99.1**). It includes (1) the arterial baroreceptors, whose sensory endings lie within the aortic arch, at the origin of the right subclavian artery and within the carotid sinuses, and (2) the cardiopulmonary, or low-pressure, receptors in the walls of the atria and the pulmonary artery. When healthy adult humans are at rest, the baroreflex tonically inhibits sympathetic activity and enhances parasympathetic activity, so that parasympathetic tone predominates. With changes in vascular pressure, multiple mechanisms come into play, primarily driven by information sensed by the baroreceptors and integrated in the vasomotor center of the brain, which alter the sympathetic and parasympathetic outflow to modify the cardiac contractility, HR, and tone of the arterial and venous circulations.

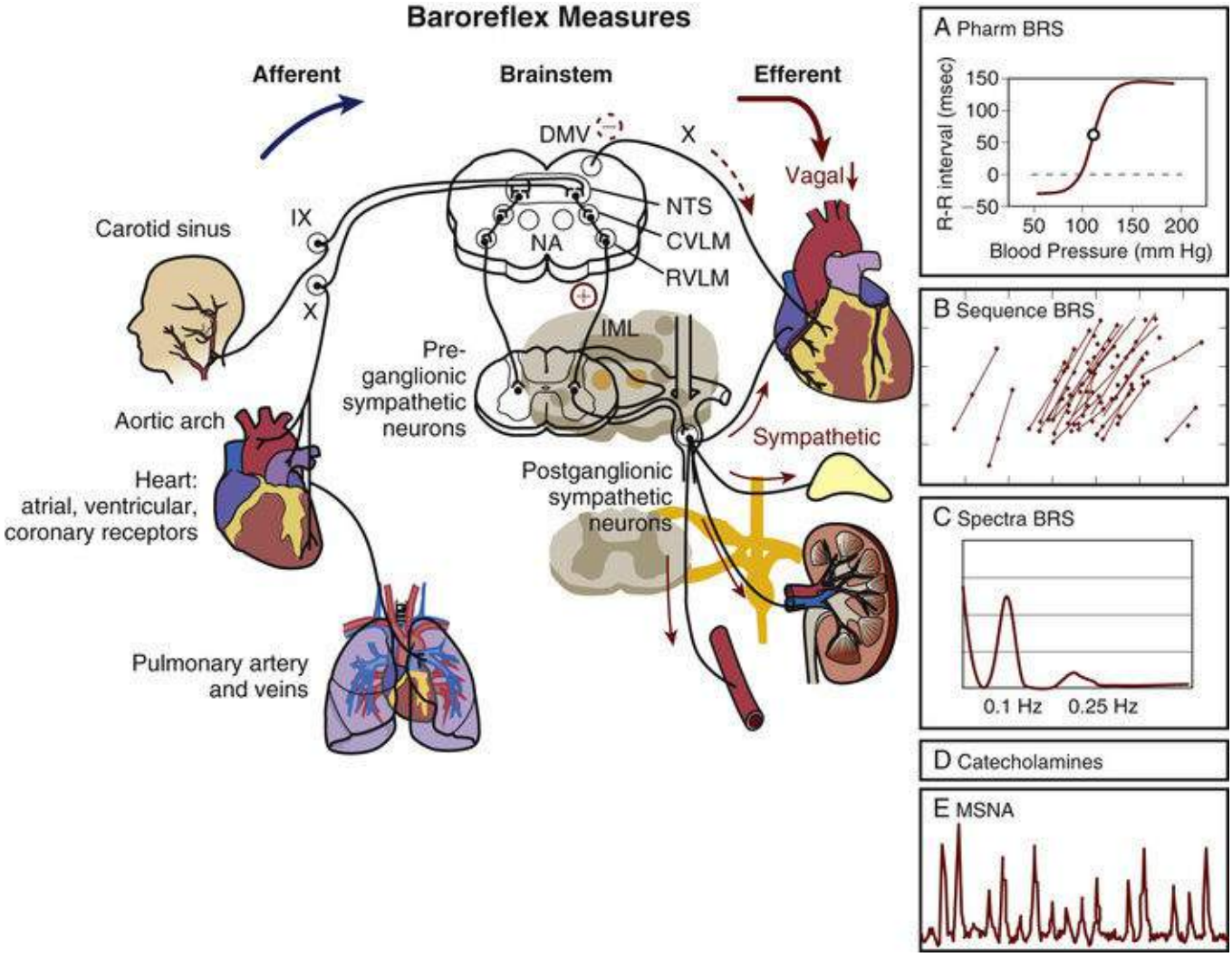


FIGURE 99.1 Diagram of the baroreflex in humans with methods of assessment. In boxes A to E are depicted five methods of assessing baroreflex sensitivity (BRS). **Box A:** Baroreflex properties can be assessed by pharmacologic probing with graduated doses of BP–elevating and/or BP-lowering drugs such as phenylephrine and nitroprusside. Changes in slope of the regression line between R-R interval changes and BP changes is referred to as baroreflex sensitivity. **Box B:** The same can be done by using spontaneous fluctuations of BP and R-R intervals, where sequences of heart beats with increasing or decreasing BP and R-R prolongation are identified and analyzed. **Box C:** Spectral analysis of HR and BP variability allows assessment of sympathetic and vagal modulation of HR and BP. Cross-spectral transfer function analysis can be used to study the interactions and determine baroreflex sensitivity. **Box D:** Plasma catecholamine levels are essential markers for sympathetic activity. **Box E:** Recording of muscle sympathetic nerve activity (MSNA). MSNA is an instantaneous signal of current sympathetic activation, and it allows the estimation of sympathetic baroreflex sensitivity. CVLM, caudal ventrolateral medulla; DMV, dorsal motor nucleus of vagus; IML, intermediolateral column of spinal cord; NA, nucleus ambiguous (vagus); NTS, nucleus tractus solitarius; RVLM, rostral ventrolateral medulla.

Arterial Baroreceptors

The location of the arterial (or high-pressure) baroreceptors is ideal for providing sufficient BP and volume to protect cerebral perfusion (**see Fig. 99.1**). These mechanoreceptors are stretch-dependent, so that elevation of vascular pressure increases the discharge frequency of the branch of the glossopharyngeal nerve innervating the baroreceptors in the carotid sinus, and of the aortic nerve, which innervates the aortic arch baroreceptors, and then combines with the vagus nerve. The arterial baroreceptors are essentially silent when the mean arterial pressure (MAP) is lower than the baroreceptor set point (≈ 70 mm Hg in healthy adults), but when the MAP rises above the set point, the baroreceptors become active.[1] Importantly, baroreceptor function varies between individuals, and the set point can vary in the same individual at different times or in different experimental or disease states. For

example, the set point is often increased in chronic hypertension and decreased in chronic hypotension. The first synapse of both baroreceptor nerves lies in the nucleus tractus solitarius (NTS) in the posterior medulla. In the NTS, afferent information from the baroreceptors is integrated on a beat-to-beat basis and variations in arterial pressure are minimized via the balance of activity of the inhibitory fibers, which run from the NTS to the vasomotor center and determine the efferent sympathetic activity, and the excitatory fibers, which run to the vagal nuclei and regulate the parasympathetic activity. For example, a sudden increase in BP, increasing the stretch of the baroreceptors, causes increased firing, leading to decreased sympathetic and increased parasympathetic activity. Decreased sympathetic activity reduces the arteriolar resistance, venous tone, cardiac contractility, and HR, and increased parasympathetic activity decreases the HR and has a slightly negative effect on contractility. Cardiac output is reduced, and arterial pressure falls toward the baseline. A sudden fall in BP produces the opposite compensatory effects.

Although it is generally recognized that both sympathetic and parasympathetic activity influence the HR, it is often not appreciated that the intrinsic automaticity of the sinus node produces a rate of 95 to 110 beats/min at rest. The normal resting HR of 60 to 70 beats/min in humans is due to parasympathetic dominance, which suppresses the intrinsic sinus nodal rate, along with minimal sympathetic activity at rest. With physical or mental activity, and even with assumption of the upright posture, sympathetic activity increases and parasympathetic activity withdraws, producing an increase in HR. When the activity ceases, parasympathetic dominance and a normal resting HR are restored.[1]

Cardiopulmonary Baroreceptors

The low-pressure cardiopulmonary receptors are located in the heart and the venae cavae, and are activated primarily in response to volume. They send vagal afferents to the NTS and spinal sympathetic afferents to the spinal cord. When stimulated by an increase in intracardiac volume, they produce vasodilation, a fall in BP, and inhibition of vasopressin release. The latter leads to an increase in salt and water excretion and reduces the sensed increase in volume. The cardiopulmonary receptors have minimal direct influence on the HR.

Chemoreflexes and the Diving Reflex

Sympathetic activity can also be modulated by the chemoreflexes, which respond to hypoxemia and hypercapnia. When either or both occur, the reflex response produces hyperventilation and sympathetic vasoconstriction. The actual peripheral chemoreceptors, which respond to hypoxia, are found in the carotid bodies, and the central chemoreceptors, found in multiple areas in the brainstem, sense the pH of the interstitial fluid of the brain. This allows them to integrate information about ventilation (arterial pCO_2), the brain blood flow and metabolism, and the acid-base balance, responding primarily to hypercapnia and modulating the BP via sympathetic tone and adjusting breathing.[3] For example, both hypoxemia and hypercapnia produce hyperventilation and sympathetic vasoconstriction. Inhibitory influences on the overall chemoreflex drive occur with stretch of the pulmonary afferents and with activation of the baroreflex, both of which have a greater influence on peripheral than on central chemoreflexes.

In early hypertension, the ventilatory response to hypoxemia may be increased, in addition to an increase in sympathetic tone, and it has been suggested that an increased chemoreflex drive may contribute to this, as well as impaired baroreflex sensitivity. In obstructive sleep apnea (OSA) (**see also Chapter 87**), the response of the chemoreflexes to hypoxia can be significantly enhanced, with the repetitive episodes of hypoxemia and apnea at night producing bradycardia and a sympathetic

vasoconstrictor response, potentiated because of a reduced or eliminated pulmonary afferent inhibitory influence on the chemoreflex. Responses to hypercapnia do not appear to be enhanced.[4] The tonic chemoreflex drive in patients with OSA can be reversed with 100% oxygen, reducing the sympathetic outflow, HR, and BP. Administering 100% oxygen to patients with borderline hypertension and to spontaneously hypertensive rats reduces not only the ventilator drive but the vasoconstrictor tone, as well.[1]

In diving mammals and sometimes in humans during submersion in water and prolonged apnea, a simultaneous and powerfully increased parasympathetic drive to the heart and an increased sympathetic drive to the vasculature occurs, referred to as the *diving reflex*. In this setting of prolonged hypoxia due to apnea, autonomic mechanisms are utilized to protect oxygen delivery to the most critical organs, the brain and the heart. Whereas sympathetic vasoconstriction reduces the oxygen delivery to much of the body, the cerebral vascular tone is under autoregulatory control and therefore is not increased, and the profound bradycardia that is induced by parasympathetic activation reduces the myocardial oxygen demand. Although this constellation of protective features allows humans and animals to survive and explore underwater without oxygen for 5 or more minutes at a time, it may also be associated with ventricular arrhythmias and increased rates of cardiovascular mortality, especially in susceptible individuals such as those with long QT syndrome (**see also Chapter 33**). The diving reflex has been studied for many years, but the methods used to elicit the relevant stimuli have varied and have not always been standardized, nor has stimulation of other reflexes always been avoided. A reproducible method has been described for such studies, which has included protection for the eyes, so that information can be gathered safely in broader groups of normal persons and patients.[5]

Autonomic Testing

Orthostatic Blood Pressure and the Heart Rate

When we stand, the effect of gravity on the blood volume causes 500 to 800 mL of blood to pool in the lower extremities and splanchnic venous capacitance vessels of the abdomen[6] (**Fig. 99.2**), reducing the venous return, stroke volume, and cardiac output. The reduction in stretch of the arterial and cardiopulmonary baroreceptors is sensed, and the reduced activity of the baroreceptor afferent nerves at their synapses in the NTS leads to a decrease in cardiac vagal tone and an increase in sympathetic activity. The release of norepinephrine causes both arterial vasoconstriction and venoconstriction and an increase in cardiac contractility and heart rate, and protects the arterial pressure and cerebral perfusion. To perform the orthostatic blood pressure test at the bedside, the patient should lie supine for 10 minutes before the baseline BP and HR are measured and recorded, and then should stand at the side of the bed. BP and HR measurements are repeated at 1 and 3 minutes, and at 5 minutes if possible, with the patient queried about symptoms each time. In young healthy persons, baroreflex compensation is so perfect that the systolic BP (SBP) at 1, 3, and 5 minutes of quiet standing is often unchanged, whereas the diastolic BP (DBP) pressure rises 5 to 10 mm Hg and the HR rises less than 10 beats/min. If beat-to-beat BP rather than sphygmomanometric BP is being assessed, as when a Finapres device is being used or an arterial line is in place, one will often see a transient fall (lasting only seconds) in both the SBP and DBP with standing before the compensatory mechanisms readjust the system. In older individuals, compensation is often not as rapid or as complete. Criteria for orthostatic hypotension (OH) are not met in either young or old adults unless there is a fall in SBP of more than 20 mm Hg, or of DBP of more than 10 mm Hg at 3 minutes of standing quietly.[7] An abnormal rise in HR is more than 20 beats/min. A feature of severe

autonomic disorders with OH can be a BP that is extremely posture dependent. Some patients may have marked supine hypertension, with an SBP at or above 200 mm Hg, a nearly normal SBP when seated, and an SBP that falls to less than 60 mm Hg within less than a minute of standing. The upright BP clearly cannot be documented by sphygmomanometry in these patients at the bedside. For safety reasons, in the absence of beat-to-beat BP monitoring or an available tilt table, one may resort to documenting the "standing time" (i.e., the number of seconds the patient can stand before typical symptoms of light-headedness occur and the patient sits). This time can be used to assess the response to medications or other therapeutic maneuvers.

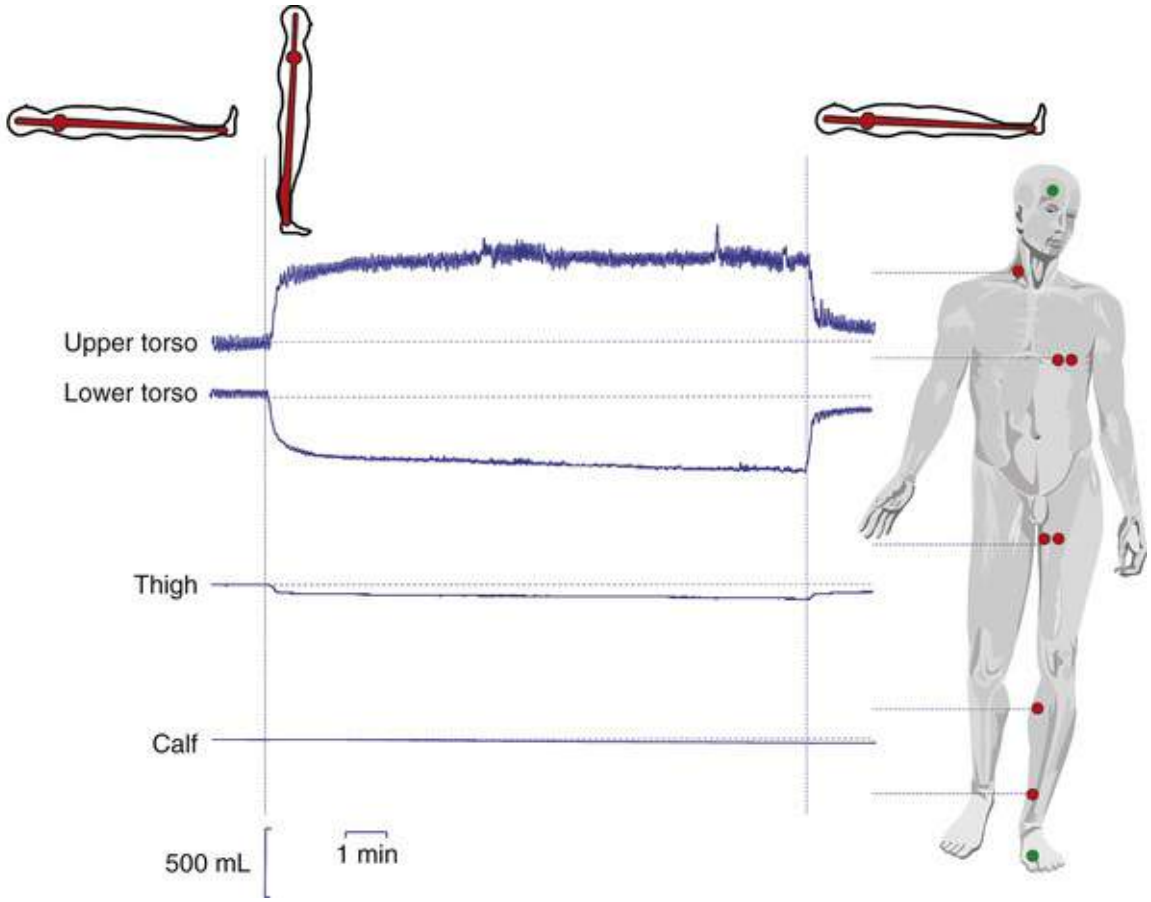


FIGURE 99.2 Orthostatic fluid shifts estimated by impedance. This figure shows the change in impedance within segments of the human body during upright posture, reflecting shifts in fluid volume from the upper torso to the lower torso and to a lesser degree to the thighs. The increase in fluid in the splanchnic circulation forms the basis for considering studies of an abdominal binder to improve orthostatic tolerance in patients with orthostatic hypotension and orthostatic tachycardia.

It is important to realize that in the absence of autonomic disorders, significant OH and even syncope can still be seen, most commonly with volume depletion due to gastrointestinal fluid loss, hemorrhage, excessive sweating, fever, or disorders such as Addison disease (decreased or absent adrenal function, with glucocorticoid and mineralocorticoid insufficiency). OH, especially with prolonged standing, can also be seen with loss of muscle tone and reduced vascular responsiveness, as with prolonged bedrest; it also occurs in astronauts who have been exposed to microgravity during spaceflight. In these situations, the rise in HR with standing will be excessive but appropriate for the fall in BP, unlike the blunted or absent rise seen in sympathetic incompetence.

Valsalva Maneuver

The Valsalva maneuver is a convenient way to test multiple aspects of the autonomic nervous system with a single maneuver. It can be done at the bedside with continuous electrocardiographic monitoring, but it is most useful if performed with continuous beat-to-beat BP, HR, and expiratory pressure. After a baseline recording has been made, the patient is asked to blow into a closed system to a level of 40 mm Hg with an open glottis for 12 seconds (**Fig. 99.3**). In phase I, the increase in expiratory pressure transmitted to the intrathoracic vessels causes a transient increase in BP. In early phase II, there is a dramatic fall in the SBP and pulse pressure because the venous return is blocked and the LV stroke volume falls. By late phase II, arterial and cardiopulmonary baroreceptors have sensed the fall in BP. Sympathetic activation produces a modest rise in BP toward baseline, and the combination of sympathetic cardiac innervation and parasympathetic withdrawal elevate the HR well above baseline. In phase III, the release of the intrathoracic pressure mechanically causes a fall in BP lasting only a few beats. In phase IV, the previously impeded venous return is restored abruptly to the chest and is pumped out by a sympathetically activated heart into a vasoconstricted circulation. The BP rises well above baseline (the overshoot), and that increase in baroreceptor stretch leads to immediate sympathetic withdrawal and parasympathetic activation, greatly slowing the HR. The simplest analysis involves dividing the highest HR during late phase II by the slowest HR in phase IV. A result of less than 1.4 suggests autonomic dysfunction; additional characteristics of the response to the Valsalva maneuver, such as the “sympathetic index” described by Novak, using the change in BP at baseline and during phase II,[8] can provide further information that helps in the diagnosis of autonomic disorders (**Fig. 99.4**). The abnormalities of the Valsalva maneuver can be specific to particular disorders, as demonstrated in this figure; this differentiation will be discussed in detail with the descriptions of the specific disorders below.

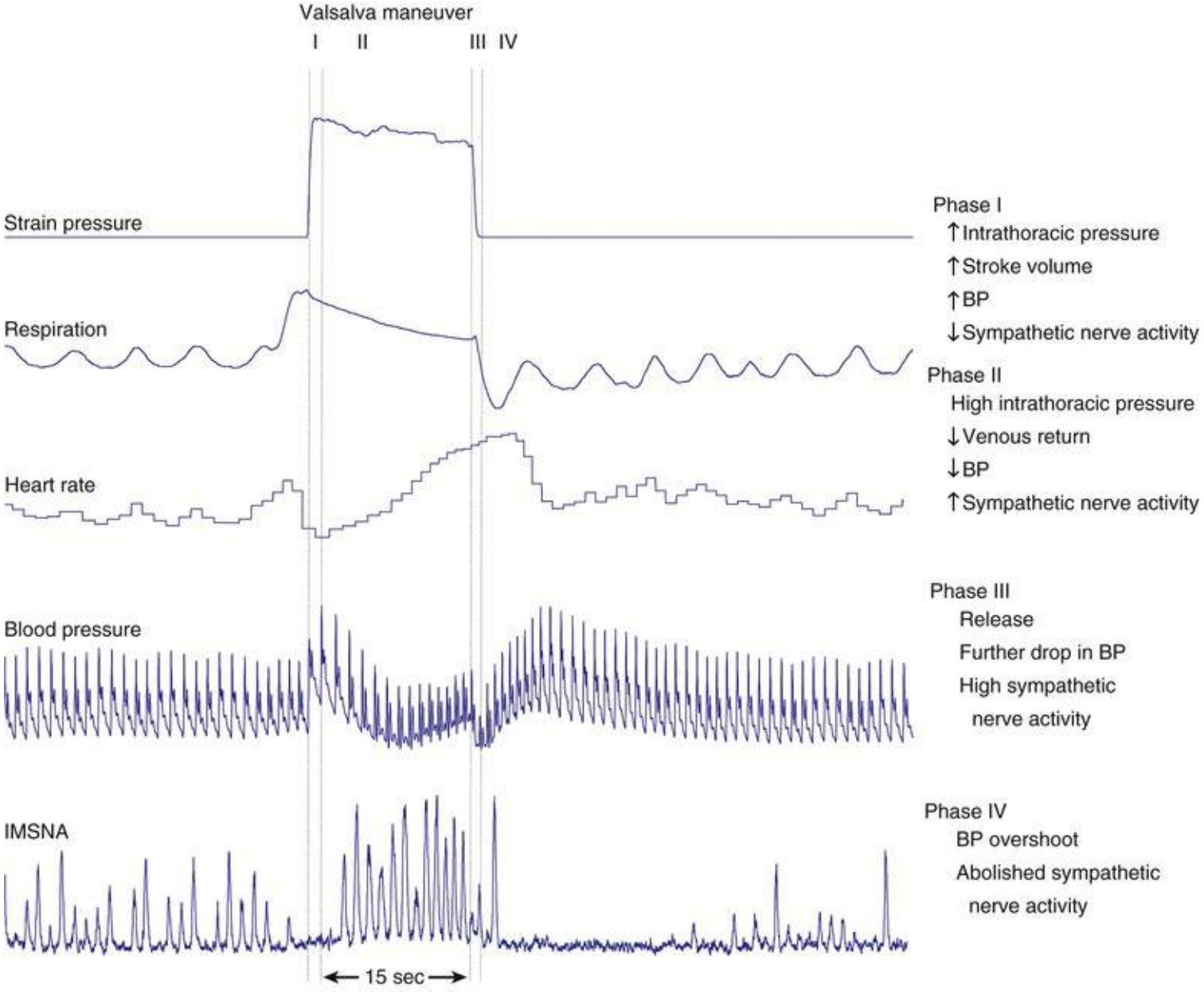


FIGURE 99.3 The Valsalva maneuver in a healthy subject. In phase I, the increase in expiratory pressure transmitted to the intrathoracic vessels causes a very transient increase in BP; in early phase II, there is a dramatic fall in SBP and pulse pressure as venous return is blocked and left ventricular stroke volume falls; by late phase II, arterial and cardiopulmonary baroreceptors have sensed the fall in BP and sympathetic activation produces a modest rise in BP toward baseline. The combination of sympathetic cardiac innervation and parasympathetic withdrawal elevate HR well above baseline. In phase III, the release of intrathoracic pressure mechanically causes a fall in BP lasting only a few beats; in phase IV, the previously impeded venous return is restored abruptly to the chest and is pumped out by a sympathetically activated heart into a vasoconstricted circulation. The BP rises well above baseline (the overshoot), and that increase in baroreceptor stretch leads to immediate sympathetic withdrawal and parasympathetic activation, greatly slowing the HR.

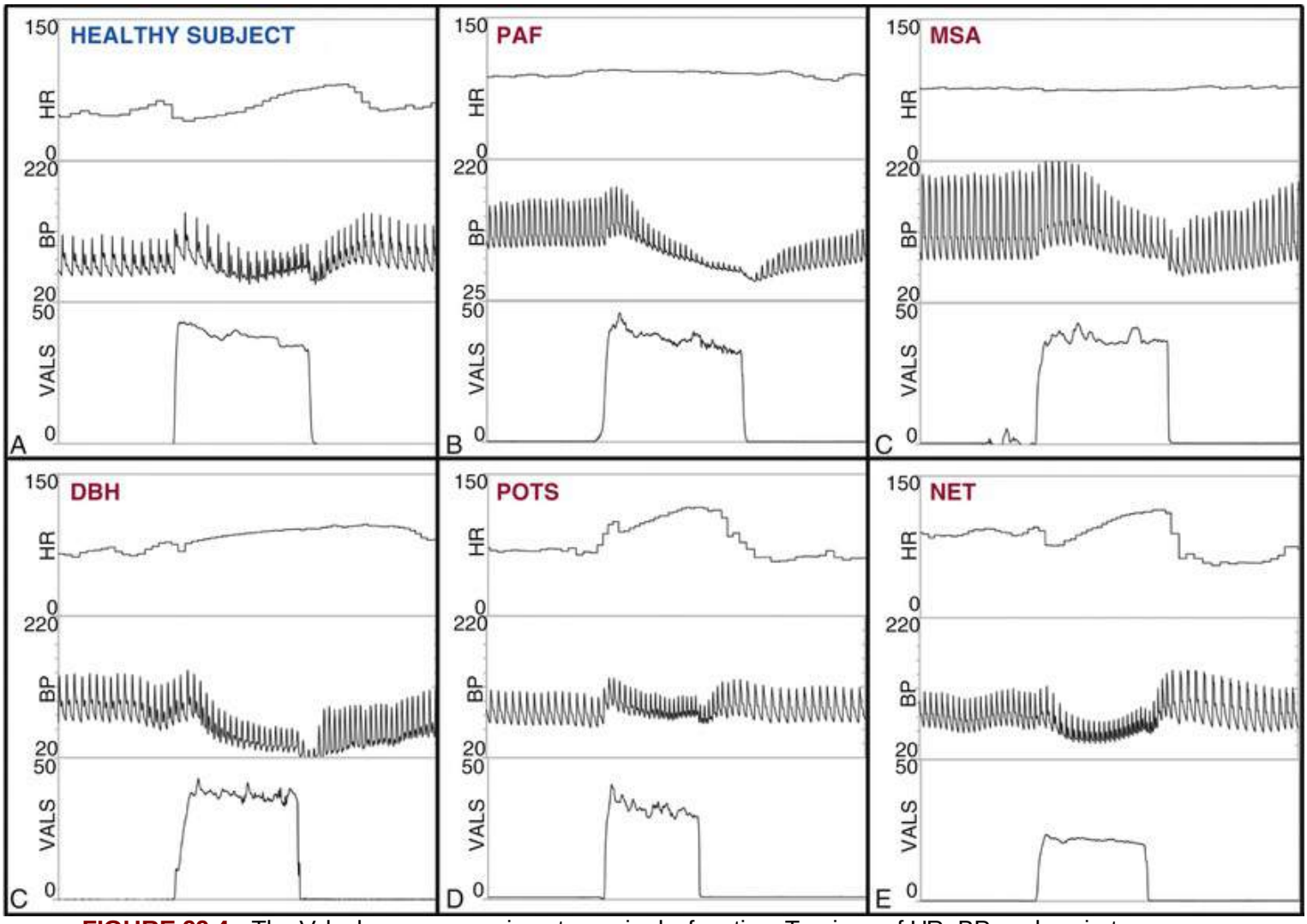


FIGURE 99.4 The Valsalva maneuver in autonomic dysfunction. Tracings of HR, BP, and expiratory pressure in **A,** a healthy subject; **B,** a patient with pure autonomic failure; **C,** a patient with multiple system atrophy; **D,** a patient with dopamine beta-hydroxylase deficiency; **E,** a patient with postural tachycardia syndrome; and **F,** a patient with norepinephrine transporter deficiency.

A further use of the Valsalva maneuver is assessment of the baroreflex sensitivity (**see Fig. 99.1**). The relationship between an increase in SBP and the resultant increase in the R-R interval can be used to define the baroreflex slope, reflecting the sensitivity of the arterial baroreflex and, particularly, its vagal component. This assessment requires the availability of beat-to-beat SBP and the R-R interval, but it can be obtained noninvasively with a continuous ECG recording and Finapres recording of the finger arterial pressure. Spontaneous changes in the SBP and HR can be used,[9] or the SBP can be raised with phenylephrine. To assess the adrenergic component of the baroreflex (the control of peripheral resistance), measurements during and after the Valsalva maneuver have related the recovery of BP to the Valsalva maneuver–induced fall in BP. This characterization of the sympathetic vasoconstrictor response has been effective in differentiating patients with autonomic failure and in documenting the reduction in adrenergic baroreflex sensitivity with age.[1] An additional approach uses a spectral analysis of the HR and BP variability to assess the sympathetic and vagal modulation of the HR and BP. Cross-spectral transfer function analysis can be used to study the interactions and define the baroreflex sensitivity.[10]

Tilt-Table Testing

Tilt-table testing in the evaluation of patients with syncope (**see also Chapter 43**) can also be used as a substitute for standing to evaluate orthostatic changes in the BP, HR, and symptoms. It provides a head-up

posture in patients who are too frail or weak to stand, or whose OH is so severe that standing long enough to obtain BP readings is not possible. Because engagement of the skeletal muscle pump of the lower extremities is not needed, results of this test are not identical to those of orthostatic testing, but it does provide a safe way to assess orthostatic tolerance. The fluid shifts seen with standing occur during this test as well, and are often accentuated by the absence of the function of the skeletal muscle pump (**Fig. 99.5**).

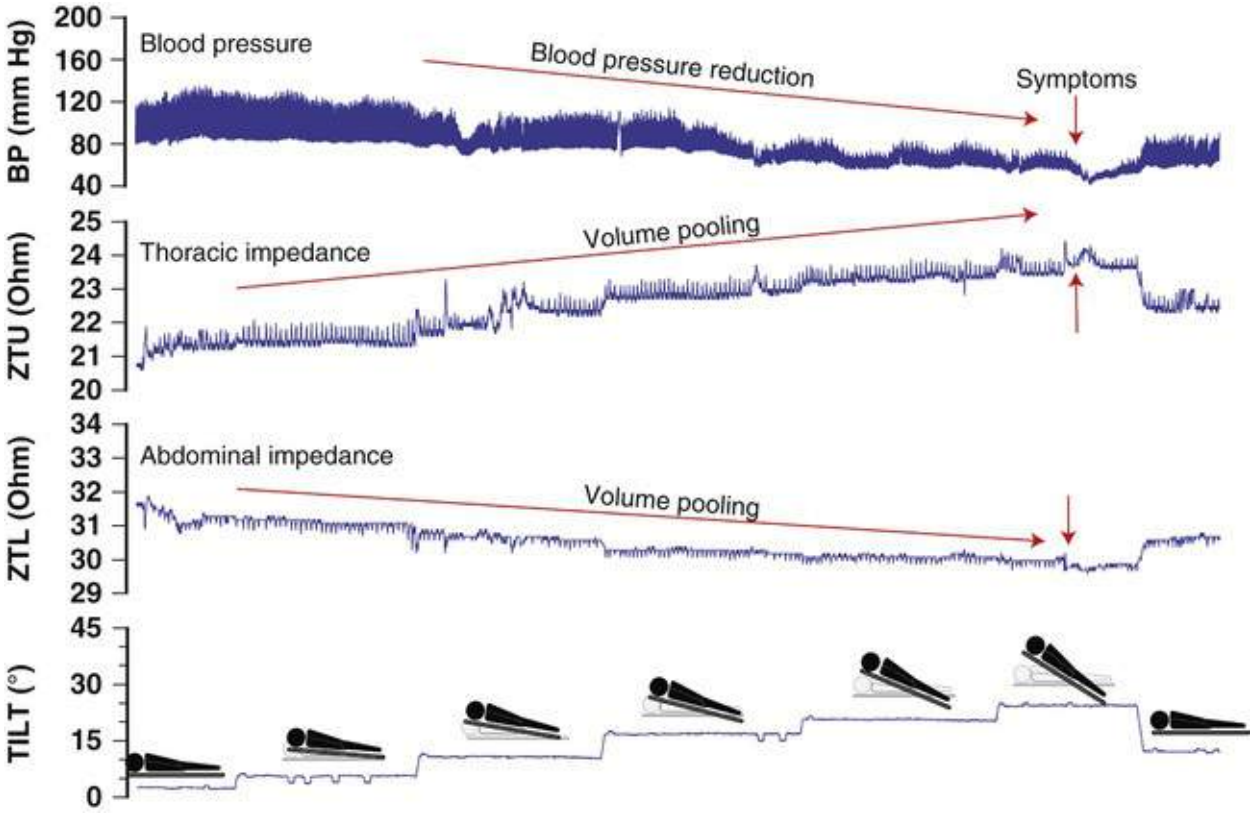


FIGURE 99.5 Impedance assessment of fluid shifts with head-up tilt. Note that with increasing head-up tilt, there is a gradual shift in fluid volume from the chest to the abdomen, reflecting pooling in the splanchnic/mesenteric circulation. Recovery of pooling begins immediately with the assumption of the supine posture. ZTL (ohm), measure of resistance inversely related to fluid volume in the bodily segment referred to.

Cold Pressor Testing

Cold pressor testing of the sympathetic neural response to a nociceptive stimulus is simple to perform at the bedside when beat-to-beat BP and continuous HR recording is available. After 3 to 5 minutes of recording with the patient at rest supine, the hand in which the BP is not being taken is immersed to the wrist in a mixture of ice and water for 1 minute and then removed, with recording continued for 3 to 5 minutes of recovery. Studies using muscle sympathetic nerve recording (**Fig. 99.6**) have demonstrated that this response is an important component of the rise in BP caused by peripheral vasoconstriction in skeletal muscle. Sympathetic outflow to the heart causes an increase in the HR that can be blocked by beta-adrenergic receptor antagonists. The cold pressor test can be used to assess autonomic function and monitor autonomic dysfunction over time.

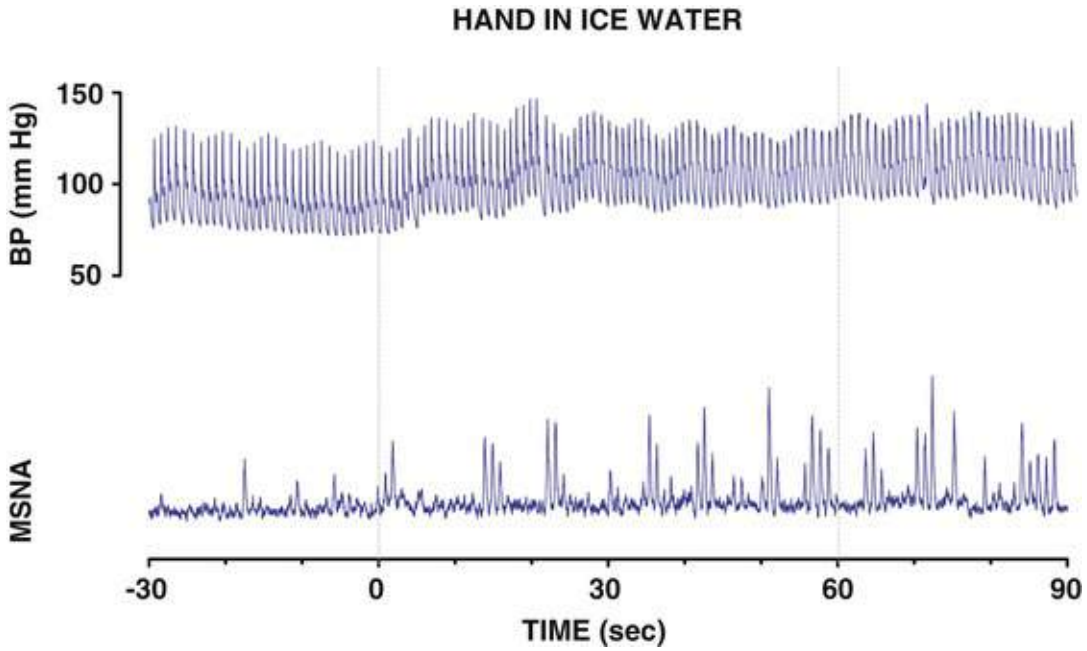


FIGURE 99.6 Cold pressor testing. Placing the hand in a mixture of ice and water for 1 minute elicits a rise in BP of 20 to 30 mm Hg (upper register). The lower register indicates the increase in muscle sympathetic nerve activity (MSNA), which elicits the BP increase.

Plasma Catecholamines

Biochemical assessment of plasma dopamine (D), epinephrine (E), and norepinephrine (NE) and their metabolites can be useful in assessing the function of the autonomic nervous system and diagnosing a number of autonomic disorders. Plasma NE is released from sympathetic nerve endings upon their activation, and most NE is taken back up into the neurons via the norepinephrine transporter (NET), with only 10% to 20% spilling over into the circulation. The plasma E reflects the E produced from NE within the adrenal medulla, with a minimal amount salvaged by the NET and coreleased with NE. Either NE or E (and rarely D) may be produced and released by pheochromocytomas, both benign and malignant, with the clinical picture of these tumors dependent on the neurotransmitter released. The finding of markedly elevated levels of NE, E, or D and an inability to suppress them with clonidine have been useful in the diagnosis of pheochromocytoma. The rare disorder of dopamine- beta-hydroxylase deficiency, a cause of profound orthostatic hypotension due to the inability to convert dopamine to norepinephrine, can easily be diagnosed by the absence of detectable NE and very high levels of D in the plasma.[11] Because effective treatment is available, accurate diagnosis is important. The plasma NE is only an indirect measure of the activity of the sympathetic nervous system (SNS), given the rapid reuptake by the neuron and metabolism by multiple pathways, but its behavior at baseline and with physiologic stimuli can be useful in diagnosis and will be discussed later with specific disorders. Given the rapid response of the SNS to stimuli such as postural changes, practical consideration requires that blood for baseline sampling of catecholamines be drawn from an indwelling catheter after 10 minutes of supine rest. If plasma catecholamines are drawn supine and after 3 minutes of standing, the norepinephrine level should approximately double in healthy individuals, from a combination of increased sympathetic neuronal release and decreased hepatic flow and thus delivery of norepinephrine to its metabolic fate. In volume depletion, after bedrest or after spaceflight, the rise in norepinephrine will generally parallel the elevated rise in the heart rate although the latter is due to a combination of increased sympathetic input to the cardiac conduction system and parasympathetic withdrawal.

Autonomic Disorders

From the perspective of the consultant, autonomic disorders, also referred to as *dysautonomias*, can generally be classified according to their BP abnormalities at presentation and results of a simple bedside evaluation of the history, physical examination, orthostatic BP, and HR. Although there are many different disorders of the ANS and they can produce lesions in many different areas, both central and peripheral, this simple workup will in many cases suggest a presumptive differential diagnosis. This usually will direct the diagnostic workup needed and provide options for management. This last can be critically important for some patients with ANS disorders, who can have marked and dangerous hypersensitivity to commonly used medications. Arriving at the correct diagnosis is important because, although these disorders are rare, some can significantly affect longevity and many seriously impair the quality of life.

It is also useful to consider the settings in which the various autonomic disorders present. Newly acquired autonomic disorders that begin abruptly can appear in hospitalized patients, and they may often prompt consultation because of new and severe hypertension or because a patient cannot be discharged because of profound OH. Patients with gradually progressive disorders over months to years may be referred for consultation in the outpatient setting, but subclinical autonomic disorders can become problematic for the first time during hospitalization for an unrelated problem, with the autonomic disorder enhanced either by that problem or by some aspect of its treatment. In the history, chronic disorders may often seem acute to the patient, especially if the first symptom they note is dramatic, such as syncope or a fall. A careful review of the history by a clinician aware of unusual features such as anosmia or an orthostatic headache relieved by recumbency or of initial presentations, such as erectile dysfunction in men, will often reveal that premonitory symptoms have been present but unrecognized.

Severe Lability of Blood Pressure– and Afferent Dysfunction

Patients with dysfunction of the afferent portion of the baroreflex arc have some of the most remarkably high BPs encountered and are often the subjects of urgent consultation. A detailed personal and family history with attention to possible causative factors can often clarify the diagnosis and greatly improve the patient's outlook.

Baroreflex Failure

The term *baroreflex failure* is sometimes mistakenly used for any disorder impairing the function of the baroreflex system and thus causing autonomic dysfunction. Currently, however, it specifically refers to a syndrome of extremely labile BP that is not buffered by normal baroreflex control mechanisms. The lack of control can be due to a number of different mechanisms that affect afferent neuronal input via injury to the vagus and glossopharyngeal nerves, or their projections to the brainstem, or via damage to the brainstem nuclei themselves or their interneurons. The damage can be caused by trauma, surgery (e.g., carotid endarterectomy, carotid body tumor resection), neoplasm (paragangliomas or other tumors), radiation injury, brainstem stroke,[12] or rare genetic disorders. Ultimately, the damage deprives the integrative central control areas of the information they need to adjust the sympathetic and parasympathetic outflow and stabilize the BP on a moment-to-moment basis. In these patients, it appears that the BP at any given time is dependent on the sum of inputs from higher brain centers to autonomic brainstem nuclei.[13] Thus, the BP tends to be low when the patient is asleep or resting in a quiet room, but to rise excessively with waking, exercising, engaging in conversation (especially if it is emotionally charged), or being exposed to pain or even simply to ambient noise. To assess the response to pain, the

cold pressor test is effective. This stimulus normally results in an elevation of 15 to 40 mm Hg in SBP, with a return to baseline over 1 to 3 minutes, but in these patients, with an absence of baroreflex buffering, SBPs of 250 mm Hg are not uncommon, and pressures as high as 320 mm Hg can sometimes be seen. In addition, the BP may remain elevated for more than 30 minutes after the stimulus is removed.

Baroreflex failure (BRF) can present in several different ways, depending on the cause. In patients with an autosomal dominant disorder causing a high incidence of carotid body, glomus jugulare, or glomus vagale tumors, which can damage the adjacent glossopharyngeal and vagal nerves, baroreflex failure may be related to the phase of disease and its surgical treatment. We have been able to study a large kindred of such patients before and after surgical procedures to remove the tumors, which in some cases cause further unavoidable damage to these nerves. The location of nerve damage in these and other patients can produce a variable presentation. Hypertensive crisis, labile hypertension, usually with concomitant tachycardia, orthostatic tachycardia, and malignant vagotonia have all been described in baroreflex failure; a patient may pass through several of these conditions, each requiring careful assessment and treatment. Recognition of the anatomy and physiology of the baroreflex and how lesions in different locations can affect BP and HR control is instructive (**Fig. 99.7**). In both selective and nonselective BRF, for example, baroreflex afferents are damaged, but in selective BRF, the efferent parasympathetic nerves are intact. Thus, in nonselective BRF, arousal produces a rise in both the BP and HR, but in selective BRF, the intact parasympathetic efferents provide some modulation of the HR during hypertensive crises via vagal withdrawal.[13]

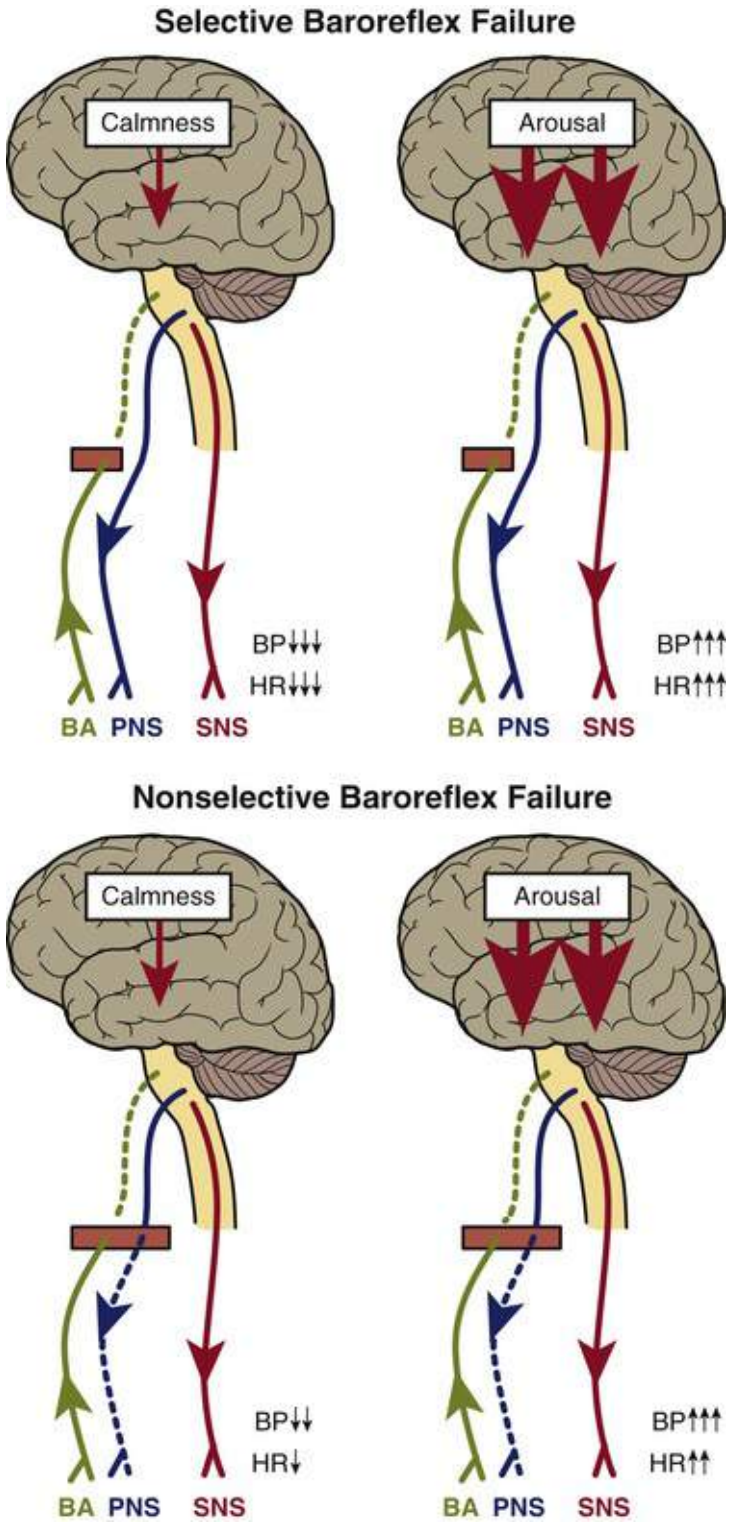


FIGURE 99.7 Selective baroreflex failure (top) contrasted with nonselective baroreflex failure (bottom). Baroreflex afferents (BAs) are damaged in both selective and nonselective baroreflex failure patients. Efferent sympathetic (SNS) and parasympathetic nerves (PNS) are intact in selective baroreflex failure. In nonselective baroreflex failure, efferent parasympathetic nerves are damaged to some degree. These differential changes lead to the differences in BP and HR seen with calm and aroused states. (From Jordan J: Baroreflex failure. In Robertson D, Biaggioni I, Burnstock G, et al (editors): Primer on the autonomic nervous system, 3rd ed. San Diego, Academic Press, 2013.)

BRF is an uncommon condition, and not every patient with labile hypertension suffers from it. Pheochromocytoma, hyperthyroidism, panic attacks, alcohol withdrawal, and 1 such as cocaine and amphetamines can all produce similar hypertensive crises. Pheochromocytoma can be eliminated in the usual manner, but for the other conditions, baroreflex testing should be done. A simple initial approach may be sufficient, because patients with have an exaggerated pressor response to both mental activation (mental arithmetic) and physiologic stimuli, such as cold pressor and isometric handgrip testing. If the

history and signs do not provide a clear diagnosis, pharmacologic baroreflex testing can be used; a rise in BP induced by phenylephrine will assess the bradycardic response, or a fall in BP induced by nitroprusside will assess the tachycardic response. Because patients with BRF exhibit marked hypersensitivity to these and other vasoactive agents, one begins with very low dosages (phenylephrine 12.5 µg; nitroprusside 0.1 µg/kg) and increases the dosage cautiously to produce an eventual change in SBP of 20 to 40 mm Hg. In BRF, the change in the HR will be less than 5 beats/min[12-14] (**Fig. 99.8**). There are other methods for noninvasively assessing the baroreflex control of the HR, for instance, cross-spectral analysis[10] or the sequence method[9] (**see Fig. 99.1**), although they have not been formally assessed in BRF.

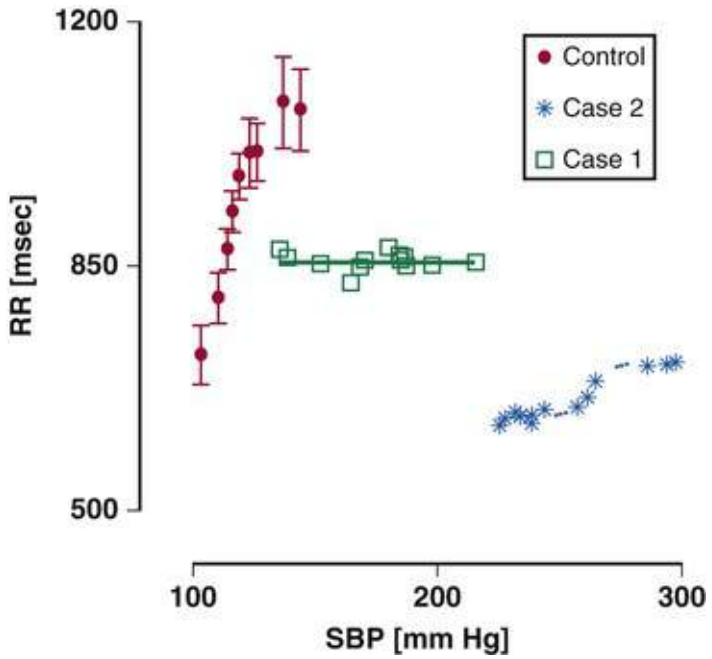
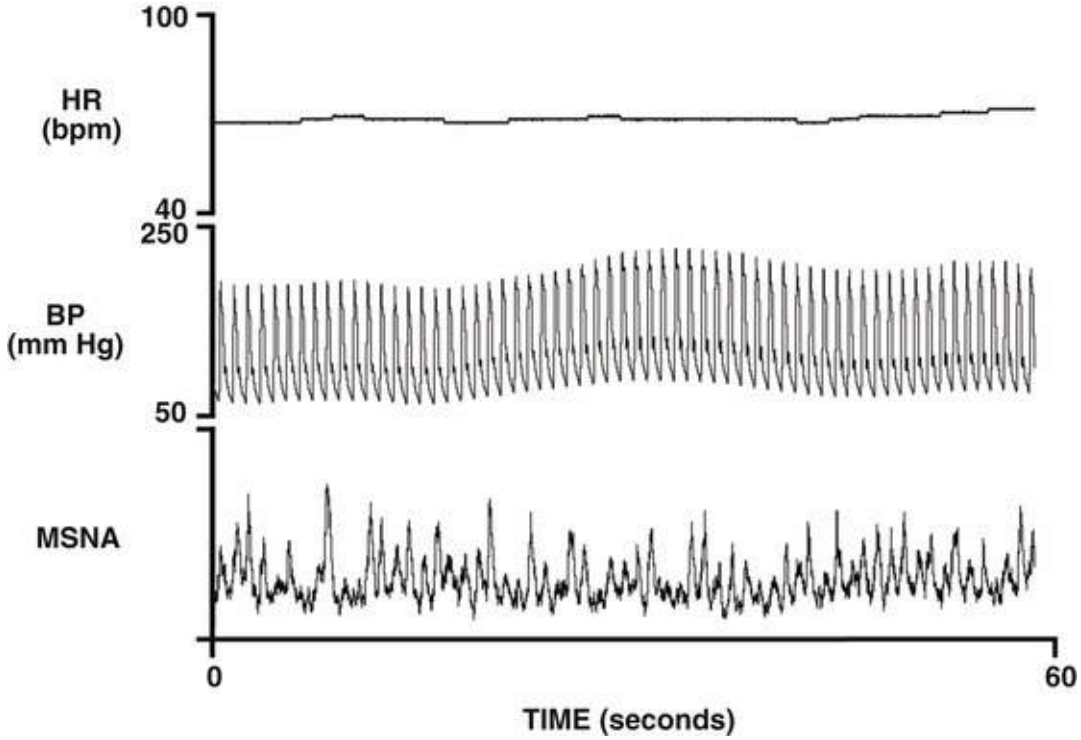


FIGURE 99.8 Pharmacologic assessment of baroreflex sensitivity. Changes in the R-R interval were plotted over changes in SBP during phenylephrine and nitroprusside application to obtain baroreflex HR curves in baroreflex failure patients and in a group of younger healthy subjects. The physiologic baroreflex response is virtually abolished in both baroreflex failure patients. (From Heusser K, Tank J, Luft FC, Jordan J: Baroreflex failure. Hypertension 2005;45(5):834-9.)

In addition to pharmacologic testing of BR function, plasma catecholamines can also be useful, with dramatic surges of NE to more than 2500 pg/mL seen during hypertensive crises. The ability of clonidine to reduce both the BP and the norepinephrine levels in BRF can differentiate it from pheochromocytoma.

eFig. 99.1 shows a pressor response of 40 mm Hg to phenylephrine 50 µg in a patient with BRF, with no change in HR. Normal subjects would demonstrate a decrease in the HR of 7 to 20 beats/min and a rise in BP of 20 mm Hg.



EFIGURE 99.1 Response to phenylephrine in a patient with baroreflex failure. Note that BP rises in response to the intravenous bolus of phenylephrine, a peripheral vasoconstrictor. Normally, both the HR and muscle sympathetic nerve activity (MSNA) would be reduced by the baroreceptor-mediated increase in parasympathetic activity, but neither change in this patient.

Treatment of patients with BRF is often difficult. It is critical to be certain that patients and any health care providers they encounter know that stimuli and drugs that have a minor effect or no effect on normal persons or other patients may provoke dramatic elevations of BP in baroreflex failure patients. This is especially true of medications that affect vascular tone or sympathetic activity, some of which are available without a prescription. Clonidine, which is available orally or by patch, is helpful in avoiding hypertensive crises, and other centrally acting sympatholytic agents may be helpful as well. **Table 99.1** lists therapeutic options for these patients when they are in a phase with malignant vagotonia.

TABLE 99.1

Indications for Unique Treatment Strategies in Patients with Selective Baroreflex Failure and Malignant Vagotonia

INDICATION	INTERVENTION
Bradycardia, asystole	Cardiac pacemaker
Hypotension	Fludrocortisone/high-salt diet
Tachycardia/hypertension	Guanadrel

Glossopharyngeal Neuralgia

Glossopharyngeal neuralgia results when the glossopharyngeal nerve is traumatized in the area of the carotid sinus, for example, by accident, neoplasm, surgery (either incidental or to remove a neoplasm), or radiation, causing intermittent spontaneous activation of the nerve. The patient experiences sudden, severe, lancinating pain in the neck, face, or jaw on the affected side, and the BP and HR fall suddenly and profoundly. It is often these episodes of sudden hypotension in the surgical intensive care unit that prompt a consultation, with the focus drawn to the hemodynamic instability. The consulting cardiologist may be the first to ask the patient whether pain preceded the events. This critical historical finding strongly suggests the diagnosis, which can be confirmed by simultaneous monitoring of the BP and HR. In

most patients, the episodes are self-limited and resolve as healing proceeds, but in some patients the sudden drops in BP and HR may prevent safe ambulation or even the upright posture. In these cases, yohimbine may improve the situation more rapidly, and can be tapered after recovery. If pain and hemodynamic instability persist, however, transection of the nerve may be necessary.

Carotid Sinus Hypersensitivity

Carotid sinus hypersensitivity is an increased or exaggerated response to stimulation of the arterial baroreceptors in the carotid sinus, producing more than the usual reduction in HR and BP seen with carotid massage (**see also Chapter 43**). To meet current criteria, carotid massage in the supine position must produce asystole lasting more than 3 seconds (a "cardioinhibitory response") or a reduction in SBP greater than 50 mm Hg independent of HR slowing (a "vasodepressor response"), or a combination of the two. Alternatively, carotid massage can be performed both supine and at 60 degrees of head-up tilt as well, with more positive results seen during head-up tilt. Carotid sinus hypersensitivity is seen more frequently in males than females, and it is rarely seen in individuals younger than 50 years old, despite the fact that baroreflex sensitivity generally is reduced with age.[15] It appears to be more frequent in patients with unexplained syncope, which suggests it may contribute to those episodes. If other investigations fail to uncover a potential cause of syncope, carotid sinus hypersensitivity should be considered and the patient evaluated, with care taken regarding contraindications to carotid massage and appropriate technique, including monitoring.

An alternate view of the previous criteria and diagnostic approaches has recently been presented,[16] with the suggestion that the current distinction of carotid sinus hypersensitivity and carotid sinus syncope into a cardioinhibitory, vasodepressor, or mixed response should be discarded. The investigators believe that the isolated cardioinhibitory variety does not occur in the absence of a fall in BP, and that carotid sinus hypersensitivity should be conceived of as always or usually being mixed to some degree, and thus described as a "predominant cardioinhibitory" or "predominant vasodepressor" response. In addition, they suggest that stricter criteria (i.e., > 6 seconds of asystole and a fall in BP of > 75 mm Hg, or a fall in SBP to ≤ 80 mm Hg with the patient supine, or if this maneuver is negative, with the patient standing and carotid sinus massage) would be more consistent with observed data. Therapeutic options including atrioventricular pacing can be considered.

Chronic Autonomic Disorders with Orthostatic Hypotension

When asked to evaluate patients with OH for the possibility of an autonomic disorder, it is useful to first consider and eliminate situations and conditions that can produce OH even in patients without autonomic disorders. Several of them are commonly seen in the emergency department or inpatient setting and are mentioned earlier in discussions of orthostatic BP and HR testing. Whether the OH is caused by an autonomic disorder, such as one of the disorders described later, or a condition other than an autonomic disorder, the physician should recognize that OH in middle-aged individuals carries some population risk for the future.[21] In patients with the chronic autonomic disorders with OH described later, a careful personal and family history, physical examination, and bedside testing will often allow a presumptive diagnosis. Typical HR and BP responses to the Valsalva maneuver for these disorders, as well as for the postural tachycardia syndrome (POTS) and NET deficiency, are seen in **Fig. 99.4**. Although some patients with OH have more complex syndromes, with multiple types of ANS damage, for many patients the features described in **Table 99.2** can help differentiate baroreflex failure from OH.

TABLE 99.2

Distinction Between Baroreflex Failure and Autonomic Failure with Orthostatic Hypotension

	BAROREFLEX FAILURE	AUTONOMIC FAILURE WITH ORTHOSTATIC HYPOTENSION
Labile hypertension	+++	+/-
Orthostatic hypotension	+/-	+++
Orthostatic hypertension	++	—
Supine hypertension	+/-	++
Postprandial hypotension	+/-	++
Episodic tachycardia	++	—
Bradycardic episodes	++*	+/-
Hypersensitivity to vasoactive drugs	+++	+++

*Bradycardia associated with hypotension is a typical feature of malignant vagotonia due to selective baroreflex failure.

Congenital Disorders of Autonomic Function with Symptoms Present From Birth

A number of genetic disorders have been described in patients with abnormalities of autonomic function. An extensive review is available.[17] Continued progress should also be expected.

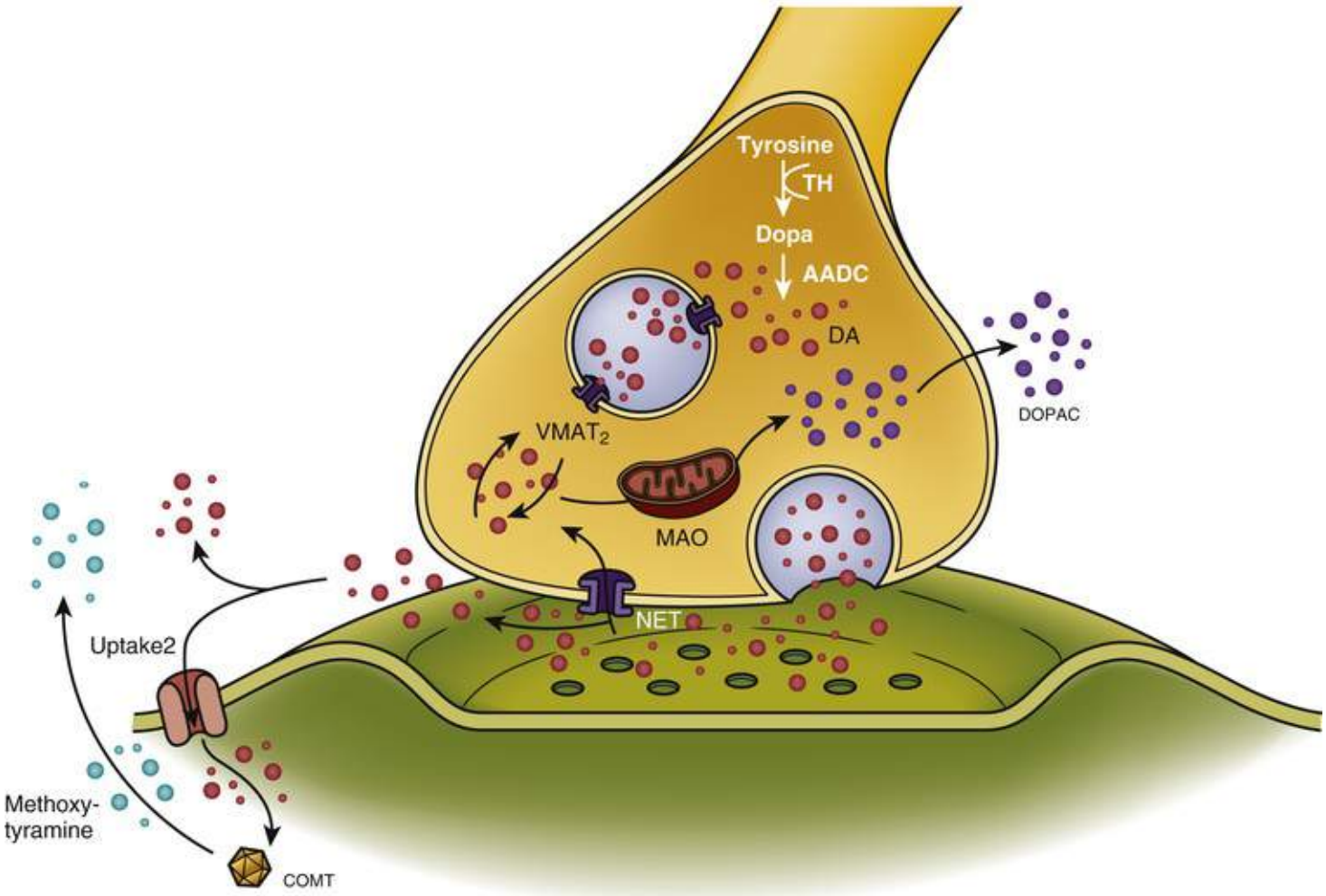
Dopamine Beta-hydroxylase Deficiency

Dopamine beta-hydroxylase deficiency, a rare congenital syndrome, was recognized in Nashville and in Rotterdam, when the evaluation of several adult patients with severe OH revealed remarkable abnormalities of their plasma catecholamines.[11] Norepinephrine levels were below the lower limits of detection at that time, epinephrine levels were likewise impaired, and dopamine levels were elevated to measurements not previously seen. With further testing, norepinephrine and epinephrine were confirmed to be absent not only in blood but also in urine and cerebrospinal fluid. Despite the absence of norepinephrine in the brain, patients given a battery of cognitive tests had no substantial deficits and appeared to have normal intelligence.[18]

Physical findings in these patients included severe OH that had produced lifelong habits of compensatory posture. All patients avoided standing for any length of time and chose occupations that could be done seated. Some patients also were in the habit of folding their legs beneath them when sitting in a chair, and would stand (which was often possible for only a few seconds) with a camptocormic posture (severe anterior flexion of the spine) to reduce the elevation of the head above the heart and with legs twisted and the skeletal muscle pump engaged to reduce pooling. They also demonstrated ptosis of the eyelids, intact sweating, anemia, and retrograde ejaculation in males.

The dramatic plasma catecholamine levels in these patients directed attention to dopamine beta-hydroxylase, the enzyme that converts dopamine to norepinephrine within the sympathetic neuron. The site of the genetic defect that produces the absence of functional dopamine beta-hydroxylase was ultimately determined to be 9q34. Without norepinephrine-mediated negative feedback of tyrosine hydroxylase and with no conversion of dopamine to norepinephrine, increased levels of dopamine are seen, and dopamine responds to physiologic and pharmacologic stimuli in the same manner as norepinephrine would in a normal subject. **eFig. 99.2** is a diagram of the noradrenergic neuron synapse in dopamine beta-hydroxylase deficiency. Measurement of norepinephrine and dopamine levels and their metabolites, DHPG and DHPAA, should be diagnostic. Norepinephrine levels will be less than 25 pg/mL, and dopamine levels are frequently more than 100 pg/mL. An even more definitive measure is the ratio of DHPAA to DHPG, which will be at least over 100 and can be over 1000. In normal healthy persons, the ratio is less than 5. Even in the absence of these data, physiologic testing can be quite helpful. The lack of

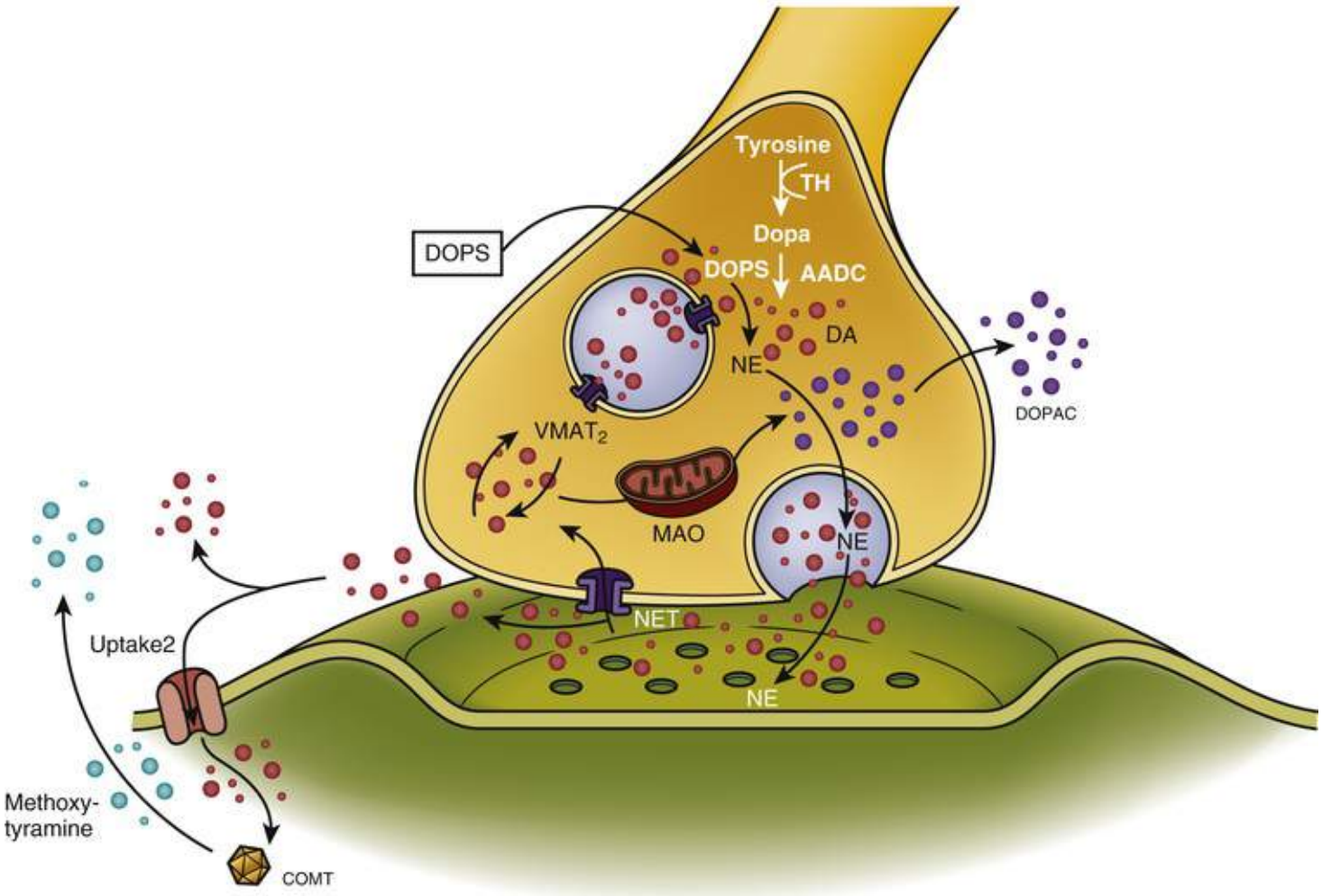
norepinephrine produces an absence of sympathetic noradrenergic function and adrenomedullary function, but the vagal and sympathetic cholinergic function is intact. With the Valsalva maneuver, this leads to exaggerated hypotension with no compensatory vasoconstriction during phase II, but a normal increase in HR. **Fig. 99.4D** shows a typical Valsalva maneuver in dopamine beta-hydroxylase deficiency. In testing the orthostatic BP and HR, the absence of sympathetic noradrenergic function leads to a lower BP at baseline and even more prominently disables the baroreflex's ability to support the BP with sympathetic vasoconstriction while one is standing or even seated.



EFIGURE 99.2 Diagrammatic representation of a noradrenergic synapse in a patient with dopamine beta-hydroxylase deficiency. Because of a mutation at 9q34 in the gene that produces the deficiency, patients with this disorder are unable to convert dopamine (DA) into norepinephrine (NE). Because the remainder of the biosynthetic pathway is intact and there is no norepinephrine-mediated negative feedback of tyrosine hydroxylase (TH), more dopamine is produced than usual, and it replaces norepinephrine as the neurotransmitter released with physiologic and pharmacologic stimuli. However, it produces little vasoconstriction and some diuresis, making these patients significantly affected by OH. *AADC*, aromatic amino acid decarboxylase; *COMT*, catechol-o-methyl transferase; *Dopa*, dihydroxyphenylalanine; *DOPAC*, 3,4-dihydroxyphenylacetic acid; *MAO*, monoamine oxidase; *NET*, norepinephrine transporter; *$VMAT_2$*, vesicular monoamine transporter 2.

Fortunately, L-threo-3,4-dihydroxyphenylserine (droxidopa [DOPS]), a synthetic precursor to norepinephrine that can be given orally, is taken up into the sympathetic neuron and converted to norepinephrine, and it can restore norepinephrine to within the normal range when given at 100 to 600 mg orally three times a day.[11] **eFig. 99.3** is a diagram of the noradrenergic neuron synapse in dopamine beta-

hydroxylase deficiency while a patient is receiving treatment with droxidopa. Droxidopa, unlike norepinephrine, can cross the blood-brain barrier. Restoration of the BP is excellent, orthostasis can be restored, and the quality of life is substantially improved. Truly long-term data are not yet available, but it is known that patients who begin replacement therapy early in life may not only have a greatly improved quality of life but also an increased level of health and longevity.



EFIGURE 99.3 Diagrammatic representation of a noradrenergic synapse in a patient with dopamine beta-hydroxylase deficiency who is being treated with L-threo-3,4-dihydroxyphenylserine (DOPS or droxidopa). Fortunately, DOPS can be taken orally and transported into the neuron, where it can be converted to norepinephrine by AADC (aromatic amino acid decarboxylase). Norepinephrine can then be packaged into vesicles and used as usual.

Familial Dysautonomia (Riley-Day Syndrome)

Familial dysautonomia, a rare congenital syndrome, is due to mutations in the gene encoding the I-K-B kinase complex–associated protein (IKAP), primarily in patients of Ashkenazi Jewish heritage, and the diagnosis is confirmed by genetic testing.[17] The largely conserved gene product is present in all eukaryotic cells, and its complete absence is fatal. However, a common mutation causing familial dysautonomia causes a splicing error that is expressed variably, so that some cells have functional IKAP and others, such as neurons in the central nervous system, have mostly mutant mRNA and produce little if any functional protein. In the past, most patients died in childhood; today, with improved supportive care (much of which was developed and applied at New York University's Medical Center's Familial

Dysautonomia Center by Dr. Felicia Axelrod and her colleagues[17,19,20] and at the Israeli Familial Dysautonomia Center at Tel Hashomer Sheba Hospital in Tel Aviv), patients may live into adulthood.

Patients may be seen because they are having “dysautonomic crises,” with prolonged retching and vomiting, hypertension with SBP over 250 mm Hg, tachycardia, and a blotchy appearance of the skin. Even in the absence of this constellation, they can demonstrate baroreflex failure, with hypertensive episodes that may require the combined use of a benzodiazepine and clonidine. Episodic hypotensive episodes and/or OH can sometimes be improved with fludrocortisone and midodrine prior to prolonged standing. The history can reveal episodic hyperhidrosis, absence of tears, insensitivity to pain and temperature, nausea, difficulty swallowing with aspiration, mild cognitive impairment, scoliosis, bone fractures, and an impaired ventilatory drive. The last issue can be sufficiently problematic that during high-altitude plane flights, positive-pressure ventilation should be available. The syndrome overall remains difficult to treat,[19] and patients will benefit from consultation with one of the centers mentioned above.

Autonomic Symptoms Beginning Later in Life

The Synucleinopathies[22]

In recent years, some common histopathologic features have been recognized in a number of progressive, neurodegenerative autonomic disorders, including pure autonomic failure (PAF), Parkinson disease, multiple system atrophy (MSA), and dementia with Lewy bodies, as well as in several neurodegenerative disorders without autonomic features, such as Alzheimer disease and neurodegeneration with brain iron accumulation type I.[23,24] In these disorders, the intracellular accumulation of α-synuclein aggregates, suggesting that abnormal protein deposition in the cytoplasm of both glial cells and neurons is involved in the development of the central and/or peripheral neurodegenerative disease. Subsequently, it has become clear that some patients with autonomic dysfunction also have abnormal aggregates of tau protein, previously thought to only be characteristic of some forms of dementia; the disorders are referred to as *tauopathies*. Both tau and α-synuclein are abnormal, partially unfolded proteins, and there is evidence that they can form toxic oligomers and promote each other's fibrillization and solubility. In some cases, both α-synuclein aggregates and tau inclusions are seen; this suggests that there may be an interaction or some common mechanism(s) linking them; the precise mechanisms and even conclusive theories remain elusive.[23] In this section, we will describe and differentiate the chronic autonomic disorders in which OH is a major clinical feature.

Pure Autonomic Failure.

Pure autonomic failure (PAF) is a neurodegenerative disorder appearing in middle age, with slowly progressive OH as its primary symptom.[25] First described by Bradbury and Eggleston in 1925, it generally does not shorten the lifespan, and some patients have survived into their 90s, though they can succumb to complications such as sepsis due to urinary tract infections.

Patients with PAF have been thought to differ from those with the other synucleinopathies in that they do not develop symptoms or signs of central nervous system dysfunction and can maintain good functional abilities with treatment. However, there are occasional reports of patients followed with a presumptive diagnosis of PAF who later developed central cerebral lesions; this fortunately appears to be rare. It is important, however, for patients and their families to know whether to expect progression to any of the other OH disorders described later. Directing them to report any new symptoms is essential to

maintaining an accurate prognosis. Hoarseness is often an early sign of multiple system atrophy (MSA), and sleep apnea and disturbances of REM sleep are more commonly seen in patients with MSA or Parkinson disease than PAF. We will here discuss patients with PAF limited to the periphery, because most patients fall into that category.

In these patients, the documented pathology includes a loss of cells in the intermediolateral column of the spinal cord and reduced catecholamine uptake and catecholamine fluorescence in sympathetic postganglionic neurons. In addition to gradually worsening OH as the primary symptom, patients often complain of erectile dysfunction, orthostatic neck pain or headache relieved by sitting or lying, and supine hypertension. They have extremely low levels of plasma norepinephrine when supine, in contrast to patients with MSA, whose supine norepinephrine levels are often near normal. In addition, in PAF, the plasma norepinephrine rises only minimally with standing, and despite marked OH, these patients have little chronotropic response to standing or to the Valsalva maneuver. **Fig. 99.4B** shows the appearance of the Valsalva maneuver in a patient with PAF, with a marked drop in BP during phase II, no vasoconstrictor rise in BP in late phase II, and no overshoot in phase IV. In addition, there is no cardioexcitatory rise in HR during phase II, despite the profound drop in BP. Plasma vasopressin responds normally to hypotension in PAF, but not in MSA.[26]

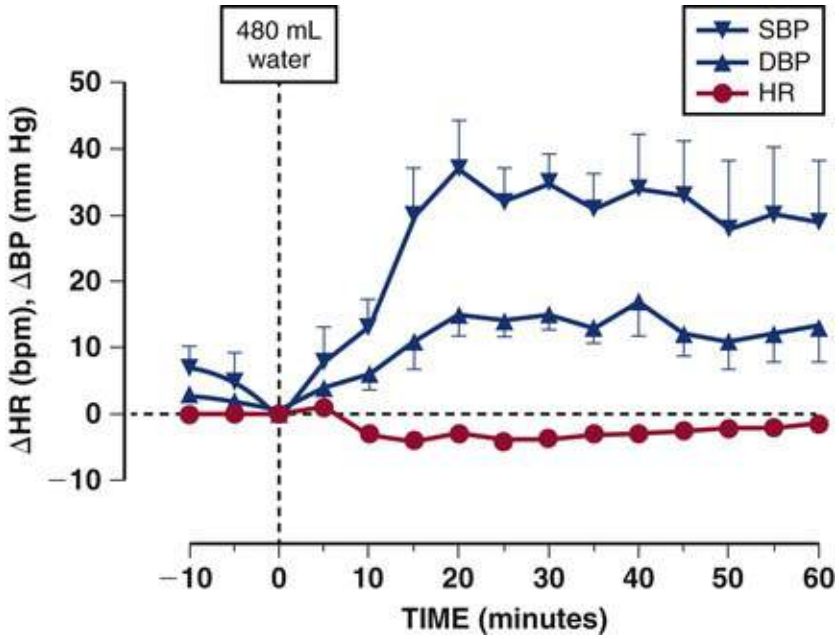
As PAF progresses over a long lifespan, the OH worsens, and there continues to be an inadequate chronotropic response, but the BP can often be managed well enough using the modalities below to allow most normal daily activities.[26,27] The cognitive function does not decline, and patients often become quite adept at their own management.

In patients with PAF, helpful interventions include raising the head of the bed by 30 degrees to reduce both supine hypertension,[27,28] which is commonly seen in PAF, and the nocturnal solute/water diuresis seen with autonomic failure; wearing compression stockings to reduce pooling; and liberalization of fluid and salt intake. The important effects of food and water (**eFig. 99.4**) on the BP can be incorporated to assist with maintaining the orthostatic BP and reducing the supine hypertension (**Table 99.3**).

TABLE 99.3

Factors Altering Blood Pressure in Patients with Autonomic Dysfunction

FACTOR	RAISES BLOOD PRESSURE	LOWERS BLOOD PRESSURE
Intake	Water drinking	Food ingestion
Volume	Hypervolemia	Hypovolemia
Ventilation	Hypoventilation	Hyperventilation
Environment	Cold	Heat
Medications	Sympathomimetics	Vasodilators
Other	—	Infection (even subclinical)



EFIGURE 99.4 The effect on systolic and diastolic BP (SBP and DBP) and on heart rate (HR) of drinking 480 mL of water in patients with pure autonomic failure. Patients were seated comfortably and began drinking tap water at 0 time. SBP and DBP both began to rise by 5 minutes after drinking, and remained elevated for more than 60 minutes. On separate occasions, the patient's upright BP and/or standing time was improved by this intervention. Healthy young persons did not demonstrate an elevation of BP after water drinking, but healthy elderly persons showed a rise in SBP of 11 mm Hg.

Medications may also be helpful and are often required. Midodrine acts as an α-agonist after its conversion to desglymidodrine, and droxidopa is converted to norepinephrine. Because these drugs produce vasoconstriction, they will worsen supine hypertension. Patients should usually be instructed to take their first dose 20 to 30 minutes prior to arising in the morning, and to adjust the timing of their remaining doses to support their ability to stand throughout the day, while allowing time for the drug's effect to wear off before they lie down at night. Frequent assessment of orthostatic BPs at home throughout the day followed by discussion with the health care provider and adjustments of dose and timing is often required over the initial weeks at home after a hospitalization. Fludrocortisone is also commonly used in the treatment of OH, both for its effect on the retention of sodium and water, which is relatively transient, and because its use is also accompanied by an increase in peripheral resistance. A missing area of management has been a method for treating one important mechanism for OH, the failure of sympathetic vasoconstriction of capacitance beds in the splanchnic circulation. This has recently been addressed by the development of a servocontrolled inflatable abdominal binder, which has been shown to be as effective as midodrine in terms of protecting the standing BP, but it can also be deflated by the patient when seated or supine, thus avoiding a deleterious effect on supine hypertension. In addition, for patients with severe OH, its combination with midodrine is greater than additive[6] (**Fig. 99.9**).

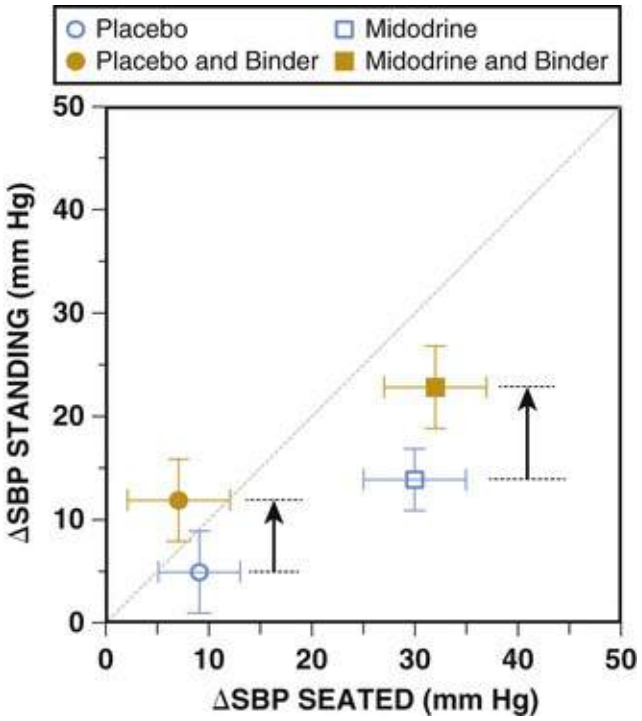


FIGURE 99.9 Effect of a servocontrolled abdominal binder and midodrine on OH. Changes from baseline in seated SBP and standing (1 minute) SBP 1 hour after placebo or midodrine. The *unfilled circle* and *square* indicate the mean change plus SEM for 19 patients with autonomic failure after the administration of placebo or midodrine. The *filled circle* and *square* indicate the same results after these agents plus the inflation of a servocontrolled abdominal binder. Standing SBP is not significantly improved by placebo. In contrast, the *orange circle* indicates the increase in BP with placebo and binder inflation. When the α_1-agonist midodrine alone is introduced, an increase in SBP is seen while seated, and the increase in SBP with the binder is greater than with placebo, suggesting more than an additive effect.

Finally, it is important to note that denervation hypersensitivity can cause dangerous elevations of BP in patients if they are given alpha agonists. For example, norepinephrine infusion markedly increases the BP in PAF patients, and even over-the-counter sympathomimetic agents can be dangerous. Patients undergoing surgery should be certain that their anesthesiologist is knowledgeable about this characteristic response.

Multiple System Atrophy.

Multiple system atrophy (MSA) is a rare, progressive, fatal neurodegenerative disease that generally presents in the 50s, with autonomic failure and complexes of other symptoms. Autonomic failure and the other symptoms do not always present in the same order, and the nonautonomic features can resemble parkinsonism or cerebellar ataxia. The initial diagnosis is therefore often one or the other of these conditions until symptoms appear that are related to OH and thus suggestive of MSA. Whether patients are thought to have Parkinson disease or olivopontocerebellar atrophy (OPCA) depends on the location of the neuropathologic lesions. The lesions consist of neuronal loss or atrophy in several of the following areas: the basal ganglia, cerebellum, pons, inferior olivary nuclei, or intermediolateral column and Onuf's nucleus of the spinal cord. In addition to neuronal loss, the critical neuropathologic feature of MSA is the presence of glial cytoplasmic inclusions in both the oligodendroglia and the neurons.[29,30,31] These structures contain a misfolded, hyperphosphorylated protein, fibrillar α-synuclein, which is also seen in the Lewy bodies of Parkinson disease or dementia with Lewy bodies. However, in MSA the primary problem in the relevant brain regions appears to involve the oligodendroglia, and it has been felt that the α-synucleinopathy there could lead to neurodegeneration. However, studies by Cykowski et al. found that in addition to the glial inclusions, neuronal inclusions in relevant areas are present; this may be important

in the pathology of MSA.[32] Recent studies have shown that α-synuclein can migrate or be transported from one cell to another or from human MSA brain homogenates to mouse cells in culture.[33] It has been suggested that this transmissibility could account for the progression of MSA, and has led some[34] to consider that MSA is due to "the accumulation of toxic α-synuclein prions in the brain."

During history taking, patients are likely to complain of the following symptoms appearing for the first time after the age of 30: light-headedness with upright posture; headache while upright, relieved by lying down; parkinsonian features such as tremor, rigidity, and progressive difficulty with ambulation, poorly responsive to treatment with levodopa; and urinary incontinence and erectile dysfunction in males. Patients with features more like those of OPCA may have, in addition to orthostatic symptoms, a cerebellar syndrome with dysarthria, limb ataxia, or oculomotor dysfunction.

By the time orthostatic symptoms occur, one will generally find an orthostatic decrease in SBP of 30 mm Hg or less within 3 minutes of standing, parkinsonism that is poorly responsive to levodopa, or cerebellar abnormalities. **Fig. 99.4C** shows a typical response of HR and BP to the Valsalva maneuver in a patient with MSA. Note the high resting BP and the absence of HR response to marked changes in BP. Additional features strongly supporting MSA, especially later in the course, include orofacial dystonia, disproportionate antecollis (anterior flexion of the neck), camptocormia (severe anterior flexion of the spine), contractures of hands or feet, inspiratory sighs, dysphonia (especially reduction in loudness of speech), cold hands and feet, and new or increased snoring.[29,30] If stridor is identified early in the course of the disease, it implies a poorer prognosis.[35]

Management.

In managing OH in patients in the earlier stages of MSA, techniques similar to those used in patients with PAF are helpful. These include elevating the head of the patient's bed by 30 degrees to reduce supine hypertension and the nocturnal solute/water diuresis commonly seen. If detrusor hyperactivity adds to the clinical significance of nocturia in patients with OH, peripherally acting anticholinergic agents such as oxybutynin or intermittent self-catheterization may be helpful.

Parkinsonian features are commonly prominent, and treatment with levodopa can be helpful, although it is generally not as effective as in Parkinson disease. It has been suggested that evaluating the pharmacodynamics of a low dose of levodopa can help separate MSA from Parkinson disease.[36] If levodopa causes problematic side effects, such as worsening of postural hypotension, dystonias, or dyskinesias, a dopamine-agonist may be warranted. About 20% of patients benefit from amantadine. However, there is no effective medical treatment for cerebellar symptoms. Spasticity and myoclonus rarely require treatment with baclofen, clonazepam, or valproate, but clonazepam may also ameliorate the REM sleep behavior disorder. Sildenafil is usually not effective in treating male erectile dysfunction in patients with MSA, and it can aggravate postural hypotension. For many patients, practical interventions, such as physical therapy, occupational therapy, and speech therapy including attention to swallowing difficulty, may yield the most benefit. To ensure the patient's safety, visits to the home by social workers and experts who can assess the patient's capacity to effectively use a walker or determine the need for, and ability to use, a motorized wheelchair are vital services, as is recognition by caregivers of the alterations in the ventilatory and cardiac responses to hypercapnia and hypoxia in MSA.[37] In the latter stages of MSA, hospice and palliative care facilities may provide additional relief to overburdened patients and families. Patient organizations, such as the Multiple System Atrophy Support Group and the MSA Coalition, may also provide needed support and information.[29]

Disease-Modifying Therapy.

There are currently no medical agents that slow or stop the progression of MSA. Two drugs that were effective in a transgenic mouse model of MSA have recently been tested in well-designed, adequately powered, placebo-controlled clinical trials but demonstrated no significant benefit. Rasagiline, an MAOB inhibitor, had been suggested to delay disease progression in Parkinson disease and had shown neuroprotective effects in the mouse model of MSA, but was ineffective in patients with MSA and had significant side effects.[38] Rifampicin, an antibiotic that can inhibit the formation of α-synuclein fibrils and remove aggregates of this toxic protein, showed no difference from placebo.[39]

Understandably, families dealing with the difficult course of MSA are concerned about whether this is a heritable disease. Although MSA is primarily a sporadic disease, there have been multiplex families described in Japan and Europe, and an association between single-nucleotide polymorphisms (SNPs) within the SNCA gene and the risk of sporadic MSA has been reported. However, a recent genome-wide association study was performed with more than 5 million genotyped and imputed SNPs in 918 patients with MSA and 3864 controls of European ancestry from North American and European centers. One third of the MSA cases were confirmed by pathologic studies. No significant loci were identified after a stringent multiple-testing correction, and no association of common genetic variants in the genes *SNCA* and *COQ2* with MSA was seen. The investigators suggested several potentially interesting gene loci, including the *MAPT* locus, whose significance must be evaluated in a larger sample set.[24]

Dementia With Lewy Bodies.

Patients who have dementia with Lewy bodies experience detrimentally progressive and fluctuating cognitive decline, with pronounced variations in attention, recurrent visual hallucinations, delusions, depression, and an REM sleep behavior disorder, accompanied by parkinsonism, severe neuroleptic sensitivity, and unexplained episodes of loss of consciousness or syncope.[40] Progressive autonomic dysfunction is also seen and can become quite severe, and OH is often the reason for the cardiac consultation. The order in which the multiple aspects of dementia with Lewy bodies becomes evident is variable, and arriving at an accurate diagnosis may require observation over a number of years. Some patients can present, for example, with autonomic symptoms before cognitive decline is evident.

Parkinson Disease With Autonomic Dysfunction.

Parkinson disease is a neurodegenerative disease that presents with an asymmetric resting tremor, rigidity, bradykinesia, and postural instability. Eosinophilic cytoplasmic inclusions called Lewy bodies are concentrated in the substantia nigra, and there is generally a good response to dopamine replacement therapy. Parkinson disease also is often associated with depression, cognitive dysfunction, anosmia, and sleep abnormalities. Differentiating between MSA and Parkinson disease is important because the prognosis in MSA is much worse, with an average of only 5 to 9 years of survival after the diagnosis. In MSA, as is consistent with a preganglionic lesion, norepinephrine transport is usually preserved. Uptake is impaired in Parkinson disease, suggesting cardiac sympathetic denervation.[1]

Although autonomic symptoms can occur in Parkinson disease, they are more typical and more serious in MSA. It is sometimes difficult to identify clearly the patient with parkinsonian features, but use of the smell test can be extremely helpful because anosmia or hyposmia is much more common in Parkinson disease than it is in MSA.[29]

Autoimmune Autonomic Failure

The syndrome of acute panautonomic failure results from antibodies to the ganglion of acetylcholine

receptors.[41] It manifests as OH, gastrointestinal dysmotility, urinary retention, and pupillary dysfunction. The syndrome usually appears acutely, and frequently but not always follows symptoms of an infectious disease. Once present, it often persists for life. It can be as severe as the late stages of PAF, which it mimics except for the acuteness of onset. It has only rarely been reported in children.[42] An important additional item in the differential diagnosis is the possibility that the antibodies involved are paraneoplastic, and these have appeared even when cancer has not been detected; it becomes clinically apparent only weeks to months later. A diagnostic panel of relevant antibodies is available at the Mayo Clinic, where there has been a long-standing interest in this disorder; the panel can, in some cases, suggest a cause.[41] Supportive treatment can be modeled after that of PAF (see earlier discussion). In terms of the underlying cause, patients may respond well to immunotherapies such as prednisone, intravenous immunoglobulin, plasma exchange, or oral immunosuppressants, although success is variable, and absent in some. The likelihood of full or partial reversal appears greater when the therapies are given as early as possible in the course of the disease, but rare responses have been seen even after years, so the duration of illness should not discourage aggressive treatment. Ancillary treatment of symptomatic patients with cholinergic agents such as pyridostigmine or bethanechol may sometimes be helpful. Increased fiber may help severe constipation.

Secondary Autonomic Neuropathies Associated with Other Diseases

Autonomic neuropathies may appear in the course of several diseases, producing a wide variety of symptoms and signs, including OH, as well as cardiac, gastrointestinal, sudomotor, or genitourinary dysfunction. Although these symptoms can appear late in the course of the underlying disease, some can be the presenting complaint or may even be subclinical, found with autonomic testing. Recognition of the connection between secondary autonomic dysfunction and previously unrecognized underlying diseases can be important clinically in directing attention and appropriate therapy to the primary disease and, occasionally, in better understanding the patient's prognosis. Specific treatment for any autonomic symptoms is not likely to alter the course of the disease, but can improve the quality of life.

The diseases that should be considered in this category include diabetes, amyloidosis, Guillain-Barré syndrome, Fabry disease, Tangier disease, leprosy, HIV neuropathy, connective tissue disorders, plasma cell dyscrasia–associated polyneuropathy, and a number of toxic neuropathies (e.g., *cis*-platinum, vincristine, paclitaxel, thalidomide, organic solvents, acrylamide).

Diabetes Mellitus

In diabetes mellitus, diabetic neuropathy may not only affect the peripheral autonomic nerves, leading to OH, which is generally manageable with the same modalities as in PAF, but may also cause abnormalities in the cardiac response to simple testing, such as measurements of the HR in response to a fall in BP with standing and with the Valsalva maneuver. Diabetic neuropathy and OH are also associated with diabetic nephropathy.[43,44] Optimal care of renal failure is obviously critical and is the most important way to reduce or prevent later nephrotic dysautonomia. Unfortunately, the appearance of autonomic dysfunction in a patient with diabetes presages an increased risk[45] and a reduction in lifespan.

Amyloidosis

In amyloidosis, a progressive, fatal disease, secondary autonomic dysfunction may be an early manifestation and is classically accompanied by carpal tunnel syndrome and small-fiber neuropathy. It is important to consider the underlying diagnosis, so that the amyloidosis can be treated as early and

aggressively as possible. Most cases are sporadic, but rare hereditary amyloidosis can be seen, as well. Physical pressure on nerve fibers or autonomic ganglia produces abnormal pathologic features when examined and has been considered the mechanism of neurologic dysfunction; the same pressure can interfere with blood flow and cause ischemic damage. Immunologic mechanisms have also been suggested. However, regardless of the mechanism, both sympathetic and parasympathetic abnormalities can be seen, and the widespread nature of the disease can lead to similarly widespread autonomic symptoms, including impotence, dysphagia, early satiety, and either diarrhea or constipation. Dry mouth and reduced sweating are often noted by patients, and OH can become a limiting feature. Cardiac involvement includes infiltration of the myocardium, visible on echocardiography, and often a prolonged QT interval, thought to be related to amyloid effects on cardiac nerves. The latter is associated with reduced survival times. Abnormal pupillary reflexes are often seen as well. A combination of several of these multiple autonomic symptoms and signs should suggest amyloidosis. Multiple novel approaches to diagnosis are now available. Examination of tissue during surgery, by abdominal fat aspiration, or by rectal, gingival, or sural nerve biopsy often allows specificity of the amyloid type. Treatment approaches aimed at slowing or reversing the progression of the underlying amyloidosis have expanded in recent years, and treatment of arrhythmias is appropriate, but the prognosis remains poor for most forms of the disease. Attention to mitigating the autonomic symptoms as much as possible can at least improve the patient's quality of life. Limited responsiveness to conventional treatments for OH may in fact suggest underlying amyloidosis if the diagnosis has not already been made. Early satiety may respond to metoclopramide, and octreotide is helpful in treating diarrhea. To improve the OH, fludrocortisone, midodrine, support garments, and an abdominal binder can be helpful. Erythropoietin, pyridostigmine, and L-threo-3,4-dihydroxyphenylserine (DOPS) have also been reported to reduce symptoms.

Guillain-Barré Syndrome

The key features of the Guillain-Barré syndrome are the acute onset of an inflammatory ascending, primarily motor polyradiculoneuropathy with absent reflexes and elevated cerebrospinal fluid protein, first described in 1916. Autonomic dysfunction complicates the course of the disease in approximately two thirds of cases. The disorder is believed to be immune mediated,[46] with three fourths of patients reporting a prior illness consistent with a viral or bacterial infection 7 to 10 days before the neuropathic symptoms appear. The illness is often mononucleosis, cytomegalovirus infection, or an enteric infection due to food poisoning with *Campylobacter jejuni*, and there have been some reports of antecedent *Mycoplasma* pneumonia, influenza, and, recently, Zika virus infection.[47] Guillain-Barré syndrome has been reported to be associated with vaccination in the past, but there has been no association with vaccines developed after 1977. It has been estimated that the risk of developing the syndrome after influenza significantly outweighs the risk from the influenza vaccine. Further supporting an immune cause are pathologic findings on sural nerve biopsy or at autopsy (rarely, because few patients die), the presence of serum antibodies against multiple types of antigens, and the response to immunotherapy.[48] Surgery has also been suggested as a trigger. Loss of tendon reflexes is usual, and ascending weakness (and sometimes sensory dysfunction) progresses over 1 to 2 weeks, followed by a plateau period of about 3 weeks, with severe weakness and respiratory paralysis being common. In some patients, recovery requires months to years, and may not be complete. Not all patients develop autonomic impairment, but it does occur in about two thirds of patients. If it occurs during the acute phase of the illness, it is likely to present as sympathetic hyperactivity, and some patients will have what are referred to as *autonomic storms*, with hypertension, tachycardia, and hyperhidrosis. The autonomic abnormalities may be mild in most patients, but life-threatening dysautonomia can be seen in this phase, especially in those severely

affected with motor abnormalities and/or respiratory failure, and OH may alternate with hypertensive episodes.[49] During the recovery phase, parasympathetic failure can be seen, with resting tachycardia, and testing commonly reveals cardiovagal, sudomotor, and adrenergic vasomotor function abnormalities. Cardiac rhythm abnormalities can include bradycardias, with heart block and periods of asystole sufficient to require a cardiac pacemaker, at least transiently. In this setting, vagal stimulation such as tracheal suction may be particularly likely to cause sinus arrest. The autonomic abnormalities require careful monitoring and adjustment of BP and HR, and recognition that patients may be supersensitive to pressor and depressor drugs. If there is prolonged hypertension, a combination of alpha-adrenergic and beta-adrenergic blockade has been suggested.

In general, the autonomic complications of Guillain-Barré syndrome abate in parallel with the motor and sensory abnormalities, either spontaneously or after treatment with plasma exchange or intravenous immunoglobulin (IvIg), 0.4 g/kg over 4 hours daily for 5 days. IvIg appears to have little effect if begun later than 14 days after the onset of the syndrome.[49] **See Table 99.3** for factors most likely to worsen symptoms in patients with autonomic dysfunction and thus bring subclinical disorders to attention.

Dysautonomias Without Chronic Orthostatic Hypotension

For neurally mediated syncope, **see Chapter 43**.

Postural Tachycardia Syndrome

Postural tachycardia syndrome (POTS) is a common reason for referral, and for many patients represents a disabling change in their lives. As data have accumulated, it seems apparent that POTS is not a single entity but is rather a syndrome that can be caused by multiple mechanisms, some of which will be discussed here, and exacerbated or improved by a number of factors that increasingly are being more precisely defined.

The postural tachycardia criteria for POTS have been defined in a consensus statement in the following way: (1) an increase in the HR of 30 beats/min or more (> 40 beats/man in those 12 to 19 years of age) within 10 minutes of standing or 70 to 80 degrees of head-up tilt for 10 minutes, in the absence of a drop in SBP of more than 20 mm Hg; (2) an associated constellation of symptoms worsened by upright posture and improved with recumbency, and lasting more than 6 months, in the absence of medications (vasodilators, diuretics, antidepressants, or anxiolytic agents) or other disorders known to cause orthostatic tachycardia (e.g., dehydration, anemia, hyperthyroidism).[7,50,51] Criteria are more likely to be met in the morning than in the afternoon or evening. Additional common symptoms not dependent on posture include abdominal pain, bloating, nausea and diarrhea, and fatigue. **Fig. 99.4E** shows a typical response to the Valsalva maneuver in a patient with POTS. The prevalence of patients with POTS in the United States has been thought to be about 0.2% of the population, but patient support groups, who reach individuals who may not yet have presented to the health care system, estimate that there may be as many as 3 million Americans who meet these criteria. This likely includes many groups of patients with a number of different causes and overlapping symptoms, several of which (such as mast cell activation disorder, tryptase excess, Ehlers-Danlos syndrome/joint hyperextensibility, and NET deficiency) are discussed later. Others, including neuropathic POTS, central adrenergic POTS, and autoimmune POTS, were recently reviewed by Garland et al.[50] For many patients, the cause remains unknown. Most patients are recognized at 15 to 35 years of age, with approximately a fivefold greater incidence in women as compared with men. The disorder does not appear to shorten the lifespan. With the increase in recognition of patients with POTS, a number of advocacy groups have emerged and have greatly increased patient

understanding of the disorder. Treatment options will be discussed later after review of some of the recently described disorders that can produce POTS.

Mast Cell Activation Disease

In recent surveys, as many as 20% of patients with POTS have been found to have characteristics that suggest some effects of mast cell activation disease,[52] an umbrella term including mastocytosis, an abnormal proliferation of tissue mast cells,[53] and other disorders in which there is abnormal activation of mast cells, even without excessive proliferation. These patients often have episodes of flushing and can have other associated symptoms, including shortness of breath, headache, excessive diuresis, diarrhea, and nausea. A hyperadrenergic response to posture, sometimes accompanied by light-headedness and even syncope, can occur, but symptoms frequently resolve when the patient is supine. They may in part be due to the fluid shifts and even fluid loss caused by mast cell products. Other patients may experience an increase in HR and BP during mast cell activation episodes, suggesting that other mediators or mechanisms may be involved. Following an episode, patients frequently experience lethargy and extreme fatigue for hours.[52]

The diagnosis of mastocytosis is frequently suggested by small pigmented urticaria pigmentosa skin lesions, but in their absence, evidence of mast cell proliferation can be sought in a skin or bone marrow biopsy, or by high levels of histamine and prostaglandin D_2 in a 4-hour urine aliquot, especially if obtained during or immediately after symptomatic episodes.[54] Effective treatment for episodes of vasodilation has included inhibitors of prostaglandin biosynthesis and antihistamines.[53] However, if a patient is “aspirin hypersensitive,” a prostaglandin inhibitor may provoke severe mastocyte activation.

Recently, an idiopathic activation disorder of mast cells has emerged with episodes of systemic mast cell activation without evidence of abnormal proliferation, and this disorder is now seen more frequently than the uncommon mastocytosis itself.[53] In the majority of cases, symptoms are virtually identical to those seen in systemic mastocytosis. Anaphylaxis can be seen,[55] and OH is frequently experienced during mastocyte activation. Exposure to heat, emotional upset, and exertion are common precipitating triggers, but beta blockers can also trigger episodes. Ketotifen has been effective in treating patients with mast cell activation disorder with idiopathic anaphylaxis episodes due to the drug's antihistamine and mast cell–stabilizing properties.[55] Centrally acting sympatholytic agents such as methyldopa or clonidine are often effective, and antihistamines can also be helpful. When patients frequently or continuously suffer from anaphylactoid dysautonomic episodes, their symptoms are poorly controlled by steroids, epinephrine, and antihistamines. However, infusions of diphenhydramine often effectively suppress mast cell activation, anaphylaxis, and allergic reactions.[52]

Tryptase Abnormalities

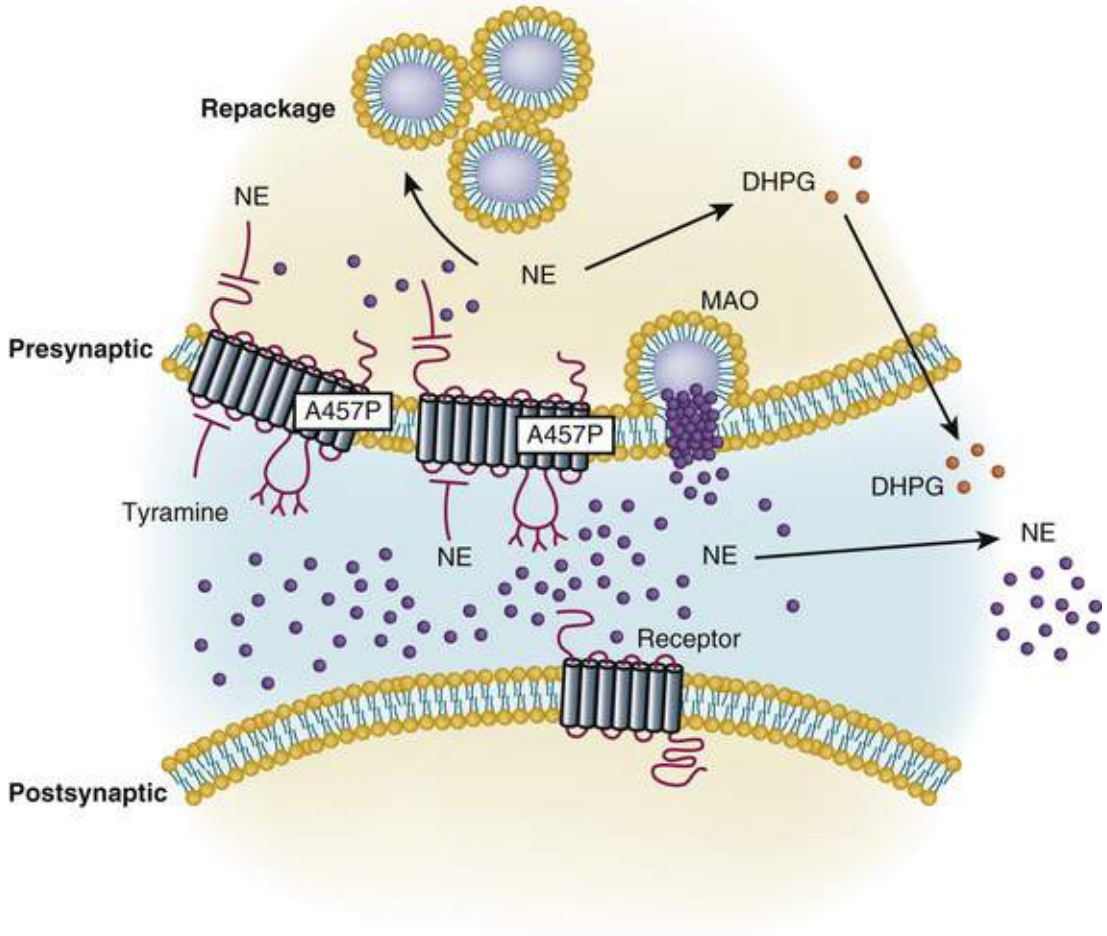
In a recent study, germline duplications and triplications in the *TPSAB1* gene, which encodes alpha-tryptase, a protein often associated with allergic reactions, have been discovered,[56] and an inherited increase in basal serum tryptase levels was found. Duplications in the *TPSAB1* gene were linked with symptoms of dysautonomia, such as orthostatic light-headedness and tachycardia characteristic of POTS, along with skin flushing and itching, gastrointestinal complaints, chronic pain, and bone and joint problems. Those with three copies of α-tryptase had even higher basal serum levels of tryptase and more symptoms than those with two copies, suggesting a gene-dose effect.[56] More studies will be required to confirm this report.

Ehlers-Danlos Syndrome

The Ehlers-Danlos syndrome includes several different disorders united by genetic abnormalities and affecting the structure of collagen. It has been estimated that nearly 20% of patients with POTS[50] may have characteristic features of Ehlers-Danlos syndrome (most commonly, type III), with hyperextensible skin and excessive joint mobility.[57] In patients with Ehlers-Danlos syndrome, orthostatic palpitations and tachycardia, chest pain, presyncope, and syncope are frequently seen, with episodes of these symptoms often triggered by a hot environment, exercise, or meals. Whether the POTS-like symptoms are due to connective tissue abnormalities, with excessive blood pooling with standing leading to orthostatic intolerance, or whether the syndrome is associated with a peripheral neuropathy is uncertain. Support garments and an abdominal binder might be of help, particularly in patients where there is evidence of pooling.

Norepinephrine Transporter Deficiency

One of the very rare specific causes of POTS has been shown to be a deficiency in the ability of the NET to transport released norepinephrine back into the sympathetic nerve terminal. This results in elevated synaptic levels of norepinephrine whenever release is triggered, so that upright posture produces symptoms consistent with the definition of POTS (**eFig. 99.5**). The genetic mutation producing an abnormal NET has been identified, and leads to a more than 98% reduction in transport efficacy. Even heterozygotes can have severe deficiency of norepinephrine transport. This has been explained by studies showing that the mutant form of the gene exerts a dominant negative effect when it is transfected into a heterologous expression system, causing a conformational disruption that interferes with the biosynthetic progression of the transporter and trafficking of both the mutant transporter and the wild-type NET.



EFIGURE 99.5 Schematic representation of the hypothesized effect of the mutation seen in norepinephrine transporter (NET) deficiency (A457P) at a noradrenergic synapse. Normally, the NET takes up released norepinephrine, which once in the cytoplasm can be repackaged into vesicles for exocytosis or be metabolized by monoamine oxidase (MAO) to dihydroxyphenylglycol (DHPG). Some norepinephrine escapes the reuptake process and appears in plasma. DHPG can diffuse out of the neuron and can be measured in plasma. The failure of A457P to transport norepinephrine generates greater than normal norepinephrine in the synapse, norepinephrine spillover, and diminished clearance of norepinephrine from the plasma. The lack of uptake diminishes the flux of norepinephrine through the MAO degradation pathway, and following release of norepinephrine, plasma DHPG levels do not increase as compared with normal. Tyramine is a substrate for the NET; once inside the cell, it displaces norepinephrine from vesicles, thereby increasing cytoplasmic norepinephrine levels and resulting in the exit of norepinephrine from the neuron via a reverse transport mechanism. The effect of tyramine on inducing release of norepinephrine is blunted in the presence of A457P. (From Hahn MK: Norepinephrine transporter deficiency. In Robertson D, Biaggioni I, Burnstock G, et al (editors): Primer on the autonomic nervous system, 3rd ed. San Diego, Academic Press, 2013.)

Medications and Norepinephrine Transporter Blockers

It is important to recognize that a number of medications (vasodilators, diuretics, antidepressants, or anxiolytic agents) can produce a syndrome of orthostatic tachycardia, especially those which act as NET inhibitors or inhibitors of both serotonin and norepinephrine reuptake or which have these characteristics as secondary, off-target effects. These can either worsen orthostatic tachycardia in patients with POTS when used to treat depression or can produce a POTS-like syndrome in patients who have not previously had such symptoms.

Additional uncommon but specific causes of POTS have been described in case reports or series, including neuropathic POTS, central adrenergic POTS, and autoimmune POTS.[50,59] This may account for the heterogeneity of the response to specific medications. Referral to an autonomic center may be helpful

in finding optimal medical management for patients who do not respond to conventional approaches.

Because POTS is a very heterogeneous illness, and the effect of symptoms on the patient's life can have major consequences for both mental and physical health, a number of therapeutic interventions have been proposed to improve health.[50,57] These begin with volume expansion, with a higher salt and fluid intake than is normally recommended for healthy individuals. Although intravenous saline (1 to 2L) can reduce tachycardia and improve symptoms acutely, it is not recommended as a repetitive chronic treatment regimen, given the complications that can accompany frequent venous access. Waist-high compression garments or the use of abdominal binders can reduce the splanchnic-mesenteric pooling of volume with upright posture, and the resultant increase in stroke volume can reduce upright tachycardia. Sustained exercise programs have also been reported to have benefit in patients with POTS, but have been difficult to implement because exercise-provoked symptoms lead most patients to become deconditioned over time. Shibata et al have described a 3-month aerobic and resistance exercise program. It starts with seated, supine, or swimming exercise and progresses slowly. Patients should be told that they may feel worse in the beginning and that the eventual improvement in blood volume and decrease in postural tachycardia can take 5 to 6 weeks.[60]

Although the above measures can improve symptoms, many patients will require medications in addition, and we find that low-dose (10 to 20 mg) propranolol is well tolerated and helpful. If this is insufficient, we usually add either midodrine (2.5 to 10 mg every 4 hours 3 times a day) or fludrocortisone (0.05 to 0.2 mg daily). We may, less commonly, use other medications, depending on the patient's specific characteristics. Garland et al.[50] provide a useful guide to alternative agents, consistent with the consensus statement of the Heart Rhythm Society, endorsed by multiple international organizations.[51] All of these short-term drug therapies may have positive effects, but it is unclear whether there are long-term benefits of drug therapy.

Disorders of Increased Sympathetic Outflow

Obstructive Sleep Apnea

The disorder of obstructive sleep apnea (OSA; **see also Chapter 87**) is a chronic condition in which patients have multiple episodes of partial or complete upper airway collapse during sleep, causing hypoxia and hypercapnia and interruption of normal sleep patterns. The actual prevalence is difficult to determine; it is likely that the disease is significantly underreported, and with the population increase in obesity over recent decades, it presumably is more common than previously thought. During episodes of apnea while sleeping, the hypoxia and hypercapnia cause an increase in sympathetic outflow. It has been suggested that the hyperadrenergic state while awake may be due to a tonic increase in chemoreflex sensitivity. Conventional treatment of OSA with CPAP treatment at night appears to improve the hyperadrenergic state as well.[1]

Pheochromocytoma and Paraganglioma

Pheochromocytoma and paraganglioma are rare catecholamine-secreting tumors derived from the chromaffin cells of the adrenal gland or the paraganglion chromaffin tissue of the SNS[61] (**see also Chapter 95**). They are diagnosed (or excluded) by detection of the catecholamines they produce, whether norepinephrine, epinephrine, and/or dopamine. These can be assayed in plasma, along with free metanephrines and methoxytyramine, but catecholamines have a short half-life in plasma, so 24-hour urine

collection is often beneficial if baseline samples are negative and episodes are infrequent. Paraganglioma effects are described earlier as one of the causes of baroreflex failure. Pheochromocytomas often arise from the adrenal glands, but they may also develop in sympathetic ganglia anywhere. The increased secretion of catecholamines can result in life-threatening hypertension or cardiac arrhythmias, especially with norepinephrine and epinephrine release. Pheochromocytomas can be sporadic or familial and benign or malignant. MRI has nearly 100% sensitivity for the detection of adrenal pheochromocytomas. When clinical suspicion is high because of positive laboratory test results but imaging reveals no source, a ^{131}I-MIBG scan may be useful. Definitive treatment is via surgical resection, with appropriate alpha and beta blockade preoperatively.

Future Perspectives

Progress in the exploration of autonomic cardiovascular control has been substantial in recent years, and multiple areas are at the point of further advances. The recent past has expanded our understanding of testing and of the physiology and pathophysiology of the ANS. This knowledge has the potential to assist in risk assessment and the finding of new therapeutic approaches to improve the outlook for specific disorders.[63] Continued studies of the biochemical and, in some cases, genetic underpinning of disorders such as POTS and MSA[64] are likely to lead to a more precise definition of subsets of patients who may benefit from more specific diagnostic and therapeutic approaches. This has been seen in recent years in amyloidosis, where new discoveries have been made with imaging studies, and in studies of pheochromocytoma and paraganglioma.[61] Uncovering connections between OSA and coronary disease[62] is one example of an area needing further research. New technologies that could provide more continuous monitoring of skin sympathetic activity[65] may also provide information during normal activities, rather than simply in the autonomic laboratory. Spectral analysis of cardiac sympathovagal balance can be useful in assessing cardiovascular risk (e.g., in patients with diabetic neuropathy). The technique has recently suggested that habitual e-cigarette use may be associated with an increase in risk for autonomic disorders.[66]

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Disclosure Index

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334—UpToDate (Wolters-Kluwer)
335—US Diagnostics Standards
336—VA
337—Valeant
338—Vascular Biogenics
339—Verseon
340—Vertex
341—Vestion, Inc.
342—Veterans Health Administration
343—VHA, Inc.
344—Victor Chang Cardiac Research Institute
345—VivaLink
346—Vox Media
347—WebMD
348—WeillCornell Medicine/NYP
349—Wiley-Blackwell
350—Winston and Strawn LLP
351—WISE CD
352—Wolters/Kluwer
353—WomenHeart
354—Women'sHealth Congress
355—World Heart Federation
356—Xbiotech Inc.
357—Xoma
358—Yungjin
359—Zafgen
360—Zensun
361—ZOLL

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